UNIVERSITY OF SOUTHAMPTON

THIOL MEDIATED RADICAL CYCLISATIONS OF ISOCYANIDES: SYNTHESIS OF *N*-HETEROCYCLES

By

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Abstract

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This thesis is concerned with the synthesis and radical cyclisations of alkenyl and alkynyl isocyanides with thiols. Special interest is given to developing a fast and efficient synthetic route to functionalised *N*-heterocycles and polycyclic systems.

Chapter 2 describes the synthesis of simple alkenyl isocyanides and their radical cyclisations, mediated by thiols, to access pyrrolines and pyroglutamates. Radical cyclisations of alkenyl isocyanides were also investigated on solid phase.

Chapter 3 describes the synthesis of functionalised alkenyl and alkynyl isocyanides and their thiol mediated radical cyclisations promoted by microwave irradiation. The microwave assisted radical cyclisations were found to proceed in good to excellent yields in very short time, compared to traditional thermal heating techniques.

Chapter 4 reports the investigation into the synthesis of polycyclic systems via a novel radical cyclisation/*N*-alkylation/ring closing metathesis strategy, starting from simple bis-alkenyl isocyanides. Several indolizidines and bicyclic lactams were successfully synthesised. Tricyclic indolizidines were also accessed via Pauson-Khand reaction of functionalised pyroglutamates in good yields.

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Preface

The research described in this thesis was carried out under the supervision of Prof. Jeremy D. Kilburn at the University of Southampton between October 2000 and September 2003. No part of this thesis has been previously submitted at this or any other University.

to Antonella and Maria

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Last but not least, I want to say a big thank you to Antonella for her constant support and love.

Abbreviations

ACN	1,1'-Azobis(cyclohexanecarbonitrile)
AIBN	2,2'-Azobisisobutyronitrile
BEMP	2-*tert*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine
BTPP	2-*tert*-butylimino-*tris*(1-pyrrolidinyl)phosphorane
Bn	benzyl
Boc	*tert*-Butoxycarbonyl
br s	broad singlet
C.I.	chemical ionisation
d	doublet
DCM	dichloromethane
DEPT	distortionless enhancement by polarisation transfer
DTBP	Di-*tert*-butyl peroxide
DCC	Dicyclohexylcarbodiimide
DMAP	4-Dimethylaminopyridine
DMF	*N*, *N*-dimethylformamide
DIC	Diisopropylcarbodiimide
DMSO	Dimethylsulfoxide
DPPA	diphenylphosphoryl azide
E.I.	electron impact
Eq.	Equivalent
Fmoc	Fluorenylmethoxycarbonyl
h	hour
HMPA	Hexamethylphosphoramide
HOBt	*N*-Hydroxybenzotriazole
In.	Initiator
I.R.	Infrared Spectroscopy
J	coupling constant
m	multiplet
M.A.S.	Magic Angle Spinning

MS	Mass Spectrometry
N.M.R.	Nuclear Magnetic Resonance
NMP	1-Methyl-2-pyrrolidinone
NMO	4-Methylmorpholine *N*-oxide
p	para
PTC	Phase Transfer Catalysis
PMB	paramethoxybenzyl
PKR	Pauson-Khand Reaction
PG	protecting group
q	quartet
R_f	retention factor
rt	room temperature
RCM	Ring Closing Metathesis
t	triplet
TBAB	Tetrabutylammonium bromide
TBDMS	*tert*-butyldimethylsilyl
THF	tetrahydrofuran
TIPS	triisopropylsilane
TMS	trimethylsilyl
TMANO	trimethylamine *N*-oxide
TFA	trifluoroacetic acid
UPS	Unnatural Peptide Synthesis

Chapter 1

INTRODUCTION

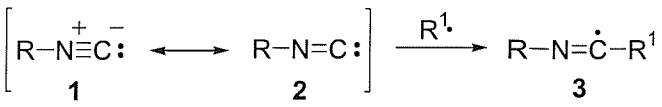
1.1 Isocyanides: Structure and properties

Isocyanides are a unique class of organic compounds, as they are the only stable organic compounds, apart from carbon monoxide, with a formally divalent carbon (the carbon atom in carbenes is divalent, but most carbenes are extremely short-lived compounds). Owing to its reactivity the isocyanide group greatly differs from other functional groups. Their discovery by Lieke, Gautier and Hofmann dates back more than 130 years, but up to the 1960s only a few studies concerning their chemistry had been reported.[1, 2]

The classical synthetic routes to isocyanides remained for a long time the "carbylamine reaction"[2] and the "alkylation method".[2] The former involves the reaction of a primary amine with chloroform and a strong base and entails addition of a dichlorocarbene to the amino group, followed by elimination of hydrogen chloride. This method was used for qualitative detection of primary amines, due to the strong unpleasant odour of the resulting isocyanide. The alkylation method requires treatment of metal cyanides with alkylating agents such as dialkyl sulfates or alkyl halides. The reaction gives mixtures of nitrile and isocyanide, it is however possible to obtain preferentially the isocyanide in the presence of silver cyanides. These two methods proved to be unsuitable for the preparation of appreciable quantities of pure isocyanides and they have been replaced by the more widely applicable "dehydration method".[2, 3] This was first discovered by Hagedorn in 1956 and requires the transformation of primary amines into the corresponding formamides, followed by dehydration either with phosgene (or its derivatives) and triethylamine, or other dehydrating agents and diisopropylamine. This very general method granted easy accessibility to isocyanides and, as a

consequence, their chemistry has flourished in the last four decades, proving their outstanding versatility. Remarkable synthetic procedures, involving attack of electrophilic species (e.g. carbenium and iminium ions) on the nucleophilic carbon of the isocyanide, include Ritter-type processes[4] and the Passerini and Ugi reactions.[3] The latter are noteworthy one-pot multicomponent reactions that easily afford a wide range of functionalised carboxamides, lactams, amino acids and peptides.

The structure of isocyanides can be described in terms of a divalent carbon atom, but, in valence bond terms, a full description of the isocyanide moiety requires the two resonance structures **1** and **2** (Scheme 1).

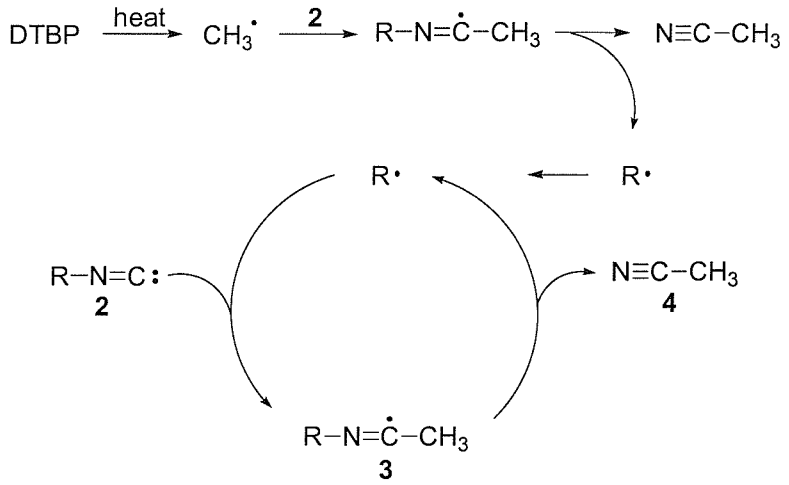


Scheme 1. Resonance in isocyanide structure.

Physical properties indicate that the dipolar contribution **1** is the major one and this structure accounts for the nucleophilic behavior of the terminal carbon of isocyanides. However, in terms of radical chemistry, the more interesting form is the divalent one **2**. It clearly shows that the isocyanide group does not behave toward radical species like a *vicinal* radical acceptor/radical donor synthon, that is, like a normal unsaturated bond. Instead it reacts like a *geminal* acceptor/donor synthon, where an incoming radical attacks the same carbon atom that will be the new radical center in the resulting imidoyl intermediate **3** (Scheme 1). Isocyanides can then be used as very efficient radical traps.

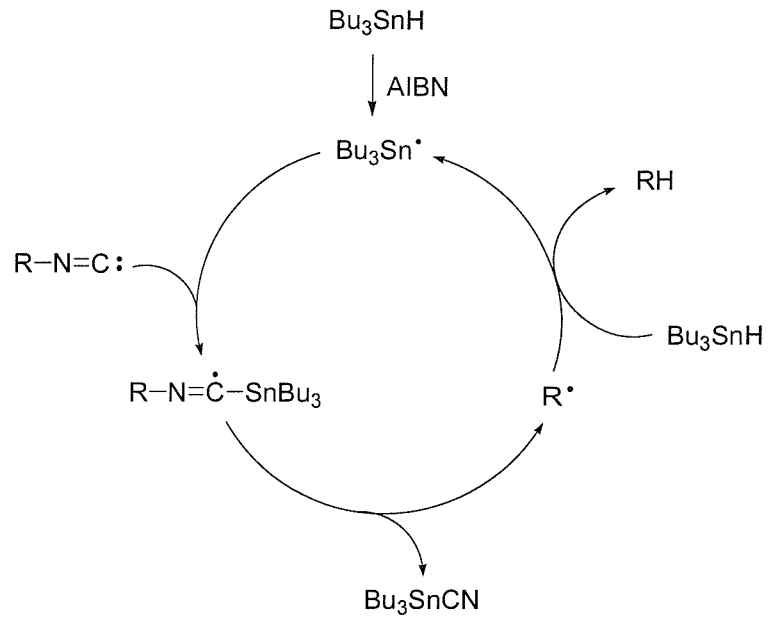
1.1.1 Isocyanides as radical traps: Radical addition/fragmentation reactions.

The first example of radical addition to isocyanides was reported in the sixties. In 1967 Shaw[5] observed the isocyanide-nitrile isomerisation of methyl and ethyl isocyanide when heated in the presence of catalytic amounts of di-*tert*-butyl peroxide (DTBP) (Scheme 2). The concerted isocyanide-nitrile thermal or photochemical isomerisation had been known for many years[4] but he suggested a radical chain mechanism, based on thermodynamic and kinetic data, involving addition of methyl radicals to isocyanide **2**.
β-Scission of the resulting radical adduct (**3**) gives rise to an alkyl radical, the chain propagating species, that gives complete conversion of the starting isocyanide into nitrile **4**.



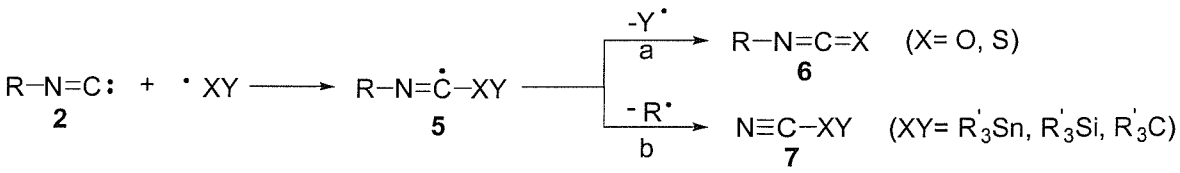
Scheme 2. Di-*tert*-butyl peroxide mediated isomerisation of isocyanides.

The feasibility of a radical attack on the carbon atom of isocyanide was then claimed by Saegusa,[6] who studied the reaction of tri-*n*-butyltin hydride with alkyl isocyanides. Formation of an alkane and tributyltin cyanide, and the need to use a radical initiator (AIBN), supported the radical chain mechanism with the addition of tin radicals to the isocyanide (Scheme 3).



Scheme 3. Radical chain reaction of isocyanides with tributyltin hydride.

In the seventies several papers reported the addition of carbon,[7-10] sulfur,[6, 9, 11] silicon,[9, 11] oxygen,[7, 9, 11, 12] phosphorus[9, 11] and tin radicals[13] to isocyanides. Interestingly, the fate of the intermediate imidoyl radical depends on the nature of both the attacking radical and the R alkyl group of the isocyanide (Scheme 4).



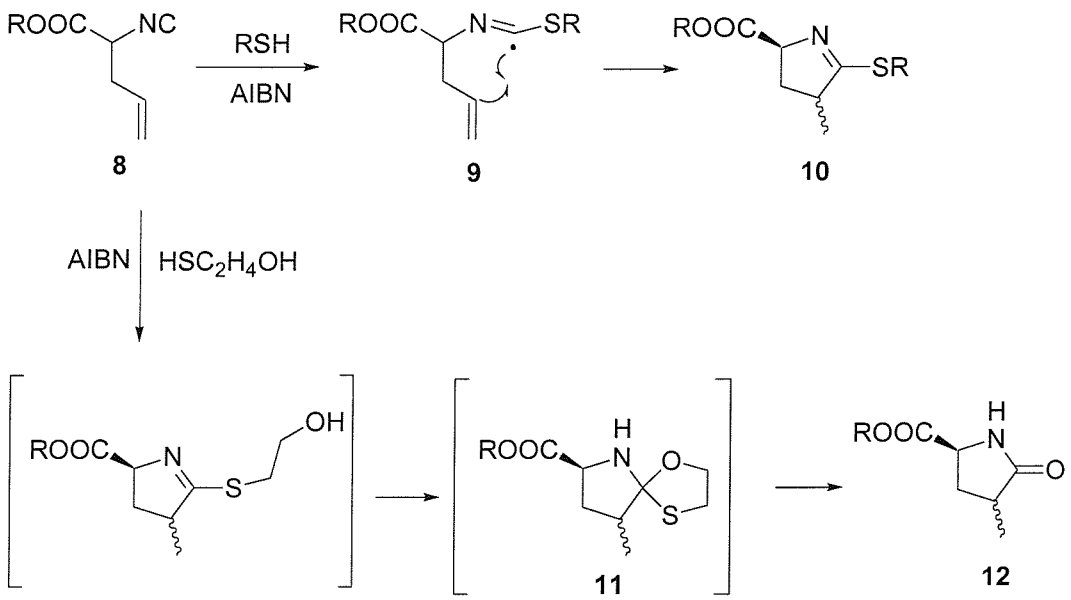
Scheme 4. Fragmentation patterns of imidoyl radicals.

Addition of oxygen- or sulfur-centered radicals gives an imidoyl radical (**5**) that undergoes *β*-fragmentation of the O-Y or S-Y bond of the attacking radical to give isocyanates or isothiocyanates (**6**), respectively (scheme 4, path a). Carbon, tin and silicon radicals produce nitriles (**7**) through *β*-fragmentation of the N-R bond of the isocyanide (scheme 4, path b). However this behavior is not always general, since fragmentation of likewise substituted imidoyl radical (**5**) can follow two competitive pathways depending on the stability of the released radical (R or Y). For example, addition of methylsulfanyl radicals to *tert*-butyl isocyanide does not give *tert*-

butyl isothiocyanate (**6**, R= *tert*-bu, X = S) but instead methyl thiocyanate (**7**, XY = SMe), due to preferential formation of the more stable *tert*-butyl radical.[9] These reactions showed great synthetic potential and they were used as an efficient way to introduce a cyano group into a molecule or, by prior conversion of an amino group into the corresponding isocyanide, as a useful deamination method.[13, 14] Radicals of type **5**, when generated by other routes, can undergo an additional fragmentation reaction, which is an α-scission with release of the XY radical. This process was observed with α-(triphenylmethyl)imidoyl,[15] α-(tributyltin)thio[16-18] and α-(arylsulfanyl)[19, 20] radicals, generated by either radical addition to isothiocyanates or hydrogen abstraction from the corresponding imines. When imidoyl radicals are generated from isocyanides, this behavior would result in a reversibility of the radical addition process. Evidence has been reported that formation of imidoyl **5** from **2** seems to be reversible, with particularly stable XY radicals.[21]

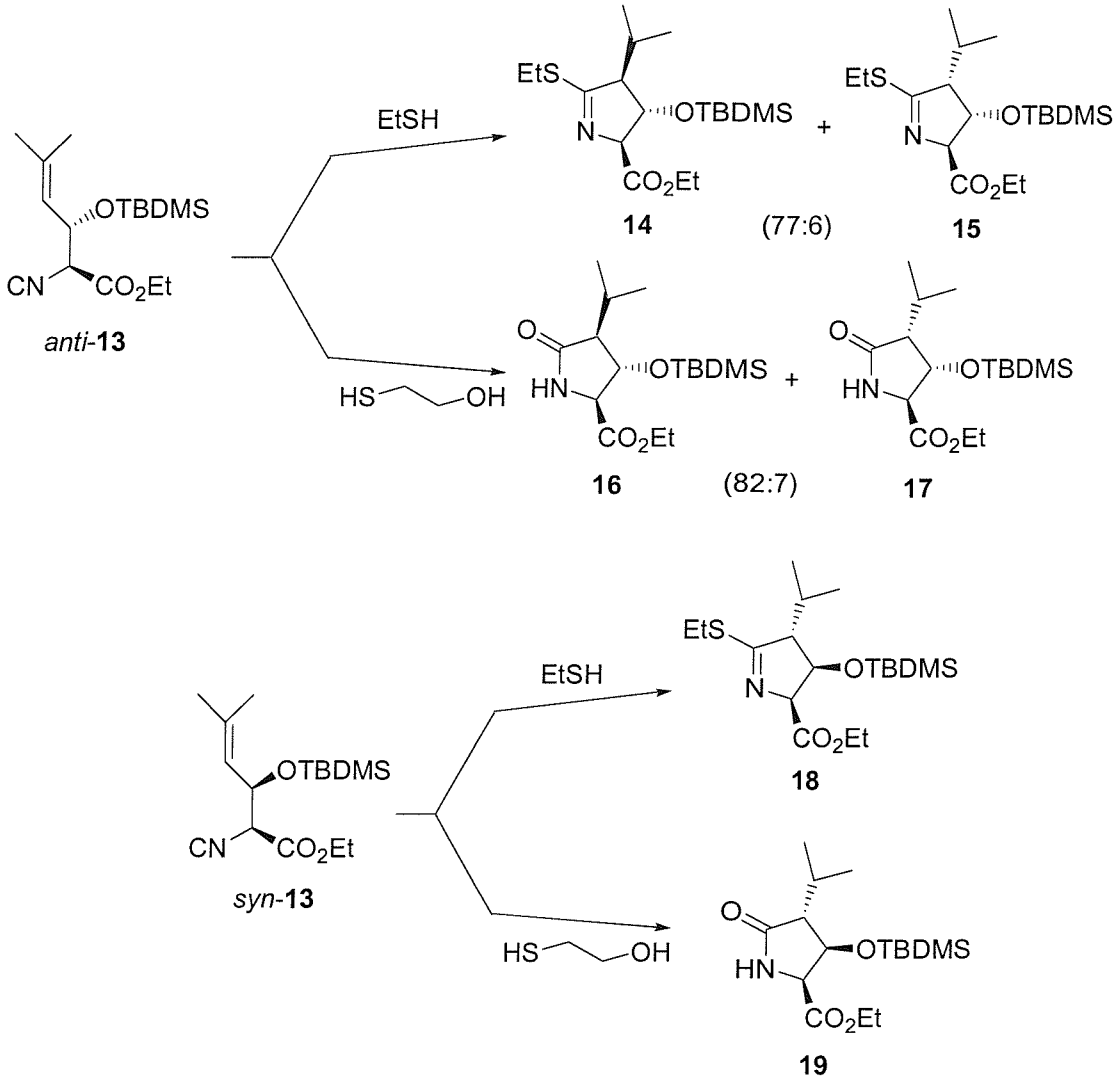
1.1.2 Isocyanides as radical traps: Addition to aliphatic isocyanides.

In 1970 Saegusa[6] paved the way for applications based on radical addition of thiols to isocyanides, but, surprisingly, for more than twenty years, no synthetic work followed his observations. Only in the 1990's Bachi[22-27] exploited the potential of Saegusa's work for the synthesis of 5-membered nitrogen heterocycles, starting from aliphatic isocyanides bearing a suitable unsaturated side chain. The first results were obtained with alkenyl isocyanides **8**, easily accessible from glycine (scheme 5).



Scheme 5. Bachi's synthesis of pyrrolines and pyroglutamates.

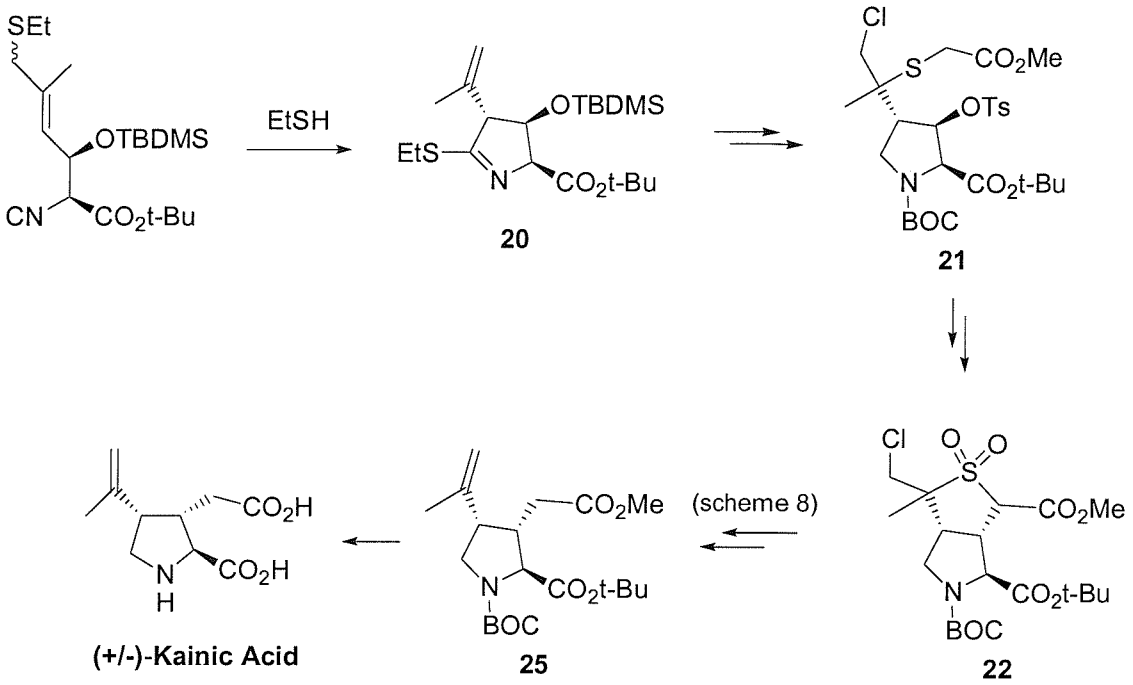
Treatment of isocyanide **8** with thiophenol or ethanethiol, in the presence of AIBN, gave high yields of the corresponding *cis*- and *trans*-pyrroline derivatives **10**,[22] through the imidoyl intermediate **9** and subsequent 5-*exo*-*trig*-cyclisation. Reaction with 2-mercaptoethanol gave instead the corresponding pyroglutamates **12**, through the intermediacy of the cyclic derivative **11** which undergoes hydrolysis during the reaction.[22] Fragmentation of the imidoyl radical to the isothiocyanate was sometimes a competing process, especially when the scission yields a fairly stable radical; in those cases, control over the two competing processes was gained by temperature adjustment. Several functionalised isocyanides of type **8** were also synthesised and cyclised in good yields. Very little or no diastereoselectivity was observed in the formation of pyrrolines whereas better results were obtained with pyroglutamates. However an efficient stereocontrol of the key cyclisation step was achieved with suitably designed starting materials bearing a bulky OTBDMS group vicinal to the site of radical addition (scheme 6).[23]



Scheme 6. Stereocontrol in the Bachi reaction.

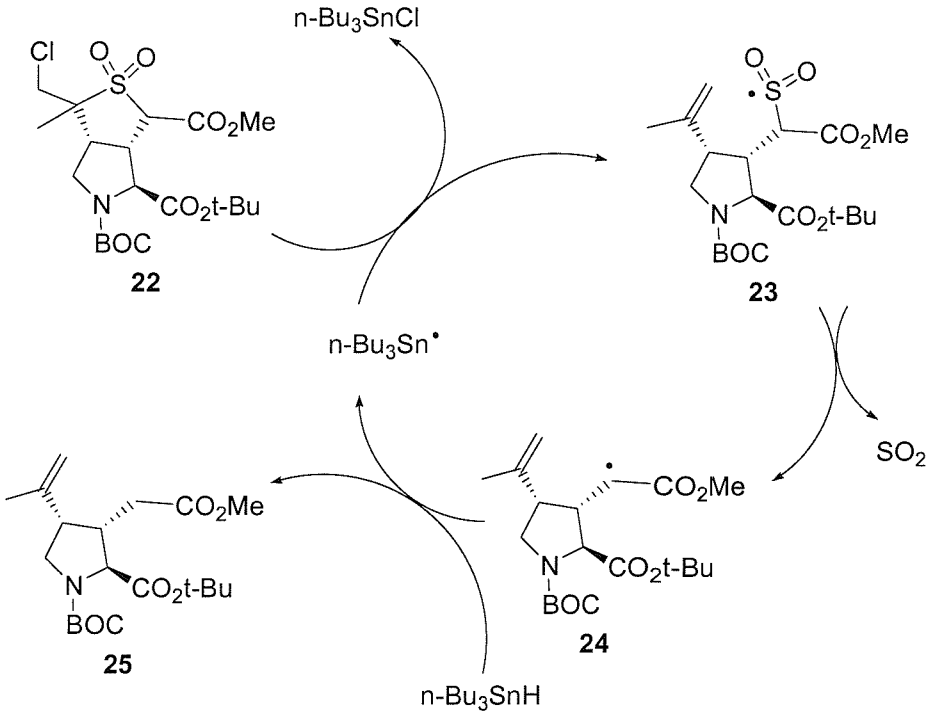
Cyclisation of the *syn*-isocyanide **13** with either ethanethiol or 2-mercaptoethanol proceeded in high yields and excellent stereocontrol, giving pyrroline **18** and pyroglutamate **19** as pure diastereoisomers. Lower diastereoselectivity was instead observed starting from the corresponding *anti*-isocyanide **13**.

This methodology was used by Bachi as the key cyclisation step in the enantio- and stereoselective synthesis of (-)- and (+/-)-α-Kainic acid (scheme 7), the prototype of a group of neuroexcitatory amino acids that are important substrates in pharmacological studies of the central nervous system.[24-27]



Scheme 7. The Bachi synthesis of Kainic acid.

One of the major obstacles in the synthesis of Kainic acid was the establishment of the 3,4-*cis* stereochemistry. This problem was overcome by using the pyrroline intermediate **20** and a novel method of temporary sulfur connection entailing linking of the CH_2CO_2Me moiety to the chiral *iso*-propenyl anchor (**21**), intramolecular connection to the pyrrolidine ring (**22**), and subsequent disconnection from the anchor by a sequential reductive double elimination (scheme 8).[26]

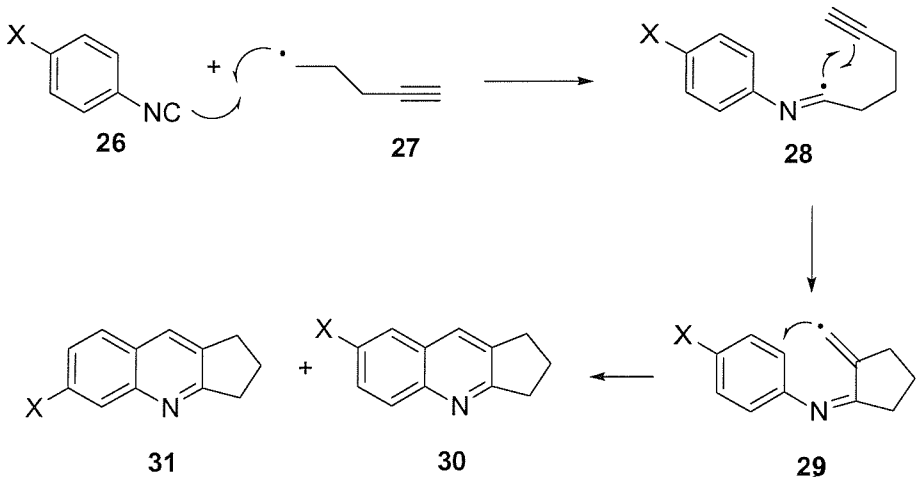


Scheme 8. Mechanism of the reductive double elimination employed by Bachi.

The disconnection of the acetic acid moiety from it's temporary anchor with regeneration of the isopropenyl double bond was achieved by treatment of bicyclic sulfone **22** with n-Bu_3SnH/AIBN (SmI_2 gave higher yield). First, extrusion of the chlorine atom with concomitant β-cleavage gives the sulfonyl radical **23**, which undergoes elimination of SO_2 to give a stabilized carbon centered radical **24** and finally, after hydrogen atom abstraction, the protected kainic acid **25**. Ester hydrolysis and Boc deprotection finally afforded Kainic acid.

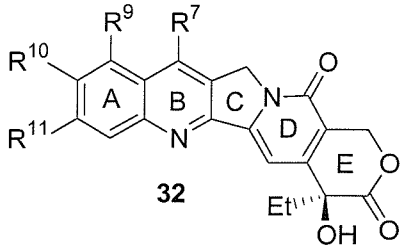
1.1.3 Isocyanides as radical traps: Addition to aromatic isocyanides.

Imidoyl radicals are in principle very attractive intermediates in the synthesis of *N*-heterocycles but only since 1990 has generation of radicals from isocyanides been successfully employed in the synthesis of heterocycles. In his pioneering work, Curran[28] carried out several [4+1] radical annulations using aryl isocyanides **26** and alkyn-5-yl radicals **27**, generated from the corresponding iodides. The reactions afforded cyclopenta-fused quinolines **30** and **31** (36-70% yield) through addition of radical **27** to the isocyanide, 5-*exo*-*dig*-cyclisation of the resulting imidoyl radical **28** onto the carbon-carbon triple bond, and final ring closure of vinyl radical **29** (scheme 9). The rearranged product **31** was explained in terms of competitive 6- and 5-membered ring closures of the vinyl radical, as previously suggested for similar annulations involving imidoyl radicals and alkynes.[29]



Scheme 9. Curran's synthesis of cyclopenta-fused quinolines.

The cyclopenta-fused quinolines moiety is one of the main structural features of the antitumor agents of the Camptothecin family (**32**, Fig. 1), a group of molecules that has recently moved to the forefront of research in the treatment of solid tumors by chemotherapy.



Camptothecin (**a**) R^7-R^{11}= H

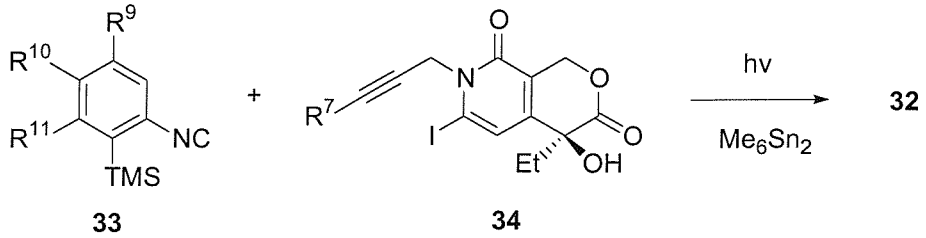
9-Aminocamptothecin (9-AC) (**b**) R^7, R^{10}, R^{11}= H; R^9= NH_2

Topotecan™ (TPT) (**c**) R^7, R^{11}= H; R^9= CH_2NMe_2; R^{10}= OH

Irinotecan™ (CPT-11) (**d**) R^9, R^{11}= H; R^7= Et; R^{10}= OCON

Figure 1. Camptothecin derivatives.

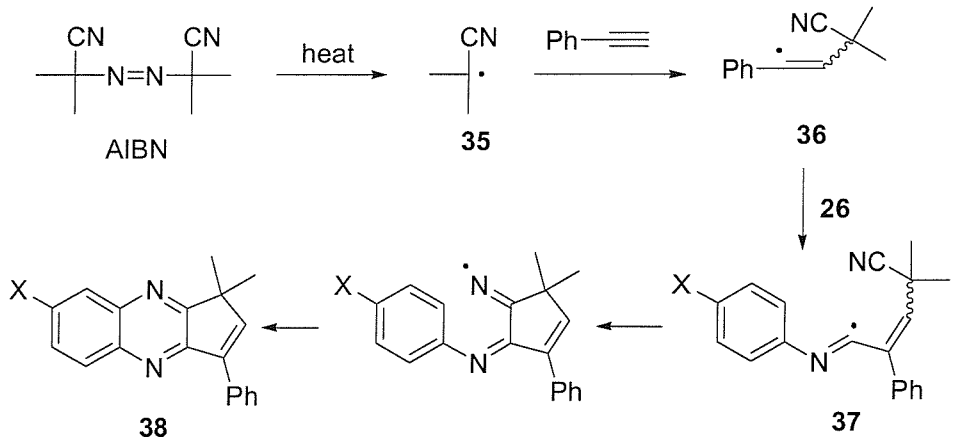
Starting from key intermediates containing the pyridone (D) and lactone (E) rings, the cascade radical reaction shown in scheme 10 represented an outstanding breakthrough for the synthesis of (20*S*)-Camptothecin (**32a**) and other drugs (topotecan and irinotecan).[30-37] The stereochemical requirements for the synthesis were fulfilled starting from enantiomerically pure alkynes **34**, whereas the regiocontrol was achieved, when necessary, using *ortho*-(trimethylsilyl)-substituted aryl isocyanides **33** (scheme 10).



Scheme 10. Synthesis of Camptothecin derivatives.

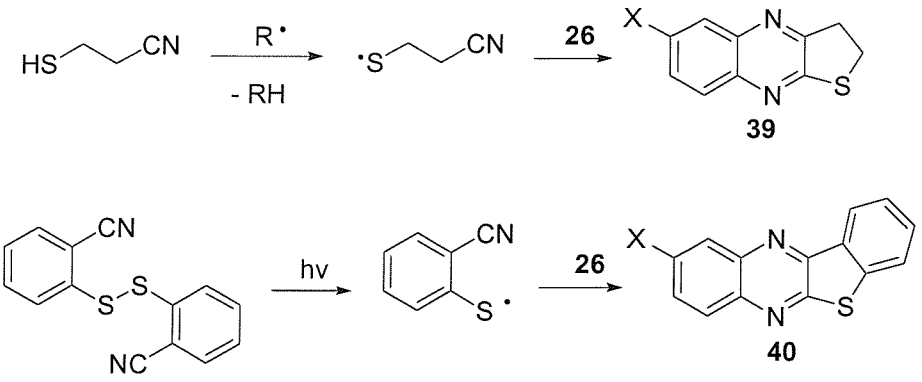
The authors set up an asymmetric, regioselective and widely applicable protocol for the synthesis of Camptothecin analogs, proving the broad scope and functional group tolerance of radical reactions.

In the same years Tundo and coworkers[38] performed similar reactions leading to heterocyclic compounds, employing aromatic isocyanides with alkyl and sulfanyl radicals bearing a cyano-substituted side chain (scheme 11).



Scheme 11. Tundo's three component annulation for cyclopenta-fused quinoxalines.

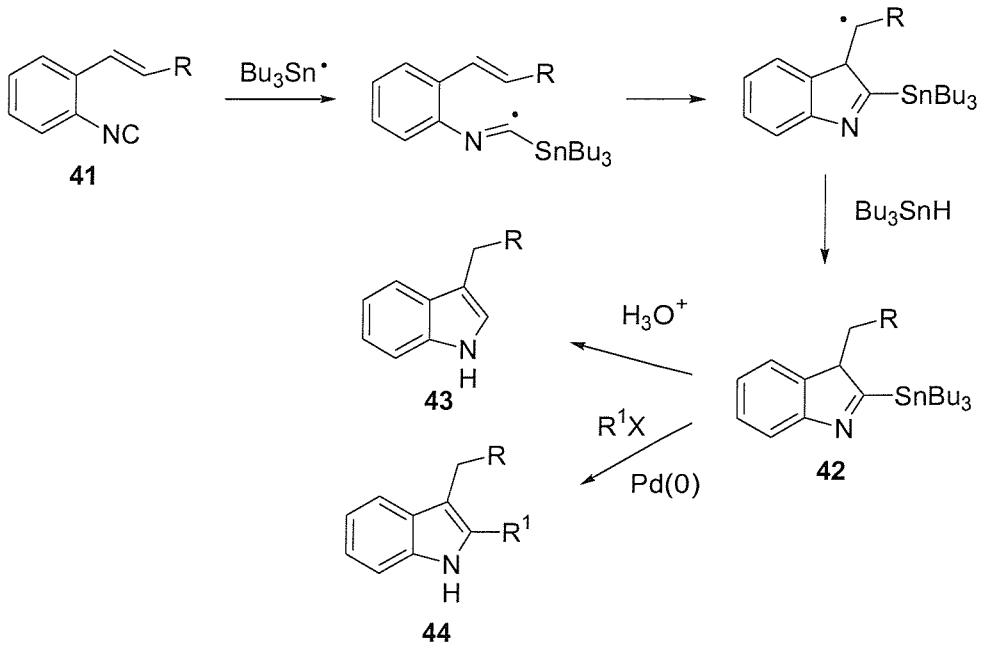
An alkyl radical was generated in a three component system comprising an isocyanide, AIBN and phenylacetylene. Decomposition of AIBN gives radical **35**, which adds to the terminal carbon of phenylacetylene to give vinyl radical **36**; addition of this radical to the aryl isocyanide **26** affords the imidoyl radical **37**, subsequent tandem cyclisation leads to the quinoxaline derivative **38**. Analogous [4+1] annulations were also performed starting from isocyanides and *β*-cyano-substituted sulfanyl radicals, generated either by hydrogen abstraction from aliphatic thiols or photolysis of aromatic disulfides.[39] These reactions afforded thieno- (**39**) and benzothienoquinoxalines (**40**) respectively (scheme 12).



Scheme 12. [4+1] annulations of isonitriles and β-cyano-substituted sulfanyl radicals.

It is interesting to note that in these annulations, involving the cyano group, a unique quinoxaline derivative was obtained, because the final iminyl radical cyclises onto the aromatic ring of the isocyanide in an exclusive 1,6 fashion.

Aromatic isocyanides were also successfully employed in the synthesis of indole derivatives by Fukuyama and coworkers (scheme 13).[40]

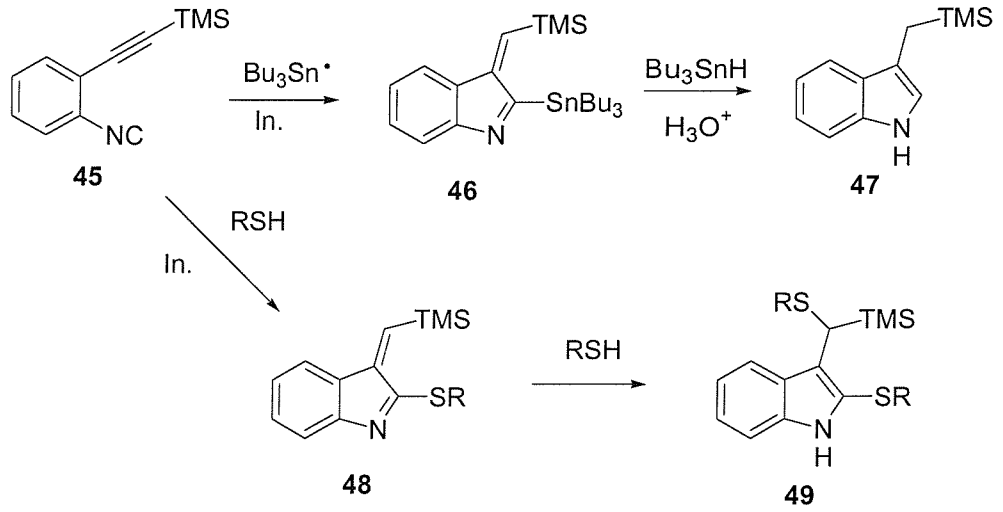


Scheme 13. Synthesis of indole derivatives by Fukuyama.

Cyclisation of compounds **41** was accomplished by the tributyltin hydride method, and six-membered ring closure did not significantly compete except in one case (R = *n*-Bu). This problem was alleviated by using the *Z*-alkene instead of the *E*-alkene. The reaction products are the 2-stannylindoles **42**,

which can be further transformed through the Stille palladium-mediated coupling with aromatic or unsaturated halides or triflates to **44** or protonated to **43**. This synthesis represented an interesting innovation for the construction of 3- or 2,3-substituted indoles. Recently, a variant of this methodology was developed by the same author through tin-mediated radical cyclisation of *ortho*-alkenyl-substituted thioanilides.[41]

Rainier[42] also demonstrated that indoles can be synthesised starting from *ortho*-alkynyl aryl isocyanides, provided that a TMS group is linked to the alkyne moiety (scheme 14).



Scheme 14. The Rainier synthesis of indoles.

With substrate **45**, the ring closure can be accomplished with either stannyl or sulfanyl radicals with no concomitant formation of the six-membered-cyclisation quinolines product, which is predominantly formed with groups other than TMS. Substituted indoles **47** and **49** were obtained with high efficiency.

All the above examples have proved that isocyanides, rather than being a mere curiosity in the field of organic chemistry, are exceptionally versatile intermediates for useful transformations. This was confirmed by the great deal of work on their use as radical traps that has flourished in recent years. Cyclisations, annulations and other cascade reactions have proven to be a

useful tool for the synthesis of heterocyclic compounds and other interesting derivatives. Furthermore, the geminal radical acceptor/radical donor properties of isocyanides, a feature shared with carbon monoxide, place them in a very distinct class of radicophiles, whose potential has not yet been fully exploited.

1.2 Solid phase synthesis.

In the early 1960s Merrifield[43] pioneered the concept of performing organic synthesis with a substrate immobilized on an insoluble matrix. Merrifield described the synthesis of a tetrapeptide on polymeric resins, an *N*-protected amino acid was attached to a chloromethylated copolymer of styrene and divinylbenzene through a benzyl ester linkage. The *N*-terminus of the bound amino acid was deprotected and coupled with another *N*-protected amino acid. The deprotection and amide coupling sequence was repeated. Cleavage of the benzyl ester linkage released the tetrapeptide from the solid support. In each step, the product bound to the polymer was purified by simple filtration to remove excess reagents and side products. Solid phase synthesis [44] (figure 2) begins with attachment of a substrate onto a polymeric solid support. The bound substrate can undergo several transformations and the final product can be detached from the solid support.

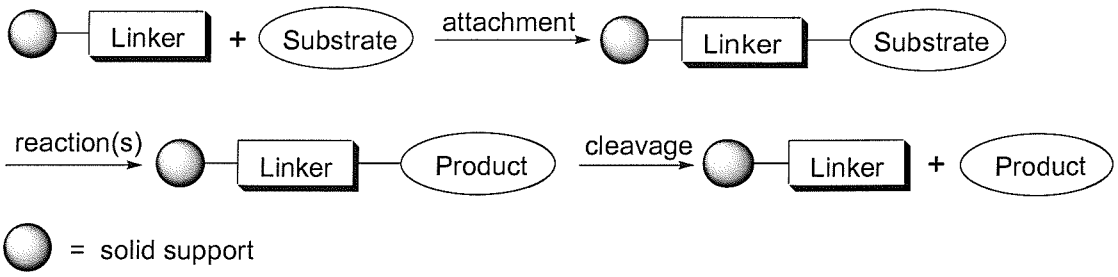


Figure 2. Solid phase synthesis.

Large excess of reagents and reactants are usually used to drive the reaction to completion. Purification of the solid support bound intermediates can be achieved by filtering off soluble reagents and reactants. Finally the product is cleaved from the solid support, and purification carried out in solution. The advantages of this technique are straightforward. The separation processes are quick and simple, and can also be automated, there is also a great time and labour advantage over the corresponding operations performed in solution, which often involve techniques of crystallisation, solvent extraction, filtration

and evaporation. These often lead to losses of material, so that solid phase synthesis could be much more effective in this sense also. The further advantage of the solid phase technique is that reactions can be driven to completion by a large excess of reagents, with a simple filtration work-up. Unfortunately there are some inbuilt disadvantages, such as the need for very high reaction efficiencies if purifiable products are to be reliably obtained. Although soluble reagents and by-products are easily filtered off, insoluble by-products, and those attached to the solid support, are retained throughout the synthesis and accumulate to contaminate the final product. Amongst these insoluble by-products will be products of incomplete reactions.

1.2.1 Solid phase reaction monitoring

Conventional analytical tools for following reactions in solution, like TLC, NMR or MS, unfortunately, are not yet generally applicable to resin bound compounds. As a consequence, in order to monitor the solid phase chemistry and characterise the reaction products, it is often necessary to cleave the bound compound from the solid support and then use standard techniques for analysis. This process is sometimes not very efficient and can give rise to artifacts during cleavage of reactive intermediates.

1.2.1.1 Combustion analysis

Combustion (elemental) analysis of polymeric supports has been used to determine the amounts of halogens, nitrogen or sulfur present in samples of cross linked polystyrene. The obtained information can be used to estimate the loading of a support, and to verify that displacement of a halide has proceeded to completion. In solid phase peptide synthesis nitrogen determination has been used to estimate the loading of the first amino acid.[45]

1.2.1.2 Colorimetric assays

One of the first assays used for monitoring solid phase synthesis of peptides was the ninhydrin test, in which ninhydrin reacts with free primary amines to yield a blue dye (Kaiser test).[46] This sensitive test enables the detection of

even small amounts of primary amines on solid support. Other reagents suitable for detecting amines include 2,4,6-trinitrobenzensulfonic acid and *p*-chloranil/RCOMe.[47, 48] The latter gives blue stained beads with secondary amines. It is also possible to use sensitive tests for the detection of alcohols,[49] useful to monitor the esterification of polymer supported alcohols. In this assay the alcohol is first converted into a tosylate which is then used to quaternise 4-(4-nitrobenzyl)-pyridine. Upon deprotonation, the pyridinium salt absorbs visible light, giving a deep blue or red colour. Other alkylating agents, such as support bound alkyl halides, Mannich bases or reactive epoxides can also give a positive result. Thiols can be detected by treatment with the symmetric disulfides of 4-mercaptonitrobenzene or 5-mercapto-2-nitrobenzoic acid.[50] These reagents are reduced by thiols to the corresponding thiophenolates, intensely coloured.

1.2.1.3 Infrared Spectroscopy

I.R. spectroscopy is a simple and fast method for qualitative detection of certain functional groups. Dried supports can be used directly to prepare KBr pellets for standard recording of I.R. spectra.[51-53] Recent IR-based techniques, which require smaller amounts of resin than the KBr method, include single-bead FT-IR spectroscopy,[54-57] single-bead Raman spectroscopy,[58] near-IR-multispectral imaging,[59] and the simultaneous analysis of several different beads by FT-IR microscopy.[60] Unfortunately I.R. spectroscopy is not a very sensitive analytical technique and is, therefore, not well suited for detection of small amounts of material. If, however, intermediates have intense and well resolved I.R. absorptions it can be very useful.

1.2.1.4 Mass Spectrometry

Mass spectrometry has recently emerged as a useful tool in solid phase reaction monitoring. The use of photosensitive linkers enables the direct analysis of support-bound intermediates by MALDI-TOF MS.[61,62] Alternatively, compounds linked to insoluble supports by non-photolable

linkers can be analysed directly with TOF-SIMS.[63] In both MALDI-TOF MS and ion-spray MS, molecules must be positively charged to be detected. To facilitate detection of all type of immobilised substrates, linkers incorporating a charged spacer (e.g. quaternary ammonium salts), which is also released during MALDI analysis, have proven very useful.[61, 64]

1.2.1.5 Nuclear Magnetic Resonance Spectroscopy

NMR spectroscopy is undoubtedly the most utilised method of compound characterization in solution phase chemistry, therefore intense research has been directed towards adapting this technique to identify reaction products covalently attached to resins. Standard (gel-phase) NMR spectra of polymers usually show significant line broadening, because of chemical-shift anisotropy and dipolar coupling.[65] Only nuclei with strong chemical shift dispersion (^{13}C, ^{15}N, ^{19}F and ^{31}P)[66-71] give sufficiently resolved spectra. The resolution can be improved when the mobility of polymer supported molecules increases, as a consequence PEG-polystyrene supports normally give better spectra. Gel-phase ^{1}H NMR spectra are too poorly resolved to be used for the characterization of polymer-supported intermediates. Recently, it has been shown that the resolution of ^{1}H NMR spectra of organic molecules covalently attached to resins (3 to 5 mg of resin suspended in deuterated solvents) is significantly improved by the magic angle spinning NMR technique.[65] This technique requires a special accessory, which keeps a sample of swollen support spinning at 1-2 KHz at the "magic angle" relative to the magnetic field. M.A.S. NMR enables the recording of much better resolved spectra than gel-phase NMR, and ^{1}H NMR spectra of high quality can be obtained.[51, 72-75] C,H-Correlated and other two-dimensional spectra can also be obtained.[76]

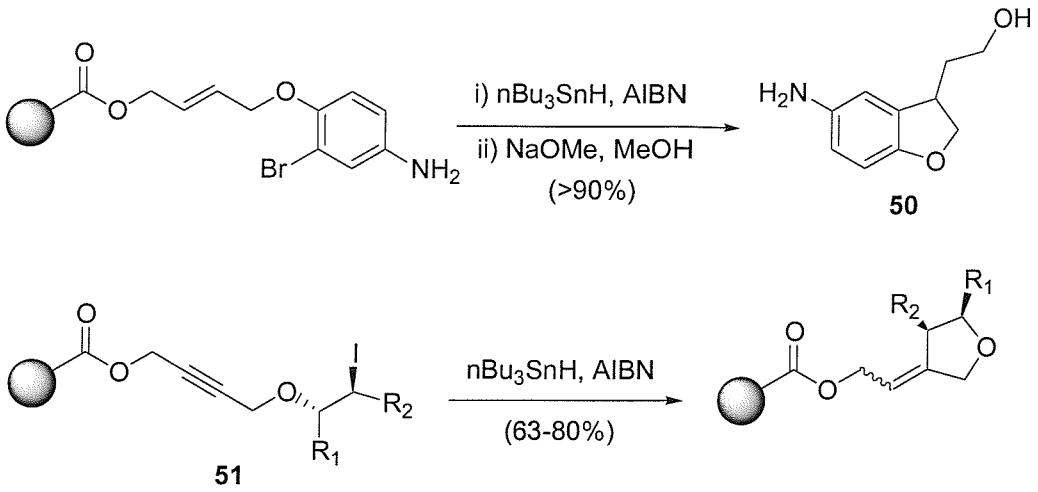
1.2.2 Radical reactions on solid support.

The application of solid phase synthesis was initially restricted to the synthesis of oligomers such as peptides, oligonucleotides and oligosaccharides, because these syntheses rely on repetitive and reliable reaction sequences.[77, 78] To expand the applications of solid phase synthesis to non-oligomer synthesis, Leznoff synthesised hormones through solid support monoprotection of symmetrical bifunctional compounds such as diols, dialdehydes and dicarboxylic acids.[79] In 1992, Bunin and Ellmann[80] prepared a library of drug-like molecules (1,4-benzodiazepins) on solid support. This triggered the development of solid phase synthesis in the last decade, stimulating intensive efforts in the application of reactions, broadly used in solution, to the solid phase synthesis. While a number of reaction conditions have been widely applied to the solid support, examples of radical reactions are still limited.

Radical reactions on solid phase are carried out in similar fashion to the solution phase reactions, but the solvent choice is crucial, in order to swell the solid support (usually 1% or 2% cross-linked polystyrene) and enable free diffusion of reagents. In the swollen phase the kinetics of these reactions are often slower than their solution phase counterparts, and there are also differences in rate between one type of resin and another. Due to the complex series of elementary steps often involved in radical reactions, there may be contexts where this rate deceleration is advantageous. Compared to solution-phase reactions, larger amounts of radical initiator are typically employed, but the slower kinetics appear tolerant of relatively high concentrations of initiator (for example tin hydride).

1.2.2.1 Intramolecular radical reactions.

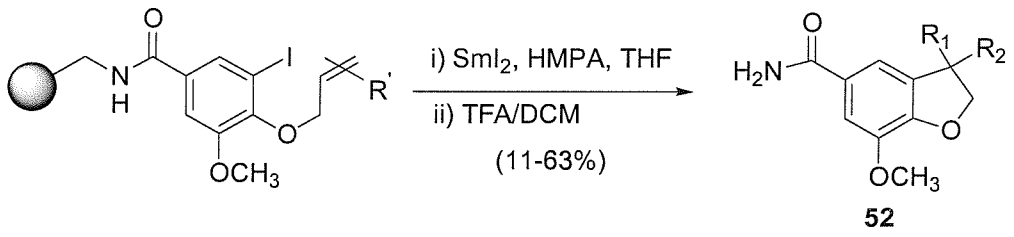
Intramolecular carbon-carbon bond forming radical reactions on solid support were first reported by Routledge *et al*[81] in 1997. Routledge investigated aryl radical 5-*exo* cyclisations, synthesis of dihydrobenzofuran **50** was achieved in high yield (scheme 15).



Scheme 15. Routledge's synthesis of furan rings.

The authors used two different solid supports, carboxylated polystyrene and TentaGel resin (which has a polyethylene spacer between the polystyrene and the site of compound attachment). With polystyrene more than 1 equivalent of AIBN and excess n-Bu_3SnH were used to drive the reaction to completion, while the reaction was complete in 20 hours using 6 mol% of AIBN on TentaGel. The authors also investigated the cyclisation of iodides **51** (scheme 15), and good results were also obtained. A direct comparison of the same reaction in solution was attempted but yields could not be determined due to contamination of the cyclised product by tin residues. This illustrated one advantage of performing tin mediated radical reactions on solid support.

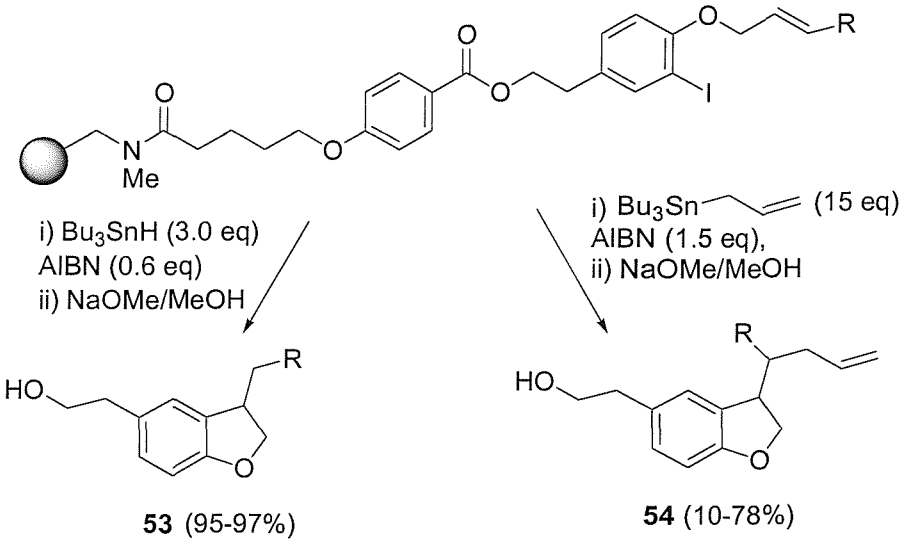
Similar cyclisations were reported by Du and Armstrong,[82] who used samarium diiodide for radical generation from aryl iodides immobilized on polystyrene-Rink resin (scheme 16).



Scheme 16. Du and Armstrong synthesis of benzofurans.

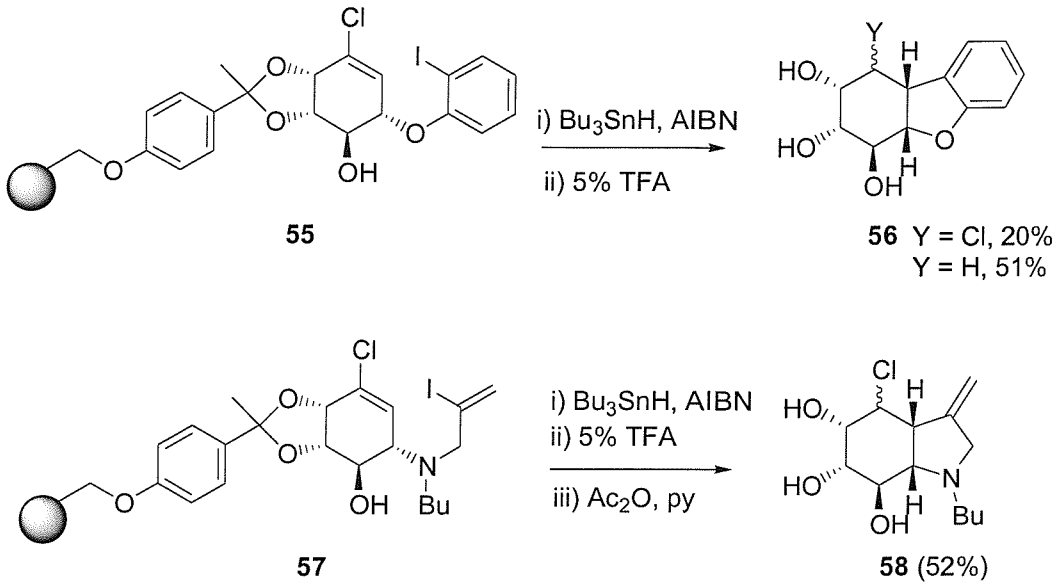
Benzofuran derivatives **52** were obtained in good overall yields, using mild conditions. The reactions were conducted at room temperature using an excess of SmI_2 (10 eq), without any precautions, such as degassing, although HMPA (40 eq) was found necessary for the reaction. Use of a TentaGel-type resin allowed polymer swelling in aqueous solvents, so that samarium impurities in the beads could be removed by saturated $NaHCO_3$, prior to cleavage.

Dihydrobenzofurans **53** (scheme 17), were synthesised by the tributyl-tin hydride mediated radical cyclisation of iodo alkynes, immobilised on polystyrene through a linker, by De Mesmaeker.[83-86] It was also possible to perform a tandem cyclisation using allyltributyltin to give the allylated product **54**, but the yields were not as good as for **53**.



Scheme 17. Aryl iodide cyclisations by De Mesmaeker.

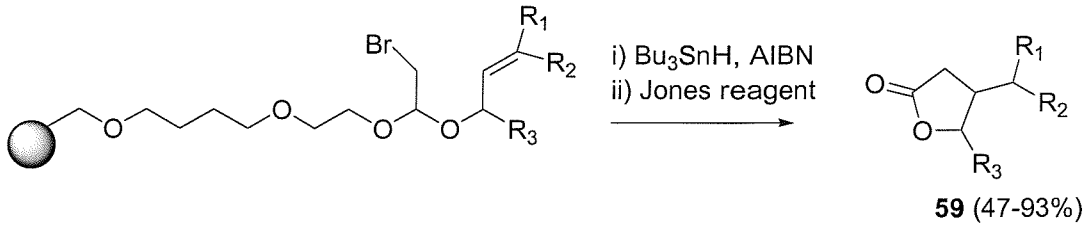
The same authors also successfully demonstrated the radical cyclisation onto enol ethers, also studying radical cyclisation of cyclohenendiols, immobilized by a ketal linkage on polystyrene (scheme 18).



Scheme 18. Aryl and vinyl iodide cyclisations by Berteina.

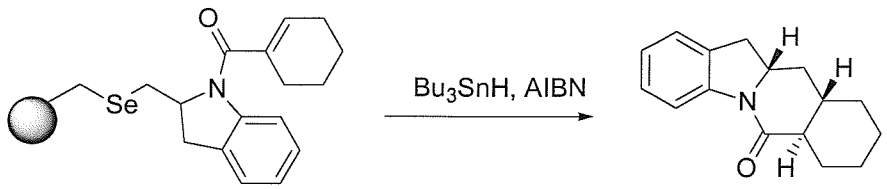
Cyclisation of immobilized aryl iodide **55** afforded the desired dihydrobenzofuran **56** in good yield (also the direct reduction product was obtained), allyl amine **57** afforded similar results. A similar cyclisation, but on Wang resin, was also reported by Jia *et al.*[87]

Watanabe *et al*[88] reported the synthesis of γ-butyrolactones **59**, by radical cyclisation of bromoacetals (scheme 19).



Scheme 19. Synthesis of γ-butyrolactones by Watanabe.

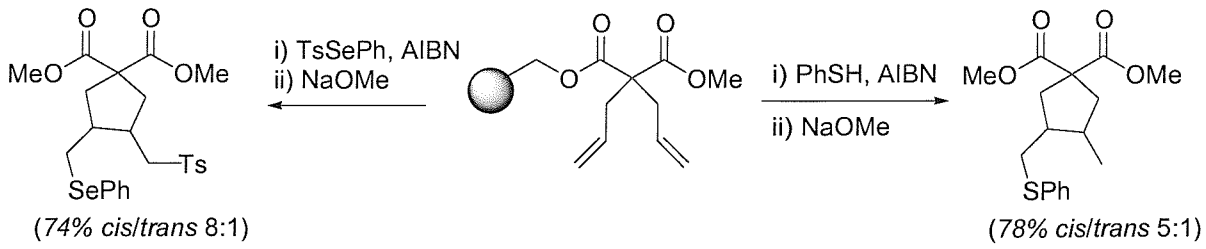
Another interesting example of intramolecular cyclisation, reported by Nicolau *et al*,[89] features the generation of the radical from a selenide rather than an halide (scheme 20).



Scheme 20. Radical cyclisation of a polymer bound selenide.

In this example the tributyltin hydride mediated reaction of polymer bound selenide **60** gives indoline **61**, in good yield, in a 6-*endo* fashion. The radical reaction itself results in a cyclisative-cleavage from the resin.

Recently Harrowen *et al*[90] reported the radical addition of thiyl or tosyl radicals to 1,6-dienes (scheme 21), good yields and diastereoselectivity were obtained.

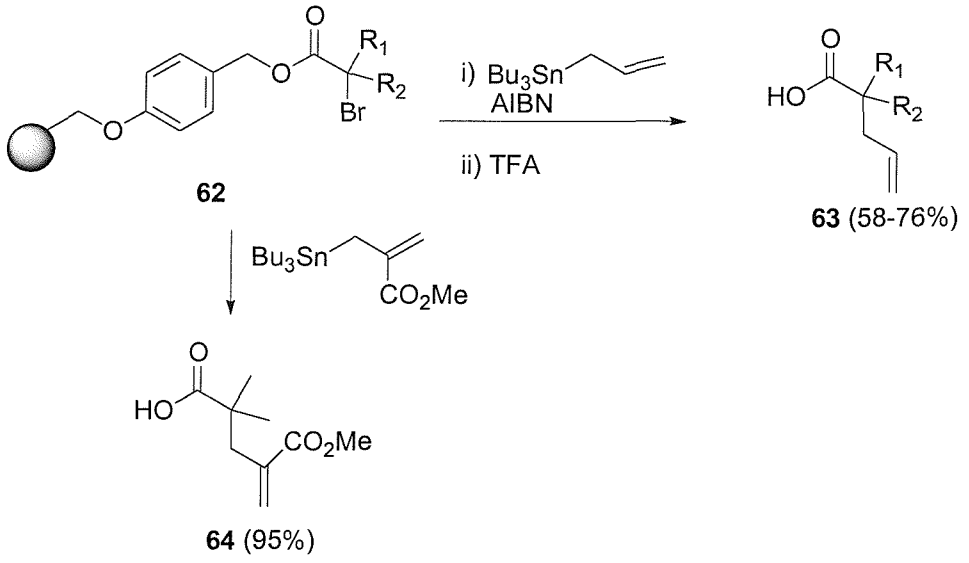


Scheme 21. Radical addition of thiyl and tosyl radicals to 1,6-dienes.

1.2.2.2 Intermolecular radical reactions.

The first example of intermolecular radical reactions on a solid support, reported by Sibi and Chandramouli,[91] featured the allylation of polymer bound alkyl radicals, generated from α-bromo esters **62** to give unsaturated acids **63** (scheme 22). Large excess of reagents had to be used to obtain good yields, the use of Et_3B/O_2 to initiate the radical reaction (room temperature)

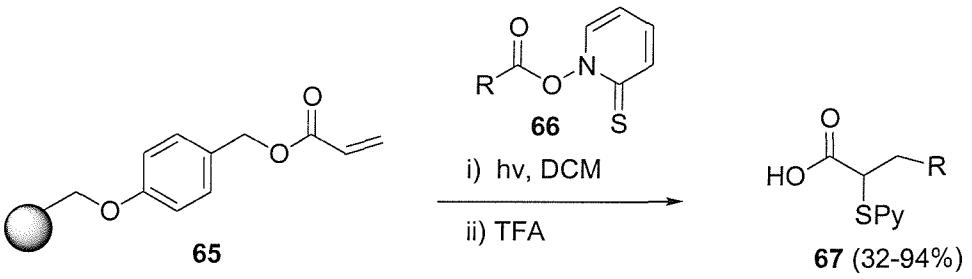
was less successful. The yields obtained were comparable with the solution phase reactions.



Scheme 22. Intermolecular allylations.

Electron withdrawing groups at the 2-position of the allylstannane were also found to improve the reaction yield (scheme 22).

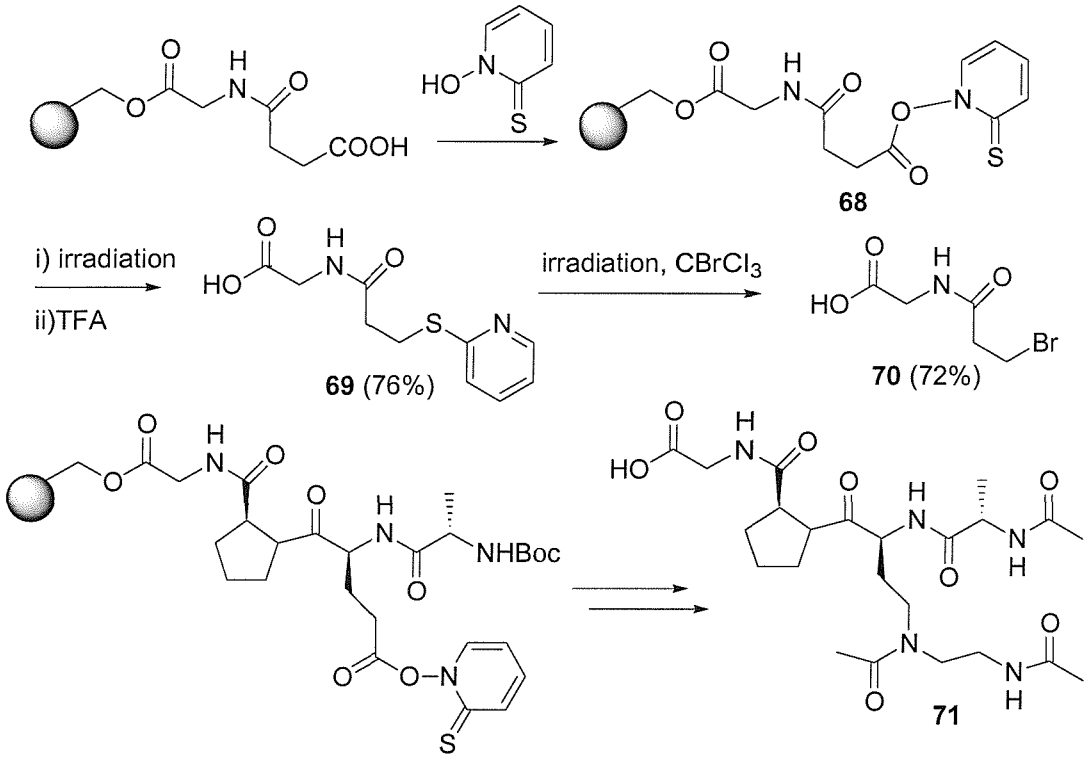
Conjugate additions of radicals photochemically generated from Barton esters were reported by Zhu.[92] Acrylic acid was immobilized as the ester **65** (scheme 23), using the Wang linker, on both polystyrene and TentaGel resins, and reacted with Barton esters **66** to give the conjugate addition products **67** in good to excellent yields.



Scheme 23. Use of Barton esters in conjugate additions by Zhu.

Noteworthy was the ability to use large excess of reagents (as in tin-mediated reactions) without final product isolation problems. Barton esters have also

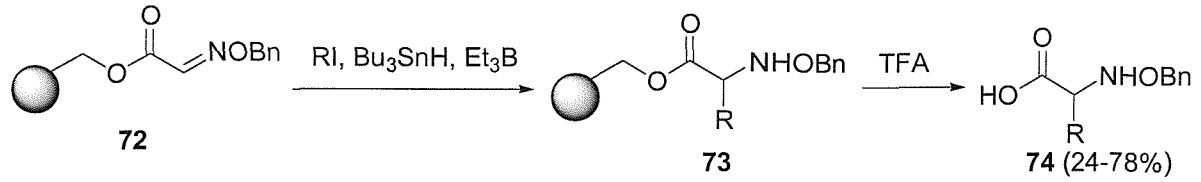
been immobilized on solid support by Taddei and coworkers,[93] the Barton radical decarboxylation was then used as a synthetic tool for the synthesis of modified peptides (scheme 24).



Scheme 24. The Barton radical decarboxylation on solid support.

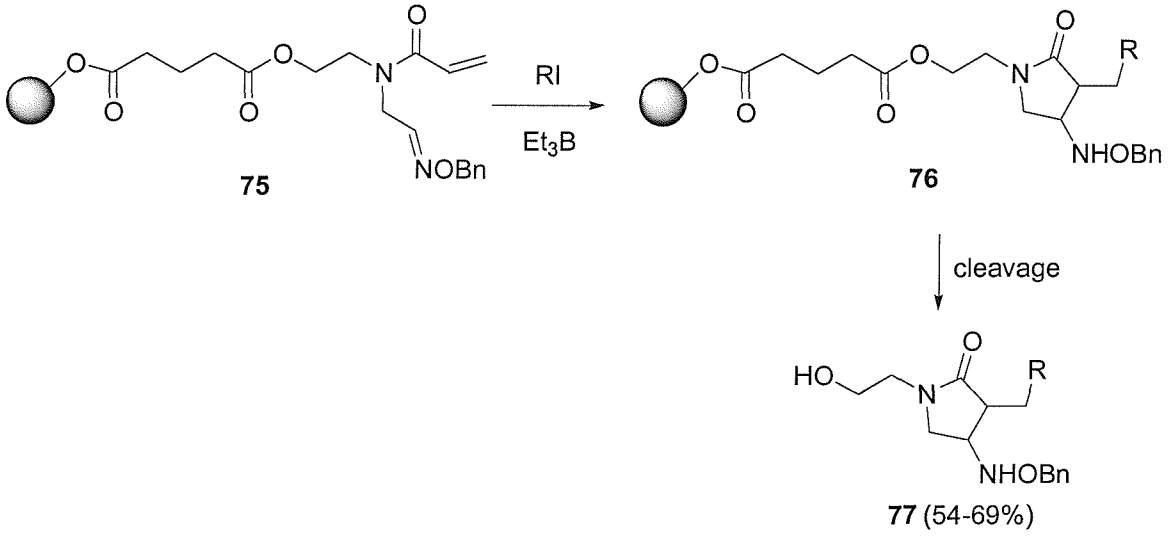
The polymer supported Barton ester **68** was synthesised in a few simple steps from Wang resin and FmocGlyOH, irradiation afforded the decarboxylation product **69**, after TFA cleavage, which was then further manipulated to obtain bromo-derivative **70**. This strategy allowed the authors to synthesise interesting unnatural peptides of type **71**.

Intermolecular additions to oxime ethers have been published by Naito's group.[94-97] Alkyl radicals generated by the tributyltin/triethyl borane method were reacted with immobilised glyoxylic oxime ether **72** (scheme 25), to give amino acid derivatives **74**.



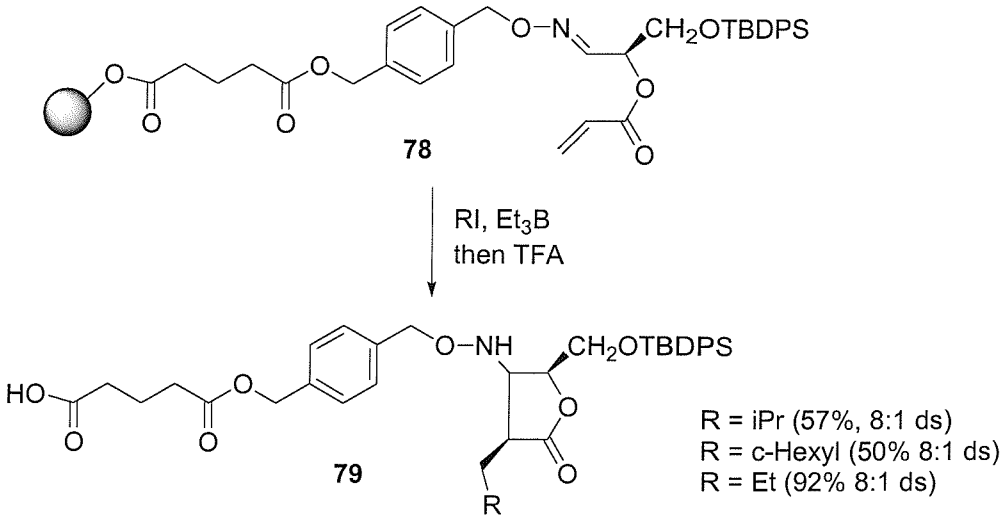
Scheme 25. Intermolecular oxime ether additions by the Naito group.

The same group also prepared pyrrolidines **77** by a novel tandem radical addition-cyclisation reaction of oxime ethers (**75**) immobilised on Wang resin (scheme 26).[98]



Scheme 26. Tandem radical addition-cyclisation of polymer supported oxime ethers.

The authors also examined the control of stereochemistry in the above reaction, substrate **78** (scheme 27) was synthesised and then subjected to the addition-cyclisation reaction.



Scheme 27. Stereocontrol in the solid phase tandem radical addition-cyclisation of oxime ethers.

The obtained results proved to be extremely interesting, because products **79** were obtained in good yields and diastereoselectivity. Similar radical additions to a phenylsulfonyl oxime ether were also reported by Jeon *et al.*[99]

In conclusion, inter- and intramolecular carbon-carbon bond forming radical reactions on solid support were uncharted territory until a few years ago, but several examples have appeared in the literature, showing the feasibility of radical chemistry on solid phase. Early concerns about benzylic hydrogen abstraction from the polystyrene matrix has proven unfounded, to the point that the Wang linker (which contains benzylic protons) is the most widely used. Compared to solution phase reactions, larger amounts of radical initiator and propagator are employed, but this proved not to be a problem in terms of product purification. The slower kinetics of solid phase reactions also appears tolerant of high concentrations of tin hydride without premature substrate reduction.

1.3 Program of work

The main objective of this project was the synthesis and radical cyclisations of alkenyl and alkynyl isocyanides with thiols, both in solution and on solid support. The extension of isocyanide radical chemistry to solid phase could allow further progress in combinatorial organic synthesis and could also have the great advantage of easy reaction workup and product purification.
Functionalised pyrrolines and pyroglutamates could be accessed and then used as building blocks for the synthesis of polycyclic *N*-heterocycles (e.g. indolizidines).

Chapter 2

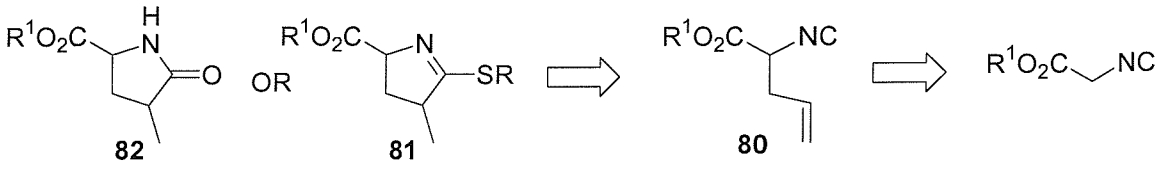
THIOL MEDIATED RADICAL CYCLISATIONS OF ISOCYANIDES ON SOLID PHASE

2.1 Introduction

Thiol mediated radical cyclisations of isocyanides have been successfully investigated by Bachi,[18, 22-27] but, in order to apply it to solid phase synthesis, it was first necessary to perform model studies in solution, by synthesising substrates that could mimic a polymer supported isocyanide (for example alkenyl isocyanides with a benzyl or *p*-methoxybenzyl ester group).

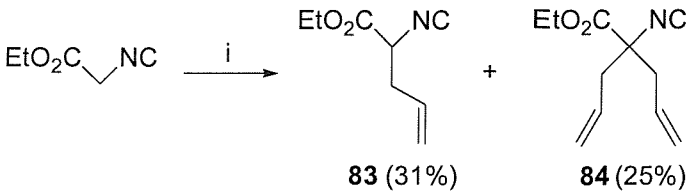
2.2 Solution phase model studies

The synthetic plan (scheme 28) entailed the synthesis of simple alkenyl isocyanides (**80**), and then to perform radical cyclisations with thiols to obtain pyroglutamates **82** or pyrrolines **81**.



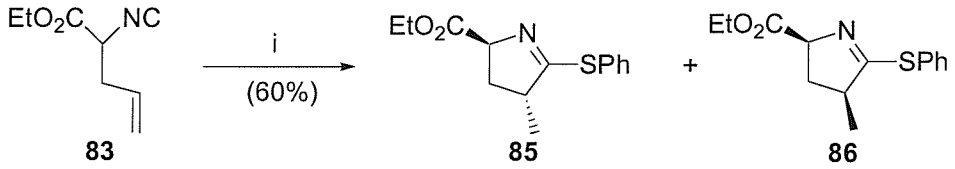
Scheme 28. Synthetic plan.

As shown in scheme 29, ethyl-2-isocyanopent-4-enoate (**83**) and ethyl-2-allyl-2-isocyanopent-4-enoate (**84**) were synthesised starting from ethylisocyanoacetate, commercially available, in one step.[100, 101]



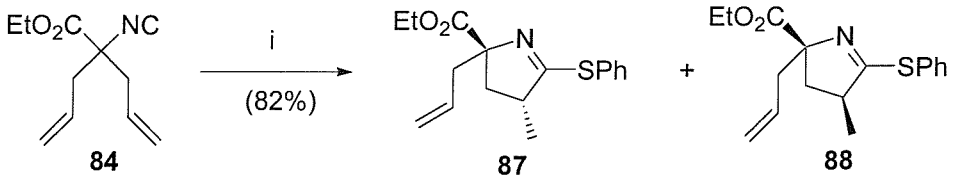
Scheme 29. Synthesis of mono- and di-allylated ethylisocyanoacetate. Reagents and conditions: i) allyl bromide (1.0 eq), TBAB (0.1 eq), K_2CO_3 (3.0 eq.), MeCN, 20-22 hr at reflux.

The best conditions for this reaction used TBAB/K_2CO_3. The products **83** and **84** were obtained in satisfactory yields. Isocyanide **83** was then cyclised using thiophenol and AIBN as radical initiator (scheme 30).[22]



Scheme 30. Reagents and conditions: i) PhSH (1.1 eq), AIBN (0.2 eq), toluene, 1 hr at 110 °C.

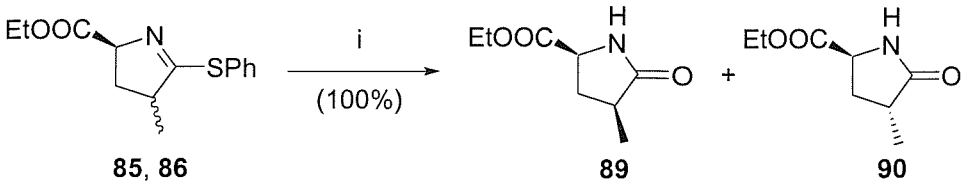
The cyclised products **85** and **86** were obtained in 60% yield (for the reaction mechanism see scheme 5, **1.1.2**), and as a mixture of *cis* and *trans* isomers (1: 1 ratio by NMR). Cyclisation using isocyanide **84** as substrate (scheme 31), under the same conditions but 3.5 hr reaction time, gave **87** and **88** in 82% yield as a 1:1 diastereomeric mixture (by NMR). It was not possible to separate the *cis* from the *trans* isomer.



Scheme 31. Reagents and conditions: i) PhSH (1.1 eq), AIBN (0.2 eq), toluene, 110 °C, 3.5 hr.

These preliminary results showed that thiophenol efficiently reacts, under radical conditions, with alkenyl isocyanides to give the corresponding pyrrolines, although with poor diastereoselectivity. To test the stability of the

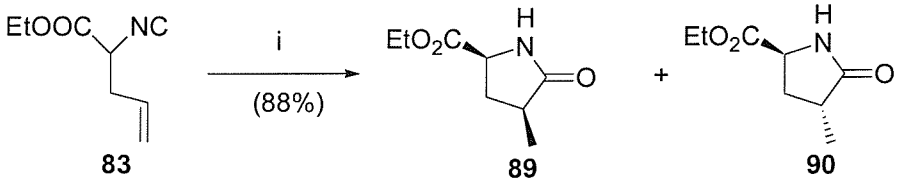
obtained pyrrolines to acidic conditions (typically employed to cleave final products from Wang resin, the most widely used solid support for organic synthesis) a 1:1 mixture of **85** and **86** was stirred with trifluoroacetic acid (scheme 32).



85, 86 **89** **90**

Scheme 32. Reagents and conditions: i) TFA 95% in CH_2Cl_2, 5.5 hr at rt.

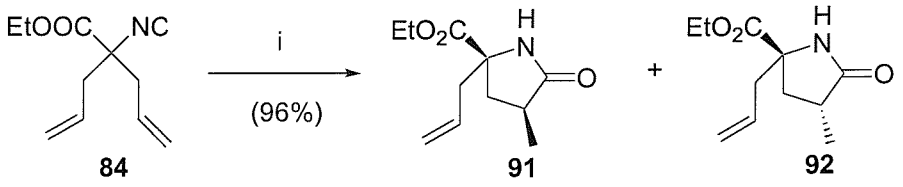
Quantitative conversion to the hydrolysed products **89** and **90**, was obtained. These pyroglutamates were also directly synthesised by using 2-mercaptoethanol, known to react under radical conditions with **83** (scheme 33).[18, 22]



83 **89** **90**

Scheme 33. Reagents and conditions: i) $HO(CH_2)_2SH$ (1.1 eq), AIBN (0.2 eq), toluene, 40 °C, 1.5 h.

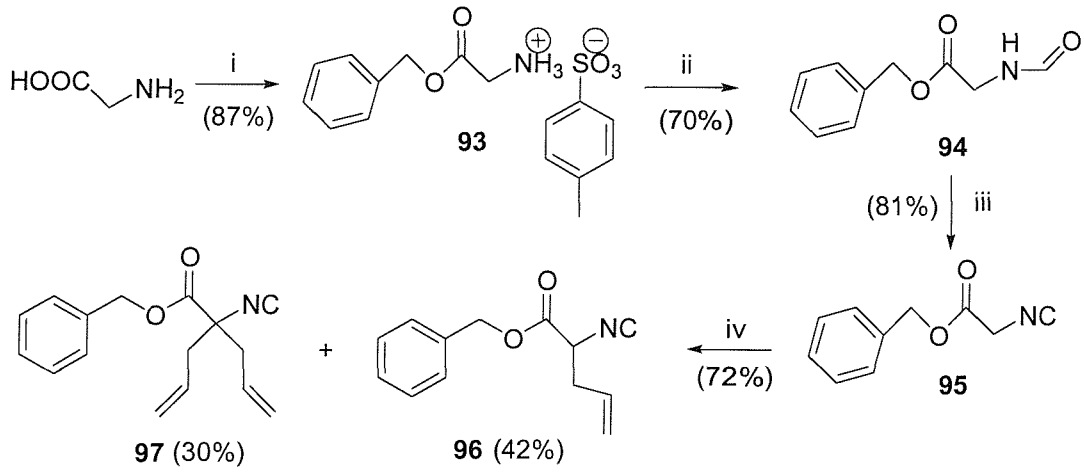
The two cyclised products, **89** and **90**, were obtained as 1:1 *cis/trans* mixture in good yield (88%). The mechanism of this reaction is not completely clear but Bachi[18] proposed the mechanism shown in scheme 5 (**1.1.2**). The same mediated cyclisation with 2-mercaptoethanol, using isocyanide **84** as substrate, was also attempted (scheme 34).



84 **91** **92**

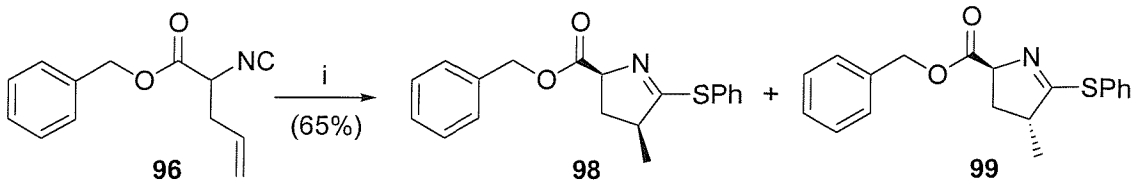
Scheme 34. Reagents and conditions: i) $HO(CH_2)_2SH$ (2.2 eq), AIBN (0.2 eq), toluene, 40 °C 7 hr.

The reaction was accomplished successfully, the two isomers **91** and **92** were obtained in 96% yield, as a 1:1 mixture of diastereoisomers. The only difference with similar reactions, previously carried, was the longer reaction time (7 hr) and the use of 2.2 equivalents of thiol. Encouraged by these results it was decided to synthesise a substrate that could resemble a polystyrene resin, normally used in solid phase chemistry. It was identified in the benzyl-2-isocyanopent-4-enoate (**96**), which was synthesised according to scheme 35.



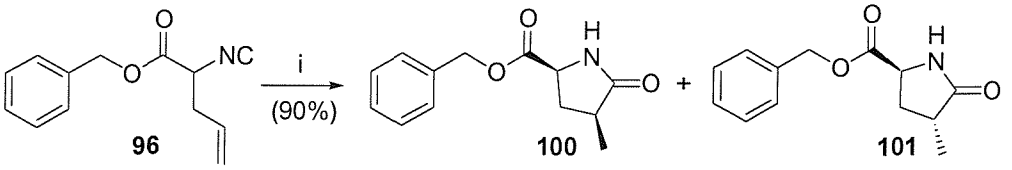
Scheme 35. Reagents and conditions: i) p-toluensulfonic acid, $PhCH_2OH$, toluene, reflux 3 hr; ii) a)Et_3N, b) HCOOH, Ac_2O; iii) $POCl_3$ (1.1 eq), Et_3N (3.5 eq) in dry CH_2Cl_2, 1 hr at 0 °C; iv) TBAB (0.1 eq), allyl bromide (1.0 eq), K_2CO_3 (3.0 eq) in MeCN, 20 hr, reflux.

Glycine benzyl ester, as its *p*-toluensulfonate salt (**93**),[102] was obtained in good yield (87%). **93** was then formylated by using formic acid and acetic anhydride [103,104] which gave **94** in 70% yield. The next step was to dehydrate formylamino-acetic acid benzyl ester (**94**) to the corresponding benzyl isocyanoacetate **95**. Reaction with phosphoryl chloride in presence of an excess of triethylamine[22] gave the desired isocyanide in 81% yield. Finally **95** was alkylated, with allyl bromide under phase transfer conditions (K_2CO_3/TBAB). Both the mono and dialkylated products **96** (42%) and **97** (30%) were obtained. Isocyanide **96** was then used as substrate for the thiol mediated cyclisation, using thiophenol and AIBN as radical initiator (scheme 36).



Scheme 36. Reagents and conditions: i) PhSH (1.1 eq), AIBN (0.2 eq), toluene 110 °C, 4 hr.

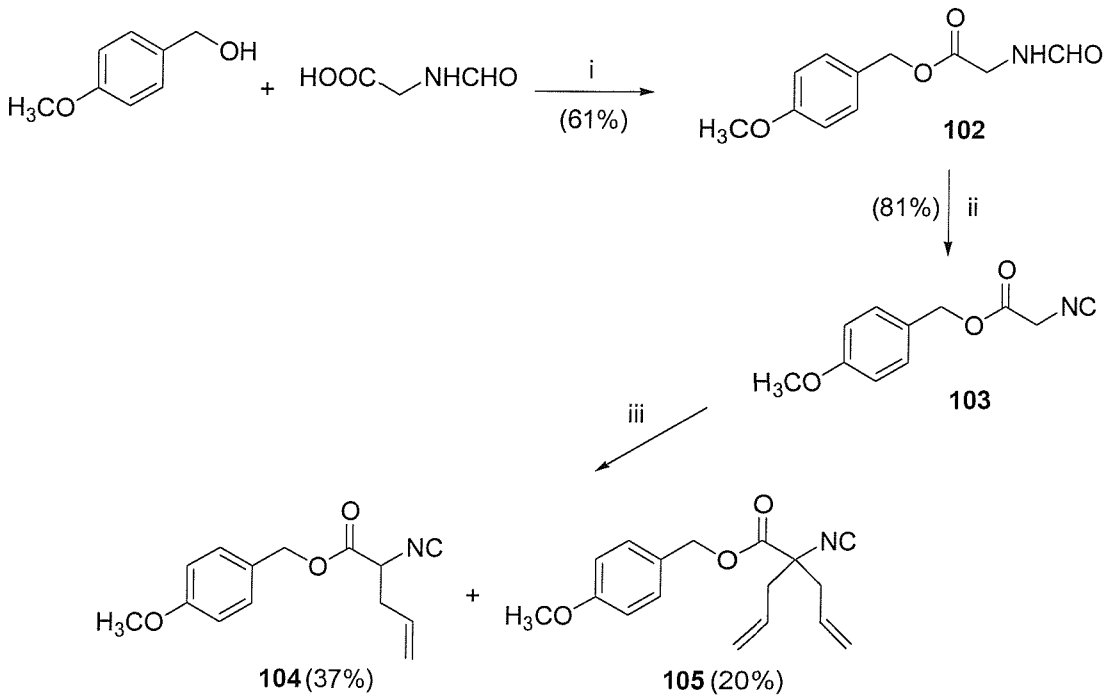
The *cis* and *trans* pyrrolines **98** and **99** were obtained as a 1:1 mixture (by NMR), with a 65% yield. 2-Mercaptoethanol mediated radical cyclisation of **96** gave also good results (scheme 37).



Scheme 37. Reagents and conditions: i) 2-mercaptoethanol (2.2 eq), AIBN (0.2 eq), toluene, 40 °C, 5.5 hr.

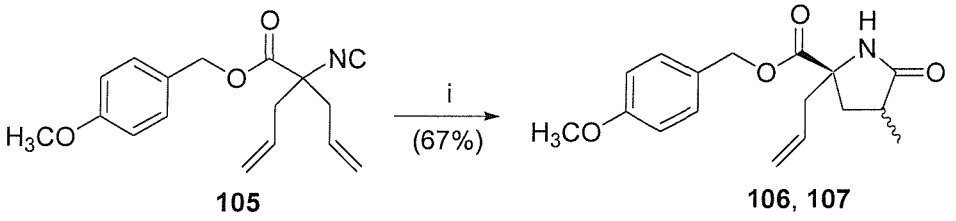
The two desired products, **100** and **101**, were obtained in ~1:1 ratio, with an excellent 90% yield and they could be separated by chromatography.

In order to complete the solution phase model alkenyl isocyanides bearing a *p*-methoxybenzyl ester group were also synthesised (scheme 38). *p*-Methoxybenzyl-formyl-glycinate **102** was synthesised from formylglycine and *p*-methoxybenzyl alcohol in good 61% yield, subsequent dehydration with $POCl_3/Et_3N$ gave the corresponding isocyanide **103** (81%). The next step was alkylation of **103** (K_2CO_3/TBAB), to give the desired compounds **104** (37%) and the dialkylated **105** (20%), in reasonable yields.



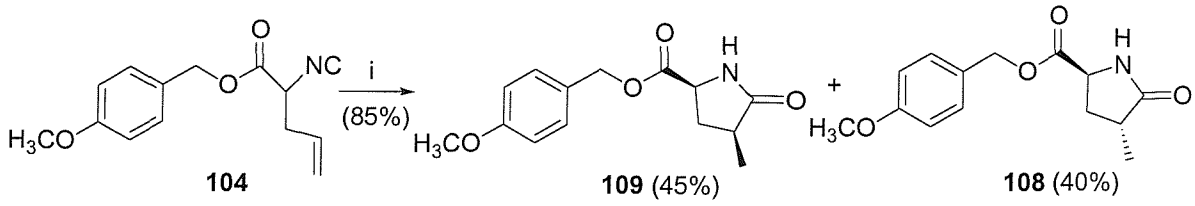
Scheme 38. Reagents and conditions: i) DCC, DMAP, CH_2Cl_2, 12hr at rt; ii) $POCl_3$ (1.1 eq), Et_3N (3.5 eq) in dry CH_2Cl_2, 1 hr at 0 °C; iii) TBAB (0.1 eq), allyl bromide (0.9 eq), K_2CO_3 (3.0 eq) in MeCN, 20 hr, reflux.

Isocyanide **105** was then reacted with 2-mercaptoethanol and AIBN (scheme 39).



Scheme 39. Reagents and conditions: i) 2-mercaptoethanol (2.2 eq), AIBN (0.2 eq), toluene 40 °C, 12 hr.

The *cis* and *trans* *p*-methoxybenzyl-2-allyl-4-methyl-5-oxopyrrolidine-2-carboxylate (**106** and **107**) were obtained as an inseparable mixture (2:1 by NMR), with a 67% yield. The radical cyclisation of **104** gave better results (scheme 40).

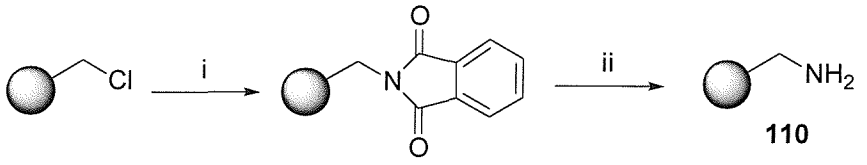


Scheme 40. Reagents and conditions: i) 2-mercaptoethanol (2.2 eq), AIBN (0.2 eq), toluene 40 °C, 24 hr.

The expected products **108** (40%) and **109** (45%) were obtained in excellent yield and they could be separated by column chromatography.

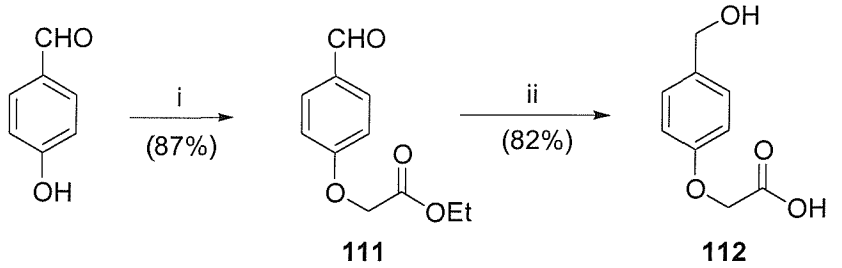
2.3 Solid Phase Synthesis: Choice of the solid support.

A range of polystyrene resins can be purchased incorporating various linkers.[47] Among these the Wang resin is one of the most commonly employed, due to its versatility, however more homogeneous materials can be prepared directly starting from Merrifield resin: a chloromethylated polystyrene resin. It was initially decided to use commercially available Wang resin and to prepare a Wang-type resin, through the amino methyl resin.[105, 106] The latter was synthesised from Merrifield resin which was first converted to amino methyl resin (**110**) by heating in a solution of potassium phthalimide followed by hydrazinolysis under reflux in ethanol (Scheme 41).[107]



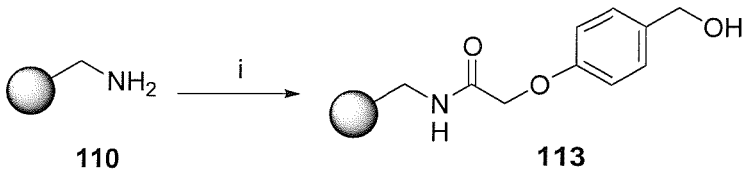
Scheme 41. Synthesis of amino methyl resin. Reagents and conditions: i) potassium phthalimide, DMF, 120°C overnight; ii) EtOH, $N_2H_4.H_2O$, reflux, overnight.

The substitution of resin **110** was calculated by indirect Fmoc test, after coupling the resin with Fmoc-Gly-OH and gave a value of 0.88 mmol/g. To complete the synthesis of the Wang-type resin it was necessary to synthesise the Wang linker (**112**). It was readily prepared in two steps starting from 4-hydroxybenzaldehyde (Scheme 42).[108]



Scheme 42. Reagents and conditions: i) ethyl-bromoacetate, KO^{t}Bu, DMF, 12 hr at 110°C; ii) NaOH/EtOH (pH 11), $NaBH_4$, 12 hr at rt.

The Wang linker (**112**) was obtained in 82% yield. It was then coupled to the amino methyl resin (**110**) to obtain the Wang-type resin **113** (scheme 43).

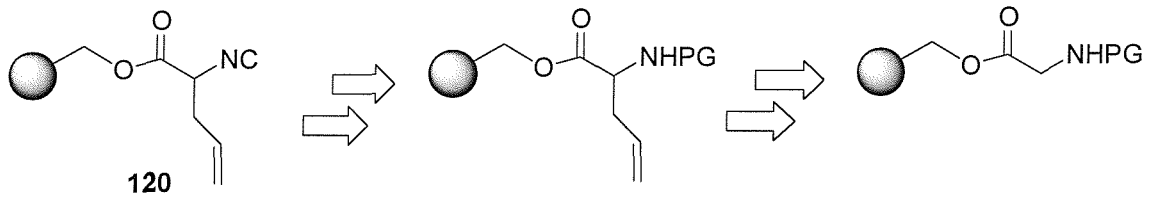


110 **113**

Scheme 43. Reagents and conditions: i) **112**, HOBt, DIC, in CH_2Cl_2, 2hr at RT.

2.4 Synthesis of polymer supported isocyanides

The next step in the synthetic plan was to prepare a resin bound alkenyl isocyanide (scheme 44).

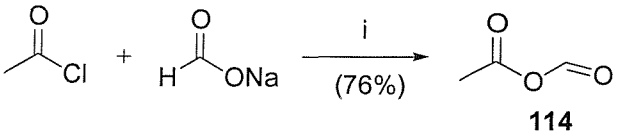


120

Scheme 44. Synthetic route to polymer supported isocyanide.

It was envisaged that it could be prepared from resin bound amino acids by alkylation, using the O'Donnell "Solid Phase UPS" methodology,[109-112] prior to isocyanide formation.

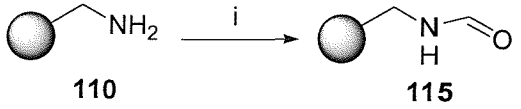
The synthesis of isocyanides is usually performed in solution phase chemistry by formylation of a primary amine and subsequent dehydration. The formylating agent employed is acetic-formic anhydride that was synthesized following the procedure described by Krimen (Scheme 45).[113]



114

Scheme 45. Synthesis of Acetic Formic Anhydride. i) Et_2O, 5.5 hr at rt.

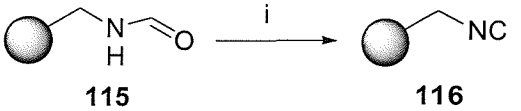
Thus formylation of resin **110** was simply accomplished by reaction of the resin with freshly prepared **114** (Scheme 46).



110 **115**

Scheme 46. Reagents and conditions: i) **114** in NMP, 3hr at rt.

The formylamino methyl resin obtained showed an intense I.R. absorption at 1675 cm^{-1}. Qualitative ninhydrin test was negative, also indicating completion of the reaction. Resin **115** was then dehydrated using triphenylphosphine, carbon tetrachloride and triethylamine (Scheme 47).[114]

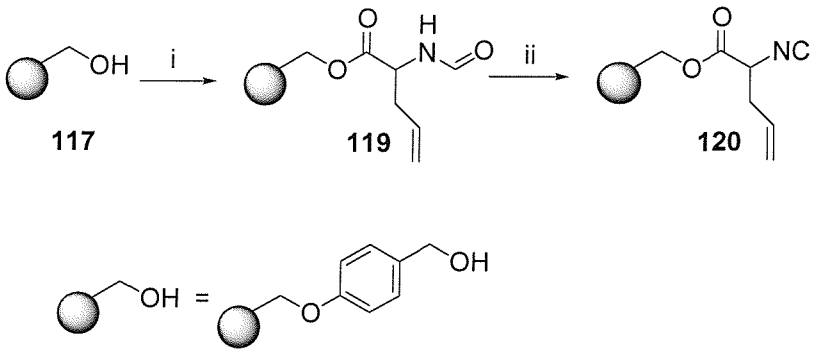


115 **116**

Scheme 47. Reagents and conditions: i) Ph_3P, CCl_4, Et_3N, in CH_2Cl_2, 2.5hr at 45°C.

Resin **116** showed an I.R. absorption at 2146 cm^{-1}, typical of isocyanides, no absorption was observed at 1675 cm^{-1} indicating complete conversion to the isocyanide group.

The next objective was to find a simple route to the alkenyl resin bound isocyanide **120**, to be used as substrate in thiol mediated free radical cyclisations. It was synthesised, according to scheme 48, in two steps.

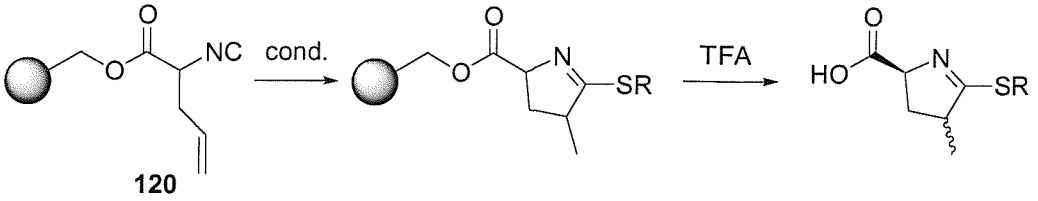


Scheme 48. Reagents and conditions: i) 2-Formylamino-pent-4-enoic acid (**118**), DIC/DMAP in DCM:DMF (9:1), 6 hr at rt; ii) $POCl_3/Et_3N$ in DCM, 3 hr at 0 °C.

Formylamino resin (**119**) was synthesised from commercially available Wang resin (**117**) and 2-formylaminopent-4-enoic acid (**118**), obtained from 2-aminopent-4-enoic acid by formylation, using DIC/DMAP.[44] The reaction was checked by IR, which showed the appearance of the expected carbonyl signal, and by MAS ^{1}H NMR. The next step was the dehydration of **119** to give the corresponding isocyanide **120**, using triphenylphosphine, carbon tetrachloride and triethylamine.[114-117] Although this methodology had been used to synthesise **116**, it did not prove to be successful here. The same transformation was also attempted using different conditions (e.g. amount of reagents, temperature and reaction times), but only in few cases a weak signal at 2146 cm^{-1} was observed. Use of carbon tetrabromide, instead of CCl_4, did not give any result. Other dehydrating agents were then used.[118-120] Phosphorus pentoxide also proved to be inefficient. Finally, by using phosphoryl chloride in combination with triethylamine, it was possible to obtain the desired isonitrile resin **120** (scheme 48). IR showed the expected isocyanide absorption and MAS ^{1}H NMR showed the disappearance of the formyl proton, indicating completion of the reaction. The same synthetic strategy was used with Wang-type resin **113**, but the obtained results were unsatisfactory, due to poor conversion to the isocyanide, so commercial Wang resin was the polymer support of choice.

2.5 Thiol mediated free radical cyclisations of alkenyl isocyanide 120.

The polymer supported isocyanide **120** was then reacted with ethanethiol or thiophenol and AIBN, under various radical conditions (scheme 49 and table 1), toluene was the solvent.



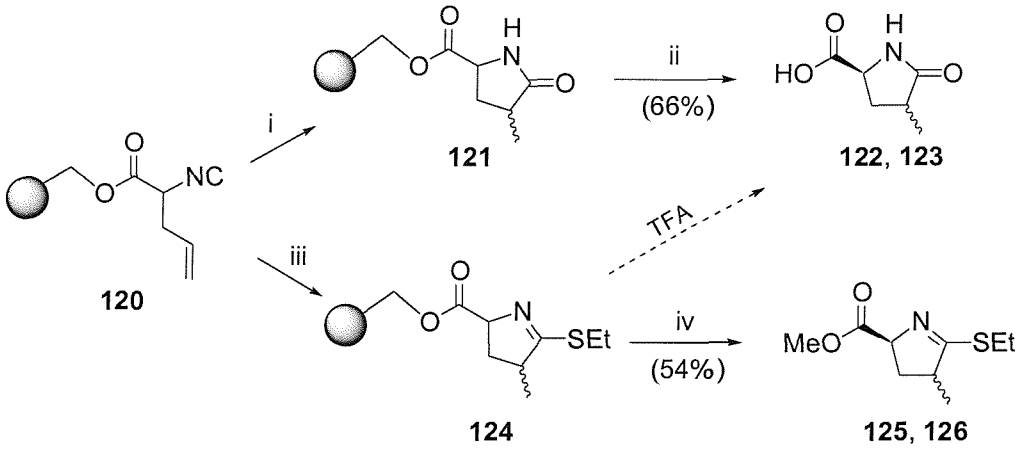
Scheme 49. Radical cyclisation of isocyanide bound resin with PhSH and EtSH. Reagents and reaction conditions are shown in Table 1.

Table 1. Radical cyclisation reagents and conditions.

PhSH (eq)	AIBN (eq)	T (°C)	React. Time (h)
1.0	0.2	reflux	1.5
1.1	1.1	reflux	1.5
2.2	2.2	reflux	1.5
25	10	80-90	1.5
25	10	100	10
25	5	reflux	48
EtSH (eq)	AIBN (eq)	T (°C)	React. Time (h)
25	10	reflux	48
25	10	reflux	48

Each pyrroline resin was then treated with trifluoroacetic acid (95% in dichloromethane) and the crude cleaved product analysed by NMR. The results showed that no cyclised product was obtained. The reasons of the failure of this reactions were later found to be in the solvent choice, toluene, which did not swell the resin very well, so it was decided to use DMF instead. Also AIBN addition, done in one pot, was thought to be a problem so that

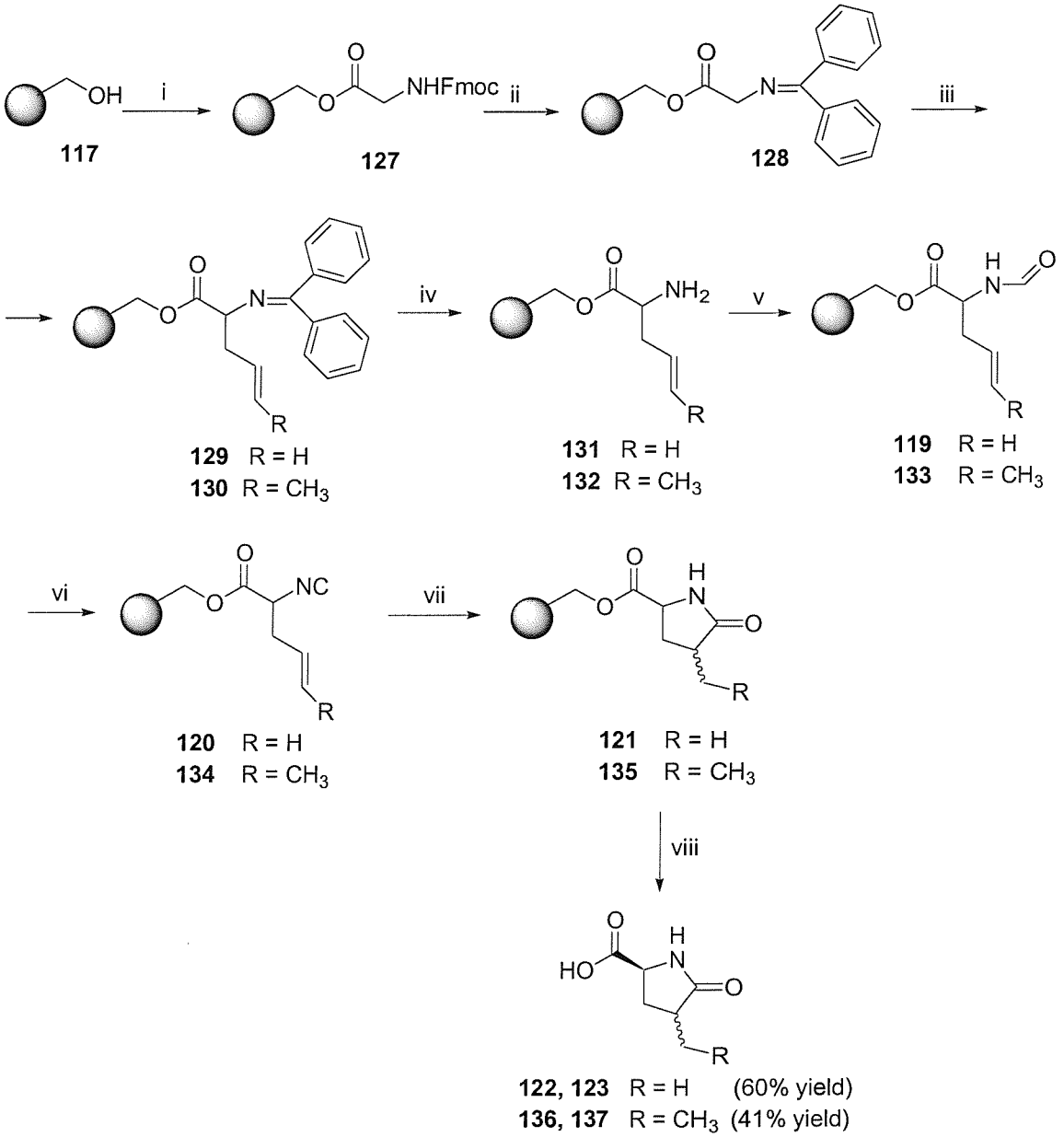
portion wise addition (over a few hours) could have been more effective. These conditions were used for the next radical cyclisations. Resin **120** was then reacted with 2-mercaptoethanol in DMF, using AIBN as radical initiator, to give the corresponding cyclised product **121** (scheme 50). The reaction was monitored by IR, which showed the complete disappearance of the isocyanide absorption and the appearance of a carbonyl signal. MAS ^{1}H NMR gave a more accurate picture and showed almost complete reaction (>98%). The cyclised product was then cleaved from the solid support with TFA, and purified by column chromatography to give **122** and **123**, as a 1:1 diastereomeric mixture, in good 66% isolated yield. The supported isocyanide **120** was also reacted with ethanethiol and AIBN to give pyrroline **124**, and the product was cleaved under nucleophilic conditions[47] to give pyrrolines **125** and **126**, as an inseparable mixture (1:1) of diastereoisomers, in good 54% yield (scheme 50). TFA cleavage conditions could not be used in the latter case due to hydrolysis of the product to the corresponding pyroglutamate.



Scheme 50. Reagents and Conditions: i) 2-mercaptoethanol (35eq), AIBN (15eq), DMF, 48 hr at 45 °C; ii) 95% TFA in H_2O, 5.5 hr; iii) Ethanethiol (35 eq), AIBN (15 eq), DMF, 48 hr at 80 °C; iv) MeOH/Et_3N/KCN, 24 hr at reflux.

The solvent choice and the slow addition of the radical initiator over a few hours proved to be crucial for the success of the radical cyclisations.

With optimized conditions for the isocyanide synthesis and the radical cyclisation, the possibility of introducing different alkenes in α to the isocyano group was investigated, using the O'Donnell "UPS" procedure (scheme 51).[109]



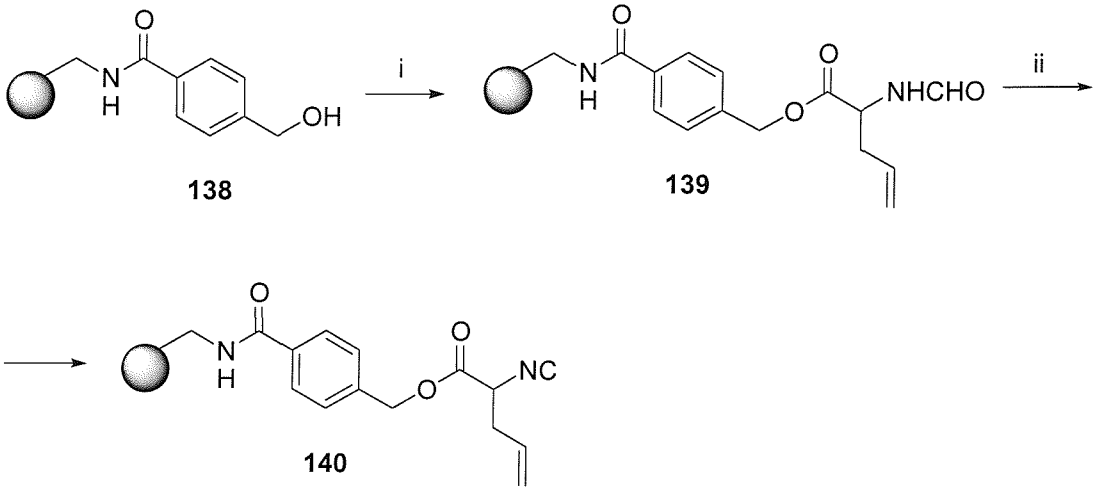
Scheme 51. Solid phase synthesis of pyroglutamates. Reagents and conditions: i) Fmoc-GlyOH, DIC/DMAP, DCM, 3h rt; ii) a) 20% Piperidine in DMF, b) Ph_2C=NH, AcOH, NMP, 12h at rt; iii) R-X, BEMP, NMP, 12h at rt; iv) $NH_2OH.HCl$ 1N; v) $(CH_3CO)OCHO$, NMP, 3h at rt; vi) $POCl_3$, Et_3N in CH_2Cl_2, 3h at 0 ^oC; vii) 2-mercaptoethanol, AIBN, DMF, 48h at at 50 ^oC; viii) 50% TFA in CH_2Cl_2.

The Fmoc-Glycine bound resin **127** was prepared by coupling the protected amino acid to commercial Wang resin **117**, by standard coupling conditions.[44, 121] The reaction was repeated twice to ensure completion. The Fmoc protecting group was then removed with piperidine (20% solution in DMF), and the free amino group was reacted with benzophenone imine to activate the resin bound glycine for the next alkylation step. Simultaneous deprotonation and alkylation of the benzophenone imine resin **128** with allyl bromide and crotyl bromide was accomplished using the organic-soluble, neutral, strong iminophosphorane "Schweisinger base", BEMP.[122] The imine residue of the alkylated resins **129** and **130** was then hydrolysed, neutralized to afford the free amino group, and finally formylated, with acetic formic anhydride, to obtain the desired formyl amino resins **119** and **133**. All the reactions were monitored by I.R., ^{1}H MAS NMR and colorimetric tests where possible. Small amounts of the obtained resins were then treated with trifluoroacetic acid (95%) to cleave the product from the solid support. The expected alkenyl formylamino acids were obtained in excellent crude yields and good purity (>90%). Subsequent dehydration afforded the desired polymer supported isocyanides **120** and **134**. The isocyanides were then cyclised, with 2-mercaptoethanol, to give resins **121** and **135** and the obtained products cleaved off the solid support with TFA. After purification, the expected compounds **122**, **123**, **136** and **137** were obtained in good 60% and 41% isolated yields respectively, as mixtures of *cis/trans* diastereoisomers (1:1 by NMR).

The results obtained proved the efficiency of the strategy and its potential for library synthesis. However, when the introduction of other alkenes was attempted (cinnamyl, propargyl and trimethylsilylpropyne), incomplete alkylation and poor conversion to isocyanides led to complex mixtures, after cleavage, so this route was abandoned.

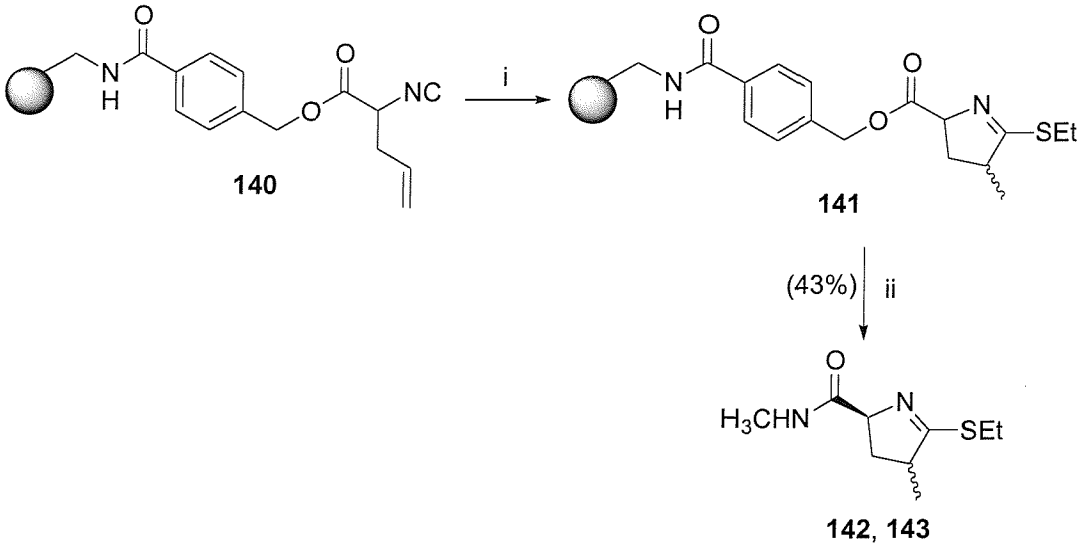
2.6 Thiol mediated radical cyclisations of an alkenyl isocyanide immobilized on HMBA-AM resin.

In order to extend the established methodology further, an alkenyl isocyanide was also synthesised on a different solid support, HMBA-AM resin.[44, 47] This resin can be easily cleaved under nucleophilic conditions (primary or secondary amines) giving access to amide derivatives. The polymer supported alkenyl isocyanide **140**, was synthesised in two steps (scheme 52). Formylamino resin **139** was obtained from commercially available HMBA-AM resin (**138**) and 2-formylaminopent-4-enoic acid (**118**), using DIC/DMAP, subsequent dehydration afforded isocyanide **140**.



Scheme 52. Reagents and conditions: i) 2-Formylaminopent-4-enoic acid (**118**), DIC/DMAP in DCM:DMF (9:1), 6 hr at rt; ii) $POCl_3/Et_3N$ in DCM, 3 hr at 0 °C.

Cyclisation of **140** with ethanethiol, under standard conditions, afforded the corresponding pyrroline resin **141**. Cleavage with methylamine afforded **142** and **143** in good 43% overall yield, as a mixture of diastereoisomers (scheme 53).



Scheme 53. Reagents and conditions: i) ethanethiol, AIBN, DMF, 48h at 80 ^{O}C; ii) $MeNH_2$ in THF, 2h at RT.

Unfortunately, also in this case, attempts to synthesise a library of pyrrolines, using the chemistry previously employed for Wang resin failed, due to poor conversion of the polymer supported formamides to the isocyanides.

2.7 Conclusions.

Thiol mediated free radical cyclisations of alkenyl isocyanides, synthesised in a few steps from simple starting materials, were first investigated in solution with good results. The chemistry was then studied on the solid phase. Polymer supported alkenyl isocyanides were synthesised, both on Wang and HMBA-AM resins, and reacted with thiols to give pyrrolines and pyroglutamates in good yields. Unfortunately this methodology could not be applied to library synthesis.

Chapter 3

MICROWAVE ASSISTED FREE RADICAL CYCLISATIONS OF ISOCYANIDES WITH THIOLS

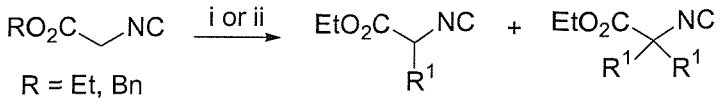
3.1 Introduction

The rapidly growing field of combinatorial chemistry has precipitated the development of new technologies aimed at improving the efficiency of performing chemical reactions. The microwave "flash heating" technique provides such a method. Its efficiency in dramatically accelerating reaction rates has recently been proven in several different fields of organic chemistry,[123, 124] but only a few examples of radical reactions have been reported.[125, 126] It was envisaged that this technique could be used to give rapid access to functionalised pyroglutamates and pyrrolines, by thiol mediated radical cyclisations of alkenyl and alkynyl isocyanides.

3.2 Synthesis of Alkenyl and Alkynyl Isocyanides

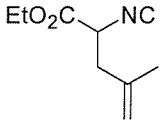
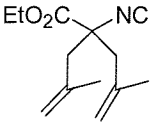
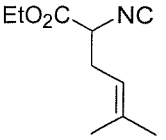
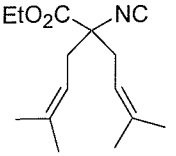
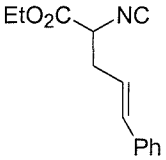
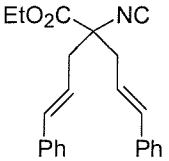
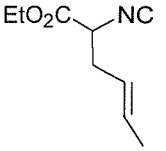
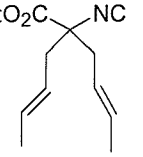
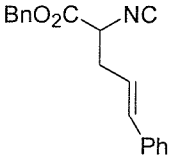
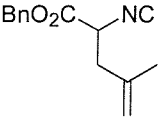
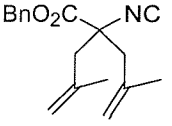
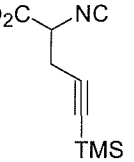
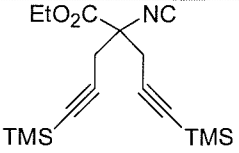
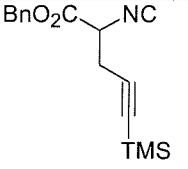
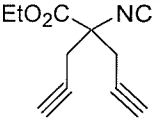
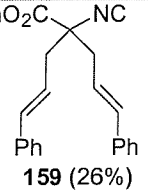
Functionalised alkenyl and alkynyl isocyanides were synthesised, as previously described for simpler substrates (chapter 2), by direct alkylation of ethyl-, benzyl- and *p*-methoxybenzyl-isocyanoacetate (synthesised according to scheme 35 and 38, chapter 2), using phase transfer catalysis or microwave irradiation conditions (scheme 54 and table 2). The expected mono alkylated isocyanides (**144**, **146**, **148**, **150**, **152**, **153**, **155** and **157**) were obtained in reasonable yields, and the corresponding dialkylated isocyanides were also obtained as minor products. The dialkylated isocyanides could also be accessed in high yields, using 2.0 equivalents of R^1-X under the same conditions. The microwave flash heating methodology was employed, as an alternative to PTC conditions, in an attempt to reduce the alkylation reaction times and to improve the yields. Compounds **144**, **145**, **148**, **149**, **153** and **154**

were synthesised using microwave conditions in only ten minutes, but in comparable yields to PTC conditions.



Scheme 54. Synthesis of alkenyl and alkynyl isocyanides by PTC. Reagents and conditions: i) R^1-X (1.0 eq), K_2CO_3 (3.0 eq), TBAB (0.3 eq) in MeCN, 12-20h at reflux. ii) R^1-X (1.0 eq), BEMP (1.0 eq) in MeCN, 10 min at 110 °C.

Table 2. Alkenyl and alkynyl isocyanides synthesised from ethyl- or benzylisocyanoacetate by PTC or microwave irradiation .

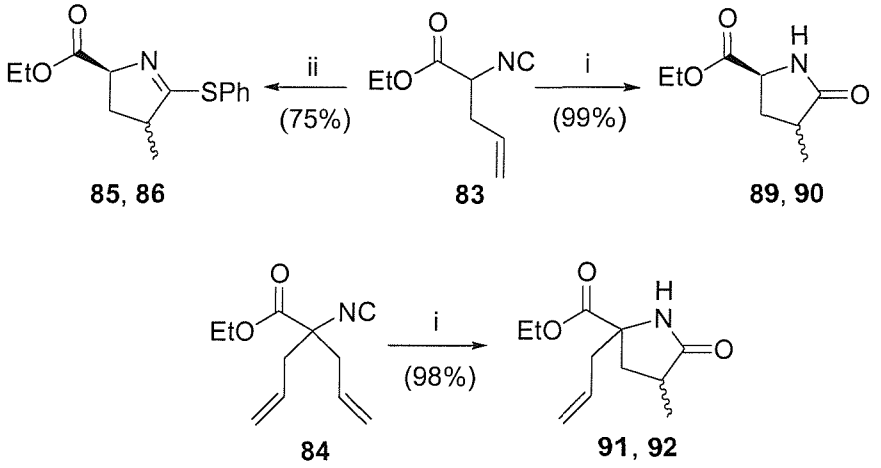
 **144** (47%)	 **145** (87%)	 **146** (38%)	 **147** (17%)
 **148** (35%)	 **149** (24%)	 **150** (50%)	 **151** (7%)
 **152** (29%)	 **153** (38%)	 **154** (86%)	 **155** (25%)
 **156** (92%)	 **157** (25%)	 **158** (97%)	 **159** (26%)

With these substrates in hand it was possible to study thiol mediated radical cyclisations promoted by microwave irradiation.

3.3 Microwave Assisted Radical Cyclisations of Alkenyl and Alkynyl Isocyanides with Thiols

3.3.1 Thiol Mediated Radical Cyclisations of Alkenyl Isocyanides

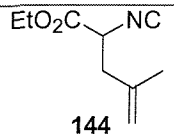
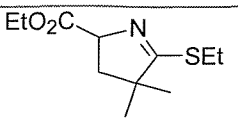
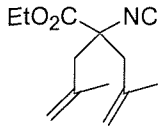
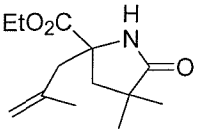
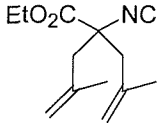
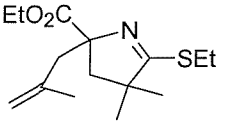
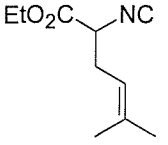
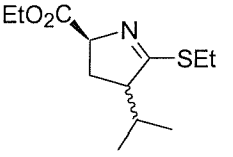
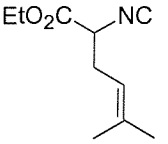
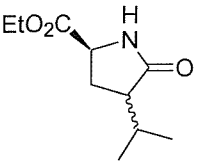
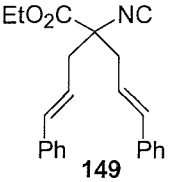
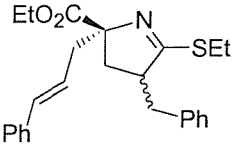
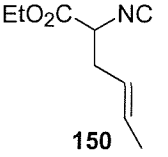
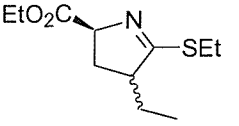
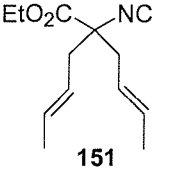
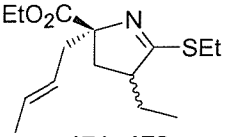
The first microwave assisted cyclisations were done on two isocyanides previously synthesised (**83** and **84**), using thiophenol and 2-mercaptoethanol (scheme 55) with AIBN as the radical initiator.



Scheme 55. Reagents and Conditions: i) 2-mercapto-ethanol (2eq), AIBN (0.2eq), toluene, 5 min. at 130 °C; ii) thiophenol (2.2eq), AIBN (0.2eq), toluene, 5 min. at 130 °C.

Pyrrolines **85** and **86** were obtained in good yield (75%), in five minutes at 130 °C. Pyroglutamates **89-92** were also obtained in excellent yields. The same compounds had been previously synthesised (chapter 2), under standard thermal conditions, in lower yields and reaction times varying from 1 to 7 hours. The products were obtained as *cis/trans* diastereomeric mixtures (~1:1 by NMR). These preliminary results showed that microwave irradiation could be successfully used to promote radical cyclisations of isocyanides with thiols. In order to further extend this methodology, cyclisations of more functionalised alkenyl isocyanides (**144-146** and **149-151**) were attempted. The results obtained are shown in table 3.

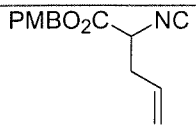
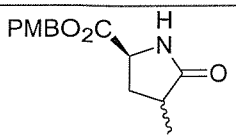
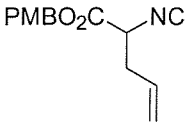
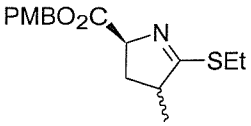
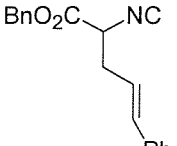
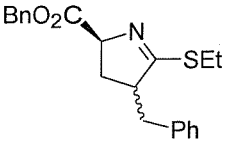
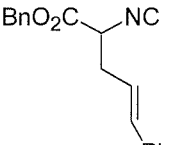
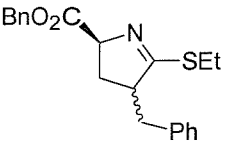
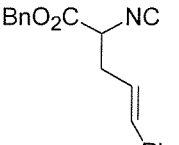
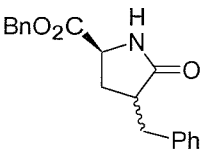
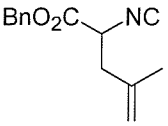
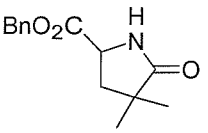
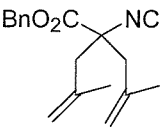
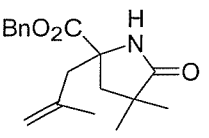
Table 3. Microwave Assisted Thiol mediated radical cyclisations of functionalised alkenyl isocyanides.

Entry	Isocyanide	Conditions	Product	Yield	*cis/trans*
1	 **144**	EtSH (2.0 eq), ACN (0.2 eq) in toluene, μω 130 °C 5 min.	 **160**	47%	---
2	 **145**	HOC_2H_4SH (2.0 eq), ACN (0.2 eq) in toluene, μω 130 °C 5 min.	 **161**	61%	---
3	 **145**	EtSH (2.0 eq), ACN (0.2 eq) in toluene, μω 130 °C 5 min.	 **162**	51%	---
4	 **146**	EtSH (2.0 eq), ACN (0.2 eq) in toluene, μω 130 °C 5 min.	 **163, 164**	80%	1.4 : 1
5	 **146**	HOC_2H_4SH (2.0 eq), ACN (0.2 eq) in toluene, μω 130 °C 5 min.	 **165, 166**	94%	1.4 : 1
6	 **149**	EtSH (2.0 eq), AIBN (0.2 eq) in toluene, μω 130 °C 5 min.	 **167, 168**	76%	1:1
7	 **150**	EtSH (2.0 eq), AIBN (0.2 eq) in toluene, μω 130 °C 5 min.	 **169, 170**	77%	1:1
8	 **151**	EtSH (2.0 eq), AIBN (0.2 eq) in toluene, μω 130 °C 5 min.	 **171, 172**	80%	1:1

Microwave assisted cyclisation of isocyanide **144**, with ethanethiol, gave pyrroline **160** in good 47% yield (table 3, entry 1), the regiochemistry of the cyclisation was not altered by the methyl group on the double bond at the site of addition of the imidoyl radical. Similarly isocyanide **145** gave pyrroline **162** and pyroglutamate **161** in 51% and 61% yields respectively (Table 3, entries 3 and 2). Cyclisations of a less hindered isocyanide (**146**) gave the corresponding pyrrolines **163** and **164** and pyroglutamates **165** and **166** in excellent yields in five minutes only. Isocyanides **149-151** also gave pyrrolines **167-172** in high yields.

Thiol mediated microwave assisted cyclisations of *p*-methoxybenzyl and benzyl alkenyl isocyanides were also attempted, using standard conditions (table 4). 2-Mercaptoethanol mediated cyclisation of **104** gave pyroglutamates **108**, **109** in excellent 96% yield, ethanethiol gave instead pyrrolines **173** and **174** in 90% yield (table 4, entries 1 and 2). Cyclisation of isocyanide **152** with ethanethiol gave pyrrolines **175** and **176** in excellent 78% yield, under microwave conditions (table 4, entry 3). When the reaction was performed under standard thermal conditions, the products were obtained in 40% yield with a longer reaction time (table 4, entry 4), thus proving an obvious advantage in using microwave irradiation. Cyclisation of the same substrate (**152**) with 2-mercaptoethanol, under microwave irradiation, afforded pyroglutamates **177** and **178** in 76% yield. Radical cyclisations of more hindered substrates **153** and **154** (entries 6 and 7, table 4), also gave good results.

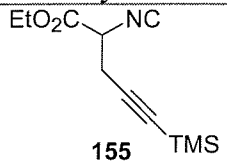
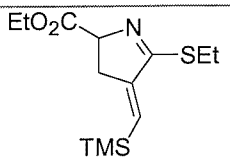
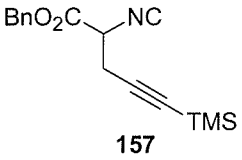
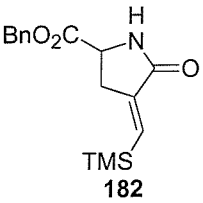
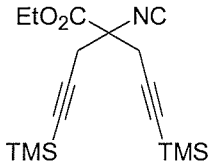
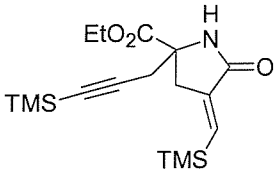
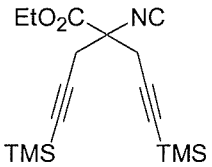
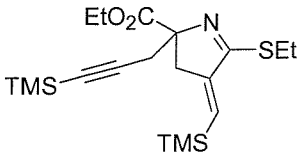
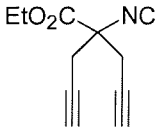
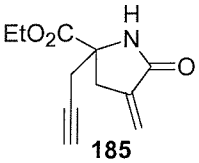
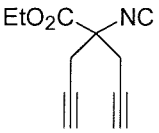
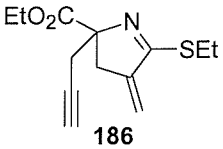
Table 4. Microwave Assisted thiol mediated radical cyclisations of functionalised *p*-methoxybenzyl- and benzyl-isocyanides.

Entry	Isocyanide	Conditions	Product	Yield	cis/trans
1	 **104**	HOC_2H_4SH (2.0 eq), AIBN (0.2 eq) in toluene, μω 130 °C 5 min.	 **108, 109**	96%	1 : 1
2	 **104**	EtSH (2.0 eq), AIBN (0.2 eq) in toluene, μω 130 °C 5 min.	 **173, 174**	90%	1.1 : 1
3	 **152**	EtSH (2.0 eq), ACN (0.2 eq) in toluene, μω 130 °C 5 min.	 **175, 176**	78%	1.2 : 1
4	 **152**	EtSH (2.0 eq), ACN (0.2 eq) in toluene, 110 °C 5 h.	 **175, 176**	40%	1 : 1
5	 **152**	HOC_2H_4SH (2.0 eq), ACN (0.2 eq) in toluene, μω 130 °C 5 min.	 **177, 178**	76%	1.3 : 1
6	 **153**	HOC_2H_4SH (2.0 eq), AIBN (0.2 eq) in toluene, μω 130 °C 5 min.	 **179**	64%	---
7	 **154**	HOC_2H_4SH (2.0 eq), AIBN (0.2 eq) in toluene, μω 130 °C 5 min.	 **180**	81%	---

3.3.2 Thiol Mediated Cyclisations of Alkynyl Isocyanides

When alkynyl radical traps (isocyanides **155-158**) were reacted with thiols, under microwave or traditional thermal conditions, the reactions followed a similar pattern to that of alkenyl isocyanides (Table 5).[22]

Table 5. Microwave assisted thiol mediated radical cyclisations of alkynyl isocyanides.

Entry	Isocyanide	Conditions	Product	Yield
1	 **155**	EtSH (2.0 eq), ACN (0.2 eq) in toluene, μω 130 °C 5 min.	 **181**	86%
2	 **157**	HOC_2H_4SH (2.0 eq), ACN (0.2 eq) in toluene, μω 130 °C 5 min.	 **182**	72%
3a	 **156**	HOC_2H_4SH (2.0 eq), ACN (0.2 eq) in toluene, μω 130 °C 5 min.	 **183**	73%
3b		HOC_2H_4SH (2.0 eq), ACN (0.2 eq) in toluene, 110 °C 2.5 h.		37%
4	 **156**	EtSH (2.0 eq), ACN (0.2 eq) in toluene, μω 130 °C 5 min.	 **184**	80%
5a		HOC_2H_4SH (2.0 eq), ACN (0.2 eq) in toluene, μω 130 °C 5 min.		60%
5b	**158**	HOC_2H_4SH (2.0 eq), ACN (0.2 eq) in toluene, 80 °C 6 h.	**185**	37%
6	 **158**	EtSH (2.0 eq), ACN (0.2 eq) in toluene, μω 130 °C 5 min.	 **186**	41%

Under standard thermal conditions, cyclisation of alkynyl isocyanides **156** and **158**, using 2-mercaptoethanol, gave surprisingly poor yields of the corresponding pyroglutamates **183** and **185** (table 5, entries 3b and 5b).

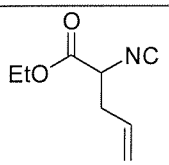
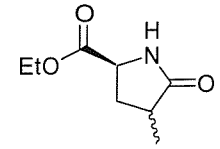
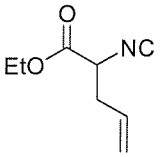
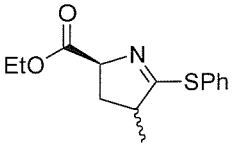
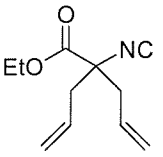
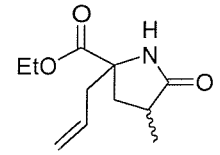
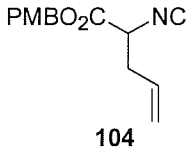
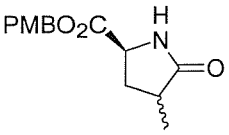
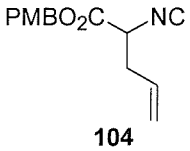
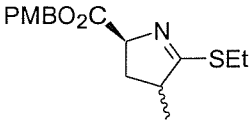
Substrate **155** gave only traces of the corresponding pyroglutamate. When microwave flash heating was used good yields were instead obtained (table 5, entries 2, 3a, and 5a). Microwave assisted conditions also afforded pyrrolines **181**, **184** and **186** in good yields (table 5, entries 1, 4 and 6).

In conclusion reaction times were dramatically reduced and cyclisations of alkynyl isocyanides, which gave poor results under standard thermal heating conditions, were improved.

3.3.3 Thiol Mediated Cyclisations of Alkenyl Isocyanides in the Absence of Radical Initiator

The good results obtained by using the microwave "flash heating" methodology to perform radical cyclisations prompted an investigation on the reaction of alkenyl isocyanides with thiols, in the absence of radical initiator. Alkenyl isocyanides were reacted, under microwave irradiation, with 2-mercaptoethanol, ethanethiol and thiophenol (table 6).

Table 6. Thiol mediated cyclisations of alkenyl isocyanides in the absence of radical initiator.

Entry	Isocyanide	Conditions	Product	Yield	cis/trans
1	 **83**	HOC_2H_4SH (4.0 eq), toluene, μω 130 °C 10 min.	 **89, 90**	70%	1 : 1
2	 **83**	PhSH (4.0 eq), toluene, μω 130 °C 10 min.	 **85, 86**	58%	1 : 1
3	 **84**	HOC_2H_4SH (4.0 eq), toluene, μω 130 °C 10 min.	 **91, 92**	85%	1.4 : 1
4	 **104**	HOC_2H_4SH (4.0 eq), toluene, μω 130 °C 10 min.	 **108, 109**	91% [a]	n.d.[b]
5	 **104**	EtSH (4.0 eq), toluene, μω 130 °C 10 min.	 **173, 174**	54% [a]	n.d.[b]

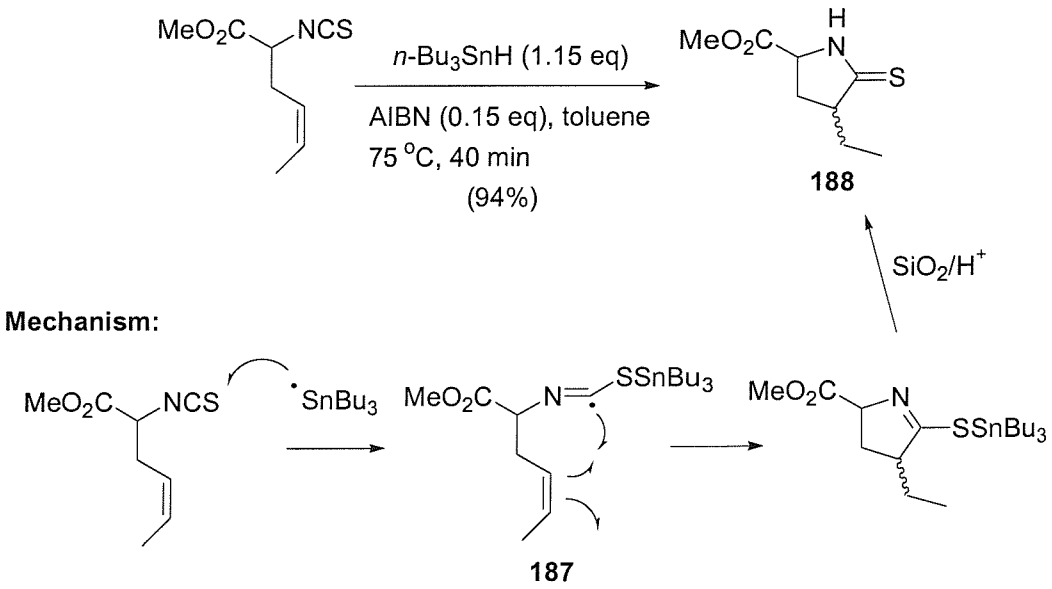
[a] Calculated by HPLC, by comparison with a standard. [b] The *cis/trans* ratio could not be determined.

Isocyanides **83**, **84** and **104** all cyclised in good yields with this method (table 6, entries 1-5), although the reaction time had to be increased to 10 minutes

with 4.0 eq of thiol. The obtained yields were lower than with the radical initiator but still comparable to thermal methods.

3.3.4 Microwave Assisted Synthesis of γ-Thiolactams

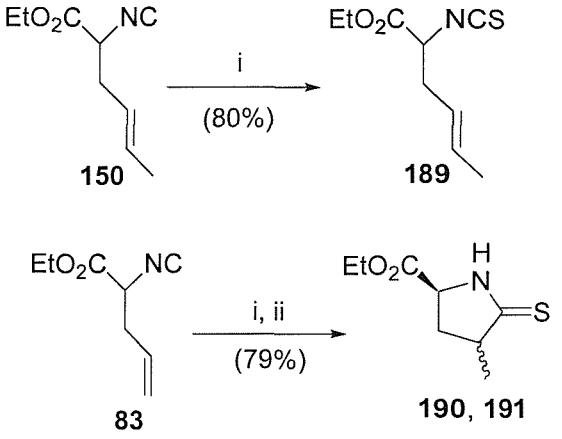
In the early 1990s Bachi reported n-Bu_3SnH mediated radical cyclisations of alkenyl isothiocyanates, to give γ-thiolactams (scheme 56).[18] The mechanism of this reaction involves addition of organotin radicals to isothiocyanates, as in the first step of Barton's method for deamination of primary amines,[16] to generate a tinthioimidoyl radical (**187**) which undergoes 5-*exo* cyclisation onto the alkenyl side chain, to give a tinthioimidate, which spontaneously hydrolysed during chromatography to thiolactam **188**.



Scheme 56. Bachi's synthesis of thiolactams from isothiocyanates.

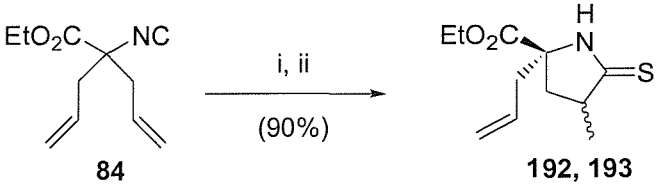
It was envisaged that alkenyl isothiocyanates could be easily synthesised by reaction of isocyanides with *tert*-butyl mercaptan (see chapter **1.1.1**), under microwave irradiation, and then reacted with organotin reagents to give functionalised thiolactams (scheme 57).

Isocyanide **150** was first reacted with *tert*-butyl thiol under radical conditions, using microwave irradiation, to give the corresponding isothiocyanate **189** in good 80% yield (scheme 57). The reaction was complete in only 6 minutes. Then a one pot (two step) conversion of isocyanide **83** directly to thiolactams **190** and **191** was attempted, by reaction with *tert*-butyl thiol first and then *n*-Bu_3SnH. The desired products were obtained in overall 79% isolated yield (1:1 mixture of diastereoisomers by NMR). The reaction was complete in 12 minutes (scheme 57).



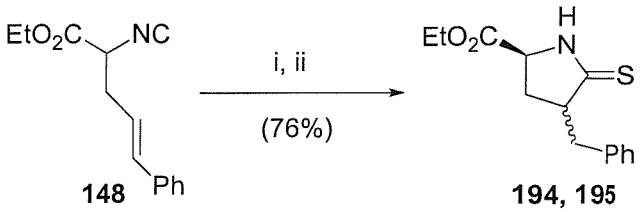
Scheme 57. Reagents and conditions: i) *t*-BuSH (1.5 eq), AIBN (0.2 eq), toluene, μω 6 min at 140 °C; ii) *n*-Bu_3SnH (1.15 eq), AIBN (0.2 eq), toluene, μω 6 min at 140 °C.

When isocyanide **84** was reacted, under the above conditions, with *tert*-butyl mercaptan and *n*-BuSnH, the corresponding thiolactams **192** and **193** were obtained in excellent 90% yield as a 1:1 diastereomeric mixture (scheme 58).



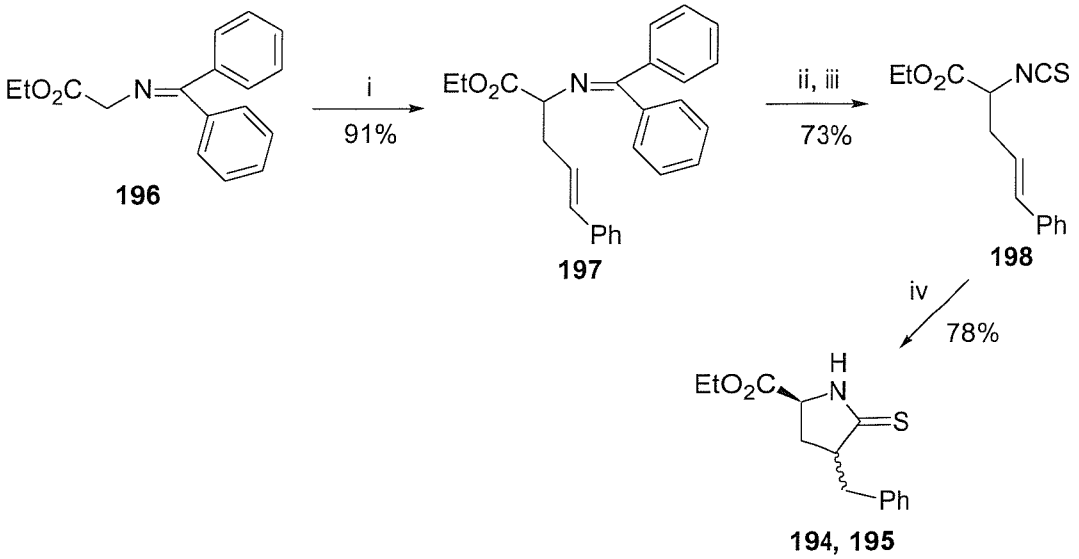
Scheme 58. Reagents and conditions: i) *t*-BuSH (1.5 eq), AIBN (0.2 eq), toluene, μω 6 min at 140 °C; ii) *n*-Bu_3SnH (1.15 eq), AIBN (0.2 eq), toluene, μω 6 min at 140 °C.

Reaction of isocyanide **148**, bearing a substituted double bond, with *tert*-butyl mercaptan and *n*-BuSnH, also afforded thiolactams **194** and **195** in good yield, as 2:1 diastereomeric mixture, (scheme 59).



Scheme 59. Reagents and conditions: i) *t*-BuSH (1.5 eq), AIBN (0.2 eq), toluene, μω 6 min at 140 °C; ii) *n*-Bu_3SnH (1.15 eq), AIBN (0.2 eq), toluene, μω 6 min at 140 °C.

Thiolactams **194** and **195** were also synthesised by a more traditional synthetic route, from commercially available diphenylmethylene-glycine ethyl ester (**196**) in a few steps (scheme 60).

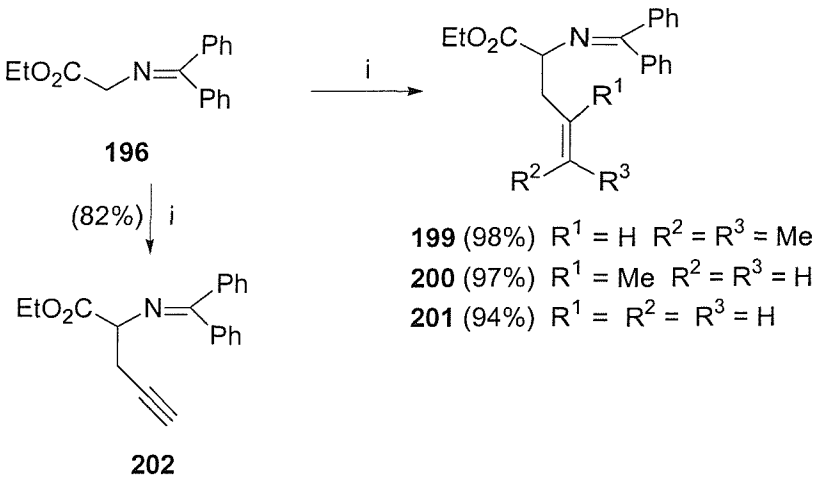


Scheme 60. Reagents and conditions: Cinnamyl bromide (1.5 eq), BEMP (1.5 eq), MeCN, μω 10 min at 110 °C; ii) 1N HCl in Et_2O, 12h at rt; iii) $NaHCO_3/CSCl_2$; iv) *n*-Bu_3SnH (1.15 eq), AIBN (0.2 eq), toluene, μω 6 min at 140 °C.

The key monoalkylation step, to synthesise **197**, was performed by using BEMP chemistry under microwave irradiation. The desired product was obtained in excellent yield in a very short time, compared to traditional PTC methods. Simple acidic hydrolysis to free the amino group and reaction with

thiophosgene[127, 128] afforded isothiocyanate **198** in good 73% yield over two steps. Finally microwave assisted tri-*n*-butylstannane mediated radical cyclisation afforded thiolactams **194** and **195** in good yield, 1.3:1 diastereomeric ratio.

Alkylation of protected glycine **196** is a widely employed reaction in the synthesis of unnatural amino acids, it is normally performed under phase transfer catalysis conditions, in high yields, but long reaction times are often required.[129-131] The combination of BEMP chemistry and microwave irradiation could represent an interesting improvement over the existing methodology, in terms of faster reaction. For this reason, alkylation of **196** with different alkenyl bromides, under the above conditions, was attempted (scheme 61).



Scheme 61. Reagents and conditions: R-X (1.5 eq), BEMP (1.5 eq), MeCN, μω 10 min at 110 °C.

Compounds **199-202** were obtained in very short time with excellent yields.

3.4 Conclusions

Several alkenyl and alkynyl isocyanides were synthesised and reacted with various thiols under microwave irradiation, giving access to functionalised pyrrolines and pyroglutamates in good to excellent yields and in very short reaction times (5 minutes), compared to traditional thermal heating techniques. The microwave flash heating methodology was also employed to efficiently synthesise thiolactams and proved to be very useful in the alkylation of a glycine equivalent, commonly employed to synthesise unnatural amino acids.

Chapter 4

SYNTHESIS OF INDOLIZIDINES

4.1 Introduction

Indolizidine alkaloids (Figure 3), isolated from the skin secretions of Central and South American frogs, fungi and plants, represent a class of pharmacologically important compounds.[132] For example, polyhydroxylated derivatives such as castanospermine, lentiginosine and swainsonine have been known to inhibit glycosidase and cardiotonic activity with potential antibacterial, antitumoral, antiviral, antidiabetic activity and also act as anti-HIV agents.[133]

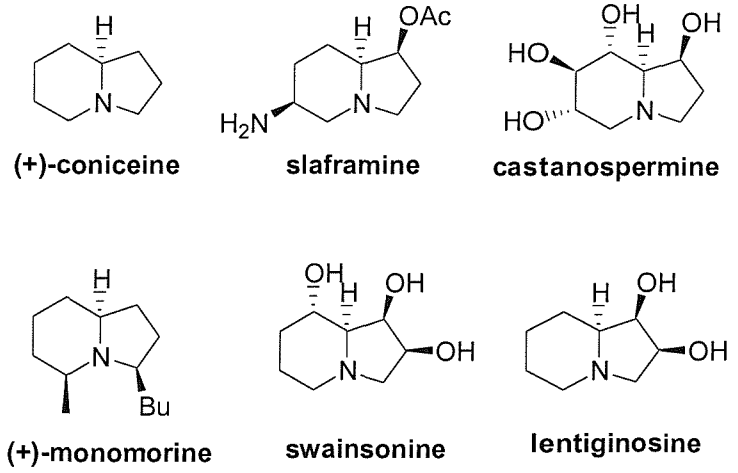
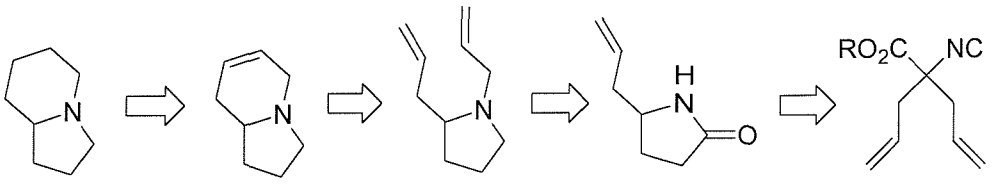


Figure 3. Some examples of indolizidine alkaloids.

These alkaloids are very important targets in organic synthesis due to their scarcity in natural sources and important physiological effects. Coniceine, containing the simplest indolizidine skeleton, has attracted great attention from synthetic chemists to establish a general route for the preparation of more complex derivatives and this has resulted in several successful approaches to the compound both in racemic and optically active form.[134-138]

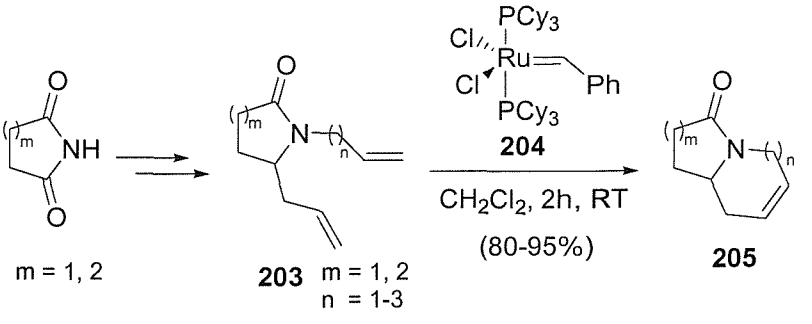
4.2 Synthetic Plan

It was envisaged that indolizidine analogues could be accessed starting from bis-alkenyl isocyanides, easily accessible with already established methodology (chapters 2 and 3), using a radical cyclisation/*N*-alkylation/ring closing metathesis strategy for the formation of the 1-azabiciclo-[4.3.0]-nonane skeleton (scheme 62).



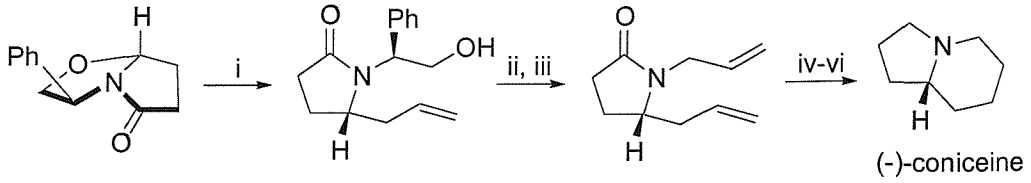
Scheme 62. Retrosynthetic strategy to access indolizidines.

Ring-closing metathesis (RCM) has recently emerged as a powerful method for the synthesis of a variety of ring systems. Ring sizes from five to complex macrocycles have been synthesised;[139-143] bicyclic γ- and δ-lactams have also been synthesised by Holmes and coworkers (scheme 63).[144] The authors synthesised bis-alkenyl lactams **203**, from simple starting materials, which were then reacted with Grubbs catalyst **204**[145] to give access to the corresponding bicyclic lactams **205** in high yields.



Scheme 63. Synthesis of bicyclic lactams by Holmes.

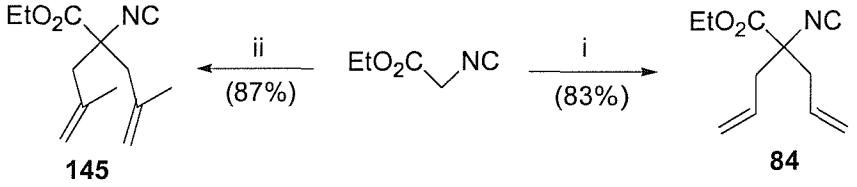
The RCM approach has also been successfully used in the total synthesis of (-)-Coniceine by Meyers (scheme 64).[134]



Scheme 64. Total synthesis of (-)-coniceine. Reagents and conditions: i) allyltrimethylsilane, $TiCl_4$; ii) Ca/NH_3; iii) NaH, allyl bromide; iv) Grubbs catalyst (10 mol%); v) H_2, $Pd(OH)_2$; vi) $LiAlH_4$.

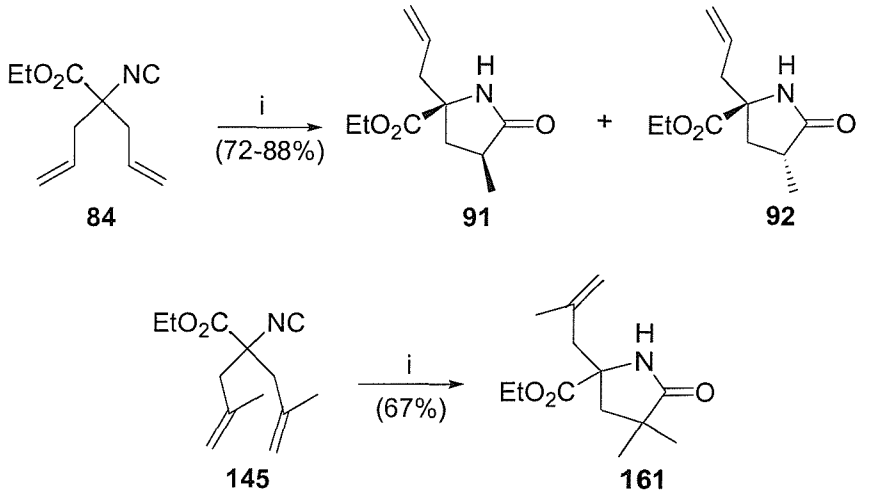
4.3 Synthesis of Ring Closing Metathesis precursors

Two alkenyl isocyanides were synthesised using phase transfer conditions (K_2CO_3/TBAB), according to scheme 65.



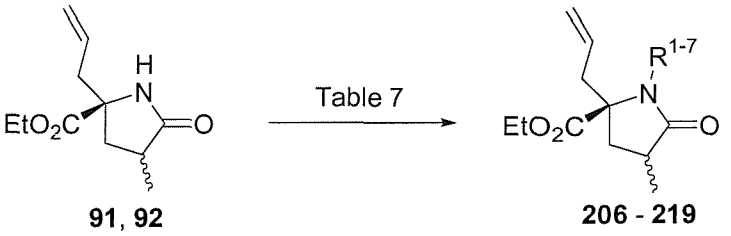
Scheme 65. Synthesis of bis-alkenyl isocyanides. Reagents and conditions: i) allyl bromide (2.5 eq), K_2CO_3, TBAB, MeCN, reflux 20 h; ii) methallyl bromide (2.5 eq), K_2CO_3, TBAB, MeCN, reflux 20 h.

Ethylisocyanoacetate was alkylated, as described in chapter 2, with allyl bromide and methallyl bromide to give the corresponding dialkylated isocyanides **145** and **84** in high yields. 2-Mercaptoethanol mediated radical cyclisation of these two substrates, under microwave irradiation, gave the expected pyroglutamates **91** and **92** (as a 1.6:1 *cis/trans* diastereomeric mixture), and **161**, in good yields (scheme 66).



Scheme 66. Microwave assisted radical cyclisation of dialkylated isocyanides **84** and **145**. Reagents and conditions: i) 2-mercaptoethanol (3.0 eq), AIBN (0.2 eq) in toluene, μω 130 °C 2 x 5 min.

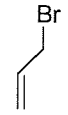
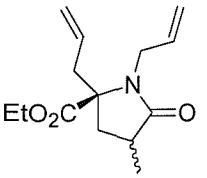
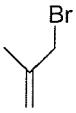
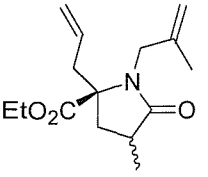
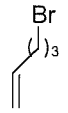
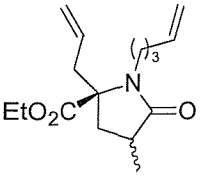
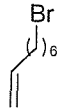
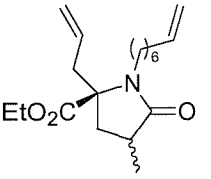
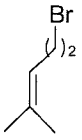
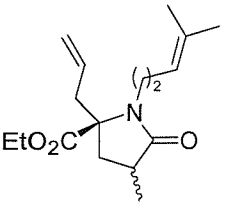
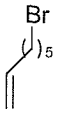
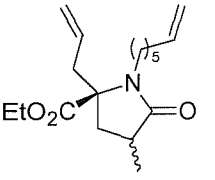
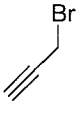
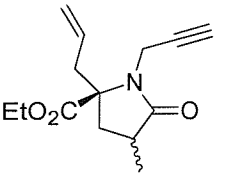
Pyroglutamates **91/92** were then *N*-alkylated with various alkenyl bromides and propargyl bromide to give the corresponding *N*-alkylated pyroglutamates **206-219** (scheme 67 and table 7).



Scheme 67. *N*-Alkylation of alkenyl pyroglutamates.

Although NaH or NaOH, under phase transfer conditions, are the bases employed for *N*-alkylation of either proline or pyroglutamates in the literature,[146] the successful use of iminophosphorane bases throughout the research project prompted an investigation into their use. Alkylation of pyroglutamates **91/92** was successfully achieved using BEMP (table 7, entries 1a-5 and 7a). *N*-Alkylated pyroglutamates were obtained in good yields, except in one case (table 7, entry 5) where competing elimination was a problem.

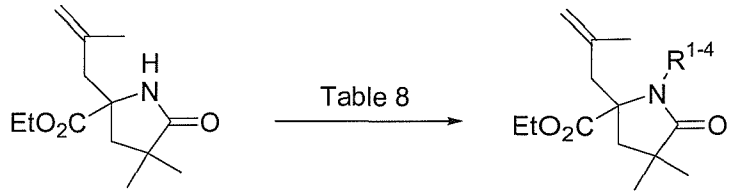
Table 7. Reagents and conditions for *N*-Alkylation of alkenyl pyroglutamates **91/92**.

Entry	R-X	Conditions	Product	Yield	*cis/trans*
1a		R-X (1.5 eq), BEMP (2.0 eq), MeCN, 12h at 80 °C	 **206, 207**	67%	2:1
1b		R-X (1.5 eq), BEMP (2.0 eq), MeCN, μω10 min at 110 °C		19%	2:1
2		R-X (1.5 eq), BEMP (1.5 eq), MeCN, 12h at 80 °C	 **208, 209**	95%	2:1
3		R-X (1.5 eq), BEMP (2.0 eq), MeCN, 12h at 80 °C	 **210, 211**	38%	1.3:1
4		R-X (1.5 eq), BEMP (1.5 eq), MeCN, 12h at 80 °C	 **212, 213**	38%	1.2:1
5		R-X (1.5 eq), BEMP (2.0 eq), MeCN, 12h at 80 °C	 **214, 215**	15%	1.8:1
6		R-X (1.5 eq), BTPP (1.5 eq), MeCN, 12h at 80 °C	 **216, 217**	46%	1:1
7a		R-X (1.5 eq), BEMP (1.5 eq), MeCN, 12h at 80 °C	 **218, 219**	82%	1.6:1
7b		R-X (1.5 eq), BTPP (1.5 eq), MeCN, 12h at 80 °C		100%	1.7:1

Microwave irradiation was also used, in an attempt to reduce reaction times and increase yields, but it proved to be inefficient (table 7, entry 1b). Use of a

stronger iminophosphorane base (BTPP) gave instead better results (table 7, entries 6 and 7b), in terms of better yields, and was used for the next alkylations.

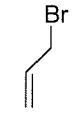
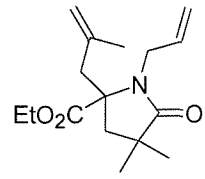
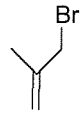
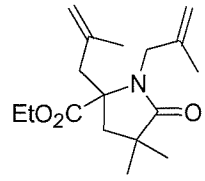
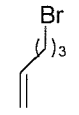
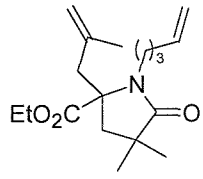
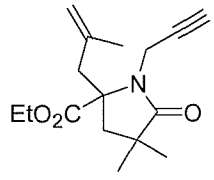
Pyroglutamate **161** was then *N*-alkylated, under BTPP conditions, (scheme 68 and table 8). The expected *N*-alkylated products **220-223** were obtained in good yields.



161 **220 - 223**

Scheme 68. *N*-alkylation of pyroglutamate **161**.

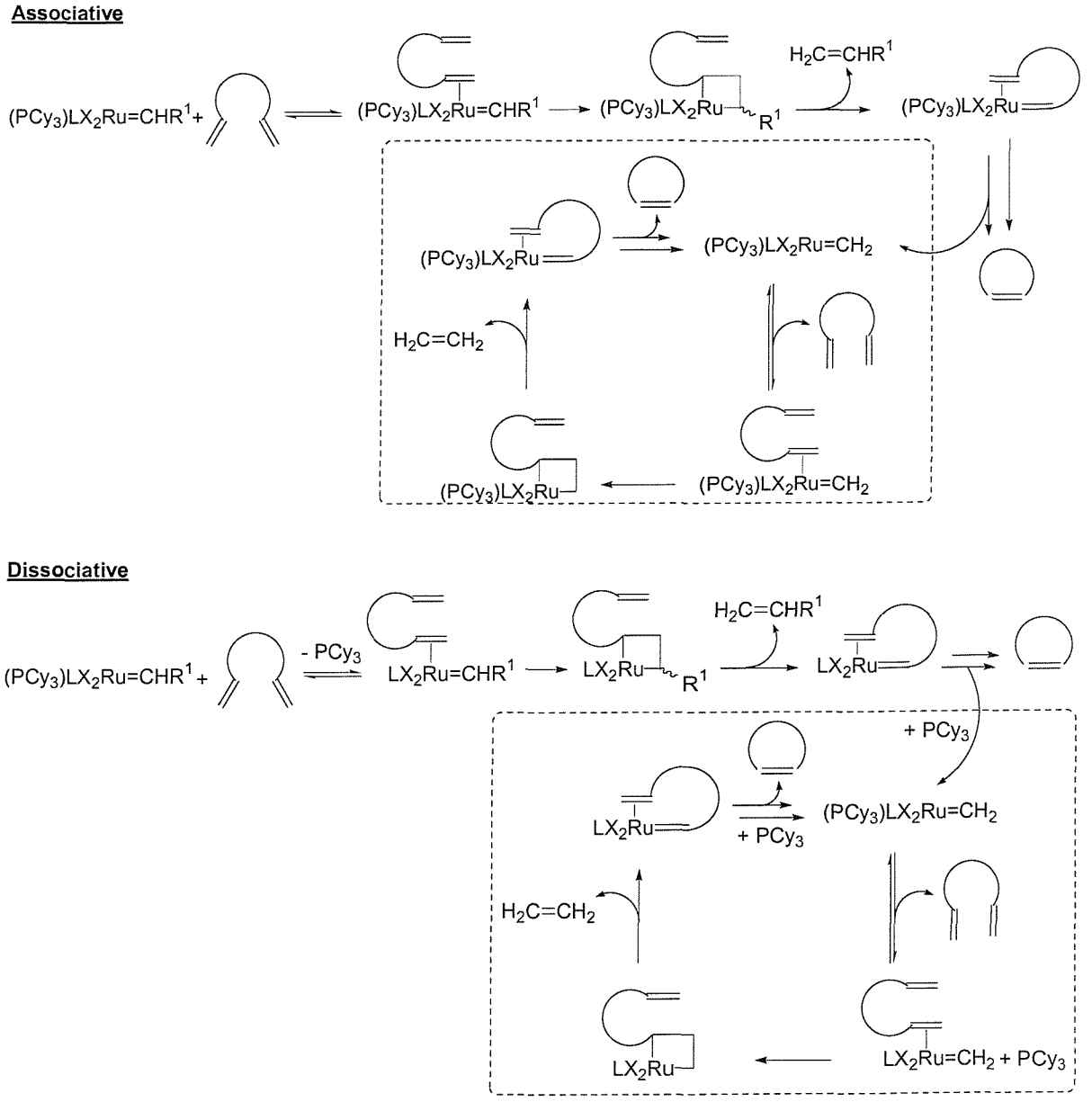
Table 8. Reagents and conditions for *N*-Alkylation of alkenyl pyroglutamate **160**.

Entry	R-X	Conditions	Product	Yield
1		R-X (1.5 eq), BTPP (1.5 eq), MeCN, 12h at 80 °C	 **220**	85%
2		R-X (1.5 eq), BTPP (1.5 eq), MeCN, 12h at 80 °C	 **221**	79%
3		R-X (1.5 eq), BTPP (1.5 eq), MeCN, 12h at 80 °C	 **222**	76%
4		R-X (1.5 eq), BTPP (1.5 eq), MeCN, 12h at 80 °C	 **223**	99%

The *N*-alkylated pyroglutamates **206-222** were then used to test the Ring Closing Metathesis to access indolizidines.

4.4 Ring Closing Metathesis Mechanism.

Two general competing mechanisms for olefin metathesis with catalyst **204** (and the other Ruthenium based catalysts) have been proposed (scheme 69).[145]

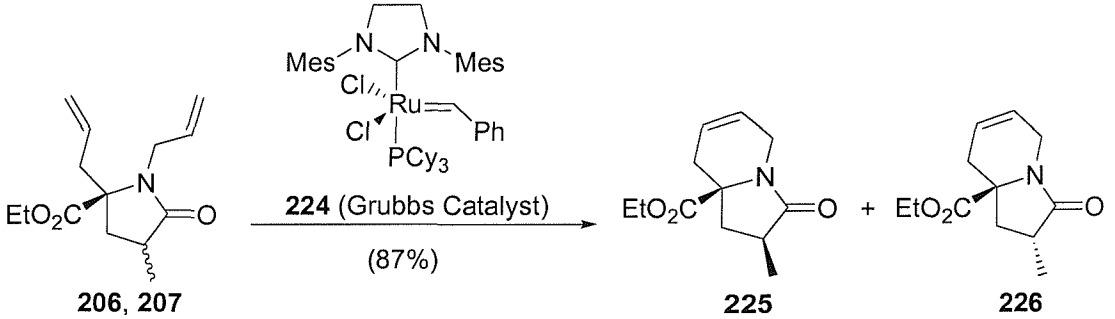


Scheme 69. Proposed mechanisms for olefin ring closing metathesis.

The top pathway, termed "associative", assumes that the olefin simply coordinates to the catalyst to form the intermediate 18-electron olefin complex, followed by the actual metathesis steps to form the product. The bottom pathway, termed "dissociative", assumes that upon binding of the olefin, a phosphine is displaced from the metal center to form a 16-electron olefin complex, which undergoes metathesis to form the cyclised product, regenerating the catalyst upon recoordination of the phosphine. Mechanistic studies, by Grubbs,[145] showed that the major pathway was found to involve phosphine dissociation from the metal center, such that a minor "associative" pathway in which the phosphine ligand remains bound can be considered to operate only at higher phosphine concentrations (when excess phosphine is added to the reaction). The relative importance of the "dissociative" pathway suggests that there is a 14-electron metallacyclobutane intermediate, an electron deficient intermediate for a late transition metal such as ruthenium.

4.5 RCM of pyroglutamates: synthesis of indolizidines and bicyclic γ-lactams

Pyroglutamates **206/207** were reacted with 10 mol% of second generation Grubbs catalyst (**224**) in DCM at room temperature (scheme 70). The reaction was complete in two hours and the expected indolizidines **225** and **226** were obtained in good 87% yield (*cis*/*trans* ratio 1.6:1).

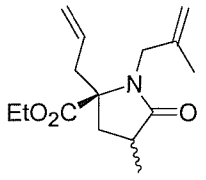
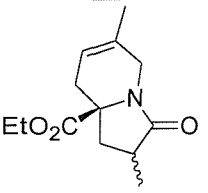
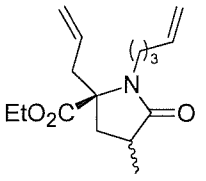
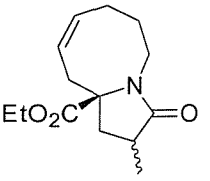
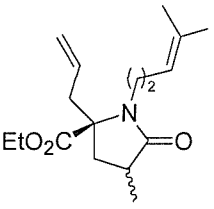
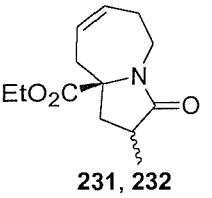
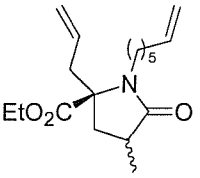
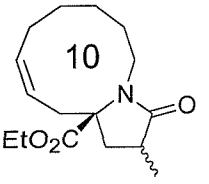
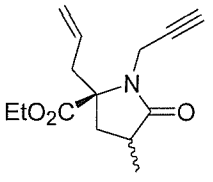
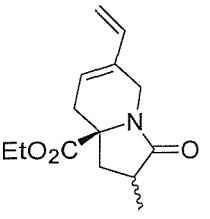


206, 207 **225** **226**

Scheme 70. Reagents and conditions: **224** (10 mol%), DCM, 2h at rt.

It was also possible to separate the two diastereoisomers by column chromatography. The ring closing metathesis of pyroglutamates **208-211** and **214-219** was then performed using a catalytic amount of **224** (table 9).

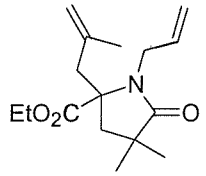
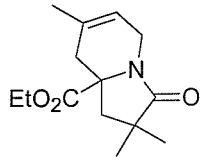
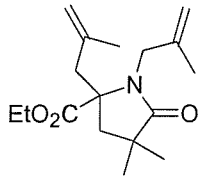
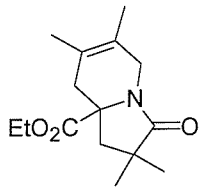
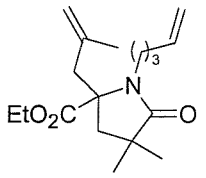
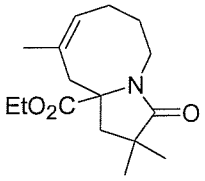
Table 9. Ring closing metathesis of pyroglutamates.

Entry	Substrate	Conditions	Product	Yield	*cis/trans*
1	 **208, 209**	**223** (10 mol%), DCM, 2h at RT	 **227, 228**	99%	2.5:1
2	 **210, 211**	**223** (10 mol%), DCM, 2h at RT	 **229, 230**	89%	1.1:1
3	 **214, 215**	**223** (10 mol%), DCM, 2h at RT	 **231, 232**	81%	1.8:1
4	 **216, 217**	**223** (14 mol%), DCM, 48h at RT or μω 30 min at 100 °C	 **233, 234**	traces	---
5	 **218, 219**	**223** (8-14 mol%), DCM, 12-48h at RT	 **235, 236**	72%	1:1

Excellent results were obtained with substrates **208/209**, **210/211** and **214/215** (table 9, entries 1-3), which gave the expected bicyclic lactams in 99%, 89% and 81% isolated yields respectively. The reactions were completed in two hours, using 10 mol% of catalyst **224**. Surprisingly only traces of compounds **233/234** were obtained, although the reaction was prolonged for 48 hours (entry 4), or perfomed under microwave irradiation. Ring closing enyne metathesis of **218/219** afforded indolizidines **235/236** in good 72% yield, even though slightly contaminated by the styrene addition byproduct (2% by NMR). In order to avoid this problem the amount of catalyst used was reduced (5 mol%) but it was still not possible to obtain pure products.

Ring closing metathesis of more hindered substrates (**220-222**) was also studied, the results obtained are shown in table 10.

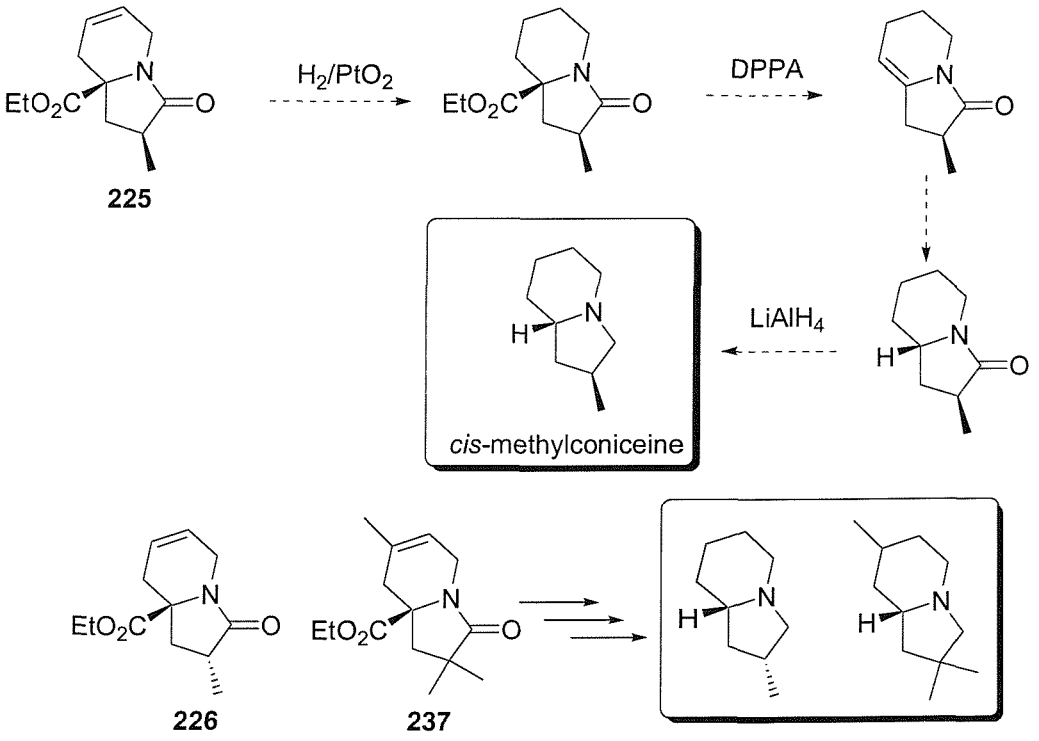
Table 10. RCM of pyroglutamates **220-222**.

Entry	Substrate	Conditions	Product	Yield
1	 **220**	**224** (10 mol%), DCM, 6h at RT	 **237**	98%
2a	 **221**	**224** (20 mol%), DCM, 4d at RT	 **238**	0%
2b		**224** (10 mol%), DCM, μω 30 min at 100 °C		97%
3	 **222**	**224** (10 mol%), DCM, 20h at RT	 **239**	86%

Pyroglutamates **220** and **222** gave the corresponding cyclised products in excellent yields (table 10, entries 1 and 3), but long reaction times had to be

employed. Cyclisation of **221** was unsuccessful, even after four days and use of 20 mol% of Grubbs catalyst only starting material could be recovered (table 10, entry 2a). However when the substrate was reacted with 10 mol% catalyst under microwave irradiation (table 10, entry 2b), the expected indolizidine **238** was obtained in excellent 97% yield.

Some of the indolizidines synthesised (**225**, **226** and **237**) could be used to access coniceine analogues in a few simple steps, by using already published methodology (scheme 71).[135, 136, 147, 148]

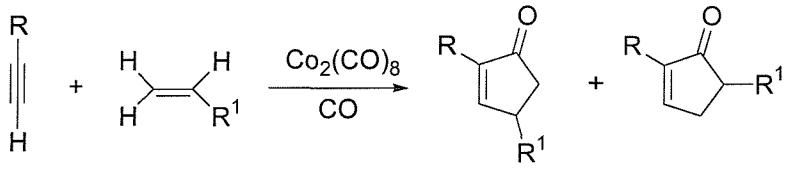


Scheme 71. Coniceine analogs that could possibly be accessed.

4.6 Synthesis of Tricyclic Indolizidines via Pauson-Khand Reaction

4.6.1 The Pauson-Khand Reaction

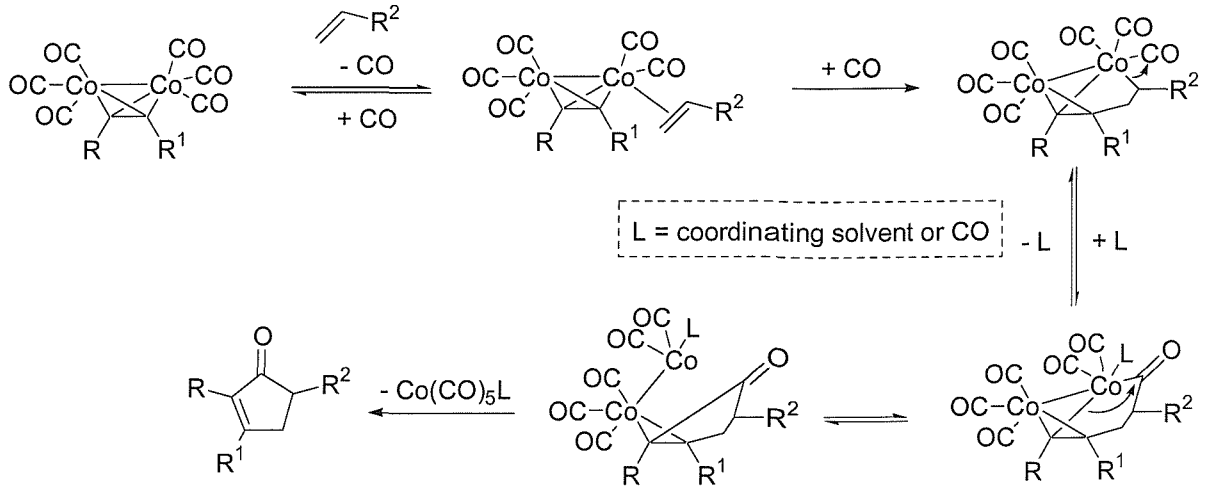
Since it's discovery in the early seventies,[149, 150] the cobalt-mediated carbonylative cocyclisation of an alkyne and alkene, known as the Pauson-Khand reaction, has become nowadays one of the most convergent and versatile methods for the synthesis of cyclopentenones (scheme 72).[151-153]



Scheme 72. General Pauson-Khand reaction.

The cyclopentenone is formed by cyclisation of an alkyne, olefin and carbon monoxide in the presence of $Co_2(CO)_8$ in a formal [2 + 2 + 1] cycloaddition. While the reaction had shown to tolerate many functional groups, it also had many limitations. A stoichiometric amount of catalyst and harsh conditions were employed to perform the transformation, and such high temperatures often led to decomposition of substrates and/or products. Regioselectivity was also a problem. The reaction is usually selective with respect to substituents on the alkyne, the alkene substituents are not selectively incorporated, so strained olefins had to be used for efficient conversion to the product, with the exception of ethylene itself. The first examples of intramolecular Pauson-Khand reactions also appeared in 1981 entailing the synthesis of bicyclic product from an acyclic substrate.[154] Strained alkenes are not necessary for the intramolecular cycloaddition, and regioselectivity is not an issue.

While there is no solid mechanistic data for the Pauson-Khand reaction, a mechanism has been proposed based on regio- and stereochemical observations from many examples (scheme 73).[155]

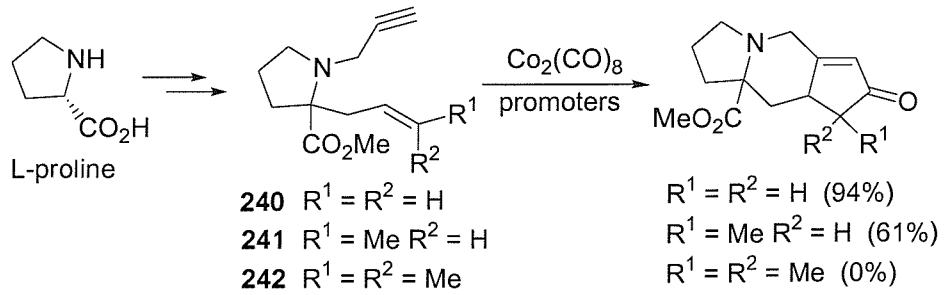


Scheme 73. Proposed mechanism of the Pauson-Khand reaction.

The only intermediate that has been isolated is the initial, stable, alkyne-$Co(CO)_6$ complex. It is assumed that the next step involves dissociation of a CO ligand and coordination of the alkene. The alkene then irreversibly inserts into one of the cobalt-carbon bonds. This step is thought to be rate-determining as well as product-determining. Migratory insertion of a CO ligand bound to cobalt to form the carbonyl moiety and reductive elimination of the $Co(CO)_3$ fragment follows. Finally loss of the $Co_2(CO)_5L$ fragment liberates the cyclopentenone product.

In order to avoid the use of high temperatures and long reaction times, necessary to perform the Pauson-Khand reaction, tertiary amine *N*-oxides (like NMO or TMANO) were found to be useful promoters. It is assumed that loss of a CO ligand is one of the first steps of the mechanism leading to coordination of the alkene. Schreiber[156] found that NMO was an effective promoter of the PKR at room temperature. The use of *N*-oxides in promoting the Pauson-Khand cycloaddition has been prevalent since its discovery, due to the mild conditions required to perform the transformation. Other promoters such as silica, amines, sulfides, molecular sieves and microwave irradiation have also been reported.[157-161]

Recently Tanimori *et al*[162] reported the synthesis of tricyclic indolizidines via Pauson-Khand reaction of enynes **240-242** (scheme 74).



Scheme 74. Tanimori's synthesis of tricyclic indolizidines via PKR.

Enynes **240-242** were synthesised from *L*-proline, and then reacted with a stoichiometric amount of $Co_2(CO)_8$, in the presence of various promoters (CO, DMSO, NMO and TMANO). Two of the desired products were obtained in good yields, whether substrate **242** did not give any product.

Tricyclic indolizidines could be useful substrates for the synthesis of indolizidine alkaloids such as asperparaline and its derivatives (figure 4), which exhibit potent paralytic, insecticidal and antifeedant activity.[163, 164]

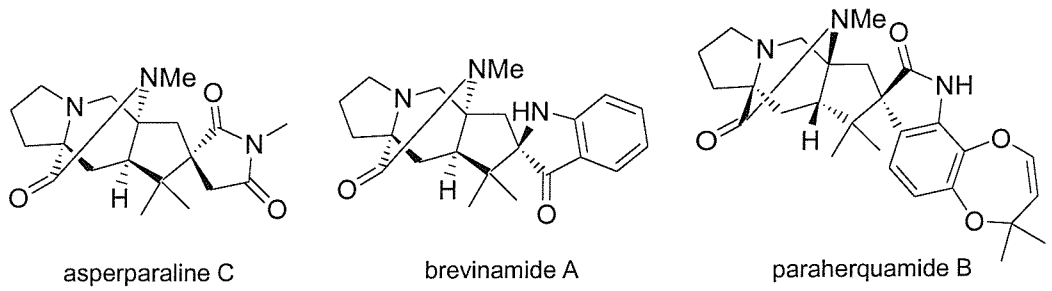
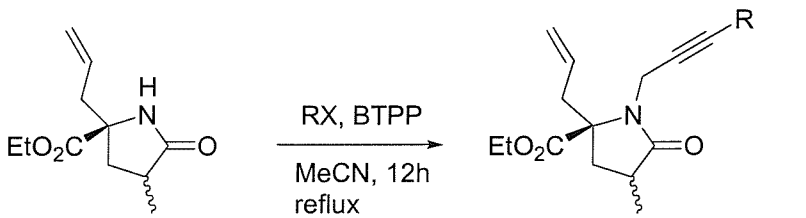


Figure 4. Asperparaline and its derivatives

It was envisaged that pyroglutamates of type **218/219** and **223**, bearing an alkene and alkyne moiety, could be reacted under Pauson-Khand conditions to access tricyclic indolizidines in one step.

4.6.2 Synthesis of Cyclisation Precursors

Substrates **218/219** and **223** had already been synthesised using BTPP conditions (table 7, entry 7a-b; and table 8, entry 4). Alkylation of pyroglutamates **91/92**, under standard conditions, afforded compounds **243/244** and **245/246**, bearing substituted alkynes (scheme 75).



91, 92

243, 244 R = Me (72%)
245, 246 R = TMS (30%)

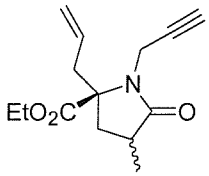
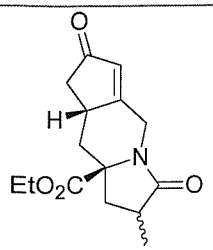
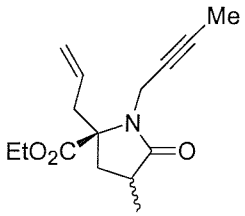
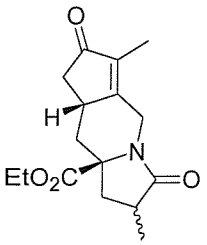
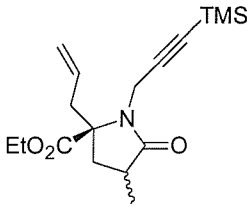
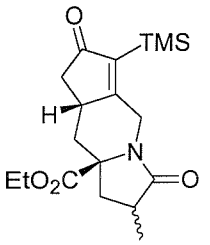
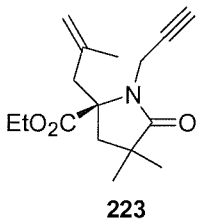
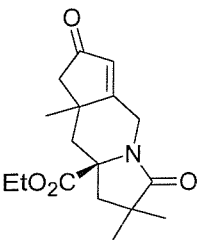
Scheme 75. Synthesis of cyclisation precursors bearing functionalised alkynes.

Compounds **243/244** were obtained in good 72% yield (1.4:1 ratio), but pyroglutamates **245/246**, with a terminal TMS group, were obtained in poor 30% yield (1.9:1 *cis/trans* ratio), due to loss of the TMS group and consequent formation of **218/219** (isolated in 31% yield). With these substrates in hand it was possible to test the Pauson-Khand cycloaddition.

4.6.4 Synthesis of Tricyclic Indolizidines

Substrates **218/219**, **243/244**, **245/246** and **223** were then reacted with $Co_2(CO)_8$, under Pauson-Khand conditions (table 11).

Table 11. Synthesis of tricyclic indolizidines.

Entry	Substrate	Conditions	Product	Yield
1a	 **218, 219**	$Co_2(CO)_8$ (1.0 eq), NMO (3.0 eq), 2d rt	 **247, 248** (1.8 : 1 ratio)	traces
1b		$Co_2(CO)_8$ (1.0 eq), μω 10 min at 100 °C		65%
2	 **243, 244**	$Co_2(CO)_8$ (1.0 eq), μω 10 min at 100 °C	 **249, 250** (1.2 : 1 ratio)	56%
3	 **245, 246**	$Co_2(CO)_8$ (1.0 eq), μω 10 min at 100 °C	 **251, 252** (2.1 : 1 ratio)	87%
4	 **223**	$Co_2(CO)_8$ (1.0 eq), μω 20 min at 100 °C	 **253**	0%

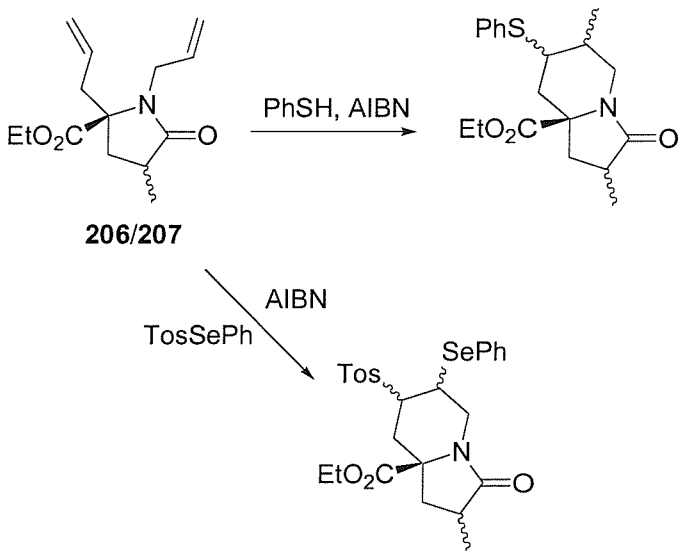
Reaction of substrates **218/219** with an equimolar amount of $Co_2(CO)_8$ at rt, using NMO as promoter, gave only traces of the tricyclic indolizidines **247** and **248**, even after a few days. The use of microwave irradiation, instead, afforded the desired compounds **247** (42%) and **248** (23%) in good overall 65% yield, in ten minutes only. Microwave irradiation was then used to test the other substrates. Compounds **243/244** and **245/246**, bearing a functionalised terminal alkyne, cyclised in good to excellent yield, under microwave irradiation. Indolizidines **249/250** and **251/252** were obtained as mixtures of two diastereoisomers (1.2:1 and 2.1:1 ratio, respectively), as expected according to Tanimori's work.[162] Surprisingly when pyroglutamate **223** was reacted, under the above conditions, with $Co_2(CO)_8$, no cyclised product was obtained.

4.7 Conclusions and Future Work

Thiol mediated radical cyclisations of functionalised alkenyl and alkynyl isocyanides have been successfully investigated both in solution and on solid phase. Pyrrolines and pyroglutamates have been synthesised in good to excellent yields. The microwave flash heating technology, employed to perform the above reactions, proved to be extremely useful. Pyrrolines and pyroglutamates were synthesised in five minutes with very good yields.

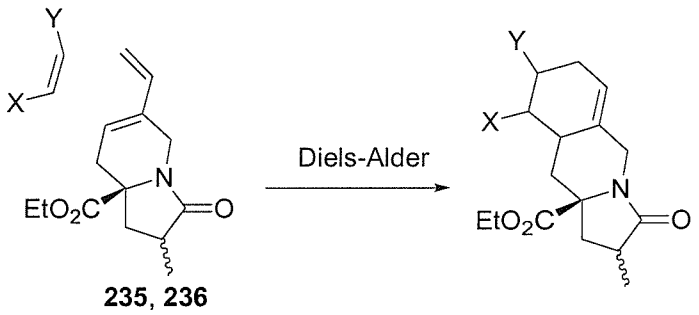
Indolizidines and bicyclic lactams were also successfully synthesised from simple dialkylated isocyanides via a novel thiol mediated radical cyclisation/alkylation/ring closing metathesis strategy, in good yields. It was also possible to access tricyclic indolizidines via Pauson-Khand cyclisation of functionalised pyroglutamates. The synthesised substrates could be used for the synthesis of natural products (for example coniceine) analogues, as outlined in scheme 71 (chapter 4).

Bis-alkenyl pyroglutamates (like **206/207**) could also be used as radical traps. Reaction with benzenethiol or tosylselenides could give access to functionalised indolizidines (scheme 76).



Scheme 76. Synthesis of functionalised indolizidines.

This strategy could be used as an alternative to the ring closing metathesis. Furthermore, indolizidines **235/236** bearing a diene could be reacted with suitable dienophiles to give the corresponding Diels-Alder products (scheme 77).



Scheme 77. Synthesis of tricyclic indolizidines via Diels-Alder reaction.

This would represent a novel route to functionalised tricyclic indolizidines.

Chapter 5

Experimental

General Experimental

Whenever possible solvents and reagents were purified according to the procedures outlined in Perin and Amarego, "*Purification of Laboratory Chemicals*", Pergamon Press, 3rd Edition (1989).[165]

All reactions requiring anhydrous conditions were conducted in oven-dried apparatus under inert atmosphere.

Flash column chromatography was performed according to the procedure outlined by Still, [166] using Sorbsil C60, 40-60 mesh silica.

Solvents were all commercial grade and used without further purification, unless otherwise stated. DCM and Toluene were distilled from calcium hydride, diethyl ether from sodium wire.

Instrumental

Proton NMR spectra were all obtained at 300 MHz on a Brucker AC 300 spectrometer, and at 400 MHz on a Brucker DPX400 spectrometer. Peak positions are quoted against the δ scale relative to the chloroform signal (δ 7.26), using the following abbreviations: singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), broad singlet (br s).
Carbon-13 NMR spectra at 75 MHz were obtained on a Brucker AC300 and at 100 MHz on a Brucker DPX400 spectrometer.

I.R. spectra were recorded on a Nicolet Impact 400, on a Bio-Rad Golden Gate ATR FT-IR and on a FTIR Perkin-Elmer 2000 Spectrometer coupled with an AutoIMAGE FTIR microscope.

U.V. analyses were performed on a Agilent 8453.

Mass spectrometry data was obtained on a ThermoQuest TraceMS gas chromatograph-mass spectrometer configured for open access and on a LC-MS.

Microwave reactions were performed on a Smith Microwave Synthesiser.

General Resin Procedures

Qualitative Ninhydrin Test

A known mass of resin (5mg) in a small test tube was treated with 6 drops of reagent A (preparation described below) and 2 drops of reagent B (preparation described below) and heated in a heating block at 110 ^{o}C for 10 minutes. A deep blue (or purple) coloration of the solution indicates a positive test.

Reagent A:

Solution 1: Reagent grade phenol (40 g) was dissolved in absolute ethanol (10 mL) with warming and then stirred over Amberlite mixed-bed resin MB3 (4g) for 45 minutes. The mixture was then filtered.

Solution 2: Potassium cyanide (65 mg) was dissolved in water (100 mL). A 2 mL aliquot of this solution was diluted with pyridine (freshly distilled from ninhydrin) and stirred over Amberlite mixed-bed resin MB3 (4g). The solution was filtered and mixed with solution 1 to give reagent A

Reagent B: Ninhydrin (2.5g) was dissolved in absolute ethanol (50 mL).

Quantitative Fmoc Test

A known quantity of resin (ca. 5mg) was treated with a solution of 20% piperidine in DMF (1 mL) for 15 minutes. The solution was filtered through glass wool and the volume of filtrate made up to 25 mL with 20% piperidine in DMF.

The absorbance at 302 nm was measured against a blank of 20% piperidine in DMF. The resin substitution was deduced from the following equation:

$$Mmol/g = [\ (A_{302} \times V) / (\varepsilon_{302} \times W)\ ] \times 10^3$$

Where A_{302} is the absorbance of the piperidyl–fulvene adduct, V is the total volume (mL), W is the weight of the resin sample (mg) and ε_{302} is the extinction coefficient of the adduct at 302 nm (7800 M^{-1} cm^{-1}).

Method A: Solid Phase Peptide Coupling Conditions [44, 108, 121]

i) The resin was swollen in the minimum volume of CH_2Cl_2 (2.0 mL/g of resin) for 30 minutes. *N*-Fmoc-amino acid (2 eq) and HOBt (2.0 eq) were dissolved in CH_2Cl_2 containing a few drops of DMF and stirred at rt for 10 minutes. DIC (2.2 eq) was added and the mixture stirred for a further 10 minutes before addition to the resin. The resin was shaken at rt for 3 hours to effect the coupling. The resin was then washed with DMF (25 mL x 3), DCM (25 mL x 3), MeOH (25 mL x 3) and Et_2O (25 mL x 3). The resin was then dried under high vacuum.

ii) The resin was swollen in CH_2Cl_2 (2.0 mL/g of resin) for 30 minutes. *N*-Fmoc-amino acid (2.0 eq) was dissolved in CH_2Cl_2 with a few drops of DMF and stirred at rt for 10 minutes. DIC (2.2 eq) and DMAP (0.3 eq) were added to the mixture and it was stirred for a further 5 minutes before addition to the resin. The resin was shaken at rt for 3 hours to allow complete esterification. The resin was then washed with DMF (25 mL x 3), DCM (25 mL x 3), MeOH (25 mL x 3) and Et_2O (25 mL x 3). It was then dried under high vacuum for 2 hours.

Method B: N-terminal Fmoc Removal. [44, 108, 121]

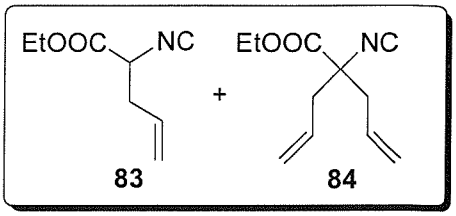
Cleavage of the Fmoc protecting group was performed using 20% piperidine in DMF with sequential treatments of 20 minutes (x 3). The resin was then filtered and washed with DMF (25 mL x 3), CH_2Cl_2 (25 mL x 3), MeOH (25 mL x 3) and Et_2O (25 mL x 3) and dried under high vacuum.

Method C: Cleavage of the Product from the Solid Support.

i) The resin (100 mg) was swollen in CH_2Cl_2 (1.0 mL) for 10 minutes. TFA (5.0 mL) in DCM (4.0 mL) was added and the resin stirred at rt for 3 to 5 hours. The resin was removed by filtration, washed with 50% TFA in DCM (3 x 5 mL) and the filtrates concentrated to dryness.

ii) The resin (100 mg) was swollen in THF (1.0 mL) for 10 minutes. Methylamine (3.0 mL) in DCM (2.0 mL) was added and the resin stirred at rt for 2 hours. The resin was removed by filtration, washed with THF (3 x 6 mL) and the filtrates concentrated to dryness.

EXPERIMENTAL-CHAPTER 2



Ethyl-2-isocyanopent-4-enoate (83)

Ethyl-2-allyl-2-isocyanopent-4-enoate (84)

An heterogeneous mixture of ethyl isocyanoacetate (3.0 mL, 25.8 mmol, 1.0 eq), allyl bromide (2.21 mL, 25.8 mmol, 1.0 eq), tetra-*N*-butyl-ammonium bromide (832.6 mg, 2.59 mmol, 0.1 eq), finely ground technical grade potassium carbonate (10.7 g, 77.5 mmol, 3.0 eq) and acetonitrile (50 mL) was refluxed with stirring for 20 hours. The reaction mixture was then cooled, filtered and the solvent removed *in vacuo*. The residue was then dissolved in dry diethyl ether 100 mL, and formation of a precipitate was observed, filtered and washed with water (3 x 100 mL), brine (3 x 100 mL) and dried over $MgSO_4$. After filtration the ether was removed *in vacuo* to give a crude brownish oil. Purification by flash chromatography (hexane:ethyl acetate 7:1) gave the title compound **83** as a yellow oil (1.19 g, 31%), R_f = 0.5, and the dialkylated isocyanide **84** as a yellow oil (0.9 g, 25%), R_f = 0.6.

Ethyl-2-isocyanopent-4-enoate (83)

δ_H (300 MHz; $CDCl_3$): 1.3 (3H, t, J = 7.0 Hz, CH_3CH_2O), 2.6-2.7 (2H, m, $CHCH_2$), 4.23 (2H, q, J = 7.0 Hz, CH_2O), 4.3 (1H, t, J = 5.0 Hz, NCH), 5.2-5.3 (2H, m, $CH=CH_2$), 5.7-5.9 (1H, m, $CH=CH_2$);

δ_C (75 MHz; $CDCl_3$): 14.1, 37.1, 56.4, 62.8, 120.6, 130.5, 160.3, 166.2;

I.R. (neat) ν_{max} = 2145, 1753 (cm^{-1});

The spectroscopic data agrees with Bachi.[22, 23]

Ethyl-2-allyl-2-isocyanopent-4-enoate (84)

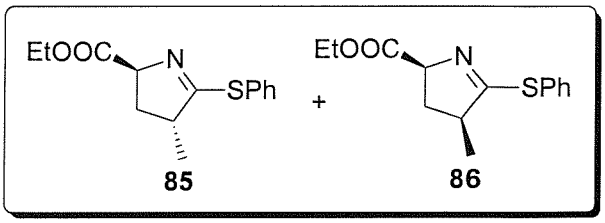
δ_H (300 MHz; $CDCl_3$): 1.3 (3H, t, J = 7.0 Hz, CH_3CH_2O), 2.5-2.7 (4H, m, 2 x CCH_2), 4.23 (2H, q, J = 7.0 Hz, CH_2O), 5.2-5.3 (4H, m, 2 x $CH=CH_2$), 5.7-5.9 (2H, m, 2 x $CH=CH_2$);

δ_C (75 MHz; $CDCl_3$): 14.3, 42.7, 56.3, 62.8, 121.2, 130.0, 159.6, 167.9;

GC/MS (C.I.). m/z, relative intensity and ion. 211 (12%), $[M+NH_4]^+$; 194 (100%), $[M+H]^+$; 168 (38%), $[(M-NC)+H]^+$; 152 (8%), $[(M-allyl)+H]^+$;

HRMS (EI): m/z calculated for $C_{11}H_{16}NO_2$ $[M+H]^+$ 194.11810, found 194.11811;

I.R. (neat) ν_{max} = 2138, 1746 (cm^{-1}).



***trans*-2*H*-Pyrrole-2-carboxylic acid, 3,4-Dihydro-4-methyl-5-(phenylthio), Ethyl ester (85)**

***cis*-2*H*-Pyrrole-2-carboxylic acid, 3,4-Dihydro-4-methyl-5-(phenylthio), Ethyl ester (86)**

A solution of ethyl-2-isocyanopent-4-enoate **83** (300 mg, 1.96 mmol, 1.0 eq), thiophenol (0.271 mL, 2.156 mmol, 1.1 eq) and AIBN (60.3 mg, 0.286 mmol, 0.2 eq) in dry toluene (40 mL) was stirred at 110 °C for 1 hour. The solution was then cooled to room temperature and the solvent evaporated *in vacuo*. The product was obtained a crude oil (450 mg). Purification by flash chromatography (hexane:ethyl Acetate, 6:1) gave the title compounds **85** and **86** as an inseparable mixture (1:1 by NMR), (colourless oil, 310 mg, 60%).

trans-2_H_-Pyrrole-2-carboxylic acid, 3,4-Dihydro-4-methyl-5-(phenylthio), Ethyl ester (85)

δ_H (300 MHz; $CDCl_3$): 1.15 (3H, d, J = 7.5 Hz, CH_3CH), 1.25 (3H, t, J = 7.0 Hz, CH_3CH_2O), 1.86 (1H, ddd, J = 13.0, 8.5, 6.0 Hz, NCHC*H*H), 2.31-2.40 (1H, m, NCHCH*H*), 3.1-3.2 (1H, m, CH_3CH), 4.15 (2H, q, J = 7.0 Hz, CH_2O), 4.62 (1H, m, CHN), 7.3-7.61 (5H, m, PhH);

δ_C (75 MHz; $CDCl_3$): 14.3, 18.6, 36.3, 45.8, 61.0, 72.2, 128.9, 129.1, 129.2, 129.5, 134.1, 172.6, 179.6;

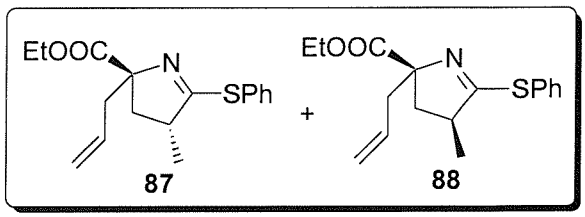
cis-2_H_-Pyrrole-2-carboxylic acid, 3,4-Dihydro-4-methyl-5-(phenylthio), Ethyl esters (86)

δ_H (300 MHz; $CDCl_3$): 1.15 (3H, d, J = 7.5 Hz, CH_3CH), 1.25 (3H, t, J = 7.0 Hz, CH_3CH_2O), 1.75 (1H, dt, J = 13.0, 6.5 Hz, NCHC*H*H), 2.52 (1H, dt, J = 12.5, 9.5 Hz, NCHCH*H*), 2.95-3.1 (1H, m, CH_3CH), 4.15 (2H, q, J = 7.0 Hz, CH_2O), 4.54 (1H, dd, J = 8.0, 7.5, CHN), 7.3-7.61 (5H, m, PhH);

δ_C (75 MHz; $CDCl_3$): 14.3, 17.9, 35.9, 46.4, 61.0, 72.5, 128.9, 129.1, 129.2, 129.5, 134.2, 173.0, 180.7;

ES$^+$/MS: m/z 264 (100%), $[M+H]^+$; m/z 286 (62%), $[M+Na]^+$; m/z 549 (20%), $[2M+Na]^+$;

The spectroscopic data was consistent with literature.[22]



trans-2_H_-Pyrrole-2-allyl-2-carboxylic acid, 3,4-Dihydro-4-methyl-5-(phenylthio), Ethyl ester (87)
cis-2_H_-Pyrrole-2-allyl-2-carboxylic acid, 3,4-Dihydro-4-methyl-5-(phenylthio), Ethyl ester (88)

A solution of ethyl-2-allyl-2-isocyanopent-4-enoate **84** (300 mg, 1.55 mmol), thiophenol (0.214 mL, 1.7 mmol) and AIBN (47.6 mg, 0.226 mmol) in dry toluene (40 mL) was stirred at 110 °C for 3.5 hours. The solution was then

cooled to room temperature and the solvent evaporated *in vacuo*, to give a crude oil (401 mg). Purification by flash chromatography, using hexane:ethyl acetate 6:1, gave the title compounds **87** and **88** (inseparable mixture, 1:1 by NMR) as a colorless oil (383 mg, 82%).

trans-2H-Pyrrole-2-allyl-2-carboxylic acid, 3,4-Dihydro-4-methyl-5-(phenylthio), Ethyl esters (87)

δ_H (300 MHz; $CDCl_3$): 1.15 (3H, t, J = 6.0 Hz, C*H*$_3$CH), 1.25 (3H, d, J = 7.0 Hz, C*H*$_3$CH$_2$O), 1.98 (1H, dd, J = 13.0, 6.0 Hz, NCC*H*H), 2.17-2.26 (1H, dd, J = 13.0, 9.5 Hz, NCCH*H*), 2.52-2.60 (2H, m, C*H*$_2$CH=CH$_2$), 3.12-3.26 (1H, m, CH$_3$C*H*), 4.15 (2H, q, J = 7.0 Hz, CH$_2$O), 5.04-5.15 (2H, m, CH=C*H*$_2$), 5.6-5.78 (1H, m, C*H*=CH$_2$), 7.27-7.58 (5H, m, PhH);

δ_C (75 MHz; $CDCl_3$): 14.3, 18.3, 39.6, 42.8, 46.4, 61.1, 81.2, 118.7, 128.6, 128.7, 129.1, 129.9, 133.2, 133.6, 173.4, 178.04;

cis-2H-Pyrrole-2-allyl-2-carboxylic acid, 3,4-Dihydro-4-methyl-5-(phenylthio), Ethyl esters (88)

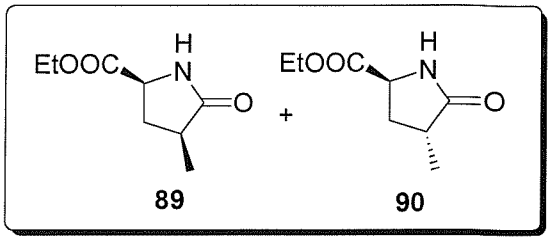
δ_H (300 MHz; $CDCl_3$): 1.15 (3H, d, J = 6.0 Hz, C*H*$_3$CH), 1.22 (3H, t, J = 7.0 Hz, C*H*$_3$CH$_2$O), 1.5-1.6 (1H, m, NCC*H*H), 2.51-2.65 (3H, m, C*H*$_2$CH=CH$_2$ and NCCH*H*), 2.94-3.06 (1H, m, CH$_3$C*H*), 4.15 (2H, q, J = 7.0 Hz, CH$_2$O), 5.04-5.12 (2H, m, CH=C*H*$_2$), 5.61-5.7 (1H, m, C*H*=CH$_2$), 7.3-7.61 (5H, m, PhH);

δ_C (75 MHz; $CDCl_3$): 14.3, 18.7, 40.3, 42.9, 46.6, 61.2, 81.4, 119.0, 128.6, 128.7, 129.1, 129.9, 133.2, 133.6, 174.05, 178.3;

ES$^+$/MS: m/z 304 (100%), $[M+H]^+$; m/z 326 (50%), $[M+Na]^+$; m/z 629 (25%), $[2M+Na]^+$;

I.R. (neat) ν_{max} = 1724, 1703, 1580, 1477, 1440, 1259 (cm^{-1});

Compounds proved to be unstable on standing, they hydrolysed to **91** and **92**.



89 90

Ethyl-*cis*-4-methyl-5-oxopyrrolidine-2-carboxylate (89)
Ethyl-*trans*-4-methyl-5-oxopyrrolidine-2-carboxylate (90)

Ethyl-2-isocyanopent-4-enoate **83** (100 mg, 0.65 mmol, 1.0 eq) was dissolved in dry toluene (10 mL) and stirred at room temperature for 5 min. 2-Mercapto-ethanol (50 μL, 0.718 mmol, 1.1 eq) and AIBN (35.6 mg, 0.169 mmol, 0.2 eq) in dry toluene (10 mL) were added and the total volume was brought up to 40 mL, by adding dry toluene, and the mixture heated at 40 °C for 1.5 hours (under nitrogen). The solvent was then evaporated to give a crude yellow oil (125 mg). Purification by flash chromatography (hexane:ethyl acetate, 1:1) afforded the title compounds **89** and **90** (98 mg, 88%) as an inseparable mixture (1:1 by NMR).

Ethyl-*cis*-4-methyl-5-oxopyrrolidine-2-carboxylate (89)

δ_H (300 MHz; $CDCl_3$): 1.22 (3H, d, J = 7.5 Hz, CH_3CH), 1.30 (3H, t, J = 7.0 Hz, CH_3CH_2O), 1.80 (1H, dt, J = 12.5, 9.5 Hz, NCHC*H*H), 2.45-2.59 (1H, m, CH_3CH), 2.71 (1H, dt, J = 13.0, 8.0 Hz, NCHCH*H*), 4.20 (1H, m, CHN), 4.24 (2H, q, J = 7.0 Hz, CH_2O), 6.2 (1H, br s, NH);

δ_C (75 MHz; $CDCl_3$): 14.1, 15.8, 33.5, 36.1, 53.8, 61.6, 172.1, 180.3;

Ethyl-*trans*-4-methyl-5-oxopyrrolidine-2-carboxylate (90)

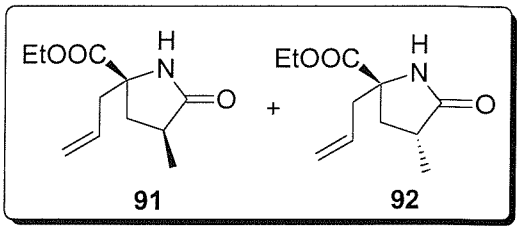
δ_H (300 MHz; $CDCl_3$): 1.22 (3H, d, J = 6.5 Hz, CH_3CH), 1.30 (3H, t, J = 7.0 Hz, CH_3CH_2), 1.95-2.11 (1H, m, NCHC*H*H), 2.45-2.58 (2H, m, CH_3CHCHH), 4.1-4.2 (1H, m, CHN), 4.23 (2H, q, J = 7.0, CH_2O), 6.2 (1H, br s, NH);

δ_C (75 MHz; $CDCl_3$): 14.2, 15.9, 33.6, 34.6, 53.9, 61.6, 172.5, 181.2;

ES$^+$/MS: m/z 172 (3%), $[M+H]^+$; m/z 194 (100%), $[M+Na]^+$; m/z 365 (47%), $[2M+Na]^+$;

Data agrees with Bachi.[22]

Compounds **89** and **90** were also synthesised by direct hydrolysis of **85** and **86** with 95% TFA. Data agrees with that above.



Ethyl-2-allyl-*cis*-4-methyl-5-oxopyrrolidine-2-carboxylate (91)
Ethyl-2-allyl-*trans*-4-methyl-5-oxopyrrolidine-2-carboxylate (92)

Ethyl-2-allyl-2-isocyanopent-4-enoate **84** (85 mg, 0.435 mmol, 1.0 eq) was dissolved in dry toluene (5 mL), then a solution of AIBN (25 mg, 0.113 mmol, 0.26 eq) and 2-mercapto-ethanol (67 μL, 0.957 mmol, 2.2 eq) in dry toluene (15 ml) was added and the resulting mixture stirred at 40 °C for 7 hours, under nitrogen atmosphere. The reaction mixture was then cooled and evaporated to dryness. It was obtained 109 mg of crude, as a white solid. The crude was dissolved in ethyl acetate (10 mL) and washed with H_2O (3 x 6 mL) to remove the unreacted thiol. TLC analysis confirmed the disappearance of the thiol. Purification by flash chromatography (hexane:ethyl Acetate, 1:1) afforded the title compounds **91** and **92** (88 mg, 96%) as an inseparable mixture (1:1 by NMR).

Ethyl-2-allyl-*cis*-4-methyl-5-oxopyrrolidine-2-carboxylate (91)

δ_H (300 MHz; $CDCl_3$): 1.13 (3H, d, J = 7.0 Hz, C*H*$_3$CH), 1.23 (3H, t, J = 7.0 Hz, C*H*$_3$CH$_2$O), 1.68 (1H, dd, J = 13.0, 10.5 Hz, NCC*H*H), 2.32-2.42 (1H, m, C*H*HCH=CH$_2$), 2.47-2.54 (2H, m, CH*H*CH=CH$_2$ and CH$_3$C*H*), 2.71 (1H, dd, J = 13.0, 8.0 Hz, NCCH*H*), 4.1 (2H, q, J = 7.0 Hz, CH$_2$O), 5.07-5.15 (2H, m, CH=C*H*$_2$), 5.5-5.72 (1H, m, C*H*=CH$_2$), 6.59 (1H, br s, NH);

δ_C (75 MHz; $CDCl_3$): 14.5, 16.1, 35.8, 38.8, 43.8, 62.0, 63.4, 120.6, 131.4, 173.5, 179.2;

Ethyl-2-allyl-*trans*-4-methyl-5-oxopyrrolidine-2-carboxylate (92)

δ_H (300 MHz; $CDCl_3$): 1.13 (3H, d, J = 7.0 Hz, CH_3CH), 1.24 (3H, t, J = 7.0 Hz, CH_3CH_2O), 2.05 (1H, dd, J = 13.5, 8.5 Hz, NCC*H*H), 2.32-2.42 (1H, m, C*H*HCH=CH_2), 2.38 (1H, dd, J = 13.0, 9.0 Hz, NCCH*H*), 2.47-2.54 (1H, m, CH*H*CH=CH_2), 2.60 (1H, m, CH_3CH); 4.17 (2H, q, J = 7.0 Hz, CH_2O), 5.07-5.15 (2H, m, CH=CH_2), 5.5-5.72 (1H, m, CH=CH_2), 6.64 (1H, br s, NH);

δ_C (75 MHz; $CDCl_3$): 14.5, 16.5, 35.9, 39.7, 43.8, 62.1, 63.6, 120.8, 131.6, 173.6, 179.8;

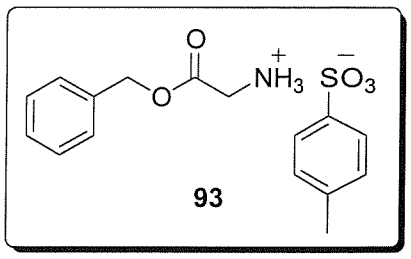
ES$^+$/MS: m/z 212 (100%), $[M+H]^+$; m/z 234 (43%), $[M+Na]^+$; m/z 423 (55%), $[2M+H]^+$; m/z 445 (65%), $[2M+Na]^+$;

HRMS (ES$^+$): m/z calculated for $C_{11}H_{17}NO_3$ $[M+H]^+$ 212.1281, found 212.1279.

I.R. (neat) ν_{max} = 1700, 1460 (cm^{-1});

M.P. = 45°-47°C

Elemental Analysis: Found C, 62.26; H, 8.15; N, 6.58: $C_{11}H_{17}NO_3$ requires C, 62.54; H, 8.11; N, 6.63.



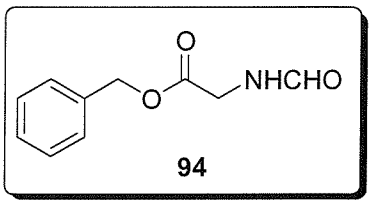
93

Benzyl glycinate-*p*-toluensulfonate

In a two necked round bottom flask, fitted with a reflux condenser and an addition funnel, was placed glycine (7.0 g, 0.093 mol), *p*-toluensulfonic acid monohydrate (18.5 g, 0.097 mol) and benzyl alcohol (18.6 mL, 0.179 mmol). The mixture was heated under gentle reflux for 1 hour. Toluene (18.6 mL) was placed in the addition funnel, and a Dean-Stark apparatus attached to the flask. Approximately 5.0 mL of toluene was added and then the remaining

toluene added over a period of 15 minutes. The resulting solution was refluxed for two hours and approximately 8.0 mL of H_2O azeotropically removed. The mixture was then poured in a beaker and cooled in ice. The resulting precipitate was filtered, washed with anhydrous diethyl ether and dried under high vacuum overnight to yield the title compound **93** as a white solid (27g, 87%).

δ_H (300 MHz; CD_3OD): 2.21 (3H, s, CH_3Ph), 3.75 (2H, s, NCH_2), 5.3 (2H, s, $PhCH_2$), 6.96 (2H, d, J = 7.0 Hz, CH_3PhH), 7.16-7.22 (5H, m, PhH), 7.66 (2H,d, J = 7.0 Hz, CH_3PhH).
M.P.: 116-118 °C (Lit.[102] mp 116-125 °C).
Data agrees with literature.[102]



94

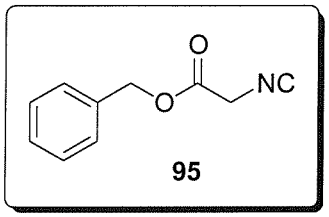
Benzyl-*N*-formyl glycinate

Benzyl glycinate-*p*-toluensulfonate **93** (5.0 g, 14.5 mmol), was stirred for 5 minutes in THF (25.0 mL), a solution of Et_3N (4.2 mL, 28.0 mmol) was then added and the resulting solution stirred for further 15 minutes. Formic acid (193 mL, 5.02 mol) was then slowly added over five minutes and then acetic anhydride (63.5 mL, 0.625 mol) was added dropwise to the reaction mixture. The resulting solution was stirred at rt for further 3 hours. H_2O (60 ml) was added and the mixture extracted with dichloromethane (3 x 100 mL). The extracts were combined and washed with 5% aq. $NaHCO_3$ (3 x 100 mL) and H_2O (3 x 100 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield the title compound **94** as a yellow oil (1.96 g, 70%).

δ_H (300 MHz; $CDCl_3$): 4.0 (2H, dd, J = 5.0, 2.0 Hz, CH_2NH), 5.05 (2H, s, $PhCH_2$), 6.6 (1H, br s, NH), 7.2 (5H, s, PhH), 8.08 (1H, s, CHO);

δ_C (75 MHz; $CDCl_3$): 40.1, 67.4, 128.5, 128.7, 128.8, 135.2, 161.7, 169.6.

Data agrees with literature.[102]



95

Benzyl isocyanoacetate

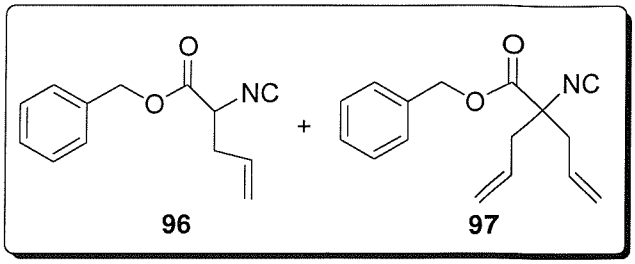
Benzyl-*N*-formyl glycinate (500 mg, 2.59 mmol) was dissolved in dry dichloromethane (6 mL) and the solution stirred at 0 °C for 5 minutes. Triethylamine (1.309 mL, 9.065 mmol, 3.5 eq) was then added and the resulting solution stirred at 0 °C for further 10 minutes (under inert atmosphere, N_2). Phosphoryl chloride (0.266 mL, 2.849 mmol, 1.1 eq) was added dropwise over a few minutes, the resulting reaction mixture (which turned to brownish) was stirred at 0 °C for 1 hour and was then poured into ice water (37 g) containing sodium hydrogen carbonate (3.7 g). After stirring for 2 hours, water (30 mL) and dichloromethane (50 mL) were added, the organic layer separated and washed with water (3 x 50 mL), dried over $MgSO_4$ and evaporated to give 385 mg of brownish crude (liquid). Purification by flash chromatography (hexane:ethyl acetate, 4:1) afforded compound **95** (369 mg, 81%) as a yellowish oil.

δ_H (300 MHz; $CDCl_3$): 4.2 (2H, s, CH_2NC), 5.2 (2H, s, $PhCH_2$), 7.35 (5H, s, Ph*H*);

δ_C (75 MHz; $CDCl_3$): 43.7, 68.4, 128.8, 128.9, 129.0, 129.4, 161.3, 164.1;

I.R. (neat) ν_{max} = 2161, 1754, 1190 (cm^{-1}).

Data agrees with literature.[102]



Benzyl-2-isocyanopent-4-enoate (96)

Benzyl-2-allyl-2-isocyanopent-4-enoate (97)

A heterogeneous mixture of **95** (321 mg, 1.83 mmol), allyl bromide (180 μL, 2.108 mmol), tetrabutylammonium bromide (67.8 mg, 0.21 mmol), potassium carbonate (873 mg, 6.324 mmol) and acetonitrile (20 mL) was refluxed with stirring for 22 hours. The reaction mixture was then cooled, filtered, and the solvent removed *in vacuo*, the residue was then dissolved in dry diethyl ether, filtered and washed with water (3 x 100 mL), brine (3 x 100 mL) and dried over $MgSO_4$. After filtration the solvent was evaporated to give a crude yellowish oil (343 mg). Purification by flash chromatography (hexane:ethyl acetate, 6:1) afforded the title compound **96** as a brown oil (164.7 mg, 42%), R_f = 0.5 and compound **97** as a brown oil (120 mg, 30%), R_f = 0.6.

Benzyl-2-isocyanopent-4-enoate (96)

δ_H (300 MHz; $CDCl_3$): 2.56-2.76 (2H, m, $CH_2CH=CH_2$); 4.37 (1H, dd, J = 7.5, 5.0, CHNC); 5.18-5.22 (2H, m, $CH=CH_2$); 5.25 (2H, s, $PhCH_2$); 5.7-5.86 (1H, m, $CH=CH_2$); 7.3 (5H, s, PhH);

δ_C (75 MHz; $CDCl_3$): 37.1, 68.4, 120.8, 121.3, 128.6, 128.8, 128.9, 130.3, 134.7, 160.6, 166.1;

GC/MS (C.I.). m/z, relative intensity and ion. 233 (40%), $[M+NH_4]^+$; 216 (4%), $[M+H]^+$; 108 (54%), $[ArCH_2O+H]^+$; 91 (100%), $[ArCH_2]^+$;

I.R. (neat) ν_{max} = 2147, 1750 (cm^{-1});

HRMS (EI): m/z calculated for $C_{13}H_{12}NO_2$ (M-H) 214.08666, found 214.08680.

Benzyl-2-allyl-2-isocyanopent-4-enoate (97)

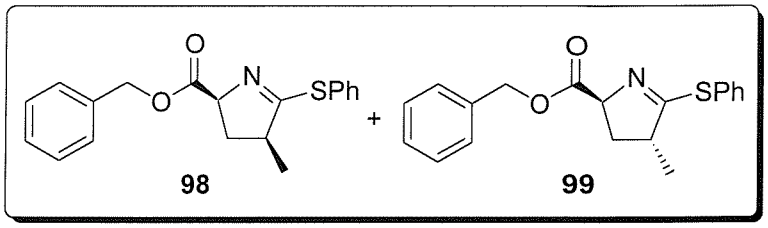
δ_H (300 MHz; $CDCl_3$): 2.51-2.72 (4H, m, 2 x $CH_2CH=CH_2$); 5.13-5.21 (4H, m, 2 x $CH=CH_2$); 5.23 (2H, s, $PhCH_2$); 5.69-5.84 (2H, m, 2 x $CH=CH_2$); 7.4 (5H, s, PhH);

δ_C (75 MHz; $CDCl_3$): 42.7, 68.2, 121.3, 128.6, 128.8, 129.9, 134.8, 160.0, 167.8;

GC/MS (C.I.): m/z, relative intensity and ion. 256 (4%), $[M+H]^+$; 108 (12%), $[PhCH_2O+H]^+$; 91 (100%), $[PhCH_2]^+$;

I.R. (neat) ν_{max} = 2136, 1750 (cm^{-1});

HRMS (EI): m/z calculated for $C_{16}H_{16}NO_2$ (M-H) 254.11825, found 254.11810.



2*H*-Pyrrole-2-carboxylic acid, 3,4-Dihydro-*cis*-4-methyl-5-(phenylthio), Benzyl ester (98)

2*H*-Pyrrole-2-carboxylic acid, 3,4-Dihydro-*trans*-4-methyl-5-(phenylthio), Benzyl ester (99)

A solution of benzyl-2-isocyanopent-4-enoate **96** (97 mg, 0.451 mmol, 1.0 eq), thiophenol (62 µL, 0.496 mmol, 1.1 eq) and AIBN (25 mg, 118 mmol, 0.2 eq) in dry toluene (20 mL) was stirred at 110 °C for 1 hour. The solution was then cooled to room temperature and the solvent evaporated *in vacuo*. It was obtained a crude yellow oil. Purification by flash chromatography (hexane: ethyl acetate, 6:1) gave the title compounds **98** and **99**, 1:1 mixture (by NMR), as a colourless oil (100 mg, 65%).

cis-2*H*-Pyrrole-2-carboxylic acid, 3,4-Dihydro-4-methyl-5-(phenylthio), Benzyl ester (98)

δ_H (300 MHz; $CDCl_3$): 1.29 (3H, d, J = 7.0 Hz, CH_3CH); 1.82 (1H, dt, J = 12.5, 6.5 Hz, NCHC*H*H); 2.58 (1H, dt, J = 13.0, 8.5 Hz, NCHCH*H*); 3.0-3.1 (1H, m, CH_3CH); 4.66 (1H, dt, J = 6.5, 1.5 Hz, CHN); 5.2 (2H, s, $PhCH_2$); 7.3-7.7 (10H, m, PhH);

δ_C (75 MHz; $CDCl_3$): 18.0, 36.3, 45.9, 66.7, 72.2, 128.2, 128.3, 128.4, 128.7, 129.1, 129.2, 129.5, 134.4, 172.5, 181.0;

trans-2*H*-Pyrrole-2-carboxylic acid, 3,4-Dihydro-4-methyl-5-(phenylthio), Benzyl ester (99)

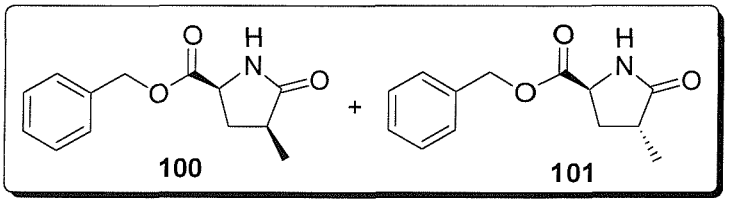
δ_H (300 MHz; $CDCl_3$): 1.23 (3H, d, J = 7.0 Hz, CH_3CH); 1.92 (1H, m, NCHC*H*H); 2.43 (1H, ddd, J = 13.5, 8.0, 4.0 Hz, NCHCH*H*); 3.12-3.25 (1H, m, CH_3CH); 4.74-4.78 (1H, ddd, J = 12.5, 5.0, 1.5 Hz, CHN); 5.2 (2H, s, $PhCH_2$); 7.3-7.7 (10H, m, PhH);

δ_C (75 MHz; $CDCl_3$): 18.6, 35.9, 46.4, 66.7, 72.4, 128.2, 128.3, 128.4, 128.7, 129.1, 129.2, 129.5, 134.4, 172.9, 179.9;

GC/MS (C.I.). m/z, relative intensity and ion. 326 (4%), $[M+H]^+$; 234 (18%), $[M-PhCH_2]^+$; 108 (30%), $[PhCH_2O+H]^+$; 91 (100%), $[PhCH_2]^+$; 78 (18%), $[Ph+H]^+$;

I.R. (neat) ν_{max} = 1743, 1703, 1264 (cm^{-1}).

Compounds proved to be unstable on standing and hydrolysed to **100** and **101**.



Benzyl-_cis_-4-methyl-5-oxopyrrolidine-2-carboxylate (100)

Benzyl-_trans_-4-methyl-5-oxopyrrolidine-2-carboxylate (101)

Benzyl-2-isocyanopent-4-enoate **96** (100 mg, 0.465 mmol, 1.0 eq) was dissolved in dry toluene (10 mL) and stirred at room temperature for 5 min.

2-Mercaptoethanol (71.2 μL, 1.022 mmol, 2.2 eq) and AIBN (25.2 mg, 0.12 mmol, 0.2 eq) in dry toluene (10 mL) were added and the total volume was brought up to 35 mL, by adding dry toluene, and the mixture heated at 40 °C for 5.5 hours (under nitrogen). The solvent was then evaporated to give a crude white solid (184 mg). Purification by flash chromatography (hexane:ethyl acetate, 1:1) afforded the title compounds **101** (47.4 mg, 43.5%) and **100** (50.5 mg, 46.5%), as white solids.

Benzyl-*cis*-4-methyl-5-oxopyrrolidine-2-carboxylate (100)

δ_H (300 MHz; $CDCl_3$): 1.19 (3H, d, J = 7.5 Hz, C*H*$_3$CH); 1.78 (1H, dt, J = 12.5, 9.0 Hz, NCHC*H*H); 2.42-2.57 (1H, m, CH_3C*H*); 2.69 (1H, dt, J = 13.0, 8.0 Hz, NCHCH*H*); 4.24 (1H, t, J = 8.0 Hz, CHN); 5.13 (2H, s, $PhCH_2$); 6.7 (1H, br s, NH); 7.3 (5H, s, PhH);

δ_C (75 MHz; $CDCl_3$): 16.0, 33.6, 36.0, 53.8, 67.4, 128.5, 128.7, 128.8, 135.2, 171.8, 179.8;

GC/MS (C.I.). m/z, relative intensity and ion. 234 (22%), $[M+H]^+$; 108 (24%), $[PhCH_2O+H]^+$; 91 (100%), $[PhCH_2]^+$; Retention time: 9.08 min;

I.R. (neat) ν_{max} = 1740 (s), 1699 (s) (cm^{-1}).

HRMS (ES^+): m/z calculated for $C_{13}H_{15}NO_3Na$ $[M+Na]^+$ 256.0945230, found 256.0944144;

M.P. = 96°-98°C;

Elemental Analysis: Found C, 65.10; H, 6.31; N, 5.78. $C_{13}H_{15}NO_3$ requires C, 66.94; H, 6.48; N, 6.00.

Benzyl-*trans*-4-methyl-5-oxopyrrolidine-2-carboxylate (101)

δ_H (300 MHz; $CDCl_3$): 1.18 (3H, d, J = 7.0 Hz, C*H*$_3$CH); 2.0-2.1 (1H, m, NCHC*H*H); 2.4-2.6 (2H, m, NCHCH*H* and CH_3C*H*); 4.2 (1H, dd, 7.5, 3.0 Hz, CHN); 5.19 (2H, s, $PhCH_2$); 6.9 (1H, br s, NH); 7.35 (5H, s, PhH);

δ_C (75 MHz; $CDCl_3$): 15.8, 33.6, 34.6, 53.7, 67.3, 128.4, 128.7, 128.8, 135.3, 172.3, 180.9;

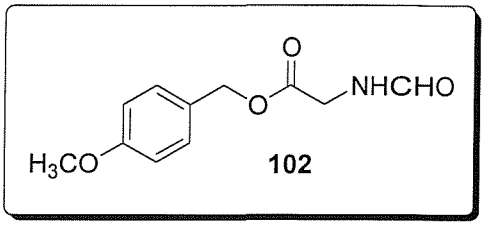
I.R. (neat) ν_{max} = 1743, 1700 (cm^{-1});

ES$^+$/MS: m/z 234 (80%), $[M+H]^+$; m/z 255 (48%), $[M+Na]^+$; m/z 489 (100%), $[2M+Na]^+$;

GC/MS (C.I.). m/z, relative intensity and ion. 234 (70%), $[M+H]^+$; 98 (100%), $[M-PhCH_2OCO]^+$; 91 (60%), $[PhCH_2]^+$;

HRMS (ES$^+$): m/z calculated for $C_{13}H_{16}NO_3$ $[M+H]^+$ 234.1124698, found 234.1124500;

M.P. = 82°-83°C;



102

***p*-Methoxybenzyl-formyl-glycinate**

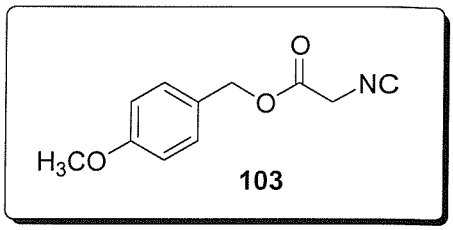
Formylglycine (870 mg, 8.43 mmol, 1.0 eq) was dissolved in 100 mL of dry CH_2Cl_2, stirred at rt for 10 minutes, then DCC (1.9 g, 9.28 mmol, 1.1 eq) and DMAP (113 mg, 0.84 mmol, 0.1 eq) were added and the resulting solution stirred for further 10 minutes. *p*-Methoxybenzyl alcohol (1.15 mL, 9.28 mmol, 1.1 eq) was then added and the resulting reaction mixture was stirred at rt for 12 hours. The reaction mixture was then filtered and the organic phase washed with H_2O (3 x 100 mL), 5% AcOH (3 x 100 mL), H_2O (3 x 100 mL) and dried over $MgSO_4$. Filtration and evaporation of the solvent gave a white solid which was purified by flash column chromatography (hexane : ethyl acetate, 2:1) to give the title compound **102** as a white solid (1.07 g, 61%). R_f = 0.2.

δ_H (300 MHz; $CDCl_3$): 3.8 (3H, s, CH_3O), 4.1 (2H, d, J = 6.0 Hz, CH_2NH), 5.1 (2H, s, $PhCH_2$), 6.6 (1H, br s, NH), 6.9 (2H, d, J = 9.0 Hz, PhH), 7.3 (2H, d, J = 9.0 Hz, PhH), 8.2 (1H, s, CHO);

δ_C (75 MHz; $CDCl_3$): 40.1, 55.4, 67.4, 114.1, 127.2, 130.5, 160.0, 161.4, 169.6;

Elemental analysis: Found C, 59.17; H, 5.72; N, 6.27: $C_{11}H_{13}NO_4$ requires C, 59.19; H, 5.87; N, 6.27;

M. P. = 58-60 °C.



103

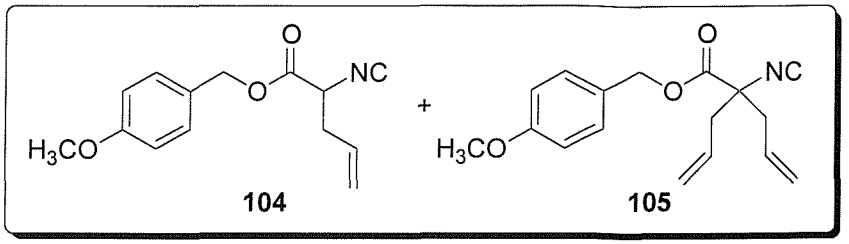
***p*-Methoxybenzyl-isocyanoacetate**

Compound **102** (1.07 g, 4.8 mmol, 1.0 eq) was dissolved in dry CH_2Cl_2 (15 mL) and the resulting solution stirred at 0 °C for 5 minutes. Freshly distilled triethylamine (2.5 mL, 17 mmol, 3.5 eq) was added and the stirring continued at 0 °C for further 10 minutes, $POCl_3$ (493.6 μL, 5.2 mmol, 1.1 eq) was then added and the reaction mixture stirred at 0 °C for 1 hour. It was then poured into ice water (21.0 g) containing sodium hydrogen carbonate (2.1 g). After stirring for 2 hours, H_2O (50 mL) and CH_2Cl_2 (50 mL) were added and the organic layer separated. It was then washed with water (3 x 50 mL), dried over $MgSO_4$ and the solvent evaporated to dryness to give a brownish oil. Purification by flash column chromatography, using dichloromethane as eluting solvent, afforded isocyanide **103** (798 mg, 81%) as a yellow liquid. R_f = 0.5.

δ_H (300 MHz; $CDCl_3$): 3.8 (3H, s, CH_3O), 4.2 (2H, s, CH_2NC), 5.2 (2H, s, $PhCH_2$), 6.9 (2H, d, J = 9.0 Hz, PhH), 7.3 (2H, d, J = 9.0 Hz, PhH);

δ_C (75 MHz; $CDCl_3$): 43.7, 55.5, 68.3, 114.2, 126.6, 130.7, 160.2, 164.1, 174.0;

I.R. (neat) ν_{max} = 2159, 1758, 1620 (cm^{-1}).



_p_-Methoxybenzyl-2-isocyanopent-4-enoate (104)

_p_-Methoxybenzyl-2-allyl-2-isocyanopent-4-enoate (105)

A heterogeneous mixture of **103** (798 mg, 3.89 mmol, 1.0 eq), allyl bromide (300 μL, 3.5 mmol, 0.9 eq), tetrabutylammonium bromide (125 mg, 0.389 mmol, 0.1 eq), potassium carbonate (1.61 g, 11.6 mmol, 3.0 eq) and acetonitrile (40 mL) was refluxed with stirring for 22 hours. The reaction mixture was then cooled, filtered, and the solvent removed *in vacuo*, the residue was then dissolved in dry diethyl ether, filtered and washed with water (3 x 100 mL), brine (3 x 100 mL) and dried over $MgSO_4$. After filtration the solvent was evaporated to give a crude yellowish oil. Purification by flash chromatography (hexane:ethyl acetate, 4:1) afforded the title compound **104** as an oil (317 mg, 37%), R_f = 0.4, and compound **105** as an oil (204 mg, 20%), R_f = 0.5.

_p_-Methoxybenzyl-2-isocyanopent-4-enoate (104)

δ_H (300 MHz; $CDCl_3$): 2.53-2.74 (2H, m, $CH_2CH{=}CH_2$); 3.8 (3H, s, CH_3O), 4.3 (1H, dd, J = 8.0, 5.0 Hz, CHNC); 5.18-5.22 (2H, m, $CH{=}CH_2$); 5.25 (2H, s, $PhCH_2$); 5.6-5.8 (1H, m, $CH{=}CH_2$); 6.9 (2H, d, J = 9.0 Hz, PhH), 7.3 (2H, d, J = 9.0 Hz, PhH);

δ_C (75 MHz; $CDCl_3$): 37.1, 50.9, 55.4, 68.3, 114.2, 120.7, 126.7, 130.3, 130.6, 160.1, 166.1;

GC/MS (C.I.). m/z, relative intensity and ion. 263 (8%), $[M+NH_4]^+$; 246 (28%), $[M+H]^+$; 121 (100%), $[MeOArCH_2]^+$;

I.R. (neat) ν_{max} = 2149, 1754, 1612, 1514 (cm^{-1});

HRMS (EI): m/z calculated for $C_{14}H_{15}NO_3$ (M^+) 245.10497, found 245.10519.

***p*-Methoxybenzyl-2-allyl-2-isocyanopent-4-enoate (105)**

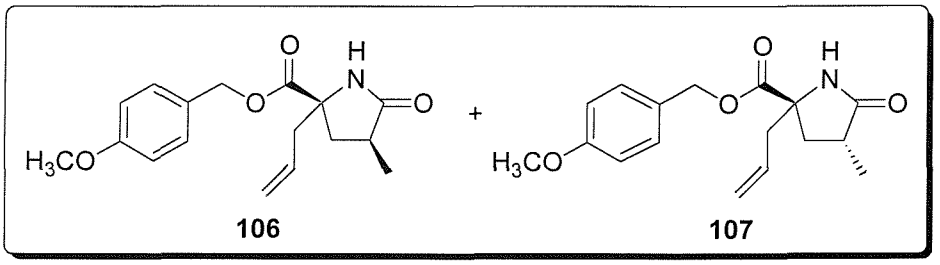
δ_H (300 MHz; $CDCl_3$): 2.42-2.72 (4H, m, 2 x $CH_2CH=CH_2$); 3.8 (3H, s, CH_3O), 5.1 (2H, s, $PhCH_2$), 5.12-5.21 (4H, m, 2 x $CH=CH_2$), 5.6-5.8 (2H, m, 2 x $CH=CH_2$), 6.9 (2H, d, J = 9.0 Hz, PhH), 7.3 (2H, d, J = 9.0 Hz, PhH);

δ_C (75 MHz; $CDCl_3$): 42.6, 55.4, 68.1, 114.1, 121.2, 127.0, 129.9, 130.5, 160.1, 167.7;

GC/MS (C.I.). m/z, relative intensity and ion. 303 (16%), $[M+NH_4]^+$; 286 (50%), $[M+H]^+$; 121 (100%), $[MeOArCH_2]^+$;

I.R. (neat) ν_{max} = 2145, 1760 (cm^{-1});

HRMS (EI): m/z calculated for $C_{17}H_{19}NO_3$ $(M)^+$ 285.13656, found 285.13649.



106 **107**

***p*-Methoxybenzyl-2-allyl-*cis*-4-methyl-5-oxopyrrolidine-2-carboxylate (106)**

***p*-Methoxybenzyl-2-allyl-*trans*-4-methyl-5-oxopyrrolidine-2-carboxylate (107)**

p-Methoxybenzyl-2-allyl-2-isocyanopent-4-enoate **105** (102 mg, 0.357 mmol, 1.0 eq) was dissolved in dry toluene (10 mL) and stirred at room temperature for 5 min. 2-Mercaptoethanol (55 μL, 0.787 mmol, 2.2 eq) and AIBN (19 mg, 0.092 mmol, 0.26 eq) in dry toluene (10 mL) were added and the total volume was brought up to 40 mL, by adding dry toluene, and the mixture heated at 40 °C for 12 hours (under nitrogen). The solvent was then evaporated to give a crude colourless oil (150 mg). Purification by flash chromatography (hexane:ethyl Aacetate, 1:1), afforded the title compounds **106** and **107** (colourless oil, 72 mg, 67%) as an inseparable mixture (2:1 by NMR), R_f = 0.42.

_p_-Methoxybenzyl-2-allyl-_cis_-4-methyl-5-oxopyrrolidine-2-carboxylate (106)

δ_H (300 MHz; $CDCl_3$): 1.11 (3H, d, J = 7.0 Hz, CH_3CH), 1.68 (1H, dd, J = 12.0, 9.0 Hz CH_3CHCHH), 2.32-2.42 (1H, m, $CHHCH=CH_2$), 2.45-2.54 (2H, m, $CHHCH=CH_2$ and CH_3CH), 2.70 (1H, m, CH_3CHCHH), 3.8 (3H, s, CH_3O), 5.07-5.17 (2H, m, $CH=CH_2$), 5.49-5.72 (1H, m, $CH=CH_2$), 6.2 (1H, br s, NH), 6.9 (2H, d, J = 9.0 Hz, PhH), 7.3 (2H, d, J = 9.0 Hz, PhH);

δ_C (75 MHz; $CDCl_3$): 15.9, 35.5, 38.5, 43.6, 55.4, 63.2, 67.4, 114.1, 120.5, 127.3, 130.3, 131.05, 159.9, 173.1, 178.9;

GC/MS (C.I.). m/z, relative intensity and ion. 304 (60%), $[M+H]^+$; 121 (100%) $[MeOArCH_2]^+$; 138 (50%), $[MeOArCH_2O]^+$; Retention time: 15.95 min;

_p_-Methoxybenzyl-2-allyl-_trans_-4-methyl-5-oxopyrrolidine-2-carboxylate (107)

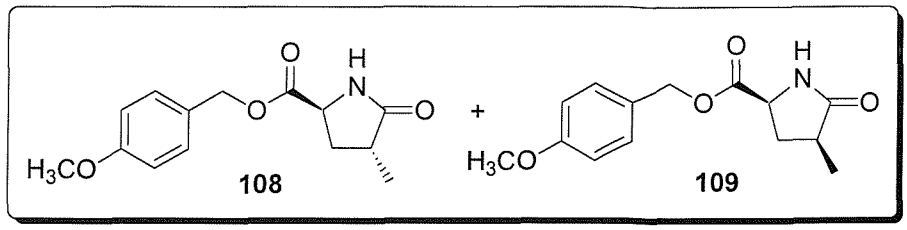
δ_H (300 MHz; $CDCl_3$): 1.16 (3H, d, J = 7.0 Hz, CH_3CH), 1.9-2.1 (1H, dd, J = 13.5, 8.5 Hz, CH_3CHCHH), 2.32-2.42 (1H, m, $CHHCH=CH_2$), 2.45-2.54 (1H, m, $CHHCH=CH_2$), 2.49 (1H, dd, J = 13.0, 9.0 Hz, CH_3CHCHH), 2.60 (1H, m, CH_3CH); 3.8 (3H, s, CH_3O), 5.07-5.17 (2H, m, $CH=CH_2$), 5.49-5.72 (1H, m, $CH=CH_2$), 6.38 (1H, br s, NH), 6.9 (2H, d, J = 9.0 Hz, PhH), 7.3 (2H, d, J = 9.0 Hz, PhH);

δ_C (75 MHz; $CDCl_3$): 16.2, 35.6, 39.5, 43.6, 55.4, 63.4, 67.4, 114.1, 120.7, 127.4, 130.4, 131.2, 159.9, 173.3, 179.4;

GC/MS (C.I.). m/z, relative intensity and ion. 304 (48%), $[M+H]^+$; 121 (100%) $[MeOArCH_2]^+$; 138 (20%), $[MeOArCH_2O]^+$; Retention time: 16.00 min;

I.R. (neat) ν_{max} = 1743, 1700 (cm^{-1});

HRMS (ES^+): m/z calculated for $C_{17}H_{22}NO_4$ $[M+H]^+$ 304.1544, found 304.1542.



_p_-Methoxybenzyl-_trans_-4-methyl-5-oxopyrrolidine-2-carboxylate (108)
_p_-Methoxybenzyl-_cis_-4-methyl-5-oxopyrrolidine-2-carboxylate (109)

_p_-Methoxybenzyl-2-isocyanopent-4-enoate **104** (125 mg, 0.51 mmol, 1.0 eq) was dissolved in dry toluene (15 mL) and stirred at room temperature for 5 min. 2-mercaptoethanol (78.7 μL, 1.12 mmol, 2.0 eq) and AIBN (10 mg, 0.051 mmol, 0.1 eq) in dry toluene (15 mL) were added and the total volume was brought up to 50 mL, by adding dry toluene, and the mixture heated at 40 °C for 24 hours (under nitrogen). The solvent was then evaporated and the crude purified by flash chromatography (hexane:ethyl acetate, 1:1), to give the title compound **108** (yellowish oil, 53 mg, 40%), R_f = 0.19 and compound **109** as a yellowish oil (60 mg, 45%), R_f = 0.10.

_p_-Methoxybenzyl-_trans_-4-methyl-5-oxopyrrolidine-2-carboxylate (108)

δ_H (400 MHz; $CDCl_3$): 1.13 (3H, d, J = 7.0 Hz, C*H*$_3$CH), 2.0 (1H, m, NCHC*H*H), 2.45 (2H, m, NCHCH*H* and CH_3C*H*), 3.8 (3H, s, CH_3O), 4.1 (1H, dd, J = 8.0, 5.0 Hz, CHN), 5.08 (2H, s, $PhCH_2$), 6.1 (1H, br s, NH), 6.84 (2H, d, J = 9.0 Hz, PhH), 7.25 (2H, d, J = 9.0 Hz, PhH);

δ_C (100 MHz; $CDCl_3$): 16.1, 33.8, 34.7, 53.8, 55.7, 67.6, 114.5, 127.6, 130.6, 160.3, 172.4, 180.6;

ES$^+$/MS. m/z 264 (8%), $[M+H]^+$; m/z 327 (30%), $[M+Na+MeCN]^+$; m/z 527 (100%), $[2M+H]^+$; m/z 549 (55%), $[2M+Na]^+$; m/z 812 (47%), $[3M+Na]^+$;

HRMS (ES$^+$): m/z calculated for $C_{14}H_{18}NO_4$ $[M+H]^+$ 264.1231, found 264.1223;

I.R. (neat) ν_{max} = 1747, 1700 (cm^{-1});

_p_-Methoxybenzyl-_cis_-4-methyl-5-oxopyrrolidine-2-carboxylate (109)

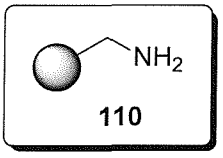
δ_H (400 MHz; $CDCl_3$): 1.2 (3H, d, J = 8.0 Hz, CH_3CH); 1.75 (1H, dt, J = 13.0, 9.5 Hz, NCHC*H*H), 2.5 (1H, m, CH_3CH); 2.7 (1H, dt, J = 13.0, 9.0 Hz, NCHCH*H*); 3.8 (3H, s, CH_3O); 4.2 (1H, t, J = 8.0 Hz, CHN); 5.14 (2H, s, $PhCH_2$); 6.1 (1H, br s, NH); 6.9 (2H, d, J = 9.0 Hz, PhH), 7.3 (2H, d, J = 9.0 Hz, PhH);

δ_C (100 MHz; $CDCl_3$): 14.9, 32.7, 35.0, 52.7, 54.5, 66.3, 113.2, 126.3, 129.5, 159.1, 170.7, 178.5;

ES$^+$/MS. m/z 549 (100%), $[2M+Na]^+$; m/z 590 (53%), ($[2M+Na]^+$+ MeCN); m/z 811 (48%), $[3M+Na]^+$;

HRMS (ES$^+$): m/z calculated for $C_{14}H_{17}NO_4Na$ $[M+Na]^+$ 286.1050320, found 286.1049791;

I.R. (neat) ν_{max} = 1743, 1698 (cm^{-1});

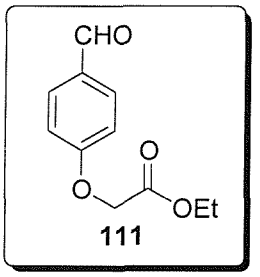


110

Aminomethyl Resin [108]

Polystyrene Merrifield resin (3.0 g, 4.8 mmol, 1.0 eq, Loading = 1.6 mmol/g) was stirred for 10 minutes at rt in DMF (25 mL). Potassium phthalimide (4.4 g, 24.0 mmol, 5.0 eq) was added portion wise and the resulting mixture stirred at 120 °C overnight. After cooling, the resin was filtered and washed with DMF (50 mL x 3), DMF:H_2O 1:1 (50 mL x 3), H_2O (50 mL x 3), Dioxane (50 mL x 3), MeOH (50 mL x 3) and Et_2O (50 mL x 3), then dried under high vacuum to yield 3.83 g of pale yellow phthalimidomethyl resin. This resin (3.83 g, 1.0 eq) was treated with ethanol (62.0 mL) and hydrazine hydrate (2.25 mL, 15.0 eq) and the resulting mixture was refluxed overnight. After cooling the mixture was filtered, washed with hot DMF (50 mL x 3), hot DMF:H_2O 1:1 (50 mL x 3), hot H_2O (50 mL x 3), Dioxane (50 mL x 3), MeOH 50 mL x 3) and Et_2O (50 mL x 3), and dried over high vacuum to yield 2.83 g of pale yellow amino methyl resin. The loading was calculated by

indirect Fmoc test, after coupling the amino methyl resin (50 mg) with Fmoc-Gly-OH under standard peptide conditions (Method $A_{(i)}$). L = 0.88 mmol/g.

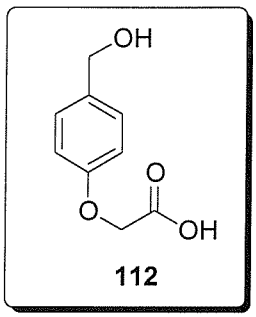


111

Ethyl-(4-Formyl-1-Phenoxy)-Ethanoate [108]

4-Hydroxybenzaldehyde (5g, 0.04 moles, 1.0 eq) was dissolved in dry DMF (37.5 mL) and KO^{t}Bu (4.95g, 1.1 eq) added slowly over 10 minutes. After stirring at rt for 15 minutes, ethylbromoacetate (5.0 mL, 1.1 eq) was added dropwise and the reaction stirred at 110 °C for 12 hours. Ethyl acetate (37.5 mL) was added and the resulting mixture filtered to remove the inorganic salts present. Concentration of the filtrate yielded an oil which was dissolved in ethyl acetate (37.5 mL), washed with water (25 mL), 5% $Na_2CO_{3\,(aq)}$ (3 x 25 mL) and brine (2 x 25 mL). The organic layer was dried ($MgSO_4$), then filtered and concentrated to give an orange oil (7.3g, 87%). R_f = 0.50 (1:1 EtOAc : Hexane).

δ_H (300 MHz; $CDCl_3$): 1.25 (3H, t, J = 7.0 Hz, OCH_2CH_3), 4.28 (2H, q, J = 7.0 Hz, OCH_2), 4.70 (2H, s, OCH_2CO), 7.04 (2H, d, J = 8.0 Hz, PhH), 7.82 (2H, d, J = 8.0 Hz, PhH), 9.90 (1H, s, CHO);
Data agrees with the literature.[108]



112

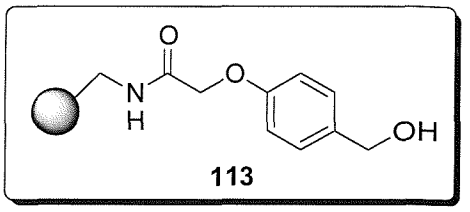
(4-Hydroxymethyl-1-Phenoxy)-Ethanoic Acid [108]

Ethyl-(4-formyl-1-phenoxy)-ethanoate **111** (7.3g, 35 mmol, 1.0 eq) was dissolved in NaOH 1M (28.3 mL) and ethanol (25.0 mL). The solution was adjusted to pH 11 with solid NaOH before the portion wise addition of $NaBH_4$ (1.6 g, 1.2 eq). The reaction mixture was stirred at room temperature overnight. Solid NaOH (12.3 g, 8.7 eq) was added portion wise and the reaction mixture stirred at rt for a further hour. The mixture was then cooled to 0 °C and water (133 mL) added. The mixture was then acidified to pH 2 with HCl 4M, brine (100 mL) was added and the solution extracted with ethyl acetate (3 x 75 mL). The combined organic layers were washed with brine (3 x 50 mL) and the combined aqueous layers were washed with ethyl acetate (100 mL). The combined organic layers were dried ($MgSO_4$) and concentrated to dryness to give **112** as a white solid (5.24g, 82%). R_f = 0.38 (EtOAc).

δ_H (300 MHz, $CD_3S(O)CD_3$): 4.37 (2H, s , CH_2OH), 4.63 (2H, s , $COCH_2$), 5.10 (1H, bs , CH_2OH), 6.86 (2H, d , J = 8.0 Hz, PhH), 7.22 (2H, d , J = 8.0 Hz, PhH), 13.0 (1H, bs, COOH);

δ_C (75 MHz; $CD_3S(O)CD_3$): 62.7, 64.5, 114.2, 128.1, 135.2, 156.8, 170.5;

Data agrees with literature.[108]

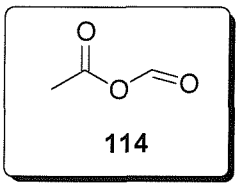


113

HO–Wang–Type–Resin[108, 121]

The Wang linker (4-hydroxymethyl-1-phenoxy)-ethanoic acid **112** (160.16 mg, 1.21 mmol, 2.0 eq) was coupled to the amino methyl resin **110** (687 mg, 0.604 mmol, 1.0 eq) according to method $A_{(i)}$. The qualitative ninhydrin test was positive so the coupling was repeated using the same quantities of reactants in the above conditions. The resin was washed with DMF (25 mL x 3), CH_2Cl_2 (25 mL x 3), Et_2O (25 mL x 3) and dried over high vacuum. The qualitative ninhydrin test was negative. To avoid the formation of dimers of the linker on the resin, it was necessary to wash it with a NaOH (1M):Dioxane (1:1, v/v) (3 x 10 mL). The resin was then washed again with DMF (25 mL x 3), CH_2Cl_2 (25 mL x 3), MeOH (25 mL x 3), Et_2O (25 mL x 3) and dried over high vacuum to yield 816 mg of **113**.

I.R. (neat) ν_{max} = 1613, 1509, 1492, 1450 (cm^{-1});



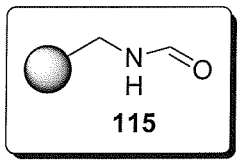
114

Acetic-Formic Anhydride (114).[113]

A dry 250 mL three necked round bottom flask equipped with a thermometer, a reflux condenser with calcium chloride tube and a dropping funnel was charged with sodium formate (30 g, 0.441 moles, 1.0 eq) and 30 mL of anhydrous Et_2O. To this stirred mixture was added acetyl chloride (26.6 mL, 0.85 eq) as rapidly as possible (~ 5 minutes), while the temperature was maintained at 21-23 °C. After the addition was completed, the mixture was

stirred for 6 hours at 21-23 °C to ensure complete reaction. The mixture was then filtered and the solid residue washed with dry Et_2O (30 mL). The washings were added to the original filtrate. The ether was removed by distillation at reduced pressure and the residue was then distilled (using a Kugelhor) to yield 30.0 g of acetic formic anhydride (42 °C at 36 mm/Hg)[44] (30g, 76%).

δ_H (300 MHz, $CDCl_3$): 2.25 (3H, s, CH_3CO), 9.05 (1H, s, CHO).
Data agrees with literature.[113]

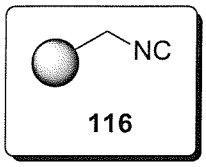


115

Formyl-Aminomethyl Resin

Aminomethyl resin **110** (86 mg, 0.075 mmol, 1.0 eq) was swollen in minimum amount of NMP (1.0 mL) for 30 minutes. A solution of **114** (180 mg, 26 eq) in NMP (1.0 mL) was added, after stirring at rt for 5 minutes, to the resin. The resulting mixture was shaken at rt for 3 hours. The resin was then filtered, washed with DMF (10 mL x 3), DCM (10 mL x 3), Et_2O (10 mL x 3) and dried under high vacuum to yield 84.7 mg of white resin **115**. The qualitative ninhydrin test was negative, indicating complete reaction.

I.R. (ν_{max}/cm^{-1}): 1675, 1511, 1495, 1449.

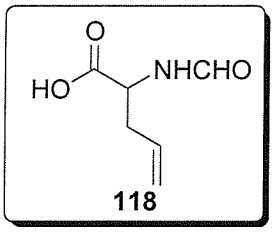


116

Isonitrile Methyl Resin[114, 115]

Resin **115** (35 mg, 0.056 mmol) was swollen in DCM (1.0 mL) for 30 minutes; a solution of Ph_3P (70 mg, 0.26 mmol), CCl_4 (25 μL, 0.26 mmol) and Et_3N (27 μl, 0.2 mmol) in DCM (1 mL) was stirred at rt for 10 minutes and then added to the resin. The resulting reaction mixture was shaken at rt for 2.5 hours at 45-50 °C. After cooling, the resin was filtered, washed with DMF (10 mL x 3), DCM (10 mL x 3), Et_2O (10 mL x 3) and dried under high vacuum to yield 25 mg of brown isonitrile resin.

I.R. (ν_{max}/cm^{-1}): 2146, 1490, 1444.



118

2-Formylamino-pent-4-enoic acid

Commercially available 2-aminopent-4-enoic acid (1.01 g, 8.78 mmol) was dissolved in formic acid (85 mL, 2.25 mol), to the stirred cooled solution, was added acetic anhydride (33 mL, 0.32 mol), dropwise over 15 minutes. The reaction mixture was stirred at 0 °C for 3 hours. The reaction mixture was then allowed to warm up to room temperature and the solvent evaporated to dryness under vacuum. The product was obtained as a white solid (1.17 g, 93% yield). No further purification was necessary.

δ_H (300 MHz; CD_3OD): 2.60 (2H, m, $CH_2CH=CH_2$), 4.48 (1H, m, NCH), 5.15 (2H, m, $CH=CH_2$), 5.75 (1H, m, $CH=CH_2$), 8.10 (1H; s; CHO);

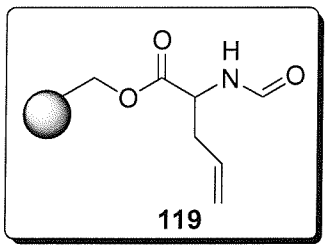
δ_C (75 MHz; $CDCl_3$): 36.9, 51.8, 118.8, 133.9, 163.3, 172.1;

ES$^-$/MS. 285 (100%), $[2M-H]^-$;

I.R. (neat) ν_{max} = 1903, 1717, 1605, 1523, 1352, 1220 (cm^{-1});

M. P. = 104-105 °C.

Elemental analysis: Found C, 50.99; H, 6.70; N, 9.61: $C_6H_9NO_3$ requires C, 50.35; H, 6.34; N, 9.78.



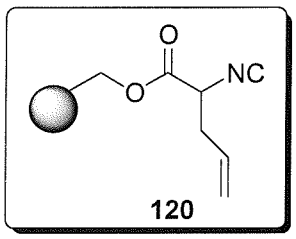
Formylamino-allyl-Gly-Wang resin

Commercial Wang resin (400 mg, 0.344 mmol, 1.0 eq, L = 0.86 mmol/g) was swollen in DCM (4.0 mL) for 30 minutes. 2-Formylaminopent-4-enoic acid (**118**) (300 mg, 2.06 mmol, 6.0 eq) was dissolved in dichloromethane with a few drops of dimethylformamide (4.0 mL, 9:1 ratio) and stirred at rt for 10 minutes, DIC (324 µL, 2.06 mmol, 6.0 eq), DMAP (13 mg, 0.103 mmol, 0.3 eq) were added and the resulting mixture stirred at room temperature for further 10 minutes. This mixture was then added to the resin and the resulting reaction mixture shaken at rt for 6 hours. The resin was then filtered, washed with DMF (15 mL x 3), DCM (15 mL x 3), MeOH (15 mL x 3), Et_2O (15 mL x 3) and dried under high vacuum overnight to yield 443 mg of yellowish resin **119**. The loading was calculated by theoretical molecular weight increase. Loading: 0.77 mmol/g. Resin **119** was also synthesised on a multigram scale (3.0 g).

I.R. (neat) ν_{max} = 1605, 1685, 1740 (cm^{-1});

M.A.S. δ_H (400 MHz; $CDCl_3$): 2.6 (2H, $CH_2CH{=}CH_2$), 4.7 (1H, NC*H*), 5.1 (2H, $CH{=}CH_2$), 5.6 (1H, $CH{=}CH_2$), 8.1 (1H; CHO);

M.A.S. δ_C (100 MHz; $CDCl_3$): 36.9, 51.0, 115.4, 132.3, 161.2.



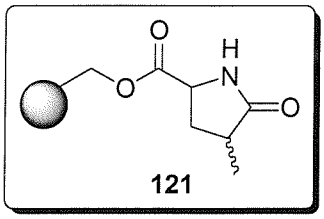
Isocyano-allyl-Gly-Wang resin

Resin **119** (425 mg, 0.32 mmol, 1.0 eq, L = 0.77 mmol/g) was swollen in 7.0 mL of dry dichloromethane for 20 minutes at rt, dry triethylamine (1.22 mL, 8.5 mmol, 26 eq) was added and the resulting mixture cooled to 0 °C (ice-water bath) under gentle stirring. Phosphoryl chloride (304 µL, 3.27 mmol, 10 eq) was added dropwise to the cooled reaction mixture over 30 minutes, the reaction mixture was then stirred at 0 °C for 3 hours under inert atmosphere (N_2). The resin was then filtered, washed with DMF (3 x 10 mL), DCM (3 x 10 mL), MeOH (3 x 10 mL), Et_2O (3 x 10 mL) and dried under high vacuum. It was obtained 420 mg of brown isocyanide resin **120**. Loading 0.77 mmol/g (calculated by molecular weight decrease).

I.R. (neat) ν_{max} = 2146, 1740, 1600 (cm^{-1});

M.A.S. δ_H (400 MHz; $CDCl_3$): 2.6 (2H, $CH_2CH{=}CH_2$), 4.3 (1H, m, NCH), 5.1 (2H, m, $CH_2{=}CH$), 5.7 (1H, m, $CH{=}CH_2$);

M.A.S. δ_C (100 MHz; $CDCl_3$): 37.3, 56.7, 121.0, 166.4.



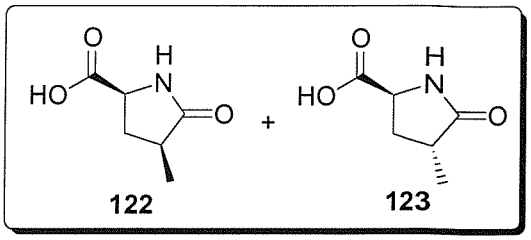
121

Oxopyrrolidine-Wang resin

The isonitrile resin **120** (420 mg, 0.32 mmol, 1.0 eq) was swollen in dry DMF (2.5 mL) for 30 minutes (under N_2). 2-Mercaptoethanol (574 μL, 8.17 mmol, 25 eq) was then added and the reaction mixture heated up to 45 °C under inert atmosphere (N_2). Gentle stirring was then started. AIBN (817 mg, 3.27 mmol, 10 eq), dissolved in 5 mL DMF, was added in 0.5 mL portions every 10 minutes and the resulting reaction mixture stirred for 24 hours at 45 °C. After 24 hours 2-mercaptoethanol (229 μL, 10 eq) and AIBN (408 mg, 5.0 eq, in 2 mL of DMF, 0.5 mL every 10 minutes) were added and the reaction continued for further 24 hours. The resin, which became yellowish, was then filtered, washed with dimethylformamide (5 x 15 mL), dichloromethane (5 x 15 mL), methanol (5 x 15 mL), diethylether (5 x 15 mL) and dried under high vacuum. It was obtained 427 mg of yellow resin **121**. Loading 0.769 mmol/g (calculated by molecular weight increase).

I.R. (neat) ν_{max} = 1740, 1695, 1595 (cm^{-1});

M.A.S. δ_H (400 MHz; $CDCl_3$): 2.4 (2H, CH_3CH); 2.6 (1H, m, OCOCHCH*H*); 4.1 (1H, m, HOCOC*H*N). (Signals were difficult to assign due to overlapping with the resin backbone, but disappearance of the allyl signals was observed).



122 123

cis-4-Methyl-5-oxo-pyrrolidine-2-carboxylic acid (122)

trans-4-Methyl-5-oxo-pyrrolidine-2-carboxylic acid (123)

Oxopyrrolidine resin **121** (422 mg, 0.32 mmol) was swollen in dry CH_2Cl_2 (2 mL) for 20 minutes. Then a solution of TFA/H_2O/TIS (36 mL : 4 mL : 0.1 mL) was added and the resulting mixture gently stirred at rt for 5.5 hours. The resin was then filtered and washed with 95% TFA in H_2O, the collected filtrates were evaporated to dryness to give 46 mg of brownish solid (>99% crude recovery). The crude mixture was purified by flash column chromatography, using DCM:MeOH:AcOH 9:1:0.1 as eluting solvents, to afford the title compounds (**122** and **123,** 1.1:1 mixture by NMR) as a racemic mixture (white solid, 30 mg, 66% yield).

cis-4-Methyl-5-oxo-pyrrolidine-2-carboxylic acid (122)

δ_H (400 MHz; CD_3OD): 1.15 (3H, d, J = 7.0 Hz, C*H*$_3$CH); 1.71 (1H, dt, J = 13.0, 8.5 Hz, NCHC*H*H); 2.49-2.50 (1H, m, CH_3C*H*); 2.71 (1H, dt, J = 13.0, 8.5 Hz, NCHCH*H*); 4.18 (1H, t, J = 8.0 Hz, CHN).

δ_C (100 MHz; CD_3OD): 16.4, 35.08, 36.5, 55.3, 176.1, 183.1.

trans-4-Methyl-5-oxo-pyrrolidine-2-carboxylic acid (123)

δ_H (300 MHz; CD_3OD): 1.16 (3H, d, J = 7.0 Hz, C*H*$_3$CH); 2.08 (1H, dt, J = 13.0, 9.0 Hz, NCHC*H*H); 2.39-2.53 (2H, m, NCHCH*H* and CH_3C*H*); 4.15 (1H, dd, J = 8.0, 2.5 Hz, CHN);

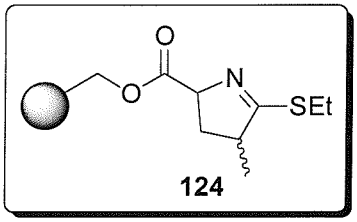
δ_C (75 MHz; CD_3OD): 16.8, 35.2, 37.8, 55.5, 176.4, 183.7;

I.R. (neat) ν_{max} = 1732 (s), 1679 (s), 1214 (s) (cm^{-1});

ES$^-$/MS. m/z 142 (100%), $[M-H]^-$;

ES$^+$/MS. m/z 144 (35%), $[M+H]^+$, m/z 166 (67%), $[M+Na]^+$;

HRMS (EI): m/z calculated for $C_6H_9NO_3$ $(M)^+$ 143.05824, found 143.05834;
M.P. = 95-97 °C;

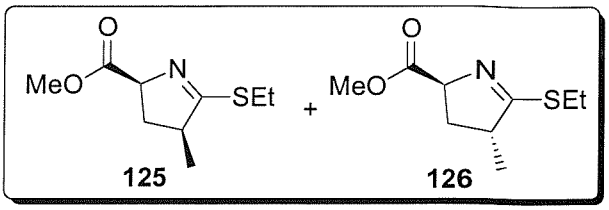


124

Pyrroline-Wang resin

The isonitrile resin **120** (500 mg, 0.38 mmol, 1.0 eq) was swollen in dry DMF (3.0 mL) for 30 minutes (under N_2). Ethanethiol (718 µL, 9.5 mmol, 25 eq) was then added and the reaction mixture heated up to 80 °C under inert atmosphere (N_2). Gentle stirring was then started. ACN (898 mg, 3.8 mmol, 10 eq), dissolved in 6 mL DMF, was added in 0.5 mL portions every 10 minutes and the resulting reaction mixture stirred for 24 hours at 80 °C. After 24 hours Ethanethiol (359 µL, 10 eq) and ACN (449 mg, 5.0 eq, in 2 mL DMF, 0.5 mL every 15 minutes) were added and the reaction continued for further 24 hours. The resin, which became yellowish, was then filtered, washed with dimethylformamide (5 x 15 mL), dichloromethane (5 x 15 mL), methanol (5 x 15 mL), diethylether (5 x 15 mL) and dried under high vacuum. It was obtained 530 mg of yellow resin **124**. Loading 0.726 mmol/g (calculated by molecular weight increase).

I.R. (neat) ν_{max} = 1744, 1659, 1538, 1494, 1452, 1272 (cm^{-1});



5-Ethylsulfanyl-*cis*-4-methyl-3,4-dihydro-2*H*-pyrrole-2-carboxylic acid methyl ester (125)
5-Ethylsulfanyl-*trans*-4-methyl-3,4-dihydro-2*H*-pyrrole-2-carboxylic acid methyl ester (126)

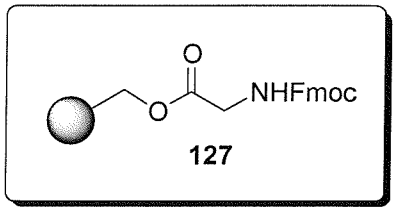
Resin **124** (530 mg, 0.38 mmol) was stirred at reflux with a solution of MeOH/Et_3N (4:1, 5 mL) and KCN (5 mg, 0.076 mmol, 0.2 eq). The resin was then filtered and washed with DCM (2 x 5 mL) and MeOH (2 x 5 mL). The filtrates were then concentrated *in vacuo*, redissolved in DCM (10 mL) and washed with 5% $NaHCO_3$ solution (3 x 10 mL), brine (3 x 10 mL), H_2O (3 x 10 mL), dried over $MgSO_4$ and concentrated to dryness to give a crude brownish oil. Purification by flash column chromatography (hexane:ethyl acetate 7:1) afforded the title compounds **125** and **126** (yellowish liquid, 41 mg, 54%), as 1:1 diastereomeric mixture (by NMR).

5-Ethylsulfanyl-*cis*-4-methyl-3,4-dihydro-2*H*-pyrrole-2-carboxylic acid methyl ester (125)
δ_H (400 MHz; $CDCl_3$): 1.20 (3H, d, J = 7.0 Hz, C*H*$_3$CH), 1.32 (3H, t, J = 7.0 Hz, C*H*$_3$CH$_2$S), 1.65 (1H, dt, J = 13.0, 7.5 Hz, NCHC*H*H), 2.48 (1H, dt, J = 13.0, 8.5 Hz, NCHCH*H*), 2.82 (1H, m, CH$_3$C*H*), 3.0 (2H, m, CH$_2$S), 3.70 (3H, s, CH$_3$O), 4.61 (1H, dd, J = 7.5, 1.5 Hz, CHN);
δ_C (100 MHz; $CDCl_3$): 14.4, 18.4, 25.4, 36.6, 46.2, 52.5, 72.1, 173.5, 179.5;

5-Ethylsulfanyl-*trans*-4-methyl-3,4-dihydro-2*H*-pyrrole-2-carboxylic acid methyl ester (126)
δ_H (400 MHz; $CDCl_3$): 1.23 (3H, d, J = 7.0 Hz, C*H*$_3$CH), 1.32 (3H, t, J = 7.0 Hz, C*H*$_3$CH$_2$S), 1.79 (1H, ddd, J = 12.5, 8.5, 7.0 Hz, NCHC*H*H), 2.36 (1H, ddd, J = 13.5, 8.0, 5.0 Hz, NCHCH*H*), 3.0 (3H, m, CH$_3$C*H*CH$_2$ and CH$_2$S), 3.74 (3H, s, CH$_3$O), 4.77 (1H, ddd, J = 8.5, 4.5, 1.5 Hz, C*H*N);
δ_C (100 MHz; $CDCl_3$): 14.4, 18.4, 25.4, 36.4, 46.8, 53.8, 72.3, 173.9, 181.4;
Other data available: DEPT, H-H and H-C correlations;
ES$^+$/MS: m/z 202 (100%), $[M+H]^+$;

HRMS (ES^+): m/z calculated for $C_9H_{15}NO_2S$ $[M+H]^+$ 202.0896, found 202.0898;

I.R. (neat) ν_{max} = 1732, 1574, 1514, 1226, 1165 (cm^{-1}).

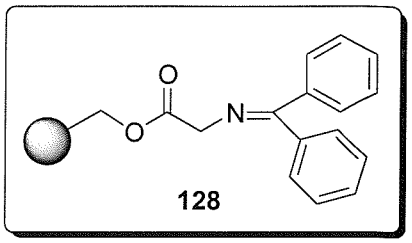


Fmoc-Gly-Wang resin

Commercial Wang resin (6.0 g, 6.0 mmol, 1.0 eq, L = 1.0 mmol/g) was swollen in a minimum amount of dichloromethane (20 mL) for 30 minutes. Fmoc-Gly-OH (6.0 g, 18.0 mmol, 3.0 eq) was dissolved in dichloromethane with a few drops of dimethylformamide (9:1 ratio) and stirred at rt for 10 minutes, DIC (3.74 mL, 24.0 mmol, 4.0 eq) and DMAP (226 mg, 1.8 mmol, 0.3 eq) were added and the resulting mixture stirred at room temperature for further 10 minutes. This mixture was then added to the resin and the resulting reaction mixture shaken at rt for 3 hours. The esterification was repeated to ensure completion of the reaction. The resin was then filtered, washed with dimethylformamide (50 mL x 3), dichloromethane (50 mL x 3), methanol (50 mL x 3), diethylether (50 mL x 3) and dried under high vacuum overnight to yield 7.68 g of resin **127**. The loading was calculated by Fmoc test. Loading: 0.78 mmol/g.

M.A.S. δ_H (400 MHz; $CDCl_3$): 4.1 (2H, $COCH_2NH$); 4.3 (1H, $CHCH_2O$); 4.5 (2H, $CHCH_2O$); 7.4 (2H, Ar*H*); 7.5 (2H, Ar*H*); 7.7 (2H, Ar*H*); 7.9 (2H, Ar*H*).

I.R. (neat) ν_{max} = 1726, 1511, 1454, 1198 (cm^{-1}).



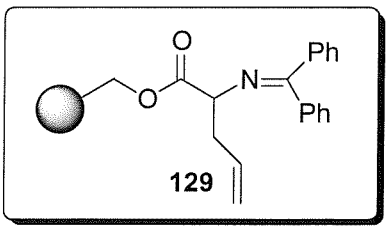
128

Benzophenone imine-Gly-Wang resin

Resin **127** (4.0 g, 3.12 mmol, 1.0 eq, L = 0.78 mmol/g) was deprotected, using piperidine 20% in dimethylformamide (60 mL), according to method B. The deprotected resin was then swollen in minimum amount of NMP (20 mL) for 30 minutes. Benzophenone imine (2.71 mL, 15.6 mmol, 6.0 eq) and acetic acid (230 μL, 4.04 mmol, 1.3 eq) were dissolved in 6.0 mL of NMP, the resulting solution stirred at room temperature for 5 minutes and then added to the resin. The resulting mixture was shaken at rt for 12 hours. The reaction mixture was filtered, washed with NMP and the reaction repeated again to ensure completion. The resin was then filtered, washed with NMP (30 mL x 3), DMF (30 mL x 3), DCM (30 mL x 3), MeOH (30 mL x 3), Et_2O (30 mL x 3) and dried under high vacuum overnight to yield 3.82 g of yellow resin. Theoretical Loading: 0.81 mmol/g (calculated by molecular weight decrease).

M.A.S. δ_H (400 MHz; $CDCl_3$): 4.2 (2H, $COCH_2N$); 7.3 (4H, Ar*H*); 7.4 (4H, Ar*H*); 7.7 (2H, Ar*H*).

I.R. (ν_{max}/cm^{-1}): 1740 (s), 1610 (s), 1575 (m).



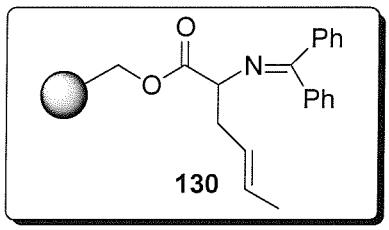
129

Allyl-Benzophenone imine-Gly-Wang-Resin

Resin **128** (1.2g, 0.938 mmol, 1.0 eq, L = 0.78 mmol/g) was swollen in 6 mL of NMP for 30 minutes. BEMP (1084 μL, 3.75 mmol, 4.0 eq) and allyl

bromide (346 μL, 3.75 mmol, 4.0 eq) were dissolved in NMP (1.0 mL) and the resulting solution stirred at room temperature for 5 minutes prior to addition to the resin. The resulting reaction mixture was shaken at rt for 12 hours. The resin was then filtered, washed with NMP (25 mL x 3) and the reaction repeated again to ensure completion. The resin was then filtered, washed with NMP (25 mL x 3), DMF (25 mL x 3), DCM (25 mL x 3), MeOH (25 mL x 3), Et_2O (25 mL x 3) and dried over high vacuum to yield 1.238 g of yellow resin **129**. Loading: 0.75 mmol/g (calculated by molecular weight increase).

M.A.S. δ_H (400 MHz; $CDCl_3$): 2.7 (2H, $CH_2CH{=}CH_2$); 4.2 (1H, CHN), 5.0-5.1 (2H, $CH_2CH{=}CH_2$); 5.7 (1H, $CH_2CH{=}CH_2$); 7.0-7.7 (2H, ArH).
I.R. (ν_{max}/cm^{-1}): 1733 (s), 1612 (s), 1515, 1494, 1225, 1172 (m).

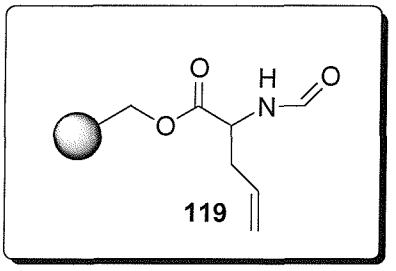


Benzophenone imine-crotyl-Gly-WANG Resin

Resin **128** (1.279g, 0.997 mmol, 1.0 eq, L = 0.78 mmol/g) was swollen in 6 mL of NMP for 30 minutes. BEMP (1084 μL, 3.75 mmol, 4.0 eq) and *trans*-crotyl bromide (484 μL, 4 mmol, 4.0 eq) were dissolved in NMP (2.0 mL) and the resulting solution stirred at room temperature for 5 minutes prior to addition to the resin. The resulting reaction mixture was shaken at rt for 12 hours. The resin was then filtered, washed with NMP (25 mL x 3) and the reaction repeated again to ensure completion. The resin was then filtered, washed with NMP (25 mL x 3), DMF (25 mL x 3), DCM (25 mL x 3), MeOH (25 mL x 3), diethyl ether (25 mL x 3) and dried over high vacuum to yield

1.333 g of yellow resin **130**. Loading: 0.747 mmol/g (calculated by molecular weight increase).

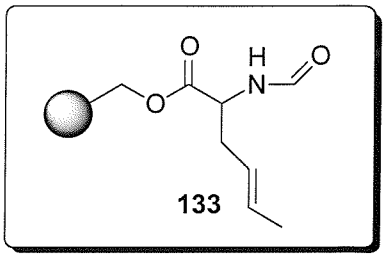
I.R. (ν_{max}/cm^{-1}): 1730 (s), 1610 (s), 1515, 1495, 1451, 1220, 1172 (m).



Formylamino-allyl-Gly-Wang resin

Resin **129** (1.238g, 0.938 mmol, 1.0 eq, L = 0.75 mmol/g) was swollen in tetrahydrofuran (6 mL) for 20 minutes; an aqueous solution of hydroxylamine chloridrate ($NH_2OH.HCl$) 1N (3/7 in tetrahydrofuran) (10 mL) was added and the resulting mixture shaken for 5.5 hours at room temperature. The mixture was then filtered and a solution of diisopropylamine 10% in NMP (2 x 10 mL) was added to neutralize and afford the free amino group. The resin was then filtered, washed with DMF (25 mL x 3), DCM (25 mL x 3), MeOH (25 mL x 3), Et_2O (25 mL x 3) and dried over high vacuum to yield a yellowish resin (**131**). Ninhydrin qualitative test was positive. The obtained resin **131** was then swollen in NMP (5 mL) for 30 minutes, a solution of acetic formic anhydride (1.6g, 18.7 mmol, 20 eq) in NMP (3 mL) was added and the mixture shaken at room temperature for 3 hours. The resin was then filtered and washed with NMP (25 mL x 3), DMF (25 mL x 3), DCM (25 mL x 3), MeOH (25 mL x 3), Et_2O (25 mL x 3) and dried over high vacuum to yield 1.11g of formylated resin **119**. Qualitative ninhydrin test was negative. Loading was 0.84 mmol/g.

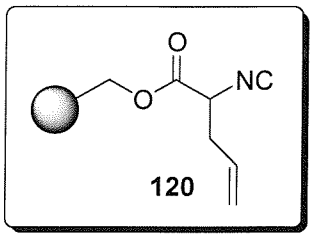
I.R. (neat) ν_{max} = 1675, 1735 (cm^{-1}).
Data agrees with that reported above.



Formylamino-crotyl-Gly-Wang resin

Resin **130** (1.33g, 0.997 mmol, 1.0 eq, L = 0.747 mmol/g) was swollen in tetrahydrofuran (6 mL) for 20 minutes; an aqueous solution of hydroxylamine chloridrate ($NH_2OH.HCl$) 1N (3/7 in THF) (10 mL) was added and the resulting mixture shaken for 5.5 hours at room temperature. The mixture was then filtered and a solution of diisopropylamine 10% in NMP (2 x 10 mL) was added to neutralize and afford the free amino group. The resin was then filtered, washed with DMF (25 mL x 3), DCM (25 mL x 3), MeOH (25 mL x 3), Et_2O (25 mL x 3) and dried over high vacuum to yield a yellowish resin (**132**). Ninhydrin qualitative test was positive. The obtained resin was then swollen in NMP (5 mL) for 30 minutes, a solution of acetic formic anhydride (1.6g, 18.7 mmol, 20 eq) in NMP (3 mL) was added and the mixture shaken at room temperature for 3 hours. The resin was then filtered and washed with NMP (25 mL x 3), DMF (25 mL x 3), DCM (25 mL x 3), MeOH (25 mL x 3), Et_2O (25 mL x 3) and dried over high vacuum to yield 1.194g of formylated resin **133**. Qualitative ninhydrin test was negative. Loading was 0.83 mmol/g.

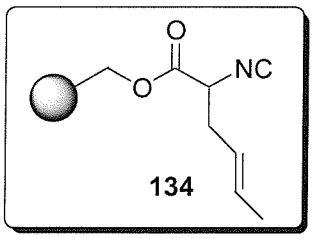
I.R. (neat) ν_{max} = 1780, 1685, 1640, 1605 (cm^{-1}).



Isocyano-allyl-gly-Wang resin

Resin **119** (900 mg, 0.756 mmol, 1.0 eq, L = 0.84 mmol/g) was swollen in 5 mL of dry dichloromethane for 20 minutes at rt, dry triethylamine (2.74 mL, 19.6 mmol, 26 eq) was added and the resulting mixture cooled to 0 °C (ice-water bath) under gentle stirring. Phosphoryl chloride (756 μL, 7.56 mmol, 10 eq) was added dropwise to the cooled reaction mixture over 30 minutes, the reaction mixture was then stirred at 0 °C for 3 hours under inert atmosphere (N_2). The resin was then filtered, washed with dimethylformamide (3 x 10 mL), dichloromethane (3 x 10 mL), methanol (3 x 10 mL), diethylether (3 x 10 mL) and dried under high vacuum. The reaction was then repeated on the same resin to ensure completion. The product was obtained as 886 mg of brown resin **120**. Loading 0.85 mmol/g.

I.R. (neat) ν_{max} = 2146, 1741, 1681, 1604 cm^{-1}.
Data agrees with that reported above.

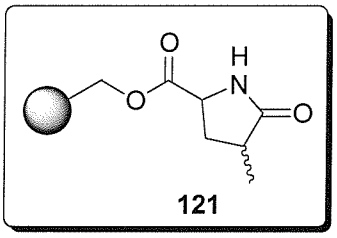


Isocyano-crotyl-gly-Wang resin

Resin **133** (1.0 g, 0.83 mmol, 1.0 eq, L = 0.83 mmol/g) was swollen in 5 mL of DCM for 20 minutes at rt, dry triethylamine (3.01 mL, 21.5 mmol, 26 eq)

was added and the resulting mixture cooled to 0 °C (ice-water bath) under gentle stirring. Phosphoryl chloride (830 μL, 8.3 mmol, 10 eq) was added dropwise to the cooled reaction mixture over 30 minutes, the reaction mixture was then stirred at 0 °C for 3 hours under inert atmosphere (N_2). The resin was then filtered, washed with dimethylformamide (3 x 10 mL), dichloromethane (3 x 10 mL), methanol (3 x 10 mL), diethylether (3 x 10 mL) and dried under high vacuum. The reaction was then repeated on the same resin to ensure completion. The product was obtained as 985 mg of brown resin **134**. Loading 0.84 mmol/g.

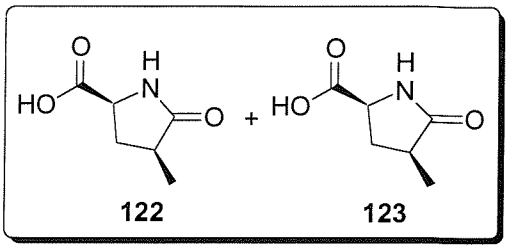
I.R. (neat) ν_{max} = 2146, 1746, 1683, 1603 cm^{-1}.



121

Oxopyrrolidine-Wang resin

The functionalised isonitrile resin **120** (800 mg, 0.68 mmol, L = 0.85 mmol/g) was swollen in dry DMF (4 mL) for 30 minutes (under N_2). 2-Mercaptoethanol (714 μL, 10.2 mmol, 15 eq) was then added and the reaction mixture stirred at 50 °C. AIBN (820 mg, 5.0 mmol, 7.0 eq) dissolved in 3.0 mL of DMF was added in 0.1 mL portions over 3 hours. After 24 hours the same amounts of reagents were added again and the resulting reaction mixture stirred for further 24 hours. The reaction was then cooled down, the resin filtered and washed with DMF (3 x 20 mL), DCM (3 x 20 mL), MeOH (3 x 20 mL), Et_2O (3 x 20 mL) and dried under high vacuum to yield 820 mg of **121**, as an orange resin (theoretical loading: 0.83 mmol/g).
Data agrees with that reported above.



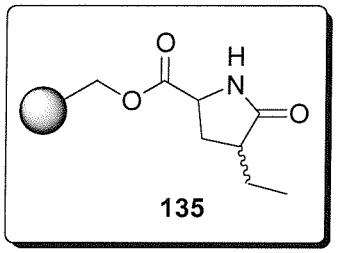
122 123

***cis*-4-Methyl-5-oxo-pyrrolidine-2-carboxylic acid (122)**

***trans*-4-Methyl-5-oxo-pyrrolidine-2-carboxylic acid (123)**

Resin **121** (820 mg, 0.68 mmol) was then treated with TFA, according to method $C_{(i)}$, to give a crude mixture that was purified by flash column chromatography (DCM:MeOH:AcOH 10:1:0.01). The two cleavage products **122** and **123** were obtained as an inseparable mixture of diastereoisomers (white solid, 58 mg, 60% isolated yield), 1:1 by NMR.

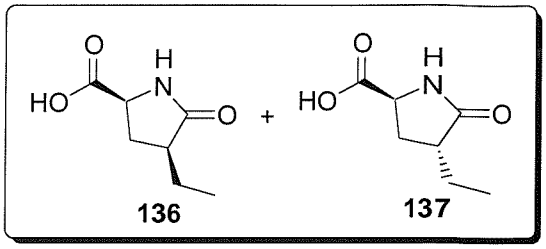
Data agrees with that reported above.



135

4-Ethyl-5-oxo-pyrrolidine-Wang resin

The functionalised isonitrile resin **134** (900 mg, 0.758 mmol, L = 0.84 mmol/g) was swollen in dry DMF (5 mL) for 30 minutes (under N_2). 2-mercaptoethanol (796 μL, 11.3 mmol, 15 eq) was then added and the reaction mixture stirred at 50 °C. AIBN (870 mg, 5.3 mmol, 7.0 eq) dissolved in 3.5 mL of DMF was added in 0.1 mL portions over 3 hours. After 24 hours the same amounts of reagents were added again and the resulting reaction mixture stirred for further 24 hours. The reaction was then cooled down, the resin filtered and washed with DMF (3 x 20 mL), DCM (3 x 20 mL), MeOH (3 x 20 mL), Et_2O (3 x 20 mL) and dried under high vacuum to yield 914 mg of yellow resin (**135**) (theoretical loading: 0.829 mmol/g).



136 137

***cis*-4-Ethyl-5-oxo-pyrrolidine-2-carboxylic acid (136)**

***trans*-4-Ethyl-5-oxo-pyrrolidine-2-carboxylic acid (137)**

Resin **135** (914 mg, 0.758 mmol) was then treated with TFA, according to method $C_{(i)}$, to give a crude mixture that was purified by flash column chromatography (DCM:MeOH:AcOH 10:1:0.01). The two cleavage products **136** and **137** (white solid, 49 mg, 41% isolated yield), were obtained as an inseparable mixture of diastereoisomers, 1:1 by NMR.

***cis*-4-Ethyl-5-oxo-pyrrolidine-2-carboxylic acid (136)**

δ_H (400 MHz; CD_3OD): 0.94 (3H, t, J = 7.5 Hz, CH_3CH_2), 1.34-1.44 (1H, m, CH_3CHH), 1.74-1.82 (2H, m, NCHC*H*H and CH_3CHH); 2.36-2.43 (1H, m, CH_3CH_2CH); 2.60-2.69 (1H, m, NCHCH*H*); 4.14-4.26 (1H, m, CHN);

δ_C (100 MHz; CD_3OD): 12.8, 26.1, 32.9, 44.0, 56.5, 175.8, 183.3;

***trans*-4-Ethyl-5-oxo-pyrrolidine-2-carboxylic acid (137)**

δ_H (400 MHz; CD_3OD): 0.95 (3H, t, J = 7.5 Hz, CH_3CH_2), 1.34-1.44 (1H, m, CH_3CHH), 1.74-1.82 (1H, m, CH_3CHH); 2.10-2.19 (1H, m, NCHC*H*H); 2.31-2.43 (1H, m, NCHCH*H* and CH_3CH_2CH); 4.14-4.26 (1H, m, CHN);

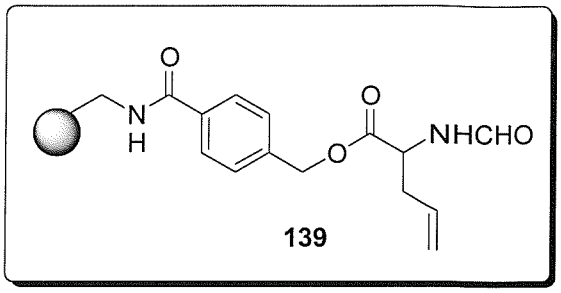
δ_C (100 MHz; CD_3OD): 13.0, 26.3, 33.1, 44.1, 56.5, 176.1, 183.9;

ES$^-$/MS. m/z 156 (65%), $[M-H]^-$, m/z 313 (100%), $[2M-H]^-$;

HRMS (ES$^-$): m/z calculated for $C_7H_{10}NO_3$ $[M-H]^-$ 156.0666, found 156.0661;

M.P.= 105-107 °C;

I.R. (neat) ν_{max} = 1699, 1640, 1423, 1233 cm^{-1};

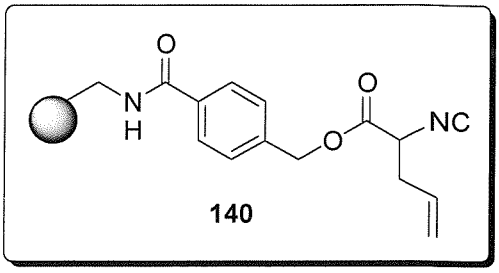


139

Formylamino-allyl-Gly-HMBA-AM resin

Commercial HMBA-AM resin (2.0 g, 2.32 mmol, 1.0 eq, L = 1.16 mmol/g) was swollen in a minimum amount of DCM (8.0 mL) for 30 minutes. 2-Formylaminopent-4-enoic acid (**118**) (497 mg, 3.48 mmol, 3.0 eq) was dissolved in DCM with a few drops of DMF (4.0 mL, 9:1 ratio) and stirred at rt for 10 minutes, DIC (544 μL, 3.48 mmol, 3.0 eq), DMAP (85 mg, 0.696 mmol, 0.3 eq) were added and the resulting mixture stirred at room temperature for further 10 minutes. This mixture was then added to the resin and the resulting reaction mixture shaken at rt for 6 hours. The resin was then filtered, washed with DMF (15 mL x 3), and the reaction repeated again to ensure completion. The resin was then filtered, washed with DMF (25 mL x 3), DCM (25 mL x 3), MeOH (25 mL x 3), Et_2O (25 mL x 3) and dried under high vacuum overnight to yield 2.29 g of yellowish resin **139**. The loading was calculated by theoretical molecular weight increase. Loading: 1.01 mmol/g.

I.R. (neat) ν_{max} = 1740, 1685, 1605 (cm^{-1}).

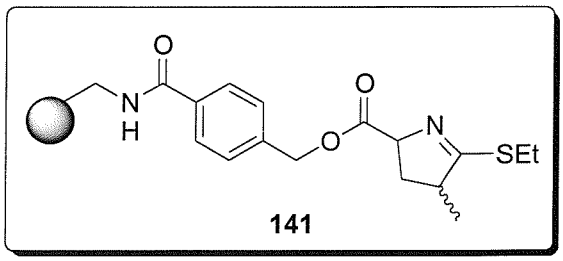


140

Isocyano-allyl-gly-HMBA-AM resin

Resin **139** (2.24 g, 2.21 mmol, 1.0 eq, L = 1.01 mmol/g) was swollen in 10 mL of DCM for 20 minutes at rt, dry triethylamine (10.7 mL, 77.6 mmol, 35 eq) was added and the resulting mixture cooled to 0 °C (ice-water bath) under gentle stirring. Phosphoryl chloride (2.18 mL, 22.1 mmol, 10 eq) was added dropwise to the cooled reaction mixture over 30 minutes, the reaction mixture was then stirred at 0 °C for 3 hours under inert atmosphere (N_2). The resin was then filtered, washed with DMF (3 x 20 mL), DCM (3 x 20 mL), MeOH (3 x 20 mL), Et_2O (3 x 20 mL) and dried under high vacuum. The reaction was then repeated on the same resin to ensure completion. It was obtained 2.2 g of brown resin **140**. The loading was calculated by theoretical molecular weight increase. Loading: 1.0 mmol/g.

I.R. (neat) ν_{max} = 2145, 1748, 1655 (cm^{-1}).



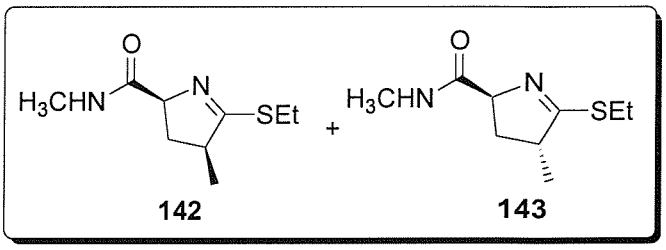
141

Pyrroline-HMBA-AM resin

The isonitrile resin **140** (1.143 g, 1.143 mmol, 1.0 eq) was swollen in dry DMF (6.0 mL) for 30 minutes (under N_2). Ethanethiol (1.75 mL, 22.86 mmol, 20 eq) was then added and the reaction mixture heated up to 80 °C under inert atmosphere (N_2). Gentle stirring was then started. ACN (1.4 g, 5.71 mmol, 5

eq), dissolved in 4 mL DMF, was added in 0.25 mL portions every 10 minutes and the resulting reaction mixture stirred for 24 hours at 80 °C. After 24 hours ethanethiol (875 μL, 10 eq) and ACN (700 mg, 2.5 eq, in 2 mL DMF, 0.1 mL every 10 minutes) were added and the reaction continued for further 24 hours. The resin, which turned yellowish, was then filtered, washed with DMF (3 x 20 mL), DCM (3 x 20 mL), MeOH (3 x 20 mL), Et_2O (3 x 20 mL) and dried under high vacuum. It was obtained 1.21g of yellow resin **141**. Loading 0.94 mmol/g (calculated by molecular weight increase).

I.R. (neat) ν_{max} = 1744, 1659, 1602, 1272 (cm^{-1}).



142 **143**

5-Ethylsulfanyl-cis-4-methyl-3,4-dihydro-2H-pyrrole-2-carboxylic acid methylamide (142)
5-Ethylsulfanyl-trans-4-methyl-3,4-dihydro-2H-pyrrole-2-carboxylic acid methylamide (143)

Resin **141** (1.197 g, 1.1 mmol) was cleaved according to method $C_{(ii)}$. Purification by flash column chromatography (DCM:MeOH 15:1) afforded the title compounds **142** and **143** (yellowish oil, 98 mg, 43% yield), as a 1.1:1 inseparable mixture of diastereoisomers.

5-Ethylsulfanyl-cis-4-methyl-3,4-dihydro-2H-pyrrole-2-carboxylic acid methylamide (142)
δ_H (400 MHz; $CDCl_3$): 1.08 (3H, d, J = 7.0 Hz, CH_3CH), 1.25 (3H, t, J = 7.0 Hz, CH_3CH_2S), 1.4-1.5 (1H, dt, J = 13.0, 7.5 Hz, NCHCH*H*), 2.5-2.6 (1H, dt, J = 13.0, 8.5 Hz, NCHC*H*H), 2.70 (3H, d, J = 7.0 Hz, CH_3NH), 2.8-2.9 (1H, m, CH_3CHCH_2), 3.0 (2H, m, CH_3CH_2S), 4.3 (1H, t, J = 7.5, CHN), 6.5 (1H, bs, NH).
δ_C (75 MHz; $CDCl_3$): 14.6, 17.9, 25.3, 37.0, 46.9, 73.0, 174.1, 180.7

5-Ethylsulfanyl-trans-4-methyl-3,4-dihydro-2H-pyrrole-2-carboxylic acid methylamide (143)

δ_H (400 MHz; $CDCl_3$): 1.1 (3H, d, J = 7.0 Hz, CH_3CH), 1.25 (3H, t, J = 7.0 Hz, CH_3CH_2S), 1.95 (1H, ddd, J = 12.5, 8.5, 7.0 Hz, NCHCHH), 2.20 (1H, ddd, J = 13.5, 8.0, 5.0 Hz, NCHCHH), 2.71 (3H, d, J = 7.0 Hz, CH_3NH), 2.9-3.0 (3H, m, CH_3CHCH_2 and CH_3CH_2S), 4.5 (1H, t, J = 7.5, CHN), 6.7 (1H, bs, NH).

δ_C (75 MHz; $CDCl_3$): 14.6, 18.5, 26.2, 36.3, 46.3, 72.9, 174.2, 181.3

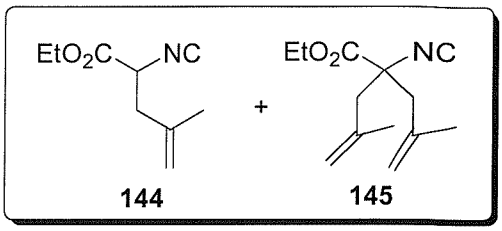
Other data available: DEPT, H-H and H-C correlations;

ES^+/MS: m/z 201 (100%), $[M+H]^+$;

HRMS (EI): m/z calculated for $C_9H_{17}N_2OS$ $[M+H]^+$ 201.1056103, found 201.1054400;

I.R. (neat) ν_{max} = 1732, 1574, 1514, 1226, 1165 (cm^{-1}).

EXPERIMENTAL – CHAPTER 3



2-Isocyano-4-methylpent-4-enoic acid ethyl ester (144)

2-Isocyano-4-methyl-2-(2-methyl-allyl)-pent-4-enoic acid ethyl ester (145)

An heterogeneous mixture of ethylisocyanoacetate (1.017 mL, 8.8 mmol, 1.0 eq), 3-bromo-2-methyl-propene (915 μL, 8.8 mmol, 1.0 eq), finely ground potassium carbonate (3.6 g, 26.4 mmol, 3.0 eq), TBAB (850 mg, 2.64 mmol, 0.3 eq) and dry acetonitrile (60 mL) was refluxed with stirring for 3 hours. The reaction mixture was then cooled, filtered and the solvent removed *in vacuo*. The residue was then dissolved in dry diethyl ether 100 mL, formation of a precipitate was observed, filtered and washed with water (3 x 100 mL), brine (3 x 100 mL) and dried over $MgSO_4$. After filtration the ether was removed *in vacuo* to give a crude brownish oil. Purification by flash chromatography (hexane:ethyl acetate, 7:1) gave the title compounds **144** as a yellow oil (111 mg, 8% yield), R_f = 0.5, and **145** (yellow oil, 504 mg, 26% yield), R_f = 0.7.

2-Isocyano-4-methylpent-4-enoic acid ethyl ester (144)

δ_H (300 MHz; $CDCl_3$): 1.30 (3H, t, J = 7.0 Hz, CH_3CH_2O), 1.77 (3H, s, $CH_3C{=}CH_2$), 2.53-2.66 (2H, m, $CHCH_2$), 4.25 (3H, q, J = 7.0 Hz, CH_2O), 4.36 (1H, dd, J = 8.5, 5.0 Hz, CHN), 4.88 (1H, s, C=C*H*H), 4.96 (1H, s, C=CH*H*);

δ_C (75 MHz; $CDCl_3$): 14.4, 22.1, 41.4, 55.7, 63.1, 116.0, 138.8, 160.7, 166.8;

C.I. GC/MS. m/z, relative intensity and ion. 168 (100%), $[M+H]^+$; 185 (72%), $[M+NH_4]^+$; Retention time: 8.28 min;

HRMS (EI): m/z calcd for $C_7H_9NO_2$ $(M\text{-}Et+H)^+$ 139.06300, found 139.06333;

I.R. (neat) ν_{max} = 2138, 1742, 1445, 1202, 1080 (cm^{-1}).

2-Isocyano-4-methyl-2-(2-methyl-allyl)-pent-4-enoic acid ethyl ester (145)

δ_H (300 MHz; $CDCl_3$): 1.3 (3H, t, J = 7.0 Hz, CH_3CH_2O), 1.81 (6H, s, 2 x $CH_3C=CH_2$), 2.48 (2H, d, J = 14.0 Hz, 2 x $CCHHC=CH_2$), 2.70 (2H, d, J = 14.0 Hz, 2 x $CCHHC=CH_2$), 4.22 (3H, q, J = 8.0 Hz, CH_2O), 4.85 (2H, s, 2 x $C=CHH$), 4.97 (2H, s, 2 x $C=CHH$);

δ_C (75 MHz; $CDCl_3$): 14.1, 23.3, 47.6, 62.7, 67.2, 117.0, 138.8, 161.0, 168.5;

C.I. GC/MS. m/z, relative intensity and ion. 222 (100%), $[M+H]^+$; 239 (6%), $[M+NH_4]^+$; Retention time: 9.94 min;

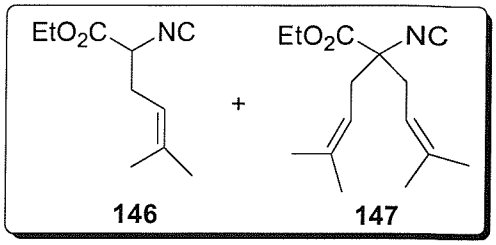
HRMS (EI): m/z calculated for $C_{13}H_{19}NO_2$ $(M)^+$ 221.14118, found 221.14158;

I.R. (neat) ν_{max} = 2138, 1742, 1445, 1269, 1201, 1080 (cm^{-1});

Compounds **144** and **145** were also synthesised by alkylation under microwave irradiation:

To a heavy walled Pyrex tube were added ethylisocyanoacetate (500 μL, 4.35 mmol, 1.0 eq), 3-bromo-2-methyl-propene (226 μL, 4.35 mmol, 1.0 eq), BEMP (630 μL, 4.35 mmol, 1.0 eq) in 3.0 mL of dry acetonitrile. The Pyrex tube was then capped and the reaction mixture was flushed with nitrogen. Heating was then applied by means of microwave irradiation (110 °C) for 15 minutes. The reaction tube was then allowed to cool for a couple of minutes before any handling of the reaction took place. The solvent was removed under reduced pressure. Purification by flash chromatography (hexane:ethyl acetate, 7:1) afforded the title compound **144** (344 mg, 47% yield) and the dialkylated compound **145** (126 mg, 13% yield).

Data agrees with that above.



2-Isocyano-5-methyl-hex-4-enoic acid ethyl ester (146)

2-Isocyano-5-methyl-2-(3-methyl-but-2-enyl)-hex-4-enoic acid ethyl ester (147)

An heterogeneous mixture of Ethyl isocyanoacetate (1.0 mL, 8.7 mmol, 1.0 eq), 1-bromo-3-methyl-2-butene (0.5 mL, 8.7 mmol, 1.0 eq), TBAB (840 mg, 2.61 mmol, 0.3 eq), finely ground technical grade potassium carbonate (3.6 g, 26.1 mmol, 3.0 eq) and dry acetonitrile (40 mL) was refluxed with stirring for 18 hours. The reaction mixture was then cooled, filtered and the solvent removed *in vacuo*. The residue was then dissolved in dry diethyl ether 100 mL, filtered and washed with water (3 x 100 mL), brine (3 x 100 mL) and dried over $MgSO_4$. After filtration the ether was removed *in vacuo* to give a crude brownish oil. Purification by flash chromatography (hexane:ethyl acetate, 7:1) gave the title compounds **146** as a yellowish oil (600 mg, 38% yield), $R_f = 0.51$, and **147** (380 mg, 17% yield), $R_f = 0.65$.

2-Isocyano-5-methyl-hex-4-enoic acid ethyl ester (146)

δ_H (300 MHz; $CDCl_3$): 1.32 (3H, t, J = 7.0 Hz, CH_3CH_2O), 1.67 (3H, s, CH_3CCH_3), 1.75 (3H, s, CH_3CCH_3), 2.64 (2H, t, J = 7.0 Hz, $CHCH_2$), 4.20 (1H, m, CHN), 4.23 (2H, q, J = 7.0 Hz, CH_2O), 5.16 (1H, t, J = 7.0 Hz, C=CH);

δ_C (75 MHz; $CDCl_3$): 14.1, 18.1, 25.9, 31.8, 56.7, 62.6, 116.3, 137.8, 159.9, 166.6;

C.I. GC/MS. m/z, relative intensity and ion. 182 (100%), $[M+H]^+$; 199 (72%), $[M+NH_4]^+$; Retention time: 9.17 min;

HRMS (EI): m/z calcd for $C_{10}H_{15}NO_2$ $(M + H)^+$ 181.11082, found 181.11028;

I.R. (neat) ν_{max} = 2148, 1702, 1271, 1203, 1053 (cm^{-1}).

2-Isocyano-5-methyl-2-(3-methyl-but-2-enyl)-hex-4-enoic acid ethyl ester (147)

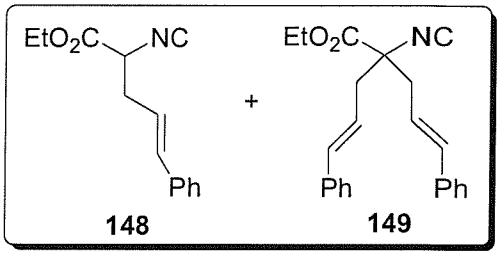
δ_H (300 MHz; $CDCl_3$): 1.28 (3H, t, J = 7.0 Hz, CH_3CH_2O), 1.65 (6H, s, 2 x CH_3CCH_3), 1.74 (6H, s, 2 x CH_3CCH_3), 2.48-2.67 (4H, m, 2 x CCH_2), 4.22 (2H, q, J = 7.0 Hz, CH_2O), 5.14-5.19 (2H, m, 2 x C=CH);

δ_C (75 MHz; $CDCl_3$): 14.2, 18.3, 26.1, 37.2, 62.5, 116.1, 137.6, 169.0, 173.8;

C.I. GC/MS. m/z, relative intensity and ion. 250 (100%), $[M+H]^+$; 267 (22%), $[M+NH_4]^+$; Retention time: 10.90 min;

HRMS (EI): m/z calculated for $C_{15}H_{23}NO_2$ $(M)^+$ 249.17264, found 249.17288;

I.R. (neat) ν_{max} = 2149, 1741, 1371, 1216 (cm^{-1}).



2-Isocyano-5-phenyl-pent-4-enoic acid ethyl ester (148)

2-Isocyano-5-phenyl-2-(3-phenyl-allyl)-pent-4-enoic acid ethyl ester (149)

To a heavy walled Pyrex tube were added ethylisocyanoacetate (250 μL, 2.17 mmol, 1.0 eq), cinnamyl bromide (450 mg, 2.17 mmol, 1.0 eq), BEMP (600 μL, 2.17 mmol, 1.0 eq) in 3.0 mL of dry acetonitrile. The Pyrex tube was then capped and the reaction mixture was flushed with nitrogen. Heating was then applied by means of microwave irradiation (110 °C) for 10 minutes. The reaction tube was then allowed to cool for a couple of minutes before any handling of the reaction took place. The solvent was removed under reduced pressure. Purification by flash chromatography (hexane:ethyl acetate, 7:1) afforded the title compound **148** (174 mg, 35% yield) and the dialkylated compound **149** (183 mg, 24% yield).

2-Isocyano-5-phenyl-pent-4-enoic acid ethyl ester (148)

δ_H (400 MHz; $CDCl_3$): 1.3 (3H, t, J = 7.0 Hz, C*H*$_3$CH$_2$O), 2.65-2.95 (2H, m, CHC*H*$_2$), 4.3 (3H, q, J = 7.0 Hz, CH_2O), 4.4 (1H, t, J = 7.0 Hz, CHN) 6.1-6.25 (1H, m, C*H*=CHPh), 6.6 (1H, d, J = 16.0 Hz, PhC*H*=CH), 7.2-7.4 (5H, m, PhH);

δ_C (100 MHz; $CDCl_3$): 14.4, 36.8, 53.8, 57.0, 63.1, 121.9, 126.8, 128.3, 129.0, 135.7, 136.8, 161.0, 166.4;

C.I. GC/MS. m/z, relative intensity and ion. 230 (85%), $[M+H]^+$; 247 (47%), $[M+NH_4]^+$. Retention time: 12.62 min

HRMS (EI): m/z calculated for $C_{14}H_{15}NO_2$ (M^+) 229.11042, found 229.11028.

I.R. (neat) ν_{max} = 2139, 1742, 1250, 1209, 1060 (cm^{-1}).

2-Isocyano-5-phenyl-2-(3-phenyl-allyl)-pent-4-enoic acid ethyl ester (149)

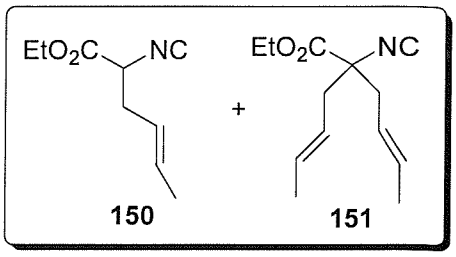
δ_H (400 MHz; $CDCl_3$): 1.3 (3H, t, J = 7.0 Hz, C*H*$_3$CH$_2$O), 2.65-2.95 (4H, m, 2 x CC*H*$_2$), 4.3 (3H, q, J = 7.0 Hz, CH_2O), 6.1-6.3 (2H, m, C*H*=CHPh), 6.6 (2H, d, J = 16.0 Hz, PhC*H*CH), 7.2-7.4 (10H, m, 2 x Ph*H*);

δ_C (100 MHz; $CDCl_3$): 14.5, 42.2, 63.1, 68.4, 121.5, 126.9, 128.8, 129.4, 136.7, 137.0, 160.7, 168.3;

C.I. GC/MS. m/z, relative intensity and ion. 346 (68%), $[M+H]^+$; 363 (36%), $[M+NH_4]^+$. Retention time: 16.63 min

HRMS (EI): m/z calculated for $C_{23}H_{23}NO_2$ (M^+) 345.17329, found 345.17288

I.R. (neat) ν_{max} = 2141, 1741, 1519, 1482, 1261, 1211 (cm^{-1}).



2-Isocyano-hex-4-enoic acid ethyl ester (150)

2-But-2-enyl-2-isocyano-hex-4-enoic acid ethyl ester (151)

An heterogeneous mixture of ethylisocyanoacetate (1.0 mL, 8.7 mmol, 1.0 eq), crotyl bromide (1.053 mL, 8.7 mmol, 1.0 eq), TBAB (840 mg, 2.61 mmol, 0.3 eq), finely ground technical grade potassium carbonate (3.6 g, 26.1 mmol, 3.0 eq) and dry acetonitrile (30 mL) was refluxed with stirring for 12 hours. The reaction mixture was then cooled, filtered and the solvent removed *in vacuo*. The residue was then dissolved in dry diethyl ether (80 mL), formation of a precipitate was observed, filtered and washed with water (3 x 100 mL), brine (3 x 100 mL) and dried over $MgSO_4$. After filtration the ether was removed *in vacuo* to give a crude brownish oil. Purification by flash chromatography (hexane:ethyl acetate, 8:1) gave the title compounds **150** as a yellow oil (735 mg, 50% yield), and **151** (yellow oil, 140 mg, 7% yield).

2-Isocyano-hex-4-enoic acid ethyl ester (150)

δ_H (300 MHz; $CDCl_3$): 1.28 (3H, t, J = 7.0 Hz, CH_3CH_2O), 1.67 (3H, d, J = 6.0 Hz, $CH_3CH{=}C$), 2.5-2.69 (2H, m, $CHCH_2$), 4.23 (3H, q, J = 7.0 Hz, CH_2O), 4.25 (1H, m, CHN) 5.34-5.44 (1H, m, $CH{=}CHCH_3$), 5.58-5.75 (1H, m, $CH{=}CHCH_3$);

δ_C (75 MHz; $CDCl_3$): 14.1, 18.0, 36.1, 56.8, 62.6, 123.0, 131.5, 160.0, 166.3;

C.I. GC/MS. m/z, relative intensity and ion. 168 (100%), $[M+H]^+$; 185 (42%), $[M+NH_4]^+$; Retention time: 8.46 min;

HRMS (EI): m/z calculated for $C_7H_9NO_2$ $(M\text{-}Et + H)^+$ 139.06320, found 139.06333;

I.R. (neat) ν_{max} = 2147, 1739, 1495, 1265, 1202, 1027 (cm^{-1}).

2-But-2-enyl-2-isocyano-hex-4-enoic acid ethyl ester (151)

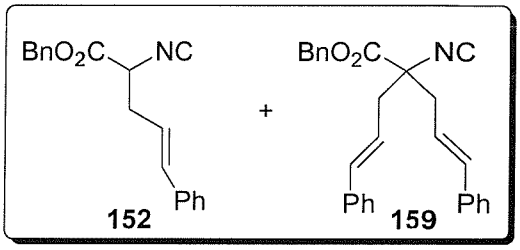
δ_H (300 MHz; $CDCl_3$): 1.28 (3H, t, J = 7.0 Hz, CH_3CH_2O), 1.68 (6H, d, J = 6.0 Hz, 2 x CH_3CH=C), 2.39-2.69 (4H, m, 2 x $CHCH_2$), 4.22 (3H, q, J = 7.0 Hz, CH_2O), 5.35-5.45 (2H, m, 2 x CH=C$H$$CH_3$), 5.55-5.75 (2H, m, 2 x CH=$CHCH_3$);

δ_C (75 MHz; $CDCl_3$): 14.2, 18.1, 31.7, 41.7, 62.4, 122.6, 131.8, 159.0, 168.2;

C.I. GC/MS. m/z, relative intensity and ion. 222 (100%), $[M+H]^+$; 239 (10%), $[M+NH_4]^+$; Retention time: 10.02 min;

HRMS (EI): m/z calcd for $C_{13}H_{19}NO_2$ $(M)^+$ 221.14207, found 221.14158;

I.R. (neat) ν_{max} = 2147, 1751, 1268, 1210, 1032 (cm^{-1}).



2-Isocyano-5-phenyl-pent-4-enoic acid benzyl ester (152)

2-Isocyano-5-phenyl-2-(3-phenyl-allyl)-pent-4-enoic acid benzyl ester (159)

An heterogeneous mixture of benzyl isocyanoacetate (1.54 g, 8.8 mmol, 1.0 eq), (3-bromo-propenyl)-benzene (1.72 g, 8.8 mmol, 1.0 eq), TBAB (850 mg, 2.64 mmol, 0.3 eq), finely ground technical grade potassium carbonate (3.6 g, 26.4 mmol, 3.0 eq) and dry acetonitrile (50 mL) was refluxed with stirring for 12 hours. The reaction mixture was then cooled, filtered and the solvent removed *in vacuo*. The residue was then dissolved in dry diethyl ether 50 mL, filtered and washed with water (3 x 50 mL), brine (3 x 50 mL) and dried over $MgSO_4$. After filtration the ether was removed *in vacuo* to give a crude brownish oil. Purification by flash chromatography (hexane:ethyl acetate, 7:1) gave the title compounds **152** as a yellowish oil (756 mg, 29% yield), R_f = 0.26, and the dialkylated isocyanide **159** as a yellowish solid (936 mg, 26% yield), R_f = 0.32.

2-Isocyano-5-phenyl-pent-4-enoic acid benzyl ester (152)

δ_H (400 MHz; $CDCl_3$): 2.8 (2H, m, CHC*H*$_2$), 4.4 (1H, t, J = 7.0 Hz, C*H*N), 5.2 (2H, s, PhC*H*$_2$), 6.0-6.1 (1H, m, C*H*=CHPh), 6.5 (1H, d, J = 16.0 Hz, PhC*H*=CH), 7.2-7.4 (10H, m, Ph*H*);

δ_C (100 MHz; $CDCl_3$): 36.8, 56.9, 68.7, 121.6, 126.8, 128.3, 128.9, 129.1, 134.9, 135.9, 136.7, 161.3, 166.3;

C.I. GC/MS. m/z, relative intensity and ion. 309 (7%), $[M+NH_4]^+$, 91 (100%), $[PhCH_2]^+$; Retention time: 16.49 min;

HRMS (EI): m/z calculated for $C_{19}H_{17}NO_2$ $(M)^+$ 291.12593, found 291.12598;

I.R. (neat) ν_{max} = 2148, 1745, 1265, 1189 (cm^{-1}).

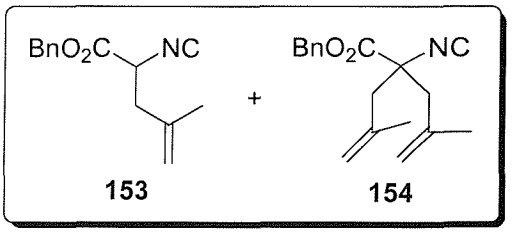
2-Isocyano-5-phenyl-2-(3-phenyl-allyl)-pent-4-enoic acid benzyl ester (159)

δ_H (400 MHz; $CDCl_3$): 2.7-2.9 (4H, m, 2 x CHC*H*$_2$), 5.2 (4H, s, 2 x PhC*H*$_2$), 6.0-6.1 (2H, m, 2 x C*H*=CHPh), 6.5 (2H, d, J = 16.0 Hz, 2 x PhC*H*=CH), 7.2-7.4 (15H, m, Ph*H*);

δ_C (100 MHz; $CDCl_3$): 42.4, 68.6, 121.2, 126.9, 128.3, 128.9, 128.9, 129.0, 129.0, 135.1, 136.3, 136.8, 160.7, 168.2;

I.R. (neat) ν_{max} = 2136, 1747, 1496, 1449, 1213, 1191 (cm^{-1});

Elemental analysis: Found C, 82.12; H, 6.22; N, 3.49: $C_{28}H_{25}NO_2$ requires C, 82.53; H, 6.18; N, 3.44.



2-Isocyano-4-methyl-pent-4-enoic acid benzyl ester (153)

2-Isocyano-4-methyl-2-(2-methyl-allyl)-pent-4-enoic acid benzyl ester (154)

To a heavy walled Pyrex tube were added benzyl isocyanoacetate (489 mg, 2.79 mmol, 1.0 eq), 3-bromo-2-methyl-propene (261 µL, 2.51 mmol, 0.9 eq),

BEMP (740 μL, 2.51 mmol, 0.9 eq) in 3.0 mL of dry acetonitrile. The Pyrex tube was then capped and the reaction mixture was flushed with argon. Heating was then applied by means of microwave irradiation (110 °C) for 10 minutes. The reaction tube was then allowed to cool for a couple of minutes before any handling of the reaction took place. The solvent was removed under reduced pressure. Purification by flash chromatography (hexane:ethyl acetate, 6:1) afforded the title compound **153** (248 mg, 38% yield) and the dialkylated compound **154** (128 mg, 16% yield).

2-Isocyano-4-methyl-pent-4-enoic acid benzyl ester (153)

δ_H (400 MHz; $CDCl_3$): 1.8 (3H, s, CCH_3=CH_2), 2.5-2.7 (2H, m, $CHCH_2$), 4.4 (1H, dd, J = 9.0, 5.0 Hz, CHN), 4.85 (1H, s, C=CH*H*), 4.95 (1H, s, C=C*H*H), 5.2 (2H, s, $PhCH_2$), 7.4 (5H, s, Ph*H*);

δ_C (100 MHz; $CDCl_3$): 21.7, 41.1, 55.4, 68.3, 115.8, 128.5, 128.8, 128.8, 134.6, 138.3, 160.7, 166.4;

C.I. GC/MS. m/z, relative intensity and ion. 247 (10%), $[M + NH_4]^+$; 230 (10%), $[M+H]^+$; 108 (34%), $[PhCH_2O + H]^+$; 91 (100%), $[PhCH_2]^+$;

Retention time: 12.97 min;

HRMS (EI): m/z calculated for $C_{14}H_{15}NO_2$ $(M)^+$ 229.11028, found 229.10989;

I.R. (neat) ν_{max} = 2139, 1743, 1428, 1370, 1213, 1059 (cm^{-1}).

2-Isocyano-4-methyl-2-(2-methyl-allyl)-pent-4-enoic acid benzyl ester (154)

δ_H (400 MHz; $CDCl_3$): 1.8 (6H, s, 2 x CCH_3=CH_2), 2.5 (2H, d, J = 14.0 Hz, 2 x CC*H*H), 2.7 (2H, d, J = 14.0 Hz, 2 x CCH*H*), 4.87 (2H, s, 2 x C=CH*H*), 4.97 (2H, s, 2 x C=C*H*H), 5.2 (2H, s, $PhCH_2$), 7.4 (5H, s, Ph*H*);

δ_C (100 MHz; $CDCl_3$): 23.5, 47.9, 68.6, 117.4, 129.0, 129.0, 129.1, 129.1, 134.9, 139.0, 161.6, 168.6;

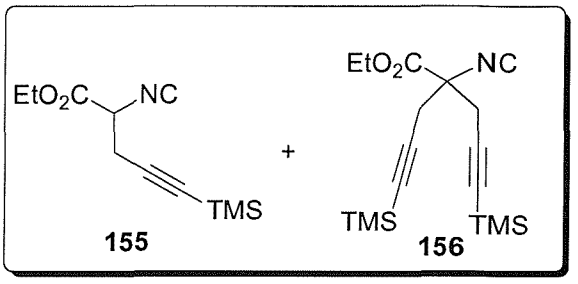
C.I. GC/MS. m/z, relative intensity and ion. 302 (6%), $[M+NH_4]^+$; 284 (10%), $[M+H]^+$; 107 (46%), $[PhCH_2O]^+$; 91 (100%), $[PhCH_2]^+$;

Retention time: 14.00 min;

HRMS (EI): m/z calculated for $C_{18}H_{20}NO_2$ (M-H) 282.14940, found 282.14966;

I.R. (neat) ν_{max} = 2136, 1739, 1435, 1366, 1216 (cm^{-1}).

Compound **154** was also synthesised directly from benzyl-isocyanoacetate (161 mg, 0.92 mmol, 1.0 eq), 3-Bromo-2-methyl-propene (201 μL, 1.93 mmol, 2.1 eq), BEMP (570 μL, 1.93 mmol, 2.1 eq) in 3.0 mL of dry acetonitrile, under microwave conditions. It was obtained as a yellowish oil (224 mg, 86% yield). Data agrees with that reported above.



2-Isocyano-5-trimethylsilanylpent-4-ynoic acid ethyl ester (155)

2-Isocyano-5-trimethylsilanyl-2-(3-trimethylsilanyl-prop-2-ynyl)-pent-4-ynoic acid ethyl ester (156)

An heterogeneous mixture of ethylisocyanoacetate (349 μL, 3.09 mmol, 1.0 eq), (3-bromo-prop-1-ynyl)-trimethyl-silane (446 μL, 3.09 mmol, 1.0 eq), TBAB (298 mg, 0.92 mmol, 0.3 eq), finely ground technical grade potassium carbonate (1.28 g, 9.27 mmol, 3.0 eq) and dry acetonitrile (25 mL) was refluxed with stirring for 3 hours. The reaction mixture was then cooled, filtered and the solvent removed *in vacuo*. The residue was then dissolved in dry diethyl ether (50 mL), filtered and washed with water (3 x 50 mL), brine (3 x 50 mL) and dried over $MgSO_4$. After filtration the ether was removed *in vacuo* to give a crude dark brownish oil. Purification by flash chromatography (hexane:ethyl acetate, 7:1) gave the title compounds **155** as a yellowish oil (173 mg, 25% yield), $R_f = 0.37$, and traces of the dialkylated isocyanide **156**.

Compound **156** was then synthesised directly from benzyl-isocyanoacetate (574 μL, 5.0 mmol, 1.0 eq), (3-bromo-prop-1-ynyl)-trimethyl-silane (1.44 mL, 10 mmol, 2.0 eq), TBAB (483 mg, 1.5 mmol, 0.3 eq), potassium carbonate (2.75 g, 20 mmol, 4.0 eq) and dry acetonitrile (40 mL) as described above.

The title compound was obtained as a dark yellow oil (1.54 g, 92% yield), R_f = 0.62.

2-Isocyano-5-trimethylsilanylpent-4-ynoic acid ethyl ester (155)

δ_H (400 MHz; $CDCl_3$): 0.15 (9H, s, $(CH_3)_3Si$), 1.32 (3H, t, J = 7.0 Hz CH_3CH_2O), 2.87 (2H, dd, J = 7.0, 3.0 Hz, $CHCH_2$), 4.28 (2H, q, J = 7.0 Hz, CH_2O), 4.35 (1H, t, J = 6.0 Hz, CHN);

δ_C (100 MHz; $CDCl_3$): 0.0, 14.3, 25.2, 60.5, 63.2, 90.0, 98.5, 161.5, 165.3;

C.I. GC/MS. m/z, relative intensity and ion. 241 (100%), $[M+NH_4]^+$; 224 (50%), $[M+H]^+$; 208 (72%), $[M-CH_3]^+$; Retention time: 10.67 min;

HRMS (EI): m/z calculated for $C_{10}H_{14}NO_2Si$ $(M-CH_3)$ 208.07938, found 208.07937;

I.R. (neat) ν_{max} = 2184, 2149, 1747, 1250, 1204, 1022 (cm^{-1}).

2-Isocyano-5-trimethylsilanyl-2-(3-trimethylsilanyl-prop-2-ynyl)-pent-4-ynoic acid ethyl ester (156)

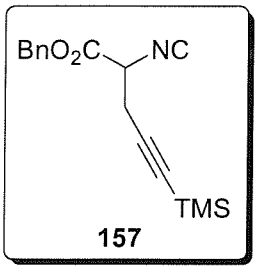
δ_H (400 MHz; $CDCl_3$): 0.39 (18H, s, 2 x $(CH_3)_3Si$), 1.34 (3H, t, J = 7.0 Hz CH_3CH_2O), 2.74 (4H, s, 2 x $CHCH_2$), 4.14 (2H, q, J = 7.0 Hz, CH_2O);

δ_C (100 MHz; $CDCl_3$): 0.0, 14.2, 29.8, 63.4, 65.3, 90.6, 98.2, 161.3, 166.5;

C.I. GC/MS. m/z, relative intensity and ion. 351 (12%), $[M+NH_4]^+$; 334 (8%), $[M+H]^+$; 73 (100%), $[TMS]^+$; Retention time: 10.67 min;

HRMS (EI): m/z calculated for $C_{17}H_{27}NO_2Si_2$ $(M)^+$ 333.15804, found 333.15748;

I.R. (neat) ν_{max} = 2183, 2136, 1749, 1520, 1206, 1025 (cm^{-1}).



157

2-Isocyano-5-trimethylsilanylpent-4-ynoic acid benzyl ester

An heterogeneous mixture of benzyl isocyanoacetate (541 mg, 3.09 mmol, 1.0 eq), (3-bromo-prop-1-ynyl)-trimethyl-silane (446 μL, 3.09 mmol, 1.0 eq), TBAB (298 mg, 0.92 mmol, 0.3 eq), finely ground technical grade potassium carbonate (1.28 g, 9.27 mmol, 3.0 eq) and dry acetonitrile (45 mL) was refluxed with stirring for 3 hours. The reaction mixture was then cooled, filtered and the solvent removed *in vacuo*. The residue was then dissolved in dry diethyl ether 70 mL, filtered and washed with water (3 x 50 mL), brine (3 x 50 mL) and dried over $MgSO_4$. After filtration the ether was removed *in vacuo* to give a crude brownish oil. Purification by flash chromatography (Hexane:Ethyl Acetate, 7:1) gave the title compound **157** as a yellowish oil (173 mg, 25% yield), R_f = 0.44; the dialkylated isocyanide was not isolated.

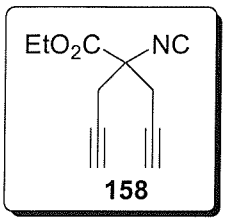
δ_H (400 MHz; $CDCl_3$): 0.14 (9H, s, $(CH_3)_3Si$), 2.87 (2H, dd, J = 7.0, 2.0 Hz, $CHCH_2$), 4.40 (1H, t, J = 6.0 Hz, CHN), 5.25 (2H, s, $PhCH_2$), 7.37 (5H, s, PhH);

δ_C (100 MHz; $CDCl_3$): 0.0, 25.1, 60.5, 68.6, 90.1, 98.4, 116.5, 128.5, 128.9, 129.0, 134.6, 161.8, 165.1;

C.I. GC/MS. m/z, relative intensity and ion. 303 (10%), $[M+NH_4]^+$; 286 (2%), $[M+H]^+$; 91 (100%), $[PhCH_2]^+$; Retention time: 13.91 min;

HRMS (EI): m/z calculated for $C_{15}H_{16}NO_2Si$ (M-CH_3) 270.09503, found 270.09514;

I.R. (neat) ν_{max} = 2186, 2149, 1750, 1250, 1214, 1190.



158

2-Isocyano-2-prop-2-ynyl-pent-4-ynoic acid ethyl ester

An heterogeneous mixture of ethylisocyanoacetate (1.5 mL, 13.04 mmol, 1.0 eq), propargyl bromide (3.66 mL, 32.62 mmol, 2.5 eq), TBAB (2.1 g, 6.52 mmol, 0.5 eq), potassium carbonate (7.2 g, 52.2 mmol, 4.0 eq) and dry acetonitrile (65 mL) was refluxed with stirring for 5 hours. The reaction mixture was then cooled, filtered and the solvent removed *in vacuo*. The residue was then dissolved in dry diethyl ether 100 mL, filtered and washed with water (3 x 100 mL), brine (3 x 100 mL) and dried over $MgSO_4$. After filtration the ether was removed *in vacuo* to give a crude dark yellowish oil. Purification by flash chromatography (hexane:ethyl acetate, 5:1) gave the title compounds **158** as a yellowish oil (2.39 g, 97% yield), $R_f = 0.41$.

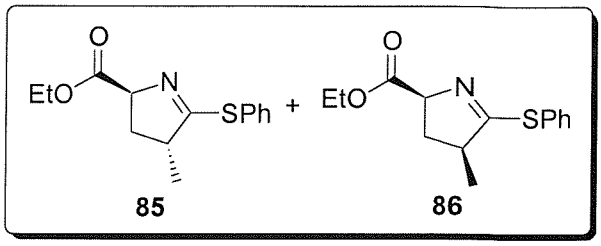
δ_H (400 MHz; $CDCl_3$): 1.34 (3H, t, J = 7.0 Hz CH_3CH_2O), 2.19 (2H, t, J = 2.5 Hz, 2 x CC*H*), 2.92 (4H, d, J = 3.0 Hz, 2 x CCH_2), 4.32 (2H, q, J = 7.0 Hz, CH_2O);

δ_C (100 MHz; $CDCl_3$): 14.3, 28.6, 63.9, 73.8, 76.2, 162.1, 166.3;

C.I. GC/MS. m/z, relative intensity and ion. 207 (80%), $[M+NH_4]^+$; 190 (100%), $[M+H]^+$; Retention time: 8.99 min;

HRMS (EI): m/z calculated for $C_9H_6NO_2$ $(M-CH_3CH_2)^+$ 160.03985, found 160.03974;

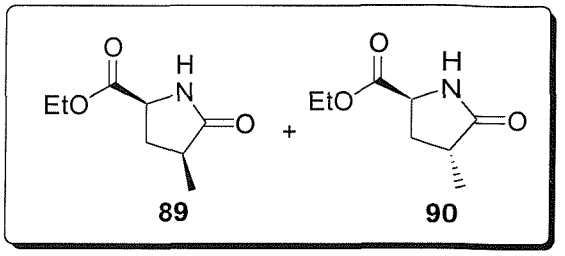
I.R. (neat) ν_{max} = 2148, 1747, 1265, 1208 (cm^{-1}).



***trans*-4-Methyl-5-phenylsulfanyl-3,4-dihydro-2H-pyrrole-2-carboxylic acid ethyl ester (85)**
***cis*-4-Methyl-5-phenylsulfanyl-3,4-dihydro-2H-pyrrole-2-carboxylic acid ethyl ester (86)**

To a heavy walled Pyrex tube were added 2-isocyano-pent-4-enoic acid ethyl ester (45 mg, 0.29 mmol, 1.0 eq), thiophenol (68 μL, 0.64 mmol, 2.2 eq), AIBN (15 mg, 0.058 mmol, 0.2 eq) in 3 mL of dry toluene. The Pyrex tube was then capped and the reaction mixture was flushed with argon. Heating was then applied by means of microwave irradiation (130 °C) for 5 minutes. The reaction tube was then allowed to cool for a couple of minutes before any handling of the reaction took place. The solvent was removed under reduced pressure. Purification by flash chromatography (hexane:ethyl acetate, 6:1) afforded the title compounds **85** and **86** (57 mg, 75%) as an inseparable mixture (1:1 by NMR). Data agrees with that reported in chapter 2.

Compounds **85** and **86** were also synthesised by the above method in the absence of radical initiator, using 4.0 eq of thiophenol and performing the reaction for 10 minutes. The title compounds were obtained in 58% yield as a 1:1 mixture of diastereoisomers (by NMR). All data for products **85** and **86** agrees with that reported in chapter 2.



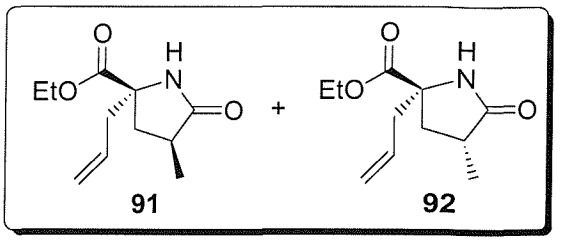
cis-4-Methyl-5-oxo-pyrrolidine-2-carboxylic acid ethyl ester (89)

trans-4-Methyl-5-oxo-pyrrolidine-2-carboxylic acid ethyl ester (90)

To a heavy walled Pyrex tube were added 2-isocyano-pent-4-enoic acid ethyl ester (50 mg, 0.32 mmol, 1.0 eq), 2-mercaptoethanol (45 μL, 0.64 mmol, 2.0 eq), AIBN (16 mg, 0.065 mmol, 0.2 eq) in 4 mL of dry toluene. The Pyrex tube was then capped and the reaction mixture was flushed with argon. Heating was then applied by means of microwave irradiation (130 °C) for 5 minutes. The reaction tube was then allowed to cool for a couple of minutes before any handling of the reaction took place. The solvent was removed under reduced pressure. Purification by flash chromatography (hexane:ethyl acetate, 1:1) afforded the title compounds **89** and **90** (53 mg, 99%) as an inseparable mixture (1:1 by NMR). Data agrees with that reported in chapter 2.

Compounds **89** and **90** were also synthesised by the above method in the absence of radical initiator, using 4.0 eq of thiophenol and performing the reaction for 10 minutes. The title compounds were obtained in 70% yield as a 1:1 mixture of diastereoisomers (by NMR).

All data for products **89** and **90** agrees with that reported in chapter 2.



91 92

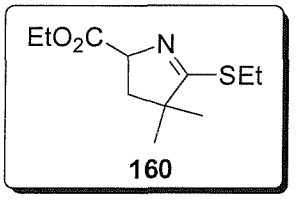
2-Allyl-*cis*-4-methyl-5-oxo-pyrrolidine-2-carboxylic acid ethyl ester (91)

2-Allyl-*trans*-4-methyl-5-oxo-pyrrolidine-2-carboxylic acid ethyl ester (92)

To a heavy walled Pyrex tube were added 2-allyl-2-isocyano-pent-4-enoic acid ethyl ester (50 mg, 0.26 mmol, 1.0 eq), 2-mercaptoethanol (36.5 μL, 0.52 mmol, 2.0 eq), AIBN (13 mg, 0.05 mmol, 0.2 eq) in 3 mL of dry toluene. The Pyrex tube was then capped and the reaction mixture was flushed with argon. Heating was then applied by means of microwave irradiation (130 °C) for 5 minutes. The reaction tube was then allowed to cool for a couple of minutes before any handling of the reaction took place. The solvent was removed under reduced pressure. Purification by flash chromatography (hexane:ethyl acetate, 1:1) afforded the title compounds **91** and **92** (46 mg, 98%) as an inseparable mixture (2:1 by NMR). Data agrees with that reported in chapter 2.

Compounds **91** and **92** were also synthesised by the above method in the absence of radical initiator, using 4.0 eq of thiophenol and performing the reaction for 10 minutes. The title compounds were obtained in 85% yield as a 1:1 mixture of diastereoisomers (by NMR).

All data for products **91** and **92** agrees with that reported in chapter 2.



160

5-Ethylsulfanyl-4,4-dimethyl-3,4-dihydro-2*H*-pyrrole-2-carboxylic acid ethyl ester

To a heavy walled Pyrex tube were added 2-isocyano-4-methylpent-4-enoic acid ethyl ester **144** (50 mg, 0.29 mmol, 1.0 eq), ethanethiol (49.8 μL, 0.65

mmol, 2.2 eq), ACN (14 mg, 0.058 mmol, 0.2 eq) in 3 mL of dry toluene. The Pyrex tube was then capped and the reaction mixture was flushed with nitrogen. Heating was then applied by means of microwave irradiation (130 °C) for 5 minutes. The reaction tube was then allowed to cool before any handling of the reaction took place. The solvent was removed under reduced pressure. Purification by flash chromatography (hexane:ethyl acetate, 5:1) afforded the title compound **160** as yellowish liquid (32 mg, 47%), R_f = 0.41.

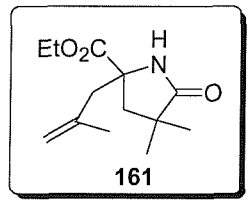
δ_H (400 MHz; $CDCl_3$): 1.18 (3H, s, CH_3CCH_3), 1.23 (3H, s, CH_3CCH_3), 1.30 (3H, t, J = 7.0 Hz, CH_3CH_2O), 1.32 (3H, t, J = 7.0 Hz, CH_3CH_2S), 2.02 (1H, dd, J = 12.5, 5.5 Hz, CHCHH), 2.17 (1H, dd, J = 13.0, 8.0 Hz, CHCHH), 3.02 (1H, m, CH_3CHHS), 3.05 (1H, m, CH_3CHHS), 4.20 (2H, q, J = 7.0, CH_2O), 4.58 (1H, t, J = 8.0 Hz, CHN);

δ_C (100 MHz; $CDCl_3$): 14.4, 14.5, 25.2, 26.5, 26.8, 43.6, 52.1, 61.3, 70.9, 173.6, 184.2;

ES^+/MS: m/z 230 (100%), $[M+H]^+$;

HRMS (ES^+): m/z calculated for $C_{11}H_{19}NO_2S$ $[M+H]^+$ 230.1209, found 230.1211;

I.R. (neat) ν_{max} = 1738, 1580, 1449, 1368, 1268, 1180, 1052 (cm^{-1}).



161

4,4-Dimethyl-2-(2-methyl-allyl)-5-oxo-pyrrolidine-2-carboxylic acid ethyl ester

To a heavy walled Pyrex tube were added 2-isocyano-4-methyl-2-(2-methyl-allyl)-pent-4-enoic acid ethyl ester **145** (51 mg, 0.23 mmol, 1.0 eq), 2-mercaptoethanol (35.5 µL, 0.507 mmol, 2.2 eq), ACN (11 mg, 0.046 mmol, 0.2 eq) in 4 mL of dry toluene. The Pyrex tube was then capped and the reaction mixture was flushed with nitrogen. Heating was then applied by

means of microwave irradiation (130 °C) for 5 minutes. The reaction tube was then allowed to cool before any handling of the reaction took place. The solvent was removed under reduced pressure. Purification by flash chromatography (hexane:ethyl acetate, 2:1) afforded the title compound **161** as white solid (33 mg, 61%), R_f = 0.27.

δ_H (400 MHz; $CDCl_3$): 1.08 (3H, s, CH_3CCH_3), 1.18 (3H, s, CH_3CCH_3), 1.26 (3H, t, J = 7.0 Hz, CH_3CH_2O), 1.67 (3H, s, $CH_2=CCH_3$), 1.97 (1H, d, J = 13.5, CCHH), 2.31 (1H, d, J = 13.5 Hz, $CH_2=CCH_3CHH$), 2.45 (1H, d, J = 13.5 Hz, CCHH), 2.67 (1H, d, J = 13.5 Hz, $CH_2=CCH_3CHH$), 4.17 (2H, q, J = 7.0, CH_2O), 4.73 (1H, d, J = 1.5 Hz, $CHH=CCH_3$), 4.88 (1H, d, J = 1.5 Hz, $CHH=CCH_3$), 6.0 (1H, bs, NH);

δ_C (100 MHz; $CDCl_3$): 14.4, 23.7, 26.1, 26.4, 47.3, 48.9, 62.1, 116.5, 140.3, 171.5, 174.5, 181.7;

Other data available: DEPT, H-H and H-C correlations;

C.I. GC/MS. m/z, relative intensity and ion. 240 (74%), $[M+H]^+$; 184 (100%), $[M-CH_2=CCH_3CH_2]^+$. Retention time: 12.55 min

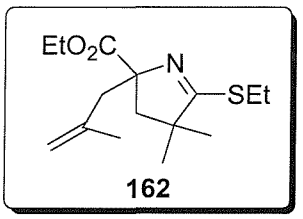
HRMS (ES^+): m/z calculated for $C_{26}H_{42}N_2O_6Na$ $[2M+Na]^+$ 501.2934, found 501.2940.

I.R. (neat) ν_{max} = 3225, 1698, 1449, 1389, 1221, 1150;

M.P. = 61-62 °C;

Elemental analysis: Found C, 65.10; H, 8.96; N, 5.69: $C_{13}H_{21}NO_3$ requires C, 65.25; H, 8.84; N, 5.85.

Crystal structure was also obtained (appendix).



162

5-Ethylsulfanyl-4,4-dimethyl-2-(2-methyl-allyl)-3,4-dihydro-2H-pyrrole-2-carboxylic acid ethyl ester

To a heavy walled Pyrex tube were added 2-isocyano-4-methyl-2-(2-methyl-allyl)-pent-4-enoic acid ethyl ester **145** (53 mg, 0.239 mmol, 1.0 eq), ethanethiol (40 μL, 0.527 mmol, 2.2 eq), ACN (11 mg, 0.046 mmol, 0.2 eq) in 3 mL of dry toluene. The Pyrex tube was then capped, the reaction mixture was flushed with nitrogen and heating was then applied by means of microwave irradiation (130 °C) for 5 minutes. The reaction tube was then allowed to cool before any handling of the reaction took place. The solvent was removed under reduced pressure. Purification by flash chromatography (hexane:ethyl acetate, 7:1) afforded the title compound **162** as yellowish liquid (33 mg, 51%), R_f = 0.66.

δ_H (400 MHz; $CDCl_3$): 1.15 (3H, s, CH_3CCH_3), 1.16 (3H, s, CH_3CCH_3), 1.23 (3H, t, J = 7.0 Hz, CH_3CH_2O), 1.30 (3H, t, J = 6.5 Hz, CH_3CH_2S), 1.73 (3H, s, $CH_2=CCH_3$), 1.90 (1H, d, J = 14.0 Hz, CCHH), 2.38 (1H, d, J = 14.0 Hz, CCHH), 2.58 (2H, s, $CH_2=CCH_3CH_2$), 2.96 (1H, m, CH_3CHHS), 3.07 (1H, m, CH_3CHHS), 4.14 (2H, q, J = 7.0, CH_2O), 4.71 (1H, d, J = 1.5 Hz, $CHH=CCH_3$), 4.82 (1H, d, J = 1.5 Hz, $CHH=CCH_3$);

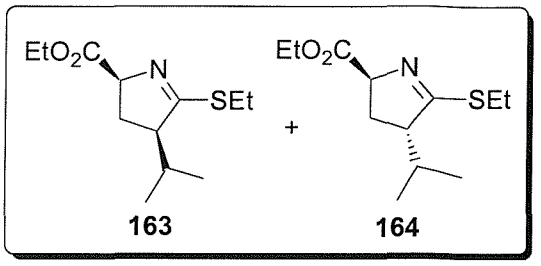
δ_C (100 MHz; $CDCl_3$): 14.5, 14.6, 24.4, 25.2, 27.9, 28.0, 47.8, 47.9, 52.2, 61.3, 80.7, 115.0, 142.6, 174.7, 181.3;

Other data available: DEPT, H-H and H-C correlations;

ES^+/MS: m/z 589 (80%), $[2M+Na]^+$; m/z 306 (40%), $[M+Na]^+$; m/z 284 (100%), $[M+H]^+$;

HRMS (ES^+): m/z calculated for $C_{15}H_{25}NO_2SNa$ $[M+Na]^+$ 306.1499100, found 306.1498208;

I.R. (neat) ν_{max} = 1728, 1584, 1448, 1336, 1214, 1192, 1022 (cm^{-1}).



5-Ethylsulfany-*cis*-4-isopropyl-3,4-dihydro-2*H*-pyrrole-2-carboxylic acid ethyl ester (163)
5-Ethylsulfany-*trans*-4-isopropyl-3,4-dihydro-2*H*-pyrrole-2-carboxylic acid ethyl ester (164)

To a heavy walled Pyrex tube were added 2-isocyano-5-methyl-hex-4-enoic acid ethyl ester **146** (50 mg, 0.276 mmol, 1.0 eq), ethanethiol (45.9 μL, 0.607 mmol, 2.2 eq), ACN (13 mg, 0.055 mmol, 0.2 eq) in 3 mL of dry toluene. The Pyrex tube was then capped, the reaction mixture was flushed with nitrogen and heating was then applied by means of microwave irradiation (130 °C) for 5 minutes. The reaction tube was then allowed to cool before any handling of the reaction took place. The solvent was removed under reduced pressure. Purification by flash chromatography (hexane:ethyl acetate, 7:1) afforded the title compounds **163** and **164** (1.4:1 diastereomeric mixture by NMR) as colourless liquid (54 mg, 80%), $R_f = 0.38$.

5-Ethylsulfany-*cis*-4-isopropyl-3,4-dihydro-2*H*-pyrrole-2-carboxylic acid ethyl ester (163)
δ_H (400 MHz; $CDCl_3$): 0.78 (3H, d, J = 6.5 Hz, CH_3CHCH_3), 0.93 (3H, d, J = 6.5 Hz, CH_3CHCH_3), 1.27 (3H, t, J = 7.0 Hz, CH_3CH_2O), 1.32 (3H, t, J = 7.5 Hz, CH_3CH_2S), 1.88 (1H, dt, J = 13.5, 8.0 Hz, NCHCHH), 2.01-2.15 (1H, m, CH_3CHCH_3), 2.27 (1H, dt, J = 13.0, 9.5 Hz, NCHCHH), 2.92 (1H, m, CH_3CHCH_3CH), 2.96-3.18 (2H, m, CH_3CH_2S), 4.18 (2H, q, J = 7.0, CH_2O), 4.53 (1H, ddd, J = 9.04, 7.53, 1.5 Hz, CHN);
δ_C (100 MHz; $CDCl_3$): 14.5, 16.4, 21.4, 23.8, 25.3, 27.7, 28.4, 29.3, 58.1, 72.4, 173.4, 178.4.

5-Ethylsulfany-*trans*-4-isopropyl-3,4-dihydro-2*H*-pyrrole-2-carboxylic acid ethyl ester (164)
δ_H (400 MHz; $CDCl_3$): 0.77 (3H, d, J = 6.5 Hz, CH_3CHCH_3), 0.94 (3H, d, J = 6.5 Hz, CH_3CHCH_3), 1.28 (3H, t, J = 7.0 Hz, CH_3CH_2O), 1.32 (3H, t, J = 7.5 Hz, CH_3CH_2S),

2.06-2.20 (3H, m, NCHCH_2 and CH_3CHCH_3), 2.96-3.18 (3H, m, CH_3CHCH_3CH and CH_3CH_2S), 4.19 (2H, q, J = 7.0, CH_2O), 4.61 (1H, ddd, J = 9.0, 6.0, 1.5 Hz, CHN);

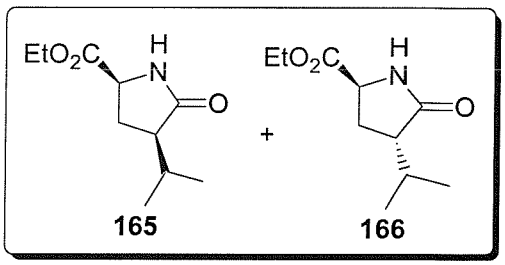
δ_C (100 MHz; $CDCl_3$): 14.5, 16.5, 21.7, 23.8, 25.4, 27.7, 28.4, 29.3, 61.3, 73.2, 173.5, 179.2;

Other data available: DEPT, H-H and H-C correlations;

ES^+/MS: m/z 244 (100%), $[M+H]^+$;

HRMS (ES^+): m/z calculated for $C_{12}H_{22}NO_2S$ $[M+H]^+$ 244.1366, found 244.1368;

I.R. (neat) ν_{max} = 1735, 1583, 1464, 1370, 1179, 1035 (cm^{-1}).



***cis*-4-Isopropyl-5-oxo-pyrrolidine-2-carboxylic acid ethyl ester (165)**
trans-4-Isopropyl-5-oxo-pyrrolidine-2-carboxylic acid ethyl ester (166)

To a heavy walled Pyrex tube were added 2-isocyano-5-methyl-hex-4-enoic acid ethyl ester **146** (53 mg, 0.292 mmol, 1.0 eq), 2-mercaptoethanol (45 μL, 0.643 mmol, 2.2 eq), ACN (14 mg, 0.058 mmol, 0.2 eq) in 3 mL of dry toluene. The Pyrex tube was then capped, the reaction mixture was flushed with nitrogen and heating was then applied by means of microwave irradiation (130 °C) for 5 minutes. The reaction tube was then allowed to cool before any handling of the reaction took place. The solvent was removed under reduced pressure. Purification by flash chromatography (hexane:ethyl acetate, 2:1) afforded the title compounds **165** (32 mg, 55% yield), R_f = 0.12, and **166** (23 mg, 39% yield), R_f = 0.23, as colourless liquids.

cis-4-Isopropyl-5-oxo-pyrrolidine-2-carboxylic acid ethyl ester (165)

δ_H (400 MHz; $CDCl_3$): 0.89 (3H, d, J = 6.5 Hz, CH_3CHCH_3), 0.99 (3H, d, J = 6.5 Hz, CH_3CHCH_3), 1.28 (3H, t, J = 7.0 Hz, CH_3CH_2O), 1.65 (1H, m, NCHCHH), 2.19 (1H, m,

CH_3CHCH_3), 2.25 (1H, m, NCHCH*H*), 2.42 (1H, m, $(CH_3)_2CHCH$), 4.11 (1H, t, J = 7.0 Hz, CHN), 4.21 (2H, q, J = 7.0, CH_2O), 5.99 (1H, bs, NH);

δ_C (100 MHz; $CDCl_3$): 14.5, 17.9, 20.8, 26.9, 28.3, 45.7, 54.1, 62.0, 172.6, 179.4;

Other data available: DEPT, H-H and H-C correlations;

ES$^+$/MS: m/z 421 (70%), $[2M+Na]^+$.

HRMS (ES$^+$): m/z calculated for $C_{10}H_{17}NO_3Na$ $[M+Na]^+$ 222.1100645, found 222.1101380;

I.R. (neat) ν_{max} = 1735, 1699, 1450, 1389, 1215 (cm^{-1}).

***trans*-4-Isopropyl-5-oxo-pyrrolidine-2-carboxylic acid ethyl ester (166)**

δ_H (400 MHz; $CDCl_3$): 0.85 (3H, d, J = 6.5 Hz, CH_3CHCH_3), 0.99 (3H, d, J = 7.0 Hz, CH_3CHCH_3), 1.29 (3H, t, J = 7.0 Hz, CH_3CH_2O), 1.96 (1H, m, NCHC*H*H), 2.15-2.23 (1H, m, CH_3CHCH_3), 2.39-2.50 (2H, m, NCHCH*H* + CH_3CHCH_3CH), 4.16 (1H, t, J = 8.0 Hz, NC*H*), 4.22 (2H, q, J = 7.0, CH_2O), 5.98 (1H, bs, NH);

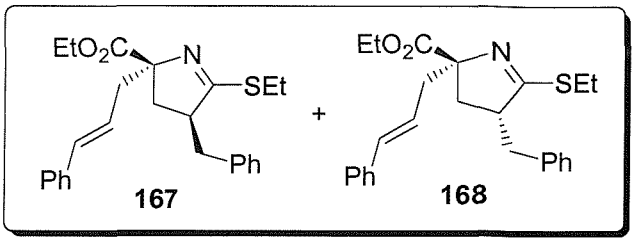
δ_C (100 MHz; $CDCl_3$): 14.5, 17.9, 21.0, 26.6, 27.9, 47.0, 53.8, 62.0, 172.1, 178.5;

Other data available: DEPT, H-H and H-C correlations;

ES$^+$/MS: m/z 421 (100%), $[2M+Na]^+$;

HRMS (ES$^+$): m/z calculated for $C_{10}H_{17}NO_3Na$ $[M+Na]^+$ 222.1100645, found 222.1101960;

I.R. (neat) ν_{max} = 1732, 1694, 1453, 1385, 1215 (cm^{-1}).



cis-4-benzyl-5-ethylsulfanyl-2-(3-phenyl-allyl)-3,4-dihydro-2*H*-pyrrole-2-carboxylic acid ethyl ester (167)

trans-4-benzyl-5-ethylsulfanyl-2-(3-phenyl-allyl)-3,4-dihydro-2*H*-pyrrole-2-carboxylic acid ethyl ester (168)

To a heavy walled Pyrex tube were added 2-isocyano-5-phenyl-2-(3-phenyl-allyl)-pent-4-enoic acid ethyl ester **149** (163 mg, 0.472 mmol, 1.0 eq), ethanethiol (81 μL, 1.039 mmol, 2.2 eq), AIBN (15 mg, 0.091 mmol, 0.2 eq) in 4 mL of dry toluene. The Pyrex tube was then capped, the reaction mixture was flushed with nitrogen and heating was then applied by means of microwave irradiation (130 °C) for 5 minutes. The reaction tube was then allowed to cool before any handling of the reaction took place. The solvent was removed under reduced pressure. Purification by flash chromatography (hexane:ethyl acetate, 7:1) afforded the title compounds **167** and **168** (146 mg, 76% yield), as a yellowish liquid (~ 1:1 mixture by NMR). R_f = 0.32.

cis-4-benzyl-5-ethylsulfanyl-2-(3-phenyl-allyl)-3,4-dihydro-2*H*-pyrrole-2-carboxylic acid ethyl ester (167)

δ_H (400 MHz; $CDCl_3$): 1.29 (3H, t, J = 7.0 Hz, C*H*$_3$CH$_2$O), 1.45 (3H, t, J = 7.0 Hz, C*H*$_3$CH$_2$S), 1.72 (1H, dd, J = 12.5, 8.0 Hz, NCC*H*H), 2.47 (1H, dd, J = 13.5, 8.5 Hz, NCCH*H*), 2.54-2.65 (2H, m, PhC*H*$_2$), 2.74-2.87 (2H, m, CH=CHC*H*$_2$), 3.20 (2H, m, CH$_2$S), 3.39-3.48 (1H, m, PhCH$_2$C*H*), 4.20 (2H, q, J = 7.0 Hz, CH$_2$O), 6.12 (1H, m, PhCH=C*H*), 6.48 (1H, d, J = 16.0 Hz, PhC*H*=CH), 7.18-7.40 (10H, m, PhH);

δ_C (100 MHz; $CDCl_3$): 15.3, 26.3, 38.1, 39.7, 43.2, 54.4, 62.1, 82.1, 125.7, 126.3, 127.2, 128.3, 129.5, 129.9, 134.7, 138.4, 140.1, 174.5, 177.6;

***trans*-4-benzyl-5-ethylsulfanyl-2-(3-phenyl-allyl)-3,4-dihydro-2*H*-pyrrole-2-carboxylic acid ethyl ester (168)**

δ_H (400 MHz; $CDCl_3$): 1.34 (3H, t, J = 7.0 Hz, CH_3CH_2O), 1.45 (3H, t, J = 7.0 Hz, CH_3CH_2S), 2.10 (1H, m, NCCHH), 2.20 (1H, dd, J = 13.5, 5.0 Hz, NCCHH), 2.54-2.65 (2H, m, $PhCH_2$), 2.74-2.87 (2H, m, $CH=CHCH_2$), 3.20 (3H, m, $PhCH_2CH$ and CH_2S), 4.27 (2H, q, J = 7.0 Hz, CH_2O), 6.12 (1H, m, PhCH=CH), 6.48 (1H, d, J = 16.0 Hz, PhCH=CH), 7.18-7.40 (10H, m, Ph);

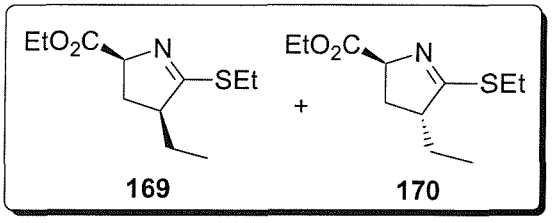
δ_C (100 MHz; $CDCl_3$): 15.4, 26.3, 38.9, 40.1, 43.3, 54.5, 62.2, 82.1, 125.7, 126.3, 127.4, 128.3, 129.5, 129.9, 134.8, 138.5, 140.4, 175.1, 178.2;

Other data available: DEPT, H-H and H-C correlations;

ES$^+$/MS: m/z 408 (100%), $[M+H]^+$;

HRMS (ES$^+$): m/z calculated for $C_{25}H_{30}NO_2S$ $[M+H]^+$ 408.1992, found 408.1987;

I.R. (neat) ν_{max} = 2252, 1731, 1578, 1448, 1373, 1216, 1031 (cm^{-1}).



169 **170**

***cis*-4-ethyl-5-ethylsulfanyl-3,4-dihydro-2*H*-pyrrole-2-carboxylic acid ethyl ester (169)**

***trans*-4-ethyl-5-ethylsulfanyl-3,4-dihydro-2*H*-pyrrole-2-carboxylic acid ethyl ester (170)**

To a heavy walled Pyrex tube were added 2-isocyano-hex-4-enoic acid ethyl ester **150** (100 mg, 0.598 mmol, 1.0 eq), ethanethiol (102.6 μL, 1.317 mmol, 2.2 eq), AIBN (20 mg, 0.119 mmol, 0.2 eq) in 5 mL of dry toluene. The Pyrex tube was then capped, the reaction mixture was flushed with nitrogen and heating was then applied by means of microwave irradiation (130 °C) for 5 minutes. The reaction tube was then allowed to cool before any handling of the reaction took place. The solvent was removed under reduced pressure. Purification by flash chromatography (hexane:ethyl acetate, 7:1) afforded the

title compounds **169** and **170** (105 mg, 77% yield), as a yellowish liquid (~ 1:1 mixture by NMR). R_f = 0.22.

***cis*-4-ethyl-5-ethylsulfanyl-3,4-dihydro-2*H*-pyrrole-2-carboxylic acid ethyl ester (169)**

δ_H (400 MHz; $CDCl_3$): 0.89 (3H, t, J = 7.0 Hz, CH_3CH_2CH), 1.24 (3H, t, J = 7.0 Hz, CH_3CH_2S), 1.29 (3H, t, J = 7.0 Hz, CH_3CH_2O), 1.34 (1H, m, CH_3CHHCH), 1.69-1.80 (2H, m, $NCHCHH$ and CH_3CHHCH), 2.44 (1H, dt, J = 13.5, 8.0 Hz, $NCHCHH$), 2.77 (1H, m, $NCHCH_2CH$), 2.95-3.13 (2H, m, CH_2S), 4.14 (2H, q, J = 7.0 Hz, CH_2O), 4.49 (1H, ddd, J = 9.03, 7.53, 1.5 Hz, NCH);

δ_C (100 MHz; $CDCl_3$): 11.6, 14.5, 25.3, 25.7, 33.4, 53.1, 61.2, 72.4, 173.2, 179.3;

***trans*-4-ethyl-5-ethylsulfanyl-3,4-dihydro-2*H*-pyrrole-2-carboxylic acid ethyl ester (170)**

δ_H (400 MHz; $CDCl_3$): 0.90 (3H, t, J = 7.0 Hz, CH_3CH_2CH), 1.25 (3H, t, J = 7.0 Hz, CH_3CH_2S), 1.30 (3H, t, J = 7.0 Hz, CH_3CH_2O), 1.34 (1H, m, CH_3CHHCH), 1.69-1.80 (1H, m, CH_3CHHCH), 1.90 (1H, ddd, J = 13.0, 8.5, 6.5 Hz, $NCHCHH$), 2.29 (1H, ddd, J = 13.5, 8.5, 5.0 Hz, $NCHCHH$), 2.90 (1H, m, $NCHCH_2CH$), 2.95-3.13 (2H, m, CH_2S), 4.15 (2H, q, J = 7.0 Hz, CH_2O), 4.64 (1H, ddd, J = 9.0, 5.5, 1.5 Hz, NCH);

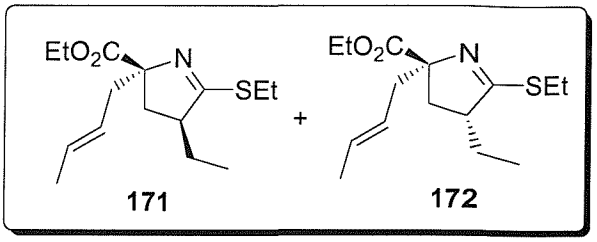
δ_C (100 MHz; $CDCl_3$): 12.0, 14.5, 25.3, 25.8, 33.6, 53.6, 61.3, 72.5, 173.5, 180.1;

Other data available: DEPT, H-H and H-C correlations;

ES^+/MS: m/z 230 (100%), $[M+H]^+$;

HRMS (ES^+): m/z calculated for $C_{11}H_{20}NO_2S$ $[M+H]^+$ 230.1209, found 230.1209;

I.R. (neat) ν_{max} = 2253, 1737, 1446, 1374, 1216 (cm^{-1}).



cis-2-but-2-enyl-4-ethyl-5-ethylsulfanyl-3,4-dihydro-2*H*-pyrrole-2-carboxylic acid ethyl ester (171)

trans-2-but-2-enyl-4-ethyl-5-ethylsulfanyl-3,4-dihydro-2*H*-pyrrole-2-carboxylic acid ethyl ester (172)

To a heavy walled Pyrex tube were added 2-but-2-enyl-2-isocyano-hex-4-enoic acid ethyl ester **151** (145 mg, 0.656 mmol, 1.0 eq), ethanethiol (112 μL, 1.44 mmol, 2.2 eq), AIBN (21.5 mg, 0.131 mmol, 0.2 eq) in 4 mL of dry toluene. The Pyrex tube was then capped, the reaction mixture was flushed with nitrogen and heating was then applied by means of microwave irradiation (130 °C) for 5 minutes. The reaction tube was then allowed to cool before any handling of the reaction took place. The solvent was removed under reduced pressure. Purification by flash chromatography (hexane:ethyl acetate, 7:1) afforded the title compounds **171** and **172** (148 mg, 80% yield), as a yellowish liquid (~ 1:1 mixture by NMR). $R_f = 0.37$.

cis-2-but-2-enyl-4-ethyl-5-ethylsulfanyl-3,4-dihydro-2*H*-pyrrole-2-carboxylic acid ethyl ester (171)

δ_H (400 MHz; $CDCl_3$): 0.87 (3H, t, J = 7.5 Hz, CH_3CH_2CH), 1.21 (3H, t, J = 7.0 Hz, CH_3CH_2O), 1.28 (3H, t, J = 7.0 Hz, CH_3CH_2S), 1.29 (1H, m, CH_3CHHCH), 1.48 (1H, dd, J = 13.0, 9.0 Hz $NCCHH$), 1.61 (3H, d, J = 5.0 Hz, $CH_3CH{=}CH$), 1.74 (1H, m, CH_3CHHCH), 2.44 (2H, dd, J = 12.5, 5.0 Hz, $CH_3CH{=}CHCH_2$), 2.51 (1H, dd, J = 13.0, 9.0 Hz, $NCCHH$), 2.89 (1H, m, $NCCH_2CH$), 2.96-3.10 (2H, m, CH_2S), 4.13 (2H, q, J = 7.0 Hz, CH_2O), 5.29 (1H, m, $CH_3CH{=}CH$), 5.5 (1H, m, $CH_3CH{=}CH$);

δ_C (100 MHz; $CDCl_3$): 11.9, 14.5, 18.4, 25.3, 25.7, 26.0, 37.7, 42.2, 53.5, 61.2, 81.3, 125.6, 129.4, 174.0, 178.0;

trans-2-but-2-enyl-4-ethyl-5-ethylsulfanyl-3,4-dihydro-2*H*-pyrrole-2-carboxylic acid ethyl ester (172)

δ_H (400 MHz; $CDCl_3$): 0.88 (3H, t, J = 7.5 Hz, CH_3CH_2CH), 1.21 (3H, t, J = 7.0 Hz, CH_3CH_2O), 1.28 (3H, t, J = 7.0 Hz, CH_3CH_2S), 1.29 (1H, m, CH_3CHHCH), 1.62 (3H, d, J = 5.0 Hz, $CH_3CH{=}CH$), 1.98 (1H, m, $NCCHH$), 2.11 (1H, m, $NCCHH$), 2.64 (2H, dd, J

= 13.5, 7.5 Hz, $CH_3CH{=}CHCH_2$), 2.68-2.79 (1H, m, $NCCH_2CH$), 2.96-3.10 (2H, m, CH_2S), 4.13 (2H, q, J = 7.0 Hz, CH_2O), 5.29 (1H, m, $CH_3CH{=}CH$), 5.5 (1H, m, $CH_3CH{=}CH$);

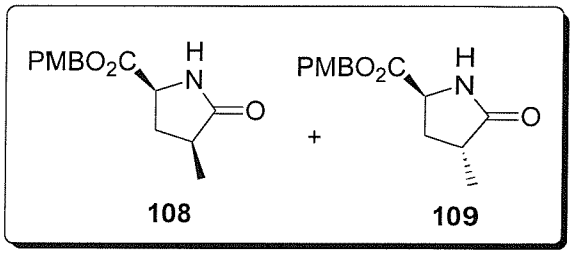
δ_C (100 MHz; $CDCl_3$): 11.9, 14.5, 18.4, 25.3, 25.7, 26.0, 38.1, 42.4, 53.7, 61.2, 81.4, 126.3, 129.7, 174.7, 178.1;

Other data available: DEPT, H-H and H-C correlations;

ES^+/MS: m/z 284 (100%), $[M+H]^+$.

HRMS (ES^+): m/z calculated for $C_{15}H_{26}NO_2S$ $[M+H]^+$ 284.1679, found 284.1679.

I.R. (neat) ν_{max} = 2253, 1730, 1581, 1446, 1375, 1193, 1036 (cm^{-1}).



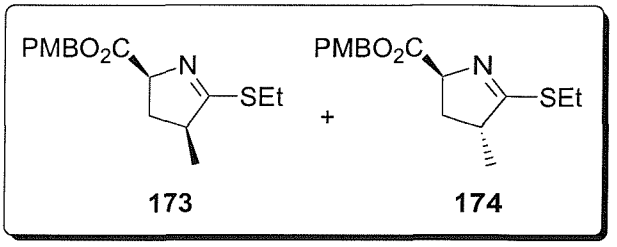
***cis*-4-Methyl-5-oxo-pyrrolidine-2-carboxylic acid 4-methoxy-benzyl ester (108)**

***trans*-4-Methyl-5-oxo-pyrrolidine-2-carboxylic acid 4-methoxy-benzyl ester (109)**

To a heavy walled Pyrex tube were added 2-isocyano-pent-4-enoic acid 4-methoxy-benzyl ester **104** (29 mg, 0.118 mmol, 1.0 eq), 2-mercaptoethanol (18.3 μL, 0.26 mmol, 2.2 eq), AIBN (6 mg, 0.023 mmol, 0.2 eq) in 1.5 mL of dry toluene. The Pyrex tube was then capped and the reaction mixture was flushed with argon. Heating was then applied by means of microwave irradiation (120 °C) for 5 minutes. The reaction tube was then allowed to cool for a couple of minutes before any handling of the reaction took place. The solvent was removed under reduced pressure. Purification by flash chromatography (hexane:ethyl acetate, 1:2) afforded the title compounds **108** (yellow liquid, 15 mg, 48% yield) and **109** (yellow liquid, 15 mg, 48%) in overall 96% yield.

Data for compounds **108** and **109** agrees with that of chapter 2.

Compounds **108** and **109** were also synthesised by the above method in the absence of radical initiator, using 4.0 eq of thiophenol and performing the reaction for 10 minutes. The title compounds were obtained in 91% yield (calculated by HPLC by comparison with a standard, the *cis/trans* ratio could not be calculated due to overlap of the peaks).



173 **174**

***cis*-5-ethylsulfanyl-4-methyl-3,4-dihydro-2*H*-pyrrole-2-carboxylic acid 4-methoxy-benzyl ester (173)**

***trans*-5-ethylsulfanyl-4-methyl-3,4-dihydro-2*H*-pyrrole-2-carboxylic acid 4-methoxy-benzyl ester (174)**

To a heavy walled Pyrex tube were added 2-isocyano-pent-4-enoic acid 4-methoxy-benzyl ester **104** (95 mg, 0.387 mmol, 1.0 eq), ethanethiol (67 μL, 0.853 mmol, 2.2 eq), AIBN (13 mg, 0.077 mmol, 0.2 eq) in 2.5 mL of dry toluene. The Pyrex tube was then capped and the reaction mixture was flushed with argon. Heating was then applied by means of microwave irradiation (120 °C) for 5 minutes. The reaction tube was then allowed to cool for a couple of minutes before any handling of the reaction took place. The solvent was removed under reduced pressure. Purification by flash chromatography (hexane:ethyl acetate, 3:1) afforded the title compounds **173** and **174**, as a yellowish liquid (106 mg, 90%, 1:1 diastereomeric mixture by NMR).

***cis*-5-ethylsulfanyl-4-methyl-3,4-dihydro-2*H*-pyrrole-2-carboxylic acid 4-methoxy-benzyl ester (173)**

δ_H (400 MHz; $CDCl_3$): 1.20 (3H, d, J = 7.0 Hz, CH_3CH), 1.36 (3H, t, J = 7.5 Hz, CH_3CH_2S), 1.74 (1H, dt, J = 13.0, 7.5 Hz, NCHC*H*H), 2.55 (1H, dt, J = 13.0, 8.5 Hz, NCHCH*H*), 2.94 (1H, m, CH_3CHCH_2), 3.10 (2H, m, CH_2S), 3.84 (3H, s, CH_3O), 4.59 (1H, dd, J = 7.5, 1.5 Hz, CHN), 5.14 (2H, s, MeOArCH_2), 6.91 (2H, d, J = 9.0 Hz, Ar*H*), 7.33 (2H, d, J = 9.0 Hz, Ar*H*);

δ_C (100 MHz; $CDCl_3$): 14.1, 17.9, 25.0, 36.0, 45.8, 55.2, 66.4, 71.8, 113.8, 127.9, 130.0, 172.6, 180.1;

***trans*-5-ethylsulfanyl-4-methyl-3,4-dihydro-2*H*-pyrrole-2-carboxylic acid 4-methoxy-benzyl ester (174)**

δ_H (400 MHz; $CDCl_3$): 1.23 (3H, d, J = 7.0 Hz, CH_3CH), 1.36 (3H, t, J = 7.5 Hz, CH_3CH_2S), 1.88 (1H, ddd, J = 12.5, 8.5, 7.0 Hz, NCHC*H*H), 2.40 (1H, ddd, J = 13.5, 8.0, 5.0 Hz, NCHCH*H*), 3.10 (3H, m, CH_3CHCH_2 and CH_2S), 3.84 (3H, s, CH_3O), 4.77 (1H, ddd, J = 8.5, 4.5, 1.5 Hz, C*H*N), 5.17 (2H, s, MeOArCH_2), 6.92 (2H, d, J = 9.0 Hz, Ar*H*), 7.35 (2H, d, J = 9.0 Hz, Ar*H*);

δ_C (100 MHz; $CDCl_3$): 14.4, 18.1, 25.0, 36.2, 46.3, 55.2, 66.4, 72.0, 113.8, 127.9, 130.3, 173.0, 181.0;

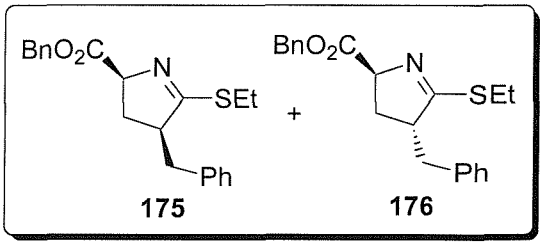
Other data available: DEPT, H-H and H-C correlations;

ES$^+$/MS: m/z 308 (100%), $[M+H]^+$;

HRMS (ES$^+$): m/z calculated for $C_{16}H_{22}NO_3S$ $[M+H]^+$ 308.1315, found 308.1320;

I.R. (neat) ν_{max} = 1735, 1613, 1579, 1514, 1246, 1165 (cm^{-1}).

Compounds **173** and **174** were also synthesised by the above method in the absence of radical initiator, using 4.0 eq of thiophenol and performing the reaction for 10 minutes. The title compounds were obtained in 54% yield (calculated by HPLC by comparison with a standard, the *cis*/*trans* ratio could not be calculated due to overlap of the peaks).



175 **176**

***cis*-4-benzyl-5-ethylsulfanyl-3,4-dihydro-2*H*-pyrrole-2-carboxylic acid benzyl ester (175)**

***trans*-4-benzyl-5-ethylsulfanyl-3,4-dihydro-2*H*-pyrrole-2-carboxylic acid benzyl ester (176)**

To a heavy walled Pyrex tube were added 2-isocyano-5-phenyl-pent-4-enoic acid benzyl ester **152** (50 mg, 0.171 mmol, 1.0 eq), ethanethiol (28.6 μL, 0.378 mmol, 2.2 eq), ACN (13 mg, 0.051 mmol, 0.2 eq) in 3.5 mL of dry toluene. The Pyrex tube was then capped

and the reaction mixture was flushed with argon. Heating was then applied by means of microwave irradiation (120 °C) for 5 minutes. The reaction tube was then allowed to cool for a couple of minutes before any handling of the reaction took place. The solvent was removed under reduced pressure. Purification by flash chromatography (hexane:ethyl acetate, 5:1) afforded the title compounds **175** and **176**, as a yellowish liquid (47 mg, 78%, 1.2:1 diastereomeric mixture by NMR). $R_f = 0.39$.

***cis*-4-benzyl-5-ethylsulfanyl-3,4-dihydro-2*H*-pyrrole-2-carboxylic acid benzyl ester (175)**

δ_H (400 MHz; $CDCl_3$): 1.28 (3H, t, J = 7.0 Hz, CH_3CH_2S), 1.76 (1H, m, NCHC*H*H), 2.20 (1H, m, NCHCH*H*), 2.47 (2H, m, PhCH_2CH), 3.0 (1H, m, $PhCH_2CH$), 3.08 (2H, m, CH_2S), 4.51 (1H, t, J = 8.0 Hz, CHN), 5.0 (2H, s, PhCH_2O), 7.02-7.28 (10H, m, PhH);

δ_C (100 MHz; $CDCl_3$): 14.3, 23.8, 25.6, 33.7, 38.7, 53.1, 67.0, 72.2, 126.7, 128.6, 128.9, 136.1, 139.1, 172.8, 179.1;

***trans*-4-benzyl-5-ethylsulfanyl-3,4-dihydro-2*H*-pyrrole-2-carboxylic acid benzyl ester (176)**

δ_H (400 MHz; $CDCl_3$): 1.28 (3H, t, J = 7.1 Hz, CH_3CH_2S), 1.92 (1H, ddd, J = 13.0, 8.5, 6.0 Hz, NCHC*H*H), 2.10 (1H, ddd, J = 13.0, 9.0, 5.5 Hz, NCHCH*H*), 2.47 (2H, m, PhCH_2CH), 3.08 (2H, m, CH_2S), 3.22 (1H, m, $PhCH_2CH$), 4.45 (1H, ddd, J = 8.5, 5.5, 1.5 Hz, CHN), 5.1 (2H, s, $PhCH_2O$), 7.02-7.28 (10H, m, PhH);

δ_C (100 MHz; $CDCl_3$): 14.5, 23.8, 26.0, 33.7, 39.2, 53.7, 67.0, 72.3, 126.9, 128.7, 129.2, 136.2, 139.7, 173.2, 179.5;

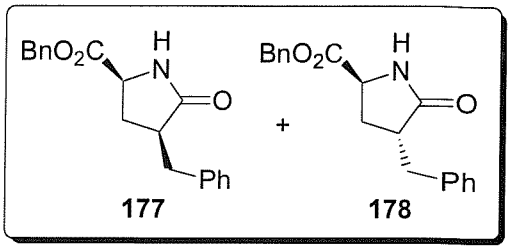
Other data available: DEPT, H-H and H-C correlations;

EI GC/MS: m/z 354 (70%), $[M+H]^+$, m/z 91 (100%), $[ArCH_2]^+$; Retention time: 17.92 min;

HRMS (ES^+): m/z calculated for $C_{21}H_{24}NO_2S$ $[M+H]^+$ 354.1522, found 354.1523;

I.R. (neat) ν_{max} = 1737, 1579, 1496, 1453, 1264, 1168, 1026 (cm^{-1}).

Compounds **175** and **176** were also synthesised using traditional thermal heating, 110 °C for 5 hours, with a 40% isolated yield (1:1 diastereomeric mixture). Data agrees with that reported above.



cis-4-benzyl-5-oxo-pyrrolidine-2-carboxylic acid benzyl ester (177)

trans-4-benzyl-5-oxo-pyrrolidine-2-carboxylic acid benzyl ester (178)

To a heavy walled Pyrex tube were added 2-isocyano-5-phenyl-pent-4-enoic acid benzyl ester **152** (44 mg, 0.151 mmol, 1.0 eq), 2-mercaptoethanol (26.6 μL, 0.378 mmol, 2.5 eq), ACN (13 mg, 0.051 mmol, 0.2 eq) in 3 mL of dry toluene. The Pyrex tube was then capped and the reaction mixture was flushed with argon. Heating was then applied by means of microwave irradiation (120 °C) for 5 minutes. The reaction tube was then allowed to cool for a couple of minutes before any handling of the reaction took place. The solvent was removed under reduced pressure. Purification by flash chromatography (hexane:ethyl acetate, 2:1) afforded the title compounds **177** and **178**, as a yellowish liquid (35 mg, 76%, 1.3:1 diastereomeric mixture by NMR). $R_f = 0.16$.

cis-4-benzyl-5-oxo-pyrrolidine-2-carboxylic acid benzyl ester (177)

δ_H (400 MHz; $CDCl_3$): 1.83 (1H, ddd, J = 13.0, 8.5, 7.5 Hz, NCHC*H*H), 2.41 (1H, dt, J = 13.0, 8.5 Hz, NCHCH*H*), 2.67 (1H, m, $PhCH_2CH$), 3.11 (2H, dd, J = 13.5, 3.5 Hz, $PhCH_2CH$), 4.11 (1H, t, J = 7.5 Hz, CHN), 5.07 (2H, s, $PhCH_2O$), 5.99 (1H, bs, NH), 7.05-7.31 (10H, m, PhH);

δ_C (100 MHz; $CDCl_3$): 30.8, 36.8, 41.6, 53.9, 67.7, 126.8, 128.7, 128.9, 129.1, 135.3, 139.0. 171.8, 178.3;

trans-4-benzyl-5-oxo-pyrrolidine-2-carboxylic acid benzyl ester (178)

δ_H (400 MHz; $CDCl_3$): 2.11 (1H, m, NCHC*H*H), 2.21 (1H, m, NCHCH*H*), 2.47-2.63 (1H, m, $PhCH_2CH$), 3.19 (2H, dd, J = 14.0, 4.0 Hz, $PhCH_2CH$), 3.95 (1H, dd, J = 9.0, 3.5 Hz, CHN), 5.09 (2H, s, $PhCH_2O$), 6.04 (1H, bs, NH), 7.05-7.31 (10H, m, PhH);

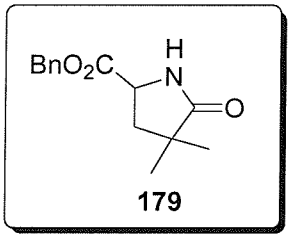
δ_C (100 MHz; $CDCl_3$): 31.0, 37.0, 43.1, 54.0, 67.7, 126.9, 128.8, 129.0, 129.2, 129.4, 139.3, 172.2, 179.0;

Other data available: DEPT, H-H and H-C correlations;

ES$^+$/MS: m/z 641 (100%), $[2M+Na]^+$.

HRMS (ES$^+$): m/z calculated for $C_{19}H_{19}NO_3Na$ $[M+Na]^+$ 332.1262970, found 332.1257146;

I.R. (neat) ν_{max} = 1739, 1703, 1454, 1373, 1200 (cm^{-1}).



179

4,4-dimethyl-5-oxo-pyrrolidine-2-carboxylic acid benzyl ester

To a heavy walled Pyrex tube were added 2-isocyano-4-methyl-pent-4-enoic acid benzyl ester **153** (112 mg, 0.489 mmol, 1.0 eq), 2-mercaptoethanol (69 μL, 0.978 mmol, 2.0 eq), AIBN (16 mg, 0.097 mmol, 0.2 eq) in 3 mL of dry toluene. The Pyrex tube was then capped and the reaction mixture was flushed with nitrogen. Heating was then applied by means of microwave irradiation (130 °C) for 5 minutes. The reaction tube was then allowed to cool before any handling of the reaction took place. The solvent was removed under reduced pressure. Purification by flash chromatography (hexane:ethyl acetate, 5:1) afforded the title compound **179** as white solid (77 mg, 64%), R_f = 0.21.

δ_H (400 MHz; $CDCl_3$): 1.12 (3H, s, CH_3CCH_3), 1.16 (3H, s, CH_3CCH_3), 1.30 (3H, t, J = 7.0 Hz, CH_3CH_2O), 2.05 (1H, dd, J = 13.0, 6.0 Hz, NCHCHH), 2.31 (1H, dd, J = 13.0, 8.5 Hz, NCHCHH), 4.20 (2H, dd, J = 8.5, 6.5 Hz, CHN), 6.6 (1H, bs, NH), 7.34 (5H, s, ArH);

δ_C (100 MHz; $CDCl_3$): 25.1, 25.3, 40.2, 40.4, 52.7, 67.6, 128.8, 129.0, 129.0, 172.4, 182.6;

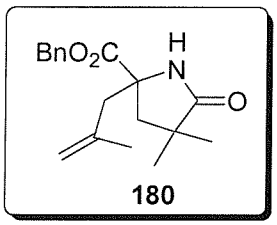
Other data available: DEPT, H-H and H-C correlations;

EI GC/MS: m/z 248 (14%), $[M+H]^+$, m/z 91 (100%), $[ArCH_2]^+$. Retention time: 11.13 min;

HRMS (ES$^+$): m/z calculated for $C_{28}H_{35}N_2O_6$ $[2M+H]^+$ 495.2489, found 495.2491;

I.R. (neat) ν_{max} = 1747, 1699, 1456, 1258, 1191;

M.P.= 98-101 °C.



180

4,4-dimethyl-2-(2-methyl-allyl)-5-oxo-pyrrolidine-2-carboxylic acid benzyl ester

To a heavy walled Pyrex tube were added 2-isocyano-4-methyl-2-(2-methyl-allyl)-pent-4-enoic acid benzyl ester **154** (65 mg, 0.229 mmol, 1.0 eq), 2-mercaptoethanol (32.3 μL, 0.459 mmol, 2.0 eq), AIBN (7.5 mg, 0.046 mmol, 0.2 eq) in 3 mL of dry toluene. The Pyrex tube was then capped and the reaction mixture was flushed with nitrogen. Heating was then applied by means of microwave irradiation (130 °C) for 5 minutes. The reaction tube was then allowed to cool before any handling of the reaction took place. The solvent was removed under reduced pressure. Purification by flash chromatography (hexane:ethyl acetate, 2:1) afforded the title compound **180** as a white solid (56 mg, 81%), R_f = 0.29.

δ_H (400 MHz; $CDCl_3$): 1.03 (3H, s, CH_3CCH_3), 1.18 (3H, s, CH_3CCH_3), 1.64 (3H, s, CH_2=$CHCH_3$), 1.99 (1H, d, J = 13.5, NCCHH), 2.34 (1H, d, J = 14.0 Hz, CH_2=CCH_3CHH), 2.47 (1H, d, J = 13.5 Hz, NCCHH), 2.70 (1H, d, J = 14.0 Hz, CH_2=CCH_3CHH), 4.71 (1H, s, CHH=CCH_3), 4.86 (1H, s, CHH=CCH_3), 5.11 (1H, d, J = 12.0 Hz, PhCHH), 5.18 (1H, d, J = 12.0 Hz, PhCHH), 5.9 (1H, bs, NH), 7.34 (5H, s, PhH);

δ_C (100 MHz; $CDCl_3$): 23.0, 25.3, 25.6, 39.7, 46.6, 48.2, 61.5, 67.2, 115.9, 128.3, 128.3, 134.5, 139.5, 173.6, 180.9;

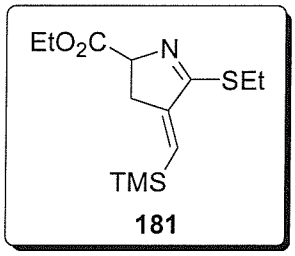
Other data available: DEPT, H-H and H-C correlations;

C.I. GC/MS: m/z, relative intensity and ion. m/z 302 (35%), $[M+H]^+$; m/z 246 (35%), $[M-CH_2=CCH_3CH_2]^+$, m/z 91 (100%), $[ArCH_2]^+$; Retention time: 15.55 min;

HRMS (ES$^+$): m/z calculated for $C_{36}H_{47}N_2O_6$ $[2M+H]^+$ 603.3429, found 603.3443.

I.R. (neat) ν_{max} = 1735, 1696, 1454, 1389, 1215, 1150 (cm^{-1}).

M.P.= 74-75 °C.



181

5-ethylsulfanyl-4-trimethylsilanylmethylene-3,4-dihydro-2*H*-pyrrole-2-carboxylic acid ethyl ester

To a heavy walled Pyrex tube were added 2-Isocyano-5-trimethylsilanylpent-4-ynoic acid ethyl ester **155** (35 mg, 0.156 mmol, 1.0 eq), ethanethiol (26 μL, 0.343 mmol, 2.2 eq), ACN (7.5 mg, 0.03 mmol, 0.2 eq) in 3 mL of dry toluene. The Pyrex tube was then capped and the reaction mixture was flushed with nitrogen. Heating was then applied by means of microwave irradiation (130 °C) for 5 minutes. The reaction tube was then allowed to cool before any handling of the reaction took place. The solvent was removed under reduced pressure. Purification by flash chromatography (hexane:ethyl acetate, 5:1) afforded the title compound **181** as colourless liquid (38 mg, 86%), R_f = 0.41.

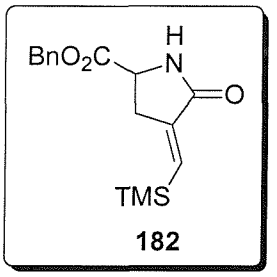
δ_H (400 MHz; $CDCl_3$): 0.17 (9H, s, $(CH_3)_3Si$), 1.28 (3H, t, J = 7.0 Hz, CH_3CH_2O), 1.36 (3H, t, J = 7.0 Hz, CH_3CH_2S), 2.73 (2H, m, $NCHCH_2$), 3.08 (1H, m, CHHS), 3.16 (1H, m, CHHS), 4.24 (2H, q, J = 7.0 Hz, CH_2O), 5.80 (1H, s, TMSCH=C);

δ_C (100 MHz; $CDCl_3$): 0.0, 15.2, 25.6, 25.8, 34.6, 62.2, 72.5, 125.8, 154.5, 173.2, 175.5;

ES$^+$/MS: m/z 593 (65%), $[2M+Na]^+$;

HRMS (ES$^+$): m/z calculated for $C_{13}H_{24}NO_2SSi$ $[M+H]^+$ 286.1291527, found 286.1292920;

I.R. (neat) ν_{max} = 1728, 1581, 1448, 1191 (cm^{-1}).



182

5-Oxo-4-trimethylsilanylmethylene-pyrrolidine-2-carboxylic acid benzyl ester

To a heavy walled Pyrex tube were added 2-isocyano-5-trimethylsilanylpent-4-ynoic acid benzyl ester **157** (42 mg, 0.147 mmol, 1.0 eq), 2-mercaptoethanol (21 μL, 0.294 mmol, 2.0 eq), AIBN (7.6 mg, 0.029 mmol, 0.2 eq) in 3 mL of dry toluene. The Pyrex tube was then capped and the reaction mixture was flushed with nitrogen. Heating was then applied by means of microwave irradiation (130 °C) for 5 minutes. The reaction tube was then allowed to cool before any handling of the reaction took place. The solvent was removed under reduced pressure. Purification by flash chromatography (hexane:ethyl acetate, 4:1) afforded the title compound **182** as white solid (33 mg, 72%), $R_f = 0.43$.

δ_H (400 MHz; $CDCl_3$): 0.17 (9H, s, $(CH_3)_3Si$), 2.94 (1H, ddd, J = 18.5, 4.0, 3.0 Hz, NCHC*H*H), 3.16 (1H, ddd, J = 17.5, 9.0, 2.5 Hz, NCHCH*H*), 4.30 (1H, dd, J = 8.5, 5.0 Hz, NCH), 5.19 (2H, s, $PhCH_2$), 6.61 (1H, bs, NH), 6.69 (1H, t, J = 2.5 Hz, TMSC*H*=C), 7.36 (5H, s, PhH);

δ_C (100 MHz; $CDCl_3$): 0.0, 31.5, 53.5, 68.7, 129.6, 129.9, 134.5, 136.2, 143.6, 170.7, 172.5;

Other data available: DEPT, H-H and H-C correlations;

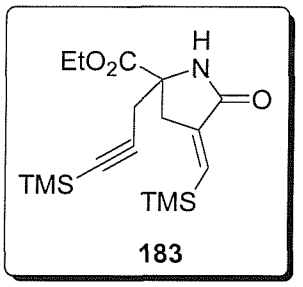
C.I. GC/MS: m/z, relative intensity and ion. m/z 304 (8%), $[M+H]^+$; m/z 91 (100%), $[ArCH_2]^+$; Retention time: 16.67 min;

HRMS (ES^+): m/z calculated for $C_{16}H_{21}NO_3SiNa$ $[M+Na]^+$ 326.1183, found 326.1184;

I.R. (neat) ν_{max} = 3225, 1743, 1696, 1455, 1363, 1247, 1191 (cm^{-1});

Elemental analysis: Found C, 63.03; H, 6.97; N, 4.60: $C_{16}H_{21}NO_3Si$ requires C, 63.33; H, 6.98; N, 4.61; Silicon could not be analysed;

M. P. = 91-92 °C.



183

5-Oxo-4-trimethylsilanylmethylene-2-(3-trimethylsilanyl-prop-2-ynyl)-pyrrolidine-2-carboxylic acid ethyl ester

To a heavy walled Pyrex tube were added 2-Isocyano-5-trimethylsilanyl-2-(3-trimethylsilanyl-prop-2-ynyl)-pent-4-ynoic acid ethyl ester **156** (50 mg, 0.148 mmol, 1.0 eq), 2-mercaptoethanol (22 μL, 0.296 mmol, 2.0 eq), ACN (7.0 mg, 0.029 mmol, 0.2 eq) in 4 mL of dry toluene. The Pyrex tube was then capped and the reaction mixture was flushed with nitrogen. Heating was then applied by means of microwave irradiation (130 °C) for 5 minutes. The reaction tube was then allowed to cool before any handling of the reaction took place. The solvent was removed under reduced pressure. Purification by flash chromatography (hexane:ethyl acetate, 7:1) afforded the title compound **183** as white solid (37 mg, 73%), $R_f = 0.21$.

δ_H (400 MHz; $CDCl_3$): 0.10 (9H, s, $(CH_3)_3Si$), 0.14 (9H, s, $(CH_3)_3Si$), 1.27 (3H, t, J = 7.0 Hz, CH_3CH_2O), 2.57 (1H, s, $CHHC{\equiv}CTMS$), 2.61 (1H, s, $CHHC{\equiv}CTMS$), 2.79-2.86 (1H, m, $TMSCH{=}CCHH$), 3.12 (1H, dd, J = 17.5, 3.0 Hz, $TMSCH{=}CCHH$), 4.22 (2H, q, J = 7.0 Hz, CH_2O), 6.57 (1H, bs, NH), 6.67 (1H, t, J = 2.0 Hz, $TMSCH{=}C$);

δ_C (100 MHz; $CDCl_3$): 0.0, 0.9, 15.3, 32.8, 37.5, 62.5, 63.4, 90.6, 100.7, 134.5, 144.3, 169.7, 173.1;

Other data available: DEPT, H-H and H-C correlations;

ES^+/MS: m/z 725 (100%), $[2M+Na]^+$, m/z 703 (35%), $[2M+H]^+$;

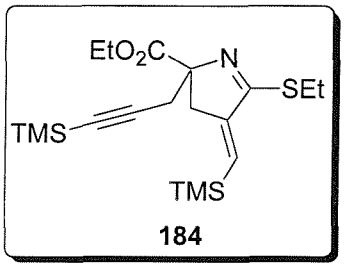
HRMS (ES^+): m/z calculated for $C_{17}H_{29}NO_3Si_2Na$ $[M+Na]^+$ 374.1578, found 374.1581;

I.R. (neat) ν_{max} = 3215, 2180, 1736, 1702, 1414, 1314, 1247, 1196, 1026;

Elemental analysis: Found C, 57.64; H, 8.30; N, 3.91: $C_{17}H_{29}NO_3Si_2$ requires C, 58.07; H, 8.31; N, 3.98; Silicon could not be analysed;

M. P. = 70-71 °C.

Compound **183** was also synthesised using traditional thermal heating, 110 °C for 2.5 hours, with a 37% isolated yield. Data agrees with that reported above.



184

5-Ethylsulfanyl-4-trimethylsilanylmethylene-2-(3-trimethylsilanyl-prop-2-ynyl)-3,4-dihydro-2H-pyrrole-2-carboxylic acid ethyl ester

2-Isocyano-5-trimethylsilanyl-2-(3-trimethylsilanyl-prop-2-ynyl)-pent-4-ynoic acid ethyl ester **156** (50 mg, 0.148 mmol, 1.0 eq), was dissolved in 3.0 mL of dry toluene, to the stirred solution (under Argon) were added ethanethiol (22.6 μL, 0.296 mmol, 2.0 eq) and ACN (7.0 mg, 0.029 mmol, 0.2 eq). The resulting reaction mixture was heated by means of microwave irradiation at 130 °C for 5 min. The reaction was then stopped and the solvent removed under reduced pressure. Purification by flash chromatography (hexane:ethyl acetate, 7:1) afforded the title compound **184** as colourless liquid (44 mg, 80%), $R_f = 0.46$.

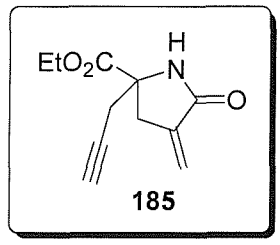
δ_H (400 MHz; $CDCl_3$): 0.09 (9H, s, $(CH_3)_3Si$), 0.17 (9H, s, $(CH_3)_3Si$), 1.26 (3H, t, J = 7.0 Hz, CH_3CH_2O), 1.35 (3H, t, J = 7.5 Hz, CH_3CH_2S), 2.81 (1H, d, J = 17.0 Hz, CHHC≡CTMS), 2.86 (1H, dd, J = 17.0, 2.5 Hz, TMSCH=CCHH), 2.92 (1H, d, J = 17.0 Hz, HHCC≡CTMS), 3.06 (1H, dd, J = 17.0, 3.0 Hz, TMSCH=CCHH), 3.08 (1H, m, CHHS), 3.13 (1H, m, CHHS), 4.20 (2H, q, J = 7.0 Hz, CH_2O), 5.93 (1H, t, J = 2.5 Hz, TMSCH=C);

δ_C (100 MHz; $CDCl_3$): -1.1, -0.2, 14.1, 14.4, 24.7, 29.9, 38.2, 61.5, 78.7, 87.5, 101.9, 124.3, 154.6, 172.4, 173.7;

ES$^+$/MS: m/z 396 (100%), $[M+H]^+$;

HRMS (ES$^+$): m/z calculated for $C_{19}H_{34}NO_2SSi_2Na$ $[M+H]^+$ 396.1843295, found 396.1844350;

I.R. (neat) ν_{max} = 1738, 1583, 1461, 1369, 1178 (cm^{-1}).



185

4-Methylene-5-oxo-2-prop-2-ynyl-pyrrolidine-2-carboxylic acid ethyl ester

To a heavy walled Pyrex tube were added 2-isocyano-2-prop-2-ynyl-pent-4-ynoic acid ethyl ester **158** (50 mg, 0.264 mmol, 1.0 eq), 2-mercaptoethanol (37.3 μL, 0.529 mmol, 2.0 eq), ACN (12.5 mg, 0.052 mmol, 0.2 eq) in 3 mL of dry toluene. The Pyrex tube was then capped and the reaction mixture was flushed with nitrogen. Heating was then applied by means of microwave irradiation (130 °C) for 5 minutes. The reaction tube was then allowed to cool before any handling of the reaction took place. The solvent was removed under reduced pressure. Purification by flash chromatography (hexane:ethyl acetate, 2:1) afforded the title compound **185** as yellow liquid (33 mg, 60%), R_f = 0.23.

δ_H (400 MHz; $CDCl_3$): 1.29 (3H, t, J = 7.0 Hz, CH_3CH_2O), 2.07 (1H, t, J = 2.5 Hz, $CH{\equiv}CCH_2$), 2.59 (1H, dd, J = 16.5, 3.0 Hz, $CHHC{=}CH_2$), 2.81 (1H, dd, J = 16.5, 2.5 Hz, $CHHC{=}CH_2$), 2.87 (1H, d, J = 17.5 Hz, $CH{\equiv}CCHH$), 3.18 (1H, d, J = 17.0 Hz, $CH{\equiv}CCHH$), 4.24 (2H, q, J = 7.0 Hz, CH_2O), 5.40 (1H, t, J = 2.5 Hz, $CH_2C{=}CHH$), 6.05 (1H, t, J = 2.5 Hz, $CH_2C{=}CHH$), 6.44 (1H, bs, NH);

δ_C (100 MHz; $CDCl_3$): 14.5, 30.4, 36.4, 61.8, 62.7, 72.8, 118.1, 128.7, 137.4, 169.1, 172.0.

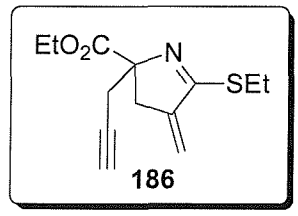
Other data available: DEPT, H-H and H-C correlations;

ES^+/MS: m/z 437 (100%), $[2M+Na]^+$;

HRMS (ES^+): m/z calculated for $C_{11}H_{13}NO_3Na$ $[M+Na]^+$ 230.0787, found 230.0790;

I.R. (neat) ν_{max} = 1728, 1704, 1656, 1426, 1261, 1198 (cm^{-1}).

Compound **185** was also synthesised using traditional thermal heating, 80 °C for 6.0 hours, with a 37% isolated yield. Data agrees with that reported above.



186

5-Ethylsulfanyl-4-methylene-2-prop-2-ynyl-3,4-dihydro-2H-pyrrole-2-carboxylic acid ethyl ester

To a heavy walled Pyrex tube were added 2-isocyano-2-prop-2-ynyl-pent-4-ynoic acid ethyl ester **158** (50 mg, 0.264 mmol, 1.0 eq), ethanethiol (40 μL, 0.529 mmol, 2.0 eq), ACN (12.5 mg, 0.052 mmol, 0.2 eq) in 3 mL of dry toluene. The Pyrex tube was then capped and the reaction mixture was flushed with nitrogen. Heating was then applied by means of microwave irradiation (130 °C) for 5 minutes. The reaction tube was then allowed to cool before any handling of the reaction took place. The solvent was removed under reduced pressure. Purification by flash chromatography (hexane:ethyl acetate, 5:1) afforded the title compound **186** as yellow liquid (27 mg, 41%), $R_f = 0.60$.

δ_H (400 MHz; $CDCl_3$): 1.26 (3H, t, J = 7.0 Hz, CH_3CH_2O), 1.34 (3H, t, J = 7.0 Hz, CH_3CH_2S), 1.92 (1H, t, J = 2.5 Hz, $CH{\equiv}C$), 2.68 (1H, dd, J = 16.5, 2.5 Hz, $CH{\equiv}CCHH$), 2.85 (1H, dt, J = 17.0, 2.5 Hz, $CHHC{=}CH_2$), 2.93 (1H, dd, J = 16.5, 2.5 Hz, $CH{\equiv}CCHH$), 3.11 (2H, m, CH_2S), 3.16 (1H, dt, J = 17.0, 2.5 Hz, $CHHC{=}CH_2$), 4.20 (2H, q, J = 7.0 Hz, CH_2O), 5.27 (1H, dt, J = 19.0, 2.5 Hz, $CH_2C{=}CHH$), 5.37 (1H, dt, J = 19.0, 2.5 Hz, $CH_2C{=}CHH$);

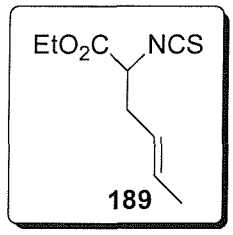
δ_C (100 MHz; $CDCl_3$): 14.4, 14.5, 25.0, 28.6, 38.5, 61.5, 61.8, 70.9, 109.8, 123.5, 129.0, 172.3, 172.9;

Other data available: DEPT, H-H and H-C correlations;

ES$^+$/MS: m/z 252 (100%), $[M+H]^+$;

HRMS (ES$^+$): m/z calculated for $C_{13}H_{17}NO_2SNa$ $[M+Na]^+$ 274.872206, found 274.874270;

I.R. (neat) ν_{max} = 1731, 1580, 1543, 1447, 1261, 1198, 1040 (cm^{-1}).

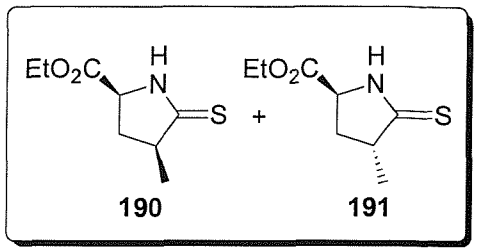


189

2-Isothiocyanato-hex-4-enoic acid ethyl ester

To a heavy walled Pyrex tube were added 2-isocyano-hex-4-enoic acid ethyl ester **150** (112 mg, 0.67 mmol, 1.0 eq), *tert*-butyl mercaptan (107 μL, 0.951 mmol, 1.4 eq), AIBN (23 mg, 0.146 mmol, 0.2 eq) in 2.0 mL of dry toluene. The Pyrex tube was then capped and the reaction mixture was flushed with argon. Heating was then applied by means of microwave irradiation (140 °C) for 6 minutes. The reaction tube was then allowed to cool for a couple of minutes before any handling of the reaction took place. The solvent was removed under reduced pressure. Purification by flash chromatography (hexane:ethyl acetate, 8:1) afforded the title compound **189** (106 mg, 80% yield)

δ_H (300 MHz; $CDCl_3$): 1.3 (3H, t, J = 7.0 Hz, CH_3CH_2O), 1.7 (3H, d, J = 6.0 Hz, CH_3CH=CH), 2.5-2.8 (2H, m, $CHCH_2CH$=CH), 4.20 (3H, q, J = 7.0 Hz, CH_2O), 4.25 (1H, m, NCH) 5.3-5.4 (1H, m, $CHCH_2CH$=CHMe), 5.5-5.8 (1H, m, $CHCH_2CH$=CHMe).
δ_C (75 MHz; $CDCl_3$): 14.3, 18.1, 37.1, 59.7, 62.6, 122.6, 131.7, 168.2.
C.I. GC/MS. m/z, relative intensity and ion. 200 (78%), $[M+H]^+$; 217 (58%), $[M+NH_4]^+$.
HRMS (EI): m/z calcd for $C_9H_{13}NO_2S$ (M^+) 199.06691, found 199.06670;
I.R. (neat) ν_{max} = 2048, 1744, 1250, 1198, 1022 (cm^{-1}).



190 **191**

***cis*-4-Methyl-5-thioxo-pyrrolidine-2-carboxylic acid ethyl ester (190)**

***trans*-4-Methyl-5-thioxo-pyrrolidine-2-carboxylic acid ethyl ester (191)**

To a heavy walled Pyrex tube were added 2-isocyanopent-4-enoic acid ethyl ester **83** (118 mg, 0.771 mmol, 1.0 eq), *tert*-butyl mercaptan (112 μL, 1.0 mmol, 1.3 eq), AIBN (23 mg, 0.146 mmol, 0.2 eq) in 2.0 mL of dry toluene. The Pyrex tube was then capped and the reaction mixture was flushed with argon. Heating was then applied by means of microwave irradiation (140 °C) for 6 minutes. The reaction tube was then allowed to cool for a couple of minutes before any handling of the reaction took place. It was then added tri-*n*-butyltin hydride (235 μL, 0.848 mmol, 1.1 eq) and AIBN (23 mg), the Pyrex tube was then capped and the reaction mixture was flushed with argon. Heating was then applied by means of microwave irradiation (140 °C) for 6 minutes. The reaction tube was then allowed to cool. The solvent was removed under reduced pressure. Purification by flash chromatography (hexane:ethyl acetate, 8:1) afforded the title compounds **190** and **191**, as 1:1 diastereomeric mixture, (115 mg, 79% yield).

***cis*-4-Methyl-5-thioxo-pyrrolidine-2-carboxylic acid ethyl ester (190)**

δ_H (400 MHz; $CDCl_3$): 1.22 (3H, d, J = 7.0 Hz, CH_3CH), 1.30 (3H, t, J = 7.0 Hz, CH_3CH_2O), 1.89 (1H, dt, J = 12.0, 9.0 Hz, NCHC*H*H), 2.76 (1H, dt, 12.0, 8.0 Hz, NCHCH*H*), 2.80-2.97 (1H, m, CH_3CH), 4.23 (2H, q, J = 7.0 Hz, CH_2O), 4.4 (1H, m, CHN), 8.0 (1H, br s, N*H*);

δ_C (100 MHz; $CDCl_3$): 14.5, 19.2, 35.5, 47.4, 60.2, 62.4, 170.3, 211.2;

E.I. GC/MS. m/z, relative intensity and ion. m/z 188 (%), $[M+H]^+$; m/z 156 (100%), $[M-Et]^+$; Retention time: 12.97 min;

trans-4-Methyl-5-thioxo-pyrrolidine-2-carboxylic acid ethyl ester (191)

δ_H (400 MHz; $CDCl_3$): 1.22 (3H, d, J = 7.0 Hz, CH_3CH), 1.30 (3H, t, J = 7.0 Hz, CH_3CH_2O), 2.15 (1H, dt, J = 13.0, 7.5 Hz, CH_3CHCHH), 2.54-2.62 (1H, m, CH_3CHCHH), 2.80-2.97 (1H, m, CH_3CH), 4.23 (2H, q, J = 7.0 Hz, CH_2O), 4.4 (1H, m, CHN), 8.0 (1H, br s, NH);

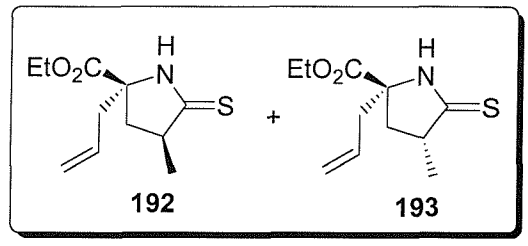
δ_C (100 MHz; $CDCl_3$): 14.5, 19.3, 35.2, 46.7, 60.3, 62.4, 170.5, 212.2.

E.I. GC/MS. m/z, relative intensity and ion. m/z 188 (44%), $[M+H]^+$; m/z 156 (100%), $[M-Et]^+$; Retention time: 12.99 min;

Other data available: DEPT, H-H and H-C correlations;

HRMS (EI): m/z calculated for $C_8H_{13}NO_2S$ $[M]^+$ 187.06670, found 187.06715;

I.R. (neat) ν_{max} = 1736, 1494, 1453, 1374, 1251, 1208, 1027 (cm^{-1}).



192 193

2-Allyl-_cis_-4-methyl-5-thioxo-pyrrolidine-2-carboxylic acid ethyl ester (192)

2-Allyl-_trans_-4-methyl-5-thioxo-pyrrolidine-2-carboxylic acid ethyl ester (193)

To a heavy walled Pyrex tube were added 2-isocyano-pent-4-enoic acid ethyl ester **84** (108 mg, 0.559 mmol, 1.0 eq), tert-butyl mercaptan (81.5 μL, 0.727 mmol, 1.3 eq), AIBN (17.5 mg, 0.111 mmol, 0.2 eq) in 2.0 mL of dry toluene. The Pyrex tube was then capped and the reaction mixture was flushed with argon. Heating was then applied by means of microwave irradiation (140 °C) for 6 minutes. The reaction tube was then allowed to cool for a couple of minutes, it was then added tri-_n_-butyltin hydride (170 μL, 0.614 mmol, 1.1 eq) and AIBN (23 mg), the Pyrex tube was then capped and the reaction mixture was flushed with argon. Heating was then applied by means of microwave irradiation (140 °C) for 6 minutes. The reaction tube was then allowed to cool and the solvent was removed under reduced pressure. Purification by flash chromatography (hexane:ethyl

acetate, 7:1) afforded the title compounds **192** and **193**, as 1:1 diastereomeric mixture, (113 mg, 90% yield).

2-Allyl-*cis*-4-methyl-5-thioxo-pyrrolidine-2-carboxylic acid ethyl ester (192)

δ_H (400 MHz; $CDCl_3$): 1.27 (3H, d, J = 7.0 Hz, CH_3CH), 1.31 (3H, t, J = 7.0 Hz, CH_3CH_2O), 1.77 (1H, dd, J = 16.0, 13.0 Hz, CH_3CHCHH), 2.41-2.51 (1H, m, CH_2=$CHCHH$), 2.64 (1H, dd, J = 14.0, 6.5 Hz, CH_2=$CHCHH$), 2.81-2.86 (2H, m, CH_3CHCHH), 4.23 (2H, q, J = 7.0 Hz, CH_2O), 5.2 (2H, m, CH_2=CH), 5.6 (1H, m, CH_2=CH), 7.98 (1H, br s, N*H*);

δ_C (100 MHz; $CDCl_3$): 14.9, 19.7, 41.5, 43.4, 47.1, 62.8, 70.6, 121.8, 131.3, 172.3, 210.7;

E.I. GC/MS. m/z, relative intensity and ion. m/z 227 (80%), $[M]^+$; m/z 154 (100%), $[M\text{-}EtO_2C]^+$; Retention time: 13.24 min;

2-Allyl-*trans*-4-methyl-5-thioxo-pyrrolidine-2-carboxylic acid ethyl ester (193)

δ_H (400 MHz; $CDCl_3$): 1.28 (3H, d, J = 7.0 Hz, CH_3CH), 1.32 (3H, t, J = 7.0 Hz, CH_3CH_2O), 2.12 (1H, dd, J = 13.0, 8.5 Hz, CH_3CHCHH), 2.41-2.51 (2H, m, CH_2=$CHCHH$ and CH_3CHCHH), 2.71 (1H, dd, J = 14.0, 6.5 Hz, CH_2=$CHCHH$), 2.91 (1H, m, CH_3CH), 4.22 (2H, q, J = 7.0 Hz, CH_2O), 5.2 (2H, m, CH_2=CH), 5.6 (1H, m, CH_2=CH), 8.06 (1H, br s, N*H*);

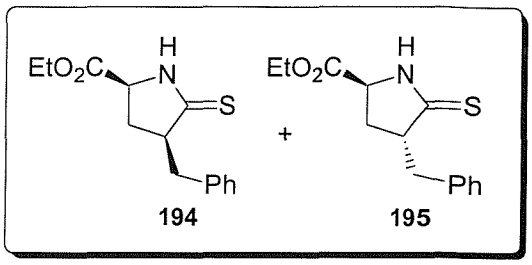
δ_C (100 MHz; $CDCl_3$): 14.9, 19.9, 40.6, 43.6, 47.1, 62.9, 70.7, 121.9, 131.1, 172.3, 211.4;

Other data available: DEPT, H-H and H-C correlations;

E.I. GC/MS. m/z, relative intensity and ion. m/z 227 (86%), $[M]^+$; m/z 154 (96%), $[M\text{-}EtO_2C]^+$; Retention time: 13.34 min;

HRMS (ES^+): m/z calculated for $C_{11}H_{18}NO_2S$ $[M+H]^+$ 228.1053, found 228.1055;

I.R. (neat) ν_{max} = 1736, 1494, 1452, 1216, 1174, 1029.



cis-4-Benzyl-5-thioxo-pyrrolidine-2-carboxylic acid ethyl ester (194)

trans-4-Benzyl-5-thioxo-pyrrolidine-2-carboxylic acid ethyl ester (195)

To a heavy walled Pyrex tube were added 2-isocyano-5-phenylpent-4-enoic acid ethyl ester **148** (128 mg, 0.559 mmol, 1.0 eq), tert-butyl mercaptan (81.5 μL, 0.727 mmol, 1.3 eq), AIBN (17.5 mg, 0.111 mmol, 0.2 eq) in 2.5 mL of dry toluene. The Pyrex tube was then capped and the reaction mixture was flushed with nitrogen. Heating was then applied by means of microwave irradiation (140 °C) for 6 minutes. The reaction tube was then allowed to cool for a couple of minutes, it was then added tri-*n*-butyltin hydride (170 μL, 0.614 mmol, 1.1 eq) and AIBN (23 mg), the Pyrex tube was then capped and the reaction mixture was flushed with nitrogen. Heating was then applied by means of microwave irradiation (140 °C) for 6 minutes. The reaction tube was then allowed to cool and the solvent was removed under reduced pressure. Purification by flash chromatography (hexane:ethyl acetate, 7:1) afforded the title compounds **194** and **195**, as 2:1 diastereomeric mixture, (112 mg, 76% yield).

cis-4-Benzyl-5-thioxo-pyrrolidine-2-carboxylic acid ethyl ester (194)

δ_H (400 MHz; $CDCl_3$): 1.19 (3H, t, J = 7.0 Hz, CH_3CH_2O), 1.90 (1H, dt, J = 13.0, 9.0 Hz, NCHC*H*H), 2.43 (1H, dt, 13.0, 8.0 Hz, NCHCH*H*), 2.52 (1H, dd, J = 14.0, 10.5 Hz, PhCH*H*), 3.0 (1H, m, $PhCH_2CH$), 3.56 (1H, dd, J = 14.0, 4.0 Hz, PhC*H*H), 4.04 (1H, dd, J = 9.0, 5.0 Hz, CHN), 4.14 (2H, q, J = 7.0 Hz, CH_2O), 7.82 (1H, br s, N*H*);

δ_C (100 MHz; $CDCl_3$): 14.5, 31.9, 32.7, 40.0, 54.1, 60.5, 62.4, 126.9, 129.0, 129.3, 129.5, 139.4, 170.1, 209.1;

***trans*-4-Benzyl-5-thioxo-pyrrolidine-2-carboxylic acid ethyl ester (195)**

δ_H (400 MHz; $CDCl_3$): 1.21 (3H, t, J = 7.0 Hz, CH_3CH_2O), 2.15-2.30 (2H, m, NCHC*HH*), 2.69 (1H, dd, J = 13.5, 9.5 Hz, PhCH*H*), 3.07-3.15 (1H, m, $PhCH_2CH$), 3.36 (1H, dd, J = 13.5, 4.0 Hz, PhC*H*H), 4.11 (2H, q, J = 7.0 Hz, CH_2O), 4.30 (1H, t, J = 8.0 Hz, CHN), 7.70 (1H, br s, N*H*);

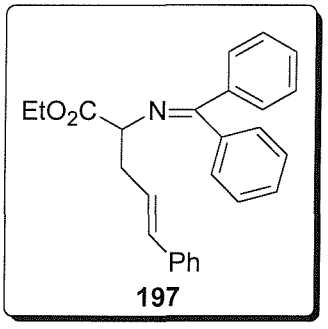
δ_C (100 MHz; $CDCl_3$): 14.5, 32.2, 39.9, 53.5, 60.7, 62.5, 127.1,129.0, 129.3, 129.5, 138.9, 170.1, 209.1;

Other data available: DEPT, H-H and H-C correlations;

E.I. GC/MS. m/z, relative intensity and ion. m/z 263 (10%), $[M]^+$; m/z 91 (100%), $[PhCH_2]^+$; Retention time: 16.40 min;

HRMS (EI): m/z calculated for $C_{14}H_{17}NO_2S$ $[M]^+$ 263.09800, found 263.09789;

I.R. (neat) ν_{max} = 1736, 1494, 1251, 1208, 1027.



197

2-(Benzhydrylidene-amino)-5-phenylpent-4-enoic acid ethyl ester

To a heavy walled Pyrex tube were added diphenylmethylene-glycine ethyl ester **196** (500 mg, 1.87 mmol, 1.0 eq), cinnamyl bromide (426 mg, 2.05 mmol, 1.1 eq) and BEMP (811 μL, 2.8 mmol, 1.5 eq) in 3.0 mL of dry acetonitrile. The Pyrex tube was then capped and the reaction mixture was flushed with nitrogen. Heating was then applied by means of microwave irradiation (110 °C) for 10 minutes. The reaction tube was then allowed to cool for a couple of minutes before any handling of the reaction took place. The solvent was removed under reduced pressure. Purification by flash chromatography (hexane:ethyl acetate, 7:1) afforded the title compound **197** (653 mg, 91% yield).

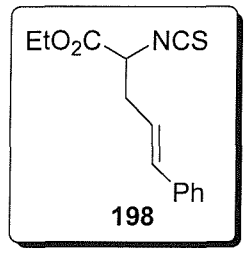
δ_H (400 MHz; $CDCl_3$): 1.18 (3H, t, J = 7.0 Hz, CH_3CH_2O), 2.66-2.81 (2H, m, $CHCH_2$), 4.08-4.15 (3H, m, CHN + CH_2O), 5.93-6.0 (1H, m, CH=CHPh), 6.32 (1H, d, J = 14.0 Hz, PhCH=CH), 7.0-7.6 (15H, m, PhH);

δ_C (100 MHz; $CDCl_3$): 14.6, 37.6, 61.3, 66.0, 126.4, 126.5, 127.4, 128.3, 128.4, 128.8, 129.0, 129.2, 130.7, 133.0, 136.8, 137.8, 139.9, 137.85, 171.0, 172.1;

Also available: DEPT, H-H and H-C correlations;

I.R. (neat) ν_{max} = 1736, 1659, 1446, 1277, 1024.

Data were consistent with Lopez.[133]



198

2-Isothiocyanato-5-phenylpent-4-enoic acid ethyl ester

Compound **197** (552 mg, 1.44 mmol, 1.0 eq.) was dissolved diethyl ether (7.0 mL) and then 1N HCl (1.73 mL, 1.73 mmol, 1.2 eq.) was added and the resulting mixture stirred at room temperature for 12 hours. The aqueous phase was then separated, basified with K_2CO_3, and extracted with ethyl acetate (3 x 5 mL). The organic phase was then dried over $MgSO_4$, filtered and evaporated to dryness to give 2-amino-5-phenylpent-4-enoic acid ethyl ester as a brown foam (313 mg, 99% yield).

δ_H (400 MHz; $CDCl_3$): 1.09 (3H, t, J = 7 Hz, CH_3CH_2O), 2.8-2.9 (2H, m, $CHCH_2CH$=CH_2), 4.0-4.2 (3H, m, EtOOCCH + CH_3CH_2O), 6.0-6.2 (1H, m, $CHCH_2CH$=CHAr), 6.45 (1H, d, J = 14 Hz, ArCHCH), 7.0-7.3 (5H, m, ArH), 8.8 (bs, NH_2);

δ_C (100 MHz; $CDCl_3$): 14.45, 34.32, 53.52, 62.93, 122.18, 127.06, 128.01, 128.87, 135.84, 137.09, 169.06;

Also available: DEPT, H-H and H-C correlations;

ES$^+$/MS. m/z, relative intensity and ion. 220 (82%), $[M+H]^+$; 439 (100%), $[2M+H]^+$.

2-amino-5-phenylpent-4-enoic acid ethyl ester (60 mg, 0.235 mmol, 1.0 eq) was dissolved in a mixture of chloroform (7.0 mL) and aqueous $NaHCO_3$ solution (152 mg in 5.0 mL H_2O, 1.81 mmol, 7.7 eq.), and the mixture was vigorously stirred. Thiophosgene (25.7 μL, 0.336 mmol, 1.3 eq.) was added dropwise at 0 °C. After the addition the reaction mixture was stirred for further 3 hours. The two layers were then separated, and the aqueous phase washed with chloroform (3 x 5 mL). The combined organic layer was dried over $MgSO_4$ and concentrated. The residue was purified by flash column chromatography (DCM as eluent). It was obtained 44.6 mg of isothiocyanate **198** as a brownish liquid (73% yield).

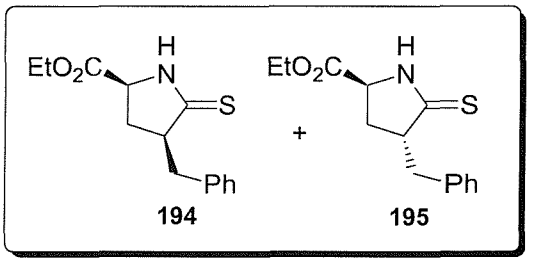
δ_H (300 MHz; $CDCl_3$): 1.2 (3H, t, J = 7.0 Hz, CH_3CH_2O), 2.7-2.9 (2H, m, $CHCH_2CH{=}CH$), 4.18 (3H, q, J = 7.0 Hz, CH_3CH_2O), 4.25 (1H, t, J = 7.0 Hz, CHN) 6.0-6.1 (1H, m, $CH{=}CHPh$), 6.48 (1H, d, J = 14.0 Hz, PhC*H*), 7.1-7.3 (5H, m, Ph*H*);

δ_C (75 MHz; $CDCl_3$): 14.3, 37.4, 59.6, 62.7, 122.4, 126.5, 127.9, 128.7, 135.4, 136.7, 168.0;

C.I. GC/MS. m/z, relative intensity and ion. 262 (66%), $[M+H]^+$; 279 (18%), $[M+NH_4]^+$; Retention time: 13.86 min;

HRMS (EI): m/z calcd for $C_{14}H_{15}NO_2S$ (M^+) 261.08235, found 261.08235;

I.R. (neat) ν_{max} = 2049, 1743, 1199, 1023 (cm^{-1}).



194 195

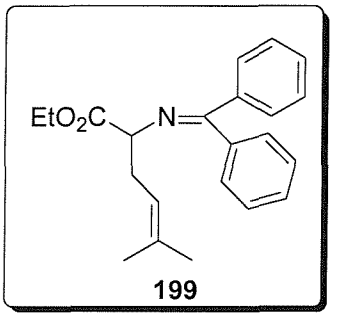
***cis*-4-Benzyl-5-thioxo-pyrrolidine-2-carboxylic acid ethyl ester (194)**

***trans*-4-Benzyl-5-thioxo-pyrrolidine-2-carboxylic acid ethyl ester (195)**

To a heavy walled Pyrex tube were added 2-isothiocyanato-5-phenylpent-4-enoic acid ethyl ester **198** (128 mg, 0.559 mmol, 1.0 eq), tri-*n*-butyltin hydride (46.2 μL, 0.166 mmol, 1.5

eq) and AIBN (3.6 mg, 0.022 mmol, 0.2 eq), the Pyrex tube was then capped and the reaction mixture was flushed with nitrogen. Heating was then applied by means of microwave irradiation (140 °C) for 6 minutes. The reaction tube was then allowed to cool and the solvent was removed under reduced pressure. Purification by flash chromatography (hexane:ethyl acetate, 7:1) afforded the title compounds **194** and **195**, as 1.3:1 diastereomeric mixture, (22.6 mg, 78% yield).

All data agrees with that reported above.



199

2-(Benzhydrylidene-amino)-5-methylhex-4-enoic acid ethyl ester

To a heavy walled Pyrex tube were added protected glycine ethyl ester **196** (500 mg, 1.87 mmol, 1.0 eq), 1-bromo-3-methyl-but-2-ene (246 μL, 2.05 mmol, 1.1 eq), BEMP (811 μL, 2.8 mmol, 1.5 eq) in 2.5 mL of dry acetonitrile. The Pyrex tube was then capped and the reaction mixture was flushed with argon. Heating was then applied by means of microwave irradiation (110 °C) for 10 minutes. The reaction tube was then allowed to cool for a couple of minutes before any handling of the reaction took place. The solvent was removed under reduced pressure. Purification by flash chromatography (Hexane:Ethyl Acetate, 7:1) afforded the title compound **199** (617 mg, 98% yield).

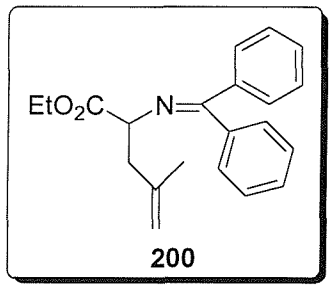
δ_H (400 MHz; $CDCl_3$): 1.31 (3H, t, J = 7.0 Hz, CH_3CH_2O), 1.60 (3H, s, CH_3CHCH_3), 1.70 (3H, s, CH_3CHCH_3), 2.56-2.71 (2H, m, CH_2CH=C), 4.12 (1H, dd, J = 7.5, 5.0 Hz, CHN), 4.23 (2H, q, J = 7.0 Hz, CH_2O), 5.04 (1H, m, CH=C), 7.19-7.70 (10H, m, Ph-H);

δ_C (100 MHz; $CDCl_3$): 13.3, 17.0, 24.9, 31.5, 59.9, 65.0, 119.0, 127.1, 127.4, 127.5, 127.6, 127.9, 129.33, 133.3, 135.7, 138.8, 169.1, 171.3;

Also available: DEPT, H-H and H-C correlations;

C.I. GC/MS. m/z, relative intensity and ion. 336 (70%), $[M+H]^+$; 266 (100%), $[M-CH_2CH=C(CH_3)_2]^+$; Retention time: 15.69 min;

I.R. (neat) ν_{max} = 1734, 1660, 1445, 1276, 1178 (cm^{-1}).



200

2-(Benzhydrylidene-amino)-4-methylpent-4-enoic acid ethyl ester

To a heavy walled Pyrex tube were added protected glycine ethyl ester **196** (500 mg, 1.87 mmol, 1.0 eq), 3-bromo-2-methyl-propene (211.5 μL, 2.05 mmol, 1.1 eq), BEMP (811 μL, 2.8 mmol, 1.5 eq) in 3.0 mL of dry acetonitrile. The Pyrex tube was then capped and the reaction mixture was flushed with argon. Heating was then applied by means of microwave irradiation (110 °C) for 10 minutes. The reaction tube was then allowed to cool for a couple of minutes before any handling of the reaction took place. The solvent was removed under reduced pressure. Purification by flash chromatography (hexane:ethyl acetate, 7:1) afforded the title compound **200** (581 mg, 97% yield).

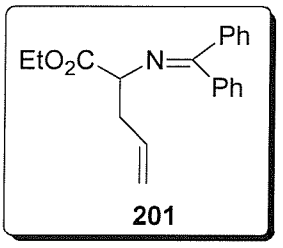
δ_H (400 MHz; $CDCl_3$): 1.32 (3H, t, J = 7.0 Hz, CH_3CH_2O), 1.55 (3H, s, CH_2CCH_3), 2.61-2.74 (2H, m, $CHCH_2$), 4.22-4.28 (3H, m, CHN and CH_2O), 4.77 (1H, s, C=CHH), 4.79 (1H, s, C=CHH),.7.21-7.69 (10H, m, Ar-H);

δ_C (100 MHz; $CDCl_3$): 14.0, 22.3, 41.8, 60.7, 64.1, 113.4, 127.8, 127.9, 128.2, 128.4, 128.6, 129.8, 130.0, 133.2, 136.1, 139.5, 141.3, 170.1, 171.9;

Also available: DEPT, H-H and H-C correlations;

E.I. GC/MS. m/z, relative intensity and ion. 321 (64%), $[M]^+$; 266 (86%), $[M-CH_2CCH_3=CH_2]^+$; Retention time: 15.26 min;

I.R. (neat) ν_{max} = 1736, 1660, 1445, 1277, 1179 (cm^{-1}).



201

2-(Benzhydrylidene-amino)-pent-4-enoic acid ethyl ester

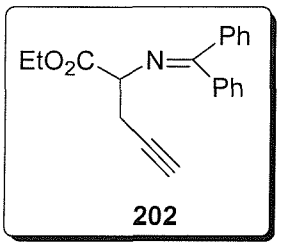
To a heavy walled Pyrex tube were added protected glycine ethyl ester **196** (100 mg, 0.374 mmol, 1.0 eq), allyl bromide (32.4 μL, 0.374 mmol, 1.0 eq), BEMP (162 μL, 0.561 mmol, 1.5 eq) in 2.5 mL of dry acetonitrile. The Pyrex tube was then capped and the reaction mixture was flushed with nitrogen. Heating was then applied by means of microwave irradiation (110 °C) for 10 minutes. The reaction tube was then allowed to cool for a couple of minutes before any handling of the reaction took place. The solvent was removed under reduced pressure. Purification by flash chromatography (hexane:ethyl acetate, 8:1) afforded the title compound **201** (109 mg, 94% yield). R_f = 0.38.

δ_H (400 MHz; $CDCl_3$): 1.27 (3H, t, J = 7.0 Hz, CH_3CH_2O), 2.59-2.80 (2H, m, $CHCH_2$), 4.11-4.27 (3H, m, CHN and CH_2O), 7.14-7.59 (10H, m, Ar-*H*);

E.I. GC/MS. m/z, relative intensity and ion. 307 (44%), $[M]^+$; 266 (100%), $[M-CH_2CH{=}CH_2]^+$; Retention time: 15.02 min;

I.R. (neat) ν_{max} = 1736, 1660, 1446, 1277, 1180 (cm^{-1}).

Data agrees with Lopez.[133]



202

2-(Benzhydrylidene-amino)-pent-4-ynoic acid ethyl ester

To a heavy walled Pyrex tube were added protected glycine ethyl ester **196** (500 mg, 1.87 mmol, 1.0 eq), propargyl bromide (188 μL, 2.05 mmol, 1.1 eq), BEMP (811 μL, 2.8 mmol, 1.5 eq) in 4.0 mL of dry acetonitrile. The Pyrex tube was then capped and the reaction mixture was flushed with nitrogen. Heating was then applied by means of microwave irradiation (110 °C) for 10 minutes. The reaction tube was then allowed to cool for a couple of minutes before any handling of the reaction took place. The solvent was removed under reduced pressure. Purification by flash chromatography (Hexane:Ethyl Acetate, 7:1) afforded the title compound **202** (467 mg, 82% yield).

δ_H (400 MHz; $CDCl_3$): 1.19 (3H, t, J = 7.0 Hz, CH_3CH_2O), 1.87 (1H, t, J = 2.5 Hz, CH≡C), 2.67-2.81 (2H, m, $CHCH_2$), 4.11 (2H, q, J = 7.0 Hz, CH_2O), 4.21 (1H, dd, J = 8, 5.5 Hz, CHN), 7.17-7.59 (10H, m, Ar-*H*);

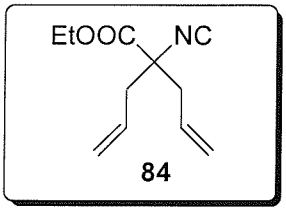
δ_C (100 MHz; $CDCl_3$): 14.5, 23.7, 61.6, 64.5, 70.6, 81.3, 128.4, 128.6, 128.8, 129.1, 129.4, 130.8, 136.4, 139.9, 170.9, 172.2;

Also available: DEPT, H-H and H-C correlations;

I.R. (neat) ν_{max} = 1733, 1659, 1445, 1277, 1180 (cm^{-1}).

Data agrees with Lopez.[133]

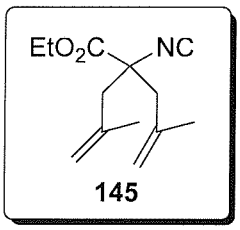
EXPERIMENTAL-CHAPTER 4



84

Ethyl-2-allyl-2-isocyanopent-4-enoate

An heterogeneous mixture of ethylisocyanoacetate (2.0 mL, 17.4 mmol, 1.0 eq), allyl bromide (3.32 mL, 38.2 mmol, 2.2 eq), TBAB (1.68 g, 5.2 mmol, 0.3 eq), finely ground technical grade potassium carbonate (7.2 g, 52.2 mmol, 3.0 eq) and acetonitrile (100 mL) was refluxed with stirring for 12 hours. The reaction mixture was then cooled, filtered and the solvent removed *in vacuo*. The residue was then dissolved in dry diethyl ether 100 mL, formation of a precipitate was observed, filtered and washed with water (3 x 100 mL), brine (3 x 100 mL) and dried over $MgSO_4$. After filtration the ether was removed *in vacuo*. Purification by flash chromatography (hexane:ethyl acetate, 8:1) gave the title compound **84** as a yellow oil (2.78 g, 83%). $R_f = 0.4$.
All data for product **84** agrees with that reported in chapter 2.

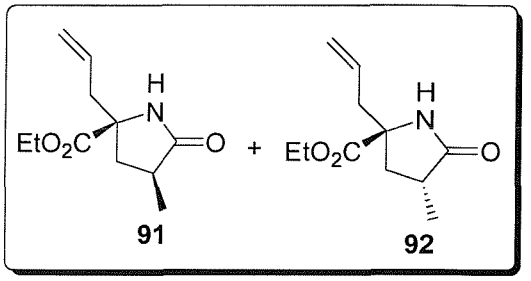


145

2-Isocyano-4-methyl-2-(2-methyl-allyl)-pent-4-enoic acid ethyl ester

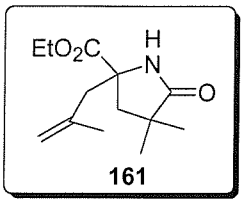
An heterogeneous mixture of ethylisocyanoacetate (1.5 mL, 13.05 mmol, 1.0 eq), 3-bromo-2-methyl-propene (3.11 mL, 30 mmol, 2.3 eq), finely ground potassium carbonate (7.2 g, 52.2 mmol, 4.0 eq), TBAB (2.1 g, 6.52 mmol, 0.5

eq) and dry acetonitrile (80 mL) was refluxed with stirring for 3 hours. The reaction mixture was then cooled, filtered and the solvent removed *in vacuo*. The residue was then dissolved in dry diethyl ether 100 mL, formation of a precipitate was observed, filtered and washed with water (3 x 100 mL), brine (3 x 100 mL) and dried over $MgSO_4$. After filtration the ether was removed *in vacuo*. Purification by flash chromatography (hexane:ethyl acetate, 4:1) gave the title compound **145** (yellow oil, 2.49 g, 86% yield), $R_f = 0.74$.
All data for product **145** agrees with that reported in chapter 3.



***cis*-2-Allyl-4-methyl-5-oxo-pyrrolidine-2-carboxylic acid ethyl ester (91)**
***trans*-2-Allyl-4-methyl-5-oxo-pyrrolidine-2-carboxylic acid ethyl ester (92)**

To a heavy walled Pyrex tube were added isocyanide **84** (2.785 g, 14.4 mmol, 1.0 eq), 2-mercaptoethanol (4.12 mL, 57.7 mmol, 4.0 eq), AIBN (236 mg, 1.44 mmol, 0.1 eq) in 1.5 mL of dry toluene. The Pyrex tube was then capped and the reaction mixture was flushed with nitrogen. Heating was then applied by means of microwave irradiation (130 °C) for 5 minutes. The solvent was removed under reduced pressure. Purification by flash chromatography (hexane:ethyl acetate, 3:2) afforded the title compound **91** and **92** (2.6 g, 86% yield) as a white solid (1.6:1 inseparable mixture of diastereoisomers).
All data for products **91** and **92** agrees with that reported in chapter 2.



161

4,4-Dimethyl-2-(2-methyl-allyl)-5-oxo-pyrrolidine-2-carboxylic acid ethyl ester

To a heavy walled Pyrex tube were added 2-isocyano-4-methyl-2-(2-methyl-allyl)-pent-4-enoic acid ethyl ester **145** (1.0 g, 4.5 mmol, 1.0 eq), 2-mercaptoethanol (1.285 mL, 18.01 mmol, 4.0 eq), ACN (220 mg, 0.9 mmol, 0.2 eq) in 3.5 mL of dry toluene. The Pyrex tube was then capped and the reaction mixture was flushed with nitrogen. Heating was then applied by means of microwave irradiation (130 °C) for 5 minutes. The reaction tube was then allowed to cool before any handling of the reaction took place. The solvent was removed under reduced pressure. Purification by flash chromatography (hexane:ethyl acetate, 3:2) afforded the title compound **161** as white crystalline solid (1.448 g, 67%), $R_f = 0.41$.

All data for product **161** agrees with that reported in chapter 3.

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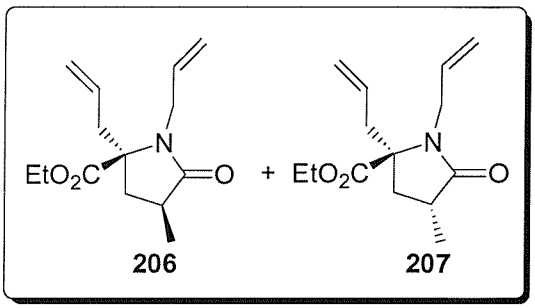


206 207

1,2-Diallyl-*cis*-4-methyl-5-oxo-pyrrolidine-2-carboxylic acid ethyl ester (206)
1,2-Diallyl-trans-4-methyl-5-oxo-pyrrolidine-2-carboxylic acid ethyl ester (207)

An homogeneous mixture of pyroglutamates **91/92** (180 mg, 0.853 mmol, 1.0 eq), allyl bromide (111.6 µL, 1.287 mmol, 1.5 eq), BEMP (503 µL, 1.706 mmol, 2.0 eq) in dry acetonitrile (15 mL) was refluxed with stirring for 12 hours. The reaction mixture was then cooled, and the solvent removed *in vacuo*. Purification by flash chromatography

(hexane:ethyl acetate, 3:2) gave the title compounds **206** and **207** as a yellowish oil (144.5 mg, 67% yield), 2:1 inseparable mixture of diastereoisomes.

The same reaction was performed using microwave irradiation, but the products were obtained in 19% yield only.

1,2-Diallyl-*cis*-4-methyl-5-oxo-pyrrolidine-2-carboxylic acid ethyl ester (206)

δ_H (400 MHz; $CDCl_3$): 1.18 (3H, d, J = 7.0 Hz, CH_3CH), 1.25 (3H, t, J = 7.0 Hz, CH_3CH_2O), 1.62 (1H, dd, J = 13.0, 10.5 Hz, CH_3CHCHH), 2.38 (1H, dd, J = 13.0, 9.0 Hz, CH_3CHCHH), 2.48-2.65 (2H, m, $CCH_2CH=CH_2$), 2.72 (1H, m, CH_3CH), 3.79-4.0 (2H, m, $NCH_2CH=CH_2$), 4.14 (2H, q, J = 7.0 Hz, CH_2O), 5.08-5.21 (4H, m, $NCH_2CH=CH_2$ and $CCH_2CH=CH_2$), 5.58-5.69 (2H, m, $CCH_2CH=CH_2$), 5.72-5.86 (1H, m, $NCH_2CH=CH_2$);

δ_c (100 MHz; $CDCl_3$): 14.4, 16.6, 35.2, 36.4, 39.3, 44.3, 61.9, 66.7, 117.6, 120.6, 131.8, 133.8, 173.4, 178.2;

C.I. GC/MS. m/z, relative intensity and ion. 252 (100%), $[M+H]^+$; Retention time: 11.71 min;

1,2-Diallyl-trans-4-methyl-5-oxo-pyrrolidine-2-carboxylic acid ethyl ester (207)

δ_H (300 MHz; $CDCl_3$): 1.21 (3H, d, J = 7.0 Hz, CH_3CH), 1.27 (3H, t, J = 7.0 Hz, CH_3CH_2O), 1.92 (1H, dd, J = 7.5, 13.5 Hz, CH_3CHCHH), 2.31 (1H, dd, J = 13.5, 10.0 Hz, CH_3CHCHH), 2.5-2.65 (3H, m, $CCH_2CH=CH_2$ and CH_3CH), 3.79-4.0 (2H, m, $NCH_2CH=CH_2$), 4.13 (2H, q, J = 7.0 Hz, CH_2O), 5.08-5.21 (4H, m, $NCH_2CH=CH_2$ and $CCH_2CH=CH_2$), 5.58-5.69 (2H, m, $CCH_2CH=CH_2$), 5.72-5.86 (1H, m, $NCH_2CH=CH_2$);

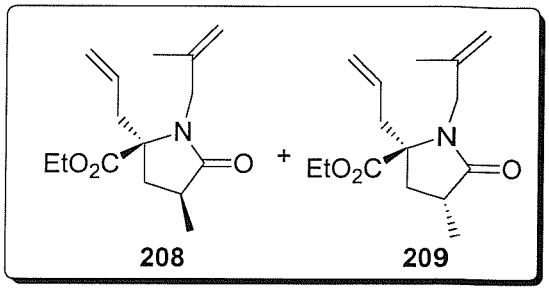
δ_c (100 MHz; $CDCl_3$): 14.4, 17.5, 35.3, 37.5, 39.6, 44.7, 62.0, 67.5, 117.8, 120.7, 131.8, 133.9, 173.5, 178.5;

Data available: DEPT, H-H, H-C correlations.

C.I. GC/MS. m/z, relative intensity and ion. 252 (100%), $[M+H]^+$; Retention time: 11.58 min;

HRMS (ES^+): m/z calculated for $C_{14}H_{21}NO_3Na$ $[M+Na]^+$ 274.1413, found 274.1413;

I.R. (neat) ν_{max} = 1731, 1693, 1451, 1391, 1254, 1192, 1144 (cm^{-1}).



208 209

2-Allyl-*cis*-4-methyl-1-(2-methyl-allyl)-5-oxo-pyrrolidine-2-carboxylic acid ethyl ester (208)
2-Allyl-*trans*-4-methyl-1-(2-methyl-allyl)-5-oxo-pyrrolidine-2-carboxylic acid ethyl ester (209)

An homogeneous mixture of pyroglutamates **91/92** (300 mg, 1.42 mmol, 1.0 eq), 3-bromo-2-methyl-propene (221 μL, 2.13 mmol, 1.5 eq), BEMP (628 μL, 2.13 mmol, 1.5 eq) in dry acetonitrile (15 mL) was refluxed with stirring for 12 hours. The reaction mixture was then cooled, and the solvent removed *in vacuo*. Purification by flash chromatography (hexane:ethyl acetate, 3:2) gave the title compounds **208** and **209** as a yellowish oil (358 mg, 95% yield), 2:1 inseparable mixture of diastereoisomes.

2-Allyl-*cis*-4-methyl-1-(2-methyl-allyl)-5-oxo-pyrrolidine-2-carboxylic acid ethyl ester (208)
δ_H (400 MHz; $CDCl_3$): 1.18 (3H, d, J = 7.0 Hz, CH_3CH), 1.23 (3H, t, J = 7.0 Hz, CH_3CH_2O), 1.59 (1H, dd, J = 13.5, 10.5 Hz, CH_3CHCHH), 1.69 (3H, s, $NCH_2=CCH_3CH_2$), 2.42 (1H, dd, J = 13.0, 8.5 Hz, CH_3CHCHH), 2.60 (1H, m, CH_3CHCH_2), 2.63-2.74 (1H, m, $CH_2=CHCH_2$), 3.82 (2H, m, $NCH_2CCH_3=CH_2$), 4.1 (2H, q, J = 7.0 Hz, CH_2O), 4.73 (1H, s, $CCH_3=CHH$), 4.79 (1H, s, $CCH_3=CHH$), 5.12-5.17 (2H, m, $CCH_2CH=CH_2$), 5.61 (1H, m, $CCH_2CH=CH_2$);
δ_c (100 MHz; $CDCl_3$): 14.5, 16.7, 20.9, 35.3, 37.9, 39.6, 47.2, 61.8, 66.9, 112.9, 120.4, 131.9, 141.6, 173.1, 178.6;
C.I. GC/MS. m/z, relative intensity and ion. 266 (100%), $[M+H]^+$; Retention time: 11.82 min;

2-Allyl-*trans*-4-methyl-1-(2-methyl-allyl)-5-oxo-pyrrolidine-2-carboxylic acid ethyl ester (209)
δ_H (400 MHz; $CDCl_3$): 1.21 (3H, d, J = 7.0 Hz, CH_3CH), 1.23 (3H, t, J = 7.0 Hz, CH_3CH_2O), 1.69 (3H, s, $NCH_2=CCH_3CH_2$), 2.0 (1H, dd, J = 13.0, 9.0 Hz, CH_3CHCHH), 2.42 (1H, dd, J = 13.0, 10.0 Hz, CH_3CHCHH), 2.51 (1H, m, CH_3CHCH_2), 2.63-2.74 (1H, m, $CH_2=CHCH_2$), 3.82 (2H, m, $NCH_2CCH_3=CH_2$), 4.1 (2H, q, J = 7.0 Hz, CH_2O), 4.68

(1H, s, CCH_3=C*H*H), 4.77 (1H, s, CCH_3=CH*H*), 5.12-5.17 (2H, m, CCH_2CH=CH_2), 5.61 (1H, m, $CHCH_2CH$=CH_2);

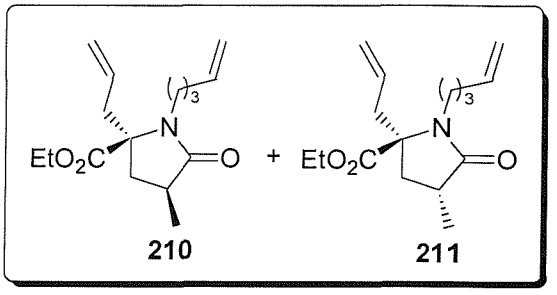
δ_c (100 MHz; $CDCl_3$): 14.4, 17.6, 20.8, 35.1, 37.9, 39.4, 47.1, 60.7, 67.3, 112.4, 120.6, 131.9, 141.5, 173.0, 178.4;

Data available: DEPT, H-H, H-C correlations.

C.I. GC/MS. m/z, relative intensity and ion. 266 (100%), $[M+H]^+$; Retention time: 11.95 min;

HRMS (ES^+): m/z calculated for $C_{15}H_{23}NO_3Na$ $[M+Na]^+$ 288.1570, found 288.1572;

I.R. (neat) ν_{max} = 1731, 1695, 1451, 1388, 1251, 1195, 1143 (cm^{-1}).



2-Allyl-*cis*-4-methyl-5-oxo-1-pent-4-enyl-pyrrolidine-2-carboxylic acid ethyl ester (210)
2-Allyl-*trans*-4-methyl-5-oxo-1-pent-4-enyl-pyrrolidine-2-carboxylic acid ethyl ester (211)

An homogeneous mixture of pyroglutamates **91/92** (327 mg, 1.549 mmol, 1.0 eq), 5-bromopent-1-ene (283.8 µL, 2.324 mmol, 1.5 eq), BEMP (685 µL, 2.324 mmol, 1.5 eq) in dry acetonitrile (10 mL) was refluxed with stirring for 12 hours. The reaction mixture was then cooled, and the solvent removed *in vacuo*. Purification by flash chromatography (hexane:ethyl acetate, 4:1) gave the title compounds **210** and **211** as a yellowish oil (162 mg, 38% yield), 1.3:1 inseparable mixture of diastereoisomes.

2-Allyl-*cis*-4-methyl-5-oxo-1-pent-4-enyl-pyrrolidine-2-carboxylic acid ethyl ester (210)

δ_H (400 MHz; $CDCl_3$): 1.16 (3H, d, J = 7.0 Hz, C*H*$_3$CH), 1.24 (3H, t, J = 7.0 Hz, C*H*$_3$$CH_2O$), 1.57 (1H, dd, J = 13.0, 10.5 Hz, CH_3CHCHH), 1.63 (2H, m, NCH_2CH_2), 2.03 (2H, m, $NCH_2CH_2CH_2$), 2.38 (1H, dd, J = 13.0, 8.5 Hz, CH_3CHCHH), 2.59 (1H, m, CH_3CHCHH), 2.60-2.77 (1H, m, CCH_2=$CHCH_2$), 3.13-3.22 (2H, m, NCH_2), 4.11-4.21

(2H, m, CH_2O), 4.97 (2H, m, $CH_2CH_2CH{=}CH_2$), 5.18 (2H, m, $CCH_2CH{=}CH_2$), 5.57-5.68 (1H, m, $CCH_2CH{=}CH_2$), 5.72-5.82 (1H, m, $CH_2CH_2CH{=}CH_2$);

δ_C (100 MHz; $CDCl_3$): 14.4, 16.6, 27.7, 31.8, 35.4, 36.4, 39.7, 41.5, 61.9, 66.8, 115.3, 120.5, 131.8, 138.0, 173.6, 178.7;

C.I. GC/MS. m/z, relative intensity and ion. 280 (100%), $[M+H]^+$; Retention time: 12.50 min;

2-Allyl-*trans*-4-methyl-5-oxo-1-pent-4-enyl-pyrrolidine-2-carboxylic acid ethyl ester (211)

δ_H (400 MHz; $CDCl_3$): 1.19 (3H, d, J = 7.0 Hz, CH_3CH), 1.27 (3H, t, J = 7.0 Hz, CH_3CH_2O), 1.63 (2H, m, NCH_2CH_2), 1.89 (1H, dd, J = 13.5, 7.0 Hz, CH_3CHCHH), 2.03 (2H, m, $NCH_2CH_2CH_2$), 2.28 (1H, dd, J = 13.0, 9.5 Hz, CH_3CHCHH), 2.51 (1H, m, CH_3CHCHH), 2.60-2.77 (1H, m, $CCH_2{=}CHCH_2$), 3.13-3.22 (2H, m, NCH_2), 4.11-4.21 (2H, m, CH_2O), 4.97 (2H, m, $CH_2CH_2CH{=}CH_2$), 5.18 (2H, m, $CCH_2CH{=}CH_2$), 5.57-5.68 (1H, m, $CCH_2CH{=}CH_2$), 5.72-5.82 (1H, m, $CH_2CH_2CH{=}CH_2$);

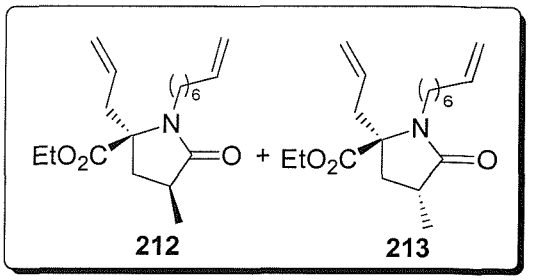
δ_C (100 MHz; $CDCl_3$): 14.4, 17.5, 27.6, 31.7, 35.3, 37.6, 39.9, 42.1, 62.0, 67.8, 115.3, 120.7, 131.9, 138.1, 173.7, 178.4;

Data available: DEPT, H-H, H-C correlations.

C.I. GC/MS. m/z, relative intensity and ion. 280 (100%), $[M+H]^+$; Retention time: 12.61 min;

HRMS (ES^+): m/z calculated for $C_{16}H_{25}NO_3Na$ $[M+Na]^+$ 302.1726, found 302.1729;

I.R. (neat) ν_{max} = 1729, 1695, 1454, 1392, 1198, 1146, 1201 (cm^{-1}).



2-Allyl-*cis*-4-methyl-1-oct-7-enyl-5-oxo-pyrrolidine-2-carboxylic acid ethyl ester (212)

2-Allyl-*trans*-4-methyl-1-oct-7-enyl-5-oxo-pyrrolidine-2-carboxylic acid ethyl ester (213)

An homogeneous mixture of pyroglutamates **91/92** (317 mg, 1.50 mmol, 1.0 eq), 8-bromooct-1-ene (651 μL, 3.75 mmol, 2.5 eq), BEMP (664 μL, 2.25 mmol, 1.5 eq) in dry acetonitrile (12 mL) was refluxed with stirring for 12 hours. The reaction mixture was then cooled, and the solvent removed *in vacuo*. Purification by flash chromatography (hexane:ethyl acetate, 4:1) gave the title compounds **212** and **213** as a yellowish oil (183 mg, 38% yield), 1.2:1 inseparable mixture of diastereoisomes. $R_f = 0.25$.

2-Allyl-*cis*-4-methyl-1-oct-7-enyl-5-oxo-pyrrolidine-2-carboxylic acid ethyl ester (212)

δ_H (400 MHz; $CDCl_3$): 1.15 (3H, d, J = 7.0 Hz, CH_3CH), 1.24 (3H, t, J = 7.0 Hz, CH_3CH_2O), 1.25-1.38 (6H, m, CH_2=$CHCH_2CH_2CH_2CH_2$), 1.42-1.58 (2H, m, NCH_2CH_2), 1.56 (1H, dd, J = 13.0, 10.5 Hz, CH_3CHCHH), 1.98-2.05 (2H, m, CH_2=$CHCH_2CH_2$), 2.37 (1H, dd, J = 13.0, 8.5 Hz, CH_3CHCHH), 2.57 (1H, m, CH_3CHCHH), 2.60-2.76 (1H, m, CH_2=$CHCH_2C$), 3.05-3.20 (2H, m, NCH_2), 4.15 (2H, q, J = 7.0 Hz, CH_2O), 4.92 (2H, m, CH_2CH_2CH=CH_2), 5.13-5.19 (2H, m, CCH_2CH=CH_2), 5.57-5.68 (1H, m, CCH_2CH=CH_2), 5.76 (1H, m, CH_2CH_2CH=CH_2);

δ_C (100 MHz; $CDCl_3$): 14.3, 16.6, 25.9, 27.4, 28.7, 29.1, 34.0, 35.4, 36.3, 39.6, 41.9, 62.0, 67.7, 114.5, 120.4, 131.9, 139.3, 173.7, 178.6;

C.I. GC/MS. m/z, relative intensity and ion. 322 (100%), $[M+H]^+$; Retention time: 13.90 min;

2-Allyl-*trans*-4-methyl-1-oct-7-enyl-5-oxo-pyrrolidine-2-carboxylic acid ethyl ester (213)

δ_H (400 MHz; $CDCl_3$): 1.18 (3H, d, J = 7.0 Hz, CH_3CH), 1.26 (3H, t, J = 7.0 Hz, CH_3CH_2O), 1.25-1.38 (6H, m, CH_2=$CHCH_2CH_2CH_2CH_2$), 1.42-1.58 (2H, m, NCH_2CH_2), 1.88 (1H, dd, J = 13.0, 7.0 Hz, CH_3CHCHH), 1.98-2.05 (2H, m,

CH_2=CHC$H_2$$CH_2$), 2.27 (1H, dd, J = 13.0, 10.0 Hz, CH_3CHC*H*H), 2.49 (1H, m, CH_3C*H*CHH), 2.60-2.76 (1H, m, CH_2=CHCH_2C), 3.05-3.20 (2H, m, NCH_2), 4.16 (2H, q, J = 7.0 Hz, CH_2O), 4.92 (2H, m, CH_2CH_2CH=CH_2), 5.13-5.19 (2H, m, CCH_2CH=CH_2), 5.57-5.68 (1H, m, CCH_2CH=CH_2), 5.76 (1H, m, CH_2CH_2CH=CH_2);

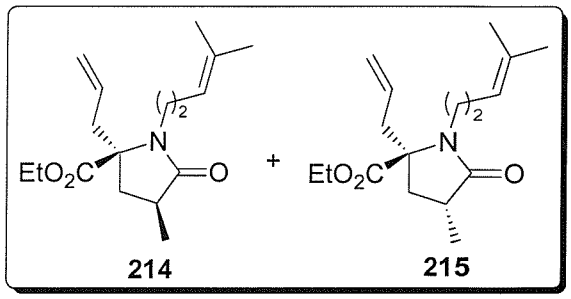
δ_c (100 MHz; $CDCl_3$): 14.4, 17.5, 25.9, 27.5, 28.5, 29.1, 34.0, 35.3, 37.5, 39.8, 42.6, 61.8, 66.7, 114.5, 120.6, 131.9, 139.3, 173.6, 178.3;

Data available: DEPT, H-H, H-C correlations.

C.I. GC/MS. m/z, relative intensity and ion. 322 (100%), $[M+H]^+$; Retention time: 14.01 min;

HRMS (ES^+): m/z calculated for $C_{19}H_{31}NO_3Na$ $[M+Na]^+$ 344.2196, found 344.2194;

I.R. (neat) ν_{max} = 1731, 1692, 1455, 1400, 1239, 1196, 1143 (cm^{-1}).



214 **215**

2-Allyl-*cis*-4-methyl-1-(4-methyl-pent-3-enyl)-5-oxo-pyrrolidine-2-carboxylic acid ethyl ester (214)

2-Allyl-*trans*-4-methyl-1-(4-methyl-pent-3-enyl)-5-oxo-pyrrolidine-2-carboxylic acid ethyl ester (215)

An homogeneous mixture of pyroglutamates **91/92** (119 mg, 0.563 mmol, 1.0 eq), 5-bromo-2-methylpent-2-ene (116.7 µL, 0.845 mmol, 1.5 eq), BEMP (250 µL, 0.845 mmol, 1.5 eq) in dry acetonitrile (3 mL) was refluxed with stirring for 12 hours. The reaction mixture was then cooled, and the solvent removed *in vacuo*. Purification by flash chromatography (hexane:ethyl acetate, 3:1) gave the title compounds **214** and **215** as a yellowish oil (25 mg, 15% yield), 1.8:1 inseparable mixture of diastereoisomes. R_f = 0.24.

2-Allyl-*cis*-4-methyl-1-oct-7-enyl-5-oxo-pyrrolidine-2-carboxylic acid ethyl ester (214)

δ_H (400 MHz; $CDCl_3$): 1.17 (3H, d, J = 7.0 Hz, CH_3CH), 1.25 (3H, t, J = 7.0 Hz, CH_3CH_2O), 1.57 (1H, dd, J = 13.0, 11.0 Hz, CH_3CHCHH), 1.61 (3H, s, CCH_3CH_3), 1.67 (3H, s, CCH_3CH_3), 2.20 (2H, m, NCH_2CH_2), 2.40 (1H, dd, J = 13.0, 8.5 Hz, CH_3CHCHH), 2.58 (1H, m, CH_3CHCHH), 2.61-2.77 (1H, m, CCH_2=$CHCH_2$), 3.02-3.18 (2H, m, NCH_2), 4.14 (2H, q, J = 7.0 Hz, CH_2O), 5.05 (2H, m, CH=CCH_3), 5.14-5.21 (2H, m, CH_2CH=CH_2), 5.58-5.70 (1H, m, CCH_2CH=CH_2);

δ_c (100 MHz; $CDCl_3$): 14.4, 16.5, 17.4, 26.0, 27.3, 36.4, 37.6, 39.7, 41.8, 61.9, 67.8, 120.5, 120.9, 131.8, 134.5, 173.5, 178.7;

C.I. GC/MS. m/z, relative intensity and ion. 294 (100%), $[M+H]^+$; Retention time: 12.92 min;

2-Allyl-*trans*-4-methyl-1-oct-7-enyl-5-oxo-pyrrolidine-2-carboxylic acid ethyl ester (215)

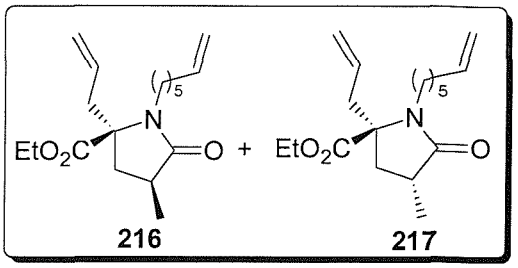
δ_H (400 MHz; $CDCl_3$): 1.19 (3H, d, J = 7.0 Hz, CH_3CH), 1.27 (3H, t, J = 7.0 Hz, CH_3CH_2O), 1.61 (3H, s, CCH_3CH_3), 1.67 (3H, s, CCH_3CH_3), 1.89 (1H, dd, J = 13.0, 7.5 Hz, CH_3CHCHH), 2.20 (2H, m, NCH_2CH_2), 2.29 (1H, dd, J = 13.0, 9.0 Hz, CH_3CHCHH), 2.52 (1H, m, CH_3CHCHH), 2.61-2.77 (1H, m, CCH_2=$CHCH_2$), 3.02-3.18 (2H, m, NCH_2), 4.15 (2H, q, J = 7.0 Hz, CH_2O), 5.05 (2H, m, CH=CCH_3), 5.14-5.21 (2H, m, CH_2CH=CH_2), 5.58-5.70 (1H, m, CCH_2CH=CH_2);

δ_c (100 MHz; $CDCl_3$): 14.4, 16.5, 18.1, 26.0, 27.2, 36.4, 37.6, 39.9, 42.4, 62.0, 66.8, 120.6, 120.8, 131.9, 134.5, 173.7, 178.4;

Data available: DEPT, H-H, H-C correlations.

C.I. GC/MS. m/z, relative intensity and ion. 294 (100%), $[M+H]^+$; Retention time: 13.04 min;

I.R. (neat) ν_{max} = 1734, 1696, 1400, 1370, 1202, 1141 (cm^{-1}).



2-Allyl-1-hept-6-enyl-*cis*-4-methyl-5-oxo-pyrrolidine-2-carboxylic acid ethyl ester (216)
2-Allyl-1-hept-6-enyl-*trans*-4-methyl-5-oxo-pyrrolidine-2-carboxylic acid ethyl ester (217)

An homogeneous mixture of pyroglutamates **91/92** (210 mg, 0.995 mmol, 1.0 eq), 7-bromo-hept-1-ene (234 μL, 1.49 mmol, 1.5 eq), BTPP (469 μL, 1.49 mmol, 1.5 eq) in dry acetonitrile (15 mL) was refluxed with stirring for 12 hours. The reaction mixture was then cooled, and the solvent removed *in vacuo*. Purification by flash chromatography (hexane:ethyl acetate, 4:1) gave the title compounds **216** and **217** as a yellowish oil (140 mg, 46% yield), 1:1 inseparable mixture of diastereoisomes. $R_f = 0.39$.

2-Allyl-1-hept-6-enyl-*cis*-4-methyl-5-oxo-pyrrolidine-2-carboxylic acid ethyl ester (216)

δ_H (400 MHz; $CDCl_3$): 1.16 (3H, d, J = 7.0 Hz, CH_3CH), 1.24 (3H, t, J = 7.0 Hz, CH_3CH_2O), 1.24-1.30 (2H, m, CH_2=$CHCH_2CH_2CH_2$), 1.34-1.41 (2H, m, CH_2=$CHCH_2CH_2CH_2$), 1.44-1.56 (2H, m, NCH_2CH_2), 1.57 (1H, dd, J = 13.0, 10.5 Hz, CH_3CHCHH), 1.99-2.04 (2H, m, CH_2=$CHCH_2CH_2$), 2.37 (1H, dd, J = 13.0, 9.0 Hz, CH_3CHCHH), 2.55 (1H, m, CH_3CHCHH), 2.60-2.76 (1H, m, CH_2=$CHCH_2C$), 3.06-3.20 (2H, m, NCH_2), 4.17 (2H, q, J = 7.0 Hz, CH_2O), 4.94 (2H, m, CH_2CH_2CH=CH_2), 5.17 (2H, m, CCH_2CH=CH_2), 5.57-5.68 (1H, m, CCH_2CH=CH_2), 5.71-5.78 (1H, m, CH_2CH_2CH=CH_2);

δ_c (100 MHz; $CDCl_3$): 14.4, 16.6, 27.1, 28.6, 28.9, 34.0, 35.4, 36.4, 39.9, 42.6, 62.0, 67.8, 114.7, 120.7, 131.9, 139.2, 173.6, 178.6;

C.I. GC/MS. m/z, relative intensity and ion. 308 (70%), $[M+H]^+$, 234 (100%), $[M-CO_2Et]^+$; Retention time: 14.41 min;

2-Allyl-1-hept-6-enyl-*trans*-4-methyl-5-oxo-pyrrolidine-2-carboxylic acid ethyl ester (217)

δ_H (400 MHz; $CDCl_3$): 1.18 (3H, d, J = 7.0 Hz, CH_3CH), 1.27 (3H, t, J = 7.0 Hz, CH_3CH_2O), 1.24-1.30 (2H, m, CH_2=$CHCH_2CH_2CH_2$), 1.34-1.41 (2H, m,

CH_2=CHCH$_2$C*H*$_2$CH$_2$), 1.44-1.56 (2H, m, NCH$_2$C*H*$_2$), 1.88 (1H, dd, J = 13.0, 7.0 Hz, CH$_3$CHC*H*H), 1.99-2.04 (2H, m, CH_2=CHC*H*$_2$CH$_2$), 2.27 (1H, dd, J = 13.0, 10.0 Hz, CH$_3$CHCH*H*), 2.47 (1H, m, CH$_3$C*H*CH$_A$H$_B$), 2.60-2.76 (1H, m, CH_2=CHC*H*$_2$C), 3.06-3.20 (2H, m, NCH$_2$), 4.18 (2H, q, J = 7.0 Hz, CH$_2$O), 4.94 (2H, m, CH$_2$CH$_2$CH=C*H*$_2$), 5.17 (2H, m, CCH$_2$CH=C*H*$_2$), 5.57-5.68 (1H, m, CCH$_2$C*H*=CH$_2$), 5.71-5.78 (1H, m, CH$_2$CH$_2$C*H*=CH$_2$);

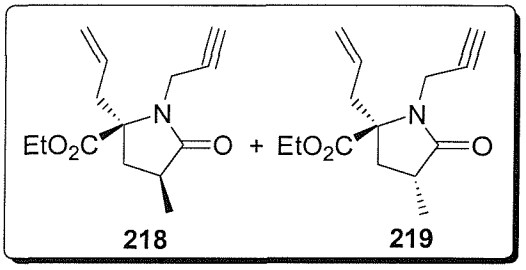
δ_c (100 MHz; $CDCl_3$): 14.5, 17.5, 27.0, 28.4, 28.9, 34.0, 35.4, 37.6, 39.7, 41.9, 61.9, 66.8, 114.7, 120.5, 131.9, 139.1, 173.7, 178.4;

Data available: DEPT, H-H, H-C correlations.

C.I. GC/MS. m/z, relative intensity and ion. 308 (100%), $[M+H]^+$; Retention time: 14.01 min;

HRMS (ES$^+$): m/z calculated for $C_{36}H_{58}N_2O_6Na$ $[2M+Na]^+$ 637.4186, found 637.4188;

I.R. (neat) ν_{max} = 1730, 1456, 1390, 1302, 1212, 1154 (cm^{-1})



2-Allyl-*cis*-4-methyl-5-oxo-1-prop-2-ynyl-pyrrolidine-2-carboxylic acid ethyl ester (218)
2-Allyl-*trans*-4-methyl-5-oxo-1-prop-2-ynyl-pyrrolidine-2-carboxylic acid ethyl ester (219)

An homogeneous mixture of pyroglutamates **91/92** (208 mg, 0.985 mmol, 1.0 eq), 3-Bromo-propyne (164.6 µL, 1.478 mmol, 1.5 eq), BEMP (435.9 µL, 1.478 mmol, 1.5 eq) in dry acetonitrile (10 mL) was refluxed with stirring for 12 hours. The reaction mixture was then cooled, and the solvent removed *in vacuo*. Purification by flash chromatography (hexane:ethyl acetate, 4:1) gave the title compounds **218** and **219** as a yellowish oil (200 mg, 82% yield), 1.7:1 inseparable mixture of diastereoisomes. R_f = 0.35.

2-Allyl-*cis*-4-methyl-5-oxo-1-prop-2-ynyl-pyrrolidine-2-carboxylic acid ethyl ester (218)

δ_H (400 MHz; $CDCl_3$): 1.19 (3H, d, J = 7.0 Hz, CH_3CH), 1.26 (3H, t, J = 7.0 Hz, CH_3CH_2O), 1.66 (1H, dd, J = 13.0, 10.5 Hz, CH_3CHCHH), 2.15 (1H, t, J = 2.5 Hz, $CH{\equiv}CCH_2N$), 2.41 (1H, dd, J = 12.5, 8.5 Hz, CH_3CHCHH), 2.48-2.62 (1H, m, CH_3CHCHH), 2.65-2.82 (1H, m, $CH_2{=}CHCH_2$), 3.99-4.28 (2H, m, NCH_2), 4.10-4.16 (2H, m, CH_2O), 5.21 (2H, m, $CH_2CH{=}CH_2$), 5.74 (1H, m, $CH_2CH{=}CH_2$);

δ_c (100 MHz; $CDCl_3$): 14.4, 16.3, 30.5, 35.2, 37.4, 39.3, 62.0, 66.6, 72.0, 78.8, 120.8, 131.8, 173.1, 178.0;

C.I. GC/MS. m/z, relative intensity and ion. 250 (100%), $[M+H]^+$; Retention time: 11.79 min;

2-Allyl-*trans*-4-methyl-5-oxo-1-prop-2-ynyl-pyrrolidine-2-carboxylic acid ethyl ester (219)

δ_H (400 MHz; $CDCl_3$): 1.25 (3H, d, J = 7.0 Hz, CH_3CH), 1.29 (3H, t, J = 7.0 Hz, CH_3CH_2O), 1.89 (1H, dd, J = 13.0, 7.0 Hz, CH_3CHCHH), 2.16 (1H, t, J = 2.5 Hz, $CH{\equiv}CCH_2N$), 2.34 (1H, dd, J = 13.5, 10.0 Hz, CH_3CHCHH), 2.48-2.62 (1H, m, CH_3CHCHH), 2.65-2.82 (1H, m, $CH_2{=}CHCH_2$), 3.99-4.28 (2H, m, NCH_2), 4.10-4.16 (2H, m, CH_2O), 5.21 (2H, m, $CH_2CH{=}CH_2$), 5.74 (1H, m, $CH_2CH{=}CH_2$);

δ_c (100 MHz; $CDCl_3$): 14.4, 17.2, 30.9, 35.1, 36.7, 39.7, 62.1, 67.4, 71.8, 79.1, 120.8, 132.0, 173.4, 177.8;

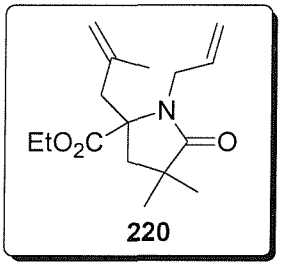
Data available: DEPT, H-H, H-C correlations.

C.I. GC/MS. m/z, relative intensity and ion. 250 (1000%), $[M+H]^+$; Retention time: 11.94 min;

HRMS (ES^+): m/z calculated for $C_{14}H_{19}NO_3Na$ $[M+Na]^+$ 272.1257, found 272.1258;

I.R. (neat) ν_{max} = 1728, 1693, 1455, 1390, 1302, 1212, 1154 (cm^{-1}).

Compounds **218** and **219** were also synthesised according to the above conditions but using BTPP as base in 100% yield (1.7:1 diastereomeric mixture). Data agrees with that reported above.



220

1-Allyl-4,4-dimethyl-2-(2-methyl-allyl)-5-oxo-pyrrolidine-2-carboxylic acid ethyl ester

An homogeneous mixture of pyroglutamate **161** (357 mg, 1.49 mmol, 1.0 eq), 3-bromo-propene (193 μL, 2.23 mmol, 1.5 eq), BTPP (703 μL, 2.23 mmol, 1.5 eq) in dry acetonitrile (15 mL) was refluxed with stirring for 12 hours. The reaction mixture was then cooled, and the solvent removed *in vacuo*. Purification by flash chromatography (hexane:ethyl acetate, 4:1) gave the title compound **220** as a yellowish oil (331 mg, 85% yield). $R_f = 0.26$.

δ_H (400 MHz; $CDCl_3$): 1.17 (3H, s, CH_3CCH_3), 1.18 (3H, s, CH_3CCH_3), 1.26 (3H, t, J = 7.0 Hz, CH_3CH_2O), 1.68 (3H, s, $CH_2=CCH_3$), 2.01 (1H, d, J = 13.5, CH_3CCHH), 2.40 (1H, d, J = 13.5 Hz, $CH_2=CCH_3CHH$), 2.40 (1H, d, J = 13.5 Hz, CH_3CCHH), 2.77 (1H, d, J = 13.5 Hz, $CH_2=CCH_3CHH$), 3.85-4.06 (2H, m, NCH_2), 4.13 (2H, q, J = 7.0, CH_2O), 4.70 (1H, d, J = 1.5 Hz, $CHH=CCH_3$), 4.91 (1H, d, J = 1.5 Hz, $CHH=CCH_3$), 5.06-5.13 (2H, m, $CH_2=CH$), 5.81 (1H, m, $CH_2=CH$);

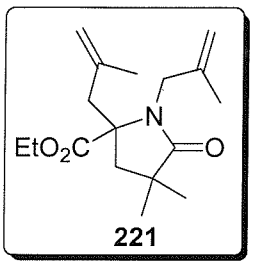
δ_C (100 MHz; $CDCl_3$): 14.3, 24.2, 26.5, 27.3, 39.6, 43.0, 44.1, 44.6, 61.9, 66.2, 116.5, 116.9, 134.2, 140.3, 173.4, 180.3;

Data available: DEPT, H-H, H-C correlations.

C.I. GC/MS. m/z, relative intensity and ion. 280 (100%), $[M+H]^+$; Retention time: 12.97 min;

HRMS (ES$^+$): m/z calculated for $C_{32}H_{50}N_2O_6Na$ $[2M+Na]^+$ 581.3560, found 581.3560;

I.R. (neat) ν_{max} = 1731, 1690, 1447, 1395, 1222, 1197, 1150, 1027 (cm^{-1}).



221

4,4-Dimethyl-1,2-bis-(2-methyl-allyl)-5-oxo-pyrrolidine-2-carboxylic acid ethyl ester

An homogeneous mixture of pyroglutamate **161** (357 mg, 1.49 mmol, 1.0 eq), 3-bromo-2-methyl-propene (231 μL, 2.23 mmol, 1.5 eq), BTPP (703 μL, 2.23 mmol, 1.5 eq) in dry acetonitrile (15 mL) was refluxed with stirring for 12 hours. The reaction mixture was then cooled, and the solvent removed *in vacuo*. Purification by flash chromatography (hexane:ethyl acetate, 4:1) gave the title compound **221** as a yellowish oil (323 mg, 79% yield). $R_f = 0.27$.

δ_H (400 MHz; $CDCl_3$): 1.19 (3H, s, CH_3CCH_3), 1.21 (3H, s, CH_3CCH_3), 1.26 (3H, t, J = 7.0 Hz, CH_3CH_2O), 1.68 (3H, s, $CH_2=CCH_3$), 1.70 (3H, s, $CH_2=CCH_3CH_2N$), 1.98 (1H, d, J = 13.5, CH_3CCHH), 2.39 (1H, d, J = 14.0 Hz, $CH_2=CCH_3CHH$), 2.52 (1H, d, J = 13.5 Hz, CH_3CCHH), 2.80 (1H, d, J = 14.0 Hz, $CH_2=CCH_3CHH$), 3.84 (1H, d, J = 16.0 Hz, NCHH), 3.98 (1H, d, J = 16.0 Hz, NCHH), 4.10 (2H, q, J = 7.0, CH_2O), 4.65 (1H, d, J = 1.5 Hz, $CHH=CCH_3CH_2N$), 4.68 (1H, d, J = 1.5 Hz, $CHH=CCH_3$), 4.78 (1H, d, J = 1.5 Hz, $CHH=CCH_3CH_2N$), 4.89 (1H, d, J = 1.5 Hz, $CHH=CCH_3$);

δ_C (100 MHz; $CDCl_3$): 14.2, 20.9, 24.1, 26.5, 27.5, 39.6, 43.0, 44.4, 47.0, 61.8, 66.2, 111.3, 116.2, 140.4, 141.7, 173.0, 180.3;

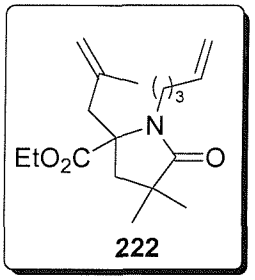
Data available: DEPT, H-H, H-C correlations;

C.I. GC/MS. m/z, relative intensity and ion. 294 (100%), $[M+H]^+$;

Retention time: 13.24 min;

HRMS (ES$^+$): m/z calculated for $C_{34}H_{54}N_2O_6Na$ $[2M+Na]^+$ 609.3874, found 609.3876;

I.R. (neat) ν_{max} = 1732, 1692, 1447, 1393, 1198, 1147, 1028 (cm^{-1}).



222

4,4-Dimethyl-2-(2-methyl-allyl)-5-oxo-1-pent-4-enyl-pyrrolidine-2-carboxylic acid ethyl ester

An homogeneous mixture of pyroglutamate **161** (215 mg, 0.899 mmol, 1.0 eq), 5-bromopent-1-ene (165 μL, 1.349 mmol, 1.5 eq), BTPP (425 μL, 1.349 mmol, 1.5 eq) in dry acetonitrile (12 mL) was refluxed with stirring for 12 hours. The reaction mixture was then cooled, and the solvent removed *in vacuo*. Purification by flash chromatography (hexane:ethyl acetate, 4:1) gave the title compound **222** as a yellowish oil (208 mg, 76% yield). $R_f = 0.5$.

δ_H (400 MHz; $CDCl_3$): 1.15 (6H, s, CH_3CCH_3), 1.27 (3H, t, J = 7.0 Hz, CH_3CH_2O), 1.61-1.70 (2H, m, NCH_2CH_2), 1.69 (3H, s, $CH_2=CCH_2$), 1.97 (1H, d, J = 13.5, CH_3CCHH), 2.04 (2H, m, $CH_2=CHCH_2$), 2.39 (1H, d, J = 13.5, CH_3CCHH), 2.39 (1H, d, J = 13.5 Hz, $CH_2=CCH_3CHH$), 2.78 (1H, d, J = 14.5 Hz, $CH_2=CCH_3CHH$), 3.17-3.33 (2H, m, NCH_2), 4.16 (2H, q, J = 7.0, CH_2O), 4.70 (1H, d, J = 1.5 Hz, $CHH=CCH_3$), 4.91 (1H, d, J = 1.5 Hz, $CHH=CCH_3$), 4.93-5.04 (2H, m, $CH_2=CH$), 5.74-5.84 (1H, m, $CH_2=CH$);

δ_C (100 MHz; $CDCl_3$): 14.3, 24.2, 26.5, 27.3, 27.7, 31.8, 39.6, 42.1, 43.0, 44.4, 62.0, 66.4, 115.3, 116.5, 138.2, 140.3, 173.6, 180.4;

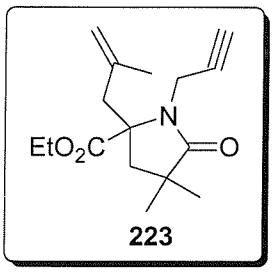
Data available: DEPT, H-H, H-C correlations;

C.I. GC/MS. m/z, relative intensity and ion. 308 (92%), $[M+H]^+$;

Retention time: 13.80 min

HRMS (ES$^+$): m/z calculated for $C_{36}H_{58}N_2O_6Na$ $[2M+Na]^+$ 637.4186, found 637.4193;

I.R. (neat) ν_{max} = 1731, 1692, 1448, 1395, 1288, 1223, 1052 (cm^{-1}).



223

4,4-Dimethyl-2-(2-methyl-allyl)-5-oxo-1-prop-2-ynyl-pyrrolidine-2-carboxylic acid ethyl ester

An homogeneous mixture of pyroglutamate **161** (187 mg, 0.782 mmol, 1.0 eq), 3-bromo-propyne (131.7 μL, 1.173 mmol, 1.5 eq), BTPP (369 μL, 1.173 mmol, 1.5 eq) in dry acetonitrile (13 mL) was refluxed with stirring for 12 hours. The reaction mixture was then cooled, and the solvent removed *in vacuo*. Purification by flash chromatography (hexane:ethyl acetate, 4:1) gave the title compound **223** as a yellowish oil (215 mg, 100% yield). $R_f = 0.32$.

δ_H (400 MHz; $CDCl_3$): 1.15 (3H, s, CH_3CCH_3), 1.18 (3H, s, CH_3CCH_3), 1.28 (3H, t, J = 7.0 Hz, CH_3CH_2O), 1.71 (3H, s, $CH_2=CCH_3$), 2.02 (1H, d, J = 13.5, CH_3CCHH), 2.14 (1H, t, J = 2.5 Hz, $CH{\equiv}CCH_2N$), 2.42 (1H, d, J = 13.5 Hz, CH_3CCHH), 2.56 (1H, d, J = 14.5 Hz, $CH{\equiv}CCHH$), 2.88 (1H, d, J = 14.5 Hz, $CH{\equiv}CCHH$), 4.17 (2H, q, J = 7.0, CH_2O), 4.18 (2H, m, NCH_2), 4.76 (1H, s, $CHH=CCH_3$), 4.93 (1H, d, J = 1.5 Hz, $CHH=CCH_3$);

δ_C (100 MHz; $CDCl_3$): 14.3, 24.2, 26.2, 27.0, 31.2, 39.6, 43.3, 44.3, 62.1, 66.2, 71.5, 79.7, 116.8, 140.1, 173.3, 179.9;

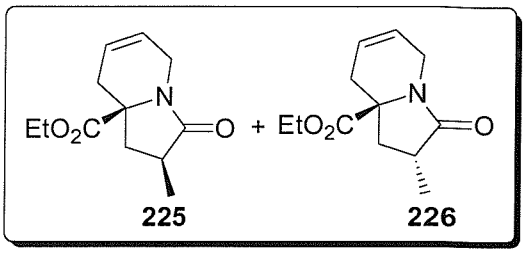
Data available: DEPT, H-H, H-C correlations.

C.I. GC/MS. m/z, relative intensity and ion. 278 (92%), $[M+H]^+$;

Retention time: 13.17 min;

HRMS (ES$^+$): m/z calculated for $C_{32}H_{46}N_2O_6Na$ $[2M+Na]^+$ 577.3248, found 577.3253;

I.R. (neat) ν_{max} = 1731, 1691, 1447, 1396, 1277, 1222, 1150, 1020 (cm^{-1}).



cis-2-Methyl-3-oxo-2,3,5,8-tetrahydro-1*H*-indolizine-8a-carboxylic acid ethyl ester (225)

trans-2-Methyl-3-oxo-2,3,5,8-tetrahydro-1*H*-indolizine-8a-carboxylic acid ethyl ester (226)

Pyroglutamates **206/207** (112 mg, 0.446 mmol, 1.0 eq) were dissolved in dry DCM (20 mL), under nitrogen, and stirred at rt for 5 minutes. Grubbs second generation catalyst (37.8 mg, 0.044 mmol, 0.1 eq) was dissolved in dry DCM (10 mL) and added to the stirred solution over five minutes. The reaction mixture was then stirred for 2 hours at rt. Evaporation of the solvent afforded a crude which was purified by flash column chromatography (hexane:ethyl acetate, 3:2) to give compounds **225** and **226** in overall 87% isolated yield, as colourless liquids. Compound **225** was isolated pure (49 mg, 49% yield); **226** (37 mg, 33% yield) was contaminated by a small amount of **225** (5% by NMR).

cis-2-Methyl-3-oxo-2,3,5,8-tetrahydro-1*H*-indolizine-8a-carboxylic acid ethyl ester (225)

δ_H (400 MHz; $CDCl_3$): 1.19 (3H, d, J = 7.0 Hz, CH_3CH), 1.21 (3H, t, J = 7.0 Hz, CH_3CH_2O), 1.61 (1H, dd, J = 13.0, 10.0 Hz, CH_3CHCHH), 2.09-2.16 (1H, m, $NCH_2CH{=}CHCHH$), 2.45-2.55 (1H, m, CH_3CH), 2.62 (1H, dd, J = 13.0, 8.5 Hz, CH_3CHCHH), 2.97-3.03 (1H, m, $NCH_2CH{=}CHCHH$), 3.64-3.70 (1H, m, $NCHHCH{=}CHCH_2$), 4.08-4.19 (1H, m, $NCHHCH{=}CHCH_2$), 4.15 (2H, q, J = 7.0 Hz, CH_2O), 5.67-5.74 (2H, m, $NCH_2CH{=}CH$);

δ_c (100 MHz; $CDCl_3$): 14.5, 16.5, 35.4, 35.7, 40.4, 41.3, 62.0, 62.8, 123.0, 123.7, 173.6, 177.3;

Data available: DEPT, H-H, H-C correlations.

C.I. GC/MS. m/z, relative intensity and ion. 224 (100%), $[M+H]^+$; Retention time: 11.91 min;

HRMS (EI): m/z calculated for $C_{12}H_{17}NO_3$ $(M)^+$ 223.12084, found 223.12073.

I.R. (neat) ν_{max} = 1729, 1690, 1596, 1453, 1416, 1305, 1269, 1201 (cm^{-1}).

***trans*-2-Methyl-3-oxo-2,3,5,8-tetrahydro-1*H*-indolizine-8a-carboxylic acid ethyl ester (226)**

δ_H (400 MHz; $CDCl_3$): 1.22 (3H, d, J = 7.0 Hz, CH_3CH), 1.24 (3H, t, J = 7.0 Hz, CH_3CH_2O), 1.89 (1H, dd, J = 13.5, 6.5 Hz, CH_3CHCHH), 2.14-2.21 (1H, m, $NCH_2CH{=}CHCHH$), 2.29 (1H, dd, J = 13.0, 9.5 Hz, CH_3CHCHH), 2.51 (1H, m, CH_3CH), 2.83-2.89 (1H, m, $NCH_2CH{=}CHCHH$), 3.68-3.74 (1H, m, $NCHHCH{=}CHCH_2$), 4.18 (2H, q, J = 7.0 Hz, CH_2O), 4.27-4.33 (1H, m, $NCHHCH{=}CHCH_2$), 5.65-5.74 (2H, m, $NCH_2CH{=}CHCH_2$);

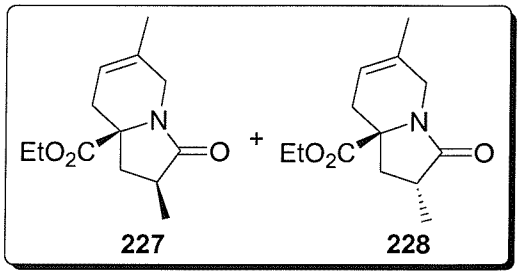
δ_c (100 MHz; $CDCl_3$): 14.4, 17.3, 34.2, 35.6, 39.0, 40.4, 62.0, 63.1, 123.4, 124.5, 173.9, 176.8;

Data available: DEPT, H-H, H-C correlations;

C.I. GC/MS. m/z, relative intensity and ion. 224 (100%), $[M+H]^+$; Retention time: 12.07 min;

HRMS (ES^+): m/z calculated for $C_{12}H_{17}NO_3Na$ $[M+Na]^+$ 246.1100, found 246.1099;

I.R. (neat) ν_{max} = 1731, 1690, 1409, 1304, 1267, 1194,1141, 1026 (cm^{-1}).



2,6-Dimethyl-3-oxo-2,3,5,8-tetrahydro-1H-indolizine-8a-carboxylic acid ethyl ester (227)

2,6-Dimethyl-3-oxo-2,3,5,8-tetrahydro-1H-indolizine-8a-carboxylic acid ethyl ester (228)

Pyroglutamate **208/209** (138 mg, 0.520 mmol, 1.0 eq) were dissolved in dry DCM (20 mL), under nitrogen, and stirred at rt for 5 minutes. Grubbs second generation catalyst (44.6 mg, 0.052 mmol, 0.1 eq) was dissolved in dry DCM (10 mL) and added to the stirred solution over five minutes. The reaction mixture was then stirred for 2 hours at rt. Evaporation of the solvent afforded a crude which was purified by flash column

chromatography (hexane:ethyl acetate, 3:2) to give the title compounds **227** and **228** (colourless liquid, 122 mg, 99% yield), as 2.5:1 diastereomeric mixture. $R_f = 0.23$.

2,6-Dimethyl-3-oxo-2,3,5,8-tetrahydro-1H-indolizine-8a-carboxylic acid ethyl ester (227)

δ_H (400 MHz; $CDCl_3$): 1.18 (3H, d, J = 7.0 Hz, C*H*$_3$CH), 1.20 (3H, t, J = 7.0 Hz, C*H*$_3$CH$_2$O), 1.59 (1H, dd, J = 12.5, 9.5 Hz, CH$_3$CHC*H*H), 1.66 (3H, s, CH=CC*H*$_3$), 2.06-2.11 (1H, m, NCH$_2$C=CHC*H*H), 2.46-2.54 (1H, m, CH$_3$C*H*), 2.58 (1H, dd, J = 13.0, 8.5 Hz, CH$_3$CHCH*H*), 2.93 (1H, dd, J = 16.5, 6.5 Hz, NCH$_2$C=CHCH*H*), 3.52 (1H, d, J = 18.0 Hz, NCH*H*C=CHCH$_2$), 4.02 (1H, d, J = 18.0 Hz, NC*H*HC=CHCH$_2$), 4.12 (2H, q, J = 7.0 Hz, CH$_2$O), 5.37-5.40 (1H, m, NCH$_2$C*H*=C);

δ_c (100 MHz; $CDCl_3$): 14.5, 16.5, 20.7, 34.0, 35.8, 38.7, 41.0, 43.9, 62.0, 117.4, 131.1, 173.7, 177.0;

C.I. GC/MS. m/z, relative intensity and ion. 238 (100%), $[M+H]^+$; Retention time: 12.23 min;

***trans*-2-Methyl-3-oxo-2,3,5,8-tetrahydro-1*H*-indolizine-8a-carboxylic acid ethyl ester (228)**

δ_H (400 MHz; $CDCl_3$): 1.21 (3H, d, J = 7.0 Hz, C*H*$_3$CH), 1.22 (3H, t, J = 7.0 Hz, C*H*$_3$CH$_2$O), 1.64 (3H, s, CH=CC*H*$_3$), 1.84 (1H, dd, J = 13.5, 6.5 Hz, CH$_3$CHC*H*H), 2.10-2.16 (1H, m, NCH$_2$C=CHC*H*H), 2.27 (1H, dd, J = 13.0, 9.5 Hz, CH$_3$CHCH*H*), 2.46-2.54 (1H, m, CH$_3$C*H*), 2.77 (1H, dd, J = 16.5, 6.5 Hz, NCH$_2$C=CHCH*H*), 3.56 (1H, d, J = 18.0 Hz, NCH*H*C=CHCH$_2$), 4.14 (2H, q, J = 7.0 Hz, CH$_2$O), 4.15-4.18 (1H, m, NC*H*HC=CHCH$_2$), 5.37-5.40 (1H, m, NCH$_2$C=C*H*);

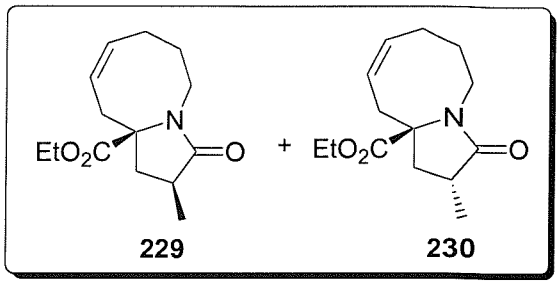
δ_c (100 MHz; $CDCl_3$): 14.4, 17.3, 20.7, 34.0, 35.7, 38.7, 41.0, 43.9, 62.8, 117.7, 131.9, 174.0, 176.6;

Data available: DEPT, H-H, H-C correlations.

C.I. GC/MS. m/z, relative intensity and ion. 238 (100%), $[M+H]^+$; Retention time: 12.33 min;

HRMS (ES$^+$): m/z calculated for $C_{13}H_{19}NO_3Na$ $[M+Na]^+$ 260.1257, found 260.1257;

I.R. (neat) ν_{max} = 1732, 1698, 1671, 1451, 1409, 1305, 1202 (cm^{-1}).



229 230

***cis*-2-Methyl-3-oxo-2,3,5,6,7,10-hexahydro-1*H*-pyrrolo[1,2-a]azocine-10a-carboxylic acid ethyl ester (229)**

***trans*-2-Methyl-3-oxo-2,3,5,6,7,10-hexahydro-1*H*-pyrrolo[1,2-a]azocine-10a-carboxylic acid ethyl ester (230)**

Pyroglutamates **210/211** (113 mg, 0.405 mmol, 1.0 eq) were dissolved in dry DCM (20 mL), under nitrogen, and stirred at rt for 3 minutes. Grubbs second generation catalyst (35 mg, 0.0405 mmol, 0.1 eq) was dissolved in dry DCM (10 mL) and added to the stirred solution over five minutes. The reaction mixture was then stirred for 2 hours at rt. Evaporation of the solvent afforded a crude which was purified by flash column chromatography (hexane:ethyl acetate, 3:2) to give compounds **229** and **230** (colourless liquid, 89 mg, 89% yield), as 1.1:1 diastereomeric mixture. $R_f = 0.19$.

***cis*-2-Methyl-3-oxo-2,3,5,6,7,10-hexahydro-1*H*-pyrrolo[1,2-a]azocine-10a-carboxylic acid ethyl ester (229)**

δ_H (400 MHz; $CDCl_3$): 1.16 (3H, d, J = 7.0 Hz, CH_3CH), 1.27 (3H, t, J = 7.0 Hz, CH_3CH_2O), 1.44 (1H, m, NCH_2CHH), 1.57 (1H, m, NCH_2CHH), 1.81 (1H, dd, J = 13.5, 7.5 Hz, CH_3CHCHH), 1.99-2.21 (2H, m, $NCH_2CH_2CH_2$), 2.29 (1H, dd, J = 13.0, 9.5 Hz, CH_3CHCHH), 2.47 (2H, m, CH_3CH and $N(CH_2)_3CH{=}CHCHH$), 2.65-2.81 (2H, m, $N(CH_2)_3CH{=}CHCHH$ and $NCHH$), 3.85 (1H, dt, J = 14.5, 3.5 Hz, $NCHH$), 4.20 (2H, q, J = 7.5 Hz, CH_2O), 5.60-5.73 (1H, m, $N(CH_2)_3CH{=}CH$), 5.79-5.94 (1H, m, $N(CH_2)_3CH{=}CH$);

δ_c (100 MHz; $CDCl_3$): 14.5, 16.6, 25.9, 26.7, 34.5, 35.3, 36.8, 43.4, 61.9, 70.2, 125.0, 135.6, 174.0, 178.2;

C.I. GC/MS. m/z, relative intensity and ion. 252 (100%), $[M+H]^+$; Retention time: 12.80 min;

***trans*-2-Methyl-3-oxo-2,3,5,6,7,10-hexahydro-1*H*-pyrrolo[1,2-a]azocine-10a-carboxylic acid ethyl ester (230)**

δ_H (400 MHz; $CDCl_3$): 1.17 (3H, d, J = 7.0 Hz, CH_3CH), 1.25 (3H, t, J = 7.0 Hz, CH_3CH_2O), 1.44 (1H, m, NCH_2CHH), 1.57 (1H, m, NCH_2CHH), 1.63 (1H, dd, J = 13.0, 10.0 Hz, CH_3CHCHH), 1.99-2.21 (2H, m, $NCH_2CH_2CH_2$), 2.35 (1H, dd, J = 13.0, 9.0 Hz, CH_3CHCHH), 2.47 (2H, m, CH_3CH and $N(CH_2)_3CH{=}CHCHH$), 2.65-2.81 (2H, m, $N(CH_2)_3CH{=}CHCHH$ and $NCHH$), 3.91 (1H, dt, J = 14.5, 3.5 Hz, $NCHH$), 4.18 (2H, q, J = 7.5 Hz, CH_2O), 5.60-5.73 (1H, m, $N(CH_2)_3CH{=}CH$), 5.79-5.94 (1H, m, $N(CH_2)_3CH{=}CH$);

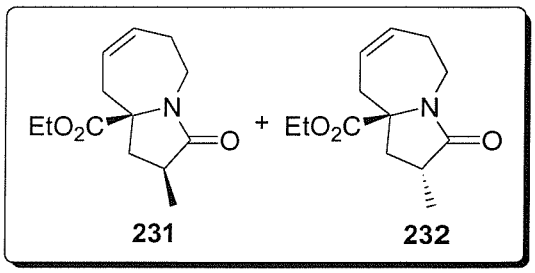
δ_c (100 MHz; $CDCl_3$): 14.5, 17.0, 25.1, 28.2, 33.2, 35.3, 38.3, 42.8, 61.9, 70.2, 125.1, 135.1, 174.2, 178.7;

Data available: DEPT, H-H, H-C correlations.

C.I. GC/MS. m/z, relative intensity and ion. 252 (100%), $[M+H]^+$; Retention time: 12.94 min;

HRMS (ES^+): m/z calculated for $C_{14}H_{21}NO_3Na$ $[M+Na]^+$ 274.1413, found 274.1412;

I.R. (neat) ν_{max} = 1732, 1692, 1401, 1365, 1210 (cm^{-1}).



231 232

***cis*-2-Methyl-3-oxo-2,3,6,9-tetrahydro-1*H*,5*H*-pyrrolo[1,2-a]azepine-9a-carboxylic acid ethyl ester (231)**
***trans*-2-Methyl-3-oxo-2,3,6,9-tetrahydro-1*H*,5*H*-pyrrolo[1,2-a]azepine-9a-carboxylic acid ethyl ester (232)**

Pyroglutamates **214/215** (20 mg, 0.068 mmol, 1.0 eq) were dissolved in dry DCM (4 mL), under nitrogen, and stirred at rt for 3 minutes. Grubbs second generation catalyst (6 mg, 0.0068 mmol, 0.1 eq) was dissolved in dry DCM (2 mL) and added to the stirred solution over five minutes. The reaction mixture was then stirred for 2 hours at rt. Evaporation of the solvent afforded a crude which was purified by flash column

chromatography (hexane:ethyl acetate, 3:2) to give compounds **231** and **232** (colourless liquid, 13 mg, 81% yield), as 1.8:1 diastereomeric mixture. $R_f = 0.46$.

***cis*-2-Methyl-3-oxo-2,3,6,9-tetrahydro-1*H*,5*H*-pyrrolo[1,2-a]azepine-9a-carboxylic acid ethyl ester (231)**

δ_H (400 MHz; $CDCl_3$): 1.18 (3H, d, J = 6.5 Hz, C*H*$_3$CH), 1.24 (3H, t, J = 7.0 Hz, C*H*$_3$CH$_2$O), 1.63 (1H, dd, J = 13.5, 10.5 Hz, CH$_3$CHC*H*H), 2.27 (2H, m, NCH$_2$C*H*$_2$), 2.33 (1H, dd, J = 15.0, 5.0 Hz, CC*H*HCH=CH), 2.43 (1H, m, CH$_3$C*H*), 2.46 (1H, dd, J = 13.0, 8.5 Hz, CH$_3$CHCH*H*), 2.84 (1H, dd, J = 15.0, 7.5 Hz, CCH*H*CH=CH), 3.0-3.07 (1H, m, NCH*H*), 4.03 (1H, dt, J = 14.5, 4.5 Hz, NC*H*H), 4.17 (2H, q, J = 7.0 Hz, CH$_2$O), 5.69-5.78 (1H, m, N(CH$_2$)$_2$CH=C*H*), 5.85-5.94 (1H, m, N(CH$_2$)$_2$C*H*=CH);

δ_c (100 MHz; $CDCl_3$): 14.5, 16.2, 28.1, 35.4, 37.0, 39.9, 40.6, 60.7, 67.7, 126.7, 133.5, 173.5, 177.8;

C.I. GC/MS. m/z, relative intensity and ion. 238 (75%), $[M+H]^+$; Retention time: 13.35 min;

***trans*-2-Methyl-3-oxo-2,3,6,9-tetrahydro-1*H*,5*H*-pyrrolo[1,2-a]azepine-9a-carboxylic acid ethyl ester (232)**

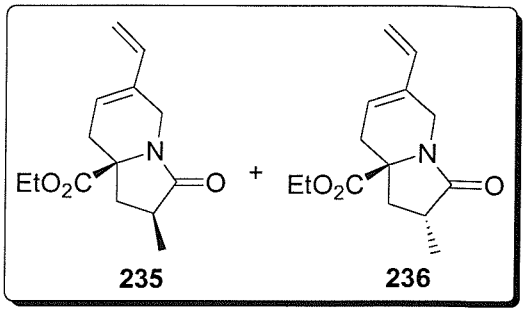
δ_H (400 MHz; $CDCl_3$): 1.18 (3H, d, J = 6.5 Hz, C*H*$_3$CH), 1.24 (3H, t, J = 7.0 Hz, C*H*$_3$CH$_2$O), 1.86 (1H, dd, J = 13.0, 6.0 Hz, CH$_3$CHC*H*H), 2.19 (1H, dd, J = 13.0, 9.5 Hz, CH$_3$CHCH*H*), 2.27 (2H, m, NCH$_2$C*H*$_2$), 2.37 (1H, m, CC*H*HCH=CH), 2.56-2.62 (1H, m, CH$_3$C*H*), 2.77 (1H, dd, J = 15.0, 7.5 Hz, CCH*H*CH=CH), 2.97 (1H, m, NCH*H*), 4.12-4.17 (1H, m, NC*H*H), 4.16 (2H, q, J = 7.0 Hz, CH$_2$O), 5.69-5.78 (1H, m, N(CH$_2$)$_2$CH=C*H*), 5.85-5.94 (1H, m, N(CH$_2$)$_2$C*H*=CH);

δ_c (100 MHz; $CDCl_3$): 14.5, 17.2, 28.6, 35.7, 38.0, 39.8, 40.6, 61.8, 67.7, 127.6, 133.6, 173.7, 177.4;

C.I. GC/MS. m/z, relative intensity and ion. 238 (83%), $[M+H]^+$; Retention time: 13.42 min;

HRMS (ES$^+$): m/z calculated for $C_{26}H_{38}N_2O_6Na$ $[2M+Na]^+$ 497.2622, found 497.2624;

I.R. (neat) ν_{max} = 1733, 1699, 1453, 1404, 1315, 1265, 1192, 1140 (cm^{-1}).



235 **236**

***cis*-2-Methyl-3-oxo-6-vinyl-2,3,5,8-tetrahydro-1*H*-indolizine-8a-carboxylic acid ethyl ester (235)**

***trans*-2-Methyl-3-oxo-6-vinyl-2,3,5,8-tetrahydro-1*H*-indolizine-8a-carboxylic acid ethyl ester (236)**

Pyroglutamates **218/219** (125 mg, 0.502 mmol, 1.0 eq) were dissolved in dry DCM (20 mL), under nitrogen, and stirred at rt for 5 minutes. Grubbs second generation catalyst (43 mg, 0.0502 mmol, 0.1 eq) was dissolved in dry DCM (10 mL) and added to the stirred solution over five minutes. The reaction mixture was then stirred for 12 hours at rt. Evaporation of the solvent afforded a crude which was purified by flash column chromatography (hexane:ethyl acetate 3:2) to give the title compounds **235** and **236** (colourless liquid, 90 mg, 72% yield), as 1:1 diastereomeric mixture. R_f = 0.29. The product was contaminated by the styrene addition product (2% by NMR).

***cis*-2-Methyl-3-oxo-6-vinyl-2,3,5,8-tetrahydro-1*H*-indolizine-8a-carboxylic acid ethyl ester (235)**

δ_H (400 MHz; $CDCl_3$): 1.20 (3H, d, J = 7.0 Hz, C*H*$_3$CH), 1.24 (3H, t, J = 7.0 Hz, C*H*$_3$CH$_2$O), 1.65 (1H, dd, J = 12.5, 9.0 Hz, CH$_3$CHC*H*H), 2.23-2.30 (1H, m, C=CHC*H*H), 2.53-2.61 (1H, m, CH$_3$C*H*), 2.64 (1H, dd, J = 12.0, 9.0 Hz, CH$_3$CHCH*H*), 3.12 (1H, dd, J = 17.5, 6.5 Hz, NCH$_2$C=CHCH*H*), 3.80 (1H, d, J = 16.0 Hz, NCH*H*), 4.16 (2H, q, J = 7.0 Hz, CH$_2$O), 4.50 (1H, d, J = 18.0 Hz, NC*H*HC=CHCH$_2$), 5.03 (1H, d, J = 12 Hz, C*H*H=CH), 5.14 (1H, dd, J = 17.5, 4.5 Hz, CH*H*=CH), 5.73 (1H, t, J = 7.0 Hz, CH$_2$C*H*=C), 6.28 (1H, m, CH$_2$=C*H*);

δ_c (100 MHz; $CDCl_3$): 14.5, 16.6, 34.4, 35.8, 38.7, 39.6, 41.1, 62.2, 112.9, 124.1, 132.9, 136.4, 173.5, 177.3;

C.I. GC/MS. m/z, relative intensity and ion. 250 (100%), $[M+H]^+$; Retention time: 12.90 min;

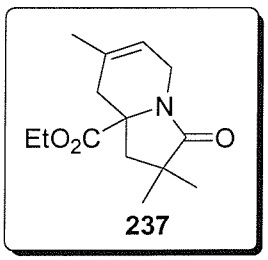
***trans*-2-Methyl-3-oxo-6-vinyl-2,3,5,8-tetrahydro-1*H*-indolizine-8a-carboxylic acid ethyl ester (236)**

δ_H (400 MHz; $CDCl_3$): 1.22 (3H, d, J = 7.0 Hz, C*H*$_3$CH), 1.24 (3H, t, J = 7.0 Hz, C*H*$_3$CH$_2$O), 1.90 (1H, dd, J = 13.5, 6.5 Hz, CH$_3$CHC*H*H), 2.23-2.30 (1H, m, C=CHC*H*H), 2.33 (1H, dd, J = 13.5, 9.5 Hz, CH$_3$CHCH*H*), 2.53-2.61 (1H, m, CH$_3$C*H*), 2.97 (1H, dd, J = 17.5, 6.5 Hz, NCH$_2$C=CHCH*H*), 3.84 (1H, d, J = 16.0 Hz, NCH*H*), 4.18 (2H, q, J = 7.0 Hz, CH$_2$O), 4.36 (1H, d, J = 18.0 Hz, NC*H*H), 5.03 (1H, d, J = 12.0 Hz, C*H*H=CH), 5.14 (1H, dd, J = 17.5, 4.5 Hz, CH*H*=CH), 5.73 (1H, t, J = 7.0 Hz, CH$_2$C*H*=C), 6.28 (1H, m, CH$_2$=C*H*);

δ_c (100 MHz; $CDCl_3$): 14.5, 17.4, 34.4, 36.0, 38.7, 39.6, 40.1, 63.3, 112.9, 124.4, 133.6, 136.4, 173.8, 176.8;

Data available: DEPT, H-H, H-C correlations.

C.I. GC/MS. m/z, relative intensity and ion. 250 (100%), $[M+H]^+$; Retention time: 13.02 min; **HRMS** could not be obtained for this compounds.



237

2,2,7-Trimethyl-3-oxo-2,3,5,8-tetrahydro-1*H*-indolizine-8a-carboxylic acid ethyl ester

Pyroglutamate **220** (148 mg, 0.53 mmol, 1.0 eq) was dissolved in dry DCM (30 mL), under nitrogen, and stirred at rt for 5 minutes. Grubbs second generation catalyst (46.6 mg, 0.053 mmol, 0.1 eq) was dissolved in dry DCM (10 mL) and added to the stirred solution over five minutes. The reaction mixture was then stirred for 6 hours at rt. Evaporation of the solvent afforded a crude which was purified by flash column chromatography (hexane:ethyl acetate 3:2) to give the title compound **237** (colourless liquid, 130 mg, 98% yield). R_f = 0.44.

δ_H (400 MHz; $CDCl_3$): 1.11 (3H, s, C*H*$_3$CCH$_3$), 1.16 (3H, s, CH$_3$CC*H*$_3$), 1.19 (3H, t, J = 7.0 Hz, C*H*$_3$CH$_2$O), 1.65 (3H, s, CH=CC*H*$_3$), 1.88 (1H, d, J = 13.5 Hz, CH$_3$CCH*H*), 2.08 (1H, d, J = 16.0 Hz, C*H*HC=CH), 2.23 (1H, d, J = 13.5 Hz, CH$_3$CCH*H*), 2.73 (1H, d, J =

16.0 Hz, CH*H*C=CH), 3.63 (1H, d, J = 17.0 Hz, NCH*H*), 4.12 (2H, q, J = 7.0 Hz, CH_2O), 4.13-4.16 (1H, m, NC*H*H), 5.34 (1H, broad s, C=C*H*);

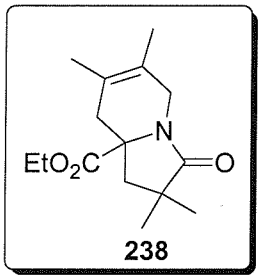
δ_c (100 MHz; $CDCl_3$): 14.3, 23.5, 26.3, 27.2, 40.1, 40.4, 41.0, 46.9, 61.8, 117.5, 130.8, 174.0, 178.7;

Data available: DEPT, H-H, H-C correlations.

C.I. GC/MS. m/z, relative intensity and ion. 252 (60%), $[M+H]^+$; Retention time: 13.10 min;

HRMS (ES^+): m/z calculated for $C_{14}H_{21}N_1O_3$ $[M+H]^+$ 252.1594, found 252.1598;

I.R. (neat) ν_{max} = 1732, 1693, 1627, 1453, 1409, 1362, 1301, 1197, 1155, 1023 (cm^{-1}).



238

2,2,6,7-Tetramethyl-3-oxo-2,3,5,8-tetrahydro-1*H*-indolizine-8a-carboxylic acid ethyl ester

To a heavy walled Pyrex tube were added pyroglutamate **221** (219 mg, 0.747 mmol, 1.0 eq), and Grubbs second generation catalyst (65.6 mg, 0.074 mmol, 0.1 eq) in 6.5 mL of dry DCM. The Pyrex tube was then capped, the reaction mixture was flushed with nitrogen and heating was then applied by means of microwave irradiation (100 °C) for 30 minutes. The reaction tube was then allowed to cool before any handling of the reaction took place. The solvent was removed under reduced pressure. Purification by flash chromatography (hexane:ethyl acetate, 3:1) afforded the title compound **238** as colourless liquid (258 mg, 97%), R_f = 0.24.

δ_H (400 MHz; $CDCl_3$): 1.14 (3H, s, C*H*$_3$CCH$_3$), 1.18 (3H, s, CH$_3$CC*H*$_3$), 1.20 (3H, t, J = 7.0 Hz, C*H*$_3$CH$_2$O), 1.59 (3H, s, CCH$_3$=CC*H*$_3$), 1.61 (3H, s, CC*H*$_3$=CCH$_3$), 1.90 (1H, d, J = 13.5 Hz, CH$_3$CCH*H*), 2.13 (1H, d, J = 16.5 Hz, CC*H*HC=C), 2.23 (1H, d, J = 13.5 Hz,

$CH_3CCH\mathit{H}$), 2.73 (1H, d, J = 16.0 Hz, $CCH\mathit{H}C$=C), 3.55 (1H, d, J = 17.0 Hz, $NCH\mathit{H}$), 4.04 (1H, d, J = 17.0 Hz, $NC\mathit{H}H$), 4.14 (2H, q, J = 7.0 Hz, CH_2O);

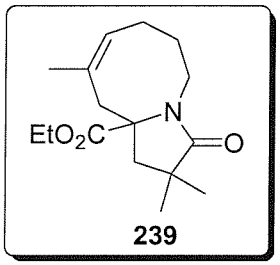
δ_c (100 MHz; $CDCl_3$): 14.5, 16.3, 19.3, 26.5, 27.3, 40.5, 42.2, 44.5, 46.9, 61.8, 62.2, 122.7, 122.9, 174.3, 178.5;

Data available: DEPT, H-H, H-C correlations.

C.I. GC/MS. m/z, relative intensity and ion. 266 (80%), $[M+H]^+$; Retention time: 13.52 min;

HRMS (ES^+): m/z calculated for $C_{30}H_{46}N_2O_6$ $[2M+Na]^+$ 553.3248, found 5573.3256;

I.R. (neat) ν_{max} = 1732, 1695, 1451, 1413, 1312, 1197, 1154, 1020 (cm^{-1}).



239

2,2,9-Trimethyl-3-oxo-2,3,5,6,7,10-hexahydro-1*H*-pyrrolo[1,2-a]azocine-10a-carboxylic acid ethyl ester

Pyroglutamate **222** (81 mg, 0.263 mmol, 1.0 eq) was dissolved in dry DCM (20 mL), under nitrogen, and stirred at rt for 5 minutes. Grubbs second generation catalyst (23 mg, 0.0263 mmol, 0.1 eq) was dissolved in dry DCM (10 mL) and added to the stirred solution over five minutes. The reaction mixture was then stirred for 20 hours at rt, under inert atmosphere. Evaporation of the solvent afforded a crude which was purified by flash column chromatography (hexane:ethyl acetate, 3:2) to give the title compound **239** as colourless liquid (63 mg, 86% yield). R_f = 0.48.

δ_H (400 MHz; $CDCl_3$): 1.05 (3H, s, $C\mathit{H}_3CCH_3$), 1.17 (3H, s, $CH_3CC\mathit{H}_3$), 1.24 (3H, t, J = 7.0 Hz, $C\mathit{H}_3CH_2O$), 1.37 (2H, m, $NCH_2C\mathit{H}_2$), 1.77 (3H, s, $CH{=}CC\mathit{H}_3$), 1.93 (1H, d, J = 13.5 Hz, $CH_3CCH\mathit{H}$), 2.02 (2H, m, $C\mathit{H}_2CH{=}C$), 2.16 (1H, d, J = 13.5 Hz, $CH_3CCH\mathit{H}$), 2.52 (1H, d, J = 14.0 Hz, $CH\mathit{H}C{=}CH$), 2.66 (1H, d, J = 14.0 Hz, $C\mathit{H}HC{=}CH$), 2.79-2.86 (1H, m, $NCH\mathit{H}$), 3.77-3.83 (1H, m, $NC\mathit{H}H$), 4.13 (2H, q, J = 7.0 Hz, CH_2O), 5.50 (1H, m, $C{=}C\mathit{H}$);

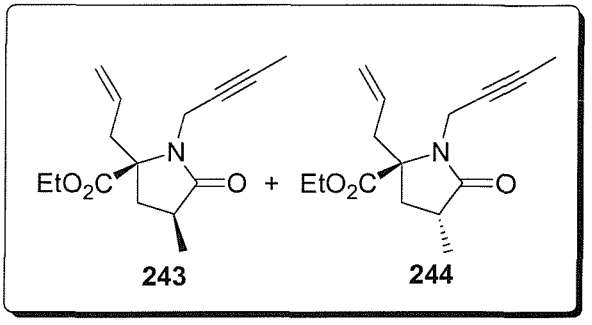
δ_c (100 MHz; $CDCl_3$): 14.4, 23.0, 25.4, 26.1, 26.3, 27.5, 39.7, 42.2, 47.2, 61.8, 68.2, 128.9, 133.4, 174.6, 180.8;

Data available: DEPT, H-H, H-C correlations.

ES$^+$/MS: m/z, relative intensity and ion. m/z 581 (25%), $[2M+Na]^+$; m/z 559 (44%), $[2M+H]^+$; m/z 280 (50%), $[M+H]^+$;

HRMS (ES$^+$): m/z calculated for $C_{32}H_{50}N_2O_6Na$ $[2M+Na]^+$ 581.3560, found 581.3554;

I.R. (neat) ν_{max} = 1732, 1691, 1459, 1402, 1363, 1292, 1199, 1154 (cm^{-1}).



2-Allyl-1-but-2-ynyl-*cis*-4-methyl-5-oxo-pyrrolidine-2-carboxylic acid ethyl ester (243)
2-Allyl-1-but-2-ynyl-*trans*-4-methyl-5-oxo-pyrrolldine-2-carboxylic acid ethyl ester (244)

An homogeneous mixture of pyroglutamates **91/92** (554 mg, 2.625 mmol, 1.0 eq), 1-bromobut-2-yne (348 µL, 3.93 mmol, 1.5 eq), BTPP (1.238 mL, 3.93 mmol, 1.5 eq) in dry acetonitrile (30 mL) was refluxed with stirring for 12 hours. The reaction mixture was then cooled, and the solvent removed *in vacuo*. Purification by flash chromatography (hexane:ethyl acetate, 3:1) gave the title compounds **243** and **244** as a yellowish oil (494 mg, 72% yield), 1.4:1 inseparable mixture of diastereoisomes. R_f = 0.43.

2-Allyl-*cis*-4-methyl-5-oxo-1-prop-2-ynyl-pyrrolidine-2-carboxylic acid ethyl ester (243)

δ_H (400 MHz; $CDCl_3$): 1.17 (3H, d, J = 7.5 Hz, CH_3CH), 1.25 (3H, t, J = 7.0 Hz, CH_3CH_2O), 1.64 (1H, dd, J = 13.0, 10.5 Hz, CH_3CHCHH), 1.73 (3H, t, J = 2.5 Hz, $CH_3C{\equiv}C$), 2.33 (1H, dd, J = 13.5, 9.0 Hz, CH_3CHCHH), 2.56-2.69 (1H, m, CH_3CHCHH), 2.67-2.83 (1H, m, $CH_2{=}CHCH_2$), 3.96 (1H, d, J = 18.0 Hz, $NCHH$), 4.09-

4.21 (3H, m, CH_2O and NCH*H*), 5.15-5.22 (2H, m, $CH_2CH=CH_2$), 5.65-5.79 (1H, m, $CH_2CH=CH_2$);

δ_c (100 MHz; $CDCl_3$): 3.8, 14.4, 16.4, 30.8, 35.2, 37.2, 38.9, 61.9, 66.4, 73.8, 79.8, 120.6, 132.1, 173.4, 178.0;

2-Allyl-*trans*-4-methyl-5-oxo-1-prop-2-ynyl-pyrrolidine-2-carboxylic acid ethyl ester (244)

δ_H (400 MHz; $CDCl_3$): 1.18 (3H, d, J = 7.5 Hz, CH_3CH), 1.26 (3H, t, J = 7.0 Hz, CH_3CH_2O), 1.73 (3H, t, J = 2.5 Hz, $CH_3C\equiv C$), 1.84 (1H, dd, J = 13.0, 7.0 Hz, CH_3CHCHH), 2.32 (1H, dd, J = 13.5, 10.0 Hz, CH_3CHCHH), 2.45-2.54 (1H, m, CH_3CHCHH), 2.67-2.83 (1H, m, $CH_2=CHCH_2$), 3.95 (1H, d, J = 18.0 Hz, NC*H*H), 4.09-4.21 (3H, m, CH_2O and NCH*H*), 5.15-5.22 (2H, m, $CH_2CH=CH_2$), 5.65-5.79 (1H, m, $CH_2CH=CH_2$);

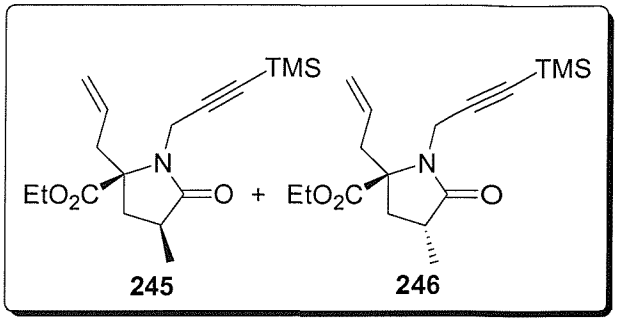
δ_c (100 MHz; $CDCl_3$): 3.8, 14.4, 17.3, 31.3, 35.4, 36.6, 39.6, 62.0, 67.4, 74.1, 80.0, 120.6, 132.2, 173.6, 177.9;

Data available: DEPT, H-H, H-C correlations.

C.I. GC/MS. m/z, relative intensity and ion. 322 (92%), $[M+H]^+$; Retention time: 13.87 min;

HRMS (ES^+): m/z calculated for $C_{15}H_{21}NO_3Na$ $[M+Na]^+$ 344.1652, found 344.1654;

I.R. (neat) ν_{max} = 1736, 1711, 1368, 1305, 1251, 1204, 1140 (cm^{-1}).



2-Allyl-*cis*-4-methyl-5-oxo-1-(3-trimethylsilanyl-prop-2-ynyl)-pyrrolidine-2-carboxylic acid ethyl ester (245)

2-Allyl-*trans*-4-methyl-5-oxo-1-(3-trimethylsilanyl-prop-2-ynyl)-pyrrolldine-2-carboxylic acid ethyl ester (246)

An homogeneous mixture of pyroglutamates **91/92** (560 mg, 2.654 mmol, 1.0 eq), (3-bromo-prop-1-ynyl)-trimethyl-silane (636 μL, 3.98 mmol, 1.5 eq), BTPP (1.254 mL, 3.98 mmol, 1.5 eq) in dry acetonitrile (30 mL) was refluxed with stirring for 12 hours. The reaction mixture was then cooled, and the solvent removed *in vacuo*. Purification by flash chromatography (hexane:ethyl acetate, 3:1) gave the title compounds **245** and **246** as a yellowish oil (249 mg, 30% yield), 1.9:1 inseparable mixture of diastereoisomes. $R_f = 0.5$.

2-Allyl-*cis*-4-methyl-5-oxo-1-prop-2-ynyl-pyrrolidine-2-carboxylic acid ethyl ester (245)

δ_H (400 MHz; $CDCl_3$): 0.09 (9H, s, $(CH_3)_3Si$), 1.16 (3H, d, J = 7.0 Hz, CH_3CH), 1.23 (3H, t, J = 7.0 Hz, CH_3CH_2O), 1.64 (1H, dd, J = 13.0, 10.5 Hz, CH_3CHCHH), 2.33 (1H, dd, J = 13.0, 8.5 Hz, CH_3CHCHH), 2.46-2.57 (1H, m, CH_3CHCHH), 2.61-2.90 (1H, m, $CH_2=CHCH_2$), 3.93 (1H, d, J = 18.0 Hz, NCHH), 4.12 (2H, q, J = 7.0 Hz, CH_2O), 4.36 (1H, d, J = 18.0 Hz, NCHH), 5.12-5.22 (2H, m, $CH_2CH=CH_2$), 5.67-5.82 (1H, m, $CH_2CH=CH_2$);

δ_c (100 MHz; $CDCl_3$): 0.0, 14.3, 16.3, 31.4, 35.1, 37.1, 38.8, 61.7, 66.6, 88.7, 100.4, 120.4, 132.2, 173.1, 177.8;

C.I. GC/MS. m/z, relative intensity and ion. 264 (30%), $[M+H]^+$; 190 (100%), $[M-TMS]^+$; Retention time: 13.49 min;

2-Allyl-*trans*-4-methyl-5-oxo-1-prop-2-ynyl-pyrrolidine-2-carboxylic acid ethyl ester (246)

δ_H (400 MHz; $CDCl_3$): 0.08 (9H, s, $(CH_3)_3Si$), 1.15 (3H, d, J = 7.0 Hz, CH_3CH), 1.25 (3H, t, J = 7.0 Hz, CH_3CH_2O), 1.79 (1H, dd, J = 13.5, 7.5 Hz, CH_3CHCHH), 2.33 (1H, dd, J = 13.0, 8.5 Hz, CH_3CHCHH), 2.46-2.57 (1H, m, CH_3CHCHH), 2.61-2.90 (1H, m, CH_2=$CHCH_2$), 3.92 (1H, d, J = 18.0 Hz, NCHH), 4.16 (2H, q, J = 7.0 Hz, CH_2O), 4.35 (1H, d, J = 18.0 Hz, NCHH), 5.12-5.22 (2H, m, CH_2CH=CH_2), 5.67-5.82 (1H, m, CH_2CH=CH_2);

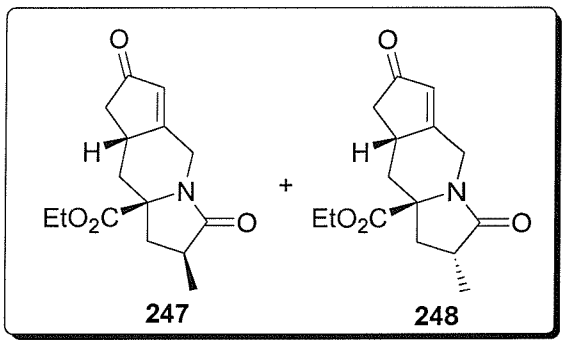
δ_c (100 MHz; $CDCl_3$): 0.0, 14.4, 17.2, 31.7, 35.0, 36.8, 39.6, 61.9, 67.4, 88.9, 100.7, 120.4, 132.3, 173.4, 177.6;

Data available: DEPT, H-H, H-C correlations.

C.I. GC/MS. m/z, relative intensity and ion. 264 (30%), $[M+H]^+$; 190 (100%), $[M-TMS]^+$; Retention time: 13.53 min;

HRMS (ES^+): m/z calculated for $C_{17}H_{28}NO_3Si$ $[M+H]^+$ 264.1594, found 264.1597;

I.R. (neat) ν_{max} = 1733, 1697, 1456, 1394, 1304, 1256, 1199 (cm^{-1}).



247 **248**

cis-2-Methyl-3,6-dioxo-2,3,6,7,7a,8-hexahydro-1H,4H-3a-aza-s-indacene-8a-carboxylic acid ethyl ester (247)

trans-2-Methyl-3,6-dioxo-2,3,6,7,7a,8-hexahydro-1H,4H-3a-aza-s-indacene-8a-carboxylic acid ethyl ester (248)

To a heavy walled Pyrex tube were added pyroglutamates **218/219** (113 mg, 0.453 mmol, 1.0 eq) and dicobaltoctacarbonyl (155 mg, 0.453 mmol, 1.0 eq) in 3 mL of dry toluene. The Pyrex tube was then capped and the reaction mixture was flushed with nitrogen. Heating was then applied by means of microwave irradiation (100 °C) for 10 minutes.

The reaction tube was then allowed to cool for a couple of minutes before any handling of the reaction took place. The reaction mixture was then filtered on celite and the solvent removed under reduced pressure. Purification by flash chromatography (ethyl acetate) afforded the title compounds **247** (52 mg, 42%, $R_f = 0.64$) and **248** (29 mg, 23%, $R_f = 0.58$) as colourless liquids.

cis-2-Methyl-3,6-dioxo-2,3,6,7,7a,8-hexahydro-1H,4H-3a-aza-s-indacene-8a-carboxylic acid ethyl ester (247)

δ_H (400 MHz; $CDCl_3$): 1.17 (3H, d, J = 7.0 Hz, C*H*$_3$CH), 1.23-1.30 (1H, m, C*H*HCO), 1.28 (3H, t, J = 7.0 Hz, CH_3CH_2O), 1.56 (1H, dd, J = 12.5, 10.0 Hz, CH_3CHCHH), 2.00 (1H, dd, J = 18.5, 2.5 Hz, C*H*HCHCH$_2$), 2.50-2.56 (1H, m, CH$_3$C*H*), 2.61 (1H, dd, J = 12.5, 8.5 Hz, CH_3CHCHH), 2.62 (1H, dd, J = 18.5, 6.5 Hz, CH*H*CHCH$_2$), 2.78-2.84 (1H, m,CH_2CHCH_2), 2.86 (1H, dd, J = 12.5, 5.0 Hz, CH*H*CO), 3.80 (1H, d, J = 16 Hz, NC*H*H), 4.24 (2H, q, J = 7.0 Hz, CH_2O), 4.97 (1H, d, J = 16 Hz, NCH*H*), 6.01 (1H, s, C=CH);

δ_c (100 MHz; $CDCl_3$): 14.6, 16.1, 35.8, 37.7, 40.9, 41.4, 41.5, 42.0, 62.6, 64.9, 129.3, 172.3, 172.9, 176.5, 207.1;

Data available: DEPT, H-H, H-C correlations.

C.I. GC/MS. m/z, relative intensity and ion. 278 (60%), $[M+H]^+$;

Retention time: 16.06 min;

HRMS (EI): m/z calculated for $C_{15}H_{19}NO_4$ $(M)^+$ 277.13141, found 277.13061;

I.R. (neat) ν_{max} = 1707, 1455, 1384, 1302, 1274, 1195, 1021 (cm^{-1}).

trans-2-Methyl-3,6-dioxo-2,3,6,7,7a,8-hexahydro-1H,4H-3a-aza-s-indacene-8a-carboxylic acid ethyl ester (248)

δ_H (400 MHz; $CDCl_3$): 1.21 (3H, d, J = 7.0 Hz, C*H*$_3$CH), 1.31-1.37 (1H, m, C*H*HCO), 1.32 (3H, t, J = 7.0 Hz, CH_3CH_2O), 1.97-2.02 (2H, m, CH_3CHCHH and C*H*HCHCH$_2$), 2.26 (1H, dd, J = 13.5, 9.5 Hz, CH_3CHCHH), 2.52-2.58 (1H, m, CH$_3$C*H*), 2.63 (1H, dd, J = 18.5, 6.5 Hz, CH*H*CHCH$_2$), 2.78 (1H, dd, J = 12.5, 5.0 Hz, CH*H*CO), 2.79-2.87 (1H, m, CH_2CHCH_2), 3.92 (1H, d, J = 16.0 Hz, NC*H*H), 4.28 (2H, q, J = 7.0 Hz, CH_2O), 5.05 (1H, d, J = 16.0 Hz, NCH*H*), 6.01 (1H, s, C=CH);

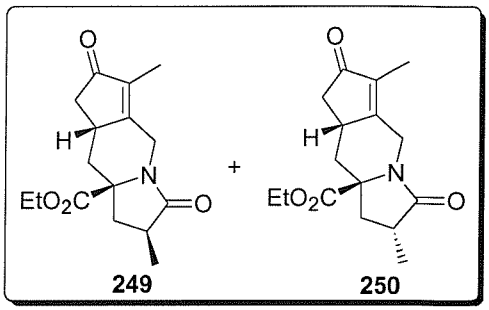
δ_c (100 MHz; $CDCl_3$): 14.6, 17.5, 35.9, 37.8, 38.7, 41.4, 41.6, 41.9, 62.5, 65.3, 129.2, 172.3, 173.5, 176.7, 206.9;

Data available: DEPT, H-H, H-C correlations.

C.I. GC/MS. m/z, relative intensity and ion. 278 (45%), $[M+H]^+$;

Retention time: 16.21 min;

I.R. (neat) ν_{max} = 1705, 1455, 1388, 1278, 1195, 1022 (cm^{-1}).



249 **250**

2, 5-Dimethyl-3,6-dioxo-2, 3, 6, 7, 7a, 8-hexahydro-1H,4H-3a-aza-s-indacene-8a-carboxylic acid ethyl ester (249)

2, 5-Dimethyl-3, 6-dioxo-2, 3, 6, 7, 7a, 8-hexahydro-1H,4H-3a-aza-s-indacene-8a-carboxylic acid ethyl ester (250)

To a heavy walled Pyrex tube were added pyroglutamates **243/244** (98 mg, 0.372 mmol, 1.0 eq) and dicobaltoctacarbonyl (127 mg, 0.372 mmol, 1.0 eq) in 2.5 mL of dry toluene. The Pyrex tube was then capped and the reaction mixture was flushed with nitrogen. Heating was then applied by means of microwave irradiation (100 °C) for 10 minutes. The reaction tube was then allowed to cool for a couple of minutes before any handling of the reaction took place. The reaction mixture was then filtered on celite and the solvent removed under reduced pressure. Purification by flash chromatography (ethyl acetate) afforded the title compounds **249** and **250** (61 mg, 56%, R_f = 0.67) as colourless liquid (1.2:1 diastereomeric ratio by NMR).

2, 5-Dimethyl-3,6-dioxo-2, 3, 6, 7, 7a, 8-hexahydro-1H,4H-3a-aza-s-indacene-8a-carboxylic acid ethyl ester (249)

δ_H (400 MHz; $CDCl_3$): 1.19 (3H, d, J = 7.0 Hz, CH_3CH), 1.24-1.27 (1H, m, $CHHCO$), 1.32 (3H, t, J = 7.0 Hz, CH_3CH_2O), 1.56 (1H, dd, J = 12.0, 10.5 Hz, CH_3CHCHH), 1.74 (3H,s, $C=CCH_3$), 1.93-2.03 (1H, m, $CHHCHCH_2$), 2.51-2.57 (1H, m, CH_3CH), 2.61 (1H,

dd, J = 12.5, 8.5 Hz, $CH_3CHCH\mathit{H}$), 2.61-2.67 (1H, m, $CH\mathit{H}CHCH_2$), 2.66-2.73 (1H, m, $CH_2C\mathit{H}CH_2$), 2.85 (1H, dd, J = 12.5, 4.5 Hz, $CH\mathit{H}CO$), 3.74 (1H, d, J = 16.0 Hz, $NC\mathit{H}H$), 4.27 (2H, q, J = 7.0 Hz, CH_2O), 5.00 (1H, d, J = 16.0 Hz, $NCH\mathit{H}$);

δ_c (100 MHz; $CDCl_3$): 8.3, 14.7, 16.1, 35.8, 36.1, 38.9, 39.9, 40.7, 42.0, 62.5, 65.2, 136.1, 163.7, 173.1, 176.6, 207.5;

C.I. GC/MS. m/z, relative intensity and ion. 292 (100%), $[M+H]^+$;

Retention time: 16.10 min;

2, 5-Dimethyl-3, 6-dioxo-2, 3, 6, 7, 7a, 8-hexahydro-1H,4H-3a-aza-s-indacene-8a-carboxylic acid ethyl ester (250)

δ_H (400 MHz; $CDCl_3$): 1.21 (3H, d, J = 7.0 Hz, $C\mathit{H}_3CH$), 1.24-1.27 (1H, m, $C\mathit{H}HCO$), 1.31 (3H, t, J = 7.0 Hz, CH_3CH_2O), 1.73 (3H,s, $C{=}CCH_3$), 1.93-2.03 (2H, m, $CH_3CHC\mathit{H}H$ and $C\mathit{H}HCHCH_2$), 2.24 (1H, dd, J = 13.5, 9.5 Hz, $CH_3CHCH\mathit{H}$), 2.51-2.57 (1H, m, $CH_3C\mathit{H}$), 2.61-2.73 (2H, m, $CH\mathit{H}CHCH_2$ and $CH_2C\mathit{H}CH_2$), 2.75 (1H, dd, J = 12.5, 5.0 Hz, $CH\mathit{H}CO$), 3.84 (1H, d, J = 16.0 Hz, $NC\mathit{H}H$), 4.26 (2H, q, J = 7.0 Hz, CH_2O), 5.06 (1H, d, J = 16.0 Hz, $NCH\mathit{H}$);

δ_c (100 MHz; $CDCl_3$): 8.3, 14.6, 17.5, 35.9, 36.0, 38.9, 39.8, 41.0, 41.9, 62.5, 65.6, 136.1, 163.8, 173.7, 176.8, 207.3;

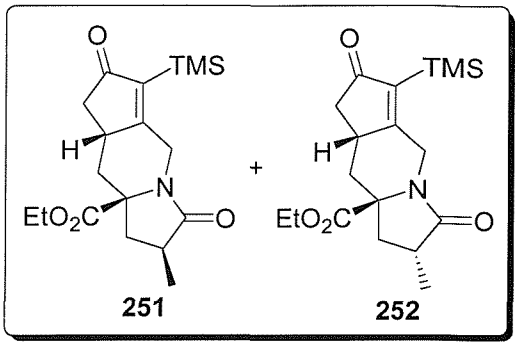
Data available: DEPT, H-H, H-C correlations.

C.I. GC/MS. m/z, relative intensity and ion. 292 (100%), $[M+H]^+$;

Retention time: 16.27 min;

HRMS (EI): m/z calculated for $C_{16}H_{20}NO_4$ $(M-H)^-$ 290.13923, found 290.13892;

I.R. (neat) ν_{max} = 1705, 1456, 1395, 1301, 1199, 1022 (cm^{-1}).



cis-2-Methyl-3, 6-dioxo-5-trimethylsilanyl-2, 3, 6, 7, 7a, 8-hexahydro-1*H*, 4*H*-3a-aza-s-indacene-8a-carboxylic acid ethyl ester (251)

trans-2-Methyl-3, 6-dioxo-5-trimethylsilanyl-2, 3, 6, 7, 7a, 8-hexahydro-1*H*, 4*H*-3a-aza-s-indacene-8a-carboxylic acid ethyl ester (252)

To a heavy walled Pyrex tube were added pyroglutamates **245/246** (68 mg, 0.211 mmol, 1.0 eq) and dicobaltoctacarbonyl (72.5 mg, 0.211 mmol, 1.0 eq) in 2.5 mL of dry toluene. The Pyrex tube was then capped and the reaction mixture was flushed with nitrogen. Heating was then applied by means of microwave irradiation (100 °C) for 10 minutes. The reaction tube was then allowed to cool for a couple of minutes before any handling of the reaction took place. The reaction mixture was then filtered on celite and the solvent removed under reduced pressure. Purification by flash chromatography (ethyl acetate) afforded the title compounds **251** and **252** (62 mg, 87%, $R_f = 0.73$) as colourless liquid (2.1:1 diastereomeric ratio by NMR).

cis-2-Methyl-3, 6-dioxo-5-trimethylsilanyl-2, 3, 6, 7, 7a, 8-hexahydro-1*H*, 4*H*-3a-aza-s-indacene-8a-carboxylic acid ethyl ester (251)

δ_H (400 MHz; $CDCl_3$): 0.23 (9H, s, $(CH_3)_3Si$), 1.19 (3H, d, J = 7.0 Hz, CH_3CH), 1.21-1.27 (1H, m, $CHHCO$), 1.29 (3H, t, J = 7.0 Hz), 1.56 (1H, t, J = 10.0 Hz, CH_3CHCHH), 1.89-2.01 (1H, m, $CHHCHCH_2$), 2.50-2.62 (3H, m, CH_3CHCHH and $CHHCHCH_2$), 2.72-2.77 (1H, m, CH_2CHCH_2), 2.85 (1H, dd, J = 12.5, 4.5 Hz, $CHHCO$), 3.75 (1H, d, J = 16.0 Hz, NCH*H*), 4.25 (2H, q, J = 7.0 Hz, CH_2O), 5.17 (1H, d, J = 16.0 Hz, NC*H*H);

δ_c (100 MHz; $CDCl_3$): 0.3, 14.4, 16.0, 31.9, 35.8, 38.6, 39.3, 40.8, 41.7, 41.9, 62.4, 64.7, 140.4, 173.0, 178.3, 211.2;

C.I. GC/MS. m/z, relative intensity and ion. 350 (66%), $[M+H]^+$;

Retention time: 16.29 min;

trans-2-Methyl-3, 6-dioxo-5-trimethylsilanyl-2, 3, 6, 7, 7a, 8-hexahydro-1_H_, 4_H_-3a-aza-s-indacene-8a-carboxylic acid ethyl ester (252)

δ_H (400 MHz; $CDCl_3$): 0.23 (9H, s, $(CH_3)_3Si$), 1.20 (3H, d, J = 7.0 Hz, CH_3CH), 1.21-1.27 (1H, m, $CHHCO$), 1.30 (3H, t, J = 7.0 Hz), 1.89-2.01 (2H, m, CH_3CHCHH and $CHHCHCH_2$), 2.25 (1H, dd, J = 13.5, 10.0 Hz, CH_3CHCHH), 2.50-2.62 (2H, m, CH_3CHCH_2 and $CHHCHCH_2$), 2.72-2.77 (1H, m, CH_2CHCH_2), 2.85 (1H, dd, J = 12.5, 4.5 Hz, $CHHCO$), 3.84 (1H, d, J = 16.0 Hz, $NCHH$), 4.25 (2H, q, J = 7.0 Hz, CH_2O), 5.24 (1H, d, J = 16.0 Hz, $NCHH$);

δ_c (100 MHz; $CDCl_3$): 0.3, 14.6, 17.4, 31.2, 35.8, 38.6, 39.4, 40.8, 41.8, 42.0, 62.4, 65.0, 140.3, 173.5, 178.4, 211.1;

C.I. GC/MS. m/z, relative intensity and ion. 350 (50%), $[M+H]^+$;

Retention time: 16.37 min;

HRMS (ES^+): m/z calculated for $C_{18}H_{27}NO_4SiNa$ $(M+Na)^+$ 372.1601, found 372.1607;

I.R. (neat) ν_{max} = 1731, 1690, 1603, 1454, 1402, 1247, 1193, 1023 (cm^{-1}).

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Appendix

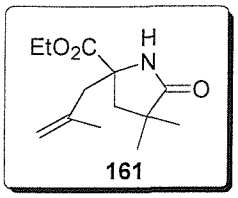

Table 1. Crystal data and structure refinement.

Identification code	**03yli144**	
Empirical formula	$C_{13}H_{21}NO_3$	
Formula weight	239.31	
Temperature	293(2) K	
Wavelength	0.71073 Å	
Crystal system	Momoclinic	
Space group	$P2_1/n$	
Unit cell dimensions	a = 9.8308(5) Å	α = 90°
	b = 14.9693(11) Å	β = 116.834(4)°
	c = 10.4539(6) Å	γ = 90°
Volume	1372.74(15) Å^3	
Z	4	
Density (calculated)	1.158 Mg / m^3	
Absorption coefficient	0.082 mm^{-1}	
$F(000)$	520	
Crystal	Colourless; Block	
Crystal size	0.4 x 0.3 x 0.2 mm^3	
θ range for data collection	3.49 – 25.03°	
Index ranges	$-11 \le h \le 11$, $-17 \le k \le 17$, $-12 \le l \le 12$	
Reflections collected	10719	
Independent reflections	2360 [R_{int} = 0.1072]	
Completeness to θ = 25.03°	96.9 %	
Absorption correction	Semi-empirical from equivalents	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2360 / 0 / 167	
Goodness-of-fit on F^2	1.066	
Final R indices [$F^2 > 2\sigma(F^2)$]	$R1$ = 0.0518, $wR2$ = 0.1246	
R indices (all data)	$R1$ = 0.0661, $wR2$ = 0.1344	
Extinction coefficient	0.030(5)	
Largest diff. peak and hole	0.248 and −0.326 e Å^{-3}	

Diffractometer: *Enraf Nonius KappaCCD* area detector (ϕ scans and ω scans to fill *Ewald* sphere). **Data collection and cell refinement**: *Denzo* (Z. Otwinowski & W. Minor, *Methods in Enzymology* (1997) Vol. **276**: *Macromolecular Crystallography*, part A, pp. 307–326; C. W. Carter, Jr. & R. M. Sweet, Eds., Academic Press). **Absorption correction**: *SORTAV* (R. H. Blessing, Acta Cryst. A**51** (1995) 33–37; R. H. Blessing, J. Appl. Cryst. **30** (1997) 421–426). **Program used to solve structure**: *SHELXS97* (G. M. Sheldrick, Acta Cryst. (1990) A**46** 467–473). **Program used to refine structure**: *SHELXL97* (G. M. Sheldrick (1997), University of Göttingen, Germany).

Further information: http://www.soton.ac.uk/~xservice/strat.htm

Special details:

Table 2. Atomic coordinates [$\times 10^4$], equivalent isotropic displacement parameters [$Å^2 \times 10^3$] and site occupancy factors. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
O001	4059(2)	1357(1)	4247(1)	32(1)	1
O002	−1286(2)	278(1)	805(2)	31(1)	1
N003	886(2)	980(1)	1045(2)	23(1)	1
O004	3998(2)	710(1)	2283(1)	29(1)	1
C005	1955(2)	1676(1)	1892(2)	22(1)	1
C006	−276(2)	843(1)	1360(2)	24(1)	1
C007	3452(2)	1238(1)	2966(2)	24(1)	1
C008	5424(2)	250(2)	3148(2)	33(1)	1
C009	2318(2)	2289(1)	896(2)	24(1)	1
C010	3519(2)	2989(1)	1676(2)	28(1)	1
C011	1091(2)	2134(1)	2625(2)	26(1)	1
C012	−117(2)	1468(1)	2570(2)	26(1)	1
C013	3064(3)	3788(2)	2255(3)	42(1)	1
C014	428(3)	899(2)	3938(2)	36(1)	1
C015	5743(3)	−340(2)	2157(3)	44(1)	1
C016	−1634(2)	1908(2)	2245(2)	36(1)	1
C017	4917(3)	2894(2)	1826(3)	41(1)	1

Table 3. Bond lengths [Å] and angles [°].

O001–C007	1.208(2)
O002–C006	1.232(2)
N003–C006	1.340(3)
N003–C005	1.461(2)
O004–C007	1.330(2)
O004–C008	1.454(2)
C005–C011	1.538(3)
C005–C007	1.538(3)
C005–C009	1.544(3)
C006–C012	1.524(3)
C008–C015	1.499(3)
C009–C010	1.512(3)
C010–C017	1.319(3)
C010–C013	1.498(3)
C011–C012	1.531(3)
C012–C016	1.522(3)
C012–C014	1.538(3)
C006–N003–C005	114.84(16)
C007–O004–C008	117.20(15)
N003–C005–C011	102.20(15)
N003–C005–C007	109.09(15)
C011–C005–C007	112.79(15)
N003–C005–C009	109.71(14)
C011–C005–C009	114.76(15)
C007–C005–C009	108.06(15)
O002–C006–N003	125.77(18)
O002–C006–C012	124.85(17)
N003–C006–C012	109.32(16)
O001–C007–O004	124.46(17)
O001–C007–C005	125.27(18)
O004–C007–C005	110.27(15)
O004–C008–C015	107.04(17)
C010–C009–C005	114.17(14)
C017–C010–C013	121.5(2)
C017–C010–C009	120.5(2)
C013–C010–C009	117.95(17)
C012–C011–C005	106.59(15)
C016–C012–C006	110.92(16)
C016–C012–C011	113.12(16)
C006–C012–C011	102.58(15)
C016–C012–C014	110.00(17)
C006–C012–C014	107.10(16)
C011–C012–C014	112.75(16)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters [$Å^2 \times 10^3$]. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + \cdots + 2\,h\,k\,a^*\,b^*\,U^{12}]$.

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O001	28(1)	42(1)	18(1)	0(1)	2(1)	−2(1)
O002	26(1)	31(1)	33(1)	−9(1)	12(1)	−6(1)
N003	22(1)	24(1)	20(1)	−5(1)	8(1)	−2(1)
O004	24(1)	32(1)	24(1)	3(1)	5(1)	7(1)
C005	22(1)	22(1)	18(1)	−2(1)	4(1)	−1(1)
C006	23(1)	23(1)	22(1)	1(1)	7(1)	2(1)
C007	22(1)	24(1)	22(1)	2(1)	6(1)	−4(1)
C008	23(1)	37(1)	33(1)	10(1)	7(1)	7(1)
C009	25(1)	26(1)	19(1)	1(1)	6(1)	2(1)
C010	26(1)	32(1)	20(1)	7(1)	5(1)	−2(1)
C011	29(1)	24(1)	23(1)	−3(1)	8(1)	0(1)
C012	26(1)	28(1)	23(1)	−2(1)	11(1)	1(1)
C013	44(1)	33(1)	43(1)	−7(1)	15(1)	−12(1)
C014	46(1)	38(1)	26(1)	1(1)	18(1)	−2(1)
C015	36(1)	40(1)	52(1)	5(1)	17(1)	10(1)
C016	32(1)	37(1)	43(1)	−6(1)	19(1)	1(1)
C017	29(1)	48(2)	41(1)	10(1)	11(1)	−5(1)

Table 5. Hydrogen coordinates [$\times 10^4$] and isotropic displacement parameters [$Å^2 \times 10^3$].

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
H2	5200(30)	2400(17)	1440(20)	35(6)	1
H1	1080(30)	626(17)	490(30)	40(7)	1
H3	5680(30)	3361(18)	2330(30)	48(7)	1
H00A	5337	−105	3884	40	1
H00B	6243	678	3609	40	1
H00C	2658	1922	332	29	1
H00D	1387	2587	238	29	1
H01A	1784	2280	3611	32	1
H01B	612	2680	2124	32	1
H01C	2010	3739	2044	62	0.50
H01D	3211	4320	1818	62	0.50
H01E	3680	3819	3274	62	0.50
H01F	3924	4180	2713	62	0.50
H01G	2723	3599	2940	62	0.50
H01H	2254	4099	1483	62	0.50
H01D	1384	624	4134	54	1
H01E	−314	445	3803	54	1
H01F	555	1274	4729	54	1
H01A	6676	−661	2694	66	1
H01B	5837	19	1440	66	1
H01C	4921	−757	1702	66	1
H01D	−1963	2264	1394	54	1
H01E	−1516	2281	3035	54	1
H01F	−2382	1455	2100	54	1