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THE SYNTHESIS OF 3,5-DISUBSTITUTED INDOLIZIDINES

Penelope Sue Cheesman

A dissertation submitted to the Faculty of Science, University of the Witwatersrand, Johannesburg, in fulfilment of the requirements for the degree of Master of Science

January 1996

ABSTRACT

Aspects of the literature of the ant venom alkaloid monomorine I and its stereoisomers were reviewed.

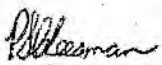
Racemic 5-butyl-2-pyrrolidinone was synthesised in two steps from methyl acrylate and 1-nitropentane. A thionation step yielded 5-butylpyrrolidine-2-thione. The Michael addition reaction between 5-butylpyrrolidine-2-thione and ethyl crotonate proceeded with difficulty to form a separable mixture of diastereomers of 5-butyl-1-(2-ethoxycarbonyl-1-methylethyl)pyrrolidine-2-thione. Salt formation with ethyl bromoacetate followed by an Eschenmoser sulphide contraction yielded (*E*)-5-butyl-1-(2-ethoxycarbonyl-1-methylethyl)-2-ethoxycarbonylmethylenepyrrolidine. Acylative ring closure was used to obtain two diastereomers of 9-butyl-5-ethoxycarbonyl-2-methyl-1-azabicyclo[4.3.0]non-5-en-4-one, which were separated and characterised as the *trans* and *cis* isomers. The hydrolysis and decarboxylation of the ester functionality and the reduction of the carbon-carbon double bond of the separated diastereomers was performed but the expected products, isomers of 9-butyl-2-methyl-1-azabicyclo[4.3.0]nonan-4-one, could not be characterised completely. This aspect of the synthesis will need to be confirmed in the future.

Progress toward a chiral lactam for use in the approach described above, yielded (*S*)-(+)-5-(*p*-toluenesulphonyloxymethyl)-2-pyrrolidinone, obtained from L-glutamic acid. In another stereoselective approach, (2-thioxopyrrolidin-5-yl)methyl 2-(*E*)-butenoate was synthesised and an intramolecular Michael addition reaction unsuccessfully attempted.

Preliminary investigations of the alternative approach to 5-butyl-3-methylindolizidine were initiated. 4-Oxooctanoic acid and racemic ethyl 3-aminobutanoate were synthesised and used to synthesise ethyl 3-(4-oxooctanoylamino)butanoate, which is intended as an alternative precursor for (*E*)-5-butyl-1-(2-ethoxycarbonyl-1-methylethyl)-2-ethoxycarbonylmethylenepyrrolidine. (3*S*)-Ethyl 3-(tosylamino)butanoate was synthesised from L-aspartic acid in a preliminary investigation aimed at the synthesis of enantiomerically pure ethyl 3-aminobutanoate.

DECLARATION

I declare that this dissertation is my own unaided work. It is submitted for the degree of Master of Science in the University of the Witwatersrand, Johannesburg. It has not been submitted before for any other degree or examination in any other university.



Penelope Sue Cheesman

ACKNOWLEDGEMENTS

I would like to express my sincere gratitude to the following:

My supervisor, Prof. J.P. Michael, for his guidance and assistance throughout the project. I also thank Dr M.I. Zwane , my co-supervisor;

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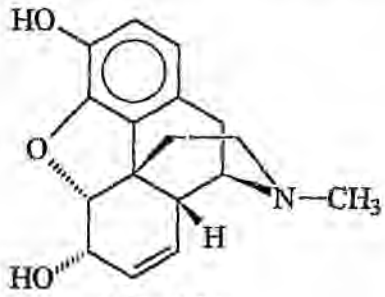
List of Abbreviations

conc.	concentrated
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DEPT	Distortionless Enhancement by Polarization Transfer
DMAP	4-dimethylaminopyridine
DMF	N,N-dimethylformamide
DMSO	dimethyl sulphoxide
IR	infrared
NMR	nuclear magnetic resonance
NOESY	nuclear Overhauser enhancement spectroscopy
TMS	trimethylsilyl
Tosyl	*p*-toluenesulphonyl

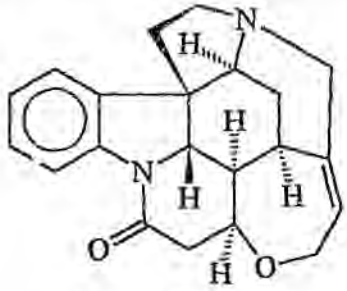
CHAPTER 1
INTRODUCTION AND BACKGROUND

1.1 Alkaloids

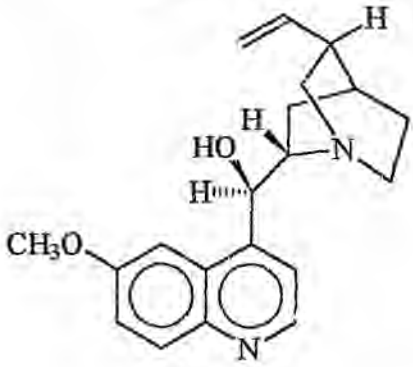
Alkaloids are generally defined as being basic, nitrogen-containing compounds in which the nitrogen is part of the heterocyclic ring[1]. There are over 5000 known alkaloids and these have an enormous structural diversity[2]. Some well known examples of alkaloids are morphine, strychnine, quinine and coniine. Morphine is used as a narcotic analgesic and is found in the opium poppy, *Papaver somniferum* L. Isolated in 1805 by Serturner, it was the first pure alkaloid to be isolated. Strychnine (obtained from *Strychnos nux-vomica* L. and S. *ignatii* Berg), quinine (obtained from *Cinchona* bark and various *Cinchona* species and known for its antimalarial activity[3]) and coniine (from poison hemlock, *Conium maculatum* L.), were all isolated by Pelletier and Caventou in 1817, 1820 and 1826, respectively. Coniine, synthesised in 1886 by Ladenburg, was the first alkaloid to be synthesised.



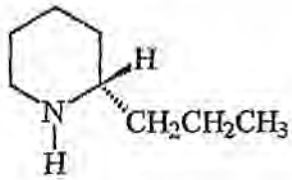
Morphine



Strychnine

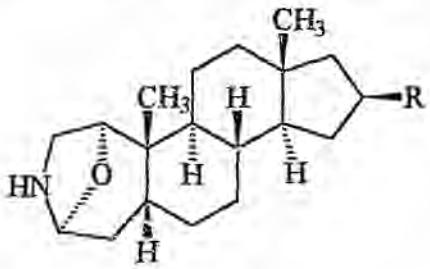


Quinine



Coniine

It was originally thought that alkaloids were only found in the plant kingdom. However, they are now known to be present in animals, both invertebrates and vertebrates[4]. The first alkaloid to be isolated from animals was "samandarine" from the skin glands of the European fire salamander (*Salamandra maculosa* Laurenti). "Samandarine" was later found to be a mixture from which the alkaloids samandarine and samandarone were isolated[4]. Since then, alkaloids have been found in frogs, toads, tree frogs, mammals, arthropods and marine organisms[4].

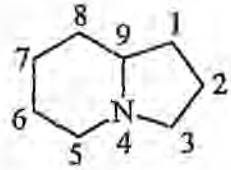


R = OH : samandarine
R = O : samandarone

This dissertation is concerned specifically with some 3,5-disubstituted indolizidine alkaloids found in the animal kingdom. Their occurrence in ants was first demonstrated in 1973[5] and in frogs in 1978[6]. The following section contains an overview of this class of indolizidine alkaloids.

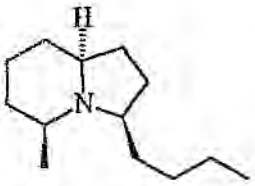
1.2 3,5-Disubstituted Alkaloids from Frogs and Ants

The indolizidine nucleus consists of a fused five- and six-membered ring with nitrogen at the bridgehead position. The numbering of the indolizidine skeleton is shown below.

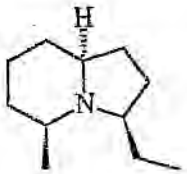


Some examples of 3,5,-dialkylindolizidines obtained from frogs and ants are shown below. Where known, the absolute configuration is shown.

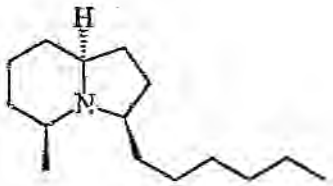
From ants:



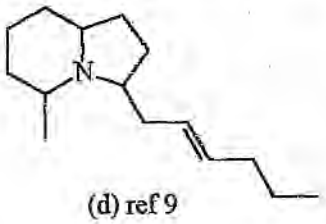
(a) (+)-Monomorine I
ref 7



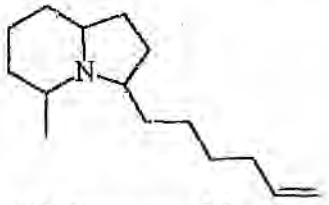
(b) ref 8
(relative configuration only)



(c) ref 8
(relative configuration only)

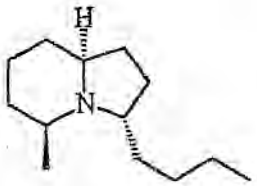


(d) ref 9

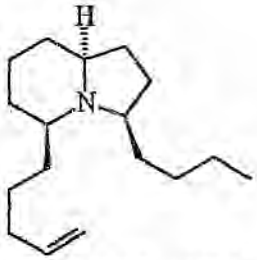


(e) Monomorine VI
ref 10

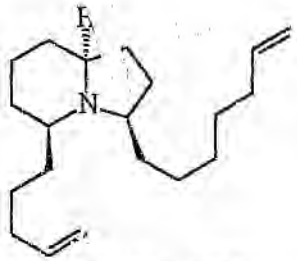
From frogs:



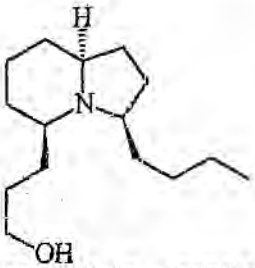
(f) (+)-Indolizidine 195B
ref 11



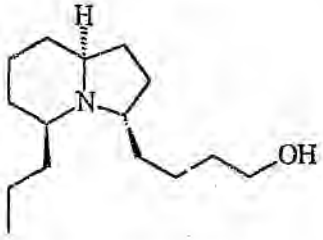
(g) Indolizidine 249A
ref 12



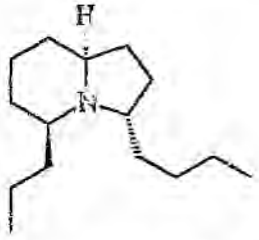
(h) Indolizidine 275C
ref 12



(i) Indolizidine 239AB
ref 12



(j) Indolizidine 239CD
ref 12



(k) (+)-Alkaloid 223AB
ref 13 and 14

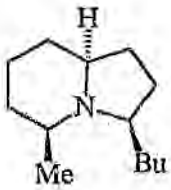
In this project, attention will be focussed on the 3-butyl-5-methylindolizidines: monomorine I, indolizidine **195B** and their stereoisomers.

Monomorine I was the first indolizidine derivative to have been found in the animal kingdom[15]. It has been isolated from Pharaoh's ants, *Monomorium pharaonis*, and has been identified in the odour trail as well as in excretions from the insect's sting. It originates from the abdominal glands. Monomorine I was first isolated by preparative gas chromatography of the dichloromethane extract of about 6000 (1g) of homogenised ants[5].

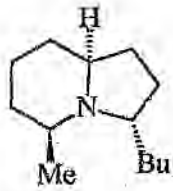
This tiny ant of 2 to 3 mm originates from the tropics but is a pest in North America and Western Europe. It is found mainly in heated buildings and is a health hazard in places such as hospitals, bakeries and kitchens since it carries pathogenic bacteria[15]. The ants can enter sophisticated isolation units and penetrate bandages and sterile packs. They are known to feed on wound exudates[16]. The science fiction novel *Spirals*, by William Patrick, Houghton Mifflin, Boston, 1983, was based on an incident in the Biological Laboratories of Harvard University during the 1960's and 1970's. A colony of Pharaoh ant workers was found carrying radioactive chemicals from culture dishes into the surrounding walls[17].

The nests containing the queens are well hidden and usual insecticides do not work. The possibility of pest control by pheromone manipulations was investigated by Ritter and co-workers[15] at the request of the Dutch Ministry of Public Health and Environmental Hygiene and hence the subsequent intense activity on the synthesis of monomorine I.

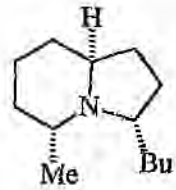
A great deal of elucidative and synthetic work has been done on monomorine I since it was first isolated. It was shown to have all-*cis* stereochemistry after the four diastereomers (1), (2), (3) and (4) were synthesised by a number of different procedures[18, 19]. Since then all four of the stereoisomers have been isolated from bufonid toads of the genus *Melanophryniscus*[12, 20].



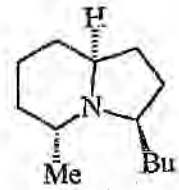
monomorine I
(5*Z*, 9*Z*)
(1)



indolizidine **195B**
(5*E*, 9*E*)
(2)



(5*Z*, 9*E*)
(3)



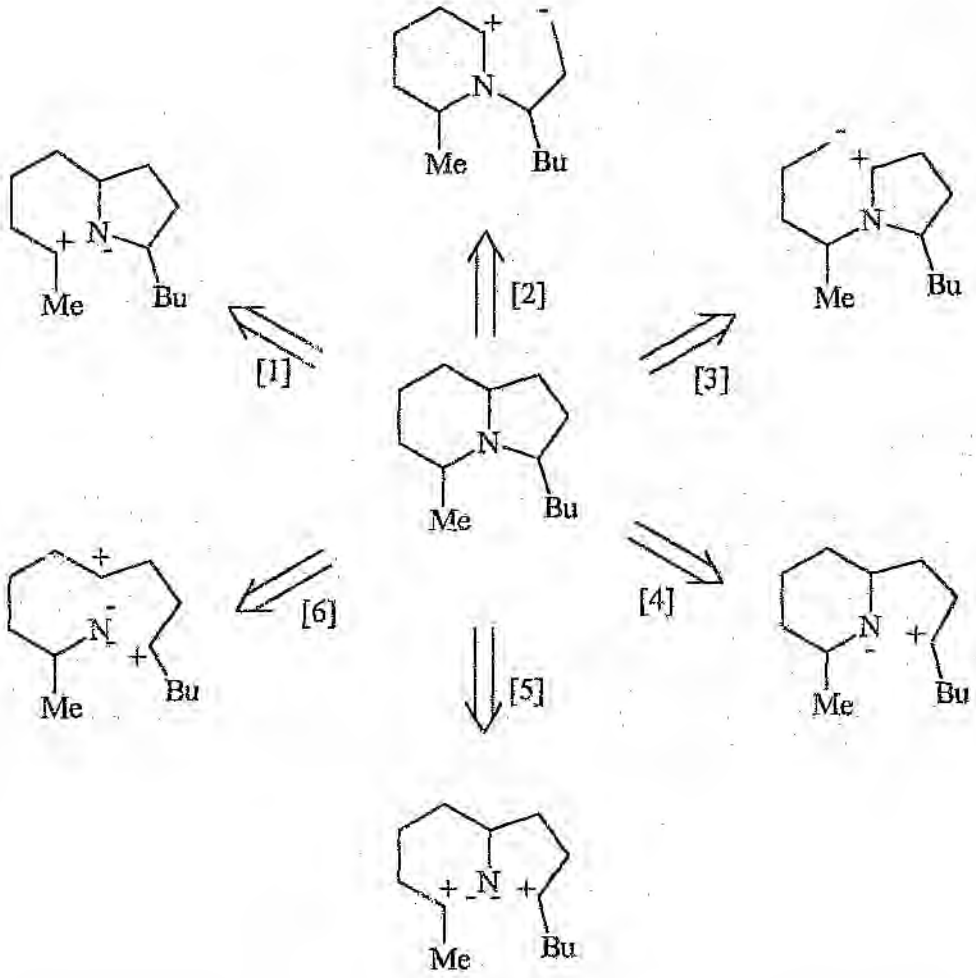
(5*E*, 9*Z*)
(4)

The absolute configuration of the natural (+)-monomorine I was established as 3*R*,5*S*,9*S* after the first asymmetric synthesis of (-)-monomorine I[7].

(+)-Indolizidine **195B** (2) has been extracted from the skin of the Colombian poison frog *Dendrobates histrionicus*. The absolute stereochemistry was established as 3*S*,5*S*,9*S* after the first enantioselective total synthesis[21]. (+)-Indolizidine **195B** is diastereomeric with monomorine I.

1.3 Reported Syntheses of 3-Butyl-5-methylindolizidine

Although a vast number of syntheses for both monomorine I and indolizidine **195B** have been reported in the literature, these can be divided into six groups in terms of the indolizidine skeleton disconnections shown below. The references for the syntheses are given in Table 1.



SCHEME 1

Table 1: References for the syntheses using the various disconnection approaches.

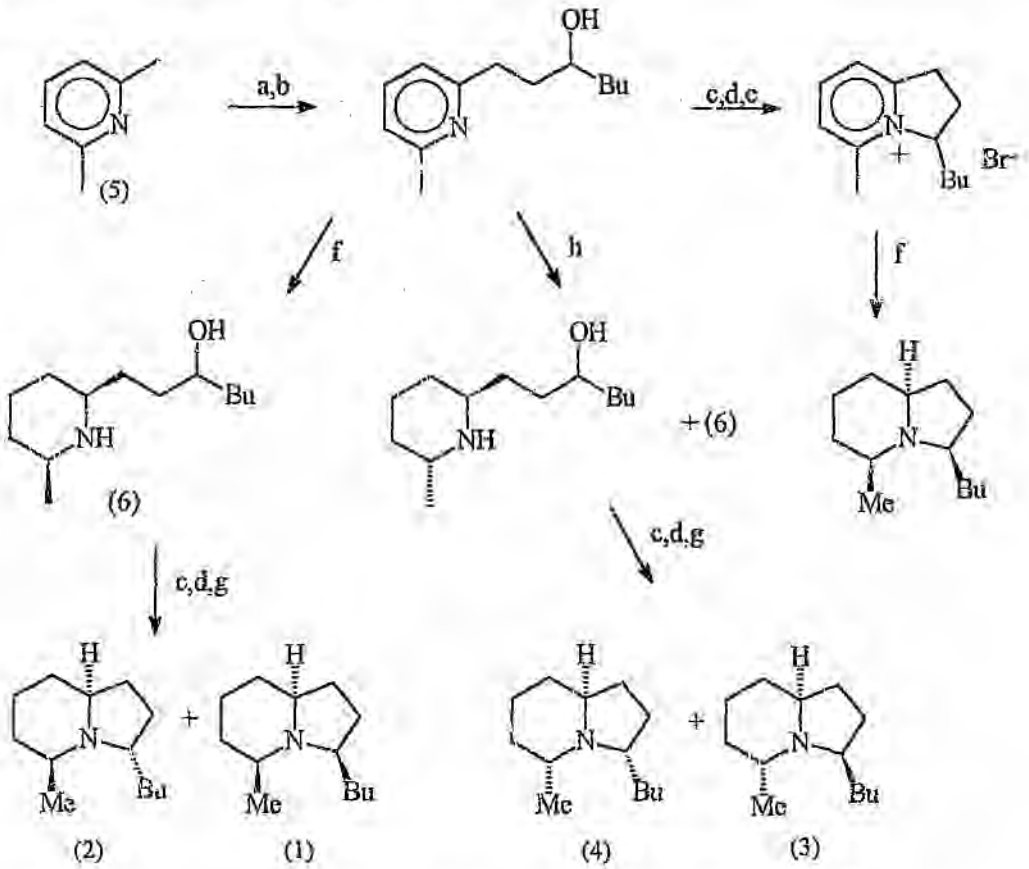
	Disconnection	(+)	(-)	Racemic
Monomorine I	1	22		24,25,26,27
	2			28
	3	29		30
	4	8, 31, 32	7, 33	34,35,36,37
	5	38		
	6			39
195B	1	40, 11	41, 42	27, 43

All the reported syntheses of indolizidine **195B** use disconnection 1. The synthesis of four stereoisomers of monomorine I using disconnection 4 is given in reference 19 and disconnection 1 and 2 in reference 18. The synthesis of (+)- and (-)-indolizidine **195B** and the two (5*Z*, 9*E*) stereoisomers using disconnection 1 is given in reference 42.

A selection of these syntheses will now be highlighted to illustrate the key cyclisation step.

1.3.1 The First Synthesis of Monomorine I

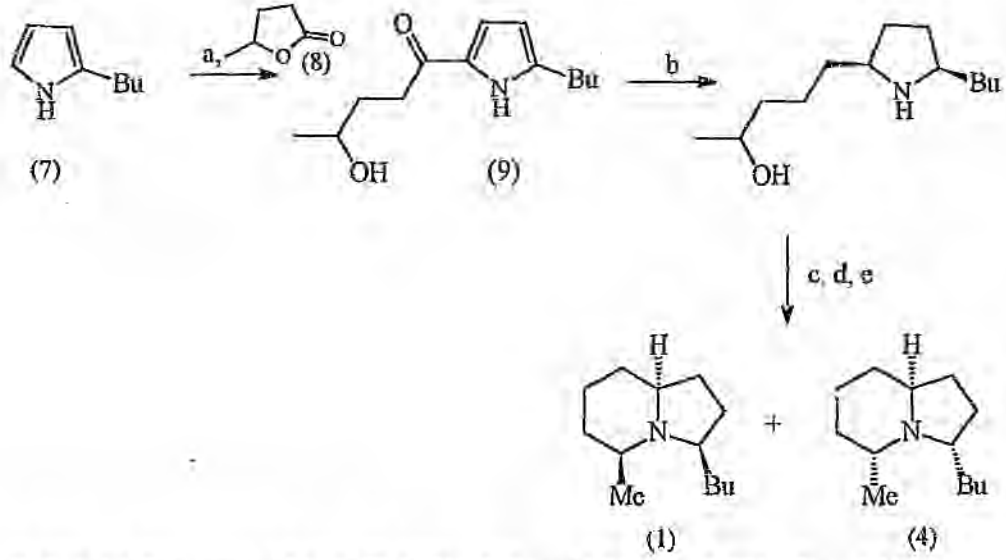
The first synthesis of monomorine I was by Oliver and Sonnet in 1974[18, 19]. They synthesised all four of the stereoisomers from 2,6-lutidine (5). The method starts with the 6-membered ring and builds on the 5-membered ring (see Scheme 2). Isomers were separated by spinning band distillation.



Ref 18, 19: Reagents: a) n-BuLi; b) 1,2-epoxyhexane; c) 48%HBr; d) PPh_3, Br_2; e) $(CH_3)_2CO$, heat; f) H_2, PtO_2, g) Et_3N; h) Na, EtOH.

SCHEME 2

A second, very similar method, starting with the 5-membered ring, was also used to synthesise (1) and (4) (see Scheme 3). Compound (9) was obtained from γ-valerolactone (8) and the anion of 2-butylpyrrole (7). Hydrogenation and treatment with hydrobromic acid, triphenylphosphine, bromine and triethylamine gave the cyclised products (1) and (4).



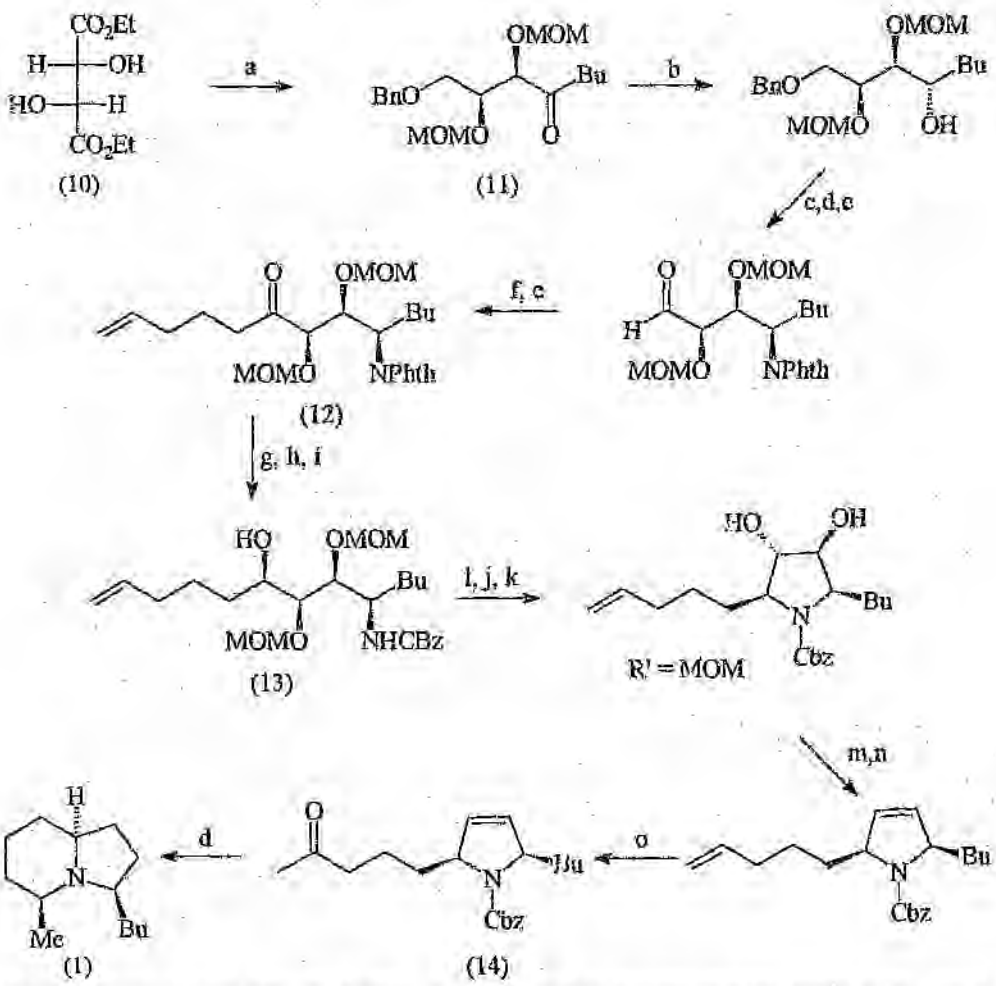
Ref 18, 19: Reagents: a) MeMgCl; b) H_2, PtO_2; c) 48% HBr; d) PPh_3, Br_2; e) NEt_3.

SCHEME 3

These syntheses allowed for the unambiguous determination of the relative stereochemistry of monomorine I and its stereoisomers.

1.3.2 The First Enantioselective Synthesis of (+)-Monomorine I

The first enantioselective total synthesis of (+)-monomorine I was by Yamazaki and Kibayashi[22] in 1988 (see Scheme 4). The method uses disconnection 1 and starts with diethyl L-tartrate (10). It results exclusively in (+)-monomorine I (1) in a 76% yield. A twofold diastereoselective hydride addition was used to obtain the *syn,syn,syn* alcohol (13). The reduction of (11) with zinc borohydride yielded the alcohol with an *anti* selectivity of greater than 99:1 whereas the reduction of (12) with lithium tri-*sec*-butylborohydride yielded the alcohol with high *syn* selectivity (*syn*: *anti* = 98:2). The hydrogenation of the ketone (14) was the final step to form the bicyclic ring system.



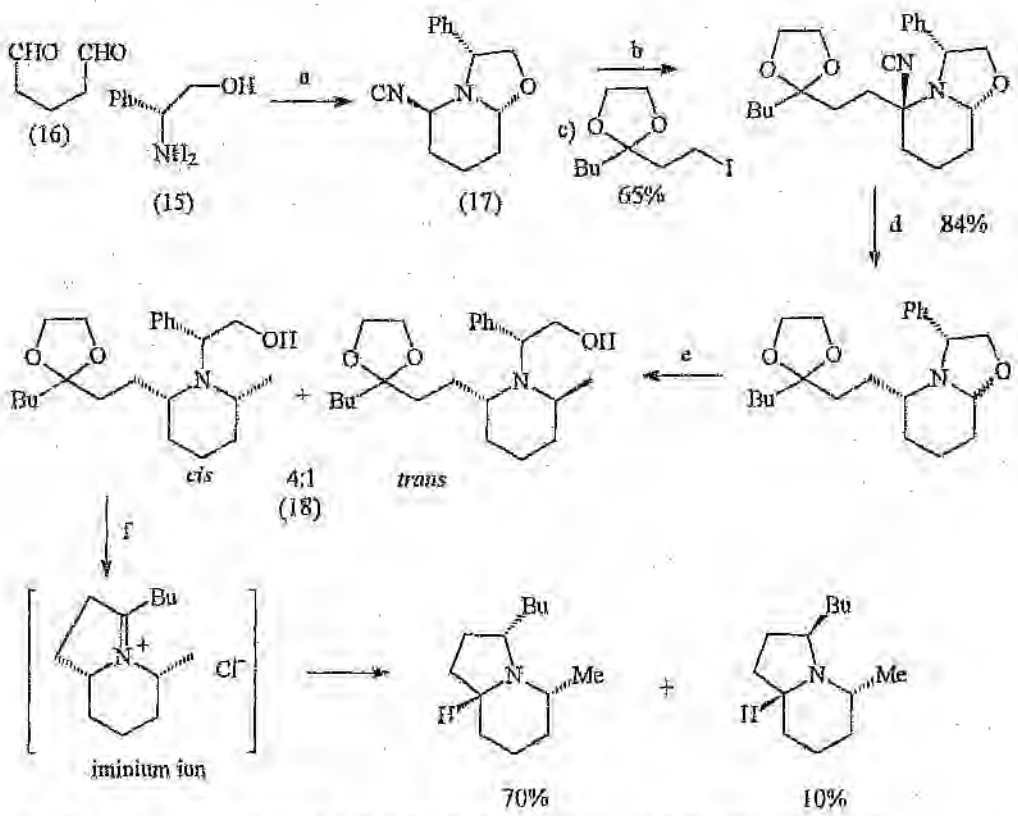
Ref 23; Reagents: (a) ref. 22b; (b) $Zn(BH_4)_2$, Et_2O, -20 ° C; (c) phthalimide, $(=NCO_2Et)_2$, THF; (d) H_2, Pd/C, MeOH; (e, $(COCl)_2$, Me_2SO, Et_3N, CH_2Cl_2, -78 °C; (f) $CH_2=CH(CH_2)_3MgBr$, THF, -78 °C; (g) LiBH(sec-Bu)$_3$, THF, -78 ° C; (h) $(NH_2)_2 \cdot H_2O$, EtOH, refl; (i) $PhCH_2OCOCl$, aq. Na_2CO_3, CH_2Cl_2, 0 °C; (j) MsCl, Et_3N, CH_2Cl_2, 0 °C; (k) *t*-BuOK, THF, r.t.: (l) conc HCl, MeOH, refl; (m) imidazole, triiodoimidazole, Ph_3P, toluene, refl; (n) Ph_3P, Zn, toluene, reflux; (o) O_2, $PdCl_2$, DMF-H_2O, 70 °C.

SCHEME 4

1.3.3 The First Enantioselective Synthesis of (-)-Monomorine I

The first total synthesis of (-)-monomorine I was by Royer and Husson in 1985[7] (see Scheme 5). This asymmetric synthesis established the absolute configuration of (+)-monomorine I as *3R,5S,9S*. This synthesis uses the disconnection 4 approach of starting with the six-membered ring and building on the five-membered ring. Compound (17), prepared from (-)-phenylglycinol (15),

glutaraldehyde (16) and potassium cyanide was important in influencing the chemo- and stereoselectivity of the subsequent reactions. The *cis* and *trans* isomers of (18) were separated by column chromatography on silica gel before the final step of hydrogenation was carried out on the *cis* isomer.



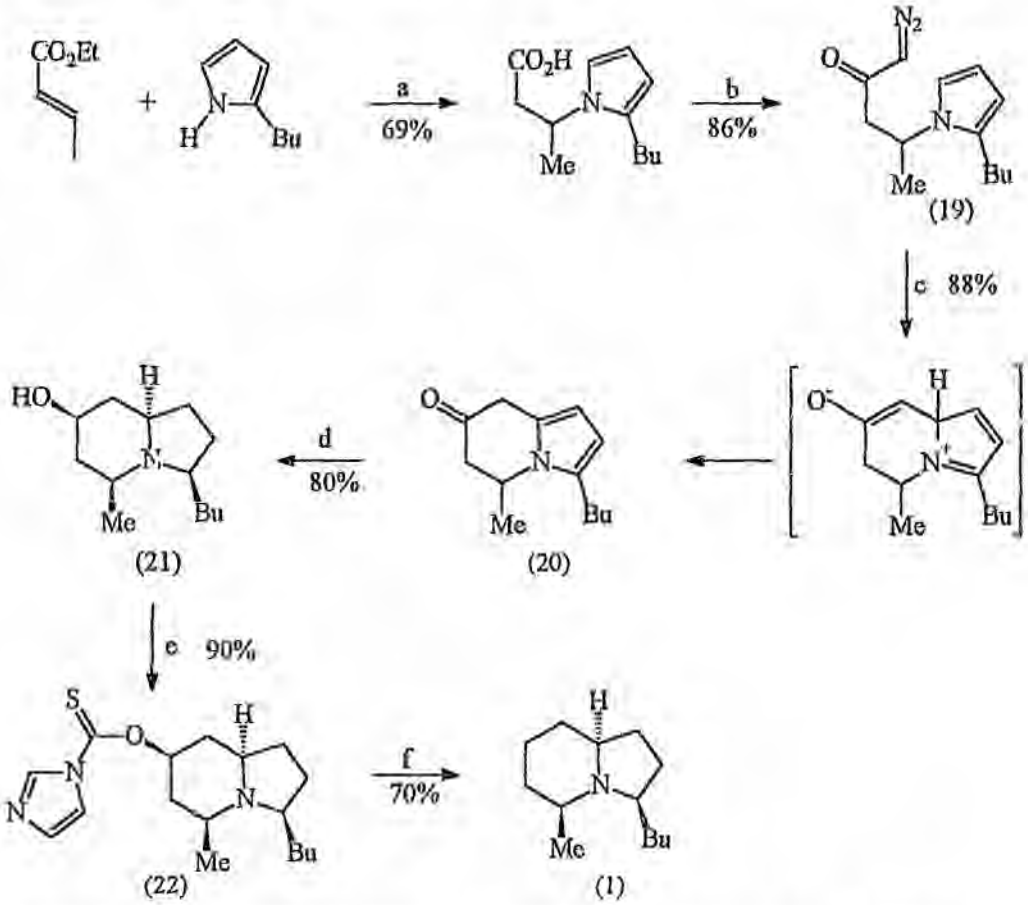
Ref 7: Reagents: (a) KCN pH 3-4; (b) LDA, THF, -78 °C; (c) iodo ketal; (d) $AgBF_4$, THF, $Zn(BH_4)_2$, -50 °C; (e) CH_3MgI; (f) H_2, Pd/C.

SCHEME 5

1.3.4 Two Recent Syntheses of (±)-Monomorine I

In 1989 Jefford synthesised (±)-monomorine I in an overall yield of 26% using a disconnection 3 approach[30] (see Scheme 6). The key intermediate is a diazoketone (19) which decomposes in the presence of rhodium(II) acetate in dichloromethane to attack the pyrrole ring and form the bicyclic ring structure (20). Catalytic hydrogenation with PtO_2 under hydrogen pressure resulted in compound (21) in

which the hydroxy, butyl and methyl groups were all *cis*. This is due to the way in which the hydrogen atoms are transferred from the surface of the catalyst. The hydroxy group was removed by first forming the imidazolecarbothioate (22) and then reducing with tributylstannane.



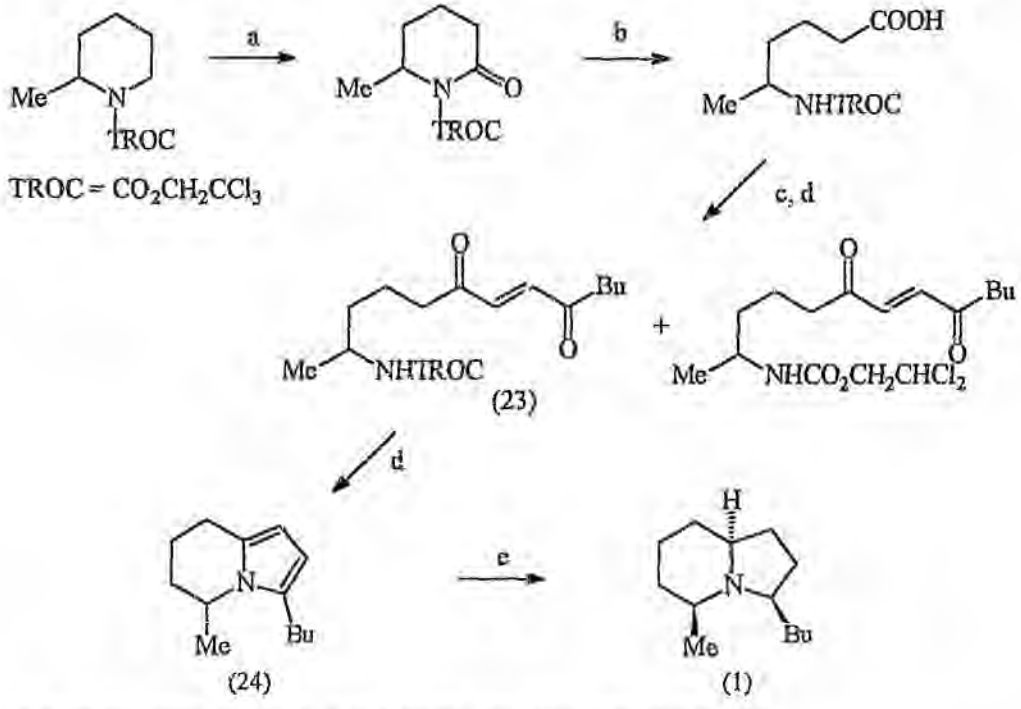
Ref 30: Reagents: a) KOH, CH_3CN; b) 1. i-BuOCOCl, N-methylmorpholine, 2. CH_2N_2, Et_2O; c) $Rh_2(OAc)_4$, CH_2Cl_2; d) PtO_2, EtOH, AcOH, H_2, 20 bar;
e) N,N'-thiocarbonyldiimidazole, $ClCH_2CH_2Cl$; f) Bu_3SnH/toluene.

SCHEME 6

A recent synthesis of (±)-monomorine I was carried out by Echavarren and co-workers in 1994[39]. This synthesis uses disconnection 6 where the precursor to the bicyclic compound is acyclic (see Scheme 7).

Diketone (23) was obtained by the reductive coupling of an acid chloride and a β-stannyl enone using palladium as catalyst. On treating (23) with cadmium in a 1:1

mixture of N,N'-dimethylformamide and acetic acid and sonication, the protective group on the amine was cleaved and the bicyclic ring structure (24) formed. The final step was the catalytic hydrogenation of the two double bonds using hydrogen and a rhodium on carbon catalyst.



TROC = $CO_2CH_2CCl_3$

Ref 39: Reagents: (a) $RuCl_3$ (cat.), $NaIO_4$ (b) H_2O, heat (c) $SOCl_2$, (*E*)-$Bu_3SnCH{=}CHCOBu$, $Pd(PPh_3)_4$,dioxane, 100°C (d) Cd, AcOH-DMF (e) H_2, Rh/C.

SCHEME 7

1.3.5 The First Synthesis of (+)-Indolizidine 195B

The first synthesis of (+)-indolizidine **195B** (2) was by Yamazaki and Kibayashi in 1989[42]. The method employed was essentially the same as in their synthesis of (+)-monomorine I[22] (see Scheme 4) In contrast with the synthesis of monomorine I, the configuration of alcohol (13) is *anti, syn, syn*. In this case both reduction steps were carried out using zinc borohydride.

1.4 The Stereochemistry of Indolizidines

Cis-trans isomerism of the ring junction is possible in indolizidines because of the ability of the nitrogen atom to undergo atomic inversion. In the case of indolizidine, the equilibrium lies towards the *trans* isomer. When there are substituents present, as in 3-butyl-5-methylindolizidine, the balance of the equilibrium changes. ^{1}H NMR and infrared spectroscopy may be used to determine the configuration. The magnitude of the coupling constants and chemical shifts may be used to decide between conformers.

The absence of Bohlmann bands in the infrared spectrum usually indicates *cis* fusion[44] Bohlmann[45] discovered that the infrared spectra of tertiary amines in which the α carbon atoms have at least two hydrogen atoms antiperiplanar to the lone electron pair on the nitrogen show a series of absorption bands in the 2800 to 2700cm^{-1} region. These bands are sensitive to deformation of the nitrogen heterocycle[46]. The intensity of these Bohlmann bands is proportional to the number of hydrogen atoms on the carbon atoms α to the nitrogen which are antiperiplanar to the lone electron pair at the nitrogen. A single antiperiplanar hydrogen atom can also show an absorption in the 2800 to 2700 cm^{-1} region. This is contrary to Bohlmann's original conclusion. This absorption appears at the upper end of the range and may be masked by overlapping CH_2 symmetry stretching vibrations. This Bohlmann method has been used mainly to differentiate between *trans* and *cis* quinolizidines but is also applicable for indolizidines[46].

This technique may be used to differentiate between different stereoisomers of 3-butyl-5-methylindolizidines[12]. A broad Bohlmann band pattern with weak fine structure is present when H-3, H-5 and H-9 are all *cis* (5*Z*, 9*Z*). The other stereoisomers have Bohlmann bands decreasing in intensity in the order 5*E*,9*Z* > 5*E*, 9*E* > 5*Z*, 9*E*. (See page 5)

Numerous papers containing ^{13}C NMR data of monomorine I and its stereoisomers have been published, so once a synthesis of 3-butyl-5-methylindolizidine has been achieved, it should be relatively easy to determine what stereoisomer has been obtained. The ^{13}C NMR data for four of the stereoisomers are tabulated below[47].

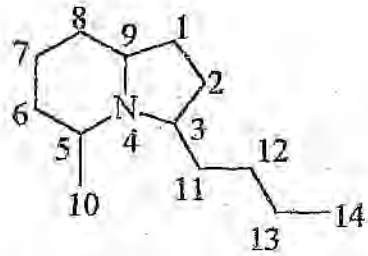


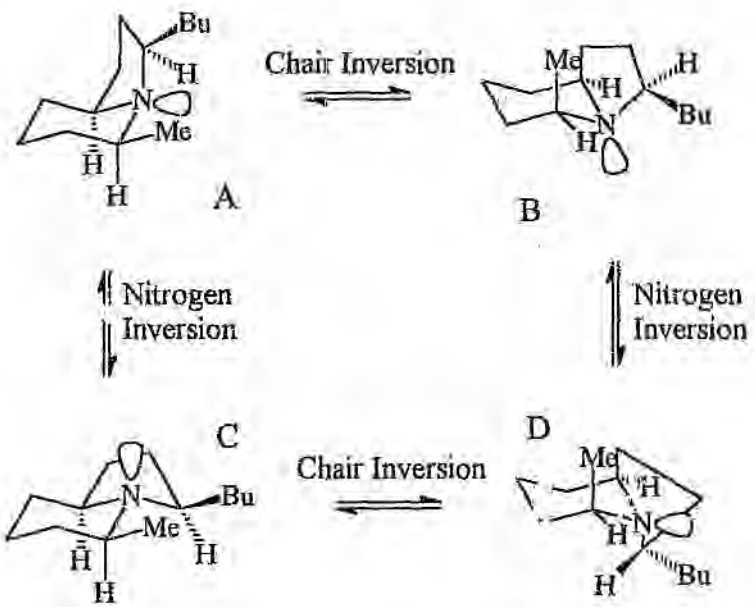
Table 2: ^{13}C NMR Data of Four of the Stereoisomers of 3-Butyl-5-methylindolizidine

Carbon	*3S,5R,9R* (-)-monomorine I	*3R,5R,9S*	*3R,5R,9R* (-)-indolizidine **195B**	*3S,5R,9S*
14	14,17	7,53	14,24	14,17
10	22,90	14,09	20,45	19,03
13	---	19,31	23,03	20,52
7	24,90	23,10	24,72	23,04
12	29,42	28,19	24,89	26,86
2	29,76	28,80	26,32	26,94
1	30,33	29,25	29,18	28,58
8	30,90	31,58	30,02	28,91
6	35,83	32,37	32,39	29,10
11	39,73	32,44	34,52	36,19
5	60,27	47,33	52,00	48,67
3	62,91	55,39	58,80	55,29
9	67,16	59,13	58,96	59,67

The carbon-13 spectrum of (+)-monomorine I[48] is ,as expected, identical to that of (-)-monomorine I. Similarly, the carbon-13 spectrum of (+)-indolizidine **195B**[49] is

similar to that of (-)-indolizidine **195B**. The most significant differences between the different stereoisomers are at C-3, C-5 and C-9. This is due to the different chemical environment of each of these carbons in the different stereoisomers. It is interesting to note that the δ values of the butyl chain carbons in the ^{13}C NMR spectrum of the 3*R*,5*R*,9*S* isomer are much lower than the corresponding δ values of the carbons in the spectra of the other isomers.

Lhommet *et al*[48] used NMR data to establish the preferred conformations of (+)-monomorine I. It was found that the spectra showed significantly broadened signals when the temperature was lowered to 223K. This may be due to the equilibrium that occurs between different forms at a rate which does not result in rapid averaging. In Scheme 8 below, four different forms need to be considered due to the nitrogen and chair inversion.



SCHEME 8

Structure D is particularly unstable due to the three axial substituents of the six-membered ring. Chemical shifts and amount of signal broadening was used to

determine that the exchange was between A and C which related to the inversion of the nitrogen atom. There was also a small contribution of form B.

Sonnet *et al.*[50] only mentioned one form. This may be due to the fact that the spectra were recorded at 20MHz, this low resolution making the distinction of the conformations impossible. They ruled out *cis* fusion of the rings because of the presence of the Bohlmann bands. In the *trans*-fused six-ring chair arrangement, structure C, the substituents at C-3 and C-5 would be eclipsed. It was concluded that a *trans*-fused boat arrangement could be used to explain the stereochemistry of (+)-monomorine I.

CHAPTER 2
ORIGINS AND AIMS OF THIS PROJECT

At the University of the Witwatersrand we have been synthesising alkaloids for a number of years using what has informally become known as the "Wits approach". The aim of this project is to attempt the synthesis of monomorine I and its stereoisomers using this approach. In the following sections, I shall:

(a) discuss the "Wits approach" to alkaloid synthesis,

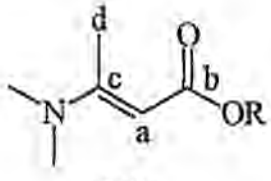
(b) discuss the strategy for the synthesis of 3-butyl-5-methylindolizidines, and

(c) summarise the aims of this project.

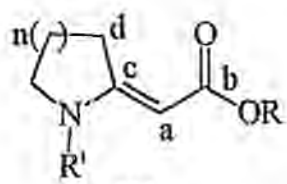
2.1 The " Wits Approach" to Alkaloid Synthesis

A long-standing research theme at Wits university is the development of a "generalised approach" to alkaloid synthesis. In other words, a central strategy has been developed which, with minor changes, can be used to synthesise a variety of alkaloids of varying structures.

At Wits, the nucleophilicity of exocyclic vinylogous urethanes has been extensively investigated[51-59]. Vinylogous urethanes (25) and (26) are versatile synthetic intermediates since they exhibit ambident nucleophilicity at nitrogen, the α-carbon (site a) and the carbonyl oxygen, and ambident electrophilicity (at sites b and c). An anion can be formed at site d, hereby providing another nucleophilic site. Attention has been focused on the nucleophilic sites, and reactivity at these positions has been exploited in the synthesis of alkaloids.

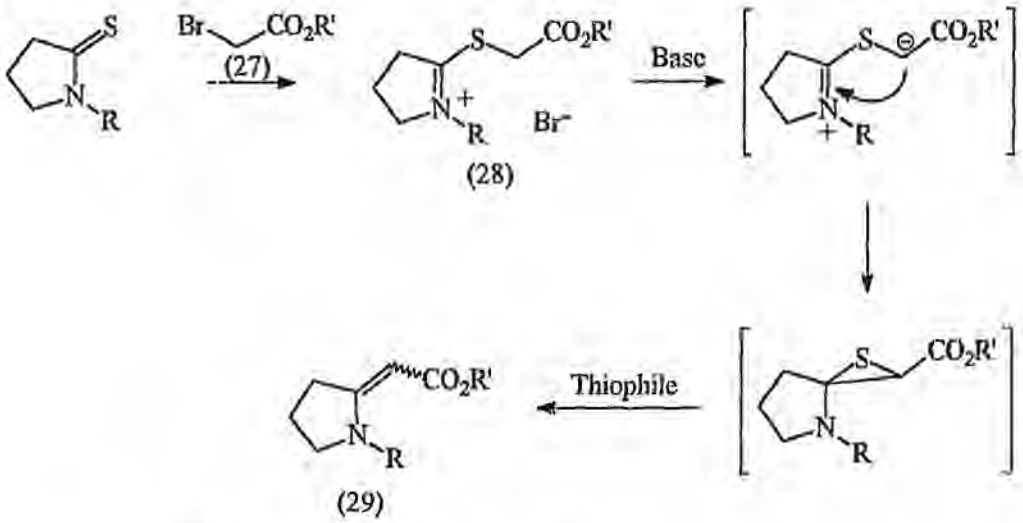


(25)



(26)

The sulphide contraction reaction developed by Eschenmoser has proved to be very effective in the synthesis of these vinylogous urethanes[61]. This reaction introduces a carbon-carbon double bond α to the nitrogen. In these laboratories, the procedure of Eschenmoser has been adapted to the preparation of vinylogous urethanes and related compounds in which the nitrogen is tertiary. When an N-alkylthiolactam is treated with an α-bromocarbonyl compound (27), a thioiminium ether (28) forms, and extrusion of the sulphur from this species by adding a base and a sulphur scavenger (thiophile) yields product (29). It has been proposed that the intermediate is a thioepoxide (also called an episulphide). The postulated mechanism is shown in Scheme 9. Thiolactams in which the nitrogen is tertiary require milder sulphide contraction conditions and produce higher yields than when the nitrogen is secondary.

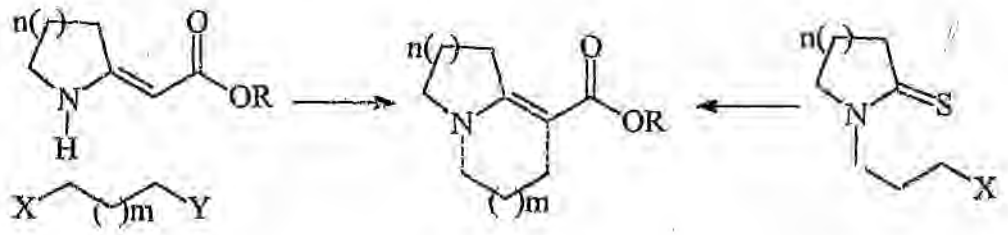


R = H: double bond has *Z* geometry
R not = H: double bond usually has *E* geometry
Ref 60

SCHEME 9

Bifunctionalised electrophiles may be employed to bridge between two of the nucleophilic sites in the vinylogous urethane intermediates (see Scheme 10). In this way, functionalised indolizidine and quinolizidine systems may be formed.

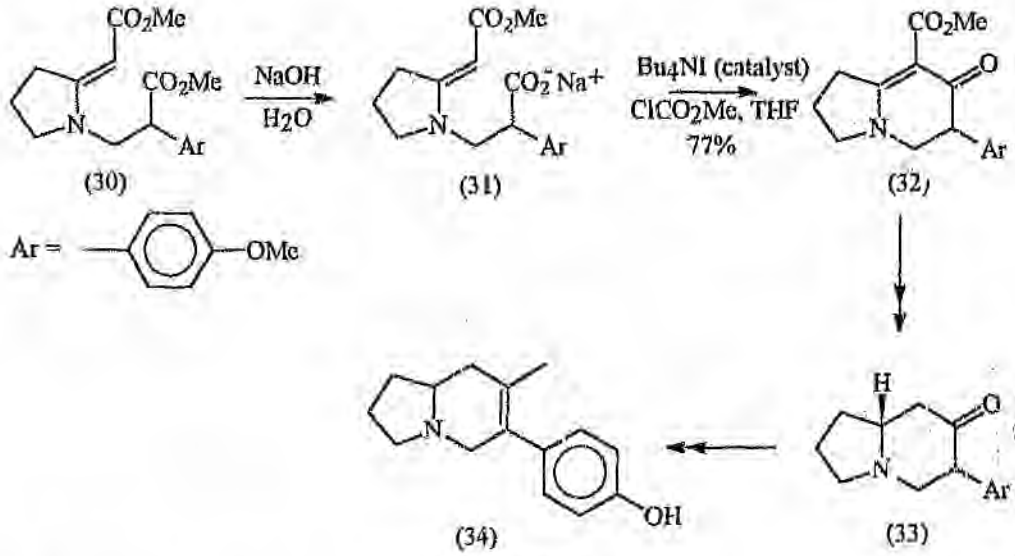
Once cyclisation has occurred, the ester functionality is well situated for further modification.



SCHEME 10

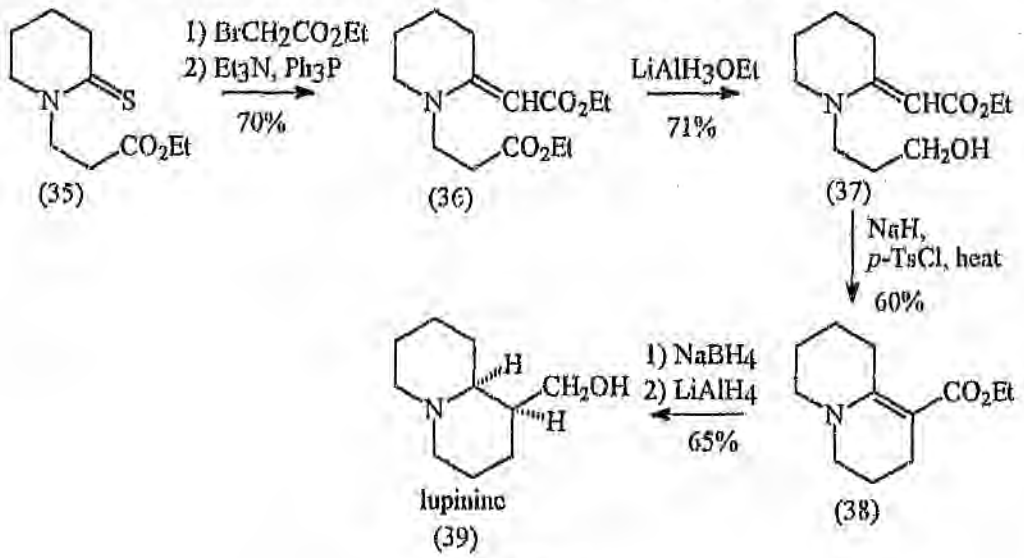
Variation in the oxidation levels of the electrophilic carbon sites is possible, and both alkylative and acylative cyclisations have been investigated[51, 53-59]. Some examples of the Wits use of vinylogous urethanes as intermediates for alkaloid syntheses are shown below.

Vinylogous urethanes have been used in the synthesis of ipalbidine (34)[56] (see Scheme 11). The bicyclic ring structure was formed using the acylative ring closure approach. In the key step, the saturated ester group was hydrolysed by heating (30) in aqueous sodium hydroxide. The sodium salt was dried and a mixed anhydride was formed on treatment with methyl chloroformate in the presence of a catalytic amount of tetrabutylammonium iodide. The mixed anhydride cyclised spontaneously to form the indolizidine skeleton (32). The hydrolysis and decarboxylation of the ester functionality and selective reduction of the carbon-carbon double bond yielded (33), which could be converted to ipalbidine (34).



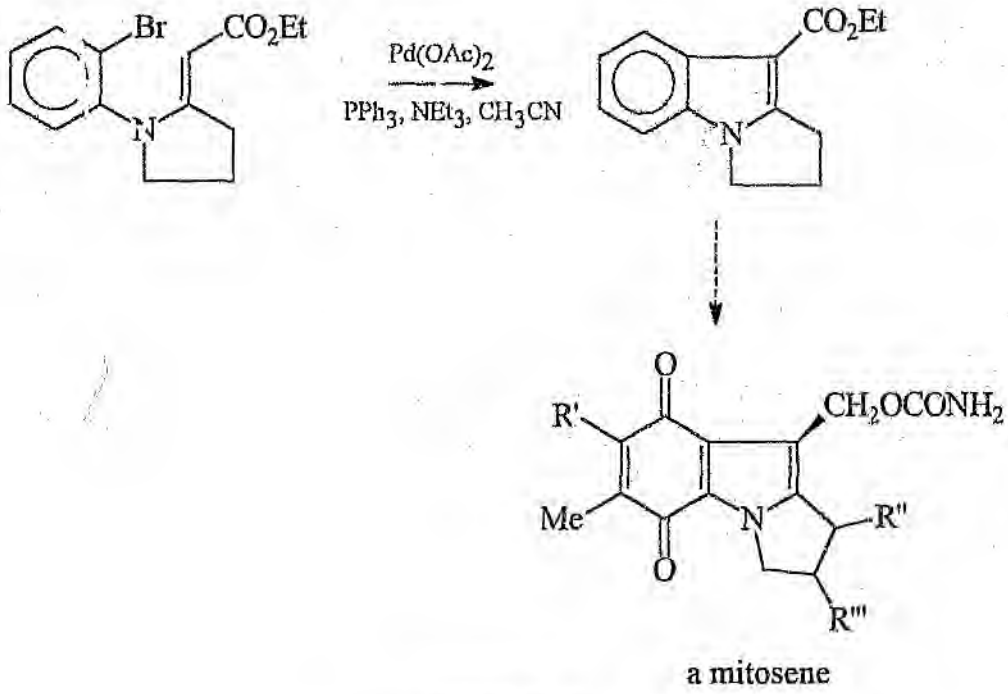
SCHEME 11

The alkylative cyclisation approach was used in the synthesis of a quinolizidine alkaloid, *lupinine* (39)[62] (see Scheme 12 below). The reaction of (35) with ethyl bromoacetate followed by a sulphide contraction with triethylamine and triphenylphosphine yielded the vinylogous urethane (36). The saturated ester group was selectively reduced to the alcohol (37) which on treatment with sodium hydride and *p*-toluenesulphonyl chloride followed by warming in acetonitrile, gave the bicyclic vinylogous urethane (38). Lupinine (39) was then obtained by reducing the ester and the carbon-carbon double bond of (38).



SCHEME 12

A vinylogous urethane was also used in the synthesis of a pyrrolo[1,2-*a*]indole[58]. This was achieved using an intramolecular Heck reaction[61] on N-(2-bromoaryl) vinylogous urethanes. The tricyclic ring system is present in mitomycins, which have pronounced antibacterial and antitumour activity, and their degradation products, mitosenes, which are also biologically active.

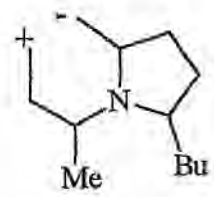


a mitosene

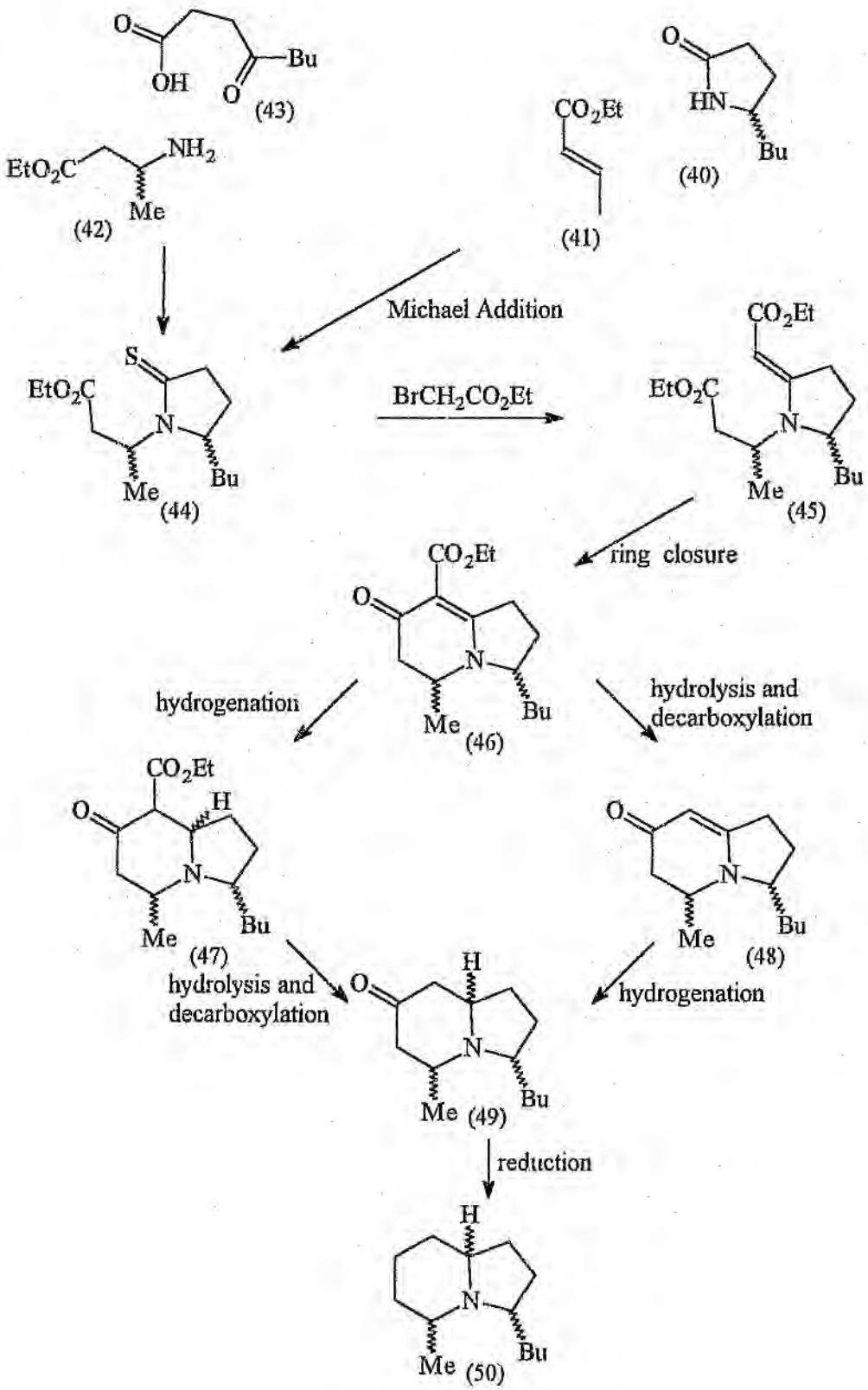
SCHEME 13

2.2 Strategy for the Synthesis of 3-Butyl-5-methylindolizidines

The disconnection that we have chosen to explore does not correspond to any of the disconnections mentioned previously (Scheme 1) and is shown below. This disconnection was chosen since it makes use of a nucleophilic site of a vinylogous urethane as described earlier on in the "Wits approach". The nucleophilicity of the site marked "-" is utilised in the cyclisation step to form the indolizidine skeleton.



The envisaged approach is shown in Scheme 14 below. The methods will first be attempted on racemic reagents to determine suitable reaction conditions. They will then be repeated using optically pure versions of the starting materials to ensure that, where possible, the desired absolute configurations are present at the start. This should also limit the number of stereoisomers obtained. Methods for enantioselective preparations of these starting materials will be discussed later.

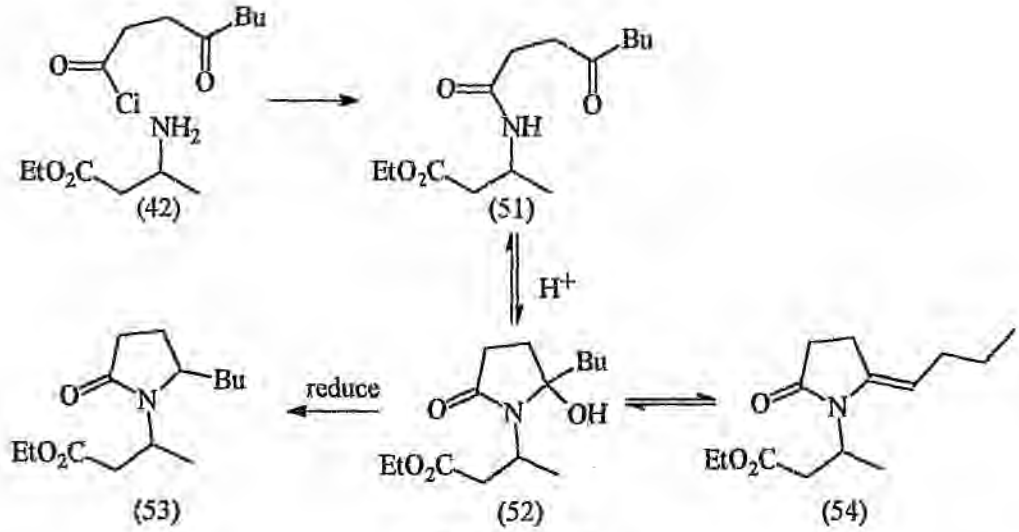

(43)
(42)
(41)
(40)
Michael Addition
$BrCH_2CO_2Et$
(44)
(45)
ring closure
(46)
hydrogenation
hydrolysis and decarboxylation
(47)
(48)
hydrolysis and decarboxylation
hydrogenation
(49)
reduction
(50)

SCHEME 14

The strategy involves two routes which converge at compound (44). The first approach starts with the five-membered nitrogen-containing ring in place already and uses a conjugate addition reaction to add the ethyl crotonate. In the case of the stereoselective approach, the absolute stereochemistry of the butyl side chain will already be in place. Diastereomers are most likely to be formed during the conjugate addition reaction. If possible, these will be separated.

One of the ways of achieving this addition is by first forming the thiolactam of 5-butyl-2-pyrrolidinone (40) and using a base to remove the proton from the nitrogen so that the Michael addition with the ethyl crotonate (41) is able to take place.

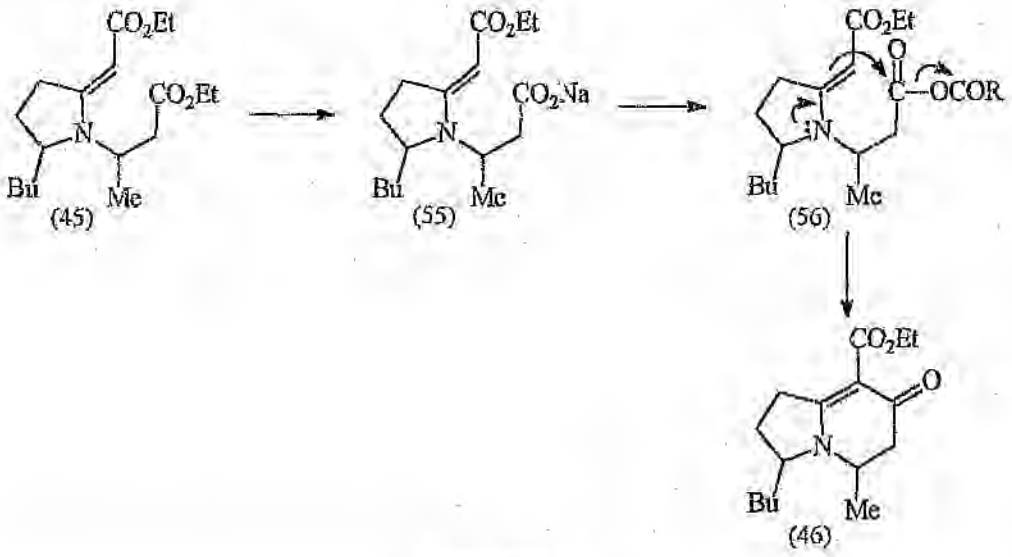
In the second approach, the five-membered ring with the butyl side chain is built around the nitrogen of a β-aminoester (42). This should be possible using the acid chloride of 4-oxooctanoic acid (43). This reaction scheme is shown below (Scheme 15). The β-amino-ester (42) and the acid chloride should combine to form the oxoamide (51) which is likely to be in equilibrium with its ring tautomer (52) under acidic conditions. This α-hydroxylactam (52) is possibly also in equilibrium with the enamine (54) which is the dehydrated product. These predictions are based on the findings of Lete and co-workers[64] who did work on similar compounds. The hydroxy group may be removed with triethylsilane (Et_3SiH) in the presence of trifluoroborane etherate ($BF_3.OEt_2$). This type of reaction has been used successfully by Yoda, Takabe and co-workers[65, 66] in the synthesis of chiral lactams. Once the lactam (53) has been obtained, a thionation step may be performed to yield the desired thiolactam (44) in Scheme 14. In the case of the enantioselective synthesis, the absolute stereochemistry of the methyl group will be known. The butyl side chain is most likely to result in diastereomers.



SCHEME 15

Once compound (44) is obtained by either of these methods, the exocyclic vinylogous urethane (45) may be synthesised using Eschenmoser's sulphide contraction with compound (44) and ethyl bromoacetate as described in Section 2.1, Scheme 9.

The next step is the formation of the six-membered ring. Experience in these laboratories has shown that direct acylative ring closure by an intramolecular reaction of the vinylogous urethane and free ester is not possible since the ester is not an active enough electrophile[67]. To overcome the problem, the ester will first have to be converted to a more suitable leaving group by hydrolysing it to the salt (55) and forming a mixed anhydride (56). Acylative ring closure should then take place spontaneously. These steps are shown in the Scheme 16 below.



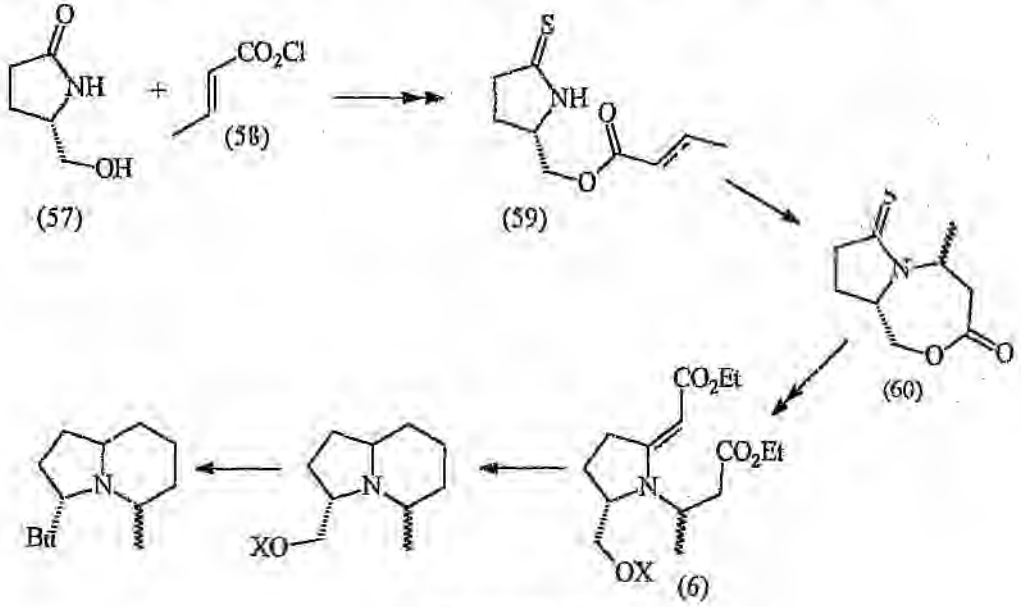
SCHEME 16

The indolizidine ring structure is now in place. The following two steps in the synthesis of 3-butyl-5-methylindolizidine are the hydrolysis and decarboxylation of the ester functionality and the reduction of the carbon-carbon double bond of (46). The best order for these reactions will have to be investigated. The reduction step is important since it is at this stage that stereochemistry can be controlled. Previous workers in this laboratory have obtained largely *cis*-hydrogenation by catalytic hydrogenation over platinum oxide with acetic acid as the solvent, while a nearly equal mixture of isomers has been obtained when sodium cyanoborohydride in ethanol at pH *ca* 4 was used in the reduction step[52]. The stereochemistry of the substituents on C-3 and C-5 of the indolizidine structure will also need to be considered in the reduction step as they could influence the direction of approach of the hydrogen during the reaction.

The final step is the removal of the carbonyl group of (49). This may be achieved by forming a thio-acetal which may be removed using Raney nickel. A different method involves the use of (*p*-toluenesulphonyl)hydrazine and sodium borohydride. This method has been used by Pilli *et al.*[68] in the synthesis of alkaloid

223AB which is similar to a stereoisomer of monomorine I; the difference being that the methyl group is replaced by a propyl group.

An alternative enantioselective approach involves an intramolecular Michael addition of a thiolactam and a crotonate. A single enantiomer of alcohol (57) is reacted with the acid chloride of crotonic acid (58). This is followed by a thionation step to form the thiolactam (59). An intramolecular Michael addition may now be attempted. It is hoped that the addition will occur preferentially on one face of the double bond to limit the formation of diastereomers. A seven-membered ring will be obtained in the process. This will be followed by a sulphide contraction reaction to form the vinylogous urethane. The next step will involve the cleaving of the ester with sodium hydroxide to obtain (61). The cyclisation, hydrolysis and decarboxylation, hydrogenation of the double bond and the reduction of the carbonyl group may be performed as described in an earlier synthetic strategy. The final step is the formation of the butyl side chain. It is likely that this will be possible using a propyl metallic reagent such as propylmagnesium bromide or lithium dipropylcuprate[69]. If necessary the alcohol (or protected alcohol) will be converted to a suitable leaving group first.



SCHEME 17

It is hoped that this synthetic strategy will allow better stereochemical control in the synthesis of monomorine I or any one of its stereoisomers.

2.3 Summary of Aims

The aims of this project are to

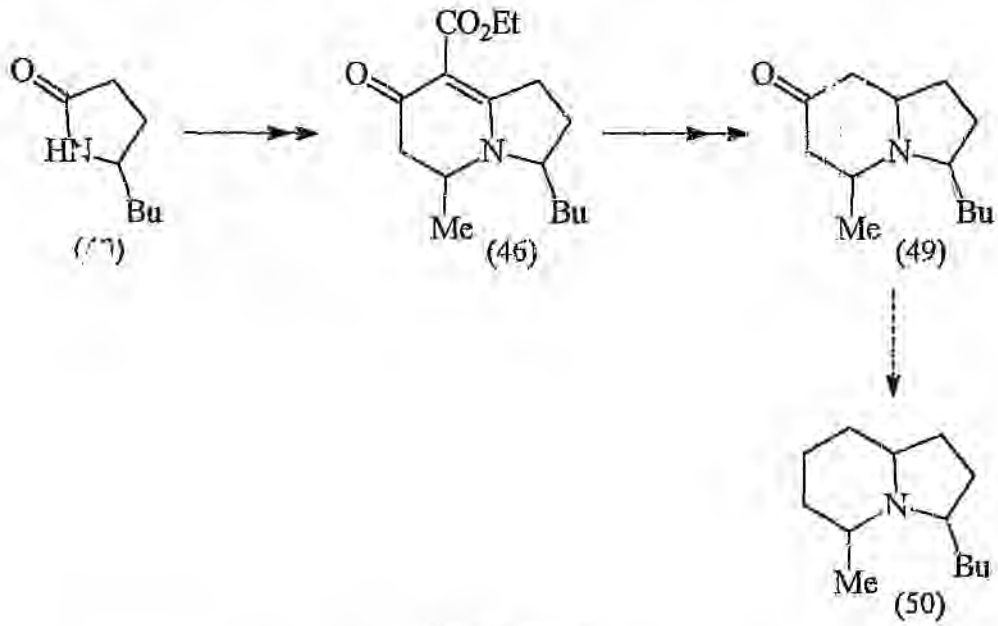
- synthesise 3-butyl-5-methylindolizidine racemically, and
- synthesise 3-butyl-5-methylindolizidine enantioselectively.

In the case of the enantioselective approaches, the use of optically pure starting materials will make it possible to control the stereochemistry of the subsequent products. It is most likely that the reactions will result in the formation of more than one isomer so separation of these isomers will be required. Fortunately, since all four diastereomers are natural products, all results will have potential value.

CHAPTER 3

TOWARDS THE SYNTHESIS OF RACEMIC MONOMORINE I

In this chapter the progress towards the synthesis of racemic monomorine I will be discussed. The approach that will be used is summarised in Scheme 18 below. The synthesis of the racemic lactam (40) is first described. This is followed by the steps involved in the "Wits approach" to obtain the indolizidine skeleton. The reduction of the double bond and the hydrolysis and decarboxylation of the ester group to obtain 9-butyl-2-methyl-1-azabicyclo[4.3.0]nonan-4-one (49) are then covered. The final step of the reduction of the keto group was not carried out, but a possible way of achieving this reaction will be discussed.

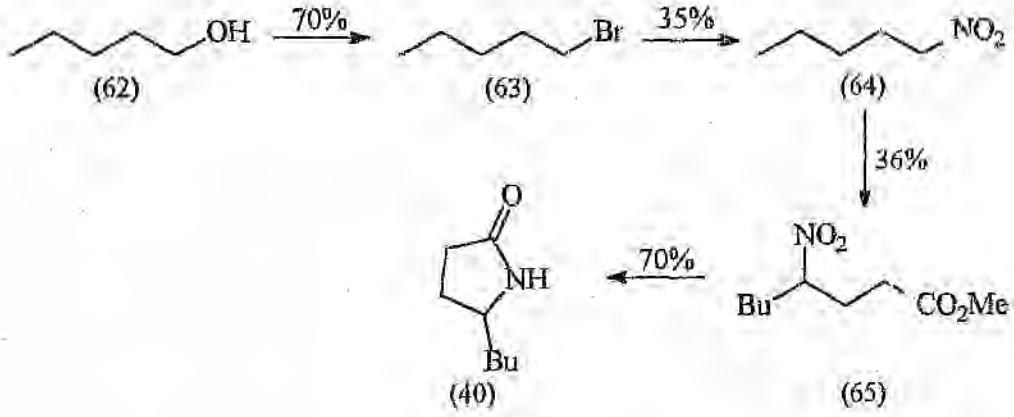


SCHEME 18

3.1 Synthesis of Racemic 5-Butyl-2-pyrrolidinone (40)

In this section the synthesis of racemic 5-butyl-2-pyrrolidinone (40) will be discussed. An overview of the approach that was used, followed by a discussion of each of the steps, is given below. 5-Butyl-2-pyrrolidinone (40) was synthesised

from 1-pentanol (62) in four steps as shown in Scheme 19 below. The overall yield was a very low 6%. This may be accounted for by the low yields of approximately 35% each for the conversion of 1-bromopentane (63) into 1-nitropentane (64) and the conjugate addition step.



SCHEME 19

3.1.1 Conversion of 1-Pentanol (62) into 1-Bromopentane (63)

The conversion of 1-pentanol (62) into 1-bromopentane (63) was achieved by heating 1-pentanol (62) under reflux in the presence of sodium bromide and concentrated sulphuric acid. 1-Bromopentane (63) was isolated as a clear liquid by distillation at 122-125°C. The yield for this reaction ranged between 62 and 74%.

The compound was identified using infrared and NMR spectroscopy. The infrared spectrum showed the disappearance of the strong broad band between 3500 and 3300cm^{-1} characteristic of the OH stretching of an alcohol, thus indicating the absence of the alcohol. Three fairly strong peaks were present between 750 and 500cm^{-1} which is the region in which the C-Br peak is present. The ^{1}H NMR spectrum showed a triplet at 3,41 ppm which is in the characteristic region for methylene protons on the same carbon as a bromine atom. In the ^{13}C NMR spectrum the carbon to which the bromine is bonded gave rise to a peak at 33,91ppm. All other signals were consistent with the expected structure.

3.1.2 Conversion of 1-Bromopentane (63) into 1-Nitropentane (64)

1-Nitropentane (64) was synthesised from 1-bromopentane (63) using the method described by Samah and Barua[70] for the synthesis of 4-methyl-1-nitropent-3-ene from 1-bromo-4-methylpent-3-ene. This involved adding the alkyl bromide to a solution of sodium nitrite in dimethyl sulfoxide (DMSO). After an aqueous work-up, the product was extracted with petroleum ether and the DMSO was removed by washing with water. 1-Nitropentane (64) was isolated as a clear liquid by vacuum distillation (27 mHg) at 80-82°C. The yield for this reaction was low and ranged between 29 and 36%. This yield is very low in comparison to the yield of 64% for the reported procedure for 4-methyl-1-nitropent-3-ene[70]. Increasing the time of the reaction and increasing the concentration of the sodium nitrite in DMSO did not increase the yield of 1-nitropentane (64).

The product was identified using infrared and NMR spectroscopy. The infrared spectrum showed strong peaks at 1554 and 1382cm^{-1} which are due to asymmetrical and symmetrical stretching of the NO bonds. The ^{1}H NMR spectrum shows that the triplet at 3,41ppm of 1-bromopentane has shifted downfield to 4,39ppm, which is characteristic of methylene protons on the same carbon as NO_2. This downfield shift is caused by the greater electron-withdrawing effect and hence greater deshielding effect of the nitro group relative to the bromine. In the ^{13}C NMR spectrum the carbon containing the nitro group results in a peak at 75,48ppm. This downfield shift is similarly due to the high electronegativity of the nitro group. All the other signals were consistent with the expected structure.

3.1.3 Synthesis of Methyl 4-Nitrooctanoate (65)

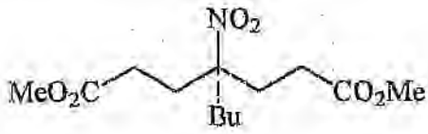
Several methods to synthesise methyl 4-nitrooctanoate (65) by conjugate addition of 1-nitropentane (64) to methyl acrylate were attempted. The most successful method was that of Ballini, Petrini and Rosini[71], which involved the use of Amberlyst A-21, a basic solid-phase catalyst, and in the absence of solvent.

Amberlyst A-21 was added to a cooled mixture of 1-nitropentane (64) and methyl acrylate. The mixture was stirred overnight at room temperature and the product was obtained after extraction with diethyl ether and purification by column chromatography on silica gel. The best yield for this reaction was 47% although a typical yield was 36%. Inadequate mixing of the reaction mixture due to the nature of the beads of Amberlyst A-21 may have resulted in this low yield. In future it may be better to make use of an overhead stirrer rather than a magnetic stirrer. The yield reported in the literature[71] was 77%.

The product was identified using infrared and NMR spectroscopy, the results of which compared favourably with those of literature[71]. The infrared spectrum showed strong peaks at 1740cm^{-1}, characteristic of the ester carbonyl group, and 1550 and 1366cm^{-1}, characteristic of the nitro group. The ^{1}H NMR spectrum showed a multiplet between 4,63 and 4,52ppm due to the single proton on the carbon bearing the nitro group. The only other peaks that were clearly separate were the singlet at 3,69ppm characteristic of the methoxy protons, and the triplet at 0,90ppm due to the methyl protons at the end of the butyl chain. The ^{13}C NMR spectrum had peaks at 172,22 and 87,62ppm characteristic of the carbonyl carbon and carbon attached to the nitro group respectively. The other signals were consistent with the expected structure.

Two less successful methods using the base DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) to remove the acidic proton of 1-nitropentane (64) in the conjugate addition reaction with methyl acrylate, were attempted. The first method involved the use of two mole equivalents of base[70] and tetrahydrofuran as the solvent. The product, methyl 4-nitrooctanoate (65), was obtained as a clear liquid in a yield of 21% by vacuum distillation (~0,1 mm Hg) at 130°C. This yield is low because a second product is also formed. Further distillation yielded a yellow liquid at 170°C. This appeared to be the disubstituted product (66) as indicated by the absence of a signal around 4,5ppm in the ^{1}H NMR spectrum due the proton α to the nitro group. This disubstituted product is a result of both the protons α to the nitro

group of 1-nitropentane being removed since there are two equivalents of base present.



(66)

The other less successful method involved the use of only one mole equivalent of DBU and acetonitrile as solvent as described by Ono *et al*[72] for the Michael addition of secondary nitroalkanes to β-substituted α,β-unsaturated compounds. Judging by ^{1}H NMR spectroscopy, the desired product was formed but purification was difficult. Thin layer chromatography showed that there were several products present which were difficult to separate by column chromatography. An attempt at distillation resulted in a wide boiling point range with none of the fractions collected being pure. It was stated in the literature[72] that the DBU/acetonitrile system may, in some cases, be too strong to obtain the desired reaction and that polymerisation of the α,β-unsaturated compound may occur. It seems to be that this method is not suitable for our system.

3.1.4 5-Butyl-2-pyrrolidinone (40)

The reduction of the nitro group of methyl 4-nitrooctanoate (65) was expected to lead to spontaneous cyclisation to yield a lactam. The amine formed by the reduction of the nitro group is certainly nucleophilic enough to attack the carbonyl carbon. Since the methoxy group is a good leaving group, 5-butyl-2-pyrrolidinone (40) was expected to be formed.

The most successful method for achieving the reduction of the nitro group was with hydrogen gas and a palladium-on-carbon catalyst using the method described by Werner[73]. Methyl 4-nitrooctanoate (65) and 10% palladium-on-carbon catalyst were added to a 2:1 mixture of absolute ethanol and acetic acid and stirred under 3

atmospheres of hydrogen gas for six days. After the work-up and purification by column chromatography on silica gel, 5-butyl-2-pyrrolidinone (40) was isolated as a pale yellow oil in a 70% yield.

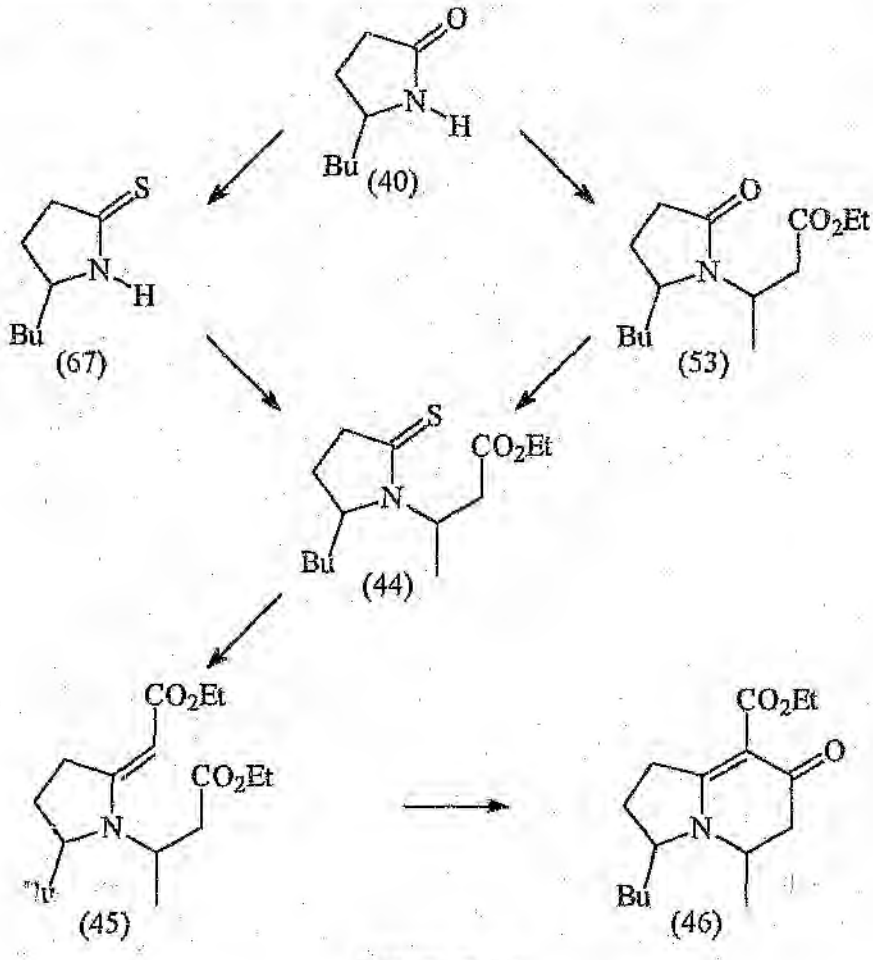
The product was identified using infrared and NMR spectroscopy. The infrared spectrum showed a strong absorption at 1740cm^{-1}, characteristic of the NC=O group in a five-membered lactam ring. The ^{1}H NMR spectrum showed a broad singlet at 7,41ppm due to the proton on the nitrogen. The proton on the tertiary carbon adjacent to the nitrogen resulted in a multiplet between 3,67 and 3,60ppm. The protons α to the carbonyl carbon showed up as part of a multiplet between 2,38 and 2,14ppm. The ^{13}C NMR spectrum showed a peak at 178,53ppm due to the carbonyl carbon and at 54,65ppm owing to the tertiary carbon adjacent to nitrogen. All other signals were consistent with the expected product.

Other methods for converting methyl 4-nitrooctanoate (65) into the desired lactam were less successful. A method using ammonium formate as a catalytic hydrogen transfer agent[74] was attempted. Anhydrous ammonium formate and 10% palladium-on-carbon catalyst were added to a solution of the nitroester (65) in dry methanol under a nitrogen atmosphere. After the work-up and purification by column chromatography on silica gel, the desired 5-butyl-2-pyrrolidinone (40) was obtained as a pale yellow oil in a yield of 35%. It was identified by infrared and NMR spectroscopy as described above.

An attempt to reduce the nitro group using aluminium amalgam, tetrahydrofuran and ultrasound, as described for the reduction of 2-nitroalkanols[75], was unsuccessful. The product obtained was not the desired lactam and could not be identified from the NMR spectra.

3.2 Forming the Indolizidine Skeleton

With lactam (40) in hand, we were now in a position to follow the sulphide contraction approach. The route that was followed is summarised in Scheme 20 below. Each of these steps will be discussed in greater detail below.



SCHEME 20

3.2.1 Thionation of 5-Butyl-2-pyrrolidinone (40)



(40) (67)

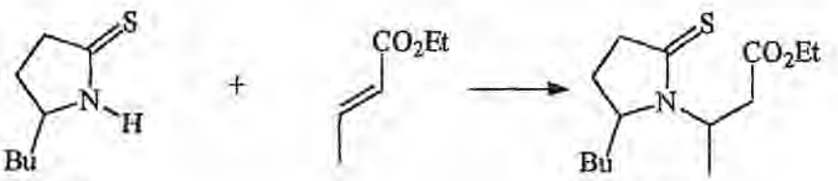
SCHEME 21

5-Butylpyrrolidine-2-thione (67) was obtained by thionating 5-butyl-2-pyrrolidinone (40) following the method of Brillon[76]. A 1:1 molar ratio of phosphorous decasulphide and sodium carbonate in tetrahydrofuran at 25°C results in the formation of the thionating agent, a homogeneous solution of $(P_4S_{10}O)^{2-}$ Na_2^{2+}, after about 20 minutes. Carbon dioxide is given off during this time. The lactam (40), dissolved in tetrahydrofuran, was added to this *in situ* reagent and after 4 hours the reaction was worked up. The desired product, 5-butylpyrrolidine-2-thione (67), was obtained after purification by column chromatography on silica gel. The highest yield for this reaction was 81% although the average yield was 69%.

The structure of the product was confirmed by infrared and NMR spectroscopy and the microanalysis results. The infrared spectrum showed an absorption at 3406cm^{-1} which is due to the NH stretching. There are two very strong absorptions at 1532 and 1504cm^{-1}, which is in the characteristic region for N-C=S. In the ^{1}H NMR spectrum, the broad singlet at 9,05ppm is due to the proton on the nitrogen. The proton on the carbon adjacent to the nitrogen resulted in a multiplet between 3,95 and 3,86ppm. The protons on the carbon adjacent to the thiocarbonyl carbon resulted in a multiplet between 2,99 and 2,77ppm. All the peaks of the protons on the ring carbons have shifted downfield relative to those of the lactam. This is owing to the larger sulphur atom in the thiolactam (67) having a greater π-cloud through-space deshielding effect than the oxygen in the lactam

(40). The signals of the protons on the butyl side chain were not affected. The ^{13}C NMR spectrum also showed a downfield shift for the ring carbons. Again this is due to the greater π-cloud through-space deshielding effect of the sulphur relative to the oxygen. The thiocarbonyl carbon peak appeared at 204,56ppm and the carbon adjacent to the nitrogen at 62,71ppm. There was very little change in the positions of the butyl side chain peaks.

3.2.2 Michael Reaction of 5-Butylpyrrolidine-2-thione (67) and Ethyl Crotonate



(67) (44)

SCHEME 22

The addition reaction between 5-butylpyrrolidine-2-thione (67) and ethyl crotonate will result in a product with two stereogenic centres. Thus four stereoisomers are possible: two diastereomers each consisting of two enantiomers. Although it would not be a simple process to separate the enantiomers, it should be possible to separate the diastereomers.

The reaction between 5-butylpyrrolidine-2-thione (67) and ethyl crotonate was attempted in tetrahydrofuran, using a catalytic amount of sodium hydride as base to remove the proton from the nitrogen. Judging by thin layer chromatography, no reaction occurred even after stirring the solution overnight and heating it under reflux for 5 hours. The addition of a full equivalent of sodium hydride resulted in a reaction occurring within 30 minutes. In order to drive the reaction to completion, the mixture was heated under reflux conditions overnight but judging by thin layer chromatography, no further starting material was converted. It is possible that an

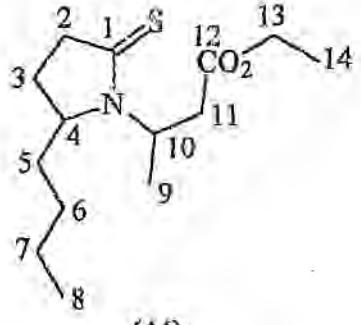
equilibrium had been reached. The R_f values of 5-butylpyrrolidine-2-thione (67) and the desired product, 5-butyl-1-(2-ethoxycarbonyl-1-methylethyl)pyrrolidine-2-thione (44), differ by only 0,12 (15% ethyl acetate in hexane) so flash column chromatography was used to separate them. The yield for the reaction was 37%. Starting material was recovered in a yield of 16%, so the yield of the converted starting material was 44%. ^{13}C NMR spectroscopy showed that diastereomers were present in roughly equal amounts.

In an attempt to increase the yield, the thiolactam (67) and a full equivalent of sodium hydride were stirred together in dry tetrahydrofuran for 15 minutes before the ethyl crotonate was added. This was so that the acidic proton of the thiolactam could be removed completely before the thiolactam came into contact with the ethyl crotonate. It was hoped that the equilibrium conditions that appeared to be present in the previous reaction could be overcome by adding pre-formed anion to the acceptor. However, 30 minutes after the addition of the ethyl crotonate, starting material was still present. The reaction mixture was then stirred overnight at room temperature and heated under reflux for 5 hours. No further reaction appeared to have occurred. After flash column chromatography, the conjugate addition product was obtained in a 23% yield.

A similar low yield was obtained when trying to carry out a Michael reaction between piperidine-2-thione and ethyl crotonate during my Honours project[77]. These low yields are in contrast to the high yields obtained when the reaction is carried out with ethyl acrylate instead of ethyl crotonate[78]. It is possible that the electrophilicity of the carbon-carbon double bond is weakened by the additional weakly electron donating methyl group, reducing the possibility of attack by the thiolactam anion. The methyl group may also sterically hinder the addition reaction. However, a worker in these laboratories has achieved a successful Michael addition reaction using pyrrolidine-2-thione and ethyl 2-octenoate in a much higher yield of 74%[78]. These results are not fully understood and require further investigation.

A mass spectrum was obtained for the mixture of the diastereomers. This was used to confirm that the molecular mass was equal to that of 5-butyl-1-(2-ethoxycarbonyl-1-methylethyl)pyrrolidine-2-thione (44), 271,16. It was also possible to get partial separation of the diastereomers. Diastereomer A has R_f value 0,29 and diastereomer B has R_f value 0,24 in a 15% ethyl acetate in hexane solution. Sufficient quantities of each of the diastereomers were obtained for NMR and infrared characterisation. Characteristic absorptions in the infrared spectra of each of the diastereomers were the ester carbonyl group at 1460cm^{-1} and the N-C=S absorption at 1734cm^{-1}. In diastereomer A, the C-O-C stretching absorption appeared at 1196cm^{-1} while in diastereomer B it appeared at 1180cm^{-1}.

The assignments of the NMR spectra were made by comparison with spectra of similar compounds made by workers in the laboratory and using a C-H correlation spectrum. A complete analysis of the NMR spectra for the two diastereomers A and B is given below. The NMR spectra were run in deuterated chloroform at 200MHz for diastereomer A and at 400 MHz for diastereomer B.



(44)

Table 3: NMR Data of the Two Diastereomers of (44)

^{1}H NMR of A	^{1}H NMR of B	^{13}C NMR of A	^{13}C NMR of B
5,26-5,15 (1H, m, H-10\	4,79-4,74 (1H, m, H-10)	201,54 (C-1)	200,53 (C-1)
4,14 (2H, q, 7Hz, H-13)	4,15 (2H, q, 7Hz, H-13)	170,5 (C-12)	171,17 (C-12)
4,19-3,98 (1H, m, H-4)	4,19-4,04 (1H, m, H-4)	65,09 (C-4)	67,27 (C-4)
3,05-2,94 (2H, m, H-2)	3,54 (1H, dd, 16 & 6Hz, H-11)	60,83 (C-13)	60,62 (C-13)
2,85 (1H, dd, 15 & 7 Hz, H-11)	3,04-2,90 (2H, m, H-2)	50,61 (C-10)	50,90 (C-10)
2,73 (1H, dd, 15 & 8Hz, H-11)	2,48 (1H, dd, 16 & 8Hz, H-11)	43,96 (C-2)	44,65 (C-2)
2,17-2,05 (1H, m, H-3)	2,22-2,08 (1H, m, H-3)	38,41 (C-11)	37,85 (C-11)
1,87-1,22 (7H, m, H-3, 5, 6 & 7)	1,84-1,20 (7H, m, H-3, 5, 6 & 7)	33,75 (C-5)	33,24 (C-5)
1,42 (3H, d, 7Hz, H-9)	1,52 (3H, d, 7Hz, H-9)	27,58 (C-6)	27,56 (C-6)
1,25 (3H, t, 7Hz, H-14)	1,26 (3H, t, 7Hz, H-14)	26,02 (C-3)	25,66 (C-3)
0,92 (3H, t, 7Hz, H-8)	0,93 (3H, t, 7Hz, H-8)	22,57 (C-7)	22,58 (C-7)
		18,50 (C-9)	17,07 (C-9)
		14,13 (C-4)	14,13 (C-4)
		13,93 (C-8)	13,93 (C-8)

The following comments for diastereomer B give an indication of how the assignments were made. In the ^{1}H NMR spectrum of B, the disappearance of the peak at 9,05ppm of the 5-butylpyrrolidine-2-thione (67) showed that the addition of the ethyl crotonate had indeed taken place on the nitrogen. The peaks of the thiolactam part of the molecule have remained relatively unchanged with respect to the starting material. The quartet at 4,15ppm and the triplet at 1,26ppm are characteristic of the methylene and methyl groups, respectively, of the ethoxy group. The stereogenic centre α to both the nitrogen and methyl group has resulted in the protons α to the carbonyl group being in different stereochemical environments. This results in different coupling constants and hence a more complex splitting pattern than would be expected if the protons were in the same chemical environment. The two protons α to the carbonyl group have each

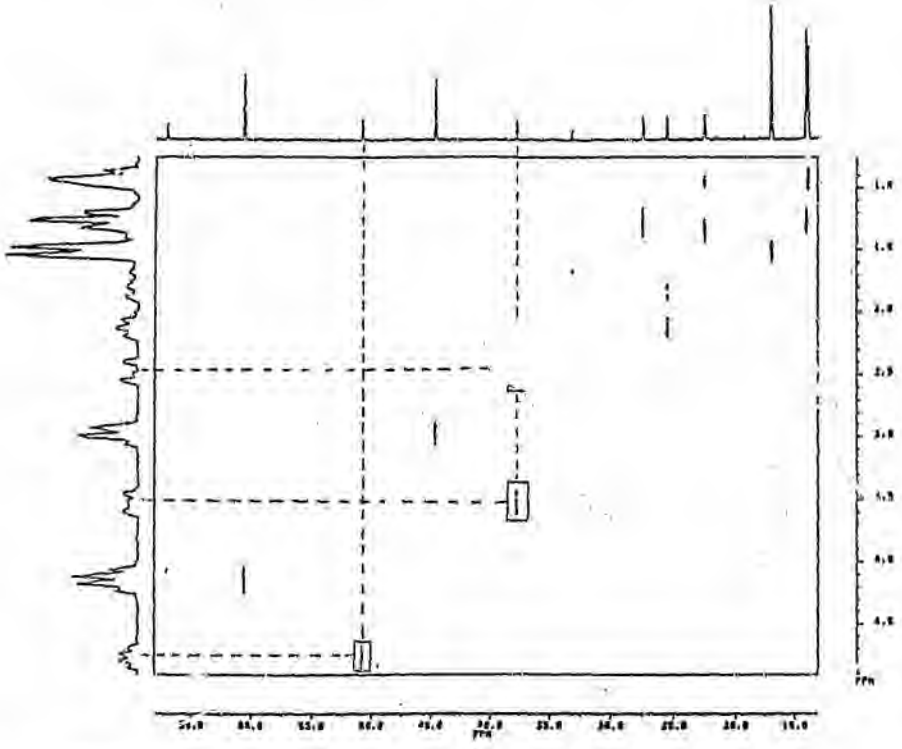
resulted in a double doublet. One is centred at 3,54ppm and the other at 2,48ppm. The geminal coupling constant is 16Hz and the vicinal coupling constants are 6 and 8Hz. The proton β to the carbonyl group resulted in a multiplet between 4,79 and 4,74ppm. The splitting pattern is a result of the three protons of the methyl group and the two non-equivalent protons α to the carbonyl group.

A C-H correlation spectrum was used to assist with the assignment of the peaks in the ^{13}C NMR spectrum since most of the peaks of the ^{1}H NMR spectrum could be assigned unambiguously. The ^{13}C NMR spectrum confirmed the presence of the thiocarbonyl group and the ester carbonyl group by the presence of the peaks at 200,53 and 171,17ppm, respectively. The peaks at 60,62 and 14,13ppm are in the characteristic region for the methylene and methyl carbons, respectively, of an ethoxy group. The C-H correlation spectrum shows that the two double doublets at 3,54 and 2,48ppm on the ^{1}H NMR spectrum are due to protons on the same carbon. The carbon peak is at 37,85ppm. The carbon α to the nitrogen and β to the carbonyl carbon resulted in a peak at 50,90ppm (See C-H correlation spectrum). The other tertiary carbon α to the nitrogen resulted in a peak at 67,27ppm.

The spectra for diastereomer A are very similar to those of diastereomer B. The only significant difference was in the ^{1}H NMR spectrum. The chemical shifts of the two protons α to the carbonyl group each resulted in a double doublet, one centred at 2,85ppm and the other centred at 2,73ppm. The peaks at 2,73ppm are further downfield and the peaks at 2,85ppm further upfield than the corresponding peaks of the other diastereomer. These differences are most likely due to the different stereochemical environments of the protons in the different diastereomeric pairs.

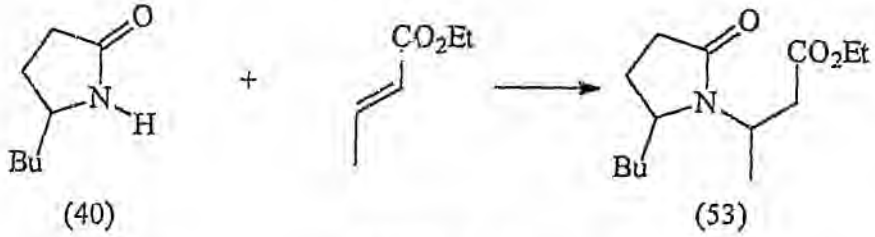
From the available information it is not possible to determine the relative configurations of the two diastereomers. However, if each of the separate diastereomers is taken through the reaction sequence to form 3-butyl-5-

methylindolizidine (50), it will eventually be possible to correlate the results since all the indolizidine diastereomers are known[20].



C-H Correlation spectrum of diastereomer B of 5 butyl-1-(2-ethoxycarbonyl-1-methylethyl)pyrrolidine-2-thione (44)

3.2.3 Attempted Synthesis of 5-Butyl-1-(2-ethoxycarbonyl-1-methylethyl)-2-pyrrolidinone (53)



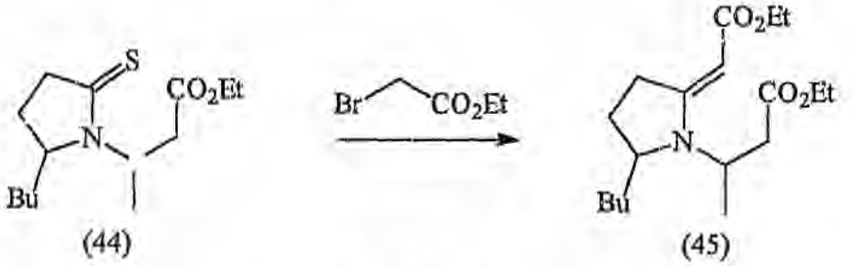
(40) (53)

SCHEME 23

Since the Michael addition reaction between 5-butylpyrrolidine-2-thione (67) and ethyl crotonate was giving low yields of around 30%, it was hoped that the conjugate addition using 5-butyl-2-pyrrolidinone (40) would be more successful. The thionation step could be carried out afterwards. The method used was that of Ahn and Lee[79] and involved a silyl enol ether intermediate. A yield of 96% was reported in the literature[79] for a reaction between 2-piperidinone and ethyl crotonate using this approach, making the reaction between 5-butyl-2-pyrrolidinone (40)and ethyl crotonate appear feasible.

Ethyl crotonate was added to a suspension of the lactam (40), 1 equivalent of tetraethoxysilane and 0,1 equivalent of cesium fluoride under a nitrogen atmosphere and without using a solvent. After subjecting the reaction mixture to column chromatography on silica gel, NMR spectroscopy indicated that the desired compound was not obtained. No attempt was made to identify the product and no further work was done on this reaction.

3.2.4 Sulphide Contraction of 5-Butyl-1-(2-ethoxycarbonyl-1-methylethyl)-pyrrolidine-2-thione (44)



(44) (45)

SCHEME 24

The exocyclic vinylogous urethane system was achieved by the sulphide contraction reaction using a 1:1 mixture of diastereomers of 5-butyl-1-(2-ethoxycarbonyl-1-methylethyl)pyrrolidine-2-thione (44) and ethyl bromoacetate. After reacting (44) with ethyl bromoacetate in dry acetonitrile, the α-thioiminium

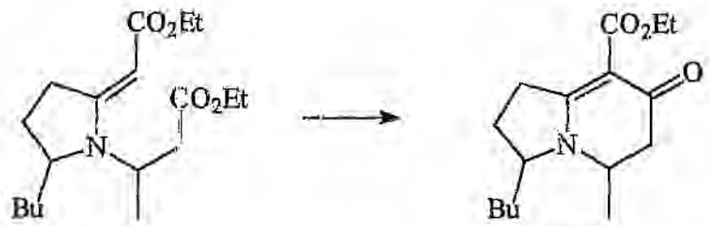
salt was formed. This was confirmed using thin layer chromatography since the starting material had all been consumed and the product remained on the baseline. A thiophile (triphenylphosphine) and a base (triethylamine) were added so that the sulphur could be extruded and the double bond formed. The product obtained was filtered through Celite to remove the triethylammonium bromide that had formed as a product of the reaction. Triphenylphosphine sulphide and the remaining triphenylphosphine were removed by column chromatography before isolating the desired (*E*)-5-butyl-1-(2-ethoxycarbonyl-1-methylethyl)-2-ethoxycarbonyl-methylenepyrrolidine (45) as a yellow oil. The product was obtained as a mixture of diastereomers in yields of between 84 and 90%.

The structure of the product was confirmed using infrared and NMR spectroscopy. Strong absorptions present in the infrared spectrum were at 1142cm^{-1} from the C-O-C stretching of the two ester groups, 1586cm^{-1} from the carbon-carbon double bond, and 1686 and 1734cm^{-1} from the carbonyl groups. The absorptions at 1586cm^{-1} and 1686cm^{-1} are low for double bonds and carbonyl groups, respectively, but are typical for vinylogous urethanes because of the conjugation with the lone pair of electrons on the nitrogen.

It was evident from the ^{13}C NMR spectrum that both diastereomers were present in a ratio of 3:7. This is most likely due to the sample used in the NMR experiment not being representative of the entire sample. Since the mixture was not 1:1, it was possible to assign the peaks of the ^{13}C NMR spectrum separately for each of the diastereomers. The vinyl carbon α to the nitrogen resulted in a peak in the region of 163/164ppm depending on the diastereomer in question. This is an upfield shift relative to the corresponding carbon of the starting material, and is due to the replacement of the electronegative sulphur atom by the vinyl group. The vinyl carbon β to the nitrogen resulted in a peak at 78,79ppm in the one diastereomer and at 78,71ppm in the other. The peaks at 169,36ppm, 58,24ppm and 14,72ppm were due to the carbonyl, methylene and methyl carbons respectively, of the ethyl ester of the vinylogous urethane. In the ^{1}H NMR spectrum, the formation of the

vinylogous urethane was characterised by the appearance of a singlet at 4,59ppm due to the vinyl proton. The appearance of a quartet at 4,08ppm and a triplet at 1,25ppm confirmed the presence of an additional ethoxy group. The rest of the signals were similar to those of the starting material.

3.2.5 Cyclisation of (*E*)-5-Butyl-1-(2-ethoxycarbonyl-1-methylethyl)-2-ethoxycarbonylmethylenepyrrolidine (45)



(45) (46)

SCHEME 25

Direct acylative ring closure by an intramolecular reaction of the vinylogous urethane and the ester group does not occur since the ester is not an active enough electrophile. An approximately 1:1 diastereomeric mixture of the ester (45) was therefore first hydrolysed to the sodium salt. Exactly one equivalent of aqueous sodium hydroxide was added as it is difficult to remove excess base after hydrolysis has occurred. This is because both the sodium hydroxide and hydrolysed product are water-soluble. It is important that there is no excess base present as this adversely affects the second step of the cyclisation. Special care was also taken to remove all traces of water from the salt as water would result in low yields in the next step of the reaction. The drying was achieved by heating the salt at 60°C under vacuum for 8 hours, grinding the solid to a fine powder and then heating the powder at 60°C under vacuum for another hour.

A mixed anhydride was formed *in situ* using acetic anhydride. The reaction was performed under a nitrogen atmosphere using dry acetonitrile as solvent. The

formation of the mixed anhydride made it possible for the cyclisation to occur to give the indolizidine skeleton. 9-Butyl-6-ethoxycarbonyl-2-methyl-1-azabicyclo[4.3.0]non-5-en-4-one (46) was isolated and the approximately 1:1 ratio of the two diastereomers was separated using column chromatography on silica gel. It was possible to separate diastereomers since the difference in R_f values was 0,15 in a 5:2 ethyl acetate: methanol mixture. The overall yield for the salt formation and cyclisation was 36%. There was approximately 260mg of each of the diastereomers available for the subsequent reactions. From this point on, the reactions were carried out separately on the two diastereomers.

The identity of the products was confirmed by NMR spectra, which were fully assigned by using C-H correlation spectra and decoupling experiments. Since the bicyclic system that had now been synthesised was comparatively rigid, the spatial relationships of the methyl and butyl side chains are now fixed. NOESY experiments were performed in an attempt to work out the relative stereochemistry of these groups.

In the infrared spectrum of the *cis* isomer (see explanation of the assignment below), the ester carbonyl absorption band is at 1710cm^{-1}. This is lower than the normal absorption for a α,β-unsaturated ester carbonyl group. This is because there is also electron donation from the lone pair of the electrons on the nitrogen. In the same way, the ketone carbonyl group absorption is at 1650cm^{-1}, which is low for a ketone. The carbon-carbon double bond resulted in an absorption at 1554cm^{-1}. This low value is a result of conjugation with both the ester and ketone carbonyl groups. The C-O-C stretching absorption was present at 1150cm^{-1}.

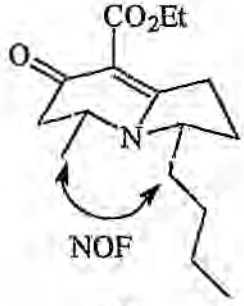
The assignments of the ^{1}H NMR spectrum was made using information from the decoupling experiments. In the case of the *cis* diastereomer, the absence of the singlet at 4,59ppm for a vinyl proton confirmed that cyclisation had occurred. The presence of only one quartet in the vicinity of 4ppm and one triplet in the vicinity of 1,3ppm indicated that only one ethoxy group was present. The proton α to

both the nitrogen and the butyl side chain resulted in a multiplet between 3,88 and 3,82ppm, and the proton α to the nitrogen and the methyl group resulted in a multiplet between 3,81 and 3,69ppm. The NOESY experiment (see below) assisted with the distinguishing between these two multiplets by taking into account their interaction with other protons in close proximity to them. The two double doublets due to the two protons α to the keto group appeared further upfield at 2,79 and 2,22ppm relative to the corresponding protons of the starting material. In the ^{13}C NMR spectrum of the *cis* isomer, the peaks at 186,89ppm and 166,21ppm were due to the ketone and ester carbonyl carbons, respectively. The vinyl carbon α to nitrogen resulted in a peak at 171,24ppm. The vinyl carbon β to the nitrogen resulted in a peak at 97,27ppm, which is further downfield than for the corresponding carbon of the starting material. This is due to the carbon now being α to two electron-withdrawing carbonyl groups, resulting in a greater deshielding effect.

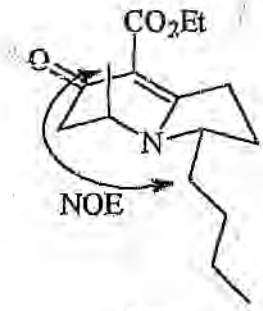
The *trans* isomer (see explanation of the assignment below) resulted in very similar spectra to the *cis* isomer. The most significant difference in the ^{1}H NMR spectrum was that the peaks due to the two protons α to the nitrogen overlapped and could not be assigned separately. In the ^{13}C NMR spectrum, the carbon to which the butyl chain is bonded, resulted in a peak at 66,28ppm (as opposed to 62,32ppm in the other diastereomer) and the methyl carbon β to the nitrogen resulted in a peak at 18,04ppm (as opposed to 15,50ppm in the other diastereomer). This is most likely explained by the configurational arrangement of the different diastereomers.

NOESY experiments were used to determine in which diastereomer the two protons α the nitrogen were *trans* and in which they were *cis*. The two dimensional technique is used to determine the interaction between protons through space as opposed to along a bond. Thus protons that are in close proximity to one another will result in an interaction, whereas protons far apart will not. In the case of the *cis* isomer, the two protons α to the nitrogen each result in separate multiplets in the ^{1}H NMR spectrum. The chemical shifts of these signals

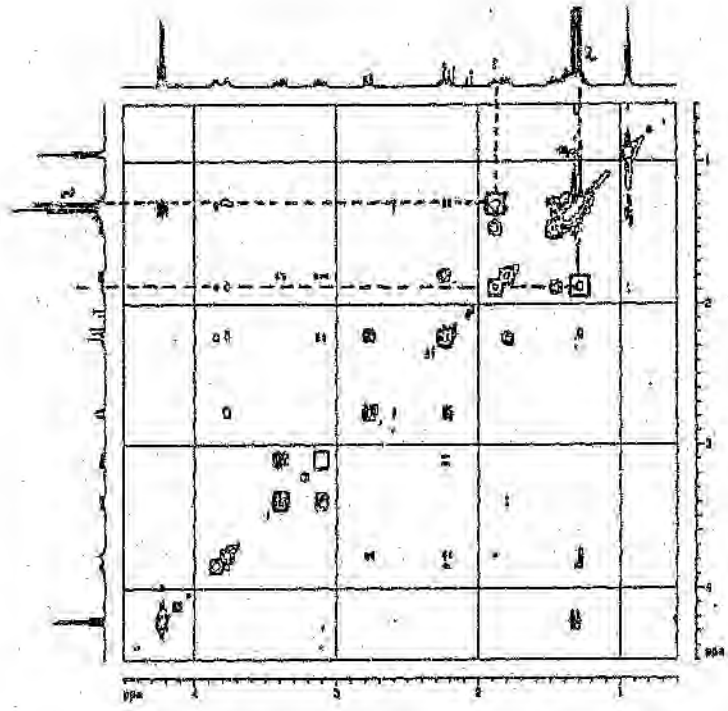
are, however, too close together to determine if there is any through-space interaction between the two α protons. Fortunately, we found that the protons of the methyl side chain and the methylene protons of the butyl side chain β to the nitrogen result in an interaction. This is illustrated in the spectrum below. This indicates that the relative stereochemistry of the two side-chains is *cis* since they are in close proximity to each other (see diagram below). In the case of the *trans* isomer, the interaction between the two protons α to the nitrogen could, once again, not be used in the determination since the ^{1}H NMR signals due to these protons overlap and cannot be distinguished. There is no interaction between the protons of the methyl side-chain and the methylene protons of the butyl side-chain β to the nitrogen, indicating that these protons are further apart than in the previous case (see diagram and spectrum below)

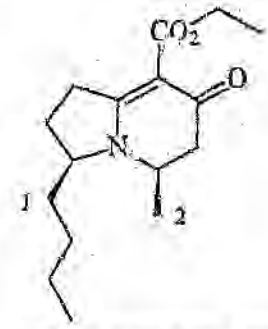


cis



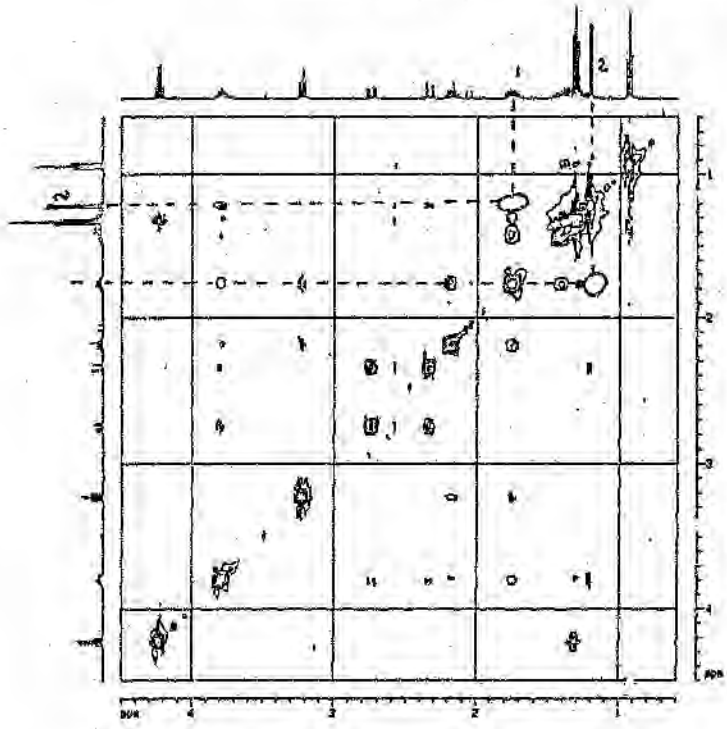
trans

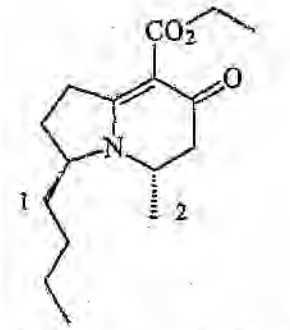




(relative stereochemistry)
Cis-(46)

NOESY Spectrum of *cis*-9-Butyl-6-ethoxycarbonyl-2-methyl-1-azabicyclo[4.3.0]non-5-en-4-one (46)



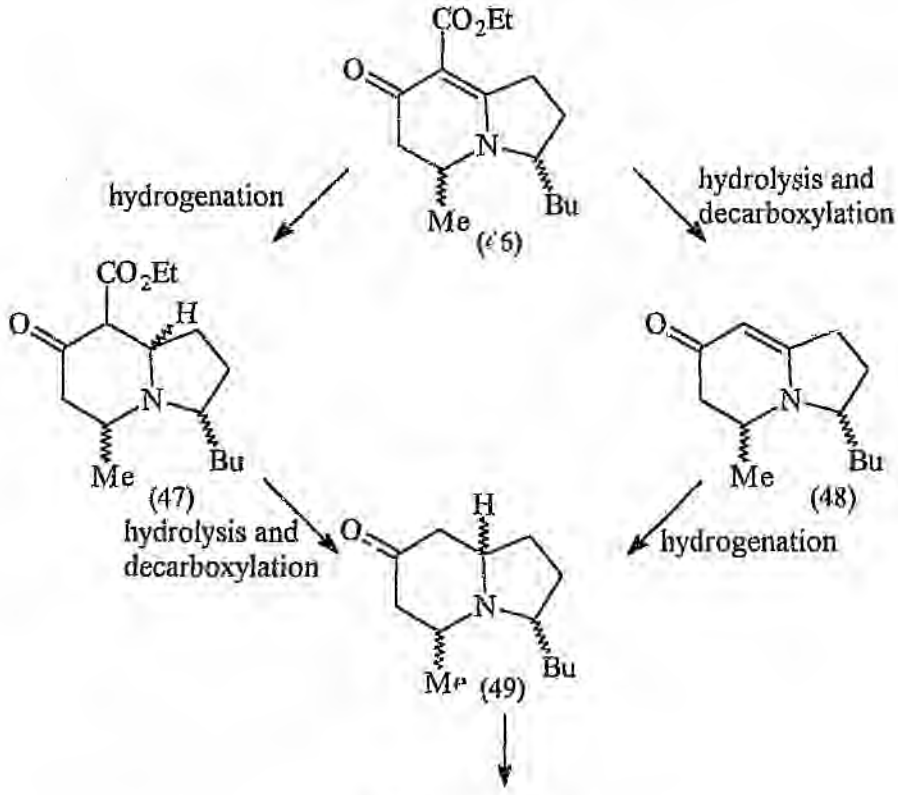


(relative stereochemistry)
Trans-(46)

NOESY Spectrum of *trans*-9-Butyl-6-ethoxycarbonyl-2-methyl-1-azabicyclo[4.3.0]non-5-en-4-one (46)

3.3 Approaches to 9-Butyl-2-methyl-1-azabicyclo[4.3.0]nonan-4-one (49)

The next two steps in the reaction sequence were the reduction of the carbon-carbon double bond and the hydrolysis and decarboxylation of the ester group of 9-butyl-5-ethoxycarbonyl-2-methyl-1-azabicyclo[4.3.0]non-5-en-4-one (46). It was not known which order of these reactions would result in the greatest overall yield so both pathways were attempted.



SCHEME 25

3.3.1 Hydrolysis and Decarboxylation of 9-Butyl-5-ethoxycarbonyl-2-methyl-1-azabicyclo[4.3.0]non-5-en-4-one (46)

The hydrolysis and decarboxylation was only carried out on the *trans* isomer of 9-butyl-5-ethoxycarbonyl-2-methyl-1-azabicyclo[4.3.0]non-5-en-4-one (46). The reaction was not performed using the *cis* isomer since the reduction step that

followed was unsuccessful when attempted on the *trans* isomer. Compound (46) was hydrolysed by heating it under reflux it in an aqueous solution of potassium hydroxide to form the carboxylate ion. On acidification with hydrochloric acid, the acidic hydrogen is transferred to the carboxylate, after which carbon dioxide is lost. The desired product, *trans*-9-butyl-2-methyl-1-azabicyclo[4.3.0]non-5-en-4-one (48), was obtained after purification by column chromatography on silica gel. The yield for this reaction was a low 48%. This may be partly due to the small scale on which the reaction was carried out.

The product was identified using infrared and NMR spectra. The infrared spectrum showed the disappearance of the ester carbonyl band at 1712cm^{-1}. The ketone carbonyl group appeared at 1626cm^{-1}. This is low for a keto group. It is however conjugated with the double bond and the lone pair of electrons on the nitrogen. In the ^{1}H NMR spectrum, the appearance of the vinyl proton as a singlet at 4,93ppm confirmed that decarboxylation had taken place. The disappearance of the quartet at 4,23ppm and the triplet at 1,32ppm corresponds to the loss of the ethyl ester. The rest of the spectrum remained very similar to that of the starting material. In the ^{13}C NMR spectrum, the disappearance of the ester carbonyl carbon peak at 171,62ppm and the ethyl carbon peaks at 59,30 and 14,39ppm confirmed the loss of the ethoxycarbonyl group.

3.3 Attempted Reduction of the Double Bond of 9-Butyl-2-methyl-1-azabicyclo[4.3.0]non-5-en-4-one (48)

The reduction reaction was carried out on the *trans* isomer of 9-butyl-2-methyl-1-azabicyclo[4.3.0]non-5-en-4-one (48). It was attempted at 0°C using one equivalent of lithium aluminium hydride in dry tetrahydrofuran under a nitrogen atmosphere. After several hours, judging by thin layer chromatography, no reaction appeared to have taken place. After an aqueous work-up and purification by column chromatography on silica gel, most of the starting material was recovered. This reaction was not attempted again in view of the time constraints.

The reduction of the double bond was then attempted before the hydrolysis and decarboxylation step.

3.3.3 Reduction of the Double Bond of 9-Butyl-5-ethoxycarbonyl-2-methyl-1-azabicyclo[4.3.0]non-5-en-4-one (46)

The reduction of the double bond of 9-butyl-5-ethoxycarbonyl-2-methyl-1-azabicyclo[4.3.0]non-5-en-4-one (46) was carried out on the separated *cis* and *trans* diastereomers. In each case, the reaction was attempted using lithium aluminium hydride in dry tetrahydrofuran at -78°C. It was hoped that at this low temperature the reaction would be stereospecific and that a mixture of diastereomers would not be formed. The reaction was monitored using thin layer chromatography which indicated that the reaction was not going to completion as starting material was still present. The product on the chromatogram was viewed using iodine since the reduction of the double bond meant that the product was no longer visible under ultraviolet light. The temperature was increased to -50°C before the reaction was quenched in the hope that the yield could be increased. Column chromatography on silica gel was used to purify the product. This was only partly successful since there were still impurities present afterwards.

In the infrared spectra of each of the products, the absorptions due to the ester and ketone carbonyl groups had shifted to 1744 and 1718cm^{-1} respectively. These are the expected absorptions for these groups now that the conjugated double bond has been removed.

The interpretation of the ^{1}H NMR spectrum was difficult since many of the signals overlapped as the number of functional groups on the molecule diminished. The ^{13}C NMR spectrum provided more information. In each of the cases the product was not pure as indicated by the extra peaks. DEPT and C-H correlation spectra were therefore not obtained to fully interpret the spectra. Thus, although the

results are not conclusive, it is possible to obtain an idea of what is to be expected when the reaction is repeated in future. The disappearance of the peaks in the region of 172 and 98ppm confirmed that the double bond had been reduced. The peak due to the keto carbonyl carbon shifted downfield from the region of 187ppm to 205ppm now that it was no longer conjugated with the double bond. The electron-donating effect of the double bond has been removed.

When the *trans* diastereomer was used as starting material, the product appeared to be a mixture of diastereomers as most of the signals had doubled up. The peaks that did not appear to be duplicated may be due to the overlapping of the peaks of the two diastereomers. The ratio of the diastereomers was approximately 1:3. No attempt was made to separate these diastereomers. When the *cis* diastereomer was used as starting material, only one stereoisomer was formed. In the case where the side-chains are *cis*, it is possible that one face of the molecule is sufficiently blocked so that the hydrogenation can only occur from the other face. In the case where the side-chains are *trans*, the hydrogenation can occur from either face although one of the faces is preferred as seen by the 1:3 ratio of the diastereomers.

3.3.4 Hydrolysis and Decarboxylation of 9-Butyl-6-ethoxycarbonyl-2-methyl-1-azabicyclo[4.3.0]nonan-4-one (47)

The hydrolysis and decarboxylation of 9-butyl-6-ethoxycarbonyl-2-methyl-1-azabicyclo[4.3.0]non-4-one (47) was carried out on the impure products as obtained from the previous reaction. The *cis* and *trans* isomers were still kept separate. In each case, the reaction was achieved by heating the relevant stereoisomer of 9-butyl-5-ethoxycarbonyl-2-methyl-1-azabicyclo[4.3.0]nonan-4-one (47) with an aqueous potassium hydroxide solution under reflux, acidifying, basifying and extracting with dichloromethane. The product was purified by column chromatography on silica gel. In each case, the ^{13}C NMR spectrum seemed to suggest that 9-butyl-2-methyl-1-azabicyclo[4.3.0]non-4-one (49) had been formed. However, the reactions will need to be repeated to provide conclusive results since impurities were still present.

The disappearance of the carbonyl carbon peak in the vicinity of 168ppm in the ^{13}C NMR spectra of both the stereoisomers indicated that decarboxylation had occurred. Although the presence of impurities made it difficult to assign the peaks unambiguously, there appear to be the correct number of peaks in the desired region. In each case, only one diastereomer was present. This is expected in the case when the methyl and butyl side-chains are *cis*. It is possible that in the case where the side-chains are *trans*, one of the diastereomers was lost during the purification process.

The infrared spectra showed only one absorption in the carbonyl region at 1718cm^{-1} due to the keto group. This confirmed that the decarboxylation had taken place. The relative intensities of the Bohlmann bands between 2800 and 2700cm^{-1} were very similar, making it difficult to determine the relative stereochemistry of the methyl and butyl side-chains by means of infrared spectroscopy.

3.4 Removal of the Keto Group



(49) (50)

SCHEME 26

The final step in the synthesis of racemic monomorine I is the removal of the keto group. No attempt was made to carry out this step due to insufficient quantities of 9-butyl-2-methyl-1-azabicyclo[4.3.0]non-4-one (49) being available. The reaction may, however, be achieved by forming a thio-acetal which is removed using Raney nickel, in line with similar work carried out in these laboratories by Gravestock[78]. However, many other methods for defunctionalising ketones may be found in the literature.

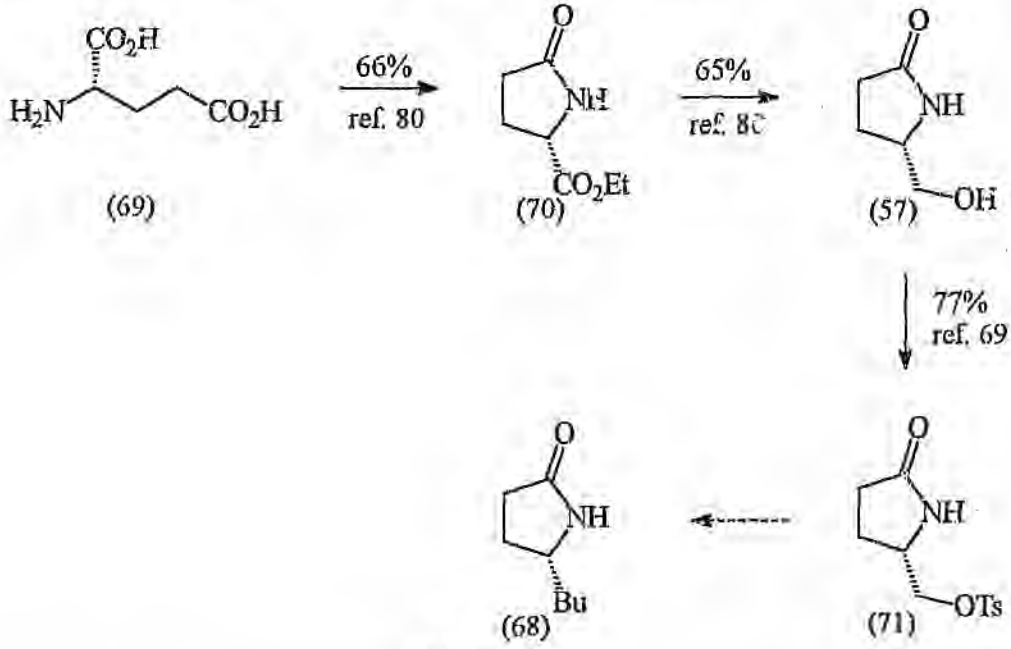
CHAPTER 4

STUDIES WITH OPTICALLY ACTIVE LACTAMS

This chapter covers the work done involving chiral lactams. A method of synthesising (*S*)-(+)-5-butyl-2-pyrrolidine (68) from L-glutamic acid is discussed. This is followed by an intramolecular Michael addition approach to indolizidines.

4.1 Progress Towards (*S*)-(+)-5-Butyl-2-pyrrolidinone (68)

With a convenient, though not very high yielding, method for the synthesis of the racemic lactam (40) in hand, we felt it was also appropriate to investigate the synthesis of the optically active compound. The approach for the synthesis of (*S*)-(+)-5-butyl-2-pyrrolidinone (68) is shown in Scheme 26 below.



SCHEME 26

This method used L-glutamic acid (69) as the starting material to ensure that the correct absolute stereochemistry is already present for the final product. The tosylated compound (71) was obtained in an overall yield of 33% for the three

steps. These steps will be discussed in detail below Although attempted, the final step was not achieved.

4.1.1 (*S*)-(+)-5-Carbethoxy-2-pyrrolidinone (70)

(*S*)-(+)-5-Carbethoxy-2-pyrrolidinone (70) was obtained from L-glutamic acid (69) using essentially the same method as that described by Silverman and Levy[80]. Diethyl glutamate was obtained by forming the di-acid chloride *in situ* followed by esterification. This was achieved by adding thionyl chloride to a cooled suspension of L-glutamic acid (69) and absolute ethanol, stirring the mixture at room temperature for 1 hour, and finally heating under reflux for 45 minutes. Owing to the acidic nature of the conditions and the presence of the basic amino group, the hydrochloride of diethyl glutamate was formed. The free base was liberated by treatment with potassium hydroxide in absolute ethanol.

After all the solvent had been removed, the crude diethyl glutamate was heated to 130-150°C under vacuum (~0,5 mm Hg). This resulted in elimination of ethanol, and cyclisation to form the lactam (70). An attempt was made to purify the product by distillation as described in the literature[80, 81]. This proved to be unsuccessful and resulted in a thick tarry mass. However, purification by column chromatography on silica gel yielded white crystals in yields of between 61 and 66%. The melting point, optical rotation and infrared and ^{1}H NMR spectra were in agreement with literature[80], confirming that (*S*)-(+)-5-carbethoxy-2-pyrrolidine (70) had been synthesised.

The infrared spectrum showed strong absorptions at 1740cm^{-1}, 1708cm^{-1} and 1198cm^{-1} due to the ester carbonyl group, the lactam carbonyl group and C-O-C stretching, respectively. The ^{1}H NMR spectrum showed that the signal at 7,48ppm corresponding to the proton on the nitrogen was split into a doublet by the proton on the carbon α to nitrogen. This proton itself showed up as a multiplet between 3,95 and 3,88ppm. Since the product contains a stereogenic centre the methylene

protons β to nitrogen should not be equivalent. Two separate signals are seen for these protons, the one appearing as a multiplet between 2,17 and 1,92ppm and the other between 1,87 and 1,73ppm. The ethoxy group resulted in a quartet at 3,85ppm and a triplet at 0,92ppm. In the ^{13}C NMR spectrum, the peak at 178,03ppm was due to the carbonyl group of the lactam and the peak at 171,70ppm was due to the ester carbonyl group. The methylene and methyl carbons of the ethoxy group were at 60,65 and 13,36ppm, respectively. The tertiary carbon in the ring gave a peak at 55,01ppm, the downfield shift arising from the deshielding effect of the ester carbonyl group. The other signals were consistent with the expected product. No ^{13}C NMR data were found in the literature.

4.1.2 Reduction of the Ester Group of (*S*)-(+)-5-Carbethoxy-2-pyrrolidinone (70)

The ester group of (*S*)-(+)-5-Carbethoxy-2-pyrrolidinone (70) was reduced using lithium borohydride which was formed *in situ* according to the method of Silverman and Levy[80]. Sodium borohydride and lithium chloride were mixed in diglyme for 20 minutes, followed by the addition of tetrahydrofuran. The solid was allowed to settle and the supernatant liquid containing the dissolved lithium borohydride was filtered directly into a solution of (*S*)-(+)-5-carbethoxy-2-pyrrolidinone (70) in tetrahydrofuran. Purification by column chromatography on silica gel yielded (*S*)-(+)-5-hydroxymethyl-2-pyrrolidinone (57) as white crystals. The best yield was 76% although a typical yield was 64%. The melting point was 70-73°C which is slightly higher than the literature value of 66-68°C[80]. The optical rotation and infrared and ^{1}H NMR spectra were comparable with those reported in the literature[80].

In the infrared spectrum, the appearance of a strong broad band between 3600 and 3000cm^{-1} indicated that a hydroxy group was present, confirming that the reduction had taken place. The band at 1060cm^{-1} was a result of the C-O

stretching. There are two very strong bands at 1690 and 1678cm^{-1}, that at 1690cm^{-1} being due to the carbonyl absorption of the lactam ring.

The reduction of the ester group was confirmed by the disappearance of the quartet at 3,85ppm and the triplet at 0,92ppm in the ^{1}H NMR spectrum. A broad singlet at 3,20ppm was due to the hydroxy proton. The methylene protons α to the hydroxy group resulted in a multiplet between 3,84 and 3,66ppm. The proton on the tertiary carbon of the lactam ring has shifted upfield to between 3,52 and 3,43ppm relative to the same proton on the ester (70). This is because it is no longer adjacent to an electron-withdrawing carbonyl group. The other ring protons have remained relatively unchanged.

The ^{13}C NMR spectrum contained only one signal in the carbonyl region. This, along with the disappearance of the peaks at 60,65 and 13,36ppm, indicated the loss of the ester group. The lactam carbonyl carbon resulted in a peak at 179,20ppm. The peak at 171,70ppm due to the ester carbonyl group carbon of the starting material has shifted upfield to 65,93ppm now that the ester functionality has been reduced to an alcohol. The other peaks remained relatively unchanged after the reduction step.

4.1.3 Formation of (*S*)-(+)-5-(*p*-Toluenesulphonyloxymethyl)-2-pyrrolidinone (71)

The tosylate (71) was formed by treating a solution of the alcohol (57) in dichloromethane with triethylamine, a catalytic amount of DMAP (4-dimethylaminopyridine) and *p*-toluenesulphonyl chloride[69]. An aqueous work-up and purification by recrystallisation from ethyl acetate and hexane yielded (*S*)-(+)-5-(*p*-toluenesulphonyloxymethyl)-2-pyrrolidinone (71) as a white solid in a yield of 78%. The identity of the product was confirmed by comparison of the melting point, optical rotation, infrared spectrum and ^{1}H and ^{13}C NMR spectra with those

of literature[69]. The specific optical rotation was +9,9 (*c* 2,03, CH_2Cl_2) which was slightly lower than that of the literature (+10,8° (*c* 1,88, CH_2Cl_2))[69].

Characteristic absorptions in the infrared spectrum were a strong peak at 1702cm^{-1} corresponding to the lactam carbonyl group, strong peaks at 1366 and 1190cm^{-1} due to the -SO_2-O- of the toluenesulphonyl group and a peak at 816cm^{-1}, indicating the *para* substitution pattern of the aromatic ring. The ^{1}H NMR spectrum showed the disappearance of the signal at 3,20ppm for the hydroxy proton. The appearance of two doublets at 7,79 and 7,37ppm in the aromatic region and a singlet integrating for three protons at 2,46ppm for the methyl group on the aromatic ring indicated the introduction of the toluenesulphonyl group. The protons on the carbon adjacent to the tosyl group moved slightly downfield as a result of the greater electronegativity of the tosyl group relative to the hydroxy group while the rest of the spectrum remained unchanged. The ^{13}C NMR spectrum showed the appearance of four peaks in the aromatic region. The peaks at 130,02 and 127,86ppm each resulted from two of the tertiary aromatic carbons and the peak at 145,31ppm was due to the aromatic carbon containing the methyl group. This methyl group resulted in a peak at 21,61ppm. The methylene carbon adjacent to the tosyl group shifted downfield to 71,93ppm owing to the greater electron withdrawing effect of the tosyl group.

4.1.4 Reduction and Tosylation Steps without Isolating the Alcohol (57)

Initially two methods for reducing the ester (70) to the alcohol (57) followed by immediate conversion into the tosylate (71) without purifying and characterising the alcohol were attempted.

The first method[82] used lithium borohydride to reduce the ester, and pyridine and *p*-toluenesulphonyl chloride to form the tosylate. The desired product was obtained in an overall yield of 2% for the two steps after purification by column chromatography on silica gel. The ^{1}H NMR spectrum showed that all the

necessary peaks were present when compared with the literature[69] although there were still impurities present. No attempt was made to optimise the reaction conditions.

The second method[83] involved adding 0,5 equivalents of sodium borohydride in water to an aqueous solution of the ester at 0°C and allowing the mixture to reach room temperature. After 90 minutes, acetone was added to the mixture at 0°C to destroy any unreacted sodium borohydride. After concentrating the solution to half the volume, potassium hydroxide, *p*-toluenesulphonyl chloride, a phase transfer catalyst (tetra-n-butylammonium hydrogen sulphate) and chloroform were added. The mixture was stirred for three days before being worked-up. Purification by recrystallisation from toluene resulted in a yield of 7%. The ^{1}H NMR spectrum was comparable with that of literature[83] although impurities were still present. No further work was done using this method.

4.1.5 Attempted Alkylation of (*S*)-(+)-5-(*p*-Toluenesulphonyloxymethyl)-2-pyrrolidinone (71)

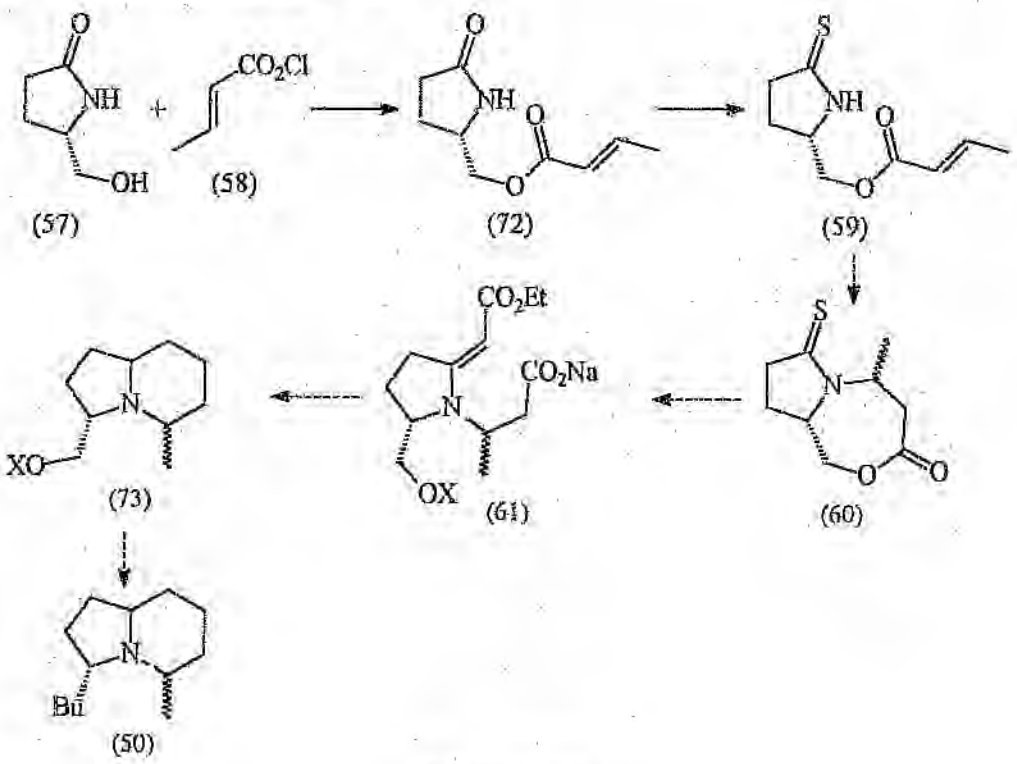
It has been reported in the literature[69] that (*R*)-5-pentyl-2-pyrrolidinone can be synthesised from (*S*)-(+)-5-(*p*-toluenesulphonyloxymethyl)-2-pyrrolidinone (71) by reaction with the cuprate made from n-butyllithium. Our reaction would require n-propyllithium, which was not readily available. The method was therefore adapted to use the Grignard reagent made from 1-bromopropane.

Dipropylcopper magnesium bromide was formed by adding cuprous iodide to the tetrahydrofuran solution of propylmagnesium bromide cooled to -40°C. The tosylate (71) was added, and the mixture was stirred for three hours at -40°C and overnight at -20°C. The reaction mixture was worked up but only starting material was recovered. It was hoped that the tosyl group would be displaced by the nucleophilic propyl group to introduce the butyl side chain. Owing to a lack of time, no further work was done.

Since our attempt, Pilli *et al.*[68] have achieved this addition of the propyl group using an excess (5,0 equivalents) of $(n\text{-}C_3H_7)_2CuCNLi_2$. This was however after unsuccessful attempts using CuBr.DMS, CuI or lithium 2-thienylcyanocuprate and propyllithium.

4.2 Intramolecular Michael Addition Approach

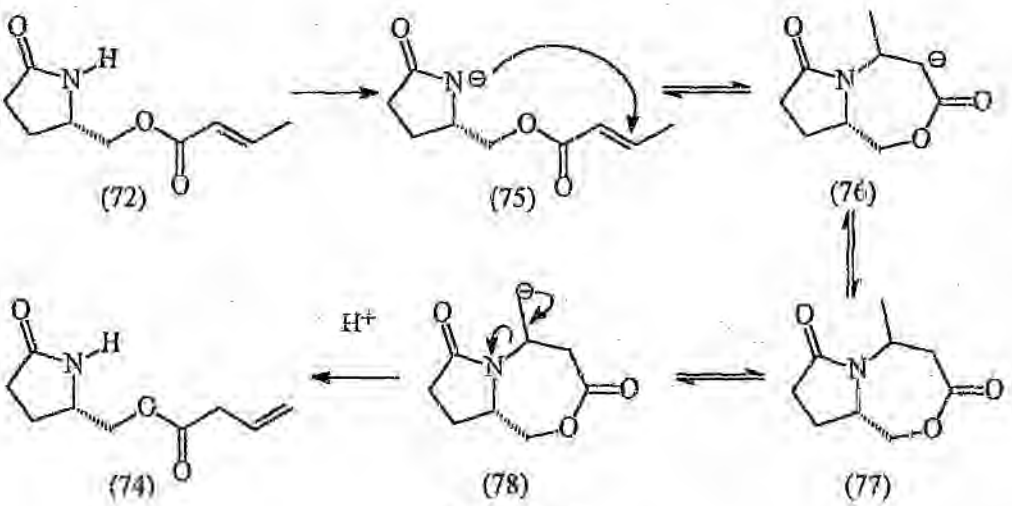
(*S*)-(+)-5-Hydroxymethyl-2-pyrrolidinone (57) (described in section 4.1.2) was also used to synthesise (*S*)-(+)-(2-oxopyrrolidin-5-yl)methyl 2-butenoate (72). The thiolactam of (72) was then formed In an attempt to synthesise 3-butyl-5-methylindolizidine enantioselectively, an intramolecular Michael addition reaction was carried out on thiolactam (59). It was hoped that the stereochemistry of this addition could be controlled by intramolecular constraints since there was a stereogenic centre present in the molecule. As will be discussed below, this reaction was unsuccessful and requires further attention. An outline of the approach is shown in Scheme 27 below.



SCHEME 27

4.2.1 The Addition of (*E*)-Crotonyl Chloride to (*S*)-(+)-5-Hydroxymethyl-2-pyrrolidine (57)

In an attempt to synthesise (*S*)-(+)-(2-oxopyrrolidin-5-yl)methyl 2-butenoate (72), (*E*)-crotonyl chloride and triethylamine were added to a solution of (*S*)-(+)-5-hydroxymethyl-2-pyrrolidinone (57) in dichloromethane under a nitrogen atmosphere at 0°C. The triethylamine was added to remove the proton from the hydroxy group of the lactam (57). The anion thus formed should attack the carbonyl group of the crotonyl chloride and displace the chloride. After purification by column chromatography on silica gel, a yellow oil was obtained in a yield of 61%. The NMR spectra showed that it was however not the desired product but (*S*)-(+)-(2-oxopyrrolidin-5-yl)methyl 3-butenoate (74). The double bond had isomerised out of conjugation! A possible explanation for this is shown in Scheme 28 below. The presence of a base results in the removal of the proton on the nitrogen. This is followed by an intramolecular conjugate addition to form a seven-membered ring (76). The resulting anion participates in a protonation-deprotonation equilibrium, which probably also involves the transient anion (78). A transfer of electrons may then result in the opening of the seven-membered ring and the double bond forming in the non-conjugated position.



SCHEME 28

Infrared and NMR spectroscopy was used to identify the product. The infrared spectrum showed strong absorption at 1738cm^{-1} due to the ester carbonyl group and at 1694cm^{-1} due to the lactam carbonyl group. The NMR spectra were assigned with the aid of a C-H correlation and a DEPT spectrum. The ^{1}H NMR spectrum showed that the signals of the proton α to the nitrogen and the protons on the secondary carbon adjacent to the oxygen of the ester group had shifted downfield due to the greater electron withdrawing effect of the ester group relative to the alcohol. The signals of the two protons on this secondary carbon have now separated since the molecule contains a stereogenic centre and the protons are thus no longer equivalent. The absence of a signal at approximately 1,9ppm, integrating for three protons, due to the methyl group of the crotonyl group indicated that the desired addition product had not been obtained. The protons α to the ester carbonyl group resulted in a doublet of triplets. The splitting pattern was a result of two 1Hz and one 7Hz coupling constants. The 7Hz coupling constant was a result of the proton on the adjacent carbon and the 1Hz couplings due to long-range coupling with the two protons at the end of the chain.

The DEPT spectrum showed that there were only two tertiary carbons instead of the three that would be present in the desired product. These were at 129,75ppm, the tertiary carbon of the carbon-carbon double bond, and 52,74ppm, the tertiary carbon in the lactam ring. In the ^{13}C NMR spectrum, the peaks at 178,19 and 171,24ppm were due to the carbonyl carbons of the lactam and ester, respectively. The peaks of the tertiary and secondary carbons of the carbon-carbon double bond appeared at 129,70 and 118,95ppm respectively.

The addition reaction was repeated, this time using a milder base, disodium hydrogen phosphate, resulting in a heterogeneous reaction mixture. This reaction was much slower than the previous attempt with triethylamine. After purification by column chromatography on silica gel, the desired product, (*S*)-(+)-(2-

oxopyrrolidin-5-yl)methyl 2-(*E*)-butenoate (72), was obtained as a white solid in a 56% yield. This was confirmed using NMR spectroscopy.

As in the previous compound, the signals of the protons on the carbon adjacent to the nitrogen and the protons on the secondary carbon adjacent to the oxygen of the ester group had shifted downfield due to the greater electronegativity of the ester group. Also, the two protons on this secondary carbon are not equivalent since there is a stereogenic centre present, resulting in separate peaks for the two protons. The signals due to these protons are a multiplet between 4,27 and 4,20ppm and another between 4,02 and 3,92ppm. The signal of the proton α to the nitrogen is also contained in this multiplet. The vinyl proton α to the ester carbonyl group resulted in a quartet of doublets at 5,86ppm. The coupling constants were 2 and 16Hz. The coupling constant of 2Hz was due to the long-range coupling with the methyl group and the 16Hz coupling constant indicated that the hydrogens of the carbon-carbon double bond were *trans*. The proton β to the ester carbonyl group resulted in a double quartet at 7,03ppm with coupling constants of 7 and 16Hz. The 7Hz coupling constant was due to the methyl group. The methyl protons resulted in a double doublet at 1,90ppm. The coupling constant of 7Hz was a result of coupling with the β proton and the coupling constant of 2Hz due to the long-range coupling with the α proton. The ^{13}C NMR spectrum showed that there was not much change in the lactam part of the molecule. The peak at 166,02ppm was due to the ester carbonyl carbon, the peaks at 145,82 and 121,67ppm a result of the sp^2 carbons and the peak at 17,96ppm due to the methyl carbon.

Characteristic peaks on the infrared spectrum was the N-H stretching of a lactam at 3430cm^{-1}, the very strong ester carbonyl group absorption at 1704cm^{-1} and the strong lactam carbonyl group at 1660cm^{-1}.

4.2.2 Thionation of (*S*)-(+)-(2-Oxopyrrolidin-5-yl)methyl 2-(*E*)-butenoate (72)

The lactam carbonyl group of (*S*)-(+)-(2-oxopyrrolidin-5-yl)methyl 2-(*E*)-butenoate (72) was thionated using the procedure of Brillon[76] without affecting the ester carbonyl group. The thionating agent was formed *in situ* from a 1:1 molar ratio of phosphorous decasulfide and sodium carbonate in tetrahydrofuran. The desired product, (*S*)-(+)-(2-thioxopyrrolidin-5-yl)methyl 2-(*E*)-butenoate (59), was obtained as a white solid in a 76% yield after purification by column chromatography.

The product was identified using infrared and NMR spectroscopy. The infrared spectrum showed a strong absorption at 1720cm^{-1} due to the ester carbonyl group and at 1180cm^{-1} due to the N-C=S absorption. In the ^{1}H NMR spectrum the chemical shifts and splitting patterns of the crotonate part of the molecule remained unchanged relative to those of the starting material. All the chemical shifts of the cyclic part increased. This is because sulphur has a greater π-cloud through-space deshielding effect than oxygen. The two methylene protons on the carbon adjacent to the oxygen have each resulted in a double doublet, one at 4,34ppm and the other at 4,01ppm. The geminal coupling constant is 11Hz.

In a similar way to the ^{1}H NMR spectrum, the ^{13}C NMR spectrum remained unchanged as far as the peaks due to the crotonate part of the molecule was concerned. The thiocarbonyl carbon peak appeared at 206,06ppm and the other carbons in the ring all shifted downfield owing to the sulphur having a greater π-cloud through-space deshielding effect than oxygen. The degree to which this downfield shift took place decreased with distance from the sulphur atom; that is, the carbon α to the thiocarbonyl group experienced a greater deshielding effect than the γ carbon.

4.2.3 An Attempted Intramolecular Michael Addition

An intramolecular Michael addition reaction was attempted on (*S*)-(+)-(2-thioxopyrrolidin-5-yl)methyl 2-(*E*)-butenoate (59) to obtain a seven-membered ring. It was hoped that the reaction would take place on a single face of the double bond since the direction of approach of the nitrogen would be restricted by the intramolecular nature of the reaction. Since only the *trans* carbon-carbon double bond is present, the stereoselectivity of the addition reaction should be better than if a mixture of both the *E* and *Z* isomers were present. The reaction was carried out using a catalytic amount of sodium hydride as base. The reaction did not go to completion and the product that was isolated was not the desired one. It could not be identified from the ^{1}H NMR spectrum. Due to time constraints, no further work was done on this reaction.

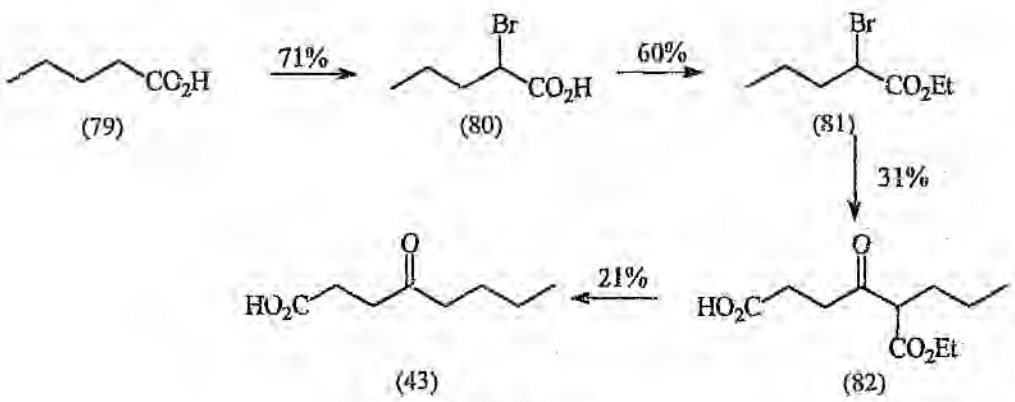
CHAPTER 5

AN ALTERNATIVE APPROACH TOWARDS THE SYNTHESIS OF MONOMORINE I

An alternative approach to the synthesis of 3-butyl-5-methylindolizidine is discussed in this chapter. The synthesis of the two precursors, 4-oxooctanoic acid (43) and racemic ethyl 3-aminobutanoate (42), used in this approach is first covered. This is followed by the reaction to combine these products. Finally, progress towards the synthesis of optically active ethyl 3-aminobutanoate (42) is discussed.

5.1 Synthesis of 4-Oxooctanoic Acid (43)

The precursor, 4-oxooctanoic acid (43), was synthesised in four steps, starting with 1-pentanoic acid (79). The reaction sequence is shown in Scheme 29 below. The overall yield for these four steps was a mere 4%. This is mainly due to the final two steps both having yields of 30% or lower.



SCHEME 29

5.1.1 α-Bromination of 1-Pentanoic Acid (79)

1-Pentanoic acid (79) was brominated by heating it with bromine in the presence of a catalytic amount of phosphorus tribromide. 2-Bromopentanoic acid (80) was obtained as a clear liquid after distillation in a yield of 82%.

The infrared spectrum showed a broad band in the region of 3200cm^{-1} due to the OH stretch of the acid. The carboxylic acid carbonyl group absorption appeared at 1718cm^{-1}. A strong absorption between 750 and 500cm^{-1} for C-Br was not observed but the ^{1}H and ^{13}C NMR spectra were consistent with bromination. In the ^{1}H NMR spectrum, the broad singlet at 11,5ppm is due to the carboxylic acid proton. The proton α to the carboxylic acid group resulted in a triplet at 4,26ppm which is in the expected region for a single proton on the same carbon as a bromine. The triplet at 0,97ppm is owing to the methyl group. In the ^{13}C NMR spectrum, the carbonyl carbon appeared at 176,04ppm and the carbon to which the bromine is bonded, appeared at 44,96ppm. The other three carbons resulted in peaks at 36,41, 20,33 and 13,07ppm, which is in the usual region for alkyl chains.

5.1.2 Esterification of 2-Bromopentanoic Acid (80)

2-Bromopentanoic acid (80) was esterified by heating it under reflux in the presence of absolute ethanol and a catalytic amount of concentrated sulphuric acid. Ethyl 2-bromopentanoate (81) was obtained as a clear liquid in a yield of 68% after purification by distillation at 55-56°C under vacuum (~0,5mm Hg).

Infrared and NMR spectroscopy was used to identify the product. In the infrared spectrum the carbonyl absorption at 1718cm^{-1} of the acid shifted to 1740cm^{-1} as a result of the ester formation. The broad absorption in the vicinity of 3200cm^{-1} had disappeared, confirming the loss of the hydroxy group. The ^{1}H NMR spectrum showed the loss of the broad singlet at 11,5ppm due to the carboxylic acid proton. The appearance of a quartet at 4,24ppm and a triplet at 1,30ppm was the result of

the methyl and methylene groups of the additional ethoxy group of the ester. In the ^{13}C NMR spectrum, the peak at 169,86ppm was assigned to the ester carbonyl carbon and the peaks at 61,61 and 13,90ppm to the methylene and methyl carbons of the ethoxy group. The other carbon peaks remained relatively unchanged.

5.1.3 Synthesis of 5-Ethoxycarbonyl-4-oxooctanoic Acid (82)

5-Ethoxycarbonyl-4-oxooctanoic acid (82) was synthesised using a Reformatsky reaction according to the method of Schick *et al*[84]. Zinc-copper couple[85] was added to a solution of succinic anhydride and ethyl 2-bromopentanoate (81) in dry dimethylformamide (DMF). It was stated in the literature[84] that the success of the reaction depends partly on the choice of solvent. In the case of DMF, the reaction is strongly exothermic. After an aqueous work-up and purification by column chromatography on silica gel, the desired product, 5-ethoxycarbonyl-4-oxooctanoic acid (82), was isolated in a yield of 31%. Some succinic acid was recovered which indicated that the reaction had not gone to completion. However the several attempts to increase the yield were unsuccessful. The yield quoted in the literature[84] was 57%.

The identity of the product was confirmed using NMR spectroscopy. The NMR data obtained were in agreement with that of the literature[84]. In the ^{1}H NMR spectrum, the carboxylic acid proton resulted in a broad singlet at 10,9ppm. The proton α to both the ketone and the ester group is downfield at 3,52ppm owing to the deshielding effects of both the carbonyl groups. In the ^{13}C NMR spectrum, the three carbonyl carbons of the ketone, carboxylic acid and ester resulted in peaks at 203,36ppm, 177,82ppm and 169,49ppm respectively. The tertiary carbon adjacent to the ketone group resulted in a peak at 58,41ppm. This carbon is influenced by the electron withdrawing effects of both the ketone and ester carbonyl groups and is thus so far downfield.

5.1.4 Decarboxylation of 5-Ethoxycarbonyl-4-oxooctanoic Acid (82)

4-Oxooctanoic acid (43) was obtained by heating 5-ethoxycarbonyl-4-oxooctanoic acid (82) with hydrochloric acid under reflux using the method of Schick *et al*[84]. This resulted in the ester group being hydrolysed to the acid. The evolution of carbon dioxide completed the decarboxylation step. This reaction was possible since the ester was β to a ketone group. The mixture was concentrated under reduced pressure and the last traces of water removed by azeotropic distillation with benzene. The product was obtained as a white solid in a yield of 21% after recrystallisation from hexane. This yield is low in comparison to the yield of 65% quoted in the literature[84] and could not be explained.

The structure of the product was confirmed by comparison of the NMR data with those in literature[84]. The ^{1}H NMR spectrum showed that decarboxylation had taken place by the disappearance of the quartet at 4,19ppm and the triplet at 1,29ppm. These peaks correspond to the protons of the ethoxy group. Most of the other signals showed a slight upfield shift due to the loss of an electron withdrawing group. In the ^{13}C NMR spectrum, the decarboxylation was confirmed by the disappearance of the peaks for the ethoxycarbonyl group at 169,49ppm, 61,07ppm and 13,64ppm.

5.2 Synthesis of Ethyl 3-Aminobutanoate (42)

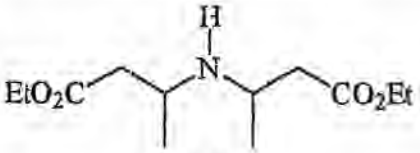
Once 4-oxooctanoic acid (43) had been obtained, the focus was shifted to the other precursor, racemic ethyl 3-aminobutanoate (42).

Ethyl 3-aminobutanoate (42) was obtained by the conjugate addition of ammonia to the carbon-carbon double bond of ethyl crotonate based on the method of Morsch[86]. This was achieved by adding liquid ammonia to a chilled solution of the ethyl crotonate and ethanol. Although the reaction was carried out in an

autoclave, the pressure did not rise. The reaction was slow and after four days only 8% yield of ethyl 3-aminobutanoate (42) was obtained.

The infrared spectrum showed only weak bands in the region of 3500 to 3300cm^{-1} which is the N-H stretching region. The only other characteristic absorptions were at 1730cm^{-1} due to the ester carbonyl group and at 1188cm^{-1} due to C-O-C stretching of the ester group. The ^{1}H NMR spectrum showed a quartet at 4,14ppm and a triplet at 1,27ppm which are due to the protons of the methylene and methyl protons of the ethoxy group, respectively. The amine protons resulted in a singlet at 1,51ppm. The peak integrated for two protons, indicating that the amine was primary. The two protons α to the carbonyl group each appeared as a double doublet, one centred at 2,40ppm and the other at 2,28ppm, indicating that the two protons are not equivalent. The geminal coupling constant was 16Hz and the vicinal coupling constant was 5Hz for the one proton and 8Hz for the other. The proton α to the amine group resulted in a multiplet between 3,42 and 3,34ppm and the methyl protons β to the amine group resulted in a doublet at 1,13ppm. The ^{13}C NMR spectrum showed amongst others, a peak at 43,92ppm which is due to the carbon α to the amine group and a peak at 172,24ppm owing to the carbonyl carbon.

When attempting the reaction with liquefied ammonia and no solvent, the pressure in the autoclave rose to four atmospheres. This is most likely due to the formation of gaseous ammonia when the reaction mixture warmed up to room temperature. After seven days, the product (83) that was isolated was that of two molecules of ethyl crotonate reacting with one mole of ammonia to yield a secondary amine.



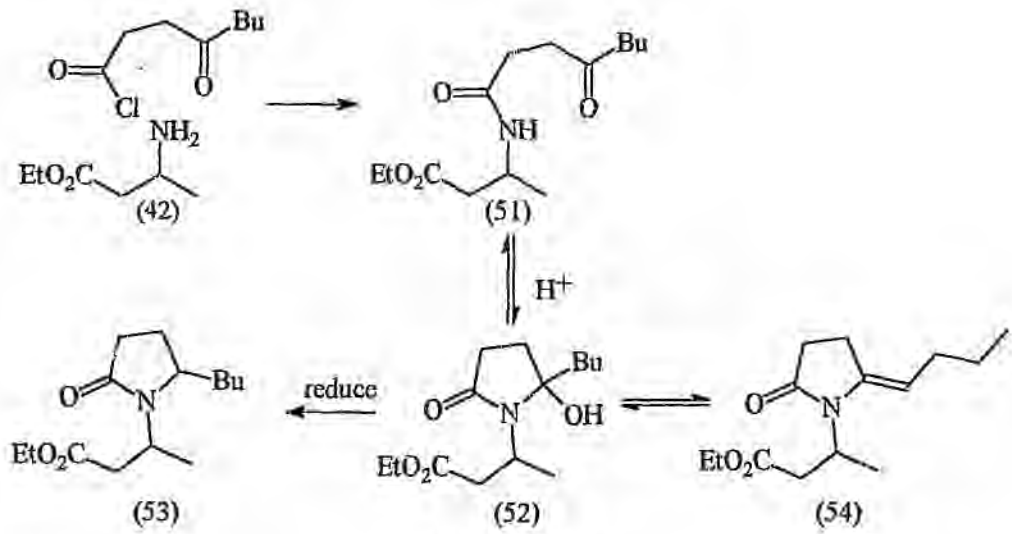
(83)

In the ^{1}H NMR spectrum, the signal of the proton on the nitrogen at 1,5ppm only integrated for one proton. This indicated that the amine was secondary. The

protons of the two methyl groups β to the nitrogen resulted in two almost identical doublets, one at 1,12ppm and 1,10ppm. This is due to two diastereomers being present since the molecule contains two stereogenic centres. The rest of the spectrum was the same as for the ethyl 3-aminobutanoate (42) except that the integration of each of the signals was twice that of the same peaks of ethyl 3-aminobutanoate (42). The ^{13}C NMR spectrum was similar to that of ethyl 3-aminobutanoate (42) except for the doubling up of some of the peaks. This confirmed that two diastereomers were present.

5.3 The Reaction Between 4-Oxooctanoic acid (43) and Ethyl 3-Aminobutanoate (42)

Now that the two precursors had been synthesised it was possible to explore the approach to indolizidine synthesis wherein the five-membered ring is not a precursor but is formed during the reaction sequence. The approach is shown in Scheme 15, repeated below. The approach for the reaction was to form the acid chloride of 4-oxooctanoic acid (43) *in situ* and then add ethyl 3-aminobutanoate (42) and a mild base to abstract a proton from the amine. Compound (51) was obtained. The work of Lete *et al.*[54], on similar compounds, gave an indication that cyclisation would occur in the presence of an acid to form the lactam (52). Reduction of the hydroxy group would result in (53).



SCHEME 15

In the first attempt, thionyl chloride and a catalytic amount of dimethylformamide were added to a solution of 4-oxooctanoic acid (43) in chloroform to form the acid chloride. The second stage of the reaction involved the addition of ethyl 3-aminobutanoate (42) and disodium hydrogen phosphate to remove a proton from the amine. After heating under reflux for six hours and stirring overnight, thin layer chromatography indicated that the amine starting material was still present. It was not possible to determine which stage of the reaction had been unsuccessful since thin layer chromatography could not be used to monitor the first stage of the reaction as the acid chloride just hydrolyses back to the acid on the chromatogram.

In the next attempt, the acid chloride was formed by adding oxalyl chloride and a catalytic amount of triethylamine to a solution of 4-oxooctanoic acid (43) in dichloromethane at 0°C. Once the acid chloride had formed, the dichloromethane and excess oxalyl chloride were removed by distillation. Fresh dichloromethane, the amine (42) and triethylamine were added. This time the addition reaction occurred although the 5-membered ring did not form. Judging by NMR spectroscopy the product was (51). This was obtained as white crystals in a yield of 53%.

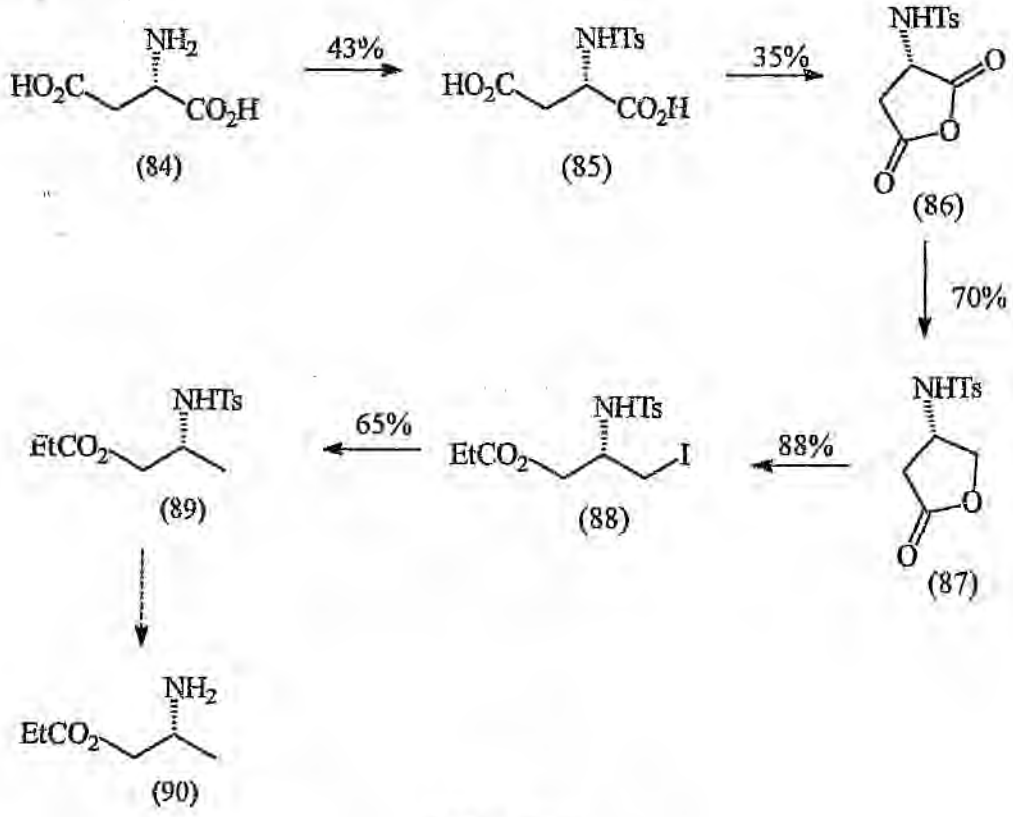
The infrared spectrum had three absorptions in the carbonyl absorption region. The absorptions appeared at 1730cm^{-1}, 1676cm^{-1} and 1506cm^{-1} due to the ester, ketone and amide carbonyl peaks, respectively. The ^{13}C NMR spectrum contained three peaks in the carbonyl region: the ketone at 210,09ppm, the ester at 171,61 and the amide at 171,14ppm. The presence of the ketone at 210,09ppm indicated that the five-membered ring had not formed. In the ^{1}H NMR spectrum, the signal at 6,2ppm, corresponding to the proton on the nitrogen, integrating for one proton. This indicated that the addition had occurred and confirmed that cyclisation had not occurred. The other signals were consistent with the expected structure.

It is apparent from the literature that under idic conditions, the oxoamide (51) is in equilibrium with its ring tautomer (52), an α-hydroxylactam[64, 87, 88]. The hydroxy of this α-hydroxylactam may be replaced by hydrogen using triethylsilane in the presence of $BF_3.OEt_2$ at 0°C[65, 66]. These steps will need to be carried out in the future. These steps, followed by the formation of the thiolactam of (53) will leave us with 5-butyl-1-(2-ethoxycarbonyl-1-methylethyl)pyrrolidine-2-thione (44), the product discussed in section 3.2.2., thus converging with the approach discussed in chapter 3. If this route proves to be successful, the low yielding step of the Michael addition discussed in section 3.2.2 may be avoided. However, it is very likely that there will be no stereocontrol and a mixture of diastereomers of 5-butyl-1-(2-ethoxycarbonyl-1-methylethyl)pyrrolidine-2-thione (44) is to be expected.

5.4 An Enantioselective Approach to (3*S*)-Ethyl 3-Aminobutanoate (90)

With a view to synthesising 3-butyl-5-methylindolizidines stereoselectively, an enantioselective approach to (3*S*)-ethyl 3-aminobutanoate (90) was investigated in the hope that it could be used in the approach discussed above. Several methods are available for enantioselective synthesis of β-amino acid derivatives[89]. We chose to use the method devised by Jefford *et al.*[90] since the starting material was readily available.

Jefford *et al.*[90] synthesised numerous β-amino acids enantiospecifically starting with L-aspartic acid which provided the required stereochemistry. This approach was used in an attempt to synthesise (3*S*)-ethyl 3-aminobutanoate (90). The approach is summarised in Scheme 30 below. (3*S*)-Ethyl 3-(tosylamino)butanoate (89) was obtained in an overall yield of 6%. The yields obtained in the first two steps were both below 45%, resulting in this low figure. All that remains to be done is the deprotection of the amino group. The steps shown will be described in detail below.



SCHEME 30

5.4.1 Protecting the Amine of L-Aspartic Acid (84)

The amino group of L-aspartic acid (84) was protected by making the N-tosyl derivative based on the methods of Harington and Moggridge[91] and Ressler[92]. This

was achieved using *p*-toluenesulphonyl chloride in the presence of sodium hydroxide. A thick syrup was obtained which yielded white crystals when dissolved in a minimum amount of hot water which was subsequently cooled. The filtration had to be carried out while still cold. (*S*)-N-Tosylaspartic acid (85) was obtained in yields ranging from 40 to 47% which is low in comparison to the 93% quoted in the literature[90]. It is possible that the *p*-toluenesulphonyl chloride that was used was old and that some of it had been converted to *p*-toluenesulphonic acid by moisture in the atmosphere, resulting in this low yield. The product was identified by means of infrared and NMR spectroscopy.

In the infrared spectrum, the carboxylic acid carbonyl groups resulted in a strong absorption at 1727cm^{-1} and the SO_2-N in a signal at 1156cm^{-1}. The ^{1}H NMR spectrum showed a broad singlet at 10,83ppm which integrated for two protons as a result of the protons of the two carboxylic acid groups. The aromatic protons resulted in two doublets, each with a coupling constant of 8Hz at 7,79 and 7,39ppm which is the characteristic region of aromatic protons. A coupling constant of 8Hz indicates that the protons are *ortho* to each other implying that the aromatic ring is *para* substituted. The proton on nitrogen resulted in a doublet with a coupling constant of 8Hz at 6,70ppm. This splitting is caused by the proton α to nitrogen. The multiplet between 4,31 and 4,25ppm was due to the proton α to nitrogen. The electron withdrawing effects of both the carboxylic acid and the amine groups have caused this peak to be so far downfield. The singlet at 2,40ppm was a result of the three methyl protons on the aromatic ring. In the ^{13}C NMR spectrum the peaks at 171,82 and 171,79ppm were due to the carbonyl carbons. The aromatic carbons showed peaks between 144 and 127ppm. The carbon α to both the nitrogen and the carboxylic acid was downfield at 53,02ppm due to the deshielding effect of the two groups.

5.4.2 (*S*)-N-Tosylaspartic Anhydride (86)

(*S*)-N-Tosylaspartic anhydride (86) was obtained by reacting (*S*)-N-tosylaspartic acid (85) with acetic anhydride at room temperature. Two very similar methods were used to isolate the anhydride, neither of which resulted in very high yields. The method of Ressler[92] involved removing the excess acetic anhydride under vacuum, keeping the temperature below 40°C. White crystals were obtained in a yield of 48% after trituration with dry toluene and recrystallisation from 1,2-dichloroethane. The method of Jefford and McNulty[93] involved removing the excess acetic anhydride without heat and trituration with diethyl ether. The yield in this case was 31% which is low in comparison to the yield of 93% quoted in the literature[90]. The difficulty encountered in removing the excess acetic anhydride and subsequent loss of product remaining in the mother liquor may account for the low yield. The product was confirmed to be (*S*)-N-tosylaspartic anhydride (86) by comparison of the melting point, optical rotation and NMR spectra with those from literature[92-94]. The chemical shifts of the protons were slightly higher than those in the literature[94], most likely due to the different solvents being used.

In the infrared spectrum, the presence of the absorption band of the C-O stretching at 1158cm^{-1} and the bands at 1794 and 1710cm^{-1} due to the carbonyl group absorptions confirmed that the anhydride had formed. In the ^{1}H NMR spectrum the peaks of the protons on the anhydride were further downfield than the equivalent protons of the (*S*)-N-tosylaspartic acid (85). This is due to the greater deshielding effect of the anhydride. The proton α to the nitrogen resulted in a multiplet between 5,13 and 5,00ppm. Due to the more rigid nature of the cyclic anhydride relative to the di-acid, the two protons β to the nitrogen have resulted in two separate double doublets. The one at 3,29ppm has coupling constants of 10 and 18Hz and the one at 2,96ppm, 8Hz and 18Hz. The 18Hz coupling constant is due to the geminal coupling and the smaller ones due to the coupling with the proton α to nitrogen. The ^{13}C NMR spectrum showed the two carbonyl carbons to be at 171 and 169ppm. The one further downfield is due to the one closest to

the nitrogen. The rest of the spectrum remained relatively unchanged with respect to the starting material.

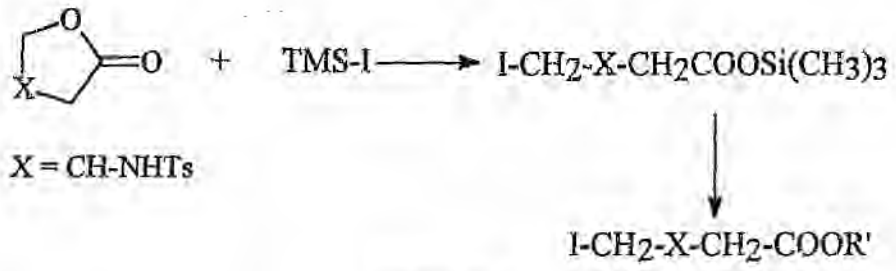
5.4.3 Regioselective Reduction of (*S*)-N-Tosylaspartic Anhydride (86)

(*S*)-N-Tosylaspartic anhydride (86) was selectively reduced using sodium borohydride in tetrahydrofuran[95] to yield (3*S*)-3-(tosylamino)-γ-butyrolactone (87) as a white solid in yields of between 62 and 82% after purification by column chromatography on silica gel. These yields are comparable to the 85% obtained in the literature[90]. It has been found that in the case of most acid anhydrides, the reduction occurs mainly at the carbonyl group adjacent to the more highly substituted carbon atom[95]. There are several references to the regioselective reduction of (*S*)-N-tosylaspartic anhydride (86) in the literature where this is indeed the case[90, 93, 94].

In the infrared spectrum, the carbonyl group resulted in an absorption at 1772cm^{-1} which is in the correct region for 5-membered lactones. The absorption band of the C-O stretching appeared at 1198cm^{-1}. The two absorptions at 1340 and 1160cm^{-1} were due to the absorption by the SO_2-N group. The NMR spectroscopy data are in agreement with that of literature values[94]. In the ^{1}H NMR spectrum all the peaks were slightly lower than the corresponding peaks of the anhydride. This is most likely due to the different solvents in which the samples were dissolved for the NMR experiments. The appearance of a multiplet between 4,20 and 4,08ppm integrating for two protons confirmed that the reduction had taken place. The most significant change in the ^{13}C NMR spectrum was the upfield shift of the peak at 169pm to 73ppm. This confirmed that the reduction had taken place since the peak was no longer in the carbonyl region.

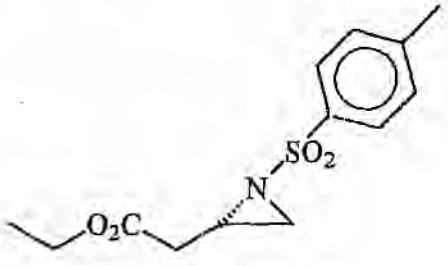
5.4.4 (3*S*)-Ethyl 4-iodo-3-(tosylamino)butanoate (88)

(3*S*)-3-(Tosylamino)-γ-butyrolactone (87) was ring-opened to form (3*S*)-ethyl 4-iodo-3-(tosylamino)butanoate (88) using iodotrimethylsilane and ethanol in dichloromethane at 0°C. The silyl ester is first formed and then replaced by the ethyl ester *in situ* as shown in Scheme 31 below[96].



SCHEME 31

This reaction was first attempted using the method of Kolb *et al.*[96] whereby iodotrimethylsilane was added to a solution of the lactone (87) and ethanol in dichloromethane at 0°C. The molar ratio was 3:2:5 of TMS-I: lactone: ethanol. The amount of dichloromethane was 1ml for every millimole of lactone. Two products were always found to be present: the desired (3*S*)-ethyl 4-iodo-3-(tosylamino)butanoate (88) as a white solid in a yield of 40% and an aziridine, (2*S*)-1-(*p*-toluenesulphonyl)-2-ethoxycarbonylmethylaziridine (91) as a yellow oil. The aziridine (91) was most likely formed by nucleophilic substitution of the iodine by the nitrogen.



Aziridine (91)

A more successful method of synthesising (88) was that of Jefford *et al*[93]. The same reagents were used but amounts, method of addition and work-up procedure were different. The iodotrimethylsilane and ethanol were added in two aliquots each, six hours apart. A total of five equivalents of iodotrimethylsilane were used in the reaction. The work-up involved partitioning between water and dichloromethane and washing the organic extracts with sodium thiosulphate to remove the traces of iodine. (3*S*)-Ethyl 4-iodo-3-(tosylamino)butanoate (88) was obtained as a white solid in a yield of 88% after purification by column chromatography on silica gel. The yield is the same as that quoted in the literature[90]. There was also none of the aziridine (91) present that was obtained when using the previous method.

(3*S*)-Ethyl 4-iodo-3-(tosylamino)butanoate (88) was identified by means of infrared and NMR spectroscopy. In the infrared spectrum, the absorption at 1726cm^{-1}, due to the ester carbonyl group, and at 1160cm^{-1}, due to the C-O stretching indicated that the ester was present. An absorption at 550cm^{-1} was a result of the C-I bond. The ^{1}H NMR spectrum confirmed that the ethyl ester had formed by the presence of the triplet at 1,21ppm and a double quartet at 4,06ppm. The quartet has doubled due to the presence of the chiral centre which makes the hydrogens of the CH_2 group non-equivalent. The two protons α to the iodine have each resulted in a double doublet, one at 3,34ppm and the other at 3,24ppm. The coupling constants of 4 and 7Hz are due to the coupling of the protons α to the iodine with the proton α to nitrogen. The chemical shifts are characteristic of protons α to iodine. These protons have resulted in separate peaks since the presence of the chiral centre in the molecule has caused them to be non-equivalent. This is also the case for the two protons α to the carbonyl group which have each resulted in a double doublet as well. The one appears at 2,69ppm and the other at 2,55ppm. The proton α to nitrogen appears as a multiplet between 3,63-3,50ppm. In the ^{13}C NMR spectrum, the appearance of the peaks at 60,97 and 13,92ppm confirmed the presence of the ethyl ester. The peak at 13,92ppm was due to the methyl carbon and the peak at 60,97ppm due to the methylene carbon. The

carbonyl carbon resulted in a peak at 170,23ppm which is slightly lower than that of the carbonyl carbon in the lactone of the starting material. The peak at 10,56ppm is characteristic of the carbon α to the iodine.

The aziridine (91) was identified using NMR spectroscopy. The absence of a peak due to the proton on nitrogen in the ^{1}H NMR spectrum indicated that the amine was tertiary and not secondary. The methylene protons α to the nitrogen resulted in a double doublet at 2,48ppm which is lower than the corresponding peaks of the iodo compound (88) (3,34 and 3,24ppm) but is in the expected region for methylene protons α to nitrogen. In the ^{13}C NMR spectrum, the secondary carbon α to the nitrogen has resulted in a peak at 32,70ppm which is downfield relative to the equivalent carbon in the iodo compound (10,56ppm).

5.4.5 De-iodination of (3*S*)-Ethyl 4-iodo-3-(tosylamino)butanoate (88)

(3*S*)-Ethyl 4-iodo-3-(tosylamino)butanoate (88) was de-iodinated by heating it under reflux with benzene in the presence of tributyltin hydride. When the reaction was complete, the benzene was removed and the residue dissolved in acetonitrile. The tin residues were extracted with hexane before purification by column chromatography on silica gel. (3*S*)-Ethyl 3-(tosylamino)butanoate (89) was obtained as an oil in a yield of 65%. This is comparable with the 66% quoted in the literature[90].

The product was identified by comparison of the ^{1}H NMR spectrum with that of literature[90]. The only significant change in the ^{1}H NMR spectrum was the change of the two double doublets at 3,34 and 3,24ppm, due to the protons α to the iodine, together integrating for two protons, to a doublet at 1,14ppm integrating for three protons. This confirmed that the iodine had been replaced by hydrogen. In the ^{13}C NMR spectrum the most significant change was the downfield shift of the peak at 10,56ppm to 20,93ppm once the iodine had been replaced by hydrogen.

5.4.6 Final Steps

The final step is the reductive deprotection of the amino functionality. This has been achieved in the literature[93] using aqueous hydrobromic acid and phenol followed by treatment with propylene oxide. If the ester is hydrolysed during this step, it should be relatively simple to re-esterify the acid by heating it in ethanol in the presence of an acid.

CHAPTER 6
CONCLUSION AND PROSPECTS FOR FUTURE WORK

The work of this M.Sc project may be summarised as follows:

1. Towards the racemic synthesis of Monemorine I

A conjugate addition reaction between methyl acrylate and 1-nitropentane (64) resulted in the formation of methyl 4-nitrooctanoate (65) in a yield of 36%. Racemic 5-butyl-2-pyrrolidinone (40) was successfully synthesised from this methyl 4-nitrooctanoate (65) by reducing the nitro group, which resulted in the spontaneous cyclisation and hence the formation of the lactam. The yield for this reaction was 70%. The thiolactam, 5-butylpyrrolidine-2-thione (67) was formed in a yield of 69%. The Michael reaction between this thiolactam (67) and ethyl crotonate proceeded with difficulty, possibly due to an equilibrium being established. The highest yield obtained was 37% as a mixture of diastereomers. It was possible to separate sufficient quantities of the diastereomers to characterise each one separately. An attempt to perform the Michael addition reaction with 5-butyl-2-pyrrolidinone (40) and ethyl crotonate in the hope that the yield would be higher than when the thiolactam (67) was used, was unsuccessful.

The sulphide contraction reaction was carried out on a mixture of diastereomers of 5-butyl-1-(2-ethoxycarbonyl-1-methylethyl)pyrrolidine-2-thione (44), and (*E*)-5-butyl-1-(2-ethoxycarbonyl-1-methylethyl)-2-ethoxycarbonylmethylenepyrrolidine (45) was obtained in a yield of 90%. The cyclisation reaction to form the six-membered ring and hence 9-butyl-5-ethoxycarbonyl-2-methyl-1-azabicyclo[4.3.0]non-5-en-4-one (46), was achieved via the formation of a mixed anhydride in a yield of 36%. At this stage it was possible to separate the two diastereomers of 9-butyl-5-ethoxycarbonyl-2-methyl-1-azabicyclo[4.3.0]non-5-en-4-one (46) and from this point onwards, the reactions were performed separately on these diastereomers. The indolizidine skeleton introduced some rigidity into the

structure, making it possible to assign the relative stereochemistry of the butyl and methyl side-chains by means of NOESY spectra.

Hydrolysis and decarboxylation of *trans*-9-butyl-5-ethoxycarbonyl-2-methyl-1-azabicyclo[4.3.0]non-5-en-4-one (46) yielded *trans*-9-butyl-2-methyl-1-azabicyclo[4.3.0]non-5-en-4-one (48) in a low yield of 48%. An attempt at reducing the carbon-carbon double bond of *trans*-9-butyl-2-methyl-1-azabicyclo[4.3.0]non-5-en-4-one (48) with lithium aluminium hydride was unsuccessful. The order of the previous two steps was then reversed. The reduction of the carbon-carbon double bond of *trans*-9-butyl-5-ethoxycarbonyl-2-methyl-1-azabicyclo[4.3.0]non-5-en-4-one (46) with lithium aluminium hydride resulted in the formation of diastereomers now that a third stereogenic centre had been introduced. The ratio of the diastereomers was 1:3, indicating that attack from one of the faces of the carbon-carbon double bond was preferred. In future, experimentation with different reducing agents may result in different diastereomeric excesses. In the case of the reduction of *cis*-9-butyl-5-ethoxycarbonyl-2-methyl-1-azabicyclo[4.3.0]non-5-en-4-one (46), only one diastereomer was obtained. This is a result of one of the faces of the carbon-carbon double bond being sufficiently sterically hindered to avoid attack of the reducing agent from that face. In the case of both the *cis* and *trans* diastereomers, the products that were obtained were not pure. The hydrolysis and decarboxylation of the ester group of both of the diastereomers of 9-butyl-5-ethoxycarbonyl-2-methyl-1-azabicyclo[4.3.0]nonan-4-one (47) to form 9-butyl-2-methyl-1-azabicyclo[4.3.0]nonan-4-one (49) was achieved but the products were not pure. The reduction of the carbon-carbon double bond and the hydrolysis and decarboxylation of the ester group need to be repeated to obtain pure samples for the complete characterisation of the products.

The final step in the synthesis of 3-butyl-5-methylindolizidine that still needs to be carried out, is the removal of the keto group. This may be achieved by forming a thioacetal which can be removed with Raney nickel.

Overall, this route towards the synthesis of monomorine I is feasible but there are a number of problems. The yields of several of the reactions are poor and there is little control over diastereoselectivity. Attention will need to be focused on these aspects in the future.

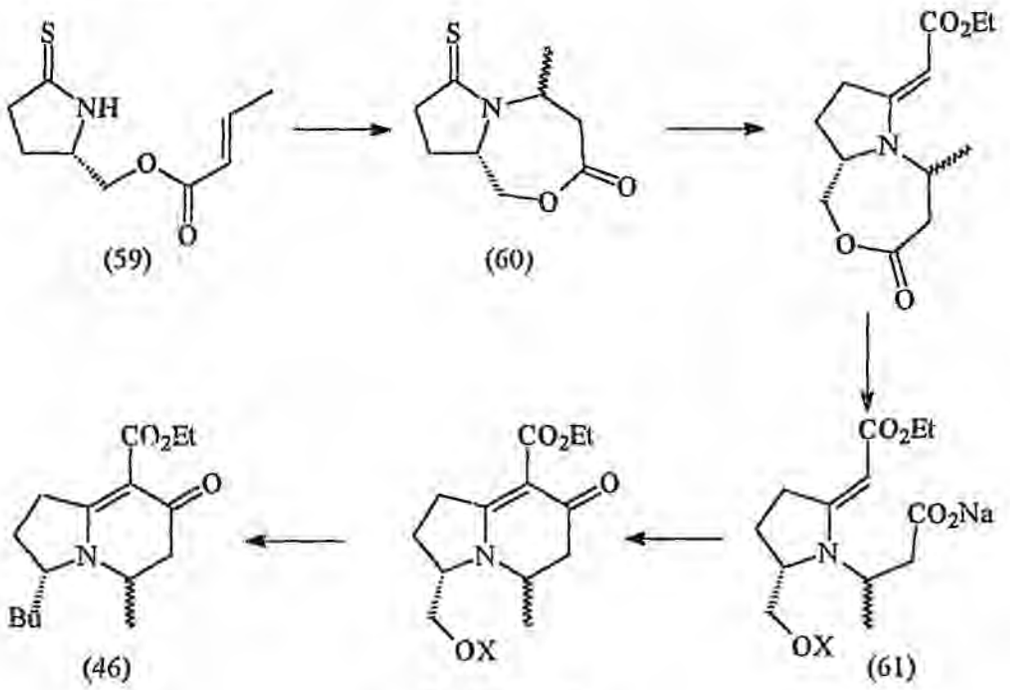
2. (*S*)-(+)-5-Butyl-2-pyrrolidinone (68)

The use of a chiral lactam in the above approach would limit the number of stereoisomers obtained. With this in mind, the synthesis of (*S*)-(+)-5-butyl-2-pyrrolidinone (68) was investigated. (*S*)-(+)-5-(*p*-Toluenesulphonyloxymethyl)-2-pyrrolidinone (71) was synthesised in three steps from L-glutamic acid (69) in an overall yield of 33%. The replacement of the tosyl group by a propyl group to complete the butyl side-chain was attempted using dipropylcopper magnesium bromide. The reaction was unsuccessful but since then, a reaction was published in the literature[68] whereby the reaction was achieved with $(n\text{-}C_3H_7)_2CuCNLi_2$. This method requires some investigation. Once (*S*)-(+)-5-butyl-2-pyrrolidinone (68) is obtained, the approach discussed in chapter 3 may be repeated with this chiral lactam.

3. Approach using an intramolecular Michael addition reaction

An alternative stereoselective approach made use of (*S*)-(+)-5-hydroxymethyl-2-pyrrolidinone (57), an intermediate in the synthesis of (*S*)-(+)-5-butyl-2-pyrrolidinone (68). (*S*)-(+)-(2-oxopyrrolidin-5-yl) (*E*)-2-butenoate (72) was synthesised from (*S*)-(+)-5-hydroxymethyl-2-pyrrolidinone (57) and (*E*)-crotonic acid chloride in a yield of 56%. After forming the thiolactam (59), an intramolecular Michael addition reaction was attempted in the hope that the stereogenic centre in the molecule would result in one of the faces of the carbon-carbon double bond being favoured and thus limit the number of stereoisomers that are formed. The use of only the *E* isomer of crotonic acid chloride should also

influence the stereoselectivity of the reaction. This reaction was unsuccessful and requires further investigation. The remaining steps in this approach are illustrated in Scheme 32 below.



SCHEME 32

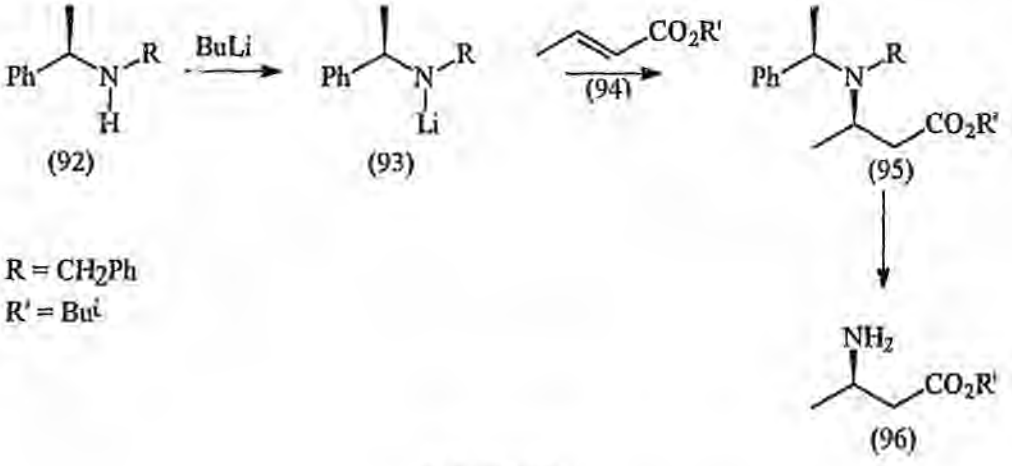
4. An alternative approach towards Monomorine I

An approach was investigated in which the acid chloride of 4-oxooctanoic acid (43) is used to build a 5-membered ring lactam, containing a butyl side-chain, around the nitrogen of ethyl 3-aminobutanoate (42). Thionation of the lactam would result in 5-butyl-1-(2-ethoxycarbonyl-1-methylethyl)pyrrolidine-2-thione (44), an intermediate in the approach discussed in chapter 3. Success of this method would alleviate the problem of the low yielding Michael addition reaction between 5-butylpyrrolidine-2-thione (67) and ethyl crotonate. 4-Oxooctanoic acid (43) was obtained in a yield of 3% from 1-pentanoic acid (79). Racemic ethyl 3-aminobutanoate (42) was synthesised from liquefied ammonia and ethyl crotonate. The yield was only 8%. Much attention will need to be focused on increasing the yields of both these reactions, or finding alternative methods of making 4-oxooctanoic acid (43) and ethyl 3-aminobutanoate (42). The reaction in which the

acid chloride of 4-oxooctanoic acid (43) and ethyl 3-aminobutanoate (42) were combined resulted in the formation of ethyl 3-(4-oxooctanoylamino)butanoate (51).

With a long-term goal of synthesising 3-butyl-5-methylindolizidine (50) enantioselectively using the approach described above, the enantioselective synthesis of (3*S*)-ethyl 3-aminobutanoate (90) was investigated. The method of Jefford[90] was followed whereby L-aspartic acid was used to synthesise (3*S*)-ethyl 3-(tosylamino)butanoate (89) in five steps in an overall yield of 7%. All that remains to be done is the deprotection of the amine.

A more convenient method of synthesising chiral β-amino acid derivatives has since been found. The method of Davies *et al.*[97] makes use of a Michael addition between the lithium amide derivative (93) of a chiral secondary amine (92) and a crotonate ester (94) to obtain (95). Debenzylation of the amine group yields the chiral β-aminobutanoate ester (96). When (*R*)-N-benzyl-1-phenylethylamine (R=CH_2Ph) and the *tert*-butyl crotonate (R'=Bu^t) were used, (*R*)-*tert*-butyl 3-aminobutanoate was obtained in a yield of 82% and a diastereomeric excess of greater than 99%[97]. It is also possible to obtain (*S*)-*tert*-butyl 3-aminobutanoate by using (*S*)-N-benzyl-1-phenylethylamine. More conveniently, both (*R*)- and (*S*)-*tert*-butyl 3-aminobutanoate are now commercially available from Oxford Asymmetry, England[98].



SCHEME 33

EXPERIMENTAL

General Details

A. Purification of Solvents and Reagents

All solvents were distilled before use. Tetrahydrofuran and diethyl ether were distilled from sodium and benzophenone; benzene from sodium; acetonitrile, triethylamine, dimethylformamide and dimethylsulphoxide from calcium hydride; and pyridine from potassium hydroxide.

B. Chromatographic Separations

The R_f values quoted are for thin-layer chromatography (TLC) on Merck silica gel 60 F_{254} coated on aluminium. Unless otherwise stated, compounds were viewed under ultraviolet light or with iodine vapours. Merck silica gel (particle size 0,063-0,200mm) was used as the adsorbent for conventional preparative column chromatography and Merck silica gel (particle size 0,040-0,063mm) was used for preparative flash chromatography[99].

C. Spectroscopic and Physical Data

Melting point determinations were carried out on a Reichart micro hotstage apparatus and are uncorrected. ^{1}H NMR spectra were recorded at 200,13 MHz and ^{13}C NMR spectra at 50,32 MHz on a Bruker AC200 spectrometer or ^{1}H NMR spectra at 400,132 MHz and ^{13}C NMR spectra at 100,625 MHz on a Bruker DRX 400 spectrometer. Unless otherwise specified the NMR spectra were measured in deuterated chloroform and the chemical shifts are reported on the δ scale relative to tetramethylsilane. The chemical shifts of the ^{1}H NMR spectra are reported: value (number of protons, description of absorption, coupling constant(s) in hertz where applicable, assignment). Abbreviations used: s = singlet, d = doublet, t =

triplet, q = quartet, m = multiplet, and br = broad. Infrared spectra were recorded on a Bruker IFS 25 spectrometer as 0,05g.ml^{-1} solutions in chloroform, using a cell with a path length of 0,1mm and sodium chloride windows unless otherwise stated. Band positions are given in cm^{-1}. Abbreviations used in quoting spectra are: s = strong, m = medium, and w = weak. Mass spectra were recorded on a Kratos MS 902/50 high resolution mass spectrometer at 70eV and 200μA. All peaks in the higher mass ranges having a relative abundance greater than 10% have been quoted. Data are quoted: m/z value (assignment if known, relative abundance in %). Specific optical rotations were measured using a Jasco DIP-370 digital polarimeter and are quoted: value (concentration in grams per 100ml, solvent).

D. Other General Procedures

When aqueous solutions were extracted with an organic solvent, the organic phase after separation was dried over anhydrous magnesium sulphate before removal of the solvent. Evaporation of solvent *in vacuo* refers to the removal of solvent under reduced pressure on a rotary evaporator, followed by final drying on an oil pump at ~0,1mm Hg.

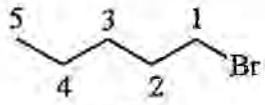
EXPERIMENTAL PROCEDURES RELATING TO SECTION 3.1

1. 1-Bromopentane (63)

Sodium bromide (56,0g, 0,54mol) was dissolved in distilled water (60ml) and 1-pentanol (62) (50,0ml, 40,6g, 0,46mol) was added. Concentrated sulphuric acid (60,0ml) was added dropwise and the flask was agitated during the addition. The solution turned orange and became very hot during the addition. A condenser was fitted, boiling chips were added and the mixture heated under reflux for 2 hours. The mixture was allowed to cool slightly before the layers were separated and the lower aqueous layer discarded. The organic layer was washed with concentrated sulphuric acid (16ml), water (33ml), $NaHCO_3$ (0,1M, 67ml) and water (33ml). Emulsions formed on addition of water, but the layers separated when saturated NaCl solution was added. The organic layer was dried ($MgSO_4$) and distilled at 122-125°C to yield **1-bromopentane (63)** (43,30g, 62%) as a clear liquid.

IR (neat)

3004 (w); 2958 (s); 2932 (s); 2870 (s); 2862 (s); 1464 (s); 1438 (m); 1380 (w); 1296 (w); 1268 (m); 1250 (s); 1208 (m); 920 (w); 730 (m); 642 (m); 564 (m); 456 (w); 442 (w); 426 (w) cm^{-1}.



(63)

^1H NMR ($CDCl_3$)

3,41 (2H, t, 7Hz, H-1), 1,93-1,79 (2H, m, H-2), 1,49-1,28 (4H, m, H-3 and H-4), 0,92 (3H, t, 7Hz, H-5)

^{13}C NMR ($CDCl_3$)

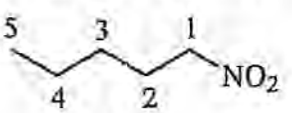
33,91 (C-1); 32,52 (C-2); 30,30 (C-3); 21,85 (C-4); 13,86 (C-5)

2. 1-Nitropentane (64)

The method used was that of Sarmah and Barua[70]. A solution of 1-bromopentane (63) (25ml, 30g, 0,20mol) in DMSO (130ml) was added dropwise to a solution of sodium nitrite (25g, 0,36mol) in DMSO (150ml) at room temperature and stirred overnight. The yellow liquid was poured into ice-water (500ml). The reaction with the water was exothermic. Petroleum ether (40-60°C) was added and the aqueous phase was further extracted with petroleum ether (4x250ml). The combined extracts were washed with water (3x250ml), dried ($MgSO_4$) and evaporated under reduced pressure to yield a yellow liquid. This was distilled under vacuum to yield **1-nitropentane (64)** (8,37g, 36%) as a clear liquid, b.p. 80-82°C (27mm Hg).

IR (neat)

2960 (s); 2934 (s); 2874 (s); 2742 (w); 1728 (m); 1714 (m); 1554 (s, NO_2 stretch); 1466 (m); 1436 (m); 1382 (s, NO_2); 1200 (w) cm^{-1}.



(64)

^1H NMR ($CDCl_3$)

4,39 (2H, t, 7Hz, H-1), 2,05-1,97 (2H, m, H-2), 1,42-1,33 (4H, m, H-3 and H-4), 0,98-0,89 (3H, m, H-5).

^{13}C NMR ($CDCl_3$)

75,48 (C-1); 28,06 (C-2); 26,85 (C-3); 21,73 (C-4); 13,41 (C-5).

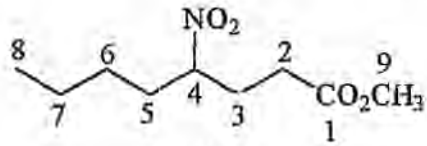
3. Methyl 4-nitrooctanoate (65)

The method used was that of Ballini, Petrini and Rosini[71]. 1-Nitropentane (64) (4,0ml, 3,8g, 32mmol) was cooled in an ice-bath and methyl acrylate (2,9ml, 2,8g, 32mmol) was added. This was stirred for 5 minutes. Amberlyst A-21 (18g) was

added and the mixture was stirred overnight at room temperature. The resultant mixture was extracted with diethyl ether (3x40ml) and the extract concentrated under reduced pressure to yield a yellow liquid (3,84g, 58%). This was purified by column chromatography on silica gel (solvent: 20% ethyl acetate in hexane) to yield **methyl 4-nitrooctanoate (65)** (3,08g, 47%) as a clear liquid. R_f 0,77 (30% ethyl acetate in hexane).

IR (neat)

2958 (s); 2936 (s); 2872 (m); 1740 (s, C=O); 1550 (s, NO_2); 1440 (s); 1366 (s, NO_2), 1330 (m); 1246 (m); 1202 (s, C-O-C); 1176 (s); 1130 (w); 1002 (w); 828 (w) cm^{-1}.



(65)

^1H NMR ($CDCl_3$)

4,63-4,52 (1H, m, H-4), 3,69 (3H, s, H-9), 2,42-1,69 (6H, m, H-2, 3 and 5), 1,40-1,24 (4H, m, H-6 and 7), 0,90 (3H, t, 7Hz, H-8).

^{13}C NMR ($CDCl_3$)

172,22 (C-1); 87,62 (C-4); 51,66 (C-9); 33,37 (C-2); 29,77 (C-3); 28,4; 27,58 (C-6); 21,87 (C-7); 13,52 (C-8).

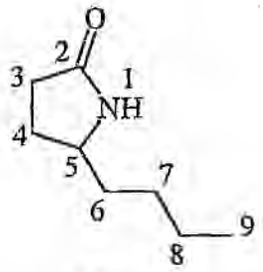
4. 5-Butyl-2-pyrrolidinone (40)

The method of Werner[73] was used. A mixture of methyl 4-nitrooctanoate (65) (1,5g, 7,4mmol), absolute ethanol (65ml), acetic acid (33ml) and 10% Pd/C (0,650g) was stirred under H_2 pressure (3 atmospheres) for 6 days. The mixture was filtered through celite and the solvents were removed under reduced pressure. The residue was dissolved in water and the pH adjusted to 11 with solid sodium carbonate. The solution was extracted with dichloromethane (3x30ml). The

organic layer was dried ($MgSO_4$) and evaporated to give a red liquid (2,65g) which was purified by column chromatography on silica gel (solvent: 50% ethyl acetate in hexane gradually increasing the polarity to neat ethyl acetate) to yield **5-butyl-2-pyrrolidinone (40)** as a pale yellow oil (0,73g, 70%). R_f 0,27 (3:1 ethyl acetate: hexane, viewed with chromosulphuric acid spray reagent).

IR (neat)

2958 (s); 2936 (s); 2872 (m); 1740 (s, C=O); 1550 (s); 1440 (m); 1360 (m); 1330 (m); 1202 (m); 1176 (m); 1130 (w); 1002(w); 828(w); 458 (w); 440 (w); 418 (w); 410 (w) cm^{-1}.



(40)

^1H NMR ($CDCl_3$)

7,41 (1H, s, br, H-1), 3,67-3,60 (1H, m, H-5), 2,38-2,14 (3H, m, H-3 and 4), 1,77-1,21 (7H, m, H-4, 6, 7 and 8), 0,91 (3H, t, 7Hz, H-9).

^{13}C NMR ($CDCl_3$)

178,53 (C-2); 54,65 (C-5); 36,30 (C-3); 30,29 (C-4); 27,77 (C-6); 27,10 (C-7); 22,42 (C-8); 13,79 (C-9).

EXPERIMENTAL PROCEDURES RELATING TO SECTION 3.2

1. 5-Butylpyrrolidine-2-thione (67)

The method of Brillon[76] was used. P_4S_{10} (2,68g, 6,03mmol) was added to dry tetrahydrofuran (30ml) under nitrogen and stirred for 5 minutes. Sodium carbonate

(0,39g, 6,03mmol) was added. After stirring for 20 minutes, by which time the CO_2 evolution had ceased, 5-butyl-2-pyrrolidinone (40) (0,710g, 5,03mmol) dissolved in tetrahydrofuran (10ml) was added. This was stirred for 4 hours and then a 10% aqueous solution of Na_3PO_4 (25ml), ethyl acetate (20ml) and hexane (20ml) were added in turn. The aqueous phase was washed with ethyl acetate (15ml). The combined organic layers were dried ($MgSO_4$) and the solvent removed under reduced pressure to yield a yellow solid. This was purified by column chromatography on silica gel to yield **5-butylpyrrolidine-2-thione (67)** as a white solid (0,639g, 81%). R_f 0,58 (30% ethyl acetate in hexane). M.p. 60,0-61,5°C.

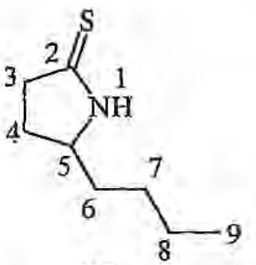
Microanalysis:

Found: C, 61,04; H, 9,86; N, 8,83.

$C_8H_{15}NS$ requires C, 61,10; H, 9,61; N, 8,91%.

IR ($CHCl_3$)

3406 (m); 3172 (w); 3036 (w); 2960 (s); 2934 (s); 2872 (s); 2862 (s); 1532 (vs, N-C=S); 1504 (vs, N-C=S); 1460 (s); 1424 (m); 1380 (m); 1316 (s); 1278 (s); 1234 (m); 1160 (w); 1148 (m); 1114 (s); 1076 (w); 1056 (m); 1038 (w); 664 (m); 644 (w); 476 (w); 418 (m) cm^{-1}.



(67)

^1H NMR ($CDCl_3$)

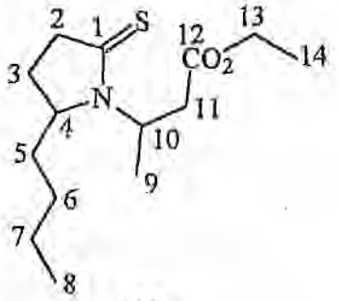
9,05 (1H, s, br, H-1), 3,95-3,86 (1H, m, H-5), 2,99-2,77 (2H, m, H-3), 2,41-2,24 (1H, m, H-4), 1,88-1,23 (7H, m, H-4, 6, 7 and 8), 0,91 (3H, t, 7Hz, H-9).

^{13}C NMR ($CDCl_3$)

204,56 (C-2); 62,71 (C-5); 43,00 (C-3); 34,92 (C-4); 29,17 (C-6); 27,96 (C-7); 22,37 (C-8); 13,82 (C-9).

2. 5-Butyl-1-(2-ethoxycarbonyl-1-methylethyl)pyrrolidine-2-thione (44)

Sodium hydride (50% suspension in oil) (0,302g, 6,29mmol) was added to a solution of 5-butylpyrrolidine-2-thione (67) (0,989g, 6,28mmol) in dry tetrahydrofuran (20ml) under nitrogen. After 15 minutes, ethyl crotonate (0,78ml, 0,72g, 6,3mmol) was added dropwise. The solution turned orange. This was stirred overnight and then heated under reflux for 5 hours. Judging by thin layer chromatography, the starting material had not all been consumed. The solution was neutralised with 2M hydrochloric acid. The tetrahydrofuran was removed under reduced pressure and the residue separated using water and dichloromethane. The aqueous layer was extracted with dichloromethane (2x20ml) and the combined organic layers evaporated to give a yellow oil (1,67g). The starting material and product was separated using flash chromatography on silica gel (15% ethyl acetate in hexane) to yield recovered thiolactam (67) (0,23g, 23%) and two diastereomers of **5-butyl-1-(2-ethoxycarbonyl-1-methylethyl)pyrrolidine-2-thione (44)** (0,993g combined, 23%) as a yellow oil. With careful chromatography, diastereomers could be separated partially and each characterised separately. Diastereomer A: R_f 0,29 (15% ethyl acetate in hexane), Diastereomer B: R_f 0,24 (15% ethyl acetate in hexane).



(44)

Diastereomer A

^{1}H NMR ($CDCl_3$) (200MHz)

5,26-5,15 (1H, m, H-10), 4,14 (2H, q, 7Hz, H-13), 4,19-3,98 (1H, m, H-4), 3,05-2,94 (2H, m, H-2), 2,85 (1H, dd, 15 & 7Hz, H-11), 2,73 (1H, dd, 15 & 8Hz, H-11), 2,17-2,05 (1H, m, H-3), 1,87-1,22 (7H, m, H-3, 5, 6 and 7), 1,42 (3H ,d, 7Hz, H-9), 1,25 (3H, t, 7Hz, H-14), 0,92 (3H, t, 7Hz, H-8).

^{13}C NMR ($CDCl_3$)

201,54 (C-1); 170,5 (C-12); 65,09 (C-4); 60,83 (C-13); 50,61 (C-10); 43,96 (C-2); 38,41 (C-11); 33,75 (C-5); 27,58 (C-6); 26,02 (C-3); 22,57 (C-7); 18,50 (C-9); 14,13 (C-14); 13,93 (C-8).

IR (neat)

2958 (m); 2934 (m); 2870 (w); 1734 (s, C=O); 1494 (w); 1460 (s, N-C=S); 1424 (m); 1374 (m); 1352 (w); 1322 (m); 1300 (m); 1274 (m); 1234 (w); 1196 (m); 1142 (w); 112 (w); 1088 (w); 1030 (w); 464 (s); 444 (s) cm^{-1}.

Diastereomer B

^{1}H NMR ($CDCl_3$) (400MHz)

4,79-4,74 (1H, m, H-10), 4,15 (2H, q, 7Hz, H-13), 4,19-4,04 (1H, m, H-4), 3,54 (1H, dd, 16 & 6Hz, H-11), 3,04-2,90 (2H, m, H-2), 2,48 (1H, dd, 16 & 8Hz, H-11), 2,22-2,08 (1H, m, H-3), 1,84-1,20 (7H, m, H-3, 5, 6 and 7), 1,52 (3H, d, 7Hz, H-9), 1,26 (3H, t, 7Hz, H-14), 0,93 (3H, t, 7Hz, H-8).

^{13}C NMR ($CDCl_3$)

200,53 (C-1); 171,17 (C-12); 67,27 (C-4); 60,62 (C-13); 50,90 (C-10); 44,65 (C-2); 37,85 (C-11); 33,24 (C-5); 27,56 (C-6); 25,66 (C-3); 22,58 (C-7); 17,07 (C-9); 14,13 (C-14); 13,93 (C-8).

IR (neat)

2958 (m); 2932 (m); 2870 (w); 1734 (s, C=O); 1498 (w); 1460 (s, N-C=S); 1424 (m); 1374 (m); 1312 (m); 1274 (w); 1234 (w); 1180 (s, C-O-C); 1130 (w); 1098 (w); 1032 (w); 466 (s); 450 (s); 416 (s) cm^{-1}.

Mass spectrum of the mixture

41 (67); 55 (40); 69 (48); 100 (61); 114 (75); 130 (68); 157 (16); 158 (42); 198 (M^+ - CO_2Et, 88); 214 (M^+ - Bu, 26); 215 (23); 226 (M^+ - OEt, 34); 238 (65); 242 (M^+ - Et, 76); 243(13); 271 (M^+, 100); 272 (M+1, 20).

Accurate mass: Found M^+, 271,1611.

$C_{14}H_{25}NO_2S$ requires 271,1606.

3. Attempted Synthesis of 5-Butyl-1-(2-ethoxycarbonyl-1-methylethyl)-2-pyrrolidinone (53)

The method followed was that of Ahn and Lee[79]. Ethyl crotonate (0,22ml, 0,197g, 1,73mmol) was added dropwise to a suspension of lactam (40) (0,222g, 1,57mmol), cesium fluoride (0,1 eq, 0,027g, 0,18mmol) and tetraethoxysilane (0,35ml, 0,33g, 1,6mmol) at room temperature under a nitrogen atmosphere. This was stirred overnight and then passed through a column of silica gel. NMR showed that the desired product was not obtained.

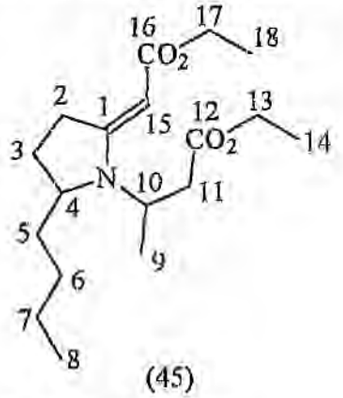
4. (E)-5-Butyl-1-(2-ethoxycarbonyl-1-methylethyl)-2-ethoxycarbonyl-methylenepyrrolidine (45)

5-Butyl-1-(2-ethoxycarbonyl-1-methylethyl)pyrrolidine-2-thione (44) (0,165g, 0,61mmol) was dissolved in acetonitrile (2ml) and the solution was cooled in ice. Ethyl bromoacetate (0,075ml, 0,11g, 0,68mmol) was added dropwise and the mixture was stirred overnight. Judging by thin layer chromatography, a salt had formed and all the starting material had reacted. Triphenylphosphine (0,193g,

0,74mmol) was added, followed as soon as possible thereafter by dropwise addition of triethylamine (0,09ml, 0,068g, 0,67mmol). After stirring for 2 hours, the solvent was evaporated to yield a yellow solid. Ethyl acetate was added and the reaction mixture was filtered through Celite to remove triethylammonium bromide. The solvent was evaporated and the partially solid residue purified by column chromatography on silica gel. (solvent: benzene to elute triphenylphosphine sulphide and triphenylphosphine, then 30% ethyl acetate in hexane). **(*E*)-5-Butyl-1-(2-ethoxycarbonyl-1-methylethyl)-2-ethoxycarbonyl-methylenepyrrolidine (45)** was obtained as a yellow oil (0,198g, 90%) as a mixture of diastereomers in a ratio of 3:7. R_f 0,58 (30% ethyl acetate in hexane).

IR (neat)

2974 (m); 2958 (m); 2934 (m); 2872 (w); 1734 (s, C=O); 1686 (s, C=O); 1586 (vs, C=C); 1462 (w); 1414 (w); 1376 (m); 1352 (w); 1300 (m); 1205 (w); 1210 (m); 1142 (s, C-O-C); 1098 (m); 1060 m); 1032 (w) cm^{-1}.



(45)

^1H NMR ($CDCl_3$) of a mixture of diastereomers

4,59 (2H, s, H-15), 4,12 (4H, q, 7Hz, H-13), 4,08 (4H, q, 7Hz, H-17). 4,21-3,99 (2H, m, H-10), 3,76-3,62 (2H, m, H-4), 3,40 (1H, dd, 9 & 3Hz, H-11), 3,31 (1H, dd, 9 & 3Hz, H-11), 3,03-2,85 (4H, m, H-2), 2,65 (1H, dd, 7 & 3Hz, H-11), 2,39 (1H, dd, 16 & 9Hz, H-11), 2,00-1,21 (16H, m, H-3, 5, 6 and 7), 1,34 (6H, t, 7Hz, H-14), 1,25 (6H, t, 7Hz, H-18), 1,26 (6H, d, 5Hz, H-9), 0,91 (6H, t, 7Hz, H-8).

^{13}C NMR ($CDCl_3$)

The diastereomers were not separated but the 3:7 ratio made it possible to assign the signals separately for the two diastereomers.

Major diastereomer:

171,22 (C-12); 169,36 (C-16); 163,42 (C-1); 78,79 (C-15);) 62,41 (C-4); 60,68 (C-13); 58,24 (C-17); 48,28 (C-10); 38,48 (C-11); 34,09 (C-2); 31,40 (C-5); 27,75 (C-6); 26,14 (C-3); 22,73 (C-7); 17,64 (C-9); 14,72 (C-18); 14,13 (C-14);) 14 02 (C-8).

Minor diastereomer:

170,82 (C-12); 169,36 (C-16); 164,13 (C-1); 78,71 (C-15), 62,41 (C-4); 61,30 (C-13); 58,24 (C-17); 48,17 (C-10); 38,88 (C-11); 34,45 (C-2); 31,15 (C-5); 27,75 (C-6); 26,50 (C-3), 22,73 (C-7); 18,26 (C-9); 14,72 (C-18); 14,13 (C-14); 14,02 (C-8).

Mass spectrum:

108 (57); 154 (36); 168 (31); 169 (27); 194 (23); 196 (49); 210 (M^+ - $CH_3CHCH_2CO_2Et$, 17); 238 (M^+ - CH_2CO_2Et, 59); 252 (M^+ - CO_2Et, 66); 268 (M^+ - Bu, 67); 269 (56); 280 (M^+ - OEt, 100); 281 (19); 296 (M^+ - Et, 32); 325 (M^+ 71); 326 (M^++1, 15).

Accurate mass: Found: M^+, 325,2258.

$C_{18}H_{31}NO_4$ requires 325,2253.

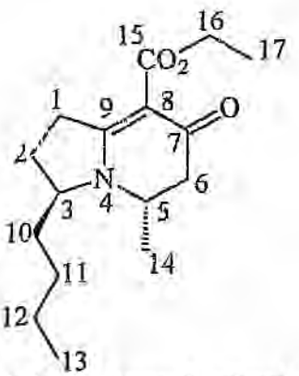
5. 9-Butyl-5-ethoxycarbonyl-2-methyl-1-azabicyclo[4.3.0]non-5-en-4-one (46)

Sodium hydroxide (0,2108g, 5,270mmol) was dissolved in distilled water (10ml) and added to (*E*)-5-butyl-1-(2-ethoxycarbonyl-1-methylethyl)-2-ethoxy-carbonylmethylenepyrrolidine (45) (1,775g, 5,453mmol). The mixture was heated under reflux for 90 minutes until it became homogeneous. The solution was cooled to room temperature and extracted with diethyl ether (2x5ml). The

aqueous phase was evaporated to give a yellow solid. The final traces of water were removed by heating the solid at 60°C under vacuum for 8 hours. The solid was ground to a fine powder and dried for a further hour at 60°C to yield the sodium salt of (*E*)-5-butyl-1-(2-ethoxycarbonyl-1-methylethyl)-2-ethoxycarbonylmethylenepyrrolidine (45) (1,142g, 3,576mmol, 68%). The sodium salt was suspended in dry acetonitrile (40ml) and stirred under a nitrogen atmosphere at room temperature. Acetic anhydride (0,51ml, 0,56g, 5,5mmol) was added dropwise. The mixture was stirred at 60°C for 4 hours and at room temperature overnight. The solvent was evaporated and the yellow residue dissolved in dichloromethane (30ml). This was poured into cold aqueous sodium bicarbonate solution (30ml). The aqueous phase was extracted with dichloromethane (2x20ml) after separating the two phases. The combined organic phases were dried ($MgSO_4$) and evaporated to yield a dark yellow/brown oil (1,16g). This was purified and the diastereomers separated by column chromatography on silica gel to yield two diastereomers of **9-butyl-5-ethoxycarbonyl-2-methyl-1-azabicyclo-[4.3.0]non-5-en-4-one (46)** as yellow oils.

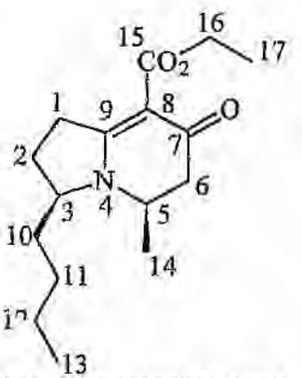
Trans diastereomer: Yield: 0,257g, 17%. R_f 0,51 (5:2 ethyl acetate:methanol).

Cis diastereomer: Yield: 0,286g, 19%. R_f 0,66 (5:2 ethyl acetate:methanol).



(relative stereochemistry)

Trans-(46)



(relative stereochemistry)

Cis-(46)

Trans diastereomer:

IR (neat)

3498 (w); 2958 (m); 2932 (m); 2868 (w); 1712 (m, C=O); 1652 (s, C=O); 1552 (s, C=C); 1450 (m); 1374 (m); 1302 (w); 1274 (m); 1232 (m); 1152 (s, C-O-C); 1130 (m); 1092 (m) cm^{-1}.

^1H NMR ($CDCl_3$) (400MHz)

4,23 (2H, q, 7Hz, H-16); 3,83-3,76 (2H, m, H-3 and 5); 3,22 (2H, t, 8Hz, H-1); 2,75 (1H, dd, 16 & 7Hz, H-6); 2,34 (1H, dd, 16 & 4Hz, H-6); 2,23-2,14 (1H, m, H-2); 1,81-1,72 (2H, m, H-2 and 10); 1,46-1,24 (5H, m, H-10, 11 and 12); 1,32 (3H, t, 7Hz, H-17); 1,21 (3H, d, 7Hz, H-14); 0,94 (3H, t, 7Hz, H-13).

Irradiation at	1,22ppm:	change in shape of multiplet at 3,83-3,76ppm
	1,76ppm:	t at 3,22ppm collapses to d, 8Hz
	2,19ppm:	t at 3,22ppm collapses to d, 8Hz
		multiplet at 1,81-1,72ppm simplifies
	2,35ppm:	change in shape of multiplet at 3,83-3,76ppm
		dd at 2,75ppm collapses to d
	2,76ppm:	dd at 2,34ppm collapses to d, 2Hz
		change in shape of multiplet at 3,83-3,76ppm
	3,23ppm:	multiplet at 2,23-2,14ppm simplifies
		multiplet at 1,81-1,72ppm simplifies
	3,8ppm:	dd at 2,75ppm collapses to d, 16Hz
		dd at 2,34ppm collapses to d, 16Hz
		d at 1,21ppm collapses to s.

^{13}C NMR ($CDCl_3$) 200MHz

186,85 (C-7); 171,62 (C-9); 166,16 (C-15); 97,62 (C-8); 62,32 (C-3); 59,30 (C-16); 47,39 (C-5); 42,92 (C-6); 33,21 (C-1); 31,97 (C-10); 26,96 (C-11); 26,40 (C-2); 22,52 (C-12);) 15,50 (C-14); 14,39 (C-17); 13,82 (C-13).

Mass spectrum:

150 (M^+ - Bu & CO_2Et, 30); 176 (M^+ - Bu & OEt, 100); 177 (14); 206 (M^+ - CO_2Et, 6); 207 (45); 208 (8); 222 (M^+ - Bu, 36); 223 (7); 234 (M^+ - OEt, 38); 235 (9); 279 M^+, 23).

Accurate mass. Found: M^+, 279,1822.

$C_{16}H_{25}NO_3$ requires 279,1834.

Cis diastereomer:

IR (neat)

3486 (w); 2958 (m); 2932 (m); 2870 (w); 1710 (s, C=O); 1650 (s, C=O); 1554 (vs, C=C); 1452 (m); 1422 (w); 1374 (s); 1342 (w); 1302 (w); 1272 (m); 1228 (m); 1150 (s, C-O-C); 1132 (s); 1092 (m); 1034 (w); 77 ' (w) cm^{-1}.

^1H NMR ($CDCl_3$) (400 MHz)

4,23 (2H, q, 7Hz, H-16); 3,88-3,82 (1H, m, H-3); 3,81-3,69 (1H, m, H-5); 3,46-3,31 (1H, m, H-1); 3,10 (1H, ddd, 19, 9 & 5Hz, H-1); 2,79 (1H, dd, 16 & 6Hz, H-6); 2,22 (1H, dd, 16 & 3Hz, H-6); 2,34-2,15 (1H, m, H-2); 1,92-1,75 (2H, m, H-2 and 10); 11,52-1,20 (5H, m, H-10, 11 and 12); 1,33 (3H, t, 7Hz, H-17); 1,29 (3H, d, 7Hz, H-14); 0,94 (3H, t, 7Hz, H-13).

^{13}C NMR ($CDCl_3$) (200MHz)

186,89 (C-7); 171,24 (C-9); 166,21 (C-15); 97,27 (C-8);) 66,28 (C-3); 59,32 (C-16); 48,55 (C-5);) 42,95 (C-6); 33,21 (C-1); 33,01 (C-10); 27,66 (C-11); 26,90 (C-2); 22,55 (C-12); 18,04 (C-14); 14,44 (C-17); 13,86 (C-13).

Mass spectrum: As for *trans* diastereomer.

Accurate mass. Found: M^+, 279,1838.

$C_{16}H_{25}NO_3$ requires 279,1834.

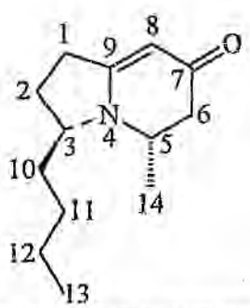
EXPERIMENTAL PROCEDURES RELATING TO SECTION 3.3

1. 9-Butyl-2-methyl-1-azabicyclo[4.3.0]non-5-en-4-one (48)

Trans-9-Butyl-5-ethoxycarbonyl-2-methyl-1-azabicyclo[4.3.0]non-5-en-4-one (46) (81mg, 0,29mmol) in an aqueous solution of potassium hydroxide (1M, 5ml) was heated under reflux for 4 hours. The solution was then cooled, acidified (concentrated hydrochloric acid), refluxed for 1 hour, cooled, basified (concentrated ammonia) and extracted with dichloromethane (3x5ml). The combined organic extracts were dried ($MgSO_4$), filtered and the solvent evaporated *in vacuo* to yield an orange oil. This was purified by column chromatography on silica gel (solvent: 5:2 ethyl actate:methanol) to yield ***trans*-9-butyl-2-methyl-1-azabicyclo[4.3.0]non-5-en-4-one (48)** as an orange oil (29mg, 48%). R_f 0,63 (5:2 ethyl acetate:methanol, viewed with iodine).

IR (neat)

3442 (m); 2958 (s); 2930 (s); 2860 (m); 1626 (s, C=O); 1574 (s, C=C); 1468 (w); 1232 (w); 1192 (w) cm^{-1}.



(relative stereochemistry)

Trans-(48)

^1H NMR ($CDCl_3$)

4,93 (1H, s, H-8); 3,83-3,62 (2H, m, H-3 and 5); 2,75-2,51 (2H, m, H-1); 2,69 (1H, dd, 16 & 7Hz, H-6); 2,24 (1H, dd, 16 & 5Hz, H-6); 2,22-2,04 (1H, m, H-2); 1,80-1,62 (2H, m, H-2 and 10); 1,46-1,23 (5H, m, H-10, 11 and 12); 1,20 (3H, d, 7Hz, H-14); 0,93 (3H, t, 7Hz, H-13).

^{13}C NMR ($CDCl_3$)

190,07 (C-7); 167,07 (C-9); 92,14 (C-8); 61,03 (C-3); 48,09 (C-5); 42,27 (C-6); 31,88 (C-1); 30,67 (C-10); 27,34 (C-11); 26,70 (C-2); 22,72 (C-12); 15,07 (C-14); 13,95 (C-13).

Mass spectrum:

80 (9); 108 (68); 150 (M^+ - Bu, 100); 151 (11); 192 (M^+ - Me, 8); 207 (M^+, 19).

Accurate mass. Found: M^+, 207,1633.

$C_{13}H_{21}NO$ requires 207,1623.

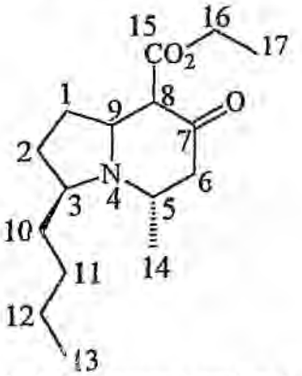
2. 9-Butyl-5-ethoxycarbonyl-2-methyl-1-azabicyclo[4.3.0]nonan-4-one (47)

Using *trans* diastereomer as starting material:

Lithium aluminium hydride (0,1078g, 3,86mmol) was added in portions to a stirred solution of *trans*-9-butyl-5-ethoxycarbonyl-2-methyl-1-azabicyclo-[4.3.0]non-5-en-4-one (46) (0,2235g, 0,800mmol) in dry tetrahydrofuran (10ml) at -78°C. This was stirred for 5 hours. Judging by thin layer chromatography, starting material was still present. The temperature was allowed to increase to -50°C before the reaction was quenched by the sequential addition of water (0,1ml), sodium hydroxide solution (15% w/w, 0,1ml) and water (0,3ml). The lithium and aluminium hydroxides were filtered off and washed with dichloromethane. The filtrate was dried ($MgSO_4$) and evaporated *in vacuo* to give a yellow oil. This was purified by column chromatography to yield a mixture of two diastereomers of ***trans*-9-butyl-5-ethoxycarbonyl-2-methyl-1-azabicyclo[4.3.0]nonan-4-one (47)** as a yellow oil (80,6mg, 29%). R_f 0,63 and 0,44 (30% ethyl acetate in hexane, viewed with iodine).

IR (neat)

2960 (s); 2930 (m); 2872 (m); 2860 (s); 1744 (s); 1718 (s); 1648 (m); 1376 (m), 1348 (w); 1298 (w); 1262 (w); 1228 (w); 1190 (w); 1148 (w); 1118 (w) cm^{-1}.



(relative stereochemistry)
Trans-(47)

^{1}H NMR ($CDCl_3$)

It was not possible to assign all the peaks since many of the signals overlapped. The peaks that could be identified were assigned as follows:

4,27-4,16 (2H, m, H-16); 2,28 (1H, dd, 2 & 14Hz, H-6); 1,28 (3H, t, 7Hz, H-17); 1,20 (3H, d, 6Hz, H-14); 0,94 (3H, t, 7Hz, H-13).

^{13}C NMR ($CDCl_3$)

Diastereomer A:

205,00 (C-7); 168,54 (C-15); 64,01 (C-9); 60,81(C-8); 57,78 (C-16); 57,68 (C-3); 48,19 (C-5); 47,60 (C-6); 33,00 (C-1); 28,91 (C-10); 28,64 (C-11); 28,21 (C-2); 23,03 (C-12); 14,17 (C-14); 14,06 (C-17); 9,95 (C-13).

The assignments for 5 and 6 may be interchanged.

Diastereomer E:

203,98 (C-7); 63,93 (C-9); 60,81 (C-8); 58,19 (C-16); 50,65 (C-5); 48,52 (C-6); 28,98 (C-1); 26,93 (C-10); 25,49 (C-11); 22,83 (C-2); 20,60 (C-12).

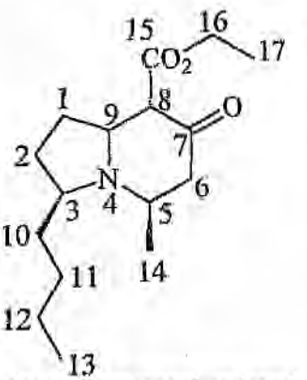
It was not possible to assign a peak to each of the carbons. This may be due to overlapping with peaks of the other diastereomer.

Using *cis* diastereomer as starting material:

The method that was used was the same as when the *trans* diastereomer was used as starting material. An overall yield of 76% was obtained although judging from the ^{13}C NMR spectrum, this was not pure. Only one diastereomer appeared to be present. Owing to a lack of time and small quantity of the material, no further steps were taken to purify it. R_f 0,76 or 0,56 (30% ethyl acetate in hexane, viewed with iodine). It is not known which of these values is that of the desired product and which is a result of the impurities.

IR (neat)

2960 (s); 2932 (s); 2872 (m); 1744 (s, C=O); 1716 (s, C=O); 1658 (m); 1620 (m); 1464 (w); 1426 (w); 1400 (w); 1372 (m); 1346 (m); 1332 (w); 1310 (m); 1274 (m); 1228 (m); 1208 (m, C-O-C); 1148 (m); 1114 (w); 1098 (w); 1078 (w); 1042 (w); 1030 (w); 448 (s) cm^{-1}.



(relative stereochemistry)

Cis-(47)

^1H NMR ($CDCl_3$)

4,33-4,12 (m); 4,02-3,94 (m); 3,68-3,60 (m); 0,98-0,87 (m).

^{13}C NMR ($CDCl_3$)

Although there were more than the expected 16 peaks due to the presence of impurities, the most likely assignments have been made.

204,90 (C-7); 168,32 (C-15); 60,58 (C-9); 60,24 (C-8); 60,08 (C-16) 53,70 (C-3); 46,50 (C-5); 35,46 (C-6); 30,79 (C-1); 30,45 (C-10); 29,89 (C-11); 28,56 (C-2); 22,) (C-12); 22,96(C-12), 20,14 (C-14); 14,12 (C-17); 14,04 (C-13).

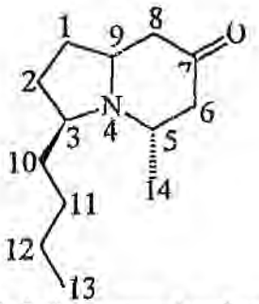
3. 9-Butyl-2-methyl-1-azabic; clo[4.3.0]nonan-4-one (49)

Using the *trans* diastereomer as starting material:

An aqueous solution of potassium hydroxide (1M, 10ml) was added to *trans*-9-butyl-5-ethoxycarbonyl-2-methyl-1-azabicyclo[4.3.0]non 4-one (47) (85mg, 0,30mmol). The mixture was heated under refl cooled, acidified (concentrated hydrochloric acid), refluxed for ed, ba fied (concentrated ammonia) and extracted with dichlo il). The combined organic extracts were dried ($MgSO_4$) and evap to yiel an orange oil. This was purified by flash column chromatography a gel to yield ***trans*-9-butyl-2-methyl-1-azabicyclo[4.3.0]nonan-4-one (49)** as an orange oil (24,2mg, 38%). R_f 0,41 or 0,17 (30% ethyl acetate in hexane, viewed with iodine). The product was impure but judging from the ^{13}C NMR spectrum, only one diastereomer was present.

IR (neat)

2958 (s); 2928 (s); 2870 (m); 2858 (m); 2814 (m); 2732 (w); 2684 (w); 2610 (w); 1718(s, C=O); 1462 (w); 1378 (w); 1346(w); 1276(w); 1248 (w); 1212 (w); 438 (s) cm^{-1}.



(relative stereochemistry)

Trans-(49)

^{1}H NMR ($CDCl_3$)

Since many of the signals overlapped, it was difficult to distinguish the peaks.

3,73-3,55 (m); 3,01-1,04 (m); 0,94-0,83 (m).

^{13}C NMR ($CDCl_3$)

It was not possible to purify the product so numerous peaks were present along with those of the product. It was however possible to tentatively assign the peaks likely to be the product.

210,55 (C-7); 57,89 (C-3); 52,03 (C-9); 47,94 (C-5); 44,48 (C-8); 42,45 (C-6); 35,61 (C-1); 29,40 (C-10); 28,52 (C-11); 28,40 (C-2); 23,03 (C-12); 14,10 (C-14); 9,64 (C-13).

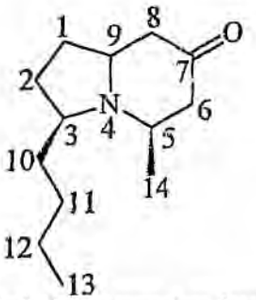
Using the *cis* diastereomer:

The same method was used as for the *trans* diastereomer:

Only one diastereomer was present. R_f 0,60 or 0,33 (30% ethyl acetate in hexane, viewed with iodine). It is not known which of the values is due to the product and which is due to the impurities.

IR (neat)

2958 (s); 2928 (s); 2870 (m); 2858 (m); 1720 (s, C=O); 1666 (w); 1630 (w); 1572 (w); 1460(w); 1416 (w); 1378 (w); 1346 (w); 1336 (w); 1314 (w); 1296 (w); 1276 (w); 1250 (w); 1210 (w); 1194 (w); 1166 (w); 446 (s) cm^{-1}.



(relative stereochemistry)

Cis-(49)

^{1}H NMR ($CDCl_3$) 400MHz

3,73-3,62 (1H, m, H-3); 3,61-3,55 (1H, m, H-5); 3,01-2,92 (1H, m, H-8); 2,90-2,82 (1H, m, H-8); 2,66 (1H, dd, 6 & 13 Hz, H-6); 2,47-2,00 (5H, m, H-9, 1 and 6); 1,65-1,06 (8H, m, H-2, 10, 11 and 12); 1,16 (3H, d, 7Hz, H-14); 0,94-0,83 (3H, m, H-13).

^{13}C NMR ($CDCl_3$) 400MHz

It was not possible to purify the product so numerous peaks were present along with those of the product. It was however possible to tentatively assign the peaks likely to be due to the product.

210,58 (C-7); 57,89 (C-3); 52,02 (C-9); 44,49 (C-5); 42,43 (C-8); 35,63 (C-6); 29,05 (C-1); 28,50 (C-10); 28,39 (C-11); 23,03 (C-2); 21,36 (C-12); 14,12 (C-14); 14,10 (C-13).

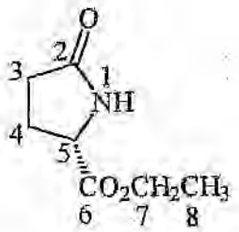
EXPERIMENTAL PROCEDURES RELATING TO SECTION 4.1

1. (*S*)-(+)-5-Carbethoxy-2-pyrrolidinone (70)

The method followed was that of Silverman and Levy[80]. Distilled thionyl chloride (13,0ml, 19,7g, 166mmol) was added to a suspension of L-(+)-glutamic acid (69) (10,0g, 68mmol) in absolute ethanol (100ml) cooled in an ice bath. The reaction was exothermic. The mixture was stirred at room temperature for 1 hour during which time the solution became clear. It was heated under reflux for 45 minutes before the excess ethanol and thionyl chloride were removed under reduced pressure. The remaining syrup was diluted with absolute ethanol (40ml) and the acid neutralised with potassium hydroxide in absolute ethanol. A fine precipitate of potassium chloride was formed. The solution was filtered through celite and the ethanol removed under reduced pressure to yield diethyl glutamate as a syrup. This was heated to 130-150°C under vacuum (~0,5mmHg) for 90 minutes. A liquid nitrogen trap was used to collect the ethanol which was formed during the cyclisation. The crude product, a yellow oil (8,0g), was purified using column chromatography on silica gel using 3:1 ethyl acetate : hexane as solvent. **(*S*)-(+)-5-Carbethoxy-2-pyrrolidinone (70)** was obtained as white crystals (7,1g, 66%). M.p. 48-52°C Lit.[80] 48-50°C, R_f 0,36 (ethyl acetate, viewed with iodine), $[\alpha]_D$ 2,4° (c 9,96, EtOH), Lit. 2,4° (c 10, EtOH)[80].

IR ($CHCl_3$)

3438 (m); 3216 (m); 3104 (w); 3006 (s); 2940 (m); 2908 (w); 1740 (s, C=O); 1703 (s, C=O); 1462 (m); 1446 (m), 1414 (s); 1398 (m); 1378 (m); 1328 (m); 1234 (s); 1198 (s, C-O-C stretching); 1154 (m); 1112 (m); 1098 (m); 1030 (s); 1004 (w); 664 (m); 578(w); 496 (w); 410 (w) cm^{-1}.



(70)

^{1}H NMR ($CDCl_3$)

7,48 (1H, d, 9Hz, H-1); 3,95-3,88 (1H, m, H-5); 3,85 (2H, q, 7Hz, H-7); 2,17-1,92 (3H, m, H-3 and 4); 1,87-11,73 (1H, m, H-4); 0,92 (3H, t, 7Hz, H-8).

^{13}C NMR ($CDCl_3$)

178,03 (C-2); 171,70 (C-6); 60,65 (C-7); 55,01 (C-5); 28,67 (C-3); 24,08 (C-4); 13,36 (C-8).

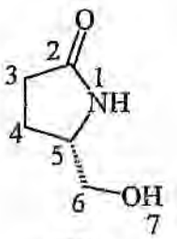
2. (*S*)-(+)-5-(Hydroxymethyl)-2-pyrrolidinone (57)

The method of Silverman and Levy[80] was used. A mixture of sodium borohydride (0,64g, 0,17mmol), dry lithium chloride (0,63g, 0,15mmol) and dry diglyme (10ml) was stirred vigorously under nitrogen for 20 minutes. Dry tetrahydrofuran (7ml) was added and the solid allowed to settle. The supernatant liquid containing dissolved lithium borohydride was filtered directly into a stirred solution of (*S*)-(+)-5-carbethoxy-2-pyrrolidinone (70) (2,04g, 0,13mmol) in dry tetrahydrofuran (15ml) using a vacuum pump. During the filtration the solution in the second flask became cloudy. The reaction was exothermic. The reaction mixture was stirred overnight and then cooled in an ice bath. It was quenched by the slow addition of 30% acetic acid in water (12ml). The tetrahydrofuran was evaporated and the remaining solution was applied to a column of Dowex 50 (30ml). The column was washed with distilled water (80ml), which was then concentrated to give a white solid suspended in a liquid. Ethyl acetate was added, dissolving the liquid. The solid was removed by filtration and the liquid purified by column chromatography on silica gel (solvent: ethyl acetate to 10% methanol in ethyl acetate) to give (*S*)-

(+)-5-(hydroxymethyl)-2-pyrrolidinone (57) as a white solid (1,11g, 76%). R_f 0,26 (5:1 ethyl acetate :methanol), M.p. 70-73°C, Lit.[80] 66-68°C, $[\alpha]_D$ +30° (*c*5,18, EtOH), Lit +29° (*c*5, EtOH)[80].

IR ($CHCl_3$)

3420 (s); 3306 (s); 3006 (s); 2942 (m); 2876 (w); 1690 (s, C=O); 1678 (s); 1462 (w); 1436 (w); 1420 (m); 1392 (w); 1318 (m); 1288 (m); 1260 (m); 1238 (m); 1200 (w); 1090 (m); 1060 (m, C-O-C stretching); 1030 (w); 706 (w); 662 (m); 510 (w) cm^{-1}.



(57)

^1H NMR ($CDCl_3$)

7,10 (1H, s, br, H-1); 3,84-3,66 (2H, m, H-6); 3,52-3,43 (1H, m, H-5); 3,20 (1H, s, br, H-7); 2,42-2,13 (3H, m, H-3 and 4); 1,86-1,83 (1H, m, H-4).

^{13}C NMR ($CDCl_3$)

179,20 (C-2); 65,93 (C-6); 56,34 (C-5); 30,18 (C-3); 22,58 (C-4).

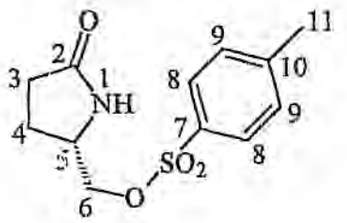
3. (*S*)-5-(*p*-Toluenesulphonyloxymethyl)-2-pyrrolidinone (71)

The method of Holmes, Smith and Williams was used[69]. A solution of (*S*) (+)-5-(hydroxymethyl)-2-pyrrolidinone (57) (0,111g, 0,96mmol) in dry dichloromethane (5ml) was treated with dry triethylamine (1,30ml, 0,944g, 9,33mmol), DMAP (0,012g, 0,098mmol) and *p*-toluenesulphonyl chloride (0,26g, 1,36mmol). The resulting solution was stirred at room temperature overnight and then poured into distilled water (6ml) and acidified (conc. HCl). The upper aqueous layer was extracted with dichloromethane (3x5ml), and the combined organic layers dried

($MgSO_4$) and evaporated *in vacuo* to give a yellow solid. This was recrystallised from ethyl acetate/hexane to give **(*S*)-5-(*p*-toluenesulphonyl)oxy)methyl)-2-pyrrolidinone (71)** as white crystals (0,203g, 78%). M.p. 126-128°C, Lit.[69] 125-126°C, $[\alpha]_D$ +9,9° (*c*2,03, CH_2Cl_2), Lit[69]. +10,8° (*c*1,88, CH_2Cl_2).

IR ($CHCl_3$)

3432 (w); 3030 (w); 3010 (m); 2956 (w); 1702 (s, C=O); 1598 (w); 1460 (w); 1418 (m); 1394 (w); 1366 (s, SO_2-O); 1322 (w); 1310 (w); 1290 (w); 1232 (w); 1216 (w); 1190 (s, SO_2-O); 1176 (s, C-O stretching); 1098 (m); 1020 (w); 996 (m); 966 (s); 864 (w); 828 (m); 816 (m); 785 (w); 744 (w); 734 (w); 688 (w); 662 (m); 572 (m); 554 (s); 530 (w); 500 (w) cm^{-1}.



(71)

^1H NMR ($CDCl_3$)

7,79 (2H, d, 8Hz, H-8); 7,37 (2H, d, 8Hz, H-9); 6,54 (1H, br, H-1); 4,06-3,83 (3H, m, H-5 and 6); 2,46 (3H, s, H-11); 2,42-2,15 (3H, m, H-3 and 4); 1,89-1,73 (1H, m, H-4).

^{13}C NMR ($CDCl_3$)

177,75 (C-2); 145,31 (C-7); 132,2 (C-10); 130,02 (C-9); 127,86 (C-8); 71,93 (C-6); 52,52 (C-5); 29,17 (C-3); 22,72 (C-4); 21,61 (C-11).

4. Attempted Synthesis of (*S*)-(+)-5-Butyl-2-pyrrolidinone (68)

A Grignard reagent was formed using magnesium (0,091g, 3,74mmol) and 1-bromopropane (0,35ml, 0,47g, 3,85mmol) in diethyl ether. This was cooled to -40°C. After 1 hour cuprous iodide (0,053g, 0,28mmol) was added. The colour

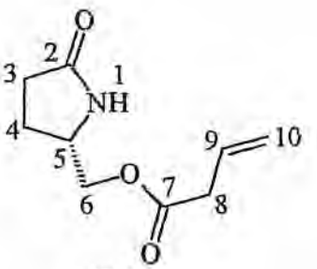
of the reaction mixture became dark green. After 15 minutes, the tosylate (71) (0,509g, 1,89mmol) in tetrahydrofuran was added dropwise. The solution was maintained at -40°C for 4 hours followed by -20°C overnight. Saturated ammonium chloride solution (50ml) was added and the precipitate that formed was filtered off. The ether layer was washed with saturated ammonium chloride solution (10ml) and the aqueous layer extracted with dichloromethane (2x15ml). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure. Judging from thin layer chromatography, only starting material was present.

EXPERIMENTAL PROCEDURES RELATING TO SECTION 4.2

1. (*S*)-(+)-(2-Oxopyrrolidin-5-yl)methyl 3-butenoate (74)

Crotonyl chloride (0,17ml, 0,18g, 1,77mmol) and triethylamine (0,25ml, 0,18g, 1,77mmol) were added to a solution of (*S*)-(+)-5-(hydroxymethyl)-2-pyrrolidinone (57) (0,205g, 1,81mmol) in dichloromethane (5ml) under nitrogen at 0°C. The solution turned orange during the addition of the triethylamine. A solid formed which dissolved on the further addition of dichloromethane (5ml). After 30 minutes the solution was allowed to warm to room temperature and was stirred overnight. The solid was evaporated under reduced pressure to give an orange solid (1,34g). This was purified by column chromatography on silica gel (solvent: 20% hexane in ethyl acetate to ethyl acetate) to yield **(*S*)-(+)-(2-oxopyrrolidin-5-yl)methyl 3-butenoate (74)** as a yellow oil (0,199g, 61%). R_f 0,65 (5:1 ethyl acetate: methanol). $[\alpha]_D$ +11,11° (*c* 0,99 EtOH).

IR (neat)
3242 (m); 3086 (w); 2956 (w); 1738 (s, C=O); 1694 (s, C=O); 1462 (w); 1424 (w); 1402 (w); 1382 (w); 1318 (m); 1290 (m); 1258 (m); 1170 (m); 1106 (w); 1012 (w); 996 (w); 926 (w); 738 (w); 644 (w) cm^{-1}.



(74)

^{1}H NMR ($CDCl_3$)

6,75 (1H, br s, H-1); 6,02-5,82 (1H, m, H-9); 5,24-5,13 (2H, m, H-10); 4,27-4,17 (1H, m, H-6); 3,99-3,89 (2H, m, H-5 and 6); 3,14 (2H, dt, 1 & 7Hz, H-8); 2,47-1,75 (4H, m, H-3 and 4).

^{13}C NMR ($CDCl_3$)

178,19 (C-2); 171,24 (C-7); 129,70 (C-9); 118,95 (C-10); 67,13 (C-6); 52,71 (C-5); 38,80 (C-8); 29,53 (C-3); 23,10 (C-4).

Mass spectrum:

28 (21); 39 (13); 41 ($CH_2CHCH_2^+$, 42); 55 (11); 56 (9); 69 (8); 84 (M^+ - $CH_2OCOCH_2CHCH_2$; 100); 97 (M^+ - $OCOCH_2CHCH_2$, 18); 183 (M^+ , <1); 184 (M^+ + 1, <1).

Accurate Mass: Found: M^+ 183,0981.

$C_9H_{13}NO_3$ requires 183,0895.

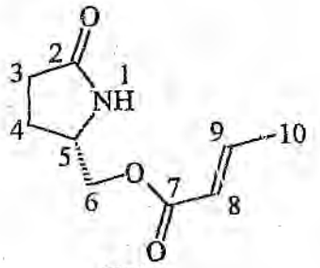
2. (*S*)-(+)-(2-Oxopyrrolidin-5-yl)methyl 2-butenoate (72)

Na_2HPO_4 (0,25g, 1,76mmol) was added to a solution of crotonyl chloride (0,17ml, 0,18g, 1,77mmol) and (*S*)-(+)-5-(hydroxymethyl)-2-pyrrolidinone (57) (0,1982g, 1,75mmol) in dichloromethane (10ml) under a nitrogen atmosphere. After stirring for 2 days, the solvent was evaporated and the residue purified by column chromatography on silica gel to yield **(*S*)-(+)-(2-oxopyrrolidin-5-yl)methyl 2-**

butenoate (72) as a white solid (0,1805g, 56%). R_f 0,61 (5:1 ethyl acetate : methanol), m.p. 55-58°C, $[\alpha]_D$ 9,90 (*c* 1,01, EtOH).

IR ($CHCl_3$)

3430 (m); 3212 (w); 3098 (w); 3010 (m); 2952 (w); 2920 (w); 2896 (w); 1704 (vs, C=O); 1660 (s, C=O); 1460 (m); 1442 (m); 1420 (m); 1378 (w); 1296 (s); 1266 (s); 1220 (m); 1182 (s); 1104 (m); 1030 (m); 968 (m); 838 (w); 688 (w); 664 (w); 648 (w); 588 (w); 500 (w) cm^{-1}.



(72)

^1H NMR ($CHCl_3$)

7,03 (1H, dq, 7 & 16Hz, H-9); 6,79 (1H, br s, H-1); 5,86 (1H, dq, 2 & 16Hz, H-8); 4,27-4,20 (1H, m, H-6); 4,02-3,92 (2H, m, H-5 and 6); 2,43-1,81 (4H, m, H-3 and 4); 1,90 (3H, dd, 2 & 7Hz, H-10).

^{13}C NMR ($CDCl_3$)

178,22 (C-2); 166,02 (C-7); 145,82 (C-8); 121,67 (C-9); 66,60 (C-6); 52,89 (C-5); 29,55 (C-3); 23,16 (C-4); 17,96 (C-10).

Mass spectrum:

29 (70); 33 (12); 39 (11); 41 ($^+CH_2CHCH_2$, 30); 55 (4); 56 (7); 69 ($CH_2CHCHCO^+$, 22); 84 (M^+ - $CH_2OCOCHCHCH_3$, 100); 85 (5); 79 (30); 183 (M^+, <1).

Accurate mass: Found: M^+,183,0890.

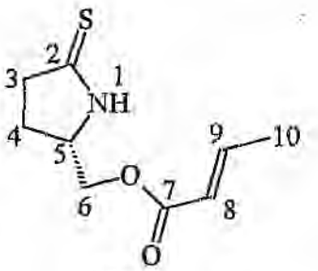
$C_9H_{13}NO_3$ requires 183,0895.

3. (*S*)-(+)-(2-Thioxopyrrolidin-5-yl)methyl 2-butenoate (59)

The procedure followed was that of Brillon[76]. P_4S_{10} (3,17g, 7,13mmol) and sodium carbonate (0,76g, 7,13mmol) were added to tetrahydrofuran (45ml) under a nitrogen atmosphere and stirred for 20 minutes. The lactam (72) (1,088g, 5,94mmol) in tetrahydrofuran was added to the clear yellow solution. After 4 hours, judging by thin layer chromatography, all the lactam had been consumed. A 10% aqueous solution of Na_3PO_4 (20ml), ethyl acetate (20ml) and hexane (20ml) were added in turn. The aqueous layer was washed with ethyl acetate (20ml). The combined organic layers were dried ($MgSO_4$) and evaporated to give an off-white solid. This was purified by column chromatography on silica gel to yield **(*S*)-(+)-(2-thioxopyrrolidin-5-yl)methyl 2-butenoate (59)** as a white solid (0,8996g, 76%). Recrystallisation from ethyl acetate/hexane resulted in white needle-like crystals. M.p. 58,0-60,5°C. R_f 0,78 (ethyl acetate). $[\alpha]_D$ 10,68 (*c*1,03, EtOH).

IR ($CHCl_3$)

3404 (w); 3166 (w); 2978 (m); 2920 (w); 1720 (s, C=O); 1658 (m); 1526 (m); 1500 (s,); 1458 (w); 1444 (w); 1424 (w); 1376 (w); 1364 (w); 1304 (s); 1296 (s); 1262 (s); 1220 (m); 1180 (s, N-C=S); 1140 (w); 1126 (w); 1104 (m); 1040 (w); 1018 (w); 968 (w); 664 (w) cm^{-1}.



(59)

^1H NMR ($CDCl_3$)

8,65 (1H, br s, H-1); 7,04 (1H, dq, 7 & 16Hz, H-9); 5,87 (1H, dq, 2 & 16Hz, H-8); 4,34 (1H, dd, 4 & 11Hz, H-6); 4,28-4,16 (1H, m, H-5); 4,01 (1H, dd, 7 &

11Hz, H-6); 3,07-2,83 (2H, m, H-3); 2,46-2,18 (1H, m, H-4); 1,92 (3H, dd, 2 & 7Hz, H-10).

^{13}C NMR ($CDCl_3$)

206,06 (C-2); 165,91 (C-7); 146,43 (C-9); 121,60 (C-8); 65,44 (C-6); 60,82 (C-5); 42,63 (C-3); 25,51 (C-4); 18,07 (C-10).

Microanalysis

Found: C, 54,10; H, 6,29; N, 6,92.

$C_9H_{13}NO_2S$ requires C, 54,25; H, 6,58; N, 7,03%.

4. Attempted intramolecular Michael reaction

The thiolactam (59) (0,1098g, 0,55mmol) was dissolved in dry tetrahydrofuran (3ml) and sodium hydride (50% suspension in oil) (0,004g, 0,08mmol) was added. Effervescence occurred. The reaction mixture was stirred overnight, heated under reflux for 6 hours and stirred overnight again. Judging by thin layer chromatography, not all the starting material had been consumed. Nevertheless the solvent was removed under reduced pressure and the residue separated using water and dichloromethane. The aqueous layer was extracted with dichloromethane (2x5ml) and the combined organic layers evaporated. The starting material was removed using column chromatography on silica gel. The desired product could not be detected in the ^1H NMR spectrum.

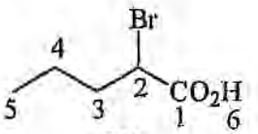
EXPERIMENTAL PROCEDURES RELATING TO SECTION 5.1

1. 2-Bromopentanoic acid (80)

The method used was that of Marvel[100]. Pentanoic (valeric) acid (79) (20,0ml, 18,78g, 184mmol) was placed in a two-necked round-bottomed flask fitted with a long condenser and a dropping funnel. Bromine (10ml) was added dropwise. Phosphorous tribromide (0,6ml) was added as a catalyst. The mixture was heated at 70-80°C for 5 hours until the condenser did not show the deep red colour of bromine. The temperature was then increased to 105°C and maintained for 2 hours. The crude bromoacid was distilled under vacuum (0,5mm Hg) at 84-91°C to yield **2-bromopentanoic acid (80)** as a clear liquid (27,23g, 82%).

IR (neat)

3102 (m); 3028 (m); 2964 (m); 2936 (m); 2876 (m); 2678 (w); 1718 (s, C=O) 1464 (m); 1424 (m); 1384 (w); 1280 (m); 1256 (m); 1208 (m); 1174 (m); 1104 (w), 924 (m); 748 (w); 674 (w); 648 (w) cm^{-1}.



(80)

^1H NMR ($CDCl_3$)

11,5 (1H, s, br, H-6); 4,26 (1H, t, 7Hz, H-2); 2,14-1,60 (2H, m, H-3); 1,60-1,38 (2H, m, H-4); 0,97 (3H, t, 7Hz, H-5).

^{13}C NMR ($CDCl_3$)

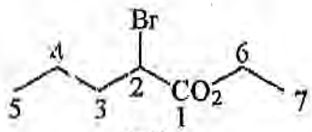
176,04 (C-1); 44,96 (C-2); 36,41 (C-3); 20,33 (C-4); 13,07 (C-5).

2. Ethyl 2-bromopentanoate (81)

2-Bromopentanoic acid (80) (27,23g, 0,150mmol), absolute ethanol (150ml) and concentrated sulphuric acid (0,5ml) were heated under reflux for 90 minutes. The excess ethanol was removed under reduced pressure and the residue was diluted with diethyl ether (30ml). The organic phase was washed with distilled water (2x15ml) to remove the sulphuric acid. The ether layer was dried ($MgSO_4$) and evaporated under reduced pressure. The crude product was distilled at 55-56°C (~0,5mmHg) to yield **ethyl 2-bromopentanoate (81)** as a clear liquid (21,43g, 68%).

IR (neat)

2964 (s); 2936 (m); 2876 (m); 1740 (vs, C=O); 1464 (m); 1372 (m); 1338 (m); 1272 (m); 1242 (m); 1198 (m); 1154 (s); 1110 (m); 1098 (m); 1052 (w); 1012 (m); 446 (s); 416 (s) cm^{-1}.



(81)

^1H NMR ($CDCl_3$)

4,24 (2H, q, 7Hz, H-6); 4,21 (1H, t, 7Hz, H-2); 2,07-1,94 (2H, m, H-3); 1,54-1,25 (2H, m, H-4); 1,30 (3H, t, 7Hz, H-7); 0,95 (3H, t, 7Hz, H-5).

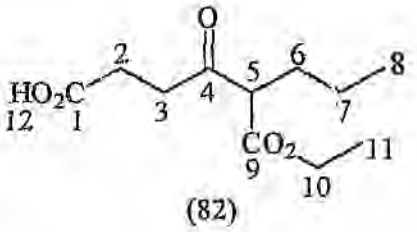
^{13}C NMR ($CDCl_3$)

169,86 (C-1); 61,61 (C-6); 45,87 (C-2); 36,79 (C-3); 20,50 (C-4); 13,90 (C-7); 13,22 (C-5).

3. 5-Ethoxycarbonyl-4-oxooctanoic acid (82)

The method of Schick and Ludwig[84] was used. Succinic anhydride (0,35g, 3,6mmol) and ethyl 2-bromopentanoate (81) (1,00g, 4,78mmol) were dissolved in

dry dimethylformamide (4ml). Zinc-copper couple[85] (0,48g) was then added. The reaction was exothermic. After stirring overnight, the mixture was poured onto ice (15g) and 5% aqueous hydrochloric acid (15ml). Ethyl acetate (15ml) was added and the solution filtered to remove the zinc. The solution was extracted with ethyl acetate (4x10ml), dried ($MgSO_4$) and evaporated under reduced pressure to yield a yellow oil (0,76g, 92%) which was purified by column chromatography on silica gel to yield **5-ethoxycarbonyl-4-oxooctanoic acid (82)** (0,256g, 31%) as an oil. R_f 0,76 (3:1 ethyl acetate: hexane, viewed with 0,5% bromocresol green in ethanol spray reagent).



(82)

^{1}H NMR ($CDCl_3$)

10,9 (1H, br s, H-12); 4,19 (2H, q, 7Hz, H-10); 3,52 (1H, t, 7Hz, H-5); 3,03-2,82 (2H, m, H-3); 2,67-2,60 (2H, m, H-2); 1,90-1,78 (2H, m, H-6); 1,37-1,22 (2H, m, H-7); 1,29 (3H, t, 7Hz, H-11); 0,92 (3H, t, 7Hz, H-8).

^{13}C NMR ($CDCl_3$)

203,36 (C-4); 177,82 (C-1); 169,49 (C-9); 61,07 (C-10); 58,41 (C-5); 35,74 (C-3); 29,86 (C-6); 27,34 (C-2); 20,20 (C-7); 13,64 (C-11); 13,37 (C-8).

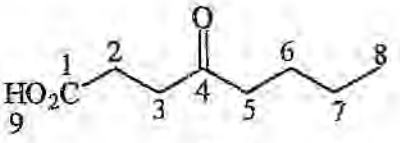
4. 4-Oxooctanoic acid (43)

The method used was that of Schick and Ludwig[84]. A mixture of 5-ethoxycarbonyl-4-oxooctanoic acid (82) (3,87g, 16,8mmol), concentrated hydrochloric acid (8ml) and water (8ml) were heated under reflux with vigorous stirring for 90 minutes. The mixture was concentrated under reduced pressure and the last traces of water removed by azeotropic distillation with benzene. The crude product was recrystallised from hexane to yield **4-oxooctanoic acid (43)** as a white

solid (0,56g, 21%). M.p. 50-53°C, Lit. 49-51°C[84]. R_f 0,67 (ethyl acetate, viewed with bromocresol green spray reagent).

IR ($CHCl_3$)

3028 (m); 2962 (s, OH stretch); 2934 (s, OH stretch); 2874 (m); 2670 (w); 1710 (vs, C=O); 1462 (w); 1430 (m); 1406 (m); 1372 (w); 1288 (m); 1256 (m); 1232 (m); 1198 (w); 1166 (w); 1128 (w); 1092 (w); 1076 (w); 940 (w); 926 (w); 778 (w) cm^{-1}.



(43)

^1H NMR ($CDCl_3$)

9,5 (1H, br s, H-9); 2,76-2,50 (4H, m, H-3 and 5); 2,45 (2H, t, 7Hz, H-2); 1,65-1,50 (2H, m, H-6); 1,41-1,22 (2H, m, H-7); 0,90 (3H, t, 7Hz, H-8).

^{13}C NMR ($CDCl_3$)

209,09 (C-4); 178,63 (C-1); 42,40 (C-3); 36,70 (C-5); 27,75 (C-2); 25,84 (C-6); 22,23 (C-7); 13,76 (C-8).

EXPERIMENTAL PROCEDURES RELATING TO SECTION 5.2

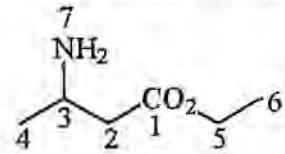
1. Ethyl 3-aminobutanoate (42)

The method used was based on that of Morsch[86]. Ethyl crotonate (10,0ml, 9,18g, 80mmol) and absolute ethanol (10ml) were placed in the autoclave vessel and chilled in liquid nitrogen. Liquid ammonia (10ml) was slowly added. The autoclave was sealed but the pressure did not rise. The mixture was stirred for 4 days. The red solution was washed into a round-bottomed flask with absolute ethanol and the ethanol distilled off under a nitrogen atmosphere. The remaining solution was distilled under reduced pressure (~10mm Hg) at 59-65°C (1,5ml).

NMR spectroscopy showed that there was both the desired product and starting material present. The mixture was diluted with diethyl ether (5ml) and acidified (2M HCl). The aqueous layer was basified (conc. NH_4OH), extracted with dichloromethane (3x30ml), dried (Na_2SO_4) and evaporated under reduced pressure to yield **ethyl 3-aminobutanoate (42)** as a clear oil (0,83g, 8%).

IR (neat)

3356 (w), 3284 (m); 3068 (w); 2976 (m); 2936 (w); 2878 (w); 1730 (s, C=O); 1648 (m); 1552 (m); 1454 (m); 1418 (w); 1376 (m); 1302 (m); 1254 (w); 1188 (m); 1154 (w); 1094 (w); 1030 (w); 466 (s); 446 (s); 418 (s) cm^{-1}.



(42)

^1H NMR ($CDCl_3$)

4,14 (2H, q, 7Hz, H-5); 3,42-3,34 (1H, m, H-3); 2,40 (1H, dd, 5 & 16Hz, H-2); 2,28 (1H, dd, 8 & 16Hz, H-2); 1,51 (2H, s, H-7); 1,27 (3H, t, 7Hz, H-7); 1,13 (3H, d, 7Hz, H-4).

^{13}C NMR ($CDCl_3$)

172,24 (C-1); 60,11 (C-5); 44,26 (C-2); 43,92 (C-3); 23,47 (C-4); 14,07 (C-6).

EXPERIMENTAL PROCEDURES RELATING TO SECTION 5.3

1. Ethyl 3-(4-oxooctanoylamino)butanoate (51)

4-Oxooctanoic acid (43) (91,7mg, 0,58mmol) was dissolved in dry dichloromethane (3ml) and cooled to 0°C in an ice-bath. Oxalyl chloride (2 eq, 0,10ml, 0,147g, 1,16mmol) and one drop of triethylamine were added. Bubbles could be seen forming. After stirring for 1 hour at room temperature, the dichloromethane and excess oxalyl chloride was distilled off. More

dichloromethane (3ml), ethyl 3-aminobutanoate (42) (0,085ml, 0,076g, 0,58mmol) and triethylamine (0,081ml, 0,059g, 0,58mmol) were added. After 2 hours, judging by thin layer chromatography, all the ethyl 3-aminobutanoate had been consumed. The solvent was removed and the product isolated using column chromatography on silica to yield **ethyl 3-(4-oxooctanoylamino)butanoate (51)** as a white solid (83mg, 53%). R_f 0,28 (50% ethyl acetate and hexane, faintly visible with bromocresol green spray reagent). M.p. 55-58°C (recrystallised from ethyl acetate/hexane).

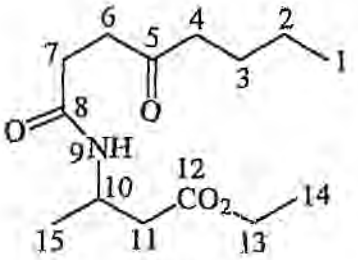
Microanalysis:

Found: C, 61,95; H, 9,29; N, 5,16.

$C_{14}H_{25}NO_4$ requires C, 61,97; H, 9,29; N, 5,16%.

IR ($CHCl_3$)

3386 (m); 3028 (w); 3008 (w); 2984 (m); 2938 (w); 1730 (s, C=O); 1676 (s, C=O); 1506 (s, C=O); 1474 (w); 1454 (m); 1416 (m); 1396 (m); 1376 (m); 1352 (m); 1302 (m); 1262 (m); 1232 (m); 1190 (s, C-O-C stretch); 1148 (m); 1096 (m); 1028 (m); 406 (m) cm^{-1}.



(51)

^1H NMR ($CDCl_3$)

6,2 (1H, br d, H-9); 4,36-4,28 (1H, m, H-10); 4,115 (2H, q, 7Hz, H-13); 2,76 (2H, t, 7Hz, H-9); 2,49 (2H, d, 5Hz, H-11); 2,44 (2H, t, 7Hz, H-5); 2,41 (2H, t, 7Hz, H-7); 1,64-1,48 (2H, m, H-3); 1,39-1,19 (2H, m, H-2); 1,27 (3H, t, 6Hz, H-14); 1,21 (3H, d, 7Hz, H-15); 0,90 (3H, t, 7Hz, H-1). H-5 and H-7 may be interchanged.

^{13}C NMR ($CDCl_3$)

210,09 (C-5); 171,61 (C-12); 171,14 (C-8); 60,53 (C-13); 42,49 (C-6); 42,01 (C-10); 40,03 (C-4); 37,56 (C-11); 30,01 (C-7); 25,89 (C-3); 22,27 (C-2); 19,94 (C-14); 14,14 (C-14); 13,78 (C-1). C-6 and C-10 may be interchanged.

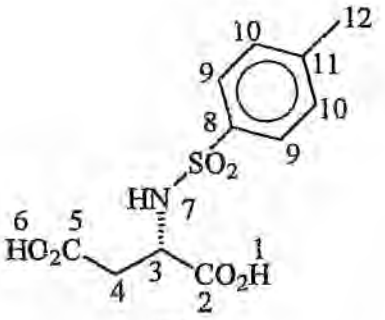
EXPERIMENTAL PROCEDURES RELATING TO SECTION 5.4

1. (*S*)-N-Tosylaspartic Acid (85)

The methods of Harington and Moggridge[91] and Ressler[92] were used. L-Aspartic acid (84) (20,0g, 150mmol), *p*-toluenesulphonyl chloride (28,6g, 1,50mmol) and an aqueous sodium hydroxide solution (2M, 250ml) were warmed to 70°C and stirred until the solution became clear. This was cooled, acidified to pH 4 with hydrochloric acid (conc.), saturated with sodium chloride and extracted with ethyl acetate (4x80ml). The organic layer was evaporated to a thick syrup. This was dissolved in a small amount of boiling water. White crystals formed when the solution was cooled in the fridge overnight. The crystals were filtered, washed with a small amount of ice-water and dried over P_2O_5 after the excess water had been removed under vacuum. **(*S*)-N-Tosylaspartic acid (85)** was obtained as white crystals (17,3g, 40%). M.p. 110-112°C, $[\alpha]_D$ 2,9° (*c*1,10, H_2O), Lit. m.p. 86-89°C, $[\alpha]_D$ 3,4° (*c*0,8, H_2O)[92].

IR (nujol)

3308 (w); 3088 (w); 3050 (w); 3038 (s); *2952 (s); *2922 (s); 2854 (s); 2596 (m); 1727 (s, C=O); *1458 (m); 1326 (m); 1280 (m); 1186 m); 1156 (s, SO_2-N); 1118 (w); 1090 (m); 568 (m); 560 (w) cm^{-1}. [* indicates nujol peaks]



(85)

^{1}H NMR (acetone-d_6)

10,83 (2H, s br, H-1 and 6); 7,79 (2H, d, 8Hz, H-9); 7,39 (2H, d, 8Hz, H-10); 6,70 (1H, d, 8Hz, H-7); 4,31-4,25 (1H, m, H-3); 2,84 (2H, d, 6Hz, H-4); 2,40 (3H, s, H-12).

^{13}C NMR (acetone-d_6)

171,82 (C-2); 171,79 (C-5); 144,04 (C-8); 138,94 (C-11); 130,30 (C-10); 127,88 (C-9); 53,02 (C-3); 38,04 (C-4); 21,39 (C-12).

2. (*S*)-N-Tosylaspartic Anhydride (86)

Method 1:

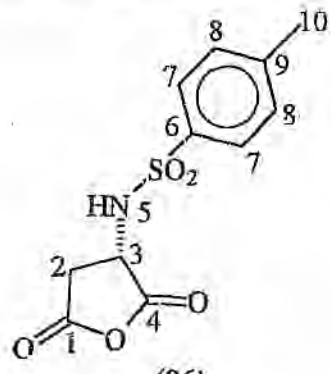
The method of Ressler[92] was used. A solution of (*S*)-N-tosylaspartic acid (85) (2,00g, 6,96mmol) in acetic anhydride (10ml) was stirred at room temperature overnight. Excess acetic anhydride and other volatile materials were distilled off under vacuum (~0,5mmHg) keeping the temperature below 40°C. The product crystallised with difficulty. The white crystals were triturated with dry toluene and collected by filtration. Recrystallisation from 1,2-dichloroethane yielded **(*S*)-N-tosylaspartic anhydride (86)** as white crystals (0,90g, 48%). M.p. 136-137°C, $[\alpha]_D$ +7,0° (*c*0,90, $CHCl_3$), Lit. m.p. 149°C[92], $[\alpha]_D$ low.

Method 2:

The method of Jefford and McNulty[93] was used. A solution of (*S*)-N-tosylaspartic acid (85) (6,95g, 24,1mmol) was stirred in acetic anhydride (18ml) overnight. As much solvent as possible was removed under high vacuum (~0,5mmHg) without heating. The remaining solution was triturated with diethyl ether (50ml) and the resultant crystalline suspension chilled, filtered by suction, washed with diethyl ether and dried to give **(*S*)-N-tosylaspartic anhydride (86)** as white crystals (2,00g, 31%). M.p. 136-138°C, $[\alpha]_D$ +7,0° (*c*0,90, $CHCl_3$), Lit.[93] m.p. 137-138, $[\alpha]_D$+7,2° (*c* 1,0, $CHCl_3$).

IR (nujol)

3584 (w); 3350(w); 3298 (w); *2954 (s); *2924 (s); *2854 (s); 1794 (w); 1710 (s, C=O); *1456 (m); 1434 (w); *1378(m); 1332 (m); 1304 (w); 1286 (w); 1230 (w); 1186 (w); 1158 (s, C-O stretching); 1126 (w); 1090 (w); 950 (w); 916 (w); 816 (w); 666 (w) cm^{-1}. [* indicates nujol peaks]



(86)

^{1}H NMR (acetone-d_6)

7,81 (2H, d, 8Hz, H-7); 7,43 (2H, d, 8Hz, H-8); 7,23 (1H, d, 9Hz, H-5); 5,13-5,00 (1H, m, H-3); 3,29 (1H, dd, 10Hz and 18Hz, H-2); 2,96 (1H, dd, 8Hz and 18Hz, H-2); 2,43 (3H, s, H-10).

^{13}C NMR (acetone-d_6)

171,1 (C-4), 169,1 (C-1); 144,67 (C-6); 139,03 (C-9); 130,65 (C-7); 127,79 (C-8); 53,42 (C-3); 36,60 (C-2); 21,43 (C-10).

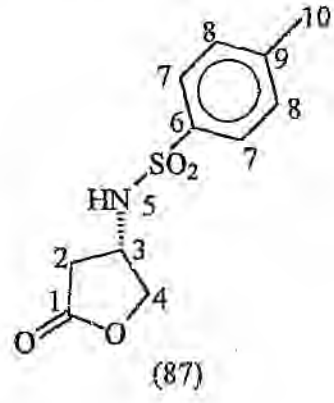
3. (3*S*)-3-(Tosylamino)-γ-butyrolactone (87)

The method of Bailey and Johnson[95] was used. A mixture of sodium borohydride (0,77g, 20,3mmol) and dry tetrahydrofuran (40ml) was stirred and cooled in an ice bath. (*S*)-N-Tosylaspartic anhydride (86) (4,4g, 16,3mmol) was added and the mixture stirred for 2 hours at room temperature. Hydrochloric acid (5M, 7ml) was added cautiously, causing effervescence. A white solid formed. The tetrahydrofuran was removed under vacuum and water (50ml) was added. The solid dissolved when dichloromethane (50ml) was added. The layers were separated and the aqueous layer washed with dichloromethane (25ml). The combined organic layers were evaporated to give an off-white solid (3,69g) which was purified by column chromatography on silica gel to yield **(3*S*)-3-(tosylamino)-γ-butyrolactone (87)** as a white solid (2,59g, 62%). R_f 0,80 (75% ethyl acetate in hexane), m.p. 110-113°C, $[\alpha]_D$ +15,4° (*c*1,12, EtOH). Lit[93] m.p. 112-113°C, $[\alpha]_D$ -15,7° (*c*1,0, EtOH) for the *R* configuration.

IR (nujol)

3278 (s); 3208 (m); 3088 (w); *2952 (s); *2924 (s); *2854 (s); 1772 (s, C=O); 1596 (w); *1460 (s); 1406 (w); *1378 (m); 1340 (s, SO_2-N); 1304 (m); 1290 (m); 1240 (w); 1198 (s, C-O stretch); 1160 (s, SO_2-N); 1092 (m); 1064 (m); 1016 (m); 1000 (s); 922 (w); 814 (m); 664 (m); 566 (s); 546 (s); 470 (s); 446 (s) cm^{-1}.

[* indicates nujol peaks]



(87)

^{1}H NMR ($CDCl_3$)

7,74 (2H, d, 8Hz, H-7); 7,33 (2H, d, 8Hz, H-8); 6,03 (1H, br s, H-5); 4,42-4,33 (1H, m, H-3); 4,20-4,08 (2H, m, H-4); 2,65 (1H, dd, 18 & 8Hz, H-2); 2,44 (3H, s, H-10); 2,35 (1H, dd, 5 & 18Hz, H-2).

^{13}C NMR ($CDCl_3$)

175,18 (C-1); 144,22 (C-6); 136,54 (C-9); 130,03 (C-7); 126,96 (C-8); 73,05 (C-4); 49,67 (C-3); 34,60 (C-2); 21,50 (C-10).

4. (3*S*)-Ethyl 4-iodo-3-(tosylamino)butanoate (88)

Method 1:

The methods of Jefford and Wang[90] and Kolb and Barth[96] were used. Iodotrimethylsilane (0,35ml), 0,49g, 2,5mmol) was added to a mixture of (3*S*)-3-(tosylamino)-γ-butyrolactone (87) (0,443g, 1,97mmol) and absolute ethanol (0,2ml, 0,16g, 4,9mmol) in dichloromethane (2ml) at 0°C under a nitrogen atmosphere. This was stirred at 0°C for 5 hours. The iodine coloured solution was evaporated under vacuum and judging by thin layer chromatography, 2 products were present. These were separated by flash column chromatography on silica gel. The desired iodo compound, **(3*S*)-ethyl 4-iodo-3-(tosylamino)butanoate (88)** (0,320g, 40%) was isolated as a white solid and an aziridine, **(2*S*)-1-(*p*-toluenesulphonyl)-2-ethoxycarbonylmethylaziridine (91)** was isolated as a yellow oil.

(3*S*)-Ethyl 4-iodo-3-(tosylamino)butanoate (88): R_f 0,26 (20% ethyl acetate in hexane), m.p. 59,0-60,5°C, $[\alpha]_D$ -7,43° (*c*0,90, $CHCl_3$). Lit[90]. m.p. 59,0-60,0°C, $[\alpha]_D$ -7,59° (*c*0,87, $CHCl_3$).

(2*S*)-1-(*p*-Toluenesulphonyl)-2-ethoxycarbonylmethylaziridine (91): R_f 0,19 (20% ethyl acetate in hexane), $[\alpha]_D$ -9,09° (*c*1,21, EtOH).

Method 2:

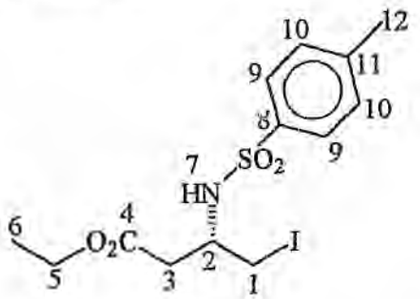
The method of Jefford and McNulty[93] was used. To a solution of (3*S*)-3-(tosylamino)-γ-butyrolactone (87) (0,504g, 1,97mmol) in dry dichloromethane (7ml) at 0°C under a nitrogen atmosphere was added iodotrimethylsilane (0,75ml, 1,1g, 5,3mmol) and absolute ethanol (0,55ml, 0,43g, 9,3mmol). The mixture was stirred at room temperature for 6 hours and further aliquots of iodotrimethylsilane (0,75ml, 1,1g, 5,3mmol) and absolute ethanol (0,55ml, 0,43g, 9,3mmol) were added. This was stirred at room temperature overnight. Ethanol (2ml) was added and after 30 minutes the mixture was partitioned between water (20ml) and dichloromethane (20ml). The aqueous layer was extracted with dichloromethane (3x20ml). The combined organic phases were washed with 5% $Na_2S_2O_3$ solution

to remove traces of iodine, dried ($MgSO_4$) and evaporated to give a white solid and an oil. Purification by column chromatography on silica gel yielded **(3*S*)-ethyl 4-iodo-3-(tosylamino)butanoate (88)** as a white solid (0,714g, 88%). R_f 0,35 (20% ethyl acetate in hexane), m.p. 59,0-60,5°C, $[\alpha]_D$ -7,43° (c0,90, $CHCl_3$). Lit. 59,0-60,0°C, $[\alpha]_D$ -7,59° (c0,87, $CHCl_3$)[90].

(3*S*)-Ethyl 4-iodo-3-(tosylamino)butanoate (88):

IR ($CHCl_3$)

3362 (w); 3030 (w); 2986 (w); 1726 (s, C=O); 1598 (w); 1444 (w); 1414 (m); 1378 (m); 1340 (m); 1306 (w); 1290 (w); 1276 (w); 1230 (m); 1200 (m); 1186 (m); 1160 (s, C-O stretch); 1118 (w); 1092 (m); 1060 (w); 1024 (w); 954 (w); 870 (w); 814 (w); 782 (w); 772 (w); 740 (w); 662 (m); 580 (w); 550 (m, C-I); 518 (w), 480 (w); 444 (w); 424 (m); 406 (m) cm^{-1}.



(88)

^1H NMR ($CDCl_3$)

7,77 (2H, d, 8Hz, H-9); 7,32 (2H, d, 8Hz, H-10); 5,48 (1H, br d, H-7); 4,06 (2H, dq, 3 & 7Hz, H-5); 3,63-3,50 (1H, m, H-2); 3,34 (1H, dd, 4 & 10Hz, H-1); 3,24 (1H, dd, 7 & 10Hz, H-1); 2,69 (1H, dd, 5 & 17Hz, H-3); 2,55 (1H, dd, 6 & 17Hz, H-3); 2,43 (3H, s, H-12); 1,21 (3H, t, 7Hz, H-6).

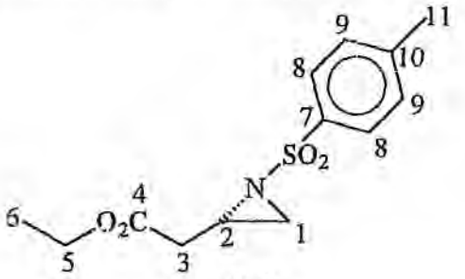
^{13}C NMR ($CDCl_3$)

170,23 (C-4); 143,67 (C-8); 137,28 (C-11); 129,69 (C-9); 126,96 (C-10); 60,97 (C-5); 50,41 (C-2); 38,88 (C-3); 21,45 (C-12); 13,92 (C-6); 10,56 (C-1).

(2*S*)-1-(*p*-Toluenesulphonyl)-2-ethoxycarbonylmethylaziridine (91):

IR (neat)

2984 (m); 2930 (m); 1734 (vs, C=O); 1598 (m); 1494 (w); 1454 (m); 1402 (s); 1368 (s, SO_2-N); 1324 (vs); 1258 (s); 1244 (s); 1186 (s); 1160 (vs, SO_2-N); 1092 (s); 1060 (w); 1028 (s); 986(m); 962 (m); 918 (s); 882 (m); 860 (s); 816 (s); 714 (s); 692 (s), 658 (m); 634 (w); 566 (m); 470 (w); 420 (w) cm^{-1}.



(91)

^{1}H NMR ($CDCl_3$)

7,83 (2H, d, 8Hz, H-8); 7,34 (2H, d, 8Hz, H-9); 4,06 (2H, q, 7Hz, H-5 ; 3,14-3,04 (1H, m, H-2); 2,71 (1H, d, 7Hz, H-3); 2,48 (2H, dd, 3 & 6Hz, H-1); 2,45 (3H, s, H-11); 2,16 (1H, d, 4Hz, H-3); 1,21 (3H, t, 7Hz, H-6).

^{13}C NMR ($CDCl_3$)

169,67 (C-4); 144,57 (C-7); 134,72 (C-10); 129,61 (C-8); 128,04 (C-9); 60,94 (C-5); 36,62 (C-3); 35,80 (C-2); 32,70 (C-1); 21,58 (C-11); 14,02 (C-6).

Mass spectrum

56 (12); 65 (11); 77 (5); 82 (19); 91 (39, $^+C_6H_4CH_3$); 100 (19); 128 (100, M^+ - $SO_2C_6H_4CH_3$); 155 (17,); 210 (2, M^+ - CO_2Et); 238 (4, M^+ - OEt); 183 (1, M^+).

Accurate mass. Found: M^+, 283,0864.

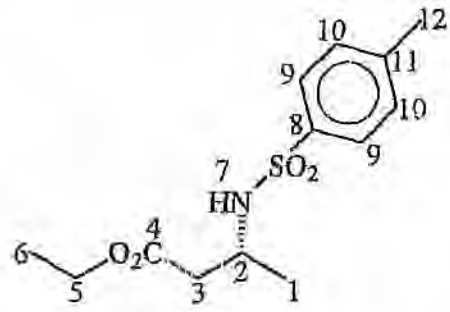
$C_{13}H_{17}NO_4S$ requires 283,0878.

5. (3*S*)-Ethyl 3-(tosylamino)butanoate (89)

The method of Jefford and Wang[90] and Vo Quang[101] was used. A mixture of (3*S*)-ethyl 4-iodo-3-(tosylamino)butanoate (88) (640mg, 1,6mmol), tributyltin hydride (0,60ml, 0,65g, 2,2mmol) and benzene (15ml) was heated under reflux for 5 hours and stirred overnight. Judging by thin layer chromatography not all the starting material had been consumed so the mixture was heated under reflux for a further 5 hours. The solvent was removed under reduced pressure and the residue dissolved in acetonitrile (25ml). The solution was washed with hexane (5x15ml) to remove the tin residues and evaporated under reduced pressure to yield a yellow oil. This was purified by column chromatography on silica gel to yield **(3*S*)-ethyl 3-(tosylamino)butanoate (89)** (0,286g, 65%). R_f 0,21 (20% ethyl acetate in hexane). $[\alpha]_D$ +26,9° (*c*1,00, $CHCl_3$), Lit.[90] $[\alpha]_D$ +28,1° (*c*1,05, $CHCl_3$).

IR (neat):

3282 (m); 3092 (w); 3064 (w); 3030 (w); 2982 (m); 2936 (w); 2876 (w); 1732 (s, C=O); 1666 (w); 1634 (w); 1598 (w); 1494 (w); 1426 (m); 1398 (m); 1374 (m); 1330 (s); 1306 (s); 1294 (s); 1256 (m); 1188 (s); 1162 (s); 1090 (s); 1028 (m); 996 (m); 950 (w); 916 (m); 884 (w); 854 (w); 816 (m); 710 (s), 666 (s); 552 (s); 468 (s); 450 (s); 438(*s*) cm^{-1}.



(89)

^1H NMR ($CDCl_3$)

7,77 (2H, d, 8Hz, H-9); 7,30 (2H, d, 8Hz, H-10); 5,36 (1H br d, 1Hz, H-7); 4,13-4,00 (2H, m, H-5); 3,72-3,65 (1H, m, H-2); 2,50-2,40 (2H, m, H-3); 2,42 (3H, s, H-11); 1,22 (3H, t, 7Hz, H-6); 1,14 (3H, d, 7Hz, H-1).

^{13}C NMR ($CDCl_3$)

171,09 (C-4); 143,25 (C-8); 137,90 (C-11); 129,61 (C-9); 126,99 (C-10); 60,64 (C-5); 46,54 (C-2); 40,71 (C-3); 21,43 (C-12); 20,93 (C-1); 14,02 (C-6).

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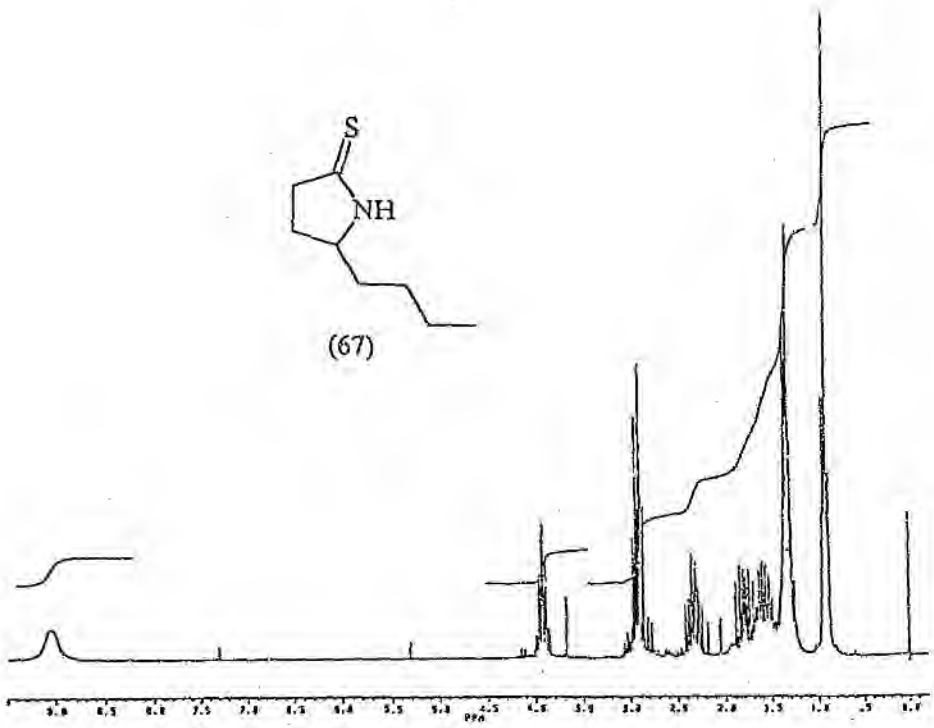
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APPENDIX

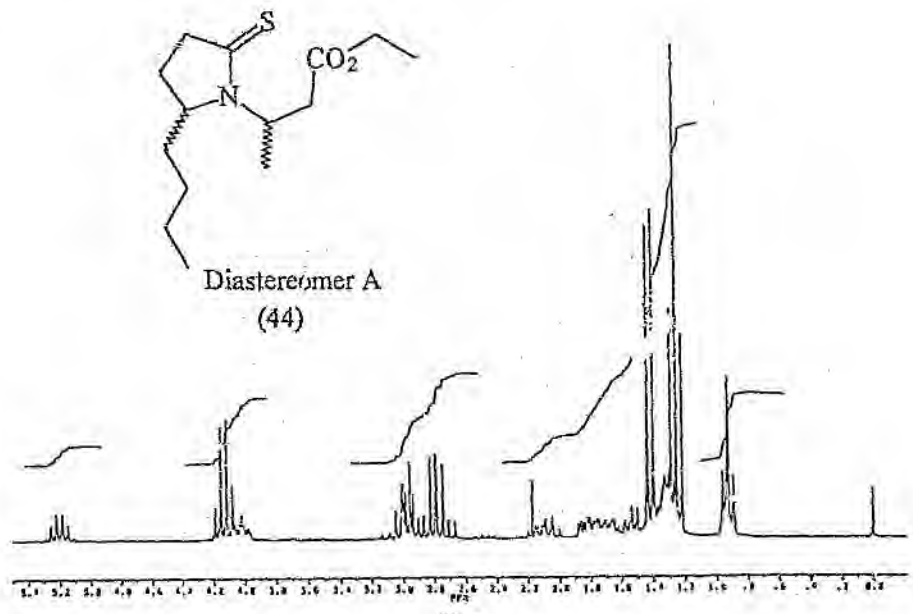
^{1}H, ^{13}C, ^{13}C-^{1}H correlation and DEPT spectra are included in this appendix. Chemical shifts for the spectra are reported on the δ scale.

Spectrum	Compound	Page
H-1, C-1	5-Butylpyrrolidine-2-thione (67)	144
H-2, C-2	Diastereomer A of 5-butyl-1-(2-ethoxycarbonyl-1-methylethyl)pyrrolidine-2-thione (44)	144
H-3, C-3, Corr-3	Diastereomer B of 5-butyl-1-(2-ethoxycarbonyl-1-methylethyl)pyrrolidine-2-thione (44)	145
H-4, C-4	(*E*)-5-Butyl-1-(2-ethoxycarbonyl-1-methylethyl)-2-ethoxycarbonylmethylenepyrrolidine (45)	146
H-5, C-5	*cis*-9-Butyl-5-ethoxycarbonyl-2-methyl-1-azabicyclo-[4.3.0]non-5-en-4-one (46)	146
H-6, C-6 Corr-6	*trans*-9-Butyl-5-ethoxycarbonyl-2-methyl-1-azabicyclo-[4.3.0]non-5-en-4-one (46)	147
H-7, C-7	*trans*-9-Butyl-2-methyl-1-azabicyclo[4.3.0]non-5-en-4-one (48)	148
H-8, C-8	(2*S*)-1-(*p*-Toluenesulphonyl)-2-ethoxycarbonylmethyl-aziridine (91)	148
H-9, C-9 Corr-9, DEPT-9	(*S*)-(+)-(2-Oxopyrrolidin-5-yl)methyl 3-butanoate (74)	149
H-10, C-10	(*S*)-(+)-(2-Oxopyrrolidin-5-yl)methyl 2-butanoate (72)	150
H-11, C-11	(*S*)-(+)-(2-Thioxopyrrolidin-5-yl)methyl 3-butanoate (59)	150
H-12, C-12 Corr-12	Ethyl 3-(4-oxooctanoylamino)butanoate (51)	151



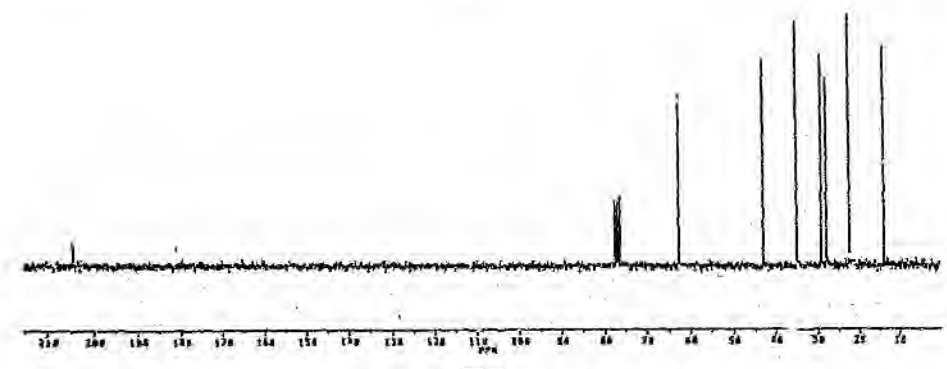
(67)

H-1

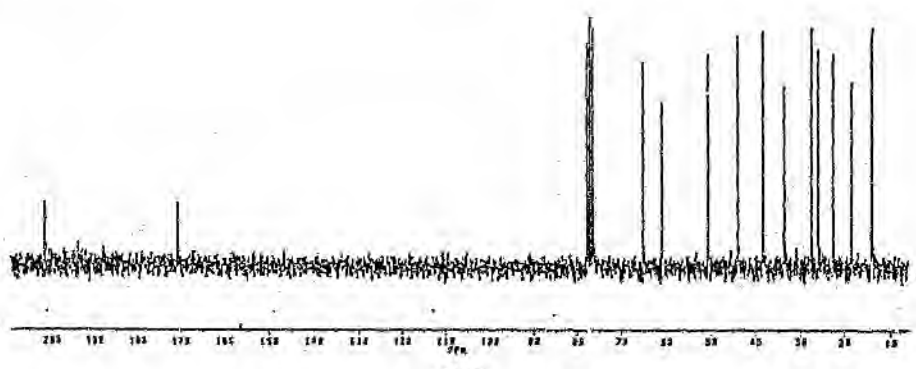


Diastereomer A
(44)

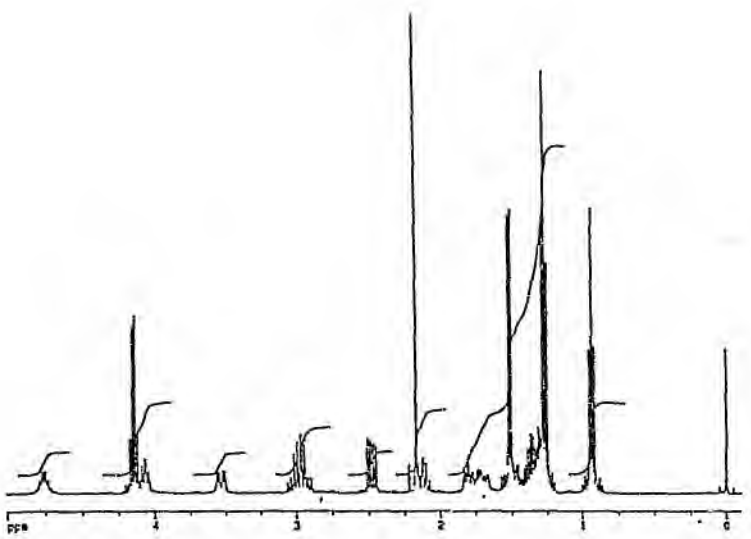
H-2



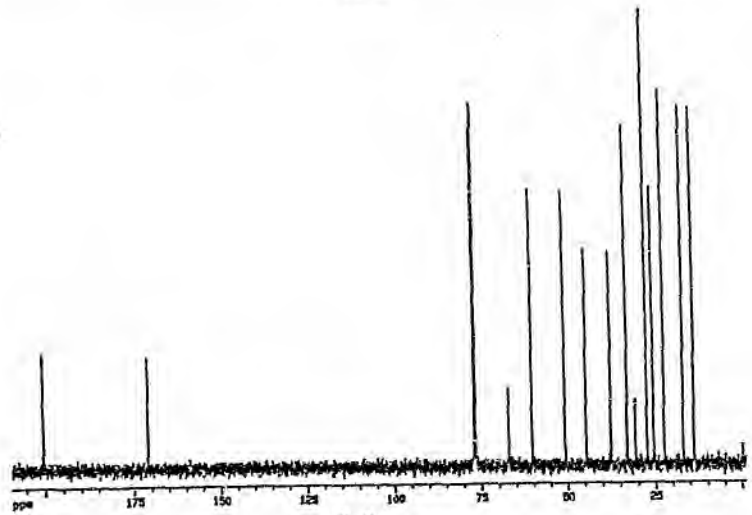
C-1



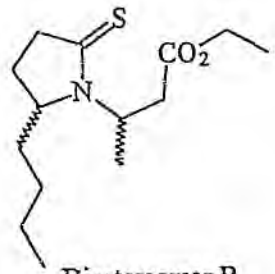
C-2



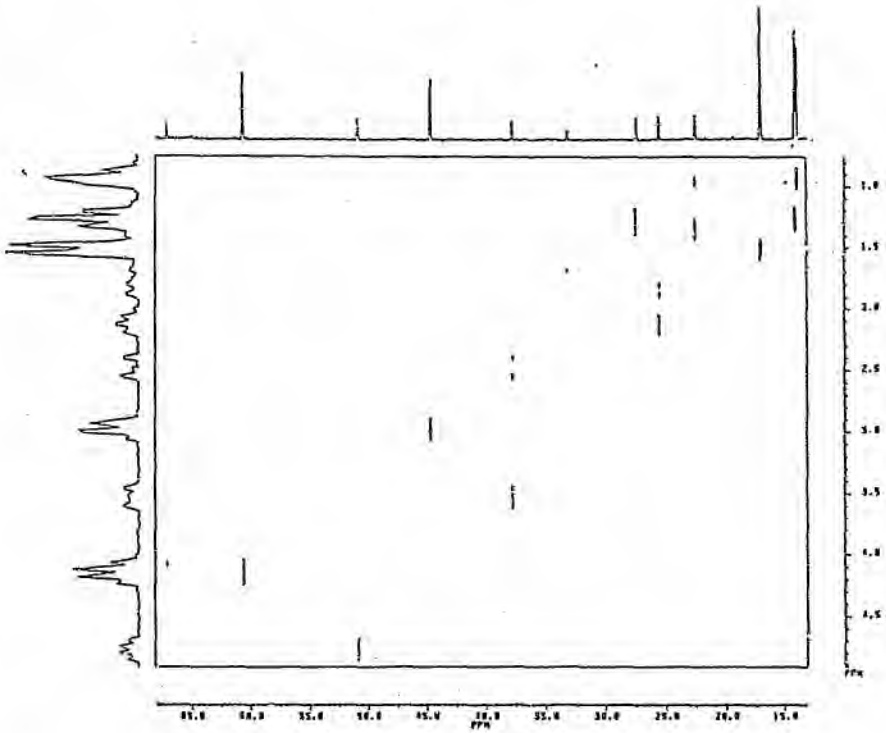
H-3



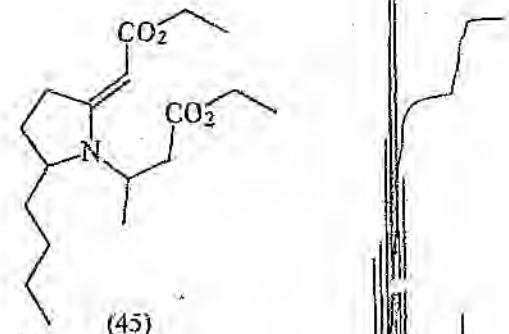
C-3



Diastereomer B
(44)

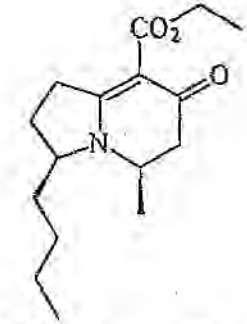


Corr-3



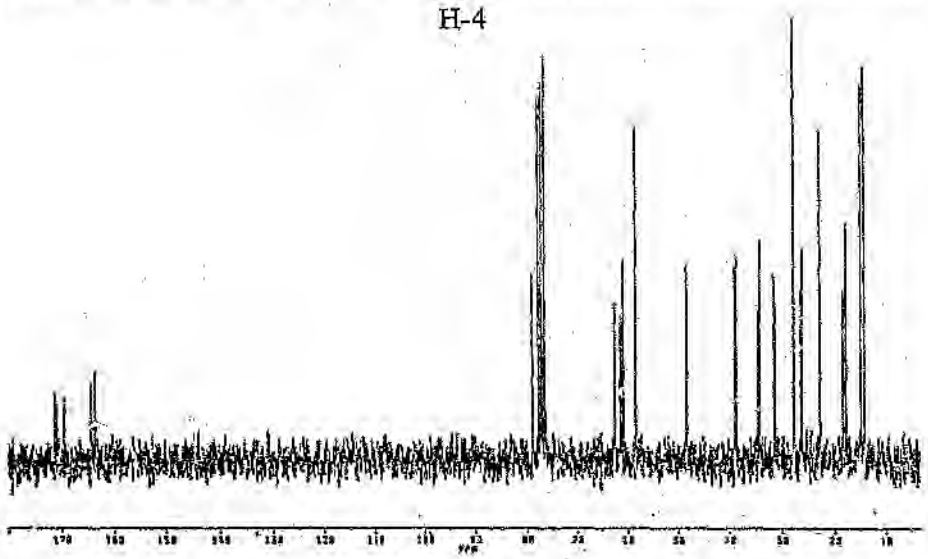
(45)

H-4

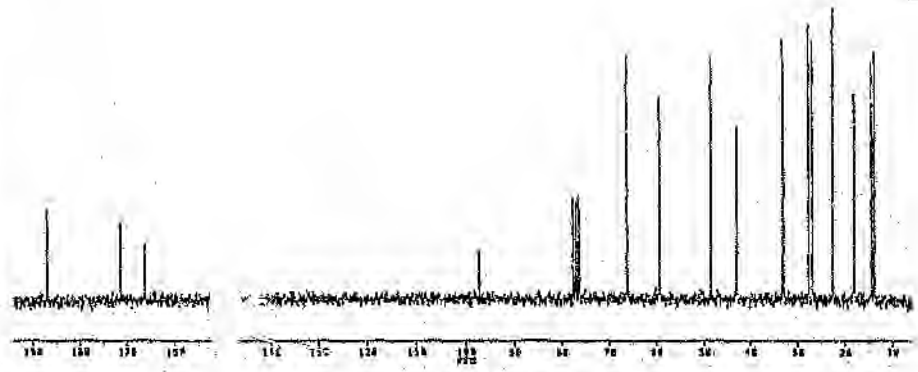


(relative stereochemistry)
Cis-(46)

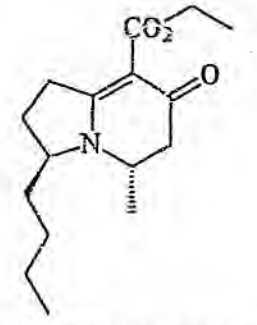
H-5



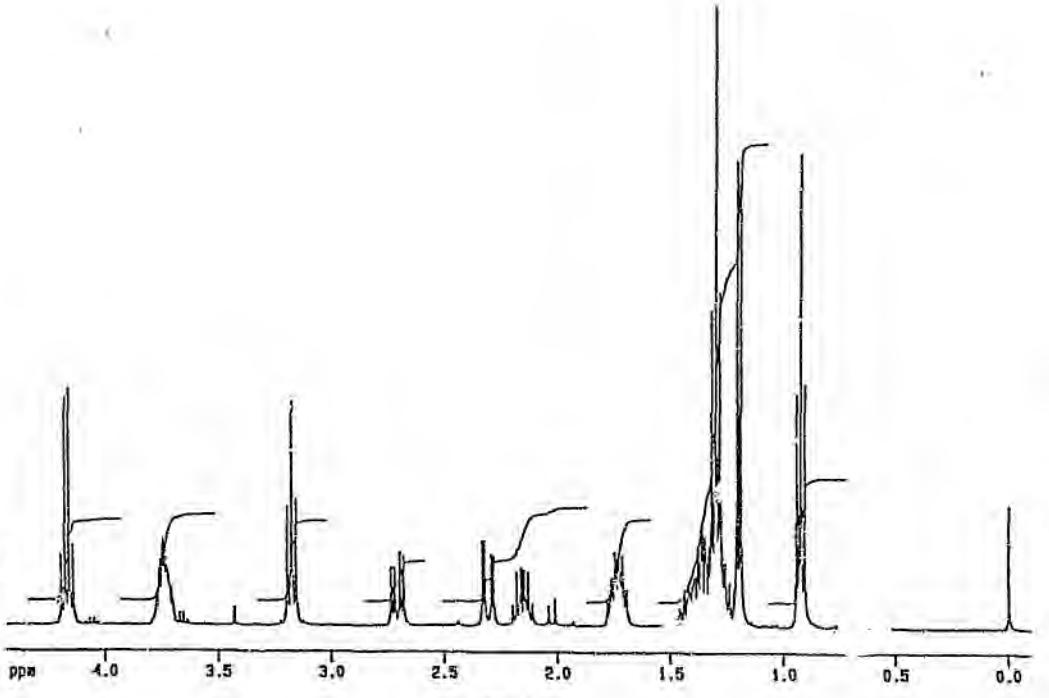
C-4



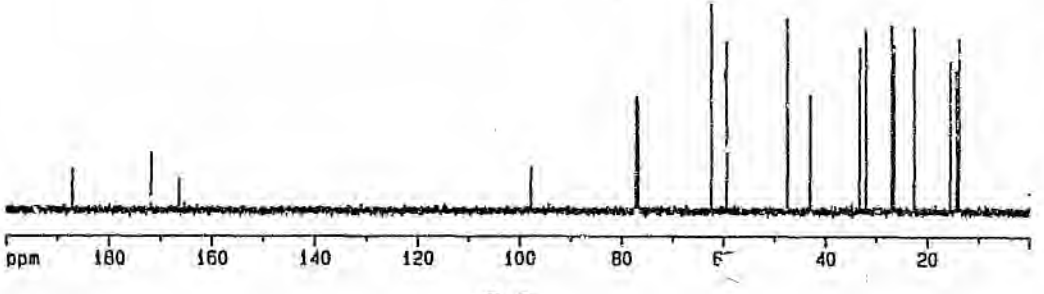
C-5



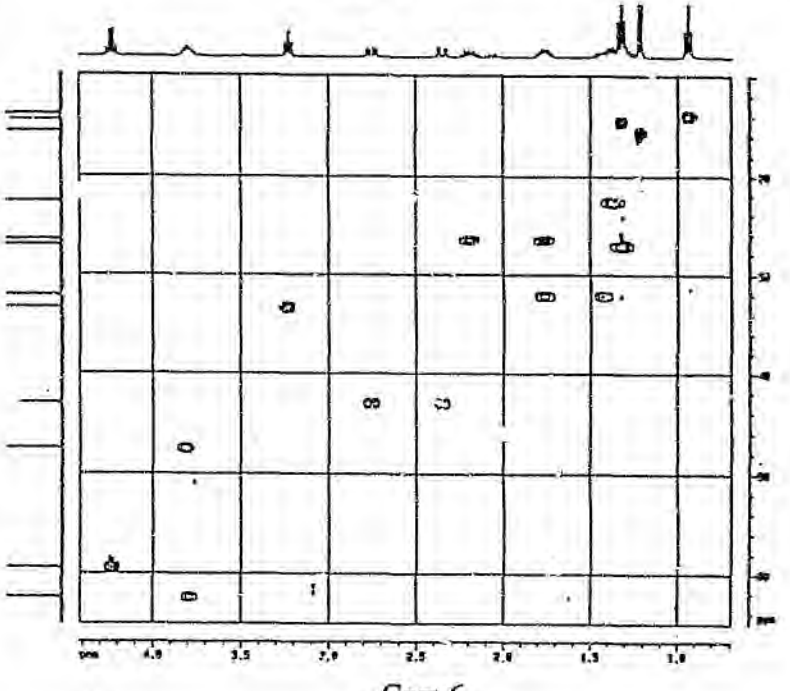
(relative stereochemistry)
Trans-(46)



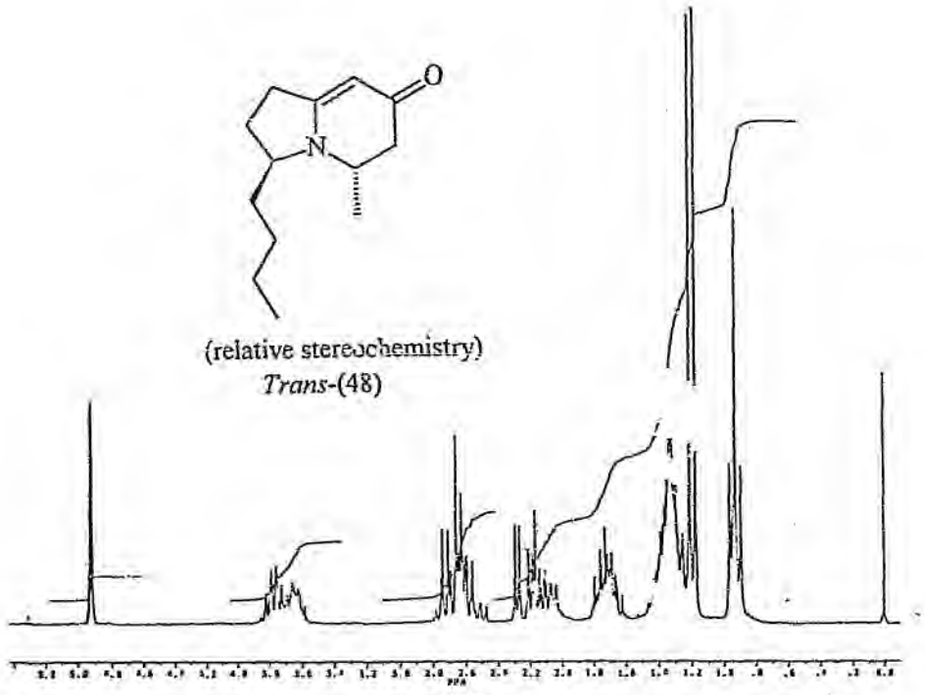
H-6



C-6

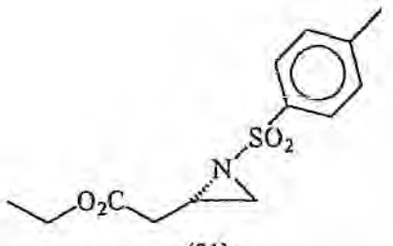


Corr-6



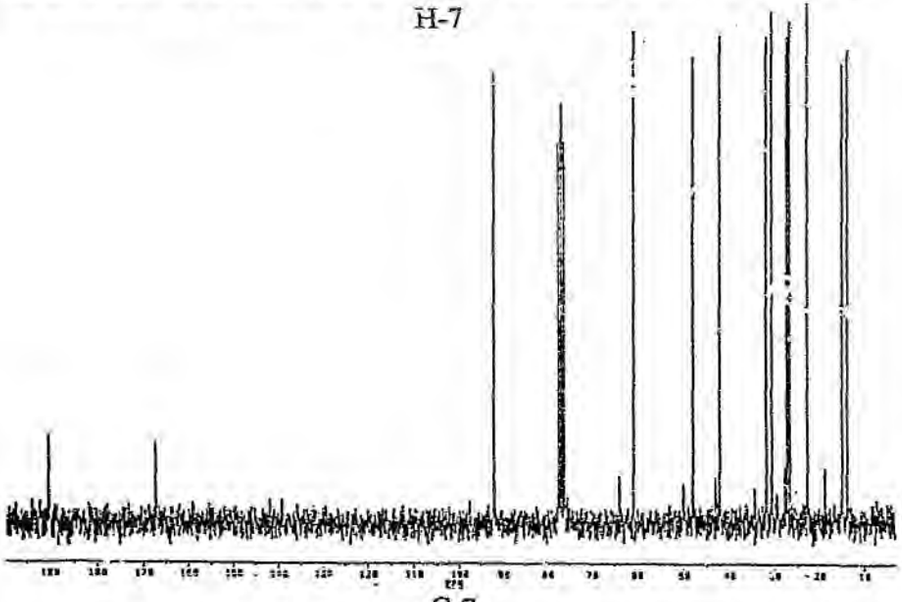
(relative stereochemistry)
Trans-(48)

H-7

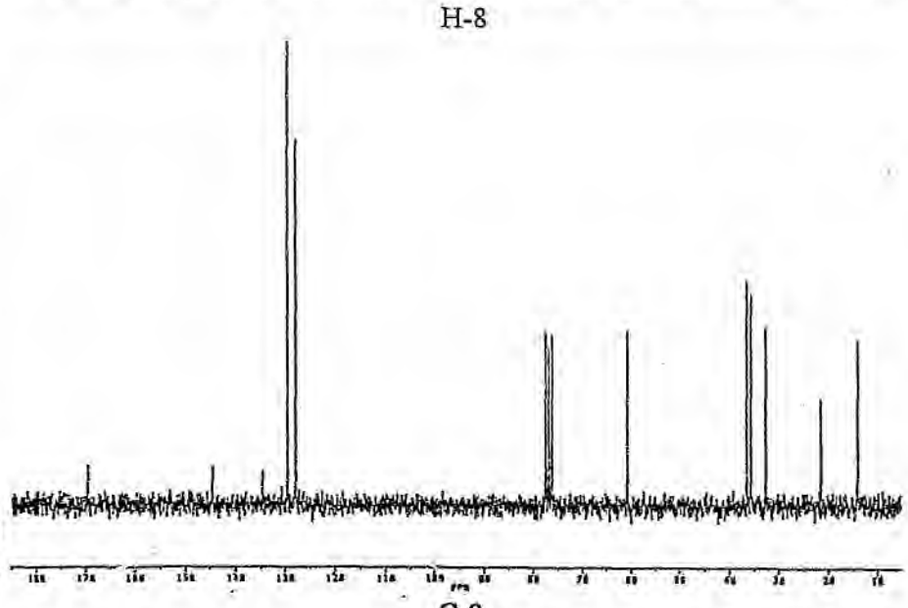


(91)

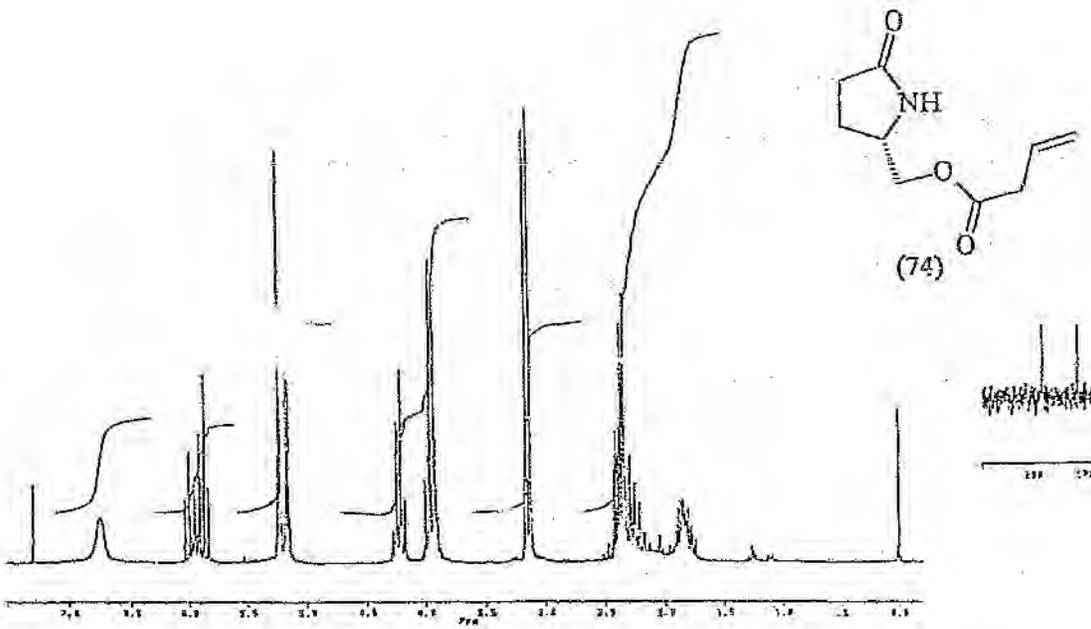
H-8



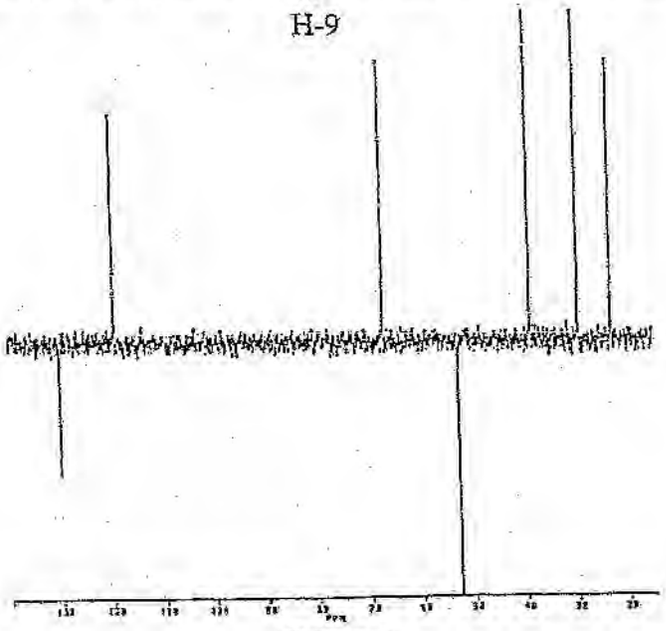
C-7



C-8

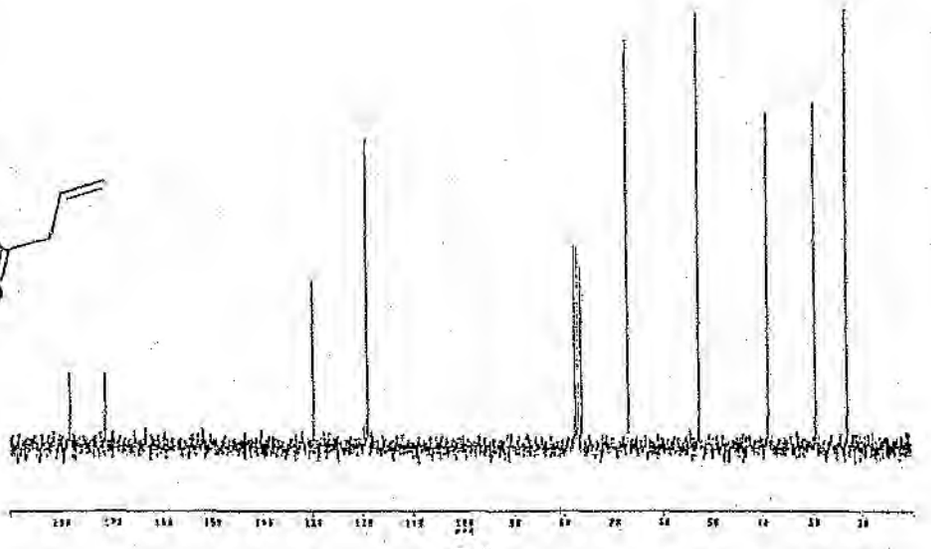


H-9

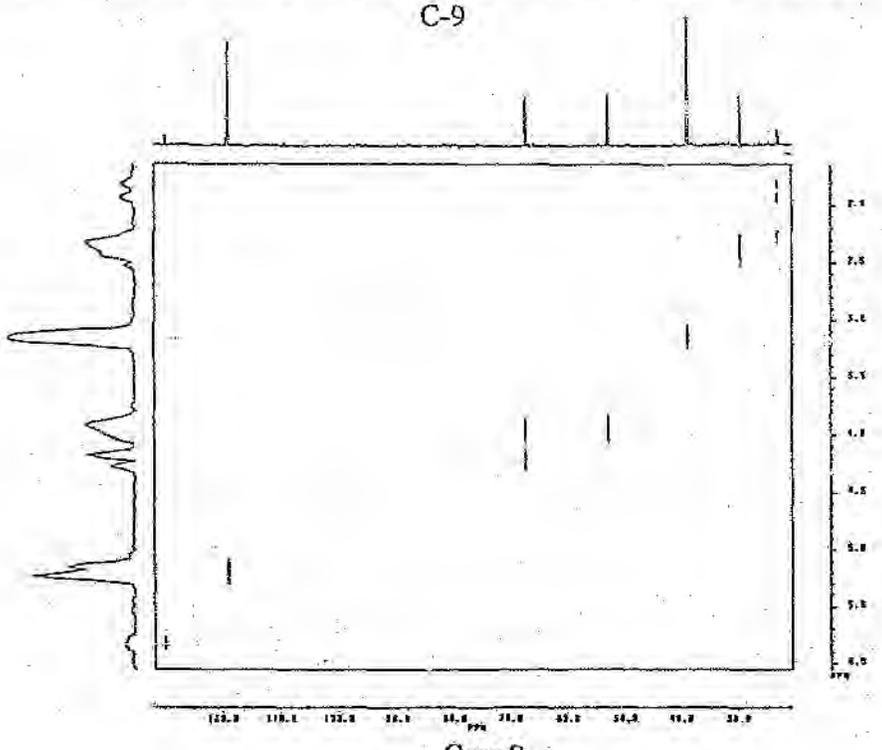


DEPT-9

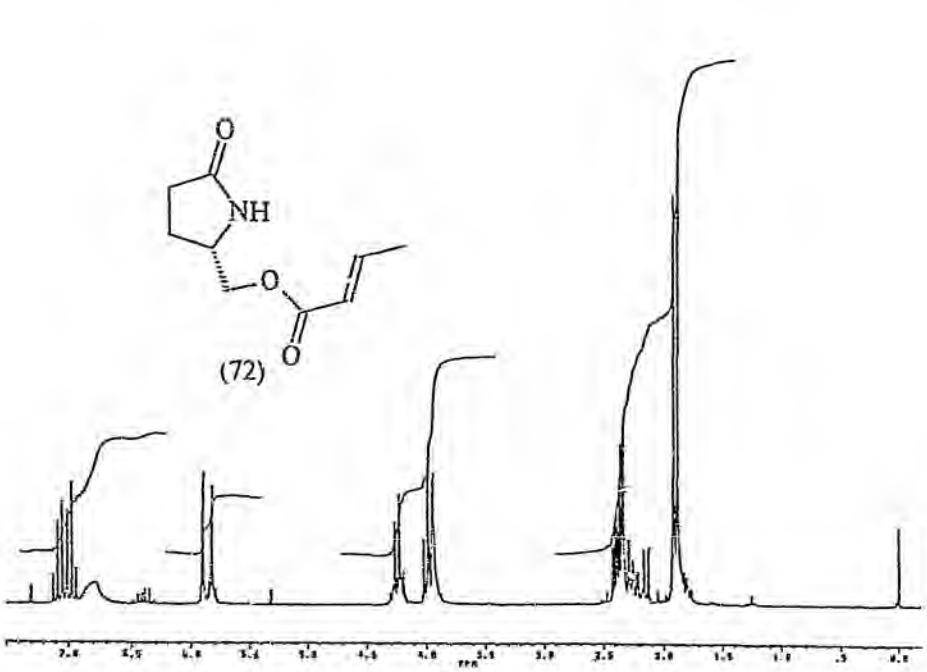
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C-9

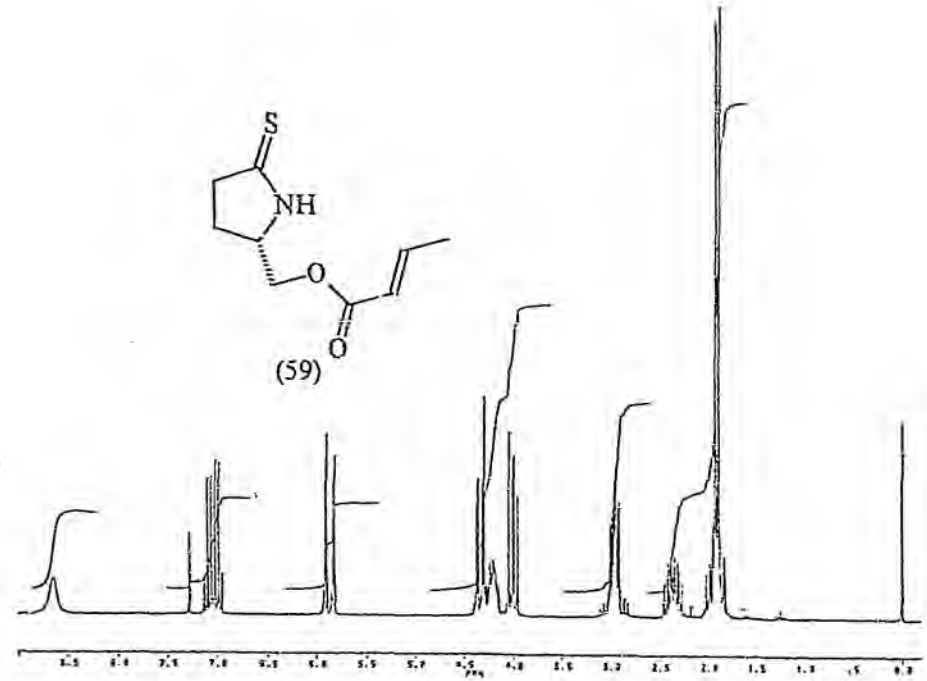


Corr-9



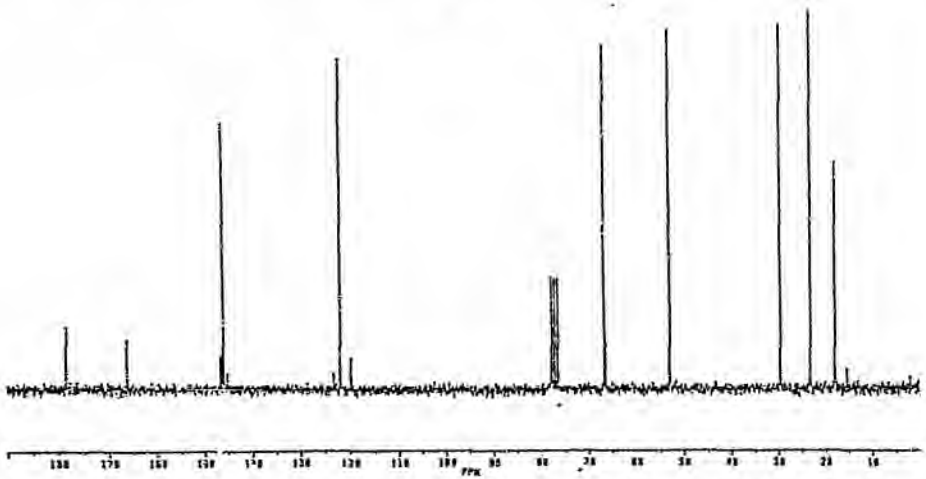
(72)

H-10

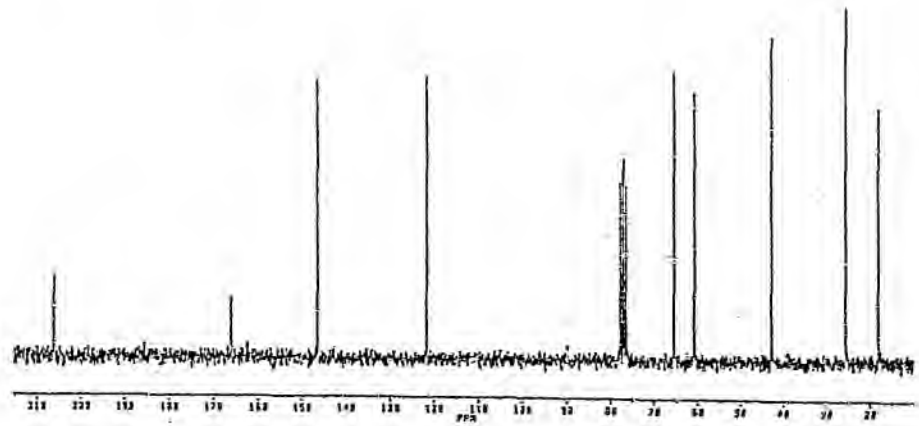


(59)

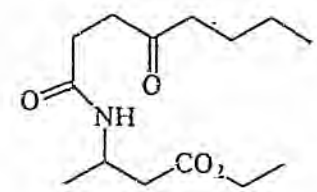
H-11



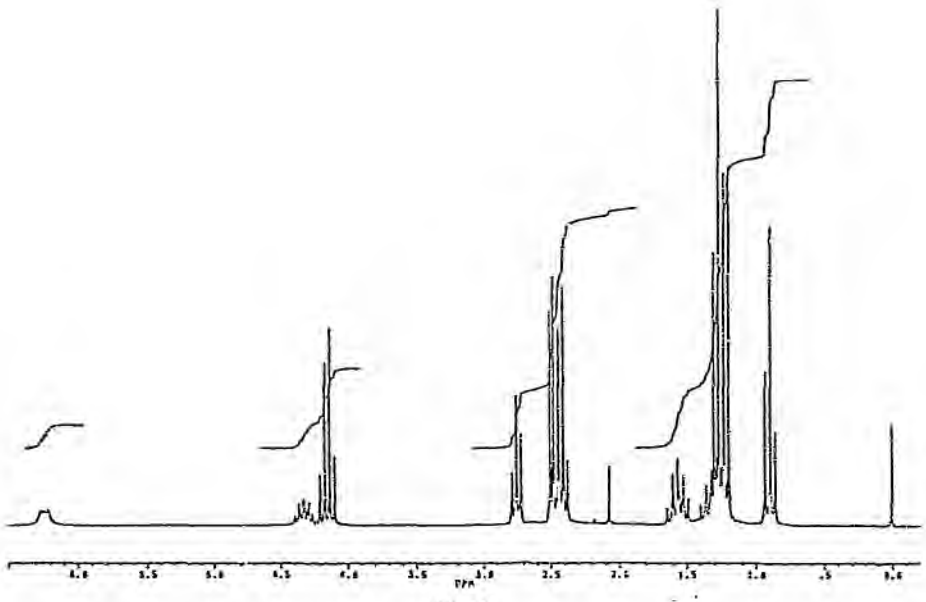
C-10



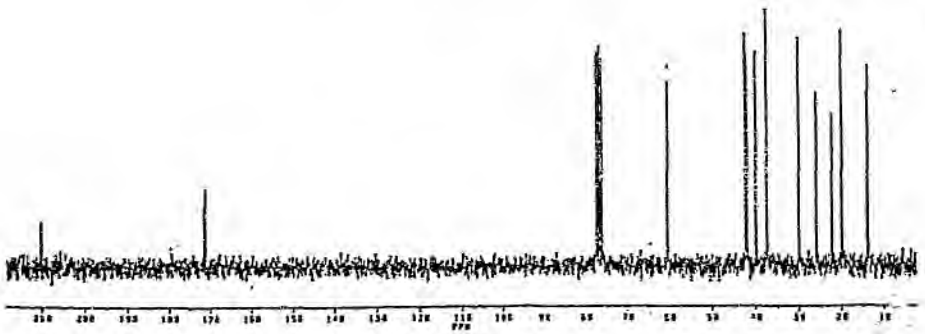
C-11



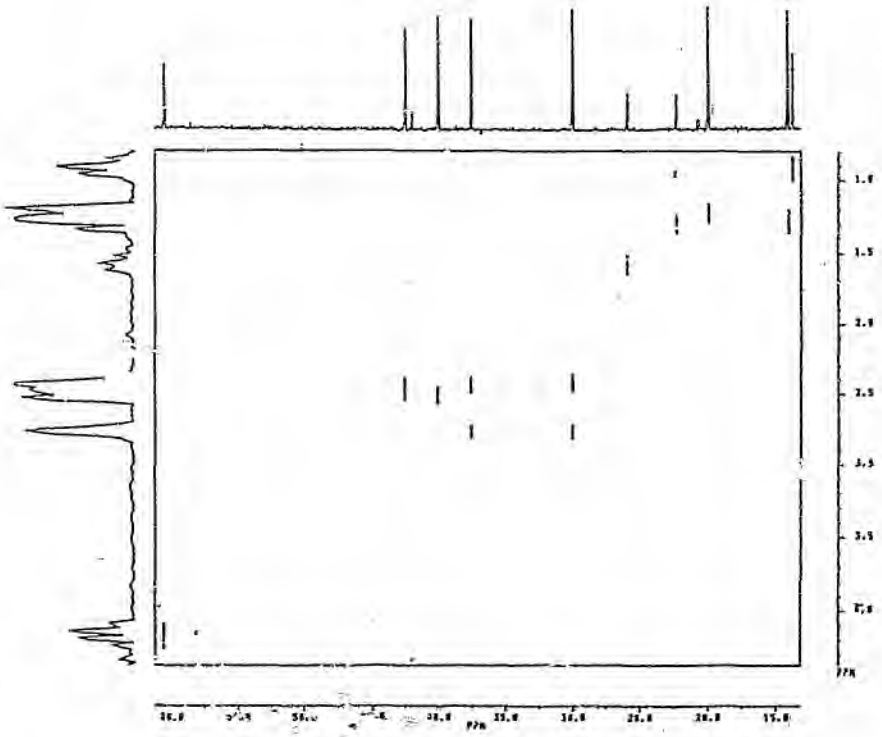
(51)



H-12



C-12



гг-12

Author: Cheesman Penelope Sue.
Name of thesis: The synthesis of 3,5-disubstituted indolizidines.

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