SYNTHETIC STUDIES TOWARDS PYRROLIZIDINE AND INDOLIZIDINE ALKALOIDS

BY

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A thesis submitted to the Council of National Academic Awards in partial fulfilment of the requirements for the degree of Doctor of Philosophy

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Collaborating establishment : Glaxo Group Research, Ware

July 1992

ABSTRACT

This project was concerned with the synthesis of the pyrrolizidine alkaloids supinidine, trachelanthamidine and isoretronecanol and also synthetic studies towards the indolizidine alkaloid 251D. In all cases, the synthesis began from a cheap, readily-available, simple amino acid, in this case glutamic acid, and proceeded to a suitable monocyclic intermediate which could then undergo an intramolecular Horner-Wittig cyclisation reaction to form the required bicyclic core structure. Subsequent modification reactions then led in the pyrrolizidine series to penultimate precursors of the target alkaloids supinidine, trachelanthamidine and isoretronecanol, and in the indolizidine series to a bicyclic intermediate in the synthesis towards the toxin 251D. The intramolecular Horner-Wittig cyclisation reaction was found to proceed with retention of chirality, thus leading to the enantiospecific synthesis of the pyrrolizidine alkaloids. The use of alternative monocyclic intermediates in the intramolecular Horner-Wittig cyclisation reaction, thus leading to other pyrrolizidine alkaloids is also discussed.

One of the major problems encountered in this project was the solubility of the unprotected monocyclic amide intermediates, and this was overcome by the use of N-benzyl and N-carbobenzyloxy protecting groups; in the indolizidine synthesis where the unprotected monocyclic amides were necessary, the reaction work-up for these intermediates usually required continuous solvent extraction. Another major problem was the instability of the bicyclic amide intermediates and some of the monocyclic intermediates.

As well as covering a comprehensive background of each class of alkaloid, this report also contains an in-depth discussion of the key intramolecular Horner-Wittig cyclisation reaction and suggestions for its use in the possible synthesis of other classes of alkaloids.

CONTENTS

Conventions

A solid line		denotes a β configuration
A broken line		denotes an α configuration
A wavy line		denotes either an α or a β configuration

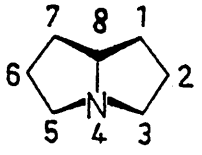
INTRODUCTION

The alkaloids constitute a very large, miscellaneous group of natural products. They all contain at least one nitrogen atom, which is usually of a basic character and which, in the large majority of cases, makes up part of a heterocyclic ring. Alkaloids exhibit a wide range of biological and pharmaceutical activities and thus have attracted much attention. Isolation from natural sources has often proved very difficult and produced the alkaloid in very low yield, and a lot of interest has focussed on their chemical synthesis.

This project is concerned with the synthesis of the pyrrolizidine alkaloids supinidine, trachelanthamidine and isoretronecanol and the indolizidine alkaloid 251D. In all cases the synthesis begins with a cheap, readily-available, simple amino acid and proceeds thereon to a suitable monocyclic intermediate which could then undergo an intramolecular Horner-Wittig type cyclisation reaction to form the bicyclic core structure. Subsequent modification reactions then proceed towards the target alkaloids.

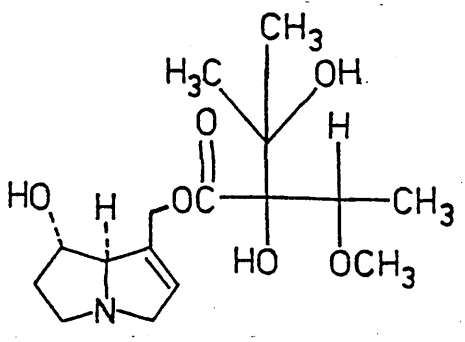
1.1. General

The pyrrolizidine alkaloids are a large class of natural products which is very broadly distributed throughout the plant and animal kingdoms. They exhibit a vast range of biological activity, including anti-tumour, hypotensive, local anaesthetic, anti-spasmotic, anti-inflammatory, carcinogenic, hepatotoxic and especially neurotoxic action[1]. All the pyrrolizidine alkaloids possess the core skeletal structure:

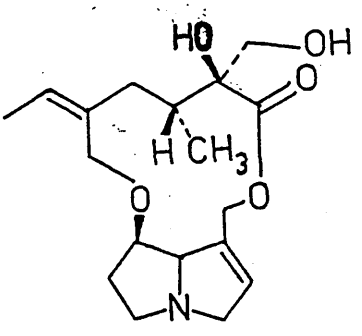


1-Azabicyclo(3.3.0)octane

Naturally-occurring pyrrolizidine alkaloids usually exist as alcohols ("necine" bases) esterified with a carboxylic acid ("necic acid") that normally contains a hydroxyl substituent; as in the cases of europine and retrorsine.



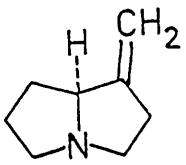
europine



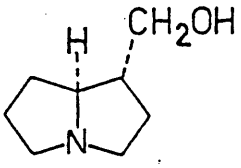
retrorsine

The pyrrolizidine alcohols can be monohydric, dihydric or trihydric.

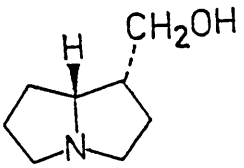
1-methylene pyrrolizidine and related compounds can occur in the free state and hence are termed "non-ester" pyrrolizidine alkaloids[2].



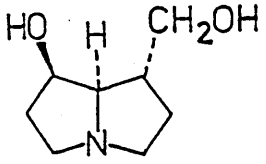
1-methylenepyrrolizidine



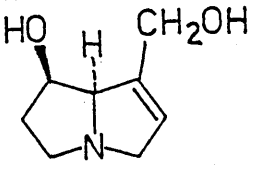
trachelanthamidine



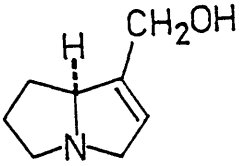
lindelofidine



turneforcidine



retronecine



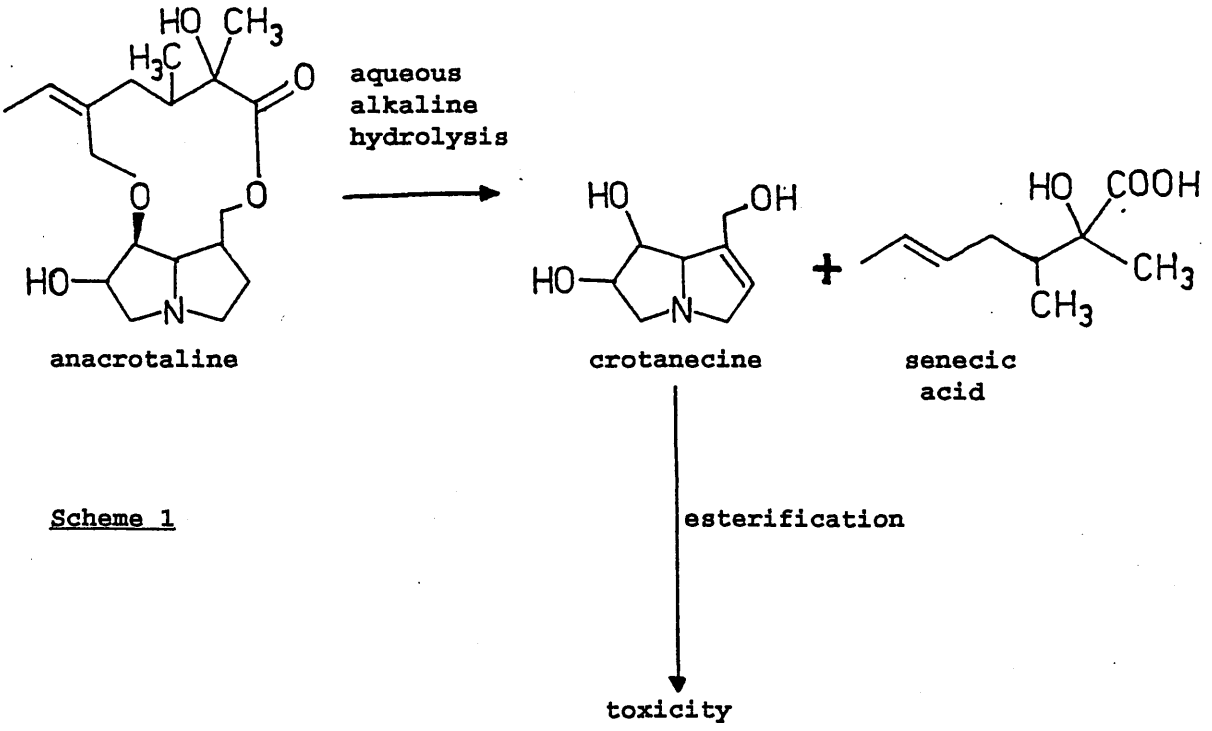
supinidine

A few pyrrolizidine alkaloids have been isolated from plants in their naturally-occurring N-oxide form; one example is isatidine (retrorsine N-oxide)[1,2].

Pyrrolizidine alkaloids have been identified in several genera of the plant families of *Compositae*, *Leguminosae*, *Boraginaceae*, *Euphorbaceae*, *Glumiflorae*, *Fabaceae* and many others[1]. These plants can grow in temperate, sub-tropical and tropical climates. Most are spring or summer annuals, but some are biennial or perennial[1]. They are mainly herbacious species such as *Senecio*, *Crotalaria* and *Amsinckia*, in which the alkaloid content reaches a maximum at the onset of flowering[3], and include a few shrubs and climbers and a small number of trees[2].

There are few areas in the world where grazing animals are not exposed to one or more pyrrolizidine-containing species. The pyrrolizidines attack the animal's nervous system, and have accounted for heavy losses in livestock. Hay and silage made from

Senecio alpinus retained constantly high levels of pyrrolizidine alkaloids for several months after harvest; the content decreased steadily with time in silage. The principal alkaloid present was retronecine[1,3]. The alkaloid itself need not necessarily be toxic, but a metabolite of it can be, as in the case of anacrotaline; the induced disease is characteristically chronic, and death can occur months after consumption of the alkaloid has ceased[3,4].

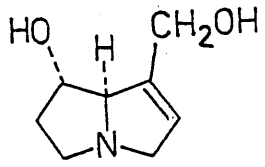


Scheme 1

Anything which stimulates plant growth also increases alkaloid production, which is maximal in alkaline soils[1c] (eg limestone, chalk, clay).

Culvenor has stressed that the presence of toxic pyrrolizidine alkaloids in many Australian weeds that grow amongst natural grasses constitutes a major health hazard to both livestock and humans. The toxicity depends on their conversion into reactive pyrrole metabolites[5].

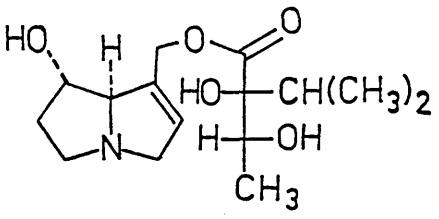
Culvenor suggested that the alkaloids evolved as relatively inert compounds which can be mobilised at short notice to repel microbial infections (ie they are phytoalexins[1,3]), and also herbivores. Especially potent neurotoxins were macrocyclic diesters of retronecine, monocrotaline, fulvine and heliotridine.



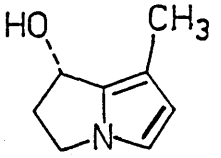
heliotridine

Two examples of plants producing such toxic alkaloids are *Senecio douglasii* var *longilobus* (threadleaf groundsel) and *Senecio riddelli* (Riddell's groundsel) which are very common grassland weeds in the South-Western United States of America[3]. Toxic pyrrolizidine alkaloids were also found in fresh shoots of *Crotalaria saltiana* fed to Nubian goats and in the seeds of *Crotalaria spectabilis* fed to turkeys[4]. Apart from esterification at the C-9 carbon, the other major feature deemed necessary for toxicity is the 1,2 double bond[5b].

Not all pyrrolizidines are toxic, however, and some have useful properties exploited by man and nature. Many plant species that contain them attract butterflies and moths (*Lepidopterae*) to feed, and some of these insects convert pyrrolizidines such as heliotrine into pyrrolizines such as hydroxydanaidal which function as pheromones[3].



heliotrine

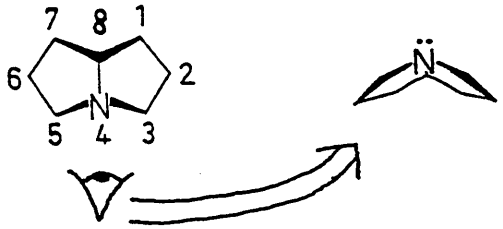


hydroxydanaidal

The basic pyrrolizidine skeletal structure, 1-azabicyclo(3.3.0)octane, and simple alkylpyrrolizidines are used as catalysts for the preparation of polymers and resins[5a].

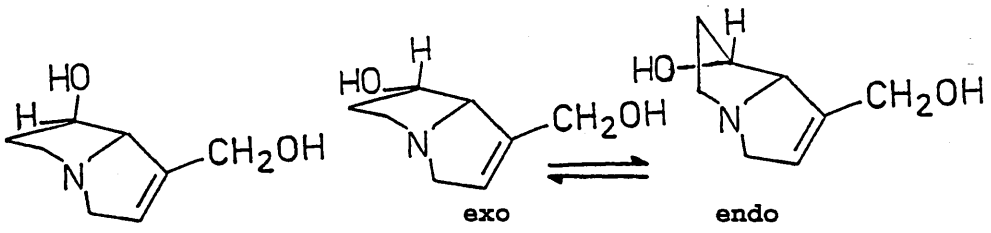
1.2 Pyrrolizidine Stereochemistry

The trans bicyclo(3.3.0)octane skeleton is a rigid and strained system but its cis isomer is virtually strain-free[6]. The trivalent nitrogen present in the pyrrolizidine skeleton does not rigidly fit the bicyclic system, and so there are no diastereoisomers of the fused ring system[6]. The two rings of the pyrrolizidine system form a dihedral angle with the axis along the C(8)-N bond:



Pyrrolizidine derivatives with at least one substituent, and particularly the pyrrolizidine alkaloid components, have at least two asymmetric carbon atoms, one of these being C(8) at the bis ring junction.

Retronecine was concluded to exist preferentially in an exo-buckled form whereas heliotridine was a mixture of rapidly interconverting exo- and endo-buckled forms[7]:

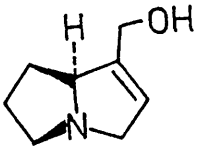


retronecine heliotridine

Torsional strain and non-bonded, steric interactions cause puckering of the saturated 5-membered ring system, whilst the unsaturated ring system has virtual planarity. The fused bicyclic system is unlikely to invert owing to the very large energy

difference (6 kcal/mol)[7] between the cis and trans fused ring systems; hence the bicycle is basically rigid with buckling occurring via carbons 5-6-7 only.

In the case of supinidine, the unsaturated ring will likewise have virtual planarity. With regards to the stereochemistry at C(8), only the (S)-(-) form is enzymatically active in natural systems[8].



(S)-(-)-supinidine

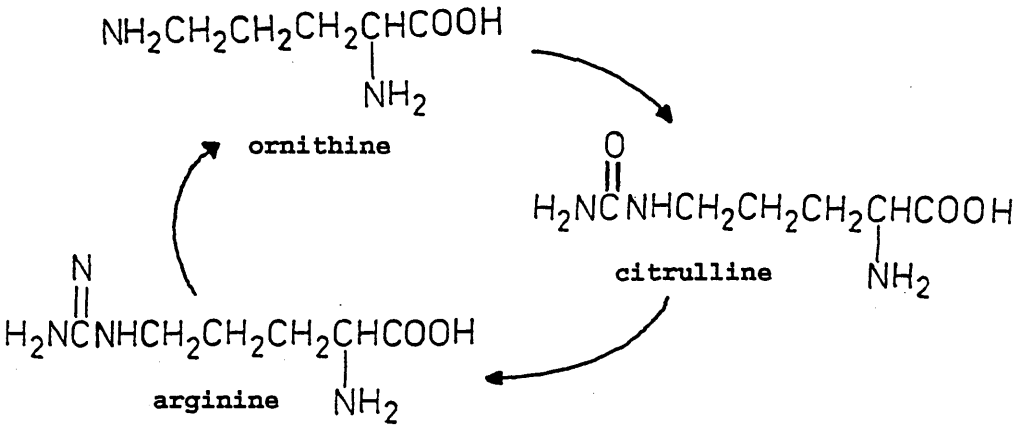
The absolute configuration of (S)-(-)-supinidine was established following the degradation of (S)-(-)-heliotridane to (R)-(+)-3-methylheptane[8].

1.3 Pyrrolizidine Biosynthesis

Retronecine, found in *Senecio sp.* grasses, is the most commonly encountered pyrrolizidine base[9] and is the only pyrrolizidine base (necine) whose biosynthesis has been investigated in detail. It is believed that most, if not all, pyrrolizidine bases are synthesised via a similar pathway[1c,10].

The starting material is S-ornithine; some sources state that it is S-arginine; this confusion arises from their interconversion via a natural cyclic pathway known as the ornithine cycle[11] (Scheme 2).

Scheme 2



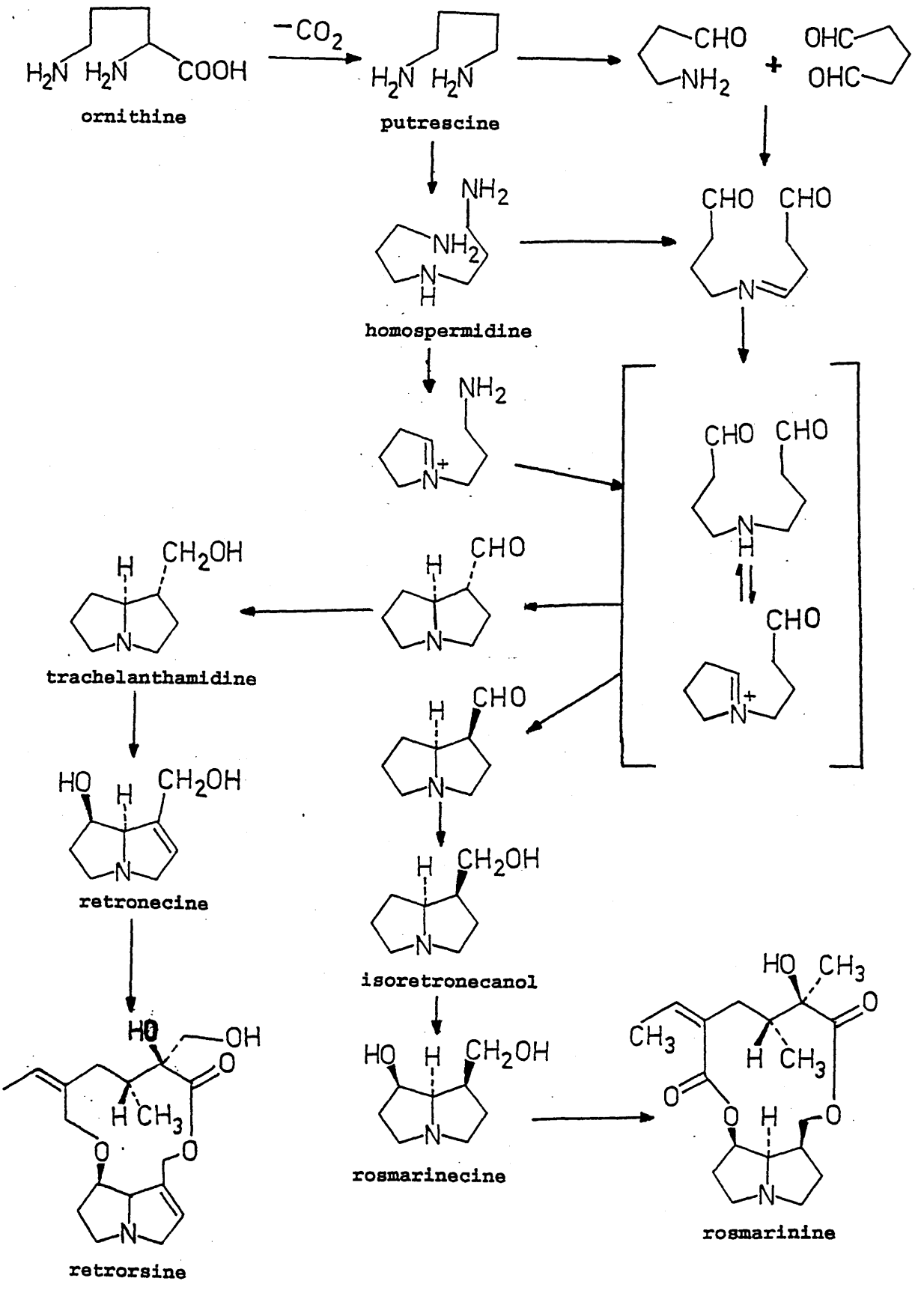
It has been established that retronecine is derived naturally from S-ornithine via a decarboxylation reaction leading to putrescine[12], and this has been confirmed using ^{14}C-labelled compounds[13]. Thereafter the biogenesis of retronecine, based on existing knowledge of amino acid metabolism, was thought to proceed via mono-deamination and bis-deamination of putrescine to form 4-amino butanal and 1,6-hexanedial respectively. These two species would then combine to form the Schiff base (condensation of a primary amine with an aldehyde, ketone, or pyruvic acid to form a Schiff base is one of the two major processes by which carbon-nitrogen bond formation occurs). Hydrogenation of this imine would

then lead to the saturated dialdehyde; intramolecular condensation would give the monocyclic iminium species; the dialdehyde was thought to be the active form, because this could then undergo a Mannich reaction to form the bicyclic aldehyde, and this type of reaction was known to be the second major process of carbon-nitrogen bond formation. Reduction of the bicyclic aldehyde would lead to trachelanthamidine, which after subsequent dehydrogenation and hydroxylation would afford retronecine[1a].

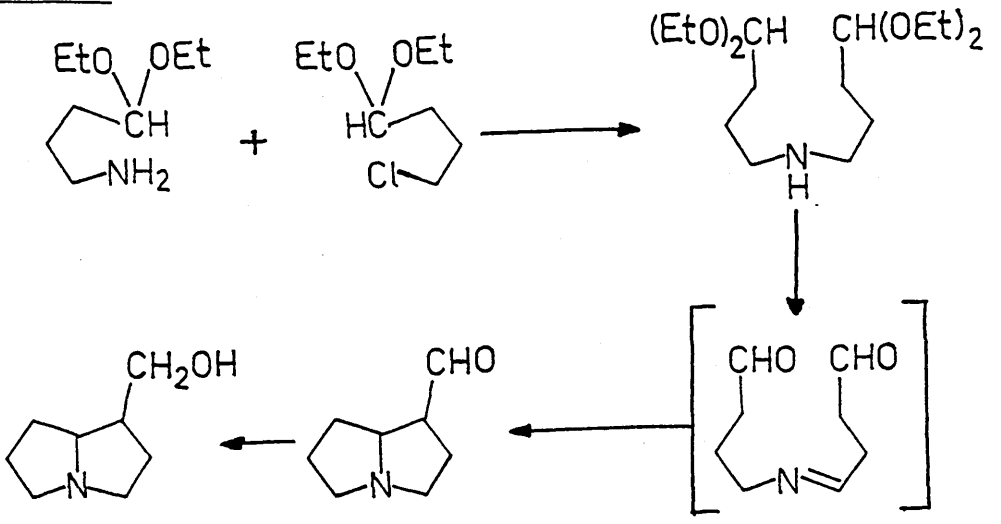
The biosynthesis of retronecine was later proved to proceed from putrescine to homospermidine by carrying out feeding experiments with ^{13}C-labelled precursors[14] and ^{2}H-labelled precursors[15]. The next intermediate whose structure has been similarly confirmed is trachelanthamidine[15a,16]. Spectroscopic studies based on the feeding of deuterated putrescine to *Senecio sp.* reinforce the proposal that 1-formyl pyrrolizidine is the immediate precursor of trachelanthamidine[16]. The same work strongly suggested that this is arrived at from homospermidine not via the Schiff base but via the cyclic iminium amine, which could then go to the cyclic iminium aldehyde and then the saturated bis-aldehyde and proceed as previously proposed. Feeding of the ^{14}C-labelled cyclic iminium amine to *Senecio pleistocephalus* and *Senecio isatideus* has shown it to be a better precursor for retronecine than is putrescine[17].

Bis-esterification of retronecine with the relevant senecic acid would produce retrorsine, the major alkaloidal component of *Senecio isatideus*.

Scheme 3


ornithine
putrescine
homospermidine
trachelanthamidine
retronecine
retrorsine
isoretronecanol
rosmarinecine
rosmarinine

Scheme 4



Similar feeding experiments using ^{13}C-labelled precursors and subsequent spectroscopic studies in *Senecio pleistocephalus* have elucidated that S-ornithine is a precursor for the pyrrolizidine base rosemarinecine via a similar pathway with isoretronecanol as the penultimate precursor[14b]. Subsequent bis-esterification then leads to rosmarinine.

Although the biosyntheses of retronecine and rosmarinecine appear to proceed via a common pathway as far as the open chain dialdehyde, the two pathways must then diverge according to the particular species, since the formation of 1-formyl pyrrolizidine is stereospecific at C1 and remains so for the rest of the pathway[11].

Biosynthesis from the open chain dialdehyde to the 1-hydroxymethyl pyrrolizidine stage has been confirmed by chemical synthesis *in vitro* under physiological conditions[5a] according to scheme 4. The bis-diethylacetal of di-(4-oxo-n-butyl)amine was obtained from γ-aminobutyraldehyde diethylacetal and γ-chlorobutyraldehyde diethylacetal via a condensation reaction with the elimination of hydrogen chloride. After deprotection of both

aldehyde groups, 1-formyl pyrrolizidine was formed via a Mannich condensation reaction. Babor *et al* obtained 1-formyl pyrrolizidine in *ca.* 10-15% yield at pH 4.0-4.5 and then hydrogenated the compound over platinum to give 1-hydroxymethyl pyrrolizidine, which they claimed as (+)-isoretronecanol. Leonard and Blum performed the same Mannich reaction at pH 7.0 and reduced the crude aldehyde with sodium borohydride to 1-hydroxymethyl pyrrolizidine, which they isolated as its benzyl ether, in *ca.* 50% yield and which they claimed to be (+)-trachelanthamidine[5a].

The biosynthesis of pyrrolizidines from S-ornithine as far as the 1-hydroxymethyl pyrrolizidine stage appears to be common to all naturally-occurring pyrrolizidines[10]. The investigations have mainly been on the grasses *Senecio* and *Crotalaria*.

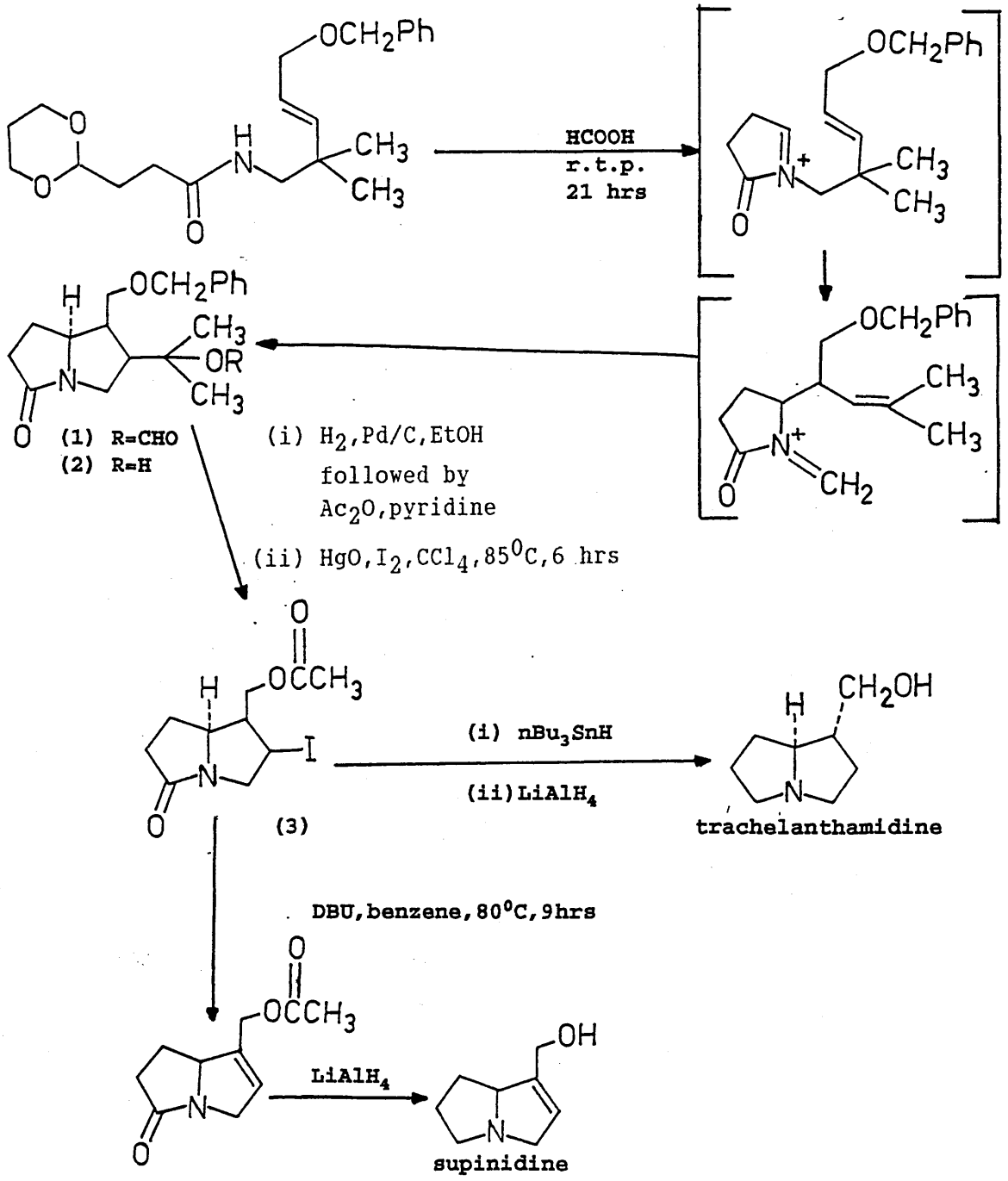
Other precursors have been suggested, eg (+/-)-β-hydroxyornithine and (+/-)-β-hydroxy-N-methylnorvaline[5a], but in the main the route appears to be common in all species. Insects which contain pyrrolizidines have so far been shown not to have produced the compounds themselves but to have acquired them through feeding on plants which produce them; the insect *Heliopeltis*, which feeds on *Cinchona* bark, accumulates amorphous cinchonine-like alkaloids and becomes unpalatable to its predators, as does *Attacus atlas*, which also accumulates cinchonine[18].

1.4 Pyrrolizidine Chemical Syntheses

Many of the earlier routes led to racemic pyrrolizidines, but more recent work has provided enantiospecificity; several excellent reviews have been published[5a,19]. The literature regarding pyrrolizidine alkaloids is reviewed annually in Natural Product Reports.

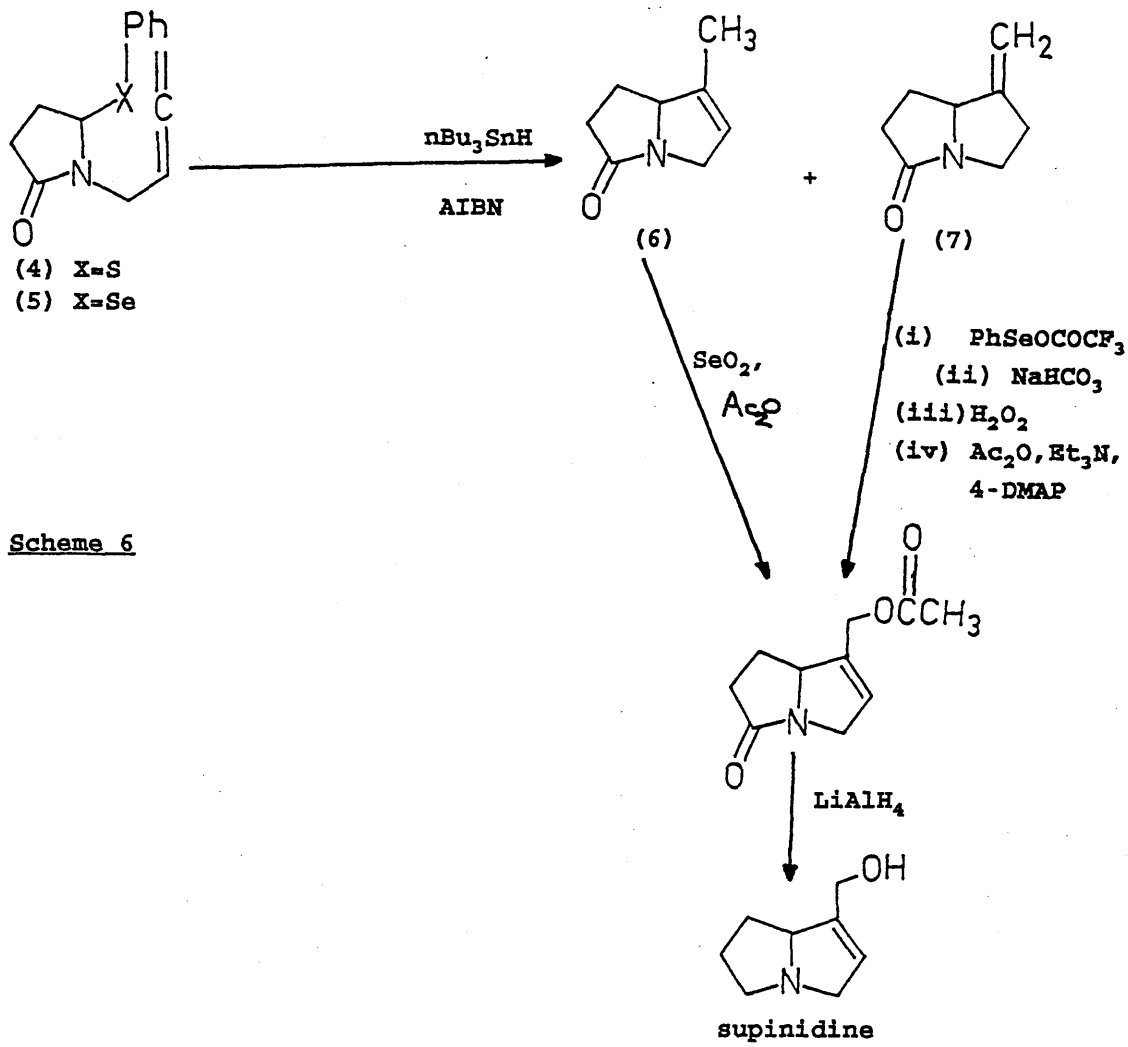
Hart and Yang[20] used an aza-Cope rearrangement of an acyliminium ion followed by cyclisation to give a mixture of pyrrolizidinones (1) and (2). After complete hydrolysis of (1) to (2) and replacement of the benzyl ether with an acetoxyl group, the side chain was degraded to the iodide (3). Reduction of (3) led to (+/-)-trachelanthamidine, while dehydrohalogenation and reduction of (3) gave (+/-)-supinidine (Scheme 5).

Scheme 5



Burnett *et al* used allenes as unsaturated precursors to radical cyclisation[21]. The phenylthio derivative (4) did not produce the

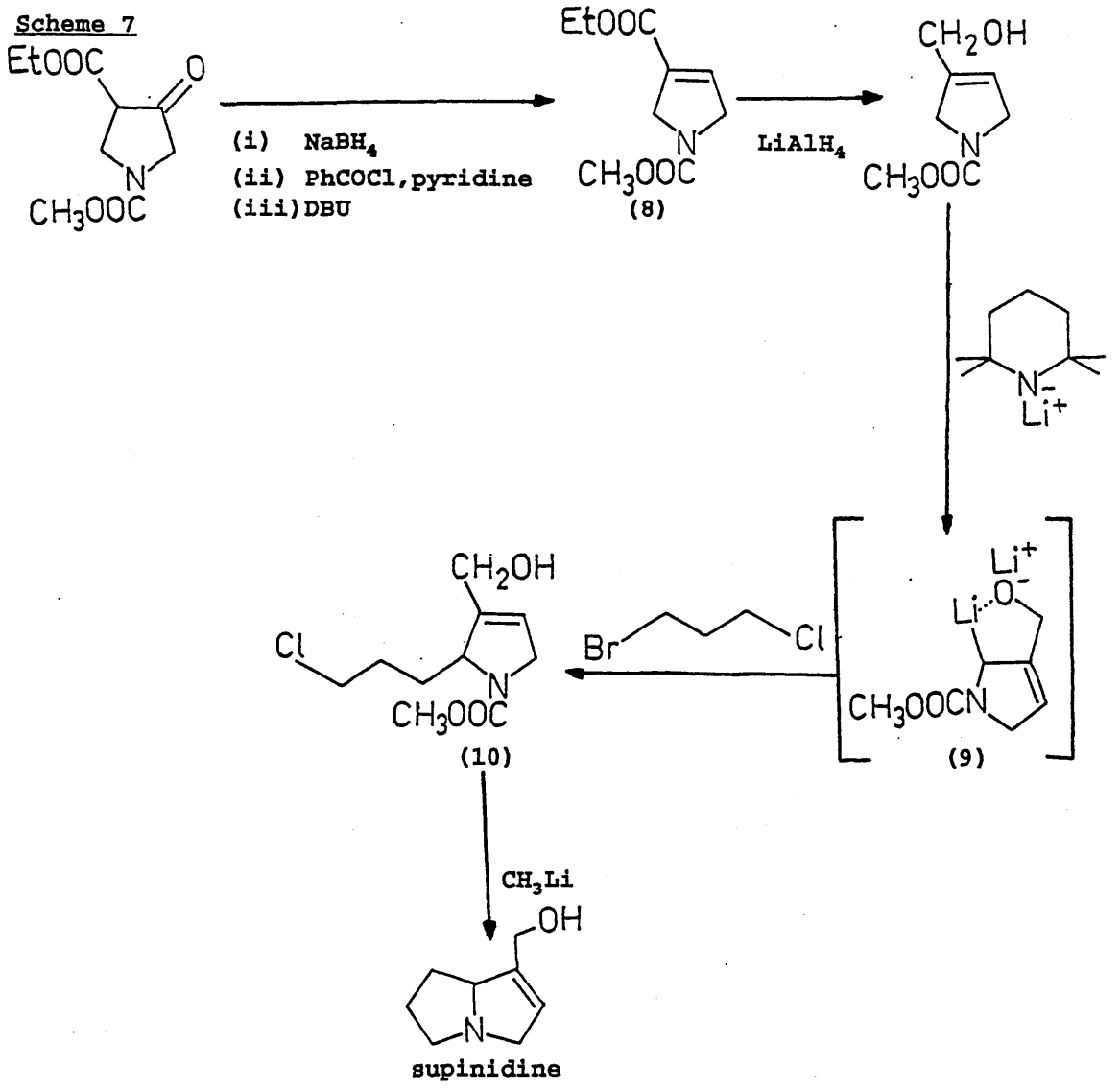
required radicals, but the phenylselenyl-lactam derivative (5) did act as a radical precursor. Intramolecular cyclisation afforded the pyrrolizidinones (6) and (7), which were separated by chromatography. Each racemate was then modified to (+/-)-supinidine (Scheme 6).



Scheme 6

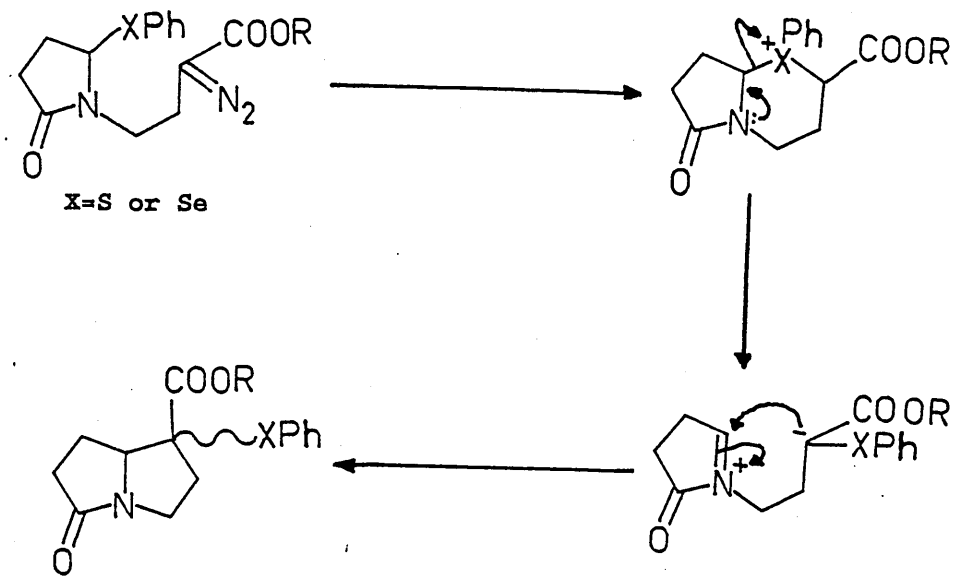
McDonald and Narayanan[22] used vicinal annulation of a bifunctional alkylating system generated from the 3-pyrroline derivative (8). The dianion (9) derived from the pyrroline and presumably stabilised by internal chelation, was stereoselectively alkylated to produce the chloro compound (10). Intramolecular cyclisation to (+/-)-supinidine was achieved after removal of the N-protecting group in (10) (Scheme 7).

Scheme 7

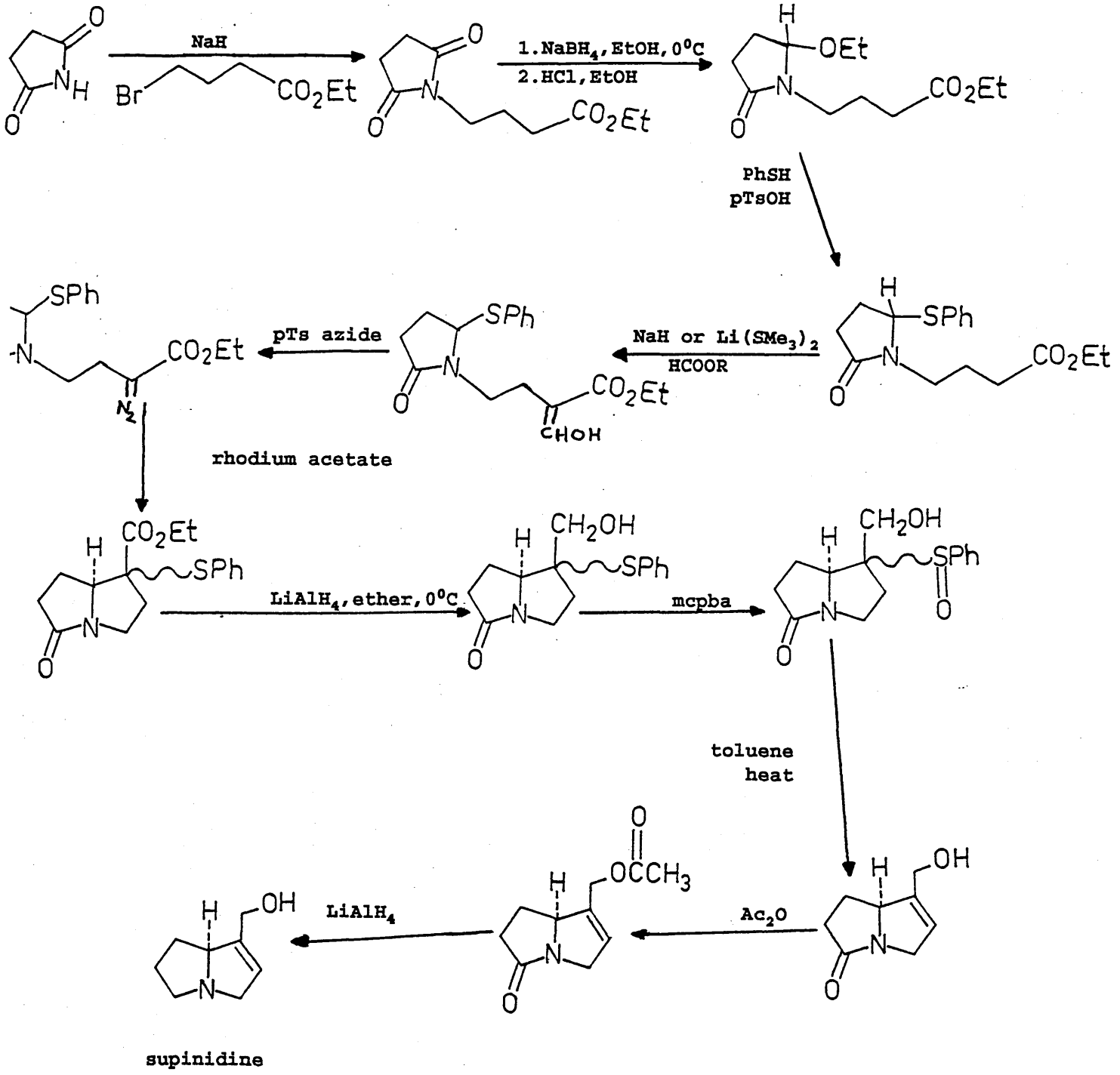


Kametani *et al*[23] used an intramolecular carbenoid displacement reaction of diazosulphide and diazoselenide intermediates for their synthesis of (+/-)-supinidine (scheme 9). The key reaction probably proceeded via the following mechanism (Scheme 8):

Scheme 8



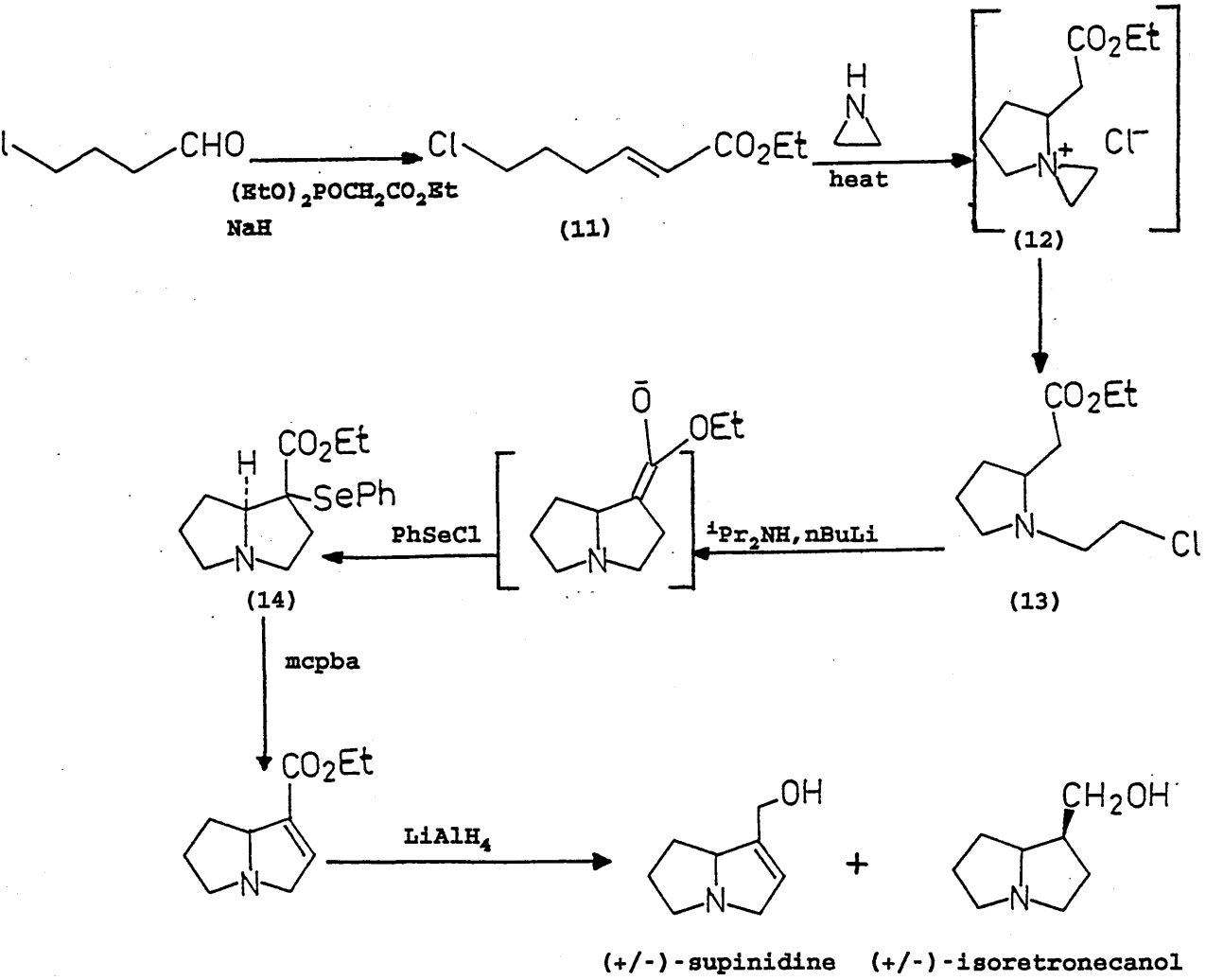
Scheme 9



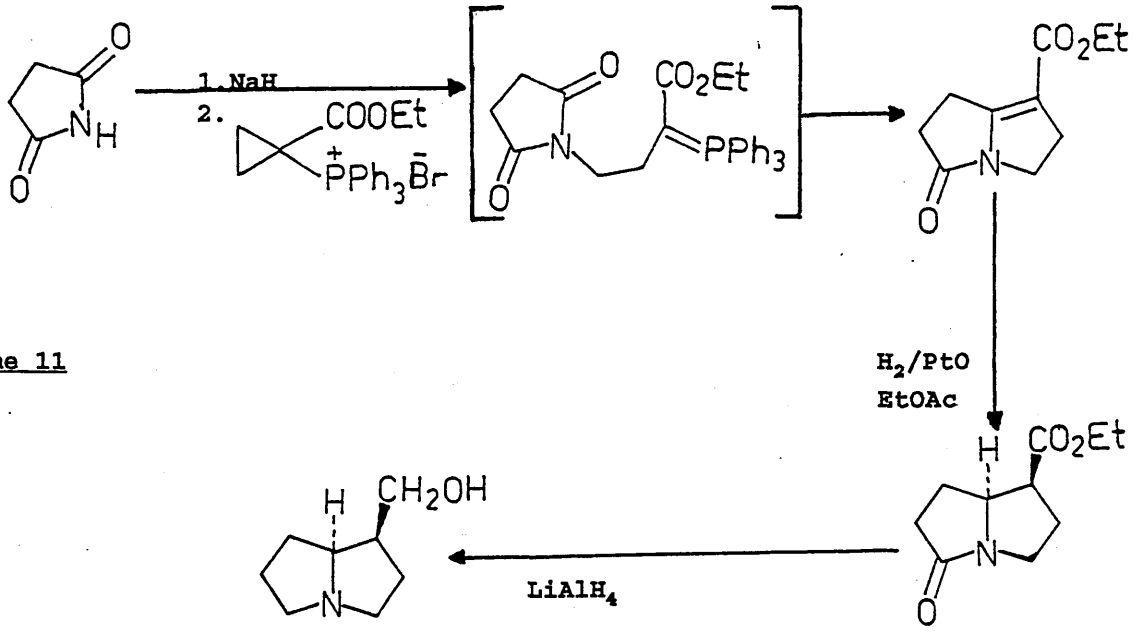
supinidine

Kametani *et al*[24] have also used aziridine in their more recent synthesis of (+/-)-supinidine. Michael addition of aziridine to the 2,3-unsaturated ester (11) led to the pyrrolidine ester (13), probably via the aziridinium salt (12). Treatment of (13) with excess base produced the enolate, which could then be trapped with phenylselenyl chloride to give roughly equal amounts of the two diastereoisomeric selenides (14). After separation of the isomers, syn-elimination of the corresponding selenoxides and reduction with lithium aluminium hydride, (+/-)-supinidine and (+/-)-isoretronecanol were produced (Scheme 10).

Scheme 10



Flitsch and Russkamp[25] achieved a simple diastereoselective synthesis of (+/-)-isoretronecanol by way of reaction of cyclic imides with 1-ethoxycarbonyl cyclopropyl triphenyl phosphonium tetrafluoroborate (Scheme 11).

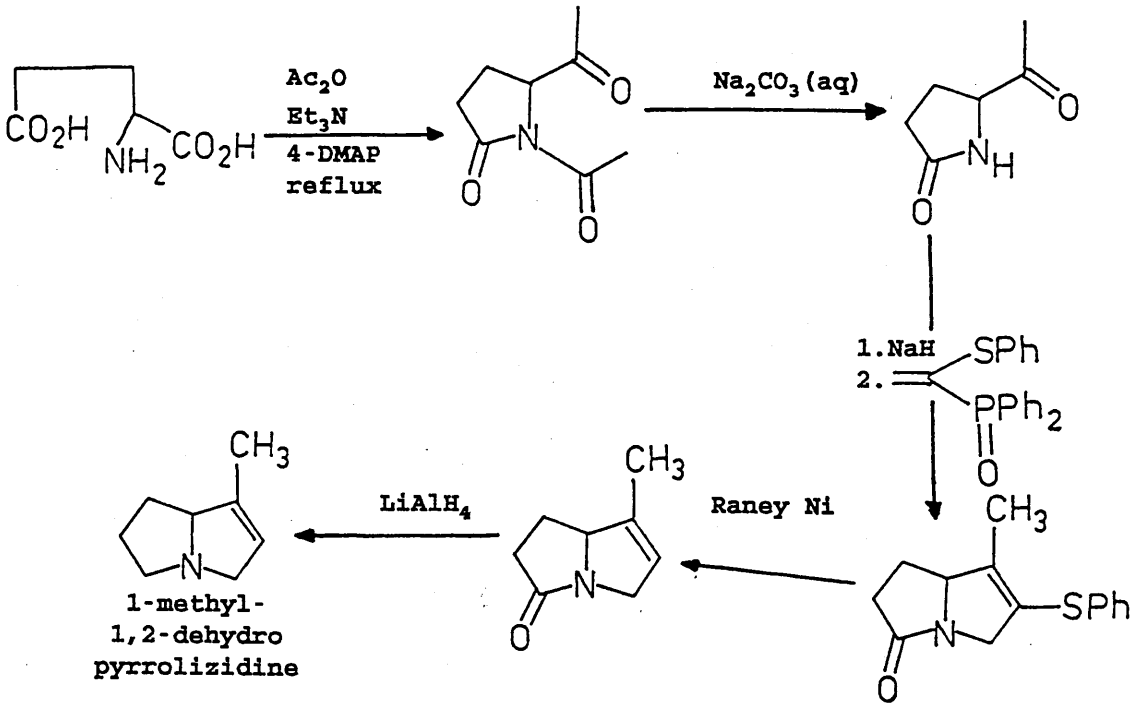


Scheme 11

(-)-isoretronecanol

The following method was developed recently at Sheffield City Polytechnic[26] and provided the basis for this project. The key cyclisation step involved the use of an intramolecular Horner-Wittig reaction using a vinyl phosphine oxide derivative (Scheme 11).This reaction will be discussed in sections 1.5 and 1.6.

Scheme 12

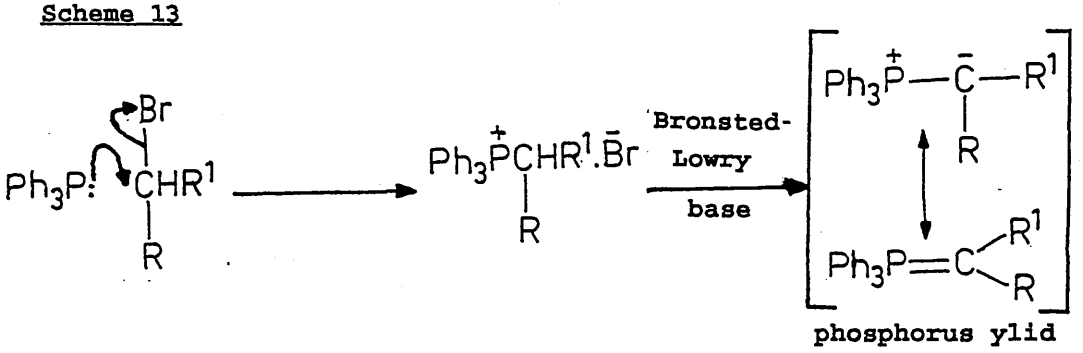

Ac2O
Et3N
4-DMAP
reflux
Na2CO3 (aq)
1.NaH
2.
SPh
PPh2
O
CH3
SPh
Raney Ni
LiAlH4
1-methyl-
1,2-dehydro
pyrrolizidine

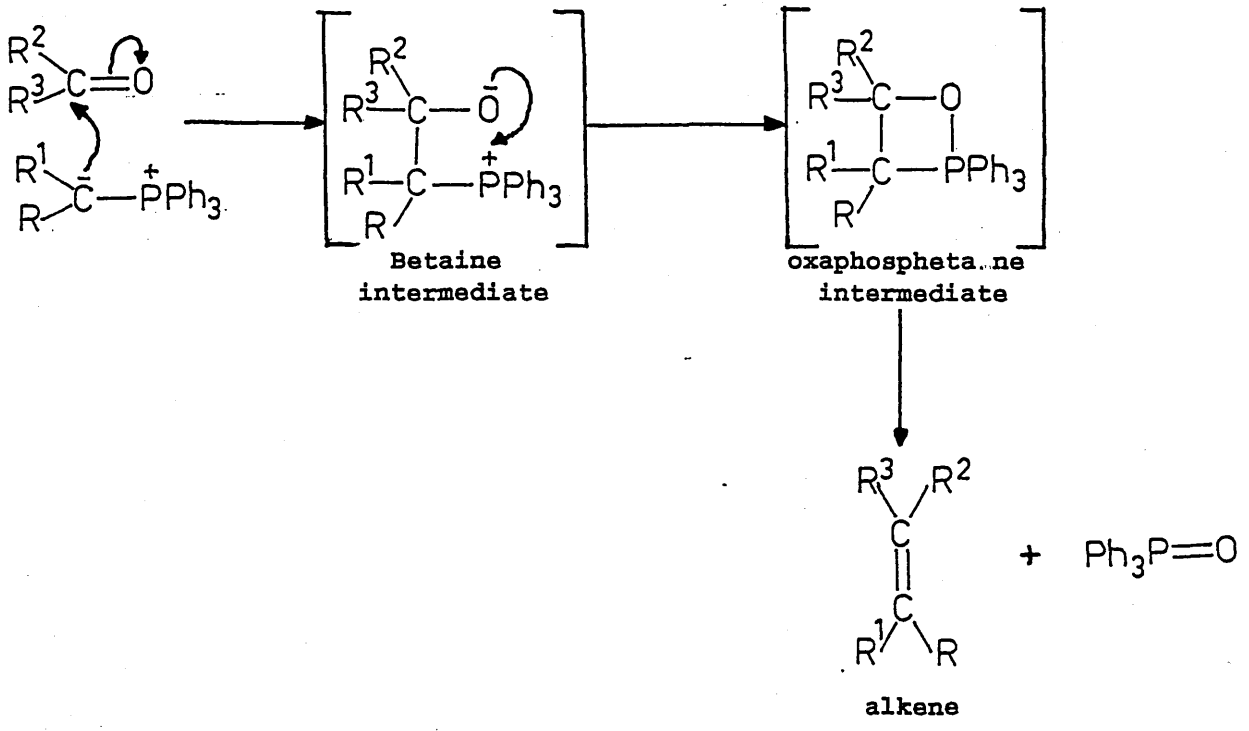
1.5 The Intramolecular Horner-Wittig Reaction

1.5.1 Reaction and Reagents

The Wittig reaction is the condensation of a carbonyl compound with an alkylidene triphenylphosphorane to give an alkene and triphenyl phosphine oxide (Scheme 13):

Scheme 13

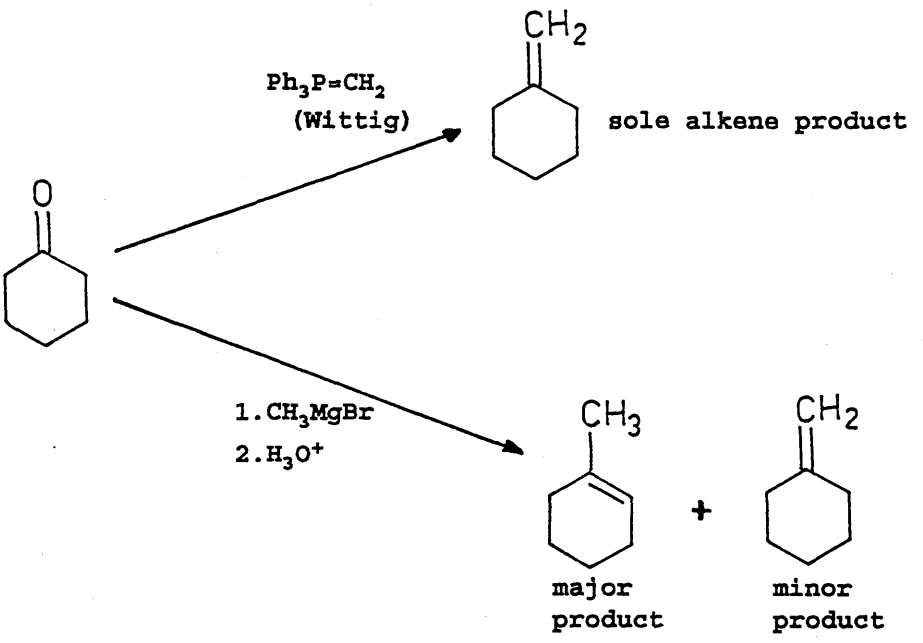




(in all cases, R, R^1, R^2 and R^3=H, alkyl or aryl)

The advantage of the preparation of alkenes in this way as opposed to other methods is that the newly-formed carbon-carbon double bond always appears at the site of the former carbonyl

bond, even when it occupies an energetically unfavourable position[27], eg

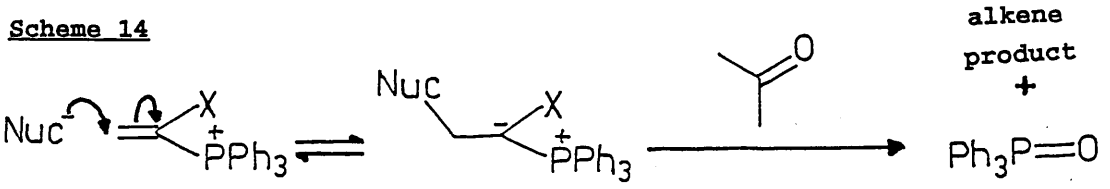


In the case where the phosphorus ylid and/or the carbonyl compound is unsymmetrically substituted, the Wittig reaction can lead to mixtures of (E)- and (Z)-alkenes, but the configuration can be considerably influenced by choice of reaction conditions[2]. An example is the use of the phosphine oxide derivative of the phosphorus ylid; in most cases, PO-activated alkene synthesis leads to the (Z)-isomer[28]. PO-stabilised carbanions are more nucleophilic than the corresponding phosphonium ylids, facilitating their reaction with a wider range of carbonyl compounds under milder conditions. Another advantage of using such phosphine oxide derivatives is that the phosphorus-containing by-product of the reaction (phosphonic acid) is then water-soluble, and so is more easily removed from the alkene than is triphenyl phosphine oxide[28]. Much of the work on phosphine oxide derivatives for use in the Wittig synthesis of alkenes was done by Horner and his co-workers[29], and this adaptation is thus recognised as the Horner-Wittig reaction.

The phosphorus ylid carbanion can also be stabilised by the presence of a sulphur substituent on the α -carbon atom[30].

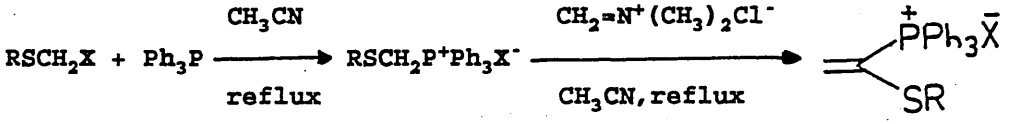
Phosphorus ylids can also be generated by addition of a nucleophile to a vinyl phosphonium salt (or other phosphorus derivative):

Scheme 14



Such chemistry was originally developed by Schweizer[31], who worked largely with the compound where X=H. Work in these laboratories[30] has produced the compounds with X=SCH_3 and X=SPh by the route shown in scheme 15.

Scheme 15



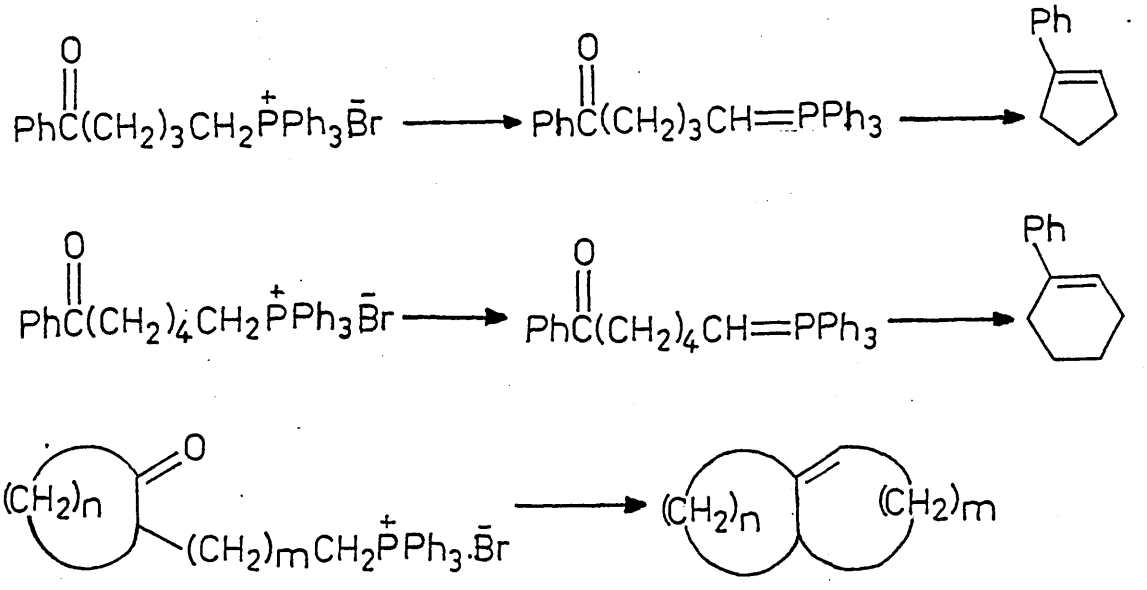
R=Me, X=Cl
R=Ph, X=I

The SR group is advantageous since it stabilises the intermediate ylid, thereby leading to higher yields of the alkene product via reaction with a carbonyl compound, as in scheme 14.The product in this case is a vinyl thioether, which allows easy conversion via hydrolysis to give a ketone. Previous applications from our laboratories of this chemistry to natural product synthesis are included in the following sections.

1.5.2 Formation of Carbocyclic Alkenes

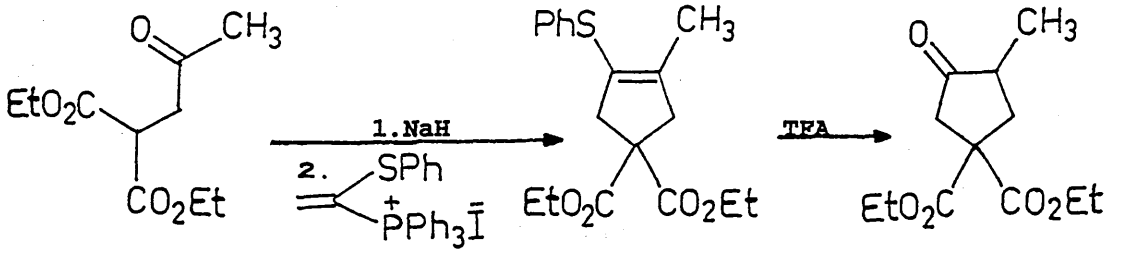
A good review of intramolecular Wittig reactions was reported by Becker[32]. The process has been used to form 5- and 6-membered monocyclic carbon ring systems and also fused bicyclic carbon ring systems (scheme 16):

Scheme 16



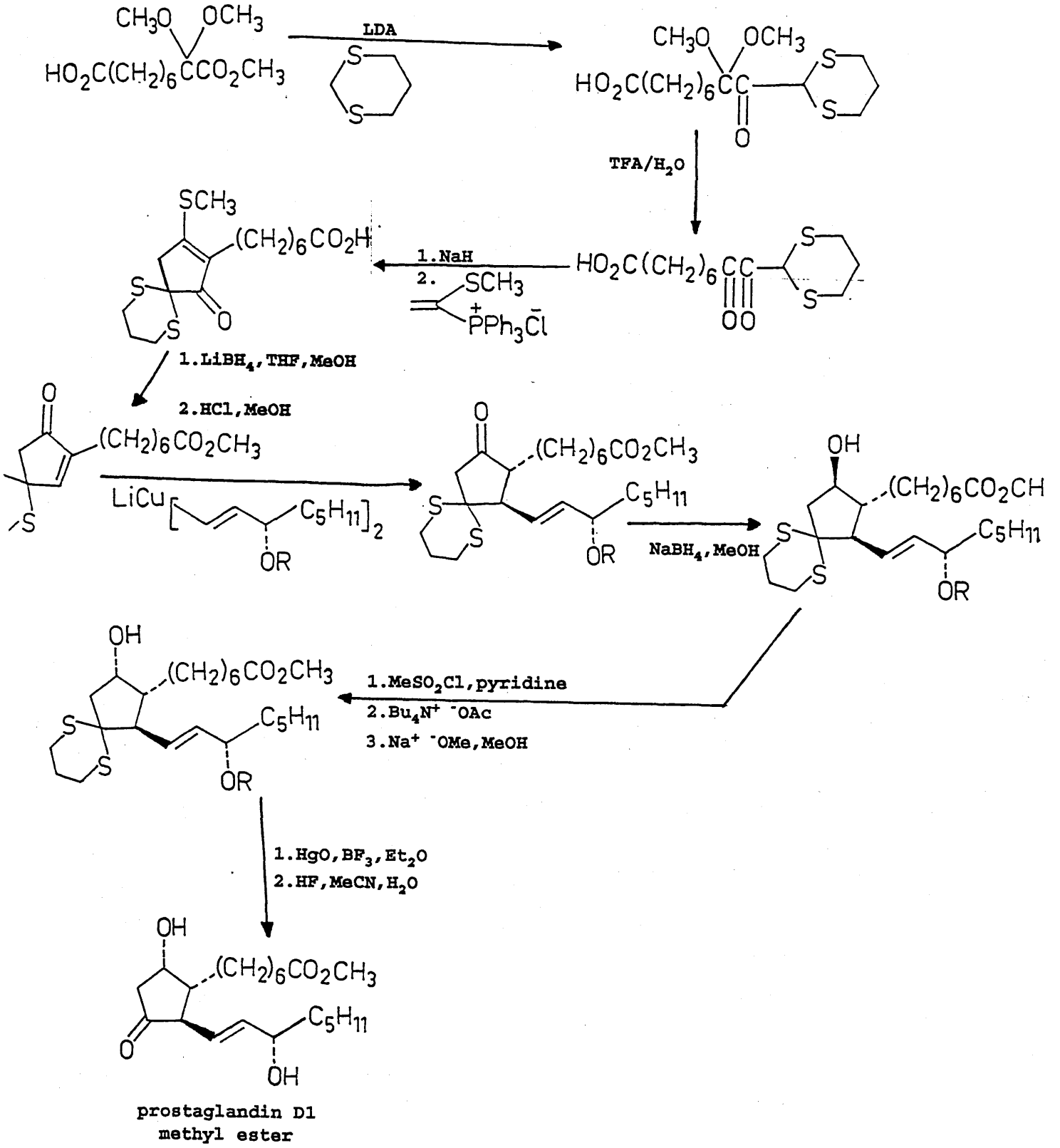
One application of this process using the Wittig reaction and was the synthesis of cyclopentanones[30]:

Scheme 17



Subsequent development of this work utilised these vinyl phosphonium salts in the total synthesis of highly functionalised cyclopentanoid natural products such as prostaglandin D1 methyl ester[33] (Scheme 18):

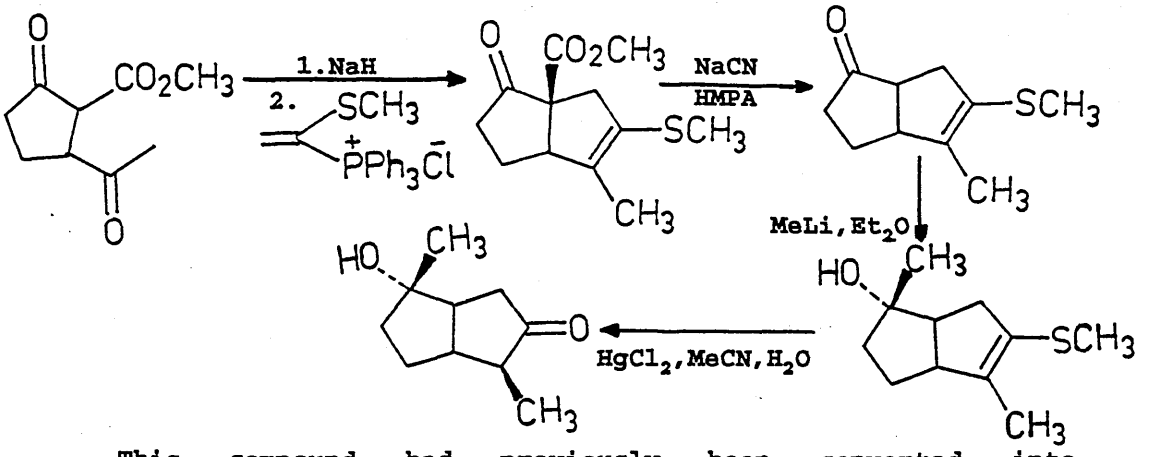
Scheme 18



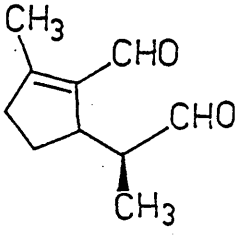
prostaglandin D1
methyl ester

This work, in turn, has led to the formation of the following functionalised bicyclo(3.3.0)octane[34] (Scheme 19):

Scheme 19



This compound had previously been converted into chrysomelidial, the defence secretion of a chrysomelide beetle[35].



chrysomelidial

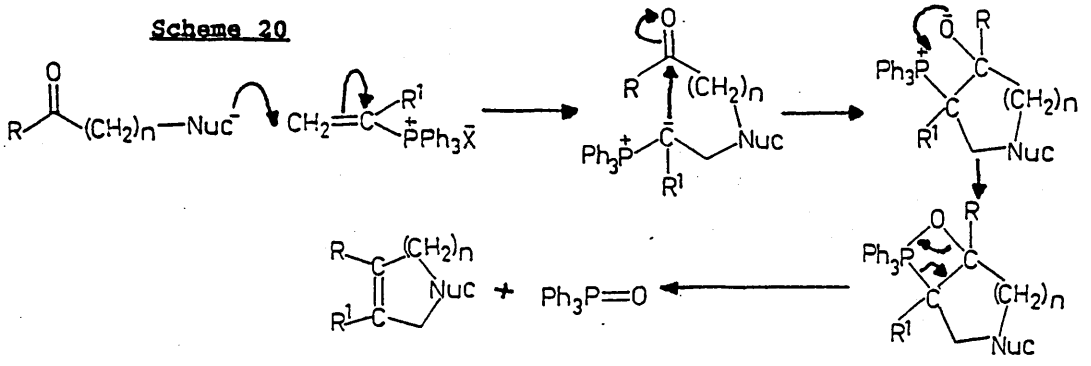
Other syntheses which have involved this kind of carbocyclic annulation reaction include those of loganin[34,36], hirsutene[36] and sarkomycin[36,37].

1.5.3 Formation of Heterocyclic Systems

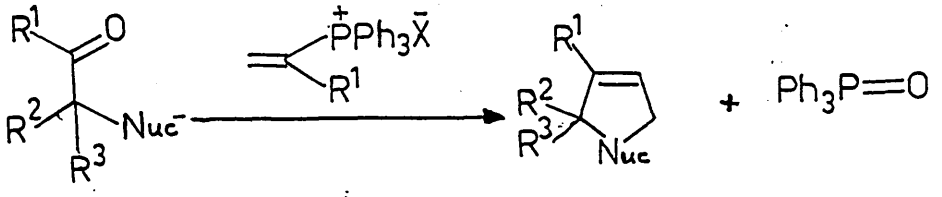
If a system is created where the carbonyl group is attached to a nucleophile, Nuc⁻, this base could then undergo a nucleophilic addition reaction with one of the previously mentioned vinyl phosphonium salts to form a phosphorus ylid which

could then perform an intramolecular Wittig reaction to form a cyclic alkene with Nuc as part of the ring (Scheme 20);

Scheme 20

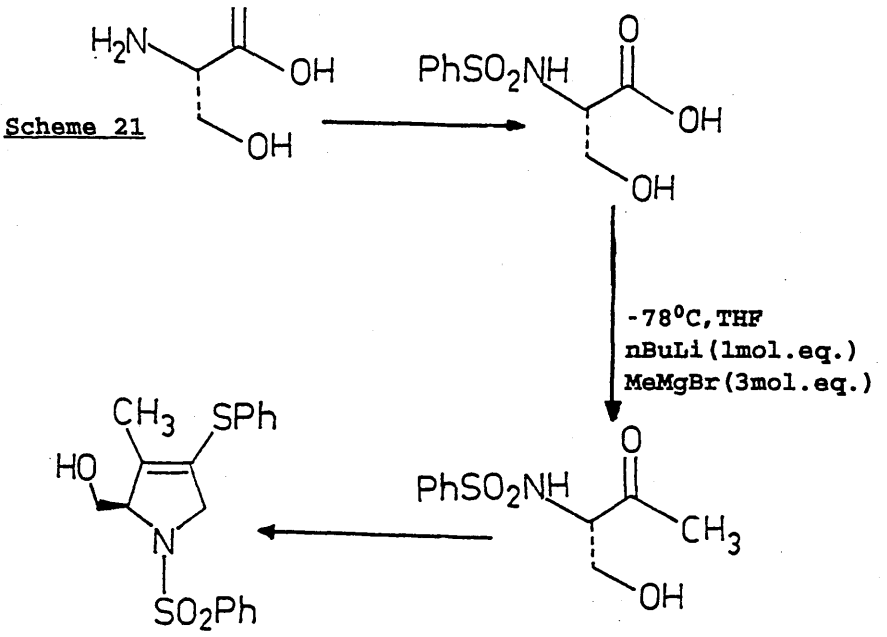


If the nucleophile Nuc⁻ was present as an α-substituent with regard to the carbonyl group participating in the intramolecular cyclisation reaction, a 5-membered ring system would be produced, as in the carbocyclic synthesis described earlier.

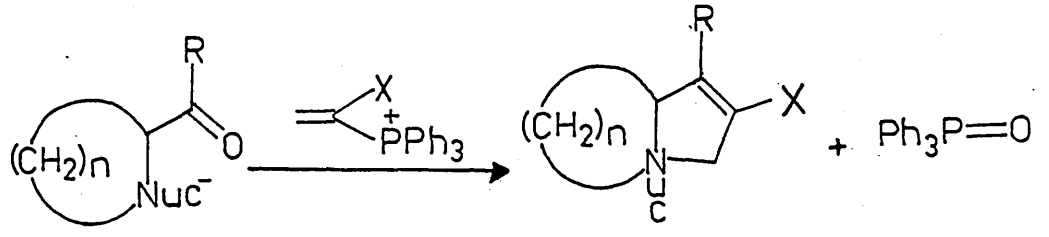


The nucleophile Nuc⁻ could be a heteroatom such as oxygen, sulphur or nitrogen. An example of such a process has been used in the synthesis of a functionalised pyrroline (Scheme 21)[38]:

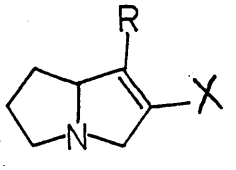
Scheme 21



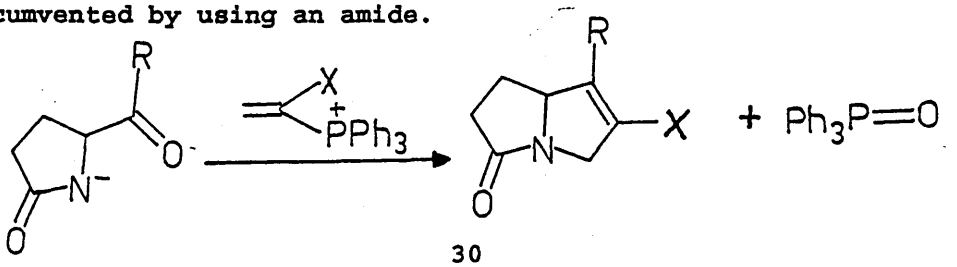
If Nuc$^-$ was already part of a ring system, this type of reaction could lead to a fused bicyclic system with Nuc at one of the ring junctions:



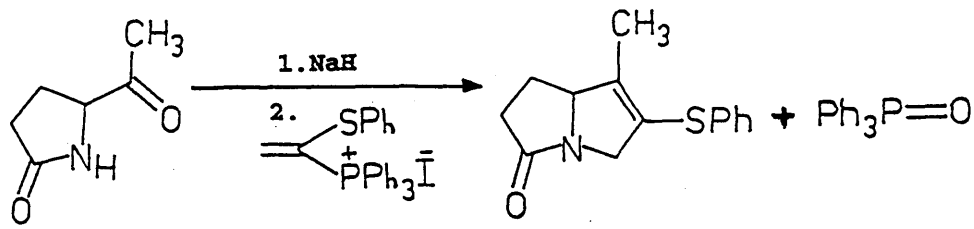
Where Nuc is nitrogen and n=3, a fused 5,5 bicyclic ring system could be formed, which would be the pyrrolizidine alkaloid skeleton:



Formation of the required nitrogen anion would create problems from the weakly acidic amine, but these problems might be circumvented by using an amide.



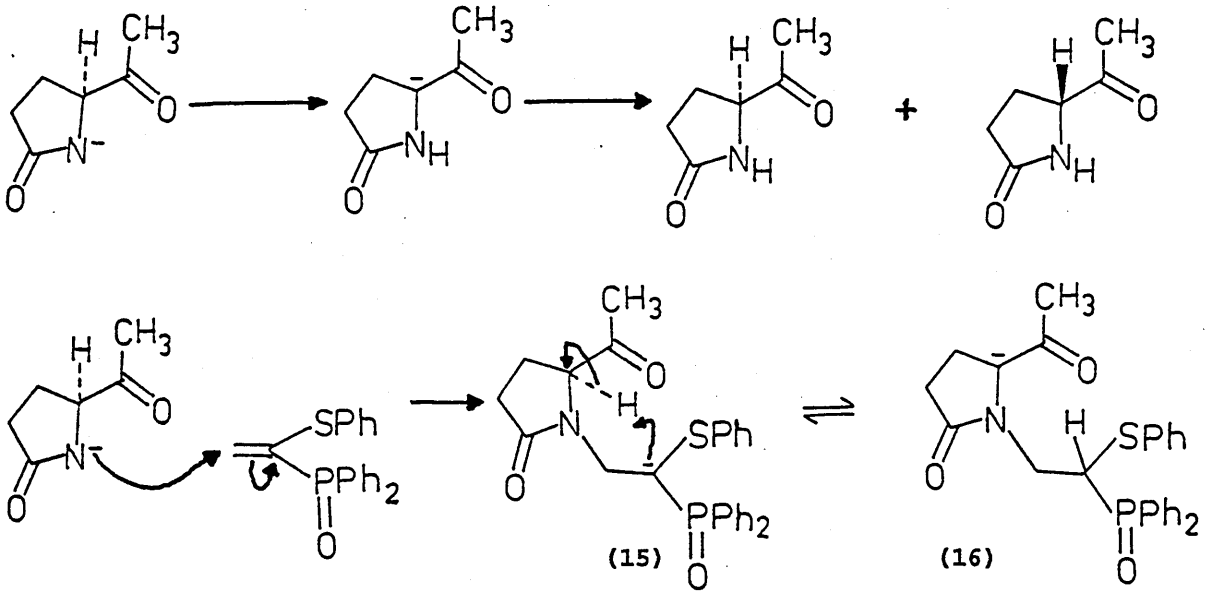
As has been previously mentioned, this adaptation of the Wittig reaction has been used to synthesise the pyrrolizidine skeleton[26]:



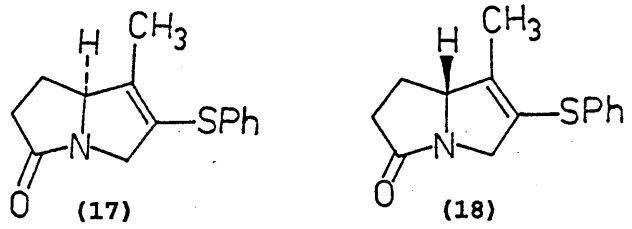
Initial attempts used the triphenyl phosphonium salt, but triphenyl phosphine oxide proved inseparable from the fused bicycle via conventional chromatography. The Horner modification using the diphenyl phosphine oxide produced diphenyl phosphonic acid, which was water-soluble and easily removed.

For any pyrrolizidine or indolizidine alkaloid to exhibit pharmacological activity, the carbon atom at the bis-ring junction must be in the (S)-configuration. It is not sufficient to rely on the monocyclic amide having its chiral carbon in the correct configuration and producing a bicycle of the same configuration, since both sodium hydride and also the carbanionic intermediate are basic enough to remove the proton from this carbon atom; subsequent replacement of the proton could result in this carbon being in either the (S)- or (R)-configuration; thus whether the monocyclic amide is racemic or chiral, both could lead to a racemic bicyclic system (Scheme 22):

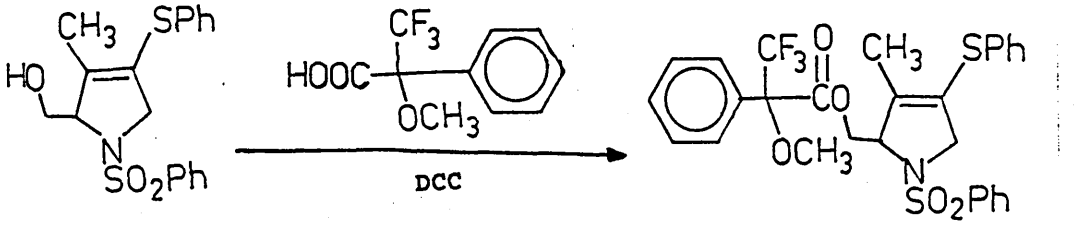
Scheme 22



In this case, only the carbanion (15) goes on to form the betaine intermediate, but the tautomeric regeneration of (15) from (16) can racemise the originally chiral (*) carbon, leading to the bicyclic enantiomers (17) and (18).



This project involved the use of such an intramolecular Horner-Wittig cyclisation process to form pyrrolizidine and indolizidine alkaloid systems, and one of the aims of the project was to determine whether this key reaction proceeded with retention of chirality. In the work on the pyrroline systems described earlier[38],proof of retention of chirality was achieved through functionalisation of the alcohol group as the chiral Mosher's ester, and subsequent NMR studies.



In the previous work on the synthesis of the pyrrolizidine core[26] no attempt had been made to optimise the reaction conditions and our work began with this study in order to maximise yields and develop conditions which would be used in our later work. The results of this study are described in the next section.

1.6. Optimisation of the Intramolecular Horner-Wittig Route to the Pyrrolizidine Core

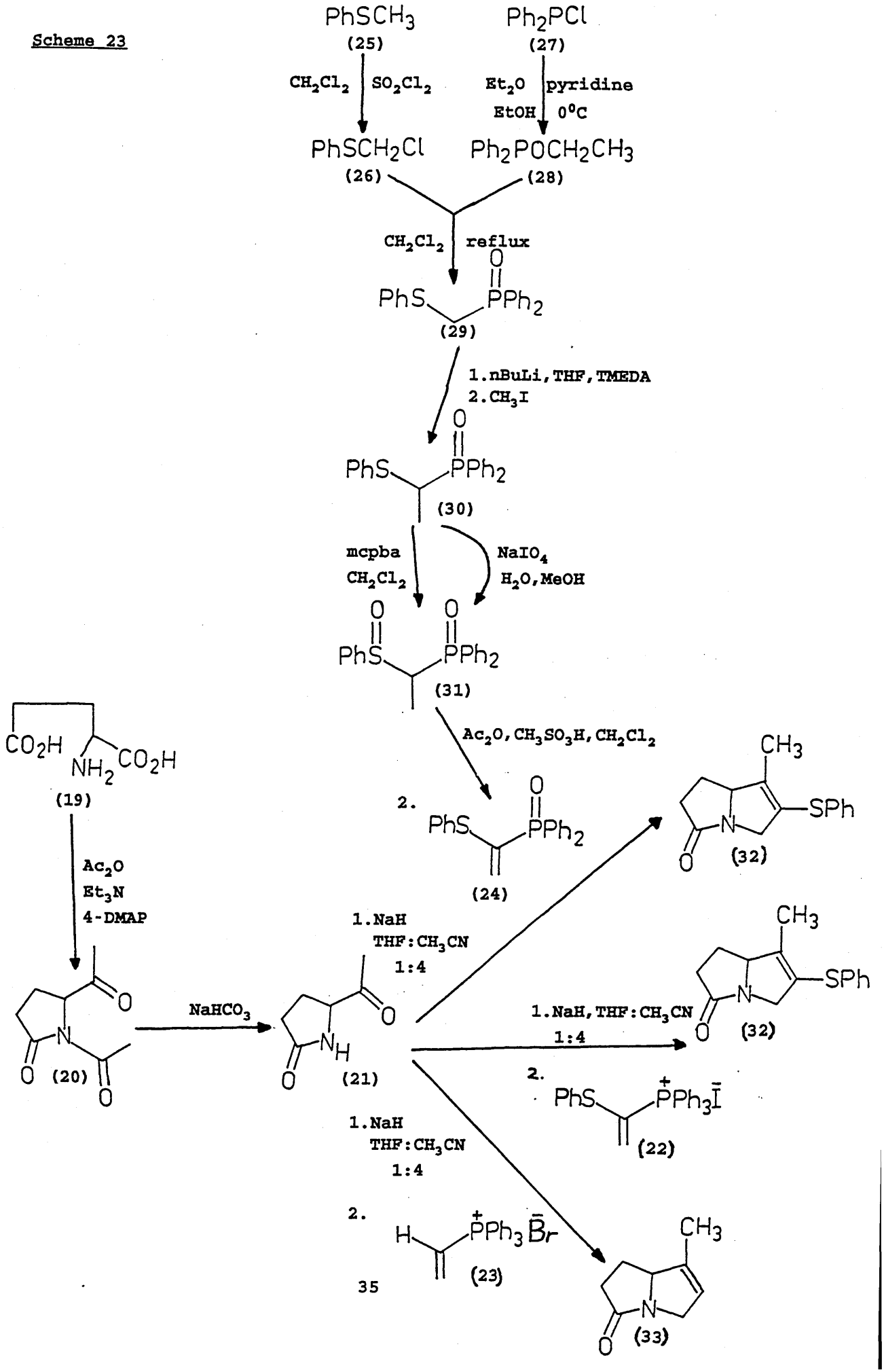
The reaction was investigated to determine the solvent, temperature, Wittig reagent and purification procedure giving the maximum yield of the the bicyclic product (Scheme 23).

(S)-glutamic acid (19) was subjected to a Dakin-West reaction with acetic anhydride which involved both C2- and N-acetylation followed by cyclisation to form 1,5-diacetylpyrrolidin-2-one (20) in racemic form[39]. Treatment of water-soluble (20) with aqueous sodium carbonate followed by continuous extraction into dichloromethane at pH 7 gave racemic 5-acetylpyrrolidin-2-one[40] (21).

The vinyl phosphonium salt (22) was taken from a stock prepared by the method outlined earlier. The vinyl phosphonium salt (23) was commercially available. The vinyl phosphine oxide (24) was synthesised as follows[41].

Chlorination of thioanisole (25) was effected by refluxing it with sulphuryl chloride in dichloromethane to give chloromethyl phenyl sulphide (26) in quantitative yield[42]. Ethoxydiphenyl phosphine (28) was prepared from chlorodiphenyl phosphine (27) via a condensation reaction involving (27) and ethanol; the eliminated hydrogen chloride was taken up by the pyridine catalyst to produce pyridinium hydrochloride as an easily-removable by-product[43]. Refluxing (26) and (28) together in dichloromethane solution produced the phosphine oxide (29) via a condensation reaction eliminating chloroethane and oxidising the phosphorus in the same process[44]. Methylation was effected by first forming the carbanion using n-butyl lithium followed by nucleophilic substitution of this carbanion on methyl iodide to give the saturated sulphide[44] (30). Oxidation of (30) to its sulphoxide (31) was effected by

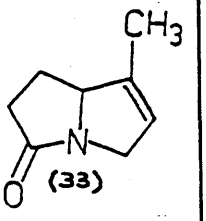
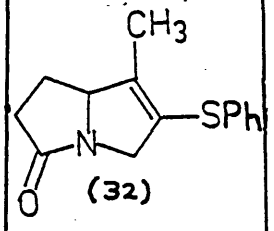
Scheme 23


PhSCH3
(25)
CH2Cl2
SO2Cl2
PhSCH2Cl
(26)
Ph2PCl
(27)
Et2O
pyridine
EtOH
0°C
Ph2POCH2CH3
(28)
CH2Cl2
reflux
PhS
PPh2
(29)
1.nBuLi, THF, TMEDA
2.CH3I
(30)
mcpba
CH2Cl2
NaIO4
H2O, MeOH
(31)
Ac2O, CH3SO3H, CH2Cl2
2.
(24)
CO2H
NH2
CO2H
(19)
Ac2O
Et3N
4-DMAP
(20)
NaHCO3
1.NaH
THF:CH3CN
1:4
(21)
(32)
1.NaH, THF:CH3CN
1:4
2.
(22)
1.NaH
THF:CH3CN
1:4
2.
(23)
(33)

using metachloroperbenzoic acid[41] or by using sodium metaperiodate[26]. The sulphoxide (31) then underwent a Pummerer elimination process involving methanesulphonic acid and acetic anhydride to give the vinyl phosphine oxide[41] (24).

Yields of the bicyclic products (32) and (33) were found to be maximal in all three cases when the reaction was carried out at room temperature with the solvent mixture tetrahydrofuran : acetonitrile, 1:4. Other ratios of these solvents, tetrahydrofuran alone and acetonitrile alone still facilitated the production of the required product but in lower yields (table 1). For this solvent mixture, heating under reflux reduced the reaction time but also reduced the the yield of the required product. When the reactions were carried out at $0^{0}C$, reaction times were longer and yields were substantially reduced.

Table 1

solvent ratio (THF:CH_3CN)	temp. (^0C)	time (hrs)	product	yield %
5:0	0	o'night	 (33)	14
4:1	0	o'night		17
2.5:2.5	0	9		26
1:4	0	8		30
0:5	0	11		24
5:0	r.t.	o'night		24
4:1	r.t.	o'night		35
2.5:2.5	r.t.	9		36
1:4	r.t.	6		40
0:5	r.t.	8		37
5:0	reflux	o'night		12
4:1	reflux	12		15
2.5:2.5	reflux	10		13
1:4	reflux	5		20
0:5	reflux	7		20
5:0	0	o'night	 (32)	17
4:1	0	o'night		20
2.5:2.5	0	11		26
1:4	0	9		37
0:5	0	12		27
5:0	r.t.	o'night		43
4:1	r.t.	14		52
2.5:2.5	r.t.	11		57
1:4	r.t.	6		68
0:5	r.t.	8		60
5:0	reflux	o'night		27
4:1	reflux	11		38
2.5:2.5	reflux	8		46
1:4	reflux	5		53
0:5	reflux	6		48

For the reaction of the amide salt of (21) with the phosphonium salt (22), the bicyclic sulphide (32) proved very difficult to separate from triphenyl phosphine oxide. Even when using flash chromatography, separation was not always complete. When the vinyl phosphine oxide (24) was used, the by-product sodium diphenyl phosphonate was water-soluble and was easily separated from the required product (32) via solvent extraction. Although (32) did run on tlc just behind the unreacted phosphine oxide (24) in ethyl acetate, a chromatography solvent of ethyl

acetate : petrol, 1:1, facilitated easy separation using flash chromatography.

Yields of the bicyclic amide (33) using the vinyl phosphonium salt (23) exhibited the same behaviour under corresponding conditions as yields of (32) from the other two reactions, but the yields of (33) were lower than those of (32) from (24) and (22) in all cases. Clearly the yield of the required product was being improved by the presence of the sulphur atom. The time of the reaction involving the commercially-available phosphonium salt (23) could not be extended very much , as the bicyclic product (33) began to decompose after only a few hours at room temperature (this was found after isolation of the pure material). This instability was exhibited by all the bicyclic compounds produced during the course of this project.

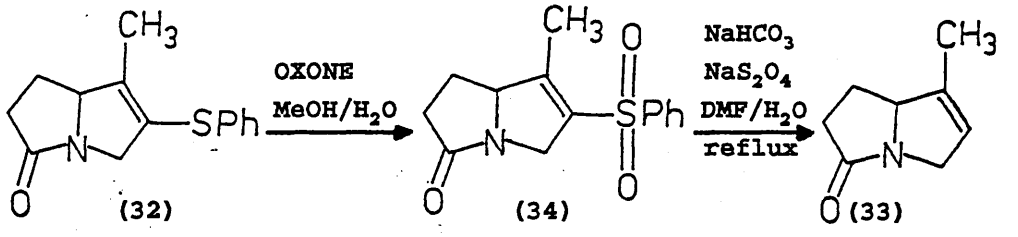
Removal of the sulphenyl group from the bicyclic core had previously been carried out using Raney nickel[26], but this reaction had proved somewhat temperamental and had often resulted in reduction of the olefinic bond as well, and so another part of this project involved finding an alternative method of removing the sulphenyl group, since we would require the olefinic bond to remain for the synthesis of supinidine.

1.8 Removal of the Sulphenyl Group

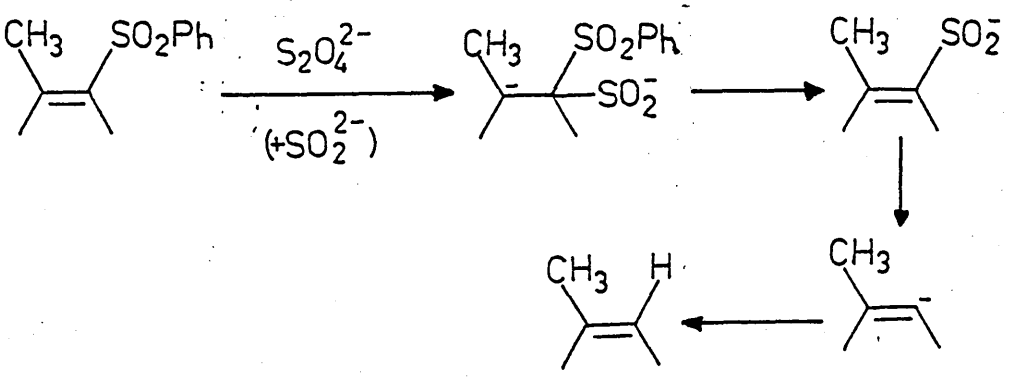
An alternative method which proved successful here was to firstly oxidise the bicyclic sulphide (32) to its corresponding sulphone (34) by stirring with oxone ($2KHSO_5.KHSO_4.K_2SO_4$) in a methanol : water mixture, (1:1), at room temperature for 4 hours[45] to produce the sulphone, after solvent extraction and subsequent

flash chromatography, in 88% yield. Removal of the arylsulphonyl group was then effected by refluxing the sulphone (34) with sodium hydrogen carbonate and sodium dithionite[46] in dimethylformamide : water, (1:1), (scheme 24) via α-addition-elimination to give the bicyclic amide (33) (Scheme 25):

Scheme 24



Scheme 25



A maximum yield of only 44% was obtained, probably due to some of the unstable bicycle being destroyed during the reaction as a result of the high reflux temperature; no reaction was observed (tlc analysis) at room temperature over a period of 7 hours. A greater yield of the bicyclic amide (33) was obtained from the bicyclic sulphide (32) when the sulphone was not purified prior to elimination of the sulphonyl group (58% as opposed to 44%).

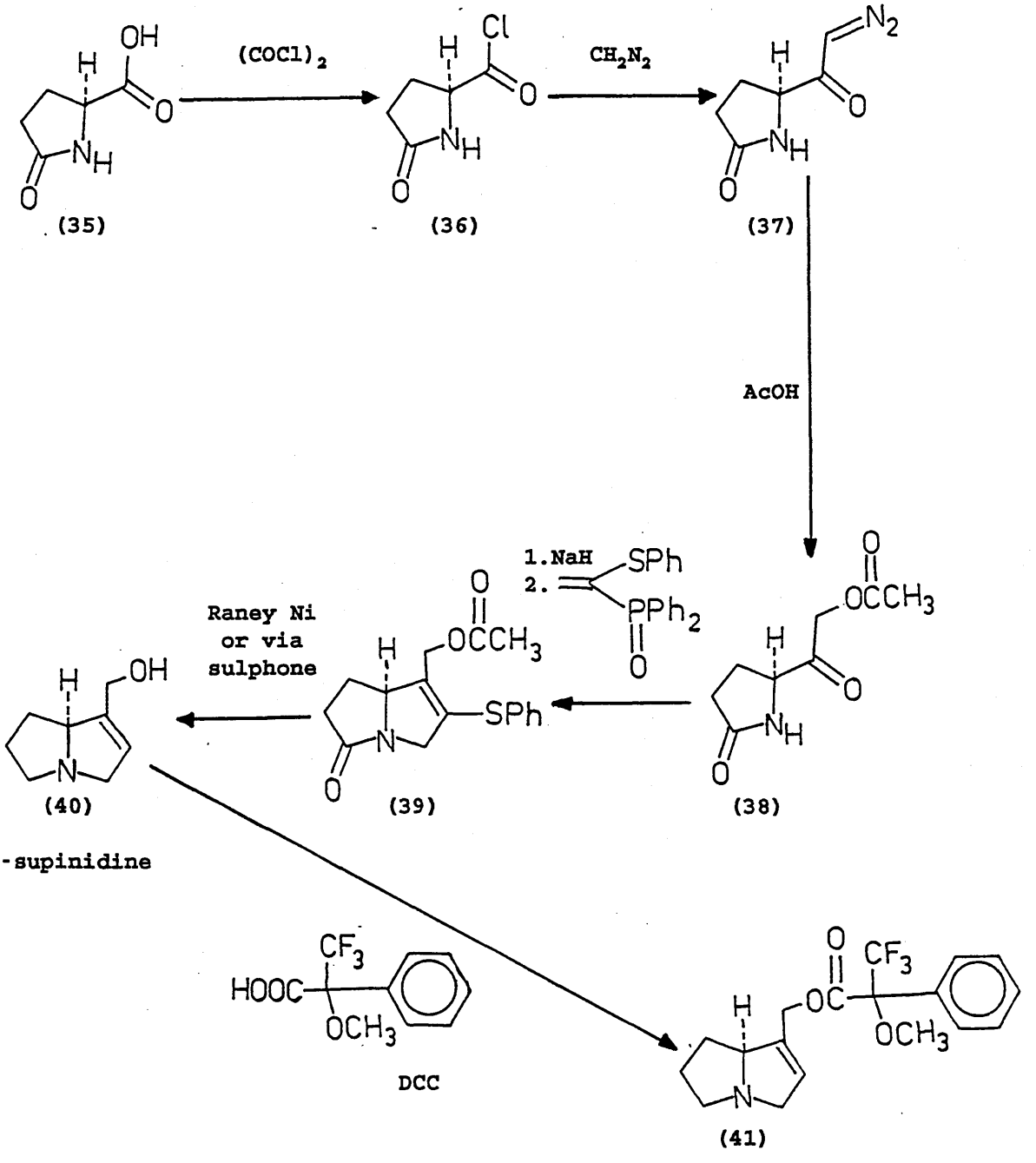
With the investigation of the intramolecular Horner-Wittig cyclisation reaction and the development of a better method for

the subsequent removal of the sulphenyl group completed, the total synthesis of (hopefully) chiral (-)-supinidine could now be addressed.

1.7. Proposed Enantiospecific Synthesis of Supinidine

Scheme 26 outlines the original plan for the enantiospecific synthesis of supinidine. Section 1.9 will describe the modifications that became necessary to this plan in order to achieve success.

Scheme 26



(S)-pyroglutamic acid (or 4-oxoproline) (35) is readily available in chiral form. The synthesis was to involve firstly its conversion to its acid chloride (36). The acid chloride was then to have been converted to its corresponding diazoketone (37) using diazomethane. On treatment with glacial acetic acid, the diazoketone was then to form its acetoxy derivative (38). This intermediate was then to have undergone an intramolecular Horner-Wittig cyclisation reaction to form the functionalised pyrrolizidine core (39). Hydrogenolysis with Raney nickel, or alternatively oxidation to the sulphone followed by elimination of the sulphonyl group, was to have removed the sulphenyl group from the bicyclic ester (39), and subsequent reduction using lithium aluminium hydride was to have cleaved the ester and reduced the amine to produce supinidine (40).

Retention of chirality was to be investigated using the Mosher's ester of an appropriate bicyclic alcohol.

The key step in this proposal was the intramolecular Horner-Wittig cyclisation reaction, whereby the acetoxyketone (41) was used to create the fused bicyclic core. It is therefore appropriate at this point to look in detail at this reaction in terms of its mechanism and development, and thus to show the reasons for its choice as the basis of this project.

1.8.1. Attempts to synthesise supinidine according to the proposed pathway

(S)-pyroglutamyl chloride (36) was prepared from (S)-pyroglutamic acid (35) by stirring with oxalyl chloride in chloroform at 0^0C with dimethylformamide as catalyst[48]. The product was obtained as a black tar which showed all the correct signals on proton NMR and infrared but which was obtained in >100% yield and still produced a faint odour of the chlorinating agent. The preparation was repeated without using dimethylformamide as a catalyst. The reaction took slightly longer to complete and after work-up gave the same results.

Reaction with diazomethane[49] produced numerous fractions on tlc which were UV-active and gave positive reactions with 2,4-dinitrophenylhydrazine spray and with acidified potassium manganate (VII) spray, indicating unsaturation and the presence of a carbonyl group; many of these fractions also exhibited the diazo stretch signal on infrared spectra as a strong, sharp peak at 2100cm^{-1}. All fractions produced proton NMR spectra, which showed more peaks than would be expected, were not well resolved and were very difficult to integrate with any confidence.

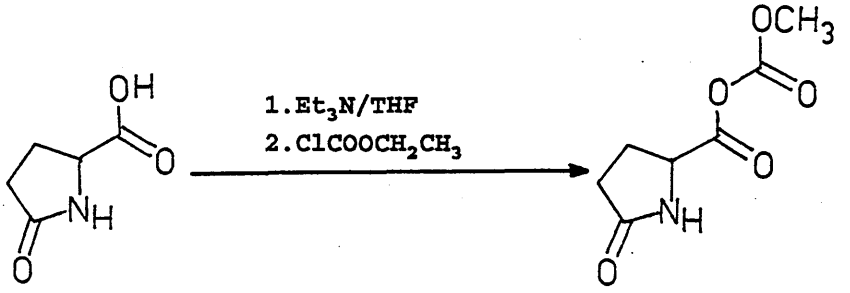
Since the reaction of acid chlorides with diazomethane is reputed to be very fast, giving the required product in good yield[50], the problem here appeared to lie in the preparation of the acid chloride (36) from the acid (37).

The acid (35) was refluxed with thionyl chloride both neat and in chloroform solution, but evaporation again gave a black tar in >100% yield with the same, correct signals on infrared and still with a faint odour of the chlorinating agent. The tar was washed several times with dry diethyl ether with rotary

evaporation in order to remove any residual thionyl chloride that might have been occluded in the tar[49b], but with no visible change in the appearance of the product. Reaction with diazomethane produced the same results as before.

Another attempted route to the diazoketone (37) was to firstly convert (S)-pyroglutamic acid (35) to the mixed anhydride (42) by forming the triethylammonium salt of the acid and reacting this salt with ethyl chloroformate[50d] (scheme 27).

Scheme 27



(35) (42)

Only the starting acid (35) as its triethylammonium salt could be isolated, as shown by its ^1H NMR spectrum. Possibly no reaction occurred due to this salt not being soluble in tetrahydrofuran. These results were disappointing since a recent report[51] describes diazoketone preparation from amino acids with no apparent problems. It seems that the cyclic nature of pyroglutamic acid alters its chemical behaviour in some subtle way. We were to encounter this problem in other reactions to be described later.

Acid chloride preparation from N-protected pyroglutamic acid derivatives has been done before with apparent ease where the protecting group was a methyl or a tertiary butyloxy carbonyl group[52]; we chose to initially investigate the use of a benzyl group; this group would provide UV-activity and characteristic

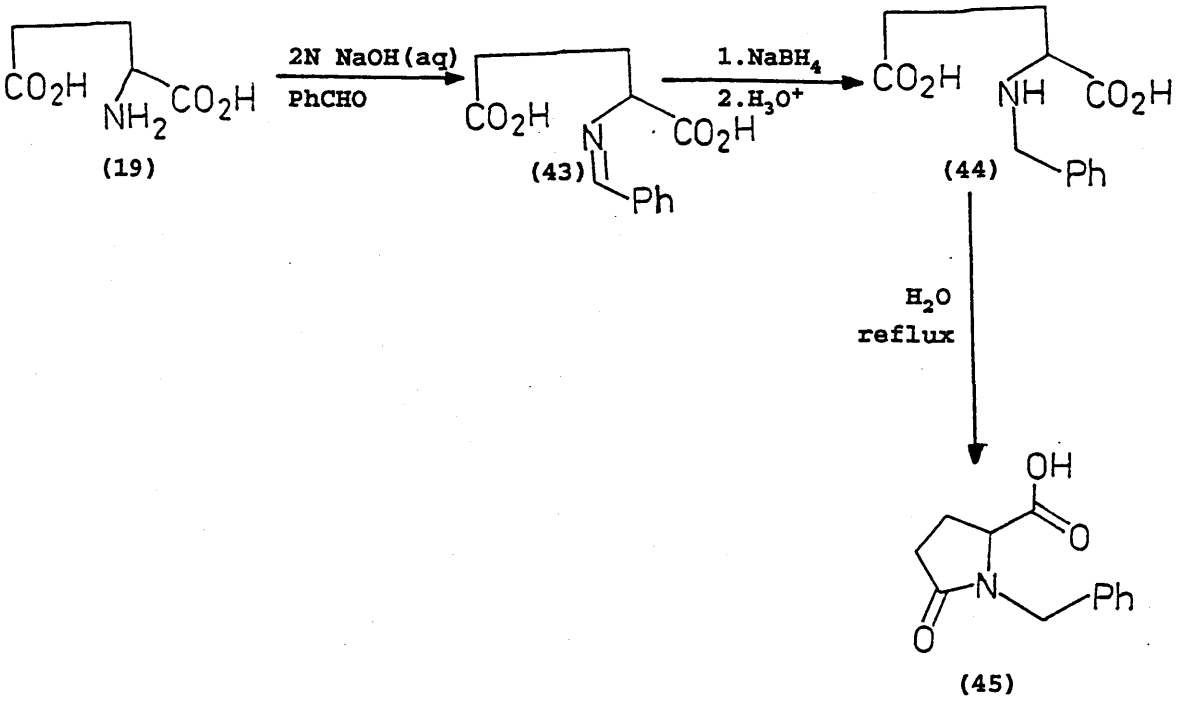
proton NMR signals, both of these properties being useful in monitoring reactions and confirming isolation of the correct product. Removal of the N-benzyl group was hoped to be effected via hydrogenolysis using palladium on activated charcoal as the catalyst; such a reaction has been done on a diverse range of N-benzylated amide systems before with apparent ease[53].

1.8.2. Progress via the N-benzyl series

Reaction of a fine suspension of (S)-pyroglutamic acid (35) in tetrahydrofuran firstly with sodium hydride to convert the acid to its amide and carboxylate disodium salt, followed by addition of benzyl bromide gave two major products in the form of the required (S)-N-benzyl pyroglutamic acid and its benzyl ester, along with unreacted (S)-pyroglutamic acid (35), although the required N-benzyl acid was in rather poor yield. This reaction was not investigated further, since a more fruitful procedure had been found[54] (scheme 28).

This preparation had been adapted from a standard, general procedure for N-benzylation of amino acids[55]. Since (S)-glutamic acid (19) is reluctantly soluble in anything, it was firstly converted to its disodium salt by adding it to aqueous sodium hydroxide solution. Once in solution, it was then reacted with benzaldehyde as a heterogeneous mixture to form the imine (43), which was then reduced *in situ* by adding sodium borohydride to form (S)-N-benzyl glutamic acid (44) after a work-up culminating in its precipitation from aqueous solution at its isoelectric point. This was then refluxed in distilled water to give (S)-N-benzyl pyroglutamic acid (45) in very good yield.

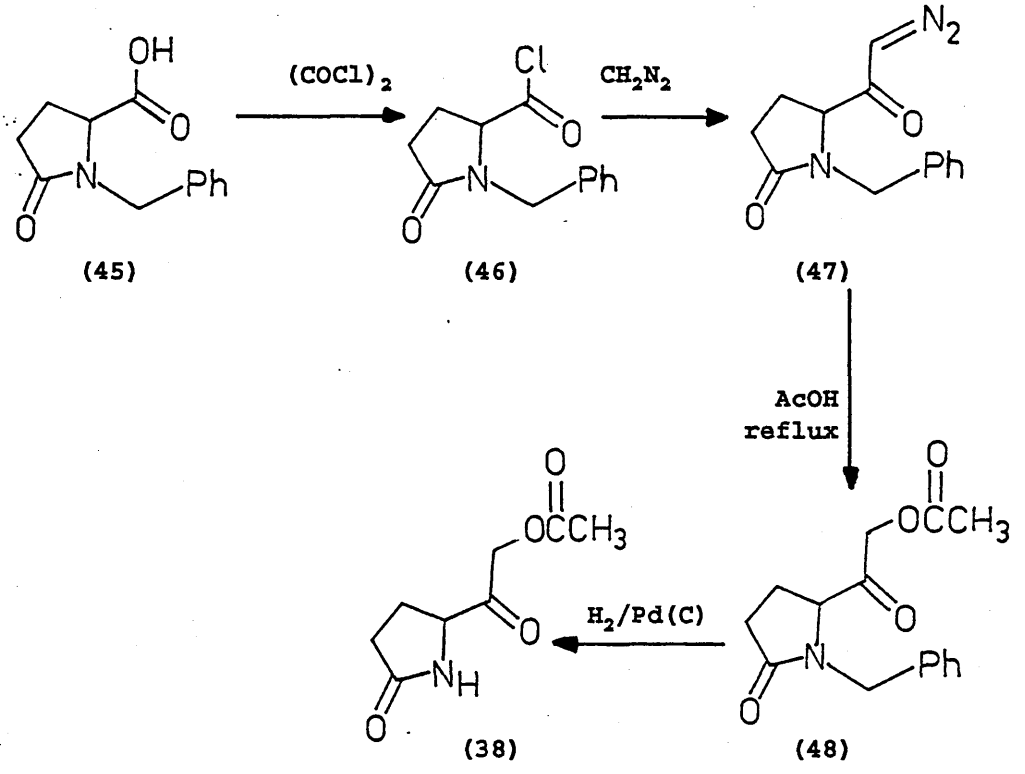
Scheme 28



A major problem encountered in this preparation was that the benzaldehyde disproportionated in aqueous sodium hydroxide solution to a small extent, producing benzyl alcohol and benzoic acid; removal of the benzyl alcohol was effected easily simply by washing the crude aqueous mixture with diethyl ether, but removal of all the benzoic acid was never so easy. Most was removed through washing the crude product with acetone on the filter after its precipitation (this was at pH 4.3-3.0; benzoic acid is insoluble in cold, acidic aqueous solution, and so it was also precipitated). Any which remained was carried through the cyclisation and also extracted into dichloromethane along with the cyclised N-benzyl acid. Since (S)-N-benzyl pyroglutamic acid had an r.f. of around 0.15 in ethyl acetate, whereas benzoic acid had an r.f. of around 0.8-0.9, it was usual to column out the unwanted

benzoic acid at this stage. However, conventional chromatography often failed to remove it all, so flash chromatography had to be used here; this was, of course, a much quicker and more efficient method of purification, but when large amounts of (S)-N-benzyl pyroglutamic acid were required, it served to make the progress significantly slower,as only relatively small amounts could be used at any one time.

Scheme 29

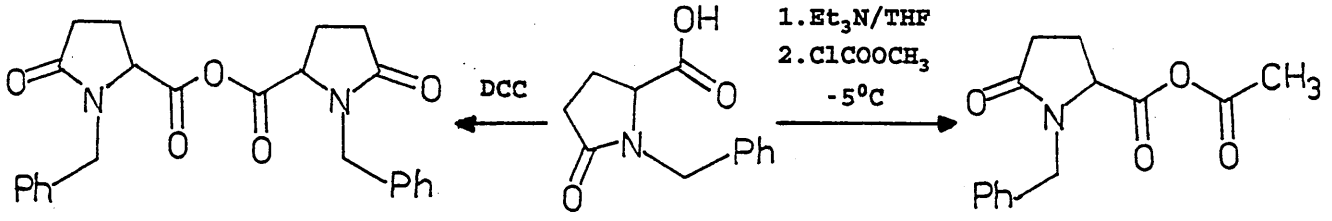


(S)-N-benzyl pyroglutamic acid (45),which now provided almost universal solubility as compared with (S)-pyroglutamic acid (35), was converted to its acid chloride (46) by reaction with oxalyl chloride in tetrahydrofuran at $0^{0}C$. This reaction also resulted in a black tar, but spectra were very clear and resolved, and subsequent reaction with diazomethane did produce the diazoketone (47) in a very reasonable 64% yield, its infrared

spectrum showing very clearly the diazo stretch signal as a sharp peak at 2110cm^{-1} and its proton NMR showing the characteristic multiplets at 1.8-2.6(4H) and 3.8(1H), the latter being overlaid by a multiplet signal for one of the aliphatic benzyl protons; the other aliphatic benzyl proton always appeared as a doublet closer to the aromatic singlet, and in this case occurred at 5.1. The unsaturated proton belonging to the diazomethine group was present as a sharp singlet at 5.4.

(S)-N-benzyl pyroglutamic acid was successfully converted to its symmetrical anhydride (49) using dicyclohexylcarbodiimide and also to the mixed anhydride (50) using the method described earlier for the conversion of (S)-pyroglutamic acid (35) into its mixed anhydride (42)[50d,56] (scheme 30).

Scheme 30



(49) (35) (50)

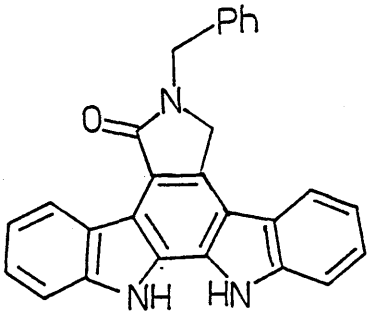
Both of these anhydrides successfully produced the diazoketone (47), but the yield of (47) was maximal from the acid chloride (46).

The diazoketone (47) was converted to the acetoxy ketone (48) by refluxing it in excess glacial acetic acid[49a]. The characteristic proton NMR signals for the benzyl group were retained, with the aromatic singlet at 7.2 and the aliphatic doublet and triplet at 5.0 and 3.8; the singlet for the

unsaturated diazomethylene proton had disappeared and instead a sharp singlet for the saturated methylene group was seen at 4.4.

Unfortunately, hydrogenolysis in tetrahydrofuran using palladium black on activated charcoal as catalyst failed to remove the N-benzyl group to give (38); only the starting material (54) could be recovered. This was surprising, since Fleet and his co-workers[57] had successfully removed an N-benzyl group from a functionalised, saturated, 6-membered cyclic amide in their synthesis of nojirimycin to afford the target molecule in 72% yield. No reaction was visible in our case when the solvent was changed to methanol or when the methanol was acidified 5% with concentrated hydrochloric acid.

Raphael *et al*[58] also experienced the failure of hydrogenolysis of an amide N-benzyl group by this method in their efforts to synthesise staurosporinone.



N-benzyl staurosporinone

Despite the fact that this failure occurred at the final stage of their synthesis, no investigation of the reaction was carried out and they proceeded with unprotected amides. Our work had shown that this was not possible in our case, and so it was decided to go back to glutamic acid and use an alternative N-protecting group. The one we decided on was a carbobenzyloxy grouping, which

would give characteristic aromatic and methylene signals on proton NMR spectra, ester signals on infrared spectra and also the very useful UV-activity for tlc monitoring of reactions. The carbobenzyloxy grouping was also hoped to provide good enough solubility of the cyclic acid and subsequent intermediates to facilitate the choice of a reasonable range of solvents. It was similarly hoped to remove this grouping from a suitable monocyclic amide via hydrogenolysis in tetrahydrofuran with palladium black on activated charcoal as the catalyst, since Fleet *et al* had also successfully removed this group in their work on the synthesis of nojirimycin, deoxynojirimycin and deoxymannojirimycin[59].

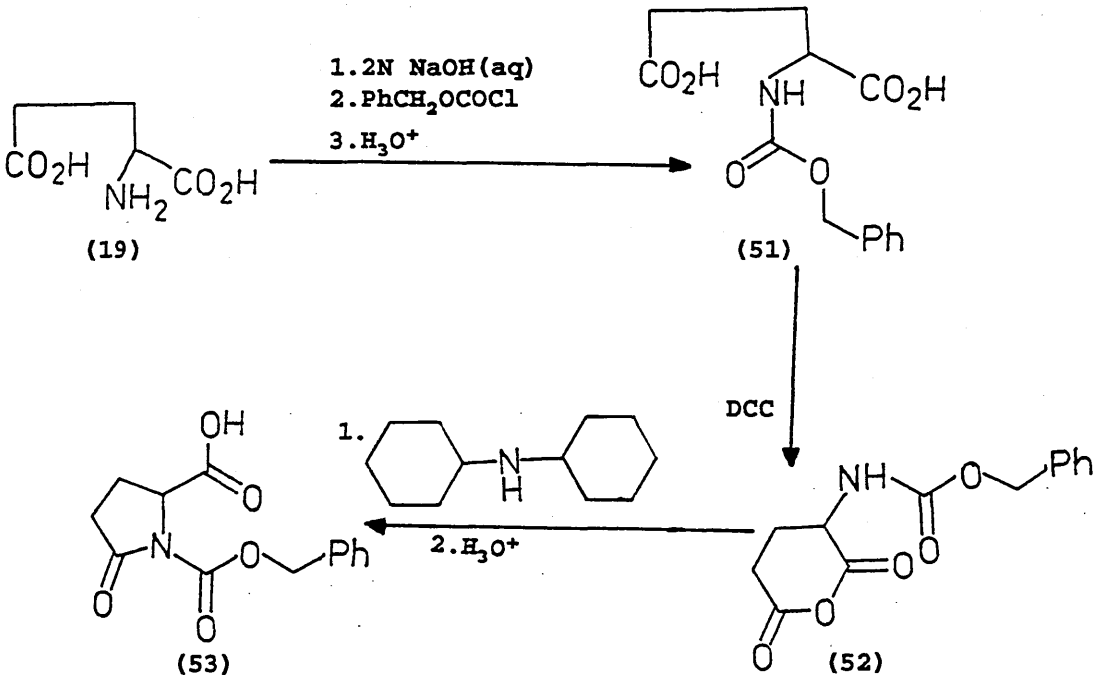
1.8.3. Progress Via the N-carbobenzyloxy Series

(S)-glutamic acid (19) was again converted to its disodium salt by its addition to aqueous sodium hydroxide solution. Reaction of this solution with benzyl chloroformate as a heterogeneous mixture gave the (S)-N-carbobenzyloxy disodium salt with the elimination of hydrogen chloride. An extra mole of sodium hydroxide was present to stop this from forming the amine hydrochloride salt of an unreacted glutamate species; the nitrogen of such an amine hydrochloride salt would not possess a nucleophilic nitrogen atom, and thus would not itself undergo reaction with benzyl chloroformate, therein reducing the yield of the required product. After washing with diethyl ether to remove the by-product benzyl alcohol, acidification of the solution to pH 3 followed by solvent extraction gave (S)-N-carbobenzyloxy glutamic acid (51). The work-up was not a simple matter, however, as most of the product was obtained as a viscous oil at the solvent interface, and had to be isolated separately; this soon solidified on standing but it was not always a clean process. The product which was extracted into dichloromethane very soon began to precipitate out of solution. Precipitation from aqueous solution at the isoelectric point of N-carbobenzyloxy glutamic acid, probably around pH 4 may also have precipitated any unreacted (S)-glutamic acid, whose pI is at about 4.3), and so drying over magnesium sulphate followed its removal via filtration had to be a speedy operation in order not to lose the product.

(S)-N-carbobenzyloxy glutamic was then converted to its intramolecular anhydride (52) using dicyclohexylcarbodiimide. Cleavage of this anhydride followed by immediate intramolecular formation of the amide was catalysed by dicyclohexylamine,

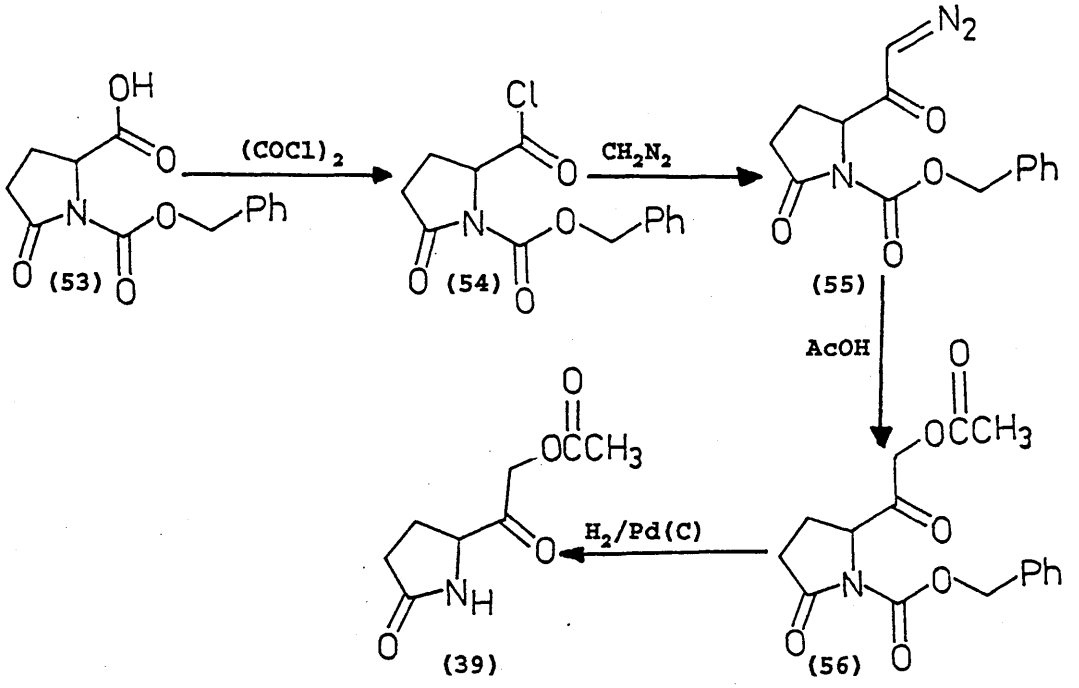
producing (S)-N-carbobenzyloxy pyroglutamic acid (53) in very good yield (scheme 31).

Scheme 31



Conversion of (S)-N-carbobenzyloxy glutamic acid (53) into (S)-5-acetoxyacetyl pyrrolidin-2-one (39) proceeded via a pathway analogous to those for the unprotected and N-benzyl series (scheme 32).

Scheme 32



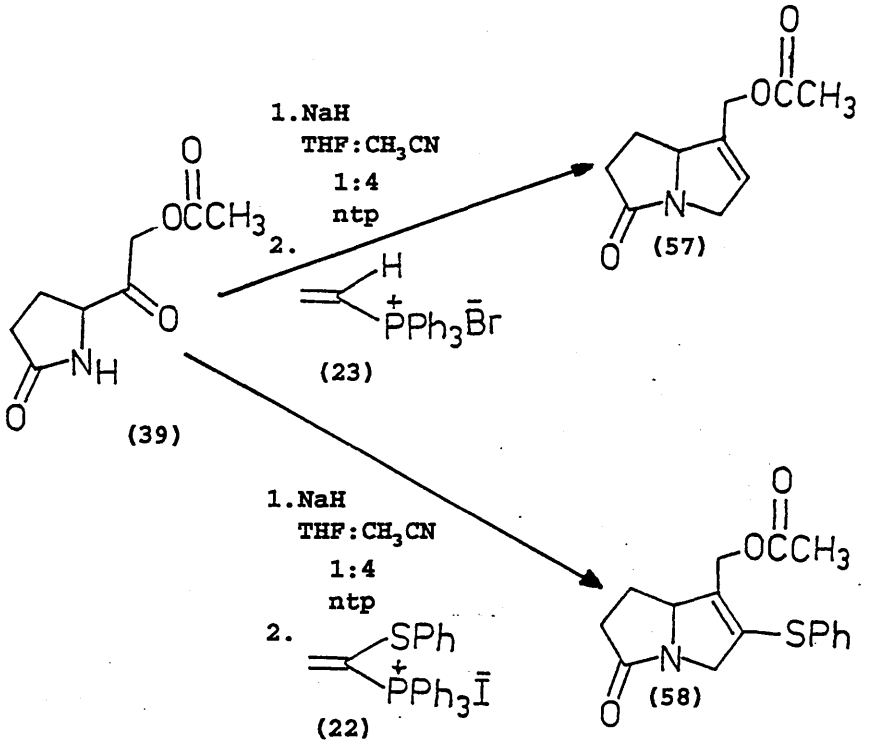
(S)-N-carbobenzyloxy pyroglutamic acid (53) was converted to its acid chloride (54) by stirring with oxalyl chloride in tetrahydrofuran at 0°C. Subsequent work-up again afforded the product as a black tar with clear spectral data, the aliphatic benzyl protons occurring as a singlet at 5.2 on proton NMR. This acid chloride (54) was successfully converted to the corresponding diazoketone (55) in excellent yield (84%), the product for the chiral series being in the form of a bright yellow, crystalline solid, the characteristic benzyl and pyrrolidone signals being retained on proton NMR and infrared along with the production of the diazo stretch signal as a sharp signal at 2100cm^{-1} on infrared . The singlet due to the unsaturated methylene proton of the diazomethyl grouping overlaid the aliphatic benzyl singlet on proton NMR. A melting point was obtained, although it is highly likely that decomposition via a loss of nitrogen occurred during heating. The racemic diazoketone (55) remained as a bright yellow oil. The diazoketone (55) was converted to the acetoxy ketone

through refluxing in glacial acetic acid to give the product as a white solid in 78% yield. The diazomethyl grouping signals were lost and the now saturated acetoxyacetyl methylene group was seen as a sharp singlet at 4.6. The diazo stretch signal was lost from the infrared sprectrum, but extra ester signals were seen. The racemic compound was obtained as a white tar with identical spectral data. The N-protected acetoxy ketone (56) was successfully hydrogenolysed to the key intermediate (S)-5-acetoxyacetyl pyrrolidin-2-one (39) as a white solid in 87% yield. The characteristic signals for the carbobenzyloxy grouping had disappeared from proton NMR and were replaced with the amide proton seen as a characteristic shallow multiplet at 7.1-7.3. This compound proved to be very unstable and the only satisfactory method of storage was in the freezer. All compounds from the acid chloride (54) were rather unstable, although refrigeration had thus far been adequate. The racemic unprotected acetoxyketone (39) was obtained as a colourless oil, and its purity was always in some doubt because the singlets at 2.1 and 4.7 due to the acetoxyacetyl methyl and methylene groups were always seen as doublets on proton NMR; although this product was a mixture of optical isomers, the enantiomers should have had identical physical and chemical properties, so these peaks should still have been seen as singlets. No large, broad peak due to O-H stretch was seen on infrared, which would have indicated that at least some of the the acetoxyacetyl ketone had been hydrolysed during work-up to the hydroxyacetyl ketone. Although the racemic compound did not appear very reliable, no further attention was paid to it at this stage.

Having achieved the synthesis of the required chiral precursor for the key intramolecular cyclisation reaction, which was the core of the project, we were now in a position to attempt the synthesis of the functionalised pyrrolizidine nucleus.

1.9.4. Cyclisation Reactions Leading to Supinidine

Scheme 33



(S)-5-acetoxyacetyl pyrrolidin-2-one (39) was converted to its amide salt using sodium hydride in the co-solvent mixture tetrahydrofuran : acetonitrile, 1:4, at room temperature. Subsequent addition of the vinyl phosphonium salt (23) gave the bicyclic ester (57) in 58% yield after isolation using flash chromatography. Conventional chromatography did not separate the ester (57) from the by-product triphenyl phosphine oxide, and handling time during purification prior to freezing of the ester had to be short because the ester had decomposed on standing on the bench overnight at room temperature during earlier preparations.

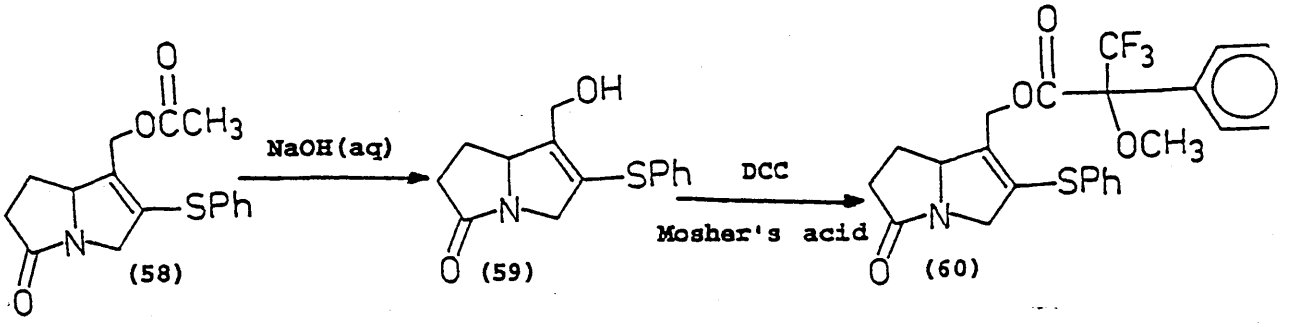
Similarly, reaction of the amide salt of (39) with the vinyl phosphonium salt (22) afforded the bicyclic sulphenyl ester (58),

which proved very difficult to separate from triphenyl phosphine oxide, even when using flash chromatography. The best solvent system proved to be neat ethyl acetate, but even then the ester ran only very slightly ahead of triphenyl phosphine oxide. Thus, the only way of isolating the ester (58) to get an accurate yield was to run several successive columns on those fractions contaminated with triphenyl phosphine oxide, combining the fractions of pure ester only and discarding those of triphenyl phosphine oxide only, although the involvement of more practical steps would inevitably result in the loss of some of the required product. A crude yield based on proton NMR could not be taken, since the integral ratio of the product was based on the aromatic singlet of the sulphenyl group product, and if some of the by-product triphenyl phosphine oxide remained, the aromatic singlet of the required ester (58) was overlaid by the aromatic signals due to triphenyl phosphine oxide, making it impossible to determine the amount of the required product (58) was present in the mixture. Once complete data had been obtained, it was usual to put the ester (58) through the saponification step to its corresponding alcohol in crude form, as the alcohol ran far enough behind triphenyl phosphine oxide in ethyl acetate to facilitate easy separation using flash chromatography. When the acetoxyketone (39) was cyclised using the vinyl phosphine oxide (24), the product ester (58) could not be separated from the excess vinyl phosphine oxide; when the acetoxy ketone (39) was used in excess relative to the vinyl phosphine oxide (24), lower yields of the ester (58) were obtained than from its preparation via the vinyl phosphonium salt (22), despite the long-winded purification process in the latter case.

Lower yields of the esters (57) and (58) were obtained from the racemic acetoxy ketone (39) than from the chiral acetoxy ketone (42% and 45% as opposed to 58% and 62% respectively). This could reinforce the idea that the racemic acetoxy ketone was not pure. The racemic acetoxy ketone always gave the same signals on proton NMR, though the ratios of the peaks in each of the two doublets did vary. The compound could not be investigated more thoroughly due to its high degree of instability.

1.8.5. Investigation of Chirality Following the Intramolecular Horner-Wittig Cyclisation Reaction

Scheme 34

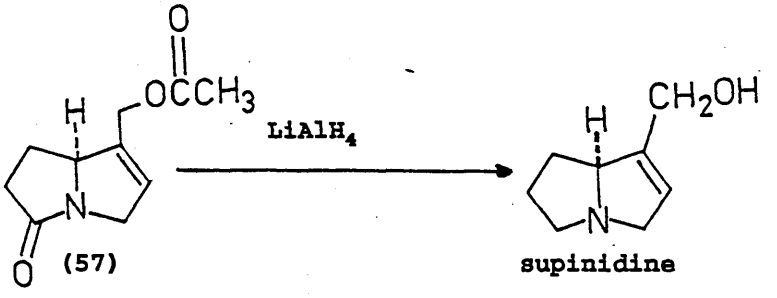


Hydrolysis of the ester (58) to its corresponding alcohol (59) was effected by reaction with aqueous sodium hydroxide solution. Removal of the methanol, solvent extraction and flash chromatography gave the alcohol (59) in 77% yield.

Conversion of the alcohol (59) to its Mosher's ester (60) using dicyclohexylcarbodiimide and (R)-Mosher's acid. The 250MHz ^{1}H NMR spectrum of the Mosher's ester (60) suggested that only one diastereoisomer (S,R) was present, since the $-OCH_3$ and $-OCH_2-$ groups particularly appeared as sharp singlets. Thus it can be deduced that the tertiary carbon at the bis ring junction had remained in its chiral (S)-configuration; if at any stage thus far in the synthesis some material had been converted to the (R)-form, this would have led to the production of the Mosher's ester as (S,R) and (R,R) diastereoisomers. Consequently these diastereoisomers would have had slightly different physical properties, and the mixture should have shown some doubling up of these (and other peaks). Optical purity was also confirmed by ^{13}C NMR. Ideally the corresponding Mosher's ester should have also been prepared from racemic glutamic acid, but unfortunately insufficient material and time were available.

1.8.6. Modifications of the Bicyclic Core towards Pyrrolizidine Alkaloids

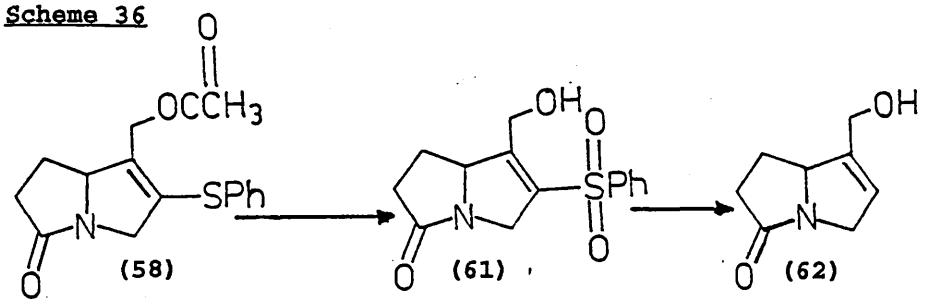
Scheme 35



(57) supinidine

Since the bicyclic ester (57) has already been reported as being converted into supinidine[20,21,23] (scheme 35), we can already claim its synthesis via our pathway, although optical purity cannot be claimed without further investigation. There remained, however, the problem of removing the sulphenyl group from the bicyclic ester (58). Previous work[26] on the analogous 1-methyl series involved its hydrogenolysis using a Raney nickel catalyst, but this proved temperamental in that it often also reduced the 1,2 carbon-carbon double bond. Earlier work on this project found a more reliable method consisting of firstly oxidation of the sulphide to the corresponding sulphone using oxone ($2KHSO_5.KHSO_4.K_2SO_4$), followed by elimination of the sulphonyl group using sodium hydrogen carbonate and sodium dithionite, and so the removal of the sulphenyl group from the bicyclic ester (58) by this latter method was investigated (scheme 36).

Scheme 36

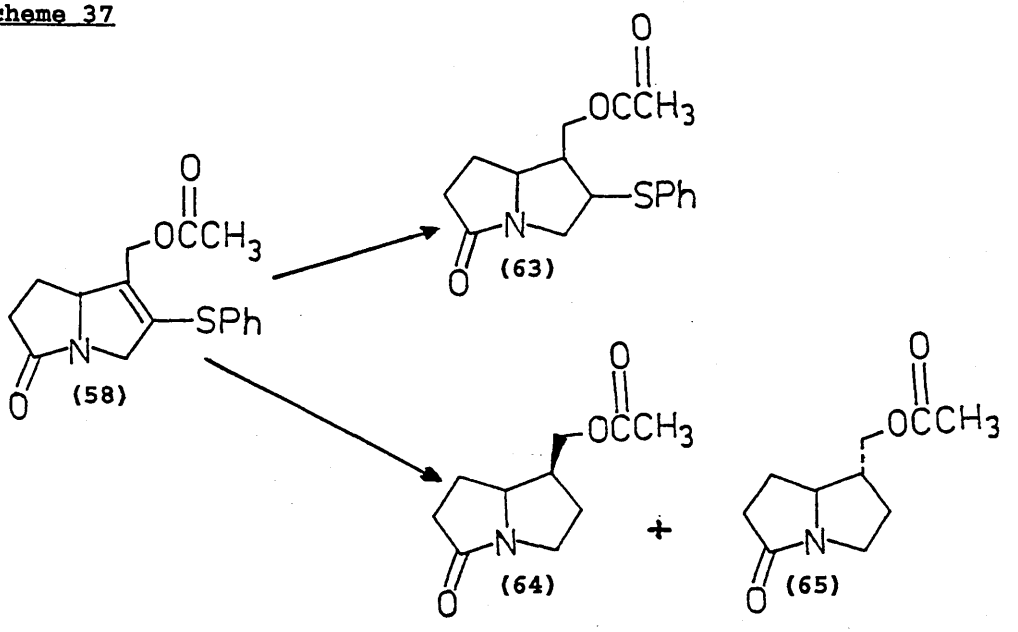


The bicyclic ester (58) was treated with oxone, stirring at room temperature in water : methanol, 1:1, for 4.5 hours followed by solvent extraction and flash chromatography. Subsequent proton NMR analysis showed that although the sulphide had indeed been oxidised to the sulphone by the replacement of the aromatic singlet with a multiplet with a splitting ratio of roughly 2:3. The same spectrum also showed no sign of the sharp singlet due to the methyl group of the acetyl functionality, which for (58) had occurred at 2.0. Infrared showed a broad peak at 3450cm^{-1} along with the disappearance of the ester carbonyl signals at 1740 and 1700cm^{-1}, thus indicating that in the oxidation process, the ester grouping had been saponified to the corresponding alcohol to produce the sulphone alcohol (61) in a very respectable yield of 77%. This was not really surprising, since the hydrolysis of the bicyclic ester (58) prior to the Mosher's protection was effected simply by stirring it in aqueous sodium hydroxide solution at room temperature, and since oxone is a complex of potassium salts, a similar hydrolysis could be expected. The sulphone alcohol (61) refluxed with sodium hydrogen carbonate and sodium dithionite in water : dimethylformamide, 1:1, which afforded the unprotected alcohol (62) after solvent extraction and subsequent flash chromatography in 42% yield, presumably by the same mechanism as for the 1-methyl series described earlier. This alcohol has been

previously reported as being converted to supinidine via reduction of the amide using lithium aluminium hydride[23].

It was hoped that by stirring the bicyclic ester (58) in tetrahydrofuran with tris (triphenyl phosphine) rhodium (I) chloride under a hydrogen atmosphere, the sulphenyl grouping would be removed via hydrogenolysis and the carbon-carbon double bond would be reduced to form a mixture of the esters (64) and (65). Reduction of the amide goup with lithium aluminium hydride would then have led to the naturally-occurring pyrrolizidine alkaloids isoretronecanol and trachelanthamidine respectively; some form of analysis (it was now known that the Mosher's acid protection reaction had not worked on the ester (58)) would prove they had been synthesised in chiral, pharmacologically-active (S) form. However, the principal product isolated using flash chromatography was shown to be the saturated sulphenyl ester (63). This was deduced from proton NMR, which showed a doubling of the singlets due to the aromatic and methyl protons at 7.25 and 2.1 respectively. Doubling of these peaks would be expected, because the rhodium atom could co-ordinate to the carbon-carbon double bond from either face. The peaks comprising these doublets were not equivalent; in each case one peak was very small compared to the other, suggesting preferential attack from one particular face, despite the fact that such a bicyclic system, due to the amide and alkene groups, would be expected to be close to planar.

Scheme 37

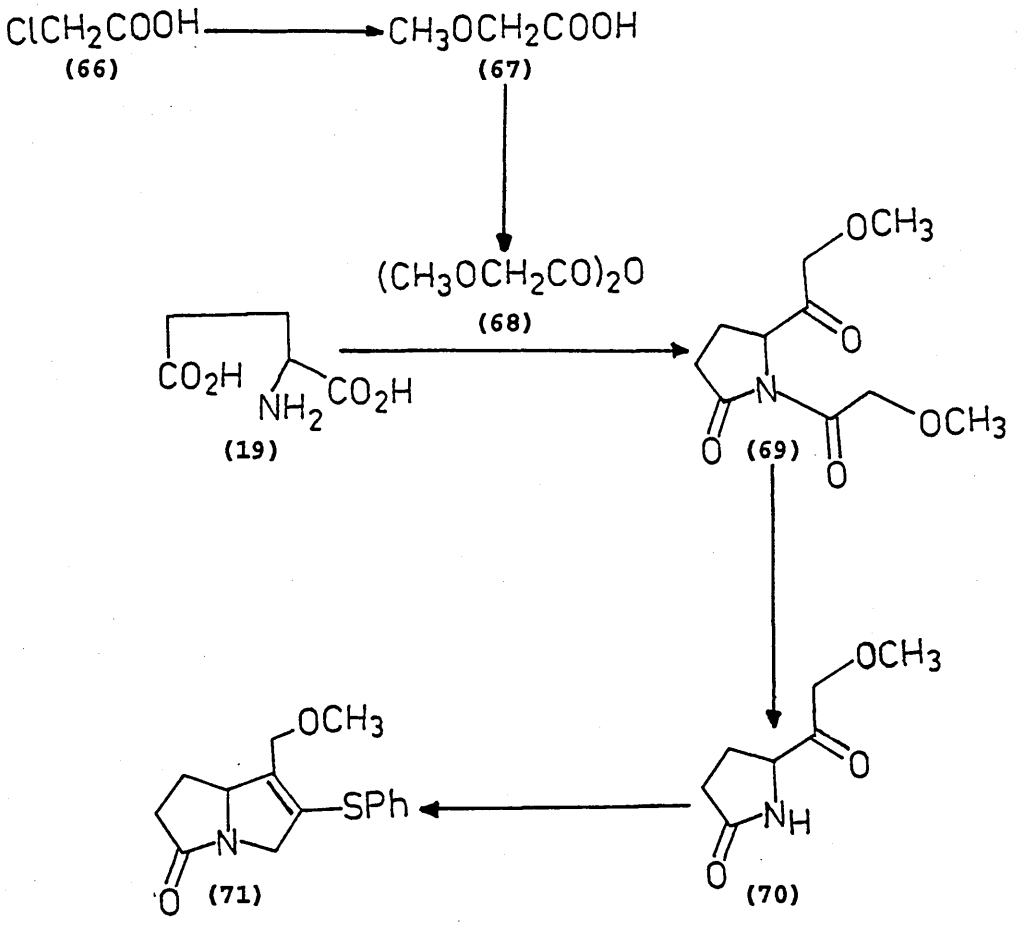


Removal of the sulphenyl group from (63) either via hydrogenolysis with a Raney nickel catalyst or via its oxidation to the corresponding sulphone and cleavage of the sulphone group to afford the esters (64) and (65) was not attempted because we had run out of the sulphenyl ester and there was insufficient time to produce any more of it.

1.8.7. Other routes to Pyrrolizidine Alkaloids from Glutamic acid (19)

During the course of the initial attempts to synthesise supinidine according to the proposed pathway, several alternative routes were investigated. Some of these were hoped to achieve the target alkaloid in chiral form, whereas others would have been expected to produce it in racemic form. All of these schemes were problematic, and none of them got as far as the formation of the pyrrolizidine core.

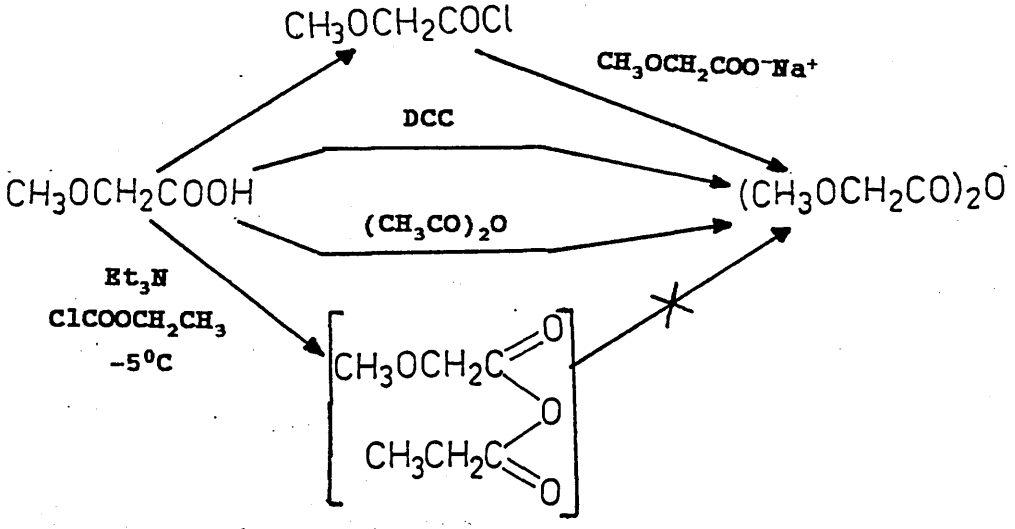
(a) Scheme 38



Methoxyacetic acid (67) was prepared from chloroacetic acid (66) via a straightforward nucleophilic reaction[63]. However, despite the sodium methoxide being present in excess, not all the chloroacetic acid was used up, and the latter proved inseparable

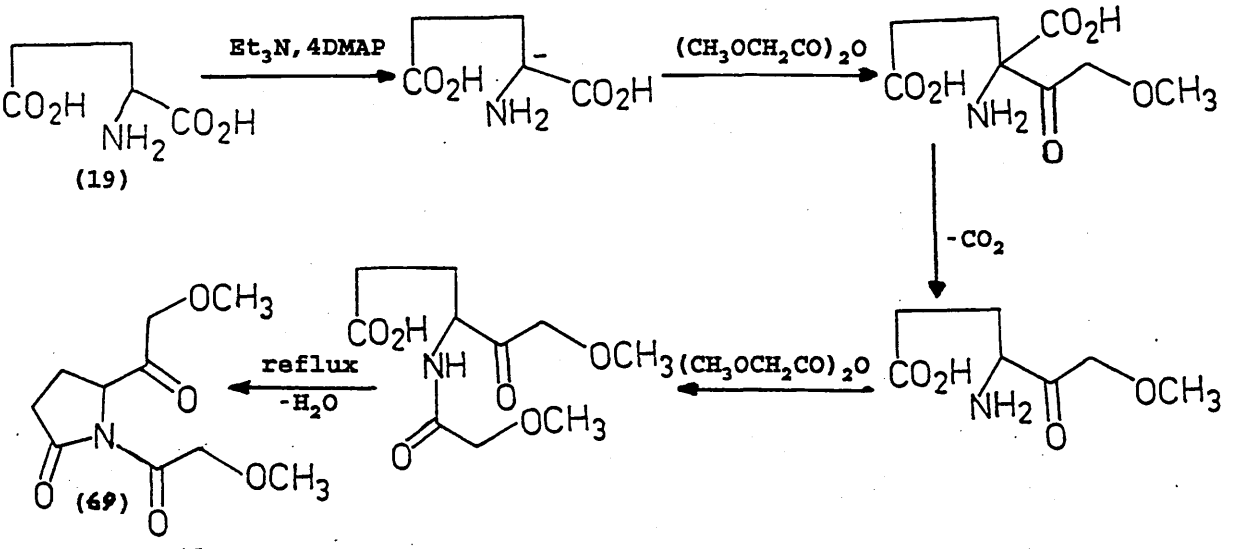
from methoxyacetic acid during vacuum distillation. Commercially-available methoxyacetic acid (67) was converted to its symmetrical anhydride (68) via a number of different methods[64] (scheme 39), but once again, purification from the starting acid and by-products proved very problematic; various columns and column packings were used for the vacuum distillation, including a 6ft. spinning band vacuum distillation apparatus. The pure anhydride was obtained on a few occasions, but its isolation was unreliable.

Scheme 39



Glutamic acid (19) was put through a Dakin-West reaction with methoxyacetic anhydride (68), triethylamine and 4-dimethylamino pyridine to produce 1,5-dimethoxyacetyl pyrrolidin-2-one (69), probably via the following mechanism[65] (scheme 40).

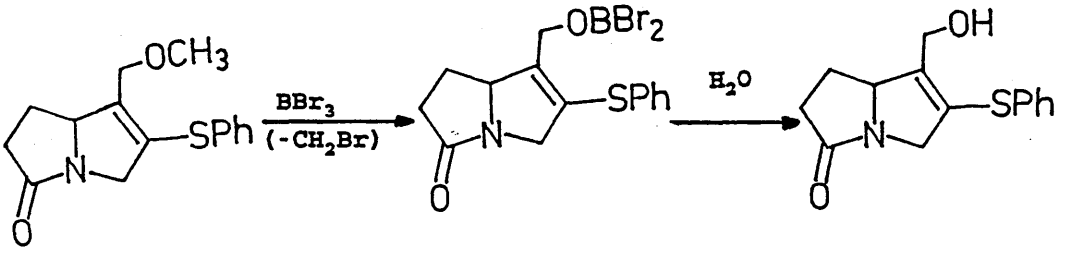
Scheme 40



Isolation of (69) proved difficult. Since the work-up for the similarly-produced, analogous 1,5-diacetyl pyrrolidin-2-one (20) was removal of triethylamine on the rotary evaporator followed by vacuum distillation of the remaining crude mixture to afford the product, this work-up was also tried in this case. Unfortunately, the product could not be distilled at 1.5mmHg. After addition of dichloromethane to the charred residue followed by filtration to remove the carbon and evaporation, chromatography with ethyl acetate as eluent gave the required product but in only 2% yield, probably because most of it had been destroyed during the attempted distillation. The product was in the form of a bright yellow oil, and its ^1H NMR spectrum clearly showed two sharp singlets for the two methyl groups at 3.4 and 3.6, the remaining pyrrolidone signals being consistent with those of 1,5-diacetyl pyrrolidin-2-one (20). Unfortunately, despite several attempts, the reaction could not be reproduced, and by this time further

data on the batch already synthesised could not be obtained because it had meanwhile decomposed.

Should (69) have been reproduced on a large enough scale, it was then hoped to have undergone aqueous alkaline hydrolysis to give 5-methoxyacetyl pyrrolidin-2-one (70). Cyclisation of this amide via the intramolecular reaction would then have led to the 1-methoxymethyl pyrrolizidin-5-one core (71). Cleavage of the methyl ether might then have been effected by firstly forming the orthoboric ester of the corresponding alcohol followed by its hydrolysis using 10% alkali[66].

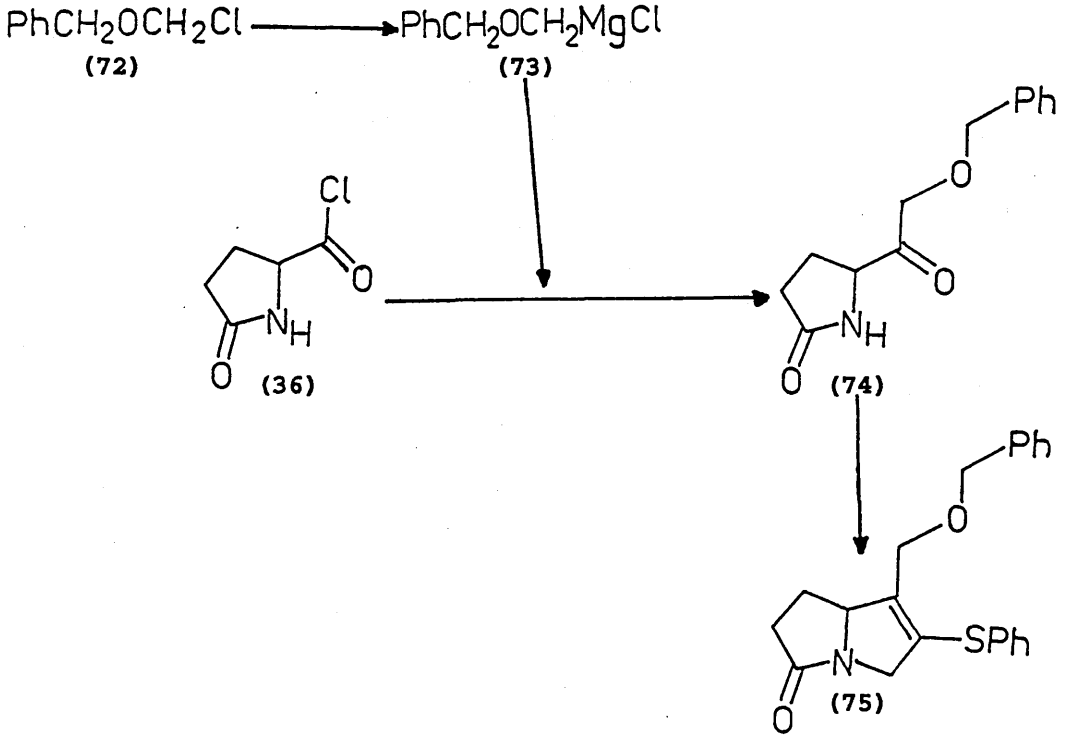


(b) Another route attempted involved the conversion of benzyl chloromethyl ether (72) to its corresponding Grignard reagent (73) by reaction with magnesium turnings in tetrahydrofuran. After the introduction of an iodine crystal as an inititator[67] no reaction was visible, so a few drops of 1,2-dibromoethane were added as an initiator[68]. A definite reaction was observed, producing a darkening of the reaction mixture to a brown colour. The preparation was put through the standard qualitative colour test for a Grignard using Michler's ketone[69]; although definite reactions occurred, they were not as expected[69]. Another test was to react the Grignard with a solution of p-chlorobenzaldehyde in tetrahydrofuran, but despite stirring overnight followed by refluxing, subsequent work-up only isolated the bulk of the starting aldehyde. A further attempt using "active magnesium"

instead of magnesium turnings by refluxing magnesium chloride in tetrahydrofuran with potassium metal for 3 hours[70] followed by reaction with firstly benzyl chloromethyl ether and then p-chlorobenzaldehyde also failed to give positive results; once again, only the original aldehyde was recovered.

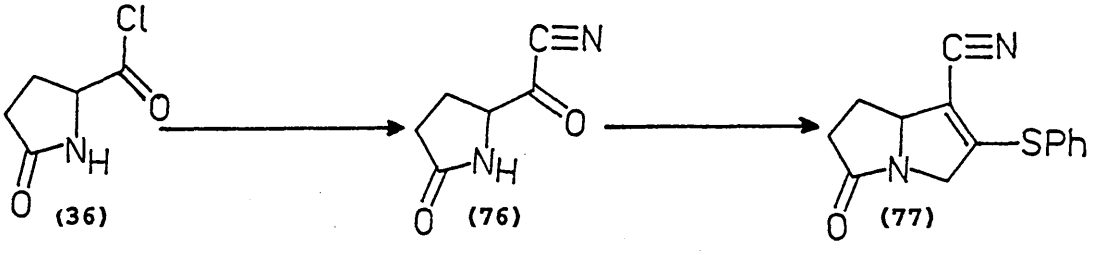
The problems that were currently being encountered in the formation of (S)-pyroglutamyl chloride (36) from (S)-pyroglutamic acid (35) rendered this pathway a non-starter. This was unfortunate, since if it had been successful it could have provided a chiral synthesis of the bicyclic core (74). Cleavage of the benzyl ether was to have been effected using boron tribromide followed by hydrolysis of the orthoboric ester, the pathway ultimately leading to an alternative chiral synthesis of the pyrrolizidine alkaloids supinidine, isoretronecanol and trachelanthamidine (scheme 41).

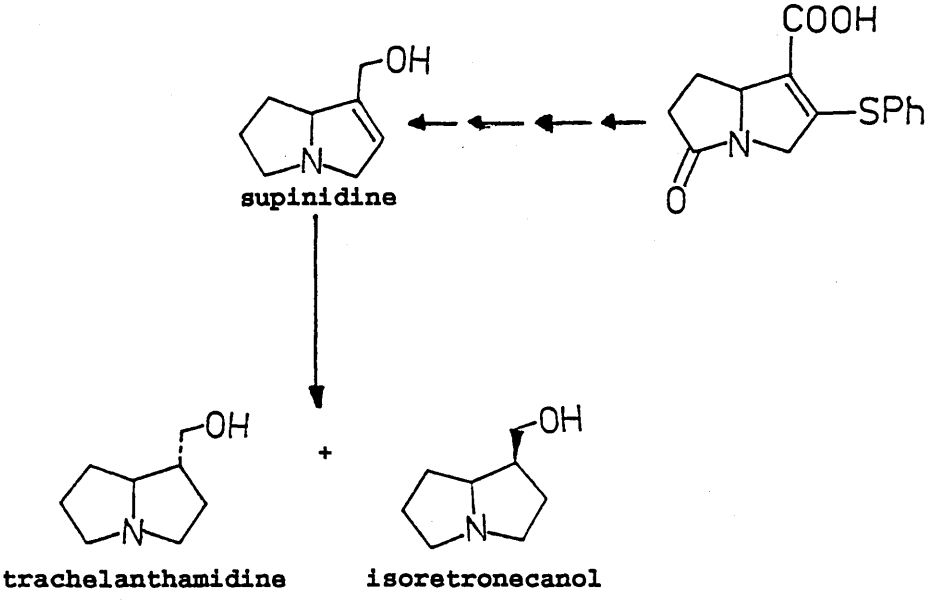
Scheme 41



(c) It was attempted to produce the ketonitrile (76) by reaction of (S)-pyroglutamyl chloride (36) with cuprous cyanide in tetrahydrofuran[71] (scheme 42), but this reaction proved unsuccessful; only unreacted (S)-pyroglutamic acid was recovered. This was another pathway doomed to failure by the problematic acid chloride (36). Should it have worked to produce the monocyclic ketonitrile (76), and had this been successfully cyclised to the bicyclic nitrile (77), it could have provided yet another chiral route from (S)-pyroglutamic acid (35) to the three naturally-occurring pyrrolizidines supinidine, trachelanthamidine and isoretronecanol.

Scheme 42

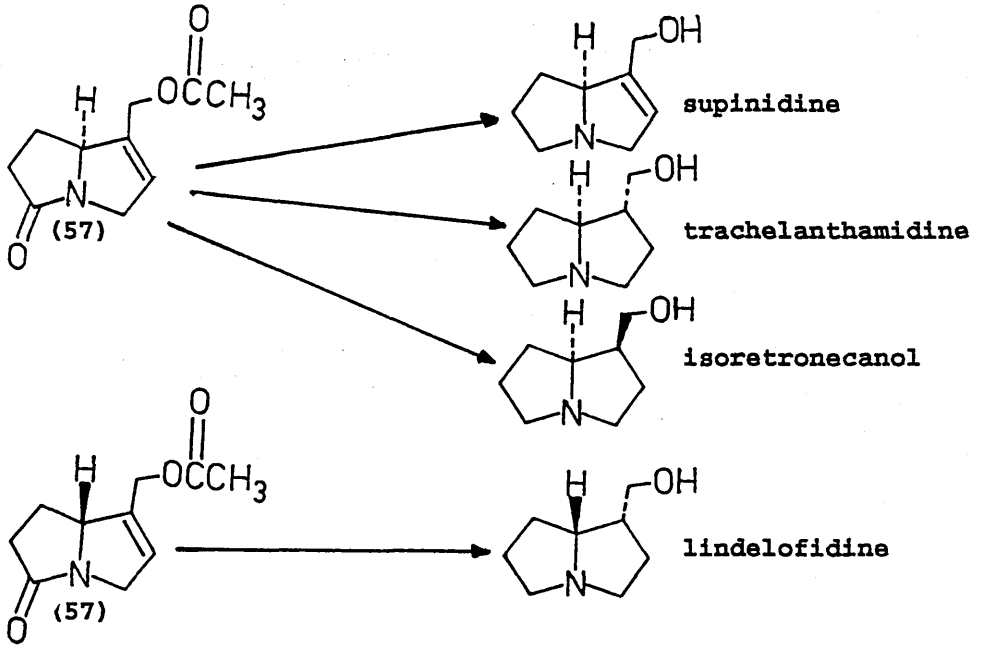




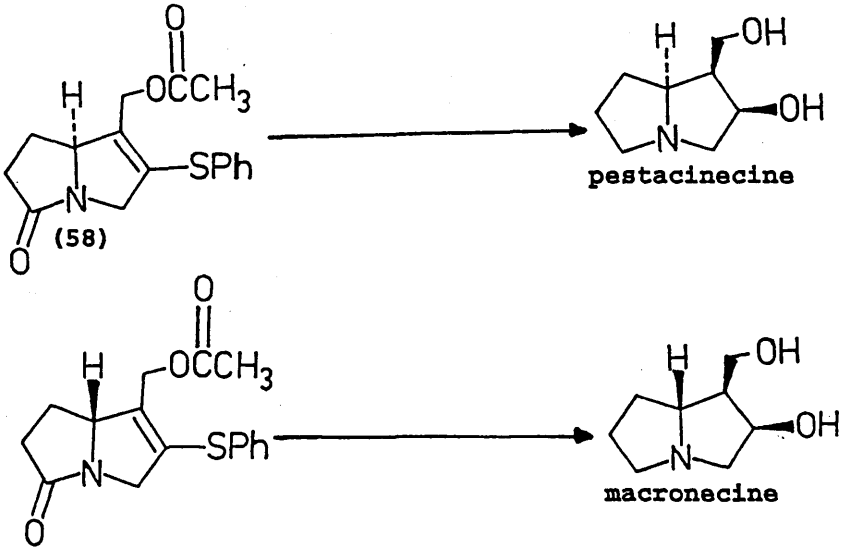
1.8.8. Suggestions for further work

a) Synthesis of necine bases

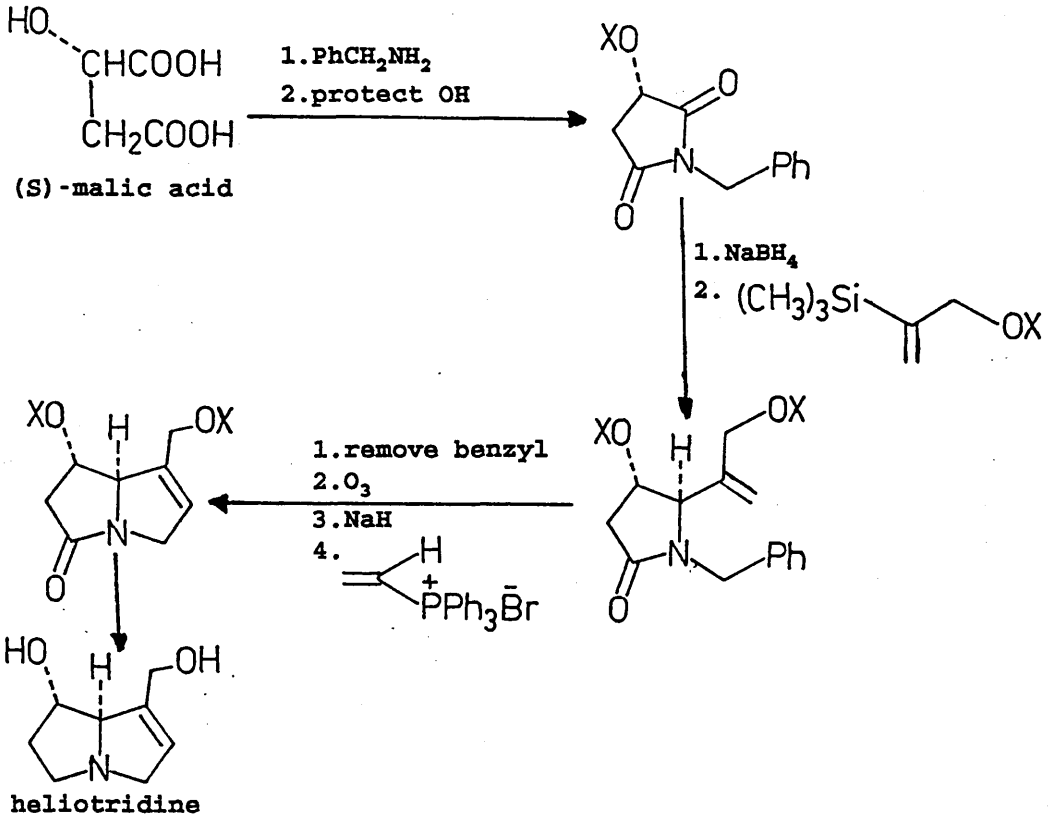
This project has covered the chiral synthesis of the pyrrolizidine bases supinidine, trachelanthamidine and isoretronecanol via the bicyclic acetate (57). The enantiomer of (57) could also lead to the chiral synthesis of the pyrrolizidine base lindelofidine:-



Similarly, the sulphenylated bicyclic ester (58) could lead to the chiral synthesis of the pyrrolizidine bases macronecine and pestacinecine:

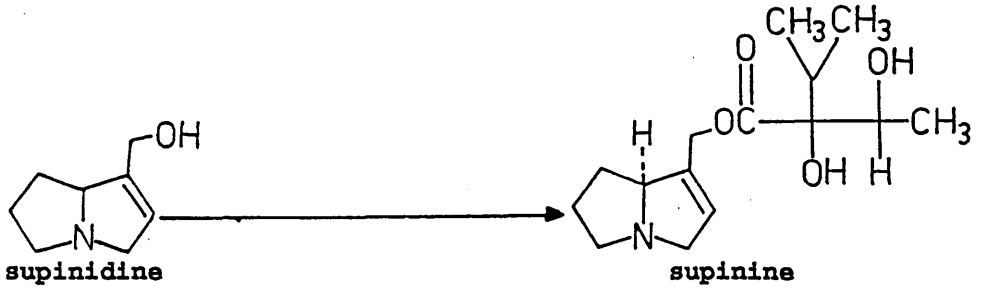


The synthesis of analogues of 5-acetoxyacetyl pyrrolidin-2-one could lead to the chiral synthesis of several other pyrrolizidine bases, as illustrated by the following approach to heliotridine:-



b) Synthesis of naturally-occurring esters

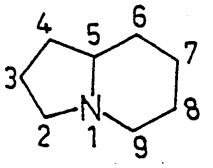
Mono-esterification of the base supinidine could lead to the naturally-occurringpyrrolizidine ester supinine.



INDOLIZIDINE ALKALOIDS

2.1 General

The indolizidine alkaloids constitute quite a large group of compounds which have been isolated from a range of both plant and animal sources. All the indolizidine alkaloids have the core skeletal structure



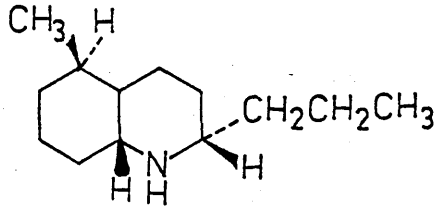
1-azabicyclo(4.3.0)nonane

Some of the indolizidine alkaloid-producing families include *Ipomoea, Elaeocarpus, Tylophora, Prosopsis, Swainsona, Dendrobatidaceae,* and many more[73]. Perhaps the most notable plant family here is *Elaeocarpaceae;* the genus *Elaeocarpus* comprises over two hundred known species, which occur mainly in tropical regions[74,75]. However, the family that is directly relevant to this project is *Dendrobatidaceae,* which includes the brightly-coloured South American poison dart frogs.

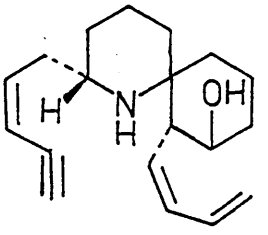
3.2 Dendrobatid Alkaloids

These frogs produce and store their alkaloids in glands in the skin, and their release in secretions is triggered as a defence mechanism under stress[76]. The alkaloids have an extremely potent destructive effect on the mammalian nervous system, and this property was exploited by the South American natives in using the secretions to make poison-tipped arrows[77].

The first class of alkaloids from *Dendrobatidaceae* to be isolated and structurally identified were the batrachotoxins, reported in 1968-69. These were all extremely toxic[77], and are produced only by the Colombian poison-dart frog *Phyllobates aurotaenia*[76,77]. Simpler alkaloids were subsequently isolated from other species of poison frogs of the same family, and in 1969 pumiliotoxin-C was structurally identified. Although it is termed a toxin, this compound has relatively low toxicity[77].



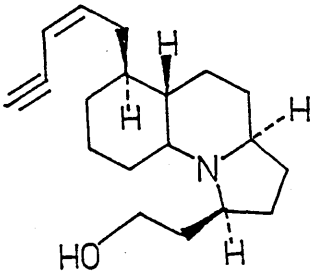
pumiliotoxin-C



histrionicotoxin

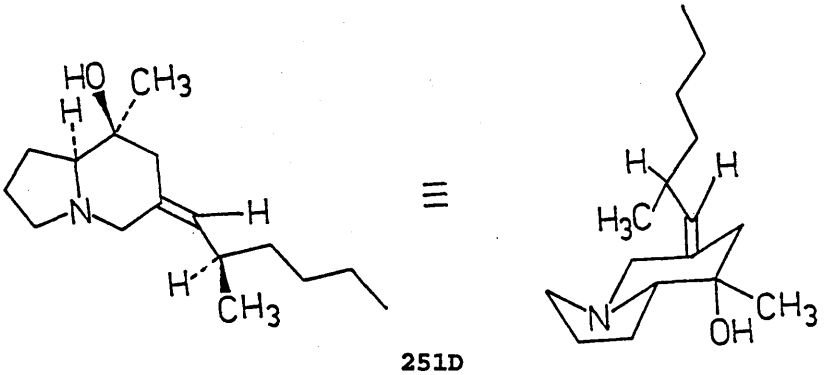
Another class of alkaloids, the histrionicotoxins, was reported in 1971 from another poison frog, *Dendrobates histrionicus*. These were unique to the species and had a spiropiperidine core structure with intriguing acetylenic and allenic centres of unsaturation in the side chain substituents. This class of alkaloids also exhibited relatively low toxicity to mammals[77].

A principal alkaloid isolated from *Dendrobates histrionicus* was gephryotoxin. This was a tricyclic alkaloid which combined the cis-decahydroquinoline bicyclic core as in pumiliotoxin-C with an indolizidine bicyclic core structure, and so was placed in a class of its own. It also exhibited relatively low toxicity to mammals[77].



gephryotoxin

The pumiliotoxin-A class of indolizidine alkaloids were isolated from the Ecuadorean poison frog *Dendrobates tricolor*, and after very difficult separation, the structure of a relatively simple member of the class, the toxin 251D, was elucidated in 1979[78].



251D

Further investigations subsequently isolated and identified some 24 indolizidine alkaloids of the pumiliotoxin-A class, bringing the total number of known alkaloids peculiar to *Dendrobatidaceae* to over 100. This class of pumiliotoxin-A alkaloids differ principally only in the side chain[79]; an allo series of the class contains a 7-hydroxy substituent in the indolizidine core[79].

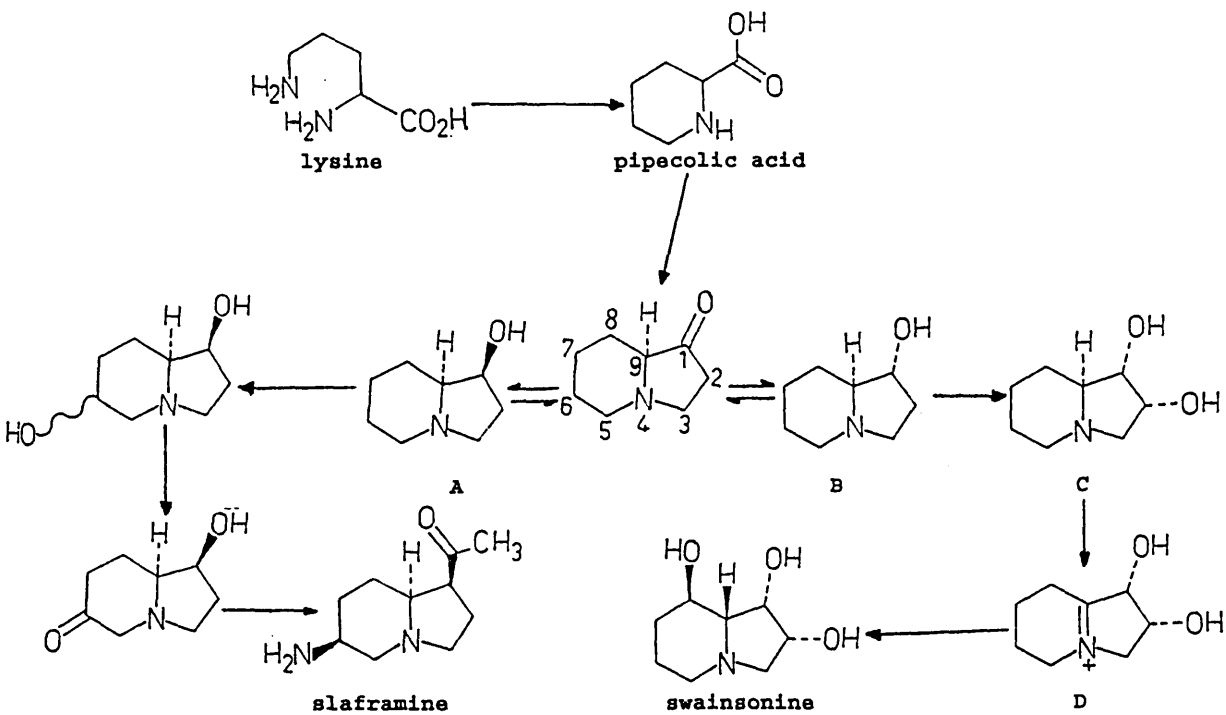
This class of alkaloids is highly toxic, though at least two orders of magnitude less toxic than the batrachotoxins. To give an idea of the potency of the toxins, the extract from one *Phyllobates aurotaenia*, which produces the batrachotoxins, provided the natives with enough poison to tip 50 arrows, each of which was fatal within seconds[77].

This project is concerned with an approach to the synthesis of the toxin 251D. Isolation of the pure alkaloid from natural sources was extremely inefficient - methanolic extracts from 750 *Dendrobates tricolor* provided only 80mg of crude alkaloids and only 21mg of pure 251D[77].

2.3 Indolizidine Biosynthesis

The biosynthetic pathways leading to indolizidine heterocycles still largely remain a mystery, with only a few being reported as a result of investigations into microbial metabolism.

Slaframine and swainsonine are two toxins produced by the fungus *Rhizoctonia leguminicola*. These compounds have been shown to originate from S-lysine and pipecolic acid[80].



Using deuterated material, pipecolic acid has been found to be incorporated into swainsonine with the loss of two deuterium atoms for each metabolite isolated[81]. The bicyclic intermediates A,B and C have been isolated from the fungus and the use of feeding experiments involving deuterated and tritiated A,B and pipecolic acid demonstrated that these materials were incorporated into slaframine and swainsonine[82]. Configuration at C(8a) in

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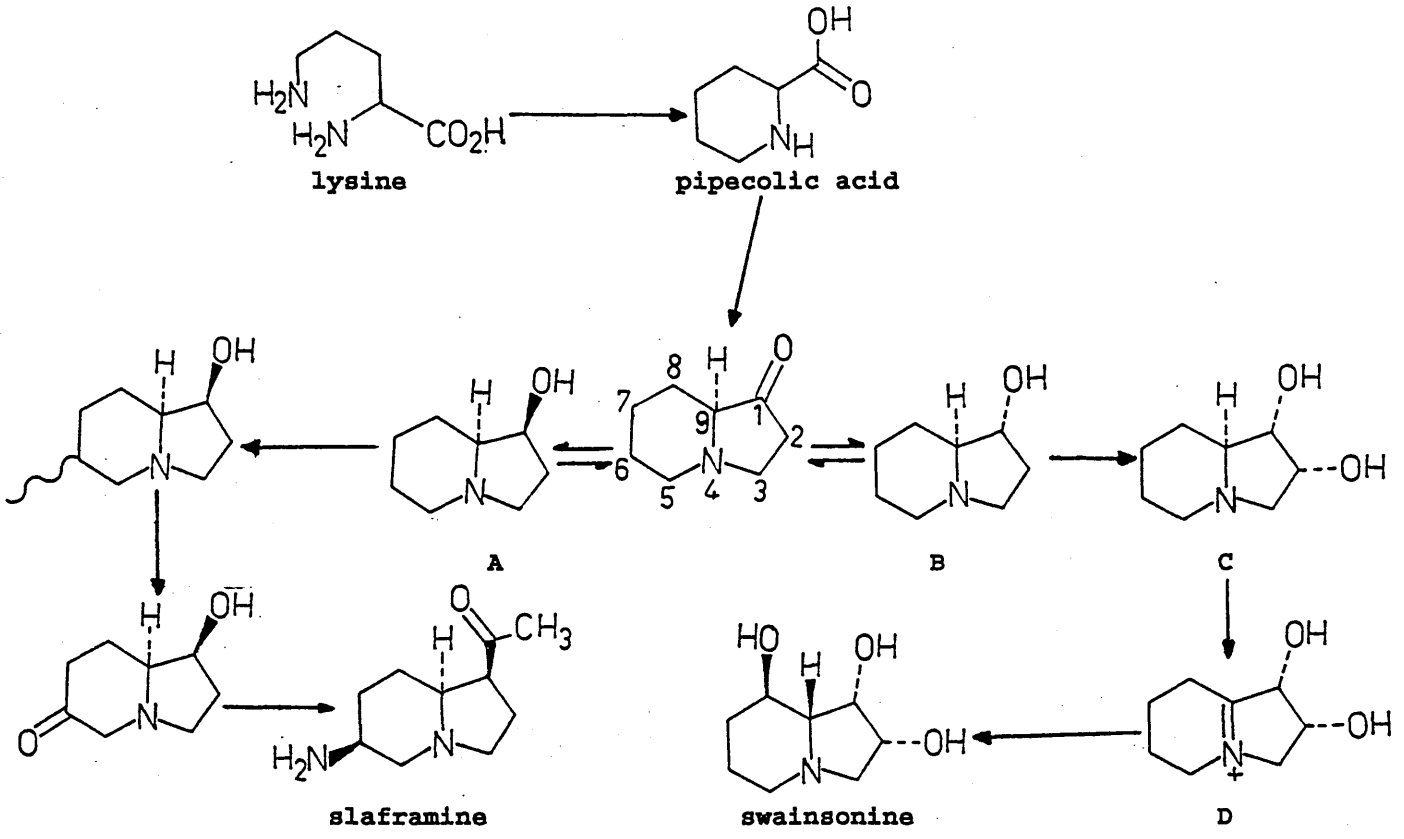

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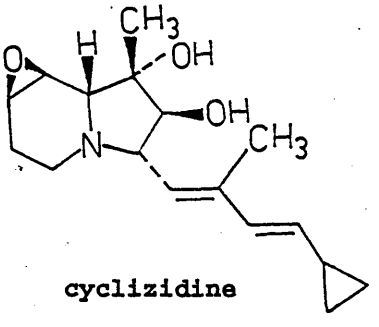
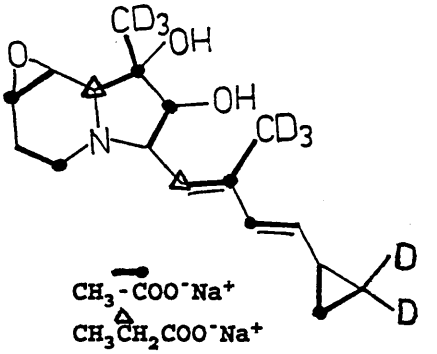
swainsonine is opposite to that in the respective carbon of pipecolic acid. This led to the deduction of D as a suitable intermediate, but this has not been isolated[82,83]. Deuterium was shown to incorporated at C(8a) of swainsonine when (1-$^2H_2$)ethanol was used as a precursor[83]. Swainsonine also occurs in *Swainsona canescens* and *Astragalus sp.* (locoweeds) but its synthesis in these species has not yet been deduced[84]. Swainsonine is a potent inhibitor of the enzyme 2-mannosidase[84]; this is supported by the fact that its absolute configuration in protonated form is similar to that of the mannosyl cation[85].

Cyclizidine is one of only two indolizidine bases produced by *Streptomyces sp.*



cyclizidine



CH_3-$\overset{\bullet}{C}$OO$^-$Na$^+$

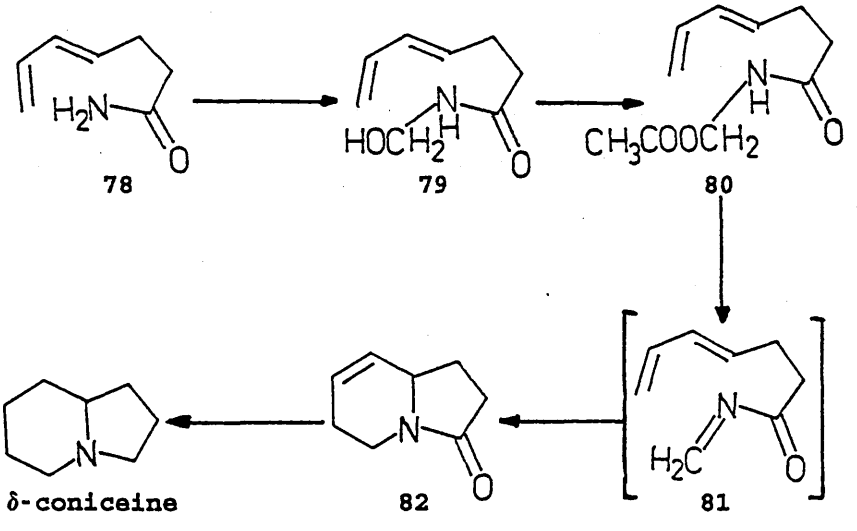
$CH_3\overset{\bullet}{C}H_2COO^-Na^+$

$CD_3CH_2COO^-Na^+$

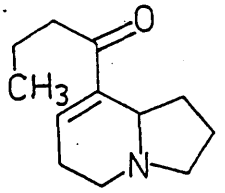
The labelling of C2,C5,C7 and C12 due to feeding with 1-^{13}C acetate indicated biosynthesis via a polyketide pathway. Subsequent experiments using ^{13}C2 acetate and also ^{2}H- and ^{13}C-labelled propionate afforded confirmation[86]. The other toxin produced in *Streptomyces sp.* is indolizomycin, whose structure and hence biosynthesis is very similar.

2.4 Indolizidine Chemical Syntheses

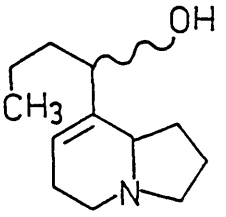
δ-Coniceine, the simplest indolizidine alkaloid, has recently been synthesised via an intramolecular imino Diels-Alder cycloaddition reaction[87]. The amide diene (78) was synthesised in two steps from divinyl carbinol and was converted to its N-methylol (79) with aqueous formaldehyde and sodium hydroxide in glyme. Acetylation of the crude product with acetic acid and pyridine gave the methylol acetate in good yield. Pyrolysis of the acetate through a hot tube of glass helices afforded the lactam in 73% yield via the unstable N-acylimine intermediate formed by elimination of acetic acid from the acetate (80). The N-acylimine was never detected, but was thought to be involved as a result of earlier work by Lasne *et al*[88]. Catalytic hydrogenation of the double bond of (82) followed by reduction of the amide to an amine with diborane gave δ-coniceine.



Weinreb subsequently successfully adapted this method to produce the *Elaeocarpus* alkaloids elaeokinine A and B[87].



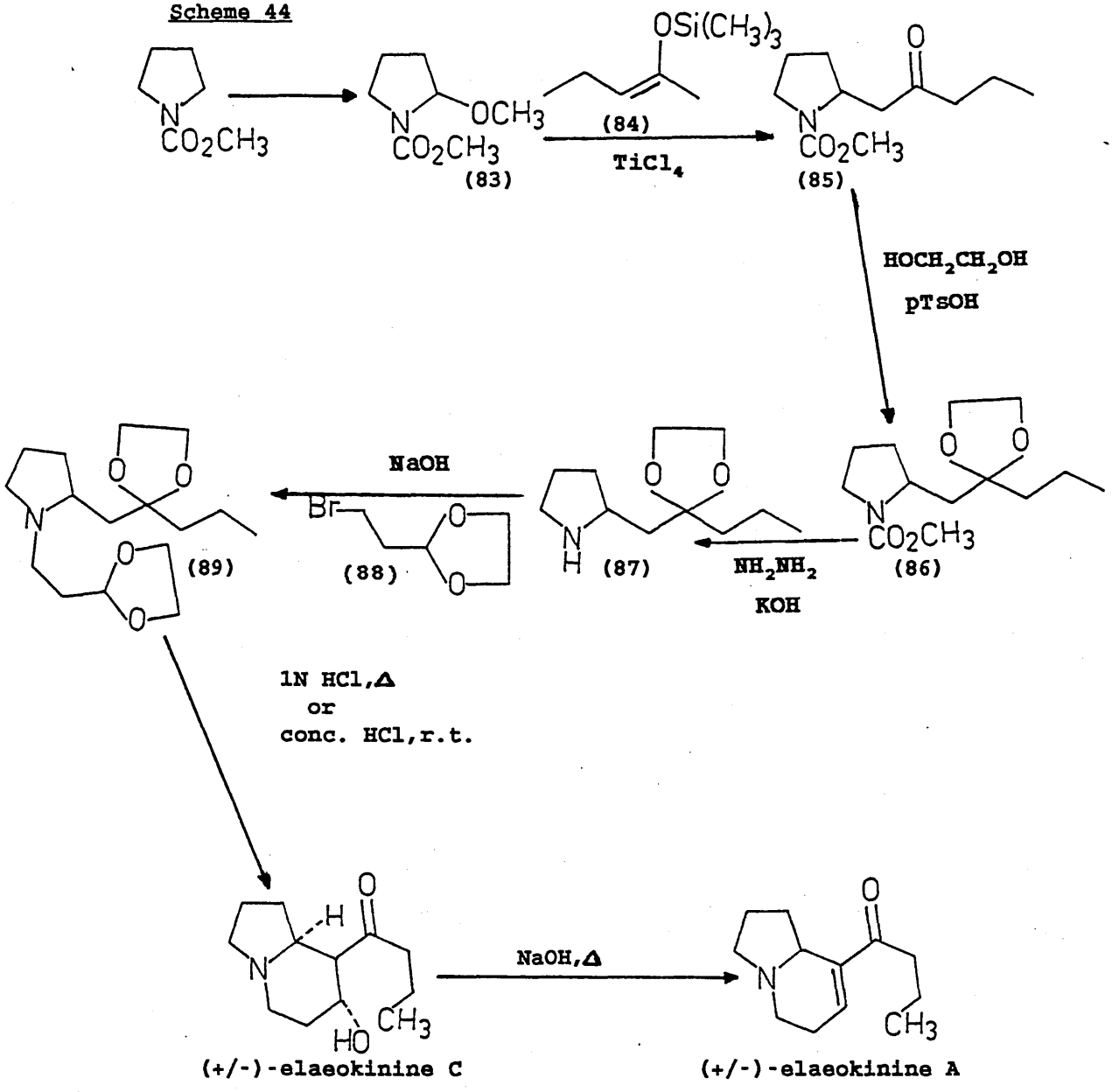
elaeokinine A



elaeokinine B

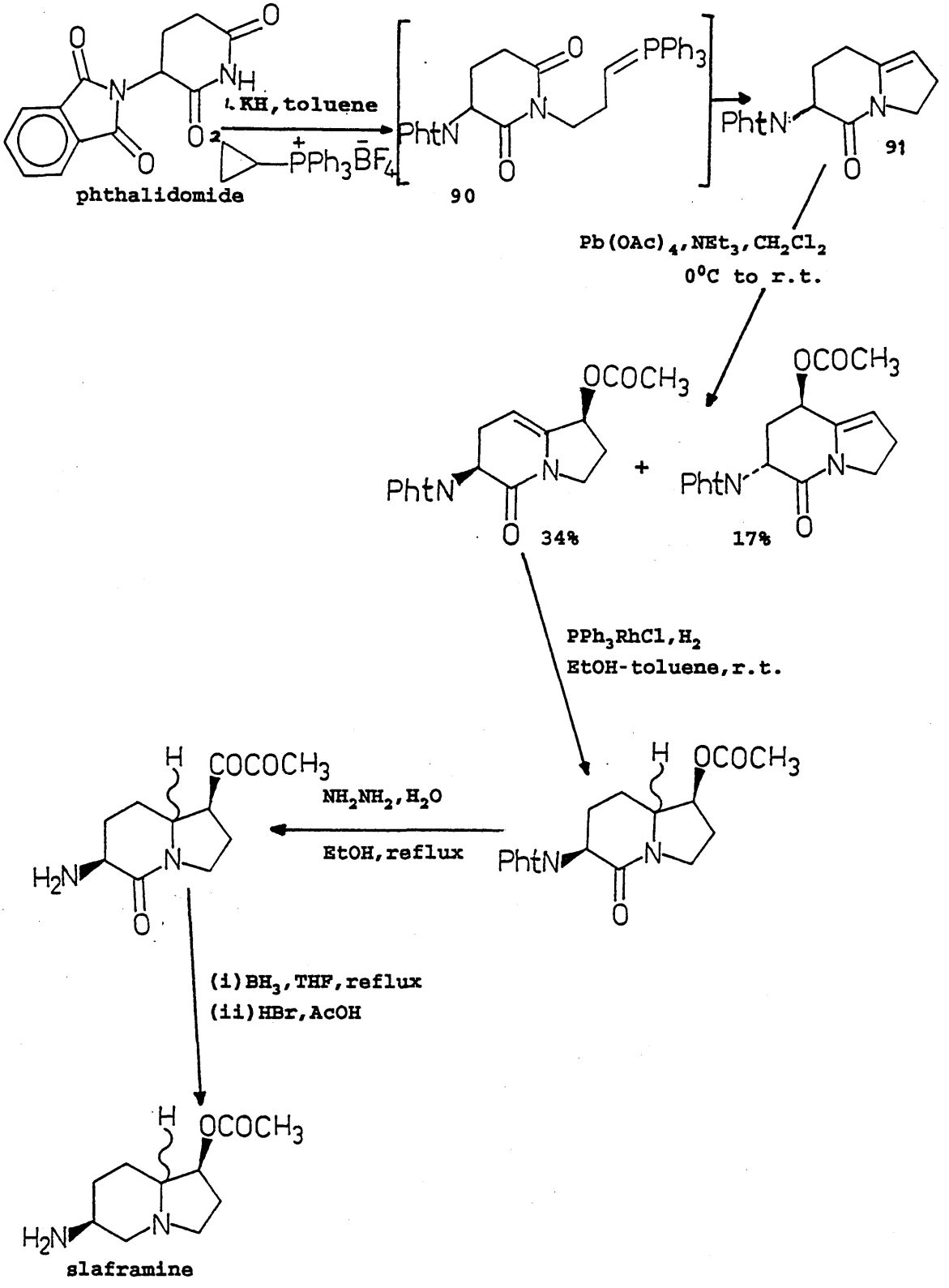
Elaeokinine A has also been successfully synthesised using an anodically-prepared 2-methoxy carbamate as a key intermediate[89]. The carbamate (83) was anodically prepared from 1-(methoxycarbonyl) pyrrolidine in 80% yield. Reaction of (83) with $TiCl_4$ followed by the addition of silyl enol ether (84) gave (85) in 81% yield. The carbonyl of (85) was protected with ethylene glycol, the carbomethoxyl group of (86) was hydrolysed with alkali to give (87), and the bis-ketal (89) of the key intermediate was obtained through N-alkylation of (87) with bromo acetal (88). Aldol condensation of (89) with acid catalysts (1N HCl with heating or conc. HCl at room temperature) gave (+/-)-elaeokinine-C. Successive heating of (89) in 1N HCl and in 1N NaOH gave (+/-)-elaeokinine-A (scheme 44).

Scheme 44



Flitsch *et al*[90] achieved the synthesis of racemic slaframine using intramolecular Wittig olefination of an imide carbonyl group to create the indolizidine core. Cyclisation of the intermediate phosphorane (90) formed from cyclopropyl triphenyl phosphonium tetrafluoroborate and the phthalidomide anion occured regiospecifically at the less sterically hindered carbonyl group to produce the indolizidinone (91). This was oxidised with lead tetraacetate in the presence of triethylamine to a mixture of the allylic acetate (92) and its isomer (93) (scheme 45).

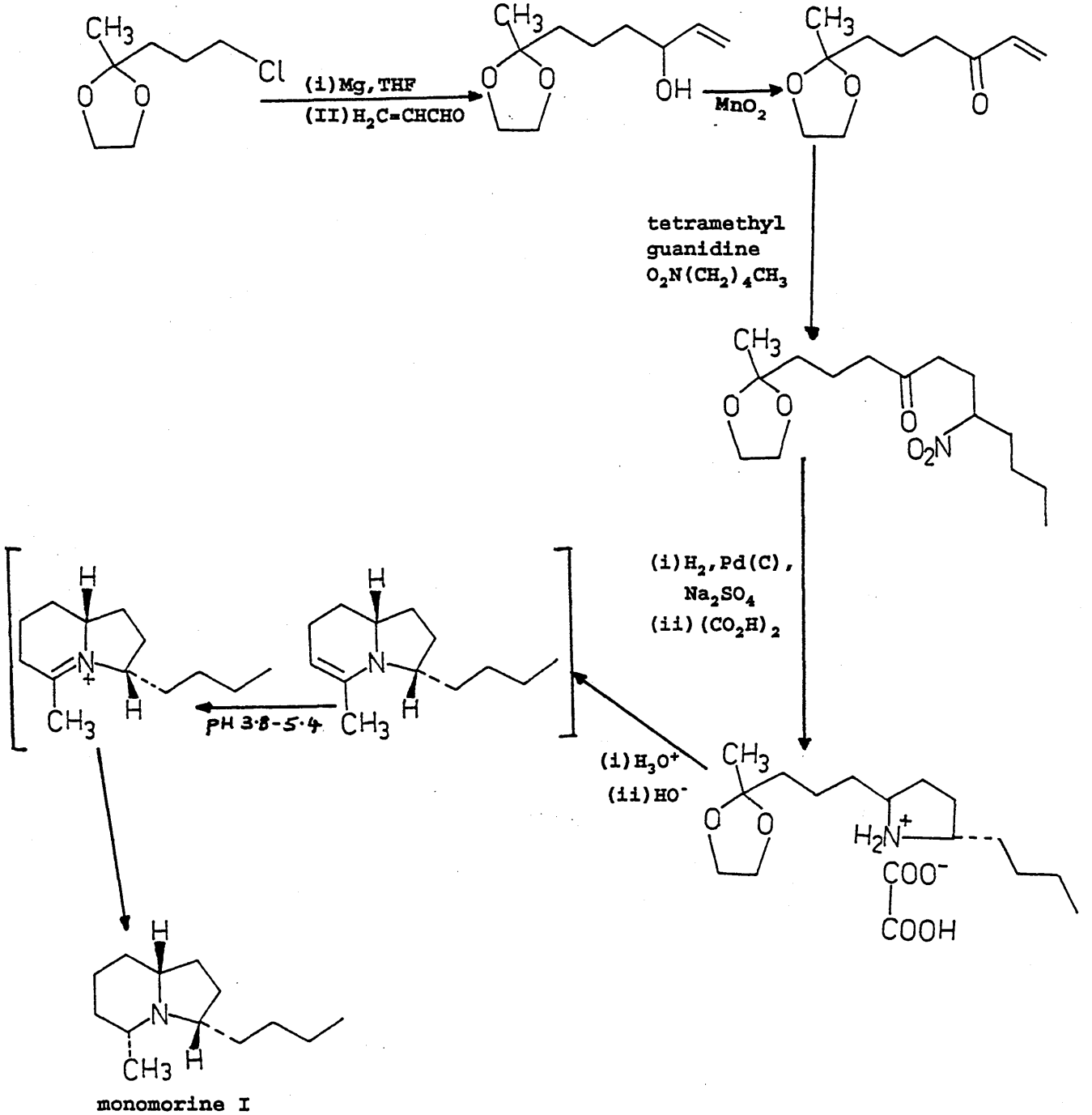
Scheme 45



A synthesis of monomorine I, a component of the trail pheromone of the ant *Monomorium pharaonis*, was developed which utilised a stereoelectronically controlled nucleophilic capture of a

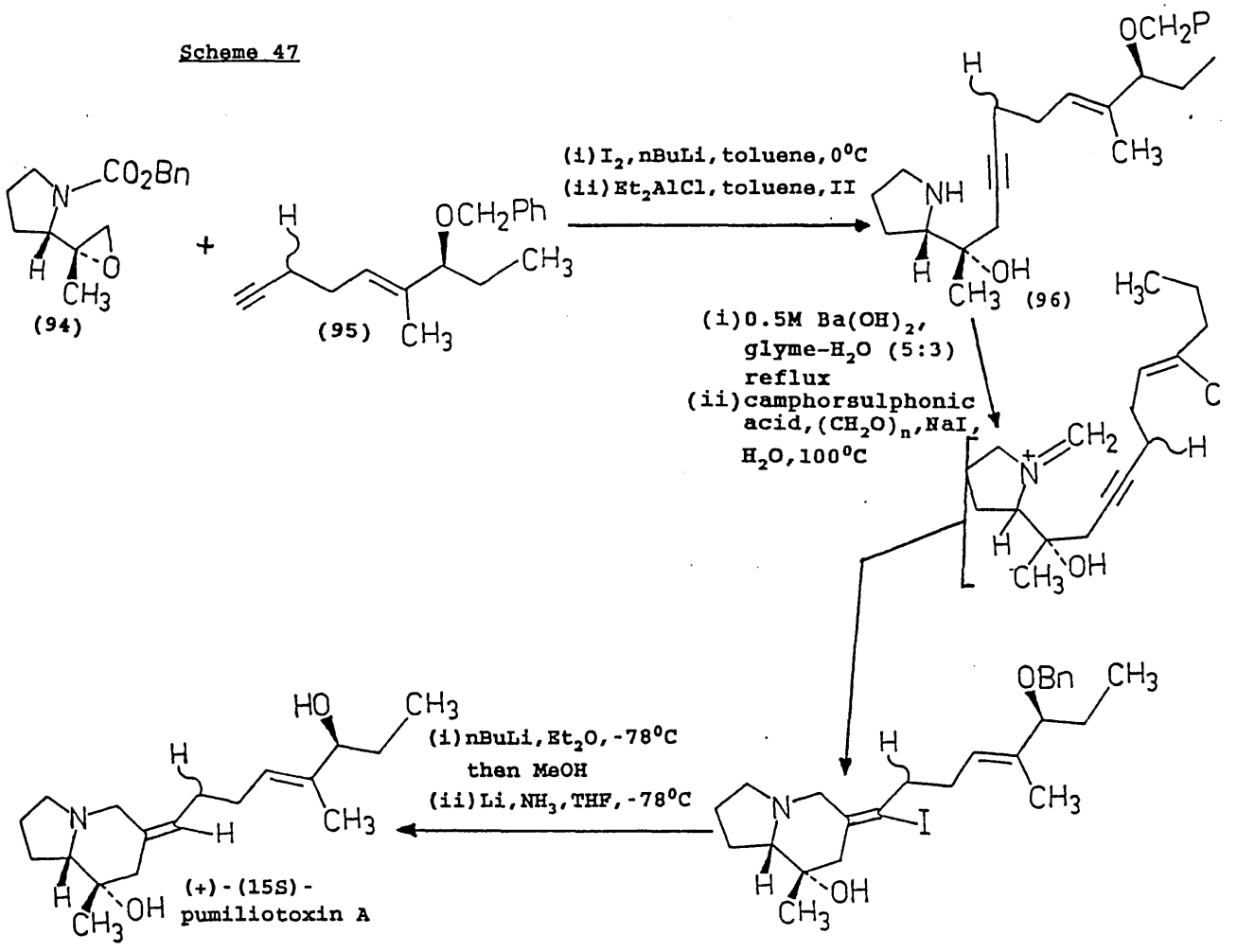
tetrahydropyridinium salt[91]. The unstable endocyclic enamine was reduced directly. The formation of monomorine I was consistent with the maintenance of a maximum orbital overlap with respect to the attacking hydride and the developing lone pair on nitrogen (scheme 46).

Scheme 46



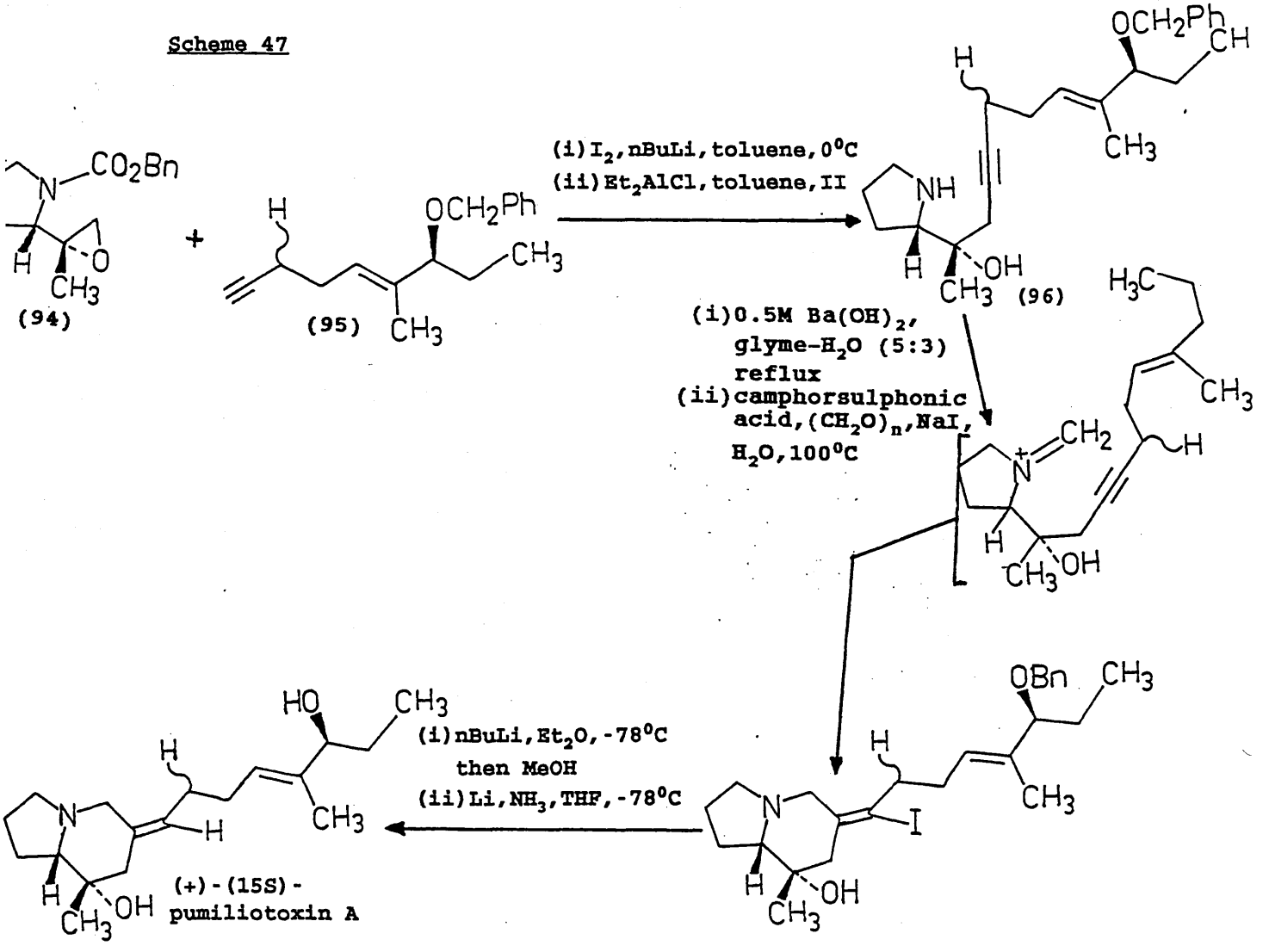
The number of syntheses of *Dendrobatid* alkaloids recently has been more profuse than usual[92]. Several pumiliotoxin alkaloids have been produced based on iminium ion cyclisations[93]. Coupling of the chiral epoxide (94) with a 5:1 C-11 epimeric mixture of the alkyne (95) followed by deprotection gave the key intermediate (96). The iminium ion was generated *in situ* by treatment with paraformaldehyde in aqueous acidic solution containing a large excess of iodide ions. Iodide is a strong nucleophile for carbon centres, and in this case it induced a highly stereoselective cyclisation between the normally poorly compatible iminium ion and alkyne, resulting in the formation of the isomerically pure indolizidine (97) and its C-11 epimer. De-iodination and deprotection produced (+)-(15S)-pumiliotoxin A (scheme 47).

Scheme 47



The total synthesis of 251D in chiral form was first achieved in 10 steps with an overall yield of 6% of the pure alkaloid from S-proline and 1-heptyne-3-one[94] (Scheme 48).

Scheme 47



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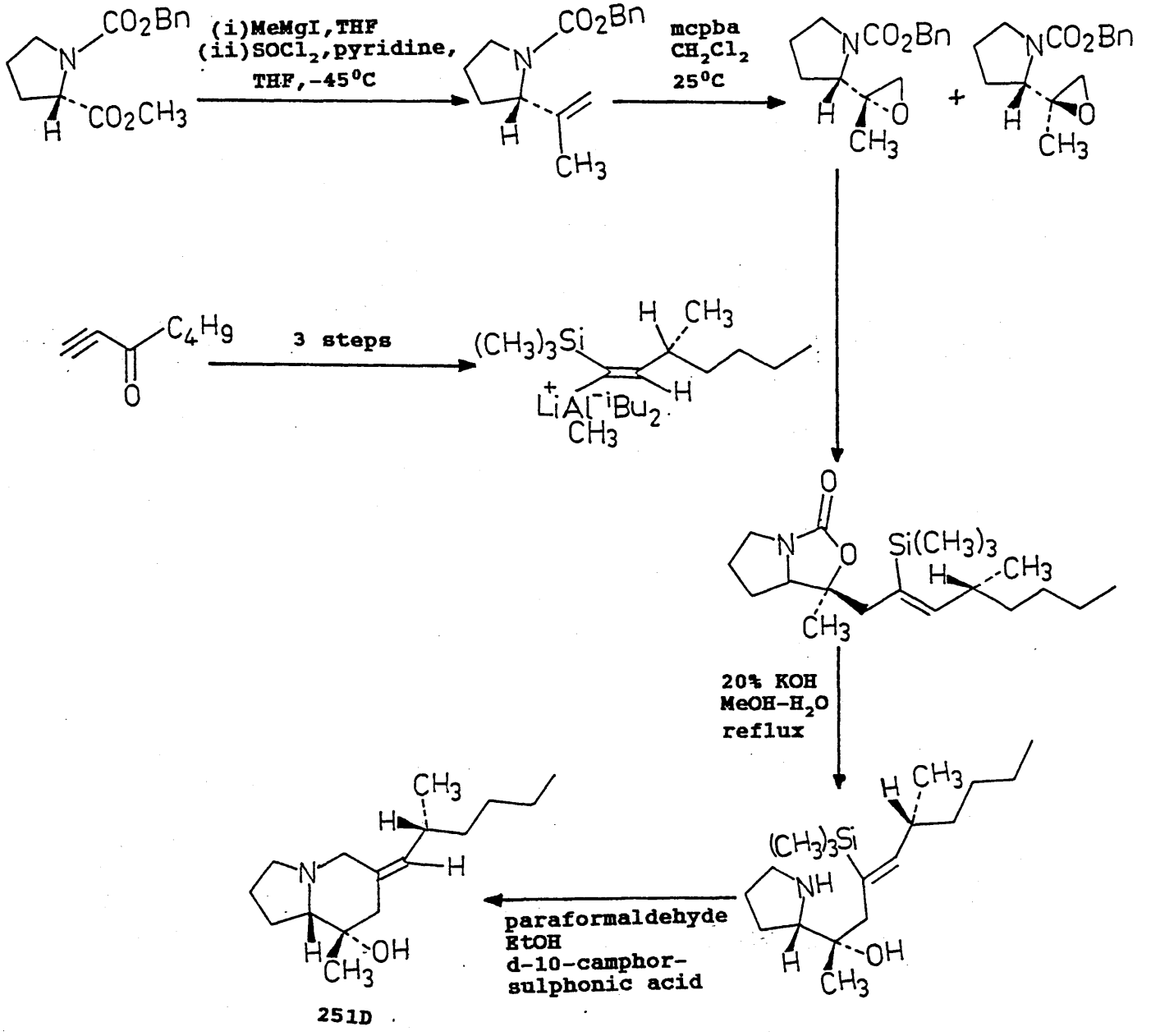
Scheme 48



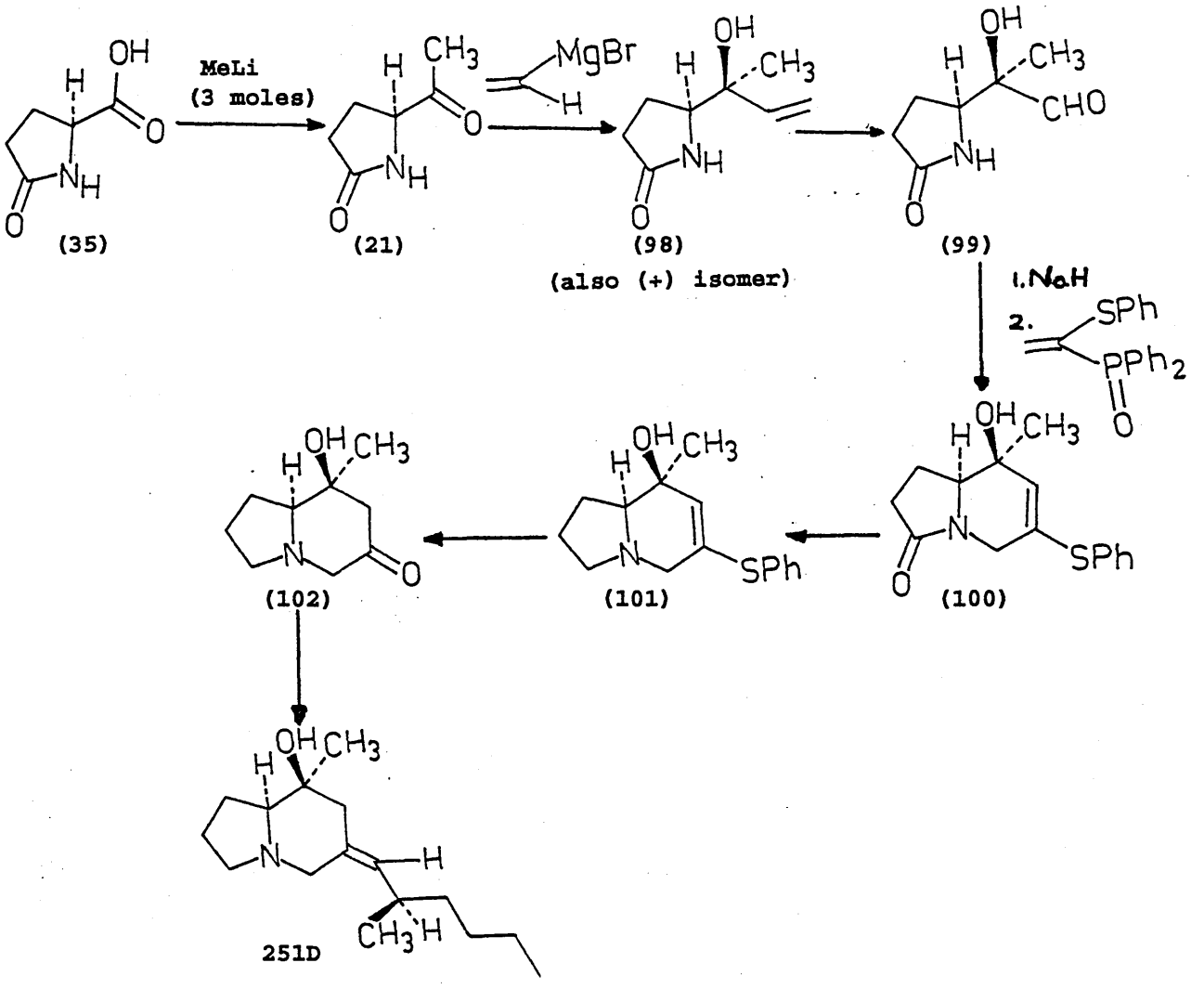
251D

This process afforded the isomeric epoxides in a 1:1 mixture; the required one being isolated using column chromatography. A subsequent investigation into the formation of possible intermediates of 251D synthesis, looking at conditions which favour one isomer over the other, was reported[95], but none of these possible intermediates was taken through to 251D.

2.5 Proposed Synthesis of 251D

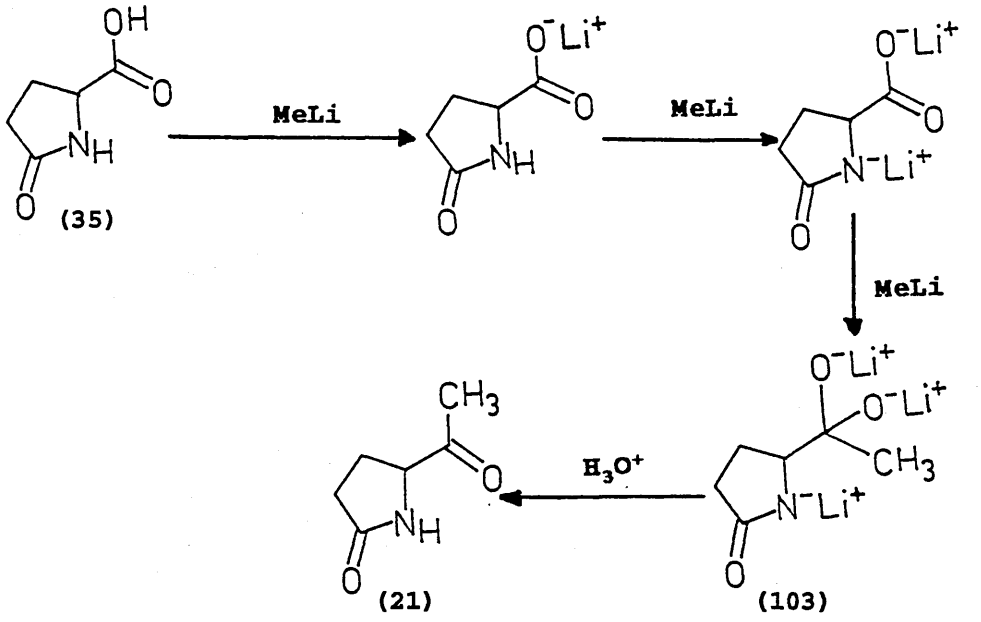
Part of this project involved the proposed synthesis of 251D in chiral, pharmacologically-active form from a readily-available amino acid, (S)-pyroglutamic acid (Scheme 49):

Scheme 49



(S)-pyroglutamic acid (35) was to be converted to its methyl ketone (21) via the following route according to Rapoport *et al*[96] (scheme 50):

Scheme 50



This ketone was then to be converted to its corresponding vinyl alcohol(98) as a mixture of diastereoisomers. Ozonolysis of the alkene was to lead to the aldehyde (99), still as an isomeric mixture. This aldehyde was then to undergo an intramolecular Horner-Wittig cyclisation reaction. The resultant bicyclic core (100) would then be in the form of diastereoisomers and so these could hopefully be resolved by flash chromatography. The amide was then to be reduced to the amine (101) using lithium aluminium hydride. The sulphenyl group was then to be converted to the ketone (102) using aqueous mercuric chloride; the sulphenyl group would be displaced by a hydroxyl group to form the enol, followed by preferential tautomerism to form the ketone. A conventional Wittig reaction at the ketone carbonyl was then to lead to the toxin 251D as a mixture of E- and Z-alkene isomers, which would hopefully be separable by flash chromatography.

2.6. Results and Discussion

2.6.1. Conversion of (S)-pyroglutamic acid (35) to (S)-5-acetyl pyrrolidin-2-one (21) (scheme 50, p90)

The conversion of (S)-pyroglutamic acid (35) firstly to its acid and amide salts and then to a ketal-type species (103) (since lithium salts exhibit a fair degree of covalency)[98], which was quenched during work-up to give (S)-5-acetyl pyrrolidin-2-one (21), only provided (21) in an exceptionally low yield (2%), even after continuous extraction into dichloromethane at pH 7. The reaction was also performed by firstly making the lithium carboxylate salt with 1 molar equivalent of n-butyl lithium followed by formation of the magnesium amide salt and the magnesium alkoxide salt using 2 molar equivalents of methyl magnesium bromide; Knudsen and Rapoport[96b] found the lithium salt to be more reactive to methyl magnesium bromide than the magnesium salt; n-butyl lithium is also reported to be more reactive than methyl lithium[98].

One major problem with the reaction on this particular acid was that (S)-pyroglutamic acid (35) is not soluble in tetrahydrofuran; it had previously been hoped that an ultra-fine dispersion of (35) in a relatively large amount of tetrahydrofuran might overcome this problem; obviously it didn't. A co-solvent mixture was therefore tried comprising tetrahydrofuran : tetramethylethylenediamine, 1:1. This, coupled with the n-butyl lithium - methyl magnesium bromide development did improve the yield, but only to a maximum of 10%.

Isobutyryl lithium has been treated with benzoic acid at room temperature to give isobutyrophenone in 60% yield[1]; low

temperatures were used in this case because the reactivity of methyl lithium and methyl magnesium bromide is so high that the reaction would be difficult to arrest at the ketone stage and would more likely continue through to the tertiary alcohol[97]. Despite working at -78^{0}C on (S)-pyroglutamic acid (35), the tertiary alcohol was not isolated, but in all cases a significant amount of the starting acid was recovered.

A Dakin-West reaction using (S)-pyroglutamic acid (35), acetic anhydride, triethylamine and 4-dimethylamino pyridine as catalyst was tried, though it was not sure whether the required methyl ketone (21), if produced at all, would be in chiral or racemic form. Many fractions were seen on tlc but none of these reacted with 2,4-dinitrophenylhydrazine spray. None of the required product was isolated by vacuum distillation of the crude mixture, or from a subsequent attempt using solvent extraction followed by continuous extraction from the aqueous washings into dichloromethane at pH 7, plus similar continuous extraction at pH 3 which gave only the starting acid (35) and none of the required product (21).

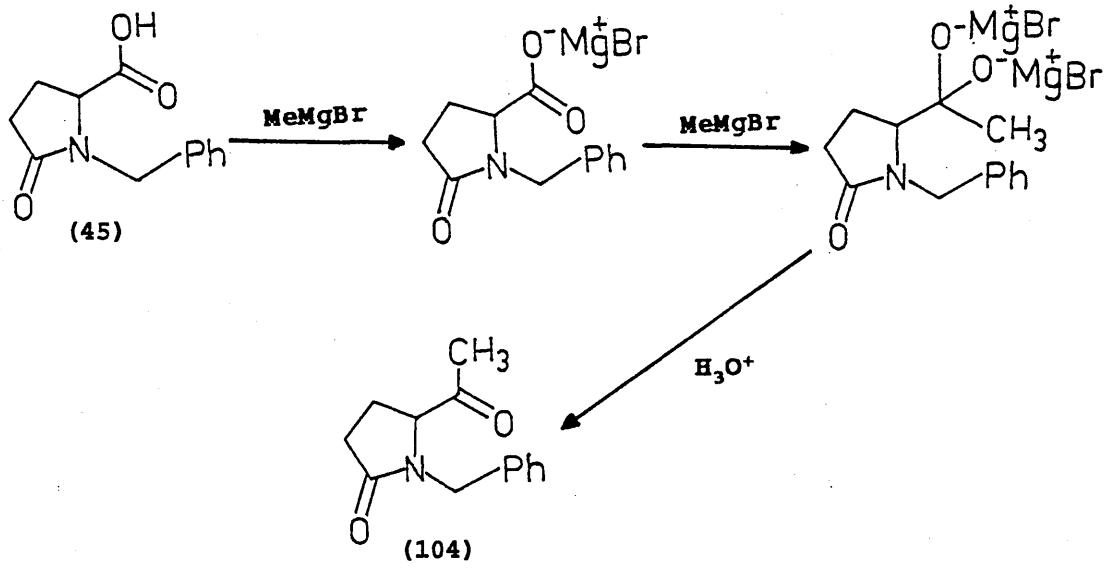
Since the underlying problem with the reaction involving the organometallic reagents appeared to be the insolubility of the starting acid, especially when in its carboxylate and amide salt form (visibly, formation of the salts as a white precipitate seemed to proceed with no problems), it was decided to try an N-protected derivative of (S)-pyroglutamic acid (35) which would give it solubility in tetrahydrofuran.

Attempts to protect 5-acetyl pyrrolidin-2-one (21) using the racemic compound prepared according to scheme 23, p35, were tried by first forming the sodium amide salt through stirring with

sodium hydride in tetrahydrofuran at room temperature followed by the addition of benzyl bromide. Many fractions were observed on tlc and chromatography isolated the required product in only 11% yield. This was not improved by changing the solvent to dimethylformamide. It was decided to try a Dakin-West reaction on (S)-N-benzylpyroglutamic acid (45) using acetic anhydride, triethylamine and 4-dimethylamino pyridine as catalyst in order to make the N-benzyl ketone (104), though again it was not clear whether this product, if produced at all, would be in chiral or racemic form. Many fractions were observed on tlc, though none was reactive to 2,4-dinitrophenylhydrazine spray, and none of the required product was isolated by subsequent chromatography. Some of the starting acid (45) was recovered, however.

The current work on pyrrolizidines at this stage was proceeding quite well using (S)-N-benzyl pyroglutamic acid (45), which was found to be readily soluble in tetrahydrofuran, so this was put through the organometallic route to the N-benzyl ketone (104) (scheme 51).

Scheme 51



The maximum yield of the ketone (104) from the acid (45) was 40% when 2 molar equivalents of methyl magnesium bromide were used in tetrahydrofuran only. Lower yields were obtained when the co-solvent mixture tetrahydrofuran :tetramethylenediamine, 1:1, was used and also for combinations of methyl magnesium bromide with methyl lithium and n-butyl lithium. In all cases, the tertiary alcohol was produced in significant yield (table 2). It was decided to investigate the reaction further by first converting the N-benzyl acid (45) to its acid chloride (46) and reacting this with one molar equivalent of each of various methyl-metallic species[99] (table 2).

Table 2

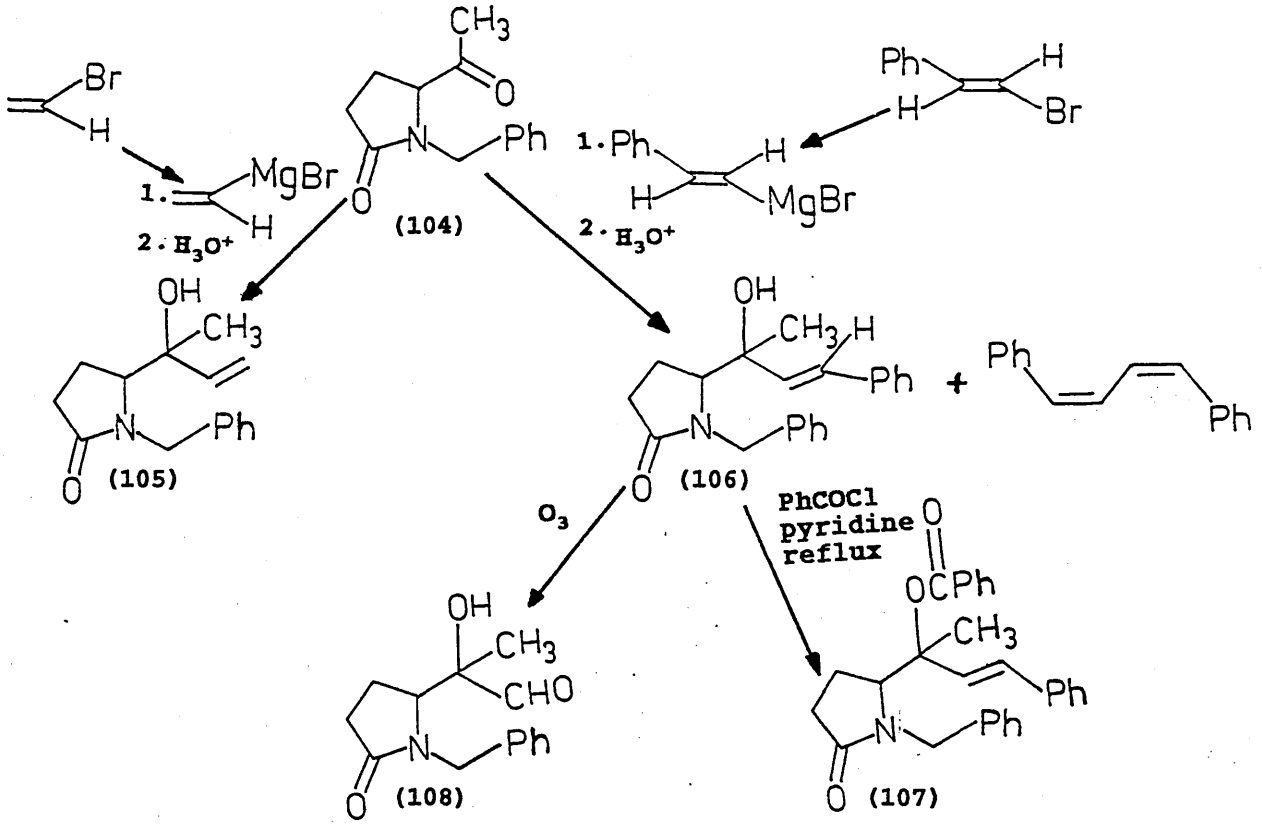
metallo-methyl species used	temp. (^{0}C)	solvent	yield of ketone(%)	yield of tertiary alcohol(%)
MeMgBr only	-78	THF	40	20
MeLi only	-78	THF	10	10
MeCuLi	-78	THF	26	15
Me_2Cd	0	THF	33	17

(In all cases, some of the starting acid (36) was recovered). Other reagents which might have been used here are Me_2Co[100] and Me_3Tl[101].

Rather than investigate the reaction further, it was decided to continue the synthesis towards the key intermediate, (S)-(1-formyl-1-hydroxy)ethyl pyrrolidin-2-one.

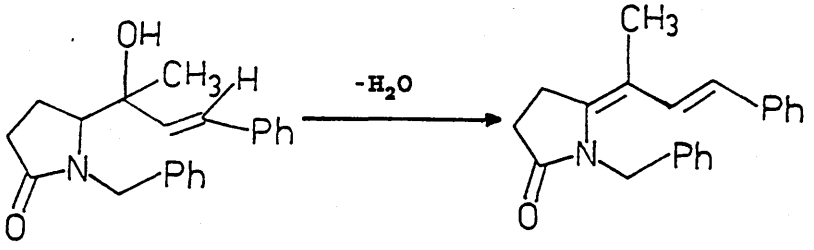
2.6.2. Progression of the N-benzyl ketone (104) towards the N-benzyl aldehyde (108)

Scheme 52



Vinyl magnesium bromide was prepared from vinyl bromide and magnesium turnings in tetrahydrofuran at room temperature using a dry ice condenser[98a,102]. Reaction of this Grignard with the ketone (104) provided the vinyl alcohol (105) in 39% yield. Another similar alkene preparation involved the production of styryl magnesium bromide from a mixture of cis and trans 1-bromostyrene, and the reaction of this species with the ketone (104) to produce the styryl alcohol (106) in 43% yield. The splitting patterns of the alkene signals on proton NMR indicated that the styryl alcohol was produced in its trans (E) form only. The major fraction (by mass) ran at the solvent front during chromatography in ethyl acetate and was strongly reactive to acidified potassium manganate (VII) spray. This fraction was usually isolated as a yellow tar,

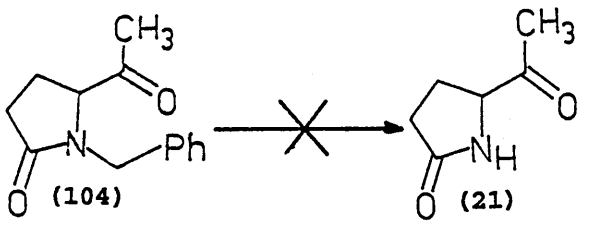
and its proton NMR indicated that it was possibly impure 1,4-diphenyl butadiene (by comparison with the NMR of pure 1,4-diphenyl butadiene). The type of dimerisation reaction required to produce this kind of by-product is characteristic for Grignard reactions and the amount of dimeric by-product produced relative to the amount of the required product is determined by the relative rates of the two reactions[67]; therefore in this case the dimerisation reaction would appear to be quite fast relative to the reaction with the ketone (104). On one occasion the dimeric by-product was isolated pure enough to confirm its identity via ^{1}H NMR, ^{13}C NMR and mass spectrometry. With this species running just behind the solvent front, it would co-elute with other species such as styrene resulting from unreacted styryl magnesium bromide and also unreacted styryl bromide, so it is not surprising that it was always isolated in crude form as a yellow tar (the pure compound is a yellow crystalline solid, mpt.151-153^{0}C[102]). Ammonium chloride was used as the quenching agent rather than hydrochloric acid in order to minimise (and hopefully avoid) elimination of water from the tertiary alcohol, which could have led to a diene.



Ozonolysis of the alkene (106) with dimethyl sulphide as a reductive quenching agent produced many fractions on tlc which were UV-active and reacted with acidified potassium manganate (VII) spray, but only one spot reacted with 2,4-dinitrophenylhydrazine spray to give a bright yellow colour. Unfortunately, the yield was atrocious; not enough of this

fraction was isolated via chromatography from 1g of the alkene as to be sufficient even for an infrared spectrum. This reaction was not investigated at this stage, since attempts to remove the benzyl group from (S)-N-benzyl pyrrolidin-2-one (104) to give the unprotected 5-acetyl pyrrolidin-2-one (21) (scheme 32, p54) were proving fruitless in tetrahydrofuran, methanol and even acidified methanol.

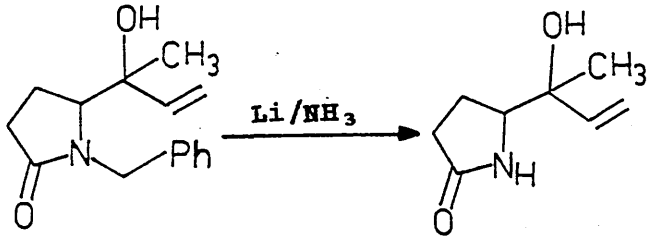
Scheme 53



Only the starting ketone (104) could be recovered.

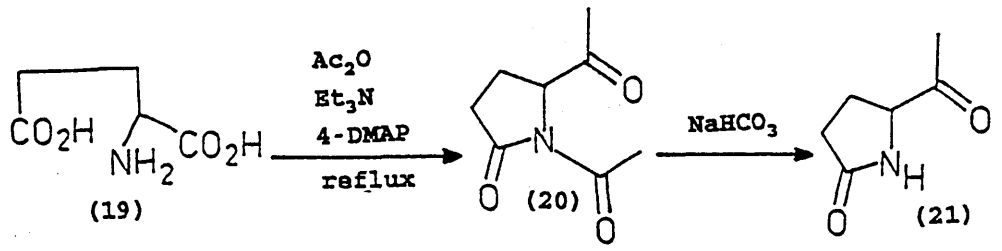
Another possibility which wasn't tried might have involved Birch reduction of the vinyl alcohol[103] (scheme 54).

Scheme 54



It was decided at this stage to abandon attempts at a chiral synthesis of the unprotected aldehyde and instead to proceed via a racemic pathway that far, since (R/S)-5-acetyl pyrrolidin-2-one (21) could already be produced in good yield from glutamic acid (19) via firstly a Dakin-West reaction to give (R/S)-1,5-diacetyl pyrrolidin-2-one (20)[39] followed by aqueous alkaline hydrolysis to give the deprotected amide (21)[40] (scheme 55).

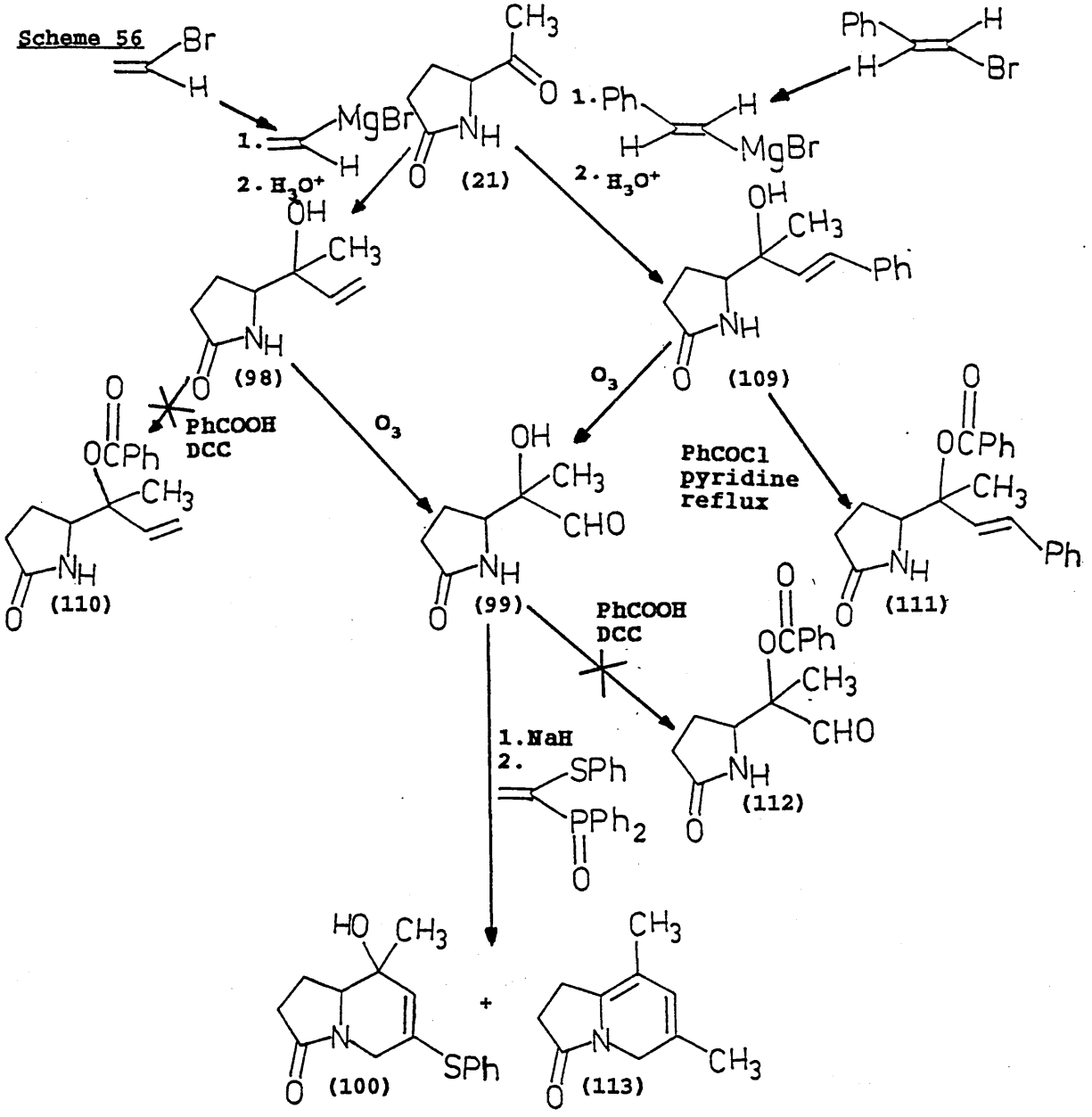
Scheme 55



Since all intermediates hereon would be in the form of diastereoisomers, the yield of 251D in its pharmacologically-active form would be much lower than if the synthesis had proceeded with at least one of the optically-active carbon centres, namely the one at the bis-ring junction, being in the correct configuration. Therefore only one of the 4 diastereoisomers of the resultant bicyclic core would be in the correct stereochemical configuration. The last stage in the synthesis, the conventional Wittig reaction, would produce E- and Z- alkene isomers, so only one out of 8 isomers would then be in the naturally-occurring form, although if the starting 5-acetyl pyrrolidin-2-one was in its chiral (S) form, this could still have led to 4 possible isomers, so some method of separating the required, naturally-occurring isomer would still have been necessary.

2.5.3. Progression Along the Racemic Route

Scheme 56



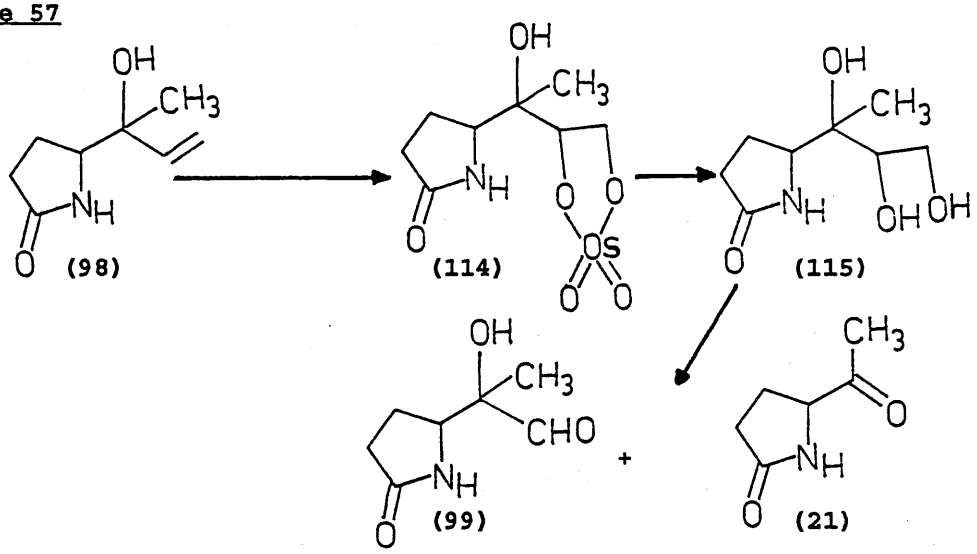
Using a pathway analogous to that for the N-benzyl series, the ketone (21) was converted to the alkenes (98) and (109) in 54% and 40% yields respectively. In the latter case, the by-product 1,4-diphenyl butadiene was isolated crude again using flash chromatography and its identity was confirmed through spectral analysis. Both (98) and (109) required continuous extraction into dichloromethane after adjustment of the pH of the aqueous phase to 7; continuous extraction was always maximal at this pH, lower

yields of each product being obtained at pH 3 and pH 10. This behaviour was exhibited by all of the unprotected monocyclic intermediates. In each case, after work-up of the organic phase, the adjustment of the aqueous residue back to pH 7 followed by a further continuous extraction always resulted in the isolation of a negligible further amount of the required product. All of the monocyclic intermediates appeared to have a very high water affinity, possibly due to conjugation of the amide group in an iminol form.

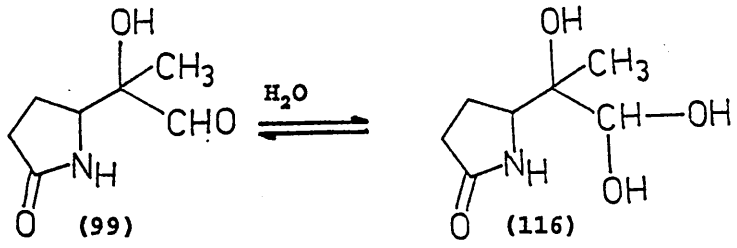
Ozonolysis of the alkenes (98) and (109) to the aldehyde (99) was effected in yields of 55% and 57% respectively, though the yield from (98) was reliable whereas the yield from (109) was more often around 40%. Changes in the ratios of the solvents used for the reaction, dichloromethane and methanol, gave the above yields as maximal at the ratio dichloromethane : methanol, 9:1; other solvents tried included chloroform with acetone and chloroform with dimethyl sulphoxide in various ratios, but all these failed to improve on the above yields. The observation of several fractions on tlc that were reactive to 1,4-dinitrophenylhydrazine might indicate that the aldehyde was rather unstable.

An alternative route from the vinyl alcohol (98) to the aldehyde (99) involved conversion of the alcohol (98) to the osmate ester (114) followed by its conversion *in situ* to the diol and oxidative cleavage without prior isolation to the aldehyde (99) (scheme57), with identical spectral data to the product obtained from ozonolysis of (98).

Scheme 57

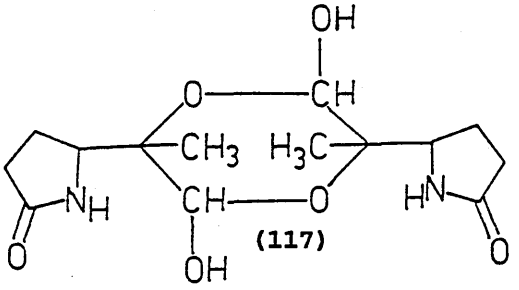


All steps thus from (98) to (99) were performed in one pot in aqueous solution. Continuous extraction into dichloromethane after adjustment of the pH of the aqueous phase to 7 provided the aldehyde in only 23% yield with a 10% production of 5-acetyl pyrrolidin-2-one (21) where the oxidant sodium metaperiodate had cleaved the tertiary alcohol-amide ring carbon-carbon bond rather than at the diol. The yield of aldehyde might have been lowered due to either incompletion of one or more of the reactions involved (no investigation of the reaction at different temperatures was carried out) or its possible existence as its probably more water-soluble hydrate:



The hydrate was never isolated but could have remained in the aqueous phase due its higher water affinity. All proton NMR

spectra of the aldehyde (99) either showed the aldehyde proton with too low an integral value or else did not show it at all; all the remaining signals, namely the methyl and pyrrolidone signals, were present in the characteristic form and in the right integral ratios. Another possible form of the aldehyde could therefore have been as its intermolecular hemiacetal:

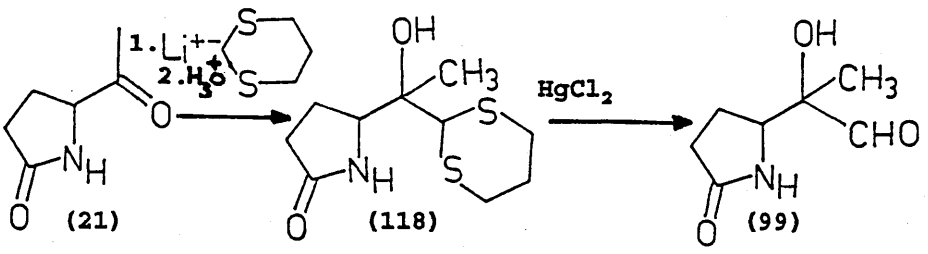


(117)

Such a structure could be well camouflaged on infrared spectra; the aldehyde carbonyl signal could occur in the same place as the amide carbonyl signal, O-H stretch signals would be expected anyway due to the tertiary alcohol, C-O stretch signals would also be expected due to the tertiary alcohol. The existence of the aldehyde in its hydrate form could have presented similar signals on infrared. Washing the product with methanol followed by removal of the methanol on the rotary evaporator in the hope of removing water from the product via azeotropic extraction (if the product was in the hydrate form failed to produce any change in the spectral data. A peak at M/Z 312 for the hemiacetal was not seen on the mass spectrum, nor was one seen at M/Z 175 for the hydrate, although the hydrate could have lost water during the running of the spectrum. Since the base peak was at M/Z 84 for the N-acyl imine ring, the products from the loss of two such rings from the intermolecular hemiacetal would quickly decompose via loss of CO_2, so the intermolecular hemiacetal could escape detection on the mass spectrum as well.

Another alternative route to the aldehyde (99) was via the employment of the dithiane adduct (118) (scheme 58).

Scheme 58



Initial attempts along this route involved addition of the amide (21) to an excess of the lithium dithiane salt at -78°C, resulting in no reaction and recovery of the amide (21) and 1,3-dithiane; it was believed that the dithiane anion merely abstracted the acidic amide proton to regenerate 1,3-dithiane and thus produce the lithium amide salt; quenching with aqueous ammonium chloride would then regenerate the amide (21). Subsequent efforts involved the preparation of the lithium amide salt in one flask and addition to it of the previously prepared lithium dithiane salt from a separate flask via a cannula. Quenching, continuous extraction at pH 7 into dichloromethane and flash chromatography afforded the dithiane adduct as a pink tar which was recrystallised to a white solid with characteristic signals on proton NMR, infrared and mass spectra but which was in only 16% yield. The aqueous phase retained a fraction which during thin layer chromatography in ethyl acetate remained on the base line and gave strong reactions with acidified potassium manganate (VII) spray (bright yellow spot) and molybdophosphoric acid spray (dark blue-green spot, characteristic of a sulphur species); thus it appeared that even at pH 7 there was some form of sulphur species present in ionic form. The yield of the dithiane adduct (118) was not improved by a further continuous extraction or by continuous

extraction at pH 3 or at pH 10, and was so low that there didn't seem much point in attempting to convert it to the aldehyde (99) using aqueous mercuric chloride in conjunction with aqueous mercuric oxide[106], since this would have required a work-up involving continuous extraction with the foreboding possibility of the aldehyde being in its hydrate form once again, and this route would not now improve on the yield of the aldehyde (99) from the ozonolysis route.

It was decided once again to look at the production of the aldehyde (99) from the alkenes (98) and (109) via the ozonolysis route. Since there seemed to be a great many possible mechanisms of conversion of an alkene through a molozonide and an ozonide followed by cleavage of the latter to a carbonyl compound[107], it was suggested that the tertiary alcohol group might be interfering with this reaction in some way, thus accounting for the appearance of so many fractions on tlc prior to such a simple work-up. Thus it was decided to protect the alcohol with a benzoyl group prior to ozonolysis (scheme 56).

Attempts to protect the vinyl alcohol (98) by addition of dicyclohexylcarbodiimide followed by addition of benzoic acid led only to the production of benzoic anhydride and the recovery of the vinyl alcohol (98). Production of the O-benzoyl protected styryl alcohol (111) was effected by refluxing the styryl alcohol (109) with benzoyl chloride in triethylamine with 4-dimethylamino pyridine as a co-catalyst in 24% yield maximum with recovery of some of the starting styryl alcohol (109); lower yields were obtained when 4-dimethylamino pyridine was not used.

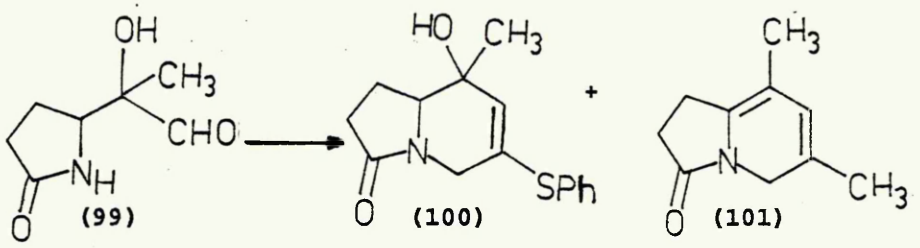
The difficulty of protecting the alcohol group prior to ozonolysis showed that the maximum yield of the aldehyde (99) was

going to be 54% from ozonolysis of the unprotected alcohol. It was now decided to abandon efforts to improve on this and to press on with the synthesis via the intramolecular Horner-Wittig cyclisation reaction on the aldehyde (99) to try to form the functionalised indolizidine core (100).

2.5.4. Intramolecular Horner-Wittig Cyclisation of the Aldehyde (99)

With the aldehyde (99) in normal, molecular form it was not clear whether the tertiary alcohol proton would be acidic enough relative to the amide proton to produce its sodium alkoxide salt on addition of sodium hydride; such a salt formation would reduce the amount of sodium amide salt available for the reaction and also lead to various by-products.

An attempt was made to protect the alcohol group of (99) at this stage using dicyclohexylcarbodiimide followed by benzoic acid; as with the behaviour exhibited during the similar reaction with the vinyl alcohol (98), benzoic anhydride, and dicyclohexylurea only were produced, and the starting aldehyde was recovered using flash chromatography.



Cyclisation of the aldehyde (99) using 1 molar equivalent of sodium hydride in the co-solvent mixture tetrahydrofuran : acetonitrile, (1:4) at room temperature gave the required product in 33% yield, with the production of a sharp singlet at 1.3ppm due to the methyl group and a singlet at 6.9ppm due to the aromatic protons on its ^{1}H NMR spectrum, the remaining signals occurring as characteristic multiplets; infrared showed the retention of a broad peak at 3200cm^{-1} due to O-H stretch, along with the retention of a strong signal due to the amide C=O stretch and the production of a strong peak at 1590cm^{-1} due to C=C stretch, a

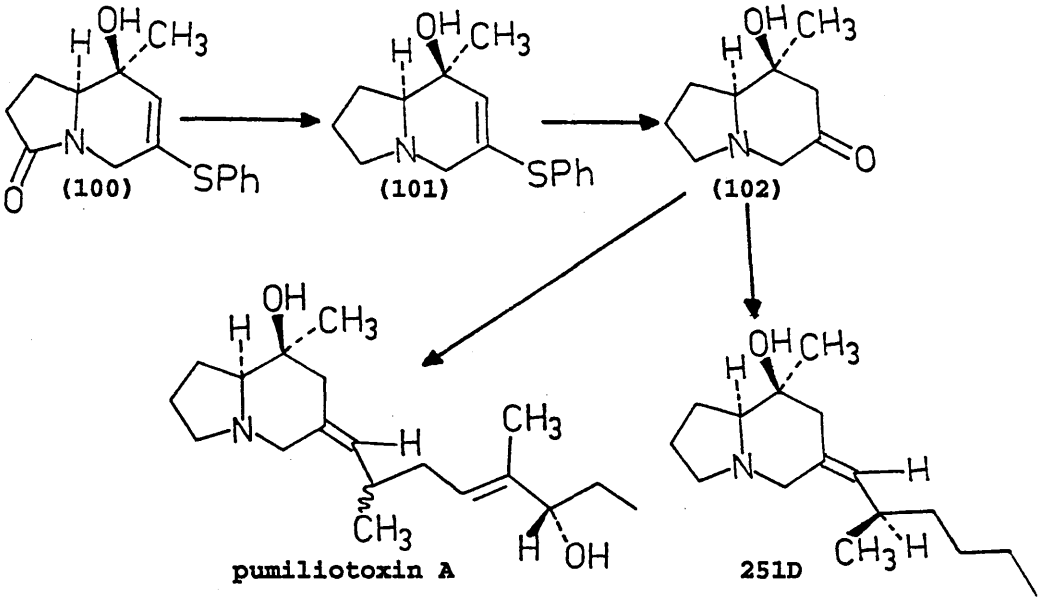
strong peak at 1280cm^{-1} due to C-S stretch and peaks at 750 and 700cm^{-1} due to aromatic C-H bending; high resolution mass spectrometry provided microanalysis with an error of +1.2mmu. The first fraction afforded by flash chromatography gave a proton NMR spectrum which, apart from a sharp singlet at 2.6, was identical with the spectrum for the 1-methyl pyrrolizidone (32). Similarly, the infrared of this by-product was identical with that of (32) apart from a strong peak at 1180cm^{-1}, which indicated C-O or C-S stretch. A possible structure for this data could have been the 5,6-fused bicyclic alkene (113), which could have arisen through loss of water from either the aldehyde or the required product. Although this material was a significant product by mass (50mg as opposed to 76mg of the required indolizidinone (100), this material was not investigated further. Procedure from this point would most probably have followed the proposed pathway (scheme 49, page 89).

The work on the indolizidine series thus far was now more promising with achieving the formation of the indolizidine core structure (100), albeit in rather low yield. Further investigation of the intramolecular Horner-Wittig cyclisation reaction to try and improve on this yield was not carried out due to a shortage of time. This was unfortunate, since we were hopefully only 3 steps away from acheiving the synthesis of the target alkaloid 251D:

2.6. Suggestions for further work

a) Completion of the synthesis of 251D

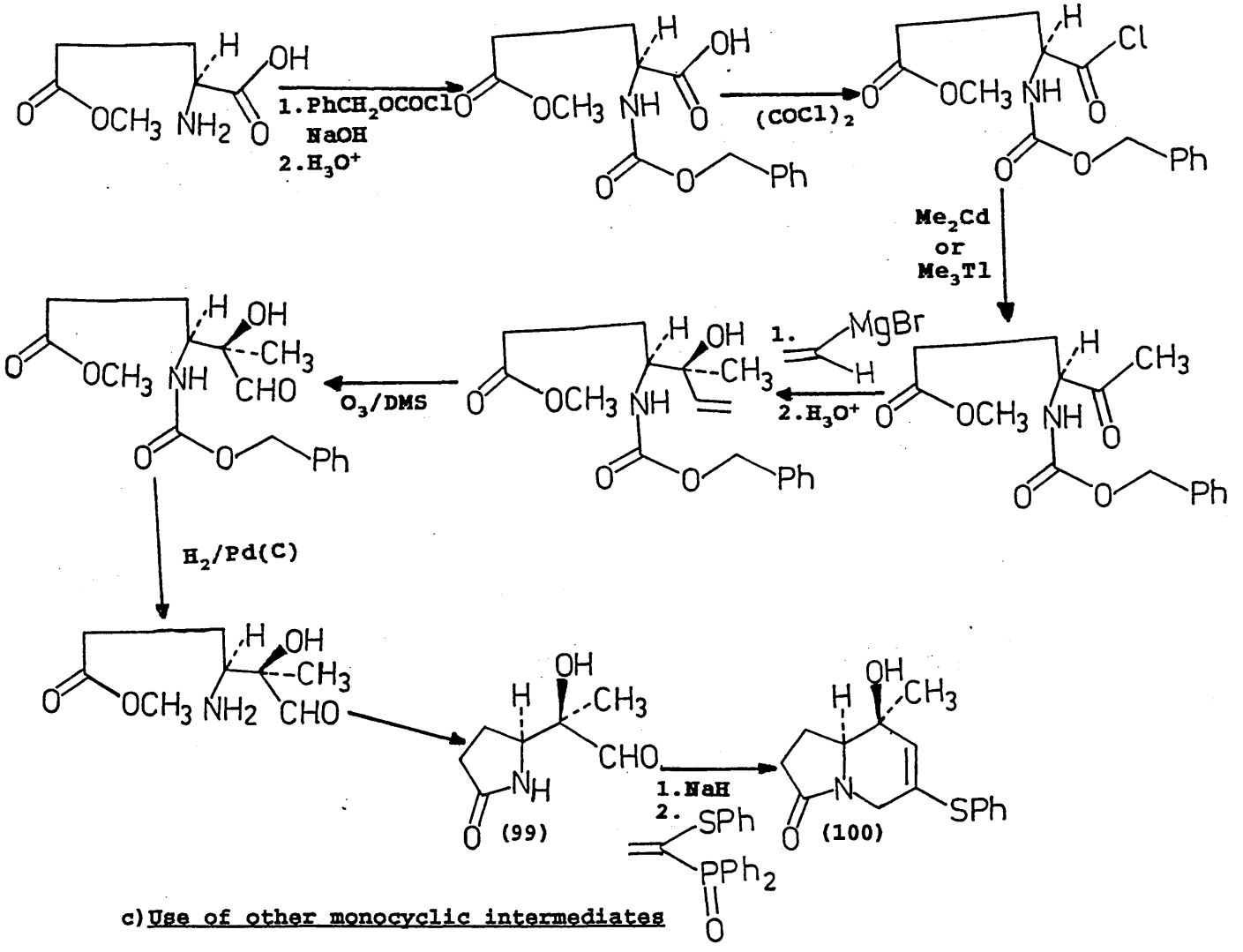
The work so far had achieved the synthesis of the required indolizidine core structure (100), albeit in rather low yield. This intermediate was only 3 steps away from the target alkaloid:-



b) Improvement of the overall yield

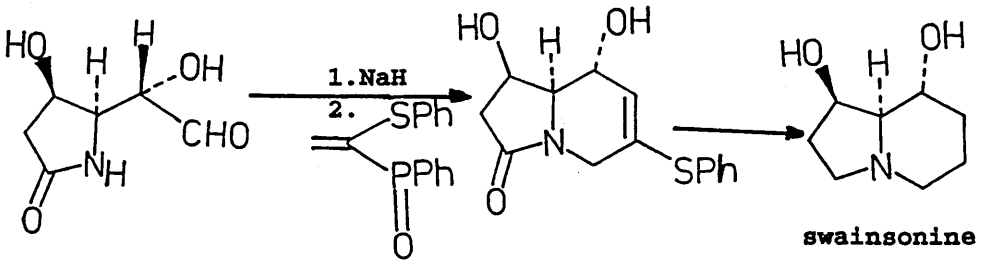
A strong possibility in this direction would be to start from glutamic acid monomethyl ester, which is cheap and readily-available, and protect the amine group with a carbobenzyloxy grouping in a similar way to protection of glutamic acid described in section 1.8.3. The next stage would be to convert the acid functionality to its corresponding acid chloride. Reaction of the acid chloride with either dimethyl cadmium or trimethyl thallium should convert the acid chloride to its corresponding methyl ketone without further reaction to the tertiary alcohol, based on the work on the production of N-benzyl-5-acetyl pyrrolidin-2-one described in section 2.6.1. The N-carbobenzyloxy group should facilitate better solubility in tetrahydrofuran ready for the

conversion of the methyl ketone to the vinyl alcohol using vinyl magnesium bromide. Ozonolysis of the alkene followed by hydrogenolysis of the N-carbobenzyloxy group should lead to the open chain ester aldehyde. Refluxing this material in methanol could potentially cyclise via loss of methanol to give the required monocyclic pyrrolidone aldehyde (99) in much better yield.

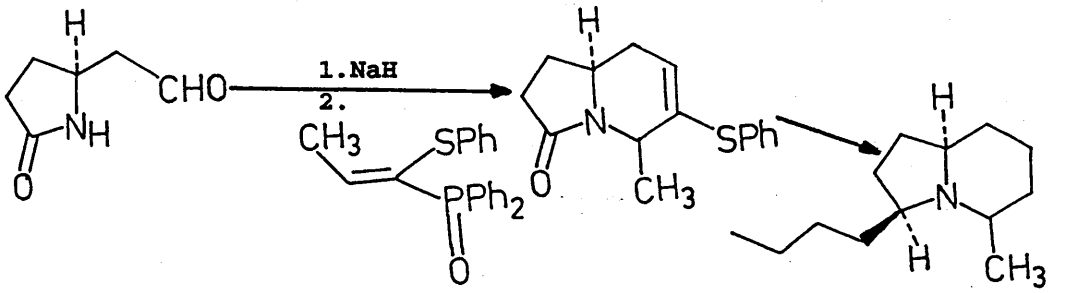


c) Use of other monocyclic intermediates

Analogues of the aldehyde (99) could lead to different indolizidine alkaloids such as swainsonine or monomorine I:



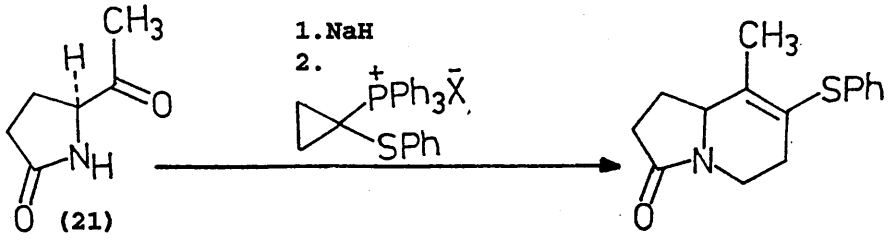
swainsonine



monomorine I

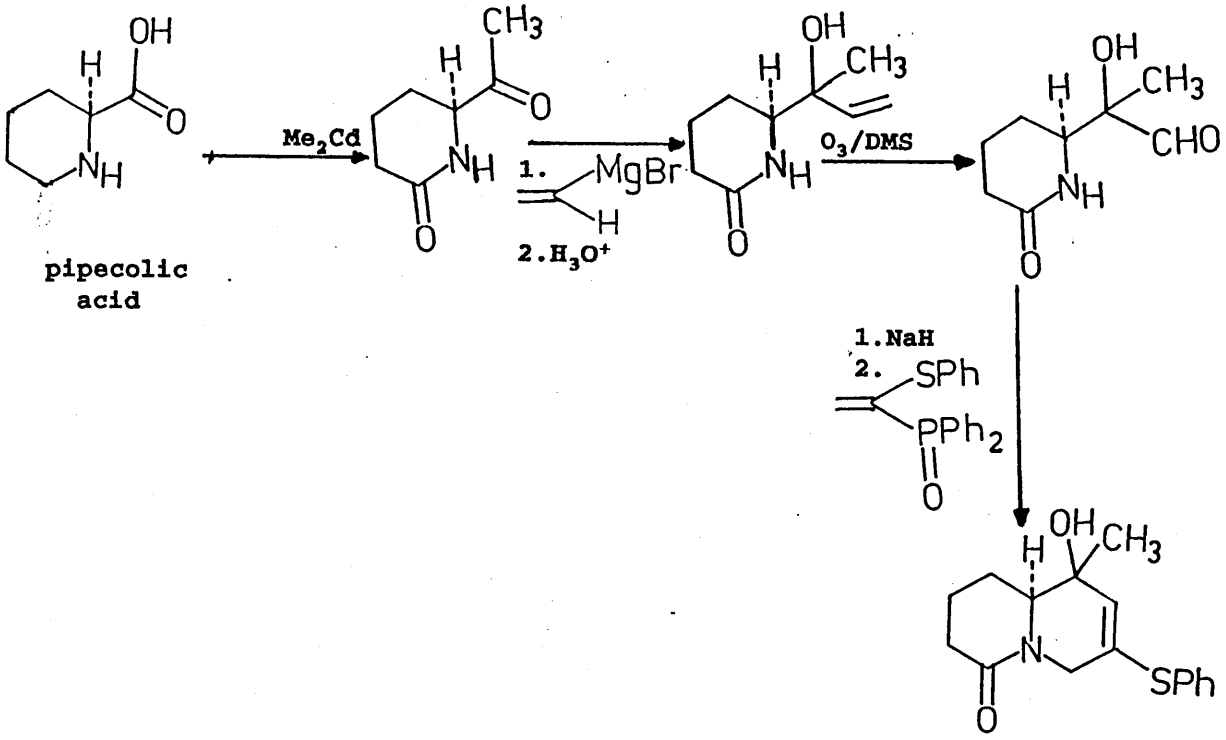
d) Cyclopropyl phosphonium salts

The use of such reagents might provide a similar, alternative route to the indolizidine core structure:



e) Other classes of alkaloids

The employment of a derivative of pipecolic acid in an intramolecular Horner-Wittig cyclisation reaction might provide a route to a quinolizidine core structure:-


OH
H
O
NH
pipecolic
acid
Me2Cd
CH3
H
O
NH
O
1.
MgBr
H
2.H3O+
OH
CH3
H
O
NH
O3/DMS
OH
CH3
H
CHO
NH
O
1.NaH
2.
SPh
PPh2
O
OH
CH3
H
N
SPh
O

General Information

Infrared spectra were obtained on a Pye-Unicam SP3-100 spectrophotometer. Samples were prepared as potassium bromide (KBr) discs or liquid films.

IR data is given in cm^{-1}.

^{1}H NMR spectra were obtained using a Jeol JNM PMX-60 SI 60MHz spectrometer, a Bruker WP 80 SY 80MHz spectrometer and a Bruker 250MHz spectrometer.

^{13}C NMR spectra were obtained on a Bruker WP 80 SY 80MHz spectrometer.

^{1}H NMR data is given on the δ scale using tetramethyl silane as the internal reference. Abbreviations for the form of the signal are as follows: s=singlet, d=doublet, t=triplet, q=quartet and m=multiplet.

Samples for NMR spectra were prepared in the solvent stated in each method.

Mass spectra and high resolution mass spectra were obtained on a VG Micromass 7070F spectrometer.

Ozonolysis reactions were performed using a BOC Mark II ozoniser.

Column chromatography was performed on Merck 7734 Kieselgel 60 (coarse) and Merck 7736 Kieselgel 60H (fine) silica gel.

Flash chromatography was performed on Sorbisil C-60H (40-60mm) silica gel.

Thin layer chromatography was performed on Merck 5554 Alufoilen Kieselgel $60F_{254}$ plates.

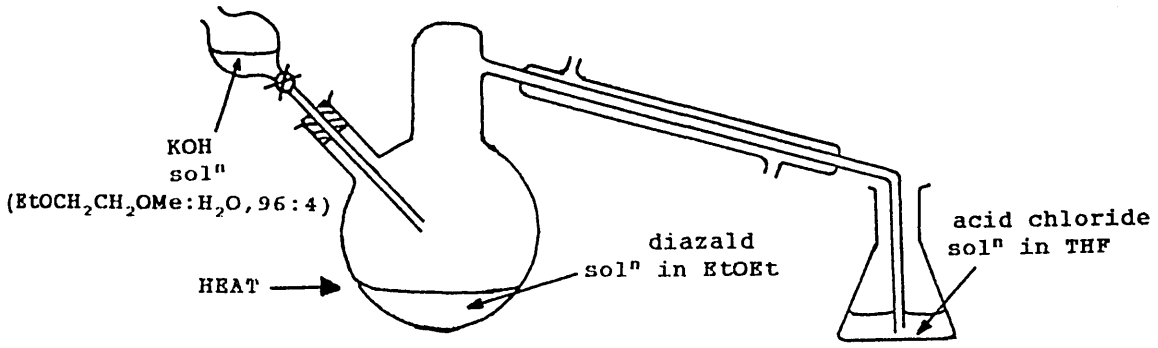
Petrol refers to that fraction of petroleum spirit boiling between 40 and $60^{0}C$. Dry tetrahydrofuran was obtained by distillation from potassium metal. Dry diethyl ether was obtained through standing

over sodium wire. Dry dimethylformamide was obtained by heating over calcium hydride followed by distillation under reduced pressure onto 4A molecular sieves. Dry pyridine was obtained by storage over potassium hydroxide. Dry dichloromethane was obtained by distillation from P_2O_5 and was stored over molecular sieves.

All reactions requiring inert atmospheres were performed under nitrogen.

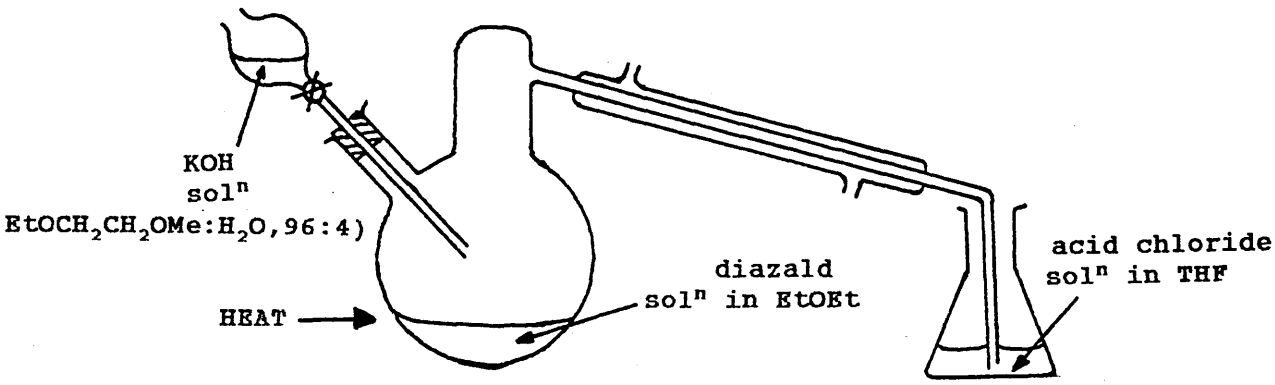
All bicyclic products were stored in a freezer, since many were found to be rather unstable at room temperature.

Apparatus and General Method for Diazomethane Reactions



The above glassware was used for the reactions involving diazomethane. All glassware was flame-polished to avoid the presence of any sharp surfaces. Ground glass joints were avoided by the use of the rubber bung at the junction of the dropping funnel with the 1-litre round-bottomed flask and also the fusion of the still head and the condenser with the round-bottomed flask. The round-bottomed flask was of a suitable size as to allow the performance of the reaction on a fairly large scale whilst still allowing sufficient room to prevent a build-up of too high a pressure or too high a concentration of diazomethane above the surface of the diazomethane preparation mixture prior to its distillation in dilute ethereal solution. Distillation was effected using a hair dryer on a low setting and playing the hair dryer around the round-bottomed flask at the surface of the mixture so as to avoid heating the gas too strongly at a point where it was in a relatively high concentration. All the apparatus as shown was maintained behind a glass or perspex safety screen in the fume cupboard throughout the preparation and distillation of the diazomethane.

This apparatus thus avoided all the reported conditions responsible for detonation of the diazomethane, namely excessive



The above glassware was used for the reactions involving diazomethane. All glassware was flame-polished to avoid the presence of any sharp surfaces. Ground glass joints were avoided by the use of the rubber bung at the junction of the dropping funnel with the 1-litre round-bottomed flask and also the fusion of the still head and the condenser with the round-bottomed flask. The round-bottomed flask was of a suitable size as to allow the performance of the reaction on a fairly large scale whilst still allowing sufficient room to prevent a build-up of too high a pressure or too high a concentration of diazomethane above the surface of the diazomethane preparation mixture prior to its distillation in dilute ethereal solution. Distillation was effected using a hair dryer on a low setting and playing the hair dryer around the round-bottomed flask at the surface of the mixture so as to avoid heating the gas too strongly at a point where it was in a relatively high concentration. All the apparatus as shown was maintained behind a glass or perspex safety screen in the fume cupboard throughout the preparation and distillation of the diazomethane.

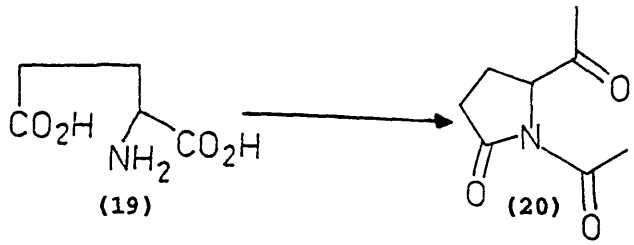
This apparatus thus avoided all the reported conditions responsible for detonation of the diazomethane, namely excessive

heat direct sunlight, sharp surfaces, high pressure and high concentration of the gas[108].

At the start of the preparation, the round-bottomed flask was charged with diazald in a very dilute solution in diethyl ether, the dropping funnel was charged with a solution of potassium hydroxide in ethylene glycol monoethyl monomethyl diether and the suitably sized receiving conical flask was charged with a solution of the acid chloride or acid anhydride under test in tetrahydrofuran. The amounts of the reagents were based on a 70% yield of diazomethane from the reaction of diazald with potassium hydroxide.

The potassium hydroxide solution was added to the diazald solution in one portion and the tap on the dropping funnel was closed immediately. The apparatus was then immediately set up for distillation as shown and the diazomethane was distilled in ethereal solution using the hair dryer. Distillation was continued until no further diazomethane, present as a yellow colouration in the distillate, was observed. The conical flask was then separated from the rest of the apparatus so as to avoid suck-back of the contents of the receiver flask, and the reaction was left for at least 6 hours prior to work-up to allow the escape of any unreacted, excess diazomethane gas.

(R/S)-1,5-diacetyl pyrrolidin-2-one (20)[39]

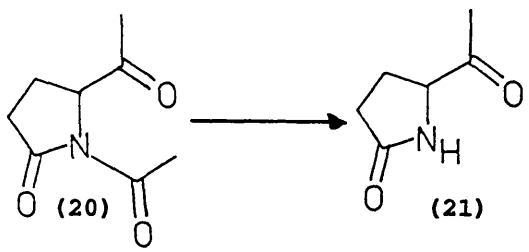


(19) (20)

Glutamic acid (19) (92.56g,0.590mol), acetic anhydride (320ml), triethylamine (320ml) and 4-dimethylaminopyridine (320mg) were stirred at 60°C for 8 hours under reflux. The black, oily mixture was cooled and vacuum distilled to afford the product (20) as a bright yellow oil, bpt.120-126°C/1.5mmHg, which formed pale yellow crystals on cooling. 72.8g,73%

mpt.64-66°C (lit.[39]68-69°C)
IR (KBr) 3500,2995,1730,1700,1390,1300
^{1}H NMR ($CDCl_3$) 1.9-3.5(m,10H,sharp singlets for the two methyl groups at 2.2 and 2.4), 4.7-5.0(m,1H), 8.3(broad singlet,1H)
^{13}C NMR ($CDCl_3$) 19.8,24.3,26.8,31.6,63.1,170.9,174.5,205.9

(R/S)-5-acetyl pyrrolidin-2-one (21)[40]



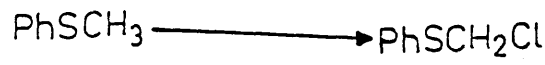
(20) (21)

(R/S)-1,5-diacetyl pyrrolidin-2-one (20) (8.64g,0.051mol) and sodium carbonate (6.36g,0.060mol) were dissolved in water (100ml) and the solution was stirred at room temperature for 5 hours. The pH was adjusted to 7.0 (meter) using dilute hydrochloric acid and the product was extracted into dichloromethane using a continuous extraction apparatus over 25 hours. After drying ($MgSO_4$) and concentration under reduced pressure, the organic phase gave an off-white solid which was recrystallised from ethyl acetate. 4.54g,70%

mpt.75-78°C (lit.[40]74-76°C)

IR (KBr) 3190,3100,3000-2900,1710,1420,1380,1350,1280,1245,1185
^{1}H NMR ($CDCl_3$) 1.7-2.9(m,7H,sharp singlet for -CH_3 at 2.2), 4.1-4.3(m,1H), 7.2(broad singlet,1H)
^{13}C NMR ($CDCl_3$) 21.9,24.5,30.3,61.9,62.6,179.2,205.1

Chloromethyl phenyl sulphide (26)[42]



(25) (26)

Thioanisole (25) (83.90g,80.0ml,0.675mol) was dissolved in dichloromethane (500ml). A solution of sulphuryl chloride (90.00g,54.0ml,0.667mol) in dichloromethane (150ml) was added dropwise over a 1 hour period, and the mixture was refluxed for 2 hours. After cooling, the mixture was concentrated under reduced pressure to leave the product (26) as a yellow liquid, 104.60g,99%, which was used directly in the next step.

IR 3100,2900,1640,1600,1500,1460,1410,1240,740,700
^{1}H NMR ($CDCl_3$) 4.8(s,2H), 7.2-7.8(m,5H)

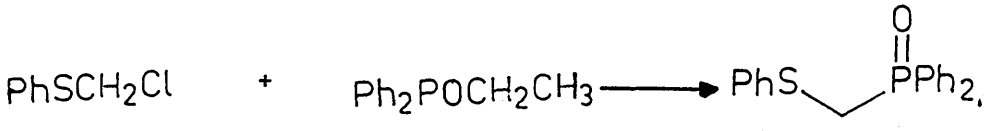
Ethoxydiphenyl phosphine (28)[43]

(27) (28)

A solution of chlorodiphenyl phosphine (27) (25.00g,0.120mol) in dry diethyl ether (65ml) was added dropwise with stirring to absolute ethanol (11.50g,0.250mol) and anhydrous pyridine (13.50g,0.170mol) at 0^{0}C (ice bath) and was allowed to warm temperature overnight with stirring. The mixture was filtered under suction with a dry nitrogen atmosphere and the residue was washed with dry ether (125ml). After concentration under reduced pressure the filtrate was vacuum distilled to afford the product (28) as a colourless oil. 17.04g,93%

bpt.118-124°C/o.5mmHg (lit.[43]108-116°C/0.5mmHg)
^{1}H NMR ($CDCl_3$) 1.2(t,3H), 3.6-4.2(m,2H), 7.1-8.0(m,10H)

Diphenyl phenylthiomethyl phosphine oxide (29)[44]

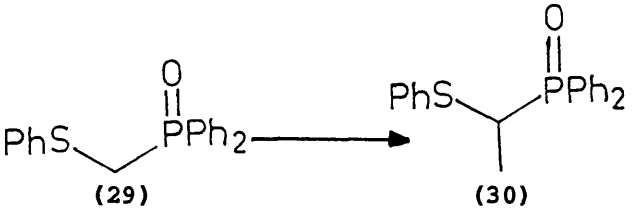


(26) (28) (29)

Ethoxydiphenyl phosphine (28) (25.00g,0.109mol) and chloromethyl phenyl sulphide (26) (17.23g,0.139mol) were refluxed together under nitrogen for 6 hours at 150°C (oil bath) On cooling a pale yellow solid separated, which was recrystallised from ethyl acetate and petrol to give the product (29) as a white solid. 29.90g,85%

mpt.100-103°C (lit.[44]101-102°C)
IR (KBr) 3100,2995,1640,1600,1500,1460,1400,1200,1120,1100,1000, 820,800,740,700
^{1}H NMR ($CDCl_3$) 3.7(d,2H), 7.0-8.0(m,15H)

Diphenyl-1-phenylthioethyl phosphine oxide (30)[44]



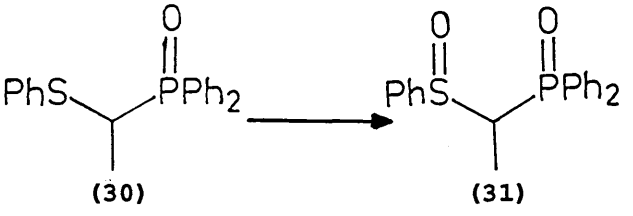
(29) (30)

Diphenyl phenylthiomethyl phosphine oxide (29) (15.00g,0.045mol) in dry tetrahydrofuran (200ml) and N,N,N',N'-tetramethylethylenediamine (6.15g,0.060mol) was treated with n-butyl lithium (33.0ml,1.6M,0.060mol) at -78°C. After stirring for 15 minutes, methyl iodide (7.50g,0.060mol) was added, and the solution was allowed to warm to room temperature over 30 minutes. Aqueous ammonium chloride (2N,70ml) was added and the product was

extracted with chloroform (3x250ml). The combined organic extracts were washed with dilute hydrochloric acid and dried ($MgSO_4$). Filtration and concentration under reduced pressure afforded the product (30) as a pale yellow solid. 14.87g,98%.

mpt.154-156^{0}C (lit.[44]154-155^{0}C)
IR (KBr) 3400,3050,3000-2900,1480,1430,1180,1120,1020,740-720,700-680
^{1}H NMR($CDCl_3$) 1.4-1.9(q,3H), 3.7-3.8(m,1H), 7.0-8.0(m,15H)

Diphenyl-1-phenylsulphinylethyl phosphine oxide (31)



(30) (31)

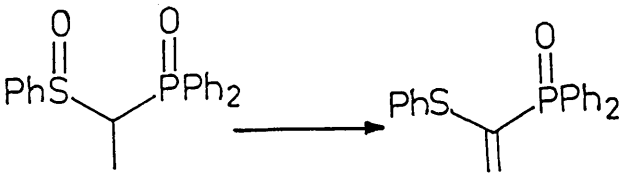
(a)[26] Sodium metaperiodate (0.63g,2.94mmol) in water (25ml) was added dropwise to a solution of diphenyl-1-phenylthioethyl phosphine oxide (30) (1.00g,2.96mmol) in methanol (25ml). The mixture was stirred at room temperature for 6 hours, during which a pale yellow precipitate was produced. The mixture was filtered and the residue was washed with methanol (25ml). The filtrate was concentrated under reduced pressure and partitioned between chloroform (50ml) and water(50ml). The aqueous layer was washed with chloroform (2x50ml) and the combined organic extracts were dried ($MgSO_4$), filtered and concentrated under reduced pressure to produce an orange solid. Chromatography (ethyl acetate) afforded a deep yellow solid. 0.70g,67%

mpt.140-144^{0}C (lit.[41] reports the compound as a colourless oil)
^{1}H NMR ($CDCl_3$) 1.0-1.8(m,3H), 3.2-4.0(m,1H), 7.0-8.0(m,15H)
^{13}C NMR ($CDCl_3$) 58.6, 61.6, 124.3, 128.5, 129.2, 129.3, 130.6, 131.1, 131.5, 131.6, 132.4, 134.2, 134.5, 145.0

(b)[41] A solution of diphenyl-1-phenylthioethyl phosphine oxide (30) (3.38g,0.010mol) in dry tetrahydrofuran (25ml) was cooled to -78°C and to it was added a solution of metachloroperbenzoic acid (2.16g,0.010mol) in dichloromethane (25ml). The reaction mixture was stirred for 1 hour at -78°C and thereafter allowed to warm to room temperature. After washing with aqueous sodium hydrogen carbonate, drying ($MgSO_4$) and filtration under suction, subsequent concentration under reduced pressure afforded a crude yellow solid. Chromatography (ethyl acetate) gave the product as a colourless oil. 2.05g,58%

Spectral data were identical to the product from (a).

Diphenyl-1-phenylthiovinyl phosphine oxide (24)[41]



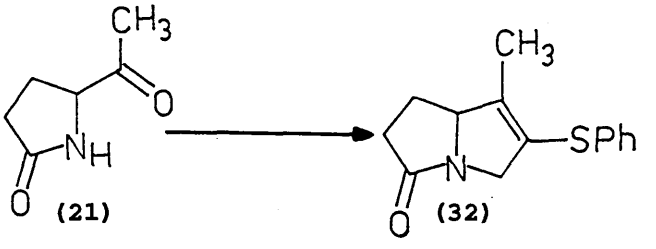
(31) (24)

Acetic anhydride (0.18g,1.76mmol) and methanesulphonic acid (4 drops) were added to a solution of diphenyl-1-phenylsulphinylethyl phosphine oxide (31) (0.50g,1.55mmol) in dichloromethane (20ml). The mixture was stirred at room temperature for 8 days and then poured into saturated aqueous sodium carbonate (50ml). The aqueous layer was washed with dichloromethane (2x50ml). The combined organic extracts were dried ($MgSO_4$), filtered and evaporated to leave a deep orange solid. Chromatography (ethyl acetate) gave the product (24) as a white, crystalline solid. 0.32g,61.4%

mpt.91-92°C
IR (KBr) 3080,3000,1720,1620,1590,1480,1440,1220,1190,1120,1100, 1030,1005,910,700,670
^1H NMR ($CDCl_3$) 5.3-6.2(m,2H), 7.0-8.0(m,15H)
^{13}C NMR ($CDCl_3$)128.2,128.8,129.6,132.4,134.1

Literature[41] reports the product as a colourless oil, with identical spectral data, previous work at Sheffield City Polytechnic[26] agrees with the product obtained by the author of this thesis, with identical spectral data.

(R/S)-5,6,7,7a-tetrahydro-1-methyl-2-phenylthio-3H-pyrrolizin-5-one (32)[26]



(a) Sodium hydride (0.48g,12.0mmol,60% dispersion in mineral oil) was placed in a 100ml 3-necked round-bottomed flask and washed with petrol. Dry tetrahydrofuran (10ml) and acetonitrile (40ml) were added, followed by (R/S)-5-acetyl pyrrolidin-2-one (21) (1.51g,11.9mmol). The reaction mixture was stirred at room temperature for 15 minutes and then diphenyl-1-phenylthiovinyl phosphine oxide (24) (2.00g,6.00mmol) was added. The mixture was stirred for a further 8 hours and then evaporated. Chromatography (ethyl acetate : petrol, 1:1) afforded the product (32) as a colourless oil. 2.46g,84.4%

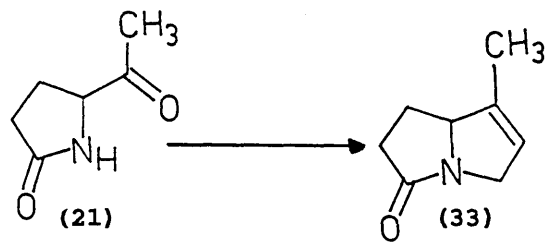
IR 3100,3000-2880,1690,1580,1480,1440,1380,1300,1280,1160,1030, 750,700,680
^{1}H NMR ($CDCl_3$) 1.8(s,3H), 2.0-3.0(m,4H), 3.3-3.8(m,1H), 4.0-4.8(m,2H), 7.1(s,5H)
mass spec. 246.0969(MH^+,$C_{14}H_{16}NOS$ requires 246.0953 amu), 245.0852(M,$C_{14}H_{15}NOS$ requires 245.0874 amu),230,219,189,99,93,84, 71,56(base peak),55,40,39

(b) Sodium hydride (0.32g,7.95mmol) was added portionwise to a solution of (R/S)-5-acetyl pyrrolidin-2-one (21) (1.00g,7.87mmol)

in tetrahydrofuran : acetonitrile, (1:4) (50ml) with vigorous stirring. After 15 minutes, 1-phenylthiovinyl triphenyl phosphonium iodide (22) (3.93g,7.50mmol) was added and the mixture was stirred at room temperature for 6 hours. The mixture was then evaporated, and subsequent flash chromatography (dry diethyl ether : methanol, 95:5) afforded the product as a colourless oil. 1.31g,68% max yield (see table 1, page 37).

Spectral data were identical with the product from (a).

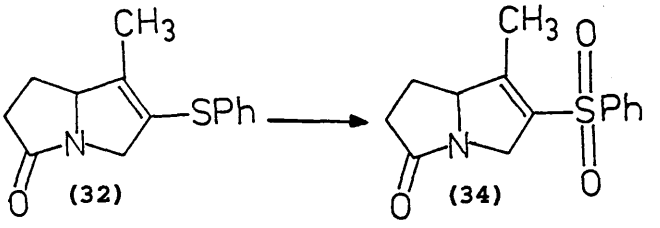
(R/S)-5,6,7,7a-tetrahydro-1-methyl pyrrolizin-5-one (33)[26]



This preparation involved the use of triphenyl vinyl phosphonium bromide (23), and the procedure was similar to the preparation of the bicycle (32) from 5-acetyl pyrrolidin-2-one (21), sodium hydride and 1-phenylthiovinyl triphenyl phosphonium iodide (22). The product bicycle (33) was obtained as a colourless oil. Yield 0.43g,40% max yield from identical amounts of (21) and sodium hydride (see table 1, page 37).

IR 2930,2860,1710-1650,1460,1380,1150,1120-1100
^{1}H NMR ($CDCl_3$) 1.7(s,3H,-CH_3), 2.0-3.0(m,4H), 3.2-3.9(m,1H), 4.0-4.6(m,2H), 5.3(s,1H)

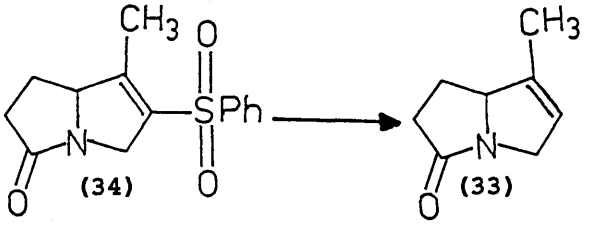
(R/S)-5,6,7,7a-tetrahydro-1-methyl-2-phenylsulphonyl-3H-pyrrolizin-5-one (34)



The sulphide (32) (0.75g,3.06mmol) was dissolved in methanol (5.0ml). To this solution was added a solution of oxone ($2KHSO_5.KHSO_4.K_2SO_4$,6.14g,10.0mmol) in water (5.0ml). and the mixture was stirred at room temperature for 4 hours. The methanol was removed on the rotary evaporator, and the aqueous residue was diluted with water (30ml) and washed with ethyl acetate (3x30ml). The combined organic extracts were dried ($MgSO_4$), filtered and evaporated. Flash chromatography (dry diethyl ether) gave the sulphone (34) as a white foam. 0.75g,88%

IR 3080,2940,2890,1700,1630,1590,1440,1380,1330,1310,1240,1150, 1120,1105,1000,850,760,740,700,680
^1H NMR ($CDCl_3$) 1.8-2.8(m,7H, sharp singlet for $-CH_3$ at 2.1), 3.2-3.9(m,2H), 4.3(m,1H), 7.0-8.0(m,5H)
mass spec. 278.0839(MH^+,$C_{14}H_{16}NO_3S$ requires 278.0853 amu), 277.0754(M,$C_{14}H_{15}NO_3S$ requires 277.0772 amu),199,183,149,77,57,43, 41,40

(R/S)-5,6,7,7a-tetrahydro-1-methyl-3H-pyrrolizin-5-one (33)

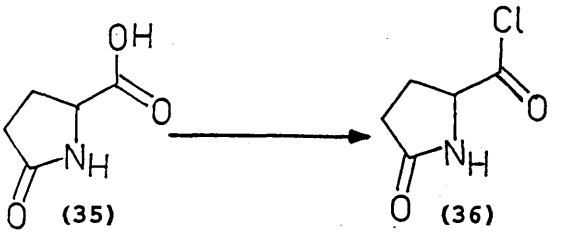


The sulphone (34) (0.40g,1.44mmol) was dissolved in dimethylformamide (15ml). To this solution was added a solution of sodium hydrogen carbonate (0.73g,8.66mmol) and sodium dithionite

(0.75g,4.33mmol) in water (15ml), and the mixture was refluxed for 4 hours, cooled, and partitioned between water (60ml) and ethyl acetate (60ml). The aqueous phase was washed with ethyl acetate (2x60ml). The combined organic extracts were dried ($MgSO_4$), filtered and evaporated. Flash chromatography (dry diethyl ether : methanol, 95:5) afforded the product as a colourless oil. 0.08g,44%

Spectral data were identical with the product obtained from the intramolecular cyclisation reaction involving 5-acetyl pyrrolidin-2-one (21), sodium hydride and triphenyl vinyl phosphonium bromide (q.v.)

(S)-Pyroglutamyl chloride (36)



(a) To a solution of (S)-pyroglutamic acid (1.00g,7.75mmol) in dichloromethane (20ml) at 0^0C was added N,N'-dimethylformamide (0.1ml) and oxalyl chloride (15ml,98mmol%) in one portion. The reaction mixture was allowed to warm to room temperature and stirred for a further 1.5 hours. The reaction was monitored by infrared and then the mixture was concentrated under reduced pressure to leave the product as a thick, black, tarry residue in quantitative yield.

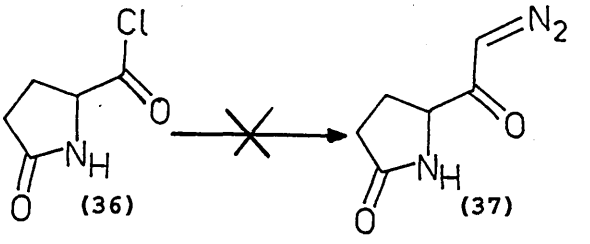
IR 3600(br.),3540(sharp),3050-2900,1770,1690,730,700

^{1}H NMR ($CDCl_3$) 2.0-3.0(m,4H),3.5-3.8(m,1H),8.6-9.0(m,1H)

(b) To a solution of (S)-pyroglutamic acid (1.00g,7.75mmol) in chloroform (20ml) was added thionyl chloride (0.93g,7.85mmol). The mixture was refluxed for 6 hours, cooled and evaporated to leave a black tar in quantitative yield.

Spectral details were identical with those for the product from (a).

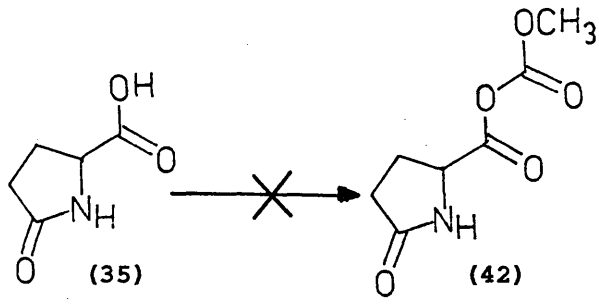
Attempted preparation of (S)-5-diazoacetyl pyrrolidin-2-one (37)



(Refer to the apparatus and general method outlined at the beginning of this section).

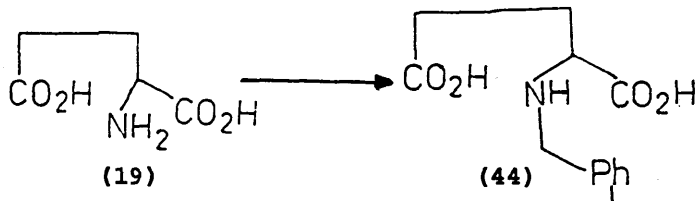
The 1-litre round-bottomed flask was charged with a solution of diazald (5.00g,0.023mol) in dry ether (50ml). The receiver flask was charged with a solution of (S)-pyroglutamyl chloride (36) (0.85g,5.75mmol) in dry tetrahydrofuran (20ml). The dropping funnel was charged with a solution of potassium hydroxide (1.29g,0.023mol) in ethylene glycol monoethyl monomethyl diether : water, (96:4), and this was added to the diazald solution in one portion. Distillation of the yellow solution of diazomethane solution was effected using a hair dryer, and was continued until no further yellow colour was observed in the distillate. The reaction mixture was left to stand overnight and then concentrated under reduced pressure to leave a yellow tar. Many fractions which reacted with 2,4-dinitrophenyl hydrazine spray were observed on tlc. Isolation via chromatography (ethyl acetate) and subsequent infrared analysis showed most of these fractions to exhibit the characteristic sharp peak for the diazo stretch at 2100cm^{-1}, but none of these fractions produced the characteristic pyrrolidone signals on proton NMR.

Attempted preparation of (S)-pyroglutamic acetic anhydride (42)



(S)-pyroglutamic acid (3.00g,0.023mol) was suspended in ethyl acetate (50ml). On addition of triethylamine (3.20ml) most appeared to dissolve. The mixture was then cooled to -5°C (ice/salt bath) and ethyl chloroformate (2.20ml,2.98g,0.027mol) was added dropwise with vigorous stirring and a white precipitate of triethylammonium chloride was formed immediately. After warming to room temperature over 1 hour, the mixture was filtered and evaporated, but only the starting acid was isolated. 1.70g,56.7%

(S)-N-Benzyl glutamic acid (44)[54]



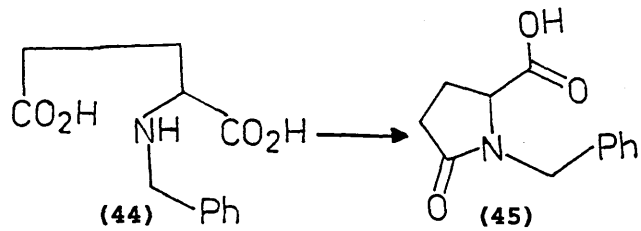
(19) (44)

(S)-Glutamic acid (46.14g,0.310mol) was dissolve in aqueous sodium hydroxide solution (2N,300ml) to give a colourless solution. Benzaldehyde (104g,0.980mol), freshly distilled (bpt.178-181°C), was added at room temperature over a 10 minute period to produce a heterogeneous mixture, and stirring was continued overnight, whereupon most of the benzaldehyde had apparently been taken up. The pH was adjusted to 9.2 with sodium hydroxide pellets and the mixture was cooled in an ice bath. Sodium borohydride (13.05g,0.344mol) was added slowly, keeping the internal temperature below 20°C. The mixture was then stirred at room temperature for 1.5 hours, filtered with suction to remove the excess sodium borohydride and then washed with dichloromethane (250ml) and diethyl ether (250ml) to remove any unreacted benzaldehyde and benzyl alcohol produced via disproportionation of the benzaldehyde. The pH of the aqueous phase was then adjusted to 4.3 (meter). The induced white precipitate was filtered off and the pH of the filtrate was adjusted to 3.0 (meter) and this was left to stand overnight. This induced precipitate was also filtered off. The precipitates were each washed with acetone (50ml) and combined to give the product as a white solid. 60.25g,82%

mpt.160-162°C (lit.[54]162-163°C)
IR (KBr) 3490(broad),1700,1630,1270,1190,1100,760,700,620
^{1}H NMR (DDMSO) 2.0-3.0 (m,5H), 7.6 (s,5H). Large water peak at 3.4-5.7 probably masking benzyl -CH_2- protons.
^{13}C NMR (DDMSO) 22.6,29.2,44.8,58.7,127.6,127.9,128.7,129.4,133.0, 175.1

mass spec. 219,174,91,65,39

(S)-N-benzyl pyroglutamic acid (45)[54]



(S)-N-benzyl glutamic acid (50.00g,0.211mol) was added to distilled water (500ml) and the mixture was refluxed for 17 hours. The solution was then cooled, whereupon a white precipitate was formed. The mixture was washed with chloroform (3x200ml) and the combined organic extracts were dried ($MgSO_4$),filtered and evaporated to leave the product as a white solid. 35.12g,76%

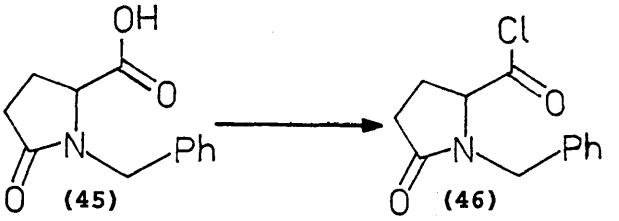
mpt.61-64°C (lit.[54]62-63°C)
IR (KBr) 3450 (broad), 3100-2940, 1740-1640 (messy and strong), 1500,1470-1420,1360,1230-1180,710
^1H NMR ($CDCl_3$) 2.0-2.8(m,4H), 3.6-4.0(m,2H), 5.1(d,2H), 7.3(s,5H), 10.5(s,1H)
^{13}C NMR ($CDCl_3$) 22.9,29.7,45.9,58.9,128.0,128.6,128.9,135.3,173.7, 176.9
mass spec. 219.0904(M,$C_{12}H_{13}NO_3$ requires 219.0895 amu), 174,91,65,58,42

In the majority of preparations of the preceding (S)-N-benzyl glutamic acid the principal by-product benzoic acid, produced as a result of disproportionation of benzaldehyde, could not be completely removed and was thus carried through the cyclisation stage. It was therefore customary to purify the (S)N-benzyl pyroglutamic acid via flash chromatography (ethyl acetate). This allowed confirmation of the identity of the annoying by-product:

IR(KBr)3100-2500(broad),1680,1600,1580,1450,1420,1330,1290,1180, 1130,1070,1030,1000,940,810,740,710,690,670

Column chromatography often failed to remove all the benzoic acid.

(S)-N-benzyl pyroglutamyl chloride (46)

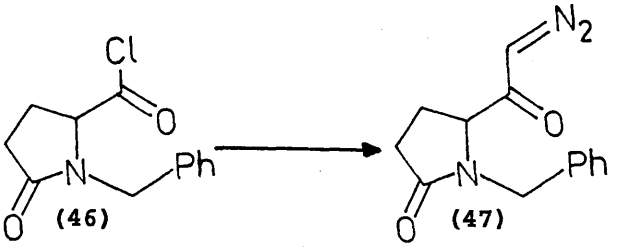


To a solution of (S)-N-benzyl pyroglutamic acid (5.00g,0.023mol) in tetrahydrofuran (40ml) was added oxalyl chloride (6.67g,0.530mol) dropwise with cooling (ice bath) and vigorous stirring. After effervescence had ceased, the mixture was allowed to warm to room temperature over 4 hours and monitored by infrared. Concentration under reduced pressure afforded the acid chloride as a dark brown tar in quantitative yield.

IR 3100-2990,1770,1450,1410,1260,1230,1200,1170,1140,1020,970,900, 870,790,730,700,690,670,650

^1H NMR ($CDCl_3$) 1.8-2.8(m,4H), 4.0(m,2H), 5.15(d,1H,J=7Hz), 7.0(s,5H)

(S)-5-diazoacetyl-N-benzyl pyrrolidin-2-one (47)



(Refer to the apparatus and general method outlined at the beginning of this section).

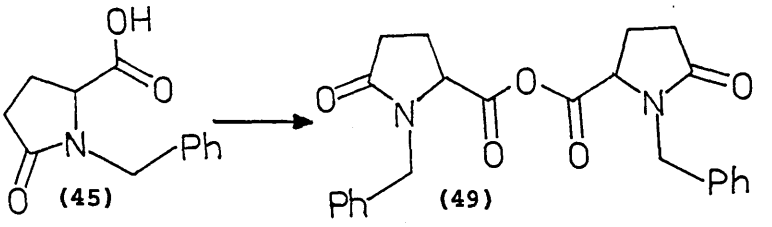
The 1-litre round-bottomed flask was charged with a solution of diazald (5.42g,0.025mol) in dry ether (100ml). The receiver flask was charged with a solution of (S)-N-benzyl pyroglutamyl chloride (2.00g,8.44mmol) in dry tetrahydrofuran (100ml). The dropping funnel was charged with a solution of potassium hydroxide (1.42g,0.025mol) in ethylene glycol monoethyl monomethyl diether : water, (96:4), and this was added to the diazald solution in one portion. Distillation of the yellow ethereal solution of diazomethane was effected using a hair dryer and was continued until no further yellow colour was observed in the distillate. The reaction mixture was left to stand overnight and was then dried ($MgSO_4$), filtered and evaporated to leave a bright yellow oil. Flash chromatography (ethyl acetate) and subsequent work-up provided the product as a bright yellow oil. 3.91g,64.4%

IR3100-3040,3000-2900,2110,1690,1640,1500,1450,1410,1360,1320, 1280,1230, 1200,1145,1030,960,900,820,740,705,660
^1H NMR ($CDCl_3$) 1.8-2.6(m,4H), 3.7-4.0(m,2H), 5.1(d,1H,J=7Hz), 5.4(s,1H), 7.25(s,5H)
^{13}C NMR ($CDCl_3$) 23.3,29.5,45.6,53.7,127.8,128.4,128.7,135.7,175.3, 175.5,193.0
mass spec. 215($M-N_2$),174,91(base peak),65,39

Preparation of the diazoketone (47) was similarly effected from the symmetrical anhydride (49) in 58% yield and also from the mixed anhydride (50) in 48% yield; some (S)-N-benzyl pyroglutamic

acid was recovered in each case, produced as a result of hydrolysis of the starting acid chloride derivative.

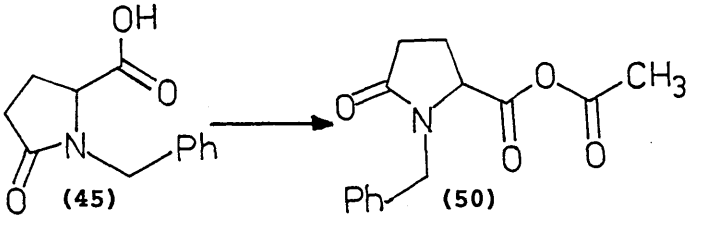
(S)-N-benzyl pyroglutamic anhydride (49)



To a solution of dicyclohexylcarbodiimide (1.03g,5.02mmol) in dry diethyl ether (20ml) at 0°C was added a solution of (S)-N-benzyl pyroglutamic acid (2.00g,9.13mmol) in dry tetrahydrofuran (30ml). The reaction mixture was allowed to warm to room temperature and then filtered, concentrated under reduced pressure, filtered again and evaporated to leave the product as a white wax. 1.73g,90%

IR 3100-3000,2995-2800,1820,1745,1720,1460,1420,1370,1280,1250, 1190,1120,1080,900,730,700,660
^{1}H NMR ($CDCl_3$) 1.8-2.7(m,8H), 3.8-4.2(m,4H), 5.0(m,2H), 7.2(s,10H)

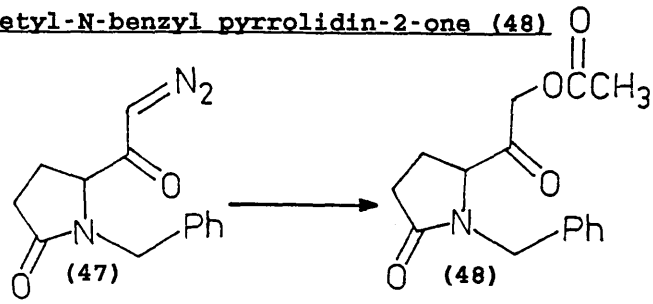
(S)-N-benzyl-5-(1,3-dioxo-2-oxa-1-butyl)-pyrrolidin-2-one (50)



To a solution of (S)-N-benzyl pyroglutamic acid (1.00g,4.57mmol) in dry tetrahydrofuran (30ml) at -5°C (ice/salt bath) was added triethylamine (0.92g,9.14mmol) followed by methyl chloroformate (0.86g,9.14mmol) dropwise with vigorous stirring. The mixture was allowed to warm to room temperature over 2 hours and then evaporated to leave the product as a white wax. 1.08g,86%

IR 3100-3000,2950,1780,1750,1700,1610,1450,1420,1360,1290-1200, 1180,1070,1040,990,760,700
^{1}H NMR ($CDCl_3$) 1.8-2.6(m,4H), 3.6(s,3H), 4.0(m,2H), 4.8(d,1H), 7.2(s,5H)

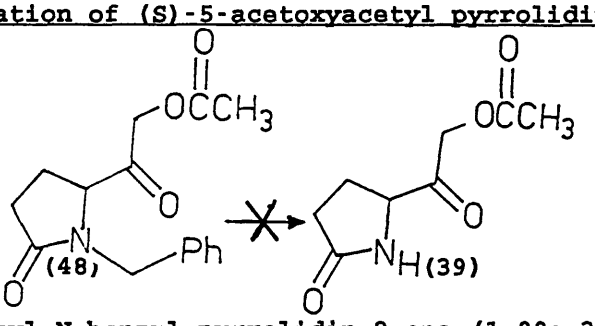
(S)-5-acetoxyacetyl-N-benzyl pyrrolidin-2-one (48)



(S)-N-benzyl-5-diazoacetyl pyrrolidin-2-one (2.36g,9.71mmol) was added to glacial acetic acid (40ml) and the mixture was heated under reflux for 1 hour. The acetic acid was then removed on the rotary evaporator and the residue was columned using flash chromatography (ethyl acetate) to afford the product as a viscous, colourless oil. 1.83g,68.5%

IR 3100-2850,1735,1685,1640,1410,1360,1230,1040,740,700,670
^{1}H NMR ($CDCl_3$) 1.9-2.7(m,7H,sharp singlet for $-CH_3$ at 2.1), 3.6-4.2(m,2H), 4.4(s,2H), 5.0(d,1H), 7.2(s,5H)
^{13}C NMR ($CDCl_3$) 21.9,29.4,45.7,61.6,63.8,66.0,128.0,128.7,130.0, 135.5,135.8,174.0,175.3,201.8
mass spec. 274.9985(M,$C_{15}H_{17}NO_4$ requires 274.9971 amu),174,91(base peak)

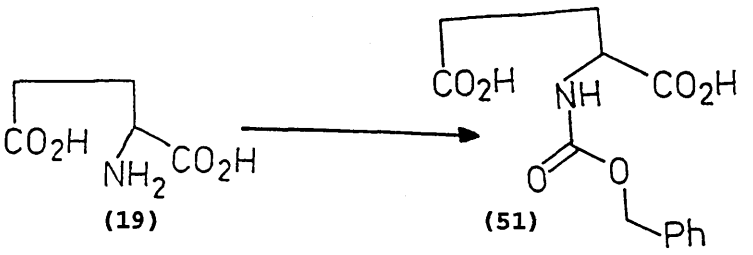
Attempted preparation of (S)-5-acetoxyacetyl pyrrolidin-2-one (39)



(S)-5-acetoxyacetyl-N-benzyl pyrrolidin-2-one (1.00g,3.64mmol) was dissolved in dry tetrahydrofuran (30ml). Palladium black on activated charcoal (5%,0.25g) was added and the mixture was maintained under a hydrogen atmosphere at room temperature with stirring. Thin layer chromatography (ethyl acetate) failed to show any reaction, even after stirring was continued overnight. The catalyst was filtered off and the solvent was removed on the rotary evaporator to leave the original ketone (0.90g,90%).

Subsequent modifications involving the use of methanol as the solvent still failed to produce any reaction.

(S)-N-carbobenzyloxy glutamic acid (51)

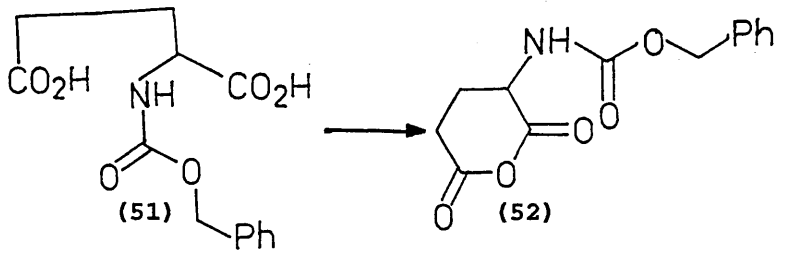


(S)-glutamic acid (11.76g,0.080mol) was dissolved in aqueous sodium hydroxide solution (2N,120ml,3mol.equiv.) and cooled to 0^0C. Benzyl chloroformate (14.00g,9.22ml,0.082mol) was added dropwise with vigorous stirring. After stirring overnight, the mixture was washed with ether (3x50ml) and the organic extracts were discarded. The pH of the aqueous layer was then adjusted to 3 (universal indicator paper) using conc. hydrochloric acid and the aqueous solution was washed with dichloromethane (3x50ml), during which approximately half of the product formed a thick, yellow oil at the solvent interface. The combined organic extracts were dried ($MgSO_4$) and filtered quickly and then concentrated under reduced pressure to give the product as a white solid. 17.42g,73.8%

mpt.114-115^{0}C
IR (KBr) 3400(broad),3310,3050,3000-2900,1690,1640,1540,1440,1400, 1320,1290,1260,1245,1210,1180,1160,1070,1040,1010,990,930,795,775, 740,720,690
^{1}H NMR (DDMSO) 1.7-2.7(m,5H), 5.0(s,2H), 7.3(s,5H), 7.2-7.6(m,6H)
^{13}C NMR (DDMSO) 26.4,30.3,53.3,65.6,127.7,127.9,137.1,156.2,173.6, 173.8

The racemic compound was also isolated as a white solid with identical IR and ^{1}H NMR spectra.

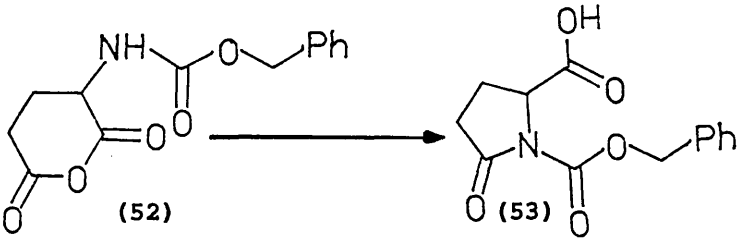
(S)-N-carbobenzyloxy glutamic anhydride (52)



(S)-N-carbobenzyloxy glutamic acid (8.80g,0.031mol) was dissolved in dry tetrahydrofuran (50ml) and to it was added a solution of dicyclohexylcarbodiimide (7.21g,0.035mol) in dry tetrahydrofuran (50ml). The reaction mixture was stirred overnight. The resultant white precipitate of dicyclohexylurea was filtered off and washed with tetrahydrofuran. The filtrate and washings were concentrated under reduced pressure and to the residue was added dry tetrahydrofuran (50ml). The mixture was again filtered in order to remove any more dicyclohexylurea and again concentrated under reduced pressure to give the anhydride as a thick, off-white grease. Full purification was not possible, and the anhydride was used crude for the next step. Yield (based on ^{1}H NMR), 7.23g,89%

IR (thin film) 3340,2930,2860,1780,1770,1700,1500,1450,1380, 1300,1220,1040,890,700,665
^{1}H NMR ($CDCl_3$) 1.7-2.5(m,4H), 3.8(m,1H), 5.0(s,2H), 7.2(s,5H), 7.4(m,1H)

(S)-N-carbobenzyloxy pyroglutamic acid (53)



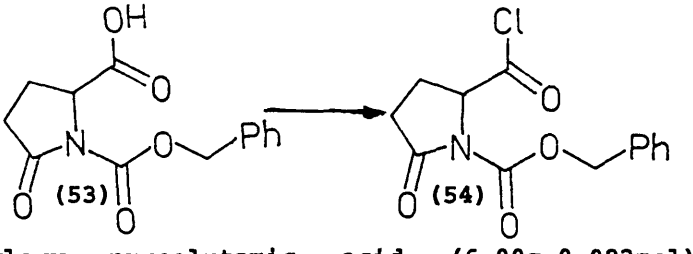
(S)-N-carbobenzyloxy glutamic anhydride (7.23g,0.028mol) was dissolved in dry tetrahydrofuran (20ml). Dicyclohexylamine (5.5ml)

was added and the mixture was stirred overnight at room temperature to produce a white suspension of the dicyclohexylammonium salt of the required acid. The solid was filtered off, washed with dry tetrahydrofuran and dissolved in water (30ml). After acidification with conc. hydrochloric acid the aqueous solution was washed with dichloromethane (3x50ml). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated under reduced pressure to give the product as a white solid. 6.03g,83%

mpt.133-135^{0}C (lit.[109] 134-135^{0}C)
IR (KBr) 3100-3000,2940,1780,1740,1720,1300,1260,1180,1050,910, 730, 700
^{1}H NMR ($CDCl_3$) 2.0-2.6(m,4H), 4.6(m,1H), 5.2(s,2H), 7.2(s,5H)
^{13}C NMR ($CDCl_3$)
21.8,31.0,58.6,68.2,127.9,128.5,131.8,135.1,173.2,173.4, 173.5
mass spec. 263.0800(M,$C_{13}H_{13}NO_5$ requires 263.0794 amu),224,143, 130,107,91,84,70,56(base peak),55,43,41,39

The corresponding racemic compound was isolated as a yellow tar and took several days to crystallise, even with refrigeration. The melting point was very close to room temperature.

(S)-N-carbobenzyloxy pyroglutamyl chloride (54)

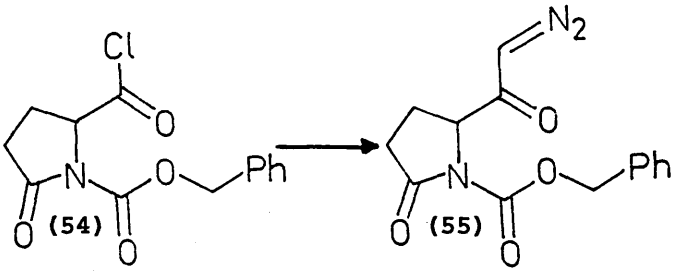


(S)-N-carbobenzyloxy pyroglutamic acid (6.00g,0.023mol) was dissolved in dry tetrahydrofuran (50ml) and cooled to 0^{0}C (ice bath). Oxalyl chloride (6.43g,0.101mol) was added slowly with

vigorous stirring. The mixture was stirred at room temperature for 3 hours and then evaporated to leave a brown tar. 6.00g,93%

IR 3020,2920-2800,1790,1770,1720,1380,1300,1180,1030,960,920,750, 730,690
^{1}H NMR ($CDCl_3$) 2.0-2.6(m,4H), 4.6(m,1H), 5.2(s,2H), 7.2(s,5H)

(S)-N-carbobenzyloxy-5-diazoacetyl pyrrolidin-2-one (55)



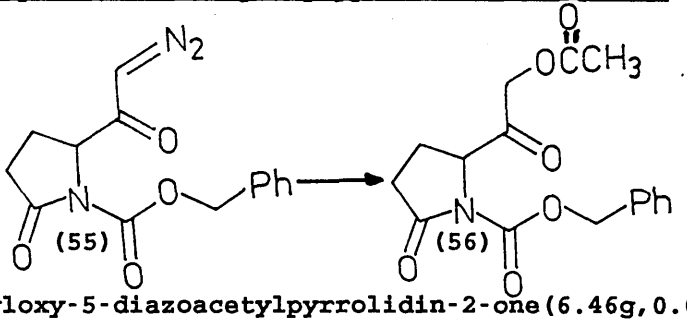
(Refer to the apparatus and general method outlined at the beginning of this section).

The 1-litre round-bottomed flask was charged with a solution of diazald (38.11g,0.178mol) in dry diethyl ether (300ml). The receiver flask was charged with a solution of (S)-N-carbobenzyloxy pyroglutamyl chloride (10.00g,0.036mol) in dry tetrahydrofuran (100ml). The dropping funnel was charged with a solution of potassium hydroxide (10.24g,0.183mol) in ethylene glycol monoethyl monomethyl diether : water, (96:4), (100ml), and this was added to the diazald solution in one portion. Distillation of the yellow ethereal solution of diazomethane was effected using a hair dryer, and was maintained until no further yellow colour was observed in the distillate. The reaction mixture was left to stand overnight and then concentrated under reduced pressure to leave the product as a bright yellow solid. 8.68g,84%

mpt.121-123^{0}C
IR (KBr) 3010,2930,2100,1780,1720,1630,1380,1300,1210,1030,900, 750,730,690,660
^{1}H NMR ($CDCl_3$) 1.8-2.6(m,4H), 3.6(m,1H), 5.1(s,3H), 7.4(s,5H)
mass spec. 278,197,115,107,91(base peak),83,82,81,55,41

The racemic compound remained as a bright yellow tar; spectral data were identical to the chiral compound.

(S)-5-acetoxyacetyl-N-carbobenzyloxy pyrrolidin-2-one (56)

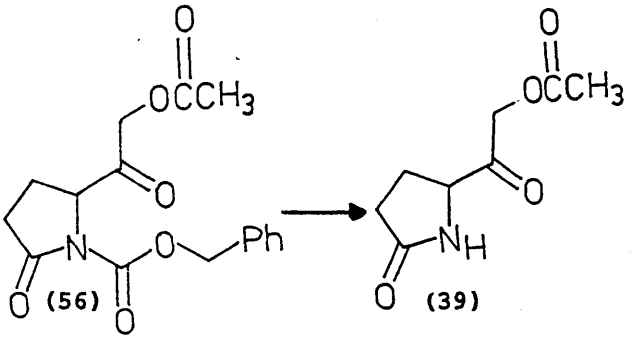


(S)-N-carbobenzyloxy-5-diazoacetylpyrrolidin-2-one(6.46g,0.023mol) was added to acetic acid (65ml) and the mixture was heated under reflux for 1 hour. The excess acetic acid was removed on the rotary evaporator to leave an off-white solid. Flash chromatography (ethyl acetate : methanol, (95:5)) afforded the product as a white solid. 5.60g,78%

mpt.64-66^{0}C
IR (KBr) 3100,2940,1730,1680,1450,1410,1360,1260,1220,1050,1040, 700,660
^{1}H NMR ($CDCl_3$) 2.3-2.7(m,7H,singlet due to $-CH_3$ at 2.1), 3.9-4.3(m,1H), 4.6(s,2H,acetyl $-CH_2-$), 5.1(s,2H,benzyl $-CH_2-$), 7.1(s,5H)
mass spec. 319,295,218,174(base peak),107,91(base peak),84,65,43

The racemic compound remained as a white tar. Infrared, proton NMR and mass spectral data were identical to the chiral compound.

(S)-5-acetoxyacetyl pyrrolidin-2-one (39)

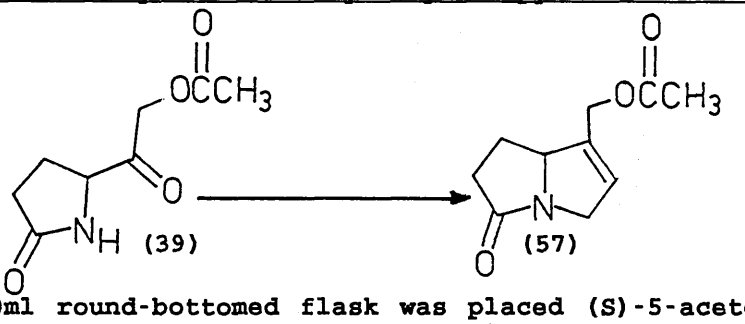


(S)-5-acetoxyacetyl-N-carbobenzyloxypyrrolidin-2-one (3.00g,9.40 mmol) was dissolved in dry tetrahydrofuran (40ml). Palladium black catalyst on activated charcoal (0.50g) was added and the mixture was maintained under a hydrogen atmosphere for 6 hours at room temperature with stirring. The catalyst was then filtered off and the filtrate was evaporated to leave a white solid. 1.51g,87%

The melting point was very close to room temperature.
IR (KBr) 3400-3300,2940,1740,1700,1420,1380,1240,1050,910,730
^1H NMR ($CDCl_3$) 2.1(s,3H,-CH_3), 2.2-2.5(m,4H), 4.1-4.4(m,1H), 4.7(s,2H, acetyl-CH_2-), 7.1-7.3(m,6H,singlet at 7.1)
mass spec. 186.0089(MH^+,$C_8H_{12}NO_4$ requires 186.0114 amu),185.0122(M,$C_8H_{11}NO_4$ requires 185.0138 amu),154,84(base peak),41

The racemic compound remained as a pale yellow tar. Spectral data were identical with the chiral compound.

(S)-5,6,7,7a-tetrahydro-1-acetoxymethyl-3H-pyrrolizin-5-one (57)

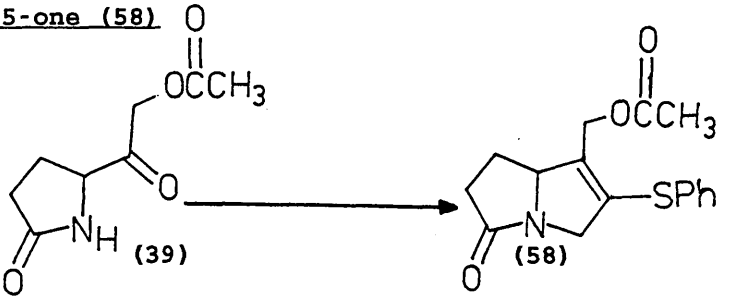


Into a 100ml round-bottomed flask was placed (S)-5-acetoxyacetyl pyrrolidin-2-one (0.23g,1.24mmol), tetrahydrofuran (10ml), acetonitrile (40ml) and sodium hydride (0.04g,1.50mmol). After stirring for 20 minutes, during which hydrogen was given off, vinyl triphenyl phosphonium bromide (0.55g,1.50mmol) was added, and stirring was continued overnight. After removal of the solvents on the rotary evaporator, flash chromatography (ethyl acetate) gave the product as a pale yellow solid. 0.14g,58.3%

mpt.89-91^{0}C
IR 3000-2880,1740,1700,1650,1440,1380,1280,1240,1200,1120,1050, 1030,965,840,725,700,655
^{1}H NMR ($CDCl_3$) 1.6-2.9(m,8H,sharp singlet for -CH_3 at 2.05), 3.35-4.9(m,4H,sharp singlet for -CH_2-O- at 4.6), 5.7(m,1H)
mass spec. 195.0906(M, $C_{10}H_{13}NO_3$ requires 195.0895 amu), 135(base peak), 134,122,106,93,80,79,68,55,53,52,43,39

The racemic compound was also isolated as a pale yellow solid, mpt.85-87^{0}C, with identical spectral data.

(S)-5,6,7,7a-tetrahydro-1-acetoxymethyl-2-phenylthio-3H-pyrrolizin-5-one (58)



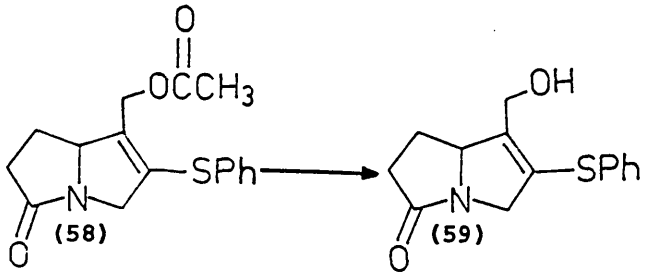
Sodium hydride (0.04g,1.82mmol) was placed in a 3-necked, round-bottomed flask. Dry tetrahydrofuran (10ml), acetonitrile (40ml) and (S)-5-acetoxyacetyl pyrrolidin-2-one (0.28g,1.51mmol) were added. Hydrogen was visibly produced, and after stirring for 0.5 hours, 1-phenylthiovinyl triphenyl phosphonium iodide (0.95g,1.82mmol) was added. Stirring was continued for a further 8 hours, during which a strong brown colour was produced. After removal of the solvents on the rotary evaporator, the crude mixture was flash chromatographed (ethyl acetate) to afford the product as a brown oil. 0.24g,62.3%

IR 3080,3000-2900,2880,1740,1700,1585,1480,1460,1440,1380,1300, 1280,1230,1030,970,750,730,700

^{1}H NMR ($CDCl_3$) 1.9-2.7(m,8H,sharp singlet for -CH_3 at 2.0), 3.2-4.5(m,2H), 5.75(s,2H, -CH_2-O-), 7.1(S,5H)

mass spec. 303.0920(M,$C_{16}H_{17}NO_3S$ requires 303.0929 amu), 277,245,244,230,210,188,186,149,134,121,109,106,91,77,71,55 (base peak),43,39

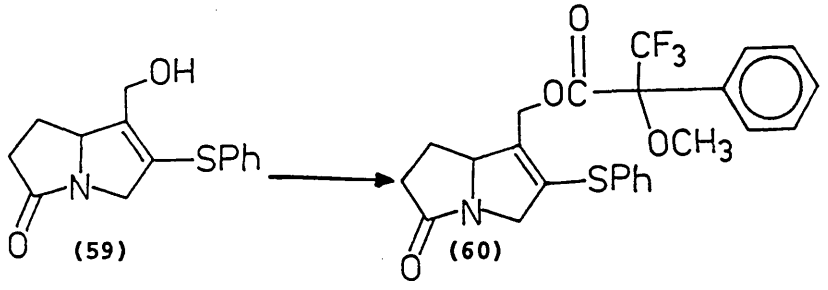
(S)-5,6,7,7a-tetrahydro-1-hydroxymethyl-2-phenylthio-3H-pyrrolizin-5-one (59)



A solution of the ester (58) (0.30g,1.15mmol) in methanol (5ml) was added to aqueous sodium hydroxide solution (2N,20ml) and the mixture was stirred for 4.5 hours. After removal of the methanol on the rotary evaporator, the mixture was washed with dichloromethane (3x20ml). The combined organic extracts were dried ($MgSO_4$),filtered and evaporated. Flash chromatography (ethyl acetate) gave the product as a colourless oil. 0.20g,77%

IR 3400(broad),3100,2960-2900,1680,1630,1440,1390,1300,1210,1150, 1100-1010,680,660
^1H NMR ($CDCl_3$) 1.9-3.0(m,5H), 3.5-4.9(m,4H,singlet for $-CH_2-O-$ at 4.4), 7.0(s,5H), 7.2(s,1H,O-H)

Mosher's ester of (S,R)-5,6,7,7a-tetrahydro-1-hydroxymethyl -2-phenylthio-3H-pyrrolizin-5-one

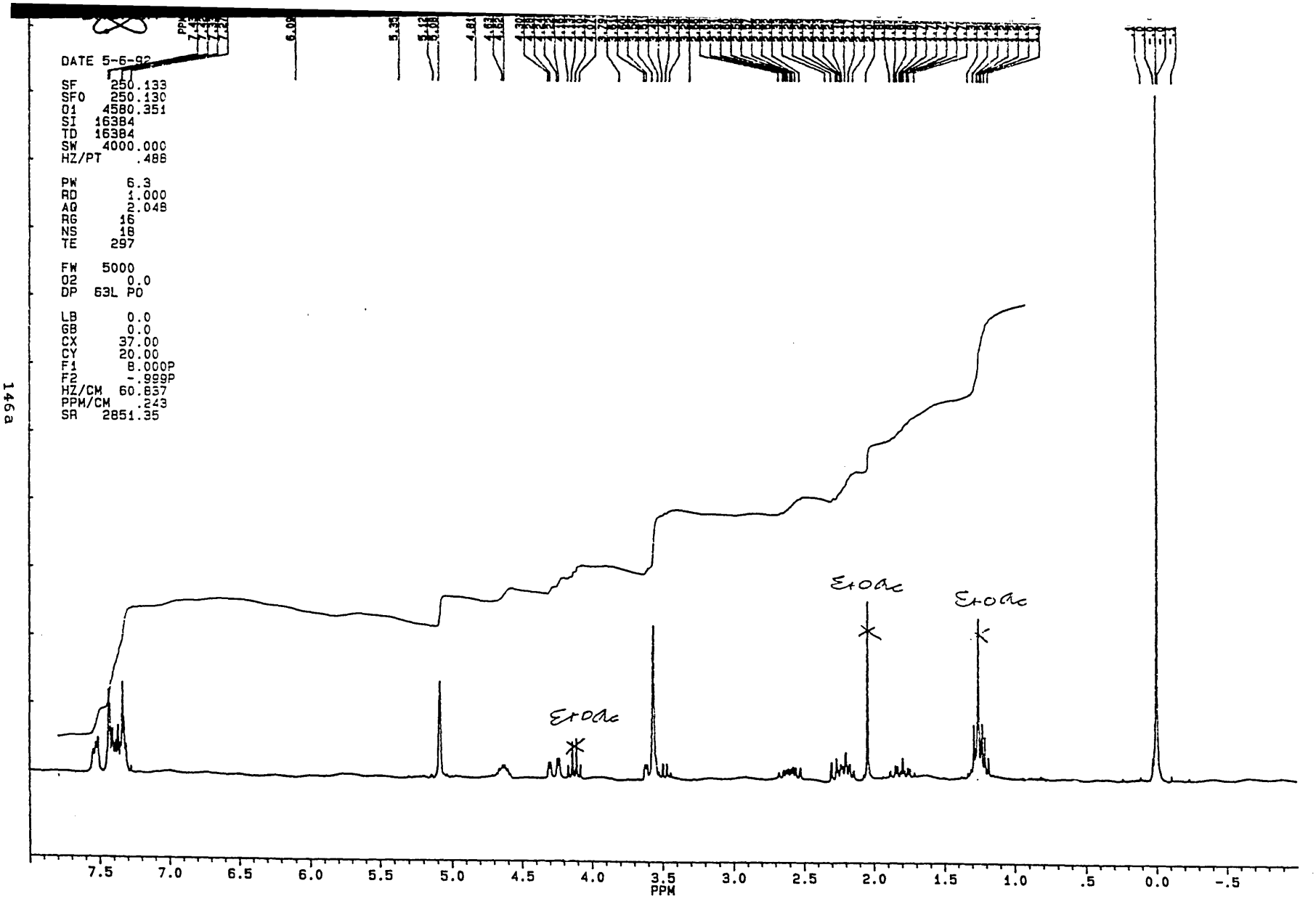


The alcohol (59) (0.10g,0.35mmol) was dissolved in dry dichloromethane (10ml) in a 50ml round-bottomed flask. To this solution was added 4-dimethylamino pyridine (10mg), dicyclohexylcarbodiimide (0.0825g,0.4mmol) and (R)-Mosher's acid

(0.0875g,0.38mmol) was added and the mixture was stirred for 8 hours, whereupon a white precipitate was produced. This was filtered off and the filtrate was concentrated under reduced pressure. The mixture was flash chromatographed (ethyl acetate : 40/60 petrol, 1:1) to give the product as a colourless oil. 0.14g,77%

^{1}H NMR ($CDCl_3$) 1.7-1.9(m), 2.1-2.3(m), 2.5-2.7(m), 3.5(s), 4.2-4.3(m), 4.6(m), 5.1(s), 7.3-7.4(m)

^{13}C NMR ($CDCl_3$) 28.6,33.1,52.4,59.8,60.4,65.8,68.7,84.6, 127.4,128.6,128.8,129.6,129.8,130.4,132.1, 132.7,134.5,136.0,171.0,177.3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TD 16384
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AQ 2.048
RG 16
NS 18
TE 297
FW 5000
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GB 0.0
CX 37.00
CY 20.00
F1 8.000P
F2 -.999P
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PPM/CM .243
SR 2851.35
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EtOAc
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7.0
6.5
6.0
5.5
5.0
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1.0
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0.0
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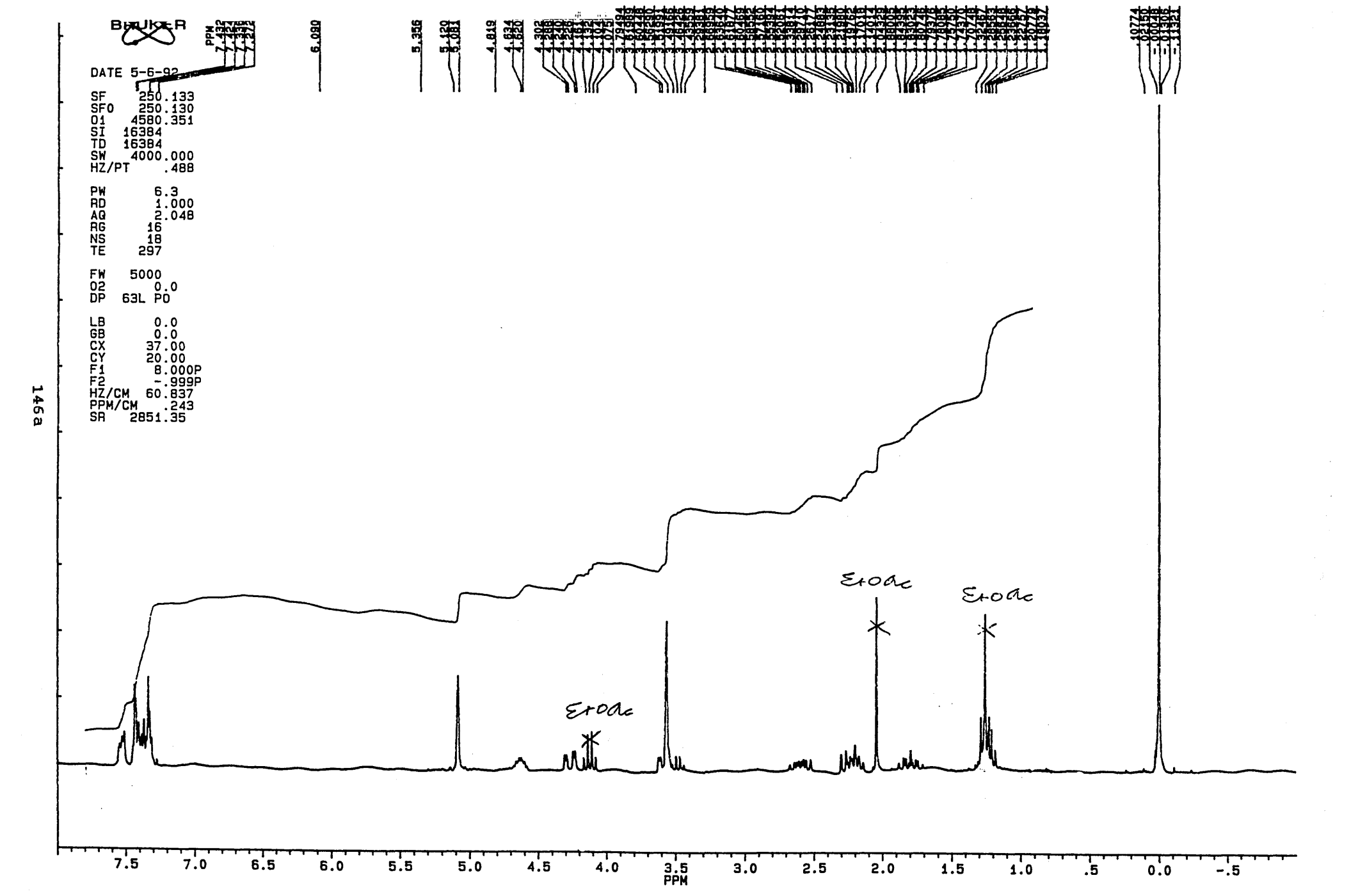
PPM


BRUKER
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TD 16384
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F2 -.999P
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EtOAc
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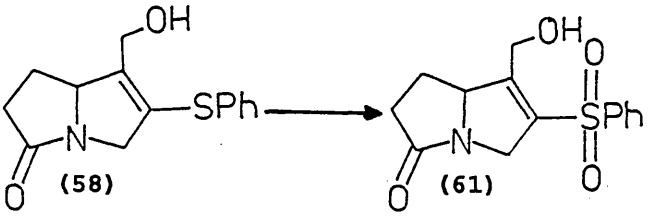
PPM

146a

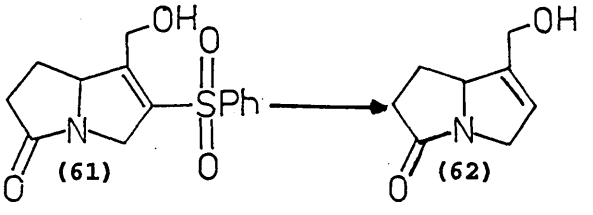
(S)-5,6,7,7a-tetrahydro-1-hydroxymethyl-2-phenylsulphonyl-3H-pyrrolizin-5-one (61)



The sulphide (58) (0.08g,0.26mmol) was dissolved in methanol (15ml). To this solution was added a solution of oxone ($2KHSO_5.KHSO_4.K_2SO_4$,0.62g,1.35mmol), and the mixture was stirred for 3 hours at room temperature. The methanol was removed on the rotary evaporator, and the aqueous residue was diluted with water (30ml) and washed with ethyl acetate (3x25ml). The combined organic extracts were dried ($MgSO_4$), filtered and evaporated. Flash chromatography (ethyl acetate :methanol, 95:5) afforded the product as a colourless tar. 0.04g,52.5%

IR 3400(very broad),3000-2890,1680,1630,1450,1400,1310,1230,1150, 1105,1085,1020,1000,755,730,695
^1H NMR ($CDCl_3$) 1.5-2.8(m,4H), 3.3-5.0(m,4H), 7.15-7.75(m,5H,2:3 split)

(S)-5,6,7,7a-tetrahydro-1-hydroxymethyl-3H-pyrrolizin-5-one (62)

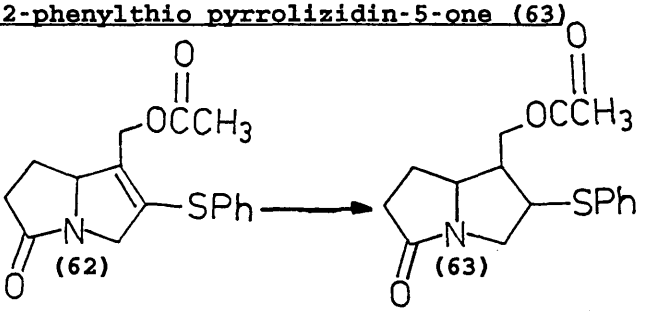


The sulphone (61) (0.06g,0.18mmol) was dissolved in dimethylformamide (15ml). To this solution was added a solution of sodium hydrogen carbonate (0.11g,1.3mmol) and sodium dithionite (0.11g,0.7mmol) in water (15ml) and the mixture was refluxed for

4.5 hours, cooled and partitioned between dilute hydrochloric acid (2N,30ml) and dichloromethane (10ml). The aqueous layer was washed with dichloromethane (2x10ml). The combined organic extracts were dried ($MgSO_4$), filtered and evaporated. Flash chromatography (ethyl acetate : methanol, 97:3) gave the product as a colourless oil. 0.01g,20%

IR 3400(broad),3000-2870,1715,1660,1455,1370,1290,1150-1080 ,1020,950,865
^1H NMR ($CDCl_3$) 1.3-2.7(m,5H), 3.0(s,2H,-CH_2-O-), 3.2-4.4(m,2H), 4.9(s,1H), 7.1(s,1H)
mass spec. 153.0879(M,$C_8H_{11}NO_2$ requires 153.0790 amu), 151,143, 136,124,117,113,101,97,91,83,70,65,57,51(base peak),50,40,36

1-acetoxymethyl-2-phenylthio pyrrolizidin-5-one (63)



The sulphide (62) (0.06g,0.20mmol) was dissolved in dry tetrahydrofuran (25ml). Chloro tris(triphenylphosphine) rhodium (I) (Wilkinson's catalyst) (0.23g,0.25mmol) was added, and the mixture was maintained under a hydrogen atmosphere with stirring for 3.5 hours at room temperature. The tetrahydrofuran was then removed on the rotary evaporator and the residual mixture was flash chromatographed (ethyl acetate) to afford the product as a colourless oil. 0.04g,66.2%

IR 3060,3000-2880,1745,1705,1585,1480,1440,1380,1300,1280,1235, 1190,1120,1030,970,925,755,730,700

^1H NMR ($CDCl_3$) 1.85-2.6(m,10H,sharp singlets for the isomeric methyl groups at 2.0 and 2.2), 3.4-4.3(m,2H), 4.8(s,2H), 7.25(5H,2 singlets for the isomeric SPh groups)

mass spec. 305.1099(M,$C_{16}H_{19}NO_3S$ requires 305.1086 amu), 303,244, 230,210,201,188,186,181,152,134,121,106,91,80,77,65,53,43(base peak),39

Methoxyacetic acid (67)

$$ClCH_2COOH \longrightarrow CH_3OCH_2COOH$$

(66) (67)

A 1-litre round-bottomed flask was charged with methanol (420ml) and fitted with two 3ft. water reflux condensers in series. Metallic sodium (23.00g,1.000mol) was added fast enough to keep the solution refluxing gently. When all the sodium had been used up, a solution of chloroacetic acid (47.30g,0.500mol) in methanol (60ml) was added dropwise to keep the solution boiling. After all the acid was added, the mixture was heated under reflux for 0.5 hours. It was then cooled and acidified with conc. hydrochloric acid. Sodium chloride was thus precipitated, subsequently filtered off and washed on the filter with diethyl ether (2x50ml). Concentration of the filtrate under reduced pressure precipitated more sodium chloride, which was likewise filtered and washed with diethyl ether. The filtrate was again concentrated under reduced pressure and then distilled. However, despite several distillations using various columns of the process, the product could not be separated from unreacted chloroacetic acid. Commercially-available methoxyacetic acid was thus used hereon.

Methoxyacetyl chloride

$$CH_3OCH_2COOH \longrightarrow CH_3OCH_2COCl$$

(67)

(a) To a solution of methoxyacetic acid (5.00g,0.056mol) in chloroform (50ml) at 0^oC was added dimethylformamide (0.7ml) and

oxalyl chloride (15.22g,0.112mol) in one portion. The reaction mixture was allowed to warm to room temperature and stirred for a further 1.5 hours; the reaction was monitored by infrared. The mixture was then concentrated under reduced pressure to leave a pale yellow liquid. 5.23g,86%

IR 3000-2800,1800,1450,1400,1330,1200,1130,1050,1000,940,910,750
^{1}H NMR ($CDCl_3$) 3.4(s,3H), 4.3(s,2H)

(b) To a solution of methoxyacetic acid (5.00g,0.056mol) in chloroform (70ml) was added thionyl chloride (7.93g,0.066mol). The mixture was refluxed for 2 hours and monitored by infrared. It was then cooled, and distillation at atmospheric pressure produced the acid chloride, bpt.203-206^{0}C. 3.78g,62%

(Spectral data were identical with the product from (a)).

Methoxyacetic anhydride (68)

$$CH_3OCH_2COOH \longrightarrow (CH_3OCH_2CO)_2O$$

(67) (68)

(a) To a solution of dicyclohexylcarbodiimide (5.77g,0.028mol) in dry diethyl ether (50ml) at 0^{0}C was added a solution of methoxyacetic acid (5.00g,0.056mol) in dichloromethane (40ml) dropwise at such a rate that the temperature did not exceed 5^{0}C. Dicyclohexylurea was precipitated as a white solid. The mixture was allowed to warm to room temperature and the reaction was

monitored by infrared. When all acid was used up, the dicyclohexylurea was filtered off and the filtrate was evaporated. Dry diethyl ether (40ml) was added and the mixture was again filtered and evaporated to leave a colourless oil. Vacuum distillation afforded the product as a colourless liquid. 2.32g,52%

bpt.124-128^{0}C/20mmHg
IR 3000-2800,1830,1760,1700,1650,1510,1440,1410,1200,1120,1050,930
^{1}H NMR ($CDCl_3$) 3.4(s,3H), 4.2(s,2H)

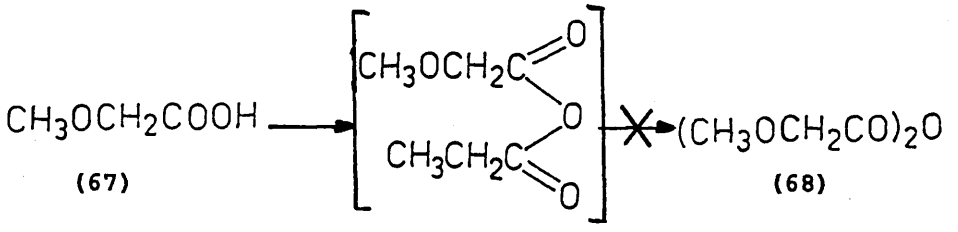
(b)[64] Methoxyacetic acid (5.00g,0.056mol) and freshly distilled acetic anhydride (5.00g,0.038mol,bpt.138-140^{0}C) were heated together under gentle reflux for 18 hours. The mixture was then distilled to give the crude product as a colourless liquid. Modifications of the vacuum distillation apparatus, including the use of a 6ft. spinning-band column all failed to purify the product. Yield (based on ^{1}H NMR) 5.75g,63%

(Spectral data were consistent with the product from (a)).

(c) To methoxyacetic acid (4.14g,0.046mol) in dry tetrahydrofuran (30ml) was added sodium hydride (1.84g,0.046mol) portionwise with vigorous stirring. The mixture was then stirred for a further 20 minutes at room temperature and a solution of methoxyacetyl chloride (5.00g,0.046mol) in dry tetrahydrofuran (20ml) was then added dropwise. After stirring at room temperature for 4 hours with monitoring by infrared, the white precipitate of sodium

chloride was filtered off and the filtrate was concentrated under reduced pressure to leave a colourless liquid which was vacuum distilled to afford the product as a colourless liquid which was contaminated with unreacted methoxyacetic acid. yield (based on ^1H NMR) 3.64g,73%

Attempted preparation of methoxyacetic anhydride (68)[64]



(67) (68)

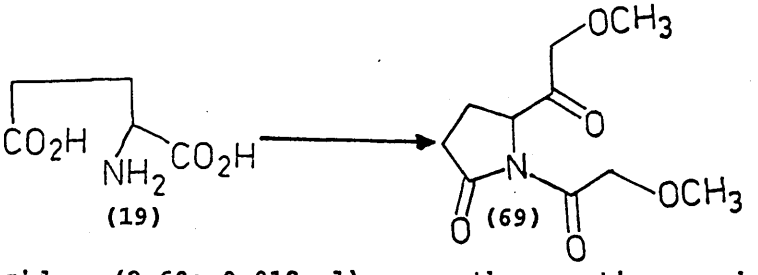
Methoxyacetic acid (67) (5.00g,0.056mol) was added to dry triethylamine (5.66g,0.056mol) and the resultant solution was cooled over an ice/salt bath. Ethyl chloroformate (6.08g,0.056mol), freshly distilled (bpt.93-96^{0}C), was added dropwise with vigorous stirring, producing a violent reaction and a white suspension. The mixture was allowed to warm to room temperature over 2 hours and then again cooled and addition of identical quantities of methoxyacetic acid and triethylamine respectively was carried out. The mixture was left to stir at room temperature overnight, dissolved in chloroform (50ml), washed with water (2x50ml), dried ($MgSO_4$), filtered and evaporated to leave a white tar. Dry diethyl ether (50ml) was added to create a white suspension. The solid was filtered off, and concentration of the filtrate under reduced pressure followed by vacuum distillation afforded the mixed anhydride as a colourless liquid. 13.65g,84%

IR 3000-2800,1830,1740,1450-1360,1260,1200,1120,1030,980,930,850, 750,660

^1H NMR ($CDCl_3$) 1.2(t,3H), 3.4(s,3H), 3.9-4.4(m,4H)

No methoxyacetic acid was isolated.

(R/S)-1,5-dimethoxyacetyl pyrrolidin-2-one (69)



Glutamic acid (2.60g,0.018mol), methoxyacetic anhydride (8.55g,0.053mol), triethylamine (9ml) and 4-dimethylamino pyridine (18mg) were stirred at 60°C for 5 hours. Many fractions were observed on tlc and vacuum distillation failed to isolate the product. The residue from the distillation was dissolved in dichloromethane (50ml), the "carbon" was filtered off and the filtrate was concentrated under reduced pressure. Chromatography (ethyl acetate : petrol, 85:15) gave the product as a bright yellow oil, which very slowly crystallised to a bright yellow solid. 0.08g,2%

^{1}H NMR ($CDCl_3$) 1.9-2.8(m,4H), 3.5(d,6H), 4.2(s,2H), 4.6(s,2H), 5.1(m,1H)

The sample proved to be somewhat unstable, and after 2 days at room temperature it had completely decomposed. Attempts to repeat this procedure all resulted in failure.

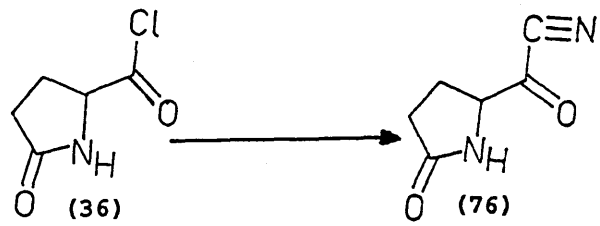
Benzyloxymethyl magnesium chloride (73)

$$PhCH_2OCH_2Cl \longrightarrow PhCH_2OCH_2MgCl$$

(72) (73)

Magnesium turnings (0.60g,0.025mol) were covered with dry tetrahydrofuran (20ml) and cooled to -25°C (CCl_4/CO_2). A crystal of iodine was added, foolowed by a solution of benzyl chloromethyl ether (3.13g,0.020mol) in dry tetrahydrofuran (20ml) dropwise with vigorous stirring. It was some time before a reaction visibly occured. No heat was used, since the reagents were believed to be unstable to heat. The reaction appeared to be normal for a Grignard preparation, so to confirm it a solution of p-chlorobenzaldehyde (2.81g,0.020mol) in dry tetrahydrofuran (20ml) was added dropwise. The mixture was allowed to warm to room temperature over 2 hours, poured into dilute hydrochloric acid (300ml), and the tetrahydrofuran was removed on the rotary evaporator. The aqueous phase was washed with ether(3x75ml). The combined organic extracts were dried ($MgSO_4$), filtered and evaporated to give a dark brown oil. Chromatography (petrol : diethyl ether, 80:20) revealed that there had been negligible reaction of the Grignard with the aldehyde, based on a 91% recovery of the aldehyde.

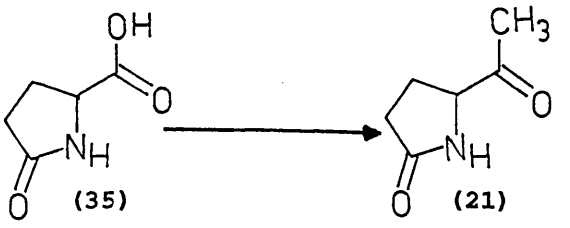
(S)-5-cyanoacetyl pyrrolidin-2-one (76)



(S)-pyroglutamyl chloride (4.57g,0.031mol) in chloroform (100ml) and cuprous cyanide (3.35g,0.037mol) were refluxed for 20 hours. After filtration to remove the excess cyanide,the filtrate was washed with aqueous sodium carbonate (sat.,100ml), then with water (100ml). After drying ($MgSO_4$), filtration and evaporation a dark brown tar was produced. Chromatography (ethyl acetate : methanol, 4:1) gave (S)-pyroglutamic acid (3.35g,0.026mol), but nothing resembling the required product.

IR (KBr) 3495,3000-2500,1720,1645,1440,1410,1230,1100,1000,980, 960,820,710,660,610

(S)-5-acetyl pyrrolidin-2-one (21)



(a) To a suspension of (S)-pyroglutamic acid (35) (1.00g,7.75mmol) in dry tetrahydrofuran (40ml) at -78°C was added N,N,N',N'-tetramethylethylenediamine (50ml), followed by n-butyl lithium (2.5M,6.5ml,7.80mmol). The mixture was stirred at -78°C for 15 minutes and then methyl magnesium bromide (3.0M,5.20ml,15.5mmol) was added. The mixture was allowed to warm to room temperature over 7 hours and then poured into aqueous ammonium chloride (2N,200ml). The tetrahydrofuran was removed on the rotary evaporator, the pH of the aqueous layer was adjusted to 7 (universal indicator paper) and the product was extracted into dichloromethane (500ml) using a continuous extraction apparatus over 2 days. The organic extract was dried ($MgSO_4$), filtered and evaporated. Chromatography (ethyl acetate) gave the product as a pale yellow solid. 0.10g,10%

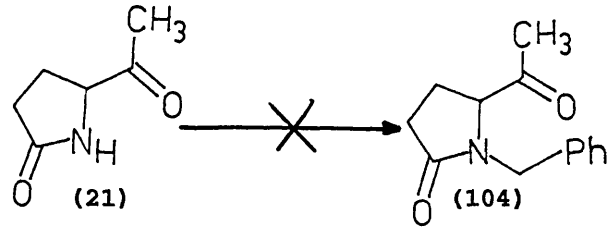
Spectral data were identical with the compound obtained via the Dakin-West reaction described earlier.

(b) (S)-pyroglutamic acid (35) (5.00g,0.039mol) was suspended in dry tetrahydrofuran (50ml) and cooled to -78°C. Methyl lithium (1.4M,33.5ml,0.040mol) was injected slowly and the mixture was stirred vigorously for 20 minutes. Methyl magnesium bromide (3.0M,13.0ml,0.040mol) was injected slowly and after 15 minutes a further, identical amount of methyl magnesium bromide was introduced. The mixture was left to warm to room temperature overnight. It was

then poured into dilute hydrochloric acid (2N,200ml). The tetrahydrofuran was removed on the rotary evaporator, and the pH of the aqueous residue was adjusted to 7 (universal indicator paper). The product was then extracted into dichloromethane (500ml) using a continuous extraction apparatus over 2 days. The organic extract was dried ($MgSO_4$), filtered and evaporated to leave a brown solid. Chromatography (ethyl acetate) afforded the product as a pale yellow solid. 0.09g,1.8%

Spectral data were identical with the compound prepared via the Dakin-West reaction described earlier.

Attempted preparation of (R/S)-5-acetyl-N-benzyl pyrrolidin-2-one (104)



To sodium hydride (0.80g,0.019 mol,60% dispersion in mineral oil) in residual petrol was added (R/S)-5-acetyl pyrrolidin-2-one (2.00g,0.016mol) in dry tetrahydrofuran (20ml) at 0°C (ice bath). The mixture was stirred for 20 minutes until effervescence had ceased, leaving a bright yellow precipitate. Benzyl bromide (2.75g,1.91ml,0.016mol) was added in one portion and the mixture was allowed to warm to room temperature with stirring over 3 hours. The mixture was poured into cold water (200ml) to give a bright yellow emulsion. This was washed with diethyl ether (3x200ml). The combined organic extracts were dried ($MgSO_4$), filtered and evaporated to give a pale brown tar. Many fractions were observed on tlc (ethyl acetate) which were UV-active, but the only one that reacted with 2,4-dinitrophenylhydrazine had the same r.f. as 5-acetyl pyrrolidin-2-one; the N-benzylated product would be expected to be less polar, more soluble in ethyl acetate and run further up the plate. ^1H NMR of the tar showed the major component to be unreacted benzyl bromide (sharp singlets at 4.35 ($-CH_2-$) and 7.1 (aromatics)). Since the crude tar was only 1.87g, the overwhelming majority being unreacted benzyl bromide, the other components were not investigated. Continuous extraction of the aqueous phase at pH 7 into dichloromethane recovered the starting (R/S)-5-acetyl pyrrolidin-2-one, 1.46g,73%.

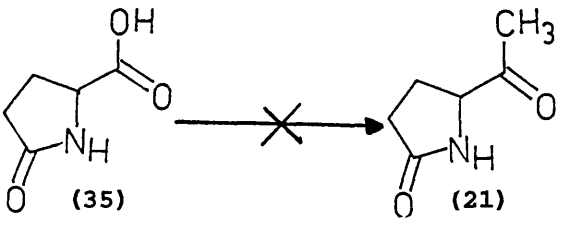
A subsequent attempt using dimethylformamide as the solvent with washing of the combined organic extracts with HCl (2N,100ml) again

showed many fractions on tlc which were UV-active, one of these also producing a positive reaction with 2,4-dinitrophenylhydrazine spray. Chromatography (ethyl acetate) gave many fractions with aromatic signals on ^{1}H NMR, but none gave spectral data consistent with the product produced from the reaction of (S)-N-benzyl pyroglutamic acid (36) with methyl magnesium bromide. The major fraction was isolated as a white, crystalline solid, 0.76g, the spectra of which were clearly resolved but the identity of which could not be established.

IR (KBr) 3530,3470,3180,3080,2970-2850,1730,1670,1490, 1415,1390,1350,1290,1250,1220,1175,1110,960,890,835, 790,750,710,660,610
^{1}H NMR ($CDCl_3$) 1.6(s), 1.8-2.2 (t), 3.1(s) 4.2(d,2:1 splitting), 4.9 (d,1:2 splitting), 6.9-7.5 (m,sharp singlet at 7.3)
^{13}C NMR ($CDCl_3$) 26.2,29.7,43.4,71.2,75.5,77.1,78.6, 127.5,128.8, 130.1,134.8,177.5,209.1
mass spec. 218,174(base peak),122,91,65,55,43

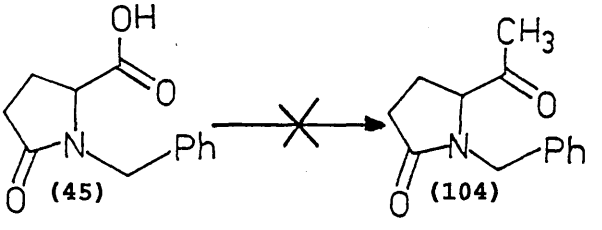
Continuous extraction of the aqueous phase at pH 7 into dichloromethane recovered only a very small amount of 5-acetyl pyrrolidin-2-one, 0.06g,3%

Attempted preparation of (R/S)-5-acetyl pyrrolidin-2-one (21)



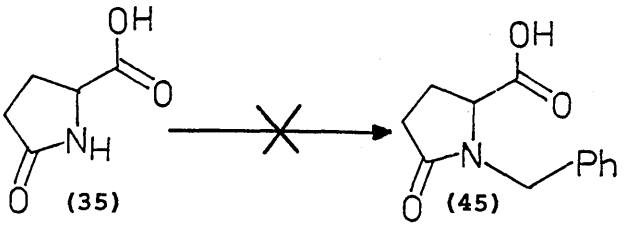
(S)-pyroglutamic acid (1.00g,7.75mmol), acetic anhydride (3.95g,3.7ml,38.8mmol), triethylamine (3.7ml) and 4-dimethylamino pyridine (7.4mg) were refluxed together at 60°C. Many fractions were seen on tlc (ethyl acetate), but no fraction was observed with an r.f. the same as the 5-acetyl pyrrolidin-2-one standard which was reactive to 2,4-dinitrophenyl hydrazine.

Attempted preparation of (R/S)-5-acetyl-N-benzyl pyrrolidin-2-one (104)



(S)-N-benzyl pyroglutamic acid (1.00g,4.57mmol), acetic anhydride (3.5ml), triethylamine (3.5ml) and 4-dimethylamino pyridine (6.9mg) were refluxed together at 60°C (oil bath). Many UV-active fractions were seen on tlc, but none of these reacted with 2,4-dinitrophenyl hydrazine spray. After distillation to remove acetic acid and triethylamine (and some acetic acid), the residue was chromatographed (ethyl acetate) and some of the starting acid was recovered. 0.44g,44%. Spectral data were identical with the product from the preparation of (S)-N-benzyl pyroglutamic acid from glutamic acid (q.v.).

Attempted preparation of (S)-N-benzyl pyroglutamic acid (45)



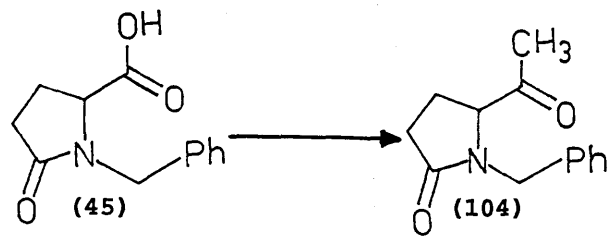
To sodium hydride (0.62g,0.016mol,60% dispersion in mineral oil) was added a solution of (S)-pyroglutamic acid (35) (1.00g,0.08mol) in dimethylformamide (20ml). Effervescence was observed, and after stirring for 30 minutes at room temperature, benzyl bromide (2.67g,1.86ml,0.016mol) was added and the mixture was heated at 60°C for 6 hours (oil bath), cooled and poured into cold water (200ml). The mixture was washed with dilute hydrochloric acid (100ml), dried ($MgSO_4$), filtered and evaporated. Chromatography (ethyl acetate : petrol, 1:1) gave the first fraction as a brown, greasy solid, 1.38g. The next fraction was isolated as a brown oil, 0.86g.

^1H NMR ($CDCl_3$) 2.1-2.6(m,3H), 2.9(d,1H), 5.2(s,1H), 7.3(s,5H), (integral ratios based on the aromatic singlet)

Both fractions were UV-active but both proved to be rather unstable (it was at first thought that the first fraction was the benzyl ester of the required acid and the second fraction was the required acid, but an attempt at confirming this by stirring the first fraction with aqueous sodium hydroxide at room temperature followed by tlc of this reaction against the second fraction showed both materials to have decomposed into many UV-active products). Consequently, further data could not be obtained. The method of producing (S)-N-benzyl pyroglutamic acid (45) from (S)-N-benzyl glutamic acid, as reported by Rapoport[54] gave the

required product as a stable, white solid in good yield whose spectral data were clear, resolved and conclusive (q.v.). The products from this attempt were nothing like the required product at all.

(S)-5-acetyl-N-benzyl pyrrolidin-2-one (104)



(a) To a solution of (S)-N-benzyl pyroglutamic acid (5.00g,0.023mol) in dry tetrahydrofuran (5oml), cooled to -78°C under nitrogen, was added methyl magnesium bromide (3.0M,22.4ml,0.073mol). The reaction was stirred at -78°C for 8 hours and allowed to warm to room temperature overnight. The mixture was then poured into aqueous ammonium chloride (2N,100ml). The tetrahydrofuran was removed on the rotary evaporator and the mixture was then partitioned between water (100ml) and dichloromethane (100ml). The aqueous phase was further washed with dichloromethane (2x100ml). The combined organic extracts were dried ($MgSO_4$), filtered and evaporated. Chromatography (ethyl acetate) gave the product as a bright yellow oil. 1.82g,40%

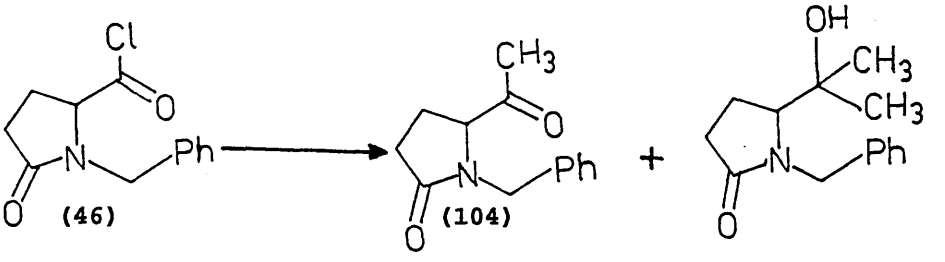
IR 3100-3000,3000-2900,1720,1690,1500,1420,1360,1250,1165,1050, 950,710
^1H NMR ($CDCl_3$) 1.9-2.6(m,7H,sharp singlet due to $-CH_3$ at 2.1), 3.9(m,2H), 5.0(m,1H), 7.2(s,5H)
^{13}C NMR ($CDCl_3$) 21.4,26.0,29.2,45.4,64.6,127.6,128.3,128.6, 135.9,174.7,205.9
mass spec. 217.1095(M,$C_{13}H_{13}NO_2$ requires 217.1102 amu),174,91(base peak)

Some unreacted acid was also recovered. Yield 2.05g,41% based on recovered starting materials.

Modifications on this method involving the use of various ratios of different organolithium reagents and methyl magnesium bromide in tetrahydrofuran only and several co-solvent ratios of

tetrahydrofuran and tetramethylethylenediamine all failed to improve on this yield.

(b)

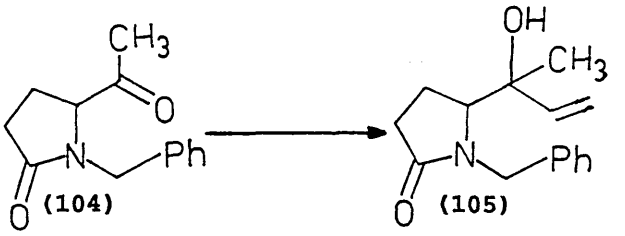


To a suspension of anhydrous cadmiun chloride (1.11g,6.11mmol) in dry tetrahydrofuran (40ml) at 0°C (ice bath) was added methyl magnesium bromide (3.0M,3.22ml,9.67mmol). After stirring at 0°C for 1 hour, the mixture was refluxed for 1.5 hours and cooled to 0°C (ice bath) again. A solution of (S)-N-benzyl pyroglutamyl chloride (2.00g,8.42mmol) in dry tetrahydrofuran (50ml) was added dropwise and the mixture was allowed to warm to room temperature over 5 hours. After removal of the solvent on the rotary evaporator, the residue was chromatographed (dry diethyl ether) to give firstly the required ketone, 0.44g,33.3%, (spectral data as for the product from (a)), followed by the tertiary alcohol, also as a yellow oil. 0.24g,16.9%

A small amount of unreacted starting acid was also recovered. 0.08g,

Modifications on this method employing different organometallic reagents all failed to improve on this yield.

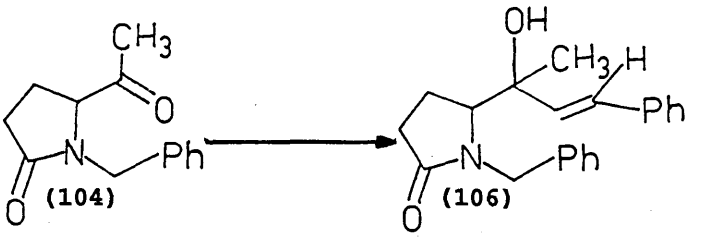
N-benzyl-5-(1-hydroxy-1-methyl prop-2-enyl) pyrrolidin-2-one (105)



A 250ml 3-necked, round-bottomed flask was charged with magnesium turnings (0.27g,11.1mmol), dry tetrahydrofuran (50ml) and a crystal of iodine. A dry ice condenser was fitted, and a solution of vinyl bromide (1.39g,13.3mmol) in dry tetrahydrofuran (30ml) was added dropwise with vigorous stirring. When the addition was complete, the mixture was heated under gentle reflux for 0.5 hours and then cooled to room temperature. A solution of (S)-N-benzyl pyrrolidin-2-one (2.00g,9.22mmol) in dry tetrahydrofuran (30ml) was introduced dropwise with vigorous stirring, after which the mixture was refluxed for 4 hours and cooled to room temperature. It was then poured into aqueous ammonium chloride (2N,200ml) with rapid stirring. After removal of the tetrahydrofuran on the rotary evaporator, the mixture was washed with dichloromethane (3x100ml). The combined organic extracts were dried ($MgSO_4$), filtered and evaporated. Flash chromatography (ethyl acetate) afforded the product as a bright yellow oil. 1.05g,38.6%

IR 3400(broad),3100-2940,1680,1605,1500,1450,1420,1360,1280,1220, 1160,1100,1040,980,920,760,705
^1H NMR ($CDCl_3$) 1.4(2 singlets,3H), 1.7-2.4(m,4H), 3.0-3.6(m,2H), 5.3-7.4(m,8H,sharp singlet due to aromatics at 7.2)

N-benzyl-5-(E)-(1-hydroxy-1-methyl-(3-phenyl-prop-2-enyl)pyrrolidin-2-one (106)

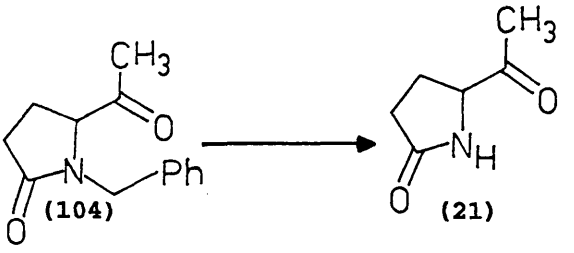


Into a dry, round-bottomed flask were placed magnesium turnings (0.66g,0.028mol), dry tetrahydrofuran (50ml) and a crystal of iodine. 1-bromostyrene (6.29g,0.034mol) in dry tetrahydrofuran (30ml) was added dropwise with rapid stirring and steady reflux. The mixture was then heated under reflux for a further 90 minutes and cooled to room temperature. (S)-5-acetyl-N-benzyl pyrrolidin-2-one (5.00g,0.023mol) in dry tetrahydrofuran (30ml) was added dropwise, after which the mixture was refluxed for 2 hours and cooled to room temperature. The mixture was poured into aqueous ammonium chloride (2N,200ml) with vigorous stirring. The tetrahydrofuran was removed on the rotary evaporator and the aqueous mixture was washed with dichloromethane (3x75ml). The organic extracts were dried ($MgSO_4$), filtered and evaporated. Flash chromatography (dry diethyl ether) afforded the product as a yellow oil. 3.17g,42.6%

IR 3400(broad),3100-3000,2970,1680,1450,1380,1290,1130,1080,750, 700

^1H NMR ($CDCl_3$) 1.3(2 singlets,3H), 1.8-2.6(m,4H), 3.5(m,1H), 4.2(d,1H, benzyl -CH_2- proton), 5.1(d,1H, benzyl -CH_2- proton), 6.3(q,2H, alkene protons), 7.1(2 singlets,10H, aromatic protons)

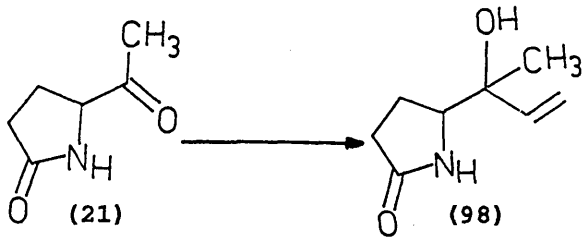
Attempted preparation of (S)-5-acetyl pyrrolidin-2-one (21)



(S)-5-acetyl-N-benzyl pyrrolidin-2-one (1.00g,4.61mmol) was dissolved in dry tetrahydrofuran (30ml). Palladium black on activated charcoal (0.25g) was added and the mixture was maintained under a hydrogen atmosphere at room temperature with stirring for 12 hours, after which thin layer chromatography (ethyl acetate) still failed to show any signs of a reaction occurring. The catalyst was filtered off and the filtrate was evaporated to leave the starting ketone. 0.92g,92%

Modifications comprising changing the solvent to methanol and also methanol mildly acidified with conc. hydrochloric acid all failed to produce any of the required product.

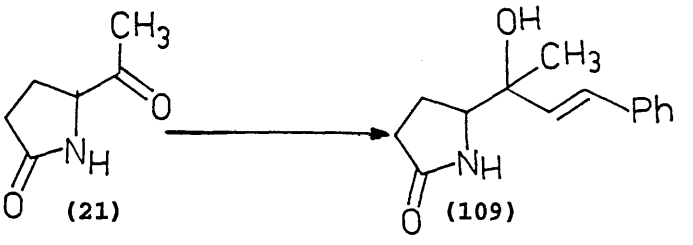
5-(1-hydroxy-1-methyl prop-2-enyl) pyrrolidin-2-one (98)



A 250ml, 2-necked, round-bottomed flask was charged with magnesium turnings (1.52g,0.064mol),dry tetrahydrofuran (30ml) and a crystal of iodine. A dry ice condenser was fitted, and a solution of vinyl bromide (5.64g,0.052mol) in dry tetrahydrofuran (20ml) was added dropwise with vigorous stirring. The mixture was then heated under gentle reflux for 0.5 hours and cooled to room temperature. A solution of 5-acetyl pyrrolidin-2-one (2.79g,0.022mol) in dry tetrahydrofuran (50ml) was added dropwise with vigorous stirring, after which the mixture was refluxed for 3 hours and cooled to room temperature. It was then poured into aqueous ammonium chloride (2N,100ml) with rapid stirring. The tetrahydrofuran was removed on the rotary evaporator and the pH of the aqueous phase was adjusted to 7 (universal indicator paper). The product was extracted into dichloromethane (500ml) using a continuous extraction apparatus over 25 hours. The organic extract was dried ($MgSO_4$), filtered and evaporated. Chromatography (ethyl acetate) gave the product as a pale yellow, crystalline solid. 1.84g,54%

mpt.116-118^{0}C
IR (KBr) 3450(broad),3000-2920,1690(C=C stretch),1655,1410,1360, 1280,1225,1110,1085,1000,930
^{1}H NMR ($CDCl_3$) 1.25(2 singlets,3H), 1.9-2.6(m,4H), 3.1(broad singlet, 1H, -OH), 3.6(m,1H), 5.0-6.0(m,3H,alkene protons), 6.2-6.9(m,1H)
mass spec. 156.0964(M as ^{13}C isotope, *$C_8H_{14}NO_2$ requires 156.0979 amu),126,110,86,84(base peak),71,55,41
microanalysis gave C,58.01,H,8.06,N,8.17 ($C_8H_{13}NO_2.1/2H_2O$ requires C,58.54,H,8.54,N,8.54)

(E)-5-(1-hydroxy-1-methyl-(3-phenyl-prop-2-enyl)) pyrrolidin-2-one (109)



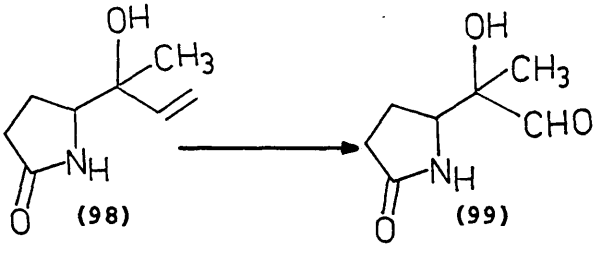
Into a dry round-bottomed flask were placed magnesium turnings (9.96g,0.415mol), dry tetrahydrofuran (200ml) and a crystal of iodine. 1-bromostyrene (37.50g,0.204mol) in dry tetrahydrofuran (150ml) was added dropwise with rapid stirring and maintenance of steady reflux. The mixture was then refluxed for a further 90 minutes and cooled to room temperature. 5-acetyl pyrrolidin-2-one (12.70g,0.100mol) in dry tetrahydrofuran (150ml) was added dropwise, after which the mixture was refluxed for 2 hours and cooled to room temperature.The mixture was poured into saturated aqueous ammonium chloride (200ml) with vigorous stirring. The tetrahydrofuran was removed on the rotary evaporator and the pH of the aqueous residue was adjusted to 7 (universal indicator paper). The crude product was then extracted into dichloromethane (500ml) using a continuous extraction apparatus over 2 days. The organic extract was dried ($MgSO_4$), filtered and evaporated. Flash chromatography (ethyl acetate) gave the first, major product as apparently impure 1,4-diphenyl butadiene.

^1H NMR ($CDCl_3$) 6.7-7.0(m,alkene signals) and 7.0-7.6(m,aromatic signals), unresolvable. Very shallow multiplets observed over the range 0.8-4.2, of negligible integration.
^{13}C NMR ($CDCl_3$) 126.6,127.7,128.8,129.1,129.4,129.7,129.8,133.0, 137.5
mass spec. 206(base peak,M),204,191,179,165,128,127,114,105,91,77, 65,51,39

Several other fractions followed before the product, which after work-up was obtained as a brown, crystalline solid. 9.21g,40%

IR (KBr) 3380(broad),2990,2940,1680,1600,1500,1450,1420,1360,1270, 1220,1100,1070,1030,970,750,700
^{1}H NMR ($CDCl_3$) 1.2(2 singlets,3H), 1.5-2.7(m,4H), 3.4-3.7(m,1H), 6.15(d,1H,J=20Hz, plus diastereomeric splitting, J=3Hz), 6.65(d,1H,J=20Hz), 7.2(s,5H), 7.6(s,1H)
^{13}C NMR ($CDCl_3$) 21.0,30.3,62.8,74.1,126.5,127.7,128.6,129.2, 133.8,136.7,179.6
mass spec. 232(MH^+),231(M),229,213,211,186,170,158,147(base peak), 129,85,84,77,57,43,41

5-(1-formyl-1-hydroxy)ethyl pyrrolidin-2-one (99)

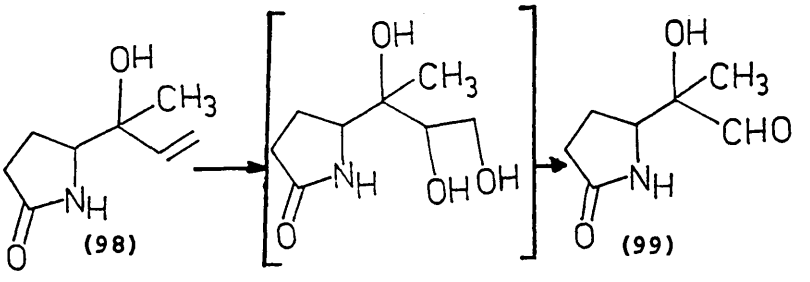


a) The alcohol (90) (0.11g,0.71mmol) was dissolved in dichloromethane : methanol, 9:1, (25ml) and cooled to -78°C. Ozone was bubbled through until a permanent deep blue solution was produced after 1.5 hours. The solution was purged with nitrogen, which caused the solution to change to a pale yellow colour, and then dimethyl sulphide (6 drops, (excess)) was added. After warming to room temperature, the mixture was evaporated to leave a brown oil. Chromatography (ethyl acetate : methanol, 90:10) afforded the product as a colourless, crystalline solid. 0.06g,55%

IR (KBr) 3420(broad),3000-2940,1670,1420,1290,1080,1025,960
^{1}H NMR ($CDCl_3$) 1.3(2 singlets,3H), 2.0-2.5(m,4H), 3.9(m,1H), 4.2(m,1H), 7.0(m,1H), 9.4(2 singlets,<1H)
mass spec. 158.0794(MH^+,$C_7H_{12}NO_3$ requires 158.0817 amu), 157.0736(M,$C_7H_{11}NO_3$ requires 157.0739 amu),149,140,126,112,98, 84,41

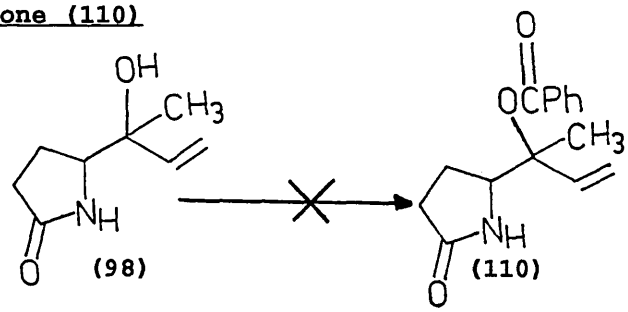
b) Ozonisation of the styryl alcohol (109) (0.07g,0.43mmol) gave an identical product. 0.04g,57% (usual yields were approximately 40%)

c)



A 100ml round-bottomed flask was charged with the alkene (98) (1.00g,6.45mmol), water(40ml) and osmium tetroxide (25mg) and the mixture was stirred at room temperature for 1.5 hours. Sodium metaperiodate (1.38g,6.45mmol) was added and stirring was continued overnight. The pH was adjusted to 7.0 (meter) and the products were extracted into dichloromethane (200ml) using a continuous extraction apparatus over 25 hours. Many fractions were observed on tlc which reacted with 2,4-dinitrophenylhydrazine. The organic extract was dried ($MgSO_4$), filtered and evaporated. Flash chromatography (ethyl acetate) isolated first 5-acetyl pyrrolidin-2-one (49), 0.08g,9.8% (spectral data q.v.), followed by the required aldehyde. 0.23g,22.8%. Spectral data were identical with the product obtained from the ozonolysis reactions.

Attempted preparation of 5-(1-benzoyloxy-1-methyl prop-2-enyl) pyrrolidin-2-one (110)



A 100ml round-bottomed flask was charged with 5-(1-hydroxy-1-vinyl) ethyl pyrrolidin-2-one (0.20g,1.29mmol) and dry tetrahydrofuran (25ml). To the resulting solution was added a solution of dicyclohexylcarbodiimide (0.28g,1.35mmol) in dry tetrahydrofuran (25ml). After stirring for 30 minutes, benzoic acid (0.16g,1.35mmol) was added. Stirring was continued for a further 5 hours, during which a white precipitate was produced. This was filtered off, and the filtrate was dried ($MgSO_4$), filtered and evaporated. Flash chromatography (dry diethyl ether) produced firstly dicyclohexylurea, 0.07g.

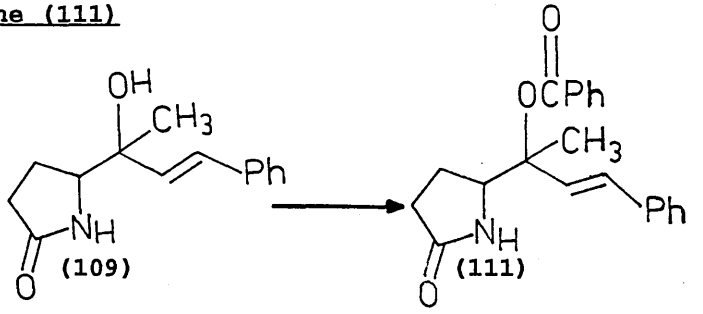
IR (KBr) 3430,2930,2850,1620,1570,1530,1435,1310,1240,1090,1045, 890,640
^1H NMR ($CDCl_3$) 0.6-2.3(m,22H), 6.1(broad singlet,1H)

Next to elute was benzoic anhydride. 0.26g,85.2%

IR (KBr) 3080,3040,1700,1650,1540,1450,1350,1280,1250,1235,1160, 1130,1080,1030,1005,895,880,830,810,780,730,700,670,640
^1H NMR ($CDCl_3$) 7.4(s)

The third fraction was the starting alcohol. 0.17g,85%

(E)-5-(1-benzoyloxy-1-methyl-(3-phenyl-prop-2-enyl))ethyl pyrrolidin-2-one (111)

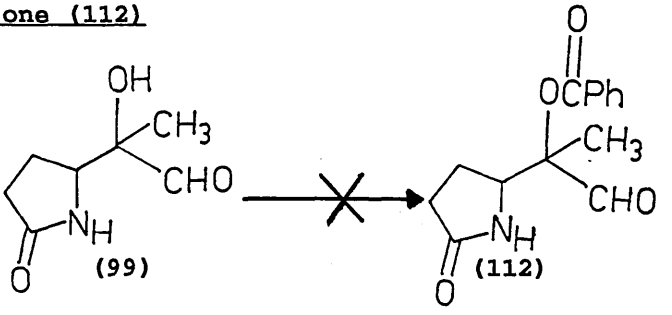


The alcohol (109) (0.23g,1.00mmol) was dissolved in dry tetrahydrofuran (10ml). Triethylamine (5ml), 4-dimethylamino pyridine (0.25g,2.2mmol) and benzoyl chloride (0.31g,2.20mmol) were added and the mixture was refluxed for 4.5 hours. It was then cooled to room temperature and poured into aqueous ammonium chloride solution (2N,150ml) with vigorous stirring. after removal of the tetrahydrofuran on the rotary evaporator, the aqueous phase was acidified with dilute hydrochloric acid (2N,250ml) and washed with dichloromethane (3x100ml). The combined organic extracts were dried ($MgSO_4$), filtered and evaporated to leave a dark brown tar. Chromatography (ethyl acetate) gave the product as a dark brown oil. 0.08g,23.9%

mpt.239-241^{0}C
^{1}H NMR ($CDCl_3$) 1.5-3.0(m,7H,sharp singlets for the isomeric methyl groups at 1.9), 4.2(m,1H), 6.4-8.2(3 multiplets,13H,amide, alkene and aromatic protons)
mass spec. 281,213,194,122,105(base peak),84,77,51,41

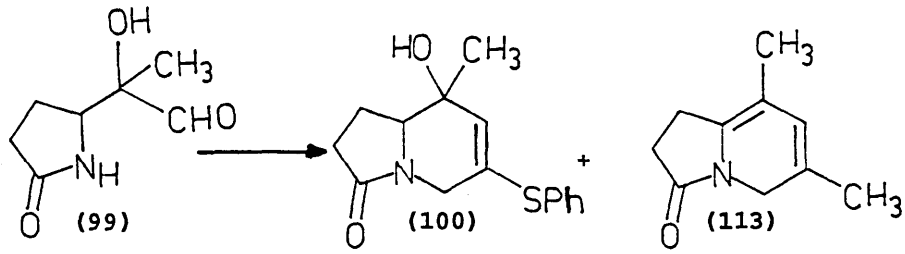
Further elution with ethyl acetate recovered some of the starting alcohol (109). 0.05g,21.7%

Attempted preparation of 5-(1-benzoyloxy-1-formyl)ethyl pyrrolidin-2-one (112)



To a solution of 5-(1-formyl-1-hydroxy) ethyl pyrrolidin-2-one (0.20g,1.27mmol) in dry tetrahydrofuran (25ml) was added a solution of dicyclohexylcarbodiimide (0.27g,1.30mmol) in dry tetrahydrofuran (25ml), and the mixture was stirred at room temperature for 30 minutes. Benzoic acid (0.16g,1.30mmol) was added and stirring was continued for a further 4 hours, whereupon a white precipitate was formed. This was filtered off, and the filtrate was evaporated. Flash chromatography (dry diethyl ether) gave firstly dicyclohexylurea. 0.05g (Spectral data identical with the first fraction from a similar protection involving the vinyl alcohol (98). Next to elute was benzoic anhydride. 0.26g,88.5% (Spectral data similarly identical with the second fraction from the same aforementioned protection reaction). The third fraction eluted was the starting aldehyde. 0.13g,65%

7,8,9,9a-tetrahydro,1-hydroxy-1-methyl-3-phenylthio-4H-indolizin-6-one (100)



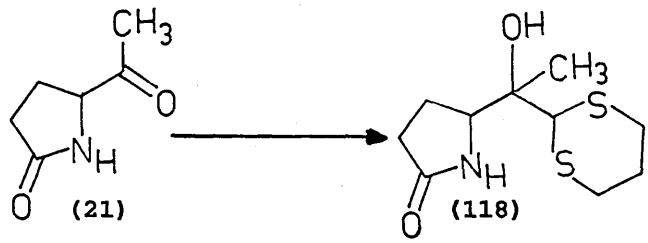
A 100ml round-bottomed flask was charged with 5-(1-formyl-1-hydroxy) ethyl pyrrolidin-2-one (0.21g,1.34mmol), dry tetrahydrofuran (10ml), acetonitrile (40ml) and sodium hydride (0.04g,1.61mmol). Evolution of a gas, most probably hydrogen, was observed. After stirring for 20 minutes, 1-phenylthiovinyl triphenyl phosphine oxide (0.84g,1.61mmol) was added, and stirring was continued for a further 10 hours, during which a brown colouration was formed. The mixture was evaporated and flash chromatographed (ethyl acetate). The first fraction appeared to be not unlike a sample of crude 5,6,7,7a-tetrahydro-1-methyl-2-phenylthio-3H-pyrrolizin-5-one (32), and could therefore possibly have been the bicyclic bis-alkene (113), although its identity was not investigated further. It was isolated as a colourless oil.50mg

IR 3200,3060,2990,2940,2870,2765,1775,1710,1580,1480,1440-1350, 1290,1190,1130,740,700,630
^{1}H NMR ($CDCl_3$) 1.8(s,3H), 2.0-3.0, 3.4-4.8(m,2H), 7.2(s,5H)

Next to elute was the required product as a colourless oil.76mg,33%

IR 3400(broad),3080,3000-2880,1675,1590,1440,1370,1280,1255,1190, 1120,1030,750,700
^{1}H NMR ($CDCl_3$) 0.9-2.6(m,7H,singlet at 1.3), 3.6(m,1H), 4.5(s,2H),5.2-5.8(m,1H), 6.9(s,1H), 7.3(2 unresolved singlets,5H)
mass spec. 275.0968(M,$C_{15}H_{17}NO_2S$ requires 275.0980 amu),191,149,110,109, 84,82,42,41

5-(1-(1,3)-dithianyl-1-hydroxy) ethyl pyrrolidin-2-one (118)



To a solution of 5-acetyl pyrrolidin-2-one (1.00g,7.87mmol) in dry tetrahydrofuran (30ml) at -78°C was added n-butyl lithium (2.5M,4.08ml,10.2mmol). To a separate solution of 1,3-dithiane (0.90g,10.2mmol) in dry tetrahydrofuran (30ml) at -78°C was added n-butyl lithium (2.5M,4.90ml,12.2mmol). After 20 minutes this suspension was transferred to the amide suspension using a cannula. The mixture was stirred at -78°C for 5 hours and then allowed to warm to room temperature. The mixture was then poured into aqueous ammonium chloride (2N,200ml). After removal of the tetrahydrofuran on the rotary evaporator, the pH of the residual aqueous phase was adjusted to 7.0 (meter) and the crude product was extracted into dichloromethane (500ml) using a continuous extraction apparatus over 2 days. The organic extract was dried ($MgSO_4$), filtered and evaporated. Flash chromatography (ethyl acetate) afforded the product as a pink crystalline solid, which was recrystallised from ethyl acetate to a white crystalline solid. 0.31g,16%

mpt.110-112°C
IR (KBr) 3300(broad),3000-2860,1690,1460,1420,1380,1280,1230,1180, 1130,1090,1020,950,910,870,840,810,790,690,660,630
^1H NMR ($CDCl_3$) 1.25(2 singlets,3H,-CH_3), 1.8-2.3(m,6H), 2.6-3.1(m,4H), 3.7-4.3(m,2H), 6.5-7.2(broad singlet,1H)
^{13}C NMR ($CDCl_3$) 13.2,21.6,23.3,23.7,25.5,30.7,36.4,62.5,63.3, 73.4,179.6
mass spec. 247.0712(M,$C_{10}H_{17}NO_2S_2$ requires 247.0701 amu),218, 176,164,128,120,110,85(base peak),84

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ACKNOWLEDGEMENTS

I would like to extend my sincere gratitude to Dr. Alan Hewson for his seemingly limitless support in the course of this degree.

I would also like to thank the Science and Engineering Research Council for funding, and Glaxo Group Research, Ware, for sponsoring the project.

I would like to thank all the staff at Sheffield City Polytechnic for their teaching, encouragement, co-operation, provision of equipment, analysis, assistance and advice during the course of the degree.

I would like to thank all the doctors, medical staff and friends who nursed me through my nervous breakdown towards the end of the project.

I would like to thank all the students at Sheffield City Polytechnic for their friendship and support, and I wish them all the very best for their future careers.

Finally, I would like to thank my family, particularly my mother, for their invaluable and eternal encouragement, assistance and support, without which the completion of this degree would not have been possible.