A Thesis Entitled

RIGID ANALOGUES OF METALLOPEPTIDASE INHIBITORS

by

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DECLARATION

I declare that the research presented herein is original work carried out by the author and has not been submitted for any degree.

Signed: Date

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Rigid analogues of metallopeptidase inhibitors

Tadeusz A. Podgorski

ABSTRACT

As an introduction the role of angiotensin -converting enzyme (ACE) in the renin-angiotensin system and the design of ACE inhibitors are discussed.

The synthesis of azabicyclo [3.3.0] octane systems was investigated using established and novel methods. The azabicyclo [3.3.0] octane, 8-(hydroxymethyl)-1-azabicyclo [3.3.0] octan-2-one was synthesized from 5-(3-butenyl)-2-pyrrolidinone. Synthetic studies towards the latter system are also presented. Two procedures have been developed for the synthesis of 8-(hydroxymethyl)-1-azabicyclo [3.3.0] octan-2-one. The first involved epoxidation of 5-(3-butenyl)-2-pyrrolidinone which afforded the expoxy pyrrolidinone and subsequent treatment with sodium hydride gave the 8-(hydroxymethyl)-1-azabicyclo [3.3.0] octan-2-one. The second relied on cyclisation of 5-(3-butenyl)-2-pyrrolidinone initiated by electrophilic reagents such as iodine and mercuric acetate which resulted in the formation of azabicyclo [3.3.0] octanes. The azabicyclo [3.3.0] octanes were elaborated to complete the 8-(hydroxymethyl)-1-azabicylo [3.3.0] octan-2-one syntheses.

The synthesis of 3-oxa-1-azabicyclo [3.3.0] octanes was also investigated. Two procedures have been developed using the key intermediate 5-(3-hydroxymethyl)-2-pyrrolidinone. The first of these involved a deprotection-reprotection technique. The second relied on hydroxyalkylation using butyl glyoxylate. The latter route has proved more successful and various 3-oxa-1-azabicyclo [3.3.0] octanes have been made using this procedure.

Finally, synthesis of bicyclo [3.3.0] octanes, 8-hydroxybicyclo-[3.3.0] octan-2-one and bicyclo [3.3.0] octan-2-one-8-carboxylic acid was investigated. Two approaches to the synthesis of 8-hydroxybicyclo-[3.3.0] octan-2-one were investigated. The first, cyclopentannulation via copper catalysed conjugate addition of Grignard and lithium reagents derived from 2-(2-bromoethyl)-1,3-dioxolane, 2-(2-bromoethyl)-1, 3-dioxane and 1-ethoxyethyl 3-bromopropyl ether, respectively, to cyclopenten-2-one was unsuccessful in giving the 8-hydroxybicyclo-[3.3.0] octan-2-one. The second approach relied on cyclopentannulation via nitrile oxide-olefin cycloaddition. The latter route was successful and the 8-hydroxybicyclo [3.3.0] octan-2-one was made using this approach. The 8-hydroxybicyclo [3.3.0] octan-2-one was transformed over four steps to bicyclo [3.3.0] octan-2-one-8-carboxylic acid. A set of conditions for the transformation are presented.

1.1 Renin - angiotensin system

The renin - angiotensin system is one of the humoral mechanisms involved in the regulation of blood pressure. There have been continued efforts to understand and determine the role of the renin - angiotensin system in the regulation of blood pressure.[1]

Renin is a proteolytic enzyme, produced mainly in the juxtaglomerular apparatus of the kidney, which acts on the circulating α- globulin angiotensinogen, produced by the liver, (Figure 1.). The result of this enzymatic action is the formation of the decapeptide angiotensin I, which has very little if any biological activity. Removal of the C- terminal dipeptide, histidylleucine from this decapeptide by angiotensin - converting enzyme (ACE), present in the lungs and other organs yields the octapeptide angiotensin II.

Angiotensin II is a potent peptide that causes vasoconstriction of blood vessels and is involved in regulation of blood pressure. This peptide is also the main physiological stimulus for the release of aldosterone from the adrenal gland. This mineralocorticoid in turn induces sodium and water retention leading to an increase in blood pressure by a "volume mechanism".[2]

Angiotensin - converting enzyme (ACE) is also involved in the inactivation of the vasodepressor nonapeptide bradykinin, present in blood plasma, the final mediator of the kallikrein-kinin system[3], (Figure 2.).

Angiotensin - converting enzyme inactivation of bradykinin occurs by successively removing two dipeptides.

Asp-Arg-Val-Tyr-Ile-His-Pro-Phe-His-Leu-Leu-Val-Tyr-Ser....

Angiotensinogen

↓ RENIN (Blood and blood vessel walls) RENIN (Kidney and blood vessel walls)

Asp-Arg-Val-Tyr-Ile-His-Pro-Phe-His-Leu

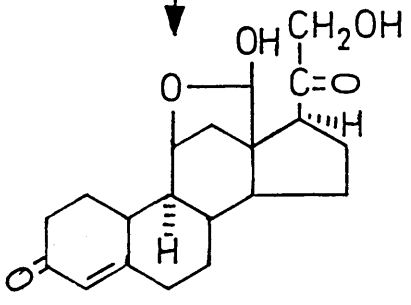
Angiotensin I

↓ ANGIOTENSIN-CONVERTING ENZYME (Lungs, blood, blood vessel walls, kidney)

Asp-Arg-Val-Tyr-Ile-His-Pro-Phe

VASO CONSTRICTION ← Angiotensin II

↓



SODIUM RETENTION ← ALDOSTERONE

Figure 1.

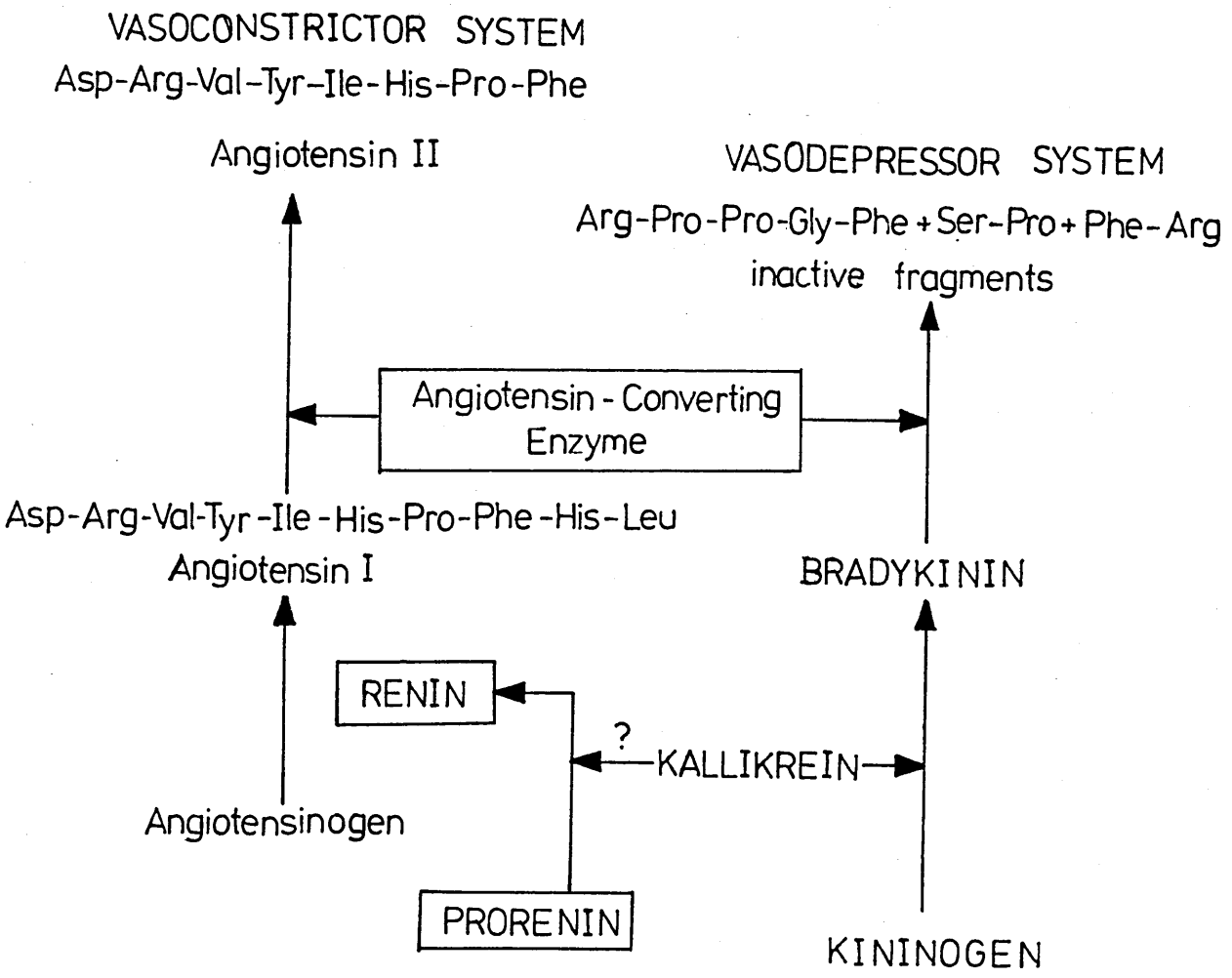


Figure 2.

1.2 Design of Specific inhibitors of angiotensin-converting enzyme.

Inhibition of angiotensin - converting enzyme was demonstrated with the peptide inhibitors isolated from the venom of Bothrops jararacca and their synthetic analogues. The most extensively studied of these peptide inhibitors was the nonapeptide teprotide (SQ20,881) (1).

The nonapeptide (1) was shown to be a competitive inhibitor that binds to the active site of ACE by multiple interactions with different subsites, resulting in tighter binding than that observed

with the substrate angiotensin I,(Figure 3.)[4].

SQ20,881 (1) was shown to be a specific and potent inhibitor of ACE in <u>vitro</u>[5] and in <u>vivo</u>[6].

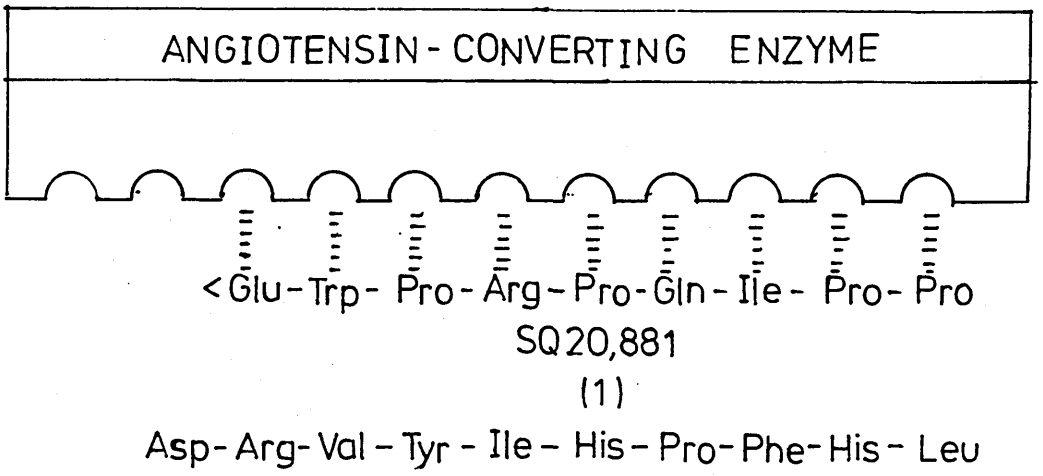


Figure 3.

Preliminary clinical studies[7] showed the great potential of (1) as a novel antihypertensive drug, limited only by its lack of oral activity. This therapeutic potential led investigators to test other structural types in search for new specific, and orally active inhibitors.

Specific inhibitors of ACE would be expected to show the profile of activities exemplified by (1) with respect to inhibition of the isolated enzyme. Only a small fraction of the compounds that were tested by investigators were potent inhibitors of ACE and very few showed the desired specificity.

Earlier studies with substrates and inhibitors of ACE suggested that this peptidase was a carboxypeptidase similar to pancreatic carboxypeptidase A, even though it releases dipeptides rather than single amino acids from the carboxylic acid end of the peptide substrate.

Investigations also indicated that angiotensin - converting enzyme, like carboxypeptidase A, enkephalinase,[8] and collagenase[9] was a zinc containing metalloprotein, which has been verified by other workers.[10]

Investigators assumed that the mechanism of action and, therefore, the active site of angiotensin - converting enzyme would be similar (though not identical) to that of carboxypeptidase A.

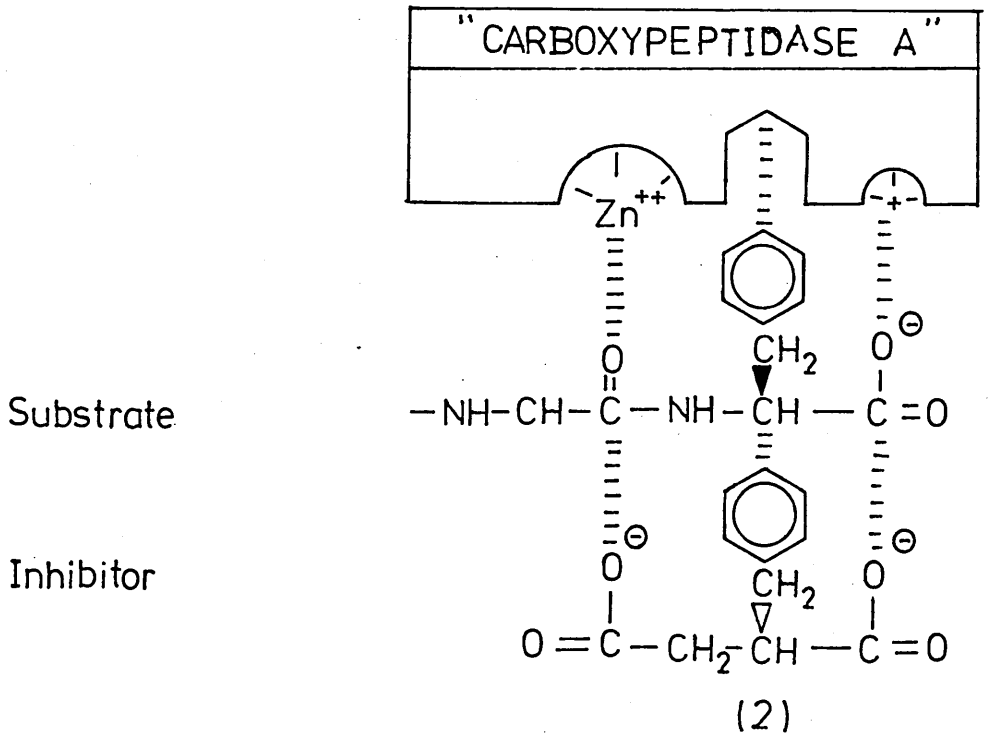
The important substrate-binding groups at the active site of carboxypeptidase A[11] and at the active site of the hypothetical model of ACE are shown in Figure 4.

A positively charged residue at the active site (analogous to $Arginine^{145}$, in case of carboxypeptidase A) is postulated to form ionic bonds with the negatively charged C- terminal carboxyl group of the peptide substrate.

An adjacent "hydrophobic pocket" is responsible for the specificity of carboxypeptidase A towards substrates containing C- terminal aromatic acids. Angiotensin - converting enzyme having no such specificity is not expected to have a hydrophobic pocket at its active site, but it may have some affinity for the side chain R_1 and R_2 of two terminal amino-acid residues of a peptide substrate (Figure 4.).

In addition the angiotensin - converting enzyme active site binds through a group capable of interacting with the terminal nonscissile peptide bond of the substrate, probably by hydrogen bonding with the COOH - terminal bond of the substrate.

Also a zinc ion is suitably located at the active site of both enzymes to polarise the carbonyl groups of the scissile amide



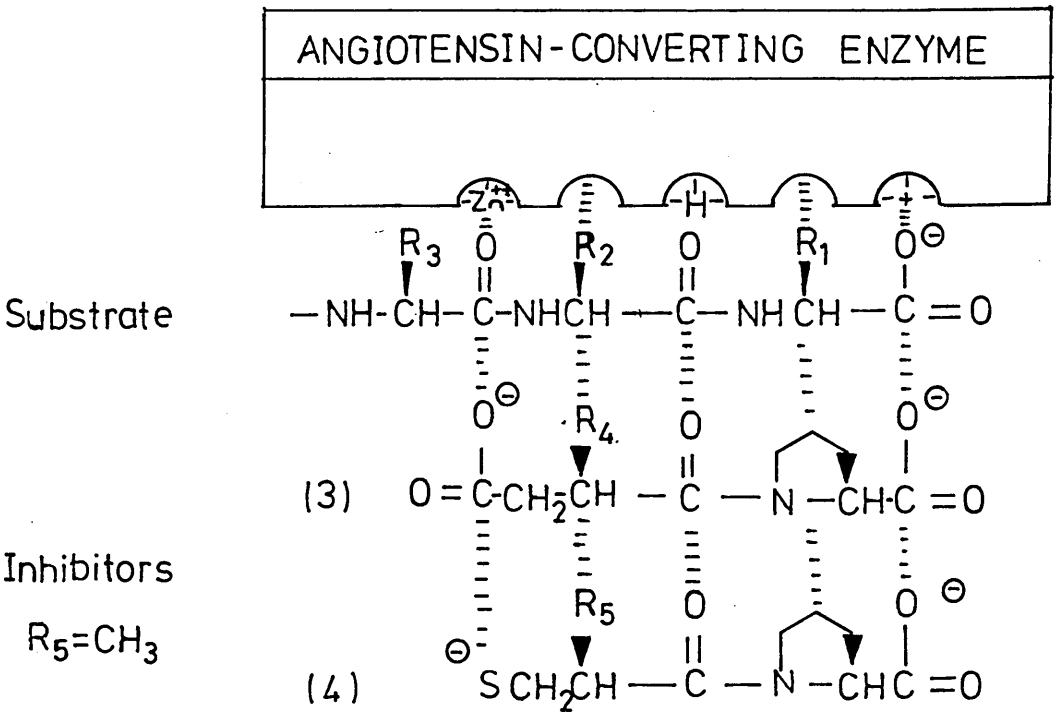


Figure 4: Diagramatic representation of the binding of substrates and inhibitors at the active site of pancreatic carboxypeptidase A, and at the hypothetical active site of angiotensin-converting enzyme.

bond making them more susceptible to hydrolytic cleavage.

An excellent opportunity to test this proposed hypothetical model of the active site of angiotensin - converting enzyme came from the observation of Byers and Wolfenden[12], that D- benzylsuccinic acid(2) was a potent inhibitor of carboxypeptidase A. The explanation[12,13] for this potent inhibitory activity was the simultaneous and stereospecific interaction of the inhibitor molecule with the three -substrate binding groups at the active site of carboxypeptidase A, namely the positive charge of Arginine[145], the hydrophobic pocket and zinc atom, (Figure 4.). Using this observation along with the above mentioned speculations about the nature of the active site of angiotensin - converting enzyme, led investigators like Ondetti and Cushman to pursue the design of specific inhibitors of this peptidase along similar lines.

It was shown that in angiotensin - converting enzyme, a "dipeptidyl" carboxypeptidase, the distance between the cationic carboxy - binding site and the zinc atom was greater than in carboxypeptidase A, by approximately the length of one amino-acid residue (Figure 4.).

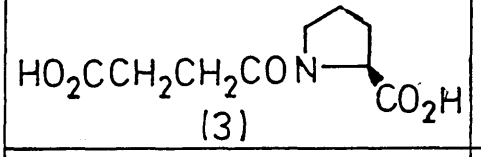
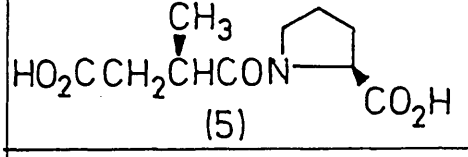
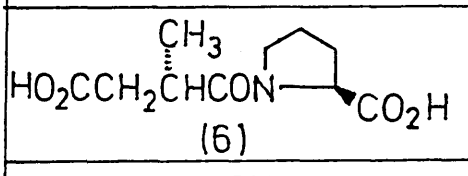
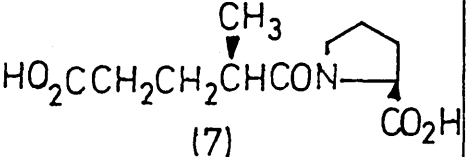
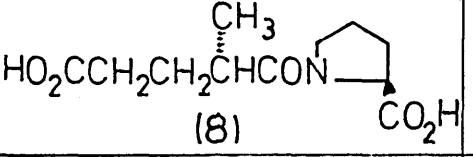
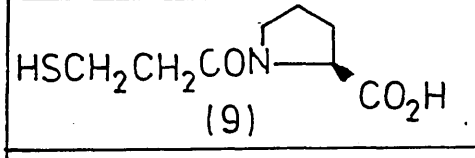
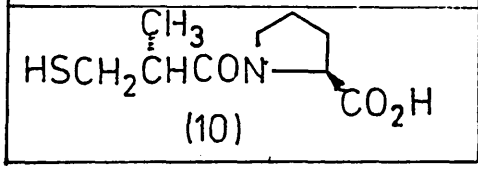
Ondetti et al postulated that a succinyl derivative of an amino acid, rather than a succinic acid should serve as the prototype for inhibitors of angiotensin - converting enzyme. This hypothesis was tested by the synthesis of succinyl-L-proline (3) (where R_4 = H, Figure 4.).

Proline was originally chosen as the amino-acid moiety because all of the naturally occuring peptidic inhibitors of angiotensin - converting enzyme have this amino-acid as the COOH- terminal residue.

Proline containing inhibitors were shown to be more potent than those incorporating other naturally occuring amino-acids.
The activity of succinyl-L-proline (3) (Table 1) indicated that this compound was a specific inhibitor of angiotensin-converting enzyme.
Exploring the influence of different structural modifications, including length and substitutions of acyl moiety, Ondetti et al were able to considerably increase the inhibitory activity of the prototype compound by the synthesis of 2-D-methylsuccinyl-L-proline (5) (SQ13,297) and 2-D-methylglutaryl-L-proline (7) (Table 1).
These compounds were found to be potent inhibitors of angiotensin-converting enzyme. The corresponding 2-L-methyl analogues of these inhibitors were 100 times less active.

If the interaction of a carboxyl group of compounds such as (5), (7) with the zinc atom of the enzyme (Figure 4.) plays an important role in determining the inhibitory potency, then replacement by other functional groups capable of serving as zinc-ion ligands should yield inhibitors of equal or greater potency.
Nitrogen-containing functionalities (amines, amides, or guanidines) showed no enhanced inhibitory activity.
Replacements of the carboxyl residue by a mercapto group (Figure 4.) led to a dramatic improvement of inhibitory potency.
3-mercaptopropanoyl-L-proline (SQ13,863) (9) and 2-D-methyl-3-mercaptopropanoyl-L-proline (SQ14,225) (4) proved to have high potency equal to and better than that of nonapeptide SQ20,881 (1). One of these derivatives SQ14,225 (4) (captopril) proved to be a potent inhibitor of angiotensin-converting enzyme and an effective oral

Table 1: Activities in vitro of inhibitors of angiotensin-converting enzyme. Abbreviations IC_{50}, concentration of compound producing 50% inhibition of enzyme activity or agonist effect.

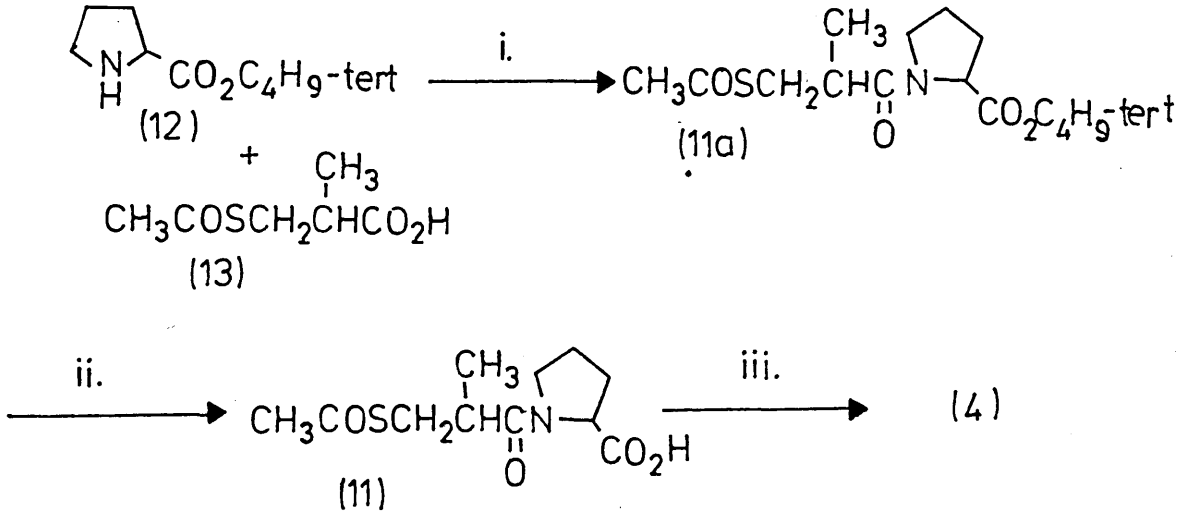
Structure	Designation	Angiotensin-converting enzyme of rabbit lung (IC_{50}) / μg/ml
(1)	SQ20,881	1·0
 (3)		135
 (5)	SQ13,297	12
 (6)		340
 (7)		1·0
 (8)		230
 (9)	SQ13,863	0·04
(4)	SQ14,225	0·005
 (10)		1·7

antihypertensive drug. The L-methyl enantiomer of SQ14,225 (4) was shown to be 100 times less active.

1.3 Synthesis of Captopril

The preparation of 2-D-methyl-3-mercaptopropanoyl-L-proline (4) (captopril, SQ14,225)[14], shown in scheme 1, was carried out by synthesizing the 1-D-3-acetylthio-2-methylpropanoyl-L-proline (11), which was obtained by the treatment of proline tert-butyl ester (12) and 3-acetylthio-2-methylpropionic acid (13) with dicyclohexylcarbodiimide.

The intermediate (13) was obtained by treatment of thiolacetic acid with methacrylic acid[15]. The tert-butyl ester (11a) was subsequently treated with trifluoroacetic acid to yield the free acid (11). Fractional recrystallisation gave the required S,S isomer.



i. $C_6H_{11}N{=}C{=}NC_6H_{11}$; ii. CF_3COOH, anisole ; iii. 5.5N CH_3OH-NH_3 .

Scheme 1.

The next step involved the cleavage of the acetyl group by treatment of 1-D-3-acetyl-2-methylpropanoyl-L-proline (11) with methanolic ammonia to yield the desired product (4).

Captopril (SQ14,225) (4) exhibited in one molecule the carboxyl group, the amide bond carbonyl and sulfhydryl group that could establish effective and regio and stereospecific interactions with other functional groups on the enzyme surface (Figure 5.).

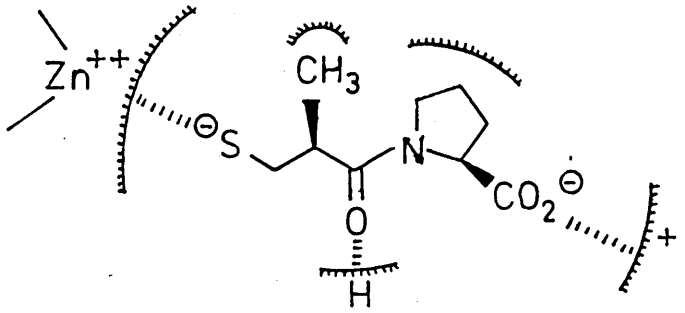
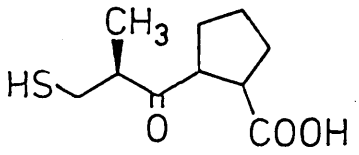


Figure 5.

The pyrrolidine ring of the proline residue and the α-methyl substituent of the mercaptopropanoyl moiety contribute to strengthening the interaction with the enzyme by restricting the mobility or the degrees of freedom of the inhibitor molecule and, probably, also through dispersion interaction with the enzyme surface.

The carbocyclic analogue (14) of captopril[16] was also demonstrated to have significant angiotensin-converting enzyme inhibitory activity.



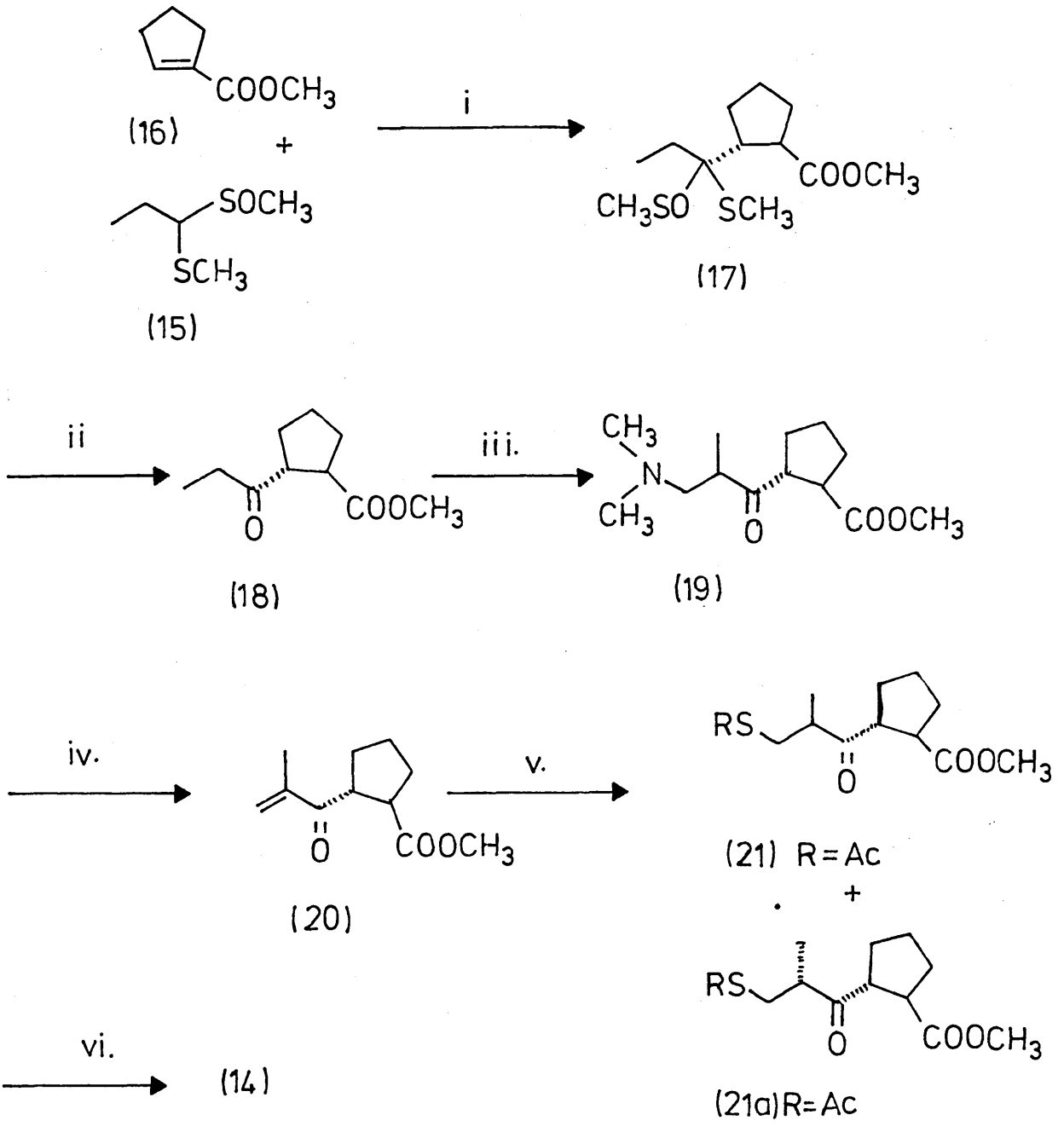
(14)

The preparation of the carbocyclic analogue (14) shown in scheme 2, was carried out by Michael reaction of the lithio derivative of methyl 1-(methylthio)-propyl sulfoxide [16a] (15) to methyl cyclopentene carboxylate (16), to yield the conjugate addition product (17). Hydrolysis of (17) with 9N sulphuric acid in aqueous acetone gave the ketone (18).

Treatment of (18) with a mixture of 30% aqueous formaldehyde, dimethylamine hydrochloride yields the dimethylaminomethyl ketone (19). Heating (22) gave the methylacryloyl cyclopentane carboxylate (20).

Introduction of the mercapto group to (20) was achieved by conjugate addition with thiol acetic acid giving an equal mixture of diastereoisomers (21).

Hydrolysis of (21) with 1N sodium hydroxide yielded a mixture of mercapto acids. Subsequent separation gave the desired isomer (14).



i.BuLi; ii. 9N H_2SO_4 , aq CH_3COCH_3; iii. 30% aq HCHO, $(CH_3)_2NH \cdot HCl$; iv. Δ; v. CH_3COSH ; vi. 1N NaOH, separation.

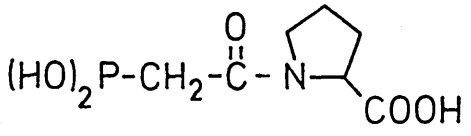
Scheme 2.

This proved that the proline residue can be replaced by a cyclopentane carboxylic acid, with only a moderate loss of activity. This also confirmed that the nitrogen atom in the prototype plays little part in its interaction with the enzyme.

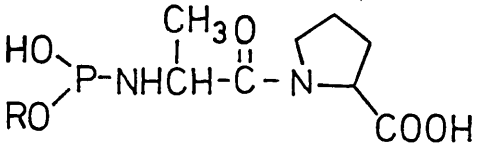
The importance of these multiple interactions was demonstrated by the synthesis of suitably modified analogues [17-21], where modifications such as substitution [22], enlargement [23] of the 3-mercapto-2-methyl-propanoyl residue (e.g. by amino-propyl) [24] have been reported. A drawback of captopril (4) is its toxicity. The most common adverse effects were skin rashes [25,26], fever and loss of taste [27-29]. Other side effects were renal failure [30-32], nephrotic syndrome [33-36] and oral ulcers [37]. The mercapto group of captopril was shown to be implicated in the occurrence of these effects.

1.3.1 Captopril analogues

Numerous attempts were made to obtain captopril analogues without the mercapto group. Phosphoric acid derivatives [38-41] (22), (23) and (23a) were shown to display interesting activity.



(22)

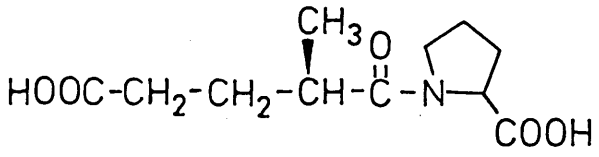


(23) R=H

(23a) R= $C_6H_5CH_2$

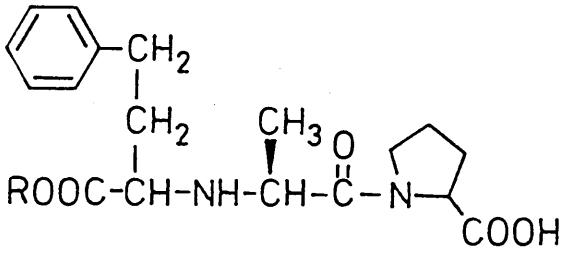
Of the various captopril analogues described (Table 1) the carboxylic acid (7) was shown to have moderate activity (approx $^{1}/_{200}$ x captopril) as an inhibitor of angiotensin - converting enzyme.

Merck ingeniously varied this structure and this finally led to compounds that were more potent and longer acting than captopril.[42-43]



(7)

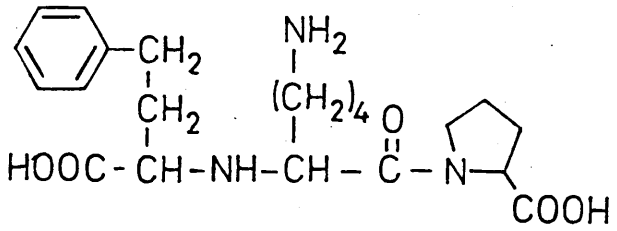
Enalpril (24), lacks the thiol group but contains an alternative zinc binding function. Enalpril (24) is metabolised to the acid (25) (Enalaprilat) which subsequently inhibits angiotensin - converting enzyme.



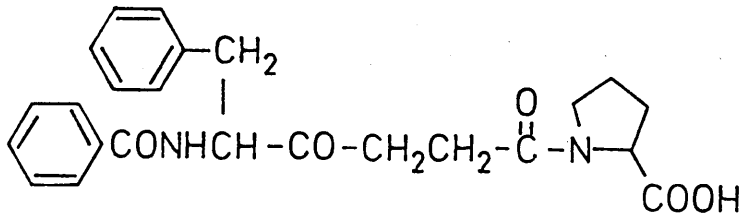
(24) R=C_2H_5 (Enalpril)

(25) R=H (Enalaprilat)

Also compound (26) shows the same ACE inhibitory potency and a long duration of action *in vivo*.



(26)



(27)

Compound(27) is another analogue of captopril with *in vitro* activity superior to that of captopril.[44]

1.4 *Design of bicyclic inhibitors of angiotensin-converting enzyme.*

Study[45-47] of the previously discussed inhibitors and related compounds allowed investigators to establish a two-dimensional picture of the molecular features which were important for binding of inhibitor to the active site of the enzyme. By orientating the three-binding functions of the inhibitor very specifically in space, by attachment to a rigid framework, C.H.Hassall[48] and coworkers. postulated more potent inhibitors could be expected. Also the three-dimensional relationship of the three binding sites could be defined. They designed, with the aid of computer graphics,[49] and synthesized three bicyclic systems,tetrahydro[1,2,4]triazolo[1,2a] -,

hexahydropyrazolo [1,2a]- and octahydropyridaza [1,2a]-pyridazinediones, examples of which are discussed below.

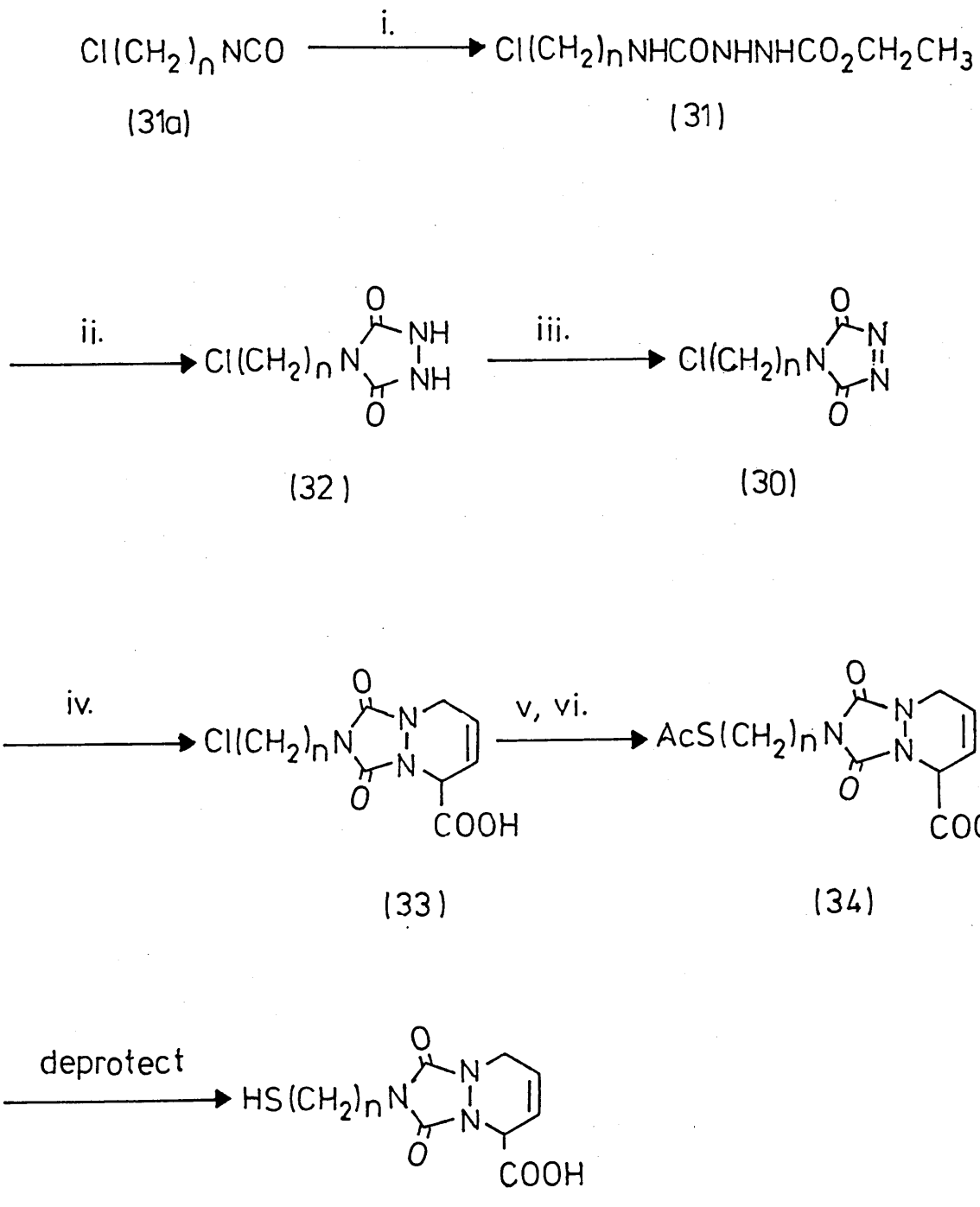
1.4.1 Tetrahydro [1,2,4] triazolo [1,2a]- systems

The acids (28) and (29) were synthesized, as shown in scheme 3, by the Diels-Alder reaction of penta - 2,4-dienoic acid with the 4- substituted 1,2,4-triazolo - 3,5-diones (30) which are known to be highly reactive dienophiles[50], prepared from the isocyanate through the intermediates (31) and (32). The sulphur substituent was introduced by displacement of chloride with potassium thioacetate and sodium iodide.

This particular reaction was carried out more easily with the ester than the free carboxylic acid and subsequently gave the fully protected bicyclic systems, (34). Deprotection gave the free thiol carboxylic acids (28) and (29).

1.4.2 Hexahydropyrazolo [1,2a]- systems

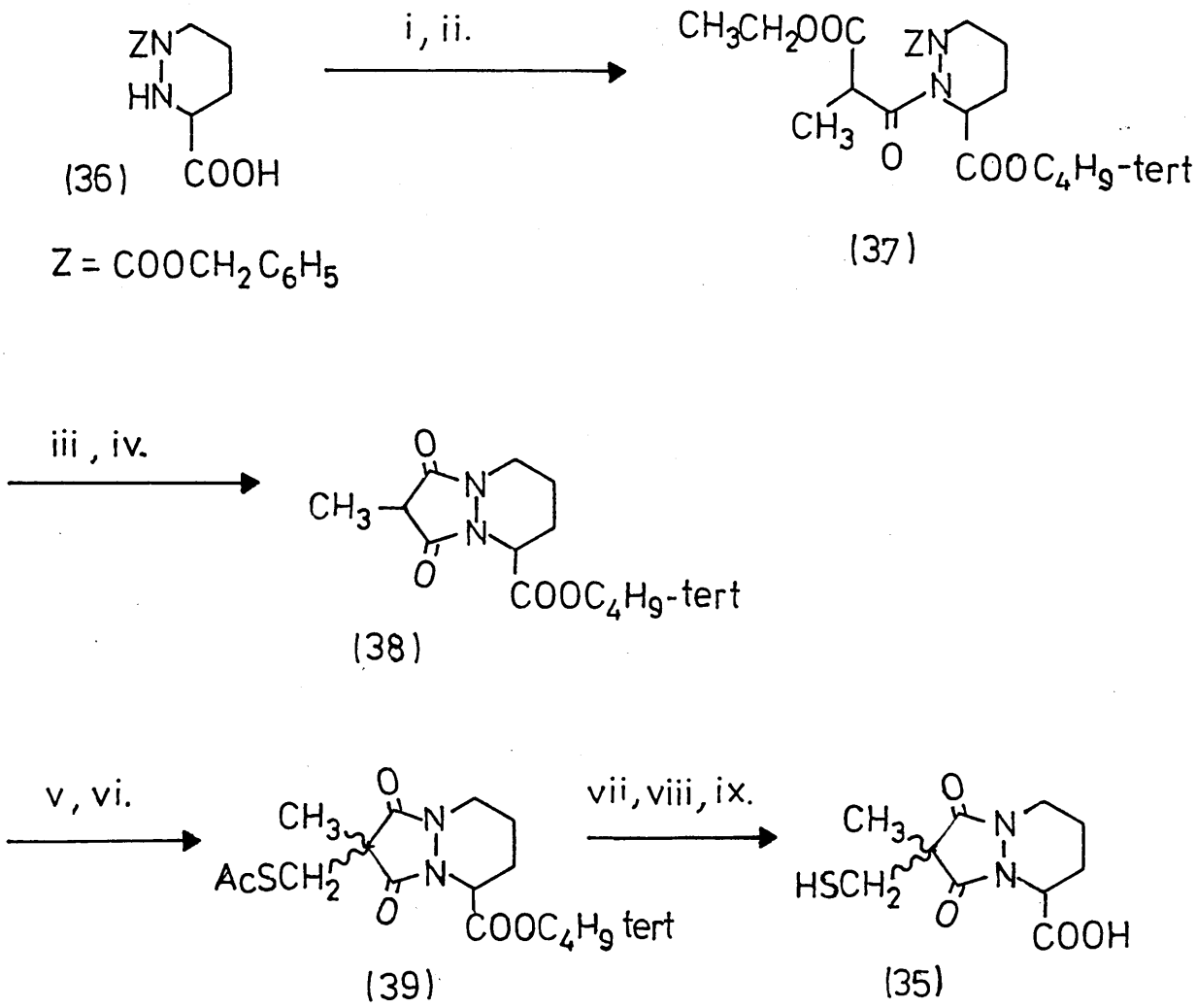
The acid (35) could also be synthesized by a Diels-Alder reaction using the dienophilic reactivity of pyrazole -3,5-dione.[50] However failure to prepare the appropriate dienophile led to a method using the monoprotected piperazic acid (36),[51] as shown in scheme 4. Esterification with isobutene gave the corresponding t-butyl ester which was acylated with ethylmethylmalonyl chloride to give the intermediate (37). Catalytic hydrogenolysis of the benzyloxycarbonyl group and treatment with acetic acid gave the pyrazolopyridazine (38).



i. $CH_3CH_2O_2CNHNH_2$; ii. 4N KOH, r.t. ; iii. tert-C_4H_9OCl; iv. penta-2,4-dienoic acid ; v. esterification ; vi. NaI, acetone, AcSK.

Scheme 3.

Alkylation of the sodium salt of (38) using S-bromomethylthioacetate [52] gave the fully protected compound (39) and deprotection gave the required thiol acid (35).

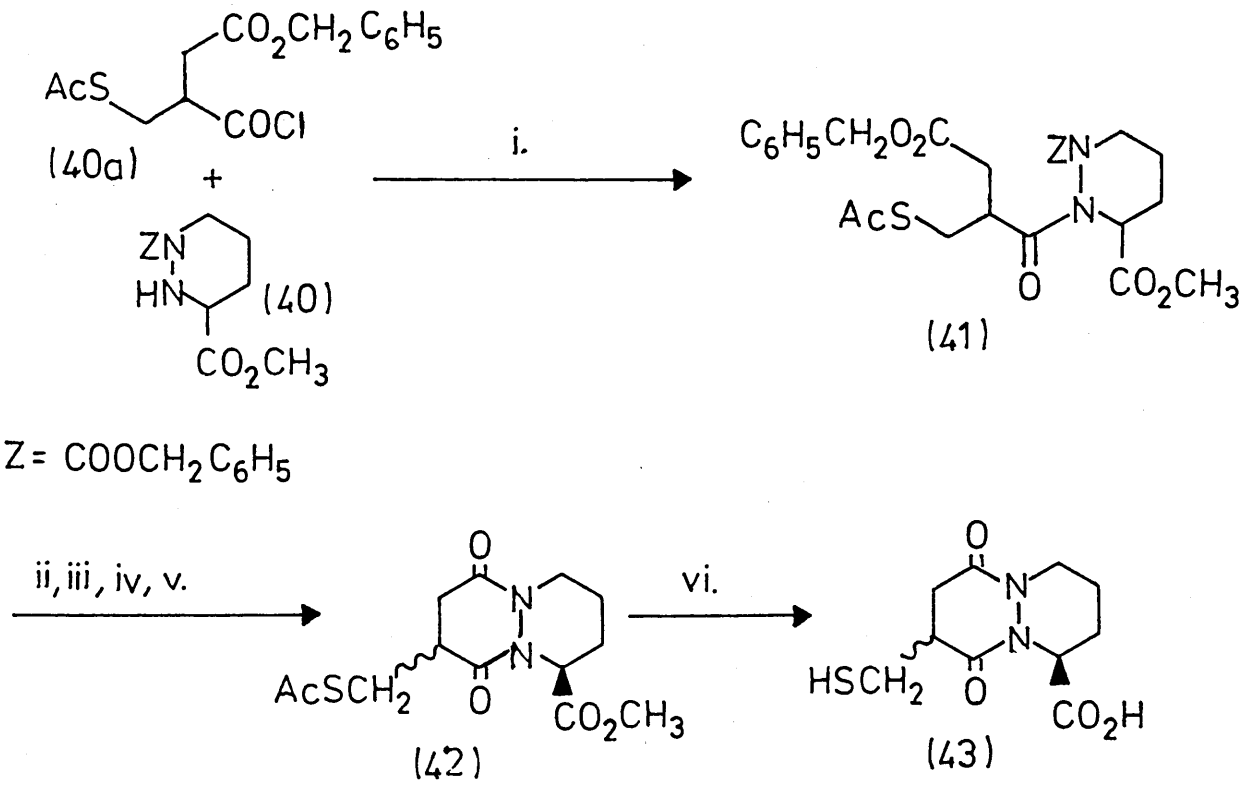


i. $(CH_3)_2C=CH_2$, H^+; ii. $CH_3CH_2OOCCH(CH_3)COCl$, NaOH, H_2O-CH_2Cl_2; iii. H_2, Pd-C; iv. AcOH, 100°C; v. NaH, DMF; vi. $AcSCH_2Br$; vii. separate diastereoisomers; viii. TFA; ix. aq. NH_3.

Scheme 4.

1.4.3 Octahydro-6,9-dioxopyridazo[1,2a]-systems

The acid (43) was prepared as shown in scheme 5. The bicyclic pyridazo[1,2a]pyridazine was prepared most conveniently by stepwise diacylation of the appropriate piperazic acid derivative as for compound (35).



i. aq.NaOH-CH_2Cl_2 ; ii.separate diastereoisomers ; iii. HBr, AcOH; iv. PCl_5 , DMF ; v. pyridine ; vi. aq. NaOH, CH_3OH.

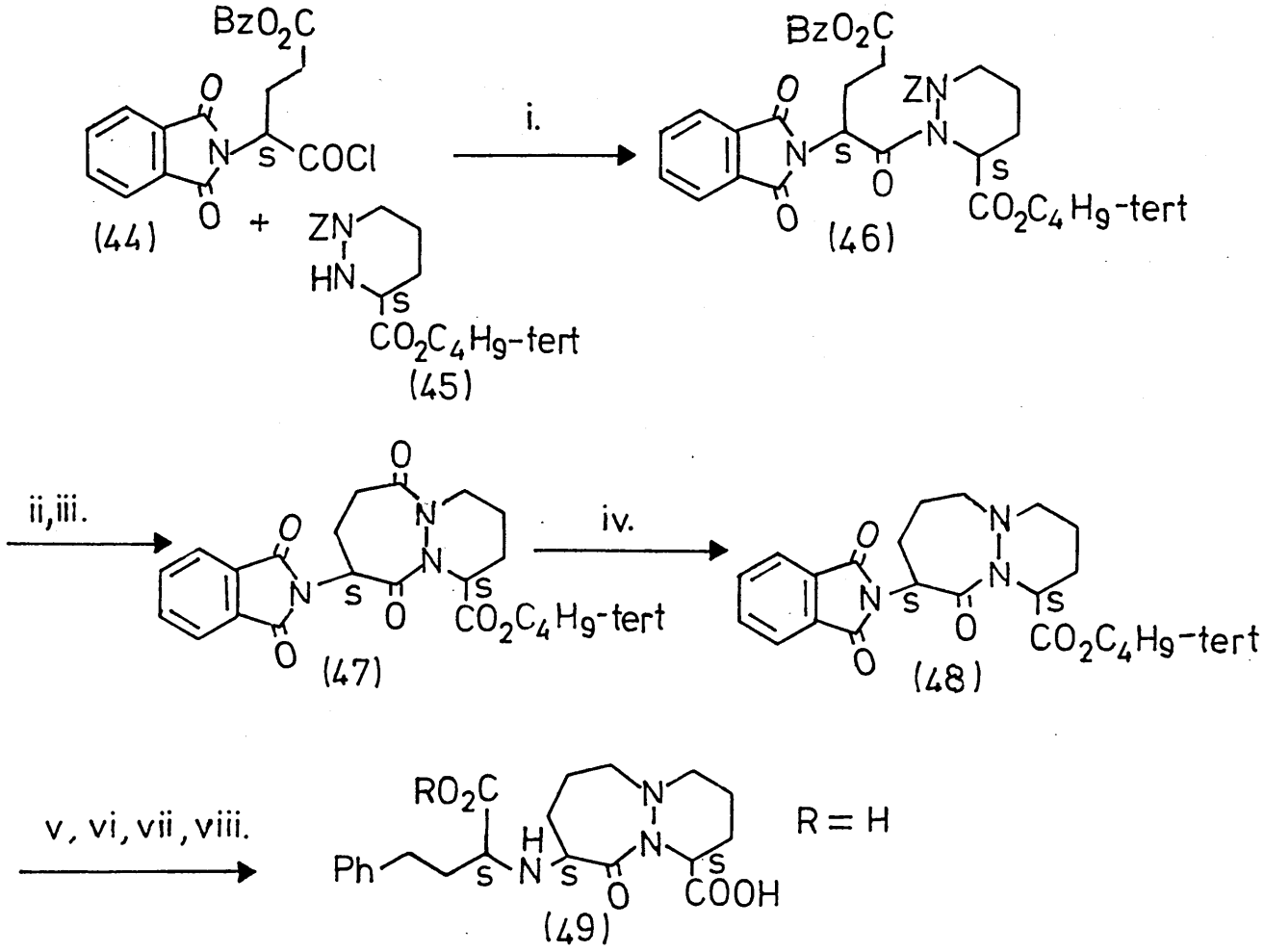
Scheme 5.

These 5,6 and 6,6 bicyclic compounds described had substantial activities as inhibitors of angiotensin - converting enzyme, but they

were less effective than captopril (4) and enalpril (24). Investigations of the conformations of the most active members of two series by the NMR spectroscopy and X - ray diffraction provided an explanation.[53]

1.5 Synthesis of Cilazpril

Structure-activity studies allowed the development of more improved inhibitors culminating in the synthesis of Cilazpril (49),[53] as shown in scheme 6.

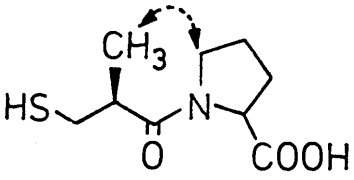


i. $C_6H_5CH_3$, H_2O-$NaHCO_3$; ii. H_2, Pd-C; iii. $SOCl_2$-CH_2Cl_2; iv. H_3B-THF; v. $N_2H_2 \cdot H_2O$ - CH_3CH_2OH; vi. $PhCH_2CH_2CH(OTf)CO_2CH_2CH_3$, Na_2CO_3-H_2O-CH_2Cl_2; vii. H^+, CH_2Cl_2; viii. NaOH, CH_3CH_2OH, H_2O.

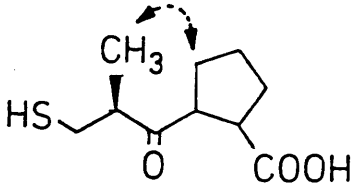
Scheme 6.

1.6 Design of rigid system of captopril and analogues

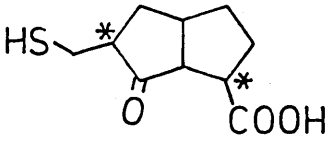
Close examination of the non - rigid ACE inhibitors, of which compounds such as captopril (4) and the carbocyclic analogue (14) are examples, indicates there is a basis for preparing more rigid bicyclic analogues using a second ring (dotted lines) to give rigidity.



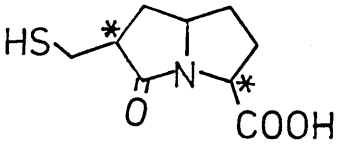
(4)



(14)



(50)

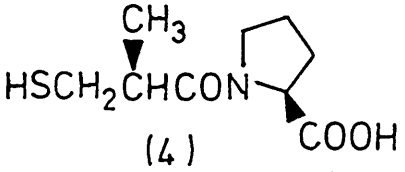
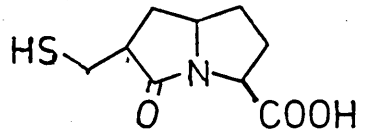
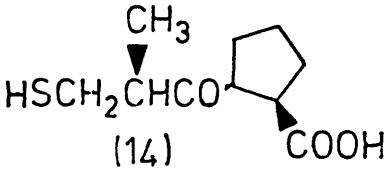
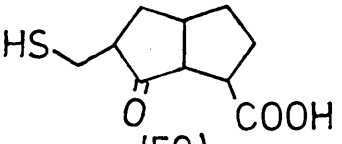
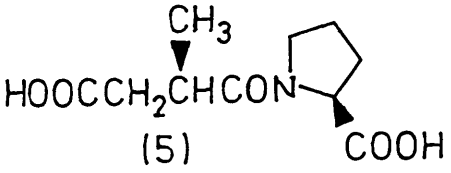
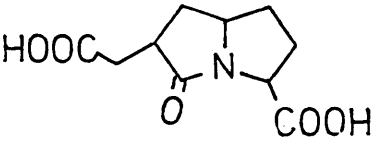
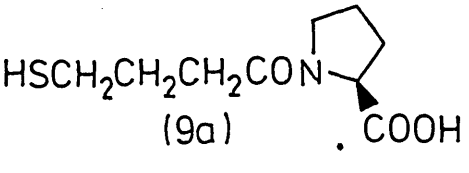
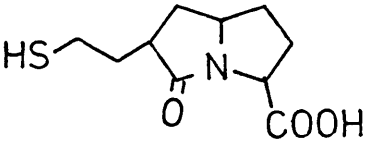
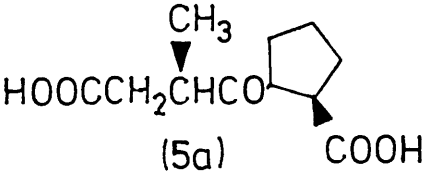
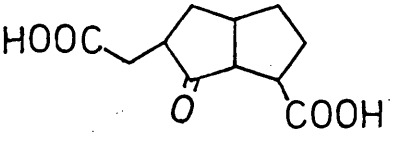
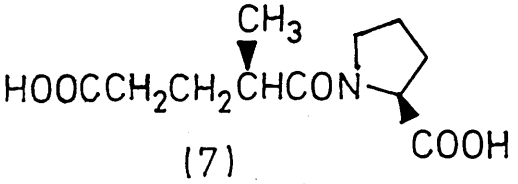
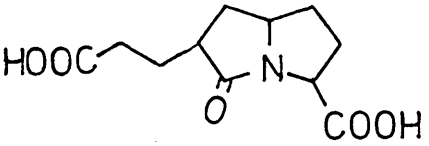


(51)

These observations directed our studies into the synthesis of rigid analogues of the type (50) and (51). Further possible rigid systems are shown in Table 2. with their non - rigid counterparts.
The relative stereochemistry in such systems is fairly easy to control and predict; the stereochemistry at the starred centres in (50) and (51) is the same as that in captopril and this relative stereochemistry has been shown to have an important effect on the biological activity.

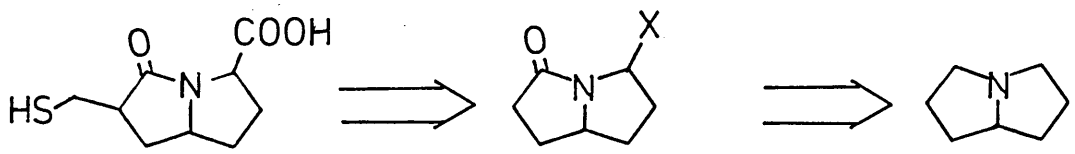
The studies form the basis for the work discussed in the following chapters.

Table 2.

Non-rigid systems	Rigid systems
 (4)	 (51)
 (14)	 (50)
 (5)	 (52)
 (9a)	 (53)
 (5a)	 (54)
 (7)	 (55)

2. Introduction

Retrosynthetic analysis of (51) features a fused cyclopentane framework, containing a bridgehead nitrogen (57) (azabicyclo[3.3.0]-octane system) as outlined in scheme 7.



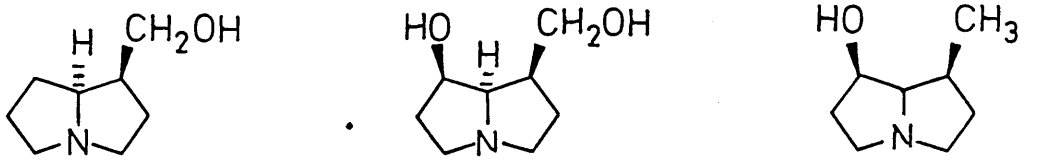
(51) (56) (57)

X = potential carboxylic acid functionality

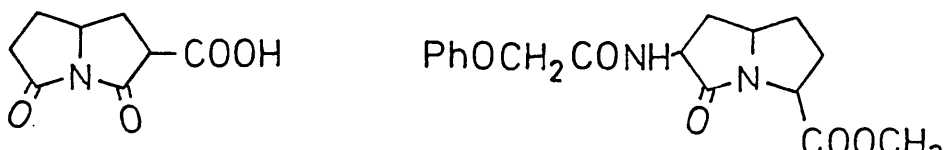
Scheme 7.

A search of literature showed a vast range of approaches towards the synthesis of various types of azabicyclo[3.3.0]oactane systems.[54]

Examples of a few azabicyclo[3.3.0]oactane systems are shown in scheme 8.



(-)-isoretronecanol (58) (-)-hastanecine (59) retronecanol (60)



(61)[55] (62)[56]

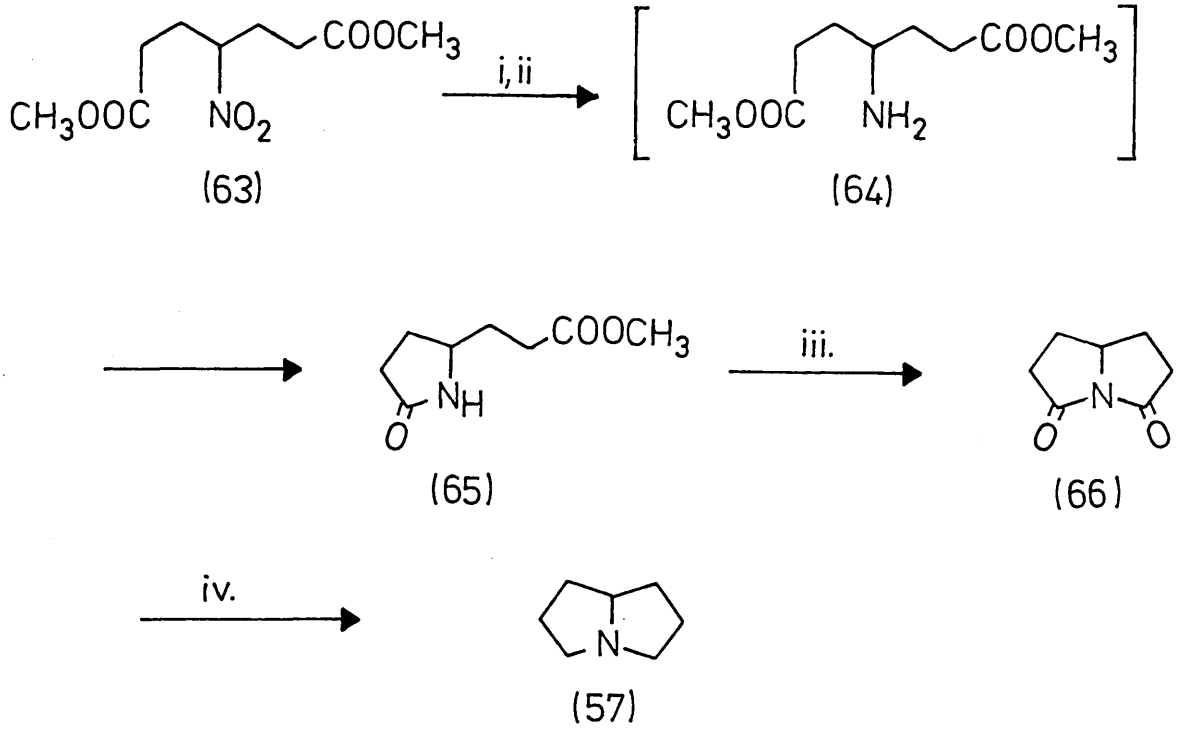
Scheme 8.

The initial undertaking was to synthesize a readily accessible system, similar in structure to (56), where X is a potential carboxylic acid functionality, which could then be elaborated towards the final target (51).

2.1 Discussion and results

2.1.1 2,8-Dioxo-1-azabicyclo[3.3.0]octane

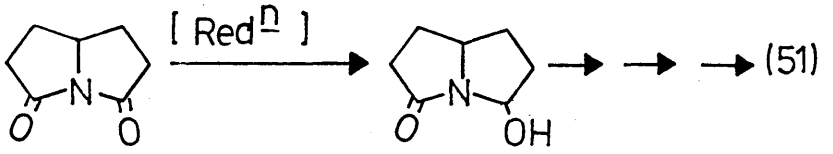
Our attention was focussed to a report by N.J.Leonard and coworkers[57] describing a method for the preparation of pyrrolizidine systems as shown in scheme 9.



i. PtO_2, CH_3OH, 2-3atm, 25°C, hydrogen; ii Distillation; iii $2CuO \cdot Cr_2O_3$, 250°C, 300 atm, hydrogen; iv $2CuO \cdot Cr_2O_3$, hydrogen, 250°C, 340 - 410 atm.

Scheme 9.

Consideration of the method showed that (66) would be a useful intermediate to obtain for several reasons. Firstly, (66) contains an imide structure, which could provide access to the type (67)[58] system, by a selectively reducing one of the carbonyl groups of (66) (scheme 10).



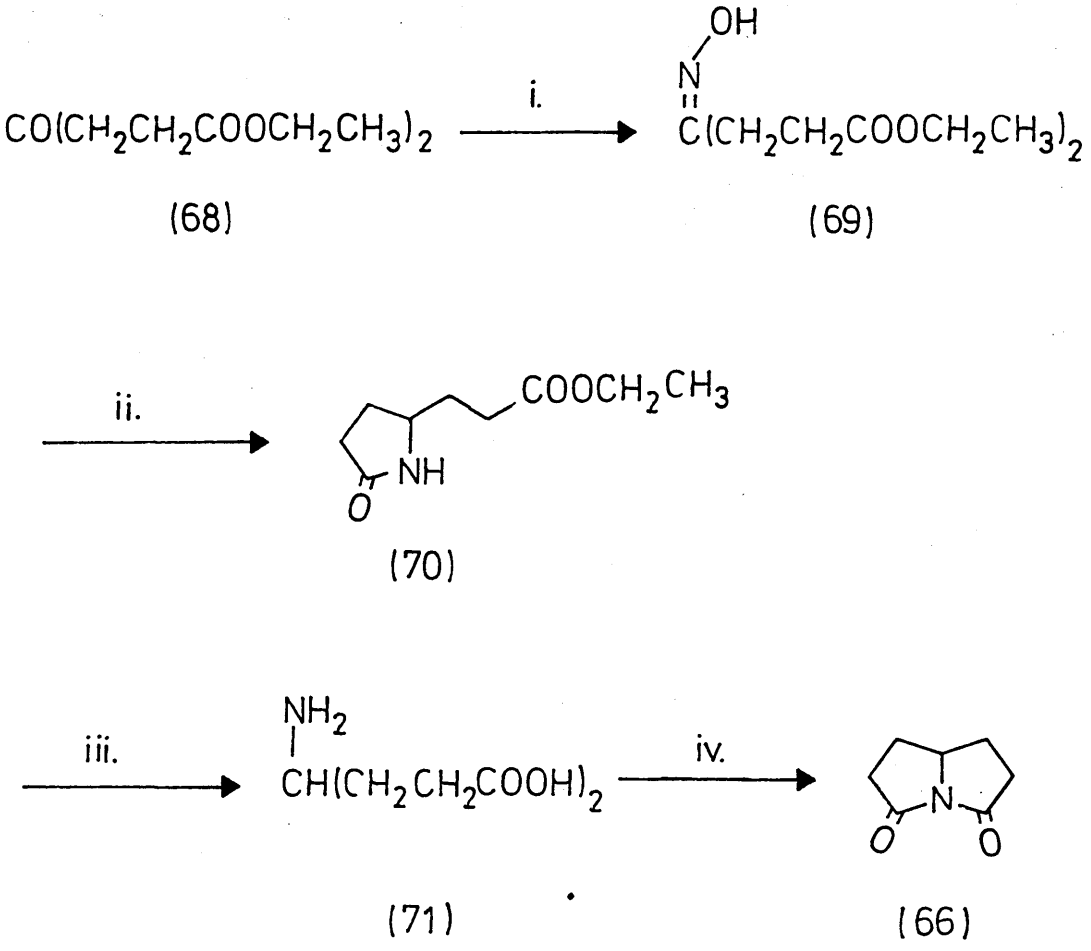
(66) (67)

Scheme 10.

Further elaboration of (67) should give the final target system (51). An attempt was made to obtain (66) using the procedure of N.J.Leonard.

The nitro diester (63) was prepared by Michael addition of nitromethane to methyl acrylate according to the procedure of Bruson.[59] Reduction of (63) with hydrogen and platinum oxide (Adams' catalyst) gave the amine ester (64), subsequent distillation of (64) gave the ester lactam (65). The undistilled residue was identified to be (66) (8%). Treatment of (65) with hydrogen at 300 atmospheres and 250°C over copper chromite (Lazier catalyst) would give the azabicyclo[3.3.0]octane (66). However, conversion of (65) to (66) according to the conditions of Leonard described above proved difficult on the existing apparatus.[60] Several attempts were made but were unsuccessful in giving (66), only starting material was recovered.

Failure to obtain the azabicyclo[3.3.0]octane (66), directed us to pursue an alternative approach towards this system, using the procedure described by R.Lukes and F.Sorm[61] as shown in scheme 11.

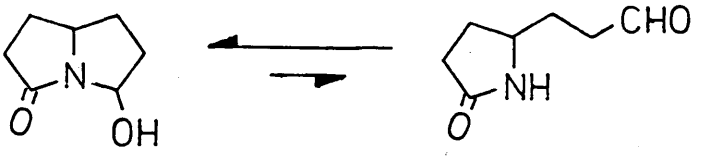


i. $NH_2OH \cdot HCl$, pyridine ; ii. PtO_2, hydrogen ; iii. conc. H_2SO_4, Δ ; iv. Δ .

Scheme 11.

The synthesis began with the reaction of furfurylacrylic acid[62] with hydrochloride gas in ethanol which gave the diethyl-γ-oxo-pimelate (68).[63] Treatment of (68) with hydroxylamine hydrochloride gave the oxime (69) which was hydrogenated over platinum oxide to give the ester (70). Treatment of (70) with concentrated sulphuric acid should have yielded the amine diacid (71). Heating (71) would have given (66). However, isolation of pure (71) proved to be difficult and after various attempts to isolate (71) failed, the decision was made to find alternative synthetic routes for preparing azabicyclo[3.3.0]octane systems.

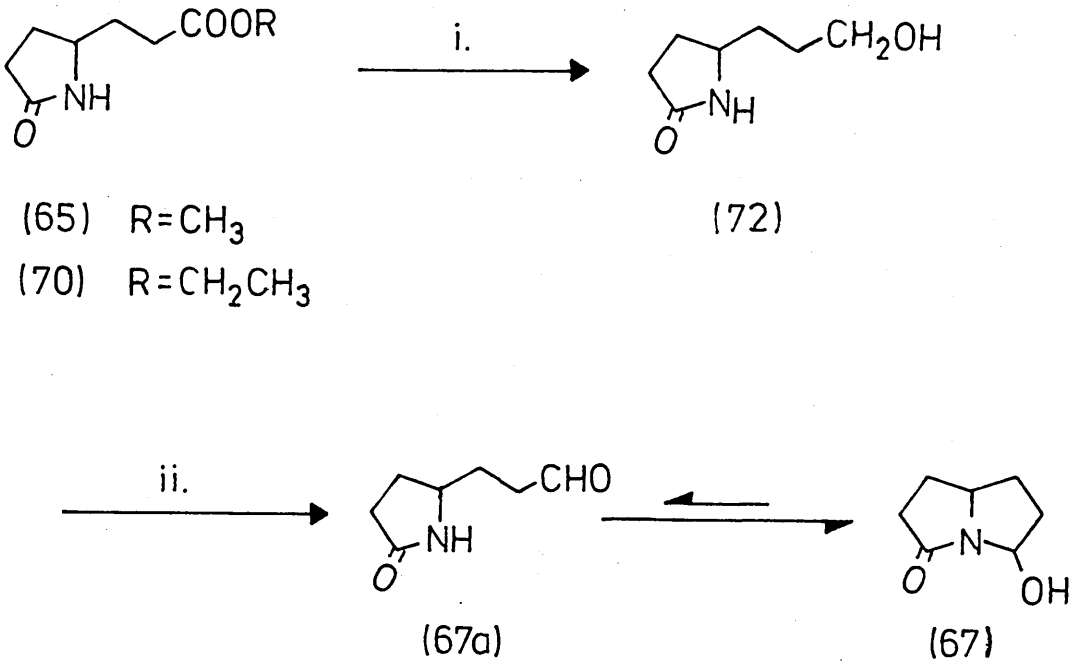
From our previous studies the ester lactams (65) and (70) proved to be readily obtainable. This prompted investigation towards obtaining the azabicyclo[3.3.0]octane (67) through the use of (65) or (70).



(67) (67a)

Buchi and Brossi[58] described the synthesis of (67) via lithium aluminium hydride reduction of (66). Unfortunately, a maximum yield of 30% of (67) was reported.

Our attempted synthesis of (67) as shown in scheme 12, involved selective reduction of the ester group of(65) or (70) to



i. $NaBH_4$, tert-C_4H_9OH, CH_3OH; ii. pyridinium dichromate, CH_2Cl_2.

Scheme 12.

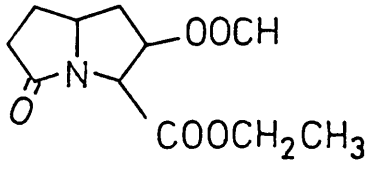
the alcohol (72), which was initially carried out with lithium borohydride prepared *in situ* using sodium borohydride and anhydrous lithium chloride in ethanol.[64] The reduction process proved to be highly unreliable and difficult to optimise. Kenso Soai and coworkers[65] selectively reduced an ester group to an alcohol using sodium borohydride in tert-butanol and methanol. Treatment of either of the esters (65) or (70) under these conditions resulted in smooth reduction of the ester group giving the alcohol (72). Oxidation of (72) with pyridinium dichromate[66] was expected to give the aldehyde (67a), which exists in solution in equilbrium with the tautomeric carbinol lactam (67). However, oxidation of the alcohol (72) gave the azabicyclo[3.3.0]octane (66) (32%) and not the desired carbinol

lactam (67). An explanation for this observation is that initially oxidation of (72) gives the aldehyde (67a) which, in solution, is in equilbrium with the tautomeric system (67), whose hydroxyl function undergoes further oxidation giving (66). Consideration of using (66), obtained from the oxidation of (72), in the synthesis of (67), employing the methodology of Brossi and Buchi[58] was rejected due to the low yield of (66) being isolated. The poor yield of (66) could be attributed to the formation of tar in the reaction mixture, which consequently involved a difficult work up. Also the low yield of (67) being reported.[58] Failure to obtain the azabicyclo[3.3.0]octane system using the synthetic process described, directed investigations towards alternative routes.

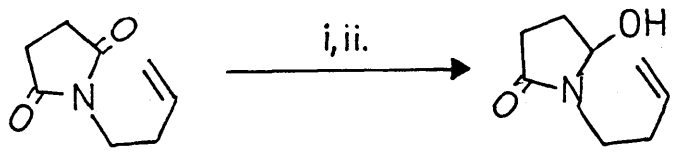
2.1.2 Azabicyclo[3.3.0]octane systems via N-acyliminium intermediate

In this phase of our study advantage was taken of reports by W.N.Speckamp[67] that described the synthesis of various azabicyclo-systems through the use of N-acyliminium intermediates. An example is shown in scheme 13, via the intermediate (74a).

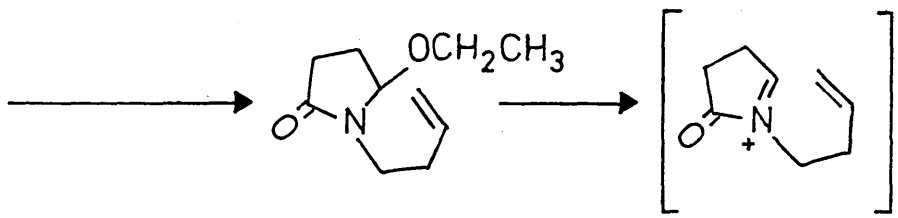
By using the above process the azabicyclo[3.3.0]octane system (76) might be prepared, containing a potential carboxylic acid functionality.



(76)

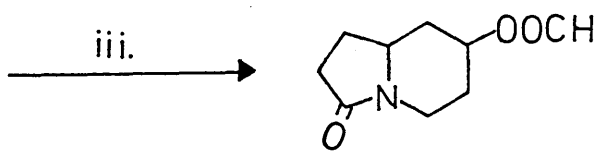


(73) (73a)



(74) N-acyliminium intermediate

(74a)

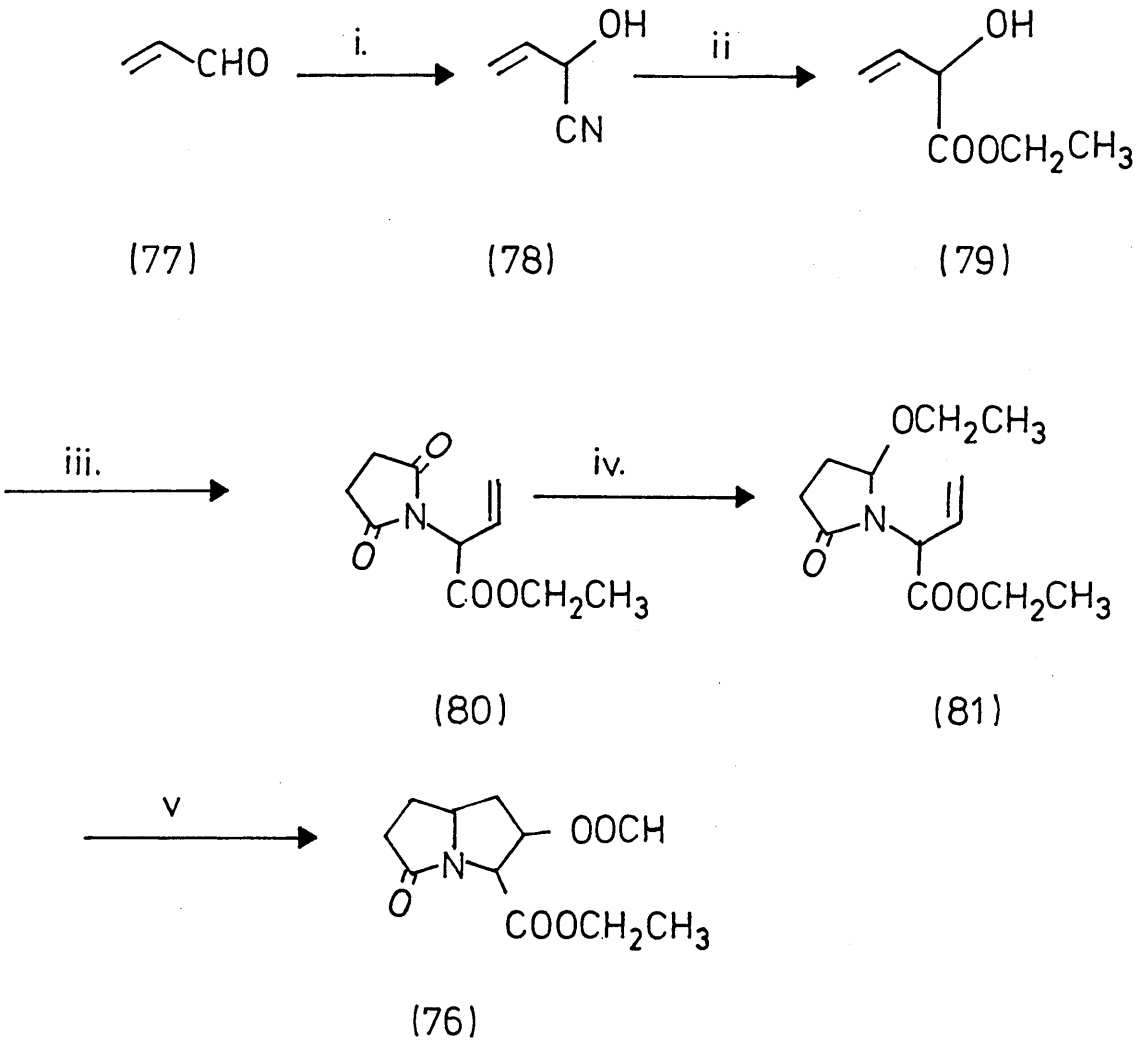


(75)

i. $NaBH_4$; ii. CH_3CH_2OH , HCl ; iii. HCOOH , r.t.

Scheme 13.

Successful synthesis of (76) would permit access towards the final target (51). The synthesis of (76) was attempted as outlined in scheme 14.

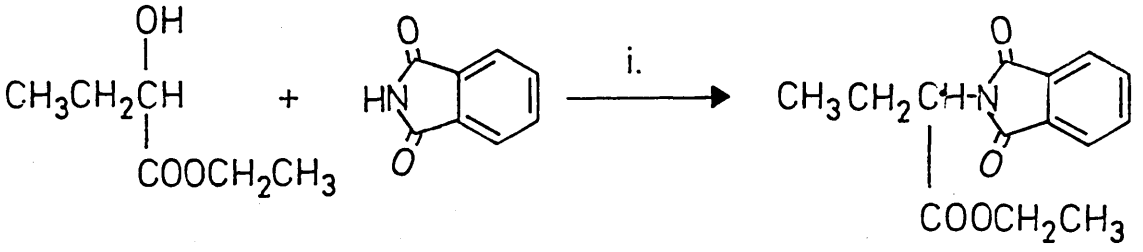


i glacial CH_3COOH, NaCN ; ii. conc. H_2SO_4 , CH_3CH_2OH, reflux ; iii. Ph_3P , succinimide , DEAD ; iv. $NaBH_4$, HCl, CH_3CH_2OH ; v. HCOOH.

Scheme 14.

The initial work involved the preparation of the secondary alcohol (79) available by reaction of acrolein (77) with sodium cyanide and glacial acetic acid,[68] followed by treatment of the duly formed cyanohydrin (78) with concentrated sulphuric acid in ethanol.[69]

The next step in the reaction sequence was the synthesis of the substituted imide (80). This was carried out using the oxidation - reduction technique developed by Mitsonubu[70] in which NH- of the imide is coupled with an alcohol in the presence of triphenylphosphine and diethyl azocarboxylate (DEAD). It was very disheartening to find that under the conditions described by Mitsonubu no substituted imide (80) was obtained. Starting materials were exclusively recovered. However, Mitsonubu[70] has reported the formation of a substituted imide system (82) using a similar type of secondary alcohol (83), as outlined in scheme 15.



(83) (84) (82)

i. Ph_3P , DEAD.

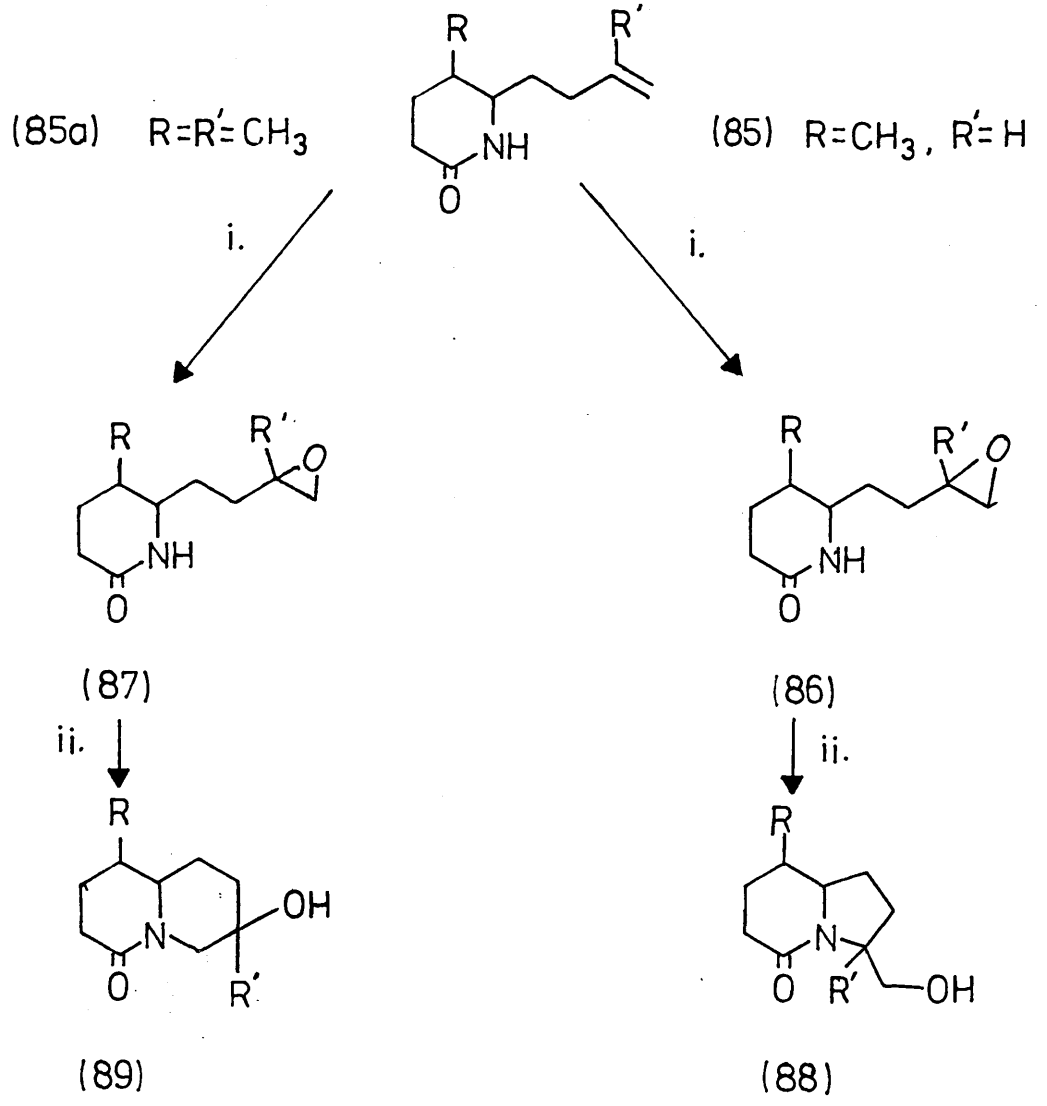
Scheme 15.

Failure to obtain (76) using the N-acyliminium approach, directed a further search of the literature.

2.1.3 Cyclisation reactions of 5-(3-butenyl)-2-pyrrolidinone to azabicyclo[3.3.0]octane systems

2.1.3.1 Synthesis of 5-(3-butenyl)-2-pyrrolidinone

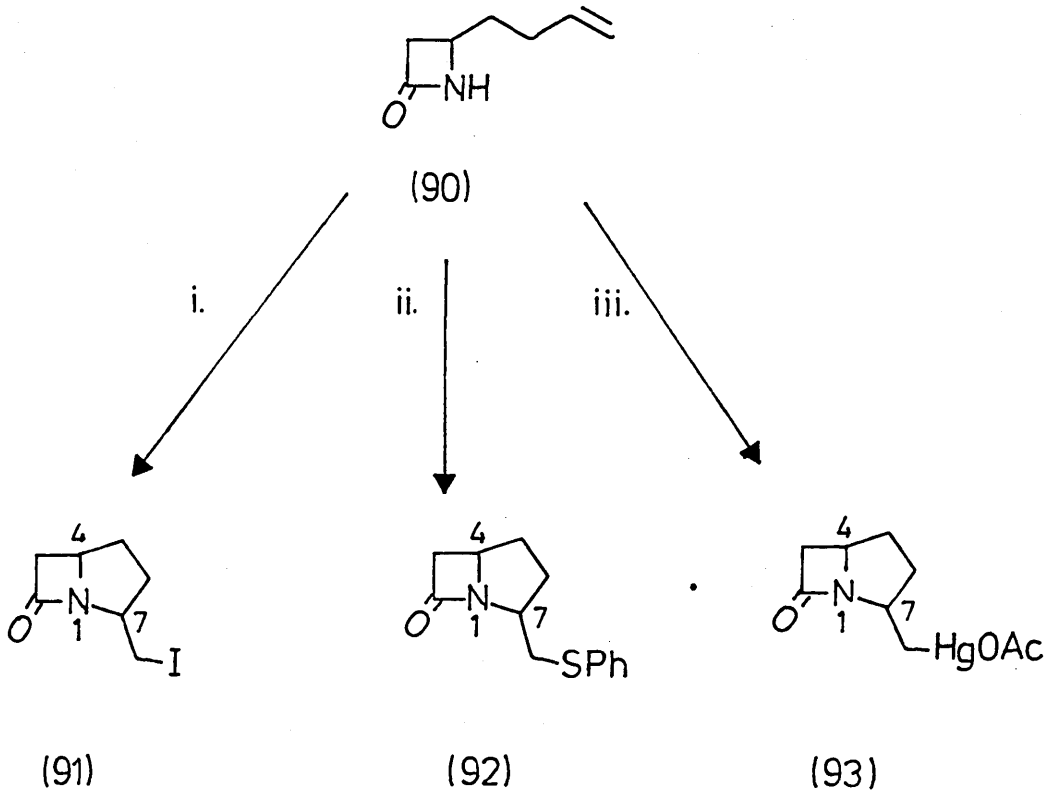
Advantage of two reports was taken. The first, by Lalonde and coworkers[71] described the synthesis of azabicyclo[4.3.0]nonanes (indolizidines) and azabicyclo[4.4.0]decanes(quinolizidines) as shown in scheme 16.



i. mcpba , CH_2Cl_2 ; ii. NaH , C_6H_6 , Δ .

Scheme 16.

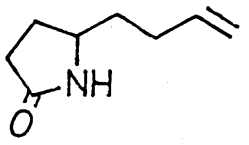
The key step in the synthesis of these systems was the cyclisation via the epoxide (scheme 16). The second report, by T.Aida and coworkers[72] described the synthesis of various azabicyclo[3.2.0]-heptane systems. The synthesis involved cyclisation of the mono-cyclic lactam (90) initiated by electrophilic reagents leading to β- lactam systems containing a potential carboxylic acid group at C-7, as shown in scheme 17.



i. I_2, Na_2CO_3, CH_2Cl_2 ; ii. PhSBr ; iii. $Hg(OAc)_2$, THF-H_2O mixture.

Scheme 17.

Consideration of the two procedures suggested that we could use similar chemistry to obtain the desired azabicyclo[3.3.0]octane systems. The key intermediates in the above procedures were the amide alkene systems (85), (85a) and (90). Therefore (94) was proposed to be the required intermediate towards eventually obtaining the azabicyclo[3.3.0]octane systems.

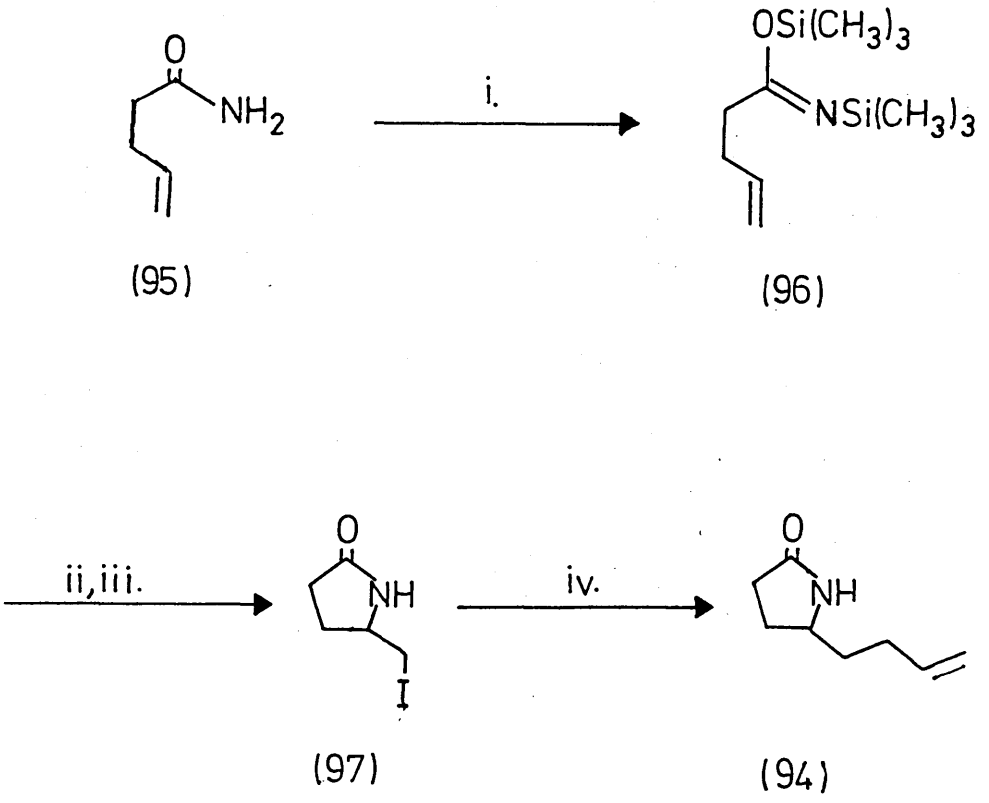


(94)

The alkene lactam (94) has been prepared by A.Toshimutsu and coworkers[73] by the combination of a recently reported "iodolactamization"[74] and replacement of the halogen (iodine) by an allyl group using allyltributylstannane,[75] as shown in scheme 18, however the yield of (94) was not reported using this process. The latter process was developed by Keck and coworkers[75] for the replacement of carbon-bound halogens (C-Br, C-Cl, C-I) by an allyl function.

The alkene lactam (94) was prepared using a similar approach except the bromo lactam (98)[76] was used instead of the iodide (97), as outlined in scheme 19.

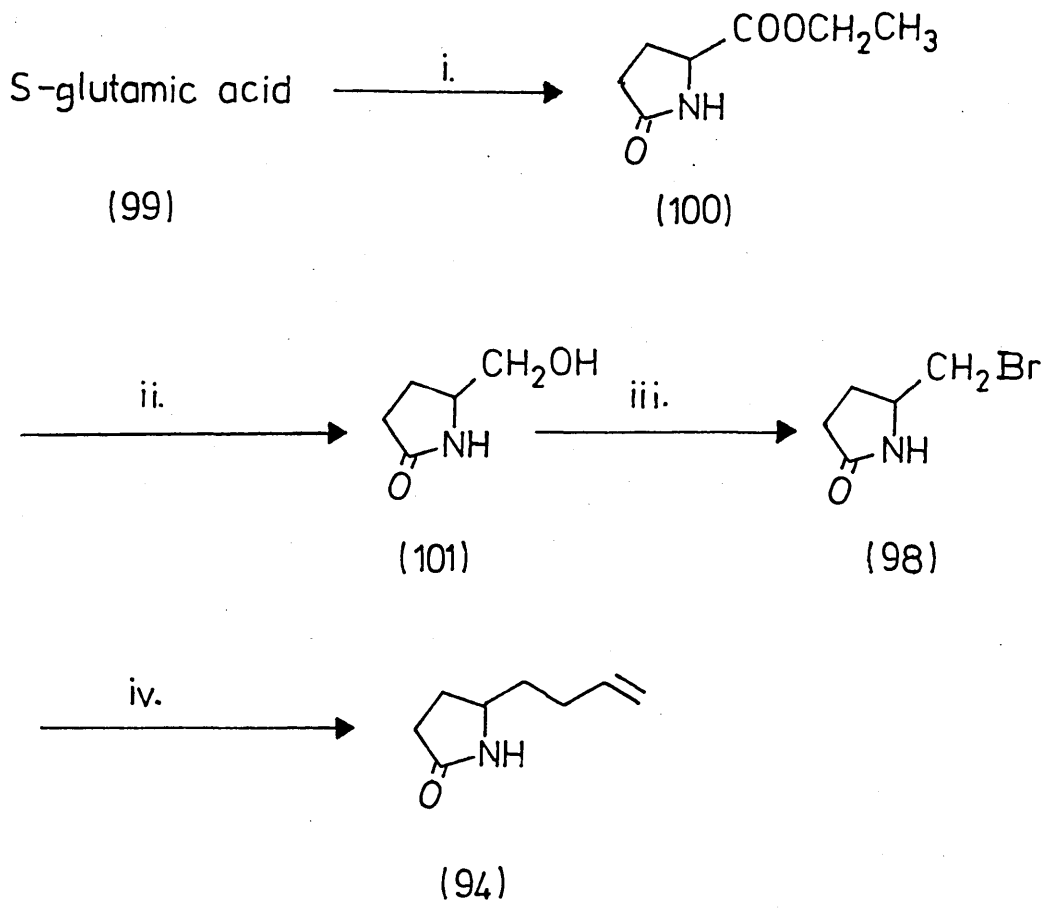
The advantage of this synthetic approach towards the preparation of (94), through the use of (98) is that the stereochemistry of



i. CH_3SiOTf , Et_3N ; ii. I_2 , THF ; iii. aq Na_2SO_3 ;
iv. $(C_4H_9)_3SnCH_2CH=CH_2$, AIBN, $C_6H_5CH_3$.

Scheme 18.

the starting glutamic acid should be unaffected during the synthesis of (98) and subsequently (94). Thus both enantiomers of (94) might be obtained depending on the stereochemistry of the starting glutamic acid (R or S) being used. Preparation of (98) was accomplished by treatment of commercially available S-glutamic acid (99) with thionyl chloride in ethanol giving the ester (100).[76] Reduction of (100)[77] with sodium borohydride in tert-butanol and methanol gave (101) (77%). The alcohol (101) was smoothly converted



i. $SOCl_2$, CH_3CH_2OH, Δ ; ii. $NaBH_4$, tert-C_4H_9OH, CH_3OH;
iii. CBr_4, Ph_3P ; iv. $(C_4H_9)_3SnCH_2CH{=}CH_2$, AIBN, $C_6H_5CH_3$.

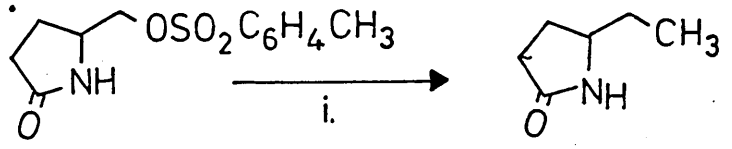
Scheme 19.

76

to the bromide (98) with triphenylphosphine and carbon tetrabromide, isolated in 65% yield. Replacement of the bromine with an allyl group using allyltributylstannane (2 equiv.) and azobis(isobutyronitrile) (AIBN) (0.15 equiv.) gave (94) (36%). Disappointingly the displacement step was a very low yielding process partly attributed to an incomplete reaction since 45% of the starting material (98) was recovered. Addition of more AIBN did not improve the yield of (94); this suggests that other side reactions might be

competing. Also the isolation of (94) proved difficult as both (94) and (98) were observed to have similar Rf values. Isolation by column chromatography involved, firstly elution of the reaction residue with the ethyl acetate/petrol, 3:2, to remove unreacted allyltributylstannane and other less polar materials formed in the reaction, followed by elution with ether-methanol, 10:1,which gave some separation to obtain (94). As (94) was required as starting material in large quantity for a total synthesis the synthetic process was not acceptable.

With failure to obtain (94) in sufficient quantities via the side chain elongation approach described above an alternative strategy was required. One possibility towards obtaining (94) was based upon the work of Marco,[78] scheme 20, which involved side chain elongation of pyrrolidinones by displacement of a tosyl group of (102) with lithium dimethylcuprate.



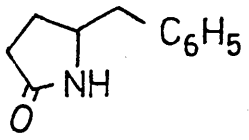
(102) (103)

i. $(CH_3)_2CuLi$

Scheme 20.

By reaction of (102) with an allyl moiety, (94) should be available. Treatment of (102), available by tosylation of the alcohol (101),[79]

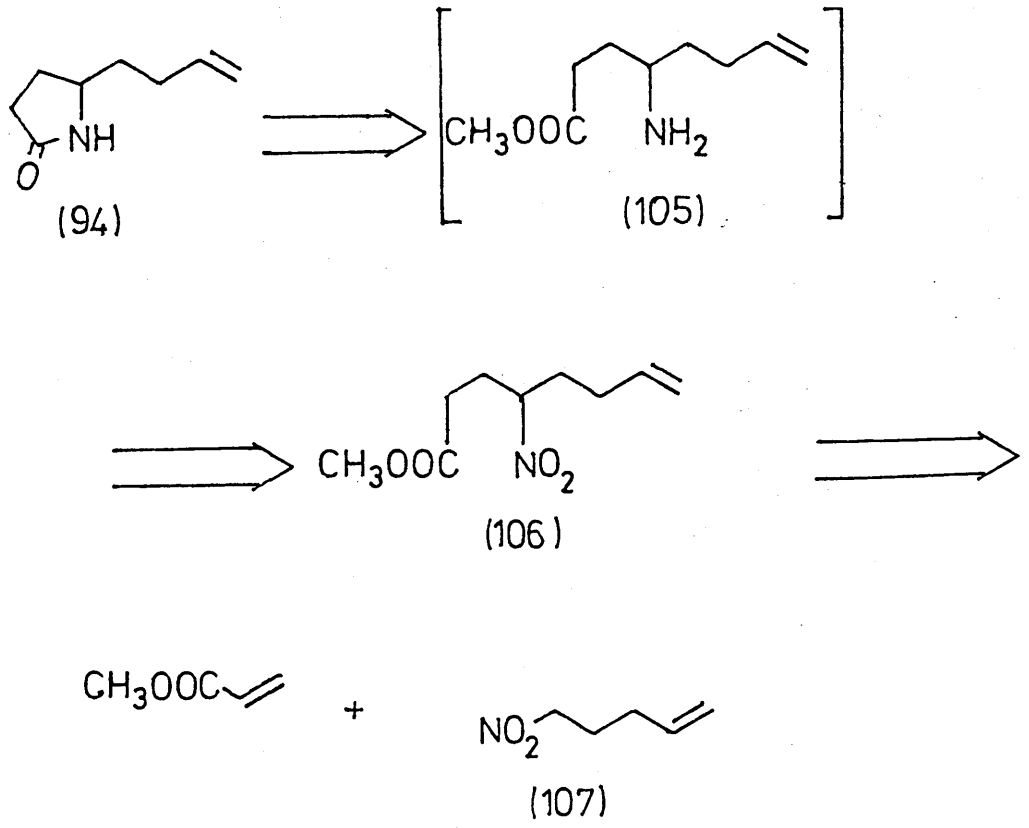
with lithium diallylcuprate, the latter generated from allyltributylstannane by treatment with phenyl lithium[80] followed by cuprous iodide, unfortunately gave the phenyl lactam (104).



(104)

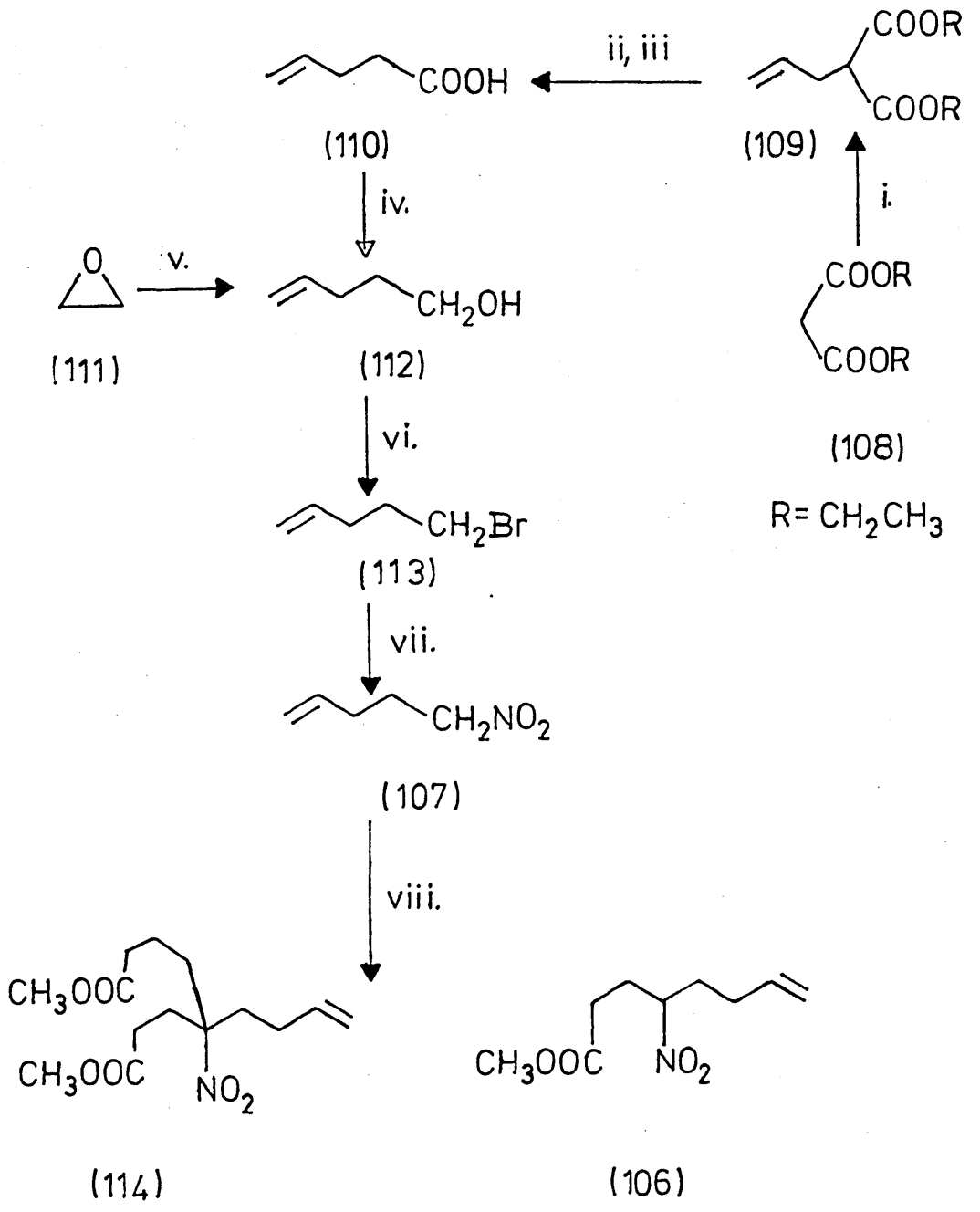
An explanation for this observation is that lithium diallyl cuprate was not generated by the above process, instead lithium diphenyl cuprate was formed, subsequently reacting with (102) to give (104). Alternatively reaction of (102) with allyl magnesium bromide, surprisingly, gave, instead of the expected alkene lactam (94) the bromide (98). We cannot ascertain the reason for this anomalous behaviour.[81]

One aspect of our earlier work provided a clue to an approach towards (94). As outlined earlier (scheme 9) the synthesis of ester lactam (65) involved Michael addition of nitromethane to methyl acrylate. Subsequent reductive cyclisation of the conjugate product gave (65). Using this Michael addition-reductive cyclisation strategy, (94) should be available. Retrosynthetic analysis of (94) (scheme 21) showed that the component required to undergo Michael addition using this approach was the nitro alkene (107). Therefore our attention was focussed on the synthesis of (107) which was carried out as shown in scheme 22.



Scheme 21.

The alcohol (112) was initially prepared by treatment of oxirane (111) with allyl magnesium chloride.[82] However preparation of (112) using this synthesis was not acceptable to us due to low yields being obtained. Alternatively the alcohol (112) could be obtained by reduction from corresponding acid (110).[83] The acid (110) was prepared by condensation of diethyl malonate (108) with allyl chloride giving the alkylated system (109) whose base hydrolysis followed by decarboxylation gave (110) (76%). Lithium aluminium hydride reduction of (110) gave (112) (73%). Conversion of the alcohol (112) to the bromide (113)[84] was carried out using phosphorous tribromide.[84a] The primary nitro alkene (107) was obtained by treatment of (113) with sodium nitrite in dimethyl

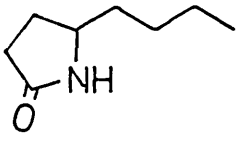


i. Na , CH_3CH_2OH , $CH_2=CHCH_2Cl$; ii. KOH, Δ ; iii. c. H_2SO_4 , Δ ; iv. $LiAlH_4$, ether ; v. Mg, $CH_2=CHCH_2Cl$, ether ; vi. PBr_4 , pyridine ; vii. $NaNO_2$, DMSO ; viii. Triton B , $CH_2=CHCOOCH_3$.

Scheme 22 .

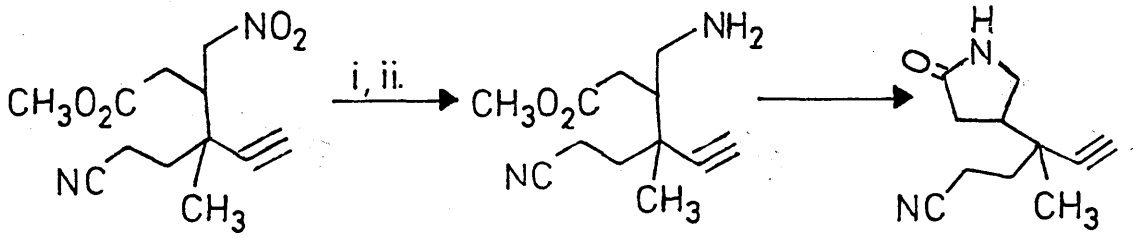
sulphoxide.[85] Michael addition of (107) to methyl acrylate was initially catalysed with diisopropylamine[86] and gave after 5 days the desired conjugate product (106) and the dialkylated product (114). The required system (106) was isolated in 41% yield. Repetition of the Michael reaction using benzyltrimethylammonium hydroxide (triton B)[87] as catalyst, furnished (106) in better yield (57%) and shorter time (8h).

Arrival at (94) required selective reduction of the nitro group of (106) to the amine (105) whose intramolecular cyclisation would give (94). Traditional methods of reduction of aliphatic nitro compounds, such as high pressure hydrogenation,[88] lithium aluminium hydride[89] or aluminium amalgam,[90] could not be used due to the multifunctionality of (106). Initial attempts at reducing the nitro group of (106) were carried out with nickel boride (Ni_2B), which has been reported to reduce aliphatic nitro compounds to amines.[91] Nickel boride was prepared <u>in situ</u> by sodium borohydride reduction of nickel chloride in methanol. Reduction of (106) using Ni_2B unfortunately gave the alkane lactam (115), indicating that apart from reduction of the nitro group, reduction of the isolated double bond also occurs. To our advantage R.V.Stevens and



(115)

coworkers[92] reported a process for the reduction of a similar multifunctional system (116) (scheme 23). The reduction of the nitro group was achieved through the use of zinc and concentrated



(116) (117) (118)

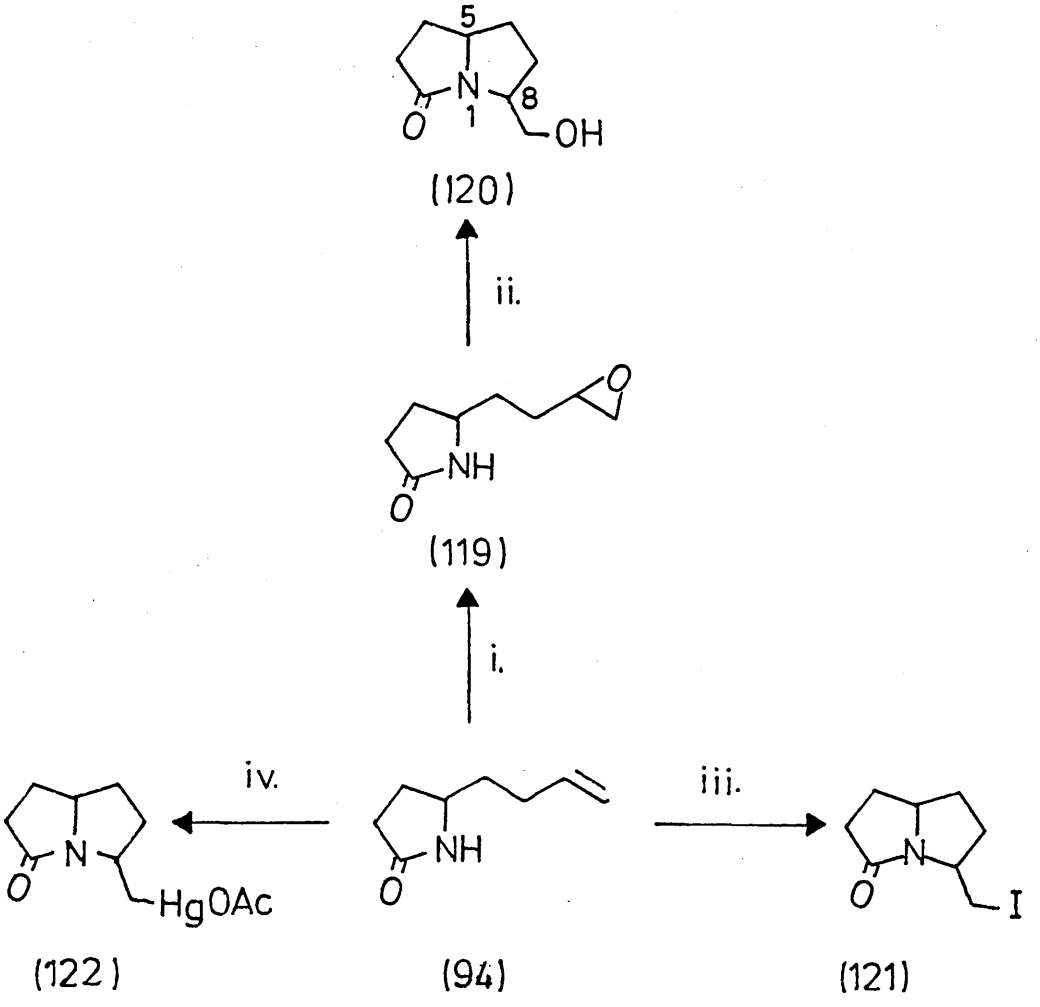
i. c.HCl , Zn , CH_3OH ; ii. 6N NaOH.

Scheme 23.

hydrochloric acid giving (117) whose intramolecular cyclisation gave (118). The other functional groups were unaffected. Treatment of our system (106) under the conditions described by Stevens resulted in smooth reduction of the nitro group to yield the amine (105) and subsequent intramolecular cyclisation gave the alkene lactam (94) isolated in 83% yield.

With isolation of (94) the next phase of study was cyclisation of (94) using the processes discussed earlier. The first method of cyclisation of (94) was carried out on similar lines to work described

by Lalonde and coworkers (scheme 16), which involved cyclisation through the use of the epoxide. Epoxidation[93] of the alkenyl side chain of (94) with 3-chloroperbenzoic acid (mcpba) gave the epoxide (119). The epoxide

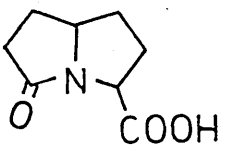


i. mcpba, CH_2Cl_2 ; ii. NaH, C_6H_6, Δ ; iii. I_2, Na_2CO_3, CH_2Cl_2 ; iv. $Hg(OAc)_2$, THF, H_2O.

Scheme 24.

(119) was employed directly in the ring formation step since Lalonde[71] showed that attempts to purify similar systems (86) and (87) by distillation or column chromatography resulted in degradation and consequent loss of material. Treatment of a benzene solution of (119) with sodium hydride, as shown in scheme 24, successfully gave the azabicyclo[3.3.0]octane (120) but only a maximum yield of 30% (from (119)) could be obtained. Formation of the alcohol (120) from the epoxypyrrolidinone was indicated by ^1H nmr which showed a two proton multiplet at 3.70δ attributed to CH_2OH, a one proton multiplet at 4.0δ attributable to hydrogen at the bridgehead carbon (C-5) and a broad singlet at 5.23δ attributable to the hydroxyl proton. Addition of Deuterium oxide (D_2O) caused the signal at 5.23δ to collapse. Due to the low yield being obtained, and as (120) was required in large quantities, alternative methods of synthesis were studied based upon the work of T.Aida and coworkers.[72] Treatment of (94) with iodine in dichloromethane containing anhydrous sodium carbonate gave the iodide (121) isolated in 44% yield. Only one isomer appeared to be formed in this cyclisation as judged by nmr spectra of the product. However, efficient cyclisation of (94) occured with mercuric acetate in THF-water mixture.[94] The organomercurial (122) was obtained in virtually quantitative yield. Structure assignment of (122) was based on its ^1H and ^{13}C spectra. The latter was particularly informative showing an extra peak in the range 170-200ppm which is typical of a RCO_2R carbon. Again, only one isomer appeared to be formed in this cyclisation as judged by the spectra. With successful cyclisation of (94) in near quantitative yield the next phase of

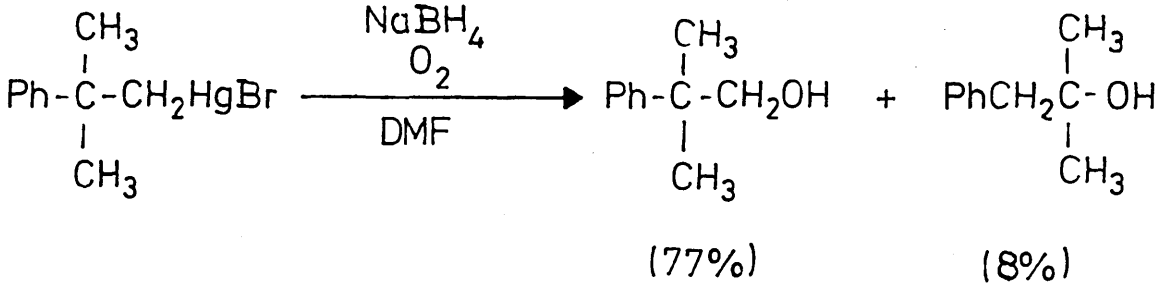
study was towards converting (122) to the acid (123).



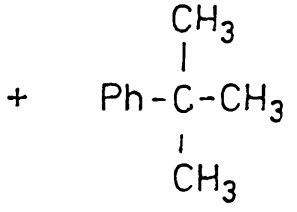
(123)

2.14 2-Oxo-1-azabicyclo[3.3.0]octane-8-carboxylic acid

Advantage was taken of a report by Whitesides[95] that described the conversion of mercury salts to alcohols by reductive-oxygenation using sodium borohydride, dimethylformamide (DMF) and oxygen. An example is shown in scheme 25



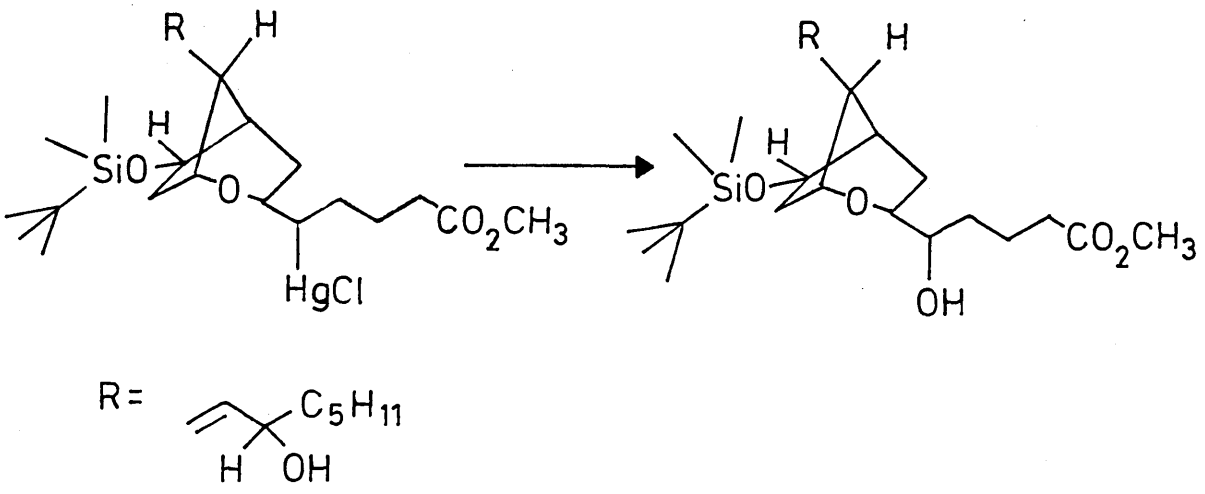
(77%) (8%)



(3%)

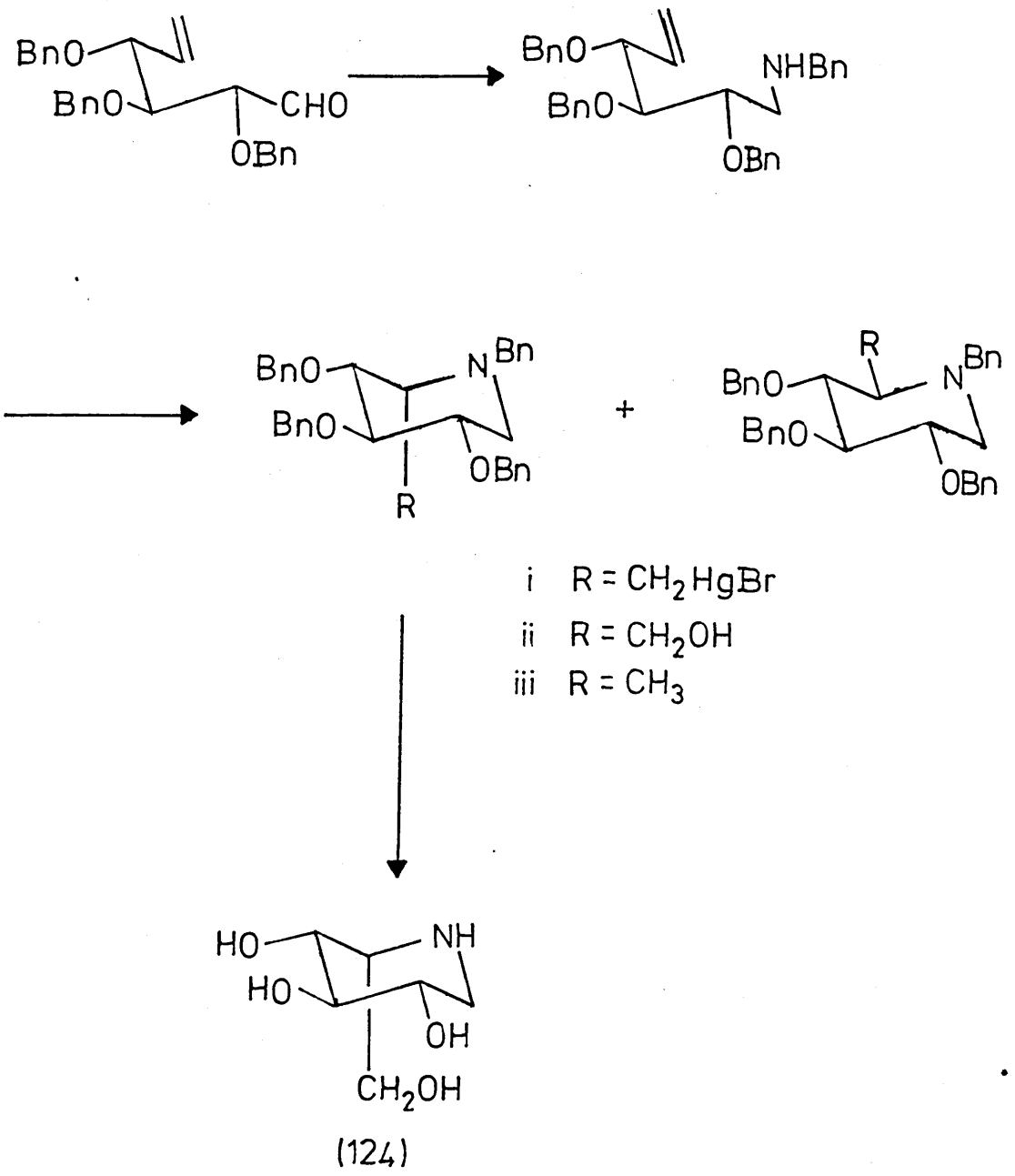
Scheme 25.

The reductive-oxygenation technique has been also used by Graber and coworkers[94] in the preparation of prostacyclin systems, as shown in scheme 26.



Scheme 26.

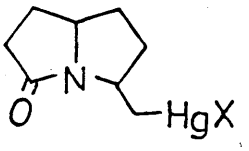
Ganem and coworkers[96] also used this reductive-oxygenation technique in their preparation of cyclic aminoalditols (124) as shown in scheme 27.



(124)

Scheme 27.

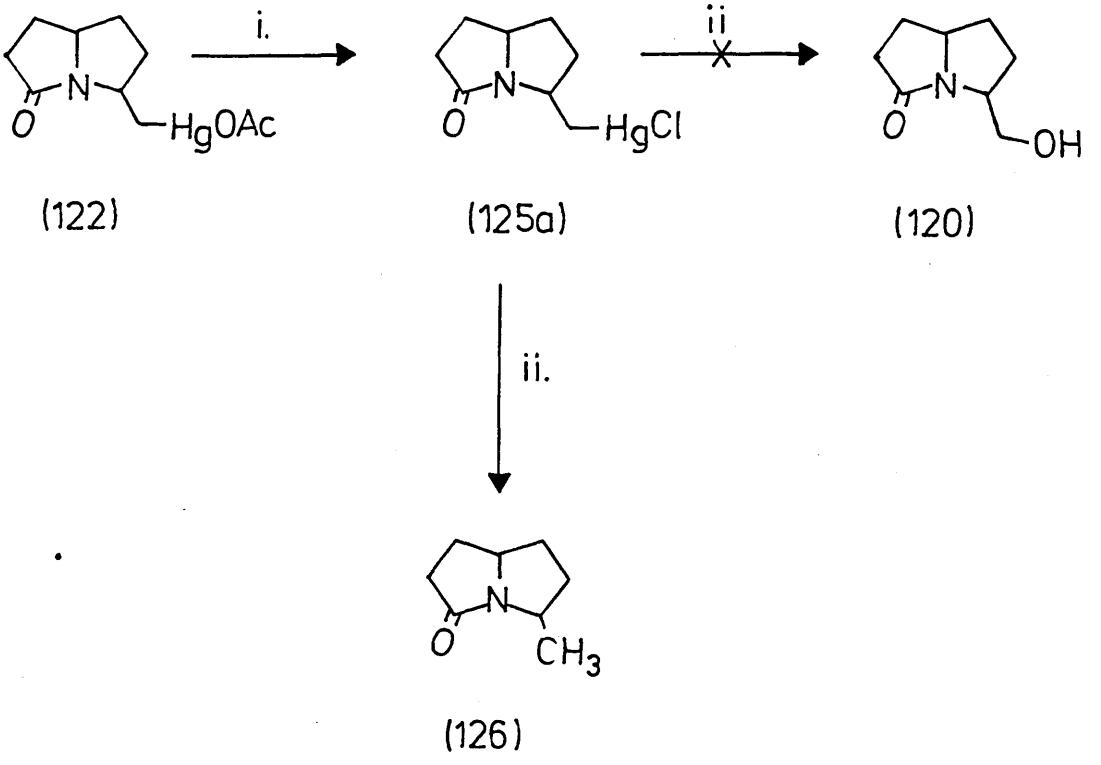
Using the reductive-oxygenation technique on (125a) could give the alcohol (120).



(125a) X = Cl

(125b) X = I

The mercurial acetate (122) was converted to the mercurial chloride (125a) using saturated sodium chloride in methanol[94] (scheme 28)



(122) (125a) (120)

(126)

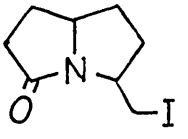
i. NaCl , CH_3OH ; ii. $NaBH_4$, DMF , O_2 .

Scheme 28.

Treatment of (125a) with sodium borohydride-dimethylformamide-oxygen[94,96] unfortunately failed to give the alcohol (120). The overreduced product (126) was isolated, as shown in scheme 28. Ganem[96] reported that the overreduced by-product could be minimised by presaturating the combination of sodium borohydride-dimethylformamide with oxygen, then adding a concentrated DMF solution of the mercurial salt while maintaining a vigorous flow of oxygen. Repetition using this modified approach still only gave the overreduced product (126). Failure to obtain the alcohol (120) in this manner directed us to pursue an alternative strategy.

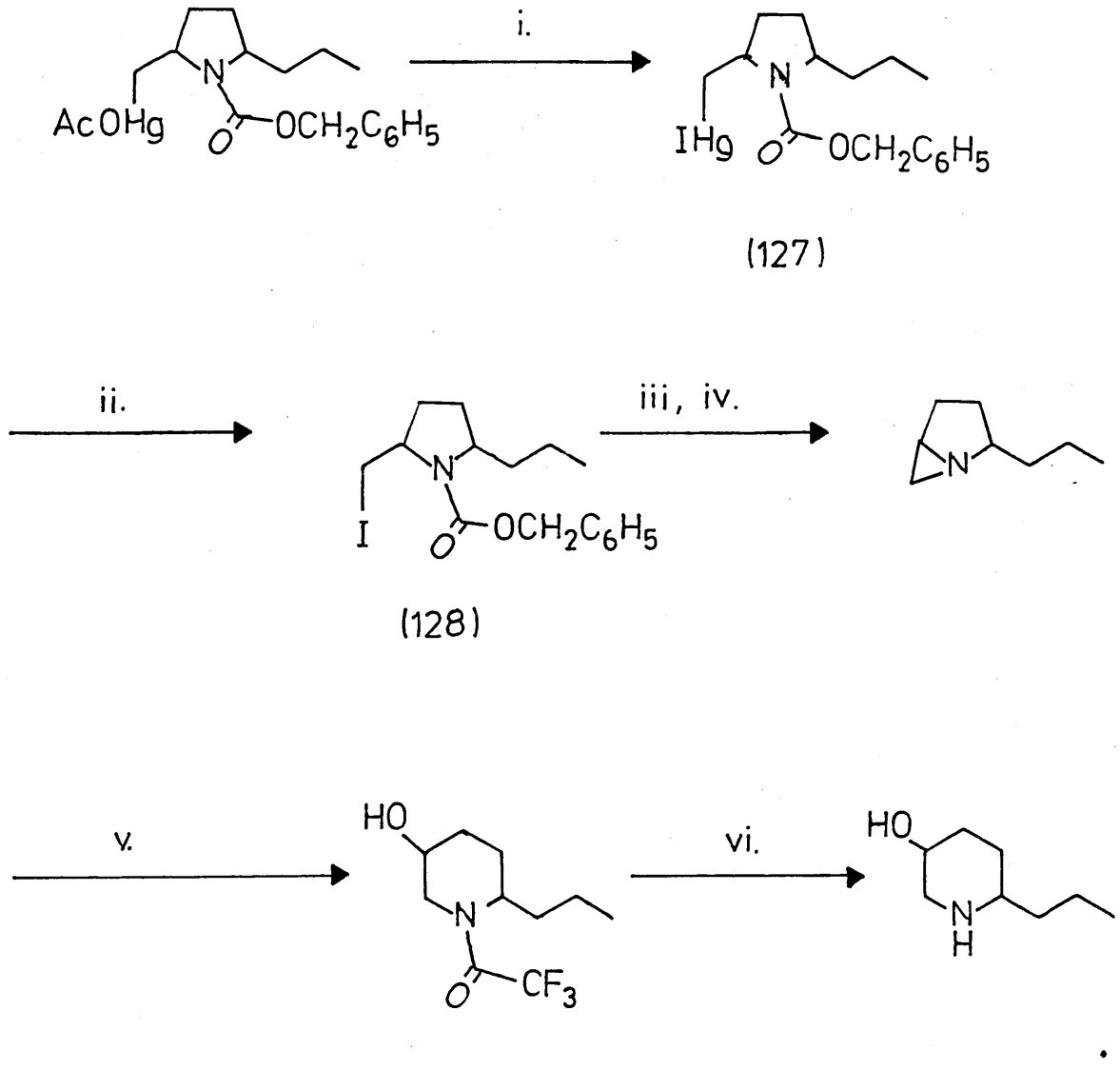
Harding and coworkers[97] described the conversion of mercury salts to iodides during work on the synthesis of 3-hydroxypiperidines as outlined in scheme 29.

The iodide (128) was obtained by treatment of the mercury halide (127) with iodine in dichloromethane. The treatment of the halide (125b) using these conditions should give the iodide (121).



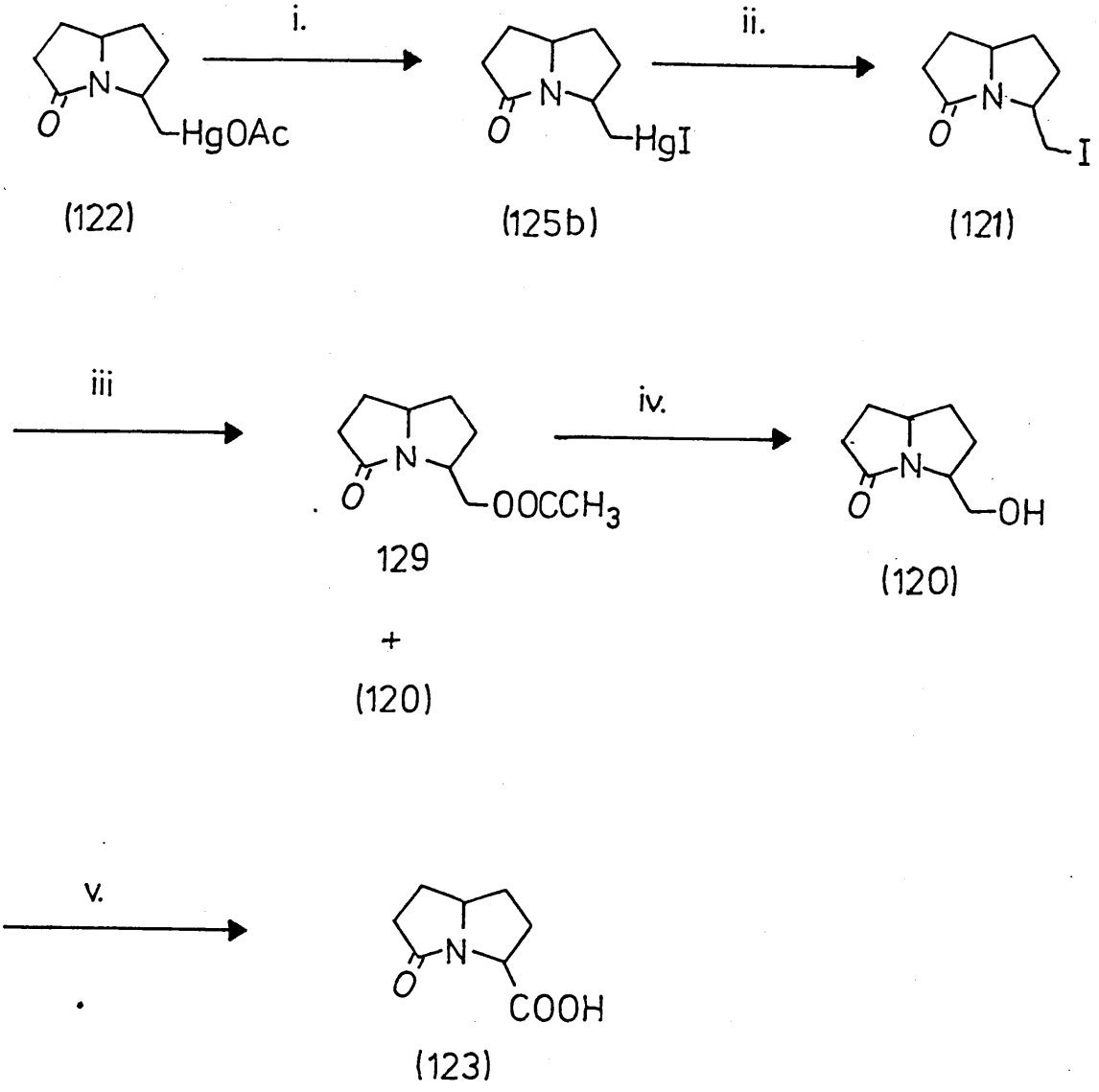
(121)

The mercurial iodide (125b) was obtained by treatment of (122) with potassium iodide. Treatment of (125b) using iodine in dichloromethane successfully gave the iodide (121), as shown in scheme 30, in 25% yield based on (94)



i. CH_3COCH_3 , KI ; ii. I_2 , CH_2Cl_2 ; iii. glacial CH_3COOH , HBr ; iv. H_2O , Na_2CO_3 ; v. CF_3COOH , 12-16h ; vi. K_2CO_3 ; CH_3OH.

Scheme 29.

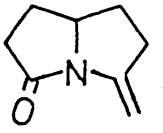


i. KI, CH_3COCH_3 ; ii. I_2, CH_2Cl_2 ; iii. $Hg(OAc)_2$, glacial CH_3COOH;
iv. $NaOH$; v. CrO_3 - c. H_2SO_4, CH_3COCH_3.

Scheme 30.

The next step in the reaction sequence involved conversion of the iodide (121) to the alcohol (12) (scheme 30). Treatment of (121) with the nucleophile, $^{\ominus}OH$, should give the alcohol (120). However,

we considered that the elimination product (130) could be obtained as well as the alcohol (121).

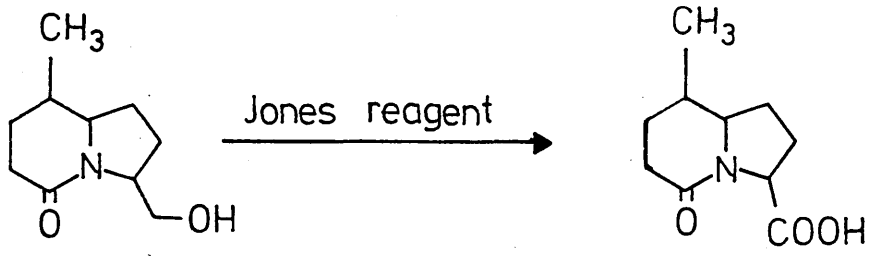


(130)

Therefore we decided to convert the iodide (121) to the acetate (129) which was carried out using mercuric acetate and glacial acetic acid,[98] (129) isolated in 8% yield. Surprisingly this process also gave the alcohol (120) (39%). A possible explanation for this observation is that the work up of the acetate (129) involved treatment with saturated sodium carbonate and this may have caused hydrolysis of (129) giving (120). Confirmation that the acetate (129) was obtained was seen in the ^1H nmr spectrum which showed a two proton doublet at 4.20δ attributable to CH_2O_2CR and a singlet at 2.0δ attributable to CH_3CO_2R. Evidence that the alcohol (120) was obtained was seen in the ^1H nmr and IR spectra which were identical with those obtained from earlier investigations (scheme 24). Further confirmation that the alcohol was present was seen by addition of D_2O which caused the signal at 5.2δ to disappear. Treatment of (129) with 10% sodium hydroxide solution also gave the alcohol (120).

The next step in the reaction sequence involved oxidation of the alcohol (120) to the acid (123). Oxidation was performed

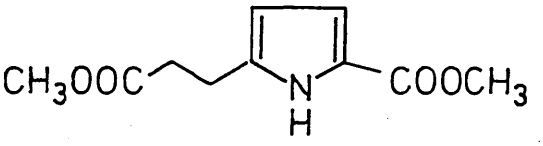
using Jones reagent, as a similar type of alcohol (88) was oxidised to the acid (131).



(88) (131)

Oxidation of (121) using Jones reagent failed to give the acid (124), since no material could be isolated from the organic extract. Several attempts at Jones oxidation of (120) gave similar results as mentioned earlier. The poor overall yield of (120) (40%) and a lack of time prevented the use of alternative oxidising agents towards the oxidation of (120) to (123) and subsequent alkylation studies upon (123) being investigated.

While our work was in progress a report by Turner[99] described the synthesis of (123), during his study towards ACE inhibitors, via the reduction of a pyrrole intermediate (132)[100] as outlined in scheme 31.



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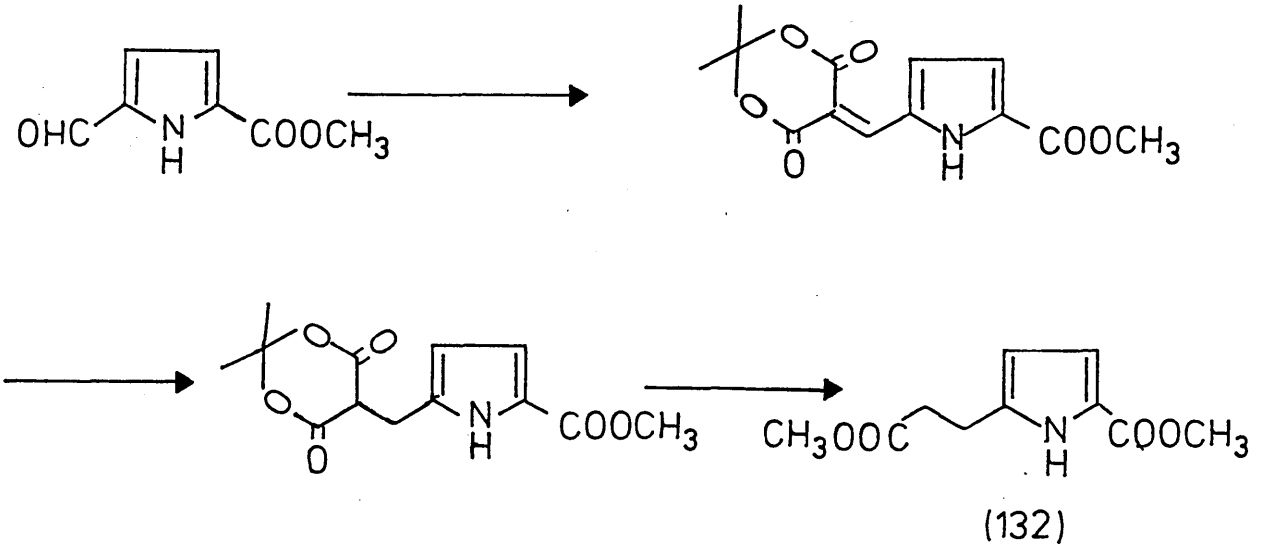

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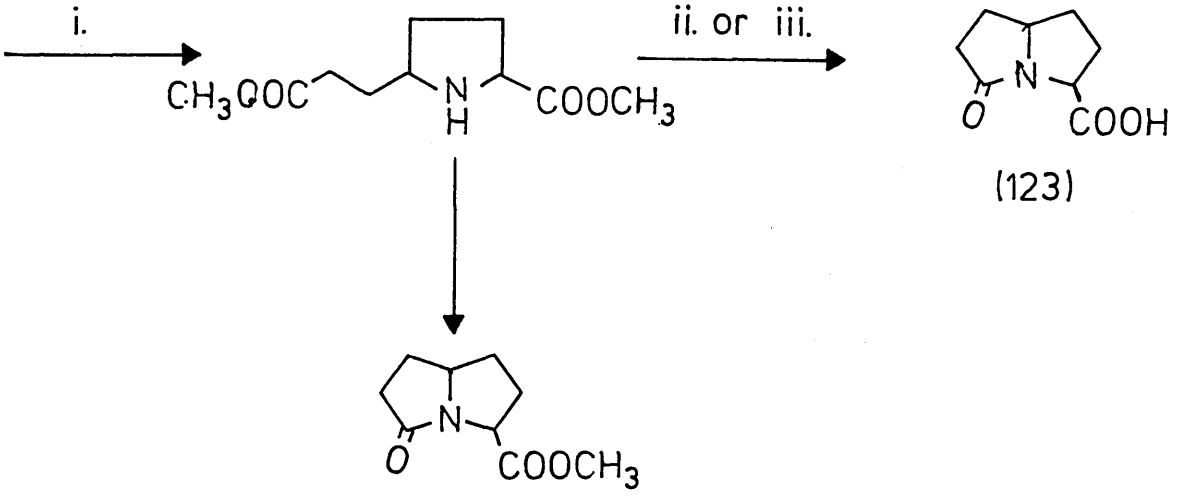


(123)

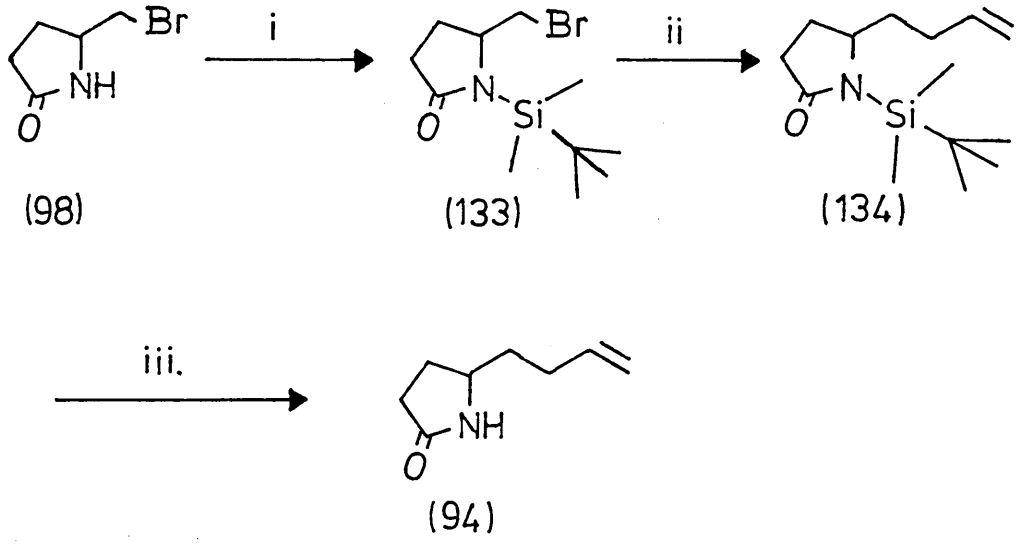
i. glacial CH_3COOH, 5% Rhodium on alumina, 60psi, H_2;
ii. glacial CH_3COOH, $C_6H_5CH_3$, Δ; iii. glacial CH_3COOH, Δ.

Scheme 31.

An advantage of Turners approach to (123) was that both isomers of the acid (123) could be obtained. A disadvantage was the use of expensive rhodium catalyst for the reduction of the pyrrole system (132).

2.2 Future work

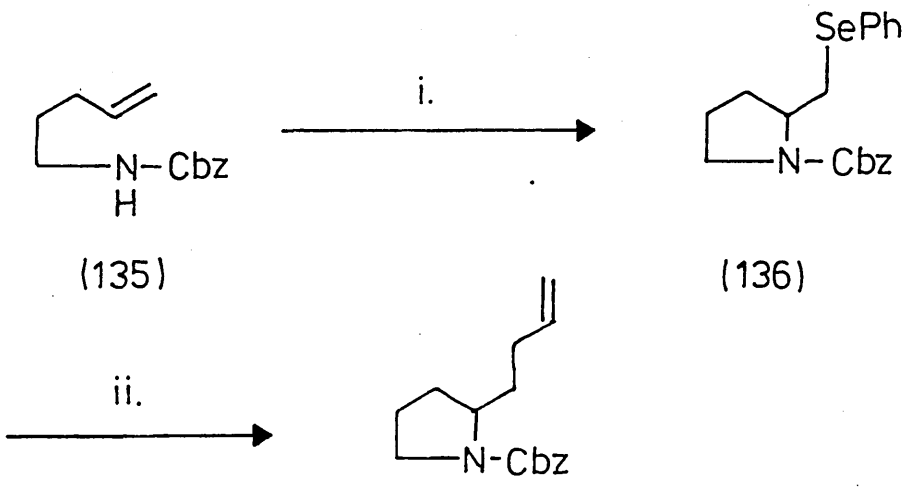
Several aspects of this work would benefit further study, firstly the synthesis of the alkene lactam (94) via the use of allyltributylstannane[101] (scheme 19). We suggest that protection of the secondary amide (98) with a suitable species such as tert-butyldimethylsilyl group to a tertiary amide and subsequent treatment with allyltributylstannane and finally deprotection should substantially improve the yield of the alkene lactam (94), as outlined in scheme 32.



i. TBDMS-Cl , $(CH_3CH_2)_3N$; ii. $(C_4H_9)_3SnCH_2CH{=}CH_2$, AIBN, $C_6H_5CH_3$; $(n\text{-}C_4H_9)_4N^{\oplus}F^{\ominus}$ or glacial CH_3COOH, THF, H_2O.

Scheme 32.

The reason for this suggestion is that Danishefsky and coworkers[102] reported the introduction of an allyl moiety using allyltributylstannane on a similar type of nitrogen system as outlined in scheme 33.



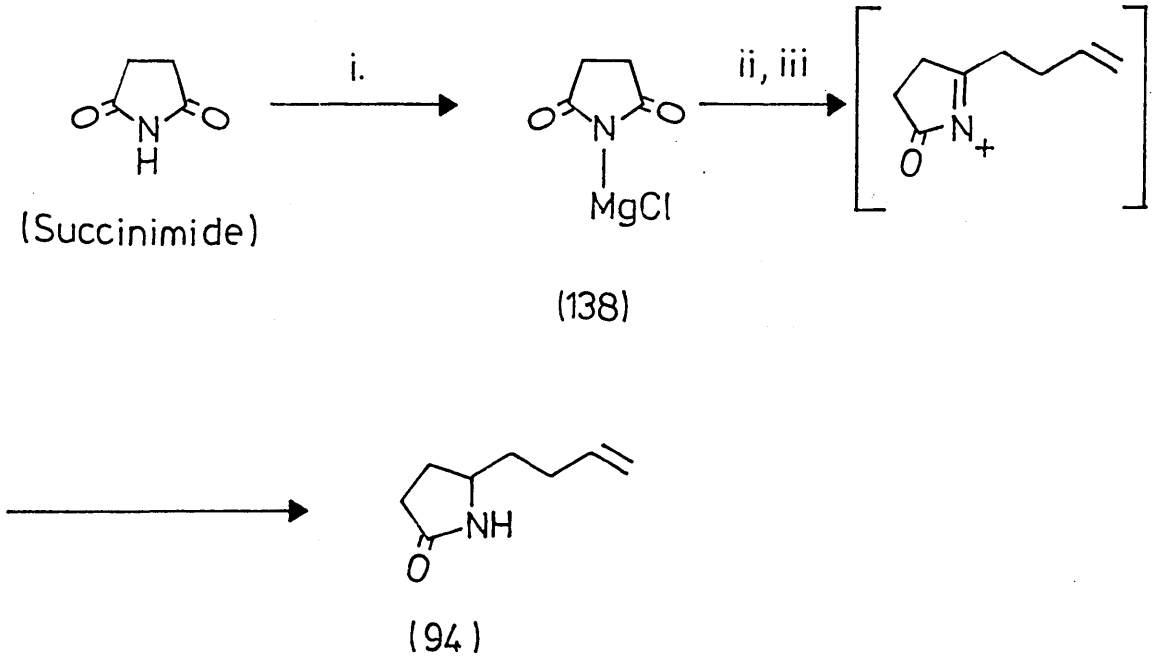
i. N-PSP, CH_2Cl_2 ; ii. $(C_4H_9)_3SnCH_2CH=CH_2$, AIBN, $C_6H_5CH_3$.

Scheme 33.

The allylated product (137) was obtained in 73% yield.

While our work was in progress on the synthesis of (94), W.N.Speckamp[103] reported a one-pot procedure for the preparation of (94). It involved the conversion of succinimide into the magnesium salt (138) (scheme 34), using methyl magnesium chloride in THF and

then treatment of (138) with two equivalents of the Grignard reagent derived from 4-bromo-1-butene. To the resultant mixture was added sodium cyanoborohydride (1 equiv.) followed by hydrochloric acid. The alkene lactam (91) was isolated in 53% yield based on succinimide.



i. CH_3MgCl, THF ; ii. Mg, $CH_2=CHCH_2CH_2Br$, THF , $NaBH_3CN$, 6N HCl.

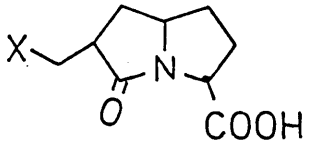
Scheme 34.

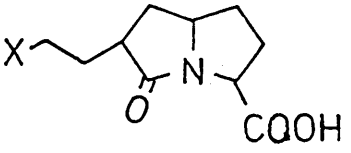
The advantage of using Speckamps procedure compared to our methods investigated is (i) the synthesis is a one-pot process (ii) the use of commercially available starting materials.

Secondly, the oxidation of the alcohol (120) to the acid (123)

could be investigated using other oxidising agents.

Upon obtaining the acid (123), alkylation using bromomethyl thioacetate[52] and/or bromoethyl thioacetate[104] using two equivalents of lithium diisopropylamide (LDA) should give the adducts (51a) and/or (53a).





(51a) X=AcS

(51) X=HS

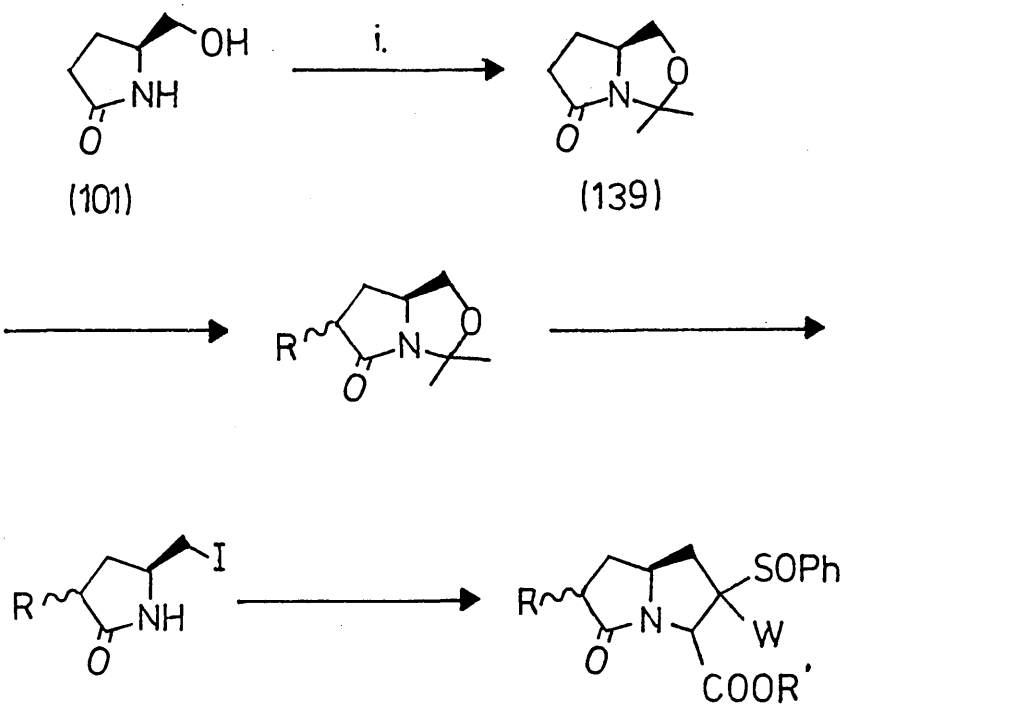
(53a) X=AcS

(53) X=HS

Subsequent hydrolysis should reveal the final target systems (51) and/or (53).

3. Introduction

During our work on the synthesis of azabicyclo[3.3.0]octanes (chapter 2) we came across a vast number of potential methods towards the preparation of these systems. One recent method that drew our attention was that described by J.E.Munroe and coworkers,[105] as illustrated in scheme 35.

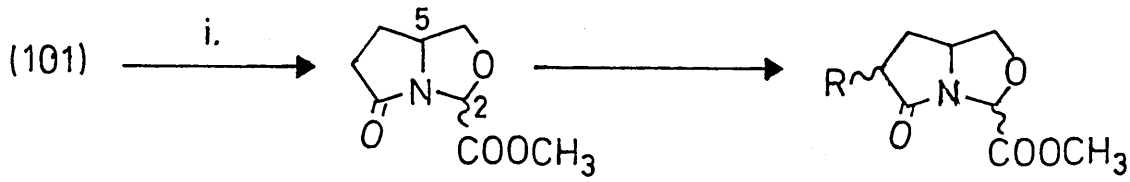


i. $(CH_3O)_2C(CH_3)_2$, $C_6H_5CH_3$, p-TsOH.

Scheme 35.

In Munroe's communication our attention was focussed on the 3-oxa-1-azabicyclo[3.3.0]octane (acetonide) (139), which was prepared by treatment of 5-hydroxymethyl -2-pyrrolidinone (101) with 2,2-dimethoxypropane and catalytic p-toluenesulphonic acid.

We envisaged that treatment of the alcohol (101) with methyl 2,2-dimethoxyacetate should give the acetonide (140), (scheme 36), containing a potential carboxylic acid functionality at C-2 and further elaboration of (140) would permit access to further novel analogues of 3-oxa-1-azabicyclo[3.3.0]octanes, as outlined in scheme 36.



(140)

(141) R = CH_2COOCH_3

(142) R = $CH_2CH{=}CH_2$

i. $(CH_3O)_2CHCO_2CH_3$, $C_6H_5CH_3$, pTsOH .

Scheme 36.

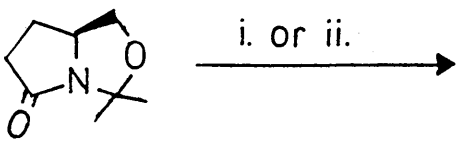
3.1 Discussion and results

3.1.1 8-Oxo-3-oxa-1-azabicyclo[3.3.0]octanes

3.1.1.1 Deprotection-reprotection approach

Our attempts at preparing (140), treating (101) with methyl 2,2-dimethoxy-acetate was unsuccessful, only starting materials being recovered. One possible explanation for this was the insolubility of (101) in the solvent, toluene, being used. After various attempts at preparing (140) failed an alternative strategy towards the synthesis of 3-oxa-1-azabicyclo[3.3.0]octanes was considered, as outlined in scheme 37. The approach involved firstly, alkylation of (139) with a suitable reagent, followed by deprotection of the alkylated product to give the substituted pyrrolidinone and finally reprotection of the substituted pyrrolidinone with 2,2-dimethoxyacetate to give the desired 3-oxa-1-azabicyclo[3.3.0]octane.

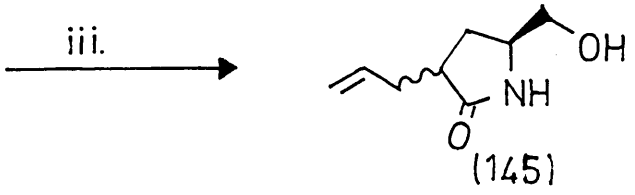
The anion of (139) (generated with lithium diisopropylamide) was initially reacted with methyl bromoacetate (this would give a potential carboxylic acid functionality at C-7) but the reaction gave a complex mixture of products which were not investigated further. Therefore we chose a simpler alkylating species, allyl bromide, the reason being that the allyl moiety can be easily observed on thin layer chromatography (tlc) and can also be easily distinguished on ^{1}H nmr spectra. Also the carbon-carbon double bond can be subjected to ozonlysis[106] followed by oxidative work up to give the carboxylic acid, thereby giving an acid functionality at C-7. The anion of (139) reacted smoothly with allyl bromide to give the allyl acetonide (144) in 87% yield after



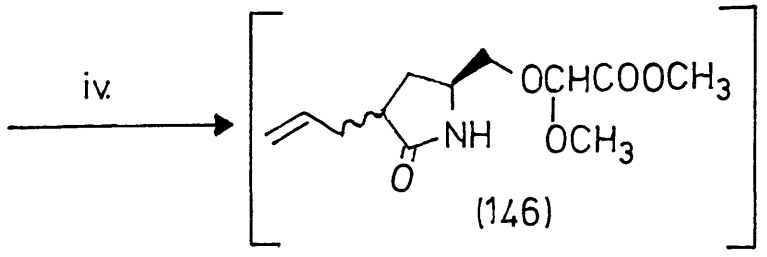
(139)

(143) $R=CH_2COOCH_3$

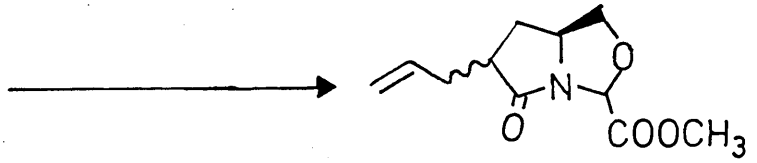
(144) $R=CH_2CH=CH_2$



(145)



(146)

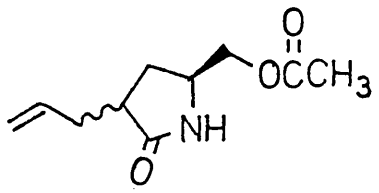


(142)

i. LDA, $BrCH_2COOCH_3$; ii. LDA, $CH_2=CHCH_2Br$; iii. glacial CH_3COOH, THF, H_2O ; iv. $(CH_3O)_2CHCOOCH_3$, $C_6H_5CH_3$, p-TsOH.

Scheme 37.

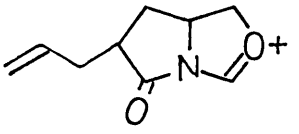
chromatography as a mixture of diastereoisomers. Evidence for (144) was seen in the ^1H nmr spectrum by the appearance of a series of multiplets at 4.70-6.30δ attributable to CH_2= CHR. IR spectra also showed an absorption at 3060cm^{-1} due to olefinic functionality. The diastereomeric mixture of (144) was transformed to the substituted alcohol (145) (40%) using glacial acetic acid and tetrahydrofuran -water mixture.[107] Although apparently homogeneous (tlc) (145) was a mixture of diastereoisomers. Also a small trace of the acetate (147) was obtained from this reaction.



(147)

Confirmation of the structure of (147) was seen in the ^1H nmr spectrum by the prescence of a 3 proton singlet of 2.08δ attributable to CH_3CO_2R and a multiplet at 3.8-4.2δ due to CH_2O. Further evedence for (147) was obtained from the mass spectrum by the dominance of the base peak m/z 124 corresponding to the loss of $CH_2CO_2CH_3$ from the molecular ion. Ester (147) is presumably formed by reaction of the alcohol (145) with acetic acid in the mixture. Treatment of (145) with methyl 2,2-dimethoxy-acetate, catalytic p-toluenesulphonic acid and toluene in a Dean-Stark trap apparatus, trapped toluene/methanol being constantly removed, gave (142) (6%) together with the intermediate (146) (16%). The alcohol (145) was

also observed to be much more soluble in toluene than the alcohol (101). Evidence for (142) was based on the ^1H nmr spectrum which showed the absence of a broad singlet at 7.2δ attributable to NH. This evidence was backed up by IR spectrum which showed a lack of strong absorption at 3210cm^{-1} due to NH of secondary amides or OH of alcohols. Further confirmation for (142) was based on the mass spectrum by dominance of the peak m/z 166, attributable to the ion (148), corresponding to the loss of CO_2CH_3 from the molecular ion.



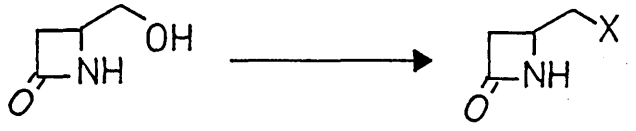
(148)

The poor yield of (142) could be attributed to only partial reaction since the remaining material isolated was identified to be the partially cyclised system (146) and not the starting material (145). Confirmation that (146) was obtained was seen in the ^1H nmr spectrum by the presence of a broad singlet at 7.2δ due to NH of the secondary amide and the absorption at 3210cm^{-1} in the ir spectrum. Conclusive evidence was obtained from the mass spectrum by the molecular ion peak m/z 257.

Subjecting (146) to treatment with catalytic p-toluenesulphonic acid gave no improved yield of (142). Due to the extremely low yield of (142) obtained it was decided to examine other routes towards the synthesis of 3-oxa-1-azabicyclo[3.3.0]octanes.

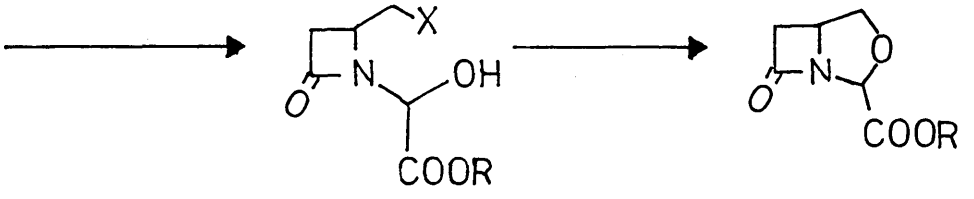
3.1.1.2 Hydroxy alkylation approach

In this phase of study advantage was taken of a report by R.J.Stoodley and coworkers[108] describing a synthesis of analogues of β- lactam antibiotics, isoclavam-3-carboxylates, as illustrated in scheme 38.



(149)

(150) X=$OSO_2C_6H_4CH_3$
(150a) X=I



(151a) X=$OSO_2C_6H_4CH_3$
(151b) X=I

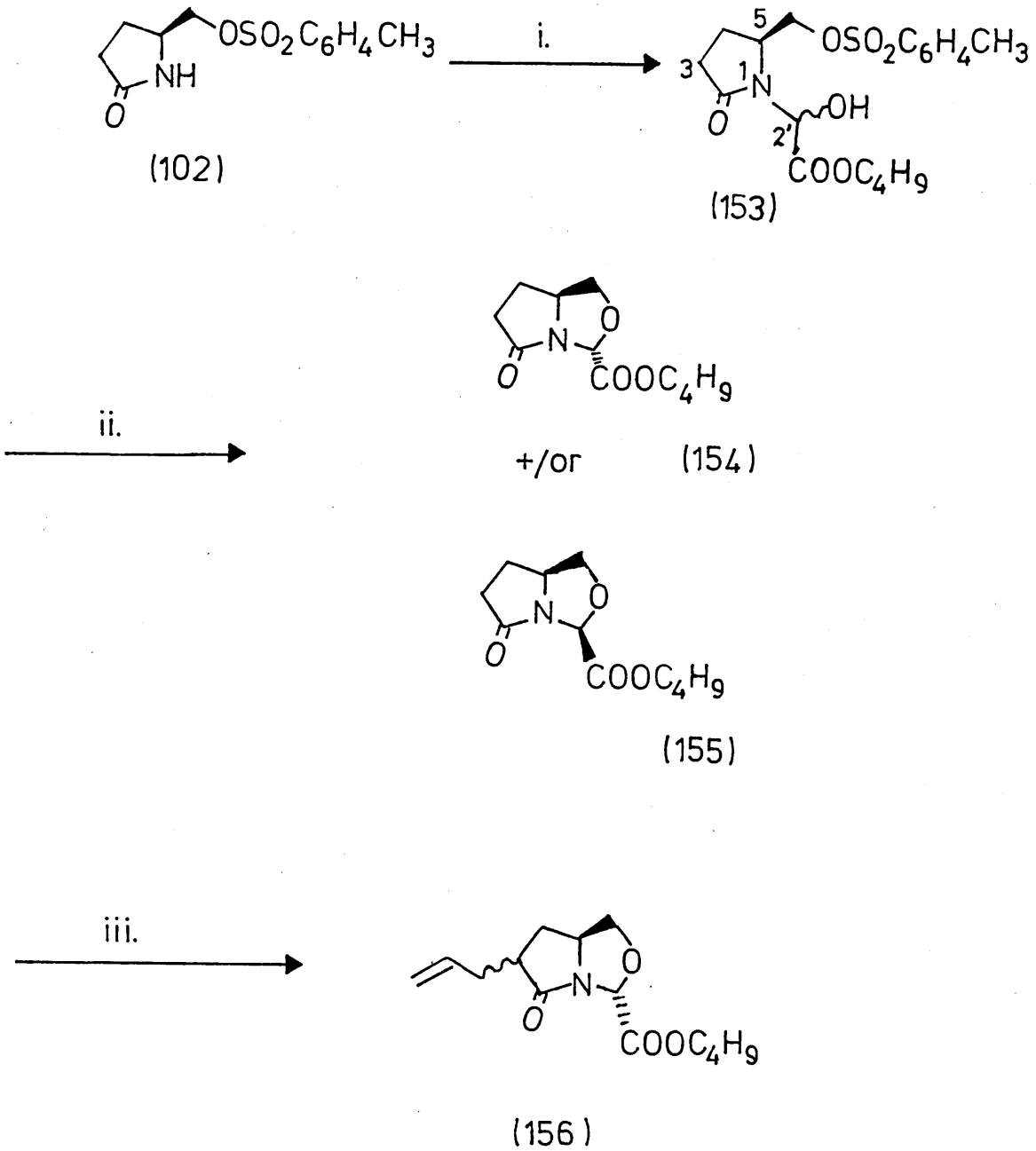
(152)

R=alkyl, benzyl.

Scheme 38.

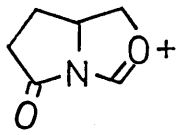
Stoodley's approach towards isoclavam-3-carboxylates of the type (152) involved final closure of the 3,4 bond. This approach defined the use of azetidinones of the type (151) (X = leaving group) and such precursors were available from compounds of the type (150) (X = leaving group by a hydroxy alkylation reaction involving glyoxylic acid esters.[109] Consideration of Stoodley's procedure suggested that we could use similar chemistry to obtain our 3-oxa-1-azabicyclo[3.3.0]octanes, as outlined in scheme 39.

Triethylamine treatment of a solution of the tosylate (102) and butyl glyoxylate, the latter generated from commercially available dibutyl-L-tartrate with lead tetraacetate,[110] in THF, gave the carbinolamide (153), isolated in 81% yield. Although apparently homogeneous the ^{1}H nmr spectrum indicated that (153) was a mixture of diastereoisomers by the presence of two doublets at 5.38 and 5.65δ attributable to the single protons at C-2' of the diastereoisomers of (153). In the presence of sodium hydride in THF the carbinolamide (153) underwent cyclisation to give (154) or [155]. Evidence for (154) or [155] was seen again in the ^{1}H nmr spectrum by the absence of the pair of doublets at 7.38δ and 7.8δ attributable to aromatic protons and also the absence of the singlet at 2.46δ due to CH_3Ar. The appearance of a sharp singlet at 5.73δ due to the proton at C-2 gave confirmation that (154) or [155] had been obtained. Accurate mass measurement of the $M^+ + 1$ ion at m/z 228 and the base peak at m/z 126 (the value corresponding to loss of $CO_2(CH_2)_3CH_3$ and attributable to the ion (157)) gave conclusive proof that the cyclic system had been obtained.



i. $(CH_3CH_2)_3N$, $OCHCOOC_4H_9$, THF ; ii. NaH , THF ;
iii. LDA , $CH_2=CHCH_2Br$.

Scheme 39.

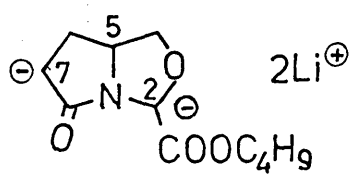


(157)

Closer examination of the ^1H nmr spectrum of the 3-oxa-1-azabicyclo-[3.3.0]octane obtained (154) or [155] suggested that only a single diastereoisomer was isolated, starting from the carbinolamide (153) as a mixture of diastereoisomers. This strongly suggests that the 3-oxa-1-azabicyclo[3.3.0]octane possesses the stereostructure (154). The cis arrangement of the 2-carboxylic acid moiety and 5-hydrogen represents the thermodynamically favoured situation in related systems.[111] Presumably a mixture of (154) and (155) is initially produced in the cyclisation reaction, but under the reaction conditions (155) is isomerized to (154).

The next step in the reaction sequence, involved treatment of (154) with LDA (1 equiv) followed by allyl bromide and produced an oil in 7% yield.[112] On the basis of the ^1H nmr spectrum the product was considered to be (156), although the spectrum could not be fully interpreted. The series of multiplets at 4.85 - 6.0δ and the singlet at 5.5δ were assigned to the CH_2=CHR moiety and the single proton at C-2 respectively. The extremely poor yield of (156) suggested that other side reactions were taking place as no starting material was recovered. One possible suggestion for the

side reactions which might be occuring is that upon treatment of (154) with LDA the abstraction of the proton at C-7 (kinetically favoured) occurs and also the proton at C-2. This may explain the mixture of products. Treatment of (154) with two equivalents of LDA should give the dianion (158), which might be expected to react with electrophiles at the least hindered C-7 centre.

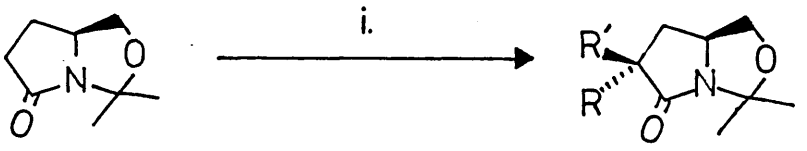


(158)

However, treatment of the dianion (158) with allyl bromide gave a complex mixture of products. The complex mixture was separated by column chromatography but none of the products isolated gave a ^{1}H nmr spectrum which resembled that of the desired product.

Alternatively, we decided to examine the synthesis of (156) as outlined in scheme 40.

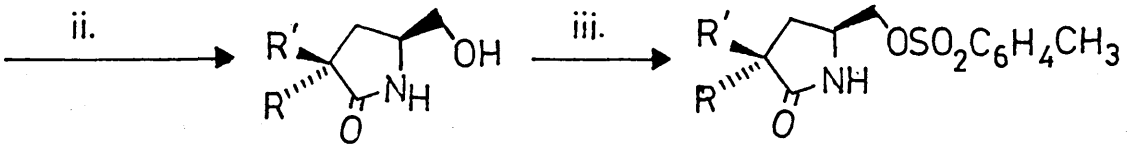
Treatment of (139) with LDA, allyl bromide gave the alkylated products (144a) and (144b) in 87% total yield. Tlc revealed that the alkylated material was a mixture of diastereoisomers. ^{13}C nmr indicated that a 2:1 mixture of diastereoisomers had been produced. In order to minimise the number of diastereoisomers of the final product, we decided to separate the diastereoisomers (144a) and (144b).



(139)

(144a) R = H , R′ = $CH_2CH=CH_2$.

(144b) R = $CH_2CH=CH_2$, R′ = H .

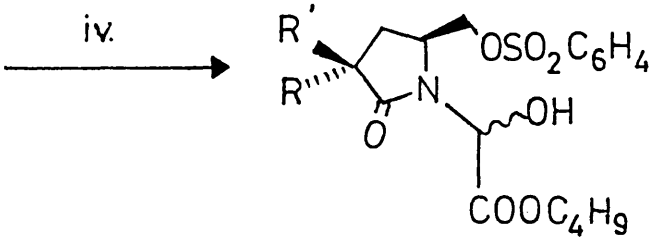


(145a) R = H , R′ = $CH_2CH=CH_2$.

(145b) R = $CH_2CH=CH_2$, R′ = H .

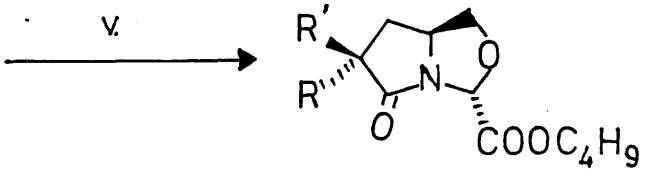
(159a) R = H , R′ = $CH_2CH=CH_2$.

(159b) R = $CH_2CH=CH_2$, R′ = H .



(160a) R = H , R′ = $CH_2CH=CH_2$.

(160b) R = $CH_2CH=CH_2$, R′ = H .



(156a) R = H , R′ = $CH_2CH=CH_2$

(156b) R = $CH_2CH=CH_2$, R′ = H

i. LDA, $CH_2=CHCH_2Br$; ii. glacial CH_3COOH, THF, H_2O ; iii. pyridine, p-$CH_3C_6H_4SO_2Cl$; iv. $(CH_3CH_2)_3N$, $OCHCOOC_4H_9$; v. NaH, THF.

Scheme 40.

The first eluted material, Rf 0.42, was isolated as a syrup in 63% yield. The second eluted material, Rf 0.31, was also isolated as a syrup in 23% yield. The weight ratio of the two individual diastereoisomers isolated confirmed ^{13}C nmr evidence that a 2:1 mixture of diastereoisomers was obtained. Separation of the two possible diastereoisomers would allow work to be carried on independently on each individual diastereoisomer from this point. Treatment of (144a) and (144b) with glacial acetic acid in the THF-water[107] to reverse the acetonide formation, provided the substituted alcohols (145a), obtained as a crystalline solid in 23% yield and (145b) as a viscous oil (20%).

At this point we decided to assign the relative stereochemistry of (145a) and (145b) with the aid of 200MHz ^{1}H nmr spectroscopy and a 2D-COSY spectrum.[113] Thus, the major component obtained (145a) was assigned the cis stereochemistry. The evidence for this was primarily based on the fairly large coupling constant of both C-4 protons to the C-3 proton (Figure 6) suggesting dihedral angles of 0-30° or 150-180°. Unfortunately the ring can be distorted such that cis or trans isomers can both give the observed couplings. However, (145a) is most likely the cis isomer as this requires less distortion. Also the chemical shifts of (145a) favour the cis stereochemistry. Both C-4 proton signals are well separated (1.58 and 2.38)and this we suggest is more likely in the cis system where one proton has two adjacent CH_2 substituents and the other has none (Figure 7).

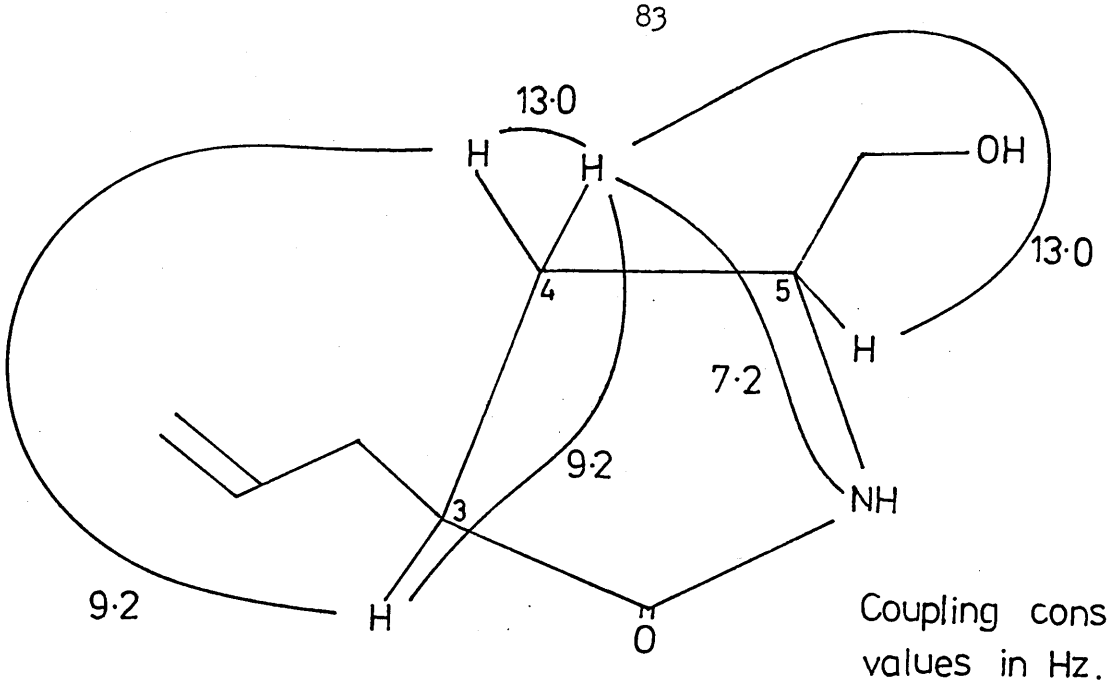
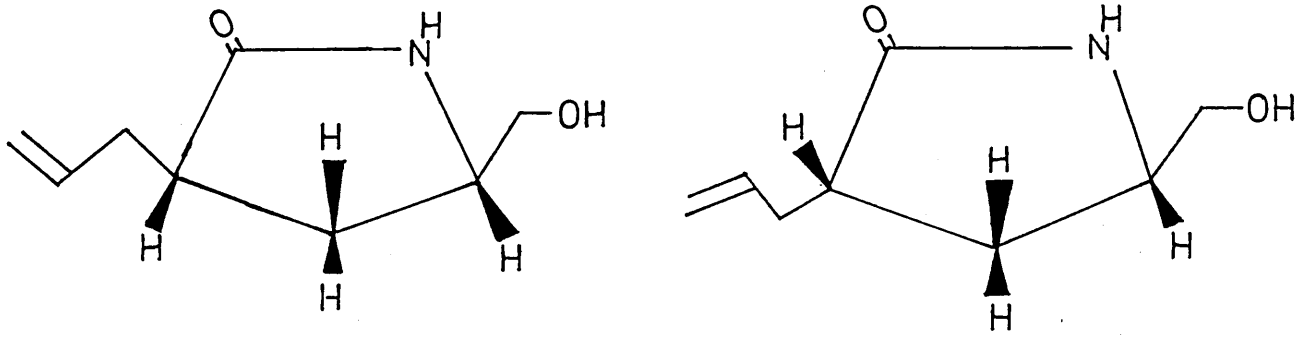


Figure 6.



(145a) - CIS

(145b) - TRANS

Figure 7.

Therefore, (145b) was assigned the trans stereochemistry. Evidence for this was based on the fact that the chemical shifts of both C-4 protons were very similar indicating that both protons have an adjacent CH_2 substituent. A spectrum of (145b) in CD_3OD showed only one clear signal (1.94 δ), but we suspect the other signal is fairly close as the 1.94 δ multiplet leans strongly to the left. In the $CDCl_3$ spectrum the two C-4 protons were observed to have identical chemical shifts giving one signal at 1.94 δ. Therefore in conclusion, based on the above evidence, (145a), H-4 of which gives the high field signal (1.5 δ) is the cis isomer (Figure 8) and (145b) the trans isomer (Figure 9).

Due to the low yield of the initial starting material (144b) we discontinued any further progress towards obtaining the final target (156b) from (145b).

p-Toluenesulphonyl chloride treatment of a solution of (145a) in pyridine gave the allyl tosylate (159a) (84%). Hydroxyalkylation with butyl glyoxylate gave the substituted carbinolamide (160a) in 91% yield as a mixture of diastereoisomers (tlc and nmr spectroscopy). Sodium hydride converted (160a) to (156a) in 45% yield. Evidence for (156a) was seen in the ^1H nmr spectrum which was similar to that of (154), except for the additional series of multiplets 4.9-6.2 δ attributable to CH_2= CHR. The low yield of (156a) was attributed to an incomplete reaction since ca 44% of the starting carbinolamide (160a) was recovered. The material isolated was apparently homogeneous by tlc and nmr spectroscopy suggesting that only a single diastereoisomer was isolated,

Figure 8 : ^1H NMR spectrum of (145a) (200MHz, CD_3OD)

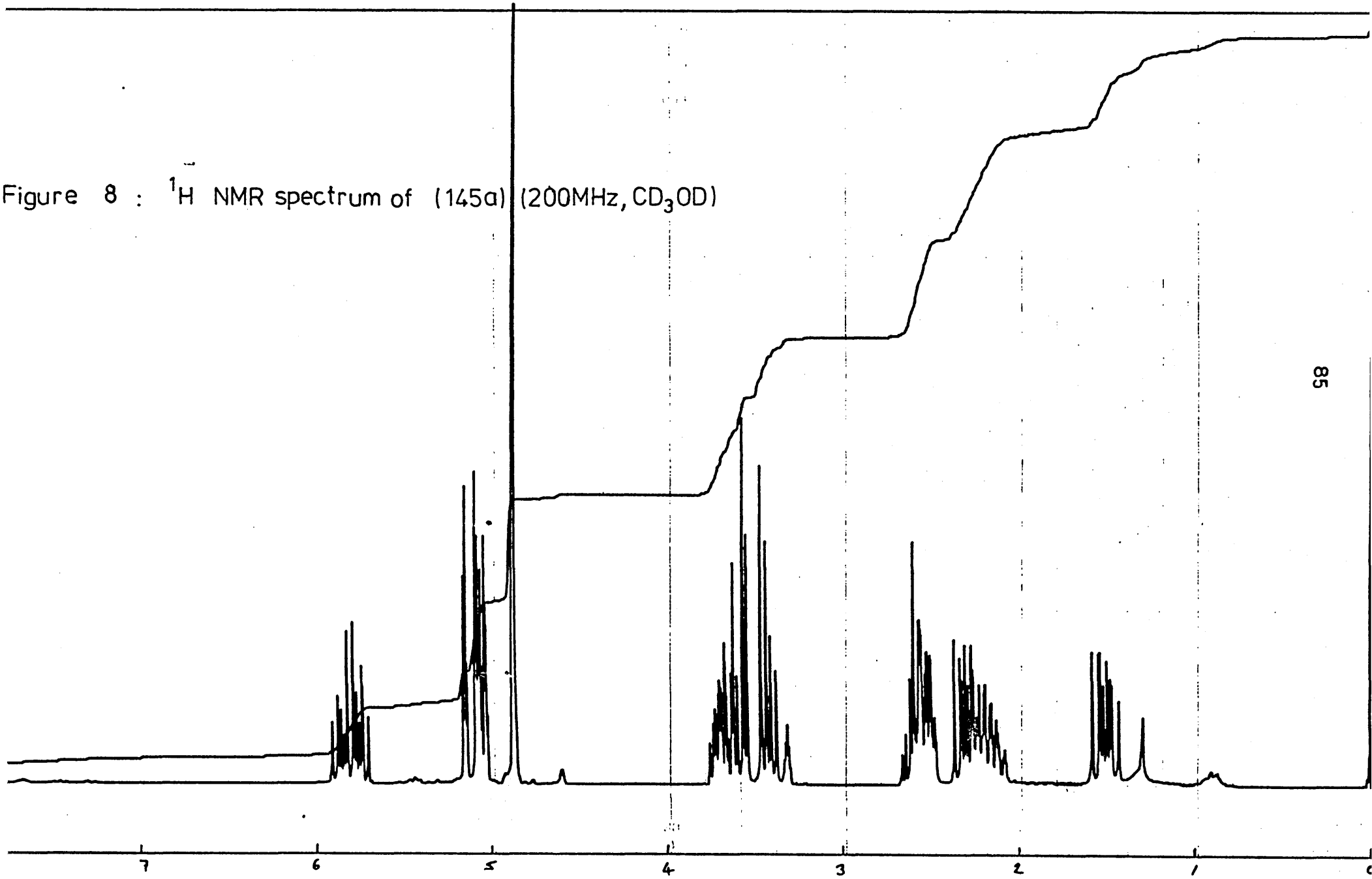
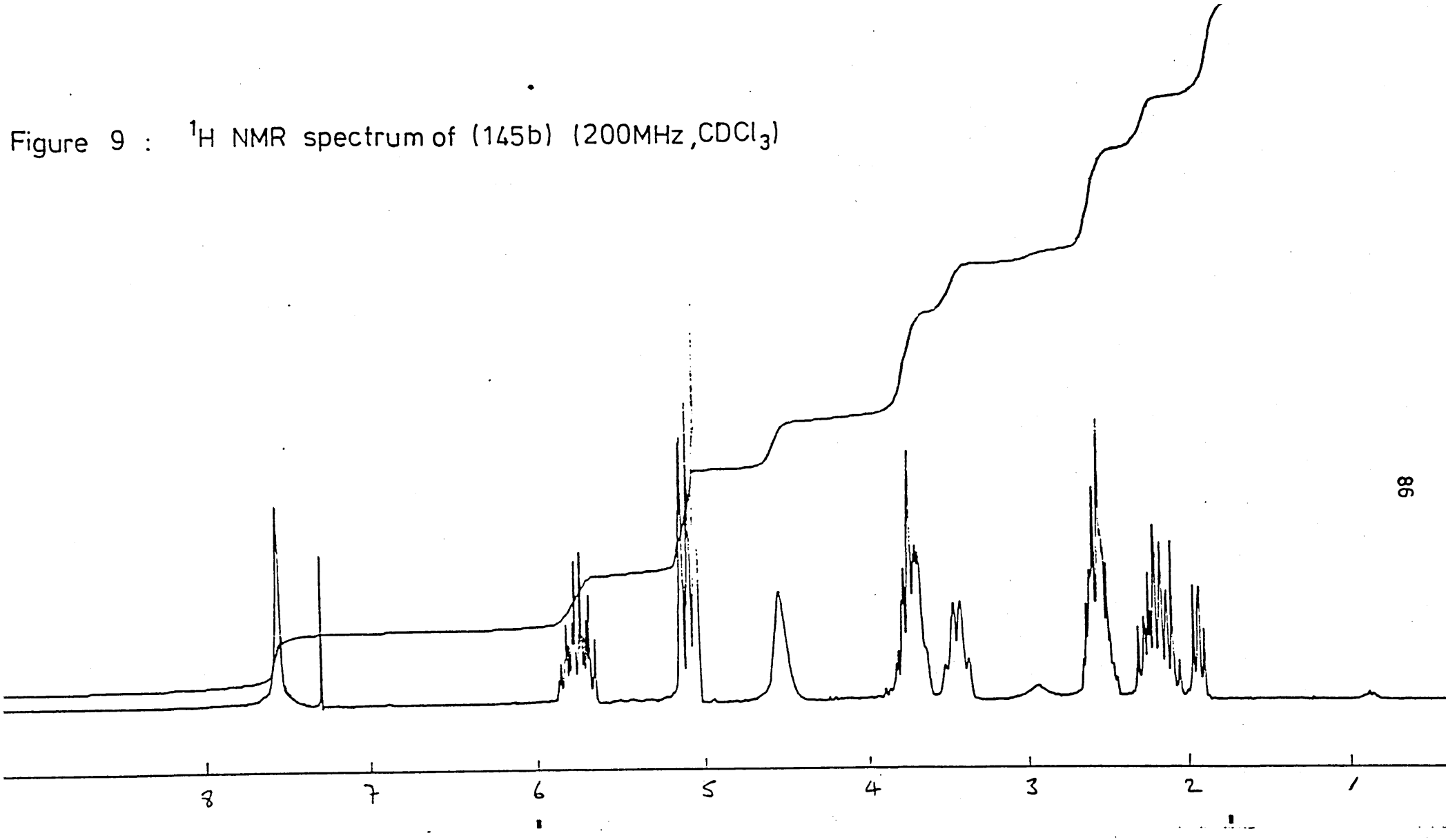
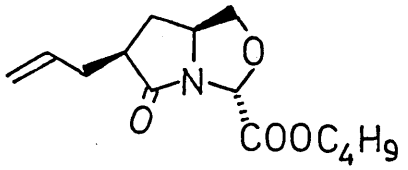


Figure 9 : ^{1}H NMR spectrum of (145b) (200MHz, $CDCl_3$)



starting from the carbinolamide (160a) as a diastereomeric mixture. This suggests that the cyclic system obtained possess the stereo-structure (156a); the cis arrangement of the 2-carboxylic acid moiety and 5-hydrogen is based on our earlier conclusion on system (154). The cis arrangement of the allyl moiety

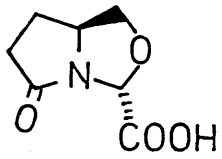


(156a)

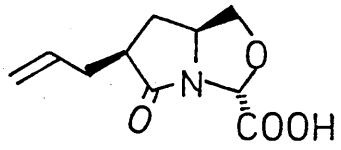
and the C-5 substituent is explained by our stereochemistry determination.

3.1.2 8-Oxo-3-oxa-1-azabicyclo [3.3.0] octane-2-carboxylic acid derivatives

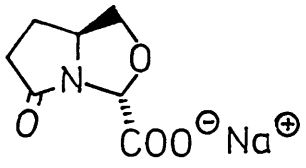
With isolation of (154) and (156a), the next step involved conversion to the acids (161), and (162a) respectively.
Our initial attempts to obtain the acid (161), involved treatment of (154) with sodium hydroxide (1mol equiv) in water followed by acidic work up but this failed to give any material from the organic extract. One possible explanation for this observation is that upon acidic work up (pH1-2), the N,O - acetal of (154) is removed leaving only the alcohol (101) which has been observed to have considerable solubility in water and therefore might not be



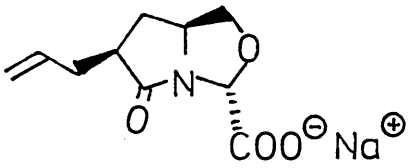
(161)



(162a)



(163)



(164a)

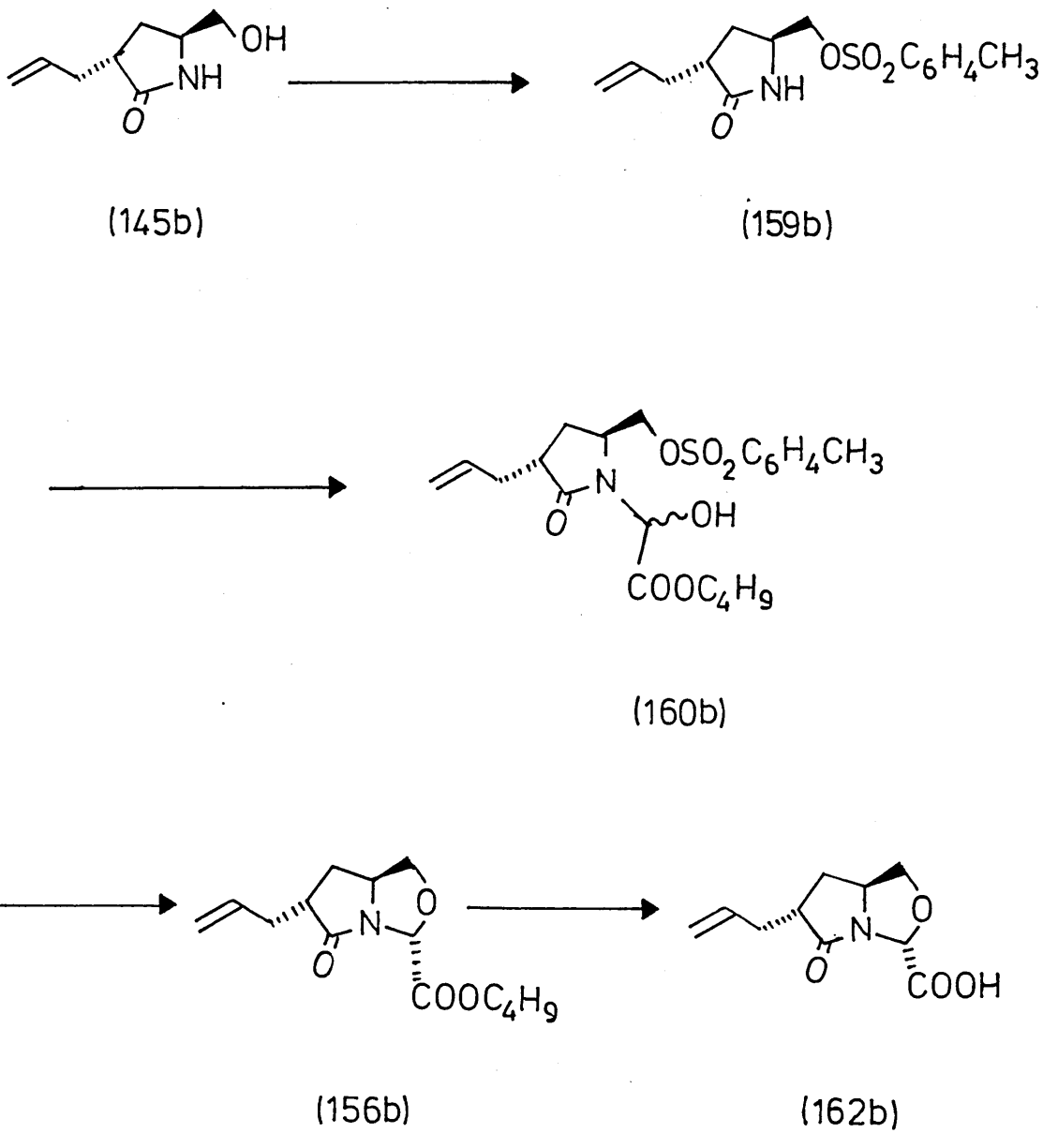
extractable by an organic solvent. To overcome this problem we decided to repeat the hydrolysis process on (154) and isolate the intermediate sodium salt (163) and subsequently acidify at a higher pH (pH4-5). Treatment of (154) with sodium hydroxide (c.a. 1mole equiv) in water, followed by concentration gave the salt (163) (59%). Evidence for (163) was seen in the ^{1}H nmr spectrum by disappearance of the series of multiplets at 0.7-2.0δ attributable to the butyl moiety. Hydrochloric acid (pH4-5) treatment of the salt (163) in water gave the acid (161) (48%). Confirmation of (161) was seen from the ^{1}H nmr spectrum by the presence of a broad singlet at 7.0 δ attributable to COOH.

Treatment of the acid (161) with D_2O caused this signal to collapse. Sodium hydroxide treatment of (156a) under these conditions described above successfully gave the salt (164a) (76%), acidification of which gave the acid (162a) (13%). Evidence for (162a) and (164a) was seen in their ^1H nmr spectra. In the latter case there was a broad singlet at 9.4δ due to COOH which collapsed when (162a) was treated with D_2O. Further confirmation of (162a) was obtained from the broad i.r. absorption 3200 - 2800 cm^{-1} attributed to hydroxyl group of carboxylic acids.

3.2 Future work

Treatment of the alcohol (145b) with p-toluenesulphonyl chloride would give the tosylate (159b). Hydroxy alkylation of (159b) with butyl glyoxylate followed by sodium hydride treatment should give the other 3-oxa-1-azabicyclo[3.3.0]octane diastereoisomer (156b) based on our early observations (scheme 41). Hydrolysis of (156b) followed by acidification should give the acid (162b).

The cyclisation of the iodides (165) and (166) could be carried out to obtain the appropriate 3-oxa-1-azabicyclo[3.3.0]-octane. As Stoodley[108] and coworkers reported that cyclisation through the use of iodides gave higher yields of cyclic product as compared to the use of the tosylates.

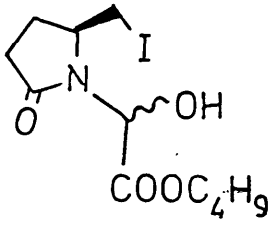


(145b) (159b)

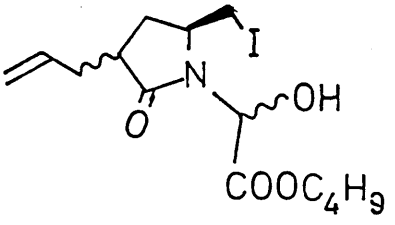
(160b)

(156b) (162b)

Scheme 41.

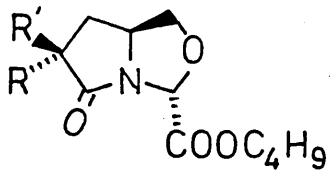


(165)



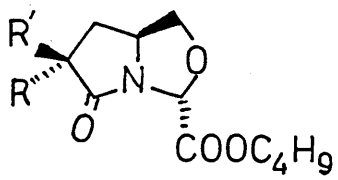
(166)

Ozonolysis of the carbon-carbon double bond of (156a,b) and (162a,b) followed by oxidation work up should give the acid (167a,b) and the dicarboxylic acid (168a,b) respectively (scheme 42).



(156a) R=H, R′=$CH_2CH=CH_2$.

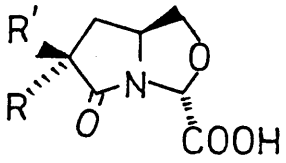
(156b) R=$CH_2CH=CH_2$, R′=H.



(167a) R=H, R′=CH_2CO_2H.

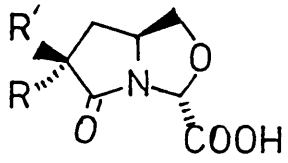
(167b) R=CH_2CO_2H, R′=H.

and/or —— i, ii. ——→ and/or



(162a) R=H, R′=$CH_2CH=CH_2$

(162b) R=$CH_2CH=CH_2$, R′=H



(168a) R=H, R′=CH_2CO_2H

(168b) R=CH_2CO_2H, R′=H

i. O_3; ii. Jones reagent.

Scheme 42.

4. Discussion and results.

4.1 Introduction.

4.2 8-Hydroxybicyclo[3.3.0]octan-2-one.

4.2.1 Cyclopentaannulation via conjugate addition.

4.2.2 Cyclopentaannulation via intramolecular nitrile oxide cyclisation (I.N.O.C.).

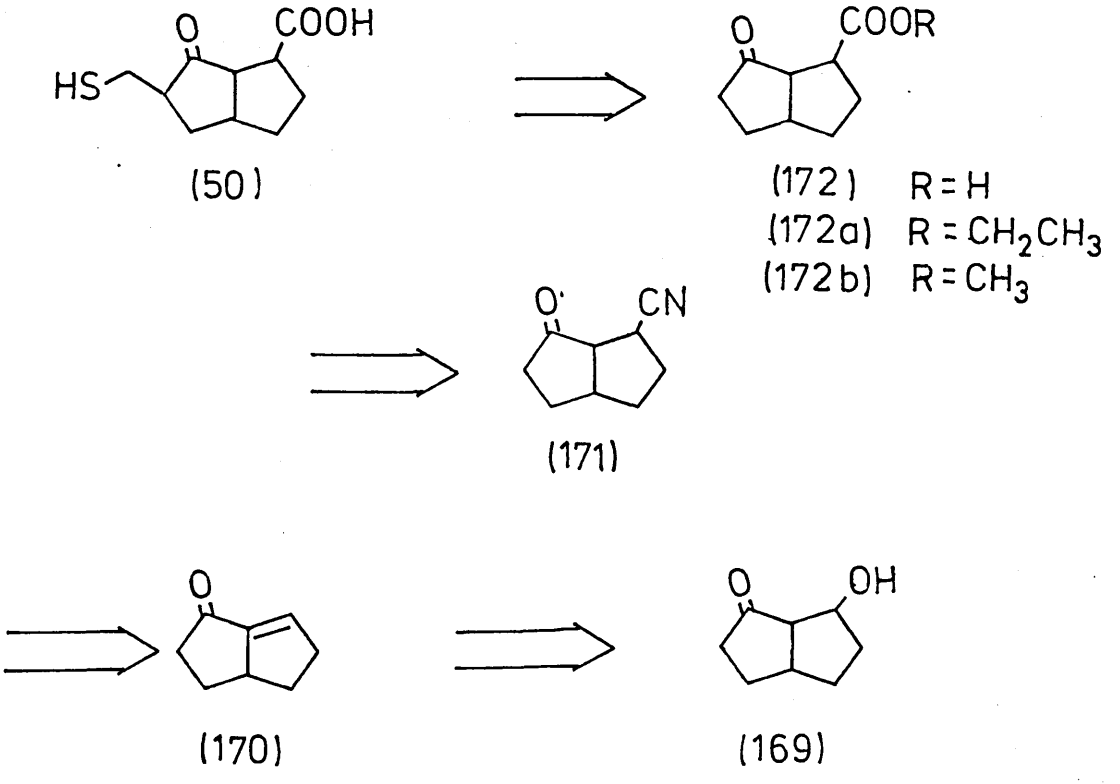
4.3 8-Oxo-bicyclo[3.3.0]octane-2-carboxylic acid.

4.4 Future work.

4. Discussion and results

4.1 Introduction

An attempt to obtain the bicyclo[3.3.0]octane (50) was carried out based upon the retrosynthetic plan shown in scheme 43.

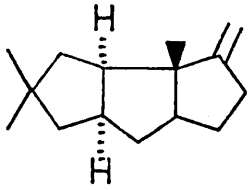


Scheme 43.

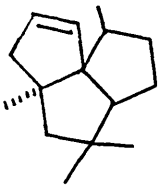
The initial objective to be secured was the fused cyclopentane system 8-hydroxybicyclo[3.3.0]octan-2-one (169).

A search of the literature revealed a vast range of approaches towards the construction of fused and bridged carbocyclic systems

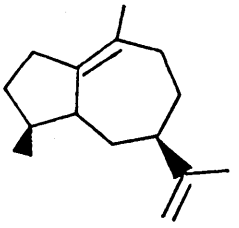
carrying various ring sizes[114] which have then been used in the synthesis of a wide range of natural products. Examples of few target molecules are shown in scheme 44.



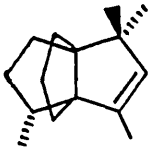
Hirsutene



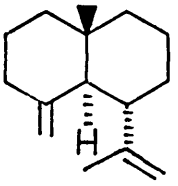
Silphinene



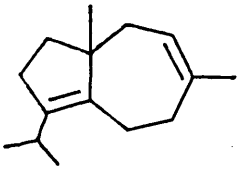
α - buinesene



modhephene



β-gorgonene



daucene

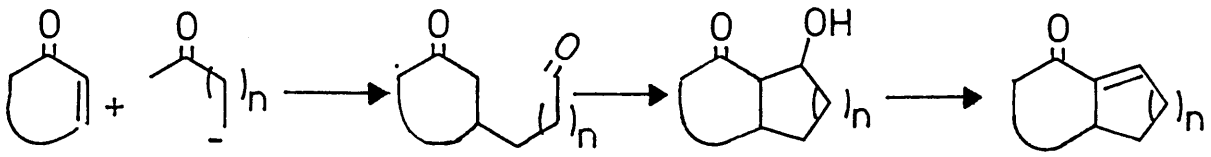
Scheme 44.

The majority of the procedures which have been used in the development[115] of fused or bridged cyclopentane systems involve incorporation of a 3-carbon unit, onto a pre-existing cyclic compound, with a variety of functional groups, and then subsequent closure into a cyclic compound.

4.2 8-Hydroxybicyclo[3.3.0]octan-2-one

4.2.1 Cyclopentaannulation via conjugate addition

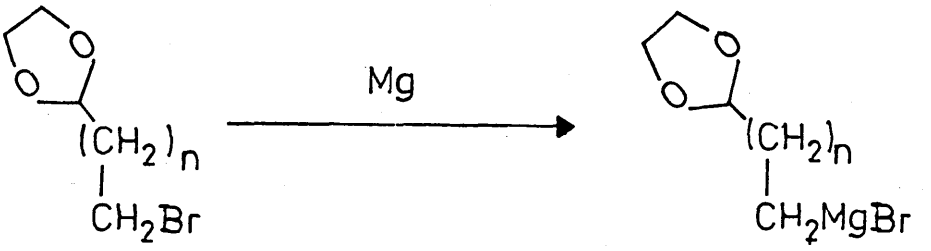
The synthesis of 8-hydroxybicyclo[3.3.0]octan-2-one (169) and related fused systems have been previously reported by Marfat and Helquist,[116] based on the process illustrated in scheme 45, in which a synthetic equivalent of the carbanionic species (173) undergoes conjugate addition to an α,β-unsaturated carbonyl compound, and the resulting 1,6-dicarbonyl system then undergoes intramolecular aldol condensation and subsequent dehydration giving the desired annulation product. In the case of (169), and other β-hydroxy ketones of this type (5,5-systems), spontaneous dehydration to the alkene (170) is not observed.



(173)

Scheme 45.

The use of reagents equivalent to (173) having n = 1 or 2 permits the annulation of cyclopentane and cyclohexene rings onto the original unsaturated carbonyl compounds. The reagents equivalent to (173), in the case of cyclopentaannulation (where n = 1), are the acetal-containing Grignard reagents (174); these and related organometallic derivatives have been known for many years.[117]



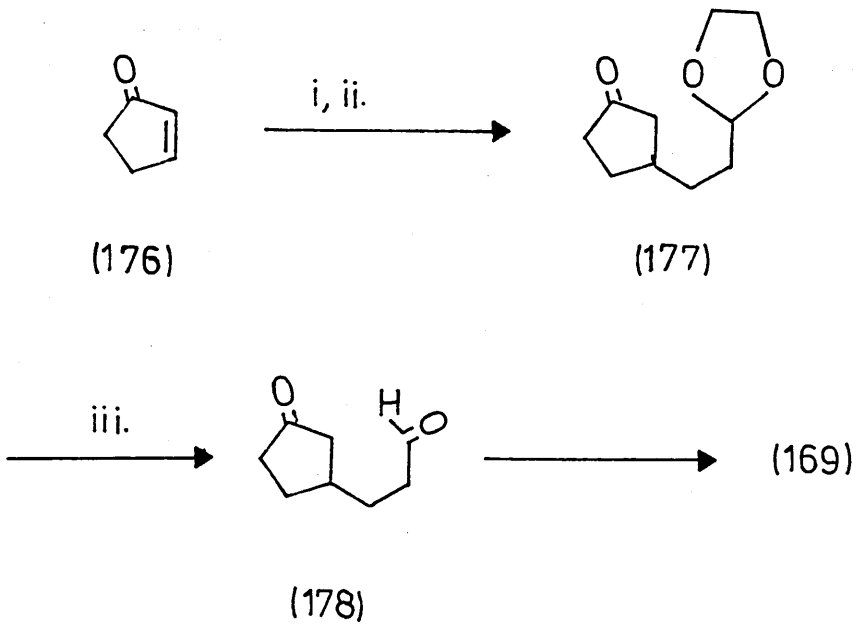
(175) n= 1 (174) n=1

(175a) n= 2 (174a) n=2

The attempted synthesis of (169) was carried out using the procedure described above.

The Grignard reagent required was generated from the primary halo acetal (175) which was readily available by reaction of acrolein, ethylene glycol and HBr.[118] Generation of the Grignard (174) was achieved through use of magnesium powder, obtained by reduction of anhydrous magnesium chloride with potassium metal, according to the procedure of Reike.[119]

The next step in the reaction sequence was copper-catalysed conjugate addition of the Grignard reagent to the α,β -unsaturated carbonyl system,[120] cyclopenten-2-one (176)[121] at -78°C, (scheme 46). The dimethylsulphide complex of cuprous bromide[122,128] was utilised as the form of copper for the catalysis of the reaction. Once conjugate addition was accomplished the resulting keto acetal (177) was isolated by quenching with aqueous ammonium chloride.



i. (174), $CuBr(CH_3)_2S$, -78°C ; ii. NH_4Cl ; iii. HCl, THF.

Scheme 46.

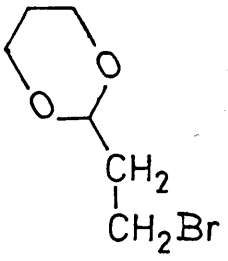
That conjugate addition had occured was indicated by the ^1H nmr spectrum of the crude product, which showed the disappearance of cyclopenten-2-one (176) (CH=CH, 6.2 and 7.8δ). Treatment of (177) with hydrochloric acid is reported[116] to induce sequential acetal hydrolysis and intramolecular aldol condensation, giving the bicyclo[3.3.0]octane (169). In our hands this particular reaction step was unexpectedly unsuccessful. Repetition under various conditions (summarized in table 3) also failed to give (169). ^1H nmr spectra indicated that the acetal groups (OCH_2CH_2O, 3.7-4.1δ) was still present confirming that acetal hydrolysis was not occuring to yield the intermediate (178) required for aldol condensation to give (169).

Table 3.

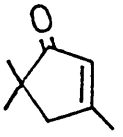
Reaction time	Reaction conditions	Temperature °C
3 days	0·1N HCl/THF/H_2O	25
6 days	0·1N HCl/THF/ H_2O	25
3 days	0·1N HCl/ THF/ H_2O	40
3 days	2N HCl / THF/H_2O	25
3 days	2NHCl/THF/H_2O	40
5min.	cH_2SO_4/$NaIO_4$/dioxan ‡	reflux
19 hr.	$FeCl_3SiO_2$/$CHCl_3$ ‡‡	20 – 25

‡ Ref. 124 , ‡‡ Ref. 125.

Paquette and Bay[126,127] in their synthesis towards triquinane sesquiterpenes, used the annulation procedure originally described by Marfat and Helquist.[116] They used the more stable magnesium cuprate obtained from the six-membered acetal (179)[125] to undergo conjugate addition with methyl containing cyclopenten-2-ones of the type (180) and (180a)

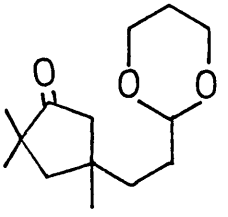


(179)

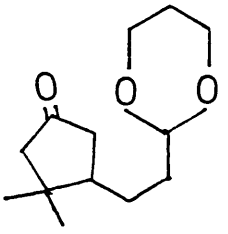


(180)

(180a)



(181)

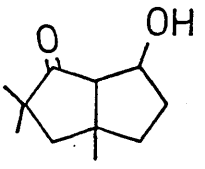


(181a)

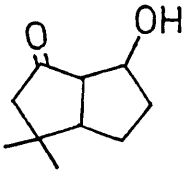
Acid hydrolysis of the duly formed keto acetals (181) and (181a) was accompanied by aldolisation, yielding the bicyclo[3.3.0]octane (182) and (182a) in 48% and 79% yield respectively.

This observation caused us to pursue the cyclopentaannulation process using the organomagnesium cuprate obtained from the acetal (179).

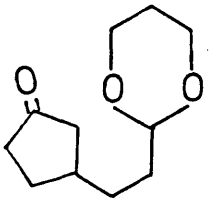
Synthesis of (179)[128] was carried out in a similar manner to that for (174), substituting 1,3-propanediol for 1,2-ethanediol. Conversion of (179) to the Grigand reagent followed by copper catalysed conjugate addition to (176) gave the keto acetal (183).



(182)



(182a)



(183)

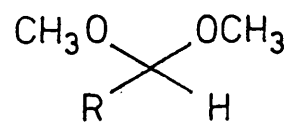
Hydrochloric acid treatment of (183) failed to yield (169). Starting material was recovered. Again, exposing (183) to a variety of conditions also failed (table 4). Evidence for this was obtained from ^{1}H nmr spectra.

In both cases discussed earlier, two equivalents of halo acetals (175) and (179) were used for conjugate addition to cyclopenten-2-one (176), as cyclopenten-2-one (176) has been reported[116] to be a notoriously difficult case to undergo conjugate addition compared to other unsaturated ketones (e.g. cyclohexen-2-one, cyclohepten-2-one) where nearly stoichiometric amounts of halide have been used.

Table 4.

Reaction time	Reaction conditions	Temperature °C
3 days	2N HCl/acetone/H_2O	25
6 days	2N HCl/acetone/H_2O	25
3 days	2N HCl/acetone/H_2O	40
6 days	2N HCl/acetone/H_2O	40
3 days	cHCl/acetone/H_2O	25

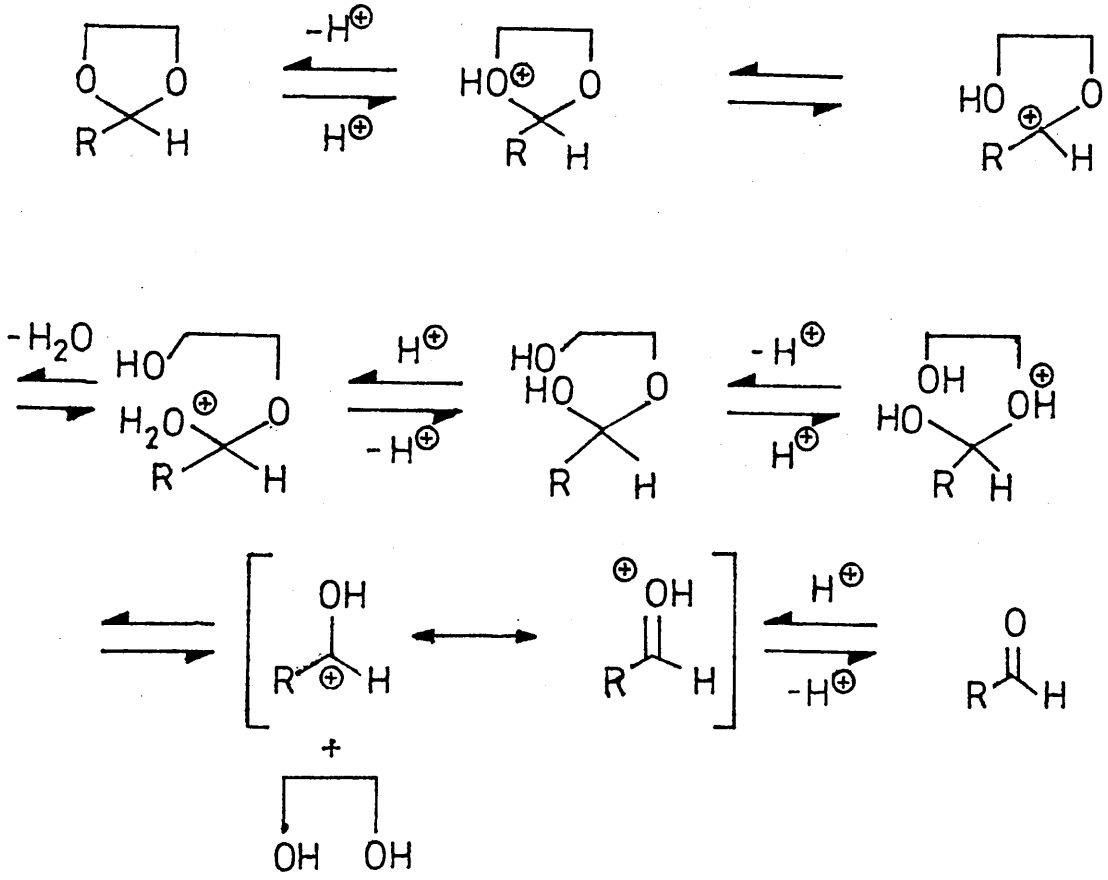
Our inability to transform the acetals (177) and (183) under the various conditions used was very frustrating (see table 3 and 4 respectively), as Marfat and Helquist[116] have succesfully achieved this in the case of (177). Other workers[126,127] have also achieved hydrolysis on similar type of systems, such as (181) and (181a). Five-membered acetals have been reported[56] to require drastic conditions for deprotection as compared to the dimethyl acetal system (see below).



dimethyl acetal

One possible explanation could be that in the formation of five-membered acetals (this may also apply to the six-membered acetal) involves a type of intramolecular reaction as outlined in scheme 47.

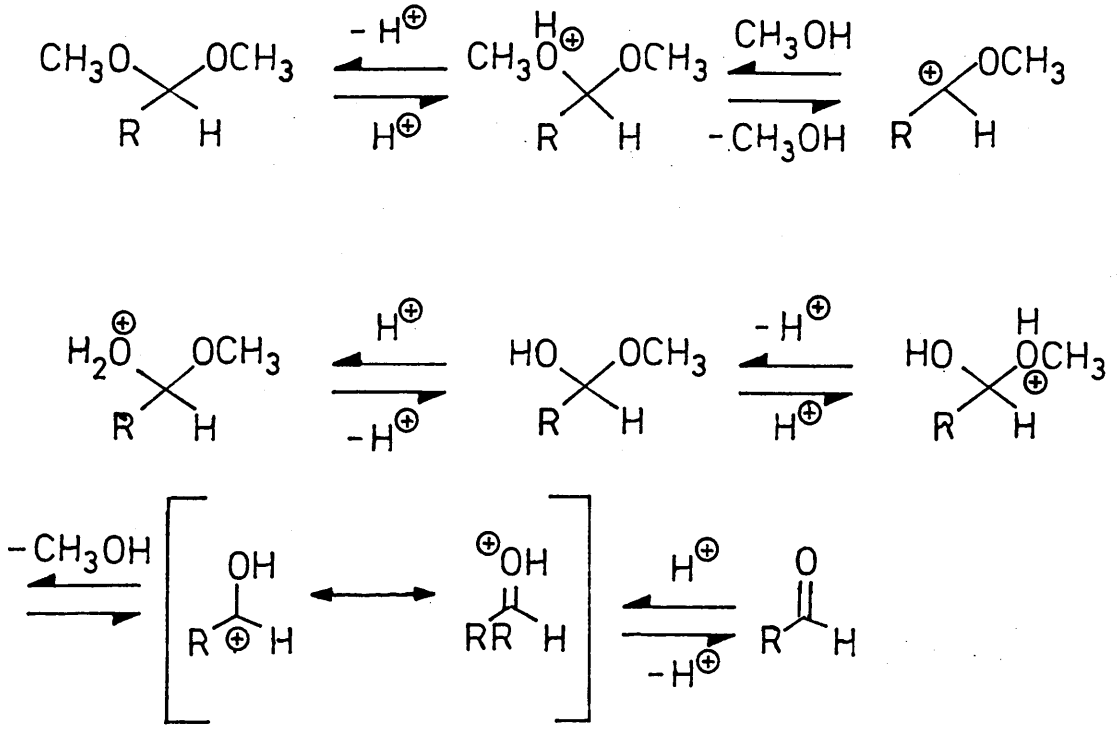
In the deprotection, one is initially opening the ring system (reverse of the intramolecular reaction). But reaction of the partially opened system seems to favour re-reaction (intramolecular reaction) back to the closed ring compared to loss of the protecting group. Thus equilibrium being displaced to the acetal rather than the carbonyl. With the dimethyl acetal system, formation of a protected species involves an intermolecular type



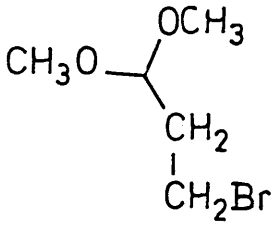
Scheme 47.

of reaction, outlined in scheme 48. Thus upon deprotection of the dimethyl acetal, there is less chance of the protecting moiety re-reacting. Therefore equilibrium should be easily displaced towards hydrolysis.

Repetition of the cyclopentaannulation process using the dimethyl acetal species (184) was considered though not investigated as an alternative strategy towards obtaining (169) was found.

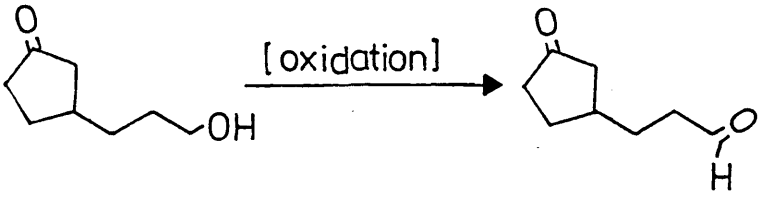


Scheme 48.



(184)

As the 1,6-dicarbonyl (178) was the key precursor in a route towards (169), an alternative attempt to obtaining (178) was examined, based upon the route shown in scheme 49. The strategy would involve obtaining (178) from the corresponding

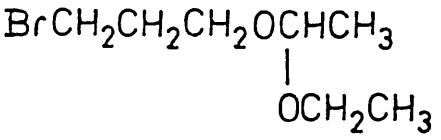


(185) (178)

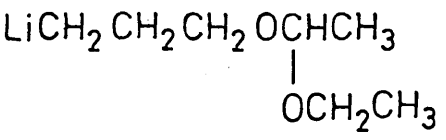
Scheme 49.

alcohol (185) by oxidation. Thus attention was focussed towards the preparation of the keto alcohol (185). A search of the literature indicated two possibilities for the synthesis of this type of system, both involving the introduction of a hydroxy propyl group on to an α,β-unsaturated carbonyl system. One of these methods was chosen for investigation.

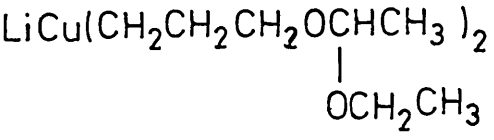
Eaton and coworkers[129] have reported the preparation of (185) via the approach outlined above using organocopper lithium reagents. The synthesis involved the reaction of (186), available by acid catalysed reaction of 3-bromopropan-1-ol with ethyl vinyl ether, with lithium to yield the organolithium (187).



(186)

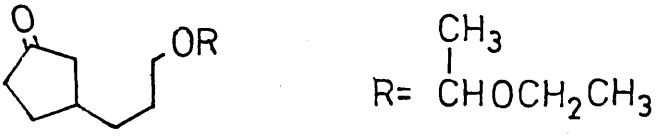


(187)



(188)

Treatment with 0.5 equivalents of cuprous iodide at -60°C gave the lithium organocuprate (188). Conjugate addition to (176) yielded (189) and

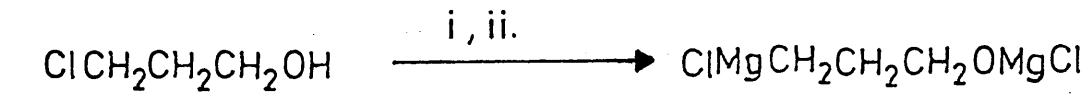


(189)

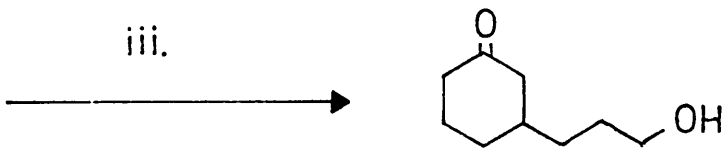
subsequent acid treatment gave the keto alcohol (185). We hoped that oxidation of (185) would give the desired 1,6-dicarbonyl system (178) which would undergo an aldol condensation and yield (169).

In the light of the literature report it proved extremely disappointing to find that in our hands the method was very unreliable and inefficient. Frequently starting materials were predominantly or exclusively recovered. The problem appeared to be the inefficient preparation of the lithium reagent (187). Failure to repeat the described methodology directed the investigation towards the use of organomagnesium reagents. Conversion of (186) to the Grignard reagent followed by copper catalysed conjugate addition failed to yield (189). Starting materials were recovered. For unknown reasons, (186) could not be induced to undergo conversion to the Grignard species; no exothermic reaction was observed during the preparation as usually is expected.[130] When all attempts to generate the Grignard species from (186) failed, alternative strategies towards obtaining (169) were considered not based upon cyclopenten-2-one (176).

The second possibility which was not investigated was that described by J.F.Normant and coworkers[131] as outlined in scheme 50. By using cyclopenten-2-one (176) it should be possible to prepare (185).



(190) (191)



(192)

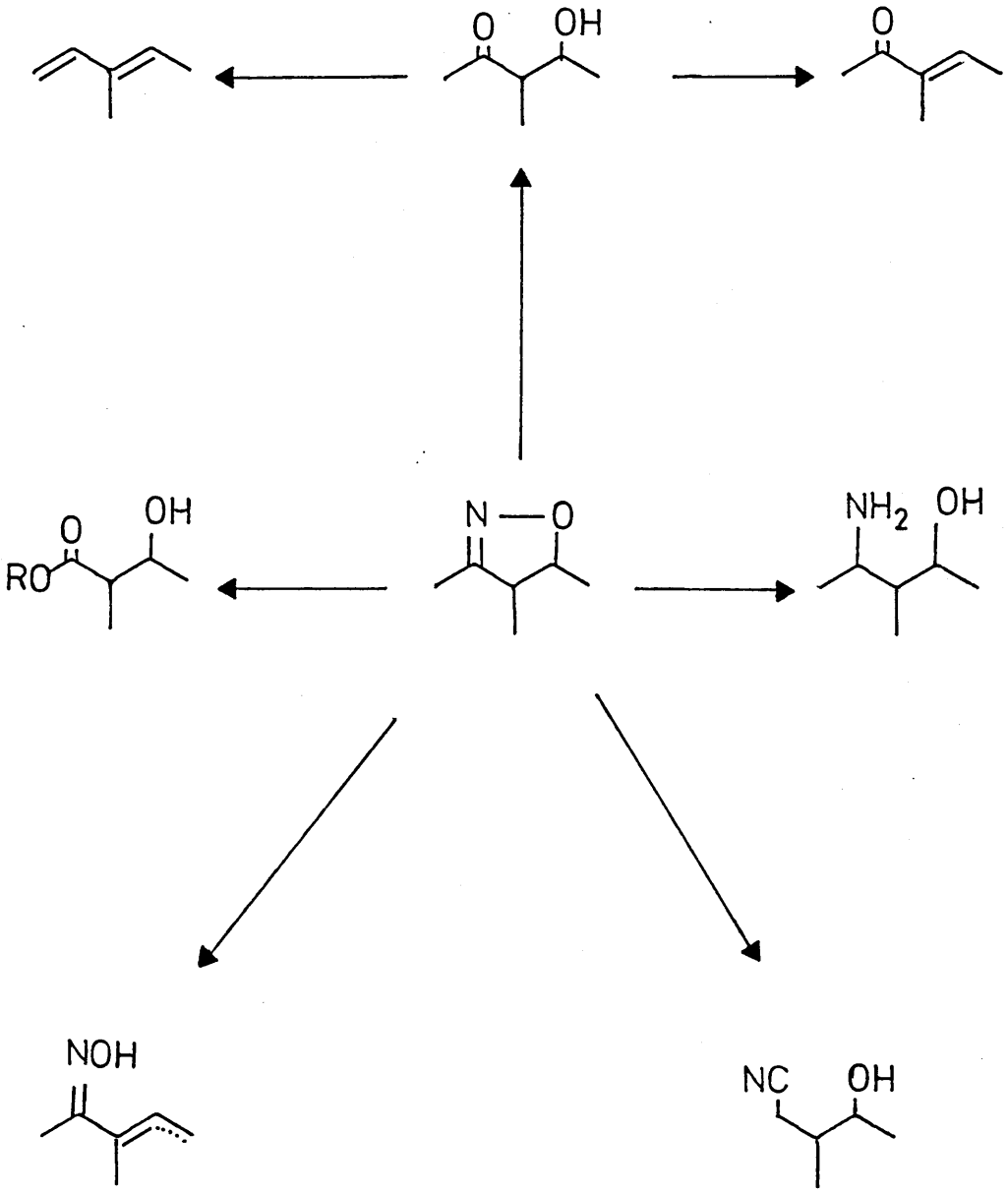
i. RMgCl , THF , (R= CH_3 , $(CH_3)_2CH$) ; ii. Mg , THF ;
iii. cyclohexenone , 5% CuBr .

Scheme 50.

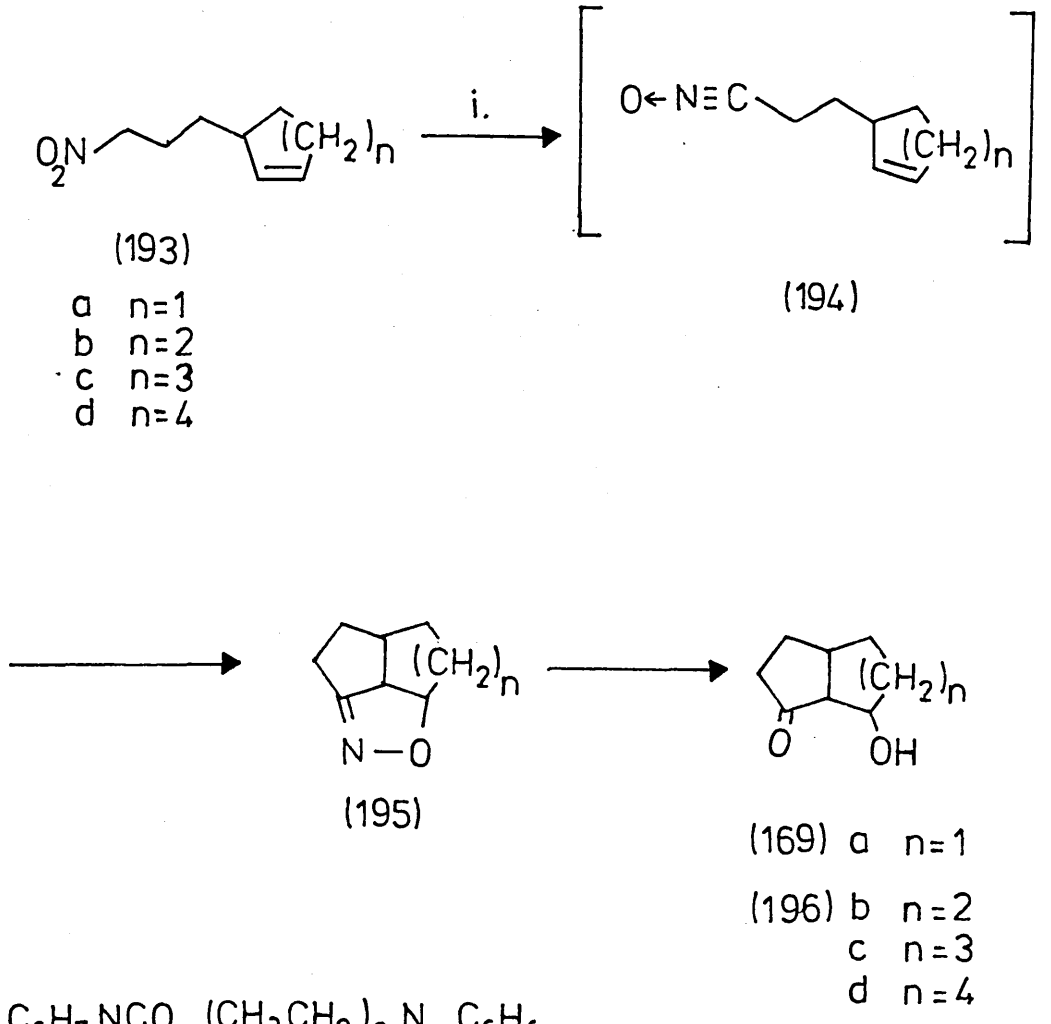
4.2.2 Cyclopentaannulation via intramolecular nitrile oxide cyclisation (INOC)

Over the past few years nitrile oxide cycloaddition has been used vastly as a tool for natural product synthesis. The first observation that nitrile oxides reacted with olefins was made by Weygand in 1927.[132] Since then, extensive studies have been carried out upon nitrile oxide chemistry.[133] The preparation of these reactive systems and investigations of their scope, mode of reactivity and utilisation in synthesis have received considerable attention in the literature.[134] The isoxazolines generated from the nitrile oxides and olefins have shown great versatility for the construction of a variety of natural products.

The isoxazoline ring represents a fairly responsive heterocyclic system (scheme 51) for its interaction with appropriate reagents can yield access to (i) γ-amino alcohols (ii) β-hydroxy ketones (and thus α,β-unsaturated ketones, allyl alcohols, 1,3 diols and 1,3 dienes) (iii) β-hydroxy nitriles, acids, ester and (iv) α,β- and β,γ-unsaturated oximes.
Of particular interest was transformation (ii) via this strategy.
To our benefit a report by R.H.Wollenberg[135] previously described a procedure for the stereospecific construction (cis-ring junction) of bicyclo [n.3.0] alkanones, including (169), by intramolecular nitrile oxide cycloaddition as outlined in scheme 52.



Scheme 51.

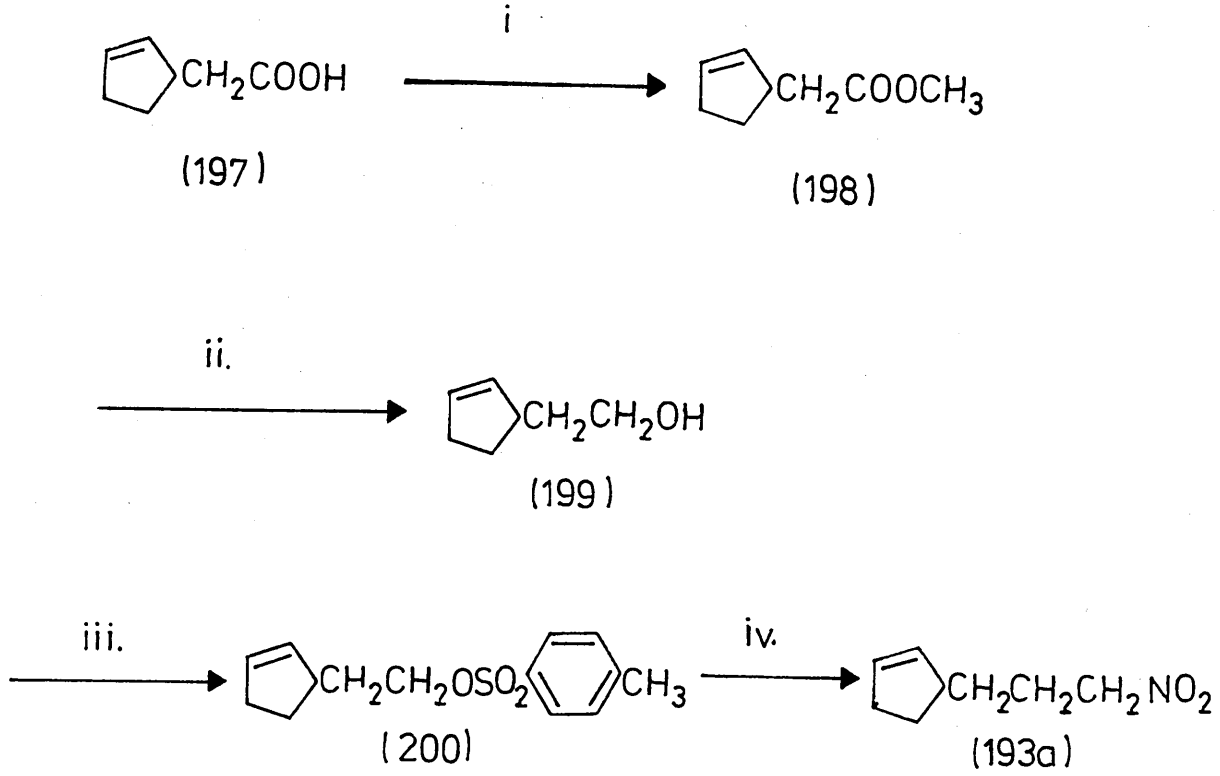


i. C_6H_5NCO, $(CH_3CH_2)_3N$, C_6H_6.

Scheme 52.

The nitrile oxides[136] are generated *in situ* from the nitrocycloalkene and phenyl isocyanate in the presence of triethylamine. Thus attention was focussed towards the synthesis of the desired nitrocycloalkene (193a), n = 1. Initial attempts towards obtaining (193a) are outlined in scheme 53.

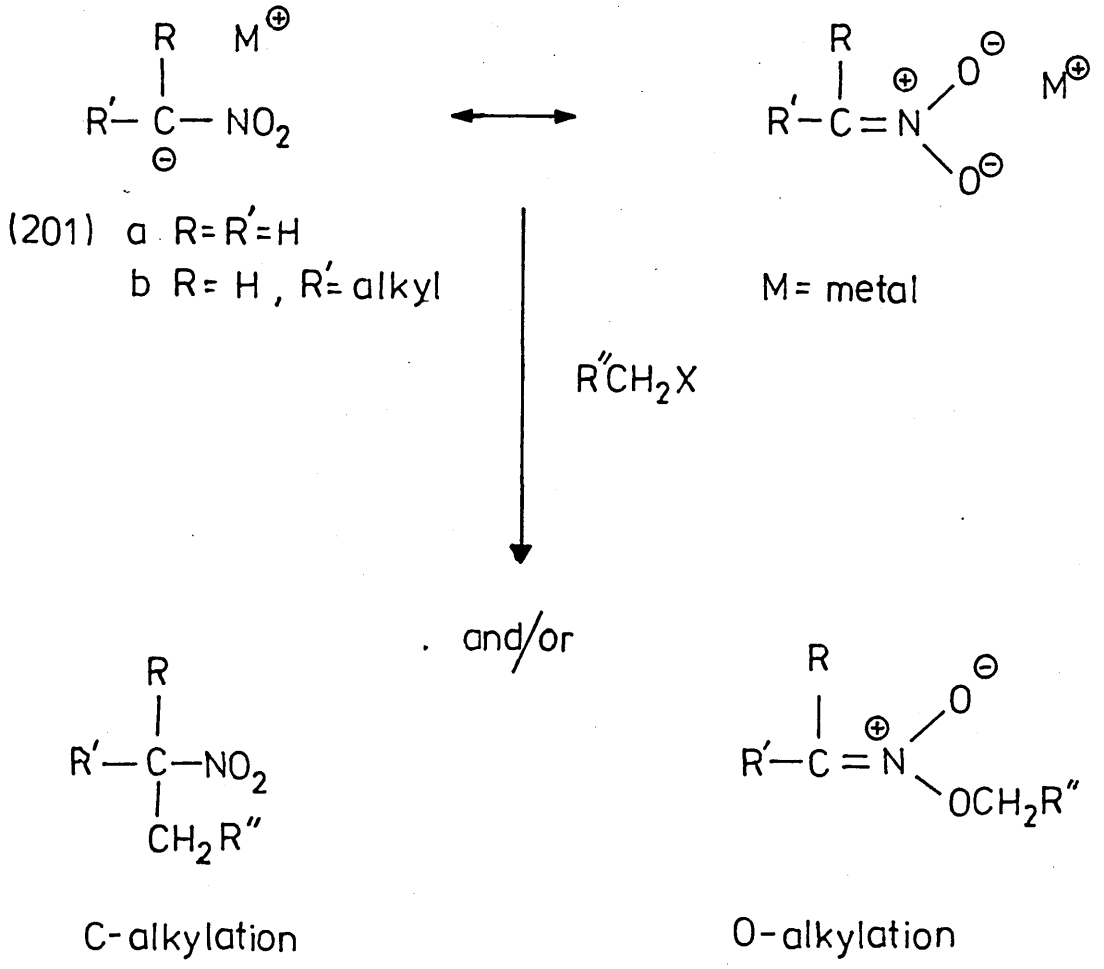
Esterification of cyclopentene-1-acetic acid (197)[137] gave the ester (198).[138] Reduction of (198) gave the alcohol (199)[138] in 73% overall yield. Reaction of (199) with p-toluenesulphonyl



i. CH_3OH, conc. H_2SO_4, CH_2Cl_2; ii. $LiAlH_4$, ether; iii. pyridine, p-$CH_3C_6H_4SO_2Cl$; iv. CH_3NO_2, n-BuLi (2 equiv.), THF, HMPT, -90°C.

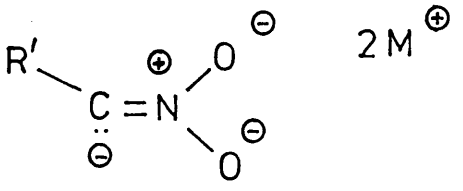
Scheme 53.

chloride in pyridine gave the tosylate (200).[138] Treatment of tosylate (200) with a salt of nitromethane (201) (nitronate) should give the nitrocycloalkane (193a).[139] Unfortunately (201)[140] (scheme 54) and homologous nitronates are rather poor nucleophiles and they usually undergo oxygen alkylation with the electrophile with little or any carbon alkylation.[141,142]



Scheme 54.

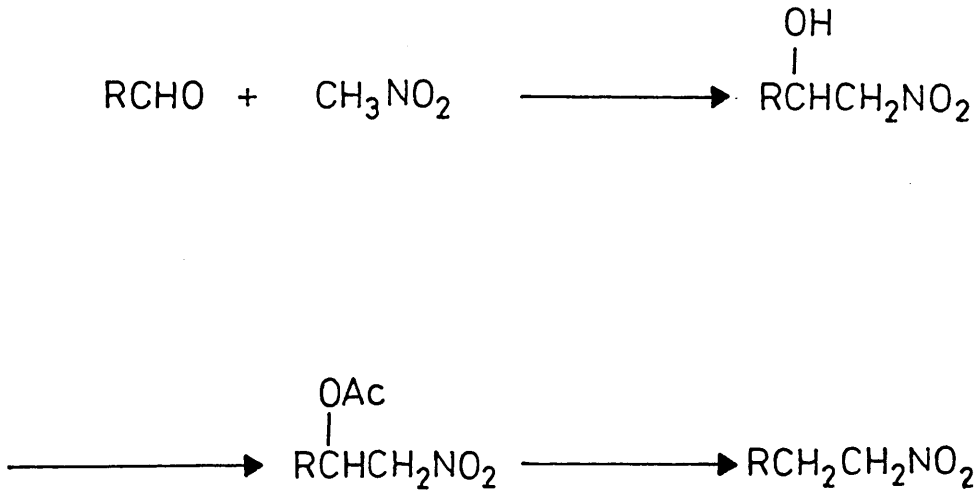
A report by D.Seebach et al[143] suggested that the poor C- nucleophilicity of nitronate anions (201) can be dramatically improved by formation of the α,α- doubly deprotonated species(202).



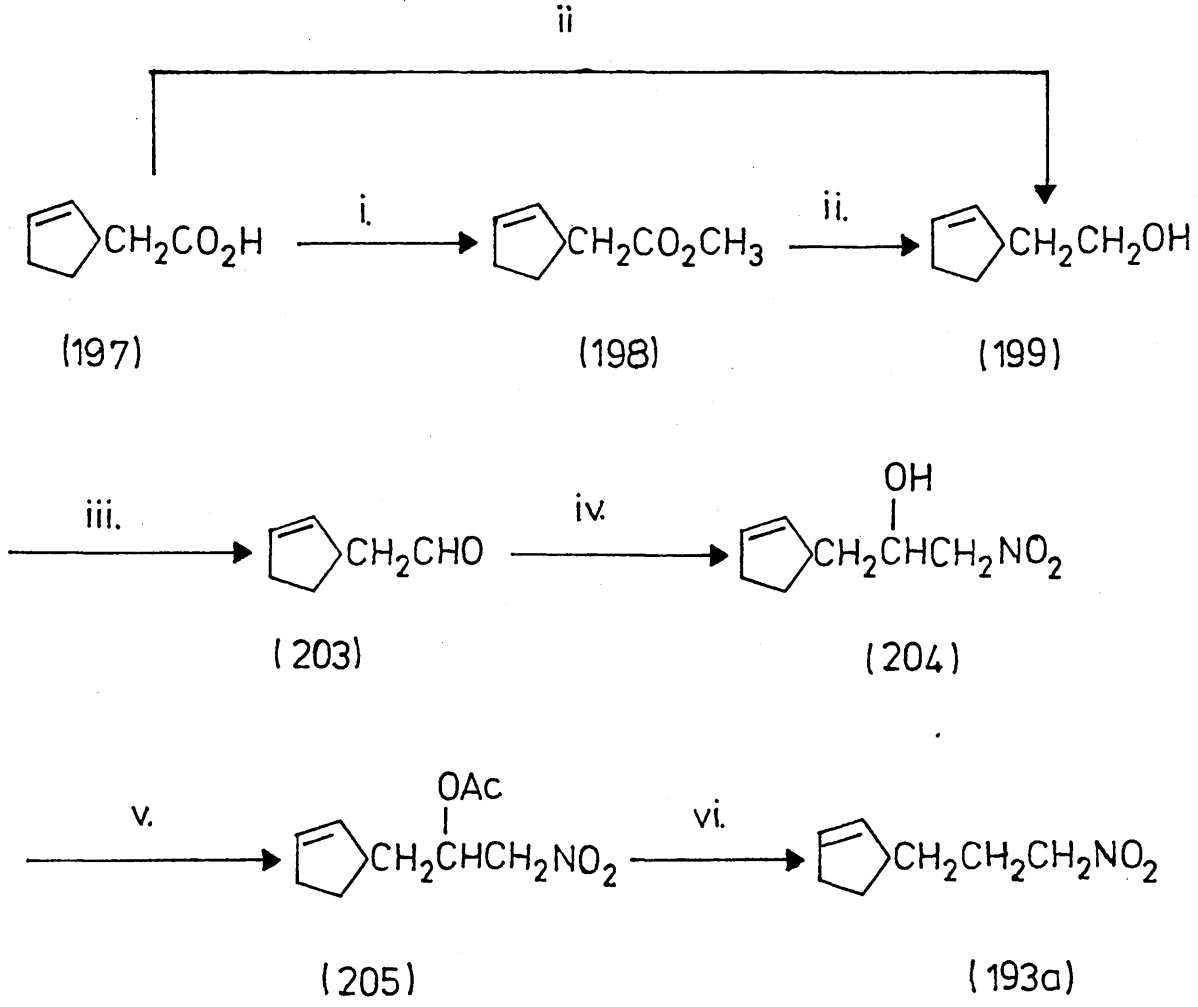
(202) a R = H
b R = alkyl

Generation of the α,α- doubly deprotonated species (202) is carried out by addition of two equivalents of n-butyl-lithium to the primary nitroalkane in tetrahydrofuran (THF) in the presence of hexamethylphosphorous triamide (HMPT). Formation of the nucleophile (201a) from nitromethane using the conditions described by Seebach and reaction with (200) should yield (193a). However, the reaction was unsucessful, only starting materials being recovered. Failure to convert (200) to (193a) directed us to pursue alternative routes towards (193a).

Base catalysed condensation of a aldehyde and a nitroalkane[144] followed by acylation and reductive elimination was reported[145] as another viable method for nitroalkane preparation as outlined in scheme 55.



Scheme 55.



i. CH_3OH, cH_2SO_4, CH_2Cl_2; ii. $LiAlH_4$, ether; iii. pyridinium chlorochromate, CH_3COONa, CH_2Cl_2; iv. CH_3NO_2, KF; v. Ac_2O, 4-dimethylaminopyridine; vi. $NaBH_4$, CH_3CH_2OH.

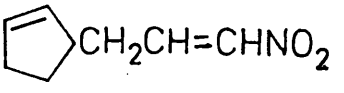
Scheme 56.

146

Advantage was taken of a report by R.H.Wollenberg and coworkers that described a one-pot procedure, using the process discussed above, for arriving at nitroalkanes. Adaptation of the conditions described by Wollenberg allowed us to obtain (193a). The sequence of reactions employed is shown in scheme 56.

Formation of the alcohol (199) was carried out as described earlier.[137] Direct reduction[137] of the acid (197) also gave the alcohol (199) isolated in 50% yield. Oxidation of the alcohol (199) with buffered pyridinium chlorochromate in dichloromethane[147] gave the foul smelling aldehyde (203).[148] Under a variety of conditions a maximum yield of only 60% of (203) could be obtained.

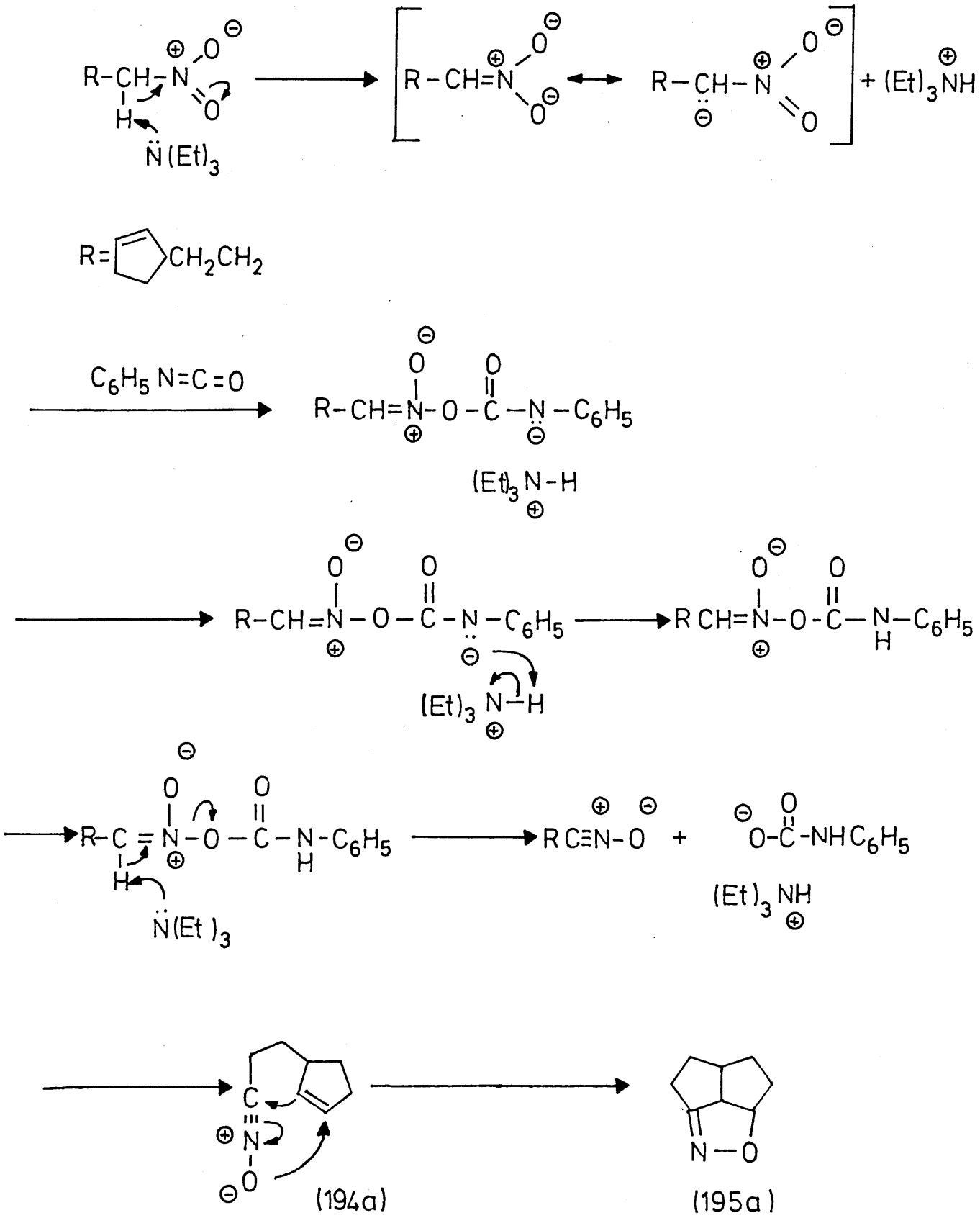
Homologation to the requisite nitro compound (193a) was accomplished using the convenient one-pot procedure of Wollenberg[146] involving (i) Henry reaction of (203) with nitromethane and anhydrous potassium fluoride, yielding the β-hydroxynitrocycloalkene (204) (ii) acetylation of (204) with acetic anhydride, 4-dimethylamino-pyridine[149] to give the β-nitro acetate (205) (iii) reduction of (205) with sodium borohydride in ethanol to give (193a). Isolation of the intermediates, for characterisation purposes (i.r. nmr spectroscopy), at each step revealed that the product obtained from (ii) was a mixture of (193a) and the α,β-unsaturated nitro system (206).



(206)

This indicates that elimination of the acetate (205) was also occurring at this stage.

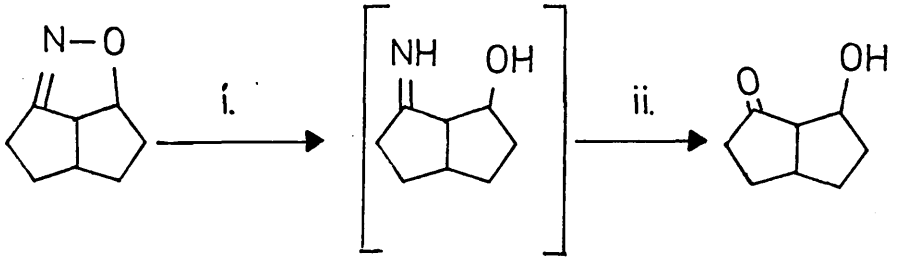
Nitrile oxide generation and cycloaddition using the Wollenberg



Scheme 57.

conditions (phenyl isocyanate, triethylamine, benzene)[135] proceeded smoothly to give the isoxazoline (195a) in 92% isolated yield. A proposed mechanism for the generation of the nitrile oxide from the nitrocycloalkene and subsequent nitrile oxide cyclisation is outlined in scheme 57.

Finally clearage of the N-O bond[150] of (195a) with Raney nickel (W-2)grade[151] and hydrogen gave the imine (207), which was not isolated, and aqueous work up resulted in hydrolysis to yield (169) (scheme 58).



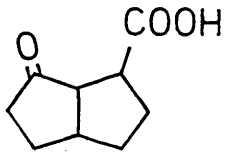
(195a) (207) (169)

i. H_2, Raney Ni, glacial CH_3COOH; ii $NaHCO_3$, H_2O.

Scheme 58.

4.3 8-Oxo-bicyclo [3.3.0] octane-2-carboxylic acid

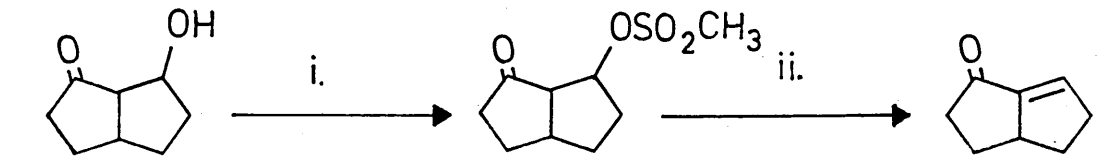
With the isolation of (169) the stage was set for elaboration towards the derivative (172)



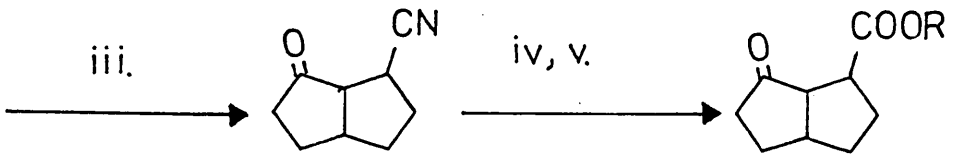
(172)

Since spontaneous dehydration is not encountered in β-hydroxy ketones of the type (169) (see also section 4.2.1), production of enone (170) required conversion to the mesylate (170a) and elimination with 1,8-diazobicyclo [5.4.0] undec-7-ene (DBU).[152] Enone (170) was isolated in 49% yield from (169) (scheme 59).

Enone (170) has been also generated by an approach described by Islam and Raphael[153] (scheme 60) but the yield reported was extremely low (7%).



(169) (170a) (170)

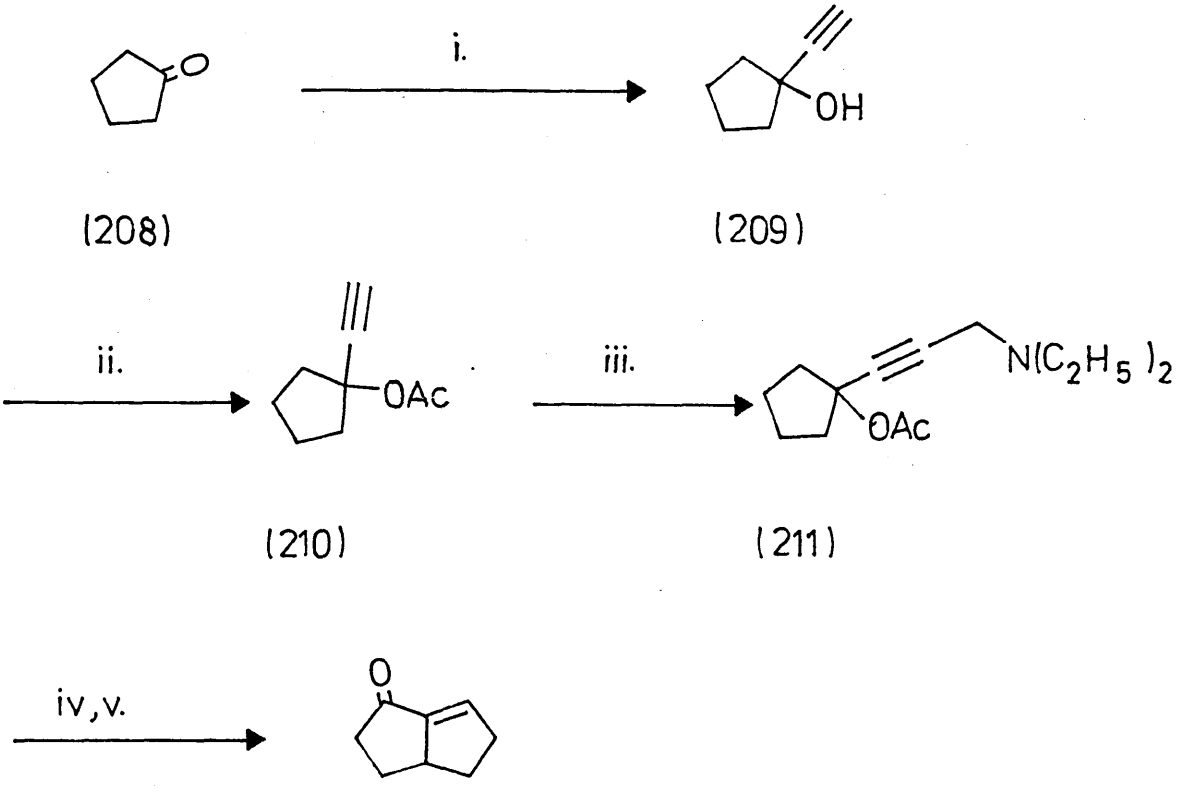


(171)

(172) R = H
(172a) R = CH_2CH_3
(172b) R = CH_3

i. CH_3SO_2Cl, $(CH_3CH_2)_3N$; ii. DBU, CH_2Cl_2 ; iii. acetone cyanohydrin, 6% Na_2CO_3, CH_3OH; iv. c H_2SO_4, CH_3CH_2OH, Δ; v. KOH .

Scheme 59.



(208) (209) (210) (211) (172)

i. Li, CH≡CH ; ii. Ac_2O, Δ, 2h; iii. $(C_2H_5)_2N$, $(HCHO)_n$, dioxan, Δ, 3h; iv. HCOOH, phosphoric acid v. $Hg(OAc)_2$, Δ, 4h.

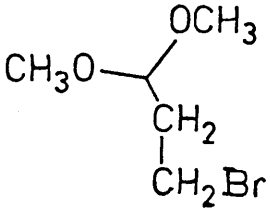
Scheme 60.

Transformation of (172) to the nitrile (171) was initially carried out with potassium cyanide in dimethylforamide.[154] Unfortunately the yield of (171) from this conjugate addition process was very low. Alternatively cyanide conjugate addition was carried out with acetone cyanohydrin[155] giving (171) in 95% yield. The next undertaking was the formation of the acid (172), which involved treatment of (171)[156] with potassium hydroxide. However, generation of (172) by this process was very inefficient. This obstacle was overcome by converting the nitrile (171) to the ester (172a).[69] Base hydrolysis of (172a) furnished the acid (172).

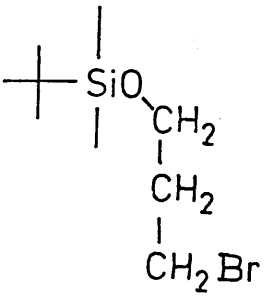
The prohibitive price of cyclopentene-1-acetic acid required as starting material for the total synthesis and poor overall yield of (172) (21%)[157] combined with a lack of time, prevented alkylation studies being carried out upon the acid (172).

4.4 Future work

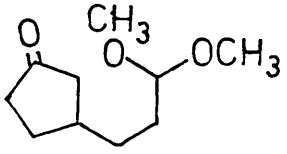
Several aspects of this work would benefit from a further study, firstly the cyclopentaannulation process using the dimethyl acetal species (184) and the masked species (213).
The masked species (184) should undergo conjugate addition to cyclopenten-2-one (176) giving the intermediate (213). Acid hydrolysis of (213) should occur smoothly and give the 1,6-dicarbonyl (178), subsequent aldolisation would yield the bicyclo[3.3.0]octane (169). Alternatively, the species (212) would be a suitable carrier



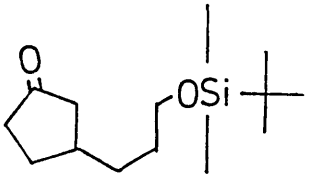
(184)



(212)



(213)

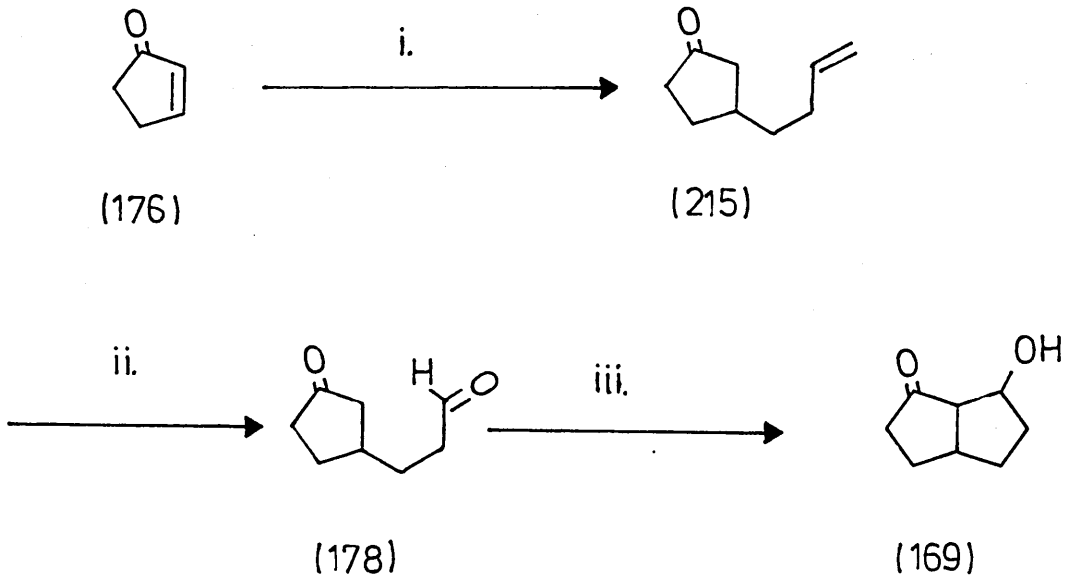


(214)

of the hydroxypropyl system. Conjugate addition to (176) should yield (214). Conversion of (214) to the keto alcohol (185), followed by oxidation would yield the 1.6-dicarbonyl (178) which would undergo aldol condensation and yield (169).

Outlined below are other possiblities towards obtaining (169) and the intermediate (172b). An alternative approach to obtaining (169) still based on cyclopentaannulation process would

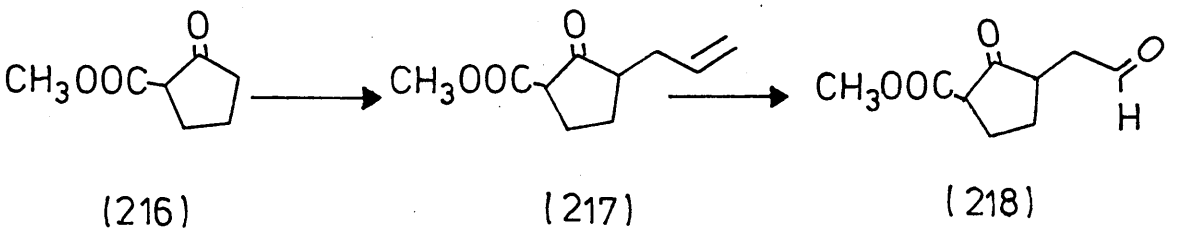
involve conversion of the keto alkene (215),[158] obtainable by conjugate addition of bromobutene to cyclopenten-2-one (176), to the 1,6-dicarbonyl (178) by ozonolysis (scheme 61). Subsequent aldol condensation of (178) should give (169).



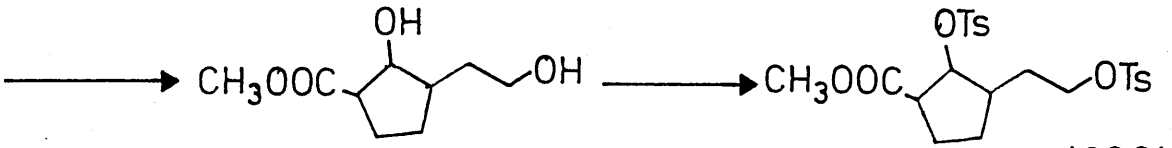
i. $(CH_2{=}CHCH_2CH_2)_2CuMgBr$, $-78^{\circ}C$; ii. O_3 ;
iii. $H^{\oplus}$.

Scheme 61.

The possibility to obtaining (172b) is outlined in scheme 62. The development of the synthetic route, outlined in scheme 62, towards obtaining (172b) resembles a similar approach used for the synthesis of the carboxylic analogue of captopril (see Chapter 1, section 1.3, scheme 2).

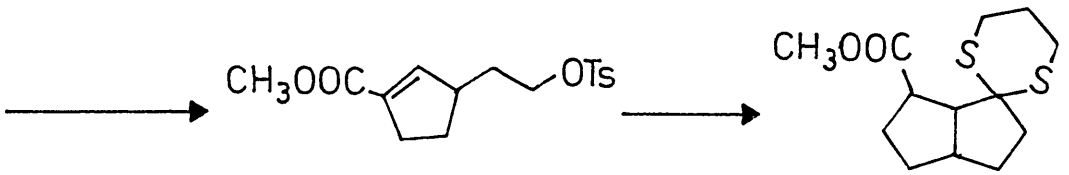


(216) (217) (218)

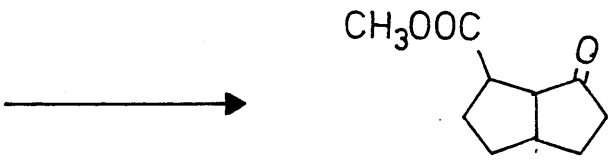


(219) (220)

Ts = $SO_2C_6H_4CH_3$



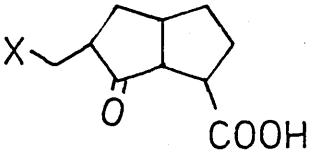
(221) (222)



(172b)

Scheme 62.

Having obtained the acid (172) alkylation using bromomethyl thioacetate[52] using two equivalents of lithium diisoproplyamide (LDA) should give the adduct (50a).



(50a) X = AcS

(50) X = HS

Base hydrolysis should reveal the final target (50).

5. Experimental

5.1 General information

^{1}H NMR spectra were obtained upon one or more of the following instruments: Jeol 60MHz C.W., Bruker 80MHz F.T. and Varian XL 200MHz spectrometers. ^{13}C NMR spectra were obtained on a Bruker 80MHz F.T. spectrometer. Chemical shifts are quoted on the δ scale using tetramethylsilane as the internal reference. Abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet and dd = doublet-doublet.

Infrared spectra were obtained on a Pye-Unicam SP3-100 or a Pye-Unicam SP3-200 spectrophotometer. Data is given in cm^{-1}. Samples were prepared as potassium bromide (KBr) discs, liquid films or $CDCl_3$ solutions.

Mass spectra data were obtained upon a VG70-70E spectrometer, linked to a VG11/250 data system, operating at 70eV.

Microanalyses were performed by microanalysis laboratories, May & Baker Ltd., Dagenham.

Thin layer chromatography (tlc) was performed on Merck 5554 Alufolien Kieselgel $60F_{254}$ plates with incorporated fluorescent indicator. Compounds were visualised by irradiation with ultra-violet light (254nm); iodine vapour adsorption and the use of one or more of the following spray reagents: basic potassium permanganate ($KMnO_4$) and 2,4-dinitrophenylhydrazine (DNP). Column chromatography was performed using Merck '7736'(15-50 μm) or '7734'(70-230 mesh) silica gel. Solvents for chromatography were distilled prior to use. Petrol refers to that fraction of petroleum spirit boiling between 40° and 60°C.

Dry tetrahydrofuran (THF) was obtained by distillation from potassium metal. Dry diethyl ether was obtained by distillation from lithium aluminium hydride. Dry diisoproplyamine was distilled from calcium hydride and stored under nitrogen over 4A molecular sieves. Dry dimethyl sulfoxide (DMSO), dimethylformamide (DMF) were obtained by distillation from calcium hydride and stored over 4A molecular sieves.

n-Butyl lithium was standardised before use and its molarity is given where needed. Sodium hydride was obtained as a 60% dispersion in mineral oil and was washed (3x) with petroleum spirit prior to use.

All reactions requiring inert atmospheres were done under either nitrogen or argon.

Melting points are uncorrected.

5.2 Experimental methods

5-(3-Hydroxy-n-propyl)-2-pyrrolidinone (72)

To a refluxing mixture of ester (65) (10.26g, 60mmol), sodium borohydride (5.67g, 0.15mol) in tert-butanol (240ml) was added methanol (48ml) over a period of 1h. Refluxed for a further 1h. The reaction mixture was cooled, quenched with water, concentrated, extracted with chloroform and dried ($MgSO_4$). The organic phase was evaporated to an oil, which was purified by column chromatography on silica gel (dichloromethane-methanol, 10:1) yielding solid (72). 6.11g, 71%. mp: 54-56°C (after recrystalisation from ethyl acetate) (lit.[58] mp 55-57°C). IR (KBr) 3300, 2945, 1680, 1440 and 1060. ^{1}H NMR ($CDCl_3$) 1.30-1.90 (m,5H), 2.0 - 2.50 (m,3H), 2.97 (broad s, 1H) 3.40-3.90 (m,3H) and 7.20 (broad s, 1H).

2,8-Dioxo-1-azabicyclo[3.3.0]octane (66)

Pyridinium dichromate (986mg, 2.61mmol) was suspended in dichloromethane (25ml) and (72) (250mg, 1.74mmol) in dichloromethane (10ml) was added in one portion. After stirring for 24h. (tlc) at room temperature, the black reaction mixture was diluted with ethyl acetate and filtered, the black sticky solid remaining was washed several times with ethyl acetate. The combined organic extracts were evaporated yielding a brown oil which solidified on standing. After recrystallisation from ethyl acetate gave pure (66). 78.3mg, 32%. mp: 176-177°C (lit.[57] mp 176-177°C). IR (KBr) 2980, 1760, 1690, 1380, 1320 and 1080. ^{1}H NMR ($CDCl_3$) 1.7-2.0 (m,2H), 2.3-2.5 (m,2H), 2.56-2.95 (m,4H) and 4.41 (m,1H).

S-5-(Hydroxymethyl)-2-pyrrolidinone (101)

To a refluxing mixture of ester (100) (13.66g, 86.9mmol), sodium borohydride (8.22g, 217mmol) in tert-butanol (348) was added methanol (70ml) over a period of 1h. Refluxed for a further 1h. The reaction mixture was cooled, quenched with water, concentrated, extracted with chloroform and dried ($MgSO_4$). The combined organic phases were concentrated, the resulting oil was purified by column chromatography on silica gel (dichloromethane-methanol, 10:1) giving solid (101). 7.72g, 77.2%.mp:66-69°C (lit.[76] mp 65-67°C). IR ($CHCl_3$) 3340 (broad), 2930, 1680, 1410, 1250 and 1040. ^1H NMR ($CDCl_3$) 1.70 (m,1H), 2.20 (m,3H), 3.20-3.80 (m,3H), 4.75 (broad s, 1H) and 7.50 (broad s, 1H).

S-5-(Bromomethyl)-2-pyrrolidinone (98)

Triphenylphosphine (7.2g, 27.4mmol) was added to a suspension of alcohol (101) (3.0g, 26.1mmol) in acetonitrile (50ml) under nitrogen. The mixture was cooled in an ice bath and carbon tetrabromide (9.1g, 27.4mmol) in acetonitrile (25ml) was added dropwise over 15 min. The resulting light yellow solution was stirred at room temperature under a nitrogen atmosphere overnight. The solvent was removed in vacuo and water (100ml) and hexane (100ml) was added to the oily residue. The mixture was stirred vigorously until a solid formed. The solid was removed by suction filtration and washed with water (100ml). The organic and aqueous layers of the filtrate were separated. The aqueous solution was extracted with $CHCl_3$ (7 x 100ml) and ether (2 x 50ml). The combined organic extracts were dried ($MgSO_4$) and the solvent was removed in vacuo to give a light yellow.

Purification by column chromatography on silica gel (chloroform-ethyl acetate, 1:1) afforded (98).3.0g,65%.mp:70-73°C (lit.[76] mp 71-74°C). IR(KBr) 3180, 2980, 1680, 1420, 1330 and 1280. ^{1}H NMR ($CDCl_3$) 1.90 (m,H), 3.40 (d,2H), 3.98 (m,1H) and 7.38 (broad s, 1H).

5-(3-Butenyl)-2-pyrrolidinone (94) from (98)

To a mixture of degassed toluene (6ml), bromide (98) (1.05g, 5.89mmol) and azobis(isobutyronitrile) (AIBN) (145mg, 0.88mmol) was added allyltri-n-butylstannane (3.90g, 11.7mmol) in one portion. After the addition of the reaction mixture was stirred at 80°C for 19h. The toluene was removed in vacuo, the residual oil was purified by column chromatography on silica gel (ethyl acetate-petrol, 3:2) followed by ether-methanol, 5:1) to give an oil (94). 294mg, 32.6%. IR (liq film) 3250, 3090 and 1700. ^{1}H NMR ($CDCl_3$) 1.5-2.5 (m,8H), 3.6 (m,1H), 4.8 (m,1H), 5.1 (m,1H), 5.3-6.2 (m,1H) and 7.5 (broad s, 1H).

4-Pentenoic acid (110)

To a 2-litre three-necked flask fitted with a mechanical stirrer, reflux condensor and addition funnel was prepared a solution of sodium ethoxide from sodium (34.4g, 1.50mol) and dry ethanol (1000ml). After the solution has cooled to about 50°C, diethyl-malonate (235ml, 1.54mol) was added over a period of 1.5h. After the addition was complete, allyl chloride (120.0g, 1.57mol) was added. The reaction mixture was subsequently refluxed for 2h. As much of the ethanol was removed by distillation. The contents were cooled and water (600ml) was added and the solution shaken.

The organic and aqueous layer were separated. The aqueous layer was extracted with ether. The combined organic layers were dried ($MgSO_4$) and the solvent evaporated to afford crude diethyl allylmalonate (109), 266.14g, 86.4%, which was used directly in the next step without further purification.

To a 2-litre three-necked flask fitted with a mechanical stirrer, reflux condensor and an addition funnel was placed a hot solution of potassium hydroxide (275g, 4.90mol) in water (300ml). To the stirred solution was added diethyl allylmalonate (109) (266g, 1.33mol). A vigorous action occurs and the solution refluxes. When all the ester has been added, the solution was refluxed for 2-3h. The reaction mixture was diluted with water (200ml) and liquid (300ml) was distilled off in order to ensure the complete removal of the alcohol formed in the hydrolysis. To the cold residue was added a cold solution of concentrated sulphuric acid (250ml) in water (250ml) (caution; frothing). The solution becomes hot. The reaction mixture was refluxed for 3-4h and allowed to cool where upon the mixture was extracted with ether (5 x 200ml) and the combined ethereal layers were washed with water (100ml) and dried ($MgSO_4$). Concentration and subsequent distillation afforded the acid (110). 101.08g, 76%. bp: 82-86°C/12mm (lit.[83] 83-85°C/16mm). IR (liq film) 3200-2800, 1715, 1415 and 1280. ^{1}H NMR ($CDCl_3$) 2.40 (s, 4H), 4.95 (m, 1H), 5.15 (m, 1H), 5.60-6.20 (m, 1H) and 10.75 (broad s, 1H).

4-Penten-1-ol (112)

A slurry of lithium aluminium hydride (9.65g, 0.225mol) in dry ether (300ml) was mechanically stirred in a 1l flask and a

solution of 4-pentenoic acid (110) (24.5g, 0.245mol) in dry ether (200ml) was slowly added with external cooling and stirred overnight. The reaction mixture was quenched (caution) with water (12.5ml), 15% sodium hydroxide solution (12.5ml), water (37.5ml). The reaction contents were filtered, the precipatate washed with ether. The filtrate was dried over $MgSO_4$, concentrated and subsequently distilled to yield pure (112). 15.32g, 72.6%. bp: 135-138°C (lit.[82] bp 138-139°C). IR (liq film) 3440, 3080, 2940, 1640, 1440 and 1060. ^1H NMR ($CDCl_3$) 1.33-2.4 (m, 4H), 3.2 (s, 1H), 3.56 (t, 2H), 4.8 (m, 1H), 5.05 (m, 1H) and 5.4-6.15 (m, 1H).

5-Bromo-1-pentene (113)

To cold (-15°) PBr_3 (24.0g, 89mmol) was added dropwise and with stirring over 2h. with continuous cooling a mixture of alcohol (112) (14.6g, 170mmol) and pyridine (5.3g, 67mmol). The resulting mixture, an orange slurry was stirred at 25°C for 2h. and then distilled to separate the bromide (113) (16.50g). Dilution with ether, washing with minimum saturated sodium bicarbonate, drying over $MgSO_4$, concentration, subsequent distillation of liquid gave pure (113). 9.8g, 39%. bp: 124-128°C (lit.[84] bp 124-128°C). IR (liq film) 1650 and 1440. ^1H NMR ($CDCl_3$) 1.60-2.60 (m, 4H), 3.32 (t, 2H), 4.98-5.05 (m, 2H) and 5.10-6.20 (m, 1H).

5-Nitro-pentene (107)

A solution of bromide (113) (4.48g, 0.03moles) and sodium nitrite (3.65g, 0.053moles) in dimethyl sulfoxide (25ml) was stirred

for 20 minutes at room temperature, after which the reaction mixture solidified and was left standing for a total of 2.5h.
The solid was dissolved with water (30ml) and the solution was extracted with $CHCl_3$. The organic layer was washed thoroughly with water and dried over $MgSO_4$. Evaporation of solvent, purification by column chromatography on silica gel (ethyl acetate-petrol, 1 : 4) gave (107) a pale yellow oil. 1.70g, 49%. IR (liq film) 3090, 2940, 1650, 1550, 1440, 1385 and 1000. ^1H NMR ($CDCl_3$) 2.0-2.30 (m, 4H), 4.40 (t, 2H), 5.05 (m, 1H), 5.12 (m, 1H), and 5.6-5.95 (m, 1H).

Methyl 4-nitro-7-octenoate (106)

The preparation of (106) using diisopropylamine as catalyst

To a stirred solution of (107) (646mg, 5.6mmol) in chloroform (6ml) was added diisopropylamine (0.3ml, 2mmol) and methyl acrylate (0.50ml, 5.6mmol). The mixture was stirred for 5 days at 50°C.
The reaction mixture was acidified with 2N hydrochloric acid, diluted with chloroform. The organic phase was separated and the aqueous phase extracted with chloroform. The combined organic phases were washed with water, dried ($MgSO_4$). Evaporation gave a dark orange oil containing two components (tlc). These were separated by column chromatography on silica gel (ethyl acetate-petrol, 1 : 4).

The first eluted material was isolated as a oil (460mg, 40.7%) was (106) IR (liq film) 3020, 2950, 1730, 1640, 1560 and 1380-1310. ^1H NMR ($CDCl_3$) 1.5-2.75 (m, 8H), 3.65 (s, 3H), 4.5 (m, 1H), 4.9 (m, 1H), 5.1 (m, 1H) and 5.3-6.1 (m, 1H).

The second eluted material, a oil, (410mg, 25.4%) was (114). IR (liq film) 3010, 2980, 1740, 1550, 1450 and 1200. ^{1}H NMR ($CDCl_3$) 2.0 (d, 4H), 2.3 (s, 8H), 3.60(s, 6H), 4.95 (m, 1H), 5.1 (m, 1H) and 5.4-6.2 (m, 1H).

The preparation of (106) using Triton B as catalyst

To a stirred solution of (107) (7.17g, 62mmol) and benzyltrimethylammonium hydroxide (40% solution in water) (Triton B) (2.80g, 16.7mmol) was slowly added methyl acrylate (5.36g, 62mmol). The mixture was stirred overnight at 50-55°C. The reaction mixture was acidified with 2N hydrochloric acid, diluted with dichloromethane. The organic phase was separated, washed with water, dried ($MgSO_4$). Evaporation of the organic phase gave a dark orange oil containing two compounds (tlc). These were separated by column chromatography on silica gel (ethyl acetate-petrol, 1 : 4).

The first eluted material, isolated as a oil (7.05g, 56.6%) was (106). IR (liq film) 3100, 2950, 2850, 1730, 1640, 1560, 1450-1380 (broad), 1000 and 920. ^{1}H NMR ($CDCl_3$) 1.60-2.70 (m, 8H), 3.65 (s, 3H), 4.3 (m, 1H), 4.9 (m, 1H), 5.15 (m, 1H) and 5.4-6.2 (m, 1H). Microanalysis found C, 53.40; H, 7.40; N, 6.92. $C_9H_{15}NO_4$ requires C, 53.76; H, 7.46; N, 6.96.

The second eluted material, a oil, (4.33g, 24.2%) was (114). IR (liq film) 3100, 2970, 1740, 1650, 1550, 1450, 1385, 1330, 1200, 1000 and 760. ^{1}H NMR ($CDCl_3$) 1.90-2.10 (d, 4H), 2.3 (s, 8H), 3.60 (s, 6H), 4.95 (m, 1H), 5.15 (m, 1H) and 5.40-6.05 (m, 1H). Microanalysis found C, 54.50; H, 7.40; N, 4.91. $C_{13}H_{21}NO_6$ requires C, 54.40; H, 7.31; N, 4.87.

5-(3-Butenyl)-2-pyrrolidinone (94) from (106)

To a mixture of concentrated HCl (40ml) and methanol (40ml) were added at the same time at 0°C the nitro-ester (106) (4.02g, 20mmol) in methanol (20ml) and zinc powder (13.1g, 0.2mol) dropwise and in small portions, respectively, over 0.5h. After the addition, the reaction mixture was stirred at 25°C for 0.5h and then filtered and treated with 6N NaOH (400ml). The clear solution was extracted with CH_2Cl_2 (3 x 200ml), and then the combined organic extracts were washed with brine (20ml) and dried ($MgSO_4$). Evaporation of the solvent gave the lactam (94) which was subsequently purified by column chromatography on silica gel (ethyl acetate-petrol, 4:1) giving pure (94). 2.3g, 82.7%. IR (liq film) 3220, 3080, 2930, 1700 and 1430. ^1H NMR ($CDCl_3$) 1.40-2.0 (m, 4H), 2.0-2.5 (m, 4H), 3.70 (m, 1H), 5.02 (m, 1H), 5.14 (m, 1H), 5.7-5.98 (m, 1H) and 6.98 (broad s, 1H). Microanalysis found C, 69.40; H, 9.68; N, 9.66. $C_8H_{13}NO$ requires C, 69.08; H, 9.34; N, 10.06.

5-(3,4-Epoxybutyl)-pyrrolidin-2-one (119)

To a solution of (94) (1.00g, 7.19mmol) in dichloromethane (20ml) was added m-chloroperbenzoic acid (mcpba, 85%) (2.18g, 0.0126mol) in small portions over 5-10 minutes. The mixture was stirred at 25°C overnight. The mixture was filtered to remove insoluble mcba. The filtrate was first washed with portions of 10% aqueous sodium sulfite (x2) and then 10% aqueous sodium bicarbonate (x2). The organic solution was dried over $MgSO_4$. Removal of the CH_2Cl_2 under vacuo gave epoxide (119). 510mg, 45.9%. IR ($CDCl_3$) 3220, 2940, 1680 (broad), 1420 and 1260. ^1H NMR ($CDCl_3$) 1.20-2.0 (m, 4H),

2.10-2.42 (m, 4H), 2.50 (m, 1H), 2.78 (m, 1H), 2.95 (m, 1H), 3.70 (m, 1H) and 7.30 (broad s, 1H). Epoxide (119) was used in the next step without further purification

8-(Hydroxymethyl)-1-azabicyclo [3.3.0] octan-2-one (120)

To a suspension of sodium hydride (650mg, 27mmol) in dry benzene (10ml) under nitrogen was added the epoxide (119) (870mg, 5.61mmol) in benzene (30ml). The heterogeneous mixture was refluxed overnight, cooled and poured onto crushed ice. The mixture was adjusted to pH4.0 with 25% aqueous sulphuric acid. The benzene solution was separated and the aqueous phase was extracted repeatedly with dichloromethane. The organic extracts were combined, dried ($MgSO_4$) and the solvent removed in vacuo to yield an oil which was chromatographed on silica gel (ether-methanol, 10:1) to give (120). 261mg, 30%. IR (liq film) 3280 (broad), 2980, 2920, 2870, 1660, 1420, 1230 and 1060. ^1H NMR ($CDCl_3$) 1.1-3.0 (m, 8H), 3.70 (s, 2H), 4.0 (m, 1H) and 5.23 (broad s, 1H). Addition of D_2O caused the signal at 5.23δ to collapse. Mass spectrum, m/z 124 ($M^+ - CH_2OH$).

8-(Iodomethyl)-1-azabicyclo [3.3.0] octan-2-one (121)

To a solution of (94) (250mg, 1.79mmol) in dry dichloromethane was added sodium carbonate (375mg, 3.53mmol) and iodine (91mg, 3.59mmol) under nitrogen. The reaction vessel was wrapped in aluminium foil and the contents stirred overnight. The reaction mixture was filtered to remove sodium carbonate and dried ($MgSO_4$). Evaporation gave a dark oil residue which was purified by column chromatography on silica gel (dichloromethane-methanol, 10:1) giving

(121). 210mg, 44.3%. IR (liq film) 2965, 1670 and 1410. ^{1}H NMR ($CDCl_3$) 1.3-3.0 (m, 9H), 3.6 (s, 2H) and 4.1 (m, 1H).

8-[(Mercurioacetoxy)methyl]-1-azabicyclo[3.3.0] octan-2-one (122)

To a magnetically stirred suspension of mecuric acetate (1.81g, 5.69mmol) in water (6.5ml) and THF (6.5ml) was added (94) (360mg, 2.58mmol) in THF (6.5ml) and stirred for 18h. The THF was removed in vacuo and the remaining solution was diluted with chloroform. The organic and aqueous layers were separated and the aqueous phase extracted with chloroform. The combined organic phases were washed with water and dried (Na_2SO_4). Evaporation afforded a viscous oil (122). 970mg, 94%. IR (liq film) 2970, 2860, 1700, 1420, 1360 and 1010. ^{1}H NMR ($CDCl_3$) 1.20-3.10 (m, 13H) and 4.0 (m, 2H). ^{13}C NMR ($CDCl_3$) 23.27, 25.78, 27.97, 29.64, 37.74, 39.56, 53.29, 65.72, 172.23 and 176.79. Mass spectrum; m z 397 (M^+), 338 ($M^+ - O_2CCH_3$).

8-[(Mercuriochloro)methyl]-1-azabicyclo[3.3.0] octan-2-one (125a)

To a solution of (122) (1.47g, 3.69mmol) in methanol (50ml) was added saturated sodium chloride (30ml) and the solution stirred for 4h at 25°C. The methanol was removed in vacuo, the residue was diluted with saturated sodium chloride (75ml) and the aqueous solution thoroughly extracted with chloroform. The chloroform extracts were dried (Na_2SO_4) and concentrated to afford a solid (125a). 1.03g, 74.5%. mp : 127-129°C. IR (KBr) 2960, 2930, 2860, 1650, 1445 and 1415. ^{1}H NMR ($CDCl_3$) 1.20-1.30 (m, 10H) and 4.00 (m, 2H). ^{13}C NMR ($CDCl_3$) 28.10, 29.15, 30.78, 37.75, 39.87, 53.44, 65.73 and 172.25.

Mass spectrum, m/z 374 (M^+), 138 (M^+-HgCl), 124.

8-Methyl-1-azabicyclo[3.3.0]octan-2-one (126)

Oxygen was vigorously bubbled into a magnetically stirred solution of sodium borohydride (212mg, 5.61mmoles) in DMF (3.5ml) for 15min. The oxygen was supplied to the bottom of the reaction flask through three 20- gauge needles. Compound (125a) (1.5g, 4mmol) was dissoved in DMF (5ml). This solution was also saturated with oxygen and then added dropwise via syringe over a period of 1h to the sodium borohydride solution. After the addition was complete, the solution was stirred and a vigorous flow of oxygen was maintained for 30min. The contents were filtered with suction through Hyflo super cell filter aid. The filtrate was concentrated and the remaining residue was diluted with water and 2N Hydrochloric acid. The aqueous solution was extracted with chloroform and the organic phase washed with a minimum amount of water and dried ($MgSO_4$). Concentration in vacuo gave an oil which was purified by column chromatography on silica gel (ether-methanol, 10:1) gave (126). 490mg, 88%. IR (liq film) 2960, 2920, 2860, 1680 and 1410. ^1H NMR ($CDCl_3$) 1.3 (d,3H), 1.3-2.8 (m, 8H) and 3.7 (m, 2H).
Mass spectrum, m/z 139 (M^+), 124 (M^+-CH_3).

8-(Iodomethyl)-1-azabicyclo[3.3.0] octan-2-one (121)

To a magnetically stirred solution of mercuric acetate (38.85g, 112.5mmol) in THF (147ml) was added (94) (7.70g, 55mmol) in THF (147ml). The solution was stirred at room temperature overnight and then concentrated. The resulting mercury acetate (122) was dissolved

in acetone (700ml) and treated with potassium iodide (50.3g, 303mmol). The flask was wrapped in aluminium foil and magnetically stirred overnight. The resulting solution was concentrated and diluted with chloroform and water. The layers were separated and the aqueous phase extracted with chloroform. The chloroform extracts were washed with water, saturated sodium chloride and dried (Na_2SO_4), filtered and concentrated to yield the crude mercury iodide (125b). This material (125b) was dissolved in dry dichloromethane (700ml) under nitrogen, placed in an ice/brine bath, and treated, with stirring, with iodine (8.26g, 32mmol). The flask was removed from the ice bath, wrapped in aluminium foil, allowed to warm slowly to room temperature, and stirred overnight. The solution decanted away from the mecuric iodide solids, concentrated and chromatographed on silica gel (ether-methanol, 10:1) to yield iodide (121). 3.68g, 25.2% based on (94). IR (liq film) 2960, 2860, 1680, 1410, 1300 and 1180. ^1H NMR ($CDCl_3$) 1.20-3.0 (m, 9H), 3.75 (s, 2H), and 4.1 (m, 1H). ^{13}C NMR ($CDCl_3$) 8.71, 27.92, 29.02, 35.68, 37.36, 53.43, 65.01 and 172.65. Mass spectrum, m/z 265 (m^+), 124 ($m^+ - CH_2I$).

8-[(Acetoxy)methyl]-1-azabicyclo[3.3.0]octan-2-one (129)

To a solution of iodide (121) (3.68g, 13.8mmol) and glacial acetic acid (28ml) was added mercuric acetate (4.42g, 13.8mmol) and the solution was heated with stirring for 3h. The mixture was cooled to room temperature, diluted with water, extracted with chloroform and the organic layer washed with saturated aqueous sodium bicarbonate, water and dried ($MgSO_4$). Filtration and concentration provided an oil containing two components (tlc), which was purified by column

chromatography on silica gel (ether-methanol, 10:1).

The first eluted material isolated as an oil was (129). 230mg, 8.5% IR (liq film) 2970, 2870, 1740, 1670, 1410, 1230 and 1040. ^{1}H NMR ($CDCl_3$) 1.10-1.95 (m, 4H), 2.0 (s, 3H), 2.05-2.80 (m, 5H), 3.60 (m, 1H) and 4.20 (d, 2H). Mass spectrum, m/z 124 (M^+-CH_2OOCCH_3). Microanalysis found C, 53.7; H, 6.87; N, 5.75. $C_{10}H_{15}NO_3$ requires C, 60.9; H, 7.7; N, 7.1.

The second eluted material (810mg, 38.6%) was identical (i.r., nmr spectroscopy) with the alcohol (120).

The preparation of alcohol (120) from (129)

To (129) (90mg, 0.456mmol) was added 10% sodium hydroxide solution (5ml) and the resultant heterogeneous solution was stirred with warming (25°C) until homogeneous. The aqueous solution was extracted with ethyl acetate and dried ($MgSO_4$). Evaporation gave an oil which was purified by column chromatography on silica gel (ether-methanol, 10:1) which gave a material (58.5g, 82.6%) that was identical (ir and nmr spectroscopy) with the alcohol (120).

2,2-Dimethyl-3-oxa-1-azabicyclo [3.3.0] octan-8-one (139)

To a solution of alcohol (101) (12.41g, 107mmol) in dry toluene (250ml) was added 2,2-dimethoxy propane (14.59g, 140mmol) and p-toluenesulphonic acid (225mg, 1.18mmol) and the mixture refluxed for 2h. The cooled reaction mixture was washed with saturated sodium bicarbonate, saturated sodium chloride solution and dried ($MgSO_4$). Concentration in vacuo gave a semi-solid which was purified

by column chromatography on silica gel (ethyl acetate-petrol, 3:2) gave solid (139). 10.0g, 59.8%. mp. 39-41°C. IR ($CHCl_3$) 2980, 1680, 1400 and 1230. ^1H NMR ($CDCl_3$) 1.46 (s, 3H) and 1.60 (s, 3H), 1.80 (m, 1H), 2.18 (m, 1H), 2.52 (m, 1H), 2.90 (m, 1H), 3.46 (m, 1H), 4.10 (m, 1H) and 4.20 (m, 1H). Mass spectrum, m/z 155 (M^+), 140 (M^+-CH_3). Microanalysis found C, 61.5; H, 8.6; N, 9.1. $C_8H_{13}NO_2$ requires C, 61.9; H, 8.44; N, 9.03.

7-(1-Propenyl)-2,2-dimethyl-3-oxa-1-azabicyclo [3.3.0] octan-8-one (144)

A solution of diisopropylamine (17.42ml, 124mmol) in THF (300ml) was cooled to -25°C and n-butyllithium (80.19ml, 124mmol of a 1.55M solution in n-hexane) was added with vigorous stirring. The solution was stirred for 5 minutes at -25°C and then cooled to -78°C and (139) (17.59g, 113mmol) in THF (100ml) was added with vigorous stirring. The mixture was stirred for another 30 minutes at -78°C and allyl bromide (10.76ml, 124mmol) was added to the reaction mixture over a period of 10 minutes. The reaction mixture was stirred for a further 1h at -78°C and then quenched by pouring onto ice-water (100ml). The organic phase was separated and the aqueous phase extracted with chloroform. The combined organic extracts were washed with water, saturated sodium chloride solution and dried ($MgSO_4$). Concentration in vacuo gave an oil containing two components (tlc). These were separated by column chromatography on silica gel (ethyl acetate-petrol, 3:2).

The first eluted material (Rf 0.42), isolated as an oil was

(144a) (5S, 7S). 14.0g, 63.3%. IR (liq film) 3060, 2970, 2910, 2860, 1700, 1405 and 1265. ^{1}H NMR ($CDCl_3$) 1.45 (s, 3H) and 1.6 (s, 3H), 1.8-3.15 (m, 5H), 3.15-3.6 (m, 1H), 3.7-4.35 (m, 2H), 4.8 (m, 1H), 5.1 (m, 1H) and 5.35-6.1 (m, 1H). Mass spectrum, m/z 195 (M^+), 180 (M^+-CH_3). Microanalysis found C, 67.7; H, 9.0; N, 7.1. $C_{11}H_{17}NO_2$ requires C, 67.67; H, 8.77; N, 7.17.

The second eluted material (Rf 0.31), isolated as a oil was (144b) (5S 7R). 5.15g, 23.3%. IR (liq film) 3070, 2970, 2910, 1710, 1405 and 1260. ^{1}H NMR ($CDCl_3$) 1.42 (s, 3H) and 1.65 (s, 3H), 1.7-3.1 (m, 5H), 3.2-3.6 (m, 1H), 3.7-4.5 (m, 2H), 4.9 (m, 1H), 5.15 (m, 1H) and 5.3-6.3 (m, 1H). Mass spectrum, m/z 180 (M^+-CH_3). Microanalysis found C, 67.4; H, 9.2; N, 6.25. $C_{11}H_{17}NO_2$ requires C, 67.66; H, 8.77; N, 7.17.

(Total yield of (144a) and (144b), 19.15g, 86.6%).

<u>The preparation of 3-(1-Propenyl)-5-hydroxymethyl-2-pyrrolidinone (145), (145a) and (145b)</u>

These were prepared in an identical manner as illustrated by the general procedure outlined below.

Aqueous acetic acid (1:2 H_2O/AcOH) was added to a solution of (144) in THF. The volume of H_2O/AcOH used was equal to twice that of THF. The solution was heated at 50-55°C for a period of 3h. The cooled reaction mixture was diluted with THF and neutralised to pH 7-8 using solid sodium carbonate (caution frothing). The solution was filtered and the precipitate washed several times with THF. The organic/aqueous filtrate was separated and the aqueous layer extracted with ethyl acetate. The combined organic phase

was dried over $MgSO_4$ and the residue after evaporation subjected to column chromatography on silica gel (ethyl acetate-petrol, 10:1) to give the products (145), (145a) and (145b).

(145) diastereomeric mixture from (144) diastereomeric mixture (500mg, 2.56mmol), glacial acetic acid (13.3ml), water (6.6ml) and THF (10ml) gives waxy solid (145). 163mg, 40.3%. IR ($CHCl_3$) 3280 (broad), 3070, 1680 and 1240. ^1H NMR ($CDCl_3$) 1.1-3.0 (m, 5H), 3.25 (s, 1H), 3.25-4.1 (m, 3H), 4.8-6.2 (m, 3H) and 7.1 (broad s, 1H). Also isolated, although apparently homogeneous (tlc) probably a mixture of diastereoisomers, acetate (147), waxy solid. 83mg, 16.4%. IR ($CHCl_3$) 3210, 3070, 2910, 1740, 1690 and 1210. ^1H NMR ($CDCl_3$) 1.4-2.1 (m, 2H), 2.1 (s, 3H), 2.1-2.9 (m, 3H), 3.5-4.4 (m, 3H), 4.9 (m, 1H), 5.1 (m, 1H), 5.35-6.2 (m, 1H) and 6.4 (broad s, 1H). Mass spectrum, m/z 198 ($M^+ + 1$), 124 ($M^+ - CH_2O_2CCH_3$).

(145a) from (144a) (14.0g, 71.8mmol), glacial acetic acid (30ml), water (15ml) and THF (23ml) gives the <u>cis isomer</u> (2S,5S), a solid, (145a). 2.65g, 23.4%. mp: 54-56°C. IR (KBr) 3360 (broad), 3080, 2920, 1620, 1430, 1310 and 1100. ^1H NMR ($CDCl_3$) 1.5 (m, 1H), 1.7-2.25 (m, 2H), 2.25-3.8 (m, 2H), 3.0-4.0 (m, 3H), 4.6 (broad s, 1H), 4.85 (m, 1H), 5.05 (m, 1H), 5.3-6.15 (m, 1H) and 7.4 (broad s, 1H). Mass spectrum, m/z 155 ($M^+ - CH_2OH$). Microanalysis found C, 62.9; H, 8.6; N, 8.4. $C_8H_{13}NO_2$ requires C, 61.9; H, 8.43; N, 9.02.

(145b) from (144b) (5.15g, 33.2mmol), glacial acetic acid (20ml), water (10ml) and THF (15ml) gives the <u>trans isomer</u> (2R,5S), a oil, (145b). 830mg, 20.2%. IR (liq film) 3300, 3080, 2940, 1680 (broad), 1440, 1310, 1270 and 1060. ^1H NMR ($CDCl_3$) 1.7-2.15 (m, 2H), 3.2-3.8 (m, 3H), 4.25 (broad s, 1H), 4.85 (m, 1H), 5.05 (m, 1H),

5.25-6.1 (m, 1H) and 7.2 (broad s, 1H). Mass spectrum, m/z 155 (M^+). Microanalysis found C, 59.6; H, 8.40; N, 8.40. $C_8H_{13}NO_2$ requires C, 61.9 ; H, 8.40; N, 9.00.

The acetate (147) was not isolated in the latter two cases.

Methyl 7-(1-propenyl)-8-oxo-3-oxa-1-azabicyclo[3.3.0]octane-2-carboxylate (142)

To a flask fitted with a Dean-Stark trap was added a solution of the alcohol (145) (1.07g, 6.90mmol) in dry toluene (50ml), methyl 2,2-dimethoxy acetate (1.20g, 8.97mmol) and p-toluenesulphonic acid (14mg, 0.0759mmol) and the mixture refluxed for 7 days. The trapped toluene/methanol was removed periodically. Also dry toluene was periodically added to the reaction mixture. The cooled reaction mixture was washed with saturated sodium bicarbonate and saturated sodium chloride solution. The organic phase was dried ($MgSO_4$) and evaporated to give an oil containing two major components (tlc). These were separated by column chromatography on silica gel (ethyl acetate-petrol, 10:1).

The first eluted material, isolated as a viscous oil was (142). 90mg, 5.8%. IR (liq film) 3030, 2980, 1770 and 1700. ^1H NMR ($CDCl_3$) 1.5-3.1 (m, 5H), 3.6-4.4 (m, 6H), 4.8 (s, 1H), 4.9 (m, 1H), 5.2 (m, 1H) and 5.25-6.2 (m, 1H). Mass spectrum, m/z 226 ($M^+ + 1$), 166 ($M^+ - CO_2CH_3$).

The second eluted material, isolated as an oil was methyl 2-methoxy-3-oxa-4-(3-[1-propenyl]-2-oxopyrrolidin-5-yl)butanoate (146). 280mg, 15.8%. IR (liq film) 3210 (broad, 2910, 1740, 1680, 1440, 1240 and 1120. ^1H NMR ($CDCl_3$) 1.2-2.9 (m, 5H), 3.3 (s, 3H), 3.3-3.8 (m, 2H), 3.8 (s, 3H), 3.8-4.3 (m, 1H), 4.8 (s, 1H),

4.9 (m, 1H), 5.15 (m, 1H), 5.45-6.0 (m, 1H) and 7.2 (broad s, 1H). Mass spectrum, m/z 257 (M^+), 124 ($M^+-C_5H_9O_4$). Microanalysis found C, 56.4; H, 7.5; N, 5.41. $C_{12}H_{19}NO_5$ requires C, 56.02; H, 7.4; N, 5.44.

The preparation of (142) from (146)

To a flask fitted with a Dean-Stark trap was added a solution of (146) (700mg, 2.72mmol) in dry toluene (25ml) and p-toluenesulphonic acid (5.70mg, 0.03mmol) and the mixture refluxed for 5 days. The trapped toluene/methanol was removed periodically. Also dry toluene was added periodically to the reaction mixture. The cooled reaction mixture was washed with saturated sodium bicarbonate and saturated sodium chloride solution. The organic phase was dried ($MgSO_4$) and evaporated to give an oil which was purified by chromatography on silica gel (ethyl acetate-petrol, 10:1) giving a material (120mg, 19.6%) that was similar (tlc and nmr spectroscopy) with (142).

S-5-(p-Tolylsulphonyloxymethyl)-2-pyrrolidinone (102)

To a solution of alcohol (101) (5.53g, 48mmol) in pyridine (20ml) cooled to 0°C was added p-toluenesulphonyl chloride (13.70g, 72mmol). After the addition, the reaction mixture was stirred for several minutes at 0°C and then allowed to stand at room temperature for 2.5h.

To the solution was then added water (15ml) and allowed to stand for a further 3h. The solution was then treated with water (40ml) and the mixture was extracted with dichloromethane.

The combined organic phases were washed with 2N hydrochloric acid,

saturated sodium bicarbonate solution and subsequently dried ($MgSO_4$). Concentration yielded (102). 4.04g, 31.2%. mp: 128–130°C (After recrystalisation from ethanol) (lit.[79] mp 130°C). IR (KBr) 3300, 2910, 1650, 1350 and 1170. ^1H NMR ($CDCl_3$) 1.90 (m, 1H), 2.30 (m, 3H), 2.45 (s, 3H), 3.90-4.20 (m, 3H), 6.50 (broad s, 1H), 7.40 (d, 2H) and 7.80 (d, 2H).

Butyl hydroxy-[2-oxo-5-(p-tolylsulphonyloxymethyl)-pyrrolidin-1-yl] acetate (153)

To a stirred solution of tosylate (102) (844mg, 3.13mmol) in dry THF (40ml) was added butyl glyoxylate (1.02g, 7.84mmol) followed by triethylamine (0.44ml, 3.17mmol). After being stirred for 16h the solution was evaporated to dryness and the residue was dissolved in ethyl acetate. The solution was washed with saturated sodium chloride (2x) and was dried ($MgSO_4$) and subsequently concentrated. Purification by column chromatography on silica gel (ethyl acetate-petrol, 1:1) afforded a pale yellow oil (153). 1.01g, 80.8%. IR (liq film) 3350 (broad), 2960, 2870, 1750, 1660, 1360 (broad), 1240 (broad), and 1090. ^1H NMR ($CDCl_3$) 0.8-2.4 (m, 11H), 2.46 (s, 3H), 3.8-4.4 (m, 6H), 5.30 (d, 1H) also observed doublet at 5.65 attributable for 1H, for other diastereoisomer , 7.38 (d, 2H) and 7.8 (d, 2H). Addition of D_2O caused a signal at 3.8-4.4δ to disappear and that 5.3δ also at 5.65δ to collapse to a singlet. Microanalysis found C, 52.6; H, 6.3; N, 3.4. $C_{18}H_{25}NO_7S$ requires C, 54.12; H, 6.30; N, 3.5.

Butyl(2R,5S)-8-oxo-3-oxa-1-azabicyclo [3.3.0] octane-2-carboxylate (154)

To a stirred solution of (153) (1.71g, 4.28mmol) in dry THF (50ml) at 0°C was added sodium hydride (124mg, 5.18mmol) in dry THF (10ml). After 0.5h the mixture was allowed to warm to room temperature. After stirring for 23h, the mixture was treated with water few drops (caution) and was then diluted with ethyl acetate. After being washed with water, the organic phase was dried ($MgSO_4$) and concentrated to leave a pale-yellow syrup which was subsequently purified by column chromatography on silica gel (ethyl acetate-petrol, 1:1) giving pure (154). 860mg, 88.6%. IR (liq film) 2960, 2870, 1760, 1700, 1470, 1380, 1290, 1180 and 1040. ^1H NMR ($CDCl_3$) 0.7-2.90 (m, 11H), 3.5 (m, 1H), 4.0-4.50 (m, 4H) and 5.73 (s, 1H). ^{13}C NMR ($CDCl_3$) 13.63, 19.02, 23.62, 32.52, 58.61, 65.61, 71.67, 83.29, 168.13 and 173.35. Mass spectrum, m/z 228 ($M^+ + 1$), 126 ($M^+ - C_5H_9O_2$).
Microanalysis found C, 57.6; H, 7.5; N, 5.98. $C_{11}H_{17}NO_4$ requires C, 58.14; H, 7.53; N, 6.16.

The preparation of (156) from (154)

To a solution of diisoproplyamine (0.41mls, 2.90 mmol) in THF (15ml) was cooled to -20°C and n-butyllithium (1.87mls, 2.90mmol of a 1.55M solution in n-hexane) was added with vigorous stirring. The solution was stirred for 5 minutes at -20°C and then cooled to -78°C and (154) (600mg, 2.64mmoles) in THF (10ml) was added with vigorous stirring. The mixture was stirred for another 30 minutes

at -78°C and allyl bromide (0.25ml, 2.97mmol) was added over several minutes. The reaction mixture was stirred for a further 1h at -78°C and then quenched by pouring onto ice-water. The organic phase was separated and the aqueous phase extracted with chloroform. The organic extracts were washed with water, saturated sodium chloride solution and dried ($MgSO_4$). Concentration in vacuo gave an oil which was purified by column chromatography on silica gel (ethyl acetate-petrol, 1:1). The material isolated as an oil, was proposed to be (156) (50mg, 7.1%) based on the nmr spectrum. ^1H NMR ($CDCl_3$) 0.7-2.9 (m, 12H), 3.3-4.4 (m, 5H) and 4.85-6.0 (m, 4H, CH_2=CH, C-2H) within this region a singlet at 5.56 was observed, probably attributable to the C-2 proton .

(2S,5S) 3-(1-Propenyl)-5-(p-tolylsulphonyloxymethyl)-2-pyrrolidinone (159a)

To a solution of alcohol (145a) (2.65g, 17mmol) in pyridine (6.9ml) cooled to 0°C (ice bath) was added p-toluenesulphonyl chloride (4.89g, 25mmol). After the addition, the reaction mixture was stirred for several minutes at 0°C and then allowed to stand at room temperature for 2.5h. To the solution was then added water (20ml) and allowed to stand for a further 1h. The solution was then treated with water (15ml) and the mixture was extracted with dichloromethane. The combined organic phases were washed with water, 2N hydrochloric acid, saturated sodium bicarbonate solution and subsequently dried ($MgSO_4$). Concentration gave (159a). 4.44g, 84.1%. mp : 129-132°C. (after recrystalisation from chloroform). IR (KBr) 3240, 3080, 3010,

2960, 2910, 1660, 1600, 1350, 1170 and 1070. ^{1}H NMR ($CDCl_3$) 1.40 (m, 1H), 1.8-2.4 (m, 2H), 2.4 (s, 3H), 2.4-3.0 (m, 21H), 3.7-4.3 (m, 3H), 4.95 (m, 1H), 5.1 (m, 1H), 5.2-6.2 (m, 1H), 6.55 (broad s, 1H), 7.35 (d, 2H) and 7.8 (d, 2H).

Microanalysis found C, 58.0 ; H, 6.23; N, 4.41 .
$C_{15}H_{19}NO_4S$ requires C, 58.2; H, 6.18; N, 4.52 .

Butyl 7-(1-propenyl)-hydroxy-[2-oxo-5-(p-tolylsulphonyloxymethyl)-pyrrolidin-1-yl] acetate (160a)

To a stirred solution of tosylate (159a) (3.03g, 9.85mmol) in dry THF (100ml) was added butyl glyoxylate (3.27g, 25.2mmol) followed by triethylamine (1.5ml, 10.7mmol). After being stirred for 18h the solution was evaporated to dryness and the residue was dissolved in ethyl avetate. The solution was washed with saturated sodium chloride (2x) and was dried ($MgSO_4$) and subsequently concentrated. Purification by column chromatography on silica gel (ethyl acetate-petrol, 1:1) gave a yellow oil (160a) mixture of diastereoisomers. 3.95g, 91.4%. IR (liq film) 3400 (broad), 3070, 2960, 2880, 1745, 1680, 1600, 1365, 1200 (broad), 1100 and 980. ^{1}H NMR ($CDCl_3$) 0.8-2.45 (m, 7H), 2.45 (s, 3H), 2.45-2.9 (m, 5H), 3.8-4.4 (m, 5H), 4.65 (s, 1H), 4.9 (m, 1H), 5.1 (m, 1H), 5.3 (d, 1H), 5.40-6.2 (m, 1H), (within this region doublet at 5.5δ attributable for 1H for other diastereoisomer) 7.3 (d, 2H) and 7.85 (d, 2H). Addition of D_2O caused the signal at 4.65δ to collapse.

Butyl (2R,5S,7S)-7-(1-propenyl)-8-oxo-3-oxa-1-azabicyclo[3.3.0]octane-2-carboxylate (156a)

To a stirred solution of (160a) (2.00g, 4.55mmol) in dry THF (60ml) at 0°C was added sodium hydride (132mg, 5.5mmol) in dry THF (10ml). After 0.5h the mixture was allowed to warm to room temperature. After stirring for 24h, the mixture was treated with few drops of water (caution) and was then diluted with ethyl acetate. After being washed with water, the organic phase was dried and concentrated to leave a oil which was purified by column chromatography on silica gel (ethyl acetate-petrol, 3:2) giving pure (156a). 570mg, 46.9%. IR (liq film) 3080, 2960, 2880, 1710 (broad), 1460, 1370, 1240 (broad), 1040 and 920. ^{1}H NMR ($CDCl_3$) 0.8-3.2 (m, 12H), 3.5 (m, 1H), 3.8-4.5 (m, 4H), 4.9 (m, 1H), 5.15 (m, 1H), 5.3-6.2 (m, 1H), also observe within this region 5.6 (s, 1H). Microanalysis found C, 63.1; H, 8.3; N, 4.35. $C_{14}H_{21}NO_4$ requires C, 62.91; H, 7.91; N, 5.24.

Sodium (2R,5S)-8-oxo-3-oxa-1-azabicyclo[3.3.0]octane-2-carboxylate (163)

To (154) (280mg, 1.23mmol) was added sodium hydroxide (44mg, 1.1mmol) in water (2ml). The mixture was stirred until homogeneous

and the aqueous solution after being washed with ethyl acetate, was evaporated to dryness with frequent additions of ethanol which gave a viscous oil (163). 140mg, 58.8%. IR (liq film) 1710 (broad) and 1630 (broad). ^{1}H NMR (D_2O) 1.70-3.1 (m, 4H), 3.55 (m, 1H), 3.8-4.5 (m, 2H) and 5.4 (s, 1H).

The sodium salt (163) was used in the next step without further purification.

(2R,5S)-8-Oxo-3-oxa-azabicyclo[3.3.0]octane-2-carboxylic acid (161)

To a solution of (163) (140mg, 1.23mmol) in water was added 2N hydrochloric acid until the solution was at pH 4-5. The aqueous solution was extracted with ethyl acetate and dried ($MgSO_4$). Evaporation gave a viscous oil (161). 60mg, 48.4%. IR (liq film) 3300-2800, 1720, 1670 and 1050. ^{1}H NMR ($CDCl_3$) 1.75-3.1 (m, 4H), 3.45 (m, 1H), 3.9-4.55 (m, 2H), 5.60 (s, 1H) and 7.0 (broad s, 1H). Addition of D_2O caused the signal at 7.0δ to collapse.
Mass spectrum, m/z 126 ($M^+ - CO_2H$).

Sodium (2R,5S,7S)-7-(1-propenyl)-8-oxo-3-oxa-1-azabicyclo[3.3.0]octane-2-carboxylate (164a)

To (156a) (390mg, 1.46mmol) was added sodium hydroxide (55mg, 1.38mmol) in water (2ml). The mixture was stirred until homogeneous and the aqueous solution, after being washed with ethyl acetate, was evaporated to dryness with frequent additions of ethanol which subsequently gave a viscous oil (164a) 260mg, 76.4%. IR (liq film) 3080, 1680 and 1620. ^{1}H NMR (D_2O) 1.8-3.1 (m, 5H), 3.45 (m, 1H),

3.85-4.50 (m, 2H), 4.90 (m, 1H), 5.20 (m, 1H), 5.30 (s, 1H) and 5.35-6.3 (m, 1H). The sodium salt (164a) was used in the next step without further purification.

(2R,5S,7S)-7-(1-Propenyl)-8-oxo-3-oxa-1-azabicyclo [3.3.0] octane-2-carboxylic acid (162a)

To a solution of (164a) (260mg, 1.11mmol) in water (1ml) was added 2N Hydrochloric acid until the solution was at pH4-5. The aqueous solution was extracted with ethyl acetate and dried ($MgSO_4$). Evaporation gave a viscous oil (162a). 30mg, 13.0%. IR (liq film) 3200-2800, 1740, 1700, 1380 and 1090. ^1H NMR ($CDCl_3$) 1.7-3.1 (m, 5H), 3.5 (m, 1H), 3.8-4.5 (m, 2H), 4.9 (m,1H), 5.2 (m, 1H), 5.35-6.2 (m, 1H), also within this region 5.65 (s, 1H) and 9.4 (broad s, 1H). Addition of D_2O caused the signal at 9.4δ to collapse. Mass spectrum, m/z 166 ($M - CO_2H$).

Methyl 2-(cyclopent-2-en-1-yl) acetate (198)

A dichloromethane solution (120ml) of (197) (50.4g, 400mmol), methanol (48.4ml, 1.2mol) and sulphuric acid (1.2ml) was refluxed for 18h. The ;ayers were separated and the aqueous layer was extracted with dichloromethane. The combined organic extracts were washed with saturated aqueous sodium carbonate solution, water, saturated sodium chloride and dried ($MgSO_4$). Concentration in vacuo gave a yellow liquid. Distillation gave pure (198). 48.6g, 86%. bp: 65 - 68°C / 14mm.

(lit.[138] bp 65-68°C/14mm) IR (liq film) 3070, 2970, 2870, 1745, 1445, 1270, 1180 and 1015. ^{1}H NMR ($CDCl_3$) 1.25-2.6 (m, 6H), 2.7-3.35 (m, 1H), 3.65 (s, 2H) and 5.3-5.8 (m, 2H).

2-(Cyclopent-2-en-1-yl)ethanol (199)

To a flame-dried 500ml three-necked flask, fitted with a mechanical stirrer and addition funnel, was placed dry ether (200ml) and lithium aluminium hydride (5.6g, 150mmol). The flask was cooled in an ice bath and a solution of (198) (28g, 200mmol) in ether (100ml) was added dropwise with vigorous stirring under nitrogen. When the addition was complete stirring was continued overnight. The reaction was cautiously quenched with water (6ml) (caution frothing), 15% aqueous sodium hydroxide solution (6ml) and water (18ml). After stirring for 5h, the solid aluminium salts were filtered off and washed with ether. The ether was removed in vacuo and the residue distilled to yield pure (199). 19g, 85%. bp: 80-83°C/10mm. (lit.[138] bp 80-83°C/10mm). IR (liq film) 3320 (broad), 3070, 2950, 2870, 1440 and 1080. ^{1}H NMR ($CDCl_3$) 1.1-2.5 (m, 6H), 2.5-3.1 (m, 1H), 3.6 (t, 3H), 2.9 (s, 1H) and 5.5-5.8 (m, 2H).

The preparation of alcohol (199) from acid (197)

To a slurry of lithium aluminium hydride (5.6g, 150mmol) in dry ether (200ml) was added acid (197) (25.2g, 200mmol) in dry ether (100ml) dropwise with vigorous stirring. When addition was complete stirring was continued overnight. The reaction was cautiously quenched with water (6ml) (caution), 15% aqueous sodium hydroxide (6ml)

and water (18ml). After stirring for 5h, the solid salts were filtered and washed with ether. The ether was removed in vacuo and the residue distilled to afford a material (11.2g, 50%) that was identical (IR and ^{1}H NMR spectroscopy) with the alcohol (199).

2-(Cyclopent-2-en-1-yl)ethyl 4-toluene sulfonate (200)[138]

A solution of the alcohol (199) (1.23g, 11mmol) in dry pyridine (35ml) was cooled to 0°C and p-toluenesulfonyl chloride (4.2g, 22mmol) was added. The solution was kept at -10°C (cooling bath) overnight, then poured onto ice-water and the solution extracted with ether. The organic extracts were washed with 2N Hydrochloric acid, water and dried (K_2CO_3 and Na_2SO_4). The solvent was removed to give a pale yellow oil which was purified by column chromatography on silica gel (ethyl acetate-petrol, 1:1) giving pure (200). 900mg, 73%. IR (liq film) 3020, 2900, 1580, 1440, 1345 and 1160. ^{1}H NMR ($CDCl_3$) 1.1-2.3 (m, 6H), 2.4 (s, 3H), 2.4-2.9 (m, 1H), 4.0 (t, 2H), 5.2-5.8 (m, 2H), 7.1 (d, 2H) and 7.65 (d, 2H).

2-Cyclopentene-1-acetaldehyde (203)[148]

Pyridinium chlorochromate (16.48g, 76.4mmol) and anhydrous sodium acetate (620mg, 7.64mmol) was suspended in methylene chloride (300ml) and (199) (5.71g, 50.9mmol) in methylene chloride (100ml) was added in one portion.

After stirring for 3h (tlc) at room temperature, the black reaction mixture was diluted with ether (1500ml), stirred for 30min and left

standing overnight. The solution was filtered through a pad of Hyperflo and $MgSO_4$, the black solid remaining was washed several times with ether. The combined ethereal extracts were removed in vacuo yielding a dark brown residue which was immediately purified by column chromatography on silica gel (ethyl acetate-petrol, 1:1) giving pure (203). 3.40g, 60.7%. IR (liq film) 3040, 2910, 2700, 1710, 1600 and 1390. ^{1}H NMR ($CDCl_3$) 1.10-2.70 (m, 6H), 2.80-3.40 (m, 1H), 5.30-5.8 (m, 2H) and 9.5 (m, 1H).

3-(2-Cyclopentenyl)1-nitropropane (193a)[146,148]

To a solution of aldehyde (203) (2.41g, 21.9mmol in isopropanol (22ml) was added anhydrous potassium fluoride (63.5mg, 1.09mmol) and nitromethane (2.63ml, 48.5mmol) and stirred overnight. Concentration in vacuo gave the nitroalcohol (204), tlc showed one spot for (204) . IR (liq film) 3400 (broad), 2930, 2850, 1540, 1380, 1200 and 1090. ^{1}H NMR ($CDCl_3$) 1.0-2.5 (m, 6H), 2.6-2.9 (m, 1H), 3.1 (broad s, 1H), 4.3 (s, 2H) and 5.3-5.9 (m, 2H).

To (204) was added dry ether (66ml) followed by a mixture of acetic anhydride (4.20g, 41.1mmol) and 4-dimethylaminopyridine (198mg, 1.62mmol). After stirring overnight at room temperature and concentration in vacuo gave a mixture of the β-nitroacetate (205) and the α,β- unsaturated nitro system (206).
IR (liq film) 3100, 3050, 2940, 2850, 1740, 1650, 1550, 1520, 1430, 1350, 1230 and 1050. ^{1}H NMR ($CDCl_3$) 1.2-2.0 (m, ring CH_2CH_2, CH_2), 2.0 (s, CH_3COO), 2.6-3.0 (m, ring CH), 4.4 (d, CH_2NO_2), 5.1-5.8 (m) and 6.5-7.3 (m) (ring CH=CH, $CH=CHNO_2$).

To a solution of sodium borohydride (2.90g, 76mmol) in ethanol (50ml) was added the mixture of (205) and (206) in ethanol ($15cm^3$) and the resultant solution stirred for 1h. The mixture was then acidified with 2N hydrochloric acid extracted with ether. The ethereal extracts were dried ($MgSO_4$) and evaporation gave an oil which was purified by column chromatography on silica gel (chloroform) giving (193a). 2.84g, 83.8% based on (203). IR (liq film) 3020, 2910, 1540, 1430 and 1375. ^1H NMR ($CDCl_3$) 1.0-2.50 (m, 8H), 2.6-2.9 (m, 1H), 4.30 (t, 2H) and 5.3-5.90 (m, 2H).

Isoxazoline (195a)[135]

A benzene solution (30ml) containing (193a) (1.50g, 9.6mmol), triethylamine (2.30g, 22mmol) and phenyl isocyanate (2.40g, 20mmol) was stirred at 25°C for 12h. The solution gradually became cloudy deposited a precipitate during this period. The mixture was filtered and the solvent evaporated, leaving a residue which was purified by column chromatography on silica gel (chloroform) giving (195a). 1.21g, 92.3%. IR (liq film) 2930, 2860, 1450 and 1240. ^1H NMR ($CDCl_3$) 1.1-2.6 (m, 9H), 3.88-4.02 (dd, 1H) and 4.8-4.9 (m, 1H).

8-Hydroxybicyclo[3.3.0]octan-2-one (169)[116,135]

To a solution of (195a)(5.88g, 43.0mmol) in dry methanol (60ml) was added a suspension of W-2 Raney nickel sludge (133mg,) in methanol (20ml). Glacial acetic acid (0.24ml), 4.30mmol) was added, and the resulting mixture was stirred overnight. The mixture was partitioned between 10% aqueous sodium bicarbonate solution and ether. The organic extracts were combined dried ($MgSO_4$), concentrated

and purified by column chromatography on silica gel (ethyl acetate-petrol, 10:1) (169). 1.53g, 25.4%.
IR (liq film) 3420, 2940, 1730, 1370 and 1010. ^{1}H NMR ($CDCl_3$) 1.10-2.80 (m, 10H), 2.90-3.30 (m, 1H), and 4.10-4.50 (m, 1H).

Bicyclo[3.3.0]oct-8-en-2-one (170)[153]

Methanesulfonyl chloride (2.47ml, 32.0mmol) was added dropwise to a stirred solution of (169) (2.12g, 15.10mmol) and triethylamine (3.98g, 39.3mmol) in dichloromethane at 0°C. After 30min at 0°C, water was added to dissolve the white precipitiate that had formed, and the organic phase was washed succesively with 10% hydrochloric acid, saturated sodium bicarbonate solution, water and brine. After drying ($MgSO_4$) and concentration the oily mesylate mixture was dissolved in dichloromethane (40ml) containing diazabicycloundecene (4.56g, 0.03mmol) and the solution was stirred overnight at room temperature. The organic phase was washed repeatedly with water then brine and dried ($MgSO_4$). Concentration and purification by column chromatography on silica gel (ethyl acetate-petrol, 3:1) gave (170). 900mg, 49.0%. IR (liq film) 3060, 2940, 2860, 1710 and 1640. ^{1}H NMR ($CDCl_3$) 1.0-3.80 (m, 9H) and 6.35-6.6 (dd,1H).

8-Cyanobicyclo[3.3.0]octan-2-one (171)

A solution of (170) (1.65g, 13mmol), acetone cyanohydrin (1.329g, 15.6mmol) and 6% aqueous sodium carbonate (2.67ml) and methanol (8ml) was refluxed for 7h. The solution was evaporated to dryness and the residue was diluted with water (0.45ml). The solution

was extracted with ether and the ethereal extracts dried ($MgSO_4$). Evaporation and purification by column chromatography on silica gel (ethyl acetate-petrol, 9:1) gave (171). 1.83g, 95%. IR (liq film) 2940, 2860, 2220 and 1730. ^1H NMR ($CDCl_3$) 1.2-2.6 (m, 10H) and 2.6-3.3 (m, 1H). Mass spectrum, m/z 149 (M^+).

Bicyclo [3.3.0] octan-2-one-8-carboxylic acid (172)

To a solution of (171) (1.83g, 12.3mmoles) in ethanol (15ml) was added concentrated sulphuric acid (1.30ml) and the resultant mixture refluxed overnight. The mixture was poured onto ice-water and extracted with chloroform and the chloroform extracts washed with 15% sodium carbonate solution, saturated sodium chloride and dried ($MgSO_4$). Evaporation gave an oil (172a), 1.80g, 74.6%. which was used in the next step directly.

A solution of potassium hydroxide (1.30g, 23.4mmol) in water (25ml) was added to (172a) (1.80g, 9.18mmol) and the mixture refluxed until homogeneous (3-5h). The solution was concentrated and the remaining liquid was cooled in an ice-bath and concentrated sulphuric acid (10ml) in water (25ml) was added. The aqueous solution was extracted with chloroform and the organic extracts washed with saturated sodium chloride solution and dried ($MgSO_4$). Evaporation gave an oil (1.1g) which was purified by column chromatography on silica gel (ethyl acetate-petrol, 9:1) giving pure (172). 802mg, 52%. IR (liq film) 3300-2500, 1720 (broad), 1410 and 1200 (broad). ^1H NMR ($CDCl_3$) 1.2-3.40 (m, 10H) and 8.9 (broad s, 1H). Addition of D_2O caused the signal at 8.9δ to collapse. Mass spectrum, m/z 168 (M^+).

5-(Benzyl)-2-pyrrolidinone (104)

To a solution of allyltriphenyltin (9.14 g, 23.4 mmol) in ether (30 ml) under argon was added a solution of 1.7 M phenyl lithium (15 ml, 25.5 mmol) and the mixture was stirred for ½h, whereupon a white precipitate formed. The solution was added to cold (-78 °C) cuprous iodide (2.22g, 11.7 mmol) in THF (6 ml) and stirred for 10 minutes. To the dark grey/black solution was added (102) (633 mg, 2.34 mmol) at -78 °C, the solution became a pale yellow/green colour, and the mixture was stirred for 1h and allowed to warm to room temperature over 2h. The reaction mixture was quenched with 15% ammonium chloride solution and the aqueous/organic phase separated. The aqueous phase was extracted with chloroform and the combined organic phases washed with saturated sodium chloride solution and dried ($MgSO_4$). Concentration in vacuo afforded an oil (104). 170 mg, 44.6%. ^1H NMR ($CDCl_3$) 1.5-2.6 (m, 4H), 2.8 (d, 2H), 3.9 (m, 1H), 6.2 (broad s, 1H) and 7.1-7.5 (m, 5H).

Attempted preparation of (123) from (120)

A solution of alcohol (120) (210 mg, 1.35 mmol) in acetone (10 ml) was cooled to 5-10 °C and 2.8 M CrO_3 in H_2SO_4- water (Jones reagent) (9.2 ml) was added dropwise over 2.5h. Thereafter several drops of methanol were added to destory excess chromic acid, the solvents were evaporated at 40 °C, and to the residue was added water (5 ml). The resulting mixture was extracted with chloroform, the solvent was removed, the residue was dissolved in acetone and the solution treated with sodium bicarbonate (250 mg, 2.97 mmol). The acetone was removed, and to the residue was added water. The mixture was extracted with chloroform. The aqueous phase remaining was acidified with 1 M HCl and the solution extracted with chloroform. Concentration afforded a very small amount of product which did not give a ^1H NMR spectrum resembling that expected for the desired product (123).

Ethyl 2-hydroxybut-3-enoate (79)

To a solution of crude (78) (23.67 g, 0.285 mol) in ethanol (70.7 ml, 1.20 mol) was added concentrated sulphuric acid (30.6 ml) and the mixture was refluxed overnight. The cooled reaction mixture was added to water and the solution was extracted with chloroform. The organic phase was washed with saturated sodium bicarbonate solution and dried ($MgSO_4$). Concentration and subsequent distillation gave (79). 13.92 g, 37.5%. bp: 173 ^{o}C (lit. Dictionary of Organic Compounds, Chapman and Hall, 5, 3013 bp. 173 ^{o}C slight dec.). IR (liq. film) 3460, 3080, 2980, 1730, 1640 and 1200 (broad). ^{1}H NMR ($CDCl_3$) 1.3 (t, 3H), 3.0 (broad s, 1H), 4.2 (q, 2H), 5.1 (m, 1H), 5.3 (m, 1H) and 5.4-6.3 (m, 1H).

Attempted preparation of (80)

To a mixture of (79) (1.79 g, 13.8 mmol), succinimide (1.37 g, 13.8 mmol) and triphenylphosphine (3.62 g, 13.8 mmol) in THF (20 ml) under nitrogen was added diethyl azodicarboxylate (2.40 g, 13.8 mmol) in THF (5.8 ml) over 1h. The resulting solution was stirred at room temperature for 48h. The reaction mixture was concentrated and subsequently chromatographed on silica gel (dichloromethane, followed by dichloromethane-methanol-petrol; 10:1:1) to yield starting material (confirmed by tlc and nmr spectroscopy).

Attempted preparation of (140) from (101)

To a flask fitted with a Dean-Stark trap was added alcohol (101) (2.04 g, 17.7 mmol), dry toluene (75 ml), methyl 2,2-dimethoxyacetate (3.09 g, 23 mmol) and p-toluenesulphonic acid (37.1 mg, 0.195 mmol) and the mixture refluxed for 5 days. Trapped toluene/methanol was removed periodically, and dry toluene was periodically added to the reaction mixture. The reaction mixture was worked up as for (142). The material isolated was identical (tlc and nmr spectroscopy) with alcohol (101).

Attempted preparation of (143) from (139)

A solution of diisopropylamine (0.71 ml, 5.06 mmol) in THF (15 ml) was cooled to -10 °C and n-butyl lithium (3.54 ml, 5.06 mmol of a 1.48 M solution in hexane) was added with vigorous stirring. The solution was stirred for 5 minutes at -10 °C and then cooled to -78 °C and (139) (713 mg, 4.6 mmol) in THF (4 ml) was added with stirring. The mixture was stirred for another 30 minutes at -78 °C and methyl bromoacetate (0.46 ml, 4.92 mmol) was added over several minutes. The reaction mixture was stirred for a further 1h at -78 °C and then allowed to warm up to -20 °C and stirred for 0.5h. The mixture was poured onto ice-water. The organic/aqueous phases were separated and the aqueous phase extracted with chloroform. The organic phase was washed with saturated sodium chloride and dried ($MgSO_4$). Concentration in vacuo gave an oil which was purified by chromatography on silica gel (ethyl acetate-petrol; 3:2). The materials isolated did not give a ^1H nmr spectra which resembled that of the desired product (143).

Attempted preparation of (156) from (154) (using 2 equivalents of LDA)

A solution of diisopropylamine (0.76 ml, 5.42 mmol) in THF (10 ml) was cooled to -20 °C and n-butyl lithium (3.50 ml, 5.42 mmol of a 1.55 M solution in n-hexane) was added with vigorous stirring. The solution was stirred for 5 minutes at -20 °C and then cooled to -78 °C and (154) (560 mg, 2.46 mmol) in THF (10 ml) was added with vigorous stirring. The mixture was stirred for another 30 minutes at -78 °C and allyl bromide (0.23 ml, 2.71 mmol) was added over several minutes. The reaction mixture was stirred for a further 1h at -78 °C and then quenched by pouring onto ice-water. The organic phase was separated and the aqueous phase extracted with chloroform. The organic extracts were washed with water, saturated sodium chloride solution and dried ($MgSO_4$). Concentration in vacuo gave an oil (100 mg), which was purified by

column chromatography on silica gel (ethyl acetate-petrol; 1:1). The materials isolated did not give a ^{1}H NMR spectra which resembled that of the desired product (156).

3-[2(1,3-dioxan-2-yl)ethyl]cyclopentanone (183)

Magnesium powder was generated under nitrogen from anhydrous magnesium dichloride (1.36 g, 14.2 mmol) and potassium (1 g, 26 mmol) in THF (20 ml) according to the procedure of Reike.[119] To the heterogeneous mixture at 25 °C was added neat (179) (2.45 g, 12.6 mmol) with a syringe over 2.5 min. After 20 min, the mixture was cooled to -78 °C, a solution of $CuBrMe_2S$ (0.6 g, 3.2 mmol) and dimethyl sulfide (6 ml) was added over a period of 3 min, the mixture was stirred at - 78 °C for 1h and a solution of (176) (0.51 g, 6.3 mmol) and ether (12 ml) was added over 2h. The mixture was stirred at -78 °C over a period of 6h and allowed to warm to room temperature overnight. The mixture was then quenched with aqueous ammonium chloride (adjusted to pH 8 with aqueous ammonia), the organic and aqueous layers were separated, and the aqueous phase was extracted with ether. The organic phases were subsequently washed with water and saturated sodium chloride solution and dried ($MgSO_4$). Concentration in vacuo gave crude (183) as an oil. 1.10 g, 88.70%. IR (liq. film) 2930, 1745, and 1140. ^{1}H NMR ($CDCl_3$) 1.0-2.65 (m, 13H), 3.2-4.15 (m, 4H) and 4.15-4.6 (m, 1H). The keto acetal (183) was used in the hydrolysis step without further purification.

Compounds (63), (64) and (65) were prepared according to the literature method.[57]

Compound (68) was prepared according to the literature method.[63]

Compound (78) was prepared according to the literature method.[68]

Compound (100) was prepared according to the literature method.[76]

Compound (177) was prepared according to the literature method.[116] The hydrolysis of (177) was carried out using the literature method[116] and also the varied conditions as shown in table 3.

Hydrolysis conditions for (183) were varied as shown in table 4.

Compounds (189) and (185) were prepared according to the literature method.[129]

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RESEARCH STUDY PROGRAMME

As part of this project the author has attended the following lecture courses at Sheffield University.

Functional group interconversions (oxidation of alcohols to aldehydes and ketones).

Some aspects of radical chemistry.

The anomeric effect and all that.

Stereodifferentiating reactions.

The biosynthesis of natural products.

The author has attended appropriate colloquia at the sponsoring and other establishments given by internal and external speakers.

The author has attended symposia on ;-

Stereochemistry (Sheffield 1986).

Organic Chemistry (Nottingham 1985, 1986 and London 1985, 1986).

The author has also undertaken a three months training period at the collaborating bodies laboratories.