CARBOCYCLIC ANALOGUES OF NIKKOMYCINS AND POLYOXINS

a thesis presented by

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I wish to dedicate
this work to my parents
Charles and Elizabeth
whose faith in my abilities
has never wavered.

Weary with toil I haste me to my bed,
The dear repose for limbs with travel tired;
But then begins a journey in my head,
To work my mind when body's work's expired;
For then my thoughts, from far where I abide,
Intend a zealous pilgrimage to thee,
And keep my drooping eyelids open wide,
Looking on darkness which the blind do see:
Save that my soul's imaginary sight,
Presents thy shadow to my sightless view,
Which like a jewel hung in ghastly night,
Makes black night bounteous and her old face new.
Lo, thus by day my limbs, by night my mind,
For thee, and for myself, no quiet find.

William Shakespeare
Sonnet No. 27

ABSTRACT

The history, structure elucidation and mode of action of the two related series of peptidyl nucleoside antibiotics, Nikkomycins and Polyoxins, are reviewed. The underlying biological advantages that can be gained from the synthesis of carbocyclic analogues of nucleosides are discussed, and the procedures which have been developed to produce the carbocyclic nucleosides Aristeromycin and Neplanocin A will be reviewed.

The main aim of these syntheses was to produce a 2,3-hydroxy-4-hydroxymethyl-cyclopentyl amine intermediate where the 1,4 substituents were *cis*- and the 1,2-,1,3- substituents were *trans*-. This intermediate was not suitable for our needs and so a new synthesis to a 2,3-hydroxy-4-(aminoacetic acid)-cyclopentyl amine intermediate was devised. This synthesis involved the Beckmann rearrangement of 5-*exo*,6-*exo*-(*iso*-propylidene dioxy) - Bicyclo [2.2.1] heptan -2- one oxime; a rearrangement which had proven to be non-regiospecific in related compounds. This rearrangement was achieved and the reasons for the variation in the related systems was investigsted using PM3 semi-empirical calculation methods. The functionalisation of the lactam produced, proved difficult however methyl, chloride, and hydrazino functions were introduced α to the lactam carbonyl. The cleavage of the lactam was found to be impossible by our methods.

The extension of the iodocyclisation methodology to substituted amidines and ureas was made and proved to be an efficient and mild entry into the 4-iodomethyl-1-alkyl-2-trichloromethyl imidazole and -2-imidazolone systems. The conversion of the iodomethyl function, of the imidazolone system, into a hydroxymethyl group was found to be possible but subsequent oxidation of this group was found to be complicated and unsuccessful.

ACKNOWLEDGEMENTS:

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My best wishes go to all the "Eastenders" who have worked with me over these three years and to all my colleagues on the seventh floor who have never failed to criticise my work and thus kept me on my toes. A very special thanks goes to Tony Beck who proof read this thesis fastidiously.

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CONTENTS

Abstract		4
Acknowledgements		5
Chapter 1	Polyoxins and Nikkomycins	8
1.1	Introduction	9
1.2	Polyoxins	9
1.2.1	Discovery	9
1.2.2	Structure elucidation	9
1.2.3	Mode of action	15
1.3	Chitin and *Candida albicans*	16
1.3.1	Fungal cell wall structure	16
1.3.2	Chitin biosynthesis	17
1.3.3	*Candida albicans*	18
1.3.4	Chitin synthesis and germ tube formation	20
1.4	Inhibition of chitin synthase	20
1.4.1	General	20
1.4.2	Structure activity relationships of polyoxins	21
1.4.3	Transport	23
1.4.4	Intracellular stability	23
1.5	Chemical synthesis	24
1.6	Biosynthesis of polyoxins	27
1.7	Nikkomycins and neopolyoxins	30
1.8	Conclusions	38
Chapter 2	The central fragment	39
2.1	Introduction	40
2.1.1	Why a carbocyclic analogue?	40
2.1.2	Disconnection	43
2.2	Results and discussion	45
2.2.1	The Beckmann rearrangement	48
2.2.2	Lactam functionalisation	60
2.2.3	Cleavage of the lactam	69
2.3	Other approaches to carbocyclics	79
2.4	Conclusions	91

CONTENTS cont.

Chapter 3	The right hand fragment	92
3.1	Introduction	93
3.1.1	The uracil base	93
3.1.2	The imidazoline base	93
3.2	Results and discussion	99
3.2.1	Formation of the 4-substituted-1-alkyl imidazolin-2-one	102
3.2.2	Cyclisation procedures	109
3.2.3	Iodomethyl group oxidation	114
3.2.4	Uracil base formation	120
3.3	Conclusions	121
Chapter 4	Experimental	122
4.1	General	123
4.2	Abbreviations	125
4.3	Experimental procedures	127
Appendix 1	X-Ray data	160
Appendix 2	References	170

CHAPTER ONE

Polyoxins and Nikkomycins

1.1 INTRODUCTION

Polyoxins and Nikkomycins are peptidyl nucleoside antibiotics which have been isolated from various strains of *Streptomyces* bacteria. Within this Chapter the history, structure elucidation and mode of action of these two related series of antibiotics will be reviewed.[1]

1.2 POLYOXINS

1.2.1 *Discovery*

The discovery of these antibiotics came from the investigations of Isono *et al*[2] into the prevention of sheath blast disease in rice, which was caused by the pathogenic fungus *Piriculara filamentosa f. sasaki.* They found a polyoxin producing strain of streptomyces called *Streptomyces cacaoi* var. *asoensis.* and also found that these compounds' antimicrobial action was limited to some species of pathogenic fungi and insects. Later research showed these compounds to be a new class of nucleoside antibiotics having unique chemical and biological features, and their efficiency as antifungal agents have made them a commonly used fungicide in Japan.

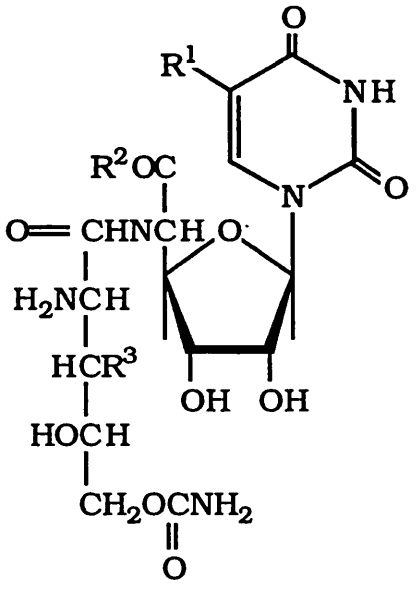
1.2.2 *Structure elucidation*

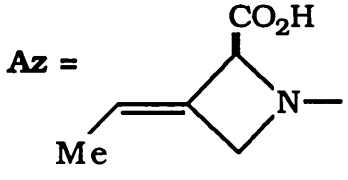
The initial structural work[3,4] was carried out on Polyoxin A which was the main component of the fermentation broth. For comparison, the structures of the isolated polyoxins are displayed in Table 1 overleaf. It was shown that polyoxin A was comprised of three unusual amino acids, one of which, polyoxin C (**1**), had been previously isolated from the fermentation complex (Polyoxin C is itself a key compound as it is the basic nucleoside building block for all the others).

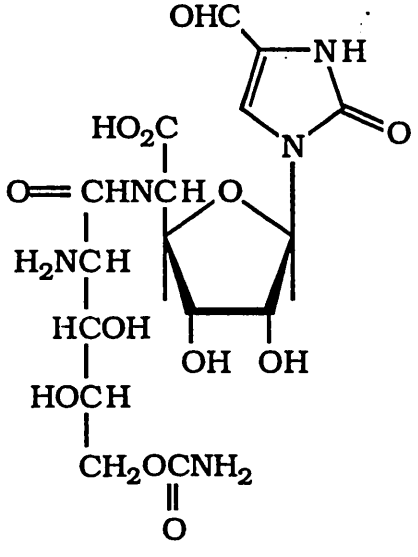
POLYOXIN series

Table 1

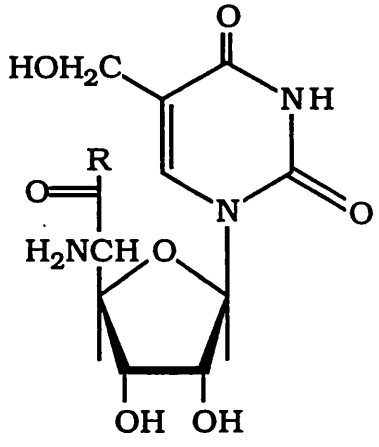
Polyoxin	R^1	R^2	R^3
A	CH_2OH	Az	OH
B	CH_2OH	OH	OH
D	CO_2H	OH	OH
E	CO_2H	OH	H
F	CO_2H	Az	OH
G	CH_2OH	OH	H
H	Me	Az	OH
J	Me	OH	OH
K	H	Az	OH
L	H	OH	OH
M	H	OH	H





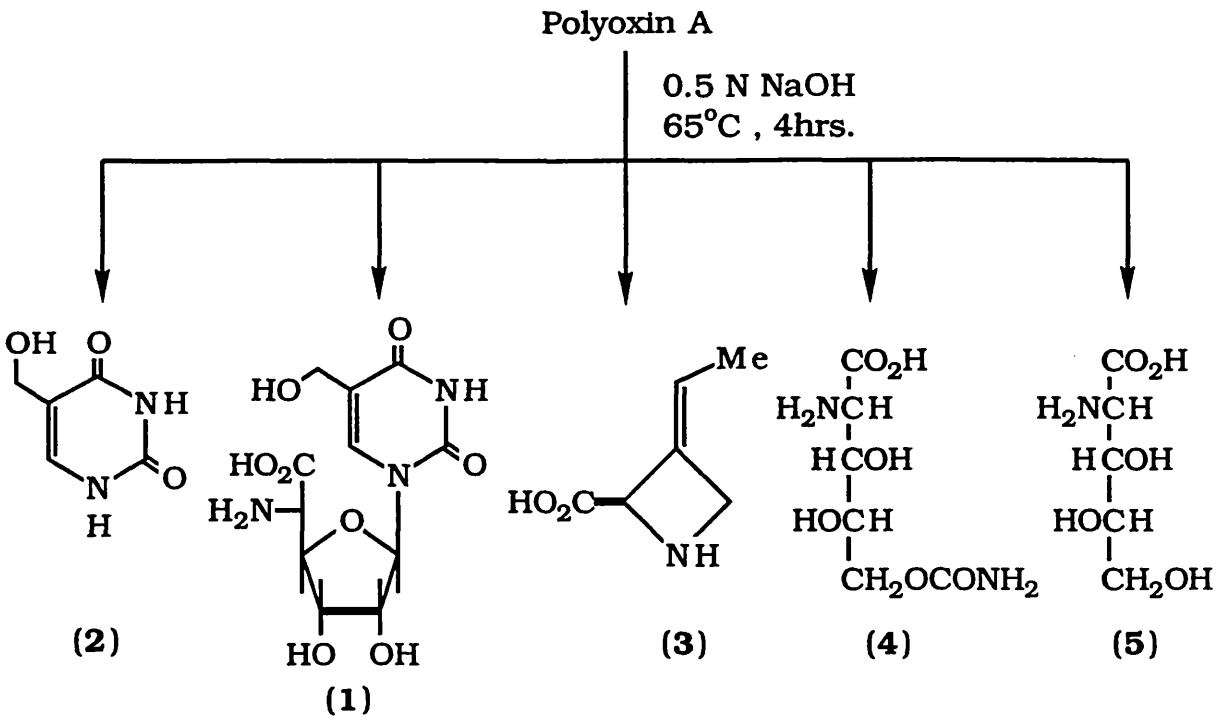


Polyoxin N



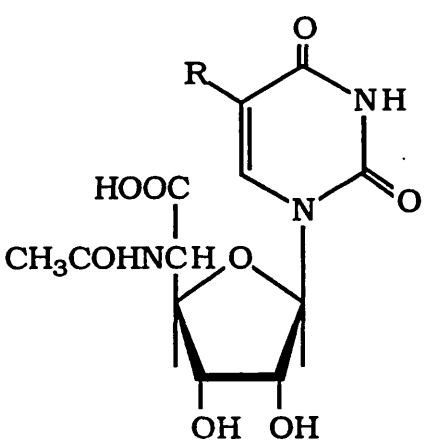
Polyoxin C R = OH

Polyoxin I R = Az



Scheme 1

The prolonged hydrolysis also gave the known 5-hydroxymethyluracil (**2**) and two amino acids which were designated polyoximic acid (**3**) and polyoxamic acid (**5**).



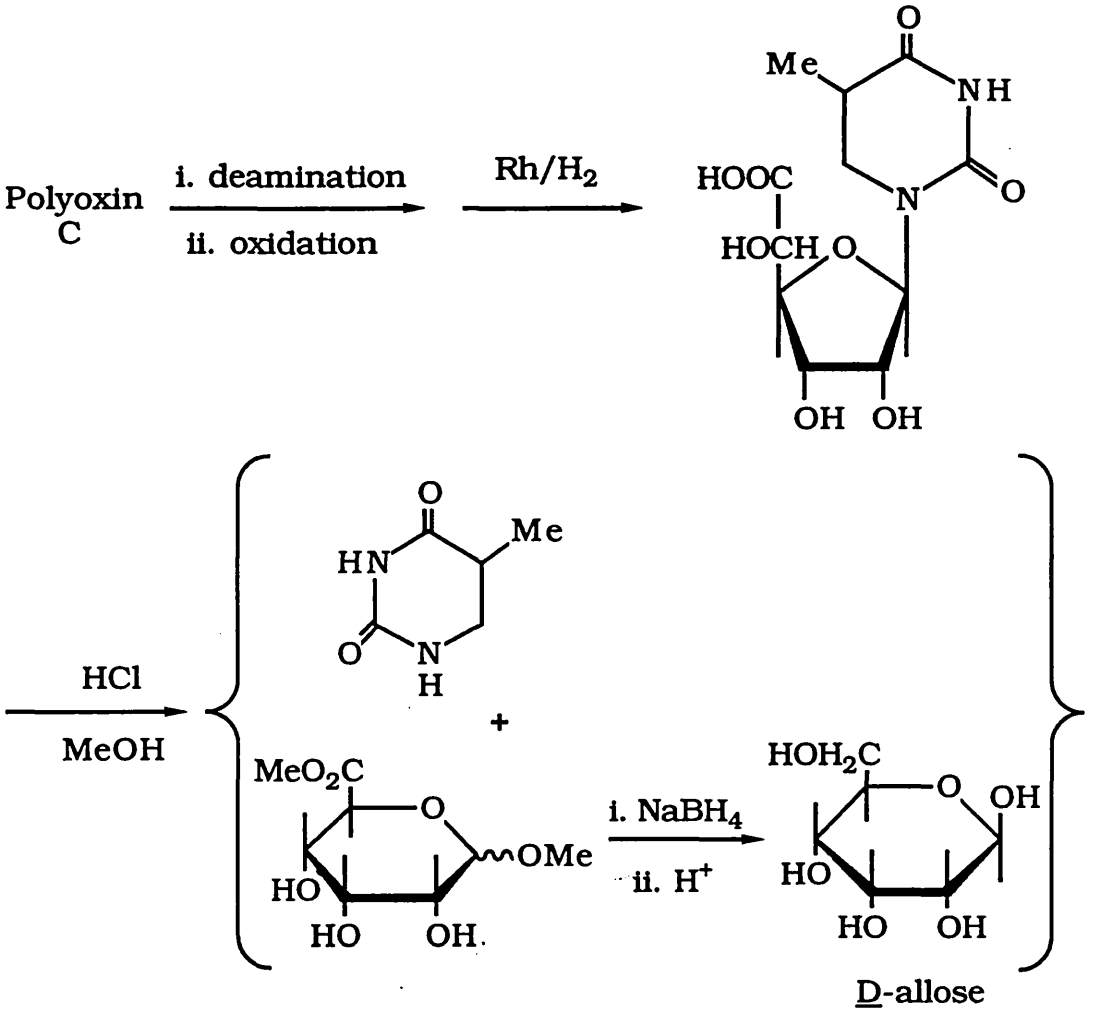
R = CH_2OH --- *N*-acetylpolyoxin C

R = Me --- *N*-acetyldeoxypolyoxin C

(**6**)

From UV data polyoxin C was shown to be an *N*-1 nucleoside and the C-5' position of the amino group was determined using NMR, by spin decoupling the H-5' signal from the NH signal of the derivative *N*-acetyldeoxypolyoxin C (**6**). This

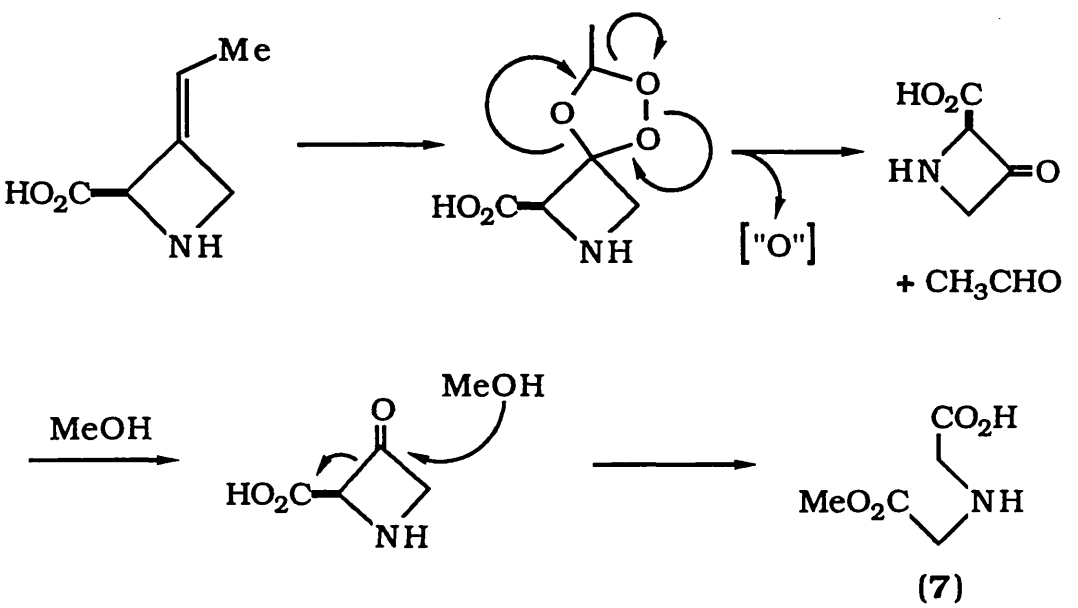
information also meant that the sugar had to be a furanose. The configuration of the sugar was confirmed by obtaining D-allose from the series of reactions shown in Scheme 2 :-



Scheme 2

The configuration drawn for C-5' was postulated from the circular dichroism spectrum of an *N*-dithiocarbethoxy derivative of polyoxin C and supported later by the synthesis of both stereoisomers.[5] The configuration at the anomeric centre was assigned on the basis of a positive Cotton effect near 280 nm and on the reduced coupling constant of the anomeric proton once the 2',3' oxygens were constrained within an isopropylidene ring. All of the above deductions were later confirmed by X-ray analysis of an *N*-brosyl derivative of polyoxin C.[9b]

The second amino acid discovered was called polyoximic acid (**3**) and it was shown to be a rare example of a naturally occurring azetidine (3-ethylidene-L-azetidine-2-carboxylic acid). Its structure was assigned on the basis of ^{1}H-NMR analysis and reductive ozonolysis in methanol which gave iminoacetic acid, half methyl ester (**7**) and acetaldehyde by the mechanism proposed in Scheme 3.



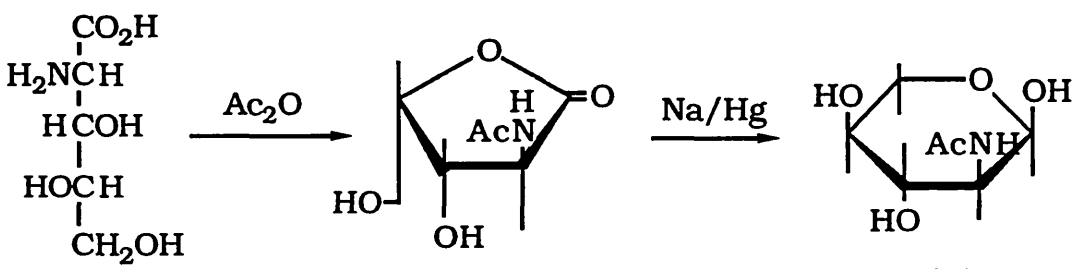
Scheme 3

Polyoximic acid (**3**) can easily undergo racemisation in either acidic or basic conditions and the optically active form was only obtained as the dihydro derivative, whose L-configuration was assigned using the Cotton effect upon the CD spectrum of an *N*-dithiocarbethoxy derivative. In the natural acid the double bond geometry was found using the nuclear Overhauser effect.

The third amino acid was found to be polyoxamic acid (**5**), 2-amino-2-deoxy-L-xylonic acid (and also a C-5 carbamoyl derivative thereof (**4**) which was obtained by either acid hydrolysis or enzymatic cleavage using leucine aminopeptidase), which was in turn converted into the lactone and from there into the known 2-acetamido-2-deoxy-α-L-xylose (**8**) as shown in Scheme 4.

There have been several syntheses of the acid[6] and of the C-

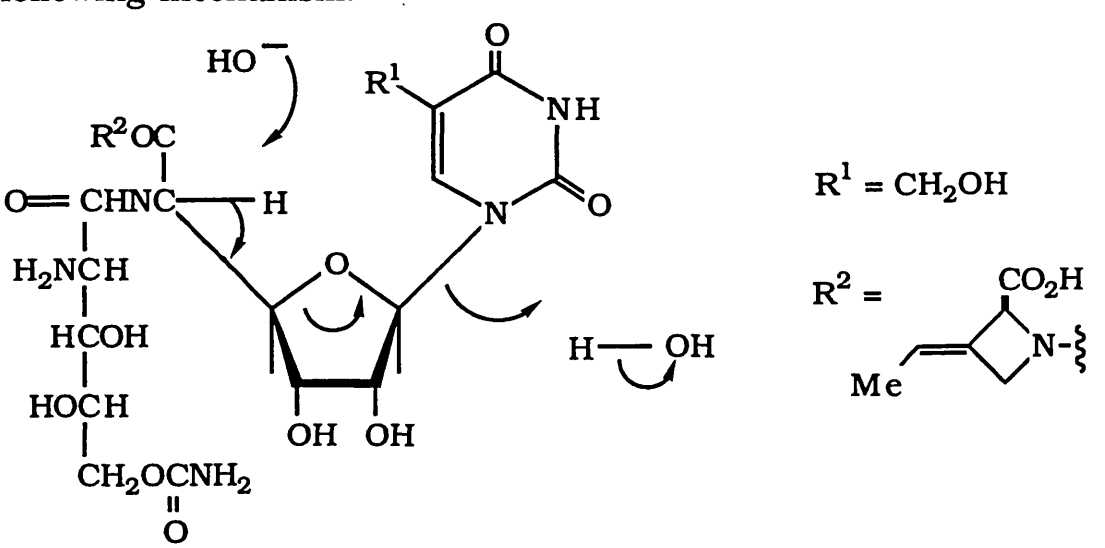
5' carbamoyl derivative[7] in both the unnatural D- and natural L-forms, however the accuracy of Mukaiyama's[7c] synthesis has been questioned by Saksena and Lovey.[8] They report that the $[\alpha]_D$ value for a protected intermediate proposed by Mukaiyama, varies quite significantly from the value they obtained from their confirmed structure which was produced by a slightly different route. They also criticise Mukaiyama for claiming to produce polyoxamic acid but giving no experimental evidence for such a conversion apart from a decomposition point of the supposed product.



(8)

Scheme 4

Sequence determination finally confirmed the full structure of polyoxin A. The nucleosidal portion of Polyoxin A was shown to be labile by the production of the 5-hydroxymethyluracil during alkaline hydrolysis, its production presumably comes *via* the following mechanism.

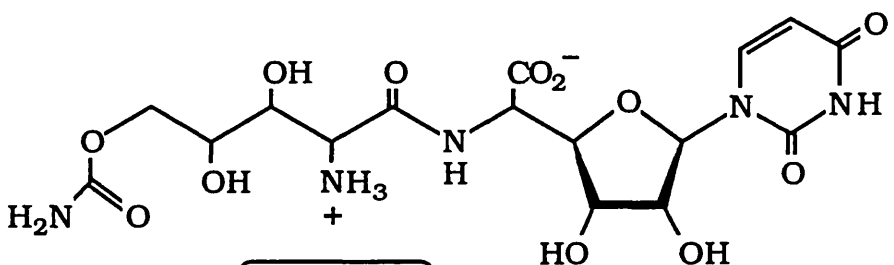


From this, the structures of the other polyoxins were determined and the possible interconversion of the various 5-substituted pyrimidines was also achieved.[4]

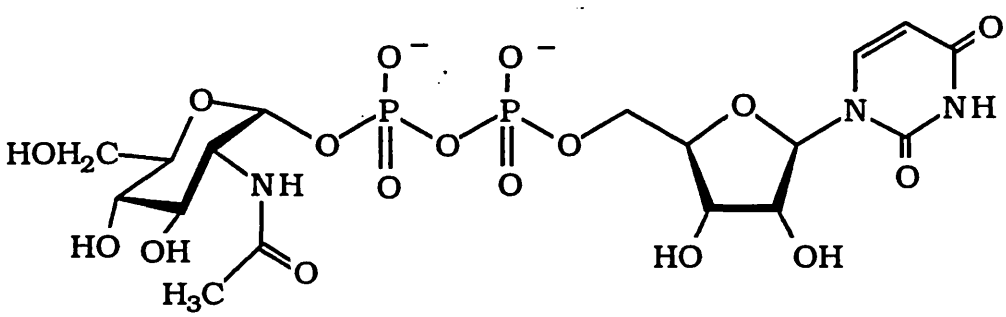
1.2.3 *Mode of action*

As has been stated, the specific nature of the polyoxins to phytopathogenic fungi and their lack of activity towards other microorganisms, fish or mammals led Sasaki *et al*[9a] to propose that the site of action of these compounds was related to the biosynthesis of the fungal cell wall.

Upon establishment of the structure of the polyoxins, their gross structural similarity to UDP-*N*-acetylglucosamine (UDP-GlcNAc) was noticed.[9b]



Polyoxin L



UDP-*N*-acetylglucosamine

UDP-*N*-acetylglucosamine is a substrate for the enzyme(s) Chitin synthase, and chitin is a fibrous component of fungal cell walls. It was shown shortly afterwards that polyoxin D was indeed a strong inhibitor of chitin synthase obtained from *Neurospora*

crassa[10a] and later, it was demonstrated that chitin synthase from many other sources, including those from insect tissue cultures,[10b,c] were also susceptible to polyoxin inhibition. These results when combined with the observation[11] that UDP-*N*-acetylglucosamine accumulated in those cells which had been treated with polyoxin D confirms the proposal made by Sasaki.

The differences found with different species of fungi were thought to be derived from the differing abilities of the polyoxins to cross the cell membranes.[12]

1.3 CHITIN AND CANDIDA ALBICANS

1.3.1 *Fungal cell wall structure*[13]

In general a fungal cell wall consists of between 80% and 90% polysaccharides with the remainder being taken up by protein and lipids. Physically it can be considered as a mesh of microfibrillar polymers embeded in a matrix of amorphous "cementing" material. In lower fungi and yeasts the cell wall contains cellulose and glucans respectively, but in all others the main component is Chitin with proteins and polysaccharides (such as mannans, glucans and galactans) making up the cementing material.

Chitin usually exists in the α–crystalline form[14] where neighbouring chains of *N*-acetylglucosamine are antiparallel to each other. Chitin microfibrils are usually no more than 2-3 μm long with a diameter of 10-25 nm (i.e. consisting of approximately 2000 GlcNAc units). Experiments which have removed the cementing components by enzymatic digestion have demonstrated that the cell walls retain their shape, proving that once formed, these structures exist as a rigid 3-dimensional network. In some fungi two types of cell wall can be identified, a thin 'plastic' primary wall and the rigid 'mature' wall. During growth of the cell the rigid wall is made more plastic presumably by the action of chitinase enzymes breaking some of the glycoside

bonds within the chitin chains. This region deforms due to the turgour pressure within the cell and allows the insertion of more chitin fibrils in the lengthening wall.

1.3.2 *Chitin biosynthesis*

Since the first description of chitin biosynthesis *in vitro* using cell-free extracts from *Neurospora crassa*[15] there has been a great deal of work performed on a variety of chitin synthesising extracts obtained from different sources[16] (insects as well as fungi) and it has been shown that these samples all have similar properties (see Table 2).

Table 2

Table of the Biochemical Properties of Fungal Chitin Synthase[13,17]

1. The enzyme is activated by limited, unspecific proteolysis.
2. The enzyme requires a divalent cation (Mg^{2+}, Mn^{2+}, Co^{2+}) for activity.
3. GlcNAc is a strong allosteric activator of the enzyme, mimicking the effect of substrate at the active site. The amino sugar itself is not incorporated into chitin.
4. Chitin synthase has unusual kinetics. K_m values for UDP-GlcNAc are in the mM range.
5. Chitin synthesis occurs in the absence of an exogenous primer.
6. The stability of chitin synthase is high in purified preparations but poor in crude fractions.
7. Chitin synthase is competitively inhibited by UDP, a product of the reaction.
8. There is no high energy lipid intermediate involved in chitin biosynthesis.

In a region of growth, vesicles in the cytoplasm have been

seen to accumulate.[13] They appear in two size ranges, large (100-400 nm in diameter) and small (30-100 nm), with the small vesicles being very similar to some microvesicles that have been isolated and proved to be able to synthesise chitin microfibrils. These microvesicles are called Chitosomes and are considered to be the carriers of inactive chitin synthase within the cell. The more detailed scheme for chitin biosynthesis is displayed in Scheme 5 overleaf.

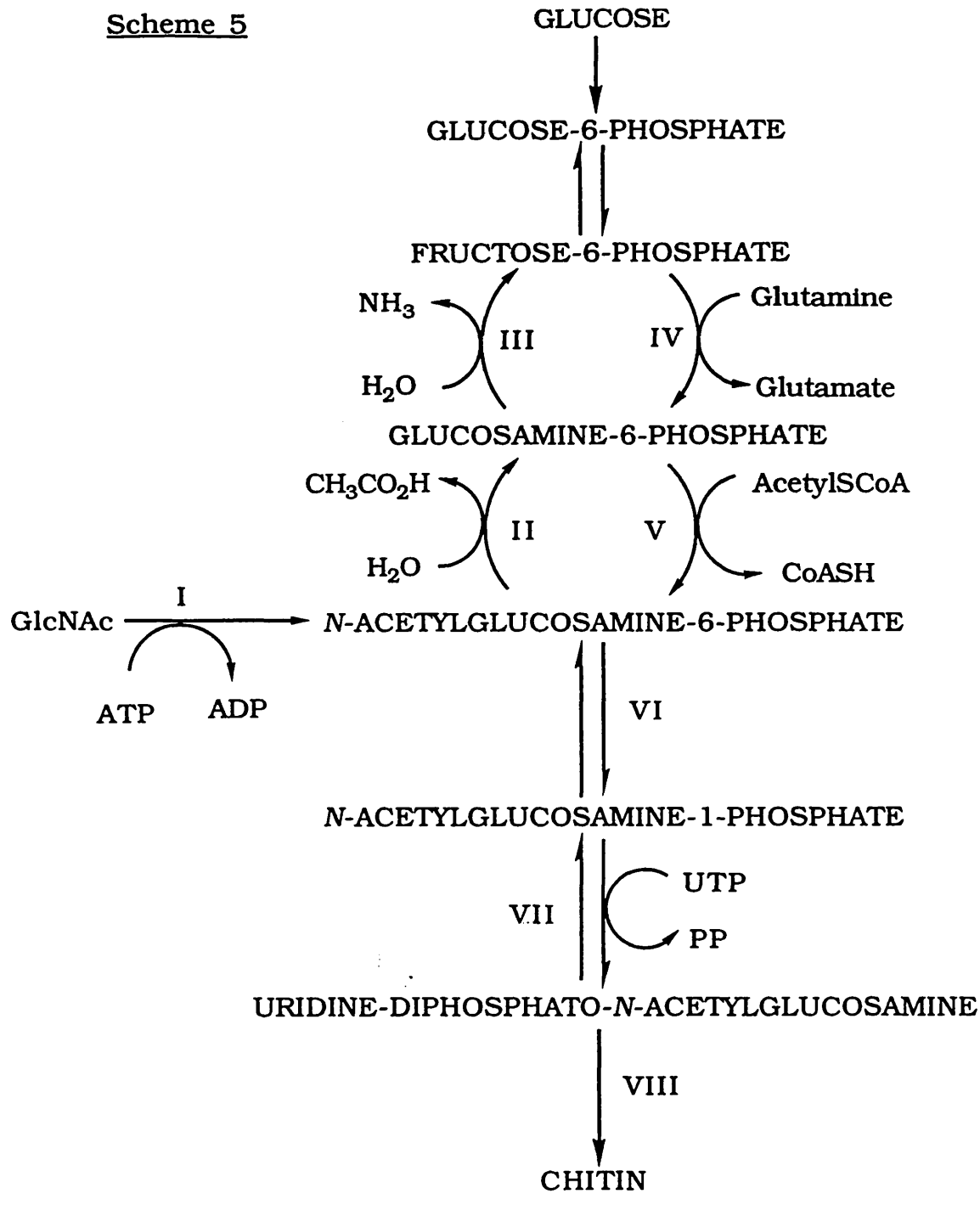
As chitin forms the major proportion of the cell wall structure in fungi (and some insects) but does not appear in the cellular structure of mammals or fish, it makes chitin inhibition the perfect target for a highly selective fungicide or insecticide. Therefore the inhibitory properties of the polyoxins towards the final step in chitin biosynthesis make them a very important target.

1.3.3 *Candida albicans*

Candida albicans is the most common agent responsible for human and animal candidosis. It is a polymorphic organism which, depending on the surrounding temperature or availability of nutrients may differentiate into one of three forms, the unicellular yeast, the mycelial form or the chlamydosporal form. The yeast form of *Candida albicans* can be found in the gastroenteric tract of healthy individuals and does not cause disease, however in its mycelial form it does initiate infection.

The exact role of this yeast to mycelial conversion in candidosis is as yet unclear but it is known that the conversion proceeds via initial 'germ tube' formation.[18a] Germ tube formation can be promoted in a number of ways but the simplest and usually the most effective way is by the feeding of GlcNAc to the yeast cells. As this is the natural precursor of chitin, many studies have been directed at its role and that of the chitin synthase enzyme in germ tube formation and hence, the dimorphic transition of a yeast into a mycelial cell.

Scheme 5



Enzymes:-

I = *N*-acetyl-D-glucosamine kinase
II = *N*-Ac-Glc-6-phosphate deacetylase
III = Glc-6-phosphate deaminase
IV = L-Glutamine-D-fructose-6-phosphate amino transferase
V = Glc-phosphate acetyl transferase
VI = Glc-phosphate isomerase
VII = UDP-*N*-Ac-Glc pyrophosphorylase
VIII = Chitin synthase

1.3.4 *Chitin synthase and germ tube formation*[18a]

As has been stated, the chitin synthase enzyme is thought to be held in the cytoplasm, in chitosomes, in an inactive form which can be activated by certain proteases (such as trypsin) and divalent metal ions. Some small *in vivo* activity with the enzyme has been found which has spread doubt as to its form or whether only one enzyme is involved. It was also noticed that in mycelial cells the chitin synthase enzyme was in an active form whilst remaining inactive in yeast cells.

Chitin concentration in mycelial cells is also three times higher than that found in yeast cells.[18b] This result has been extended to the germ tubes where there is a net increase in chitin concentration of approximately five-fold, with the concentrations of the other cell wall constituents remaining constant. With this need for extra chitin it is not surprising to find that the chitin synthase enzyme is also activated by increases in the level of GlcNAc and by using radio-labelled GlcNAc this increase in activity was seen to be concentrated at the tip of the growing germ tube.

The activation by GlcNAc is significant in other ways as was indicated by results showing that there were two different binding sites for the sugar on the enzyme.[18c] It is known that for growth to occur chitinase enzymes must first 'soften' the rigid cell wall which causes the release of GlcNAc and so stimulates chitin production to fill in the extending cell wall.

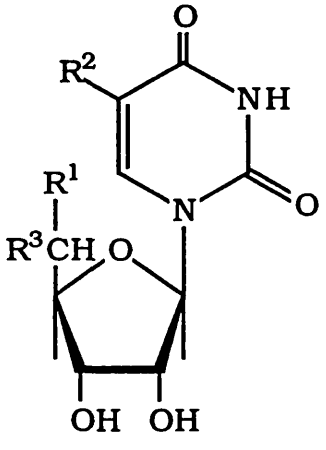
1.4 INHIBITION OF CHITIN SYNTHASE

1.4.1 *General*

In the initial work by Hori *et al*[19] they describe polyoxins as competitive inhibitors of chitin synthase which cause 50% inhibition of the enzyme at concentrations ranging from 5-25 $\mu g ml^{-1}$. The Ki values were in general 100-1000 times higher than the Km value for UDP-GlcNAc itself and so whilst polyoxin C and

UPOC were much less inhibitory than the others their Ki values were still approximately equal to the Km value of UDP-GlcNAc. Their lack of inhibitory action was therefore thought to be due to their inability to cross the cell membrane and compete with the much higher concentration of UDP-GlcNAc within the cell.

1.4.2 *Structure activity relationships of polyoxins*



$R^1=R^2=H$, $R^3=NH_2$ --- 5'-amino-5'-deoxyuridine **(9)**

$R^1=R^2=H$, $R^3=OH$ --- Uridine **(10)**

$R^1=CO_2H$, $R^2=CH_2OH$, $R^3=NH_2$ --- Polyoxin C

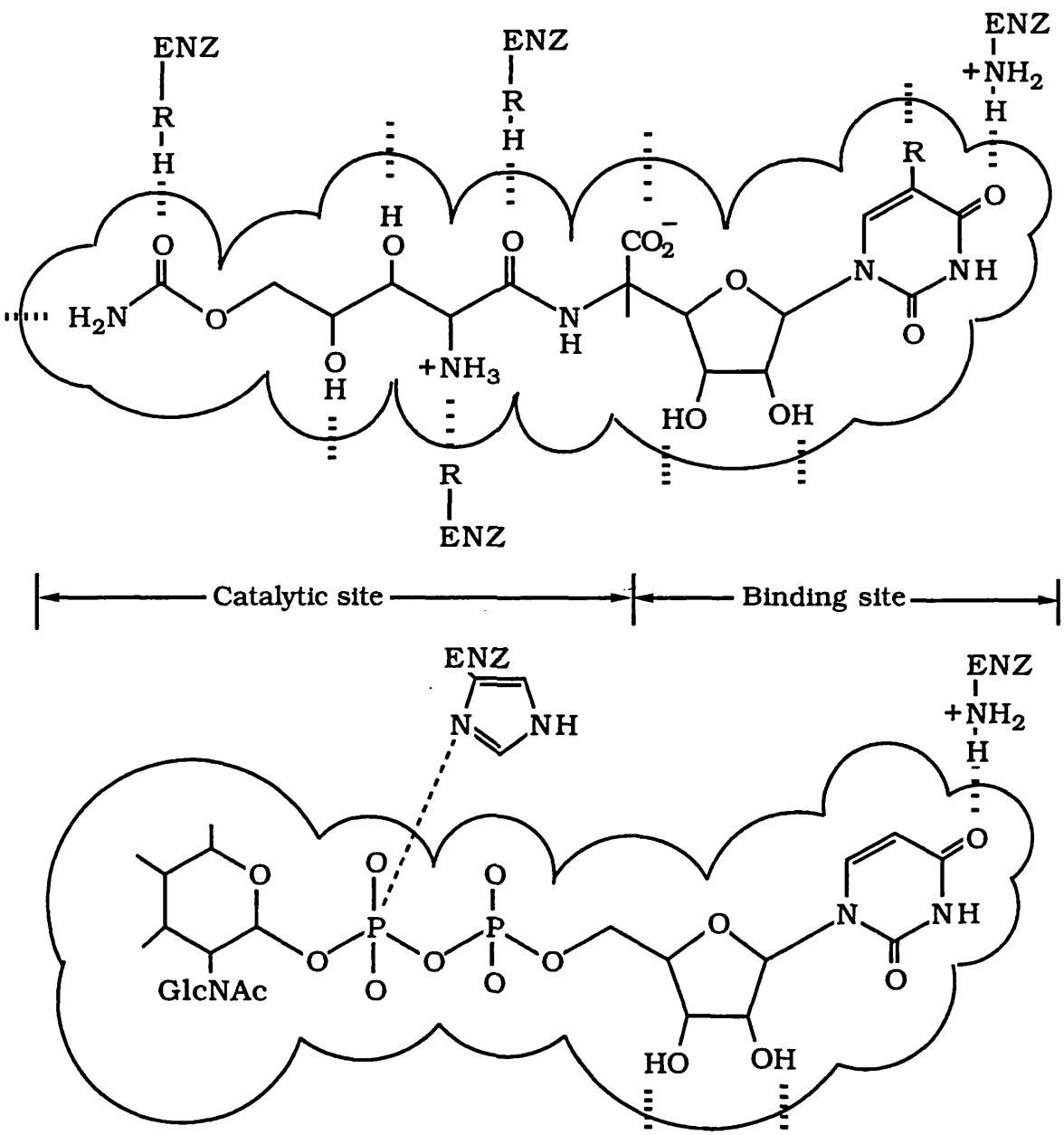
With the isolated enzyme it has been found that uridine (**10**), 5'-amino-5'-deoxyuridine (**9**) and even polyoxin C show some inhibitory activity towards chitin synthase; however uracil, carbamoyl polyoxamic acid (**4**) and polyoxamic acid (**5**) do not show activity.

These basic results when compared to the structure of UDP-*N*-acetylglucosamine indicate that the enzyme must have a specific 'binding site' for the tight binding of the nucleosidal portion of the molecules, with the side chain being less tightly bound within a 'catalytic site'.[19a]

The activity of 5'-amino-5'-deoxyuridine is only slight however and it is drastically improved by the inclusion of a 5'-carboxylic acid group which, after the synthesis of a range of analogues, has been shown to be essential for activity. Some pH experiments suggest that this CO group interacts with a positively charged group (such as an imidazole group on a histadine) within

the enzyme.[19c] An imidazole group is also thought to be required in the binding of the natural substrate's polyphosphate moiety to the enzyme.[19c]

A range of substituents at the C-5 position on the pyrimidine ring is tolerated by the enzyme as can be seen from the various active polyoxins, however by using a number of different nucleotides and nucleotide sugars the need for a carbonyl substituent at C-4 of the ring was clearly demonstrated.[19b]



The activity of polyoxin C shows that the peptidyl side chain is not essential for activity but its activity greatly increases with the addition of a peptide chain. With regards to the peptide chain the first requirement is that L-amino acids should be present in order to retain activity. With the removal or acylation of the amino group at C-2" the activity also drops dramatically.[19a] Plots of pH verses pKi for this area seem to indicate that the amino group is charged and interacts with a very specific negatively charged group on the enzyme.[19c]

The terminal groups on the peptide chain also have an effect upon the activity. Polar groups such as ureido, carbamoyl, and carbamoyloxy significantly increase the activity, whereas ionic groups like carboxylic acids or amino decrease the activity. These results support the hypothesis that the side chain is binding generally in a hydrophobic manner with the terminal carbamoyl group binding via H-bonding through the NH_2.[19b]

1.4.3 *Transport*

Polyoxins are now thought to be taken into the cell via the dipeptide transport system.[20] This system is also usually stereospecific and will only transport L-amino acids. A second peptide transport mechanism does exist for tripeptides, and it is also possible to utilise this system for polyoxin transport. However, the *in vitro* inhibitory activity of the tripeptidyl analogues of polyoxins has not proved to be very high (compared to polyoxin D),[20b,d] and *in vivo* their activity has only come from their intracellular degradation to dipeptides by the action of peptidases. This intracellular instability is another problem which hinders the use of these compounds.

1.4.4 *Intracellular stability*

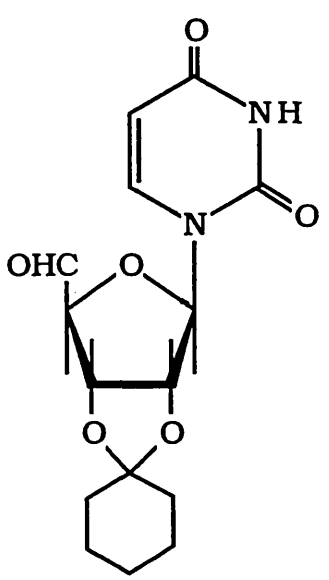
As can be seen from the above, the action of cellular peptidases helped to make the tripeptides into "prodrugs" for the more active dipeptides. However, their action

also reduces the bioavailability of the more active polyoxins and they are responsible for the deactivation of chitin synthase when there is a reduction in the levels of the GlcNAc precursor.[18c]

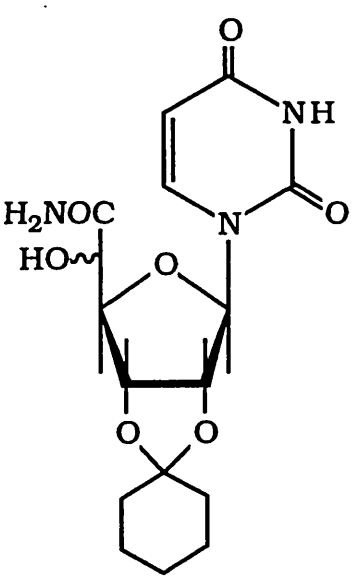
Much work has been done to improve both the transport properties and cellular stability of the polyoxins[20] including the use of D-amino acids,[20d] *N*-methylation,[20d] and replacement of the peptide bond.[20c] Unfortunately, whilst many of these compounds do improve upon the resistance to peptidases or demonstrate increased transport, they all seem to be generally less active *in vivo* than polyoxin D. Polyoxins themselves have been reported to be inactive against *Candida albicans*[21] but some analogues have shown weak activity.[20b]

1.5 CHEMICAL SYNTHESIS

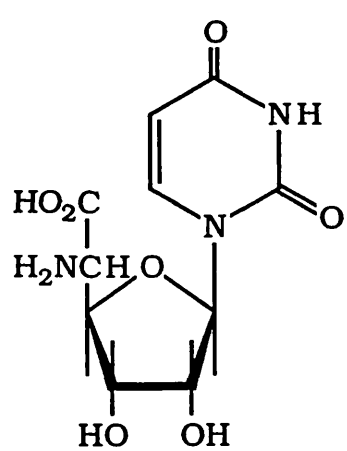
In the beginning there were several attempts to synthesise the nucleoside skeleton of the polyoxins. Moffatt *et al*[5] used 2',3'-*O*-cyclohexylidene-uridine-5'-aldehyde (**11**) (obtained from a DMSO-DCC oxidation of the corresponding uridine) as the starting point for their synthesis. Cyanohydrin formation followed by oxidation gave a mixture of epimeric hydroxamides (**12**) which were separable and were both mesylated.



(**11**)

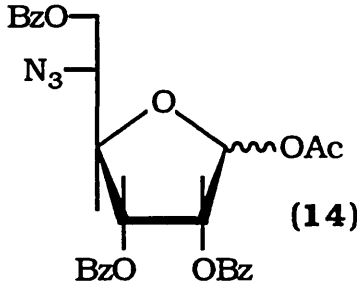


(**12**)

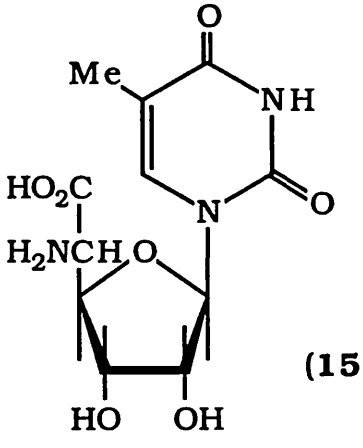


(**13**)

These mesyl derivatives were displaced using sodium azide, hydrolysed with acid, and then reduced to give both C-5' epimers of uracil polyoxin C (**13**) (again helping to confirm the stereochemistry of the natural product at that centre). Ohuri *et al*[22a] started from glucose and introduced an azido group into the C-5 position of an allofuranose derivative with double inversions. This was converted to the sugar acetate (**14**) and was coupled with silylated thymine in the presence of $SnCl_4$. Chromic acid oxidation to uronic acid, followed by reduction of the azido group gave thymine-polyoxin C (**15**).

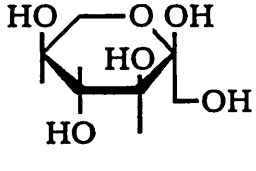


(**14**)

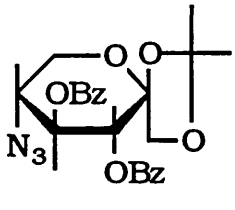


(**15**)

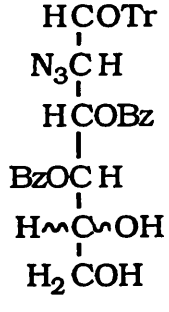
Kuzuhara *et al*[22b,7b] have succeeded in the total synthesis of polyoxin J by using Ohrui's synthesis of thymine-polyoxinC (**15**), and coupling to it the side chain amino acid synthesised from L-sorbose (**16**). This carbamoyl-polyoxamic acid synthesis utilized the sugar's inherent chirality which, through azide displacement and benzylation (**17**), became inverted for the final product.



(**16**)

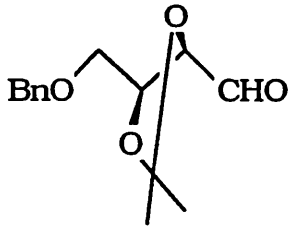


(**17**)

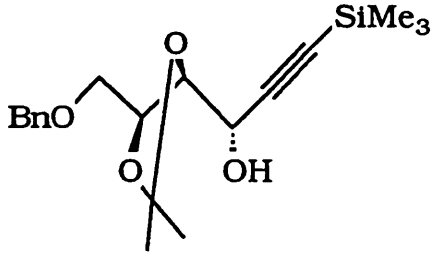


(**18**)

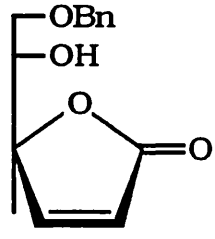
After reductive ring opening and protection (**18**) the terminal hydroxymethyl group was cleaved by sodium periodate, reduced back to the hydroxyl and carbamylated to give the carbamoyl polyoxamic acid (**4**) ready for the coupling in DMF. Much later Mukaiyama[7c] produced a formal synthesis of polyoxin J using 4-*O*-Benzyl-2,3-*O*-isopropylidene-L-threose (**19**) as a common chiral building block.



(**19**)



(**20**)



(**21**)

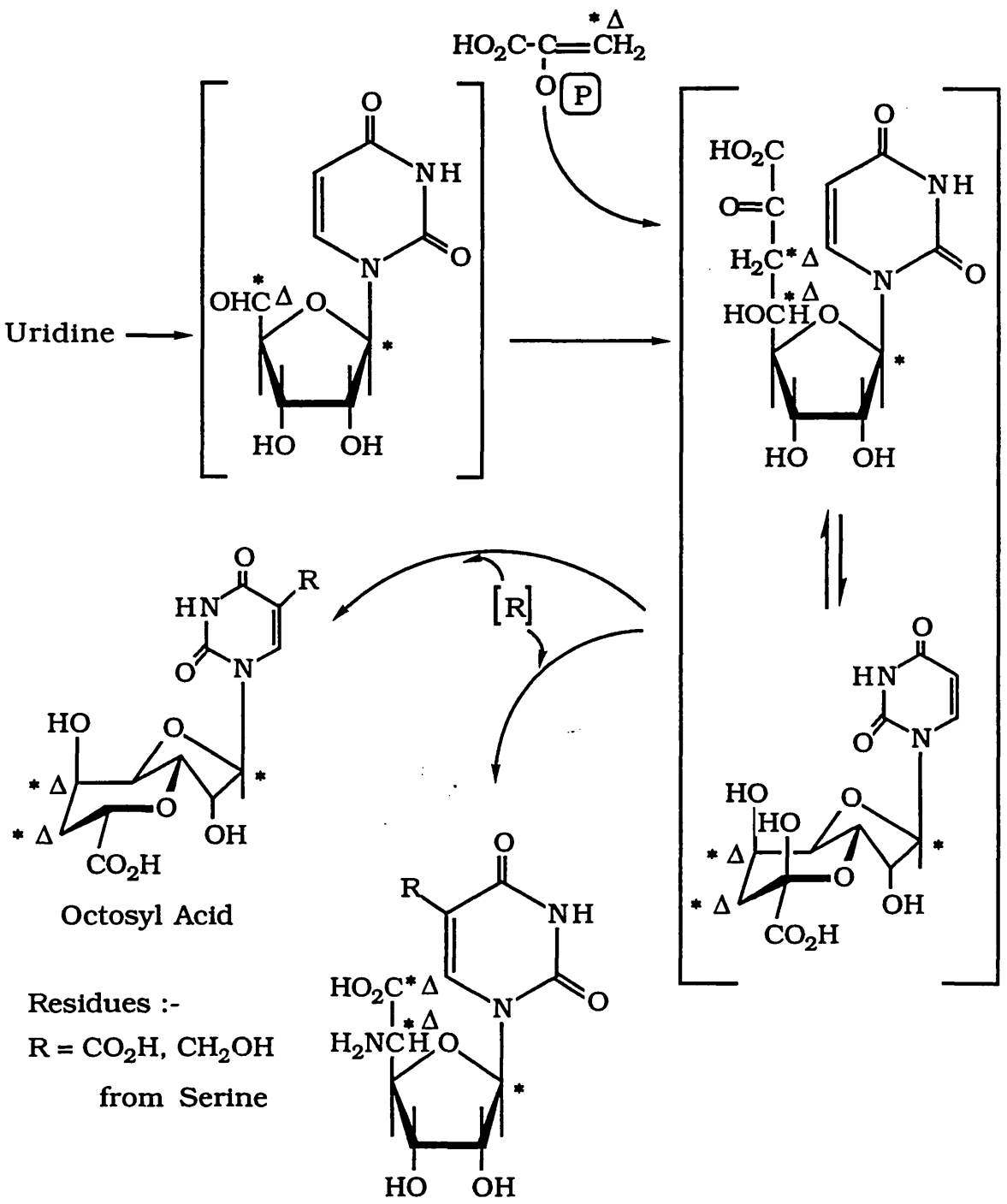
The side chain is set up by the nucleophilic addition of a lithium trimethylsilylac etylide to (**19**) in the presence of a $TiCl_4/Ti(O^iPr)_4$ mixture to give a 98 : 2 ratio of anti : syn alcohols. The free OH is replaced with inversion by azide, the terminal acetylene is reduced, the benzyl protected hydroxyl group was deprotected, carbamylated and finally the double bond was cleaved with $KMnO_4$ to give the acid in a protected form.

The furanose ring was made by reacting (**19**) in a Wittig process with the phosphorane from ethylbromoacetate, which was in turn cyclised in acid to a mixture of (**21**) and the corresponding 6-membered enone in a 7 : 1 ratio. The double bond was taken to a *cis*-diol with $KMnO_4$ and after protection of the diol and azide displacement, they had an acetate protected version of the aforementioned sugar acetate (**14**). This was then taken to a known precursor of thymine-polyoxin C by a similar procedure.

The major thrust of chemical synthesis now is in the area of forming peptidyl analogues of the polyoxins (and nikkomycins),[20] using the basic nucleoside (obtained from enzymatic hydrolysis of

the natural polyoxins) and coupling at the C-5' amino group with protected, activated amino acids.

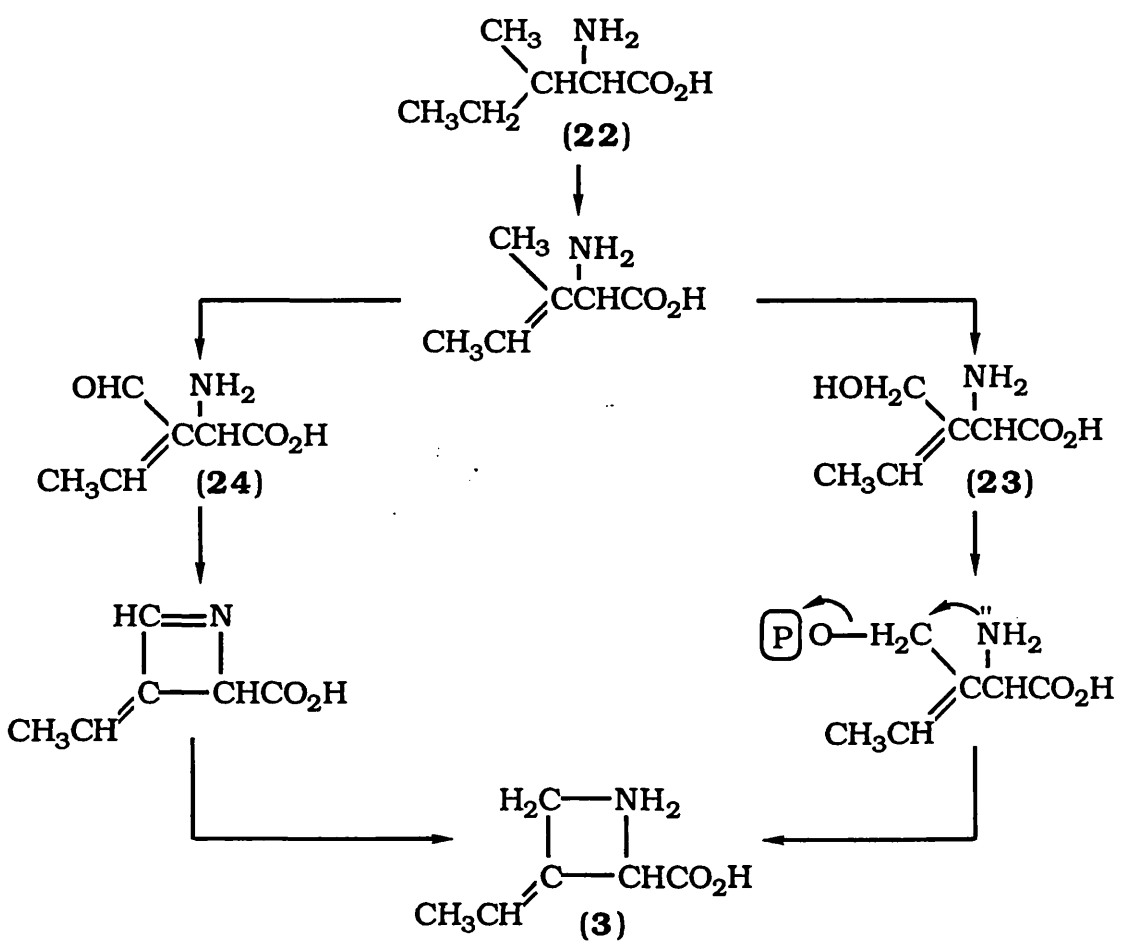
1.6 BIOSYNTHESIS OF POLYOXINS[4]



Scheme 6 :- *-label from *C-1 glucose, Δ-label from ΔC-6 glucose

The investigation of the biosynthesis of the aminouronic acid portion of the polyoxins has made use of ^{13}C-labelled glucose and ^{13}C-NMR analysis. The results suggest that uridine reacts *via* its 5'-aldehyde with phosphoenolpyruvate to give an intermediate octofuranose uronic acid nucleoside, which after oxidative elimination of the terminal two carbons and the introduction of an amino group *via* transamination at C-5' would give the desired polyoxin nucleoside (see Scheme 6).

The biosynthesis of the 5-substituted pyrimidines has aroused some interest, with the biosynthesis of the thymine polyoxins having been shown to be independent of thymidylate synthase. The substituted uracils probably come from the parent uracil with a one carbon addition probably from the C-3 of serine.

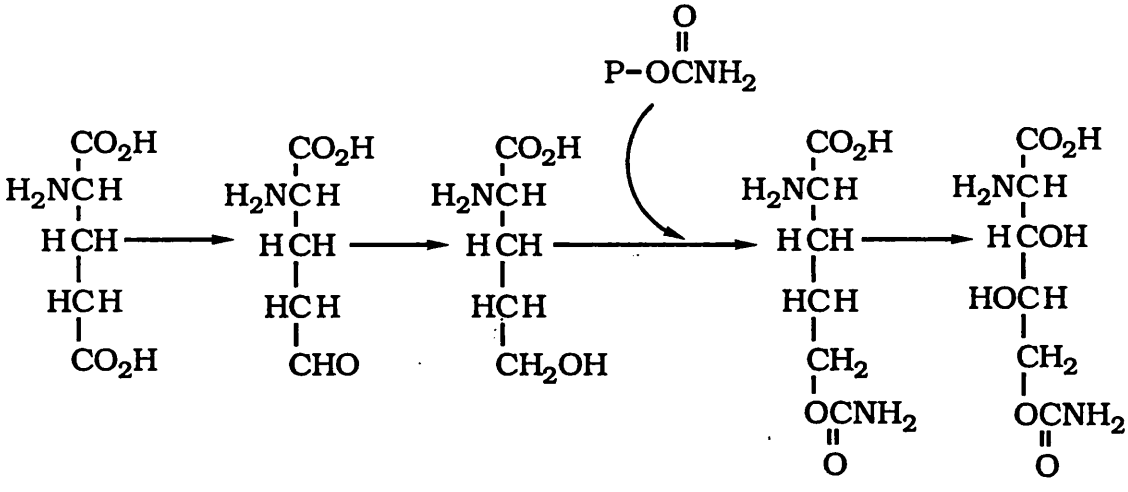


Scheme 7

Some unnatural polyoxins have been formed by feeding 5-fluoro-, 5-bromo-, or 5-azauracils to *S. cacaoi*, but these compounds seem to inhibit the natural addition of the one carbon unit to the C-5 of uracil. It should also be noted that these fluorinated polyoxins were active against *E. coli* which is not normally affected by the natural polyoxins.

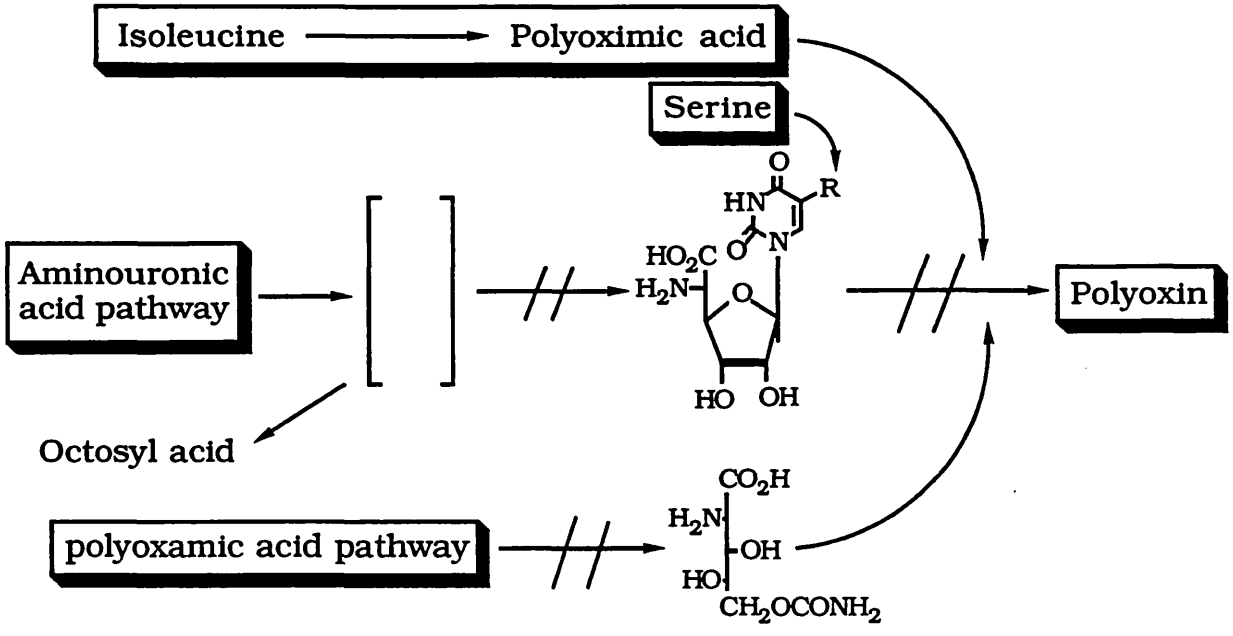
L-Isoleucine (**22**) has been proved to be a precursor to the novel azetidine, polyoximic acid (**3**). A possible pathway for this is outlined in Scheme 7 and involves dehydrogenation at the β- and γ-carbons, allylic oxidation followed by cyclisation. It has been claimed that two of the proposed intermediate amino acids (**23**,**24**) have been isolated from *Bankera fuligineoalba*.[23]

Carbamoylpolyoxamic acid (**5**) has L-glutamate as its precursor with *in vivo* and *in vitro* experimental evidence to support the biosynthetic scheme shown in Scheme 8.



Scheme 8

Evidence for the final combination of all the above products was gained from the study of three non-polyoxin producing mutants (see Scheme 9). Examination of the accumulated materials within these mutants has led to the foreshown order of biosynthesis in which the last step is the formation of the amide bond between the modified amino acids.



Scheme 9

1.7 NIKKOMYCINS AND NEOPOLYOXINS

The search for new nucleosidal antibiotics led two groups to discover yet more compounds from *Streptomyces* variants. König *et al*[24a] described the isolation of the Nikkomycins from *S. tendae* in 1976, and his continued investigations and structural analysis[24] has revealed up until now, the series of compounds shown in Tables 3 & 4 overleaf, with the nikkomycins X and Z being the major product components in the fermentation complex. The total production of nikkomycins has been improved from the original levels of 100-200 $mgdm^{-3}$ to approximately 1 gdm^{-3} by changes in the fermentation process. The selective production of nikkomycins, from either the X or Z series, can now be achieved by selective feeding or by using mutant strains of *Streptomyces*.[25] Isono *et al*[26] isolated three compounds from *S. cacaoi* subsp. *asoensis* four years later, which they referred to as Neopolyoxins.

NIKKOMYCIN Z Series

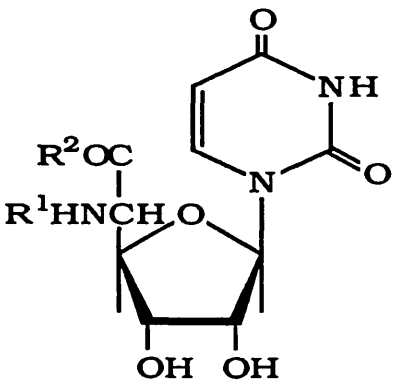
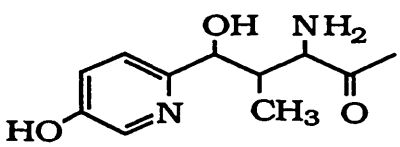
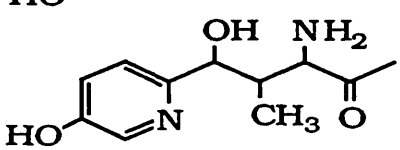
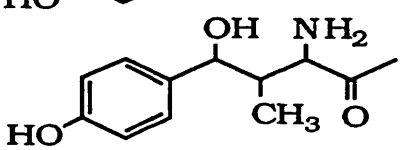
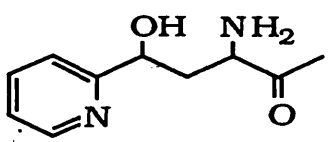
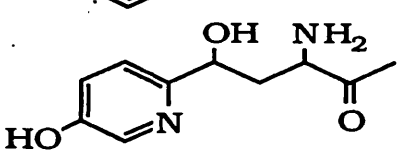
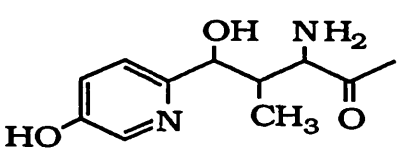
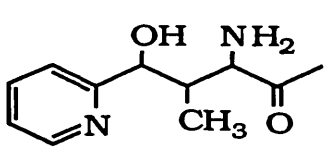
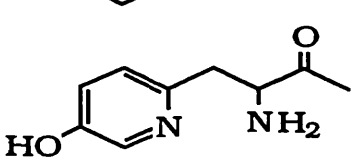
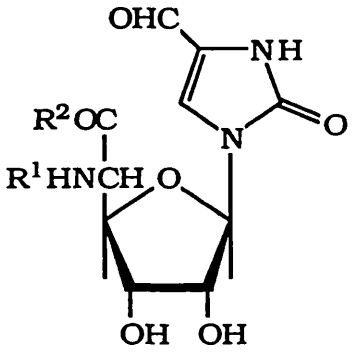


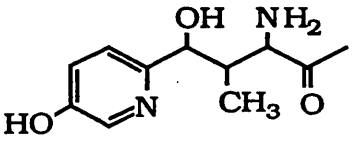
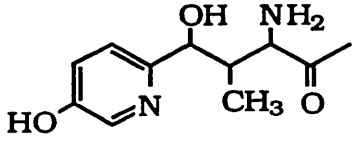
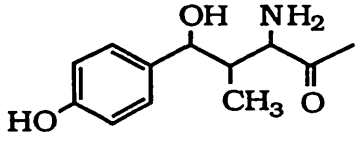
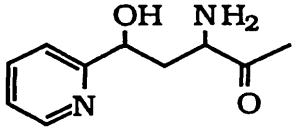
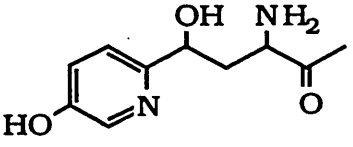
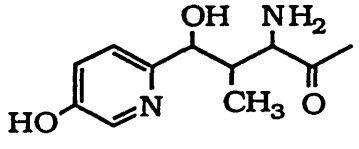
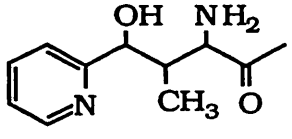
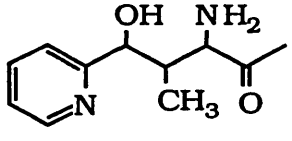
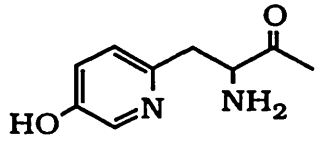
Table 3

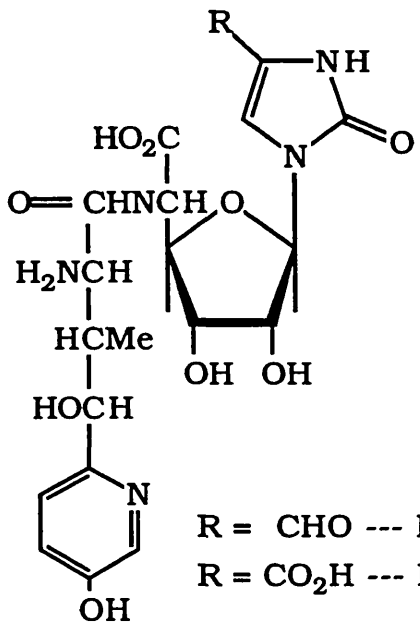
Nikkomycin	R^1	R^2
Z		OH
J		Glu
B_z		OH
K_z		OH
O_z		OH
Q_z		Homo-serine
R_z		Glu
W_z		OH

NIKKOMYCIN X Series

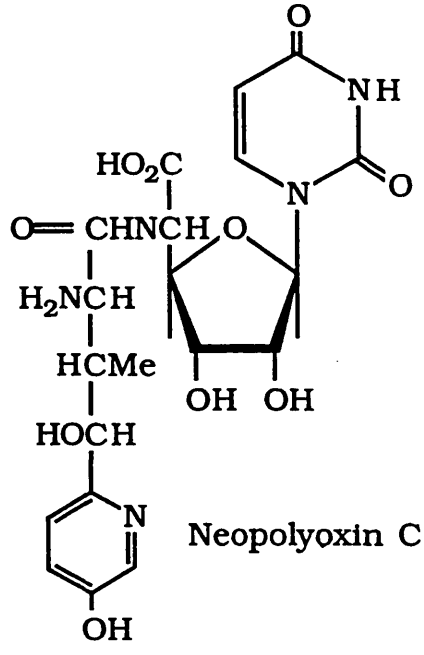
Table 4



Nikkomycin	R^1	R^2
X		OH
I		Glu
B_x		OH
K_x		OH
O_x		OH
Q_x		Homo-serine
P_x		OH
R_x		Glu
W_x		OH



R = CHO --- Neopolyoxin A
R = CO_2H --- Neopolyoxin B



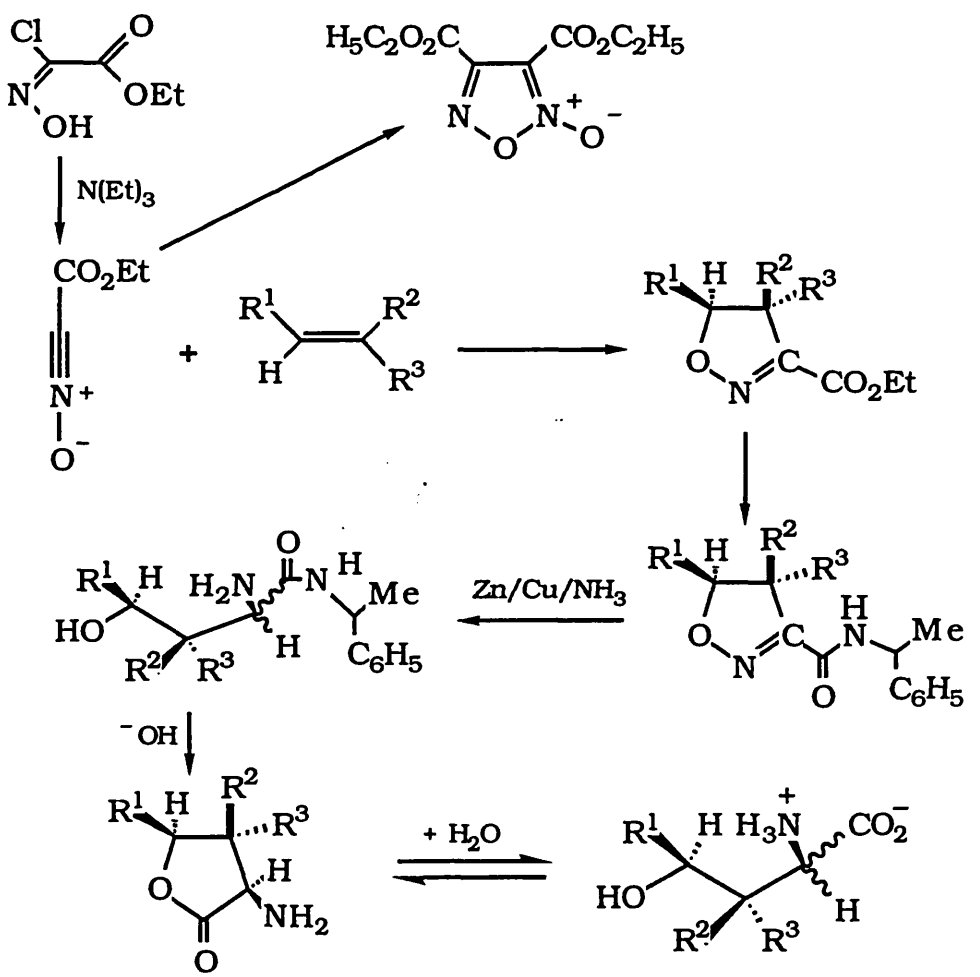
Neopolyoxin C

They found that these compounds had UV spectra that were quite distinct from the other polyoxins but had the same general antifungal and insecticidal properties. They characterised the neopolyoxins fully by transforming the known polyoxin L into the nucleosidal skeleton derived from the degradation of neopolyoxin A. The peptide side chain was characterised by nOe experiments and mass spectrometry on a tristrimethylsilyl derivative.

This proof of the absolute configuration of the neopolyoxins was not performed at the time of the discovery of the nikkomycins, which as one can see, appear to be the same as some of the neopolyoxins. Indeed König believed in his initial report that the nucleosidal portion of the nikkomycins was different from that found in the polyoxins. The final proof of the nikkomycin configuration came in 1984 when König *et al*[24c] used circular dichroism, ^{1}H and ^{13}C NMR, and X-ray spectra, to determine the structure of the nucleosidal skeleton. The elucidation of the L-configuration of the nikkomycin peptide side chain was reported in 1980[24e] and it was achieved by obtaining a positive Cotton effect in the CD spectrum of an *N*-ethyl(dithiocarbonyl) derivative. The relative configurations of C-3

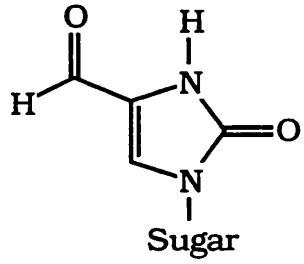
and C-4 were found by NMR and confirmed by crystal structure analysis.

From this time on König concentrated on isolating new nikkomycins from S. *tendae* or from feeding thymine and 5-hydroxyuracil to mutant *Streptomyces* which could not biosynthesise uracil.[24j,k] The side chain configurations were found using NMR and MS techniques but also by comparing the naturally produced peptide with synthetic material (of known configuration) by GC. These synthetic peptides were prepared from the 1,3-dipolar cycloadditions of (ethoxycarbonyl)methane nitrile oxide with the appropriate alkene which usually had to be synthesised *via* a Wittig type process[24b-k] (see Scheme 10).



Scheme 10 :- R^1= Aryl or Pyridyl, R^2= H or Me, R^3= H or Me

The configurations determined by this method are not however universally accepted.[24l] He also determined the structure of the new nucleoside base, 4-formylimidazolin-2-one (**25**) in 1979[24i] a year before Isono *et al* published their neopolyoxin discovery,[26a] and their new, but related, polyoxin N which also contained the imidazolinone base.[30]



(25)

The discovery and formation (either by using the method proposed by Fox *et al*[27] which Isono used, or by using Hilbert's method[28] outlined by König) of this new 4-substituted imidazolin-2-one (**25**) led to speculation as to its biosynthesis. Isono surmised that Fox's facile transformation probably indicated the ring's natural bioformation from uracil.[26b] However, the investigations of Schmidt *et al*[29] using resting cells show incorporation of C-2* adenine, U-C* and C-2* histidine only into the ring system, which they believe indicates the histidine pathway as being the likely biosynthetic route.

Little thought has been extended to the biosynthesis of the new pyridyl peptides as presumably they are thought to be derived from normal peptide synthesis (however it should be noted that nikkomycin production increases when either L-isoleucine, L-leucine or L-tyrosine has been added to the fermentation complex). Equally no different biosynthetic route has been proposed for the sugar moiety, with Isono *et al* believing that as their neopolyoxins and polyoxins can be produced by the same *Streptomyces* then their biosyntheses must be very similar[30].

Several comparisons of the antifungal activity of the nikkomycins/neopolyoxins and the polyoxins have appeared in the

literature.[30,31,32] However the figures and sources of enzyme vary from report to report so an accurate comparison is difficult, but one can see from the summary below that the nikkomycins are stronger inhibitors of chitin synthase than the polyoxins, and their *in vivo Candida* activity make them quite important targets as anticandidal agents.

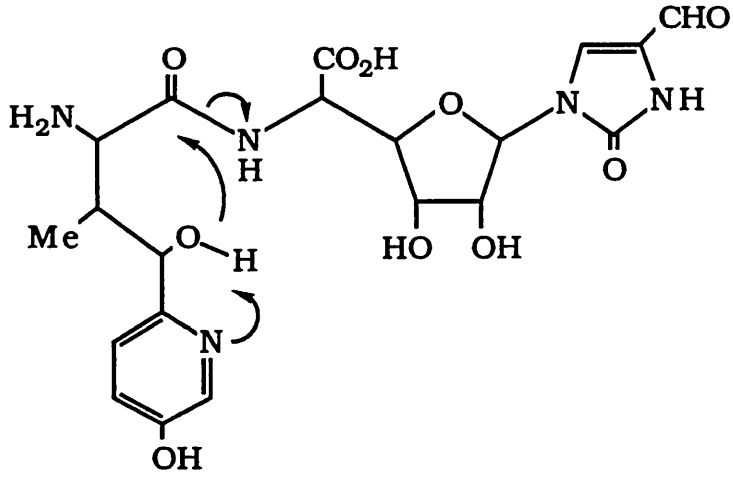
Table 5

Inhibitor	Ki for Chitin synthase	MIC against *Candida albicans*
Polyoxin D	19.8 μM	inactive
Neopoly. A	N.A.	0.4 $\mu g ml^{-1}$
Neopoly. C	N.A.	0.8 $\mu g ml^{-1}$
Nikko. X	0.7 μM	1.0 $\mu g ml^{-1}$
Nikko. Z	6.6 μM	2.0 $\mu g ml^{-1}$
Nikko. Z_T	2.1 μM	N.A.
Nikko. Z_H	2.8 μM	N.A.
Nikko. K_X	N.A	10 $\mu g ml^{-1}$
Nikko. OX	N.A.	3.0 $\mu g ml^{-1}$

From some of these results it seems that the pyridyl hydroxyl group has a significant effect on the MIC (Minimum Inhibitory Concentration) values for the nikkomycins (ie. $K_X > O_X > X$), and is probably acting in a similar manner to the NH_2 on the terminal carbamoyloxy group of the polyoxins. These results also indicate that the C-3" methyl group plays a part in the activity of the nikkomycin (ie. $O_X > X$). One can also see that the thymine and 5-hydroxyuracil derivatives of nikkomycin Z (Z_T and Z_H respectively) have smaller Ki values for the enzyme than nikkomycin Z itself, indicating their stronger binding to the enzyme.

The stability of the peptide side chain is in some doubt as Isono[26b] has reported that the side chain of the neopolyoxins is unstable in acidic conditions and decomposes *via* the mechanism

shown in Scheme 11.



Scheme 11

This is in direct contrast to that which has been found by König,[24k] who claims that the nikkomycins are stable at acid pH but decompose rapidly as the pH becomes neutral; indeed his new nikkomycins (K_X and O_X) are noted for their stability at neutral pH and even up to pH≈8. König believes that the pyridyl hydroxyl group is responsible for the peptide cleavage as the pH increases.

The transport of nikkomycins into the cell is by the dipeptide transport system[33] and their inhibitory action can be antagonised by bacto-peptones or certain dipeptides (e.g. Ala_2, L-Leu-Gly) but not D-Leu-Gly. This again shows the stereoselective nature of the transport system. From these findings it has been proposed that the Gly containing dipeptides were antagonistic because the antibiotics used the γ-glutamyl cycle to cross the cell wall.[32] This theory is supported by the result that the best single amino acid found to inhibit the polyoxins was cysteine which, under the experimental conditions, would most likely have been oxidised into cystine. Cystine is the best substrate for the membrane bound enzyme γ-glutamyl-transpeptidase which is the starting point for the γ-glutamyl cycle.

1.8 CONCLUSIONS

The existence of these two families of nucleosidal antibiotics has only been known for a short time; however within this time their structure, absolute configuration, biosynthesis, and mode of action have been determined.

Their specificity for fungi by means of inhibiting the enzyme chitin synthase, the enzyme responsible for their cell wall formation, at μM concentrations *in vitro* and mM concentrations *in vivo* make them valuable commercial, as well as academic, targets for synthesis and chemical modification.

CHAPTER TWO

The Central Fragment

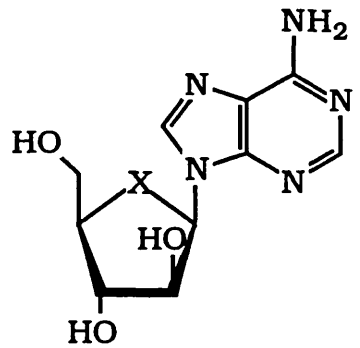
2.1 INTRODUCTION

Within this Chapter we shall describe the synthetic work towards the formation of carbocyclic analogues of the nikkomycins and polyoxins; and in particular the work towards a tetrasubstituted (1,4-*cis*-, 1,2- and 1,3-*trans*-) cyclopentane ring. The biological advantages that could be gained from the replacement of the furanose ring oxygen with a methylene group, will be outlined by considering the properties of the carbocyclic analogues of Adenine and also the natural carbocyclic nucleosides Aristeromycin and Neplanocin A. The various synthetic strategies leading to these carbocyclic compounds and their application to our targets and methodology will also be discussed.

2.1.1 *Why a carbocyclic analogue ?*

As one can see from the first Chapter, the highly potent antifungal nature of the nikkomycins and neopolyoxins towards *Candida albicans*, together with their insecticidal properties, make them very important targets; but the major problem with their use is that they are degraded very easily by hydrolase enzymes within the cell. This drawback can be overcome by using higher doses of the antibiotic, but this can prove to be impractical in medicinal use, especially if large doses are required.

The other approach is to modify the nikkomycin molecule in such a way as to retain its activity but prevent degradation. Such effects have been shown by the carbocyclic analogue of 9-β-arabinofuranosyladenine (ara-A).[34] The natural adenosine ara-A (**26**) was a promising antiviral agent but suffered from the action of the enzyme adenosine deaminase. The carbocyclic version (C-ara-A) (**27**) synthesised by Vince and Daluge[34] retained all the antiviral and antitumour activity of ara-A but also possessed resistance to adenosine deaminase.

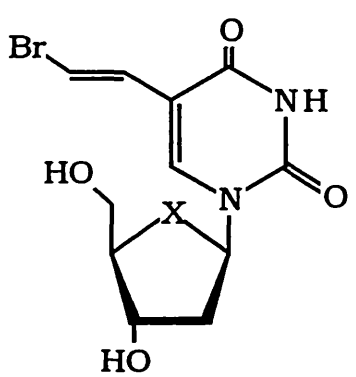


If X = O = Ara-A
(26)

If X = CH_2 = C-Ara-A
(27)

Interestingly C–ara–A **(27)** did not inhibit the deamination of ara–A **(26)** in a competitive experiment thereby showing that the slight conformational and/or electronic change brought about by the cyclopentane ring can have dramatic influences on hydrolytic enzymes.

Another example of a carbocyclic nucleoside's stability to normal degradation can be seen with the analogues of halo-vinyl deoxyuridines.[35]



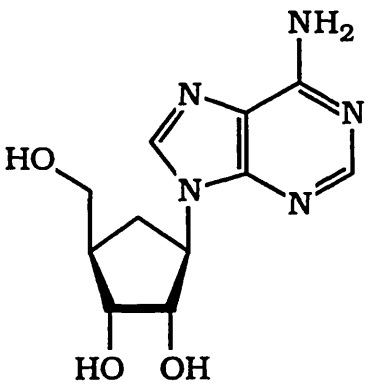
If X = O = BromoVinyl-2'-DeoxyUridine
(28)

If X = CH_2 = C-BromoVinyl-2'-DeoxyUridine
(29)

(E)-5-(2-Bromovinyl)-2'-deoxyuridine **(28)** is exceedingly effective against the Herpes Simplex Virus (HSV-1) however, it too can be degraded by dephosphorylases. Such instability was removed by changing to the carbocyclic analogue **(29)** but, in this case, its potency was slightly reduced.

With the vast range of active nucleosides and nucleotides that are now available, considerable biological interest in the possible advantages to be gained from carbocyclic analogues has

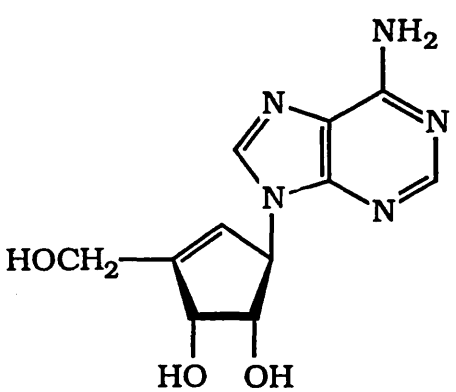
led many groups to synthesise and test such analogues.



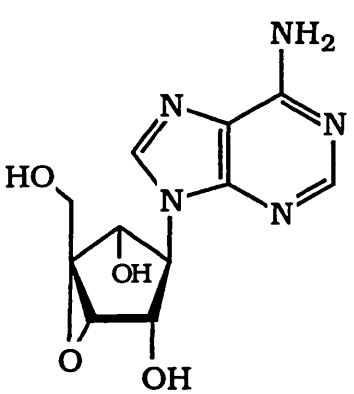
Aristeromycin

The first natural, carbocyclic nucleoside to be isolated was Aristeromycin (equivalent in structure to (-) C-Adenosine). It was discovered[36] in 1968 and its structure was determined[37] by 1972. Aristeromycin has MIC_{50}'s of between 2 and 4 μgml^{-1} for HSV-1 and -2 respectively as well as good activity against many other virus strains and the standard mouse L1210 leukemia cells.[38a]

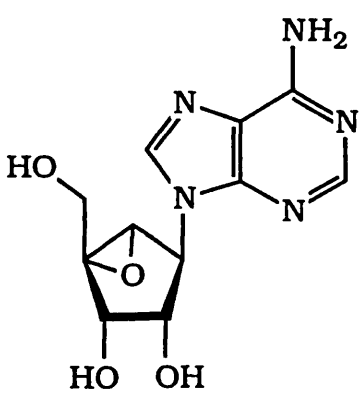
The next natural carbocyclic nucleosides to be identified were the Neplanocins, of which Neplanocin A[39] shows the highest *in vivo* antitumour activity against the L1210 leukemia cells. The unusual cyclopentenyl replacement of the furanosyl ring has been found to be vital for its activity.[40]



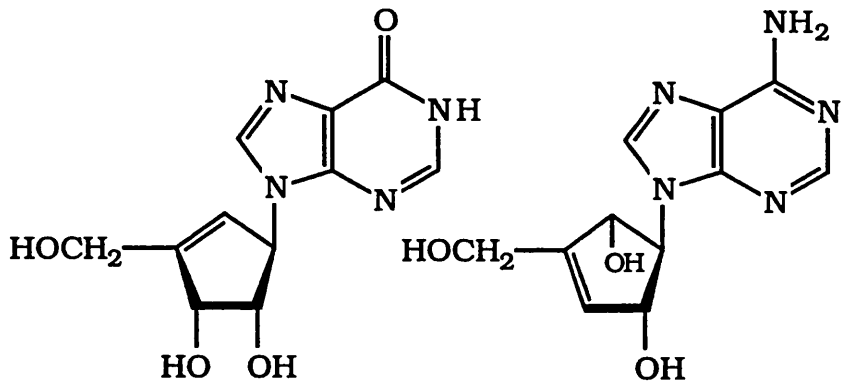
Neplanocin A



Neplanocin B



Neplanocin C

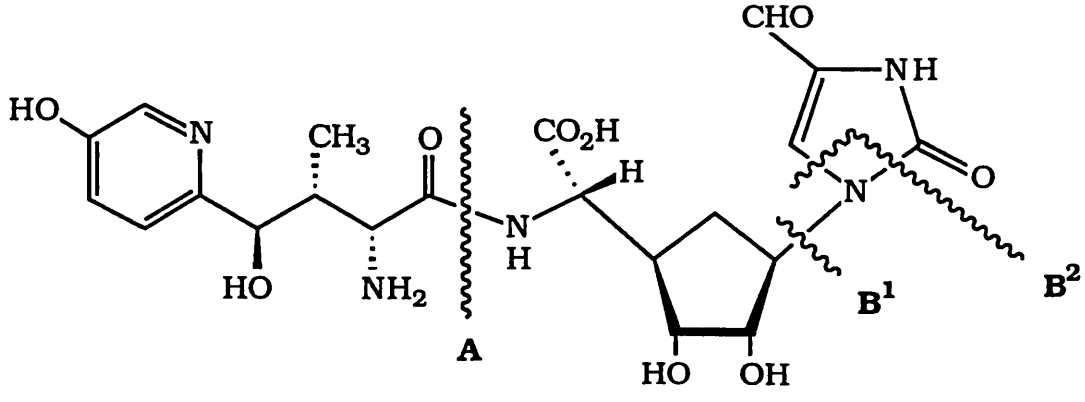


Neplanocin D **Neplanocin F**

The majority of the carbocyclic analogues have been tested in the antiviral and antitumour areas, with some 2'-deoxy-5-substituted uracil variants having excellent activity against HSV (MIC_{50}'s of 0.8 to 0.1 μgml^{-1}).[41a] However, very few, if any, have been applied to the area of antifungals. With this in mind, and also remembering the most desirable biostability properties, we investigated a route towards the carbocyclic analogues of the nikkomycins and polyoxins.

2.1.3 *Disconnection*

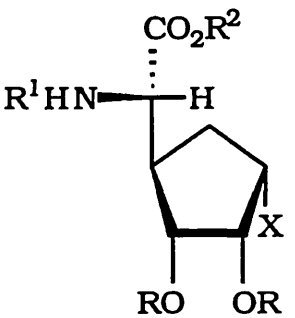
Taking carba-nikkomycin X (**30**) as an example of one of our ultimate targets, the two initial disconnections have been marked.



(30)

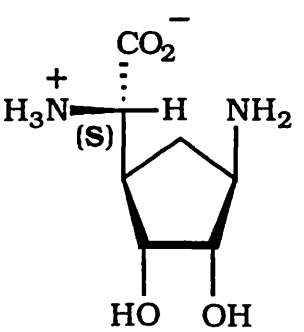
The side chain dipeptide (from disconnection A) was to be synthesised last as this, we envisaged, would have been simply coupled to the amino acid moiety by the standard peptide chemistry already described by those groups investigating the peptide analogues of the natural series.[20,22,24]

The disconnection of the nitrogen base could have followed either of the paths 'B^1' or 'B^2' as indicated. The cleavage by method 'B^1' mimicks that resulting from the enzymatic degradation seen in the natural series and would require a cyclopentyl fragment of the type shown below (**31**).



(31)

The leaving group X would then be displaced by the salt of the complete base and this is analogous to work carried out in the carbohydrate and nucleoside fields, however without the assistance of the anomeric oxygen this reaction may have proved sluggish. Therefore we decided to follow the disconnection path 'B^2' which would leave an initial cyclopentane target (known as "the central fragment") of the form below (**32**).

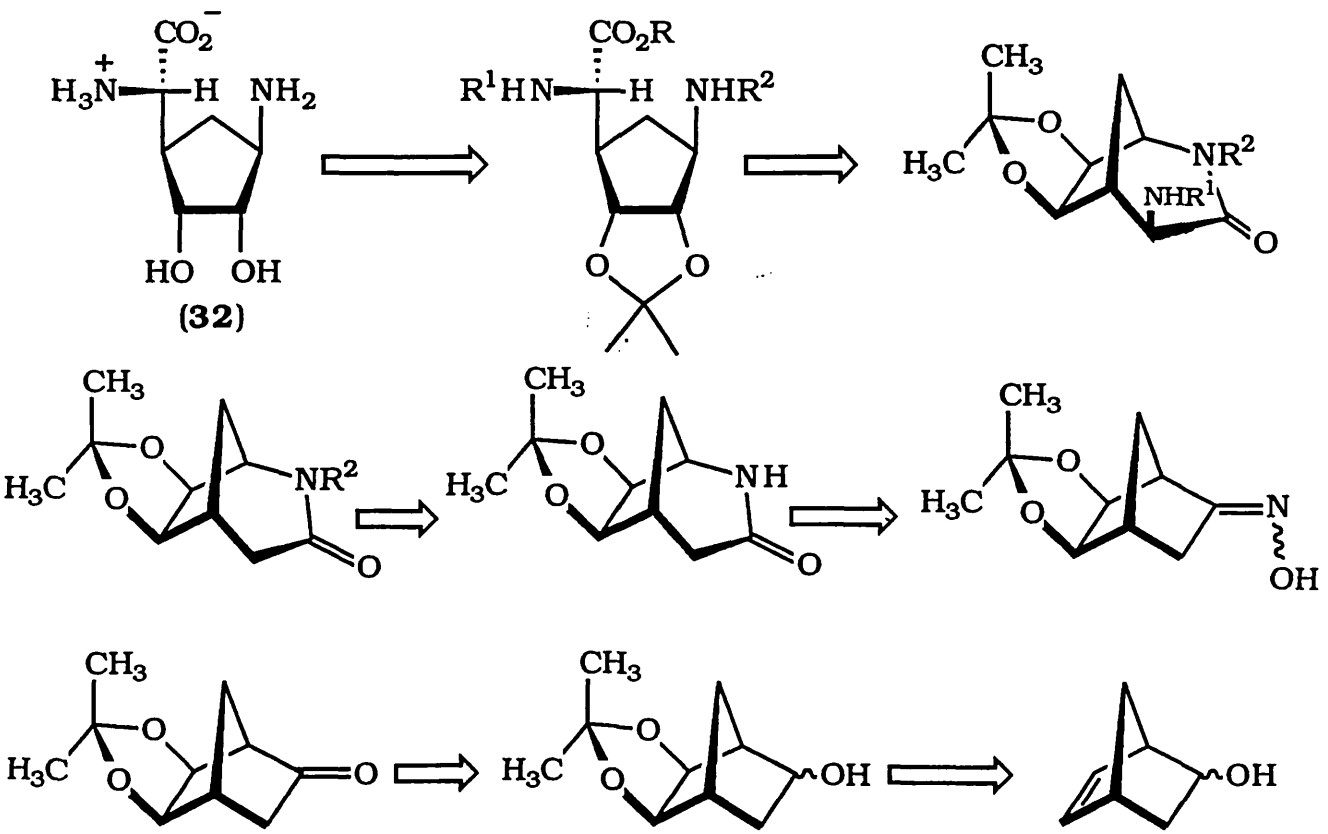


(32)

From here the uracil or imidazolinone base could be built onto the free amino group. The chemistry developed to tackle this "right hand" part of the molecule will be discussed in Chapter Three, whilst the work to form the 1,4-*cis*-,1,2-,1,3-*trans*-, 5'-(S)-cyclopentylamino acid (**32**) is described in the next section.

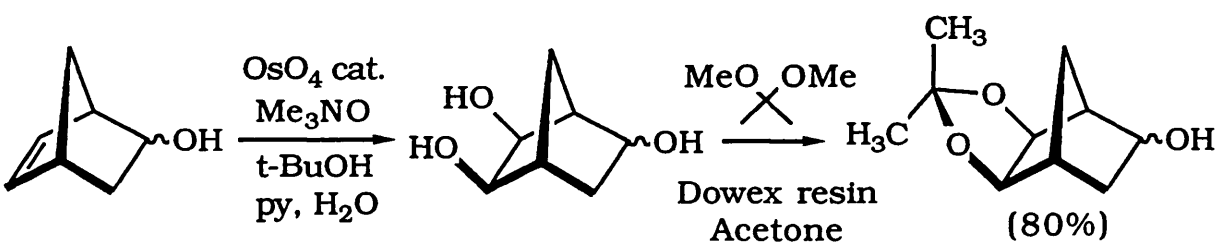
2.2 RESULTS AND DISCUSSION

A second reason for chosing path 'B^2' was that we envisaged the desired *cis*-/*trans*- relationships could easily be derived from a bicyclo[3.2.1] ring system. This system would, in turn, give us some control over the stereochemistry at the C-5' centre and enable us to achieve the desired (S) configuration. The retrosynthetic analysis for the production of the central fragment by this idea is shown below in Scheme 12.



Scheme 12

(The synthetic route that is described is a racemic one but only one enantiomer will be shown in the following Schemes). The initial steps in the synthesis of the central fragment were derived from the work of Scopes *et al.*[42] The *cis*-hydroxylation of the commercially available norborn-5-en-2-ol (**33**) was not, at first, successful, with drastically reduced yields being obtained compared to those obtained by Scopes. This problem was remedied when the purity of the starting alcohol was assessed and found to be only 30% pure. The polymeric baseline impurity was easily removed from the *exo*- and *endo*- isomers of the alcohol by dry column flash chromatography and gave the pure alcohol as a colourless waxy solid. The yellow, viscous baseline material probably consisted of dimers and polymers derived from the norbornyl double bond, although no attempt was made to confirm this.



(**33**) (**34**) (**35**)

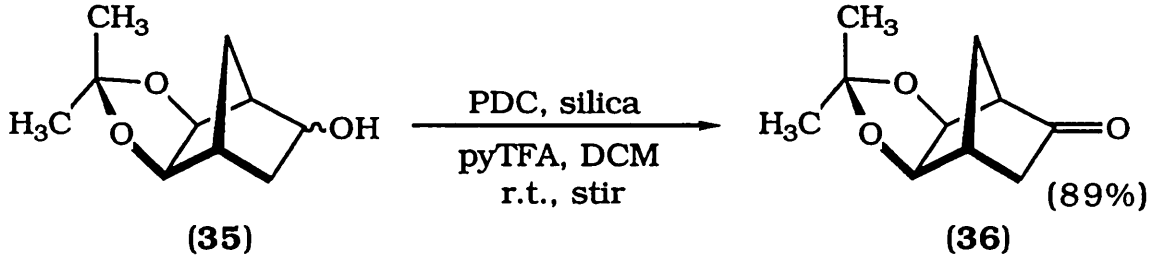
Scheme 13

Once this pure form of the alcohol was obtained, the osmium tetroxide mediated hydroxylation proceeded in an excellent yield comparable to that found in the literature.[42] Indeed, the high purity of the starting alcohol enabled us to isolate and characterise the intermediate triol (**34**) which was a colourless solid. This product had not been isolated before and, as an impure viscous oil, had previously been taken straight on to the diol protection step.

The formation of the *exo*-diol was assumed as the compounds formed were spectroscopically identical to those obtained by Scopes *et al*,[42] and to which he had assigned the

exo structure. These assignments were, in turn, probably made after considering which pathway to the intermediate osmate ester was the least sterically dèmanding.[43]

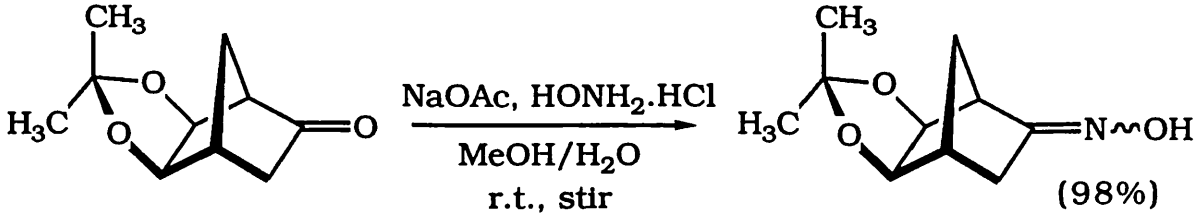
The protection of the *cis*-diol by the formation of an acetonide also went smoothly, and the mixture of *exo*- and *endo*-protected alcohols (**35**) was isolated as a viscous clear oil. This isomeric mixture was taken on without the separation of the isomers as this was not necessary. The final literature step[42] involved the oxidation of the remaining free alcohol with PDC (pyridinium dichromate). Again this reaction went in accordance with the literature, with the product ketone being easily recrystallised from pentane.



(**35**) (**36**)

Scheme 14

The formation of the previously unknown 5-*exo*,6-*exo*-(*iso*-propylidenedioxy)bicyclo[2.2.1]heptan-2-one oxime (**37**) was achieved in a virtually quantitative yield with hydroxylamine hydrochloride in a water : methanol (1 : 1) solution of sodium acetate and the ketone (**36**). Initially, a mixture of both the geometric isomers of the oxime were produced and this product took the form of a clear colourless oil; only after lengthy periods under high vacuum did the mixture slowly solidify.

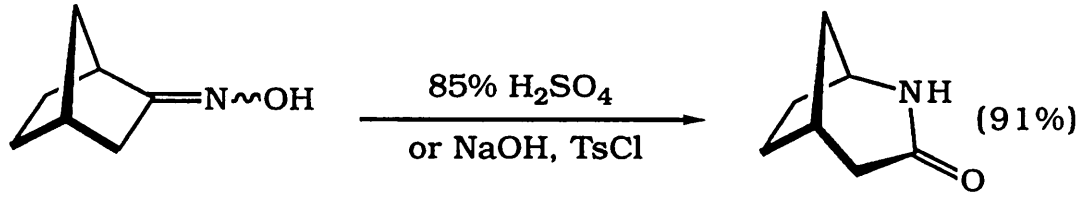


(**36**) Scheme 15 (**37**)

In an effort to differentiate between the two isomers, the methyl derivative of this oxime mixture was formed (**38**), but it did not facilitate the seperation of the *trans-* and *cis-* geometric isomers. The next step, which involved the Beckmann rearrangement of the oxime (**37**), was the key step in the synthesis. This step would set up the nitrogen function in the desired 1,4-*trans-* relationship with a two carbon unit, in a form which could be readily elaborated to give the amino acid (**32**) upon cleavage of the lactam bond.

2.2.1 *The Beckmann Rearrangement*

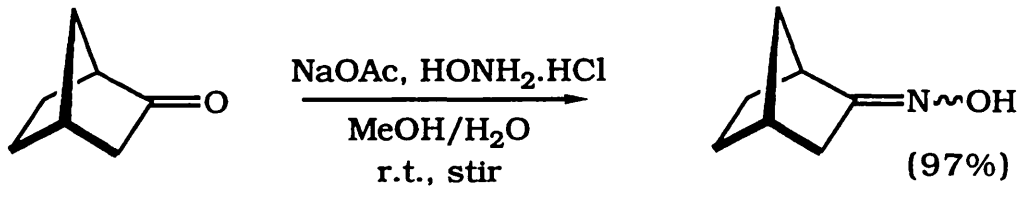
There had been reported in the patent literature,[44] by some Swiss workers, the rearrangement of norcamphor oxime (**39**) into exclusively the 2-aza-lactam (**40**) in high yield.



(**39**) Scheme 16 (**40**)

This regioselectivity was exactly what we would require for our system, however the validity of this patent work had been questioned[45] and later work had not been able to repeat their claims.[46] As this norcamphor system was so close to ours we decided to try and repeat the Swiss work and, if it proved to be inaccurate, then find a new method that could be applied to our acid sensitive analogue.

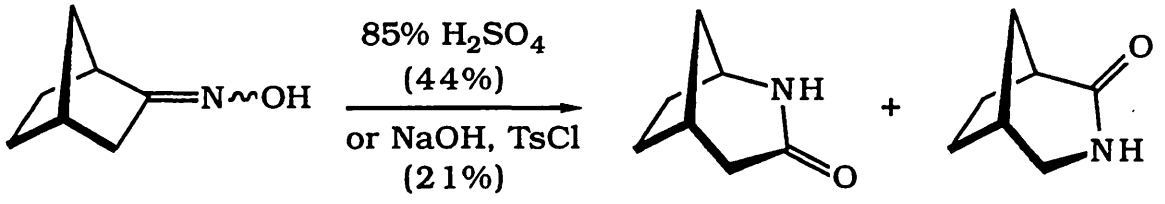
The production of norcamphor oxime (**39**) from norcamphor (**41**) was as efficient as in the previous case with our ketone (full spectroscopic data were obtained for this known compound as only the melting point and analytical data had been recorded in the literature).[46a]



(41) **(39)**

Scheme 17

Upon the repetition of the Swiss workers patent (which involved the use of 85% sulphuric acid poured directly onto the oxime) only a dissappointing 44% yield of a clear oil was obtained. This oil analysed correctly (spectrocopically and microanalytically) for the corresponding lactam but the yield of the reaction product did not agree with that quoted by the Swiss. (A small amount of this oil gave a crystalline product if left for some time in an ether solution).



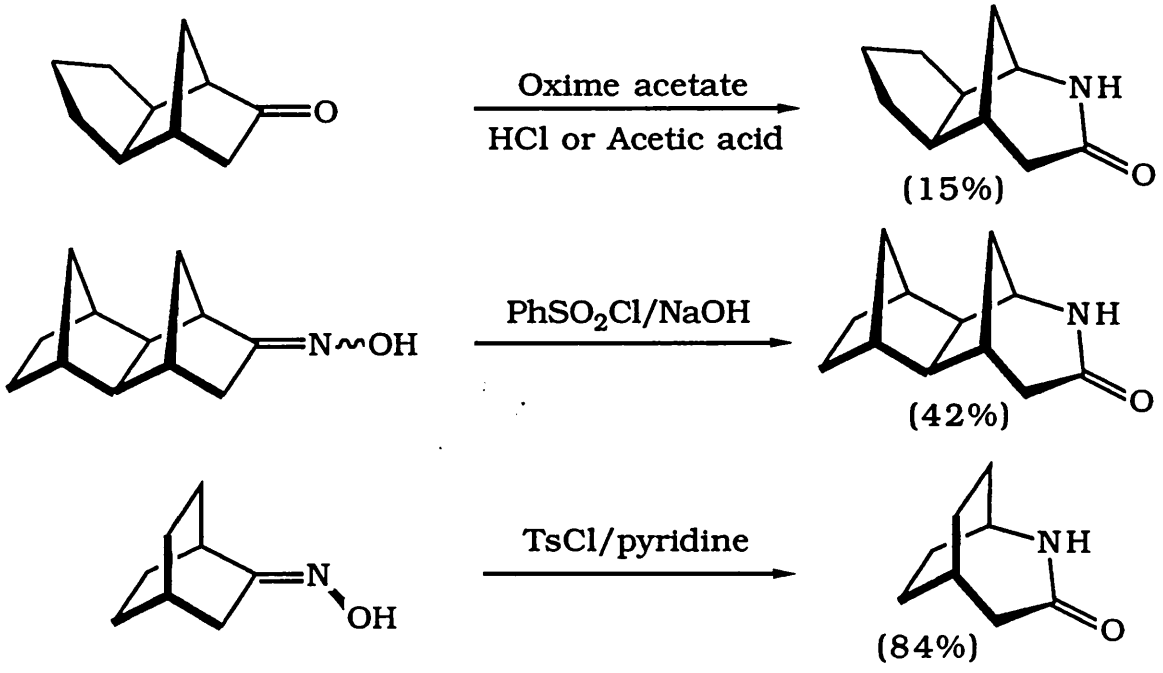
(39) **(40)** **(42)**

Scheme 18

This result was in accordance with the literature published after the Swiss patent[44] and seems to indicate that the rearrangement under these conditions is not regiospecific and gives a mixture of the 2-aza- (**40**) and 3-aza- (**42**) lactams. The NMR analysis of our reaction product was very complex and did not appear to be a single isomer. These acidic conditions, even if successful, would have been inapplicable to our system and so we investigated the alternative, more suitable, basic procedure[46a] which used sodium hydroxide with tosyl chloride. This too was only moderately (21%) successful giving again an oily mixture of lactam products.

The only successful set of conditions that had been reported for this rearrangement were boron trifluoride in tetrachloroethane.[47] These conditions were quoted as giving, regioselectively, the 2-aza-lactam (**40**) in an excellent 91% yield, but the source of these, somewhat remarkable, claims was a book which contained no experimental description. Our tentative experiments with boron trifluoride etherate (in ether) gave no reaction and the starting oxime was recovered.

At this time, we noticed that within the rest of Krow's extensive review,[45] the Beckmann rearrangements of the bicyclo[2.2.2]octanone oximes went in reasonable yield and were also regiospecific. This success was also found with the bicyclo[2.2.1]-systems which were substituted across the C-5 and C-6 positions with a cyclopentyl ring (see below).[46a,48,49,50]

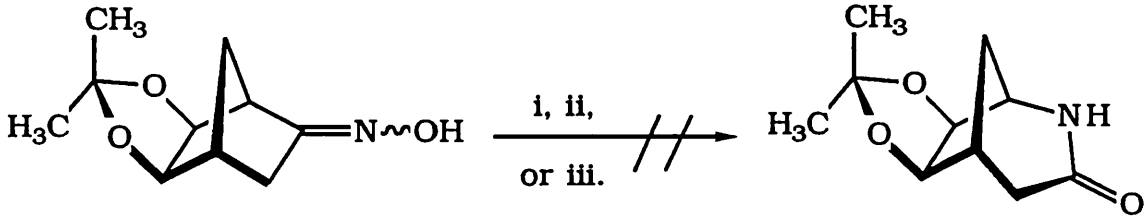


Scheme 19

These observations did not seem to have been noticed by Krow and we believed that the extra fused ring or the change in the bicyclic ring conformation inherent in the bicyclo[2.2.2] system, was having a significant effect on the course and regiospecificity of the rearrangement. With this in mind we

decided to try various rearrangement procedures on the desired acetonide protected oxime (**37**) which contained that five membered ring fusion across the C-5 and C-6 positions.

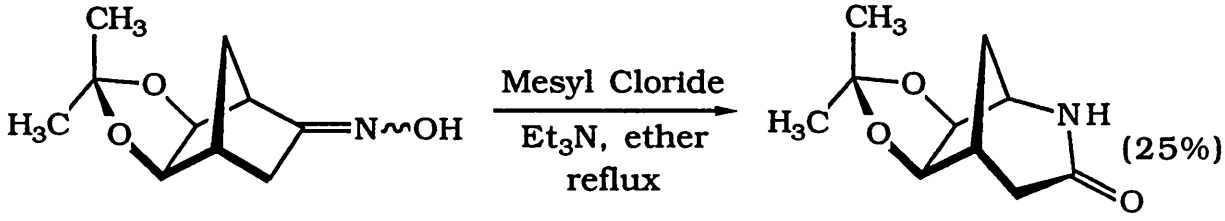
Our initial attempts using the previous acidic and basic conditions were failures. The highly acidic reaction, not surprisingly, gave a multitude of products which were not isolated and the tosyl chloride method merely returned a slightly reduced amount of the starting oxime. We were more encouraged by the experiment using triphenylphosphine with chlorine gas.[51] This produced a vigorous, exothermic reaction as expected but, after work up, no lactam material (only triphenylphosphine oxide) was recovered.



(**37**) (**43**)

Scheme 20 i. 85% H_2SO_4, ii. NaOH/TsCl, iii. Ph_3P/Cl_2

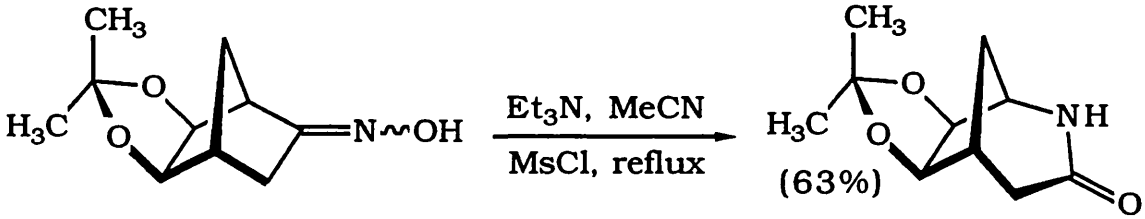
Our aim therefore seemed to be, to find the mildest, as well as the most neutral conditions, in order for this rearrangement to work; and this we did by forming *in situ* the mesylate of the oxime. The initial experiment involved the addition of triethylamine to an ethereal solution of the oxime followed by the addition of methanesulphonyl (mesyl) chloride. In refluxing ether these conditions gave a low, but significant yield[45] of the desired 2-azabicyclo[3.2.1]octyllactam (**43**) selectively.



(**37**) Scheme 21 (**43**)

The yield of this lactam (**43**) was improved by changing to chlorobenzene, a more polar solvent but one which also has a much higher refluxing temperature. In order to check whether the improvement in yield was related to temperature or solvent polarity, the experiment was repeated in refluxing benzene. As we suspected, no lactam material was recovered from this experiment and it prompted us to move to the even more polar acetonitrile as the reaction solvent.

Again, to our great pleasure, we found an increase in the yield of the lactam and an absence of some chlorinated products which had formed a significant amount of the material obtained from the previous rearrangement experiments.[52]



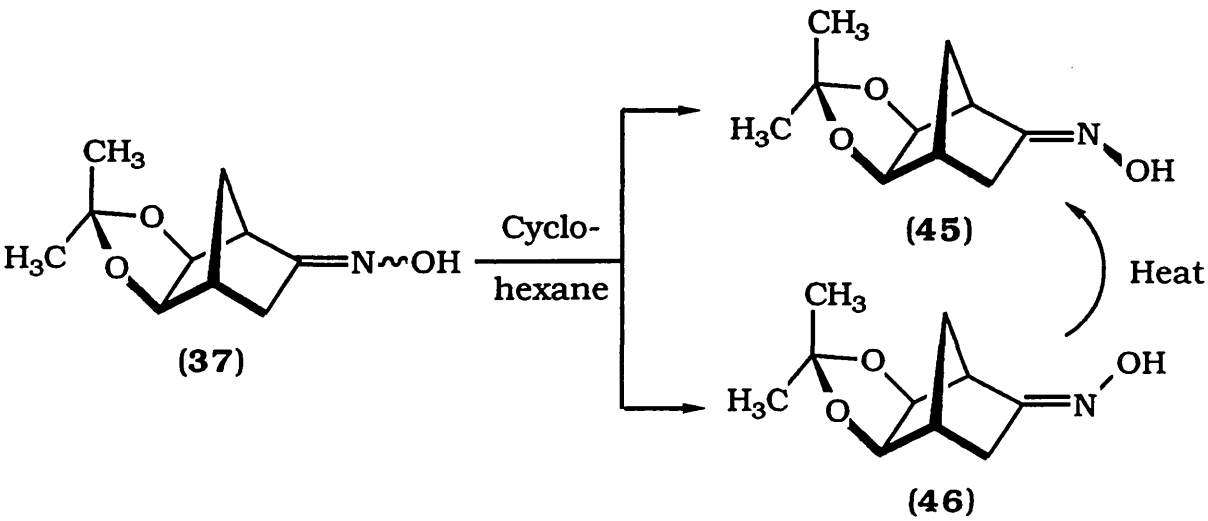
(**37**) (**43**)

Scheme 22

Our assignment of the lactam product (**43**) as being the 2-aza analogue was originally derived from the expected, better migratory ability of the secondary, compared to the primary, centre. This assignment received more support from the 2D ^{1}H NMR spectra that were obtained, and from an n.O.e. experiment performed on the *N*-methyl derivative (**44**) which showed a strong enhancement between the *N*-methyl protons and that proton which had been assigned as being attached to C-1. Final confirmation was gained from the X-ray analysis of a crystal produced from the slow evaporation of the chromatography solvent (ether/ethyl acetate) during the lactam's isolation.

In an effort to increase the yield of the lactam still further, we attempted to separate the geometric isomers of the starting oxime so that we could use specifically the *trans*- form which, by

the traditional mechanism for the Beckmann rearrangement,[53] would give us the desired lactam. This was achieved, after several solvent systems were tried, by using refluxing cyclohexane. From this solvent the *trans*-isomer (**45**) crystallised out almost immediately, and left an oily residue which slowly solidified.



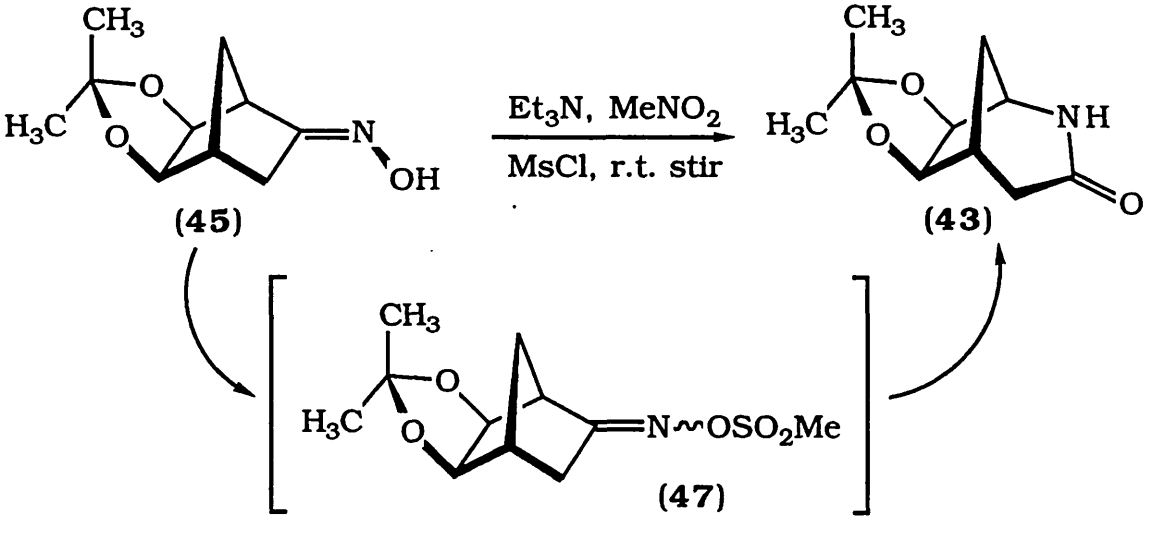
Scheme 23

This residue if treated several times to the same recrystallisation procedure, gave more of the *trans*- product but eventually left a colourless crystalline residue which was the pure *cis*- form of the oxime (**46**). The *cis*- form of the oxime could readily be converted into the *trans*- form by heating it, neat, above its melting point; the solid would then sublime and condense in the *trans*- form. Both of these forms were then subjected to the same rearrangement conditions and indeed the *trans*- oxime gave a further increase in the yield (to 73%) of the lactam (**43**). However, somewhat surprisingly, the *cis*- oxime also gave a reasonable yield of the lactam (44% with 25% recovery of a mixture of oximes) and *not* the isomeric 3-aza lactam.

This obviously shows that the oxime (**46**) is able to isomerise in the reaction conditions, but this raises questions about the formation of the 2-aza lactam (**43**). With our original work on these compounds it was thought that the ratio of the *cis*-

and *trans*-oximes was 1:1 and hence, all of the lactam product was being derived from solely the *trans*- oxime. (The *cis*- oxime was assumed to be the source of the unidentifiable chlorinated material). This would have nicely accounted for the nearly 50% yields that were obtained; but if the *cis*- oxime can isomerise under the reaction conditions then why were the yields only 50%?.

It appeared to be that further improvements in the lactam (**43**) yield could be made if we could obtain the rearrangement at lower temperatures as this would help to reduce the interconversion of the oxime isomers. The most likely way of obtaining this was to move to an even more polar solvent such as nitromethane. The rearrangement was attempted at room temperature in nitromethane overnight and some rearranged product was observed on thin-layer chromatography along with a new spot which could have corresponded to the intermediate mesylate (**47**) which had not previously been seen.



Scheme 24

However, the majority of the starting oxime was still unreacted and there also appeared to be an increase in the level of baseline material being formed. Therefore the solvent was heated

to approximately 75°C until the rearrangement had completely finished, but unfortunately a lower yield of the lactam (**43**) was recovered. A second method for improving the yield of the lactam (**43**) would have been to form the triflate derivative instead of the mesylate, as this would make the oxygen into a much better leaving group. Unfortunately, the use of triflic anhydride to form the appropriate derivative led only to a multitude of products which were not investigated.

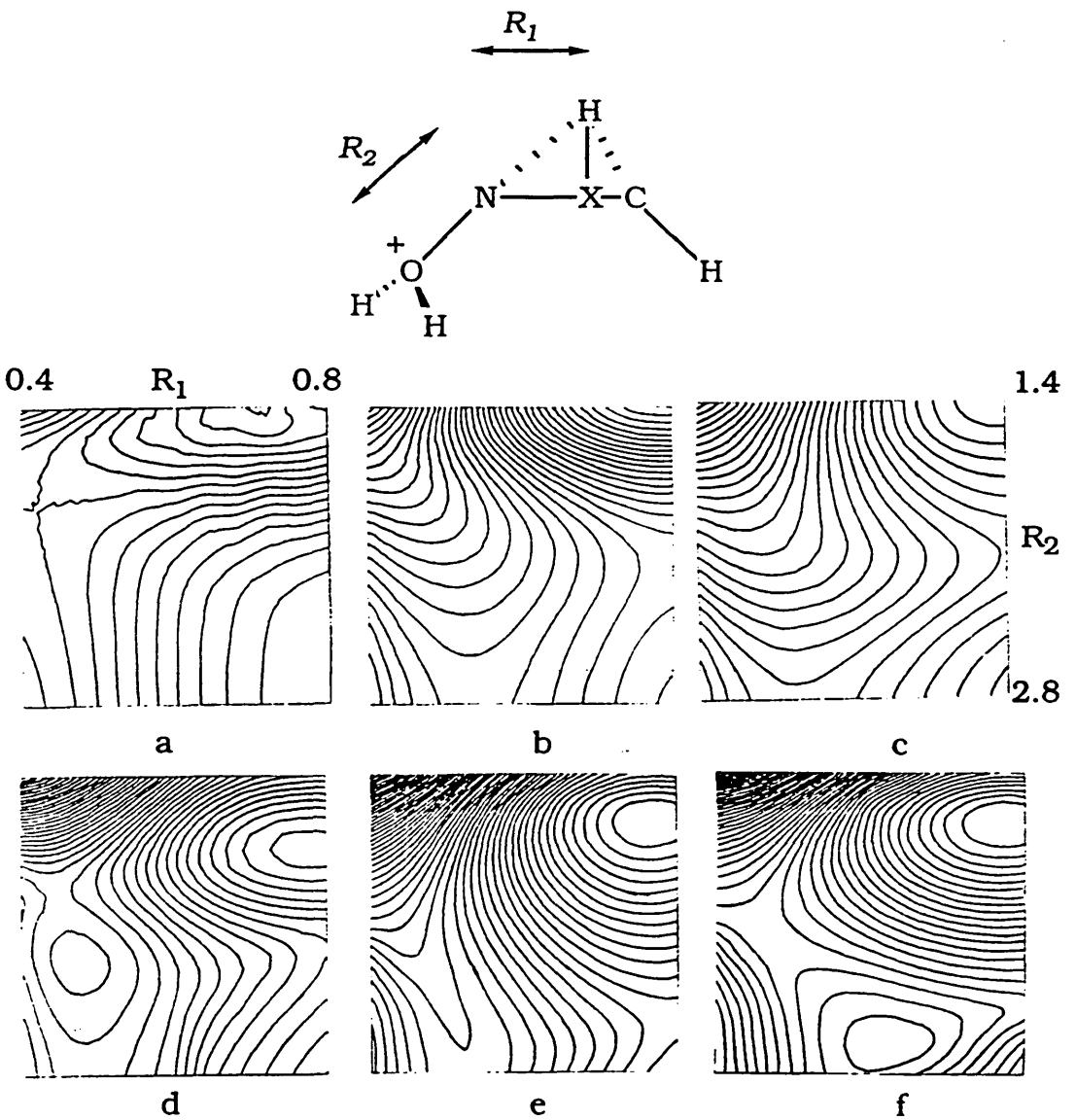
With the mesylate conditions now having been proven to work for our ring fused compound, we repeated our attempts to rearrange the norcamphor oxime (**39**) and, as before, found no lactam (**40** or **42**) material produced. This failure to produce any of either of the lactam isomers indicated to us that our original proposition of ring fusion in the [2.2.1] systems was correct and the key feature needed for this rearrangement to work. To give us further proof of this theory we turned to molecular modelling and calculations to find out exactly to what extent the extra ring (or carbon atom in the case of the bicyclo[2.2.2] systems) had upon the molecular geometry and energies of the oxime systems.

Our initial work with Macromodel (version 2.5) did show some seemingly small differences between norcamphor, the bicyclo[2.2.1]ketone, and the bicyclo[2.2.2]ketone as well as small differences between the oximes and the *cis-* and *trans-* forms of the oximes themselves. These results were encouraging but the differences seemed too small to be considered significant. Hence we, in collaboration with Dr Henry Rzepa, decided to probe into the energy changes occurring within the rearrangement itself.

Firstly we had to assess the validity of the semi-empirical methods which we would have to use due to the complex nature of the molecules. Taking the simplest Beckmann rearrangement possible, that of formaldoxime, we calculated energy contour grids for the migration of a hydrogen atom with the loss of water.

Taking four possible semi-empirical SCF-MO procedures (MINDO/3, MNDO, AM1,[54] and PM3,[55]) and comparing the

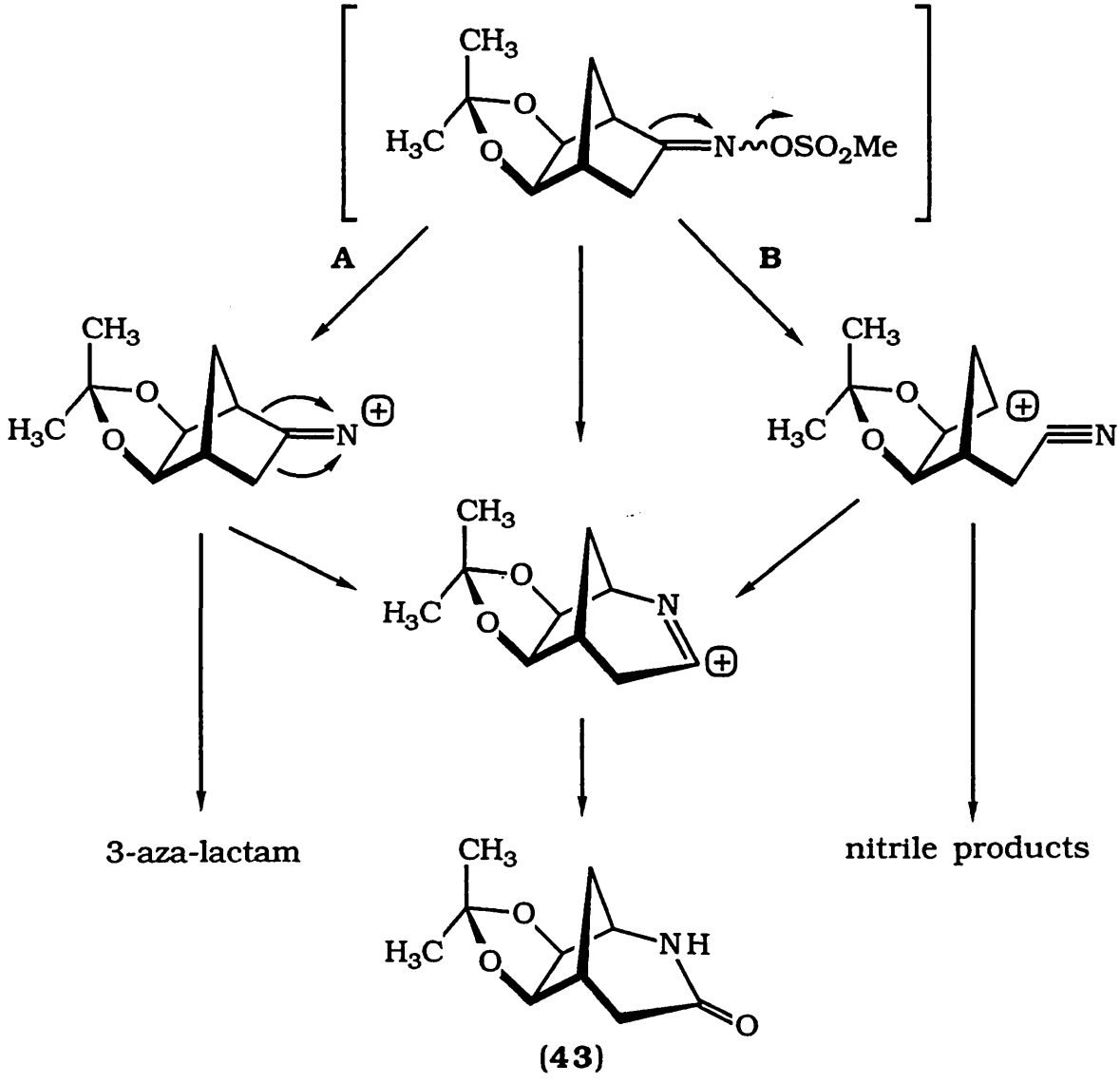
results from them with those obtained at the *ab initio* level (3-21G, 6-31G*, MP2/3-21G, and MP2/6-31G*), we found that the PM3 method was qualitatively superior to the older procedures in predicting an energy surface similar to that produced by the MP2/3-21G *ab initio* method.



Scheme 25:- a)MINDO/3, b)MNDO, c)AM1, d)PM3, e)3-21G, f)MP2//3-21G

In these methods both concerted and stepwise pathways for the Beckmann rearrangement were clearly shown by some of the above methods whilst the others tended to be restricted to only one of the possible pathways. This good correlation between the

PM3 method and the more rigorous *ab initio* method was pleasing as we can now be more confident in any further results[56] obtained, by the PM3 method, with the more complex bicyclic systems. These energy contour maps present two of the possible mechanisms by which the rearrangement could proceed. Firstly the concerted migration of the alkyl group with the expulsion of the, presumed, mesylate group and secondly the stepwise elimination of the mesylate group followed by the migration of the alkyl function. These mechanisms along with a third possibility are shown below.

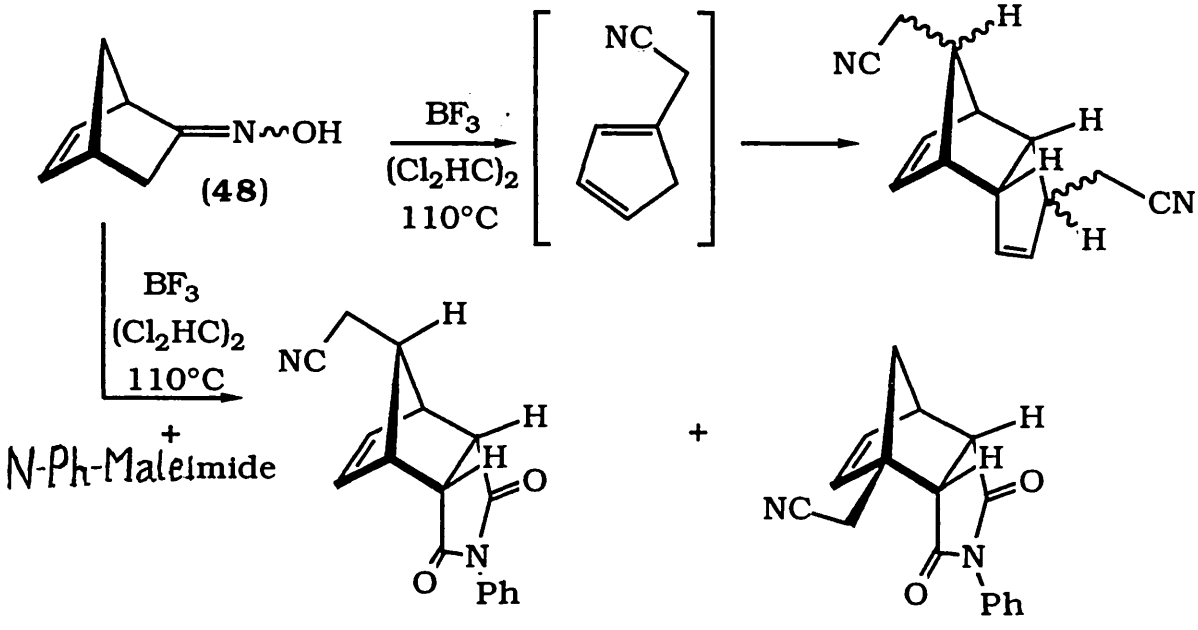


(43)

Scheme 26

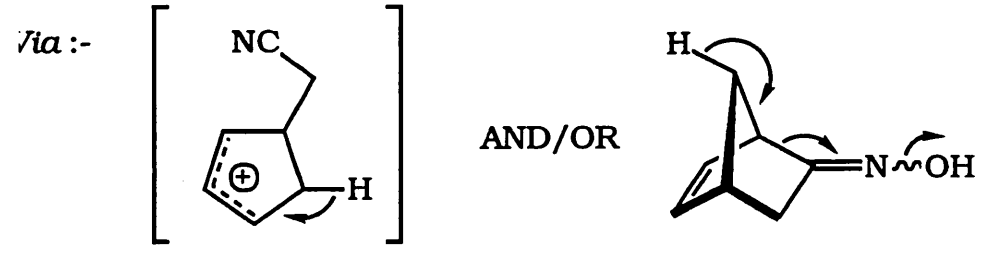
The solvent effects that we have seen in our work would normally lead one to conclude that the rearrangement follows a highly stepwise pathway (**A** or **B**), with the iminium or carbocation produced being stabilised by the more polar solvent. However, in the concerted pathway a carbocation is also produced and therefore any increase in solvent polarity is also going to stabilise this intermediate. One therefore cannot use these solvent effects as a guide to the reaction mechanism.

A consequence of the stepwise path A would be that both alkyl groups would be equally likely to migrate, giving a mixture of products (as seen with the 85% sulphuric acid procedure). The second stepwise pathway B involves an initial fragmentation of the alkyl oxime bond and the formation of a nitrile cation. This mechanism would mainly lead to nitrile products and it has been shown that the stabilisation of a cation at that centre causes the reaction to completely follow this pathway.[57] During the preparation of this Thesis, Pappalardo *et al* published[57] their work on derivatives of the bicyclo[2.2.1]heptan-5-ene-2-one system (**48**) which illustrates this pathway.



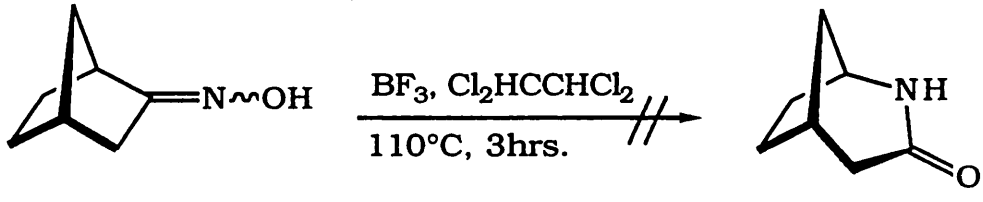
Scheme 27

He reports that the Beckmann rearrangement of the oxime of this unsaturated system does not work and that the fragmentation reaction to give nitrile products is the only process.



He chose our oxime to illustrate the importance of the double bond upon the course of the reaction and uses the acetonide protecting group as a "mask" for it (without such a mask an allylic cation is formed, lowering the energy of the fragmentation pathway and hence the Beckmann rearrangement does not proceed). Interestingly the conditions that he uses to effect the rearrangement[48] of our oxime are the boron trifluoride/*sym*-tetrachloroethane conditions mentioned earlier.

Here again, incomplete details were given about the experimental conditions used and our attempts to duplicate the norcamphor rearrangement mentioned in Krow's review,[45] with these new details, have failed to produce the desired lactam.



(39) Scheme 28 **(40)**

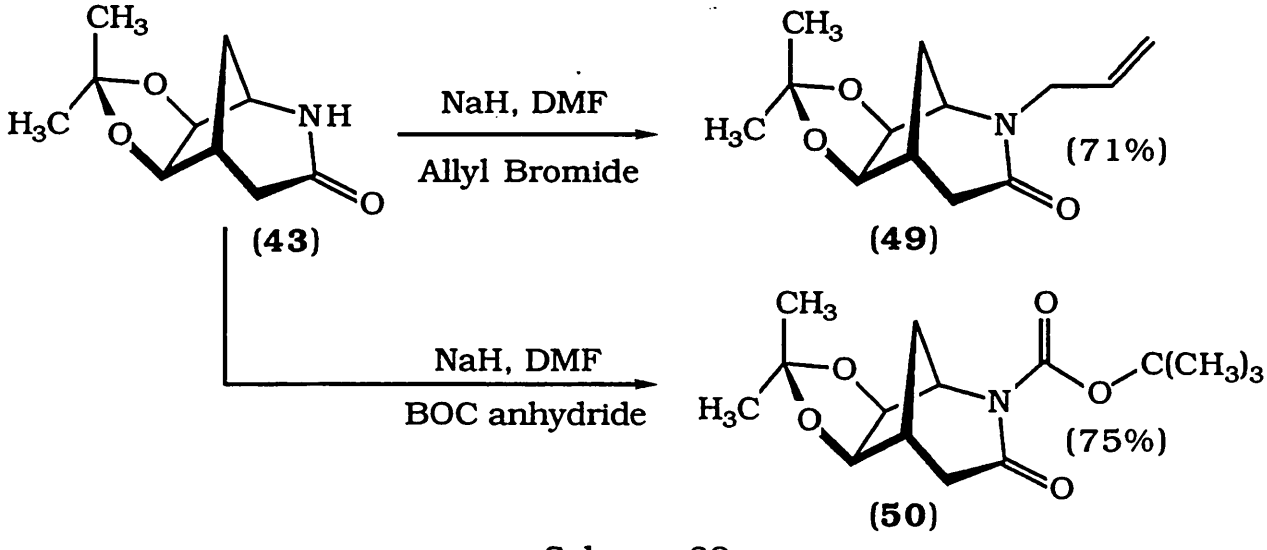
It is this very reaction which would determine the validity of either Pappalardo's or our arguements towards the course of the Beckmann reaction in these bicyclic systems. We believe that it is not the fact that the double bond is masked that causes the rearrangement to proceed (although its presence does seem to

make the fragmentation pathway the dominant one); but as we maintain, that it is the extra conformational change which is brought about by the fused five-membered ring which is the true reason for the success of the rearrangement pathway.

2.2.2 *Lactam functionalisation*

One of the reasons why this approach to the carbocyclic analogues of the nikkomycins was taken, was that the bicyclic[3.2.1]system would, in theory, give us *exo*- face selectivity in any electrophilic additions to the C-4 position.[58] This *exo*-functionalisation is again due to this face being the least sterically demanding and would, if a nitrogen electrophile were used, produce the correct chirality for the amino acid at the eventual C-5' centre.

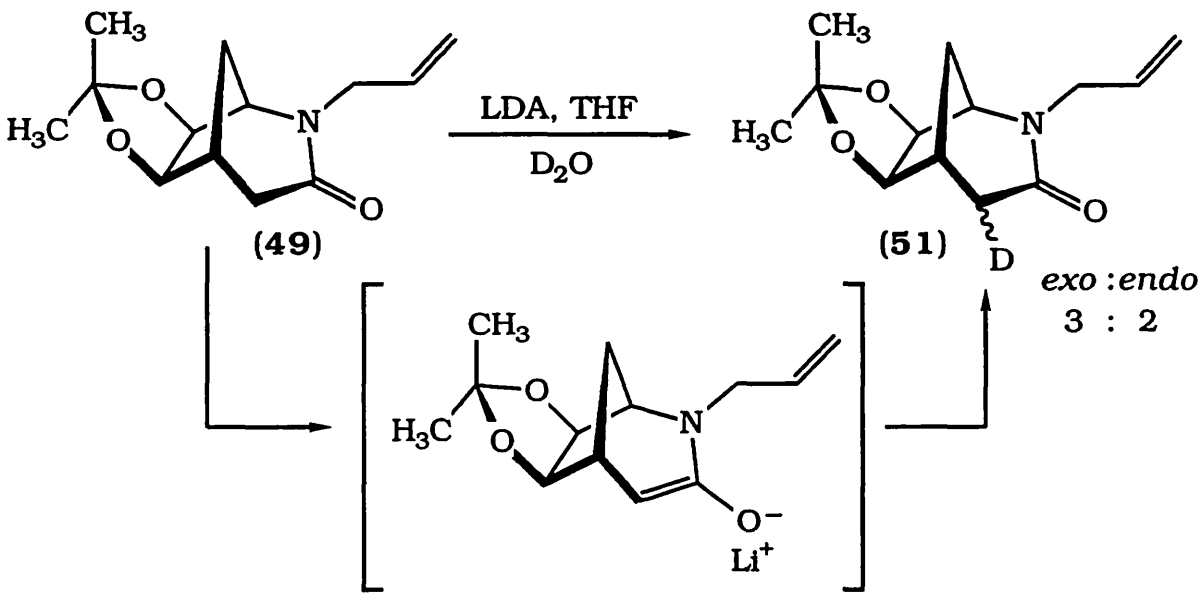
Before attempting to form the lactam enolate, the nitrogen was protected in reasonable to good yields with either an allyl group or a t-butoxycarbonyl group. These protecting groups were chosen so that they would be of use in the later work concerned with the nitrogen base (see Chapter 3).



Scheme 29

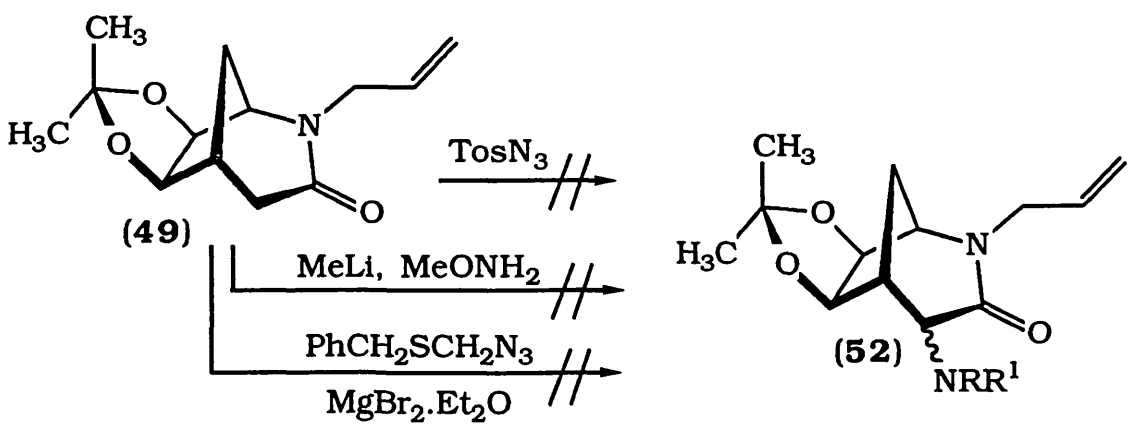
Initially we decided to quench our anion formation reactions

with deuterated water in order to check that an anion was being formed and what sort of selectivity we could expect from this system. These experiments seemed to show that the enolate was being formed at -78°C and was being quenched efficiently by the deuterated water, but that the face selectivity was only marginally in favour of the *exo*- face.



Scheme 30

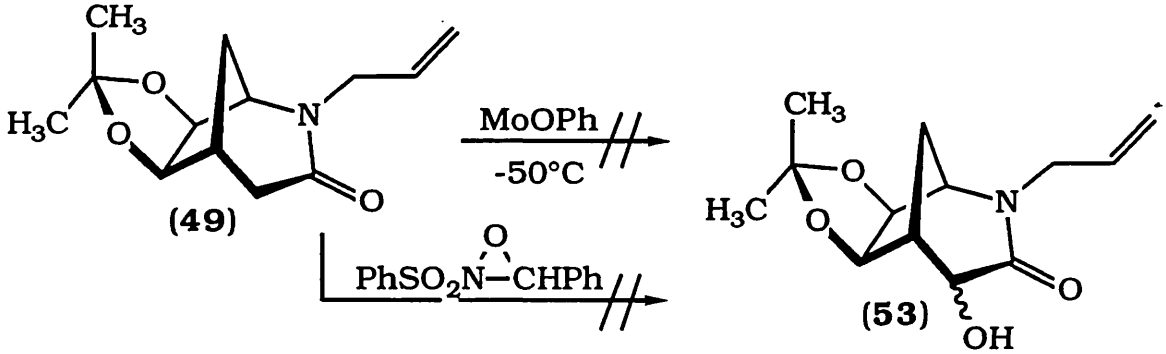
There were several methods in the literature for electrophilic amination;[59] the first one used thiophenylazido methane with magnesium bromide[59a,b] and after having the lactam enolate solution added to it, no aminated product **(52)** was isolated.



Scheme 31

The next procedure involved a mixture of methyl lithium and methoxy-amine[59c,d] but this too gave no aminated material when mixed with the lactam enolate. Finally tosyl azide[59e] was used as a possible source of electrophilic nitrogen but again no success was achieved.

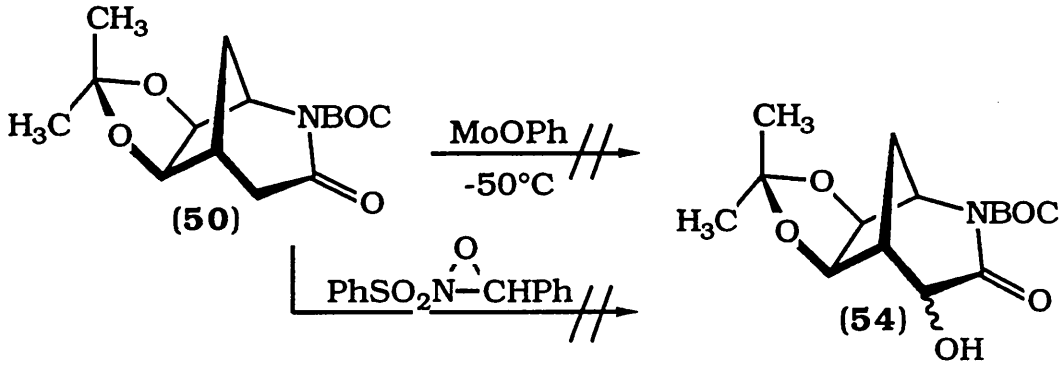
Once it seemed unlikely that the electrophilic aminations would work we turned to electrophilic hydroxylation methods.[60] These would have given us a functional group which, if *endo-*, could be displaced by azide ion and if *exo-*, would require a double inversion route to give the correct diastereomer. The MoOPh (a molybdenum peroxide.pyridine.HMPA complex) reagent has been shown to be effective in related systems giving exclusively the *exo*-hydroxy isomer,[61] however, after forming the lactam anion at -78°C and adding the MoOPh reagent at -50°C, only a moderate amount of the starting lactam was recovered. Another useful hydroxylating reagent is the Davis sulphonyl-oxaziridine, easily made from the sulphonylimine and *m*-CPBA.[60c,d,e] When the allyl lactam enolate solution was treated with this reagent the only organic materials recovered were the products of the decomposition of the oxaziridine, again no hydroxylated material (**53**) was formed.



Scheme 32

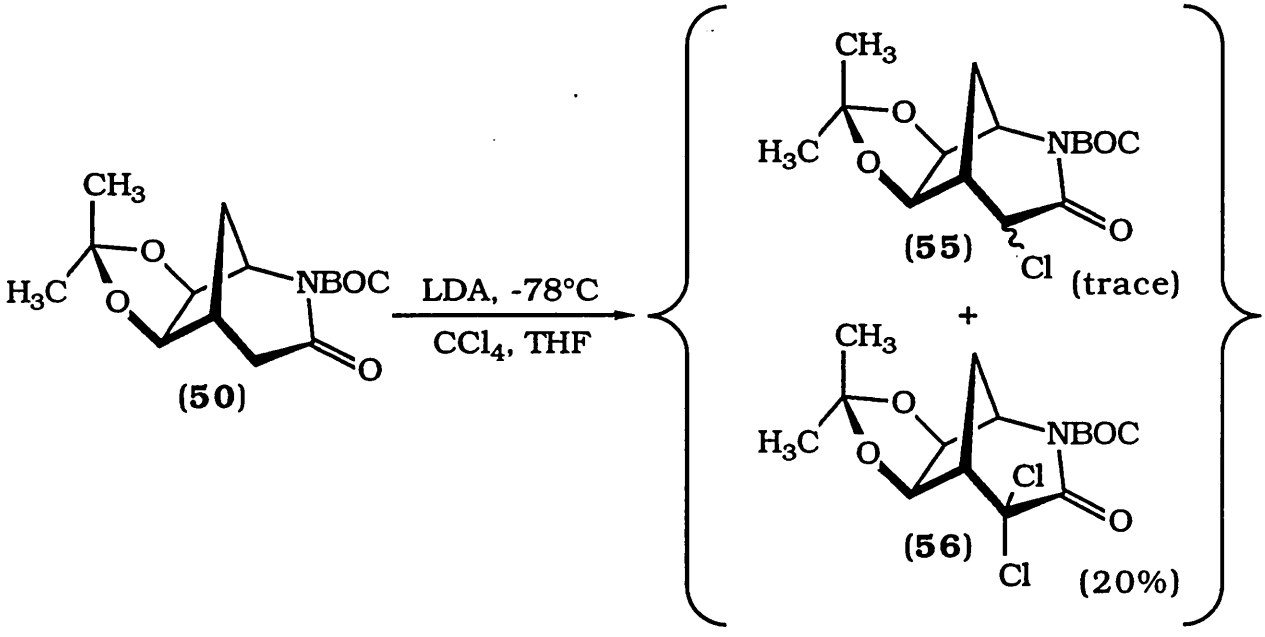
With having this lack of success with the allyl lactam we turned to the *N*-BOC protected lactam (**50**) and attempted (using the same anion forming conditions) to hydroxylate it *via* the

MoOPh and oxaziridine reagents, as these methods were somewhat easier than the electrophilic aminations. Unfortunately, as with the allyl lactam, no hydroxylated material (**54**) was found and only in the case of MoOPh was any starting material recovered (Scheme 33).



Scheme 33

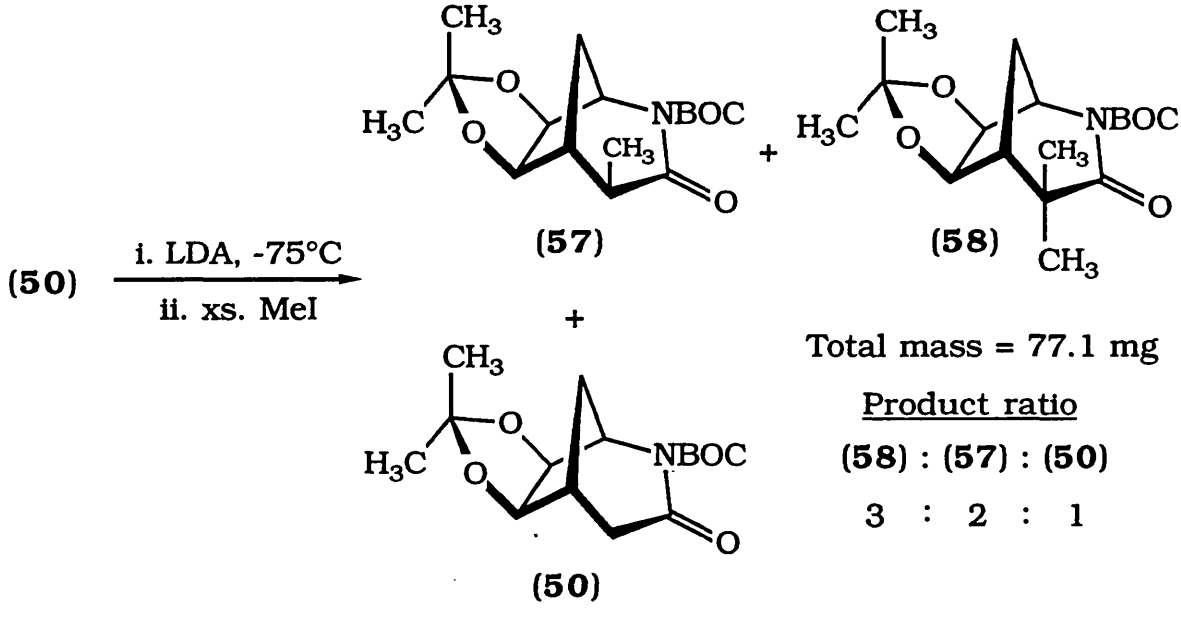
Our next possible way forward was to try and chlorinate the *N*-BOC lactam, again with a view to displacing the chlorine with azide anion. Here we did find some chlorinated products but only in a very disappointingly low yield and with dichlorination appearing to be the major product.



Scheme 34

This dichlorinated product (**56**) could have been synthetically useful, if it were produced in a good yield, as it could have been modified with hydroxide to give a keto-function at the C-4 position and then, *via* a chiral reducing agent or system[62], to a hydroxyl group again with known stereochemistry.

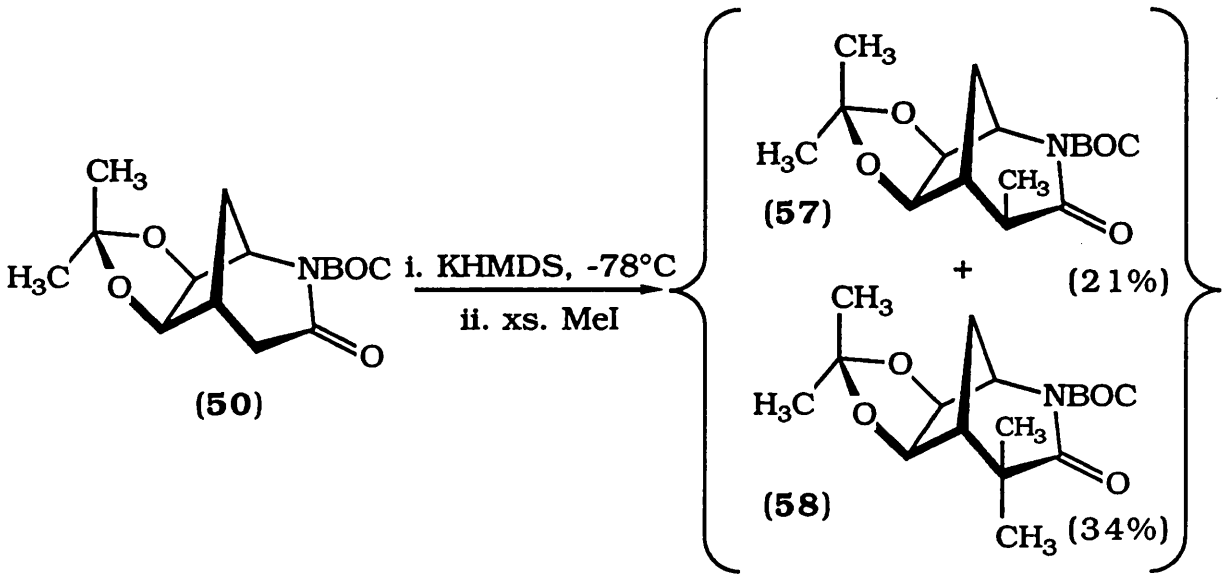
Our final attempts to gain any sort of functionalisation at the C-4 position was with methyl iodide. After the enolate formation at -75°C and the addition of excess methyl iodide, only a mixture of methylated products (**57**), (**58**) and starting material (**50**) was recovered (the product ratios being determined by SCFL chromatography).



Scheme 35

This serious failure to produce even the simplest of additions to the lactam led us to question the original enolate forming conditions, despite having good evidence for their success with the deuterium quench. With this in mind we repeated the chlorination and methylation reactions on the *N*-BOC lactam (**50**) using potassium hexamethyldisilylazide (KHMDS). This commercially available base was thought to be

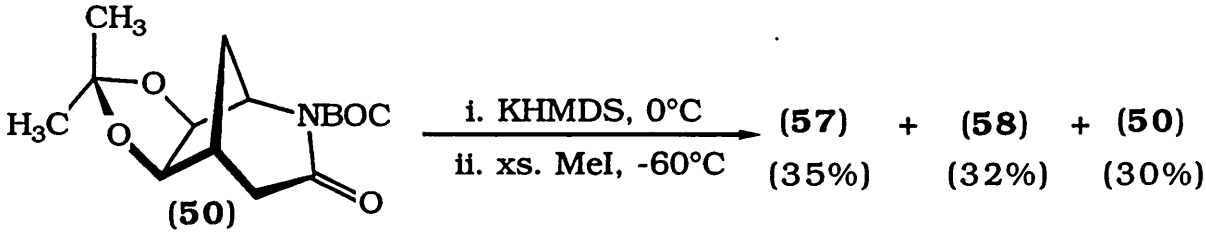
more effective at forming the enolate due to the effects of the hindered silylamine base and the potassium counter ion.[60d,63]



Scheme 36

These beliefs were, in part, borne out by our results as the methylation reaction did give a much more reasonable yield of methylated material. However, it was found that this material was a mixture of both the mono- and dimethylated lactam. The chlorination reaction was not successful and only resulted in the loss of the BOC protecting group. This was a surprise as the *tert*-butoxycarbonyl group was chosen because of its supposed stability towards bases.

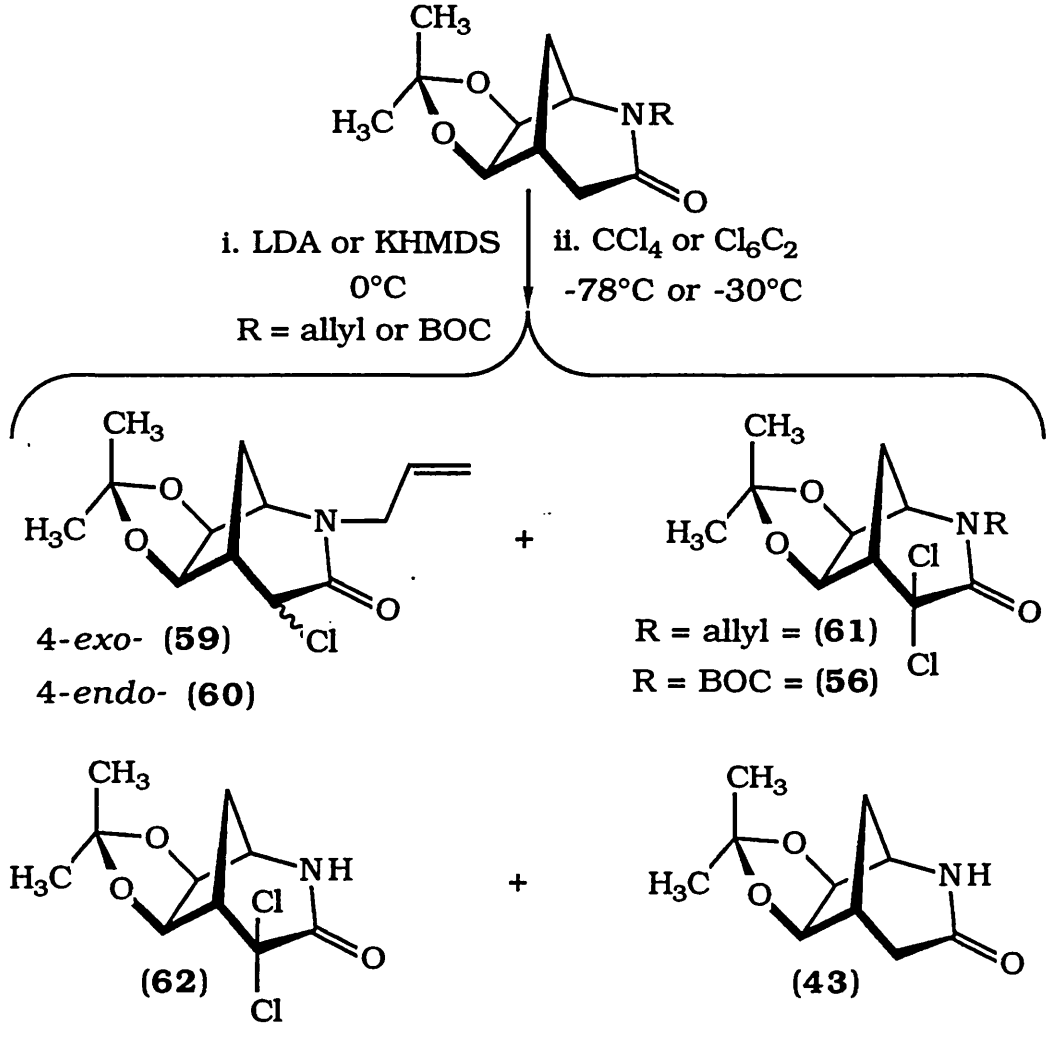
The next change that was made to the enolate forming conditions, was to let the formation reaction warm to 0°C and then recool the reaction before the quench was added.



Scheme 37

This was to be the key modification, for the methylation of the *N*-BOC lactam (**50**), under these new conditions, now went in a higher yield. However whilst the improvement in yield and the percentage of the *exo*-substitution was encouraging, the presence of the dimethylated product in this reaction was not.

The extension of these new conditions to the chlorination reactions, with both the *N*-allyl (**49**) and *N*-BOC (**50**) lactams, gave mixed results. Whilst the yields of chlorinated products did increase, the continued formation of dichlorinated material together with the monochlorinated material was a drawback.



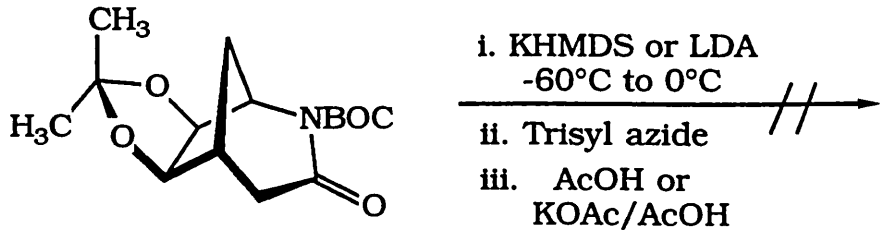
Scheme 38

The loss of the BOC group either before or after chlorination

also complicated the product mixture and a change in the chlorinating agent from carbon tetrachloride to hexachloroethane was made. With hexachloroethane a more stable product would be formed after the initial chlorination had taken place which we hoped would prevent over-chlorination, however such a change merely *increased* the proportion of dichlorinated material within the reaction products and did not eliminate the formation of the deprotected products.

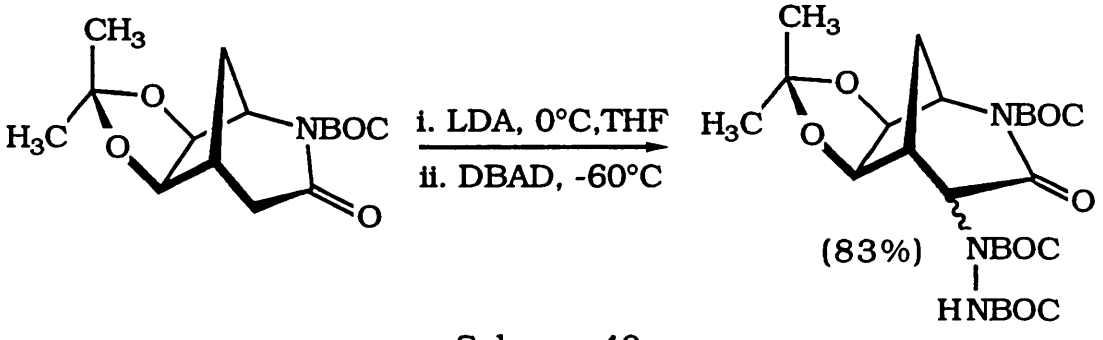
The small quantities of monochlorinated material, that were formed ((**59**) or (**60**)), were treated with a sodium azide/lithium chloride mixture in dimethylformamide, at temperatures ranging from ambient to 100°C. The expected displacement of the chlorine did not occur at the lower temperatures and the starting *N*-allyl-chlorolactam (**59** or **60**) was recovered unchanged. At the higher temperatures less of the starting lactam was recovered but no azido lactams were isolated. This seems to indicate that the displacement was not taking place and the starting materials were just being decomposed under these conditions.

It was still our aim to find a simple electrophilic amination procedure and the use of trisyl (tri-*iso*-propylbenzenesulphonyl) azide was recommended to us.[64] After the enolate was formed with KHMDS the azide was added at -68°C and worked up with acetic acid after a couple of minutes. No reaction was seen under these conditions and the azide was recovered. Addition of the azide at higher temperatures also failed to give any azidolactam products, and even if the anion was formed by LDA, with the azidosulphonyl intermediate being cleaved with a potassium acetate/acetic acid mixture, no azide products were isolated.[65]



(**50**) Scheme 39

Finally, it came to our notice that di-*tert*-butoxycarbonyl-azadicarboxylate had been used by Evans[66] *et al* in an electrophilic amination of an *N*-acyl carbamate with complete stereoselectivity and high yield. They had then taken this derivative on to an amino acid by trifluoroacetic acid cleavage of the BOC groups, followed by Raney nickel cleavage of the hydrazine. With this reagent and our new anion forming conditions we were able to produce the *N*-BOC hydrazino derivative (**63**) of the *N*-BOC lactam in an excellent yield.

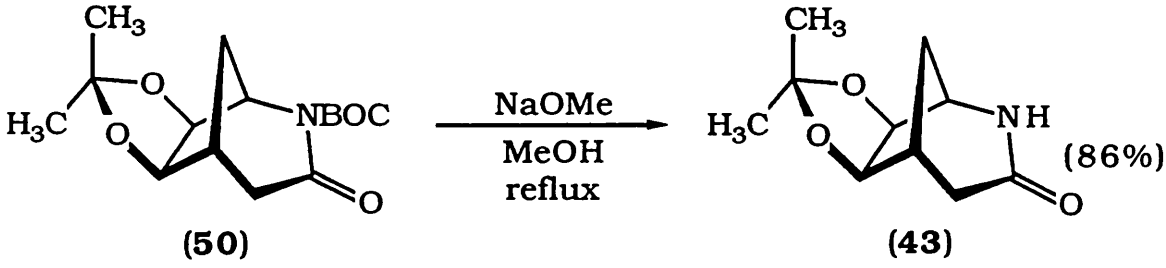


Scheme 40

No face selectivity was again seen in the *exo/endo* product ratios but it still represented the formal completion of our initial aim to functionalise the C-4 position with an electrophilic nitrogen reagent.[66c] The ^{1}H NMR of this hydrazino derivative (**63**) in deuteriochloroform is of interest because of the very broad signals which are recorded at ambient temperature. This line broadening made analysis of the *exo/endo* ratio of the products, impossible to determine; however, as this broadening was thought to be due to the slow nature of the molecule's rotation in solution, a variable temperature experiment in deuterated dimethyl-sulphoxide was run. This experiment did indeed sharpen the resonances and indicated well the positions and intensities of the two isomeric compounds.

2.2.3 *Cleavage of the lactam*

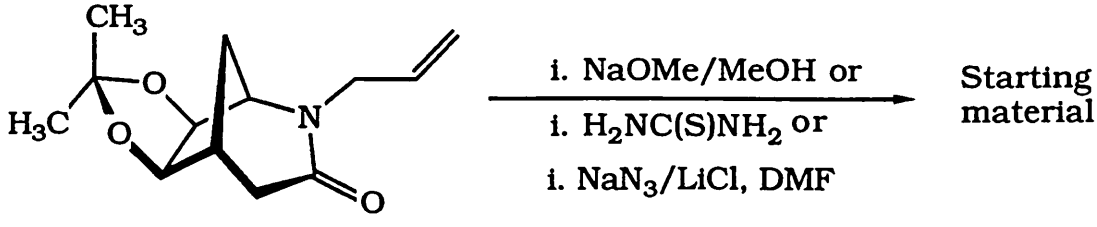
Formally, the final step in our synthesis was the cleavage of the lactam bond. In our original disconnections we envisaged that this step would be performed upon a substituted lactam. But as one can see from the previous section, this did not appear to be a viable proposition, and hence we experimented upon the C-4 unsubstituted, *N*-protected lactams. The cleavage of the lactam bond would, we thought, proceed better with an electron withdrawing substituent upon the nitrogen and it was for this reason that the t-butoxycarbonyl group was chosen. Unfortunately, this choice proved to be meritless as the protecting group was removed even under basic conditions.



(50) **(43)**

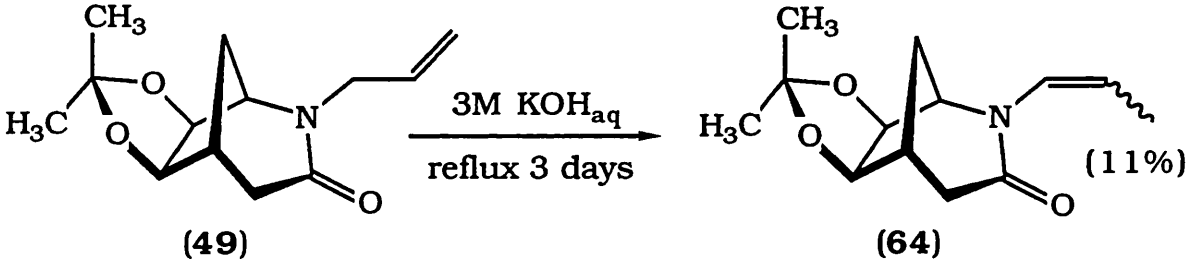
Scheme 41

For this reason, the majority of the cleavage experiments were performed on the *N*-allyl lactam (**49**). Both acidic[67] and basic[68] methods exist for the cleavage of amides and lactams but as the diol function on our molecule was protected by the acid sensitive acetonide group, our first series of experiments were done under basic conditions.



Scheme 42

The use of sodium methoxide in refluxing methanol, as from the *N*-BOC lactam (**50**) experiment, merely returned the starting lactam. Thiourea, a 'soft' nucleophile, was also tried but this too gave only the starting lactam as the product. A much more active nucleophile in the form of azide ion was used (sodium azide/lithium chloride in dimethylformamide) but at low temperature this too merely returned the starting material. More severe conditions were obviously needed and so sodium hydroxide in ethylene glycol[68a] was used. Even with these conditions no cleavage products were observed and only the starting lactam was recovered. The severest of the basic conditions tried included 3M aqueous potassium hydroxide refluxing for three days. Some reaction was seen but this led only to the rearrangement of the allyl group and the isolation of the propenyl (**64**) compound.



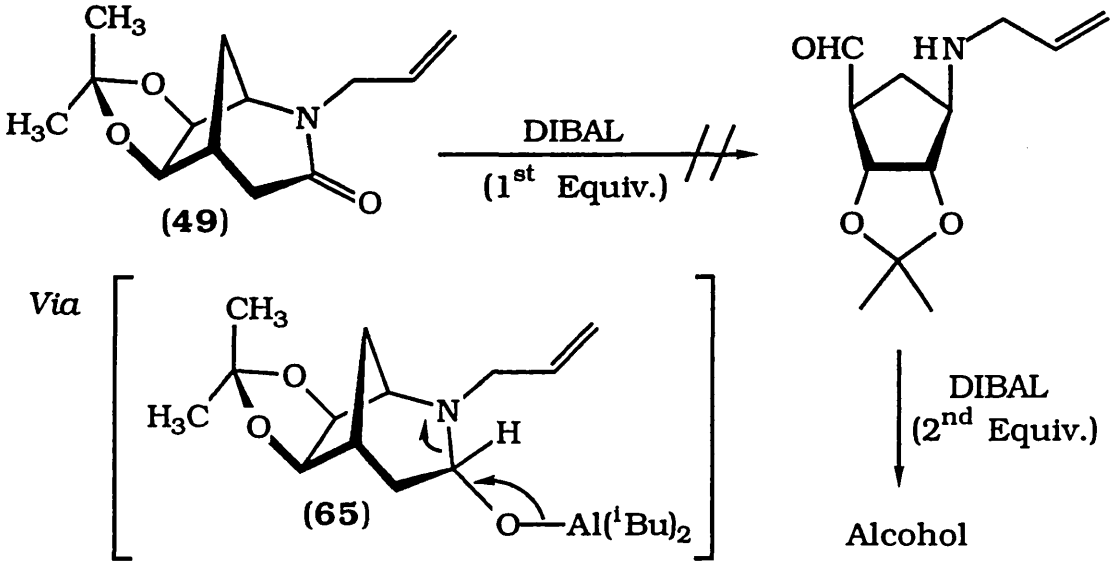
(**49**) (**64**)

Scheme 43

Finally, a hydride nucleophile was used[68b] (DIBAL, di-*iso*-butylaluminium hydride) in an attempt to reduce the lactam carbonyl and form the intermediate O-aluminium species (**65**). Once this had formed, the work up of the reaction should have cleaved the O-aluminium bond, producing an oxygen anion which, in turn, would cleave the lactam bond. This is illustrated in Scheme 44 but unfortunately this did not happen.

It seemed therefore that acidic methods had to be considered with the obvious concomitant loss of the acetonide protecting group. The loss of this protecting group in all of the following acidic procedures was compensated for in the work-up procedures by a reprotection step involving acetic anhydride in

pyridine. The basic cleavage procedures were treated in a similar fashion, but with diazomethane being used to protect, and help isolate, any carboxylic acid that may have been produced.

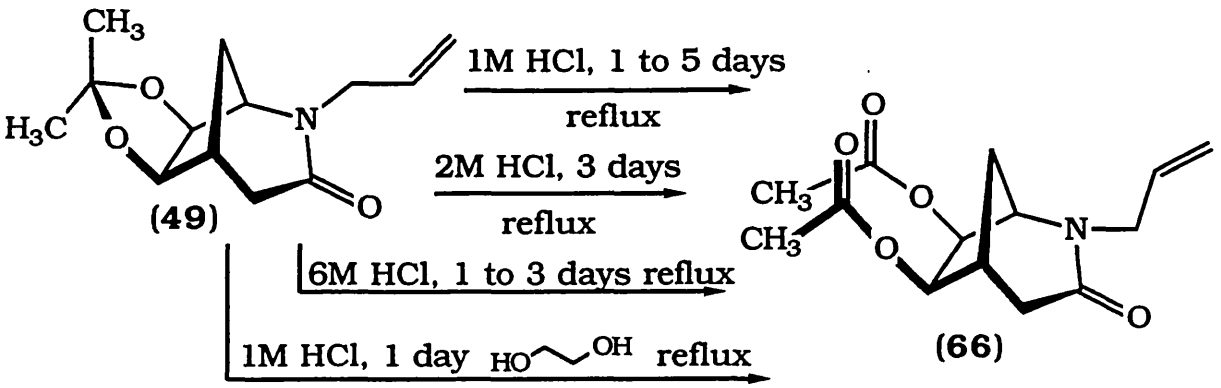


Scheme 44

Treatment of the *N*-allyl lactam (**49**) with refluxing 1M aqueous hydrochloric acid over a period of time between 1 and 5 days, gave (after neutralizing the solution and treatment with acetic anhydride in pyridine) the acetate protected diol (**66**) as the only product, with the lactam bond staying intact. This compound was a colourless solid and gave crystals of X-ray quality. The X-ray of this compound proved that the lactam bond was unchanged and also showed some interesting packing distortions on the allyl and acetyl groups respectively.

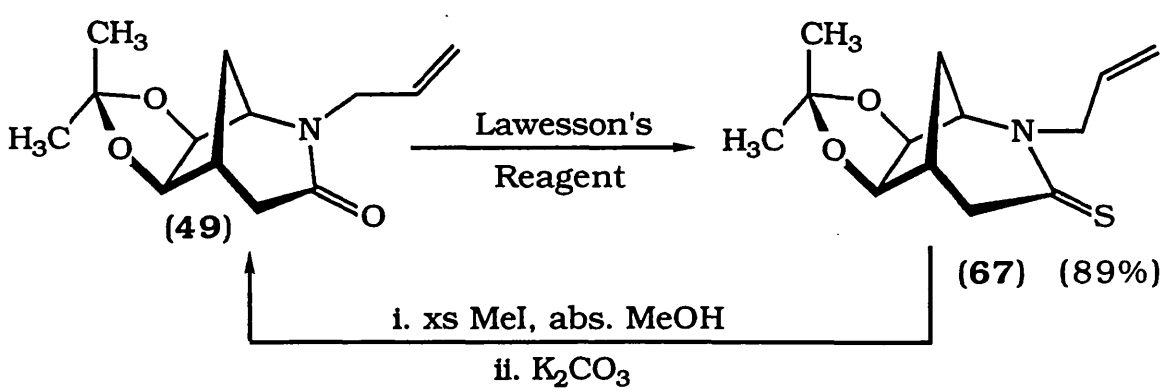
Extending the severity of the conditions to refluxing ethylene glycol had no effect on the course of the reaction but it did appear to produce more in the way of baseline material. Increasing the molarity of the acid solution from 1M to 2M (3 days reflux) and then on to 6M (1 to 3 days reflux, conditions which have been used to cleave all difficult peptides) also had no effect on the final nature of the product and only on the degree of

polymeric baseline material produced.



Scheme 45

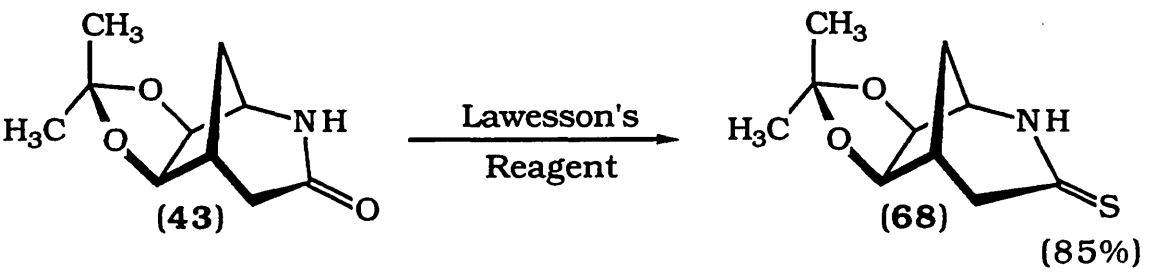
Our next approach was to change the lactam for a thiolactam which we considered would be more easily cleaved than the original oxygen analogue. Conversion of the *N*-allyl lactam (**49**) into its thio analogue (**67**) with Lawesson's reagent[69] went in very good yield but, the literature procedure for the cleavage of the thiolactam[70] merely converted it back into the starting oxygen analogue (**49**) (Scheme 46). This was half expected as the literature had expressed the reaction's apparent dependence upon the substrate containing a carbonyl substituent δ- to the thiocarbonyl.



Scheme 46

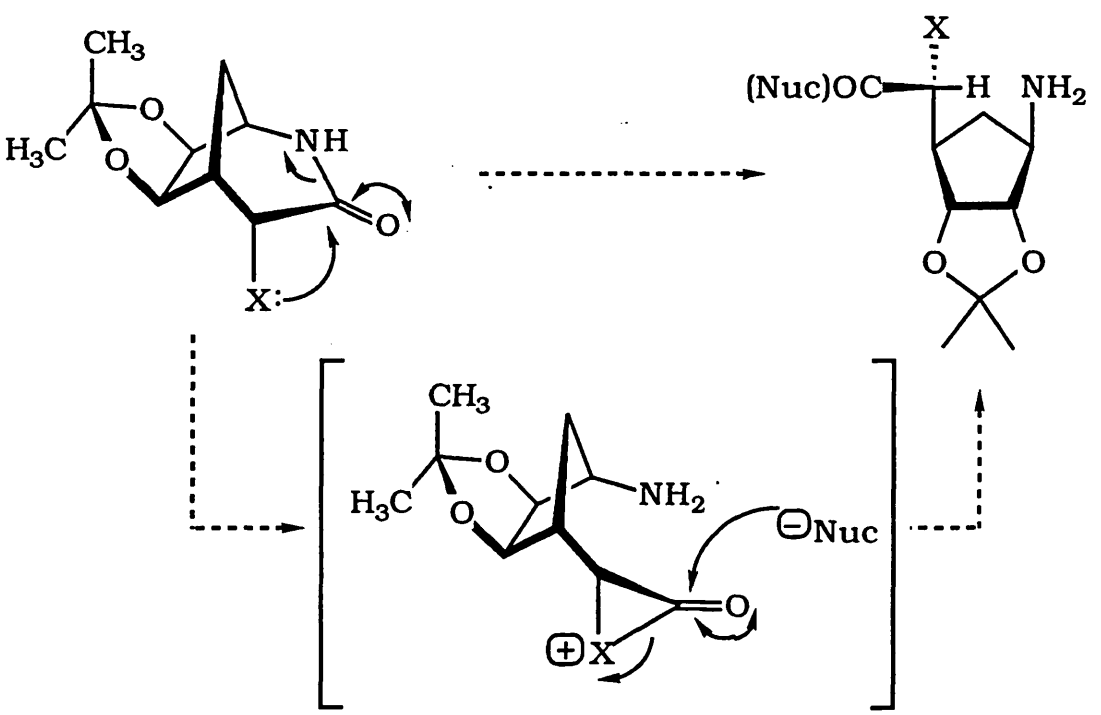
In order to introduce such a constituent easily, it was

decided to convert the unprotected lactam (**43**) into its thio-derivative (**68**) and then add onto the nitrogen a group containing a carbonyl at the appropriate position. Here too the conversion with Lawesson's reagent went smoothly and the thiolactam was formed in good yield but the further elaboration of the nitrogen was not performed.



Scheme 47

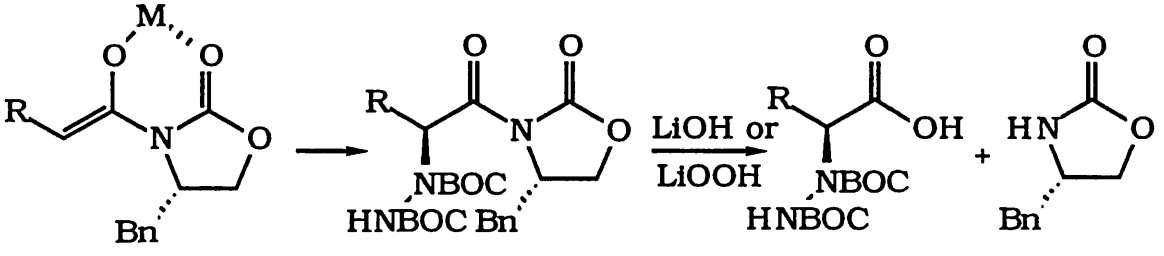
At this time the *N*-BOC hydrazino derivative of the *N*-BOC lactam (**63**) was produced and we could now investigate if the cleavage of the lactam was easier with a nucleophilic alpha substituent.



Scheme 48

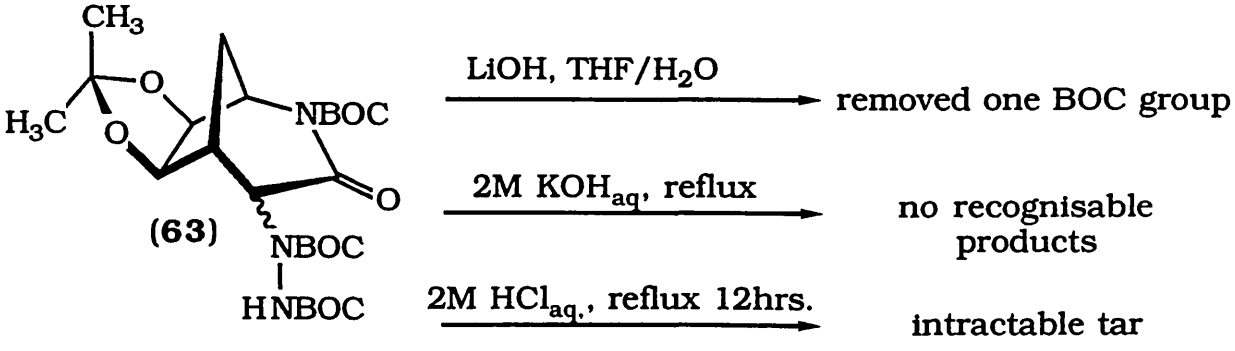
This idea came from the belief that a nucleophilic neighbouring group intramolecularly attacks the carbonyl group (displacing the amine) and forms a more reactive three membered ring keto- species (Scheme 48). This is then attacked intermolecularly by the external nucleophile.[71]

The literature describing the use of DBAD as an electrophilic aminator,[66] used lithium hydroxide to cleave the imide substrate and so give the amino acid (Scheme 49). Their conditions were used with our similar compound, but unfortunately, the basic hydroxide cleaved one of the BOC groups from the molecule and not the desired lactam bond.



Scheme 49

When the basic conditions were made a little more harsh with potassium hydroxide, no recognisable products were isolated. The treatment of the hydrazino compound with refluxing 2M hydrochloric acid overnight did produce a novel result in that only an intractable tar was produced.

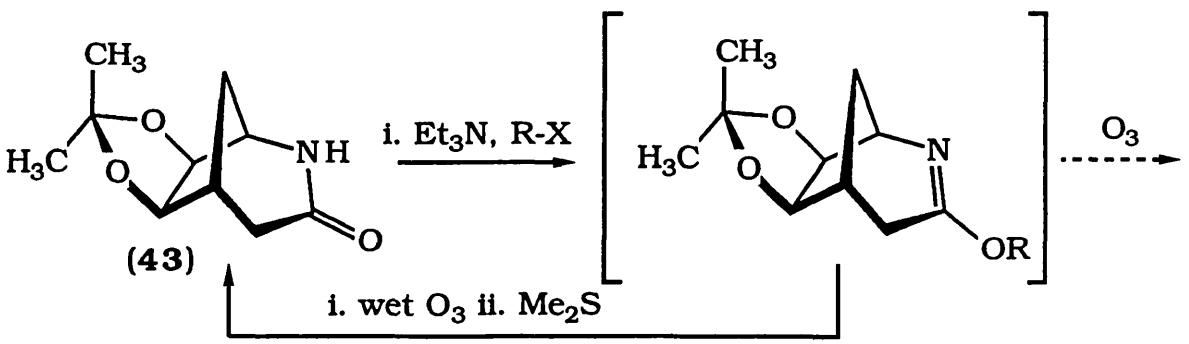


Scheme 50

This indeed shows that the neighbouring function can have a dramatic effect on the reaction as the *N*-allyl (**49**), or the parent (**43**) lactams were not destroyed, when they were submitted to these conditions. Whether the lactam (**63**) was in fact cleaved by the presence of the alpha substituent and then the product destroyed by the conditions is, as yet, unknown.

Before going to any more drastic conditions, another approach to the problem was considered. Under normal circumstances an amide or lactam is inert to the action of ozone, however if one firstly pretreats the amide with an alkylating or silylating agent then the imino ether which is formed *is* susceptible to ozone attack.[72] Therefore, we attempted to convert the lactam (**43**) into its O-trimethylsilyl and O-methyl derivatives with trimethylsilyl trifluoromethanesulphonate and trimethyl-oxonium tetrafluoroborate (Meerwein's salt). These imino species were taken directly, without isolation, onto the ozonolysis step and a reductive work up was used.

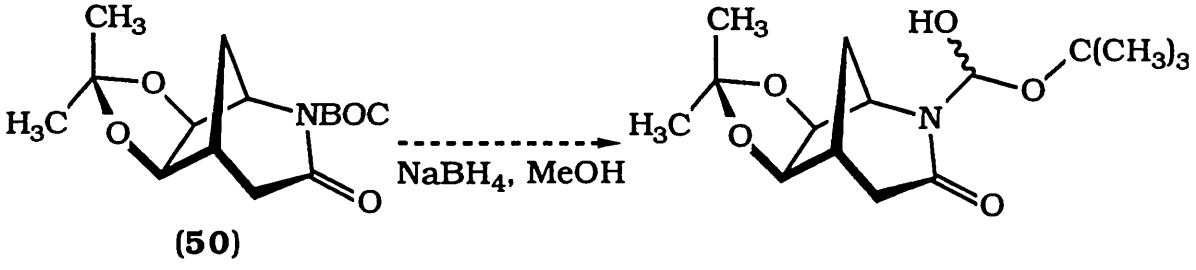
No cleavage products were isolated from these reactions but this was more likely due to the fact that the ozone used was wet and this caused the iminoethers to revert back to their inert lactam forms. Attempts were made to dry the incoming oxygen gas but it appeared that these efforts were not enough and consequently no effect on the outcome of the reaction was seen.



Scheme 51 :- R = Me or Trimethylsilyl
X = $Me_2O^{\oplus}$ or OTriflate

Despite the susceptibility of the *N*-BOC group towards basic media a couple of further experiments were tried. The reaction of the *N*-BOC compound (**50**) with potassium t-butoxide[68c] led again to the removal of the BOC group but also to a much higher degree of baseline material. This could have been due to the known elimination[73] of acetone from the acetonide protecting group giving a free hydroxyl group. The other reaction dealt with the action of sodium borohydride on the lactam (**50**). Normally amides and lactams are not reduced by sodium borohydride but, it has been shown that, if the nitrogen is substituted with a sufficiently electron withdrawing group then the carbonyl can be reduced and the lactam cleaved in a manner similar to that already described for DIBAL.[74]

Interestingly, amongst the many compounds that were produced in this reaction, one did give the correct molecular ion corresponding to the initial product of reduction. However, the alcohol produced from the reduction of the lactam carbonyl would very quickly collapse and ring open the lactam whereupon the aldehyde produced would be reduced further to the alcohol. This would give a compound with a molecular ion of two mass units greater than the one found above and therefore the only other possible product is that derived from the reduction of the *tert*-butoxycarbonyl group.

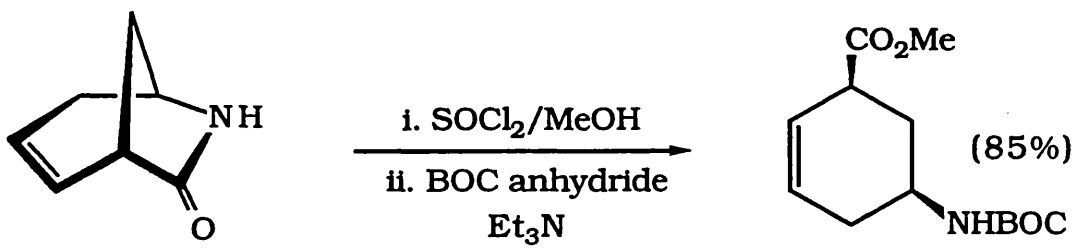


(**50**)

Scheme 52

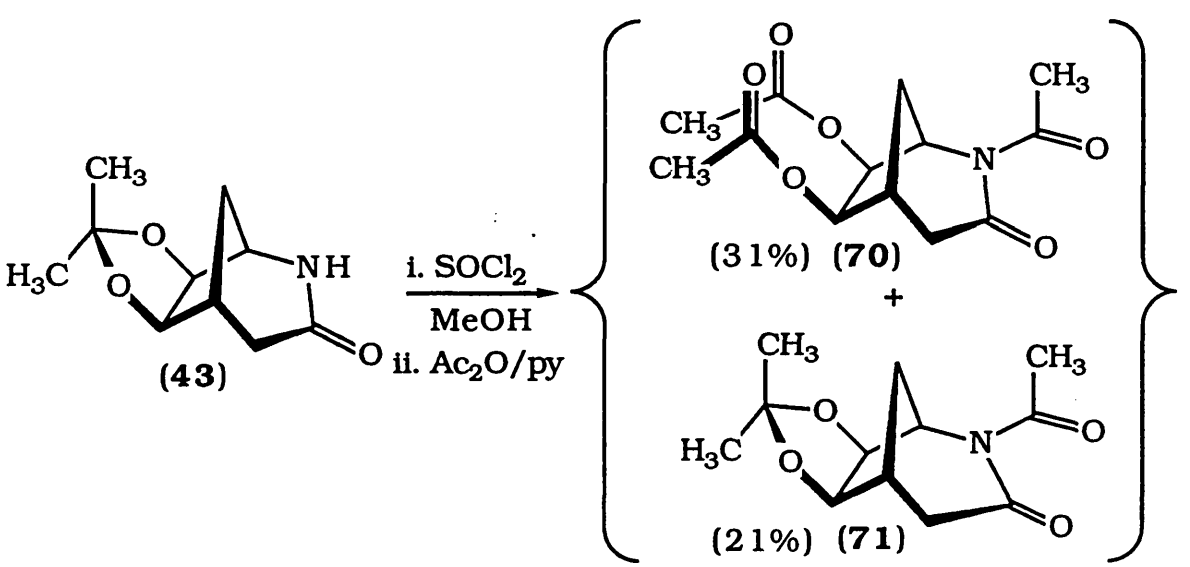
As both the protecting groups that we had chosen appeared to suffer attack under acidic or basic conditions *and* it seemed that harsher conditions had to be used in order to cleave the

lactam, we chose to perform the remaining experiments on the free *N*-H lactam (**43**). The mildest reaction conditions were those reported for the bicyclo[3.2.1]enyllactam (**69**) shown below and used thionyl chloride in absolute methanol.[75]



(**69**) Scheme 53

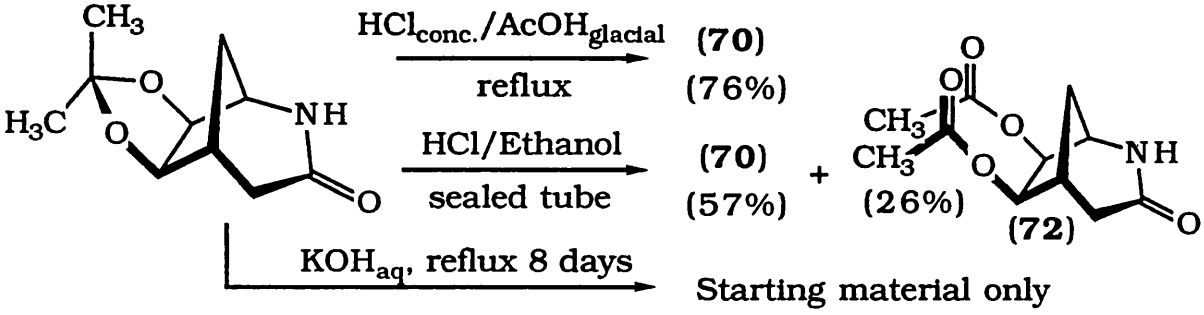
The exact mechanism for this cleavage is unclear but the conditions are probably only a mild way of forming HCl *in situ*. From this experiment no cleaved material was isolated but the interesting acetyl derivatives shown in Scheme 54 were found after a work-up involving acetic anhydride in pyridine.



Scheme 54

The use of concentrated hydrochloric acid in refluxing glacial acetic acid[67a] did not produce the desired product but merely gave the tri-acyl derivative (**70**) isolated previously. A

refluxing ethanol solution of potassium hydroxide did not give any cleaved products after 8 days and returned some of the starting lactam. In a final attempt to break the lactam bond, the *N*-H lactam (**43**) was treated with a saturated solution of hydrogen chloride gas in ethanol,[67b] in a sealed tube overnight. Even with these, unsubtle, reaction conditions the only isolable product was that of acyl derivatisation of the free hydroxy and amine groups after treatment with acetic anhydride.

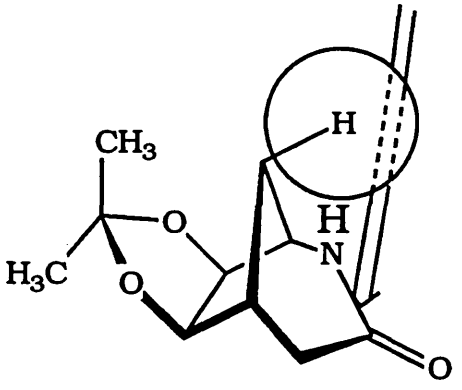


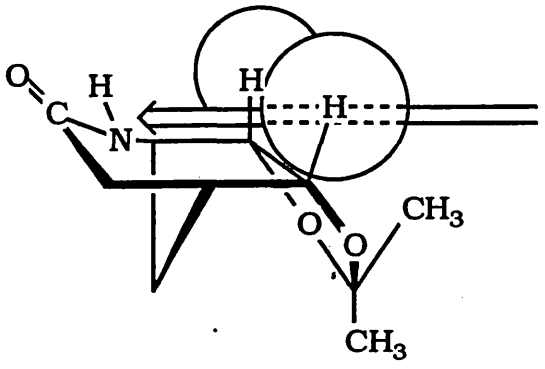
Scheme 55

It is at this point we believe that this route to the carbocyclic analogues fails and the only possible way forward is through the discovery of a suitable quench for the lactam enolate which may then help to effect the cleavage of the lactam. An alternative approach would be to use the oxygen analogue of these compounds (*i.e.* lactones)[76a] which are known to be easier to cleave.[76b] From there one could envisage a double inversion procedure on the alcohol produced to obtain either, a nitrogen function which can be elaborated or, the complete uracil (or imidazolinone) base.

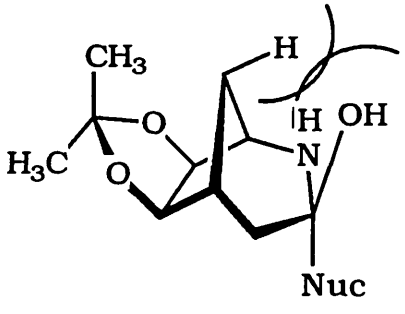
The reasons for the lactam's most obstinate refusal to cleave may be two-fold. The approach to the carbonyl group in the C-3 position is thought to be more sterically difficult than if the carbonyl was in the C-2 position. From attack in an *endo*- fashion the incoming nucleophile is impeded by the hydrogens on positions C-6 and C-7; with attack on the *exo*- face the

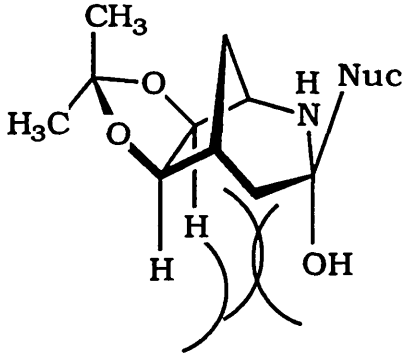
nucleophile can be affected by the bridgehead hydrogen.





The formation of the thiocarbonyl derivatives seems to disprove this theory, therefore the second reason, which is one of steric compression, must be considered. This theory is similar to the first but actually affects the tetrahedral intermediate when it is formed.



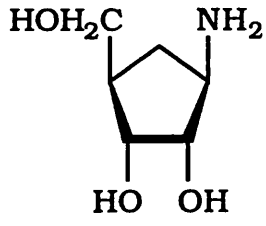


If the carbonyl is attacked then the resultant hydroxyl group would be forced into conflict with either the hydrogens on C-6 and C-7 or with the bridgehead hydrogen; this would then raise the energy of such an intermediate and reduce the likelihood of its formation.

2.3 OTHER APPROACHES TO CARBOCYCLICS

The major synthetic target, for the previous

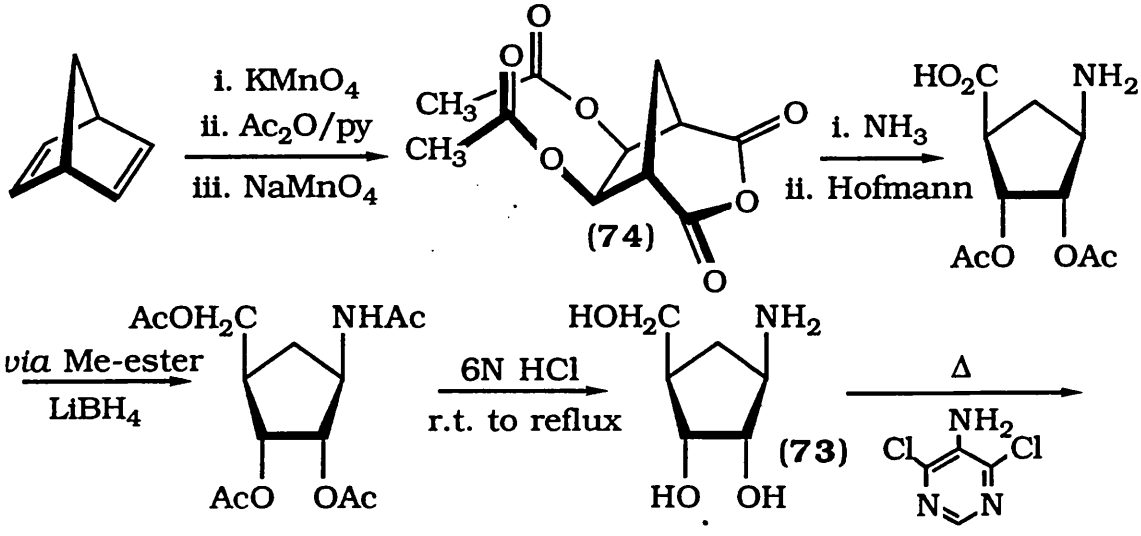
syntheses of carbocyclic nucleosides has been 2,3-dihydroxy-4-hydroxymethyl-1-cyclopentylamine (**73**).



(73)

From this intermediate, seemingly any nitrogen base can be formed and by various protection/displacement/deprotection sequences the sites of oxygenation on the cyclopentyl ring have also been widely modified.[77]

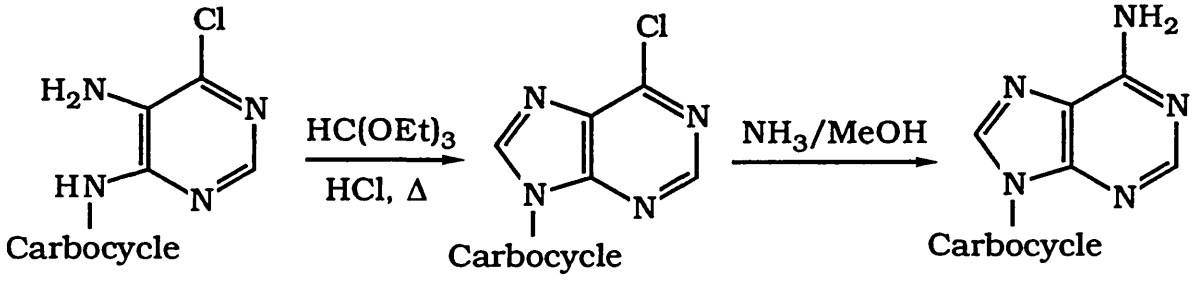
The idea of using the norbornyl ring system for stereo- and regio-control of the hydroxymethyl and amino functions has been used extensively. Shealy *et al* produced the first racemic synthesis of the carbocyclic analogue of adenosine[78] in the late 1960's.



Scheme 56

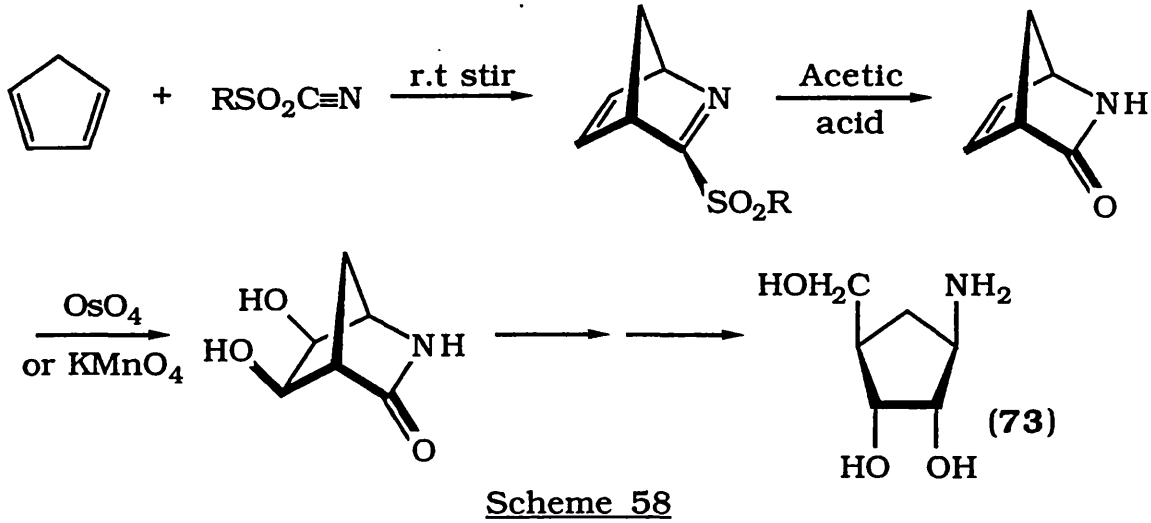
This involved the *cis*-hydroxylation of norbornadiene and the oxidative cleavage of the second double bond to set up the

meso-anhydride shown (**74**). The ring opening of this anhydride with ammonia was not selective and after the Hofmann rearrangement to give the necessary nitrogen function and reduction of the other carboxylic acid to the alcohol, the desired cyclopentane intermediate was achieved (Scheme 56). The synthesis of the adenine base then followed the standard chemistry outlined in Scheme 57, and which has featured in the majority of syntheses.



Scheme 57

The Diels-Alder cycloaddition reaction is one of the most convenient ways of synthesising these norbornyl systems, and it was the successful extension of this reaction to dienophiles containing heteroatoms that brought the next improvement.[79]

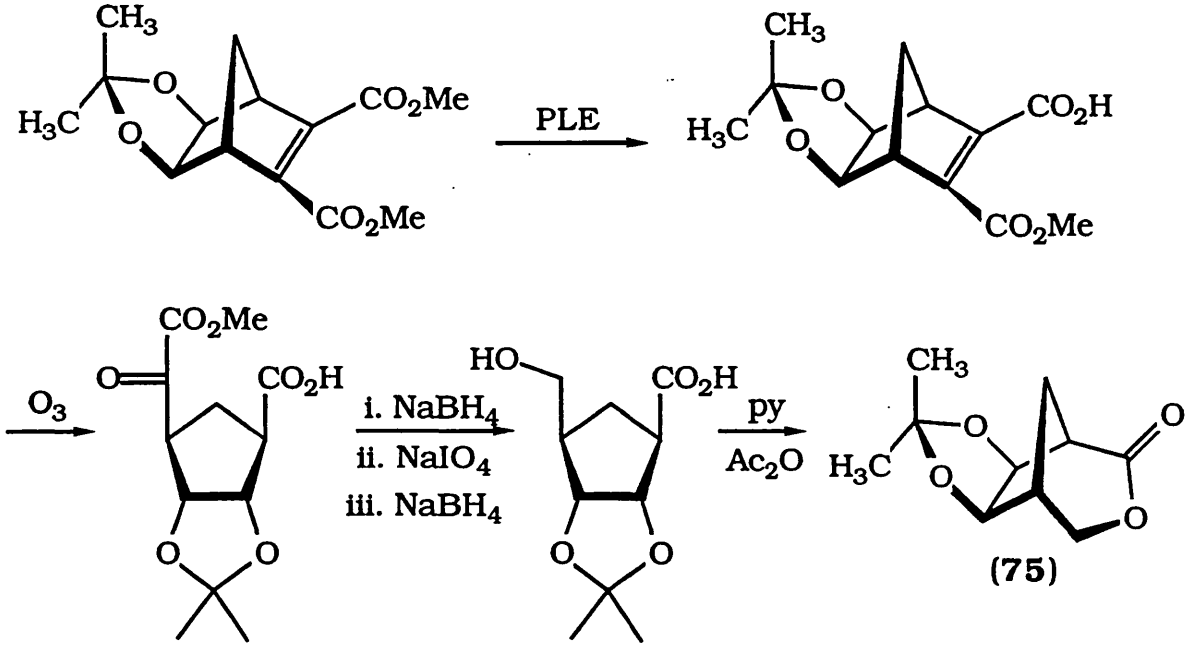


Scheme 58

By reacting sulphonyl cyanides or isocyanates with

cyclopentadiene, the 2-azabicyclo[2.2.1]hepta-5-ene system was readily produced and provided workers with easy access, *via cis*-hydroxylation, to the above cyclopentylamine intermediate (Scheme 58). The hydrolysis of the lactam bond in this system was facile (methanolic hydrogen chloride, room temperature stir, 3 days) because the steric factors, which prevented our hydrolysis, are not as prevalent when the carbonyl group is next to the bridging carbon.

The syntheses that followed this adaptation to the Diels-Alder reaction were all essentially racemic and therefore required either chromatographic separation or enzymatic resolution of the enantiomers. Enzymes have been widely used not only as reagents[80] but also to produce homochiral forms of the carbocyclic nucleosides and, depending upon the exact nature of the enzyme, have been used both at the beginning and at the end of a synthesis. Shealy *et al* have recently used Adenosine deaminase, at the end of their synthesis, to resolve the enantiomers of aristeromycin[81] and also, as a side product, give the active carbocyclic analogue of Inosine.

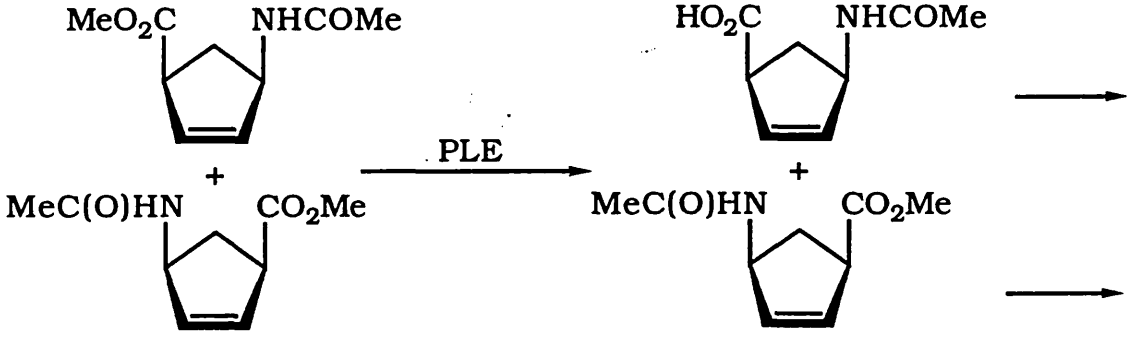


Scheme 59

Herdewijn *et al* have performed the same resolution of aristeromycin by firstly phosphorylating the aristeromycin enantiomers and then, by using (-) 5'-ribonucleotidephospho-hydrolase, hydrolysed the (-) form specifically back to (-) aristeromycin.[38a,b]

Ohno *et al* have used enzymic resolution[82] at the beginning of their chiral syntheses of aristeromycin and neplanocin A (Scheme 59). They use a Diels-Alder reaction to couple dimethylacetylenedicarboxylate (DMAD) and cyclopenta-diene and then use Pig Liver Esterase (PLE) to selectively hydrolyse one of the ester functions. Ozone is then used to cleave the ring. However, within the later steps of Ohno's synthesis a recrystallisation of an intermediate lactone (**75**) is still required to give optically pure material.

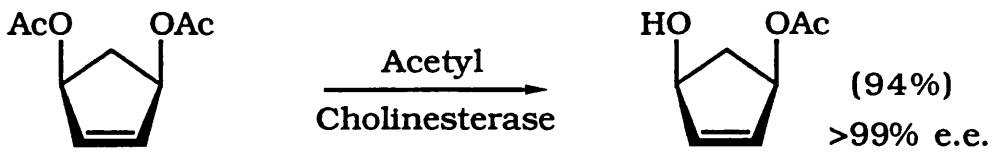
PLE has been used in the past to on a similar substrate by Just[83] but the enantiomeric excess that he achieved was only 60% and therefore not good enough for a modern medicinal synthesis. A more efficient use of PLE has recently been described by Le Goffic *et al* for the resolution of cyclopentenylamido esters.[84]



Scheme 60

Deardorff[85] has used Acetyl cholinesterase, for the hydrolysis of *cis*-3,5-diacetoxy-cyclopent-1-ene (**76**), in a high yielding, and highly enantioselective process which seems to require no enzyme cofactor. At approximately the same time Johnson and Penning[86] reported the same asymmetric hydrolysis as Deardorff[85] on the acetonide protected diol version of his

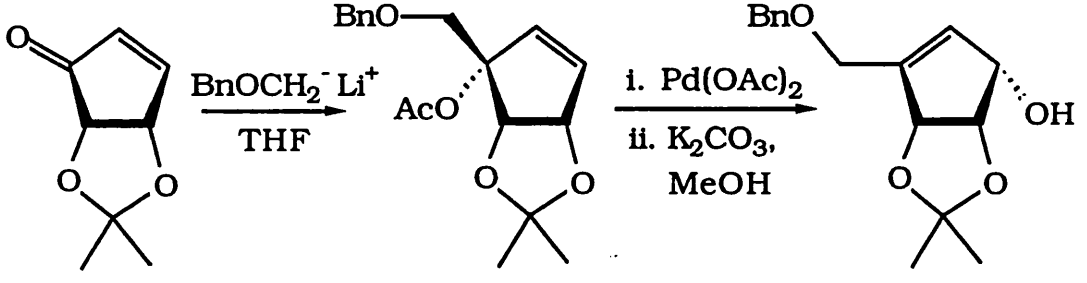
compound.



(76)

Scheme 61

This hydrolysis formed the basis of their later, chiral, synthesis of neplanocin A. Oxidation of the hydroxy acetate that was produced by the enzymatic hydrolysis, gave them (+)-cyclopentanone (**77**) in 98% optical purity and 36% overall yield from cyclopentadiene. 1,2-Addition of benzyloxy-methyllithium to the ketone followed by acetylation of the alcohol product gave them the allylic acetate[87] shown (**78**).



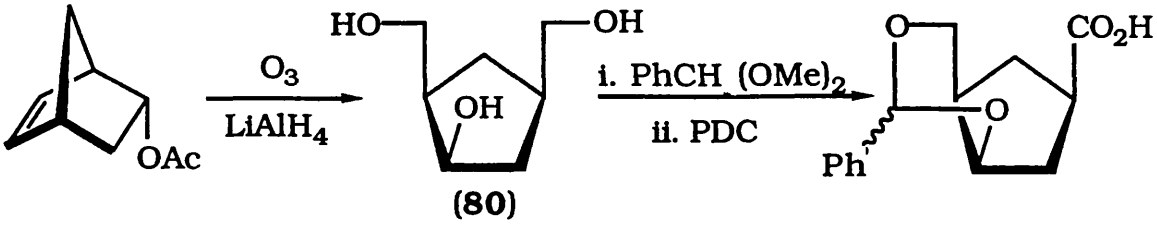
(77) **(78)** **(79)**

Scheme 62

This underwent the known palladium induced rearrangement with complete retention of optical purity and so with standard chemistry, the hydroxyl group (**79**) was displaced by the required adenine base to give, after deprotection, (-) neplanocin A in 11% overall yield.

Bodenteich and Griengl[88] have produced a variety of enantiomerically pure carbocyclic nucleosides from a cyclopentyl triol (**80**). This triol is made by reductive ozonolysis of norborn-5-

ene-2-acetate which is made enantiomerically pure by the action of a lipase enzyme on the racemate.



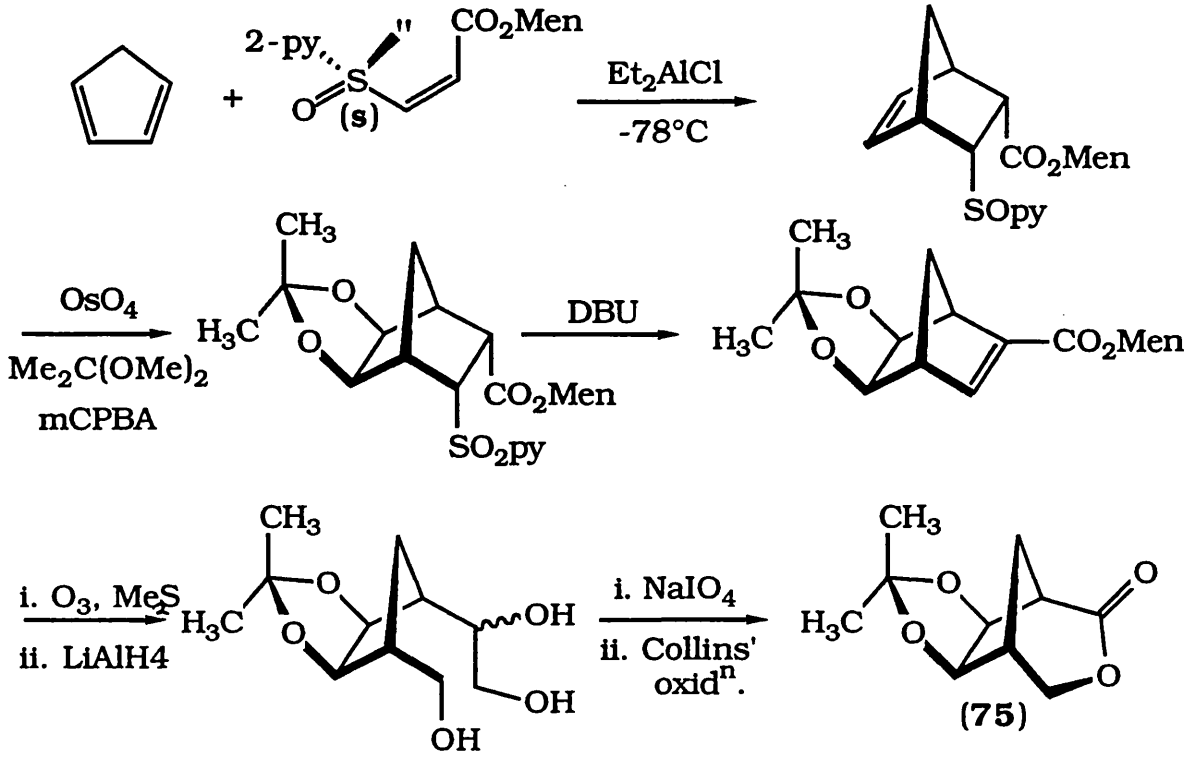
(80)

Scheme 63

The need for homochiral syntheses in the carbocyclic area can be demonstrated by the activities of the enantiomers of aristeromycin. The (-) form is the carbo-analogue of the nucleoside adenosine and, as such, has marked antiviral and antitumour properties. The (+) form, on the other hand, has been shown to be completely inactive.[81]

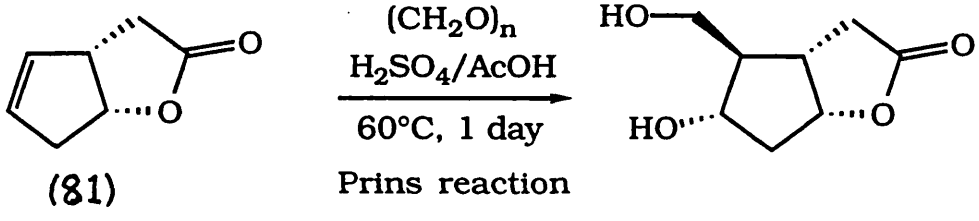
Apart from the use of enzymes to effect enantiomeric purification there are a few methods which derive their homochirality from other sources; either through the Diels-Alder cycloaddition,[89] or from sugars,[40,90] or from other specific reactions such as epoxide ring openings.[91]

Homochiral (-) neplanocin A and (-) aristeromycin have formally been synthesised by Yamamoto *et al, via* assymetric induction in the Diels-Alder cycloaddition[89] of a chiral vinyl sulphoxide with cyclopentadiene (Scheme 64). This is an efficient, low temperature process which gives them an enantiomeric excess of approximately 96%. This adduct is *cis*-hydroxylated with osmium tetroxide and the sulphoxide is removed by firstly oxidising it to the sulphone, followed by elimination with base. This unsaturated ester is cleaved with ozone and reductively worked up with methylsulphide; the diol produced is then cleaved with sodium periodate, oxidised using Collins' reagent to give the acid which immediately cyclises to give the key lactone intermediate (**75**) in Ohno's synthesis.



Scheme 64

Ötvös *et al* [92] have produced stereospecific syntheses of 2'-deoxy- and 2',3'-deoxy-carbocyclic nucleosides from the well known prostaglandin precursor (**81**) shown below.

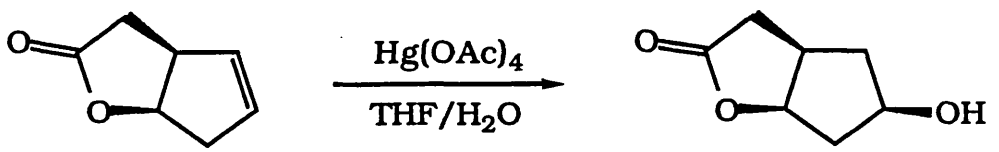


(81)

Scheme 65

Their initial work was rather lengthy[92a] and made use of the Prins reaction to set up the C-4 hydroxymethyl and C-3 hydroxyl groups *trans*-to each other. The second[92b] relied upon the regio- and stereospecific nature of a mercury assisted hydroxylation

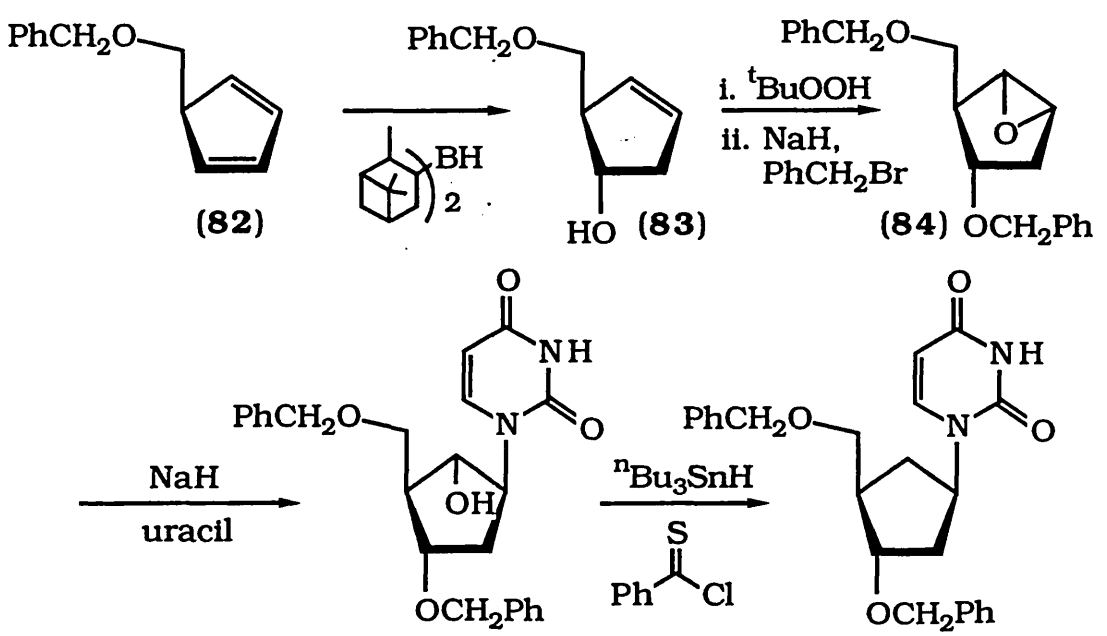
reaction. They found that this reaction proceeded with much better yields and selectivity by using the mercury method than it did with bromination or phenylselenation procedures.



(81)

Scheme 66

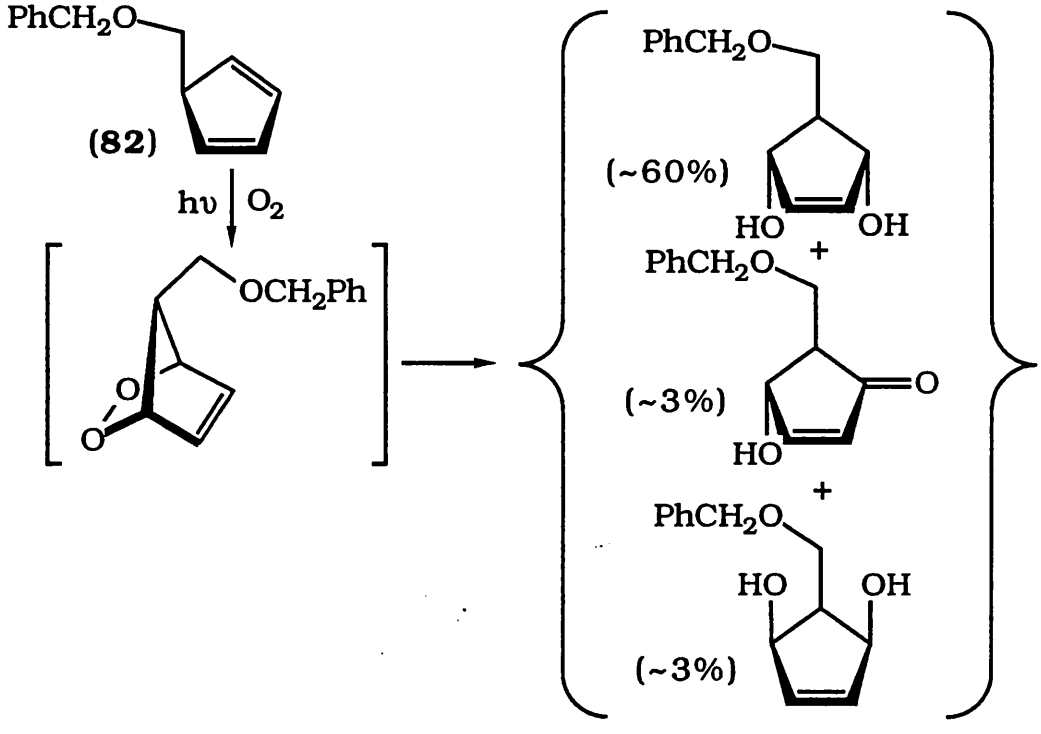
A similar hydroxylation pathway has been developed at Glaxo[93] which involved the asymmetric hydroboration of benzyloxy-methylcyclopentadiene **(82)** (made from the sodium salt of cyclopentadiene and benzyloxychloromethylether) with (-)-diisopinocampheyl borane. This gave the alcohol **(83)** in almost an optically pure form (98% e.e.) and with stereoselective epoxidation of the remaining double bond, followed by protection of the alcohol gave the oxirane **(84)** shown.



Scheme 67

This oxirane **(84)** could then be opened by treatment with

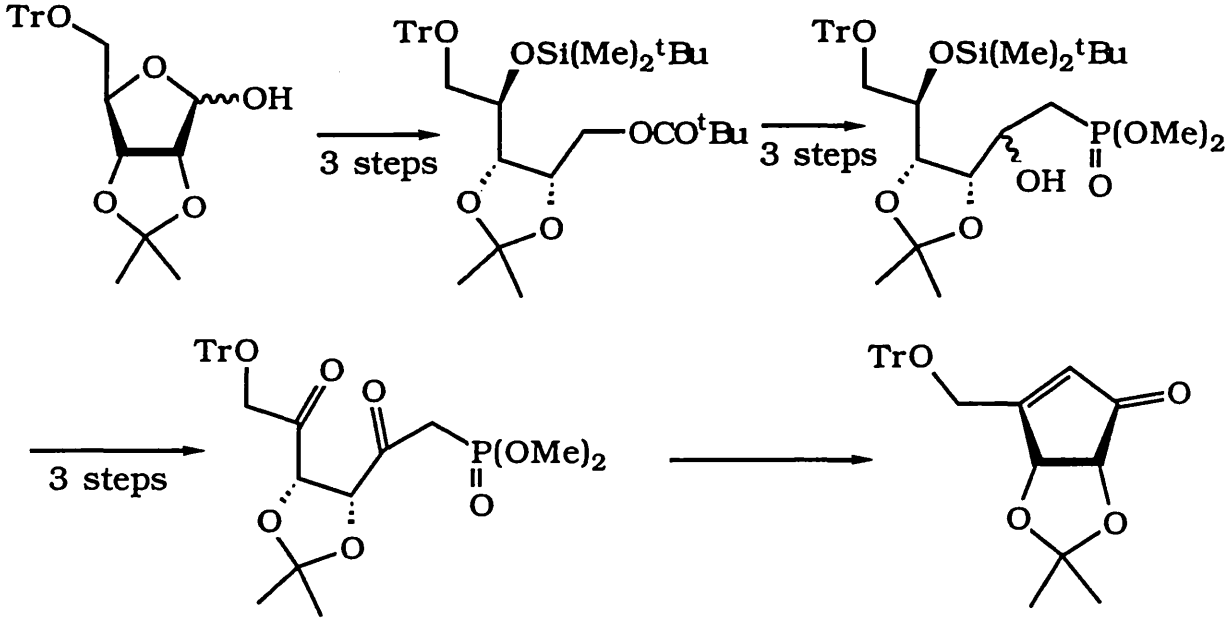
azide, or a complete purine or pyrimidine base, to give a wide variety of 2'-deoxy-carbocyclic nucleosides (the resultant hydroxyl group from this opening being removed using radical methods *via* the phenoxy thiocarbonyl derivative).[77,93] The same benzyloxycyclopentadiene (**82**) and ring opening of an epoxide has been used by Madhavan and Martin in their racemic and homochiral syntheses of aristeromycin.[94] However, they use a photochemical method involving the addition of singlet oxygen to the benzyloxymethylcyclopentadiene which produced only a moderate (60%) yield of partially pure material.



Scheme 68

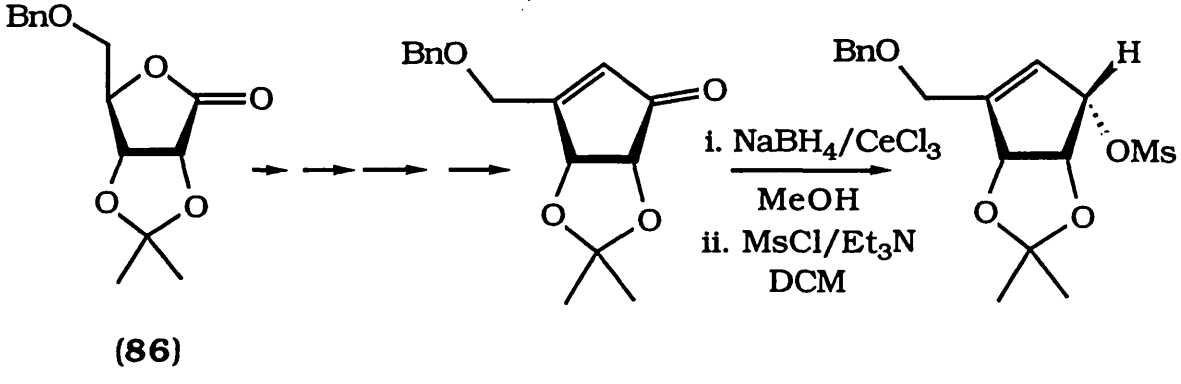
Lim and Marquez[40,95] developed a synthetic approach towards (-) neplanocin A by the use of Wittig/Horner methodology on an acyclic substrate derived from D-ribose. Their initial work described the formation of the functionalised cyclopentenone (**85**) in twelve steps which included the ones shown in Scheme 69. Almost immediately afterwards they published a much shorter

synthesis of the above cyclopentenone (**85**) from a readily available ribolactone (**86**) (again using the Wittig/Horner approach) and then completed the synthesis *via* a regio- and stereoselective reduction of the ketone using sodium borohydride with ceric chloride. The specificity of this reduction came from the curved nature of the bicyclo[3.3.0] ring system, with one face of one ring being shielded by the other ring.



Scheme 69

(**85**)



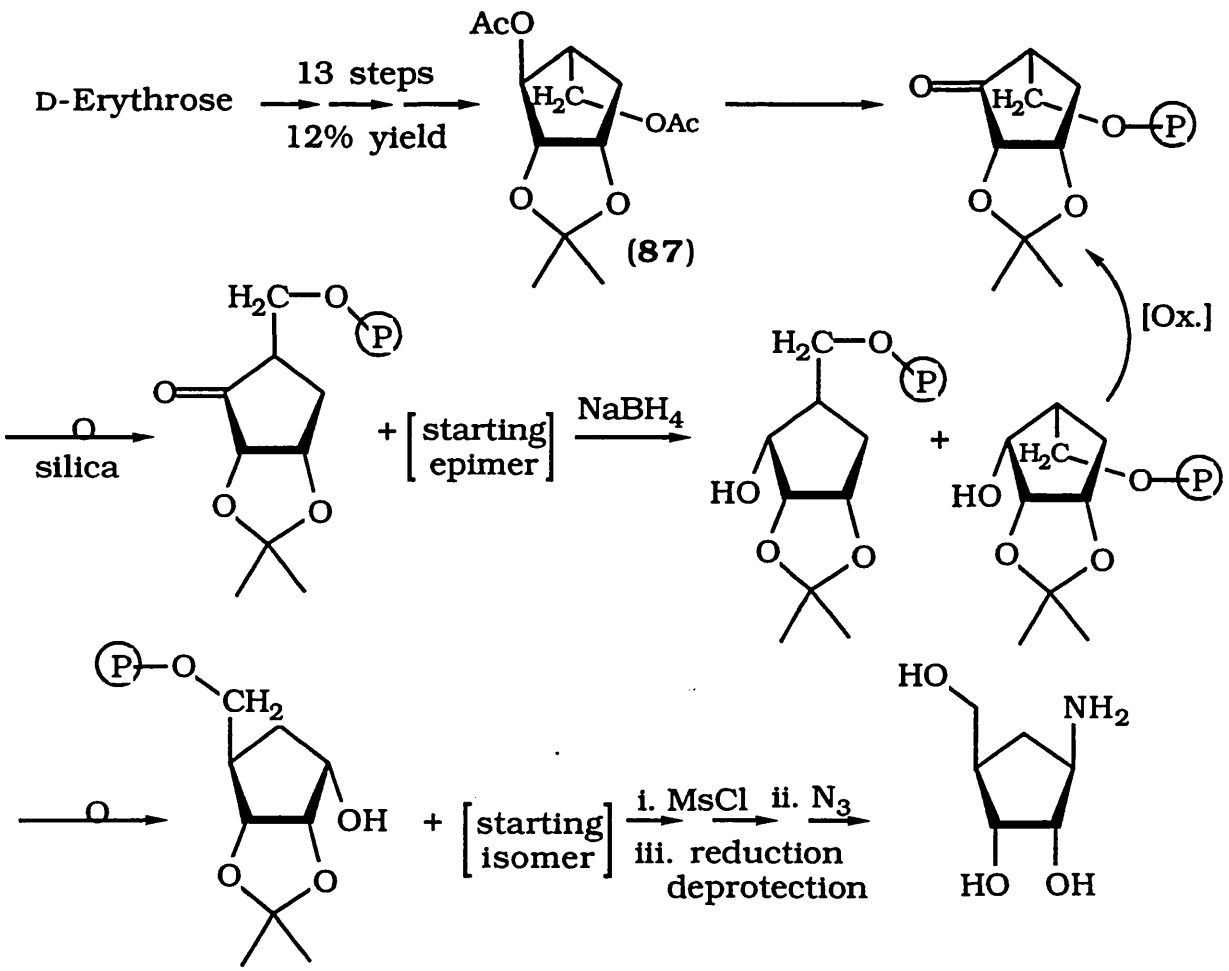
(**86**)

Scheme 70

Once the α-hydroxyl group had been formed, the production of (-) neplanocin A was completed in the usual way with azide displacement and the building of the adenine ring onto it,

however later, they developed a shorter route which used the complete base to displace the hydroxyl group.[96]

Another synthesis from a sugar, has been achieved from D-erythrose. It is a formal, and somewhat lengthy, synthesis of, enantiomerically pure, aristeromycin. Tadano *et al*[90b] took the sugar in thirteen steps (12% yield) to the cyclopentane derivative (**87**) shown.



Scheme 71

After phosphorylating the C-4 hydroxymethyl group and oxidising the C-3 hydroxyl group, they managed to epimerise the C-4 centre using silica. This gave an epimeric mixture of cyclopentanones which were separated after the ketone had been reduced with sodium borohydride. After a second poor yielding

step, which involved the shift of an acetonide protecting group from C-1/C-2 to C-2/C-3, the free hydroxyl group on C-1 was displaced, with inversion, by azide and after reduction and deprotection gave the hydroxymethyl-cyclopentylamine intermediate (**73**) shown at the beginning of this section.

2.4 CONCLUSIONS

It is the production of the hydroxymethyl-cyclopentyl intermediate (**73**) which differentiates all of the preceeding work from our own. Apart from Ohno's chemicoenzymatic approach[82] none of these methods can produce a substituted, two carbon, unit at C-4 which is essential in the synthesis of a carbocyclic analogue of one of the nikkomycins or polyoxins. Yamamoto's route[89] to Ohno's lactone can be changed by using the (R) configuration sulphoxide and this would lead to a two carbon unit on C-4, but the conversion of that compound into a nikkomycin/polyoxin analogue would be a long winded process.

It would be possible to use any of the above syntheses to the hydroxymethyl-cyclopentylamine intermediate and then take the hydroxymethyl group on to the amino acid (*via* the ketone) in a Strecker type of chain extension.[97] However, we felt that this would have not achieved anything new and that the pathway through the Beckmann rearrangement was a neat, novel and efficient adaptation of the established, bicyclo[2.2.1] ring system approach to carbocyclic nucleosides.

CHAPTER THREE

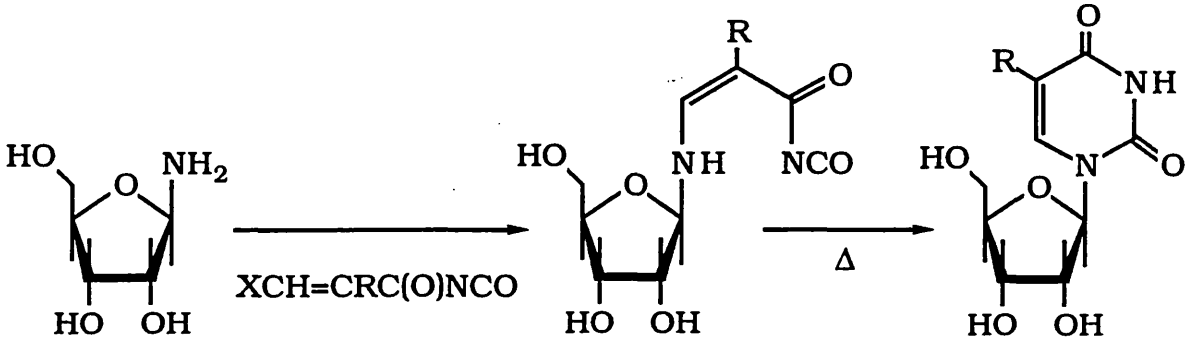
The Right Hand Fragment

3.1 INTRODUCTION

From the disconnections made in Chapter 2 the "right hand fragment" constitutes the nitrogen base part of the nucleoside antibiotic. This can either be a uracil, a 5-substituted uracil or the 4-formyl-1-alkylimidazolin-2-one ring system. Within this Chapter, the different previous approaches to these ring systems shall be reviewed and also our attempted development of the well-known halocyclisation procedure to give the basic 4-substituted imidazolin-2-one system will be discussed.

3.1.1 *The Uracil Base*[98]

The introduction of a uracil (or 5-substituted uracil) base into a sugar has usually been achieved in one of two ways. Either the complete base has been used to displace a leaving group (usually chlorine or a silylated hydroxyl group) at the anomeric centre,[91a,96] or the ring itself has been built onto a free amino group at that centre[78a,88a,98] (Scheme 72)

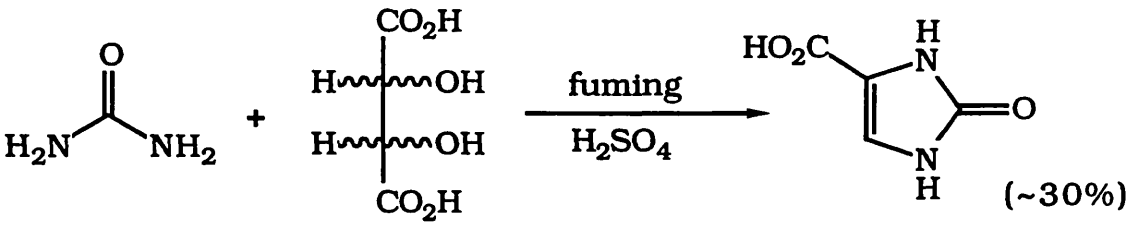


Scheme 72 :- X = a leaving group, R = H, CN, alkyl etc.

3.1.2 *The Imidazoline Base*

There have been several methods reported in the literature which form the 4-substituted imidazolin-2-one system. The earliest reference by Hilbert[28] produced a low yield of the 2-oxo-imidazoline-4-carboxylic acid (**85**) from the harsh

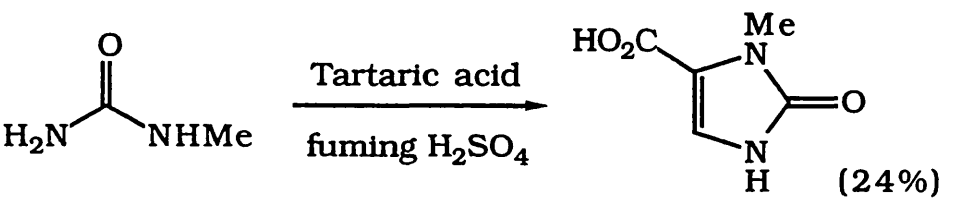
condensation of tartaric acid and urea in fuming sulphuric acid (Scheme 73).



(85)

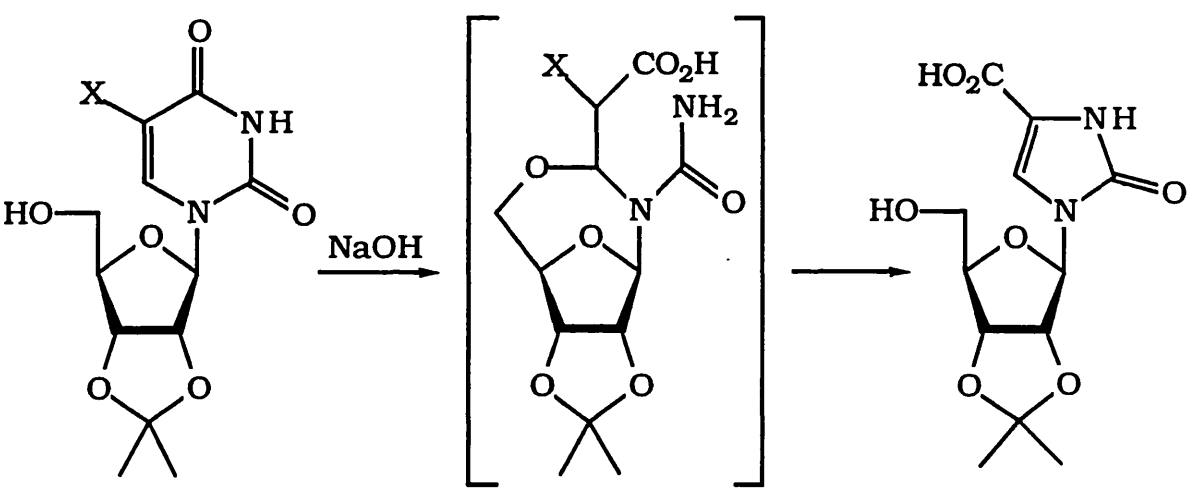
Scheme 73

When a substituted urea was used (as in Scheme 74) then the exclusive product was the 3-alkyl **(86)** and not the desired 1-alkyl derivative.



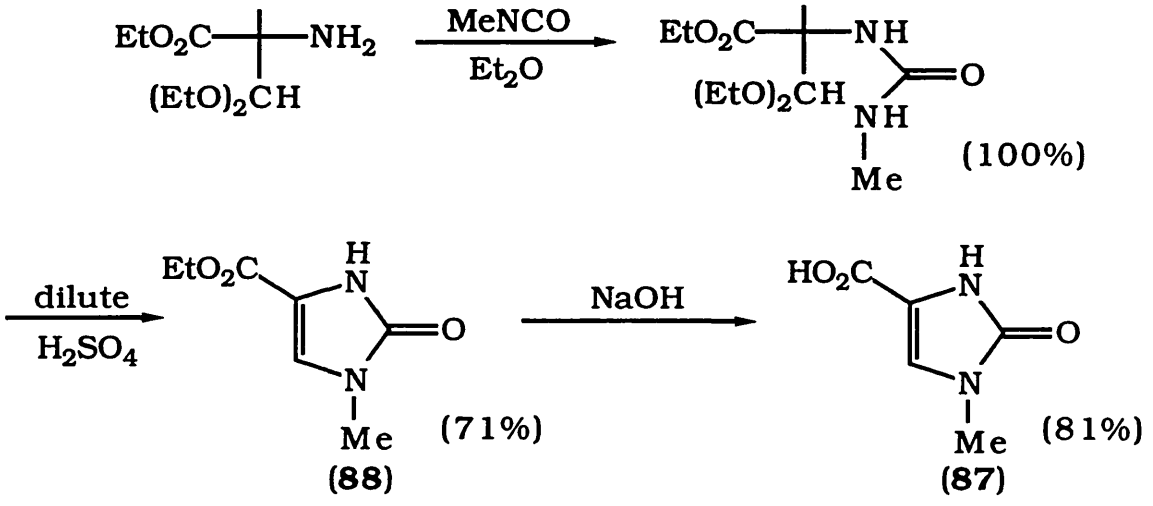
Scheme 74 **(86)**

This was shown by Fox *et al*[27,99] who produced the 1-furanose substituted imidazolinone ring system by an alkali induced ring contraction of a 5-halo-uracil, which proceeded with a neighbouring group effect by one of the furanose hydroxyls.

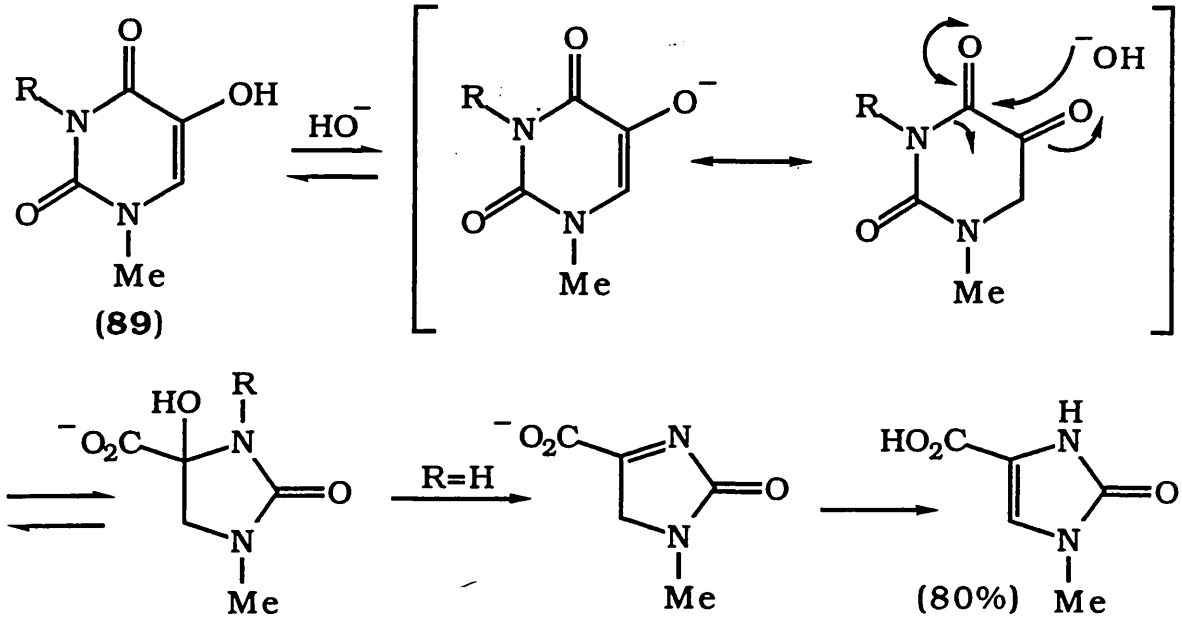


Scheme 75 :- X= Br, I, or F.

They also managed to test their substitution pattern by synthesising 1-methylimidazolin-2-one-4-carboxylic acid (**87**), and its ethyl ester (**88**) *via* a different route (Scheme 76). Later they adapted their ring contraction procedure to work on an isolated 5-hydroxyuracil (**89**) (Scheme 77), something which had proved impossible to accomplish with the original 5-halouracils because the reaction had only led to decomposition products.[99]

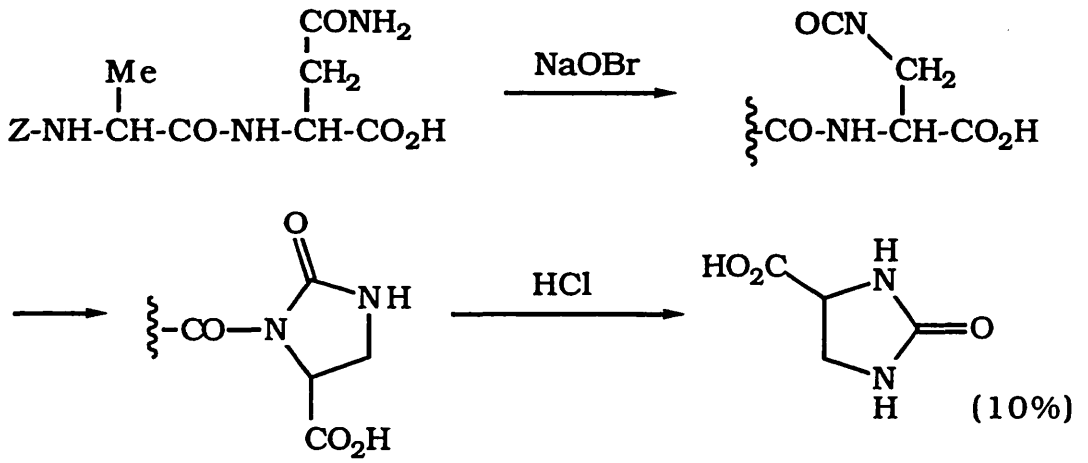


Scheme 76



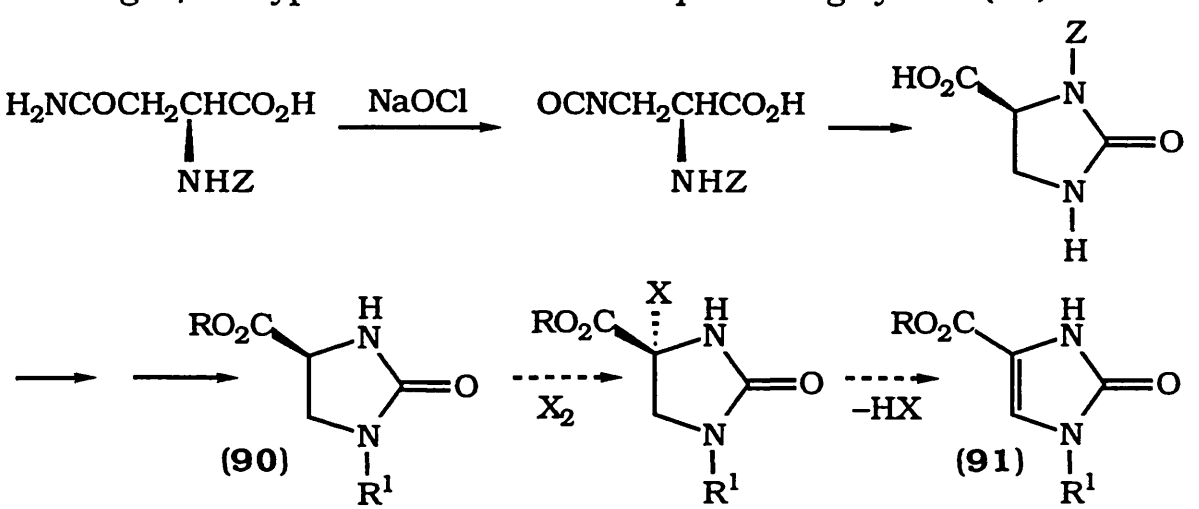
Scheme 77

An investigation into the selective cleavage of asparagine residues uses the Hofmann rearrangement to produce an isocyanate group *in situ* (Scheme 78), which leads to the imidazolin-2-one ring by the intramolecular cyclisation of an amino group onto it.[100]



Scheme 78 :- Z = CO_2CH_2Ph

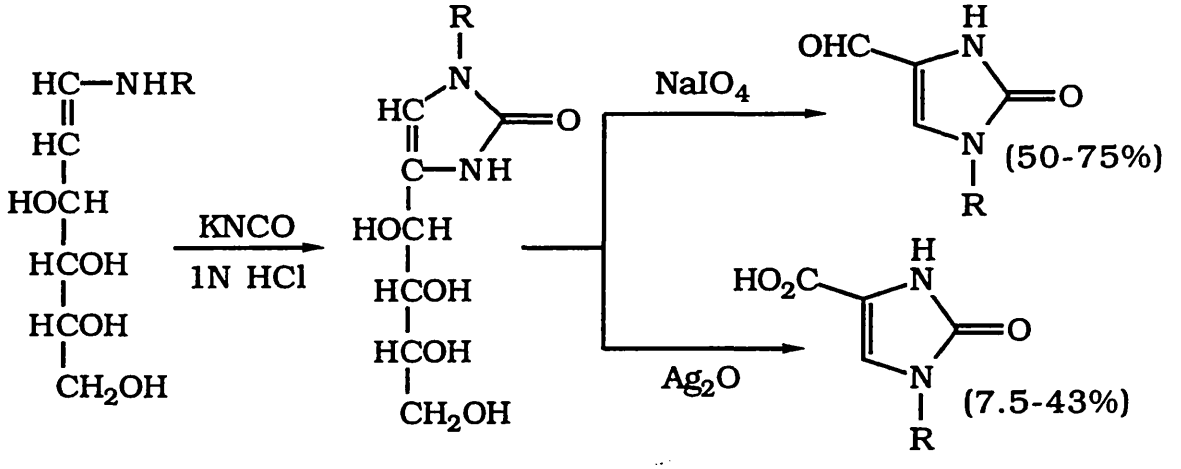
The Hofmann rearrangement is also used in a much more recent paper by Hayashi *et al*[101] when they needed a 4-carboxy-imidazolin-2-one (**90**) system for studies into ACE inhibition (Scheme 79). Although this route provided access to the saturated system only, an addition/elimination procedure of, for example, a halogen/HX type would lead to the required ring system (**91**).



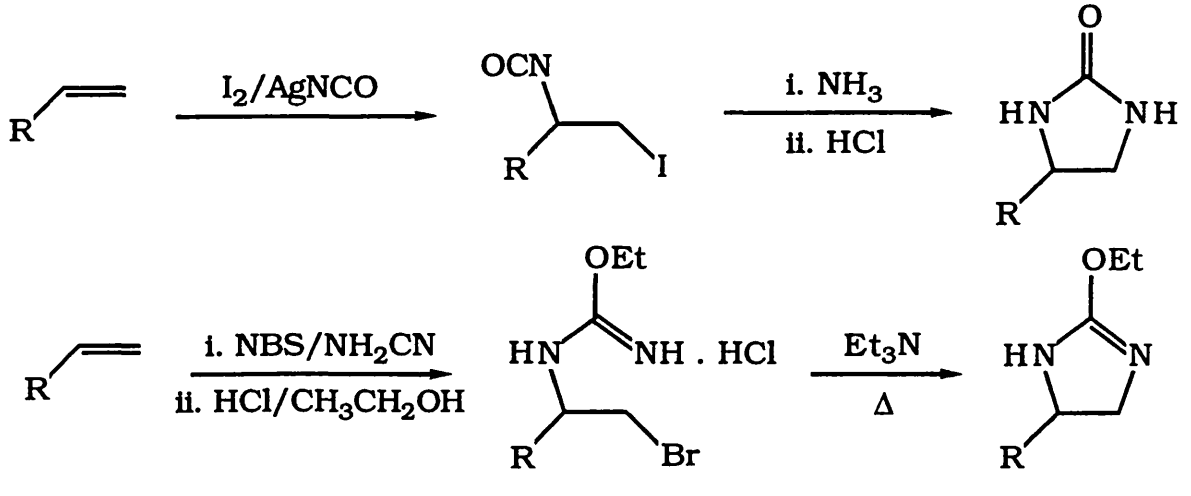
Scheme 79 :-R = ^{t}Butyl, CH_2Ph, Z = CO_2CH_2Ph, R^1 = Me, C_4H_9, CH_2Ph

A slightly different approach was taken by Bolanos[102] when he cyclised a substituted amino sugar (again using an isocyanate) to the desired ring system with the sugar moiety attached to the 4-position (Scheme 80). Two simple cleavage methods therefore furnished him with either the acid or aldehyde functional groups at the 4-position. In his examples the R groups were all straight chain alkyl groups.

The use of an isocyanate group to form the urea is the major step in almost all of the chosen methods however, the use of carbonyl equivalents (e.g. phosgene) on diamines has been another major method of synthesising ureas or cyclic ureas.



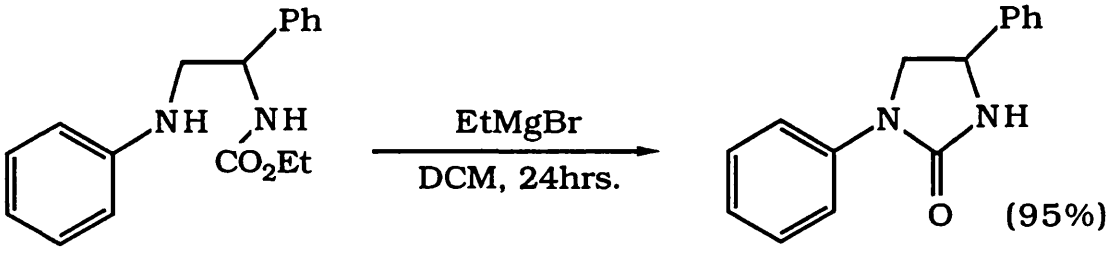
Scheme 80



Scheme 81 :- R = straight chain alkyl group.

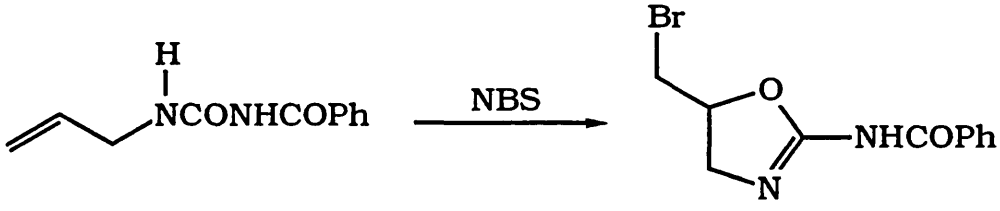
The reverse desire for new diamine syntheses has also produced methods which form imidazolinone rings. The possible use of hydantoins[103a] or the other methods discovered by Kohn and Jung,[103b,c] or Ghomi and Orr,[103d,e] (Scheme 81) could also be entries into the desired ring system; however the conditions used mean that they would be unable to tolerate functionalised side chains.

A less harsh approach has been developed by Basha[104] which involves the intramolecular attack of a magnesium salt of an amine onto a carbamate function (Scheme 82). However this too would be unlikely to work if the side chain were to contain more useful functional groups.

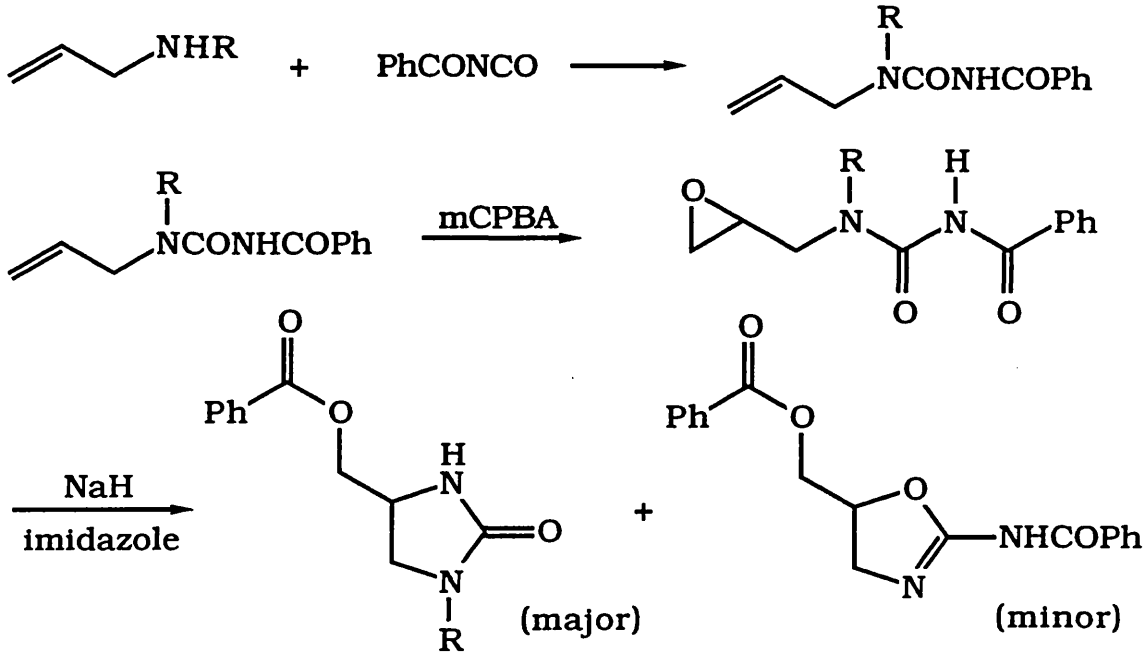


Scheme 82

The final example by McCombie,[105] is similar to the work that has been carried out in our laboratory which dealt with the cyclisations of allylic amidines[103a] and ureas. As one can see in Scheme 84, under basic conditions the formation of the N-cyclised material predominates (no yields were quoted) with a benzoyl N to O migration taking place rapidly after cyclisation. They also showed that under neutral conditions (such as with NBS) the allyl urea (**92**) gave the O-cyclised material (**93**) exclusively (Scheme 83).



(**92**) Scheme 83 (**93**)



Scheme 84

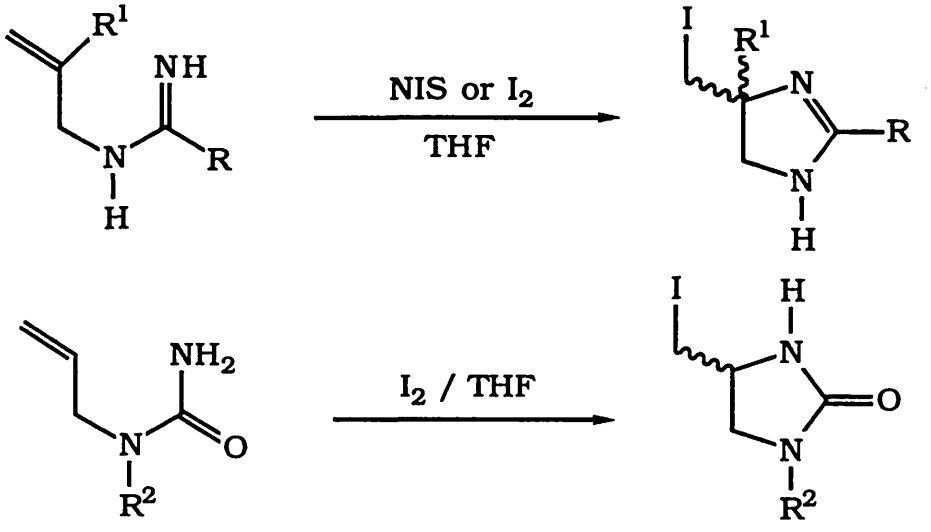
In McCombie's work the 'R' group was hydrogen, however this route could possibly be adapted to incorporate an alkyl group at position *N*-1 by the use of a disubstituted allylamine as used in the next section.

3.2 **RESULTS and DISCUSSION**

The previous work in our laboratory[103a,106] has been involved with the search for new, mild methods of imidazole and imidazolinone synthesis. These methods are important not only because these types of compounds can have significant biological importance but they can also be considered as protected vicinal diamines which are also very desirable compounds in the anti-cancer area.[103a]

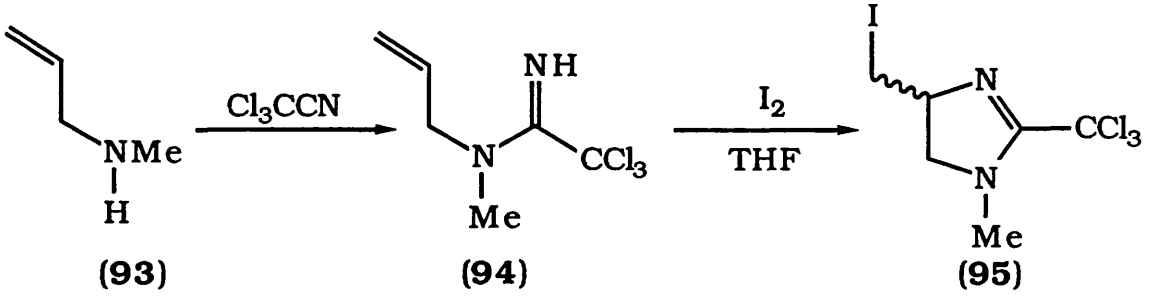
The major route under our investigation involved the halocyclisation of allylamidines and -ureas using NIS, NBS, or I_2 (Scheme 85). It was found[103a] that *N*-allylbenzamides and *N*-

allyltrichloroacetamidines could be readily cyclised in high yields by using NIS or I_2 in tetrahydrofuran. These amidines in turn, were easily prepared from commercially available allylamine and either benzonitrile or trichloroacetonitrile.



Scheme 85 :- R= Ph, CCl_3, R^1= H, Me, R^2= Me, $PhCH_2$, Cyclopentyl

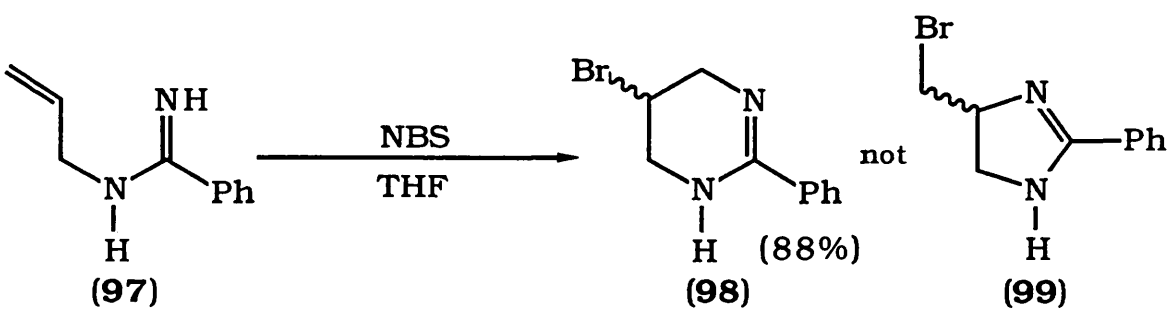
These reactions were extended to include *N*-alkylallyl amines, and for *N*-methylallylamine (**93**), the formation of the amidine (**94**) with trichloroacetonitrile and its subsequent cyclisation to the 2-trichloromethyl-4-iodomethyl-1-methyl imidazoline (**95**) were equally facile. However the product imidazoline (**95**) did discolour rapidly after its isolation.



(**93**) (**94**) (**95**)

Scheme 86

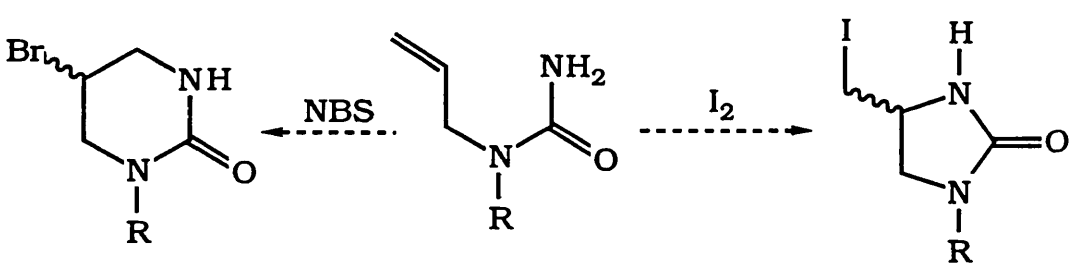
Problems were also encountered when *N*-cyclopentylallyl amine (**96**) was used with trichloroacetonitrile as only low yields of impure amidine were formed, which then gave only trace amounts of the cyclised imidazoline when subjected to the iodine induced closure conditions. Somewhat surprisingly the halocyclisation of *N*-allylbenzamidine (**97**) when carried out with NBS gave the bromotetrahydropyrimidine (**98**) and not the expected bromomethylimidazoline (**99**), possibly indicating a change in the reaction mechanism.



(**97**) (**98**) (**99**)

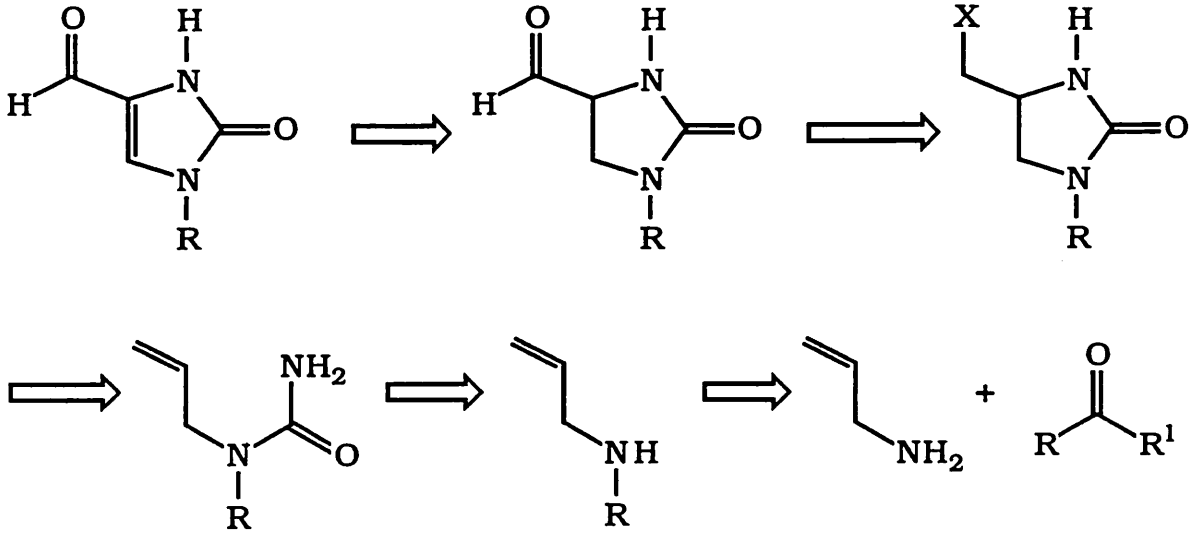
Scheme 87

This apparent ability to select the size of ring merely by changing the halogen would be of great importance in our work towards both the imidazolinone and uracil ring systems. One could envisage both systems being derived from the same allylurea starting material, a feature which would give great flexibility to our proposed synthesis of both the carba-nikkomycins and polyoxins.



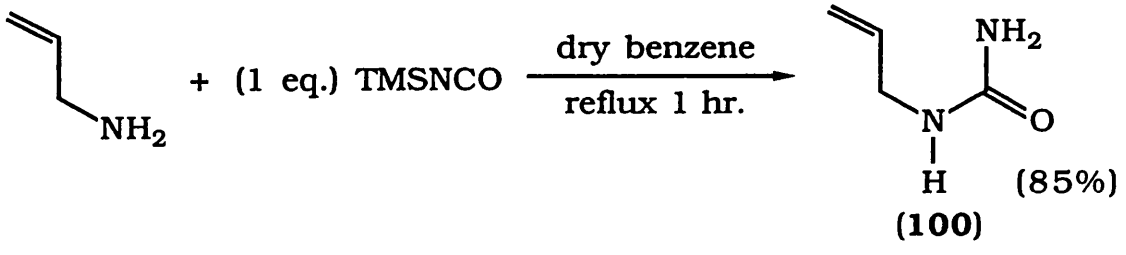
Scheme 88

3.2.1 *Formation of the 4-substituted-1-alkyl-imidazolin-2-one*



Scheme 89

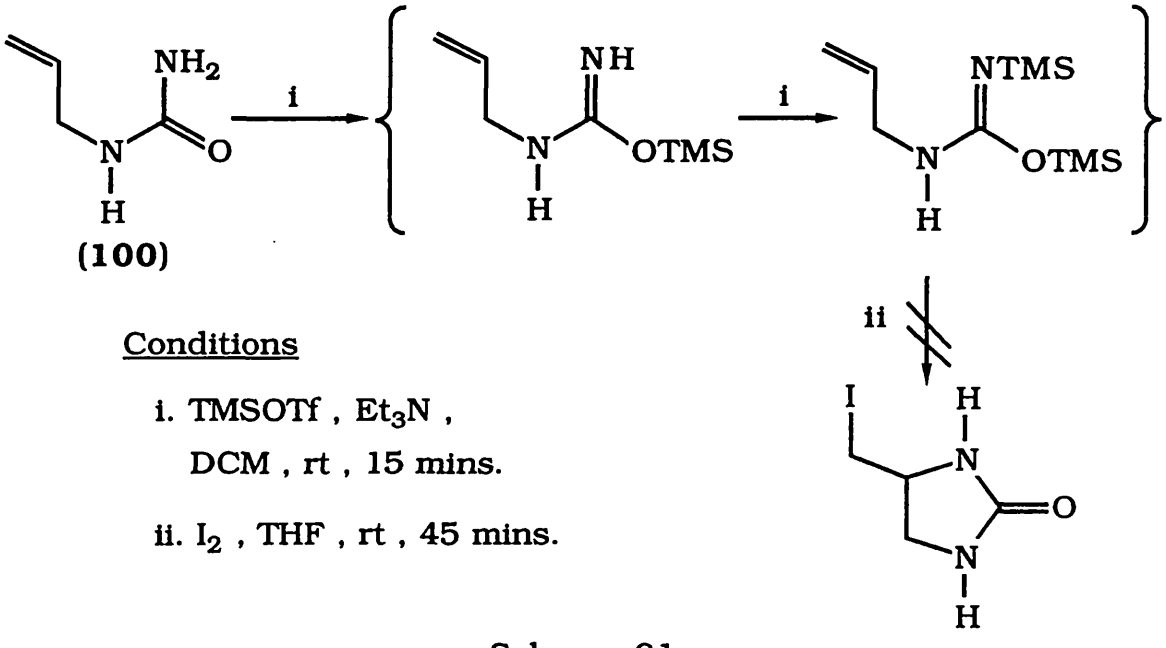
From the disconnections shown in Scheme 89 one can see that for R=H the initial step is the formation of the urea. There had been literature procedures[107] for the production of the *N*-H and *N,N*-alkylallyl ureas. These involved the formation and use of silicon isocyanates ($R_XSi(NCO)_{4-X}$ where R= Me or Ph) and produced excellent yields of ureas with the simple amines. By using these literature conditions (with slight changes) with commercially available allylamine and TMSNCO, an excellent yield of the corresponding urea (**100**) was obtained.



Scheme 90

This urea (**100**) partly precipitated out of the reaction solvent upon cooling and was filtered off. The remaining crude urea was obtained from evaporation of the solvent and purified by

recrystallisation from a benzene/40-60°C petrol mixture. Before subjecting this urea (**100**) to the cyclisation conditions it was pretreated with triethylamine and TMSOTf to produce a disilylated intermediate which was then induced to cyclise using iodine in tetrahydrofuran.



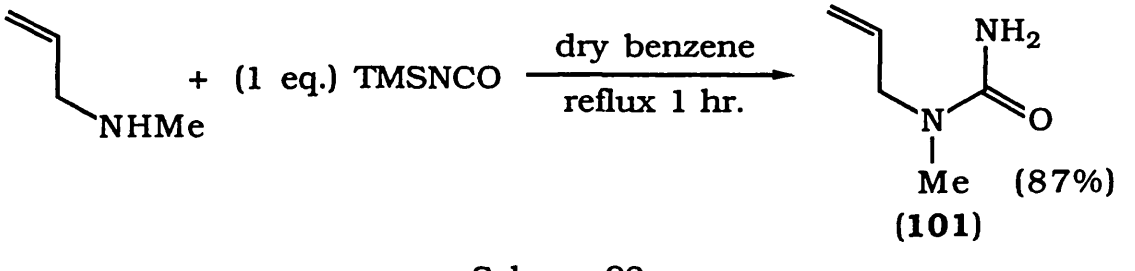
Conditions

i. TMSOTf , Et_3N ,
DCM , rt , 15 mins.

ii. I_2 , THF , rt , 45 mins.

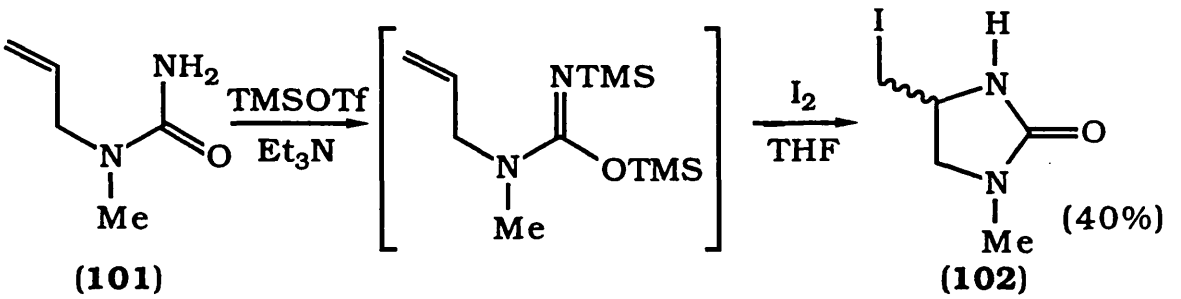
Scheme 91

Unfortunately no cyclised material was isolated from this reaction. Success was achieved however, when *N*-methylallyl amine (again commercially available) was used in place of the primary amine. The *N*-methylallylamine also formed a urea (**101**) in excellent yield and it too, partly precipitated from the reaction solvent, but the majority of the urea was again obtained from recrystallisation.



Scheme 92

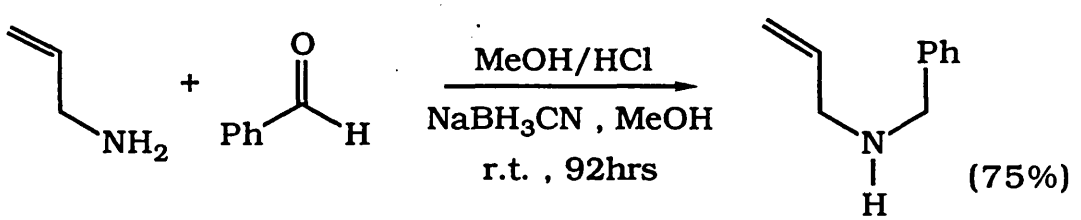
The use of this urea (**101**) under the cyclisation conditions (also after the formation of the disilylated intermediate) gave a moderate yield of the imidazolinone (**102**).



(**101**) (**102**)

Scheme 93

Encouraged by this result, it was decided to try *N*-benzylallylamine (**103**) in order to establish how general this cyclisation could be. *N*-Benzylallylamine (**103**) is not commercially available and as was shown in the initial disconnection sequence (Scheme 89) it had to be synthesised by a reductive amination method involving allylamine, benzaldehyde, and sodium cyanoborohydride. The reductive amination procedure of Borch and Durst[108] was used to form this hitherto unknown allylamine in a good yield.

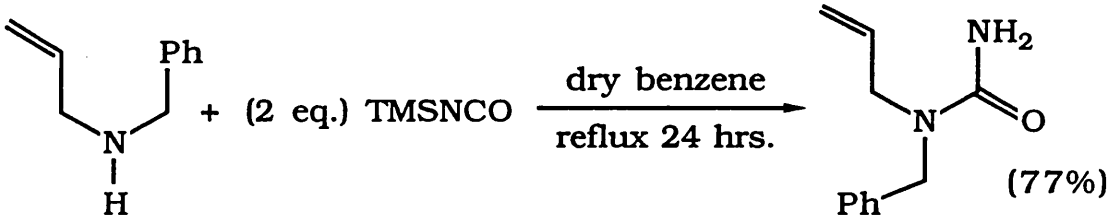


Scheme 94 (**103**)

The reactions were run at pH≈6 to prevent the reduction of the aldehyde but still provide a high enough concentration of protons to form the iminium species necessary for reduction to occur. Allylamine was present in at least 6-fold excess in order to reduce the level of dibenzylated material, although unfortunately this product was still formed in the reaction. Whilst careful

distillation could reduce the concentration of the dialkylated material some co-distillation with the mono-derivative still occurred. Therefore, flash chromatography was used to produce the pure *N*-benzylallylamine (**103**).

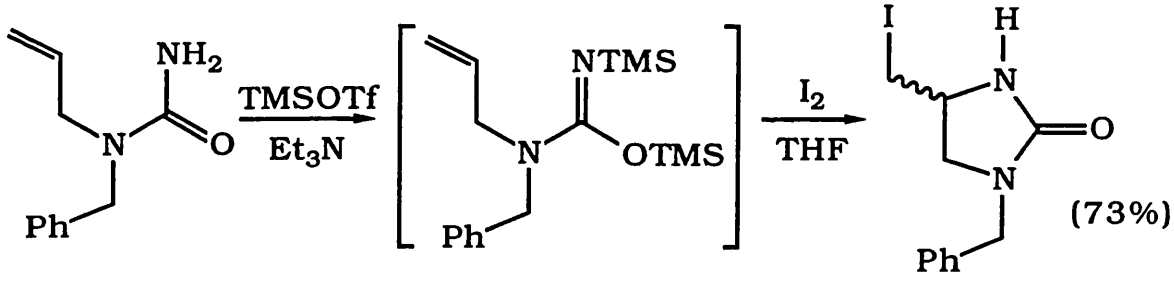
The formation of the *N,N*-benzylallylurea (**104**) from this amine was not successful when the previous conditions were applied. Urea formation was only achieved when two equivalents of TMSNCO were employed with the refluxing period extended to 24 hours. With these new conditions, a good yield of the urea (**104**) was obtained, however this urea did not precipitate out of the reaction and the residue, after the solvent had been evaporated, was an oil. Therefore, the urea had to be isolated by means of flash chromatography and was isolated as an oil (b.p. 174°C at 0.4 mmHg).



(**103**) (**104**)

Scheme 95

The *N,N*-benzylallylurea (**104**) was subjected to the same cyclisation procedure as that for the *N,N*-methylallylurea (**101**) and a surprisingly high yield of the iodomethylimidazolinone (**105**) was obtained.

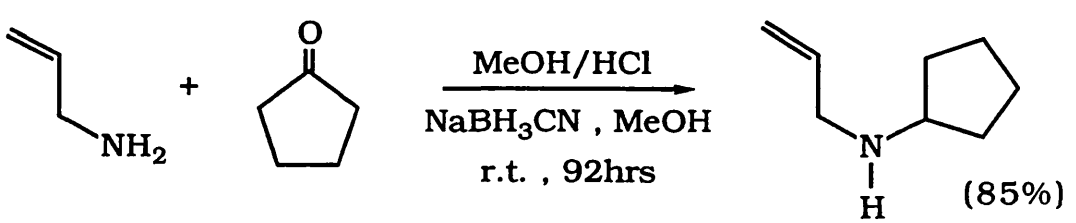


(**104**) Scheme 96 (**105**)

This dramatic increase in the product yield, accompanied by the increase in the urea's solubility in organic solvents led us to believe that the lower yield obtained in the *N*-methyl case could have been due to its greater water solubility and therefore a change in the work-up procedure may improve the yield. Indeed this was found to be the case as when the extraction solvent was changed from dichloromethane to ethyl acetate the yield of the *N*-methylimidazolinone increased sharply to 83%. Extending this improvement to the parent allylurea was not successful, and hence some other reason must be responsible for the lack of cyclised product in this case.

After proving that this methodology was suitable for forming the desired 4-substituted-1-alkylimidazolin-2-one system, it was decided to apply this to a more relevant model such as the *N*-cyclopentylallylamine (**96**). This would model the substituted cyclopentyl amine which would have been produced from the central fragment work.

This cyclopentylallylamine (**96**) was also commercially unavailable and was again synthesised *via* the reductive amination procedure. Initially, the production of high yields of the mono-cyclopentyl allylamine was problematic; however, with freshly distilled allylamine, cyclopentanone, and dry methanol the mono-cyclopentylallylamine could be routinely produced in excellent yield.

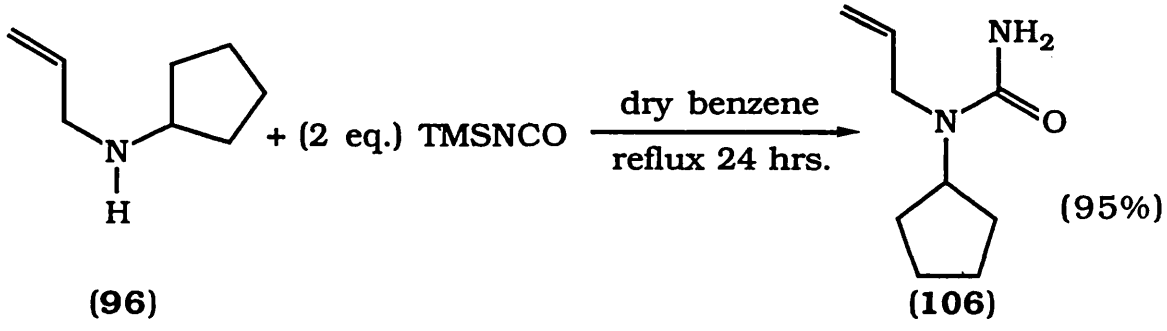


(**96**)

Scheme 97

Still some dialkylated material was formed in the reaction and had to be removed in order for the formation of the urea to

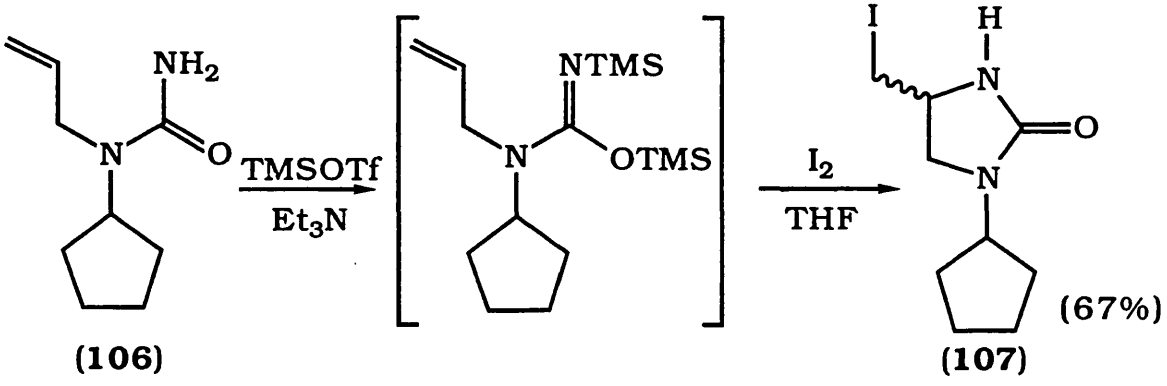
proceed in high yield. Again careful chromatography was required to accomplish this task. The urea formation again failed when the original conditions were employed, however an excellent yield of the urea was obtained by using the conditions worked out for the *N*-benzylallylamine (**104**).



(**96**) (**106**)

Scheme 98

This *N,N*-cyclopentylallylurea (**106**) was also isolated as an oil by flash chromatography (b.p. 110°C at 30 mmHg) but interestingly it solidified over a period of days at -12°C. The cyclisation of this urea also went smoothly to give a good yield (using the ethyl acetate work-up) of the desired 4-iodomethyl-1-cyclopentyl imidazolin-2-one (**107**). The yield of this compound (**107**) is slightly less than that of the *N*-benzylimidazolinone (**105**) but it is still synthetically useful and can be achieved even on multigram scales.



(**106**) (**107**)

Scheme 99

Our use of the silylated ureas to promote N-cyclisation follows a procedure which was developed by Knapp[109a,110] for his work with amides. The formation of the disilyl derivatives is stepwise as has been illustrated in the initial account (Scheme 91). The progress of the reaction can be followed by IR where one is able to see the initial double peak -NH_2 resonance change to a single peak with the formation of the monosilyl compound and then disappear altogether once the disilyl intermediate is formed.

Only once this disilyl intermediate has been formed will the urea cyclise *via* the nitrogen. This has been shown[110a] by submitting the monosilyl derivative to the cyclisation conditions and then isolating the lactone as the only product. These silyl derivatives are highly water sensitive and will revert to the monosilyl compound upon exposure to moisture, hence all our glassware was rigorously oven-dried before use and allowed to cool under an atmosphere of nitrogen.

It was found in the literature that the yield of cyclised product increased if the oily triethylaminetrifluoromethane sulphonate salt was removed before cyclisation.[110a] This was achieved by running the silylation reaction in dry pentane where the salt precipitated out and the silyl intermediate could be transferred to a fresh flask (*via* syringe or cannula) to be cyclised. This procedure would not have been suitable for our ureas as they were not soluble in pentane, hence our use of dry dichloromethane.

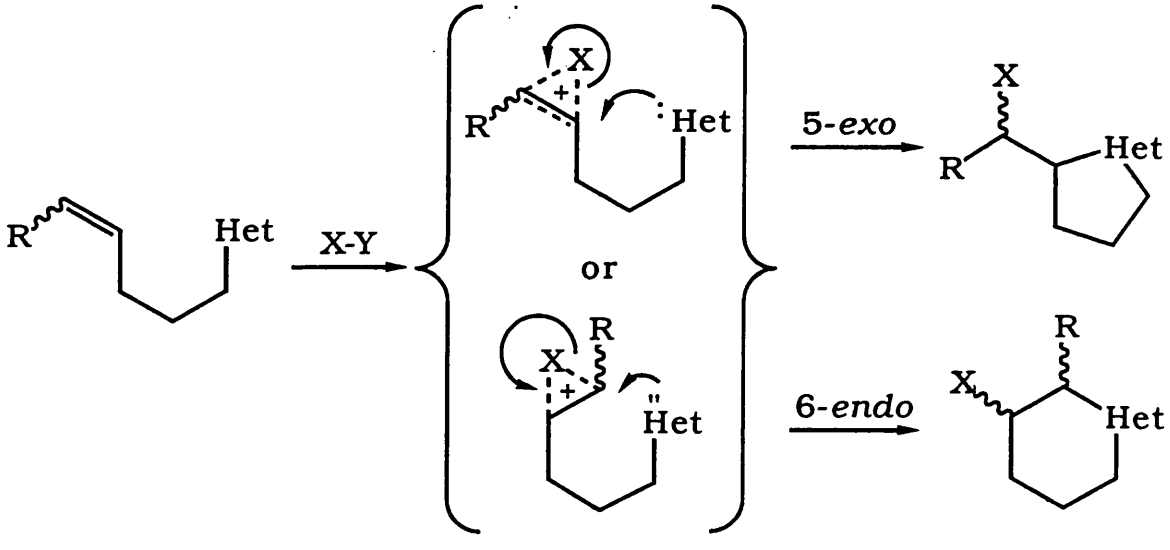
The iodocyclisation reaction was also found to work best, by Knapp,[110] in dry tetrahydrofuran and so his full literature procedure involved the pentane solution being evaporated under reduced pressure (after its removal from the triethylamine salt) followed by the addition of a tetrahydrofuran solution of iodine. The separation of the triethylamine salt from the silyl intermediate was not possible with our ureas and consequently this resulted in the lower yields of the cyclised imidazolinones

compared with the yields of the lactams obtained in the literature from the amides. After removal of the dichloromethane solvent from our reactions, the oily residue had the solution of iodine in tetrahydrofuran added to it. With the usual aqueous sodium thiosulphate work up and extraction, the cyclised products were isolated using flash chromatography.

The oily nature of the triethylamine salt made removal of all the dichloromethane solvent rather difficult and this sometimes made the work up procedure inefficient and the products impure with excess iodine. Once our work had shown that this iodocyclisation procedure was able to produce the desired ring system, the *N*-methyl- (**102**) and the *N*-cyclopentylimidazolin-2-ones (**107**) were chosen to investigate the conversion of the iodomethyl substituent into the desired formyl group.

This application of a halogen induced cyclisation to ureas is new and constitutes a mild and efficient cyclisation procedure which complements those methods already present in the literature as can be seen in the next section.

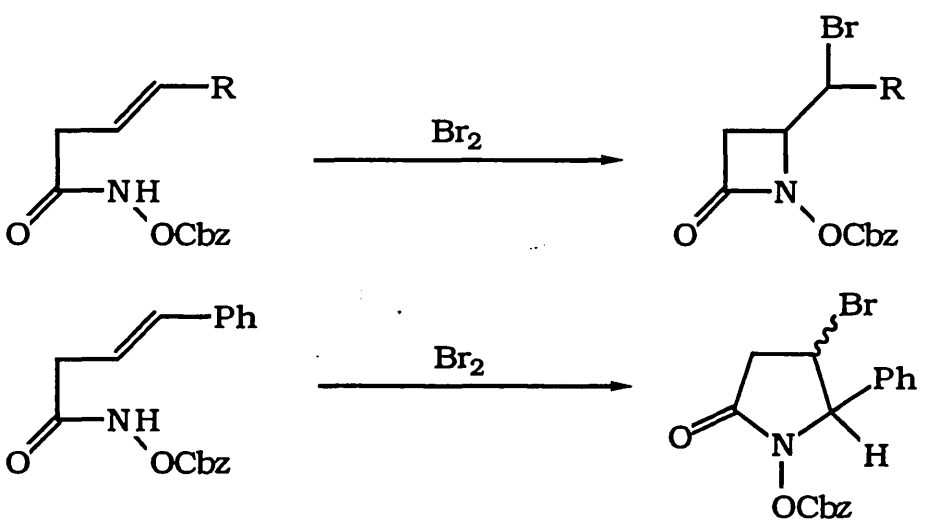
3.2.2 *Cyclisation procedures*



Scheme 100

All of the following procedures deal with the same basic premise of inducing nucleophilic heteroatom cyclisation onto a double (or triple) bond by forming an electrophilic 3-membered 2-electron species. The heteroatoms have been, most commonly, N, O, or S, whilst the inducing species has been a halogen[111], organosulphur[112], organoselenyl[113], or even metallic[114] in nature. Baldwin's rules[115] were the first step forward in the understanding of cyclisation products, however other principles can contribute greatly to the determination of the final product.

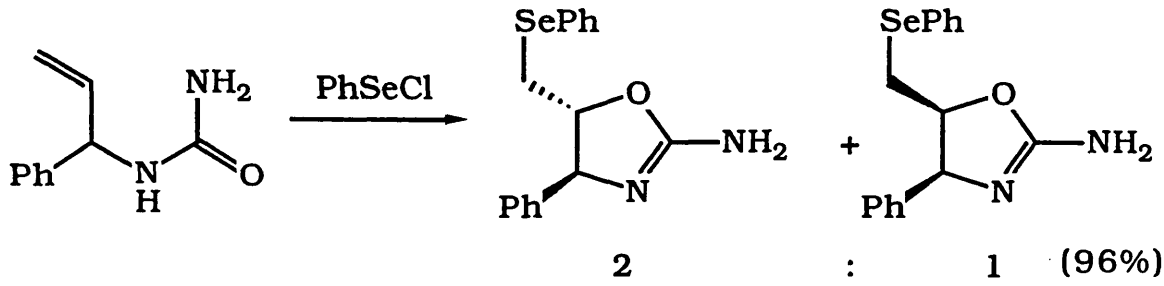
The ability of a particular group to stabilise the incipient positive charge has a great impact on the product distribution as can be seen from Scheme 101. With this system the stabilisation of the positive charge by the phenyl ring is so great as to reverse the site of closure from 4-*exo*-trig to 5-*endo*-trig, a cyclisation which by Baldwin's rules is disfavoured.[116]



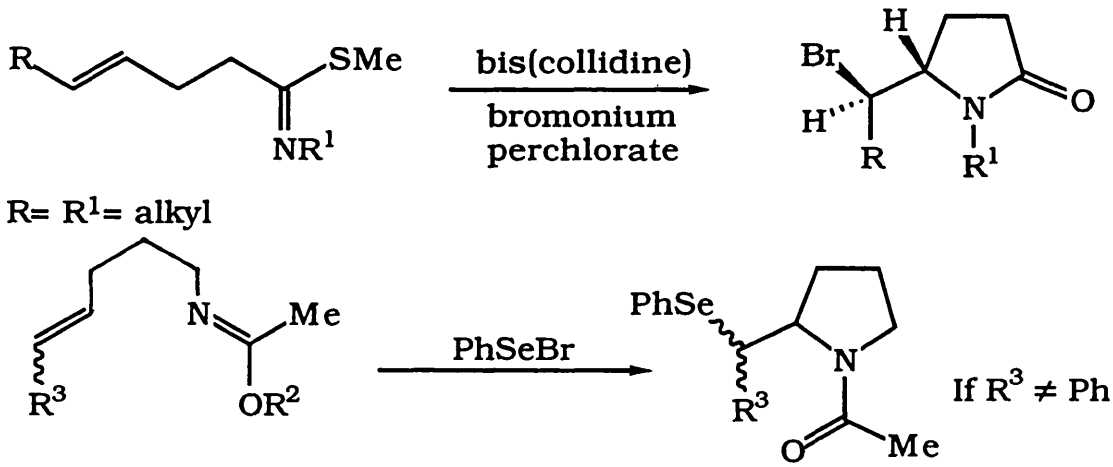
Scheme 101:- Cbz = $C(O)OCH_2Ph$

Markovnikov addition is also invoked to explain partly the preference of 5-*exo* to 6-*endo* cyclisation of species with terminal double bonds[113a] (Scheme 102). But this is not the total explanation as some alkyl substituted double bonds do not result in a mixture of products[117] (Scheme 103). The ring closure reaction can also be thought of as an irreversible one and hence it

can produce 'kinetic' type products such as the 5-membered ring.

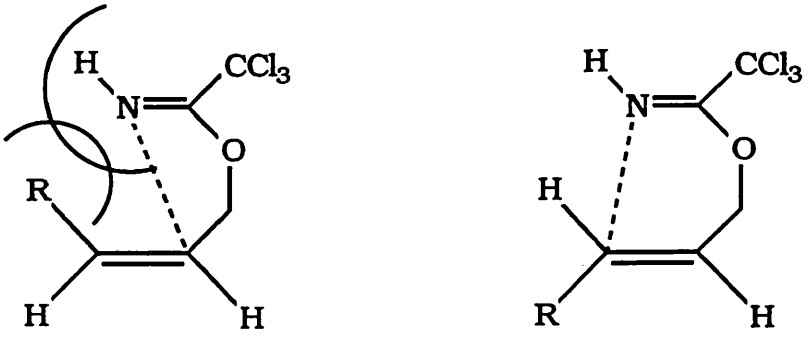


Scheme 102



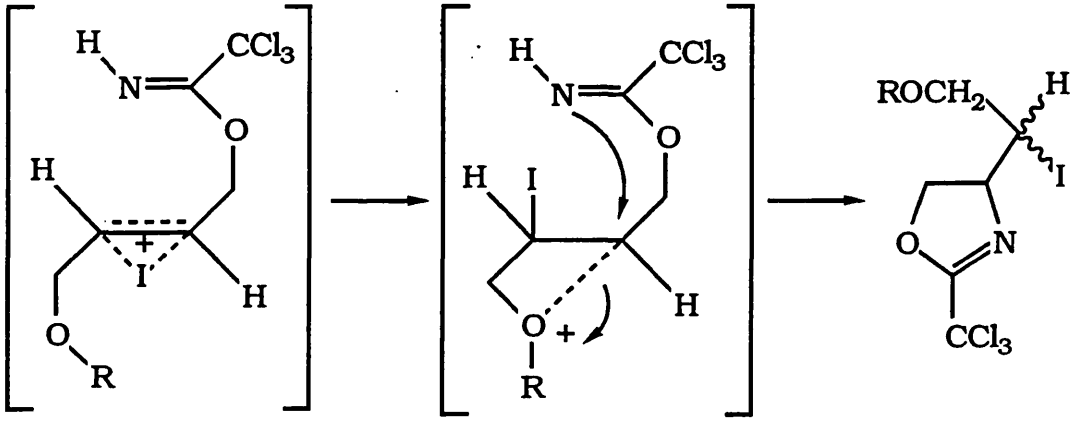
Scheme 103 :- R^2,R^3 = Alkyl

Support for this hypothesis has come from the *cis-/trans-* ratios of substituted olefins once they have cyclised. The ratios of approximately 2:1 correspond to those expected from a kinetic process whereas for a 'thermodynamic' closure one would expect to see a predominance of the *trans*-product with ratios approximating to 1:10.[118] The geometry of the double bond can also affect the site of closure. Investigations into imidate cyclisations have shown that a 'Z' geometry at the double bond exerts a steric hinderance towards 6-*endo*- closure and hence 5-*exo*- cyclisation is seen. An 'E' geometry however does not exert such an influence and so one sees 6-membered ring formation[119] from a reversible ring closure reaction (Scheme 104).



Scheme 104

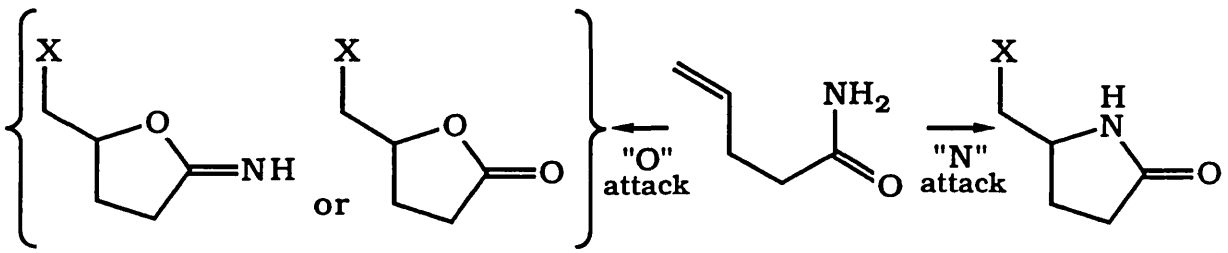
If an oxygenated substituent is present at the terminus of the double bond so that the oxygen atom is β to it, there is also a directing effect upon the site of closure. It seems to directing the closure towards forming 5-membered rings, but its effect is less severe than the steric one and where the effects of steric bulk and the β oxygen are opposed, mixtures of ring sizes are produced. The exact nature of this β oxygen effect is as yet unclear, however it could be that the oxygen interacts with the halonium species to form a charged oxetane ring and then is displaced by the nucleophilic imidate nitrogen (Scheme 105).



Scheme 105

Whilst the cyclisations of either alcohols to ethers,[120] or

carboxylic acids to lactones,[112c,121] or imidates to oxazolines,[113a,b,119] give predictable heterocyclic products, with amides and ureas there are two possible heteroatoms through which cyclisation can occur, as one can see from Scheme 106.



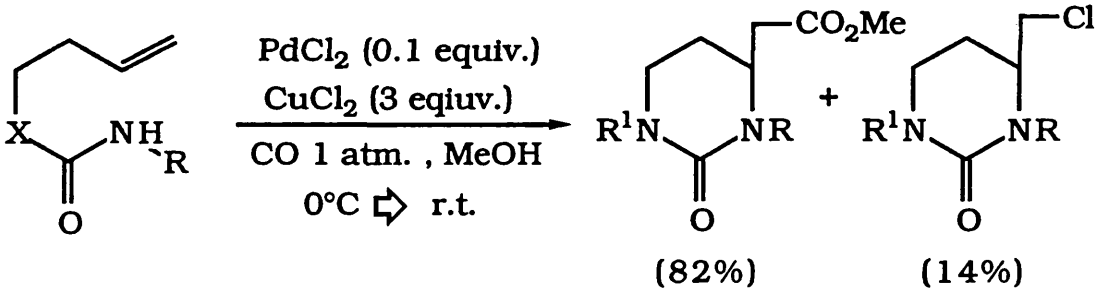
Scheme 106

In general, if there is a competition between O (or S) and N to form a 5-membered ring then cyclisation will occur *via* the O (or S) to give a lactone (or thiolactone) or an iminoether (iminothioether), depending on the work-up conditions[122]. This is due to the greater nucleophilicity of the oxygen (or sulphur), however N-cyclisation will prevail if the O-cyclisation would result in the formation of a 7-membered ring (a kinetic effect) or if the N-anion of the amide or urea was formed first.[105]

This is indicative of the most consistent method for obtaining N-cyclisation which is to pretreat the amide/urea to form an iminoether i.e. produce the 'enol' form of the functional group. In this way the nitrogen becomes the more nucleophilic atom and hence it cyclises onto the halonium species in preference to the oxygen or sulphur.[109,111c] It is for this reason that our ureas are firstly converted into their bis-silyl derivatives with TMSOTf.

One exception to this pretreatment method is used by Tamaru *et al*[114] and involves the co-ordination of divalent palladium to the olefin. With this procedure normal ureas can be cyclised *via* nitrogen to give exclusively 5- or 6-membered rings, depending on the number of 'spacer groups' between the olefin

and the NHR terminal group of the urea. Their explanation of this surprising selectivity is that the Pd^{2+} co-ordination causes the double bond to become a 'soft' electrophile which prefers the 'softer' N-nucleophile. Interestingly they also report that their method does not work if X = O but do not give any reason for this.



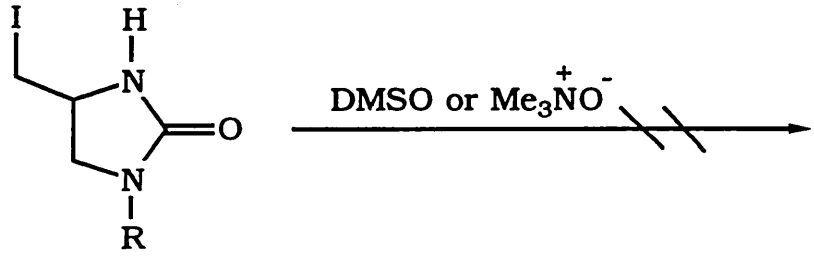
Scheme 107 :- R^1,R = H, Aryl, Alkyl X = O or NR^1

It has also been reported that some procedures will only give cyclised products if silica gel is present in the reaction and that alkyl subtitution[117] on the so-called 'spacer groups' does produce higher yields. No explanation for these effects has been ventured but it seems possible that both the silica gel and subtituents are forcing the molecules concerned into the correct rotamer for cyclisation to occur.

3.2.3 *Iodomethyl group oxidation*

There are many procedures in the literature for converting an iodomethyl group into an aldehydic function,[123] but they are inapplicable here because they displace the iodo group with a -CHO group thereby extending the chain length at the 4-position. The traditional method for the oxidation of an alkyl halide to the corresponding aldehyde is by using Kornblum's conditions.[124] This method uses dimethylsulphoxide as a nucleophile to displace the iodine and the aldehyde is generated

by the elimination of dimethylsulphide from the *in situ* charged sulphur intermediate. A similar method involves the use of anhydrous trimethylamine oxide[125] in dry $CHCl_3$ which again relies on the nucleophilic nature of the *N*-oxide oxygen to displace the iodine. When both these methods were tried on the *N*-methyl (**102**) and *N*-cyclopentylimidazolinones (**107**) no conversion of the iodide was seen and starting material was recovered in both cases.

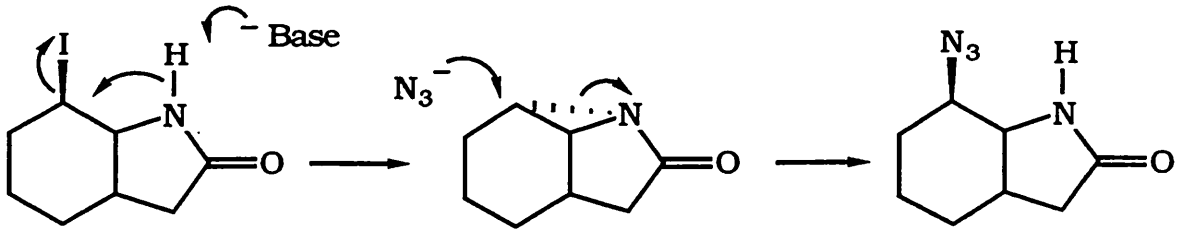


Scheme 108 :- R= Me or cyclopentyl

This was thought to be due to the rather weak nucleophilic nature of the oxygens concerned and so the reaction was repeated using potassium superoxide[126] with a crown ether present to solubilise the potassium ion. The O_2^- ion is highly nucleophilic due to the α-effect of the neighbouring oxygen atom but unfortunately this reagent proved to be too powerful for the chosen imidazolinones and only the crown ether was recovered.

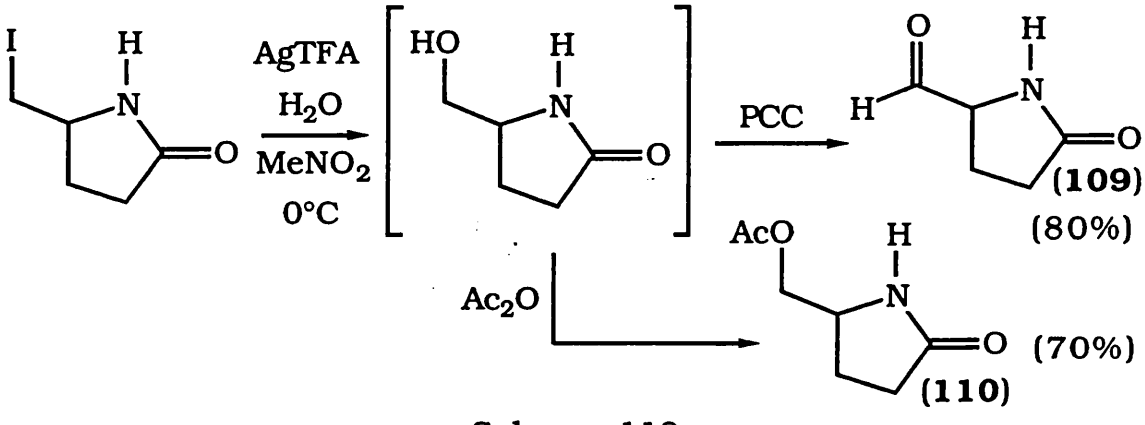
At this time Knapp[110] published results of his investigations into the reactivity of the iodomethyl group present in the lactams with which he was working. Our suspicions about the lack of reactivity of the iodomethyl group were supported by some of Knapp's own results. He too found that only good nucleophiles, which were also poor bases, would displace the iodo function. These displacements went not only with retention but also in better yields when sodium hydride was added to the reaction. He therefore concluded that the ring nitrogen was participating in an initial neighbouring group displacement (with inversion) of the iodine, forming an *N*-acyl-aziridine, followed by its displacement

(with inversion) by the external azide nucleophile (Scheme 109).



Scheme 109 **(108)**

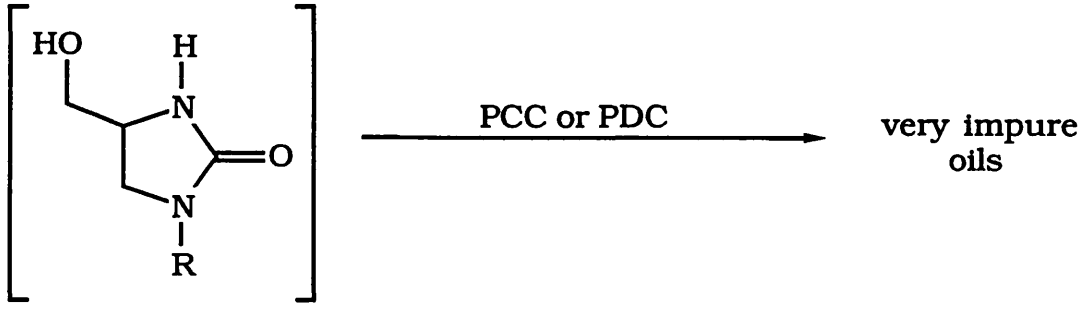
This hypothesis was borne out by the isolation of the intermediate *N*-acyl-aziridine **(108)** using potassium hydroxide base in the absence of an external nucleophile. Within his work he managed to convert the iodomethyl function into an intermediate hydroxymethyl group by means of a silver assisted cleavage of the carbon-iodine bond with water. From there he could either, oxidise the alcohol into the aldehyde **(109)** using PCC, or trap the alcohol as its acetate derivative **(110)** using acetic anhydride.



Scheme 110

This seemed to be the way forward for our compounds and so his conditions were tried on the two chosen imidazolinones. The conversion to the alcohol (**111** or **112**) appeared to go smoothly with the creation of an insoluble silver precipitate, but both the oxidation and the trapping reactions caused problems. The use of PCC as the oxidant gave impure oils as products that were highly contaminated with chromium residues. This was

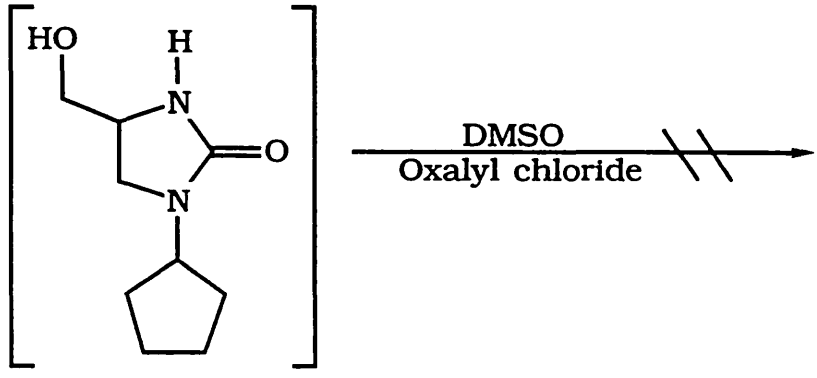
unfortunate as it meant that NMR analysis of the crude material was impossible due to the exceptional relaxation abilities imparted on the ring system by the paramagnetic chromium metal. Many attempts were made to make these chromium reactions work, as they had been reported to work for the lactams, but as before the products were isolated with severe chromium impurities.



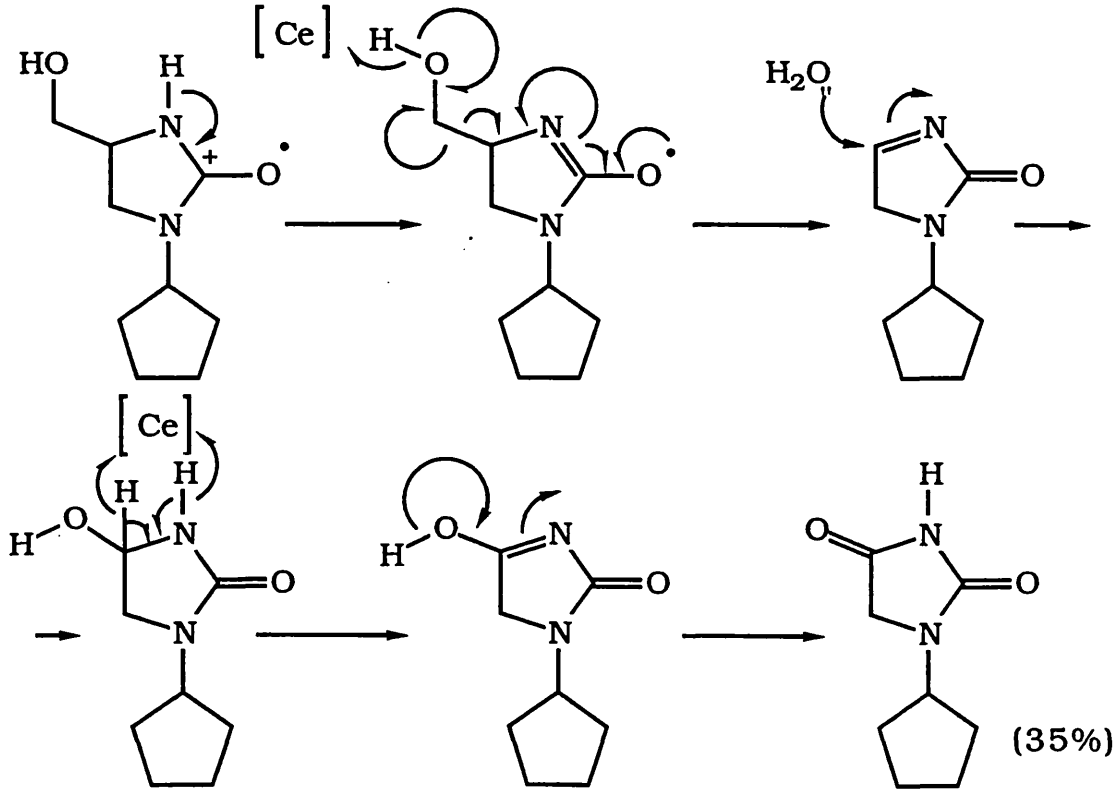
Scheme 111 :- R= Me (**111**) or cyclopentyl (**112**)

A slight change to PDC was tried, using conditions that had been so successful in the oxidation of the norbornyl hydroxyl function (*cf.* Scheme 14) however these reactions also failed. In an attempt to eliminate this chromium contamination some experiments were carried out with the addition of the known competitive complexing system of oxalic acid/sodium oxalate[127] but this did not affect the result. It is hard to explain the quite significant change in the results of these oxidations when compared with Knapp's successes obtained with his closely related lactams, however the extra nitrogen atom present in our systems must be the cause of the increased ability of the chromium to bind to the imidazolinone ring. Several non-chromium based oxidants were therefore used on the crude hydroxymethyl intermediate (**112**) formed using Knapp's conditions. The Swern method of oxidation[128] was tried. This uses oxalyl chloride to modify the reactivity of DMSO and therefore depends upon the nucleophilicity of the hydroxyl group

which is to be oxidised. This too failed with the concomittant destruction of the starting material. The use of manganese dioxide did not oxidise the hydroxyl group.[129] However the starting material was recovered from this reaction, which demonstrates that the starting hydoxymethyl compound **(112)** does have some stability and can survive refluxing chloroform. The crude hydoxymethyl **(112)** compound decomposes if it is left for a couple of weeks at room temperature or during chromatography.



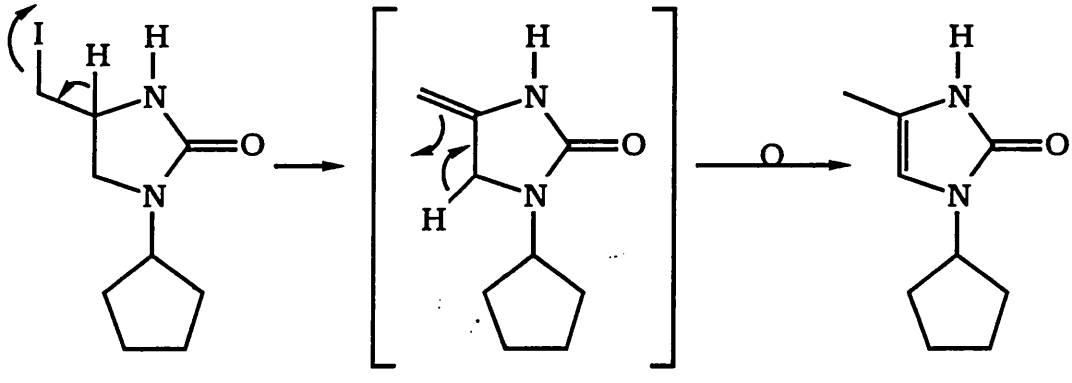
(112) Scheme 112



Scheme 113 **(113)**

The use of ceric ammonium nitrate (CAN), a single electron transfer oxidant, did produce an interesting hydantoin product in one reaction[130] (Scheme 113). The formation of the hydantoin (**113**) most likely followed the radical mechanism shown and is reminiscent of the initial cleavage of the hydroxymethyl group seen within its mass spectrum. The trapping of the alcohol (**111**) as its acetate also proved fruitless when it was tried on the *N*-methylimidazolinone, as the product decomposed upon chromatography.

Once it appeared unlikely that the oxidation of the alcohol would give the desired aldehyde our research shifted to the possibility of using the iodo function to introduce the *endo*-cyclic double bond (*via* an *exo*-cyclic elimination of HI followed by an apparent 1,3 hydrogen shift) and then try functionalising the *exo*-cyclic methyl using allylic oxidation conditions.



(107) **(114)**

Scheme 114 :- Conditions = DBU,THF, reflux, 4 hrs. (75-90%)

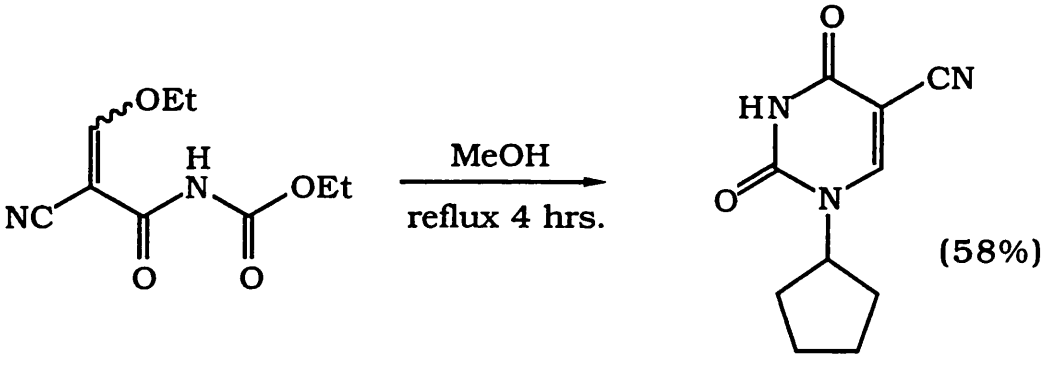
The elimination of the iodo group was accomplished with relative ease using DBU, but the yields of the rearranged methylimidazolinone (**114**) varied due to more or less polymeric byproducts being formed. This is not unusual as Knapp has also reported the ease with which his iodo lactams polymerise under basic conditions.[110] The final position of the double bond is as shown and not in the alternative position between N-3 and C-4. This can be seen in the ^{1}H NMR by the presence, not only of an

N-H resonance at δ = 10.5 ppm, but also by the position of a single hydrogen resonance at δ = 5.8 ppm corresponding to the vinylic hydrogen at C-5.

The use of catalytic SeO_2 with t-butylhydroperoxide[131] did not give any oxidised material, with a similar result being obtained when a t-butanol/$Cr(CO)_6$ oxidising mixture[132] was used (here again the chromium metal may have caused problems). DDQ[133] returned a reduced yield of the starting material whilst the traditional allylic halogenation procedure destroyed the ring system and gave only succinimide derived products. An attempt with CAN was also made but here again no recognisable organic products were recovered.

3.2.4 *Uracil base formation*

As was described in the introduction there were two traditional methods of forming the uracil ring as well as *via* possible oxidation of a six-membered ring formed by our halocyclisations. But, as no successful method for oxidising the iodomethyl group had been found, we returned to the option of building the ring onto an amino group. This procedure was chosen as the proposed product from the central fragment work could have produced a free amino group which would have then been elaborated.



(115) Scheme 115 **(116)**

Following the work of Shaw[98] the cyanourethane (**115**) was easily prepared and reacted with cyclopentyl amine in a model reaction (see Scheme 115). The product 5-cyano-1-cyclopentyl uracil (**116**) was formed in a moderate yield (58%) but, this was still higher than the reported yield for the literature reaction with a furanose sugar.[98a]

3.3 CONCLUSION

The halocyclisation procedure has been shown, by this work, to be an efficient and adaptable route to a variety of alkyl substituted imidazoles and imidazolinones as well as providing a route to tetrahydropyrimidines. The conversion of the iodomethyl function into the oxygenated function was shown to be possible in the imidazolinone systems, however the further oxidation of the hydroxymethyl group was shown to be more complicated in these systems than the literature had suggested.

The attempted allylic oxidations of the *exo*-cyclic methyl group on the pseudo-aromatic imidazolinones, indicate that the reactivity of that methyl group is not analogous to similar oxidations of aryl methyls.

CHAPTER FOUR

Experimental

4.1 GENERAL

Solvents and reagents.

Tetrahydrofuran was dry distilled from potassium benzophenone ketyl and stored under nitrogen or used immediately. Dichloromethane which was to be used as a reaction solvent was distilled from phosphorus pentoxide and used under nitrogen. Triethylamine, pyridine and di-*iso*-propylamine were distilled and stored over potassium hydroxide. Norborn-5-en-2-ol was purchased from Aldrich Chemical Company and was purified before use by dry flash filtration column chromatography (eluant petrol to ether to ethyl acetate). 40°-60°C Petroleum ether and pentane were distilled after purchase and then stored normally.

All remaining reagents and chromatography solvents were used, as purchased, without further purification.

Chromatography.

Analytical t.l.c. was carried out using Merck 0.2 mm silica gel 60 GF_{254} aluminium-backed plates, which were visualised using u.v. light (254 and 360 nm), iodine vapour, and/or molybdenum dip. The molybdenum dip was comprised in the following manner. Ammonium molybdate (5 g) was dissolved in a solution of concentrated sulphuric acid (10 g) in water (75 ml). This solution was allowed to stand overnight or until the dissolution process was complete. Wet flash and dry flash column chromatography was carried out on Merck silica gel 60 H with hand bellows providing a low pressure force for the wet flash technique and a water aspirator providing the suction needed for the dry flash technique.

Characterisation.

Melting points (m.p.) were determined on a Reichert Kofler hot stage apparatus and are uncorrected.

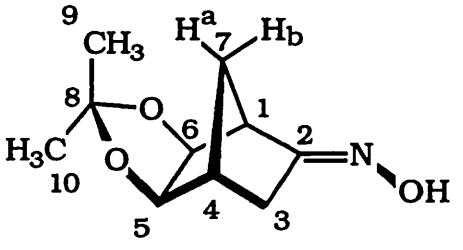
Infrared spectra (υ max.) were recorded on a Perkin-Elmer model 1710 infrared Fouriertransform spectrometer and samples were analysed as thin films, nujol mulls, or in solution as indicated. Proton Fourier transform nuclear magnetic resonance spectra (δ_H) were recorded on either a Bruker WM 250 (250 MHz), or a Jeol GSX 270 (270 MHz) spectrometer. Chemical shifts are reported in parts per million downfield of tetramethylsilane by referencing to tetramethylsilane itself or the residual proton resonances of the solvents as the appropriate internal standard. Coupling constants (J) in Hertz are included where possible. Carbon-13 Fourier transform nuclear magnetic resonance spectra (δ_C) were recorded on either a Bruker WM 250 (250 MHz), or a Jeol GSX 270 (270 MHz) spectrometer and were referenced to the solvent. Variable temperature, n.O.e., and 2D proton spectra were all recorded on the Bruker WM 250 (250 MHz) spectrometer.

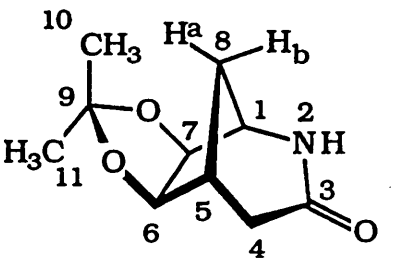
Electron ionisation mass spectra were performed on either A.E.I. MS 12 or VG Micromass 7070 B instruments and run at either 14 or 70 eV source potentials. All accurate mass determinations were performed by the S.E.R.C. mass spectrometry service centre at the chemistry department University of Swansea. Elemental analyses were provided by Imperial College microanalytical department and all X-ray crystal structure determinations were performed by Dr. D.J.Williams or Ms. A. M. Z. Slawin within the c rystalography department at Imperial College.

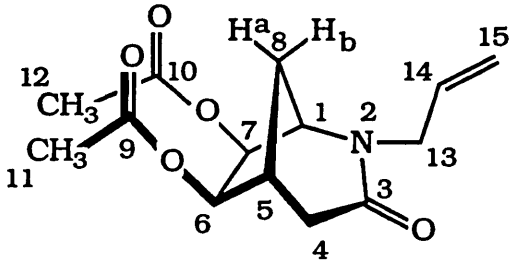
Structures

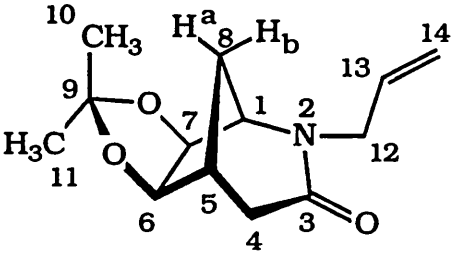
Throughout the following experimental the compound numbering system shown overleaf, has been used. The denotation 'a' or 'b' within the coupling constants refers to the hydrogens attached to the numbered centre specified. The abbreviation 't.s.', used within the coupling constants for the allyl containing molecules, is used to indicate a 'through space' coupling between the hydrogens on the terminus of the double

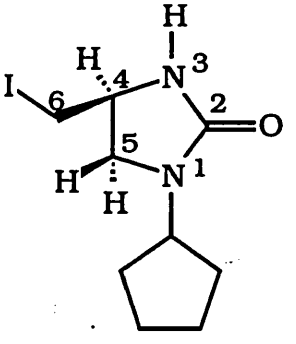
bond and the methylene hydrogens β to them (e.g. between 15-H and 13-H in the O-acyl,N-allyl example shown below).











4.2 ABBREVIATIONS

THF	Tetrahydrofuran
DCM	Dichloromethane
BOC	*tert*-butoxycarbonyl
EtOAc	Ethyl acetate
TMSOTf	Trimethylsilyltrifluoromethanesulphonate
TMSNCO	Trimethylsilylisocyanate
DIBAL	Di-*iso*-butylaluminium hydride
NBS	*N*-Bromosuccinimde

NIS	*N*-Iodosuccinimde
Pd	Palladium
CAN	Ceric ammonium nitrate
DMSO	Dimethylsulphoxide
PCC	Pyridinium chlorochromate
PDC	Pyridinium dichromate
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DDQ	Dichlorodicyanoquinone
ara-A	9-β-arabinofuranosyladenine
C-ara-A	Carbocyclic analogue of ara-A
MIC_{50}	Minimum inhibitory concentration for 50% inhibition
HSV	Herpes simplex virus
NMR	Nuclear magnetic resonance
KHMDS	Potassium hexamethyldisilylazide
LDA	Lithium di-*iso*-propylamine

4.3 EXPERIMENTAL

5-exo,6-exo-(*Isopropylidenedioxy*)*bicyclo*[2.2.1]*heptan*-2-*ol* (**35**).–To norborn-5-en-2-ol (**33**) (24 g, 0.218 mol) and trimethylamine N-oxide (33 g, 0.297 mol) in freshly distilled *tert*-butyl alcohol (440 ml), water (132 ml), and pyridine (17.4 ml) was added a freshly prepared solution of osmium tetroxide in *tert*-butyl alcohol (0.5% w/v; 17.4 ml, 87 mg). The solution was refluxed for 3 hours and then cooled, 20% aq. sodium metabisulphite (174 ml) was added dropwise quickly, followed by 2M-HCl (250 ml), and the *tert*-butyl alcohol was removed under reduced pressure. Acetone (200 ml) was then added, the mixture stirred for 1 hour and the acetone was removed. Ethyl acetate (100 ml) was added and both layers were filtered through Celite. The aqueous layer was continuously extracted for 3 days before the combined ethyl acetate layers were dried ($MgSO_4$) and the solvent removed to give a brown viscous oil. (On one occasion a colourless solid was isolable which was the pure triol (**34**), although on most occasions an oily product, a mixture of protected and unprotected alcohols, was obtained). This oil was taken up in a mixture of acetone (400 ml) and 2,2-dimethoxypropane (75 ml) with freshly activated Dowex 50-X200 cation exchange resin (5 g) and stirred at room temperature for 4 hours. After this time the solution was filtered, concentrated and taken up in ether (350 ml), washed successively with water (50 ml), and saturated aq. sodium hydrogen carbonate (50 ml). The ether layer was dried ($MgSO_4$) and the solvent removed to give a pale brown viscous oil (31.9 g, 80%) which comprised of the two alcohol isomers. The spectral data for this mixture was consistent with a combination of the literature data[42] for the individual isomers. b.p. 107°C at 0.3 mmHg, (Found: C, 65.2; H, 8.9. $C_{10}H_{16}O_3$ Calc. for C, 65.2; H, 8.7%); $\upsilon_{max.}$ (neat) 3 425 (OH), 1 384 and 1 375 (-$C(Me)_2$, –CH def.), 1 270, 1 207, 1 163, 1 049,

886, and 852 cm^{-1}; δ_H (250 MHz; $(CD_3)_2CO$) 0.7 (1 H, dt, H-3, J_{3ab} 13.1 Hz, J 3.7 Hz), 1.1-1.6 (3 H, m), 1.2 (3 H, s, Me-acetonide), 1.35 (3 H, s, Me-acetonide), 1.9 (1 H, ddd, 3-H, J 5.6 Hz, J 10.3 Hz, J_{3ab} 13.1 Hz), 2.2 (1 H, m), 2.9 (2 H, br d), 4.05 and 4.6 (2 H, br d, 5-H and 6-H, $J_{5,6}$ 5.6 Hz); *m/z* 184 (M^+, 0.1%), 169 (100, M^+ - Me), 109 (56), 82 (41), 81 (45), and 59 (42).

5-exo,6-exo-(*Dihydroxy*)-*bicyclo*[2.2.1]*heptan*-2-*ol* (**34**).- The *title compound* was isolated, as an intermediate from the above formation of the acetonide protected alcohol (**35**), m.p. 120°C (dec.), (Found: C, 58.1; H, 8.3. $C_7H_{12}O_3$ requires C, 58.3; H, 8.4%); $\upsilon_{max.}$ (Nujol) 3 355 (OH), 1 743, and 1 670 cm^{-1}; δ_H (270 MHz; $(CD_3)_2CO$) 0.7 (1 H, dt, 3-H, J_{3ab} 13.1 Hz, J 3.4 Hz), 1.1 (1 H, dt, J 10.3 Hz, J 1.5 Hz), 1.7 (1 H, dt, J 10.5 Hz, J 1.4 Hz), 1.85 (1 H, ddd, J 12.9 Hz, J 10.3 Hz, J 5.4 Hz), 1.97 (1 H, br d, J 4.6 Hz), 2.1 (1 H, m), 2.9 (1 H, br s, OH), 3.65 (1 H, br s), 3.8 (1 H, br s), 4.1 (2 H, br d), and 4.3 (1 H, br s); *m/z* 126 ($M^+ - H_2O$, 1%), 108 (3, $M^+ - 2(H_2O)$), 100 (3, [126] - C_2H_2), 97 (2), 95 (2), 82 (19, [126] - MeCHO), 41 (24), 39 (42), 31 (46), 29 (69), and 27 (100).

5-exo,6-exo-(*Isopropylidenedioxy*)*bicyclo*[2.2.1]*heptan*-2-*one* (**36**).-To a slurry of pyridinium dichromate (PDC) (63.7 g, 0.172 mol), silica gel (Kieselgel 60, 70-230 mesh, 127.3 g) and pyridinium trifluoroacetate (2.787 g, 14 mmol) in DCM (275 ml) was added a solution of the two alcohol isomers (**35**) (12.56 g, 0.068 mol) in DCM (104 ml). This mixture was stirred, under nitrogen, for 88 hours at room temperature before being diluted with ether (325 ml) and filtered through Celite. The solid was washed with ether (325 ml) and the combined ether solvent was removed under reduced pressure to give an off-white solid. This crude product was recrystallised from boiling pentane to give an initial crop of the title compound (9.6g, 77%) as colourless

crystals. The mother liquor was concentrated and after another recrystallisation gave a second crop of the title compound (1.43g, 12%) (total yield 11.03g, 89%). The spectral data obtained for this solid matched well that recorded within the literature.[42] m.p. 80°C, (Lit.,[42] 74-75°C) $\upsilon_{max.}$ ($CHCl_3$) 1 758 (CO), 1 458, 1 410, 1 383 and 1 375 (-$C(Me)_2$, –CH def.), 1 270, 1 208, 1 163, 1 133, 1 096, 1 056, 1 007, 959, and 866 cm^{-1}; δ_H (270 MHz; $CDCl_3$), 1.29 (3 H, s, Me-acetonide), 1.45 (3 H, s, Me-acetonide), 1.6-1.7 (2 H, m), 2.0-2.15 (2 H, m), 2.6-2.8 (2 H, m), 4.25 (1 H, d, 5-H or 6-H, $J_{5,6}$ 4.9 Hz), and 4.30 (1 H, d, 5-H or 6-H, $J_{5,6}$ 4.9 Hz); *m/z* 182 (M^+, 1%), 167 (100, M^+ – Me), 125 (47), 107 (41), 95 (39), 82 (38), 79 (63), 59 (53), and 43 (98).

5-exo,6-exo-(*Isopropylidenedioxy*)*bicyclo*[2.2.1]*heptan*-2-*oxime* (**37**).–The bicyclo-ketone (**36**) (0.1414 g, 0.777 mmol) was disolved in methanol (0.2 ml) and aqueous solutions (0.2 ml each) of sodium acetate (0.1019 g, 1.24 mmol) and hydroxylamine hydrochloride (0.1019 g, 1.47 mmol) were also prepared. The three solutions were mixed together and the resultant solution was stirred overnight. The mixture was then diluted with water, extracted with ether (3 x 15 ml) and the combined ether layers were washed with a saturated aqueous sodium carbonate solution (20 ml). The ether layer was dried ($MgSO_4$) and evaporated to give the *title compound* (0.1246 g, 98%) as a clear colourless oil which became solid after an extended period under high vacuum, m.p. 118-120°C. The isomeric mixture of oximes produced by this method were separated by recrystallisation of the solid mixture, from cyclohexane, which gave the pure *trans*- isomer (**45**) in the first crop. Repeated recrystallisations managed to extract all of the *trans* form and enable the *cis* form (**46**) to crystallise out, m.p. (*trans*) 148°C, (*cis*) 111-113°C. The melting point for the *cis*- isomer is not as accurate as the *trans* - isomer as the *cis*-form actually began to sublime at the quoted temperature and

condensed back as the *trans-* isomer which then proceeded to melt at its melting point. This then provides an easy and efficient route for the conversion of the *cis-* isomer into the *trans-* isomer. (Found: C, 61.2; H, 7.7; N, 7.1. $C_{10}H_{15}NO_3$ requires C, 60.9; H, 7.7; N, 7.1%); $\upsilon_{max.}$ ($CHCl_3$) 3 600, 3 294 (OH), 1 383 and 1 374 (-$C(Me)_2$, –CH def.), 1 270, 1 209, and 1 058 cm^{-1}; δ_H (270 MHz; $CDCl_3$) 1.3 (3 H, s, Me-acetonide), 1.4 (1 H, dt, 7b-H, J_{7ab} 10.3 Hz, J 1.2 Hz), 1.47 (3 H, s, Me-acetonide), 1.95 (1 H, m, 7a-H, J_{7ab} 10.3 Hz), 2.0 (1 H, d, 3_{exo}-H, J_{3ba} 18.3 Hz), 2.3 (1 H, dd, 3_{endo}-H, J_{3ab} 18.3 Hz, $J_{3endo,4}$ 4.9 Hz), 2.5 (1 H, d, 4-H, $J_{4,3endo}$ 4.9 Hz), 2.92 (1 H, s, 1-H), and 4.2 (2 H, dd, 5-H and 6-H, $J_{5,6}$ 5.4 Hz); *m/z* 197 (M^+, 1%), 182 (46, M^+ - Me), 166 (80), 152 (34), 106 (59), 94 (54), 79 (65), and 59 (100). X-Ray data is available for the *trans-* isomer; the n.m.r spectrum for the *cis-* isomer was identical to the *trans-* isomer.

5-exo,6-exo-(*Isopropylidenedioxy*)*bicyclo*[2.2.1]*heptan*-2-*oxime, methyl ether* (**38**).–In a three-necked flask fitted with a nitrogen inlet, a bubbler, and a subaseal, sodium hydride (50% dispersion, total mass 210 mg, 2.2 mmol) was placed and washed with 40-60°C petrol. The oxime (**37**) (393 mg, 2 mmol) was dissolved in DMF (5 ml) and this solution was added to the flask of sodium hydride under nitrogen. This mixture was stirred for 25 minutes before methyl iodide (0.14 ml, 2.2 mmol) was added *via* a syringe. Stirring was continued for a further 35 minutes before the reaction was poured onto ice (15 g) and extracted with ether (3 x 30 ml). These extracts were dried ($MgSO_4$), filtered, and evaporated to give the *title compound* as an oil (211 mg, 50%), b.p. 85°C at 20mmHg, (Found M^+, 211.1208. $C_{11}H_{17}NO_3$ requires M, 211.1208); $\upsilon_{max.}$ (neat) 2 988 and 2 939 (CH def.), 1 462, 1 385 and 1 374 ($C(Me)_2$ – CH def.), 1 271, 1 208, 1 163, 1 047, 886, and 849 cm^{-1}; δ_H (270 MHz; $CDCl_3$) 1.2 (3 H, s, Me-acetonide), 1.3 (1 H, dt, 7a-H, J_{7ab} 10 Hz, J 1.7 Hz), 1.4 (3 H, s, Me-acetonide), 1.75-1.85 (1 H, dd, 3_{exo}-H, J_{3ba} 18.3 Hz, J 4 Hz),

1.85-1.92 (1 H, m, 7b-H, J_{7ab} 10 Hz, J 1.7 Hz), 2.15 (1 H, dd, 3_{endo}-H, J_{3ab} 18.3 Hz, $J_{3endo,4}$ 5.0 Hz), 2.4 (1 H, d, 4-H, $J_{4,3endo}$ 5.0 Hz), 2.8 (1 H, br s, 1-H), 3.75 (3 H, s, C=N-O-*Me*), and 4.2 (2 H, dd, 5-H and 6-H, $J_{5,6}$ 5.4 Hz); *m/z* 211 (M^+, 8%), 196 (78, M^+ - Me), 167 (23), 153 (19), 124 (100), 92 (68), 81 (73), and 66 (69).

Norcamphoroxime (**39**).–Norcamphor (**41**) (5.5 g, 0.05 mole) was disolved in methanol (20 ml) and aqueous solutions (20 ml each) of sodium acetate (6.55 g, 0.08 mole) and hydroxylamine hydrochloride (6.6 g, 0.1 mole) were also prepared. The three solutions were mixed together and the resultant solution was stirred overnight. The mixture was then diluted with water, extracted with ether (3 x 45 ml) and the combined ether layers were in turn washed with a saturated sodium carbonate solution (20 ml). The ether layer was dried ($MgSO_4$) and evaporated to give the title compound (6.06 g, 97%) as a colourless solid m.p. 50-51°C. (Found: M^+ 125.0841. $C_7H_{11}NO$ requires *M*, 125.0841); $\upsilon_{max.}$ (Nujol) 3 128 (OH), 1 690 (C=N), 1 466, and 955 cm^{-1}; δ_H (270 MHz; $CDCl_3$), 1.2-1.5 (4 H, m), 1.55-1.8 (2 H, m), 2.1 (1 H, dd, J 17.1 Hz, and 3.4 Hz), 2.3 (1 H, J 17.6 Hz, 3.9 Hz, and 2.0 Hz), 2.5 (1 H, br s), 2.85 (1 H, br s), and 9.2 (1 H, br s, O-*H*); *m/z* 125 (M^+, 90%), 108 (40), 96 (35), 93 (22), 80 (35), 67 (100), and 59 (73).

2-*aza*/3-*azabicyclo*[3.2.1]*octyllactams* (**40**)(**42**).–[Sulphuric Acid route]-Norcamphor oxime (**39**) (1 g, 8 mmol) was placed in a round bottomed flask (50 ml) and had 85% concentrated sulphuric acid (10 ml) poured directly, slowly, onto it. After a short induction period of approximately 10 seconds, vigorous effervesence was observed and the colourless, solid, starting material was rapidly turned into a black viscous oil. This oil was diluted with distilled water (10 ml) and neutralised with a 24%

aqueous solution of potassium hydroxide. The precipitate was removed by filtration, washed with chloroform (2 x 25 ml) and combined with the chloroform extracts (5 x 30 ml) of the aqueous phase. These extracts were washed once with distilled water (30 ml), dried (Na_2SO_4), filtered and the solvent removed under reduced pressure. The oily residue was distilled to give the title compounds (0.449 g, 45%) as a pale oil mixture which proved inseparable, b.p. 150°C at 20mmHg, (Found: M^+, 125.0841. $C_7H_{11}NO$ requires 125.0841); $\upsilon_{max.}$ (neat) 3 226 (NH), 1 667 (CO), 1 496, 1 346, 1 294, and 1 135 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 1.5-2.1 (6 H, m), 2.15-2.7 (3 H, m), 3.8 (1 H, br d, J 4.4 Hz), and 7.0 (1 H, br s, N*H*); *m/z* 125 (*M*$^+$, 50%), 96 (100, *M*$^+$ – HCO), 82 (10), 67 (29), 54 (12), and 41 (20).

2-*aza*/3-*azabicyclo*[3.2.1]*octyllactams* (**40**)/(**42**).– [Sodium hydroxide/Tosyl chloride route]-Norcamphor oxime (**39**) (1 g, 8 mmol) was taken up into a 5N sodium hydroxide solution (11 ml) and, with stirring, the tosyl chloride (1.66 g, 8.7 mmol) was added to it. This slow addition took 20 minutes and a further 1 hour was allowed for the reaction. After this time the solution was extracted with chloroform (5 x 35 ml), dried (Na_2SO_4), filtered, and the solvent removed under reduced pressure. The oily residue was distilled and gave the *title compounds* as a pale oil mixture (0.213 g, 21%, b.p. 150°C at 20mmHg).

6-exo,7-exo-(*Isopropylidenedioxy*)-2-*azabicyclo*[3.2.1]-*heptan*-3-*one* (**43**).–The *trans*-geometric isomer of the bicyclo-oxime (**45**) (307 mg, 1.56 mmol) was dissolved in acetonitrile (25 ml). Triethylamine (242 µl, 1.74 mmol) was added to this solution, followed by methanesulphonyl chloride (129 µl, 1.66 mmol). This mixture was heated and stirred at 78°C for 21 hours whereupon the solution was allowed to cool and the solvent removed under reduced pressure. The yellow/brown residue was preabsorbed onto silica gel and columned directly using the dry

flash technique, (eluant 40-60°C petrol to ether to ethyl acetate) to give the *title compound* (221 mg, 73%) as a colourless solid. Recrystallisation was possible from the column eluant (ether:ethyl acetate), m.p. 164-166°C (possible phase change at 130°C), (Found: C, 60.8; H, 7.7; N, 6.9. $C_{10}H_{15}NO_3$ requires C, 60.9; H, 7.7; N, 7.1%); $\upsilon_{max.}$ (CCl_4) 3 201 (NH), 1 669 (CO), 1 383 and 1 374 ($C(Me)_2$ - CH def.), and 1 209 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 1.28 (3 H, s, Me-acetonide), 1.42 (3 H, s, Me-acetonide), 1.65 (1 H, d, 8b-H, J_{8ab} 12.5 Hz), 2.13 (1 H, m, 8a-H, J_{8ab} 12.5 Hz, J 1.5 Hz), 2.25 (1 H, d, 4_{endo}-H, J_{4ab} 17.5 Hz), 2.41 (1 H, t, 5-H, $J_{5,4exo}$ 5 Hz), 2.57 (1 H, dd, 4_{exo}-H, J_{4ab} 17.5 Hz, $J_{5,4exo}$ 6 Hz), 3.56 (1 H, t, 1-H, J 5 Hz), 4.50 (2 H, ddd, 6-H and 7-H, $J_{8b,(6\ or\ 7)}$ 1.5 Hz, $J_{6,7}$ 6 Hz), 6.42 (1 H, br s, NH); δ_C (250 MHz; $CDCl_3$) 23.77 (Me-acetonide), 25.63 (Me-acetonide), 29.21 (8-C), 36.22 (4-C), 37.54 (5-C), 55.09 (1-C), 83.99 (6-C or 7-C), 84.88 (6-C or 7-C), 110.22 (9-C), and 170.91 (3-C); Spin-echo ^{13}C and 2D-^1H spectra were also taken; *m/z* 197 (M^+, 19%), 182 (100, M^+ - Me), 138 (58, $[182]^+$–MeCHO), 122 (29, $[182]^+$–CH_3CO_2H), 101 (87), 96 (59), and 43 (54, $[MeCO]^+$).

6-exo,7-exo-(*Isopropylidenedioxy*)-2-*azabicyclo*[3.2.1]-(N-*methyl*)*octyllactam* (**44**).–In a three-necked flask fitted with a nitrogen inlet, a bubbler, and a subaseal, sodium hydride (50% dispersion, total mass 14 mg, 0.29 mmol) was placed, washed with 40-60°C petrol and dried by the nitrogen flow. The lactam (**43**) (52.6 mg, 0.27 mmol) was dissolved in DMF (5 ml) and this solution was added to the flask of sodium hydride under nitrogen. This mixture was stirred for 1 hour before methyl iodide (18 µl, 0.29 mmol) was added *via* a syringe. Stirring was continued for a further 30 minutes before the reaction was poured onto ice (~3 g) and extracted with ether (3 x 15 ml). These extracts were dried ($MgSO_4$), filtered, and evaporated to give the title compound (31 mg, 55%) as an oil, b.p. 110°C at 20mmHg. $\upsilon_{max.}$ (CCl_4) 1 661 (CO), 1 397, 1 383 and 1 374 ($C(Me)_2$ - CH def.), 1 267, 1 209, 1

075, 1 047, 894, and 861 cm^{-1} ; δ_H (250 MHz; $CDCl_3$) 1.26 (3 H, s, Me-acetonide), 1.40 (3 H, s, Me-acetonide), 1.68 (1 H, d, 8a-H, J_{8ab} 12.5 Hz), 2.10 (1 H, m, 8b-H, J_{8ab} 12.5 Hz), 2.21 (1 H, d, 4_{endo}-H, J_{4ab} 18 Hz), 2.40 (1 H, t, 5-H, $J_{5,4exo}$ 5 Hz), 2.55 (1 H, dd, 4_{exo}-H, J_{4ab} 18 Hz, $J_{4exo,5}$ 6 Hz), 2.92 (3 H, s, N-*Me*), 3.44 (1 H, m, 1-H), and 4.44 (2 H, m, 6-H and 7-H); *m/z* 211 (M^+, 41%), 196 (28, M^+ – Me), 152 (74), 111 (100), 110 (76), 101 (46), 97 (41), and 57 (52).

6-exo,7-exo-(*Isopropylidenedioxy*)-2-*azabicyclo*[3.2.1]-(N-*allyl*)*octyllactam* (**49**).–In a three-necked flask fitted with a nitrogen inlet, a bubbler, and a subaseal, sodium hydride (50% dispersion, total mass 100 mg, 1.1 mmol) was placed, washed with 40-60°C petrol and dried by the nitrogen flow. The lactam (**43**) (374 mg, 1.9 mmol) was dissolved in DMF (20 ml) and this solution was added to the flask of sodium hydride under nitrogen. This mixture was stirred for 50 minutes before allyl bromide (0.18 ml, 1.1 mmol) was added *via* a syringe. Stirring was continued for a further 100 minutes before the reaction was poured onto ice (15 g) and extracted with EtOAc (3 x 25 ml). These extracts were dried ($MgSO_4$), filtered, and evaporated to give the crude product as an oil which, was purified by wet flash column chromatography (eluant petrol to ether to ethyl acetate) to give the *title compound* (317 mg, 71%) as a solid, m.p. 54-55°C. (Found: C, 65.6; H, 8.2; N, 5.9. $C_{13}H_{19}NO_3$ requires C, 65.8; H, 8.1; N, 5.9%); $\upsilon_{max.}$ (CCl_4) 1 662 cm^{-1} (CO); δ_H (250 MHz; $CDCl_3$) 1.28 (3 H, s, Me-acetonide), 1.42 (3 H, s, Me-acetonide), 1.64 (1 H, d, 8b-H, J_{8ab} 12.5 Hz), 2.14 (1 H, m, 8a-H, J_{8ab} 12.5 Hz), 2.25 (1 H, d, 4_{endo}-H, J_{4ab} 18.7 Hz), 2.41 (1 H, t, 5-H, $J_{4a,5}$ 5 Hz), 2.6 (1 H, dd, 4_{exo}-H, $J_{4a,5}$ 5 Hz, J_{4ab} 18.7 Hz), 3.5-3.62 (2 H, dd and br s, 1-H and 12a-H, J 6.3 Hz, J 15 Hz), 4.3-4.5 (3 H, dd and br s, 12b-H, 6-H and 7-H, $J_{6,7}$ 5 Hz), 5.1-5.2 (2 H, m, 14-H), and 5.73 (1 H, m, 13-H); *m/z* 237 (M^+, 73%), 222 (23%, M^+ –

Me), 178 (41, [222] – MeCHO), 137 (75, [178] – allyl), 136 (55, [178] – CH_2CCH_2 + H), 101 (44), 68 (26), and 41 (100, [allyl]$^+$).

6-exo,7-exo-(*Isopropylidenedioxy*)-2-*azabicyclo*[3.2.1.]-(N-*tert-butoxycarbonyl*)*octyllactam* (**50**).–In a three-necked flask fitted with a nitrogen inlet, bubbler, and subaseal, was placed a magnetic stirrer and sodium hydride (50% dispersion, 93 mg total mass, 1.1 equiv.). The sodium hydride was washed with petrol (40-60°C range) and dried by the nitrogen flow. The lactam precursor (**43**) (277 mg, 1.41 mmol) was dissolved in DMF (30 ml) and added, *via* a syringe, to the hydride. This mixture was stirred at room temperature for 35 minutes before a solution of BOC anhydride (1.5343 g, 5 equiv.) in DMF (5 ml) was added to it, again *via* a syringe. The reaction was allowed to proceed for a further 35 minutes and then stopped by pouring the mixture onto ice (15 g). The resulting aqueous solution was extracted with EtOAc (5 x 40 ml) and the extracts were dried ($MgSO_4$), filtered and finally the solvent was removed under reduced pressure. This gave an oily residue impure with DMF which was removed using a higher vacuum. The residue from this was purified using dry flash column chromatography (eluant petrol to ether) to give the *title compound* (323 mg, 75%) as a colourless solid, m.p. 118°C dec. (Found: C, 60.3; H, 7.8; N, 4.7. $C_{15}H_{23}NO_5$ requires C, 60.6; H, 7.8; N,4.7%); $\upsilon_{max.}$ ($CHCl_3$) 1 769 and 1 719 (CO), 1 151, 1 385 and 1 372 cm^{-1} ($C(Me)_2$ – CH def.); δ_H (250 MHz; $CDCl_3$) 1.30 (3 H, s, Me-acetonide), 1.45 (3 H, s, Me-acetonide), 1.55 (9 H, s, BOC), 1.68 (1 H, d, 8b-H, J_{8ab} 12.5 Hz), 2.2 (1 H, m, 8a-H, J_{8ab} 12.5 Hz), 2.4 (2 H, m, 5-H and 4_{endo}-H), 2.7 (1 H, dd, 4_{exo}-H, $J_{4a,5}$ 6 Hz, J_{4ab} 18.5 Hz), and 4.5 (3 H, dd, 1-H, 6-H and 7-H, $J_{6,7}$ 4.7 Hz, $J_{8b,6}$ 1.5 Hz); *m/z* 282 (M^+ – Me, 24%), 241 (23), 182 (63, [282] – BOC), 138 (35, [182] – CH_2CO), 122 (19, [182] – CH_3CO_2H), 101 (48), 96 (34), and 57 (100, [^{t}Butyl]$^+$).

6-exo,7-exo-(*Isopropylidenedioxy*)*bicyclo*[3.2.1]-2-*aza*-(N-

allyl)-4-(*deutero*)*octyllactam* (**51**).–Di-*iso*-propylamine (32.6 µl, 1.1 equiv.) was dissolved in dry THF (2 ml) under nitrogen and cooled to 0°C. To it was added *n*-butyl lithium (0.15 ml, 1.6 M solution in hexane, 1.1 equiv.) and the mixture was stirred for 5 minutes at 0°C before being cooled to -78°C. The allyl lactam (**49**) (50.5 mg, 0.213 mmol) was dissolved in freshly distilled, dry THF (2 ml) and then added to the LDA solution at -78°C. This was allowed to stir for 1 hour before a solution of D_2O (0.1 ml) in THF (0.75 ml) was added and the mixture stirred for a further 20 minutes. The solvent was removed under reduced pressure and the title compound was isolated in a crude form as a yellow solid. δ_H (250 MHz; $CDCl_3$) 1.28 (3 H, s, Me-acetonide), 1.42 (3 H, s, Me-acetonide), 1.64 (1 H, d, 8b-H, J_{8ab} 12.5 Hz), 2.14 (1 H, dt, 8a-H, J_{8ab} 12.5 Hz, J 4.7 Hz), 2.25 (0.6 H, d, 4_{endo}-H, J_{4ab} 18.7 Hz), 2.41 (1 H, br d, 5-H, $J_{4a,5}$ 4.7 Hz), 2.6 (0.4 H, m, 4_{exo}-H, $J_{4a,5}$ 4.7 Hz, J_{4ab} 18.7 Hz), 3.5-3.62 (2 H, dd and br s, 1-H and 12a-H, J 6.3 Hz, J 15 Hz), 4.3-4.5 (3 H, dd and br s, 12b-H, 6-H and 7-H, $J_{6,7}$ 5 Hz), 5.1-5.2 (2 H, m, 14-H), and 5.73 (1 H, m, 13-H); *m/z* 238 (M^+, 50%), 223 (28, M^+ – Me), 179 (39, [222] – MeCHO), 138 (85, [178] – allyl), 137 (54, [178] – CH_2CCH_2 + H), 101 (67), and 41 (100, $[allyl]^+$).

Attempted hydrolysis of the BOC-protected lactam (**50**).–The BOC-protected lactam (**50**) (92.7 mg, 3.02 mmol) was dissolved in analytical grade methanol (10 ml) and commercial sodium methoxide (37 mg, 2.2 equiv.) was added to it. The mixture was refluxed for 165 hrs. after which time the solvent was removed under reduced pressure to give a buff coloured solid. The solid was columned using the dry flash technique and produced a colourless solid corresponding to the deprotected lactam (**43**) (51.2 mg, 86%).

Attempted hydroxylation of the N-BOC lactam (**50**) *using*

MoOPh (**54**).–The BOC-protected lactam (**50**) (102 mg, 0.3322 mmol) was dissolved in THF and cooled to -47°C before a commercial 0.5M solution of KHMDS in toluene (1 ml, 1.5 equiv.) was added *via* syringe. After stirring the solution for 25 minutes oxodiperoxymolybdenum(pyridine)hexamethylphosphoramide (MoOPh, 216.4 mg, 1.5 equiv.) was added, in one portion, *via* a solid addition tube fitted to the flask. This resulted in the originally yellow solution turning green and then a blue/green colour. The reaction proceeded until all of the solid MoOPh had dissolved and then a saturated aqueous solution of sodium sulphate (6 ml) was added. The reaction mixture turned a paler blue colour and was brought to room temperature. The resulting two-layer system was separated and the blue aqueous layer was extracted with ether (3 x 30 ml). The organic layers were combined, dried ($MgSO_4$), filtered and the solvent removed to give a colourless solid corresponding to the starting material (91 mg, 90% recovery).

4-*Dichloro*-6-exo,7-exo-(*isopropylidenedioxy*)-(N-*tert-butoxycarbonyl*)-2-*azabicyclo*[3.2.1]*heptan*-3-*one* (**56**).–The *N*-BOC lactam (**50**) (152 mg, 0.512 mmol) was dissolved in a solution of THF (20 ml) and cooled to -30°C before the solution of KHMDS (1.13 ml, 0.5M solution in toluene, 0.55 mmol, 1.1 equiv.) was added. This mixture was allowed to warm to -5°C and then recooled to -59°C before a solution of hexachloroethane (133 mg, 0.55 mmol), in THF (10 ml) was added to it. After a further 20 minutes stirring the solution was brought to room temperature, diluted with a small amount of water (10 ml) and extracted with EtOAc (3 x 30 ml). These extracts were dried ($MgSO_4$), filtered, and the solvent was removed to give a yellow oil. This oil was purified by wet flash column chromatography (eluant petrol to ether to EtOAc) to give the *title compound* (74 mg, 72%) as a colourless solid, m.p. 130°C (dec.) with a small amount of deprotected lactam. (Found: $M^+ - CH_3$, 350.0542. $C_{14}H_{18}Cl_2NO_5$

requires 350.0542); $\upsilon_{max.}$ (CCl_4) 1 790, 1 741 (CO), 1 384 and 1 372 ($C(Me)_2$ – CH def.), 1 281, 1 146, 1 081, 1 047, and 871 cm^{-1}; δ_H (270 MHz; $CDCl_3$) 1.30 (3 H, s, Me-acetonide), 1.45 (3 H, s, Me-acetonide), 1.53 (9 H, s, BOC), 2.28 (1 H, ddd, 8a-H, J_{8ab} 13.6 Hz, $J_{8a,1}$ 4.2 Hz, $J_{8a,5}$ 4.6 Hz), 2.39 (1 H, br d, 8b-H), 3.11 (1 H, dd, 5-H, $J_{8a,5}$ 4.6 Hz, $J_{1,5}$ 1.9 Hz), 4.44 (1 H, dd, 1-H, $J_{8a,1}$ 4.2 Hz, $J_{1,5}$ 1.9 Hz), and 4.48 - 4.92 (2 H, dd, 6-H and 7-H, $J_{6,7}$ 5.6 Hz, $J_{8b,6}$ 1.5 Hz); *m/z* 350 (M^+ – Me, 8%), 250 (15, [350] – BOC), 216 (4, [250] – Cl + H), 172 (4, [216] – CH_3CHO), 130 (13, [172] – HNCO + H), 81 (18), and 57 (100, $[^tButyl]^+$).

Methylation of the BOC protected lactam (**50**) with the formation of :-4-exo-*Methyl*-6-exo,7-exo-(*isopropylidenedioxy*)-(N-*tert-butoxycarbonyl*)-2-*azabicyclo*[3.2.1]*heptan*-3-*one* (**57**), and 4-*Dimethyl*-6-exo,7-exo-(*isopropylidenedioxy*)-(N-*tert-butoxycarbonyl*)-2-*azabicyclo*[3.2.1]*heptan*-3-*one* (**58**).–The BOC protected lactam (**50**) (97.4 mg, 0.317 mmol) was dissolved in freshly distilled THF (10 ml) and this solution was cooled to -78°C. At that temperature, a solution of KHMDS (0.7 ml, 0.5M solution in toluene, 1.1 equiv.) was added to it and the mixture was stirred for 30 minutes. After this time, methyl iodide (59.3 µl, 3 equiv.) was added and the solution was allowed to reach room temperature. The solution was diluted with distilled water (10 ml) and extracted with EtOAc (5 x 20 ml); these organic layers were combined, dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure. The yellow oily residue was purified by dry flash column chromatography (eluant petrol to ether) and gave a small amount of starting material (7.3 mg, 9% recovery), and the *title compounds* as colourless solids.
4-exo-*Methyl*-6-exo,7-exo-(*isopropylidenedioxy*)-(N-*tert-butoxycarbonyl*)-2-*azabicyclo*[3.2.1]*heptan*-3-*one* (**57**) (20.9 mg, 21%), m.p. 114-115°C dec. (Found: $M^+–CH_3$, 296.1498, $C_{15}H_{22}NO_5$ requires $M–CH_3$ 296.1498); $\upsilon_{max.}$ (CCl_4) 1 776 (BOC

C=O), 1 723 (lactam CO), 1 383 and 1 371 ($C(Me)_2$ - CH def.), 1 289, 1 268, 1 241, 1 214, 1 158, 1 122, 1 075, 1 049, 1 008, 945, 893, and 859 cm^{-1}; δ_H (270 MHz; $CDCl_3$) 1.28 (3 H, s, Me-acetonide), 1.32 (3 H, d, 4_{exo}-Me, J_{4ab} 7.6 Hz), 1.45 (3 H, s, Me-acetonide), 1.5 (9 H, s, BOC), 1.7 (1 H, d, 8b-H, J_{8ab} 12.9 Hz), 2.05 (1 H, dtd, 8a-H, J_{8ab} 12.9 Hz, J 4.6 Hz, J 1.7 Hz), 2.15 (1 H, br d, 5-H, J 4.6 Hz), 2.4 (1 H, q, 4_{endo}-H, J_{4ab} 7.6 Hz), 4.4-4.5 (3 H, m, 1-H and 6-H and 7-H); *m/z* 311 (M^+, 0.2%), 296 (14, M^+ - Me), 255 (18), 196 (39, [296] - BOC), 153 (19), 110 (23), 101 (41), and 57 (100, $[^tButyl]^+$).

4-*Dimethyl*-6-exo,7-exo-(*isopropylidenedioxy*)-(N-*tert-butoxycarbonyl*)-2-*azabicyclo*[3.2.1]*heptan*-3-*one* (**58**) (35.1 mg, 34%), m.p. 134°C (decomp. starts at 120°C) (Found: $M^+ - CH_2$, 311.1687. $C_{16}H_{25}NO_5$ requires 311.1691); $\upsilon_{max.}$ ($CHCl_3$) 1 766 (BOC C=O), 1 718 (lactam CO), 1 386 and 1 372 ($C(Me)_2$ - CH def.), 1 293, 1 269, 1 150, 1 048, and 1 022 cm^{-1}; δ_H (270 MHz; $CDCl_3$) 1.25 (3 H, s, 4_{endo}-Me), 1.27 (3 H, s, 4_{exo}-Me), 1.30 (3 H, s, Me-acetonide), 1.42 (3 H, s, Me-acetonide), 1.49 (9 H, s, BOC), 1.85 (1 H, d, 8b-H, J_{8ab} 12.7 Hz), 2.0-2.13 (2 H, m, 8a-H and 5-H), 4.3 (1 H, br t, 1-H, J ~2Hz), and 4.4 and 4.7 (2 H, dd, 6-H and 7-H, $J_{6,7}$ 5.4 Hz, J 1.7 Hz); *m/z* 325 (M^+, 0.2%), 310 (13, M^+ - Me), 269 (14, [310] - (2 x Me)), 210 (42, [310] - BOC), 167 (17), 101 (33), 81 (26), and 57 (100, $[^tButyl]^+$).

LDA/Hexachloroethane chlorination of 6-exo,7-exo-(*isopropylidenedioxy*)-2-*azabicyclo*[3.2.1](N-*allyl*)*octyllactam* (**49**) and the formation of :- 4-endo-*Chloro*-6-exo,7-exo-(*isopropylidenedioxy*)-2-*azabicyclo*[3.2.1](N-*allyl*)*octyllactam* (**60**), 4-exo-*Chloro*-6-exo,7-exo-(*isopropylidenedioxy*)-2-*azabicyclo*[3.2.1](N-*allyl*)*octyllactam* (**59**), and 4-*Dichloro*-6-exo,7-exo-(*isopropylidenedioxy*)-2-*azabicyclo*[3.2.1](N-*allyl*) *octyllactam* (**61**).-Di-*iso*-propylamine (84 µl, 0.6 mmol) was added to dry THF (5 ml) under nitrogen. To this solution *n*-butyl lithium (0.3 ml, 2M solution in cyclohexane) was added at -5°C

and stirred for 5 minutes before the solution was cooled to -78°C. At this temperature, a solution of the allyl lactam (**49**) (129 mg, 0.54 mmol) in THF (5 ml) was added and the solution was allowed to reach 0°C. The mixture was recooled to -70°C and a solution of hexachloroethane (142 mg, 0.6 mmol) in THF (2 ml) was added over a period of 5 minutes. The mixture darkened during the addition and remained so when the solution was warmed to room temperature. The organic solution was mixed water and then extracted with EtOAc (3 x 20 ml), these extracts were combined, dried ($MgSO_4$), filtered, and then the solvent was removed under reduced pressure. The oil residue was purified by wet flash column chromatography (eluant petrol to ether) and gave the *title compounds* as colourless solids.

4-exo-*Chloro*-6-exo,7-exo-(*isopropylidenedioxy*)-2-*azabicyclo*[3.2.1](N-*allyl*)*octyllactam* (**59**), (23 mg, 15%), m.p. 144-145°C. (Found: M^+, 271.0975. $C_{13}H_{18}ClNO_3$ requires 271.0975); $\upsilon_{max.}$ (CCl_4) 1 675 (CO), 1 451, 1 416, 1 384 and 1 376 (-$C(Me)_2$, -CH def.), 1 265, 1 248, 1 211, 1 162, 1 076, 1 048, 980, 930, and 867 cm^{-1} ; δ_H (270 MHz; $CDCl_3$) 1.30 (3 H, s, Me-acetonide), 1.40 (1 H, d, 8b-H, J 1.9 Hz), 1.45 (3 H, s, Me-acetonide), 2.19 (1 H, m, 8a-H), 2.71 (1 H, m, 5-H), 3.55 (1 H, dd, 12a-H, J 14.9 Hz, J 6.8 Hz), 3.62 (1 H, m, 1-H), 4.2 (1 H, t, 4_{endo}-H, J 1.7 Hz), 4.4-4.5 (3 H, m, 12b-H, 6-H and 7-H), 5.2 (1 H, m, 14_{trans}-H), 5.25 (1 H, m, 14_{cis}-H), and 5.77 (1 H, m, 13-H); *m/z* 271 (M^+, 42%), 256 (21, M^+ - Me), 236 (16, M^+ - Cl), 178 (100, [236] - (Me and allyl)), 170 (35), 135 (76, [178] - MeCO), 81 (22), 43 (33), and 41 (70, [allyl]$^+$).

4-endo-*Chloro*-6-exo,7-exo-(*isopropylidenedioxy*)-2-*azabicyclo*[3.2.1](N-*allyl*)*octyllactam* (**60**), (15 mg, 10%), m.p. 144-145°C starts to sublime at 135°C, (Found: M^+, 271.0975. $C_{13}H_{18}ClNO_3$ requires 271.0975); $\upsilon_{max.}$ (CCl_4) 1 677 (CO), 1 384 and 1 375 (-$C(Me)_2$, -CH def.), 1 210, and 1 047 cm^{-1} ; δ_H (270 MHz; $CDCl_3$) 1.31 (3 H, s, Me-acetonide), 1.44 (3 H, s, Me-acetonide), 1.78 (1 H, d, 8b-H, J_{8ab} 12.7 Hz), 2.30 (1 H, ddd, 8a-

H, J_{8ab} 12.7 Hz, $J_{8a,5}$ 5.4 Hz, $J_{8a,1}$ 4.4 Hz), 2.80 (1 H, td, 5-H, $J_{5,4exo}$ 5.4 Hz, J 1.9 Hz), 3.56 (1 H, d, 1-H, $J_{8a,1}$ 4.4 Hz), 3.62 (1 H, dd, 12a-H, J 15.1 Hz, J 6.8 Hz), 4.4 (1 H, dd, 12b-H, J 14.7 Hz, J 5.4 Hz), 4.48 (1 H, dd, 6-H or 7-H, $J_{6,7}$ 5.4 Hz, J 1.5 Hz), 4.6 (1 H, d, 4_{exo}-H, $J_{4exo,5}$ 5.4 Hz), 5.0 (1 H, dd, 6-H or 7-H, $J_{6,7}$ 5.4 Hz, J 1.5 Hz), 5.1 (1 H, dd, 14_{trans}-H, $J_{13,14trans}$ 8.3 Hz, J 1.5 Hz), 5.25 (1 H, s, 14_{cis}-H), and 5.77 (1 H, m, 13-H, $J_{13,14trans}$ 8.3 Hz, $J_{13,14cis}$ 5.4 Hz); *m/z* 271 (M^+, 31%), 256 (25, M^+ – Me), 236 (12, M^+ – Cl), 178 (100, [256] - (Cl and allyl)), 135 (75, [178] – MeCO), 83 (36), and 41 (64, [allyl]$^+$).

4-*Dichloro*-6-exo,7-exo-(*isopropylidenedioxy*)-2-*azabicyclo*[3.2.1](N-*allyl*)*octyllactam* (**61**) (115 mg, 70%), m.p. 104-105°C, (Found: M^+, 305.0585. $C_{13}H_{17}Cl_2NO_3$ requires 305.0585); $\upsilon_{max.}$ (CCl_4) 1 693 (CO), 1 451, 1 416, 1 384 and 1 376 ($C(Me)_2$ – CH def.), 1 265, 1 248, 1 213, 1 180, 1 162, 1 079, 1 047, 976, 931, and 870 cm^{-1}; δ_H (270 MHz; $CDCl_3$) 1.35 (3 H, s, Me-acetonide), 1.45 (3 H, s, Me-acetonide), 2.25 (1 H, ddd, 8a-H, J_{8ab} 13.2 Hz, J 4.9 Hz, J 3.6 Hz), 2.35 (1 H, d 8b-H, J_{8ab} 13.2 Hz), 3.15 (1 H, d, 5-H, J 4.6 Hz), 3.6 (1 H, m, 1-H), 3.65 (1 H, ddt, 12a-H, J 15.1 Hz, J 6.8 Hz, J 1 Hz), 4.4 (1 H, ddt, 12b-H, J 14,9 Hz, J 5.4 Hz, J 1.7 Hz), 4.45 (1 H, dd, 6-H or 7-H, J 5.6 Hz, J 1.5 Hz), 5.0 (1 H, dd, 6-H or 7-H, J 5.6 Hz, J 1.5 Hz), 5.25 (1 H, d, 14_{trans}-H, J 8.1 Hz), 5.3 (1 H, m, 14_{cis}-H), and 5.8 (1 H, m, 13-H); *m/z* 305 (M^+, 7%), 290 (21, M^+ – Me), 270 (21, M^+ – Cl), 212 (54), 172 (19), 171 (23), 170 (54), 169 (58), 81 (32), 43 (49) and 41 (100, [allyl]$^+$).

4-*Dichloro*-6-exo,7-exo-(*isopropylidenedioxy*)-2-*azabicyclo*-[3.2.1]*heptan*-3-*one* (**62**).–*n*-Butyl lithium (374 µl, 2.0M in cyclohexane, 1.1 equiv.) was added to a solution of di-*iso*-propylamine (105.2 µl, 0.74 mmol, 1.1 equiv.) in THF (20 ml) at -5°C. The mixture was stirred at that temperature for 5 minutes before being cooled to -40 °C and then a solution of the *N*-BOC

lactam (**50**) (200 mg, 0.67 mmol) in THF (4 ml) was added. This mixture was allowed to warm to -9°C before being recooled to -65°C and having CCl_4 (0.7ml, 7 mmol) added to it. The resulting solution was warmed to room temperature, diluted with water (10 ml) and extracted with EtOAc (3 x 50 ml). These extracts were then combined, dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure to give a yellow oil. This crude oil was purified by wet flash column chromatography (eluant petrol to ether to EtOAc) to give some deprotected lactam (38.7 mg, 29%) together with the *title compound* (82.3 mg, 46%) as a colourless solid, m.p. 192-194°C dec. (sublimation appears to start at 150°C), (Found: M^+ + H, 266.0351. $C_{10}H_{13}Cl_2NO_3$ requires *M* + H, 266.0351); $\upsilon_{max.}$ ($CHCl_3$) 3 397, 3 216 (NH), 1 697 (CO), 1 455, 1 386 and 1 378 ($C(Me)_2$ - CH def.), 1 293, 1 267, 1 212, 1 161, 1 080, 1 047, 1 003, 880, 865, and 828 cm^{-1}; δ_H (270 MHz; $CDCl_3$) 1.31 (3 H, s, Me-acetonide), 1.46 (3 H, s, Me-acetonide), 2.28 (1 H, dtd, 8a-H, J_{8ab} 13.4 Hz, J 5.1 Hz, J 1.5 Hz), 2.40 (1 H, br d, 8b-H, J_{8ab} 13.4 Hz), 3.12 (1 H, dd, 5-H, J 4.8 Hz, J 1.5 Hz), 3.66 (1 H, br t, 1-H), 4.50 to 4.98 (2 H, dd, 6-H and 7-H, $J_{6,7}$ 5.4 Hz, J 1.5 Hz) and 7.2 (1 H, br s, N-*H*); *m/z* 250 (M^+ - Me, 40%), 172 (9), 130 (27), 101 (18), 81 (100), and 43 (73).

4-(*N,N'-tert-Butoxycarbonyl-hydrazino*)-6-exo,7-exo-(*isopropylidenedioxy*)-(N-*tert-butoxycarbonyl*)-2-*azabicyclo*-[3.2.1]*heptan*-3-*one* (**63**).–To a solution of di-*iso*-propylamine (77.1 µl, 0.55 mmol) in dry, freshly distilled THF (10 ml) was added *n*-butyl lithium (353 µl, 1.6M solution in hexane, 0.55 mmol) at -10°C under nitrogen. After allowing 10 minutes for the LDA to form, the solution was taken to -58°C and a solution of the *N*-BOC lactam (**50**) (150 mg, 0.5 mmol) in THF (5 ml) was added. The solution was then allowed to warm to -2°C before being recooled to -60°C and a solution of DBAD (180 mg, 0.8 mmol) in THF (5 ml) added to it. This mixture was quenched after 2 minutes with excess acetic acid (1 ml, ~2.6 equiv.) and allowed to

Table 6

A summary of the results obtained with the chlorination reactions

Lactam	Method	Results
N-BOC	LDA, -75°C, CCl_4, THF	**(56)** 20%
N-BOC	KHMDS, -78°C CCl_4, THF	**(43)** 35%
N-BOC	KHMDS, -30°C to -5°C to -59°C, Cl_6C_2, THF	**(56)** 72% + **(43)**
N-BOC	LDA, -40°C to -9°C to -65°C 10 equiv. CCl_4, THF	**(62)** 46% + **(43)** 29%
N-BOC	LDA, -50°C to 0°C to -70°C 3 equiv. CCl_4, THF	**(56)** 63%
N-BOC	LDA, -75°C to 0°C to -78°C Cl_6C_2, THF	**(56)** 42% + **(62)** 10% + **(50)** 11%
N-BOC	LDA, -50°C to 0°C to -30°C 10 equiv. CCl_4, THF	**(62)** 35% + **(43)** 23%
N-Allyl	LDA, -78°C to 0°C to -70°C Cl_6C_2, THF	**(59)** 15% + **(60)** 10% **(61)** 70%
N-Allyl	KHMDS, -63°C to -3°C to -30°C, CCl_4, THF	**(61)** 56% + **(59)** 5%
N-Allyl	LDA, -50°C to 0°C to -30°C CCl_4, THF	**(61)** 48% + **(59)** 16% **(60)** 14%

warm to room temperature. The resulting mixture was partitioned between DCM and an aqueous layer buffered to pH 7 with phosphate. The chlorinated solvent was separated and the aqueous layer was washed with DCM (3 x 50 ml). The chlorinated layers were combined and washed with a saturated aqueous solution of $NaHCO_3$, dried with $MgSO_4$ and the solvent removed to give a crude oily mixture. This crude material was purified by wet flash column chromatography (eluant petrol to ether) to give the *title compound* (220 mg, 83%) as a oily mixture of isomers which solidified upon trituration with carbon tetrachloride, m.p. 136°C dec., (Found: C, 57.1; H, 8.0; N, 7.9. $C_{25}H_{41}N_3O_9$ requires C, 56.9; H, 7.8; N, 7.9%); $\upsilon_{max.}$ (CCl_4) 3 389 (NH), 1 779 and 1 755 and 1 728 (CO), 1 383 and 1 370 (-$C(Me)_2$, -CH def.), and 1 155 cm^{-1}; δ_H (270 MHz; $CDCl_3$) very broad low resolution spectrum obtained. V.T. spectra in $(CD_3)_2SO$ were therefore obtained. δ_H (250 MHz; $(CD_3)_2SO$) 1.26 (3 H, s, Me-acetonide), 1.37 (3 H, s, Me-acetonide), 1.4-1.45 (18 H, m, hydrazino-BOC), 1.47 (9 H, s, BOC), 1.80 (1 H, d, 8b-H, J_{8ab} 12.5 Hz), 2.0 (1 H, dt, 8a-H, J_{8ab} 12.5 Hz, J 4 Hz), 2.7 (1 H, s, 5-H), 3.0 (0.5 H, s, 4_{endo}-H), 4.1 (1 H, d, 1-H, J 4 Hz), 4.42 (1 H, dd, 6-H or 7-H, $J_{6,7}$ 5.5 Hz, J 1.5 Hz), 4.5 (1 H, br s, 4_{exo}-H), and 4.65 (1 H, dd, 6-H or 7-H, $J_{6,7}$ 5.5 Hz); *m/z* 512 (M^+, 1%), 371 (3), 342 (4), 327 (10, [371] - MeCHO), 271 (45, [371] - BOC), 227 (38, [271] - MeCHO), 211 (10, [271] - $MeCO_2H$), 57 (100, [^{t}Butyl]$^+$).

6-exo,7-exo-(*Isopropylidenedioxy*)-2-*azabicyclo*[3.2.1]-(N-*prop*-1-*ene*)*octyllactam* (**64**).–The allyl lactam (**49**) (147 mg, 0.62 mmol) was added to an aqueous 3M solution of potassium hydroxide (10 ml) and heated to reflux. After 4 days at reflux the solution was allowed to cool and the mixture was concentrated. This concentrate was extracted with ether (3 x 10 ml), the ether layers combined and dried ($MgSO_4$). The aqueous layer was neutralised with dilute HCl and the solution evaporated to

dryness, to give a pale yellow solid. The solid was treated with diazomethane and after destroying the excess diazomethane with glacial acetic acid, no methyl esters apart from methyl acetate were isolated. The *title compound* (15.1 mg, 11%) was obtained from the ether layers, after removal of the solvent under reduced pressure and purifying the residue by wet flash column chromatography (eluant petrol to ether to EtOAc), as a colourless solid, m.p. 88-92°C. (Found: M^+, 237.1365. $C_{13}H_{19}NO_3$ requires 237.1365); $\upsilon_{max.}$ (CCl_4) 1 667 (CO), 1 407, 1 383 and 1 374 ($C(Me)_2$ - CH def.), 1 262, 1 209, 1 170, 1 075, 1 048, and 892 cm^{-1}; δ_H (270 MHz; $CDCl_3$) 1.3 (3 H, s, Me-acetonide), 1.45 (3 H, s, Me-acetonide), 1.65 (3 H, dd, 14-H, $J_{14,13}$ 7.1 Hz, $J_{14,12}$ 1.9 Hz), 1.8 (1 H, d, 8b-H, J_{8ab} 12.5 Hz), 2.2 (1 H, m, 8a-H, J_{8ab} 12.5 Hz), 2.35 (1 H, d, 4_{endo}-H, J_{4ab} 18.3 Hz), 2.45 (1 H, t, 5-H, $J_{5,4exo}$ 5.4 Hz), 2.65 (1 H, dd, 4_{exo}-H, J_{4ab} 18.3 Hz, $J_{4exo,5}$ 5.4 Hz), 3.7 (1 H, d, 1-H, J 4.2 Hz), 4.4-4.6 (2 H, m, 6-H and 7-H), 5.35 (1 H, dq, 13-H, $J_{13,12}$ 8.5 Hz, $J_{13,14}$ 7.1 Hz), and 6.2 (1 H, dd, 12-H, $J_{12,13}$ 8.5 Hz, $J_{12,14}$ 1.9 Hz); *m/z* 237 (M^+, 100), 222 (37, M^+ - Me), 178 (21, [222] - MeCHO), 137 (47, [178] - (-CH=CH-Me)), 136 (41), 101 (37), 68 (23), and 41 (36, [allyl]$^+$).

6-exo,7-exo-(*Acetyl*)-2-*azabicyclo*[3.2.1]-(N-*allyl*)*octyllactam* (**66**).–The allyl lactam (**49**) (163 mg, 0.688 mmol) was mixed with a 1M aqueous HCl solution (5 ml) and heated to reflux. After 5 days the solution was allowed to cool, neutralised with a 2M KOH solution and then the solvent was removed under reduced pressure. The yellow solid residue was dissolved in a benzene/methanol mixture which was then removed in an attempt to azeotropically remove any remaining water. The residue from this was refluxed in dry methanol (15 ml) for 24 hours whereupon the solvent was removed and the residue dissolved in pyridine (1.1 ml, 20 equiv.). The solution was cooled before acetic anhydride (0.72 ml, 11 equiv.) was added to it. After allowing the mixture to warm to room temperature, it was stirred

for 1 hour before the solvent was removed. The oily residue was taken up into a DCM/EtOAc solvent mixture (30 ml) and extracted with a saturated solution of sodium bicarbonate (2 x 25 ml) followed by a saturated solution of brine (20 ml). The organic layers were dried ($MgSO_4$), filtered, and evaporated to give an oil which was purified using wet flash column chromatography (eluant petrol : ether (1:1) to ether to EtOAc). The *title compound* (150.7 mg, 76%) was isolated as an oil which solidified overnight, m.p. 161-163°C. (Found: M^+, 281.2570. $C_{14}H_{19}NO_5$ requires M, 281.2570); $\upsilon_{max.}$ ($CHCl_3$) 1 746 (CO-ester), 1 641 (CO-amide); δ_H (270 MHz; $CDCl_3$) 1.7 (1 H, d, 8b-H, J_{8ab} 12.2 Hz), 2.0 (6 H, s, 11-H and 12-H), 2.1 (1 H, m, 8a-H), 2.4 (2 H, m, 4_{endo}-H and 5-H), 2.55 (1 H, dd, 4_{exo}-H, J_{4ab} 8 Hz, $J_{4,5}$ 4.4 Hz), 3.5 (2 H, m, 1-H and 13a-H), 4.45 (1 H, m, 6-H, $J_{6,7}$ 5.9 Hz), 5.0 (1 H, d, 7-H, $J_{6,7}$ 5.9 Hz), 5.1 (2 H, s, 15-H or 13b-H), 5.15 (1 H, m, 15-H or 13b-H), and 5.7 (1 H, m, 14-H); *m/z* 281 (M^+, 100%), 266 (44, M^+ – Me), 222 (40, $M^+ - CH_3CO_2$), 194 (17, [266] – CO – CH_3CHO), 180 (25, [222] – CH_2CO), 178 (21, [222] – CH_3CHO), and 43 (35, $[CH_3CO]^+$).

6-exo,7-exo-(*Isopropylidenedioxy*)-2-*azabicyclo*[3.2.1]-(N-*allyl*)-*octylthiolactam* (**67**).–The allyl lactam (**49**) (276 mg, 1.16 mmol) was dissolved in a solution of dry toluene (10 ml) under nitrogen. To this was added Lawesson's reagent (283 mg, 0.699 mmol) and the mixture was heated to reflux. After refluxing for 0.5 hours the solution was allowed to cool and the solvent was removed under reduced pressure. The residue was purified by wet flash column chromatography (performed in a fume hood, eluant petrol to ether) to give the *title compound* (211 mg, 72%) as a colourless solid, m.p. 121-123°C, (needles form from 118°C onwards), (Found: C, 61.5; H, 7.7; N, 5.4. $C_{13}H_{19}NO_2S$ requires C, 61.6; H, 7.6; N, 5.5%); $\upsilon_{max.}$ ($CHCl_3$) 1 495 (C=S coupling bands with C-N vib.), 1 385 and 1 377 ($C(Me)_2$ – CH def.), 1 191, 1 077,

and 1 046 cm^{-1} (C=S str.); δ_H (270 MHz; $CHCl_3$) 1.3 (3 H, s, Me-acetonide), 1.44 (3 H, s, Me-acetonide), 1.71 (1 H, d, 8b-H, J_{8ab} 12.5 Hz), 2.2 (1 H, m, 8a-H, J_{8ab} 12.5 Hz), 2.38 (1 H, t, 5-H, J 5.2 Hz), 2.9 (1 H, d, 4_{endo}-H, J_{4ab} 19.5 Hz), 3.2 (1 H, dd, 4_{exo}-H, J_{4ab} 19.5 Hz, $J_{4,5}$ 5.8 Hz), 3.8 (1 H, d, 1-H, J 3.9 Hz), 4.11 (1 H, dd, 12a-H, J_{12ab} 6.3 Hz, $J_{12a,13}$ 14.7 Hz), 4.45 (2 H, dd, 6-H and 7-H, $J_{6,7}$ 5.6 Hz, $J_{8b,6}$ 1.7 Hz), 5.18 (1 H, dd, 12b-H, $J_{12a,13}$ 6.3 Hz, J_{12ab} 14.7 Hz), 5.27 (1 H, dd, (trans)14a-H, $J_{14a,13}$ 5.1 Hz, J_{14ab} 1.2 Hz), 5.33 (1 H, dd, (cis)14b-H, $J_{14b,13}$ 2.7 Hz, J_{14ab} 1.2 Hz), and 5.85 (1 H, m, 13-H); *m/z* 253 (M^+, 25%), 238 (100, M^+ – Me), 196 (2, [238] – CH_2CO), 178 (5, [238] – CH_3CO_2H), 152 (5, [196] – CS), 112 (6, [152] – CH_2CCH_2), 81 (16), and 41 (21, $[CH{=}CHCH_2]^+$).

6-exo,7-exo-(*Isopropylidenedioxy*)-2-*azabicyclo*[3.2.1]-*octyl-thiolactam* (**68**).–The lactam (**43**) (173 mg, 0.878 mmol) was dissolved in a solution of dry toluene (10 ml) under nitrogen. To this was added Lawesson's reagent (213 mg, 0.527 mmol) and the mixture was heated to reflux. After refluxing for 1.5 hours the solution was allowed to cool and the solvent was removed under reduced pressure. The residue was purified by wet flash column chromatography (performed in a fume hood, eluant petrol to ether) to give the *title compound* (125 mg, 67%) as a colourless solid, m.p.174°C dec. (Found: C, 56.0; H, 7.1; N, 6.5. $C_{10}H_{15}NO_2S$ requires C, 56.3; H, 7.1; N, 6.6%); $\upsilon_{max.}$ ($CHCl_3$) 3 171 (NH), 1 551, 1 515, 1 385 and 1 377 ($C(Me)_2$ – CH def.), 1 266, 1 209, 1 122, 1 082, 1 049, and 974 cm^{-1}; δ_H (270 MHz; $CDCl_3$) 1.29 (3 H, s, Me-acetonide), 1.43 (3 H, s, Me-acetonide), 1.73 (1 H, d, 8b-H, J_{8ab} 12.2 Hz), 2.17 (1 H, m, 8a-H, J_{8ab} 12.2 Hz), 2.4 (1 H, t, 5-H, J 5.1 Hz), 2.85 (1 H, dt, 4_{endo}-H, J_{4ab} 20.0 Hz, J 1.7 Hz), 3.2 (1 H, dd, 4_{exo}-H, J_{4ab} 20.0 Hz, $J_{4,5}$ 5.6 Hz), 3.7 (1 H, t, 1-H, J 4.6 Hz), 4.5-4.6 (2 H, dd, 6-H and 7-H, $J_{6,7}$ 5.4 Hz, $J_{8b,6}$ 1.6 Hz), and 9.6 (1 H, br s, N*H*); *m/z* 213 (M^+, 72%), 198 (16, M^+ – Me), 154 (46, [198] – CH_3CHO or CS), 138 (33, [198] – CH_3CO_2H), 126

(66, [154] – CO), 112 (84, [154] – CH_2CO), 81 (67), and 43 (100, $[CH_3CO]^+$).

Attempted cleavage of 6-exo,7-exo-(*Isopropylidenedioxy*)-2-*azabicyclo*[3.2.1.]*octyllactam* (**43**) by a sealed tube method, with the formation of :-6-exo,7-exo-*Acetyl*-N-*acyl*-2-*azabicyclo*[3.2.1] *heptan*-3-*one* (**70**), and 6-exo,7-exo-*Acetyl*-2-*azabicyclo* [3.2.1]*heptan*-3-*one* (**72**).–The lactam (**43**) (88 mg, 0.45 mmol) was dissolved in a saturated, ethanolic solution of hydrogen chloride (5 ml) which was, in turn, transferred to a thick walled glass tube which was then sealed. This tube was placed in an oven at a temperature of 150°C and left over a period of 27 hours. The sealed tube unfortunately broke during this time but the brown residue left within the tube was taken up into water, neutralised with a 2M KOH solution and evaporated to dryness. The solid residue was stirred with pyridine (5 ml) and acetic anhydride (1 ml) at room temperature for 24 hours before the solvent was removed and the oily residue purified by wet flash column chromatography (eluant petrol to ether to EtOAc). The *title compounds* were produced as colourless solids.

6-exo,7-exo-*Acetyl*-N-*acyl*-2-*azabicyclo*[3.2.1]*heptan*-3-*one* (**70**) (72 mg, 57%), as a colourless solid m.p. 168-169°C, (Found: M^+, 283.1056. $C_{13}H_{17}NO_6$ requires 283.1056); $\upsilon_{max.}$ ($CHCl_3$) 1 747 (ester CO), 1 704 (amide CO), 1 370, 1 241, 1 147, 1 096, 1 069, and 1 042 cm^{-1}; δ_H (270 MHz; $CDCl_3$) 1.7 (1 H, d, 8b-H, J_{8ab} 13.2 Hz), 2.04 (3 H, s, 11-H or 12-H), 2.09 (3 H, s, 11-H or 12-H), 2.33 (1 H, m, 8a-H, J_{8ba} 13.2 Hz), 2.48 (1 H, m, 5-H), 2.56 (3 H, s, 13-H), 2.66 (1 H, dt, 4_{endo}-H, J_{4ab} 19 Hz, J 1.9 Hz), 2.8 (1 H, dd, 4_{exo}-H, J_{4ab} 19 Hz, $J_{4exo,5}$ 5.9 Hz), 5.05 (1 H, t, 1-H, J 3.9 Hz), and 5.07-5.15 (2 H, dd, 6-H and 7-H, $J_{6,7}$ 6.4 Hz, J 1.5 Hz); *m/z* 283 (M^+, 18%), 240 (17), 198 (25), 181 (66), 156 (32), 139 (44), 138 (38), and 43 (100).

6-exo,7-exo-*Acetyl*-2-*azabicyclo*[3.2.1]*heptan*-3-*one* (**72**) (28

mg, 26%), m.p. 112-113°C, (Found: M^+, 241.0950. $C_{11}H_{15}NO_5$ requires 241.0950); $\upsilon_{max.}$ ($CHCl_3$) 3 409 (NH), 1 746 (ester CO), 1 670 (amide CO), 1 375, 1 252, 1 097, 1 068, 1 049, and 1 029 cm^{-1}; δ_H (270 MHz; $CDCl_3$) 1.77 (1 H, d, 8b-H, J_{8ab} 12.2 Hz), 2.05 (6 H, s, 11-H and 12-H), 2.2 (1 H, br d, 8a-H, J_{8ab} 12.2 Hz), 2.45 (2 H, m, 4_{endo}-H and 5-H), 2.6 (1 H, dd, 4_{exo}-H, J_{4ab} 18.6 Hz, $J_{4exo,5}$ 5.4 Hz), 3.65 (1 H, m, 1-H), 5.1-5.25 (2 H, dd, 6-H and 7-H, $J_{6,7}$ 5.9 Hz, J 1.5 Hz), and 6.92 (1 H, br s, N*H*); *m/z* 241 (M^+, 17%), 199 (100), 139 (70), 138 (49), 121 (47), 96 (51), and 43 (35).

6-exo,7-exo-(*Isopropylidenedioxy*)-N-*acyl*-2-*azabicyclo*[3.2.1] *heptan*-3-*one* (**71**).–Thionyl chloride (36.6 µl, 0.5 mmol) was added to a solution of the lactam (**43**) (90 mg, 0.46 mmol) in dry methanol (5 ml). The mixture was heated to reflux for 24 hours and then cooled. The solvent was removed under reduced pressure to leave a semi-solid residue. This residue was taken up into pyridine (5 ml) and had acetic anhydride (1 ml) added to it. After 20 hours stirring at room temperature the solvent was again removed to give an oily residue which was purified by wet flash column chromatography (eluant petrol to ether to EtOAc). The tri-acylated material (**70**) (39.4 mg, 31%) was isolated as a colourless solid along with the *title compound* (23.4 mg, 21%) as an oil, b.p. 215°C at 20 mmHg, (Found: M^+–CH_3, 224.0930 $C_{11}H_{14}NO_4$ requires *M*–CH_3, 224.0923); $\upsilon_{max.}$ (CCl_4) 1 708 (CO), 1 381, 1 246, 1 227, 1 209, 1 147, 1 122, 1 079, 1 042, and 909 cm^{-1}; δ_H (270 MHz; $CDCl_3$) 1.3 (3 H, s, Me-acetonide), 1.45 (3 H, s, Me-acetonide), 1.6 (1 H, d, 8b-H, J_{8ab} 12.7 Hz), 2.25 (1 H, m, 8a-H, J_{8ab} 12.7 Hz), 2.4-2.5 (2 H, m, 4_{endo}-H and 5-H), 2.55 (1 H, s, 12-H), 2.75 (1 H, dd, 4_{exo}-H, J_{4ab} 19 Hz, $J_{4exo,5}$ 6.4 Hz), 4.35-4.45 (2 H, dd, 6-H and 7-H, $J_{6,7}$ 5.4 Hz, J 1.5 Hz), 4.9 (1 H, br d, 1-H, J 3.4 Hz); *m/z* 239 (M^+, 1%), 224 (100, M^+ – Me), 182 (22), 138 (27), 122 (16), 101 (17), 96 (23), and 43 (84).

N,N-(*Methylallyl*)-2,2,2-*trichloroacetamidine* (**94**).–Trichloroacetonitrile (0.5 ml, 5 mmol) was dissolved in dry benzene (7.0 ml) and cooled in an ice bath. To this *N*-methylallylamine (**93**) (0.5 ml, 5.5 mmol) was added directly and the resulting yellow solution was stirred at room temperature for 14 hours. After this period the solution had turned brown and the solvent was removed under reduced pressure. Distillation of the crude oil product gave the title compound (0.77g, 73%) as a pale oil, b.p. 150°C at 1 mmHg, consistent with the literature details. $\upsilon_{max.}$ (CCl_4) 3 357 (NH), 1 683, 1 643, 1 602 (C=N), 1 421, 1 387, 1 302, 1 273, 1 083, 1 063, 985, 926, 837, 794, 758, and 641; δ_H (250 MHz; $CDCl_3$) 3.08 (3 H, s, N-Me), 4.14 (2 H, d, N-C*H*$_2$-CH, J_{NCH_2CH} 5.4 Hz), 5.19 (1 H, dd, -CH_2-CH=C*H*$_{trans}$H, J 7.4 Hz, J 1.7 Hz), 5.24 (1 H, br s, -CH_2-CH=C*H*$_{cis}$H), and 5.85 (1 H, m, -CH_2-C*H*=CH_2, J 7.4 Hz, J_{NCH_2CH} 5.4 Hz); *m/z* 214 (M^+ , 10%), 179 (27, M^+ – Cl), 143 (23, [179] – HCl), 97 (19, M^+ – CCl_3), 70 (52, [$MeNCH_2CH=CH_2$]$^+$), and 41 (100, [allyl]$^+$).

4,5-*Dihydro*-1-(*methyl*)-2-(*trichloromethyl*)-4-(*iodomethyl*) *imidazole* (**95**).–*N*-Methylallyl-2,2,2-trichloroacetamidine (**94**) (0.3 g, 1.4 mmol) was dissolved in THF (10 ml) and was added to a solution of pyridine (0.45 ml, 5 mmol) and iodine (0.5 g, 4 mmol) also in THF (10 ml). The solution was stirred for 17 hours at room temperature before being worked up with 20% aq. $Na_2S_2O_3$ (40 ml) and extracted with DCM (3 x 25 ml). After drying of the extracts ($MgSO_4$) and evaporation of the solvent the crude product was chromatographed, using the dry flash method, (eluant petrol: ether) to give the *title compound* (0.35 g, 73%) as a light green oil which rapidly turned red on standing at room temperature, and which decomposed upon distillation b.p. 100°C (dec.). (Found: C, 21.1; H, 2.4; N, 8.7, $C_6H_8Cl_3IN_2$ requires C, 21.1; H, 2.4; N, 8.2%); $\upsilon_{max.}$ (CCl_4) 1 683, 1 592, 1 451, 1 425, 1 396, 1 269, 1 171, 1 008, and 823; δ_H (250 MHz; $CDCl_3$) 3.13 (3

H, s, N-Me), 3.21 (1 H, dd, 6a-H, J_{6ab} 9.8 Hz, $J_{6,4}$ 8.6 Hz), 3.4 (1 H, t, 5a-H or 6b-H, J'=J'' 9.8 Hz), 3.43 (1 H, dd, 5a-H or 6b-H, J'' 9.8 Hz, J''' 4.9 Hz), 3.81 (1 H, dd, 5b-H, J_{5ab} 9.8 Hz, $J_{5b,4}$ 10.4 Hz), and 4.2 (1 H, m, 4-H); *m/z* 340 (M^+, 24%), 213 (22, M^+ - I), 199 (100, M^+ - CH_2I), 164 (34, [199] - Cl), 70 (32, $[CH_2=CHCH_2NMe]^+$), and 42 (38, $[CH_2=CHCH_2]^+$).

N-*Cyclopentylallylamine*(**96**).–To a solution of anhydrous *N*-allylamine (18ml, 240 mmol) in absolute methanol (100 ml) was added 5N methanolic HCl (10 ml) followed by cyclopentanone (3.5 ml, 40 mmol) and $NaBH_3CN$ (1.20g, 19 mmol). The mixture was then stirred for 89 hours at room temperature. Concentrated HCl was added until the pH<2 and the methanol was removed under reduced pressure. The residue was taken up in water (40 ml) and extracted with ether (3 x 40 ml). The aqueous layer was taken to pH>10 using solid KOH, saturated with NaCl and then extracted again with ether (3 x 50 ml). The combined ether extracts were dried ($MgSO_4$), filtered and concentrated to give a brown oil which was distilled using a Kugelrohr apparatus to give the *title compound* (4.25g, 85%) as a clear colourless viscous oil, b.p. 60°C at 50 mmHg, (Found M^+, 125.1205. $C_8H_{15}N$ requires *M*, 125.12049); $\upsilon_{max.}$ (neat) 3 284 (NH), and 1 644 cm^{-1} (C=C); δ_H (250 MHz; $CDCl_3$) 1.2-1.9 (8 H, m, cyclopentyl ring), 3.05 (1 H, q, N-C*H*-Cyclopentyl ring, J 6.8 Hz), 3.15 (2 H, dd, -CH_2-CH=CH_2, $J_{NCH_2\text{-}CH}$ 5.9 Hz, $J_{t.s.}$ 1.5 Hz), 5.0 (1 H, ddd, -CH_2-CH=CH_{cis}H, J_{cis} 10.3 Hz, J_{vic} = 3.5 Hz, $J_{t.s.}$ 1.5 Hz), 5.1 (1 H, ddd, -CH_2-CH=CH_{trans}H, J_{trans} 17.1 Hz, J_{vic} = 3.5 Hz, $J_{t.s.}$ 1.5 Hz), and 5.85 (1 H, m, -CH_2-C*H*=CH_2, J_{trans} 17.1 Hz, J_{cis} 10.3 Hz, $J_{NCH_2\text{-}CH}$ 5.9 Hz); *m/z* 125 (M^+ , 19%), 123 (9, M^+– H_2), 96 (88), 82 (18), 68 (22, $[CH=CHCH_2CH_2CH_2]^+$), 56 (14, $[CH=CHCH_2NH]^+$), and 41 (44, $[CH=CHCH_2]^+$).

N-*Allylurea* (**100**).–Allylamine (0.7 ml, 10 mmol) was added, *via* syringe, to sodium dry benzene (4 ml) under nitrogen and

trimethylsilylisocyanate (TMSNCO, 1.35 ml, 10 mmol) was added to the stirred solution. The solution was refluxed for 1 hour and after cooling, the *title compound* partially precipitated from the solution as a colourless solid and was filtered off. The remaining *title compound* was obtained after the solvent was removed. Total mass 0.85g, 85%, as a platelet solid, m.p. 85-87°C. (Found: C, 48.1; H, 7.8; N, 27.9; Calc. for $C_4H_8N_2O$: C, 48.0; H, 8.0; N, 28.0%); $\upsilon_{max.}$ (Nujol), 3 436, and 3 334 (NH), and 1 652 cm^{-1} (CO); δ_H (250 MHz; $CDCl_3$), 3.75 (2 H, br t, CH_2-N, J_{NCH_2CH} 5.3 Hz, $J_{t.s.}$ 1.5 Hz), 4.6 (3 H, br s, NH and NH_2), 5.1 (1 H, ddt, HC*H*=CH- (cis), J_{cis} 10.5 Hz, $J_{vic.}$ 3.8 Hz, $J_{t.s.}$ 1.5 Hz), 5.19 (1 H, ddt, HC*H*=CH- (trans), J_{trans} 17.6 Hz, $J_{vic.}$ 3.8 Hz, $J_{t.s.}$ 1.5 Hz), and 5.83 (1 H, ddt, CH_2=C*H*-, J_{cis} 10.5 Hz, J_{trans} 17.6 Hz, J_{NCH_2CH} 5.3 Hz); *m/z* 100 (M^+, 5%), 85 (1, M^+ – NH), 57 (100, $[CH_2=CH-CH_2NH_2]^+$), 56 (58, $[CH_2=CH-CH_2NH]^+$), and 44 (20, $[NH_2CO]^+$).

N,N-*Methylallylurea* (**101**).–*N*-Methylallylamine (**93**) (0.5 ml, 5.5 mmol) was added *via* a syringe to dry benzene (10 ml) under nitrogen and TMSNCO (0.8 ml, 6 mmol) was added to the stirred solution. The solution appeared cloudy after the addition but was refluxed for 1 hour before the mixture was allowed to cool and the partially precipitated *title compound*, obtained as a colourless solid, was removed by filtration. The solvent was removed under reduced pressure and the remainder of the *title compound* was obtained and was recrystalised from a 40-60°C petrol:benzene system. Total mass 0.627 g, 87%, as a colourless solid m.p. 98-99°C, (Found: C, 52.6; H, 8.9; N, 24.8; $C_5H_{10}N_2O$ requires C, 52.6; H, 8.8; N, 24.6%); $\upsilon_{max.}$ (Nujol) 3 416 and 3 357 (NH), 3 201 (CH def. in aromatics), 1 657 (CO), 1 609, 1 298, 1 101, 1 046, 999, 949, 923, 774, 661, and 606 cm^{-1}; δ_H (250 MHz; $CDCl_3$), 2.83 (3 H, s, N-Me), 3.8 (2 H, dt, N-C*H*$_2$CH=CH_2, J_{CH_2CH} 5.3 Hz, $J_{t.s.}$ 1.5 Hz), 4.85 (2 H, br s, NH_2), 5.10 (1 H, dd, CH*H*$_{trans}$=CH, J_{trans}

5.2 Hz, J_{vic} 1.5 Hz), 5.15 (1 H, dd, CHH_{cis}=CH, J_{cis} 3 Hz, J_{vic} 1.5 Hz), and 5.73 (1 H, ddt, CH_2=C*H*, J_{trans} 5.2 Hz, J_{cis} 3 Hz, J_{NCH_2CH} 5.3 Hz); *m/z* 114 (M^+, 41%), 99 (4, M^+ – Me), 71 (100, M^+ – HNCO), 70 (55, M^+ – H_2NCO), 56 (27), 44 (91, $[H_2NCO]^+$), and 41 (41, [allyl]$^+$).

4,5-*Dihydro*-1-*methyl*-4-(*iodomethyl*)*imidazol*-2-*one* (**102**).–*N*,*N*-Methylallylurea (**101**) (0.1140 g, 1 mmol) was dissolved in freshly dry distilled DCM (5 ml), under nitrogen, which contained a crystal of DMAP. Triethylamine (0.30 ml, 2.2 equiv.) was added *via* a syringe followed by trimethylsilyltriflate (0.39 ml, 2.0 equiv.). This mixture was stirred for 25 minutes at room temperature before the solvent was removed under reduced pressure. A solution of iodine (0.5080 g, 2.0 mmol) in dry THF (7 ml) was added to the oily residue under nitrogen and this mixture was also stirred at room temperature for a further 20 minutes. The THF solution was poured into a 20% aq. $Na_2S_2O_3$ solution (20 ml) and extracted with EtOAc (3 x 20 ml). After drying ($MgSO_4$) and evaporating the extracts the crude solid product was purified by wet flash chromatography (eluant petrol to ether to EtOAc) to give the *title compound* (199 mg, 83%) as a colourless solid, m.p. 113-114°C. (Found: C, 25.2; H, 3.5; N, 11.7. $C_5H_9IN_2O$ requires C, 25.0; H, 3.8; N, 11.7%); $\upsilon_{max.}$ ($CHCl_3$) 3 249 (NH), 1 698 (CO), and 756 cm^{-1} (H_2C-I); δ_H (250 MHz; $CDCl_3$), 2.78 (3 H, s, N-Me), 3.12 (1 H, dd, 5b-H, $J_{4,5b}$ 5.2 Hz, J_{5ab} 9.2 Hz), 3.17 (2 H, d, 6-H, $J_{6,4}$ 6.3 Hz), 3.57 (1 H, dd, 5a-H, $J_{4,5a} = J_{5ab}$ 9.2 Hz), 3.87 (1 H, m, 4-H), and 4.87 (1 H, br s, N*H*); δ_C (270 MHz; $CDCl_3$), 9.5 (6-C), 29.8 (CH_3-N), 50.4 (5-C), 53.0 (4-C); *m/z* 240 (M^+, 21%), 113 (3, M^+ – I), 99 (100, M^+ – CH_2I), and 44 (12, 99 – MeNCO).

N-*Benzylallylamine* (**103**).–To a solution of anhydrous *N*-allylamine (4.5ml, 60 mmol) in absolute methanol (25 ml) was added 5N methanolic HCl (2.5 ml) followed by benzaldehyde (1.0 ml, 10 mmol) and $NaBH_3CN$ (300 mg, 5 mmol). The mixture was

then stirred for 92 hours at room temperature. Concentrated HCl was added until the pH<2 and the methanol was removed under reduced pressure. The residue was taken up in water (10 ml) and extracted with ether (3 x 20 ml). The aqueous layer was taken to pH>10 using solid KOH, saturated with NaCl and then extracted again with ether (3 x 20 ml). The combined ether extracts were dried ($MgSO_4$), filtered and concentrated to give a brown oil which was purified by column chromatography (eluant petrol to ether) to give the *title compound* (1.10 g, 75%) as a pale green oil, b.p. 40°C at 0.5 mmHg, (Found: M^+, 147.1048. $C_{10}H_{13}N$ requires M, 147.1048); $\upsilon_{max.}$ (neat) 3 310 (NH), 3 064 and 3 028 (CH def. in aromatics), 2 979 and 2 824 (CH def. in aliphatics), 1 644, 1 495, 1 454, 1 106, 1 028, 995, 919, 737, and 699; δ_H (250 MHz; $CDCl_3$) 1.95 (1 H, br s, NH), 3.3 (2 H, dt, N-CH_2CH=CH_2, J_{CH_2CH} 6 Hz, $J_{t.s.}$ 1.3 Hz), 3.8 (2 H, s, N-CH_2-Ph), 5.1 (1 H, ddd, CH=CHH_{cis}, J_{cis} 10.5 Hz, J_{vic} 3 Hz, $J_{t.s.}$ 1.3 Hz), 5.2 (1 H, ddd, CH=CHH_{trans}, J_{trans} 17 Hz, J_{vic} 3 Hz, $J_{t.s.}$ 1.3 Hz), 5.9 (1 H, ddt, N-CH_2CH=CH_2, J_{trans} 17 Hz, J_{cis} 10.5 Hz, J_{CH_2CH} 6 Hz), and 7.2-7.4 (5 H, m, Ph); *m/z* 147 (M^+ , 6%), 146 (8, M^+ – H), 105 (4, $[PhCH_2N]^+$), 91 (31, [tropylium ion]$^+$), 56 (10, $[CH_2=CHCH_2NH]^+$), 41 (6, [allyl]$^+$), and 28 (100).

N,N-*Benzylallylurea* (**104**).–*N*-Benzylallylamine (**103**) (125.4 mg, 0.85 mmol) was dissolved in dry benzene (5 ml) under nitrogen and TMSNCO (0.23 ml, 1.7 mmol) was added to the stirred solution. The mixture was refluxed for 24 hours before the solvent was removed under vacuum to give a pale oil. This oil was purified by wet flash chromatography (eluant petrol to ether to EtOAc) and gave the *title compound* (124 mg, 77%) as a colourless viscous oil, b.p. 174°C at 0.4 mmHg. (Found: C, 69.5; H, 7.6; N, 14.9; $C_{11}H_{14}N_2O$ requires C, 69.4; H, 7.4, N, 14.7%); $\upsilon_{max.}$ (Nujol) 3 482, 3 354 (NH), 3 210 (CH def. in aromatics), 1 651 (CO), 1 599, 1 360, 1 317, 1 295, 1 077, 964, 924, 734, and 700

cm^{-1}; δ_H (250 MHz; $CDCl_3$), 3.84 (2 H, d, CH_2=CHCH_2-N, J_{CHCH_2} 4.8 Hz), 4.48 (2 H, s, N-CH_2-Ph), 4.7 (2 H, br s, NH_2), 5.15 (1 H, br s, -CH=CHH_{cis}), 5.21 (1 H, br d, -CH=CHH_{trans}, J 3.5 Hz), 5.75 (1 H, m, -CH_2=C*H*), and 7.2-7.4 (5 H, m, Ph); *m/z* 190 (M^+, 27%), 149 (36, M^+ - allyl), 122 (32), 106 (78, 149 - HNCO), 91 (100, [tropylium ion]$^+$), 77 (31, [Ph]$^+$), 56 (37, [CH_2=CH-CH_2NH]$^+$), and 41 (30, [allyl]$^+$).

4,5-*Dihydro*-1-*benzyl*-4-(*iodomethyl*)*imidazol*-2-*one* (**105**).–*N*,*N*-Benzylallylurea (**104**) (0.1434 g, 0.755 mmol) was dissolved in freshly dry distilled DCM (5 ml), under nitrogen, which contained a crystal of DMAP. Triethylamine (0.23 ml, 2.2 equiv.) was added *via* a syringe, followed by trimethylsilyltriflate (0.29 ml, 2.0 equiv.). This mixture was stirred for 25 minutes at room temperature before the solvent was removed under reduced pressure. A solution of iodine (0.3834 g, 1.5 mmol) in dry THF (7 ml) was added to the oily residue under nitrogen and this mixture was also stirred at room temperature for a further 20 minutes. The THF solution was poured into a 20% aq. $Na_2S_2O_3$ solution (20 ml) and extracted with DCM (3 x 20 ml). After drying ($MgSO_4$) and evaporating the extracts the crude solid product was columned to give the *title compound* (0.1751 g, 73%) as a colourless solid, m.p. 134-135°C. (Found: C, 41.7; H, 3.9; N, 8.8. $C_{11}H_{13}IN_2O$ requires C, 41.8; H, 4.1; N, 8.9%); $\upsilon_{max.}$ ($CHCl_3$) 3 444 (NH) and 1 700 cm^{-1} (CO); δ_H (250 MHz; $CDCl_3$) 2.98 (1 H, dd, 5b-H, J_{5ab} 9 Hz, $J_{5b,4}$ 5.5 Hz), 3.05-3.1 (1 H, dd, 6a-H, J_{6ab} 9.5 Hz, $J_{6a,4}$ 7 Hz), 3.1-3.2 (1 H, dd, 6b-H, J_{6ab} 9.5 Hz, $J_{6b,4}$ 6 Hz), 3.43 (1 H, dd, 5a-H, J_{5ab} =$J_{5a,4}$ 9 Hz), 3.85 (1 H, m, 4-H), 4.34 (2 H, dd, N-CH_2-Ph, J_{vic} 15 Hz), 5.35 (1 H, br s, NH), and 7.3 (5 H, m, Ph); δ_C (250 MHz; $CDCl_3$) 10.1 (*C*H_2-I), 47.1 (*C*H_2-Ph), 50.4 (*C*H_2-NBz), 50.7 (*C*H-N), 127.4 (Ph-p-*C*), 127.8 (Ph-o-*C*), 128.5 (Ph-m-*C*), and 161.2 (*C*=O); *m/z* 316 (M^+, 15%), 190 (4, M^+ - I+H), 175 (3, M^+ - CH_2I), 91 (27, [tropylium

ion]$^+$), and 28 (100).

N,N-*Cyclopentylallylurea* (**106**).–*N*-Allylcyclopentylamine (**96**) (1.54 g, 12.3 mmol) was taken up in dry THF (30 ml) and the solution placed under nitrogen. TMSNCO (3.3 ml, 24.6 mmol) was added to the stirred solution before the mixture was refluxed for 24 hours. The solvent was removed under reduced pressure and the residue was chromatographed using wet flash chromatography (eluant petrol to ether to EtOAc). The *title compound* (1.96 g, 95%) was isolated as a colourless viscous oil, b.p 110°C at 30 mmHg, m.p. ~ -12°C. (Found: M^+, 168.1263. $C_9H_{16}N_2O$ requires 168.1263); $\upsilon_{max.}$ ($CHCl_3$) 3 508, 3 414, 3 211 (NH), 1 706 (C=C), 1 652 (C=O), and 1 588 (combination band NH & CH); δ_H (270 MHz; $CDCl_3$), 1.2-1.9 (8 H, m, Cyclopentyl ring), 3.7 (2 H, m, CH_2=CHCH_2-N), 4.6 (1 H, q, N-C*H*-Cyclopentyl ring, J 8.1 Hz), 4.75 (2 H, br s, NH_2), 5.2-5.3 (2 H, m, CH=CH_2), and 5.8 (1 H, m, C*H*=CH_2); *m/z* 168 (M^+, 43%), 127 (38, M^+ – allyl), 96 (81), 84 (60), 68 (35, [CH_2CH=CH$(CH_2)_2$]$^+$), 56 (57), and 41 (100, [allyl]$^+$).

4,5-*Dihydro*-1-*cyclopentyl*-4-(*iodomethyl*)*imidazol*-2-*one* (**107**).–*N,N*-Cyclopentylallylurea (**106**) (1.22 g, 7.7 mmol) was taken up in freshly distilled DCM (80 ml), under nitrogen, and a crystal of DMAP was added to it. The solution was stirred with a magnetic stirrer and triethylamine (3.0 ml, 22 mmol) was added to the solution followed by TMSOTf (3.8 ml, 20 mmol). This mixture was stirred for 90 minutes before the DCM was removed under reduced pressure. A solution of iodine (5.08 g, 20 mmol) in THF (50 ml) was added to the residue and this solution was stirred for a further 25 minutes. The THF solution was then poured into a 20% aq. $Na_2S_2O_3$ solution (100 ml) and extracted with DCM (5 x 30 ml). After drying (Na_2SO_4) and evaporating the extracts the crude oily residue was purified by dry flash column chromatography (eluant petrol to ether to EtOAc) to give the *title*

compound (1.53 g, 67%) as a colourless solid, m.p. 96-97°C. (Found: C, 36.9; H, 5.2; N, 9.4. $C_9H_{15}IN_2O$ requires C, 36.8; H, 5.1; N, 9.5%); $\upsilon_{max.}$ ($CHCl_3$) 3 216 (NH) and 1 698 cm^{-1} (CO); δ_H (250 MHz; $CDCl_3$) 1.3-1.9 (8 H, m, CH_2-cyclopentyl), 3.06 (1 H, d, 5b-H, J_{5ab} 10.1 Hz), 3.09 (1 H, dd, 6a-H, $J_{6a,4}$ 8.9 Hz), 3.18 (1 H, dd, 5a-H, $J_{4,5a}$ 4.7 Hz, J_{5ab} 10.1 Hz), 3.5 (1 H, dd, 6b-H, $J_{6b,4}$ = J_{6ab} 8.9 Hz), 3.8 (1 H, m, 4-H), 4.2 (1 H, q, Cp-C*H*-N, J 8.3 Hz), and 6.0 (1 H, br s, NH); *m/z* 294 (M^+, 82%), 265 (100), 226 (42, M^+ - C_5H_8), 153 (36, M^+ - CH_2I), 99 (24, [226] - I), 85 (64, [153] - C_5H_8), and 41 (69).

4,5-*Dihydro*-1-*cyclopentyl*-4-(*hydroxymethyl*)*imidazol*-2-*one* (**112**).–The iodomethylimidazolone (**107**) (512 mg, 1.74 mmol) was dissolved in nitromethane (15 ml) and water (31.3 µl, 1 equiv.) was added to it. This mixture was stirred and cooled to 0°C in an ice bath, whereupon silver trifluoroacetate (577 mg, 1.5 equiv.) was added to it in one portion. The mixture was left to stir at 0°C for $3^1/_4$ hours after which time a precipitate had formed (presumably AgI). The precipitate was filtered off using a layer of Celite and washed with EtOAc (3 x 10 ml). The combined organic layers were removed under reduced pressure to give a crude form of the title compound as a pale brown oil which was, in general, used immediately without further purification. $\upsilon_{max.}$ ($CHCl_3$) 3 357 (OH), and 1 680 (CO); δ_H (250 MHz; $CDCl_3$) 1.3-1.9 (8 H, m, cyclopentyl CH_2), 3.15 (1 H, dd, J 9.3 Hz, J 5.9 Hz), 3.45 (2 H, m), 3.6 (1 H, m), 3.75 (1 H, m), 4.2 (1 H, q, N-C*H*-Cp ring, J 8.3 Hz), 4.4 (1 H, br s, OH), and 5.5 (1 H, br s, NH); *m/z* 184 (M^+, 20%), 155 (24, M^+ – CHO), 153 (34, M^+ – CH_2OH), 125 (11, [153] – CO), 116 (6, M^+ – ($CH{=}CHCH_2CH_2CH_2$)), 85 (100, [153] – ($CH{=}CHCH_2CH_2CH_2$)), and 41 (21, [85] – HNCO).

N-*Cyclopentylhydantoin* (**113**).–The oily hydroxymethyl derivative (**112**) from the reaction of the iodomethyl precursor (**107**) (294 mg, 1 mmol) was dissolved in a solvent mixture of

acetonitrile : water (4 : 1, 10 ml) at 0°C. To this solution was added CAN (3.29 g, 6 equiv.) and the mixture was stirred at 0°C for 2 hours before being allowed to reflux for 14 hours. The resulting solution was a pale green/yellow colour and after being extracted with $CHCl_3$ (3 x 20 ml) and dried ($MgSO_4$), the solvent was removed under reduced pressure. This gave an oily residue which solidified upon trituration with ether. This solid was purified using dry flash column chromatography (eluant petrol to ether) and finally recrystallised from a cyclohexane/ether mixture to give the *title compound* (60.5 mg, 36%), as a colourless solid m.p. 149-150°C. These crystals were also suitable for X-ray analysis, (Found: C, 57.3; H, 7.3; N, 16.6; $C_8H_{12}N_2O_2$ requires C, 57.1; H, 7.2; N, 16.7%); $\upsilon_{max.}$ ($CHCl_3$) 3 197 (NH), 1 767 and 1 719 (CO), 1 456, 1 423, and 1 109 cm^{-1}; δ_H (270 MHz; $CDCl_3$) 1.4-2.0 (8 H, m, cyclopentyl ring), 3.87 (2 H, s, 5-H), 4.2 (1 H, q, N-C*H*-Cp, J 8 Hz), and 9.18 (1 H, br s, NH); *m/z* 168 (M^+, 60%), 139 (100, M^+ – CHO), 101 (94, M^+ – ($CH{=}CHCH_2CH_2CH_2$)), 68 (59, $[CH{=}CHCH_2CH_2CH_2]^+$), 55 (20), and 41 (51, $[CH_2CO]^+$).

1-*Cyclopentyl*-4-(*methyl*)*imidazolin*-2-*one* (**114**).–The iodomethylimidazolone (**107**) (1g, 3.4 mmol) was taken up into THF (70 ml) and DBU (1.47 ml, 3 equiv.) was added to it. This mixture was refluxed for 4 hours before being left to cool. The precipitate was filtered off and the filtrate was evaporated under reduced pressure. The oily product was taken up into EtOAc (20 ml) and washed once with brine (20 ml) and after separating the layers the brine was back-extracted with EtOAc (2 x 20 ml). The combined organic layers were dried ($MgSO_4$) and the solvent was removed to give a buff solid (625.3 mg, 110%). The solid was purified using dry flash column chromatography (eluant petrol:ether (1:1) to EtOAc) and gave the *title compound* (512 mg, 91%) as a colourless solid, m.p. 154-156°C, (recrystallised

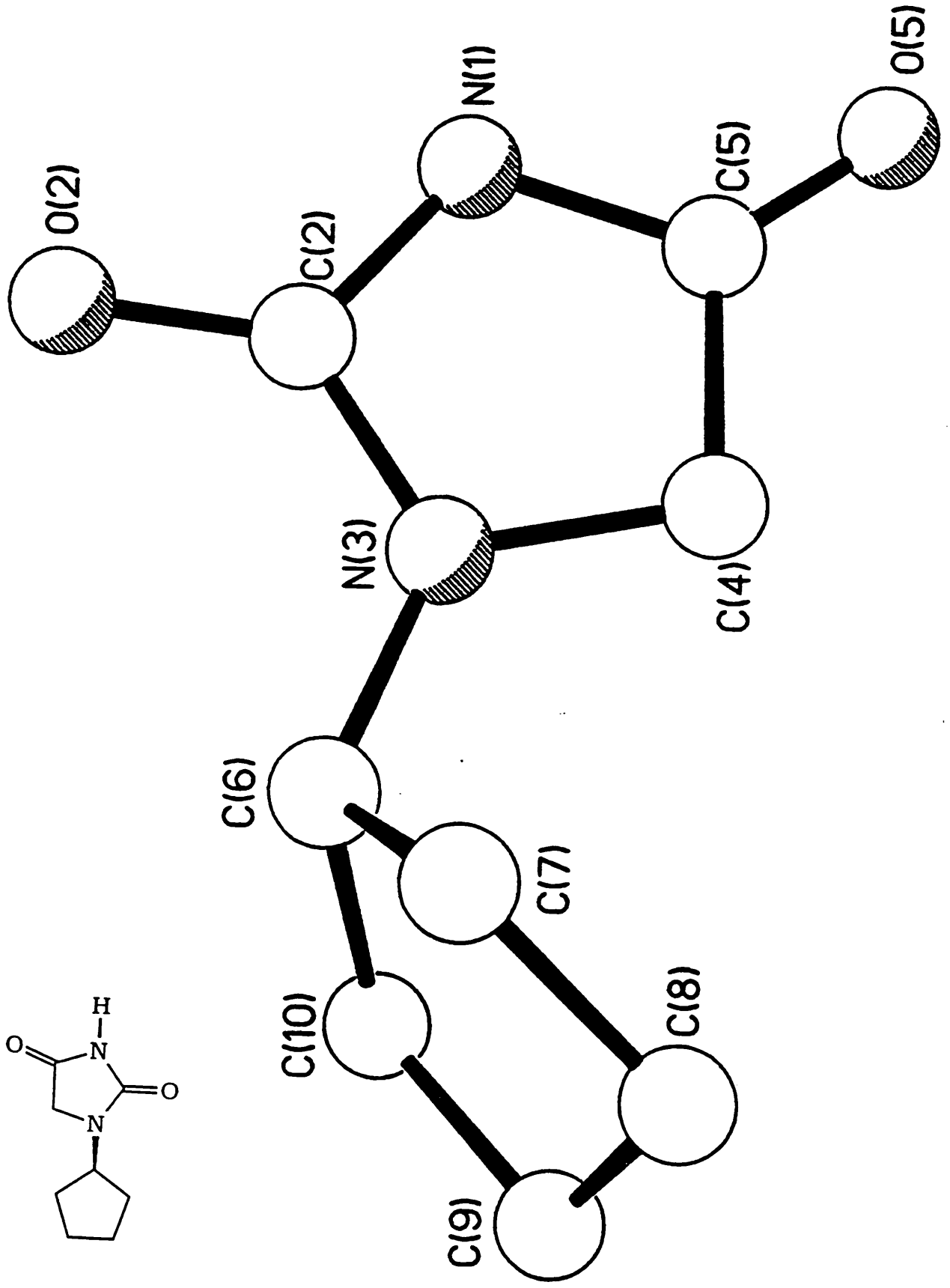
from cyclohexane), (Found: C, 64.8; H, 8.6; N, 16.6. $C_9H_{14}N_2O$ requires C, 65.0; H, 8.5; N, 16.9%); $\upsilon_{max.}$ ($CHCl_3$) 3 172 (NH), 1 709 and 1 670 (CO), and 1 416 cm^{-1}; δ_H (270 MHz; $CDCl_3$) 1.4-1.9 (8 H, m, cyclopentyl CH_2), 2.0 (3 H, s, 4-Me), 4.4 (1 H, q, N-C*H*-Cyclopentyl ring, J 7.3 Hz), 5.8 (1 H, s, 5-H), and 10.5 (1 H, br s, NH); *m/z* 166 (M^+, 6%), 115 (26), and 98 (100, $M^+ - C_5H_8$).

5-*Cyano*-1-*cyclopentyluracil* (**116**).–Cyclopentylamine (99 µl, 1 mmol) and α-cyano-β-ethoxy-*N*-ethoxycarbonylacrylamide (**115**) (217 mg, 1 mmol) were dissolved in methanol (6 ml) and heated to reflux for 4 hours. After this time the solution was cooled and stirred for 15 hours. The solvent was then removed under reduced pressure. The crude, yellow, solid residue produced was taken up into a DCM/methanol mixture and precipitated with the aid of 40-60°C petrol. The title compound (**116**) (121 mg, 59%) was isolated as a colourless solid, m.p. > 250°C. $\upsilon_{max.}$ ($CHCl_3$) 3 512, 3 441, 3 331, 3 270 (NH), 1 760 and 1 733 (CO), 1 599, 1 439, 1 404, 1 376, 1 330, 1 268, 1 207, 1 176, 1 100, 1 071, and 1 015; δ_H (270 MHz; CD_3COCD_3) 1.5-2.1 (8 H, m, Cyclopentyl CH_2's), 4.79 (1 H, q, N-C*H*-Cyclopentyl ring, J 7.8 Hz), 8.4 (1 H, s, 6-H), and 11.8 (1 H, br s, N-*H*); *m/z* 205 (M^+, 29%), 138 (100), 69 (41), 68 (55), 67 (3), and 41 (46).

APPENDIX ONE

X-Ray Data and Diagrams

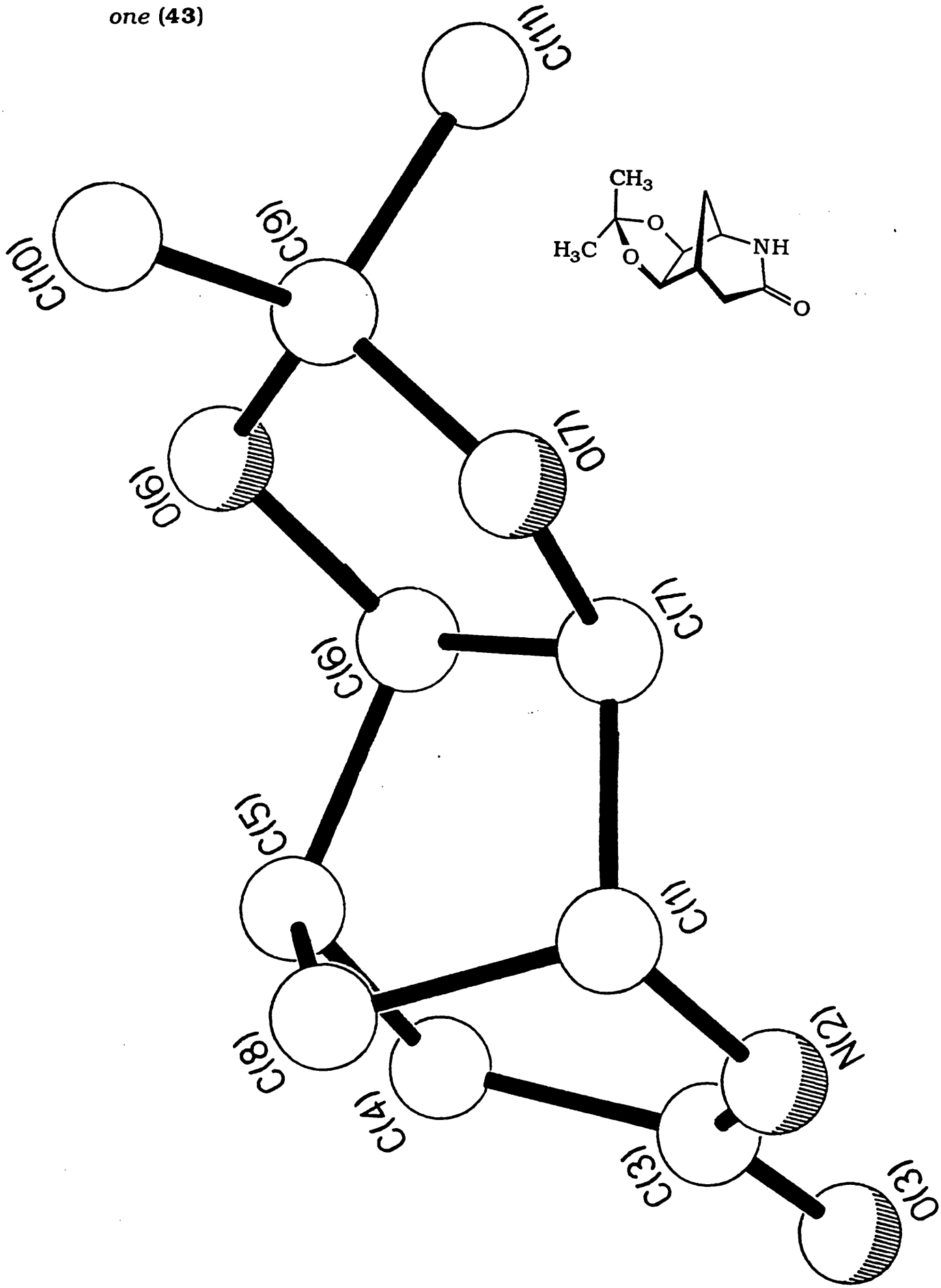
N-*Cyclopentylhydantoin* (**113**)



N-*Cyclopentylhydantoin* (**113**)

Crystal data: $C_8H_{12}N_2O_2$, M = 168.2, monoclinic, a = 11.295(4), b = 5.950(2), c = 13.248(5)Å, β = 104.84(3)°, U = 861Å^3, space group $P2_1/a$, Z = 4, D_C = 1.30 gcm^{-3}, Cu radiation, λ = 1.54178Å, μ(Cu-K_α) = 7 cm^{-1}, F(000) = 360. Data were measured on a Nicolet R3m diffractometer with Cu-K_α radiation (graphite monochromator) using ω-scans. 1149 Independent reflections were considered to be observed. The data were corrected for Lorentz and polarisation factors; no absorption correction was applied. The structure was solved by direct methods. The non-hydrogen atoms were refined anisotropically. The amine proton on N(1) was located from a ΔF map and refined isotropically. The positions of the remaining hydrogen atoms were idealised, C-H = 0.96Å, assigned isotropic thermal parameters, U(H) = 1.2 U_{eq}(C), and allowed to ride on their parent carbon atoms. Refinement was by block-cascade, full-matrix least-squares to R = 0.077, R_W = 0.089 [$w^{-1} = \sigma^2(F) + 0.00300F^2$]. The maximum and minimum residual electron densities in the final ΔF map were 0.31 and -0.31 eÅ^{-3} respectively. The mean and maximum shift/error in the final refinement were 0.013 and 0.070 respectively. Computations were carried out on an Eclipse S140 computer using the SHELXTL program system.

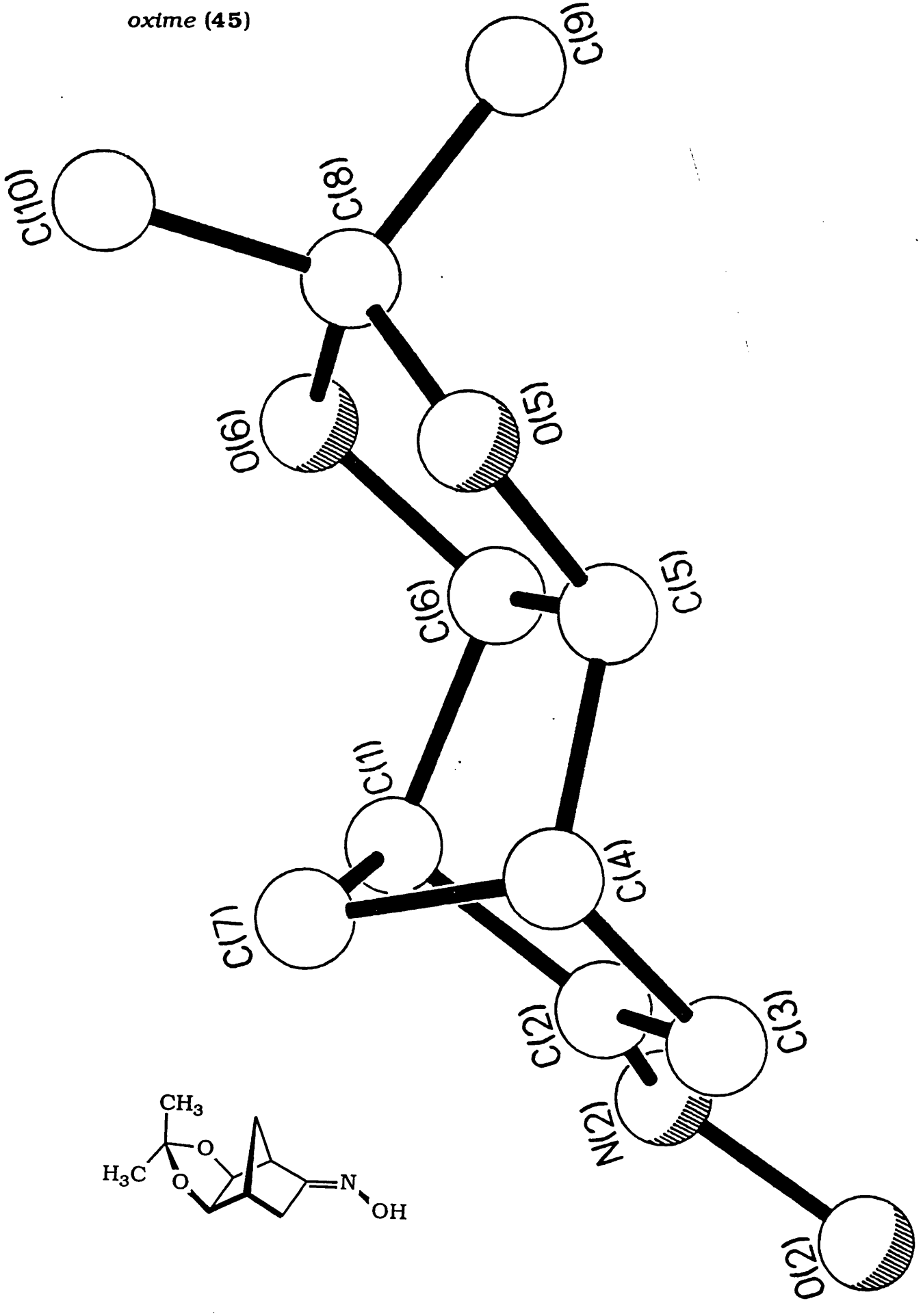
6-exo,7-exo-(*Isopropylidenedioxy*)-2-*azabicyclo*[3.2.1]*heptan*-3-*one* (**43**)



6-exo,7-exo-(*Isopropylidenedioxy*)-2-*azabicyclo*[3.2.1]*heptan*-3-*one* (**43**)

Crystal data: $C_{10}H_{15}NO_3$, M = 197.2, monoclinic, a = 6.554(3), b = 10.247(5), c = 15.141(7)Å, β = 96.78(4)°, U = 1010Å^3, space group $P2_1/a$, Z = 4, D_C = 1.30 gcm^{-3} , Cu radiation, λ = 1.54178Å, μ(Cu-K_α) = 8 cm^{-1}, F(000) = 424. Data were measured on a Nicolet R3m diffractometer with Cu-K_α radiation (graphite monochromator) using ω-scans. 853 Independent reflections were measured ($2\theta \leq 100°$), of which 815 had $|F_o| > 3\sigma(|F_o|)$ and were considered to be observed. The data were corrected for Lorentz and polarisation factors; no absorption correction was applied. The structure was solved by direct methods. The non-hydrogen atoms were refined anisotropically. The amine proton was located from a ΔF map and refined isotropically. The positions of the remaining hydrogen atoms were idealised, C-H = 0.96Å, assigned isotropic thermal parameters, U(H) = 1.2 U_{eq}(C), and allowed to ride on their parent carbon atoms. The methyl groups were refined as rigid bodies. Refinement was by block-cascade, full-matrix least-squares to R = 0.084, R_W = 0.105 [$w^{-1} = \sigma^2(F) + 0.00209F^2$]. The maximum and minimum residual electron densities in the final ΔF map were 0.26 and -0.22 eÅ^{-3} respectively. The mean and maximum shift/error in the final refinement were 0.025 and 0.127 respectively. Computations were carried out on an Eclipse S140 computer using the SHELXTL program system.

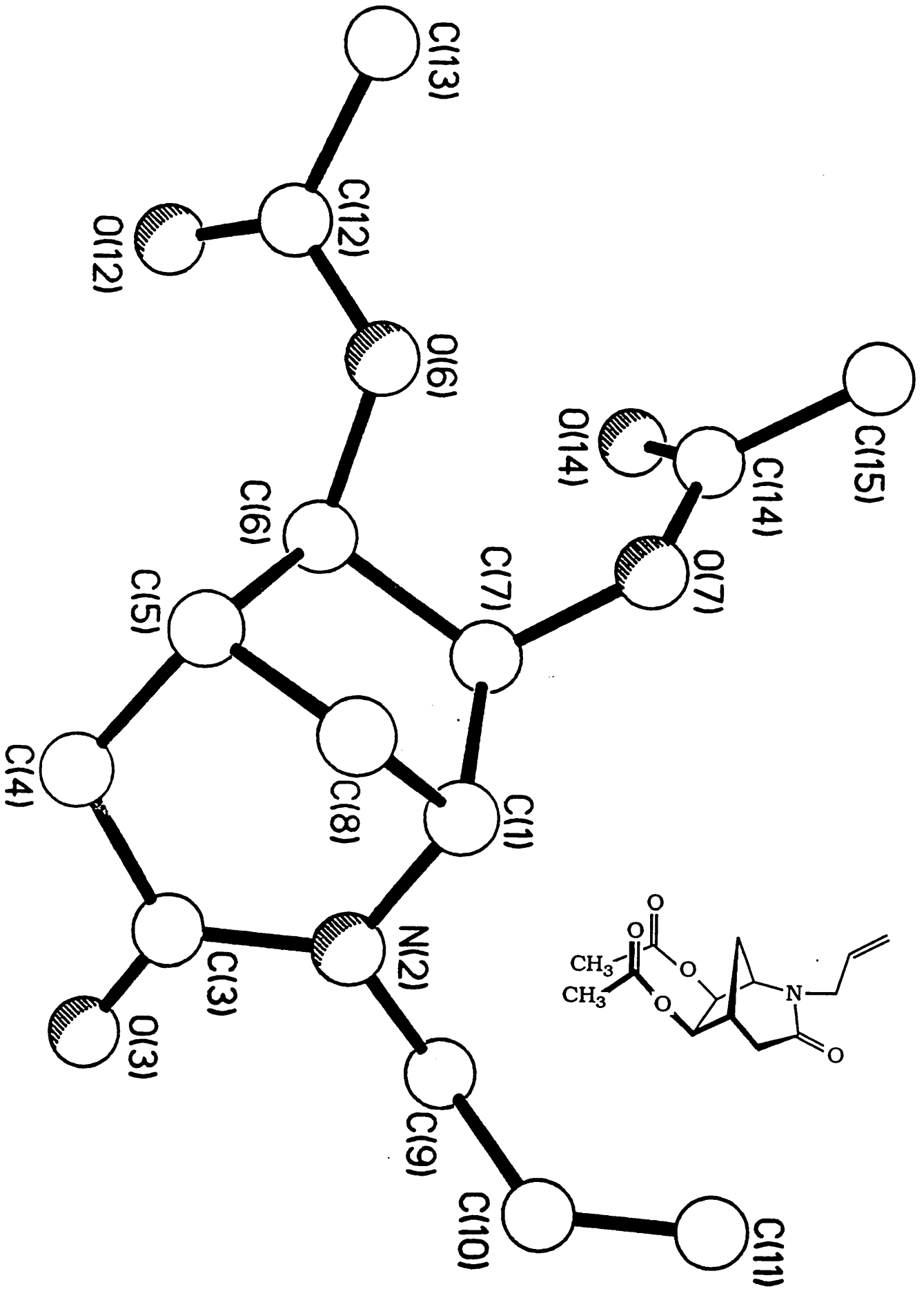
5-exo,6-exo-(*Isopropylidenedioxy*)-*bicyclo*[2.2.1]*heptan*-2-*oxime* (**45**)



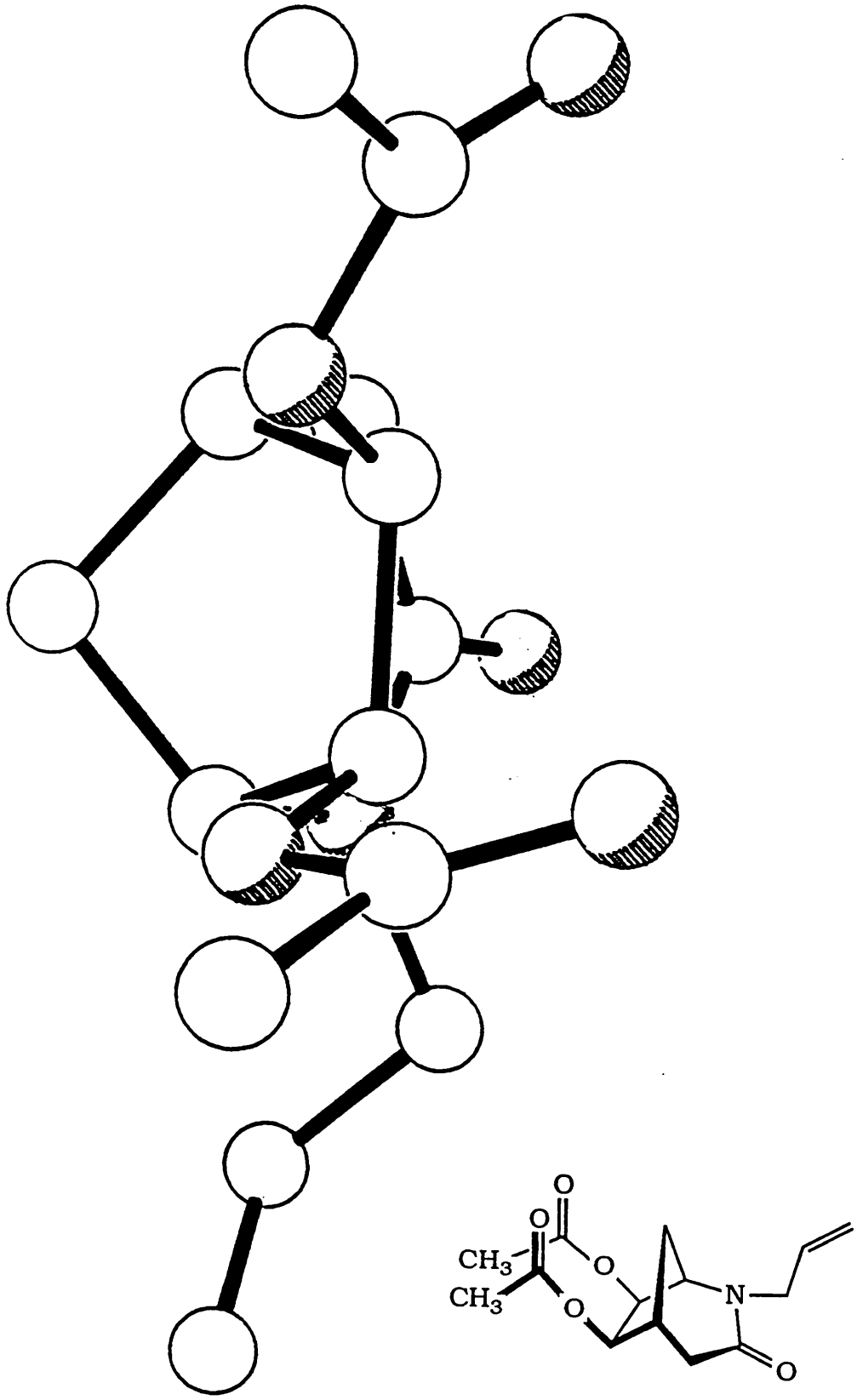
5-exo,6-exo-(*Isopropylidenedioxy*)-*bicyclo*[2.2.1]*heptan*-2-*oxime* (**45**)

Crystal data: $C_{10}H_{15}NO_3$, M = 197.2, monoclinic, a = 19.762(4), b = 8.936(2), c = 11.542(2)Å, β = 91.88(2)°, U = 2037Å^3, space group C2/c, Z = 8, D_C = 1.29 gcm^{-3}, Cu radiation, λ = 1.54178Å, μ(Cu-K_α) = 7 cm^{-1}, F(000) = 848. Data were measured on a Nicolet R3m diffractometer with Cu-K_α radiation (graphite monochromator) using ω-scans. 1374 Independent reflections were measured ($2\theta \leq 116°$), of which 1255 had $|F_o| > 3\sigma(|F_o|)$ and were considered to be observed. The data were corrected for Lorentz and polarisation factors; no absorption correction was applied. The structure was solved by direct methods. The non-hydrogen atoms were refined anisotropically. The hydroxy proton on O(2) and the protons on C(1) and C(4) were located from a ΔF map and refined isotropically. The positions of the remaining hydrogen atoms were idealised, C-H = 0.96Å, assigned isotropic thermal parameters, U(H) = 1.2 U_{eq}(C), and allowed to ride on their parent carbon atoms. The methyl groups were refined as rigid bodies. Refinement was by block-cascade, full-matrix least-squares to R = 0.039, R_W = 0.045 [$w^{-1} = \sigma^2(F) + 0.00071F^2$]. The maximum and minimum residual electron densities in the final ΔF map were 0.18 and -0.12 eÅ^{-3} respectively. The mean and maximum shift/error in the final refinement were 0.008 and 0.097 respectively. Computations were carried out on an Eclipse S140 computer using the SHELXTL program system.

6-exo,7-exo-(*Acetyl*)-*N*-*allyl*-2-*azabicyclo*[3.2.1]*heptan*-3-*one*
(66)



6-exo,7-exo-(*Acetyl*)-*N*-*allyl*-2-*azabicyclo*[3.2.1]*heptan*-3-*one*
(66)



6-exo,7-exo-(*Acetyl*)-*N-allyl*-2-*azabicyclo*[3.2.1]*heptan*-3-*one* **(66)**

Crystal data: $C_{14}H_{19}NO_5$, M = 281.3, triclinic, a = 7.167(3), b = 10.237(3), c = 11.202(4)Å, α = 63.58(3), β = 81.33(3), γ = 89.25(3)°, U = 726Å^3, space group P_1, Z = 2, D_C = 1.29 gcm^{-3}, Cu radiation, λ = 1.54178Å, μ(Cu-K_α) = 8 cm^{-1}, F(000) = 300. Data were measured on a Nicolet R3m diffractometer with Cu-K_α radiation (graphite monochromator) using ω-scans. 1956 Independent reflections were measured ($2\theta \leq 116°$), of which 1876 had $|F_o| > 3\sigma(|F_o|)$ and were considered to be observed. The data were corrected for Lorentz and polarisation factors; no absorption correction was applied. The structure was solved by direct methods. The non-hydrogen atoms were refined anisotropically. The bridgehead protons on C(1) and C(5) were located from a ΔF map and refined isotropically. The positions of the remaining hydrogen atoms were idealised, C-H = 0.96Å, assigned isotropic thermal parameters, U(H) = 1.2 U_{eq}(C), and allowed to ride on their parent carbon atoms. The methyl groups were refined as rigid bodies. Refinement was by block-cascade, full-matrix least-squares to R = 0.049, R_W = 0.068 [$w^{-1} = \sigma^2(F) + 0.00037F^2$]. The maximum and minimum residual electron densities in the final ΔF map were 0.21 and -0.19 eÅ^{-3} respectively. The mean and maximum shift/error in the final refinement were 0.035 and 0.423 respectively. Computations were carried out on an Eclipse S140 computer using the SHELXTL program system.

APPENDIX TWO

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1. The fermentation conditions and isolation methods will not be covered here. The reader is advised to see reference 3 and the references quoted therein if such information is required.
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