SYNTHETIC APPROACHES TO FUNCTIONALISED PIPERIDINES

A thesis submitted to the
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by

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ABSTRACT

Synthetic approaches to functionalised piperidines

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A thesis submitted in part fulfilment of
the requirements for the degree of D. Phil

This thesis is concerned with the synthesis of functionalised piperidines. The piperidine unit is found in numerous alkaloids and other natural products, and has also been incorporated into synthetic compounds of significant therapeutic or strategic synthetic potential. Although numerous syntheses of individual piperidine compounds have been published, there are few general routes to this class of compounds, and there is therefore a need for such routes to be developed.

Bicyclic lactams derived from (*S*)-pyroglutamic acid have been shown to be useful synthons in the synthesis of pyrrolidines. An analogous bicyclic lactam was therefore synthesised from (*S*)-lysine. Alkylations at the carbon atom α- to the lactam carbonyl group were studied in detail. A number of different groups could be introduced in good to excellent yield, and with moderate to good stereoselectivity. The selectivity of these reactions was believed to depend on the shape of the bicyclic system, and a stereoelectronic effect of the nitrogen lone pair.

The bicyclic lactam was further elaborated to an activated enone. This was shown to be relatively unreactive to cycloaddition reactions. It is believed that this is because the activating ester group is not conjugated with the carbon-carbon double bond. However, conjugate addition could be achieved in high yield and excellent stereoselectivity using a zinc enolate Reformatsky reagent. An epoxide could also be formed in excellent yield and with excellent stereoselectivity. The Reformatsky adduct was shown to be a suitable substrate for a Pb(IV)-mediated arylation reaction.

Examples of the functionalised lactams were deprotected to give hydroxymethyl piperidinones and cyclic amino acids. This route therefore allows access to the desired novel compounds.

ACKNOWLEDGEMENTS

First and foremost, I would like to thank Mark Moloney for four years of supervision over my part II and D. Phil. His enthusiasm, supportiveness, and availability have made him an ideal supervisor. I should also thank the EPSRC for a studentship, and Lancaster Synthesis for the financial support they have offered the project.

The DP technical staff have been invaluable during this work. Tim Claridge, Elisabeth McGuinness and Tina Jackson have run many spectra for me, and have always been ready to discuss them with me. The Robins have also been helpful, explaining why mass spectra sometimes suggest (erroneously) that I haven't made the desired compounds!

My colleagues in the Moloney group have been a memorable team to work with. I would particularly like to thank Paul Bulger, Phil Davies and Mark Hughes for proof-reading this thesis, and James Dyer for teaching me a great deal of experimental technique, but would also like to remember Diana, the wise woman of Hull, the notorious Kaz, the "star chemist" Phil, Rajesh, and five generations of part IIs for making rooms 65 and 69 such a distinctive place.

Oxford has been a great place to spend the last seven years, and that is due to a large extent to Tony, Paul, Eugenia, Susan, and all the other people I've known here. Thank you all.

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ABBREVIATIONS

APCI	atmospheric pressure chemical ionisation
BOC	*tert*-butyloxycarbonyl
COSY	correlation spectroscopy
c	concentration
δ	chemical shift
DCM	dichloromethane
DDQ	2, 3-dichloro-5, 6-dicyano-1, 4-benzoquinone
DMPU	N, N′-dimethylpropyleneurea
eq	equivalent
ES	electrospray
EtOAc	ethyl acetate
FMO	frontier molecular orbital
GCMS	gas chromatography mass spectrometry
HMBC	heteronuclear multiple bond correlation
HMQC	heteronuclear multiple quantum coherence
HOMO	highest occupied molecular orbital
LDA	lithium diisopropylamide
Lit.	literature value
LUMO	lowest unoccupied molecular orbital
MeOH	methanol
NMR	nuclear magnetic resonance
n. O. e.	nuclear Overhauser effect
NOESY	nuclear Overhauser effect spectroscopy
p. p. m.	parts per million
PPTS	pyridinium para-toluene sulphonate
R_f	retention factor
sat.	saturated
TFA	trifluoroacetic acid
THF	tetrahydrofuran
t. l. c.	thin layer chromatography

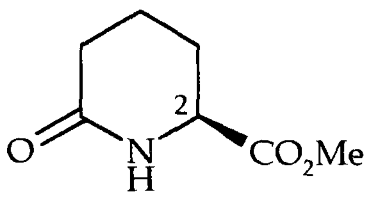
NOMENCLATURE

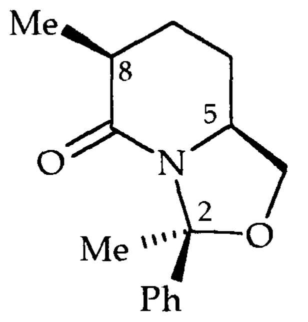
The nomenclature used to describe the compounds in this thesis is in accordance with the IUPAC conventions as detailed in "Nomenclature of Organic Chemistry. Sections A and B", Pergamon Press, Oxford, 1979, with the following exceptions:

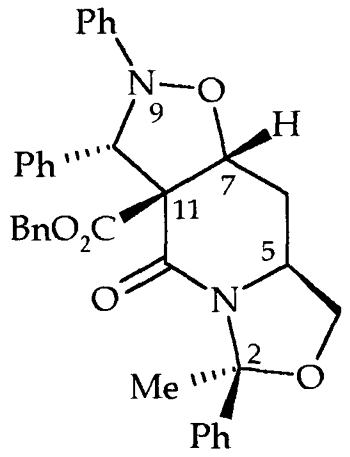
a. Known amino acids and derivatives thereof which do not increase the length of the main carbon chain are referred to as derivatives of the amino acid name, using standard amino acid nomenclature.

b. Trivial names are used when the S. I. name is cumbersome, or when the trivial name is more familiar than the S. I. name.

c. Bicyclic carbon skeletons are numbered in a non-systematic way, according to a convention within the research group, to facilitate the comparison of NMR spectroscopic data. The following are given as examples.







Introduction

1.1 An introduction to the piperidines

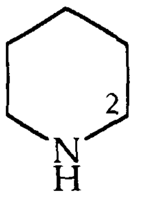


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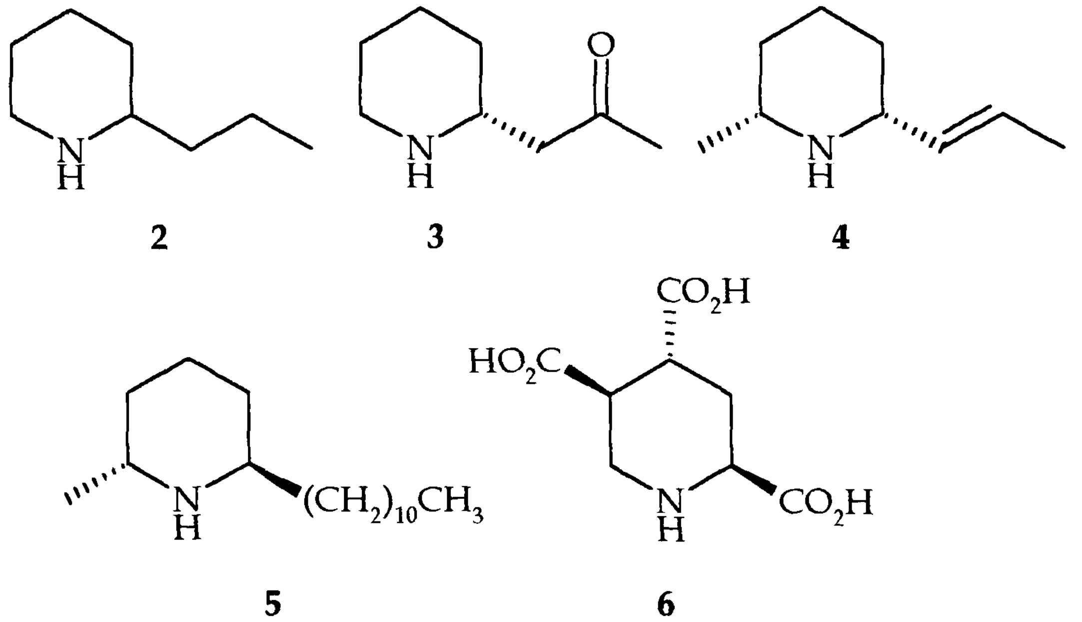
Figure 1

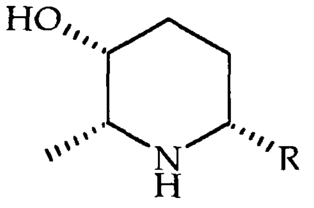
In recent years there has been considerable interest in the asymmetric synthesis of nitrogen heterocycles, including the piperidine ring system. This interest has in part been stimulated by the frequent occurrence of the piperidine sub-unit in natural systems,[1] and the biological effects shown by both natural and synthetic piperidine derivatives.[2] [3] [4] The ring system **1** is the root of the piperidine series, and displays a variety of substituents in natural systems. New piperidine alkaloids have been reviewed most recently by O'Hagan,[5] and continue to be isolated from both plants and animals.



2 **3** **4** **5** **6**

Figure 2

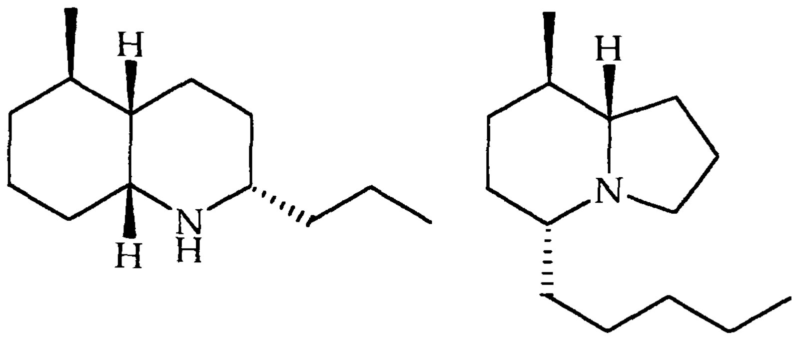
Simple piperidine molecules found in plants are often functionalised at the 2 or 6 positions of the ring. These have proved to be popular targets for synthetic chemists, including such examples as coniine (**2**), which was isolated from the hemlock *Conium* *maculatum*[6] and is found with both (*R*)- and (*S*)-stereochemistry at position 2. Another example of a naturally occurring piperidine alkaloid is (-)-pelletierine (**3**), which was isolated from pomegranate (*Punica granatum*) root bark, and has been found to have anthelmintic properties.[7] [8] A third group of piperidine alkaloids is found in pine and spruce trees. These have been investigated with particular regard to their importance in the chemical defence mechanisms of these trees against disease, insect attack and damage by herbivores such as cows. It has been observed that cows consuming needles of *Pinus ponderosa* are liable to premature parturitition or foetus abortion.[9] [10] [11] An example of a piperidine ring isolated from pines and spruces such as *Pinus ponderosa* that has been of interest to synthetic chemists is (-)-pinidine (**4**).[12] The piperidine alkaloids isolated from insects[13] [14] have included the solenopsins such as solenopsin A (**5**), A more unusual substitution pattern was recently reported when 2,4,5-piperidinetricarboxylic acid (**6**) was isolated from *Clitocybe acromelaga*.[15]



7 (-)-spectaline R=$(CH_2)_{12}COCH_3$
8 (-)-spectalinine R=$(CH_2)_{12}CH(OH)CH_3$
9 carnavaline R=$(CH_2)_{10}COCH_3$

Figure 3

The first natural piperidine alkaloids with DNA-altering properties to be reported were by Kingston *et al*[16] who isolated (-)-spectaline (**7**), (+)-spectalinine (**8**), and carnavaline (**9**) from the Brazilian legume *Cassia leptophylla*. A yeast bioassay was used to find DNA-modifying agents as for use in potential anti-cancer drugs, and tests found that spectaline and spectalinine were also cytotoxic in Vero monkey and Chinese hamster ovary cell assays.



10 **11**

Figure 4

Piperidine rings can also be found embedded in multi-cyclic systems such as indolizidine and quinoline alkaloids. Pumiliotoxin C (**10**) was isolated from the neotropical frogs *Dendrobates pumilio* and *D. auratus*, while indolizidine 209B (**11**) was isolated from *D. pumilio* and *D. histrionicus*. These have been the focus of much synthetic interest,[17] [18] as indolizidine alkaloids have been shown to act as non-competitive blockers of the passage of sodium ions through nicotinic acetylcholine receptor channels.[19]

Although a number of naturally occurring piperidine systems have been shown to have biological significance, it would seem that synthetic piperidines have exhibited greater therapeutic potential to date. One novel medical application for a piperidine derivative has been examined by Takamatsu *et al*,[20] who have used homochiral 3-aminopiperidine as a ligand in anti-tumor cis-platinum complexes.

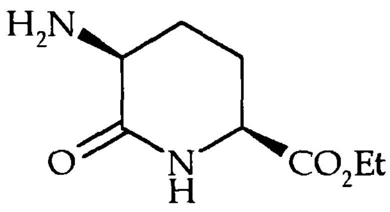


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Figure 5

Substituted piperidines have been increasingly tested as analogues for biologically important molecules. The underlying philosophy of this approach is that the behaviour of a biological system may be modified by substituting a substrate or agonist, for example, with a different molecule with similar functionality and geometry. The class of molecules known as peptidomimetics act as ligands for peptide receptors and thus block or mimic the biological effects of a peptide. This form of activity is seen when morphine coordinates to the opioid receptor, imitating β-endorphin, which is a 31 amino acid peptide, and the tetrapeptide Met-enkephalin. Efforts in this area have been reviewed by Giannis,[21] who notes that β-turns have been the most frequently imitated secondary structures, as they are common features of proteins, and are often found on their surface, serving as sites for molecular recognition. One example of a piperidine derivative that has been cited as a possible non-natural amino acid that could be incorporated into such molecular mimics is 3-amino-2-piperidone-6-carboxylic acid (Acp, **12**).[22]

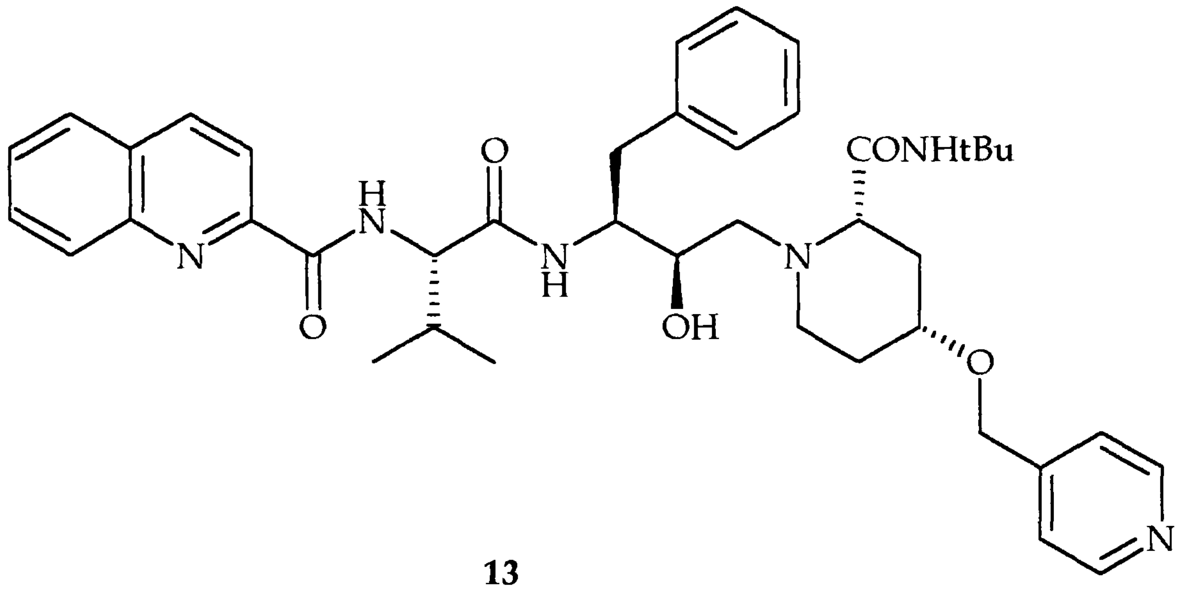

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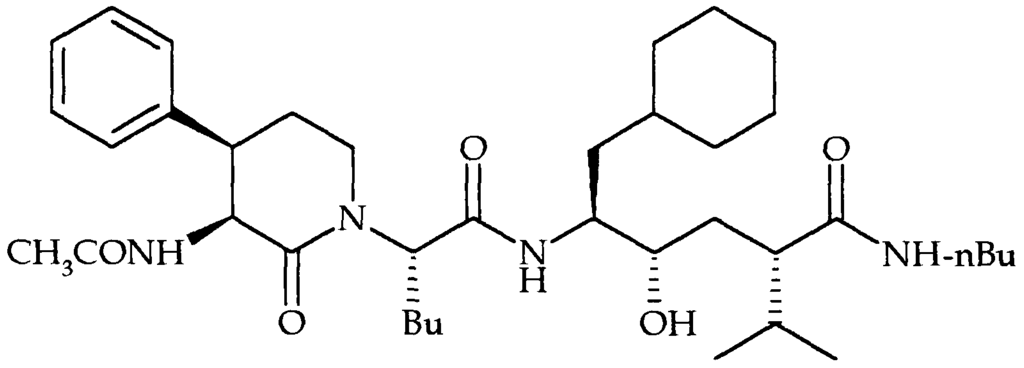
Figure 6

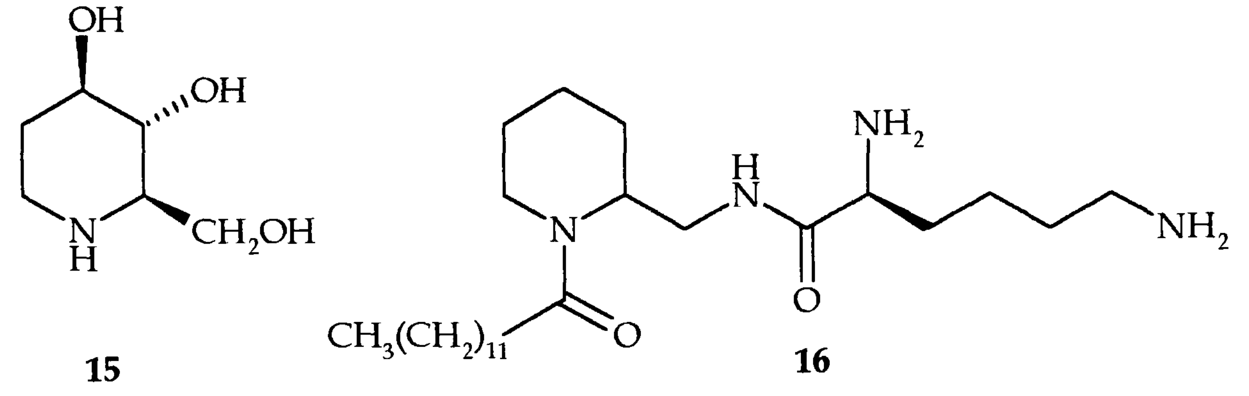
Peptidomimetics incorporating piperidine derivatives have been used in the inhibition of enzymes. In one recent example, palinavir (**13**), a 4-substituted pipecolic amide[23] is incorporated in a peptide which binds to the $S_{1'}$-$S_{2'}$ binding sites of the HIV-2 protease,[24] while a (*R*)-hydroxyethylamine residue acts as a transition state mimic.[25] Palinavir has been shown to be a highly potent inhibitor of the HIV protease enzyme, and could thus be of value in treating AIDS.



14

Figure 7

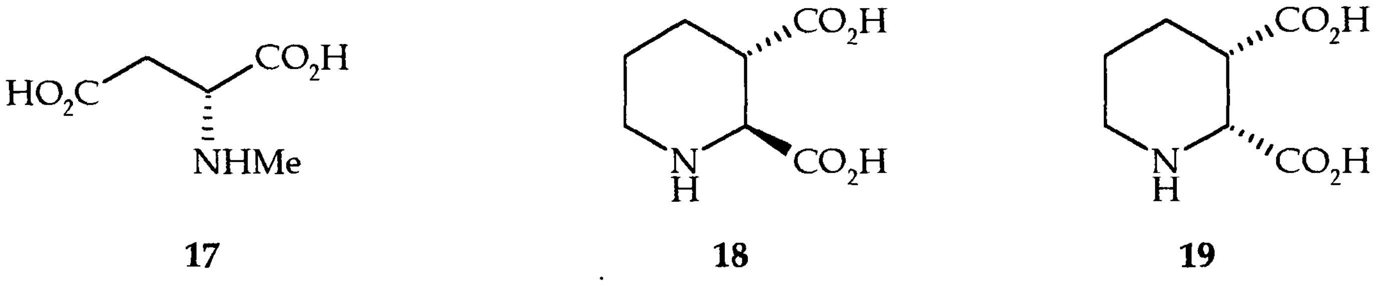
Another disease that has been the subject of much investigation is hypertension, and inhibitors of the aspartyl protease renin have thus been sought[26] in recent years. This enzyme is the first in the Renin Angiotensin System, which results in the formation of angiotensin II, a vasoconstricting hormone. De Laszlo *et al*[27] have developed 3-amino-4-phenyl-2-piperidones as phenylalanine isosteres. By using such conformationally restricted residues, the entropy change on binding the drug to its receptor or active site is reduced, which increases potency, and consequently allows the use of fewer amino acid residues, which, by reducing the molecular weight of the molecule improves its bioavailability. The use of non-amino acid residues in the drug should also improve its metabolic stability. An example of such a compound is shown in Figure 7.



15 **16**

Figure 8

Other enzymes have been shown to be susceptible to inhibition by hydroxylated piperidine derivatives including glycosidase[28] and isomaltase,[29] which is inhibited by (+)-fagomine (**15**). The piperidinemethanamines have been incorporated into several pharmaceuticals,[30] [31] [32] [33] but molecules such as **16** have been reported as having potent and selective protein kinase C inhibitory activity in their own right.[34]

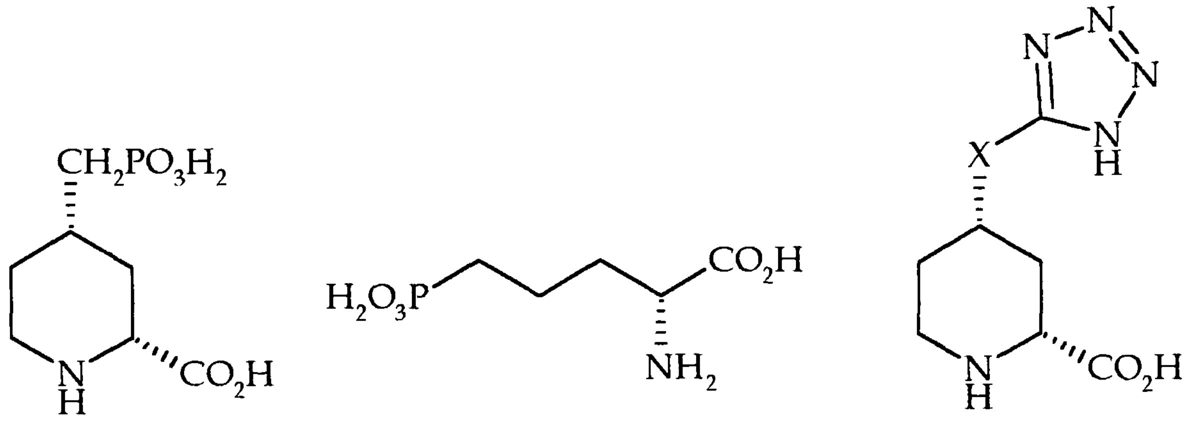


17 **18** **19**

Figure 9

Piperidine derivatives have also been developed as excitatory amino acid analogues. Excitatory amino acids, or EAAs, bind to receptors which are usually acted on by L-glutamic acid, which is the major neurotransmittor in the mammalian central nervous system. In particular, piperidines have been tested as NMDA (*N*-methyl D-aspartate, **17**) analogues. The NMDA receptor has been reviewed recently[35] and is of particular interest as its inhibition is known to attenuate excitotoxicity, since excessive activation of ionotropic glutamate receptors can be the indirect cause of cell death, which means that selective NMDA inhibitors may be useful in the treatment of CNS disorders such as epilepsy, stroke and Alzheimer's disease. The cyclic

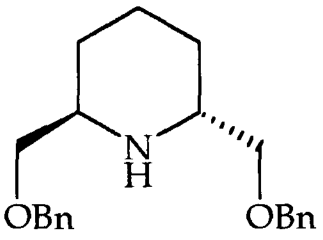
NMDA analogues **18** and **19** have thus been prepared,[36] but their biological activity is yet to be evaluated.



20 **21** **22**: X=OCH_2 **23**: X=CH_2OCH_2
24: X=S **25**: X=CH_2S

Figure 10

Antagonists of the NMDA receptor are also of interest. The phosphonate substituted piperidine CGS 19755 (**20**) has been prepared from ethyl isonicotinate,[37] while conformationally constrained analogues **22-25** of D-AP5 (**21**), a known competitive antagonist, have been prepared and found to be active. This activity may be due to hydrogen bonding to the oxygen or sulphur atom in the side chain.[38]



26

Figure 11

Chemists have also been able to exploit the piperidines as chiral auxiliaries in asymmetric synthesis. For example, the 2,6-disubstituted piperidine **26** has been shown to be of utility in both aldol and Diels-Alder reactions.[39] [40] C_2-symmetric chiral amines such as these have been investigated in detail in recent years, as the symmetry of the molecule has three important consequences for its use as an auxiliary: both faces of the auxiliary are equivalent, the number of diastereomeric transition states is reduced, and the atoms on the C_2-axis are chirotopic but not stereogenic, so there are no new centres to complicate the situation.

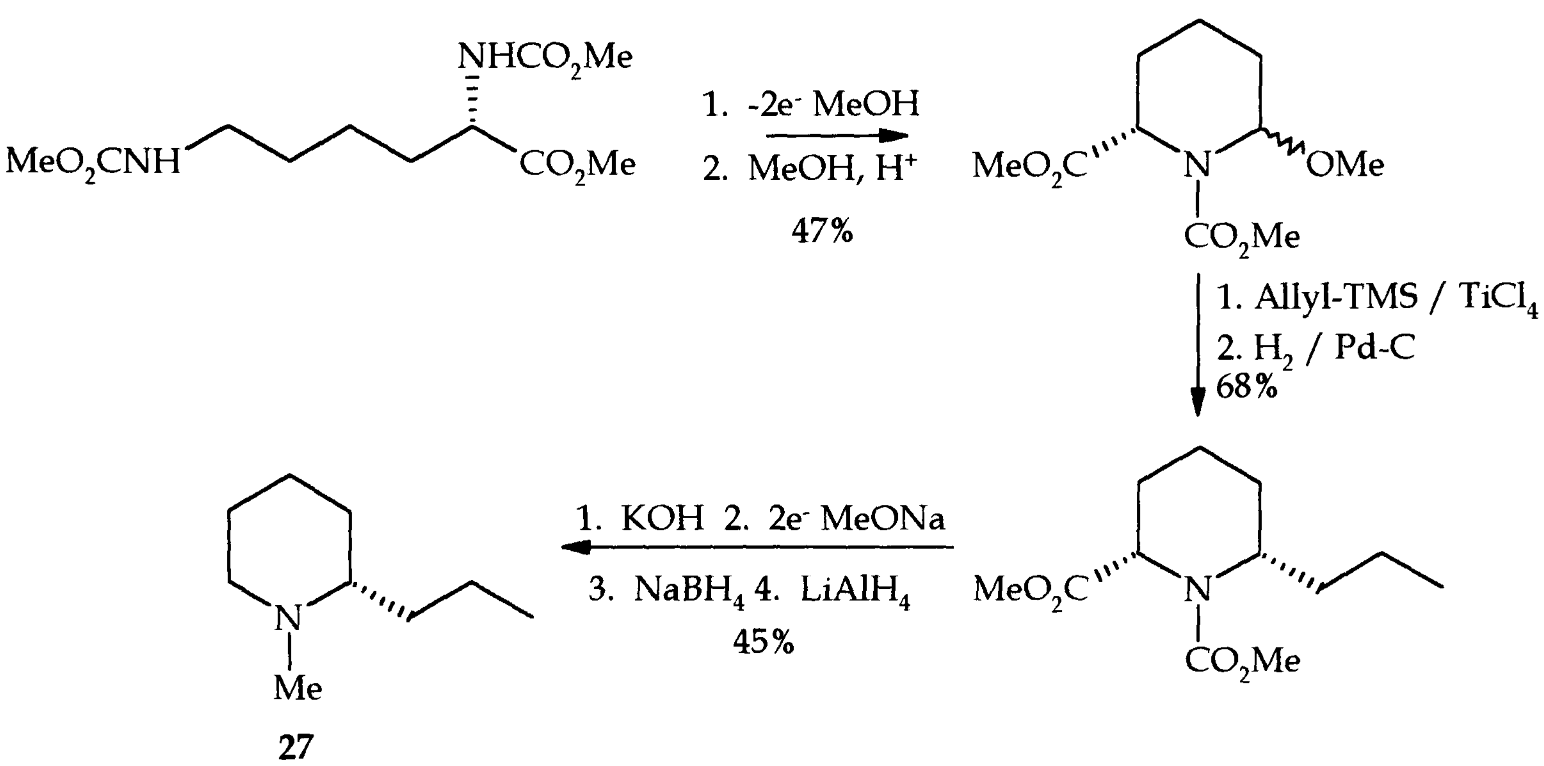
This brief survey has illustrated the wide range of applications substituted piperidines have found, and contrasted the relatively simple substitution patterns found in naturally occurring piperidine alkaloids with the variety of substituents with which chemists have functionalised the ring system in synthetic examples. Having shown why these compounds are of interest, some synthetic approaches to piperidines will now be discussed.

1.2 The asymmetric synthesis of piperidines

Historically, synthetic chemists interested in piperidines have focused on simple alkaloids such as coniine (2), and a large number of total syntheses of these compounds have been published. In recent years, however, it has become clear that non-natural piperidines displaying a more varied substitution pattern than has yet been seen in natural products not only offer far more scope for the chemist to practice their art, but afford new materials with much greater possible utility. Consequently, chemists have begun to investigate methods of functionalising all positions on the core ring stereoselectively. Some recent reviews of synthetic routes to these molecules include those by Lekevits,[41] Hammann,[42] Bailey *et al*,[43] and Nadin.[44] In this section four approaches to the synthesis of piperidines that have proved particularly popular are described. That is, the manipulation of naturally occurring amino acids, the Comins approach which utilises substituted pyridinium salts as starting materials, the so-called CN(*R*,*S*) method of Husson *et al*, and aza-Diels-Alder reactions.

1.2.1. The amino acids in piperidine synthesis.

Many workers have used starting materials from the chiral pool in their syntheses of piperidines. One recent review of the use of amino acids in the synthesis of nitrogen heterocycles by Rapoport and Sardina[45] found examples of piperidine syntheses from alanine, phenylalanine, lysine, ornithine, serine and aspartate. Lysine is the biosynthetic precursor for many piperidine alkaloids,[46] and so its popularity as a starting material for synthetic piperidines reflects nature. In one concise synthesis of *N*-methylconiine (27) the key, ring-forming, step is an anodic oxidation of protected lysine to produce an α-methoxylated carbamate. The stereochemistry of the carboxymethyl ring substituent is then used to promote exclusive formation of a *cis*-disubstituted piperidine intermediate on allylation, which on deprotection yields (+)-*N*-methylconiine exclusively (Scheme 1).



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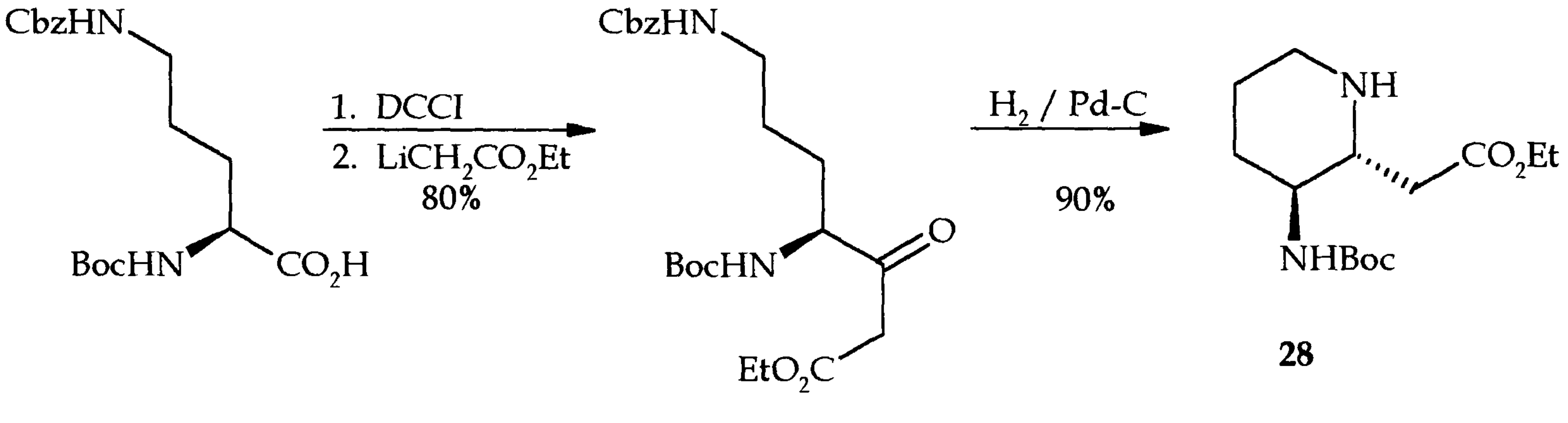
Scheme 1

In another example, ornithine is used as the starting material in the high-yielding synthesis of a *trans* 3-amino-2-piperidineacetic acid derivative (**28**) (Scheme 2). This synthesis is perhaps most remarkable for its brevity, and for the exclusive *trans*-relationship of the ring substituents.[47]



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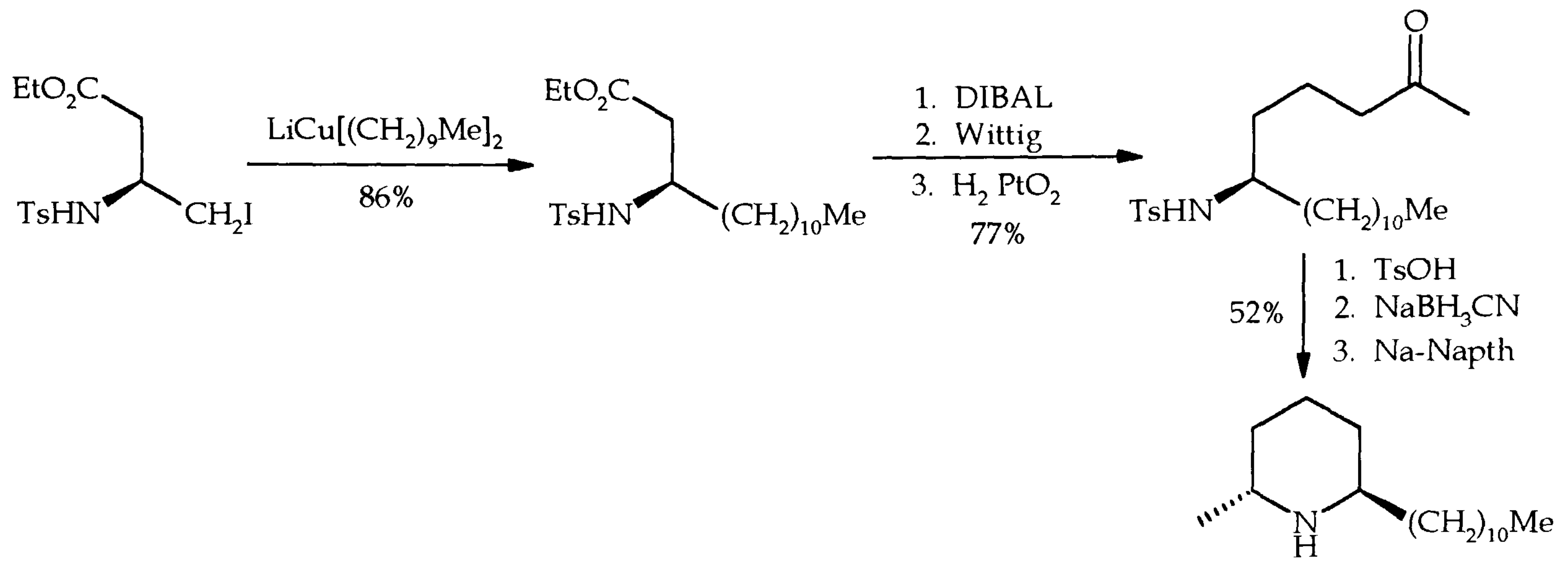
Scheme 2

An aspartate derivative was the starting point for a synthesis of solenopsin A (**5**) (Scheme 3).[48] In this case, an organo-cuprate reagent was used to extend the length of the carbon chain, and then manipulation of the carboxylic ester due to the side chain of aspartic acid allowed ring closure to give a 4.2:1 mixture of *trans*- and *cis*-diastereomers of solenopsin A (**5**).



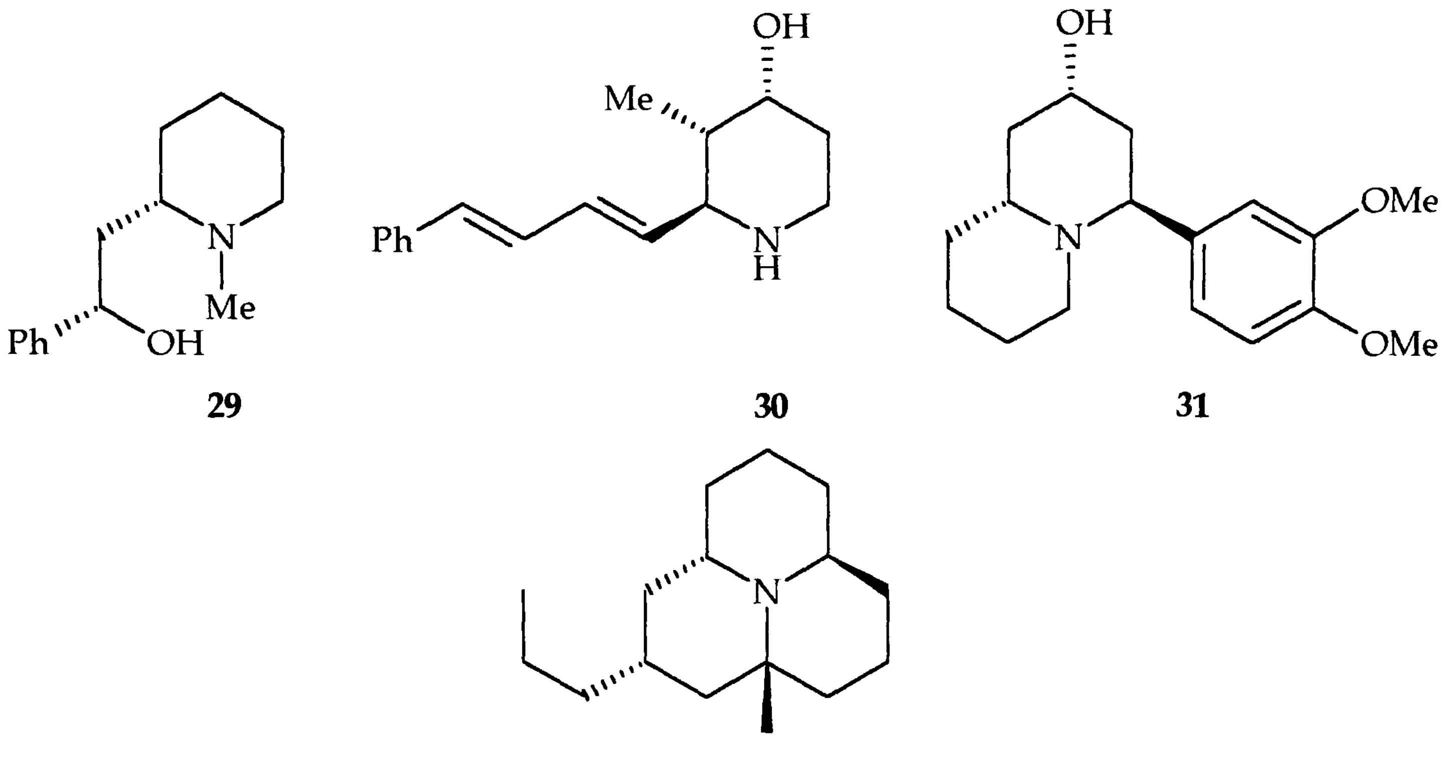
5

Scheme 3

These examples show some of the most useful syntheses of piperidines starting from amino acids, and demonstrate both the advantages and disadvantages of such an approach: the chirality of the original material may be manipulated in order to generate new molecules stereoselectively, but these syntheses are usually not suitable for use as general synthetic methods.

1.2.2. The Comins approach to functionalised piperidines

In recent years Comins has published many papers in the area of piperidine synthesis. The structural variety of the products that have been synthesised is not only an indication of the general applicability of his method, but illustrates the importance of piperidine chemistry. The same synthetic strategy has allowed the synthesis of all the compounds below, from simple monosubstituted examples such as (-)-sedamine[49] (**29**) through multi-functionalised piperidines such as (+)-dienomycin C[50] (**30**) to the more complicated alkaloids exemplified by (-)-lasubine I[51] (**31**), (-)-porantheridine[52] (**32**) and (-)-pumiliotoxin C[53] (**10**).

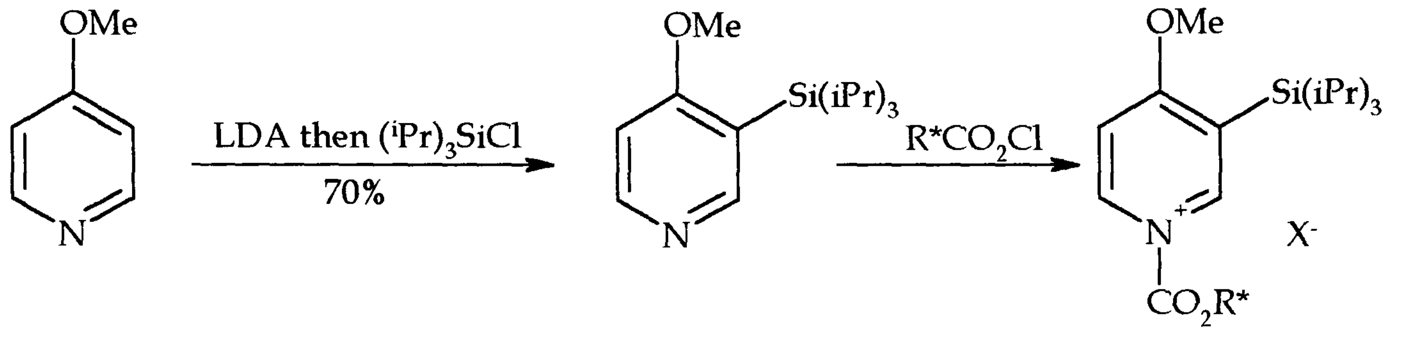


29 **30** **31**

32

Figure 12

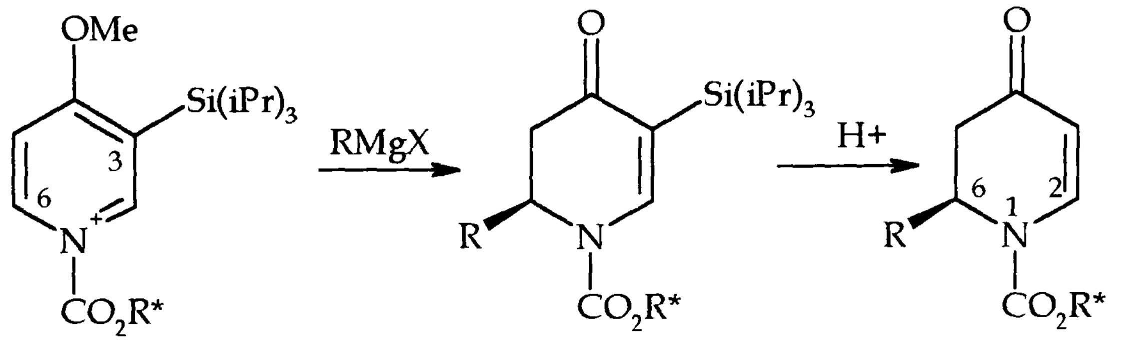
The starting point for the Comins route is an *N*-acyl pyridinium salt **33**, which can be made in two steps from commercially available materials, as shown in Scheme 4.



33

Scheme 4

First, 4-methoxypyridine is lithiated with lithium diisopropylamide, and then trapped *in situ* using chlorotriisopropylsilane to give the desired silylated pyridine in 70% yield.[54] The acyl pyridinium salt would then be generated *in situ* by treating this intermediate with the corresponding chloroformate. Model studies can be performed on achiral salts, for example where the acyl group is introduced using benzyl chloroformate, while asymmetric syntheses are performed on intermediates with a chiral acyl group. The key stages of the Comins route are shown in Scheme 5.



R*=(+)-TCC (trans-2-(α-cumyl)cyclohexanol)

Scheme 5

The selectivity of the Grignard reaction results from the substituent at position 3, and the chiral auxiliary attached to nitrogen: the bulky silyl group directs the incoming group to position 6 rather than the other α-position, position 2. The stereochemistry of the new chiral centre is determined by the auxiliary attached to nitrogen. The reverse enantiomer of the alcohol may also be used, in which case the stereochemistry at position 6 will be inverted. Initial investigations had adopted (-)-8-phenylmenthol as the chiral auxiliary, but the difficulty of obtaining its enantiomer led Comins to consider alternatives, with (-)-TCC being found to be the best option.[55] The origin of the stereoselectivity remains of interest, for though the authors have postulated that the aryl group of the auxiliary may block nucleophilic attack on one face of the pyridinium salt, the carbamate carbon-nitrogen bond has no double-bond character, and so free rotation between rotamers may be possible. However, it is thought that there may be π-stacking between the phenyl ring of the auxiliary and the pyridinium ring, which would favour one rotamer, and thus account for the asymmetric induction (see Figure 13(a) for an illustration). A crystal structure of one example of these intermediates lends support to this hypothesis.[56] The chiral auxiliary may be recovered easily by treating the intermediate with acid.

This method then affords chiral piperidinones **34** which may be elaborated further into more complex molecules, as shown in Figure 13(b):

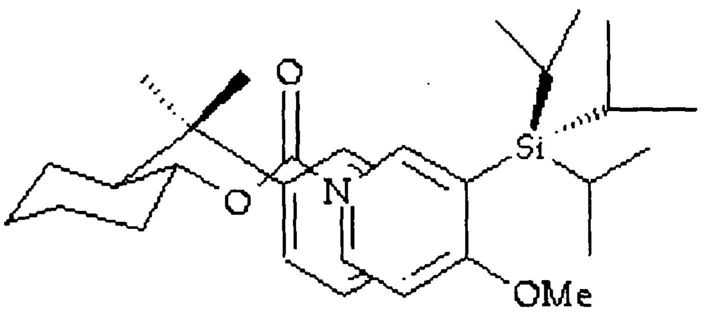
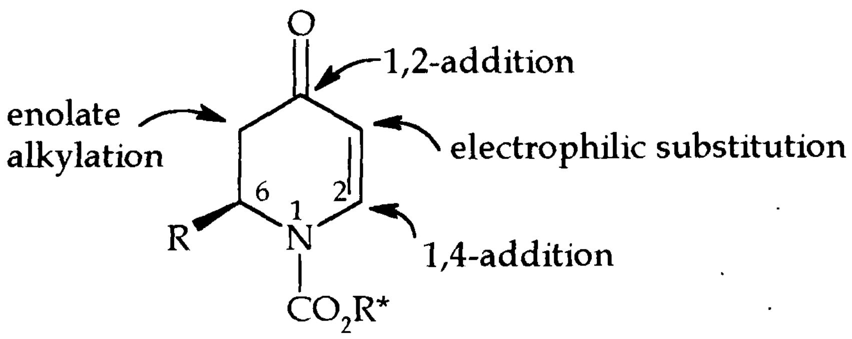


Figure 13(a)



34

Figure 13(b)

Thus, 1,2-addition to the carbonyl group may be effected using organocerium reagents,[57] 1,4-addition at C-2 may be effected using organocuprate reagents, for example,[58] functionalisation at C-3 may be achieved by electrophilic substitution[59] or an enolate formed at C-5 may be alkylated.[60]

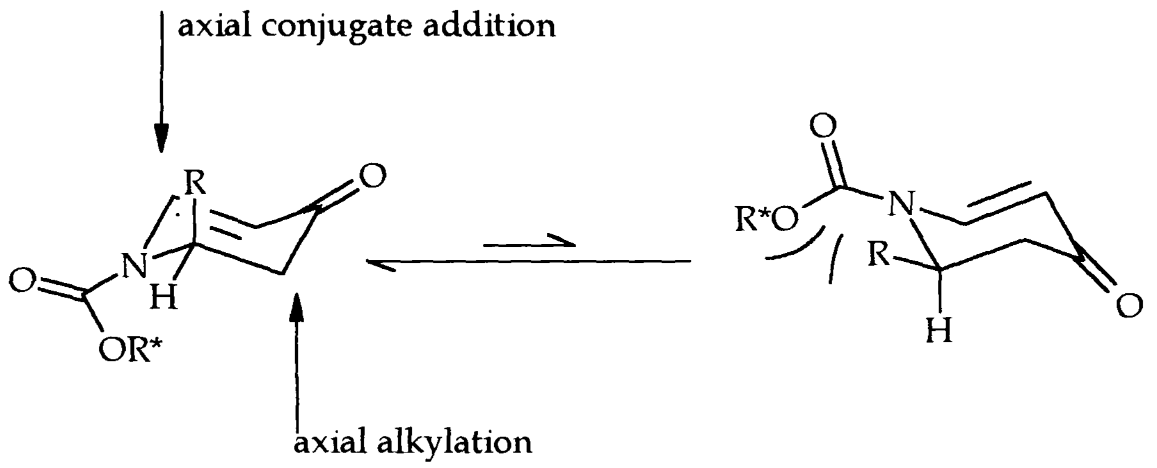
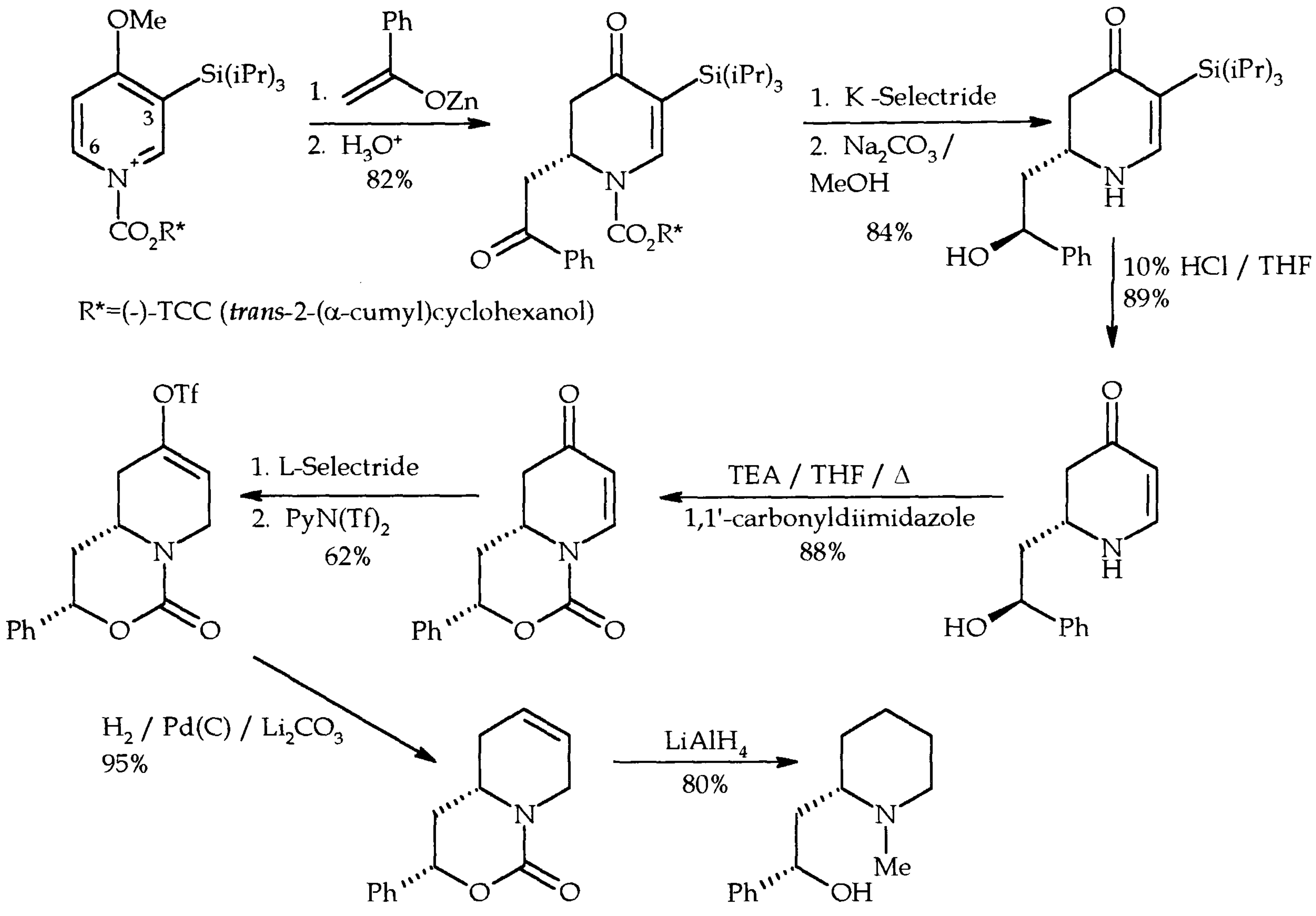


Figure 14

Comins has shown both by molecular modelling and by crystal structures[61] of various examples that the alkyl group at C-6 will adopt an axial position due to $A^{(1,3)}$ strain[62] between it and the *N*-acyl group. This means that conjugate addition at C-2 will be stereoelectronically preferred to give the *cis*-product, while alkylation at C-5 has a similar bias towards the *trans*-product, with both reagents attacking the less hindered face to introduce axial substituents.



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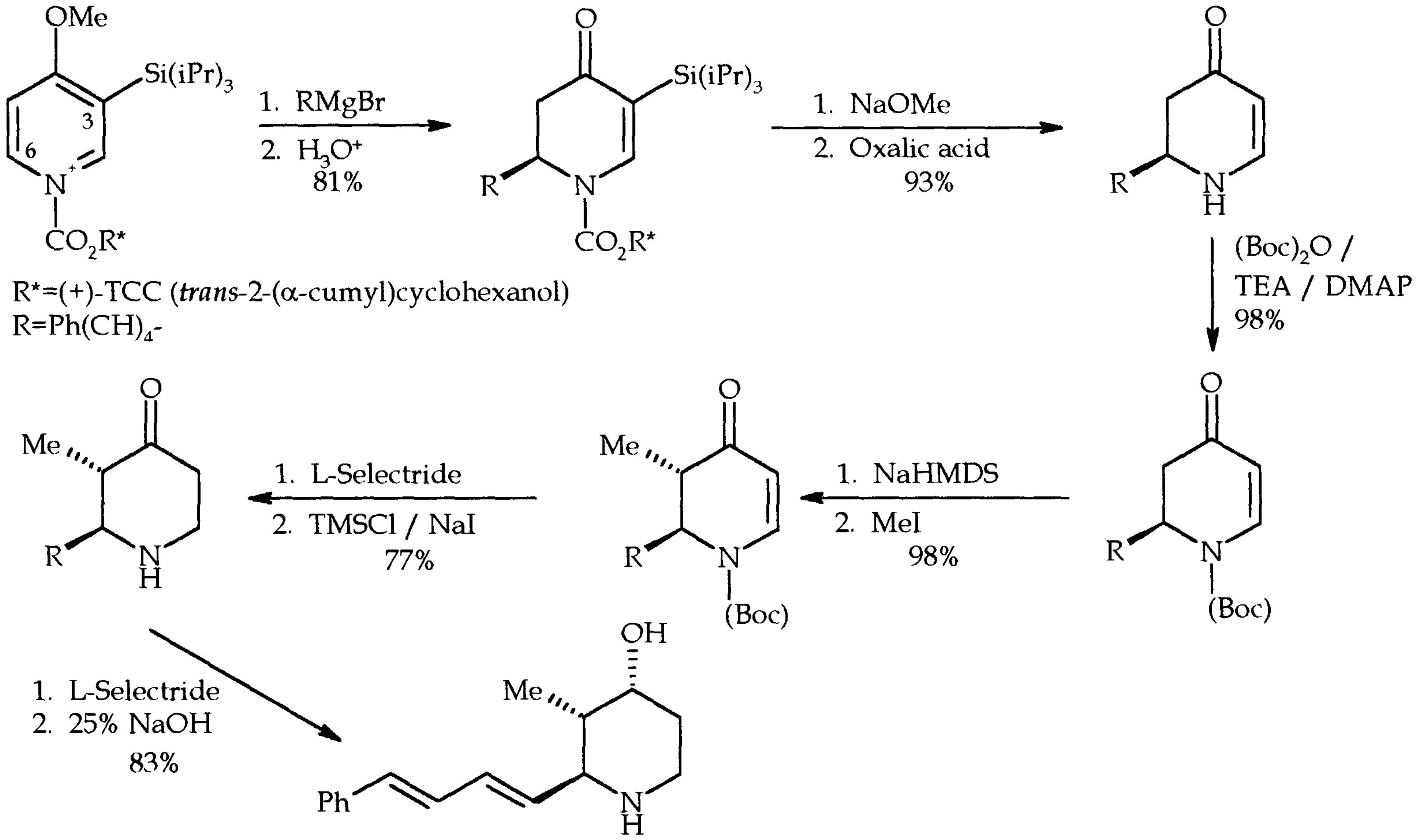
Scheme 6: Synthesis of (-)-sedamine (29)



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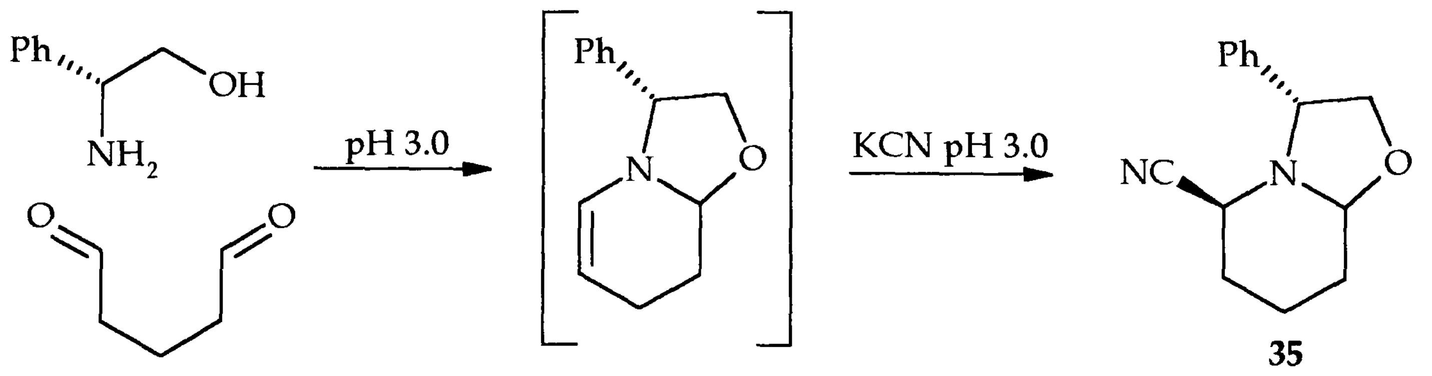
Scheme 7: Synthesis of (+)-dienomycin C (30)

It is instructive to compare the syntheses of (-)-sedamine and (+)-dienomycin C. These natural products differ in several respects, not least in the stereochemistry of the carbon atom adjacent to nitrogen. The generality of the Comins method is illustrated by the many similarities between these two syntheses. In each case, the initial step is an organometallic addition to an acyl pyridinium salt, with the stereochemistry of the new chiral centre being determined by the stereochemistry of the chiral auxiliary. In both cases the silyl group that is using as a directing group is removed by acid hydrolysis, and the reducing agents K- and L-Selectride both find applications in this work, with L-Selectride being used in both syntheses to remove the conjugated carbon-carbon double bond.

The Comins route therefore allows the preparation of a variety of compounds containing piperidine and similar ring systems, with asymmetric induction by the chiral alcohol incorporated in the N-acyl group. This auxiliary may be recovered in high yield, which makes this an especially attractive route to some classes of substituted piperidines.

1.2.3. The CN(*R*, *S*) route developed by Husson

The so-called CN(*R*, *S*) route has attracted much attention as a general route to piperidines. The starting point for the route is chiral 2-cyano-6-oxazolopiperidine (**35**), which is obtained by a Robinson-Schopf type condensation of glutaraldehyde with (-)-phenylglycinol.[63]

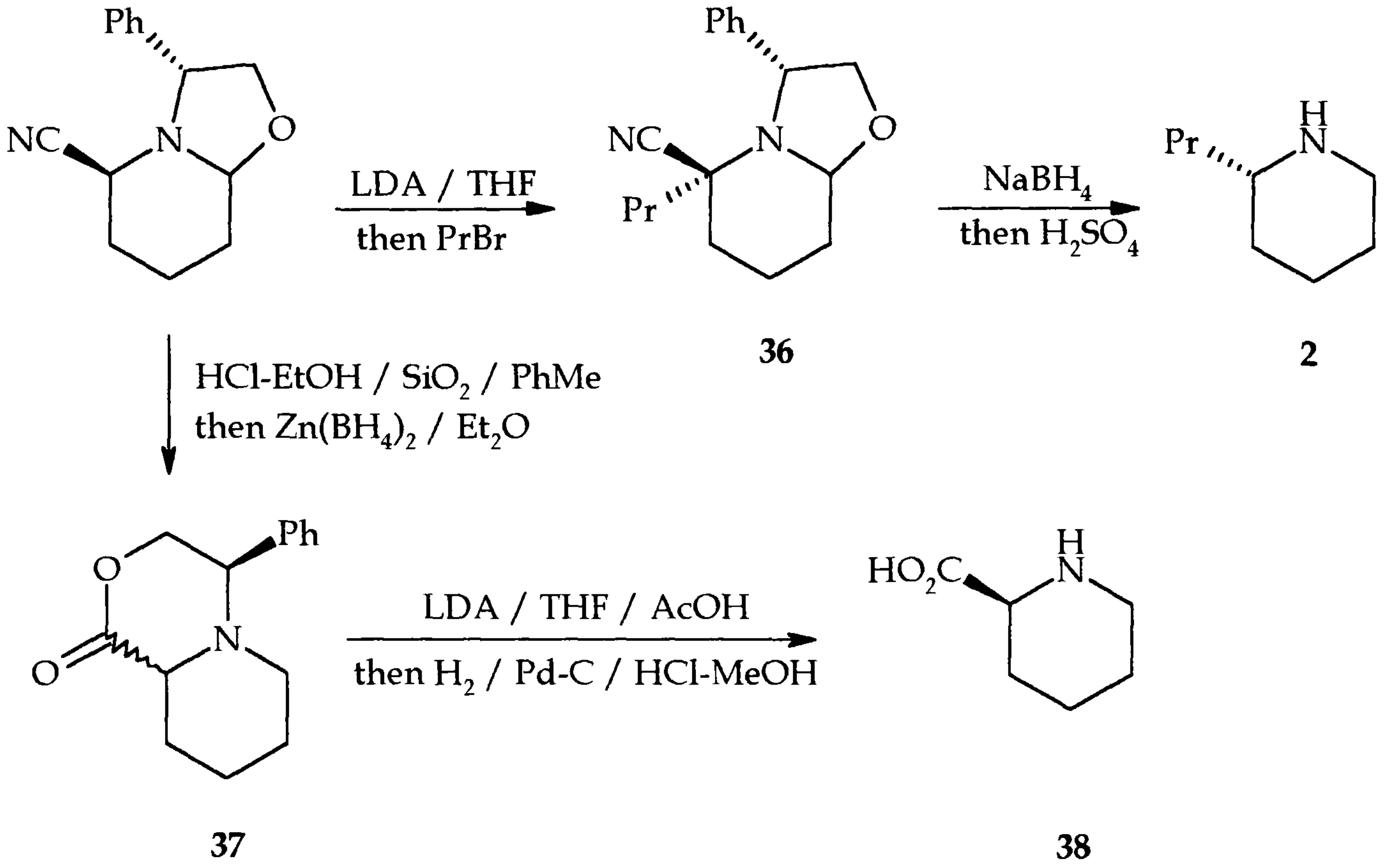


Scheme 8

Although the yield of this initial reaction is only moderate (50%), the substrate generated has potential for many manipulations, as the positions α- to nitrogen have been differentiated and consequently control over the four carbon centres C-2, C-3, C-5 and C-6 has been asserted. Manipulations of this starting material have utilised four separate reactivities:

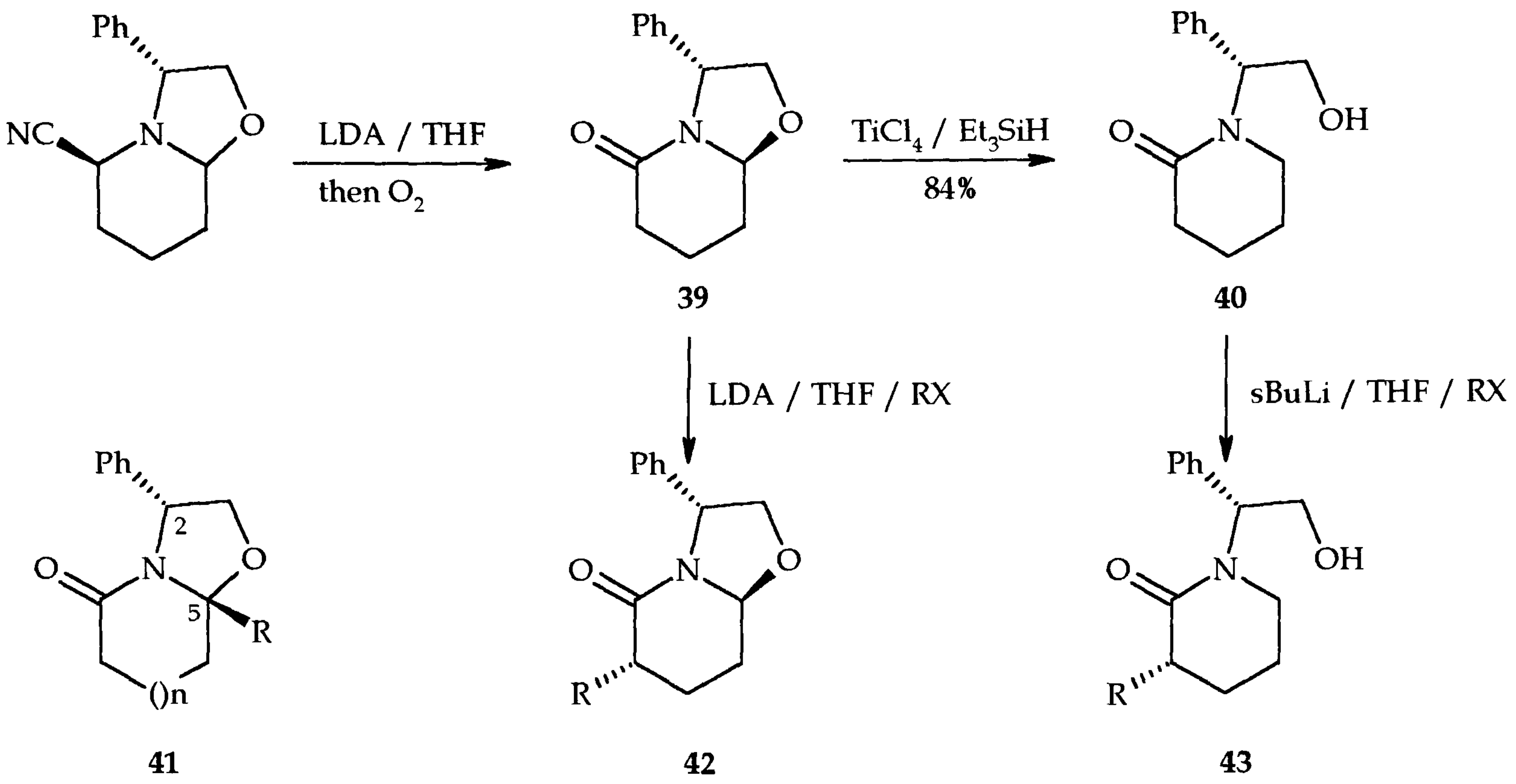
1. Deprotonation α- to the cyano group, followed by alkylation.
2. Nucleophilic substitution of the cyano group.
3. Manipulations of the cyano group itself, for example conversion to a guanidine group.
4. Base catalysed elimination of the cyano group allowing electrophilic attack at C-3.

This template has thus been a starting material for many syntheses, including those of (-)-coniine[63] (2) and (*S*)-(-)-pipecolic acid[64] (38) which are shown in Scheme 9.



Scheme 9

In the first example, deprotonation using lithium diisopropylamide followed by alkylation with propyl bromide gives the intermediate **36** as one diastereomer, which may be deprotected by sodium borohydride followed by acid to give (-)-coniine. In the second, the cyano group is hydrolysed to a carboxylic acid group, and then ring opening by zinc borohydride is followed by intramolecular esterification to give the intermediate 37. This can then be epimerised to the desired diastereomer using lithium diisopropylamide and acetic acid, and then hydrogenolysis will produce the desired product 38.

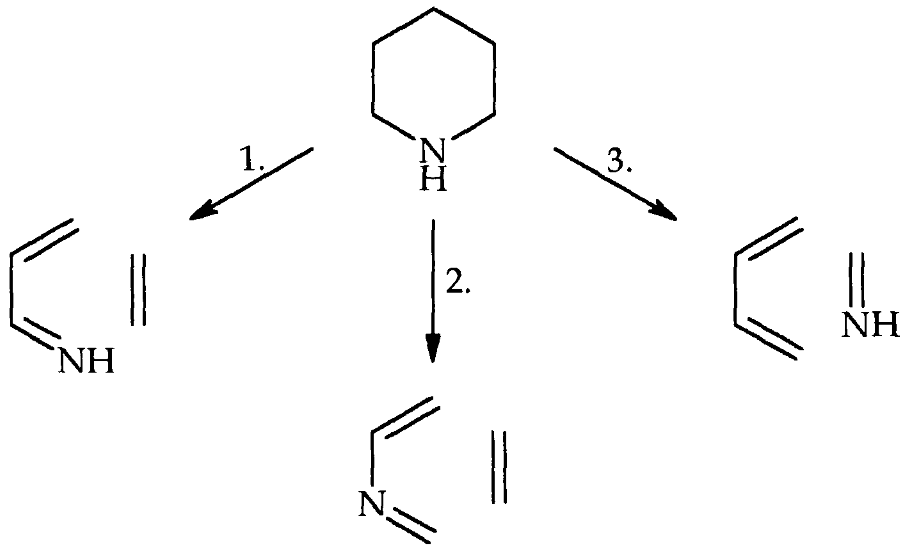


Scheme 10

Further work by Husson has shown that the bicyclic lactam **39** may be prepared in a straightforward manner from the cyano-substituted bicycle **35**. This bears an obvious similarity to the Meyers bicyclic lactams **41**[65] which have been investigated extensively for the synthesis of 5-membered nitrogen heterocycles (n=0), but are difficult to obtain and apply to the synthesis of piperidines (n=1).[66] Interestingly, Husson and co-workers were not able to alkylate at position 3,[67] but found that the monocyclic lactam (**40**) underwent stereoselective alkylation. Later workers have, however, succeeded in alkylating at this position.[68] Both these lactams are alkylated with complete diastereoselectivity, and thus offer a route to substituted piperidines. Further elaborations have been investigated by both groups of workers.

1.2.4. Aza-Diels-Alder chemistry

In recent years, Diels-Alder cycloadditions to form the six-membered piperidine ring have been investigated. There are three obvious disconnections of the ring, namely: to an alkene and a 1-azadiene (Scheme 11, 1.), to an alkene and a 2-azadiene (Scheme 11, 2.) and to a diene and an imine (Scheme 11, 3.).

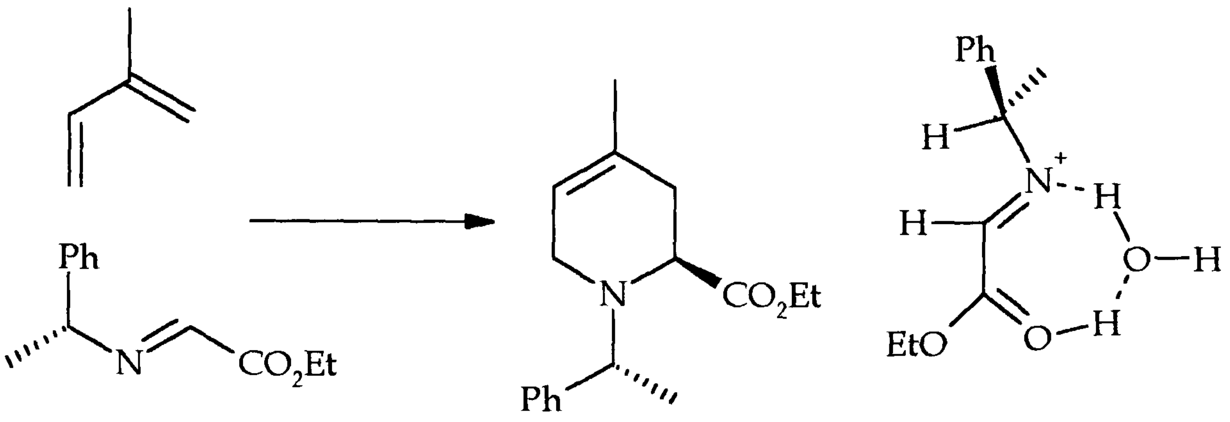


Scheme 11

These reactions have been reviewed recently by Waldmann,[69] and although all three routes have been attempted, the third has shown the most success to date. In the first route, the 1-azadienes have been shown to be unreliable reactants in cycloaddition reactions, as competing imine-type reactions frequently dominate.

It can be difficult to attach a chiral auxiliary to a 2-azadiene, which renders the second route less attractive, but Ghosez[70] has succeeded, and produced respectable yields of piperidines by this route. He and co-workers have found that substitution at C-3 by (for example) a methyl group promotes addition rather than polymerisation to give intractable tars, presumably because the *cis*-oid population is higher in the substituted azadiene. In later work[71] he has found that a copper (II) complex will catalyse these reactions effectively, so that yields are increased from the earlier range of 50-70% to between 85 and 90%. This approach is thus significantly more successful than previous attempts to form piperidines using Diels-Alder reactions.

It is, therefore, perhaps surprising that most examples of piperidine syntheses which rely on the Diels-Alder reaction feature the reaction of an imine with a chiral auxiliary attached with a diene. One such example is Bailey's use of the α-methyl benzyl group (Scheme 12):

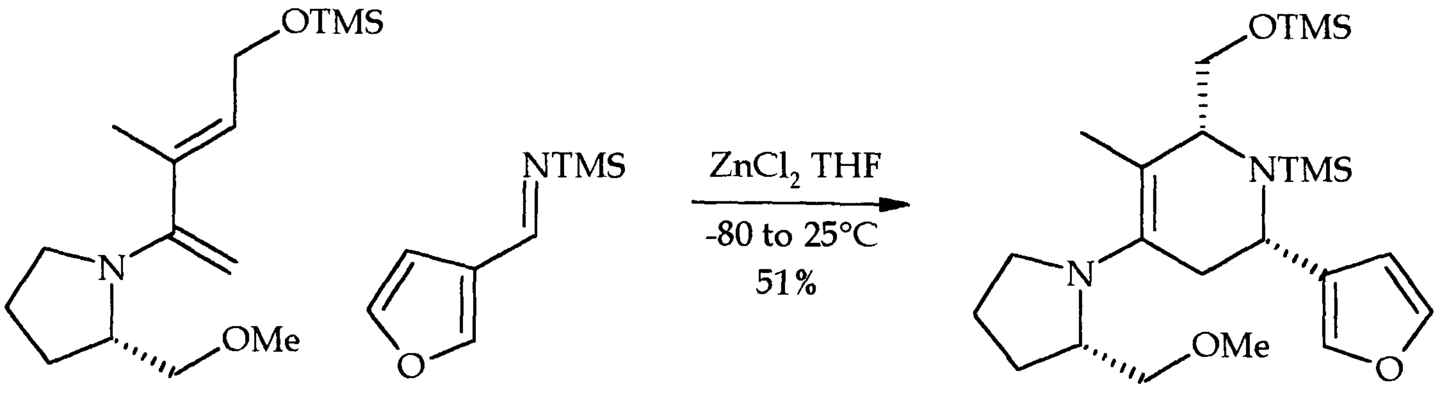


44

Scheme 12

In this case, the authors suggest that with the (*R*)-α-methylbenzyl auxiliary a seven membered ring complex **44** with water is formed, which means that dienes approach *endo* and below the plane of the iminium ion, thus giving the selectivity shown.[72] The authors note that an (*R*)-auxiliary directs the diene to attack on the *si* face of the imine to give (*S*)-stereochemistry at the chiral centre α-to the nitrogen, and that an (*S*)-auxiliary would be expected to promote attack on the *re* face to give (*R*) stereochemistry at this chiral centre.

Other workers have placed the source of chirality in the diene component, such as Barluenga in his approach to Nuphar alkaloids,[73] where a chiral diene is added to *N*-trimethylsilyl-3-furaldimine:



Scheme 13

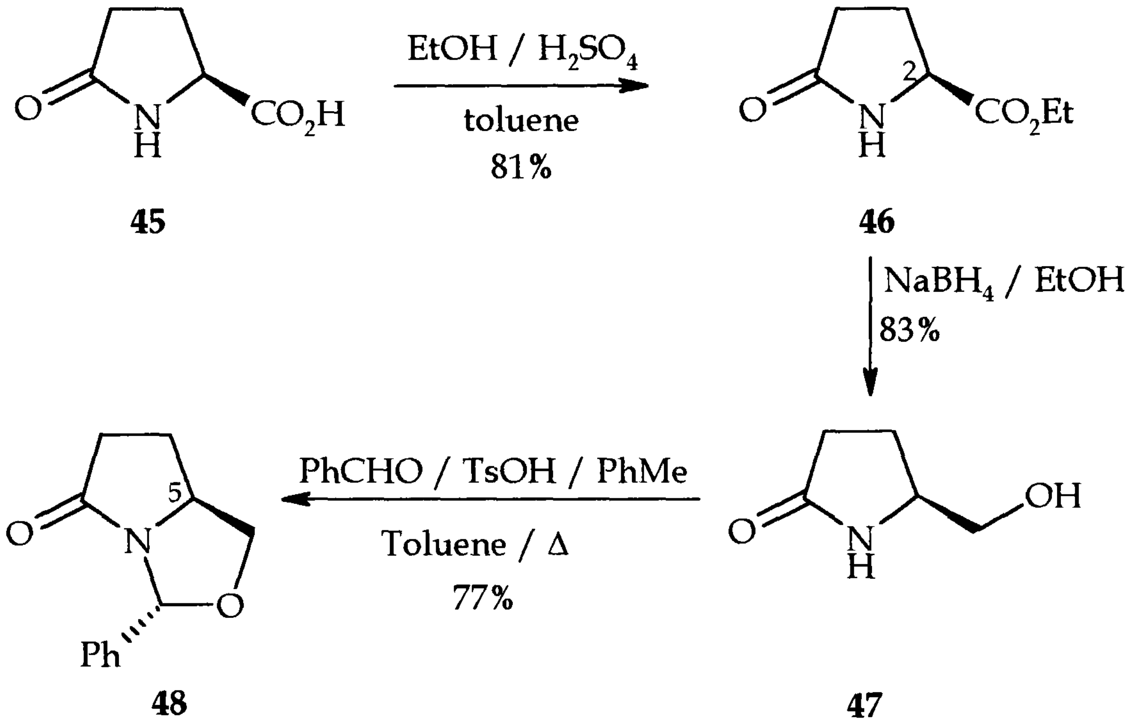
An aqueous sodium bicarbonate wash will then remove the TMS groups and hydrolyse the enamine to a ketone group to give a piperidine functionalised at three positions in the ring stereoselectively. The stereochemical course of this reaction has been controlled by the chiral pyrrolidine substituent.

In both these examples the yield of the Diels-Alder reaction has been rather disappointing (43% and 51% respectively). This means that unless the desired piperidine is formed in the cycloaddition, or after a short series of manipulations of the cycloadduct, this route will not be a method of choice. The observation that *N*-alkylated imines tend to be relatively unreactive in Diels-Alder reactions with all but the most reactive, that is, electron-rich dienes is also a serious limiting factor for this approach to piperidine synthesis.[74]

In this section some examples of popular synthetic approaches to piperidines have been described. To date, no single approach has been found that would allow the rapid asymmetric synthesis of a wide range of piperidine targets, and the apparent simplicity of the piperidine ring system has been found to mask a number of complexities in the stereoselective synthesis of these compounds. There is, therefore, a continuing need for the development of high-yielding, widely applicable synthetic routes to these interesting compounds.

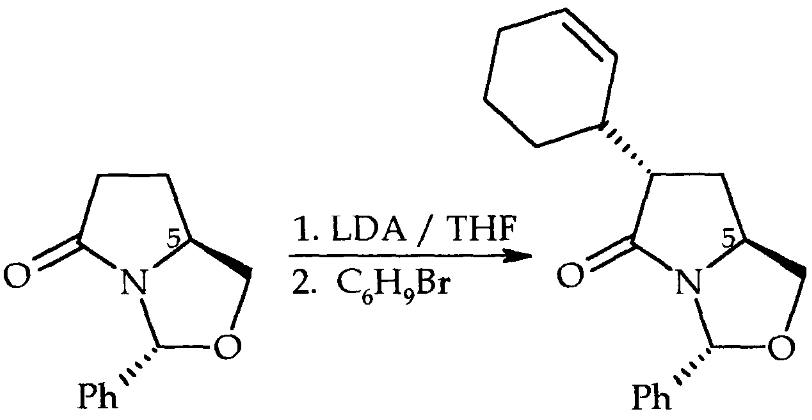
1.3 The synthesis of nitrogen heterocycles from pyroglutamic acid

One compound from the chiral pool that has found particular application in the synthesis of nitrogen heterocycles is pyroglutamic acid. Both enantiomers of this non-proteinogenic amino acid are readily available and inexpensive. A recent review[75] details many applications of this starting material in asymmetric synthesis. A notable protected form of (*S*)-pyroglutamic acid (**45**) was first synthesised by Thottathil[76] in 1986 (Scheme 14).



Scheme 14

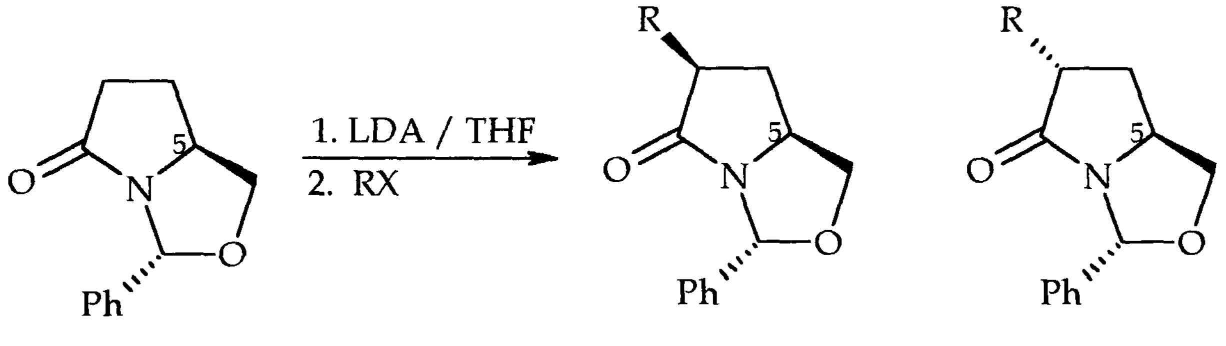
In this approach, (*S*)-pyroglutamic acid (**45**) is esterified using ethanol in refluxing toluene under acid catalysis to give the ethyl ester (**46**) in good yield. This ester is then reduced using sodium borohydride to give the pyroglutaminol (**47**) in good yield, which can be protected easily using benzaldehyde to give an *O*, *N* acetal **48**. This protection has several benefits: first, position 5 of this bicyclic system (**48**) is considerably less acidic than the corresponding position 2 of pyroglutamic acid or its ester. This means that alkylation reactions may be performed without compromising the integrity of the initial chiral centre. Secondly, both the nucleophilic nitrogen and oxygen atoms are protected, which means that reactions with electrophiles occur only at the desired position. Thirdly, both these functional groups are protected with a single protecting group, rather than separate groups for each functional group. Consequently, the molecular weight of the chiral template (**48**) is lower than it would have been had the groups been protected separately. This means that not only is the synthesis simpler, but the mass of auxiliary groups to be removed in deprotection reactions later in a synthetic strategy is reduced. Finally, the stereoselectivity of reactions on this system should be greater than those performed on the unprotected pyroglutamic acid, as the bicyclic system is rigid, with a concave and a convex face, and the latter is likely to be more easily approached by reagents. Thottathil's initial results would confirm this analysis, as he reported that alkylation using LDA and then cyclohexyl bromide (Scheme 15) gave the *exo*-product (**49**) with a diastereomeric excess of more than 95%.



48 **49**

Scheme 15

In recent years Moloney and co-workers have investigated the potential applications of this acetal to the synthesis of pyrrolidinones. Repetition of the Thottathil alkylation procedure with a number of different electrophiles allowed the introduction of a range of substituents at position 7 of this bicyclic system (Scheme 16, Table 1).[77]



48 a - "endo" b - "exo"

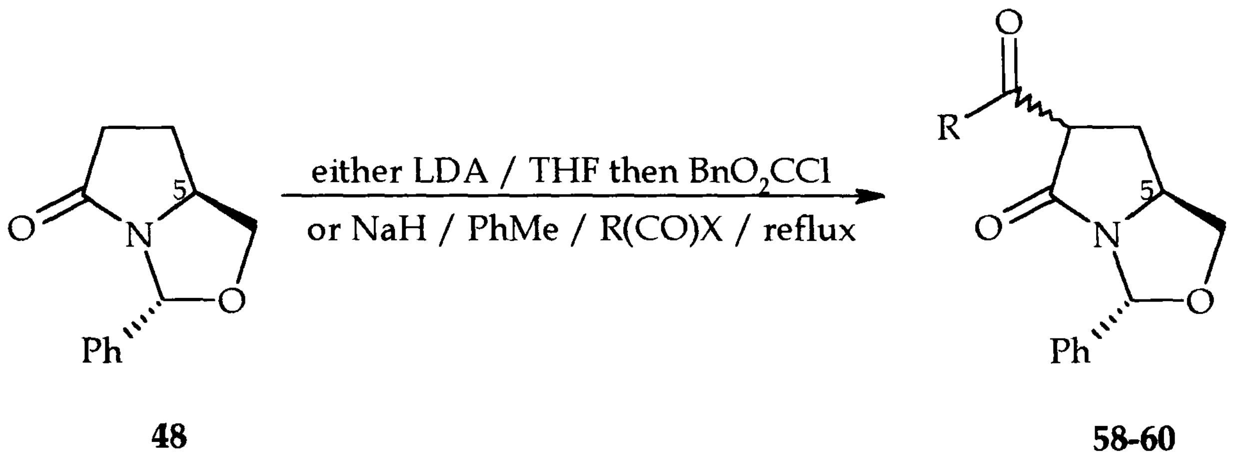
Scheme 16

Table 1: Alkylations of lactam **48**

Product	Electrophile, RX	Yield	Ratio a:b
50	CH_2=$CHCH_2Br$	74	1.0:1.3
51	$PhCH_2Br$	60	1.0:2.1
52	I_2	44	1.0:2.7
53	$pNO_2C_6H_4CH_2Br$	62	1.0:3.6
54	N-bromosuccinimide	42	1.0:3.8
55	PhSeCl	38	1.0:3.8
56	TsCl	77	2.5:1.0
57	MeI	76	2.9:1.0

Although the diastereoselectivity of these reactions is slightly disappointing given the precedent published by Thottathil, it can be seen that the *exo*-diastereomer predominates in these alkylation reactions also, with the exception of the introduction of the chloro- and methyl- groups, where the *endo*- diastereomer is favoured. This would be consistent with the steric bulk at C-5 rendering *endo* attack less favourable, as the higher diastereoselectivities are observed with more sterically demanding electrophiles.

The introduction of an acyl group has been attempted in three ways: by quenching the LDA enolate in benzyl chloroformate,[78] or by refluxing the bicyclic lactam (**48**) with sodium hydride and either methyl benzoate or diethyl carbonate in toluene[77] (Scheme 17, Table 2).



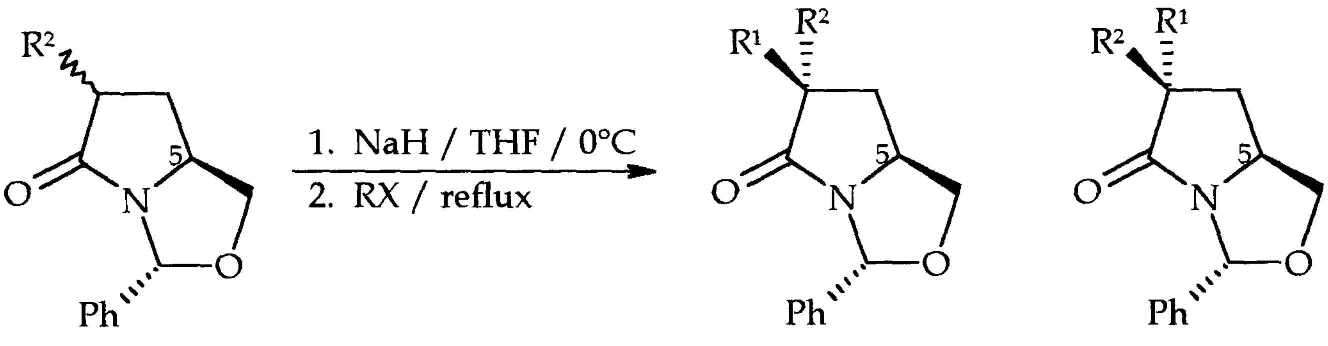
48 **58-60**

Scheme 17

Table 2: Acylation of lactam **48** according to Scheme 17

Product	**R**	**Yield / %**	***endo*:*exo*:enol tautomer ratio**
58	BnO	10	1:1:0 (inseparable)
59	EtO	70	1:1:0 (inseparable)
60	Ph	83	2:4:1 (equilibrating in solution)

These products were particularly interesting as the newly introduced group would activate position 7 to further alkylation reactions. It was found that the weaker base sodium hydride was able to deprotonate these activated lactams, and several high-yielding alkylation reactions were performed.



59 or 60

a - "endo"

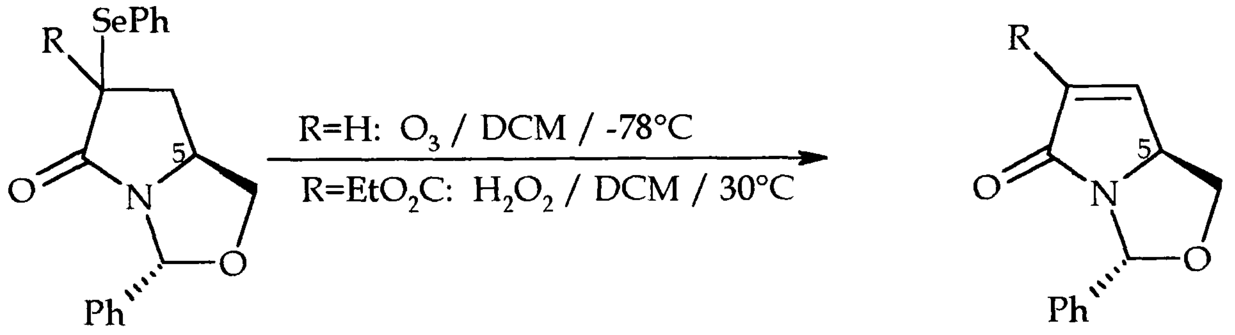
b - "exo"

Scheme 18

Table 3: Alkylations of activated lactam

Product	**Electrophile, R^1X**	**R^2**	**Yield / %**	**Ratio a:b**
61	PhSeCl	EtO_2C	73	1.0:1.5
62	MeI	EtO_2C	76	1.0:1.7
63	$CH_2=CHCH_2Br$	EtO_2C	68	1.0:4.7
64	$PhCH_2Br$	EtO_2C	75	1.0:7.5
65	$pNO_2C_6H_4CH_2Br$	EtO_2C	94	1.0:10.0
66	$CH_3C(O)$	EtO_2C	85	0:1
67	$PhCH_2Br$	PhC(O)	63	1.0:5.0
68	MeI	PhC(O)	47	1.0:2.0

In these examples, the yields and stereoselectivity are greater, with the most stereoselective reactions occurring when the electrophile and activating acyl group are most different in size - for example, the bulky para-nitrobenzyl bromide gives almost entirely the diastereomer where the new group is *exo*-to the concave bicyclic ring structure, while methyl iodide was much less discriminating. It was found that the phenacyl derivatives were liable to debenzoylate on silica gel, and so further investigations concentrated on the ethoxycarbonyl derivatives. The phenyl selenyl derivatives **55** and **61** are of particular interest, as they may be eliminated in quantitative yield to give unsaturated lactams (Scheme 19).

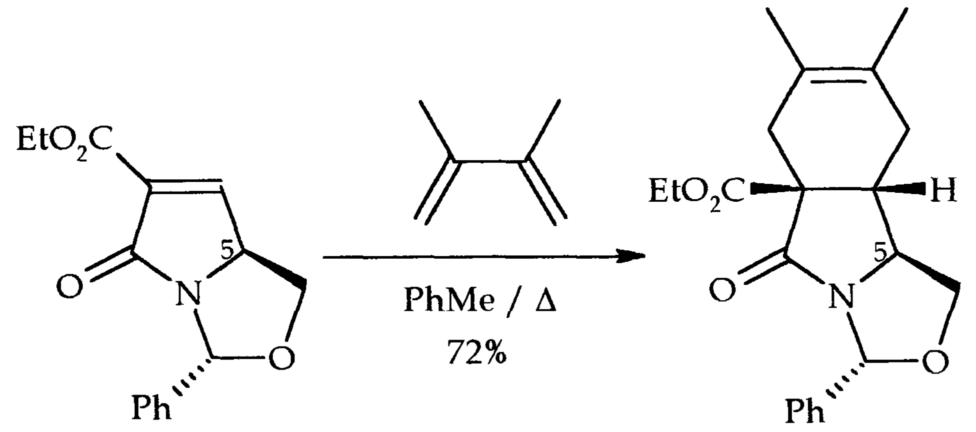


55: R=H
61: R=EtO_2C

69: R=H
70: R=EtO_2C

Scheme 19

These unsaturated lactams are then suitable substrates for a number of different reactions including cycloadditions across the double bond[79] and conjugate additions of carbon,[80] nitrogen[81] and potentially other nucleophiles. Although cycloadditions to the unactivated enone were unsuccessful, the activated enone **70** was suitably reactive (Scheme 20).

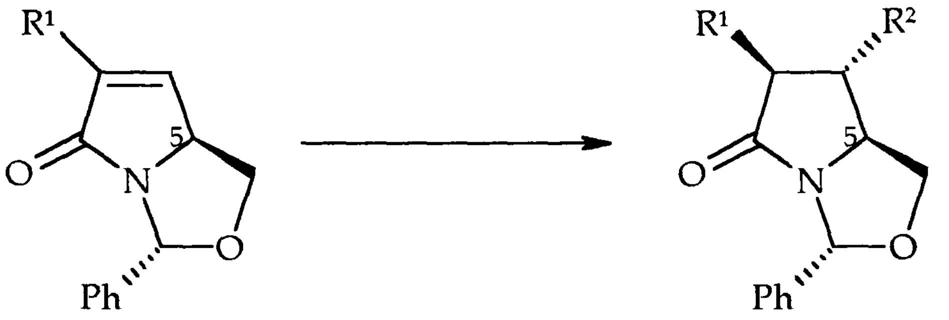


70

71

Scheme 20

Similarly, investigations of conjugate additions to the simple enone **69** were not encouraging, with a 20% yield of the (5*S*, 6*R*, 7*R*) diastereomer **72** after Michael addition of dimethyl malonate followed by alkylation with benzyl bromide, but the activated enone **70** proved to be considerably more reactive and hence more useful. Some examples of successful conjugate additions, with the predominant diastereomer of the product are described in Scheme 21 and Table 4.



69: R^1=H
70: R^1=EtO_2C

72: R^1=H, R^2=$CH(CO_2Me)_2$
73-5: R^1=EtO_2C

Scheme 21

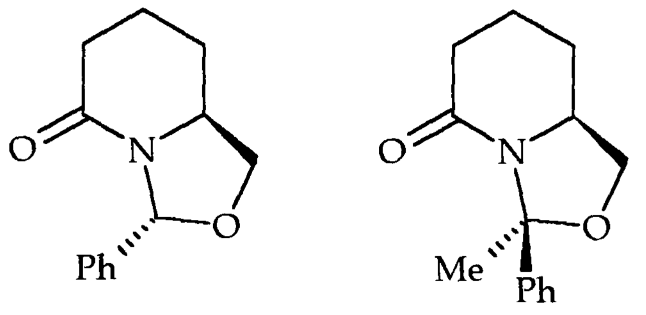
Table 4: Conjugate additions to lactams **69** and **70**

Product	**R¹**	**Nucleophile**	**Yield / %**
72	H	$NaCH(CO_2Me)_2$	20
73	EtO_2C	$NaCH(CO_2Me)_2$	66
74	EtO_2C	$BrZnCH_2CO_2tBu$	73
75	EtO_2C	$PhCH_2ONH(CH_2Ph)$	99

A number of these functionalised lactams have been deprotected, and the activating ethoxycarbonyl group removed to yield the desired pyrrolidinones. This means that the strategy of protecting a pyrrolidinone as an acetal is successful and the protecting groups may be removed in a straightforward manner to give the desired products. This approach could be seen as blending elements of the approaches described in section 1.2, as the starting material is provided by the chiral pool, but is elaborated to form a chiral template that is suitable for more general manipulations.

1.4 Aims of this project

In the previous section the scope of the chiral template **48** derived from pyroglutamic acid as a starting point for the asymmetric synthesis of five-membered nitrogen heterocycles was described. This approach has been so successful in the synthesis of functionalised pyrrolidines that it is desirable to attempt to extend this methodology to the synthesis of functionalised piperidines. Previous workers have established a route to the analogous chiral template **76** from lysine, but this was found to have a disappointing diastereoselectivity in its reactions. It is argued that the stereoselectivity might be improved by replacing the acetal protecting group with a ketal, for example that derived from acetophenone to give the bicyclic system 77.

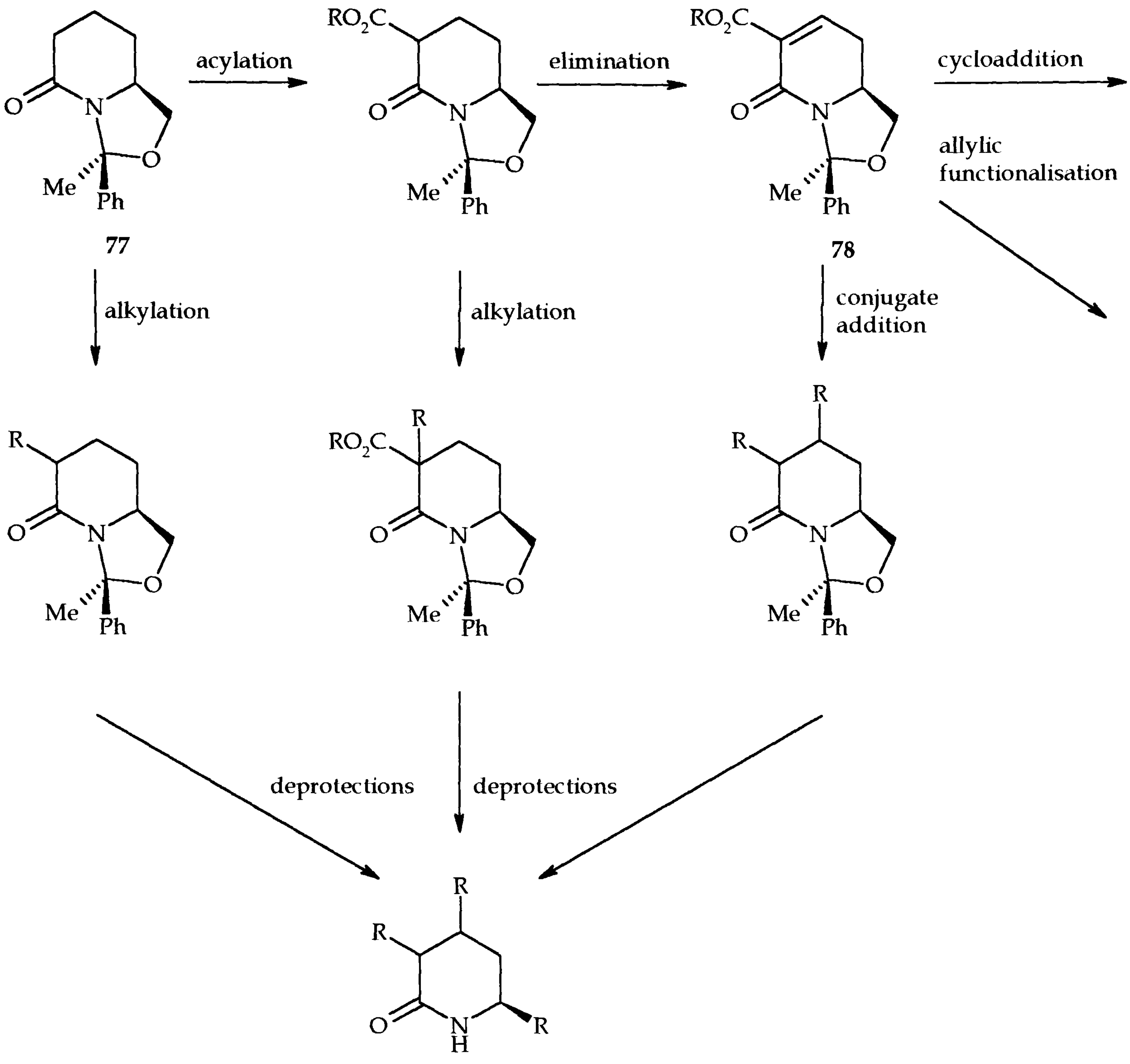


76 77

Figure 15

The aims of this project are summarised in Scheme 22, and are:

- To synthesise the chiral template 77.
- To investigate the diastereoselectivity of alkylations of this bicyclic lactam.
- To synthesise an activated enone **78**.
- To investigate the reactivity of this enone.
- To investigate the suitability of β-dicarbonyl δ-lactams as substrates for Pb(IV)-mediated arylation reactions.
- To investigate the deprotection reactions of the bicyclic intermediates synthesised in order to isolate novel piperidinone compounds.

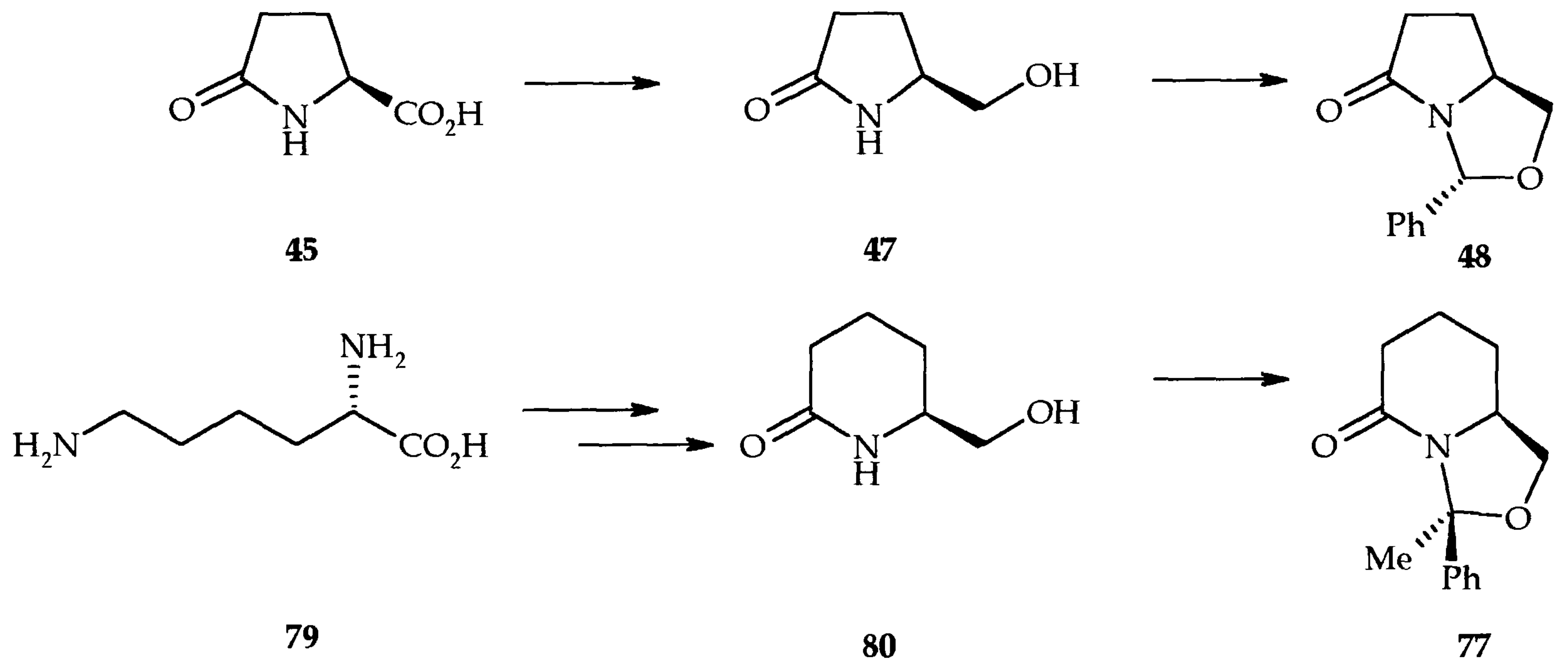

acylation
elimination
cycloaddition
allylic functionalisation
77
78
alkylation
alkylation
conjugate addition
deprotections
deprotections
RO2C
R
O
N
Me
Ph

Scheme 22

Results and discussion 1: the bicyclic lactam

2.1 Introduction

This thesis describes work undertaken to investigate the suitability of lactam 77 as a starting point for the stereoselective synthesis of piperidinones. In this chapter the synthesis of this lactam is described, and compared to the synthesis of the analogous [3.3.0] lactam **48** (Scheme 23).



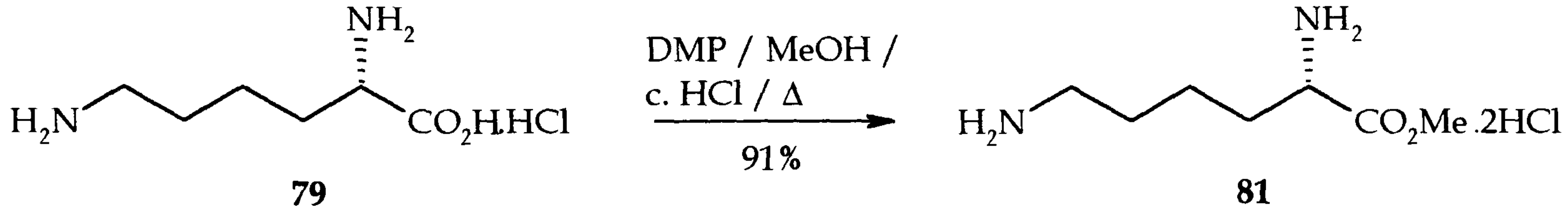
Scheme 23

Although acetal **48** has been widely used by chemists since it was first introduced by Thottathil, the extension of this methodology to a [4.3.0] system is unique to the Moloney group. It may be that this is due to the difficulty of obtaining a suitable starting material: in contrast to (*S*)-pyroglutamic acid, oxo-pipecolic acid is not generally available at a suitable price. This chapter therefore begins with a description of the Moloney route to (*S*)-2-hydroxymethyl-6-piperidinone from (*S*)-lysine **79**, and discusses the protection of this alcohol as an *O*,*N*-acetal.

2.2 Synthesis of (*S*)-2-hydroxymethyl-6-piperidinone

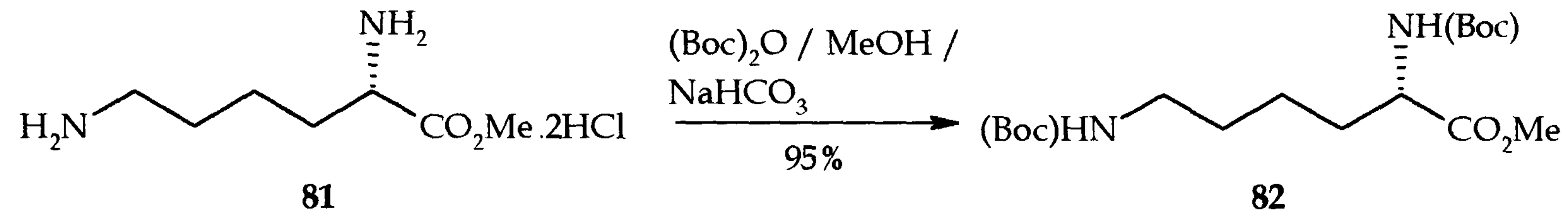
Since an enantiopure homologue of (*S*)-pyroglutamic acid was not available as a starting material for this work, it was necessary to approach this compound, or a protected form of it, from some other compound that was readily available.

Hermitage[82] [83] developed a route from (*S*)-lysine that would deliver (*S*)-2-hydroxymethyl-6-piperidinone in five steps, and this approach was adopted and refined.



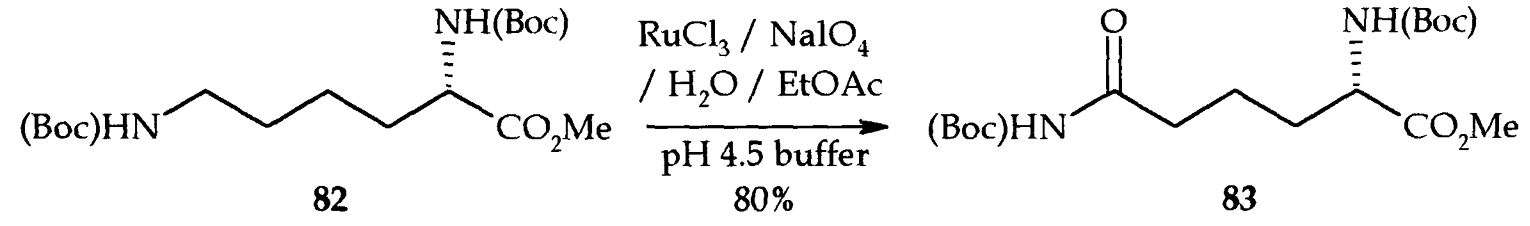
Scheme 24

The initial stage of this preparation was to esterify (*S*)-lysine using dimethoxypropane according to a literature procedure.[84] This is a mild method that avoids using such hazardous reagents as gaseous hydrogen chloride. In this case, (*S*)-lysine monohydrochloride was suspended in methanol, to which dimethoxy propane and a catalytic amount of concentrated hydrochloric acid were added. This mixture was then heated to a state of reflux for three hours and then stirred overnight. Purification was straightforward, as the lysine methyl ester dihydrochloride could be recrystallised from a mixed solvent system of methanol and diethyl ether to give a white crystalline solid ($[\alpha]_D^{20}$ +14.5 (*c* 0.33 in H_2O), lit.[85] +15.9 (*c* 1.3 in H_2O)). This reaction could be repeated on a large scale (100g) without compromising the excellent yield or the purity of the product.



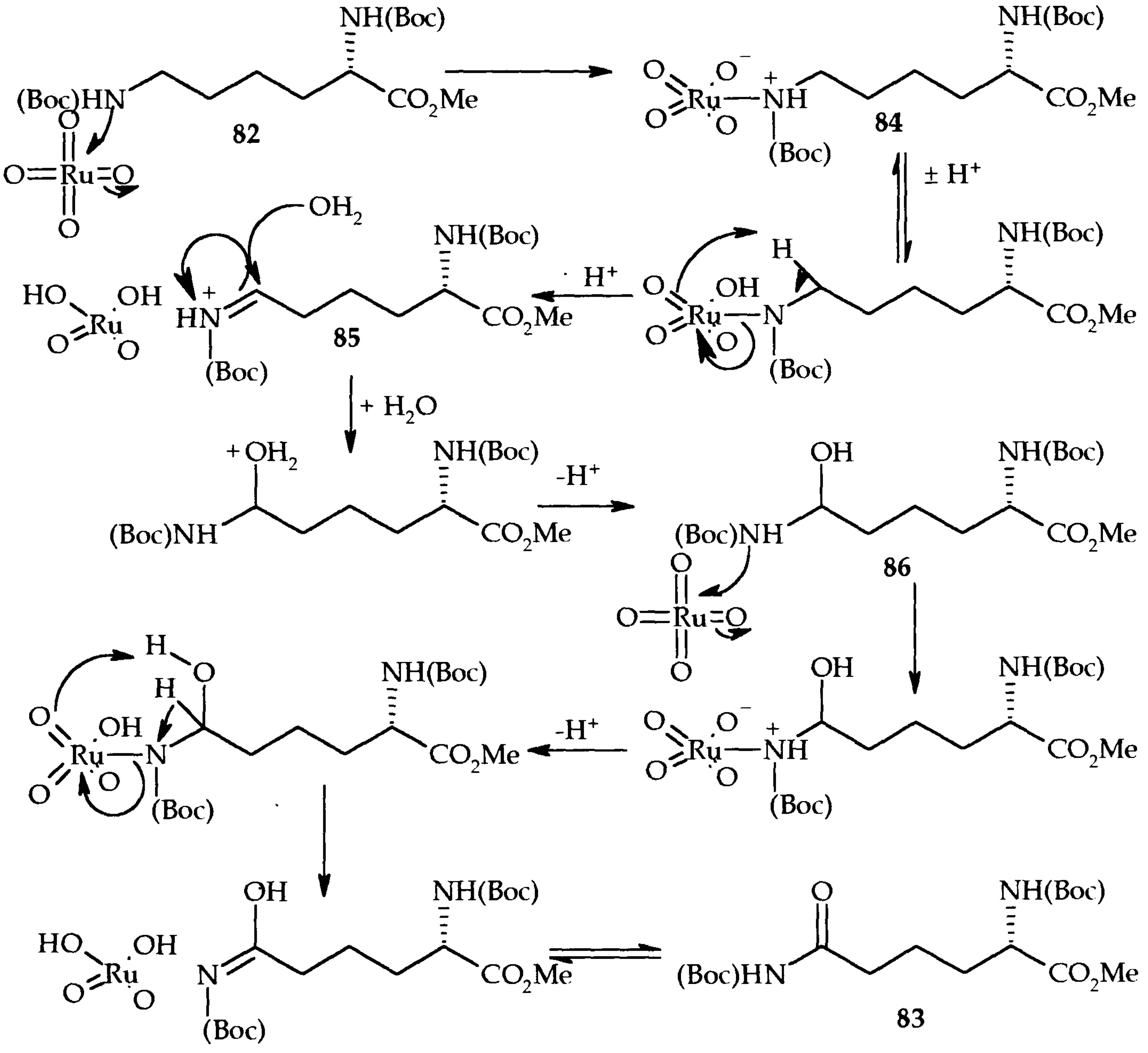
Scheme 25

The protection of the methyl ester dihydrochloride with di-*tert*-butyl dicarbonate proceeded in a similarly straightforward manner. Sonication of a suspension of the ester, the anhydride and excess sodium bicarbonate in methanol at room temperature would effect this protection in high yield. The product could be recrystallised from *iso*-propyl ether, but in view of the fire hazard associated with the use of this solvent and the existence of another satisfactory procedure this reagent was not used. In the alternative procedure material of sufficient purity for further reaction could be obtained by filtering the crude reaction mixture through Celite® to remove the inorganic solids, removing solvent *in vacuo*, re-dissolving the residue in ether, filtering again and removing ether *in vacuo* to give the desired product as a white solid ($[\alpha]_D^{20}$ +7.0 (*c* 0.83 in CHCl3), lit.[85] +7.2 (*c* 1 in CHCl3)). The choice of the Boc protecting group was justified, despite the relatively high cost of the required reagent, by the fact that an electron withdrawing protecting group was required for the next stage of the preparation.



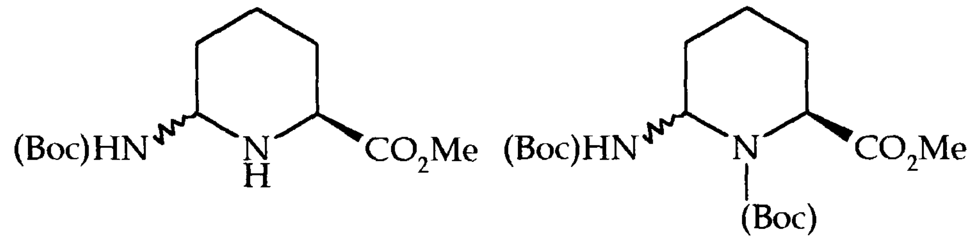
Scheme 26

The oxidation of the protected lysine ester to a protected α-amino adipate ester (**83**) is particularly noteworthy. This procedure was first developed by Yoshifuji *et al*,[85] who have developed many applications of ruthenium oxidation in organic chemistry. These workers propose that oxidation proceeds *via* an iminium ion, as shown in Scheme 27.



Scheme 27

In this proposed mechanism the first step involves the nucleophilic attack of one of the nitrogen atoms on the ruthenium oxidant. After transfer of a proton to give an uncharged molecule a further proton is extracted by the oxidant to give the iminium ion **85**. This may then be attacked by a water molecule to give an intermediate which loses a proton to give a secondary alcohol **86**. The process then repeats to give an enol, which may tautomerise to give the oxo-lysine ester.

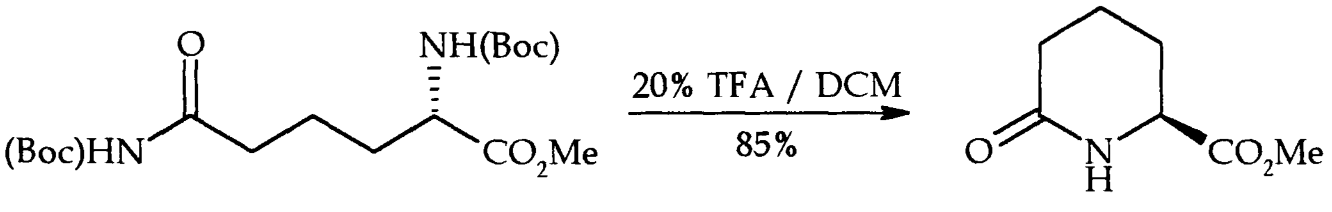


87 **88**

Figure 16

Davies[86] reported that the success of this reaction was dependent on the pH maintained in the solution. She isolated two racemic cyclised products (**87** and **88**, Figure 16) and suggested that these arose from protonation of the intermediate alcohol **85**. The acid-sensitivity of this reaction has also been noted by other workers.[87] This problem was solved by conducting the reaction in a mixture of a potassium phthalate/sodium hydroxide buffer solution and ethyl acetate, which allowed the pH of the reaction mixture to be maintained at 4.5.

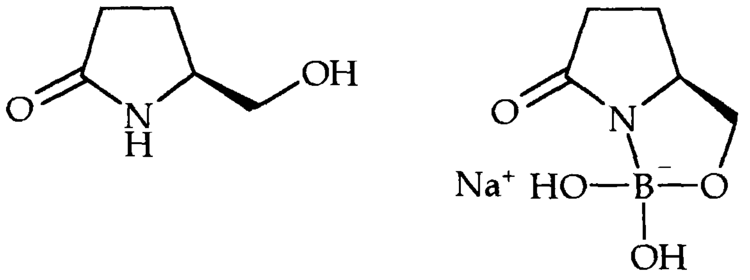
The purification of this reaction product is time consuming, as all traces of ruthenium and iodine must be removed. To this end the reaction mixture is extracted with ethyl acetate and stirred with *iso*-propanol to reduce all ruthenium species to ruthenium dioxide, which may be removed by filtering through Celite®. The solvent may then be removed *in vacuo,* and the residue redissolved in ethyl acetate, and washed with 1% sodium thiosulphate solution and 10% citric acid to remove iodine and other polar impurities. After the solvent is removed *in vacuo* the residue may then be finally purified using dry flash column chromatography (eluting sequentially with portions of ethyl acetate/petrol mixtures in which the proportion of ethyl acetate was increased in 5% increments from 20% to 45% ethyl acetate), which is quicker and requires a smaller amount of silica gel than standard flash column chromatography would do. This yields a colourless oil that may crystallise slowly (m.p. 74°C, lit.[85] 73-74°C $[\alpha]_D^{20}$ +9.2 (*c* 1.0 in $CHCl_3$), lit.[85] +9.6 (*c* 1.0 in $CHCl_3$)).



83 **89**

Scheme 28

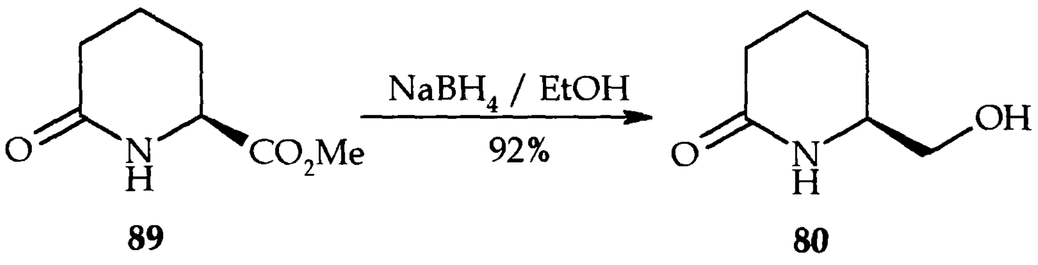
The cyclisation of the α-amino adipate ester to give a piperidinone proceeds in gratifyingly high yield. Davies reported that using neat TFA required an extended reflux (14 hours) to ensure maximum conversion, which compares unfavourably to an average of 1 hour required under the conditions shown in Scheme 28. This transformation is likely to result from the cyclisation of the deprotected adipate ester once the Boc groups have been hydrolysed by the TFA. There is precedent for such a reaction in the literature, where workers have noted that unprotected glutamine derivatives will cyclise readily if treated with acid.[88] [89] It may be that protonation of nitrogen is a significant problem in more acidic solution, which would prevent the ring closure reaction occurring, as protonated nitrogen would clearly be non-nucleophilic. This would explain the seemingly sluggish reactivity of the adipate derivative under the more acidic conditions. Purification of this compound was achieved by removing solvent *in vacuo*, using toluene to form an azeotrope to maximise the removal of TFA, and then separating the residue on silica (eluting with ethyl acetate) to give the desired ester as an oil ($[\alpha]_D^{20}$ -8.7 (*c* 1.06 in $CHCl_3$), lit.[85] -9.6 (*c* 1.06 in $CHCl_3$)).



47 **90**

Figure 17

The reduction reaction forming pyroglutaminol **47** has proved to be rather unreliable,[90] [91] with the possible formation of a borate salt of the form **90** being posed as an important side product arising from incomplete acidification of the reaction mixture on work up. Fortunately, this has not been found to be the case for the reduction of the piperidone **89** (Scheme 29).



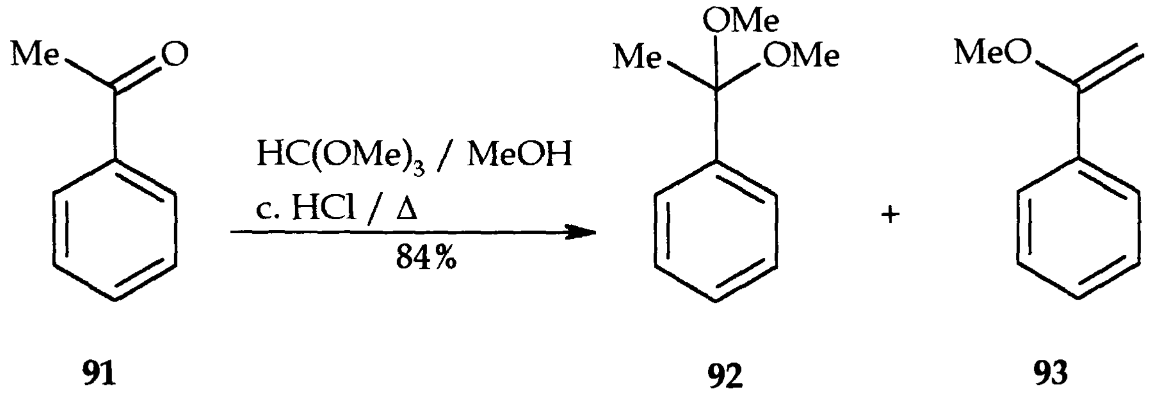
Scheme 29

This reaction proceeds in high yield to give the desired hydroxymethyl piperidine. Careful acidification to pH 4, followed by stirring at room temperature for 30 minutes ensures that boron species are precipitated out of solution, and may be removed by filtering through Celite®. Solvent is then removed *in vacuo*, and the residue purified by flash column chromatography. It has been found that a mixture of ethyl acetate, methanol and triethylamine in the ratio 90:10:0.2 allows the most satisfactory purification of the target alcohol (mp 71°C, $[\alpha]_D^{20}$ +16.3 (*c* 1.0 in $CHCl_3$), lit.[85] +17.9 (*c* 1.0 in $CHCl_3$)). If the small amount of base is omitted then the recovery of the material is more time consuming and less fruitful.

In this section a five-step synthesis of 2-hydroxymethyl-6-piperidinone has been described. This synthesis compares favourably with the two other syntheses currently published: the first uses α-amino adipic acid as a starting point for a two-step synthesis,[92] but this starting material is not commercially available, while the second is a six-step synthesis where the chirality is introduced using a Sharpless asymmetric dihydroxylation.[93] This synthesis is not only longer than the synthesis adopted in this work, but would involve large scale hydrogenation reactions, which are arguably more difficult to perform.

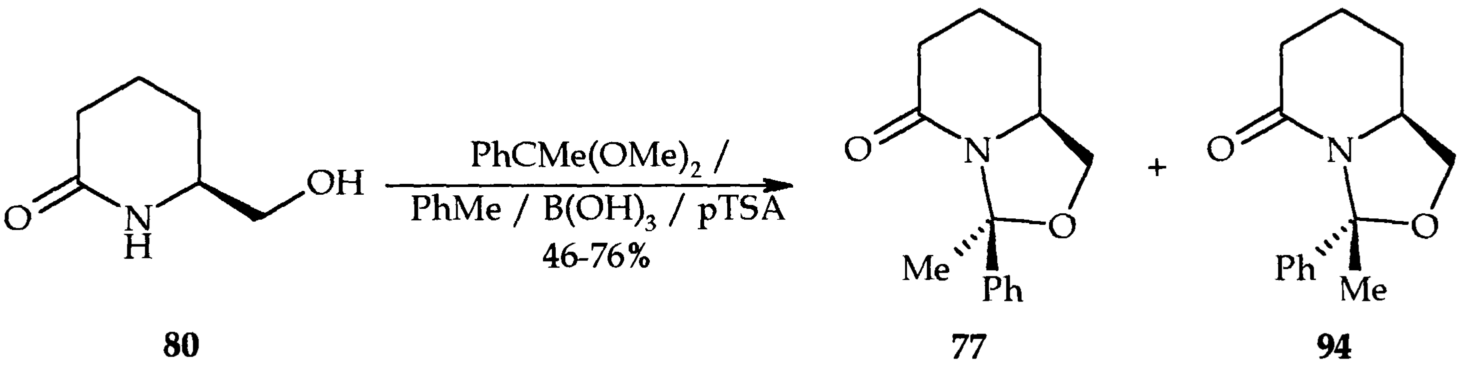
2.3 Synthesis of acetal 77

In section 1.3 the use of the Thottathil acetal (**48**) in synthesis was discussed. Preliminary investigations on an analogous benzaldehyde protection of (*S*)-2-hydroxylmethyl-6-piperidinone[86] (**80**) suggested that such a system exhibited only moderate stereoselectivity in its reactions, and so the generation of an *O, N*-acetal derived from acetophenone was pursued. Acetophenone was converted to its dimethyl acetal (**92**) according to a literature procedure,[94] as this was expected to be more reactive than the ketone.



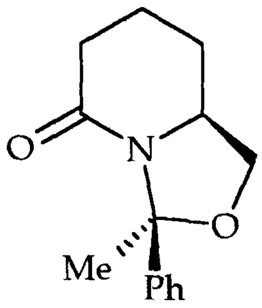
Scheme 30

So, acetophenone and 1.5eq of trimethyl orthoformate were heated to 40°C in acidified methanol for five hours (Scheme 30). The reaction mixture was then allowed to cool to room temperature and stirred for a further 16 hours. The solution was then basified to pH 9 using 0.5M NaOMe in methanol to quench the reaction, and solvent was removed *in vacuo*. The product was then isolated by Kügelrohr distillation (bp 90°C, 20mm Hg) to give a colourless oil. Trace amounts of the enol ether (**93**) were also detected, but this was not expected to affect the subsequent generation of the acetal. It was later found that this dimethyl acetal could also be obtained from commercial sources.

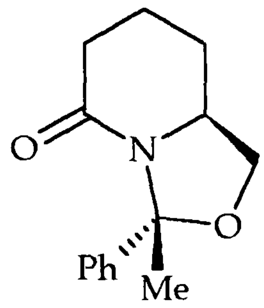


Scheme 31

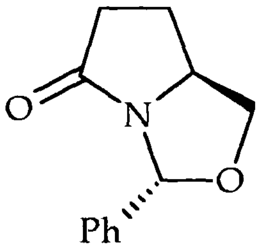
The protection of the hydroxylmethyl piperidone **80** with acetophenone dimethyl acetal was not, however, a reliable or clean reaction. Details of three typical runs are given in the experimental section. In all cases the diastereomer 77 was predominant, and the work described in this thesis concentrated on manipulations of this diastereomer. However, significant amounts of the minor diastereomer **94** were often found. The conditions for this reaction were adapted from the Thottathil report, and so acetophenone dimethyl acetal and the piperidone were added to toluene, boric acid and *para*-toluene sulphonic acid that had been pre-dried using a Dean-Stark apparatus for five hours. This mixture was then refluxed for up to 24 hours, until t. l. c. analysis indicated that none of the starting material was present. After work-up, excess acetophenone dimethyl acetal could be removed by Kügelrohr distillation, and then the residue purified by flash column chromatography on silica gel. This was not an easy separation, as large quantities of highly coloured non-polar contaminants were present. It was generally most suitable to elute initially with a 20% mixture of ethyl acetate in petrol, and gradually increase the polarity of the eluent mixture. This would give the two diastereomers as a white solid (77) (m.p. 114-117°C (lit.[86] 116-117°C), $[\alpha]_D^{20}$ -6.3 (*c* 0.27 in $CHCl_3$); and a yellow oil (94) ($[\alpha]_D^{24}$ +161.1 (*c* 1.0 in $CHCl_3$)). That diastereomer 77 is the predominant diastereomer formed is perhaps surprising, as it might be thought that the steric bulk of the phenyl group would be considerably more significant than that of the methyl group. The stereochemistry shown in Scheme 31 was, however, confirmed by Davies[86] using both n. O. e. difference spectroscopy and X-ray crystallography of diastereomer 77. The crystal structure is reproduced in Appendix 1.



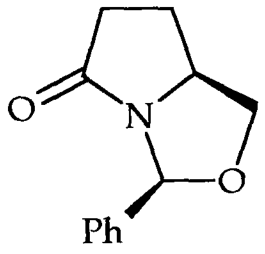
77



94



48



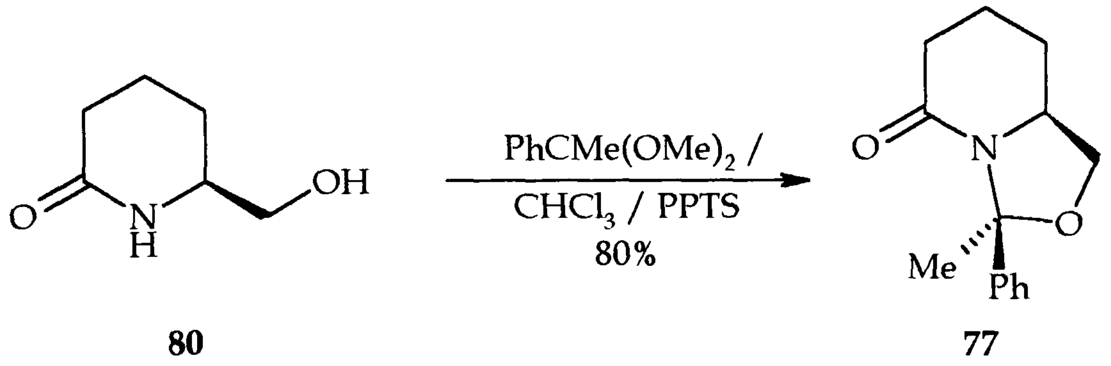
95

Figure 18

Table 5: Heats of formation of bicyclic systems from molecular modelling using Chemdraw 3D MOPAC PM3

Bicyclic system	ΔH_f / kJmol^{-1}
77 (2S)	-61.6
94 (2R)	-61.5
48 (2R)	-56.1
95 (2S)	-53.4

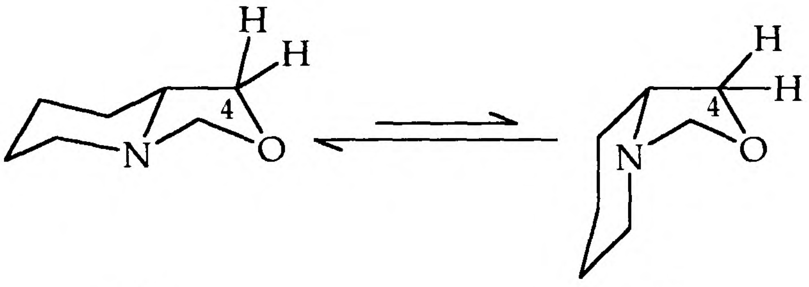
Molecular modelling (using Chemdraw 3D MOPAC PM3 parameters) suggests that diastereomer **77** is, indeed, the thermodynamically more stable form (Table 5). Given these findings, the question arises as to why the minor diastereomer is observed. It may be merely that the difference in heats of formation is smaller than that between the two possible epimers of the [3.3.0] system that has been studied extensively, as the results of the molecular modelling suggest, which would render the 2*S* diastereomer only marginally more thermodynamically stable. Another possibility is that the 2*R* diastereomer (**94**) is the kinetic product, and so an attempt to follow the course of the reaction by gas chromatography was made. Unfortunately, the retention factors of the two diastereomers proved to be too similar under a number of conditions for this to be a practical method. In order to investigate whether the stereochemistry at C-2 could be reversed a sample of the 2*R* diastereomer was heated to reflux with boric acid and tosic acid, to give a mixture of both diastereomers in a ratio of 1:1.



Scheme 32

Another worker[95] has studied this ring closure reaction in detail, but has not yet found a convincing explanation for the variability in selectivity and yield of this reaction. However, an alternative procedure[96] has been found which allows the stereoselective formation of the desired diastereomer (Scheme 32).

Although the X-ray crystal structure obtained by Davies allowed the configuration at C-2 in the major diastereomer (**77**) to be stated unambiguously, the conformation of the bicyclic systems remains unclear, and is of particular interest. A recent report on the simple, non-substituted [4.3.0] systems[97] has described the equilibrium between the two forms **96** and **97** (Scheme 33).



96 **97**

Scheme 33

In this case, the system exists as 73% *trans*-conformer (**96**), and 27% *cis*-conformer (**97**) at 183K in $CDCl_3$-$CFCl_3$ solution. Interestingly, these workers do not find any evidence for the existence of a conformer where the six-membered ring adopts a boat-type conformation. Some NMR data of the two conformers isolated by these workers, and the characteristics of the epimers **77** and **94** whose synthesis has been discussed in this chapter is shown below (Table 6).

Table 6: NMR data for bicyclic systems

System	**Solvent**	**δ (4-H_{exo}) - δ (4-H_{endo}) / ppm**	**J / Hz (between highlighted protons)**
96 (trans)*	$CDCl_3$-$CFCl_3$	0.82	0
97 (cis)*	$CDCl_3$-$CFCl_3$	0.05	5.8
94 2R†	$CDCl_3$	0.66	7.5
77 2S†	$CDCl_3$	0.64	8.0

* at 183K † at 298K

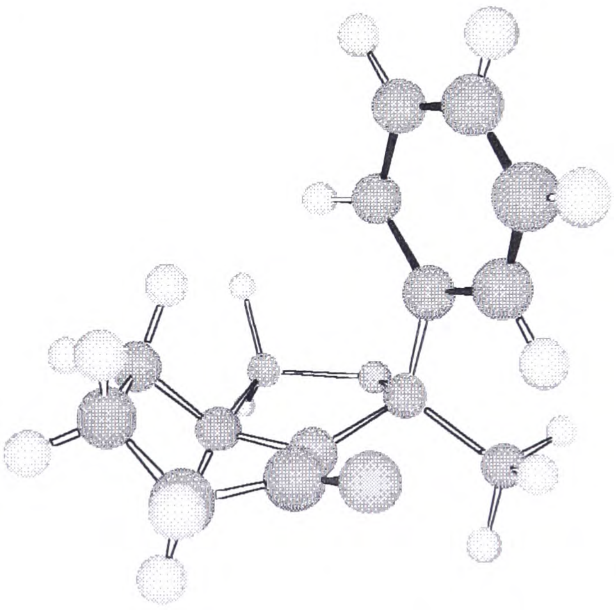


Figure 19: Molecular modelling (using Chemdraw 3D MOPAC PM3 parameters) structure of bicyclic lactam 77

It is important to note that the data in this Table has been measured under two different sets of conditions, that is at low temperature (183K) and at room temperature (298K). However, there are some interesting observations that can be made. The first observation is that the difference between the chemical shifts of the protons attached to C-4 is similar in the two epimers. The second observation is that the coupling constants between the two protons are significantly larger in the systems discussed in this chapter than in the simple systems, and that the coupling constants in the two epimers are more similar than the coupling constants of the two conformers. These facts suggest that the conformational equilibria of the two epimers (77 and 94) are similar, and that they are rather different from those of the simple molecule. X-ray diffraction of epimer (77) indicates that the conformation of the six-membered ring in the solid state is boat-like (Figure 19), and this is confirmed for both epimers by molecular modelling using Chemdraw 3D (MOPAC PM3 parameters). Comparison of the measured NMR and X-ray data, and molecular modelling would therefore suggest that the two epimers adopt similar but not identical conformations, in which the six-membered ring is in a boat-type conformation.

A comparison of the conformations of the two epimers can be made by considering the coupling constants between 4-H_{exo} and 5-H. The coupling constants between vicinal protons depend on the dihedral angle ϕ, and the valence angle θ, with J increasing as ϕ approaches 0 and 180°, following a Karplus-Conroy type curve, and as θ approaches 0°. As the concave bicyclic system flattens, a change in the coupling constant J should be observed. The variation in ϕ as the system becomes more planar is difficult to model, but θ will increase, which will reduce J. There is clearly a balance of factors in operation here, but the rule that higher values of J correspond to more open, less concave bicyclic systems appears to fit experimental data and the value of the C(5)-C(4)-4(H_{endo}) valence angle computed by molecular modelling (Chemdraw 3D MOPAC PM3 parameters) (Table 7).

Table 7: 4-H_{exo}-5-H vicinal coupling constants

Compound	J / Hz	C(5)-C(4)-4(H_{endo}) / °
2*S* diastereomer (77)	5.0	112.7
2*R* diastereomer (94)	5.5	114.4

It might appear counter-intuitive that the 2*R* diastereomer is less concave than the 2*S* diastereomer, as this implies that the *endo*-methyl substituent has a greater effect on the conformation than the *endo*-phenyl. However, the steric influence of methyl groups has indeed been found to be greater than phenyl groups in other situations: Taft equations[98] use a steric substituent parameter E_S to give an indication of the steric influence of a given substituent, with a larger value corresponding to greater influence, and these have been computed for the hydrolysis of aliphatic esters as detailed in Table 8.[99]

Table 8: Taft steric substituent parameters

Substituent	E_S
H	0
Me	1.24
Ph (depth)	1.01
Ph (width)	3.82

These figures represent an attempt to quantify the different steric significance of different alkyl groups. The effect of the phenyl group depends greatly on its orientation, and it is possible that a phenyl group will be less influential than a methyl group if it adopts a low energy orientation. All the data currently available is thus compatible with both epimers adopting similar conformations, with the 2*R* epimer adopting a less concave conformation. The significance of these conformational differences for the reactivity of the two diastereomers will be discussed in chapter three.

2.4 Summary

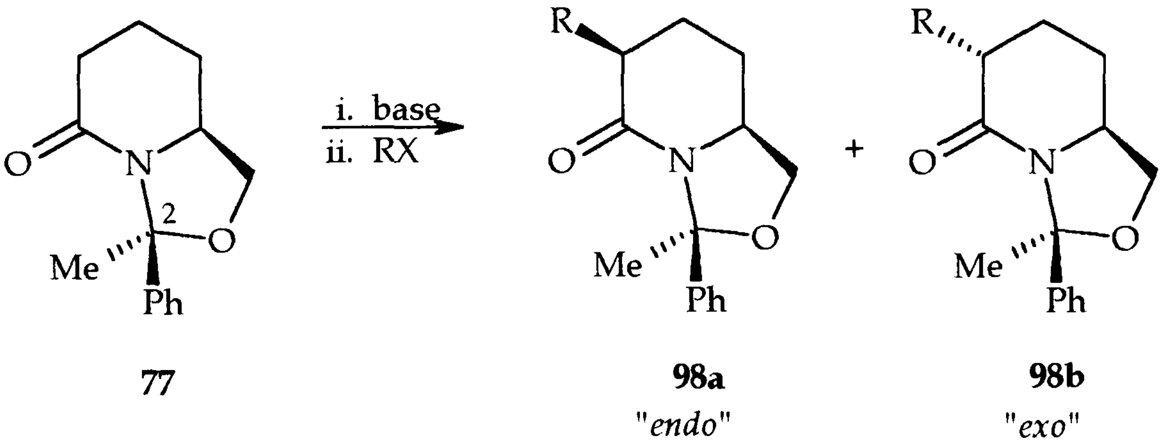
This chapter has described the synthesis of the bicyclic lactam **77** that is to be used as a chiral template in the work described in later chapters of this thesis. An established procedure for the synthesis of (*S*)-2-hydroxymethyl-6-piperidinone **80** has been optimised, both in terms of the yields obtained, and the ease of purification, and this hydroxy lactam has been protected as the acetophenone *O*, *N*-acetal. This cyclisation has not been straightforward to achieve, but a procedure has recently been found that allows the stereoselective formation of one diastereomer in good yield. This chapter therefore describes a reliable route to the target chiral template in respectable yield.

The conformations of the diastereomers **77** and **94** are believed to be similar, and NMR evidence for this conclusion was also discussed.

Results and discussion 2: alkylations of the bicyclic lactam

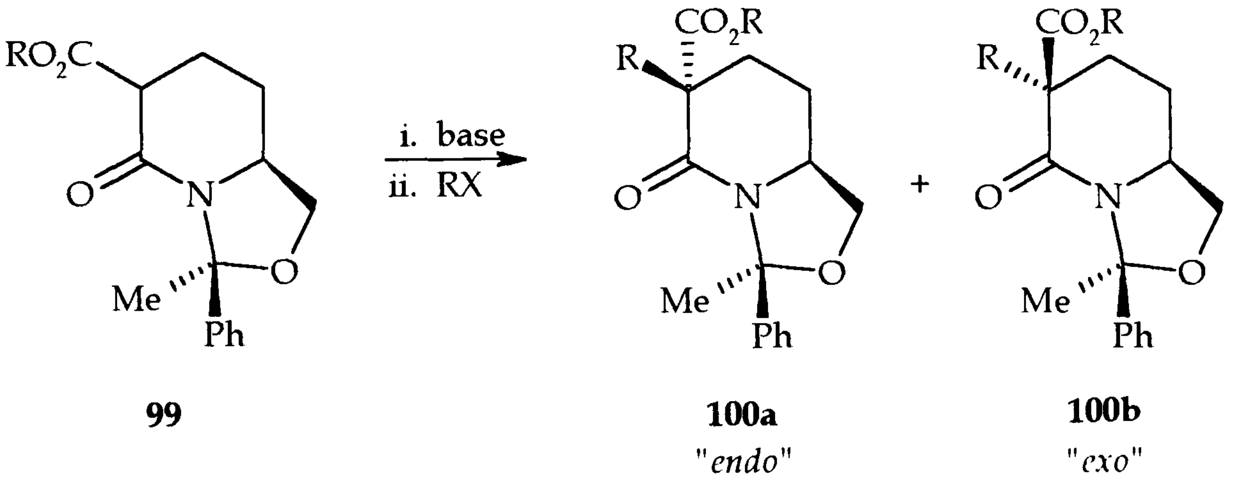
3.1 Introduction

In this Chapter the results of alkylation experiments on the bicyclic lactam 77 are presented and discussed. Alkylated piperidinones are not only of interest for the synthesis of piperidines, but also for the construction of substituted lysine analogues, and there is some literature precedent for the alkylation of 2-piperidinones.[66 68 100 101 102]



Scheme 34

The distribution of the alkylation products between those where the newly introduced substituent is *endo-* to the concavity of the bicyclic system and those where the substituent is *exo-* is particularly interesting. On simple steric grounds the adduct **98b** would be the expected product (Scheme 34), and the extent to which this predicted behaviour is found experimentally is considered and discussed in this Chapter. The effect of the stereochemistry of the *O,N*-acetal protecting group on the stereochemical course of these reactions is also discussed, as alkylations were also performed on the C-2 epimer **94**.



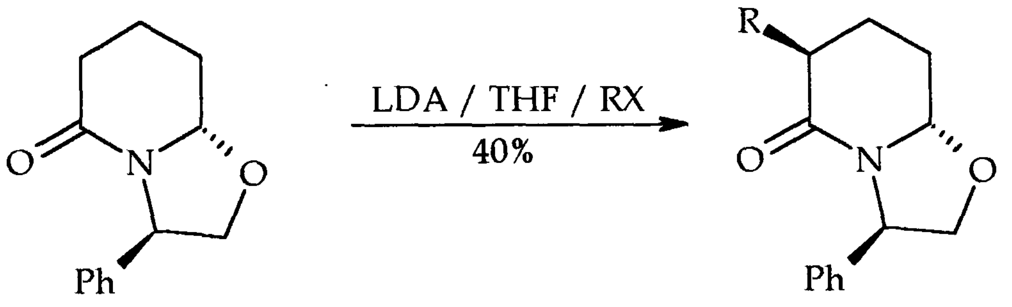
Scheme 35

Substituted lactams of the form **99** would be expected to react more readily than the lactam **77**, as the electron-withdrawing ester group would be expected to promote the stability of an anion formed at the carbon α-to the carbonyl groups. The alkylation of a system of this form is also considered.

The results of all these alkylation experiments are then compared to those obtained by Meyers[66] and Amat[68] on similar bicyclic systems, and possible rationalisations considered.

3.2 Alkylations of the 2*S* bicyclic lactam 77

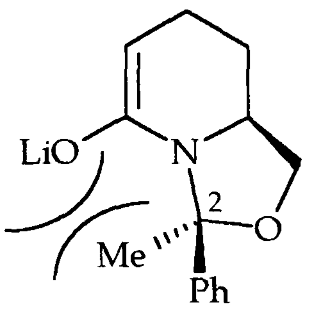
Initial investigations of the alkylation reaction of the 2*S* diastereomer found that alkylation was difficult to achieve, as deprotonation α- to the carbonyl group was not straightforward.[103] This was surprising in the light of work completed on the [3.3.0] bicyclic system **48**,[77] which was found to be susceptible to deprotonation by the non-nucleophilic base LDA under standard conditions. Fortunately, the more powerful base s-BuLi was found to be successful in this reaction. It is interesting to note that Husson and co-workers found similar difficulties in the alkylation of the bicyclic system **39**, which they were unable to alkylate after deprotonation with either LDA or s-BuLi,[67] but that Amat[68] was able to achieve the alkylation of this system readily with LDA and either methyl iodide or benzyl bromide, in moderate yield (40%) but with excellent diastereoselectivity (Scheme 36).



39 **42**

Scheme 36

The difficulty of deprotonation α- to carbonyl groups in these lactams is not an expected result. It may be that the steric conflict between the carbonyl or, more importantly, an O-Li group at position 9 of the bicyclic system and the C-2 substituents is considerably greater than that between an O-Li group and the phenyl group in the [3.3.0] bicyclic systems as a result of the wider internal angles in the six-membered ring compared to the five-membered ring (Figure 20). This conflict would render deprotonation more difficult.



101

Figure 20

Once it had been established that it was possible to deprotonate the bicyclic lactam with s-BuLi, a range of electrophiles were used to functionalise the ring at C-8, as described in Table 9.

Table 9: Reaction of bicyclic lactam 77 with electrophiles according to Scheme 34

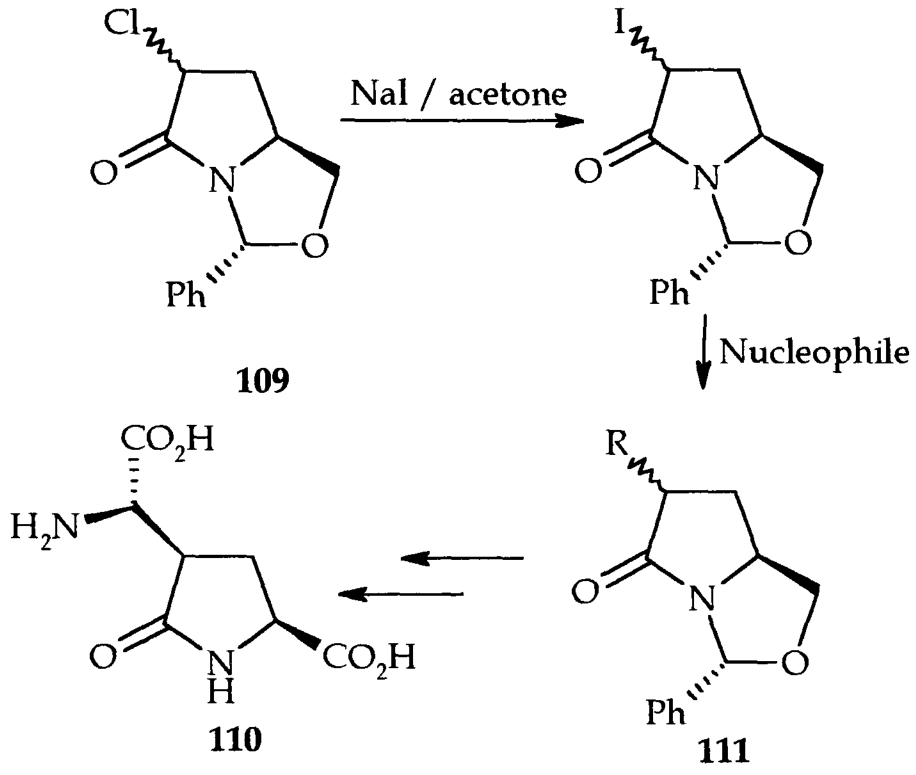
Product	**Electrophile**	**Yield**	***exo*:*endo* ratio**
102	Methyl iodide	80	1:1
103	Benzyl bromide	69	10:1
104	para-Nitrobenzyl bromide	28	3:2
105	Allyl bromide	95	2:1
106	Tosyl chloride	44	5:3
106	Tosyl chloride*	51	5:3
107	Phenyl selenenyl chloride	52	7:4
108	Benzyl chloroformate	28	1:1
108	Benzyl chloroformate*	72	1:1

* Revised conditions used: see below.

The general method for these alkylations was to add a solution of the lactam in dry THF to a solution of sBuLi in THF at -78°C. This mixture was then allowed to warm to -30°C, and when the distinctive red colour of the enolate was observed, the alkylating agent was added. When t. l. c. analysis indicated that reaction was complete, standard work-up procedures were applied, and the diastereomers of the products were separated by column chromatography on silica gel. This was not always a straightforward task, as the polarity of some diastereomeric pairs (as reflected in their R_f values) was very similar. Consequently, only some diastereomers could be obtained in an diastereopure form. The diastereomeric ratios were confirmed by NMR spectroscopic analysis of the crude reaction products.

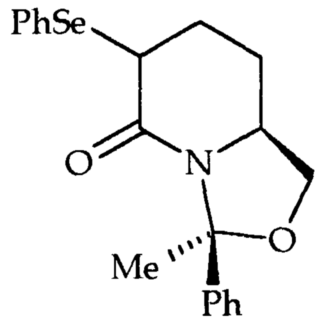
In two cases, the chlorination with tosyl chloride, and the acylation with benzyl chloroformate, the standard alkylation procedure was not found to be optimal. In both cases C-8 disubstitution occurred. The newly introduced substituents in these examples are strongly electron-withdrawing in character, and it is suggested that the mono-substituted bicyclic lactam formed in the first alkylation is rapidly deprotonated by the remaining enolate ion present, as the C-8 proton is more acidic in the substituted lactam, and this then reacts with another equivalent of the alkylating agent. Altering the procedure so that the lactam enolate is slowly added to a solution of the alkylating agent gave considerably more satisfactory results. In the second case, however, the acylated product **108** was found to be unstable to chromatography on silica, such that a significant proportion of the starting material was recovered from the column, even when NMR spectroscopic analysis of the crude reaction mixture suggested that complete reaction had occurred. Two dimensional t. l. c. confirmed the suspicion that the product was degrading on silica, and so alumina was adopted as an alternative adsorbant. This was found to be a much improved purification procedure.

The variety of electrophiles used in this work indicates the wide range of further manipulations that might be considered at C-8. Simple alkyl halides gave good yields of the desired products, with the disappointing exception of para-nitrobenzyl bromide, which gave only a moderate yield of the desired products, which were difficult to purify by column chromatography. The stereoselectivity shown appears to reflect the size of the incoming electrophile, with the small methyl iodide showing the least selectivity, and the large benzyl bromide the most.



Scheme 37

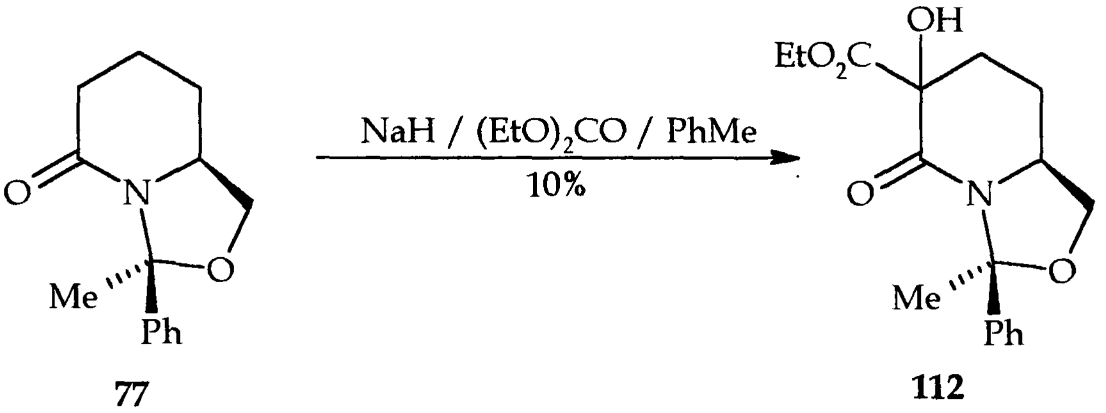
The reaction with tosyl chloride introduces a chloro-substituent. Recent work in the group[104] [105] has demonstrated the utility of the analogous chlorinated [3.3.0] bicyclic system in a synthetic approach to (+)-penmacric acid (**110**, Scheme 37). In this case the chlorine atom is displaced in an S_N2 reaction with sodium iodide, to give the iodo-lactam, which will react readily with a suitable nucleophile to give **111**, an important intermediate in the synthesis of (+)-penmacric acid. The fact that chloro-substituted [4.3.0] bicyclic lactams can be generated easily suggests that it may be possible to attempt similar syntheses in the piperidine series, with nucleophilic attack on C-8.



107

The reaction with phenylselenenyl chloride is another example of a hetero-electrophile reacting with the lactam enolate. Products such as **107** are particularly useful as they will undergo oxidation-elimination reactions to give unsaturated systems.[106] The oxidation-elimination of the phenyl selenenyl group of these products was not pursued, however, as earlier investigations on the [3.3.0] system implied that it was unlikely that an unactivated enone of this sort would be sufficiently reactive towards cycloadditions and conjugate additions to make this a profitable approach.

The introduction of the benzyl ester group at C-8 using benzyl chloroformate was a particularly important transformation. It had been confirmed that the introduction of an ester group α-to the carbonyl group in the [3.3.0] system activated the bicyclic lactam to alkylation reactions and, after selenation-oxidation-elimination, the enone to conjugate addition and cycloaddition reactions. However, earlier work on the [4.3.0] system[103] had shown that it was not possible to apply the same acylating conditions to the [4.3.0] system as had been successfully applied to the [3.3.0] system. When this was attempted the only product isolated was the autoxidised product **112**, and that was only isolated in disappointing yield (10%) (Scheme 38).

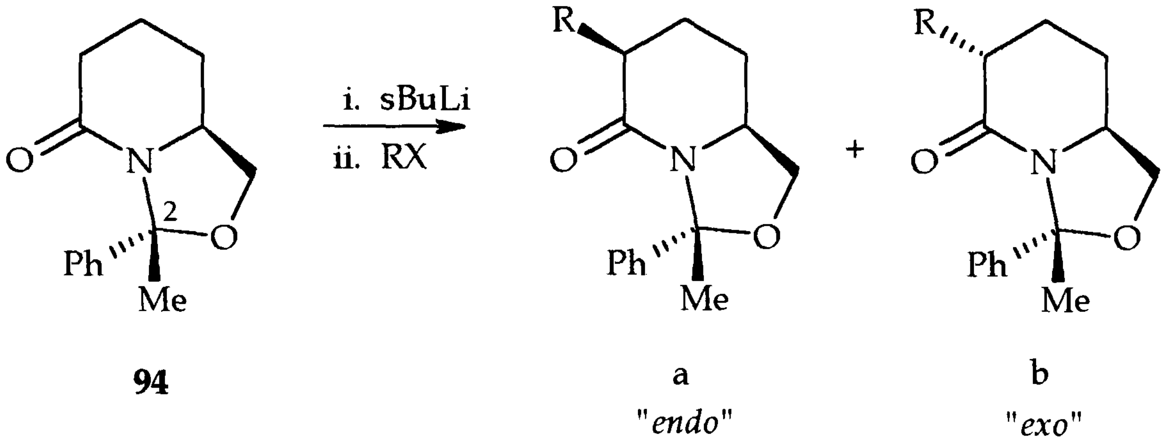


Scheme 38

It is intriguing that autoxidation should occur so readily in this system, particularly in the light of investigations of the [3.3.0] bicyclic lactam, which has proved resistant to oxidation at C-7.[107] Two mechanisms for the oxidation of enolates with molecular oxygen have been proposed: that is, by electrophilic addition promoted by complexation with the counterion (in this case sodium) in a six-membered transition state, or by single electron transfer from the enolate to oxygen to give an α-keto radical.[108] The fact that the benzyl ester was generated in high yield, albeit after careful adjustment of the conditions, is therefore a significant achievement.

3.3 Alkylation of the 2*R* bicyclic lactam

Since significant quantities of the 2*R* bicyclic lactam had been synthesised in the course of investigations of the 2*S* bicyclic lactam, it was thought instructive to investigate how the reactivity of these two systems differed. Two alkylation reactions were therefore performed on the 2*R* bicyclic lactam **94** according to Scheme 39, and the results of these are reported in Table 10.



Scheme 39

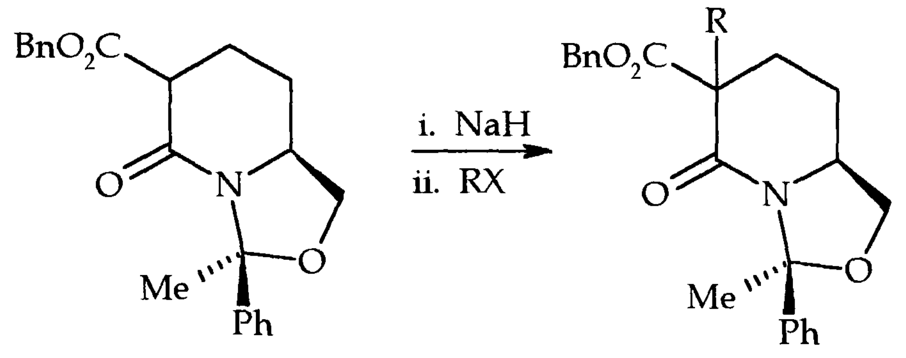
Table 10: Reaction of bicyclic lactam **94** with electrophiles according to Scheme 39

Product	Electrophile	Yield	exo:endo ratio
113	Methyl iodide	46	0:1
114	Benzyl bromide	25	2:1

It may be seen from this Table that the yield of these reactions was disappointing, although identical conditions were employed to those used when alkylating the 2*S* diastereomer. No other products were isolated from these reactions, but another worker[82] has suggested that *O*,*N*-acetals may be unstable towards ring-opening reactions under some circumstances, and it may be that such a reaction has occurred here. It is also interesting to note that only the *endo* diastereomer of the methyl adduct was isolated, and that the bias in favour of the *exo* diastereomer of the benzyl adduct was much smaller than that observed with the 2*S* diastereomer **77**. This will be considered further in section 3.6.

3.4 Alkylations of the activated lactam 108

One of the reasons that the synthesis of the acylated bicyclic lactam **108** was optimised so carefully is that it is an important intermediate in the synthesis of further substituted lactams. An initial test of its reactivity was towards simple alkylation. This would allow confirmation of the prediction that the C-8 proton was more acidic, and would test its resilience to alkylating conditions. To this end, pre-washed sodium hydride was suspended in dry THF at 0°C, and then a solution of the acylated lactam **108** in THF was added. The mixture was stirred for 45 minutes to allow the enolate to be formed, and then an alkylating agent was added (Scheme 40). The results of these experiments are reported in Table 11:



108 **115, 116**

Scheme 40

Table 11: Alkylations of acylated bicyclic lactam **108** according to Scheme 40

Product	RX	**Yield / %**	**diastereomeric ratio**
115	BnBr	55	4:1
116	PhSeCl	70	1:1

The products of this reaction were not separable by flash column chromatography, as a result of their similar polarity and hence retention factors, but the diastereomeric ratios have been estimated from the crude NMR spectra. It is gratifying to observe that it is possible to alkylate the bicyclic lactam using these milder conditions, as predicted. It is unfortunate that the diastereomeric ratios are poorer than those observed in the unactivated lactam 77, which contrasts with the results observed with the [3.3.0] bicyclic lactams, which give larger diastereomeric ratios with the activated lactam than with the unactivated lactam. Since the derivatives were not separable, it is not possible to identify which isomer is predominant.

3.5 The assignment of stereochemistry

Unfortunately, none of the products of these alkylations were crystalline, and so no X-ray crystallography was possible to allow the configurations at C-8 to be stated unambiguously. However, in some cases it was possible to obtain nOe difference and nOesy spectra which indicated the stereochemistry of certain adducts, while the stereochemistry of others could be deduced from the patterns observed in NMR data.

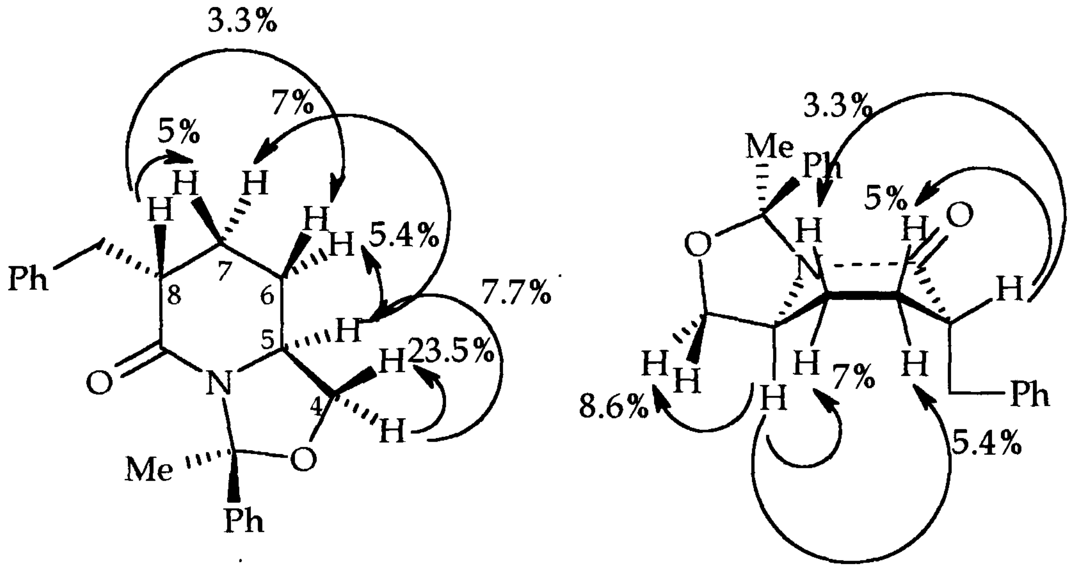


Figure 21: n. O. e. measurements for **103b**

In Figure 21 the n. O. e. enhancements observed on the major benzyl diastereomer **103b** are illustrated. Irradiation of 4-H_{endo} shows no enhancement of 5-*H*, while irradiation of 4-H_{exo} shows an enhancement of 7.7% at 5-*H* as well as a 23.5% enhancement at 4-H_{endo}, which is typical for a geminal pair. Irradiation of 5-*H* shows a 5.4% enhancement of 6-H_{exo} and a 7% enhancement of 7-H_{exo}. Irradiation of 8-*H*, on the other hand, shows no enhancement of these signals, but a 5% enhancement of 7-H_{endo} and a 3.3% enhancement of 6-H_{endo}, which implies that 8-*H* is *endo* to the bicyclic system, and hence that the newly introduced benzyl group is *exo* to the bicyclic system.

The nOe results also give information on the conformation of the six-membered ring. Although the presence of nitrogen and the carbonyl group mean that the conformation will not be a true boat or chair form, the conformation is likely to approximate to one of these forms. The right-hand figure illustrates the crucial nOe enhancements that suggest that a boat-type form is adopted. Had a chair-type formation been adopted, it is unlikely that an enhancement would have been observed between 8-H and 6-H_{endo}, as they would have been much further apart. Similarly, a chair-type system would be likely to show similarly sized enhancements from 5-H to both 6-H protons, but the only enhancement observed on irradiating 5-H is to 6-H_{exo}.

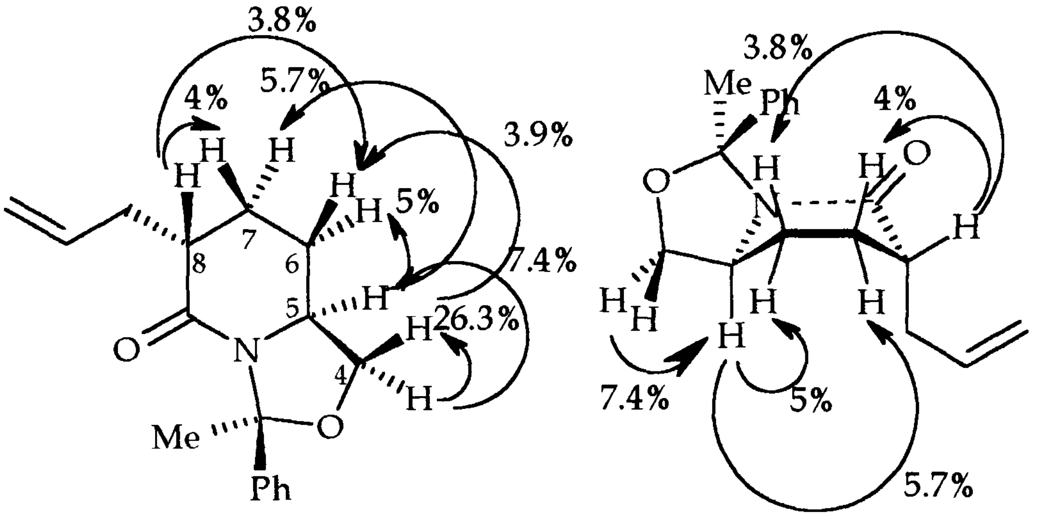


Figure 22: n. O. e. measurements for **105b**

As the measurements illustrated in Figure 22 show, the n. O. e. measurements for the major allyl derivative **105b** are similar to those exhibited by the major, *exo*-benzyl derivative **103b**. Irradiation of 4-H_{exo} gives a 26.3% enhancement of 4-H_{endo}, and a 7.4% enhancement of 5-H. Irradiation of 5-H causes enhancements of 5% at 6-H_{exo} and 5.7% and 7-H_{exo}, while irradiation of 8-H causes enhancements of 3.8% at 6-H_{endo} and 4% at 7-H_{endo}. These results imply that the major diastereomer is, again, that where the newly introduced substituent is *exo*- to the bicyclic system. Interestingly, an enhancement at 6-H_{endo} of 3.9% is seen when 4-H_{endo} is irradiated, which is useful corroborative evidence, and not an enhancement that has often been observed in the course of this work. The right-hand figure illustrates how the data suggests that a boat-type conformation is most likely in this molecule also. It is clear from this diagram that an enhancement is likely between 7-H_{exo} and the methylene protons of the side chain - unfortunately, since the signals for 6-H_{endo} and 7-H_{exo} overlap it is not possible to assert that this happens, although there is an enhancement in this region when 8-CH_2 are irradiated, as detailed in the experimental section.

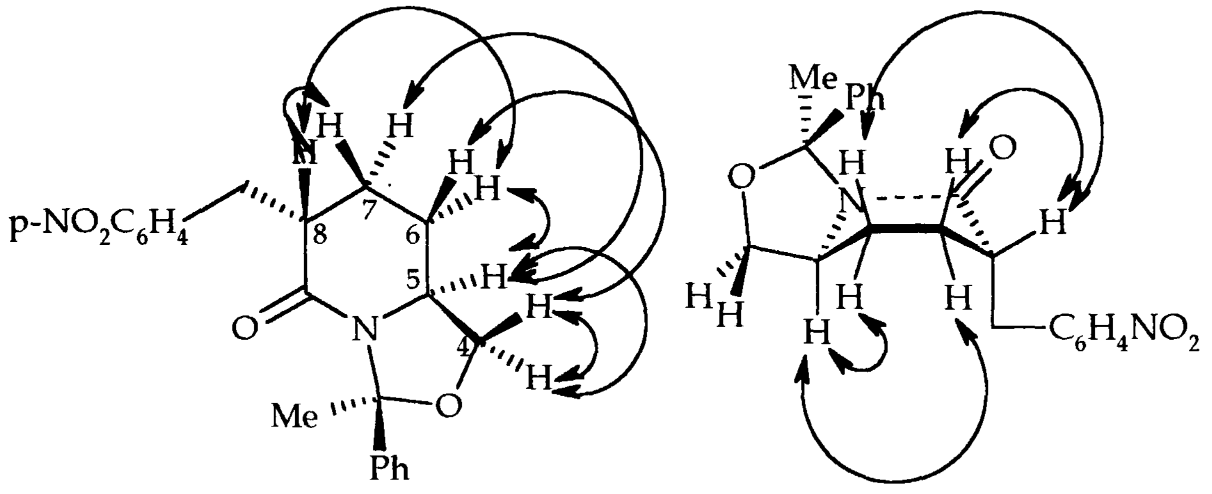


Figure 23: nOesy measurements for **104b**

For some molecules it was not possible to obtain nOe spectra, as a result of the nature of the NMR spectra. In these cases, such as the major *para*-nitrobenzyl derivative **104b**, nOesy spectra were measured where possible. This technique does not give numerical values for enhancements, but shows crosspeaks where irradiation of one peak causes an enhancement at another. The diagram in Figure 23 shows that the same pattern of nOe enhancements is seen, that is, that irradiation of 5-*H* causes enhancements to the 6-H_{exo} and 7-H_{exo} protons, and irradiation of 8-*H* causes enhancements to the corresponding *endo* protons. In all the 2*S* alkylated derivatives that have been suitable for n. O. e. analysis, therefore, the *exo*-diastereomer has been found to predominate. The right-hand figure illustrates how this nOe enhancements support a boat-type structure, as discussed with reference to compound **103b** above.

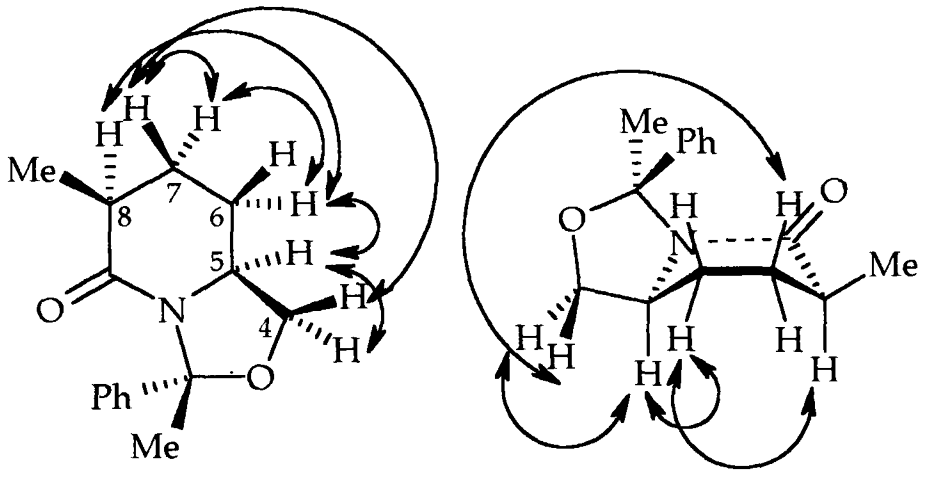
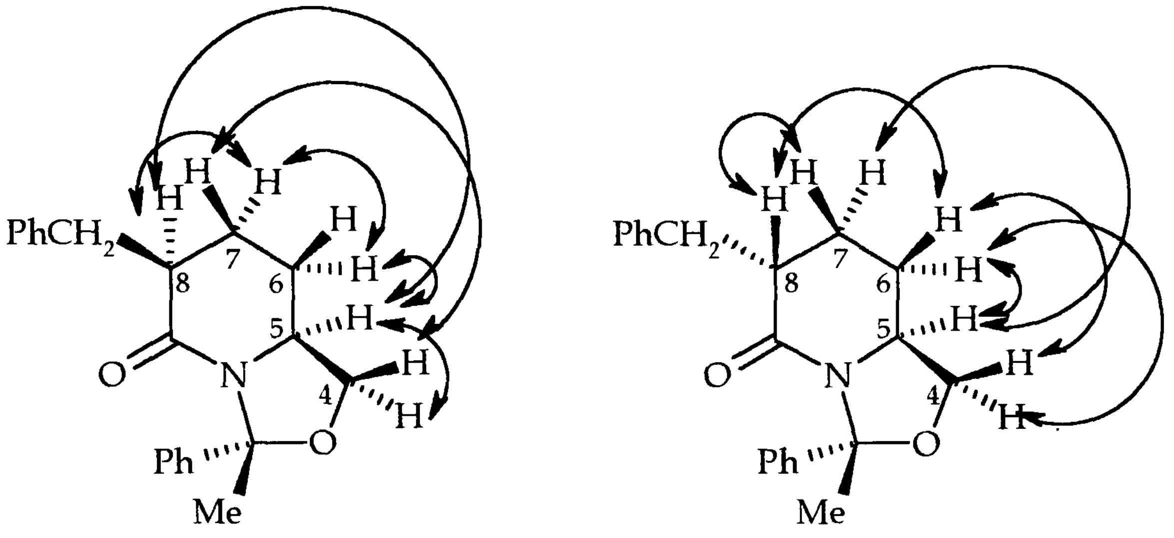


Figure 24: nOesy measurements for **113a**

In the case of the 2*R* derivatives, only nOesy spectra could be obtained. Interestingly, the spectrum for the methyl derivative clearly showed that the only diastereomer obtained on methylating the 2*R* bicyclic lactam **94** had an *endo*-methyl substituent, with enhancements seen between 8-*H* and 7-H_{exo}, between 5-*H* and

6-H_{exo}, between 6-H_{exo} and 7-H_{exo} and between 4-H_{endo} and 6-H_{endo}. Unfortunately, it is not possible to show as clearly in this case that the structure is in the boat form, as signals overlap somewhat, but the right-hand diagram shows how these enhancements support the suggested conformation.



114a **114b**

Figure 25: nOesy measurements for **114a** and **114b**

The diastereomeric pair **114a** and **114b** are the only epimers that have both been suitable for n. O. e. analysis, and it is particularly useful to be able to validate the deductions made for single diastereomers by confirming that the *endo* and *exo* diastereomers do behave differently in nOe/nOesy experiments. In the minor diastereomer, an enhancement is observed between 8-*H* and 5-*H*, which indicates that the benzyl substituent is *endo* to the bicyclic lactam. Further enhancements between 5-*H* and 8-*H* and 7-H_{exo} and 6-H_{exo}, between 7-H_{endo} and 6-H_{endo}, between 6-H_{endo} and 4-H_{endo}, and between 4-H_{exo} and 5-*H* confirm this relationship. In the major diastereomer, there is no enhancement between protons 5-*H* and 8-*H*, but there is enhancement between 5-*H* and 6-H_{exo} and 7-H_{exo}, between 4-H_{exo} and 6-H_{exo}, and between 8-*H* and 6-H_{endo} and 7-H_{endo}. These observations indicate that the major diastereomer is the *exo*-diastereomer. Both these structures are consistent with boat-type conformations in the six-membered ring.

Table 12: Optical rotation of alkylated bicyclic lactams

Product	R	endo/exo	α_D
77	H (2*S*)	-	-6.3
103b	Bn	exo	-25.8
104a	p-$NO_2C_6H_4$-	endo	-52.1
104b	p-$NO_2C_6H_4$-	exo	-65.5
105b	Allyl	exo	-60.0
106a	Cl	endo	+47.2
106b	Cl	exo	-30.4
107a	PhSe	endo	-120.5
107b	PhSe	exo	-26.8
94	H (2*R*)	-	+161.1
113a	Me	endo	+126.1
114a	Bn	endo	+134.6
114b	Bn	exo	+25.0

Comparing the α_D values of the various derivatives is also instructive. With the exception of the phenylselenyl-derivatives, the α_D of the minor, *endo-*, derivative is larger. Unfortunately, not all products could be isolated in sufficiently large quantities to allow this measurement to be carried out. Since the retention factors (R_f) of the derivatives were not all measured in the same solvent system it is not easy to compare across the range of molecules synthesised, but in each case the minor derivative was found to be less polar than the major derivative, and that any di-substituted product found was the least polar of the three products. These physical measurements thus offer a simple rule of thumb for predicting the stereochemistry at C-8, although the anomaly of the phenylselenyl derivatives is an important exception.

Table 13: NMR data of substituted lactams

Product	**R**	***endo/exo***	J / Hz	$\Delta\delta$ / ppm[†]
77	H (2*S*)	-	5.0	0.64
102a	Me	endo	6.0	0.74
102b	Me	exo	5.5	0.56
103a	Bn	endo	6.0	0.49
103b	Bn	exo*	5.5	0.54
104a	p-$NO_2C_6H_4$-	endo	6.0	0.60
104b	p-$NO_2C_6H_4$-	exo*	5.5	0.54
105a	Allyl	endo	6.0	0.72
105b	Allyl	exo*	5.5	0.56
106a	Cl	endo	6.5	0.47
106b	Cl	exo	5.5	0.58
107a	PhSe	endo	6.0	0.65
107b	PhSe	exo	5.5	0.56
108a	BnO_2C	endo	6.0	0.66
108b	BnO_2C	exo	5.5	0.62
94	H (2*R*)	-	5.5	0.66
113a	Me	endo*	5.5	0.39
114a	Bn	endo*	6.0	0.49
114b	Bn	exo*	5.5	0.53

* indicates that nOe data has been obtained on these molecules. Others are designated as *endo* or *exo* according to whether they are the minor or major diastereomer.

[†] $\Delta\delta = \delta(4\text{-}H_{exo}) - \delta(4\text{-}H_{endo})$

An interesting trend in the proton NMR data was also observed in the course of this work. In section 2.3 the significance of the 4-H_{exo} / 5-H coupling constant was discussed, and it was argued that larger values of J indicated that the bicyclic system was more open and less concave. The values of this coupling constant for the alkylated derivatives discussed in this section are tabulated above (Table 13).

The clear trend that can be drawn from this Table is that the minor derivatives all have larger values of *J* than their corresponding epimers. This confirms the extrapolation of the NMR data to deduce that major derivatives have the newly introduced substituent *exo* to the bicyclic system. Importantly, the fact that it is the minor, *endo* derivatives that show larger values of *J*, indicating that the systems are less concave, is in accordance with expectations, as there are more likely to be steric repulsions between the C-8 substituent and the bicyclic system when that substituent is *endo* to the system.

In one study of the [3.3.0] system **48**[109] the chemical shift difference between the two protons attached to the carbon β-to the carbonyl (which would correspond to C-7 in these lactams) was indicative of the stereochemistry of the α-position, with smaller splittings being observed for *exo*-substituted lactams. In the [4.3.0] systems, however, it is not a straightforward matter to assign the 6-*H* and 7-*H* proton chemical shifts, as the four signals tend to be overlaid, and the order in which the different protons are seen is not constant. The 4-*H* splitting is considerably easier to measure, and Table 13 includes the chemical shift difference between the $4\text{-}H_{\text{endo}}$ and $4\text{-}H_{\text{exo}}$ protons to allow comparison. It will be seen that although the splitting is often smaller in the *exo*-diastereomers, this is by no means an absolute rule. The exceptions found in this study are the chloride adducts **105a** and **105b**, and both the 2*S* (**103a** and **103b**) and 2*R* benzyl adducts (**114a** and **114b**). It may be that this results from the anisotropic effect of these substituents causing the $4\text{-}H_{\text{endo}}$ protons to appear at unusually high chemical shift, which weakens this measurement as a predictive tool.

3.6 The mechanism of alkylation, and the source of stereoselectivity

The alkylations described in this Chapter have, in all but one case, given two diastereomers of the substituted bicyclic lactam, with the predominant diastereomer being the *exo*-adduct. In the only example in which only one diastereomer was isolated, that diastereomer was the *endo*-adduct. These facts indicate that the origin of the stereoselectivity observed is complex. The alkylation of lactams has been studied extensively by several workers, and it has become clear that there are a number of factors to be considered.

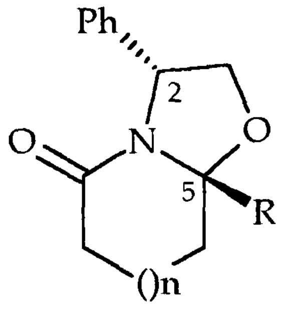


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Figure 26: Meyers lactam.

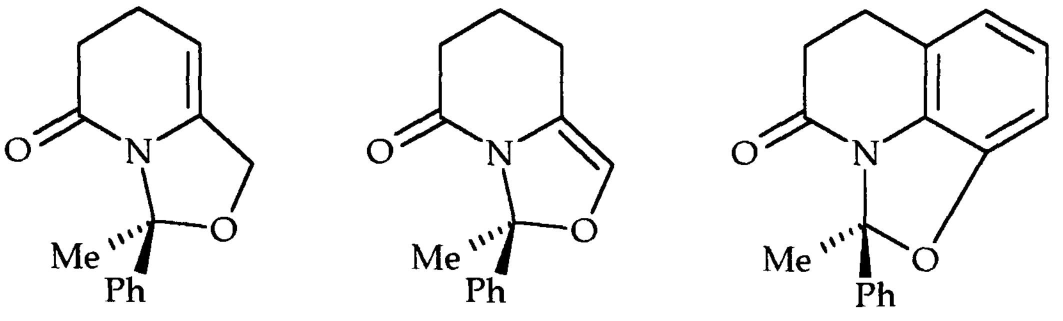
In particular, Meyers has studied both [3.3.0] (n=0) and [4.3.0] (n=1) systems that are closely related to the lactams studied in this work,[66] and identified the following possible influences on the stereoselectivity:

1. The angular substituent (R) at C-5.
2. The protecting group at C-2.
3. An electronic influence of the lone pair of the nitrogen atom.
4. The Cieplak effect,[110] whereby the newly formed bond is formed preferentially antiperiplanar to the most electron rich bond.

Meyers' investigations proved inconclusive, however, as although reducing the bulk at C-2 and C-5 did reduce the stereoselectivity, replacing the nitrogen atom with a quaternary carbon also led to *endo*-alkylation, and introducing a penta-fluoroethyl substituent at C-5 (which should introduce an extremely electron-poor bond) still led to alkylation *endo* to the bicyclic system. If, as seems likely, the stereoselectivity results from a subtle interplay of factors, then these experiments could be criticised as rather naive: the substitution of nitrogen by a methylated carbon is not going to be without steric consequences, nor is the substitution of the C-5 substituent by a perfluoroalkyl group. It could thus be possible that donation from the nitrogen lone pair into the σ* antibonding orbital of the bond being formed is, in fact, a major cause of the selectivity in these systems.

An important fact that has not yet been explained is that the position of the oxygen atom in the ring appears to play an important stereodirecting rôle. [3.3.0] and [4.3.0] systems of both the Thottathil and Meyers type have now been investigated thoroughly, and it has been founded that Meyers-type lactams give predominantly - *endo*-substitution, while Thottathil-type lactams give predominantly *exo*-substitution. In the case of the [4.3.0] Meyers-type systems this work has been done by Amat, who observed only one product on alkylation with either methyl iodide or benzyl bromide. Since molecular modelling of the Meyers [3.3.0] system by Liotta[111] suggests that the bicycle is broadly planar, it may be that the major effect of transposing the oxygen atom from position 4 to position 5 is to reduce the extent to which the steric effects which would disfavour *endo*-alkylation play a part.

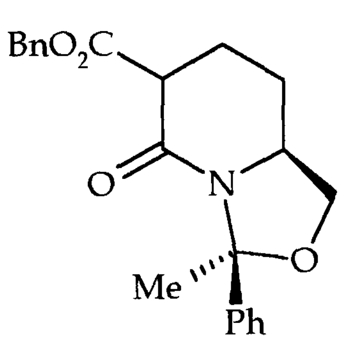
The crystal structure obtained by Davies[86] showed that the C-2 phenyl group was unlikely to play a major stereodirecting role in the alkylations of the bicyclic lactam, as it is held remote from the reacting site. In this work it has been possible to contrast the reactivity of the two C-2 epimers, and it was found that *exo*-stereoselectivity was greater in the 2*S* epimer. In the case of the 2*R* epimer, the smaller methyl iodide gave only the *endo*-alkylation product, while the 2*S* epimer gave a 1:1 mixture, and the larger benzyl bromide gave a 2:1 selectivity in favour of the *exo*-diastereomer while reaction with the 2*S* epimer showed a 10:1 selectivity. These results are consistent with a model whereby the selectivity of the alkylations of the bicyclic lactams depends on a balance of two opposing factors: the stereoelectronic effect of the nitrogen lone pair favours *endo*-alkylation, while the steric repulsions between the bicyclic system and the incoming electrophile favour *exo*-alkylation. In a more open system (that is, the 2*R* epimer) these repulsions are less important, so more *endo*-alkylation is observed, while with larger electrophiles these repulsions are more important, so *exo*-alkylation is promoted.



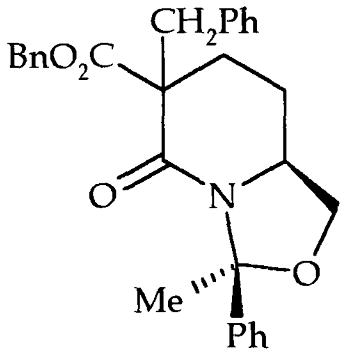
117 118 119

Figure 27

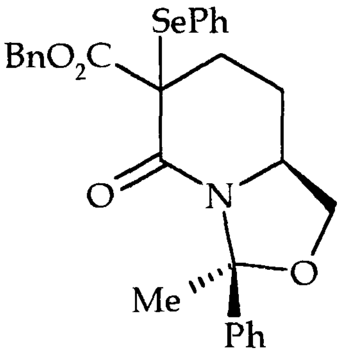
It would be interesting to attempt these alkylations on a more planar system such as **117**, **118** or **119**, in order to investigate this hypothesis. It seems likely, however, that the presence of the double bond in **117** and **118** would have major electronic effects on the reactivity of the system, which would limit the usefulness of such an investigation. A literature search for **119** revealed no previous syntheses of such molecules, and although the reactions of such a system might well be of interest, they would not furnish piperidine derivatives as products, and as such are outside the scope of this thesis.



108



115



116

The activated bicyclic lactam **108** has not yet been considered in detail in this Chapter. Since the alkylated derivatives **115** and **116** were not separable by column chromatography, their stereochemistry and the stereoselectivity of this second alkylation remains a matter for conjecture. Meyers had found that introducing a second group into a substituted lactam did not affect the stereochemistry of the first group: if the first group was *endo-* to the ring system, it would remain *endo-* even after deprotonation and alkylation. These findings are not confirmed in this case, however, as a 1:1 mixture of diastereomers of the acylated starting material gave a 1:4 mixture of diastereomers of the benzylated products. If the effect observed by Meyers had operated, then a 1:1 mixture would have been found. Studies on the [3.3.0] Thottathil lactam have suggested that the selectivity of a second alkylation depend on the relative sizes of the two electrophiles (see section 1.3), and the results described in this Chapter correspond well with the findings for the [3.3.0] system (Table 14).

Table 14: Diastereomeric ratios on alkylation of activated lactams

Electrophile	[4.3.0] system 108	[3.3.0] system 59
BnBr	1:4	1:7.5
PhSeCl	1:1	1:1.5

It is surprising to note that the reactions of the activated [4.3.0] lactam **108** are less selective than those of the activated [3.3.0] lactam **59** when the reverse trend was observed for the unactivated lactams. The fact that the activating group is larger in the [4.3.0] system may be an important factor here.

3.7 Summary

In this Chapter the alkylation reactions of the epimeric bicyclic lactams **77** and **94** are described and discussed. Deprotonation of these lactams was found to be surprisingly difficult in the light of the behaviour of the homologous [3.3.0] lactams, but there is literature precedent for this phenomenon with similar [4.3.0] systems.

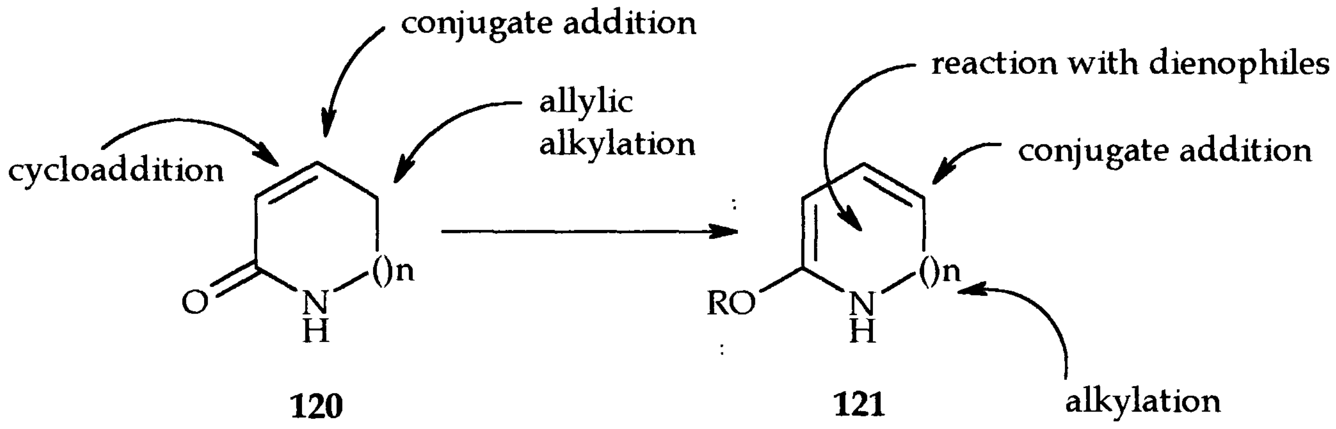
Mixtures of epimeric products were synthesised, separated by chromatography on silica, and analysed using nOe spectroscopy to assign their stereochemistry.

In general, *exo*-alkylation predominates. It is argued that this results from the greater steric influences of the bicyclic system overruling the stereoelectronic effect of the nitrogen lone pair which would be expected to promote *endo*-alkylation. This behaviour contrasts interestingly with [4.3.0] systems in which the carbon at position 4 and the oxygen at position three are transposed, in which *endo*-alkylations predominate, and where the selectivity is greater. It is argued that these systems are more planar and therefore less affected by steric interactions. This route therefore offers a synthesis of homochiral piperidinone derivatives.

Results and discussion 3: synthesis and applications of an activated enone

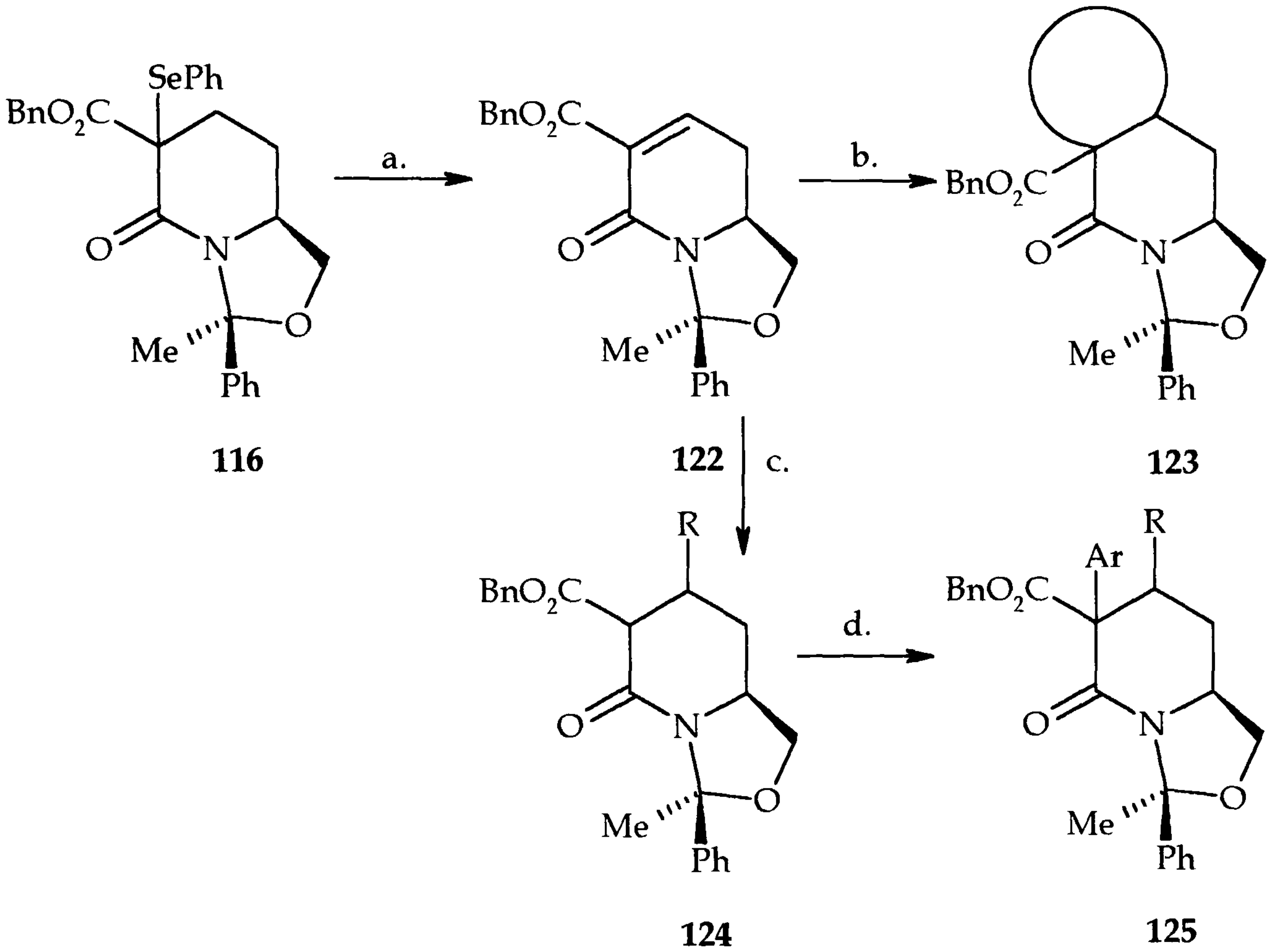
4.1 Introduction

Unsaturated lactams have become increasingly popular starting materials in organic synthesis in recent years. This is a result of the diverse range of reactions that may be performed on these substrates, and their greater synthetic availability.



Scheme 41

Some of the possible modes of reaction are detailed in Scheme 41. In addition to the potential manipulations of the amide carbonyl group, unsaturated lactams **120** have been shown to be suitable substrates for cycloaddition[112 113] and conjugate addition[68 80 81 114 115 116 117 118 119] reactions. There is also the possibility of alkylation at the allylic position, as illustrated, although there is no literature precedent for this manipulation. If the lactam is trapped as a silyl enol ether or triflate **121**, for example, then similar manipulations can be performed, but functionalising carbon atoms further round the ring.[120] This means that up to four carbon atoms may be functionalised if an unsaturated lactam is chosen as the starting material. The reactions that will be discussed in particular in this Chapter are the cycloaddition and conjugate reactions on a lactam of general form **120**, but the other routes are likely to be profitable avenues for further investigation.



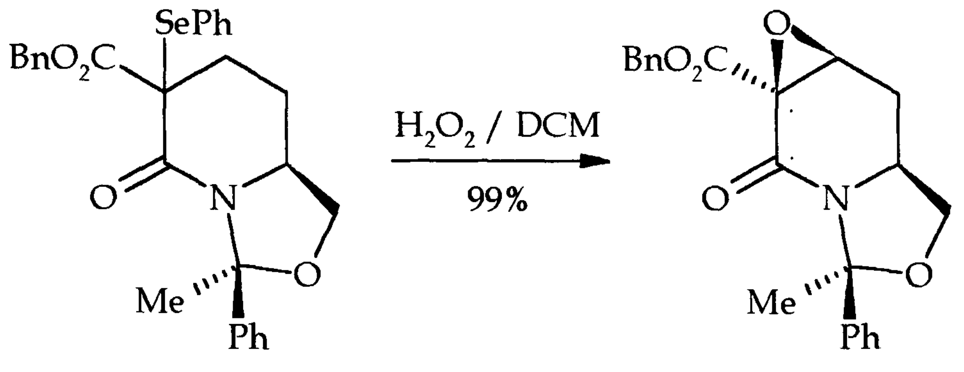
Scheme 42

In this Chapter the synthesis (a.) of an unsaturated lactam **122** is described, and investigations into its suitability for cycloaddition (b.) and conjugate addition (c.) reactions are discussed. Finally, the product of a conjugate addition reaction is used as a substrate in an Pb(IV)-mediated arylation reaction (d.), which generated a quaternary carbon centre.

4.2 The synthesis of an unsaturated lactam

Although there are many well-known methods for the transformation of a carbonyl derivative into an α,β-unsaturated system, the method chosen in the route described in this thesis was the oxidation-elimination reaction of a selenyl derivative. This strategy has the advantage of being relatively mild, as the elimination of the selenoxide will occur close to room temperature, and regiospecific. Alternatives to this would include the use of DDQ,[121] which is thought to act by the abstraction of a hydride ion, and would therefore not be guaranteed to be regiospecific, $PdCl_2$[122] and $FeCl_3$,[123] which might attack the *O*,*N*-acetal protecting group or a bromination-dehydrobromination sequence.[124]

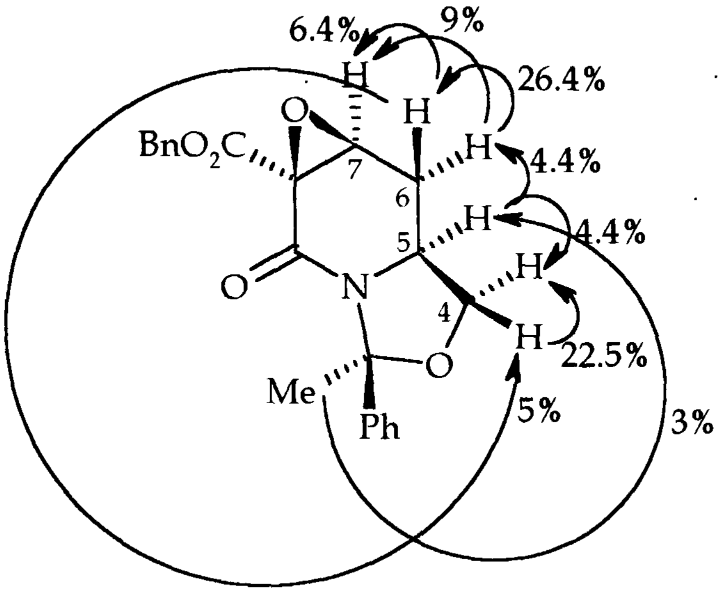
The synthesis of the selenide derivative **116** was described in section 3.4. There are several commonly used oxidants of selenide derivatives,[106] including ozone,[125] sodium perborate,[126] hydrogen peroxide and sodium periodate.[127] Previous experience on the [3.3.0] system had indicated that both ozone and hydrogen peroxide were effective oxidants, and that hydrogen peroxide was the most easily applied. Consequently, the oxidation of the selenide **116** was attempted according to these conditions (Scheme 43):



116 **126**

Scheme 43

In this reaction the mixed selenides were treated with 3 equivalents of hydrogen peroxide in dichloromethane at 30°C for an hour. The only product isolated was the epoxide **126** as a colourless oil ($[\alpha]_D^{25}$ -77.5 (*c* 0.3 in $CHCl_3$)). It was thought that this was likely to result from the conjugate addition of hydroperoxide ion to the enone, and so the reaction was repeated using only one equivalent of the oxidant. This gave a 1:1 mixture of the epoxide and the selenide starting material, which was disappointing in the context of the synthesis of the enone, but indicated that the enone was likely to be highly reactive in conjugate addition reactions. The stereochemistry of the epoxide was assigned with the aid of n. O. e. difference spectroscopy (Figure 28):



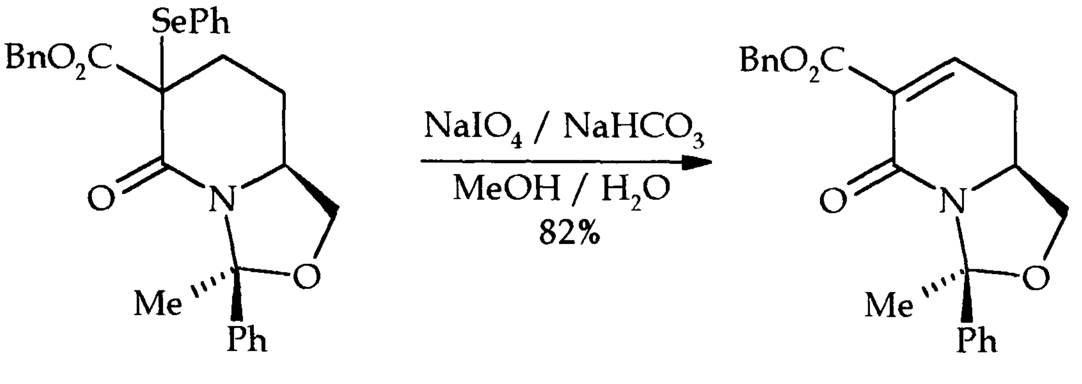
126

Figure 28

The enhancements shown in Figure 28 indicate that the epoxide group is *endo-* to the bicyclic system. The characteristic large enhancements between the 6-*H* and 4-*H* geminal protons confirm the assignments of these pairs, and the 4.4% enhancements from 5-*H* to 6-H_{exo} and 4-H_{exo} allow their assignment as *endo* or *exo*. The enhancements of 7-*H* by the 6-*H* protons are rather ambiguous, in that both protons give enhancements, but the larger enhancement seen from the 6-H_{exo} proton suggests that 7-*H* is *exo-* to the ring. Inspection of the coupling patterns in the NMR shows that 6-H_{endo} is not coupled to 7-*H*, and this was confirmed by a decoupling experiment, where irradiation of either one shows no effect on the appearance of the peak corresponding to the other. This implies that the dihedral angle between these two protons is 90°, and inspection of models suggests that this is feasible for the diastereomer shown above.

It is interesting to note that there is no sign of any other diastereomer being formed in this reaction. This would therefore be a suitable starting point for the generation of hydroxy-piperidines by ring-opening reactions using Grignard reactions, for example. Such reactions have been studied by Amat[128] on a similar substrate with promising results.

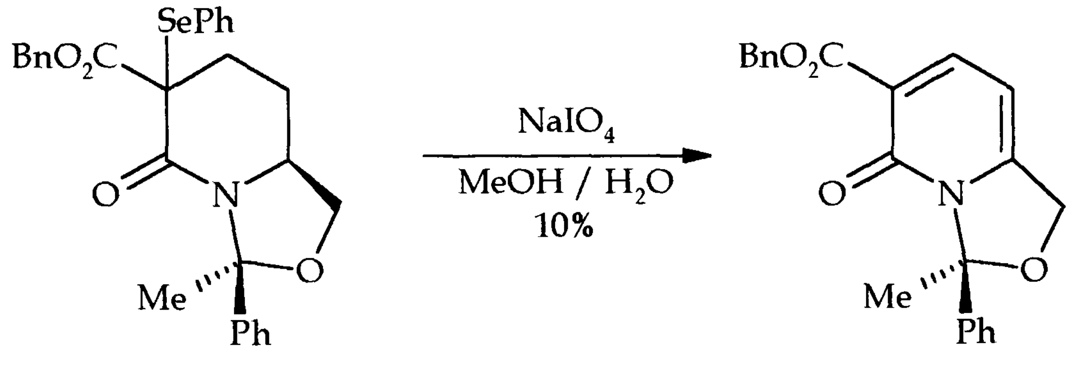
There is precedent for the conversion of epoxides to alkenes,[129] [130] [131] but it was felt more desirable to access the enone **122** directly from the selenide. Since hydrogen peroxide was not a suitable reagent for achieving this, an oxidation with sodium perborate was attempted according to literature procedure. No product was obtained from this reaction.



116 **122**

Scheme 44

Fortunately, the oxidation of the selenide **116** with sodium periodate proceeded smoothly according to literature precedent (Scheme 44). In this method, the selenide was dissolved in methanol and mixed with a solution of sodium periodate (2 eq) and sodium bicarbonate (1 eq). Oxidation then proceeded rapidly to give the desired enone, which could be purified by flash column chromatography to give the enone **122** as a colourless oil ($[\alpha]_D^{25}$ -69.9 (c 1.09 in $CHCl_3$)).



116 **127**

Scheme 45

Interestingly, if the base was omitted (Scheme 45) the only product isolated after chromatography in low yield was the pyridone derivative **127** ($[\alpha]_D^{22}$ -212.0 (c 1.13 in $CHCl_3$)). This derivative was found to decompose to a brown gum on standing, which would suggest that the low yield of product isolated was a result of rapid decomposition on the column.

It is interesting to compare the characteristics of this compound with the starting bicyclic 77, the acylated lactam **108** and the enone **122**.

Table 15: Data for compounds 77, **108**, **122** and **127**

Molecule	$[\alpha]_D$	**C=O lactam / cm^{-1}**	**C=O ester / cm^{-1}**
Lactam 77	-6.3	1651	-
Acylated lactam 108	-	1673	1732
Enone 122	-69.9	1666	1735
Pyridone 127	-212.0	1667	1734

There is a clear trend in the variation of the optical rotation of these compounds. As the six-membered ring becomes progressively more unsaturated, and hence more planar, the optical rotation increases in magnitude.

It can be seen from Table 15 that the effect of introducing an electronegative ester group at C-8 is to increase the frequency of the lactam C=O stretch from 1651cm^{-1} to 1673cm^{-1}. It would appear that there is little evidence for conjugation between the two carbonyl groups, as the frequency of the exocyclic carbonyl group stretch remains largely unchanged as the ring system is progressively dehydrogenated, while generation of the enone **122** causes a reduction in the lactam C=O stretch of approximately 7 cm^{-1}, which is a typical reduction for an unsaturated carbonyl. If the exocyclic carbonyl group had been conjugated with the new C=C bond then a corresponding reduction would be expected in its stretch frequency. The fact that the lactam C=O stretch is higher in frequency in the acylated bicyclic lactam than the starting material is therefore due to the inductive effect of this group.

Molecular modelling using MOPAC with PM3 parameters supports this interpretation of the physical data. The energy-minimised structure of the enone **122** (Figure 29) was found to have the benzyl ester group orthogonal to the plane of the enone, which would make conjugation impossible. The benzyl group was *exo-* to the bicyclic system.

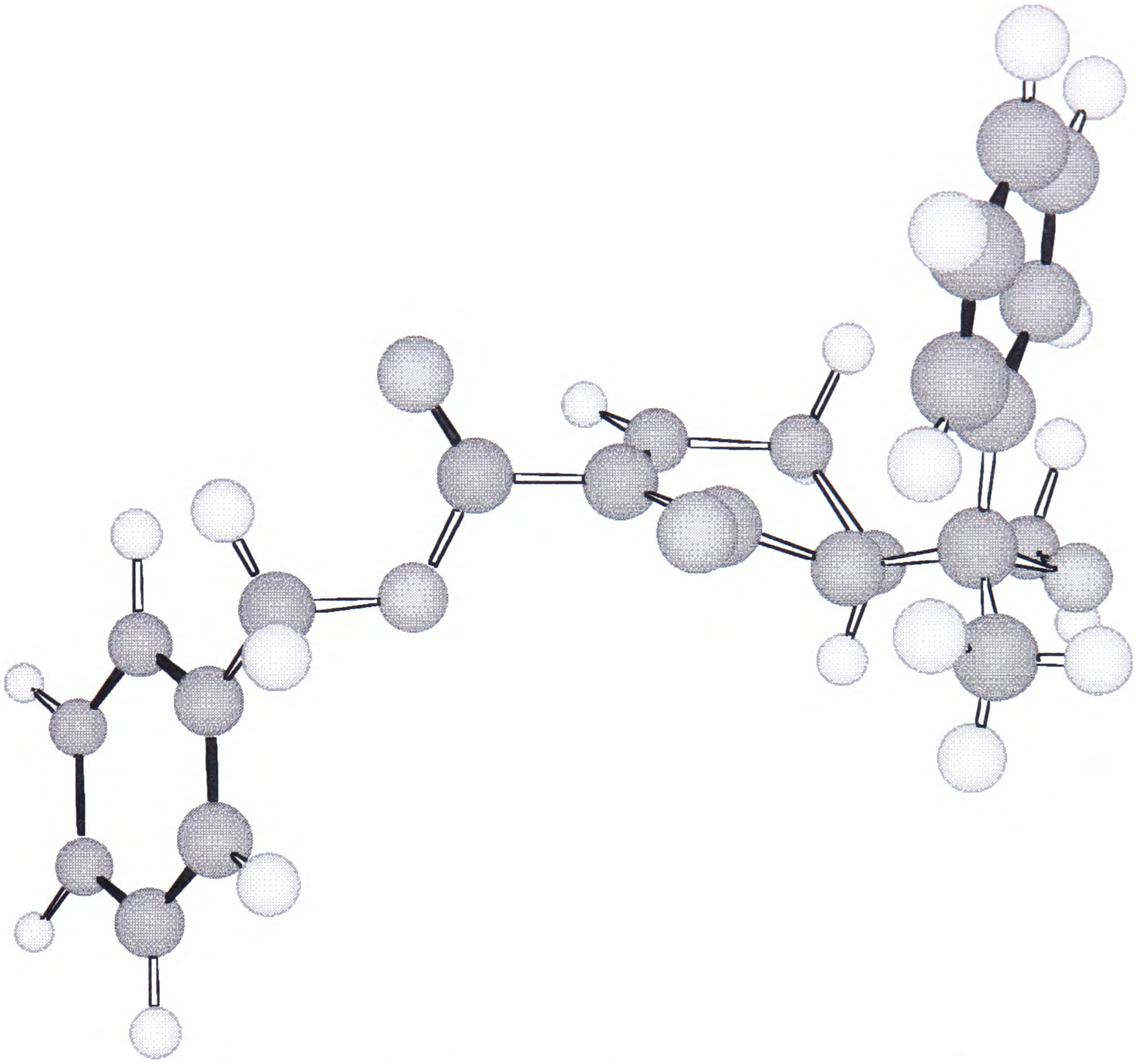
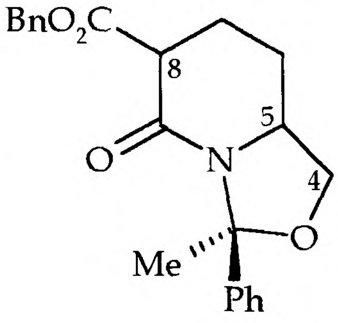


Figure 29: Molecular modelling structure of enone **122**



108

Figure 30

Table 16: δ_C / ppm for **77**, **108**, **122**, and **127**

Molecule	**C-2**	**C-4**	**C-5**	**C-6**	**C-7**	**C-8**	**C-9**	**ester C=O**
Lactam 77	95.9	69.1	57.7	20.9	24.8	32.1	168.0	-
Acylated lactam 108	96.7	69.4	56.3	22.1	28.3	64.6	163.3*	170.9*
Enone 122	96.5	66.8	55.4	27.2	145.7	131.1	158.4*	163.5*
Pyridone 127	103.3	66.6	119.6	96.8	146.2	150.5	157.4	164.2

* these assignments were confirmed by HMBC analysis.

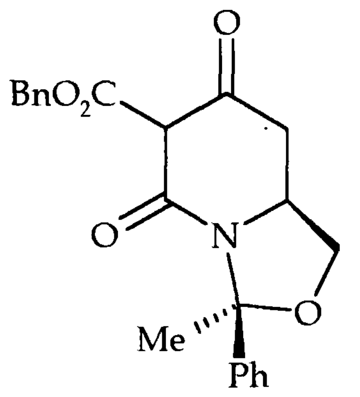
It is interesting to note how the chemical shifts of the carbon atoms in the bicyclic system change over the same sequence. Acylation at C-8 shifts this peak downfield from 32.1 to 64.6 ppm, with small effects on other resonances. In the enone both the C-8 and C-7 signals shift significantly (from 64.6 to 131.1 ppm and from 28.3 to 145.7 ppm respectively) but the allylic C-6 shifts by only 5.1 ppm to 27.2 ppm. In the pyridone C-8 again shifts significantly, to 150.5 ppm, but the C-6 only shifts to 96.8 ppm, while C-5 shifts from 55.4 to 119.6 ppm. Interestingly, C-7 is largely unchanged at 146.2 ppm. This suggests that there may be significant electron donation from nitrogen to the adjacent double bond, which would also account for the increase in shift at C-8. It would seem that C-4 is largely unaffected by changes in the six-membered ring system, varying only between 66.6 and 69.4, and with no clear pattern.

Table 17: δ_H / ppm for **77**, **108**, **122**, and **127**

Molecule	**4-H$_{endo}$**	**4-H$_{exo}$**	**5-H**	**6-H$_{endo}$**	**6-H$_{exo}$**	**7-H$_{endo}$**	**7-H$_{exo}$**	**8-H$_{endo}$**	**8-H$_{exo}$**
Lactam 77	3.47	4.11	3.84	1.50	2.08	2.08	1.85	2.45	2.45
Acylated lactam 108	3.46	4.08	3.86	*	*	*	*	3.56	-
Enone 122	3.46	4.16	4.10	2.30	2.53	7.00	-	-	-
Pyridone 127	4.94	5.08	-	6.12	-	8.22	-	-	-

* not individually assigned, but all lying between 1.51 and 2.34.

The proton shifts are less interesting than the carbon chemical shifts, for the obvious reason that there are fewer to compare. As expected, allylic and vinylic protons are shifted downfield compared to protons attached to and adjacent to saturated carbons. Inspection of the coupling constants (as discussed in sections 2.3 and 3.5) is not interesting in these molecules, except for the fact that W-coupling is observed in the pyridone **127** between 6-*H* and the 6-*H* protons of the order of 1.0 Hz. The geminal coupling constant in this case increases to 14.5 Hz (from 8.0 Hz in the bicyclic lactam **78**), which is to be expected with a more electronegative substituent.



128

Figure 31

A recent paper[132] suggested that large excesses of hydrogen peroxide might generate β-dicarbonyl compounds from selenides, and so the synthesis of compound **128** was attempted. Unfortunately, no product was isolated.

4.3 Cycloaddition reactions

Cycloaddition reactions have become popular tools in organic synthesis, as they allow the stereochemistry of a number of carbon centres to be set in one reaction.[133] In these reactions a 4π and a 2π component react together according to the Woodward-Hoffman rules, and the variety of 4π components that may be used means that not only six-membered carbon rings, but heterocycles may be synthesised. In some cases, the newly formed ring may be cleaved easily such that two new substituents have been added to one component in a *cis*-fashion.

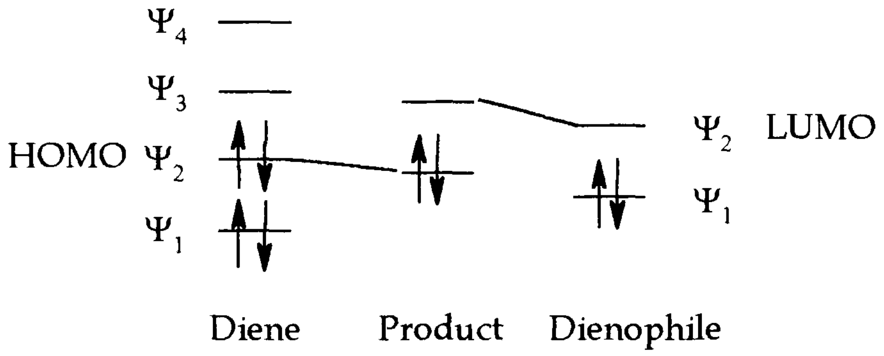
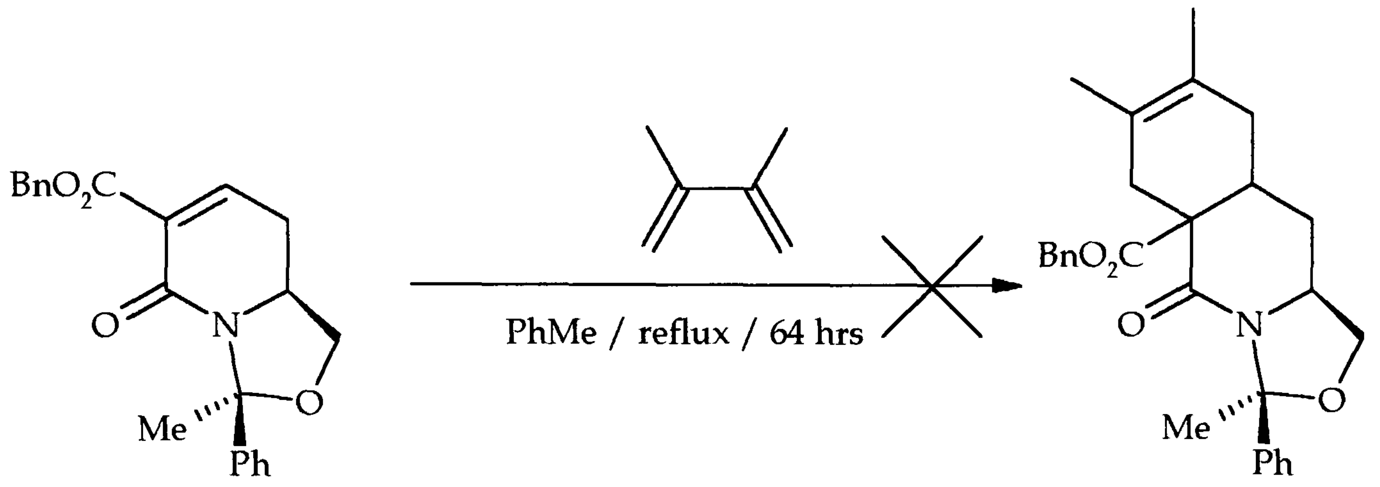


Figure 32: Correlation diagram for Diels-Alder reactions

The enone **122** whose synthesis was described in section 4.2, was specifically designed to be reactive in cycloaddition reactions. These reactions depend on the mixing of the HOMO of the 4π component (for example, a diene) with the LUMO of the 2π component (that is, the dienophile), and so changes to the reactants that will reduce the HOMO-LUMO gap will promote the reaction. In practice, this usually means that electron donating groups on the diene, and electron withdrawing groups on the dienophile will promote the reaction (Figure 32). This was the rationale behind the introduction of an ester group at C-8, and it was supported by the evidence of the [3.3.0] system (section 1.3), where Diels-Alder reactions could not be performed on the unactivated enone, but proceeded readily on the activated enone.



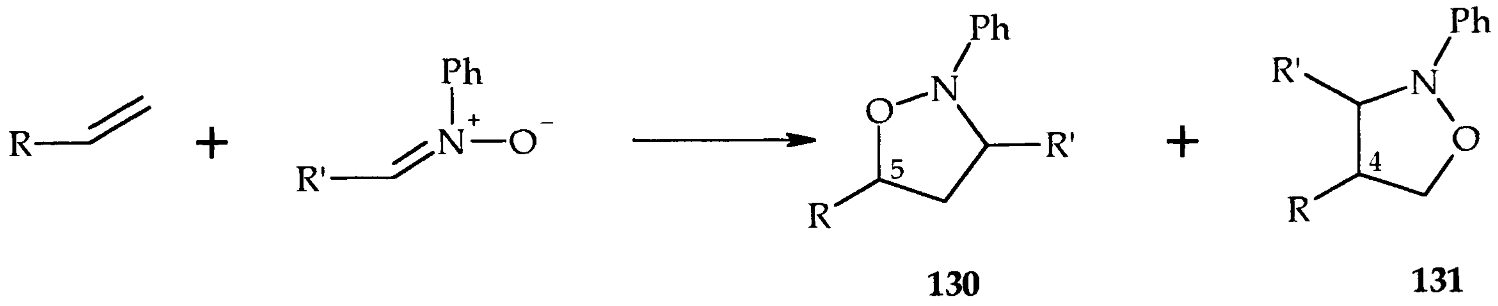
122 129

Scheme 46

The diene chosen for an initial investigation of the Diels-Alder reaction was 2,3-dimethyl-1,3-butadiene (Scheme 46). This is not a highly reactive diene, but using this diene allowed us to compare the reactivity of the [4.3.0] system with that that had already been investigated with the [3.3.0] system. In addition, the symmetry of this diene means that there are only two possible products: that where the new carbon-carbon bonds are *endo-* to the bicyclic system, and the activating C-8 ester group and 7-H, are both *exo-* to the bicyclic system, or the reverse diastereomer where the stereochemistry at both C-8 and C-7 is inverted. This simplicity would make it easier to analyse any reaction products. The reaction was attempted according to standard procedure, with regular monitoring by t. l. c., but no product was observed.

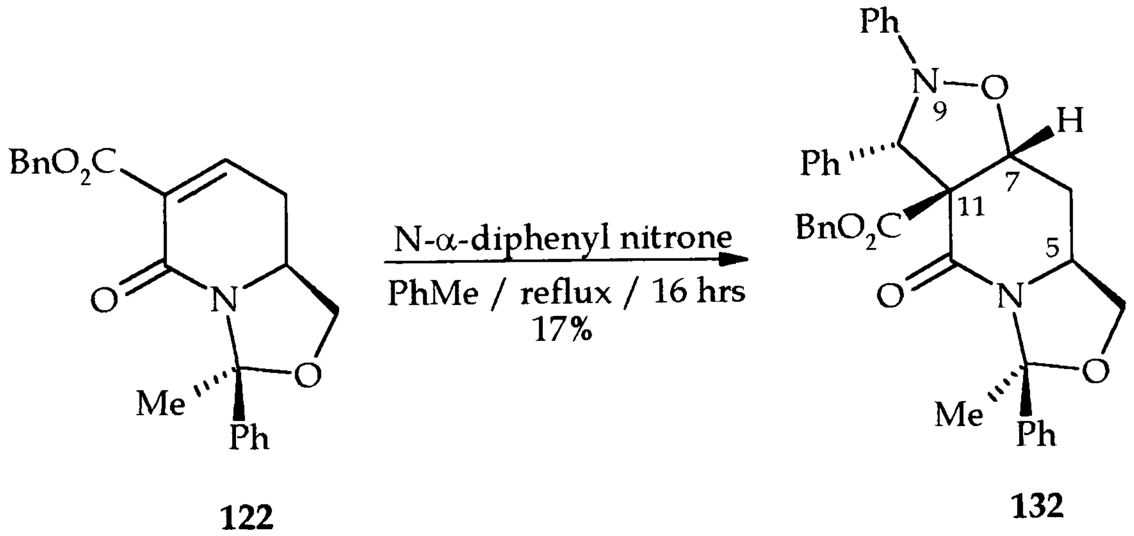
Although the lack of reactivity in a Diels-Alder reaction was disappointing, it was thought worth attempting a 1,3-dipolar cycloaddition. This reaction is mechanistically similar to the Diels-Alder reaction, though in this case the 4π component has the electrons spread over only three atoms, and is isoelectronic with the allyl anion. There are many examples of suitable 1,3-dipoles including nitrones, nitrile ylids, azomethine ylids, azides, diazoalkanes, nitrile imines and nitrile oxides, and the products are frequently cleaved to give *cis*-substituted derivatives, as

Langlois recently used a nitrone to introduce *cis-* hydroxyl and methyl groups,[134] or as Ondruš used the addition of a nitrone to an unsaturated lactone to generate a precursor for piperidine synthesis.[135] Nitrone additions have been studied extensively by Houk[136, 137] who has noted an interesting trend in their regiochemistry (Scheme 47).



Scheme 47

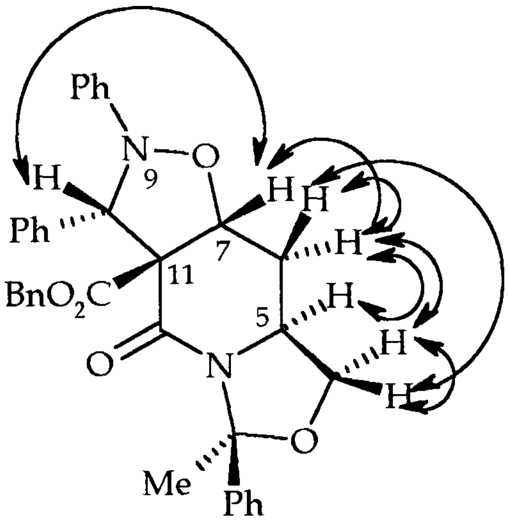
In Scheme 47 the two possible regioisomers are illustrated. In general, the major product is the 5-substituted isomer **130**, which results from the interaction of the LUMO of the nitrone and the HOMO of the dipolarophile. The 4-substituted isomer **131** results from an FMO interaction of the LUMO of the dipolarophile and the HOMO of the nitrone. Houk argues that this interaction is dominant when the dipolarophile is substituted with an electron withdrawing group R. This means that although the usual course of nitrone cycloadditions is to give a 5-substituted product, it is likely that the 4-substituted product is given in the cycloaddition of the enone **122** and a nitrone. This was, indeed, found to be the case (Scheme 48), although the product **132** was only isolated in low yield.



Scheme 48

The regiochemistry of this reaction was confirmed by a COSY spectrum. If the 5-substituted product had been formed, then 7-*H* would have been coupled to the proton α-to the nitrone nitrogen. In the 4-substituted isomer the α-proton would be a singlet. Since the COSY spectrum showed no coupling between 7-*H* and the proton assigned here as 10-*H*, the regioisomer shown is indeed that which is formed.

The stereochemistry at carbons 7, 10 and 11 was assigned using a NOESY spectrum (Figure 33).

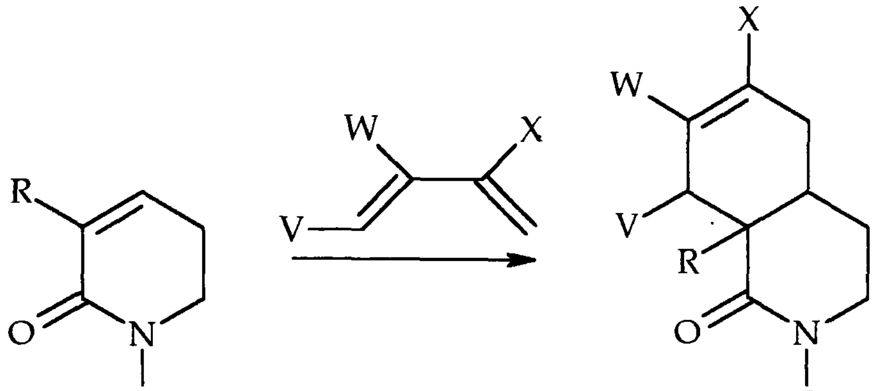


132

Figure 33: NOESY enhancements on the nitrone **132**

The enhancements shown here are for the major diastereomer. There was NMR evidence for a second diastereomer, but contributing less than 5% to the product mass. It is believed that this would be epimeric at C-10, but as it was inseparable from the other, and present in such low concentration as to be undetectable by NOESY spectroscopy, this cannot be stated unambiguously. The major diastereomer shows enhancements between 6-H_{endo} and 4-H_{endo}, and between 6-H_{endo} and 7-*H*, which suggests the stereochemistry shown, while an enhancement between 7-*H* and 10-*H* suggests that 10-*H* is also on the same face of the new five membered ring.

The yield of this nitrone cycloaddition is disappointing, as was the failure of the Diels-Alder reaction with 2,3-dimethyl-1,3-butadiene. These results suggest that the enone **122** is not, in fact, particularly susceptible to cycloaddition reactions. This is surprising in the light of the results obtained in the [3.3.0] system, but there is precedent in the literature for such additions being difficult to achieve, at least in piperidine based systems. Simpkins[111] and Bosch[112] have both investigated the Diels-Alder reactions of *N*-protected 2-piperidinones (Scheme 49):



133 **134-139**

Scheme 49

Table 18: Diels-Alder reactions of piperidinones **133**

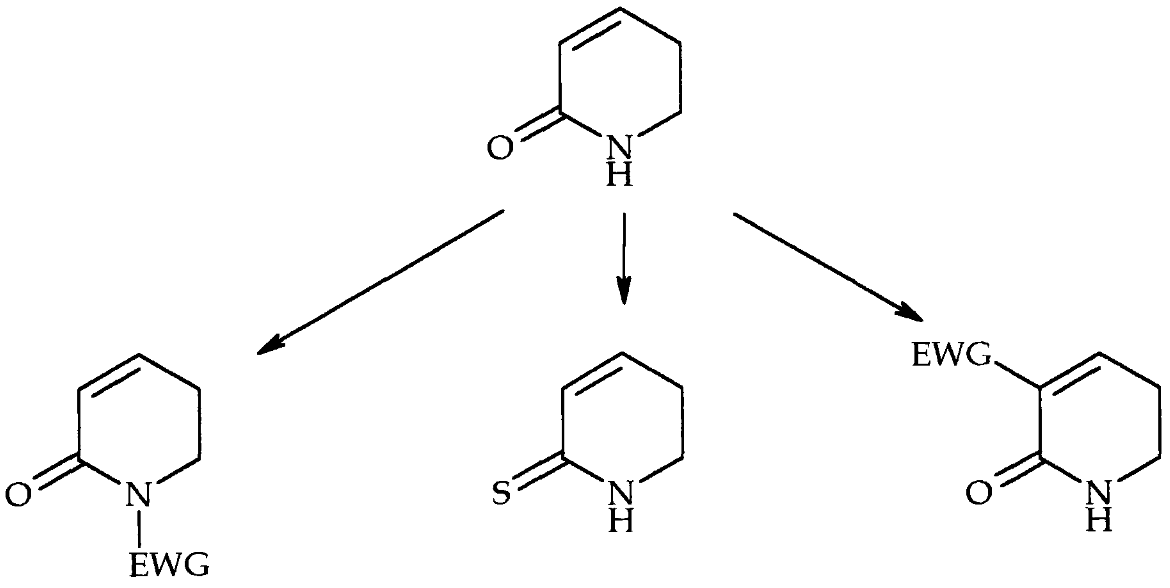
Product	**R**	**V**	**W**	**X**	**Catalyst**	**Solvent**	**Yield / %**
134	H	OMe	H	OTMS	-	*p*-cymene	0
135	CO_2Bn	OMe	H	OTMS	-	benzene	79
136	CO_2Bn	H	Me	Me	-	*p*-cymene	11
137	CO_2Bn	H	Me	Me	$ZnBr_2$	DCM	73
138	CO_2Me	H	H	OTMS	-	toluene	15
139	CO_2Me	H	H	OTMS	$ZnBr_2$	DCM	92

All those reactions in hydrocarbon solvents were performed at reflux, while those performed in DCM could be performed at 0°C. These results suggest that the activating ester group is indeed important if a Diels-Alder reaction is to occur, but that even then only the most reactive dienes will react satisfactory without Lewis acid catalysis. It was not thought wise to subject the enone **122** to Lewis acid conditions, given that the *O*, *N*-acetals are known to be particularly labile,[138] and these results do not suggest that Diels-Alder reactions will necessarily be high-yielding.

The reluctant reactivity of these piperidinone derivatives, that is, the enone **122**, the Bosch piperidinones giving **134-7**, and the Simpkins piperidinone giving **138-9**, remains unexplained. It may be that these reactions are more favoured in the [3.3.0] system as they are accompanied by a significant reduction in ring strain, given that the preferred geometry for sp^2 hybridised carbon atoms is 120°, that for sp^3 carbon atoms is 109°, and the internal angles in a regular pentagon 108°. In the [4.3.0] system, however, this relief would not feature. In addition, the fact that the ester group is not conjugated to the enone, as discussed in section 4.2, means that this is not a particularly electron-poor carbon-carbon double bond, and therefore the HOMO-LUMO gap is not as small as it would be in an acyclic enone.

4.4 Conjugate additions

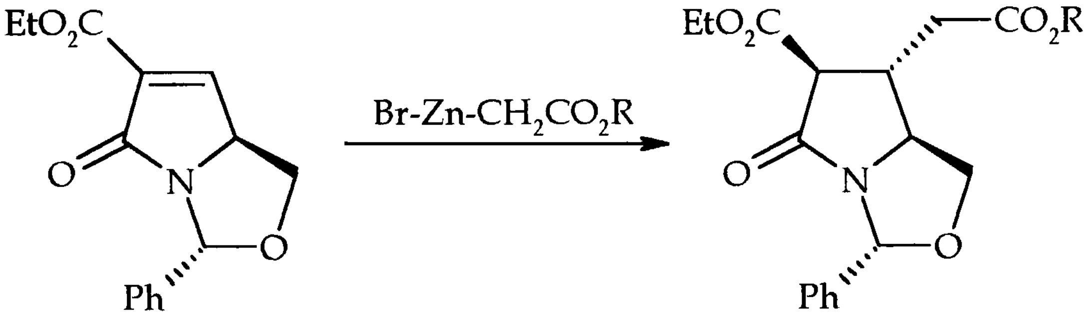
Although Overman noted in 1989[114] that unsaturated lactams were not usually particularly susceptible to conjugate addition reactions, numerous examples of such transformations have now been reported. Popular nucleophiles include cuprates[68 119 139] and malonate anions,[140] as these reagents are sufficiently soft in character to ensure that addition occurs regiospecifically to the β-carbon atom, rather than to the carbonyl group.



140 **141** **142**

Scheme 50

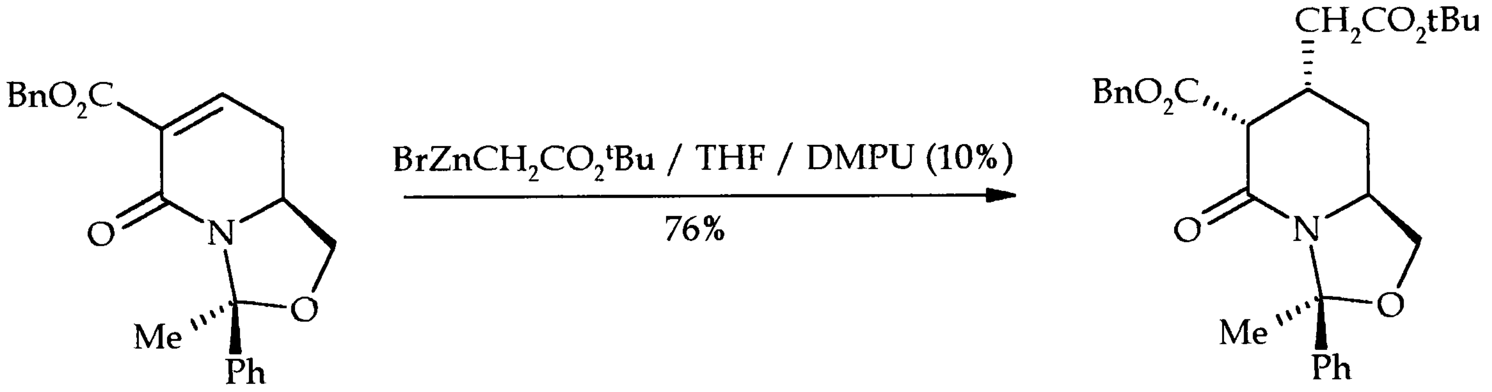
In all cases where addition has been achieved successfully the lactam has been activated in some way. There are three obvious ways in which this can be done: an electron-withdrawing group may be attached to nitrogen[141] (**140**), the carbonyl group may be converted to a thiolactam[142] (**141**), or an electron-withdrawing group may be attached to the α-carbon[68] (**142**), as has been described for the [3.3.0] system (section 1.3), and for this [4.3.0] system in this Chapter.



70 **74**

Scheme 51

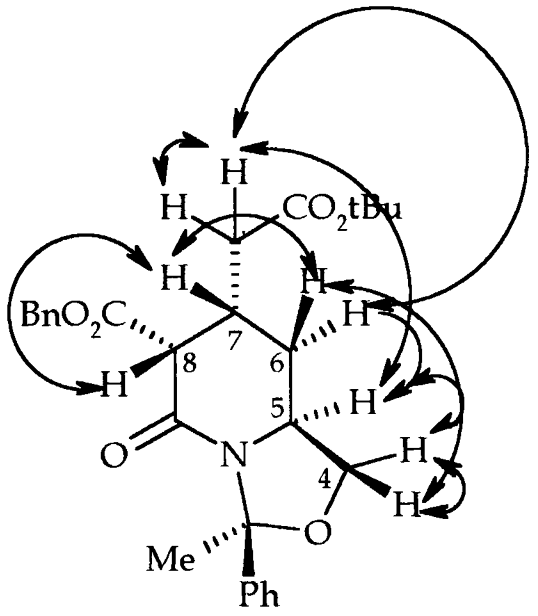
Despite the disappointing performance of the enone **122** in cycloaddition reactions, we were optimistic about its potential in conjugate addition reactions. A previous worker[80] had developed an efficient method of achieving the conjugate addition of a Reformatsky reagent to the unsaturated enone **70** (Scheme 51), with particularly promising results when the group R=^{t}Bu. These reagents are considerably less basic than their lithium analogues, which reduces the likelihood of side reactions occurring, and it was hoped that the bulk of the C-5 substituent would give good stereoselectivity.



122 **143**

Scheme 52

The conjugate addition of the Reformatsky reagent generated from α-bromo *tert*-butyl acetate to the enone **122** was therefore attempted (Scheme 52). The established procedure was used, that is, the bromoester was sonicated with zinc and a catalytic amount of iodine in THF to generate the Reformatsky reagent, and then a solution of the enone **122** was added to this solution, and the reaction was stirred until t. l. c. analysis indicated that it had gone to completion. After work up and purification by flash column chromatography (eluting initially with 20% EtOAc:Petrol and increasing the polarity to 30% EtOAc:Petrol), only one diastereomer was isolated ($[\alpha]_D^{22}$ -70.5 (*c* 0.85 in $CHCl_3$)), which was assigned as that shown in Scheme 52.

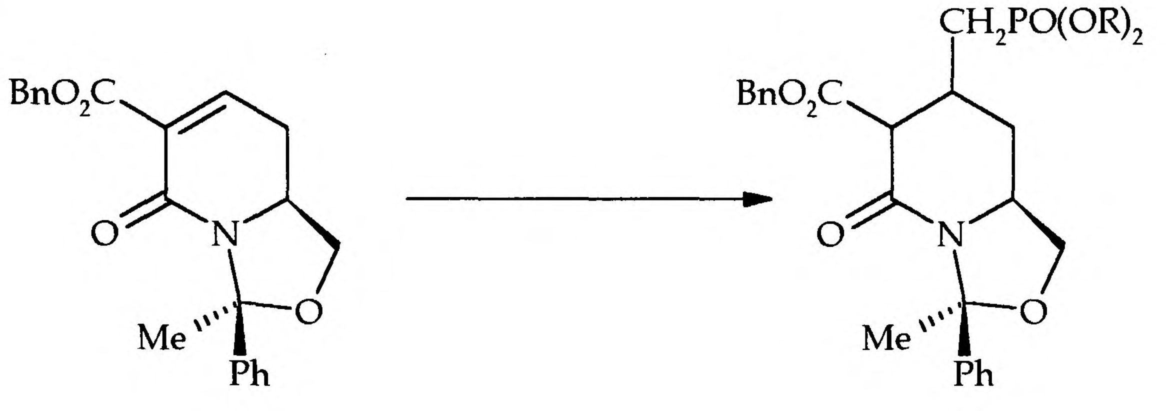


143

Figure 34

The stereochemistry of the adduct was assigned using an nOesy spectrum, and important enhancements observed are illustrated in Figure 34. Two new chiral centres have been created in this addition reaction, at C-7 and C-8. The stereochemistry of C-7 was assigned as shown because 7-*H* showed an enhancement when 6-H_{endo} was irradiated, as did 4-H_{endo}, while 6-H_{exo} and 4-H_{exo} showed an enhancement when 5-*H*, the known stereocentre, was irradiated. The stereochemistry of C-8 was assigned as also having the ester substituent *exo-* to the ring system as 8-*H* showed an enhancement when 7-*H* was irradiated.

It was pleasing to note that this reaction appeared to be stereoselective for one diastereomer. The stereochemistry of C-7 was expected to be that shown, as a result of the bicyclic system, but the stereochemistry at C-8 is slightly surprising, as such reactions often give C-7, C-8 *trans*-substituted products,[91] where the substituents suffer the least steric repulsions. The coupling constant between 7-*H* and 8-*H* was 7.5 Hz, which falls between the typical ranges for axial-axial (10-13 Hz) and axial-equatorial or equatorial-equatorial (2-5 Hz) coupling in cyclohexanes, which is not surprising given that it is believed that the six-membered ring in these systems usually adopts a boat-type conformation. It does mean, however that this coupling constant gives little useful information about the stereochemistry of these carbon centres. The significance of the 4-H_{exo}-5-*H* coupling constant was discussed extensively in sections 2.3 and 3.5, and it is interesting to note that the value observed in this case (5.5 Hz) is typical for the *exo*-substituted systems described in Chapter 3.



122 **144**

Scheme 53

It had been hoped to extend this methodology to the synthesis of piperidines substituted with phosphonate esters as described in Scheme 53. Similar compounds have been synthesised by Angst,[143] who found that they had interesting biological properties. Unfortunately, it was not possible to generate a suitable Reformatsky reagent. A literature search for a diethyl α-bromo methane phosphonate revealed only a low-yielding synthesis that had to be performed on a large scale under high pressure,[144] and so some standard brominations were attempted. None of these were successful, though in one case a small amount of the desired product was observed in the NMR spectrum of the crude product. In an alternative strategy, α-iodo diethyl methane phosphonate was used to attempt to generate the Reformatsky reagent, but this did not prove successful either.

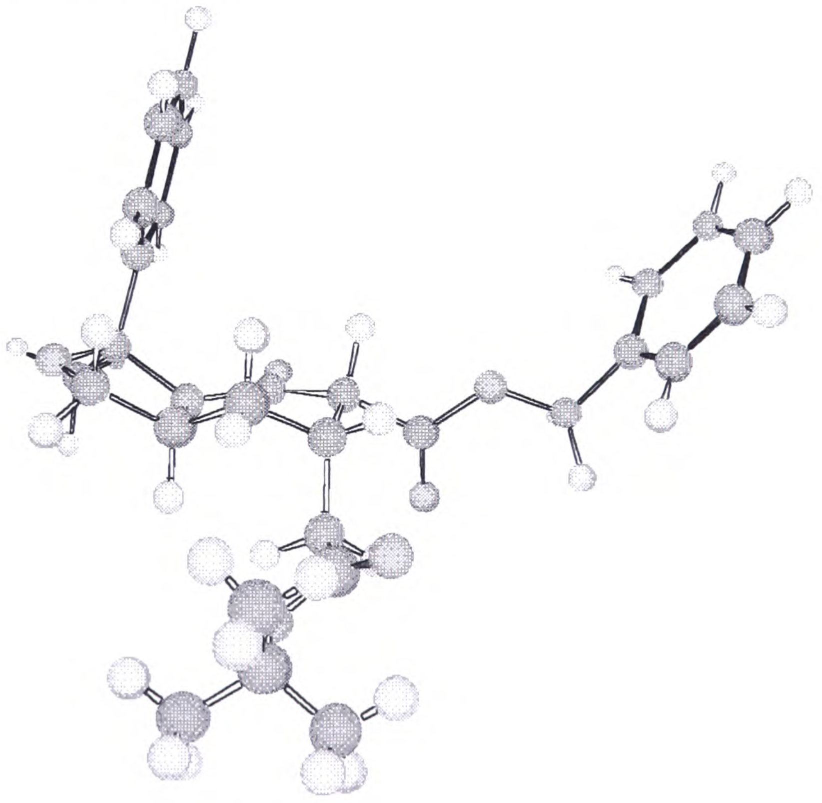


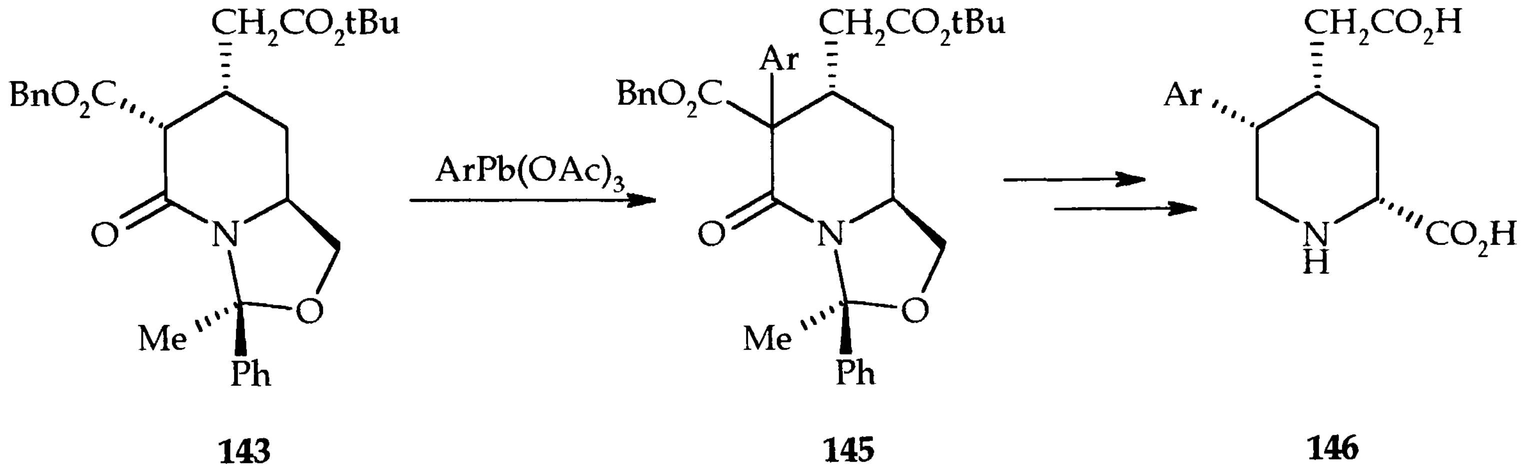
Figure 35: Molecular modelling structure of Reformatsky adduct **143**

Table 19: Molecular modelling of Reformatsky adduct **143**

C-7 substituent	**C-8 substituent**	**ΔH_f / kJmol^{-1}**
exo	exo	-204.633
endo	endo	-205.104
exo	endo	-206.950
endo	exo	-207.308

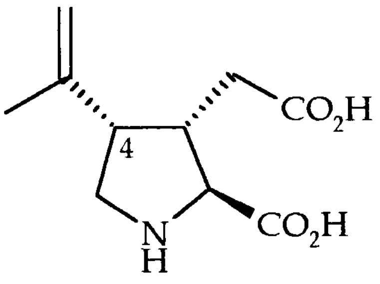
This Chapter has described two conjugate addition reactions, which proceed with opposing, excellent, stereoselectivity. The first, the proposed addition of hydroperoxide to the enone to give the epoxide **126** appears to result from attack to the *endo*- face of the bicyclic system. The second, the Reformatsky addition to give the adduct **143** results from attack to the *exo*- face of the system. Molecular modelling of the Reformatsky adduct **143** using MOPAC PM3 (Chem3D) parameters confirms that the C-7 substituent is axial to the bicyclic system (Figure 35), which is in good agreement with the known stereoelectronic effects in cyclohexenones,[145] where axial attack of nucleophiles is preferred to equatorial attack. Molecular modelling also suggests that the 7-*endo*, 8-*exo* product, where both substituents would be equatorial to the ring, would be the most thermodynamically stable of the four possible diastereomers that could be formed in this reaction (Table 19). It would seem reasonable to conclude, therefore, that the stereochemistry of C-7 is set kinetically, by the preferred, axial, direction of nucleophilic attack, and the stereochemistry of C-8 is set thermodynamically. In the opposing case of the epoxide, it may be that the nucleophile was coordinated to the oxygen atom of the acetal, which is an effect with literature precedent.[146]

4.5 Arylation reactions



Scheme 54

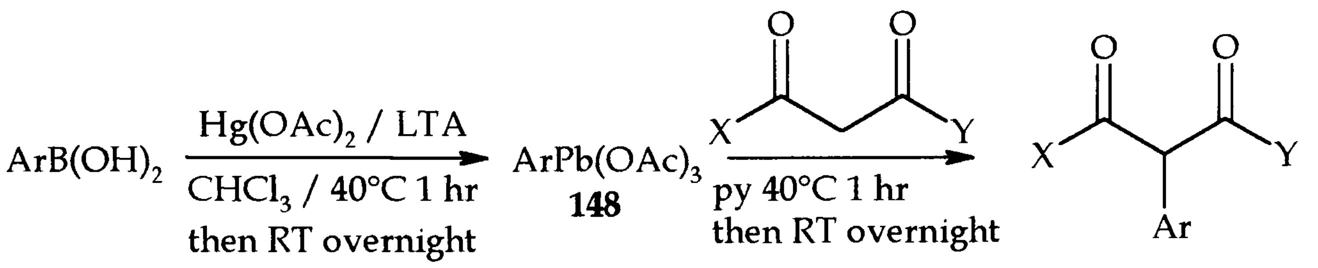
It is well known that aryllead(IV) tricarboxylate complexes may be used to generate quaternary carbon centres at β-dicarbonyl positions.[147] It was thought that the Reformatsky adduct **143** would be a suitable substrate for such reactions, as it contains a highly activated site at C-8. Such addition products **145** would be particularly interesting as they could be elaborated to homologues of kainic acid derivatives **146**.



147

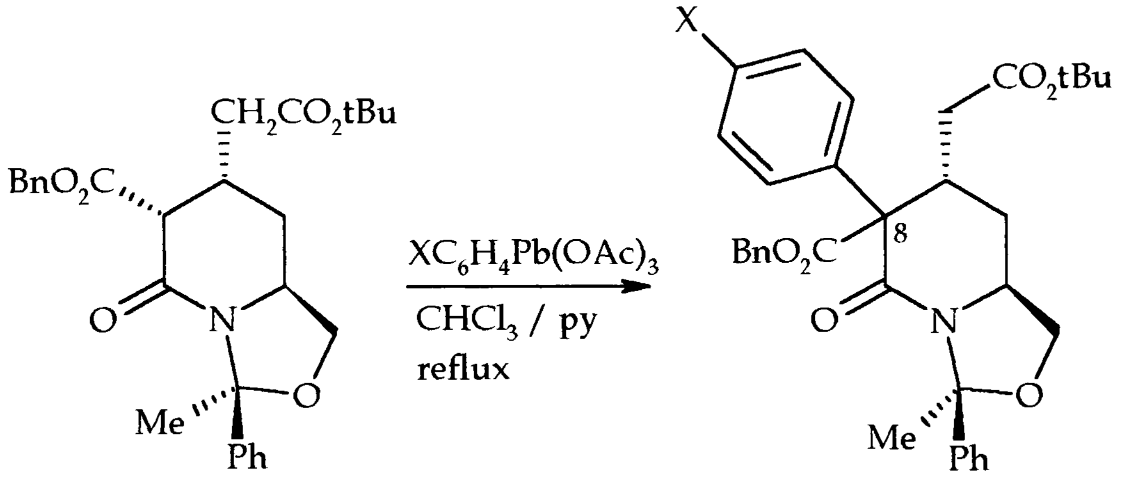
Figure 36

Kainic acid **147** (Figure 36) is an important excitatory amino acid[148] that has been the focus of much synthetic interest, and analogues have been keenly sought in order that their biological properties might be assessed.[149] The important features of kainic acid are known to be the π-electron density in the C-4 substituent and the 2*S*, 3*S*, 4*S* stereochemistry, and this route would allow access to six-membered homologues of kainic acid.



Scheme 55

In the standard lead (IV) arylation method, the reagent is first generated by treating an arylboronic acid with lead tetraacetate, and then the β-dicarbonyl substrate is added to the reaction mixture (Scheme 55). Alternatively, the lead complex **148** may be isolated and subsequently reacted with the dicarbonyl substrate. In this work, the second method was chosen.



143

149-151

Scheme 56

In these reactions the Reformatsky adduct **143** was mixed with the lead reagent and pyridine in spectroscopic grade chloroform, and the mixture heated to reflux for 72 hours. The results of the reactions with different lead reagents are summarised in Table 20:

Table 20: Reaction of adduct **143** with lead complexes according to Scheme 56

Product	Lead complex	Yield / %	Diastereomeric ratio
149	PhPb(OAc)$_3$	69	3:1
150	BrC$_6$H$_4$Pb(OAc)$_3$	93	5:1
151	MeOC$_6$H$_4$Pb(OAc)$_3$	59	2:1

The diastereomeric ratios in each case were estimated from the proton NMR spectrum, as none of these products could be isolated as separate diastereomers.

However, it is encouraging to note that all these products could be obtained in respectable yields, and that there was some selectivity in the reaction. It was not possible to ascertain which of the two possible isomers was the more abundant, but inspection of the 4-H_{exo}-5-H coupling constant is once again interesting (Table 21).

Table 21: 4-H_{exo} - 5-H coupling constants in arylated products

Products	Major diastereomer / Hz	Minor diastereomer / Hz
149	5.5	6.5
150	5.5	6.0
151	6.0	6.0

In the previous discussion of the significance of this coupling constant it was noted that coupling constant in the major diastereomer was consistently smaller than that in the minor diastereomer, and that this corresponded to *exo-* and *endo-* stereochemistry at C-8 respectively. The interpretation suggested was that bulky *endo-* substituents tended to cause the bicyclic system to be more planar, thus altering the coupling constant. It is interesting to note that, again, the major diastereomers have smaller 4-H_{exo} / 5-H coupling constants than the minor diastereomers, but it is not possible to correlate this observation with the stereochemistry of the new chiral, quaternary centre at C-8, as the diastereomers were inseparable and their stereochemistry could not, therefore, be assigned using a n. O. e. difference or nOesy experiment.

4.6 Summary

In this Chapter the synthesis and reactions of the activated enone **122** were described. It was found that the enone could be generated from the selenide **116** using sodium periodate as an oxidant, but that using hydrogen peroxide gave only an epoxide **126**.

The enone was not found to be highly reactive towards cycloaddition reactions, and it was suggested that this enone was not, in fact, as electron-poor as had been hoped.

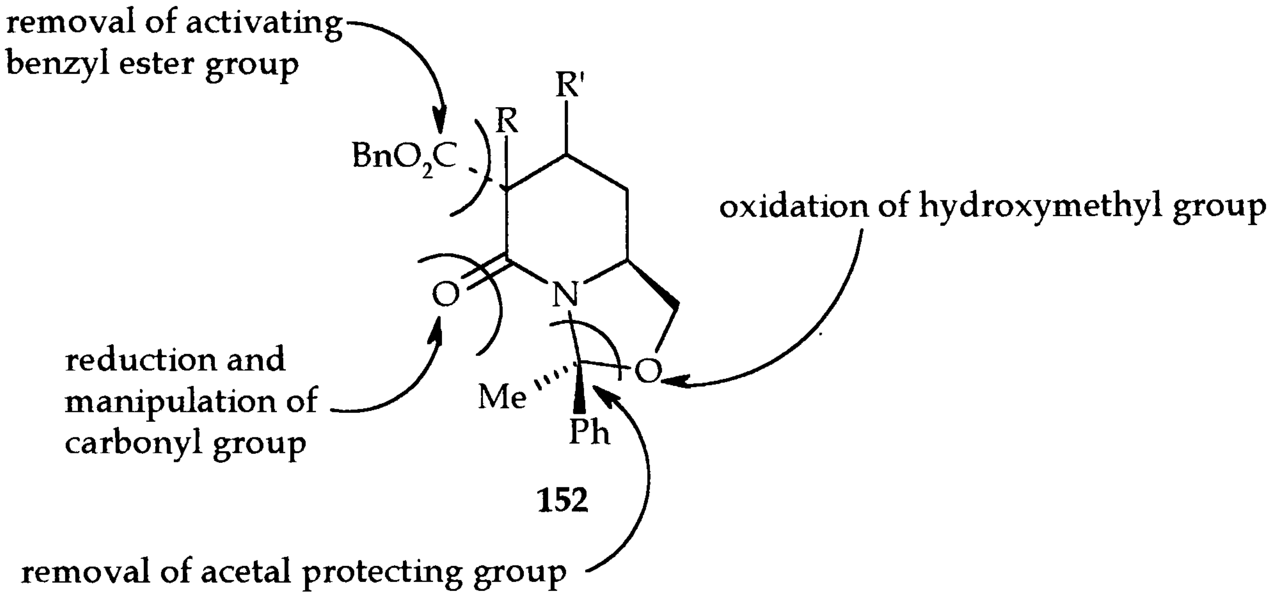
The selectivity displayed in cycloaddition was, however, excellent. Conjugate addition was found to be a more facile process, and stereoselectivity was, again, excellent. This enone could therefore be a useful tool in stereoselective synthesis.

Lead mediated arylation reactions on a conjugate addition product proceeded in good yield and moderate stereoselectivity. The products thus formed could not be separated by chromatography, nor their stereochemistry assigned.

Results and discussion 4: deprotection studies

5.1 Introduction

In Chapters 3 and 4 the functionalisation of a bicyclic lactam was described. In order to show that that bicyclic lactam was a useful intermediate in the synthesis of piperidine derivatives, it is important to investigate the deprotection reactions of the substituted bicyclic lactams.



152

Figure 37

The deprotection steps that need to be considered are illustrated in Figure 37. It is important that any strategy adopted fulfils certain criteria:

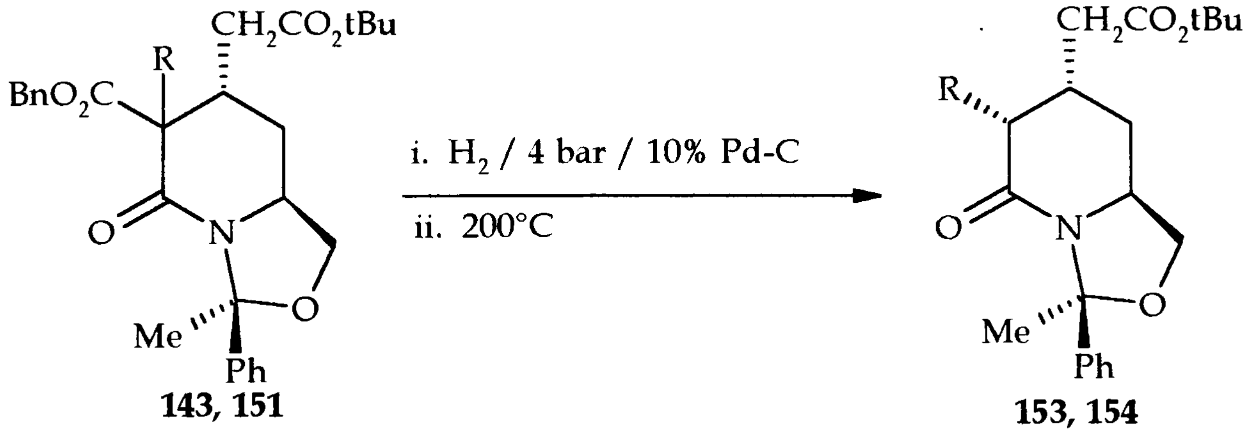
- Stereocentres must not be disrupted by the deprotection conditions.
- Protecting groups should be orthogonal if it is desirable for partially deprotected products to be manipulated further; if not, all protecting groups may be removed in a single step.
- It should be possible to recover the deprotected products easily.

The reduction of the lactam carbonyl group was not investigated in this work. This was for two reasons: firstly, there is ample literature precedent for reductions of piperidinones to piperidines[150] [151] and α-hydroxy piperidines.[152] Secondly, the lactam carbonyl group could be a valuable starting point for functionalisation at this ring position, by using organometallic reagents to convert it to a methylene group,[153] or to add in a nucleophilic fashion,[154] or by converting it to a lactim ether[155] to allow further functionalisation. The applicability and stereoselectivity of such transformations would require thorough investigation.

The order in which deprotection steps and further manipulations are attempted is important. Since the removal of the benzyl ester group will leave C-8 as a chiral centre when R is not H (Figure 37), it was thought advisable to perform this transformation before the *O*, *N*-acetal protecting group was removed, in order that the rigid bicyclic system could affect the stereochemical outcome.

5.2 Hydrogenolysis of the benzyl ester group

The benzyl ester group was introduced to the bicyclic lactam as an activating group for subsequent cycloaddition and conjugate addition reactions. The aim of the hydrogenolytic deprotection is to remove this group without affecting other ester groups that may have been introduced into the molecule, for example the *tert*-butyl ester introduced into the Reformatsky product. It was also important that the *O*, *N*-acetal protecting group should not be affected, particularly as previous experience in the research group[105] had indicated that it was difficult to ensure cleavage of the nitrogen-carbon bond by hydrogenolysis, which meant that an *N*-alkyl piperidine would be the product of hydrogenation, and recovery of a simple piperidine would be extremely difficult. The literature precedent[156] that more active catalysts could effect lactam ring opening was also a major consideration.

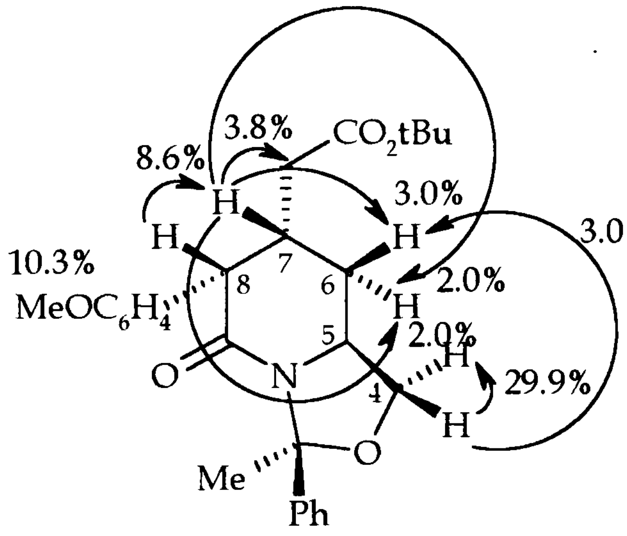


Scheme 57

Table 22: Products of hydrogenolysis according to Scheme 57

Product	**R**	**Yield / %**	$[\alpha]_D$	**ν(C=O lactam) / cm^{-1}**
153	H	84	-44.6	1654
154	$MeOC_6H_4$	67	-75.0	1654

With these constraints in mind, the chosen conditions were hydrogen at four bar of pressure, 10% palladium on carbon as the catalyst, ethyl acetate as the solvent, and a reaction time of 72 hours (Scheme 57). It was pleasing to note that these conditions effected complete removal of the benzyl group. Decarboxylation did not occur completely until the reaction product had been heated, and could be confirmed by the appearance of a doublet corresponding to 8-H in the NMR spectrum of **154**. In both cases, the presence of a free carboxyl group at C-8 resulted in extremely broad NMR spectra, as a result of the coordinated water present in the sample. When decarboxylation was complete this was not observed. There was no evidence to show that the C-7 substituent or the *O*, *N*-acetal protecting group were affected.

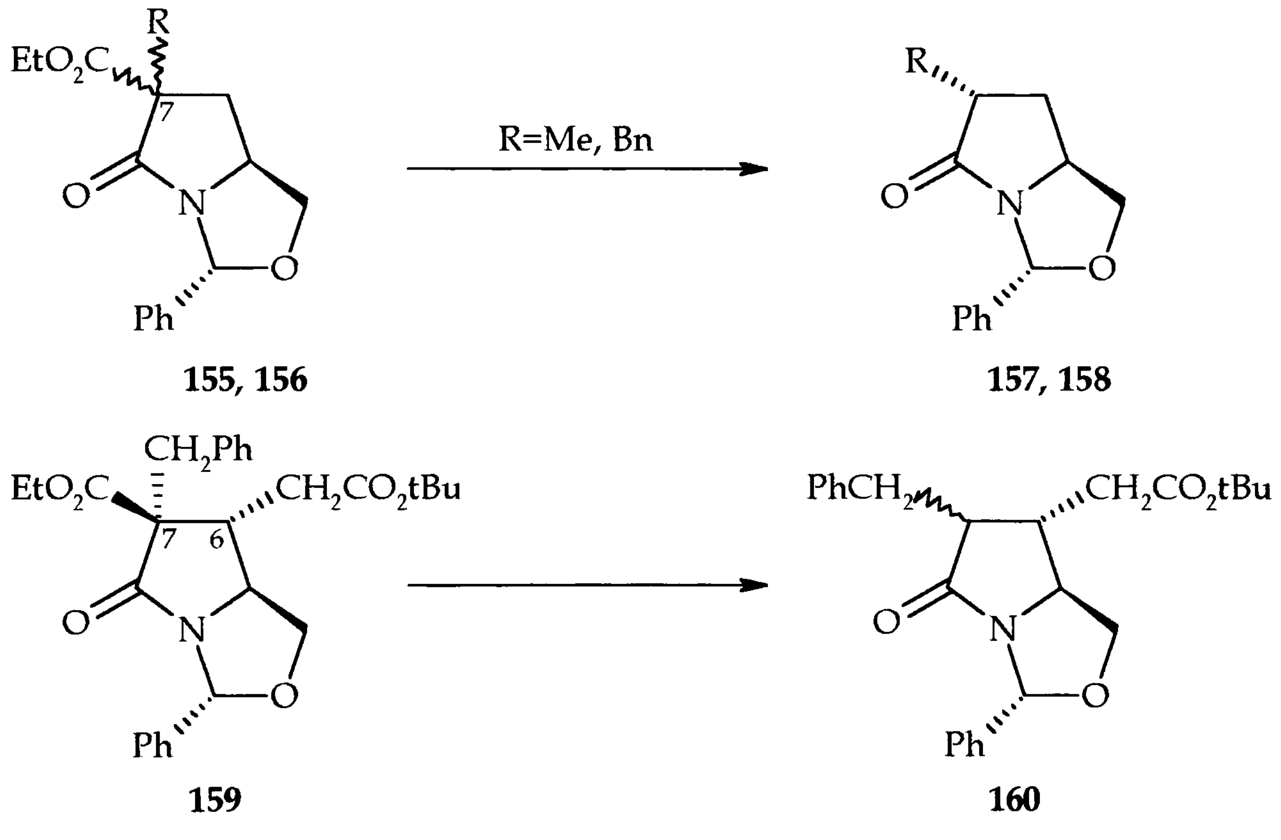


154

Figure 38

It was interesting to note that the inseparable mixture of diastereomers of the arylated Reformatsky product **151** gave only one diastereomer of the deprotected product **154**. The stereochemistry at C-8 was assigned using an n. O. e. difference experiment, and the principal enhancements are illustrated in Figure 38. The large enhancements between 7-*H* and 8-*H* suggest that these protons are both *endo*- to the bicyclic lactam. Irradiating 8-*H* only causes an enhancement at 6-H_{endo} (2.0%), while irradiating 7-H caused a larger enhancement at 6-H_{endo} (3.0%) than at 6-H_{exo} (2.0%). Irradiating 4-H_{endo} caused an enhancement at 6-H_{endo} (3.0%) and 4-H_{exo} (29.9%), which supports the assignment of the 6-H protons, but since 4-H_{exo} and 5-H are overlapping, it was not possible to state this definitively, as the only stereocentre that can be guaranteed is C-5.

It is surprising, and gratifying to find that only one diastereomer was formed in this case. In no case where an aryl or alkyl group was introduced at C-8 could the diastereomers be separated by chromatography, as their polarity was so similar. It was suspected that decarboxylation would lead to a 1:1 mixture of epimers, as reprotonation could occur from either side of the bicyclic system. However, it appears that this occurs only from the *endo*-face of the lactam, so that only the *exo*-diastereomer of the product is formed.



Scheme 58

This result compares interestingly with the decarboxylation experiments performed on [3.3.0] derivatives **155** and **156** as described in Scheme 58. Cherry[90] found that the simple derivatives **155** and **156** gave only the *exo*-diastereomers **157** and **158** on deprotection when R=Me or Bn, but a 9:1 mixture of *exo*- and *endo*- diastereomers when $R=pNO_2C_6H_4CH_2$. In contrast, Dyer[91] found that both diastereomers at C-7 were found when C-6, C-7 functionalised systems such as **159** were decarboxylated, even when only one diastereomer of starting material was used. It was suggested that decarboxylation was likely to occur through a planar enol intermediate, and reprotonation would occur to give the most thermodynamically stable isomer. In the simple derivatives **155** and **156** this would be the *exo*-isomer, but in the derivatives such as **159** there would be two opposing factors: on the one hand the bicyclic system would favour the 7-*exo* stereochemistry, but on the other, there would be significant steric repulsions between 7-*exo* and 6-*exo* substituents which would favour the 7-*endo* stereochemistry. In the [4.3.0] system it would therefore appear that the effect of the bicyclic system is significantly greater than the influence of the substituent at C-7.

Table 22 also details the optical rotations of the two products. It is interesting to note that the 8-*exo* substituted system has a lower optical rotation than the unsubstituted system. This parallels the experience with the alkylated lactams described in chapter two. There is no change in the (C=O) lactam stretch, which suggests that the electronic effect of the para-methoxyphenyl substituent on the carbonyl group is negligible.

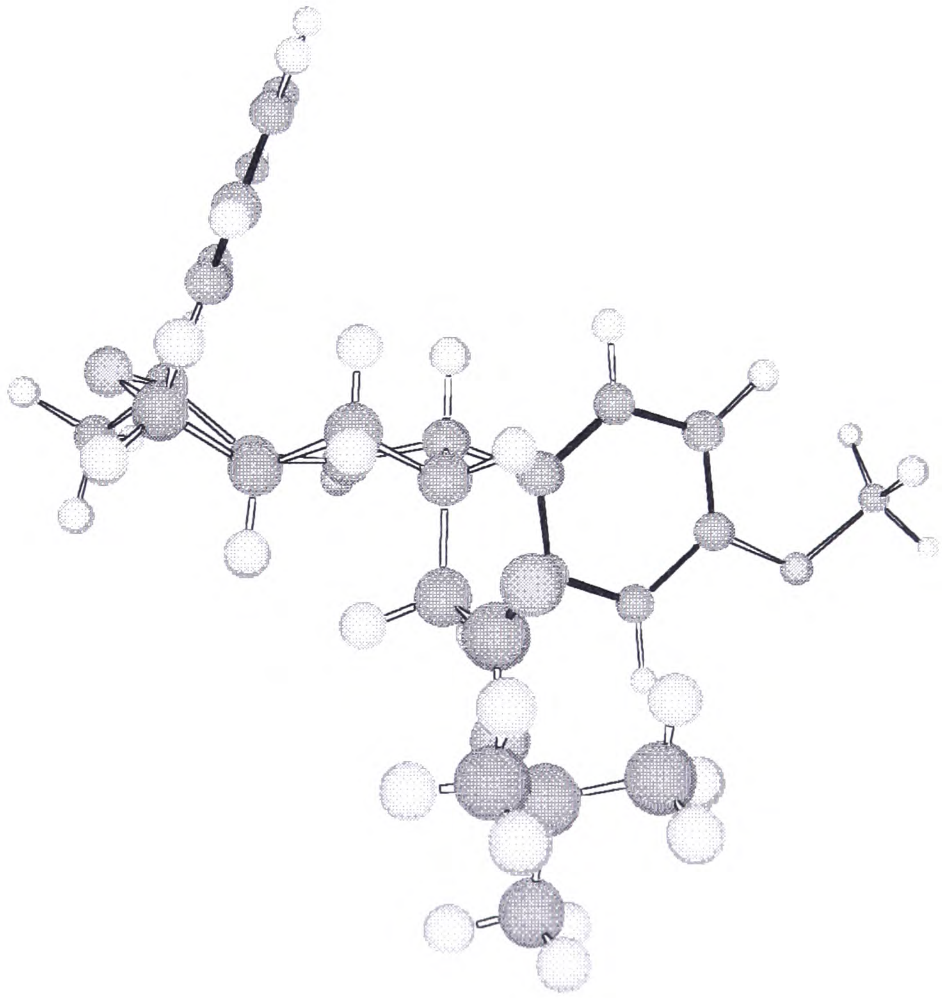
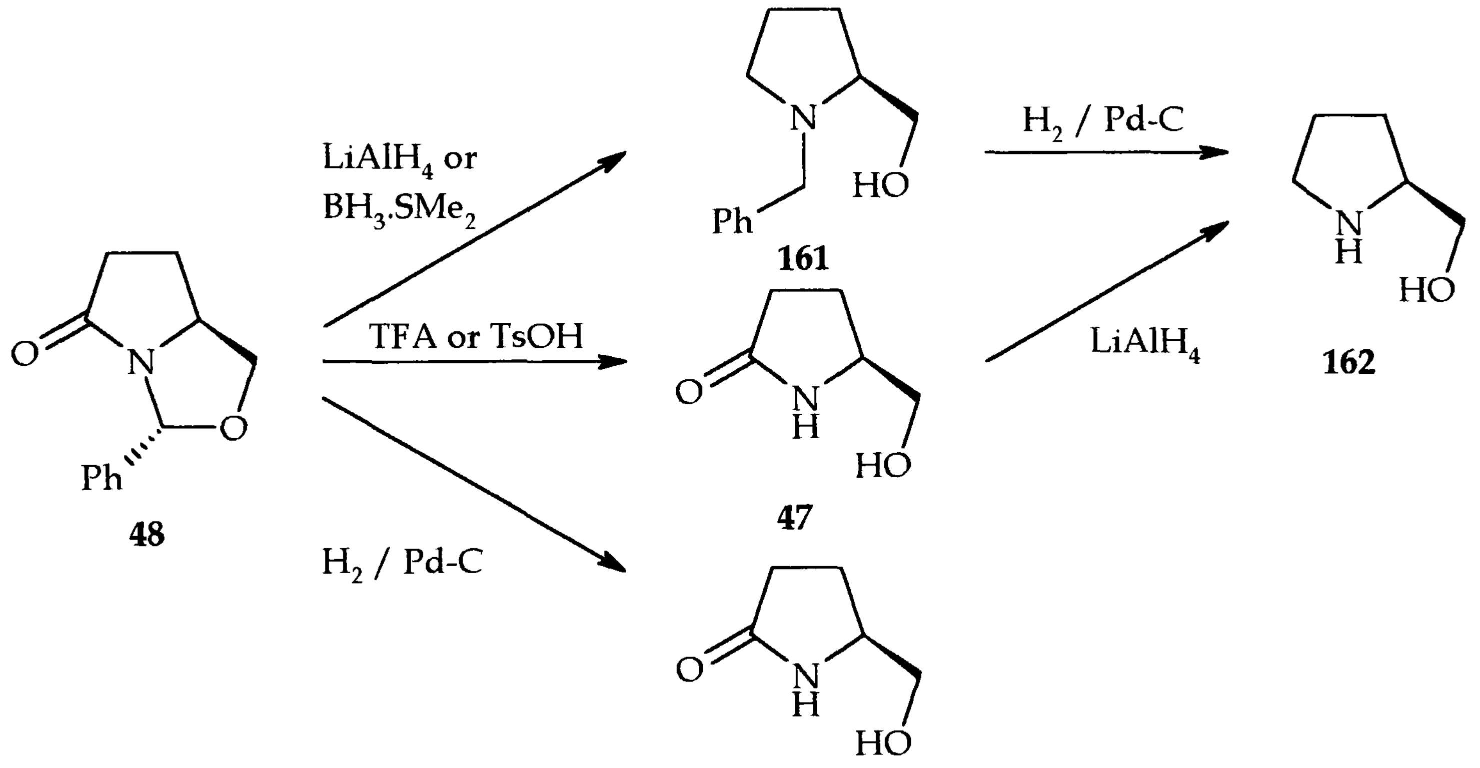


Figure 39: Molecular modelling structure of arylated product **154**

The NMR spectra of the two derivatives are also interesting. Unfortunately, the 4-*H*exo and 5-*H* signals are overlapping in the arylated derivative **154**, so the analysis of the coupling constant between these two protons discussed in previous chapters may not be applied. However, the coupling constant between the 7-*H* and 8-*H* protons can be measured as 5.5 Hz. In section 4.4 the 7-*H* / 8-*H* coupling constant in the Reformatsky product **143** was found to be 7.5 Hz, and it was noted that this value falls between the typical ranges for axial-axial (10-13 Hz) and axial-equatorial or equatorial-equatorial (2-5 Hz) coupling in cyclohexanes. The similar values of these coupling constants is therefore consistent with the *exo-/exo-* stereochemistry of these two derivatives. It is believed that the C-7 substituent is axial to the ring, and the C-8 equatorial, as in the Reformatsky adduct **143**, on the basis of molecular modelling (Chem3D MOPAC PM3 parameters), as shown in Figure 39.

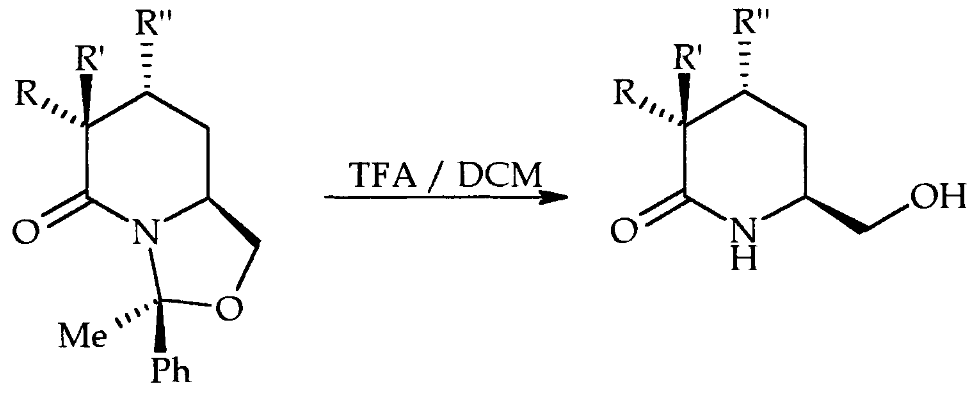
5.3 Deprotection of the *O, N*-acetal



Scheme 59

The removal of the *O,N* acetal protecting group could conceivably be achieved in a number of ways. There is no precedent for the deprotection of the [4.3.0] acetals that have been studied in this work, but a considerable body of work exists relating to the [3.3.0] acetals introduced by Thottathil, and a summary of the deprotections reported are illustrated in Scheme 59. Three general methods have been described which allow the removal of the group: reduction with nucleophilic[157] or electrophilic[158] hydride reducing agents, to give N-benzyl pyrrolidines **161** which must be hydrogenated with a Pd-C catalyst to liberate the desired products **162**, acidification, using for example trifluoracetic acid[159] or tosic acid,[160] to give the amide alcohols **47**, which can be reduced to pyrrolidines using lithium aluminium hydride,[158] or catalytic hydrogenation over Pd-C in basic[161] or acidic[162] conditions.

Given the constraints outlined in the introduction, the second method of deprotection would appear to be the most desirable. Consequently, several examples of bicyclic lactams were stirred with 20% TFA in DCM, as described in Scheme 60 and Table 23. The products were purified by flash column chromatography on silica.



103b, 108c, 153, 154 **163-166**

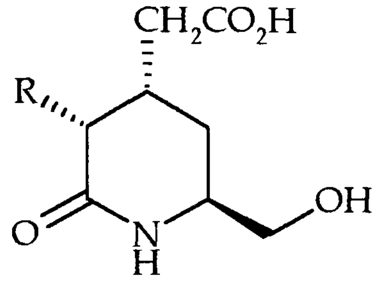
Scheme 60

Table 23: deprotection of bicyclic lactams according to Scheme 60

Acetal	Product	R	R′	R″	Yield / %	$[\alpha]_D$	R_f
103b	**163**	CH_2Ph	H	H	73	-6.96	0.32*
108c	**164**	CO_2CH_2Ph	CO_2CH_2Ph	H	74	+7.52	0.37†
153	**165**	H	H	CO_2tBu	33	+1.71	0.25†
154	**166**	$MeOC_6H_4$	H	CO_2tBu	(100)‡	-	-

*EtOAc †10% MeOH:EtOAc ‡Product formed is actually **168**.

It was pleasing to see that the deprotections of the simple bicyclic systems **103b** and **108c** proceeded in good yield. However, it was found that the *tert*-butyl group in acetals **153** and **154** was not impervious to these conditions. An initial investigation of the synthesis of **165** found that this product could be formed in moderate yield.



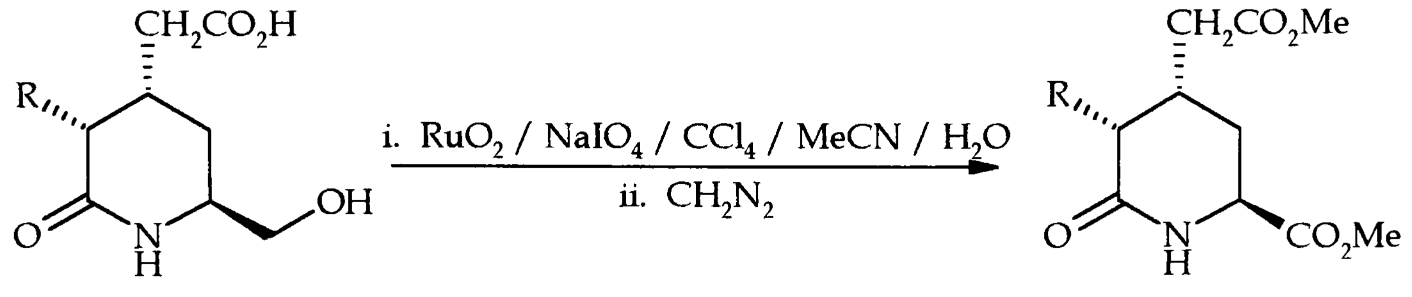
167: R=H
168: R=C_6H_4OMe

Figure 40

However, when repeated on a larger scale, the only product isolated was the corresponding acid **167** (Figure 40), which was formed in excellent yield (98%). This would suggest that the low initial yield resulted from the loss of the desired product as the acid. The arylated Reformatsky product was deprotected according to these conditions, with a crude yield of 100%, but not purified since the purification of the previous alcohol had been troublesome. Mass spectrometry and NMR spectroscopy of the crude product suggested that the derivative **168** had been formed, however. It was disappointing to find that this *tert*-butyl ester was hydrolysed under these conditions, but there was precedent for this occurring with other systems.[90]

It is interesting to note that the optical rotations of these alcohols are smaller in magnitude than the simple alcohol **80** described in section 2.2 (R=R′=R″=H, $[\alpha]_D^{20}$ +16.3). However, there was no evidence of epimerisation in the NMR spectra, and analogous pyrrolidinone alcohols have also been found to have small optical rotations.[90] The products were all less polar than the simple alcohol (R_f 0.10 (10% MeOH:EtOAc), which is in good agreement with the observation that the functionalised lactams were all less polar than the starting bicyclic lactam 77.

5.4 Oxidation reactions



167, 168

169, 170

Scheme 61

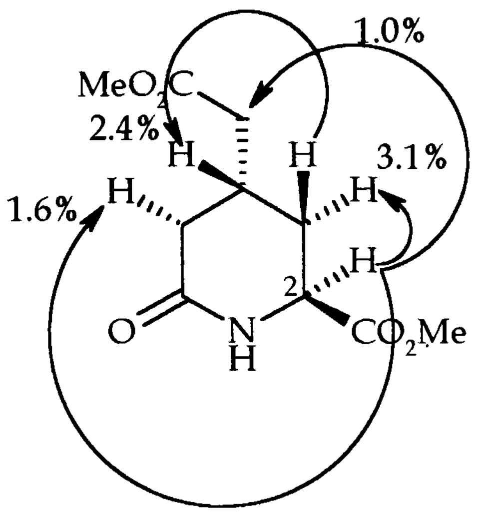
The final transformation attempted on these piperidinones was the oxidation reaction described in Scheme 61. Ruthenium tetroxide has been found to be an effective reagent for the oxidation of primary alcohols to carboxylic acids. Since ruthenium reagents are expensive and highly toxic they are often used catalytically, and common systems include ruthenium dioxide[163] and ruthenium trichloride,[164] with a stoichiometric oxidant such as sodium periodate or sodium hypochlorite. Following literature precedent, two alcohols were oxidised as described in Scheme 61, and the results are reported in Table 24.

Table 24: Oxidation of piperidinone alcohols according to Scheme 61

Alcohol	Product	R	Yield / %	$[\alpha]_D$	R_f (10% MeOH:EtOAc)
167	**169**	H	16	+30.5	0.54
168	**170**	$MeOC_6H_4$	27*	-	0.23

* over two steps.

It was disappointing to find that the yields of these reactions were relatively low. Another worker[165] has noted that pyrrolidinone systems may be liable to ring-opening reactions under these conditions. It is likely that similar products in this case would be highly polar, which might explain why none were isolated.



169

Figure 41

The stereochemistry of the simple dimethyl ester **169** was assigned using an n. O. e. difference experiment, and the important enhancements are shown in Figure 41. In this discussion I will continue to refer to protons in the ring system as being *exo-* or *endo-* according to their stereochemistry in the bicyclic system from which the piperidine was generated. Irradiating 2-*H* gave an enhancement of 3.1% to 3-H_{exo} and 1.0% to the 4-CH_2 protons, while irradiating 3-H_{endo} gave an enhancement of 2.4% to 4-*H*. This implied that the stereochemistry was indeed that shown in Figure 41, and confirmed that these conditions did not affect the chiral integrity of this compound. It was also interesting to note that W-coupling was observed between 3-H_{endo} and one of the 4-CH_2 protons of the order of 1.5 Hz.

Unfortunately, only a small sample of the arylated piperidinone **170** was isolated, which meant that complete characterisation was not possible. It is possible to state that the target was reached with some confidence, however, as high field ^{1}H and ^{13}C NMR spectra were recorded, with diagnostic signals observed in the proton spectrum for the methyl groups and *H*-2, and the expected number of resonances in the carbon spectrum. Infra-red data was also as expected, with absorption maxima at 1737 (ester C=O) and 1659 (lactam C=O) cm^{-1}, as was both low resolution and high resolution mass spectrometry, where a peak at 336.1451 Daltons was observed which is within acceptable limits for the calculated mass of MH$^+$ of 336.1447 Daltons. The low yield of this product meant that nOe or nOesy experiments could not be performed to confirm the stereochemistry at C-5. This means that this is the first example of a homo-kainoid analogue to be reported.

5.5 Summary

In this chapter the deprotection of the functionalised bicyclic lactams whose synthesis was described in earlier chapters was described. Mild conditions were found which allowed the removal of the activating benzyl ester group and *O,N*-acetal protecting group in high yield. Decarboxylation of a C-8 functionalised lactam was found to give only one of the two possible diastereomeric products, and this was argued to be the thermodynamically preferred product. The *tert*-butyl ester was found to be susceptible to mildly acid conditions, but no epimerisation at C-8 was observed.

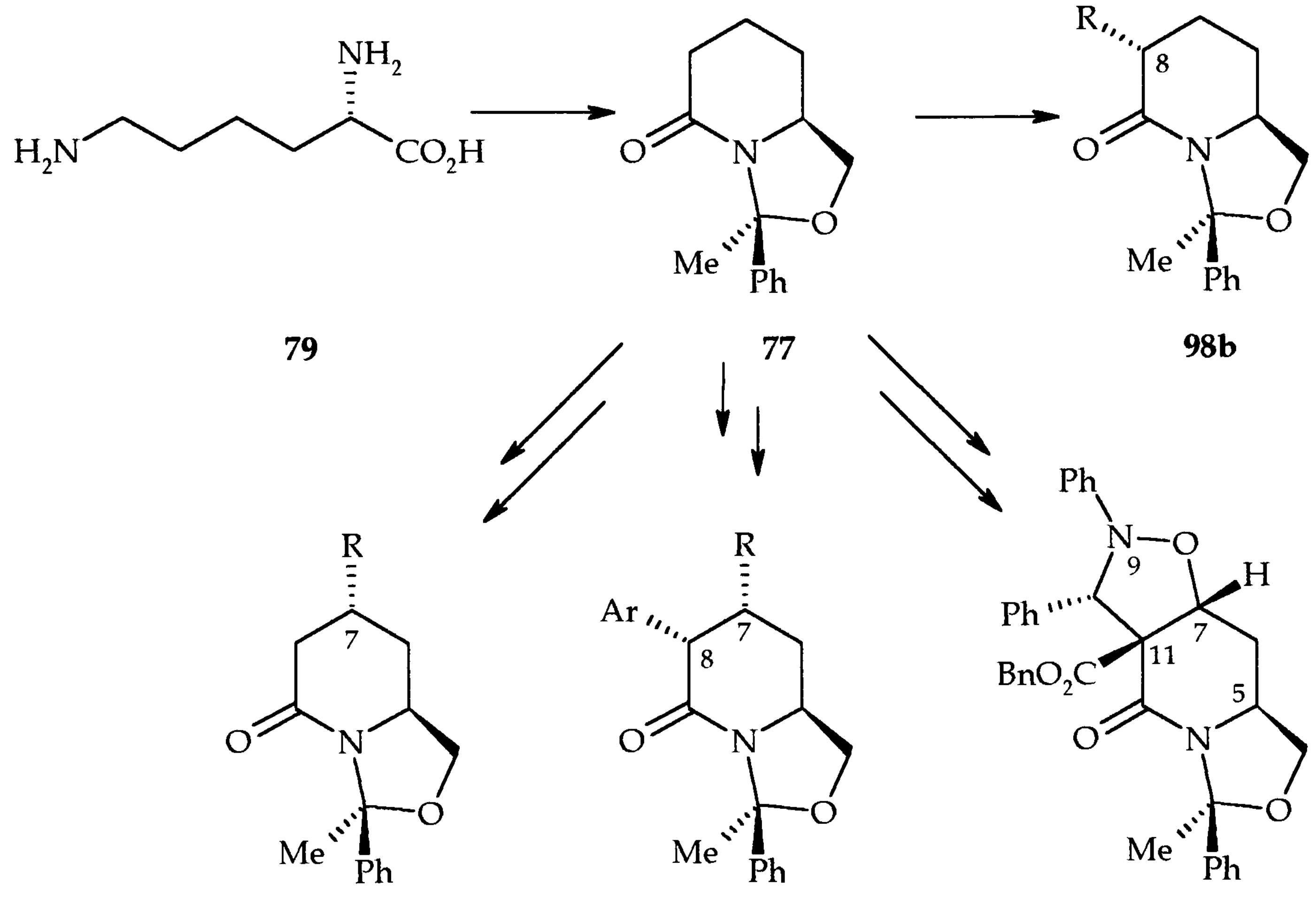
Oxidation of the hydroxymethyl group to the carboxylic acid was attempted in two cases. Ruthenium tetroxide generated *in situ* using sodium periodate as a stoichiometric oxidant was found to achieve this transformation, albeit in disappointing yield. The acids were methylated with diazomethane to aid characterisation. This allowed the first homo-kainoid derivative to be isolated.

The work described in this chapter has therefore shown that the strategy behind the work in this thesis was successful, as it allowed the stereoselective synthesis of functionalised piperidinones to be performed.

Conclusions

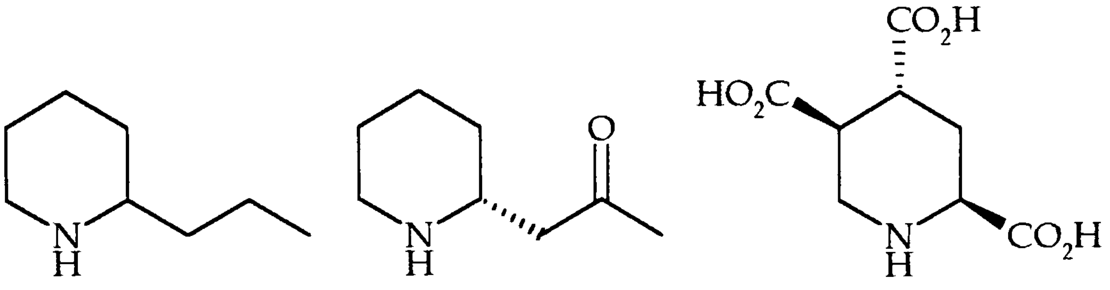
6.1 Total synthesis

This thesis describes an approach to synthetic piperidines using lysine as a starting material. Procedures were developed which allowed a range of substituents to be added to the ring with good to excellent stereocontrol. Scheme 62 below illustrates the principal products of the transformations that were investigated:



Scheme 62

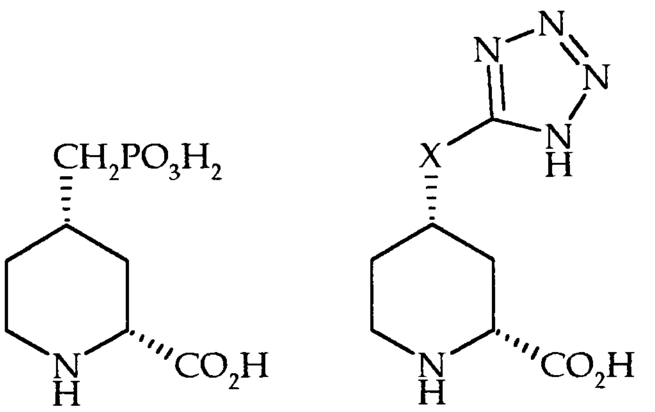
Lysine **79** was transformed into the chiral template **77**, which could be alkylated to give predominantly *exo*-substitution at C-8 (products **98b**). Multi-step strategies allowed *exo*-substitution at C-7 (e.g. **153**), or *exo*-substitution at both C-7 and C-8 (e.g. **154**), or cycloaddition (e. g. **132**). Several examples were elaborated further to illustrate the ease with which the protecting ketal could be removed, and the hydroxymethyl group oxidised (Chapter 5).



2 **3** **6**

Figure 42

The introduction to this thesis gave several examples of important natural and synthetic piperidines. Although the principle aim of this work was to develop robust synthetic methodology, it is interesting to consider whether the routes developed could be employed in the total synthesis of these examples. Since many natural products are functionalised at the 2 and 6 positions, this work would not allow a simple approach to these molecules: coniine (**2**) and pelletierine (**3**) are familiar examples which have proved popular targets for synthetic chemists, but which would not be accessed easily using this methodology. However, 2, 4, 5-piperidinetricarboxylic acid (**6**) and its analogues could be constructed using this methodology. Important steps would have to be developed, however, including the selective removal of the amide carbonyl group, and controlled epimerisation of C-5.



20

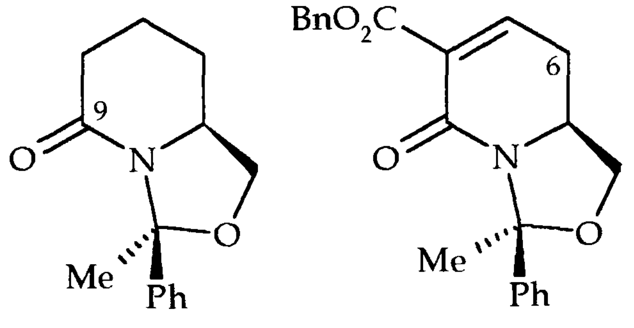
22: X=OCH$_2$ **23**: X=CH$_2$OCH$_2$
24: X=S **25**: X=CH$_2$S

Figure 43

It was noted in the introduction to this thesis that some of the most significant piperidines had, in fact, been of synthetic origin. The substitution patterns of these molecules are more varied than those of natural products, and include patterns that could easily be generated using the chemistry developed in this thesis. The NMDA analogues **20** and **22-25** are examples of significant new products that are functionalised at positions 2 and 4 - although the stereochemistry at C-2 is the reverse of that which would be found in piperidines synthesised using this methodology. However, the main reason that this work is of interest is not that it offers the possibility of synthesising known piperidines, but that it allows novel piperidines to be accessed, and hence investigated for their biological properties.

6.2 Suggestions for further work

There are several interesting directions in which this research could be pursued. In Chapter Three the alkylation reactions of the chiral template 77 and its epimer were investigated. It was clear that the interplay of factors affecting the stereoselectivity of these reactions was complex, and further experiments would be informative.



77 122

Figure 44

In terms of synthesising piperidines, there are four clear directions to pursue: conjugate additions to the enone 122 could be developed further, using heteroatom nucleophiles, for example. Allylic functionalisation at C-6 (whether by ionic or radical routes) would be a novel approach, and it is likely that the stereoselectivity of such reactions would be high, as a result of presence of the C-5 methylene group. The hydroxymethylene group itself could be transformed by nucleophilic substitution, offering amine functionality, for example. Finally, the amide carbonyl of the chiral template 77 could be reduced, or could react with carbon nucleophiles to give substitution at C-9.

This work could also allow the elaboration of multicyclic structures, which are now a major area of interest, by way of Diels-Alder chemistry, if more reactive dienes were investigated.

Experimental

7.1 General procedures

^{1}H NMR spectra were acquired on Varian Gemini 200 (200 MHz) and Bruker AM200 (200 MHz), WH300 (300 MHz), DPX400 (400 MHz), AM500 (500 MHz) and AMX500 (500 MHz) spectrometers. ^{13}C NMR spectra were acquired on Varian Gemini 200 (50.3 MHz) and Bruker AM200 (50.3 MHz), DPX400 (100.6 MHz) AM500 (125.8 MHz) and AMX500 (125.8 MHz) spectrometers. Chemical shifts (δ_H) are reported in p.p.m. and referenced to the residual solvent signal. Multiplicities are reported as broad (br), singlet (s), doublet (d), double doublet (dd), triplet (t), quartet (q) and multiplet (m). Coupling constants (*J*) are reported in Hertz to the nearest 0.5 Hz. Nuclear Overhauser experiments were acquired on a Bruker AMX500 or DPX400 spectrometer and signal intensities recorded as the percentage enhancement.

Infra-red spectra were recorded using spectroscopic grade $CHCl_3$ solutions, thin films or Nujol mulls using a Perkin-Elmer 1750 FT-IR or a Perkin-Elmer Paragon 1000 FTIR spectrometer. Absorption maxima of selected peaks are quoted in wavenumbers (cm^{-1}) being described as broad (br), strong (s), medium (m) or weak (w).

Low resolution mass spectra were recored on a VG Masslab 20-250 spectrometer using chemical ionisation (CI); or on a Hewlett Packard series 1050 spectrometer using atmospheric pressure chemical ionisation (APCI) in the positive (APCI$^+$) or negative (APCI$^-$) modes. Gas chromatography mass spectra were recorded on a VG-Trio-1 spectrometer. Selected mass-to-charge (*m/z*) peaks are quoted in Daltons as percentages of the base peak. Accurate mass spectra were recorded on a VG ZAB-E spectrometer by manual peak matching, and were conducted by Dr. J. A. Ballantine at University College, Swansea.

Optical rotations were recorded on a Perkin-Elmer 241 polarimeter at the given temperature using the D-line of sodium and a path length of 1 dm with concentrations (c) given in g/100cm^3, and are given in 10^{-1} deg cm^{2}g^{-1}.

Melting points were recorded using a Stuart Scientific SMP1 melting point apparatus and are uncorrected.

Thin layer chromatography (t. l. c.) was performed using Merck aluminium foil backed sheets precoated with Kieselgel 50 F_{254}, and the plates visualised using U.V. light (254nm), a solution of 5% w/v *dodeca*-molybdophosphoric acid in ethanol followed by heat. Flash column chromatography was performed using Prolabo silicagel 60 (35-70μm).

Small scale reduced pressure distillations were performed using a horizontal Kugelrohr apparatus (BÜCHI GKR-51) at the specified pressure and uncorrected oven temperature.

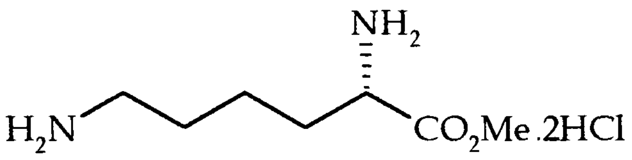
Reagents were obtained from commercial sources and used without further purification unless specified. Sodium hydride was obtained as a 60% dispersion in mineral oil and was washed with petroleum ether (40/60) followed by drying under high vacuum prior to use. Diazomethane was prepared using glassware without ground glass joints by the alkaline hydrolysis of *N*-methyl-*N*--nitroso-4-toluenesulphonamide (Diazald®).

THF was distilled from sodium/benzophenone under nitrogen prior to use. 40/60 petroleum ether (Petrol) refers to those fractions which distil at 40-60°C and was distilled prior to use. Methanol was distilled prior to use. Spectroscopic grade chloroform was used for all reactions and spectra. All other solvents were used as supplied.

Temperatures under 25°C were obtained using the following cold baths: 0°C ice; -78°C acetone/CO_2.

7.2 Experimental for chapter 2

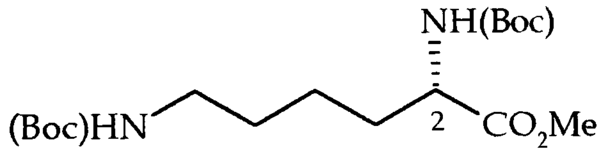
(+)-(*S*)-Lysine methyl ester dihydrochloride (81)



81

To a suspension of lysine monohydrochloride (92.34g, 0.51mol) in MeOH (250ml) and 2,2-dimethoxypropane (250ml) was added HCl (50ml) cautiously. The mixture was then refluxed overnight (16 hours), and then stirred for a further 7 hours at room temperature. Solvent was removed *in vacuo*, and then the ester was recrystallised from Et_2O/MeOH to give the product as a crystalline white solid (107.77g, 91%); m.p. 206°C (lit.[166] 207-208°C); $[\alpha]_D^{20}$ +14.5 (*c* 0.33 in H_2O) (lit.[85] +15.9 (*c* 1.3 in H_2O)); ν_{max} (Nujol)/cm^{-1} 1739s (C=O); δ_H(200 MHz; CD_3OD) 1.48-2.03 (6 H, m, 3 x CH_2), 2.96 (2 H, t, *J* 7.0, CH_2NH_2), 3.85 (3 H, s, CO_2CH_3), 4.08 (1 H, t, *J* 6.0, $CH(NH_2)CO_2Me$).

(+)-(*S*)-*N*, *N*-Di-(*tert*-butoxycarbonyl)lysine methyl ester (82)

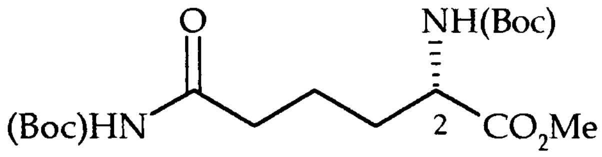


82

To a solution of lysine methyl ester dihydrochloride (**81**) (21.618g, 93mmol) in MeOH (500ml) were added sodium bicarbonate (46.742g, 556mmol) and di-tert-butyl-dicarbonate (42.501g, 195mmol). The suspension was then sonicated at room temperature for three hours. The reaction mixture was then filtered to remove excess sodium bicarbonate. Solvent was removed *in vacuo*, and the residue redissolved in Et_2O, filtered to remove remaining mineral solids, and evaporated again to yield a white solid (31.58g, 95%); m.p. 83°C (lit.[85] 83°C); $[\alpha]_D^{20}$ +7.0 (*c* 0.83 in $CHCl_3$) (lit.[85] +7.2 (*c* 1 in $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 3514br (NH), 3452br (NH), 1740s (C=O), 1710s (C=O), 1168s (C-O); δ_H(200 MHz; $CDCl_3$) 1.30-1.90 (6 H, m, 3 x

CH_2), 1.44 (18 H, s, 2 x *Boc*), 3.11 (2 H, dd, *J* 6.0 and 12.0, CH_2NH), 3.74 (3 H, s, *Me*), 4.31 (1 H, m, *CH*), 4.57-4.60 (1 H, br t, CH_2NH(Boc)), 5.09 (1 H, br d, CHN*H*(Boc)).

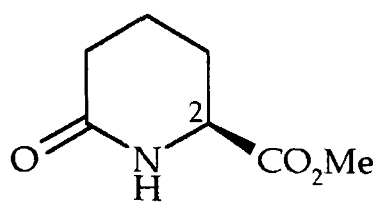
(+)-(*S*)-*N*, *N*-Di(*tert*-butoxycarbonyl) 6-oxolysine methyl ester (**83**)



83

To a solution of the protected lysine ester **82** (31.58g, 87mmol) in EtOAc (250ml) was added $NaIO_4$ (93.72g, 438mmol) and $RuCl_3.xH_2O$ (1.363g, 7mmol) in 750ml of pH 4.5 buffer solution containing 14.064g potassium hydrogen phthalate and 1.246g sodium hydroxide per litre. The biphasic system was then stirred vigorously at room temperature for five hours. The organic layer was then separated, and the aqueous layer extracted with EtOAc (4 x 100ml). 50ml isopropyl alcohol was then added to the combined organic portions, and the solution stirred overnight (16 hours). The solution was then filtered through Celite to remove precipitated RuO_2 and solvent removed *in vacuo*. The residue was re-dissolved in EtOAc (150ml), washed with 10% citric acid (3 x 50ml) and 1% sodium thiosulphate (2 x 25ml), dried with brine (50ml) and $MgSO_4$. Solvent was removed *in vacuo*, and the residue separated using dry flash chromatography eluting with portions of ethyl acetate/petrol in which the proportion of ethyl acetate was increased in 5% steps from 20% to 45% to yield the product as a colourless oil that crystallised on prolonged storage (26.11g, 80%); m.p. 74°C (lit.[86] 73-74°C); R_f 0.34 (40:60-EtOAc:Petrol); $[\alpha]_D^{20}$ +9.2 (*c* 1.0 in $CHCl_3$) (lit.[85] +9.6 (*c* 1.0 in $CHCl_3$)); ν_{max} (film)/cm^{-1} 3307w br (NH), 2981w br (NH), 1780, 1751, 1701s (C=O); δ_H (200 MHz; $CDCl_3$) 1.45 (9 H, s, *Boc*), 1.49 (9 H, s, *Boc*), 1.67-1.79 (4 H, m, 2 x CH_2), 2.71-2.75 (2 H, m, 2 x 5-*H*), 3.75 (3 H, s, *Me*), 4.32 (1 H, m, 2-*H*), 5.13 (1 H, br d, CHN*H*(Boc)), 7.42 (1 H, br, CON*H*(Boc)).

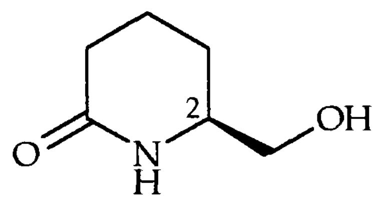
(-)-(*S*)-2-Methoxycarbonyl-6-piperidinone (89)



89

To a solution of the BOC protected oxo-lysine methyl ester **83** (22.53g, 60.2mmol) in dichloromethane (100ml) was added TFA (25ml) dropwise. The reaction mixture was then heated to reflux until t. l. c. indicated that the reaction was complete (1 hour). Solvent was then removed *in vacuo*, and the residue purified by flash column chromatography on silica gel, eluting with EtOAc, to yield the title compound as a pale yellow oil (8.07g, 85%); R_f 0.11 (20:80-EtOAc:DCM); $[\alpha]_D^{20}$ -8.7 (*c* 1.06 in $CHCl_3$) (lit.[86] -9.6 (*c* 1.06 in $CHCl_3$)) ν_{max} ($CDCl_3$)/ cm^{-1} 3241w br (NH), 1744s (ester C=O), 1670s (lactam C=O); δ_H(200 MHz; $CDCl_3$) 1.78-2.05 and 2.17-2.35 (4 H, m, 3-*H* and 4-*H*), 2.38-2.42 (2 H, m, 5-*H*), 3.79 (3 H, s, *Me*), 4.08-4.14 (1 H, m, 2-*H*), 6.34 (1 H, br, N*H*).

(+)-(*S*)-2-Hydroxymethyl-6-piperidinone (80)

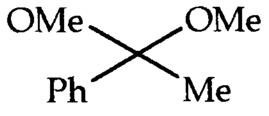


80

To a solution of the carboxymethyl piperidinone **89** (2.245g, 14.2mmol) in EtOH (100ml) at 0°C was added $NaBH_4$ (0.811g, 21.4 mmol) portionwise. The reaction mixture was stirred until t.l.c. indicated that the reaction was complete (approx. 90 minutes). Glacial acetic acid was then added cautiously until the pH had been reduced to 4. The mixture was then stirred for a further 30 minutes at room temperature to allow boron residues to be precipitated. The suspension was then filtered under suction to remove inorganic solids, and then solvent was removed *in vacuo*. The residue was then purified by flash column chromatography, eluting with MeOH:EtOAc:Et_3N in the ratio 10:9:0.5, to yield the title compound as a white solid (1.691g, 92%); m.p. 71°C; R_f 0.10 (10:90-MeOH:EtOAc); $[\alpha]_D^{20}$ +16.3 (*c* 1.0 in $CHCl_3$)

(lit.[86] +17.9 (*c* 1.0 in $CHCl_3$)); ν_{max} (film)/cm^{-1} 3289br (NH), 1636s (lactam C=O), 1412m (OH bend); δ_H (200 MHz; $CDCl_3$) 1.27-1.43 (1 H, m, 3-*H*), 1.65-1.95 (3 H, m, 4-*H* and 3-*H*), 2.18-2.46 (2 H, m, 5-*H*), 3.39-3.60 (2 H, m, CH_2OH), 3.69 (1 H, dd, *J* 2.0 and 10.0, 2-*H*), 4.19 (1 H, br, O*H*), 7.32 (1 H, br, N*H*).

Acetophenone dimethyl acetal (92)

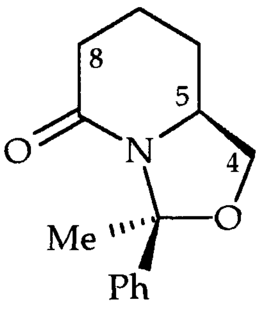


92

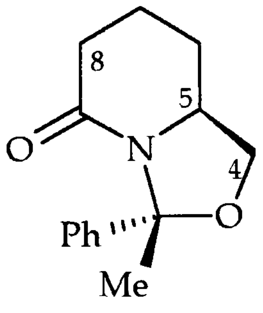
Acetophenone (43.3g, 0.360mol) and trimethyl orthoformate (58.7g, 0.553mol) were dissolved in MeOH (60ml) and conc. HCl (15 drops) was added. The mixture was then stirred at 40°C for 5 hours. The mixture was stirred for a further 16 hours at room temperature and then 0.5M NaOMe in MeOH was added until pH 9 was achieved. Solvent was removed *in vacuo* and then the residue was purified by Kügelrohr distillation, with the acetal distilling at 20mm Hg, 90°C giving a colourless oil (50.5g, 84%); δ_H(200 MHz; $CDCl_3$) 1.55 (3 H, s, CH_3), 3.21 (6 H, s, 2 x OCH_3), 7.27-7.54 (5 H, m, *Ph*).

(-)-(2*S*, 5*S*)-1-Aza-2-methyl-3-oxa-9-oxo-2-phenyl-bicyclo [4.3.0] nonane (77)

(-)-(2*R* 5*S*)-1-Aza-2-methyl-3-oxa-9-oxo-2-phenyl-bicyclo [4.3.0] nonane (94)



77



94

First method

To a suspension of the piperidine methanol (3.522g, 27.3mmol) in toluene (125ml) was added p-toluene sulphonic acid (1.298g, 6.8mmol) and pre-dried boric acid (0.424g, 6.8mmol), and the mixture heated to reflux with continuous removal of water using a Dean-Stark apparatus. After 5 hours the mixture was cooled to room temperature and the Dean-Stark apparatus was removed. Acetophenone dimethyl acetal (10ml, excess) was then added, and the mixture was again brought to reflux for a further 19 hours. The mixture was then allowed to cool to room temperature and partitioned between 100ml 1:1 EtOAc:water. The aqueous layer was then extracted with ethyl acetate (3 x 30ml). The combined organic extracts were then washed with $NaHCO_{3(sat,\ aq)}$ (30ml), water (30ml) and dried with brine (40ml) and over $MgSO_4$. Solvent was then removed *in vacuo*. Acetophenone dimethyl acetal was then removed by Kugelrohr distillation, and the residue purified by flash column chromatography on silica gel, eluting progressively with 20% EtOAc: Petrol, 40% EtOAc:Petrol, 60% EtOAc:Petrol and EtOAc to yield two products, diastereomer **94** as a yellow oil (1.50g, 24%) and diastereomer 77 as a white solid (1.968g, 31%).

Data from three typical runs:

Run	Yield of 77	Yield of 94
1	64	0
2	46	22
3	31	24

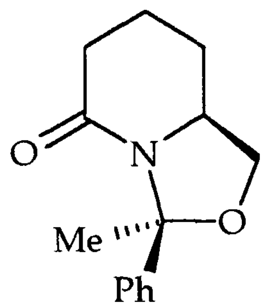
Major diastereomer (77):

m.p. 114-117°C (lit.[86] 116-117°C); R_f 0.32 (EtOAc); $[\alpha]_D^{20}$ -6.3 (*c* 0.27 in $CHCl_3$); ν_{max} (film)/cm^{-1} 1651s (lactam C=O); δ_H(200 MHz; $CDCl_3$) 1.47-1.53 (1 H, m, 6-H_{endo}), 1.80-1.90 (1 H, m, 7-H_{exo}), 2.01-2.15 (5 H, m, 6-H_{exo}, 7-H_{endo} and CH_3), 2.38-2.51 (2 H, m, 8-H_{endo} and 8-H_{exo}), 3.47 (1 H, dd, *J* 8.0 and 10.0, 4-H_{endo}), 3.79-3.89 (1 H, m, 5-*H*), 4.11 (1 H, dd, *J* 5.0 and 8.0, 4-H_{exo}), 7.31-7.46 (3 H, m, *Ph*), 7.57-7.62 (2 H, m, *Ph*); *m/z* (GCMS) 232.3 (MH^+, 100%).

Minor diastereomer (**94**):

R_f 0.36 (EtOAc); $[\alpha]_D^{24}$+161.1 (*c* 1.0 in $CHCl_3$); ν_{max} (film)/cm^{-1} 3503m, 1649s (lactam C=O), 1408m, 1325w, 764m (aromatic C-H) 699m, and 666s; δ_H (400 MHz; $CDCl_3$) 1.27-1.49 (1 H, m, 6-H_{endo}), 1.69-1.81 (1 H, m, 7-H_{exo}), 1.96-2.04 (1 H, m, 7-H_{endo}), 2.05 (1 H, s, *Me*), 2.06-2.18 (1 H, m, 6-H_{exo}), 2.34-2.49 (2 H, m, 8-*H*), 3.38-3.78 (2 H, m, 5-*H* and 4-H_{endo}), 4.24 (1 H, dd, *J* 5.5 and 7.5, 4-H_{exo}), 7.28-7.49 (3 H, m, *Ph*), 7.56-7.59 (2H, m, *Ph*). δ_C(100.6 MHz; $CDCl_3$) 20.8 (*C*-6), 24.9 (*Me*), 26.3 (*C*-7), 32.3 (*C*-8), 57.5 (*C*-5), 70.2 (*C*-4), 96.1 (*C*-2), 123.1, 125.7 and 128.0 (C-H aromatic), 142.5 (C-Ar), 167.3 (C=O); *m/z* (APCI$^+$) 232.3 (MH$^+$, 56%), 231.5 (77), 215.9 (100), 215.1 (10), 187.4 (3), 166.1 (4), 144.0 (2); *m/z* (ES$^+$) 232.1334 ($C_{14}H_{17}NO_2$ requires 232.1338 for MH$^+$).

(-)-(2*S*, 5*S*)-1-Aza-2-methyl-3-oxa-9-oxo-2-phenyl-bicyclo [4.3.0] nonane (77)



77

Second method

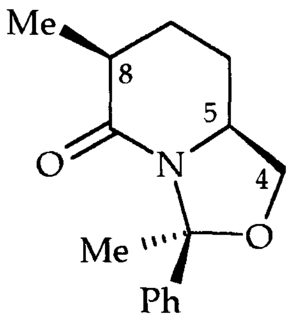
To a solution of the piperidine methanol **80** (5.249g, 40.6mmol) in $CHCl_3$ (250ml) was added pyridinium para-toluenesulphonate (1.021g, 4.1mmol) and acetophenone dimethyl acetal (8.781g, 52.8mmol). The suspension was heated to 60°C for 48 hours, and then allowed to cool to room temperature. The mixture was then filtered under suction to remove insoluble solids, and then solvent was removed *in vacuo*. The residue was then separated on silica gel, eluting with EtOAc to give the title compound as a white solid (7.564g, 80%). Spectroscopic data was identical with that measured on material synthesised by the first method.

Equilibration experiment

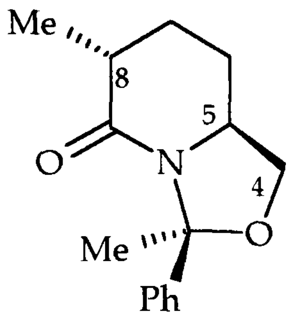
To a solution of lactam **94** (1.17g, 5.1mmol) in toluene (12ml) was added boric acid (0.080g, 1.3mmol) and tosic acid (0.241g, 1.3mmol). The mixture was heated to a state of reflux for 24 hours. NMR analysis of an aliquot taken from the mixture at this point indicated that both 77 and **94** were present, in a ratio of 1:1.

7.3 Experimental for chapter 3

(2*S*, 5*S*, 8*S*)-1-Aza-2-methyl-8-methyl-3-oxa-9-oxo-2-phenyl-bicyclo [4.3.0] nonane (102a) and (2*S*, 5*S*, 8*R*)-1-Aza-2-methyl-8-methyl-3-oxa-9-oxo-2-phenyl-bicyclo [4.3.0] nonane (102b)



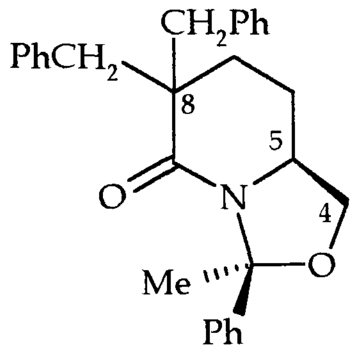
102a



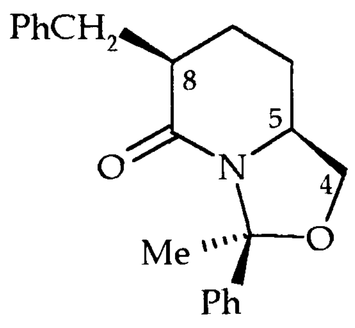
102b

To a stirred flask of THF (20ml) under N_2 at -78°C was added sBuLi (0.68ml, 0.66mmol). A solution of the lactam **77** (0.102g, 0.44mmol) in THF (10ml) was then added slowly. After five minutes a dark brown colour was observed. Methyl iodide (0.04ml, 0.66mmol) was then added by syringe, and the reaction mixture was seen to turn pink. The reaction mixture was allowed to warm to room temperature over 30 minutes, when t.l.c. indicated that reaction was complete. The reaction was then quenched with $NH_4Cl_{(sat)}$ (20ml), extracted with EtOAc (4 x 25ml) and dried over $MgSO_4$. Solvent was removed *in vacuo*, and the residue purified by flash column chromatography on silica eluting with 40% EtOAc:Petrol to yield an inseparable mixture of diastereomers as a colourless oil (0.089g, 82%); R_f 0.26 and 0.13 (40% EtOAc:Petrol); ν_{max}(film)/cm^{-1} 3583m, 1649s (C=O), 1420m, 1325m, 1240m, 1028m, 764m, 697m and 666s; δ_H(500 MHz; $CDCl_3$) 1.26 (3 H, d, *J* 3.5, 8-*Me* minor diastereomer), 1.27 (3 H, d, *J* 3.5, 8-*Me* major diastereomer), 1.51-1.73, 1.94-1.99, 2.05-2.12 and 2.17-2.21 (4 H, m, 6-*H* and 7-*H*, both diastereomers), 2.03 (3 H, s, 2-*Me*, minor diastereomer), 2.04 (3 H, s, 2-*Me*, major diastereomer), 2.43-2.53 (1 H, m, 8-*H*, both diastereomers), 3.39 (1 H, dd, *J* 8.5 and 10.0, 4-H_{endo}, minor diastereomer), 3.52 (1 H, dd, *J* 8.5 and 10.5, 4-H_{endo}, major diastereomer), 3.87-3.97 (1 H, m, 5-*H*, both diastereomers), 4.08 (1 H, dd, *J* 5.5 and 8.5, 4-H_{exo} major diastereomer), 4.13 (1 H, dd, *J* 6.0 and 8.5, 4-H_{exo} minor diastereomer), 7.26-7.57 (5 H, m, 2-*Ph*). δ_C(125.8 MHz; $CDCl_3$) 16.9 (8-*Me*, minor diastereomer), 17.0 (8-*Me*, major diastereomer), 23.3 (C-7, minor diastereomer), 24.9 (2-*Me*, major diastereomer), 25.3 (*C*-7, major diastereomer), 25.8 (2-*Me*, minor diastereomer), 28.1 (*C*-6, minor diastereomer), 30.5 (*C*-6, major diastereomer), 36.3 (*C*-8, minor diastereomer), 37.3 (*C*-8, major diastereomer), 56.8 (*C*-5, minor diastereomer), 58.2 (*C*-5, major diastereomer), 69.3 (*C*-4), 95.5 (*C*-2, minor diastereomer), 96.0 (*C*-2, major diastereomer), 125.5, 125.6, 125.7, 127.8, 128.1, 128.1 (CH aromatic), 141.7 (2-*C* aromatic, minor diastereomer), 142.3 (2-*C* aromatic, major diastereomer), 170.2 (C=O, major diastereomer), 171.7 (C=O, minor diastereomer); *m/z* (APCI+) 246.2 (MH^+, 100%), 268.2 ($(M+NH_4)^+$, 26); *m/z* (CI) 246.1492, ($C_{15}H_{20}NO_2$ (MH^+) requires 246.1494).

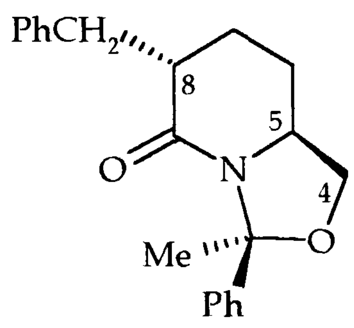
(+)-(2*S*, 5*S*)-1-Aza-8-dibenzyl-2-methyl-3-oxa-9-oxo-2-phenyl-bicyclo [4.3.0] nonane (103c), (2*S*, 5*S*, 8*R*)-1-Aza-8-benzyl-2-methyl-3-oxa-9-oxo-2-phenyl-bicyclo [4.3.0] nonane (103a) and (-)-(2*S*, 5*S*, 8*S*)-1-Aza-8-benzyl-2-methyl-3-oxa-9-oxo-2-phenyl-bicyclo [4.3.0] nonane (103b)



103c



103a



103b

To stirred THF (30ml) cooled to -78°C under N_2 was added sBuLi (0.75ml, 0.98mmol) by syringe. The lactam **77** (0.151g, 0.65mmol) was dissolved in dry THF (5ml) and then added slowly by syringe. The reaction was then allowed to warm slightly to -30°C. Benzyl bromide (0.670g, 3.92mmol) in dry THF (5ml) was then added slowly. After 15mins the reaction mixture was quenched with distilled water (25ml), extracted with EtOAc (3 x 25ml) and dried with brine (25ml) and over $MgSO_4$. Solvent was removed *in vacuo* and the residue separated by column chromatography eluting with 20% EtOAc:Petrol to yield three products.

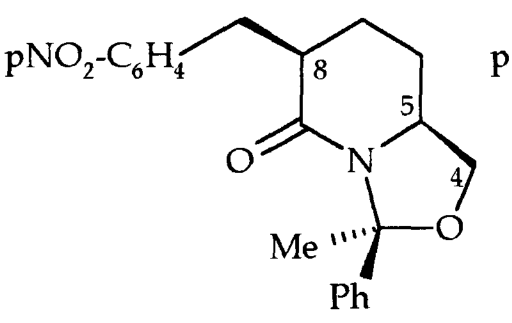
Dialkylated lactam (**103c**): Yield 0.047g (18%); R_f 0.38 (20% EtOAc:Petrol); $[\alpha]^{25}_{D}$ +2.41 (*c* 0.79 in $CHCl_3$); ν_{max}(film)/cm^{-1} 1636s (C=O), 1419m, 704m, 668s, 648w; δ_H(500 MHz; $CDCl_3$) 0.77-0.86, 0.88-0.95, 1.56-1.60, 1.87-1.95 (4 x 1 H, m, 6-*H* and

7-*H*), 1.94 (3 H, s, 2-*Me*), 2.39 (1 H, d, *J* 13.0, 8-*C*H_2), 2.67 (1 H, d, *J* 13.0, 8-*C*H_2) 3.02-3.09 (1 H, m, 5-*H*), 3.34 (1 H, dd, *J* 8.5 and 10.5, 4-H_{endo}), 3.38 (1 H, d, *J* 13.0, 8-*C*H_2), 3.48 (1 H, d, *J* 13.0, 8-*C*H_2), 3.86 (1 H, dd, *J* 6.0 and 8.5, 4-H_{exo}), 7.00-7.48 (15 H, m, 2-*Ph* and 2 x 8-CH$_2$*Ph*). δ_C(125.8 MHz; CDCl$_3$) 23.29 (*C*-6 or *C*-7), 24.31 (*C*-6 or *C*-7), 28.37 (2-*Me*), 45.69 (8-CH$_2$), 47.14 (8-CH$_2$), 48.65 (C-8), 57.34 (*C*-5), 69.92 (*C*-4), 95.92 (*C*-2), 126.28, 126.51, 126.61, 127.80, 127.87, 128.06, 128.09, 130.69, 131.09 (CH aromatic), 137.73 (2 x 8-*C* aromatic), 141.81 (2-*C* aromatic), 170.53 (C=O). *m/z* (APCI$^+$) 412.1 (MH$^+$, 100%), 292.2 (31); *m/z* (CI) 412.2277, ($C_{28}H_{29}NO_2$ (MH$^+$) requires 412.2277).

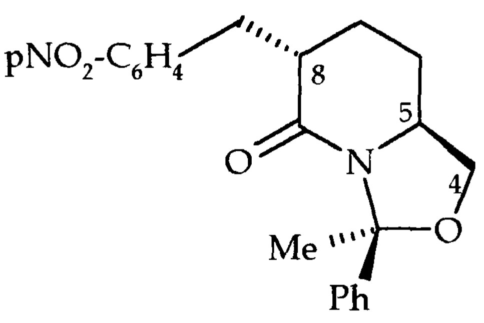
Minor diastereomer (*endo*) (**103a**): Yield 0.013g (6%); R$_f$ 0.26 (20% EtOAc:Petrol); ν_{max}(film)/cm^{-1} 1644s (C=O), 1422m, 699s, 666s; δ_H(500 MHz; CDCl$_3$) 1.39-1.48, 1.65-1.71, 1.75-1.81, 1.82-1.89 (4 x 1 H, m, 6-*H* and 7-*H*), 2.07 (3 H, s, 2-*Me*), 2.59-2.65 (1 H, m, 8-*H*), 2.73 (1 H, dd *J* 10.0 and 13.5, 8-*C*H_2), 3.33 (1 H, dd *J* 4.0 and 13.5, 8-*C*H_2), 3.67 (1 H, dd *J* 8.0 and 8.0, 4-H_{endo}), 3.72-3.78 (1 H, m, 5-*H*), 4.16 (1 H, dd *J* 6.0 and 8.0, 4-H_{exo}), 7.00-7.61 (10 H, m, 2-*Ph* and 8-CH$_2$*Ph*). *m/z* (APCI+) 322.2 (MH$^+$, 100%), 306.2 (15); *m/z* (CI) 322.1807 ($C_{21}H_{23}NO_2$ (MH$^+$) requires 322.1807).

Major diastereomer (*exo*) (**103b**): Yield 0.132g (63%); R$_f$ 0.13 (20% EtOAc:Petrol); $[\alpha]_D^{24}$ -25.8 (*c* 1.03 in CHCl$_3$); ν_{max}(film)/cm^{-1} 1648s (C=O), 1495w, 1445w, 1424m, 1379w, 1321w, 1242w, 1077w, 1029m, 990w, 870w, 790w, 764m, 698s; δ_H(500 MHz; CDCl$_3$) 1.50-1.60 (1 H, m, 6-H_{endo}), 1.55-1.62 (1 H, m, 7-H_{exo}), 1.94-1.99 (1 H, m, 7-H_{endo}), 2.00-2.06 (1 H, m, 6-H_{exo}), 2.07 (3 H, s, 2-*Me*), 2.65-2.71 (1 H, m, 8-*H*), 2.84 (1 H, dd, *J* 9.0 and 13.5, 8-*C*H_2), 3.35 (1 H, dd, *J* 4.0 and 13.5, 8-*C*H_2), 3.50 (1 H, dd, *J* 8.5 and 10.5, 4-H_{endo}), 3.70-3.76 (1 H, m, 5-*H*), 4.04 (1 H, dd, *J* 5.5 and 8.5, 4-H_{exo}), 7.21-7.50 (10 H, m, 2-*Ph* and 8-CH$_2$*Ph*); δ_C(125.8 MHz; CDCl$_3$) 24.88 (2-CH$_3$), 25.10 (*C*-6 or *C*-7), 26.93 (*C*-6 or *C*-7), 37.37 (8-CH$_2$Ph), 43.78 (*C*-8), 57.93 (*C*-5), 69.21 (*C*-4), 95.77 (*C*-2), 125.61, 126.22, 127.92, 128.13, 128.34, 129.38 (Aromatic CH), 139.73, 141.61 (Aromatic quaternary *C*), 168.74 (C=O); δ_H(500 MHz COSY; CDCl$_3$) 1.50-1.60 (6-H_{endo}) crosspeak with 1.55-1.62 (7-H_{exo}), 1.94-1.99 (7-H_{endo}), 2.00-2.06 (6-H_{exo}) and 3.70-3.76 (5-*H*); 1.55-1.62 (7-H_{exo}) crosspeak with 1.50-1.60 (6-H_{endo}), 1.94-1.99 (7-H_{endo}), 2.00-2.06 (6-H_{exo}) and 2.65-2.71 (8-H); 1.94-1.99 (7-H_{endo}) crosspeak with 1.50-1.60 (6-H_{endo}), 1.55-1.62 (7-H_{exo}), 2.00-2.06 (6-H_{exo}) and 2.65-2.71 (8-H); 2.00-2.06 (6-H_{exo}) crosspeak with 1.50-1.60 (6-H_{endo}), 1.55-1.62 (7-H_{exo}) and 1.94-1.99 (7-H_{endo}); 2.65-2.71 (8-H) crosspeak with 1.55-1.62 (7-H_{exo}), 1.94-1.99 (7-H_{endo}), 2.84 (8-CH_2) and 3.35 (8-CH_2); 2.84 (8-CH_2) crosspeak with 2.65-2.71 (8-H) and 3.35 (8-CH_2); 3.35 (8-CH_2) crosspeak with 2.65-2.71 (8-H) and 2.84 (8-CH_2); 3.50 (4-H_{endo}) crosspeak with 3.70-3.76 (5-H) and 4.04 (4-H_{exo}); 3.70-3.76 (5-H) crosspeak with 1.50-1.60 (6-H_{endo}), 3.50 (4-H_{endo}) and 4.04 (4-H_{exo}); 4.04 (4-H_{exo}) crosspeak with 3.50 (4-H_{endo}) and 3.70-3.76 (5-H); n. O. e. experiment (500 MHz; $CDCl_3$) Irradiation at δ_H 2.70 gave enhancements at δ_H 1.50-1.55 (6-H_{endo}) (3.3%), 1.94-1.99 (7-H_{endo}) (5%), 3.35 (8-CH_2) (7%); Irradiation at δ_H 2.85 gave enhancements at δ_H 3.35 (8-CH_2) (25.1); Irradiation at δ_H 3.40 gave enhancements at δ_H with 2.65-2.71 (8-H) (7.5%) and 2.84 (8-CH_2) (24%); Irradiation at δ_H 3.55 gave enhancement at δ_H 4.04 (4-H_{exo}) (23%); Irradiation at δ_H 3.75 gave enhancements at δ_H 1.55-1.62 (7-H_{exo}) (7%), 2.00-2.06 (6-H_{exo}) (5.4%) and 4.04 (4-H_{exo}) (8.6%); Irradiation at δ_H 4.05 gave enhancements at δ_H 3.50 (4-H_{endo}) (23.5%) and 3.70-3.76 (5-H) (7.7%); *m/z* (APCI+) 202.1, 322.2 (MH^+, 100%), 256.2 (2), 203.2 (10). 202.1 (94), 198.5 (4); *m/z* (CI) 322.1807 ($C_{21}H_{23}NO_2$ (MH^+) requires 322.1807).

(-)-(2*S*, 5*S*, 8*R*)-1-Aza-2-methyl-8-(*p*-nitrobenzyl)-3-oxa-9-oxo-2-phenyl-bicyclo [4.3.0] nonane (104a) and (-)-(2*S*, 5*S*, 8*S*)-1-Aza-2-methyl-8-(*p*-nitrobenzyl)-3-oxa-9-oxo-2-phenyl-bicyclo [4.3.0] nonane (104b)



104a



104b

To a solution of the lactam 77 (0.588g, 2.5mmol) in THF (50ml) cooled to -78°C under nitrogen was added sBuLi (3.1ml, 2.5mmol), and the reaction mixture was allowed to warm to -30°C over fifteen minutes. The enolate solution was then added to a solution of freshly recrystallised para-nitrobenzyl bromide (0.659g, 3.1mmol) in THF

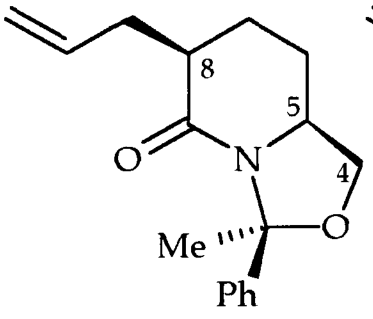
(10ml) at -78°C by cannula. After 45 minutes the reaction was quenched by the addition of $NH_4Cl_{(sat.\ aq.)}$ (25ml), and extracted with EtOAc (3 x 25ml), dried with brine (25ml) and over $MgSO_4$. Solvent was then removed *in vacuo*. The residue was separated on silica gel eluting with 40% EtOAc:Petrol to yield the products as two intense yellow oils.

Minor diastereomer (*endo*) (**104a**): Yield 0.103 (11%); R_f 0.07 (40% EtOAc:Petrol); $[\alpha]_D^{22}$ -52.1 (*c* 1.04 in $CHCl_3$); ν_{max}(film)/cm^{-1} 1648s, 1559w, 1519w, 1494w, 1426m, 1370m, 1345m, 1324m, 1243m, 1182m, 1154w, 1077m, 1029m, 981w, 911w, 872.3m, 811w, 764m, 731w, 698m, 667m, 613w; δ_H(400 MHz; $CDCl_3$) 1.50-1.62, 1.81-1.85, 1.97-2.00 and 2.34-2.49 (4 x 1 H, m, 6-*H* and 7-*H*), 2.05 (3 H, s, 2-*Me*), 3.35 (1 H, t, *J* 10.0, 8-C*H*$_2$), 3.45 (1 H, dd, *J* 8.0 and 10.0, 8-C*H*$_2$), 3.56 (1 H, dd, *J* 8.5 and 10.5, 4-H_{endo}), 3.90-3.98 (1 H, m, 5-*H*), 4.16 (1 H, dd, *J* 6.0 and 8.5, 4-H_{exo}), 7.26-7.53 (9 H, m, 2-*Ph* and 8-CH$_2$*Ph*); δ_C(100.6 MHz; $CDCl_3$) 20.6 (C-6), 24.9 (2-*Me*), 25.8 (C-7), 32.1 (8-CH$_2$), 44.0 (C-8), 58.0 (C-5), 69.5 (C-4), 96.4 (C-2), 123.6, 125.4, 125.5, 125.6, 125.7, 127.9, 128.2, 130.2 (CH aromatic), 140.8 (2-C aromatic or 8-CH$_2$C aromatic), 142.4 (2-C aromatic or 8-CH$_2$C aromatic), 163.3 (C=O), 170.3 (C-NO$_2$); *m/z* (APCI$^+$) 367.2 (MH$^+$, 100%), 337.2 (19), 263.1 (3), 247.1 (99), 217.1 (14), 129.9 (16); *m/z* (ES$^+$) 367.1661 ($C_{21}H_{22}N_2O_4$ requires 367.1658 for MH$^+$).

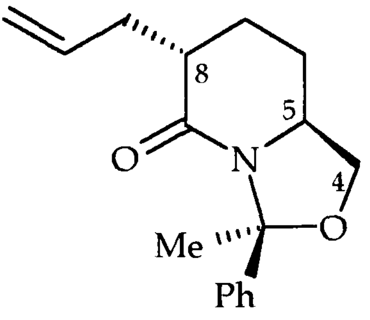
Major diastereomer (*exo*) (**104b**): Yield 0.155g (18%); R_f 0.14 (40% EtOAc:Petrol); $[\alpha]_D^{22}$-65.5 (*c* 1.0 in $CHCl_3$); ν_{max}(film)/cm^{-1} 1647s (C=O), 1603w, 1518s, 1494w, 1427m, 1370w, 1346s, 1323m, 1244m, 1109w, 1028m, 992w, 914w, 859m, 813w, 764m, 736m, 698m, 665m, 631w; δ_H(400 MHz; $CDCl_3$) 1.46-1.59 (2 H, m, 6-H_{exo} and 7-H_{endo}), 1.91-2.00 (1 H, m, 6-H_{endo}), 2.02-2.09 (1 H, m, 7-H_{exo}), 2.04 (3 H, s, 2-*Me*), 2.66-2.79 (1 H, m, 8-*H*), 2.98 (1 H, dd, *J* 9.0 and 14.0, 8-C*H*$_2$), 3.40 (1 H, dd, *J* 4.0 and 14.0, 8-C*H*$_2$), 3.50 (1 H, dd, *J* 8.5 and 10.5, 4-H_{endo}), 3.71-3.78 (1 H, m, 5-*H*), 4.04 (1 H, dd, *J* 5.5 and 8.5, 4-H_{exo}), 7.27-8.15 (9 H, m, 2-*Ph* and 8-$CH_2C_6H_4NO_2$); δ_C(100.6 MHz; $CDCl_3$) 24.8 (2-*Me*), 24.9 (C-7), 26.9 (C-6), 37.1 (8-CH$_2$), 43.4 (C-8), 56.4 (C-5), 69.1 (C-4), 95.7 (C-2), 123.6, 125.5, 128.0, 128.2, 128.5, 130.2 (CH aromatic), 141.3 (2-C aromatic or 8-C aromatic), 136.6 (2-C aromatic or 8-C aromatic), 147.8 (C-NO$_2$), 167.8 (C=O); δ_H(400

MHz NOESY; $CDCl_3$) 1.46-1.59 (6-H_{exo} and 7-H_{endo}) crosspeak with 1.91-2.00 (6-H_{endo}), 2.02-2.09 (7-H_{exo}), 2.66-2.79 (8-*H*), 3.50 (4-H_{endo}) and 3.71-3.78 (5-*H*); 1.91-2.00 (6-H_{endo}) crosspeak with 1.46-1.59 (6-H_{exo} and 7-H_{endo}) and 2.66-2.79 (8-*H*); 2.02-2.09 (7-H_{exo}) crosspeak with 1.46-1.59 (6-H_{exo} and 7-H_{endo}) and 3.40 (8-CH_2); 2.66-2.79 (8-*H*) crosspeak with 1.46-1.59 (6-H_{exo} and 7-H_{endo}), 1.91-2.00 (6-H_{endo}) and 3.40 (8-CH_2); 2.98 (8-CH_2) crosspeak with 3.40 (8-CH_2); 3.40 (8-CH_2) crosspeak with 2.66-2.79 (8-*H*) and 2.98 (8-CH_2); 3.50 (4-H_{endo}) crosspeak with 1.46-1.59 (6-H_{exo} and 7-H_{endo}), 3.71-3.78 (5-*H*) and 4.04 (4-H_{exo}); 3.71-3.78 (5-*H*) crosspeak with 1.46-1.59 (6-H_{exo} and 7-H_{endo}), 2.02-2.09 (7-H_{exo}), 3.50 (4-H_{endo}) and 4.04 (4-H_{exo}); 4.04 (4-H_{exo}) crosspeak with 2.02-2.09 (7-H_{exo}), 3.50 (4-H_{endo}) and 3.71-3.78 (5-*H*); *m/z* (APCI$^+$) 367.2 (MH$^+$, 100%), 337.2 (23), 248.3 (13), 247.1 (98), 217.1 (8), 130.0 (17), 123.5 (31); *m/z* (ES$^+$) 367.1653 ($C_{21}H_{22}N_2O_4$ requires 367.1658 for MH$^+$).

(2*S*, 5*S*, 8*R*)-8-Allyl-1-Aza-2-methyl-3-oxa-9-oxo-2-phenyl-bicyclo [4.3.0] nonane (**105a**) and (-)-(2*S*, 5*S*, 8*S*)-8-Allyl-1-Aza-2-methyl-3-oxa-9-oxo-2-phenyl-bicyclo [4.3.0] nonane (**105b**)



105a



105b

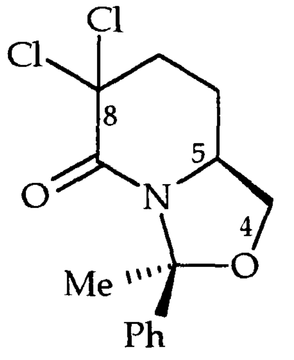
To a stirred flask of THF (20ml) cooled to -78°C under nitrogen was added sBuLi (1.08ml, 0.98mmol). The lactam 77 (0.151g, 0.65mmol) was then dissolved in THF (10ml) and added slowly to the mixture using a syringe. The reaction was allowed to warm slightly to -30°C. Freshly distilled allyl bromide (0.118g, 0.98mmol) dissolved in THF (5ml) was then added and the dark red colour of the anion disappeared. After 30 minutes the reaction was quenched with $NH_4Cl_{(sat)}$ (30ml). The aqueous layer was separated and extracted with EtOAc (3 x 30ml). The organic extracts were then combined and dried with brine (25ml) and over $MgSO_4$. Solvent was removed *in vacuo*. The residue was then separated by column chromatography on silica gel, eluting with 20% EtOAc:Petrol to give two colourless oils.

Minor diastereomer (*endo*) (**105a**): Yield 0.054g (30%); R_f 0.32 (20% EtOAc: Petrol); ν_{max}(film)/cm^{-1} 1654s (C=O), 1559 (C=C), 1507w, 1419m, 764m, 698m; δ_H(500 MHz; $CDCl_3$) 1.48-1.57, 1.72-1.80, 1.92-2.02, 2.21-2.27 and 2.63-2.72 (7 x 1 H, m, 6-*H*, 7-*H* and 8-*H*, 8-CH_2), 2.02 (3 H, s, 2-*Me*), 3.39 (1 H, dd, *J* 9.0 and 10.0, 4-H_{endo}), 3.89-3.93 (1 H, m, 5-*H*), 4.11 (1 H, dd, *J* 6.0 and 9.0, 4-H_{exo}), 5.05-5.12 (2 H, m, 8-$CH_2CH=CH_2$), 5.82-5.89 (1 H, m, 8-$CH_2CH=CH_2$), 7.25-7.44 (5 H, m, 2-*Ph*); δ_C(125.8 MHz; $CDCl_3$) 23.2 (C-7), 24.7 (C-6), 25.6 (2-*Me*), 35.7 (8-CH_2), 40.9 (C-8), 56.7 (C-5), 69.2 (C-4), 96.0 (C-2), 116.8 (8-$CH_2CH=CH_2$), 125.5, 127.8, 128.1 (CH aromatic), 136.5 (8-$CH_2CH=CH_2$), 142.1 (2-*C* aromatic), 170.4 (C=O); *m/z* (APCI$^+$) 272.2 (MH$^+$, 100%); *m/z* (CI) 272.1644 ($C_{17}H_{21}NO_2$ requires 272.1650 for MH$^+$).

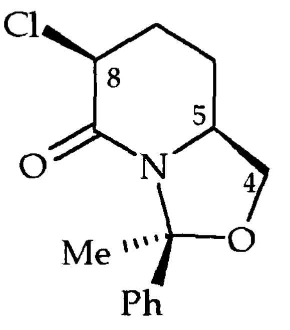
Major diastereomer (*exo*) (**105b**): Yield 0.113g (64%); R_f 0.28 (20% Petrol:EtOAc); $[\alpha]_D^{22}$ -60.0 (*c* 0.09 in $CHCl_3$); ν_{max}(film)/cm^{-1} 1660s (C=O), 1559m, 1540m, 1522m, 1506m, 1490w, 1472w, 1457m, 1420m, 764w, 698w; δ_H(500 MHz; $CDCl_3$) 1.58-1.69 (2 H, m, 6-H_{endo} and 7-H_{exo}), 2.06 (3 H, s, 2-*Me*), 2.09-2.17 (2 H, m, 6-H_{exo} and 7-H_{endo}), 2.35-2.41 (1 H, m, 8-CH_2), 2.46-2.52 (1 H, m, 8-*H*), 2.66-2.71 (1 H, m, 8-CH_2), 3.52 (1 H, dd, *J* 8.5 and 10.5, 4-H_{endo}), 3.83-3.89 (1 H, m, 5-*H*), 4.08 (1 H, dd, *J* 5.5 and 8.5, 4-H_{exo}), 5.08-5.14 (2 H, m, 8-$CH_2CH=CH_2$), 5.75-5.83 (1 H, m, 8-$CH_2CH=CH_2$), 7.28-7.47 (5 H, m, 2-*Ph*); δ_C(125.8 MHz; $CDCl_3$) 24.8 (2-*Me*), 25.0 (C-7), 26.9 (C-6), 35.7 (8-CH_2), 41.4 (C-8), 57.8 (C-5), 69.1 (C-4), 95.5 (C-2), 117.0 (8-$CH_2CH=CH_2$), 125.5, 127.7, 127.9 (CH aromatic), 135.7 (8-$CH_2CH=CH_2$), 141.5 (2-*C* aromatic), 168.7 (C=O); δ_H(300 MHz COSY; $CDCl_3$) 1.58-1.69 (6-H_{endo} and 7-H_{exo}) crosspeak with 2.09-2.17 (6-H_{exo} and 7-H_{endo}), 2.46-2.52 (8-*H*) and 3.83-3.89 (5-*H*); 2.09-2.17 (6-H_{exo} and 7-H_{endo}) crosspeak with 1.58-1.69 (6-H_{endo} and 7-H_{exo}), 2.46-2.52 (8-*H*) and 3.83-3.89 (5-*H*); 2.35-2.41 (1 H, m, 8-CH_2) crosspeak with 2.46-2.52 (8-*H*), 2.66-2.71 (1 H, m, 8-CH_2) and 5.75-5.83 (8-$CH_2CH=CH_2$); 2.46-2.52 (8-*H*) crosspeak with 1.58-1.69 (6-H_{endo} and 7-H_{exo}), 2.09-2.17 (6-H_{exo} and 7-H_{endo}), 2.35-2.41 (8-CH_2) and 2.66-2.71 (8-CH_2); 2.66-2.71 (8-CH_2) crosspeak with 2.35-2.41 (8-CH_2), 2.46-2.52 (8-*H*) and 5.75-5.83 (8-$CH_2CH=CH_2$); 3.52 (4-H_{endo}) crosspeak with 3.83-3.89 (5-*H*) and 4.08 (4-H_{exo}); 3.83-3.89 (5-*H*) crosspeak with with 1.58-1.69 (6-H_{endo} and 7-H_{exo}), 2.09-2.17 (6-H_{exo}

and 7-H_{endo}), 3.52 (4-H_{endo}) and 4.08 (4-H_{exo}); 4.08 (4-H_{exo}) crosspeak with 3.52 (4-H_{endo}) and 3.83-3.89 (5-*H*); 5.08-5.14 (8-$CH_2CH{=}CH_2$) crosspeak with 5.75-5.83 (8-$CH_2CH{=}CH_2$); 5.75-5.83 (8-$CH_2CH{=}CH_2$) crosspeak with 2.35-2.41 (8-CH_2), 2.66-2.71 (8-CH_2) and 5.08-5.14 (8-$CH_2CH{=}CH_2$); n. O. e. experiment (500 MHz; $CDCl_3$) Irradiation at δ_H 2.35 gave enhancements at δ_H 1.58-1.69 (6-H_{endo} and 7-H_{exo}) (1.5%), 2.66-2.71 (1 H, m, 8-CH_2) (26%), 5.08-5.14 (8-$CH_2CH{=}CH_2$) (2%), and 5.75-5.83 (8-$CH_2CH{=}CH_2$) (2.3%); Irradiation at δ_H 2.50 gave enhancements at δ_H 1.58-1.69 (6-H_{endo} and 7-H_{exo}) (3.8%), 2.09-2.17 (6-H_{exo} and 7-H_{endo}) (4%), 2.66-2.71 (1 H, m, 8-CH_2) (4.8%), 5.75-5.83 (8-$CH_2CH{=}CH_2$) (3.8%), 7.43 (*Ph*) (4%); Irradiation at δ_H 2.70 gave enhancements at δ_H 2.35-2.41 (8-CH_2) (21.7%), 2.46-2.52 (8-*H*) (7.4%), 5.08-5.14 (8-$CH_2CH{=}CH_2$) (2%), and 5.75-5.83 (8-$CH_2CH{=}CH_2$) (4.2%); Irradiation at δ_H 3.50 gave enhancements at δ_H 1.58-1.69 (6-H_{endo} and 7-H_{exo}) (3.9%), 4.08 (4-H_{exo}) (21.8%) and 7.43 (*Ph*) (4.1%); Irradiation at δ_H 3.85 gave enhancements at δ_H 1.58-1.69 (6-H_{endo} and 7-H_{exo}) (5.7%), 2.09-2.17 (6-H_{exo} and 7-H_{endo}) (5%) and 4.08 (4-H_{exo}) (5.9%); Irradiation at δ_H 4.10 gave enhancements at δ_H 3.52 (4-H_{endo}) (26.3%) and 3.83-3.89 (5-*H*) (7.4%); Irradiation at δ_H 7.45 gave enhancements at δ_H 2.06 (2-*Me*) (2.6%), 2.46-2.52 (8-*H*) (1.4%), 4.08 (4-H_{exo}) (2%) and 7.28-7.4 (*Ph*) (7.8%); *m/z* (APCI$^+$) 272.2 (MH$^+$, 100%), 152.0 (81); *m/z* (CI) 272.1651 ($C_{17}H_{21}NO_2$ requires 272.1650 for MH$^+$).

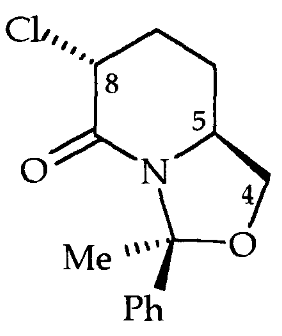
(-)-(2*S*, 5*S*)-1-Aza-8-dichloro-2-methyl-3-oxa-9-oxo-2-phenyl-bicyclo [4.3.0] nonane (**106c**), (+)-(2*S*, 5*S*, 8*S*)-1-Aza-8-chloro-2-methyl-3-oxa-9-oxo-2-phenyl-bicyclo [4.3.0] nonane (**106a**) and (-)-(2*S*, 5*S*, 8*R*)-1-Aza-8-chloro-2-methyl-3-oxa-9-oxo-2-phenyl-bicyclo [4.3.0] nonane (**106b**)



106c



106a



106b

First preparation:

To a stirred flask of THF (20ml) cooled to -78°C under nitrogen was added sBuLi (1.0ml, 0.91mmol). The lactam 77 (0.141g, 0.61mmol) was then dissolved in THF (10ml) and added slowly to the mixture using a syringe. The reaction was allowed to warm slightly to -30°C. Freshly recrystallised tosyl chloride (0.174g, 0.91mmol) dissolved in THF (10ml) was then added and the dark red colour of the anion disappeared. After 30 minutes the reaction was quenched with $NH_4Cl_{(sat)}$ (25ml). The aqueous layer was separated and extracted with EtOAc (3 x 25ml). The organic extracts were then combined and dried with brine (25ml) and over $MgSO_4$. Solvent was removed *in vacuo*. The residue was then separated by column chromatography on silica gel, eluting with 20% EtOAc:Petrol to give the products as three colourless oils, corresponding to pure **106c** 58mg (32%) and a mixture of diastereomers **106a** and **106b** (71mg, 44%), and recovered starting material (30mg, 21%);

Second preparation:

To a solution of the lactam (0.332g, 1.4mmol) in THF (20ml) cooled to -78°C under nitrogen was added sBuLi (1.69ml, 1.7mmol). The solution was stirred for 15 minutes and allowed to warm slightly to -30°C. The enolate was then transferred by syringe to a solution of tosyl chloride (0.410g, 2.2mmol) in THF (20ml) cooled to -78°C. After 1.5hrs the reaction was quenched using $NH_4Cl_{(sat.\ aq.)}$ (25ml), and the mixture extracted with EtOAc (3 x 25ml). The organic extracts were then dried with brine (25ml) and over $MgSO_4$. Solvent was removed *in vacuo* and the residue separated to by column chromatography on silica gel (40% EtOAc:Petrol) to give two colourless oils corresponding to diastereomers **106a** (74mg, 19%) and **106b** (123mg, 32%).

Dialkylated lactam (**106c**): R_f 0.32 (40%EtOAc:Petrol); $[\alpha]_D^{24}$ -75.5 (*c* 0.65 in $CHCl_3$); ν_{max}(film)/cm^{-1} 1686s (C=O), 1495w, 1447m, 1422m, 1378m, 1325m, 1226m, 1152w, 1104m, 1078m, 1036m, 986w, 933w, 873m, 835w, 787m, 764m, 726m, 698m, 680m, 656w; δ_H(500 MHz; $CDCl_3$) 2.08 (3 H, s, 2-*Me*), 2.09-2.18 (2 H, m, 6-*H*), 2.81-2.87 (1 H, m, 7-*H*), 3.06 (1 H, dt, *J* 4.0 and 15.0, 7-*H*), 3.59 (1 H, dd, *J* 8.5 and 10.0, 4-H_{endo}), 4.03-4.09 (1 H, m, 5-*H*), 4.12 (1 H, dd, *J* 5.5 and 8.5, 4-H_{exo}), 7.30-7.49 (5 H, m, 2-*Ph*);

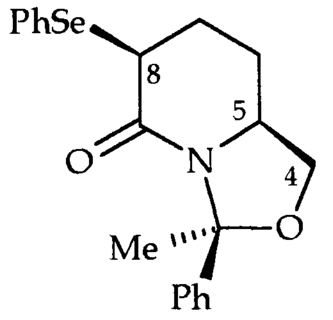
δ_C(125.8 MHz; $CDCl_3$) 22.7 (*C*-6), 25.0 (2-*Me*), 44.1 (*C*-7), 58.2 (*C*-5), 68.9 (*C*-4), 83.3 (*C*-8), 96.4 (*C*-2), 125.4, 128.3 and 128.4 (CH aromatic), 140.5 (2-*C* aromatic), 160.2 (C=O); *m/z* (APCI$^+$) 300.1 (MH^+, 100%), 301.9 (MH^+ ^{35}Cl ^{37}Cl, 50%), 304.2 (MH^+ ^{37}Cl ^{37}Cl 267.9 (15), 266.1 (32), 264.1 (6), 233.2 (6), 232.1 (44), 230.1 (12), 182.0 (21), 179.9 (38), 148.0 (11), 145.9 (38), 143.9 (7), 123.8 (19), 121.9 (52), 120.9 (15); *m/z* (CI) 300.0559 ($C_{14}H_{15}NO_2Cl_2$ requires 300.0558 for MH^+).

Minor diastereomer (*endo*) (**106a**): R_f 0.28 (40% EtOAc:Petrol); $[\alpha]_D^{24}$ +47.2 (*c* 0.11 in $CHCl_3$); ν_{max}(film)/cm^{-1} 1664s (C=O), 1494w, 1446m, 1426m, 1370m, 1325m, 1270m, 1211m, 1180m, 1162w, 1076w, 1029m, 1008w, 988w, 917w, 875w, 764m, 699m, 659w, 639w; δ_H(500 MHz; $CDCl_3$) 1.59-1.68 (1 H, m, 6-*H*), 2.03 (3 H, s, 2-*Me*), 2.11-2.21 (2 H, m, 6-*H* and 7-*H*), 2.45-2.52 (1 H, m, 7-*H*), 3.71 (1 H, t, *J* 8.5, 4-H_{endo}), 3.96-4.02 (1 H, m, 5-*H*), 4.18 (1 H, dd, *J* 6.5 and 8.5, 4-H_{exo}), 4.48 (1 H, dd, *J* 6.0 and 8.0, 8-*H*), 7.26-7.79 (5 H, m, 2-*Ph*); δ_C(125.8 MHz; $CDCl_3$) 25.0 (*C*-6 and 2-*Me*), 30.8 (*C*-7), 55.7 and 55.9 (*C*-5 and *C*-8), 69.9 (*C*-4), 96.7 (*C*-2), 125.5, 128.2, 128.2 (CH aromatic), 141.6 (2-C aromatic), 163.4 (*C*=O);); δ_H(300 MHz COSY; $CDCl_3$) 1.59-1.68 (6-*H*) crosspeak with 2.11-2.21 (6-*H* and 7-*H*), 2.45-2.52 (7-*H*) and 3.96-4.02 (5-*H*); 2.11-2.21 (6-*H* and 7-*H*) crosspeak with 1.59-1.68 (6-*H*), 2.45-2.52 (7-*H*), 3.96-4.02 (5-*H*) and 4.48 (8-*H*); 2.45-2.52 (7-*H*) crosspeak with 1.59-1.68 (6-*H*), 2.11-2.21 (6-*H* and 7-*H*) and 4.48 (8-*H*); 3.71 (4-H_{endo}) crosspeak with 3.96-4.02 (5-*H*) and 4.18 (4-H_{exo}); 3.96-4.02 (5-*H*) crosspeak with 1.59-1.68 (6-*H*), 2.11-2.21 (6-*H* and 7-*H*), 3.71 (4-H_{endo}) and 4.18 (4-H_{exo}); 4.18 (4-H_{exo}) crosspeak with 3.71 (4-H_{endo}) and 3.96-4.02 (5-*H*); 4.48 (8-*H*) crosspeak with 2.11-2.21 (6-*H* and 7-*H*) and 2.45-2.52 (7-*H*); *m/z*(APCI$^+$) 266.1 (MH^+, 21%), 268.1 (MH^+, ^{37}Cl, 7%), 254.1 (12), 233.2 (15), 232.1 (100), 230.1 (15), 202.1 (8), 170.1 (6), 147.9 (29), 145.9 (94), 127.9 (12); *m/z* (CI) 266.0948 ($C_{14}H_{16}NO_2Cl$ requires 266.0948 for MH^+).

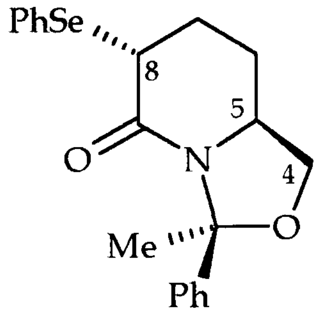
Major diastereomer (*exo*) (**106b**): R_f 0.19 (40% EtOAc:Petrol); $[\alpha]_D^{24}$ -30.4 (*c* 0.58 in $CHCl_3$); ν_{max}(film)/cm^{-1} 1666s (C=O), 1494w, 1446m, 1427m, 1371m, 1244m, 1222m, 1180w, 1153w, 1078m, 1028m, 938w, 913w, 873w, 764m, 698m, 630w; δ_H(500 MHz; $CDCl_3$) 1.92-2.04 (2 H, m, 6-*H* and 7-*H*), 2.05 (3 H, s, 2-*Me*), 2.30-2.41 (2 H, m, 6-*H* and 7-*H*), 3.51 (1 H, dd, *J* 8.5 and 10.5, 4-H_{endo}), 3.84-3.90 (1 H, m, 5-*H*), 4.09 (1 H, dd, *J* 5.5

and 8.5, 4-H_{exo}), 4.45 (1 H, dd, *J* 3.5 and 4.5, 8-*H*), 7.27-7.59 (5 H, m, 2-*Ph*); δ_C(125.8 MHz; $CDCl_3$) 20.3 (*C*-6), 24.9 (2-*Me*), 31.4 (*C*-7), 55.2 (*C*-5), 57.9 (*C*-8), 68.8 (*C*-4), 95.6 (*C*-2), 125.3, 128.1, 128.2 (CH aromatic), 140.8 (2-*C* aromatic), 163.1 (C=O); δ_H(300 MHz COSY; $CDCl_3$) 1.92-2.04 (6-*H* and 7-*H*) crosspeak with 2.30-2.41 (6-*H* and 7-*H*), 3.84-3.90 (5-*H*) and 4.45 (8-*H*); 2.30-2.41 (6-*H* and 7-*H*) crosspeak with 1.92-2.04 (6-*H* and 7-*H*), 3.84-3.90 (5-*H*) and 4.45 (8-*H*); 3.51 (4-H_{endo}) crosspeak with 3.84-3.90 (5-*H*) and 4.09 (4-H_{exo}); 3.84-3.90 (5-*H*) crosspeak with 1.92-2.04 (6-*H* and 7-*H*), 2.30-2.41 (6-*H* and 7-*H*), 3.51 (4-H_{endo}) and 4.09 (4-H_{exo}); 4.09 (4-H_{exo}) crosspeak with 3.51 (4-H_{endo}) and 3.84-3.90 (5-*H*); 4.45 (8-*H*) crosspeak with 1.92-2.04 (6-*H* and 7-*H*) and 2.30-2.41 (6-*H* and 7-*H*); *m/z* ($APCI^+$) 266.1 (MH^+, 11%), 268.1 (MH^+ ^{37}Cl, 3%), 254.1 (14), 233.2 (15), 232.1 (100), 230.1 (10), 147.9 (9), 145.9 (26), 127.9 (3), 119.9 (5); *m/z* (CI) 266.0948 ($C_{14}H_{16}NO_2Cl$ requires 266.0948 for MH^+).

(-)-(2*S*, 5*S*, 8*S*)-1-Aza-2-methyl-3-oxa-9-oxo-2-phenyl-8-phenylselenyl-bicyclo [4.3.0] nonane (107a) and (-)-(2*S*, 5*S*, 8*R*)-1-Aza-2-methyl-3-oxa-9-oxo-2-phenyl-8-phenylselenyl-bicyclo [4.3.0] nonane (107b)



107a



107b

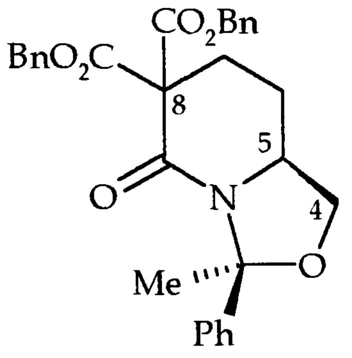
To a stirred flask of THF (20ml) cooled to -78°C under nitrogen was added sBuLi (0.94ml, 0.84mmol). The lactam 77 (0.130g, 0.56mmol) was then dissolved in THF (10ml) and added slowly to the mixture using a syringe. The reaction was allowed to warm slightly to -30°C. Phenyl selenyl chloride (0.161g, 0.84mmol) dissolved in THF (10ml) was then added and the dark red colour of the anion disappeared. After 30 minutes the reaction was quenched with $NH_4Cl_{(sat)}$ (25ml). The aqueous layer was separated and extracted with EtOAc (3 x 25ml). The organic extracts were then combined and dried with brine (25ml) and over $MgSO_4$. Solvent was removed *in vacuo*. The residue was then separated by column chromatography on silica gel, eluting initially with 20% EtOAc:Petrol and increasing the polarity to 40% EtOAc:Petrol to give the products as two yellow oils.

Minor diastereomer (*endo*) (**107a**): Yield 41mg (19%); R_f 0.11 (20% EtOAc:Petrol); $[\alpha]_D^{22}$ -120.5 (*c* 0.39, $CHCl_3$); ν_{max}(film)/cm^{-1} 1650s (C=O), 1416m, 1370m, 1322m, 1241m, 1028w; δ_H(500 MHz; $CDCl_3$) 1.53-1.60 (1 H, m, 6-*H*), 2.00-2.14 (2 H, m, 6-*H* and 7-*H*), 2.02 (3 H, s, 2-*Me*), 2.41-2.46 (1 H, m, 7-*H*), 3.44 (1 H, dd, *J* 9.0 and 10.0, 4-H_{endo}), 3.82-3.87 (1 H, m, 5-*H*), 4.03 (1 H, t, *J* 7.5, 8-*H*), 4.09 (1 H, dd, *J* 6.0 and 9.0, 4-H_{exo}), 7.28-7.71 (10 H, m, 2-*Ph* and 8-Se*Ph*); δ_C(125.8 MHz; $CDCl_3$) 25.1 (*C*-7 and 2-*Me*), 29.0 (*C*-6), 41.8 (*C*-8), 56.6 (*C*-5), 69.0 (*C*-4), 96.5 (*C*-2), 125.7, 127.9, 128.1, 128.4, 129.0 and 135.8 (CH aromatic), 131.5 (8-SeC), 141.4 (2-*C* aromatic), 166.4 (C=O); δ_H(300 MHz COSY; $CDCl_3$) 1.53-1.60 (6-*H*) crosspeak with 2.00-2.14 (6-*H* and 7-*H*) and 2.41-2.46 (7-*H*); 2.00-2.14 (6-*H* and 7-*H*) crosspeak with 1.53-1.60 (6-*H*), 2.41-2.46 (7-*H*), 3.82-3.87 (5-*H*) and 4.03 (8-*H*); 2.41-2.46 (7-*H*) crosspeak with 1.53-1.60 (6-*H*), 2.00-2.14 (6-*H* and 7-*H*) and 4.03 (8-*H*); 3.44 (4-H_{endo}) crosspeak with 3.82-3.87 (5-*H*) and 4.09 (4-H_{exo}); 3.87 (5-*H*) crosspeak with 2.00-2.14 (6-*H* and 7-*H*), 3.44 (4-H_{endo}) and 4.09 (4-H_{exo}); 4.03 (8-*H*) crosspeak with 2.00-2.14 (6-*H* and 7-*H*) and 2.41-2.46 (7-*H*); 4.09 (4-H_{exo}) crosspeak with 3.44 (4-H_{endo}) and 3.87 (5-*H*); *m/z* ($APCI^+$) 388.1 (MH^+, 100%), 385.9 (51), 384.0 (17), 268.1 (10), 266.0 (6), 232.1 (6), 111.9 (9); *m/z* (CI) 388.0819 ($C_{20}H_{21}NO_2Se$ requires 388.0816 for MH^+).

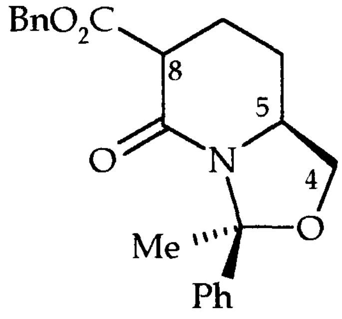
Major diastereomer (*exo*) (**107b**): Yield 71mg (33%); R_f 0.06 (20% EtOAc:Petrol); $[\alpha]_D^{22}$ -26.8 (*c* 0.37 in $CHCl_3$); ν_{max}(film)/cm^{-1} 1652s (C=O), 1578w, 1494w, 1477w, 1447m, 1438m, 1423m, 1375m, 1322m, 1242w, 1221w, 1716w, 1154w, 1076w, 1028m, 980w, 911w, 873w; δ_H(500 MHz; $CDCl_3$) 1.88-1.96 (1 H, m, 6-*H*), 2.01-2.06 (1 H, m, 7-*H*), 2.11 (3 H, s, 2-*Me*), 2.30-2.38 (2 H, m, 6-*H* and 7-*H*), 3.59 (1 H, dd, *J* 8.5 and 10.5, 4-H_{endo}), 3.93-3.99 (1 H, m, 5-*H*), 4.09 (1 H, t, *J* 5.0, 8-*H*), 4.15 (1 H, dd, *J* 5.5 and 8.5, 4-H_{exo}), 7.30-7.70 (10 H, m, 2-*Ph* and 8-Se*Ph*); δ_C(125.8 MHz; $CDCl_3$) 22.2 (*C*-6), 25.0 (2-*Me*), 28.9 (*C*-7), 43.5 (*C*-8), 58.0 (*C*-5), 69.2 (*C*-4), 95.5 (*C*-2), 125.6, 128.0, 128.2, 129.1 and 129.2 (CH aromatic), 131.57 (8-SeC), 141.4 (2-*C* aromatic), 166.6 (C=O); *m/z*

(APCI+) 388.0 (MH+, 100%), 385.9 (50), 384.1 (18), 270.1 (6), 268.0 (15), 264.0 (6), 232.1 (13), 216.1 (14); *m/z* (CI) 388.0820 ($C_{20}H_{21}NO_2Se$ requires 388.0815).

(+)-(2*S*, 5*S*)-1-Aza-8-dibenzyloxycarbonyl-2-methyl-3-oxa-9-oxo-2-phenyl-bicyclo [4.3.0] nonane (**108c**), (2*S*, 5*S*, 8*S*)-1-Aza-8-dibenzyloxycarbonyl-2-methyl-3-oxa-9-oxo-2-phenyl-bicyclo [4.3.0] nonane (**108a**) and (2*S*, 5*S*, 8*R*)-1-Aza-8-dibenzyloxycarbonyl-2-methyl-3-oxa-9-oxo-2-phenyl-bicyclo [4.3.0] nonane (**108b**)



108c



108a, b

First preparation

To THF (20ml) cooled to -78°C under nitrogen was added sBuLi (2.8ml, 3.6mmol). A solution of the lactam 77 (0.690g, 3.0mmol) in THF (10ml) was then added by syringe, and the solution was allowed to warm slightly to -30°C. After 15 minutes, benzyl chloroformate (0.763g, 4.5mmol) was added by syringe. After two hours the reaction was quenched with $NH_4Cl_{(sat.\ aq.)}$ (25ml), extracted with EtOAc (3 x 25ml), dried with brine (25ml) and over $MgSO_4$, and solvent was removed *in vacuo*. The residue was separated by flash column chromatography to yield two colourless oils, the diacylated product **108c** (0.201g, 47%), and a mixture of diastereomers **108a, b** (0.061g, 28%).

Second preparation

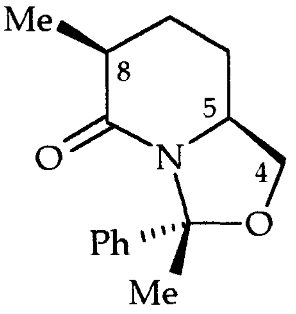
To a solution of the lactam 77 (1.586g, 6.9mmol) in THF (50ml) at -78°C under nitrogen was added sBuLi (8.2ml, 8.2mmol). The mixture was stirred for 15 minutes and allowed to warm to -30°C. The enolate solution was then transferred by cannula into a solution of benzylchloroformate (2.340g, 13.7mmol) in THF (10ml) at -78°C. The reaction was stirred for three hours, and then quenched with $NH_4Cl_{(sat.\ aq)}$ (25ml), extracted with EtOAc (3 x 30ml), dried with brine (30ml) and over $MgSO_4$, and solvent was removed *in vacuo*. Separation of the residue by flash column chromatography (20% EtOAc:Petrol) on silica gel gave 0.335g (10%) of the diacylated product and 1.128g (45%) of a mixture of diastereomers of the monoacylated product.

An improved purifaction method, whereby the residue was separated on an alumina column gave 9.17g (72%) of a mixture of the diastereomers (**108a, b**) and no diacylated product.

Diacylated lactam (**108c**): R_f 0.53 (40% EtOAc:Petrol); $[\alpha]_D^{24}$ +46.0 (*c* 2.1 in $CHCl_3$); ν_{max}(film)/cm^{-1} 1732s (ester C=O), 1673s (lactam C=O), 1221.4s, 697m; δ_H(500 MHz; $CDCl_3$) 1.55-1.63 (1 H, m, 6-*H*), 1.93-2.00 (1 H, m, 6-*H*), 1.98 (3 H, s, 2-*Me*), 2.60-2.70 (2 H, m, 7-*H*), 3.38 (1 H, dd, *J* 8.5 and 10.0, 4-H_{endo}), 3.58-3.67 (1 H, m, 5-*H*), 4.04 (1 H, dd, *J* 5.5 and 8.5, 4-H_{exo}), 5.15-5.32 (4 H, m, 2 x 8-CO_2CH_2), 7.24-7.52 (15 H, m, 2-*Ph* and 2 x 8-CO_2CH_2Ph); δ_C(125.8 MHz; $CDCl_3$) 22.1 (C-6), 25.3 (2-*Me*), 28.3 (C-7), 56.3 (C-5), 64.6 (C-8), 67.9 and 68.1 (2 x CH_2Ph), 69.4 (C-4), 96.7 (C-2), 125.6, 127.9, 128.1, 128.2, 128.4, 128.5 (CH aromatic), 134.9 and 135.1 (2 x CH_2C aromatic, 141.5 (2-C aromatic), 162.3 (lactam C=O), 167.5, 167.6 (2 x ester C=O); δ_H(300 MHz COSY; $CDCl_3$) 1.55-1.63 (6-*H*) crosspeak with 1.93-2.00 (6-*H*), 2.60-2.70 (7-*H*) and 3.58-3.67 (5-*H*); 1.93-2.00 (6-*H*) crosspeak with 1.55-1.63 (6-*H*), 2.60-2.70 (7-*H*) and 3.58-3.67 (5-*H*); 2.60-2.70 (7-*H*) crosspeak with 1.55-1.63 (6-*H*) and 1.93-2.00 (6-*H*); 3.38 (4-H_{endo}) crosspeak with 3.58-3.67 (5-*H*) and 4.04 (4-H_{exo}); 3.58-3.67 (5-*H*) crosspeak with 1.55-1.63 (6-*H*), 1.93-2.00 (6-*H*), 3.38 (4-H_{endo}) and 4.04 (4-H_{exo}); 4.04 (4-H_{exo}) crosspeak with 3.38 (4-H_{endo}) and 3.58-3.67 (5-*H*); *m/z* (APCI$^+$) 500.2 (MH$^+$, 100%), 388.1 (3), 366.1 (5), 232.1 (12), 155.9 (2); *m/z* (CI) 500.2070 ($C_{30}H_{29}NO_6$ requires 500.2073 for MH$^+$).

Diastereomeric mixture of **108a** and **108b**: R_f 0.32 and 0.22 (40% EtOAc:Petrol); ν_{max}(film)/cm^{-1} 1736s (ester C=O), 1655s (lactam C=O), 1497w, 1430m, 1372m, 1324m, 1241m, 1158m, 1028m, 871w, 764m, 698s, 666s; δ_H(500 MHz; $CDCl_3$) 1.51-1.59, 1.80-1.88, 1.96-2.01, 2.07-2.17, 2.20-2.34 (4 H, m, 6-*H* and 7-*H*), 2.03 and 2.05 (3 H, 2 x s, 2-*Me*), 3.44 (1 H, dd, *J* 8.5 and 10.0, 4-H_{endo} minor diastereomer), 3.46 (1 H, dd, *J* 8.5 and 10.0, 4-H_{endo} major diastereomer), 3.55 (1 H, dd, *J* 2.0 and 9.5, 8-*H* minor diastereomer), 3.56 (1 H, dd, *J* 4.0 and 11.0, 8-*H* major diastereomer), 3.81-3.91 (1 H, m, 5-*H*), 4.08 (1 H, dd, *J* 5.5 and 8.5, 4-H_{exo} major diastereomer), 4.10 (1 H, dd, *J* 6.0 and 8.5, 4-H_{exo} minor diastereomer), 5.16-5.26 (2 H, m, 8-CO_2CH_2 both diastereomers), 7.24-7.51 (10 H, m, 2-*Ph* and 8-CO_2CH_2*Ph*); δ_C(125.8 MHz; $CDCl_3$) 22.5 (*C*-7 major diastereomer), 24.3 (*C*-7 minor diastereomer), 25.0 (*C*-6 minor diastereomer), 25.1 (*C*-6 major diastereomer), 25.1 (2-*Me* major diastereomer), 25.2 (2-*Me* minor diastereomer), 48.1 (*C*-5 major diastereomer), 50.0 (*C*-5 minor diastereomer), 57.1 (*C*-8 major diastereomer), 57.7 (*C*-8 minor diastereomer), 66.8 (*C*-4 minor diastereomer), 67.1 (*C*-4 major diastereomer), 68.7 (8-CO_2CH_2 major diastereomer), 69.1 (8-CO_2CH_2 minor diastereomer), 96.2 (*C*-2 major diastereomer), 96.3 (*C*-2 minor diastereomer), 125.6, 127.9, 128.0, 128.1, 128.2, 128.5, 128.5 (CH aromatic), 135.5 (2-*C* aromatic), 140.9 (8-CH_2CO_2C major diastereomer), 141.3 (8-CH_2CO_2C minor diastereomer), 163.3 (lactam *C*=O), 170.6 (ester *C*=O, minor diastereomer), 170.9 (ester *C*=O, major diastereomer); *m/z* ($APCI^+$) 366.2 (MH^+, 100%), 247.3 (4), 246.2 (27), 232.2 (12), 211.1 (2), 170.1 (3), 156.0 (27), 138.0 (2), 120.0 (3); *m/z* (CI) 366.1711 ($C_{22}H_{23}NO_4$ requires 366.1705 for MH^+).

(+)-(2*R*, 5*S*, 8*S*)-1-Aza-2-methyl-8-methyl-3-oxa-9-oxo-2-phenyl-bicyclo [4.3.0] nonane (113a)

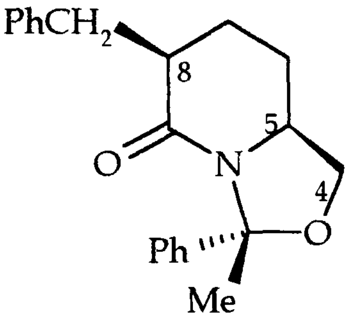


113a

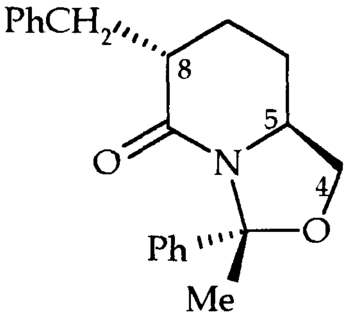
To a solution of the lactam **94** (0.208g, 0.90mmol) in THF (10ml) cooled to -78°C under nitrogen was added sBuLi (1.1ml, 0.99mmol). The reaction mixture was stirred for 30 minutes, and then methyl iodide (0.07ml, 1.08mmol) was added by syringe. The reaction mixture was stirred for 30 minutes, and then allowed to return to room temperature, and quenched with $NH_4Cl_{(sat.\ aq)}$ (25ml). The biphasic system was then extracted with EtOAc (3 x 25ml), dried with brine (20ml) and over $MgSO_4$. Solvent was removed *in vacuo,* and the residue separated by flash column chromatography on silica gel, eluting with 40% EtOAc:Petrol to yield the title compound as a colourless oil (0.102g, 46%) after two columns. A small amount (0.017g, 8%) of an inseparable mixture of the two diastereomers arising from alkylation of the (2*S*) diastereomer of the starting material was also isolated.

R_f 0.33 (40% EtOAc:Petrol); $[\alpha]_D^{24}$ +126.1 (*c* 0.53 in $CHCl_3$); ν_{max}(film)/cm^{-1} 2937m, 1648s (lactam C=O), 1420m, 1324m, 1237m, 1028m, 763m, 699m, 589w, and 471m; δ_H(400 MHz; $CDCl_3$) 1.26 (3 H, d, *J* 7.0, 8-CH_3), 1.58-1.67 (2 H, m, 6-*H* and 7-*H*), 1.94-2.11 (2 H, m, 6-*H* and 7-*H*), 2.03 (3 H, s, 2-CH_3), 2.44-2.48 (1 H, m, 8-*H*), 3.71-3.80 (2 H, m, 5-*H* and 4-H_{endo}), 4.15 (1 H, dd, *J* 5.5 and 7.5, 4-H_{exo}), 7.28-7.57 (5 H, m, 2-*Ph*); δ_C(100.6 MHz; $CDCl_3$) 17.5 (8-*Me*), 24.4 (C-6), 25.6 (2-*Me*), 27.5 (C-7), 35.9 (C-8), 56.5 (C-5), 69.8 (C-4), 96.3 (C-2), 125.6, 128.0 and 128.1 (CH aromatic), 142.6 (C aromatic), 171.4 (C=O); δ_H(400 MHz COSY; $CDCl_3$) 1.26 (8-*Me*) crosspeak with 2.44-2.48 (8-*H*); 1.58-1.67 (6-*H* and 7-*H*) crosspeak with 1.94-2.11 (6-*H* and 7-*H*), 2.44-2.48 (8-*H*) and 3.71-3.80 (5-*H*); 1.94-2.11 (6-*H* and 7-*H*) crosspeak with 1.58-1.67 (6-*H* and 7-*H*), 2.44-2.48 (8-*H*) and 3.71-3.80 (5-*H*); 2.44-2.48 (8-*H*) crosspeak with 1.26 (8-*Me*) 1.58-1.67 (6-*H* and 7-*H*) and 1.94-2.11 (6-*H* and 7-*H*); 3.71-3.80 (4-H_{endo} and 5-*H*) crosspeak with 1.58-1.67 (6-*H* and 7-*H*), 1.94-2.11 (6-*H* and 7-*H*), and 4.15 (4-H_{exo}); 4.15 (4-H_{exo}) crosspeak with 3.71-3.80 (4-H_{endo} and 5-*H*); δ_H(500 MHz NOESY; DMSO-d_6) 1.05 (7-H_{endo}) crosspeak with 1.2 (8-*Me*), 1.3 (6-H_{endo} and 7-H_{exo}), and 3.2 (4-H_{endo}); 1.15 (6-H_{exo}) crosspeak with 1.3 (6-H_{endo} and 7-H_{exo}) and 3.1 (5-*H*); 1.2 (8-*Me*) crosspeak with 1.05 (7-H_{endo}) and 2.1 (8-*H*); 1.3 (6-H_{endo} and 7-H_{exo}) crosspeak with 1.05 (7-H_{endo}), 1.15 (6-H_{exo}), 2.1 (8-*H*) and 3.1 (5-*H*); 2.1 (8-*H*) crosspeak with 1.2 (8-*Me*), 1.3 (6-H_{endo} and 7-H_{exo}) and 3.1 (5-*H*); 3.1 (5-*H*) crosspeak with 1.15 (6-H_{exo}), 1.3 (6-H_{endo} and 7-H_{exo}), 2.1 (8-*H*), 3.2 (4-H_{endo}) and 3.65 (4-H_{exo}); 3.2 (4-H_{endo}) crosspeak with 1.05 (7-H_{endo}), 3.1 (5-*H*) and 3.65 (4-H_{exo}); 3.65 (4-H_{exo}) crosspeak with 3.1 (5-*H*) and 3.2 (4-H_{endo}); *m/z* (APCI$^+$) 246.1 (MH^+), 234.1 (9%), 217.0 (6), 125.9 (14); *m/z* (CI) 246.1490 (MH^+) $C_{15}H_{19}NO_2$ requires 246.1494 for (MH^+).

(+)-(2*R*, 5*S*, 8*R*)-1-Aza-8-benzyl-2-methyl-3-oxa-9-oxo-2-phenyl-bicyclo [4.3.0] nonane (114a) and (+)-(2*R*, 5*S*, 8*S*)-1-Aza-8-benzyl-2-methyl-3-oxa-9-oxo-2-phenyl-bicyclo [4.3.0] nonane (114b)



114a



114b

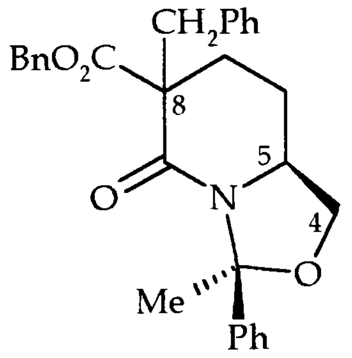
To a solution of the lactam **94** (0.208g, 0.90mmol) in THF (10ml) cooled to -78°C under nitrogen was added sBuLi (1.1ml, 0.99mmol). The reaction mixture was stirred for 30 minutes, and then a solution of benzyl bromide (0.184g, 1.08mmol) in THF (20ml) was added by syringe. The reaction mixture was stirred for 30 minutes, and then allowed to return to room temperature, and quenched with $NH_4Cl_{(sat.\ aq)}$ (25ml). The biphasic system was then extracted with EtOAc (3 x 25ml), dried with brine (20ml) and over $MgSO_4$. Solvent was removed *in vacuo,* and the residue separated by flash column chromatography on silica gel, eluting initially with 20% EtOAc:Petrol and increasing the polarity to 40% EtOAc:Petrol to yield the title compounds as two colourless oils after two columns.

Minor diastereomer (*endo*) (**114a**): Yield 27mg (9%); R_f 0.58 (40% EtOAc:Petrol); $[\alpha]_D^{22}$+134.6 (*c* 1.2 in $CHCl_3$); ν_{max}(film)/cm^{-1} 1647s (lactam C=O), 1496w, 1420m, 1370m, 1320w, 1238m, 1029m, 762m, 699s and 666s; δ_H(400 MHz; $CDCl_3$) 1.38-1.48 (1 H, m, 6-H_{endo}), 1.64-1.71 (1 H, m, 7-H_{endo}), 1.73-1.81 (1 H, m, 7-H_{exo}), 1.82-1.89 (1 H, m, 6-H_{exo}), 2.07 (3 H, s, 2-*Me*), 2.58-2.65 (1 H, m, 8-*H*), 2.73 (1 H, dd, *J* 10.0 and 13.5, 8-CH_2), 3.32 (1 H, dd, *J* 4.0 and 13.5, 8-CH_2), 3.67 (1 H, t, *J* 8.0, 4-H_{endo}), 3.72-3.79 (1 H, m, 5-*H*), 4.16 (1 H, dd, *J* 6.0 and 8.0, 4-H_{exo}), 7.19-7.61 (10 H, m, 8-*Ph* and 2-*Ph*); δ_C(100.6 MHz; $CDCl_3$) 23.7 (C-7), 23.9 (C-6), 25.2 (2-*Me*), 37.7 (8-CH_2), 56.7 (C-5), 69.9 (C-4), 96.3 (C-2), 125.8, 126.3, 128.1, 128.4 and 129.2 (CH Aromatic), 139.9 (8-CH_2CAr), 142.4 (2-CAr), 170.2 (C=O); δ_H(400 MHz COSY; $CDCl_3$) 1.38-1.48 (6-H_{endo}) crosspeak with 1.64-1.71 (7-H_{endo}), 1.73-1.81 (7-H_{exo}), 1.82-1.89 (6-H_{exo}) and 3.72-3.79 (5-*H*); 1.64-1.71 (7-H_{endo}) crosspeak with 1.38-1.48 (6-H_{endo}), 1.73-1.81

(7-H_{exo}), 1.82-1.89 (6-H_{exo}) and 2.58-2.65 (8-*H*); 1.73-1.81 (7-H_{exo}) crosspeak with 1.38-1.48 (6-H_{endo}), 1.64-1.71 (7-H_{endo}), 1.82-1.89 (6-H_{exo}) and 2.58-2.65 (8-*H*); 1.82-1.89 (6-H_{exo}) crosspeak with with 1.38-1.48 (6-H_{endo}), 1.64-1.71 (7-H_{endo}), 1.73-1.81 (7-H_{exo}), and 3.72-3.79 (5-*H*); 2.58-2.65 (8-*H*) crosspeak with 1.64-1.71 (7-H_{endo}), 1.73-1.81 (7-H_{exo}), 2.73 (8-CH_2) and 3.32 (8-CH_2); 2.73 (8-CH_2) crosspeak with 2.58-2.65 (8-*H*) and 3.32 (8-CH_2); 3.32 (8-CH_2) crosspeak with 2.58-2.65 (8-*H*) and 2.73 (8-CH_2); 3.67 (4-H_{endo}) crosspeak with 3.72-3.79 (5-*H*) and 4.16 (4-H_{exo}); 3.72-3.79 (5-*H*) crosspeak with 1.38-1.48 (6-H_{endo}), 1.82-1.89 (6-H_{exo}), 3.67 (4-H_{endo}) and 4.16 (4-H_{exo}); 4.16 (4-H_{exo}) crosspeak with 3.67 (4-H_{endo}) and 3.72-3.79 (5-*H*); δ_H(400 MHz NOESY; $CDCl_3$) 1.38-1.48 (6-H_{endo}) crosspeak with 1.64-1.71 (7-H_{endo}), 1.82-1.89 (6-H_{exo}), 2.73 (8-CH_2) and 3.67 (4-H_{endo}); 1.64-1.71 (7-H_{endo}) crosspeak with 1.73-1.81 (7-H_{exo}), 2.58-2.65 (8-*H*) and 2.73 (8-CH_2); 1.73-1.81 (7-H_{exo}) crosspeak with 2.58-2.65 (8-*H*) and 3.72-3.79 (5-*H*); 1.82-1.89 (6-H_{exo}) crosspeak with 1.38-1.48 (6-H_{endo}) and 3.72-3.79 (5-*H*); 2.07 (2-*Me*) crosspeak with 3.67 (4-H_{endo}); 2.58-2.65 (8-*H*) crosspeak with 1.64-1.71 (7-H_{endo}), 1.73-1.81 (7-H_{exo}), 2.73 (8-CH_2), 3.32 (8-CH_2), and 3.72-3.79 (5-*H*); 2.73 (8-CH_2) crosspeak with 1.38-1.48 (6-H_{endo}), 1.64-1.71 (7-H_{endo}), 2.58-2.65 (8-*H*) and 3.32 (8-CH_2); 3.32 (8-CH_2) crosspeak with 2.58-2.65 (8-*H*) and 2.73 (8-CH_2); 3.67 (4-H_{endo}) crosspeak with 1.38-1.48 (6-H_{endo}), 3.72-3.79 (5-*H*) and 4.16 (4-H_{exo}); 3.72-3.79 (5-*H*) crosspeak with 1.73-1.81 (7-H_{exo}), 1.82-1.89 (6-H_{exo}), 2.58-2.65 (8-*H*) and 4.16 (4-H_{exo}); 4.16 (4-H_{exo}) crosspeak with 3.67 (4-H_{endo}) and 3.72-3.79 (5-*H*); *m/z* (APCI$^+$) 343.5 (M+NH_4^+, 100%), 321.4 (7), 250.4 (7), 228.6 (23), 202.2 (18), 181.0 (4); *m/z* (ES$^+$) 322.1811, 322.1804 ($C_{21}H_{23}NO_2$ requires 322.1807 for MH$^+$);

Major diastereomer (*exo*) (**114b**): Yield 48mg (16%); R_f 0.48 (40% EtOAc:Petrol); $[\alpha]_D^{22}$ +25.0 (*c* 1.4 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3503w, 1645s (C=O), 1495w, 1446w, 1421m, 1377w, 1319w, 1230w, 1077w, 1030w, 762m, 698s and 665m; δ_H(400 MHz; $CDCl_3$) 1.36-1.57 (2 H, m, 6-H_{endo} and 7-H_{exo}), 1.86-1.92 (1 H, m, 7-H_{endo}), 1.97-2.02 (1 H, m, 6-H_{exo}), 2.10 (3 H, s, 2-*Me*), 2.62-2.70 (1 H, m, 8-*H*), 2.90 (1 H, dd, *J* 8.5 and 13.5, 8-CH_2), 3.23 (1 H, dd, *J* 4.0 and 13.5, 8-CH_2), 3.62-3.69 (2 H, m, 5-*H* and 4-H_{endo}), 4.18 (1 H, m, 4-H_{exo}), 7.10-7.55 (10 H, m, 8-*Ph* and 2-*Ph*); δ_C(100.6 MHz; $CDCl_3$) 24.4 (2-*Me*), 26.0 (C-7), 26.3 (C-6), 37.4 (8-CH_2), 43.9 (C-8), 58.1 (C-5), 70.2 (C-4), 96.2 (C-2), 126.2, 126.3, 128.1, 128.3 and 129.5 (CH aromatic), 139.5 (8-*C* aromatic), 142.2 (2-*C* aromatic), 168.8 (C=O); δ_H(400 MHz COSY; $CDCl_3$) 1.36-1.57 (6-H_{endo} and 7-H_{exo}) crosspeak with 1.86-1.92 (7-H_{endo}), 1.97-2.02 (6-H_{exo}), 2.62-2.70 (8-*H*) and 3.62-3.69 (5-*H* and 4-H_{endo}); 1.86-1.92 (7-H_{endo}) crosspeak with 1.36-1.57 (6-H_{endo} and 7-H_{exo}) and 2.62-2.70 (8-*H*); 1.97-2.02 (6-H_{exo}) crosspeak with 1.36-1.57 (6-H_{endo} and 7-H_{exo}) and 3.62-3. 5-*H* and 4-H_{endo}); 2.62-2.70 (8-*H*) crosspeak with 1.36-1.57 (6-H_{endo} and 7-H_{exo}), 1.86-1.92 (7-H_{endo}), 2.90 (8-CH_2) and 3.23 (8-CH_2); 2.90 (8-CH_2) crosspeak with 2.62-2.70 (8-*H*) and 3.23 (8-CH_2); 3.23 (8-CH_2) crosspeak with 2.62-2.70 (8-H) and 2.90 (8-CH_2); 3.62-3.69 (5-*H* and 4-H_{endo}) crosspeak with 1.36-1.57 (6-H_{endo} and 7-H_{exo}), 1.97-2.02 (6-H_{exo}) and 4.18 (4-H_{exo}); 4.18 (4-H_{exo}) crosspeak with 3.62-3.69 (5-*H* and 4-H_{endo}); δ_H(400 MHz NOESY; $CDCl_3$) 1.36-1.57 (6-H_{endo} and 7-H_{exo}) crosspeak with 2.62-2.70 (8-*H*), 2.90 (8-CH_2) and 3.62-3.69 (5-*H* and 4-H_{endo}); 1.86-1.92 (7-H_{endo}) crosspeak with 2.62-2.70 (8-*H*); 1.97-2.02 (6-H_{exo}) crosspeak with 3.62-3.69 (5-*H* and 4-H_{endo}); 2.62-2.70 (8-*H*) crosspeak with 1.36-1.57 (6-H_{endo} and 7-H_{exo}), 1.86-1.92 (7-H_{endo}), 2.90 (8-CH_2) and 3.23 (8-CH_2); 2.90 8-CH_2) crosspeak with 2.62-2.70 (8-*H*) and 3.23 (8-CH_2); 3.62-3.69 (5-*H* and 4-H_{endo}) crosspeak with 1.36-1.57 (6-H_{endo} and 7-H_{exo}), 1.97-2.02 (6-H_{exo}) and 4. 4-H_{exo}); 4.18 (4-H_{exo}) crosspeak with 3.62-3.69 (5-*H* and 4-H_{endo}); *m/z* (APCI$^+$) 344.5 (M + NH_4^+, 100%), 322.4 (14), 251.2 (4), 228.3 (6), 202.0 (12); *m/z* (ES$^+$) 322.1815 ($C_{21}H_{23}NO_2$ requires 322.1807 for MH$^+$);

(2*S*, 5*S*, 8*RS*)-1-Aza-8-benzyl-8-benzyloxycarbonyl-2-methyl-3-oxa-9-oxo-2-phenyl-bicyclo [4.3.0] nonane (115)

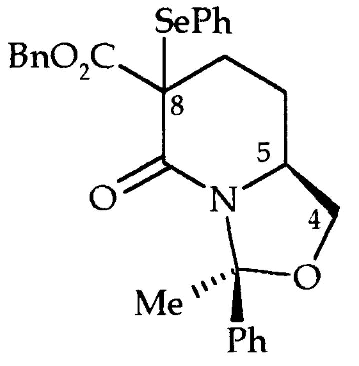


115

Prewashed sodium hydride (8mg, 0.34mmol) was suspended in THF (10ml) and cooled to 0°C under nitrogen. A solution of the lactam **108** (0.112g, 0.31mmol) in

THF (5ml) was then added, and the mixture stirred for 45 minutes. Benzyl bromide (58mg, 0.34mmol) was then added, and the reaction stirred for four hours, until t.l.c. indicated that no starting material was present. The reaction was then quenched with 50ml 1:1 EtOAc:$NH_4Cl_{(sat.\ aq.)}$, extracted with EtOAc (3 x 30ml), dried with brine (25ml) and over $MgSO_4$, and then solvent was removed *in vacuo*. The residue was separated by flash column chromatography on silica gel, eluting with 20% EtOAc: Petrol to give an inseparable mixture of diastereomers (77mg, 55%); R_f 0.23 and 0.18 (20% EtOAc:Petrol); ν_{max}(film)/cm^{-1} 1740s (ester C=O), 1653 (lactam C=O), 1496w, 1423m, 1370m, 1323w, 1223m, 1028m, 763m, 698s, 666s; δ_H(500 MHz; $CDCl_3$) 0.93-1.01, 1.78-1.84, 1.97-2.06 and 2.26-2.33 (4 x 1 H, m, *H*-6 and *H*-7), 2.96 (1 H, d, *J* 13.5, 8-C*H*$_2$ minor diastereomer), 3.24 (1 H, d, *J* 13.5, 8-C*H*$_2$ major diastereomer), 3.31 (1 H, dd, *J* 8.5 and 9.5, 4-H_{endo} major diastereomer), 3.37 (1 H, t, *J* 8.5, 4-H_{endo} minor diastereomer), 3.47 (1 H, d, *J* 13.5, 8-C*H*$_2$ major diastereomer), 3.62-3.69 (1 H, m, 5-*H*), 3.79 (1 H, d, *J* 13.5, 8-C*H*$_2$ minor diastereomer), 3.82 (1 H, dd, *J* 6.5 and 8.5, 4-H_{exo} minor diastereomer), 4.00 (1 H, dd, *J* 6.0 and 8.5, 4-H_{exo} major diastereomer), 5.10 (1 H, d, *J* 12.5, CO_2CH_2 minor diastereomer), 5.19 (1 H, d, *J* 12.0, CO_2CH_2 major diastereomer), 5.23 (1 H, d, *J* 12.0, CO_2CH_2 major diastereomer), 5.34 (1 H, d, *J* 12.5, CO_2CH_2 minor diastereomer), 7.06-7.51 (15 H, m, 2-*Ph* and 8-CH_2*Ph* and 8-CO_2CH_2*Ph*); δ_C(125.8 MHz; $CDCl_3$) 22.9 (*C*-7, minor diastereomer), 23.2 (*C*-7, major diastereomer), 24.5 (2-*Me*), 29.3 (*C*-6, major diastereomer), 29.8 (*C*-6, minor diastereomer), 40.5 (8-CH_2 minor diastereomer), 41.0 (8-CH_2, major diastereomer), 55.8 (*C*-5, major diastereomer), 55.9 (*C*-5, minor diastereomer), 67.3 (8-CO_2CH_2 major diastereomer), 68.2 (8-CO_2CH_2 minor diastereomer), 69.8 (*C*-4), 96.2 (*C*-2), 125.6, 125.9, 126.8, 127.0, 127.9, 128.1, 128.3, 128.4, 128.5, 128.6, 130.3, 130.5, 131.1 (CH aromatic), 135.3 (8-CH_2C aromatic), 136.5 (8-CO_2CH_2-C aromatic), 141.6 (2-C aromatic), 166.1 (lactam C=O), 172.0 (ester C=O); *m/z* (APCI$^+$) 456.2 (MH^+, 100%), 337.3 (7), 336.2 (23), 322.2 (10), 320.2 (4), 292.2 (2), 246.2 (2), 175.0 (2); *m/z* (APCI$^+$) 456.2178 ($C_{29}H_{29}NO_4$ requires 456.2175 for MH^+).

(2S, 5S, 8RS)-1-Aza-8-benzyloxycarbonyl-2-methyl-3-oxa-9-oxo-2-phenyl-8-phenylselenyl-bicyclo [4.3.0] nonane (116)



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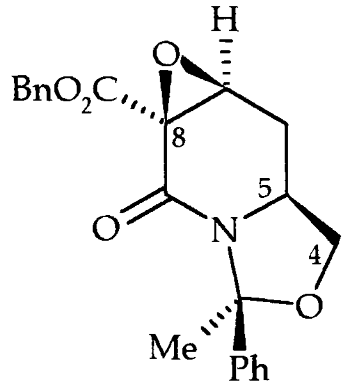
Prewashed sodium hydride (29mg, 1.20mmol) was suspended in THF (10ml) and cooled to 0°C under nitrogen. The lactam **108** (0.291g, 0.80mmol) was dissolved in THF (5ml) and added to the reaction mixture. This mixture was then stirred for 1 hour, after which phenyl selenyl chloride (0.168g, 0.88mmol) in THF (5ml) was added. The reaction was monitored by t. l. c. and quenched after 5 hours by the addition of 50ml 1:1 EtOAc:$NH_4Cl_{(sat.\ aq.)}$. The mixture was then extracted with EtOAc (3 x 25ml), dried with brine (25ml) and over $MgSO_4$, and solvent was removed *in vacuo*. The residue was then separated on silica gel eluting with 20% EtOAc:Petrol to give the products in an inseparable diastereomeric mixture of intense yellow oils (0.291g, 70%); R_f 0.23 and 0.18 (20% EtOAc:Petrol); ν_{max}(film)/cm^{-1} 1736s (ester C=O), 1655 (lactam C=O), 1438m, 1246m, 738w, 698w, 666s; δ_H(500 MHz; $CDCl_3$) 1.47-1.56, 1.81-1.88, 2.13-2.33, 2.25-2.53 (4 x 1 H, m, 6-*H* and 7-*H*), 1.96 (3 H, s, 2-*Me* major diastereomer), 1.99 (3 H, s, 2-*Me* minor diastereomer), 3.31 (1 H, t, *J* 8.5, 4-H_{endo} major diastereomer), 3.37 (1 H, dd, *J* 4.5 and 7.0, 4-H_{endo} minor diastereomer), 3.42-3.50 (1 H, m, 5-*H*), 3.93 (1 H, dd, *J* 4.0 and 7.0, 4-H_{exo} minor diastereomer), 3.98 (1 H, dd, *J* 6.0 and 8.5, 4-H_{exo} major diastereomer), 5.15 (1 H, d, *J* 12.0, 8-CO_2CH_2 major diastereomer), 5.23 (2 H, s, 8-CO_2CH_2), 5.33 (1 H, d, *J* 12.0, 8-CO_2CH_2), 7.12-7.68 (15 H, m, 2-*Ph*, 8-Se*Ph* and 8-CO_2CH_2*Ph*); δ_C(125.8 MHz; $CDCl_3$) 23.2 (C-6 major diastereomer), 24.0 (C-6 minor diastereomer), 24.8 (2-*Me* minor diastereomer), 25.7 (2-*Me* major diastereomer), 30.5 (C-7 major diastereomer), 24.8 (C-7 minor diastereomer), 55.4 (C-5 major diastereomer), 56.9 (C-8 major diastereomer), 57.9 (C-5 minor diastereomer), 60.4 (C-8 minor diastereomer), 67.7 (8-CO_2CH_2 major diastereomer), 67.9 (8-CO_2CH_2 minor diastereomer), 68.7 (*C*-4 minor diastereomer), 69.5 (*C*-4 major diastereomer), 96.6 (C-2 minor diastereomer), 96.9 (C-2 major diastereomer), 125.5, 125.8, 126.1, 126.5, 126.6, 127.9, 128.1, 128.3, 128.5, 128.5, 128.6, 128.7, 128.8, 128.9, 129.2, 129.6, 129.7 (CH aromatic), 135.2 (8-CH_2C), 138.3 (8-SeC major diastereomer), 138.4 (8-SeC minor diastereomer), 140.9 (2-*C* aromatic, minor diastereomer), 141.9 (2-*C* aromatic, major diastereomer), 163.3 (C=O lactam, minor diastereomer), 164.7 (C=O lactam, major diastereomer), 169.4 (ester C=O, major diastereomer), 170.7 (ester C=O, minor diastereomer); *m/z* ($APCI^+$) 521.8 (MH^+, 100%), 519.6 (62), 388 (14), 366 (57), 246.1 (18), 232.1 (15), 155.9 (12); *m/z* ($APCI^+$) 522.1181 ($C_{28}H_{27}NO_4Se$ requires 522.1184 for MH^+).

7.4 Experimental for chapter 4

(-)-(2*S*, 5*S*, 7*S*, 8*S*)-1-Aza-8-benzyloxycarbonyl-7, 8-epoxy-2-methyl-3-oxa-9-oxo-2-phenyl-bicyclo [4.3.0] nonane (126)

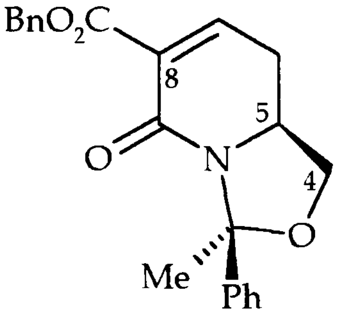


126

To a solution of a mixture of the selenides **116** (64mg, 0.12mmol) in DCM (12.5ml) was added hydrogen peroxide (70mg, 0.61mml). The mixture was then stirred vigorously for one hour at 30°C. The reaction was quenched with $NaHCO_{3(sat.\ aq.)}$ (5ml), extracted with DCM (3 x 10ml), and solvent was removed *in vacuo*. The residue was purified using flash column chromatography, eluting with 40% EtOAc:Petrol to yield the product as a colourless oil (46mg, 99%); R_f 0.28 (40% EtOAc:Petrol); $[\alpha]_D^{25}$ -77.5 (*c* 0.31 in $CHCl_3$); ν_{max}(film)/cm^{-1} 1753s (ester C=O), 1669s (lactam C=O), 1496w, 1445m, 1372m, 1333w, 1300w, 1268m, 1200w, 1165m, 1135w, 1098m, 1027m, 987w, 754m, 698m, 632w; δ_H(500 MHz; $CDCl_3$) 1.91 (1 H, dd, *J* 11.0 and 14.5, 6-H_{endo}), 2.09 (3 H, s, 2-*Me*), 2.60 (1 H, ddd, *J* 3.5, 4.0 and 11.0, 6-H_{exo}), 3.43 (1 H, t, *J* 8.5, 4-H_{endo}), 3.86 (1 H, d, *J* 3.5, 7-*H*), 3.97-4.04 (1 H, m, 5-*H*), 4.18 (1 H, dd, *J* 6.0 and 8.5, 4-H_{exo}), 5.36 (2 H, s, 8-CO_2CH_2), 7.32-7.54 (10 H, m, 2-*Ph* and 8-CO_2CH_2Ph); δ_C(125.8 MHz; $CDCl_3$) 26.0 (2-*Me*), 26.6 (C-6), 51.7 (C-5), 58.1 (C-8), 58.6 (C-7), 68.2 (C-4), 68.8 (8-CO_2CH_2), 98.0 (C-2), 126.1, 126.2, 128.7, 128.8, 128.9, 129.1 (CH aromatic), 135.5 (8-*C* aromatic), 141.4 (2-*C* aromatic), 160.9 (lactam C=O), 165.7 (ester C=O); n. O. e. experiment (500 MHz; $CDCl_3$) Irradiation at δ_H 1.90 gave enhancements at δ_H 2.60 (6-H_{exo}) (22.8%), 3.40 (4-H_{endo}) (5%), 3.85 (7-*H*) (6.4%), 4.00 (5-*H*) (2.5%); Irradiation at δ_H 2.10 gave enhancement at δ_H 4.00 (5-*H*) (3%); Irradiation at δ_H 2.60 gave enhancements at δ_H 1.90 (6-H_{endo}) (26.4%), 3.85 (7-*H*) (9%), 4.00 (5-*H*) (9%); Irradiation at δ_H 3.40 gave enhancements at δ_H 4.00 (5-*H*) (2%), 4.20 (4-H_{exo}) (22.5%); Irradiation at δ_H 3.80 gave enhancements at δ_H 1.90 (6-H_{endo}) (2.7%), 2.60 (6-H_{exo}) (3.4%); Irradiation at δ_H 4.20 gave enhancements at δ_H 3.40 (4-H_{endo}) (26.4%), 4.00 (5-*H*) (11.4%); Irradiation at δ_H 4.00 gave enhancements at δ_H 2.60 (6-H_{exo}) (4.4%) and 4.20 (4-H_{exo}) (4.4%); *m/z* (APCI$^+$) 380.2 (MH$^+$, 100%), 362.1 (4), 260.1 (2), 246.1 (6), 228.1 (7), 211.1 (5), 178.0 (2), 170.0 (7), 125.8 (17); *m/z* (ES$^+$) 380.1499 ($C_{22}H_{21}NO_5$ requires 380.1498 for MH$^+$).

Repeating the experiment with 1.0 eq of H_2O_2 gave a 1:1 mixture of epoxide and starting material.

(-)-(2*S*, 5*S*)-1-Aza-8-benzyloxycarbonyl-2-methyl-3-oxa-9-oxo-2-phenyl-bicyclo [4.3.0] non-7-ene (122)



122

First method

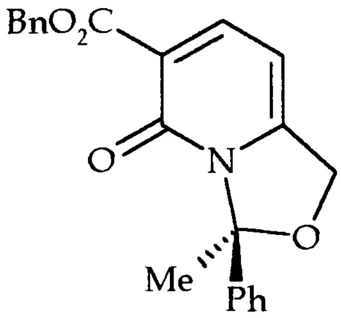
To a solution of the mixed selenides **116** (0.040g, 0.08mmol) in DCM (5ml) was added $NaBO_3.4H_2O$ (0.024g, 0.15mmol) and acetic anhydride (0.025g, 0.25mmol). The reaction was stirred for four hours and then quenched for four hours with $FeSO_{4(sat.\ aq.)}$ (5ml). The mixture was extracted with DCM (3 x 5ml) and solvent was removed *in vacuo*. No products were observed by NMR of the crude material.

Second method

To a solution of the mixed selenides **116** (0.950g, 1.8mmol) in methanol (50ml) was added a solution of sodium periodate (0.781g, 3.6mmol) and sodium bicarbonate (0.153g, 1.8mmol) in water (30ml). The mixture was stirred for one hour, when t. l. c. analysis suggested that reaction was complete. A 1:1 mixture of $NH_4Cl_{(sat.\ aq.)}$ and

EtOAc (30ml) was added, and the organic layer separated. The aqueous layer was extracted with EtOAc (3 x 25ml), the organic layers combined and dried with brine (25ml) and over $MgSO_4$, and solvent was removed *in vacuo*. The residue was separated by column chromatography eluting with 40% EtOAc:Petrol to give the product as a colourless oil (0.514g, 82%); R_f 0.24 (40% EtOAc:Petrol); $[\alpha]_D^{25}$ -69.9 (*c* 1.09 in $CHCl_3$); ν_{max}(film)/cm^{-1} 1735s (ester C=O), 1666s (lactam C=O), 1617w, 1555w, 1494w, 1423m, 1374m, 1332w, 1290w, 1246s br, 1183w, 1153m, 1077m, 1051m, 1027m, 985w, 914w, 874w, 796w, 765m, 738m, 697m, 668w, 648w; δ_H(500 MHz; $CDCl_3$) 2.10 (3 H, s, 2-*Me*), 2.27-2.33 (1 H, m, 6-H_{endo}), 2.50-2.56 (1 H, m, 6-H_{exo}), 3.46 (1 H, t, *J* 9.0, 4-H_{endo}), 4.06-4.13 (1 H, m, 5-*H*), 4.16 (1 H, dd, *J* 6.0 and 9.0, 4-H_{exo}), 5.25-5.32 (2 H, m, 8-CO_2CH_2), 7.26-7.57 (11 H, m, 7-*H*, 2-*Ph* and 8-CO_2CH_2Ph); δ_C(125.8 MHz; $CDCl_3$) 26.1 (2-*Me*), 27.2 (*C*-6), 55.4 (*C*-5), 66.8 (*C*-4), 68.4 (8-CO_2CH_2), 96.5 (*C*-2), 125.6, 127.9, 128.0, 128.1, 128.2, 128.4 (CH aromatic), 131.1 (*C*-8), 135.5 (8-CO_2CH_2C aromatic), 142.0 (2-*C* aromatic), 145.7 (*C*-7), 158.4 (C=O lactam), 163.5 (C=O ester); *m/z* (APCI$^+$) 364.2 (MH$^+$, 100%), 362.2 (19), 346.1 (3), 288.1 (3), 254.1 (4), 244.2 (6), 228.1 (3), 168.0 (3), 154.0 (7); *m/z* (ES$^+$) 364.1552 ($C_{22}H_{21}NO_4$ requires 364.1549 for MH$^+$).

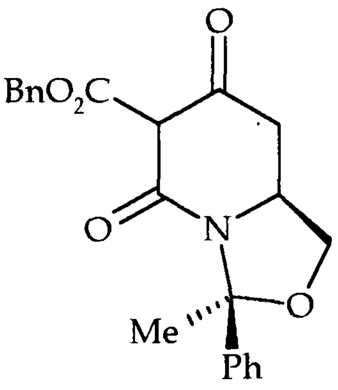
(-)-(2*S*)-1-Aza-8-benzyloxycarbonyl-2-methyl-3-oxa-9-oxo-2-phenyl-bicyclo [4.3.0] non-5, 7-diene (127)



127

To a solution of the mixed selenides **116** (1.420g, 2.7mmol) in methanol (50ml) was added a solution of sodium periodate (1.167g, 5.5mmol) in water (30ml). The mixture was stirred at room temperature for three hours, and then worked up with the addition of 50ml of a 1:1 mixture of EtOAc and $NH_4Cl_{(sat.\ aq.)}$. The aqueous layer was extracted with EtOAc (3 x 25ml), dried with brine (20ml) and over $MgSO_4$. Solvent was removed *in vacuo* and the residue separated by flash column chromatography (40% EtOAc:Petrol) to give a colourless oil (98mg, 10%) that decomposed on standing to a brown gum. R_f 0.16 (40% EtOAc:Petrol); $[\alpha]_D^{22}$ -212.0 (*c* 1.13 in $CHCl_3$); ν_{max}(film)/cm^{-1} 1734s (ester C=O), 1698m (C=C), 1667s (lactam C=O), 1605m, 1554s, 1496w, 1449m, 1426m, 1373m, 1317m, 1269m, 1169m, 1103s, 1043m, 1021m 912w, 879w, 151w, 764m, 735m, 697s, 666m; δ_H(400 MHz; $CDCl_3$) 2.30 (3 H, s, 2-*Me*), 4.94 (1 H, dd, *J* 1.0 and 14.5, 4-*H*), 5.07 (1 H, dd, *J* 1.0 and 14.5, 4-*H*), 5.28-5.38 (2 H, m, 8-CO_2CH_2), 6.12 (1 H, dt, *J* 7.5 and 1.0, 6-*H*), 7.18-7.54 (10 H, m, 2-*Ph* and 8-CO_2CH_2*Ph*), 8.22 (1 H, d, *J* 7.5, 7-*H*); δ_C(100.6 MHz; $CDCl_3$) 25.1 (2-*Me*), 66.6 (*C*-4), 68.3 (8-CO_2CH_2), 96.8 (C-6), 103.3 (C-2), 119.6 (C-5), 125.8, 127.8, 128.2, 128.4, 128.6, 129.0 (CH aromatic), 136.1 (2-C aromatic), 139.2 (8-CO_2CH_2C aromatic), 146.2 (C-7), 150.5 (C-8), 157.4 (C=O lactam), 164.2 (C=O ester); *m/z* 384.3 (M+Na, 33%), 362.0 (MH^+, 100), 255.4 (3), 253.5 (20), 113.7 (6); *m/z* (ES^+) 384.1210 ($C_{22}H_{19}NO_4$ requires 384.1212 for M+Na).

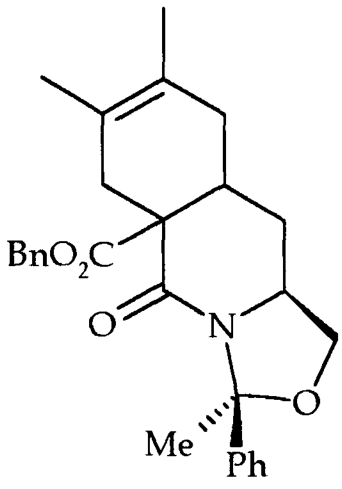
Attempted generation of β-dicarbonyl compound **128**



128

To a solution of the mixed selenides **116** (37mg, 0.07mmol) in THF (50ml) was added H_2O_2 (30%vol.) (0.121g, 1.07mmol). The mixture was stirred for 16 hours, and then quenched with the addition of 50ml 1:1 EtOAc:$NH_4Cl_{(sat.\ aq.)}$, extracted with EtOAc (3 x 20ml) and dried over $MgSO_4$. Solvent was removed *in vacuo* and the residue separated by flash column chromatography. No product was isolated.

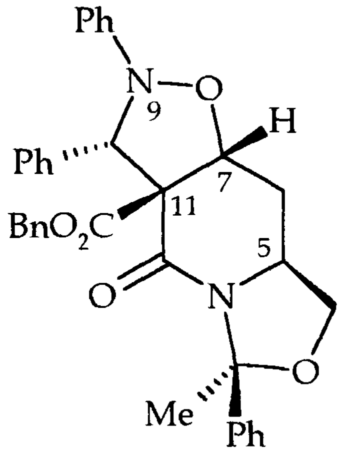
Attempted cycloaddition



129

To a solution of the enone **122** (78mg, 0.21mmol) in toluene (12.5ml) was added 2,3-dimethyl-1,3-butadiene (0.106g, 1.29mmol). The mixture was heated to reflux for 64 hours, and then solvent was removed *in vacuo*. Only starting material was isolated.

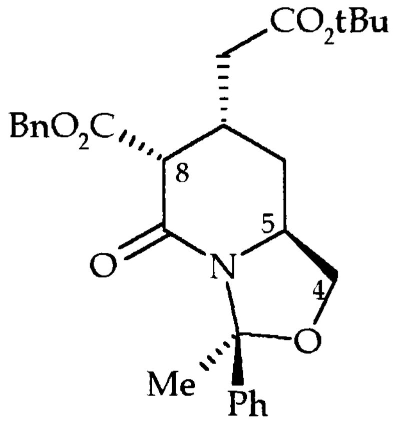
(-)-(2*S*, 5*S*, 7*R*, 8*S*, 10*S*)-8-Benzyloxycarbonyl-1, 9-diaza-3, 8-dioxa-2, 10-diphenyl-2-methyl-9-(*N*-phenyl)-9-oxo-tricyclo $[7.3^{1,5}.0^{7,11}]$ dodecane (**129**)



132

To a solution of the enone **122** (0.261g, 0.72mmol) in toluene (50ml) was added N, α-diphenylnitrone (0.283g, 1.4mmol). The mixture was heated to reflux for 24 hours, and then solvent was removed *in vacuo*. The residue was separated by column chromatography, eluting with 20% EtOAc:Petrol to give the product as a colourless solid predominantly (>95% by NMR) of one diastereomer (70mg, 17%); R_f 0.25 (20% EtOAc:Petrol); $[\alpha]_D^{22}$ -106.5 (*c* 0.82 in $CHCl_3$); ν_{max}(film)/cm^{-1} 1751s (ester C=O), 1660s (lactam C=O), 1598m, 1490m, 1428m, 1424m, 1374m, 1354w, 1332m, 1250s, 1207s, 1139w, 1077m, 1029m, 968w, 909m, 792w, 757m, 733s, 697s, 645m; δ_H(400 MHz; $CDCl_3$) 1.16 (3 H, s, 2-*Me*), 1.97 (1 H, ddd, *J* 3.0, 11.0 and 14.5, 6-H_{endo}), 2.45 (1 H, dd, *J* 2.0 and 14.5, 6-H_{exo}), 3.23-3.28 (1 H, m, 4-H_{endo}), 3.98-4.08 (2 H, m, 5-*H* and 4-H_{exo}), 4.99 (1 H, dd, *J* 2.0 and 3.0, 7-*H*), 5.12 (1 H, d, *J* 12.5, 8-CO_2CH_2), 5.17 (1 H, d, *J* 12.5, 8-CO_2CH_2), 6.25 (1 H, s, 10-*H* minor diastereomer) 6.31 (1 H, s, 10-*H* major diastereomer), 6.96-7.90 (20 H, m, 2-*Ph*, 8-CO_2CH_2*Ph*, 10-*Ph*, N*Ph*); δ_C(100.6 MHz; $CDCl_3$) 24.0 (2-*Me* major diastereomer), 25.6 (2-*Me* minor diastereomer), 28.4 (*C*-6 major diastereomer), 29.5 (*C*-6 minor diastereomer), 52.7 (*C*-5 major diastereomer), 54.2 (*C*-5 minor diastereomer), 67.4 (*C*-4 minor diasteromer), 67.7 (*C*-4 major diastereomer), 68.1 (11-CO_2CH_2 major diastereomer), 68.3 (11-CO_2CH_2 minor diastereomer) 71.6 (*C*-11 minor diastereomer), 72.7 (*C*-11 major diastereomer), 73.1 (*C*-7 minor diastereomer), 73.5 (*C*-7 major diastereomer), 78.4 (*C*-10 minor diastereomer), 80.2 (*C*-10 major diastereomer), 97.0 (*C*-2 major diastereomer), 97.4 (*C*-2 minor diastereomer), 114.2, 115.9, 116.5, 122.0, 122.7, 125.5, 125.8, 127.7, 127.9, 128.0, 128.1, 128.2, 128.3, 128.5, 128.6, 129.0 (CH aromatic), 135.0 (8-CO_2CH_2*C* aromatic), 136.8 (11-*C* aromatic), 140.2 (2-*C* aromatic major diastereomer), 141.0 (2-*C* aromatic minor diastereomer), 148.4 (N-*C* aromatic), 161.5 (*C*=O lactam major diastereomer), 163.4 (*C*=O lactam minor diastereomer), 166.5 (*C*=O ester minor diastereomer), 169.2 (*C*=O ester major diastereomer); δ_H(400 MHz COSY; $CDCl_3$) 1.97 (6-H_{endo}) crosspeak with 2.45 (6-H_{exo}), 3.98-4.08 (5-*H* and 4-H_{exo}) and 4.99 (7-*H*); 2.45 (6-H_{exo}) crosspeak with 1.97 (6-H_{endo}), 3.98-4.08 (5-*H* and 4-H_{exo}) and 4.99 (7-*H*); 3.23-3.28 (4-H_{endo}) crosspeak with 3.98-4.08 (5-*H* and 4-H_{exo}); 3.98-4.08 (5-*H* and 4-H_{exo}) crosspeak with 1.97 (6-H_{endo}), 2.45 (6-H_{exo}) and 3.23-3.28 (4-H_{endo}); δ_H(400 MHz NOESY; $CDCl_3$) 1.97 (6-H_{endo}) crosspeak with 2.45 (6-H_{exo}), 3.23-3.28 (4-H_{endo}) and 4.99 (7-*H*); 2.45 (6-H_{exo}) crosspeak with 1.97 (6-H_{endo}), 3.98-4.08 (5-*H* and 4-H_{exo}) and 4.99 (7-*H*); 3.23-3.28 (4-H_{endo}) crosspeak with 3.98-4.08 (5-*H* and 4-H_{exo}); 3.98-4.08 (5-*H* and 4-H_{exo}) crosspeak with 2.45 (6-H_{exo}) and 3.23-3.28 (4-H_{endo}); 4.99 (7-*H*) crosspeak with 1.97 (6-H_{endo}), 2.45 (6-H_{exo}) and 6.31 (10-*H*); 6.31 (10-*H*) crosspeak with 4.99 (7-*H*); *m/z* (CI) 561.2 (MH^+, 6%), 364.3 (84), 348.3 (4), 286.3 (2), 230.4 (6), 198.3 (93), 182.3 (100), 138.3 (4), 105.2 (5), 94.3 (8); *m/z* (ES$^+$) 561.2383 ($C_{35}H_{32}N_2O_5$ requires 561.2389 for MH$^+$).

(-)-(2*S*, 5*S*, 7*S*, 8*R*)-1-Aza-8-benzyloxycarbonyl-7-(*tert*-butyloxycarbonylmethyl)-2-methyl-3-oxa-9-oxo-2-phenyl-bicyclo [4.3.0] nonane (143)

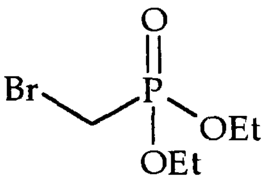


143

To a solution of α-bromo *tert*-butyl acetate (0.250g, 1.3mmol) and iodine (0.022g, 0.09mmol) in THF (11ml) was added zinc (0.139g, 2.1mmol). This mixture was heated to 35°C in an ultrasound bath for 15 minutes. The suspension was then cooled to 0°C in an ice bath, and DMPU (1ml) was added. A solution of the enone **122** (0.155g, 0.43mmol) in THF (2.5ml) was then added by syringe. The reaction mixture was then returned to the ultrasound bath for a further 15 minutes. The reaction was then quenched with ice/water (2ml), and sufficient $NH_4Cl_{(sat.\ aq.)}$ was added to ensure that the precipitate dissolved. The mixture was extracted with DCM (3 x 15ml), the organic fractions were recombined, and solvent removed *in vacuo*. The residue was purified by flash column chromatography eluting initially with 20% EtOAc:Petrol and increasing the polarity gradually to 30% EtOAc:Petrol, to give the product as a colourless oil (0.155g, 76%); R_f 0.48 (40% EtOAc:Petrol); $[\alpha]_D^{22}$ -70.5 (*c* 0.85 in $CHCl_3$); ν_{max}(film)/cm^{-1} 1728s, 1666s, 1440w, 1366m, 1250m, 1233m, 1153s, 1020w, 666w; δ_H(400 MHz; $CDCl_3$) 1.43 (9 H, s, 7-CH_2CO_2*tBu*), 1.84-1.89 (1 H, m, 6-H_{exo}), 1.94-2.02 (1 H, m, 6-H_{endo}), 2.03 (3 H, s, 2-*Me*), 2.33 (1 H, dd, *J* 8.0 and 15.5, 7-CH_2), 2.44 (1 H, dd, *J* 5.5 and 15.5, 7-CH_2), 2.93-2.97 (1 H, m, 7-*H*), 3.42 (1 H, t, *J* 9.0, 4-H_{endo}), 3.47 (1 H, d, *J* 7.5, 8-*H*), 3.95-4.07 (1 H, m, 5-*H*), 4.14 (1 H, dd, *J* 5.5 and 9.0, 4-H_{exo}), 5.23 (1 H, d, *J* 12.5, 8-CO_2CH_2), 5.28 (1 H, d, *J* 12.5, 8-CO_2CH_2), 7.26-7.50 (10 H, m, 2-*Ph* and 8-CO_2CH_2*Ph*); δ_C(100.6 MHz; $CDCl_3$) 25.8 (2-*Me*), 28.0 (CMe_3), 28.6

(C-6), 32.0 (C-7), 39.8 (7-CH$_2$), 54.1 (C-5), 54.3 (C-8), 67.2 (C-4), 69.1 (8-CO$_2$CH$_2$), 81.4 (CMe$_3$), 96.6 (C-2), 125.5, 125.7, 128.1, 128.2, 128.3, 128.6 (CH aromatic), 135.5 (8-CO$_2$CH$_2$C aromatic), 141.4 (2-C aromatic), 163.9 (C=O lactam), 169.7 (C=O ester), 170.4 (C=O ester); δ_H(400 MHz COSY; CDCl$_3$) 1.84-1.89 (6-H_{exo}) crosspeak with 1.94-2.02 (6-H_{endo}), 2.93-2.97 (7-*H*) and 3.95-4.07 (5-*H*); 1.94-2.02 (6-H_{endo}) crosspeak with 1.84-1.89 (6-H_{exo}), 2.93-2.97 (7-*H*) and 3.95-4.07 (5-*H*); 2.33 (7-CH_2) crosspeak with 2.44 (7-CH_2) and 2.93-2.97 (7-*H*); 2.44 (7-CH_2) crosspeak with 2.33 (7-CH_2) and 2.93-2.97 (7-*H*); 2.93-2.97 (7-*H*) crosspeak with 1.84-1.89 (6-H_{exo}), 1.94-2.02 (6-H_{endo}), 2.33 (7-CH_2), 2.44 (7-CH_2) and 3.47 (8-*H*); 3.42 (4-H_{endo}) crosspeak with 3.95-4.07 (5-*H*) and 4.14 (4-H_{exo}); 3.47 (8-*H*) crosspeak with 2.93-2.97 (7-*H*); 3.95-4.07 (5-*H*) crosspeak with 1.84-1.89 (6-H_{exo}), 1.94-2.02 (6-H_{endo}), 3.42 (4-H_{endo}) and 4.14 (4-H_{exo}); 4.14 (4-H_{exo}) crosspeak with 3.42 (4-H_{endo}) and (5-*H*); 5.23 (8-CO$_2$CH_2) crosspeak with 5.28 (8-CO$_2$CH_2); 5.28 (8-CO$_2$CH_2) crosspeak with 5.23 (8-CO$_2$CH_2); δ_H(500 MHz NOESY; CDCl$_3$) 1.84-1.89 (6-H_{exo}) crosspeak with 1.94-2.02 (6-H_{endo}), 2.33 (7-CH_2), and 3.95-4.07 (5-*H*); 1.94-2.02 (6-H_{endo}) crosspeak with 1.84-1.89 (6-H_{exo}), 2.93-2.97 (7-*H*), 3.42 (4-H_{endo}); 2.33 (7-CH_2) crosspeak with 2.44 (7-CH_2), 2.93-2.97 (7-*H*), 3.47 (8-*H*) and 3.95-4.07 (5-*H*); 2.44 (7-CH_2) crosspeak with 2.33 (7-CH_2), 2.93-2.97 (7-*H*), 3.47 (8-*H*) and 3.95-4.07 (5-*H*); 2.93-2.97 (7-*H*) crosspeak with 1.84-1.89 (6-H_{exo}), 1.94-2.02 (6-H_{endo}), 2.33 (7-CH_2), 2.44 (7-CH_2) and 3.47 (8-*H*); 3.42 (4-H_{endo}) crosspeak with 1.94-2.02 (6-H_{endo}) and 4.14 (4-H_{exo}); 3.47 (8-*H*) crosspeak with 2.33 (7-CH_2), 2.44 (7-CH_2) and 2.93-2.97 (7-*H*); 3.95-4.07 (5-*H*) crosspeak with 1.84-1.89 (6-H_{exo}), 2.33 (7-CH_2) and 2.44 (7-CH_2); 4.14 (4-H_{exo}) crosspeak with 3.42 (4-H_{endo}) and 3.95-4.07 (5-*H*); *m/z* (APCI$^+$) 480.1 (MH$^+$, 100%), 432.2 (6), 425.4 (10), 424.2 (73), 376.2 (9), 316.2 (4), 304.1 (2); *m/z* (APCI$^+$) 480.2381 ($C_{28}H_{33}NO_6$ requires 480.2386 for MH$^+$).

Attempted preparation of α-bromo diethyl methanephosphonate



First attempt

To a solution of diethyl methane phosphonate (0.5g, 3.29mmol) in $CHCl_3$ (50ml) was added N-bromosuccinimide (0.643g, 3.62 mmol) and the mixture was heated to 60°C for one hour. Benzoyl peroxide (70%) (0.102g, 0.30mmol) was then added and the mixture was returned to reflux. The reaction was monitored by NMR analysis of aliquots of the reaction mixture, but no reaction was observed after five days.

Second attempt

To a solution of diethyl methane phosphonate (0.5g, 3.3mmol) in THF (30ml) cooled to -78°C under nitrogen was added sBuLi (3.0ml, 3.9mmol). After fifteen minutes NBS (0.643g, 3.6mmol) was added. The reaction was then stirred for one hour. No reaction was observed.

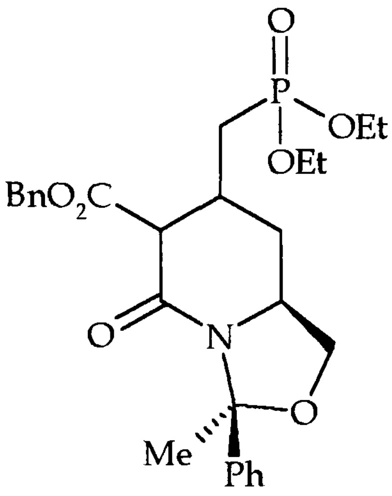
Third attempt

To a solution of diethyl methane phosphonate (0.5g, 3.3 mmol) in DCM (10ml) was added pyridine (0.260g, 3.3 mmol), bromine (0.262g, 1.6mmol) and NBS (0.643g, 3.3mmol). The mixture was stirred for eight days, but NMR analysis showed no evidence of the desired product.

Fourth attempt

Diisopropylamine (0.244g, 2.9mmol) was dissolved in THF (5ml) and cooled to -78°C. nBuLi (1.2ml, 2.9mmol) was added, and the mixture stirred for 10 minutes. Diethyl methane phosphonate (0.367g, 2.4mmol) was then added, and the mixture stirred for a further 10 minutes. The enolate solution was then transferred by cannula into a solution of NBS (0.515g, 2.9mmol) and stirred for one hour. Solvent was removed *in vacuo*, and NMR analysis showed a characteristic doublet at δ 3.31 (*J* 10.0 Hz), but integrating to only a small fraction of the mass of material (13%).

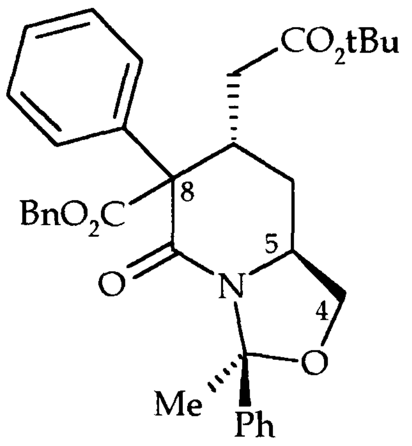
Attempted *in situ* generation of phosphono-Reformatsky reagent



144

To a solution of diethyl iodomethyl phosphonate (0.725g, 2.6mmol) and iodine (0.044g, 018mmol) in THF (20ml) was added zinc (0.284g, 4.3mmol), and the mixture was agitated in an ultrasound bath at 35°C for 15 minutes. The reaction was then cooled to 0°C, and DMPU (2ml) was added. The enone **122** (0.316g, 0.87mmol) in THF (2ml) was then added, and the mixture was returned to the ultrasound bath for 15 minutes. The reaction was then quenched with ice/water (2ml), and sufficient $NH_4Cl_{(sat.\ aq.)}$ was added to ensure that the precipitate dissolved. The mixture was extracted with DCM (3 x 20ml), and solvent was removed *in vacuo*. NMR and mass spectrometry indicated that no reaction had occurred.

(2*S*, 5*S*, 7*S*)-1-Aza-8-benzyloxycarbonyl-7-(*tert*-butyloxycarbonylmethyl)-2, 8-diphenyl-2-methyl-3-oxa-9-oxo-bicyclo [4.3.0] nonane (149)

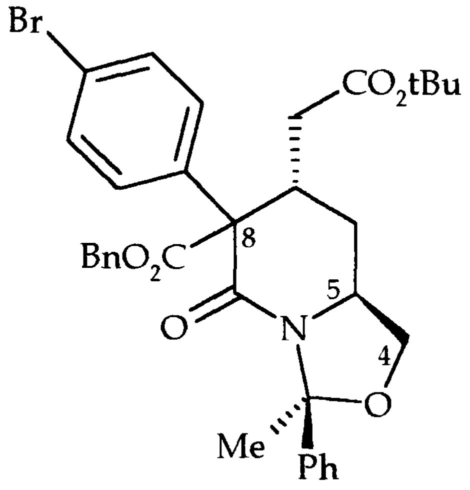


149

To a solution of the Reformatsky adduct **143** (61mg, 0.1mmol) in $CHCl_3$ (10ml) was added phenyl lead triacetate (0.117g, 0.3mmol) and pyridine (0.050g, 0.6mmol). The mixture was heated to reflux for 72 hours, and then filtered through Celite®, washed with 10% H_2SO_4 (5ml), extracted with $CHCl_3$ (3 x 15ml) and dried with brine (10ml) and over $MgSO_4$. Solvent was removed *in vacuo*, and the residue purified by flash column chromatography, eluting with 30% EtOAc:Petrol to give the product as a colourless oil as an inseparable mixture of two diasteromers in a 3:1 ratio (estimated from NMR) (0.049g, 69%); R_f 0.26 (40% EtOAc:Petrol); $[\alpha]_D^{22}$ -23.5 (*c* 1.6 in $CHCl_3$); ν_{max}(film)/cm^{-1} 1729s (ester C=O), 1681s (lactam C=O), 1497w, 1448w, 1397w, 1369m, 1324w, 1216m, 1152s, 1082w, 1040w, 1029w, 961w, 913w, 878w, 847w, 763m, 730w, 697s; δ_H(400 MHz; $CDCl_3$) 1.37 (9 H, s, C*Me*$_3$ major diastereomer), 1.41 (9 H, s, C*Me*$_3$ minor diastereomer), 1.74-1.87 (1 H, m, 6-*H*), 1.88 (3 H, s, 2-*Me* major diastereomer), 1.99 (3 H, s, 2-*Me* minor diastereomer), 2.02-2.17 (2 H, m, 6-*H* and 7-C*H*$_2$), 2.85 (1 H, dd, *J* 11.0 and 16.5, 7-C*H*$_2$), 2.93-2.98 (1 H, m, 7-*H*), 3.40 (1 H, t, *J* 8.5, 4-H_{endo} major diastereomer), 3.52-3.60 (1 H, m, 5-*H* major diastereomer), 3.77 (1 H, t, *J* 8.0, 4-H_{endo} minor diastereomer), 3.82-3.90 (1 H, m, 5-*H* minor diastereomer), 3.99 (1 H, dd, *J* 5.5 and 8.5, 4-H_{exo} major diastereomer), 4.07 (1 H, dd, *J* 6.5 and 8.0, 4-H_{exo} minor diastereomer), 5.18 (1 H, d, *J* 11.5, 8-CO$_2$C*H*$_2$ major diastereomer), 5.23-5.31 (2 H, m, 8-CO$_2$C*H*$_2$ minor diastereomer), 5.55 (1 H, d, *J* 11.5, 8-CO$_2$C*H*$_2$ major diastereomer), 7.12-7.67 (15 H, m, 2-*Ph*, 8-*Ph*, 8-CO$_2$CH$_2$*Ph*); δ_C(100.6 MHz; $CDCl_3$) 24.8 (2-*Me* minor diastereomer), 25.1 (2-*Me* major diastereomer), 27.8 (C*Me*$_3$ minor diastereomer), 28.0

(CMe_3 major diastereomer), 28.4 (*C*-6 major diastereomer), 29.7 (*C*-6 minor diastereomer), 37.8 (7-CH_2 major diastereomer), 37.9 (7-CH_2 minor diastereomer), 38.9 (*C*-7 major diastereomer), 40.1 (*C*-7 minor diastereomer), 52.1 (*C*-5 minor diastereomer), 53.1 (*C*-5 major diastereomer), 65.7 (*C*-8 major diastereomer), 66.0 (*C*-8 minor diastereomer), 67.6 (8-CO_2CH_2), 70.1 (*C*-4 major diastereomer), 70.5 (*C*-4 minor diastereomer), 80.6 (CMe_3 major diastereomer), 81.1 (CMe_3 minor diastereomer), 96.5 (*C*-2), 125.3, 125.4, 125.5, 126.4, 127.6, 127.9, 128.0, 128.1, 128.2, 128.3, 128.5, 128.6, 128.8, 129.2 (CH aromatic), 134.7 (2-*Ph*), 136.0 (8-*Ph* major diastereomer), 136.1 (8-*Ph* minor diastereomer), 141.8 (8-CO_2CH_2C minor diastereomer), 142.2 (8-CO_2CH_2C major diastereomer), 166.5 (C=O lactam), 169.7 (8-C=O major diastereomer), 170.2 (8-C=O minor diastereomer), 172.0 (7-CH_2C=O); δ_H(400 MHz COSY; $CDCl_3$) 1.74-1.87 (6-*H*) crosspeak with 2.02-2.17 (6-*H* and 7-CH_2), 2.93-2.98 (7-*H*) and 3.52-3.60 (5-*H* major diastereomer); 2.02-2.17 (6-*H* and 7-CH_2) crosspeak with 1.74-1.87 (6-*H*), 2.85 (7-CH_2), 2.93-2.98 (7-*H*) and 3.52-3.60 (5-*H* major diastereomer); 2.85 (7-CH_2) crosspeak with 2.02-2.17 (6-*H* and 7-CH_2) and 2.93-2.98 (7-*H*); 2.93-2.98 (7-*H*) crosspeak with 1.74-1.87 (6-*H*), 2.02-2.17 (6-*H* and 7-CH_2), 2.85 (7-CH_2); 3.40 (4-H_{endo} major diastereomer) crosspeak with 3.52-3.60 (5-*H* major diastereomer) and 3.99 (4-H_{exo} major diastereomer); 3.52-3.60 (5-*H* major diastereomer) crosspeak with 1.74-1.87 (6-*H*), 2.02-2.17 (6-*H* and 7-CH_2), 3.40 (4-H_{endo} major diastereomer) and 3.99 (4-H_{exo} major diastereomer); 3.99 (4-H_{exo} major diastereomer) crosspeak with 3.40 (4-H_{endo} major diastereomer) and 3.52-3.60 (5-*H* major diastereomer); *m/z* ($APCI^+$) 556.4 (MH^+, 87%), 522.1 (2), 500.2 (100), 458.2 (3), 392 (2), 380.2 (6), 186.0 (7), 113.9 (43); *m/z* (ES^+) 556.2694 ($C_{34}H_{37}NO_6$ MH^+ requires 556.2699).

(2*S*, 5*S*, 7*S*)-1-Aza-8-benzyloxycarbonyl-8-(*p*-bromophenyl)-7-(*tert*-butyloxycarbonylmethyl)-2-methyl-3-oxa-9-oxo-8-phenyl-bicyclo [4.3.0] nonane (150)

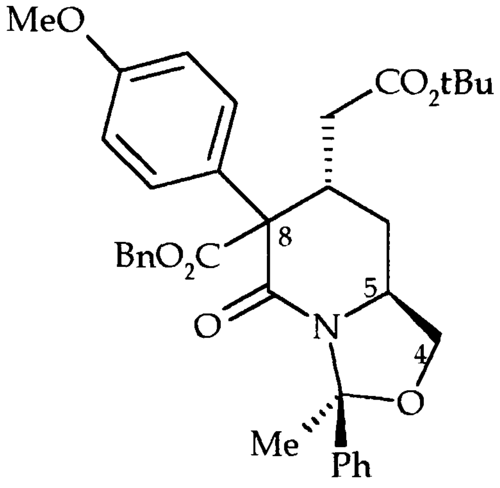


150

To a solution of the Reformatsky adduct **143** (27mg, 0.05mmol) in $CHCl_3$ (10ml) was added bromophenyl lead triacetate (61mg, 0.1mmol) and pyridine (22mg, 0.28mmol). The mixture was heated to reflux for 72 hours, and then filtered through Celite®, washed with 10% H_2SO_4 (5ml), extracted with $CHCl_3$ (3 x 15ml) and dried with brine (10ml) and over $MgSO_4$. Solvent was removed *in vacuo*, and the residue purified by flash column chromatography, eluting with 30% EtOAc:Petrol to give the product as a colourless oil as an inseparable mixture of two diasteromers in a 5:1 ratio (estimated from NMR) (0.033g, 93%); R_f 0.30 (40% EtOAc:Petrol); $[\alpha]_D^{22}$ -12.9 (*c* 0.41 in $CHCl_3$); ν_{max}(film)/cm^{-1} 1732s (C=O ester), 1684s (C=O lactam), 1654m, 1616w, 1559m, 1540m, 1522w, 1507m, 1491m, 1473m, 1457m, 1419m, 1397m, 1369m, 1325m, 1214m, 1198m, 1152s, 1080m, 1042m, 1028m, 1011m, 911w, 846w, 815w, 763m, 698m; δ_H(400 MHz; $CDCl_3$) 1.37 (9 H, s, C*Me*$_3$ major diastereomer), 1.40 (9 H, s, C*Me*$_3$ minor diastereomer), 1.75-1.82 (1 H, m, 6-*H*), 1.87 (3 H, s, 2-*Me* major diastereomer), 2.05 (3 H, s, 2-*Me* minor diastereomer), 2.07-2.14 (2 H, m, 6-*H* and 7-C*H*$_2$), 2.81 (1 H, dd, *J* 11.0 and 16.5, 7-CH_2), 2.86-2.91 (1 H, m, 7-*H*), 3.43 (1 H, t, *J* 9.0, 4-H_{endo} major diastereomer), 3.54-3.60 (1 H, m, 5-*H*), 3.73 (1 H, dd, *J* 8.0 and 11.0, 4-H_{endo} minor diastereomer), 4.00 (1 H, dd, *J* 5.5 and 9.0, 4-H_{exo} major diastereomer), 4.28 (1 H, dd, *J* 6.0 and 8.0, 4-H_{exo} minor diastereomer), 5.18 (1 H, d, *J* 12.0, 8-CO_2CH_2 major diastereomer), 5.14-5.26 (2 H, m, 8-CO_2CH_2 minor diastereomer), 5.50 (1 H , d, *J* 12.0, 8-CO_2CH_2 major diastereomer), 6.95-7.64 (14 H, m, 2-*Ph*, 8-C_6H_4 and 8-CO_2CH_2*Ph*);

δ_C(100.6 MHz; $CDCl_3$) 25.0 (2-*Me*), 27.5 (C*Me*$_3$), 28.4 (*C*-6 major diastereomer), 29.7 (*C*-6 minor diastereomer), 37.3 (7-CH_2), 38.7 (*C*-7), 53.1 (*C*-5 major diastereomer), 56.1 (*C*-5 minor diastereomer), 60.4 (*C*-8 minor diastereomer), 65.2 (*C*-8 major diastereomer), 67.8 (8-CO_2CH_2), 70.2 (*C*-4), 80.8 (CMe_3 major diastereomer), 81.2 (CMe_3 minor diastereomer), 96.5 (*C*-2 major diastereomer), 97.3 (*C*-2 minor diastereomer), 121.8, 125.3, 128.0, 128.1, 128.2, 128.3, 128.4, 128.5, 128.7, 128.9, 129.2, 130.1, 131.4, 132.3 (CH aromatic), 134.5 (8-*C* aromatic), 135.3 (8-CO_2CH_2*Ph*), 137.1 (2-*C* aromatic), 142.0 (Br-*C*), 166.0 (C=O lactam), 169.3 (7-CH_2C=O), 171.8 (8-*C*=O); δ_H(400 MHz COSY; $CDCl_3$) 1.75-1.82 (6-*H*) crosspeak with 2.07-2.14 (6-*H* and 7-C*H*$_2$), 2.86-2.91 (7-*H*) and 3.54-3.60 (5-*H*); 2.07-2.14 (6-*H* and 7-C*H*$_2$) crosspeak with 1.75-1.82 (6-*H*), 2.81 (7-CH_2), 2.86-2.91 (7-*H*) and 3.54-3.60 (5-*H*); 2.81 (7-CH_2) crosspeak with 2.07-2.14 (6-*H* and 7-C*H*$_2$) and 2.86-2.91 (7-*H*); 2.86-2.91 (7-*H*) crosspeak with 1.75-1.82 (6-*H*), 2.07-2.14 (6-*H* and 7-C*H*$_2$) and 2.81 (7-CH_2); 3.43 (4-H_{endo} major diastereomer) crosspeak with 3.54-3.60 (5-*H*) and 4.00 (4-H_{exo} major diastereomer); 3.54-3.60 (5-*H*) crosspeak with 1.75-1.82 (6-*H*), 2.07-2.14 (6-*H* and 7-C*H*$_2$), 3.43 (4-H_{endo} major diastereomer) and 4.00 (4-H_{exo} major diastereomer); 4.00 (4-H_{exo} major diastereomer) crosspeak with 3.43 (4-H_{endo} major diastereomer) and 3.54-3.60 (5-*H*); 5.18 (8-CO_2C*H*$_2$ major diastereomer) crosspeak with 5.50 (8-CO_2C*H*$_2$ major diastereomer); 5.50 (8-CO_2C*H*$_2$ major diastereomer) crosspeak with 5.18 (8-CO_2C*H*$_2$ major diastereomer); 5.14-5.26 (8-CO_2CH_2 minor diastereomer) crosspeak with 5.14-5.26 (8-CO_2CH_2 minor diastereomer); *m/z* ($APCI^+$) 636.8 (MH^+, ^{79}Br, 88%), 635.8 (MH^+, ^{81}Br, 88%), 600.3 (18), 579.7 (80), 578.2 (100), 538.2 (6), 502.7 (6), 458.0 (12); *m/z* (ES^+) 634.1808 ($C_{34}H_{36}NO_6Br$ MH^+ requires 634.1804).

(2*S*, 5*S*, 7*S*)-1-Aza-8-benzyloxycarbonyl-7-(*tert*-butyloxycarbonylmethyl)-8-(*p*-methoxyphenyl)-2-methyl-3-oxa-9-oxo-2-phenyl-bicyclo [4.3.0] nonane (151)



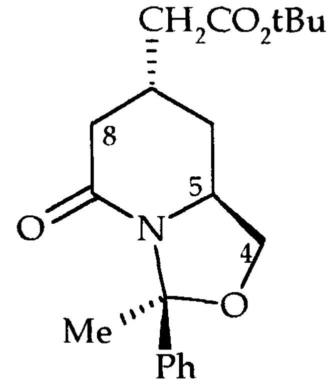
151

To a solution of the Reformatsky adduct **143** (0.353g, 0.7mmol) in $CHCl_3$ (40ml) was added para-methoxyphenyl lead triacetate (0.722g, 1.5mmol) and pyridine (0.291g, 3.7mmol). The mixture was heated to reflux for 72 hours, and then filtered through Celite®, washed with 10% H_2SO_4 (10ml), extracted with $CHCl_3$ (3 x 25ml) and dried with brine (20ml) and over $MgSO_4$. Solvent was removed *in vacuo*, and the residue purified by flash column chromatography, eluting with 30% EtOAc:Petrol to give the product as a colourless oil as an inseparable mixture of two diasteromers in a 2:1 ratio (estimated from NMR) (0.253g, 59%); R_f 0.10 (20% EtOAc:Petrol); $[\alpha]_D^{24}$ -59.7 (*c* 1.2 in $CHCl_3$); ν_{max}(film)/cm^{-1} 1732s (ester C=O), 1682s (lactam C=O), 1517m, 1458m, 1369m, 1255m, 1188m, 1154m, 1040w, 765w, 698w; δ_H(400 MHz; $CDCl_3$) 1.36 (9 H, s, C*Me*$_3$ major diastereomer), 1.40 (9 H, s, C*Me*$_3$ minor diastereomer), 1.74-1.81 (1 H, m, 6-*H*), 1.87 (3 H, s, 2-*Me* major diastereomer), 2.03-2.10 (2 H, m, 6-*H* and 7-C*H*$_2$), 2.12 (3 H, s, 2-*Me* minor diastereomer), 2.79-2.93 (2 H, m, 7-C*H*$_2$, 7-*H*), 3.41 (1 H, t, *J* 8.5, 4-H_{endo} major diastereomer), 3.46-3.56 (1 H, m, 5-*H* and 1 H, m, 4-H_{endo} minor diastereomer), 3.80 (3 H, s, O*Me* major diastereomer), 3.82 (3 H, s, O*Me* minor diastereomer), 3.98 (1 H, dd, *J* 6.0 and 8.5, 4-H_{exo} major diastereomer), 4.06 (1 H, dd, *J* 6.0 and 8.0, 4-H_{exo} minor diastereomer), 5.16 (1 H, d, *J* 12.0, 8-CO$_2$C*H*$_2$), 5.52 (1 H, d, *J* 12.0, 8-CO$_2$C*H*$_2$), 6.86 (2 H, d, *J* 9.0, 8-C(C*H*)$_2$ major diastereomer), 6.88 (2 H, d, *J* 9.0, 8-C(C*H*)$_2$ minor diastereomer), 7.03 (2 H, d, *J* 9.0, MeOC(C*H*)$_2$ major diastereomer), 7.18 (2 H, d, *J* 9.0, MeOC(C*H*)$_2$ minor diastereomer), 7.21-7.51 (10 H, m, 2-*Ph* and

8-CO_2CH_2*Ph*); δ_C(100.6 MHz; $CDCl_3$) 25.1 (2-*Me*), 28.0 (C*Me*$_3$), 28.4 (*C*-6), 37.7 (7-CH_2), 38.8 (*C*-7), 53.1 (*C*-5), 55.2 (O*Me*), 65.0 (C-8), 67.5 (8-CO_2CH_2), 70.1 (*C*-4), 80.6 (CMe_3), 96.5 (*C*-2), 113.8 (8-C$(CH)_2$), 125.4 (MeOC-$(CH)_2$), 128.0, 128.2, 128.3, 128.6, 128.8, 129.2, 129.4, 130.0 (CH aromatic), 134.7 (2-*C* aromatic), 142.2 (8-CO_2CH_2C), 158.7 (*C*-OMe), 166.7 (*C*=O lactam), 169.8 (*C*=O ester), 172.1 (*C*=O ester); δ_H(400 MHz COSY; $CDCl_3$) 1.74-1.81 (6-*H*) crosspeak with 2.03-2.10 (6-*H* and 7-C*H*$_2$), 2.79-2.93 (7-C*H*$_2$, 7-*H*), 3.46-3.56 (5-*H* and 4-H_{endo} minor diastereomer); 2.03-2.10 (6-*H* and 7-C*H*$_2$) crosspeak with 1.74-1.81 (6-*H*), 2.79-2.93 (7-C*H*$_2$, 7-*H*), 3.46-3.56 (5-*H* and 4-H_{endo} minor diastereomer); 2.79-2.93 (7-C*H*$_2$, 7-*H*) crosspeak with 1.74-1.81 (6-*H*) and 2.03-2.10 (6-*H* and 7-C*H*$_2$); 3.41 (4-H_{endo} major diastereomer) crosspeak with 3.46-3.56 (5-*H* and 4-H_{endo} minor diastereomer) and 3.98 (4-H_{exo} major diastereomer); 3.46-3.56 (5-*H* and 4-H_{endo} minor diastereomer) crosspeak with 1.74-1.81 (6-*H*) and 2.03-2.10 (6-*H* and 7-C*H*$_2$), 3.41 (4-H_{endo} major diastereomer), 3.98 (4-H_{exo} major diastereomer) and 4.06 (4-H_{exo} minor diastereomer); 4.06 (4-H_{exo} minor diastereomer) crosspeak with 3.46-3.56 (5-*H* and 4-H_{endo} minor diastereomer); 5.16 (8-CO_2C*H*$_2$) crosspeak with 5.52 (8-CO_2C*H*$_2$); 5.52 (8-CO_2C*H*$_2$) crosspeak with 5.16 (8-CO_2C*H*$_2$); 6.86 (8-C(C*H*)$_2$ major diastereomer) crosspeak with 7.03 (MeOC(C*H*)$_2$ major diastereomer); 6.88 (8-C(C*H*)$_2$ minor diastereomer) crosspeak with 7.18 MeOC(C*H*)$_2$ minor diastereomer); 7.03 (MeOC(C*H*)$_2$ major diastereomer) crosspeak with 6.86 (8-C(C*H*)$_2$ major diastereomer), 7.18 (MeOC(C*H*)$_2$ minor diastereomer) crosspeak with 6.88 (8-C(C*H*)$_2$ minor diastereomer); *m/z* (APCI$^+$) 586.7 (MH$^+$, 100%), 530.5 (23), 529.3 (11), 114.0 (35); *m/z* (ES$^+$) 586.2795 ($C_{35}H_{39}NO_7$ MH$^+$ requires 586.2805).

7.5 Experimental for chapter 5

(-)-(2*S*, 5*S*, 7*R*)-1-Aza-7-(*tert*-butyloxycarbonylmethyl)-2-methyl-3-oxa-9-oxo-2-phenyl-bicyclo [4.3.0] nonane (153)

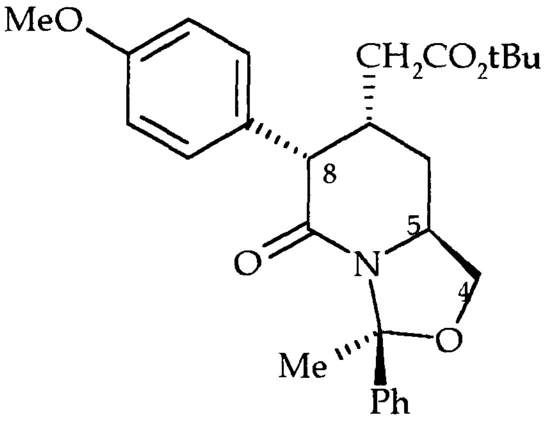


153

To a solution of the Reformatsky product **143** (0.653g, 1.3mmol) in EtOAc (30ml) was added 10% Pd-C (0.653g). The mixture was degassed carefully, and then placed under a hydrogen atmosphere (4 bar). The reaction was stirred for 72 hours, and then evacuated to remove excess hydrogen. The suspension was then filtered through Celite® to remove the catalyst, and solvent was removed *in vacuo*. The residue was purified by flash column chromatography (40% EtOAc:Petrol) to give the product as a colourless oil (0.395g, 84%); R$_f$ 0.26 (40% EtOAc:Petrol); $[\alpha]_D^{24}$ -44.6 (*c* 1.25 in CHCl$_3$); ν_{max}(film) / cm^{-1} 1726s (C=O), 1654s (lactam C=O), 1447w, 1369m, 1253m, 1151s, 1037w, 765m; δ_H(400 MHz; CDCl$_3$) 1.45 (9 H, s, 7-CH$_2$CO$_2$C*Me*$_3$), 1.73-1.79 (1 H, m, 6-H_{endo}), 1.80-1.85 (1 H, m, 6-H_{exo}), 2.05 (3 H, s, 2-*Me*), 2.27 (1 H, dd, *J* 7.5 and 16.0, 7-CH_2), 2.33 (1 H, dd, *J* 7.5 and 15.5, 8-*H*), 2.39 (1 H, dd, *J* 7.0 and 15.5, 8-*H*), 2.58 (1 H, dd, *J* 6.0 and 16.0, 7-CH_2), 2.63-2.66 (1 H, m, 7-*H*), 3.41 (1 H, dd, *J* 8.5 and 9.5, 4-H_{endo}), 3.95-3.99 (1 H, m, 5-*H*), 4.13 (1 H, dd, *J* 6.0 and 8.5, 4-H_{exo}), 7.26-7.45 (5 H, m, 2-*Ph*); δ_C(100.6 MHz; CDCl$_3$) 25.8 (*C*-7), 28.1 (C*Me*$_3$), 28.5 (2-*Me*), 30.1 (C-6), 38.8 (7-CH$_2$), 41.1 (C-8), 54.2 (C-5), 69.2 (C-4), 81.0 (CMe$_3$), 96.0 (C-2), 125.5, 128.0, 128.1 (CH aromatic), 141.9 (2-C aromatic), 167.9 (C=O lactam), 170.9 (C=O ester); δ_H(400 MHz COSY; CDCl$_3$) 1.73-1.79 (6-H_{endo}) crosspeak with 1.80-1.85 (6-H_{exo}), 2.63-2.66 (7-*H*) and 3.95-3.99 (5-*H*); 1.80-1.85 (6-H_{exo}) crosspeak with 1.73-1.79 (6-H_{endo}), 2.63-2.66 (7-*H*) and 3.95-3.99 (5-*H*); 2.27 (7-CH_2) crosspeak with 2.58 (7-CH_2) and 2.63-2.66 (7-*H*); 2.33 (8-*H*) crosspeak with 2.39 (8-*H*) and 2.63-2.66 (7-*H*); 2.39

(8-*H*) crosspeak with 2.33 (8-*H*) and 2.63-2.66 (7-*H*); 2.58 (7-CH_2) crosspeak with 2.27 (7-CH_2) and 2.63-2.66 (7-*H*); 2.63-2.66 (7-*H*) crosspeak with 1.73-1.79 (6-H_{endo}), 1.80-1.85 (6-H_{exo}), 2.27 (7-CH_2), 2.58 (7-CH_2), 2.33 (8-*H*) and 2.39 (8-*H*); 3.41 (4-H_{endo}) crosspeak with 3.95-3.99 (5-*H*) and 4.13 (4-H_{exo}); 3.95-3.99 (5-*H*) crosspeak with 1.73-1.79 (6-H_{endo}), 1.80-1.85 (6-H_{exo}), 3.41 (4-H_{endo}) and 4.13 (4-H_{exo}); 4.13 (4-H_{exo}) crosspeak with 3.41 (4-H_{endo}) and 3.95-3.99 (5-*H*); δ_H(500 MHz NOESY; C_6D_6) 1.10 (2 x 8-*H*) crosspeak with 1.90 (2 x 6-*H*), 2.25 (7-*H*), 3.00 (4-H_{endo}), 3.35 (5-*H*) and 3.55 (4-H_{exo}); 1.90 (2 x 6-*H*) crosspeak with 1.10 (2 x 8-*H*), 1.95 (7-CH_2), 2.25 (7-*H*), 2.40 (7-CH_2), 3.35 (5-*H*); 1.95 (7-CH_2) crosspeak with 1.90 (2 x 6-*H*), 2.25 (7-*H*), 2.40 (7-CH_2), 3.35 (5-*H*); 2.25 (7-*H*) crosspeak with 1.10 (2 x 8-*H*), 1.90 (2 x 6-*H*), 1.95 (7-CH_2), 2.40 (7-CH_2); 2.40 (7-CH_2) crosspeak with 1.90 (2 x 6-*H*), 1.95 (7-CH_2) and 2.25 (7-*H*); 3.00 (4-H_{endo}) crosspeak with 1.10 (2 x 8-*H*), 3.35 (5-*H*) and 3.55 (4-H_{exo}); 3.35 (5-*H*) crosspeak with 1.10 (2 x 8-*H*), 1.90 (2 x 6-*H*), 3.00 (4-H_{endo}) and 3.55 (4-H_{exo}); 3.55 (4-H_{exo}) crosspeak with 1.10 (2 x 8-*H*), 3.00 (4-H_{endo}) and 3.35 (5-*H*); *m/z* (APCI$^+$) 346.2 (MH$^+$, 100%), 342.2 (5), 290.2 (7), 170.0 (2); *m/z* (APCI$^+$) 346.2012 ($C_{20}H_{27}NO_4$ requires 346.2018 for MH$^+$).

(-)-(2*S*, 5*S*, 7*S*, 8*S*)-1-Aza-7-(*tert*-butyloxycarbonylmethyl)-8-(*p*-methoxyphenyl)-2-methyl-3-oxa-9-oxo-2-phenyl-bicyclo [4.3.0] nonane (154)

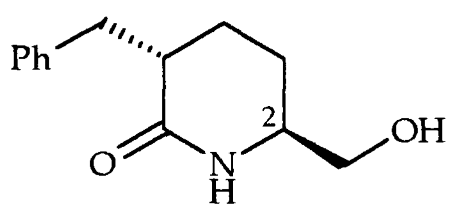


154

To a solution of the arylated Reformatsky adduct **151** (0.235g, 0.4mmol) in EtOAc (30ml) was added 10% Pd-C (0.235g). The mixture was degassed carefully, and then placed under a hydrogen atmosphere (4 bar). The reaction was stirred for 72 hours, and then evacuated to remove excess hydrogen. The suspension was then filtered through Celite® to remove the catalyst, and solvent was removed *in vacuo*. Crude

NMR analysis revealed that decarboxylation was not complete, so the residue was heated under vacuum (200°C, 1 mm) for two hours. The residue was purified by flash column chromatography (40% EtOAc:Petrol) to give the product as a colourless oil (0.121g, 67%); R_f 0.33 (40% EtOAc:Petrol); $[\alpha]_D^{25}$ -75.0 (*c* 1.18 in $CHCl_3$); ν_{max}(film) / cm^{-1} 1724s, 1654s, 1612w, 1559w, 1514s, 1427m, 1368m, 1325m, 1249s, 1180m, 1152m, 1084w, 1035m, 914w, 833w, 791w, 164m, 133w, 168m; δ_H(400 MHz; $CDCl_3$) 1.41 (9 H, s, C*Me*$_3$), 1.92-2.00 (1 H, m, 6-H_{endo}), 2.03-2.08 (1 H, m, 6-H_{exo}), 2.10 (3 H, s, 2-*Me*), 2.12-2.24 (2 H, m, 7-CH_2), 2.80-2.86 (1 H, m, 7-*H*), 3.66 (1 H, dd, *J* 8.0 and 10.0, 4-H_{endo}), 3.78 (3 H, s, O*Me*), 3.91 (1 H, d, *J* 5.5, 8-*H*), 4.09-4.26 (2 H, m, 4-H_{exo} and 5-*H*), 6.84-7.58 (9 H, m, 2-*Ph* and 8-C_6H_4); δ_C(100.6 MHz; $CDCl_3$) 25.0 (2-*Me*), 27.7 (*C*-6), 28.0 (C*Me*$_3$), 35.0 (*C*-7), 36.5 (7-CH_2), 52.7 (*C*-8), 53.1 (*C*-5), 55.2 (O*Me*), 70.0 (*C*-4), 80.9 (CMe_3), 95.7 (*C*-2), 113.9, 125.6, 128.1 (CH aromatic), 128.4 (8-C aromatic), 130.6 (CH aromatic), 141.6 (2-C aromatic), 158.5 (C-OMe), 167.9 (C=O lactam), 171.3 (C=O ester); δ_H(400 MHz COSY; $CDCl_3$) 1.92-2.00 (6-H_{endo}) crosspeak with 2.03-2.08 (6-H_{exo}), 2.80-2.86 (7-*H*) and 4.09-4.26 (4-H_{exo} and 5-*H*); 2.03-2.08 (6-H_{exo}) crosspeak with 1.92-2.00 (6-H_{endo}), 2.80-2.86 (7-*H*) and 4.09-4.26 (4-H_{exo} and 5-*H*); 2.12-2.24 (7-CH_2) crosspeak with 2.80-2.86 (7-*H*); 2.80-2.86 (7-*H*) crosspeak with 1.92-2.00 (6-H_{endo}), 2.03-2.08 (6-H_{exo}), 2.12-2.24 (7-CH_2) and 3.91 (8-*H*); 3.66 (4-H_{endo}) crosspeak with 4.09-4.26 (4-H_{exo} and 5-*H*); 3.91 (8-*H*) crosspeak with 2.80-2.86 (7-*H*); 4.09-4.26 (4-H_{exo} and 5-*H*) crosspeak with 1.92-2.00 (6-H_{endo}), 2.03-2.08 (6-H_{exo}), 3.66 (4-H_{endo}); n. O. e. experiment (500 MHz; $CDCl_3$) Irradiation at δ_H 3.95 gave enhancements at δ_H 2.00 (6-H_{endo}) (2.0%), 2.90 (7-*H*) (8.6%); Irradiation at δ_H 3.70 gave enhancements at δ_H 2.00 (6-H_{endo}) (3.0%), 4.20 (4-H_{exo} and 5-*H*) (29.9%); Irradiation at δ_H 2.90 gave enhancements at δ_H 2.00 (6-H_{endo}) (3.0%), 2.10 (6-H_{exo}) (2.0%), 2.25 (7-CH_2) (3.8%), 3.95 (8-*H*) (10.3%); Irradiation at δ_H 2.15 gave enhancement at δ_H 4.20 (5-*H* and 4-H_{exo}) (3.2%); *m/z* ($APCI^+$) 452.2 (MH^+, 100%), 396.1 (10), 276.2 (12); *m/z* (ES^+) 452.2442 ($C_{27}H_{33}NO_5$ requires 452.2437 for MH^+).

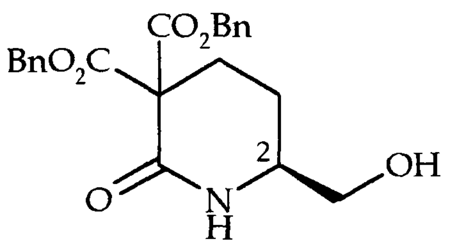
(-)-(2*S*, 5*S*)-5-Benzyl-2-hydroxymethyl-6-piperidinone (**163**)



163

To a solution of the bicyclic lactam **103b** (0.016g, 0.05mmol) in DCM (10ml) was added TFA (0.5ml). The reaction mixture was stirred for 30 minutes, at which point t. l. c. analysis suggested that no starting material was present. Solvent was removed *in vacuo*, and the residue separated by flash column chromatography (10% MeOH:EtOAc) to give a colourless oil (8mg, 73%); R_f 0.37 (10% MeOH:EtOAc); $[\alpha]_D^{25}$ -6.96 (*c* 0.23 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3554br (OH), 1641s (C=O), 1454m; δ_H(500 MHz; $CDCl_3$) 1.27-1.35 (1 H, m, 3-*H*), 1.41-1.54 (1 H, m, 3-*H*), 1.78-1.82 (2 H, m, 4-H), 2.47-2.53 (1 H, m, 5-*H*), 2.60 (1 H, br, O*H*), 2.69 (1 H, dd, *J* 10.0 and 13.5, 5-CH_2), 3.42-3.56 (3 H, m, 2-*H*, 5-CH_2, 2-CH_{endo}), 3.69 (1 H, dd, *J* 3.0 and 11.0, 2-CH_{exo}), 7.12 (1 H, br, N*H*), 7.20-7.33 (5 H, m, 5-CH_2*Ph*); δ_C(125.8 MHz; $CDCl_3$) 24.3 (C-3), 25.1 (C-4), 37.2 (5-CH_2), 42.8 (C-5), 55.1 (C-2), 66.3 (2-CH_2), 126.2, 128.4, 129.2 (CH aromatic), 139.6 (5-CH_2C aromatic), 174.7 (C=O lactam); *m/z* (APCI$^+$) 220.1 (MH$^+$, 100%); *m/z* (CI) 220.1338 ($C_{13}H_{17}NO_2$ requires 220.1338).

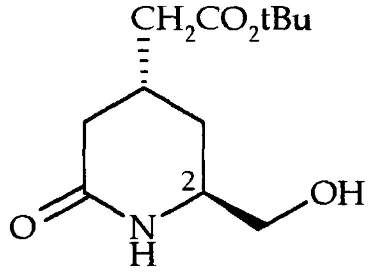
(+)-(2*S*)-5,5-Di(benzyloxycarbonyl)-2-hydroxymethyl-6-piperidinone (**164**)



164

To a solution of the diacylated bicyclic lactam **108c** (0.080g, 0.16mmol) in DCM (20ml) was added TFA (2ml). The reaction mixture was stirred for five hours at room temperature, solvent was removed *in vacuo*, and the residue separated by flash column chromatography, eluting with EtOAc to give the product as a colourless oil (47mg, 74%); R_f 0.32 (EtOAc); $[\alpha]_D^{24}$ +7.52 (*c* 0.63 in $CHCl_3$); ν_{max}(film) / cm^{-1} 3348br (OH), 1732s (C=O ester), 1673s (lactam C=O), 1498w, 1456m, 1379w, 1647w, 1322w, 1271m, 1222m 1186m, 1090m, 1054m, 1003w, 948w, 908w, 738m, 697m, 666w, 600w; δ_H(500 MHz; $CDCl_3$) 1.26-1.35 (1 H, m, 3-*H*), 1.71-1.77 (1 H, m, 3-*H*), 2.39 (1 H, dt, *J* 3.5 and 13.5, 4-*H*), 2.53 (1 H, ddd, *J* 3.5, 5.5 and 13.5, 4-*H*), 2.92 (1 H, br, O*H*), 3.29 (1 H, dd, *J* 8.0 and 12.0, 2-CH_{endo}), 3.50-3.55 (2 H, m, 2-CH_{exo} and 2-*H*), 5.22 (4 H, s, 2 x CO_2CH_2), 7.28-7.37 (10 H, m, 2 x CO_2CH_2Ph), 7.45 (1 H, br, N*H*); δ_C(125.8 MHz; $CDCl_3$) 20.5 (*C*-3), 27.4 (*C*-4), 54.5 (*C*-2), 63.2 (*C*-5), 65.3 (2-CH_2), 67.9, 68.0 (2 x CO_2CH_2), 128.0, 128.2, 128.3, 128.4, 128.5 (CH aromatic), 135.0, 135.1 (2 x CH_2C aromatic), 166.3 (C=O lactam) 167.4, 167.8 (2 x C=O ester); *m/z* ($APCI^+$) 398.2 (MH^+, 100%), 354.6 (8), 290.2 (6), 246.2 (5), 220.2 (6), 181.1 (8), 156.0 (41); *m/z* (CI^+) 398.1613 ($C_{23}H_{23}NO_6$ requires 398.1604 for MH^+).

(+)-(2*S*, 4*R*)-4-(*tert*-Butyloxycarbonylmethyl)-2-hydroxymethyl-6-piperidinone (**165**)



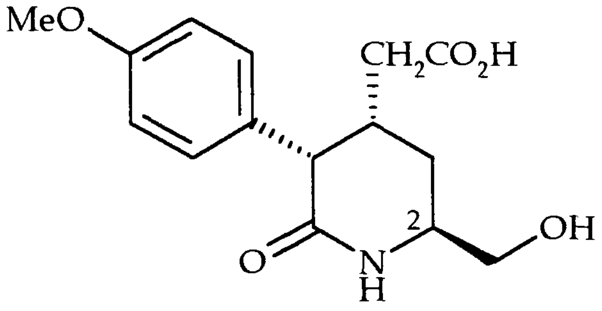
165

To a solution of the bicyclic lactam **153** (0.061g, 0.2mmol) in DCM (20ml) was added TFA (0.5ml). The reaction mixture was stirred for four hours at room temperature, at which point t. l. c. analysis indicated that no starting material was present. Solvent was removed *in vacuo*, and the residue purified by flash column chromatography eluting with 10% MeOH:EtOAc, to give the product as a brown oil (14mg, 33%); R_f 0.25 (10% MeOH:EtOAc); $[\alpha]_D^{22}$ +1.71 (*c* 0.35 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3362br (OH), 1686s (ester C=O), 1639s (lactam C=O), 1449w, 1371w, 1207m, 1141m, 843w, 801w, 724w, 666w; δ_H(500 MHz; d_4-MeOH) 1.45 (9 H, s, C*Me*$_3$), 1.60-1.66 (1 H, m, 3-*H*), 1.84-1.87 (1 H, m, 3-*H*), 2.04-2.11 (1 H, m, 5-*H*), 2.26-2.28 (1 H, m, 5-*H*), 2.29-2.50 (3 H, m, 4-*H* and 4-CH_2), 3.31 (1 H, br, N*H*), 3.48-3.60 (3 H, m, 2-CH_2, 2-*H*); δ_C(125.8 MHz; d_4-MeOH) 27.5 (C-4), 28.3 (C*Me*$_3$), 29.4 (C-5), 41.4 (4-CH_2), 52.9 (C-2), 54.8 (C-5), 65.7 (2-CH_2), 82.0 (CMe_3), 173.0 (C=O), 174.3 (C=O); δ_H(500 MHz COSY; d_4-MeOH) 1.60-1.66 (3-*H*) crosspeak with 1.84-1.87 (3-*H*), 2.29-2.50 (4-*H* and 4-CH_2) and 3.48-3.60 (2 x 2-C*H*, 2-*H*); 1.84-1.87 (3-*H*) crosspeak with 1.60-1.66

(3-*H*), 2.29-2.50 (4-*H* and 4-CH_2) and 3.48-3.60 (2 x 2-C*H*, 2-*H*); 2.04-2.11 (5-*H*) crosspeak with 2.26-2.28 (5-*H*) and 2.29-2.50 (4-*H* and 4-CH_2); 2.26-2.28 (5-*H*) crosspeak with 2.04-2.11 (5-*H*) and 2.29-2.50 (4-*H* and 4-CH_2); 2.29-2.50 (4-*H* and 4-CH_2) crosspeak with 1.60-1.66 (3-*H*), 1.84-1.87 (3-*H*), 2.04-2.11 (5-*H*) and 2.26-2.28 (5-*H*); 3.48-3.60 (2 x 2-C*H*, 2-*H*) crosspeak with 1.60-1.66 (3-*H*), 1.84-1.87 (3-*H*); *m/z* (APCI$^+$) 244.1 (MH$^+$, 100%), 230.0 (55), 215.9 (20), 189.1 (70), 157.9 (60); *m/z* (ES$^+$) 244.1552 ($C_{12}H_{21}NO_4$ requires 244.1549 for MH$^+$).

When repeated on a larger scale (0.395g, 0.8mmol) the *tert*-Bu group was hydrolysed, giving the acid (0.151g, 98%).

(2*S*, 4*S*, 5*S*)-4-(*tert*-Butyloxycarbonylmethyl)-2-hydroxymethyl-5-(*p*-methoxyphenyl)-6-piperidinone (168)

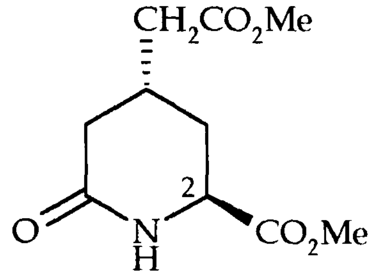


168

To a solution of the arylated Reformatsky product **154** (0.121g, 0.3mmol) in DCM (10ml) was added TFA (0.5ml). The reaction mixture was stirred with regular monitoring by t. l. c. and mass spectrometry. After five minutes there was evidence that the t-butyl group had been removed. The reaction mixture was stirred for a further hour to ensure completion. Solvent was removed *in vacuo* to give the crude product, which was used immediately in the oxidation reaction.

(+)-(2*S*, 4*R*)-2-Methyloxycarbonyl-4-(methyloxycarbonylmethyl)-6-piperidinone

(169)

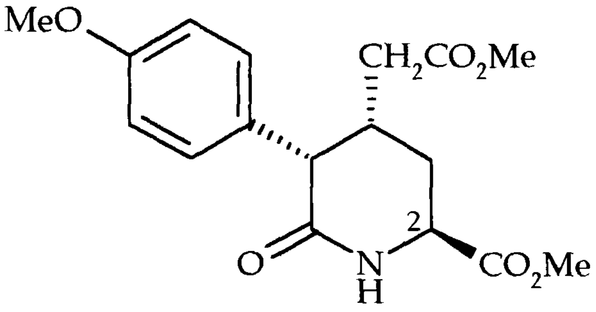


169

To a solution of the alcohol **167** (57mg, 0.3mmol) in acetonitrile (1ml) and carbon tetrachloride (2ml) was added a solution of sodium periodate (0.261g, 1.2mmol) and ruthenium tetroxide (2mg) in water (1.5ml). The reaction mixture was stirred for 72 hours, and then ethereal diazomethane solution (distilled from the dropwise addition of a solution of Diazald® (2g) in Et_2O (19ml) to a solution of KOH (0.588g) in water (0.98ml), Et_2O (2ml) and EtOH (4ml) heated to 70°C) was added until excess diazomethane was present, as shown by the persistent yellow colour of the organic phase. Acetic acid (2 drops) was then added to quench excess diazomethane. The reaction mixture was extracted with EtOAc (2 x 15ml), and solvent removed *in vacuo*. The residue was purified by flash column chromatography eluting with EtOAc to give the product as a colourless oil (11mg, 16%); R_f 0.54 (10% MeOH:EtOAc); $[\alpha]_D^{24}$ + 30.5 (*c* 0.55 in $CHCl_3$); ν_{max}(film)/cm^{-1} 1737s (ester C=O), 1659s (lactam C=O), 1440m, 1212m, 1012w; δ_H(400 MHz; $CDCl_3$) 1.81-1.90 (1 H, m, 3-H_{exo}), 2.11 (1 H, dd, *J* 9.0 and 17.5, 4-CH_2), 2.22-2.26 (1 H, m, 3-H_{endo}), 2.34-2.44 (3 H, m, 4-*H* and 2 x 5-*H*), 2.57 (1 H, ddd, *J* 1.5, 5.0 and 17.5, 4-CH_2), 3.70 (3 H, s, 4-CH_2CO_2*Me*), 3.79 (3 H, s, 2-CO_2*Me*), 4.12-4.19 (1 H, m, 2-*H*), 6.26 (1 H, br, N*H*); δ_C(100.6 MHz; $CDCl_3$) 26.9 (C-4), 29.9 (C-3), 37.0 (4-CH_2), 39.1 (C-5), 51.8 (4-CH_2CO_2*Me*), 52.8 (2-CO_2*Me*), 53.1 (C-2), 170.6 (lactam C=O), 171.6, 171.7 (2 x C=O ester); δ_H(400 MHz COSY; $CDCl_3$) 1.81-1.90 (3-H_{exo}) crosspeak with 2.22-2.26 (3-H_{endo}), 2.34-2.44 (4-*H* and 2 x 5-*H*) and 4.12-4.19 (2-*H*); 2.11 (4-CH_2) crosspeak with 2.34-2.44 (4-*H* and 2 x 5-*H*) and 2.57 (4-CH_2); 2.22-2.26 (3-H_{endo}) crosspeak with 1.81-1.90 (3-H_{exo}), 2.34-2.44 (4-*H* and 2 x 5-*H*), 2.57 (4-CH_2) and 4.12-4.19 (2-*H*); 2.34-2.44 (4-*H* and 2 x 5-*H*) crosspeak with 1.81-1.90 (3-H_{exo}), 2.11 (4-CH_2) and 2.57 (4-CH_2); 2.57 (4-CH_2) crosspeak with 2.11 (4-CH_2), 2.22-2.26 (3-H_{endo}) and 2.34-2.44 (4-*H* and 2 x 5-*H*); 4.12-4.19 (2-*H*) crosspeak with

1.81-1.90 (3-H_{exo}) and 2.22-2.26 (3-H_{endo}); n. O. e. experiment (500 MHz; $CDCl_3$) Irradiation at δ_H 4.20 gave enhancements at δ_H 1.90 (3-H_{exo}) (3.1%), 2.30 (3-H_{endo}) (1.7%) and 2.45 (4-*H* and 2 x 5-*H*) (1.6%); Irradiation at δ_H 2.60 gave enhancements at δ_H 2.15 (4-CH_2) (13.9%) and 2.45 (4-*H* and 2 x 5-*H*) (4.4%); Irradiation at δ_H 2.30 gave enhancements at δ_H 1.90 (3-H_{exo}) (17.5%), 2.45 (4-*H* and 2 x 5-*H*) (2.6%) and 4.20 (2-*H*) (2.2%); Irradiation at δ_H 2.15 gave enhancements at δ_H 2.45 (4-*H* and 2 x 5-*H*) (2.4%) and 2.60 (4-CH_2) (14.1%); Irradiation at δ_H 1.90 gave enhancements at δ_H 2.30 (3-H_{endo}) (17.7%), 2.45 (4-*H* and 2 x 5-*H*) (1.8%) and 4.20 (2-*H*) (4.0%); *m/z* (APCI$^+$) 230.1 (MH$^+$, 100%), 228.0 (4.0), 216.0 (13), 212.0 (4), 202.0 (47), 197.9 (17), 184.0 (13), 171.1 (12), 167.9 (11), 153.9 (27), 151.6 (6), 137.8 (38), 127.9 (7), 123.7 (16), 121.8 (34), 121.2 (7), 109.6 (6); *m/z* (ES$^+$) 230.1024 ($C_{10}H_{15}NO_5$ requires 230.1028 for MH$^+$).

(2*S*, 4*S*, 5*S*)-2-Methyloxycarbonyl-4-(methyloxycarbonylmethyl)-5-(*p*-methoxyphenyl)-6-piperidinone (170)



170

To a solution of the crude alcohol **168** in acetonitrile (2ml) and ethyl acetate (2ml) was added $RuCl_3$ (2mg) and sodium periodate (0.237g, 1.1mmol) in water (3ml). The reaction mixture was stirred for two hours, and then quenched with diazomethane as before. The reaction mixture was extracted with EtOAc (2 x 10ml) and solvent was removed *in vacuo*. The residue was purified by two flash columns (eluting with 10% MeOH:EtOAc) to give the product as a colourless oil (2mg, 22%); R_f 0.23 (10% MeOH:EtOAc); ν_{max}(film)/cm^{-1} 1737s (ester C=O), 1659s (lactam C=O), 1212m; δ_H(400 MHz; $CDCl_3$) 1.87 (1 H, dd, *J* 8.5 and 16.0, 4-CH_2), 2.07 (1 H, dd, *J* 6.5 and 16.0, 4-CH_2), 2.11-2.23 (1 H, m, 3-*H*), 2.25-2.51 (1 H, m, 3-*H*), 2.53-2.75 (1 H, m, 4-*H*), 3.64 (1 H, d, *J* 11.0, 5-*H*), 3.79 (1 H, s, O*Me*), 3.81 (1 H, s, 4-CH_2CO_2*Me*), 3.82 (1 H, s, 2-CO_2*Me*), 4.29-4.38 (1 H, m, 2-*H*), 6.62 (1 H, br, N*H*), 6.86 (2 H, d, *J* 8.5, 5-C(C*H*)$_2$), 7.08 (2 H, d, *J* 8.5, MeOC(C*H*)$_2$); δ_C(100.6 MHz; CDCl$_3$) 25.9 (*C*-3), 32.0 (*C*-4), 37.3 (4-CH$_2$), 50.3 (2-CO$_2$*Me*), 52.9 (*C*-5), 53.2 (*C*-2), 55.2 (*Me*O), 80.8 (4-CH$_2$CO$_2$*Me*), 114.0 (5-C(CH)$_2$), 126.4 (5-C), 129.4 (MeOC), 136.1 (MeOC(CH)$_2$), 158.8 (C=O lactam), 170.9 (C=O ester), 171.7 (C=O ester); *m/z* (APCI$^+$) 336.1 (MH$^+$, 28%), 322.1 (75), 308.1 (33), 294.2 (100), 292.1 (9), 276.1 (13), 244.0 (9), 234.0 (9), 216.0 (18), 201.9 (27), 188.0 (5), 183.9 (16), 169.8 (3), 155.8 (12), 137.8 (4); *m/z* (ES$^+$) 336.1451 ($C_{17}H_{21}NO_6$ requires 336.1447 for MH$^+$).

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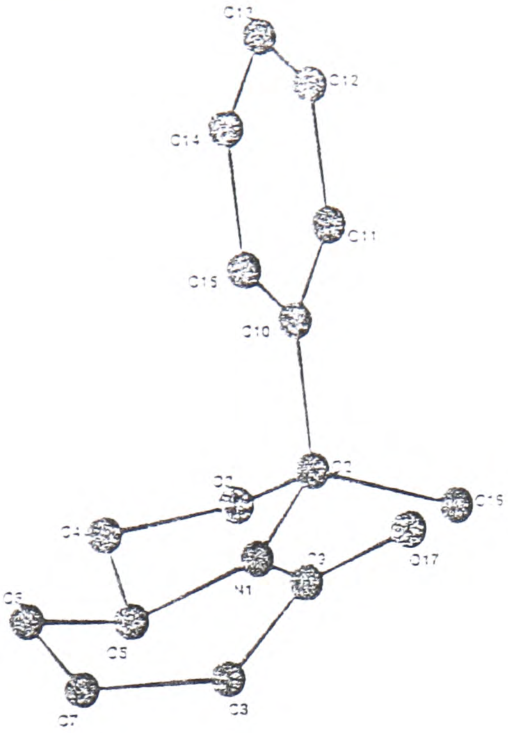
Appendices

1. Crystal structure of 77



Bond Lengths (A)

N(1) - C(2)	1.464(2)
N(1) - C(5)	1.463(2)
N(1) - C(9)	1.340(2)
C(2) - O(3)	1.424(2)
C(2) - C(10)	1.509(2)
C(2) - C(16)	1.514(2)
O(3) - C(4)	1.420(2)
C(4) - C(5)	1.501(2)
C(4) - H(41)	1.03(2)
C(4) - H(42)	0.90(2)
C(5) - C(6)	1.489(2)
C(5) - H(51)	0.94(2)
C(6) - C(7)	1.498(3)
C(6) - H(61)	0.96(3)
C(6) - H(62)	1.04(2)
C(7) - C(8)	1.446(4)
C(7) - H(71)	0.90(3)
C(7) - H(72)	1.01(5)
C(8) - C(9)	1.499(3)
C(8) - H(81)	0.82(4)
C(8) - H(82)	1.13(4)
C(9) - O(17)	1.223(2)
C(10) - C(11)	1.388(2)
C(10) - C(15)	1.380(2)
C(11) - C(12)	1.371(3)
C(11) - H(111)	0.97(2)
C(12) - C(13)	1.374(3)
C(12) - H(121)	0.99(2)
C(13) - C(14)	1.357(2)
C(13) - H(131)	1.02(2)
C(14) - C(15)	1.379(2)
C(14) - H(141)	1.01(2)
C(15) - H(151)	0.98(2)
C(16) - H(21)	0.95(3)
C(16) - H(22)	0.98(3)
C(16) - H(23)	1.03(3)

Bond Angles (degrees)

C(2) - N(1) - C(5)	111.3(1)
C(2) - N(1) - C(9)	126.1(1)
C(5) - N(1) - C(9)	122.6(1)
N(1) - C(2) - O(3)	101.5(1)
N(1) - C(2) - C(10)	113.2(1)
O(3) - C(2) - C(10)	108.8(1)
N(1) - C(2) - C(16)	113.3(2)
O(3) - C(2) - C(16)	106.3(2)
C(10) - C(2) - C(16)	112.4(1)
C(2) - O(3) - C(4)	106.2(1)
O(3) - C(4) - C(5)	103.5(1)
O(3) - C(4) - H(41)	108.5(11)
C(5) - C(4) - H(41)	112.0(10)
O(3) - C(4) - H(42)	108.3(12)
C(5) - C(4) - H(42)	115.3(12)
H(41) - C(4) - H(42)	108.9(17)
N(1) - C(5) - C(4)	99.6(1)
N(1) - C(5) - C(6)	110.7(1)
C(4) - C(5) - C(6)	117.5(1)
N(1) - C(5) - H(51)	109.4(10)
C(4) - C(5) - H(51)	112.2(10)
C(6) - C(5) - H(51)	107.2(9)
C(5) - C(6) - C(7)	109.4(2)
C(5) - C(6) - H(61)	108.8(13)
C(7) - C(6) - H(61)	109.3(13)
C(5) - C(6) - H(62)	108.5(10)
C(7) - C(6) - H(62)	110.5(11)
H(61) - C(6) - H(62)	110.2(17)
C(6) - C(7) - C(8)	117.0(2)
C(6) - C(7) - H(71)	111.5(20)
C(8) - C(7) - H(71)	124.6(21)
C(6) - C(7) - H(72)	105.5(24)
C(8) - C(7) - H(72)	109.7(25)
H(71) - C(7) - H(72)	80.1(26)
C(7) - C(8) - C(9)	119.2(2)
C(7) - C(8) - H(81)	121.7(24)
C(9) - C(8) - H(81)	108.0(25)
C(7) - C(8) - H(82)	100.4(17)
C(9) - C(8) - H(82)	103.9(17)
H(81) - C(8) - H(82)	99.4(28)
N(1) - C(9) - C(8)	114.3(2)
N(1) - C(9) - O(17)	123.1(2)
C(8) - C(9) - O(17)	122.6(2)
C(2) - C(10) - C(11)	118.9(1)
C(2) - C(10) - C(15)	123.5(1)
C(11) - C(10) - C(15)	117.6(1)
C(10) - C(11) - C(12)	120.7(2)
C(10) - C(11) - H(111)	115.9(10)
C(12) - C(11) - H(111)	123.4(10)
C(11) - C(12) - C(13)	120.7(2)
C(11) - C(12) - H(121)	118.5(12)
C(13) - C(12) - H(121)	120.8(12)
C(12) - C(13) - C(14)	119.4(2)
C(12) - C(13) - H(131)	121.2(12)

Bond Angles (degrees)

C(14) - C(13) - H(131)	119.4(12)
C(13) - C(14) - C(15)	120.3(2)
C(13) - C(14) - H(141)	123.8(13)
C(15) - C(14) - H(141)	115.8(13)
C(10) - C(15) - C(14)	121.3(2)
C(10) - C(15) - H(151)	118.0(10)
C(14) - C(15) - H(151)	120.6(10)
C(2) - C(16) - H(21)	109.9(14)
C(2) - C(16) - H(22)	111.3(14)
H(21) - C(16) - H(22)	105.8(20)
C(2) - C(16) - H(23)	111.0(14)
H(21) - C(16) - H(23)	107.8(20)
H(22) - C(16) - H(23)	110.8(19)

Atomic Coordinates And Isotropic Temperature Factors

Atom	x/a	y/b	z/c	U(iso)	Occ
N(1)	-0.0405(2)	-0.56713(9)	0.82109(9)	0.0412	1.0000
C(2)	0.0428(2)	-0.5513(1)	0.7225(1)	0.0442	1.0000
O(3)	-0.1323(2)	-0.5440(1)	0.66414(8)	0.0545	1.0000
C(4)	-0.2731(3)	-0.6104(2)	0.7080(1)	0.0516	1.0000
C(5)	-0.2534(2)	-0.5887(1)	0.8163(1)	0.0428	1.0000
C(6)	-0.3073(3)	-0.6713(1)	0.8862(1)	0.0554	1.0000
C(7)	-0.2416(5)	-0.6430(3)	0.9881(2)	0.0872	1.0000
C(8)	-0.0657(4)	-0.5807(2)	0.9963(2)	0.0756	1.0000
C(9)	0.0594(3)	-0.5627(1)	0.9065(1)	0.0516	1.0000
C(10)	0.1646(2)	-0.6400(1)	0.6865(1)	0.0390	1.0000
C(11)	0.2299(3)	-0.6406(1)	0.5894(1)	0.0516	1.0000
C(12)	0.3364(3)	-0.7210(2)	0.5531(1)	0.0604	1.0000
C(13)	0.3822(3)	-0.8023(1)	0.6123(1)	0.0622	1.0000
C(14)	0.3205(3)	-0.8027(1)	0.7075(1)	0.0592	1.0000
C(15)	0.2121(2)	-0.7225(1)	0.7446(1)	0.0472	1.0000
C(16)	0.1515(4)	-0.4513(1)	0.7120(2)	0.0665	1.0000
O(17)	0.2379(2)	-0.5464(1)	0.9112(1)	0.0690	1.0000

Atomic Coordinates And Isotropic Temperature Factors

Atom	x/a	y/b	z/c	U(iso)	Occ
H(21)	0.272(4)	-0.453(2)	0.749(2)	0.092(8)	1.0000
H(22)	0.074(4)	-0.395(2)	0.739(2)	0.101(8)	1.0000
H(23)	0.188(4)	-0.438(2)	0.639(2)	0.108(8)	1.0000
H(41)	-0.234(3)	-0.684(2)	0.691(1)	0.073(6)	1.0000
H(42)	-0.394(3)	-0.597(1)	0.682(1)	0.068(5)	1.0000
H(51)	-0.325(3)	-0.530(1)	0.835(1)	0.051(4)	1.0000
H(61)	-0.449(4)	-0.680(2)	0.886(2)	0.080(6)	1.0000
H(62)	-0.238(3)	-0.738(2)	0.863(1)	0.076(6)	1.0000
H(71)	-0.279(5)	-0.690(3)	1.033(2)	0.14(1)	1.0000
H(72)	-0.358(7)	-0.607(3)	1.019(3)	0.18(2)	1.0000
H(81)	0.009(6)	-0.584(3)	1.044(3)	0.14(1)	1.0000
H(82)	-0.136(5)	-0.504(3)	1.011(2)	0.15(1)	1.0000
H(111)	0.193(3)	-0.582(1)	0.550(1)	0.055(5)	1.0000
H(121)	0.376(3)	-0.720(2)	0.483(2)	0.089(6)	1.0000
H(131)	0.461(3)	-0.862(2)	0.586(2)	0.082(6)	1.0000
H(141)	0.347(4)	-0.860(2)	0.755(2)	0.096(7)	1.0000
H(151)	0.161(3)	-0.724(1)	0.812(1)	0.058(4)	1.0000

Aniotropic Temperature Factors

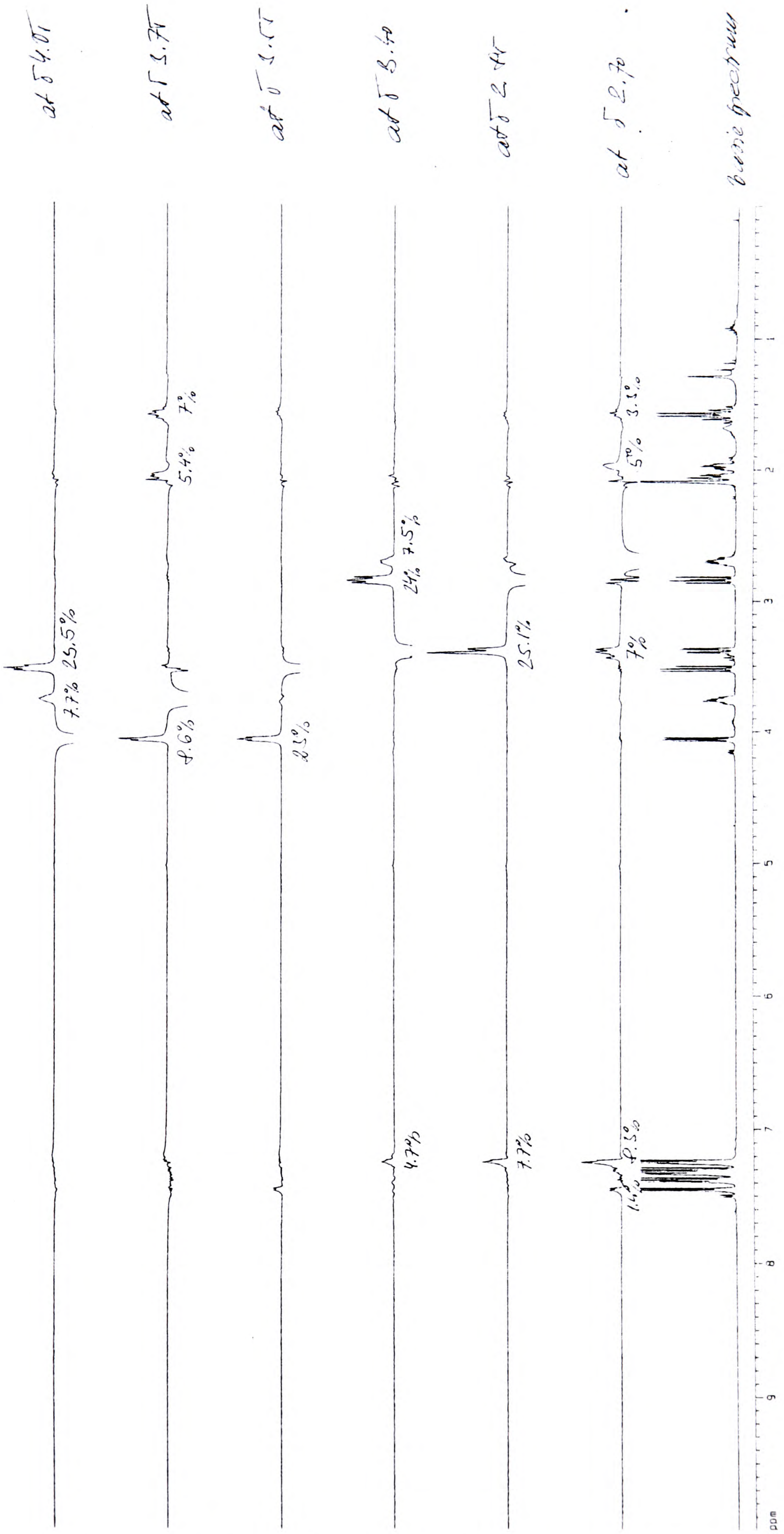
Atom	U(11)	U(22)	U(33)	U(23)	U(13)	U(12)
N(1)	0.0295(6)	0.0486(7)	0.0492(7)	-0.0043(6)	-0.0002(5)	-0.0012(5)
C(2)	0.0335(8)	0.0465(8)	0.0581(9)	0.0091(7)	0.0018(6)	-0.0039(6)
O(3)	0.0377(6)	0.0903(8)	0.0626(7)	0.0362(6)	-0.0017(5)	0.0043(6)
C(4)	0.0328(9)	0.096(1)	0.052(1)	0.0208(9)	-0.0104(7)	-0.0116(9)
C(5)	0.0312(8)	0.0463(7)	0.0554(8)	0.0074(6)	0.0015(6)	0.0014(6)
C(6)	0.053(1)	0.064(1)	0.053(1)	0.0104(7)	0.0040(7)	-0.0072(8)
C(7)	0.085(2)	0.173(3)	0.048(1)	0.004(1)	0.007(1)	-0.022(2)
C(8)	0.080(2)	0.126(2)	0.047(1)	-0.022(1)	-0.006(1)	-0.003(1)
C(9)	0.043(1)	0.066(1)	0.061(1)	-0.0264(8)	-0.0104(7)	0.0041(8)
C(10)	0.0306(7)	0.0478(7)	0.0431(7)	-0.0009(6)	-0.0022(6)	-0.0088(6)
C(11)	0.048(1)	0.071(1)	0.0424(8)	0.0032(8)	-0.0049(7)	-0.0091(8)
C(12)	0.059(1)	0.091(1)	0.0472(9)	-0.0196(9)	0.0088(8)	-0.012(1)
C(13)	0.065(1)	0.059(1)	0.076(1)	-0.0199(9)	0.021(1)	-0.0063(9)
C(14)	0.065(1)	0.0475(8)	0.071(1)	-0.0049(8)	0.0153(9)	0.0004(8)
C(15)	0.052(1)	0.0429(8)	0.0483(8)	0.0003(6)	0.0073(7)	-0.0024(7)
C(16)	0.059(1)	0.0454(9)	0.128(2)	0.003(1)	0.031(1)	-0.0067(9)
O(17)	0.0432(8)	0.114(1)	0.092(1)	-0.0458(8)	-0.0168(6)	-0.0010(8)

Scale	Du(iso)	Ou(iso)	Polarity	Flack	Extinction
2.638(6)	0.050	0.050	1.000	0.000	1372.3(401)

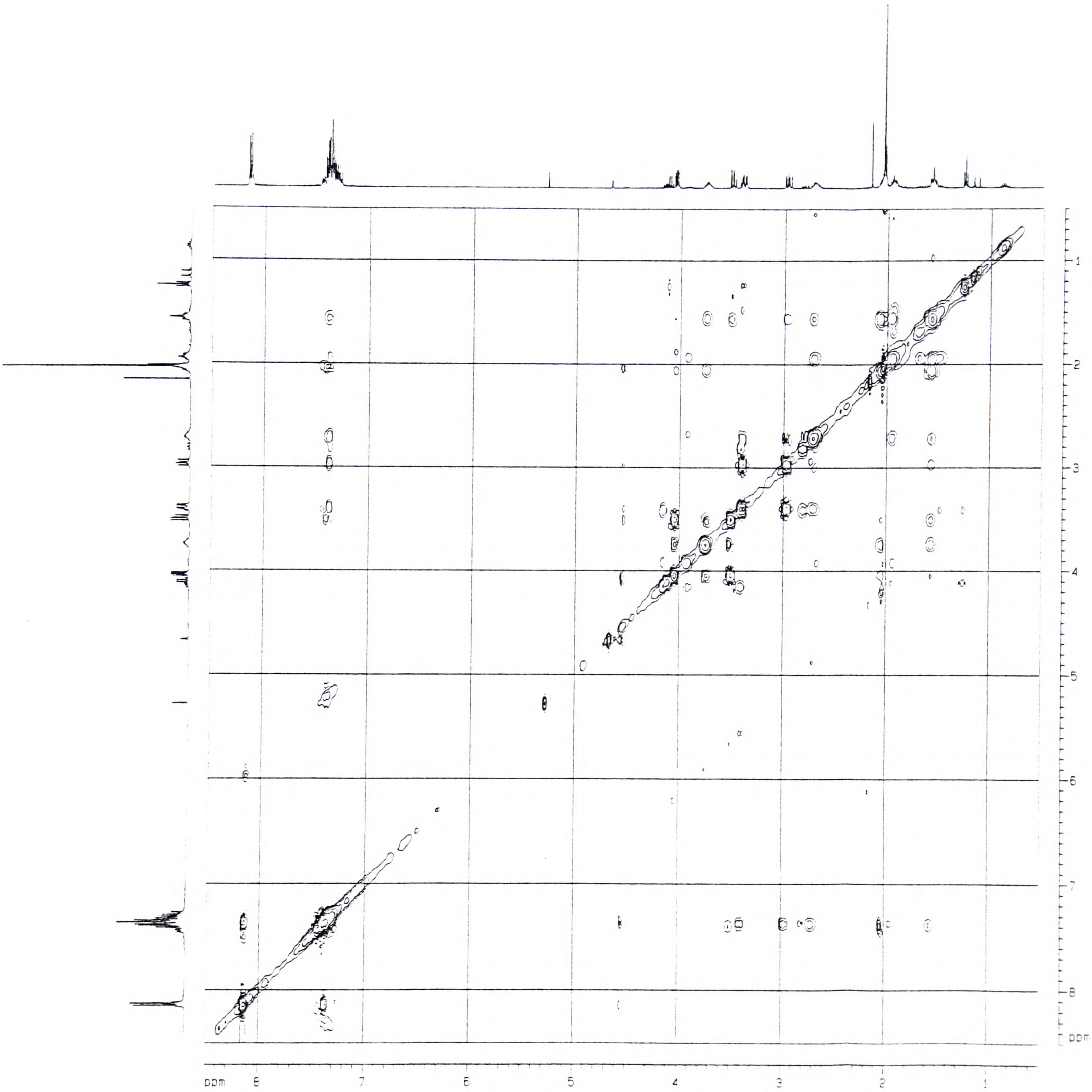
Aniotropic Temperature Factors

Atom	U(11)	U(22)	U(33)	U(23)	U(13)	U(12)
N(1)	0.0295(6)	0.0486(7)	0.0492(7)	-0.0043(6)	-0.0002(5)	-0.0012(5)
C(2)	0.0335(8)	0.0465(8)	0.0581(9)	0.0091(7)	0.0018(6)	-0.0039(6)
O(3)	0.0377(6)	0.0903(8)	0.0626(7)	0.0362(6)	-0.0017(5)	0.0043(6)
C(4)	0.0328(9)	0.096(1)	0.052(1)	0.0208(9)	-0.0104(7)	-0.0116(9)
C(5)	0.0312(8)	0.0463(7)	0.0554(8)	0.0074(6)	0.0015(6)	0.0014(6)
C(6)	0.053(1)	0.064(1)	0.053(1)	0.0104(7)	0.0040(7)	-0.0072(8)
C(7)	0.085(2)	0.173(3)	0.048(1)	0.004(1)	0.007(1)	-0.022(2)
C(8)	0.080(2)	0.126(2)	0.047(1)	-0.022(1)	-0.006(1)	-0.003(1)
C(9)	0.043(1)	0.066(1)	0.061(1)	-0.0264(8)	-0.0104(7)	0.0041(8)
C(10)	0.0306(7)	0.0478(7)	0.0431(7)	-0.0009(6)	-0.0022(6)	-0.0088(6)
C(11)	0.048(1)	0.071(1)	0.0424(8)	0.0032(8)	-0.0049(7)	-0.0091(8)
C(12)	0.059(1)	0.091(1)	0.0472(9)	-0.0196(9)	0.0088(8)	-0.012(1)
C(13)	0.065(1)	0.059(1)	0.076(1)	-0.0199(9)	0.021(1)	-0.0063(9)
C(14)	0.065(1)	0.0475(8)	0.071(1)	-0.0049(8)	0.0153(9)	0.0004(8)
C(15)	0.052(1)	0.0429(8)	0.0483(8)	0.0003(6)	0.0073(7)	-0.0024(7)
C(16)	0.059(1)	0.0454(9)	0.128(2)	0.003(1)	0.031(1)	-0.0067(9)
O(17)	0.0432(8)	0.114(1)	0.092(1)	-0.0458(8)	-0.0168(6)	-0.0010(8)

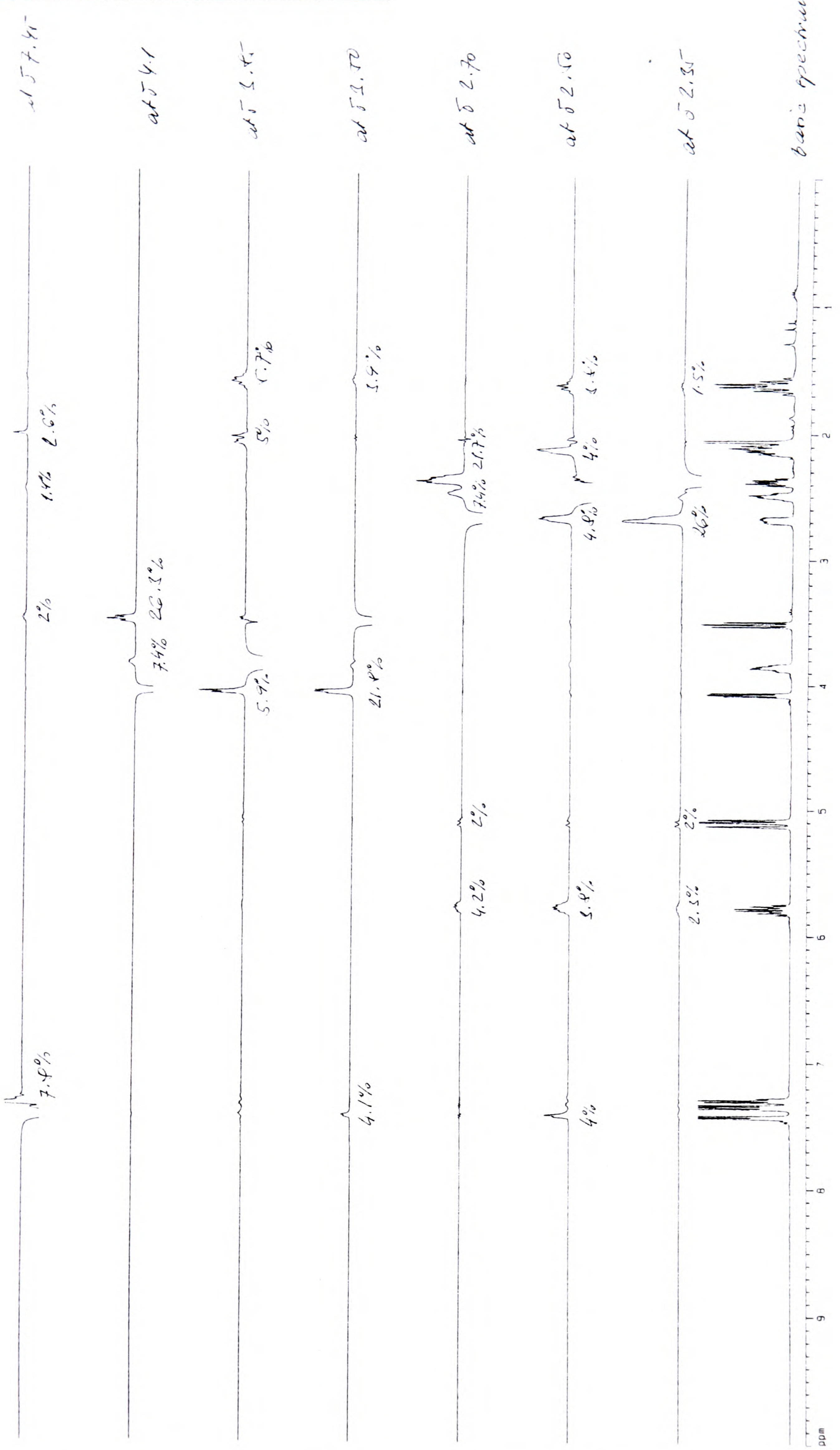
2. n. O. e. difference spectrum of 103b



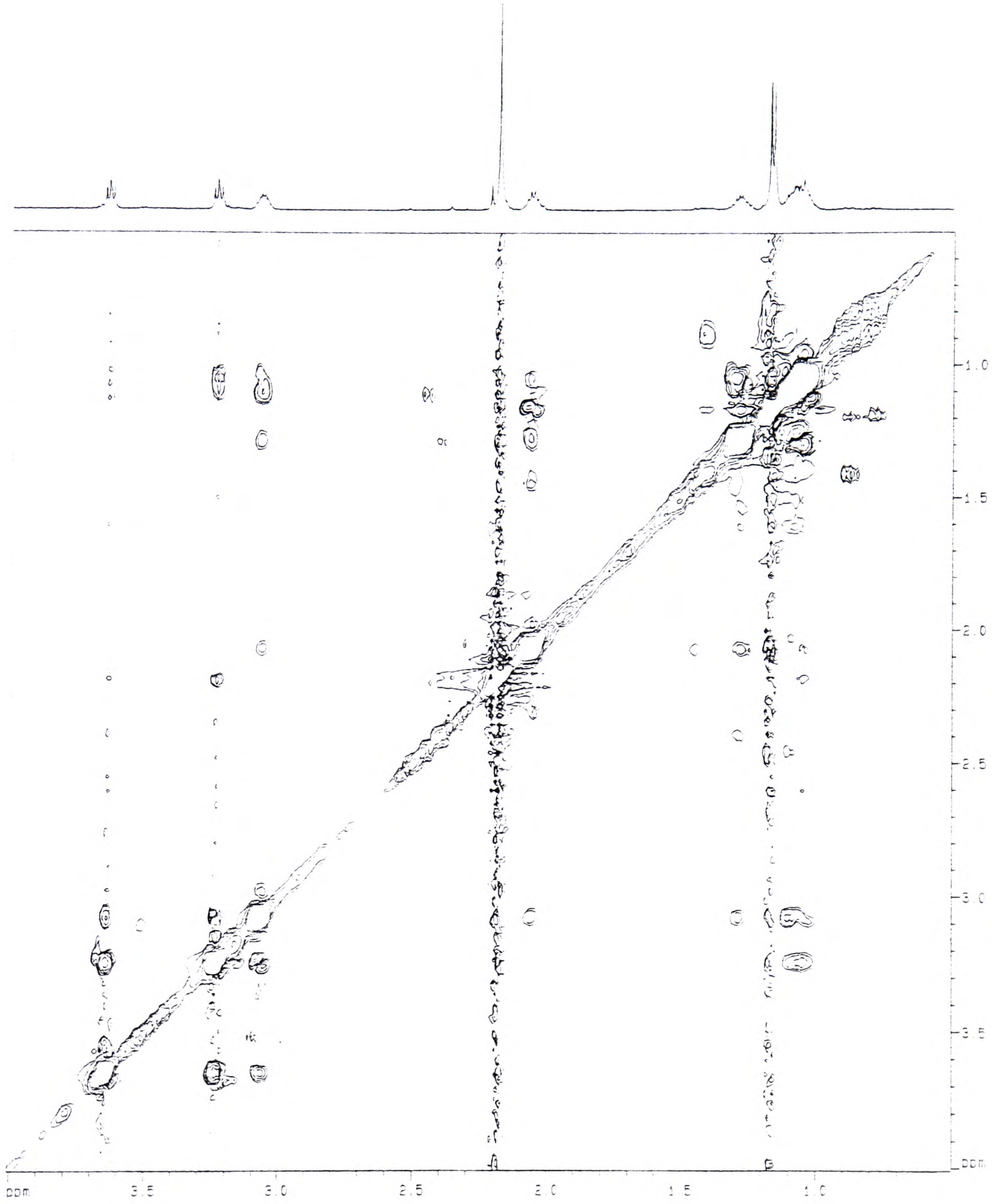
3. NOESY spectrum of 104b



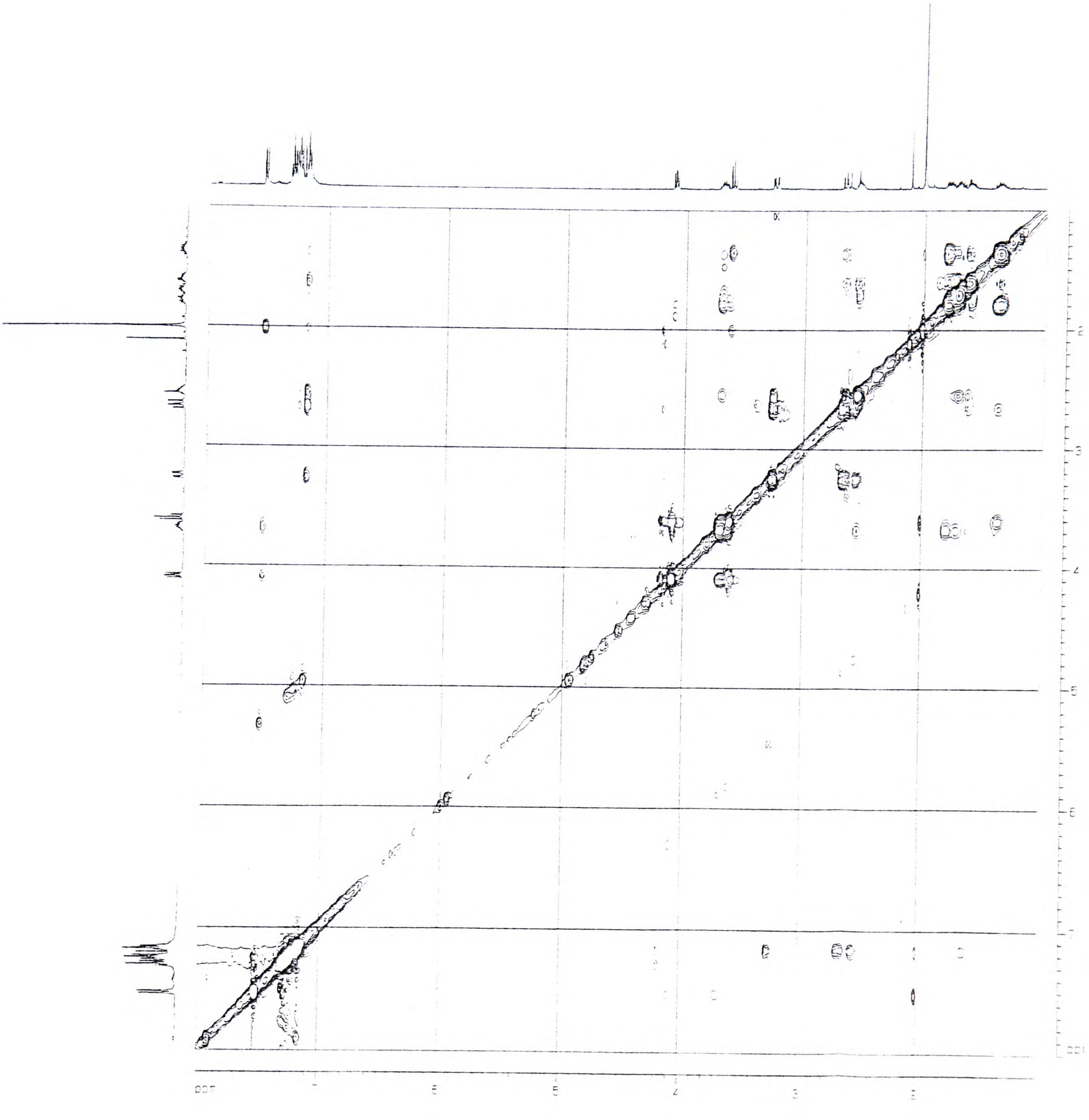
4. n. O. e. difference spectrum of 105b



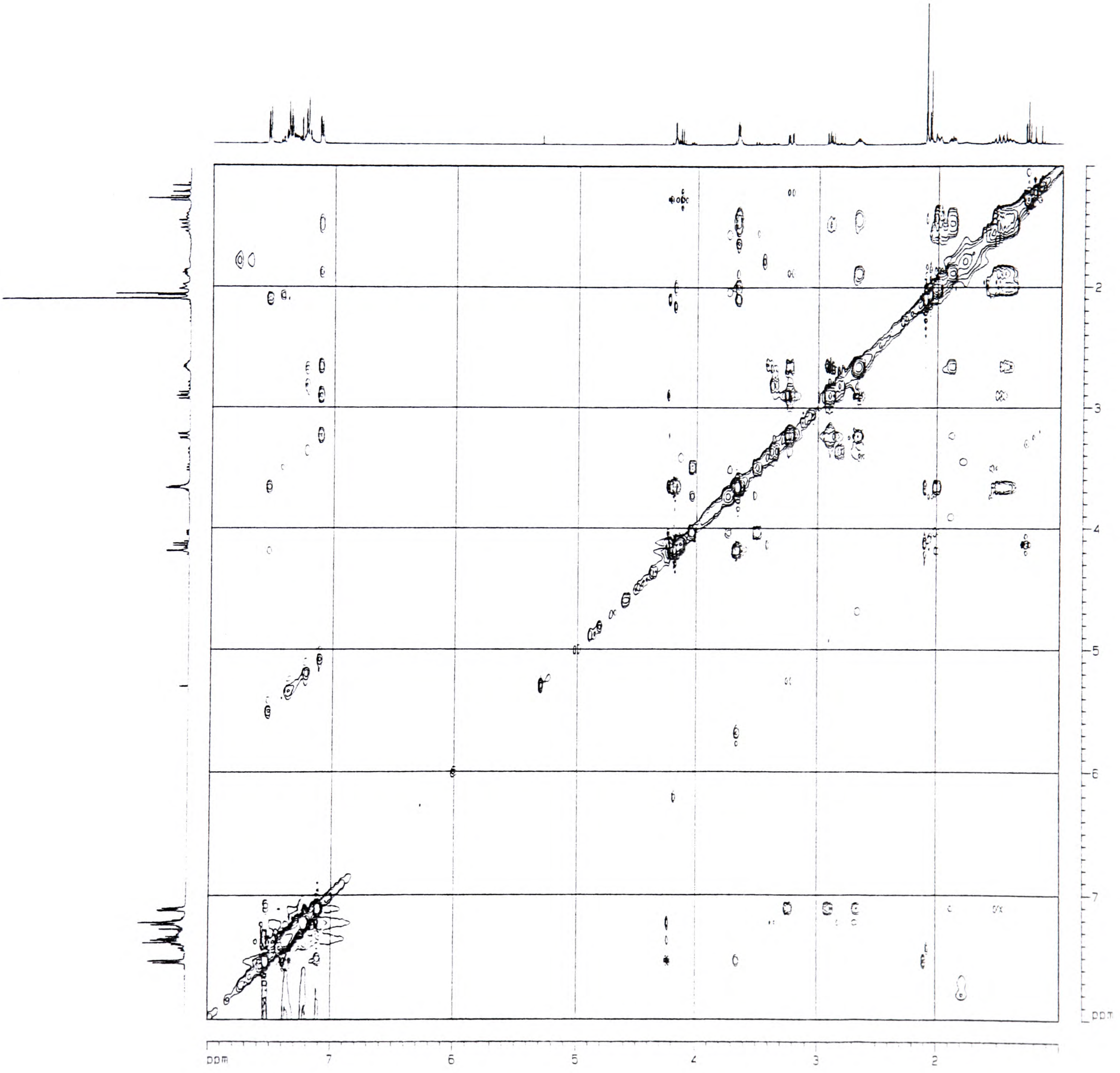
5. NOESY spectrum of 113a



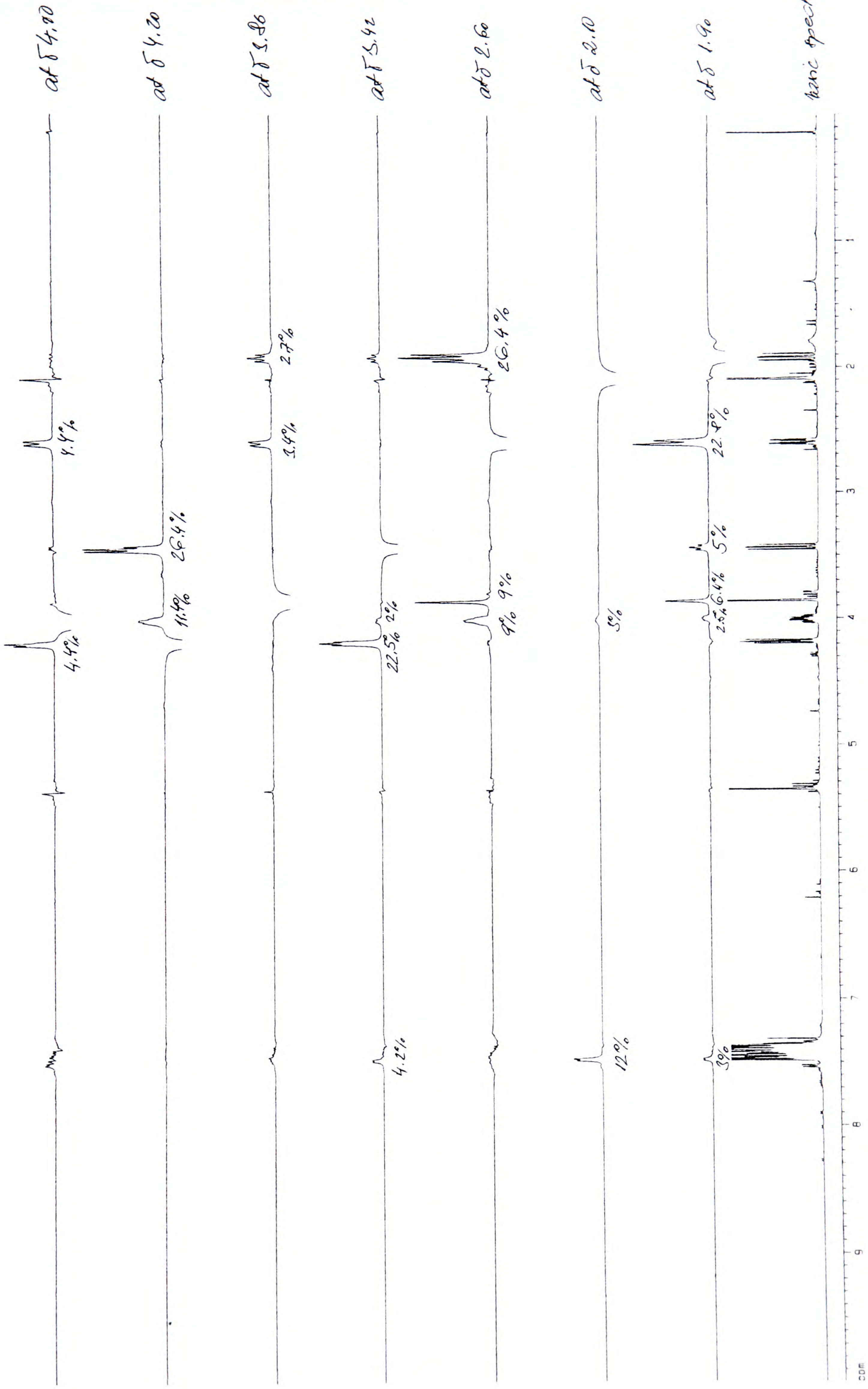
6. NOESY spectrum of 114a



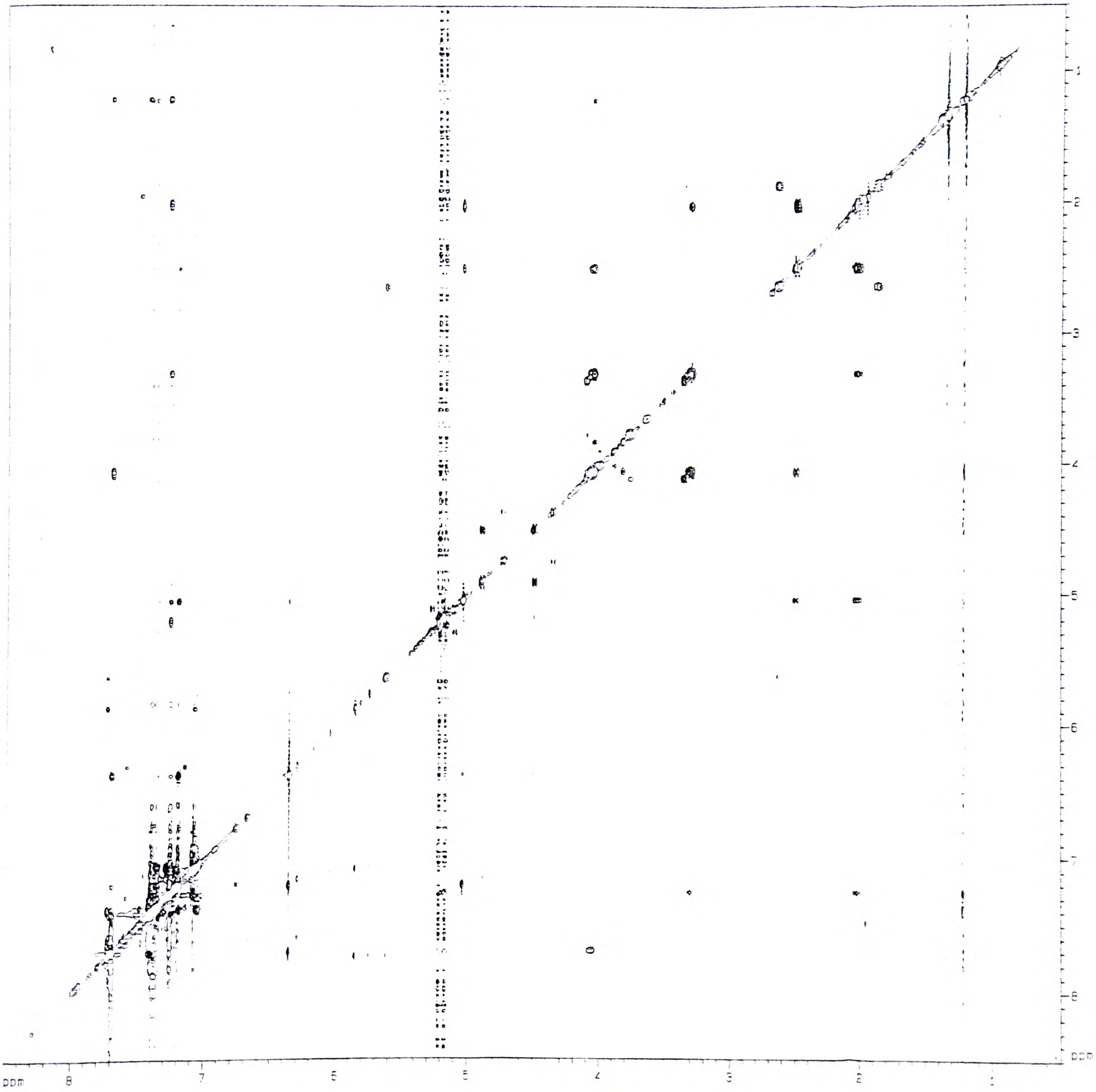
7. NOESY spectrum of 114b



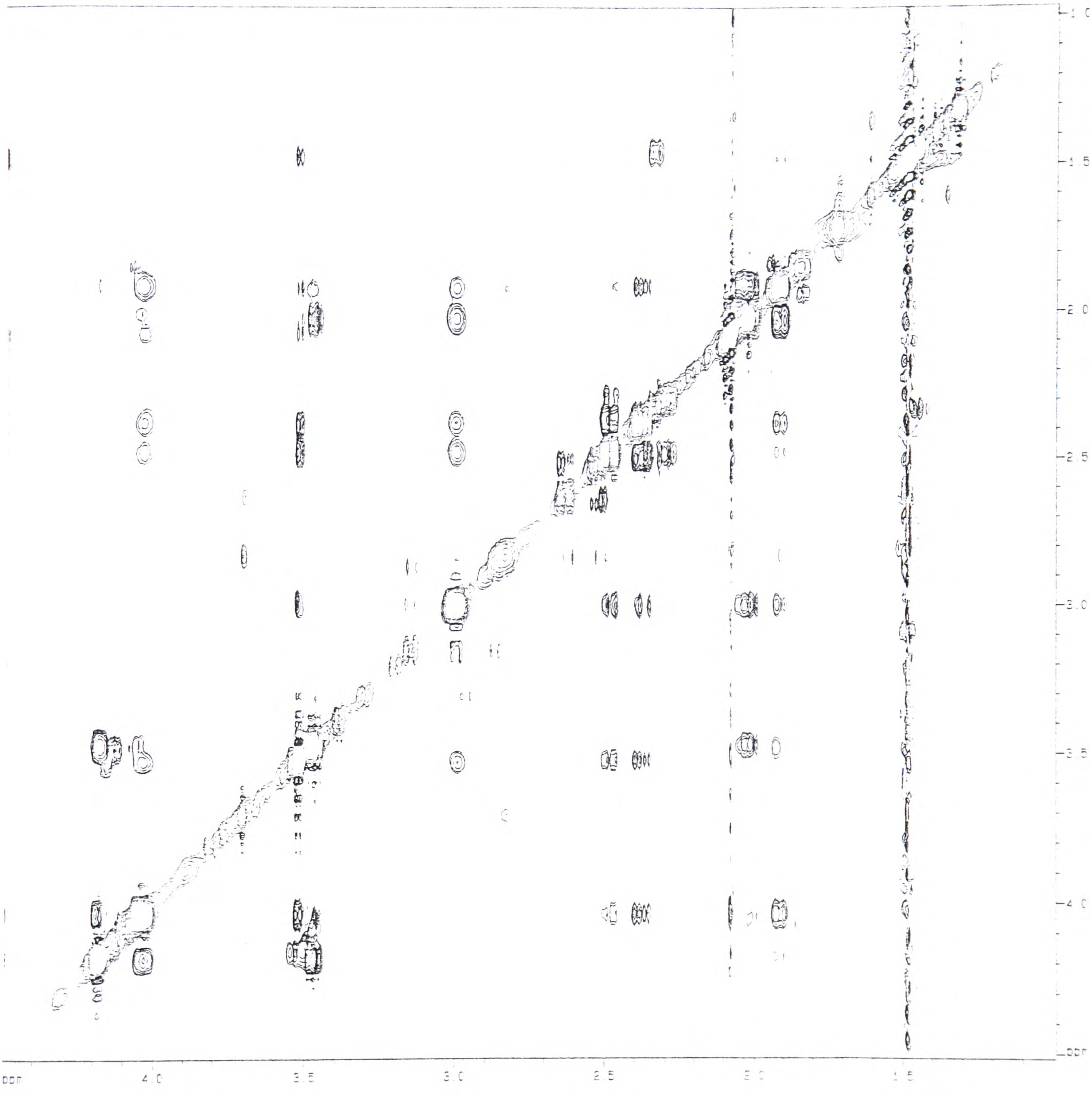
8. n. O. e. difference spectrum of 126



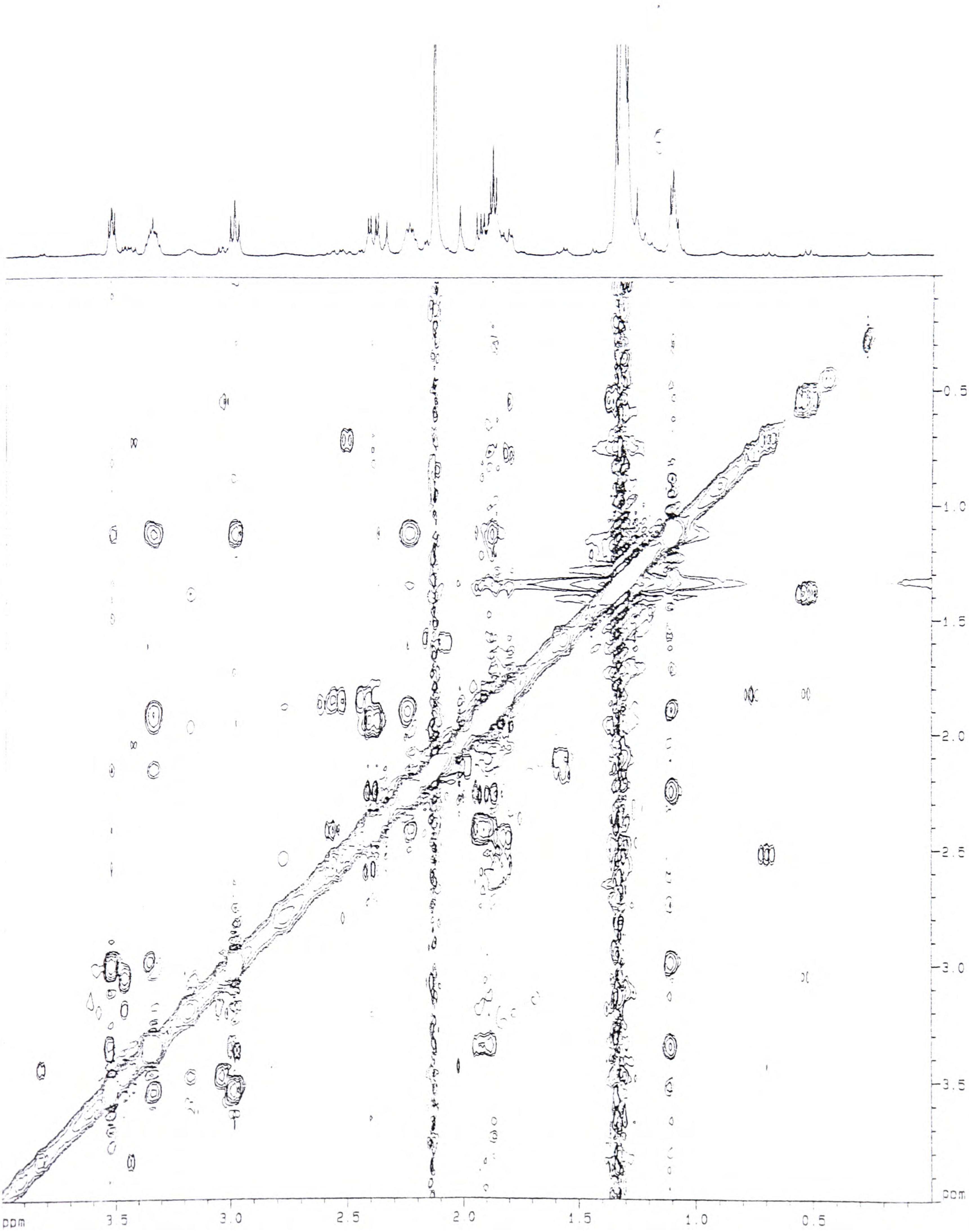
9. NOESY spectrum of 129



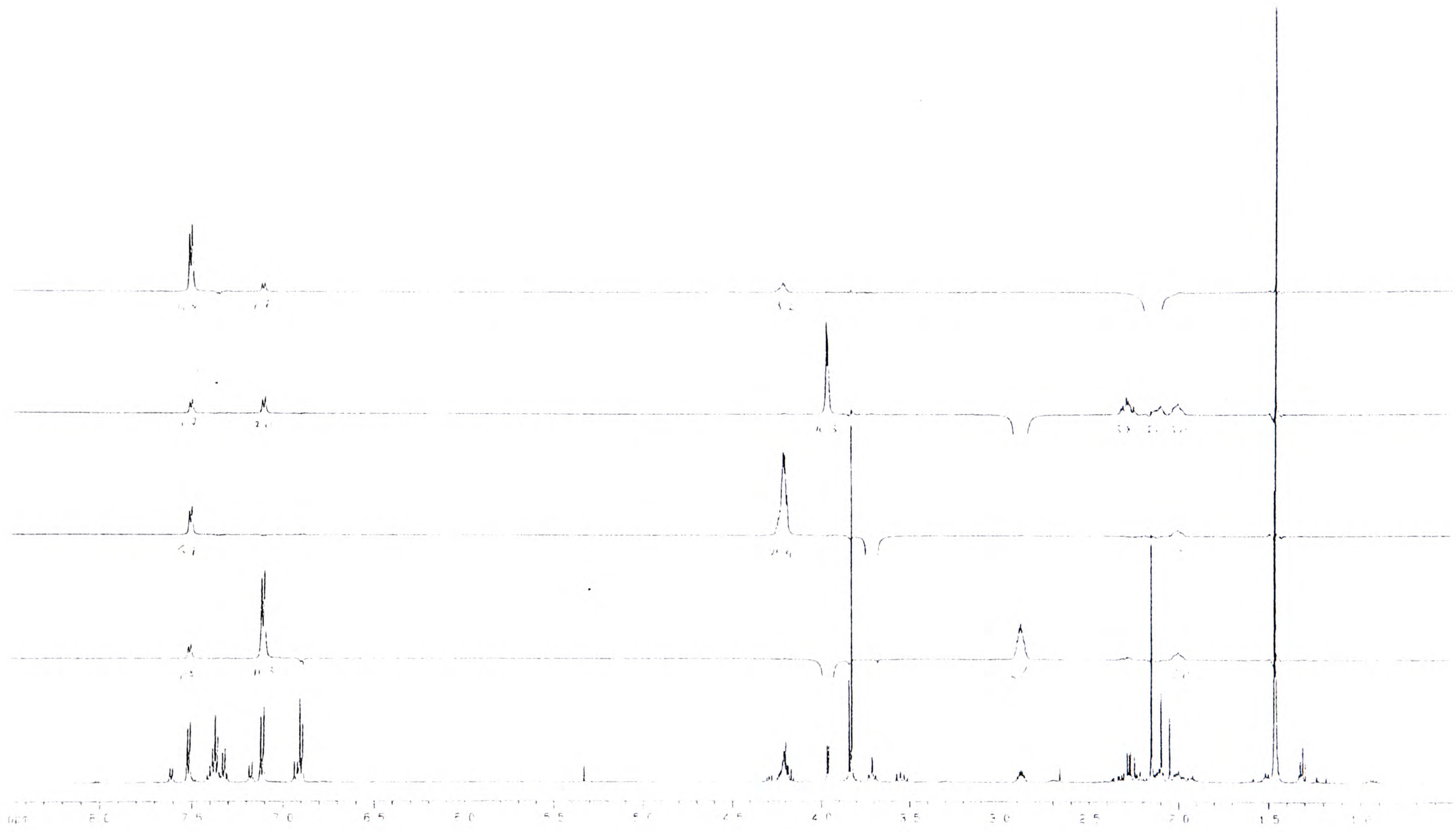
10. NOESY spectrum of 143



11. NOESY spectrum of 153



12. n. O. e. difference spectrum of 154



13. n. O. e. difference spectrum of 169