Some Studies in the Chemistry of Substituted
Azetinone and Pyrroloindole- Carboxylic Acids

By

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A thesis presented in partial fulfilment of
the requirements for the Doctor of Philosophy
Degree of the University of London.

Dept. of Chemistry
University College London
1991
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ABSTRACT

This thesis is concerned with the chemistry of azetidinone carboxylic acids and pyrrolodine carboxylic acids and their derivatives. As such, the introduction surveys the general field of β-lactam biochemistry, the more specific area of carbapenem synthesis and the chemistry of pyrroloindole-2-carboxylic acids.

The first main section of the thesis describes the free-radical chemistry of azetidin-2-one-4-carboxylic acids and the attempted elaboration of these materials into precursors to the carbapenem antibiotic 1β-methylthienamycin.

The second section involves an investigation into both the one and two electron chemistry of pyrroloindole-2-carboxylic acids. Various derivatives of these acids were also synthesized in an attempt to elucidate the mechanism for the high stereoselective formation of the endo-isomer.

The oxidative cleavage of the indole ring of tryptophan derivatives was investigated resulting in enantiospecific syntheses of R- and S-α-methyl aspartic acids. During the course of these studies, a crystalline mixed anhydride was isolated from reaction of a carboxylic acid with a chloroformate and its structure determined by single crystal X-ray analysis.
ACKNOWLEDGEMENTS

I would like to thank the Department of Chemistry at University College London and its staff for providing such excellent research facilities and services. I sincerely thank my supervisor Dr David Crich and members of his group, particularly Dr Timothy Ritchie, Dr Simon Fortt and Dr John Davies for their practical help and advice. I thank Prof Ganellin's group for allowing my occasional use of their instruments and apparatus, and Mr Wasil Tertiuk's frequent practical advice. I thank Mr Christopher Cooksey for various services which are too many to mention here. I thank Dr Margaret Mruzek for the mass spectroscopy work. I thank Dr Derek Tocher and his team for the X-ray crystallographic work done in this thesis. I thank all the technical and supporting staff for their services and help. I like to thank Mr L. C. Claude for his frequent night time companionship in the laboratory when I was working late.

I would like to thank my industrial supervisor Dr Michael Betts of I.C.I. Pharmaceuticals and his team for providing me with so much help on the β-lactam work and for giving me such a pleasant three months' stay with them.

I would also like to acknowledge my C.A.S.E. award from the Science and Engineering Research Council (SERC) in collaboration with I.C.I. Pharmaceuticals, and their generous financial support to this project.

I thank most sincerely my family for their understanding and support during my PhD.

Lastly, I like to thank all those whose help I have received but have not mentioned here.

To you all, THANK YOU!
DEDICATIONS

To:

Gran, Dad, Mum,
Pui, Pui-Yin, Chat-Kong,
Aunt Joyce,
And to the memory of Chan Chat Wah
石师乙之大師
李尚英題書於九一年四月八日
ABBREVIATIONS

Å Angstrom
AA An arbitrary amino acid residue
Ac Acetyl
AIBN 2,2'-Azoisobutyronitrile
Ala The amino acid residue alanine
Ar Aryl
Asp The amino acid residue aspartic acid
Bn Benzyl
Boc t-Butyloxycarbonyl
Bu Butyl
Bz Benzyl
Cys The amino acid residue cysteine
DAM Di-p-anisylmethyl
DCC Dicyclohexylcarbodiimide
DCU Dicyclohexylurea
de Diastereoisomeric excess
DIPA N,N-Diisopropylamine
DIEPA N-Ethyl-diisopropylamine (Hunig’s Base)
DMAP 4-Dimethylaminopyridine
DMF N,N-Dimethylformamide
DMSO Dimethylsulphoxide
EDG Electron Donating Group
ee Enantiomeric excess
<table>
<thead>
<tr>
<th>Abbreviation</th>
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<tr>
<td>Et</td>
<td>Ethyl</td>
</tr>
<tr>
<td>EWG</td>
<td>Electron Withdrawing Group</td>
</tr>
<tr>
<td>Gly</td>
<td>The amino acid residue glycine</td>
</tr>
<tr>
<td>HMPA</td>
<td>Hexamethylphosphor-tri-amide</td>
</tr>
<tr>
<td>HPLC</td>
<td>High pressure liquid chromatography</td>
</tr>
<tr>
<td>i-Pr</td>
<td>Isopropyl moiety</td>
</tr>
<tr>
<td>hr</td>
<td>Hours</td>
</tr>
<tr>
<td>IR</td>
<td>Infrared</td>
</tr>
<tr>
<td>LDA</td>
<td>Lithium diisopropylamide</td>
</tr>
<tr>
<td>MA/CM</td>
<td>Mixed anhydride Coupling Method</td>
</tr>
<tr>
<td>MCPBA</td>
<td>m-Chloroperbenzoic acid</td>
</tr>
<tr>
<td>Me</td>
<td>Methyl</td>
</tr>
<tr>
<td>Mesyl or Mes</td>
<td>Methylsulphonyl Me-SO₂⁻</td>
</tr>
<tr>
<td>Met</td>
<td>The amino acid residue methionine</td>
</tr>
<tr>
<td>Min</td>
<td>Minutes</td>
</tr>
<tr>
<td>MMPP</td>
<td>Magnesium monoperoxyphthalate</td>
</tr>
<tr>
<td>mp</td>
<td>Melting point</td>
</tr>
<tr>
<td>NBS</td>
<td>N-Bromosuccinimide</td>
</tr>
<tr>
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<td>Nuclear Magnetic Resonance</td>
</tr>
<tr>
<td>NOE</td>
<td>Nuclear Overhauser Effect</td>
</tr>
<tr>
<td>P</td>
<td>An appropriate N-Protecting group</td>
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<tr>
<td>PFP</td>
<td>Pentafluorophenyl moiety</td>
</tr>
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</tr>
<tr>
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<td>The amino acid residue phenylalanine</td>
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</tr>
<tr>
<td>Pro</td>
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<tr>
<td>Py</td>
<td>Pyridine</td>
</tr>
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<td>Abbreviation</td>
<td>Definition</td>
</tr>
<tr>
<td>--------------</td>
<td>------------</td>
</tr>
<tr>
<td>rt</td>
<td>Room temperature</td>
</tr>
<tr>
<td>s-butyl</td>
<td>Secondary Butyl moiety</td>
</tr>
<tr>
<td>SEM</td>
<td>Trimethylsilyl(ethoxymethyl) moiety</td>
</tr>
<tr>
<td>Me&lt;sub&gt;3&lt;/sub&gt;SiCH&lt;sub&gt;2&lt;/sub&gt;CH&lt;sub&gt;2&lt;/sub&gt;OCH&lt;sub&gt;2&lt;/sub&gt;-</td>
<td></td>
</tr>
<tr>
<td>Ser</td>
<td>The amino acid residue serine</td>
</tr>
<tr>
<td>t-Bu</td>
<td>tertiary butyl group</td>
</tr>
<tr>
<td>TEA</td>
<td>Triethylamine</td>
</tr>
<tr>
<td>TFA</td>
<td>Trifluoroacetic acid</td>
</tr>
<tr>
<td>THF</td>
<td>Tetrahydrofuran</td>
</tr>
<tr>
<td>tlc</td>
<td>Thin layer chromatography</td>
</tr>
<tr>
<td>TMS</td>
<td>Tetramethylsilane or Trimethylsilyl Moiety</td>
</tr>
<tr>
<td>Tol</td>
<td>Toluene</td>
</tr>
<tr>
<td>Tosyl or Tos</td>
<td>4-Methylphenylsulphonyl CH&lt;sub&gt;3&lt;/sub&gt;-Ph-SO&lt;sub&gt;2&lt;/sub&gt;-</td>
</tr>
<tr>
<td>Try</td>
<td>The amino acid residue tryptophan</td>
</tr>
<tr>
<td>Tyr</td>
<td>The amino acid residue tyrosine</td>
</tr>
<tr>
<td>Val</td>
<td>The amino acid residue valine</td>
</tr>
<tr>
<td>Z</td>
<td>Benzylxycarbonyl moiety, PhCH&lt;sub&gt;2&lt;/sub&gt;OCO-</td>
</tr>
<tr>
<td>Δ</td>
<td>Heat</td>
</tr>
<tr>
<td>*</td>
<td>Chiral centre</td>
</tr>
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</table>
CHAPTER ONE INTRODUCTION

1.1 Over-view

The work described in this thesis relates to reactions carried out on the monocyclic β-lactam 8, and to reactions carried out on L-tryptophan 1001. Derivatives of these compounds are of biological and possibly of medicinal value.

The numbering system of 1 to 100 for the azetinone carboxylic acid work, and 1001 onwards for the pyrroloindole carboxylic acid work is used in this thesis.
1.2.1 The β-lactam antibiotics

The first β-lactam antibiotic was 'discovered' by Fleming in 1929. He observed that a *Staphylococcus* strain under culture lysed under the influence of a *Penicillium* mould growing nearby. He concluded that the *Penicillium* produced a compound which diffused into the medium and when it reached the bacteria, caused the bacteria to lyse. He named the compound 'Penicillin'. The phenomenon of microbial antagonism was already well known and well described. His attempts to isolate penicillin all failed due to the fact that it decomposed during the process of isolation. He showed that it was sensitive and unstable to acids or bases. The presence or absence of the compound was assessed by biological assays.

Through chemical methods, the structure of penicillin was proposed to be a thiazolidine-β-lactam in 1943. The β-lactam structure was novel at the time and was thought by many organic chemists to be too unstable to exist. The β-lactam structure was unequivocally proved by Hodgkin in 1945 by X-ray crystallographic analyses.

![Chemical structure of penicillin](image)

The thiazolidine-β-lactam structure of penicillin explains its instability. In alkaline solutions and under the action of penicillinase, the β-lactam ring is opened. In acid solutions, a rearrangement to the imidazoline derivative penillic acid takes place. The first successful synthesis of the β-lactam ring was carried out by Sheehan and Henery-Logan in 1957 using the substituted carbo-di-imides as
the condensing agent.\textsuperscript{5}

The biological activity of penicillin is due to its \( \beta \)-lactam structure. The \( \beta \)-lactam acts as an activated acylating agent and acylates the active site of an enzyme, peptidoglycan transpeptidase, crucial in the biosynthesis of the bacterial cell wall.\textsuperscript{6,7}

In 1945 another class of \( \beta \)-lactam antibiotics was discovered with the isolation of cephalosporin C from a \textit{Cephalosporin acremonium} strain by G. Brotzu.

With the wide-spread use of the \( \beta \)-lactam antibiotics, resistance to these drugs has emerged in bacteria through the production of bacterial \( \beta \)-lactamases which catalyse the hydrolysis of the \( \beta \)-lactam to the \( \beta \)-amino acid. Over the decades, thousands of synthetic and semi-synthetic penicillins and cephalosporins have been made and tested,\textsuperscript{7} and other natural products were screened for antibacterial activities in an attempt to find antibiotics with better pharmacokinetic properties and resistance to \( \beta \)-lactamases.

In 1976, three biogenetically novel microbial \( \beta \)-lactam compounds were reported: the weakly antibacterial 'nocardicin A',\textsuperscript{9} the \( \beta \)-lactamase inhibitor 'clavulanic acid',\textsuperscript{10} and 'thienamycin'.\textsuperscript{11,12,13}

Thienamycin is a metabolite of \textit{Streptomyces cattleya}.\textsuperscript{11} It has been named to denote the then novel \( \beta \)-thioenamin chromophore. Thienamycin has a \textit{carbapenem} skeleton \textsuperscript{3}. It is so called because the sulphur in the penem system \textsuperscript{2} is replaced by a methylene group. The -em part of the name refers to the unsaturation at the C-2 position.
Thienamycin has potent, broad spectrum antibacterial activities and has a natural stability against bacterial β-lactamases. Its structure and absolute configuration has been determined to be 4 by chemical methods and X-ray analysis techniques. However it is chemically unstable particularly outside a narrow pH range near neutrality, making its isolation from fermentation difficult and furthermore the drug may be inactivated when taken orally. Thienamycin is also very susceptible to metabolism by renal dehydropeptidase I (DHP-I). These reasons prevent it from being developed as a clinical drug candidate.

In intense efforts to improve the properties of these antibiotics by chemical
modifications, Shih et al (Merck Sharp and Dohme),\textsuperscript{18,19} have first synthesized the 1β-methylcarbapenems 5a and 5b. The introduction of a methyl group at the β-C1 position of the carbapenem nucleus resulted in an exceptional increase in chemical stability and resistance to DHP-I whilst retaining excellent antibacterial activity in the molecule.\textsuperscript{18}

1.2.2 Shih's synthesis of the 1β-methylcarbapenems

Shih et al chose as their starting molecule 6 which was readily available

from the chiral synthesis of thienamycin and N-formimidoylthienamycin.\textsuperscript{27,28}

The first step of the synthesis (scheme 1) was the inversion of the hydroxyl group in the hydroxyethyl side chain by a modified Mitsunobu reaction.\textsuperscript{29} The
alcohol was then protected. The methyl group was introduced through the
generation of the enolate by 2eq of base followed by methylation of the enolate
with methyl iodide. However, the α-isomer was formed in preference to the
β-isomer (α:β = 4:1), but the α-isomer may be separated and the enolate
regenerated with 2eq of base and the α-isomer equilibrated to the β-isomer in 78%
yield. The chain was then extended using the Masamune\textsuperscript{30} condition. The alcohol
group was deprotected followed by the diazotization of the molecule by
dodecylbenzenesulphonyl azide. The cyclization was brought about by the
presence of 0.3% rhodium(II) octanoate catalyst giving the bicyclic skeleton. This
was then elaborated to 5a and 5b.
Chapter 1

-Introduction-

NaOH/MeOH

0°C

OH

H C

A S ?

O

NH O

*CH,

6b

t-Butyldimethylsilyl chloride

imidazole, DMF

Si—

O

H

H

H

H

H

H

H

H

CH

O

6c

2eq LDA

Mel

H₂O⁺

THF, -78°C, N₂

Diisopropylamine,
n-butyllithium,
HMPA, Acetic acid

Si—

O

H

H

H

H

H

H

H

H

CH

O

6e

6f

-22-
Chapter 1

-Introduction-

(i) NaOH (aq) / MeOH
(ii) HCl

Acetonitrile, N₂
Carbonyldiimidazole,
Magnesium p-nitrobenzyl malonate,
60°C, 18 hours

(i) 6N HCl MeOH
(ii) 0.1N Na₂HPO₄ 10% K₂CO₃
Chapter 1 - Introduction -

Acetonitrile, N₂
Dodecylbenzenesulphonyl azide
Hexane, triethylamine

6j

Ethyl acetate, Hexane
Rhodium (II) octanoate

6k

Acetonitrile, 0°C, N₂
N₂,N-diisopropylethylamine
diphenylchlorophosphate

6l
Scheme 1
The major problem with this synthesis is attaining the correct stereochemistry at C-5 of $7$. 

The current syntheses of the 1β-methyl carbapenems focus on the stereoselective synthesis of this key intermediate $7$ which has four contiguous chiral centres. The syntheses of $7$ reported over the past few years have been lengthy or non-stereoselective and are mostly unsatisfactory.

### 1.2.3 Synthetic strategy adopted in this project

The aim of this project was to develop a mild method of synthesizing $7$ (or its equivalent) by making use of the free radical method developed by Barton et al. $^{31,32}$

The starting molecule $8$ was used as it was readily available and it also already possessed the desired stereochemistry at C-3 and C-3α.

It has now been accepted that the monocyclic β-lactam functionality is fairly stable, but the introduction of the second ring further strains and destabilizes the β-lactam making it highly reactive. $^{35,36}$

In this scheme (Scheme 2), the free alcohol at C-3α was first protected
with the t-butyldimethylsilyl group. The free radical at C-4 was then generated using Barton's method. 4-Azetidinonyl radicals have been generated previously and have been shown not to undergo ring opening.45
Chapter 1 - Introduction -

(a) Oxaly chloride
(b) Isobutyl chloroformate

10a: X = Cl
10b: X = \(-O^\cdot\cdot\cdotO\)
The procedure to be used for the generation of the radical 12 is as follows:
The acid 9 is first activated to the acid chloride 10a or the mixed anhydride 10b.
followed by its esterification to the thiohydroxamate ester 11. The ester 11 is then allowed to react with the nitro-olefin 30 through a decarboxylative radical chain reaction to give the α-nitrosulphide adduct 14. This radical reaction may be initiated by gentle heating or by a bright tungsten light bulb at room temperature or below.

It was predicted that the azetidinone radical would be quenched by the electron deficient alkene to give the adduct such that the substitution at C-4 was on the opposite face to the substitution that was already on C-3 of the azetidinone, thus giving the desired stereochemistry at C-4. However, it was recognized that diastereomers would be obtained at C-5 when the azetinonyl radical was quenched with either the cis- or trans- nitro-olefin.

1.2.4 Barton's thiohydroxamate method of generating free radicals

The chemistry of the thiohydroxamate esters has been thoroughly studied by Barton et al. The esters were probably formed via the isomeric 2-acylthiopyridine-N-oxides, which then rearrange intramolecularly to give the O-acylthiohydroxamate esters (Scheme 3).

![Scheme 3](image)

Support for this hypothesis was provided by the fact that 2-mercaptopyridine-N-oxide reacts with methyl iodide to give isolable, stable, 2-methylmercaptopyridine-N-oxide which cannot favourably rearrange...
Support was also provided by the fact that acylation of the vinylogous thiohydroxamic acid 4-mercaptopyridine-N-oxide leads mainly to the 4-acylthiopyridine-N-oxide which is incapable of intramolecular rearrangement to the O-acyl compounds (Scheme 5).42

The radicals generated from O-acyl thiohydroxamates have already been used to form C-C bonds by addition to olefins.32 If the olefin has an electron-withdrawing group (EWG), such as a nitro group, attached to one end of
the double bond, then the radical will add regioselectively to the electron-poor end of the double bond (Scheme 6).\(^{32}\)

\[\text{R}^\bullet + \text{EWG} + \text{EWG} \rightarrow \text{R- + CO}_2\]

In our proposed synthetic scheme, advantage is taken of this regioselective addition of the radical generated to the nitro-olefin.

### 1.2.5 Conversion of the α-nitrosulphide functionality into the carbonyl functionality

There are already methods described in the literature for the conversion of the nitro functionality or the α-nitrosuphide functionality into the carbonyl functionality. McMurray and Melton\(^ {43}\) reported the use of aqueous TiCl\(_3\) in the conversion of a primary or secondary nitro compounds into the corresponding
aldehyde or ketone. The mechanism was proposed to go through the imine which is then hydrolysed to the carbonyl group (Scheme 7).
In this proposed mechanism, the nitro group is first reduced to the nitroso group through two single electron transfer steps. The nitroso group is then reduced to the hydroxylamine through another two single electron transfer steps. This is then followed by the elimination of ‘EOH’ to give the imine which is then hydrolysed to the carbonyl group.

The attraction of this method is that it could be carried out at a buffered pH of 5 or 6 which is desirable for the β-lactam system. Barton,\textsuperscript{32} using this method on \textnormal{15}, reported obtaining the aldehyde \textnormal{16}.

Hence, if McMurray's method were applied to \textnormal{14}, the aldehyde \textnormal{17} would be the expected product. Compound \textnormal{17} may then be oxidized to the acid \textnormal{18}.
Another reaction which might take place under the acidic conditions is the Nef reaction, which may then give the thiopyridyl ester which may then be hydrolyzed to the acid (Scheme 9).
Thus if this reaction took place the products would be 19 and 18.
Barton,\textsuperscript{32} also reported the conversion of the $\alpha$-nitrosulphide directly to the acid with alkaline hydrogen peroxide; and indirectly by first chlorinating with sodium hypochlorite, followed by alkaline hydrolysis (Scheme 8). Instead of chlorination with sodium hypochlorite, N-chlorosuccinamide may be used, or bromination with N-bromosuccinamide to displace the $\alpha$-hydrogen. Barton also reported the use of iodoxybenzene (PhIO$_2$) as an oxidizing agent. The use of ozone is yet another possibility.\textsuperscript{44}

1.2.6 Removal of the protecting groups

The DAM group protecting the $\beta$-lactam nitrogen may be removed by stirring with aqueous ceric ammonium nitrate and acetonitrile at around room temperature,\textsuperscript{26,46} or by stirring with anisole and trifluoroacetic.$^{33}$

The $t$-butyldimethylsilyl group protecting the alcohol may be removed by refluxing in dichloromethane with 1,3-dimethoxybenzene and boron trifluoride etherate to give the target molecule 7.$^{46}$
1.2.7 Preparation of 8

The starting compound 8 was synthesized by the Sumitomo Pharmaceutical Co Ltd, using the [2+2] cycloaddition of diketene with the appropriate imine generated in situ (Scheme 10). As R* is chiral, 20a and 20d, 20b and 20c are all diastereomers. Thus the four compounds may be separated by ordinary means such as column chromatography. The ketone is then reduced to the 21 and the two diastereomers separated. 21a is then saponified to the free acid 8.

The mechanism of this reaction is still uncertain, as it is ambiguous whether the true reactant of the cycloaddition is diketene, acetylketene or the 1-(acetoacetyl)imidazole derivative, and whether the β-lactam formation is concerted, stepwise or a mixture of both processes.

\[
\begin{align*}
\text{DAM} & \quad + \quad \begin{array}{c}
\text{NH}_2 \\
\end{array} \\
& \quad \begin{array}{c}
\text{H---C---OR}^* \\
\end{array} \\
& \quad \begin{array}{c}
\text{H---C---C---OR}^* \\
\end{array} \\
\text{imidazole, stirring for > 24 hrs} & \quad \begin{array}{c}
\text{R}^* \text{ has at least one} \\
\text{chiral centre} \\
\end{array} \\
\text{-20 °C} & \quad \begin{array}{c}
\text{DAM} \\
\end{array}
\end{align*}
\]
Scheme 10
1.3.1 Non-Proteinogenic Amino Acids

Optically active, non-proteinogenic amino acids are of interest because of their documented or potential biological activity. Some are valuable pharmaceuticals, such as L-DOPA, (S)-α-methyldopa, D-penicillamine or D-cycloserine. Others are components of pharmaceuticals, for instance D-phenylglycine or D-tyrosine in the semi-synthetic penicillins, ampicillin or amoxycillin.

In biochemistry, uncommon amino acids are valuable tools to investigate the mechanism of enzyme reactions. They may be antibiotically active, i.e. they prevent cell growth of certain microorganisms. They are all enantiomerically pure; only one enantiomer displays the specific activity. This activity discloses how they work. They are antagonists of the physiological (proteinogenic) amino acids. Interacting in the amino acid metabolism of the living cell, they either inhibit or deceive an enzyme, preventing thus the proper biosynthesis or biodegradation of a proteinogenic amino acid or the correct biosynthesis of a protein. In fact, enzyme inhibition studies with such uncommon amino acids furnish valuable information about the mode of action of certain enzymes.

1.3.2 The α-alkylated α-amino acids

The α-alkylated α-amino acids have generated considerable interest with respect to their synthesis, their recorded bioactivity and their possible use as peptoids. They are known to be powerful inhibitors of those enzymes that metabolize the corresponding simple α-substituted proteinogenic amino acids, and are also constituents of natural products such as the antibiotics, amicetin and
polypeptide antibiotics such as antiameobin I.

The simple replacement of an α-hydrogen of an amino acid residue in a peptide with a methyl group has several consequences.

Firstly, theoretical calculations made by Marshall showed that it results in the reduction of the conformational space available to the backbone of the peptide chain at the position where that residue occurs. The theoretical calculations were confirmed by experimental findings. One consequence of this is that they can be used in the study of the interaction of peptide hormones with their receptors because the peptide hormone analogs containing α-methyl amino acid residues should have a sterically rigid backbone conformation at those positions. They would correspond closely to 'conformational analogs' of the hormone, i.e. analogs which have a primary structure essentially identical with that of the native hormone, but which are capable of adopting conformations that would comprise only a small subset of the total set available to the parent molecule.

Should such an analog be biologically active, important constraints might thereby be placed on evolving models of the conformation assumed by the hormone as it interacts with its receptor. In addition if side-chain interactions are essential for binding, such analogs which retain all the native hormone's side chains, might offer a route to inhibitors which bind to the receptor but which are not capable of inducing subsequent events necessary to bring about biological responses owing to their conformational inflexibility. This sort of inhibitor might be missed by schemes of analog generation which involve varying only the character or position of side chains.

Secondly, analogs bearing α-methyl groups could also be expected to be metabolized slowly, since model compounds containing α-methyl amino acids are known to be resistant to chemical hydrolysis, and to enzyme attack by both endopeptidases and exopeptidases.

Thirdly the increased lipophilicity concurred by the α-methyl group
promotes greater penetration of cell walls.\textsuperscript{82}

Thus the synthesis of such analogs might therefore result in the generation of either long-acting agonists or antagonists or of peptides which lack either property but which nonetheless potentiates the effect of the endogenous compounds by interfering with their degradation.

Another simple modification to an amino acid is the inversion of its stereochemistry.

The amino acids are also important as neurotransmitters and modulators, in human and animal nutrition, flavourings, taste enhancers and sweeteners, and in agrochemicals and cosmetics.\textsuperscript{83}

\subsection{1.3.3 Asymmetric $\alpha$-alkylation of $\alpha$-amino acids}

Two substantially different concepts have been developed for the asymmetric $\alpha$-amino acids,\textsuperscript{84} the \textbf{Schöllkopf bis-lactim ether Method},\textsuperscript{85} which relies on a second $\alpha$-amino acid as chiral auxiliary, and the \textbf{Seebach Self-Reproduction of Chirality Method} in which the amino acid to be alkylated is itself used as a source of chirality.\textsuperscript{86}

\subsection{1.3.4 The Schöllkopf bis-lactim ether method}

Schöllkopf's approach is based on heterocyclic chemistry and has the following strategy.\textsuperscript{85}

1. From a readily available racemic lower amino acid and a chiral auxiliary, a heterocycle is built up which is CH-acidic adjacent to the potential amino group and which contains 2 sites susceptible to hydrolysis.
2. An electrophile is introduced diastereoselectively via the anion of the heterocycle.
3. Subsequently the heterocycle is cleaved by hydrolysis to liberate the chiral auxiliary and the new optically active amino acid.

In this strategy, the heterocycle is of no interest in itself. It merely serves as a vehicle to construct an acyclic molecule with the proper structure and proper configuration. It makes use of the obvious fact that a heterocyclic intermediate is necessarily more rigid than its open-chain analog so that a degree of asymmetric induction is to be expected.

This strategy may be illustrated with L-alanine as an example, which results in an \( \alpha \)-alkyl-\( \alpha \)-methyl amino acid being synthesized (Scheme 11).
Chapter 1 - Introduction -

1. Reaction with \( \text{[\((\text{CH}_3)_3\text{O}^+)\text{BF}_4^-]\) in \(\text{CH}_2\text{Cl}_2\)

2. Reaction with \(\text{BuLi/THF/-70}^\circ\text{C}\) or LDA

3. Reaction with \(\text{RX, eg PhCH}_2\text{Br}\)

Diagram:
- 1004
- 1005
- 1006
On heating of L-alanine methyl ester 1002, two molecules condense to give the diketopiperazine [cyclo(L-Ala-L-Ala)], 1003. In this reaction, the optical purity was reduced. Recrystallization from water gave 1003 with about 93% ee.87 Compound 1003 is not a suitable starting material as its CH-acidity is not high enough, and furthermore, any base would remove preferentially* the protons from the nitrogens. However a suitable starting compound was obtained by converting 1003 into its bis-lactim ether [(3S,6S)-2,5-dimethoxy-3,6-dimethyl-3,6-dihydropyrazine], 1004, with trimethyloxonium tetrafluoroborate (Meerwein type salt). Hydrolysis of the intermediate heterocycle bis-tetrafluoroborate must be carried out with phosphate buffer to avoid racemization.88 With butyllithium or LDA (in THF or glyme, -78°C), 1004 reacts smoothly to the lithium derivative 1005 which contains a stable diazapentadienyl anion, and is probably best described as an ion pair. A second metallation at C-6 is very unlikely because it would give an anti-aromatic 8π-electron system.89 The anion may then be alkylated. With benzyl bromide, it gave in 88% the product 1006. The inducing centre C-6, i.e. (R)-configuration is induced at C-3 with d.e.=93%.87 This is then hydrolyzed with 2-equivalents of 0.25N HCl at room temperature to liberate 1002 and (R)-α-methyl-phenylalanine methyl ester 1007.
which were separated by distillation. The α,α-dialkylated product 1007 retains the stereochemistry of the original L-alanine.

The stereochemistry of this reaction is explained on the basis that it proceeds via a planar transition state of the anion 1005, and that the electrophile approaches it from the less hindered face, (Scheme 12).
This method is not limited to symmetrical bis-lactim ethers and has been carried out on mixed bis-lactim ethers. For example the bis-lactim ether of cyclo(L-Val-Ala) was synthesized with the L-Val part being the chiral auxiliary. The synthesis is shown in scheme 13.
**Scheme 13**

L-valine 1008, the chiral auxiliary was converted with phosgene into N-carboxyanhydride (L-Val-NCA) 1009. This gave with D.L-Ala-OCH₃ the dipeptide 1010, which on heating in toluene cyclizes to the diketopiperazine 1011.
This was converted into the bis-lactim ether 1012, [(3RS,6S)-2,5-dimethoxy-6-isopropyl-3-methyl-3,6-dihydro pyrazine] with Meerwein's salt. This bis-lactim ether 1012 reacted with butyllithium (THF,-78°C) regiospecifically in the alanine part of the molecule to give the anion 1013. This gave the addition product 1014 with alkyl halides in good chemical yields and with >95% de. The alkyl group entered trans- to the isopropyl group at the inducing centre to give the (3R) configuration. On hydrolysis, the α-alkylated alanine formed has the configuration of L-alanine.

1.3.5 Seebach's Self-Reproduction of Chirality Method

Seebach's so called Self-Reproduction of Chirality Method is an elegant method for the preparation of α-alkyl disubstituted amino acids. Principally, it makes use of the cyclic lithium anion intermediates 1015 and 1016 which are then quenched stereoselectively by a number of electrophiles.

Chiral induction is achieved by making use of the chirality inherent in the starting α-amino acid which dictates the configuration of the lithium intermediates.
1015 and 1016. Hence unlike Schöllkopf's method, chiral induction is not achieved with a chiral auxiliary.

The chiral imidazolidinone or the oxazolidinone are formed by relatively standard procedures (Schemes 14 and 15).93

\[
\begin{align*}
\text{CHO} & \xrightarrow{\text{Esterification}} \text{CONHCH}_3 \\
\text{CONHCH}_3 & \xrightarrow{\text{CH}_2\text{Cl}_2, \Delta} \text{CONHCH}_3
\end{align*}
\]

\[
\begin{align*}
\text{R} & = \text{Me, Bn, Ph, Et, CH}_2\text{CH}_2\text{SMe} \\
\text{R} & = \text{Me, Bn, Ph, Et, CH}_2\text{CH}_2\text{SMe}
\end{align*}
\]

Scheme 14
With the imidazolidinone, the \( \alpha,\alpha \)-dialkyl substituted amino acid product
has an inverted stereochemistry from that of the parent amino acid, whereas with the oxazolidinone, the α,α-dialkyl substituted amino acid product retains the stereochemistry of the parent amino acid. This is because the trans-diastereomer was obtained as the major product for the imidazolidinone, whereas the major product for the oxazolidinone was the cis-diastereomer.

The imidazolidinone 1018 was formed by first condensing the protected chiral α-amino acid 1016 with pivaldehyde to form the imine 1017. Treatment with gaseous HCl in methanol, and benzylation afforded the cyclic derivative 1018. The trans-diastereomer being the major product.

LDA mediated deprotonation of 1018 afforded the enolate 1019 which was then quenched with a variety of electrophiles (alkyl halides, carbonyl compounds) to give the adducts 1020, with excellent de’s (>90%). The alkylation of the enolate took place preferentially from the opposite face to the t-butyl moiety and the overall transformation occurred with inversion of configuration as the trans-substituted imidazolidinone (1018) was the major diastereomer obtained.

The oxazolidinone 1024 was formed first from the condensation of the sodium salt of the appropriate α-amino acid 1022 with pivaldehyde, followed by treatment with benzoyl chloride which cyclized the Schiff base 1023 to the desired cyclic derivatives 1024 as a mixture of cis/trans isomers in a separable 4:1 ratio.

Subsequent low temperature deprotonation of the major cis-isomer 1024a with LDEA (lithium diethylamide) and quenching of the enolate 1025 with a variety of electrophiles (alkyl halides, carbonyl compounds) provided the adducts in good chemical yields (85-95%) and de’s of >90%. The overall transformation occurred with retention of stereochemistry as the cis-oxazolidinone 1024a was formed as the major diastereomer. The chiral disubstituted α-amino acid hydrochlorides, 1027, may be obtained by treatment with HCl gas.

Although both methods are comparable in terms of reactivity and stereoselectivity (and it should be noted that both cis and trans isomers of 1018
and 1024 are accessible), the milder cleavage conditions render the N,O-heterocycle 1024 a more useful intermediate than the N,N-heterocycle 1018 for the overall enantioselective synthesis of α,α-disubstituted α-amino acids.97

Both the Schöllkopf and Seebach methods have been applied to the synthesis of optically active α-substituted tryptophan.

1.3.6 Schöllkopf’s method in the synthesis of α-methyl tryptophan

In Schöllkopf’s method (Scheme 16),98 the mixed bis-lactim ether, 1012, formed from L-valine and alanine was synthesized, and the anion generated with BuLi in THF at -78°C, and then quenched with N-protected indolylmethyl bromide 1028 to give the alkylated product 1029. On hydrolysis, the (R)-α-methyl tryptophan 1030 was obtained.

\[
\begin{align*}
\text{Me} & \quad \text{OH} \\
\text{N} & \quad \text{OMe} \\
\text{Me} & \quad \text{Me} \\
\end{align*}
\]

\[
\text{BuLi, THF} \quad \text{-78°C}
\]

\[
\begin{align*}
\text{Me} & \quad \text{OH} \\
\text{N} & \quad \text{OMe} \\
\text{Me} & \quad \text{Me} \\
\end{align*}
\]

\[
\text{Li}^+
\]

\[
\begin{align*}
\text{Br} & \quad \text{N} \\
\text{Boc} & \quad \text{Me}
\end{align*}
\]

\[
\text{Si-face attack}
\]

\[
\begin{align*}
\text{Me} & \quad \text{OH} \\
\text{N} & \quad \text{OMe} \\
\text{Me} & \quad \text{Me} \\
\end{align*}
\]

\[
\text{83% de=95% Boc}
\]
1.3.7 α-Methyl tryptophan from Seebach's Oxazolidinone Method

Seebach's method has the clear and simple advantage of utilizing the existing chirality of a temporarily protected amino acid to dictate asymmetry at the new centre, the so called Self-Reproduction of Chirality Method.

Thus deprotonation of the minor oxazolidinone 1031b, derived from L-alanine by condensation with pivaldehyde, with 2 equivalents of LDA gave the enolate 1032, (Scheme17), which was then alkylated with N-Boc-3-(bromomethyl)indole to give the derivative 1033 in 65% yield.99
The configuration at the new chiral centre was a consequence of Si-face (in this case 'bottom side') attack of the anion 1032. The Re-face (in this case 'top side') being hindered by the t-butyl group. The configuration of 1033 was determined to be (S) (de of >90%) by $^1$H-NMR comparisons.

Treatment of 1033 with sodium methoxide in methanol followed by acid deprotonation afforded (S)-α-methyltryptophan methyl ester 1034 in 87% yield.

Seebach also attempted to introduce the α-methionine side chain by this method. But addition to the oxazolidinone derived from L-methionine resulted in little more than a 12% yield of the alkylated product. The de was consequently not specified.
1.3.8 Cyclic Hexahydropyrroloindoles

The α-alkylation of tryptophan thus presented a problem because of its reactive indole side chain.\textsuperscript{100} The work on tryptophan in this thesis stems from the elegant work of Crich and Davies on the α-alkylation of tryptophan.\textsuperscript{97,101} In their work, the reactive indole side chain of tryptophan was taken advantage of to form the cyclic tautomer 1035 which has already been thoroughly studied by Hino.\textsuperscript{102} Thus the cyclic tautomer became a source of chirality itself, and as such this method is a variation of Seebach’s so called Self-Reproduction of Chirality method.

Hino and Taniguchi reported the formation of the stereospecific pyrroloindole ring system on the dissolution of the protected tryptophan 1037 in neat 85% phosphoric acid followed by careful neutralization of the phosphoric acid with aqueous base.\textsuperscript{102} The cyclic products 1035 and 1036 were formed (Scheme 18).

\textbf{Scheme 18}

1035 and 1036 have a concave shape. 1035 is known as the endo-product as
the methyl ester at C-2 is on the inside of this concavity and 1036 is called the exo-product for the similar reason (Scheme 19).

Scheme 19
Through a series of kinetic studies, Hino showed that the endo-product was the thermodynamic product and was the isomer isolated.\textsuperscript{102} The more sensitive exo-product reverted to the ring opened form \textbf{1037} on attempted isolation.

Hino proposed the following mechanistic rationale for the formation of these cyclic tautomers in acid media (Scheme 20).\textsuperscript{102}

\begin{center}
\textbf{Scheme 20}
\end{center}
Reversible protonation at the 3-position of the indole 1037 can occur at the Si-face or at the Re-face of the indole and results in the formation of 1038 and 1039 respectively. But cyclization of 1039 to 1041 occurs more rapidly than that of 1038 to 1040. The kinetically controlled product 1036 gradually transforms to the thermodynamically more stable 1035 through the equilibrium

\[
1036 \rightleftharpoons 1041 \rightleftharpoons 1039 \rightleftharpoons 1037 \rightleftharpoons 1038 \rightleftharpoons 1040 \rightleftharpoons 1035
\]
on prolonged reaction time or at higher temperature. The presence of the equilibrium was shown by $^1$H-NMR of (DL)-1042 in deuterophosphoric acid at room temperature which indicated rapid deuteration of both 3a- and 8a hydrogens.

1.3.9 Protection of N-8 of 1035 and single crystal X-ray analysis of 1042

Crich and Davies protected N-8 of 1035 with the methylsulphonyl and the tosyl (4-methylphenylsulphonyl) groups to give 1042 and 1043 respectively.

Davies managed to recrystallize 1042 and to obtain a single
crystal X-ray analysis of it, which confirmed the predicted syn configuration of the 2,3a, and 8a hydrogens. Interestingly, the X-ray data (Scheme 21) also showed that the distances between the C-2 methyl ester group to be close enough to the aromatic ring to give non-bonding, secondary interactions of the π-stacking type which occur in nucleic acids.

![Scheme 21](image)

It is logical to assume that this conformation is also adopted in 1035 and therefore it is possible to explain the preferential formation of the endo-pyrroloindole, at least in part, as being due to this stabilising π-bonding interaction.

The tosylated product 1043 was however a viscous oil and no X-ray data was possible.
1.3.10 α-Alkylation of the protected pyrroloindoles

Davies attempted to deprotonate at C-2 of 1042 and then allylate the enolate formed.\(^9\) However the product 1045 obtained was in fact the one in which deprotonation occurred at the methylsulphonyl group followed by allylation (Scheme 22).

Scheme 22

With the N-tosyl protected product 1043, Davies was able to deprotonate at C-2 with 1 equivalent of LDA in THF at -78°C and on quenching with the appropriate electrophile obtained the products 1047 in good yields (Scheme 23).
Electrophile  | Product (1047) | Yield %
--- | --- | ---
RX = | | |
| MeI | a R = -CH₂⁻⁻CH=CH₂ | 79 |
| BnBr | b | Me | 80 |
| MeSCH₂CH₂I | c | Bn | 71 |
| MeO₂CCH₂Br | d | -CH₂CH₂SMe | 44 |
| (CH₃)₃SiCH₂CH₂OCH₂Cl | e | -CH₂CO₂CH₃ | 83 |
| | f | -SEM | 78 |

Scheme 23

Davies detected only one diastereomer in the crude before chromatographic separation and thus concluded that the alkylation took place with very high stereoselectivity (>98%).

By NOE studies and from X-ray analysis of a single crystal of 1047a, it was concluded that the product obtained was that where the electrophile quenched the enolate 1046 from the exo-side of the molecule.⁹⁷

Interestingly, when greater than 1 equivalent of LDA was used on 1043, and on quenching with allyl bromide, a dialkyl adduct was also obtained. The second deprotonation took place at the methyl group of the tosyl protecting group. The diallylated product was thus 1048.
The alkylated products 1047 were then ring opened with trifluoroacetic acid (TFA)\textsuperscript{102} to give 1049, and the tosyl group removed with sodium in liquid ammonia to give 1050 (Scheme 24).\textsuperscript{104}
1.3.11 The work on tryptophan described in this thesis

The work described in this thesis concerning tryptophan is threefold. Firstly, α-alkylated substituted tryptophans were synthesized, and then transformed into the corresponding aspartic acid derivatives. In this work (R)-α-methyl aspartic acid and (S)-α-methyl aspartic acid were synthesized.

Secondly, (R)-α-methyltryptamine and (S)-α-methyltryptamine derivatives were synthesized.

Thirdly, the possible π-stacking interaction described by Crich and Davies was further investigated.
1.3.12 Syntheses of α-alkylated pyrroloindoles

The pyrroloindole 1035 was synthesized according to Hino,102 and Davies.97 Because of the difficulties encountered by Davies in using the methylsulphonyl and tosyl groups in the protection of N-8 in 1035, it was decided to try the benzenesulphonyl group as a protecting group for N-8 instead. The product 1051 turned out to be a highly crystalline and easily recrystallizable solid (Scheme 25).

\[ \begin{array}{c}
\text{H} & \text{H} & \text{H} & \text{H} & \text{H} & \text{PhS} \text{O} 2 \text{C} 1 \\
\text{N} & \text{N} & \text{CO}_2\text{CH}_3 & \text{CO}_2\text{CH}_3 \\
\text{H} & \text{H} & \text{N} & \text{N} & \text{CO}_2\text{CH}_3 & \text{Ph} 1051 \\
\text{H} & \text{H} & \text{H} & \text{H} & \text{H} & \text{H}
\end{array} \]

Scheme 25

H-2 of 1051 was deprotonated without problems using LDA in THF at -78°C. The enolate 1052 formed was then quenched with excess methyl iodide or methyl bromoacetate (Scheme 26) to give the adducts 1053 and 1054.

Again like Davies, only one of the diastereomers was obtained.
THF, -78°C
LDA

Scheme 26
1.3.13 Synthesis of (S)-α-methylaspartic acid hydrochloride 1055

The preparation of 1055 was achieved by first ring opening 1053 with TFA to give 1056. This was then dissolved in a solution of water and acetonitrile. About 20 equivalents of sodium periodate and a catalytic amount RuCl₃ were added. The diprotected aspartate 1057 was isolated as a solid. It was then fully deprotected to give the hydrochloride 1055 by refluxing in 6M HCl for several hours (Scheme 27).
Scheme 27

\[ \text{RuCl}_3(\text{cat}) \]
\[ \text{NaIO}_4 \]
\[ \text{H}_2\text{O} / \text{MeCN} \]

\[ \begin{align*}
\begin{array}{c}
\text{HO}_2\text{C} \\
\text{CH}_3 \\
\text{HN} \\
\text{CO}_2\text{CH}_3 \\
\text{CO}_2\text{CH}_3
\end{array}
\end{align*} \]

1057

\[ \text{6M HCl} \Delta \]

\[ \begin{align*}
\begin{array}{c}
\text{HO}_2\text{C} \\
\text{CH}_3 \\
\text{HCl. H}_2\text{N} \\
\text{CO}_2\text{H}
\end{array}
\end{align*} \]

1055
1.3.14 Synthesis of (R)-α-methylaspartic acid hydrochloride 1058

The preparation of 1058 was achieved by first ring opening 1054 with TFA\textsuperscript{102} to give 1059. Compound 1059 was then catalytically cleaved with RuCl\textsubscript{3} and NaIO\textsubscript{4} to give the aspartic acid derivative 1060.\textsuperscript{105} The thiohydroxamate 1061 was formed and then reductively decarboxylated by Barton’s method,\textsuperscript{31,32} to give the (R)-α-methylaspartic acid derivative 1062. 1062 was then fully deprotected by refluxing in 6M HCl for several hours to give 1058 (Scheme 28).
H$_2$O, MeCN

NaI$_4$/RuCl$_3$(cat)

\[
\begin{align*}
\text{HO}_2\text{C} & \quad \text{CO}_2\text{CH}_3 \\
\text{HN} & \quad \text{CO}_2\text{CH}_3 \\
\text{CO}_2\text{CH}_3 & \\
\end{align*}
\]

1060

\[
\begin{align*}
\text{Cl}^- \cdot \text{NEt}_3, \text{CH}_2\text{Cl}_2 \\
\text{N} & \quad \text{O} \\
\text{O} & \quad \text{S} \\
\text{S} & \\
\text{HN} & \quad \text{CO}_2\text{CH}_3 \\
\text{CO}_2\text{CH}_3 & \\
\end{align*}
\]

1061

-72-
1.3.15 Preparation of (R)- and (S)-α-methyl tryptamine

The starting material previously prepared was taken and the methyl ester group at C-2 was hydrolyzed under the Claisen conditions at room
temperature to give the acid 1063. The thiohydroxamate 1064 was prepared from 1063. Compound 1064 was then reductively decarboxylated,\textsuperscript{31,32} to give the diastereomers 1065 and 1066 which were chromatographically separated. Compound 1065 was then ring opened with TFA\textsuperscript{102} to give 1067, which is the (S)-enantiomer of the α-methyltryptamine. Compound 1066 was ring opened with TFA to give 1068 which is the (R)-enantiomer of the α-methyltryptamine (Scheme 29).
Scheme 29
1.3.16 The discovery of the stable and crystalline mixed anhydride 1069 and its X-ray analysis

It was discovered that when attempting preparation of the thiohydroxamate 1064 by first making the mixed anhydride 1069 with i-butylchloroformate and then displacing with thiohydroxamic acid (Scheme 30) that a white crystalline compound was obtained.

The crystalline compound was found to be the mixed anhydride 1069 by elemental analysis. A single crystal X-ray analysis later confirmed this. This also showed a possible π-stacking interaction between the side chain at C-2 and the aromatic ring of the pyrroloindole. However, unlike in 1042, prepared by Davies, it is the oxygen of C=O which is at a short distance to the ring. In 1042, it is the oxygen of C-OMe which is close to the aromatic ring.
1.3.18 Investigation into possible π-bonding in the pyrroleindole system

It was decided to synthesize a series of aromatic esters or amides of types 1075, and 1109.
The synthetic strategy in this was to protect \( N_b \) of tryptophan 1001 first to 1076 and then esterify 1076 with the appropriate phenol or amine to give 1077. Compounds 1077 were then cyclized to give the pyrroloindole 1078. \( N-8 \) of 1078 was then protected (Scheme 31). Compound 1075e might be formed by a dehydration step from 1075d.
Scheme 31
Chapter 2 Studies on Substituted Azetinone Carboxylic Acids

2.1.1 Protection of the side chain hydroxyl group of 8

As the compounds under study are β-lactams, mild reaction conditions were desirable. The 3α-hydroxyl group of 8 had to be protected to prevent it from interfering with any subsequent reactions. The t-butyldimethylsilyl (TDBMS) group was chosen as it has already been used by Shih in his syntheses of the 1β-methylcarbapenems.\textsuperscript{18,19} The TBDMS group could be easily put on, and then removed under neutral conditions with tetrabutylammonium fluoride or with boron trifluoride etherate.\textsuperscript{46} It is also stable in basic and neutral conditions and only unstable in moderately strong acids.

The TBDMS group was put on 8 by stirring 8 with 2.2eq of TBDMS chloride and 2.5eq of imidazole in dry dimethylformamide (DMF) as solvent at room temperature for 16 hours. A twofold excess of TBDMS-Cl was necessary as the acid group of 8 was also silylated in the process. However most of the silylated acid functionality was hydrolyzed back to the free acid in the acid wash work-up, and the protected alcohol 9 was separated from the diprotected compound, excess silanol and unreacted substrate by column chromatography. The DAM group on the molecule caused the molecule to char red with an alcoholic solution of phosphomolybdic acid (PMA). The yield of this reaction was generally over 80% after recycling. Compound 9 could be made to give a solid foam and stored at -5°C.
2.2.1 Formation of the thiohydroxamate 11 from the acid chloride 10a

It was crucial to show that the radical 12 could be made and trapped. As the starting material 9 already has the acid functionality at the correct position (C-4), it only remained necessary for the straightforward conversion of this to the thiohydroxamate ester 11. This was done by activating the acid 9 to its acid chloride 10a, or to the mixed anhydride 10b.

On a small scale, the acid chloride 10a was synthesized by reacting the acid with oxalyl chloride 22 with a trace of dimethylformamide as catalyst. A plausible mechanism for this reaction is outlined in scheme 32.
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Step 2

Step 3

Step 4
The reaction proceeds via the Vilsmeier salt 23 with the loss of CO₂ and CO. The Vilsmeier salt 23 then activates the acid in step 3 and the reaction then proceeds with the regeneration of the DMF. Using this method, the acid chloride 10a was obtained only as a brown oil. A small amount of a brown solid was obtained. Hence the acid chloride 10a formed was used in situ. On large scale synthesis, the use of thionyl chloride, SOCl₂, as the chlorinating agent was envisaged.

To form the thiohydroxamate 11 from 10a, 10a was stirred with the sodium salt of thiohydroxamic acid in dry THF at 0°C under N₂. A yellow solution of the ester 11 was formed. This was then used in situ.

2.2.2 Formation of the thiohydroxamate 11 from the mixed anhydride 10b

The acid 9 may be activated by converting it to the mixed acid anhydride 10b, by stirring with 1eq of triethylamine in dry THF at -20°C, and adding 1eq of i-butylchloroformate, 24, slowly. The mixed acid anhydride 10b has to be kept at between -15°C to -20°C because above this temperature range it becomes unstable, and below this temperature it reacts too slowly in the next step. The thiohydroxamate free acid was then added to the solution of 10b in situ and allowed to react at -15°C for 15 to 20 minutes to give a bright yellow solution of 11. The precipitated
ammonium salt was filtered and the thiohydroxamate ester 11 was used in the next step in situ.

2.2.3 Generation of the radical 12 from 11

The radical 12 was readily formed from 11 by a radical initiation step. A chemical radical initiator such as AIBN may be used, but the reaction proceeds via initiation by a bright tungsten light source or by thermal heating (Scheme 2).

2.3 Non carbon-carbon bond forming reactions of 12

2.3.1 Reductive decarboxylation of 11

One simple way of showing that the radical 12 was generated was to trap it with a source of hydrogen atoms. The tertiary mercaptans provide such a source (Scheme 33).
Scheme 33
The mercaptan was added in over 2.5 equivalents.

The reduced product 26 was separated by column chromatography, and was distinguished from the parent acid 9 by its NMR spectra. In 9, H-C4 has a chemical shift of 4.10 ppm (d, 1H) and in the reduced product 26 it has shifted upfield to δ=3.16 ppm (d, 2H). The overall yields from 9 was 70% for the route via the acid chloride intermediate 10a and 80% for the mixed acid anhydride intermediate 10b.

2.3.2 Rearrangement reaction of 11 to give 27

Another simple reaction to show that the radical 12 was generated was to allow it to undergo intermolecular self-rearrangement (Scheme 34).
Again the radical step may be induced thermally by refluxing in a solvent such as benzene or photolytically at room temperature with a bright tungsten light bulb under nitrogen. The yield obtained starting from the acid 9 was 12% and 15% respectively. The low yield may be because the rearranged product 27 was sensitive to any electrophiles that may be present during the work-up process (Scheme 35).

The chemical shift of H-C4 in the rearranged product 27 was at 5.9 ppm, somewhat downfield from H-C4 of the parent acid 9 at 4.10 ppm. The presence of the pyridyl group was revealed in the ¹H-NMR by a prominent doublet with a downfield chemical shift in the region of 8.3 ppm. This is due to the single hydrogen α to the nitrogen in the pyridyl ring.

400 MHz ¹H-NMR showed that a diastereomer at C-4 was not obtained. The coupling constant between H-3 and H-4 in 27 was small (2.6 Hz), indicating that the dihedral angle between them is close to 90° and thus they are trans to each other. It was hence concluded that the radical 12 was quenched trans to the bulky substituent at C-3.
Scheme 35
2.4 Carbon-carbon bond forming reactions of 12

2.4.1 Addition of 12 to methyl acrylate 28

Methyl acrylate is an activated alkene resembling 1-nitro-1-propene. The thiohydroxamate 11 was formed via the mixed acid anhydride 10b, and methyl acrylate 28 was added and the reaction was photolyzed with a bright tungsten lamp (Scheme 36).
Scheme 36
When 1eq of 28 was used, a significant amount of the rearranged product 27 was obtained. When 10eq of methyl acrylate was used, the adduct 29 was obtained in 47% yield. 400MHz $^1$H-NMR showed it to contain two diastereomers in the ratio of approximately 2:1, and $^{13}$C-NMR showed a doubling of peaks. The distinguishing feature on the $^1$H-NMR was the appearance of the methyl ester group at $\delta=3.6$ppm.

It was suspected that quenching of 12 at C-4 still took place *trans* to the substituent at C-3, and that the two diastereomers of 29 arose at C-2'. It was decided to prove this by removing the thiopyridyl group at C-2', which would then give a simpler $^1$H-NMR.

### 2.4.2 Removal of the thiopyridyl group of 29

The thiopyridyl group of 29 was successfully removed by refluxing in dry toluene with butyltin hydride ($\text{nBu}_3\text{SnH}$) with AIBN as the radical initiator (Scheme 37).

![Scheme 37](image-url)
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The product 31 was extracted from acetonitrile by petrol and was isolated in 18% yield. $^1$H-NMR and $^{13}$C-NMR showed only one diastereomer. Hence initially the quenching of 12 by methyl acrylate at C-4 was stereospecific.

2.4.3 Addition of 12 to nitroethylene 32

Nitroethene, 32, was prepared by dehydration of 2-nitro-1-ethanol over phthalic anhydride at a temperature of over 180°C, and distilling the product (Scheme 38).

![Scheme 38](image)

The thiohydroxamate ester 11 was prepared via the mixed anhydride 10b at -15°C. The nitroethene 32 was added in excess and the solution was photolyzed with a bright tungsten light bulb at 0°C (Scheme 39).
The desired product 33 was isolated in 36% yield starting from the acid 9. 200MHz $^1\text{H}$-NMR showed two diastereomers in the ratio of 3:2. The hydrogen $\alpha$ to the thiopyridyl and nitro groups has a downfield chemical shift of $\delta=6.19$ppm(dd)
and $\delta=6.30\text{ppm (dd)}$. The NMR signals of the two hydrogens at C-4$\alpha$ were multiplets stretching from $\delta=2.0\text{ppm}$ to $\delta=2.8\text{ppm}$.

2.4.4 Preparation of 1-nitro-2-propanol (34)

Compound 34 was prepared by the method of Henry. Dry ethanol and nitromethane were mixed in equimolar quantities and cooled in an ice-bath. Water containing a catalytic amount (typically 1% equivalent) of potassium hydrogen carbonate or potassium carbonate was added and the mixture was stirred. The reaction was exothermic and was completed when the reaction became homogeneous. The product was then extracted into ether. Generally, the product was obtained in quantitative yields (Scheme 40).

\[
\begin{align*}
\text{CH}_3\text{CHO} + \text{CH}_3\text{NO}_2 & \xrightarrow{\text{cat KHCO}_3 \text{ or K}_2\text{CO}_3} \text{CH}_3\text{CHCH}_2\text{NO}_2 \\
& \text{CH}_3\text{CHO} + \text{CH}_3\text{NO}_2 & \xrightarrow{\text{cat KHCO}_3 \text{ or K}_2\text{CO}_3} \text{CH}_3\text{CHCH}_2\text{NO}_2 \\
& \text{34}
\end{align*}
\]

Scheme 40

2.4.5 Preparation of 1-nitro-1-propene (30)

1-nitro-1-propene, 30, was then prepared from 34 by dehydrating the latter over phthalic anhydride at $>180^\circ\text{C}$, and distilling the product (Scheme 41).
\textbf{1H-NMR of 30} obtained showed that the \textit{cis}- and \textit{trans}- isomers were present in a ratio of 1:10. The coupling constant for the two alkenyl protons of the major isomer has a large value of 13Hz showing that it was the thermodynamic \textit{trans}-alkene product. The two isomers were not separated.

\textbf{2.4.6 Addition of 12 to 1-nitro-1-propene (30)}

The thiohydroxamate ester 11 was prepared via the mixed acid anhydride 10b. 1-nitro-1-propene 30 was added in 2 to 3 equivalents, and the reaction was photolyzed by a bright tungsten lamp for 4 or more hours at 0°C to 20°C (Scheme 42). The products 35 were obtained in 41% yield.
It was anticipated that diastereomers at C-1' and C-2' would be formed to give four products. This was borne out in the 400MHz $^1$H-NMR spectrum which showed four separate signals of different intensities for the $\alpha$-pyridyl proton at
a chemical shift around $\delta=8.3\text{ppm}$. There were also four separate signals (doublets) for H-2' from $\delta=6.3\text{ppm}$ to $\delta=6.7\text{ppm}$. $^{13}\text{C-NMR}$ also showed quadrupling of signals.

2.4.7 Attempted conversion of 35 to 18 with TiCl$_3$

Reaction using TiCl$_3$ was reported by McMurray and Melton.$^{43}$ An aqueous solution of 1M TiCl$_3$ at pH<1 was prepared, and 35 in THF was added. A solution of TiCl$_3$ buffered at pH=6 with ammonium acetate was prepared. Compound 35 in THF was added to these solutions of TiCl$_3$. However, no identifiable product was isolated from these reactions.

2.4.8 Applying the Barton Reaction to myristic acid (36)

It was decided to study the attempted conversion of the $\alpha$-nitrothiopyridyl group on a simpler system. Myristic acid 36 was chosen. The myristic acid, 36, was converted to the acid chloride 37 by refluxing in thionyl chloride (Scheme 43).

$$\begin{align*}
\text{CH}_3\text{(CH}_2\text{)}_{12}\text{CO}_2\text{H} & + \text{SOCl}_2 \quad \rightarrow \quad \text{CH}_3\text{(CH}_2\text{)}_{12}\text{COCl} & + \text{SO}_2 & + \text{HCl} \\
36 & & 37
\end{align*}$$

Scheme 43

The acid chloride 37 was distilled out as a colourless liquid at 125°C under reduced pressure in 86% yield.

The acid chloride 37 was then esterified with sodium thiohydroxamate in THF. The NaCl byproduct formed was filtered off. The solvent was then
evaporated off to give a yellow solid of the myristyl thiohydroxamate 38 (Scheme 44).

The product 38 formed was not further purified. It was stored at -20°C in the dark.

To form the adduct 39, the thiopyridyl ester 38 was dissolved in dry THF and photolyzed as before in the presence of excess 1-nitro-1-propene under nitrogen at 0°C. It was found that the rearranged product 40 was also formed (Scheme 45).
A study on how the proportion of each product 39 and 40 varied with the number of equivalents of nitropropene 30 used was carried out, and the results are tabulated in table 1.
### Table 1

<table>
<thead>
<tr>
<th>38 / mg</th>
<th>30 / mg</th>
<th>39 / mg</th>
<th>40 / mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>500</td>
<td>197 (1.53eq)</td>
<td>131 (23.3%)</td>
<td>171 (39.3%)</td>
</tr>
<tr>
<td>3000</td>
<td>1550 (2.0eq)</td>
<td>1050 (31%)</td>
<td>813 (31.1%)</td>
</tr>
<tr>
<td>589</td>
<td>372 (2.4eq)</td>
<td>271 (40.8%)</td>
<td>33 (6.4%)</td>
</tr>
<tr>
<td>500</td>
<td>393 (3.0eq)</td>
<td>173 (30.7%)</td>
<td>93 (21.4%)</td>
</tr>
<tr>
<td>496</td>
<td>514 (4.0eq)</td>
<td>232 (41.5%)</td>
<td>67 (15.5%)</td>
</tr>
<tr>
<td>494</td>
<td>774 (6.1eq)</td>
<td>65* (11.7%)</td>
<td>35* (8.1%)</td>
</tr>
<tr>
<td>505</td>
<td>1068 (8.2eq)</td>
<td>-*</td>
<td>46* (8.1%)</td>
</tr>
<tr>
<td>497</td>
<td>1285 (10.0eq)</td>
<td>109* (19.5%)</td>
<td>-*</td>
</tr>
</tbody>
</table>

* Difficult to purify by column chromatography due to excess nitropropene

It was found that a yield of about 40% for the adduct 39 was obtained when 2.5eq to 4.0eq of 1-nitro-1-propene were used. Lower than this, then the rearranged product 40 predominated, and higher than this amount, then the reaction became extremely difficult to purify due to the excess 1-nitro-1-propene.

The proton in 39 $\alpha$ to the nitro and thiopyridyl groups could be easily identified in the NMR spectrum. 200MHz $^1$H-NMR showed two sets of doublets at $\delta=6.5$ppm and $\delta=6.6$ppm in a 1:1 ratio which belonged to the two different diastereomers. The $\beta$-CH$_3$ group gave two sets of doublets at $\delta=1.05$ppm and $\delta=1.10$ppm. The chemical shift of the $\omega$-CH$_3$ was a triplet at $\delta=0.86$ppm.

In the rearranged product 40, the chemical shift of the $\alpha$-H was a triplet at $\delta=3.0$ppm.
2.4.9 Reaction of 39 with TiCl₃

39 was dissolved in THF and added to 1M TiCl₃ (pH < 1), and stirred for 16 hours. The product of the reaction was extracted into ether and obtained in 65% yield. ¹H-NMR showed the complete absence of aromatic signals. IR showed a stretch at 1718 cm⁻¹.

Buffered TiCl₃ at pH=6 with ammonium acetate was also used. The product was obtained in 71%.

2.4.10 Re-attempting the conversion of 35 to 18 with TiCl₃

The McMurray and Melton method of using TiCl₃ on 35 was attempted again. But however no identifiable was isolated. Barrett also reported encountering a similar problem. 51

In other systems where this has been done by the Barton group, the pH of the TiCl₃ was at a pH < 1. Under this condition, other protecting groups were also removed. The reaction may thus be attributed to the acidic medium and not the TiCl₃. Similar observations were made by Crich and Davies with α-nitro sulphides. Here, when buffered TiCl₃ solutions (pH=6) was used, no reaction took place.

2.4.11 Attempted conversion of 35 to 18 using other oxidizing agents

The oxidizing agents potassium permanganate and sodium dichromate
were used on 35, but only the starting material was isolated.

When excess ozone,\textsuperscript{44} in CH\textsubscript{2}Cl\textsubscript{2} at -78°C was used, the \(\beta\)-lactam molecule was completely destroyed. Barrett also reported encountering a similar difficulty in this type of conversion.\textsuperscript{51}

\textbf{2.4.12 Synthesis of 42}

Because of the difficulties encountered above, it was decided to change the synthetic strategy. The adduct 29 had already been successfully synthesized. It was anticipated that the sulphide 29 could be oxidized to the sulphoxide 41 and elimination of the sulphenic acid would generate the \(\alpha\beta\)-unsaturated system 42.\textsuperscript{59} The methyl group could then be introduced into 42 nucleophilically to give 43,\textsuperscript{52} which could then lead up to cyclization (Scheme 46).
The sulphide 29 was oxidized to the sulphoxide 41 by the magnesium salt of monoperoxyphthalic acid (MPAA), 44, in ethanol. The sulphoxide was isolated quantitatively.

Elimination of sulphenic acid from 41 was effected by refluxing in toluene to give 42 in 83% yield. The large NMR coupling constant of 15.6Hz between the olefinic protons indicated that the trans isomer was formed.
2.4.13 Attempted methylation of 42

The first attempt to methylate 42 was by using 1eq of copper(I) iodide and 2eq of methyllithium in THF at -78°C. This proved to be unsuccessful.

Next, the commercially available copper(I) bromide - dimethylsulphide complex was used, and the cuprate was made by adding methyllithium at room temperature. The 42 was then added. The reaction was unsuccessful. From the $^1$H-NMR spectrum, 42 appeared to have undergone isomerization.

Next, a complex of copper(I) cyanide and methyllithium was prepared in ether at -78°C. 42 was added. However, on work-up only the starting material 42 was obtained.

It was decided not to continue with the cuprate method. It has been reported that in this reaction, the reaction conditions have to be very specific, and that it depends on a whole host of conditions such as which other ligands were present and the very precise number of equivalents of reagents used.

2.4.14 Addition of 12 to N-phenylmaleimide

The thiohydroxamate ester 11 was formed by reacting the acid 9 with 3-oxa-2-oxo-1-thia-indolizinium chloride, which is an activated form of the thiohydroxamic acid. This was then photolyzed with an excess of N-phenylmaleimide to give 25% of the product 44 (Scheme 47).
It was hoped that after hydrolysis of the imide it may be possible to cyclize the product and then reduce the acid group in the bicyclic system to give a 1-methyl substituent in the carbapenem system.

The 200MHz $^1$H-NMR spectrum of 44 was rather complicated with a lot of overlapping of signals, but from the two separate signals for the $\alpha$-H of the thiopyridyl group, there were at least two diastereomers present. It was decided to desulphurize 44 by refluxing with Raney Nickel in absolute alcohol. The product 45 was isolated in 88% yield. The 400MHz $^1$H-NMR showed only one diastereomer.

It was felt that it was not worthwhile pursuing this synthetic route any further because of the speculative nature of the cyclization and subsequent reduction.
of the acid group to a methyl group.

2.5.1 Attempted synthesis of a bicyclic β-lactam

The use of acyl selenides to generate acyl radicals and subsequent cyclization reactions have already been reported by Crich,\textsuperscript{60} and the Boger group.\textsuperscript{61} It has also been used in β-lactam work by Bachi.\textsuperscript{62}

It was thus decided to attempt the synthesis of a bicyclic β-lactam nucleus 56 by building up from the nitrogen part of the monocyclic β-lactam using the strategy outlined in scheme 48.
Ceric ammonium nitrate

NaH

NaOH
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\[
\begin{align*}
\text{Ph} & \quad \text{Si} \quad \text{Ph} \\
\text{Si} & \quad \text{Ph} \\
\text{O} & \quad \text{H} \quad \text{H} \\
\text{H} & \quad \text{H} \quad \text{O} \\
\text{N} & \quad \text{55} \\
\text{-CO} & \quad \text{nBu}_3\text{SnH}
\end{align*}
\]
This involved the protection of the alcohol and acid groups of 8 followed by the removal of the DAM group. The amide was then deprotected and
then allowed to add nucleophilically to allyl bromide. A selenyl ester \( 53 \) was then formed, and the radical \( 55 \) then generated.\(^{60}\)

### 2.5.2 Synthesis of 49

The first step of this synthetic scheme was to protect the acid group and prevent it from interfering with the subsequent steps of the synthesis. This was done by using diisopropylethylamine as base and methylating with methyl iodide. DMF was used as solvent. The ester was isolated and required no further purification.

As the acid group is now protected, silylation only required the use of one equivalent of silyl chloride. The \( \text{t-butyldiphenylsilyl} \) group was chosen because of its UV activity, so that after the removal of the DAM group, the molecule could still be visualized through its new UV active group.

The 48 was dissolved in DMF with 1.2eq of imidazole and 1.1eq of \( \text{t-butyldiphenylsilyl} \) chloride were added. 49 was isolated in 93% yield over the two steps.

### 2.5.3 Removal of the DAM group

The DAM group of 49 was removed by stirring it in acetonitrile : water (9:1) with ceric ammonium nitrate strictly at 0°C for 30 to 45 minutes (Scheme 49).
Scheme 49

MeCN:H₂O = 9:1 → Ceric ammonium nitrate

50 + 61

50

61
It was found that at temperatures below -10°C the reaction was stationary, and above 0°C, non-β-lactam products were obtained. The reaction was quenched by pouring into water and ethyl acetate, and the excess oxidant reduced with sodium metabisulphite.

The product 50 was purified by column chromatography and was obtained in 69% yield. It shows a distinctive N-H (amide) IR stretch at 3400 cm$^{-1}$.

2.5.4 Allylation of the β-lactam nitrogen to give 53

In an attempt to introduce an allyl group into the nitrogen of the β-lactam 50, 50 and allyl bromide were stirred together in THF with sodium hydride as base. However, surprisingly, the major product was the silanol 62 (63.7%). This was probably due to competitive deprotonation at C-3 followed by elimination of the siloxoyl group (Scheme 50).
Surprisingly though, when the β-lactam carboxylic acid 51 was used, and over 2 equivalents of sodium hydride was used, it was found that the allylation on the nitrogen was successful. The yield obtained after a column was 60.5%.

The first equivalent of sodium hydride added deprotonated the acid. The second equivalent deprotonated from the nitrogen, rather than from C-3 because the dianion formed is stabilized by the chelation of the oxygen of the acid anion to the sodium ion, 63, in a 5-membered ring system.
2.5.5 Synthesis of the selenyl ester 54

The phenylselenide 54 was prepared by first forming the mixed anhydride of 53 with i-butylchloroformate at -20°C, and then adding in a solution of phenylselenide anion, at -20°C. The phenylselenide anion was formed by dissolving diphenyl diselenide with sodium borohydride in ethanol. The product was obtained in 36.5% yield. It was easily distinguished from the starting material by its IR spectrum which did not possess an O-H stretch band. The mass spectrum also showed that 54 was formed.

2.5.6 Photolysis of 54

The β-lactam phenylselenide 54 in cyclohexane was photolyzed with a medium pressure mercury lamp under nitrogen with tri-n-butyltin hydride and α-azo-iso-butyronitrile (AIBN). The reaction was not clean. The mass spectrum did
not show the ketone $56$ or the product $59$. The molecular ion for $58$ was observed. No further investigation on this system was carried out as at a similar time in this laboratory, $60$ related acyl radical cyclization work with amino acids, eg, $64$ was attempted. There was definitely decarbonylation to give the α-amino radical, but cyclization could not compete with the subsequent quenching. Therefore, it was logical that $58$ would be formed in favour over the other possible products. Thus the procedure in scheme 26 was not worth pursuing further.

2.5.7 Conclusion of the 2-Azetinone-4-carboxylic acid work

It has been shown that the radical at C-4 of the 2-Azetinone-4-carboxylic acid $9$ could be readily generated and be quenched by a variety of radical traps $70$ giving rise to carbon-carbon bond formation or simple reduction by a hydrogen donor.

It was found however that the protected 1β-methylcarbapenem precursors $18$ or $19$ could not be formed in one simple oxidative step. Attempts to synthesize a complete bicyclic carbapenem structure also failed.

Other syntheses to the 1β-methylcarbapenems have been recently reported. $^{40,63-68}$
Chapter 3  

Studies on Substituted Pyrroloindole

Carboxylic Acids

3.1 Introduction

Tryptophan is a naturally occurring α-amino acid. It is the in vivo precursor to the synthesis of the neurotransmitter 5-hydroxytryptamine (serotonin). It also occurs in the peptide hormones gastrin, cholecystokinin, somatostatin and bombasin.

It has been shown that (+)α-methyltryptophan and (+)α-monofluoromethyltryptophan are substrates for tryptophan hydroxylase and that the 5-hydroxylated product of the fluoro-compound is a time dependent inhibitor of aromatic amino acid decarboxylase resulting in the retardation of serotonin formation. It certain derivatives of (+)-α-methyltryptophan have been shown to have micromolar affinity for the peptide cholecystokinin B receptor from the mouse cerebral cortex.

The use of D-tryptophan in the synthesis of peptide analogs of somatostatin resulted in compounds many times more potent than the native peptide. This rise in potency is thought to be due to the stabilization of the β-bend in the tertiary structure of the peptide.

The use of α-substituted tryptophan in this area of work would also be expected to give rise to conformational analogs.

The work on tryptophan described in this thesis has already been outlined in chapter 1 of this thesis.
3.1.1 Protection of L-tryptophan

Initially in scheme 51, the α-carboxylic acid and α-amino groups of the L-tryptophan 1001 were protected.

The acid was simply converted to the methyl ester hydrochloride 1080. This was achieved by adding L-tryptophan to a solution of thionyl chloride, SOCl₂, in methanol. The product was collected as a solid in 95% yield and required no further purification.\textsuperscript{97,102}

The 1080 was then dissolved in water with over 2eq of sodium hydrogen carbonate. Chloroform was added and the two-phase mixture was vigorously stirred. Methyl chloroformate was added and the product 1037 was isolated after recrystallization in 87% yield.\textsuperscript{97}

\begin{center}
\begin{tikzpicture}
\node (1001) at (0,0) {\textbf{1001}};
\node (1080) at (2,0) {\textbf{1080}};
\node (1037) at (2,-2) {\textbf{1037}};
\draw[->] (1001) -- (1080) node[midway, above] {SOCl₂, MeOH};
\draw[->] (1080) -- (1037) node[midway, above] {\text{>2eq NaHCO}_3, \text{H}_2\text{O/CHCl}_3};
\end{tikzpicture}
\end{center}

\textbf{Scheme 51}
3.1.2. Cyclization of 1037 to give the pyrroloindole 1035

The compound 1037 was dissolved in 85% H$_3$PO$_4$ as described by Hino. The reaction was neutralized by dropping slowly into a rapidly stirred mixture of 15% aqueous sodium carbonate solution and dichloromethane. The product 1035 was solidified out with seed crystals (Scheme 52).

The $^1$H-NMR spectrum obtained at room temperature was in accordance with that reported by Hino and Davies. It showed two sets of signals which were due to rotamers about N-1 of the carbamate. The carbamate has double bond characteristics (Scheme 53), thus giving rise to slow rotation about the carbamate bond.
Hino claimed that the success of this method of ring cyclization was due to the choices of the correct acid and the $N_b$-protecting group. This was substantiated by using different acids at various concentrations and other protecting groups.\textsuperscript{102}

3.1.3 Protection of $N$-8 of 1035

As the key step in the syntheses may involve deprotonation to form an enolate anion, it was thus necessary to protect $N$-8 with an appropriate group. Davies found that the sulphonyl groups were appropriate for this purpose, but however his chosen groups of methylsulphonyl and p-methylbenzenesulphonyl (tosyl) both interfered with the deprotonation step. It was also found that the tosyl derivative would not recrystallize.\textsuperscript{97,101} It was thus decided that the benzenesulphonyl group be tried for this work.

Thus 1035 was dissolved in pyridine and benzenesulphonyl chloride added and the reaction was allowed to proceed for several hours (Scheme 54). The product was precipitated out from the reaction by the addition of diethyl ether and water. The product was then redissolved in dichloromethane and recrystallized by the addition of ether to give 62% yield. Hence, unlike the tosyl derivative, the benzenesulphonyl derivative 1051 was highly crystalline (mp = 165-167°C).

$^1$H-NMR at room temperature showed broad peaks. These broad signals sharpened out when the NMR was taken at +50°C, giving only one set of signals. Thus confirming that the phosphoric acid mediated cyclization gave exclusively one diastereomer. The $^1$H-NMR was assigned according to the earlier work of Davies.\textsuperscript{97} At -20°C, two sets of sharp peaks were seen due to the two nitrogen rotamers. Thus it was concluded that at +50°C the $N$-1-C bond rotated freely and rapidly on the NMR timescale. At room temperature, the process was almost stationary, and at -20°C the rotation process had stopped altogether. This pattern was seen throughout the derivatives synthesized.
Interestingly, the substituent at N-8 probably played little or no part in the obstruction of this process as for the N-8 unprotected compound 1035, the two rotamers were clearly seen even at room temperature (which was higher than -20°C for the protected compound 1051).

It was also found that with the indole ring protected, the compounds were more stable and could be more easily handled without the fear of ring opening.

![Scheme 54](image)

3.2 Synthesis of (S) and (R)-α-methylaspartic acid hydrochlorides 1055 and 1058

An imaginative extension of the tryptophan work was the α-alkylation of the pyrroloindole derivative 1051, followed by ring opening to give the tryptophan derivatives, and then oxidative cleavage by method of Ranganathan to the α-substituted aspartic acid with retention of stereochemistry (examples in schemes 1016 and 1017). In principle, any side chain not susceptible to oxidation, including the R groups found in naturally occurring α-amino acids could be introduced into the pyrroloindole, and after oxidative cleavage would emerge as the α-substitution in the aspartate.

Using this method, the (S)-α-methylaspartic acid hydrochloride was obtained. (R)-α-methylaspartic acid hydrochloride was obtained when an additional step involving the Barton Reaction was introduced.
3.2.1 α-Alkylation of 1051 with (a) methyl iodide, and (b) methyl bromoacetate

(a) The enolate 1052 of 1051 was prepared in THF at -78°C with freshly prepared solution of lithium diisopropylamide. The enolate 1052 was then quenched with excess methyl iodide (Scheme 55). The product 1053 was recrystallized from methanol in 63% yield (mp = 144-145°C). 1H-NMR of 1053 at room temperature showed only one set of signals so free rotation about the carbamate bond was taking place at room temperature. The optical rotation was [α]D = +95.2° (c=0.725, CH2Cl2).

(b) To form the adduct 1054, the enolate 1052 was quenched with methyl bromoacetate (Scheme 56). The product was precipitated out from diethyl ether giving 90% yield (mp =113°C, [α]D = +89.7°,c=0.39, CH2Cl2). The 1H-NMR of 1054 at 25°C showed only one
set of signals indicating that the carbamate was rotating freely at +25°C.

![Chemical structure](attachment:structure.png)

**Scheme 56**

### 3.2.2 Ring-opening of 1053 and 1054

1053 and 1054 were ring opened by dissolving them in trifluoroacetic acid (TFA) (Scheme 57). The TFA was then evaporated off. However it was found that not all the TFA may be removed this way, but this did not affect the catalytic oxidative cleavage in the next step.

The residual TFA may be removed by dissolving the product in an organic solvent followed by repeated washing with 4M to 6M NaOH solutions.

The $^1$H-NMR of the ring-opened products showed the disappearance of the distinct doublet for H-8a of the pyrroloindoles.
3.2.3 Catalytic oxidative cleavage of 1056

A near saturated solution of sodium periodate (about 20eq to the 1056 used in water was prepared. The α-methyltryptophan derivative 1056 in acetonitrile was added. Water or acetonitrile was added to the reaction to make it a one-phase system. A catalytic amount of RuCl₃ was added, and the reaction was allowed to stir for several days (Scheme 58). A byproduct of this reaction was 2-(aminobenzenesulphonyl)phenol 1083. The product 1057 was separated from the byproduct 1083 by repeated recrystallization from chloroform. The product was a white solid, mp = 103-105°C, [α]D = -11.0° (c=1.45, MeOH). The yield of the crude was 55%, 17% of the product was obtained after repeated crystallization.
The mechanism of this reaction is still unclear. The actual catalyst is thought to be RuO₄ which was formed by the oxidation of RuCl₃ by NaIO₄ (Scheme 58).

Scheme 58
This is then thought to oxidize the double bond of the indole ring to the diol \textbf{1081} via the intermediate \textbf{1080}. Further oxidation then leads to carbon-carbon bond breakage to give the ketone \textbf{1082}, which then decarbonylate to give \textbf{1082a}. The ketone \textbf{1082a} then undergoes a Baeyer-Villager Oxidation to give the ester \textbf{1082b}, which is then hydrolyzed to give the product \textbf{1057} and the byproduct \textbf{1083}.

### 3.2.4 Catalytic oxidative cleavage of \textbf{1059}

\textbf{1059} was catalytically cleaved in the same way as \textbf{1056}. The product was collected as an oil in 60\% yield (Scheme 59).
3.2.5 Reductive decarboxylation of the free acid group of 1060 using the Barton Reaction

The reductive Barton Reaction has been used successfully in the β-lactam work already (Scheme 33).\textsuperscript{31,32} It involves the conversion of the acid group to the thiohydroxamate ester, which under radical initiation conditions will decarboxylate creating a radical at the centre that was α to the acid group (Scheme 60).
The radical $R^\cdot$ can then be quenched by a source of hydrogen such as a tertiary mercaptan.

When applied to 1060, the product was 1062 (Scheme 61).

\[1060\]

\[1061\]

\[1062\]

Scheme 61
The stereochemistry is the inverse to that of 1057.

The thiohydroxamate ester 1061 was formed from 1060 and the salt 60 in CH$_2$Cl$_2$. It was then photolyzed in the presence of tertiary dodecylmercaptan by a bright tungsten lamp. The product was isolated as an oil in 43% yield. Its optical rotation was $[\alpha]_D = +21.3^\circ$ (c=2.485,MeOH).

3.2.6 Deprotection of 1057 to give (S)-α-methylaspartic acid hydrochloride 1055

The protected compound 1057 was refluxed in 6M HCl for several hours. The acidic solvent was then removed under reduced pressure to give an oil (Scheme 62).
A high field $^1$H-NMR in D$_2$O confirmed the product. Its optical rotation was determined to be $[\alpha]_D = +33.4^\circ$ (c=0.84,H$_2$O).

### 3.2.7 Deprotection of 1062 to give (R)-α-methylaspartic acid hydrochloride 1058

1062 was refluxed in 6M HCl for several hours. The acidic solvent was removed under reduced pressure to give an oil (Scheme 63).
The $^1$H-NMR of 1058 in D$_2$O was identical to that of 1055. Its optical rotation was found to be $[\alpha]_D = -27.6^\circ$ (c=2,H$_2$O) which is of opposite sign, and of nearly the same magnitude as 1058. The compounds 1055 and 1058 must be pure enantiomers as the selectivity step was complete and no mechanism exists on racemization for a fully substituted carbon centre. The discrepancies in the magnitude of the optical rotation was probably due to impurities.

3.2.8 Conclusion

In this portion of the work, it has been found that the pyrroloindoles could be stereospecifically $\alpha$-alkylated, confirming the results obtained by Crich and Davies. A better N-8 protecting group (benzenesulphonyl) than those used by Davies for the pyrroloindoles, which does not interfere with the deprotonation step, has been found. The starting tryptophan skeleton was successfully transformed to the aspartic
acid skeleton with retention of stereochemistry of the original tryptophan chiral centre, and in particular (S) and (R) α-methylaspartic acid hydrochlorides were synthesized. It is envisaged that these may be used in the biological investigation of modified amino acids and peptides outlined in the introduction (chapter 1) of this thesis.

3.3 Synthesis of the (S) and (R) α-methyltryptamines 1067 and 1068

3.3.1 Introduction

5-Hydroxytryptamine (5H-T or serotonin) is a neurotransmitter. Many pharmacologically distinct types and sub-types of 5H-T receptors have been located throughout tissues of the central nervous system.\textsuperscript{106} It is thought that amongst the functions of 5H-T is the modification of behavioural systems. In humans, recent evidence has indicated the distinct possibility that brain 5H-T\textsubscript{2} receptor activation may be the causative factor in the hallucinogenic (psychoactive) effects of many drugs of abuse, including LSD.\textsuperscript{107,108}

(+)-α-Methyltryptamine and (+)-α-methylserotonin have also been described as having antihypertensive and noradrenaline depleting effects.

The in vivo biosynthesis and degradation of 5H-T is outlined in scheme 64.
The precursor for 5H-T is dietary tryptophan 1001, which is then hydroxylated to 5-hydroxytryptophan (5HTP) 1085 by tryptophan hydroxylase which is the rate-limiting enzyme in the synthetic process. 5HTP is decarboxylated to 5H-T by 5HTP decarboxylase.

5H-T is degraded to 5-hydroxyindoleacetic acid after its release into the cytoplasm by monoamine oxidase (MAO). 108

The fact that (+)α-methyltryptophan and (+)α-monofluoromethyltryptophan are substrates for tryptophan hydroxylase and that the 5-hydroxylated product of the fluoro-compound is a time dependent inhibitor of the decarboxylase has already been mentioned. 109,110

Hence, the separate isolation of (R) and (S) α-methyltryptamine and its derivatives is important to the discovery and understanding of the biological mode of action of these compounds with their receptors and enzymes.
3.3.2 Synthesis of the Pyrroloindole Carboxylic Acid 1063

The first step in the synthesis is the hydrolysis of the methyl ester 1053. 1053 was dissolved in methanol and added to a concentrated aqueous solution of KOH (7 g in 5 ml) at room temperature. Methanol or water was then added dropwise to ensure the reaction was one phase (Scheme 65). The reaction was left for several hours.

\[
\begin{align*}
1053 & \xrightarrow{\text{CH}_3 \text{KOH}} 1063 \\
\text{PhSO}_2 \text{NH}_2 \text{CO}_2\text{CH}_3 & \quad \text{MeOH,H}_2\text{O} \\
\text{PhSO}_2 \text{NH}_2 \text{CO}_2\text{H} & \\
\end{align*}
\]

Scheme 65

High field $^1$H-NMR of the product showed the loss of one methyl ester group only, hence the carbamate was stable to this hydrolysis at room temperature. The H-8a signal was also present, so no ring opening had taken place. The product was recrystallized from dichloromethane and petrol to give 72% yield, mp=138-139°C, $[\alpha]_D = +99^\circ$ (c=1, CH$_2$Cl$_2$).

3.3.3 Preparation of the 2-methylpyrroloindoles 1065 and 1066

1065 and 1066 were synthesized by refluxing in toluene or photolysis by a tungsten lamp of the thiohydroxamate 1064 in the presence of excess tertiary mercaptan (Scheme 66).$^{31,32}$
Scheme 66

1063

\[ \text{HN'N} \]

PhSO₂

\[ \text{Cl}^{-} \]

\[ \text{NEt}_3 , \text{CH}_2\text{Cl}_2 \]

1064

\[ \text{HN'N} \]

PhSO₂

\[ \text{CO₂CH}_3 \]

\[ \text{CH}_3 \]

\[ \text{S} \]

1065

\[ \text{HN'N} \]

PhSO₂

\[ \text{CO₂CH}_3 \]

\[ \text{CH}_3 \]

1066

\[ \text{HN'N} \]

PhSO₂

\[ \text{CO₂CH}_3 \]

\[ \text{CH}_3 \]

\[ \text{t-C}_12\text{H}_{25}\text{SH} , \text{hv or } \Delta \]
1064 was synthesized by stirring the acid 1063 with the salt 60 in dichloromethane at room temperature or below.

The two diastereomers 1065 (exo-methyl) and 1066 (endo-methyl) were formed. In the crude the ratio of the endo-methyl:exo-methyl were 1:2 for the thermal reaction (total yield = 21%) and 1:4 (total yield = 19.4%) for the photolytic process. Thus for this reaction, the exo-methyl product is favoured over the endo-methyl product. Thus in this reaction, steric affects make the more bulky methyl group adopt the exo-position with respect to the system.

The two diastereomers were separated by column chromatography. The two diastereomers may be easily assigned by their high field $^1$H-NMR because the C-2 methyl group of the endo-methyl diastereomer 1066 gives an upfield doublet at 0.678ppm. This is due to shielding of the methyl group by the aromatic ring of the pyrroloindole system. The exo-methyl diastereomer gives a doublet at the expected chemical shift of 1.29ppm.

3.3.4 Ring opening of 1065 and 1066 to give the α-methyltryptamines 1067 and 1068

1065 and 1066 was each ring opened by stirring with trifluoroacetic acid (TFA), (Scheme 67), to give the S-isomer 1067 and the R-isomer 1068.
The high field $^1$H-NMR's of 1067 and 1068 were identical. Attempts to make the Mosher\textsuperscript{111,122} derivatives of them in order to prove their enantiomeric nature by $^{19}$F-NMR failed due to the small amount of materials available. $^1$H-NMR taken with the shift reagent europium [D-3-heptafluoro- butyrylcamphorate]\textsubscript{3} also failed to give conclusive results that 1067 and 1068 were enantiomers.

Optical rotations were attempted in two different solvents (MeOH , CH\textsubscript{2}Cl\textsubscript{2}), but their values were so small as to be unreliable.

Glennon\textsuperscript{85} gave the optical rotations of $\alpha$-methyltryptamine as follows:

$S(+)$-$\alpha$-MeT $[\alpha]_D^{26}$= $+33.1^\circ$ (95% ethanol), mp=128-129$^\circ$

$R(-)$-$\alpha$-MeT $[\alpha]_D^{26}$= $-30.1^\circ$ (95% ethanol).
3.4 Isolable mixed anhydrides of i-butylformate

3.4.1 Introduction

A well known method of preparing amides or phenolic esters from carboxylic acids involves the activation of the acid as the mixed carboxylic-carbonic acid anhydride followed by reaction with the pertinent nucleophile. The anhydride is generated by the action of an alkyl chloroformate in the presence of a tertiary amine, and is not isolated before the subsequent reaction. The activation is carried out at low temperature in anhydrous solvent, and is usually of only one or two minutes duration, to avoid decomposition of the anhydride, and, when pertinent, the production of stereomuted products.

In the course of this work with pyrroloindoles, a stable, crystalline mixed anhydride 1069 was discovered.

It was found that mixed anhydrides of this nature have already been reported by Benoiton, but only one product Z-DL-Ala-O-COOEt was reported as being crystalline, mp=50-52°C. Generally, they were only stable at temperatures below -5°C.

3.4.2 Preparation of the mixed anhydride 1069

The mixed anhydride 1069 was prepared by the addition of i-butyl chloroformate to a solution of the acid 1063 and triethylamine in THF at -15°C (Scheme 68).
The reaction was left for over an hour and then the solvent removed without any aqueous work-up and the crude was column chromatographed to give the product in 88% yield. The product was recrystallized from ethyl acetate and petrol,
mp = 107-109°C.

It was not possible to distinguish the $^1$H-NMR's of the mixed anhydride and the ester without a source of reference, but CHN elemental analysis confirmed that the product was the mixed anhydride and not the ester. Subsequently, this was confirmed by single crystal X-ray analysis and mass spectrum which gave a molecular ion.

The X-ray analysis revealed that in the crystalline state, the oxygen of C=O in the side chain lies at a distance of 3.228 Å from C-3b and C-7a of the pyrroloindoole ring (Scheme 69).

This distance is shorter than the 3.4 Å interdistance between adjacent base-pairs in DNA. Thermodynamic studies have shown that a stabilizing π-stacking interaction occurs between these adjacent base-pairs in DNA. Interaction was possible
due to their proximity. Thus it is likely that such an interaction may also occur in the
anhydride 1069. However, this is unlike the compound 1042 prepared by Davies which
showed a distance of 3.208Å between the oxygen of the C-OMe and C-7a of the
pyrroloindole system, and not the O of C=O as in 1069.

The discovery of this stable mixed anhydride prompted further
investigation. It was decided to synthesize the mixed anhydride from the corresponding
monocyclic pyrrolidine system derived from the amino acid L-proline (Scheme 70).

The synthetic scheme was straightforward. The N-protected proline 1070
was esterified to 1071, followed by α-deprotonation and then quenching with MeI to
give the α-methyl compound 1072. The ester was hydrolyzed to the acid 1073 which was
then converted to the mixed anhydride 1074. It turned out that 1074 was isolable, but was
however not indefinitely stable (Scheme 70), in agreement with the results reported by Benoiton. 113

3.4.3 Preparation of the fully protected L-proline 1071

The N-protected L-proline 1070 was taken and esterified with methanol to give 1071. This was done by adding 1070 to a solution of thionyl chloride in methanol (Scheme 71).

![Chemical structure](image)

Scheme 71

The methyl ester was obtained as a liquid in 99% yield.

3.4.4 α-Methylation of 1071

The α-proton of 1071 was removed by the use of LDA at -78°C, and the enolate formed was then quenched by methyl iodide to give the (RS)-α-methylproline
derivative 1072 (Scheme 72).

![Chemical structure diagram]

**Scheme 72**

The product was obtained as a colourless oil in 47% yield. $^1$H-NMR at room temperature showed two rotamers of 1072. Two signals for the methyl ester and two signals for the α-methyl groups in the ratio of 4:5 were seen. These were due to the carbamate rotamers.

### 3.4.5 Synthesis of the acid 1073

The methyl ester 1072 in methanol was added to a concentrated aqueous solution of KOH at room temperature (2.5g in 2ml). Water and methanol were added dropwise until the reaction was all in one phase. The reaction was left stirring for 16 hours.
The product was obtained in 97% yield and was recrystallized from CH$_2$Cl$_2$ and petrol, mp=121°C.

Two signals for the α-CH$_3$ group in a ratio of 2.3:1 were seen in the high field $^1$H-NMR indicating that two carbamate rotamers were present at room temperature.

**3.4.6 Synthesis of the mixed anhydride 1074**

The acid 1073 and triethylamine were stirred in THF at -40°C and $i$-butylchloroformate was added. The reaction was warmed to -5°C and left for 90 minutes (Scheme 73). The reaction was then quenched with EtOAc and then washed with 2M HCl. Benoiton also reported that he could dissolve his anhydrides in an organic solvent and clean it by washing with an aqueous solution.

The product was then isolated in 86% yield as an oil. $^1$H-NMR showed two
sets of signals in a 1:1 ratio due to the two rotamers.

However, unlike the anhydride 1069, 1074 was not crystalline but an oil, and decomposed rapidly on column chromatography. It also decomposed on storage at room temperature over a few weeks.\textsuperscript{113}

3.4.7 Conclusion

In this part of the work, a stable crystalline mixed anhydride 1069 of the pyrroloindole-2-carboxylic acid 1063 was discovered. The monocyclic analogous system 1074 was also synthesized. However, 1074 unlike 1069 was an oil, and although isolable was not indefinitely stable at room temperature. The $\alpha$-methyl group may contribute some stability to the anhydride in that it may sterically hinder nucleophilic attack. Additionally, stability in the pyrroloindole system 1069 may arise because the formation of the tetrahedral intermediate 1069a in a nucleophilic attack is significantly disfavoured as rehybridization of the carbonyl from $sp^2$ to $sp^3$ will necessarily result in close approach of the carbonyl oxygen to the plane of the aromatic system (Scheme 74).

\begin{center}
\includegraphics[width=0.5\textwidth]{Scheme74.png}
\end{center}
3.5 Pyrroloindoles with aromatic groups linked to the C-2 position

3.5.1 Introduction

It has already been mentioned that there may be a possible intramolecular stacking interaction between the oxygen in the methyl ester 1042 with the aromatic portion of the pyrroloindole ring. A similar interaction may also occur in the mixed anhydride 1069. This interaction was postulated on the basis of their close proximity (< 3.3 Å) as revealed by X-ray analysis.
It would therefore be of interest to synthesize a series of compounds with aromatic groups linked to C-2 of the pyrroloindole skeleton. It might be expected that if such a stacking interaction did occur, and that the aromatic substituent at C-2 was correctly positioned, then this aromatic group linked to C-2 of the pyrroloindole may stack over a part or the entire aromatic portion of the pyrroloindole. The effect of this would be to stop free rotation of this aromatic group. It would then be possible to study this effect by examining the high field $^1$H-NMR, or $^{19}$F-NMR when appropriate, of these compounds in the aromatic regions by looking for unusual chemical shifts and split patterns. With free rotation stopped, the two ortho- positions, or the two meta- positions would no longer be in a magnetically equivalent environment. Also a proton positioned over the aromatic ring might be expected to have its chemical shift shifted upfield due to the shielding provided by the aromatic ring.

It was decided to synthesize first the three aromatic esters 1075a,b,c, which represent a normal aromatic ester, an electron poor aromatic ester, and an electron rich aromatic ester respectively.

The synthetic scheme used is outlined in scheme 75.
The pyrroloindole-2-carboxylic acid 1088 could have been used in the
syntheses of the esters 1075 in a single step process, but it was decided to start from tryptophan 1001, first protecting the nitrogen, and then esterifying the acid group to give 1077 before ring closure and protection of N-8. This route was taken to examine whether the cyclization would still give the syn- configuration for H-2, H-3a and H-8a. The products were then studied by high field NMR's.

3.5.2 Synthesis of the N-carbomethoxytryptophan 1076

The α-amino group of tryptophan 1001 was first protected by the methoxycarbonyl group. L-Tryptophan was dissolved in water containing over two equivalents of sodium carbonate, and methyl chloroformate in toluene was added. After acidification of the reaction mixture, the product was extracted into ethyl acetate which was then removed under reduced pressure to give the product in 99% yield. The product was then recrystallized from ethyl acetate and petrol, mp = 155°C. 1H-NMR in D₂O showed that the product has the carbamate methyl group at δ=3.82ppm.

3.5.3 Synthesis of the phenyl ester 1077a

The acid 1076 was first activated to the mixed anhydride with i-butyl chloroformate in THF at -20°C. The anhydride was then displaced by phenol to give the phenol ester in 80% yield (Scheme 76).
Scheme 76

1077a was recrystallized with ethyl acetate and petrol, mp=164°C.

3.5.4 Cyclization of 1077a to 1078a

1077a was dissolved in 85% H$_3$PO$_4$ and stirred for 8 hours. It was then quenched by dropping slowly into a rapidly stirring mixture of CH$_2$Cl$_2$ and 15% Na$_2$CO$_3$ (Scheme 77).
The product was extracted into ethyl acetate and the product was isolated as an oil in quantitative yields. No further purification was carried out. High field $^1$H-NMR showed two sets of signals. H-8a signals at $\delta=5.61\text{ppm}(d)$ and $\delta=5.66\text{ppm}(d)$ confirmed the success of the cyclization. Integration of the carbamate methyl group indicate that the two rotamers were present in a ratio of 4:5.

3.5.5 N-8 Protection of 1078a

N-8 of 1078a was protected with the benzenesulphonyl group. This was done by the usual method of stirring 1078a in pyridine and then adding benzenesulphonyl chloride (Scheme 78).
Once N-8 was protected, the system was fairly stable to accidental ring opening of the pyrroloindole. The product was isolated as a colourless oil in 51% yield. Attempts to recrystallize it all failed.

High field $^1$H-NMR at room temperature showed broad peaks. These were resolved to give one set of signals when the spectrum was taken at +50°C. The signals "froze" out to two sets of signals at 0°C and below. This was explained on the basis of restricted rotation about the carbamate bond. At a low enough temperature (< 0°C), the carbamate stopped rotating to give two rotamers. At room temperature, rotation was taking place, but slow on the NMR timescale. At +50°C, the carbamate was freely rotating.

NOE difference spectra showed a positive NOE between the H-2 proton with the H-3a and H-8a protons confirming that these protons have the syn-
configuration.

The high field $^1$H-NMR at +50°C showed an upfield doublet at $\delta=6.5$ppm integrating for two hydrogens. This signal was "frozen" out into two sets of doublets on cooling, in the same ratio as for the other signals. These signals belonged to the ortho-protons of the phenyl ester, as they were also present in the $p$-methoxyphenyl ester 1075c but were absent in the pentafluorophenyl ester 1075b. As the signals integrated for two protons, the two ortho protons were thus in an magnetically equivalent environment indicating that the phenyl ester group was freely rotating. No individual signals were seen for the two ortho- protons even at -60°C. Thus it was concluded that there was no $\pi$-stacking interaction occurring between the aromatic ring of the phenyl ester and the aromatic ring of the pyrroloindole. However, this does not rule out a possible interaction between the oxygen of the ester with the pyrroloindole as in the mixed anhydride 1069.

3.6.1 Synthesis of the $p$-methoxyphenyl ester 1077c

The $p$-methoxyphenyl ester 1077c was synthesized by the same method as for the synthesis of the simple phenyl ester 1077a. The acid 1076 was activated to the mixed anhydride 1089 and then allowed to react with $p$-methoxyphenol (Scheme 79). The product was isolated in 41% yield as an oil.
Scheme 79
3.6.2 Ring closure of 1077c to 1078c

1077c was stirred in 88% $\text{H}_3\text{PO}_4$ for 16 hours and then quenched by dropping slowly into a rapidly stirring mixture of $\text{CH}_2\text{Cl}_2$ and 15% $\text{Na}_2\text{CO}_3$ solution. The product was isolated in 96% crude yield as an oil. No further purification was carried out. High field $^1\text{H}$-NMR at room temperature showed two sets of signals corresponding to the two rotamers in a 1:1 ratio. The H-8a signals at $\delta=5.58$ ppm (d, $J=6.4$ Hz) and $\delta=5.65$ ppm (d, $J=6.8$ Hz) confirmed the cyclization (Scheme 80).
3.6.3 N-8 Protection of 1078c to 1075c

N-8 of 1078c was protected in the usual way with the phenylsulphonyl group. This was done by adding phenylsulphonyl chloride to a solution of 1078a in pyridine (Scheme 80). The product was isolated as an oil after column chromatography in 62% yield.

NOE difference spectra showed a positive NOE between H-2 and H-8a, thus confirming their syn-configuration, and by steric reasons H-3a is syn to H-8a and thus H-2 also.

High field $^1$H-NMR at room temperature showed broad peaks. These were resolved when the spectrum was taken at +50°C to give one set of signals. At -20°C, two sets of signals corresponding to the two nitrogen carbamate rotamers, were seen in a 5:2 ratio. However no signals for the individual protons at the o- and m- positions of the p-methoxylphenyl ester were seen at -40°C in the high field $^1$H-NMR. This showed that even at -40°C the arene group was rotating freely and that it did not stack over the pyrroloindole ring. Of course the oxygen of the ester group may still be lying over the pyrroloindole aromatic ring.
3.7.1 Synthesis of the pentafluorophenyl ester 1077b

The method used for the synthesis of the simple phenyl ester 1077a and the p-methoxyphenyl ester 1077c could not be used for the pentafluorophenyl ester 1077b as pentafluorophenol is not nucleophilic enough to react with the mixed anhydride.

Instead the pentafluorophenol was activated with dicyclohexylcarbodiimide (DCC) (Scheme 81) in CH$_2$Cl$_2$ at 0°C.
The N₆-protected tryptophan 1076 was added in EtOAc. The urea precipitate was filtered off, and the crude obtained was column chromatographed to give a colourless oil in 71% yield.

In scheme 81, after activation of the pentafluorophenol, the ester was formed by a simple nucleophilic substitution by the carboxyl anion. The origin of this
3.7.2 Cyclization of 1077b to 1078b

The compound **1077b** was simply dissolved in 88% H₃PO₄ and stirred for 12 hours, and then the acidic reaction was added slowly to a rapidly stirring mixture of CH₂Cl₂ and 15% aqueous Na₂CO₃ (Scheme 82).

![Scheme 82](image)

This equilibrium reaction was incomplete. The crude was columned-chromatographed to give the product in 36.5% yield. The uncyclized product was recovered in 53.8%.

High field ¹H-NMR at room temperature showed two sets of signals with integration ratio of about 2:1 corresponding to the two carbamate rotamers. The H-8a signals occurred at δ=5.60ppm(d,J=6.89Hz) and δ=5.65ppm(d,J=6.68Hz).
3.7.3 N-8 protection of 1078b to 1075b

The compound 1078b was dissolved in pyridine and benzenesulphonyl chloride was added and the solution was stirred for 18 hours (Scheme 83). The crude obtained was column chromatographed to give the product in 49% as a colourless oil.

Scheme 83

High field $^1$H-NMR at room temperature showed broad signals. These were resolved at $+50^\circ$C to give one set of signals. H-8a was at a chemical shift of $\delta=6.33$ppm (d,$J=6.52$Hz). High field $^1$H-NMR at $-20^\circ$C showed two sets of sharp signals in the ratio of about 2.2:1. The two chemical shifts for H-8a were at $\delta=6.31$ppm(d,$J=6.43$Hz,major), and $\delta=6.33$ppm(d,$J=8$Hz,minor).
NOE difference spectrum irradiating at H-2 showed a positive NOE with H-8a proving their syn-configuration.

$^{19}$F-NMR at +50°C showed a triplet integrating for 2F's for the m-F's, a triplet integrating for 1F for the p-F, and a broad signal integrating for 2F's for the o-F's.

$^{19}$F-NMR at room temperature showed that all the signals for the fluorines have broadened out and there were two signals for the o-F's integrating in a ratio of about 2.4:1, which is about the same as the ratio for the two carbamate rotamers.

At 0°C, the F signals were sharpened. The m-F's gave two sets of overlapping triplets as did the p-F. The o-F's gave two sets of non-overlapping doublets in the ratio of 2.3:1 which was about ratio of the N-carbamate rotamers from the $^1$H-NMR spectrum. The same pattern was seen when the $^{19}$F-NMR was taken at -20°C.

At -40°C, the signals for the p-F and m-F's remained sharp whereas the two sets of signals for the o-F’s broadened out to two envelopes. At -60°C these two envelopes merged to give one broad envelope whilst the other signals remained sharp.

The evidence from the $^{19}$F-NMR did not show a stationary pentafluorophenyl group even at low temperatures, and thus cannot be stacked over the pyrroloindole ring. However, it does not rule out the possibility of the O of the C=O group in the ester from being stacked over the pyrroloindole aromatic ring.

### 3.8.1 Synthesis of the amide 1077d

The N$_b$-protected tryptophan 1076 was dissolved in THF at -20°C with NEt$_3$ and then activated to the mixed anhydride 1089, and then quenched with 1,8-diaminonaphthalene (Scheme 84).
Scheme 84

The product was isolated after recrystallization from CH$_2$Cl$_2$ and petrol to
give a yellow solid, which darkened on exposure to air, in 62% yield, mp=128°C. The mass spectrum gave (M-H$_2$O)$^+$ at 384.

UV spectrum$^{114}$ taken in neutral DMF showed three absorption maxima:

$\epsilon_{\text{max}}(281.8\text{nm})=7379$, $\epsilon_{\text{max}}(289.8\text{nm})=7929$, $\epsilon_{\text{max}}(330.6\text{nm})=15697$.

In DMF with a drop of conc. HCl added, four absorption maxima were seen:

$\epsilon_{\text{max}}(280.9\text{nm})=10344$, $\epsilon_{\text{max}}(289.5\text{nm})=11096$, $\epsilon_{\text{max}}(314.0\text{nm})=12773$, $\epsilon_{\text{max}}(326.6\text{nm})=13484$.

By comparison with the UV spectra of 1053 and 1037, and 1,8-diaminonaphthalene, the two shorter wavelength $\epsilon_{\text{max}}$'s belonged to the indole system, and the two longer wavelength $\epsilon_{\text{max}}$'s belonged to the naphthalene.
3.8.2 Ring closure of 1077d to 1078d

1077d was dissolved in 88% H₃PO₄ and stirred for 18 hours. The acidic reaction was then slowly dropped into a rapidly stirring mixture of CH₂Cl₂ and 15% aqueous Na₂CO₃. The product was isolated in 86% yield after a column, mp=120°C (Scheme 85).
However, it was decided that the selective N-8 protection of the pyrroloindole system over the amines of the naphthalene portion of 1078d was not possible. It was thus decided to convert the 1,8-diaminonaphthalene portion of 1078d to the pyrimidine system 1078e.

3.8.3 Attempted conversion of 1078d to 1078e

The conversion of 1078d and 1078e involves a simple dehydration (Scheme 86).
It was found that the dehydration could be effected by refluxing in toluene with phosphorous pentoxide. On work-up, a yellow solid was obtained which had a melting point of 220-221°C. The microanalysis agreed with the dehydrated product. However, the high field $^1$H-NMR showed the absence of the H-8a signals. The conclusion drawn was that although the perimidine system was formed, the pyrroloindole ring opened and reverted to the tryptophan $^{1077e}$ (Scheme 87).

![Scheme 87](image)

UV spectra taken in neutral DMF showed three absorption maxima: $\epsilon_{\text{max}}(281.2\text{nm})=3628$, $\epsilon_{\text{max}}(289.6\text{nm})=3676$, $\epsilon_{\text{max}}(330.8\text{nm})=8048$.

UV spectra taken in DMF with a drop of conc. HCl showed four absorption
maxima : \( \varepsilon_{\text{max}}(280.4\text{nm})=5838, \ \varepsilon_{\text{max}}(289.6\text{nm})=6054, \ \varepsilon_{\text{max}}(313.6\text{nm})=6727, \ \varepsilon_{\text{max}}(326.2\text{nm})=7207. \)

The UV absorption spectrum of 1077e was not distinguishable from those that of 1077d.

3.8.4 Attempted ring closure of 1077e to 1078e

It was thought that to reform the pyrroloindole ring from 1077e to 1078e, 88\% H\textsubscript{3}PO\textsubscript{4} could again be employed. 1077e was dissolved in 88\% H\textsubscript{3}PO\textsubscript{4}, but the product isolated was 1078d, identified from its high field \(^1\)H-NMR. The pyrroloindole ring was formed, but in the process the perimidine ring was opened to give the 1,8-diaminonaphthalene system (Scheme 88).
No further work was done on this system, but a better approach to obtaining 1075d and 1075e would probably be to start from the N-8 protected pyrroloindole-2-carboxylic acid 1090 obtainable from the hydrolysis of 1051 (Scheme 89).
Chapter 3 - Pyrroloindole Carboxylic Acids

\[
\begin{align*}
\text{KOH / MeOH / H}_2\text{O}
\end{align*}
\]
Scheme 89
1090 may be activated to the mixed anhydride 1091 which could then react with 1,8-diaminonaphthalene to give 1075d as required. As H-8 of 1075d was protected, the pyrroloindole system would be less prone to ring opening, and so 1075d could then be dehydrated to 1075e as required with less of a likelihood of the pyrroloindole ring opening.

3.9.1 Synthetic scheme to (+)1112 and (+)1113

The synthesis of the 2-phenyl pyrroloindoles (+)1112 and (+)1113 is outlined in scheme 90.
Scheme 90
This scheme to the syntheses of (+)1112 and (+)1113 involves the synthesis of the ketone 1094. 1094 was synthesized by two different routes, from the nitrile 1092, and from gramine 1093. The ketone 1094 was then converted to the racemic amine (+)1095. (+)1095 was then N$_b$-protected and then cyclized in 88% H$_3$PO$_4$. A mixture of the (+) endo-phenyl product 1110 and (+) exo-phenyl product 1111 were then expected. The products were then N-8 protected to (+)1112 and (+)1113.

3.9.2 Synthesis of 1094 from Gramine 1093

The synthesis of 1094 from gramine 1093 was reported by Stetter et al. It involves heating gramine in DMF with one equivalent of NaCN and two equivalents of benzaldehyde. The mechanism of this reaction is outlined in scheme 91.
(iii)
Scheme 91
In the first part of the reaction, the first equivalent of benzaldehyde and sodium cyanide react to give the cyanohydrin sodium salt 1098. In the second part, gramine reacts with the second equivalent of benzaldehyde to give the addition product 1099 which then eliminates the tertiary amine 1101 to give the reactive intermediate 1100. In the third part, 1101 equilibrates with 1098 to give the cyanohydrin anion 1102 which then go on to react with the reactive intermediate 1100 to give 1103 in part four. Finally, the catalyst NaCN was eliminated to give the desired ketone 1094.

In our hands, the yield obtained after recrystallization was low—typically about 10%, whereas Stetter reported a 52% yield (mp=123-124°C, lit 123-125°C).

3.9.3 Synthesis of 1094 from 1092

A different approach to the synthesis of the ketone 1094 was to react the nitrile 1092 with phenyllithium (Scheme 92).
Scheme 92

The reaction was carried out in ether at 0°C. The product was recrystallized from ether in 6% yield, mp=123-124°C. No starting material was recovered. The low yields in these reactions were probably due to the reactive indole ring.

3.9.4 Conversion of the ketone 1094 to the amine(+)1095

The ketone was converted to the amine via the method of Borch et al. The ketone with about 20 equivalents of ammonium acetate was dissolved in methanol under nitrogen and sodium cyanoborohydride was added (Scheme 93).
3.9.5 N$_{\alpha}$-Protection of (+)1095

The amine (+)1095 in CH$_2$Cl$_2$ was added to an aqueous solution of Na$_2$CO$_3$. Methyl chloroformate was added in CH$_2$Cl$_2$ (Scheme 94). The reaction was allowed to proceed to completion. The product (+)1109 was isolated after column chromatography in 97% yield.
3.9.6 Cyclization of (+)-1109

Crude (+)-1109 was dissolved in 88% H₃PO₄ and stirred for 16 hours. The acidic reaction was then added dropwise to a rapidly stirring mixture of CH₂Cl₂ and 15% aqueous Na₂CO₃ (Scheme 95). The product was extracted into CH₂Cl₂. 200MHz ¹H-NMR showed impurities, but the H-8a signal at δ=6.0ppm could be seen. There were also two peaks for the carbamate methyl ester at δ=3.64ppm and δ=3.68ppm. No purification was carried out at this stage.
Scheme 95
3.9.7 N-8 Protection of (+)1110 and (+)1111

The crude mixture of (+)1110 and (+)1111 was dissolved in pyridine and benzenesulphonyl chloride was added in pyridine. The reaction was stirred for 16 hours (Scheme 96).

The products were isolated, and then column chromatographed to remove the impurities. High field $^1$H-NMR showed a mixture of products. Three doublets in the H-8a region of the spectrum were seen at $\delta=6.00$ppm($J=7.3$Hz), $\delta=6.42$ppm($J=7.9$Hz), and $\delta=6.32$ppm($J=6.66$Hz). Three singlets for the carbamate methyl ester were also seen at $\delta=3.661$ppm, $\delta=3.667$ppm and $\delta=3.671$ppm. However no unusual signals were seen at the aromatic regions of the spectrum to indicate any aromatic ring - aromatic ring stacking.
interaction between the 2-phenyl and the pyrroloindole rings.

Further work in the Crich group to improve the yield and purity of this reaction is underway so that the possible stacking interaction can be further examined.

3.10.1 Phosphoric acid mediated cyclization of (+)α-methyltryptamine

It was of interest to see whether phosphoric acid mediated cyclization of α-substituted tryptamine would also favour the formation of the endo product as with the tryptophan esters. To this end, the cyclization of (+)α-methyltryptamine was carried out (Scheme 97).
Cyclization of the R-series would give rise to one optical isomer of 1106 and one optical isomer of 1107a. Cyclization of the S-series would give 1106a and 1107, where 1106a is the optical isomer of 1106 and 1107 the optical isomer of 1107a. If the endo-methyl isomer were favoured in the acid mediated cyclization, as with the cyclization of the esters of tryptophan, then 1066 and its optical isomer 1066a would be expected to be obtained almost exclusively, and little or no 1065 and its optical isomer 1065a formed. 1065 and 1066 could be easily distinguished as their $^1$H-NMR spectra were already available from previous work.

If there was little or no selectivity, then it was expected that 1065 and 1065a would be formed too, and thus both the (+)endo-methyl and (+)exo-methyl products would be in the product mixture.

3.10.2 $N_b$-Protection of (+)$\alpha$-methyltryptamine

$N_b$ of (+)$\alpha$-methyltryptamine was protected as the carbamate as before. This was done by stirring a solution of the (+)1104 in CH$_2$Cl$_2$ with an aqueous solution of Na$_2$CO$_3$. Methyl chloroformate was added. The product (RS)-1105 was obtained quantitatively as an oil.
3.10.3 Phosphoric acid mediated cyclization of (RS)-1105

(RS)-1105 was dissolved in 88% H₃PO₄ and stirred for 16 hours. The products were isolated quantitatively. High field ¹H-NMR was complicated by the rotamers, but the H-8a protons and signals corresponding to the endo- and exo- methyl groups were seen.

3.10.4 N-8 Protection of the cyclized products

The cyclized products 1106, 1106a, 1107, and 1107a were protected with the benzenesulphonyl group as before. This was done in pyridine, and benzenesulphonyl chloride was added. The products were isolated. 200MHz ¹H-NMR showed the exo-methyl:endo-methyl products in a ratio of about 4:5. The chemical shifts of the products were the same as that observed for 1066 and 1065 prepared previously.

3.10.5 Conclusion

From the results obtained here, there was virtually no selectivity in the phosphoric acid mediated cyclization of the (+)α-methyltryptamine (RS)-1105 as opposed to the cyclization of the tryptophan esters. This suggests that the α-COOR group of the tryptophan esters may play a crucial role during the phosphoric acid mediated cyclization process. It lends support to the theory that the 2-alkoxycarbonyl group in the pyrroloindole may be interacting with the pyrroloindole aromatic ring and giving rise to a stabilizing interaction.

However, the non-selective cyclization of the α-methyltryptamine may be due to the fact that the α-methyl group is too small to produce any effects in the cyclization process. Further work by the Crich group is now underway to synthesize the
α-isopropyl tryptamine 1108, and its cyclization in phosphoric acid.
Experimental Section

Preparation of
(3S,4R)-1-(di-p-anisylmethyl)-3-[(1R)-1-t-butyl
dimethylsilyloxyethyl]-2-azetidinone-4-carboxylic acid (9)

Compound 8 (9.99g) was dissolved in dry N,N-dimethylformamide
(DMF) and stirred under nitrogen. t-Butyldimethylsilyl chloride (TBDMSCl)(8.87g,
2.27eq), was added. Imidazole (4.44g, 2.5eq) dissolved in 10ml of dry DMF was
added dropwise and the solution was left stirring for 18 hours at room temperature.

The reaction mixture was then diluted with 550ml of water, 400ml of
ethyl acetate and acidified with 200ml of 2M HCl. The organic phase was separated
and the aqueous phase was then again extracted with ethyl acetate (2x). The combined
organic phases was then washed with water (400ml,2x), separated, and then washed
with saturated brine. The organic phase was then dried over anhydrous magnesium
sulphate. The solvent was then removed on the rotatory evaporator and the viscous
colourless liquid was left under vacuum for 4 hours. The yield was 15.06g(> 100%).
NMR showed the presence of silanol. TLC showed 3 β-lactam products (charring red
with PMA).

The crude product (0.452g) was taken and columned in 5% ethyl
acetate in dichloromethane. The desired product (0.2095g, 54%) was obtained. 0.125g
of a product identified to be the starting material 8 was recovered.

The silylation procedure was repeated to convert the unchanged 8 to 9.

$^1$H-NMR
$\delta$=0.11 (6H, Si(CH$_3$)$_2$); $\delta$=0.91(9H, SiC(CH$_3$)$_3$)
$\delta$=1.32(d,3H,H-3β); $\delta$=4.28(m,1H,H-3α);
$\delta$=3.22(dd,1H,H-3); $\delta$=4.10(d,1H,H-4);
$\delta$=4.5(broad,1H,COOH): $\delta$=5.83(s,1H,N-CH);
Preparation of
(3S)-1-(di-p-anisylmethyl)-3-[(1R)-1-t-butyldimethyl-
silyl oxyethyl]-2-azetidinone, 26, via the acid chloride
10a, and the mixed acid anhydride 10b

9 (0.2095g) was dissolved in 2ml of sodium dried benzene. A drop of
DMF was added as catalyst. Oxalyl chloride (3ml, excess) was added and the solution
was stirred until gaseous evolution stopped. This solution was then added dropwise to
a refluxing solution of sodium thiohydroxamate (69mg, 1.1 eq) and the mercaptan 25
(94mg, 1.1eq) in benzene (10ml) under nitrogen. The reaction was left refluxing for 4
hours.

The product was separated by column chromatography (SiO₂,
CH₂Cl₂:Et₂O = 9:1). The desired product (0.1347g, 70%) was isolated.

9 (0.5397g) and triethylamine (0.115g, 1.05eq) were dissolved in dry
THF (5ml) and stirred at -15°C. i-Butylchloroformate, 24, (0.151g, 1.02eq) dissolved
in dry THF (2ml) and cooled to -15°C was added and the solution was stirred at
-15°C for 20 minutes. Then the free thiohydroxamic acid (0.149g, 1.0eq) was added in
dry THF (5ml) and immediately a bright yellow solution was formed. The solution
was allowed to stir at -15°C for 30 minutes. It was then filtered over celite to remove
the ammonium salt byproduct. The mercaptan 25 (0.219g, 1.0eq) was then added and
the solution was photolyzed at room temperature with a tungsten lamp (500W) under
nitrogen until tlc showed the complete disappearance of the thiohydroxamate ester 11.
The product was column chromatographed as before to give the desired product(0.3937g,80%).
**Experimental** 191

400MHz $^1$H-NMR ref CDCl$_3$

$\delta=0.065,0.026$ (6H, Si(CH$_3$)$_2$); $\delta=0.839$ (9H, SiC(CH$_3$)$_3$);

$\delta=1.16$ (d,3H,H-3$o$); $\delta=4.2$ (dq,1H,H-3$\alpha$)

$\delta=3.26$ (dt,1H,H-3); $\delta=3.15$ (d,2H,H-4)

$\delta=6.06$ (s,1H,N-CH); $\delta=3.799, 3.805$ (s,6H,2x O-CH$_3$)

$\delta=6.7$ to 7.2 (aromatics).

$^{13}$C-NMR ref CDCl$_3$

$\delta=-4.163, -4.214$ (Si(CH$_3$)$_2$); $\delta=18.421$ (SiCM)$_3$;

$\delta=23.055$ (C-3$\beta$); $\delta=65.730$ (C-3$\alpha$);

$\delta=57.058$ (C-3); $\delta=40.254$ (C-4); $\delta=58.132$ (N-C);

$\delta=55.682, 55.669$ (O-CH$_3$); $\delta=168.514$ (C-2);

$\delta=132.834, 131.628$ (aromatic C-1');

$\delta=129.739, 129.726, 129.643, 129.635$ (aromatic C-2');

$\delta=114.290, 114.277, 114.265, 114.252$ (aromatic C-3');

$\delta=159.299$ (aromatic C-4').

**Preparation of**

(3S,4R)-1-(di-p-anisylmethyl)-3-[(1R)-1-t-butyl-
dimethylsilyloxyethyl]-4-(2-thiopyridyl)-2-azetinone

(27)

The acid chloride (10a) (2.37g) prepared as a brown oil was dissolved in dry THF (15ml). It was added dropwise to a solution of sodium thiohydroxamate (0.73g, 1.1eq) in dry THF (20ml) with stirring in the dark and under nitrogen. A yellow solution was formed. It was then photolyzed with a 500W tungsten lamp for 2
hours. The products were separated by column chromatography (SiO₂, CH₂Cl₂:Et₂O = 9:1). The desired product was isolated (0.3318g, 12.9%).

9 (0.7201g) was weighed out and the acid chloride 10a in sodium dried benzene (10ml) was added dropwise to a refluxing mixture of sodium thiohydroxamate (0.23g, 1.17eq) in benzene under nitrogen. The mixture was left refluxing for 5 hours. The product was separated by column chromatography (SiO₂, CH₂Cl₂:Et₂O =9:1). The desired product was isolated (0.1256g, 15.4%).

400MHz ¹H-NMR (ref CDCl₃)
δ=0.000, 0.065 (6H, Si(CH₃)₂) ; δ=0.815 (s, 9H, SiC(CH₃)₃) ;
δ=1.24 (d, 3H, H-3α) ; δ=4.26 (m, 1H, H-3α) ;
δ=3.33 (dd, 1H, H-β) ; δ=5.92 (d, 1H, H-4) ;
δ=5.735 (s, 1H, N-CH) ; δ=3.747, 3.800 (s, 6H, 2x OCH₃) ;
δ=8.32 (d, 1H, pyridyl α-H) ;
δ=6.6 to 7.5 (aromatics).

¹³C-NMR ref CDCl₃
δ=17.933 (SiCMe₂) ; δ=25.718 ((CH₃)₃) ;
δ=22.304 (C-3β) ; δ=65.310 (C-3α) ; δ=60.983 (C-3) ;
δ=63.874 (C-4) ; δ=165.882 (C-2) ; δ=58.498 (N-C) ;
δ=55.175, 55.099 (2x OCH₃) ; δ=131.935, 131.278 (DAM-C-1) ;
δ=129.716, 129.463 (DAM-C-2) ; δ=113.556, 113.411 (DAM-C-3) ;
δ=158.587, 158.639 (DAM-C-4) ; δ=157.010 (pyridyl-C-2) ;
δ=149.331 (pyridyl-C-6) ;
δ=120.231, 122.824, 136.071 (pyridyl C-4, C-5, C-3).
Preparation of (3S,4R)-1-(di-p-anisylmethvl)-3-[(1R)-1-t-butyldimethvl-silyloxvethyl]-4-[(2RS)-2-methoxvcarbonyl-2-(2-thiopyridyl)ethyl]-2-azetidinone (29)

9 (0.509g) was dissolved and stirred in dry THF (4ml) with triethylamine (0.120g, 1.17eq) and cooled to -20°C. i-Butylchloroformate (0.158g, 1.14eq) was added in THF (1ml) at -20°C and the mixture was stirred for 10 minutes. Thiohydroxamic acid (0.130g, 1.0eq) was added, and immediately a bright yellow solution was formed. The solution was then quickly filtered over celite under suction to removed the precipitated ammonium salt byproduct. The celite was washed with more THF.

Methyl acrylate (0.872g, 10eq) was then added to the yellow solution. The solution was then photolyzed under nitrogen at room temperature for 90 minutes when tlc showed the absence of the thiohydroxamate ester 11. The products were separated by column chromatography (SiO$_2$, CH$_2$Cl$_2$:Et$_2$O = 19:1). The desired products were collected (0.260g, 47%). The 400MHz $^1$H-NMR and $^{13}$C-NMR were taken. The NMR's showed the products to be clean, but two diastereomers in the ratio of 2:1 were present.

400MHz $^1$H-NMR ref CDCl$_3$

$\delta$=0.001, -0.034, 0.019, 0.025 (6H, Si(CH$_3$)$_2$) ;
$\delta$=0.778, 0.773 (9H, SiC(CH$_3$)$_3$) ;
$\delta$=3.82(m,1H,H-3\alpha) ;
$\delta$=1.176(d), 1.271(d), (3H, H-3\beta) ;
$\delta$=5.87(s),5.89(s) (1H, N-CH)
$\delta$=2.91(dd), 3.03(dd) (1H, H-3) ;
$\delta$=4.1(td),4.2(td) (1H,H-4)
$\delta$=3.727, 3.735, 3.748, 3.753 (6H, 2xArOCH$_3$) ;
δ=1.9(m), 2.07(m), 2.25(m), 2.35(m) (2H, H-4α);
δ=4.3(dd), 4.5(dd) (1H, H-4β);
δ=3.609(s), 3.616(s) (3H, COOCH₃);
δ=8.29(d), 8.33(d) (1H, α-H pyridyl);
δ=6.7 to 7.6 (aromatics).

$^{13}$C-NMR ref CDCl₃

δ=4.921, 4.883, 4.523, 4.481 (Si(CH₃)₂);
δ=17.835, 17.868 (Si-CMe₃); δ=25.718, 25.745 (SiC(CH₃)₃);
δ=22.540, 22.803 (C-3β); δ=65.073, 65.414 (C-3α);
δ=62.786, 62.894 (C-3); δ=42.406, 43.066 (C-4);
δ=167.529, 167.726 (C-2); δ=59.303, 59.706 (N-C);
δ=55.105 (DAM, OCH₃);
δ=130.595, 130.644, 131.722, 131.906 (DAM C-1);
δ=128.869, 129.814, 129.870, 129.926 (DAM C-2);
δ=113.573, 113.737, 113.696, 113.655 (DAM C-3);
δ=158.629, 158.666, 158.820 (DAM C-4);
δ=35.641, 37.031 (C-4α); δ=52.414, 52.523 (C-4β);
δ=171.809, 172.065 (COO)=Me; δ=53.051 (COOCH₃);
δ=156.143, 156.169 (pyridyl C-2);
δ=149.232, 149.194 (pyridyl C-6);

Other pyridyl carbons have $^{13}$C-NMR signals at:
δ= 136.027,136.175; 119.889,120.153; 122.010,122.147,122.168.
Preparation of

\((3S,4R)-1-(dip-anisymethyl)-3-[(1R)-t-butyldimethyl-silyloxyethyl]-4-(2-methoxycarbonyl)-2-azetinone, (31)\)

9 (503mg) was taken and the ester 11 was prepared via the mixed acid anhydride 10b in THF. The ester 11 was photolyzed with methylacrylate (434mg, 5eq) for 1 hour. The THF solvent was evaporated and the crude product was redissolved in 100% ethanol (10ml). An excess of Raney Nickel in 100% ethanol was added and the solution was stirred for 2 hours.

The crude product of the above was column chromatographed (SiO\textsubscript{2}, petrol:ether = 2:1). A product (302mg) identified as the unreduced adduct 29 was collected.

The recovered 29 from above was then dissolved in 1ml of dry toluene and stirred under nitrogen. Butyltin hydride (nBu\textsubscript{3}SnH) (305mg) was added together with a few crystals of AIBN as a radical initiator. The solution was then refluxed under nitrogen.

The toluene was then evaporated off and the product redissolved in acetonitrile (CH\textsubscript{3}CN) and extracted with petrol. The petroleum phase was then washed with more acetonitrile (5ml, 5x). The petroleum phase was kept. The petrol solvent was then evaporated and the product was column chromatographed (SiO\textsubscript{2}, petrol followed by CH\textsubscript{2}Cl\textsubscript{2}). The desired product (45mg, 18%) was collected. \textsuperscript{1}H-NMR and \textsuperscript{13}C-NMR showed a clean product with no diastereomeric mixtures.

400MHz \textsuperscript{1}H-NMR ref CDCl\textsubscript{3}

\[ \delta = 0.019, 0.047 \text{ (6H, Si(CH\textsubscript{3})\textsubscript{2})}; \delta = 0.834 \text{ (9H, SiC(CH\textsubscript{3})\textsubscript{3})}; \]
\[ \delta = 1.2205 \text{ (d, 3H, H-3\textbeta}); \delta = 4.05 \text{ (m, 1H, H-3\alpha)}; \]
\[ \delta = 2.7295 \text{ (dd, 1H, H-3)}; \delta = 3.5455 \text{ (ddd, 1H, H-4)}; \]
Experimental

\[ \delta = 1.64(m), 1.92(m) \text{ (2H, H-4α)}; \ \delta = 2.2(m, 2H, H-4β); \]
\[ \delta = 3.622(s, 3H, COOCH_3); \ \delta = 5.861(s, N-CH); \]
\[ \delta = 3.795(s), 3.805(s) \text{ (6H, 2x OCH}_3\text{)}; \]
\[ \delta = 6.85 \text{ to } 7.19 \text{ (aromatics).} \]

\[ ^{13}C-\text{NMR ref C}_6\text{H}_4\text{Cl}_3 \]

\[ \delta = 17.907 \text{ (SiCMe}_3\text{)}; \ \delta = 25.787 \text{ (SiC(CH}_3\text{)}_3\text{)}; \]
\[ \delta = 22.950 \text{ (C-3β)}; \ \delta = 66.048 \text{ (C-3α)}; \ \delta = 62.509 \text{ (C-3)}; \]
\[ \delta = 51.613 \text{ (C-4)}; \ \delta = 167.474 \text{ (C-2)}; \ \delta = 59.248 \text{ (N-C)}; \]
\[ \delta = 131.708, 130.720 \text{ (DAM C-1)}; \]
\[ \delta = 129.797, 129.999 \text{ (DAM C-2)}; \]
\[ \delta = 113.728, 113.849 \text{ (DAM C-3)}; \]
\[ \delta = 158.809, 158.941 \text{ (DAM C-4)}; \ \delta = 55.209 \text{ (Ar-OCH}_3\text{)}; \]
\[ \delta = 28.372(C-4α); \ \delta = 30.163(C-4β); \ \delta = 172.998(CO}_2\text{)}; \]
\[ \delta = 54.868(COOCH}_3\text{).} \]

**Preparation of nitroethene (32)**

The commercially available 2-nitro-1-ethanol (5.00g) was mixed with phththalic anhydride (5.11g) in a distillation apparatus. The mixture was distilled at a reduced pressure provided by a water pump. The oil bath temperature was allowed to rise up to 210°C. A mixture of water and nitroethene distilled out. The mixture was then left in the freezer for 16 hours to allow the water phase to freeze out. The liquid nitroethene was then separated and dried over anhydrous magnesium sulphate and then filtered over celite. It was then redistilled at 80°C-100°C to give a pale yellow and very pungent liquid (1.93g, 48%). It was then stored in the freezer.
Preparation of 1-nitro-2-propanol (34)

Nitromethane (100.0g) and ethanal (72.2g, 1.00eq) were mixed and water (100ml) with 1.01g of potassium hydrogen carbonate was added. The solution was stirred in an ice-bath. After 60 minutes the solution became homogeneous. The solution was extracted with ether and dried over anhydrous magnesium sulphate. After the removal of the solvent, the product (17.0g, 98%), a colourless liquid, was collected.

60MHz $^1$H-NMR ref external TMS

$\delta$=5.5 to 7.4 (m, olefinic H’s)

Preparation of 1-nitro-1-propene (30)

1-Nitro-2-propanol (34)(30.0g) was mixed with phthalic anhydride (30g) and distilled under a short column. The oil bath temperature was allowed to rise to 200°C. A mixture of the nitropropene and water distilled out. The mixture was left in the freezer for 16 hours to allow the water phase to freeze. The nitropropene was
then separated from the ice and dried over magnesium sulphate. A pungent yellow liquid (14.7g, 59%) was obtained. The product was stored in the freezer with molecular sieves. The integration on the 200MHz NMR showed the product to be a mixture of trans- and cis-1-nitro-1-propene in the ratio of about 10:1.

200MHz $^1$H-NMR ref CDCl$_3$
\[ \delta=1.99 \text{ (dd), 2.18 (dd) (3H, CH}_3) ; \]
\[ \delta=6.9 \text{ to 7.3 (m, 2H, olefinic)} \]

**Preparation of**

(3S,4R)-1-(di-p-anisylmethyl)-3-[(1R)-1-t-butyldimethylsilyloxyethyl]-4-[(2RS)-2-nitro-2-(2-thiopyridyl)ethyl]-2-azetidinone (33)

9 (254mg) was dissolved in THF(3ml) and the thiohydroxamate ester 11 was prepared via the mixed acid anhydride 10b route as described above.

Nitroethene (98mg, 2.64eq) was added to the thiohydroxamate ester 11 solution from above and the solution was photolyzed with a tungsten lamp under nitrogen at 0°C for 2 hours. The solvent was then evaporated and the products were separated by column chromatography (SiO$_2$, petrol:CH$_2$Cl$_2$=2:3). The product (118mg, 36%) was collected.

400MHz $^1$H-NMR ref CDCl$_3$
\[ \delta=-0.030, 0.013, 0.063, 0.092 \ (6H, \text{Si(CH}_3)_2) ; \]
\[ \delta=0.797, 0.837 \ (9H, \text{Si(CH}_3)_3) ; \]
\[ \delta=1.142(d), 1.250(d) \ (3H, \text{H-3}) ; \]
\[ \delta=2.96(dd), 3.02(dd) \ (1H, \text{H-3}) ; \]
Experimental

\[ \delta = 4.08 (m), 4.15 (m) \text{ (1H, H-4)}; \]
\[ \delta = 6.22 (dd), 6.34 (t) \text{ (1H, H-4\beta)}; \]
\[ \delta = 5.927, 5.934 \text{ (1H, NCH)}; \]
\[ \delta = 3.768, 3.792, 3.799, 3.817 \text{ (6H, OCH}_3\text{)}; \]
\[ \delta = 8.36 (d), 8.39 (d) \text{ (1H, pyridyl H-6)}; \]
\[ \delta = 6.8 \text{ to } 7.3 \text{ (aromatics)}; \]

Signal for H-3\alpha was under the OCH\textsubscript{3} signals.

\textbf{\textsuperscript{13}C-NMR ref CDCl\textsubscript{3}}

\[ \delta = 17.911, 17.867 \text{ (CMe}_3\text{)}; \delta = 25.788, 25.729 \text{ (C(CH}_3)_3\text{)}; \]
\[ \delta = 22.258, 22.376, 22.502, 22.689 \text{ (C-3\beta)}; \]
\[ \delta = 65.440, 65.185 \text{ (C-3\alpha)}; \delta = 63.026, 62.960 \text{ (C-3)}; \]
\[ \delta = 52.222, 51.926 \text{ (C-4)}; \delta = 37.467, 36.930 \text{ (C-4\alpha)}; \]
\[ \delta = 85.123, 85.164, 85.762, 85.798 \text{ (C-4\beta)}; \]
\[ \delta = 167.354, 167.201 \text{ (C-2)}; \delta = 59.588, 59.665 \text{ (N-C)}; \]
\[ \delta = 130.265, 130.190, 131.295, 131.186 \text{ (DAM C-1)}; \]
\[ \delta = 129.780, 129.704, 128.935, 128.877 \text{ (DAM C-2)}; \]
\[ \delta = 114.017, 113.981, 113.856, 113.830 \text{ (DAM C-3)}; \]
\[ \delta = 159.104, 159.063, 258.985, 258.890 \text{ (DAM C-4)}; \]
\[ \delta = 55.211, 55.178, 55.144, 55.112 \text{ (OCH}_3\text{)}; \]
\[ \delta = 153.493, 153.471 \text{ (pyridyl C-2)}; \]
\[ \delta = 149.740, 149.838 \text{ (pyridyl C-6)}; \]

Other pyridyl signals are at:
\[ \delta = 122.361, 122.069, 121.354, 121.180; 136.892, 136.759 \]
Preparation of
(3S,4R)-1-(di-p-anisylmethyl)-3-[(1R)-1-t-butyldimethylsilyloxyethyl]-4-[(1RS,2RS)-1-nitro-1-(2-thiopyridyl)-propyl]-2-azetidinone (35)

9 (501mg) was dissolved in THF (1ml) and triethylamine (126mg). The thiohydroxamate ester 11, was prepared via the mixed acid anhydride 10b in THF. 1-Nitro-1-propene (210mg, 2.4eq) was added and the solution was photolyzed for 2 hours with a tungsten lamp under nitrogen at room temperature. The THF solvent was evaporated and the product was separated by column chromatography (SiO₂, CH₂Cl₂). The product (266mg, 41%) was isolated.

400MHz ¹H-NMR showed a mixture of diastereomers, and 400MHz ¹³C-NMR showed quadrupling of signals.

Attempted ozonolysis on 33

33 (386.5mg) was dissolved in CH₂Cl₂(5ml), and triethylamine (67mg, 1.1eq) was added. The solution was stirred at -78°C and ozone was passed through the solution for 90 minutes. The solution was then purged with oxygen and then allowed to warm to room temperature. It was then washed with 2M HCl and extracted into more dichloromethane. The organic phase was then dried over anhydrous magnesium sulphate. The solution was filtered and the solvent evaporated. Column chromatography (SiO₂,CH₂Cl₂ followed by CH₂Cl₂:ether =9:1) was carried out on the crude product, but no identifiable product was obtained.

Attempted ozonolysis on 35
Experimental 201

35 (160mg) was dissolved in CH$_2$Cl$_2$ (2ml) with triethylamine (36mg, 1.5eq). The solution was stirred at -78°C and ozone was passed through the solution for 110 minutes. The solution was then purged with oxygen and then allowed to warm to room temperature. The solution was acidified with 2M HCl and extracted with dichloromethane which was then dried over anhydrous magnesium sulphate. The solution was then filtered and the solvent was evaporated. The crude product was columned, but no identifiable product was obtained.

**Reaction of 35 with aqueous solution of titanium trichloride**

35 (196mg) was dissolved in methanol (4ml) with sodium methoxide (34mg, 2.1eq). 4ml (=4mmol) of aqueous titanium trichloride buffered at pH6 with ammonium acetate were added and the solution was left stirring for 14 hours.

The reaction was then acidified with 2M HCl and then extracted into dichloromethane. The organic solution was then washed with water followed by saturated brine. It was then dried over anhydrous magnesium sulphate. The solvent was evaporated off. The crude product was column chromatographed (SiO$_2$, petrol:ether 2:1) to give a product(44.7mg). The 400MHz $^1$H-NMR showed the absence of the thiopyridyl group. However the IR did not show the $\beta$-lactam C=O stretch.

**Preparation of tetradecanoyl chloride 37**

Tetradecanoic (myristic) acid (25.0g) was added slowly over 20
minutes to thionyl chloride (32g) at reflux. The solution was then refluxed for a further 30 minutes.

The solution was then distilled under high vacuum at 125°C to give a colourless liquid. 23.4g (86%) were obtained. The IR spectrum showed a stretch at 1795cm⁻¹(s) which corresponds to a carbonyl stretch.

**Preparation of (1H)-Pyridine-1-(tetradecanoyloxy)-2-thione (38)**

37 (5.00g) was dissolved in THF (20ml) and stirred at 0°C for 10 minutes in the dark. Sodium thiohydroxamate (3.28g, 1.08eq) was added as the solid and a bright yellow solution was formed immediately. The solution was then stirred in the dark at 0°C for a further hour, and then at room temperature for 45 minutes.

The solution was then filtered to remove the sodium chloride byproduct and excess sodium thiohydroxamate. The THF solvent was then removed on the rotatory evaporator in the dark to give a bright yellow solid. This was then left under high vacuum for 1 hour. 6.68g (>100%) of the solid was collected. The solid was not further purified.

**Reaction of 38 with 30 to give (1RS,2RS)-1-nitro-1-(2-thiopyridyl)-2-methyl-pentadecane (39), and 1-(2-thiopyridyl)tridecane (40)**

A quantity of 38 (typically 500mg) was dissolved in dry THF and 1-nitro-1-propene from 1.5eq to 10eq were added and the solution was photolyzed at 0°C for about 4 hours. The solvent was then evaporated and the products were separated by column chromatography.
200MHz $^1$H-NMR of 39

$\delta =$ 8.38 (1H, pyridyl H-6);  
$\delta =$ 6.9 to 7.8 (m, 3H, pyridyl);  
$\delta =$ 3.11 (t, 2H, H-1);  $\delta =$ 1.85 (t, 3H, H-13);  
$\delta =$ 1.3 (broad, alkyl)

**Reaction of 39 with unbuffered aqueous titanium trichloride solution at pH<1**

39 (130mg) was dissolved in THF (5ml). 5ml of TiCl$_3$(≈5mmol) unbuffered at pH<1 were added and the solution was stirred for 16 hours. The products were then extracted into ether. The ethereal layer was separated, washed with saturated brine and dried over anhydrous magnesium sulphate. The solvent was evaporated and the product was column chromatographed (SiO$_2$,CH$_2$Cl$_2$). Product (57mg) was obtained. 60MHz $^1$H-NMR showed the complete absence of the thiopyridyl group; only a broad alkyl signal was seen. IR showed a stretch at 1718.2cm$^{-1}$ and a weak stretch at 2124.1cm$^{-1}$.

**Reaction of 39 with aqueous titanium trichloride solution buffered at pH6 with ammonium acetate**

39 (98mg) was dissolved in THF(3ml). 3ml of TiCl$_3$(≈3mmol) buffered by ammonium acetate solution to pH6 were added and the solution was stirred for 16 hours. The solution was then extracted with ether, washed with saturated
brine and dried over anhydrous magnesium sulphate. Product (47mg) was obtained and 60MHz\textsuperscript{1}H-NMR showed the absence of the pyridyl group.

**Preparation of**

(3S,4R)-1-(di-p-anisylmethyl)-3-[(1R)-1-t-butyl-dimethylsiloxyethyl]-4-[2-methoxycarbonyl-1-ethenyl]-2-azetidinone (42)

29 (1.1566g, 1.78eq) was dissolved in absolute ethanol (5ml) and stirred at 0°C. Monoperoxyphthalic acid magnesium salt hexahydrate (MPPA) (0.51g, 1.16eq) in ethanol (2ml) was added and the solution was left stirring for 2 hours after which tlc showed complete removal of starting material.

The ethanol was evaporated under reduced pressure, and the crude redissolved in dichloromethane. It was then washed with 5% sodium hydrogen carbonate solution, followed by water, and then dried over anhydrous magnesium sulphate. After filtration the solvent was removed under reduced pressure to give the sulphoxide 41 (1.1331g, >100%).

The sulphoxide 41 thus obtained was then redissolved in toluene (5ml) and refluxed for 90 minutes, after which tlc showed the complete disappearance of the sulphoxide 41 and the presence of a less polar product. The solution was then cooled, and the toluene evaporated under reduced pressure. The crude was then redissolved in dichloromethane, washed with 5% sodium hydrogen carbonate solution, followed by a wash with 2M HCl, and then a wash with water. The organic phase was then dried over anhydrous magnesium sulphate. After filtration, the solvent was removed under reduced pressure to give the desired product (0.7889g, 83.3%).

400MHz \textsuperscript{1}H-NMR ref CDCl\textsubscript{3}

δ=0.043, 0.078 (6H, Si(CH\textsubscript{3})\textsubscript{2}) ;
\[ \delta = 0.856 \ (9H, SiC(CH_3)_3) \]
\[ \delta = 1.150 \ (3H, d, J=6.29Hz, CH_3) \]
\[ \delta = 2.9575 \ (dd, 1H, J=2.39Hz, 4.35Hz, H-3) \]
\[ \delta = 3.683 \ (3H, COOCH_3) \]
\[ \delta = 3.780, 3.803 \ (6H, DAM-OCH_3) \]
\[ \delta = 4.1785 \ (dd, 1H, J=2.39Hz, 9.25Hz, H-4) \]
\[ \delta = 4.246 \ (dq, J=4.35Hz, 6.29Hz, H-3\alpha) \]
\[ \delta = 5.896 \ (s, 1H, N-CH) \]
\[ \delta = 5.6605 \ (d, J=15.58Hz, H-4\beta) \]
\[ \delta = 6.621 \ (dd, J=15.58Hz, 9.33Hz, H-4\alpha) \]
\[ \delta = 6.8 \text{ to } 7.2 \ (aromatics). \]

**\(^{13}\text{C-NMR ref CDCl_3}\)**

\[ \delta = 17.930 \ (SiC(CH_3)_3) ; \delta = 25.745 \ (C(CH_3)_3) \]
\[ \delta = 22.390 \ (C-3\beta) ; \delta = 65.129 \ (C-3\alpha) \]
\[ \delta = 63.248 \ (C-3) ; \delta = 51.573, 51.511 \ (C-4) \]
\[ \delta = 122.440 \ (C-4\alpha) ; \delta = 145.996 \ (C-4\beta) \]
\[ \delta = 166.867 \ (COOMe) ; \delta = 54.394, 54.366 \ (COOCH_3) \]
\[ \delta = 165.761 \ (C-2) ; \delta = 59.410, 59.382 \ (N-O) \]
\[ \delta = 131.320, 130.352 \ (aromatic C-1') \]
\[ \delta = 129.609, 129.372 \ (aromatic C-2') \]
\[ \delta = 113.717, 113.694 \ (aromatic C-3') \]
\[ \delta = 158.983, 158.952 \ (aromatic C-4') \]
\[ \delta = 55.198, 55.137, 55.094 \ (aromatic OCH_3). \]
Attempted methylation of 42

A

CuI (60mg, 0.315mmol) was stirred in THF (3ml) at -78°C under nitrogen. 1.4M methyllithium in ether (0.71ml, 0.994mmol) was injected, and the mixture was stirred for 30 minutes. 42 (144.6mg, 0.268mmol) in THF (2ml) was injected. The reaction was allowed to stir for 12 hours and allowed to warm to room temperature over this time. The reaction was then quenched by pouring into 2M HCl (40ml), and then stirred for 4 hours. It was then diluted by dichloromethane and extracted into it. The dichloromethane layer was separated and dried over anhydrous magnesium sulphate and then filtered. The solvent was then evaporated under reduced pressure to give 110mg of residue. A 200MHz ¹H-NMR showed it to be the starting material.

B

Copper(I)bromide-dimethyl sulphide (74mg, 0.36 mmol) was dissolved in dimethyl sulphide (5ml) and stirred under nitrogen at room temperature. 0.5ml of 1.4M methyllithium in ether (0.7mmol) was injected and a yellow precipitate was formed. Then 42 (119.4mg, 0.221mmol) in THF (2ml) was injected and stirred for 4 hours. The solvent was then removed under reduced pressure and the residue redissolved in ether and 2M HCl was added to dissolve the inorganic residue. The ether layer was separated and washed with 5% sodium hydrogen carbonate. On removal of the ether under reduced pressure the crude product (107.8mg) was collected. Column chromatography using dichloromethane:ether (9:1) was carried out, and a product (83.1mg) was collected. A 200MHz ¹H-NMR showed olefinic signals with a smaller coupling constant.
200MHz $^1$H-NMR ref CDCl$_3$,

$\delta = 0.023, -0.009 \ (6H, \text{Si}(\text{CH}_3)_2)$ ;
$\delta = 0.779 \ (9H, \text{SiC}(\text{CH}_3)_3) ; \ \delta = 1.086 \ (1H, \text{d}, J=6.35Hz)$ ;
$\delta = 2.96 \ (1H, \text{dd}, \text{H}-3) ; \ \delta = 3.08 \ (m, 1H, \text{H}-4)$ ;
$\delta = 4.18 \ (1H, \text{m}, \text{H}-3\alpha) ; \ \delta = 3.58 \ (3H, \text{s}, \text{COOCH}_3)$ ;
$\delta = 5.1 \text{ to } 6.2 \ (3H, \text{overlap, olefinics and N-CH})$ ;
$\delta = 3.73 \ (\text{Ar-OCH}_3)$ ;
$\delta = 6.7 \text{ to } 7.4 \ (\text{aromatics})$.

C

Copper (I) cyanide (52mg, 0.58mmol), azeotropically dried with toluene was stirred in diethyl ether (2ml) at -78°C under nitrogen. 1.2ml of 1.4M methyllithium in ether (1.68mmol) were introduced and stirred until the copper(I) cyanide dissolved. 42 (242mg, 0.448mmol) was added in ether (2ml) and immediately an orange precipitate was formed. The reaction was stirred for 90 minutes and then quenched by pouring into ether. Saturated ammonium chloride was added and the solution was stirred for 2 hours to remove the copper. The ethereal layer was separated and the aqueous layer extracted with more ether. The combined ethereal extracts was dried over anhydrous magnesium sulphate, filtered and the solvent removed. Column chromatography was performed using dichloromethane as the eluting solvent, and 147mg of a product was collected. A 200MHz $^1$H-NMR showed the starting material 42.

Preparation of 3-Oxa-2-oxo-1-thiaindolizinum chloride

A saturated solution of phosgene in benzene (9ml) was prepared by
Experimental

bubbling phosgene through for 15 minutes.

A benzene solution of thiohydroxamic acid (1.029g, 8.10mmol) was added dropwise to the phosgene solution, and a white precipitate was formed immediately. The solution was then purged with nitrogen for 30 minutes. The precipitate was filtered and washed with benzene and then dried under vacuum to give the product (1.418, 7.48mmol, 92%).

Preparation of
(3S,4R)-1-(di-p-anisylmethyl)-3-[(1R)-1-t-butyldimethyl-
siloxethyl]-4-[(3RS),(4RS)-2,5-dioxo-1-phenyl-3-
(2-thiopyridyl)-2,3,4,5-tetrahydropyrrole]-2-azetidinone
(44)

9 (537mg, 1.07mmol) was dissolved in dichloromethane and stirred under nitrogen at 0°C. Triethylamine (120mg, 1.19mmol) was introduced and the solution stirred at 0°C for 5 minutes. Then freshly prepared 3-oxa-2-oxo-1-thia-indolizinium chloride 60 (230mg, 1.21mmol) was added as the solid and immediately a yellow solution was formed. N-phenylmaleimide (484mg, 2.60mmol) was then introduced and the solution was then photolyzed with a 500W tungsten lamp for 5 hours under nitrogen.

The solvent was then removed under reduced pressure, and the crude extract was purified by column chromatography to give the product (196mg, 24.7%). The 200MHz \textsuperscript{1}H-NMR showed that there were at least two products present.
Preparation of
\((3S,4R)-1-(di-p-anisylmethyl)-3-[(1R)-1-t-butyldimethylsiloxylethyl]-4-[(3RS)-2,5-dioxo-1-phenyl-2,3,4,5-tetrahydropyrrole]-2-azetidinone (45)\)

\([44]\) (196mg, 0.266mmol) was dissolved in absolute alcohol (2ml).

Raney Nickel in absolute alcohol was prepared by rinsing commercial Raney Nickel (in water, pH10) 10 times with absolute alcohol.

The Raney Nickel in absolute alcohol was then added to \([44]\) and stirred and refluxed. After tlc had showed the complete consumption of \([44]\) and the formation of a new product, the solution was filtered to remove the nickel and the ethanol evaporated under reduced pressure to give the crude. The crude was purified by column chromatography (\(\text{SiO}_2,\text{CH}_2\text{Cl}_2\) followed by \(\text{CH}_2\text{Cl}_2\cdot\text{Et}_2\text{O}=9:1\)). A compound (147mg) was obtained. A 400MHz \(^1\text{H}-\text{NMR}\) showed it to be only one diastereomer of \(45\). (Yield=88%)

400MHz \(^1\text{H}-\text{NMR\ ref CDCl}_3\)
\(\delta=0.00, 0.077\ (6\text{H, Si(\text{CH}_3)_2})\);
\(\delta=0.842\ (9\text{H, SiC(\text{CH}_3)_3})\);
\(\delta=1.1395\ (d, 3\text{H, J}=6.26\text{Hz, H-3}\beta);\)
\(\delta=2.771\ (1\text{H, dd, J}=2.25\text{Hz, 4.33Hz, H-3});\)
\(\delta=4.235\ (m, \text{H-3}\alpha);\)
\(\delta=4.510\ (1\text{H, dd, J}=2.25\text{Hz, 4.33Hz});\)
\(\delta=3.016\ (m, 1\text{H, H-3}');\)
\(\delta=2.554\ (1\text{H, dd, J}=4.12\text{Hz, 19.07Hz, H-4}');\)
\(\delta=2.1995\ (1\text{H, dd, J}=19.09\text{Hz, 9.60Hz, H-4}');\)
\(\delta=6.03\ (1\text{H, NCH});\)
\(\delta=3.829, 3.817\ (6\text{H, OCH}_3);\)
\(\delta=6.8\) to 7.6 (aromatics)
Preparation of
(3S,4R)-1-(di-p-anisylmethyl)-3-[(1R)-1-t-butyldiphenylsiloxyethyl]-4-methoxycarbonyl-2-azetidinone (49)

8 (5.067g, 13.16mmol) was dissolved in DMF. Diisopropylethylamine (1.701g, 16.5mmol) was added and the resulting solution was stirred for 5 minutes. Then methyl iodide (2.668g, 18.8mmol) was added and the solution was left stirring for 24 hours, after which tlc showed the complete consumption of starting material and formation of a new product.

The reaction was then quenched with ethyl acetate and water and acidified with 2M HCl. It was extracted into ethyl acetate, washed with water and dried over anhydrous magnesium sulphate. After filtration, the solvent was removed under reduced pressure. A 200MHz $^1$H-NMR showed that it was the methyl ester 48 of 8, and it was used in the next stage without further purification.

The product obtained from above was redissolved in DMF and imidazole (1.255g, 18.43mmol) was added and the solution was stirred for 10 minutes. t-Butyldiphenylsilyl chloride (3.99.4g, 14.53mmol) was added, and the solution was allowed to stir for 24 hours after which tlc showed the complete consumption of 48 and the formation of a new product.

The reaction was then quenched with ethyl acetate and water and acidified with 2M HCl. The ethyl acetate layer was separated, washed with water and dried over anhydrous magnesium sulphate. After filtration, the solvent was removed under reduced pressure, and the DMF removed under vacuum. The crude thus obtained was purified by column chromatography ($\text{SiO}_2, \text{CH}_2\text{Cl}_2$) to give the product (7.85g, 93.6%).
Microanalysis

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Mass spectrum
1275 (2MH⁺); 638, 637, 636 (MH⁺, M⁺, M-H⁺);
580 (M-tBu⁺); 560 (M-Ph⁺); 530(M-PhOMe⁺)

200MHz ¹H-NMR ref CDCl₃
δ=1.03 (9H, SiC(CH₃)₃) ;  δ=1.05(3H, H-3β) ;
δ=3.22 (1H, dd, J=2.7Hz, 5Hz, H-3) ;  δ=4.03 (d, J=2.7Hz, H-4) ;
δ=4.27 (1H, m, H-3α) ;  δ=3.48 (3H, COOCH₃) ;
δ=3.78 (6H, OCH₃) ;  δ=5.87 (1H, NCH) ;
δ=6.6 to 7.8 (aromatics)

200MHz ¹H-NMR of 48 ref CDCl₃
δ=1.27 (3H, d, J=6.7Hz, H-3β) ;  δ=4.27 (1H, m, H-3α) ;
δ=2.1 (broad, OH) ;  δ=3.20 (1H, dd, J=2.7Hz, 5Hz, H-3) ;
δ=4.14 (d, 1H, J=2.7Hz , H-4) ;  δ=3.53 (3H, s, COOCH₃) ;
δ=5.87 (1H, s, NCH) ;  δ=3.78, 3.79 (6H, ArOCH₃) ;
δ=6.7 to 7.3 (aromatics).
Preparation of 
(3S,4R)-3-[(1R)-1-tert-butyl-diphenylsiloxyethyl]-4-methoxycarbonyl-2-azetidinone (50)

49 (442mg, 0.694mmol) was dissolved in acetonitrile (4ml) and stirred at -5°C to 0°C. Ceric ammonium nitrate (1.578g, 2.88mmol), dissolved in acetonitrile (5ml), and water (1ml), was added slowly with stirring. The solution was allowed to stir for 30 minutes, after which TLC showed the complete disappearance of the starting material. The reaction was then quenched with ethyl acetate (150ml) and the excess oxidant was reduced with sodium metabisulphite and the pH adjusted to 7 with sodium hydrogen carbonate. The solution was then filtered over sand. The organic phase was then separated and washed with water (20ml), and then dried over anhydrous magnesium sulphate. The solvent was then removed under reduced pressure. An IR spectrum of the crude showed a new stretch at 3400cm⁻¹ due to an N-H stretch. The crude was then purified by column chromatography (SiO₂, CH₂Cl₂) to give 197mg (69%) of a white solid. Spectra taken subsequently showed it to be the desired product 50.

Microanalysis

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<td>3.3%</td>
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</tbody>
</table>

Melting point = 103-104°C (sharp)
Infra-red

v/cm\(^{-1}\) : 3400 (N-H), 1770 (C=O,\(\beta\)-lactam), 1740 (C=O, methyl ester)

200MHz \(^1\)H-NMR ref CDCl\(_3\)

\(\delta=1.041\) (9H, SiC(CH\(_3\))\(_3\); \(\delta=1.0816\) (3H, d, J=6.36Hz, H-3\(\beta\));

\(\delta=4.32\) (1H, m, H-3\(\alpha\)); \(\delta=3.283\) (1H, m, H-3);

\(\delta=4.371\) (1H, d, J=2.58Hz, H-4); \(\delta=3.779\) (3H, COOCH\(_3\));

\(\delta=6.302\) (1H, s, N-H);

\(\delta=7.3\) to 7.8 (aromatics)

\(^{13}\)C-NMR

\(\delta=21.94\) (C-3\(\beta\)); \(\delta=19.29\) (SiC(CH\(_3\))\(_3\));

\(\delta=26.76\) (SiC(CH\(_3\))\(_3\)); \(\delta=64.92\) (C-3\(\alpha\));

\(\delta=49.61\) (C-3); \(\delta=65.87\) (C-4); \(\delta=167.14\) (C-2);

\(\delta=171.74\) (COOMe); \(\delta=52.40\) (COOCH\(_3\));

\(\delta=132.57, 134.27\) (Ph,C-1');

\(\delta=122.40, 122.63\) (Ph,C-2');

\(\delta=135.96, 135.75\) (Ph,C-3');

\(\delta=129.82, 129.56\) (Ph,C-4').

Mass spectrum

429 (M+NH\(_4\))\(^+\), 412 (M+H)\(^+\), 354 (M-tBu)\(^+\), 334 (M-Ph)\(^+\)

Attempted allylation of 50

50 (1.116g, 2.715mmol) was dissolved in dry THF (6ml) under nitrogen. 129mg (3.225mmol) of 60% sodium hydride dispersed in oil were added and the solution was stirred for 10 minutes at room temperature. Then allyl bromide (551mg, 4.55mmol, 1.68eq) was added in THF (3ml). The solution was stirred for 90
minutes and then quenched with ethyl acetate and water, and then acidified with 2M HCl. The organic layer was separated and washed with water, and then dried over anhydrous magnesium sulphate. After filtration, the solvent was evaporated under reduced pressure to give a white solid (1.169g). TLC showed the disappearance of 50 and a new UV active spot. This UV active product was purified by column chromatography (SiO₂, CH₂Cl₂:Et₂O=19:1) and a 60MHz ¹H-NMR showed it to be the silanol. 443mg (63.7%) were collected.

60MHz ¹H-NMR ref external CDCl₃
δ=0.7 (9H, SiC(CH₃)₃);
δ=2.4 (1H, SiOH);
δ=6.9 to 7.8 (10H, aromatics)

Preparation of
(3S,4R)-3-[(1R)-1-t-butyldiphenylsiloxyethyl]-2-azetidinone-4-carboxylic acid (51)

50 (1.09g, 2.65mmol) was dissolved in 8ml of a THF:MeOH (2:1) solvent mixture and stirred. Sodium hydroxide (0.132g, 3.3mmol) in water (1.5ml) was added and the solution was allowed to stir for 2 hours after which tlc showed the complete disappearance of 50 and the formation of a product which streaked on tlc. The reaction was quenched with water (75ml) and acidified with 1ml of 2M HCl. Saturated sodium chloride solution (5ml) was added. The organic layer was separated, washed with water (10ml) and dried over anhydrous magnesium sulphate. After filtration, the solvent was evaporated under reduced pressure. 1.00g (95%) of a white solid was obtained. A 200MHz showed the absence of the methyl ester group.

IR v/cm⁻¹
3400 (N-H), 2900 (broad, COOH),
1770 (C=O, β-lactam), 1725 (C=O, acid)

Melting point- 113-115°C.

250MHz $^1$H-NMR ref CDCl$_3$

$\delta$=1.030 (9H, SiC(CH$_3$)$_3$);
$\delta$=1.071 (3H, d, J=6.35Hz);
$\delta$=4.35 (1H, m, C-3α) ; $\delta$=3.35 (1H, m, H-3);
$\delta$=4.47 (1H, d, J=4Hz, H-4) ; $\delta$=6.50 (1H, s, NCH);
$\delta$=4.75 (broad, COOH);
$\delta$=7.3 to 7.8 (aromatics).

Preparation of
(3S,4R)-1-[3-(prop-1-ene)]-3-[(1R)-1-t-butyldiphenyl-
siloxethyl]-2-azetidinone-4-carboxylic acid (53)

51 (878mg, 2.212mmol) and allyl bromide (355mg, 2.93mmol) were dissolved together in freshly distilled THF (10ml) and stirred under nitrogen. 244mg (6.1mmol, 2.76eq) of 60% sodium hydride dispersed in oil were added in small portions. Effervescence was seen and the solution was stirred for 16 hours. Tlc showed the complete consumption of starting material and the formation of a new compound.

The reaction was quenched by pouring into ethyl acetate and water and acidified with 2M HCl. The ethyl acetate layer was separated, washed with water and dried over anhydrous magnesium sulphate. After filtration the solvent was evaporated off under reduced pressure. The product was purified by column chromatography
Experimental

(SiO₂,CH₂Cl₂ + 5%Et₂O +0.5%AcOH). 585mg (60.5%) of the product were collected.

IR ν/cm⁻¹
1750 (C=O, β-lactam), 1715 (C=O, acid), 3000 (OH, acid, broad)
No N-H signal was seen

400MHz ¹H-NMR ref CDCl₃
δ=1.053 (9H, SiC(CH₃)₃) ;
δ=1.066 (3H, d, J=6.38Hz, H-3β) ;
δ=3.27 (1H, m, H-3) ;
δ=4.36 (2H, overlap, H-3α, H-4) ;
δ=3.763 (1H, dd, J=14.7Hz, 8Hz, H-1α) ;
δ=4.191 (1H, dd, J=15.8Hz, 5Hz, H-1α) ;
δ=5.8 (1H, m, H-1β) ;
δ=5.25 (, m, overlap, H-1γ).

Preparation of
(3S,4R)-4-(carbonylselenylphenyl)-1-[3-(prop-1-ene)]-
3-[(1R)-1-t-butyldiphenylsiloxyethyl]-2-azetidinone (54)

A solution of phenylselenide anion was prepared by adding sodium borohydride (56mg, 1.48mmol) in absolute ethanol to an ethanolic solution of diphenyldiselenide (195mg, 0.625mmol). After the solution became colourless, it was cooled to -20°C.

54 (487mg, 1.11mmol) and triethylamine (126mg, 1.25mmol) were dissolved in freshly distilled THF (2ml) and stirred under nitrogen at -15°C to -20°C.
Then i-butylchloroformate (172mg, 1.26mmol) was added and the solution was stirred for 20 minutes at -15°C to -20°C to make the mixed anhydride. After 20 minutes of stirring, the phenylselenide solution prepared above was introduced at -20°C. After 2 hours, tlc showed the complete disappearance of the starting material. The reaction was quenched by pouring it into ether and water and acidified with 2M HCl. The ether layer was separated, washed with water and dried over anhydrous magnesium sulphate. After filtration, the solvent was removed under reduced pressure to give the crude product (674mg).

The crude product was purified by column chromatography (SiO₂, petrol, followed by petrol:ether=10:1). The petrol was used to remove any diphenyldiselenide that had reformed. The desired product (234mg, .36.5%) was collected.

IR v/cm⁻¹
1760 (C=O, β-lactam); 1715 (C=O, selenyl ester)
No N-H or O-H (acid) stretches were seen

200MHz ¹H-NMR ref CDCl₃

δ=1.05 (9H, SiC(CH₃)₃) ; δ=1.07 (3H, H-3β) ;
δ=4.33 (1H, m, H-3α) ;
δ=3.38 (1H, dd, J=2.7Hz, 2.4Hz, H-3) ;
δ=4.49 (1H, d, J=2.4Hz, H-4) ;
δ=3.81 (1H, dd, J=14.9Hz, 7.7Hz, H-1α) ;
δ=4.27 (1H, dd, J=15.2Hz, 5.2Hz, H-1α) ;
δ=5.85 (1H, m, H-1β) ;
δ=5.28 (2H, m, H-1γ) ;
δ=7 to 8 (aromatics).
Preparation of L-Tryptophan methyl ester hydrochloride salt (1080)

MeOH (28ml) was stirred at -20°C. SOCl$_2$ (11.5ml) was added over 35 minutes so that the temperature of the reaction remained below -15°C. Tryptophan (1001) (10.03g) was added in small portions over 30 minutes. The mixture formed was then allowed to warm to room temperature, and then heated to 45°C at which all the solid dissolved. On cooling, the product solidified. The solid was filtered and left under vacuum to remove solvent and gaseous byproducts. 11.9g (95%) was collected. No further purification was carried out.

200MHz $^1$H-NMR in D$_2$O ref D$_2$O=4.08ppm
$\delta =$ 3.12 (s, 3H, COOCH$_3$),
$\delta =$ 3.74 (t, J=6Hz, 1H, $\alpha$-H),
$\delta =$ 2.80 (bs, 1H, $\beta$-H),
$\delta =$ 2.76 (bs, 1H, $\beta$-H),
$\delta =$ 6.4 to 7.2 (aromatics)

Preparation of N$_3$-acetyl-L-tryptophan methyl ester (1037)

1080 (11.8g) was dissolved in aqueous NaHCO$_3$ (8.32g, 2.12eq, in 120ml of water). CHCl$_3$ was added. The 2-phase mixture was vigorously stirred. Methyl chloroformate (5.944g, 1.3eq) in CHCl$_3$ (10ml) was added dropwise. The solution was then left stirring for 2.5 hours. The CHCl$_3$ layer was separated and the aqueous phase back-extracted with more CHCl$_3$. The combined CHCl$_3$ extracts was then washed with H$_2$O, dried over MgSO$_4$(anh), filtered and the
solvent removed under reduced pressure. The crude solid obtained was then recrystallized from CHCl₃ and Et₂O, yield=11.16g (87.1%) mp=85°C.

200MHz ¹H-NMR in CDCl₃ ref CDCl₃
δ=3.643, 3.666 (2x s, 2 x COOCH₃),
δ=3.29 (d, J=5.3Hz, 2H, β-H),
δ=4.69 (bs, 1H, α-H),
δ=5.22 (d, J=7.2Hz, H-N₆),
δ=8.37 (bs, 1H, H-N₆),
δ=6.8 to 7.7 (aromatics)

UV-spectra

In neutral DMF $\varepsilon_{\text{max}}$(281.0nm)=8213,
$\varepsilon_{\text{max}}$(289.2nm)=70833

In acidic DMF $\varepsilon_{\text{max}}$(281.4nm)=6644,
$\varepsilon_{\text{max}}$(289.8nm)=5601.4

Preparation of
(2S,3aS,8aS)-1,2-dicarbomethoxy-1,2,3,3a,8,8a-hexahydropyrrolo[2,3b]indole (1035)

1037 (1.020g) was added as the solid to 88% H₃PO₄ (12ml) and stirred until all the solid was dissolved. The acid solution was then allowed to stir for a further 3 hours. The acid solution was then added dropwise to a rapidly stirring mixture of 15% Na₂CO₃ (335ml) and CH₂Cl₂ (150ml). The organic phase was
Experimental

separated, and the aqueous phase back-extracted with CH₂Cl₂. The combined organic extracts were washed with H₂O, dried over MgSO₄(anh), filtered, and the solvent removed under reduced pressure. The crude product solidified on standing. Yield=995mg(97%).

No further purification was carried out. High field 200MHz NMR showed 2 rotamers.

200MHz ¹H-NMR in CDCl₃ ref CDCl₃
δ=3.670(s) and 3.799(s) (3H, carbamate COOCH₃),
δ=3.140(s), 3.169(s) (3H, methyl ester COOCH₃),
δ=4.45(m), 4.57(m) (1H,H-2),
δ=2.59(bs, 2H, H-3),
δ=3.90(bs, 1H, H-3a),
δ=4.79(bs) and 5.14(bs) (1H, H-8),
δ=5.52(m, 1H, H-8a),
δ=6.5 to 7.4 (aromatics)

Preparation of
(2S,3aS,8aS)-8-benzenesulphonyl-1,2-dicarbomethoxy-1,2,3,3a,8a-hexahydropyrrolo[2,3b]indole (1051)

1035 (24.47g, 88.6mmol) was stirred in pyridine (50ml) until all dissolved. PhSO₂Cl (18.43g, 1.13eq) was added and the solution was stirred for 5 hours. The reaction was then quenched with Et₂O and H₂O. The product precipitated out as a white solid and was filtered off. The ether layer was separated and high field NMR showed only unreacted starting material, pyridine,
Experimental

but no product.

The product was redissolved in CH₂Cl₂, washed with water, dried over MgSO₄ (anh), filtered, and the solvent removed under reduced pressure to give 27.37g (74.1%) of the crude product. The product was then recrystallized by adding ether to a CH₂Cl₂ solution of the crude product. Yield=22.95g (62.2%).

High field 200MHz NMR showed only one isomer.

<table>
<thead>
<tr>
<th>Microanalysis</th>
<th>Theory</th>
<th>found</th>
</tr>
</thead>
<tbody>
<tr>
<td>C</td>
<td>57.683%</td>
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<tr>
<td>H</td>
<td>4.840%</td>
<td>4.68%</td>
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<tr>
<td>N</td>
<td>6.727%</td>
<td>6.83%</td>
</tr>
<tr>
<td>S</td>
<td>7.699%</td>
<td>7.69%</td>
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</table>

Mp=165-167°C
[α]₀D=+91.1° (c=1 , CH₂Cl₂)

200MHz ¹H-NMR at room temperature ref CDCl₃
δ=3.6 (bs, carbamate COOCH₃ and overlapping H-3a) ,
δ=3.113 (s, 3H, methyl ester COOCH₃) ,
δ=4.56 (broad doublet, 1H, H-2) ,
δ=2.5 (m, 2H, H-3) ,
δ=6.23 (d, 1H, J=7Hz, H-8a) ,
δ=6.9 to 8.8 (aromatics).

400MHz ¹H-NMR in CDCl₃ ref CDCl₃ at +50°C
δ=3.586 (s, 3H, N-COOCH₃) ,
δ=3.148 (s, 3H, COOCH₃) ,
δ=4.588 (d, J=8.9Hz, 1H, H-2) ,
δ=2.452 (dd of part of AB quartet, J=13.1Hz,8.9Hz,7.2Hz, 1H, H-3) ,
Experimental

δ=2.576 (part of AB quartet, J=13.1Hz, 1H, H-3),
δ=3.660 (t, J=6.8Hz, 1H, H-3a),
δ=6.280 (d, J=6.4Hz, 1H, H-8a),
δ=7.0 to 7.9 (aromatics).

400MHz ¹H-NMR in CDCl₃ ref CDCl₃ at -20°C
Two rotamers were seen
δ=3.573(major), 3.702(minor) (3H, N-COOCH₃),
δ=3.109(s,minor), 3.144(s,major) (3H, COOCH₃),
δ=4.518(d, J=8.50Hz, minor), 4.630(d, J=8.60, major) (H-2),
δ=2.55(m, H-3),
δ=3.42(t, J=6Hz, minor), 3.634(t, J=6.5Hz, major) (H-3a),
δ=6.230(d, J=6.32Hz, major), 6.271(d, J=6.32Hz, minor) (H-8a),
δ=7.0 to 7.8 (aromatics).

Preparation of
(2S,3aS,8aS)-8-benzenesulphonyl-1,2-dicarbomethoxy-2-methyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3b]indole
(1053)

1051 (2.5729g, 6.1774mmol) was dissolved in THF (30ml) under nitrogen with warming. It was then cooled to -78°C under nitrogen.

A solution of LDA was prepared by adding 2.1M nBuLi (4ml, 8.4mmol, 1.36eq) to a stirring solution of diisopropylamine (875.8mg, 8.67mmol, 1.40eq) at -78°C in THF (10ml) under nitrogen. The solution was left stirring at -78°C for 20 minutes, and then quickly added to the THF solution of the starting material at -78°C. The resulting solution was left stirring at -78°C for 20 minutes and then
Mel (2.38g, 16.77mmol, 2.7eq) was introduced. The solution was left stirring and then allowed to warm to -60°C over 1 hour. TLC showed the complete removal of the starting material. The reaction was then quenched by pouring into EtOAc and water, and then acidified with HCl. The organic phase was separated and the water phase back extracted with EtOAc. The combined EtOAc extracts was washed with water, dried over MgSO₄(anh), filtered and then the solvent removed under reduced pressure to give 2.692g of crude product.

The product was crystallized out from a solution of the crude in MeOH. Yield=1.1025g (41.1%). The mother liquor was kept and then column chromatographed with EtOAc:petrol (1:1). The product obtained from the column was then recrystallized from MeOH to give 561.6mg (21.1%). Combined yield=62.6%.

High field NMR showed only one isomer. Mp=144-145°C.

UV Spectra

$\epsilon_{\text{max}}(274.2\text{nm})=2250$ in acidic DMF

$\epsilon_{\text{max}}(273.2\text{nm})=2720$ in neutral DMF

<table>
<thead>
<tr>
<th>Microanalysis</th>
<th>Theory</th>
<th>Found</th>
</tr>
</thead>
<tbody>
<tr>
<td>C</td>
<td>58.593%</td>
<td>58.57%</td>
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<tr>
<td>H</td>
<td>5.151%</td>
<td>5.03%</td>
</tr>
<tr>
<td>N</td>
<td>6.507%</td>
<td>6.65%</td>
</tr>
<tr>
<td>S</td>
<td>7.448%</td>
<td>7.67%</td>
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</table>

$[\alpha]_D^{\circ}=+95.2^\circ (\epsilon=0.725, \text{CH}_2\text{Cl}_2)$

400MHz $^1$H-NMR in CDCl₃ ref CDCl₃

$\delta=3.594$ (s, 3H, carbamate COOCH₃),
δ=3.045 (s, 3H, methyl ester COOCH₃),
δ=1.674 (s, 3H, α-CH₃),
δ=2.1765 (dd, J=7.4Hz, 13.4Hz, 1H, H-3),
δ=2.737 (d, J=13.4Hz, 1H, H-3),
δ=3.397 (t, 1H, J=6.7Hz, H-3a),
δ=6.279 (d, J=6.4Hz, 1H, H-8a),
δ=6.9 to 7.8 (aromatics)

Preparation of (2S,3aS,8aS)-8-benzenesulphonyl-1-carbomethoxy-2-methyl
-1,2,3,3a,8,8a-hexahydropyrrolo[2,3b]indole-2-
carboxylic acid (1063)

1053 (1.7791g, 4.133mmol) was dissolved in methanol (30ml). A
solution of KOH (7g) in water (5ml) was added and the reaction was vigorously
stirred at room temperature. A further solution of KOH (14g) in water (10ml) was
added. The reaction was stirred and more MeOH added dropwise until it became
one phase. TLC showed the complete disappearance of the starting material after
1 hour.

The reaction was quenched with EtOAc and water and then acidified
with HCl. The organic phase was separated, and the aqueous phase back
extracted with EtOAc. The combined organic extracts were washed with water,
dried over MgSO₄(anh), filtered, and the solvent removed under reduced pressure
to give a yellow oil. The product was recrystallized from CH₂Cl₂ and petrol,
yield=1.235g(71.8%), mp=138-139°C, [α]D=+99°(c=1,CH₂Cl₂)

400MHz ¹H-NMR in CDCl₃ ref CDCl₃
δ=3.816 (s, 3H, carbamate COOCH₃),
Experimental

\[ \delta = 1.616 \text{ (s, 3H, } \alpha-\text{CH}_3) , \]
\[ \delta = 2.070 \text{ (dd, } J=7.36\text{Hz, 13.41Hz, 1H, } H-3) , \]
\[ \delta = 3.021 \text{ (broad doublet, } J=8.41, 1H, H-3a) , \]
\[ \delta = 3.244 \text{ (t, } J=6.6\text{Hz, 1H, } H-3a) , \]
\[ \delta = 6.126 \text{ (d, } J=6.2\text{Hz, 1H, } H-8a) , \]
\[ \delta = 7 \text{ to 7.7 (aromatics)} \]

**Preparation of**

(2S,3aS,8aS)-8-benzenesulphonyl-1-carbomethoxy-2-(2,4-dioxa-1,3-dioxo-6-methylheptan-1-yl)-2-methyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3b]indole

**1069**

1063 (204.6mg, 0.4913mmol) was dissolved in dry THF (2ml). NEt\textsubscript{3} (64.3mg, 0.637mmol, 1.30eq) in THF (1ml) was added, and the solution was stirred in a cold acetone bath (external temperature = -15°C).

Isobutyl chloroformate (83.4mg, 0.61mmol 1.24eq) was added in THF (2ml) at -15°C. NEt\textsubscript{3}.HCl precipitated out. The solution was stirred for 80 minutes.

The THF solvent was then removed under reduced pressure. EtOAc was then added, and then removed under reduced pressure. The residue was then column chromatographed (SiO\textsubscript{2}, petrol:EtOAc=2:1). The product was collected as a solid (0.223g, 88%). The solid was then slowly recrystallized from ethyl acetate and petrol. Large colourless crystals were obtained. A single crystal X-ray diffraction analysis gave the 3-D structure of the molecule. Mp=107-109°C.

**Microanalysis**

<table>
<thead>
<tr>
<th></th>
<th>Theory</th>
<th>Found</th>
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<tr>
<td>C</td>
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<td>H</td>
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<td>N</td>
<td>5.423%</td>
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Experimental

400MHz $^1$H-NMR in CDCl$_3$ ref CDCl$_3$

$\delta=3.54$ (s, 3H, carbamate COOCH$_3$),
$\delta=3.82$ (m, 2H, mixed anhydride CH$_2$),
$\delta=1.88$ (m, 1H, CHMe$\_2$),
$\delta=0.864$ (d, 6H, J=6.74, i-butyl CH$_3$),
$\delta=1.708$ (s, 3H, $\alpha$-CH$_3$),
$\delta=2.267$ (dd, J=7.5Hz, 13.6Hz, H-3),
$\delta=2.768$ (d, J=13.76Hz, H-3),
$\delta=3.473$ (t, J=6.8Hz, H-3a),
$\delta=6.263$ (d, J=6.46Hz, H-8a),
$\delta=6.9$ to 7.8 (aromatics)

**Preparation of N-carbobenzoxy-L-proline methyl ester**

Methanol (5ml) was cooled to -30°C. SOCl$_2$ (2ml) was injected into the methanol. The N-protected L-proline $^{1070}$ (2.007g, 8.052mmol) was added as the solid. The reaction was then allowed to warm up to room temperature. The solvent and excess SOCl$_2$ were then removed under reduced pressure. The residue was then diluted with EtOAc, washed with 2M HCl, water and then dried over MgSO$_4$(anh), filtered, and the solvent removed under reduced pressure. 2.1g(99%) of a colourless liquid was obtained.

<table>
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<th>Theory</th>
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<td>H</td>
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<td>6.50%</td>
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<tr>
<td>N</td>
<td>5.320%</td>
<td>5.24%</td>
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</table>
200MHz ¹H-NMR in CDCl₃ ref CDCl₃
2 rotamers of the amide were seen
δ=5.08 (m, 2H, COOCH₂Ph),
δ=3.56 (s), 3.72 (s) (3H, COOCH₃),
δ=4.35 (m, 1H, H-α),
δ=1.9 (m), 2.2 (m) (4H, H-β, H-γ),
δ=3.5 (m, 2H, H-δ),
δ=7.2 to 7.5 (aromatics).

Preparation of
2-Methoxycarbonyl-2(RS)-methyl-1-phenylmethoxy carbonyl-tetrahydropyrrole (+)1072

LDA was prepared by adding 1.3M BuLi (2.5ml,3.25mmol) to diisopropylamine (323.4mg, 3.20mmol) stirring in THF (2ml) at -78°C under nitrogen. The LDA solution formed was then added to a solution of 1071 (760.5mg, 2.89mmol) in THF (2ml) at -78°C under nitrogen. The reaction was allowed to stir for 15 minutes. MeI(1.65g, 11.6mmol, 4.0eq) in THF (2ml) was added. The reaction was stirred for 4 hours. The reaction was quenched by diluting with EtOAc and water, and then acidified with 2M HCl. The organic phase was separated, and the aqueous phase back extracted with EtOAc. The combined organic extracts was dried over MgSO₄(anh), filtered and the solvent removed under reduced pressure to give 710mg of crude product. The crude was columned chromatographed (SiO₂, EtOAc:petrol=1:2) to give 375mg (47%) of the product which was a liquid.

Accurate mass Theory 277.1313976
Found 277.1340
200MHz $^1$H-NMR in CDCl$_3$ ref CDCl$_3$

2 rotamers of the amide were seen.

$\delta=4.96$ (m, CH$_2$Ph),

$\delta=3.28$ (s), 3.54 (s) (3H, COOCH$_3$),

$\delta=1.40$ (s), 1.46 (s) (3H, $\alpha$-CH$_3$),

$\delta=1.74$ (m), 2.00 (m) (4H, H-$\beta$, H-$\gamma$),

$\delta=3.44$ (m, 2H, H-$\delta$),

$\delta=7.0$ to 7.4 (aromatics)

Preparation of 2(RS)-methyl-1-phenylmethyloxycarbonyl-
tetrahydropyrrole-2-carboxylic acid(+)$^{1073}$

1072 (257mg) was dissolved in methanol. A solution of KOH (2.5g) in water (2ml) and methanol (1ml) was added and the single phase reaction was stirred for 16 hours.

The reaction was quenched with EtOAc, and 2M HCl. The organic phase was separated. The aqueous phase was back extracted. The combined organic extracts were dried over MgSO$_4$(anh), filtered, and the solvent removed under reduced pressure. The crude was column chromatographed (EtOAc:petrol=1:2) to give 237.2mg (97%), which was recrystallized from CH$_2$Cl$_2$ and petrol. Mp=121°C

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<th>Theory</th>
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200MHz $^1$H-NMR in CDCl$_3$ ref CDCl$_3$

Rotamers in the ratio of 2.3:1 were seen in the NMR

$\delta=1.520$ (s, minor) , 1.616 (s, major) (3H, $\alpha$-CH$_3$),

$\delta=1.89$ (m, 3H) , 2.28 (m, 1H) (H-$\beta$, H-$\gamma$),

$\delta=3.58$ (m, 2H, H-$\delta$),

$\delta=5.09$ (s, minor) , 5.14(s, major) (2H, COOCH$_2$Ph),

$\delta=7.2$ to 7.5 (aromatics).

**Preparation of 2(RS)-methyl-1-phenylmethyloxycarbonyl-2-(2,4-dioxa-1,3-dioxo-6-methylheptan-1-yl)-tetrahydropyrrole (+)1074**

1073 (93mg, 0.353mmol) was dissolved in THF (1ml). NEt$_3$ (44.2mg, 0.438mmol, 1.24eq) in THF (1ml) was added, and the solution was stirred under nitrogen at -40°C (external temperature) for 10 minutes. Isobutylchloroformate (58.2mg, 0.422mmol, 1.20eq) in THF (2ml) was injected slowly into the reaction. The reaction was allowed to warm to -5°C over 90 minutes. The reaction was then diluted with EtOAc (30ml) and washed with 2M HCl (5ml), followed by water (5ml). The organic phase was separated and dried over MgSO$_4$(anh), filtered and the solvent removed under reduced pressure to give 111mg (86%) of the crude product. High field NMR was taken of the crude product. It was then column chromatographed (EtOAc:petrol=1:2) and 68mg (53%) of the product was collected. A high field NMR of this was identical to that of the crude. A second column was carried out and 28.6mg (22.3%) of the product was collected. Thus the mixed anhydride was unstable with respect to column chromatography.

200MHz $^1$H-NMR in CDCl$_3$ ref CDCl$_3$

Rotamers of the amide were seen on the NMR

$\delta=0.9165$ (d,$J=4.51$Hz), 0.950 (d, $J=4.51$Hz) (6H, isopropyl CH$_3$),
Experimental

\[ \delta = 2.33 \text{ (m, 1H, isopropyl CH)} \], \\
\[ \delta = 3.996 \text{ (d, J=5.64Hz), 4.029 (d, J=5.6Hz) (2H, isopropyl CH}_2) \], \\
\[ \delta = 1.542 \text{ (s), 1.640 (s) (3H, } \alpha\text{-CH}_3) \], \\
\[ \delta = 1.96 \text{ (m, 4H, H-} \beta\text{, H-} \gamma) \], \\
\[ \delta = 3.60 \text{ (m, 2H, H-} \delta) \], \\
\[ \delta = 5.12 \text{ (m, COOCH}_2\text{Ph)} \], \\
\[ \delta = 7.2 \text{ to 7.5 (aromatics).} \]

Preparation of

\[ \text{N}_b\text{-acetyl-N}_{\alpha}\text{-benzenesulphonyl-(S)-}\alpha\text{-methyl-L-tryptophan methyl ester (1056)} \]

1053 (1.336g) was dissolved in trifluoroacetic acid (4ml) and stirred for 2 hours. The TFA was then evaporated under reduced pressure. The product was then redissolved in CH\(_2\)Cl\(_2\) and washed with 2M NaOH. The organic phase was separated, dried over MgSO\(_4\) (anh), filtered and the solvent removed under reduced pressure to give a white foam, 1.336g (100%).

400MHz \(^1\text{H-NMR in CDCl}_3\) ref CDCl\(_3\)

\[ \delta = 5.441 \text{ (bs, 1H, H-N}_b) \], \\
\[ \delta = 3.695 \text{ (s, 3H, N}_b\text{-COOCH}_3) \], \\
\[ \delta = 3.653 \text{ (s, 3H, COOCH}_3) \], \\
\[ \delta = 1.643 \text{ (s, 3H, } \alpha\text{-CH}_3) \], \\
\[ \delta = 3.284 \text{ (d, J=14.65Hz, 1H, H-} \beta) \], \\
\[ \delta = 3.567 \text{ (d, J=14.23Hz, 1H, H-} \beta) \], \\
\[ \delta = 7.1 \text{ to 8.0 (aromatics).} \]
Preparation of
2(S)-2-(N-carbomethoxy)amino-1-methoxycarbonyl-4-butanoic acid 1057

NaIO₄ (7.9g) was dissolved in water (30ml) with warming. 1056 (779mg, 1.86mmol) in MeCN (10ml) was added to the NaIO₄ solution. The resulting mixture was then heated until it was in a single phase. Then RuCl₃.3H₂O (5.6mg) was added. The solution was then left stirring for 7 days. The solution was then acidified with conc. HCl (5ml) to redissolve the contents, and then left stirring for 18 hours. The reaction was then extracted into ethyl acetate. The organic phase was separated, washed with water, dried over MgSO₄(anh), filtered, and the solvent was removed under reduced pressure to give the crude (0.65g). The byproduct 1083 (mp=153-155°C) was crystallized out with ether/petrol. The mother liquor was then column chromatographed (SiO₂,Et₂O+AcOH), but the product and 1083 did not separate perfectly, 226.4mg (55%) was obtained. More of the 1083 was then recrystallized from CHCl₃. The product was then recrystallized in CHCl₃ (70mg, 17%), mp=103-105°C.

Microanalysis

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<td>N</td>
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<td>6.46%</td>
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[α]D= -11.0° (c=1.45, MeOH)

200MHz ¹H-NMR ref CDCl₃
δ=5.94 (bs, 1H, NH),
δ=3.773 (s, 3H, N-COOCH₃),
\[ \delta = 3.640 \text{ (s, 3H, COOCH}_3) , \]
\[ \delta = 1.608 \text{ (s, 3H, } \alpha\text{-CH}_3), \]
\[ \delta = 3.0 \text{ (d, } J=16\text{Hz, 1H, H-}\beta), \]
\[ \delta = 3.44 \text{ (broad doublet, } J=16\text{Hz, 1H, H-}\beta) \]

**Preparation of (S)-\(\alpha\)-methyl aspartic acid hydrochloride**

1055

1057 (20.0mg) was refluxed in 6M HCl (2ml) for 6 hours. The solvent was then removed under reduced pressure to give an oil. Theoretical yield = 16.75mg. An optical rotation based on the theoretical yield gave \([\alpha]_D = +33.4^\circ \) (c=0.84, H\(_2\)O).

\(^1H\)-NMR in D\(_2\)O ref D\(_2\)O=4.111

\[ \delta = 0.879 \text{ (s, 3H, } \alpha\text{-CH}_3) , \]
\[ \delta = 2.23, 2.51 \text{ (AB quartet, 2H, } J=18.3\text{Hz, H-}\beta). \]

**Preparation of**

(2S,3aS,8aS)-8-benzenesulphonyl-1,2-dicarbomethoxy-2-(methoxycarbonyl)methyl-1,2,3,3a,8,8a-hexahydropyrrolo-[2,3b]indole (1054)

LDA was prepared by adding 2.1M BuLi (2.6ml, 5.46mmol) to a solution of diisopropylamine (603.3mg, 5.97mmol) in THF (2ml) at -78\(^\circ\)C under nitrogen.

1051 (2.0683g, 4.97mmol) dissolved in THF (20ml) with warming was cooled to -78\(^\circ\)C under nitrogen. LDA prepared from above was quickly added
and the resulting reaction was stirred at -78°C under nitrogen for 10 minutes. Bromomethyl acetate (2.299g, 15.0mmol, 3eq) in THF (2ml) was injected into the reaction. Tic showed the reaction to be complete after 30 minutes. The reaction was then diluted with ethyl acetate and then acidified with HCl. The organic phase was separated, and the aqueous phase back extracted. The combined organic extracts was washed with water, dried over MgSO₄(anh), filtered, and the solvent removed under reduced pressure. The crude was then column chromatographed with petrol:EtOAc (1:1) to give the product, 2.127g (90%). The product solidified in Et₂O, mp=113°C, [α]D=+89.7° (c=0.39, CH₂Cl₂)

400Mhz ¹H-NMR in CDCl₃ ref CDCl₃
δ=3.60 (s, 3H, N-COOCH₃),
δ=3.58 (s, 3H, C-2 COOCH₃),
δ=2.98 (s, 3H, side chain COOCH₃),
δ=2.48 (d, J=14Hz, 1H, H-1'),
δ=2.84 (d, J=16Hz, 1H, H-1'),
δ=2.70 (m, 1H, H-3),
δ=3.37 (m, 1H, H-3),
δ=3.30 (t, J=8Hz, 1H, H-3a),
δ=6.20 (d, J=8Hz, 1H, H-8a),
δ=6.8 to 7.6 (aromatics)

Preparation of-Nᵦ-acetyl-Nᵦ-benzenesulphonyl-
α-(carbomethoxymethyl)-L-tryptophan methyl ester
(1059)

1054 (765.7mg, 1.614mmol) was dissolved in CF₃COOH (4ml) and stirred for 90 minutes. The CF₃COOH was then evaporated under reduced
pressure. No further purification was carried out, and the product was used in the next stage.

200MHz $^1$H-NMR in CDCl$_3$ ref CDCl$_3$

$\delta$=6.16 (s, 1H, H$_N$),
$\delta$=3.65 (s, $\alpha$-COOCH$_3$),
$\delta$=3.71 (s, N$_B$-COOCH$_3$),
$\delta$=3.58 (s, COOCH$_3$),
$\delta$=3.17 (m, 2H, $\beta'$-CH$_2$),
$\delta$=3.6 (m, overlapping with the methyl esters, $\beta$-CH$_2$),
$\delta$=7.0 to 8.0 (aromatics)

Preparation of (3R)-3-(N-methoxycarbonyl)amino-3-carboxymethyl-4-carboxymethyl-1-butanoic acid 1060

A solution of NaIO$_4$ (7.5g) in water (30ml) and MeCN (15ml) was prepared. 1059 (1.614mmol) in MeCN (3ml) was added. RuCl$_3$.3H$_2$O (8.9mg) was added. The reaction was left stirring for 72 hours. The reaction was then quenched with ethyl acetate and acidified with HCl. The organic phase was separated, and the aqueous phase back extracted. The combined organic extracts was washed with water, dried over MgSO$_4$(anh), filtered, and the solvent removed under reduced pressure. The crude was then column chromatographed (SiO$_2$.Et$_2$O), and the desired product was collected as an oil,153.6mg (60%).

Accurate mass Theory 278.0871
Preparation of (R)-α-methyl-N-carboxymethyl aspartic acid methyl diester 1062

60 (236.6mg, 1.25mmol) was stirred in CH$_2$Cl$_2$ (2ml) at -10°C under nitrogen. A solution of 1060 (270mg, 0.9739 mmol) and NEt$_3$(139.2mg, 1.38mmol) in CH$_2$Cl$_2$ (5ml) was injected. A yellow solution was formed as the thiohydroxamate salt dissolved. This solution was allowed to stir for 10 minutes. Then t-C$_{12}$H$_{25}$SH (647.7mg, 3.206mmol) in CH$_2$Cl$_2$ (2ml) was injected, and the solution was then photolyzed at 0°C for 3 hours.

The solvent was evaporated off, and the residue redissolved in water and Et$_2$O. The Et$_2$O layer was separated, washed with brine and then dried over MgSO$_4$(anh), filtered and the solvent removed under reduced pressure. High field NMR at this stage showed no starting material.

The crude was column chromatographed (SiO$_2$, EtOAc:petrol=1:2) to give 150mg of product. High field NMR showed some of the ‘rearranged’ product. This was redissolved in Et$_2$O (4ml) and washed with 6M HCl (1ml). The Et$_2$O layer was separated, washed with brine, dried over MgSO$_4$(anh), filtered, and the solvent removed under reduced pressure to give 98.3mg (43.3%).

[$\alpha$]$_D^{20}$ = +21.3° (c=2.485, MeOH)
Experimental 236

200MHz $^1$H-NMR in CDCl$_3$ ref CDCl$_3$

$\delta$=5.941 (bs, 1H, NH),

$\delta$=3.771 (s, 3H, N-COOCH$_3$),

$\delta$=3.622 (s, 3H, COOCH$_3$),

$\delta$=3.637 (s, 3H, COOCH$_3$),

$\delta$=2.91 (d, J=16.5Hz, 1H, CH$_2$),

$\delta$=3.36 (d, J=16.1Hz, 1H, CH$_2$),

$\delta$=1.598 (s, 3H, CH$_3$)

Preparation of (R)-$\alpha$-methyl-aspartic acid hydrochloride 1058

1062 (49.7mg, 0.2131mmol) was dissolved in 6M HCl (3ml) and refluxed for 5 hours. The solvent was then evaporated to give an oil. An optical rotation in water (based on the theoretical yield of 39.1mg) gave $[\alpha]_D$=−27.6° (c=2, H$_2$O).

200MHz $^1$H-NMR in D$_2$O ref D$_2$O=4.182

$\delta$=0.733 (s, 3H,$\alpha$-CH$_3$),

$\delta$=2.10, 2.38 (AB quartet, J=18.3Hz, H-β)

Preparation of N$_\beta$-acetyl-L-tryptophan (1076)

1001 (1.00g, 4.90mmol) was dissolved in water and Na$_2$CO$_3$ (1.43g, 13.5mmol, 2.75eq) and stirred at 0°C.

Methylchloroformate (559mg, 1.17eq) in toluene (2ml) was added and
Experimental

the reaction was left stirring for 2.5 hours by which time tlc showed the complete disappearance of tryptophan. The reaction was then quenched with ethyl acetate. The organic phase was separated and the aqueous phase was back extracted. The combined organic phases was washed with water, separated, dried over MgSO_4(anh), filtered and the solvent removed under reduced pressure to give a white solid (1.24g, 99%). The crude was then recrystallized from ethyl acetate and petrol to give 0.90g (70%), mp=155°C.

200MHz 1H-NMR in D_2O ref D_2O=4.11
δ=2.54 (m,2H, β-CH_2),
δ=3.82 (s,3H, COOCH_3),
δ=3.78 (t, J=6Hz, 1H, H-α),
δ=6.3 to 7.0 (aromatics)

Preparation of N_b-acetyl-L-tryptophan phenyl ester

(1077a)

1076 (509mg, 1.941mmol) was dissolved in THF (8ml). NEt₃ (230mg, 2.28mmol, 1.17eq) in THF (2ml) was added, and the solution was stirred at -20°C under nitrogen. Isobutyl chloroformate (303.6mg, 2.22mmol, 1.15eq) was added in THF (1ml). The resulting solution was then stirred at -15°C to -20°C for 25 minutes.

A solution of phenol (209.7mg, 2.18mmol, 1.1eq) and NEt₃ (215.8mg, 2.14mmol, 1.1eq) in THF (2ml) was added. The reaction was then allowed to warm to room temperature. The reaction was filtered, and the solvent removed under reduced pressure. The residue was redissolved in ethyl acetate, washed with 2M HCl, water, 2M NaOH, water, dried over MgSO₄(anh), filtered and the
Experimental

solvent removed under reduced pressure to give a white solid (524.5mg, 80%).
The product was recrystallized from ethyl acetate and petrol.
Yield=370mg (56%), mp=164°C

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<td>H</td>
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<td>N</td>
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<td>8.20%</td>
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200MHz $^1$H-NMR in CDCl$_3$ ref CDCl$_3$
\[ \delta=5.32 \text{ (d, J=7Hz, 1H, H-N$_b$) }, \]
\[ \delta=3.688 \text{ (s, 3H, carbamate COOCH$_3$) }, \]
\[ \delta=4.93 \text{ (m, 1H, H-}\alpha), \]
\[ \delta=3.45 \text{ (d, J=5.4Hz, 2H, H-}\beta), \]
\[ \delta=8.13 \text{ (bs, 1H, H-N$_a$) }, \]
\[ \delta=6.8 \text{ to 7.8 (aromatics)} \]

Preparation of
(2S,3aS,8aS)-1-carbomethoxy-2-carbophenoxy-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-b]indole (1078a)

1077a (0.16g, 0.473mmol) was stirred in 88% H$_3$PO$_4$ (2ml) for 8 hours
and then quenched by dropping slowly into a rapidly stirring mixture of CH$_2$Cl$_2$
(40ml) and 15% Na$_2$CO$_3$ (45ml). The CH$_2$Cl$_2$ phase was separated, and the
aqueous phase back extracted. The combined organic layers were washed with
water, dried over MgSO$_4$(anh), filtered, and the solvent removed under reduced
pressure to give 168mg (100%) of an oil. No further purification was carried out.
High field $^1$H-NMR showed a mixture of 2 rotamers.
Experimental

200MHz $^1$H-NMR in CDCl$_3$ ref CDCl$_3$

$\delta$=3.750 (s), 3.824 (s), (3H, carbamate COOCH$_3$),  
$\delta$=4.72 (m), 4.86 (m), (2H, H-2 and H-8),  
$\delta$=2.74 (m, 2H, H-3),  
$\delta$=4.0 (m, 1H, H-3a),  
$\delta$=5.61 (d, J=6.77Hz), 5.66 (d, J=6.77Hz), (H-8a),  
$\delta$=6.3 to 7.5 (aromatics)

Preparation of
(2S,3aS,8aS)-1-carbomethoxy-2-carbophenoxy-8-benzenesulphonyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3b]indole (1075a)

1078a (0.16g, 0.47mmol) was dissolved in pyridine (2ml). PhSO$_2$Cl (108mg, 0.587mmol, 1.24eq) was added in pyridine (1ml). The reaction was left stirring for 16 hours and then quenched with Et$_2$O and CH$_2$Cl$_2$, washed with 2M HCl, brine, dried over MgSO$_4$(anh), filtered, and the solvent removed under reduced pressure to give the crude (192mg). The crude was column chromatographed (SiO$_2$ , EtOAc:petrol=1:1) to give the product (114.8mg, 50.7%).

High field $^1$H-NMR at room temperature showed broad peaks due to the carbamate rotamers. These peaks were resolved at +50°C, and ‘froze’ out at below 0°C.

NOE difference spectrum showed a positive NOE between the H-2 proton with the H-3a and H-8a protons, and thus confirming the configuration at these positions.
Experimental

400MHz $^1$H-NMR at room temperature
$\delta$=3.48 (bs), 3.70 (bs), (3H, COOCH$_3$),
$\delta$=4.86 (bs, 1H, H-2),
$\delta$=2.7 (m, 2H, H-3),
$\delta$=3.90 (bs, 1H, H-3a),
$\delta$=6.38 (bs, 1H, H-8a),
$\delta$=6.5 to 7.8 (aromatics)

400MHz $^1$H-NMR at +50°C in CDCl$_3$ ref CDCl$_3$
$\delta$=3.55 (s, 3H, COOCH$_3$),
$\delta$=4.86 (d, $J$=8Hz, 1H, H-2),
$\delta$=2.78 (m, 2H, H-3),
$\delta$=2.65 (m, 1H, H-3),
$\delta$=3.86 (m, 1H, H-3a),
$\delta$=6.41 (d, $J$=8Hz, 1H, H-8a),
$\delta$=6.5 to 7.9 (aromatics).

400MHz $^1$H-NMR at -15°C in CDCl$_3$ ref CDCl$_3$
2 rotamers in the ratio of 3:1 were seen
$\delta$=3.429 (s, major), 3.708 (s, minor) (3H, COOCH$_3$),
$\delta$=4.753(minor,d,$J$=8.85Hz), 4.883(major,d,$J$=8.99Hz)(H-2)
$\delta$=2.7 (m, H-3),
$\delta$=3.641(minor,t,$J$=7.2Hz), 3.890(major,t,$J$=6.7Hz) (H-3a)
$\delta$=6.353(major,d,$J$=6.46Hz), 6.381(minor,d,$J$=6.6Hz)(H-8a)
$\delta$=6.4 to 7.9 (aromatics).
**Preparation of N<sub>α</sub>-acetyl-L-tryptophan-pentafluorophenyl ester (1077b)**

Dicyclohexylcarbodiimide, DCC, (287mg, 1.377mmol) was dissolved in dichloromethane (1.5ml) and cooled to 0°C. Pentafluorophenol, PFP, (246mg, 1.323mmol) in ethyl acetate (2ml) was added and the solution was stirred for 15 minutes.

1076 (341mg, 1.30mmol) was dissolved in ethyl acetate (20ml) with heating. It was then added to the DCC and PFP reaction above, and allowed to stir at room temperature for 4 hours. The white precipitate urea byproduct was filtered, and the solvent was then removed under reduced pressure to give the crude which was column chromatographed (SiO<sub>2</sub>, EtOAc:petrol=1:1) to give the product as an oil (401mg, 71%).

Accurate mass

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High field NMR at room temperature showed broad peaks due to slow carbamate bond rotation. The peaks were resolved at +50°C.

400MHz <sup>1</sup>H-NMR at +50°C in CDCl<sub>3</sub> ref CDCl<sub>3</sub>

δ=5.08 (m, 1H, H-α),
δ=3.5 (m, 2H, H-β),
δ=5.3 (bs, 1H, H-N<sub>b</sub>),
δ=8.25 (bs, 1H, H-N<sub>α</sub>),
δ=7.0 to 7.7 (aromatics)
Preparation of
(2S,3aS,8aS)-1-carbomethoxy-2-carbopentafluorophenoxy-
1,2,3,3a,8,8a-hexahydropyrrolo[2,3-b]indole (1078a)

1077b (407mg, 0.951mmol) was dissolved in 88% H₃PO₄ (4ml) and
stirred for 12 hours. The acidic solution was then added slowly to a rapidly
stirring mixture of 15% Na₂CO₃ (90ml) and dichloromethane (50ml). The
organic phase was separated, and the aqueous phase back extracted with
dichloromethane. The combined organic extracts was dried over MgSO₄(anh),
filtered and the solvent removed under reduced pressure. The crude was column
chromatographed (SiO₂, petrol:EtOAc=1:1). The product (148.7mg, 36.5%) was
isolated as an oil. Some starting material was recovered (219mg, 53.8%).

Accurate mass
Theory 428.0792
Found 428.0818

400MHz ¹H-NMR in CDCl₃ ref CDCl₃
δ=3.721(s), 3.833(s) (3H, COOCH₃),
δ=4.80(m), 4.92(m) (1H, H-2),
δ=2.8 (m, 2H, H-3),
δ=4.05 (m, 1H, H-3a),
δ=5.60(d, J=6.89Hz), 5.65(d, J=6.68Hz) (1H, H-8a),
δ=6.5 to 7.2 (aromatics)

Preparation of
(2S,3aS,8aS)-1-carbomethoxy-2-carbopentafluorophenoxy-
8-benzenesulphonyl-1,2,3,3a,8,8a-
hexahydropyrrolo[2,3-b]indole (1075b)

1078b (101.3mg, 0.2365mmol) was dissolved in pyridine (0.5ml) and stirred. PhSO₂Cl (63.7mg, 0.346mmol, 1.46eq) was added and the solution was stirred for 18 hours. The reaction was then diluted with ethyl acetate and washed with 2M HCl. The organic layer was separated and the aqueous phase back extracted. The combined organic extracts was washed with water, dried over MgSO₄(anh), filtered, and the solvent removed under reduced pressure. The crude was then column chromatographed (SiO₂, Et₂O) to give the product as an oil (66.4mg, 49%).

NOE difference spectrum, irradiating at H-2 showed a positive NOE with H-8a, showing that the designated stereochemistry was correct. High field ¹H-NMR at room temperature showed broad peaks which were resolved when the NMR spectrum was taken at +50°C. When the NMR spectrum was taken at -20°C two sets of signals due to the carbamate rotamers were seen in the ratio of 2.2:1.

400MHz ¹H-NMR in CDCl₃ at +50°C ref CDCl₃
δ=3.607 (s, 3H, COOCH₃),
δ=4.90 (m, 1H, H-2),
δ=2.7 (m, 2H, H-3),
δ=3.78 (bs, 1H, H-3a),
δ=6.330 (d, J=6.52Hz, H-8a),
δ=7.0 to 7.8 (aromatics)

400MHz ¹H-NMR in CDCl₃ at -20°C ref CDCl₃
δ=3.548(s, major), 3.746(s, major) (COOCH₃),
δ=4.86(d,J=8.7Hz,minor), 4.98(m,major) (H-2),
δ=2.7 (m, H-3),
Experimental

\[ \delta = 3.83(\text{bs, major}); 3.57(\text{overlapping COOCH}_3, \text{m, minor})(\text{H-3a}) \]
\[ \delta = 6.31(\text{d, J}= 6.43\text{Hz, major}); 6.329(\text{d, J}= 8\text{Hz, minor})(\text{H-8a}) \]
\[ \delta = 7.0 \text{ to } 7.8 \text{ (aromatics)} \]

\[ ^{19}\text{F-NMR at room temperature in CDCl}_3 \text{ ref} \]
\[ \text{hexafluorobenzene}=0\text{ppm. Operating frequency } = 376.3\text{MHz} \]

Rotamers were seen in the ratio of 2.4:1
\[ \delta = 10.0 \text{ (bs, major), } 9.4 \text{ (bs, minor) (2F, ortho)} \]
\[ \delta = -0.496 \text{ (t, J}=20.3\text{Hz, 2F, meta)} \]
\[ \delta = 4.1 \text{ (bs, 1F, para)} \]

\[ ^{19}\text{F-NMR at } +50^\circ\text{C in CDCl}_3 \text{ referenced on the most}\]
\[ \text{upfield peak} \]
\[ \delta = 10.6 \text{ (bs, 2F, ortho)} \]
\[ \delta = 0 \text{ (t, J}=19.3\text{Hz, 2F, meta)} \]
\[ \delta = 4.587 \text{ (t, J}=21.2\text{Hz, 1F, para)} \]

\[ ^{19}\text{F-NMR at } 0^\circ\text{C in CDCl}_3 \text{ ref hexafluorobenzene } = 0\text{ppm} \]

Rotamers were seen in the ratio of 2.3:1
\[ \delta = 9.3335 \text{ (minor, d, J}=20.1\text{Hz)}, \]
\[ 9.91 \text{ (major, d, J}=19.3\text{Hz) (ortho)} \]
\[ \delta = -0.46 \text{ (major, t, J}=21.4\text{Hz)}, \]
\[ -0.408 \text{ (minor, t, J}=21.4\text{Hz) (meta)} \]
\[ \delta = 4.15 \text{ (major, t, J}=22\text{Hz)}, \]
\[ 4.263 \text{ (minor, t, J}=21\text{Hz) (para)} \]
Experimental

19F-NMR at -40°C in CDCl₃ ref hexafluorobenzene=0ppm
δ=9.18 (bs, minor, ortho)
9.69 (bs, major, ortho),
δ=−0.361 (t, J=22Hz, meta)
δ=4.262 (t, J=23Hz, para)
4.327 (t, J=23Hz, para)

19F-NMR at -60°C in CDCl₃ ref hexafluorobenzene=0ppm
δ=9.3 (bs, ortho),
δ=−0.3 (m, meta),
δ=4.3 (m, para)

Preparation of N₆-acetyl-L-tryptophan
para-methoxyphenyl ester (1077c)

1076 (508.3mg, 1.938mmol), NEt₃ (215.4mg, 2.13mmol, 1.1eq) was dissolved in THF (7ml) under nitrogen and then cooled to -20°C. Isobutyl chloroformate (305.2mg, 2.21mmol, 1.14eq) in THF (3ml) was added and the solution was stirred for 20 minutes. Then p-methoxyphenol (280.2mg, 2.21mmol, 1.14eq) in THF (2ml) was added, and the reaction was stirred for 3 hours. The reaction was quenched with ethyl acetate, water and Na₂CO₃. The organic phase was separated, and the aqueous layer back extracted. The combined organic extracts was washed with water, dried over MgSO₄(anh), filtered and the solvent removed under reduced pressure. The crude was column chromatographed (SiO₂, EtOAc:petrol=1:1) to give the product as an oil (293.4mg, 41%).
Experimental

200MHz $^1$H-NMR in CDCl$_3$ ref CDCl$_3$

$\delta=5.62$ (d, J=8Hz, H-$N_a$),
$\delta=3.6$ to $3.8$ (singlets, 6H, 2x COOCH$_3$),
$\delta=4.94$ (m, 1H, H-$\alpha$),
$\delta=3.44$ (d, J=5.4Hz, 2H, H-$\beta$),
$\delta=8.6$ (bs, H-$N_a$),
$\delta=6.7$ to $7.8$ (aromatics)

Preparation of
$(2S,3aS,8aS)$-1-carbomethoxy-2-carbo-p-methoxyphenoxy-1,
2,3,3a,8a-hexahydropyrrolo[2,3b]indole (1078c)

1077c (293.4mg, 0.796mmol) was dissolved in 88% H$_3$PO$_4$ (3ml) and stirred for 16 hours. The acidic solution was then added dropwise to a rapidly stirring mixture of 15% Na$_2$CO$_3$ (90ml) and dichloromethane (50ml). The dichloromethane phase was separated, and the aqueous phase back extracted. The combined organic extracts was washed with water, dried over MgSO$_4$(anh), filtered, and the solvent removed under reduced pressure to give the product (281mg, 96%) as an oil. High field $^1$H-NMR showed 2 rotamers.

200MHz $^1$H-NMR in CDCl$_3$ ref CDCl$_3$

$\delta=3.7$ to $3.84$ (singlets, 6H, COOCH$_3$ and Ar-OCH$_3$),
$\delta=4.69$ (m), 4.84 (m) , (1H, H-2),
$\delta=2.73$ (m, 2H, H-3),
$\delta=3.96$ (m, 1H, H-3a),
$\delta=5.58$ (d, J=6.4Hz, minor, H-8a),
5.65 (d, J=6.8Hz, major, H-8a),
$\delta=6.7$ to $7.8$ (aromatics)
Preparation of
(2S,3aS,8aS)-1-carbomethoxy-2-carbo-p-methoxyphenoxy-8-benzenesulphonyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3b]-indole (1075c)

1078c (280mg, 0.760mmol) was dissolved in pyridine (0.5ml) and stirred. Benzenesulphonyl chloride (154mg, 0.837mmol, 1.10eq) was added, and the solution was stirred for 16 hours. The reaction was quenched with ethyl acetate and water. The organic layer was separated and the aqueous phase back extracted. The combined organic extracts was dried over MgSO₄(anh), filtered and the solvent removed under reduced pressure. The crude was column chromatographed (SiO₂, EtOAc:petrol=1:1) to give the product (240mg, 62%).

NOE difference spectrum irradiating at H-2 showed positive NOE with H-8a, indicating the assigned stereochemistry is correct.

¹H-NMR at room temperature showed broad peaks, which were resolved at +50°C.

400MHz ¹H-NMR in CDCl₃ ref CDCl₃ at 50°C
δ=3.717 (s, 3H, COOCH₃),
δ=3.511 (bs, 3H, ArOCH₃),
δ=4.799 (d, J=8.92Hz, H-2),
δ=2.60 (m, 1H, H-3),
δ=2.73 (m, 1H, H-3),
δ=3.832 (t, J=6Hz, H-3a),
δ=6.370 (d, J=6.8Hz, H-8a),
δ=6.3 to 7.8 (aromatics)
Experimental

400MHz $^1\text{H}$-NMR in CDCl$_3$ ref CDCl$_3$ at -20°C
Rotamers in the ratio of 2.7:1 were seen.

$\delta=$3.419(s,major), 3.718(s,minor) (COOCH$_3$),
$\delta=$3.766(s, ArOCH$_3$),
$\delta=$4.748(d,J=8.81Hz,minor), 4.882(d,J=8.99Hz,major)(H-2),
$\delta=$2.75(m, 2H, H-3),
$\delta=$3.642(t,J=6.8Hz,minor), 3.918(t,J=6.8Hz,major) (H-3a)
$\delta=$6.335(d,J=9Hz,minor), 6.368(d,J=6.5Hz,major) (H-8a),
$\delta=$6.3 to 7.9 (aromatics)

Preparation of
N-(8-Aminonaphthalene-1-yl)-(N$_{\text{b}}$-acetyl-L-tryptophan)-2-carboxamidine 1077d

1076 (2.0369g, 7.77mmol) and NEt$_3$(881.3mg, 8.73mmol, 1.12eq) were dissolved in dry THF (8ml) and stirred under nitrogen and cooled to -20°C.

Isobutyl chloroformate (1188.9mg, 8.62mmol, 1.1 eq) in THF (2ml) was introduced slowly. A white ppt of NEt$_3$.HCl was formed. The reaction was then stirred at -20°C for 15 minutes.

1,8-Diaminonaphthalene (1408.1mg, 8.63mmol, 1.11eq) in THF (10ml) was introduced and the reaction was allowed to warm to 5°C over 2 hours. The reaction was then quenched by pouring into ethyl acetate and 15% Na$_2$CO$_3$. The organic phase was separated and washed with water. It was then dried over MgSO$_4$(anh), filtered and the solvent removed under reduced pressure to give the crude (3.324g). The crude was column chromatographed (SiO$_2$,EtOAc:petrol=1:1) to give the product (2.896g, 92.6%). This was then recrystallized from dichloromethane and petrol to give a yellow solid (1.941g, 62%), mp=128°C. The solid darkened on exposure to air.
Mass spectrum gave $(M-H_2O)^+$ at 384.

400MHz $^1$H-NMR in CDCl$_3$ ref CDCl$_3$

$\delta=3.504$ (s, 3H, COOCH$_3$),
$\delta=4.55$ (m, 1H, H-α),
$\delta=3.3$ (m, 2H, H-β),
$\delta=5.8$ to 9 (aromatics and N-H’s)

UV Spectra

In neutral DMF

$\varepsilon_{\text{max}}$(281.8nm)= 7379
$\varepsilon_{\text{max}}$(289.8nm)= 7929
$\varepsilon_{\text{max}}$(330.6nm)=15698

In acidic DMF

$\varepsilon_{\text{max}}$(280.9nm)=10344
$\varepsilon_{\text{max}}$(289.5nm)=11096
$\varepsilon_{\text{max}}$(314.0nm)=12773
$\varepsilon_{\text{max}}$(326.6nm)=13484

Preparation of N-(8-aminonaphthalene-1-yl)-
$(2S,3aS,8aS$)-1-carbomethoxy-1,2,3,3a,8,8a-hexahydropyrrolo[2,3b]indole]-2-
carboxamide

1078d

1077d (1.0548g, 2.620mmol) was stirred with 88% H$_3$PO$_4$ (10ml) for 18 hours. The acidic solution was then dropped slowly into a rapidly stirring mixture of dichloromethane (50ml) and 15% Na$_2$CO$_3$ (180ml). The organic layer was separated and the aqueous phase back extracted. The combined organic extracts
was washed with water, dried over MgSO$_4$(anh), filtered and the solvent removed under reduced pressure to give the crude (1.071g). The crude was column chromatographed (SiO$_2$, EtOAc) to give the product (911mg, 86%), and starting material (97mg, 9%). Mp=120°C.

400MHz $^1$H-NMR in CDCl$_3$ ref CDCl$_3$

$\delta$=3.742 (s, 3H, COOCH$_3$),
$\delta$=4.707 (d, J=9.14Hz, 1H, H-2),
$\delta$=2.50 (bs, 1H, H-2),
$\delta$=2.95 (bs, 1H, H-2),
$\delta$=4.017 (t, J=8Hz, 1H, H-3a),
$\delta$=5.3(bs), 5.65(bs), 5.85(bs), (2x N-H, and H-8a)
$\delta$=6.5 to 8.0 (aromatics and 2NH’s)

Attempted preparation of

(2S,3aS,8aS)-1-carbomethoxy-8-benzenesulphonyl-2-(perimidine-2-yl)-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-b]indole 1078e

1078d (1247.2mg, 3.10mmol) was dissolved in toluene (20ml) and refluxed with P$_2$O$_5$ (12g). The reaction was then quenched by adding slowly to a rapidly stirring mixture of ethyl acetate and 15% Na$_2$CO$_3$. 2M NaOH was added to bring the aqueous phase to pH14. The organic phase was then separated out and the aqueous phase back extracted. The combined organic extracts was dried over MgSO$_4$(anh), filtered, and the solvent removed under reduced pressure to give the crude (1.150g).

The crude product was column chromatographed (SiO$_2$, EtOAc). The starting material (114mg,9.1%), and the product (940mg,79%) were obtained.
The product was recrystallized from ethyl acetate and petrol to give a yellow solid. Mp=220-221°C. High field $^1$H-NMR showed however that it was the ring opened isomer 1077e.

<table>
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<tr>
<th>Microanalysis</th>
<th>Theory</th>
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<tr>
<td>C</td>
<td>71.859%</td>
<td>71.86%</td>
</tr>
<tr>
<td>H</td>
<td>5.243%</td>
<td>5.34%</td>
</tr>
<tr>
<td>N</td>
<td>14.574%</td>
<td>14.12%</td>
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</table>

400MHz $^1$H-NMR in CDCl$_3$ and DMSO ref CDCl$_3$

$\delta=6.01$ (bs, 1H, H-N$_b$),
$\delta=3.50$ (bs, 3H, COOCH$_3$),
$\delta=4.45$ (bs, 1H, H-\(\alpha\)),
$\delta=3.20$ (bs, 2H, H-\(\beta\)),
$\delta=6.5$ to 7.7 (aromatics and NH's).

UV spectra

In neutral DMF

$\epsilon_{\text{max}}(281.2\text{nm})=3628$
$\epsilon_{\text{max}}(289.6\text{nm})=3676$
$\epsilon_{\text{max}}(330.8\text{nm})=8048$

In acidic DMF

$\epsilon_{\text{max}}(280.4\text{nm})=5838$
$\epsilon_{\text{max}}(289.6\text{nm})=6054$
$\epsilon_{\text{max}}(313.6\text{nm})=6727$
$\epsilon_{\text{max}}(326.2\text{nm})=7207$
Attempted cyclization of 1077e with 88% $\text{H}_3\text{PO}_4$

1077e (26.1mg) was stirred in 88% $\text{H}_3\text{PO}_4$ (1ml) for 48 hours. The acidic solution was then slowly added to a rapidly stirring mixture of 15% $\text{Na}_2\text{CO}_3$ (100ml) and dichloromethane (50ml). The organic phase was separated and the aqueous phase back extracted. The combined organic extracts was dried over $\text{MgSO}_4$ (anh), filtered, and the solvent was removed under reduced pressure to give the crude (38.7mg). High field $^1\text{H}$-NMR showed the crude was identical to the previously prepared 1078d.

Preparation of 3-Indolylmethyl phenyl ketone 1094, from Gramine (1093)

1093 (1.0207g, 5.858mmol) and NaCN (312.2mg, 6.37mmol, 1.09eq) were stirred in DMF (8ml) at 70°C under nitrogen. Then benzaldehyde (1.2694g, 11.96mmol, 2.04eq) in DMF (3ml) was injected in over 30 minutes. The reaction was left at 50°C for 4 hours and then at 120°C for 20 minutes. The reaction was then cooled and then quenched with ethyl acetate and water, and acidified with 2M HCl. The organic phase was separated, washed with water and dried over $\text{MgSO}_4$ (anh), filtered, and the solvent removed under reduced pressure to give the crude. The crude was column chromatographed (SiO$_2$, EtOAc:petrol=1:4). The fractions containing the product were combined and the solvent removed under reduced pressure. The product was then recrystallized from ether to give a white solid (206mg, 15%).


$^{200}\text{MHz }^1\text{H}$-NMR in CDCl$_3$ ref CDCl$_3$

$\delta=4.41$ (s, CH$_2$),

$\delta=7.0$ to 8.3 (aromatics)
Preparation of 3-Indolylmethyl phenyl ketone 1094 from 3-Indolylacetonitrile 1092

1092 (3.6815g, 23.57mmol) was dissolved in diethyl ether (30ml) and stirred at 0°C. 1.4M PhLi (38ml, 53.2mmol, 2.26eq) was added and the reaction was stirred for 1 hour at 0°C, and then left at -10°C for 14 hours. The reaction was then diluted with ether, ethyl acetate, water and then acidified with 2M HCl. The organic phase was separated, dried over MgSO₄(anh), filtered, and the solvent removed under reduced pressure. The crude was column chromatographed (SiO₂, Petrol:EtOAc=4:1). The product (1.409g, 25.4%) was collected from the column. Recrystallization from Et₂O yielded the product (325.3mg, 5.9%), mp=123-124°C.

Preparation of (+)-α-Phenyl tryptophan (+)1095

1094 (282.2mg, 1.20mmol) and NH₄OAc (1.8915g, 19.7eq) was dissolved in methanol(17ml) and stirred under nitrogen. NaBH₄CN (86.8mg, 1.15eq) was added, and the reaction was stirred for 18 hours. The reaction was then acidified with conc. HCl. The solvent and the acid were then removed under reduced pressure. The residue was then redissolved in water and extracted with ether, keeping the aqueous phase. The ethereal extract from this was separated and discarded.

The aqueous phase was then made alkaline with solid KOH, and the alkaline solution was then extracted with ether. The organic phase was separated, and the aqueous phase back extracted. The combined organic extracts was dried over MgSO₄(anh), filtered, and the solvent removed under reduced pressure to give the product (166.4mg, 59%).
200MHz $^1$H-NMR in CDCl$_3$ ref CDCl$_3$

$\delta$=4.35 (dd, J=8Hz,4Hz, H-$\alpha$),
$\delta$=3.010 (d of AB quartet, J=14Hz,8Hz , H-$\beta$),
$\delta$=3.228 (d of AB quartet, J=14Hz, 4Hz, H-$\beta$),
$\delta$=6.7 to 8.8 (aromatics and NH's)

**Preparation of (+)-N$_b$-Carboxymethyl-$\alpha$-phenyl-tryptophan, 1109**

(±)1095 (120mg, 0.456mmol) in dichloromethane (3ml) was added to a solution of Na$_2$CO$_3$ (117.2mg, 1.1mmol, 2.4eq) in water (2ml). Methyl chloroformate (83.6mg) in dichloromethane (0.5ml) was added. After the reaction was completed, the organic phase was separated and the aqueous phase back extracted. The combined organic extracts was dried over MgSO$_4$(anh), filtered and the solvent removed under reduced pressure. The crude was column chromatographed (SiO$_2$, petrol:EtOAc=1:1) to give the product (131mg, 97.6%).

200MHz $^1$H-NMR in CDCl$_3$ ref CDCl$_3$

$\delta$=5.31 (bs, 1H, H-N$_b$),
$\delta$=3.604 (s, 3H, COOCH$_3$),
$\delta$=5.10 (bs, 1H, H-$\alpha$),
$\delta$=3.230 (broad doublet, J=6Hz, 2H, H-$\beta$),
$\delta$=6.6 to 8.3 (aromatics and NH)
Preparation of
(2RS,3aRS,8aRS)-1-carbomethoxy-2-phenyl-1,2,3,3a,8,8a-
hexahydropyrrolo[2,3b]indole (+)1110 and (+)1111

Crude (+)1109 (234.7mg) was dissolved in 88% H$_3$PO$_4$ and stirred for 16 hours. The reaction was then added to a rapidly stirring mixture of dichloromethane (50ml) and 15% Na$_2$CO$_3$ (90ml). The dichloromethane phase was separated, and the aqueous phase back extracted. The combined organic extracts was dried over MgSO$_4$(anh), filtered, and the solvent removed under reduced pressure to give the product (205.4mg). 200MHz $^1$H-NMR showed impurities, but the H-8a signal at $\delta=6.0$ppm could be seen. There were two peaks for the carbamate methyl ester at $\delta=3.64$ppm and $\delta=3.68$ppm.

Preparation of
(2RS,3aRS,8aRS)-1-carbomethoxy-8-benzenesulphonyl-
2-phenyl-1,2,3,3a,8,8a-
hexahydropyrrolo[2,3b]indole (+)1112 and (+)1113

Crude (+)1110 and (+)1111 (205mg) was dissolved in pyridine (0.5ml) and benzenesulphonyl chloride (167.1mg, 0.908mmol) in pyridine (0.5ml) was added. The reaction was stirred for 16 hours. The reaction was then quenched with ethyl acetate and water, and made alkaline by adding 2M NaOH. The organic phase was separated, and the aqueous phase back extracted. The combined organic extracts was dried over MgSO$_4$(anh), filtered and the solvent removed under reduced pressure. The crude obtained was column chromatographed (EtOAc:petrol=1:1). The products were obtained in 45.7mg. 200MHz $^1$H-NMR showed a mixture of products. Three doublets in the H-8a region were seen at $\delta=6.00$ppm ($J=7.3$Hz), $\delta=6.42$ppm ($J=7.9$Hz), $\delta=6.32$ppm ($J=6.66$Hz).
Three singlets for the carbamate methyl ester were also seen at δ=3.661 ppm, δ=3.667 ppm, δ=3.671 ppm.

**Preparation of**

(2S,3aS,8aS)-8-benzenesulphonyl-1-carbomethoxy-2-methyl
-1,2,3,3a,8,8a-hexahydropyrrol[2,3b]indole (1065) and
(2R,3aS,8aS)-8-benzenesulphonyl-1-carbomethoxy-2-methyl
-1,2,3,3a,8,8a-hexahydropyrrol[2,3b]indole (1066) in refluxing toluene

1063 (198.4 mg, 0.4764 mmol) and NEt₃ (57.3 mg, 0.567 mmol, 1.19 eq) were dissolved in dry THF (3 ml) and stirred at room temperature. 60 (108.5 mg, 1.2 eq) was added as the solid, and a yellow solution was formed. t-C₁₂H₂₅SH (240 mg, 2.5 eq) was then injected. The reaction was then quickly injected into refluxing toluene (20 ml) under nitrogen. The reaction was refluxed for 3 hours. Then the toluene was removed under reduced pressure. The crude was then redissolved in ethyl acetate and washed with 4M HCl. The crude product obtained was then column chromatographed (SiO₂, petrol:EtOAc=1:1). The desired products were collected (38.8 mg, 21%). 200MHz ¹H-NMR showed the ratio of endo-methyl product to exo-methyl product to be 1:2.

The two isomers were separated by column chromatography (SiO₂, petrol:EtOAc=1:1).

The starting material was recovered (112.4 mg, 57%).

200MHz ¹H-NMR of the exo-methyl product (1065)

δ=3.74 (s, 3H carbamate COOCH₃),
δ=3.36 (m, 1H, H-2),
δ=1.29 (d, J=5.78Hz, 3H, CH₃),
δ=1.73 (m, 1H, H-3),
δ=2.16 (dd, J=6Hz,14Hz, 1H, H-3),
δ=3.19 (broad t, J=8Hz, 1H, H-3a),
δ=6.05 (d, J=6.1Hz, 1H, H-8a),
δ=6.8 to 8.5 (aromatics)

200MHz ¹H-NMR of the endo-methyl product (1066)

δ=3.701 (s, 3H, carbamate COOCH₃),
δ=4.11 (m, 1H, H-2),
δ=0.678 (d, J=6.84Hz, 3H, CH₃),
δ=2.34 (m, H-3),
δ=1.80 (broad doublet, J=13Hz, H-3),
δ=3.46 (t, J=7Hz, H-3a),
δ=6.148 (d, J=7Hz, H-8a)
δ=6.8 to 8.5 (aromatics)

Preparation of
(2S,3aS,8aS)-8-benzenesulphonyl-1-carbomethoxy-2-methyl
-1,2,3,3a,8,8a-hexahydropyrrolo[2,3b]indole (1065) and
(2R,3aS,8aS)-8-benzenesulphonyl-1-carbomethoxy-2-methyl
-1,2,3,3a,8,8a-hexahydropyrrolo[2,3b]indole (1066)
photolytically at 0°C from 1063

Freshly prepared 60 (266.3mg, 1.40mmol, 1.27eq) was stirred in
dichloromethane (4ml) in a dry flask with 4Å molecular sieves under nitrogen at
-10°C.

**1063** (460mg, 1.1045mmol) was dissolved in dichloromethane (1ml) with molecular sieves. NEt$_3$ (266.3mg, 1.73mmol, 1.57eq) in CH$_2$Cl$_2$(1ml) was added. The solution was stirred, and then injected into the solution of 60 to give a bright yellow solution.

The solution was stirred for 10 minutes when all the solid dissolved. t-C$_{12}$H$_{25}$SH (775.2mg, 3.84mmol, 3.47eq) in CH$_2$Cl$_2$(2ml) was injected. The solution was stirred for 5 minutes, and then photolyzed in an ice-bath for 3 hours.

The reaction was then quenched with water and ethyl acetate. The organic phase was separated and the aqueous phase back extracted. The combined organic extracts was washed with water, dried over MgSO$_4$(anh), filtered, and the solvent removed under reduced pressure.

45.5mg (11%) of the exo-methyl product and 31.6mg (7.7%) of the endo-methyl product were isolated after column chromatography.

**Preparation of**
(2S,3aS,8aS)-8-benzenesulphonyl-1-carbomethoxy-2-methyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3b]indole (1065) and
(2R,3aS,8aS)-8-benzenesulphonyl-1-carbomethoxy-2-methyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3b]indole (1066)
photolytically at -78°C from **1063**

**1063** (147.7mg, 0.3547mmol) was dissolved in CH$_2$Cl$_2$(3ml) and NEt$_3$(66.5mg, 0.66mmol, 1.86eq) was added in CH$_2$Cl$_2$(2ml). The solution was then cooled to 0°C under nitrogen. 60 (79.9mg, 0.4216mmol, 1.19eq) was added. The bright yellow solution formed was allowed to stir at 0°C for 15 minutes. t-C$_{12}$H$_{25}$SH (180mg, 0.891mmol, 2.5eq) was added in CH$_2$Cl$_2$(2ml). The solution
was then cooled to -78°C and then photolyzed by a tungsten lamp for 4 hours. The solvent was then evaporated and the crude product column chromatographed with petrol:EtOAc=1:1. The products were isolated together (25.6mg, 19.4%). 200MHz $^1$H-NMR showed the ratio of the endo-methyl to exo-methyl product to be in the ratio of 1:4.

**Preparation of (+) N$_3$-acetyl-$\alpha$-methyl-tryptamine**

(+)$\text{1105 from (+)$\alpha$-methyltryptamine (+)$\text{1104}$

(+)$\alpha$-Methyltryptamine (349.2mg, 2.004mmol), Na$_2$CO$_3$ (263.5mg, 2.49mmol, 1.24eq) were dissolved in water (2ml). CH$_2$Cl$_2$ (4ml) was added and the mixture was rapidly stirred.

Methyl chloroformate (216.0mg, 1.1eq) in CH$_2$Cl$_2$ (1ml) was added, and the mixture was stirred until both phases were clear. When tlc showed no more starting material, the CH$_2$Cl$_2$ phase was separated. 15% Na$_2$CO$_3$ (4ml) was added to the aqueous phase, which was then extracted with more CH$_2$Cl$_2$ (3x). The combined CH$_2$Cl$_2$ extracts was dried over MgSO$_4$(anh), filtered, and the solvent removed under reduced pressure to give the crude product as an oil (477mg, >100%). No further purification was carried out.

**Accurate mass**

**Theory** 232.1212  
**Found** 232.1205

200MHz $^1$H-NMR in CDCl$_3$ ref CDCl$_3$  
$\delta$=4.6 (bs, 1H, carbamate NH),  
$\delta$=3.659 (s, 3H, carbamate COOCH$_3$),  
$\delta$=1.150 (d, J=6.56Hz, 3H, $\alpha$-CH$_3$),
Preparation of
(+)-1-carbomethoxy-2-methyl-
-1,2,3,3a,8,8a-hexahydropyrrolo[2,3b]indole (+)-1106 and
(+)-1107 from (+) 1105

(+)-1105 (477mg) was dissolved in 88% H₃PO₄ (8ml) and stirred for 16
hours. The acidic reaction was quenched by dropping slowly into a rapidly
stirring mixture of 15% Na₂CO₃ (200ml) and CH₂Cl₂ (100ml). The CH₂Cl₂ phase
was separated and the aqueous phase back extracted. The combined CH₂Cl₂
extracts was dried over MgSO₄ (anh), filtered and the solvent removed under
reduced pressure to give an oil (469mg).

High field ¹H-NMR gave a very complicated spectrum due to rotamers
of the isomers formed, but the signals corresponding to the endo- and exo-
α-methyl groups were seen.

Preparation of
(+)-1-carbomethoxy-2-methyl-8-benzenesulphonyl-
-1,2,3,3a,8,8a-hexahydropyrrolo[2,3b]indole (+)-1065 and
(+)-1066 from (+) 1106 and (+)1107

The crude mixture of (+)-1106 and (+)-1107 (469mg, 2.01mmol) was
dissolved in pyridine (0.5ml) and stirred. PhSO₂Cl (425mg, 2.31mmol, 1.15eq) in
pyridine (2ml) was added. The reaction was stirred for 3 hours and then diluted with EtOAc and water. The organic phase was separated and the aqueous phase back extracted. The combined organic extracts was washed with water, brine, and then dried over MgSO$_4$(anh), filtered, and the solvent removed under reduced pressure to give the crude product (698.4mg, 93.3%).

A 200MHz $^1$H-NMR showed the exo-methyl : endo-methyl isomers in the ratio of 4:5. The NMR's were identified by comparison with those of enantiomeric compounds prepared previously.
REFERENCES

16 ‘Chemistry and Biology of β-lactam antibiotics’ Vol 2
Chapter 4 (Ed. R.B. Morin and Marvin Gorman, 1982,
Academic Press).
18 D.H. Shih, F. Baker, L. Cama, B.G. Christensen,
27 R.W. Ratcliffe, T.N. Salzmann, B.G. Christensen,
28 R.W. Ratcliffe, T.N. Salzmann, B.G. Christensen,
J.A.C.S. 102, 6161 (1980).
29 O. Mitsunoh, J. Kimura, K. Iizumi, N. Yanagida,
30 D.W. Brooks, L.D. Lu, S. Masamune,
31 D.H.R. Barton, D. Crich, W.B. Motherwell,


47 Sumitomo Pharmaceutical Co. Ltd., Kasugade, Naka, Konohana-ku, Osaka 554, Japan.


49 J. Henry, Comp. Rend., 120 1265 (1895).


54 H.O. House, C-Y Chu, J.M. Wilkins, M.J. Umen,
55 B.H. Lipshutz, R.S. Wilhelm, D.M. Floyd,
56 F. Drouin, F.Leyendecker, J-M Conia,
57 F. Drouin, F.Leyendecker, J-M Conia,
58 Angeline Eustace, MSc Thesis, Dept of Chemistry,
60 D. Crich, K.A. Eustace, T.J. Ritchie,
63 R. Bayles, A.P. Flynn, R.H.B. Galt, S. Kirby, R.W. Turner,
64 R. Bayles, A.P. Flynn, R.H.B. Galt, S. Kirby, R.W. Turner,
65 M. Kitamura, K. Nagai, Y. Hsiao, R. Noyori,
66 A. V. R. Rao, M.K. Gurjar, V.B. Khare, B. Ashok,
75 G.R. Marshall et al in
  'Chemistry and Biology of Peptides' Ed. J. Meienhofer,
76 A.W. Burgess, S.J. Leach, Biopolymers 12, 2599 (1973).
77 G.R. Marshall, J. Turk and G.T. Ponse,
81 S-C J. Fu and S. M. Birnbaum, J.A.C.S., 75, 918 (1953).
82 T. Deeks, P.A. Crooks, and R.D. Waigh,
83 R.D. Seebach, E. Juaristi, D.D. Miller, C. Schickli
85 R.A. Glennon, R. Young, J.M. Jacyno,
86 D. Seebach, M. Boes, R. Naef, W. B. Schweizer,
88 K.W. Blake, A.E.A. Porter, P.G. Sammes,
  J.C.S. Perkin I, 2494 (1972).
92 D. Seebach, D.D. Miller, S. Müller, T. Weber,
References

94 D. Seebach, R. Naef, J.D. Aebi, T. Weber,
95 D. Seebach, E. Juarisiti, D.D. Miller, S. Schickli, T. Weber,
97 J.W. Davies, PhD Thesis, Dept. of Chemistry, University
98 U. Schöllkopf, R. Lonsky, P. Lehr,
103 W. Saenger in "Principles of Nucleic Acid Structure"
104 T.W. Greene in "Protecting Groups in Organic Synthesis"
105 S. Ranganathan, D. Ranganathan and D. Bhattacharyya,
106 A.M. Ismaiel, M. Titeler, K.J. Miller, T.S. Smith, R.A. Glennon,
108 Gaddum's Pharmacology, 9th Edition (Ed. A.S.V. Burgen,
and J.F. Mitchell O.M.P.).