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.

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1991

CONTENT

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 antibiotic1β-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


有情天下母心
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-Ethyldiisopropylamine (Hunig's Base)
DMAP	4-Dimethylaminopyridine
DMF	N,N-Dimethylformamide
DMSO	Dimethylsulphoxide
EDG	Electron Donating Group
ee	Enantiomeric excess

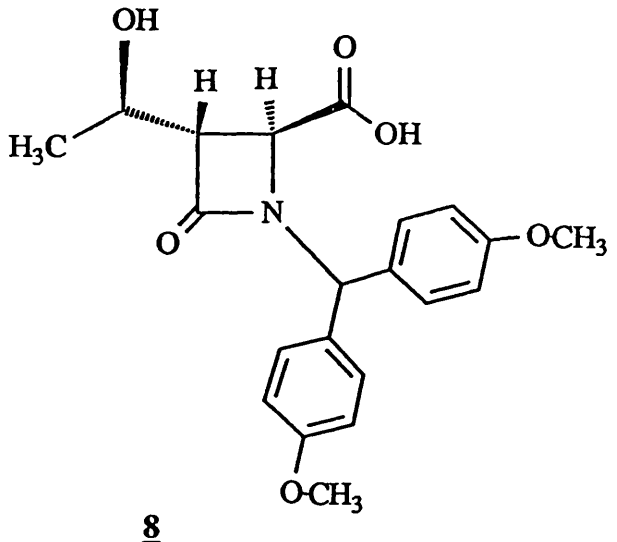
Et	Ethyl
EWG	Electron Withdrawing Group
Gly	The amino acid residue glycine
HMPA	Hexamethylphosphor-tri-amide
HPLC	High pressure liquid chromatography
i-Pr	Isopropyl moiety
hr	Hours
IR	Infrared
LDA	Lithium diisopropylamide
MA/CM	Mixed anhydride Coupling Method
MCPBA	m-Chloroperbenzoic acid
Me	Methyl
Mesyl or Mes	Methylsulphonyl Me-SO_2-
Met	The amino acid residue methionine
Min	Minutes
MMPP	Magnesium monoperoxyphthalate
mp	Melting point
NBS	N-Bromosuccinimide
NMR	Nuclear Magnetic Resonance
NOE	Nuclear Overhauser Effect
P	An appropriate N-Protecting group
PFP	Pentafluorophenyl moiety
PFP-OH	Pentafluorophenol
Ph	Phenyl
Phe	The amino acid residue phenylalanine
Pr	Propyl
Pro	The amino acid residue proline
Py	Pyridine

rt	Room temperature
s-butyl	Secondary Butyl moiety
SEM	Trimethylsilyl(ethoxymethyl) moiety $Me_3SiCH_2CH_2OCH_2$-
Ser	The amino acid residue serine
t-Bu	tertiary butyl group
TEA	Triethylamine
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
tlc	Thin layer chromatography
TMS	Tetramethylsilane or Trimethylsilyl Moiety
Tol	Toluene
Tosyl or Tos	4-Methylphenylsulphonyl CH_3-Ph-SO_2-
Try	The amino acid residue tryptophan
Tyr	The amino acid residue tyrosine
Val	The amino acid residue valine
Z	Benzyloxycarbonyl moiety, $PhCH_2OCO$-
Δ	Heat
*	Chiral centre

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-trytophan 1001**. Derivatives of these compounds are of biological and possibly of medicinal value.



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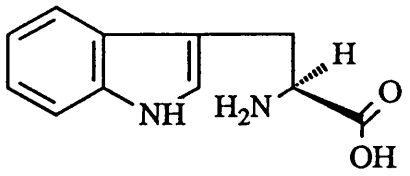


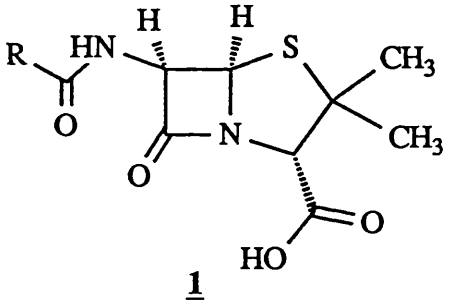
1001

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.[1] He observed that a *Staphalococcus* 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.[2] 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[3]. 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.[3,4]



1

The thiazolidine-β-lactam structure ,1, 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.[3] 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.[5]

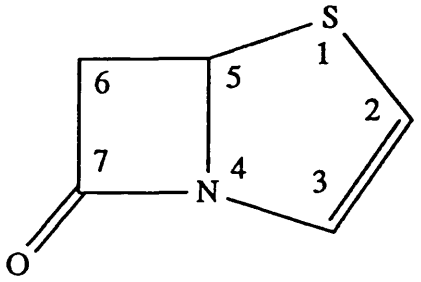
The biological activity of penicillin is due to its β-lactam structure. The β-lactam acts as an activated acylating agent and acylates the active site of an enzyme, peptidoglycan transpeptidase, crucial in the biosynthesis of the bacterial cell wall.[6,7]

In 1945 another class of β-lactam antibiotics was discovered with the isolation of cephalosporin C from a *Cephalosporin acremonium* strain by G. Brotzu.

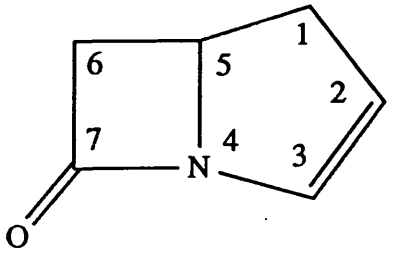
With the wide-spread use of the β-lactam antibiotics, resistance to these drugs has emerged in bacteria through the production of bacterial β-lactamases which catalyse the hydrolysis of the β-lactam to the β-amino acid. Over the decades, thousands of synthetic and semi-synthetic penicillins and cephalosporins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

In 1976, three biogenetically novel microbial β-lactam compounds were reported: the weakly antibacterial **'nocardicin A'**,[9] the β-lactamase inhibitor **'clavulanic acid'**,[10] and **'thienamycin'**.[11,12,13]

Thienamycin is a metabolite of Streptomyces cattleya.[11] It has been named to denote the then novel β-thioenamin chromaphore. Thienamycin has a **carbapenem** skeleton 3. It is so called because the sulphur in the penem system 2 is replaced by a methylene group. The -em part of the name refers to the unsaturation at the C-2 position.

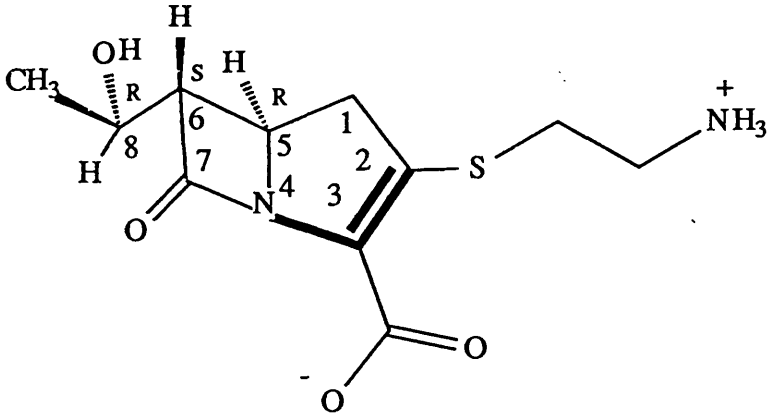


2



3

Thienamycin has potent, broad spectrum antibacterial activities and has a natural stability against bacterial β-lactamases.[11-14] Its structure and absolute configuration has been determined to be 4 by chemical methods and X-ray analysis techniques.[15] However it is chemically unstable particularly outside a narrow pH

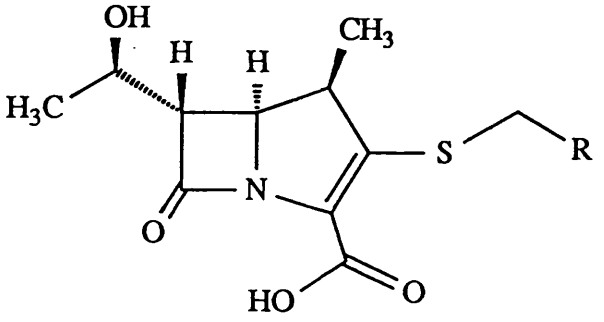


4

range near neutrality,[16] 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.[18,69]

In intense efforts to improve the properties of these antibiotics by chemical

modifications, Shih et al (Merck Sharp and Dohme),[18,19] have first synthesized the 1β-methylcarbapenems **5a** and **5b**. The introduction of a methyl group at the β-C1



5

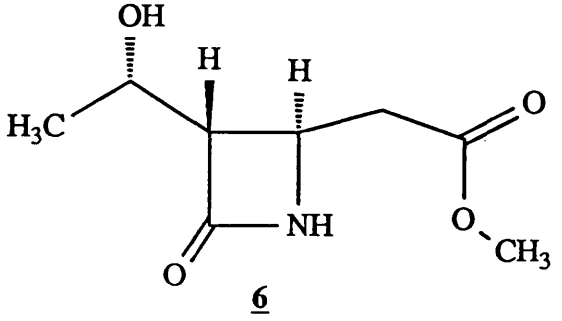
R= -C(=NH)NH$_2$ **5a**

R= -CH_2NH_2 **5b**

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.[18]

1.2.2 Shih's synthesis of the 1β-methylcarbapenems

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

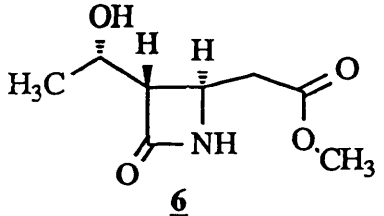


6

from the chiral synthesis of thienamycin and N-formimidoylthienamycin.[27,28]

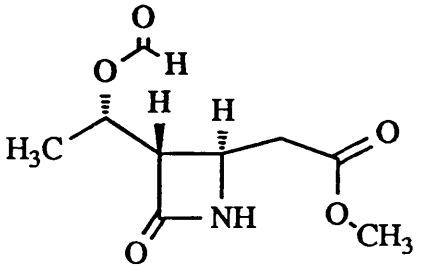
The first step of the synthesis (**scheme 1**) was the inversion of the hydroxyl group in the hydroxyethyl side chain by a modified Mitsunobu reaction.[29] The

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[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**.

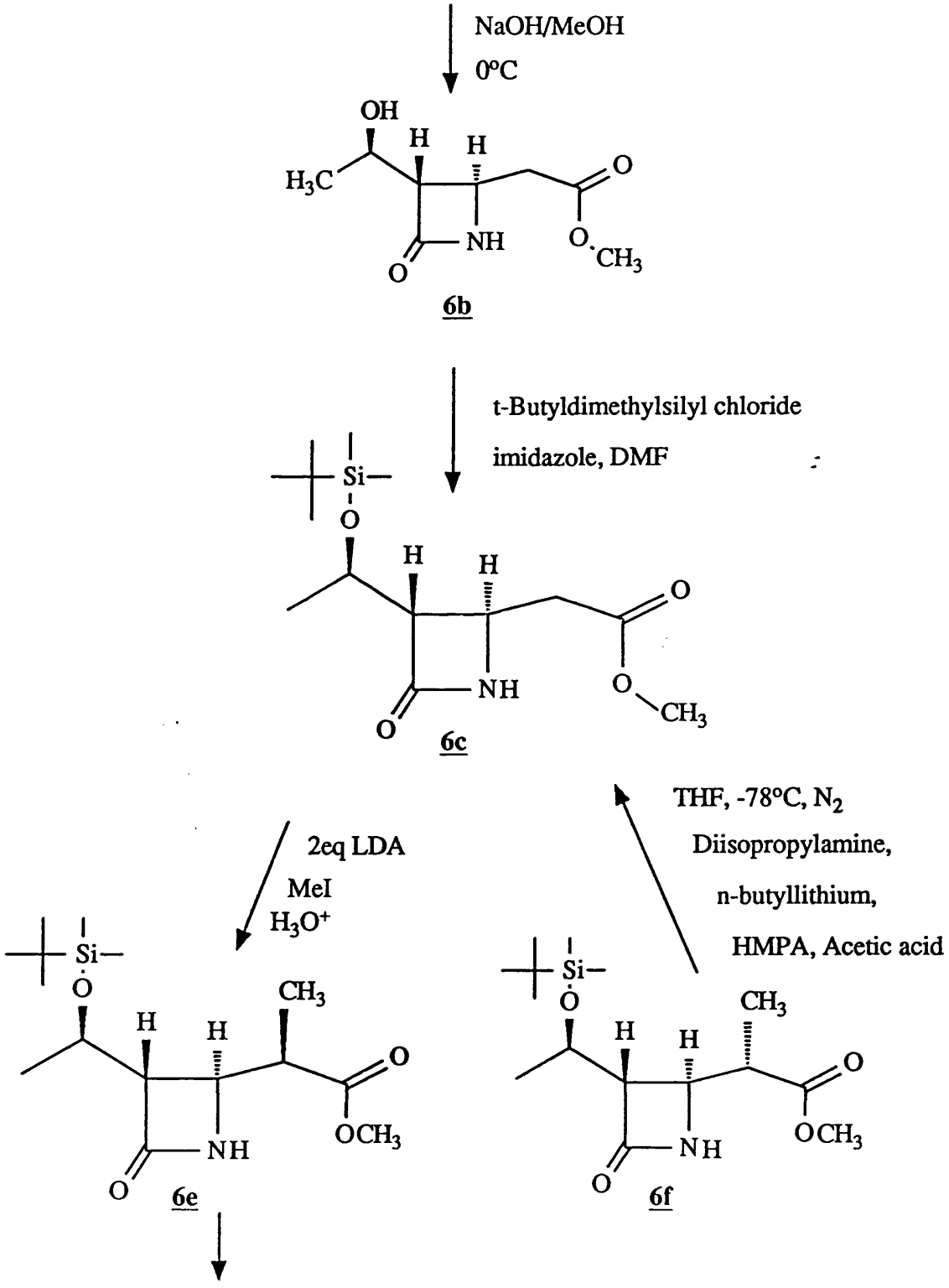


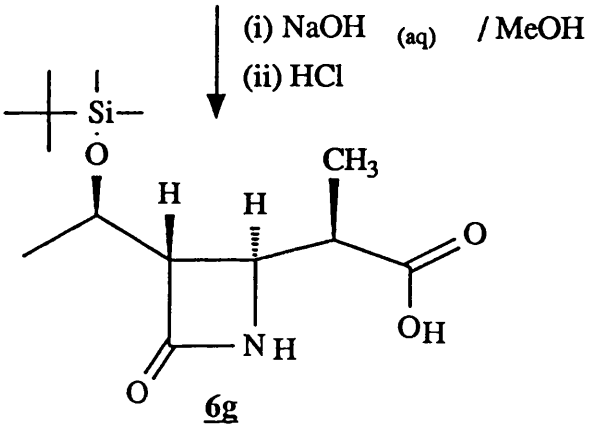
6

triphenylphosphene
diisopropyl azodicarboxylate
formic acid, THF

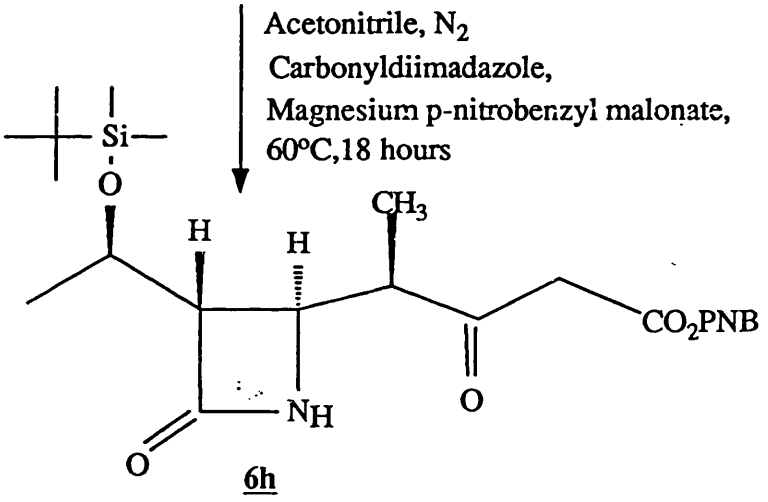


6a

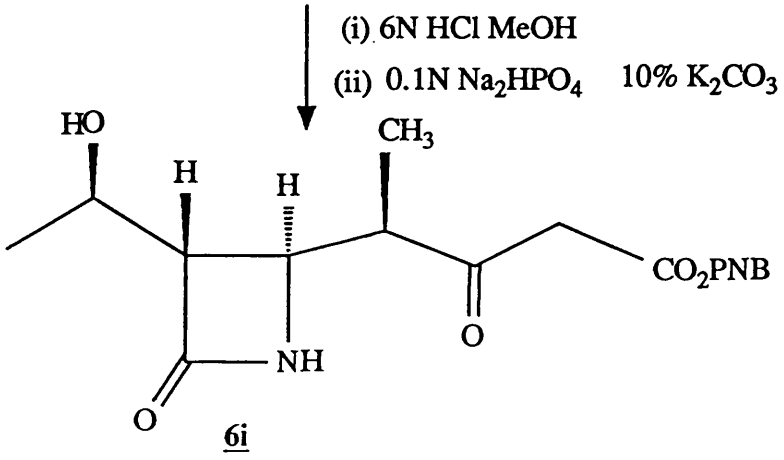

NaOH/MeOH
0°C
OH
H
H
H3C
O
NH
O
O
CH3
6b
t-Butyldimethylsilyl chloride
imidazole, DMF
Si
O
H
H
O
NH
O
O
CH3
6c
THF, -78°C, N2
Diisopropylamine,
n-butyllithium,
HMPA, Acetic acid
2eq LDA
MeI
H3O+
Si
O
CH3
H
H
O
NH
O
OCH3
6e
Si
O
CH3
H
H
O
NH
O
OCH3
6f


(i) NaOH (aq) / MeOH
(ii) HCl
Si
O
CH3
H
H
O
OH
NH
O

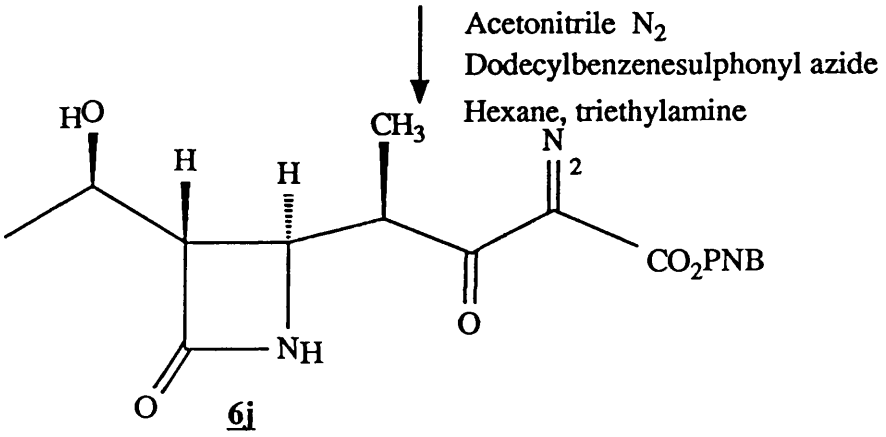
6g


Acetonitrile, N2
Carbonyldiimadazole,
Magnesium p-nitrobenzyl malonate,
60°C,18 hours
Si
O
CH3
H
H
CO2PNB
O
NH
O

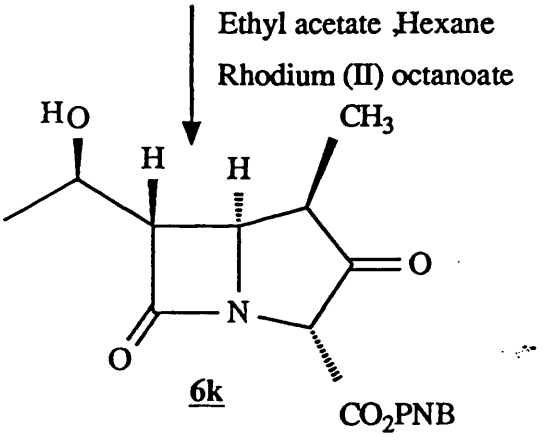
6h


(i) 6N HCl MeOH
(ii) 0.1N Na2HPO4 10% K2CO3
HO
CH3
H
H
CO2PNB
O
NH
O

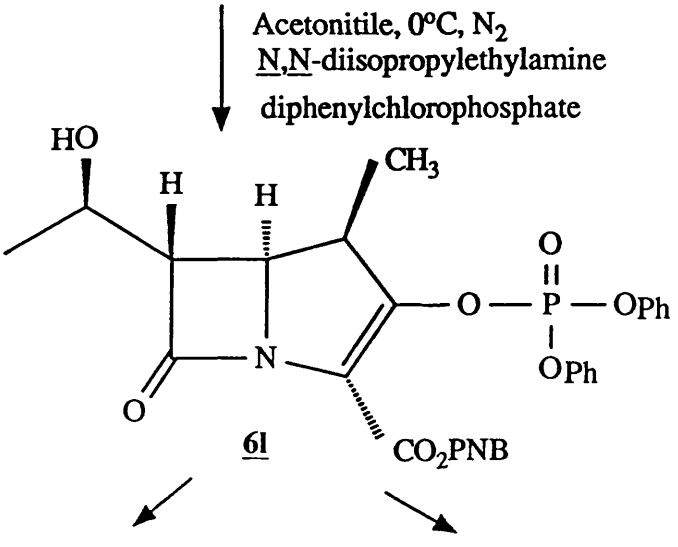
6i


Acetonitrile N_2
Dodecylbenzenesulphonyl azide
Hexane, triethylamine
HO
H
H
CH_3
N
2
CO_2PNB
O
NH
O

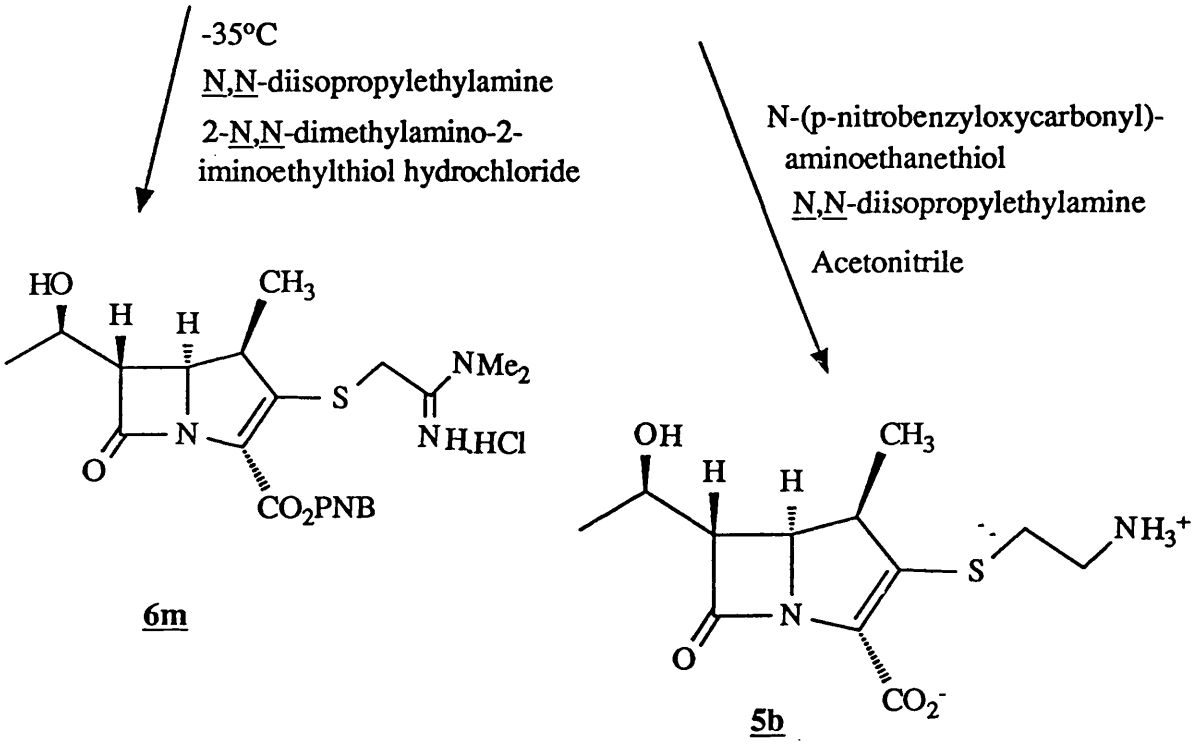
6j


Ethyl acetate ,Hexane
Rhodium (II) octanoate
HO
H
H
CH_3
O
N
O
CO_2PNB

6k

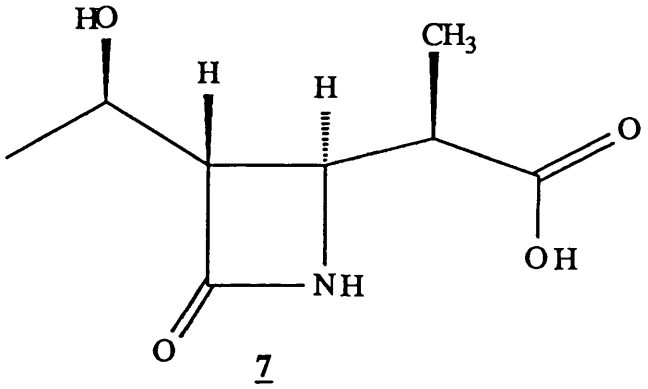

Acetonitile, 0°C, N_2
N,N-diisopropylethylamine
diphenylchlorophosphate
HO
H
H
CH_3
O
O — P — OPh
OPh
N
O
CO_2PNB

6l


-35°C
N,N-diisopropylethylamine
2-N,N-dimethylamino-2-iminoethylthiol hydrochloride
N-(p-nitrobenzyloxycarbonyl)-aminoethanethiol
N,N-diisopropylethylamine
Acetonitrile
HO
H
H
CH3
NMe2
S
N
O
NH.HCl
CO2PNB
6m
OH
H
H
CH3
NH3+
S
N
O
CO2-
5b
n-Butanol, Ethyl acetate,
N-methylmorpholine,
H2O, NaHCO3,
Pd(OH)2/C, H2
HO
H
H
CH3
NMe2
S
N
O
NH
5a
CO2H

Scheme 1

The major problem with this synthesis is attaining the correct stereochemistry at C-5 of 7.



7

The current syntheses of the 1β-methylcarbapenems focus on the stereoselective synthesis of this key intermediate 7 which has four contiguous chiral centres. [20-26] The syntheses of 7 reported over the past few years have been lengthy or non-stereoselective and are mostly unsatisfactory.

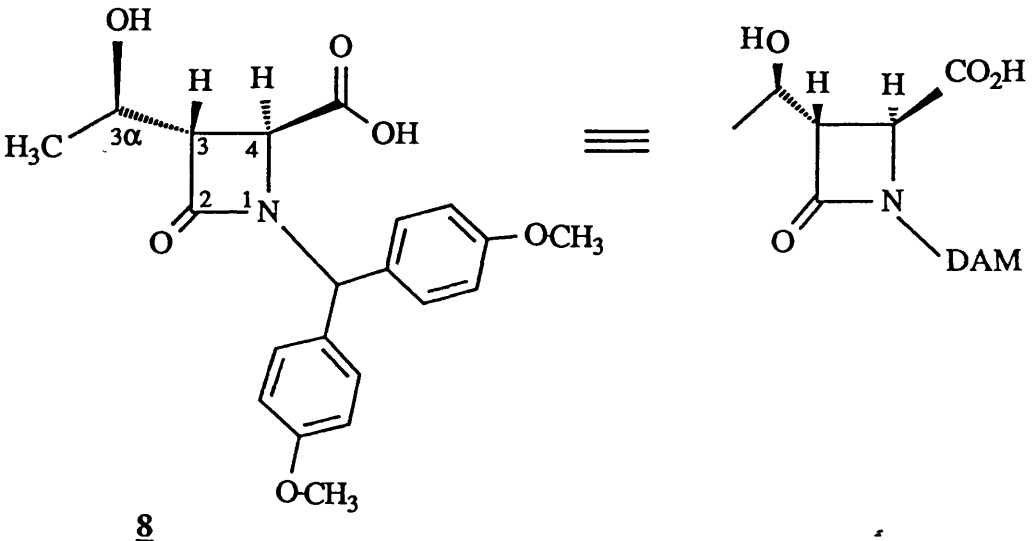
1.2.3 Synthetic strategy adopted in this project

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.

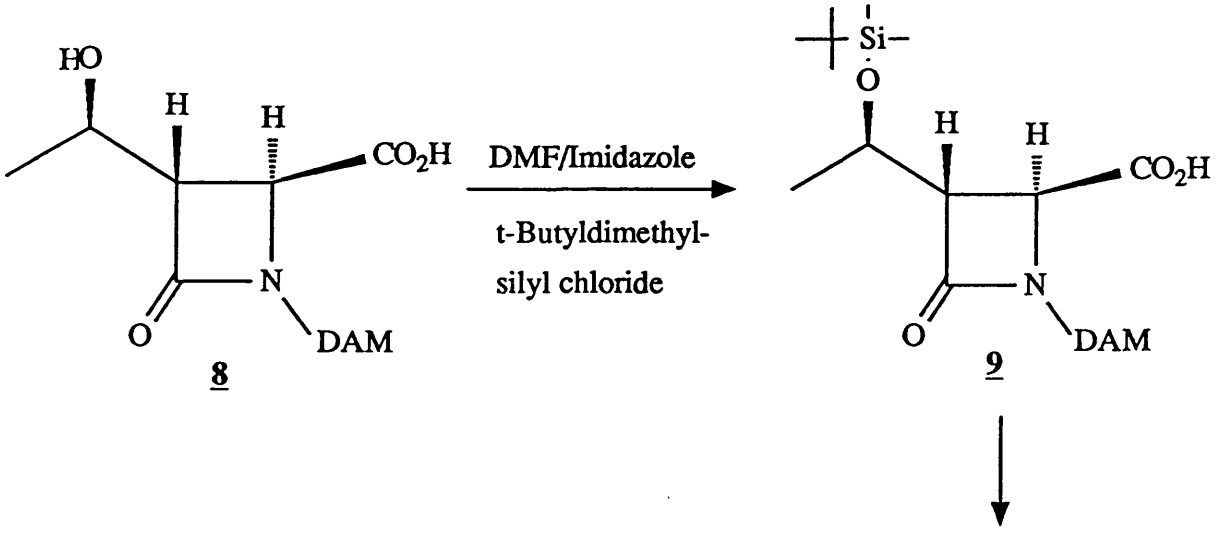
It has now been accepted that the monocyclic β-lactam functionality is fairly stable, but the introduction of the second ring further strains and destabilizes the β-lactam making it highly reactive.[35,36]

In this scheme (**Scheme 2**), the free alcohol at C-3α was first protected

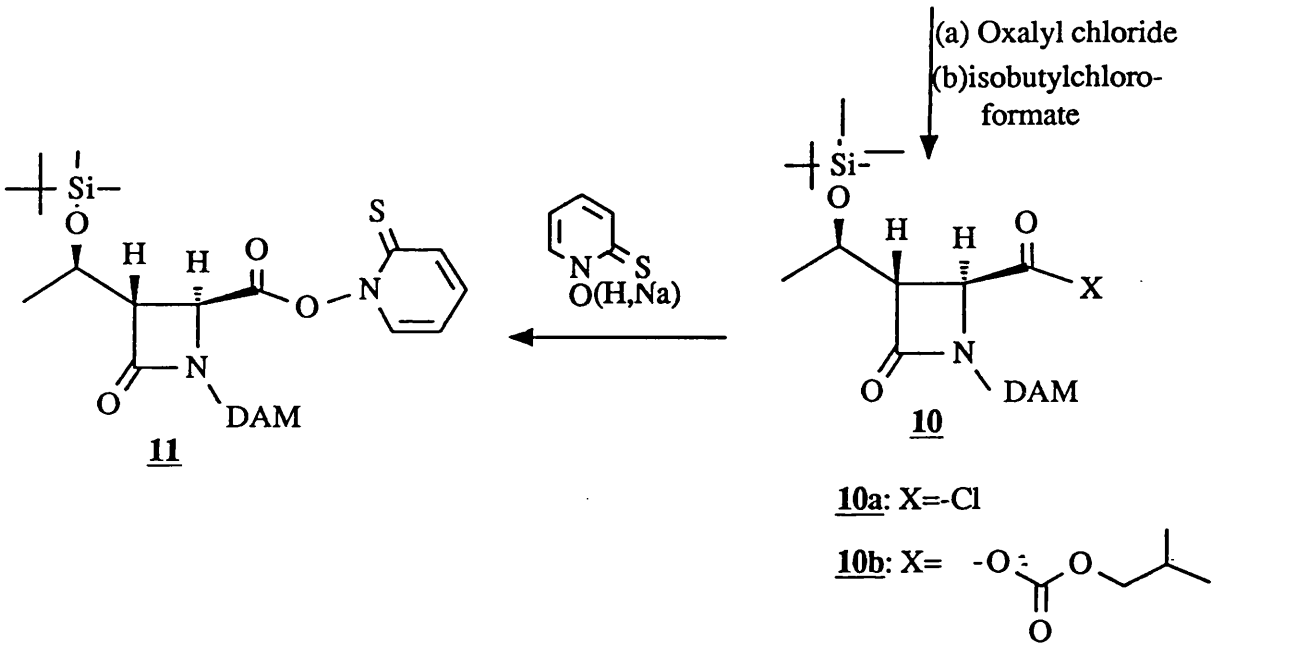


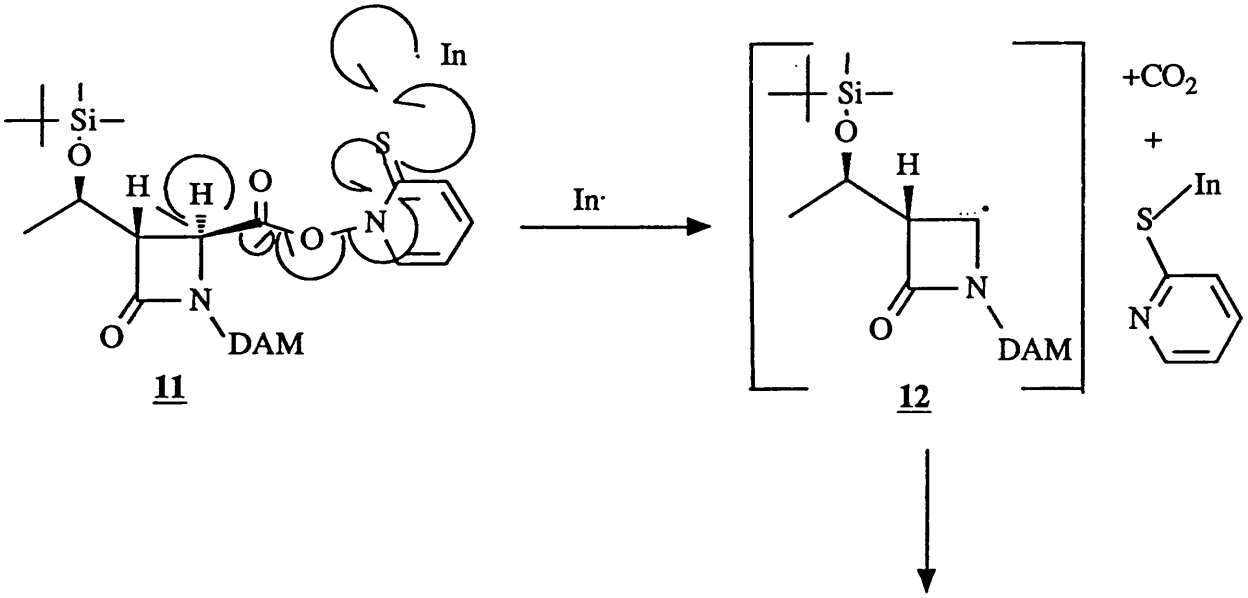
8

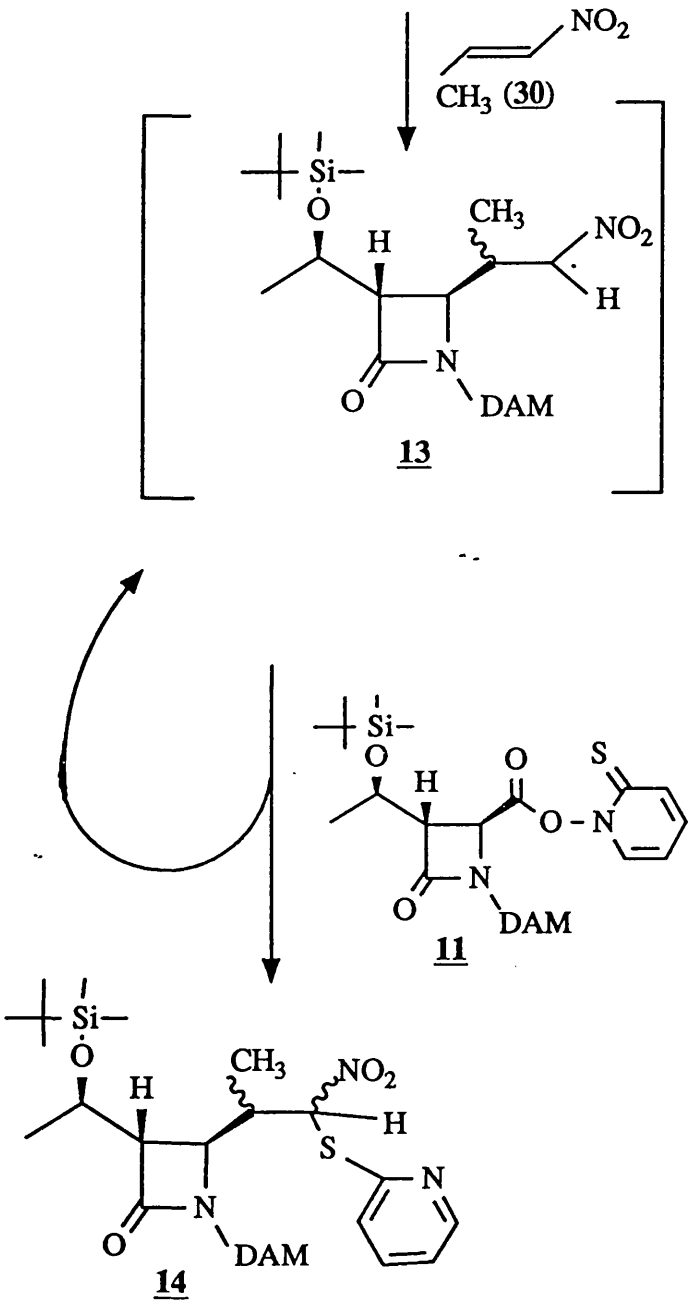
with the t-butyldimethylsilyl group. The free radical at C-4 was then generated using Barton's method. **4-Azetidinonyl** radicals have been generated previously and have been shown not to undergo ring opening.[45]



8 9


(a) Oxalyl chloride
(b)isobutylchloro-
formate
O(H,Na)
DAM
10
11
10a: X=-Cl
10b: X=


In
In·
DAM
11
12
+CO2
+



Scheme 2

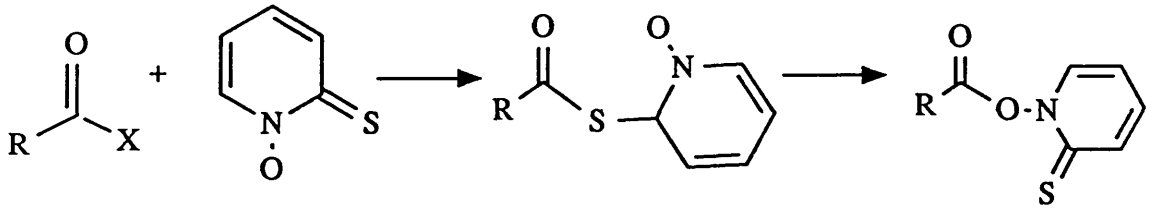
The procedure to be used for the generation of the radical **12** is as follows : The acid **9** is first activated to the acid chloride **10a** or the mixed anhydride **10b**,

followed by its esterification to the thiohydroxamate ester **11**. The ester **11** is then allowed to react with the nitro-olefin **30**[32] 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

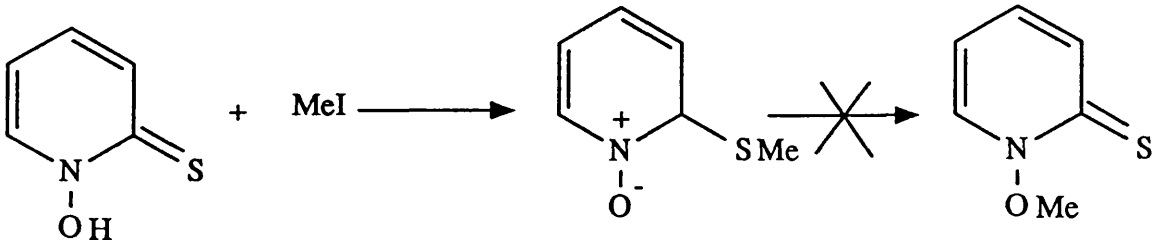
The chemistry of the thiohydroxamate esters has been thoroughly studied by **Barton** et al. The esters were probably formed via the isomeric 2-acylthiopyridine-N-oxides,[41] which then rearrange intramolecularly to give the O-acylthiohydroxamate esters **(Scheme 3)**.



Scheme 3

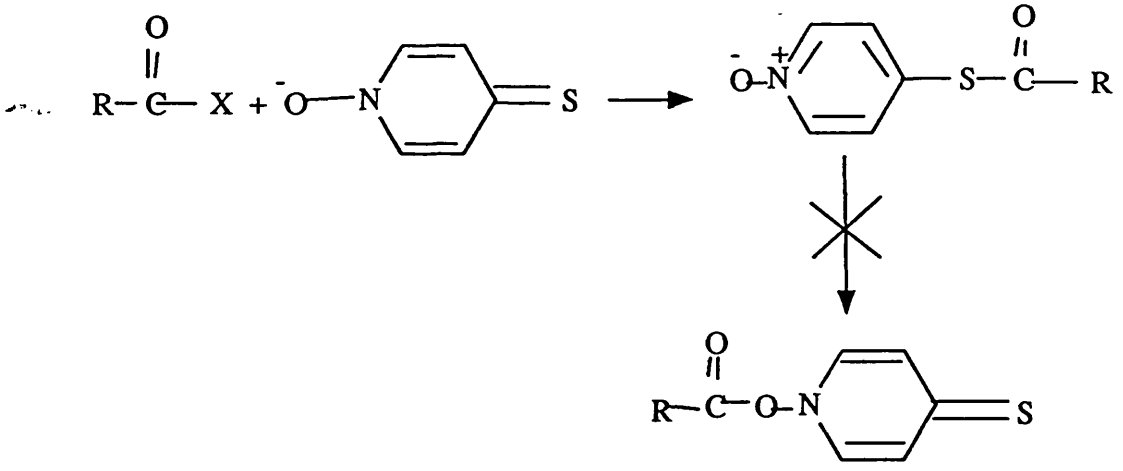
Support for this hypothesis was provided by the fact that 2-mercaptopyridine-N-oxide reacts with methyl iodide to give isolable, stable, 2-methylmercaptopyridine-N-oxide which cannot favourably rearrange

intramolecularly (**Scheme 4**).



Scheme 4

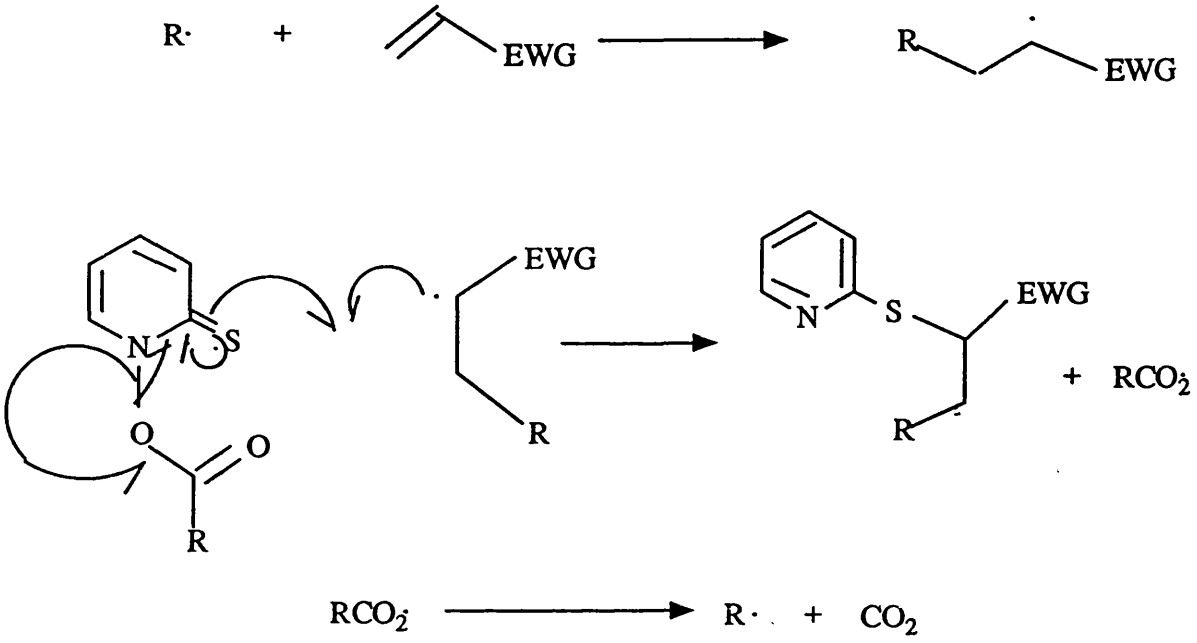
Support was also provided by the fact that acylation of the vinylogous thiohydroxamic acid 4-mercaptopyridine-N-oxide leads mainly to the 4-acylthiopyridine-N-oxide which is incapable of intramolecular rearrangement to the O-acyl compounds (**Scheme 5**).[42]



Scheme 5

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]



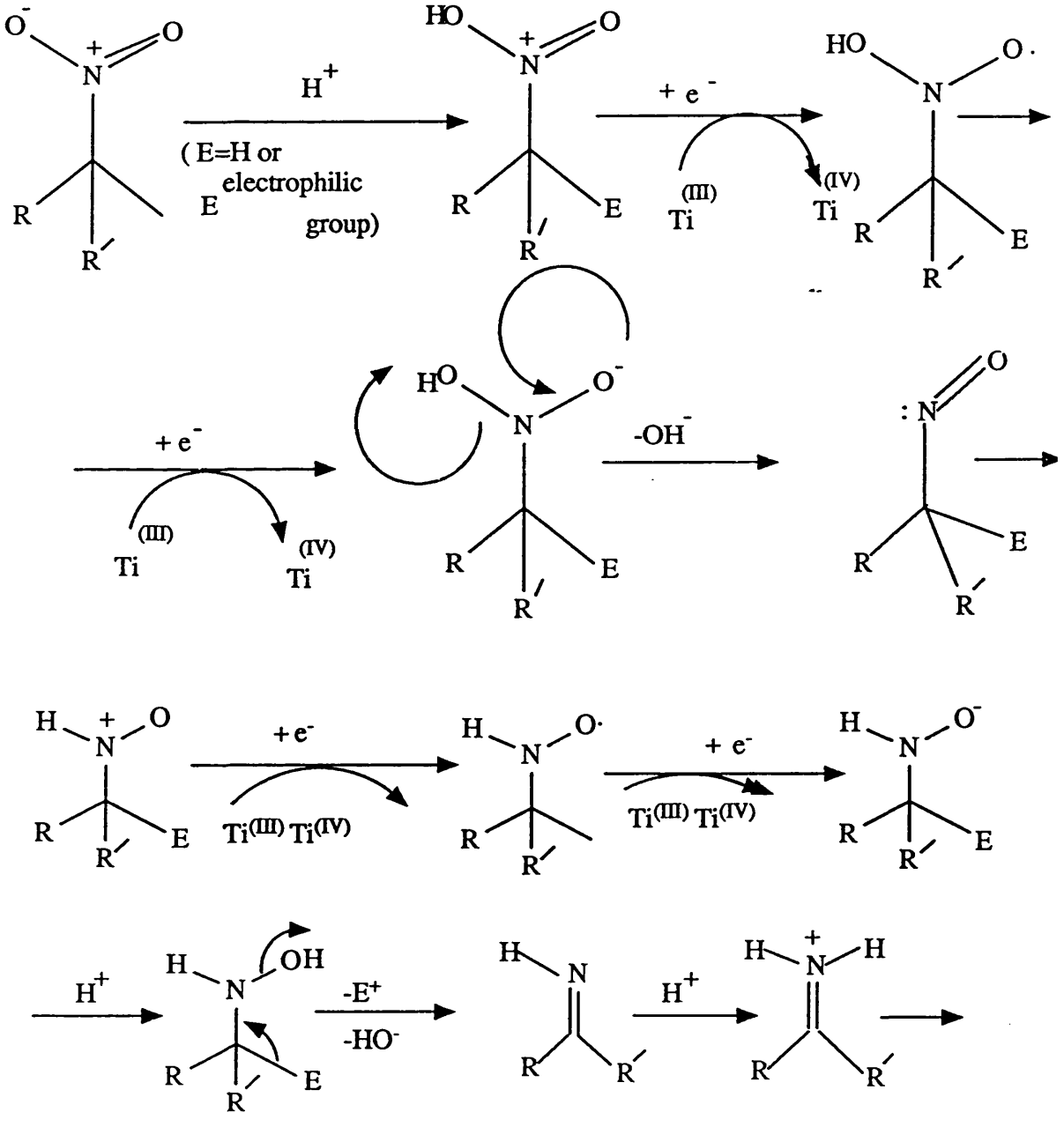
Scheme 6

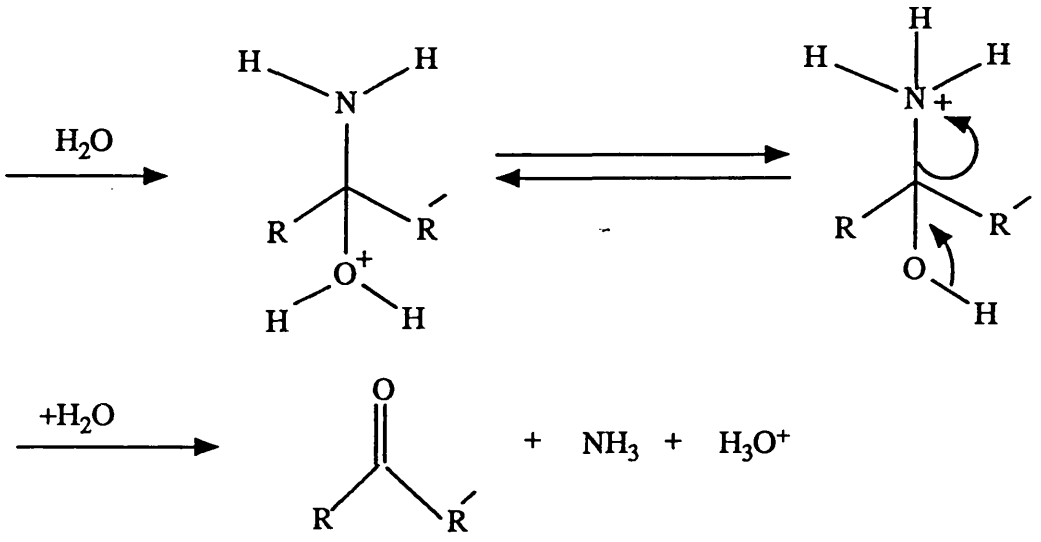
In our proposed synthetic scheme, advantage is taken of this regioselective addition of the radical generated to the nitro-olefin.

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**).



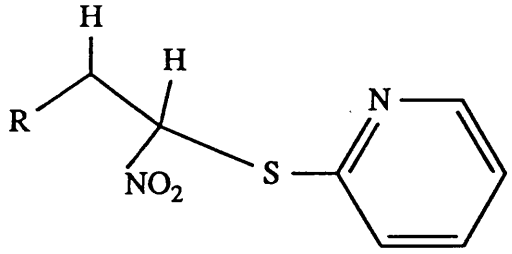


Scheme 7

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.

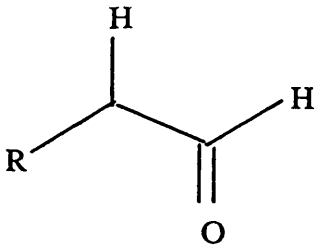
The attraction of this method is that it could be carried out at a buffered pH of 5 or 6 which is desirable for the β-lactam system. Barton,[32] using this method on **15**, reported obtaining the aldehyde **16**.

Hence, if McMurray's method were applied to **14**, the aldehyde **17** would be the expected product. Compound **17** may then be oxidized to the acid **18**.



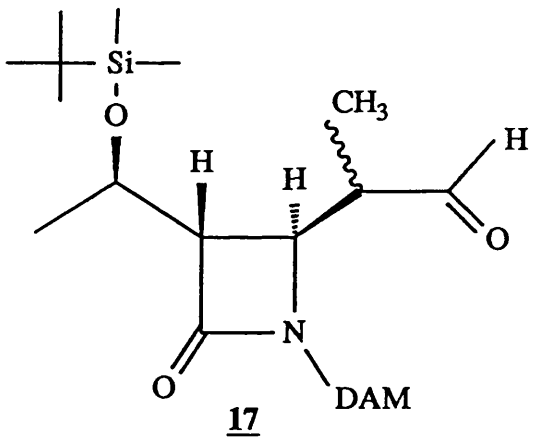
(R= 1-adamantyl)

15

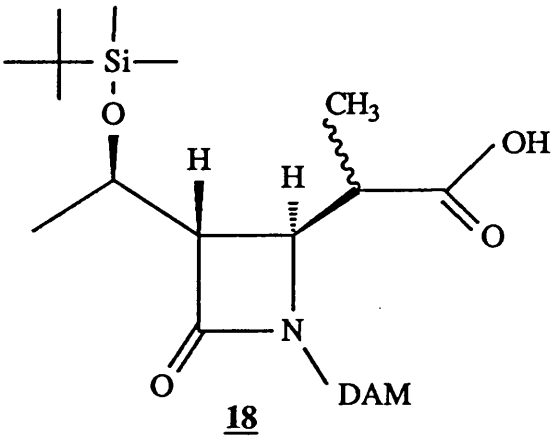


(R= 1-adamantyl)

16

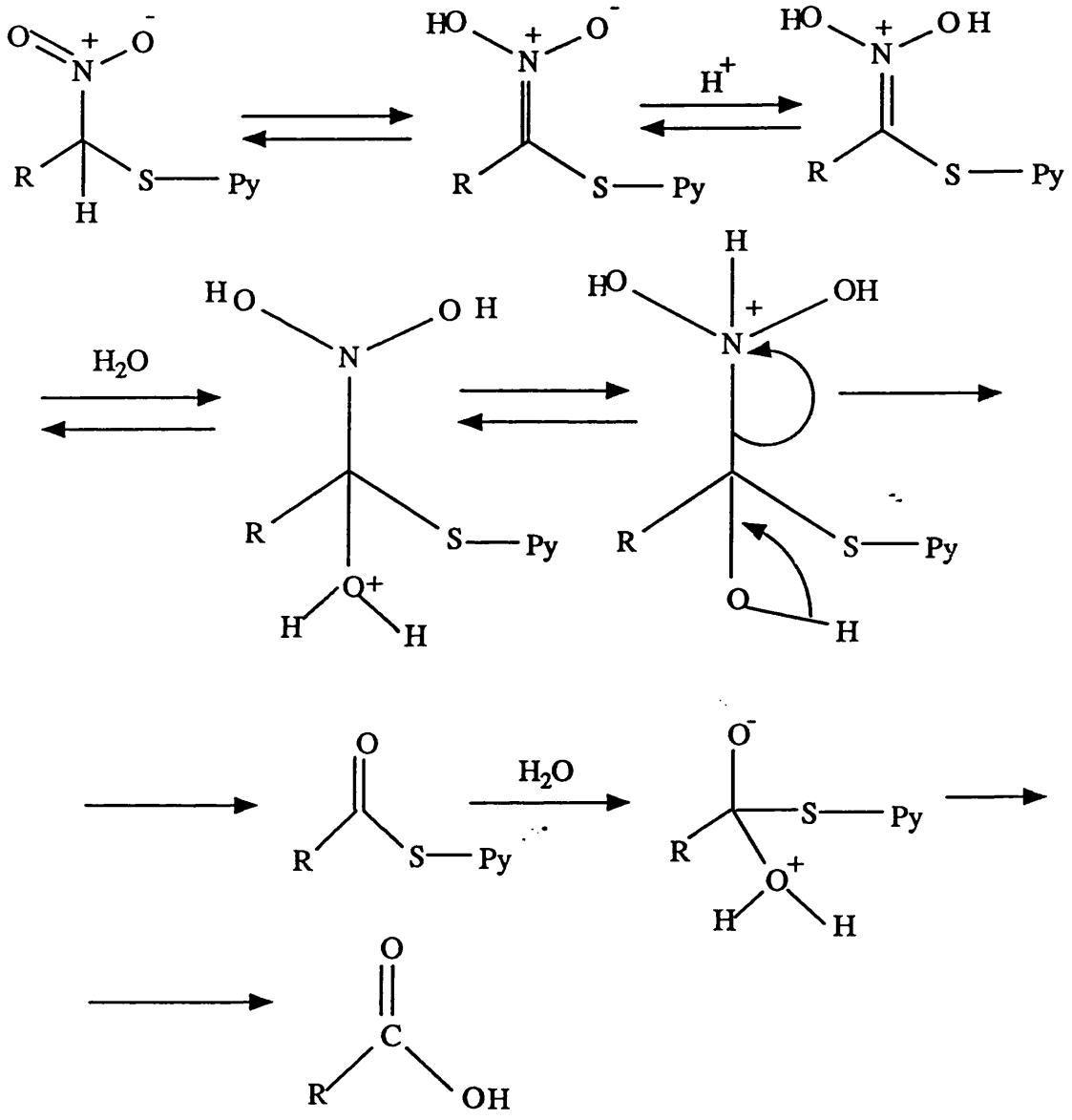


17



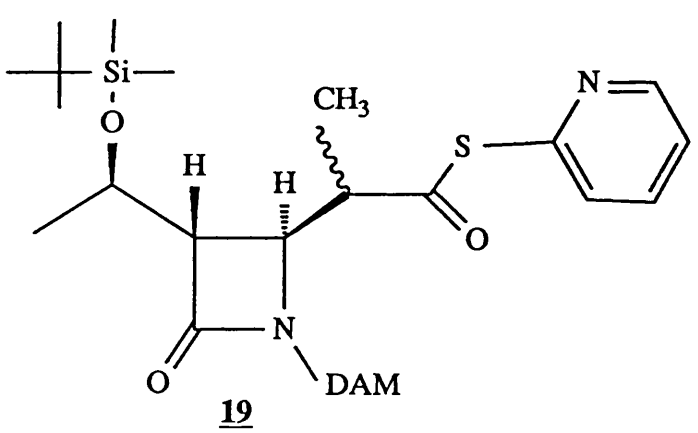
18

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**).

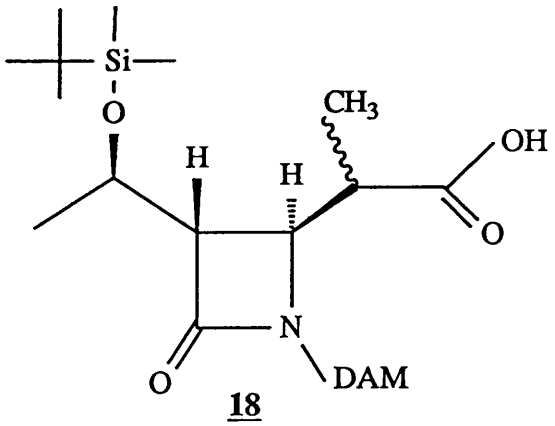


Scheme 9

Thus if this reaction took place the products would be **19** and **18**.



19



18

Barton,[32] also reported the conversion of the α-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 α-hydrogen. Barton also reported the use of iodoxybenzene (**$PhIO_2$**) as an oxidizing agent. The use of ozone is yet another possibility.[44]

1.2.6 Removal of the protecting groups

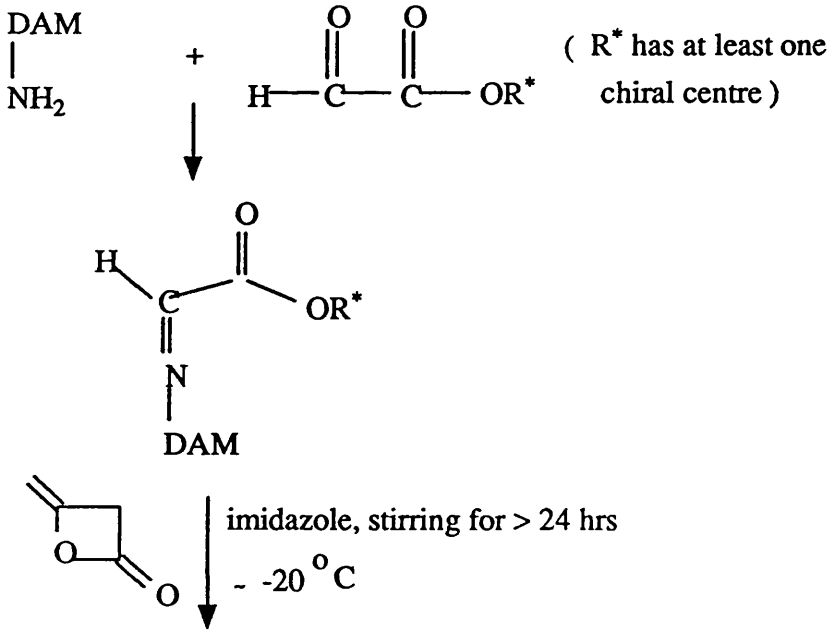
The DAM group protecting the β-lactam nitrogen may be removed by stirring with aqueous ceric ammonium nitrate and acetonitrile at around room temperature,[26,46] or by stirring with anisole and trifluoroacetic.[33]

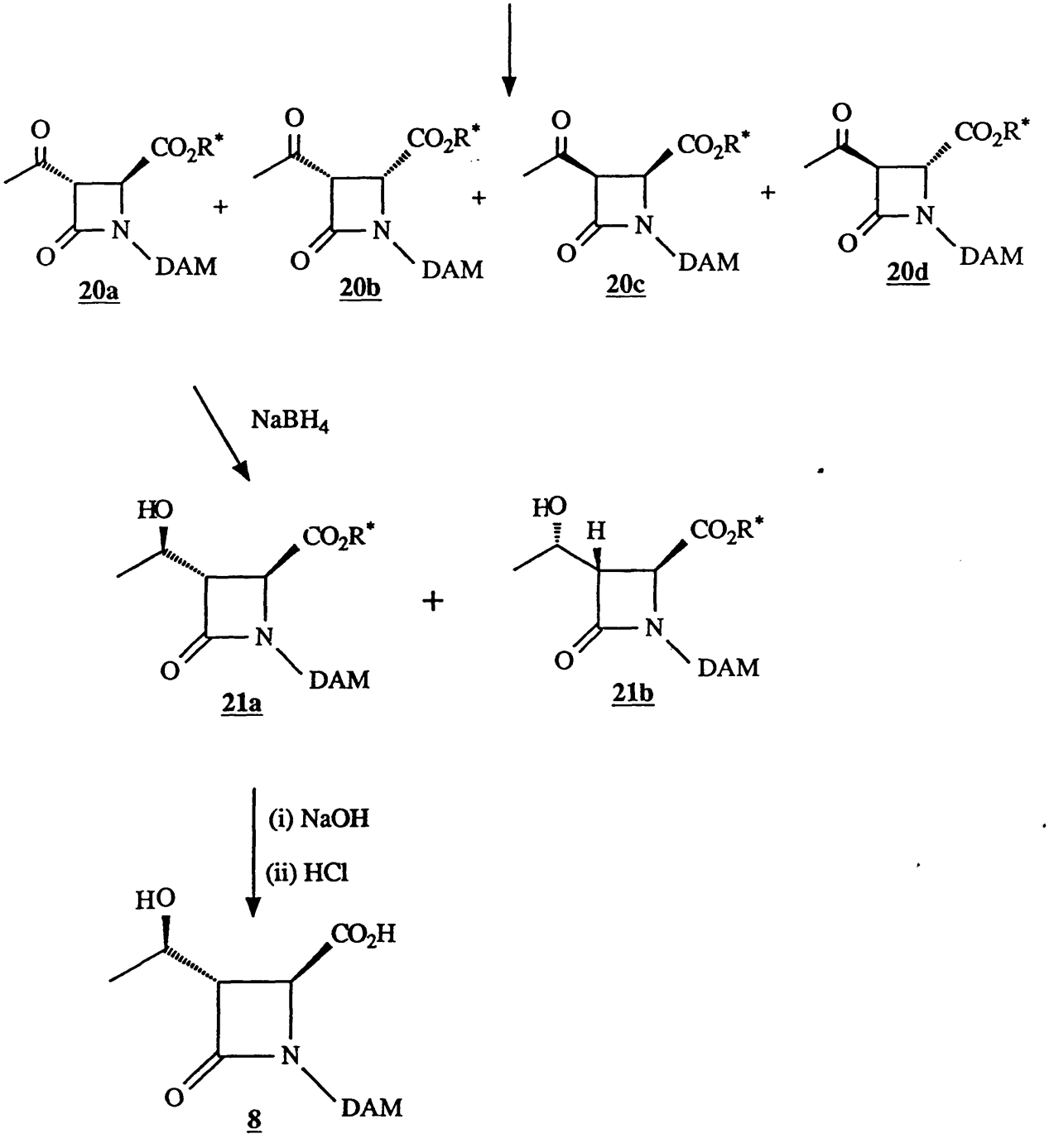
The t-butyldimethylsilyl group protecting the alcohol may be removed by refluxing in dichloromethane with 1,3-dimethoxybenzene and boron trifluoride etherate to give the target molecule 7.[46]

1.2.7 Preparation of 8

The starting compound 8 was synthesized by the **Sumitomo Pharmaceutical Co Ltd,**[47] using the [2+2] cycloaddition of diketene with the appropriate imine generated in situ (**Scheme 10**).[26,34] 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,[26] 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.





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.[71] 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.[72] 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.[73] 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.[74,75] The theoretical calculations were confirmed by experimental findings.[76,78] 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.[77] 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,[79] and to enzyme attack by both endopeptidases,[80] and exopeptidases.[81]

Thirdly the increased lipophilicity concurred by the α-methyl group

promotes greater penetration of cell walls.[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 potentiate 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.[83]

1.3.3 Asymmetric α-alkylation of α-amino acids

Two substantially different concepts have been developed for the asymmetric α-amino acids;[84] the **Schöllkopf bis-lactim ether Method,**[85] which relies on a second α-amino acid as chiral auxilliary, and the **Seebach Self-Reproduction of Chirality Method** in which the amino acid to be alkylated is itself used as a source of chirality.[86]

1.3.4 The Schöllkopf bis-lactim ether method

Schöllkopf's approach is based on heterocyclic chemistry and has the following strategy.[85]

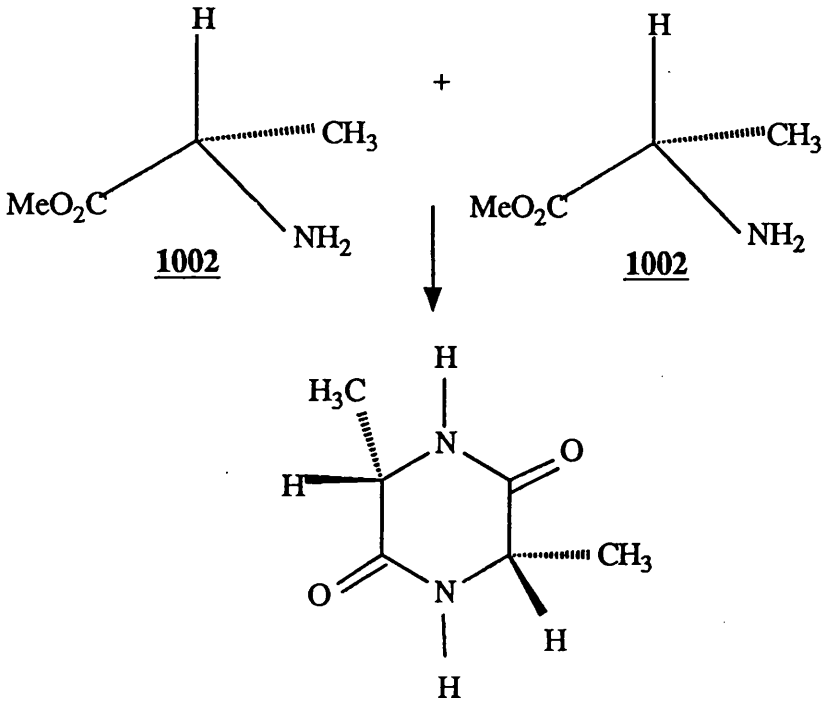
1. From a readily available racemic lower amino acid and a chiral auxiliary, a heterocycle is built up which is CH-acidic adjacent to the potential amino group and which contains 2 sites susceptible to hydrolysis.

2. An electrophile is introduced diastereoselectively via the anion of the heterocycle.

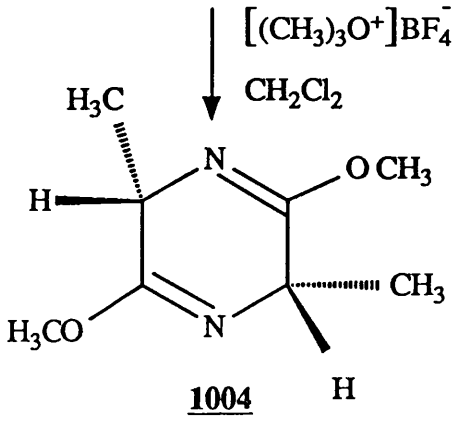
3. Subsequently the heterocycle is cleaved by hydrolysis to liberate the chiral auxiliary and the new optically active amino acid.

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.

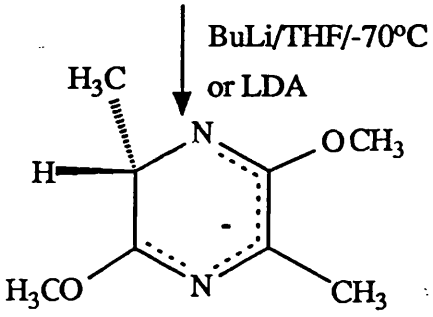
This strategy may be illustrated with **L-alanine** as an example, which results in an **α-alkyl-α-methyl amino acid** being synthesized **(Scheme 11)**.



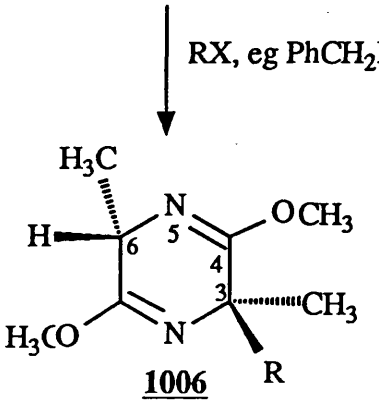
1003



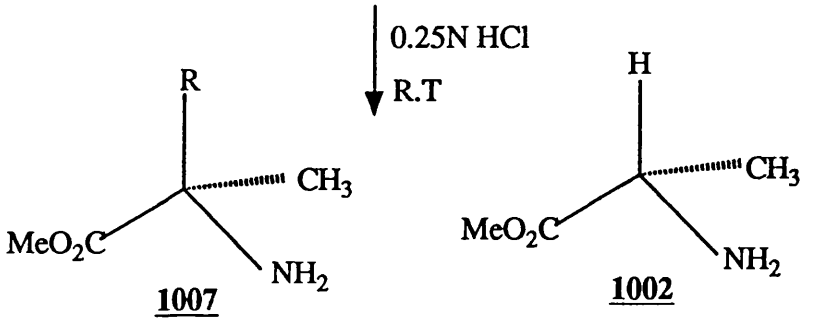
1004



1005



1006

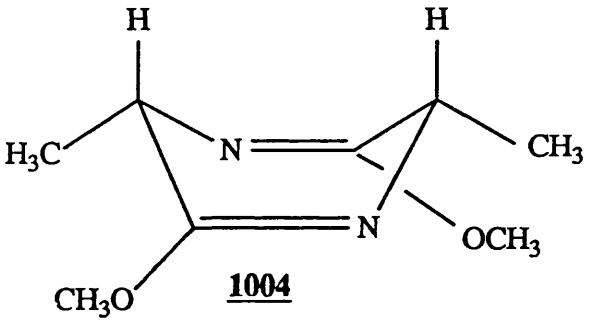


Scheme 11

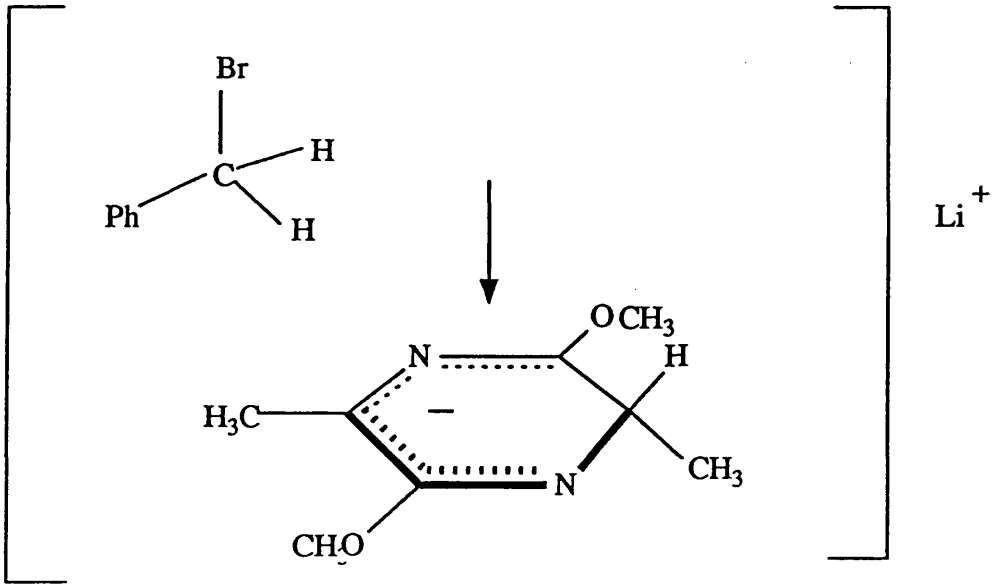
On heating of L-alanine methyl ester **1002**, two molecules condense to give the diketopiperazine [cyclo(L-Ala-L-Ala)], **1003**. In this reaction, the optical purity was reduced. Recrystallization from water gave **1003** with about 93% ee.[87] Compound **1003** is not a suitable starting material 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.

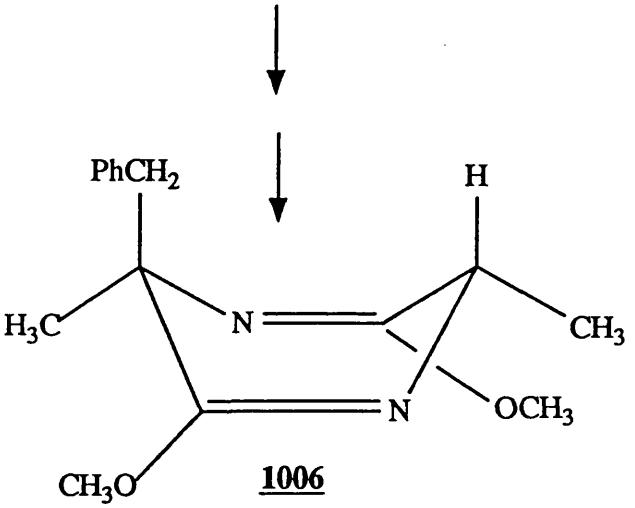
The stereochemistry of this reaction is explained on the basis that it proceeds via a planar transition state of the anion **1005**, and that the electrophile approaches it from the less hindered face, **(Scheme 12)**.



1004



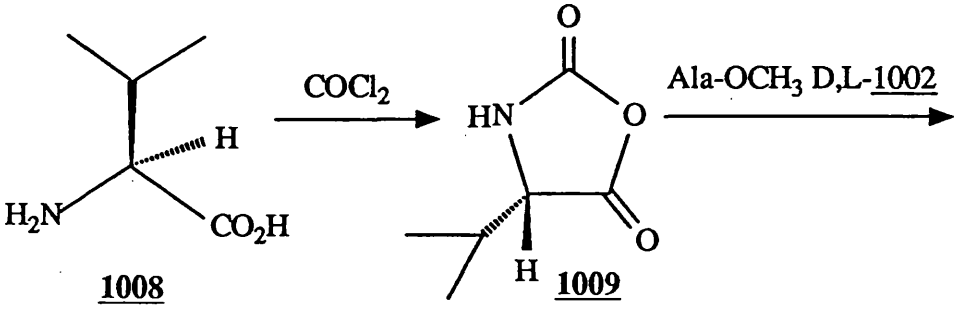
1005



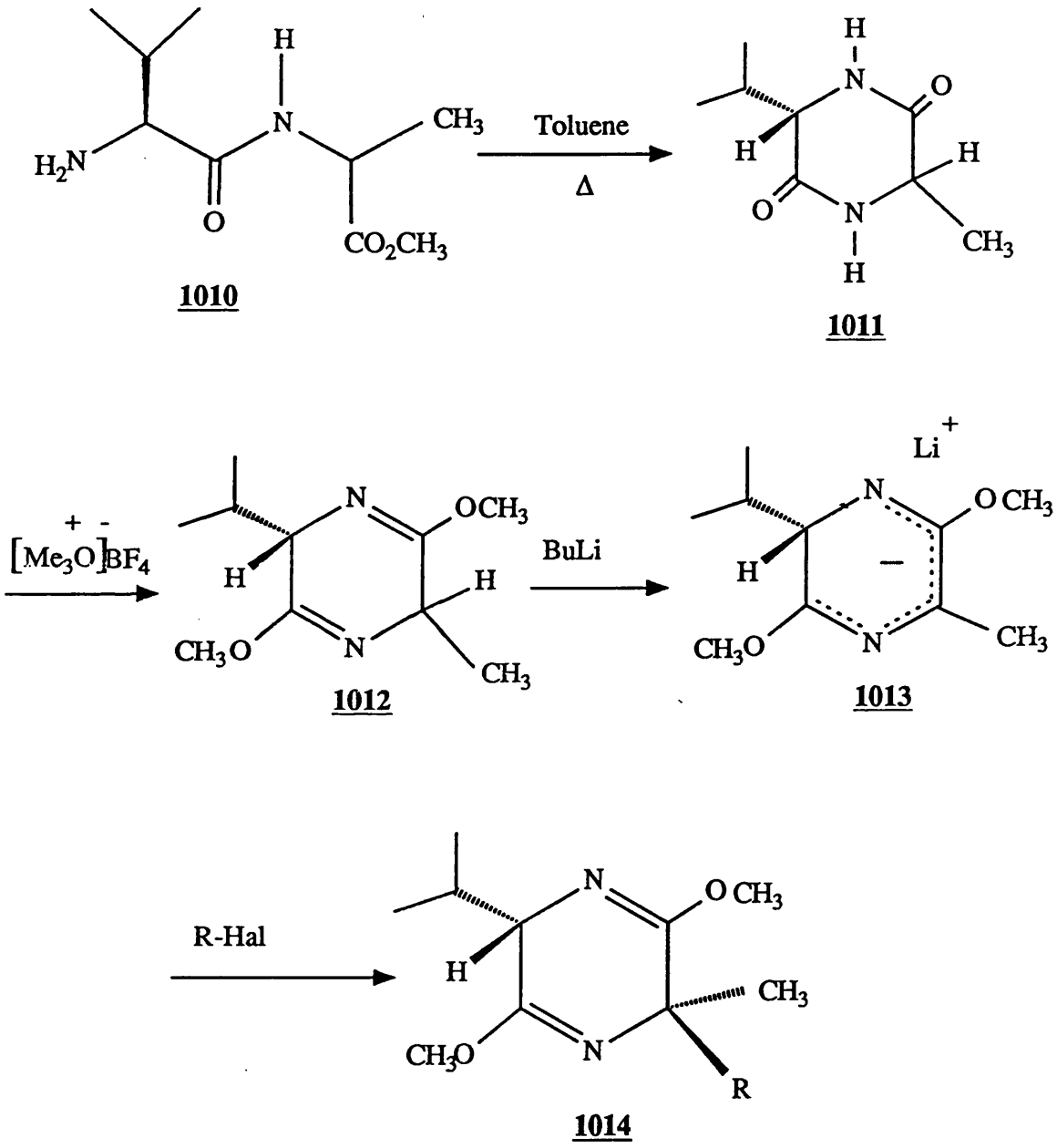
1006

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.**



1008 **1009**



1010 1011 1012 1013 1014

Scheme 13

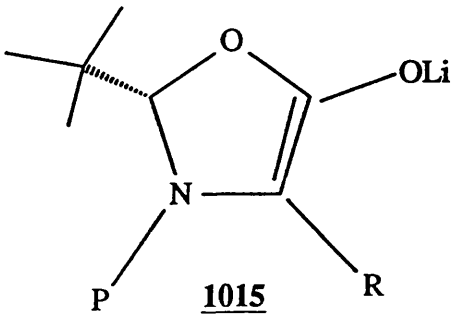
L-valine **1008** , the chiral auxiliary was converted with phosgene into N-carboxyanhydride (L-Val-NCA) **1009**.[90] This gave with D,L-Ala-OCH_3 the dipeptide **1010**, which on heating in toluene cyclizes to the diketopiperazine **1011**.

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 (3**R**) configuration. On hydrolysis, the α-alkylated alanine formed has the configuration of **L-alanine.**

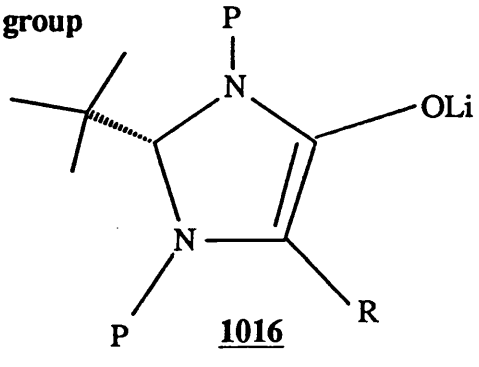
1.3.5 Seebach's Self-Reproduction of Chirality Method

Seebach's so called **Self-Reproduction of Chirality Method** is an elegant method for the preparation of α-alkyl disubstituted amino acids.[83] Principally, it makes use of the cyclic lithium anion intermediates **1015**[91] and **1016**[92] which are then quenched stereoselectively by a number of electrophiles.

P= Protecting group



1015

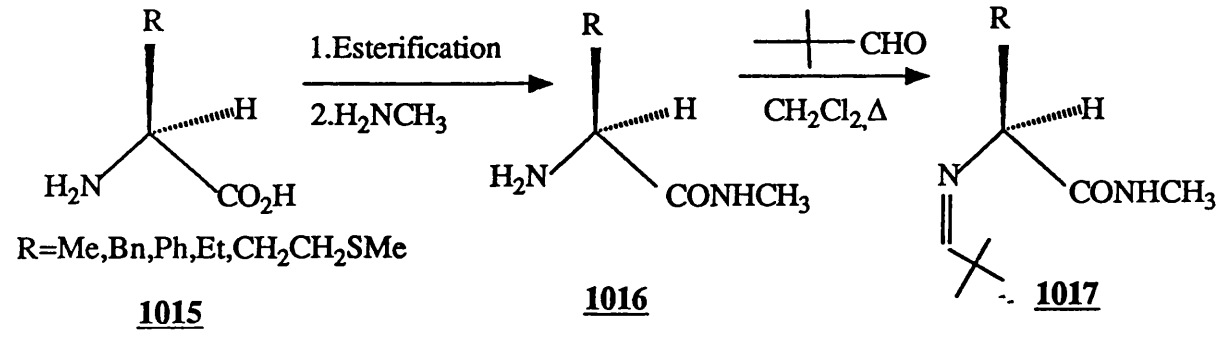


1016

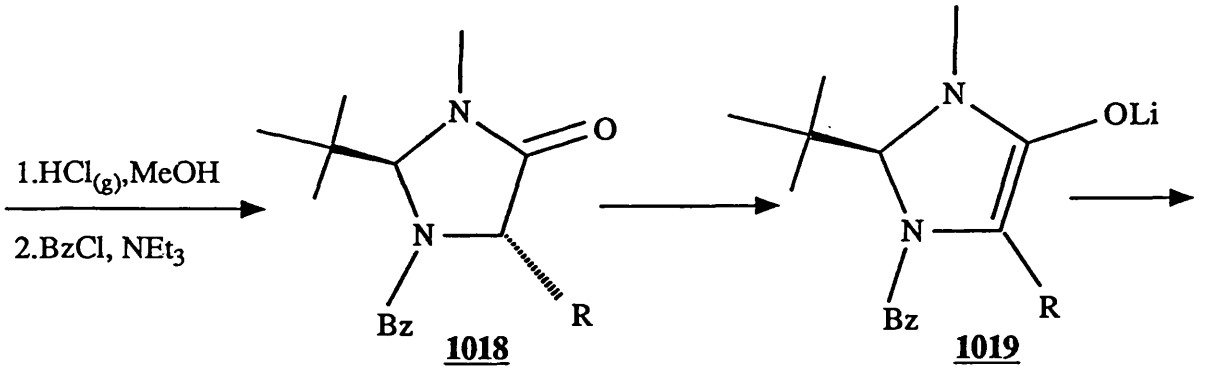
Chiral induction is achieved by making use of the chirality inherent in the starting α-amino acid which dictates the configuration of the lithium intermediates

1015 and 1016. Hence unlike **Schöllkopf's** method, chiral induction is not achieved with a chiral auxiliary.

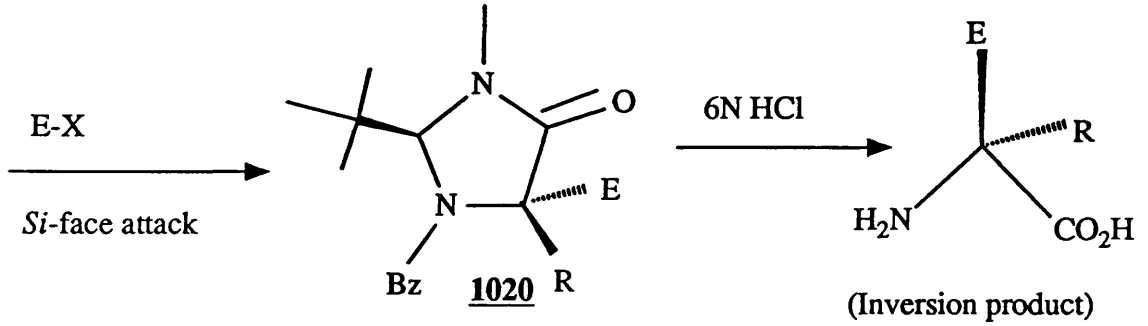
The chiral imidazolidinone or the oxazolidinone are formed by relatively standard procedures (**Schemes 14** and **15**).[93]



1015 1016 1017

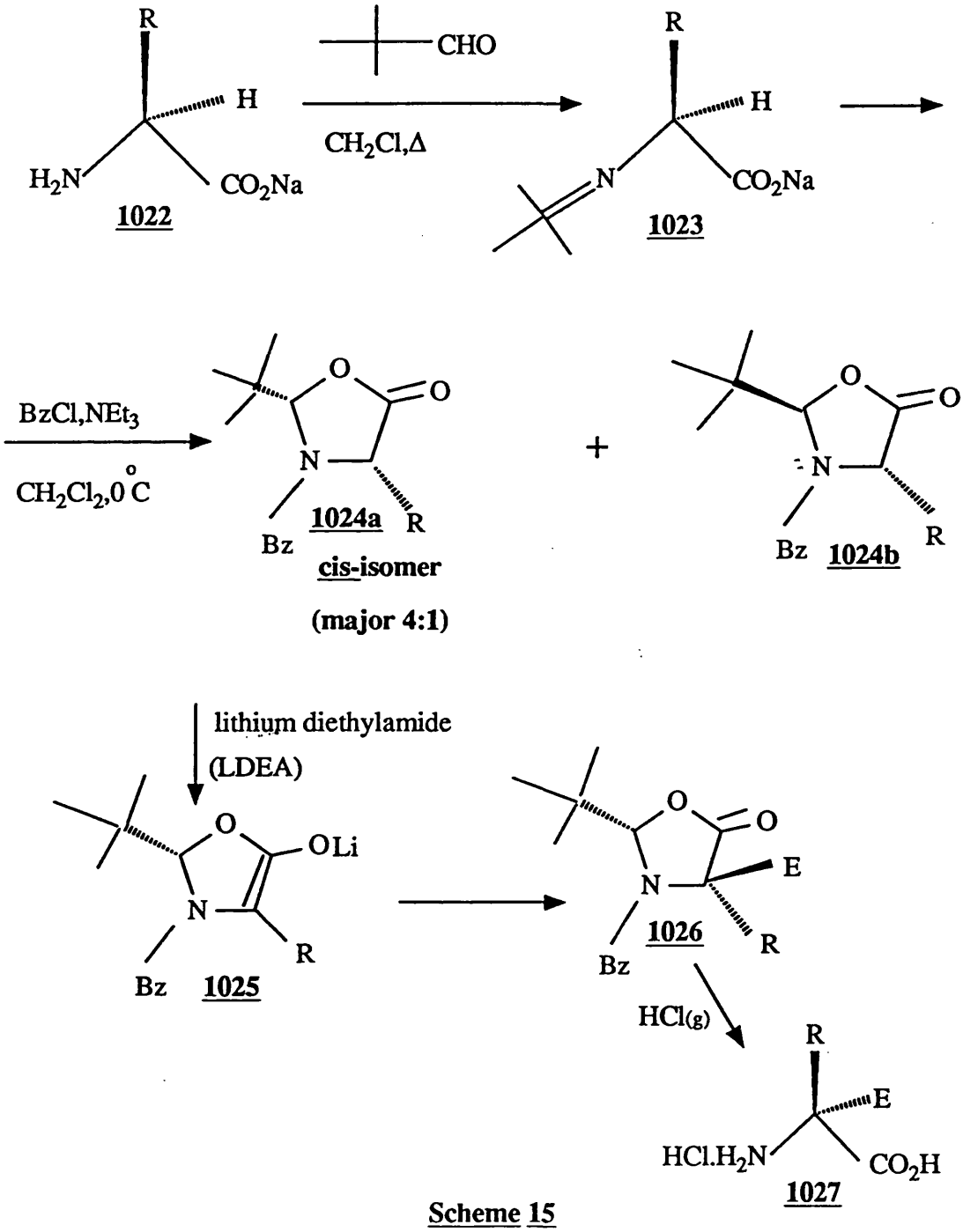


1018 1019



1020 1021

Scheme 14



Scheme 15

With the imidazolidinone, the α,α-**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.[91,93]

The imidazolidinone **1018** was formed by first condensing the protected chiral α-amino acid **1016** with pivaldehyde to form the imine **1017**.[91] 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;[94] carbonyl compounds[95]) 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.[91]

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),[96] 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.

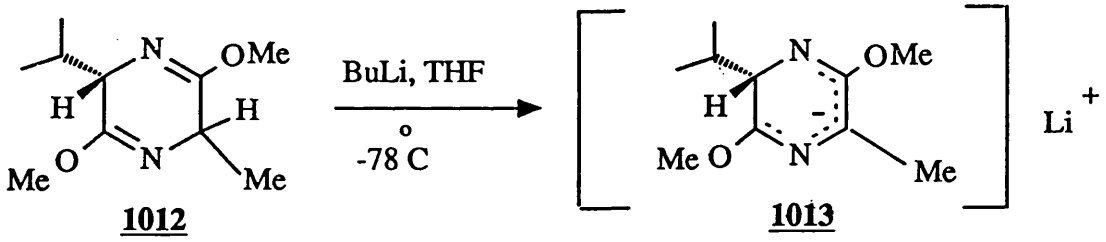
Although both methods are comparable in terms of reactivity and stereoselectivity (and it should be noted that both **cis** and **trans** isomers of **1018**

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]

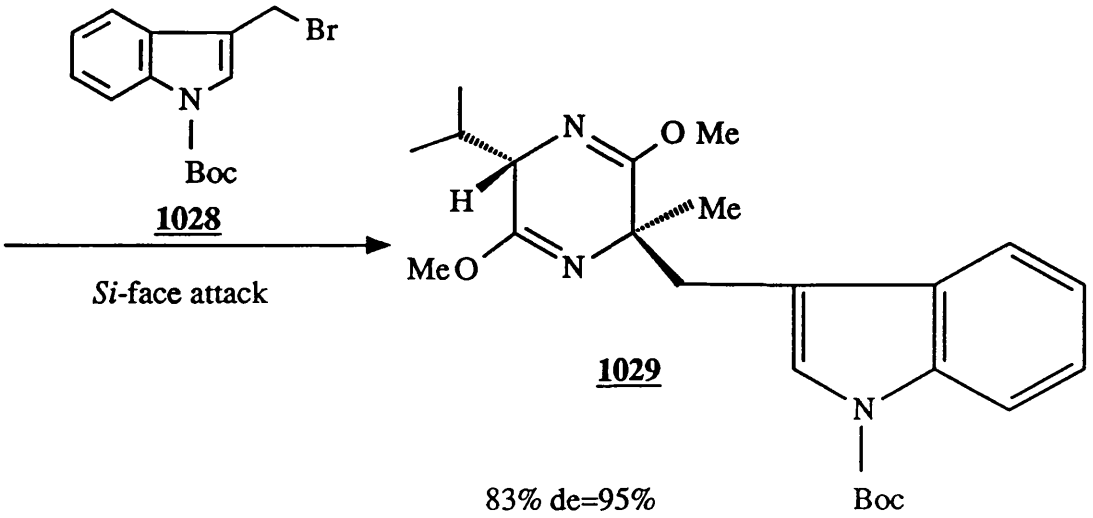
Both the Schöllkopf and Seebach methods have been applied to the synthesis of optically active α-substituted tryptophan.

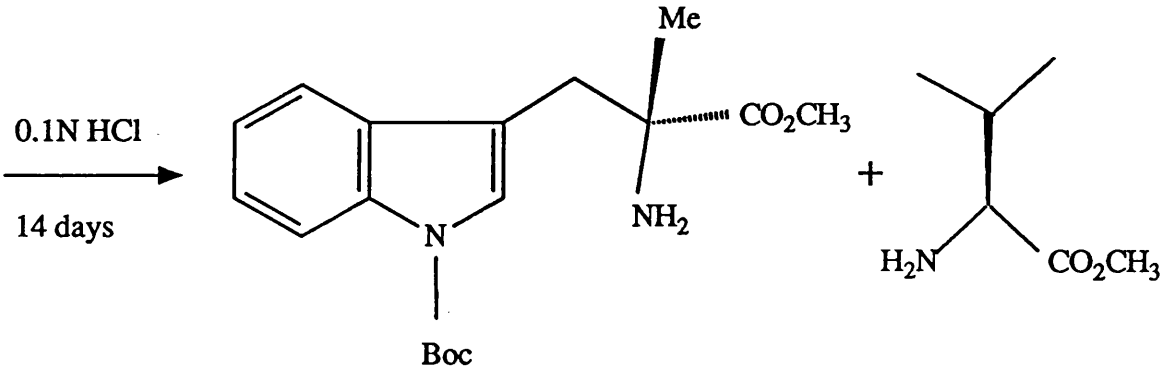
1.3.6 Schöllkopf's method in the synthesis of α-methyl tryptophan

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.



1012 **1013**





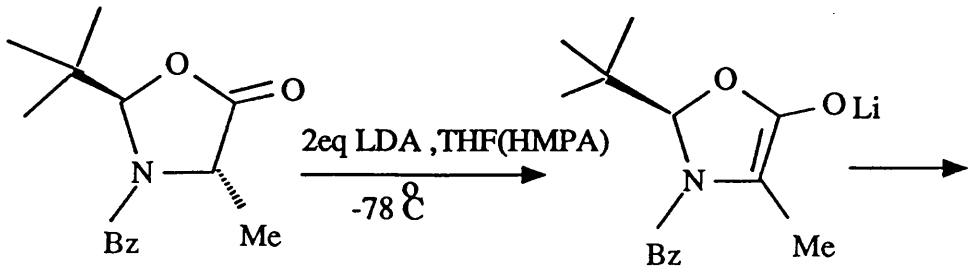
1030

Scheme 16

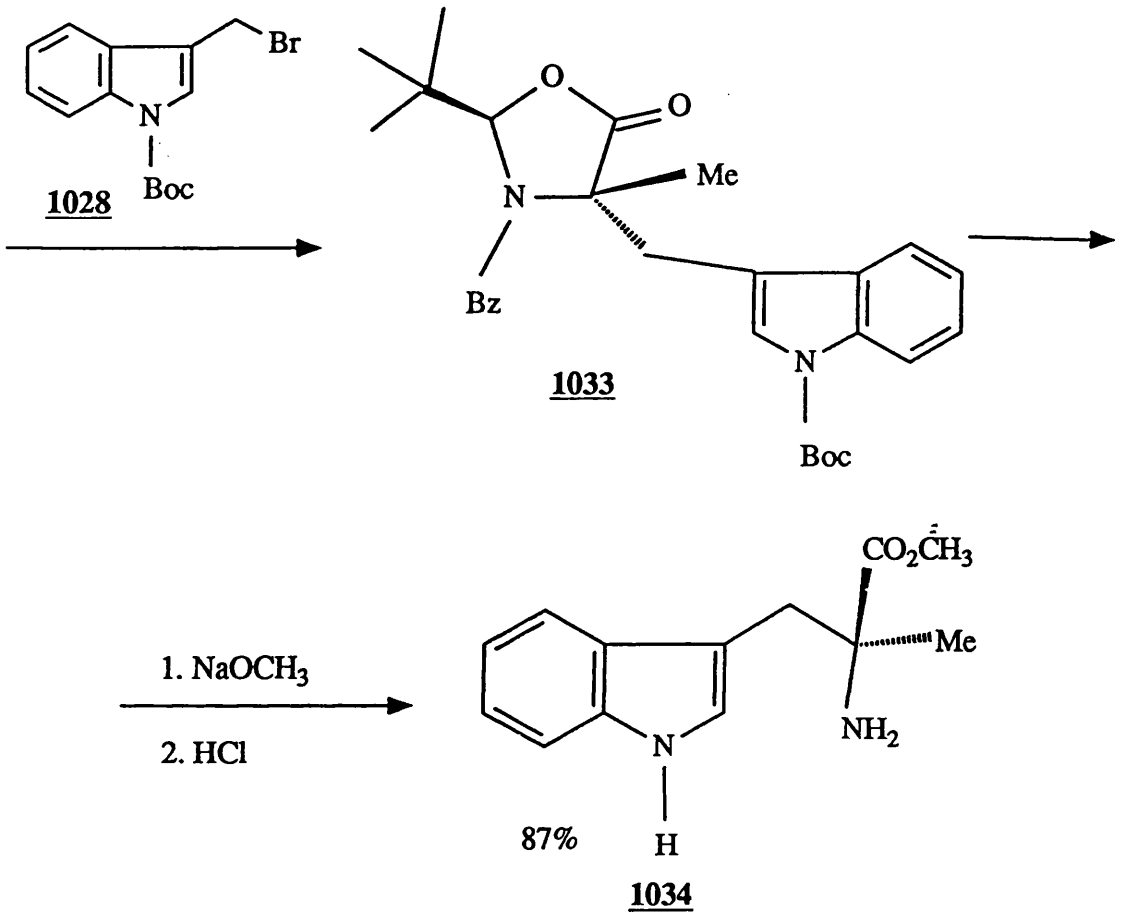
1.3.7 α-Methyl tryptophan from Seebach's Oxazolidinone Method

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]



1031b **1032**



Scheme 17

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.

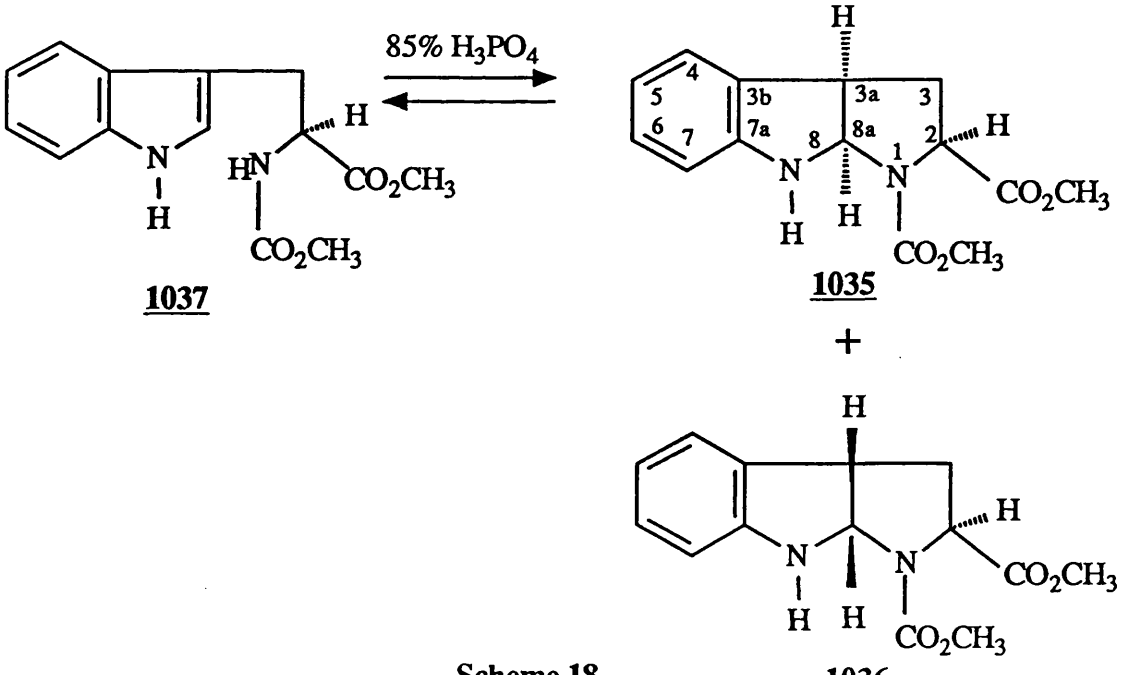
Treatment of **1033** with sodium methoxide in methanol followed by acid deprotonation afforded (S)-α-methyltryptophan methyl ester **1034** in 87% yield.

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.[100] The work on tryptophan in this thesis stems from the elegant work of Crich and Davies on the α-alkylation of tryptophan.[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.[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.

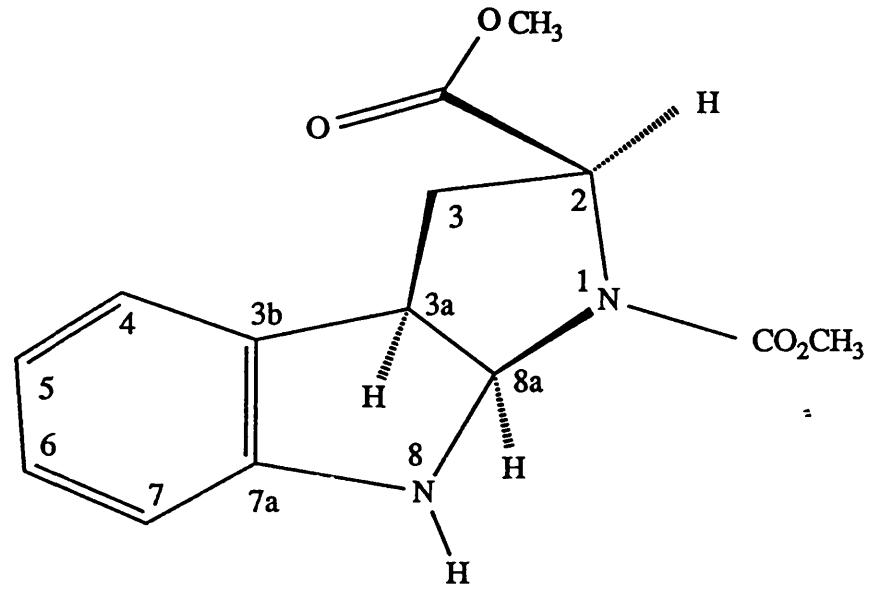
Hino and Taniguchi reported the formation of the stereospecific pyrroloindole ring system on the dissolution of the protected tryptophan **1037** in neat 85% phosphoric acid followed by careful neutralization of the phosphoric acid with aqueous base.[102] The cyclic products **1035** and **1036** were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



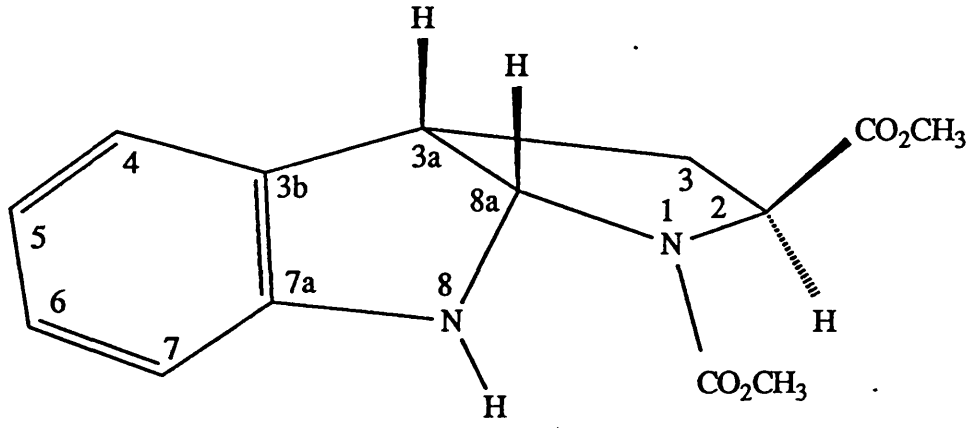
Scheme 18

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**).



1035 endo-product

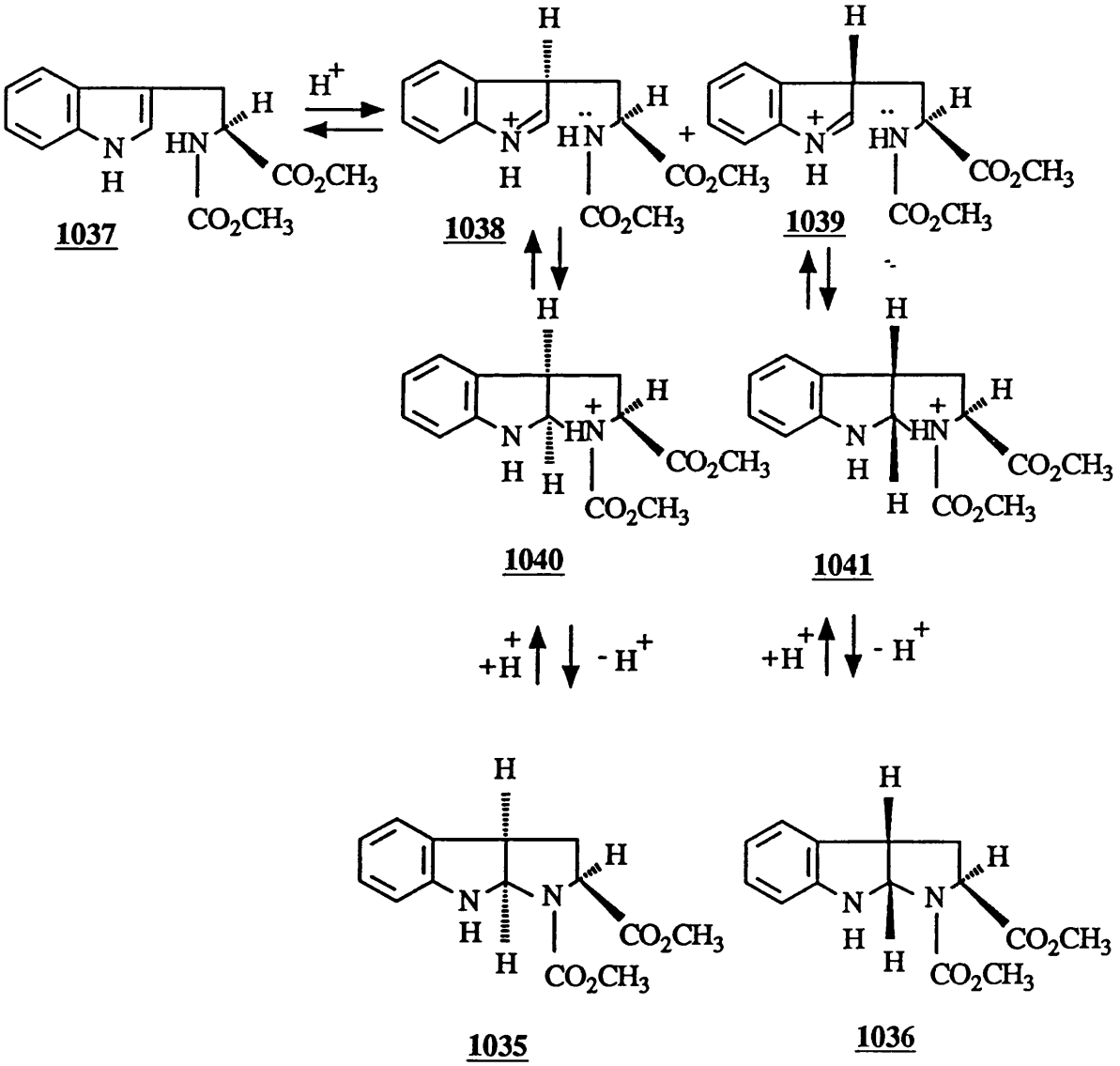


1036 exo-product

Scheme 19

Through a series of kinetic studies, Hino showed that the endo-product was the thermodynamic product and was the isomer isolated.[102] The more sensitive exo-product reverted to the ring opened form **1037** on attempted isolation.

Hino proposed the following mechanistic rationale for the formation of these cyclic tautomers in acid media (**Scheme 20**).[102]



Scheme 20

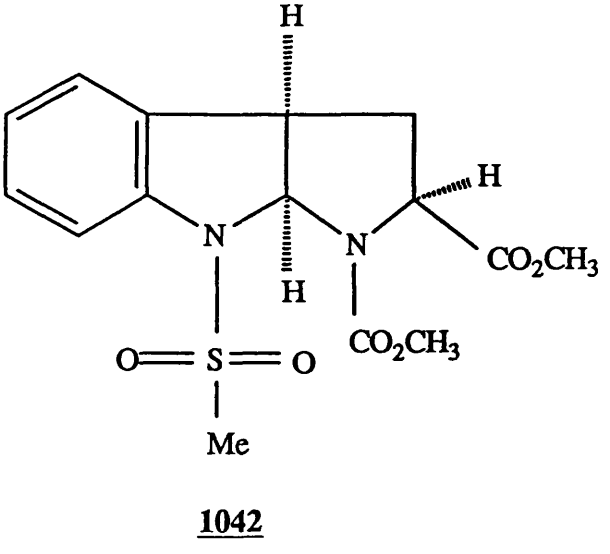
Reversible protonation at the 3-position of the indole **1037** can occur at the *Si*-face or at the *Re*-face of the indole and results in the formation of **1038** and **1039** respectively. But cyclization of **1039** to **1041** occurs more rapidly than that of **1038** to **1040**. The kinetically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

$$1036 \rightleftharpoons 1041 \rightleftharpoons 1039 \rightleftharpoons 1037 \rightleftharpoons 1038 \rightleftharpoons 1040 \rightleftharpoons 1035$$

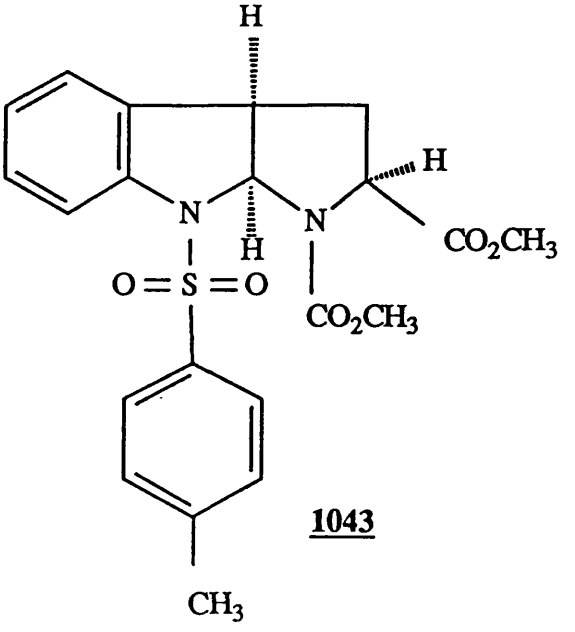
on prolonged reaction time or at higher temperature. The presence of the equilibrium was shown by ^{1}H-NMR of (DL)-**1042** in deuterophosphoric acid at room temperature which indicated rapid deuteration of both **3a**- and **8a** hydrogens.

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.



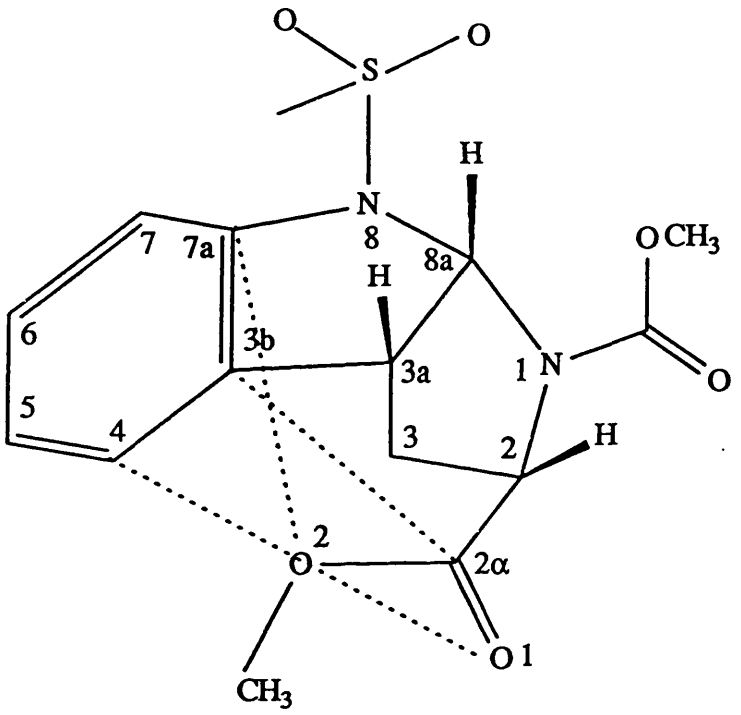
1042



1043

Davies managed to recrystallize **1042** and to obtain a single

crystal X-ray analysis of it, which confirmed the predicted <u>syn</u> configuration of the <u>2,3a</u>, and <u>8a</u> hydrogens.[97] 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.[103]



Distances

C4 to O1 = 4.026Å

C3b to C2α = 3.263 Å

C7a to O2 = 3.208 Å

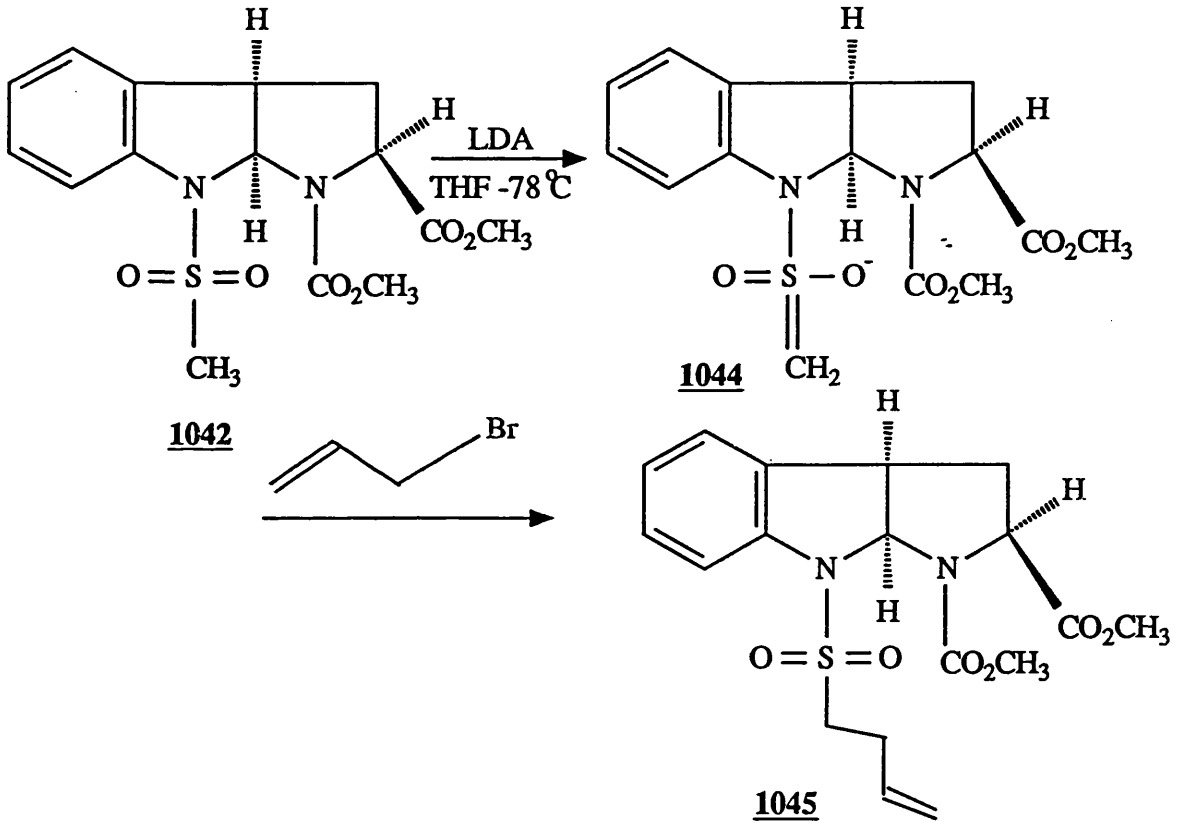
<u>Scheme 21</u>

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

The tosylated product **<u>1043</u>** was however a viscous oil and no X-ray data was possible.[97]

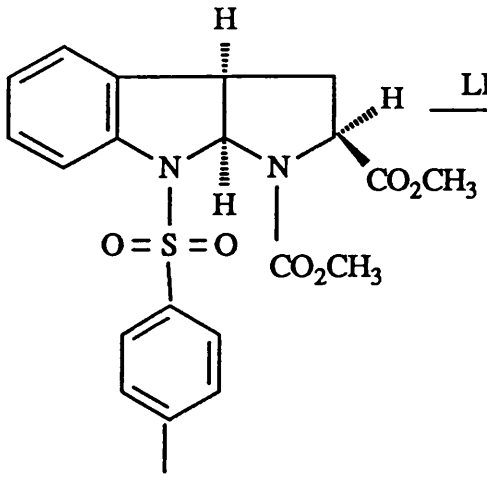
1.3.10 α-Alkylation of the protected pyrroloindoles

Davies attempted to deprotonate at C-2 of **1042** and then allylate the enolate formed.[97] However the product **1045** obtained was in fact the one in which deprotonation occurred at the methylsulphonyl group followed by allylation (Scheme 22).



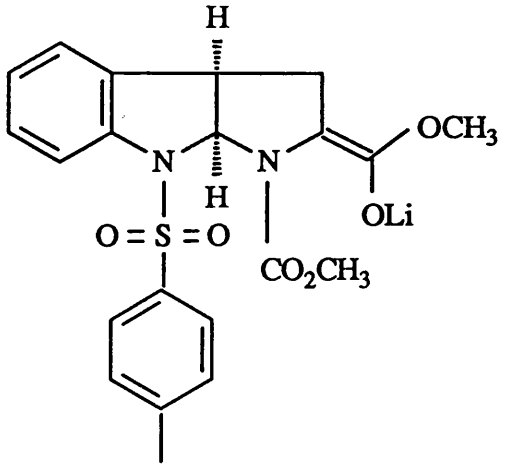
Scheme 22

With the N-tosyl protected product **1043**, Davies was able to deprotonate at C-2 with 1equivalent of LDA in THF at -78°C and on quenching with the appropriate electrophile obtained the products **1047** in good yields (Scheme 23).



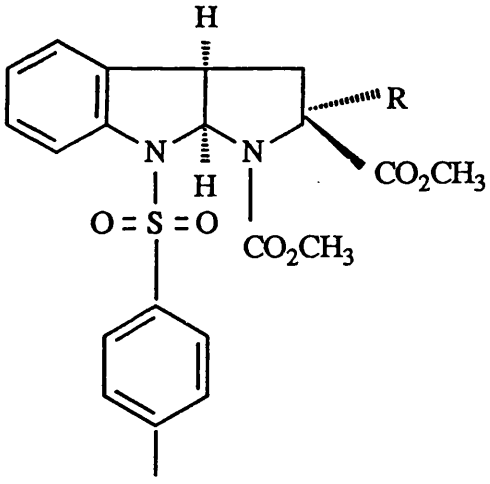
1034

LDA

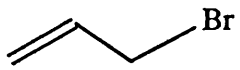


1046

RX



1047

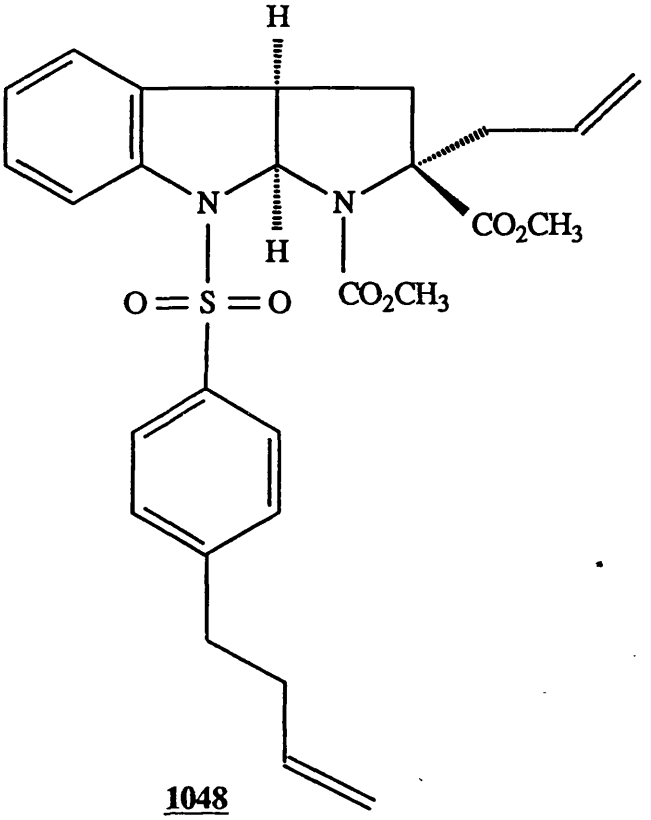
	Electrophile		Product (1047)	Yield %
RX =		a	R = $-CH_2-CH=CH_2$	79
	MeI	b	-Me	80
	BnBr	c	-Bn	71
	$MeSCH_2CH_2I$	d	$-CH_2CH_2SMe$	44
	MeO_2CCH_2Br	e	$-CH_2CO_2CH_3$	83
	$(CH_3)_3SiCH_2CH_2OCH_2Cl$	f	-SEM	78

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%).

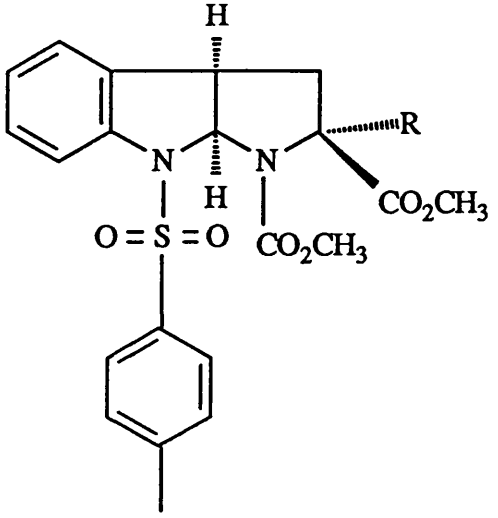
By NOE studies and from X-ray analysis of a single crystal of **1047a**, it was concluded that the product obtained was that where the electrophile quenched the enolate **1046** from the exo-side of the molecule.[97]

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**.

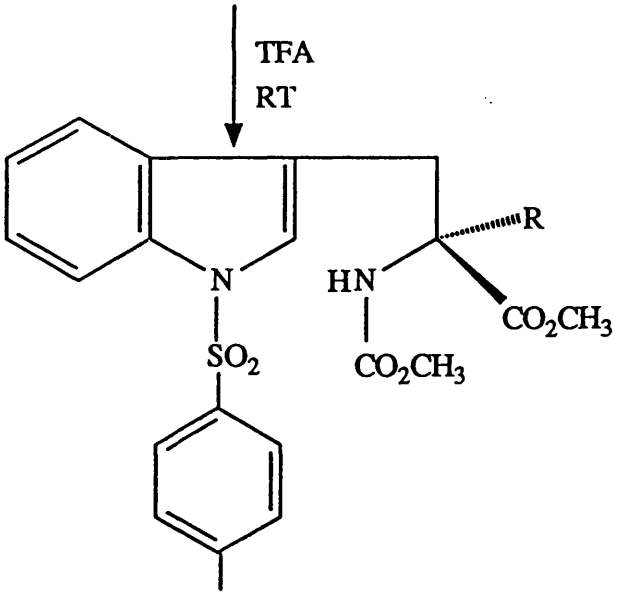


1048

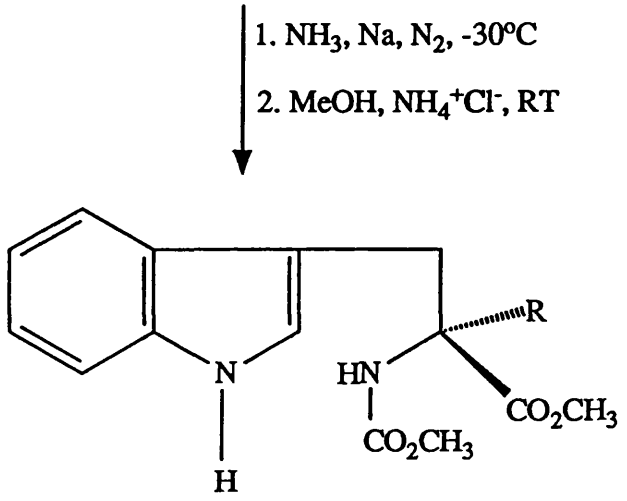
The alkylated products **1047** were then ring opened with trifluoroacetic acid (TFA)[102] to give **1049**, and the tosyl group removed with sodium in liquid ammonia to give **1050** (Scheme 24).[104]



1047



1049



1050

Scheme 24

1.3.11 The work on tryptophan described in this thesis

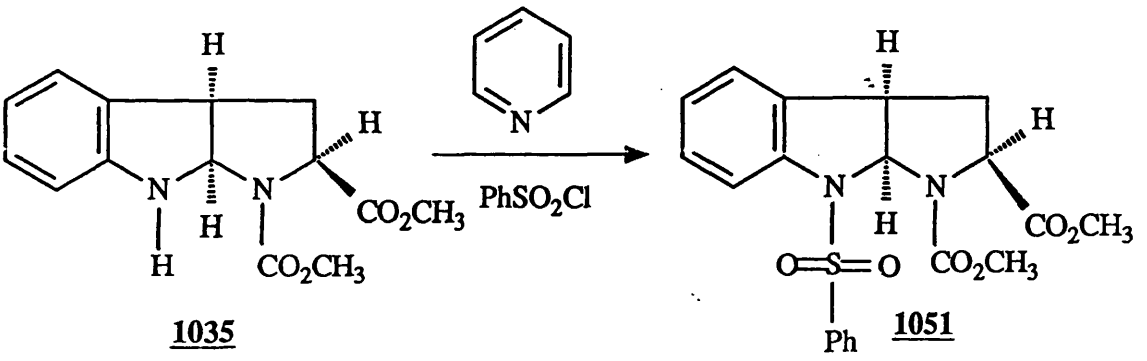
The work described in this thesis concerning tryptophan is threefold. **Firstly,** α-alkylated substituted tryptophans were synthesized, and then transformed into the corresponding aspartic acid derivatives. In this work (R)-α-methyl aspartic acid and (S)-α-methyl aspartic acid were synthesized.

Secondly, (R)-α-methyltryptamine and (S)-α-methyl- tryptamine 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

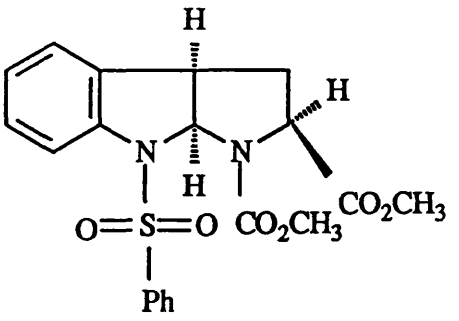
The pyrroloindole **1035** was synthesized according to Hino,[102] and Davies.[97] Because of the difficulties encountered by Davies in using the methylsulphonyl and tosyl groups in the protection of **N-8** in **1035**, it was decided to try the **benzenesulphonyl group** as a protecting group for **N-8**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



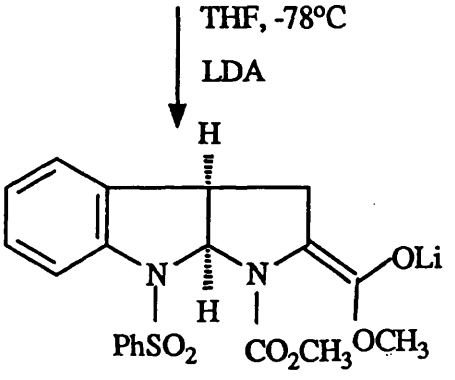
Scheme 25

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**.

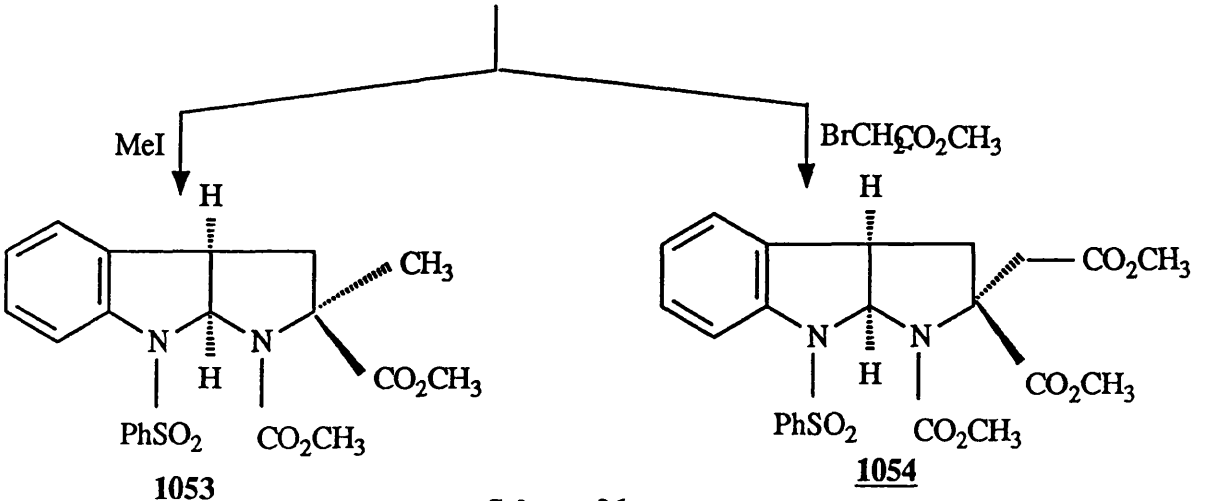
Again like Davies, only one of the diastereomers was obtained.



1051



1052

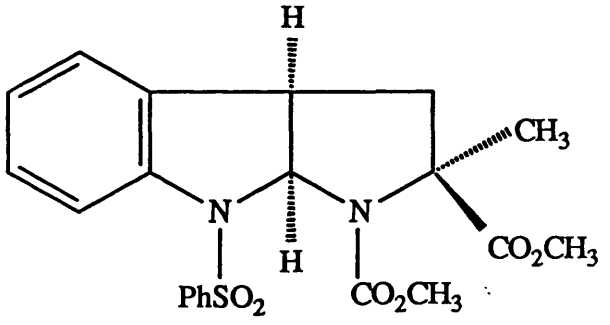


1053 1054

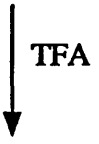
Scheme 26

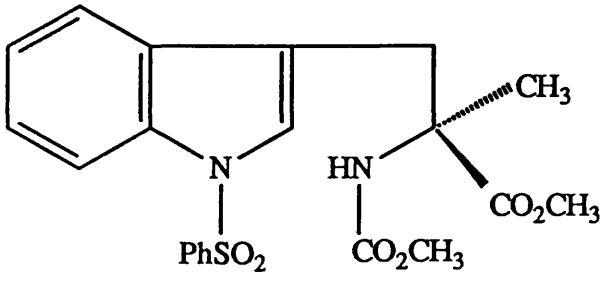
1.3.13 Synthesis of (S)-α-methylaspartic acid hydrochloride 1055

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 $RuCl_3$ were added.[105] 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**).

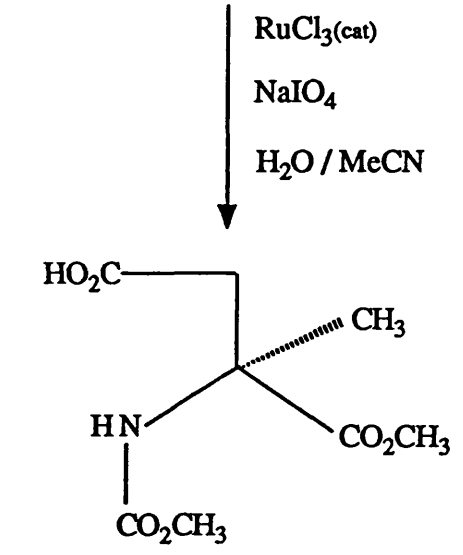


1053

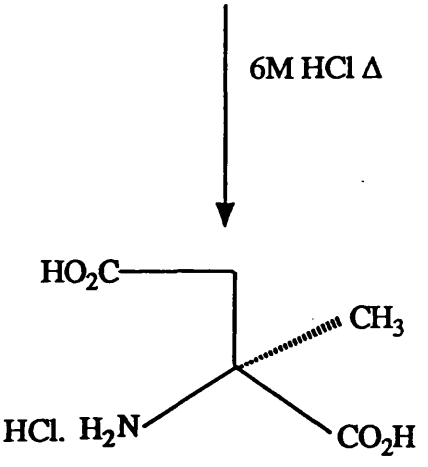




1056



1057

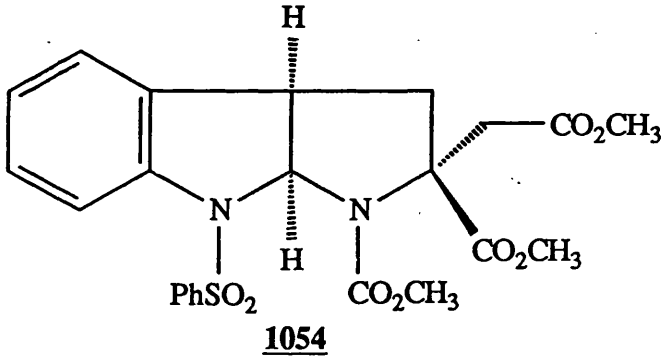


1055

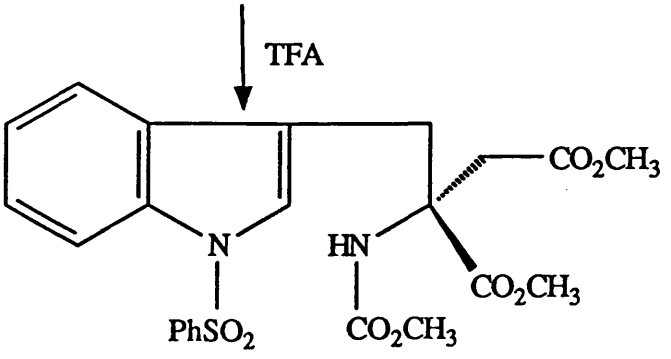
Scheme 27

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

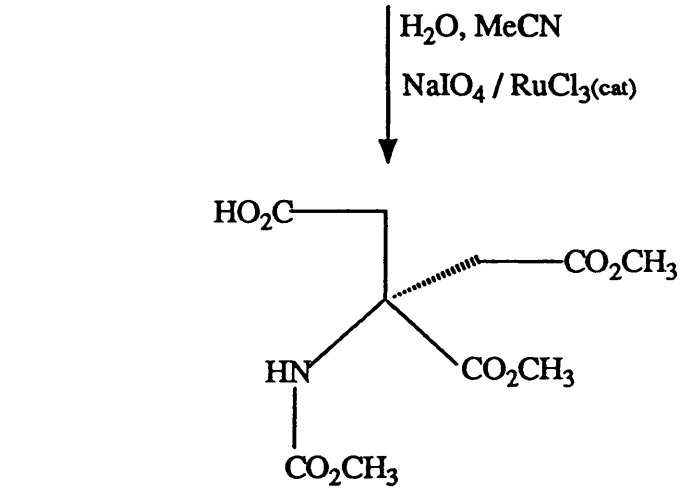
The preparation of **1058** was achieved by first ring opening **1054** with TFA[102] to give **1059**. Compound **1059** was then catalytically cleaved with $RuCl_3$ and $NaIO_4$ to give the aspartic acid derivative **1060**.[105] The thiohydroxamate **1061** was formed and then reductively decarboxylated by Barton's method,[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**).



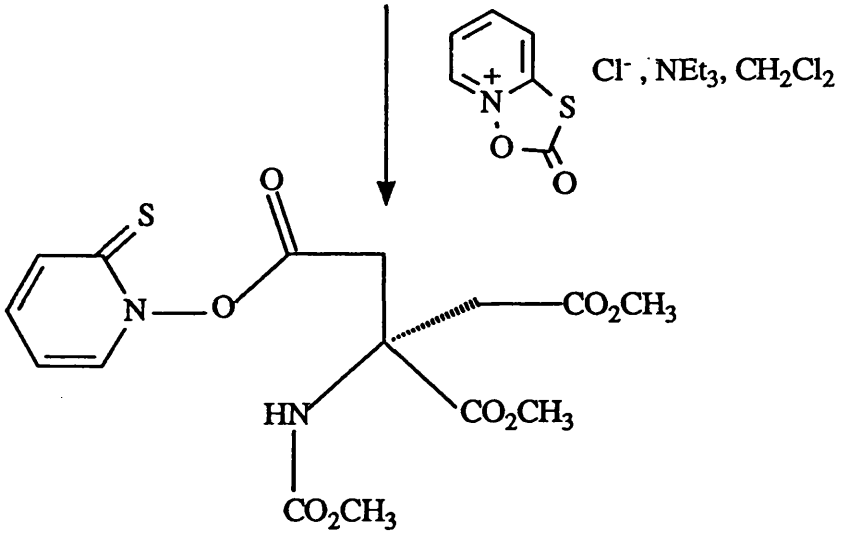
1054



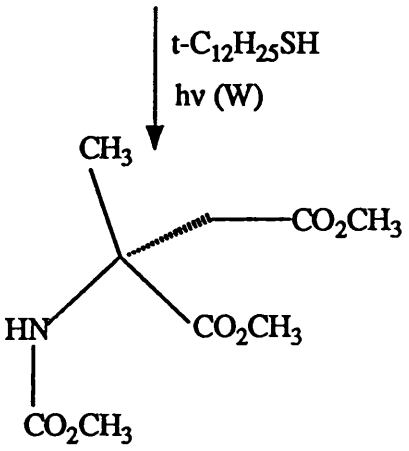
1059


H2O, MeCN
NaIO4 / RuCl3(cat)
HO2C
CO2CH3
HN
CO2CH3
CO2CH3

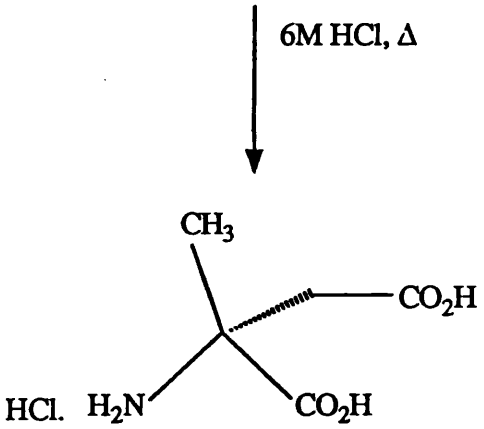
1060


Cl- , NEt3, CH2Cl2
S
N
O
O
O
S
N
O
CO2CH3
HN
CO2CH3
CO2CH3

1061



1062



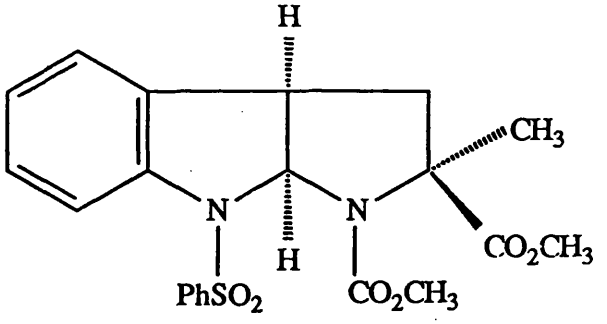
1058

Scheme 28

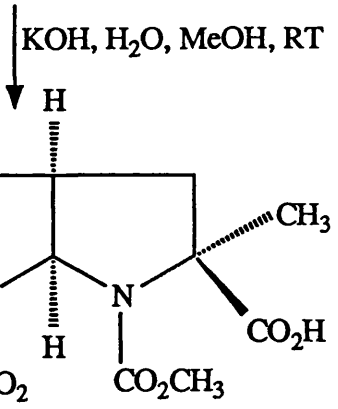
1.3.15 Preparation of (R)- and (S)-α-methyl tryptamine

The starting material **1053** previously prepared was taken and the methyl ester group at C-2 was hydrolyzed under the Claisen conditions at room

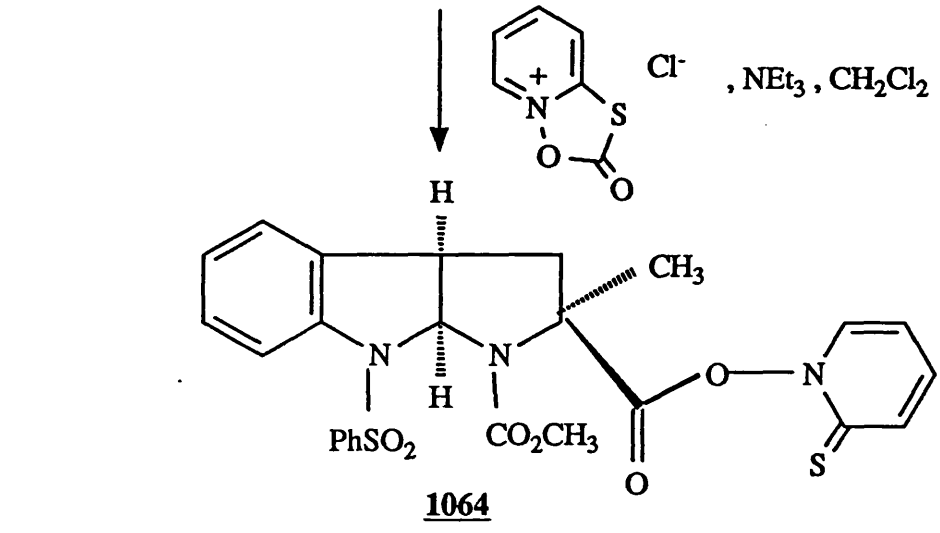
temperature to give the acid **1063**. The thiohydroxamate **1064** was prepared from **1063**. Compound **1064** was then reductively decarboxylated,[31,32] to give the diastereomers **1065** and **1066** which were chromatographically separated. Compound **1065** was then ring opened with TFA[102] 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**).



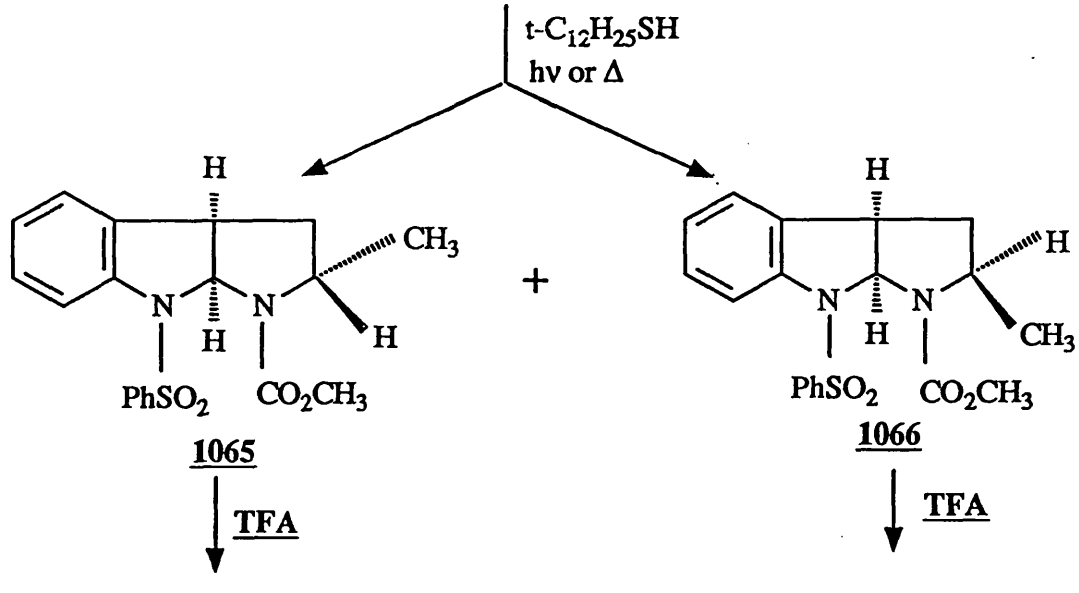
1053



1063



1064

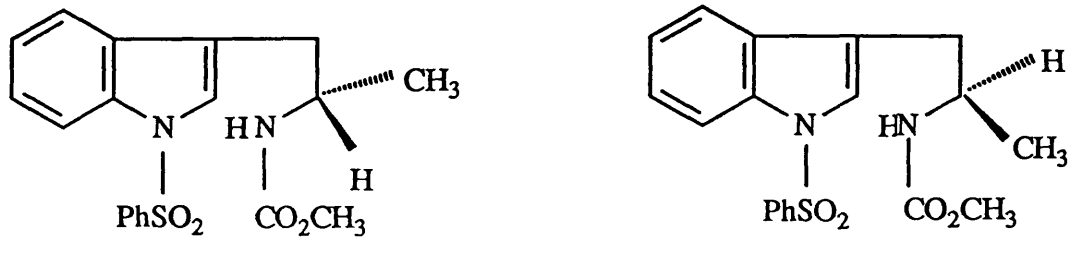


1065

TFA

1066

TFA



(S)-1067

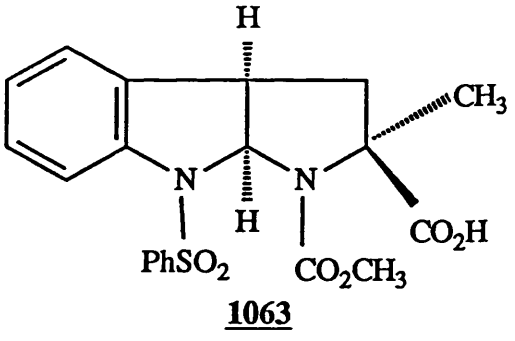
(R)-1068

Scheme 29

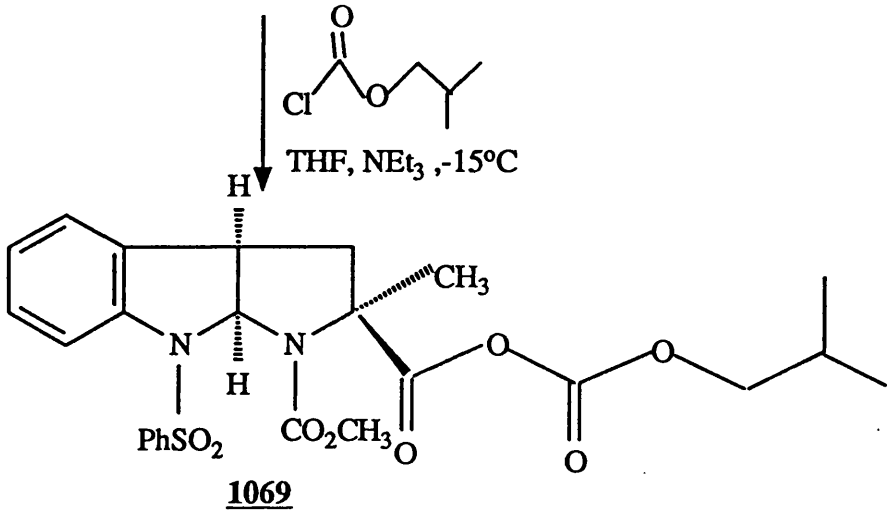
1.3.16 The discovery of the stable and crystalline mixed anhydride 1069 and its X-ray analysis

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.

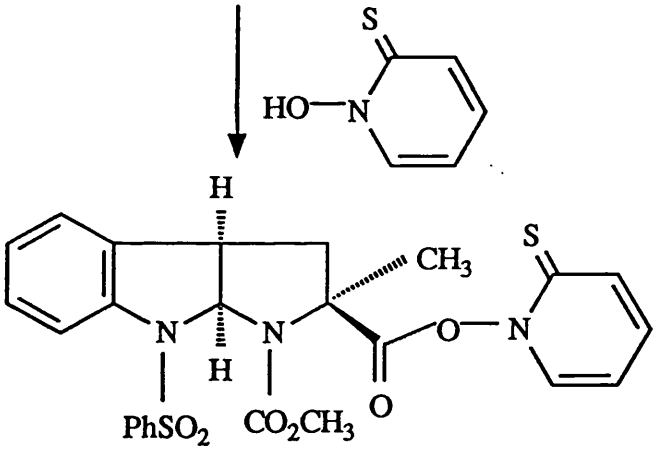
The crystalline compound was found to be the mixed anhydride **1069** by elemental analysis. A single crystal X-ray analysis later confirmed this. This also showed a possible **π-stacking** interaction between the side chain at **C-2** and the aromatic ring of the pyrroloindole. However, unlike in **1042**, 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.



1063



1069

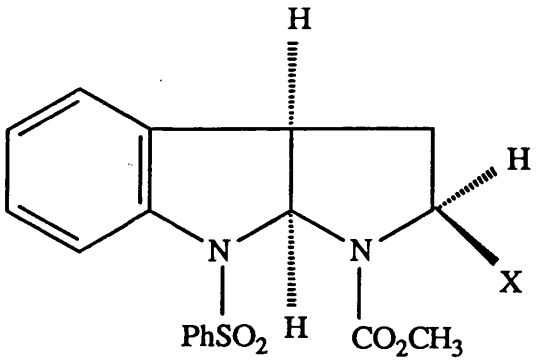


1064

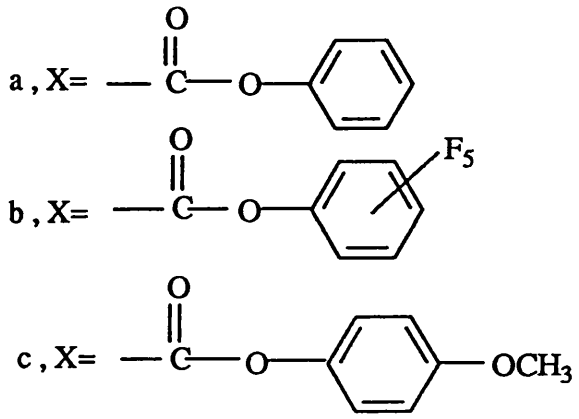
Scheme 30

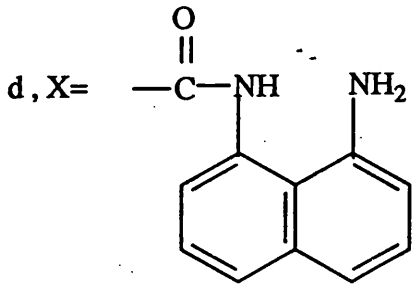
1.3.18 Investigation into possible π-bonding in the pyrroloindole system

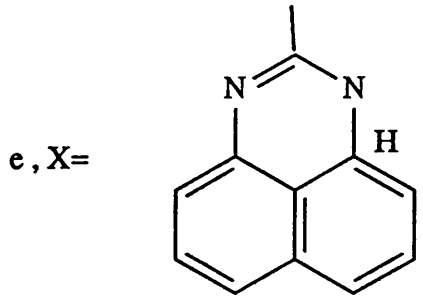
It was decided to synthesize a series of aromatic esters or amides of types 1075, and 1109.



1075

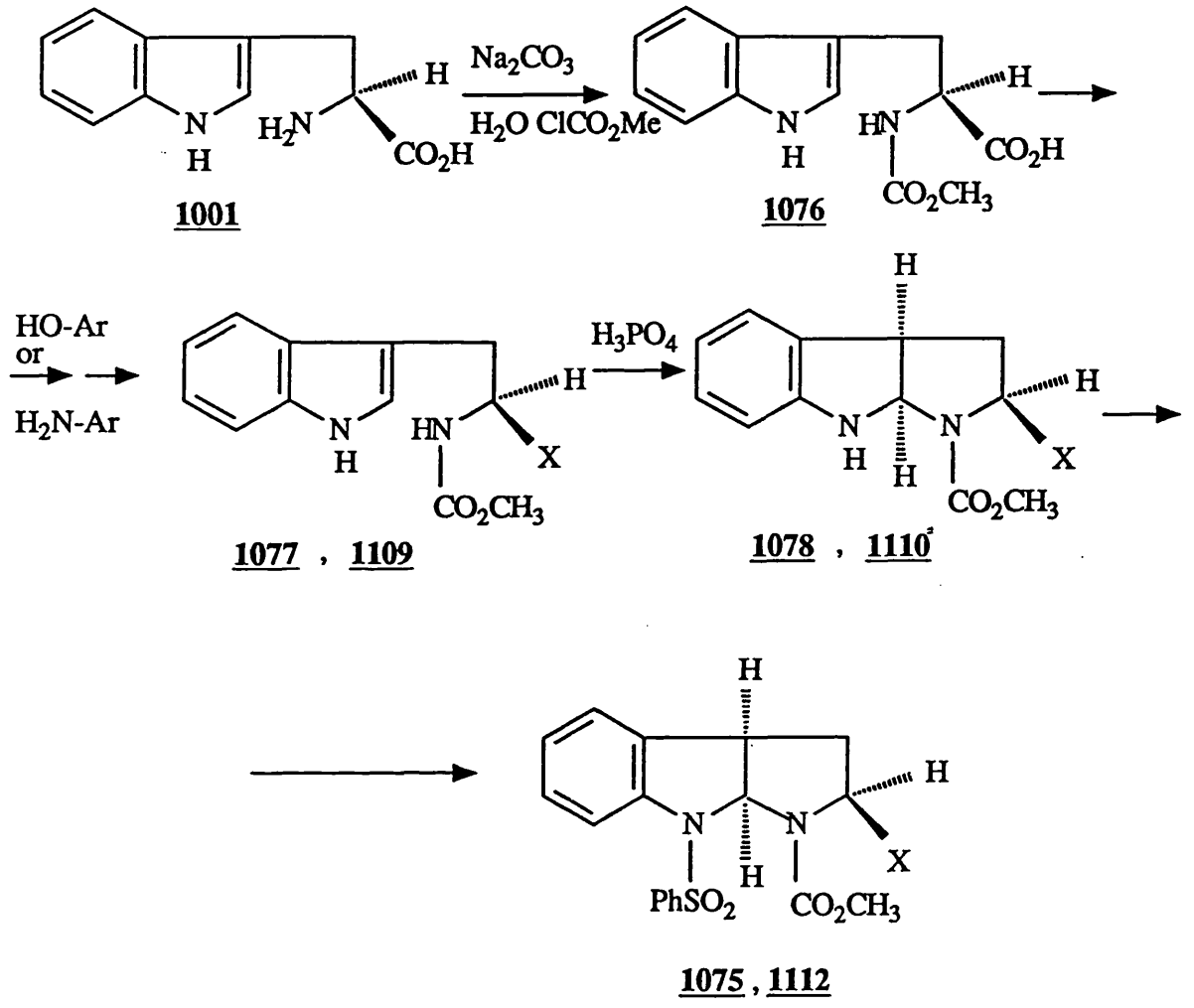






1112, 1113 X=Ph

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.



1001 1076 1077 , 1109 1078 , 1110 1075 , 1112

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.[18,19] The TBDMS group could be easily put on, and then removed under neutral conditions with tetrabutylammonium fluoride or with boron trifluoride etherate.[46] It is also stable in basic and neutral conditions and only unstable in moderately strong acids.

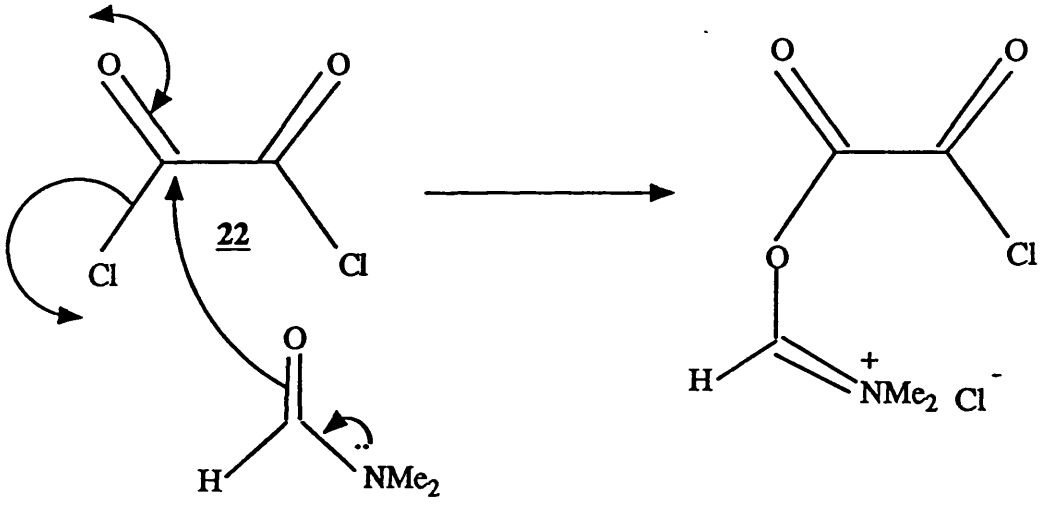
The TBDMS group was put on 8 by stirring 8 with 2.2eq of TBDMS chloride and 2.5eq of imidazole in dry dimethylformamide (DMF) as solvent at room temperature for 16 hours. A twofold excess of TBDMS-Cl was necessary as the acid group of 8 was also silylated in the process. However most of the silylated 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

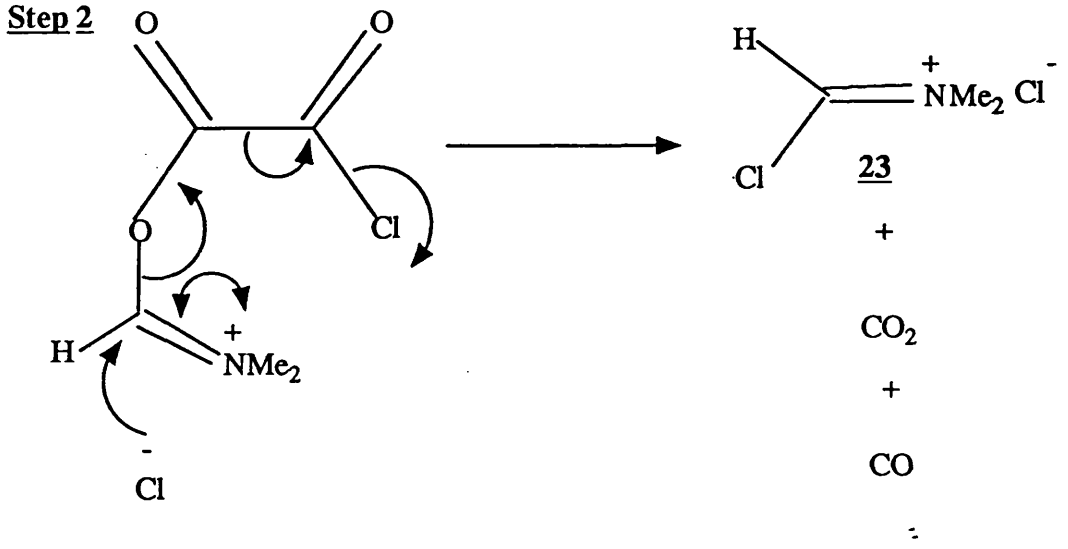
It was crucial to show that the radical 12 could be made and trapped. As the starting material 9 already has the acid functionality at the correct position (C-4), it only remained necessary for the straight forward conversion of this to the thiohydroxamate ester 11. This was done by activating the acid 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.**

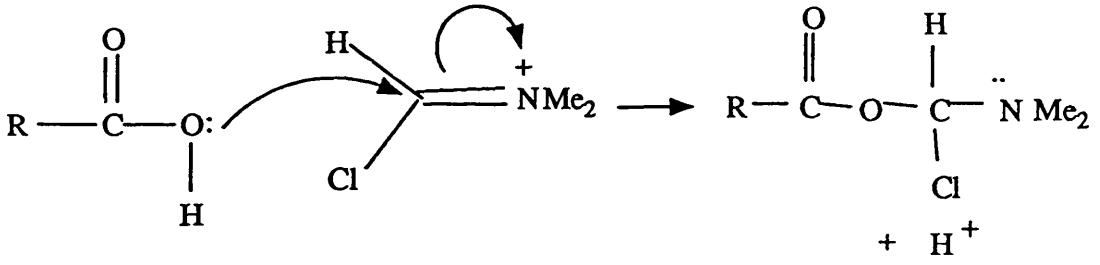
Step1



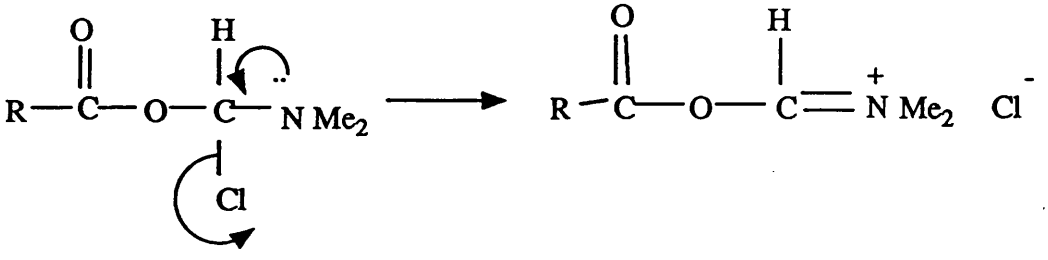
Step 2



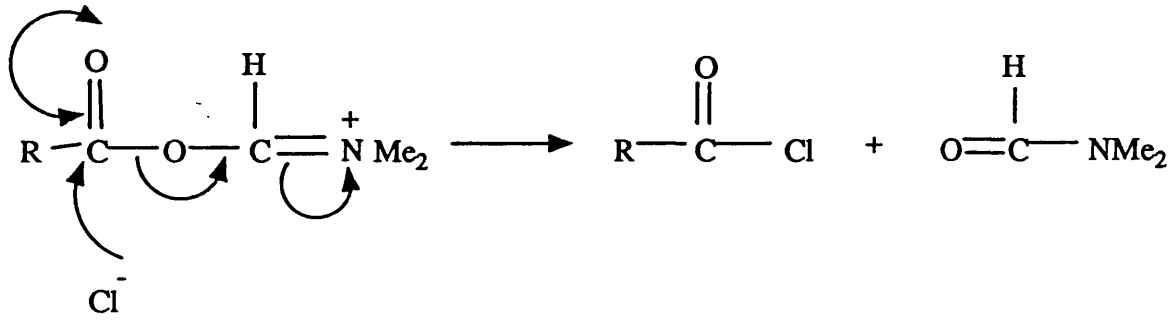
Step 3



Step 4



Step 5



Scheme 32

The reaction proceeds via the Vilsmeier salt 23 with the loss of CO_2 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, $SOCl_2$, 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 N_2. 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.

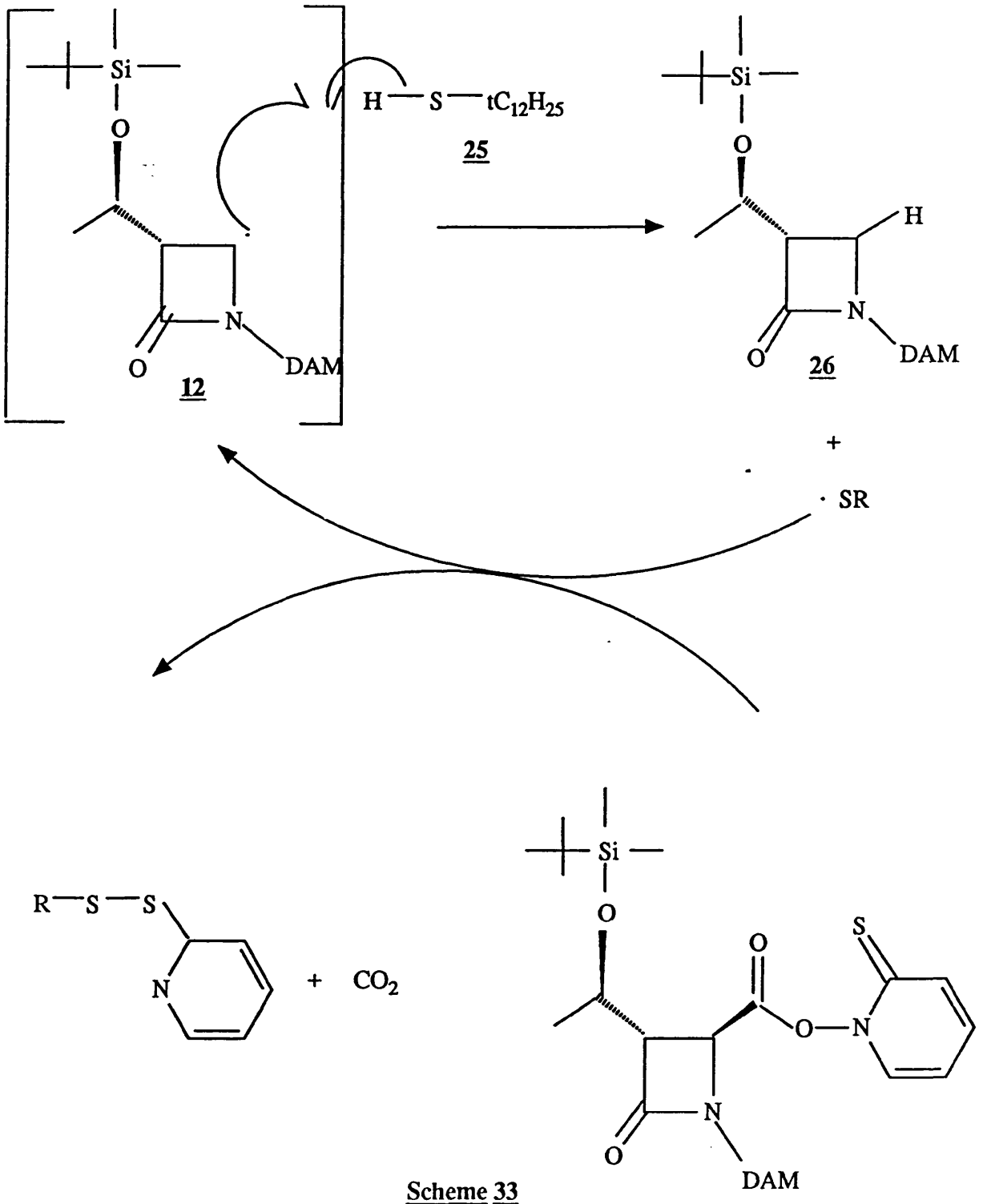
2.2.3 Generation of the radical 12 from 11

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**).



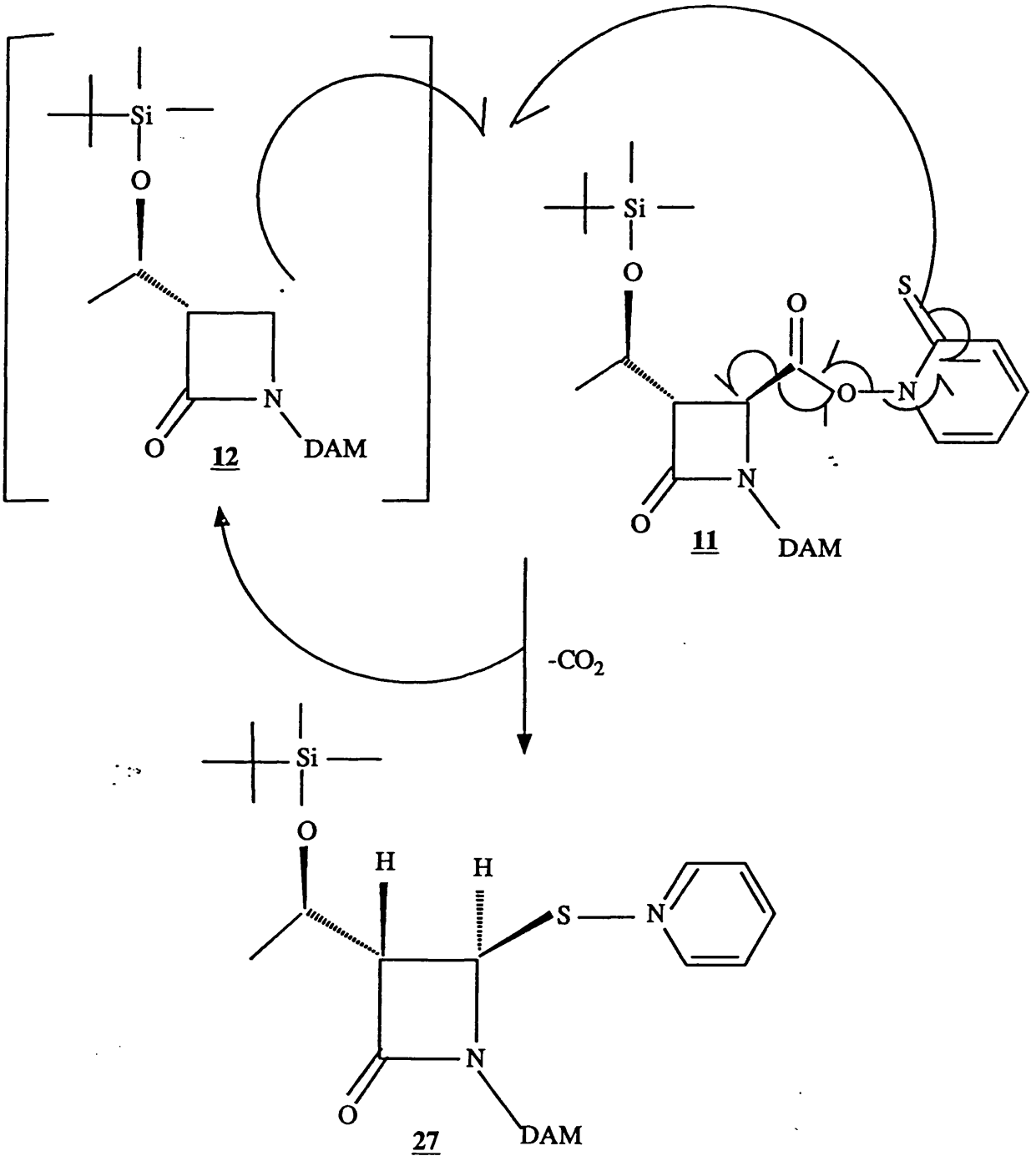
Scheme 33

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=3.16ppm (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**).

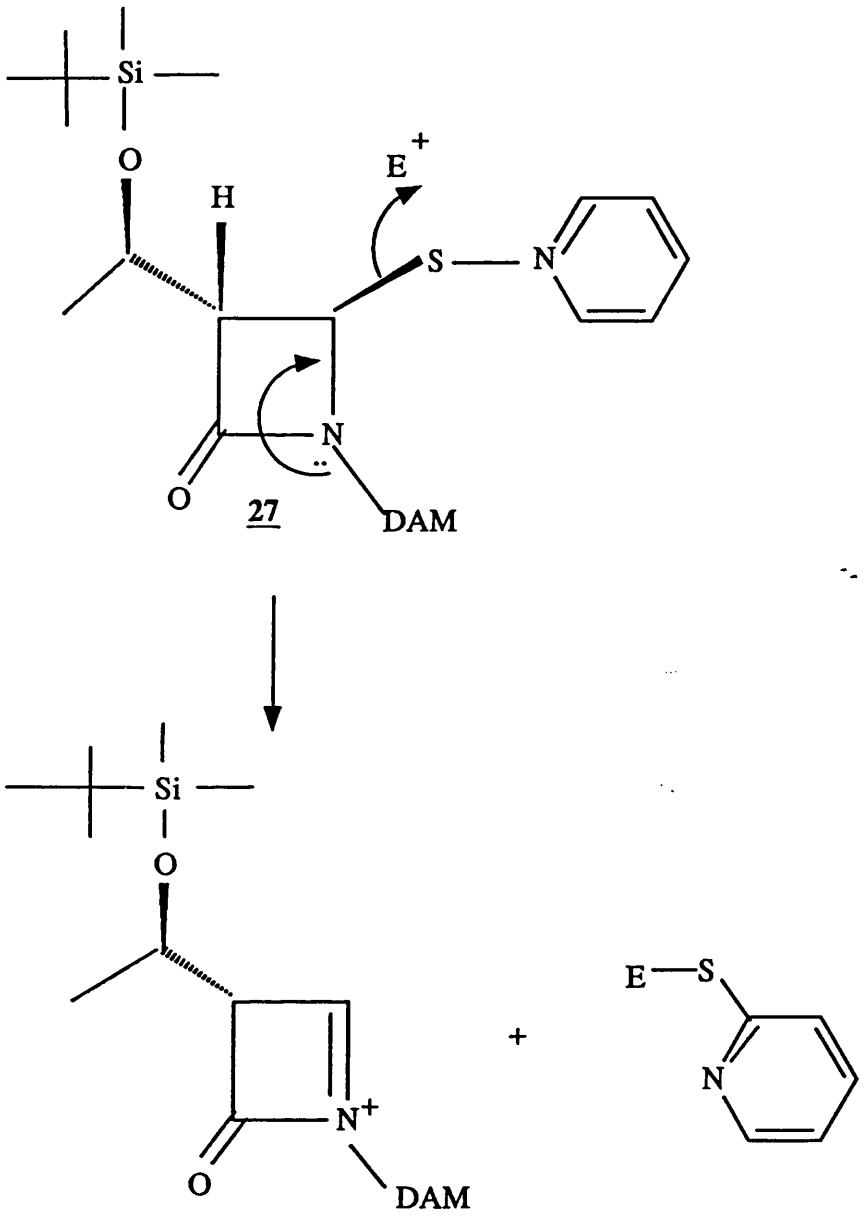


Scheme 34

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

400MHz ^{1}H-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**.

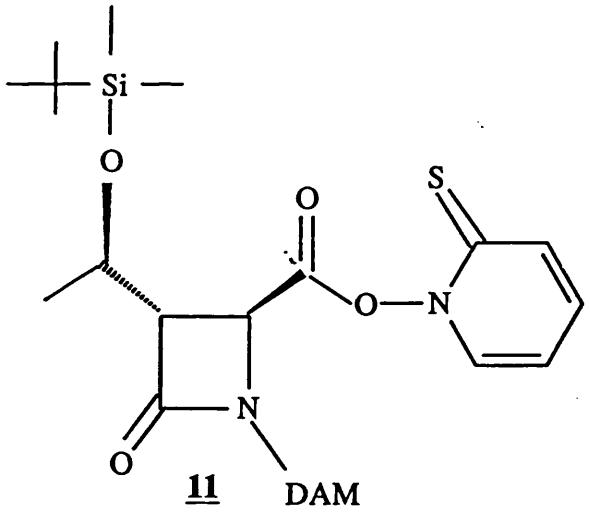


Scheme 35

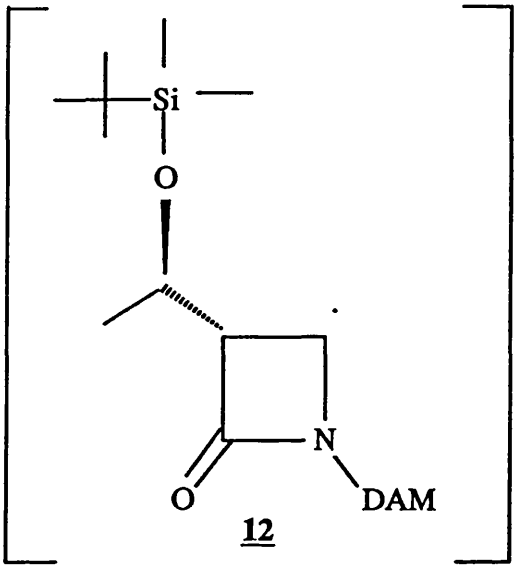
2.4 Carbon-carbon bond forming reactions of 12

2.4.1 Addition of 12 to methyl acrylate 28

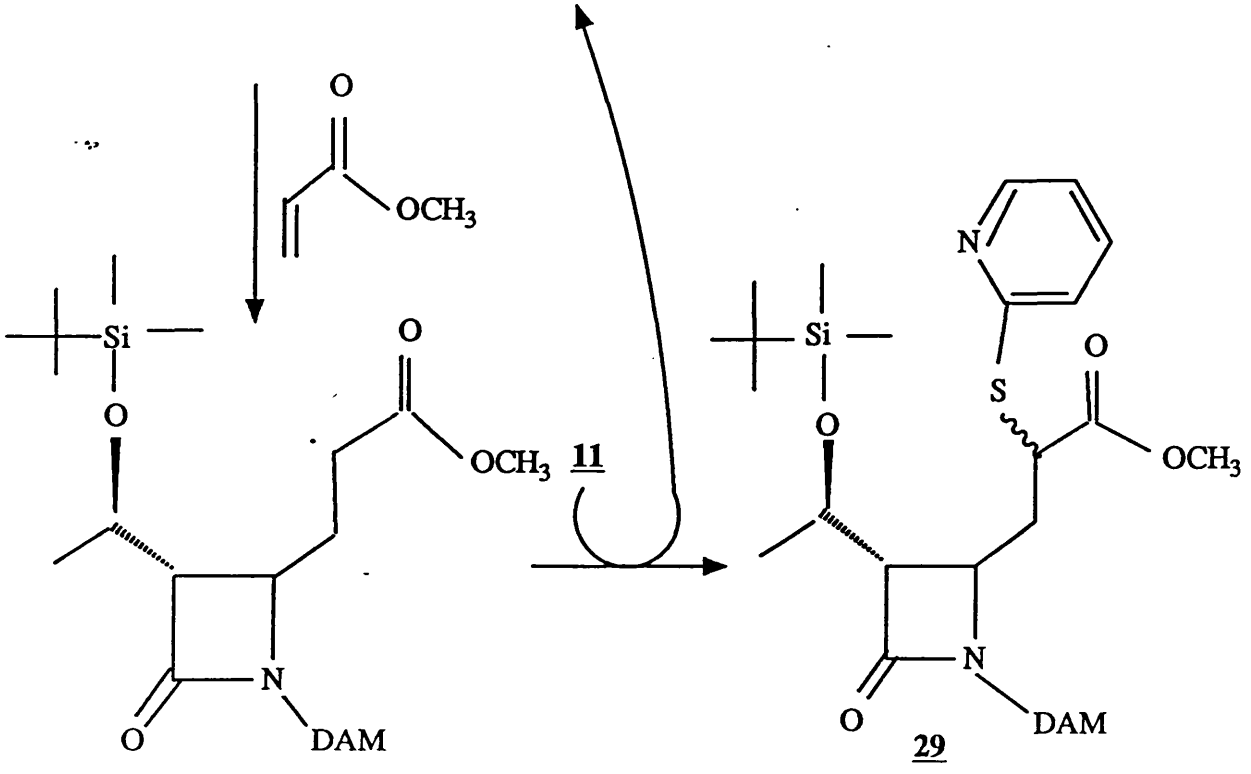
Methyl acrylate is an activated alkene resembling 1-nitro-1-propene. The thiohydroxamate **11** was formed via the mixed acid anhydride **10b**, and methyl acrylate **28** was added and the reaction was photolyzed with a bright tungsten lamp (**Scheme 36**).



11 DAM



12



29

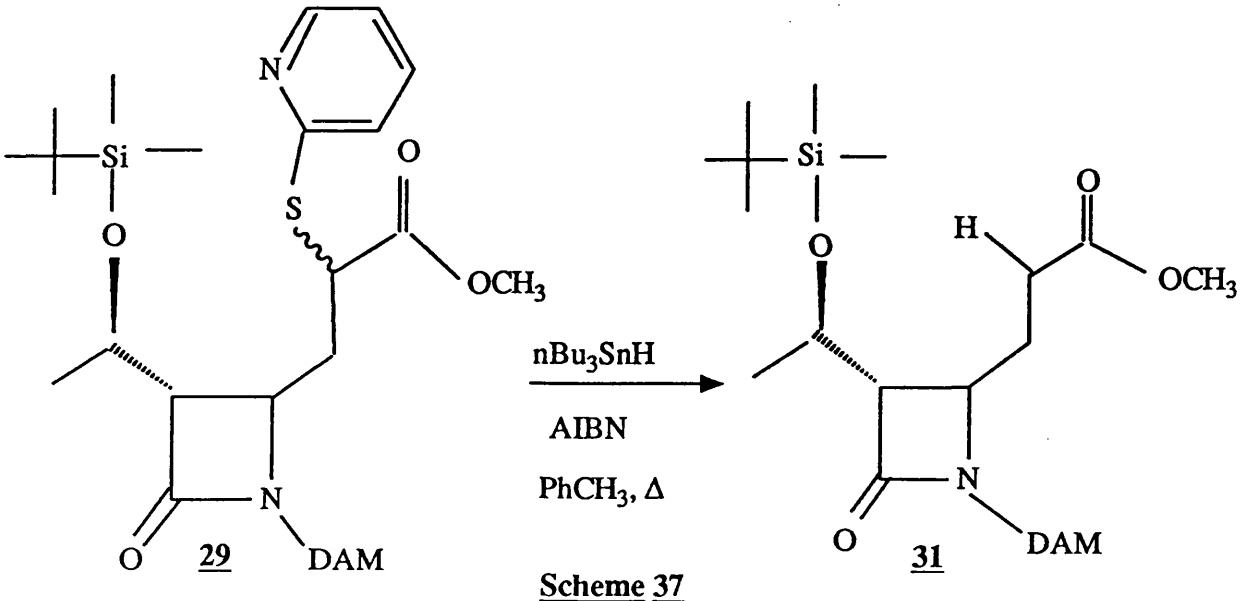
Scheme 36

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 δ=3.6ppm.

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 sucessfully removed by refluxing in dry toluene with butyltin hydride (nBu_3SnH) with AIBN as the radical initiator (Scheme 37).

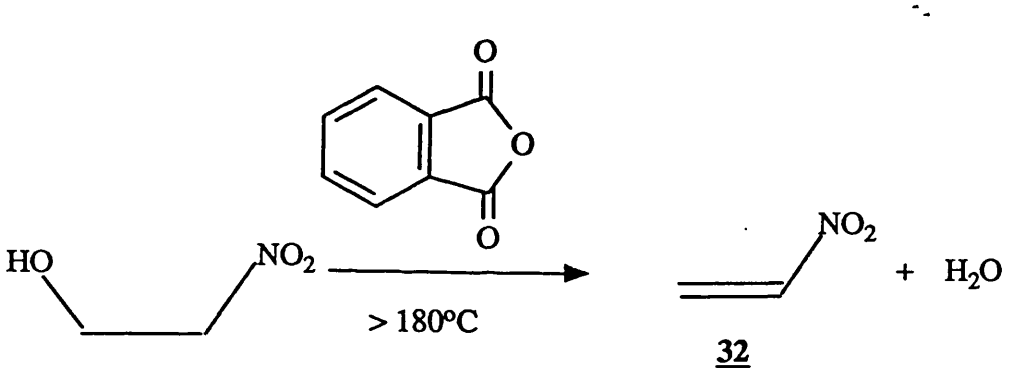


Scheme 37

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 nitroethene 32

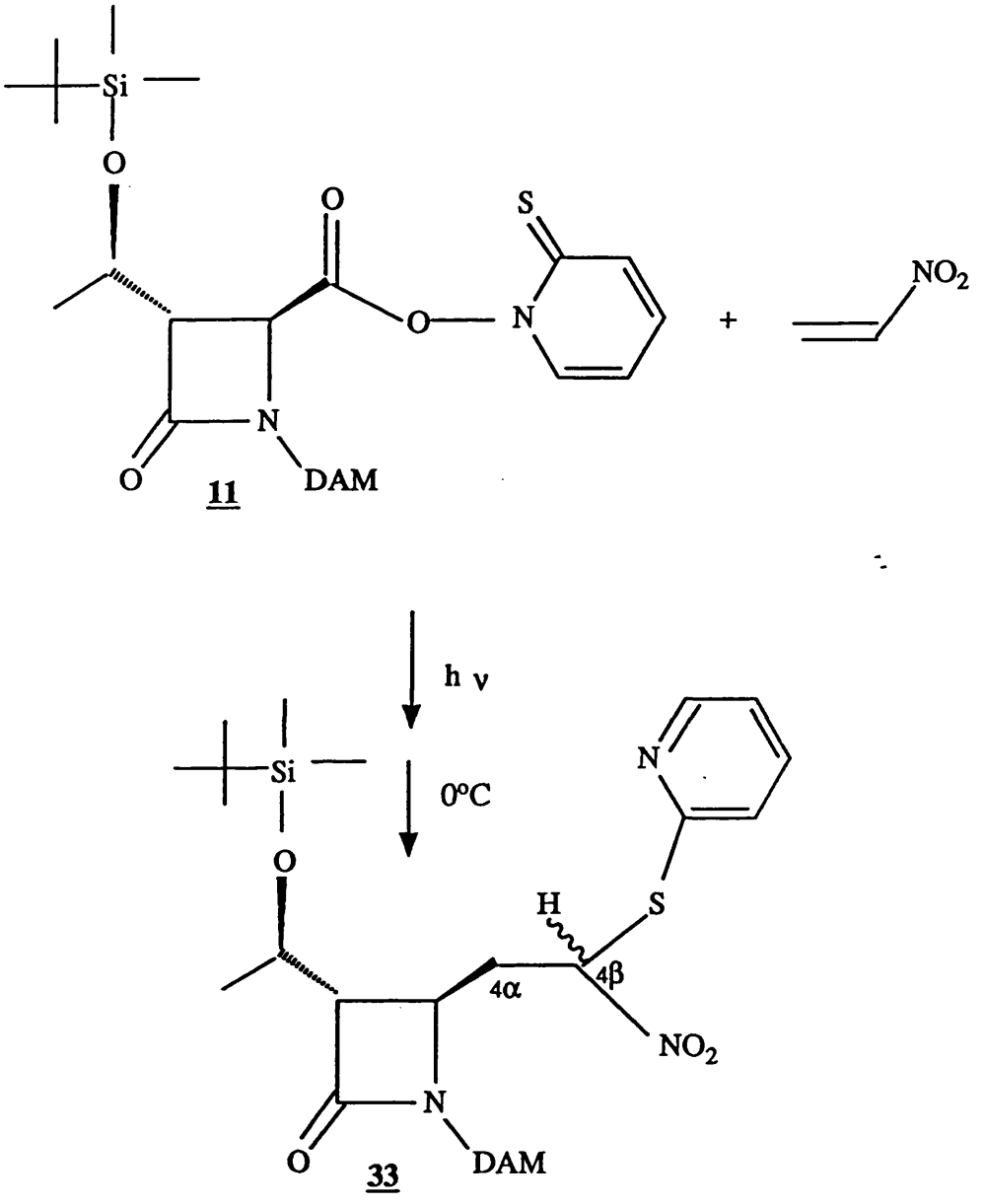
Nitroethene, **32**, was prepared by dehydration of 2-nitro-1-ethanol over phthalic anhydride at a temperature of over 180°C,[48] and distilling the product (**Scheme 38**).



32

Scheme 38

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**).



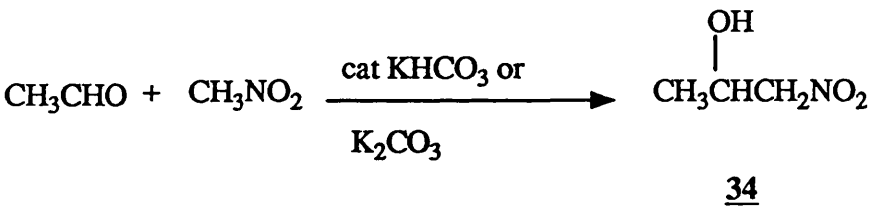
Scheme 39

The desired product **33** was isolated in 36% yield starting from the acid **9**. 200MHz ^{1}H-NMR showed two diastereomers in the ratio of 3:2. The hydrogen α to the thiopyridyl and nitro groups has a downfield chemical shift of δ=6.19ppm(dd)

and δ=6.30ppm(dd). The NMR signals of the two hydrogens at C-4α were multiplets stretching from δ=2.0ppm to δ=2.8ppm.

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

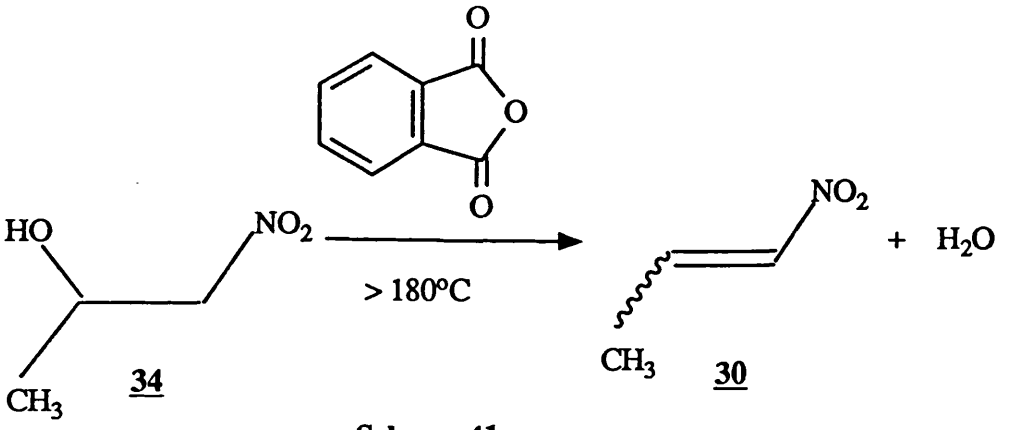
Compound **34** was prepared by the method of **Henry.**[49] Dry **ethanol** and **nitromethane** were mixed in equimolar quantities and cooled in an ice-bath. Water containing a catalytic amount (typically 1% equivalent) of potassium hydrogen carbonate or potassium carbonate was added and the mixture 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**).



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°C,[48] and distilling the product (**Scheme 41**).

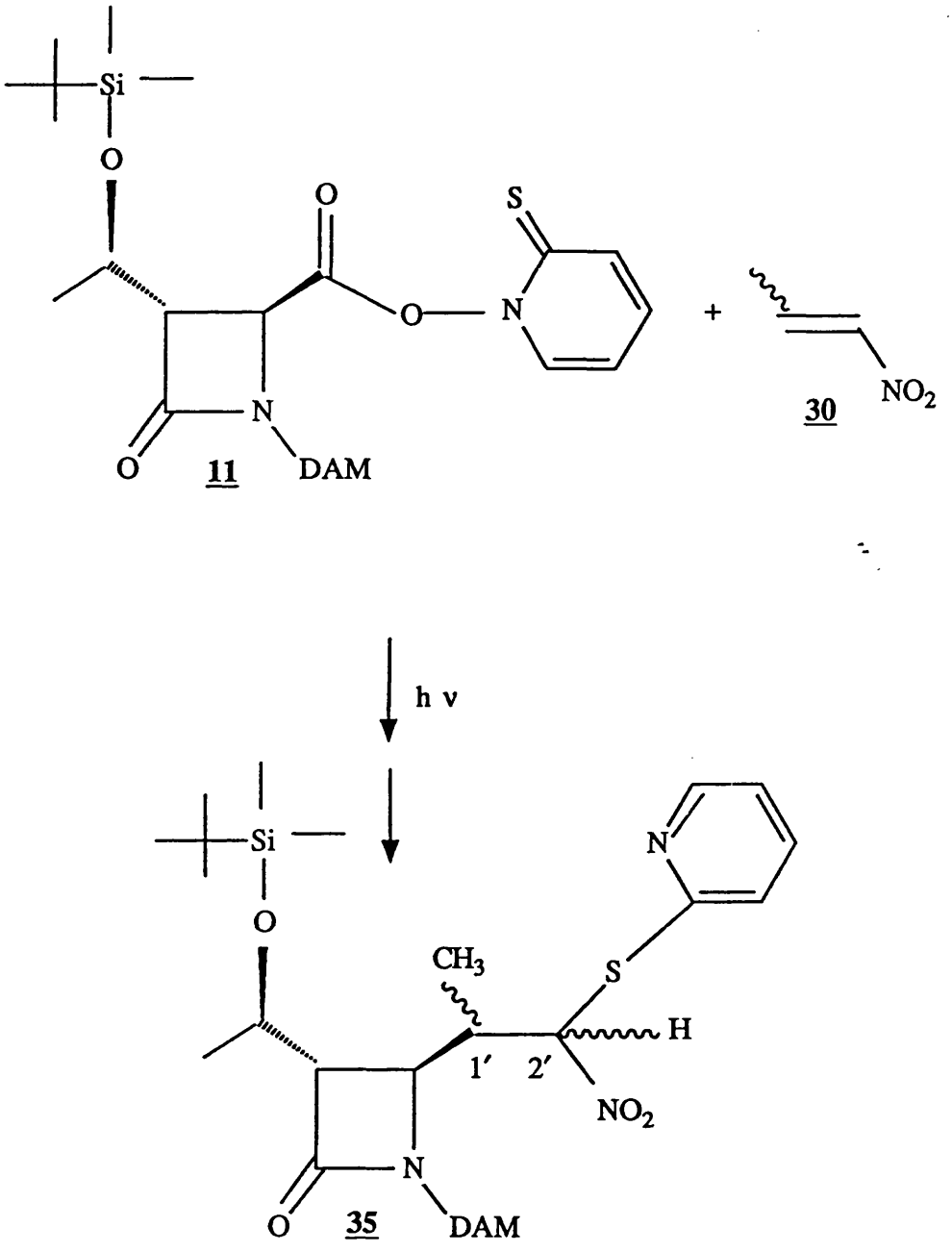


Scheme 41

^{1}H-NMR of 30 obtained showed that the cis- and 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 trans-alkene product.[50] The two isomers were not separated.

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.



Scheme 42

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 α-pyridyl proton at

a chemical shift around δ=8.3ppm. There were also four separate signals (doublets) for **H-2′** from δ=6.3ppm to δ=6.7ppm. ^{13}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 **α-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**).

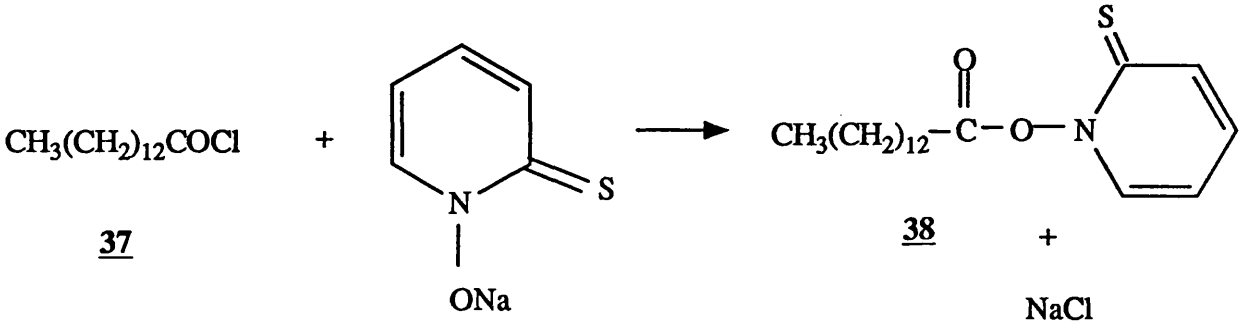
$$\underset{\textbf{36}}{CH_3(CH_2)_{12}CO_2H} + SOCl_2 \longrightarrow \underset{\textbf{37}}{CH_3(CH_2)_{12}COCl} + SO_2 + HCl$$

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).

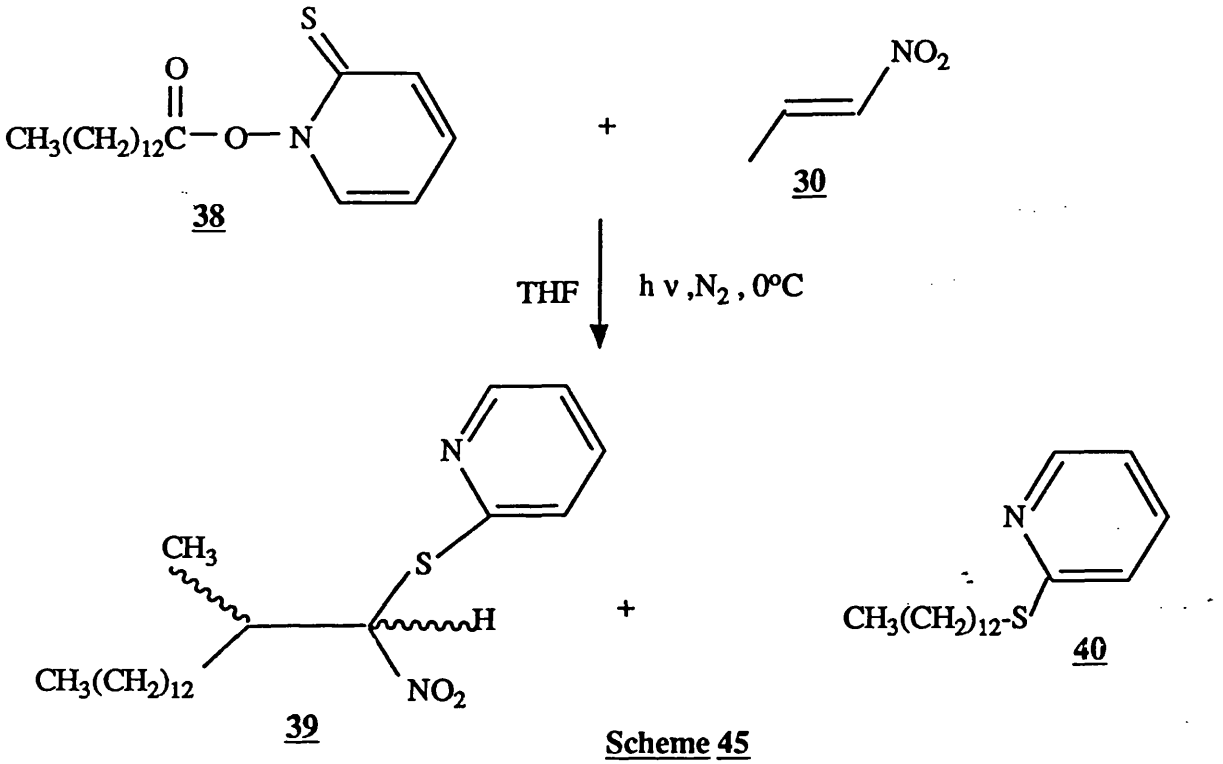


37 38

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).



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.**

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

* Difficult to purify by column chromatography due to excess nitropropene

Table 1

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 α to the nitro and thiopyridyl groups could be easily identified in the NMR spectrum. 200MHz ^{1}H-NMR showed two sets of doublets at δ=6.5ppm and δ=6.6ppm in a 1:1 ratio which belonged to the two different diastereomers. The β-CH_3 group gave two sets of doublets at δ=1.05ppm and δ=1.10ppm. The chemical shift of the ω-CH_3 was a triplet at δ=0.86ppm.

In the rearranged product 40, the chemical shift of the α-H was a triplet at δ=3.0ppm.

2.4.9 Reaction of 39 with $TiCl_3$

39 was dissolved in THF and added to 1M $TiCl_3$ (pH < 1), and stirred for 16 hours. The product of the reaction was extracted into ether and obtained in 65% yield. ^{1}H-NMR showed the complete absence of aromatic signals. IR showed a stretch at 1718cm^{-1}.

Buffered $TiCl_3$ 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 $TiCl_3$

The McMurray and Melton method of using $TiCl_3$ 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 $TiCl_3$ 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 $TiCl_3$. Similar observations were made by Crich and Davies with **α-nitrosulphides**. Here, when bufferred $TiCl_3$ solutions (pH=6) was used, no reaction took place.

2.4.11 Attempted conversion of 35 to 18 using other oxidizing agents

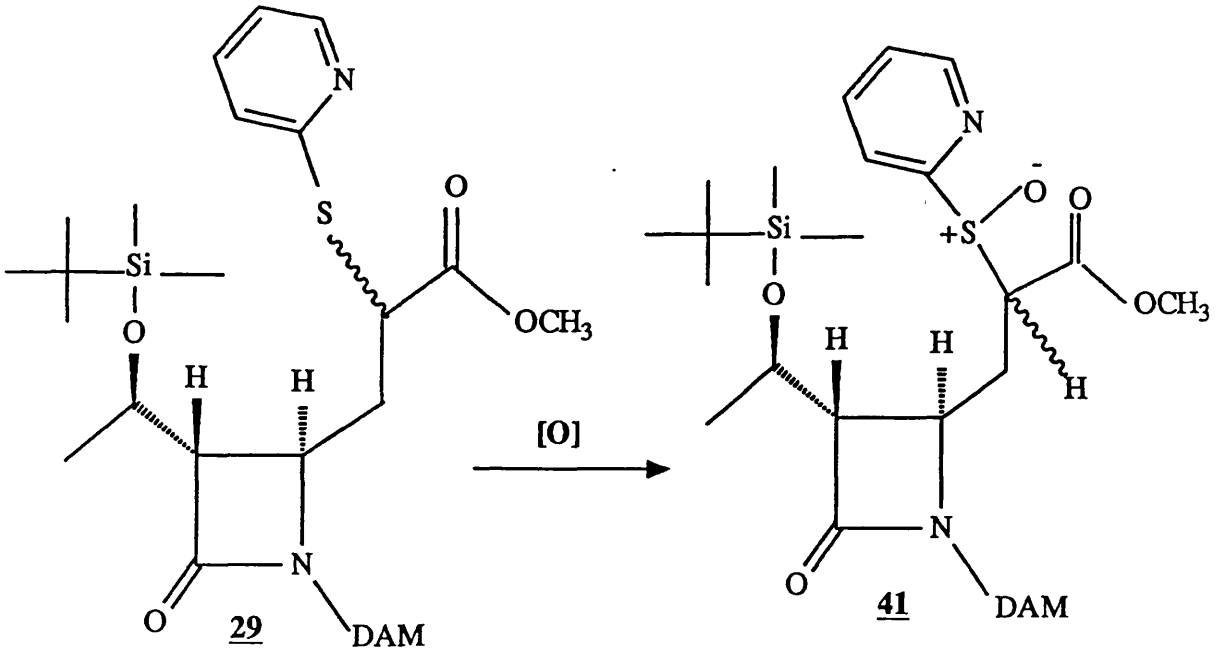
The oxidizing agents potassium permanganate and sodium dichromate

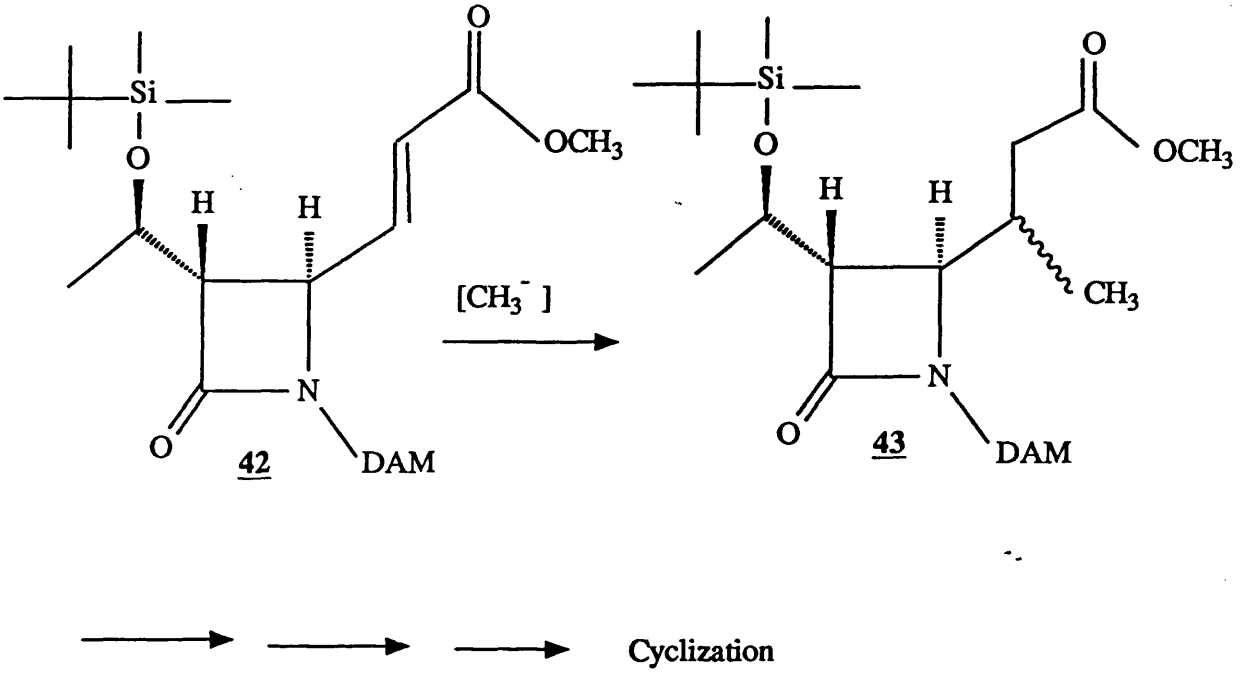
were used on 35, but only the starting material was isolated.

When excess ozone,[44] in CH_2Cl_2 at -78°C was used, the β-lactam molecule was completely destroyed. Barrett also reported encountering a similar difficulty in this type of conversion.[51]

2.4.12 Synthesis of 42

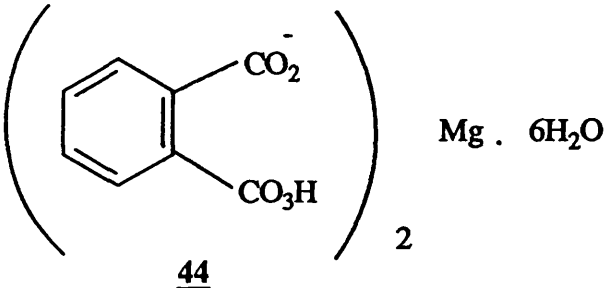
Because of the difficulties encountered above, it was decided to change the synthetic strategy. The adduct 29 had already been successfully synthesized. It was anticipated that the sulphide 29 could be oxidized to the sulphoxide 41 and elimination of the sulphenic acid would generate the αβ-unsaturated system 42.[59] The methyl group could then be introduced into 42 nucleophilically to give 43,[52] which could then lead up to cyclization (**Scheme 46**).





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.



44

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.[53] This proved to be unsuccessful.

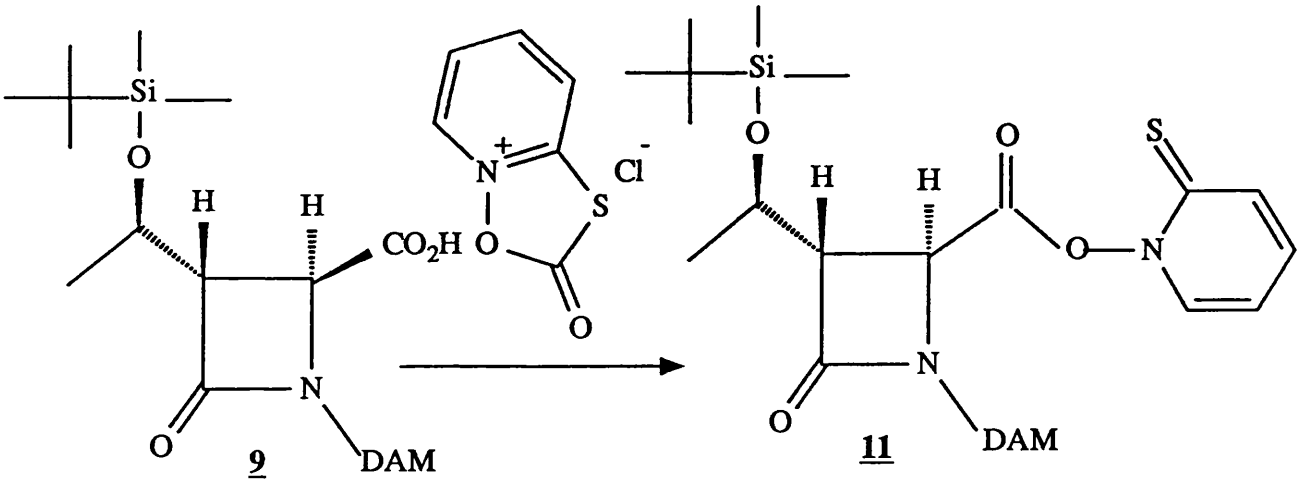
Next, the commercially available copper(I) bromide - dimethylsulphide complex was used, and the cuprate was made by adding methyllithium at room temperature.[54] The **42** was then added. The reaction was unsuccessful. From the ^{1}H-NMR spectrum, **42** appeared to have undergone isomerization.

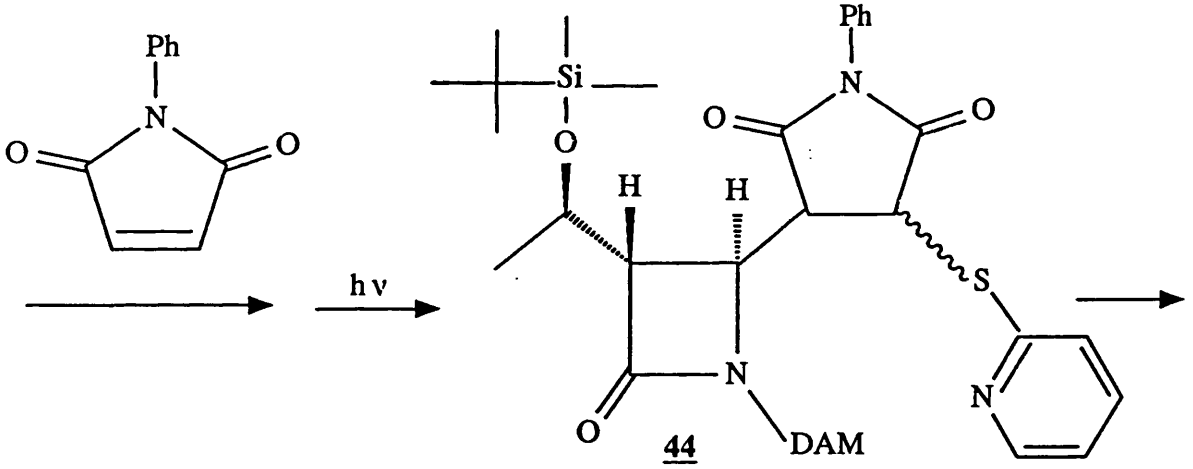
Next, a complex of copper(I) cyanide and methyllithium[55] was prepared in ether at -78°C. **42** was added. However, on work-up only the starting material **42** was obtained.

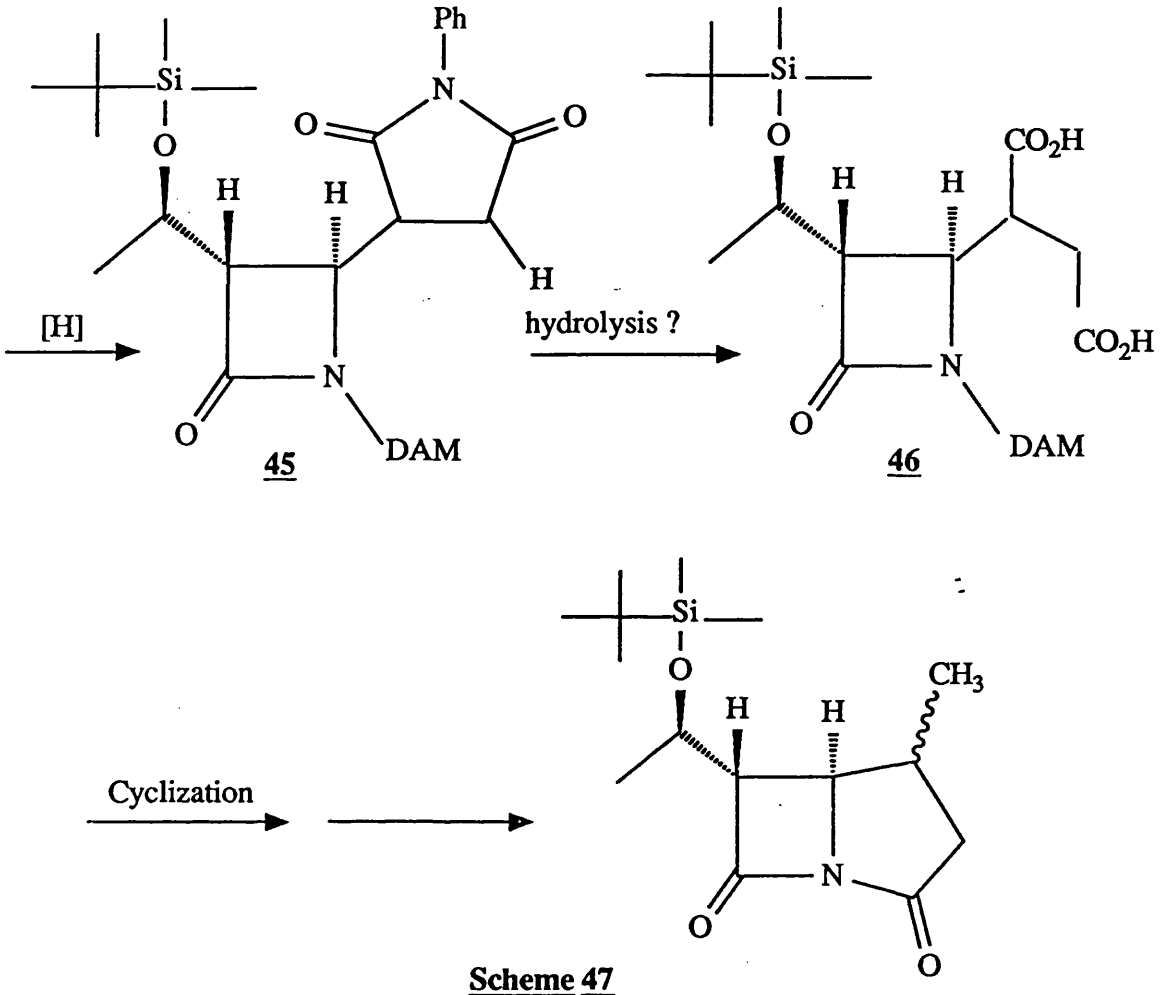
It was decided not to continue with the cuprate method. It has been reported that in this reaction, the reaction conditions have to be very specific, and that it depends on a whole host of conditions such as which other ligands were present and the very precise number of equivalents of reagents used.

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 **60**, 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**).


Si
O
H
H
CO2H
O
N
O
9
DAM
N
+
Cl
-
S
O
Si
O
H
H
O
O
S
N
N
O
11
DAM


Ph
N
O
O
hν
Si
O
H
H
Ph
N
O
O
S
N
N
O
44
DAM



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 α-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.

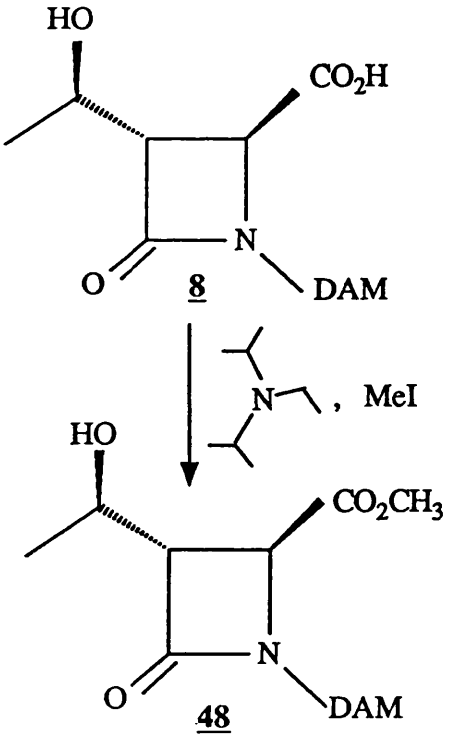
It was felt that it was not worthwhile pursueing this synthetic route any further because of the speculative nature of the cyclization and subsequent reduction

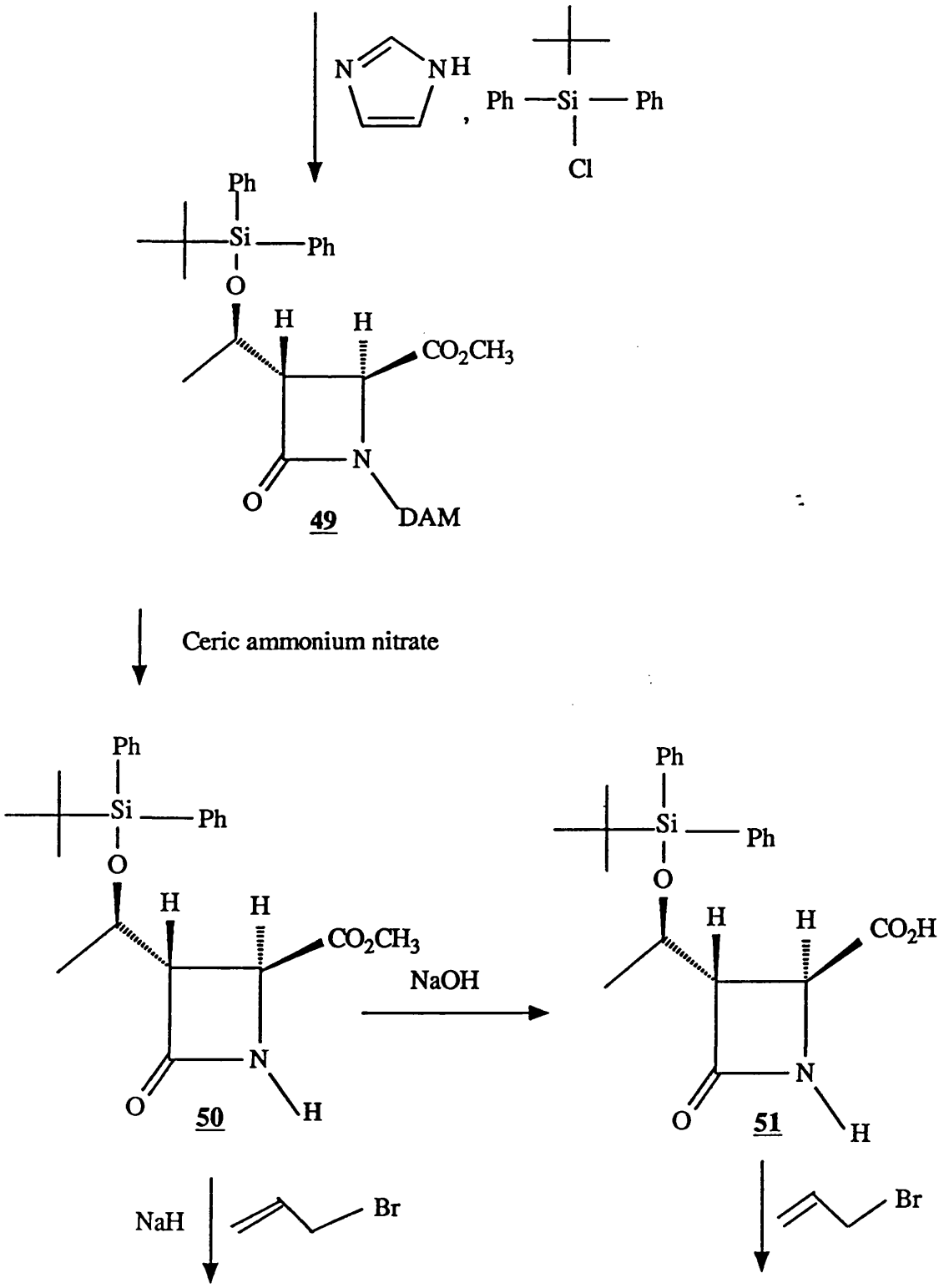
of the acid group to a methyl group.

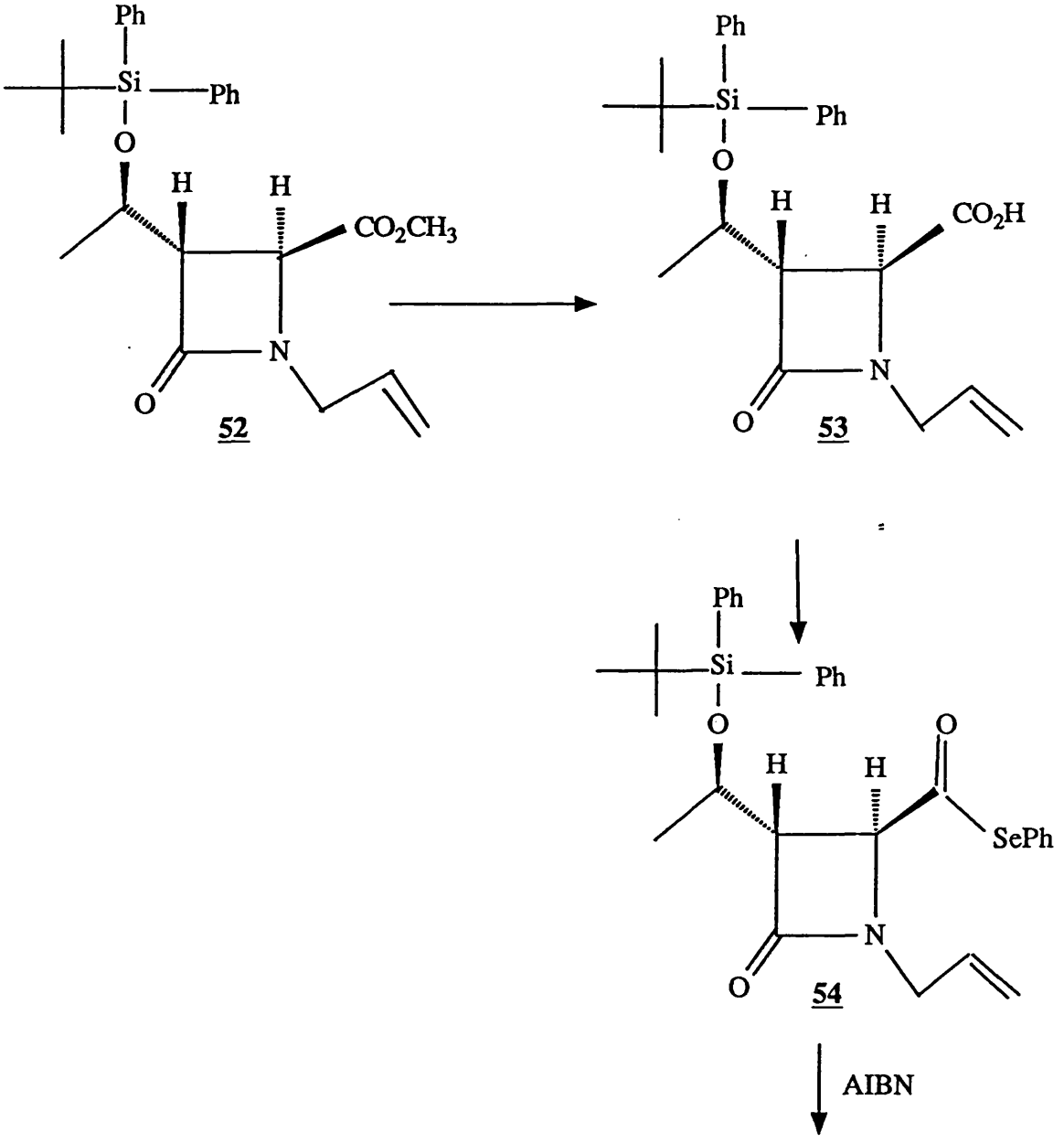
2.5.1 Attempted synthesis of a bicyclic β-lactam

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




N
NH
Ph
Si
Ph
Cl
Ph
Si
Ph
O
H
H
CO2CH3
N
O
DAM
49
Ceric ammonium nitrate
Ph
Si
Ph
O
H
H
CO2CH3
N
O
H
50
NaOH
Ph
Si
Ph
O
H
H
CO2H
N
O
H
51
NaH
Br
Br


Ph
Si
Ph
O
H
H
CO2CH3
N
O
52
Ph
Si
Ph
O
H
H
CO2H
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Ph
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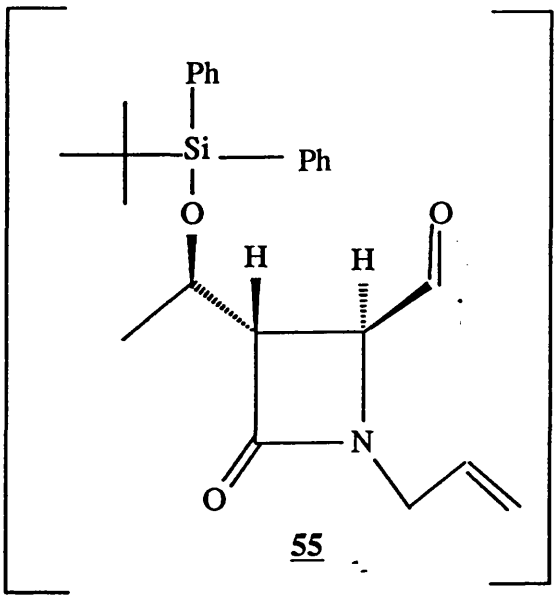
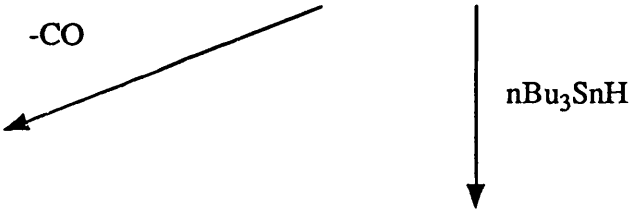
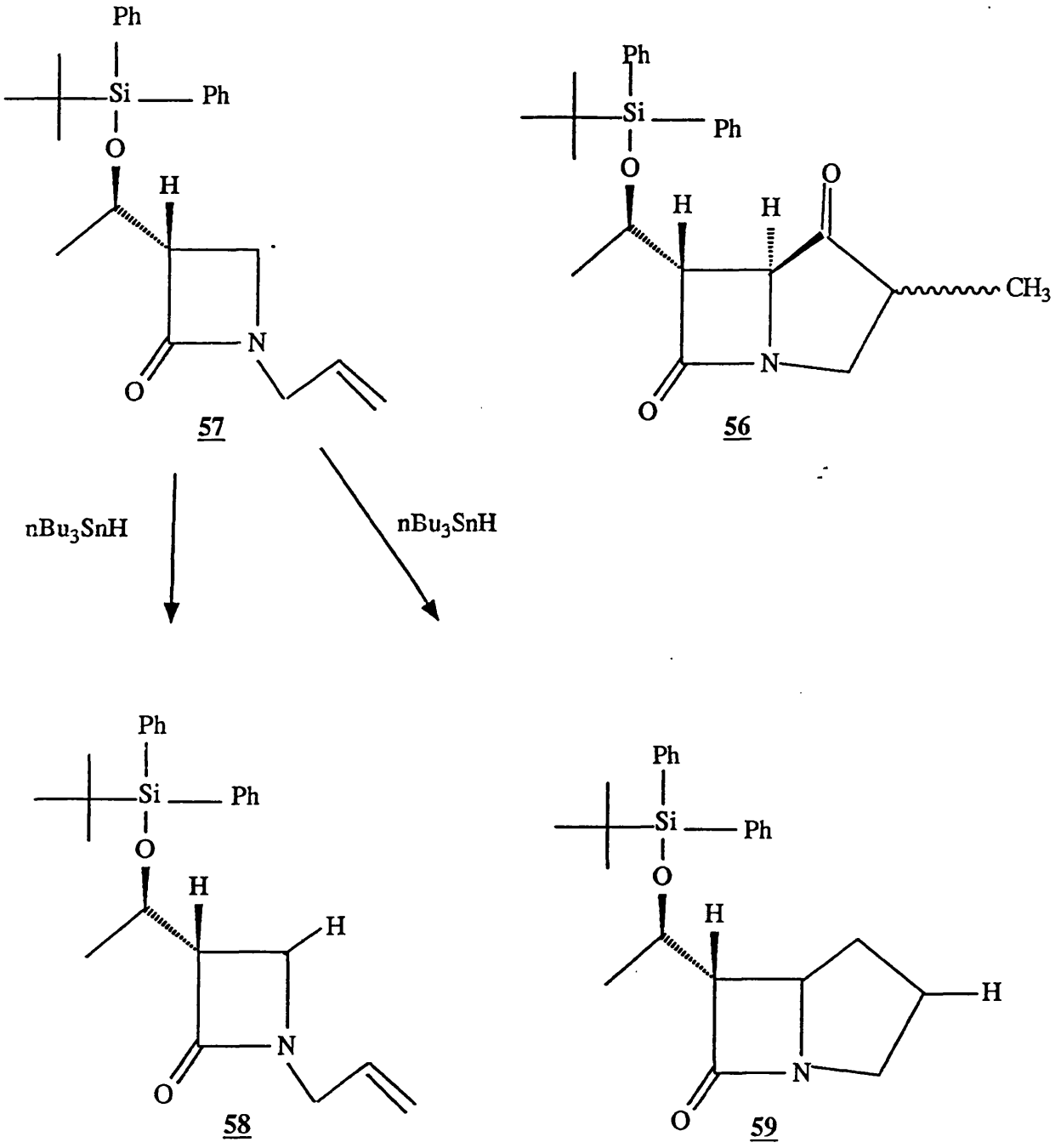
H
SePh
N
O
54
AIBN



55





Scheme 48

This involved the protection of the alcohol and acid groups of 8 followed by the removal of the DAM group.[26,46] 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

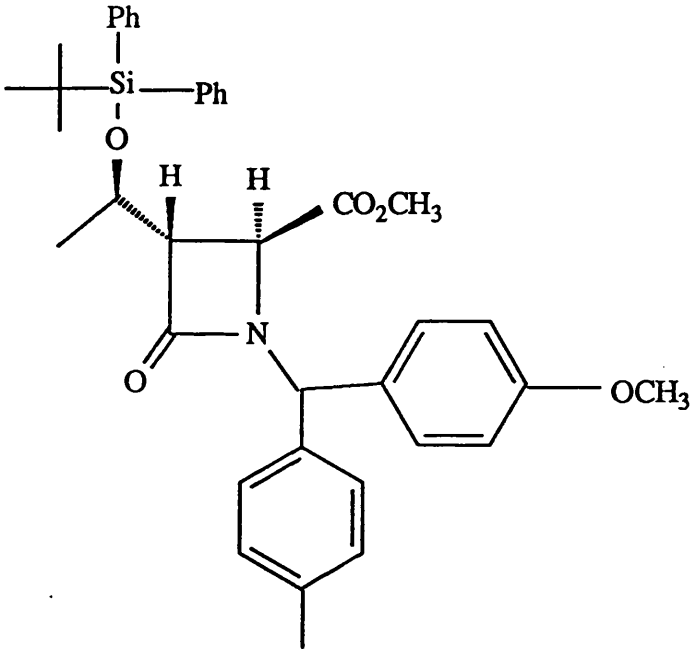
The first step of this synthetic scheme was to protect the acid group and prevent it from interfering with the subsequent steps of the synthesis. This was done by using diisopropylethylamine as base and methylating with methyl iodide. DMF was used as solvent. The ester was isolated and required no further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

As the acid group is now protected, silylation only required the use of one equivalent of silyl chloride. The **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 t-butyldiphenylsilyl chloride were added. 49 was isolated in 93% yield over the two steps.

2.5.3 Removal of the DAM group

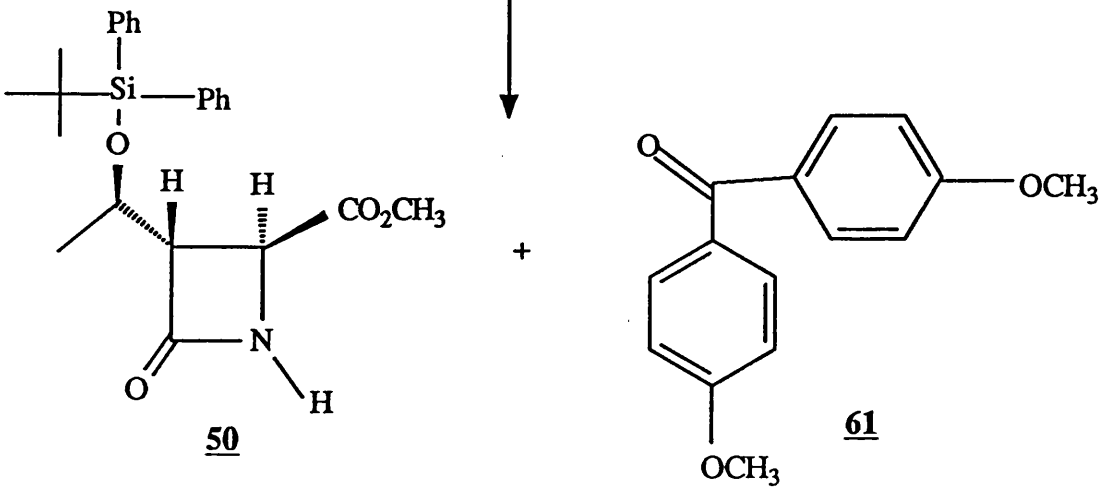
The **DAM** group of 49 was removed by stirring it in acetonitrile : water (9:1) with ceric ammonium nitrate strictly at 0°C for 30 to 45 minutes (**Scheme 49**).



49

$MeCN:H_2O = 9:1$

Ceric ammonium nitrate



50 **61**

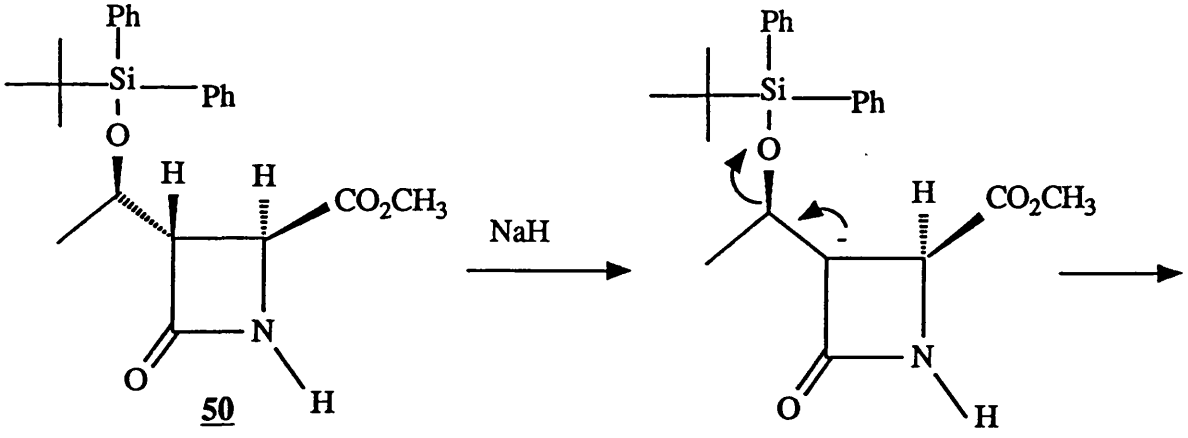
Scheme 49

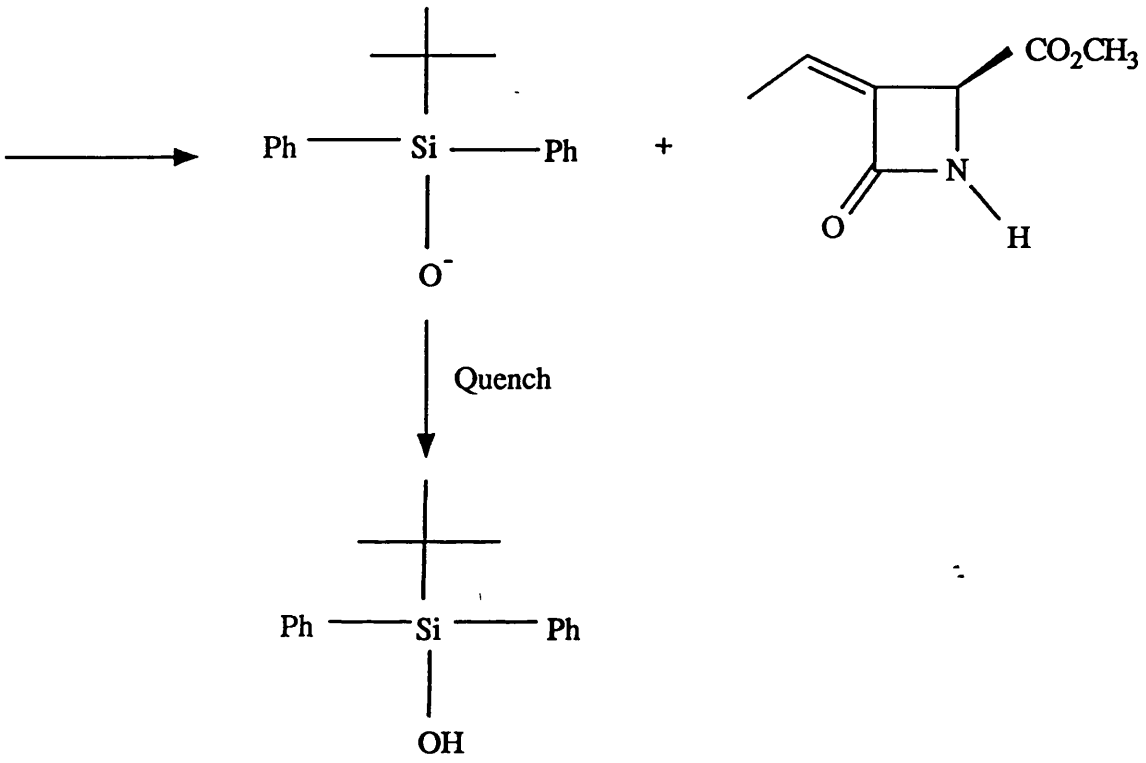
It was found that at temperatures below -10°C the reaction was stationary, and above 0°C, **non-β-lactam** products were obtained. The reaction was quenched by pouring into water and ethyl acetate, and the excess oxidant reduced with sodium metabisulphite.

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



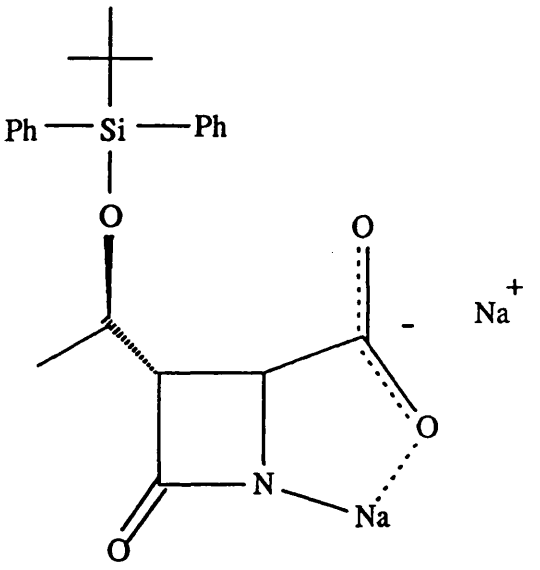


62

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.



63

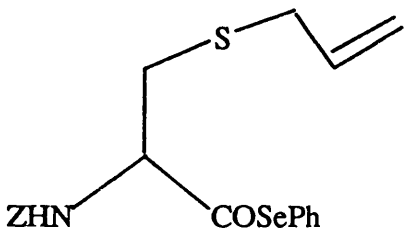
2.5.5 Synthesis of the selenyl ester 54

The phenylselenide 54 was prepared by first forming the mixed anhydride of 53 with i-butylchloro- formate 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.[60] 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



64

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.[109] Certain derivatives of (±)-α-methyltryptophan have been shown to have micromolar affinity for the peptide cholecystokinin B receptor from the mouse cerebral cortex.[110]

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.[74,75]

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

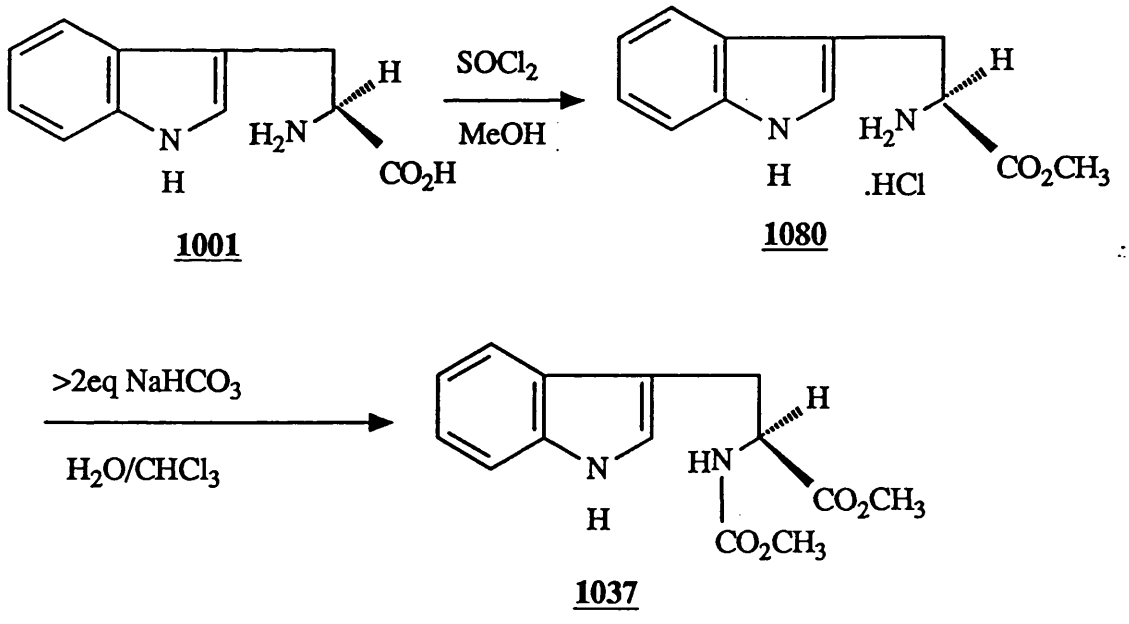
The work on tryptophan described in this thesis has already been outlined in **chapter 1** of this thesis.

3.1.1 Protection of L-tryptophan

Initially in **scheme 51**, the α-carboxylic acid and α-amino groups of the L-trytophan **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, $SOCl_2$, in methanol. The product was collected as a solid in 95% yield and required no further purification.[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.[97]

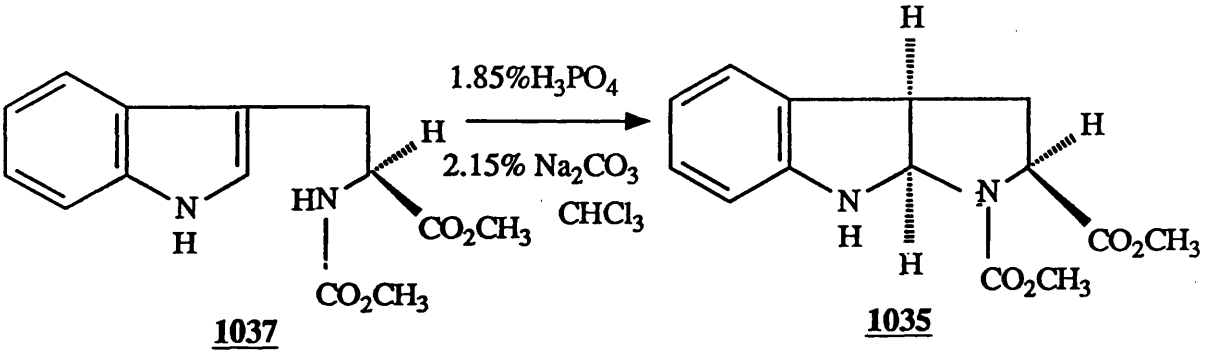


1001 **1080** **1037**

Scheme 51

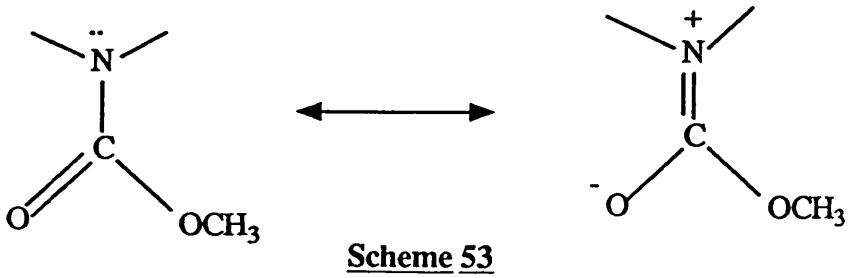
3.1.2. Cyclization of 1037 to give the pyrroloindole 1035

The compound **1037** was dissolved in 85% H_3PO_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**).



Scheme 52

The ^{1}H-NMR spectrum obtained at room temperature was in accordance with that reported by Hino and Davies.[97,102] 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.



Scheme 53

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.[102]

3.1.3 Protection of N-8 of 1035

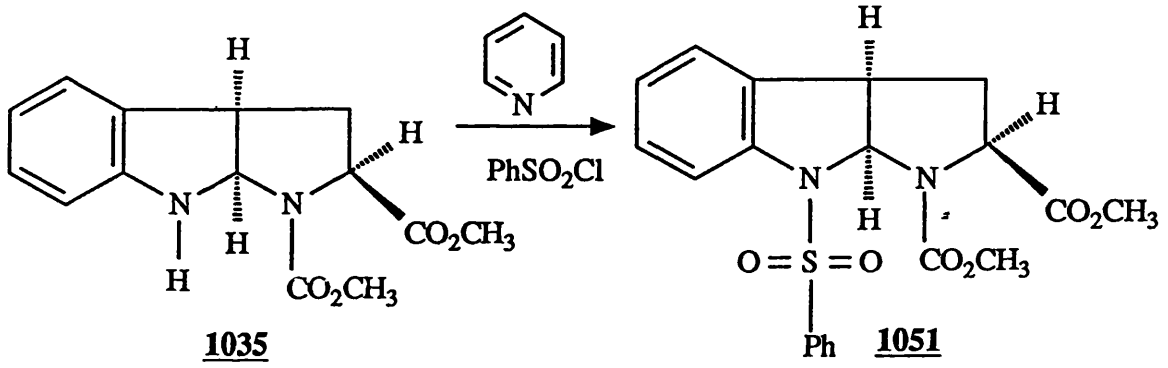
As the key step in the syntheses may involve deprotonation to form an enolate anion, it was thus necessary to protect N-8 with an appropriate group. Davies found that the sulphonyl groups were appropriate for this purpose, but however his chosen groups of **methylsulphonyl** and **p-methylbenzenesulphonyl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



1035 **1051**

Scheme 54

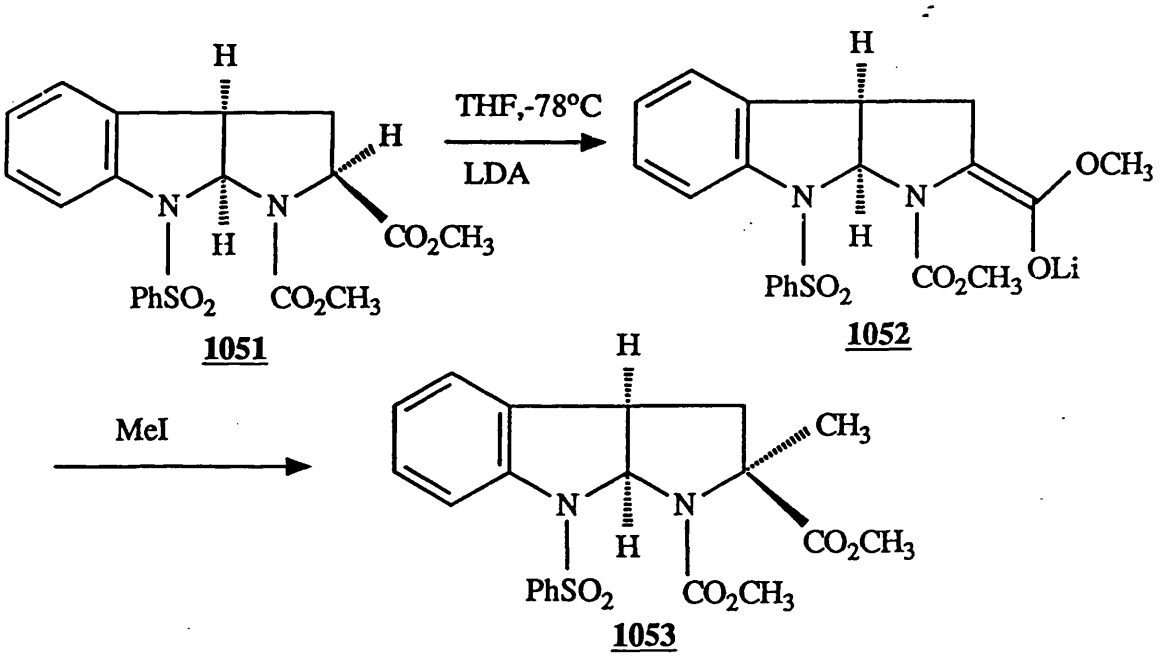
3.2 Synthesis of (S) and (R)- α-methylaspartic acid hydrochlorides 1055 and 1058

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.[97,101] 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). ^{1}H-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 $[\alpha]_D$= +95.2° (c=0.725, CH_2Cl_2).

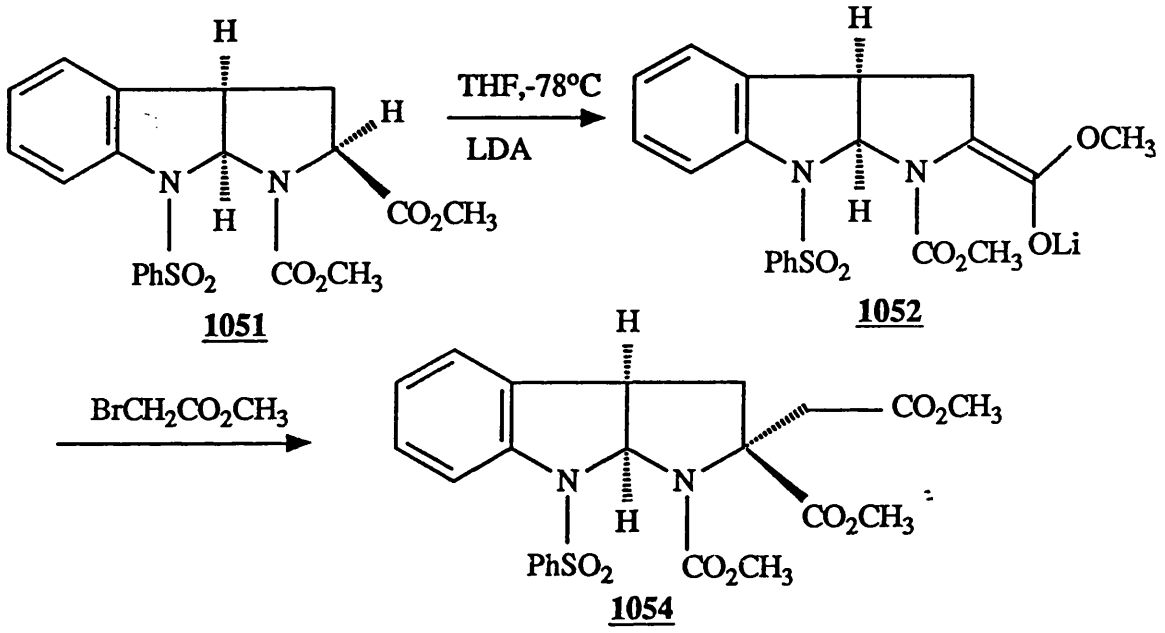


Scheme 55

(b) To form the adduct **1054**, the enolate **1052** was quenched with **methyl bromoacetate (Scheme 56).**[101]

The product was precipitated out from diethyl ether giving 90% yield.(mp =113°C, $[\alpha]_D$= +89.7°,c=0.39, CH_2Cl_2). The ^{1}H-NMR of 1054 at 25°C showed only one

set of signals indicating that the carbamate was rotating freely at +25°C.



1051 1052 1054

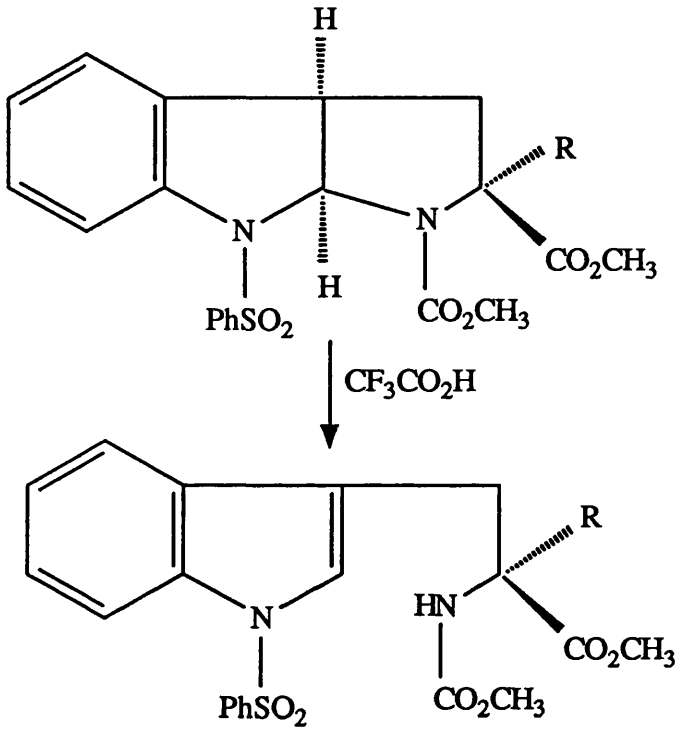
Scheme 56

3.2.2 Ring-opening of 1053 and 1054

1053 and 1054 were ring opened by dissolving them in **trifluoroacetic acid** (TFA) (Scheme 57).[97,102] The TFA was then evaporated off. However it was found that not all the TFA may be removed this way,[121] 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.



R=CH_3 1053

R=$CH_2CO_2CH_3$ 1054

R=CH_3 1056

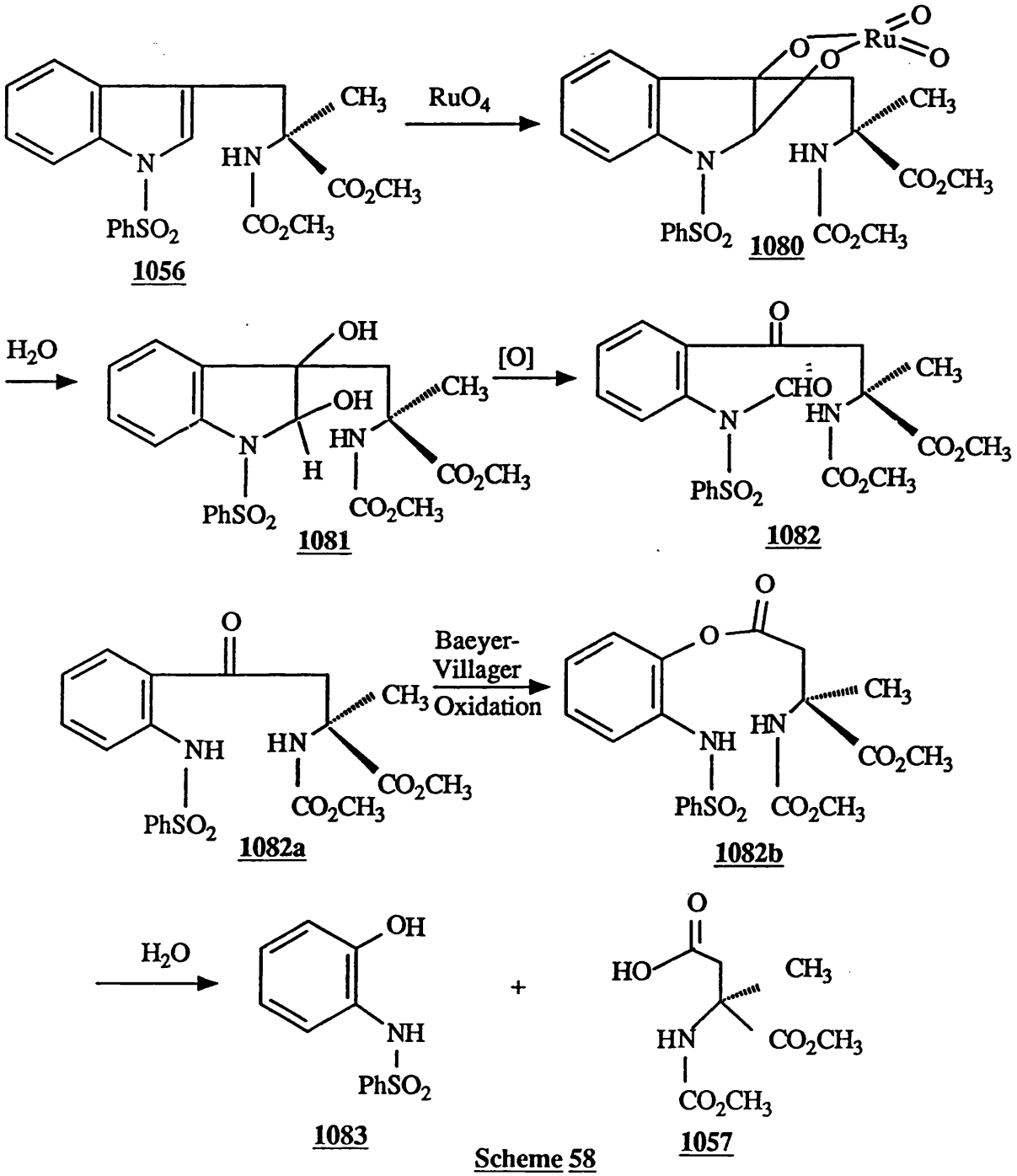
R=$CH_2CO_2CH_3$ 1059

Scheme 57

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.[105] 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 $RuCl_3$ 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, $[\alpha]_D$= -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 RuO_4 which was formed by the oxidation of $RuCl_3$ by $NaIO_4$ **(Scheme 58).**

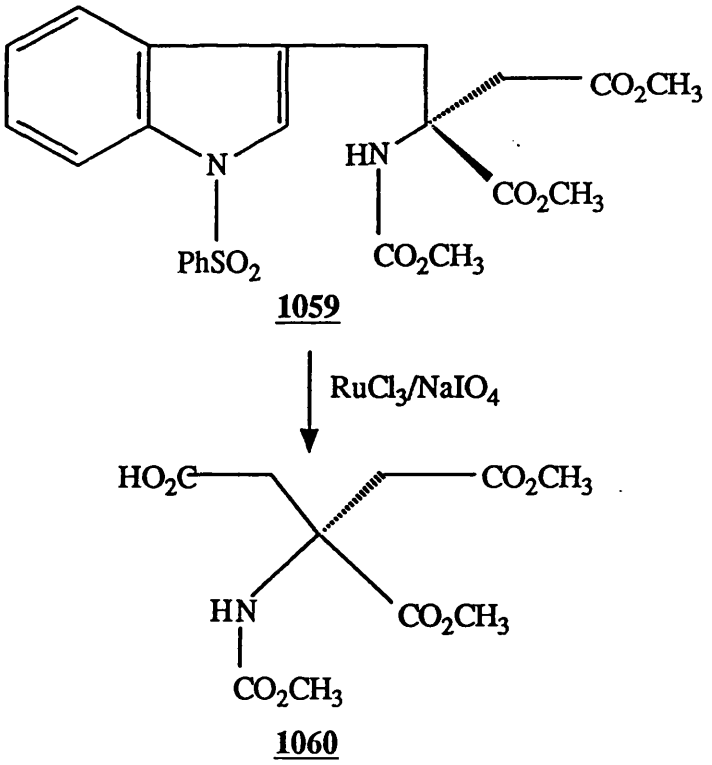


Scheme 58

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

3.2.4 Catalytic oxidative cleavage of 1059

1059 was catalytically cleaved in the same way as **1056**.[105] The product was collected as an oil in 60% yield (**Scheme 59**).

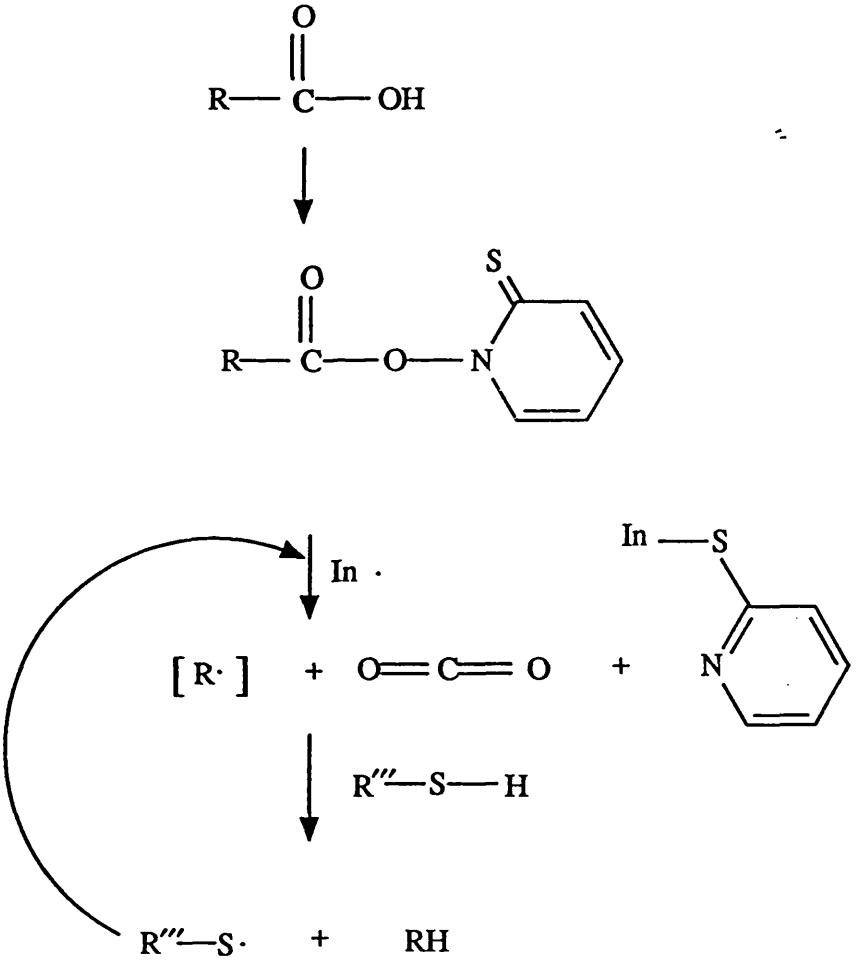


1059 → **1060**

Scheme 59

3.2.5 Reductive decarboxylation of the free acid group of 1060 using the Barton Reaction

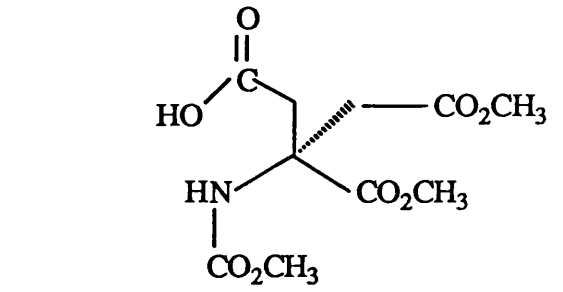
The **reductive Barton Reaction** has been used successfully in the β-lactam work already (**Scheme 33**).[31,32] It involves the conversion of the acid group to the thiohydroxamate ester, which under radical initiation conditions will decarboxylate creating a radical at the centre that was α to the acid group (**Scheme 60**).



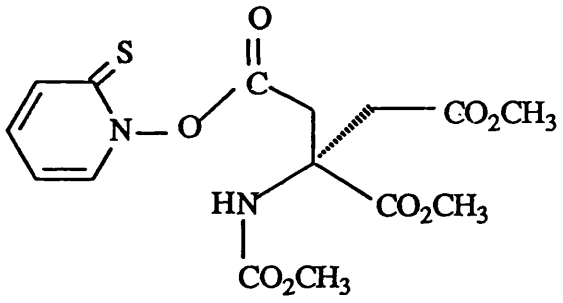
Scheme 60

The radical R· can then be quenched by a source of hydrogen such as a tertiary mercaptan.

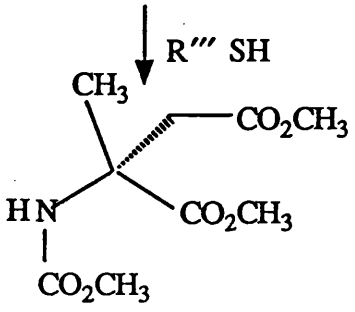
When applied to **1060**, the product was **1062** (Scheme 61).



1060



1061

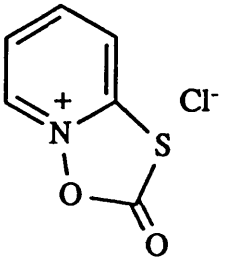


1062

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_2Cl_2. It was then photolyzed in the presence of tertiary dodecylmercaptan by a bright

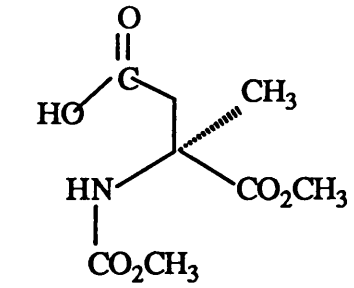


60

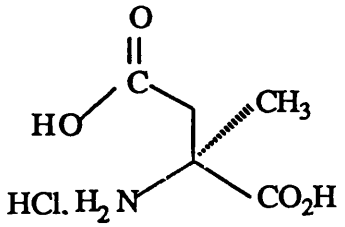
tungsten lamp. The product was isolated as an oil in 43% yield. Its optical rotation was $[\alpha]_D$= +21.3° (c=2.485,MeOH).

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**).



1057



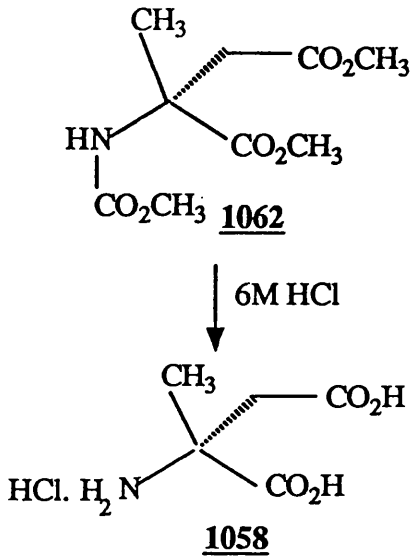
1055

Scheme 62

A high field ^{1}H-NMR in D_2O confirmed the product. Its optical rotation was determined to be $[\alpha]_D$= +33.4° (c=0.84,H_2O).

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).



Scheme 63

The ^{1}H-NMR of 1058 in D_2O was identical to that of 1055. Its optical rotation was found to be $[\alpha]_D$= -27.6° (c=2,H_2O) 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 α-alkylated, confirming the results obtained by Crich and Davies.[97,101] A better N-8 protecting group (**benzenesulphonyl**) than those used by Davies for the pyrroloindoles, which does not interfer 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.

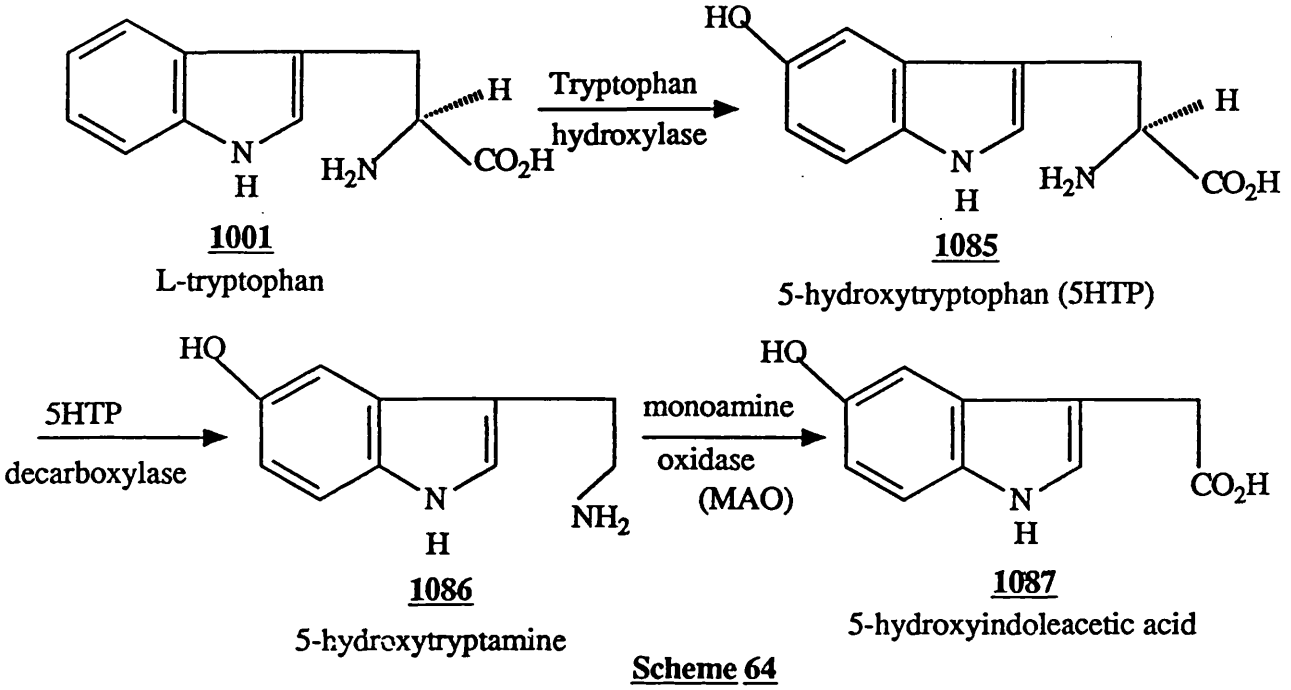
3.3 Synthesis of the (S) and (R) α-methyltryptamines 1067 and 1068

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.[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_2 receptor activation may be the causative factor in the hallucinogenic (psychoactive) effects of many drugs of abuse, including LSD.[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.**



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.

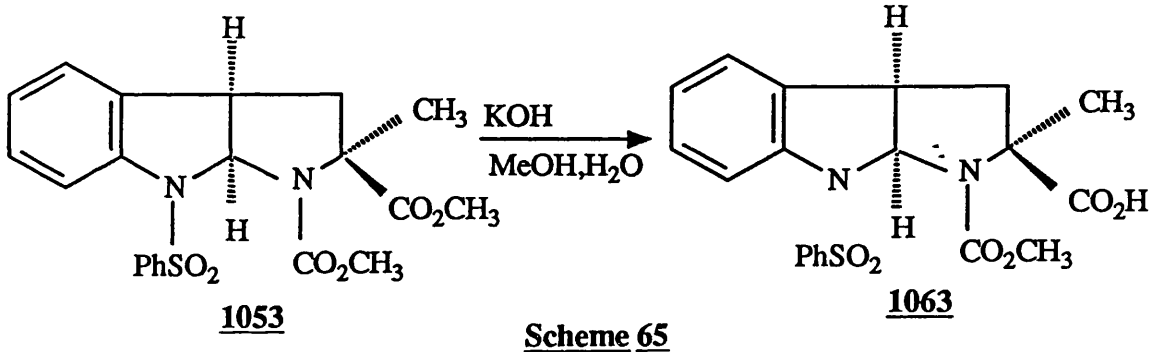
5H-T is degraded to 5-hydroxyindoleacetic acid after its release into the cytoplasm by **monoamine oxidase (MAO).**[108]

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 (7g in 5ml) 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.

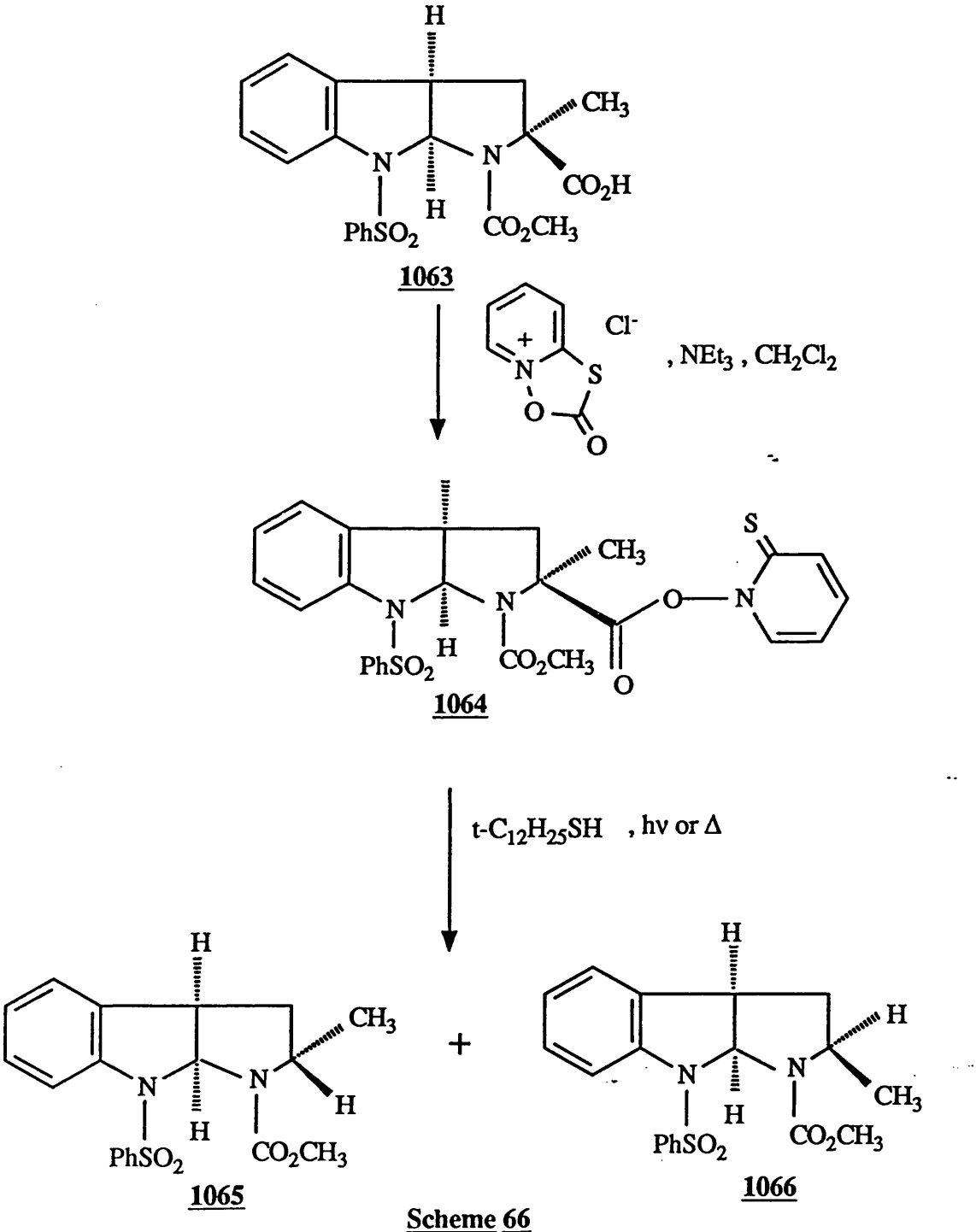


Scheme 65

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° (c=1 , CH_2Cl_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]


H
CH3
N
N
CO2H
H
PhSO2
CO2CH3
1063
Cl-
+
N
S
O
O
, NEt3 , CH2Cl2
S
CH3
N
N
O
N
H
PhSO2
CO2CH3
O
1064
t-C12H25SH , hv or Δ
H
CH3
N
N
H
H
PhSO2
CO2CH3
1065
+
H
H
N
N
CH3
H
PhSO2
CO2CH3
1066

Scheme 66

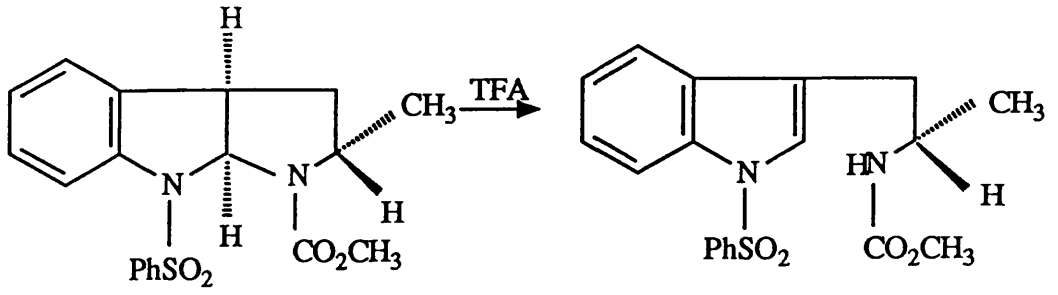
1064 was synthesized by stirring the acid 1063 with the salt 60 in dichloromethane at room temperature or below.

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.

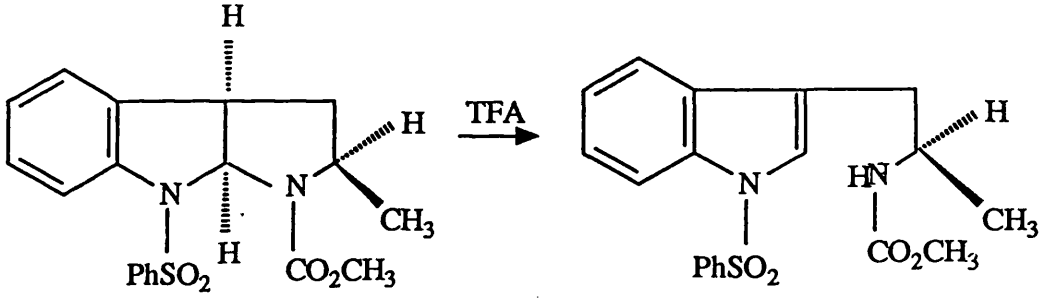
The two diastereomers were separated by column chromatography. The two diastereomers may be easily assigned by their high field ^{1}H-NMR because the **C-2 methyl** group of the **endo-methyl** diastereomer 1066 gives an upfield doublet at 0.678ppm.[71] This is due to shielding of the methyl group by the aromatic ring of the pyrroloindole system.[71] 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),[97] (**Scheme 67**), to give the S-isomer 1067 and the R-isomer 1068.



1065 (S)-1067



1066 (R)-1068

Scheme 67

The high field ^{1}H-NMR's of **1067** and **1068** were identical. Attempts to make the Mosher[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]$_3$** also failed to give conclusive results that **1067** and **1068** were enantiomers.

Optical rotations were attempted in two different solvents (MeOH , CH_2Cl_2), but their values were so small as to be unreliable.

Glennon[85] gave the optical rotations of α-methyltryptamine as follows:

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

R(-)-α-MeT $[\alpha]_D^{26}$= -30.1° (95% ethanol).

3.4 Isolable mixed anhydrides of i-butylformate

3.4.1 Introduction

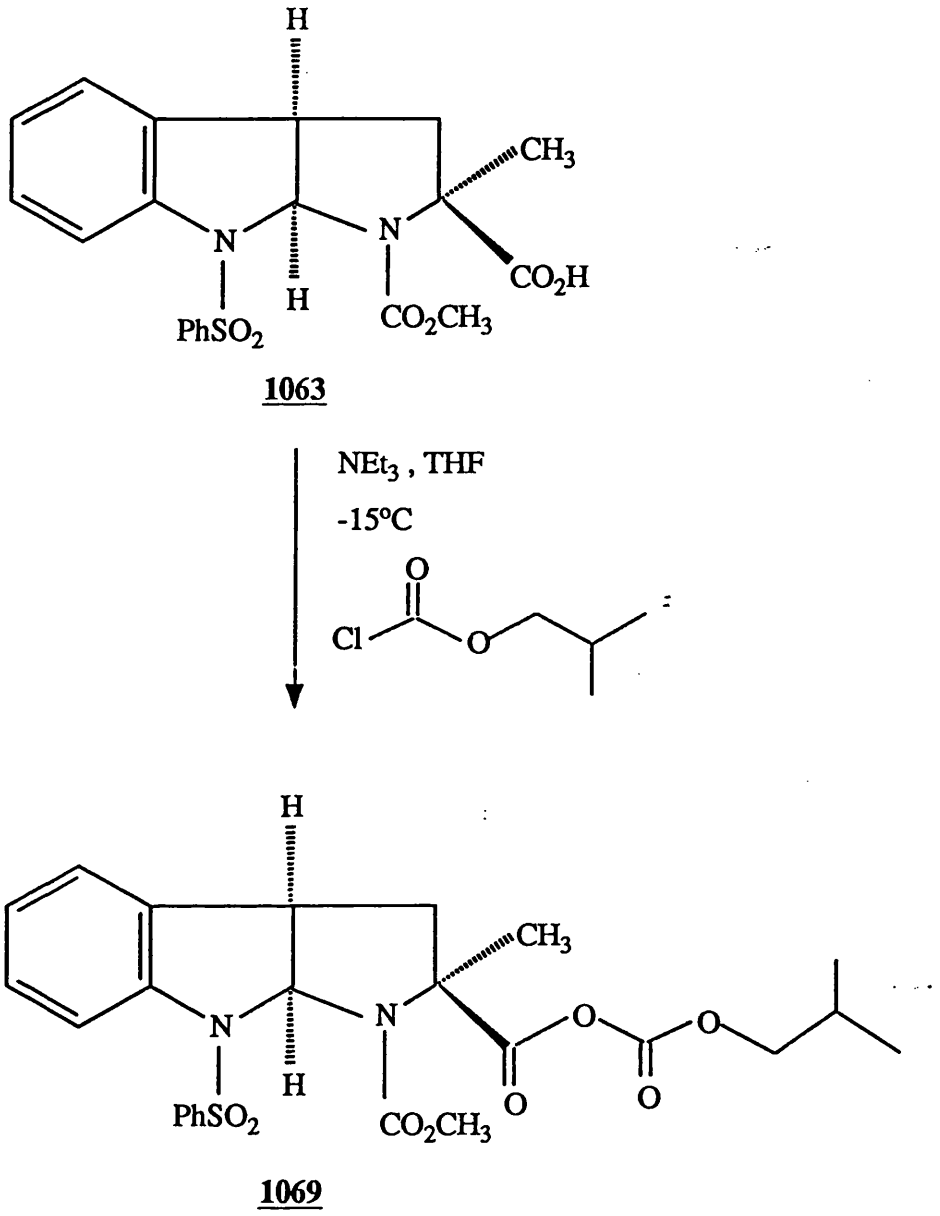
A well known method of preparing amides or phenolic esters from carboxylic acids involves the activation of the acid as the **mixed carboxylic-carbonic acid anhydride** followed by reaction with the pertinent nucleophile.[112] The anhydride is generated by the action of an alkyl chloroformate in the 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,[113] 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**).



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,

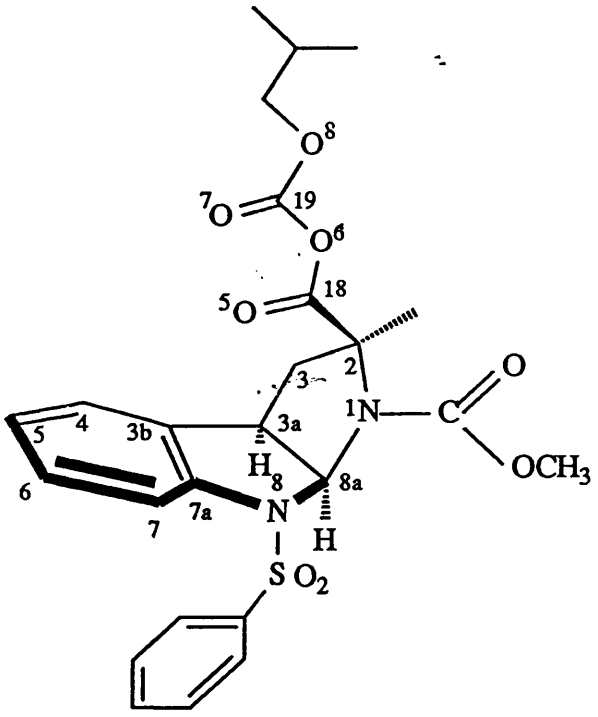
mp=107-109°C.

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 3.228Å from **C-3b** and **C-7a** of the pyrroloindole ring **(Scheme 69)**.

Distances

O5-C6	=	4.192	Å
O5-C7	=	3.793	Å
O5-C7a	=	3.279	Å
O5-C3b	=	3.279	Å
O5-C4	=	3.798	Å
C3b-C18	=	3.228	Å
C18-C4	=	3.749	Å
O6-C4	=	4.209	Å
O7-C7a	=	4.463	Å
O7-C5	=	3.828	Å
O7-C4	=	3.649	Å

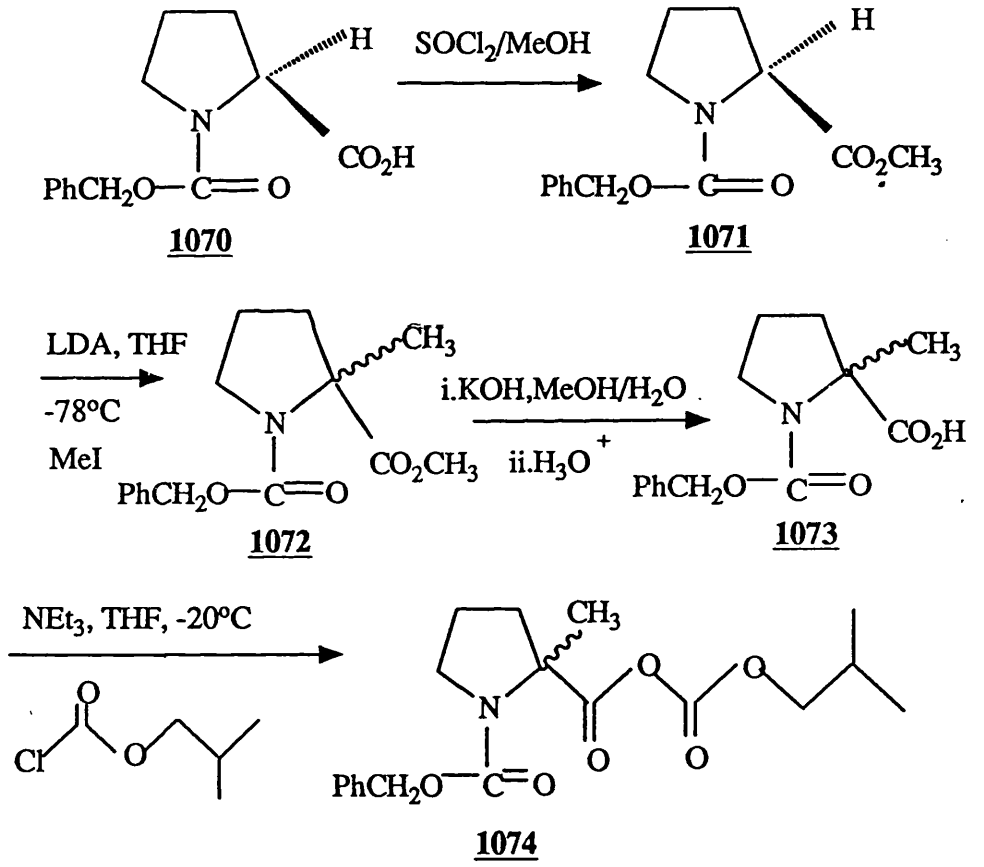


Scheme 69

This distance is **shorter** than the **3.4Å** 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.[103] 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)**.



1070 **1071** **1072** **1073** **1074**

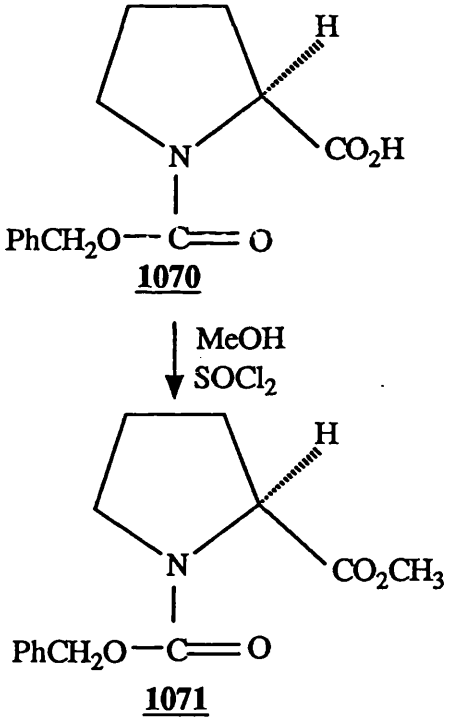
Scheme 70

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**).



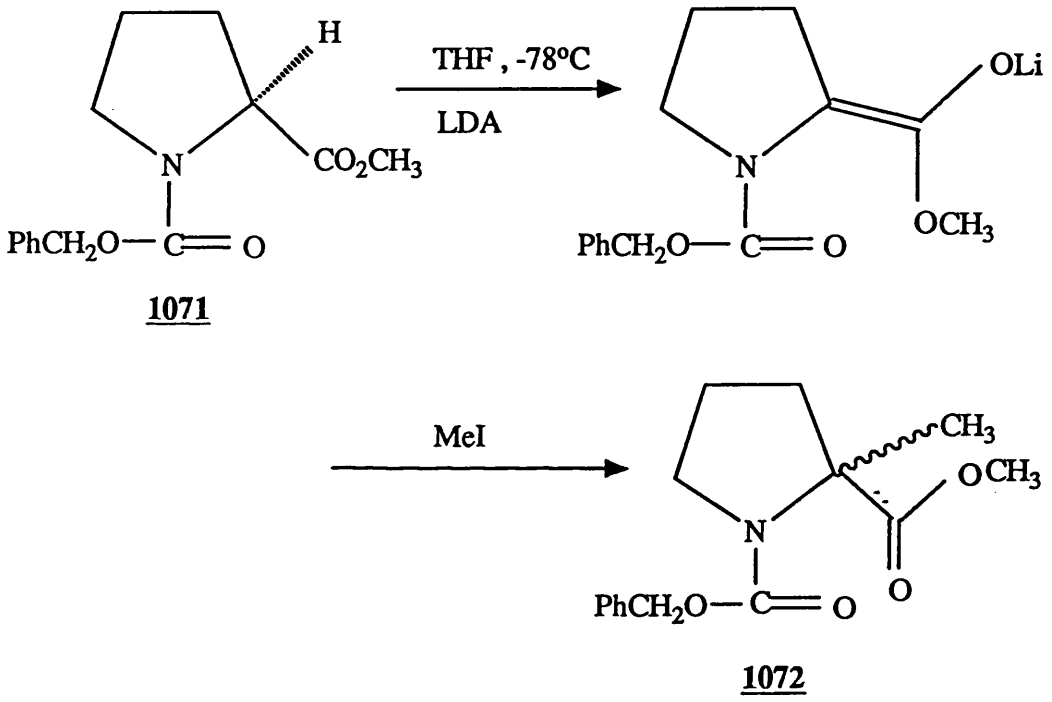
Scheme 71

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).



1071

1072

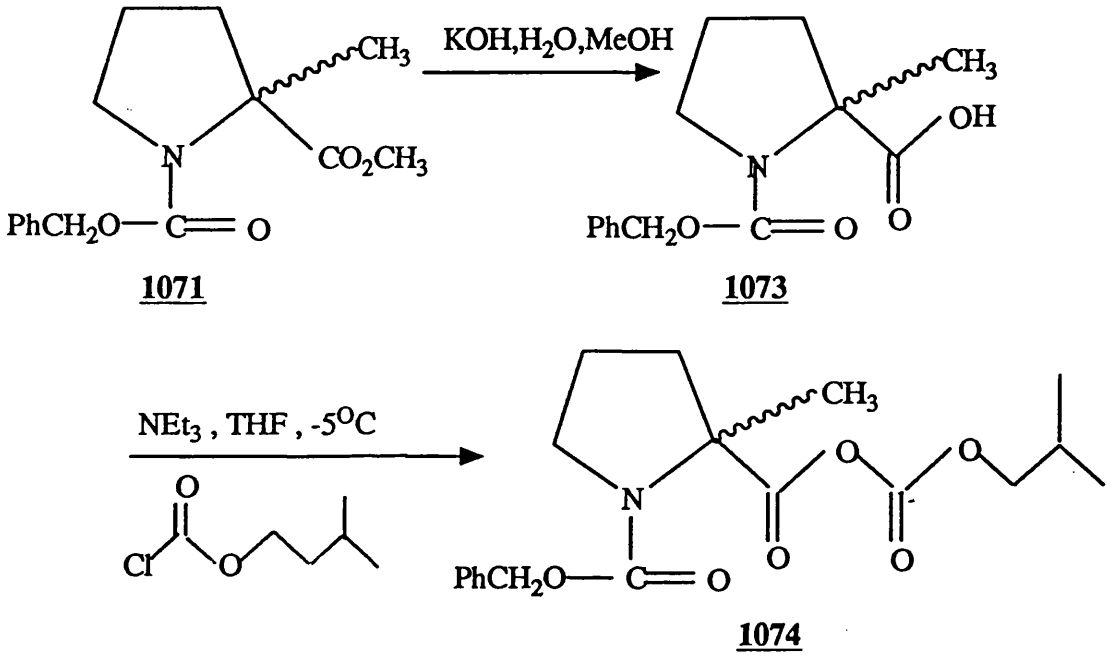
Scheme 72

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

(Scheme 73).



Scheme 73

The product was obtained in 97% yield and was recrystallized from CH_2Cl_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.

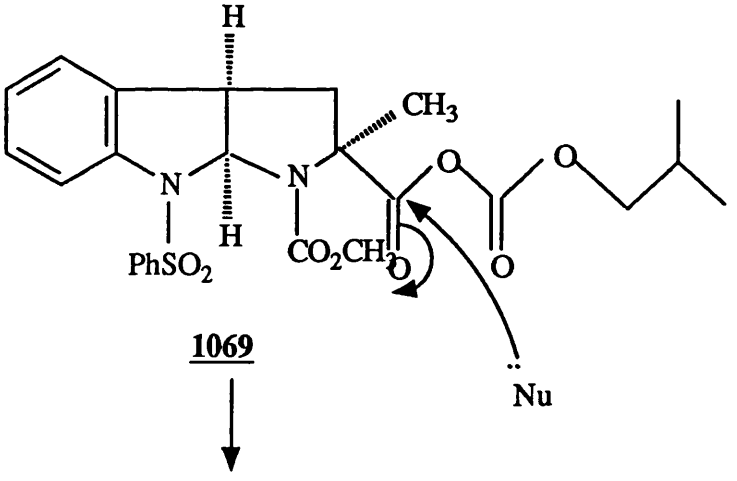
The product was then isolated in 86% yield as an oil. ^{1}H-NMR showed two

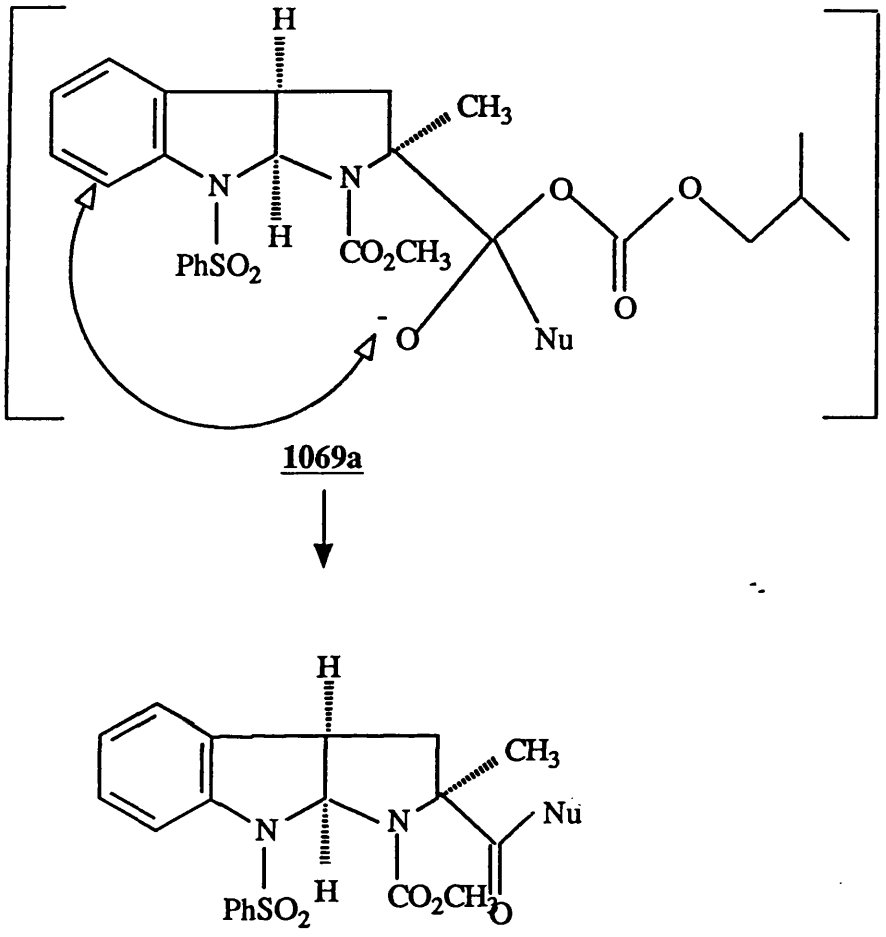
sets of signals in a 1:1 ratio due to the two rotamers.

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.[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 **α-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**).





Scheme 74

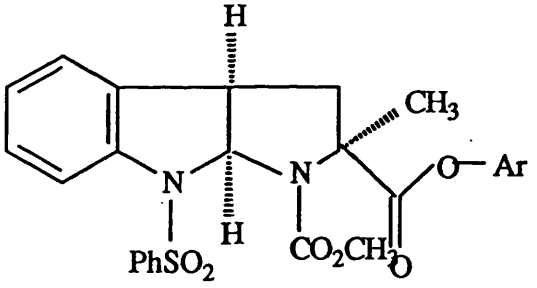
3.5 Pyrroloindoles with aromatic groups linked to the C-2 position

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.[103] A similar interaction may also occur in the mixed anhydride **1069**. This interaction was postulated on the basis of their close proximity (< 3.3Å) as revealed by X-ray analysis.

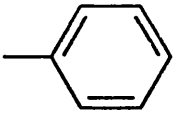
It would therefore be of interest to synthesize a series of compounds with aromatic groups linked to **C-2** of the pyrroloindole skeleton. It might be expected that if such a stacking interaction did occur, and that the aromatic substituent at **C-2** was correctly positioned, then this aromatic group 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.[71] 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.[71]

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.

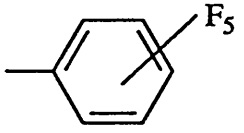


1075

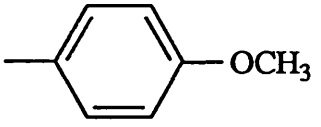
a, Ar =



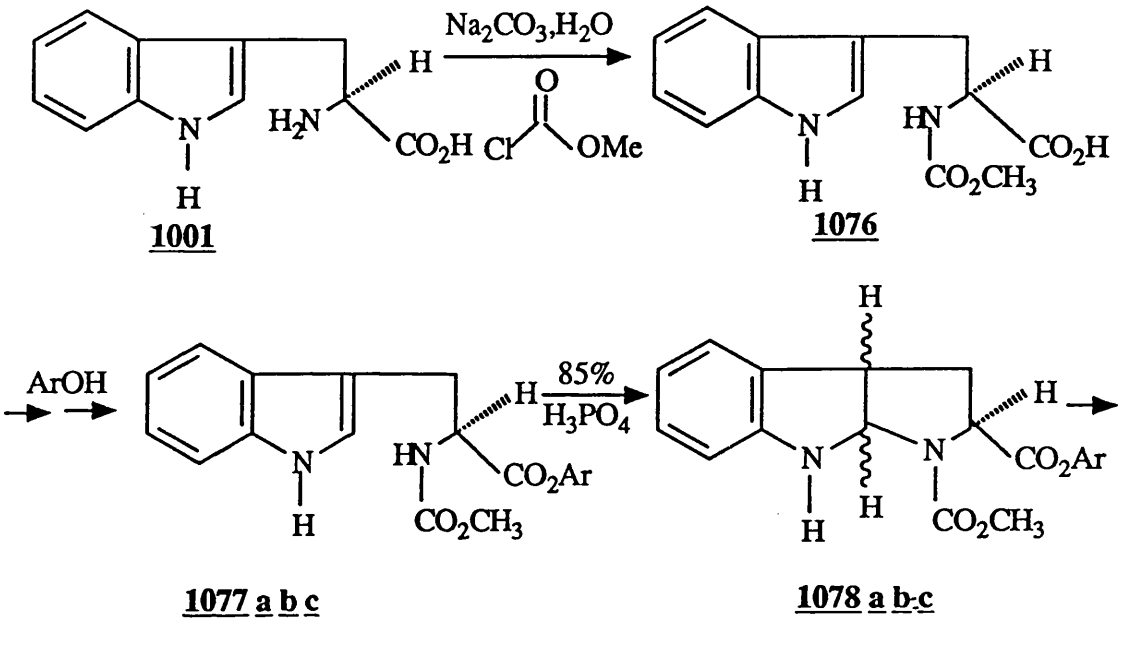
b, Ar =



c, Ar =

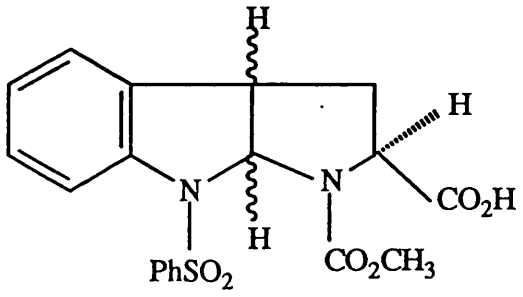


The synthetic scheme used is outlined in **scheme 75.**



Scheme 75

The pyrroloindole-2-carboxylic acid **1088** could have been used in the



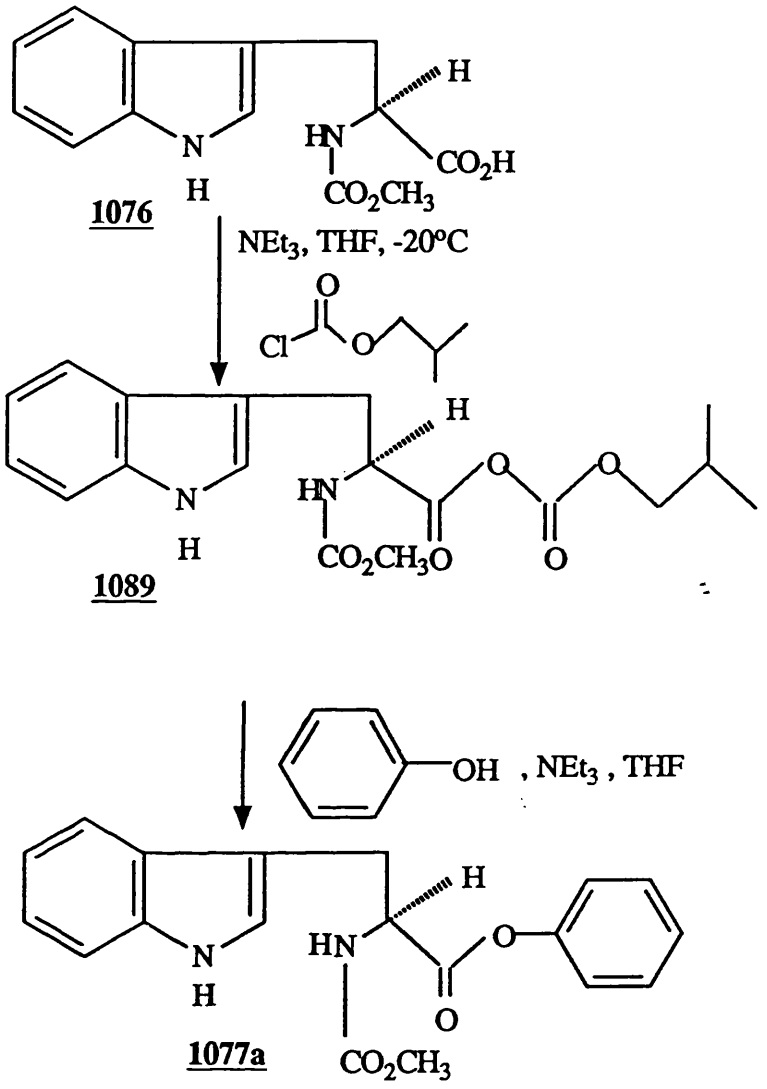
syntheses of the esters **1075** in a single step process, but it was decided to start from tryptophan **1001**, first protecting the nitrogen, and then esterifying the acid group to give **1077** before ring closure and protection of N-8. This route was taken to examine whether the cyclization would 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. ^{1}H-NMR in D_2O 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).**

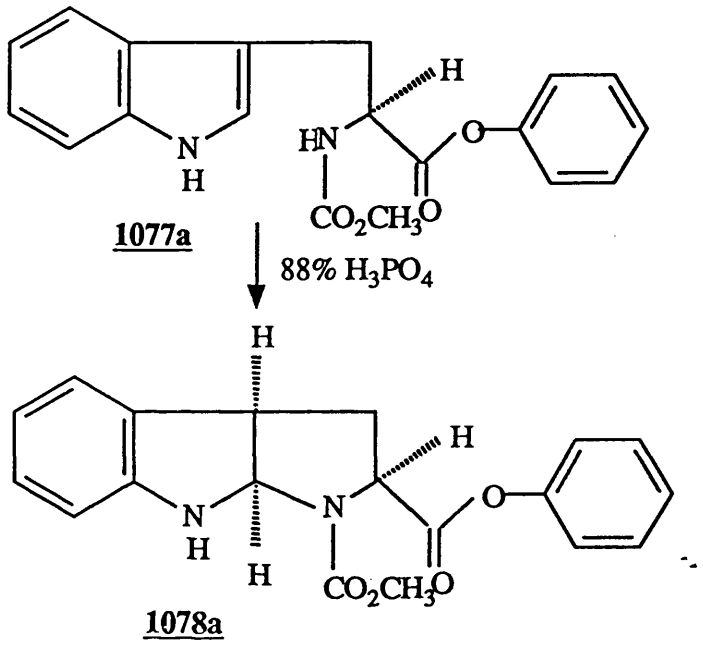


Scheme 76

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_3PO_4 and stirred for 8 hours. It was then quenched by dropping slowly into a rapidly stirring mixture of CH_2Cl_2 and 15% Na_2CO_3 (Scheme 77).

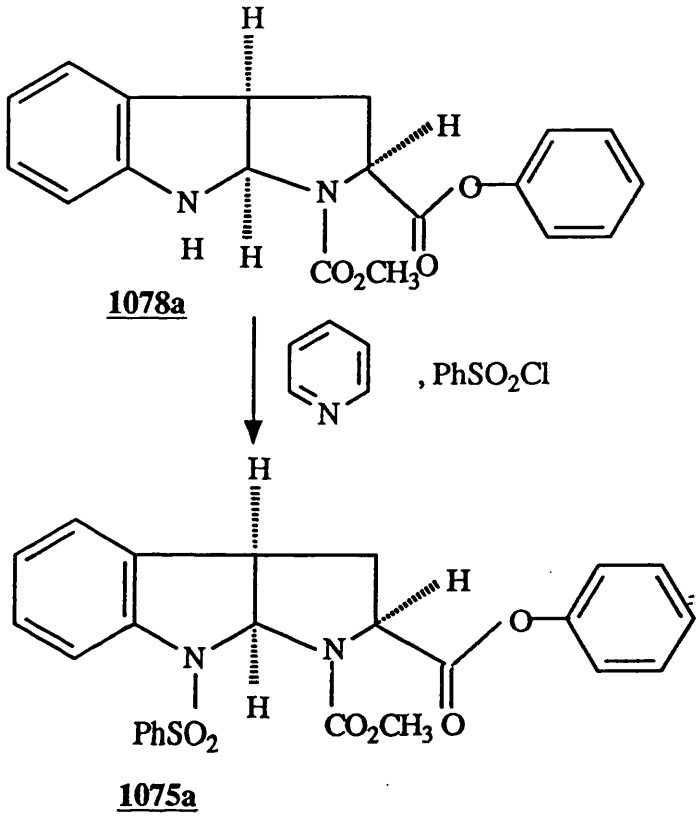


Scheme 77

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 δ=5.61ppm(d) and δ=5.66ppm(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).



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.

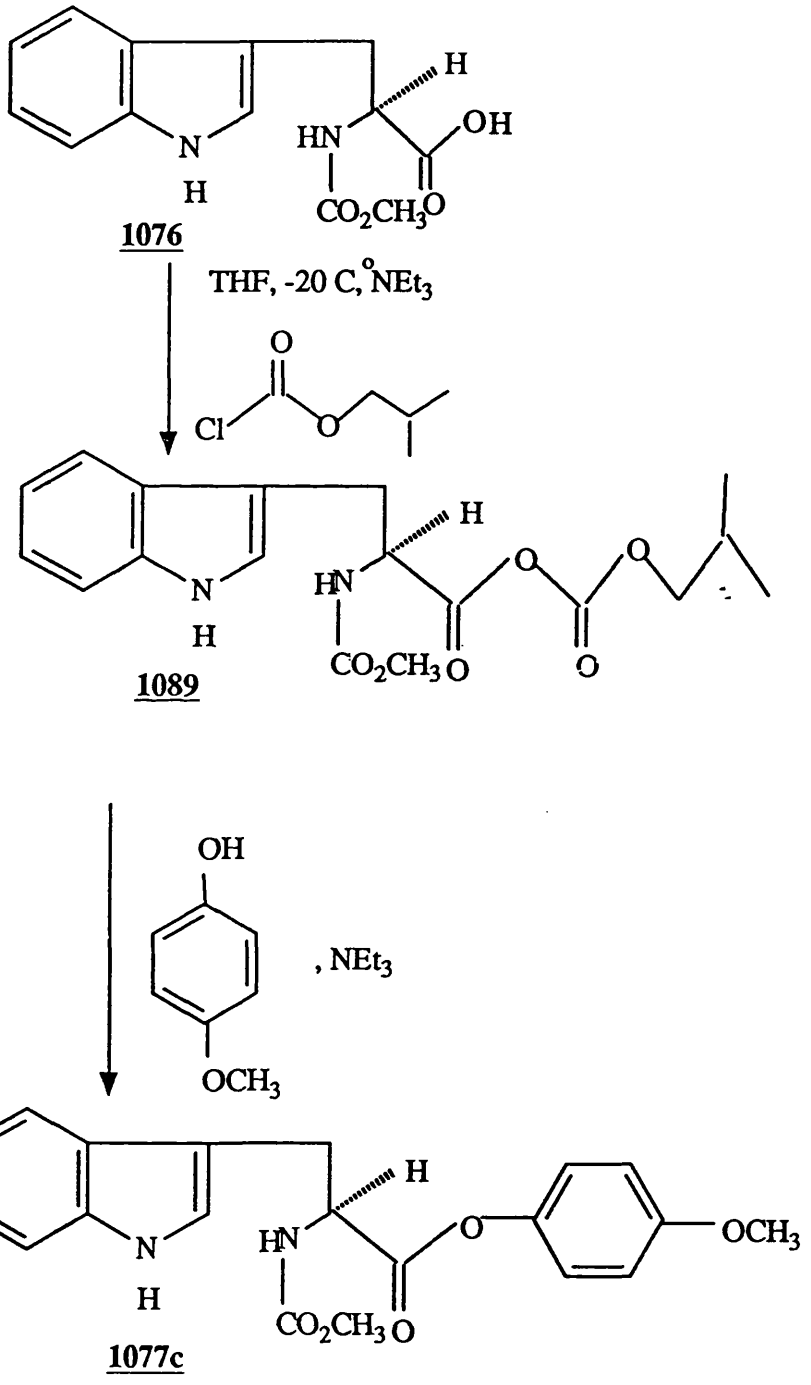
NOE difference spectra showed a positive NOE between the **H-2** proton with the **H-3a** and **H-8a** protons confirming that these protons have the syn-

configuration.

The high field ^{1}H-NMR at +50°C showed an upfield doublet at δ=6.5ppm 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 π-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

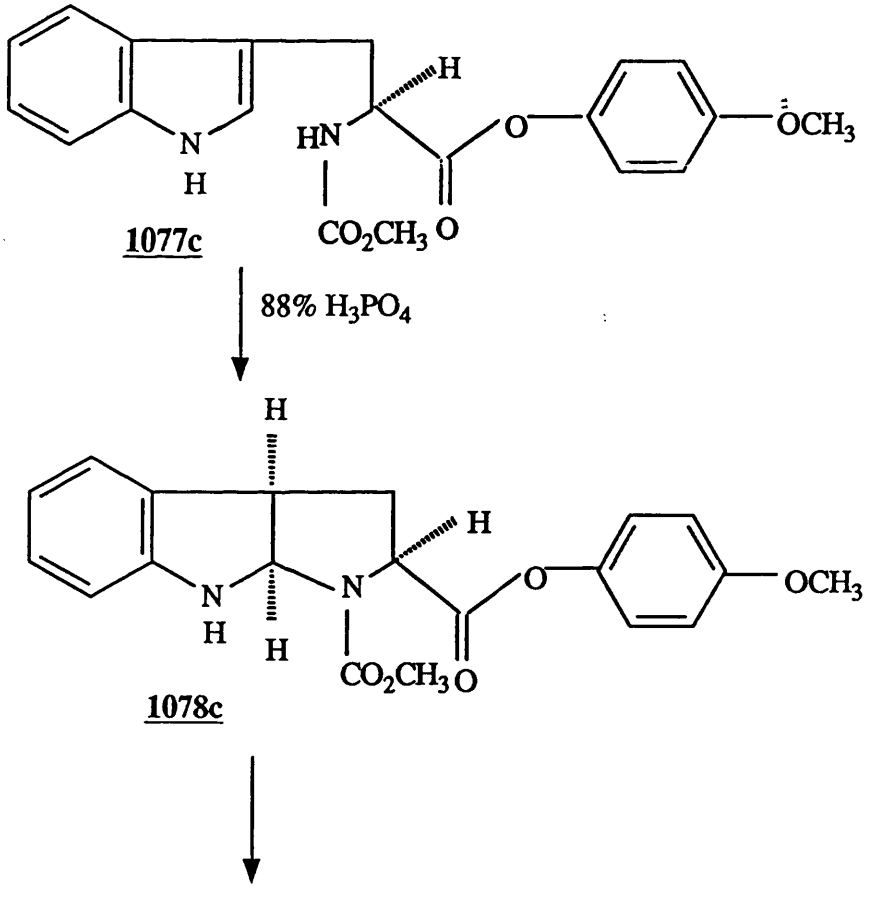
The p-methoxyphenyl ester **1077c** was synthesized by the same method as for the synthesis of the simple phenyl ester **1077a**. The acid **1076** was activated to the mixed anhydride **1089** and then allowed to react with p-methoxyphenol **(Scheme 79)**. The product was isolated in 41% yield as an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

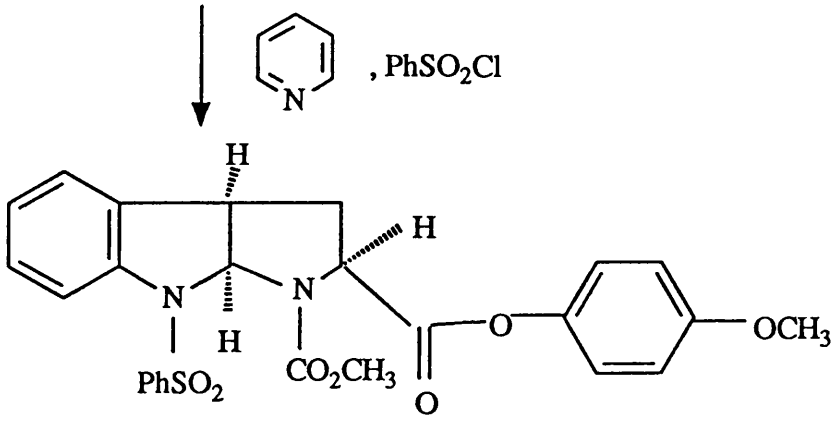

H
N
H
HN
OH
CO_2CH_3
O
1076
THF, -20 C, NEt_3
O
Cl
O
1089
, NEt_3
OH
OCH_3
1077c
OCH_3

Scheme 79

3.6.2 Ring closure of 1077c to 1078c

1077c was stirred in 88% H_3PO_4 for 16 hours and then quenched by dropping slowly into a rapidly stirring mixture of CH_2Cl_2 and 15% Na_2CO_3 solution. The product was isolated in 96% crude yield as an oil. No further purification was carried out. High field ^{1}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 δ=5.58ppm (d, J=6.4Hz) and δ=5.65ppm(d, J=6.8Hz) confirmed the cyclization (**Scheme 80**).





1075c

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**).[97]

The product was isolated as an oil after column chromatography in 62% yield.

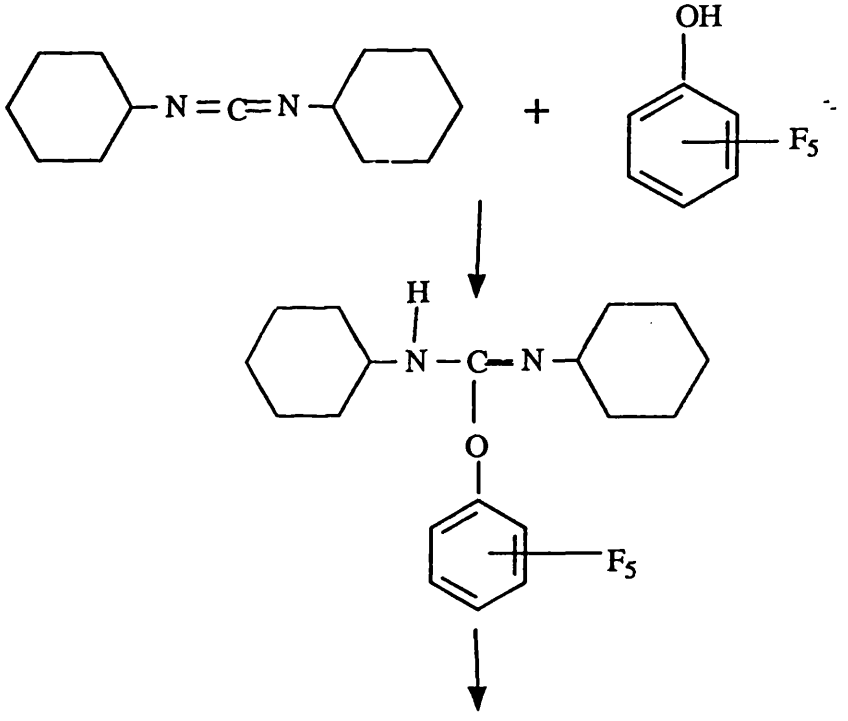
NOE difference spectra showed a positive NOE between **H-2** and **H-8a**, thus confirming their syn-configuration, and by steric reasons **H-3a** is syn to **H-8a** and thus **H-2** also.

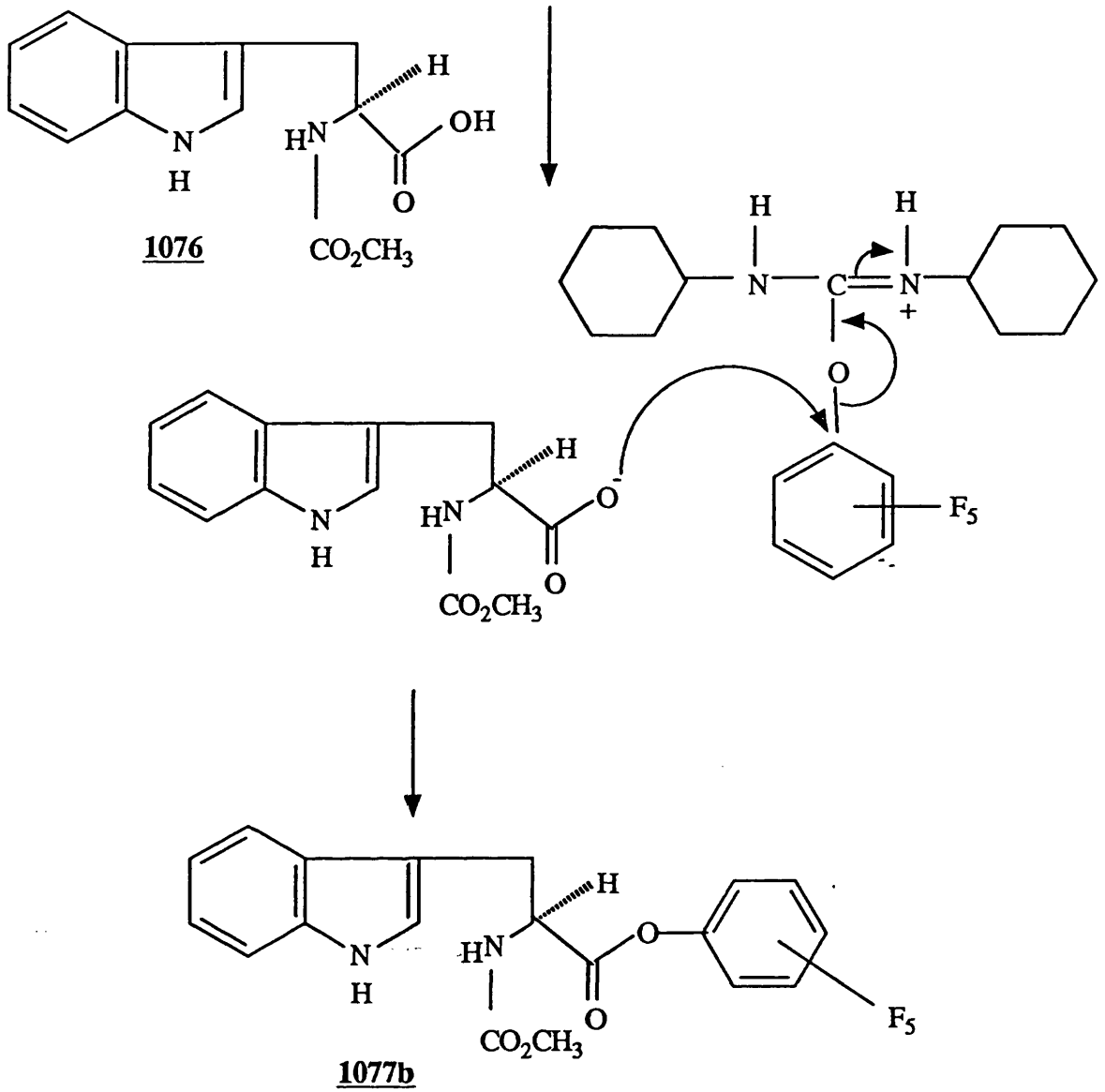
High field ^{1}H-NMR at room temperature showed broad peaks. These were resolved when the spectrum was taken at +50°C to give one set of signals. At -20°C, two sets of signals corresponding to the two nitrogen carbamate rotamers, were seen in a 5:2 ratio. However no signals for the individual protons 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_2Cl_2 at 0°C.





Scheme 81

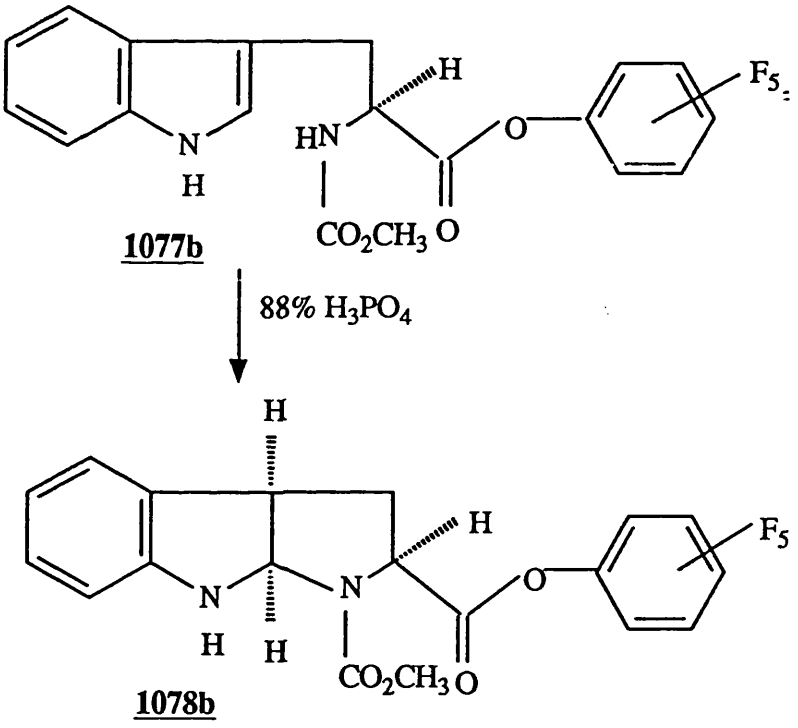
The N_b-protected tryptophan **1076** was added in EtOAc. The urea precipitate was filtered off, and the crude obtained was column chromatographed to give a colourless oil in 71% yield.

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

oxygen can be traced using labelling techniques.

3.7.2 Cyclization of 1077b to 1078b

The compound **1077b** was simply dissolved in 88% H_3PO_4 and stirred for 12 hours, and then the acidic reaction was added slowly to a rapidly stirring mixture of CH_2Cl_2 and 15% aqueous Na_2CO_3 (**Scheme 82**).



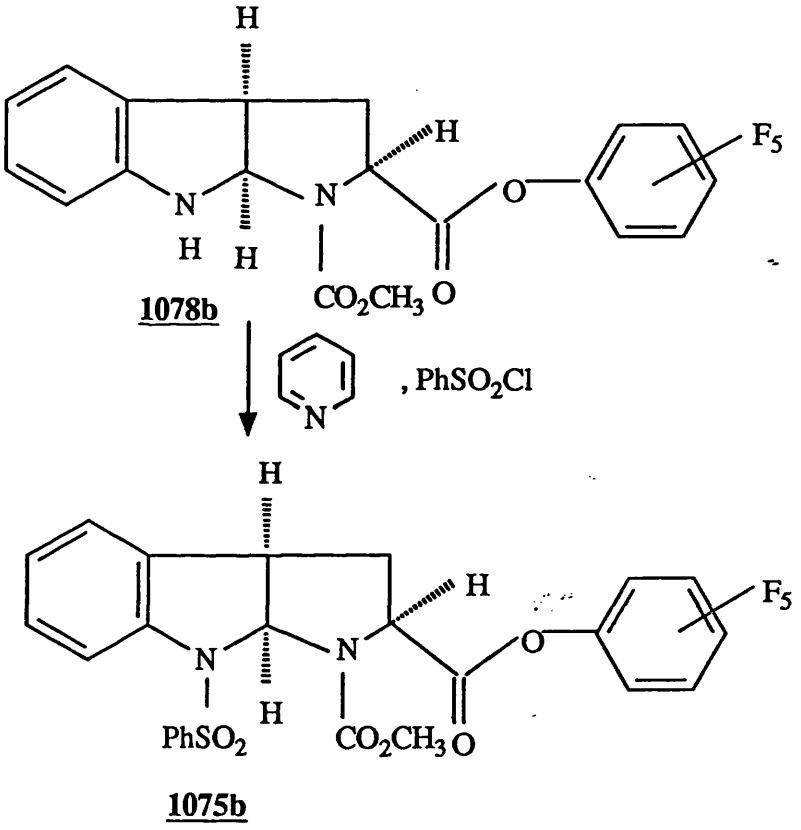
Scheme 82

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 ^{1}H-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°C to give one set of signals. **H-8a** was at a chemical shift of δ=6.33ppm (d,J=6.52Hz). High field ^{1}H-NMR at -20°C showed two sets of sharp signals in the ratio of about 2.2:1. The two chemical shifts for **H-8a** were at δ=6.31ppm(d,J=6.43Hz,major), and δ=6.33ppm(d,J=8Hz,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.

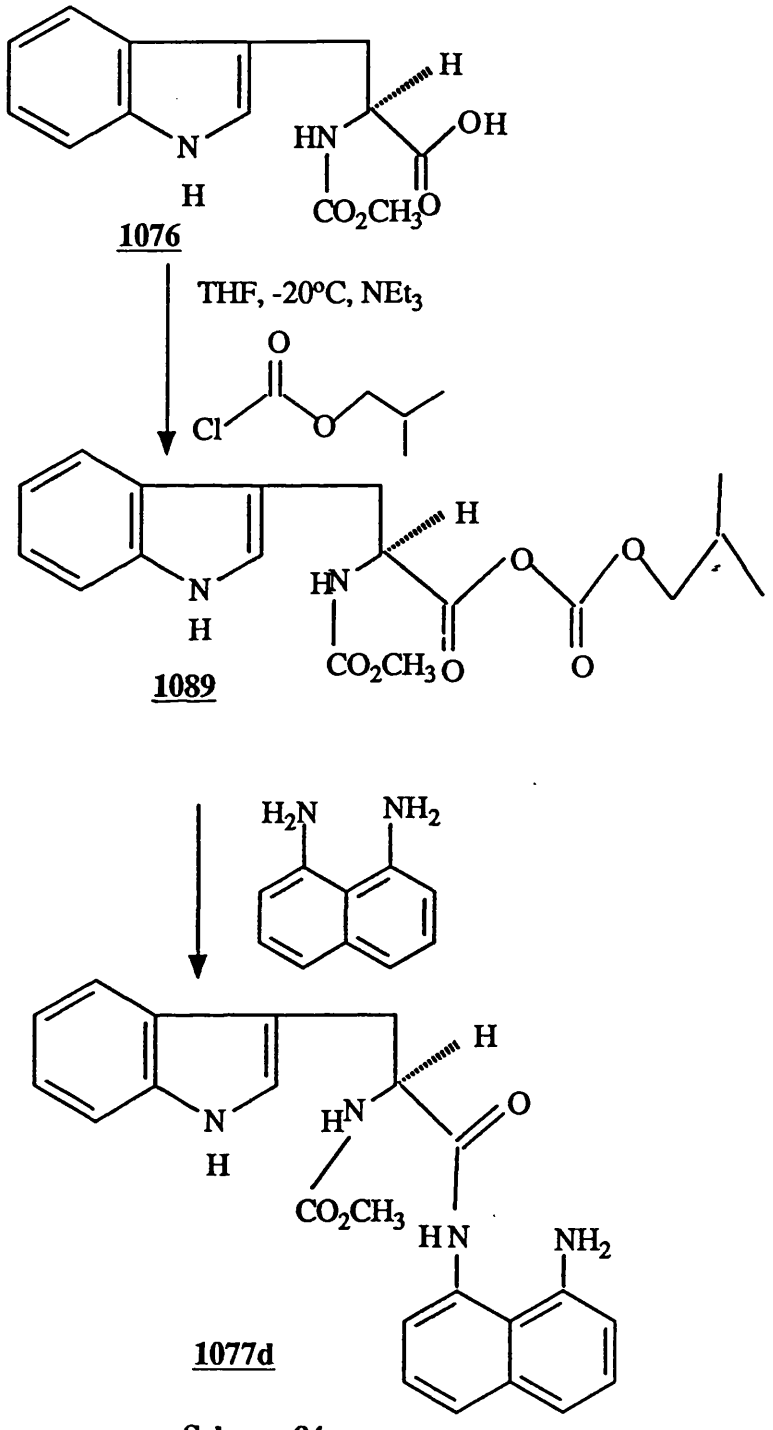
At 0°C, the **F** signals were sharpened. The **m-F's** gave two sets of overlapping triplets as did the **p-F.** The **o-F's** gave two sets of non-overlapping doublets in the ratio of 2.3:1 which was about ratio of the N-carbamate rotamers from the ^{1}H-NMR spectrum. The same pattern was seen when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

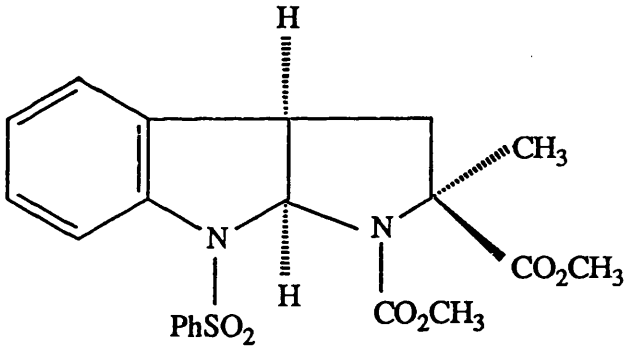
The product was isolated after recrystallization from CH_2Cl_2 and petrol to

give a yellow solid, which darkened on exposure to air, in 62% yield, **mp=128°C.** The mass spectrum gave $(M-H_2O)^+$ at 384.

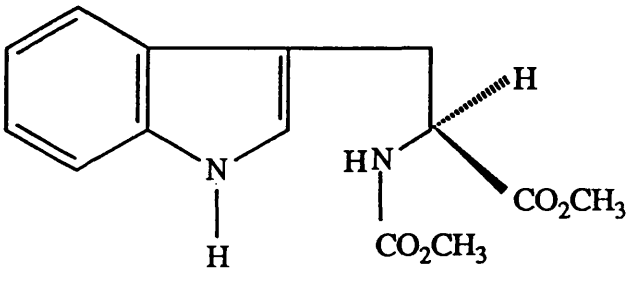
UV spectrum[114] taken in neutral DMF showed three absorption maxima : ϵ_{max}(281.8nm)=7379, ϵ_{max}(289.8nm)=7929, ϵ_{max}(330.6nm)=15697.

In DMF with a drop of conc.HCl added, four absorption maxima were seen : ϵ_{max}(280.9nm)=10344 , ϵ_{max}(289.5nm)=11096 , ϵ_{max}(314.0nm)=12773 , ϵ_{max}(326.6nm)=13484.

By comparison with the UV spectra of **1053** and **1037**, and 1,8-diaminonaphthalene, the two shorter wavelength ϵ_{max}'s belonged to the indole system, and the two longer wavelength ϵ_{max}'s belonged to the naphthalene.



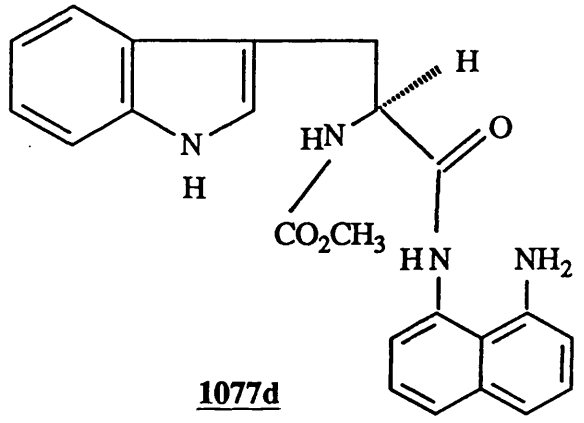
1053



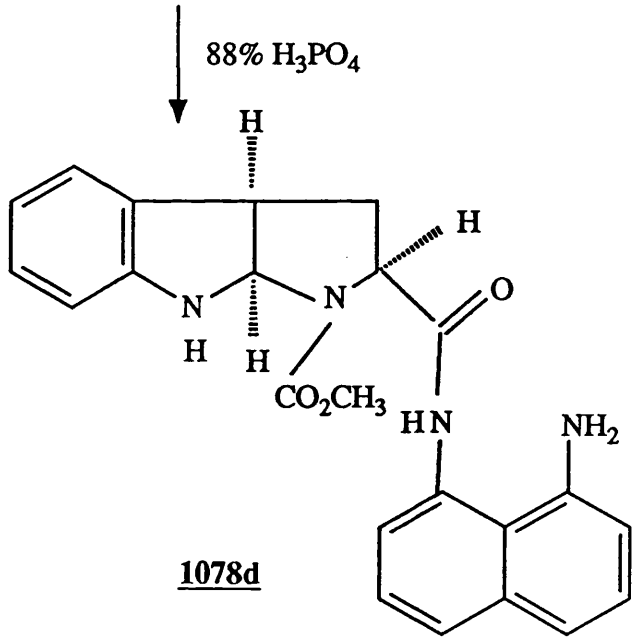
1037

3.8.2 Ring closure of 1077d to 1078d

1077d was dissolved in 88% H_3PO_4 and stirred for 18 hours. The acidic reaction was then slowly dropped into a rapidly stirring mixture of CH_2Cl_2 and 15% aqueous Na_2CO_3. The product was isolated in 86% yield after a column, mp=120°C (**Scheme 85**).



1077d



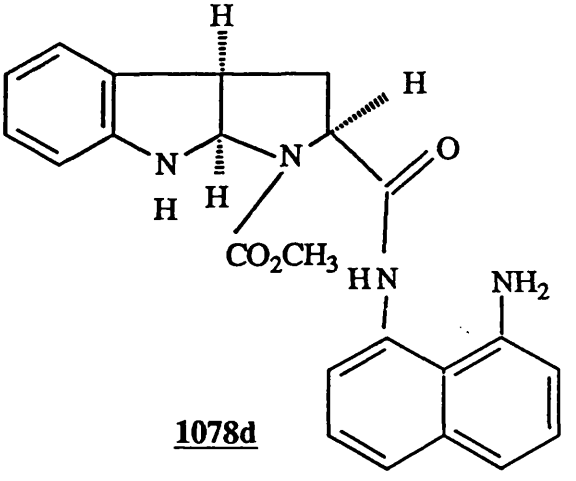
1078d

Scheme 85

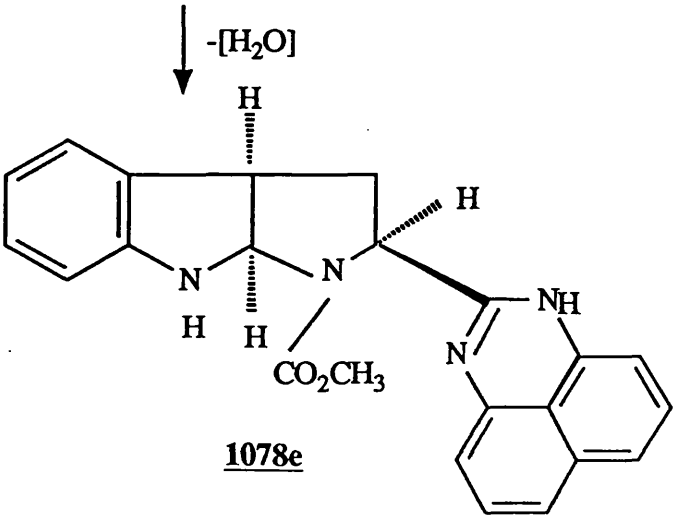
However, it was decided that the selective N-8 protection of the pyrroloindole system over the amines of the naphthalene portion of **1078d** was not possible. It was thus decided to convert the 1,8-diaminonaphthalene portion of **1078d** to the pyrimidine system **1078e**.

3.8.3 Attempted conversion of 1078d to 1078e

The conversion of **1078d** and **1078e** involves a simple dehydration (Scheme 86).



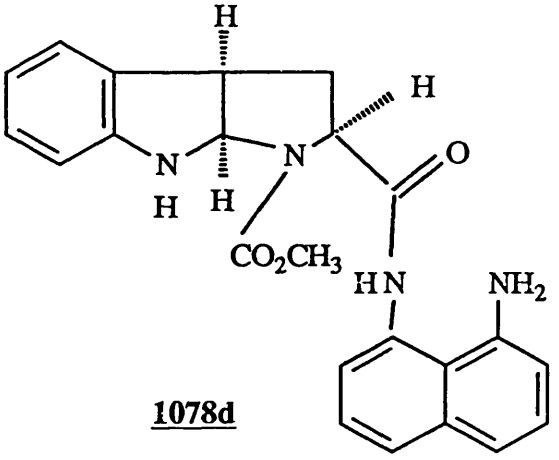
1078d



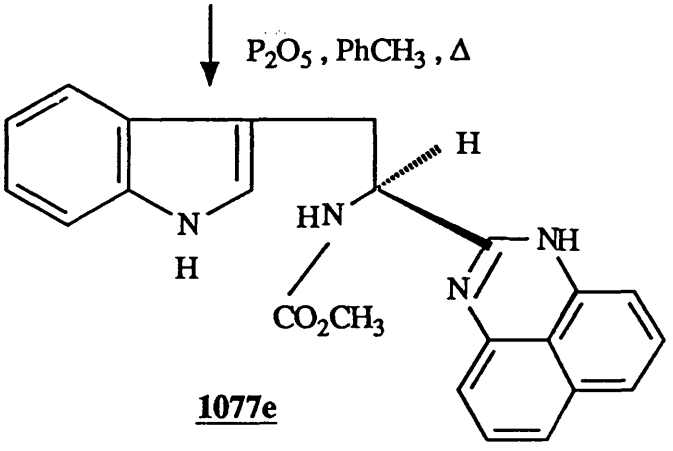
1078e

Scheme 86

It was found that the dehydration could be effected by refluxing in toluene with phosphorous pentoxide.[116] 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**).



1078d



1077e

Scheme 87

UV spectra[114] taken in neutral DMF showed three absorption maxima : ϵ_{max}(281.2nm)=3628 , ϵ_{max}(289.6nm)=3676, ϵ_{max}(330.8nm)=8048.

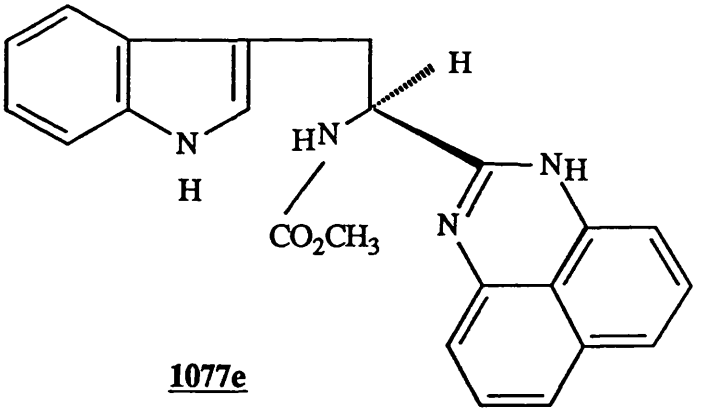
UV spectra taken in DMF with a drop of conc. HCl showed four absorption

maxima : ϵ_{max}(280.4nm)=5838, ϵ_{max}(289.6nm)=6054, ϵ_{max}(313.6nm)=6727, ϵ_{max}(326.2nm)=7207.

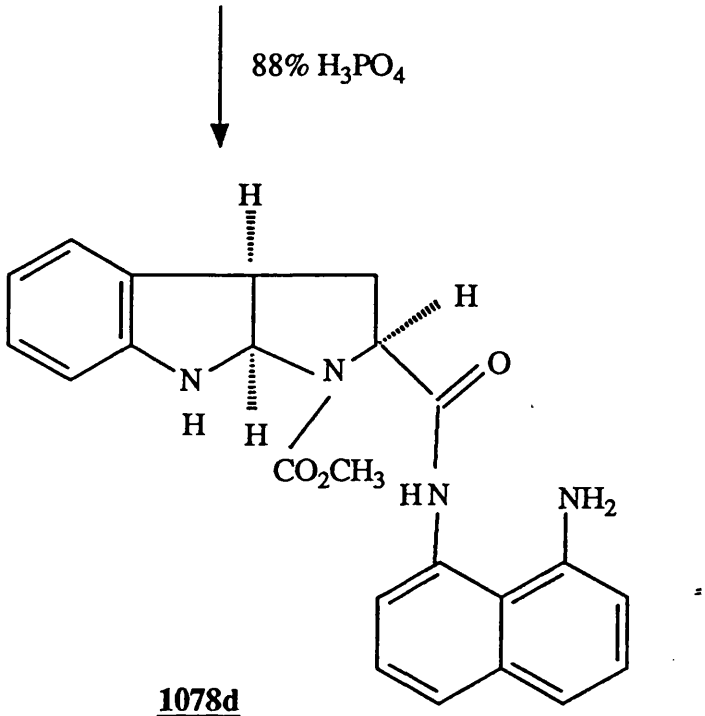
The UV absorption spectrum of **1077e** was not distinguishable from those that of **1077d**.

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_3PO_4 could again be employed. **1077e** was dissolved in 88% H_3PO_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**).



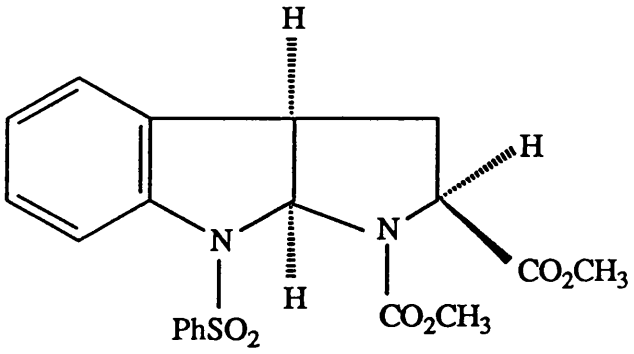
1077e



1078d

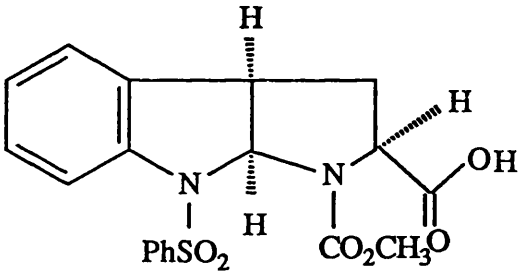
Scheme 88

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**).



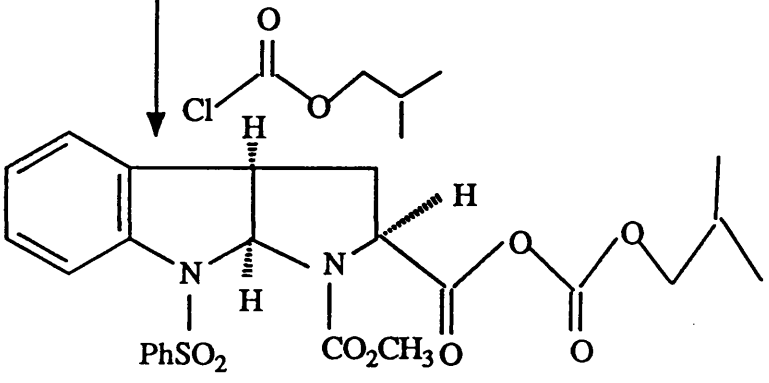
1051

KOH / MeOH / H_2O

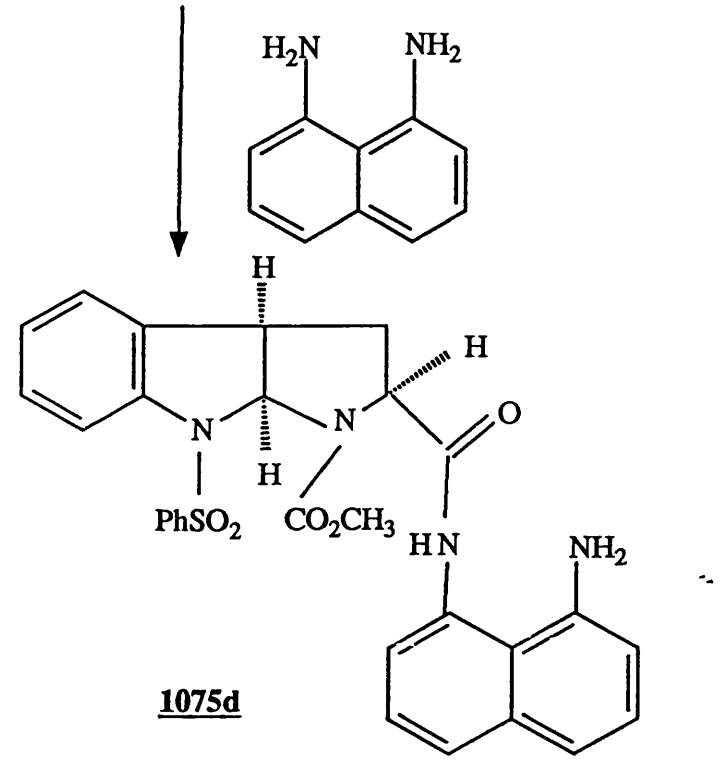


1090

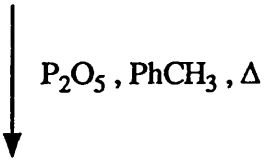
THF, -20°C, NEt_3

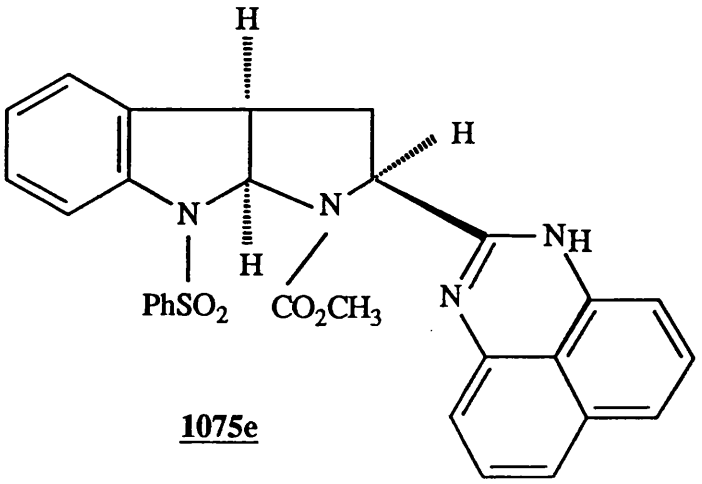


1091



1075d





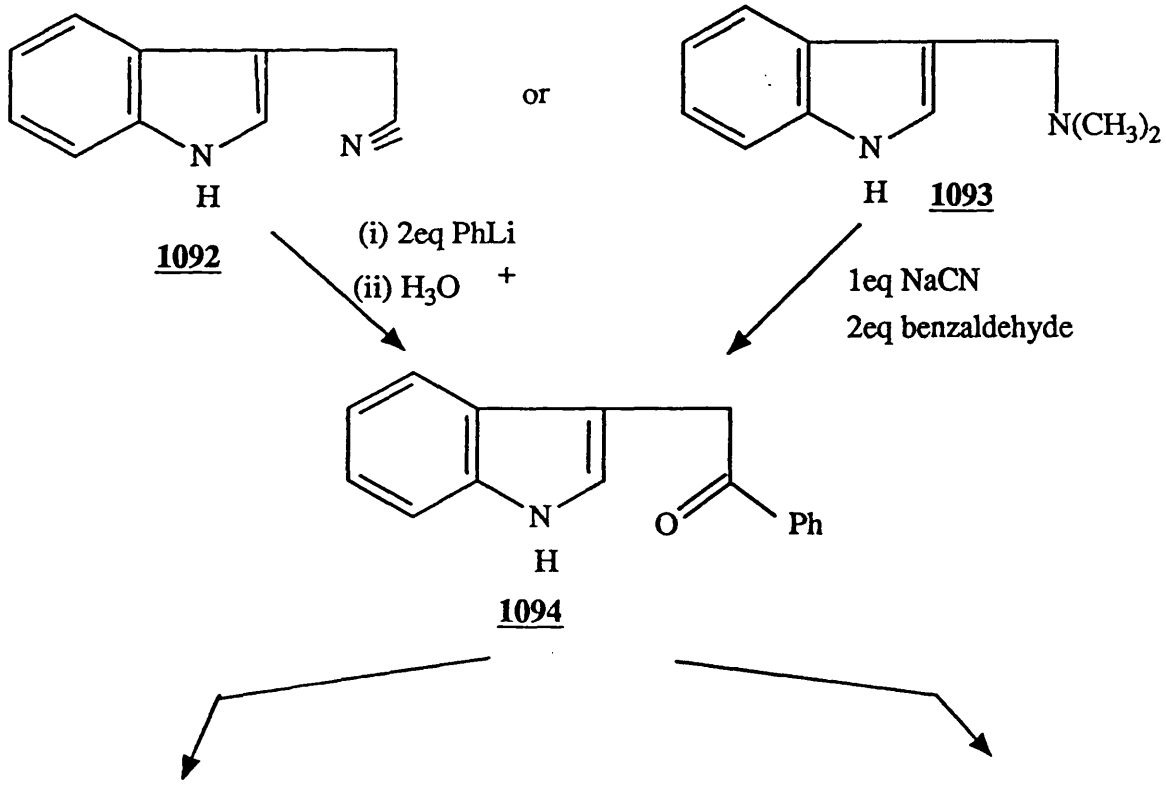
1075e

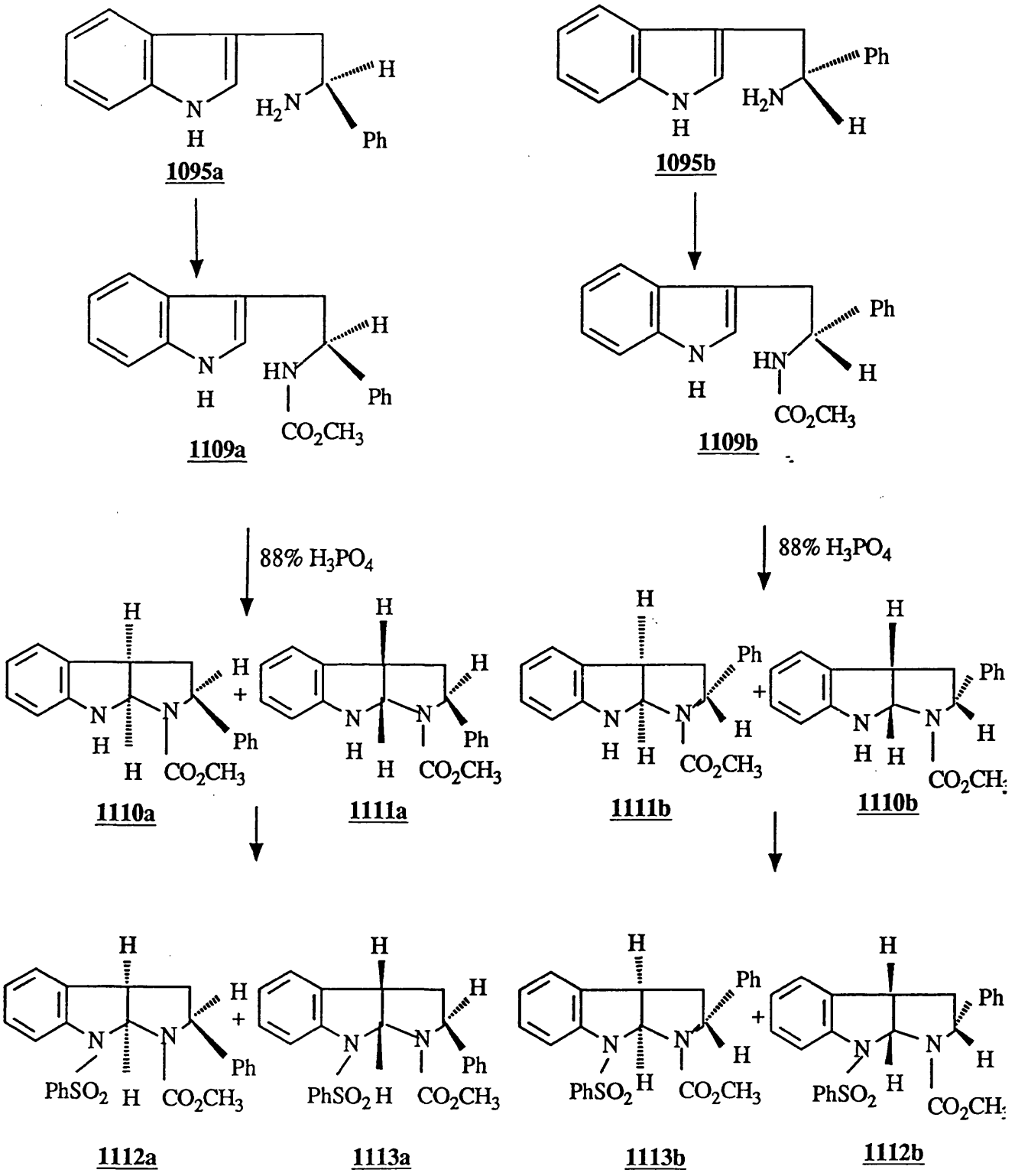
Scheme 89

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.




1095a
1095b
1109a
1109b
88% H_3PO_4
88% H_3PO_4
1110a
1111a
1111b
1110b
1112a
1113a
1113b
1112b

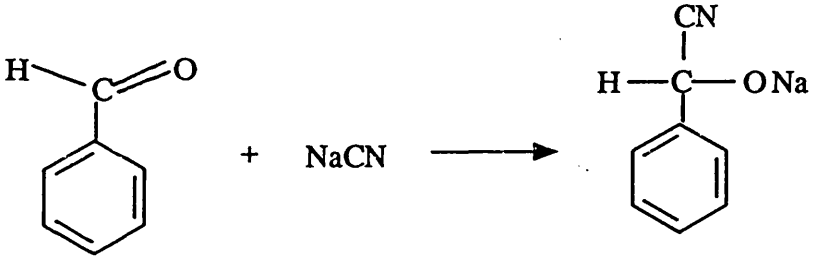
Scheme 90

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_3PO_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

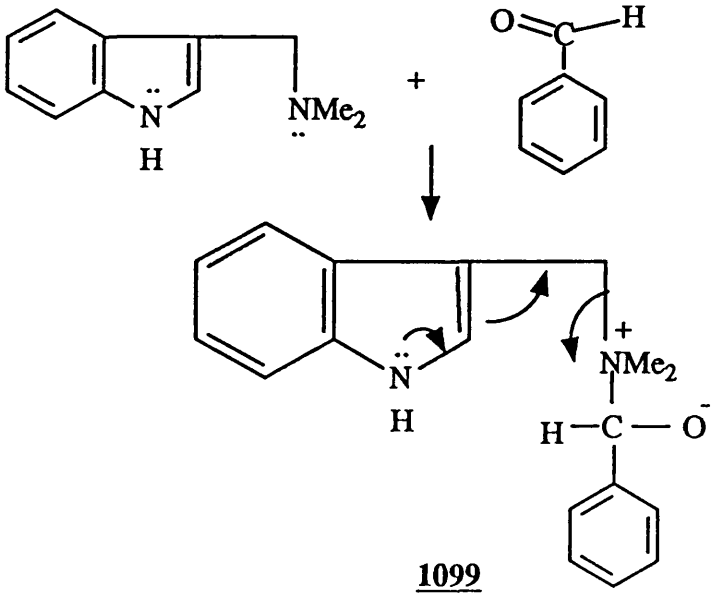
The synthesis of 1094 from gramine 1093 was reported by Stetter et al.[115] It involves heating gramine in DMF with one equivalent of NaCN and two equivalents of benzaldehyde. The mechanism of this reaction is outlined in scheme 91.

(i)

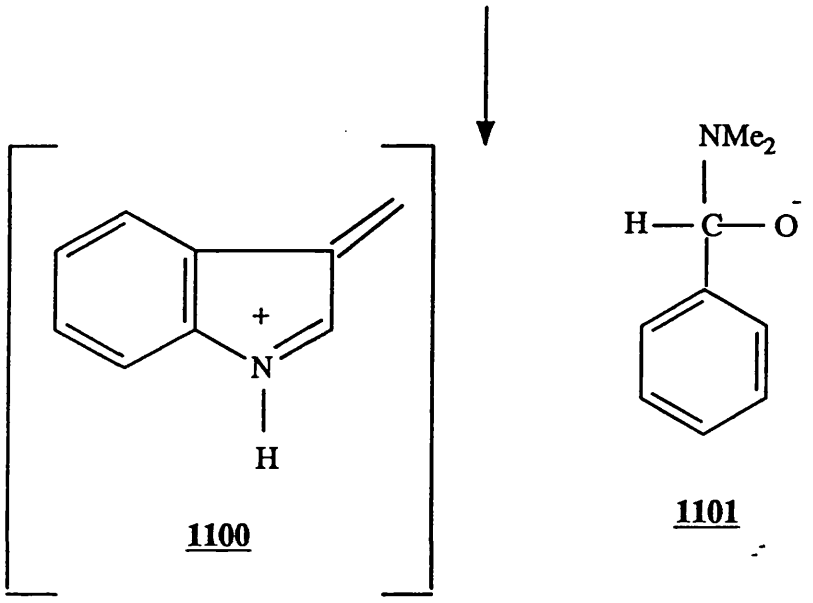


1098

(ii)

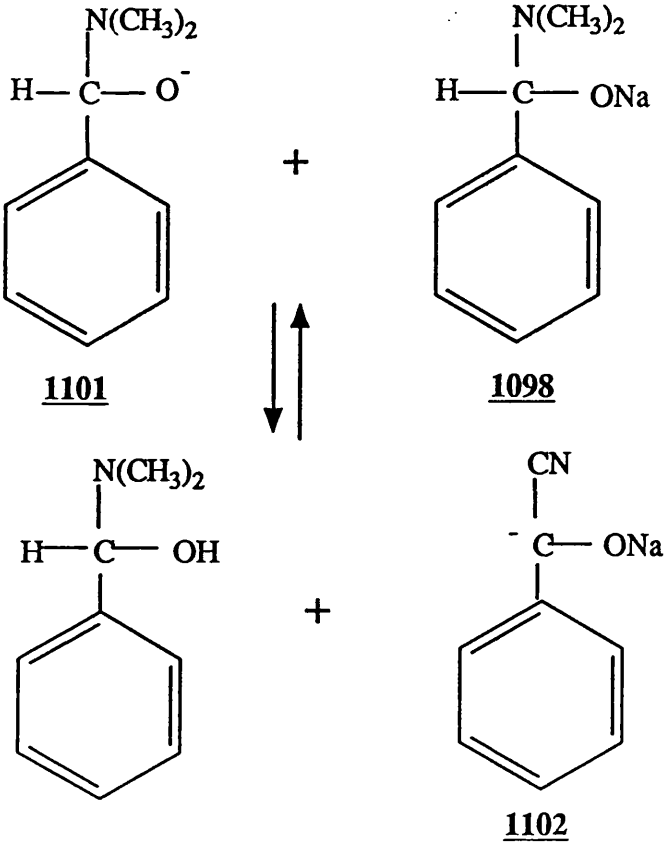


1099



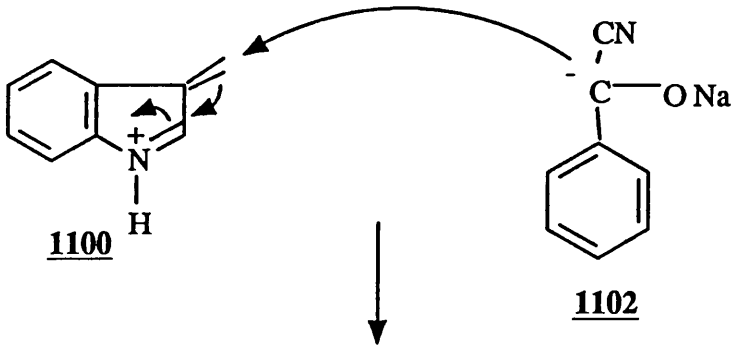
1100 1101

(iii)

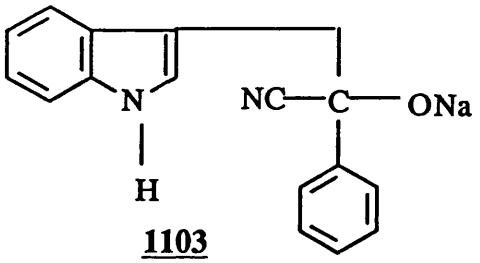


1101 1098 1102

(iv)

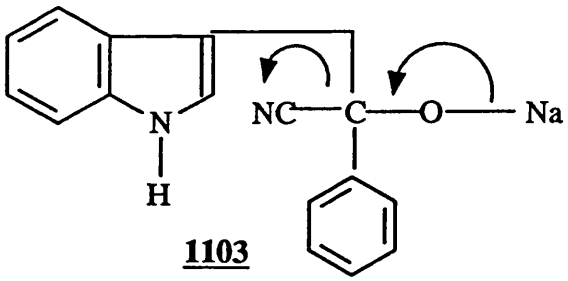


1100 1102

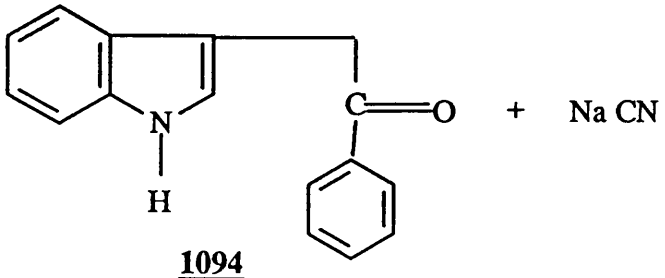


1103

(v)



1103



1094

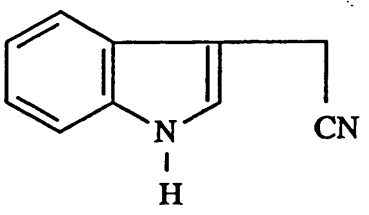
Scheme 91

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**.

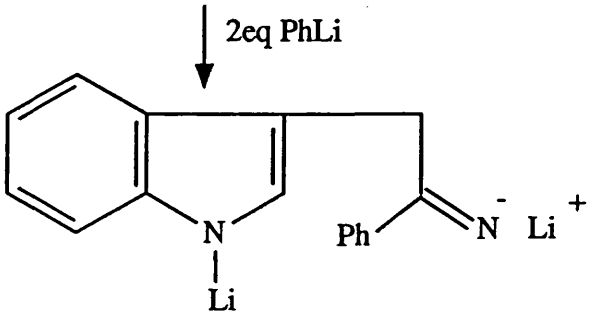
In our hands, the yield obtained after recrystallization was low- typically about 10%, whereas Stetter reported a 52% yield (mp=123-124°C, lit 123-125°C).

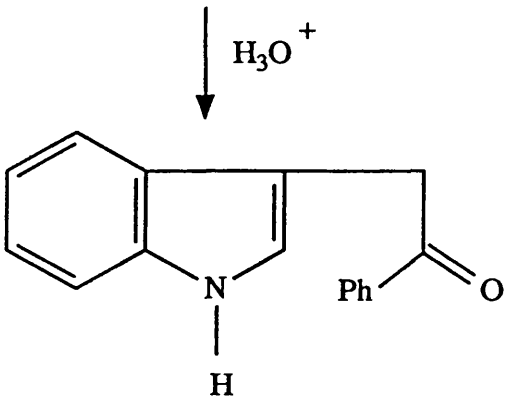
3.9.3 Synthesis of 1094 from 1092

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



1092





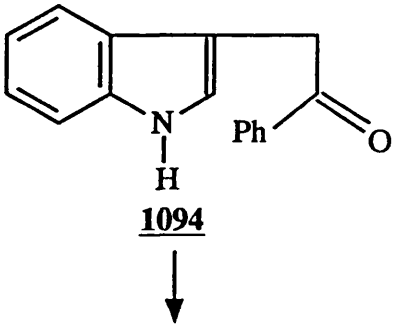
1094

Scheme 92

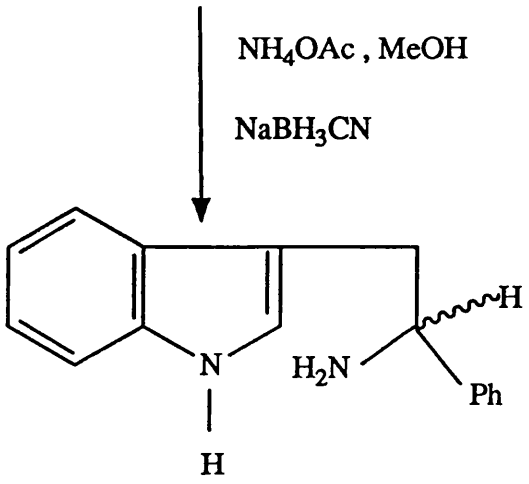
The reaction was carried out in ether at 0°C . The product was recrystallized from ether in 6% yield, mp=123-124°C. No starting material was recovered. The low yields in these reactions were probably due to the reactive indole ring.

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**).



1094

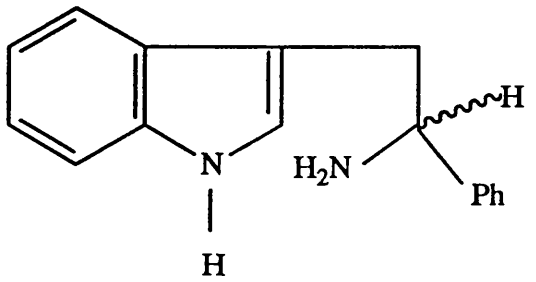


(+)-1095

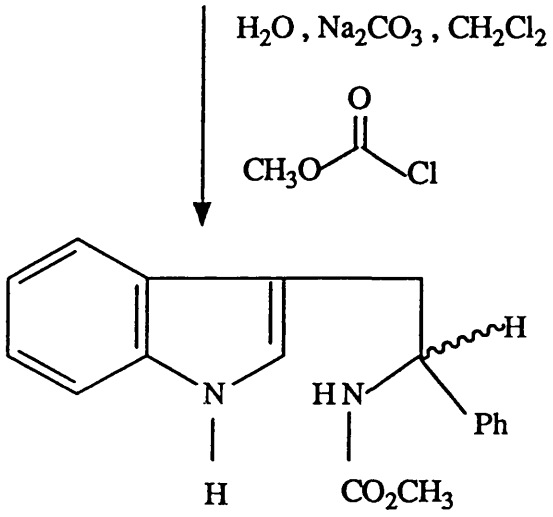
Scheme 93

3.9.5 N_b-Protection of (+)1095

The amine (+)1095 in CH_2Cl_2 was added to an aqueous solution of Na_2CO_3. Methyl chloroformate was added in CH_2Cl_2 (Scheme 94). The reaction was allowed to proceed to completion. The product (+)1109 was isolated after column chromatography in 97% yield.



(+)-1095

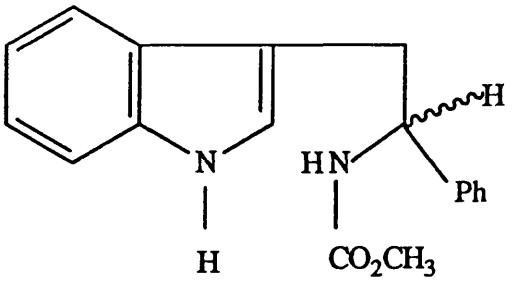


(+)-1109

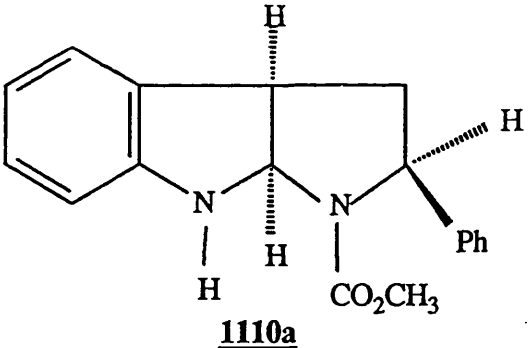
Scheme 94

3.9.6 Cyclization of (+)1109

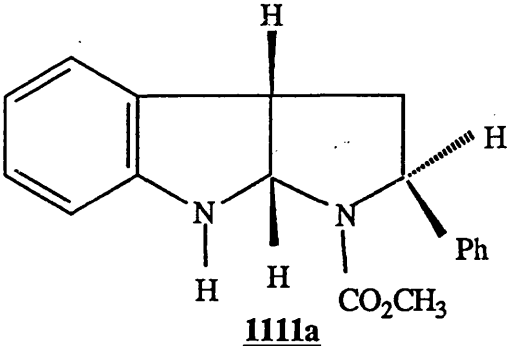
Crude (+)1109 was dissolved in 88% H_3PO_4 and stirred for 16 hours. The acidic reaction was then added dropwise to a rapidly stirring mixture of CH_2Cl_2 and 15% aqueous Na_2CO_3 (Scheme 95). The product was extracted into CH_2Cl_2. 200MHz ^{1}H-NMR showed impurities, but the **H-8a** signal at δ=6.0ppm 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.



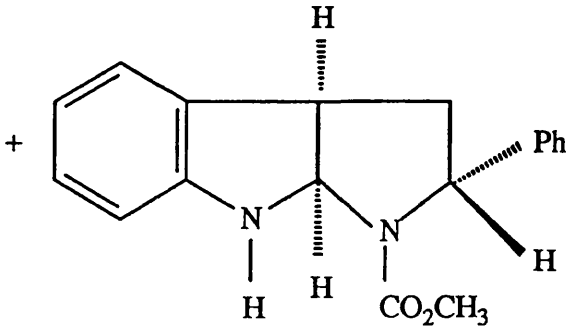
(+)-1109



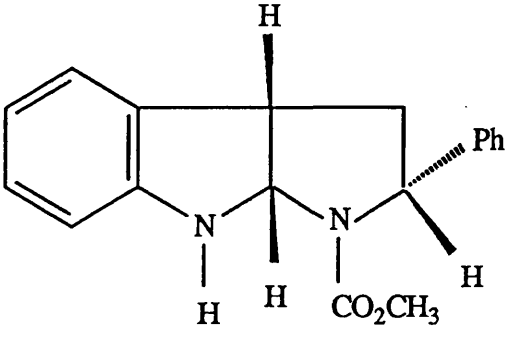
1110a



1111a



1111b

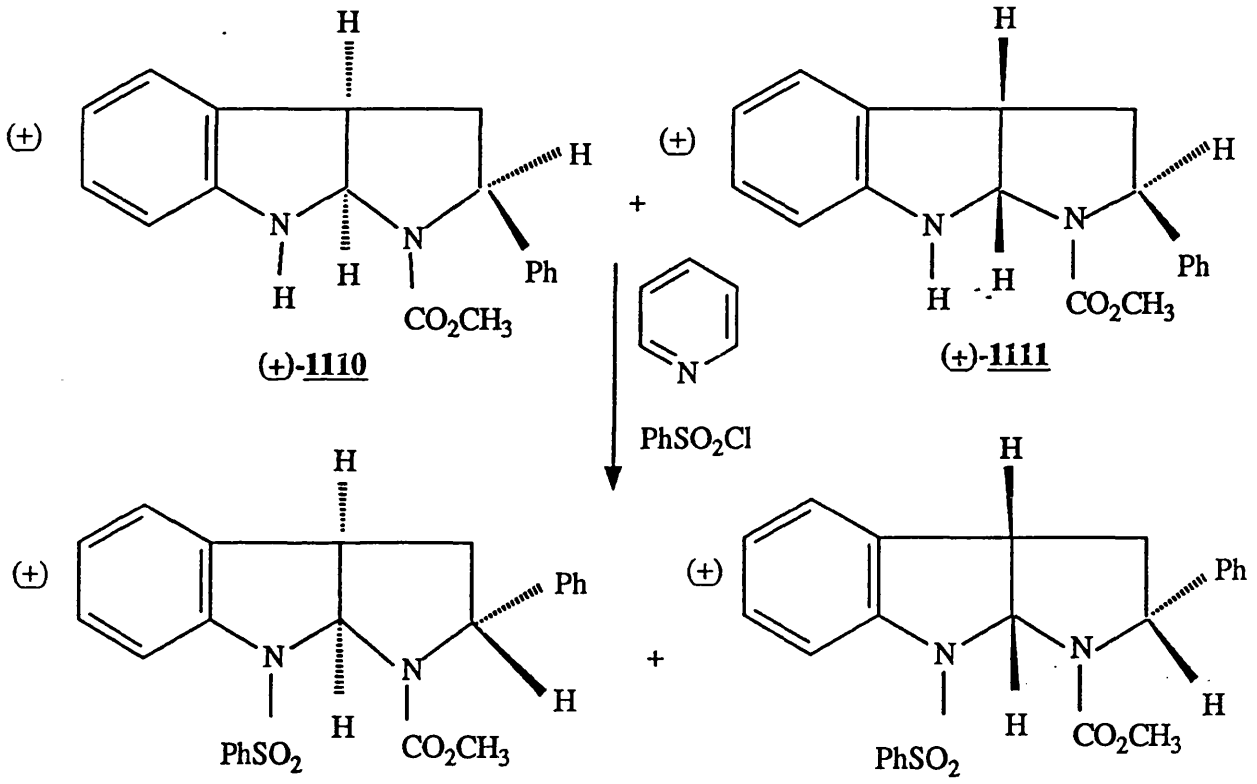


1110b

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**).



Scheme 96

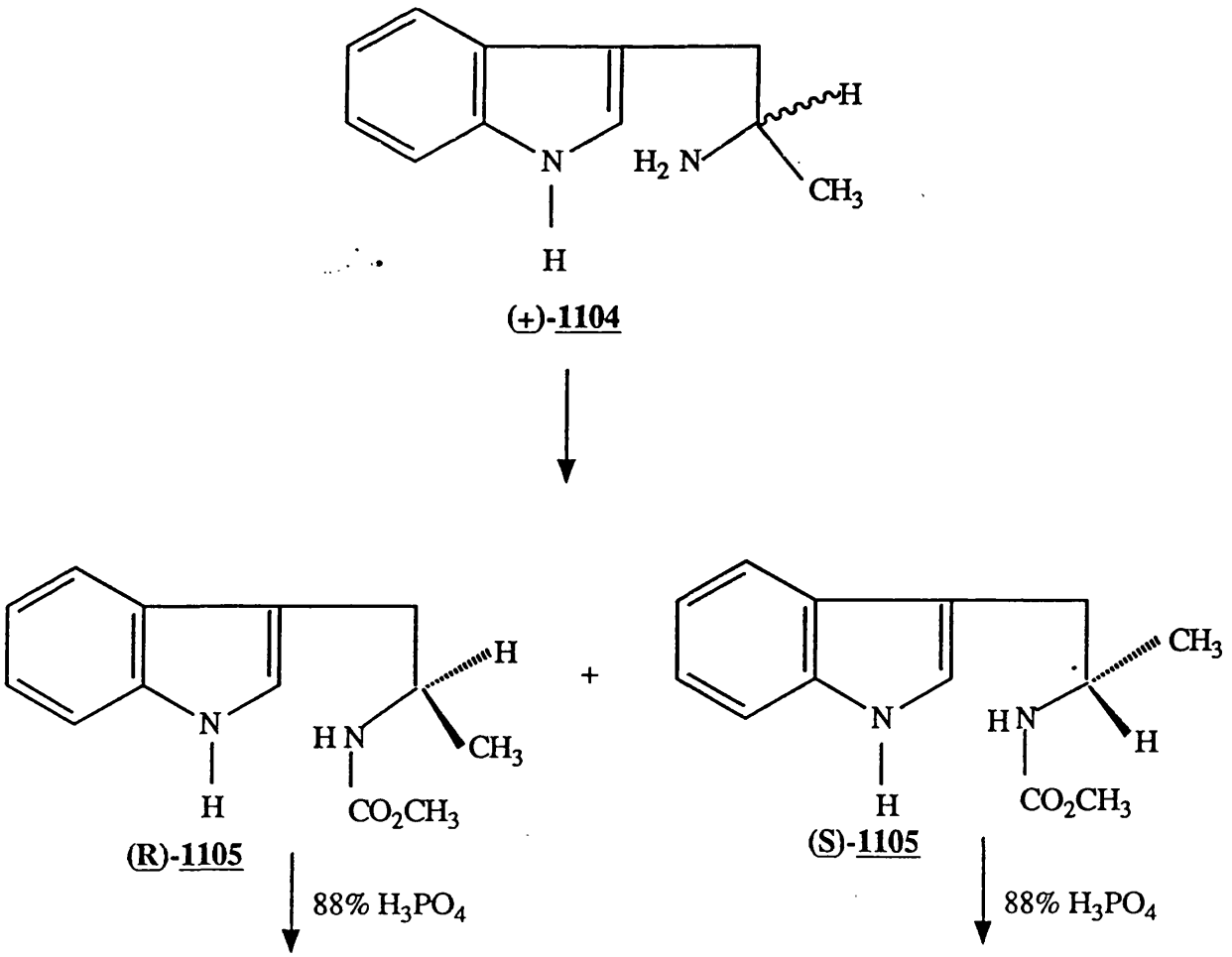
The products were isolated, and then column chromatographed to remove the impurities. High field ^{1}H-NMR showed a mixture of products. Three doublets in the H-8a region of the spectrum were seen at δ=6.00ppm(J=7.3Hz), δ=6.42ppm(J=7.9Hz), and δ=6.32ppm(J=6.66Hz). Three singlets for the carbamate methyl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

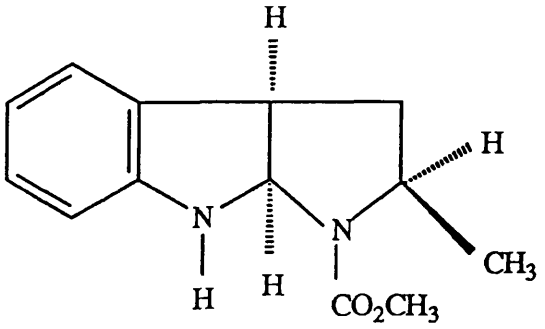
interaction between the 2-phenyl and the pyrroloindole rings.

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

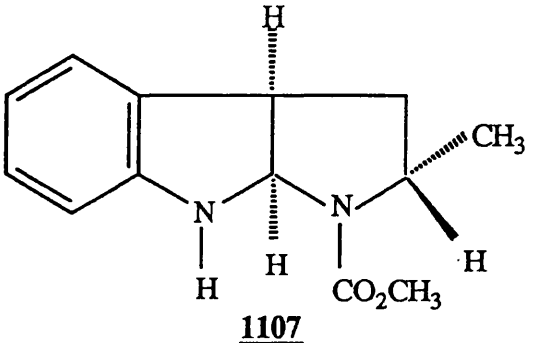
It was of interest to see whether phosphoric acid mediated cyclization of α-substituted tryptamine would also favour the formation of the endo product as with the tryptophan esters. To this end, the cyclization of **(+)α-methyltryptamine** was carried out **(Scheme 97)**.





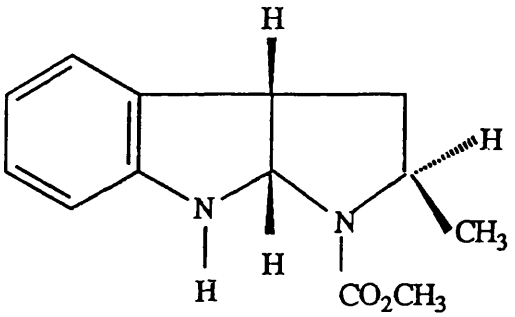
1106

+

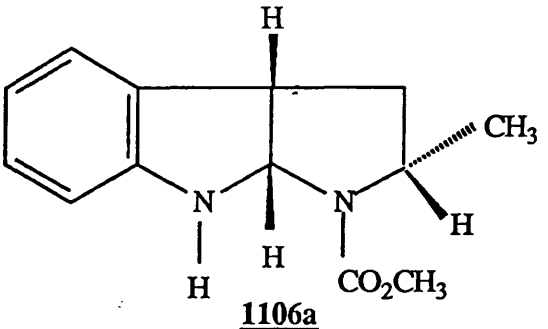


1107

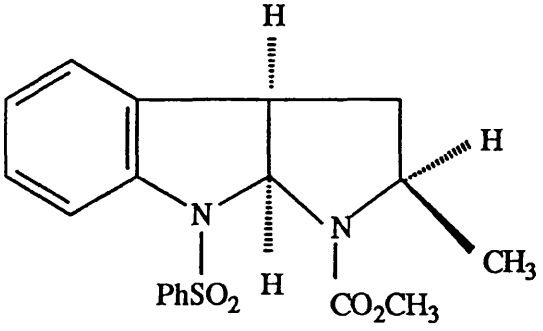
+



1107a

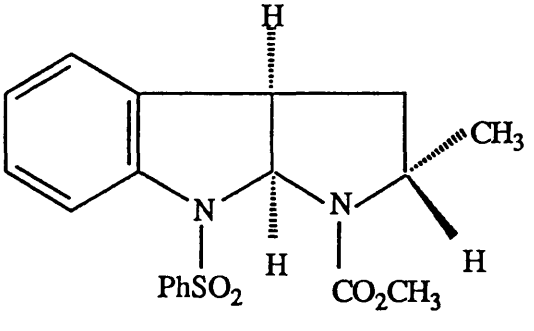


1106a



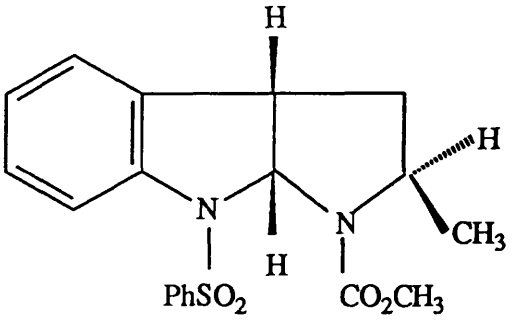
1066

+

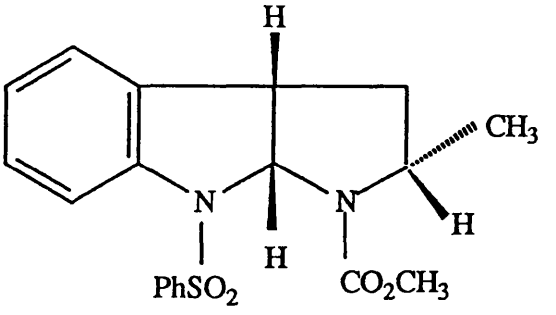


1065

+



1065a



1066a

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 (+)α-methyltryptamine

N_b of (+)α-methyltryptamine was protected as the carbamate as before. This was done by stirring a solution of the (+)**1104** in CH_2Cl_2 with an aqueous solution of Na_2CO_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% H_3PO_4 and stirred for 16 hours. The products were isolated quantitatively. High field ^{1}H-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

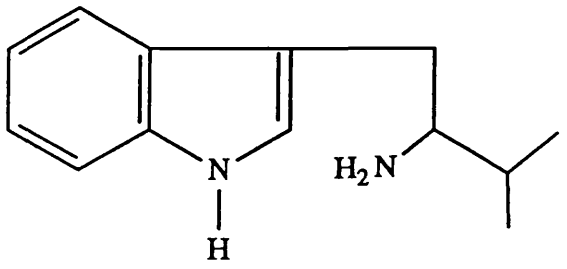
The cyclized prodicts **1106**, **1106a**, **1107**, and **1107a** were protected with the benzenesulphonyl group as before. This was done in pyridine, and benzenesulphonyl chloride was added. The products were isolated. 200MHz ^{1}H-NMR showed the exo-methyl:endo-methyl products in a ratio of about 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.



1108

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

δ=0.11 (6H, Si(CH_3)$_2$) ; δ=0.91(9H, SiC(CH_3)$_3$)

δ=1.32(d,3H,H-3β); δ=4.28(m,1H,H-3α);

δ=3.22(dd,1H,H-3); δ=4.10(d,1H,H-4);

δ=4.5(broad,1H,COOH): δ=5.83(s,1H,N-CH);

δ=3.77(s,6H,2x OCH_3); δ=6.8-7.2(8H,aromatic).

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, 1.1eq) 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 (SiO_2, CH_2Cl_2:Et_2O = 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%).

400MHz ^{1}H-NMR ref $CDCl_3$

δ=0.065,0.026 (6H, $Si(CH_3)_2$) ; δ=0.839(9H, $SiC(CH_3)_3$);

δ=1.16(d,3H,H-3β) ; δ=4.2(dq,1H,H-3α)

δ=3.26(dt,1H,H-3) ; δ=3.15(d,2H,H-4)

δ=6.06(s,1H,N-CH) ; δ=3.799, 3.805 (s,6H,2x O-CH_3)

δ=6.7 to 7.2 (aromatics).

^{13}C-NMR ref $CDCl_3$

δ=-4.163 , -4.214 ($Si(CH_3)_2$; δ=18.421 ($SiCMe_3$) ;

δ=23.055 (C-3β) ; δ=65.730 (C-3α) ;

δ=57.058 (C-3) ; δ=40.254 (C-4) ; δ=58.132 (N-C) ;

δ=55.682, 55.669 (O-CH_3) ; δ=168.514 (C-2) ;

δ=132.834, 131.628 (aromatic C-1′) ;

δ=129.739,129.726,129.643,129.635 (aromatic C-2′) ;

δ=114.290,114.277,114.265,114.252 (aromatic C-3′) ;

δ=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 (SiO_2 , CH_2Cl_2:Et_2O = 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 (SiO_2 , CH_2Cl_2:Et_2O =9:1). The desired product was isolated (0.1256g, 15.4%).

400MHz ^{1}H-NMR (ref $CDCl_3$)

δ=0.000 , 0.065 (6H , $Si(CH_3)_2$) ; δ=0.815 (s, 9H , $SiC(CH_3)_3$) ;

δ=1.24 (d, 3H , H-3β) ; δ=4.26 (m, 1H, H-3α) ;

δ=3.33 (dd, 1H, H-3) ; δ=5.92 (d, 1H, H-4) ;

δ=5.735 (s, 1H, N-CH) ; δ=3.747, 3.800 (s, 6H, 2x OCH_3) ;

δ=8.32 (d, 1H, pyridyl α-H);

δ=6.6 to 7.5 (aromatics).

^{13}C-NMR ref $CDCl_3$

δ=17.933 ($SiCMe_3$) ; δ=25.718 ($(CH_3)_3$) ;

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 OCH_3) ; 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-anisylmethyl)-3-[(1R)-1-t-butyldimethyl-silyloxyethyl]-4-[(2RS)-2-methoxycarbonyl-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_2Cl_2:Et_2O = 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 $CDCl_3$

δ=-0.001, -0.034, 0.019, 0.025 (6H, Si(CH_3)$_2$) ;
δ=0.778, 0.773 (9H, SiC(CH_3)$_3$) ; δ=3.82(m,1H,H-3α) ;
δ=1.176(d), 1.271(d), (3H, H-3β) ; δ=5.87(s),5.89(s) (1H, N-C<u>H</u>)
δ=2.91(dd), 3.03(dd) (1H, H-3) ; δ=4.1(td),4.2(td) (1H,H-4)
δ=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, $COOC\underline{H}_3$);

δ=8.29(d), 8.33(d) (1H, α-H pyridyl);

δ=6.7 to 7.6 (aromatics).

^{13}C-NMR ref $CDCl_3$

δ=4.921, 4.883, 4.523, 4.481 ($Si(\underline{C}H_3)_2$);

δ=17.835, 17.868 ($Si\text{-}\underline{C}Me_3$); δ=25.718, 25.745 ($SiC(\underline{C}H_3)_3$) ;

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-$\underline{C}$) ;

δ=55.105 (DAM, $O\underline{C}H_3$) ;

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 ($\underline{C}OOMe$) ; δ=53.051 ($COO\underline{C}H_3$) ;

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-(di-p-anisylmethyl)-3-[(1R)-t-butyldimethyl-silyloxyethyl]-4-(2-methoxycarbonylethyl)-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_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_3SnH) (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_3CN) 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_2, petrol followed by CH_2Cl_2). The desired product (45mg, 18%) was collected. ^{1}H-NMR and ^{13}C-NMR showed a clean product with no diastereomeric mixtures.

400MHz ^{1}H-NMR ref $CDCl_3$

δ=-0.019,0.047 (6H, Si(CH_3)$_2$); δ=0.834 (9H, SiC(CH_3)$_3$);
δ=1.2205 (d,3H,H-3β); δ=4.05 (m,1H,H-3α);
δ=2.7295(dd,1H,H-3); δ=3.5455(ddd,1H,H-4);

δ=1.64(m), 1.92(m) (2H, H-4α); δ=2.2(m,2H,H-4β);
δ=3.622(s,3H,COOC$\underline{H}_3$); δ=5.861(s, N-C$\underline{H}$);
δ=3.795(s), 3.805(s) (6H, 2x OC$\underline{H}_3$);
δ=6.85 to 7.19 (aromatics).

^{13}C-NMR ref $CDCl_3$

δ=17.907 (Si$\underline{C}Me_3$); δ=25.787 (SiC($\underline{C}H_3$)$_3$);
δ=22.950 (C-3β); δ=66.048 (C-3α); δ=62.509 (C-3);
δ=51.613 (C-4); δ=167.474 (C-2); δ=59.248 (N-$\underline{C}$);
δ=131.708, 130.720 (DAM C-1);
δ=129.797, 129.999 (DAM C-2);
δ=113.728, 113.849 (DAM C-3);
δ=158.809, 158.941 (DAM C-4); δ=55.209 (Ar-O$\underline{C}H_3$);
δ=28.372(C-4α); δ=30.163(C-4β); δ=172.998($\underline{C}O_2$);
δ=54.868(COO$\underline{C}H_3$).

Preparation of nitroethene (32)

The commercially available **2-nitro-1-ethanol** (5.00g) was mixed with phthalic 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°-100°C to give a pale yellow and very pungent liquid (1.93g, 48%). It was then stored in the freezer.

60MHz ^{1}H-NMR ref external TMS

δ=5.5 to 7.4 (m, olefinic H's)

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 hydrogencarbonate 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

δ=1.2ppm(d,3H,CH_3); δ=4.3ppm(d,2H,CH_2)
δ=3.5ppm(broad, 2H, CH and OH)

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 $CDCl_3$

δ=1.99(dd), 2.18(dd) (3H,CH_3) ;

δ=6.9 to 7.3 (m, 2H, olefinic)

Preparation of
(3S,4R)-1-(di-p-anisylmethyl)-3-[(1R)-1-t-butyldimethyl-silyloxyethyl]-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_2Cl_2=2:3). The product (118mg, 36%) was collected.

400MHz ^{1}H-NMR ref $CDCl_3$

δ=-0.030, 0.013, 0.063, 0.092 (6H, $Si(CH_3)_2$) ;

δ=0.797, 0.837 (9H, $SiC(CH_3)_3$) ;

δ=1.142(d), 1.250(d) (3H, H-3β) ;

δ=2.96(dd), 3.02(dd) (1H, H-3) ;

δ=4.08(m), 4.15(m) (1H, H-4) ;

δ=6.22(dd), 6.34(t) (1H, H-4β) ;

δ=5.927, 5.934 (1H, NCH) ;

δ=3.768, 3.792, 3.799, 3.817 (6H, OCH_3) ;

δ=8.36(d), 8.39(d) (1H, pyridyl H-6) ;

δ=6.8 to 7.3 (aromatics) ;

Signal for H-3α was under the OCH_3 signals.

^{13}C-NMR ref $CDCl_3$

δ=17.911,17.867 ($\underline{C}Me_3$); δ=25.788, 25.729 ($C(\underline{C}H_3)_3$) ;

δ=22.258, 22.376, 22.502, 22.689 (C-3β) ;

δ=65.440, 65.185 (C-3α) ; δ=63.026, 62.960 (C-3) ;

δ=52.222, 51.926 (C-4) ; δ=37.467, 36.930 (C-4α) ;

δ=85.123, 85.164, 85.762, 85.798 (C-4β) ;

δ=167.354, 167.201 (C-2) ; δ=59.588, 59.665 (N-C) ;

δ=130.265, 130.190, 131.295, 131.186 (DAM C-1) ;

δ=129.780, 129.704, 128.935, 128.877 (DAM C-2) ;

δ=114.017, 113.981, 113.856, 113.830 (DAM C-3) ;

δ=159.104, 159.063, 258.985, 258.890 (DAM C-4) ;

δ=55.211, 55.178, 55.144, 55.112 (OCH_3) ;

δ=153.493, 153.471 (pyridyl C-2) ;

δ=149.740, 149.838 (pyridyl C-6) ;

Other pyridyl signals are at:

δ = 122.361, 122.069; 121.354, 121.180; 136.892, 136.759

Preparation of (3S,4R)-1-(di-p-anisylmethyl)-3-[(1R)-1-t-butyldimethyl-silyloxyethyl]-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 (SiO_2, CH_2Cl_2). The product (266mg, 41%) was isolated.

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

Attempted ozonolysis on 33

33 (386.5mg) was dissolved in CH_2Cl_2(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 (SiO_2,CH_2Cl_2 followed by CH_2Cl_2:ether =9:1) was carried out on the crude product, but no identifiable product was obtained.

Attempted ozonolysis on 35

35 (160mg) was dissolved in CH_2Cl_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 bufferred 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 β-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

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

Reaction of 39 with unbuffered aqueuos 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_2Cl_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 ^{1}H-NMR showed the absence of the pyridyl group.

Preparation of (3S,4R)-1-(di-p-anysylmethyl)-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 ^{1}H-NMR ref $CDCl_3$

δ=0.043, 0.078 (6H, $Si(CH_3)_2$) ;

δ=0.856 (9H, $SiC(C\underline{H}_3)_3$) ;

δ=1.150 (3H, d, J=6.29Hz, CH_3) ;

δ=2.9575 (dd,1H, J=2.39Hz, 4.35Hz, H-3) ;

δ=3.683 (3H,$COOC\underline{H}_3$) ;

δ=3.780, 3.803 (6H, DAM-OCH_3) ;

δ=4.1785 (dd, 1H, J=2.39Hz, 9.25Hz, H-4) ;

δ=4.246 (dq, J=4.35Hz, 6.29Hz, H-3α) ;

δ=5.896 (s, 1H, N-C<u>H</u>) ;

δ=5.6605 (d, J=15.58Hz, H-4β) ;

δ=6.621 (dd, J=15.58Hz, 9.33Hz, H-4α) ;

δ=6.8 to 7.2 (aromatics).

<u>^{13}C-NMR ref $CDCl_3$</u>

δ=17.930 ($Si\underline{C}(CH_3)_3$) ; δ=25.745 ($C(\underline{C}H_3)_3$) ;

δ=22.390 (C-3β) ; δ=65.129 (C-3α) ;

δ=63.248 (C-3) ; δ=51.573, 51.511 (C-4) ;

δ=122.440 (C-4α) ; δ=145.996 (C-4β) ;

δ=166.867 (<u>C</u>OOMe) ; δ=54.394, 54.366 ($COO\underline{C}H_3$) ;

δ=165.761 (C-2) ; δ=59.410, 59.382 (N-<u>C</u>) ;

δ=131.320, 130.352 (aromatic C-1′) ;

δ=129.609, 129.372 (aromatic C-2′) ;

δ=113.717, 113.694 (aromatic C-3′) ;

δ=158.983, 158.952 (aromatic C-4′) ;

δ=55.198, 55.137, 55.094 (aromatic $O\underline{C}H_3$).

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 ^{1}H-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 ^{1}H-NMR showed olefinic signals with a smaller coupling constant.

200MHz ^{1}H-NMR ref $CDCl_3$

δ=0.023, -0.009 (6H, $Si(CH_3)_2$) ;
δ=0.779 (9H, $SiC(CH_3)_3$) ; δ=1.086 (1H, d, J=6.35Hz) ;
δ=2.96 (1H, dd, H-3) ; δ=3.08 (m, 1H, H-4) ;
δ=4.18 (1H, m, H-3α) ; δ=3.58 (3H, s, $COOCH_3$) ;
δ=5.1 to 6.2 (3H, overlap, olefinics and N-CH) ;
δ=3.73 (Ar-OCH_3) ;
δ=6.7 to 7.4 (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-thiaindolizinium chloride (60)

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

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-siloxyethyl]-4-[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 ^{1}H-NMR showed that there were at least two products present.

Preparation of (3S,4R)-1-(di-p-anisylmethyl)-3-[(1R)-1-t-butyldimethyl-siloxyethyl]-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 (SiO_2,CH_2Cl_2 followed by CH_2Cl_2:Et_2O=9:1). A compound (147mg) was obtained. A 400MHz ^{1}H-NMR showed it to be only one diastereomer of 45 .(Yield=88%)

400MHz ^{1}H-NMR ref $CDCl_3$

δ=0.00, 0.077 (6H, $Si(CH_3)_2$) ;

δ=0.842 (9H, $SiC(CH_3)_3$) ;

δ=1.1395 (d, 3H, J=6.26Hz, H-3β) ;

δ=2.771 (1H, dd, J=2.25Hz, 4.33Hz, H-3) ;

δ=4.235 (m, H-3α) ; δ=4.510 (1H, dd, J=2.25Hz, 4.33Hz) ;

δ=3.016 (m, 1H, H-3′) ; δ=2.554 (1H, dd, J=4.12Hz, 19.07Hz, H-4′) ;

δ=2.1995 (1H, dd, J=19.09Hz, 9.60Hz, H-4′) ;

δ=6.03 (1H, NCH) ; δ=3.829, 3.817 (6H, OCH_3) ;

δ=6.8 to 7.6 (aromatics)

Preparation of
(3S,4R)-1-(di-p-anisylmethyl)-3-[(1R)-1-t-butyldiphenyl-siloxyethyl]-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 (SiO_2,CH_2Cl_2) to give the product (7.85g, 93.6%).

Microanalysis

	C	H	N
Theory	71.6%	6.8%	2.2%
Found	71.3%	6.9%	2.2%

Mass spectrum

1275 ($2MH^+$); 638,637,636 (MH^+, M^+, $M\text{-}H^+$);

580 ($M\text{-}tBu^+$); 560 ($M\text{-}Ph^+$); 530($M\text{-}PhOMe^+$)

200MHz ^{1}H-NMR ref $CDCl_3$

δ=1.03 (9H, $SiC(CH_3)_3$) ; 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, $COOCH_3$) ;

δ=3.78 (6H, OCH_3) ; δ=5.87 (1H, NCH) ;

δ=6.6 to 7.8 (aromatics)

200MHz ^{1}H-NMR of 48 ref $CDCl_3$

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, $COOCH_3$) ;

δ=5.87 (1H, s, NCH) ; δ=3.78, 3.79 (6H, $ArOCH_3$) ;

δ=6.7 to 7.3 (aromatics).

Preparation of (3S,4R)-3-[(1R)-1-t-butyldiphenylsiloxyethyl]-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 (SiO_2,CH_2Cl_2) to give 197mg (69%) of a white solid. Spectra taken subsequently showed it to be the desired product 50.

Microanalysis

	C	H	N
Theory	67.1%	7.1%	3.4%
Found	67.2%, 67.0%	7.2%,7.0%	3.3%

Melting point= 103-104°C (sharp)

Infra-red

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

200MHz ^{1}H-NMR ref $CDCl_3$

δ=1.041 (9H, $SiC(CH_3)_3$; δ=1.0816 (3H, d, J=6.36Hz, H-3β) ;

δ=4.32 (1H, m, H-3α) ; δ=3.283 (1H, m, H-3) ;

δ=4.371 (1H, d, J=2.58Hz, H-4) ; δ=3.779 (3H, $COOCH_3$) ;

δ=6.302 (1H, s, N-H) ;

δ=7.3 to 7.8 (aromatics)

^{13}C-NMR

δ=21.94 (C-3β) ; δ=19.29 ($SiC(CH_3)_3$) ;

δ=26.76 ($SiC(CH_3)_3$) ; δ=64.92 (C-3α) ;

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

δ=171.74 (COOMe) ; δ=52.40 ($COOCH_3$) ;

δ=132.57, 134.27 (Ph,C-1′) ;

δ=122.40, 122.63 (Ph,C-2′) ;

δ=135.96, 135.75 (Ph,C-3′) ;

δ=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 (SiO_2, CH_2Cl_2:Et_2O=19:1) and a 60MHz ^{1}H-NMR showed it to be the silanol. 443mg (63.7%) were collected.

60MHz ^{1}H-NMR ref external $CDCl_3$
δ=0.7 (9H, $SiC(CH_3)_3$) ;
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 ν/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 $CDCl_3$
δ=1.030 (9H, $SiC(CH_3)_3$) ;
δ=1.071 (3H, d, J=6.35Hz) ;
δ=4.35 (1H, m, C-3α) ; δ=3.35 (1H, m, H-3) ;
δ=4.47 (1H, d, J=4Hz, H-4) ; δ=6.50 (1H, s, NCH) ;
δ=4.75 (broad, COOH) ;
δ=7.3 to 7.8 (aromatics).

Preparation of
(3S,4R)-1-[3-(prop-1-ene)]-3-[(1R)-1-t-butyldiphenyl-siloxyethyl]-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

(SiO_2,CH_2Cl_2 + 5%Et_2O +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 ^{1}H-NMR ref $CDCl_3$

δ=1.053 (9H, $SiC(CH_3)_3$);

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 (SiO_2, 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 ν/cm^{-1}

1760 (C=O, β-lactam) ; 1715 (C=O, selenyl ester)

No N-H or O-H (acid) stretches were seen

200MHz ^{1}H-NMR ref $CDCl_3$

δ=1.05 (9H, $SiC(CH_3)_3$) ; 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_2O ref D_2O=4.08ppm

δ=3.12 (s, 3H, $COOCH_3$),

δ=3.74 (t, J=6Hz, 1H, α-H),

δ=2.80 (bs, 1H, β-H),

δ=2.76 (bs, 1H, β-H),

δ=6.4 to 7.2 (aromatics)

Preparation of N_b-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 2.5hours. 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_2O, dried over $MgSO_4$(anh), filtered and the

solvent removed under reduced pressure. The crude solid obtained was then recrystallized from $CHCl_3$ and Et_2O , yield=11.16g (87.1%) mp=85°C .

200MHz ^{1}H-NMR in $CDCl_3$ ref $CDCl_3$

δ=3.643, 3.666 (2x s , 2 x $COOCH_3$) ,

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-N_b) ,

δ=8.37 (bs, 1H, H-N_a) ,

δ=6.8 to 7.7 (aromatics)

UV-spectra

In neutral DMF ϵ_{max}(281.0nm)=8213 ,

ϵ_{max}(289.2nm)=70833

In acidic DMF ϵ_{max}(281.4nm)=6644 ,

ϵ_{max}(289.8nm)=5601.4

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

1037 (1.020g) was added as the solid to 88% H_3PO_4 (12ml) and stirred until all the solid was dissolved. The acid solution was then allowed to stir for a further 3hours. The acid solution was then added dropwise to a rapidly stirring mixture of 15% Na_2CO_3 (335ml) and CH_2Cl_2 (150ml). The organic phase was

separated, and the aqueous phase back-extracted with CH_2Cl_2. The combined organic extracts were washed with H_2O, dried over $MgSO_4$(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 ^{1}H-NMR in $CDCl_3$ ref $CDCl_3$

δ=3.670(s) and 3.799(s) (3H, carbamate $COOCH_3$),

δ=3.140(s), 3.169(s) (3H, methyl ester $COOCH_3$),

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,8,8a-hexahydropyrrolo[2,3b]indole (1051)

1035 (24.47g, 88.6mmol) was stirred in pyridine (50ml) until all dissolved. $PhSO_2Cl$ (18.43g, 1.13eq) was added and the solution was stirred for 5 hours. The reaction was then quenched with Et_2O and H_2O. The product precipitated out as a white solid and was filtered off. The ether layer was separated and high field NMR showed only unreacted stating material, pyridine,

but no product.

The product was redissolved in CH_2Cl_2, washed with water, dried over $MgSO_4$(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 CH_2Cl_2 solution of the crude product. Yield=22.95g (62.2%).

High field 200MHz NMR showed only one isomer.

Microanalysis	Theory	found
C	57.683%	57.35%
H	4.840%	4.68%
N	6.727%	6.83%
S	7.699%	7.69%

Mp=165-167°C

$[\alpha]_D$=+91.1° (c=1 , CH_2Cl_2)

200MHz ^{1}H-NMR at room temperature ref $CDCl_3$

δ=3.6 (bs, carbamate $COOCH_3$ and overlapping H-3a) ,

δ=3.113 (s, 3H, methyl ester $COOCH_3$) ,

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 ^{1}H-NMR in $CDCl_3$ ref $CDCl_3$ at +50°C

δ=3.586 (s, 3H, N-$COOCH_3$) ,

δ=3.148 (s, 3H, $COOCH_3$) ,

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) ,

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 ^{1}H-NMR in $CDCl_3$ ref $CDCl_3$ at -20°C

Two rotamers were seen

δ=3.573(major), 3.702(minor) (3H, N-$COOCH_3$),

δ=3.109(s,minor), 3.144(s,major) (3H, $COOCH_3$),

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 ^{n}BuLi (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

MeI (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 $MgSO_4$(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

ϵ_{max}(274.2nm)=2250 in acidic DMF

ϵ_{max}(273.2nm)=2720 in neutral DMF

Microanalysis	Theory	Found
C	58.593%	58.57%
H	5.151%	5.03%
N	6.507%	6.65%
S	7.448%	7.67%

$[\alpha]_D$=+95.2° (c=0.725, CH_2Cl_2)

400MHz ^{1}H-NMR in $CDCl_3$ ref $CDCl_3$

δ=3.594 (s, 3H, carbamate $COOCH_3$) ,

δ=3.045 (s, 3H, methyl ester $COOCH_3$),

δ=1.674 (s, 3H, α-CH_3),

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 $MgSO_4$(anh), filtered, and the solvent removed under reduced pressure to give a yellow oil. The product was recrystallized from CH_2Cl_2 and petrol, yield=1.235g(71.8%), mp=138-139°C, $[\alpha]_D$=+99°(c=1,CH_2Cl_2)

400MHz ^{1}H-NMR in $CDCl_3$ ref $CDCl_3$

δ=3.816 (s, 3H, carbamate $COOCH_3$),

δ=1.616 (s, 3H, α-CH_3) ,

δ=2.070 (dd, J=7.36Hz, 13.41Hz, 1H, H-3) ,

δ=3.021 (broad doublet, J=8.41, 1H, H-3a) ,

δ=3.244 (t, J=6.6Hz, 1H, H-3a) ,

δ=6.126 (d, J=6.2Hz, 1H, H-8a) ,

δ=7 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_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_3.HCl precipitateed 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_2, petrol:EtOAc=2:1). The product was collected as a solid (0.223g, 88%). The solid was then slowly recystallized 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	Theory	Found
C	58.129%	57.88%
H	5.463%	5.45%
N	5.423%	5.37%

400MHz ^{1}H-NMR in $CDCl_3$ ref $CDCl_3$

δ=3.54 (s, 3H, carbamate $COOCH_3$),

δ=3.82 (m, 2H, mixed anhydride CH_2),

δ=1.88 (m, 1H, $C\underline{H}Me_2$),

δ=0.864 (d, 6H, J=6.74, i-butyl CH_3),

δ=1.708 (s, 3H, α-CH_3),

δ=2.267 (dd, J=7.5Hz, 13.6Hz, H-3),

δ=2.768 (d, J=13.76Hz, H-3),

δ=3.473 (t, J=6.8Hz, H-3a),

δ=6.263 (d, J=6.46Hz, H-8a),

δ=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.

Microanalysis	Theory	Found
C	63.866%	63.30%
H	6.508%	6.50%
N	5.320%	5.24%

200MHz ^{1}H-NMR in $CDCl_3$ ref $CDCl_3$

2 rotamers of the amide were seen

δ=5.08 (m,2H,$COOCH_2Ph$),

δ=3.56 (s), 3.72 (s) (3H, $COOCH_3$),

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-phenylmethyloxycarbonyl-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 $MgSO_4$(anh), filtered and the solvent removed under reduced pressure to give 710mg of crude product. The crude was columned chromatographed (SiO_2, 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.

δ=4.96 (m, CH_2Ph),

δ=3.28 (s) , 3.54 (s) (3H, $COOCH_3$) ,

δ=1.40 (s) , 1.46 (s) (3H , α-CH_3) ,

δ=1.74 (m) , 2.00 (m) (4H, H-β, H-γ) ,

δ=3.44 (m, 2H, H-δ) ,

δ=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_2Cl_2 and petrol. Mp=121°C

Microanalysis	Theory	Found
C	63.866%	63.33%
H	6.508%	6.17%
N	5.320%	5.21%

200MHz ^{1}H-NMR in $CDCl_3$ ref $CDCl_3$

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

δ=1.520 (s,minor) , 1.616 (s, major) (3H, α-CH_3) ,

δ=1.89 (m, 3H) , 2.28 (m, 1H) (H-β, H-γ) ,

δ=3.58 (m, 2H, H-δ) ,

δ=5.09 (s, minor) , 5.14(s, major) (2H, $COOCH_2Ph$) ,

δ=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

δ=0.9165 (d,J=4.51Hz), 0.950 (d, J=4.51Hz) (6H,

isopropyl CH_3),

δ=2.33 (m, 1H, isopropyl C<u>H</u>) ,

δ=3.996 (d, J=5.64Hz), 4.029 (d,J=5.6Hz) (2H, isopropyl C<u>H</u>$_2$) ,

δ=1.542 (s) , 1.640 (s) (3H, α-CH_3) ,

δ=1.96 (m, 4H, H-β, H-γ) ,

δ=3.60 (m, 2H, H-δ) ,

δ=5.12 (m, $COOC\underline{H}_2Ph$) ,

δ=7.2 to 7.5 (aromatics).

<u>Preparation of N_b-acetyl-N_a-benzenesulphonyl-(S)-α-methyl-L-tryptophan methyl ester (1056)</u>

<u>1053</u> (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_2Cl_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%).

<u>400MHz ^{1}H-NMR in $CDCl_3$ ref $CDCl_3$</u>

δ=5.441 (bs, 1H, H-N_b) ,

δ=3.695 (s, 3H, N_b-$COOCH_3$) ,

δ=3.653 (s, 3H, $COOCH_3$) ,

δ=1.643 (s, 3H, α-CH_3) ,

δ=3.284 (d, J=14.65Hz, 1H, H-β) ,

δ=3.567 (d, J=14.23Hz, 1H, H-β) ,

δ=7.1 to 8.0 (aromatics)

Preparation of

2(S)-2-(N-carbomethoxy)amino-1-methoxycarbonyl- 4-butanoic acid 1057

$NaIO_4$ (7.9g) was dissolved in water (30ml) with warming. **1056** (779mg, 1.86mmol) in MeCN (10ml) was added to the $NaIO_4$ solution. The resulting mixture was then heated until it was in a single phase. Then $RuCl_3.3H_2O$ (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 $MgSO_4$(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 (SiO_2,Et_2O+AcOH), but the product and **1083** did not separate perfectly, 226.4mg (55%) was obtained. More of the **1083** was then recrystallized from $CHCl_3$. The product was then recrystallized in $CHCl_3$ (70mg, 17%), mp=103-105°C .

Microanalysis	Theory	Found
C	43.837%	43.80%
H	5.978%	5.82%
N	6.390%	6.46%

$[\alpha]_D$= -11.0° (c=1.45, MeOH)

200MHz ^{1}H-NMR ref $CDCl_3$

δ=5.94 (bs, 1H, NH) ,

δ=3.773 (s, 3H, N-$COOCH_3$) ,

δ=3.640 (s, 3H, $COOCH_3$) ,

δ=1.608 (s, 3H, α-CH_3) ,

δ=3.0 (d, J=16Hz, 1H, H-β) ,

δ=3.44 (broad doublet, J=16Hz, 1H, H-β)

Preparation of (S)-α-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° (c=0.84, H_2O).

^{1}H-NMR in D_2O ref D_2O=4.111

δ=0.879 (s,3H, α-CH_3) ,

δ=2.23, 2.51 (AB quartet, 2H, J=18.3Hz, H-β).

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°C under nitrogen.

1051 (2.0683g, 4.97mmol) dissolved in THF (20ml) with warming was cooled to -78°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. Tlc 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 $MgSO_4$(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 Et_2O , mp=113°C, $[\alpha]_D$=+89.7° (c=0.39, CH_2Cl_2)

400Mhz ^{1}H-NMR in $CDCl_3$ ref $CDCl_3$

δ=3.60 (s, 3H, N-$COOCH_3$) ,

δ=3.58 (s, 3H, C-2 $COOCH_3$) ,

δ=2.98 (s, 3H, side chain $COOCH_3$) ,

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-N_b-acetyl-N_a-benzenesulphonyl-α-(carbomethoxymethyl)-L-tryptophan methyl ester (1059)

1054 (765.7mg, 1.614mmol) was dissolved in CF_3COOH (4ml) and stirred for 90 minutes. The CF_3COOH 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 $CDCl_3$

δ=6.16 (s, 1H, H-N_b),

δ=3.65 (s, α-$COOCH_3$),

δ=3.71 (s, N_b-$COOCH_3$),

δ=3.58 (s, $COOCH_3$),

δ=3.17 (m, 2H, β'-CH_2),

δ=3.6 (m, overlapping with the methyl esters, β-CH_2),

δ=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. $RuCl_3.3H_2O$ (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_2O), and the desired product was collected as an oil,153.6mg (60%).

Accurate mass Theory 278.0871

Found 278.0867

200MHz ^{1}H-NMR in $CDCl_3$ ref $CDCl_3$

δ=6.18 (bs,1H, N-H),

δ=3.80 (s, 3H, N-$COOCH_3$),

δ=3.64 (s, 6H, 2x $COOCH_3$),

δ=2.88 (m, 2H, 1x $C\underline{H_2}COOMe$ and 1x $C\underline{H_2}COOH$) , δ=3.50 (m, 2H, 1x $C\underline{H_2}COOMe$ and 1x $C\underline{H_2}COOH$)

Preparation of (R)-α-methyl-N-carboxymethyl aspartic acid methyl diester 1062

60 (236.6mg, 1.25mmol) was stirred in CH_2Cl_2 (2ml) at -10°C under nitrogen. A solution of 1060 (270mg, 0.9739 mmol) and NEt_3(139.2mg, 1.38mmol) in CH_2Cl_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_2Cl_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_2O. The Et_2O 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_2O (4ml) and washed with 6M HCl (1ml). The Et_2O 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%).

$[\alpha]_D$=+21.3° (c=2.485, MeOH)

200MHz ^{1}H-NMR in $CDCl_3$ ref $CDCl_3$

δ=5.941 (bs, 1H, NH),

δ=3.771 (s, 3H, N-$COOCH_3$),

δ=3.622 (s, 3H, $COOCH_3$),

δ=3.637 (s, 3H, $COOCH_3$),

δ=2.91 (d, J=16.5Hz, 1H, CH_2),

δ=3.36 (d, J=16.1Hz, 1H, CH_2),

δ=1.598 (s, 3H, CH_3)

Preparation of (R)-α-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_2O).

200MHz ^{1}H-NMR in D_2O ref D_2O=4.182

δ=0.733 (s, 3H,α-CH_3),

δ=2.10, 2.38 (AB quartet, J=18.3Hz, H-β)

Preparation of N_b-acetyl-L-tryptophan (1076)

1001 (1.00g, 4.90mmol) was dissolved in water and Na_2CO_3 (1.43g, 13.5mmol, 2.75eq) and stirred at 0°C.

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

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 ^{1}H-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). NEt_3 (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 NEt_3 (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 $MgSO_4$(anh), filtered and the

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

Microanalysis	Theory	Found
C	67.445%	66.95%
H	5.362%	5.46%
N	8.279%	8.20%

200MHz ^{1}H-NMR in $CDCl_3$ ref $CDCl_3$
δ=5.32 (d, J=7Hz, 1H, H-N_b),
δ=3.688 (s, 3H, carbamate $COOCH_3$),
δ=4.93 (m, 1H, H-α),
δ=3.45 (d, J=5.4Hz, 2H, H-β),
δ=8.13 (bs, 1H, H-N_a),
δ=6.8 to 7.8 (aromatics)

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

1077a (0.16g, 0.473mmol) was stirred in 88% H_3PO_4 (2ml) for 8 hours and then quenched by dropping slowly into a rapidly stirring mixture of CH_2Cl_2 (40ml) and 15% Na_2CO_3 (45ml). The CH_2Cl_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.

200MHz ^{1}H-NMR in $CDCl_3$ ref $CDCl_3$

δ=3.750 (s) , 3.824 (s) , (3H, carbamate $COOCH_3$) ,

δ=4.72 (m) , 4.86 (m) , (2H, H-2 and H-8) ,

δ=2.74 (m, 2H, H-3) ,

δ=4.0 (m, 1H, H-3a) ,

δ=5.61 (d, J=6.77Hz) , 5.66 (d, J=6.77Hz) , (H-8a) ,

δ=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). $PhSO_2Cl$ (108mg, 0.587mmol, 1.24eq) was added in pyridine (1ml). The reaction was left stirring for 16 hours and then quenched with Et_2O and CH_2Cl_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.

400MHz ^{1}H-NMR at room temperature

δ=3.48(bs), 3.70(bs), (3H, $COOCH_3$) ,

δ=4.86 (bs, 1H, H-2) ,

δ=2.7 (m, 2H, H-3) ,

δ=3.90 (bs, 1H, H-3a) ,

δ=6.38 (bs, 1H, H-8a) ,

δ=6.5 to 7.8 (aromatics)

400MHz ^{1}H-NMR at +50°C in $CDCl_3$ ref $CDCl_3$

δ=3.55 (s, 3H, $COOCH_3$) ,

δ=4.86 (d, J=8Hz, 1H, H-2) ,

δ=2.78 (m, 2H, H-3) ,

δ=2.65 (m, 1H, H-3) ,

δ=3.86 (m, 1H, H-3a) ,

δ=6.41 (d, J=8Hz, 1H, H-8a) ,

δ=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

δ=3.429 (s, major) , 3.708 (s, minor) (3H, $COOCH_3$) ,

δ=4.753(minor,d,J=8.85Hz), 4.883(major,d,J=8.99Hz)(H-2)

δ=2.7 (m, H-3) ,

δ=3.641(minor,t,J=7.2Hz), 3.890(major,t,J=6.7Hz) (H-3a)

δ=6.353(major,d,J=6.46Hz), 6.381(minor,d,J=6.6Hz)(H-8a)

δ=6.4 to 7.9 (aromatics).

Preparation of N_b-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_2, EtOAc:petrol=1:1) to give the product as an oil (401mg, 71%).

Accurate mass	Theory 428.0792
	Found 428.0747

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

400MHz ^{1}H-NMR at +50°C in $CDCl_3$ ref $CDCl_3$

δ=5.08 (m, 1H, H-α),

δ=3.5 (m, 2H, H-β),

δ=5.3 (bs, 1H, H-N_b),

δ=8.25 (bs, 1H, H-N_a),

δ=7.0 to 7.7 (aromatics)

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

1077b (407mg, 0.951mmol) was dissolved in 88% H_3PO_4 (4ml) and stirred for 12 hours. The acidic solution was then added slowly to a rapidly stirring mixture of 15% Na_2CO_3 (90ml) and dichloromethane (50ml). The organic phase was separated, and the aqueous phase back extracted with dichloromethane. 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). 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 ^{1}H-NMR in $CDCl_3$ ref $CDCl_3$
δ=3.721(s), 3.833(s) (3H, $COOCH_3$),
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[2,3b]indole (1075b)

1078b (101.3mg, 0.2365mmol) was dissolved in pyridine (0.5ml) and stirred. $PhSO_2Cl$ (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 $MgSO_4$(anh), filtered, and the solvent removed under reduced pressure. The crude was then column chromatographed (SiO_2, Et_2O) 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 ^{1}H-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 ^{1}H-NMR in $CDCl_3$ at +50°C ref $CDCl_3$

δ=3.607 (s, 3H, $COOCH_3$),

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 ^{1}H-NMR in $CDCl_3$ ref $CDCl_3$ at -20°C

δ=3.548(s, major), 3.746(s, major) ($COOCH_3$),

δ=4.86(d,J=8.7Hz,minor), 4.98(m,major) (H-2),

δ=2.7 (m, H-3),

δ=3.83(bs,major);3.57(overlapping $COOCH_3$,m,minor)(H-3a)

δ=6.31(d,J=6.43Hz,major);6.329(d,J=8Hz,minor) (H-8a) ,

δ=7.0 to 7.8 (aromatics)

^{19}F-NMR at room temperature in $CDCl_3$ ref hexafluorobenzene=0ppm. Operating frequency = 376.3MHz

Rotamers were seen in the ratio of 2.4:1

δ=10.0 (bs, major), 9.4 (bs, minor) (2F, ortho) ,

δ=-0.496 (t, J=20.3Hz, 2F, meta) ,

δ=4.1 (bs, 1F, para)

^{19}F-NMR at +50°C in $CDCl_3$ referenced on the most upfield peak

δ=10.6 (bs, 2F, ortho) ,

δ=0 (t, J=19.3Hz, 2F, meta) ,

δ=4.587 (t, J=21.2Hz, 1F, para)

^{19}F-NMR at 0°C in $CDCl_3$ ref hexafluorobenzene = 0ppm

Rotamers were seen in the ratio of 2.3:1 .

δ=9.3335 (minor,d,J=20.1H),

9.91 (major,d,J=19.3Hz) (ortho)

δ=-0.46 (major, t, J=21.4Hz),

-0.408 (minor, t, J=21.4Hz) (meta)

δ=4.15 (major, t, J=22Hz),

4.263 (minor, t, J=21Hz) (para)

^{19}F-NMR at -40°C in $CDCl_3$ 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)

^{19}F-NMR at -60°C in $CDCl_3$ ref hexafluorobenzene=0ppm

δ=9.3 (bs, ortho),

δ=-0.3 (m, meta),

δ=4.3 (m, para)

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

1076 (508.3mg, 1.938mmol), NEt_3 (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 Na_2CO_3. The organic phase was separated, and the aqueous layer 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 column chromatographed (SiO_2, EtOAc:petrol=1:1) to give the product as an oil (293.4mg, 41%).

200MHz ^{1}H-NMR in $CDCl_3$ref $CDCl_3$

δ=5.62 (d, J=8Hz, H-N_b) ,

δ=3.6 to 3.8 (singlets, 6H, 2x $COOCH_3$) ,

δ=4.94 (m, 1H, H-α) ,

δ=3.441 (d, J=5.4Hz, 2H, H-β) ,

δ=8.6 (bs, H-N_a) ,

δ=6.7 to 7.8 (aromatics)

Preparation of

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

1077c (293.4mg, 0.796mmol) was dissolved in 88% H_3PO_4 (3ml) and stirred for 16 hours. The acidic solution was then added dropwise to a rapidly stirring mixture of 15% Na_2CO_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 $CDCl_3$

δ=3.7 to 3.84 (singlets, 6H, $COOCH_3$ and Ar-OCH_3) ,

δ=4.69 (m), 4.84 (m) , (1H, H-2) ,

δ=2.73 (m, 2H, H-3) ,

δ=3.96 (m, 1H, H-3a) ,

δ=5.58 (d, J=6.4Hz, minor, H-8a) ,

5.65 (d, J=6.8Hz, major, H-8a) ,

δ=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 $MgSO_4$(anh), filtered and the solvent removed under reduced pressure. The crude was column chromatographed (SiO_2, 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.

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

400MHz ^{1}H-NMR in $CDCl_3$ ref $CDCl_3$ at 50°C

δ=3.717 (s, 3H, $COOCH_3$),

δ=3.511 (bs, 3H, $ArOCH_3$),

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)

400MHz ^{1}H-NMR in $CDCl_3$ ref $CDCl_3$ at -20°C

Rotamers in the ratio of 2.7:1 were seen.

δ=3.419(s,major), 3.718(s,minor) ($COOCH_3$),

δ=3.766(s, $ArOCH_3$),

δ=4.748(d,J=8.81Hz,minor), 4.882(d,J=8.99Hz,major)(H-2),

δ=2.75(m, 2H, H-3),

δ=3.642(t,J=6.8Hz,minor), 3.918(t,J=6.8Hz,major) (H-3a)

δ=6.335(d,J=9Hz,minor), 6.368(d,J=6.5Hz,major) (H-8a),

δ=6.3 to 7.9 (aromatics)

Preparation of
N-(8-Aminonaphthalene-1-yl)-(N_b-acetyl-L-tryptophan)-
2-carboxamide 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, 1.11eq) 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_2CO_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 $CDCl_3$

δ=3.504 (s, 3H, $COOCH_3$),

δ=4.55 (m, 1H, H-α),

δ=3.3 (m, 2H, H-β),

δ=5.8 to 9 (aromatics and N-H's)

UV Spectra

In neutral DMF	ϵ_{max}(281.8nm)= 7379
	ϵ_{max}(289.8nm)= 7929
	ϵ_{max}(330.6nm)=15698
In acidic DMF	ϵ_{max}(280.9nm)=10344
	ϵ_{max}(289.5nm)=11096
	ϵ_{max}(314.0nm)=12773
	ϵ_{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_3PO_4 (10ml) for 18 hours. The acidic solution was then dropped slowly into a rapidly stirring mixture of dichloromethane (50ml) and 15% Na_2CO_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 $CDCl_3$

δ=3.742 (s, 3H, $COOCH_3$) ,

δ=4.707 (d, J=9.14Hz, 1H, H-2) ,

δ=2.50 (bs, 1H, H-2) ,

δ=2.95 (bs, 1H, H-2) ,

δ=4.017 (t, J=8Hz, 1H, H-3a) ,

δ=5.3(bs), 5.65(bs), 5.85(bs), (2x N-H, and H-8a)

δ=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[2,3b]indole 1078e

1078d (1247.2mg, 3.10mmol) was dissolved in toluene (20ml) and refluxed with P_2O_5 (12g). The reaction was then quenched by adding slowly to a rapidly stirring mixture of ethyl acetate and 15% Na_2CO_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.

Microanalysis	Theory	Found
C	71.859%	71.86%
H	5.243%	5.34%
N	14.574%	14.12%

400MHz ^{1}H-NMR in $CDCl_3$ and DMSO ref $CDCl_3$

δ=6.01 (bs, 1H, H-N_b),

δ=3.50 (bs, 3H, $COOCH_3$),

δ=4.45 (bs, 1H, H-α),

δ=3.20 (bs, 2H, H-β),

δ=6.5 to 7.7 (aromatics and NH's).

UV spectra

In neutral DMF	ϵ_{max}(281.2nm)=3628
	ϵ_{max}(289.6nm)=3676
	ϵ_{max}(330.8nm)=8048
In acidic DMF	ϵ_{max}(280.4nm)=5838
	ϵ_{max}(289.6nm)=6054
	ϵ_{max}(313.6nm)=6727
	ϵ_{max}(326.2nm)=7207

Attempted cyclization of 1077e with 88% H_3PO_4

1077e (26.1mg) was stirred in 88% H_3PO_4 (1ml) for 48 hours. The acidic solution was then slowly added to a rapidly stirring mixture of 15% Na_2CO_3 (100ml) and dichloromethane (50ml). 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 was removed under reduced pressure to give the crude (38.7mg). High field ^{1}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 $MgSO_4$(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%).

Mp=123-124°C (lit. 123-125°C).

200MHz ^{1}H-NMR in $CDCl_3$ ref $CDCl_3$

δ=4.41 (s, CH_2) ,

δ=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 $MgSO_4$(anh), filtered, and the solvent removed under reduced pressure. The crude was column chromatographed (SiO_2, Petrol:EtOAc=4:1). The product (1.409g, 25.4%) was collected from the column. Recrystallization from Et_2O yielded the product (325.3mg, 5.9%), mp=123-124°C.

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

1094 (282.2mg, 1.20mmol) and NH_4OAc (1.8915g, 19.7eq) was dissolved in methanol(17ml) and stirred under nitrogen. $NaBH_4CN$ (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 $MgSO_4$(anh), filtered, and the solvent removed under reduced pressure to give the product (166.4mg, 59%).

200MHz ^{1}H-NMR in $CDCl_3$ ref $CDCl_3$

δ=4.35 (dd, J=8Hz,4Hz, H-α),

δ=3.010 (d of AB quartet, J=14Hz,8Hz , H-β),

δ=3.228 (d of AB quartet, J=14Hz, 4Hz, H-β),

δ=6.7 to 8.8 (aromatics and NH's)

Preparation of (+)-N_b-Carboxymethyl-α-phenyl-tryptophan, 1109

(+)**1095** (120mg, 0.456mmol) in dichloromethane (3ml) was added to a solution of Na_2CO_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), filterted 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 $CDCl_3$

δ=5.31 (bs, 1H, H-N_b),

δ=3.604 (s, 3H, $COOCH_3$),

δ=5.10 (bs, 1H, H-α),

δ=3.230 (broad doublet, J=6Hz, 2H, H-β),

δ=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_3PO_4 and stirred for 16 hours. The reaction was then added to a rapidly stirring mixture of dichloromethane (50ml) and 15% Na_2CO_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 δ=6.0ppm could be seen. There were two peaks for the carbamate methyl ester at δ=3.64ppm and δ=3.68ppm.

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 δ=6.00ppm (J=7.3Hz), δ=6.42ppm (J=7.9Hz), δ=6.32ppm (J=6.66Hz).

Three singlets for the carbamate methyl ester were also seen at δ=3.661ppm, δ=3.667ppm, δ=3.671ppm.

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) in refluxing toluene

1063 (198.4mg, 0.4764mmol) and NEt_3(57.3mg, 0.567mmol, 1.19eq) were dissolved in dry THF(3ml) and stirred at room temperature. 60 (108.5mg, 1.2eq) was added as the solid, and a yellow solution was formed. t-$C_{12}H_{25}SH$ (240mg, 2.5eq) was then injected. The reaction was then quickly injected into refluxing toluene (20ml) 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 (SiO_2, petrol:EtOAc=1:1). The desired products were collected (38.8mg, 21%). 200MHz ^{1}H-NMR showed the ratio of endo-methyl product to exo-methyl product to be 1:2.

The two isomers were separated by column chromatography (SiO_2, petrol:EtOAc=1:1).

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

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

δ=3.74 (s, 3H carbamate $COOCH_3$) ,

δ=3.36 (m, 1H, H-2) ,

δ=1.29 (d, J=5.78Hz, 3H, CH_3),

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 ^{1}H-NMR of the endo-methyl product (1066)

δ=3.701 (s, 3H, carbamate $COOCH_3$),

δ=4.11 (m, 1H, H-2),

δ=0.678 (d, J=6.84Hz, 3H, CH_3),

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_2Cl_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_2Cl_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_2Cl_2(3ml) and NEt_3(66.5mg, 0.66mmol, 1.86eq) was added in CH_2Cl_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_2Cl_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_b-acetyl-α-methyl-tryptamine (+)1105 from (+)α-methyltryptamine (+)1104

(+)α-Methyltryptamine (349.2mg, 2.004mmol), Na_2CO_3 (263.5mg, 2.49mmol, 1.24eq) were dissolved in water (2ml). CH_2Cl_2(4ml) was added and the mixture was rapidly stirred.

Methyl chloroformate (216.0mg, 1.1eq) in CH_2Cl_2 (1ml) was added, and the mixture was stirred until both phases were clear. When tlc showed no more starting material, the CH_2Cl_2 phase was separated. 15% Na_2CO_3 (4ml) was added to the aqueous phase, which was then extracted with more CH_2Cl_2 (3x). The combined CH_2Cl_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 $CDCl_3$
δ=4.6 (bs, 1H, carbamate NH) ,
δ=3.659 (s, 3H, carbamate $COOCH_3$) ,
δ=1.150 (d, J=6.56Hz, 3H, α-CH_3) ,

δ=4.1 (m, 1H, α-H),

δ=2.9 (m, 2H, β-H),

δ=8.2 (bs, 1H, indole NH),

δ=6.9 to 7.8 (aromatics).

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% H_3PO_4 (8ml) and stirred for 16 hours. The acidic reaction was quenched by dropping slowly into a rapidly stirring mixture of 15% Na_2CO_3(200ml) and CH_2Cl_2(100ml). The CH_2Cl_2 phase was separated and the aqueous phase back extracted. The combined CH_2Cl_2 extracts was dried over $MgSO_4$(anh), filtered and the solvent removed under reduced pressure to give an oil (469mg).

High field ^{1}H-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. $PhSO_2Cl$ (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.

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