A THESIS ENTITLED

"1,3-DIPOLAR CYCLOADDITIONS OF CHIRAL NITRONES"

Submitted to the University of Glasgow

for the Degree of Doctor of Philosophy

in the Faculty of Science

by

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To my dear mother, Elizabeth

and in memory of

my late father, David

Acknowledgements

I would like to express my sincere thanks to my supervisor, Professor Karl Overton for his help, encouragement and enthusiasm over the past three years.

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Finally, I thank Professor G.W. Kirby for provision of facilities in the Chemistry Department and the S.E.R.C. for financial support.

PUBLICATIONS

The work presented in this thesis has appeared elsewhere:

(i) Conversion of Amines into Imines by Swern Oxidation:
David Keirs and Karl Overton, J. Chem. Soc., Chem. Commun., 1987, 1660.

(ii) Enantioselective Synthesis of Optically Pure (R)- and (S)-β-Lysine via Nitrone Cycloaddition:
David Keirs, David Moffat, and Karl Overton, J. Chem. Soc., Chem. Commun., 1988, 654.

(iii) Stereocontrolled Syntheses of Aspartame [(S)-Asp-(S)-PheOMe] and its (R)-Aspartyl Congener [(R)-Asp-(S)-PheOMe] via Nitrone Cycloaddition:
David Keirs and Karl Overton, Heterocycles, 1989, 28, in press.

TABLE OF CONTENTS

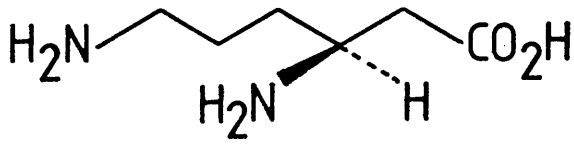
Summary

The asymmetric synthesis of natural products via 1,3-dipolar cycloadditions of chiral nitrones to prochiral olefins has been an area of intense activity over the past decade.[10-18] The work described in this thesis involves the application of two short, highly efficient asymmetric routes to the synthesis of compounds of biological (Chapter 2) and commercial (Chapter 3) interest. The key step in each synthesis involves dipolar cycloaddition of a chiral nitrone to a substituted dipolarophile.

The Introduction gives an account of the mechanistic aspects of 1,3-dipolar cycloadditions and describes some recent examples of asymmetric syntheses involving nitrone-olefin cycloaddition reactions.

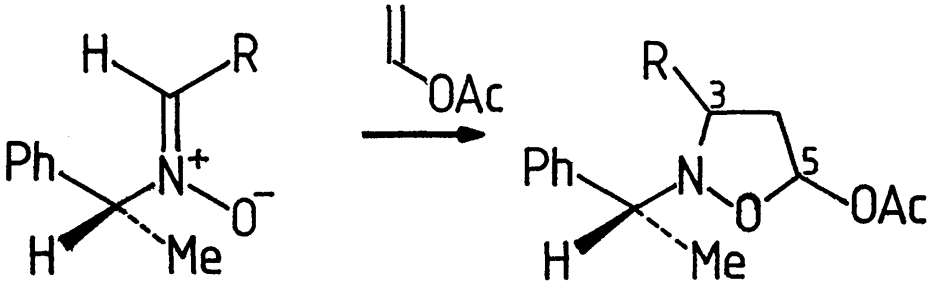
Chapter 1 provides a short discussion on the general methods of preparation of aldonitrones, in particular the chiral aldonitrones used in the syntheses described in Chapters 2 and 3. The structure of aldonitrones is also briefly discussed in Chapter 1.

Chapter 2 gives a detailed account of the asymmetric synthesis of β-lysine (62).



(62)

This is a continuation of the work described by Moffat and Overton[26] who devised a general asymmetric route to β-amino acids involving 1,3-dipolar cycloaddition of chiral nitrones to vinyl acetate to yield isoxazolidines in which substituents have been placed in a regio- and stereoselective manner on the periphery of the five-membered ring, [Scheme I].

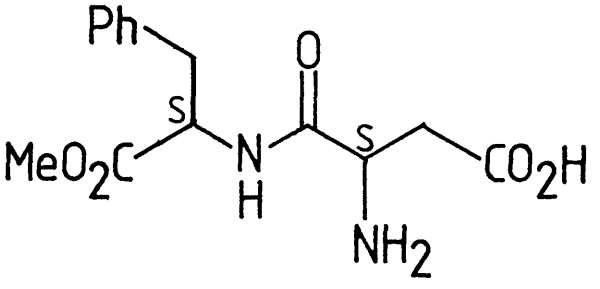


R=alkyl, aryl

Scheme I

The isoxazolidines are formed as a crude mixture of four non-racemic diastereomers with the induced chiral centre at C-3 ultimately becoming the chiral centre of the final β-amino acid. The chiral centre at C-5 is destroyed via the subsequent synthetic steps. A chromatographic separation of diastereoisomeric 5-acetoxy isoxazolidines has allowed the enantioselective synthesis of optically pure (R)- and (S)-β-lysine.

The work described in Chapter 3 involves a stereocontrolled synthesis of the dipeptide artificial sweetener, Aspartame [(S)-Aspartyl-(S)-Phenylalanine methyl ester] (95) via 1,3-dipolar cycloaddition of nitrones (119a,b,c) to the ketene equivalent 2-chloroacrylonitrile.



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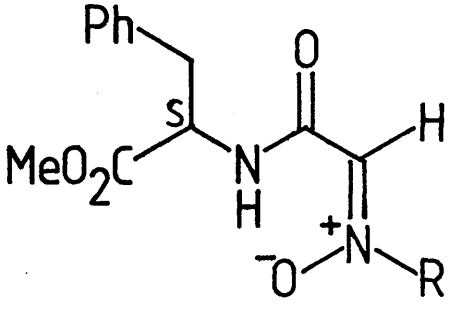


a R=CH_2Ph

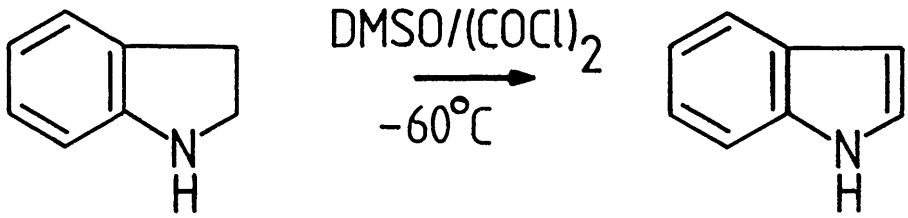
b R=(R)-CHMePh

c R=(S)-CHMePh

(119a,b,c)

The same general sequence as that used for the asymmetric synthesis of β-lysine was employed although 2-chloroacrylonitrile was shown to be far superior to vinyl acetate as a dipolarophile in terms of reactivity towards nitrones and chemical yields. The sequence also provides a potential general asymmetric route to aspartyl dipeptides.

Chapter 4 records the conversion of various amines into imines by Swern oxidation [DMSO/$(COCl)_2$], the most notable example being the conversion of indoline (141) into indole (143) in almost 90% yield, [Scheme II].



(141) (143)

Scheme II

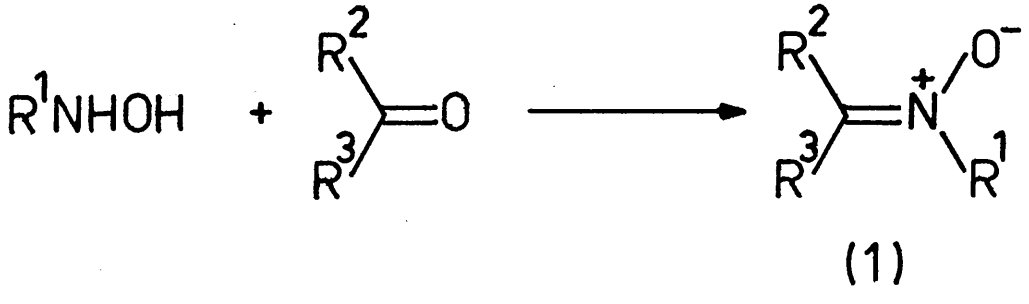
This work arose out of an unexpected observation in the synthesis of β-lysine. Although not directly related to the main topic of this thesis, the finding is of fundamental importance since Swern reagents have not been used previously for the dehydrogenation of amines into imines.

INTRODUCTION

INTRODUCTION

1. Background

Early researchers studying the condensation of carbonyl compounds with N-substituted hydroxylamines coined the term "nitrone" as a combination of the words "nitrogen" and "ketone" to emphasise the parallel between this newly discovered functionality (1) and the already established chemistry of the carbonyl group, [Scheme 1].

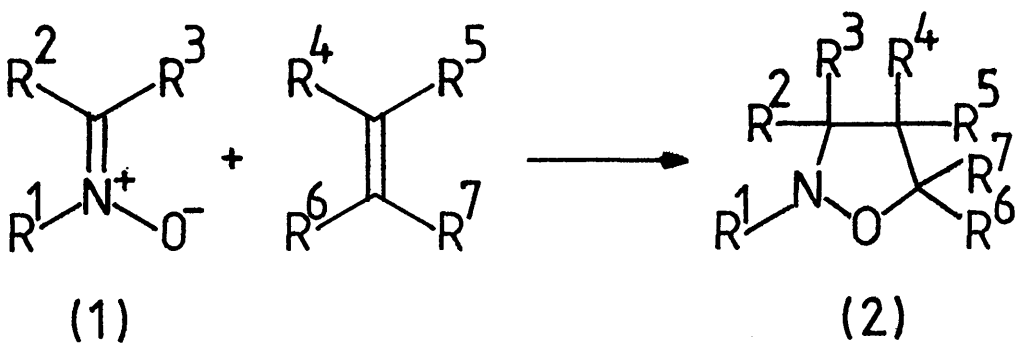


(1)

Scheme 1

For instance, the iminium character of nitrones renders them susceptible to nucleophilic attack with carbanions of various types. The work presented in this thesis, on the other hand, focuses entirely upon the tendency of nitrones to undergo [3+2]-cycloaddition reactions with a

variety of dipolarophiles. This process provides an efficient entry into isoxazolidines (2), an important class of heterocyclic compounds, which occupy a key role in the work described in this thesis, [Scheme 2]. The [3+2]-cycloaddition reaction frequently embodies a high degree of regiochemical and stereochemical control and the N-O bond of (2) can, in most cases, be easily cleaved.



(1) (2)

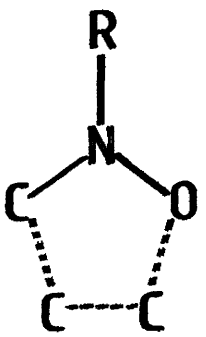
Scheme 2

The earliest example of a [3+2]-cycloaddition involving a nitrone was described in 1890. Beckmann[1] reported that a 1:1 adduct was formed when an aryl isocyanate was heated in the presence of a nitrone. Despite this important result, described nearly a century ago, the cycloaddition reactions of nitrones with alkenes were reported only relatively recently. The brilliant work of Huisgen[3] in the early 1960's

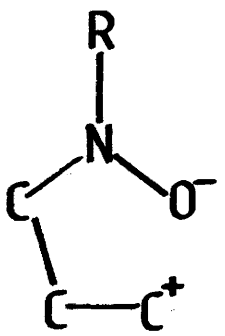
helped to establish the scope and applications of 1,3-dipolar cycloaddition reactions, including the intermolecular [3+2]-cycloadditions of nitrones to alkenes. The participation of nitrones in 1,3-dipolar cycloadditions as part of natural product synthesis has been reviewed up to the late 1970's.[2] More recent examples will be discussed later in the Introduction.

2. The Mechanism of 1,3-Dipolar Cycloaddition Reactions of Nitrones

The [3+2]-dipolar cycloaddition reaction of a nitrone to an olefin is an orbital symmetry-allowed [$\pi^2 S + \pi^4 S$] process. In general, the additions of nitrones to dipolarophiles exhibit small activation energies and large negative activation entropies, suggesting that the dipolar cycloaddition process proceeds via a single step, four centre, concerted mechanism[3c,4] passing through the highly ordered transition state (3).



(3)



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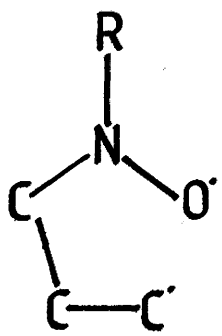
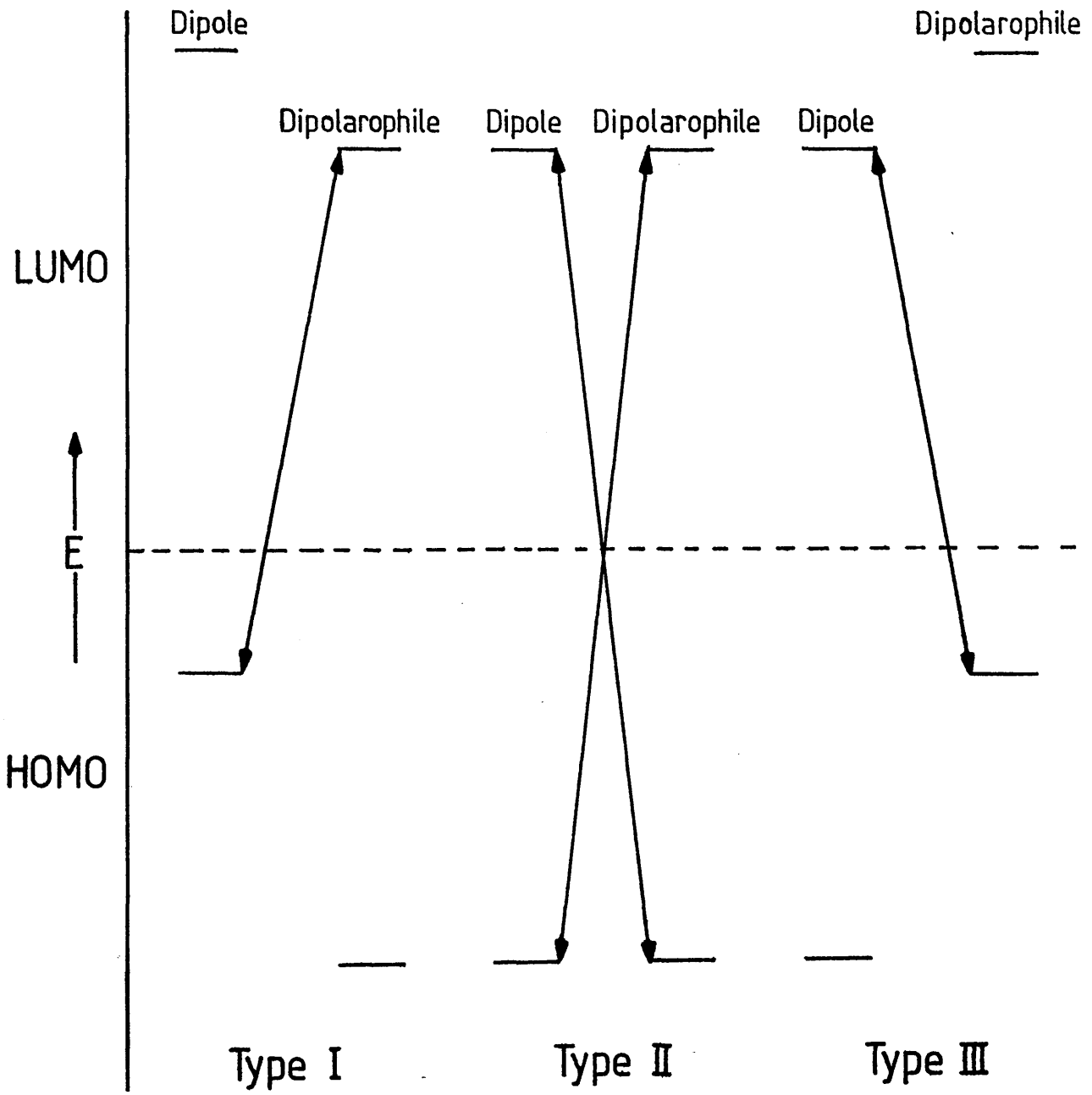
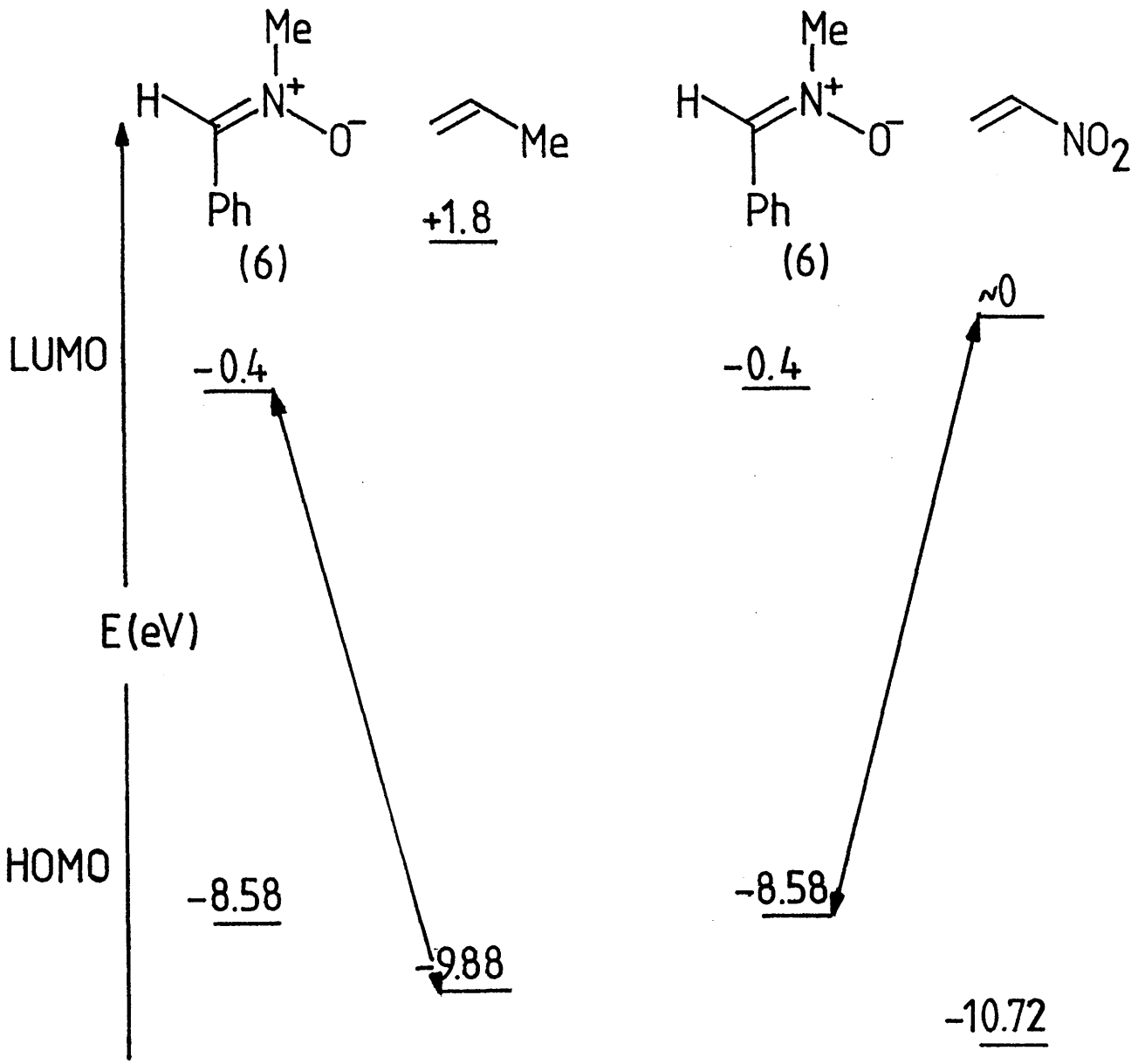


(5)


Dipole
Dipolarophile
Dipolarophile
Dipole
Dipolarophile
Dipole
LUMO
E
HOMO
Type I
Type II
Type III

Scheme 3

important in determining reactivity and regiochemistry. The dominant interaction in any particular case will depend on the nature of both the dipole and dipolarophile. Scheme 4 illustrates the cycloaddition of N-methyl-C-phenyl nitrone (6) with an electron-rich dipolarophile (propene) and an electron-deficient dipolarophile (nitroethylene).



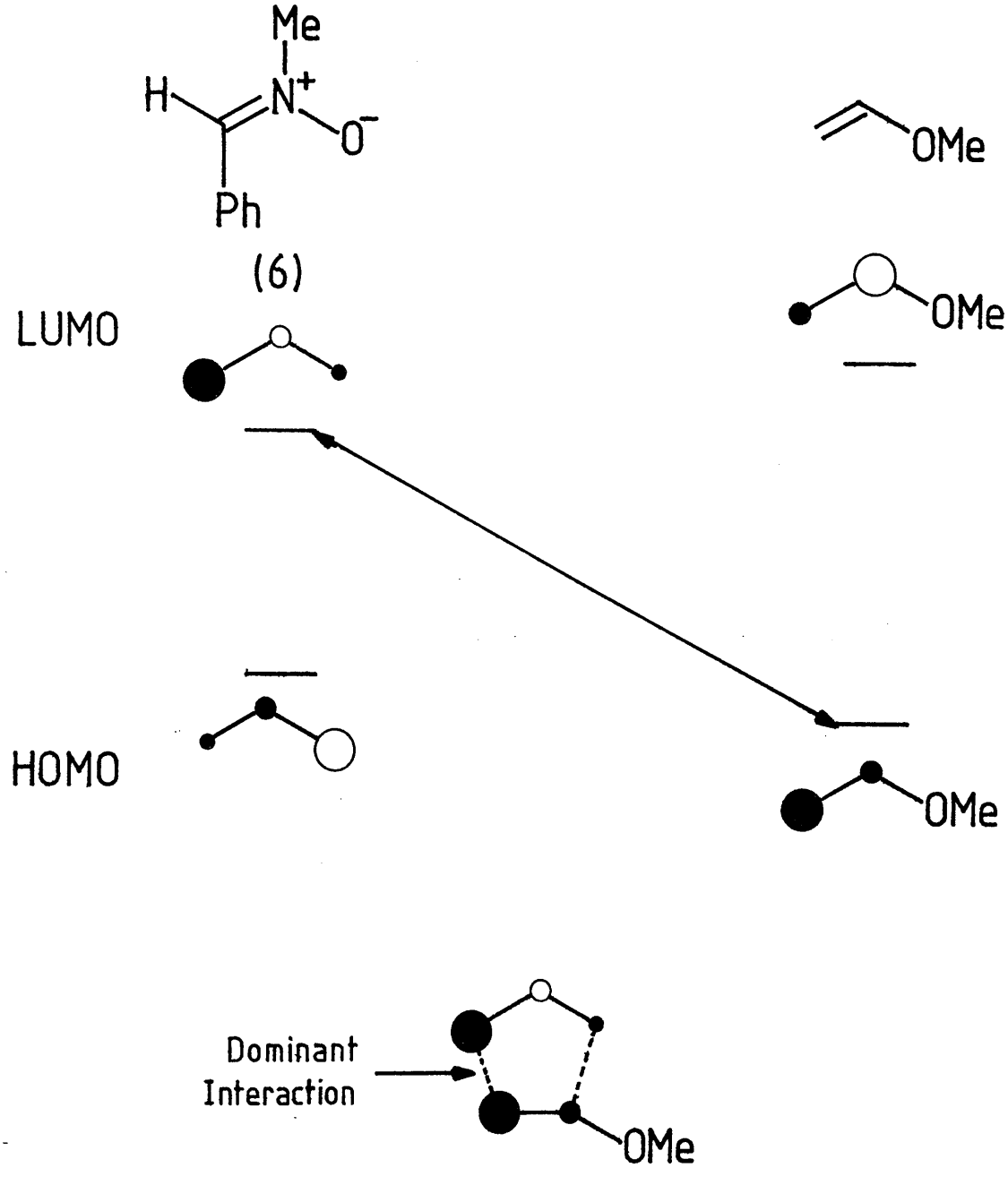
Scheme 4

Cycloaddition of (6) with propene is dominated by the LUMO-(dipole)-HOMO(dipolarophile) interaction (ΔE_{min} = 9.48 eV) as opposed to the HOMO(dipole)-LUMO(dipolarophile) interaction (ΔE_{max} = 10.38 eV). In contrast, cycloaddition of (6) with nitroethylene is dominated by the HOMO(dipole)-LUMO(dipolarophile) interaction (ΔE_{min} = 7.9 eV).

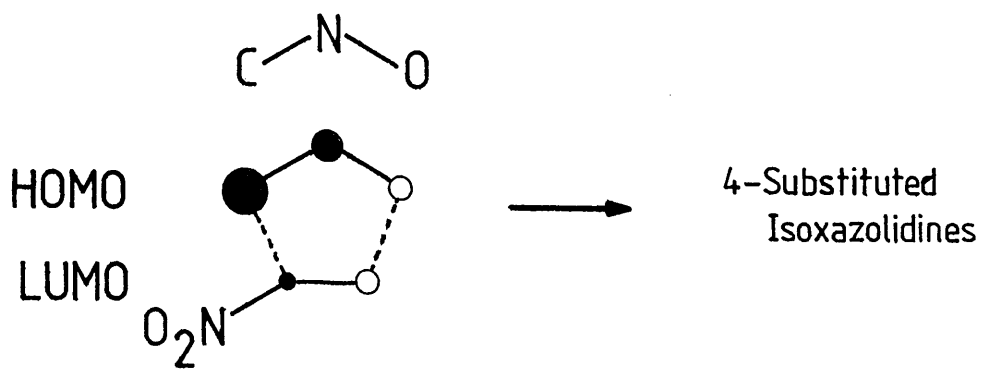
Regioselectivity in nitrone cycloadditions is determined by the relative magnitude of the atomic orbital coefficients in each of the frontier molecular orbitals. The FMO approximation states that the dominant stabilising interaction in the transition state involves overlap of those orbitals with the largest coefficients (size). Only the atomic orbital coefficients at the centres that become involved in intermolecular bond formation need be considered. This is represented in Scheme 5 for the cycloaddition of nitrone (6) with an electron-rich dipolarophile, vinyl methyl ether.

The dominant interaction is LUMO(dipole)-HOMO(dipolarophile) affording the 5-substituted isoxazolidine. For very electron-deficient dipolarophiles, such as nitroethylene, the dominant interaction involves HOMO(dipole)-LUMO(dipolarophile) leading to 4-substituted isoxazolidines, [Scheme 6].

FMO theory rationalises the experimentally observed results for 1,3-dipolar cycloadditions of nitrones with both electron-rich and electron-deficient monosubstituted olefins i.e. (i) electron-deficient mono-substituted olefins are more reactive towards nitrones than their electron-rich counterparts; (ii) 1,3-dipolar cycloadditions of nitrones to moderately electron-rich monosubstituted olefins give 5-substituted



Scheme 5



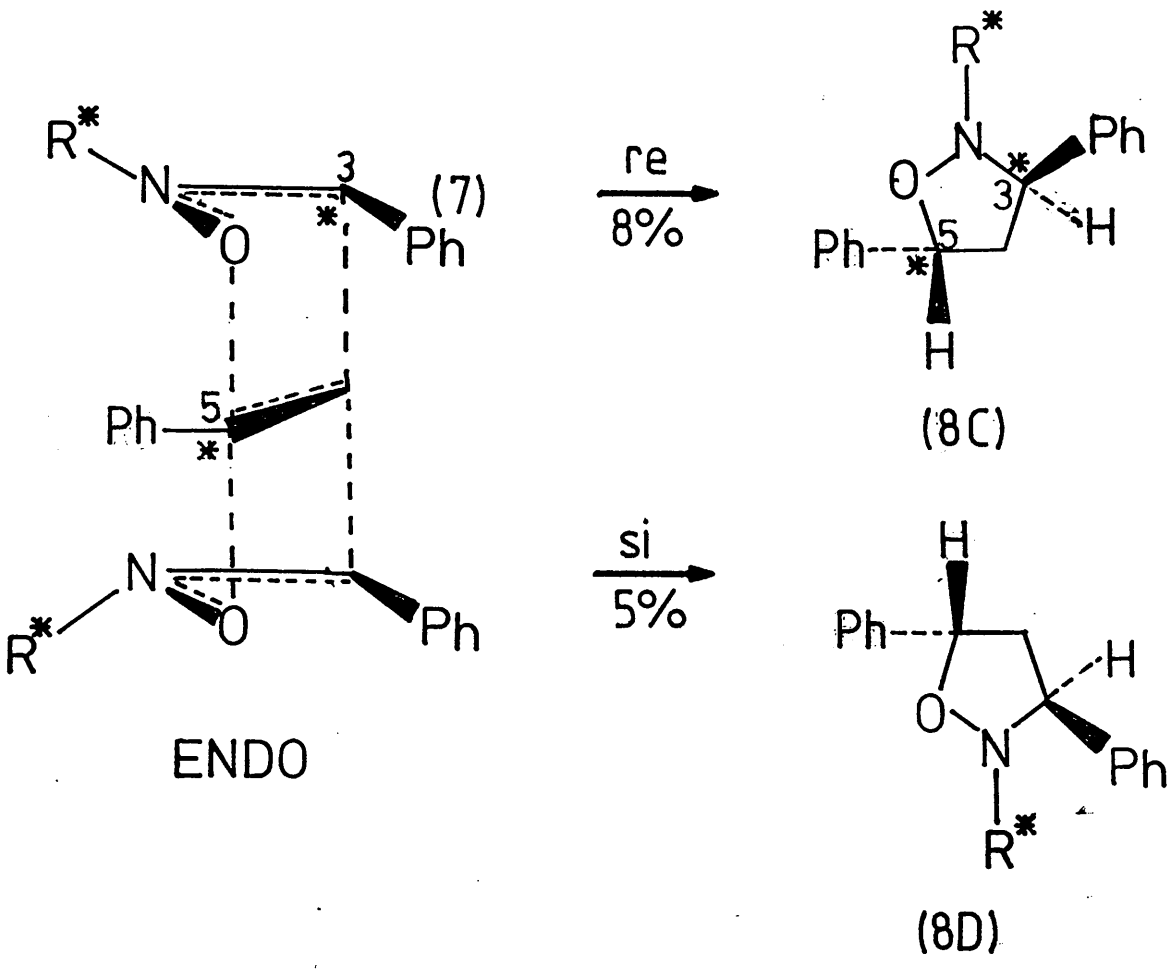
Scheme 6

isoxazolidines; (iii) 1,3-dipolar cycloadditions of nitrones to very electron-deficient monosubstituted olefins give 4-substituted isoxazolidines.

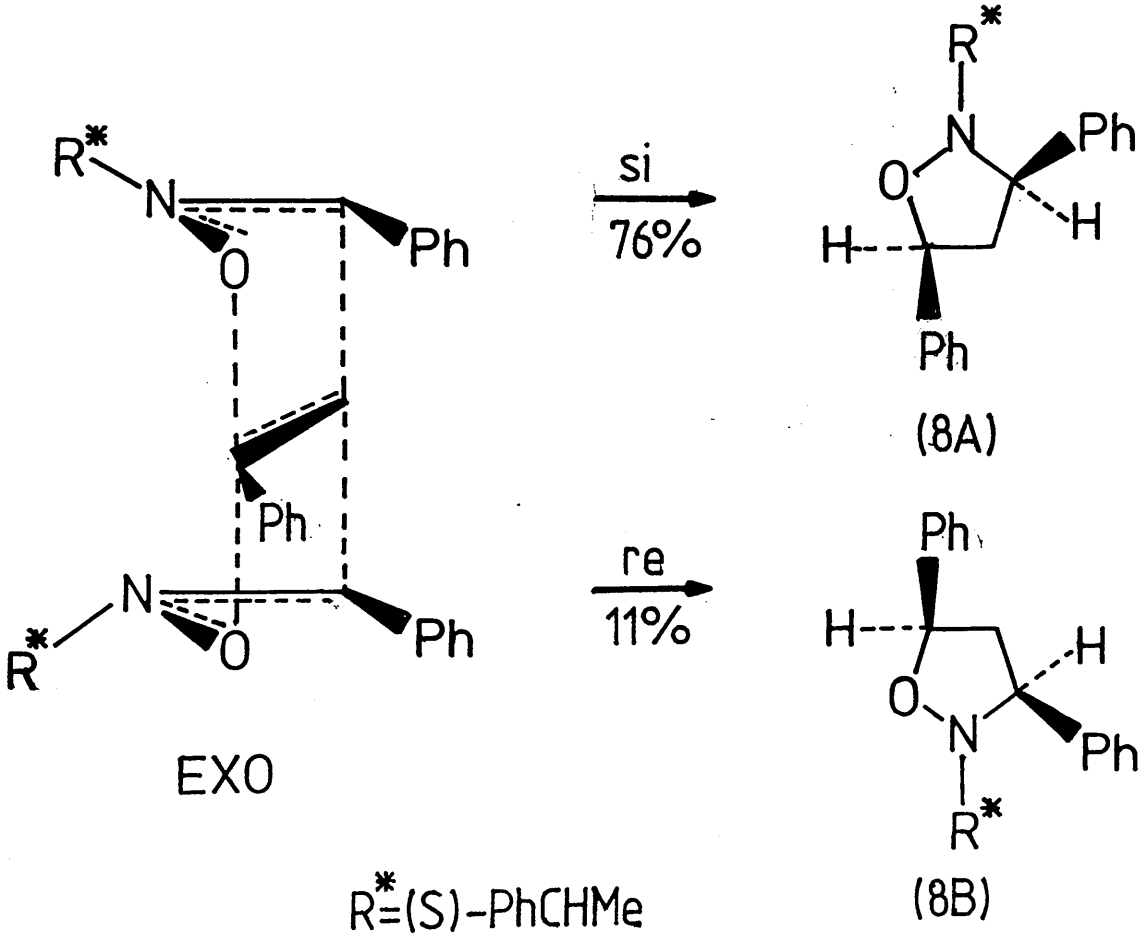
3. The Cycloaddition of Chiral Nitrones to Prochiral Alkenes

The majority of asymmetric syntheses involving 1,3-dipolar cycloadditions of chiral nitrones proceed via diastereoisomeric mixtures of 2,3,5-substituted isoxazolidines. For example, the asymmetric synthesis of β-amino acids outlined by Moffat[26] proceeds via an inseparable mixture of four non-racemic diastereomers as described earlier in the Summary (p.iii).

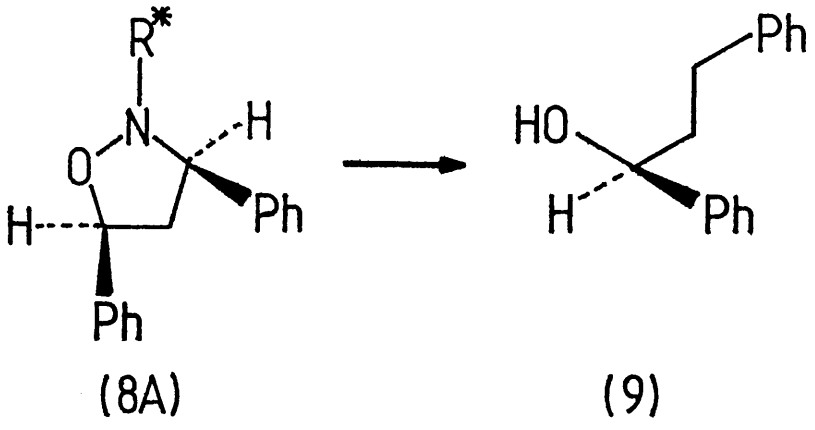
Belzecki and Panfil[9] have studied the 1,3-dipolar cycloaddition of chiral nitrones with various monosubstituted olefins. For example, the chiral C-phenyl-N-(S)-α-methylbenzyl nitrone (7) reacted with styrene to give a mixture of four non-racemic diastereomers (8A,B,C,D) in a ratio of 76:11:8:5 respectively, [Scheme 7].


R*
N
O
3
(7)
Ph
Ph
5
*
ENDO
re
8%
si
5%
(8C)
(8D)
H
Ph
O
N
R*

Scheme 7


R*
N
O
Ph
Ph
EXO
si
76%
re
11%
(8A)
(8B)
H
O
N
R*
R*=(S)-PhCHMe

Since (8A,B,C,D) could be separated as pure compounds, their absolute configurations could be determined. The hydrogenolysis of the cis diastereomer (8A) gave (S)-(-)-1,3-diphenylpropan-1-ol (9) in 92% optical purity, [Scheme 8]. Similarly the hydrogenolysis of the trans diastereomer (8C) gave (R)-(+)-1,3-diphenylpropan-1-ol.



(8A) (9)

R* = (S)-PhCHMe

Scheme 8

These results clearly showed that monosubstituted alkenes react with chiral nitrones such as (7) to give a marked excess of the cis isoxazolidines and a clear excess of one of the diastereomers in each cis and trans pair. Assuming that there was no E-Z isomerisation of (7), the diastereomers (8A,B,C,D) were formed as a result of the approach of reagents in an exo or endo manner as well as re or si

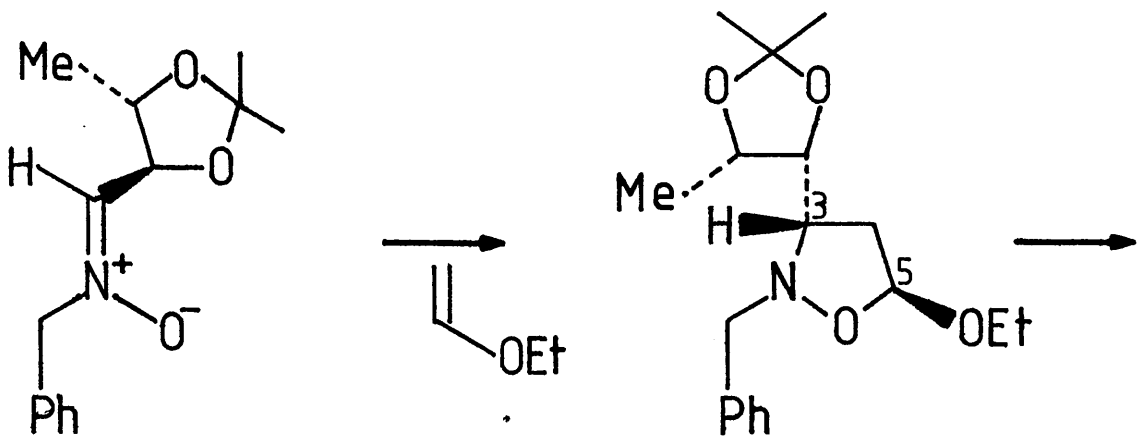
face attack at the prochiral olefin. The ratio of the sum of cis (A+B) to the sum of trans (C+D) can be accepted as a measure of the stereospecificity of the cycloaddition whereas the ratios A:B and C:D are a measure of the diastereoselectivity.

Chapter 2 describes the analysis of such a mixture of diastereomeric isoxazolidines.

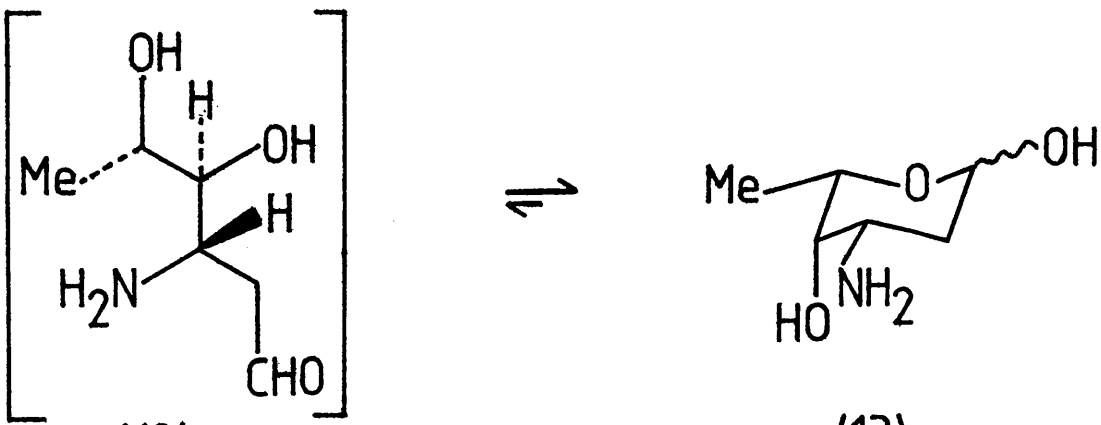
4. The Asymmetric Synthesis of Natural Products via 1,3-Dipolar Cycloadditions of Chiral Nitrones

In recent years the application of nitrone-olefin cycloaddition reactions to natural product synthesis has been an area of intense activity.[10-18] Moreover, the use of chiral nitrones in such reactions has proved to be an efficient means of controlling the stereochemistry in the final product.

A highly diastereoselective synthesis of the amino sugar, daunosamine (13) has been achieved by De Shong,[10] [Scheme 9]. Cycloaddition of nitrone (10) with excess ethyl vinyl ether gave a single anti-isoxazolidine (11). Since two new asymmetric centres were generated at C-3 and C-5, the formation of four non-racemic diastereomers was possible. Consequently nitrone (10) displayed complete stereoselectivity i.e. ethyl vinyl ether cyclo-added exclusively to one diastereotopic face of (10) in the endo transition state, [Scheme 10]. Subsequent reductive cleavage of the N-O bond of (11) followed by removal of the acetonide protecting group released the β-amino aldehyde (12) as an intermediate to (13).

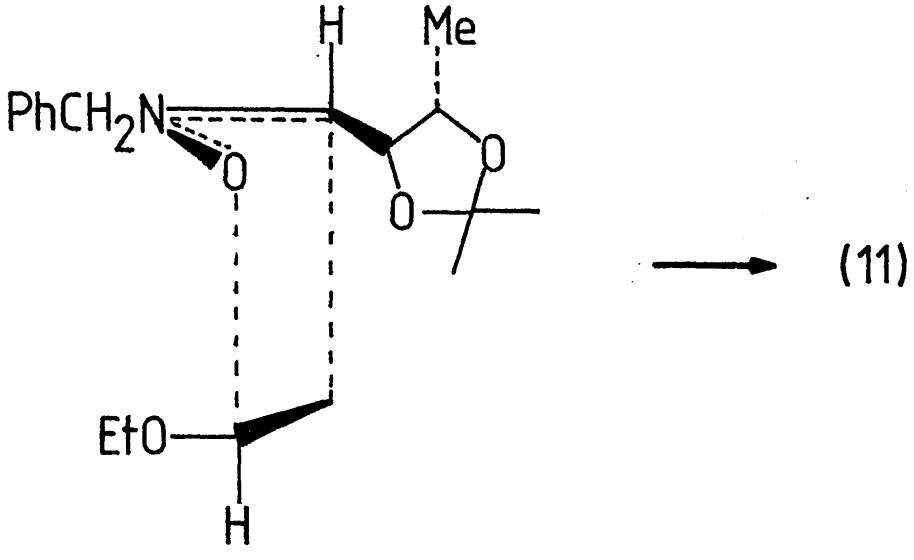


(10) (11)



(12) (13)

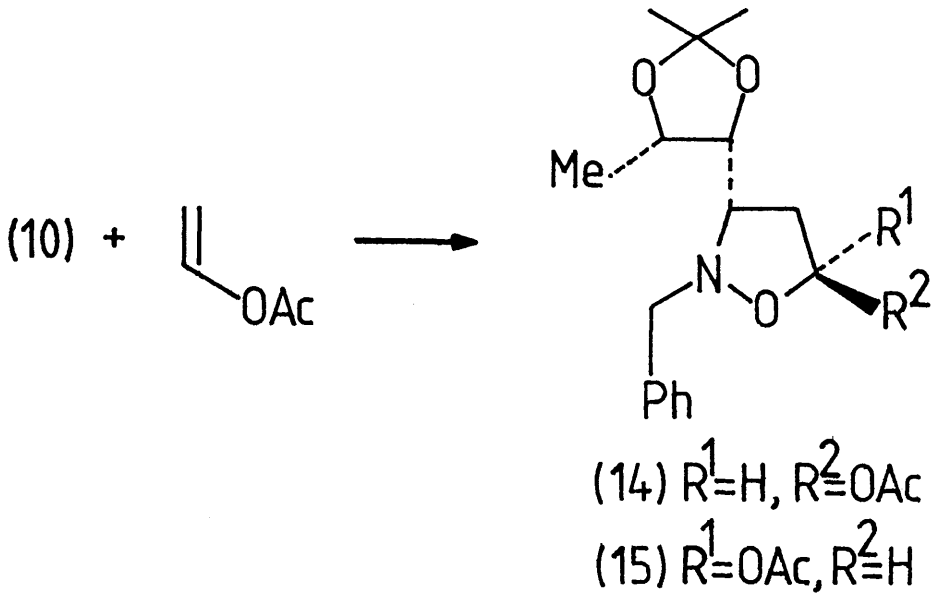
Scheme 9



Scheme 10

Nitrone (10) displayed diastereofacial selectivity in reactions with other dipolarophiles such as vinyl acetate. Dipolar cycloaddition of (10) to vinyl acetate yielded two cycloadducts (14) and (15), epimeric only at C-5 in a ratio of 1:4, resulting from addition to one face of the nitrone, [Scheme 11].

Wovkulich and Uskokovic[11] had earlier achieved an asymmetric synthesis of daunosamine via intramolecular nitrone-alkene cycloaddition, [Scheme 12].

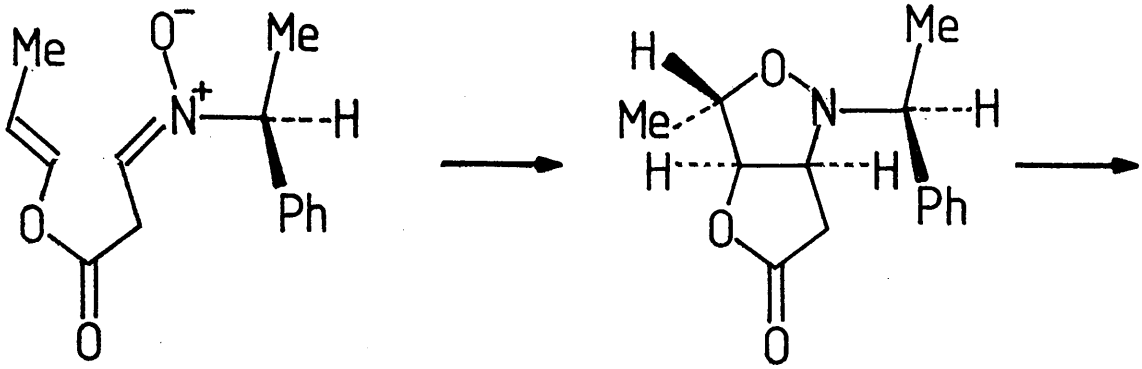


Scheme 11

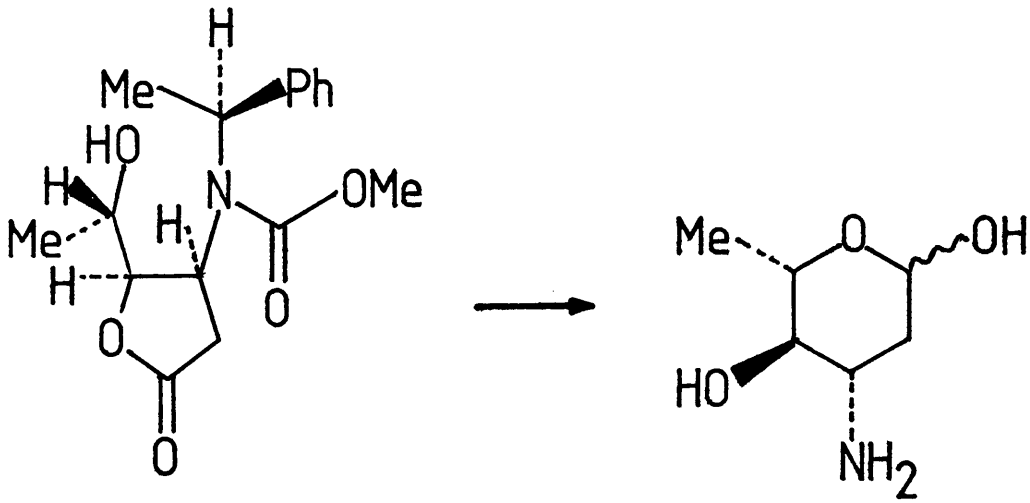
The chiral nitrone-enol ester (16) underwent intramolecular cycloaddition to give the isoxazolidine (17) as the major product. Reduction of (17), followed by protection of the amine gave the lactone carbamate (18) which was readily elaborated to daunosamine (13).

The asymmetric synthesis of α-aminophosphonic acids, analogs of α-amino acids, have been achieved by Vasella,[12] employing a new class of nitrones, C-phosphononitrones.

The N-glycosyl-C-dimethoxyphosphonoyl nitrone (19) reacted with ethylene to give the cycloaddition products (20) and (21) in the ratio 5:2 in favour of the C-3 L-configuration (20), [Scheme 13].

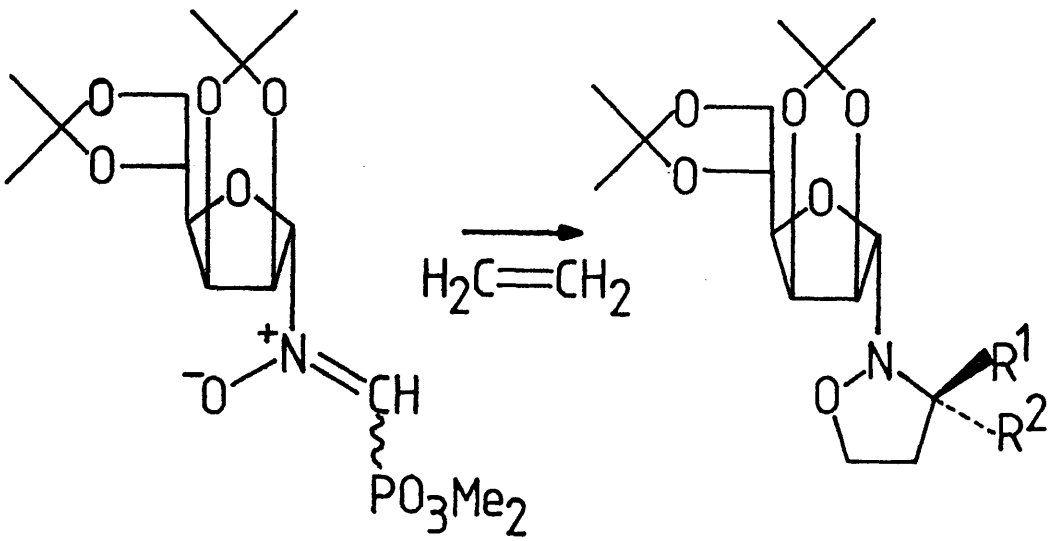


(16) (17) [major]



(18) (13)

Scheme 12



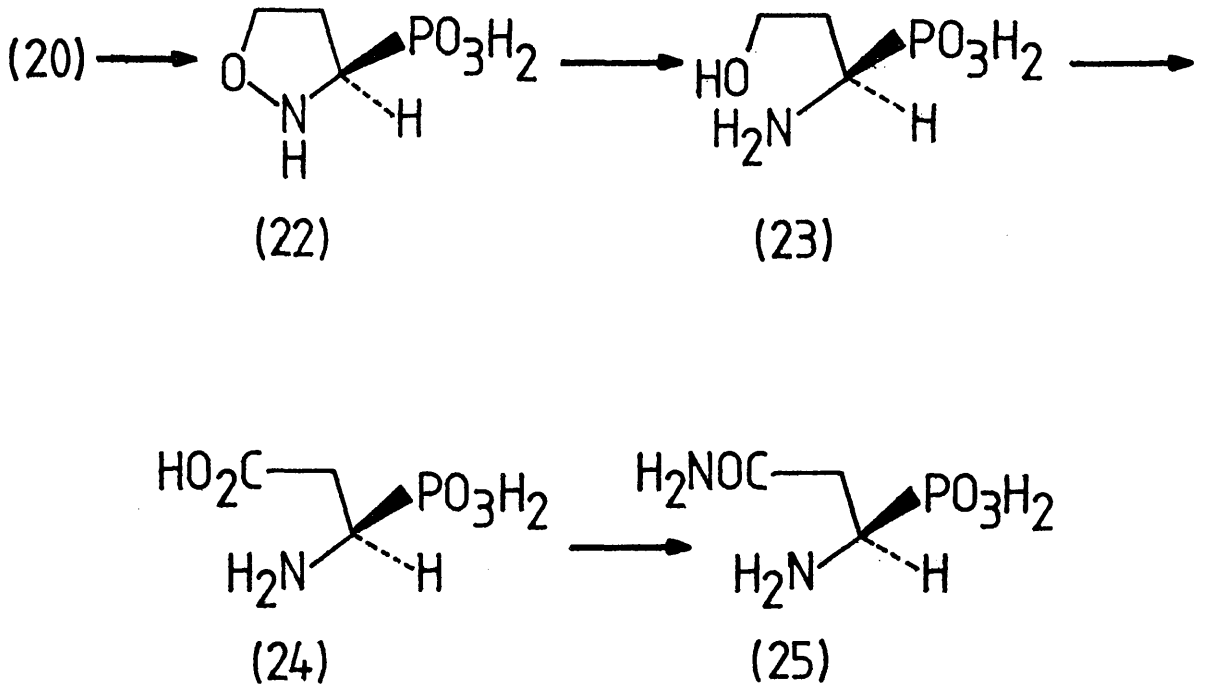
(19)

(20) $R^1 = PO_3Me_2$, $R^2 = H$

(21) $R^1 = H$, $R^2 = PO_3Me_2$

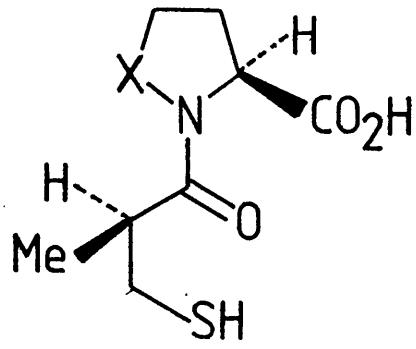
Scheme 13

The cycloaddition product (20) was transformed into the free aminophosphonic acids (22), (23), (24) and (25), analogs of L-5-oxa-proline, L-homoserine, L-aspartic acid and L-asparagine, [Scheme 14].



Scheme 14

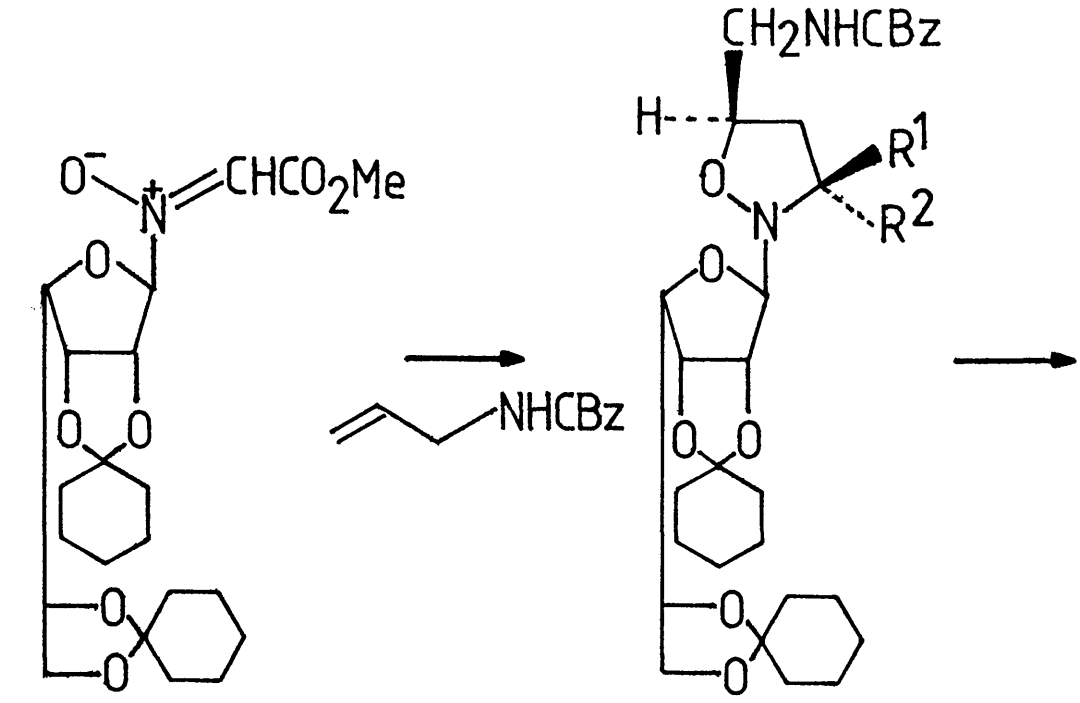
The same authors[13] have applied the above methodology to the asymmetric synthesis of L-5-oxaproline (26), an analog of captopril (27), which is a specific inhibitor of the Angiotensin-Converting-Enzyme (A.C.E.).



(26) X=O
(27) X=CH_2

The use of a carbohydrate moiety as a chiral auxiliary has also been utilised by Kibayashi[14] in an asymmetric synthesis of negamycin (33), a peptide-like natural product which exhibits striking activity against Gram-negative bacteria, [Scheme 15]. The nitrone (28) underwent dipolar cycloaddition with N-benzyl allylamine to produce an inseparable mixture of the 3(R),5(R)-trans adduct (29) and the 3(S),5(R)-cis adduct (30). Removal of the chiral auxiliary followed by N-benzylation and reduction furnished the chromatographically separable trans alcohol (31) and cis alcohol (32) in a ratio of 2:3. Alcohol (31) was converted into (+)-negamycin in six steps.

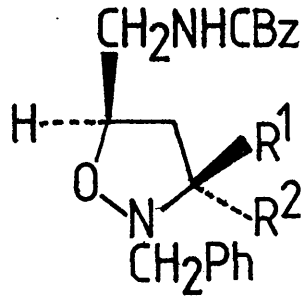
Perhaps of most topical interest is the asymmetric synthesis of key intermediates to the carbapenem antibiotics, thienamycin (34) and its 1β-methyl analog (35).[15-18]



(28)

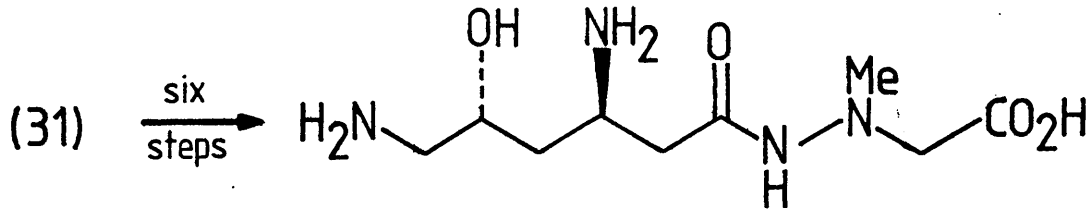
(29) R^1=H, R^2=CO_2Me

(30) R^1=CO_2Me, R^2=H



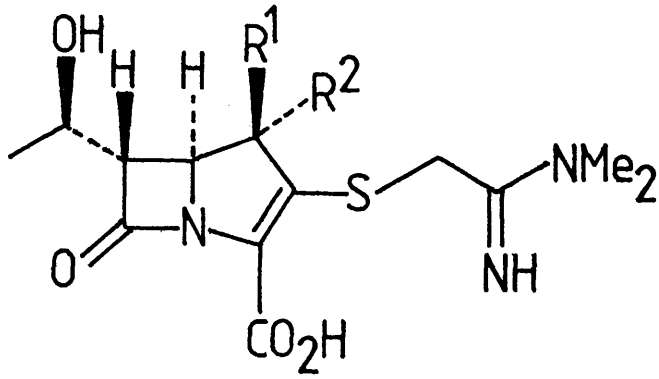
(31) R^1=H, R^2=CH_2OH

(32) R^1=CH_2OH, R^2=H



(33)

Scheme 15

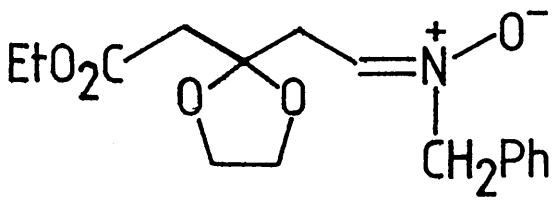


(34) $R^1 = R^2 = H$

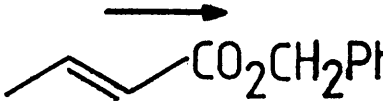
(35) $R^1 = Me, R^2 = H$

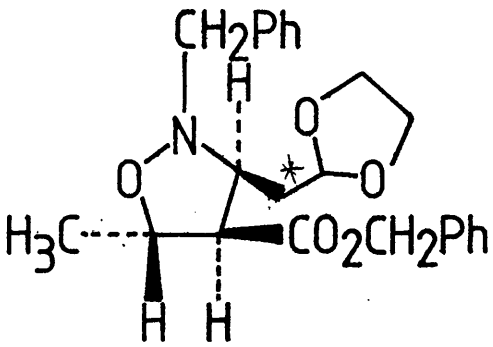
Kametani[15a] has synthesised the bicyclic β-keto ester (39), which has been shown to be an appropriate precursor for the synthesis of thienamycin,[16] [Scheme 16]. Isoxazolidine (37) was the sole isomer obtained from the cycloaddition of nitrone (36) to benzyl crotonate. Isoxazolidine (37) possessed the desired stereochemistry for the synthesis of (39). Hydrogenation of (37) gave a β-hydroxy-β-amino acid which could be cyclised to give the azetidinone (38) which was readily converted into the thienamycin precursor (39).

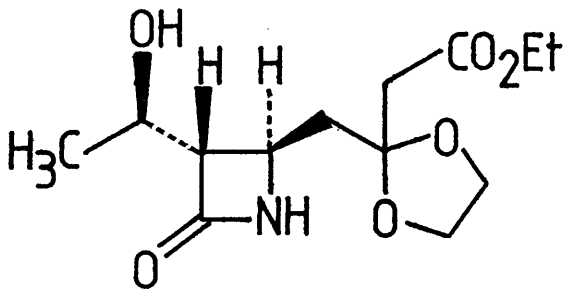
Although thienamycin is a potent broad spectrum antibiotic, it suffers the disadvantage of being chemically unstable and readily metabolised by renal dehydropeptidase-I (DHP-I). For this reason, much emphasis has recently been placed on the asymmetric synthesis of 1β-methyl thienamycin (35),[17,18] which shows a very substantial increase in stability over (34).



(36)

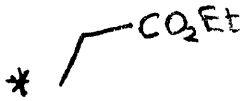




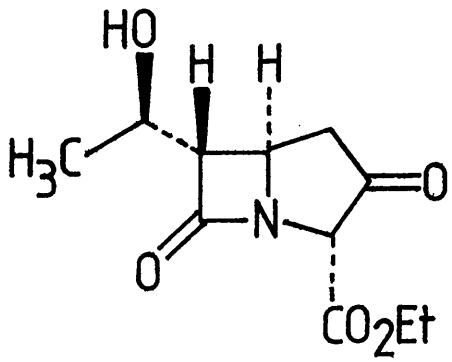


(37)

(38)

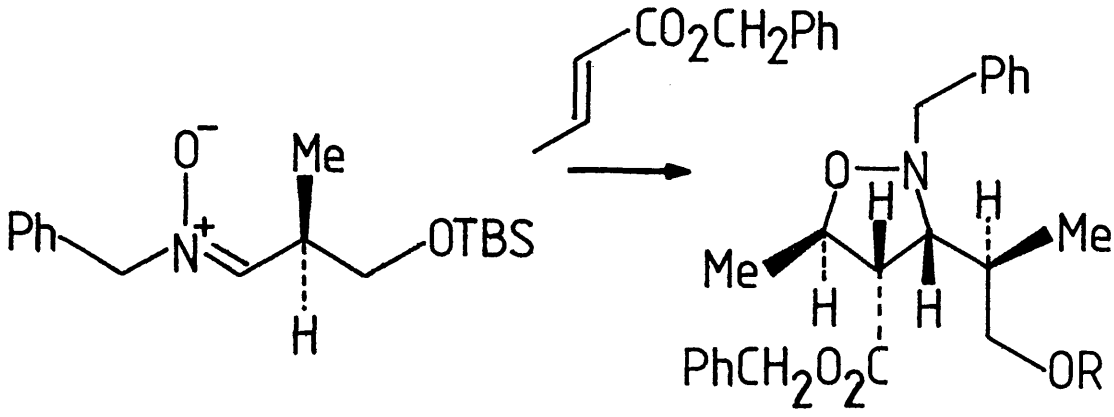


two steps



(39)

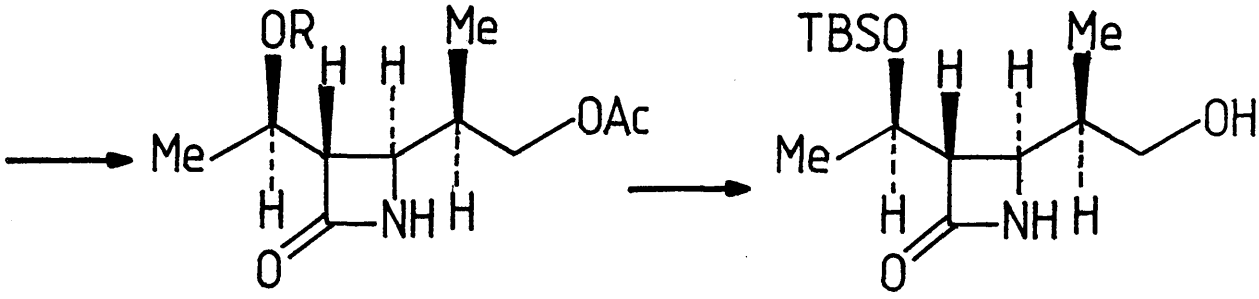
Scheme 16



(40)

(41) R=TBS

(42) R=Ac



(43) R=H [from(42)]

(44) R=TBS

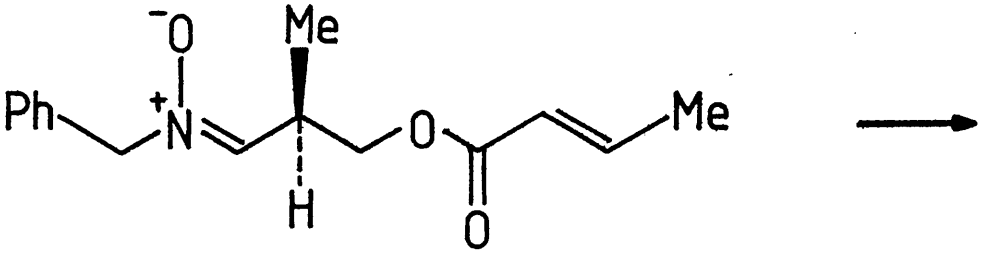
(45) [from (44)]

TBS = t-butyldimethylsilyl

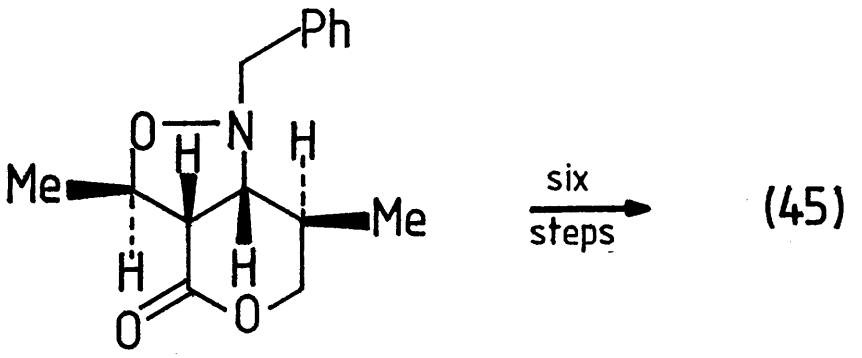
Scheme 17

Kametani[17] has synthesised the known chiral intermediate (45) from the isoxazolidine (41), prepared by the 1,3-dipolar cycloaddition of nitrone (40) with benzyl crotonate, [Scheme 17]. Exchange of the t-butyldimethylsilyl group of (41) with an acetoxy group gave isoxazolidine (42), which was hydrogenated and cyclised to give the β-lactam (43). Protection of (43) as the TBS ether gave (44), which was easily converted to the primary carbinol (45).

The intermediate (45) has also been synthesised via intramolecular nitrone 1,3-dipolar cycloaddition by Kametani et al.,[18] [Scheme 18].



(46)



(47) (45)

Scheme 18

Cycloaddition of nitrone (46) in refluxing t-amyl alcohol afforded isoxazolidine (47) as a single stereoisomer which was elaborated in six steps to (45).

Chapter 2 describes the first asymmetric synthesis of β-lysine, the most widely studied of all the naturally-occurring β-amino acids. Chapter 3 describes an asymmetric route to the commercially important dipeptide artificial sweetener, aspartame. The appropriate introductions to these topics are contained within the relevant chapters.

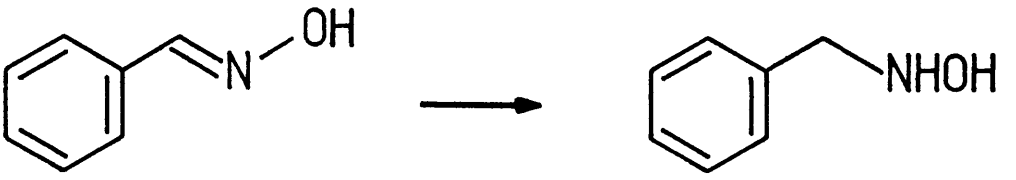
CHAPTER 1

Aldonitrones: Synthesis and Structure

1.1 SYNTHESIS OF ALDONITRONES

The condensation of N-monosubstituted hydroxylamines with aldehydes is the most general and efficient method for the preparation of aldonitrones.[19,20]

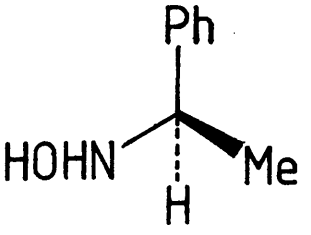
N-benzylhydroxylamine (49), required for the synthesis of N-benzyl nitrones, was prepared by cyanoborohydride reduction of benzaldoxime (48),[21] [Scheme 19].



(48) (49)

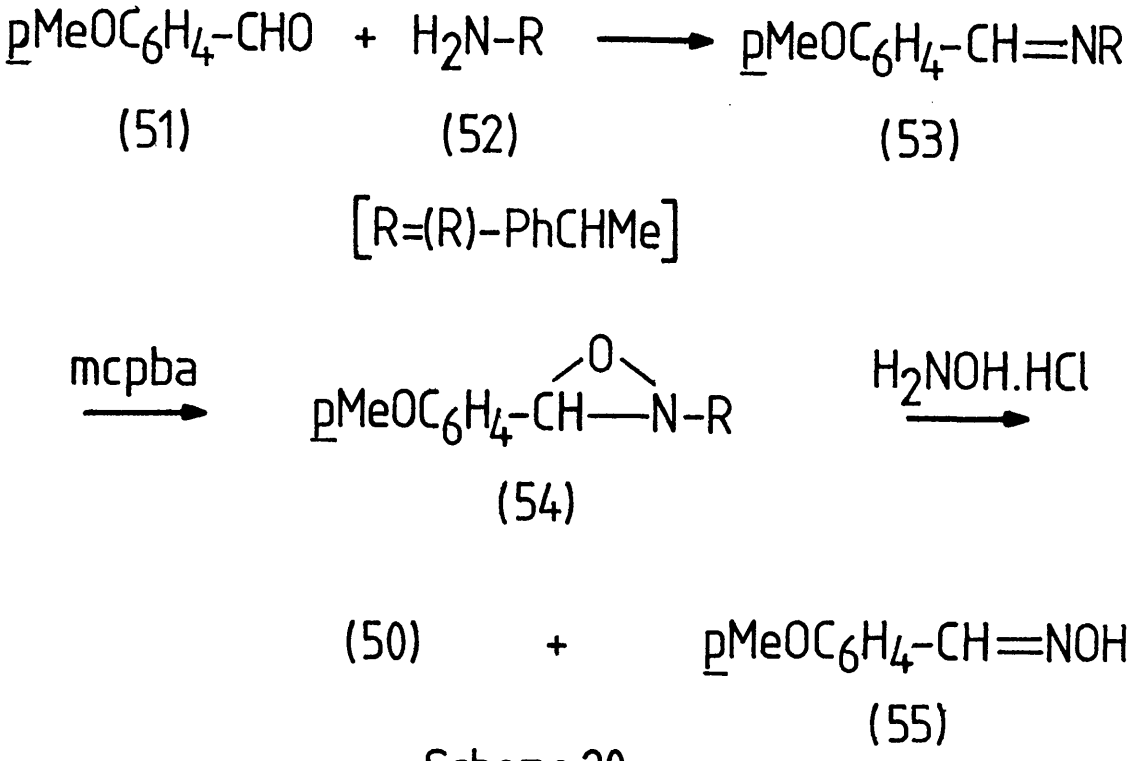
Scheme 19

The chiral benzylic nitrones used in the asymmetric syntheses described in Chapters 2 and 3 required the synthesis of optically pure (R) or (S)-α-methylbenzylhydroxylamine (50), [(R) form shown].



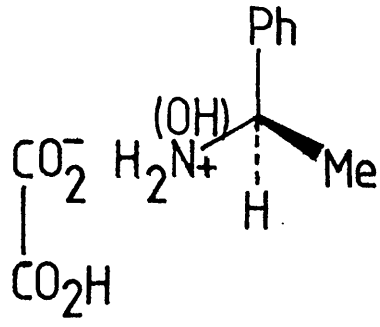
(50)

The hydroxylamine (50) was conveniently prepared in good yield by the method of Polonski and Chimiak,[22,23] [Scheme 20].



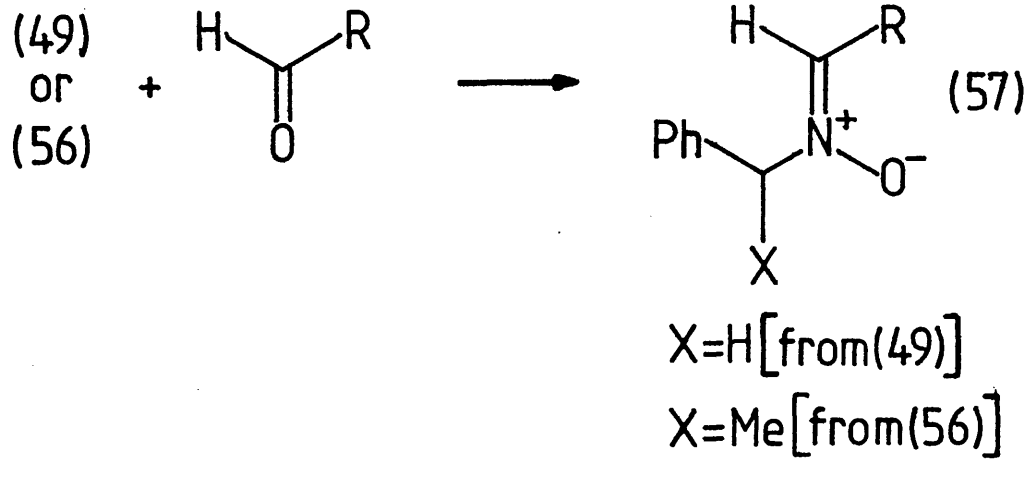
Scheme 20

The optically pure amine (52) was converted to the imine (53) by reaction with p-anisyl aldehyde (51). Imine (53) was oxidised to the corresponding oxaziridine (54) by the action of m-chloroperbenzoic acid. Oxaziridine ring cleavage was effected by hydroxylamine hydrochloride under very mild conditions to obtain (50) and the oxime (55). This process is effectively an indirect oxidation of the optically pure starting amine (52). The hydroxylamine was converted to the crystalline oxalate salt (56) by treatment with one equivalent of oxalic acid in diethyl ether.[23]



(56)

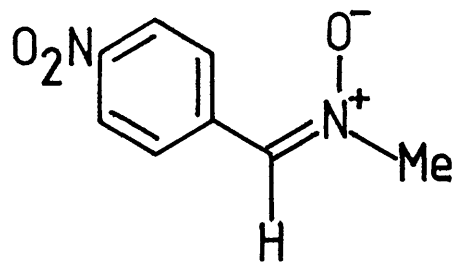
The required nitrones (57) were easily prepared by the reaction of appropriate aldehydes with (49) or (56) [plus one equivalent of triethylamine] in dichloromethane at room temperature, [Scheme 21].



Scheme 21

1.2 STRUCTURE OF ALIPHATIC ALDONITRONES

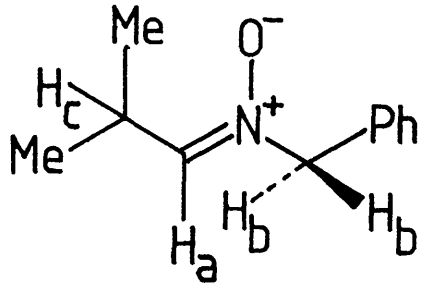
Whereas the stereochemistry and stereochemical stability of aromatic aldonitrones has been extensively investigated, their aliphatic counterparts have been largely neglected. Boyd[24] has employed nuclear Overhauser difference spectroscopy (NOEDS) to establish the trans stereochemistry of the aromatic nitrone (58).



(58)

The phenomenon of Z ⇌ E isomerisation in aromatic aldonitrones has been studied and barriers for rotation about the C=N bond have been calculated for several examples.[25] These studies reveal that E-Z aromatic aldonitrones show considerable configurational stability comparable with that of ketonitrones.

Previously, it has been assumed that aliphatic aldonitrones exist in the Z configuration by analogy with their aromatic counterparts. Recently Moffat[26] has applied NOEDS analysis to several aliphatic aldonitrones e.g. N-benzyl-C-isopropyl nitrone, (59).

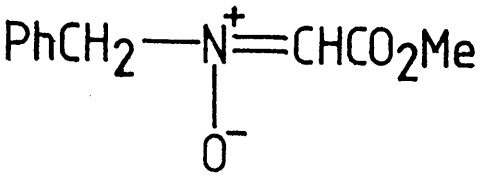


(59)

Irradiation of the N-benzyl protons H_b produced a significant signal enhancement for the vinyl proton H_a but only a negligible signal enhancement for the methine proton H_c and for the methyl protons. These results confirmed that nitrone (59) exists in the expected Z configuration. Prolonged heating of (59) in toluene at 80°C showed no isomerisation to the E-nitrone.

1.3 STRUCTURE OF N-ALKYL-α-ALKOXYCARBONYL NITRONES

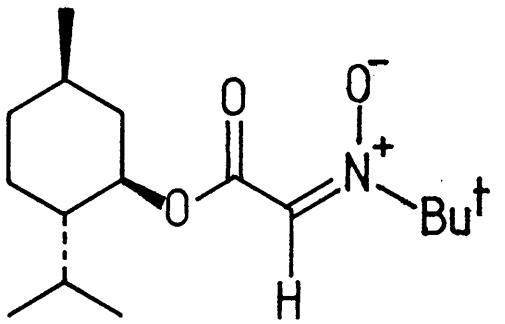
It has been shown that N-alkyl-α-alkoxycarbonyl nitrones exist in solution as both Z and E isomers at room temperature. Inoye[27] has shown that nitrone (60) clearly displays two sets of signals in the ^1H nmr spectrum (100 MHz) in $CDC\ell_3$ attributable to Z and E geometric isomers.



(60)

The olefinic protons are clearly recognised at δ6.76 for the Z isomer and δ7.06 for the E isomer. The signal at higher field is assigned to the Z isomer of (60) by analogy with S-oxides and oximes[28] where the anti-proton is always at higher field than the syn-proton. The E-Z ratio varies drastically with the solvent. In non-polar solvents the E isomer predominates, while in polar solvents, the Z isomer predominates.

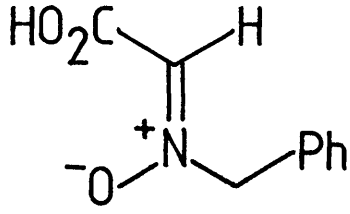
Chiral N-alkyl-α-alkoxycarbonyl nitrones have been used in various asymmetric syntheses. Belzecki,[9] has investigated the cyclo-addition reactions of nitrones bearing a chiral substituent at the carbon atom e.g. C(-)-carbomenthoxy-N-tert-butyl nitrone (61)



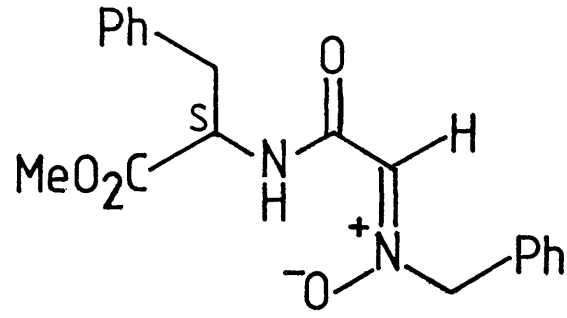
(61)

Nitrones of this type exhibit only moderate stereoselectivity in cyclo-additions with styrene and related dipolarophiles.

Chapter 3 describes, for the first time, the use of C-carboxy and C-carbamido nitrones; e.g. the nitrones (117a) and (119a) were key intermediates in the asymmetric synthesis of the artificial sweetener, aspartame (detailed discussion in Chapter 3).

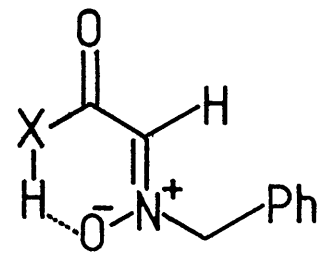


(117a)



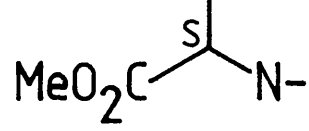
(119a)

In contrast to their C-alkoxycarbonyl counterparts, the nitrones (117a) and (119a) were both shown to exist as single geometric isomers at room temperature in chloroform. This was clearly shown by their ^{13}C and ^{1}H nmr (200 MHz) spectra. The nitrones (117a) and (119a) were assumed to exist as the Z isomer by comparison of the chemical shift values of the benzylic protons in the ^{1}H nmr (200 MHz) spectra with those of C-alkyl-N-benzyl aliphatic aldonitrones of known Z configuration. One possible explanation of this phenomenon would be the enhanced stability of the Z nitrone acquired via hydrogen bonding of the O-H or N-H protons with the oxygen atom of the nitrone, [Scheme 22].



(117a) X=O

(119a) X=Ph



Scheme 22

Significantly, the C-carbamido nitrone (119a) exhibited useful stereoselection in the 1,3-dipolar cycloaddition reaction with 2-chloro-acrylonitrile (Chapter 3).

CHAPTER 2

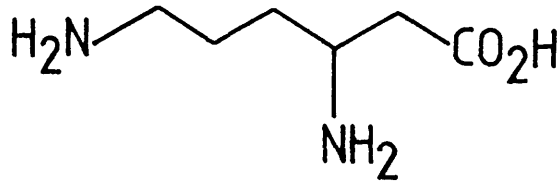
Enantioselective Synthesis of Optically Pure (R)- and (S)-β-Lysine via Nitrone Cycloaddition to Vinyl Acetate

2.1 BACKGROUND

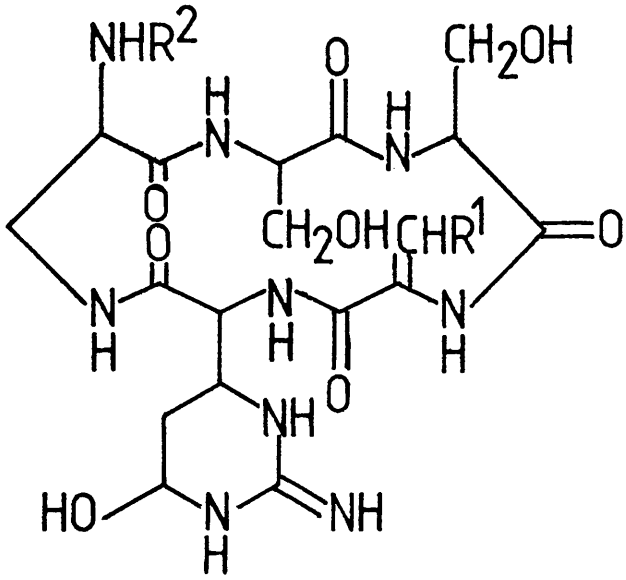
β-Lysine (62) is undoubtedly the most widely studied of all the naturally occurring β-amino acids. It was first isolated in 1951 by Carter[29] from streptothricin F (64A), one of a large family of broad-spectrum antibiotics produced by Streptomyces species. The streptothrycins (64) form an homologous series with up to seven β-lysine residues linked in a peptide chain.[30] In 1952, Haskell[31] isolated a basic amino acid from the acid hydrolysate of viomycin (63), a tuberculostatic antibiotic produced by Streptomyces floridae. This "new" amino acid was shown to be isomeric with lysine and was identical to the amino acid previously isolated by Carter.[29]

The structure and stereochemistry of naturally occurring β-lysine was established as (3S)-(+)-3,6 diaminohexanoic acid in 1953 by Van Tamelen,[32] who synthesised (3S)-β-lysine by Arndt-Eistert homologation of (2S)-ornithine (65), [Scheme 23].

The β-lysine obtained by this route was found to be identical with that obtained from streptothricin F. Yonehara and Otake[33] have since shown, by ORD, the (3S)-configuration to be the natural form of β-lysine. In 1971, Taniyama[34] isolated and characterised racemomycins A, B, C and D (R-A≡streptothricin F) from a mutant strain of Streptomyces racemochrogenus, which were found to contain one, two, three and four β-lysine residues respectively. Taniyama[34] has claimed that the biological properties of the streptothricins, such as antiviral activity and acute toxicity, become more pronounced as the number of β-lysine residues increases. More recently β-lysine has been isolated



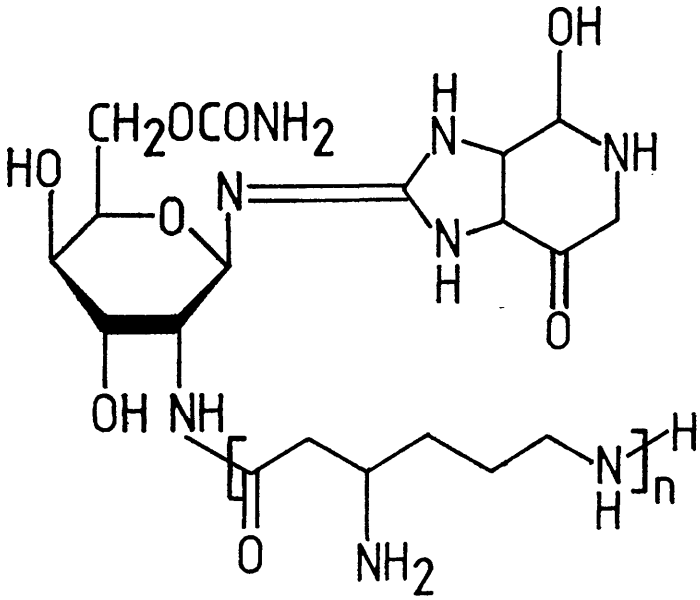
(62)



$R^1 = -NHCONH_2$

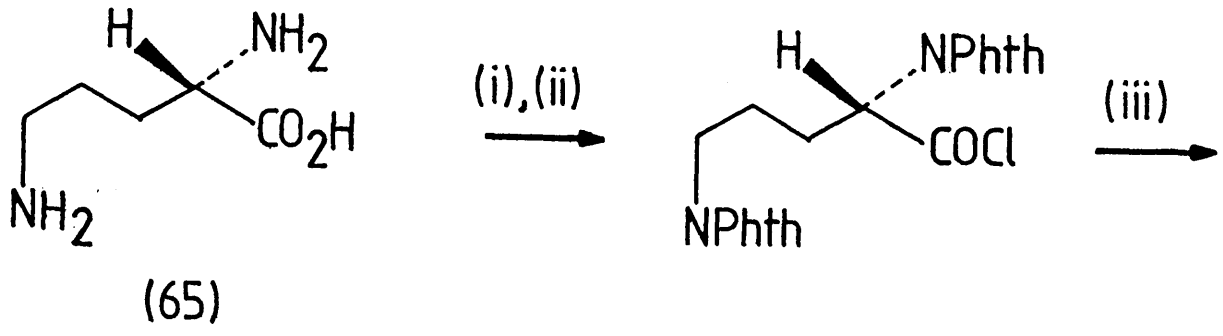
$R^2 = H_2N(CH_2)_3CHCH_2CO-$ (NH_2 on the CH)

(63)

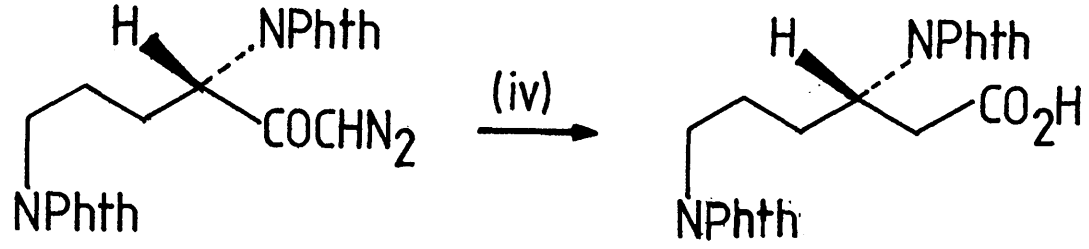


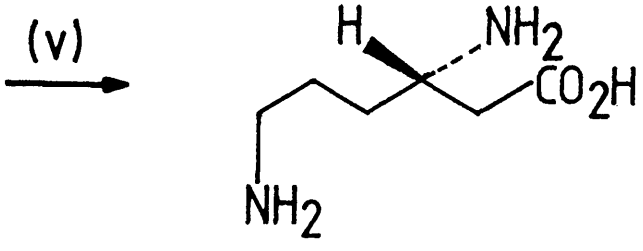
n=1,2,3,4,5,6 and 7 for steptothricins F[(64A)], E, D, C, B, A and X respectively.

(64)



(65)



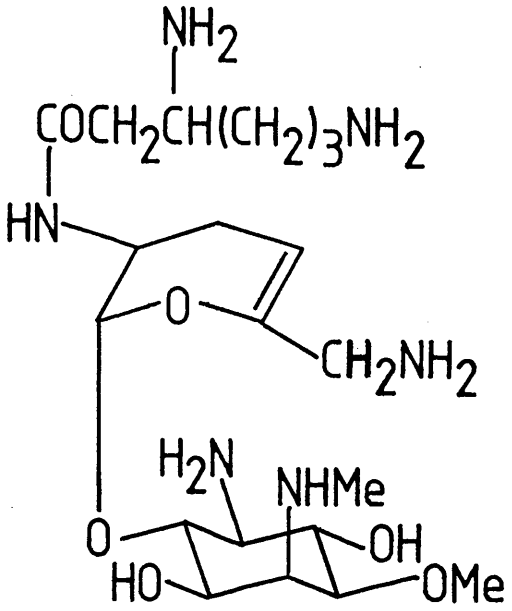


(3S)-(62)

Reagents:- (i) Phthalic anhydride, (ii) $(COCl)_2$, (iii) CH_2N_2, (iv) $Ag^{+}\,^{-}O_2CC_6H_5$, (v) NH_2NH_2, H_3O^{+}

Scheme 23

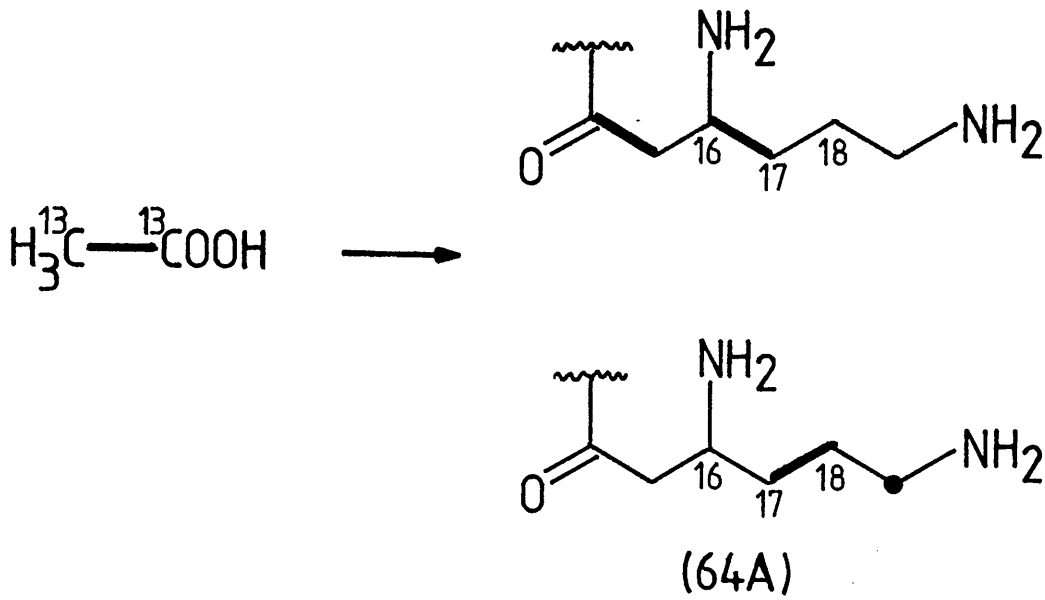
from the acid hydrolysate of lysinomycin[35] (66), a new aminoglycoside antibiotic.



(66)

The biosynthesis of streptothricin F (64A) has been extensively studied by Gould and Aberhart.[36,37] These authors have obtained specific incorporation of [1,2-$^{13}C_2$] acetate (67) into the β-lysine portion of (64A) in Streptomyces L-1689-23, [Scheme 24].

The labelling pattern in the β-lysine unit of (64A) was explained by incorporation via rearrangement of α-lysine (72), produced by the diaminopimelic acid (DAP) pathway, [Scheme 25]. The spin coupling of C-17 to both C-16 and C-18 resulted from decarboxylation of meso-



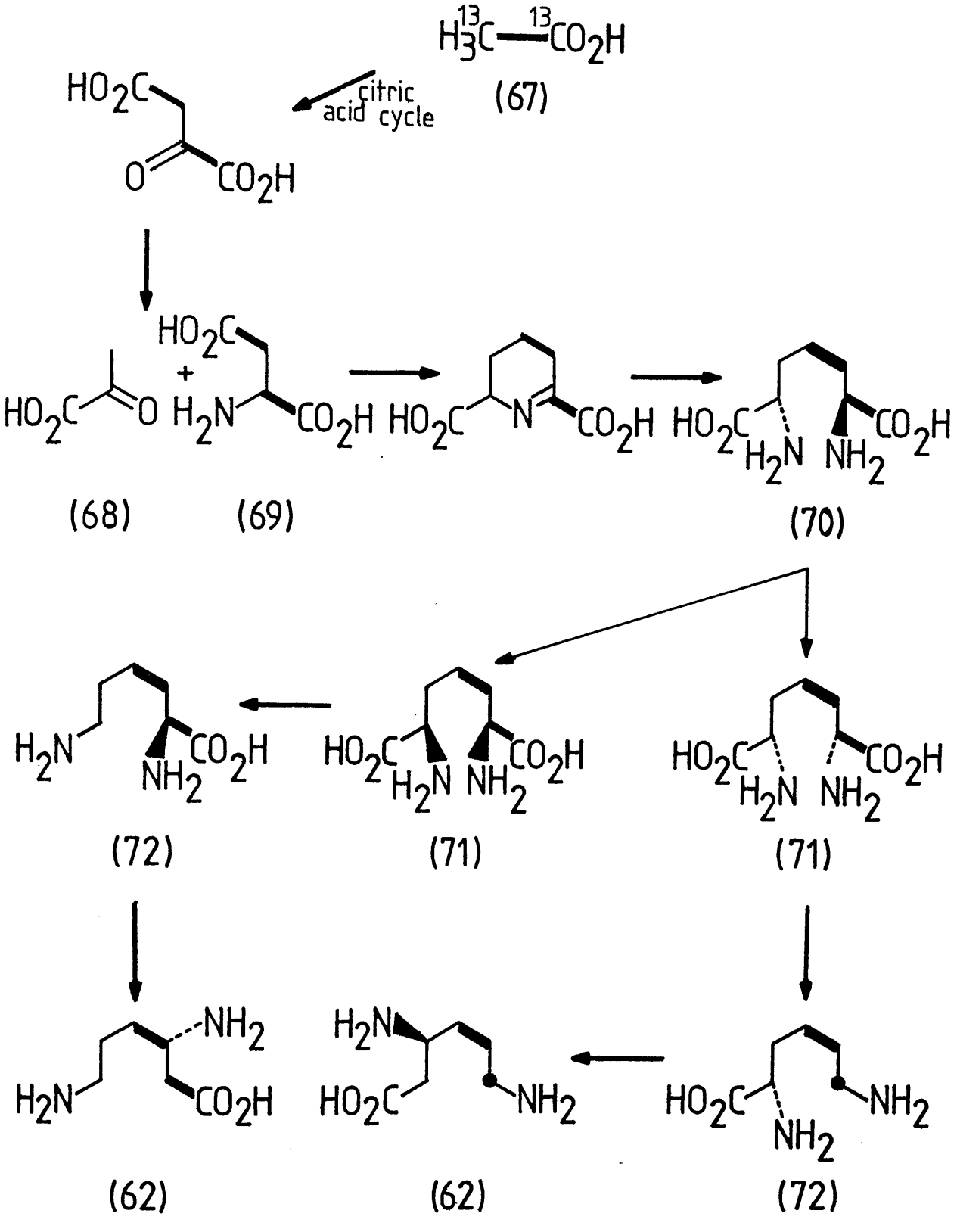
(64A)

Scheme 24

DAP (71), produced via epimerisation of (2S,6S) DAP (70) which was in turn derived from pyruvic acid (68) and aspartic acid (69).

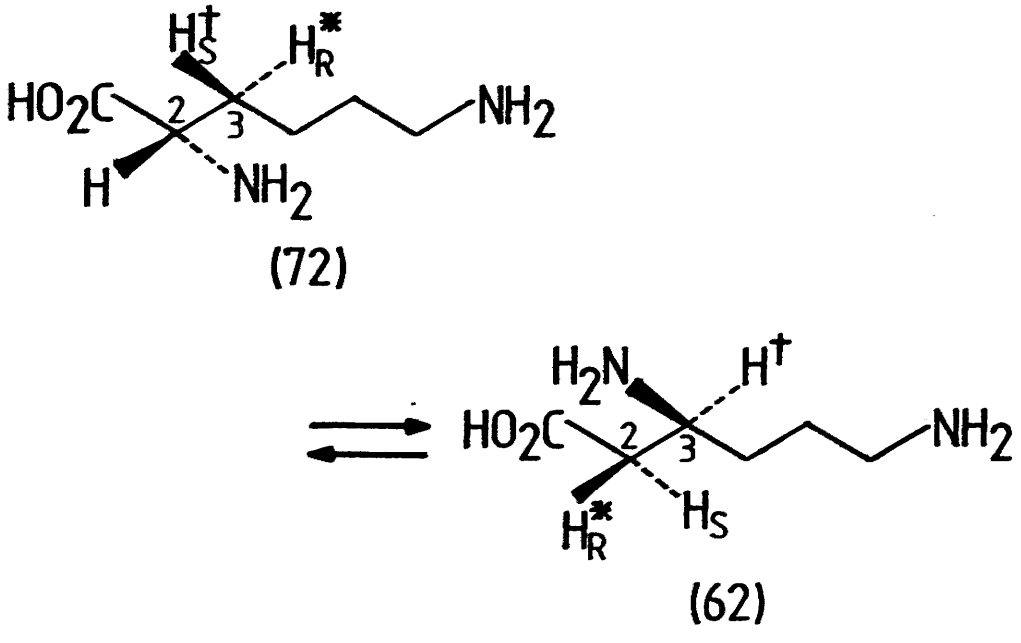
The mechanism and stereochemistry of the conversion of α-lysine to β-lysine, which is catalysed by the enzyme lysine 2,3-amino-mutase, have been investigated in species of the genera Streptomyces[36,37] (as part of the streptothricin F molecule) and in Clostridia.[38,39] (3S)-β-Lysine is the first intermediate in the anaerobic catabolism of (2S)-α-lysine in Clostridia, which terminates in the formation of butyric acid, acetic acid and ammonia.

Aberhart[38,39] has elucidated the stereochemistry of the lysine 2,3-aminomutase reaction in Clostridium subterminale strain SB4. Deuterium labelling and ^2H nmr were used to show that the transformation



Scheme 25

of (2S)-α-lysine (72) to (3S)-β-lysine (62) proceeds with inversion of configuration at both C-2 and C-3, [Scheme 26]. The 3-pro-(R) hydrogen of α-lysine (*) becomes the 2-pro-(R) hydrogen of β-lysine. The 3-pro-(S) hydrogen of α-lysine (†) is retained at C-3 of β-lysine.



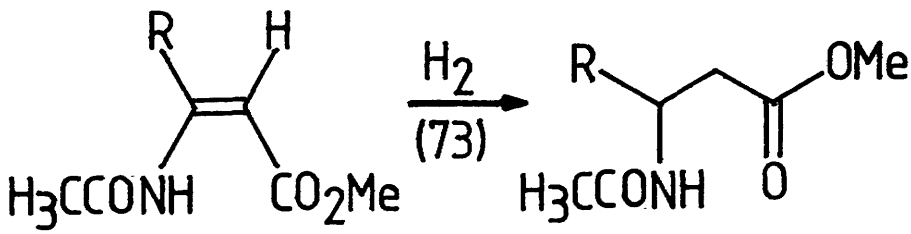
Scheme 26

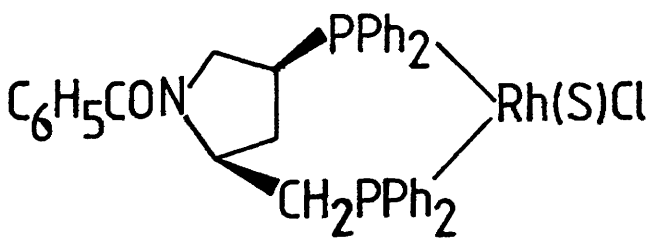
Aberhart[38,39] has also shown that, in C, SB4, amino group transfer occurs completely intramolecularly and that hydrogen migration is substantially or completely intermolecular. It has also been shown that the stereochemistry of the lysine-2,3-aminomutase reaction is identical in Streptomyces species and Clostridia.[36,37]

2.2 ASYMMETRIC SYNTHESES OF β-AMINO ACIDS

In previous asymmetric syntheses of β-amino acids, the new chiral centre at the β-carbon was generated by hydrogenation of α,β-dehydro-β-amino esters[42,43] or by nucleophilic addition at sp^2 carbon.[40,41,44] Optical yields have rarely exceeded 50% and have generally been below 20%.

Achiwa[43] has described the catalytic asymmetric hydrogenation of methyl (Z)-3-acetylaminoprop-2-enoates to give chiral amino esters in enantiomeric excesses of 3-55% using the chiral rhodium bisphosphine complex (73), [Scheme 27].



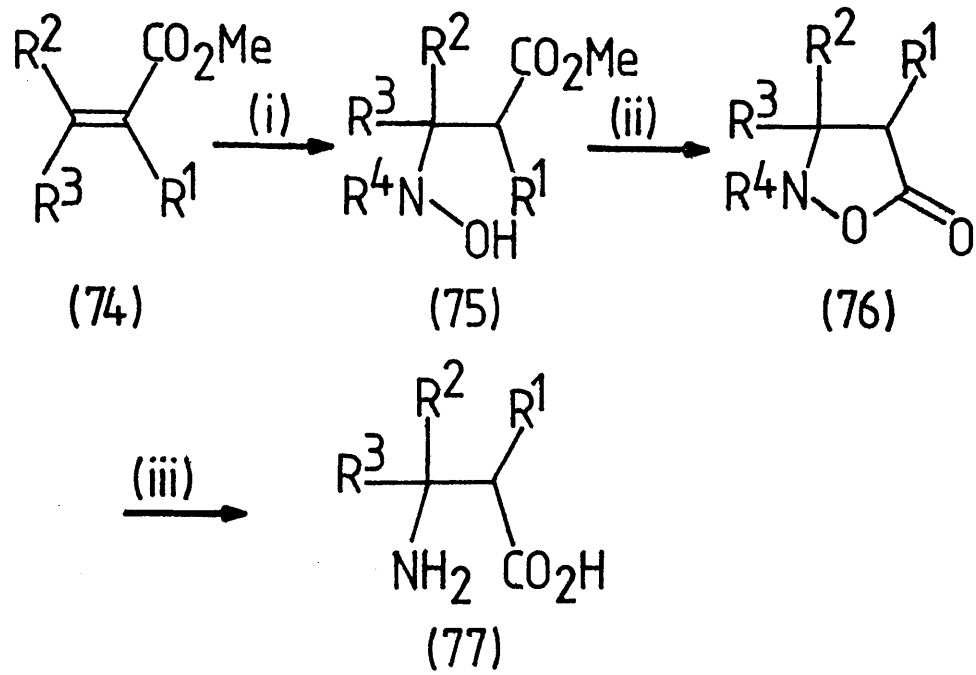


(73)

R= alkyl, aryl

Scheme 27

Baldwin[44] has established an asymmetric route to α- and β-substituted β-amino acids (77) via chiral isoxazolidinones (76), [Scheme 28].



(i) R^4NHOH ; (ii) $Li^+(SiMe_3)_2N^-$; (iii) $Pd/C/H_2$

R^1	R^2	R^3	R^4
Me	H	H	(S)-PhCHMe
H	CO_2Me	H	(S)-PhCHMe
H	H	Me	(S)-PhCHMe

Scheme 28

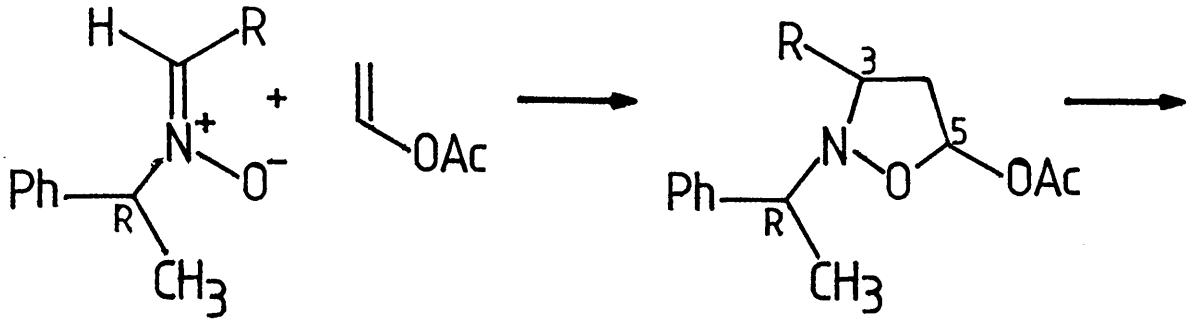
The chiral isoxazolidinones (76) were prepared by conjugate addition of a chiral hydroxylamine to an α,β-unsaturated ester (74) followed by cyclisation of the resulting adducts (75) using lithium bis(trimethylsilyl) amide. Hydrogenation of (76) involved N-O bond cleavage and removal of the chiral auxiliary to give the β-amino acids (77). Optical yields ranged between 10-28% and did not give rise to naturally occurring β-amino acids.

Recently, Moffat[26] has established a general asymmetric route to naturally occurring β-amino acids via isoxazolidinones generated via nitrone cycloaddition to vinyl acetate, [Scheme 29].*

Cycloaddition of the chiral nitrones (78) to vinyl acetate gave the 5-acetoxy isoxazolidines (79) as expected.[9] Facile hydrolysis of (79) gave the isoxazolidonols (80) which were oxidised to give the chiral isoxazolidinones (81). Hydrogenation of (81) resulted in cleavage of the N-O bond and loss of the chiral benzylic protecting group on nitrogen to give the β-amino acids (82). This sequence represents a novel method for generating the new chiral centre at the β-carbon of β-amino acids.

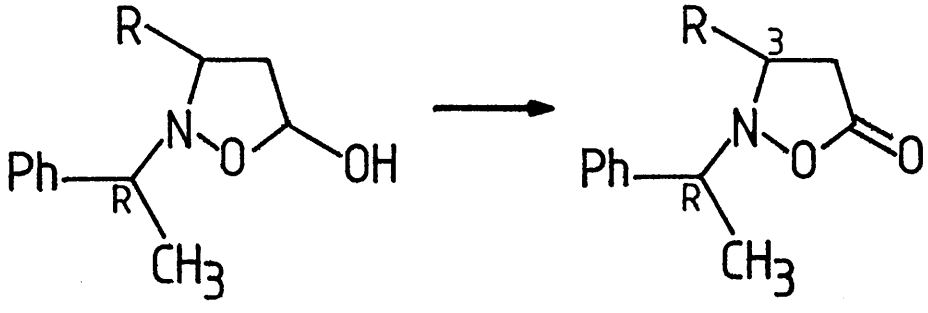
Using this route Moffat[26] synthesised β-phenyl-β-alanine, β-leucine and β-tyrosine, methyl ether (R =Ph, iPr and pMeOPh respectively). Optical yields were superior to those previously reported,[40-44] with (R)-(-)-β-tyrosine, methyl ether being prepared in optically pure form upon hydrogenation of a single isoxazolidinone

*Footnote. Moffat's work was near completion before the results of Baldwin[44] appeared.



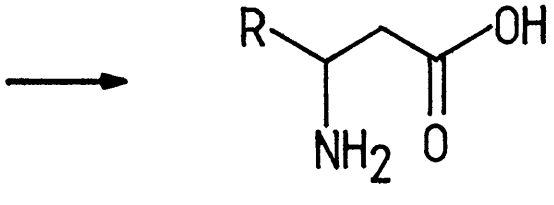
(78)

(79)



(80)

(81)



(82)

R=alkyl, aryl

Scheme 29

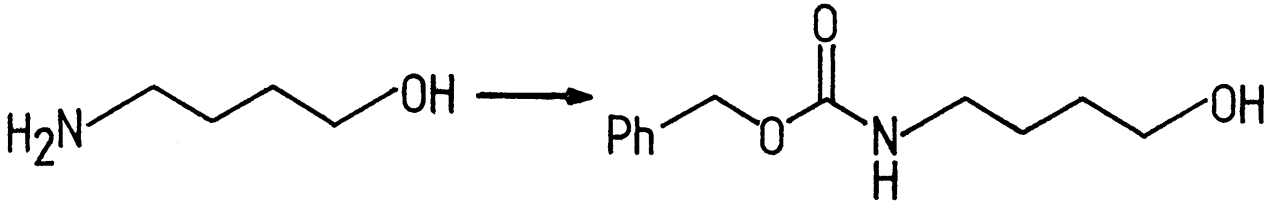
obtained from recrystallisation of a diastereomeric mixture.

The one drawback with Moffat's route is the low-yielding oxidation step (15-40%) required to transform the isoxazolidinols (80) into the isoxazolidinones (81). Moreover, there is no generally applicable method of oxidation to effect this transformation.

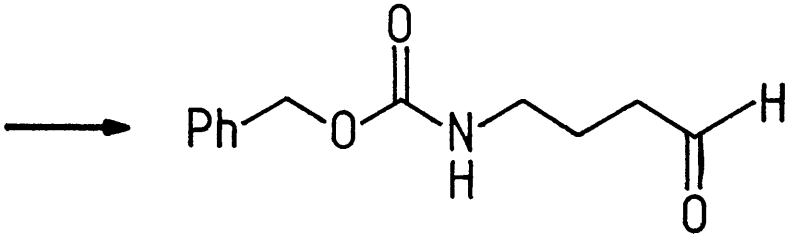
The work presented in this chapter represents the successful application of Moffat's route to the first asymmetric synthesis of β-lysine.[45]

2.3 RESULTS AND DISCUSSION

The chiral nitrone (85) was chosen as the required intermediate for the asymmetric synthesis of β-lysine. Nitrone (85) was prepared by the sequence outlined in Scheme 30. The aldehyde (84) was prepared from commercially available 4-amino-1-butanol by sequential protection of the amino function as the benzyl carbamate (5N NaOH, $PhCH_2OCOC\ell$, 0°C) followed by Swern[46] oxidation of the resulting alcohol (83). The aldehyde (84) was found to be very unstable as evidenced by the absence, after thirty minutes, of the original aldehydic singlet at δ9.80 in the ^1H nmr spectrum at 90 MHz. Provided (84) was treated immediately with R-(+)-α-methylbenzylhydroxylamine oxalate (56) [plus one equivalent of triethylamine] in dichloromethane, the nitrone (85) was obtained in excellent overall yield (91%) from the alcohol (83).

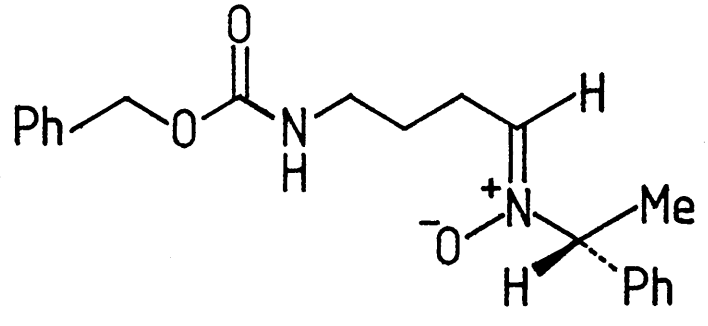


(83)

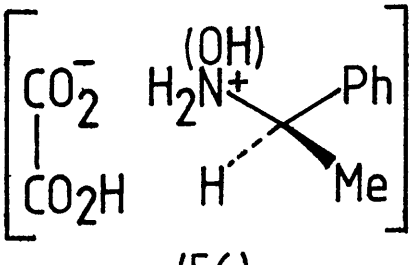


(84)

(56)
plus 1equiv.
Et_3N



(85)



(56)

Scheme 30

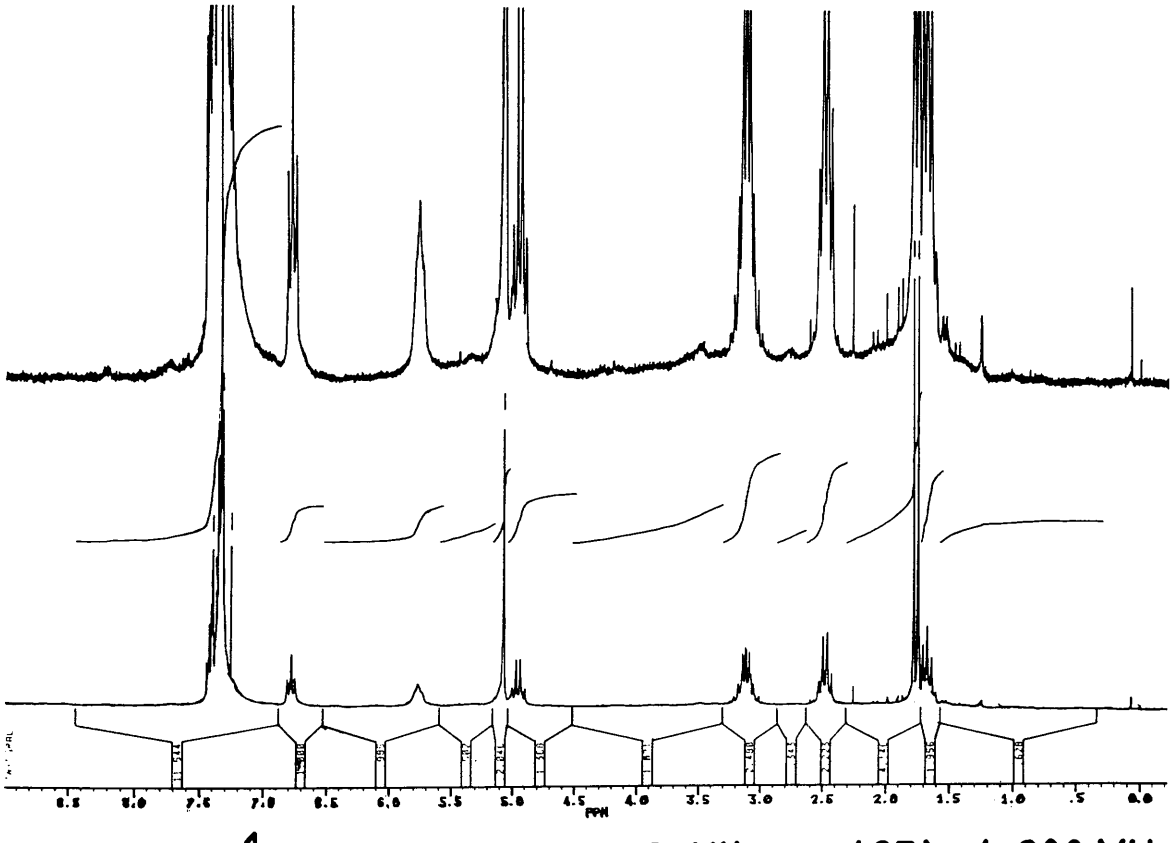


Fig.1a ^{1}H nmr Spectrum of Nitrone (85) at 200 MHz.

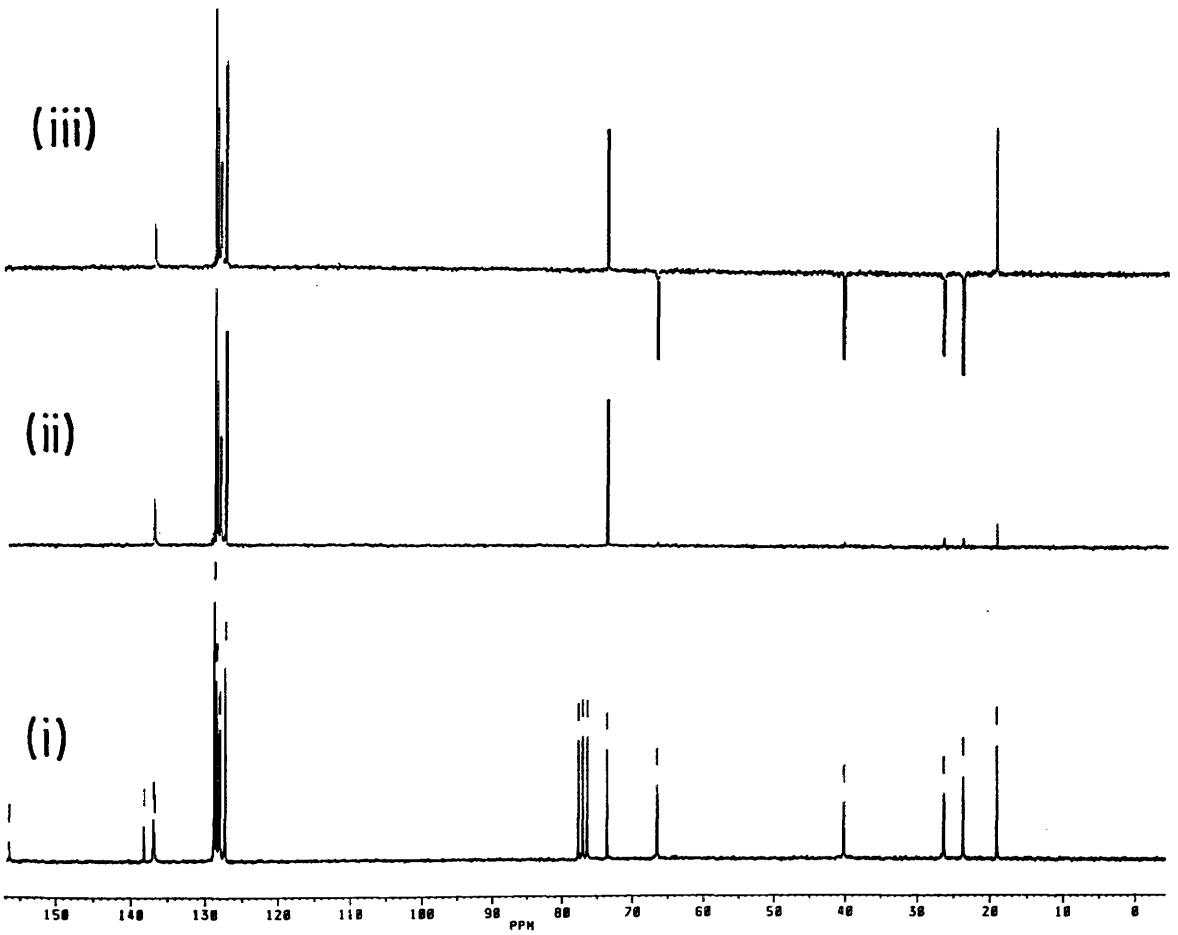
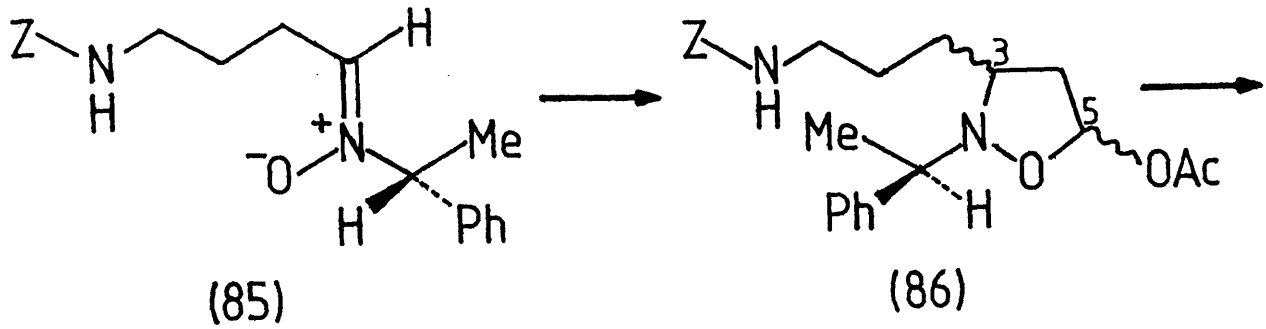


Fig. 1b (i) ^{1}H-Decoupled ^{13}C nmr Spectrum of Nitrone (85). (ii) DEPT $\theta=90^{\circ}$. (iii) DEPT $\theta=135^{\circ}$.

The crystalline nitrone (85) displayed a single set of signals in both the ^{1}H nmr (200 MHz) [Fig. 1a] and ^{13}C nmr [Fig. 1b] confirming the presence of only one geometric isomer (presumably Z) as expected. The i.r. spectrum of (85) showed carbonyl absorption at 1710 cm^{-1} ($CHC\ell_3$ solution). The molecular formula of $C_{20}H_{24}N_2O_3$ was confirmed by accurate mass measurement of $[M]^+$ at m/e = 340.1793 (calc. 340.1787).

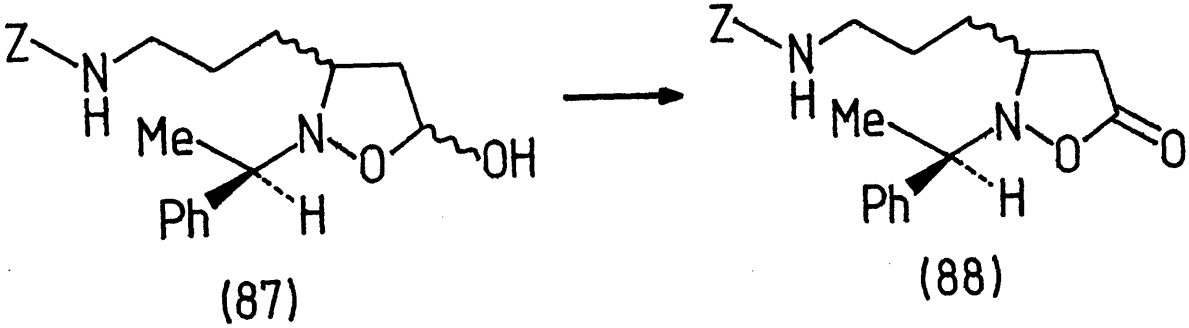
The key step in the chiral synthesis of β-lysine involved 1,3-dipolar cycloaddition of nitrone (85) to vinyl acetate, [Scheme 31]. Nitrone (85) was refluxed in neat vinyl acetate for 16h to furnish the 5-acetoxyisoxazolidine (86) as a mixture of four diastereomers in 68% yield after chromatography.

The formation of four diastereomers (86,A,B,C,D) resulting from approach of reagents in an exo or endo manner as well as re or si face attack at prochiral vinyl acetate was expected,[9] [Scheme 32]. The mixture (86A,B,C,D) was clearly separable by chromatography (SiO_2)[47] into two pairs of diastereomers in a ratio of 7:3 (eluted with 35-55% ethyl acetate:hexane). The major pair consisted of the trans (3R,5S) isomer (86B) [resulting from si face attack in the endo transition state] and the cis(3R,5R) isomer (86D) [resulting from re face attack in the exo transition state] in the ratio 1:2 (86B:86D). The minor pair consisted of the trans(3S,5R) isomer (86A) [resulting from re face attack in the endo transition state] and the cis(3S,5S) isomer (86C) [resulting from si face attack in the exo transition state] in the ratio 2:3 (86A:86C). These stereochemical assignments were based upon identification of the final β-amino acids obtained via the



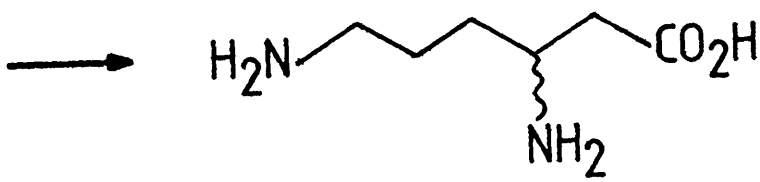
(85)

(86)

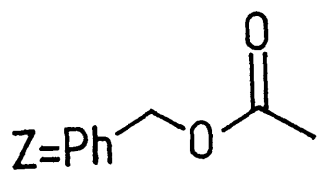


(87)

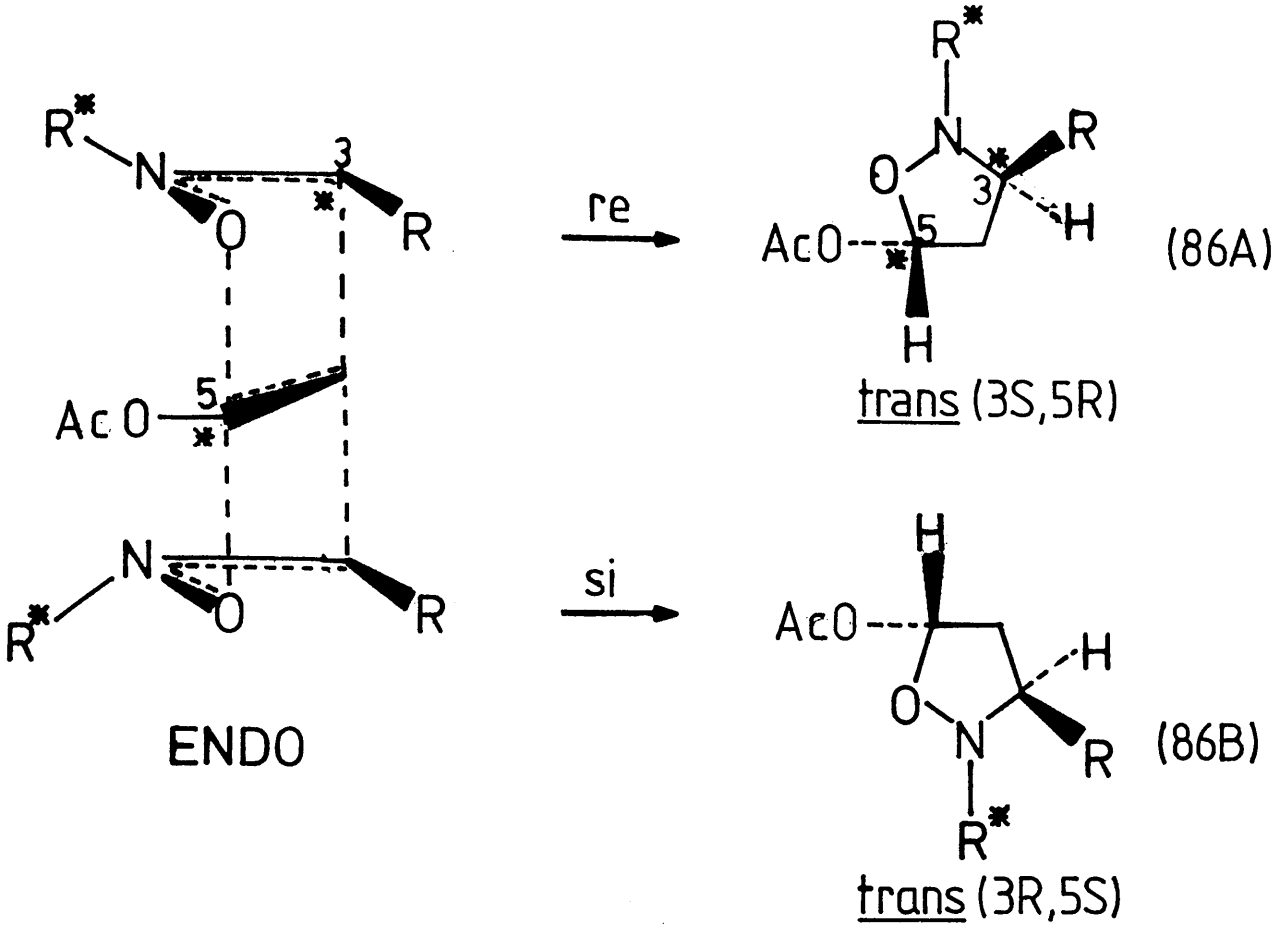
(88)



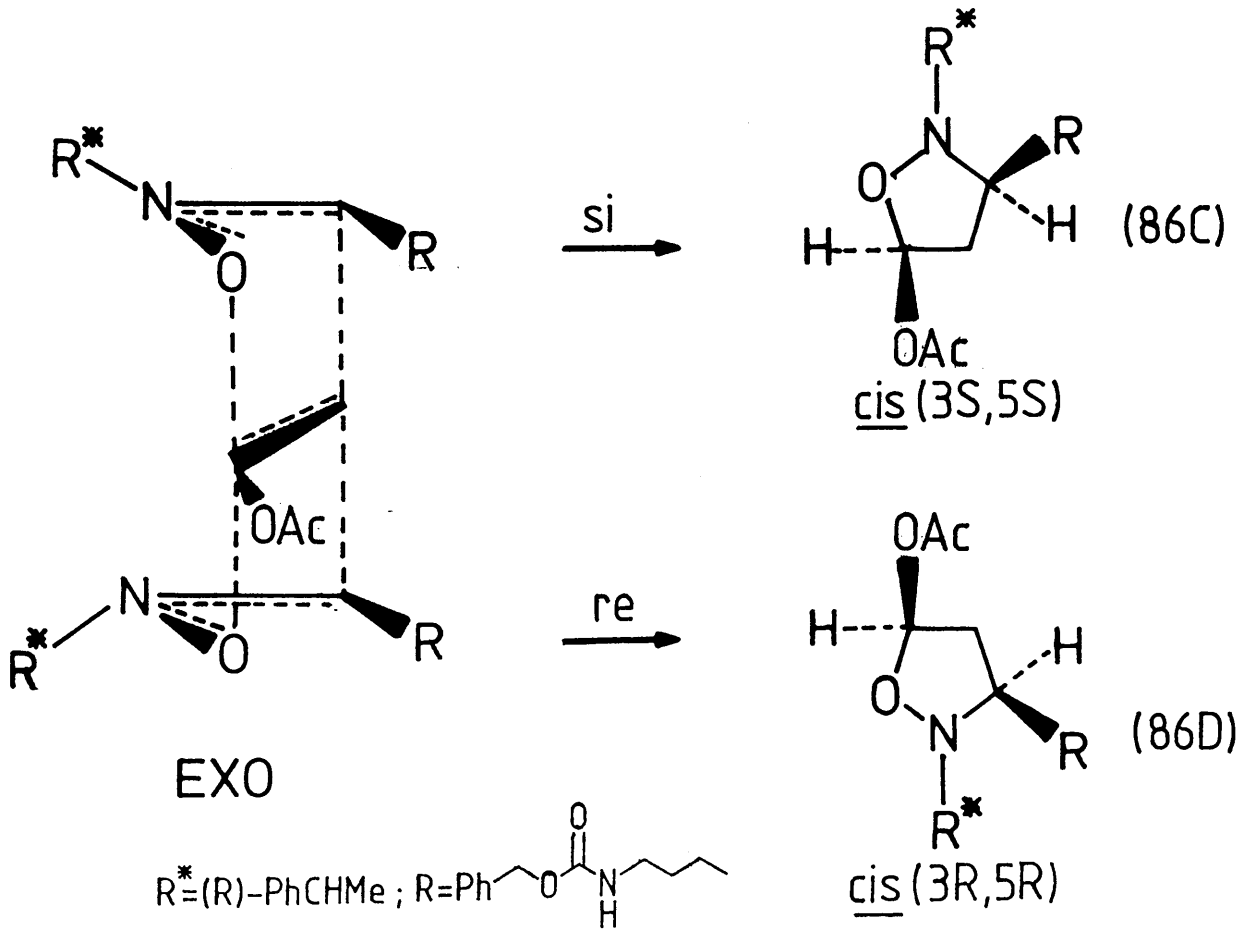
(62)



Scheme 31


re
si
ENDO
(86A)
trans (3S,5R)
(86B)
trans (3R,5S)

Scheme 32


si
re
EXO
(86C)
cis (3S,5S)
(86D)
cis (3R,5R)
R*=(R)-PhCHMe ; R=Ph

subsequent synthetic steps. The major isomers within each pair were assumed to be those arising from the exo transition state based on the observation that cycloadditions of chiral nitrones to monosubstituted alkenes show a marked preference for the exo transition state,[9] [Scheme 7, Introduction].

The presence of diastereomer pairs was clearly evident from the ^{1}H nmr (200 MHz) spectra of each of the two chromatographic fractions. Thus, the major fraction (86B+D) displayed two 1H quartets centred at δ3.78 and δ4.00 (2:1, 2 x q, PhC$\underline{H}$N) and two 3H singlets at δ2.02 and δ2.10 (2:1, 2 x s, COC$\underline{H}_3$) in the ^{1}H nmr spectrum at 200 MHz, [Fig.2]. Similarly, the minor fraction (86A+C) displayed two 1H quartets centred at δ3,95 and δ4.05 (3:2, 2 x q, PhC$\underline{H}$N) and two 3H singlets at δ1.89 and δ2.03 (2:3, 2 x s, COC$\underline{H}_3$) in the ^{1}H nmr spectrum at 200 MHz, [Fig.3]. The ^{13}C nmr spectra of each of the two pairs also revealed two sets of signals e.g. δ19.90 and δ20.68 ($\underline{C}H_3$CHN); δ170.15 and δ170.84 ($\underline{C}$OCH$_3$) in the ^{13}C nmr spectrum of (86B+D).

Assuming that, during the cycloaddition only the Z isomer of the nitrone (85) was present, the diastereomers (86A,B,C,D) were formed in the ratio 12:23.4:18:46.6, respectively. However, under the conditions of the cycloaddition (16h, reflux, neat vinyl acetate) one cannot exclude the possibility of some E isomer contribution to the final diastereomer population. The i.r. spectra of (86A+C) and (86B+D) were virtually identical, each showing carbonyl absorptions at 1730 cm^{-1} and 1750 cm^{-1} ($CC\ell_4$ solution). The molecular formula of $C_{24}H_{30}N_2O_5$ was confirmed by

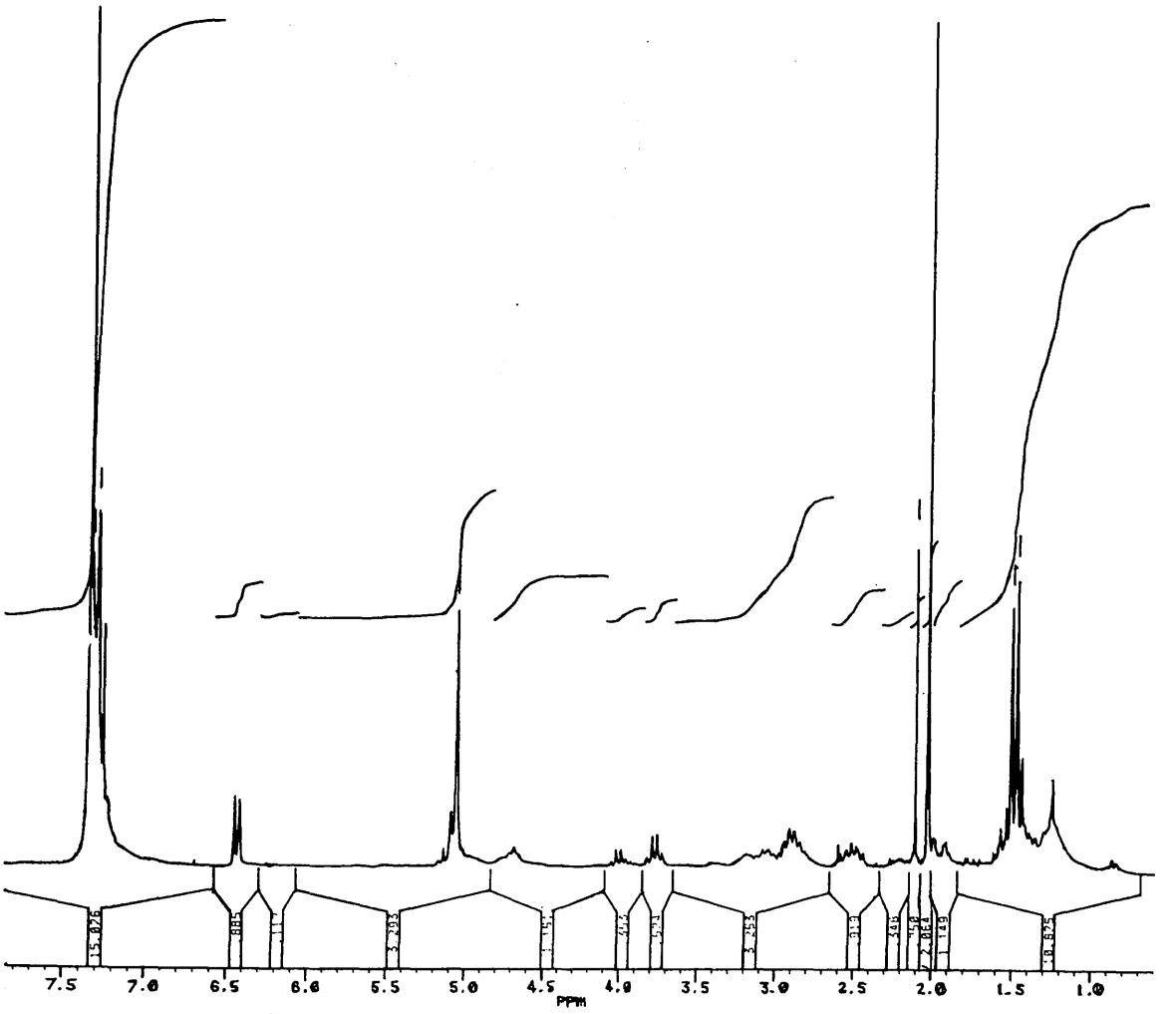


Fig. 2 ^{1}H nmr Spectrum of Isoxazolidines (86B+D) at 200 MHz.

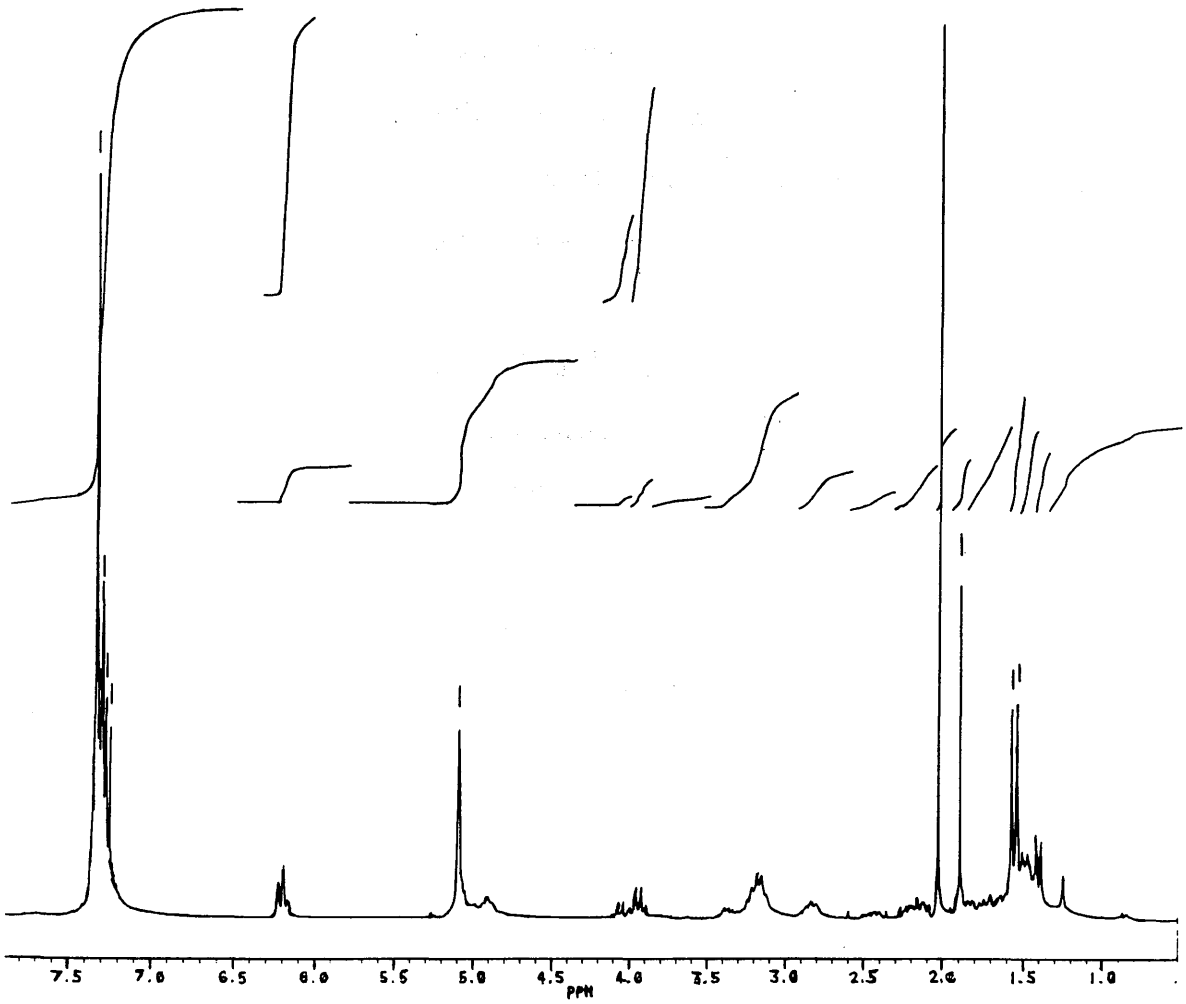


Fig.3 ^{1}H nmr Spectrum of Isoxazolidines (86A+C) at 200 MHz.

accurate mass measurement of $[M]^+$ at m/e = 426.2155 (86A+C) and 426.2185 (86B+D), [calc. 426.2155].

Provided each pair consisted of C-5 epimers but had only one configuration at C-3, both (3R)- and (3S)-β-lysine would be obtained in optically pure form, [Scheme 31] with the minor pair (86A+C) having the required (S)-configuration at C-3 leading to the naturally occurring (3S)-(+)-β-lysine.

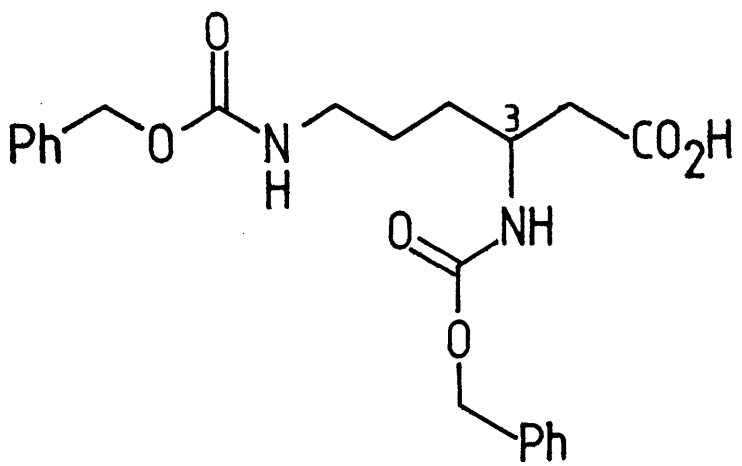
Independent hydrolysis[48] of (86A+C) and (86B+D) afforded (> 90%) the corresponding isoxazolidinols (87A+C) and (87B+D), respectively. The ^1H nmr (90 MHz) spectra of both mixtures displayed multiplets centred at δ 5.61 (1H, m, OCHOH) for (87A+C) and δ 5.35 (1H, m, OCHOH) for (87B+D). The i.r. spectra of both mixtures showed free and bonded hydroxyl absorption at 3600 and 3400 cm^{-1}.

Without purification (87A+C) and (87B+D) were individually oxidised[49] (Collins' reagent) to the isoxazolidinones (3S)-(88) and (3R)-(88), respectively (ca. 40%).

The homogeneity of the C-3 epimeric isoxazolidinones, (3S)-(88) and (3R)-(88) was apparent from the ^{13}C nmr and ^1H nmr (200 MHz) spectra of each isomer e.g. the ^1H nmr spectrum of (3S)-(88) revealed a single 1H quartet at δ 4.04 for the benzylic proton of the α-methylbenzyl group (1H, q, CH_3CHN) while the ^1H nmr spectrum of (3R)-(88) displayed a corresponding signal at δ 4.00 (1H, q, CH_3CHN). In each case the ^1H and ^{13}C nmr spectra showed complete absence of the C-3 isomeric isoxazolidinone (this confirmed that the members of each diastereomer pair (86A+C) and (86B+D) had identical configurations at C-3). The i.r. spectra of each isomer were virtually identical and

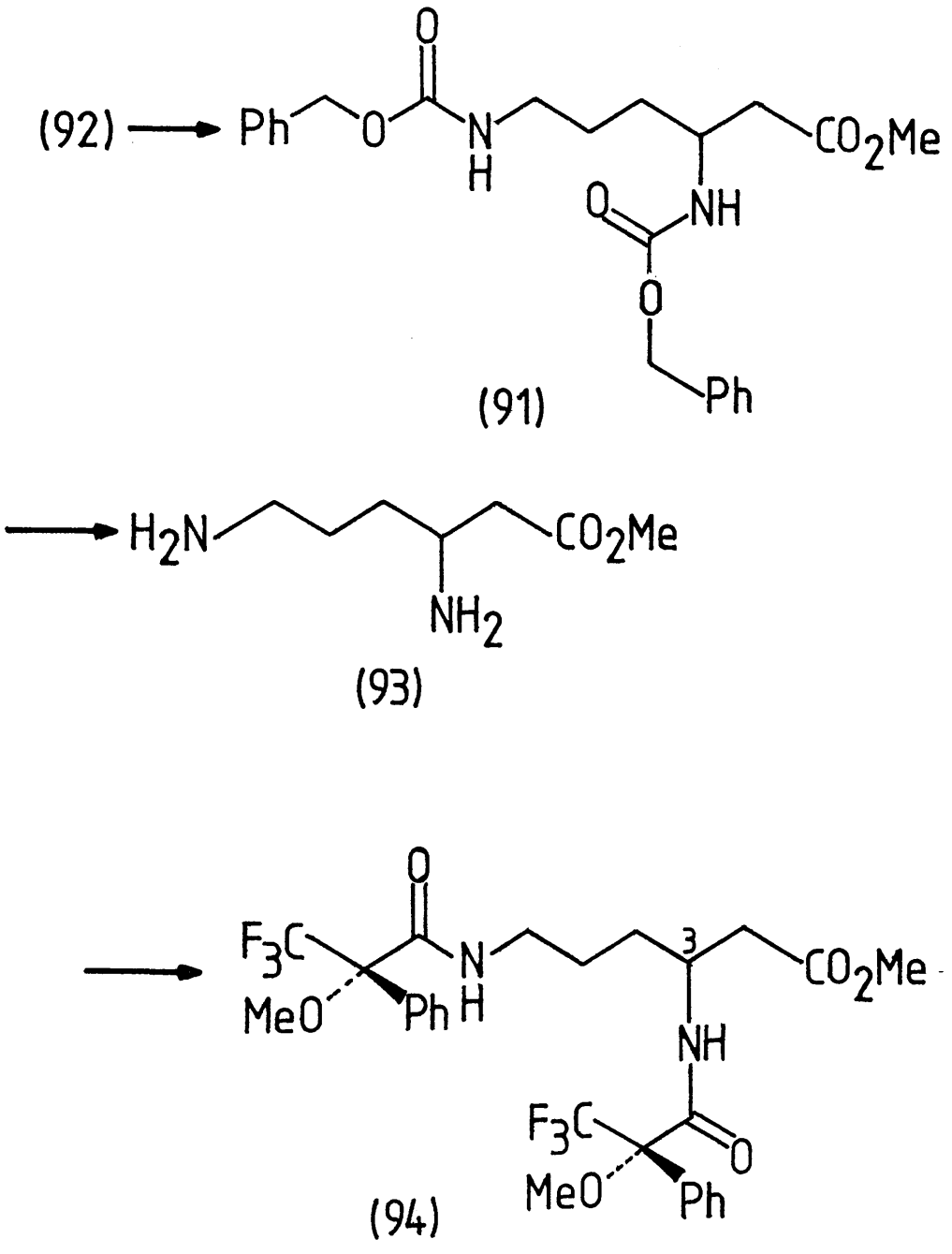
showed strong carbonyl absorption at 1790 cm^{-1} ($CC\ell_4$ solution). Accurate mass measurement of $[M]^+$ at m/e = 382.1894 for (3R)-(88) and m/e = 382.1912 for (3S)-(88) [calc. 382.1893] confirmed the molecular formula of $C_{22}H_{26}N_2O_4$ for each isomer.

Hydrogenolysis of (3S)-(88) [$PdOH_2/C$, H_2, EtOH; 20h at 20°C then 5h at 70°C] gave (3S)-β-lysine in near quantitative yield, [Scheme 31] as a light yellow hygroscopic gum[29,31] which was characterised as the known crystalline dibenzyloxycarbonyl-(3S)-β-lysine derivative, (3S)-(92) [m.p. 153-156°C (lit.[50] 155°C)], by treatment with two equivalents of benzyl chloroformate in 5N NaOH at 0°C (66%). Hydrogenolysis of (3R)-(88) as for (3S)-(88) afforded (3R)-β-lysine which was similarly characterised as the dibenzyloxycarbonyl-(3R)-β-lysine derivative (3R)-(92) [m.p. 153-156°C].



(92)

The optical purity of the (3S)- and (3R)-β-lysines, (3S)-(62) and (3R)-(62), was checked by conversion of the derivatives (3S)-(92) and (3R)-(92) into the corresponding methyl ester, bis-(S)-methoxy (trifluoromethyl)phenylacetyl [(S)-MTPA] amides,[51] (3S)-(94) and (3R)-(94), respectively, [Scheme 33].



Scheme 33

Thus, (3S)-(92) was converted into the methyl ester (3S)-(91) [m.p. 104-107°C (Lit.[50] 105-107°C)] by treatment with excess CH_2N_2 (quantitative). Hydrogenolysis of (3S)-(91) over palladium hydroxide on charcoal at atmospheric pressure and ambient temperature gave (3S)-β-lysine, methyl ester (3S)-(93) quantitatively which was treated with (S)-MTPA chloride (2 equivalents) in $CC\ell_4$-pyridine (3:2) at 70°C for 3h to afford (3S)-(94) in 58% yield. Similarly, (3R)-(92) was converted into (3R)-(94). The methyl ester, bis-(S)-MTPA amide derivatives (94) could not be clearly identified in the ^{19}F nmr spectra because other minor fluorine-containing products were formed, but they were readily differentiated by gc-ms (OV-1; 25m, 290°C, 3 ml per min). In each case the other isomer was completely absent. The results of the gc-ms analysis are summarised on Table 1.

Authentic specimens of (3S)- and (3R)-β-lysines (62) and their dibenzyloxycarbonyl derivatives (3S)-(92) and (3R)-(92) were prepared independently by Arndt-Eistert (A-E) homologation of (2S)- or (2R)-ornithine (65), respectively, according to the method of Wakamiya,[50] [Scheme 34]. There was complete correspondence in all physical and spectroscopic properties of the substances prepared by the two routes (A-E and nitrone cycloaddition). For example, the ^1H nmr (90 MHz) spectra (D_2O) of the (3S)-β-lysines (62) prepared by the two routes were virtually identical, [Fig.4].

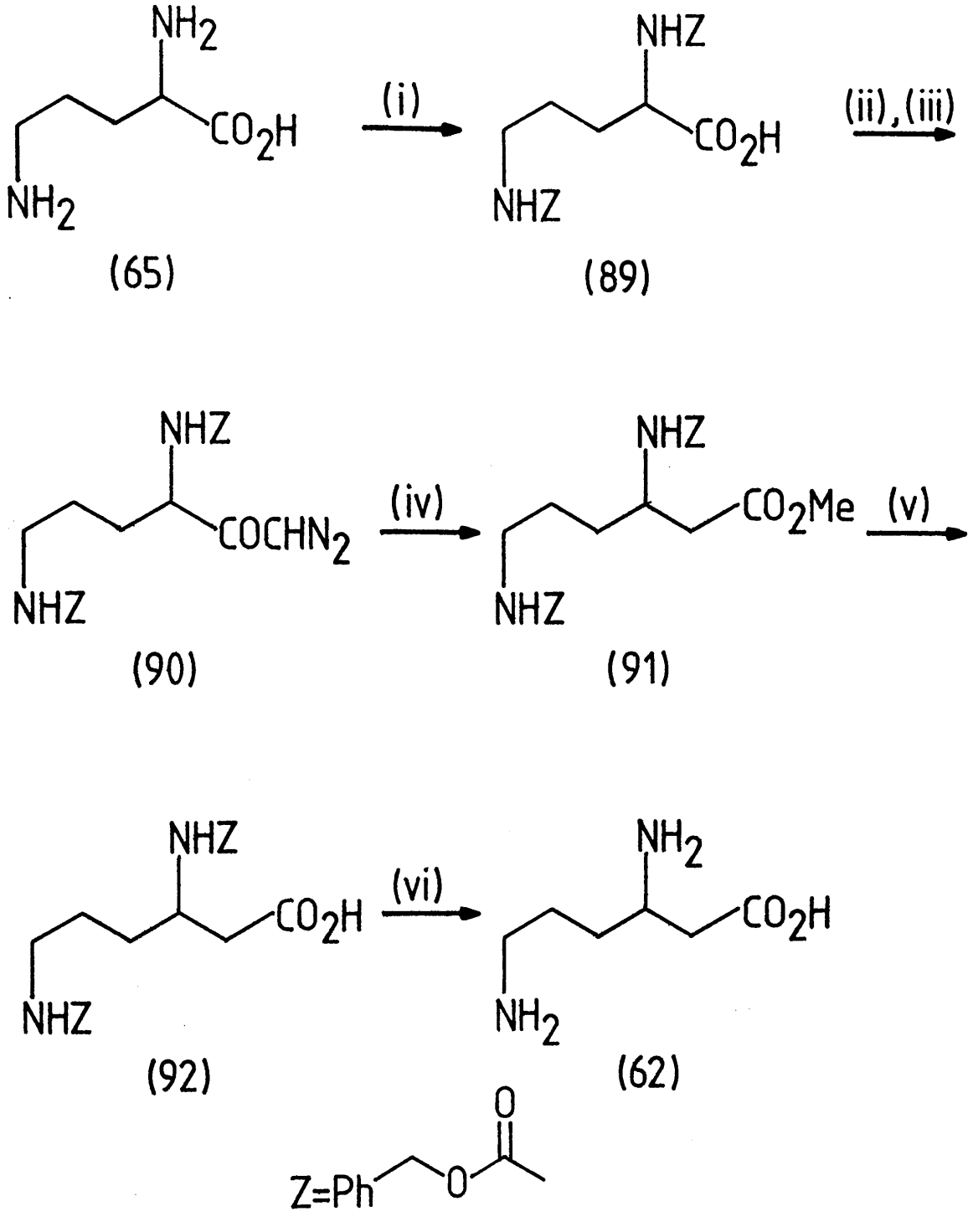
The methyl ester, bis-(S)-MTPA amides (3S)-(94) [A-E] and (3R)-(94) [A-E] were prepared from the dibenzyloxycarbonyl-(3S or 3R)-β-lysine methyl esters (3S)-(91) [A-E] and (3R)-(91) [A-E],

Table 1. gc-ms analysis of the β-lysine derivatives (3S)-(94) and (3R)-(94) prepared via nitrone cycloaddition

Isomer	Retention Time (mins)	$[M]^+$	$[M]^+-C_9H_8F_3O$ (100%)
(3S)-(94)	16.12	592	403
(3R)-(94)	16.62	592	403

Table 2. gc-ms analysis of the β-lysine derivatives (3S)-(94) and (3R)-(94) prepared via A-E homologation of (2S)- or (2R)-ornithine (65)

Isomer	Retention Time (mins)	$[M]^+$	$[M]^+-C_9H_8F_3O$ (100%)
(3S)-(94)	16.13	592	403
(3R)-(94)	16.68	592	403



(i) $PhCH_2OCOCl$, 5N NaOH ; (ii) EtOCOCl ; (iii) CH_2N_2

(iv) $PhCO_2^-\ Ag^+$, MeOH ; (v) NaOH–dioxan–H_2O

(vi) H_2/Pd/C

Scheme 34

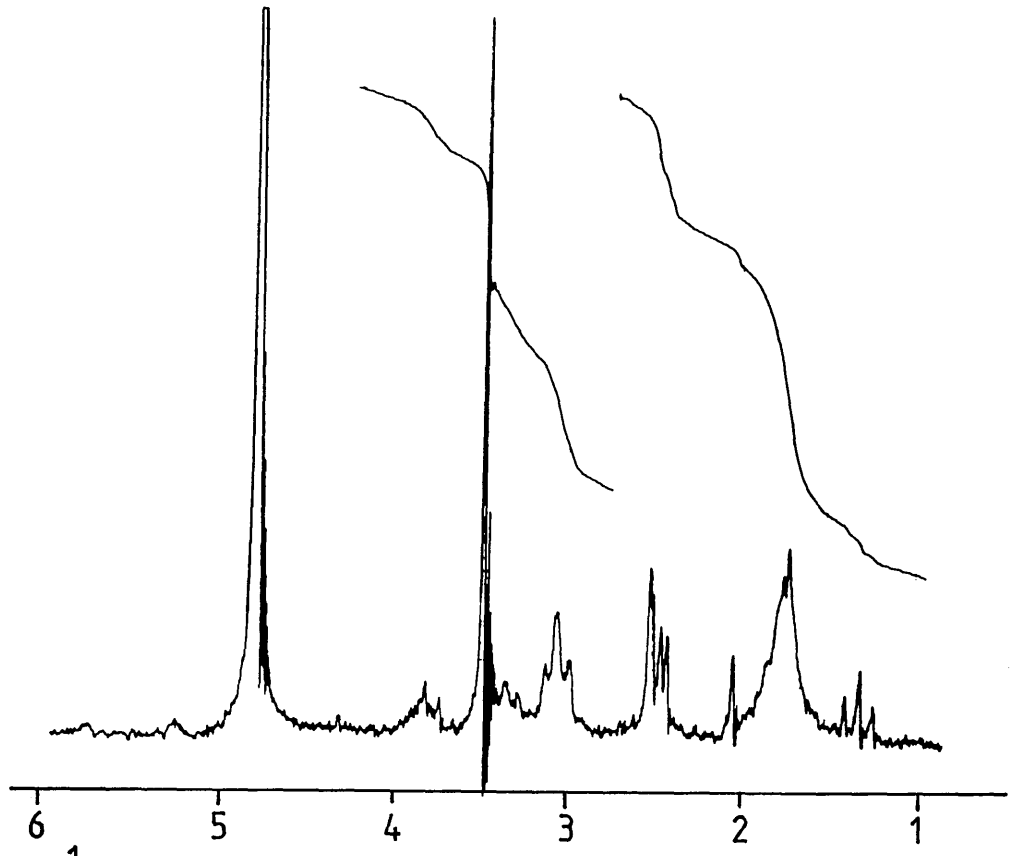


Fig. 4a ^{1}H nmr Spectrum (D_2O) at 90 MHz of (3S)-β-Lysine (62), Prepared via A-E Homologation of (2S)-Ornithine (65).

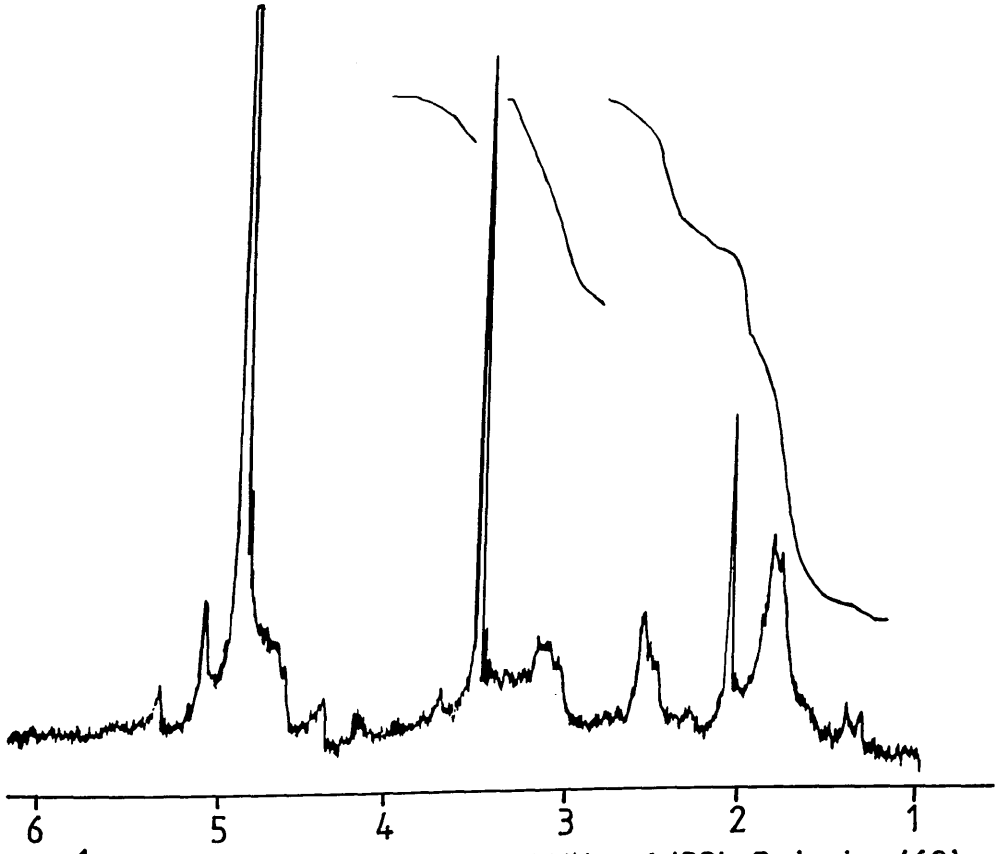


Fig. 4b ^{1}H nmr Spectrum (D_2O) at 90 MHz of (3S)-β-Lysine (62), Prepared via Nitrone Cycloaddition.

respectively, [cf. Scheme 33]. Analysis of these by gc-ms (OV-1; 25m, 290°C, 3 ml per min) showed complete correlation with the methyl ester, bis-(S)-MTPA amides (94) prepared via nitrone cycloaddition, [Table 2].

2.4 SUMMARY

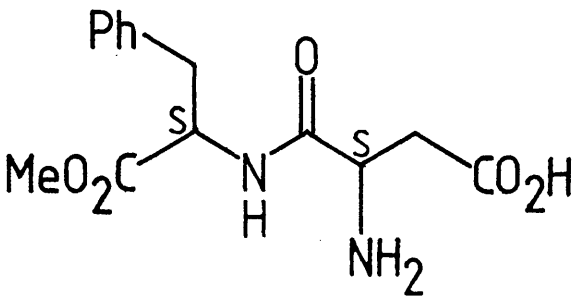
Optically pure (3S)- and (3R)-β-lysines have been obtained via 1,3-dipolar cycloaddition of a chiral nitrone (85) to vinyl acetate. followed by facile chromatographic separation of the four resulting diastereomers (86) into two pairs of C-5 epimers and conversion of each pair into diastereoisomerically pure isoxazolidinones [(3S)-(88) or (3R)-(88)]. This represents the first asymmetric synthesis of the biologically important (3S)-β-lysine and the (3R)-isomer, both in optically pure form.

CHAPTER 3

Stereocontrolled Synthesis of Aspartame [(S)-Asp-(S)-PheOMe] and its (R)-Aspartyl Congener [(R)-Asp-(S)-PheOMe] via Nitrone Cycloaddition to 2-Chloroacrylonitrile

3.1 BACKGROUND

The low-calorie dipeptide sweetener aspartame (95) [(S)-aspartyl-(S)-phenylalanine, methyl ester; (S)-Asp-(S)-PheOMe] has about 180 times the sweetness of sucrose.[52] The first synthesis was reported[53] in 1966 but its sweetness was discovered accidentally by Mazur et al.[54] three years later during work on the synthesis of the C-terminal tetrapeptide sequence of gastrin, Try.Met.Asp.Phe.NH_2, at the G.D. Searle Company in Illinois.

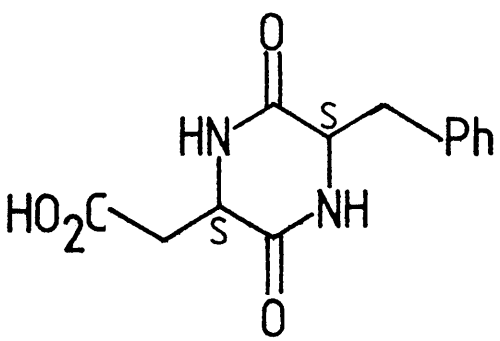


(95)

The sweet taste of aspartame in no way reflects the tastes of (S)-aspartic acid or (S)-phenylalanine. The former is tasteless while the latter is bitter. Mazur[54] has studied the structure-taste relationships of aspartame and found the absolute stereochemistry to be absolutely critical [(R)-Asp-(S)-PheOMe is tasteless while (S)-Asp-(R)-PheOMe is bitter]. The presence of the unsubstituted aspartic acid moiety was also found to be an absolute requirement for sweetness and it has been suggested that the amino and carboxyl groups of aspartic acid bind directly to a taste-triggering receptor site

in the taste buds.[54] Replacement of the phenylalanine, methyl ester with other α-amino esters, on the other hand, showed considerable tolerance in terms of the retention of sweetness e.g. (S)-aspartyl-(S)-tyrosine, methyl ester was found to be similar in potency to aspartame itself.

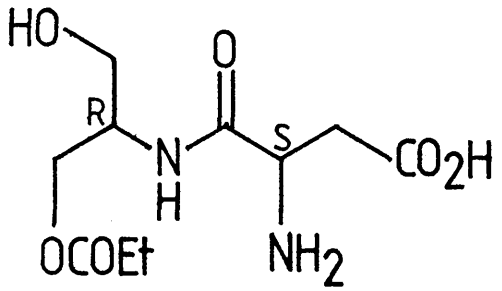
The main disadvantage of aspartame in its practical use as a low-calorie sweetener is its tendency to undergo intramolecular aminolysis in aqueous solution to form the diketopiperazine (96), which in turn leads to a loss of sweetness.[55,56]



(96)

Recently Bada[56] has shown that (96) was the main decomposition product of aspartame over a wide range of pH and temperature. Furthermore, racemisation rates in the diketopiperazine (96) were greater than in the dipeptide (95) over the same range of pH and temperature.[56] In order to prevent the cyclisation of aspartame to the diketopiperazine (96)

Sugano et al.[57] have synthesised a series of dipeptide analogs whose backbones are elongated by one or more methylene units. For example the dipeptide (97), in which the positions of the carbonyl and oxygen functions of the ester have also been exchanged, has about 200 times the sweetness of sucrose. Nevertheless, aspartame (trade names, Sweetex; Nutrasweet; Candarel) remains the most important non-toxic low-calorie artificial sweetener on the market.

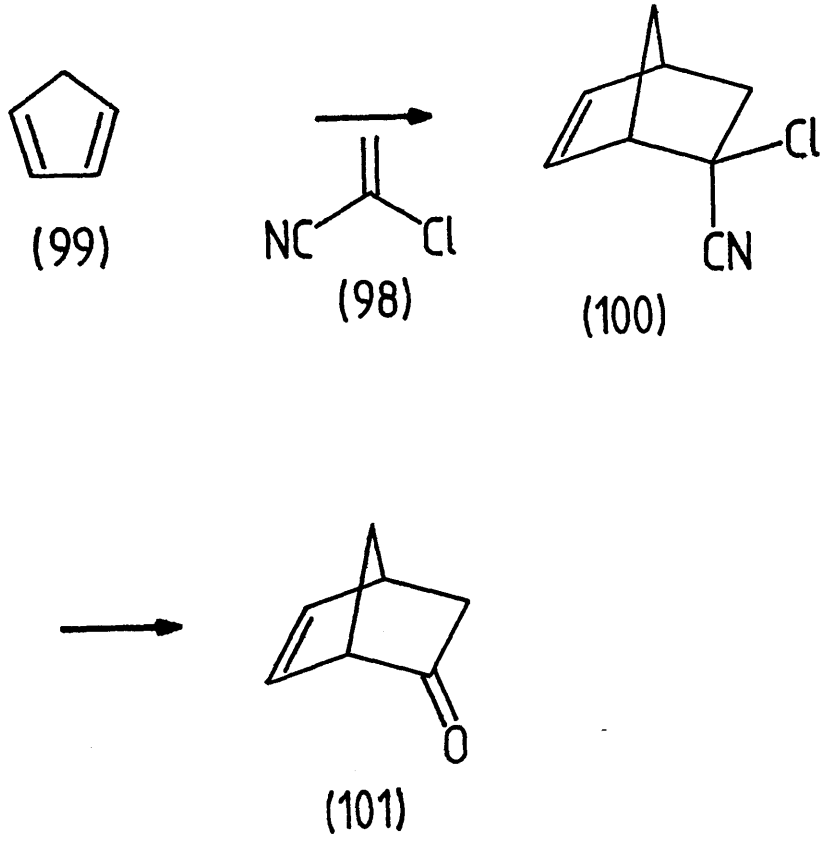


(97)

In their studies of the metabolism of aspartame in monkeys, Opperman et al.[58,59] have shown the dipeptide to be a safe, non-toxic sweetener. Aspartame is hydrolysed in the gut to its constituents, methanol, aspartic acid and phenylalanine. Aspartic acid and methanol are oxidised and converted to carbon dioxide to the extent of 60-80% of the administered dose. Phenylalanine is incorporated into body protein to a great extent, with only 20-25% excretion of the administered dose. Moreover, it has been shown[59] that even chronic ingestion of aspartame at levels as high as 4g/day does not affect normal phenylalanine metabolism in man.

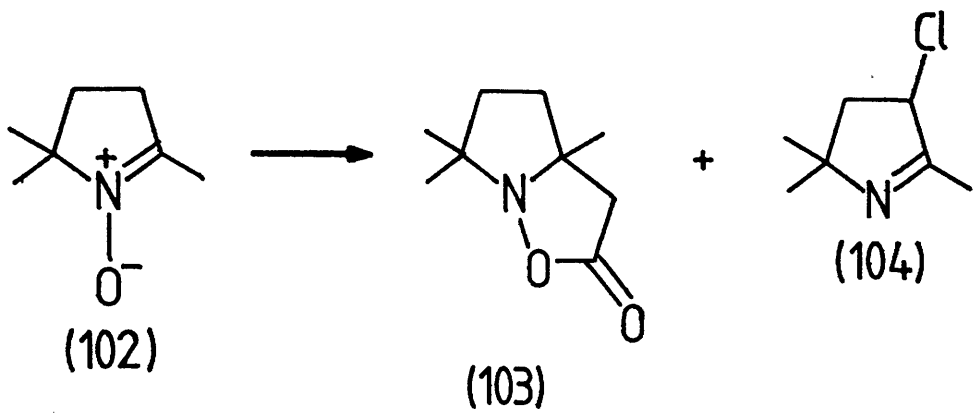
3.2 2-CHLOROACRYLONITRILE AS A KETENE EQUIVALENT IN CYCLOADDITION REACTIONS

2-Chloroacrylonitrile (98) has been widely used[60] as a ketene equivalent in [4+2]-cycloadditions. This is clearly due to the fact that ketenes themselves tend to form [2+2]-adducts. Thus, cyclopentadiene (99) undergoes [4+2]-cycloaddition with (98) to give the adduct (100) which can be transformed into the ketone (101) by treatment with concentrated aqueous potassium hydroxide in DMSO, [Scheme 35].



Scheme 35

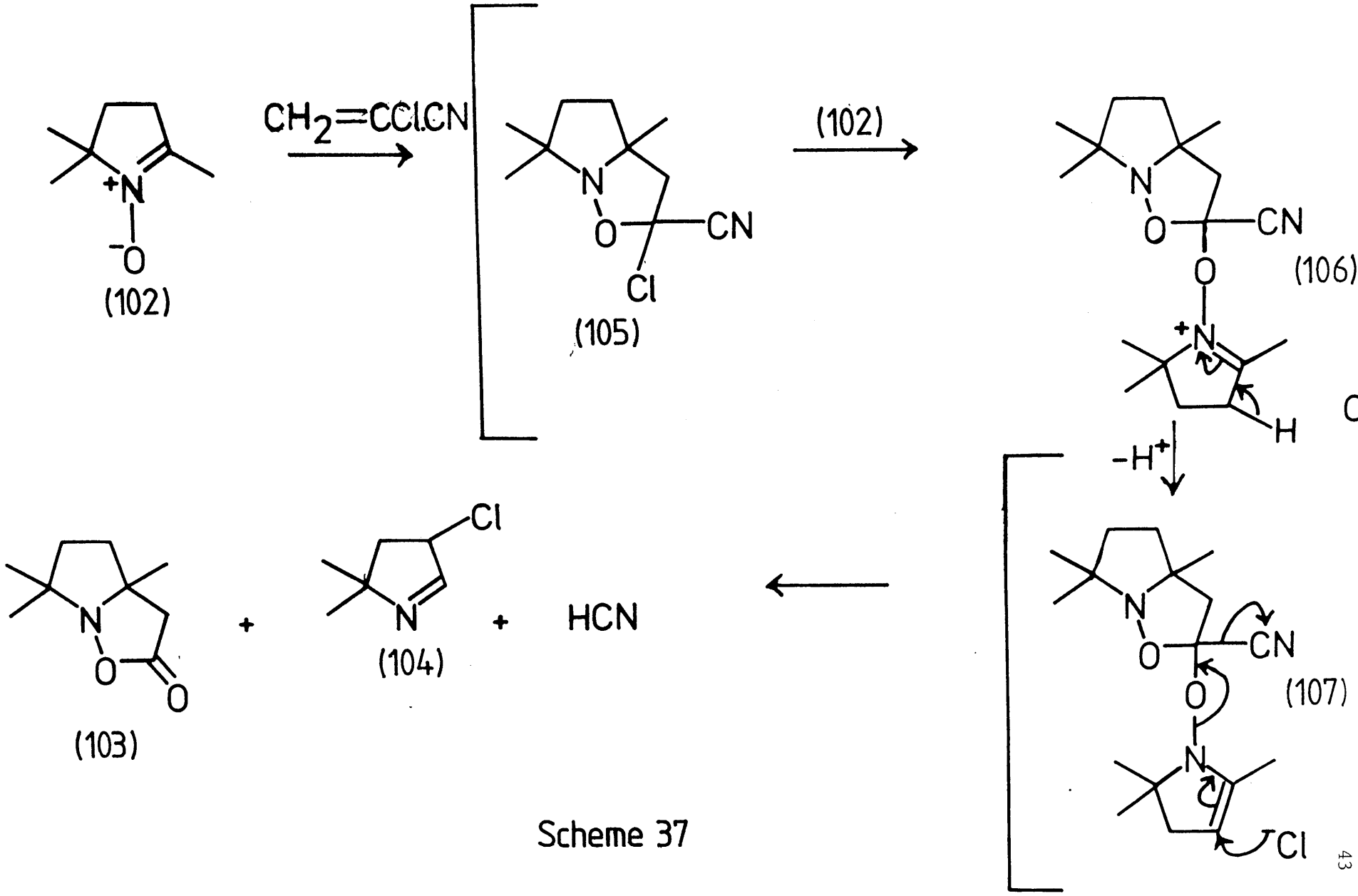
Surprisingly, there has only been one previous example of a [3+2]-cycloaddition of a nitrone to 2-chloroacrylonitrile. Schneider[61] has isolated the isoxazolidinone (103) and the chlorimine (104) from reaction of the nitrone (102) with 2-chloroacrylonitrile, [Scheme 36].



Scheme 36

Schneider[61] has rationalised the formation of (103) by postulating a mechanism whereby the nitrone (102) reacts with the initially formed 5,5-disubstituted cycloadduct (105) to give the intermediate (106) which undergoes degradation to the products (103) and (104) via the intermediate (107), [Scheme 37].

In general, 1,1-disubstituted ethylenes undergo cycloaddition with nitrones to afford 5,5-disubstituted isoxazolidines. Non-activated alkenes[62] such as α-methyl styrene and 1,1-diphenylethylene, electron-rich alkenes[63] such as ketene acetals and enamines and electron-poor



Scheme 37

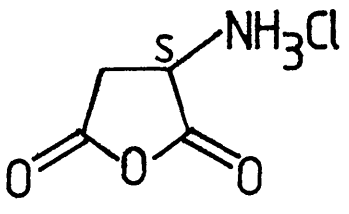
alkenes[64] such as methyl methacrylate all undergo cycloaddition in the same regiochemical sense.

This chapter describes the successful application of cycloaddition reactions of chiral nitrones with 2-chloroacrylonitrile followed by facile hydrolysis of the resulting adducts to give chiral isoxazolidinones. This was shown to be an extremely efficient process and a significant synthetic improvement on the vinyl acetate route, discussed in Chapter 2, since it avoids the low-yielding oxidation step needed to transform the initial adducts into isoxazolidinones.

3.3 PREVIOUS SYNTHESES OF ASPARTAME

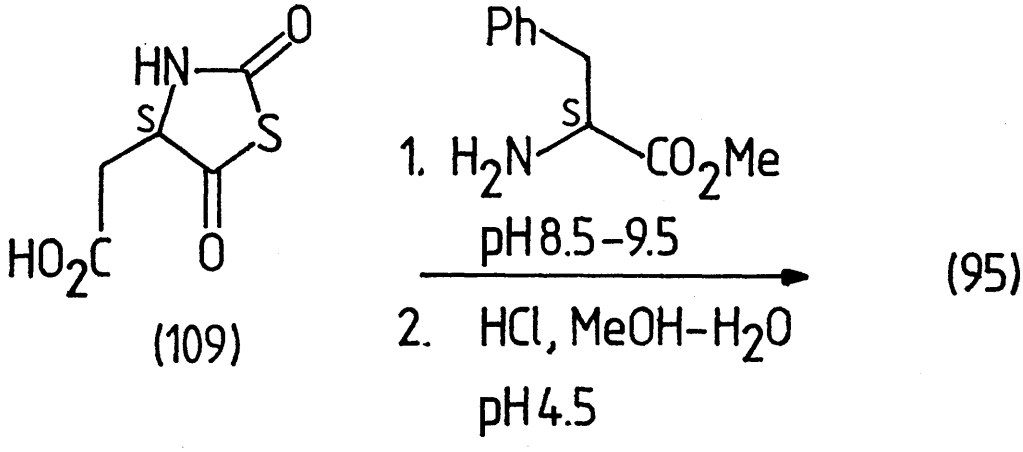
The commercial importance of aspartame as a low-calorie, non-toxic artificial sweetener has resulted in considerable synthetic effort being devoted to the discovery of a short highly efficient route to this unique substance.[67-71]

The principal difficulty with conventional syntheses based on simple peptide coupling is the problem of achieving the selective formation of a peptide bond at the α-position of the (S)-aspartic acid moiety. The most commonly used approach has involved ring opening of N-protected aspartic anhydrides such as (108).[65]



(108)

Non-regiospecific ring opening of (108) with (S)-phenylalanine, methyl ester ((S)-PheOMe) results in a mixture of α and β regioisomeric dipeptides which must then be separated. Regiospecific coupling at the α-carboxyl of N-protected aspartic acid can be achieved by enzymological methods,[66] employing the enzyme, thermolysin. In 1982, Vinick[68] achieved completely regiospecific α coupling of (S)-PheOMe with (S)-aspartic acid N-thiocarboxyanhydride (109), [Scheme 38].



Scheme 38

The previously unknown aspartic acid derivative (109) was prepared from (S)-aspartic acid and methyl ethyl xanthate followed by PBr_3 cyclisation. The critical peptide coupling reaction was carried out

under conditions of strict pH and temperature control to afford aspartame (95) in 63% yield from (109).

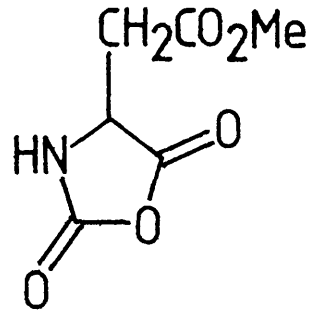
More recently, Tou[69] has reported a regioselective synthesis of aspartame from β-methyl-(S)-aspartate N-carboxyanhydride (110), [Scheme 39].

Regioselective coupling of (110) with phenylalanine (111) afforded the aspartyl methyl ester of α-(S)-aspartyl-(S)-phenylalanine (112). The coupling adduct (112) was subjected to a hydrolysis-esterification reaction without isolation to establish a series of equilibria in which all the possible esterification products were present. The insoluble (S)-aspartyl-(S)-phenylalanine methyl ester hydrochloride (113) precipitated from the reaction medium as formed. Neutralisation of (113) afforded aspartame (95) in 55% overall yield.

Recently, Duhamel[70] has synthesised aspartame via the oxaziridine-amide rearrangement of the precursor (114), [Scheme 40]. The dipeptide (S),(S)-(115) has previously been described by Pietsch[67] as the direct precursor of aspartame (95).

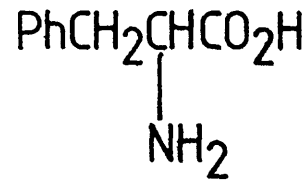
The only previous synthesis of aspartame which has involved an asymmetric step was in 1986 by Fuganti[71] who hydrogenated N-benzyloxycarbonyl dehydroaspartame (116) using a chiral rhodium catalyst, [Scheme 41] to obtain aspartame (95) in 90% diastereomeric excess.

In contrast to Fuganti's synthesis[71] where the induced chiral centre was at the phenylalanyl moiety of the dipeptide, this chapter presents a different approach to aspartame in which the aspartyl chiral



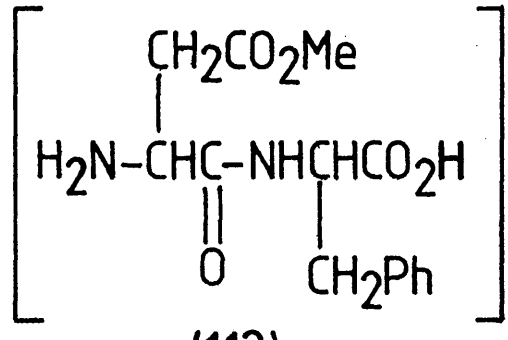
(110)

+



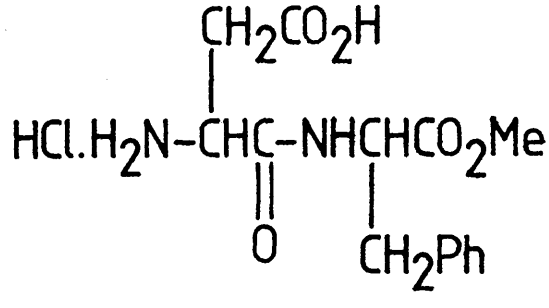
(111)

1. NaOH(aq.) pH10.1 → 2. HCl (aq.) pH3.7



(112)

1. HCl(aq.) → 2. MeOH

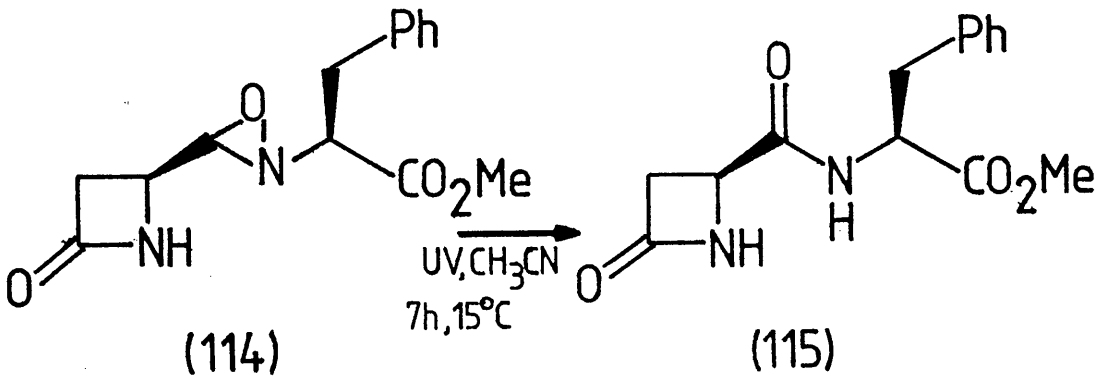


(113)

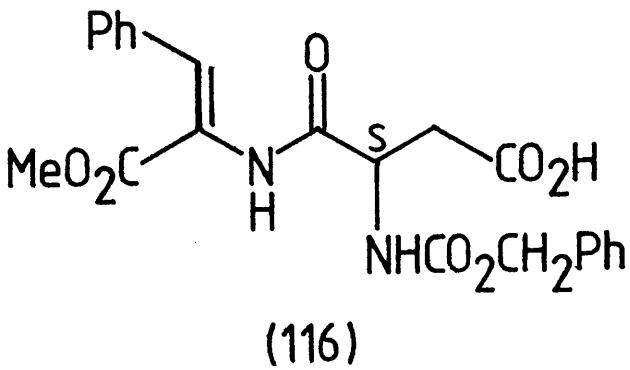
NaOH(aq.) →

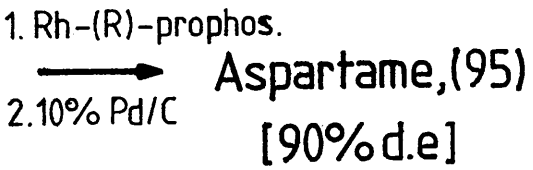
(95)

Scheme 39



Scheme 40



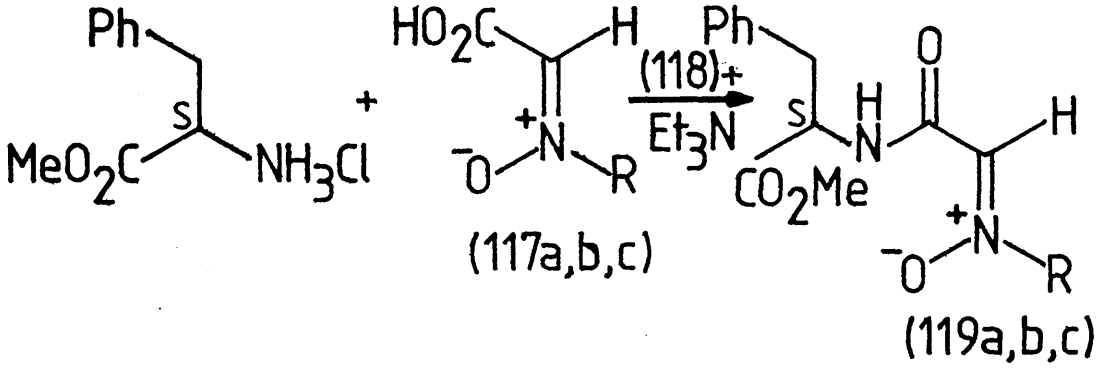


Scheme 41

centre was generated via 1,3-dipolar cycloaddition of chiral nitrones to the ketene equivalent, 2-chloroacrylonitrile.

3.4 RESULTS AND DISCUSSION

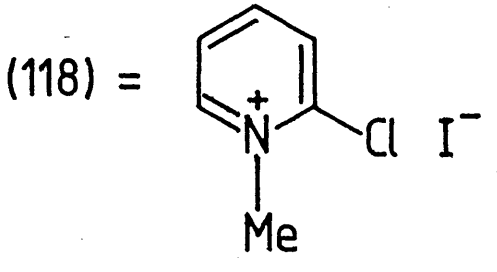
The same general strategy as that applied to the successful stereoselective synthesis of β-lysine (Chapter 2) was employed for the asymmetric synthesis of aspartame (95). The C-carbamido nitrones (119a,b,c) with the (S)-phenylalanyl moiety already incorporated into their structures were considered to be ideal dipoles, [Scheme 42].



a R=$PhCH_2$

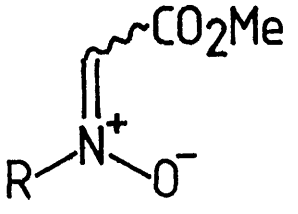
b R=(R)-CHMePh

c R=(S)-CHMePh



Scheme 42

Reaction of glyoxylic acid hydrate with N-benzylhydroxylamine (49) or (R or S)-α-methylbenzylhydroxylamine oxalate salt (56) [plus one equivalent of triethylamine] in dichloromethane for 5h at room temperature readily afforded the C-carboxy nitrones (117a,b,c), respectively (61-66%). The ir spectra of (117a,b,c) all displayed carbonyl absorption at 1715 cm^{-1} and strongly H-bonded O-H absorptions at 2500-2800 cm^{-1} ($CHC\ell_3$ solution). Nitrone (117a) was crystalline and nitrones (117b) and (117c) were oils. Significantly, the ^1H nmr spectra at 90 MHz of (117a,b,c) clearly showed each of the nitrones to be present as a single geometric isomer (presumably Z) e.g. Fig. 5 shows the ^1H nmr spectrum at 90 MHz of (117a). This contrasted with the corresponding methyl ester nitrones (123a,b,c) which were each shown by ^1H nmr (90 MHz) to be present as a 1:1 mixture of Z and E isomers ($CHC\ell_3$, room temp.) and were easily prepared in good yield (> 75%) as for (117a,b,c) but using methyl glyoxylate[72] in place of glyoxylic acid hydrate. Thus, two sets of signals were clearly distinguishable in the ^1H nmr spectrum (90 MHz) of nitrone (123a), [Fig.6].



(123a,b,c)

a R=CH_2Ph

b R=(R)-CHMePh

c R=(S)-CHMePh

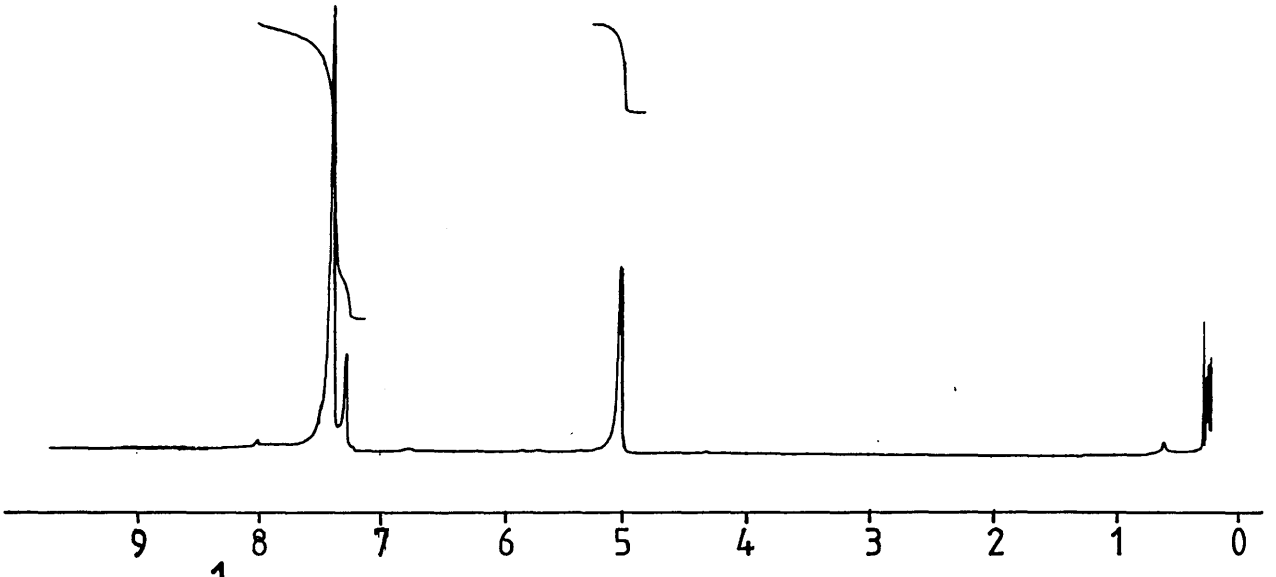


Fig.5 ^{1}H nmr Spectrum of Nitrone (117a) at 90 MHz.

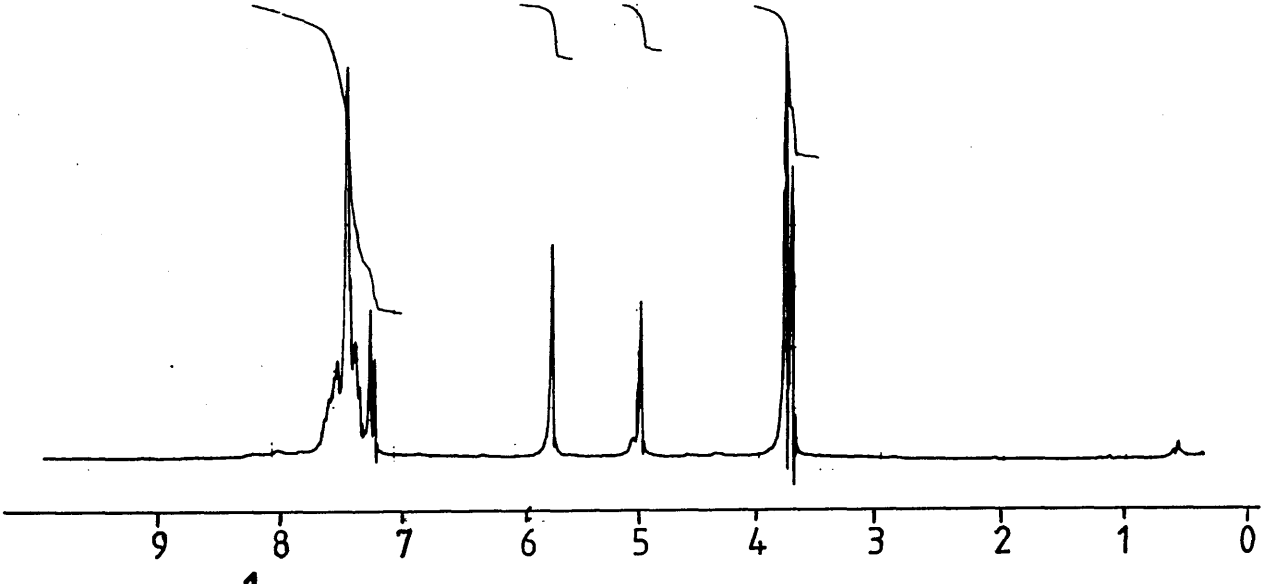


Fig. 6 ^{1}H nmr Spectrum of Nitrone (123a) at 90 MHz.

Coupling of the nitrones (117a,b,c) with (S)-phenylalanine methyl ester hydrochloride in dichloromethane using N-methyl-2-chloropyridinium iodide (118)[73] [plus three equivalents of triethylamine]. afforded the amides (119a,b,c), [Scheme 42] in 55-60% yield after purification by silica gel chromatography. The nitrones (119a) and (119b) were crystalline while (119c) was an oil. Again, each nitrone was shown to exist as a single geometric isomer ($CHC\ell_3$, room temperature) e.g. the crystalline nitrone (119a) displayed a single set of signals in both the ^1H nmr spectrum (200 MHz), [Fig.7a] and ^{13}C nmr spectrum, [Fig.7b]. The ir spectrum of (119a) showed carbonyl absorptions at 1645 cm^{-1} and 1742 cm^{-1} (KBr disc). The molecular formula of $C_{19}H_{20}N_2O_4$ for (119a) was confirmed by accurate mass measurement of $[M]^+$ at $\underline{m}/\underline{e}$ = 340.1437 (calc. 340.1423). The nitrones (119b,c) also gave spectroscopic and accurate mass data in accord with the structures shown in Scheme 42.

The key step in the asymmetric synthesis of aspartame (95) involved 1,3-dipolar cycloaddition of the nitrone (119a,b or c) [three separate runs] to the ketene equivalent 2-chloroacrylonitrile (98). Facile hydrolysis (see below) of the resulting 5,5-disubstituted adduct (120a,b or c) afforded the isoxazolidinone (121a, b or c) [Scheme 43]. The diastereoselectivity of the initial cycloaddition step was reflected in the relative proportions of the two diastereomeric dipeptides [aspartame (95) and (R)-Asp-(S)-PheOMe (122)], obtained by hydrogenolysis of (121a, b or c).

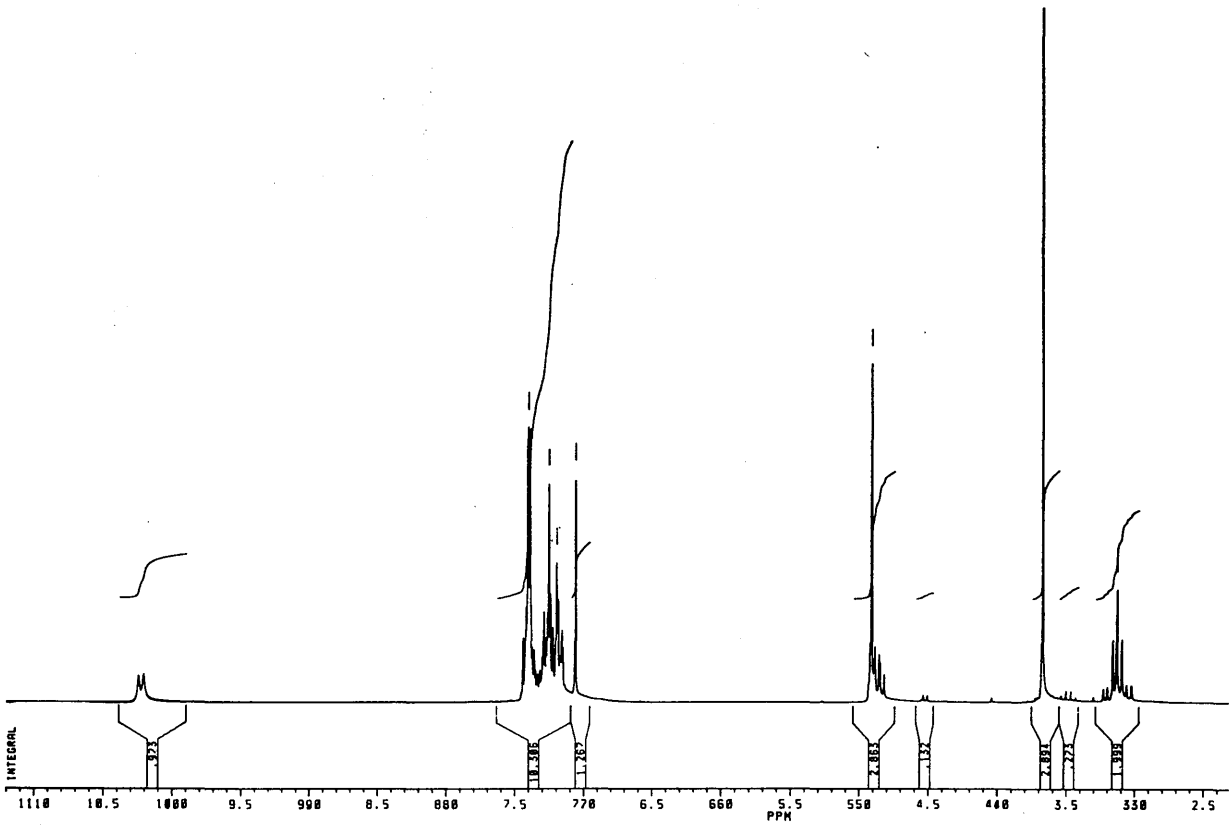


Fig. 7a ^{1}H nmr Spectrum of Nitrone (119a) at 200 MHz.

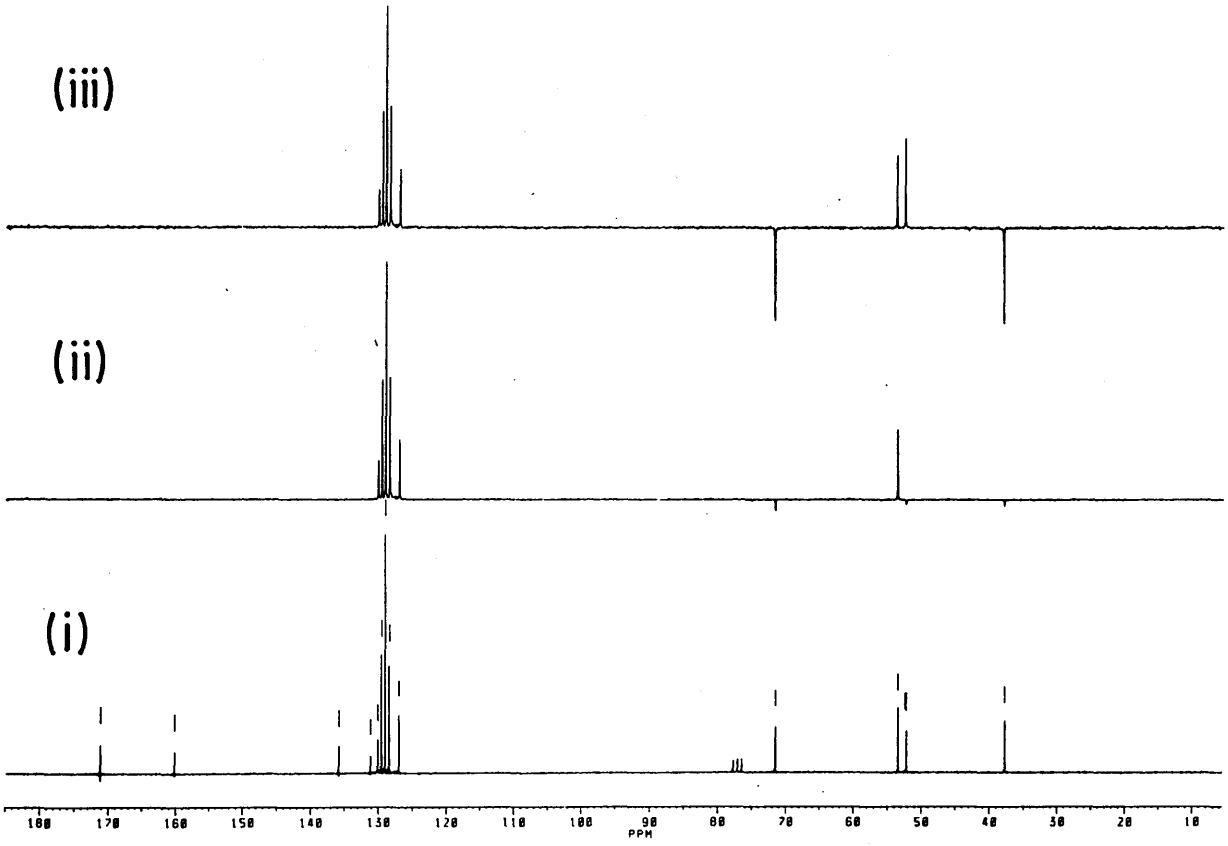
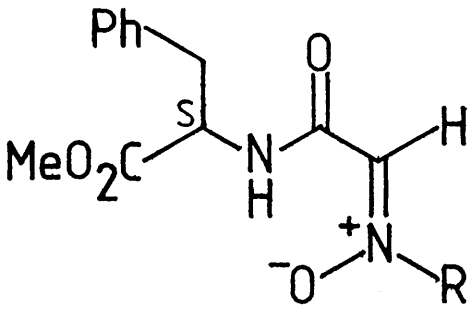
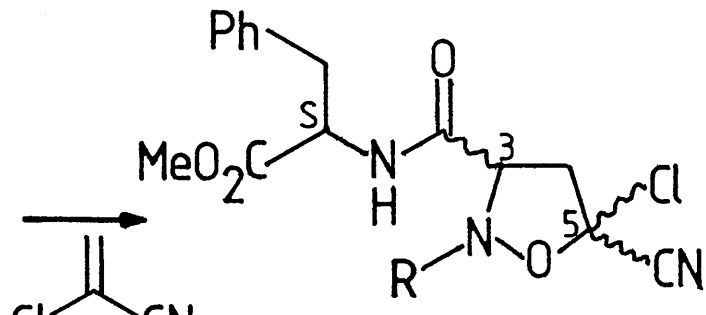


Fig.7b (i) ^{1}H-Decoupled ^{13}C nmr Spectrum of Nitrone (119a). (ii) DEPT $\theta=90^{\circ}$. (iii) DEPT $\theta=135^{\circ}$.



(119a,b,c)

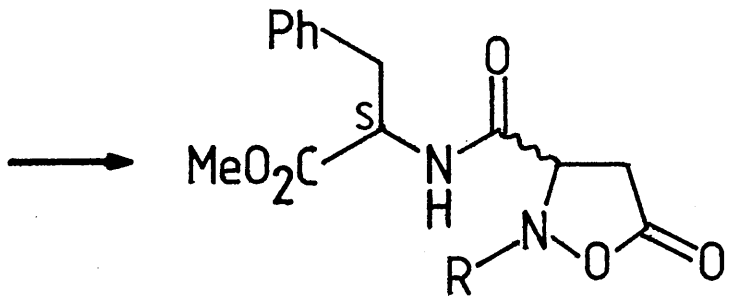


(120a,b,c)

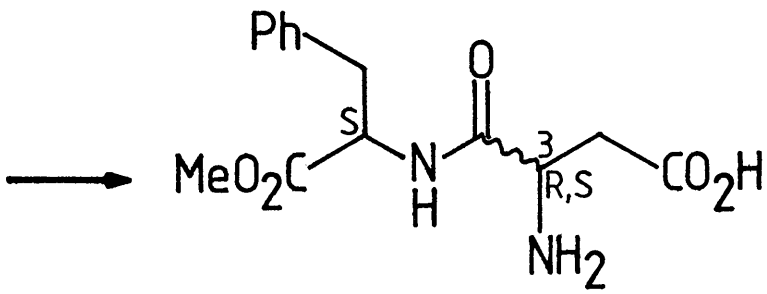
a R=CH_2Ph

b R=(R)-PhCHMe

c R=(S)-PhCHMe



(121a,b,c)



(3S) ; Aspartame,(95)

(3R) ; (R)-Asp-(S)-PheOMe,(122)

Scheme 43

3.4.1 Synthesis of the Chiral Isoxazolidinones (121a,b,c)

Cycloaddition of the N-benzyl nitrone (119a) with excess 2-chloroacrylonitrile (80°C, 15 mins) led regiospecifically to the 5,5-disubstituted adduct (120a) [100%]. The ^{1}H nmr spectrum at 90 MHz of (120a) showed complex continuous absorption (11H) between δ3 and δ5 and a complex multiplet (10H) at δ7.0-7.5. This was expected, resulting from the formation of four non-racemic diastereomers arising from transition states, analogous to those for the cycloaddition of chiral nitrones to vinyl acetate [Scheme 7, Introduction]. The adduct (120a) showed an unchanged ^{1}H nmr (90 MHz) spectrum after purification by silica gel chromatography (EtOAc/hexane 25:75, 93% recovery).

Hydrolysis of (120a) in aqueous tetrahydrofuran containing 0.2-0.4 equivalents of hydrochloric acid (20°C, 16-24h) afforded the isoxazolidinone (121a) in 82% yield after purification by silica gel chromatography (EtOAc/hexane 40:60). The ^{1}H nmr spectrum at 200 MHz of (121a) clearly revealed the presence of two diastereomers [Fig.8a]. The ratio of the two C-3 epimers was estimated as 5:2 [(3R):(3S)] from the relative integrals of the $C\underline{H}_3OCO$ signals in the ^{1}H nmr spectrum at 200 MHz [Fig.8b]. They were inseparable by glc (SE-54 capillary) and by chromatography on silica.

Cycloaddition of the N-(R)-α-methylbenzyl nitrone (119b) with excess 2-chloroacrylonitrile (80°C, 15 mins) afforded the adduct (120b) which was used without further purification. The spectroscopic properties of (120b) were analogous to those of (120a) with the changes to be expected for replacement of CH_2Ph by (R)-CHMePh.

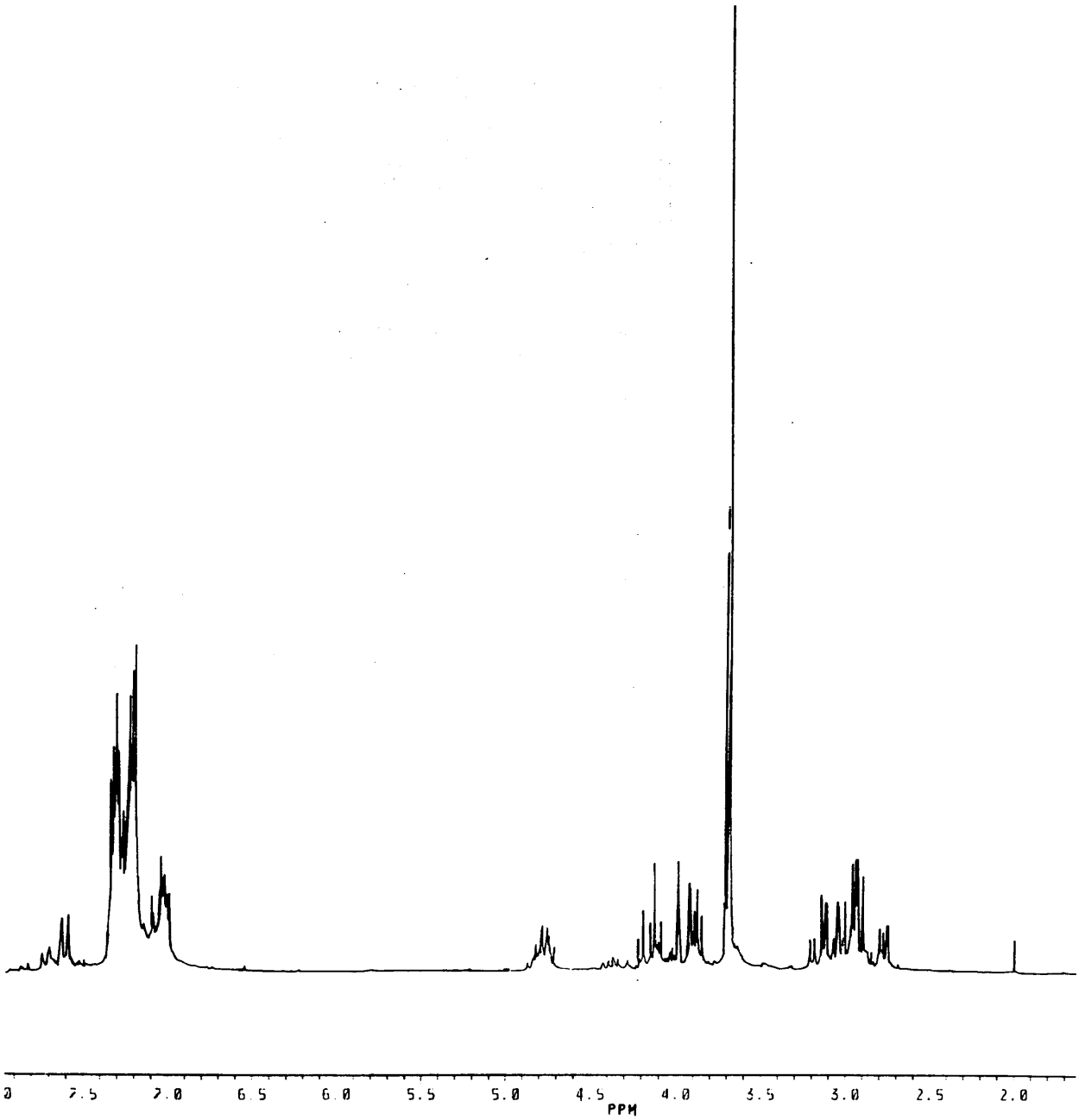


Fig. 8a ^{1}H nmr Spectrum of Isoxazolidinone (121a) at 200 MHz.

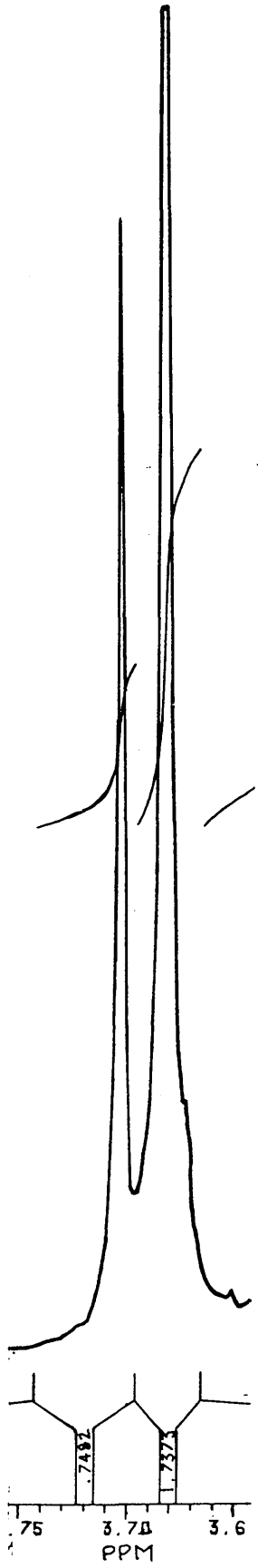


Fig. 8b ^{1}H nmr (200MHz) Expansion of CH_3OCO, Isoxazolidinone (121a).

Hydrolysis of (120b) [as for (120a)] afforded the isoxazolidinone (121b) in 83% yield after chromatography (SiO_2). The ^1H nmr spectrum at 200 MHz of (121b) again revealed the presence of two diastereomers, [Fig.9a]. The ratio of 2:3 [(3R):(3S)] was obtained from the relative integrals of the $CHC\underline{H}_3$ doublets in the ^1H nmr spectrum at 200 MHz, [Fig.9b]. Clearly, in nitrone (119b) [R=(R)-CHMePh], the two chiral directing groups were in conflict and cycloaddition was less diastereoselective than with the nitrone (119a) [R=CH_2Ph]. Fortunately, the major (3S)-isomer of (121b) was separable from the minor (3R)-isomer by chromatography over silica (see Experimental). Figure 10 shows the ^1H nmr (200 MHz) spectrum of (3S)-(121b) [containing approx. 12% of (3R)-(121b)].

Cycloaddition of the N-(S)-α-methylbenzyl nitrone (119c) with 2-chloroacrylonitrile (80°C, 15 mins) led regiospecifically to the 5,5-disubstituted cycloadduct (120c). The ^1H nmr spectrum (90 MHz) of (120c), although complex, appeared to be somewhat simpler than those of adducts (120a) and (120b). In particular, the presence of a broad singlet centred at δ3.70 ($C\underline{H}_3OCO$) and two overlapping doublets centred at δ1.49 ($CHC\underline{H}_3$) suggested that the adduct (120c) was present as a mixture of two diastereomers.

Hydrolysis of (120c) [as for (120a,b)] afforded the isoxazolidinone (121c) as a crystalline solid in 77% yield after chromatography (SiO_2). The ^1H nmr spectrum at 200 MHz [Fig.11a] and the ^{13}C nmr spectrum [Fig.11b] of (121c) clearly revealed the presence of a single diastereomer (3R). Thus, introduction of the second chiral centre,

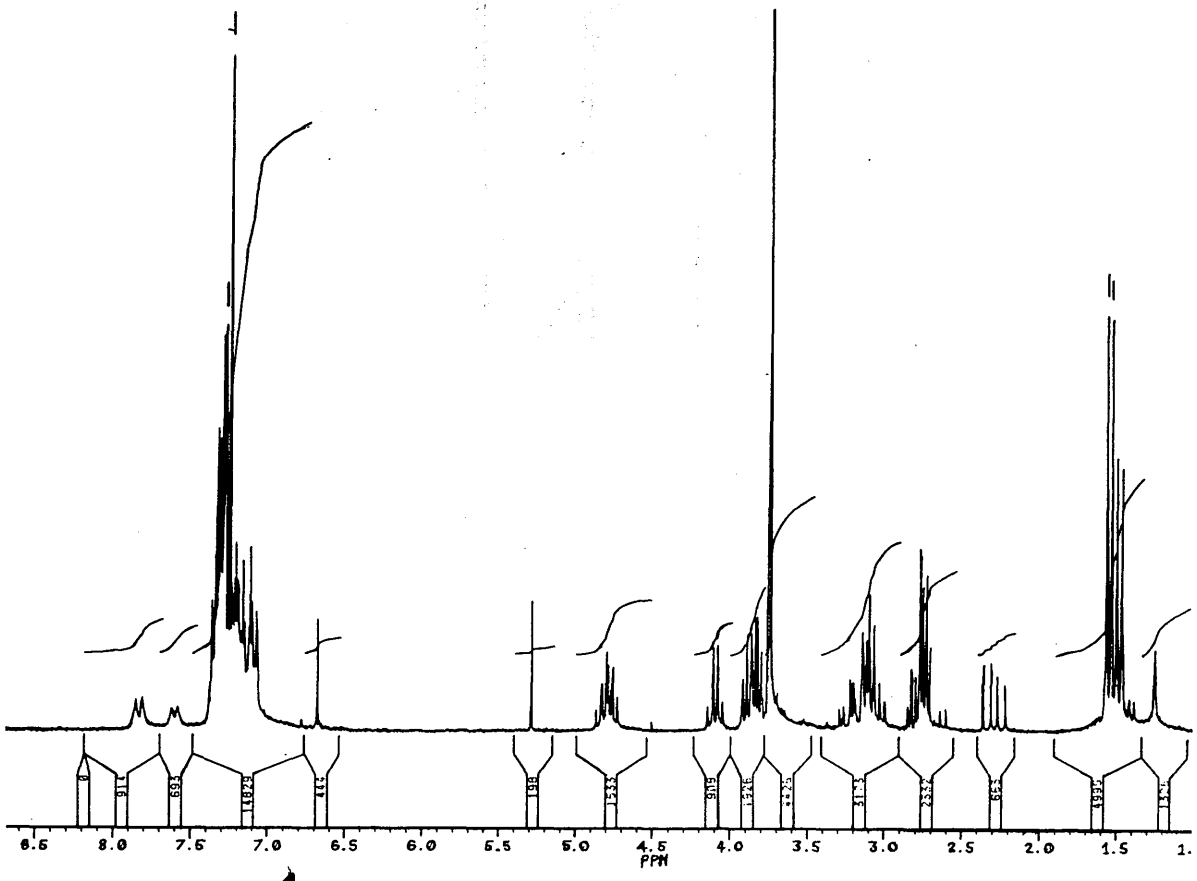


Fig.9a ^{1}H nmr Spectrum of Isoxazolidinone (121b) at 200 MHz.

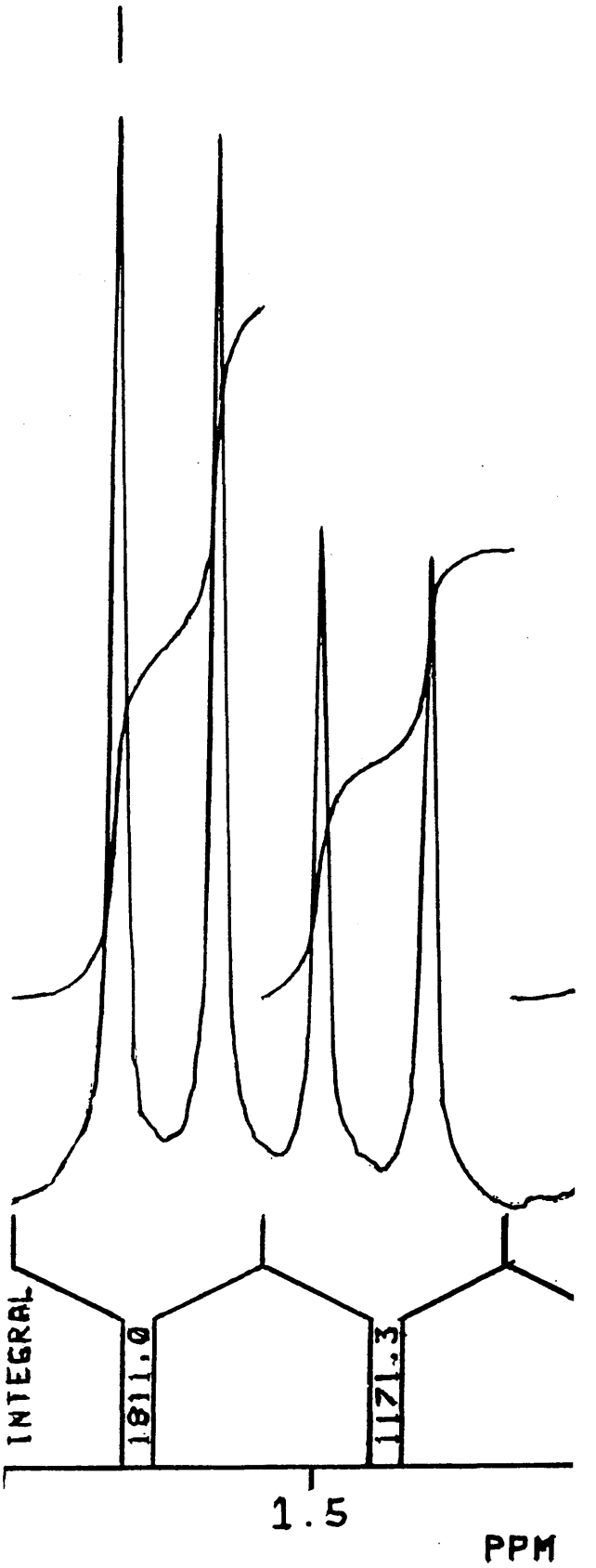


Fig. 9b ^{1}H nmr (200 MHz) Expansion of $CHC\underline{H}_3$, Isoxazolidinone (121b).

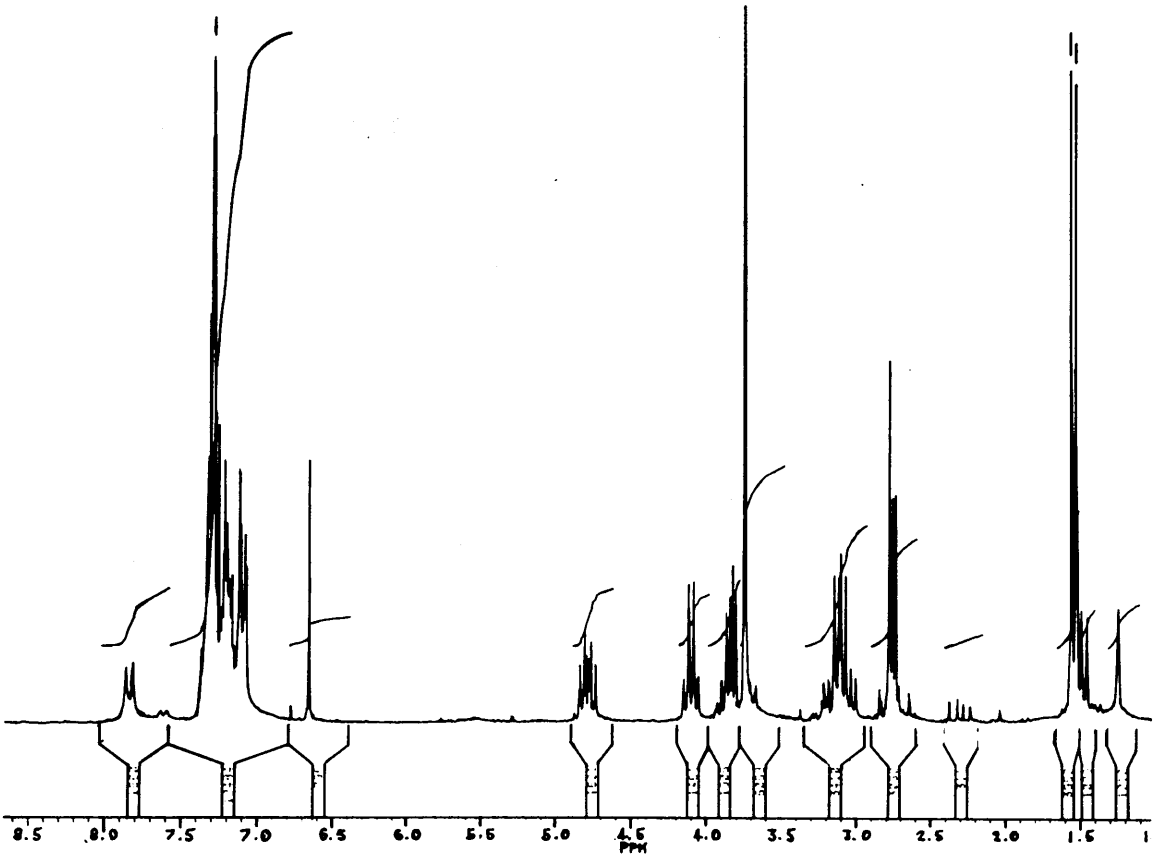
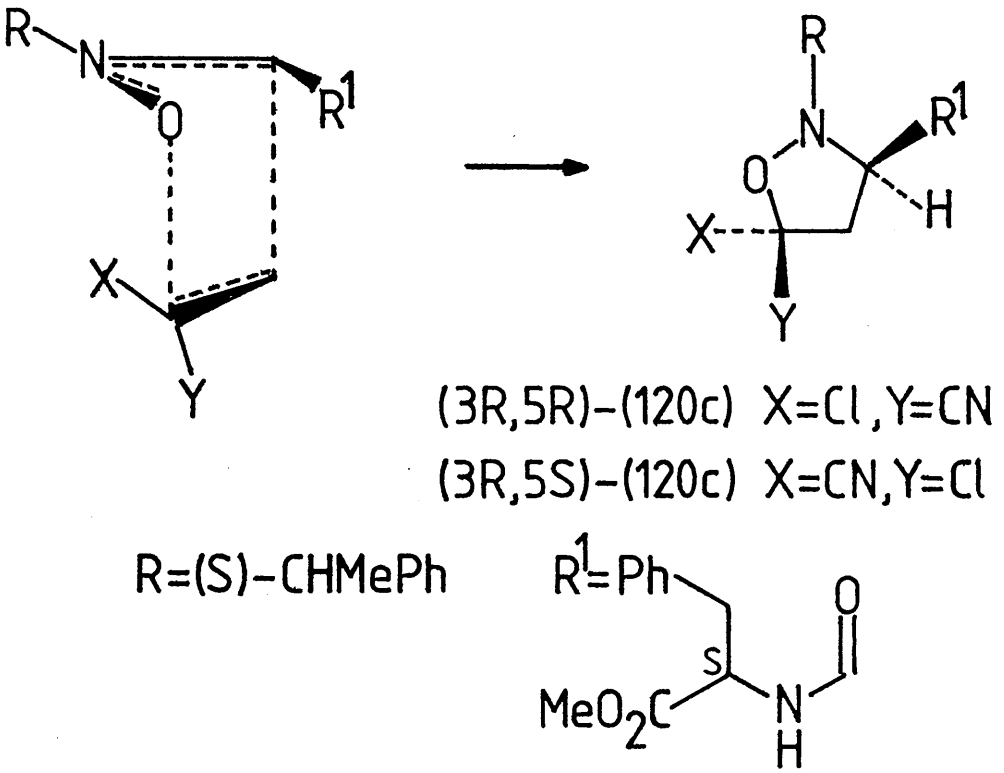


Fig.10 ^{1}H nmr Spectrum of Isoxazolidinone (3S)-(121b) at 200 MHz.

(S)-CHMePh, reinforced the directing effect[74] of (S)-PheOMe ensuring cycloaddition of 2-chloroacrylonitrile exclusively to the re, re face of nitrone (119c), [Scheme 44].



Scheme 44

The results of the cycloaddition of nitrones (119a,b,c) to 2-chloroacrylonitrile (80°C, 15mins) followed by hydrolysis of the resulting adducts to give isoxazolidinones (121a,b,c) have been summarised in Table 3.

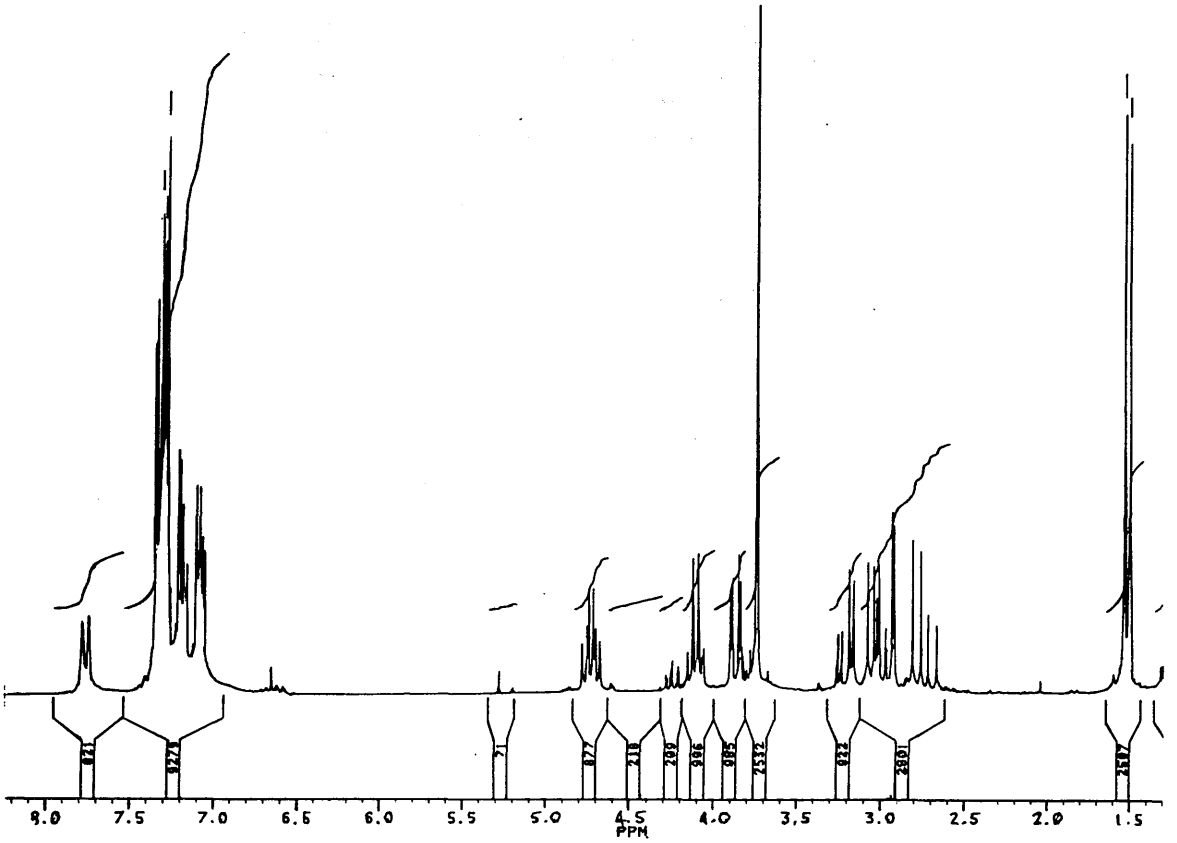


Fig. 11a ^{1}H nmr Spectrum of Isoxazolidinone (121c) at 200 MHz.

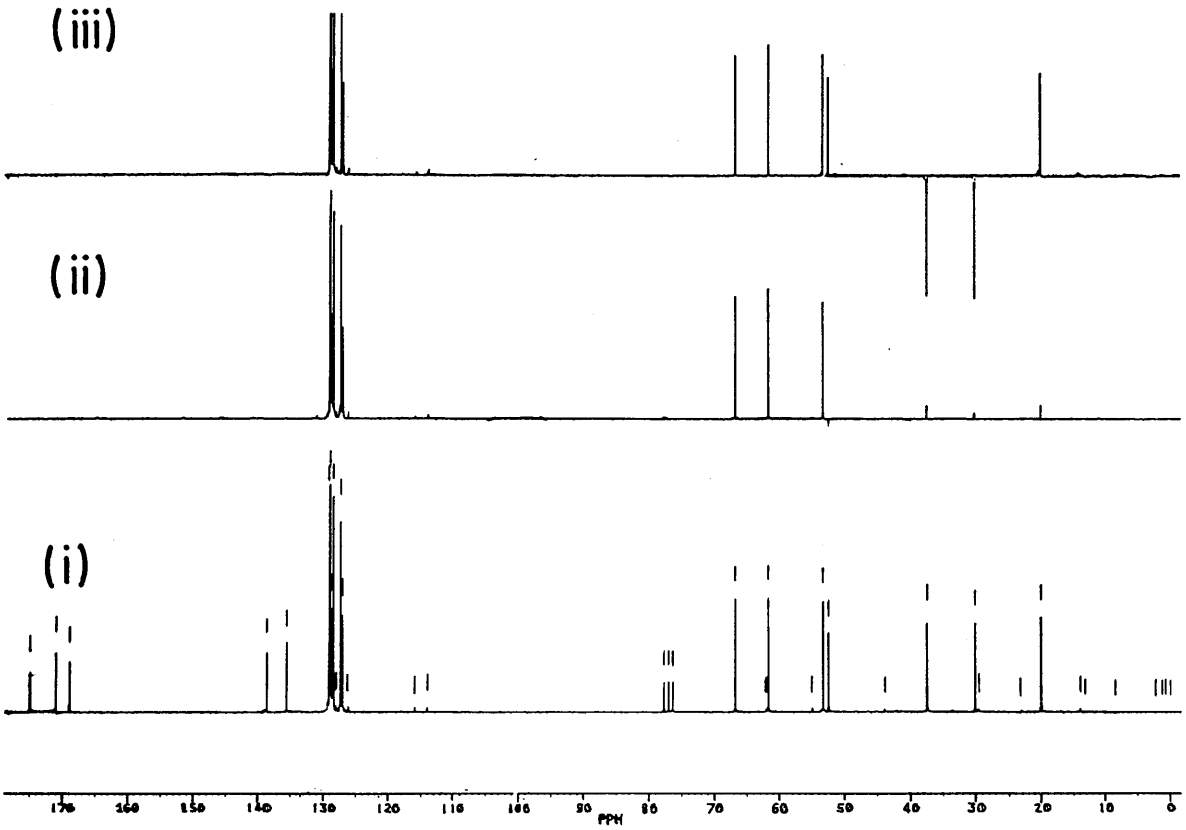


Fig. 11b (i) ^{1}H-Decoupled ^{13}C nmr Spectrum of Isoxazolidinone (121c). (ii) DEPT $\theta=90^{\circ}$. (iii) DEPT $\theta=135^{\circ}$.

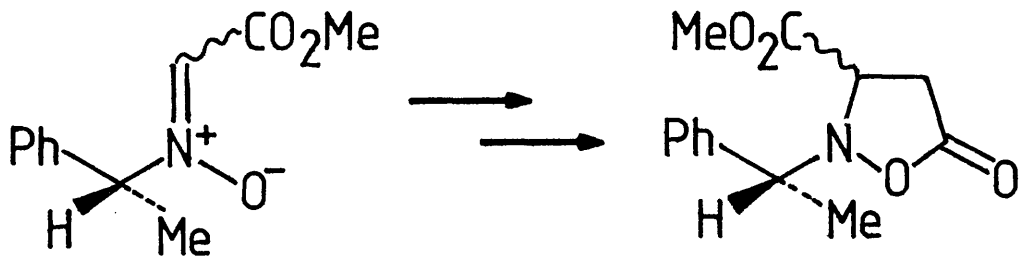
Table 3

Nitrone (119)	Isoxazolidinone (121) (3R:3S)[1]	% Yield [from Nitrones (119)]
a R=CH_2Ph	5:2	83
b R=(R)-CHMePh	2:3 (2:1)[2]	82 (52)[2]
c R=(S)-CHMePh	1:0	77

1. Stereochemical assignments follow from conversion into either aspartame (95) or (R)-Asp-(S)-PheOMe (122).

2. The figures in parentheses represent the ratio and yield of the two C-3 epimers of (121b) obtained after a 24 hour cycloaddition of nitrone (119b) followed by hydrolysis of the resulting adduct (120b). No such redistribution of products was observed in (121a) or (121c) resulting from cycloaddition of (119a) or (119c) to 2-chloroacrylonitrile at reaction times greater than 15 mins.

Cycloaddition of the α-methoxycarbonyl-N-(R)-α-methylbenzyl nitrone (123b) to 2-chloroacrylonitrile (80°C, 15 mins) followed by hydrolysis afforded the isoxazolidinone (124), [Scheme 45] in 59% yield after chromatography over silica.



(123b) (124)

Scheme 45

The ^{1}H nmr (90 MHz) spectrum of (124) showed the presence of two C-3 epimers in approximately 1:1 ratio [Fig.12]. Thus the nitrone (123b) proved useless for asymmetric cycloaddition to 2-chloroacrylontrile. and this approach was abandoned as a potential asymmetric route to aspartame.

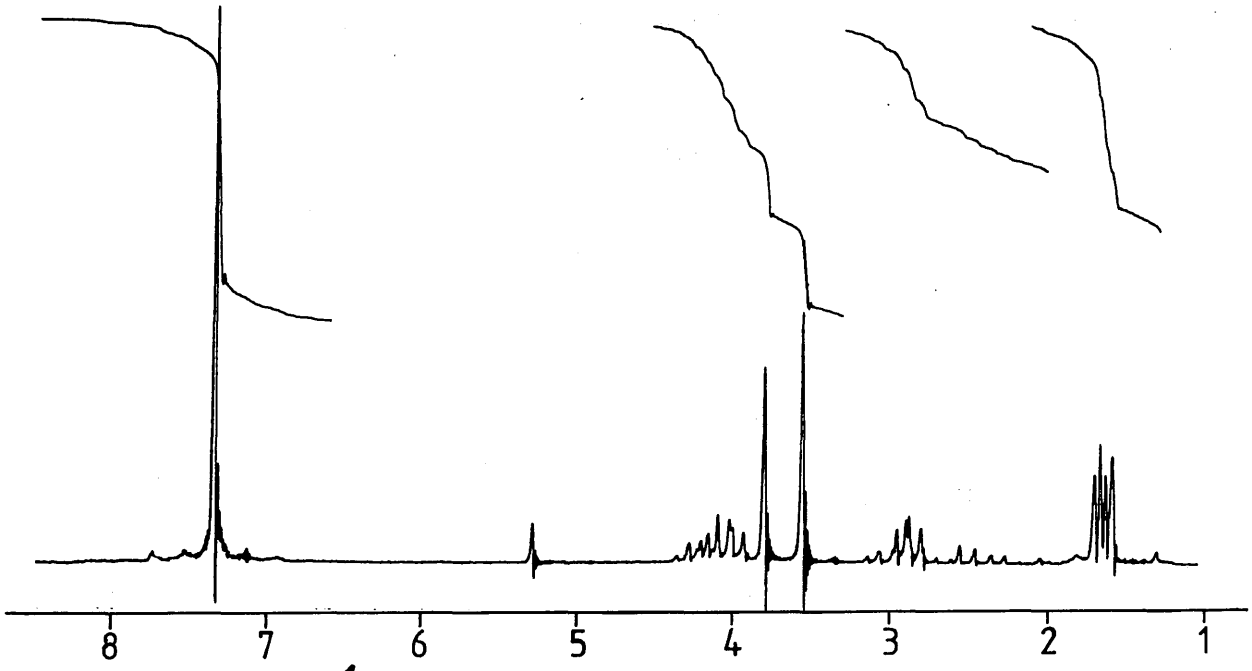


Fig. 12 ^{1}H nmr Spectrum of Isoxazolidinone (124) at 90 MHz.

3.4.2 Hydrogenolysis of Isoxazolidinones (121a,b,c)

Isoxazolidinone (3S)-(121b) was dissolved in ethanol/water (25 ml, 3:2) and the solution hydrogenated over $Pd(OH)_2$ on charcoal at atmospheric pressure and 70°C for 5h. Filtration and removal of solvent in vacuo afforded a white solid which was washed with chilled water[68] to remove the small amount of the highly water-soluble (R)-Asp-(S)-PheOMe (122), leaving the sweet-tasting aspartame, (S)-Asp-(S)-PheOMe (95) in 88% yield. The aspartame obtained in this manner was virtually identical (mp, $[\alpha]_D$, ^1H nmr [Fig.13], ^{13}C nmr and ir) with an authentic specimen.

Hydrogenation of the single isomer (121c) [as for (3S)-(121b)] afforded, quantitatively, the tasteless (R)-Asp-(S)-PhOMe (122), identified by mp and $[\alpha]_D$.[54] Not surprisingly the spectroscopic properties of (R)-Asp-(S)-PheOMe (122) showed very close correspondence with those of aspartame (95), as illustrated by the ^1H nmr (200 MHz) spectrum in d_6 dmso of (122) [Fig.14] compared with the ^1H nmr (200 MHz) spectrum in d_6 dmso of aspartame (95), [Fig.13].

Hydrogenation of the inseparable mixture (121a) under the above conditions but at 20°C afforded [100%] (R)-Asp-(S)-PhOMe (122) and (S)-Asp-(S)-PheOMe (95) in a 5:2 ratio as expected. (R)-Asp-(S)-PheOMe was easily established as the major component of the dipeptide mixture by correlation of the chemical shift values of the CH_3OCO singlets in the ^1H nmr (200 MHz) spectrum [Fig.15] with those of the diastereoisomerically pure (R)-Asp-(S)-PheOMe (122) and (S)-Asp-(S)-PheOMe (95) obtained via hydrogenolysis of isoxazolidinones (121c) and (3S)-(121b), respectively.

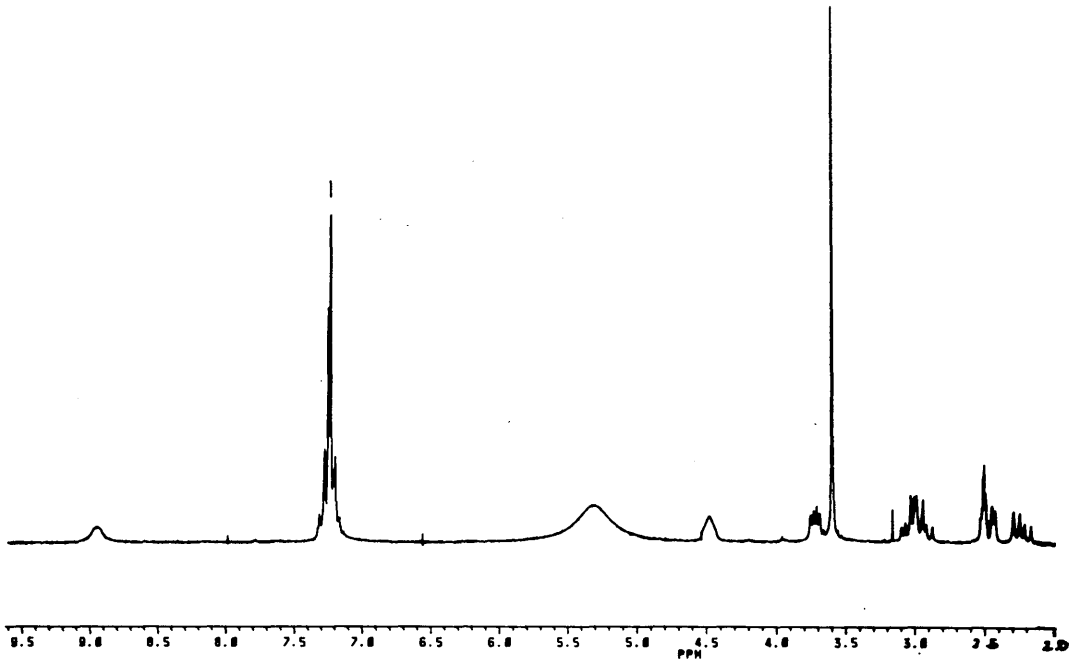


Fig.13 ^{1}H nmr Spectrum at 200 MHz ($d_6$dmso) of Aspartame (95) obtained via Hydrogenolysis of Isoxazolidinone (3S)-(121b).

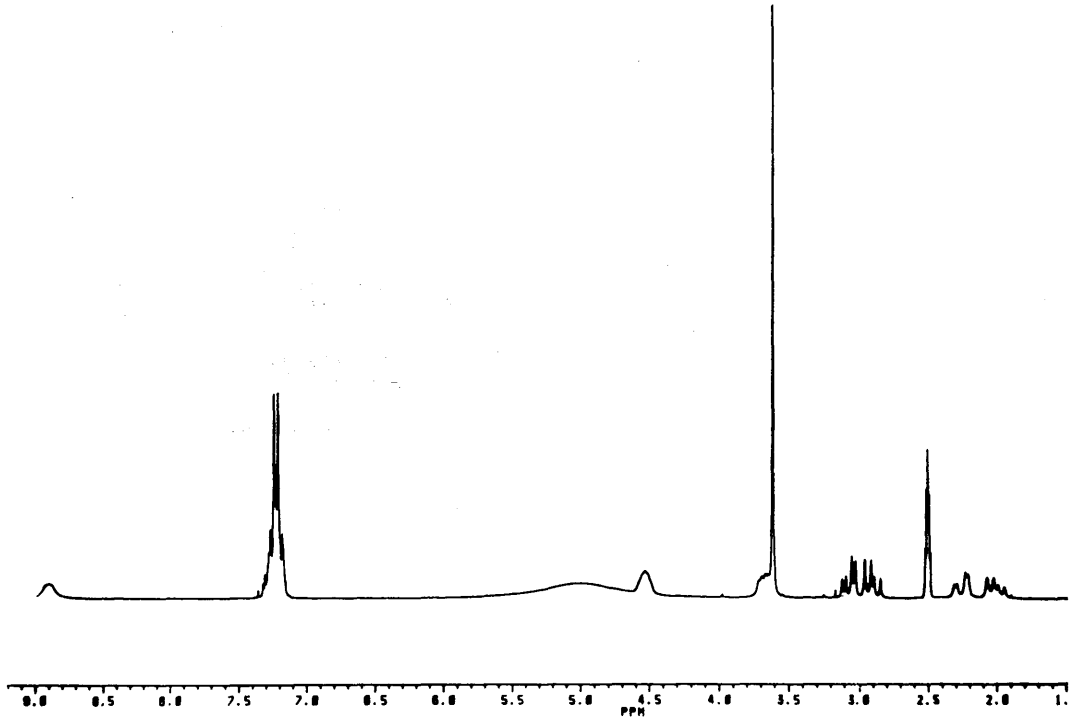


Fig.14 ^{1}H nmr Spectrum at 200 MHz ($d_6$dmso) of (R)-Asp-(S)-PheOMe (122) obtained via Hydrogenolysis of Isoxazolidinone (121c).

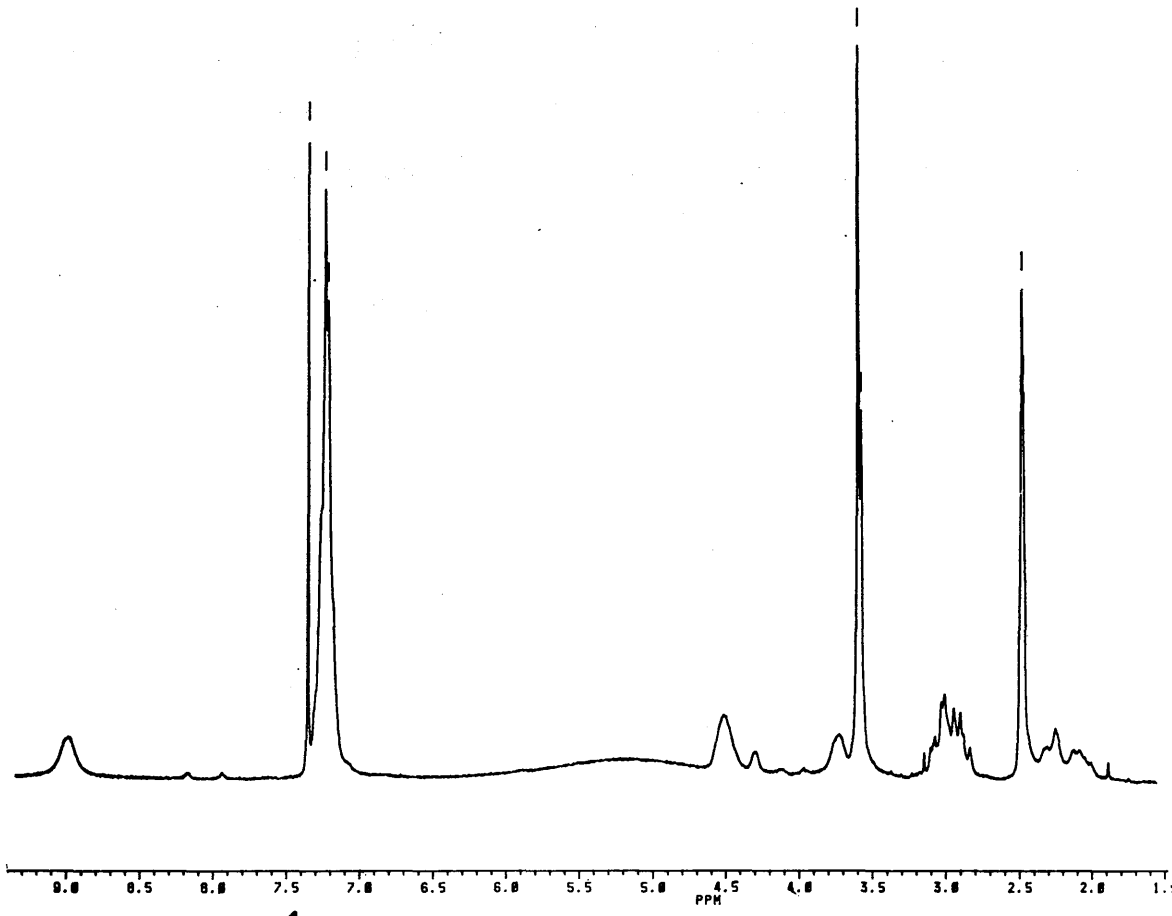
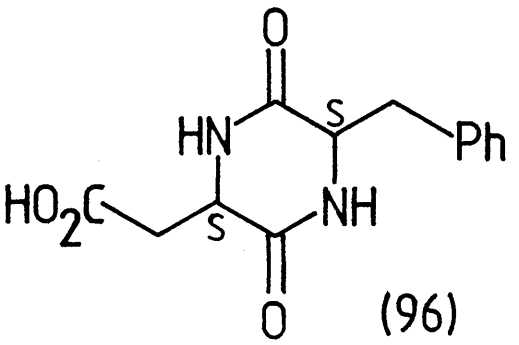


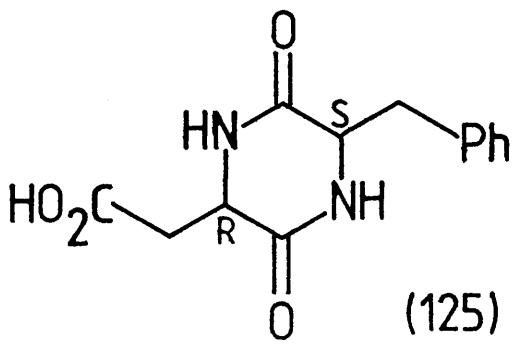
Fig. 15 ^{1}H nmr Spectrum at 200 MHz ($d_6$dmso) of Aspartame (95) and (R)-Asp-(S)-PheOMe (122) obtained via Hydrogenolysis of Isoxazolidinone (121a).

3.4.3 Rearrangement of (S)-Asp-(S)-PheOMe (95) and (R)-Asp-(S)-PheOMe (122)

Both (S)-Asp-(S)-PheOMe (95) and (R)-Asp-(S)-PheOMe (122) were shown to undergo intramolecular cyclisation, in d_6 dmso solution, to the diketopiperazines (96) and (125), respectively. This was clearly evident from the ^{13}C and ^{1}H nmr (200 MHz) spectra of the cyclised products, recorded after allowing the initial dipeptide solutions to stand at room temperature for a period of one week.



(96)



(125)

Thus the broad NH singlet, centred at δ8.95 in the ^{1}H nmr (200 MHz) spectrum of (S)-Asp-(S)-PheOMe [Fig.16], had completely disappeared after a period of one week to be replaced by two doublets centred at δ7.89 and δ8.16 for the two NH-protons of the diketopiperazine (96), [Fig.17]. The ^{13}C nmr spectrum of (96), [Fig.18] was devoid of the $CO_2\underline{C}H_3$ (δ51.99) and $\underline{C}O_2CH_3$ (δ171.63) signals, initially present in the ^{13}C nmr spectrum of aspartame (95). (R)-Asp-(S)-PhOMe (122) likewise showed corresponding spectroscopic changes

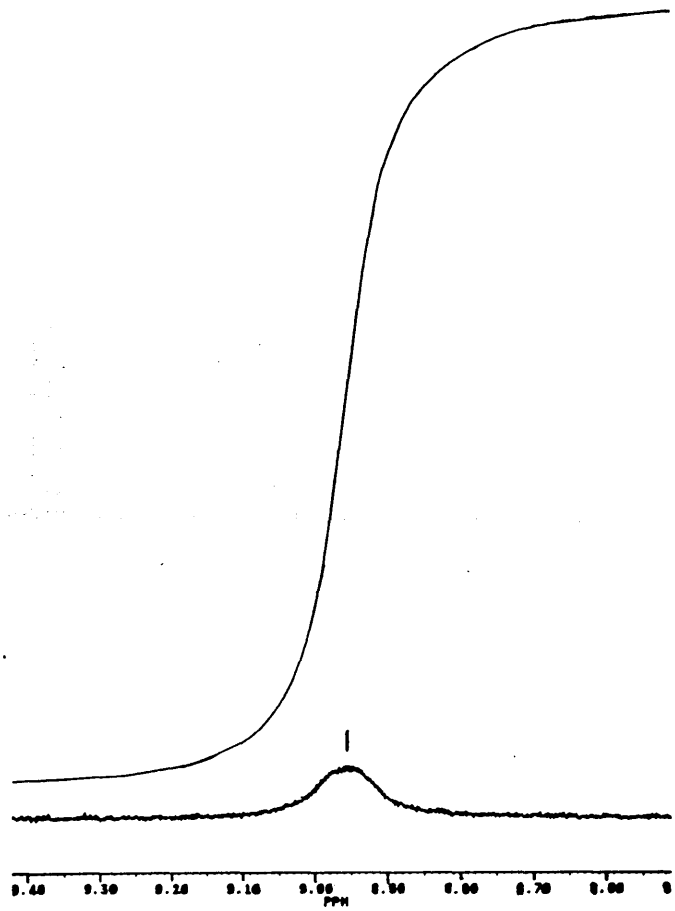


Fig.16 ^{1}H nmr (200 MHz) Expansion of N<u>H</u>CO, Aspartame (95).

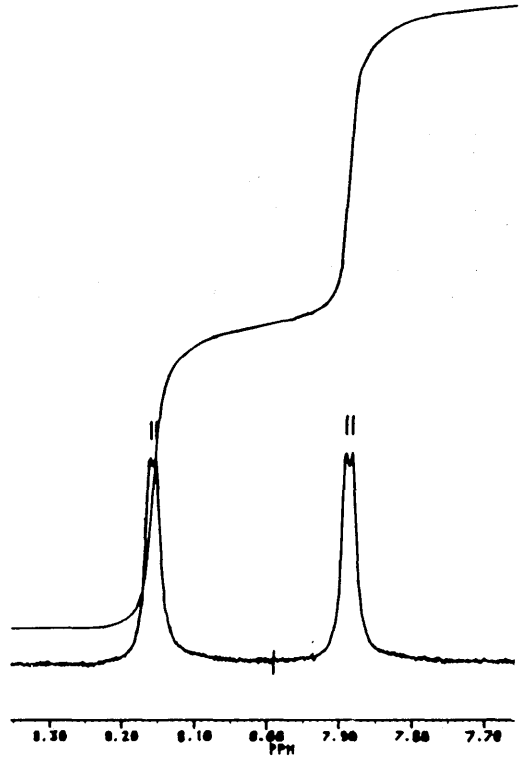


Fig. 17 ^{1}H nmr (200 MHz) Expansion of N<u>H</u>CO (×2), Diketopiperazine (96) [From (95) after 1 week in $d_6$dmso].

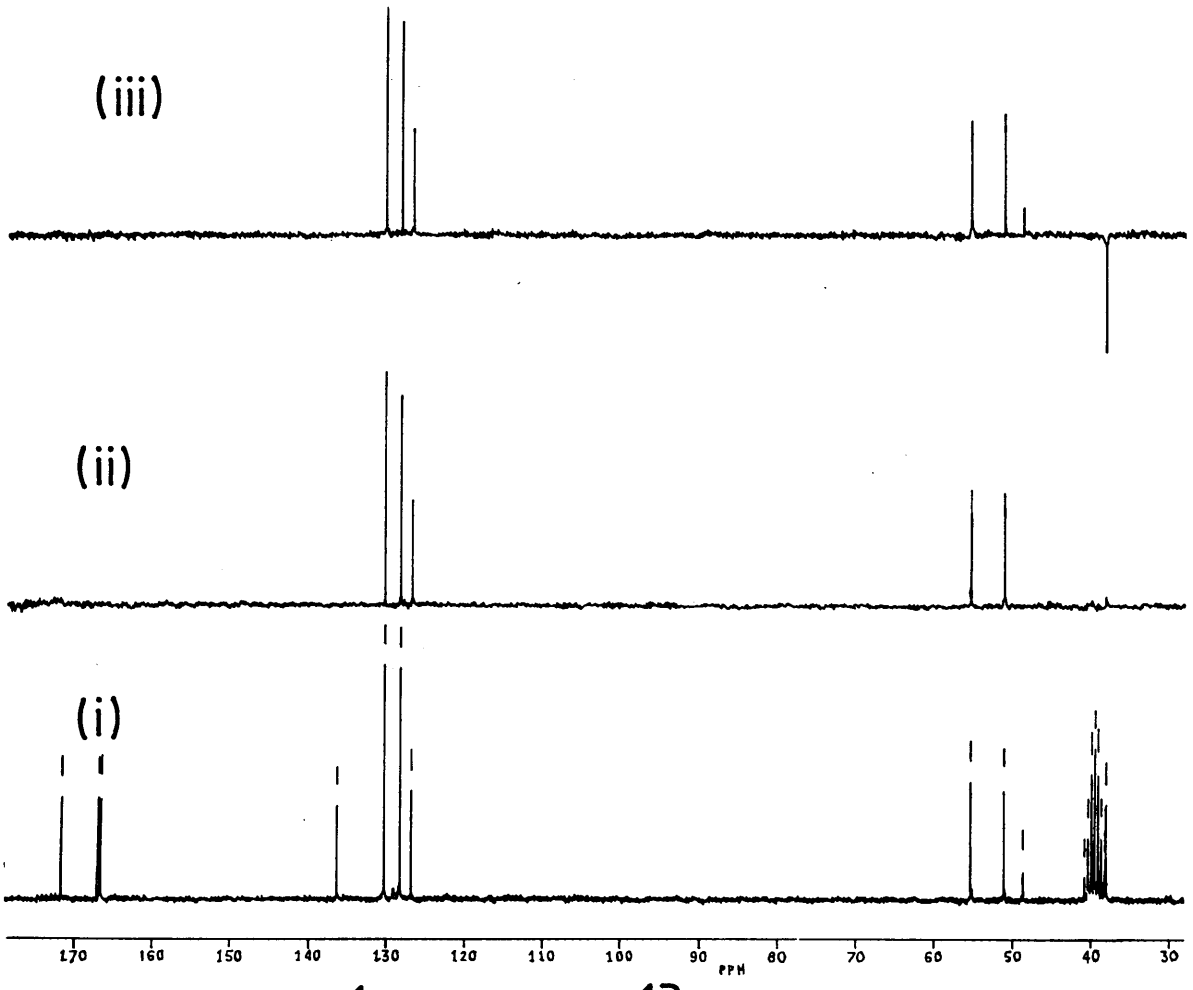


Fig.18 (i) ^{1}H-Decoupled ^{13}C nmr Spectrum of Diketopiperazine (96). (ii) DEPT $\theta = 90^{\circ}$. (iii) DEPT $\theta = 135^{\circ}$.

consistent with rearrangement to the diketopiperazine (125) [see Experimental]. The cyclisation of aspartame to form the diketopiperazine (96) is a well known phenomenon,[55-57] as mentioned earlier.

3.5 SUMMARY

The sequence which was used to synthesise stereoselectively the natural β-amino acids β-leucine, β-phenylalanine, β-tyrosine[26] and β-lysine[45] was successfully applied to the asymmetric synthesis of aspartame (95) [and (R)-Asp-(S)-PheOMe (122)]. The synthesis of chiral isoxazolidinones was achieved very efficiently employing the ketene equivalent, 2-chloroacrylonitrile. This was found to be much superior to vinyl acetate as a dipolarophile since it avoided the low-yielding oxidation step required to transform the initial adducts into isoxazolidinones.

Very respectable induction was obtained by efficient transfer of chirality to the newly generated α-aspartyl chiral centre by PheOMe in the absence of a chiral auxiliary at the N-terminus of the nitrone (119a). Introduction of a second chiral centre at N (either (R)- or (S)-CHMePh) had a dramatic effect. Most striking was the fact that nitrone (119c) [R=(S)-CHMePh] led to a single isoxazolidinone (121c). Unfortunately, hydrogenolysis of (121c) led to the tasteless (R)-Asp-(S)-PheOMe (122). However, the major (3S)-isomer of (121b), separable from the minor (3R)-isomer by chromatography, led to the sweet-tasting aspartame (S)-Asp-(S)-PheOMe (95).

This work has established a potential general asymmetric route to aspartyl dipeptides which does not depend on a protocol for

coupling of the natural amino acids and does not suffer the problem of differentiating between the α- and β-carboxyl groups of (S)-aspartic acid.

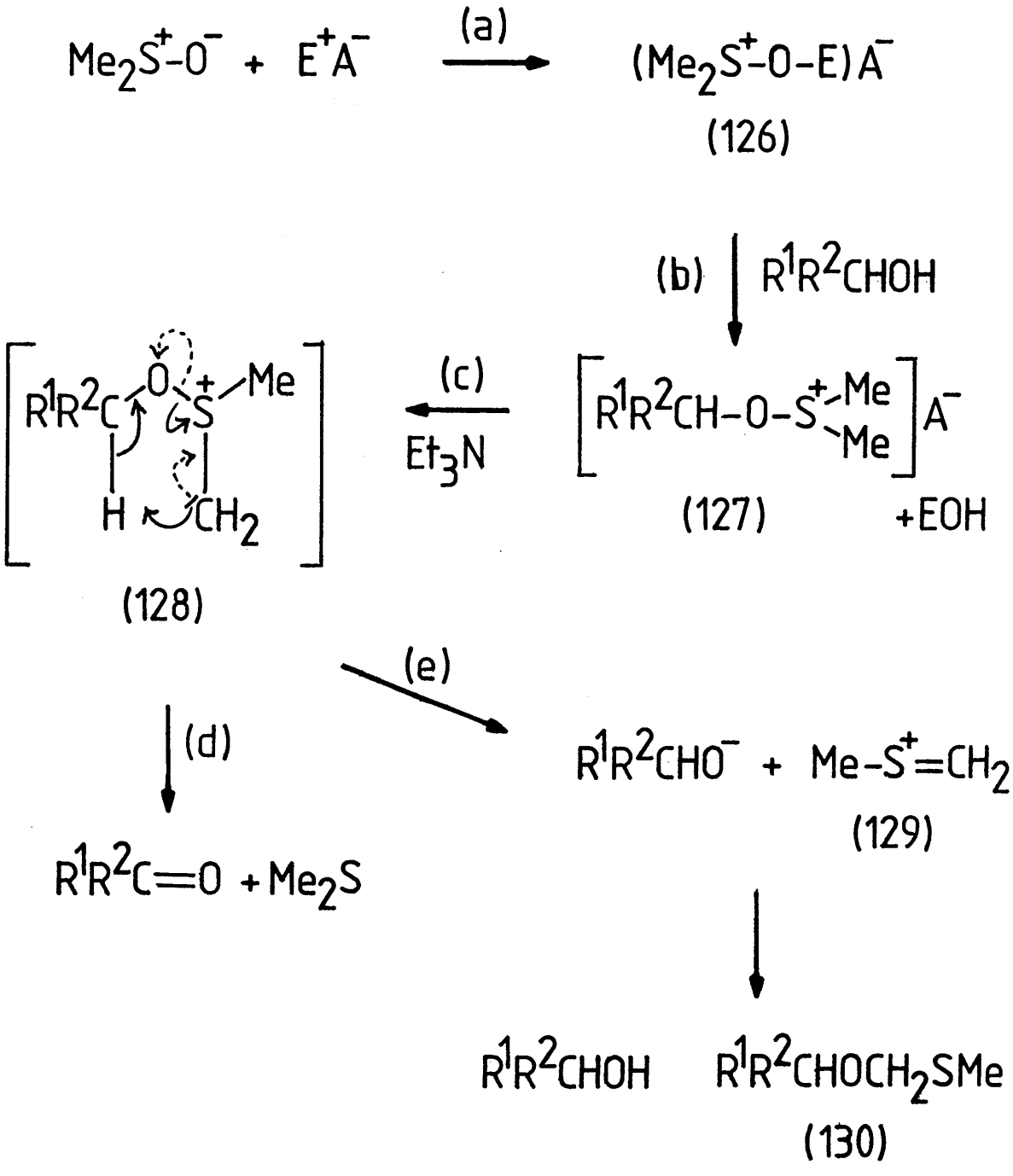
CHAPTER 4

Conversion of Amines into Imines by Swern Oxidation

4.1 BACKGROUND

The Swern oxidation of alcohols which involves dimethyl sulphoxide (DMSO) activated by one of a range of electrophiles is a widely used reaction. It works well with primary, secondary, allylic, benzylic, and also hindered alcohols. Compared with other oxidising agents it is relatively tolerant of additional functionality.[75] The mechanism of formation of carbonyls using Swern reagents is outlined in Scheme 46 and involves (a) activation of DMSO by a suitable electrophilic reagent (E^+A^-) below the Pummerer rearrangement temperature of the intermediate (126); (b) facile attack by an alcohol on the electropositive sulphur atom of the intermediate (126) with loss of a leaving group (EO^-) to form a dimethylalkoxysulphonium salt (127); (c) base, typically triethylamine, removes a proton from the methyl group of (127) to form the ylide (128); (d) the ylide (128) collapses to carbonyl and dimethyl sulphide by an intramolecular hydrogen transfer [Scheme 46, solid arrows]; (e) ylide (128) may alternatively collapse to methyl methylenesulphonium (129) and alkoxide ions [Scheme 46, dotted arrows]. Alkoxide ion can either remove a proton from the system to reform alcohol or recombine with (129) to form alkyl methylthiomethyl ether (130).

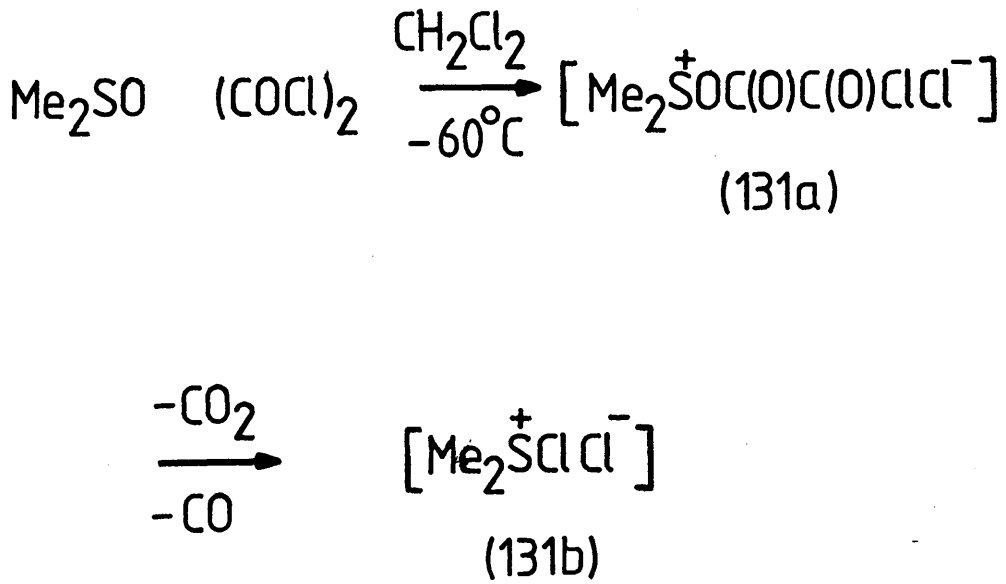
Of all the activators thus far studied, oxalyl chloride [$(COCl)_2$] is by far the most efficient,[75,76] based on yields of carbonyls, speed and ease of manipulation, general applicability to virtually all types of alcohols, relative insensitivity to reaction time and temperature, and high reactivity between -60°C and -20°C in


Me2S+-O- + E+A-
(a)
(Me2S+-O-E)A-
(126)
(b)
R1R2CHOH
[R1R2CH-O-S+(Me)(Me)]A-
(127)
+EOH
(c)
Et3N
[R1R2C(O)S+(Me)H CH2]
(128)
(d)
R1R2C=O + Me2S
(e)
R1R2CHO- + Me-S+=CH2
(129)
R1R2CHOH
R1R2CHOCH2SMe
(130)

Scheme 46

various solvents. Side reactions are minimal and the methylthiomethyl ether by-product usually comprises no more than 3-4% of the reaction product. The DMSO-$(COC\ell)_2$ reagent is particularly efficient for the mild oxidation of long-chain saturated alcohols.[76] Conversion to the corresponding aldehydes proceeds virtually quantitatively and is limited only by the solubility of the alcohol in the solvent system ($CH_2C\ell_2$-DMSO) at low temperatures.

Swern et al.[77] have used low-temperature ^{13}C nmr and ir coupled with chemical evidence to show that the activated intermediate arising from addition of DMSO to $(COC\ell)_2$ in dichloromethane at -60°C is (131b) which is derived from (131a) by virtually instantaneous loss of CO_2 and CO, [Scheme 47].

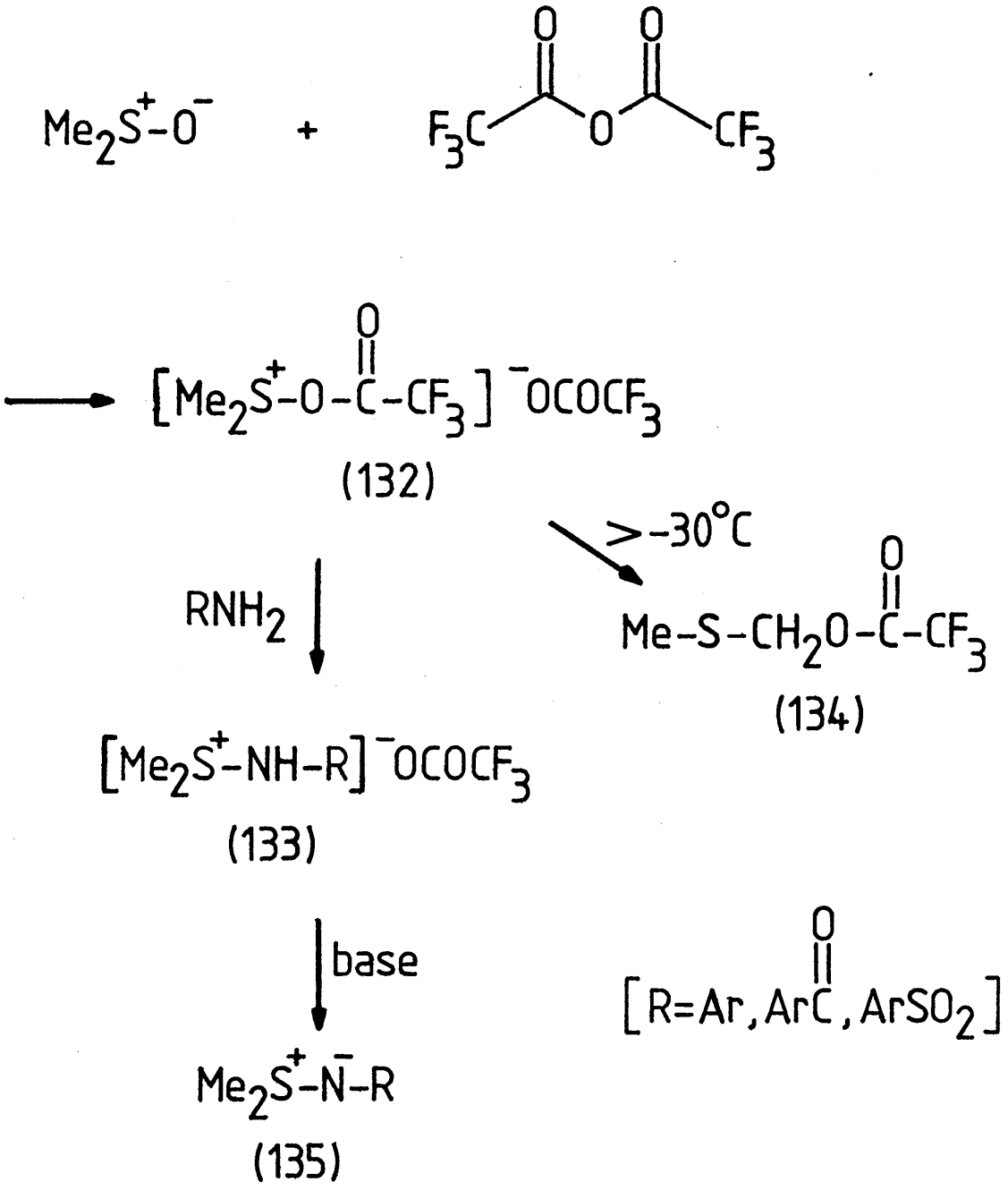


Scheme 47

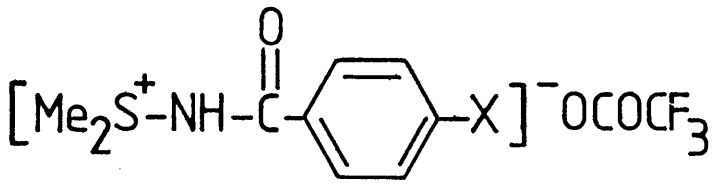
Intermediate (131b) is the same as that obtained by Corey and Kim from chlorine and dimethyl sulphide at low temperature.[78,79]

Prior to the above work Swern had carried out extensive studies on the preparation of iminosulphuranes from amines using activated DMSO reagents.[80,81] The most efficient activator for this transformation is trifluoroacetic anhydride (TFAA).[81] The mechanism of formation of iminosulphuranes from aryl amines, aryl amides and aryl sulphonamides using DMSO-TFAA reagent is outlined in Scheme 48. DMSO and TFAA react almost instantly and exothermically at -60°C in dichloromethane to give the intermediate (132) which is stable below -30°C. On warming, the Pummerer rearrangement product (134) forms. Reaction of (132) with certain aromatic amines, amides and sulphonamides gives the iminosulphonium salts (133) which, after basification (when required) with triethylamine or 5-10% aqueous sodium hydroxide affords the iminosulphuranes (135) in 40-90% yields. The order of reactivity of $R\text{-}NH_2$ is aromatic amines > aryl sulphonamides > aryl amides, reflecting the relative nucleophilicities of the amino functions in each reagent.

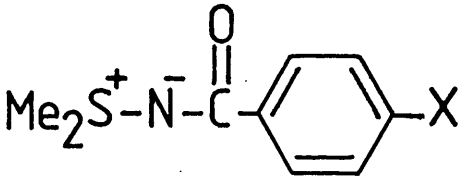
Aromatic amides are sufficiently nucleophilic to form N-acyliminosulphuranes in excellent yield with the DMSO-TFFA reagent. With benzamide, addition of base is essential to obtain the ylide (137) from the N-acyliminosulphonium salt (136). With p-nitrobenzamide, the ylide (139) precipitates during the reaction and does not require basification to obtain almost pure product in 90% yield. The additional acidity of the NH proton resulting from the p-nitro group shifts the equilibrium almost quantitatively from salt (138) to ylide (139).


Me2S+-O-
+
F3C
O
O
O
CF3
[Me2S+-O-C(=O)-CF3] -OCOCF3
(132)
>-30°C
RNH2
Me-S-CH2O-C(=O)-CF3
(134)
[Me2S+-NH-R] -OCOCF3
(133)
base
[R=Ar, ArC(=O), ArSO2]
Me2S+-N--R
(135)

Scheme 48



X=H, (136)
X=NO_2, (138)



X=H, (137)
X=NO_2, (139)

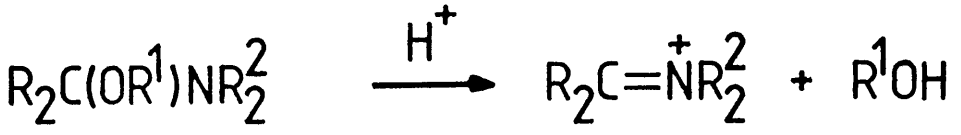
With sulphonamides basification is not required as the NH proton is readily lost and the ylides precipitate from the reaction mixture.

4.2 THE CONVERSION OF AMINES INTO IMINES[82]

There are very few good methods, particularly in non-polar solvents, for amine to imine conversion.[82] One of these is the elimination reaction of N-substituted amines. Amines substituted on the nitrogen by anionic leaving groups, X eliminate HX easily, and a C=N bond is formed. Thus N-haloamines are converted to imines by alkalis or just by heating. N-aryl sulphonamides, especially N-tosyl derivatives, also undergo elimination under the influence of strong base, [Scheme 49].

Scheme 49

This reaction requires an easily removable α-hydrogen and compounds of the type $RCH_2N(Ph)Ts$ undergo elimination by the action of alkoxides in toluene at room temperature when R is a fairly strong electron-withdrawing group. Sulphonamides of primary amines do not undergo this elimination, since the N-hydrogen is abstracted by base more easily than the C-hydrogen. Eliminations from substituted amines in which the leaving group is on the α-carbon are also well known. The elimination of water or an alcohol from α-hydroxy or alkoxyamines is the final step in the condensation of amines with carbonyl compounds or their acetals, [Scheme 50].



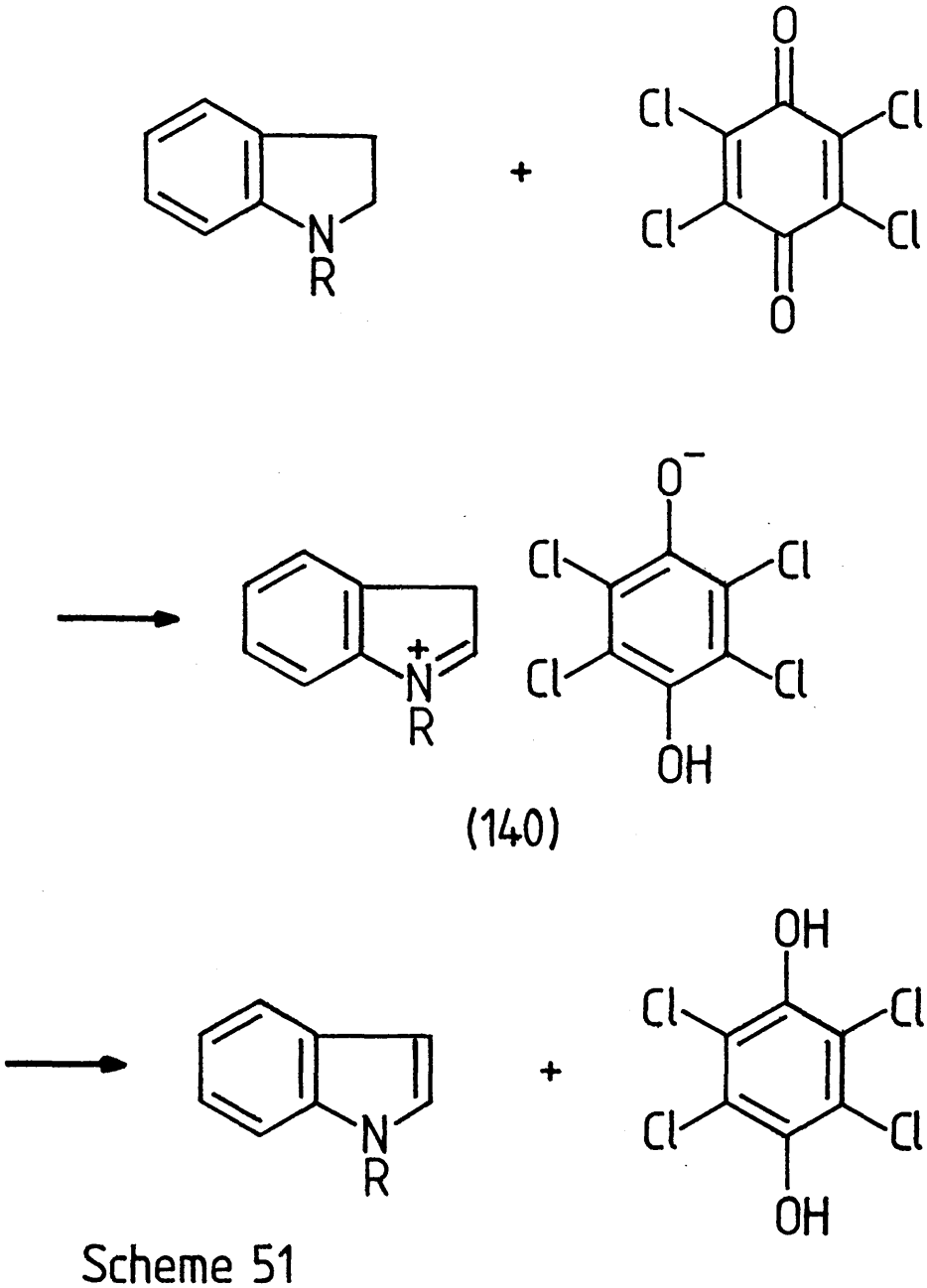
Scheme 50

Compounds containing C=N bonds are only seldom prepared by oxidation or dehydrogenation of amines. Even when C=N bonds are formed initially, and further oxidation is avoided, the imines formed

are usually hydrolysed to carbonyl compounds or converted into secondary reaction products. Dehydrogenation of a secondary amine containing an α-hydrogen can be effected either catalytically or by an organic hydrogen acceptor such as formamide in a reaction involving hydride transfer. Oxidation of amines usually does not stop at the imine stage, but proceeds further to give oximes (from primary amines) or nitrones (from secondary amines).

4.3 CONVERSION OF INDOLINES INTO INDOLES[83-86]

The various methods of converting indolines into indoles has been reviewed by Preobrazhenskaya.[83] The most popular oxidising agent is chloranil (tetrachlorobenzoquinone) usually in a high boiling solvent such as xylene since heat accelerates the rate of dehydrogenation. It is assumed that the beginning of the dehydrogenation process involves removal of a hydride ion from the indoline, this being facilitated by the high electron-donor capacity of the >NR groups, [Scheme 51]. The intermediate (140) thus produced is then converted into indole and hydroquinone. Chloranil or 2,3-dichloro-4,5-dicyano-p-benzoquinone in boiling xylene also converts 7-azaindolines into the corresponding 7-azaindoles.[85a] The high redox potential of these two reagents is sufficient to overcome the increased resistance to dehydrogenation caused by the electron-withdrawing properties of the nitrogen atom in the aryl ring of the azaindolines. The introduction of electron-withdrawing substituents into the benzene ring of indolines also increases their resistance to dehydrogenation to the indole.

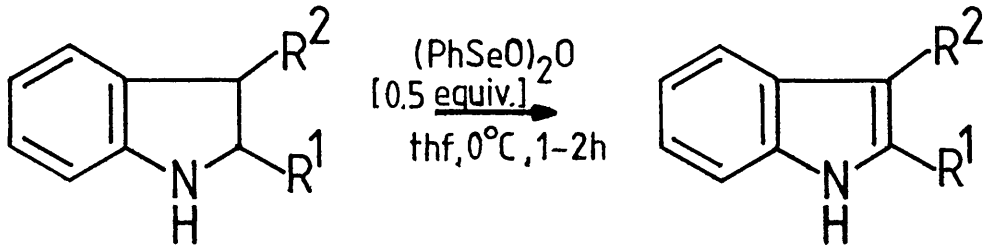


(140)

Scheme 51

Some azaindolines have been converted into the azaindoles in good yield by treatment with sodium in liquid ammonia.[83,85a]

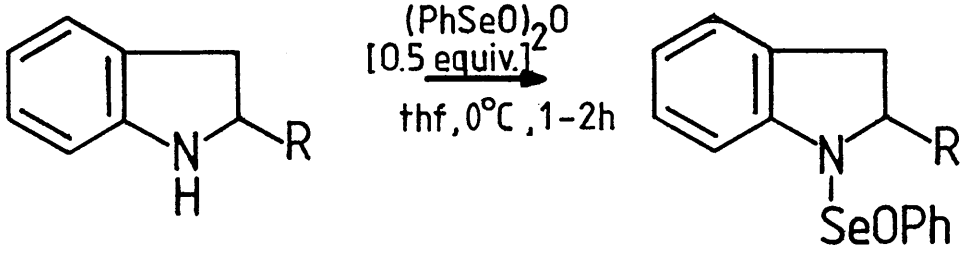
Palladium black and palladium on charcoal are also widely used in the dehydrogenation. Hydrogen acceptors such as nitrobenzene or cinnamic acid are frequently added in such reactions. The catalytic dehydrogenation of indolines using Raney nickel is

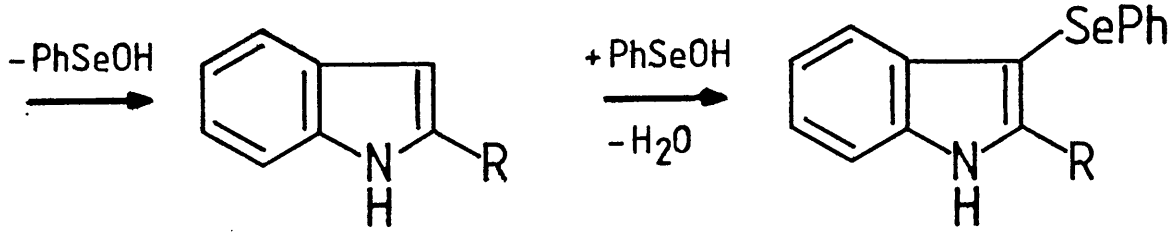


R^1=H or alkyl

R^2=alkyl

Scheme 52





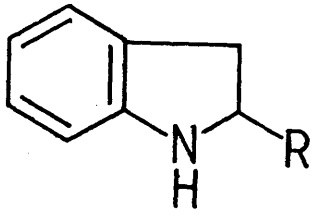
R=H or alkyl

Scheme 53

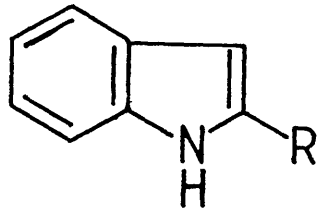
another method. This procedure causes simultaneous dehydrogenation of the pyrroline ring and reduction of any other reducible groups such as halo or nitro in the indoline molecule. The oxidation of indolines with atmospheric oxygen under various conditions is also possible. Oxidation of indolines with manganese dioxide in benzene has been achieved. Dinitroindolines can be oxidised to indoles with nitric acid, the oxidation being accompanied by the nitration of the pyrrole ring of the indole.[83] More recently Barton[86] has reported that phenylseleninic anhydride reacted rapidly with indolines at 0°C to give, when the 3-position is substituted, the corresponding indoles [Scheme 52]. When the 3-position is unsubstituted, 3-phenylselenoindoles were formed, [Scheme 53]. These were readily reduced by nickel boride to the parent indole. Yields ranged from 50-96%. The work presented in this chapter describes the mild and simple conversion of indolines into indoles under standard Swern conditions.

4.4 RESULTS AND DISCUSSION

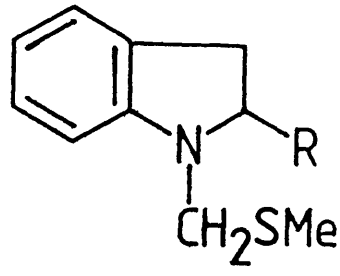
Swern reagents have not been used previously for the dehydrogenation of amines to imines. This is surprising in view of Swern's substantial early work on the conversion of amines into iminosulphuranes.[80,81] Of even greater interest would be a mild and simple general method for the conversion of indolines into indoles.[83-86] The Swern oxidation has now been extended very successfully to accomplish this transformation. Thus, indoline (141) and 2-methylindoline (142) were converted into indole (143) and 2-methylindole (144) respectively, in yields approaching 90%. The only other products in



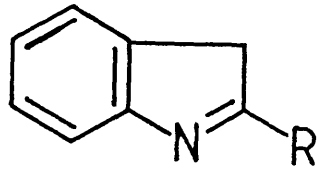
(141) R=H
(142) R=Me



(143) R=H
(144) R=Me



(145) R=H
(146) R=Me



(147) R=H
(148) R=Me

$PhCH_2NHCH_2Ph$

(149)

$PhCH_2NHPh$

(150)

$PhCH{=}NCH_2Ph$

(151)

$PhCH{=}NPh$

(152)

$PhCH_2N(CH_2Ph)CH_2SMe$

(153)

$PhCH_2N(Ph)CH_2SMe$

(154)

each case, apart from about 1% of unchanged indoline, were the methylthiomethyl amines (145) and (146). The reactions were carried out under the same conditions as for the conversion of alcohols to carbonyls using DMSO activated by $(COC\ell)_2$[75,76] (see Experimental). Yields of indole (143) and 2-methylindole (144) were obtained by glc analysis (2% SE 52 on GCQ at 115°C) of the total crude products. The reaction mixture resulting from treatment of indoline (141) with the DMSO-$(COC\ell)_2$ reagent consisted of indole (143) [87.5%], the methylthiomethyl amine (145) [11.2%] and indoline (141) [1.3%]. Bulb-tube distillation afforded indole which was identical (mp, glc, nmr, ms) with an authentic specimen, and a residue consisting essentially of the by-product (145). 2-Methylindoline (142) similarly afforded 2-methylindole (144) [88.3%] and the oily by-product (146) [10.6%] which were separable by chromatography over SiO_2.

The mechanism of formation of indole (143) and 2-methylindole (144) and the methylthiomethyl amines (145) and (146) under Swern conditions is presumably analogous to the mechanism of formation of carbonyls and methylthiomethyl ethers from alcohols under the same conditions [cf. Scheme 46]. The success of the reactions is probably due to the low basicity of (141) and (142) allowing nucleophilic attack at the electropositive sulphur atom of the activated intermediate. In both cases the indolenines (147) and (148) are likely to be formed initially followed by tautomerisation to indole (143) and 2-methylindole (144) respectively.

Dibenzylamine (149) by the same procedure afforded the Schiff base (151) [63.4%], identical (ir, nmr, ms) with an authentic

sample prepared from benzylamine and benzaldehyde, and readily separated by bulb-tube distillation from the methylthiomethyl amine (153) [36.6%]. Similarly, phenylbenzylamine (150) afforded the Schiff base (152) [52.5%] and the methylthiomethyl amine (154) [47.5%] which were inseparable. In the cases of both dibenzylamine (149) and phenylbenzylamine (150), product yields were based on ^{1}H nmr (90 MHz) analysis of the crude mixtures.

In no case, did a variation in solvent, activator or the use of bases other than triethylamine lead to improved yields.

4.5 SUMMARY

The Swern oxidation has been very successfully applied, for the first time, to the conversion of amines into imines. This transformation compares favourably with the few existing methods.[82] The procedure also provides a mild and simple general method for the conversion of indolines into indoles in excellent yields.

EXPERIMENTAL

General Experimental Procedure

All melting points (mp) were determined on a Kofler hot-stage apparatus and are uncorrected. Routine infra-red (ir) spectra were recorded on a Perkin-Elmer 983 spectrophotometer. Routine ^{1}H nmr spectra were recorded in deuterochloroform (unless otherwise indicated) using tetramethylsilane (TMS) as internal standard on a Perkin-Elmer R32 (90 MHz) spectrometer. ^{1}H nmr spectra were also recorded at 200 MHz on a Bruker WP 200 SY spectrometer, employing a deuterium lock system, setting chloroform ($C\underline{H}C\ell_3$) in $CDC\ell_3$ at δ7.25 as internal standard. Proton noise-decoupled ^{13}C nmr spectra were recorded at 55 MHz on the Bruker WP 200 SY spectrometer, in deuterochloroform, setting the reference $CDC\ell_3$ signal at δ77.0. Routine mass spectra (ms) were recorded using a VG/Kratos MS 12 spectrometer. High resolution spectra were recorded on a VG/Kratos MS 902S spectrometer.

Gas chromatography (gc) was carried out on a Perkin-Elmer F33 or F11 Gas Chromatograph using the column packings indicated and the data recorded as retention time (t_R) or Kováts Index (I). Capillary gas chromatography was carried out on a Hewlett Packard 5880A GC instrument with dual capillary columns and FID detectors. The capillary columns used were fused silica capillary 25m x 0.32mm (internal diameter) SE 54 (GCQ, Northwich, Chester). The sample was injected via Grob-type injectors operated in split mode (50:1) using helium as both carrier and make-up gas (flow rate 3 ml min^{-1} and 25 ml min^{-1} respectively). Gc-ms was performed with an LKB 9000 instrument fitted with DB-1 fused-silica capillary column, 60m x 0.30mm (internal diameter) [J. and W. Scientific, Rancho Cordova, CA, USA]

and a falling needle injector. Helium was used both as a carrier and make-up gas (flow rates, 7 ml min^{-1}, measured at ambient temperature, and 25 ml min^{-1} respectively). Mass spectra were recorded under electron impact conditions (20 eV); accelerating voltage, 3.5 kV; trap current, 60 μA; source and separator temperatures, 260°C.

Optical rotations were measured on an Optical Activity AA-100 polarimeter.

Column chromatography was performed according to the method of Harwood[47] using Fluka Kieselgel GF_{254}. Analytical thin layer chromatography (tlc) was performed using precoated Merck Kieselgel 60 F_{254} 5 x 20 cm plastic-backed plates (0.2 mm).

Purification and Drying of Solvents

Solvents and reagents were dried and purified prior to use as follows: 2 chloroacrylonitrile (Aldrich) was distilled (bp 88-89°C, atm. press.) immediately prior to use; dichloromethane was distilled over P_2O_5 and stored over molecular sieves (4A); dimethylsulphoxide (DMSO) was dried over molecular sieves (4A) then distilled under reduced pressure (bp 75°C at 12 torr); ether (Et_2O) was distilled from sodium-benzophenone immediately before use; pyridine was dried by refluxing with solid KOH followed by fractional distillation (bp 115°C atm. press.) and stored over molecular sieves (4A).

CHAPTER 1

Benzaldoxime (48)

Benzaldehyde (10g, 0.09 mol) was dissolved in aqueous methanol (100 ml). Hydroxylamine hydrochloride (6.55g, 0.09 mol) and anhydrous sodium bicarbonate (8.70g), 0.1 mol) were added and the resulting solution was heated at 80°C with stirring for 3h. The solution was reduced in volume to approximately 50 ml, added to water (150 ml), and then extracted with ethyl acetate (3 x 100 ml). The combined organic layers were dried with anhydrous Na_2SO_4, filtered and evaporated in vacuo to give benzaldoxime as a light yellow oil (10.12g, 93%) which was used without purification.

^{1}H nmr $\delta(CDC\ell_3)$: 7.30-7.71 (5H, m, $C_6\underline{H}_5$), 8.17 (1H, s, PhC<u>H</u>), 8.59 (1H, br.s, O<u>H</u>).

N-Benzylhydroxylamine (49)[21]

Benzaldoxime (6g, 0.05 mol) was dissolved in methanol (50 ml) containing a trace of bromocresol green indicator and to this solution was added sodium cyanoborohydride (2.03g, 0.03 mol). A solution of 2N HCℓ-MeOH was added dropwise with stirring until the solution turned yellow. Additional 2N HCℓ-MeOH was added as required to maintain the yellow colour. After 2h, the methanol was removed in vacuo. The residue was dissolved in water (20 ml) and 5N NaOH added until the pH exceeded 9. The basic solution was then extracted with chloroform (4 x 50 ml). The combined organic layers were dried with anhydrous Na_2SO_4 and the solvent removed in vacuo to give an oil which was crystallised from hexane to give N-benzylhydroxylamine

as a white crystalline solid (4.74g, 77%), mp 38-39°C (lit.[21] 37°C).

^{1}H nmr $\delta(CDC\ell_3)$: 3.96 (2H, s, $PhC\underline{H}_2$), 6.54 (2H, br.s, $N\underline{H}+O\underline{H}$), 7.30 (5H, s, $C_6\underline{H}_5$).

(S)-(-)-α-Methylbenzylhydroxylamine oxalate salt (56)[23]

A mixture of (S)-(-)-α-methylbenzylamine (20g, 0.165 mol), p-anisaldehyde (26g, 0.19 mol), and anhydrous $MgSO_4$ (30g) in dichloromethane (150 ml) was stirred under argon at room temperature overnight. The mixture was then filtered through a pad of $MgSO_4$ washing with 100 ml dichloromethane. The filtrate was transferred to a 500 ml round bottom flask and cooled to 0°C under argon with stirring. m-Chloroperbenzoic acid (37g, 0.22 mol) slurried in dichloromethane (80 ml) was added and the mixture stirred at 0°C for 1h then at 20°C for 2h. The mixture was filtered and the filtrate washed successively with 0.5M Na_2SO_3 (150 ml), 0.5M K_2CO_3 (150 ml), water (100 ml) and dried with anhydrous $MgSO_4$. Removal of solvent in vacuo afforded the crude oily oxaziridine (54) [43.4g] which was dissolved in absolute EtOH (200 ml). The solution was cooled to 0°C under argon with stirring and hydroxylamine hydrochloride (16g, 0.23 mol) added. The solution was allowed to warm to room temperature and left to stir overnight. Chloroform (100 ml) was added to precipitate excess hydroxylamine hydrochloride. After 2h the mixture was filtered and the solvents removed in vacuo. The residue was taken up in water (200 ml) and washed with Et_2O (2 x 100 ml). The aqueous phase was treated with saturated $NaHCO_3$ (150 ml) and extracted with Et_2O

(5 x 100 ml). The combined organic extracts were dried over anhydrous Na_2SO_4 and filtered into a flask containing anhydrous oxalic acid (18.9g, 0.21 mol) dissolved in Et_2O (150 ml). The precipitated salt was filtered and recrystallised from EtOH-MeOH to give oxalate (56) [S] as a white crystalline solid (21.7g, 58%), mp 179-181°C (lit.[23] 177-180°C).

^1H nmr $\delta(CD_3OD)$: 1.69 (3H, d, J=7.0 Hz, $C\underline{H}_3CHPh$), 4.51 (1H, q, J=7.0 Hz, $CH_3C\underline{H}Ph$), 7.35-7.70 (5H, m, $C_6\underline{H}_5$).

(R)-(+)-α-Methylbenzylhydroxylamine oxalate salt (56)

(R)-(+)-α-Methylbenzylamine afforded oxalate (56) [R] by the above procedure[23] (52%), mp 176-179°C.

CHAPTER 2

(N-Benzyloxycarbonyl)-4-Amino-1-butanol (83)

4-Amino-1-butanol (3g, 33.7 mmol) was dissolved in 5N NaOH (50 ml) and the solution stirred at 0°C. Benzyl chloroformate (4.8 ml, 33.7 mmol) was added dropwise over a 15 min period. The reaction mixture was stirred at 0°C for a further 90 min with the addition of sufficient methanol to ensure a homogeneous solution. The solution was then neutralised with 1N HCℓ and extracted with ethyl acetate (2 x 100 ml). The combined organic extracts were washed with water (100 ml), dried with anhydrous Na_2SO_4 and evaporated in vacuo to give a yellow solid which was recrystallised from Et_2O-$CHC\ell_3$ to give the benzyl carbamate (83) [4.8g, 64%], mp 58-61°C.

ir ν_{max} ($CHC\ell_3$) : 1515, 1715 cm^{-1}.

^1H nmr δ($CDC\ell_3$): 1.50 (4H, m, $CH_2CH_2CH_2OH$), 2.61 (1H, br.s, OH), 3.15 (2H, m, CH_2OH), 3.58 (2H, m, $NHCH_2$), 6.62 (1H, s, NH), 5.06 (2H, s, $PhCH_2$), 7.30 (5H, s, C_6H_5).

$[M]^+$ 223.1214 ; $C_{12}H_{17}NO_3$ requires 223.1208.

(N-Benzyloxycarbonyl)-4-Amino-1-butanal (84)

Oxalyl chloride (0.86 ml, 9.9 mmol) was dissolved in dry $CH_2C\ell_2$ (40 ml) and the solution cooled to -60°C with stirring. Dimethyl sulphoxide (1.41 ml, 19.8 mmol) in dry $CH_2C\ell_2$ (5 ml) was added dropwise over 10 min and the solution stirred for a further 3 min. Alcohol (83) [2g, 9 mmol] was dissolved in a minimum volume of $CH_2C\ell_2$ and added dropwise over 15 min. The solution was stirred for a further 15 min maintaining the temperature at -60°C.

Triethylamine (6.3 ml, 45 mmol) was added dropwise over 10 min. Water (30 ml) was added and the mixture shaken vigorously. The organic layer was separated and dried with anhydrous Na_2SO_4. Removal of solvent in vacuo at 20°C afforded the aldehyde (84) as an unstable light yellow oil (1.96g, 98%) which was immediately used without purification.

^{1}H nmr $\delta(CDC\ell_3)$: 1.85 (2H, m, $C\underline{H}_2CH_2CHO$), 2.54 (2H, t, J=6.5 Hz, $CH_2C\underline{H}O$), 3.25 (2H, m, $NHC\underline{H}_2$), 5.09 (2H, s, $PhC\underline{H}_2$), 5.54 (1H, br.s, N$\underline{H}$), 7.31 (5H, s, $C_6\underline{H}_5$), 9.80 (1H, s, C$\underline{H}$O).

Nitrone (85)

The unstable aldehyde (84), prepared as above (1.96g, 8.8 mmol) was immediately redissolved in $CH_2C\ell_2$ (40 ml). (R)-(+)-α-Methylbenzylhydroxylamine oxalate (56) [2.0g, 8.8 mmol] was added to the solution followed by triethylamine (1.4 ml, 9.7 mmol). The solution was stirred at 20°C for 5h, diluted with more $CH_2C\ell_2$ (50 ml) and washed with water (3 x 50 ml). The organic layer was dried with anhydrous Na_2SO_4 and solvent removed in vacuo to leave a white solid which was recrystallised from Et_2O-$CHC\ell_3$ to give nitrone (85) as a white crystalline solid (2.73g, 91%), mp 92-96°C, $[\alpha]_D$ -7.28° (C=0.02, EtOAc).

ir $\nu_{max}(CHC\ell_3)$: 1515, 1710 cm^{-1}.

^{1}H nmr (200 MHz) $\delta(CDC\ell_3)$: 1.67 (2H, quin, J=6.70 Hz, $NHCH_2C\underline{H}_2$), 1.76 (3H, d, J=7.0 Hz, $C\underline{H}_3CHPh$), 2.47 (2H, q, J=6.5 Hz, $C\underline{H}_2C{=}N$), 3.12 (2H, m, $NHC\underline{H}_2$), 4.95 (1H, q,

J=7.0 Hz, $CH_3C\underline{H}Ph$), 5.06 (2H, s, $PhC\underline{H}_2$), 5.76 (1H, br.s, N$\underline{H}$), 6.77 (1H, t, J=6.70 Hz, $\underline{H}$-C=N), 7.15-7.50 (10H, m, 2 x $C_6\underline{H}_5$).

^{13}C nmr $\delta(CDC\ell_3)$: 18.96 ($\underline{C}H_3CH$), 23.50 ($NHCH_2\underline{C}H_2$), 23.50 ($NHCH_2\underline{C}H_2$), 26.15 ($\underline{C}H_2CH{=}N$), 40.05 ($NH\underline{C}H_2$), 66.39 ($Ph\underline{C}H_2$), 73.51 ($CH_3\underline{C}H$), 127.20-138.13 ($\underline{C}_6H_5$), 136.64 ($\underline{C}$=N), 156.49 ($\underline{C}$ONH).

$[M]^+$ 340.1793; $C_{20}H_{24}N_2O_3$ requires 340.1787.

[Found, C 70.78, H 7.13, N 8.13%; $C_{20}H_{24}N_2O_3$ requires C 70.80, H 7.10, N 8.19%].

5-Acetoxyisoxazolidine (86)

Nitrone (85) [1.5g, 4.4 mmol] was dissolved in vinyl acetate (50 ml) and the solution heated to reflux with exclusion of light under an argon atmosphere for 16h. Removal of excess vinyl acetate in vacuo afforded the crude isoxazolidine (86) as a mixture of four diastereoisomeric C-5 acetates which were clearly separable by silica gel chromatography into two pairs (overall yield 68%).

Thus, 35-40% EtOAc-hexane eluted the major pair (86 B+D) [0.85g] having the (3R) configuration.

ir ν_{max} ($CC\ell_4$) : 1510, 1730, 1750 cm^{-1}.

^{1}H nmr (200 MHz) $\delta(CDC\ell_3)$: 1.01-1.62 (2H, 2 x m, $C\underline{H}_2CHN$ + 3H, 2 x d, $C\underline{H}_3CHN$ + 2H, 2 x m, $C\underline{H}_2C\underline{H}_2NH$), 1.95 (1H, 2 x m, $C\underline{H}_AH_BCOCO$), 2.02 + 2.10 (3H, 2 x s, $COC\underline{H}_3$), 2.50 (1H, 2 x m, $CH_A\underline{H}_BCOCO$), 2.70-3.31 (2H, 2 x m, $NHC\underline{H}_2$ + 1H, 2 x m, $C\underline{H}N$), 3.78 + 4.00 (1H, 2 x q,

PhC$\underline{H}$N), 4.68 (1H, 2 x $\underline{m}$, N$\underline{H}$), 5.05 (2H, 2 x $\underline{s}$, PhC$\underline{H}_2$), 6.41 (1H, 2 x $\underline{m}$, $CH_2C\underline{H}O$), 7.09-7.41 (10H, 2 x $\underline{m}$, $C_6\underline{H}_5$).

^{13}C nmr $\delta(CDC\ell_3)$: 20.68 + 19.90† ($\underline{C}H_3CHN$), 21.28 + 21.41 ($CO\underline{C}H_3$), 26.75 + 26.33 ($\underline{C}H_2CH_2NH$), 31.34 + 33.12 ($\underline{C}H_2CHN$), 39.63 ($\underline{C}H_2COCO$), 40.36 + 40.37 ($\underline{C}H_2NH$), 60.66 + 61.51 ($CH_2\underline{C}HN$), 66.42 (Ph$\underline{C}H_2$), 66.82 + 67.23 ($CH_3\underline{C}HN$), 96.55 + 98.89 ($\underline{C}HOCO$), 127.17 - 142.63 ($\underline{C}_6H_5$), 156.19 ($\underline{C}ONH$), 170.15 + 170.84 ($\underline{C}OCH_3$).

† Major followed by minor.

$[M]^+$ 426.2185; $C_{24}H_{30}N_2O_5$ requires 426.2155.

45-55% EtOAC-hexane eluted the minor pair (86 A+C) [0.38g] having the (3S) configuration.

ir ν_{max} ($CC\ell_4$) : 1510, 1730, 1750 cm^{-1}.

^{1}H nmr (200 MHz) $\delta(CDC\ell_3)$: 1.28 - 1.86 (2H, 2 x $\underline{m}$, $C\underline{H}_2CHN$ + 3H, 2 x $\underline{d}$, $C\underline{H}_3CHN$ + 2H, 2 x $\underline{m}$, $C\underline{H}_2CH_2NH$), 1.89 + 2.03 (3H, 2 x $\underline{s}$, $COC\underline{H}_3$), 2.20 (1H, 2 x $\underline{m}$, $C\underline{H}_A H_B COCO$), 2.81 (1H, 2 x $\underline{m}$, $CH_A\underline{H}_B COCO$), 3.05 - 3.45 (2H, 2 x $\underline{m}$, $NHC\underline{H}_2$ + 1H, 2 x $\underline{m}$, $CH_2C\underline{H}N$), 3.95 + 4.05 (1H, 2 x $\underline{q}$, PhC$\underline{H}$N), 4.91 (1H, 2 x $\underline{m}$, N$\underline{H}$), 5.09 (2H, 2 x $\underline{s}$, PhC$\underline{H}_2$), 6.20 (1H, 2 x $\underline{m}$, $CH_2C\underline{H}O$), 7.25 - 7.34 (10H, 2 x $\underline{m}$, $C_6\underline{H}_5$).

^{13}C nmr $\delta(CDC\ell_3)$: 19.90 + 21.90† ($\underline{C}H_3CHN$), 21.33 + 21.17 ($CO\underline{C}H_3$), 27.08 + 26.62 ($\underline{C}H_2CH_2NH$), 30.42 + 31.19 ($\underline{C}H_2CHN$), 40.76 ($\underline{C}H_2COCO$), 41.38 + 41.48 ($\underline{C}H_2NH$), 60.09 + 59.91 ($CH_2\underline{C}HN$), 64.05 + 65.13 ($CH_3\underline{C}HN$), 66.53 (Ph$\underline{C}H_2$),

95.63 + 96.88 (CHOCO), 127.03 - 142.33 (C_6H_5), 156.30 + 156.37 (CONH), 170.38 + 169.81 ($COCH_3$).

† Major followed by minor.

$[M]^+$ 426.2155; $C_{24}H_{30}N_2O_5$ requires 426.2155.

5-Hydroxyisoxazolidine (87): General Procedure for the Hydrolysis of Isoxazolidine Acetates (86)[48]

The acetate (0.5g, 1.17 mmol) was dissolved in aqueous methanol (approx. 10:1 MeOH-H_2O) containing potassium carbonate (0.083g, 0.59 mmol) and the resulting solution stirred at room temperature for 1h. The solvent was removed in vacuo and the residue dissolved in water (30 ml). The aqueous solution was extracted with Et_2O (3 x 40 ml). The combined organic layers were dried with anhydrous Na_2SO_4 and evaporated to leave the isoxazolidinol as a colourless foam (> 90%) which was used without purification.

Thus acetate mixture (86 B+D) afforded the corresponding isoxazolidinol mixture (87 B+D) having the (3R) configuration while the acetate mixture (86 A+C) afforded isoxazolidinols (87 A+C) having the (3S) configuration. The ^1H nmr (90 MHz) spectra of both mixtures displayed multiplets at $\delta(CDCl_3)$ 5.35 (1H, m, OCHOH) for (87 B+D) and 5.61 (1H, m, OCHOH) for (87 A+C). The ir spectra of both mixtures showed free and bonded hydroxyl absorption at 3600 and 3400 cm^{-1}.

Isoxazolidinones (88): Collins Oxidation[49] of Isoxazolidinols (87)

A solution of dry pyridine (0.74g, 9.36 mmol) in dry dichloromethane (20 ml) was cooled to 0°C with stirring. Chromium trioxide (0.47g, 4.68 mmol) was added and the deep burgundy solution was stirred at 0°C for a further 10 min before allowing to warm to room temperature. The appropriate isoxazolidinol mixture (0.3g, 0.78 mmol) in dichloromethane (5 ml) was added all at once and the mixture allowed to stir for a further 30 min. Saturated aqueous $NaHCO_3$ (15 ml) was added to the solution. The organic layer was separated, dried with anhydrous Na_2SO_4, and solvent removed in vacuo to leave a black residue. Ethyl acetate (50 ml) was added and the solution filtered through a short column of silica gel. The residue was thoroughly washed with further portions of EtOAc (3 x 20 ml) and filtered. The combined filtrates were evaporated to leave an orange oil which was purified by silica gel chromatography (40% EtOAC/hexane) affording the isoxazolidinones (88).

Thus (87 B+D) afforded (3R)-(88) [0.114g, 38%].

ir ν_{max} ($CC\ell_4$) : 1510, 1725, 1790 cm^{-1}.

^1H nmr (200 MHz) $\delta(CDC\ell_3)$: 1.23-1.51 (2H, m, CH_2CH_2 NH + 2H, m, CH_2CHN), 1.53 (3H, d, J=7.0 Hz, CH_3CH), 2.35 (2H, m, CH_2CO), 3.30 (2H, m, CH_2NH), 3.54 (1H, m, CH_2CHN), 4.00 (1H, q, J=7.0 Hz, CH_3CH), 4.70 (1H, m, NH), 5.06 (2H, s, $PhCH_2$), 7.36 (10H, m, C_6H_5).

^{13}C nmr $\delta(CDC\ell_3)$: 20.53 (CH_3CHN), 26.66 (CH_2CH_2NH), 31.57 (CH_2CHN), 39.69 (CH_2CO), 40.27 (CH_2NH), 60.08

($CH_2\underline{C}HN$), 66.60 ($Ph\underline{C}H_2$), 66.83 ($CH_3\underline{C}HN$), 127.23-140.44 ($\underline{C}_6H_5$), 156.27 ($\underline{C}ONH$), 176.52 ($CH_2\underline{C}O$).

$[M]^+$ 382.1894; $C_{22}H_{26}N_2O_4$ requires 382.1893.

Isoxazolidinols (87 A+C) afforded (3S)-(88) [0.13g, 43%].

ir ν_{max} ($CC\ell_4$): 1510, 1730, 1790 cm^{-1}.

^1H nmr (200 MHz) $\delta(CDC\ell_3)$: 1.40-1.78 (2H, m, $C\underline{H}_2CH_2NH$ + 2H, m, $C\underline{H}_2CHN$), 1.60 (3H, d, J=7.5 Hz, $C\underline{H}_3CH$), 2.30 (2H, m, $C\underline{H}_2CO$), 3.21 (2H, m, $C\underline{H}_2NH$), 3.35 (1H, m, $CH_2C\underline{H}N$), 4.04 (1H, q, J=7.5 Hz, $CH_3C\underline{H}$), 4.81 (1H, m, $N\underline{H}$), 5.10 (2H, s, $PhC\underline{H}_2$), 7.26 (5H, s, $C_6\underline{H}_5$), 7.33 (5H, m, $C_6\underline{H}_5$).

^{13}C nmr $\delta(CDC\ell_3)$: 19.72 ($\underline{C}H_3CHN$), 26.88 ($\underline{C}H_2CH_2NH$), 31.89 ($\underline{C}H_2CHN$), 40.58 ($\underline{C}H_2CO$), 40.63 ($\underline{C}H_2NH$), 60.74 ($CH_2\underline{C}HN$), 65.31 ($CH_3\underline{C}HN$), 66.72 ($Ph\underline{C}H_2$), 128.09-138.09 ($\underline{C}_6H_5$), 156.41 ($\underline{C}ONH$), 175.24 ($CH_2\underline{C}O$).

$[M]^+$ 382.1912; $C_{22}H_{26}N_2O_4$ requires 382.1893.

N,N-Dibenzyloxycarbonyl (2S or 2R)-Ornithine (89)[50]

(2S or 2R)-Ornithine hydrochloride (1.68g, 10 mmol) was dissolved in 5N NaOH (25 ml) and the solution cooled to 0°C with stirring. Benzyl chloroformate (3.6 ml, 25 mmol) was added dropwise over 10 min and the solution left to stir for 1h then diluted with water (30 ml) and extracted with EtOAc (50 ml). The aqueous phase was acidified (approx. pH 5) with 1N HCℓ and extracted into EtOAc (3 x 50 ml). This organic layer was washed with saturated brine

(2 x 50 ml), dried with anhydrous Na_2SO_4 and solvent removed in vacuo to leave a colourless viscous oil which was crystallised from Et_2O/petrol (40-60°C) to give a white crystalline solid.

Thus (2S)-ornithine hydrochloride afforded N,N-dibenzyloxycarbonyl-(2S)-ornithine [(2S)-(89)], (3.4g, 85%), mp 113-116°C (lit.[50] 112-114°C).

ir ν_{max} ($CHC\ell_3$) : 1515, 1715 cm^{-1}.

^1H nmr $\delta(CDC\ell_3)$: 1.69 (4H, m, CH_2CH_2CHNH), 3.18 (2H, m, $NHCH_2$), 4.40 (1H, m, CH_2CHCO_2H), 5.10 (4H, m, $PhCH_2$), 5.19 (1H, m, NH), 7.31 (10H, s, C_6H_5), 9.45 (1H, br.s, CO_2H).

2(R)-Ornithine hydrochloride afforded N,N-dibenzyloxycarbonyl-(2R)-ornithine [(2R)-(89)], (3.12g, 78%), mp 112-113°C.

N,N-Dibenzyloxycarbonyl-(3S)-β-Lysine [(3S)-(92)] via Arndt-Eistert [A-E] Homologation[50] of N,N-Dibenzyloxycarbonyl-(2S)-Ornithine [(2S)-(89)]

N,N-Dibenzyloxycarbonyl-(2S)-ornithine (0.74g, 1.9 mmol) was dissolved in ethyl acetate (30 ml) and the solution cooled in an ice/salt bath with stirring. N-Methyl morpholine (0.23 ml, 2.09 mmol) was added followed by dropwise addition of ethyl chloroformate (0.2 ml, 2.09 mmol) in EtOAc (3 ml). After 3h, the precipitated amine hydrochloride was rapidly filtered off in the cold. Excess diazomethane (approx. 6 mmol, ethereal solution) was added to the filtrate at 0°C and the solution left to stir overnight. Excess diazomethane was removed by warming to 50°C

and the solvent removed in vacuo to leave the oily diazoketone (2S)-(90) [0.82g, 98%] which could be crystallised from EtOAc-hexane to give a yellow solid, mp 94°C (lit.[50] 93-94°C). The solid was dissolved in dry methanol (20 ml) and the solution stirred at 20°C in darkness. Freshly prepared silver benzoate (0.1g) was dissolved in triethylamine (1.5 ml), rapidly filtered and added to the solution. Two further portions of powdered silver benzoate (0.05g) were added after 1 and 3h and the mixture left to stir in the dark overnight and then concentrated in vacuo. The residue was dissolved in EtOAc (30 ml) and filtered free of insoluble material. The filtrate was washed with saturated $NaHCO_3$ (25 ml), saturated sodium chloride (25 ml), 1M HCℓ (25 ml) and finally saturated sodium chloride (3 x 25 ml). The organic layer was dried over anhydrous Na_2SO_4 and evaporated in vacuo to give N,N-dibenzyloxycarbonyl-(3S)-β-lysine methyl ester [(3S)-(91)] as a white crystalline solid (0.69g, 85%), mp 105-107°C (lit.[50] 105-107°C). The methyl ester (3S)-(91) [0.69g, 1.6 mmol] was dissolved in a minimum volume of dioxan and aqueous NaOH (1.5 ml, 1.5M) was added. After stirring at 0°C for 30 min and then at room temperature for 1h, the reaction mixture was diluted with water (20 ml) and extracted with EtOAc (20 ml). The aqueous phase was acidified with 1M HCℓ and extracted with EtOAc (5 x 20 ml). The organic layer was washed with saturated sodium chloride solution (3 x 20 ml) and dried over anhydrous Na_2SO_4. Removal of solvent in vacuo gave a white solid which was recrystallised from EtOAc to give N,N-dibenzyloxycarbonyl-(3S)-β-lysine [(3S)-(92)] (0.48g, 72%), mp 152-154°C (lit.[50] 155°C).

ir ν_{max} (KBr Disc) : 1550, 1650, 1695, 1730 cm^{-1}.

^1H nmr $\delta(CD_3OD)$: 1.55 (4H, m, $C\underline{H}_2C\underline{H}_2CHNH$), 2.45 (2H, d, J=6.5 Hz, $C\underline{H}_2CO_2H$), 3.10 (3H, m, $C\underline{H}CH_2CO_2H$ + $NHC\underline{H}_2$), 5.05 (4H, s, $PhC\underline{H}_2$), 7.31 (10H, s, $C_6\underline{H}_5$).

N,N-Dibenzyloxycarbonyl-(3R)-β-Lysine [(3R)-(92)]

The title compound was prepared by Arndt-Eistert homologation of N,N-dibenzyloxycarbonyl-(2R)-ornithine [(2R)-(89)] by the above procedure.

(3S)-β-Lysine via Hydrogenolysis of (3S)-(92)

N,N-Dibenzyloxycarbonyl-(3S)-β-lysine [(3S)-(92)] (0.1g, 0.24 mmol) was dissolved in ethanol (30 ml) and hydrogenated over $Pd(OH)_2$ on charcoal (15 mg; 20%) for 6h at 35°C and atmospheric pressure. The catalyst was removed by filtration through a pad of Celite and was washed with ethanol. The combined filtrates were evaporated in vacuo to give (3S)-β-lysine [(3S)-(62)] as a light yellow hygroscopic gum (35 mg, 100%), $[\alpha]_D$ + 21° (C = 0.035, 1M HCℓ) [lit.[29] + 24°].

(3R)-β-Lysine via Hydrogenolysis of (3R)-(92)

Hydrogenolysis of (3R)-(92) as for (3S)-(92) [above] afforded (3R)-β-lysine [(3R)-(62)] (100%), $[\alpha]_D$ −20.5° (C = 0.03, 1M HCℓ).

(3S)-β-Lysine via Hydrogenolysis of Isoxazolidinone [(3S)-(88)] and Characterisation as N,N-Dibenzyloxycarbonyl-(3S)-β-Lysine [(3S)-(92)]

Isoxazolidinone (3S)-(88) [0.2g, 0.52 mmol] was dissolved in ethanol (50 ml) and hydrogenated over $Pd(OH)_2$ on charcoal (30 mg; 20%) for 20h at 20°C then 5h at 70°C and atmospheric pressure. The catalyst was removed by filtration through Celite and washed thoroughly with ethanol. The combined filtrates were evaporated in vacuo to give (3S)-β-lysine [(3S)-(62)] as a light yellow hygroscopic gum (76 mg, 100%), $[\alpha]_D$ + 18° (C = 0.076, 1M HCℓ) [lit.[29] + 24°]. The ^1H nmr (90 MHz) spectrum (D_2O) of the residue was virtually identical with an authentic specimen of (3S)-β-lysine generated by Arndt-Eistert homologation of N,N-dibenzyloxycarbonyl-(2S)-ornithine (see Fig. 4, p.36). The gum was dissolved in 5N NaOH (3 ml) and the solution cooled to 0°C with stirring. Benzyl chloroformate (0.16 ml, 1.14 mmol) was added and the mixture left to stir for 1h at 0°C then diluted with water (10 ml) and extracted with EtOAc (10 ml). The aqueous phase was acidified with 1N HCℓ and extracted into EtOAc (5 x 10 ml). The organic phase was washed with saturated brine (3 x 5 ml), dried with anhydrous Na_2SO_4 and evaporated in vacuo to give N,N-dibenzyloxycarbonyl-(3S)-β-lysine [(3S)-(92)] (142 mg, 66%) which was identical (mp, ir, ^1H nmr) with an authentic specimen prepared by Arndt-Eistert homologation.

(3R)-β-Lysine via Hydrogenolysis of Isoxazolidinone [(3R)-(88)] and Characterisation as N,N-Dibenzyloxycarbonyl-(3R)-β-Lysine [(3R)-(92)]

Isoxazolidinone (3R)-(88) was hydrogenated as for (3S)-(88) (above) to give (3R)-β-lysine as a hygroscopic gum (100%), $[\alpha]_D$ - 19.5° (C = 0.1, 1M HCℓ) [lit.[29] + 24°]. for (S)-(+)-β-lysine N,N-Dibenzyloxycarbonyl-(3R)-β-lysine [(3R)-(92)] was prepared as for (3S)-(92) [above] (61%) and was identical (mp 153-156°C, ir, ^{1}H nmr) with an authentic specimen prepared by Arndt-Eistert homologation.

Methyl Ester Bis 'Mosher' Amides (94)[51]

(a) via Arndt-Eistert Homologation: N,N-Dibenzyloxycarbonyl-(3S) or (3R)-β-lysine methyl ester (91) (50 mg, 0.12 mmol) was dissolved in ethanol (15 ml) and hydrogenated over $Pd(OH)_2$ on charcoal at 35°C and atmospheric pressure for 5h. Filtration from catalyst and removal of solvent in vacuo afforded the crude (3S)- or (3R)-β-lysine methyl ester (93) as an oil (19 mg, 100%). The residue was dissolved in $CC\ell_4$-pyridine (10 ml; 3:2). (S)-(-)-MTPA chloride (64 mg, 0.27 mmol) was added and the solution heated to reflux for 3h. A few drops of water were added and the solution allowed to cool before diluting with $CH_2C\ell_2$ (10 ml) and washing with 1M HCℓ (10 ml), 10% $NaHCO_3$ (10 ml) and water (2 x 10 ml). The organic layer was dried with anhydrous Na_2SO_4 and solvent removed in vacuo to leave the crude methyl ester bis 'Mosher' amides (94) [(3S) or (3R)]. [Gc-ms results - Table 2, p.34].

(b) via Nitrone Cycloadditions: N,N-Dibenzyloxycarbonyl-(3S) or (3R)-β-lysines were first converted into the methyl esters (91) by treatment with excess CH_2N_2. The methyl ester bis 'Mosher' amides (94) [(3S) or (3R)] were then generated as above. [Gc-ms results - Table 1, p.34].

CHAPTER 3

C-Carboxy Nitrones (117a, b, c)

To glyoxylic acid hydrate (40 mmol), suspended in dichloromethane (50 ml) was added the appropriate hydroxylamine [or its oxalate salt plus one equivalent of triethylamine] (40 mmol) and the solution stirred for 5h at 20°C. More dichloromethane (50 ml) was added, the solution washed with water (2 x 50 ml), dried with anhydrous Na_2SO_4, and the solvent removed in vacuo to leave the crude nitrones (117a,b,c).

Thus N-benzylhydroxylamine (49) afforded nitrone (117a) as a yellow paste which was crystallised from $Et_2O/CHCl_3$ to give a white solid (62%), mp 92-93°C.

ir ν_{max} ($CHCl_3$) : 1715 cm^{-1}.

^1H nmr δ($CDCl_3$): 5.06 (2H, s, $PhCH_2N$), 7.28 (1H, s, H-C=N), 7.45 (5H, s, C_6H_5).

^{13}C nmr $\delta CDCl_3$) : 70.48 (CH_2Ph), 129.4-130.3 (C=N + C_6H_5), 161.21 (CO_2H).

$[M]^+-CO_2$ 135.0685; C_8H_9NO requires 135.0684.

N-(R)-α-Methylbenzylhydroxylamine oxalate salt (56) afforded the oily nitrone (117b)[61%].

ir ν_{max} ($CHCl_3$) : 1715 cm^{-1}

^1H nmr δ($CDCl_3$) : 1.82 (3H, d, J=6.0 Hz, CH_3), 5.21 (1H, q, J=7.0 Hz), $CHCH_3$), 7.39 (5H, s, C_6H_5), 7.45 (1H, s, H-C=N).

^{13}C nmr δ($CDCl_3$): 17.68 (CH_3), 74.74 ($CHCH_3$), 127.0-128.9 (C_6H_5), 135.45 (C=N), 161.13 (CO_2H).

$[M]^+-CO_2$ 149.0850; $C_9H_{11}NO$ requires 149.0787.

N-(S)-α-Methylbenzylhydroxylamine oxalate salt (56) afforded the oily nitrone (117c) [74%].

ir ν_{max} ($CHC\ell_3$) : 1715 cm^{-1}

^1H nmr δ($CDC\ell_3$) : 1.85 (3H, d, J=6.0 Hz, $C\underline{H}_3$), 5.23 (1H, q, J=7.0 Hz, $C\underline{H}CH_3$), 7.35 (5H, m, $C_6\underline{H}_5$), 7.53 (1H, s, H-C=N).

Methyl Glyoxylate[72]

Dimethyl tartrate (5g, 28.1 mmol) was dissolved in dry diethyl ether (100 ml) and the solution cooled to 0°C under nitrogen with stirring. Periodic acid (6.4g, 28.1 mmol) was added to the solution in portions over 1h. After the last addition, the solution was allowed to stir for a further 15 mins. The ether phase was decanted from the white solid and left to stand overnight over molecular sieves (4A). The solvent was removed in vacuo to leave a colourless, mobile oil (4.92g, 99%). The ^1H nmr (90 MHz) spectrum was complex with continuous absorption between δ3.51-5.70 and remained unchanged after bulb-tube distillation (120°C, 0.1 mm Hg).

ir ν_{max} ($CHC\ell_3$) : 1735 cm^{-1}, 1750 cm^{-1}.

C-Carbomethoxy Nitrones (123a, b, c)

Methyl glyoxylate (1g, 11.4 mmol) and the appropriate hydroxylamine [or its oxalate salt plus one equivalent of triethylamine] (11.4 mmol) were dissolved in dichloromethane (50 ml) and the solution stirred for 5h at 20°C. The solution was washed with water (20 ml)

and the organic phase dried with anhydrous Na_2SO_4. Removal of solvent in vacuo afforded the crude nitrones (123a,b,c) as mixtures of geometric isomers, which were crystallised from $Et_2O/CHC\ell_3$.

Thus N-benzylhydroxylamine (49) afforded nitrone (123a), mp 91-93°C.

ir ν_{max} (KBr Disc) : 1215, 1565, 1725 cm^{-1}.

^1H nmr $\delta(CDC\ell_3)$: 3.76 and 3.80 (3H, 2 x s, $CO_2C\underline{H}_3$), 4.98 and 5.70 (2H, 2 x s, $PhC\underline{H}_2$), 7.11 and 7.21 (1H, 2 x s, $\underline{H}$-C=N), 7.25-7.70 (5H, m, $C_6\underline{H}_5$).

[Found, C 62.13, H 57.30, N 7.19%; $C_{10}H_{11}NO_3$ requires C 62.17, H 57.00, N 7.25%].

N-(R)-α-Methylbenzylhydroxylamine oxalate salt (56) afforded nitrone (123b), mp 84-85°C.

ir ν_{max} (KBr Disc) : 1210, 1550, 1720 cm^{-1}.

^1H nmr $\delta(CDC\ell_3)$: 1.73 and 1.82 (3H, 2 x d, $CHC\underline{H}_3$), 3.75 and 3.79 (3H, 2 x s, $CO_2C\underline{H}_3$), 5.16 and 7.07 (1H, 2 x q, $C\underline{H}CH_3$), 7.16 and 7.19 (1H, 2 x s, $\underline{H}$-C=N), 7.25-7.61 (5H, m, $C_6\underline{H}_5$).

[Found, C 63.82, H 6.26, N, 6.71; $C_{11}H_{13}NO_3$ requires C 63.77, H 6.28, N 6.76%].

N-(S)-α-Methylbenzylhydroxylamine oxalate salt (56) afforded nitrone (123c), mp 83-85°C (lit.[9] 84-86°C) whose spectroscopic properties were virtually identical with those of nitrone (123b).

L-Phenylalanine methyl ester hydrochloride

L-Phenylalanine (5g, 30.3 mmol) was suspended in dry methanol (60 ml) in a 3-necked round bottom flask equipped with a silica gel drying tube and gas inlet and the mixture heated to 60°C. Hydrogen chloride gas (dried) was bubbled through the mixture until it became homogeneous and then for a further 10 mins. Cooling to 20°C and removal of solvent in vacuo yielded L-phenylalanine methyl ester hydrochloride as a white solid which was thoroughly dried under vacuum at 50°C for 5h, mp 157-160°C.

C-Carbamido Nitrones (119a, b, c)

Nitrone (117a, b or c) [20 mmol], (S)-phenylalanine methyl ester hydrochloride (20 mmol), N-methyl-2-chloropyridinium iodide[73] (24 mmol) and triethylamine (70 mmol) in dry dichloromethane (100 ml) were refluxed for 1h. The clear solution was washed three times with HCℓ (5%; 40 ml) and once with water (40 ml). The organic phase was dried with anhydrous Na_2SO_4 and solvent removed in vacuo. The crude oils were purified by silica gel chromatography [eluted with ethyl acetate-hexane (45:55)].

Nitrone (119a) [48%], mp 98-100°C, $[\alpha]_D$ -8.1° (C = 0.1 in $CHC\ell_3$).

ir ν_{max} (KBr Disc) : 1234, 1645, 1742 cm^{-1}.

^1H nmr (200 MHz) $\delta(CDC\ell_3)$: 3.08 (1H, dd, J=6.0, 14.0 Hz, $CHCH_AH_BPh$), 3.18 (1H, dd, J=7.0, 14.0 Hz, $CHCH_AH_BPh$), 3.67 (3H, s, CO_2CH_3), 4.88 (1H, m, CH_2CHN), 4.92 (2H, s, CH_2Ph), 7.05 (1H, s, H-C=N), 7.22 (5H, m, C_6H_5), 7.40 (5H,

s, C_6H_5), 10.22 (1H, d, J=7.0 Hz, NH).

^{13}C nmr $\delta(CDC\ell_3)$: 37.68 ($\underline{C}H_2Ph$), 52.13 ($\underline{C}H_3OCO$), 53.39 ($\underline{C}H$-N-), 71.43 ($\underline{C}H_2$-N=), 126.9-135.7 (2 x $\underline{C}_6H_5$ + $\underline{C}$=N), 160.1 (NH$\underline{C}$O), 171.0 ($\underline{C}O_2CH_3$).

$[M]^+$ 340.1437; $C_{19}H_{20}N_2O_4$ requires 340.1423.

[Found, C 67.12, H 6.01, N 8.25%; $C_{19}H_{20}N_2O_4$ requires C 67.06, H 5.88, N 8.24%].

Nitrone (119b) [58%], mp 102-104°C, $[\alpha]_D$ -28.3° (C = 0.12 in $CHC\ell_3$).

ir ν_{max} (KBr Disc) : 1218, 1239, 1258, 1648, 1742 cm^{-1}.

^1H nmr (200 MHz) $\delta(CDC\ell_3)$: 1.79 (3H, d, J=7.0 Hz, $C\underline{H}_3CH$), 3.07 (1H, dd, J=6.0, 14.0 Hz, $CH_A\underline{H}_BPh$), 3.20 (1H, dd, J=7.0, 14.0 Hz, $CH_A\underline{H}_BPh$), 3.66 (3H, s, $CO_2C\underline{H}_3$), 4.86 (1H, m, $CH_2C\underline{H}N$), 5.09 (1H, q, J=7.0 Hz, PhC$\underline{H}$N), 7.14 (1H, s, $\underline{H}$-C=N), 7.23 (5H, m, $C_6\underline{H}_5$), 7.40 (5H, s, $C_6\underline{H}_5$), 10.27 (1H, d, J=7.0 Hz, N$\underline{H}$).

^{13}C nmr $\delta(CDC\ell_3)$: 18.67 ($\underline{C}H_3CH$), 37.82 ($\underline{C}H_2Ph$), 52.11 ($\underline{C}H_3OCO$), 53.53 ($\underline{C}H$-N), 76.28 ($\underline{C}H$-N=), 126.9-136.5 2 x $\underline{C}_6H_5$ + $\underline{C}$=N), 160.35 (NH$\underline{C}$O), 171.08 ($\underline{C}O_2CH_3$).

$[M]^+$ 354.1577; $C_{20}H_{22}N_2O_4$ requires 354.1580.

[Found, C 67.83, H 6.21, N 7.92%; $C_{20}H_{22}N_2O_4$ requires C 67.80, H 6.21, N 7.91%].

Nitrone (119c) [54%], oil, $[\alpha]_D$ +10.5° (C = 0.07 in $CHC\ell_3$).

ir ν_{max} ($CHC\ell_3$) : 1650, 1735 cm^{-1}.

^1H nmr (200 MHz) $\delta(CDC\ell_3)$: 1.82 (3H, d, J=7.0 Hz, $C\underline{H}_3CH$), 3.07 (1H, dd, J=6.0, 14.0 Hz, $CHC\underline{H}_A\underline{H}_BPh$), 3.18 (1H, dd,

J=7.0, 14.0 Hz, $CHCH_A\underline{H}_BPh$), 3.70 (3H, s, $CO_2C\underline{H}_3$), 4.86 (1H, m, $CH_2C\underline{H}N$), 5.09 (1H, q, J=7.0 Hz, $PhC\underline{H}N$), 7.14 (1H, s, H-C=N), 7.13-7.28 (5H, m, $C_6\underline{H}_5$), 7.42 (5H, s, $C_6\underline{H}_5$), 10.27 (1H, d, J=7.0 Hz, N$\underline{H}$).

^{13}C nmr $\delta(CDC\ell_3)$: 18.76 ($\underline{C}H_3CH$), 37.93 ($\underline{C}H_2Ph$), 52.22 ($\underline{C}H_3OCO$), 53.57 ($\underline{C}H$-N-), 76.93 ($\underline{C}H$-N=), 126.96-136.78 (2 x $\underline{C}_6H_5$ + $\underline{C}$=N), 160.37 (NH$\underline{C}$O), 171.19 ($\underline{C}O_2CH_3$).

$[M]^+$ - OH 337.1560; $C_{20}H_{21}N_2O_3$ requires 337.1552.

Cycloadducts (120a, b, c)

Nitrone (119a, b or c) [1.5 mmol) was dissolved in 2-chloroacrylonitrile (10 ml) and the solution heated at 80°C (pre-heated oil bath) under argon for 15 min. Excess 2-chloroacrylonitrile was removed *in vacuo* affording the crude adduct (120a,b or c) in 95-100% yield (oil) which could be purified by silica gel chromatography (EtOAc/hexane 25:75) or used without any further purification.

Thus nitrone (119a) afforded cycloadduct (120a).

ir ν_{max} ($CHC\ell_3$) : 1520, 1685, 1745 cm^{-1}; band for CN (2200-2260 cm^{-1}) absent.

^{1}H nmr $\delta(CDC\ell_3)$: Complex continuous adsorption (11H) between δ3 and δ5 and a complex multiplet 10H(2 x $C_6\underline{H}_5$) + 1H(N$\underline{H}$) at δ7.0-7.5.

$[M]^+$ - Cℓ 392.

The spectroscopic properties of adducts (120b) and (120c) were analogous to those of (120a), with the changes to be expected for replacement of CH_2Ph by (R)- or (S)-CHMePh.

Isoxazolidin-5-ones (121a, b, c):

General procedure for hydrolysis of cycloadducts (120a, b, c)

Cycloadduct (120a, b or c) [1.5 mmol] was dissolved in a minimum volume of tetrahydrofuran, diluted with water (10 ml) and sufficient thf added to produce a single phase. Aqueous HCℓ (0.2-0.4 equiv. of 1N) was added, the solution stirred at 20°C for 16-24h then neutralised (1N NaOH), concentrated to 1/3 volume and extracted with EtOAc (5 x 10 ml). The organic phase was dried with anhydrous Na_2SO_4 and solvent removed in vacuo to leave a light brown oil which was purified by silica gel chromatography (35-40% EtOAc/hexane) to afford the isoxazolidin-5-ones (121a, b or c) in 75-85% yield.

Hydrolysis of adduct (120a) afforded the oily isoxazolidinone (121a) [82%] consisting of a mixture of C-3 epimers [(3R):(3S)=5:2 from $C\underline{H}_3OCO$ signals in ^1H nmr spectrum at 200 MHz].

ir ν_{max} ($CHC\ell_3$) : 1675, 1740, 1780 cm^{-1}.

^1H nmr (200 MHz) δ($CDC\ell_3$) : 2.75-3.23 (4H, m, $C\underline{H}_2CO$ + $PhC\underline{H}_2CH$), 3.68 and 3.78 (3H, 2 x s, $C\underline{H}_3OCO$), 3.84-4.23 (3H, m, $PhC\underline{H}_2$-N + C$\underline{H}$-N), 4.71-4.88 (1H, m, C$\underline{H}$NCO), 6.95-7.35 (10H, m, 2 x $C_6\underline{H}_5$), 7.60 and 7.71 (1H, 2 x d, N$\underline{H}$).

^{13}C nmr δ($CDC\ell_3$): 31.35 ($C\underline{C}H_2Ph$), 37.10† + 37.58† ($\underline{C}H_2CO$), 52.19 + 52.13 ($\underline{C}H_3OCO$), 52.87 + 52.51 (N-$\underline{C}$H-CONH), 62.45 + 62.39 ($Ph\underline{C}H_2N$), 64.03 ($\underline{C}HCO_2Me$), 126.87-129.33 (2 x $\underline{C}_6H_5$), 168.38 + 168.14 ($\underline{C}ONH$), 170.92 + 170.89 ($\underline{C}O_2CH_3$), 173.59 + 173.90 ($\underline{C}OCH_2$).

† Major followed by minor.

$[M]^+ - CO_2$ 338.

Hydrolysis of adduct (120b) afforded the oily isoxazolidinone (121b) [83%] consisting of a mixture of C-3 epimers [(3R):(3S)=2:3 from $CHC\underline{H}_3$ signals in ^1H nmr spectrum at 200 MHz]. The mixture was resolved by chromatography (SiO_2) : 35% EtOAc/hexane eluted (3S)-(121b), mp 112-113°C, $[\alpha]_D$ -40° (C = 0.064 in $CHC\ell_3$).

ir ν_{max} ($CHC\ell_3$) : 1673, 1735, 1782 cm^{-1}.

^1H nmr (200 MHz) δ($CDC\ell_3$) : 1.54 (3H, d, J=6.0 Hz, $C\underline{H}_3CH$), 2.75 (2H, m, $C\underline{H}_2CO$), 3.05 (1H, dd, J=6.0, 15.0 Hz, $CHC\underline{H}_A H_B Ph$), 3.17 (1H, dd, J=5.0, 15.0 Hz, $CHCH_A\underline{H}_B Ph$), 3.74 (3H, s, $CO_2C\underline{H}_3$), 3.87 (1H, dd, J=5.5, 9.0 Hz, $COC\underline{H}N$), 4.11 (1H, q, J=6.0 Hz, $PhC\underline{H}N$), 4.81 (1H, m, $CH_2C\underline{H}N$), 7.10-7.40 (10H, m, 2 x $C_6\underline{H}_5$), 7.84 (1H, d, J=10.0 Hz, $N\underline{H}$).

^{13}C nmr δ($CDC\ell_3$) : 20.08 ($\underline{C}H_3CH$), 30.29 ($Ph\underline{C}H_2$), 38.12 ($CO\underline{C}H_2$), 52.72 ($COO\underline{C}H_3$), 52.96 ($\underline{C}H$-NHCO), 61.81 ($Ph\underline{C}H$-N), 67.12 (NHCO$\underline{C}$H-N), 116.03-138.79 (2 x $\underline{C}_6H_5$), 168.51 ($\underline{C}ONH$), 171.22 ($\underline{C}O_2CH_3$), 175.13 ($\underline{C}OCH_2$).

$[M]^+$ 396.1667; $C_{22}H_{24}N_2O_5$ requires 396.1685.

40% EtOAc/hexane eluted (3R)-(121b), oil, $[\alpha]_D$ +59.9° (C = 0.053 in $CHC\ell_3$).

ir ν_{max} ($CHC\ell_3$) : 1670, 1735, 1780 cm^{-1}.

^1H nmr (200 MHz) δ($CDC\ell_3$) : 1.47 (3H, d, J=8.0 Hz, $C\underline{H}_3CH$), 2.29 (1H, dd, J=10.0, 17.5 Hz, $C\underline{H}_A H_B CO$), 2.77 (1H, dd, J=5.0, 17.5 Hz, $CH_A\underline{H}_B CO$), 3.09 (1H, dd, J=7.5, 14.5 Hz, $CHC\underline{H}_A H_B Ph$), 3.25 (1H, dd, J=5.0, 14.5 Hz, $CHCH_A\underline{H}_B Ph$),

3.74 (3H, s, CO_2CH_3), 3.88 (1H, q, J=8.0 Hz, PhCHN), 3.88 (1H, dd, J=4.0, 17.0 Hz, COCHN), 4.82 (1H, m, CH_2CHN), 7.10-7.30 (10H, m, 2 x C_6H_5), 7.58 (1H, d, J=8.0 Hz, NH).

^{13}C nmr $\delta(CDCl_3)$: 19.01 (CH_3CH), 32.67 ($PhCH_2$), 37.50 ($COCH_2$), 52.57 ($COOCH_3$), 52.95 (CH-NHCO), 63.44 (PhCH-N), 67.14 (NHCOCH-N), 127.36-137.22 (2 x C_6H_5), 168.97 (CONH), 171.23 (CO_2CH_3), 173.73 ($COCH_2$).

$[M]^+$ 396.1692; $C_{22}H_{24}N_2O_5$ requires 396.1685.

Hydrolysis of adduct (120c) furnished a single isoxazolidinone (121c) [77%], mp 92-94°C, $[\alpha]_D$ +45° (C = 0.04 in $CHCl_3$.)

ir ν_{max} (KBr Disc) : 1678, 1787, 1790 cm^{-1}.

^1H nmr (200 MHz) $\delta(CDCl_3)$: 1.52 (3H, d, J=6.0 Hz, CH_3CH), 2.73 (1H, dd, J=14.0, 20.0 Hz, CH_AH_BCO), 2.90 1H, dd, J=3.0, 20.0 Hz, CH_AH_BCO), 3.01 (1H, dd, J=5.0, 15.0 Hz, $CHCH_AH_BPh$), 3.21 (1H, dd, J=4.5, 15.0 Hz, $CHCH_AH_BPh$), 3.74 (3H, s, CO_2CH_3), 3.88 (1H, dd, J=2.5, 15.0 Hz, COCHN), 4.12 (1H, q, J=6.0 Hz, PhCHN), 4.72 (1H, m, CH_2CHN), 7.40 (10H, m, 2 x C_6H_5), 7.78 (1H, d, J=8.0 Hz, NH).

^{13}C nmr δ ($CDCl_3$) : 19.92 (CH_3CH), 30.09 ($PhCH_2$), 37.36 ($COCH_2$), 52.36 (CH_3OCO), 53.23 ($CHCO_2Me$), 61.64 (PhCH-N-), 66.74 (NHCOCH-N-), 126.17-138.66 (2 x C_6H_5), 169.01 (CONH), 171.04 ($COOCH_3$), 174.99 ($COCH_2$).

$[M]^+$ 396.1693; $C_{22}H_{24}N_2O_5$ requires 396.1685.

[Found, C 66.65, H, 6.07, N 7.03%; $C_{22}H_{24}N_2O_5$ requires C 66.67, H 6.06, N 7.07%].

C-3 Carbomethoxy Isoxazolidinone (124)

Cycloaddition of the C-carbomethoxy-N-(R)-α-methylbenzyl nitrone (123b) [0.31g, 1.5 mmol] to 2-chloroacrylonitrile followed by hydrolysis of the resulting adduct as above afforded the oily isoxazolidinone (124) [0.22g, 59%] as a mixture of C-3 epimers.

ir ν_{max} ($CHC\ell_3$) : 1740, 1780 cm^{-1}.

^1H nmr - (see Fig. 12 , p. 68).

$[M]^+$ 249.1005; $C_{13}H_{15}NO_4$ requires 249.1001.

Aspartame (95) and (R)-Asp-(S)-PheOMe (122): Hydrogenolysis of Isoxazolidinones (121a, b, c)

Isoxazolidinone (3S)-(121b) [100 mg, 0.25 mmol) in EtOH/H_2O (25 ml, 3:2), was hydrogenated over $Pd(OH)_2$ on charcoal (20 mg, 20%) at 70°C and atmospheric pressure for 5h. The catalyst was removed by filtration through a pad of Celite and was washed with EtOH and H_2O. The combined filtrates were evaporated *in vacuo* to leave a white solid (74 mg, 100%). Washing with chilled water afforded the sweet (S)-Asp-(S)-PheOMe (Aspartame) (95) [65 mg, 86%], mp 243-247°C, $[\alpha]_D$ +29.8° (C = 0.05, acetic acid) [lit.[54] mp 248-250°C, $[\alpha]_D$ +30.3° (C = 0.1, acetic acid)].

^1H nmr (200 MHz) δ(d_6-dmso) : 2.22 (1H, dd, J=9.0, 16.5 Hz, $C\underline{H}_A H_B CO_2H$), 2.46 (1H, dd, J=4.5, 16.5 Hz, $CH_A\underline{H}_B CO_2H$), 2.93 (1H, dd, J=8.5, 13.5 Hz $PhC\underline{H}_A H_B CH$), 3.04 (1H, dd, J=5.5, 13.5 Hz, $PhCH_A\underline{H}_B CH$), 3.59 (3H, s, $CO_2C\underline{H}_3$), 3.71 (1H, dd, J=4.5, 9.0 Hz, $C\underline{H}NH_2$), 4.47 (1H, m,

$CH_2C\underline{H}CO_2Me$), 5.30 (2H, br.s, $N\underline{H}_2$), 7.10-7.35 (5H, m, $C_6\underline{H}_5$), 8.95 (1H, br.s, N$\underline{H}$).

^{13}C nmr δ(d_6 dmso) : 36.61 ($\underline{C}H_2CO_2H$), 37.88 ($\underline{C}H_2Ph$), 50.71 ($\underline{C}HCH_2CO_2H$), 51.99 ($CO_2\underline{C}H_3$), 53.72 ($\underline{C}HCH_2Ph$), 126.66-136.99 ($\underline{C}_6H_5$), 171.30 ($\underline{C}ONH$), 171.63 ($\underline{C}O_2CH_3$), 172.45 ($\underline{C}O_2H$).

Isoxazolidinone (121c), hydrogenated under the same conditions afforded the tasteless (R)-Asp-(S)-PheOMe (122) [75 mg, 100%], mp 154-157°C, $[\alpha]_D$ -17.4° (C = 0.05, H_2O) [lit.[54] mp 159°C, $[\alpha]_D$ -18° (C = 0.1, H_2O)].

^1H nmr (200 MHz) δ(d_6-dmso) : 2.16 (2H, m, $C\underline{H}_2CO_2H$), 2.89 (1H, dd, J=9.0, 13.5 Hz, PhC$\underline{H}_A$$H_B$CH), 3.06 (1H, dd, J=5.0, 13.5 Hz, PhC$H_A\underline{H}_B$CH), 3.60 (3H, s, $CO_2C\underline{H}_3$), 3.68 (1H, m, $C\underline{H}NH_2$), 4.55 (1H, m, $CH_2C\underline{H}CO_2Me$), 5.05 (2H, br. s, $N\underline{H}_2$), 7.08-7.40 (5H, m, $C_6\underline{H}_5$) 8.93 (1H, br.s, N$\underline{H}$).

^{13}C nmr δ(d_6-dmso) : 36.90 ($\underline{C}H_2CO_2H$), 38.00 ($\underline{C}H_2Ph$), 50.80 ($\underline{C}HCH_2CO_2H$), 51.99 ($CO_2\underline{C}H_3$), 53.40 ($\underline{C}HCH_2Ph$), 126.64-136-90 ($\underline{C}_6H_5$), 171.10 ($\underline{C}ONH$), 171.66 ($\underline{C}O_2CH_3$), 172.50 ($\underline{C}O_2H$).

Hydrogenation of the inseparable mixture (121a) under the above conditions but at 20°C afforded (100%) a mixture of (R)-Asp-(S)-PheOMe (122) and (S)-Asp-(S)-PheOMe (95) in a 5:2 ratio from the relative intensities of $C\underline{H}_3OCO$ signals (δ3.61 and 3.59) in the ^1H nmr spectrum (d_6-dmso, 200 MHz).

Diketopiperazines (96) and (125)

(S)-Asp-(S)-PheOMe (95) underwent intramolecular cyclisation in d_6 dmso solution to give the diketopiperazine (96) [not recovered].

^{1}H nmr (200 MHz) δ(d_6-dmso) : 1.49 (1H, dd, J=7.0, 16.5 Hz, $CHCH_AH_BCO_2H$), 2.02 (1H, dd, J=5.0, 16.5 Hz, $CHCH_AH_BCO_2H$), 2.91 (1H, dd, J=5.0, 14.0 Hz, $PhCH_AH_BCH$), 3.11 (1H, dd, J=4.5, 14.0 Hz, $PhCH_AH_BCH$), 4.02 (1H, m, $CHCH_2CO_2H$), 4.21 (1H, m, $CHCH_2Ph$), 7.10-7.33 (5H, m C_6H_5), 7.89 (1H, d, J=1.5 Hz, NH), 8.16 (1H, d, J=1.5 Hz, NH).

^{13}C nmr δ(d_6-dmso) : 38.02 (CH_2CO_2H), 38.12 (CH_2Ph), 51.10 ($CHCH_2CO_2H$), 55.27 ($CHCH_2Ph$), 126.74-136.29 (C_6H_5), 166.54 (NHCO), 166.75 (NHCO), 171.57 (CO_2H).

(R)-Asp-(S)-PheOMe (122) underwent intramolecular cyclisation to give the diketopiperazine (125) [not recovered].

^{1}H nmr (200 MHz) δ(d_6-dmso) : 2.49 (2H, m, $CHCH_2CO_2H$), 2.87 (1H, dd, J=5.0, 13.5 Hz, $PhCH_AH_BCH$), 3.12 (1H, dd, J=4.0, 13.5 Hz, $PhCH_AH_BCH$), 4.11 (1H, m, $CHCH_2CO_2H$), 4.53 (1H, m, $CHCH_2Ph$), 7.14-7.27 (5H, m, C_6H_5), 7.94 (1H, d, J=1.0 Hz, NH), 8.12 (1H, d, J=1.0 Hz, NH).

^{13}C nmr δ(d_6-dmso) : 36.87 (CH_2CO_2H), 38.25 (CH_2Ph), 50.33 ($CHCH_2CO_2H$), 55.74 ($CHCH_2Ph$), 126.70-136.15 (C_6H_5), 167.01 (NHCO), 167.33 (NHCO), 171.72 (CO_2H).

CHAPTER 4

General Procedure for Conversion of Amines into Imines by Swern Oxidation[76]

A solution of oxalyl chloride (0.96 ml, 11 mmol) was placed in a 100 ml round-bottom flask equipped with magnetic stirrer, self-equilibrating dropping funnel and a silica gel drying tube. The solution was cooled to -60°C. Dimethyl sulphoxide (1.56 ml, 22 mmol) was dissolved in dichloromethane (2 ml) and added to the solution dropwise over 5 mins with stirring. After stirring for a further 3 mins, the appropriate amine (10 mmol) in dichloromethane (3 ml) was added over 5 mins and the mixture stirred for a further 10 mins maintaining the temperature at -60°C. Triethylamine (7 ml, 50 mmol) was then added over 10 mins and the mixture allowed to warm slowly to room temperature. Water (20 ml) was added and the mixture shaken vigorously. The organic layer was separated and the aqueous layer washed with a further portion of dichloromethane (20 ml). The combined organic layers were washed with brine, dried with anhydrous Na_2SO_4 and solvent removed *in vacuo* to leave a crude oil.

Indole (143)

Indole was prepared from indoline (141) by the general procedure. Glc of the total crude product (2% SE 52 on GCQ at 115°C) showed it to consist of indoline (141) [1.3%; I (Kováts Index) 1238], indole (143) [87.5%; I 1320], and the N-methylthiomethyl amine (145) [11.2%; I 1612]. Bulb-tube distillation (bp 115°C at 2 mm Hg) afforded indole, mp 49-53°C (lit. 52-54°C), identical (glc, nmr, ms) with authentic indole. The residue consisted mainly of the N-methyl-

thiomethyl amine (145).

^{1}H nmr $\delta(CDC\ell_3)$: 1.90 (3H, s, $C\underline{H}_3S$), 3.02 (2H, t, J=8.0 Hz, $C\underline{H}_2CH_2N$), 3.56 (2H, t, J=8.0 Hz, $CH_2C\underline{H}_2N$), 3.58 (2H, s, $N\text{-}C\underline{H}_2S$), 6.6-7.4 (4H, m, $C_6\underline{H}_4$).

$[M]^+$ 179 , $[M]^+ - SCH_3$ 132.

2-Methylindole (144)

2-Methylindole (144) was prepared from 2-methylindoline (142) by the general procedure. Glc of the total crude product (2% SE 52 on GCQ at 115°C) showed it to consist of 2-methylindoline (142) [1.1%; I 1245], 2-methylindole (144) [88.3%; I 1403], and the N-methylthiomethyl amine (146) [10.6%; I 1612]. Silica gel chromatography (10% EtOAc-hexane) afforded 2-methylindole, mp 58-60°C (lit. 58-60°C), identical (glc, nmr, ms) with authentic 2-methylindole. The residue consisted of a mixture of 2-methylindole, unreacted 2-methylindoline and the N-methylthiomethyl amine (146) which was identified in the low resolution mass spectrum of the crude residue, $[M]^+$ 193, $[M]^+$-SCH_3 146.

N-Benzylidenebenzylamine (151)

N-Benzylidenebenzylamine (151) was prepared from dibenzylamine (149) by the general procedure. The Schiff base (151) [63.4%] was readily separated by bulb-tube distillation (210°C at 0.25 mm Hg) and was found to be identical (ir, nmr, ms) with an authentic sample prepared from benzylamine and benzaldehyde. The residue consisted

entirely of the oily methylthiomethyl amine (153) [36.6%].

^{1}H nmr $\delta(CDC\ell_3)$: 2.14 (3H, s, $C\underline{H}_3S$), 4.47 (4H, br.s, $C\underline{H}_2Ph$), 5.28 (2H, s, $C\underline{H}_2S$), 7.28 (10H, s, $C_6\underline{H}_5$).

$[M]^+$ 257.1262 ; $C_{16}H_{19}NS$ requires 257.1258

$[M]^+-SCH_3$ 210.1280

$[M]^+-CH_2SCH_3$ 196.1124.

N-Benzylidenebenzylamine (151) from Benzaldehyde and Benzylamine

Benzylamine (0.55 ml, 5 mmol) and benzaldehyde (0.51 ml, 5 mmol) were dissolved in dichloromethane (50 ml) and the mixture heated to reflux under a trap of molecular sieves (4A) for 2½ hrs. The solvent was removed in vacuo to give the Schiff base (151) as a yellow oil (0.93g, 95%).

^{1}H nmr $\delta(CDC\ell_3)$: 4.70 (2H, s, $PhC\underline{H}_2$) 7.15-7.80 (10H, m, $C_6\underline{H}_5$), 8.19 (1H, br.s, N=C$\underline{H}$Ph).

N-Benzylideneaniline (152)

N-Benzylideneaniline (152) was prepared from phenylbenzylamine (150) by the general procedure. The crude mixture was inseparable by distillation, sublimation or alumina chromatography. The 90 MHz ^{1}H nmr spectrum was a superposition of the spectra of the Schiff base (152) [52.5%] and the methylthiomethyl amine (154) [47.5%].

^{1}H nmr [Methylthiomethyl amine (154)] $\delta(CDC\ell_3)$: 1.92 (3H, s, $C\underline{H}_3S$), 3.70 (2H, s, $C\underline{H}_2S$), 4.38 (2H, br.s, $C\underline{H}_2Ph$).

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