A THESIS ENTITLED

"ASYMMETRIC SYNTHESES OF β-AMINO ACIDS"

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 Mum and Dad,

Elizabeth, Nan and Nellie

Acknowledgements

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SUMMARY

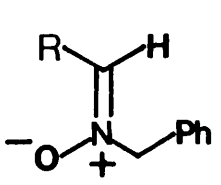
Summary

Whereas the asymmetric synthesis of α-amino acids has received considerable attention[2] over the past two decades, there have been relatively few published investigations which deal with the asymmetric synthesis of β-amino acids.[22-27]

It was the aim of the work described in this thesis to devise an improved asymmetric synthesis of β-amino acids involving the construction of heterocyclic intermediates in a diastereoselective manner, particularly by the 1,3-dipolar cycloaddition reactions of chiral nitrones with suitably substituted alkenes.

The Introduction reviews the natural occurrence of the more important β-amino acids, previous asymmetric syntheses, and the 1,3-dipolar cycloaddition chemistry of nitrones, including enantio- and diastereoselective processes.

Chapter 1 describes the synthesis of a series of chiral and achiral nitrones and the first systematic investigation of the stereochemistry of aliphatic aldonitrones, involving analysis of N-benzyl nitrones (6-8) by Nuclear Overhauser Difference Spectroscopy (NOEDS). The results of this investigation demonstrate that (6-8) are formed exclusively in the Z configuration.

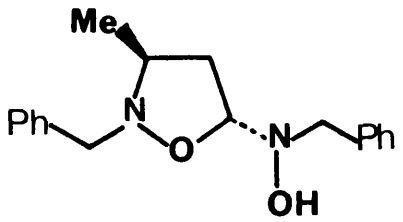


(6) R=**Me**

(7) R=*i*-**Pr**

(8) R=*t*-**Bu**

Conversion of nitrone (6) into the isoxazolidines (29) and (30) provides the first evidence for the formation of diastereomeric dimers from a nitrone.



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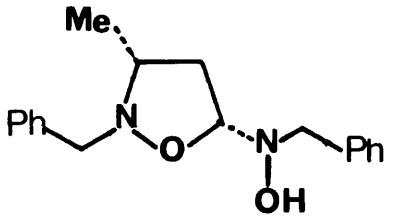
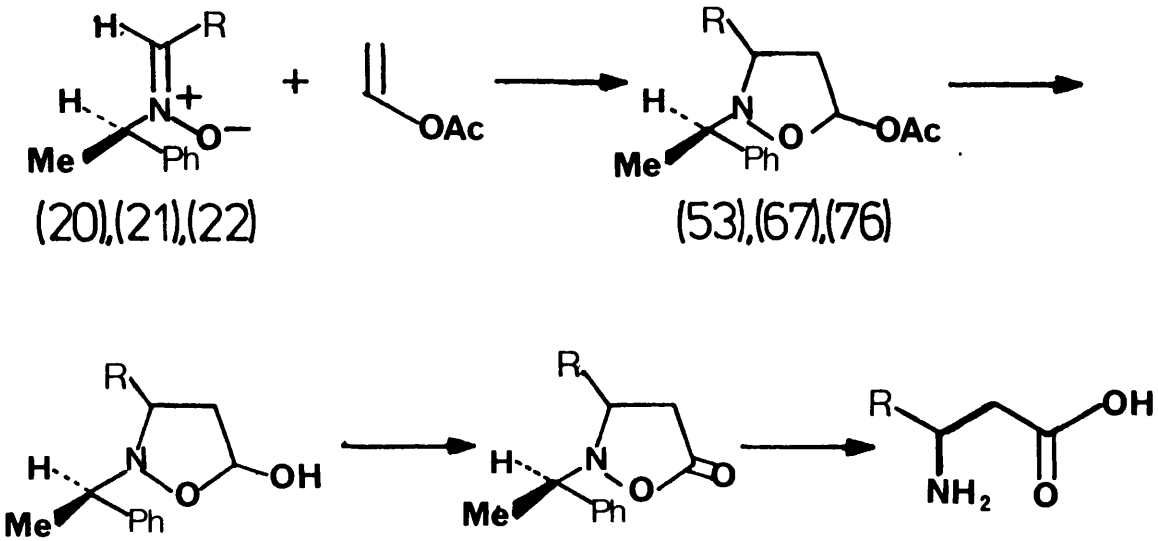


(30)

The asymmetric syntheses of β-phenyl-β-alanine (57), β-leucine (71) and β-tyrosine methyl ether (80) are described in Chapter 2. They depend upon the reaction of chiral nitrones with 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]. Subsequent hydrolysis of the acetate moiety affords a lactol which can be oxidised to the isoxazolidin-5-one system. Catalytic hydrogenolysis of these isoxazolidinones by N-O fission and deprotection of the nitrogen function leads to the free β-amino acids.

Chapter 3 describes an investigation of the 1,3-dipolar cycloadditions of nitrones with alkyl ketene acetals as a potentially new route to β-amino acids. The chiral induction observed in the formation of isoxazolidines such as (101) from the chiral phenyl nitrone (21) and



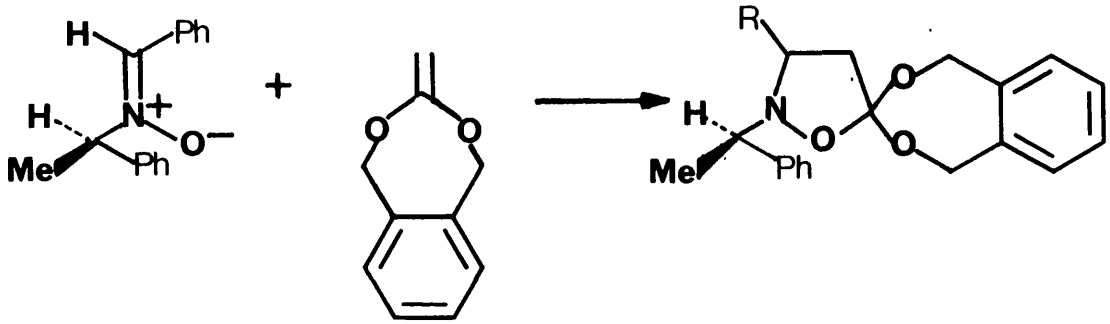
(20),(67),(68),(70),(71) R=*i*-Pr

(21),(53),(54),(56),(57) R=Ph

(22),(76),(77),(79),(80) R=pMeOPh

Scheme I

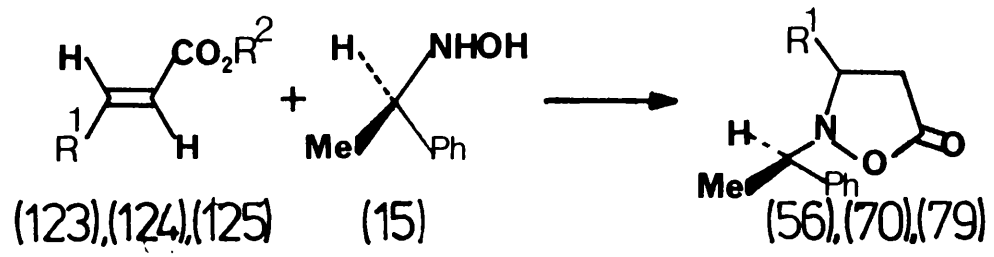
[o-xylyl]ketene acetal (85) is far superior to that observed with vinyl acetate, [Scheme II].



(21) (85) (101)

Scheme II

An alternative synthesis of the chiral isoxazolidin-5-ones (56), (70) and (79), is described in Chapter 4, entailing a one-pot reaction of hydroxylamine (15) and unsaturated esters (123-125), [Scheme III].



(123),(124),(125) (15) (56),(70),(79)

(56),(125) R^1=Ph, R^2=Et
(70),(123) R^1=*i*-Pr, R^2=Me
(79),(124) R^1=pMeOPh, R^2=Me

Scheme III

INTRODUCTION

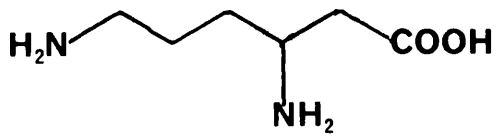
INTRODUCTION

I. Background

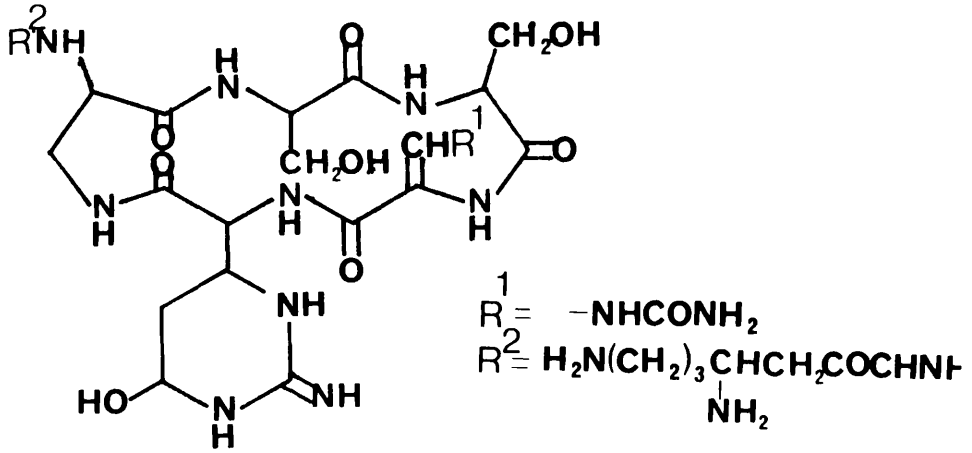
In the past decade many asymmetric syntheses, useful in the construction of optically pure natural products, have been discovered.[1] The α-amino acids, as the building blocks of proteins, have been at the centre of many such investigations.[2] However, to date, the synthesis of β-amino acids as single enantiomers has received little attention. β-Amino acids are of great current interest because of their natural occurrence as components of biologically active antibiotics and also their structural relationship to the β-lactam,[3] one of the most biologically important functional groups. In addition, β-amino acids are known to take part in several important metabolic pathways.

2. The Natural Occurrence of β-amino Acids

β-Lysine (1) is the most studied of the naturally-occurring β-amino acids, and was first isolated from several Streptomyces antibiotics in the early 1950's. In 1952, Haskell[4] isolated a basic amino acid from the acid hydrosylate of viomycin (2), a tuberculostatic antibiotic, from Streptomyces floridae. The new amino acid was shown to be isomeric with lysine, and was identical to an acid previously isolated from streptothricin (3),[5] a ubiquitous family of broad spectrum antibiotics produced by Streptomyces species.



(1)



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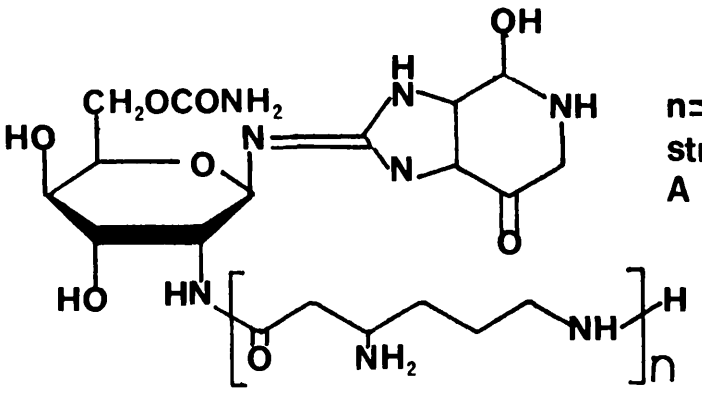
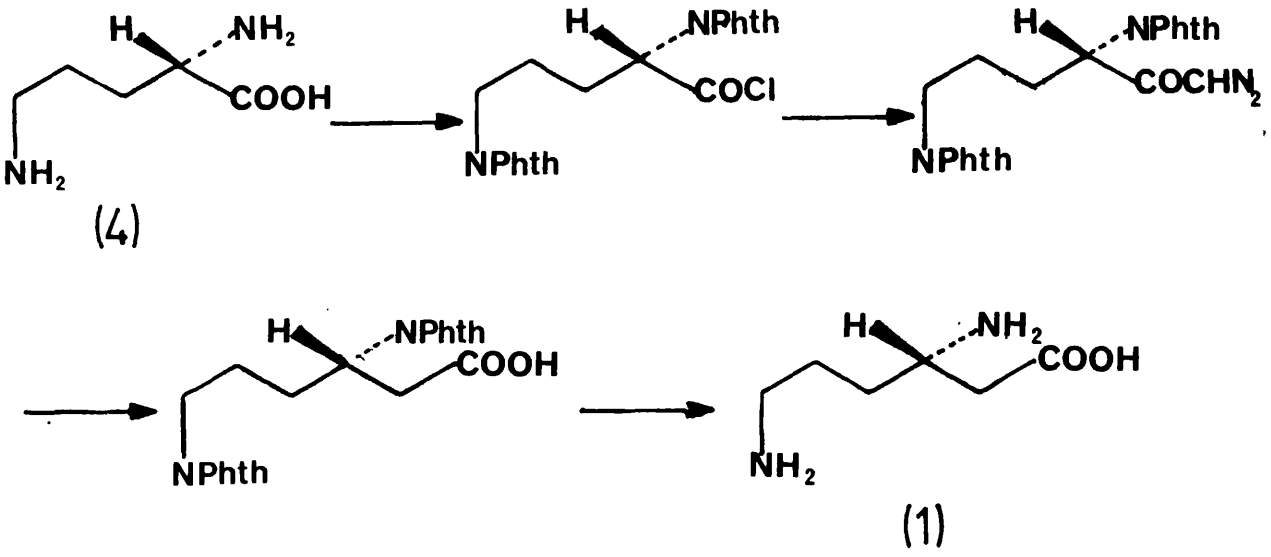


(3)

n= 1,2,3,4,5,6 and 7 for streptothricins F,E,D,C,B, A and X respectively.

The "isolysine" structure was confirmed as β-lysine in 1953 by Van Tamelen,[6] who synthesised (S)-β-lysine (1) by Arndt-Eistert homologation of L-ornithine (4), [Scheme 1].



Reagents: 1. Phthalic anhydride, 2. $(COCl)_2$, 3. CH_2N_2,
4. $Ag^+ {}^-O_2CC_6H_5$, 5. NH_2NH_2, H_3O^+.

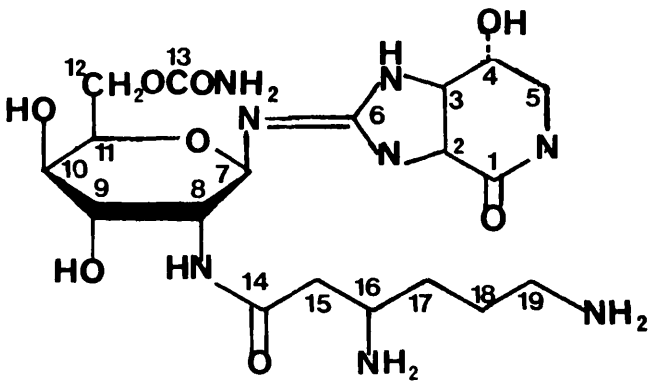
Scheme 1

Yonehara and Otake[7] have since shown, by ORD, the (S)-configuration to be the natural form of β-lysine.

The biosynthesis of β-lysine has received attention and, in particular, its incorporation into the streptothricin family of antibiotics, sometimes referred to as the racemomycins. In 1971, Taniyama[8] isolated and characterised streptothricins F, E, D and C from a mutant strain of Streptomyces racemochrogenus, which were shown to contain one, two,

three and four β-lysine residues respectively. It has been claimed[8] that the biological activities of the streptothricins such as antimicrobial, antiviral and acute toxicity become more pronounced as the number of β-lysine residues increases.

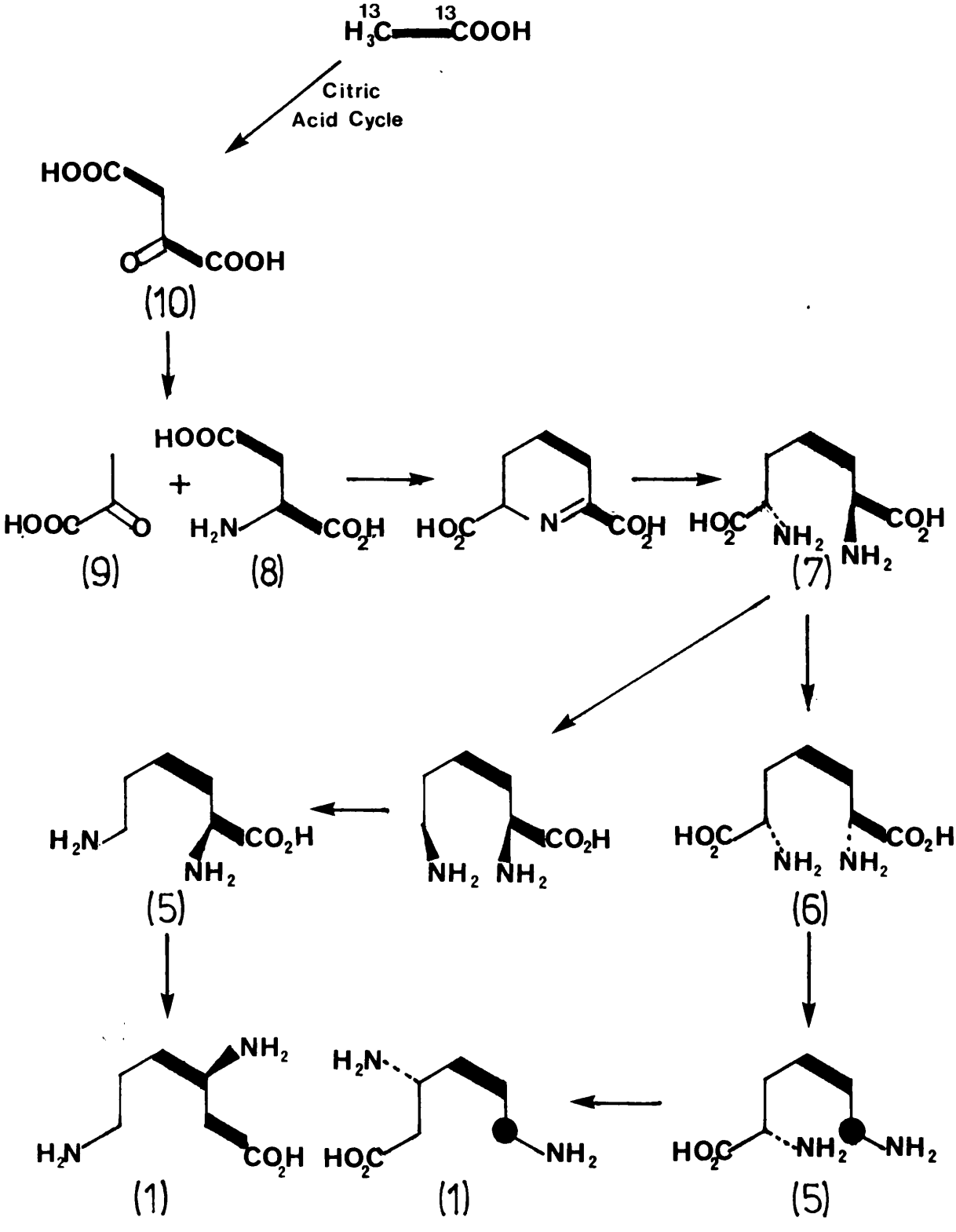
The biosynthesis of streptothricin F (3a) has been extensively investigated by Gould,[9] who has obtained specific incorporation of [1,2-$^{13}C_2$] acetate into the β-lysine portion of (3a) in Streptomyces L-1689-23.



(3a)

This finding is consistent with β-lysine being derived from α-lysine (5) which is formed via the diaminopimelic acid (DAP) pathway [Scheme 2]. In this pathway (2S, 6S) DAP (7) derived from pyruvic acid (9) and aspartic acid (8), is epimerised to meso-DAP (6) and then decarboxylated. Aspartic acid is obtained by transamination of oxaloacetic acid (10), thus revealing the specific but indirect labelling of the β-lysine moiety of streptothricin F by acetate.

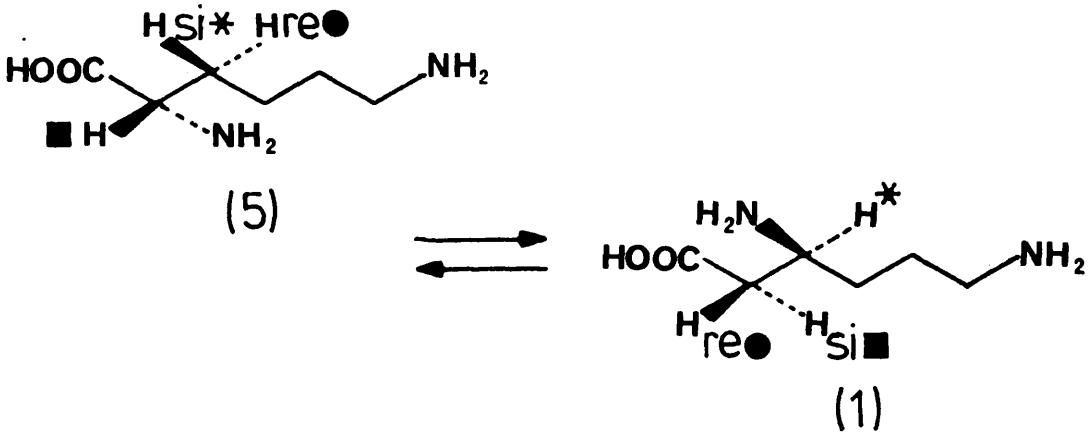
The mechanism and stereochemistry of the conversion of α-lysine to β-lysine has been investigated in species of the genera Streptomyces[10,11] [as part of the streptothricin F molecule] and Clostridium.[12,13] The transformation, catalysed by the enzyme lysine-


13 13
H3C COOH
Citric
Acid Cycle
HOOC
O
COOH
(10)
HOOC
HOOC O
(9)
+
H2N CO2H
(8)
HO2C N CO2H
HO2C NH2 CO2H
NH2
(7)
H2N CO2H
NH2
(5)
NH2 NH2
CO2H
HO2C NH2 NH2
CO2H
(6)
NH2
H2N
CO2H
(1)
H2N
HO2C NH2
(1)
HO2C NH2 NH2
(5)

Scheme 2

2,3-aminomutase constitutes the first step of a major metabolic pathway of lysine in Clostridia and other bacteria.

Aberhart[12,13] has elucidated the stereochemistry of the lysine-2,3-aminomutase reaction in Clostridium subterminae strain, SB4. Deuterium labelling and ^2H nmr were used to show that the transformation of (2S)-α-lysine (5) to (3S)-β-lysine (1) as shown in Scheme 3, proceeds with transfer of the 3-H_{re} proton of α-lysine to the 2-H_{re} position of β-lysine. The 3-H_{si} hydrogen of α-lysine is retained at C-3 of β-lysine. The H-2 of α-lysine is retained at the 2-H_{si} position of β-lysine. Thus the reaction proceeds with inversion of configuration of both C-2 and C-3.

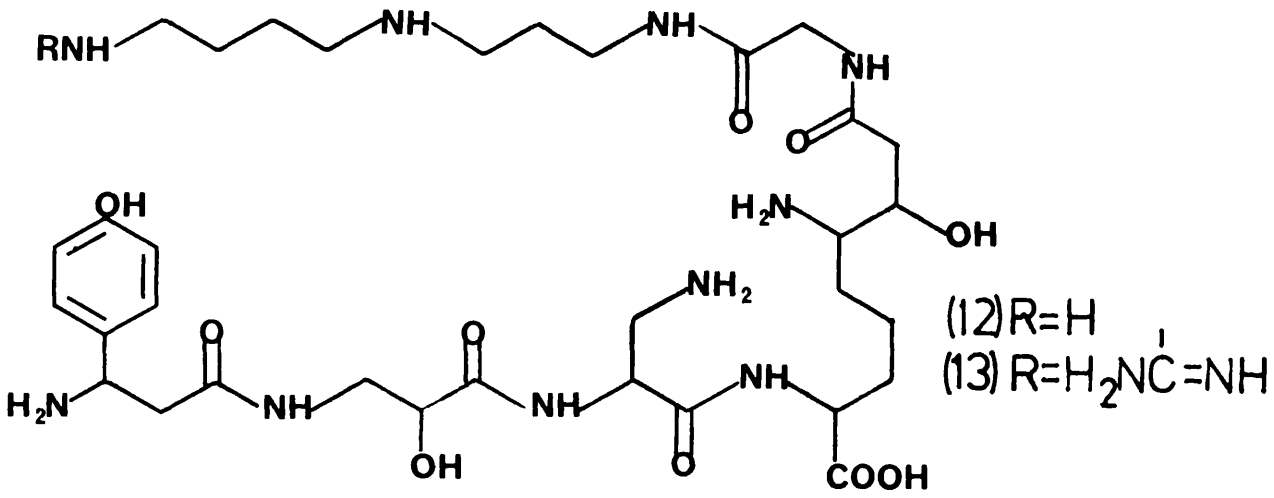


Scheme 3

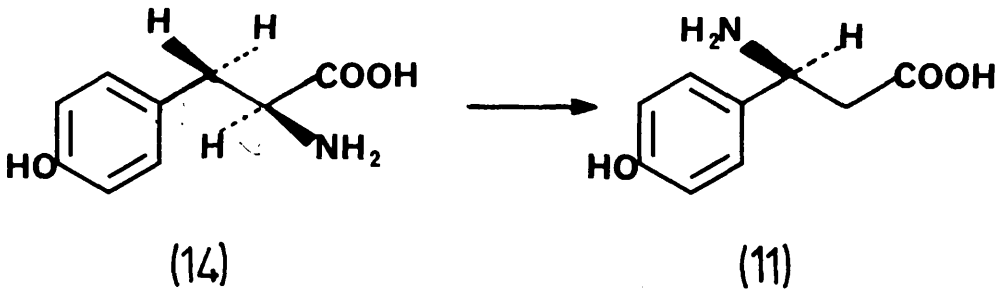
Gould and Aberhart[12,13] have demonstrated that in C.SB4, amino group transfer occurs completely intramolecularly, and that migration of hydrogen is substantially or completely intermolecular. It has also been established by the same authors that the stereochemistry of the Streptomyces α-lysine-2,3-aminomutase reaction, is identical to that of the Clostridium transformation, [c.f. Scheme 3].[11]

Of the naturally occurring β-amino acids, β-tyrosine (11) and β-leucine (15) have been shown to be derived from the corresponding α-amino acid as a result of a mutase-catalysed reaction.

β-Tyrosine[14] has been found as a constituent of the peptide antibiotics edeine A (12) and edeine B (13), isolated from cultures of Bacillus brevis Vm4.



The enzyme tyrosine-α,β-mutase, catalyses the isomerisation of L-α-tyrosine (14) to β-tyrosine [Scheme 4].

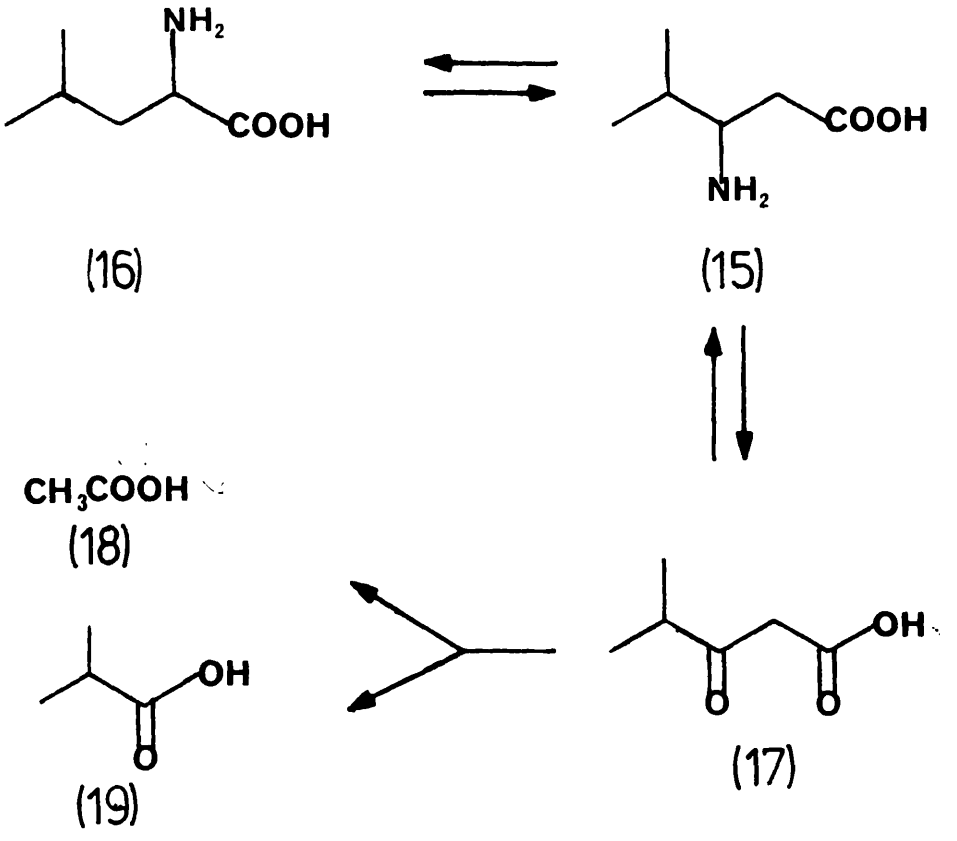


(14) (11)

Scheme 4

Parry and Kurylo-Borowska[14] have demonstrated that the interconversion proceeds with exchange of the 3-H_{si} hydrogen of L-α-tyrosine and both C-2 hydrogens of β-tyrosine, as well as of the amino group, with hydrogen and ammonium ions respectively, of the medium.

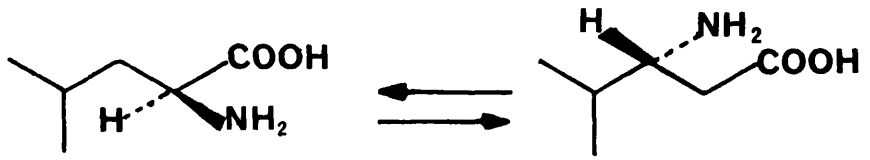
The natural occurrence of β-leucine (15) was first demonstrated by Poston in 1976.[15] Evidence has been presented that in Clostridium sporogenes, the initial step in the fermentation of leucine (16) to acetate (18), isobutyrate (19) and ammonia, involves a B_{12} coenzyme-dependent conversion to β-leucine [Scheme 5]. The amino group migration is catalysed by the enzyme leucine-2,3-amino mutase, and is reversible. The β-amino acid is then transaminated to β-ketoisocaproate (17) before breakdown to acetate and isobutyrate.



Scheme 5

Leucine-2,3-aminomutase activity has been discovered in a variety of sources, including several species of Clostridia, the livers of several mammals, human leukocytes, as well as in plant tissue such as potato tubers and ryegrass.[16] In each of these cases it is claimed that the enzyme activity is co-enzyme B_{12}-dependent.

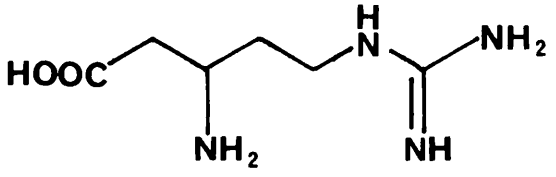
Overton[17] has however reported that leucine-2,3-aminomutase activity in tissue cultures of Andrographis paniculata does not show a co-enzyme B_{12} dependence, in contrast to the results of Poston, and has established that the metabolically active substances are (2S) α-leucine (16.a) and (3R) β-leucine (15.a), [Scheme 6].



(16a) (15a)

Scheme 6

The mechanism by which β-arginine (20) is formed has not, as yet, been established, but it has been isolated from blasticidin S (21), an antibiotic, effective against rice blast disease, from Streptomyces griseochromogenes.[18] The biosynthesis of (21) is currently under investigation by Gould.[19]



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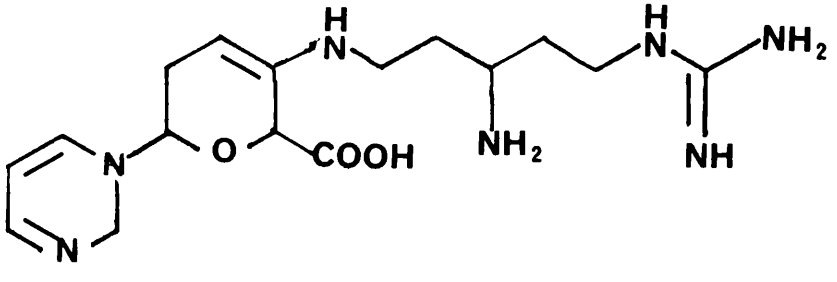
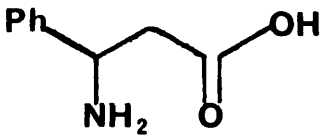


(21)

(R) β-phenyl-β-alanine (22) has been isolated from the cyclic peptide roccanin (23) from the lichen Rocella canarienses,[20] and from several toxic metabolites of Penicillium islandicum, the mold of islandia yellow rice.[21] The biosynthesis of β-phenyl-β-alanine has not been studied.



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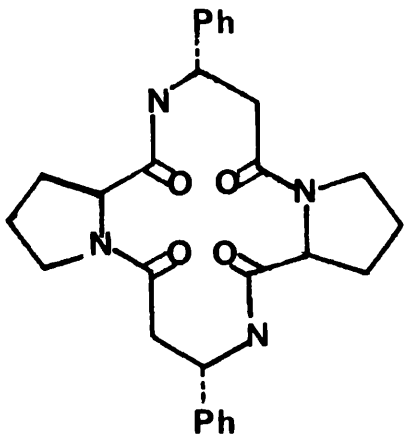


(23)

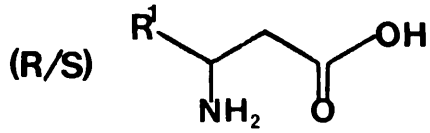
The occurrence of β-alanine and other β-amino acids has been reviewed by Drey.[45]

3. Asymmetric Synthesis of β-Amino Acids

There are relatively few reported investigations on the asymmetric synthesis of β-amino acids in comparison to those concerning α-amino acids.

In 1964, Tertentev[22] reported the first enantioselective syntheses of β-amino acids, by the addition of chiral amines to crotonic acid, in poor chemical and optical yields. It was not until 1977, that Furukawa et al,[23] performed an asymmetric synthesis of several β-amino

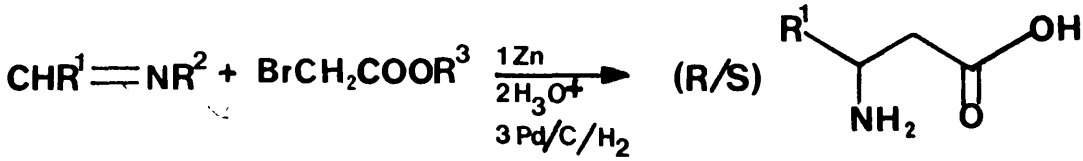
acids, by addition of chiral benzylic amines to 1-cyanopropenes and α,β-unsaturated esters, [Scheme 7]. Hydrolysis and hydrogenolysis of the adducts formed gave amino acids in enantiomeric excesses of 2-19%, and chemical yields of 10-47%.



R^1= H,Me,Ph
R^2= CN, COOMe, l-carboxymenthyl
R^3= (R)or(S)-PhCHMe

Scheme 7

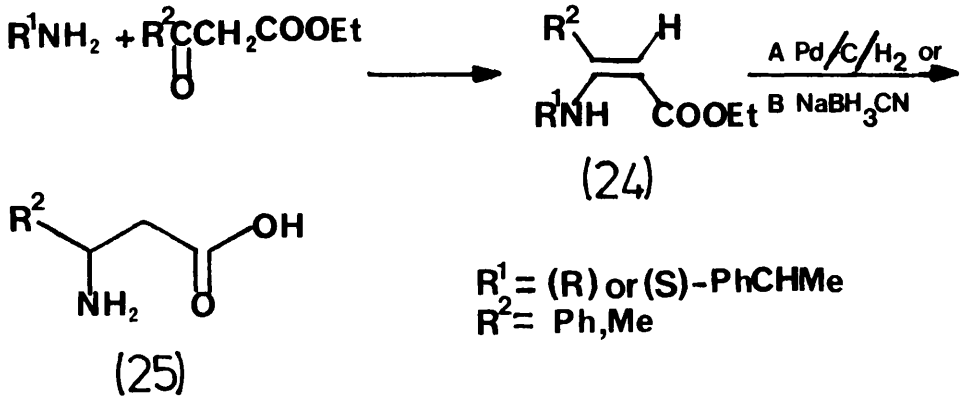
Furukawa[24] has also reported a variation of the Reformatski reaction in which a chiral Schiff base on treatment with an α-bromo ester provides β-amino acids in 2-28% enantiomeric excess, [Scheme 8].



R^1= Me, Ph
R^2= (R) or (S)-PhCHMe
R^3= Et, l-menthyl

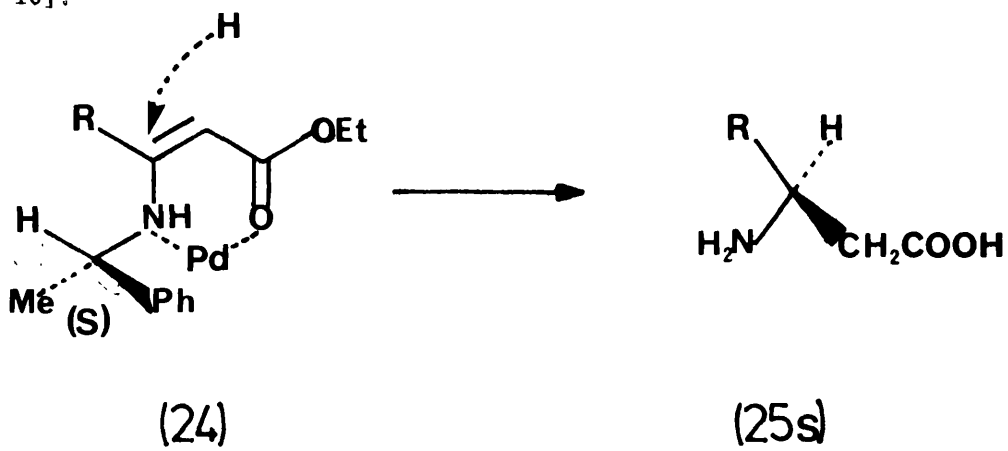
Scheme 8

Catalytic hydrogenation or hydride reduction of 3(R or S α-methylbenzyl)amino acrylates affords β-amino acids in enantiomeric excesses of 3-28%, [Scheme 9].



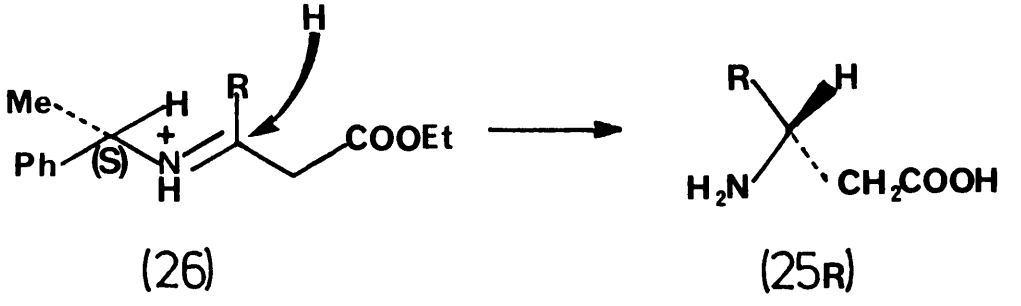
Scheme 9

In this case the configuration of the amino acid produced depends on the method of reduction employed. Catalytic hydrogenation of the enamine (24) in the Z configuration, is assumed to proceed via a six-membered chelate ring in which a hydrogen atom approaches preferentially from the less hindered re face to give the (S)-amino acid (25S), [Scheme 10].



Scheme 10

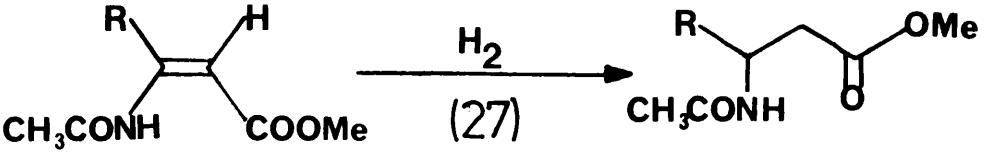
On the other hand, cyanoborohydride reduction of the enamine (24) is initiated by protonation to the imminium cation (26), which is then reduced to the (R)-amino acid (25R), [Scheme 11], by hydride attack of the si face.

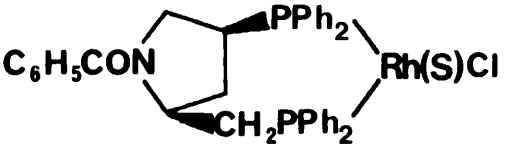


(26) (25R)

Scheme 11

Achiwa[26] has employed homogeneous chiral catalysts to effect stereoselective hydrogenation of methyl (Z)-3-acetylaminoprop-2-enoates to give chiral amino esters in enantiomeric excesses of 3-55%, [Scheme 12]. The chiral rhodium bisphosphine complex (27) may be prepared in situ.

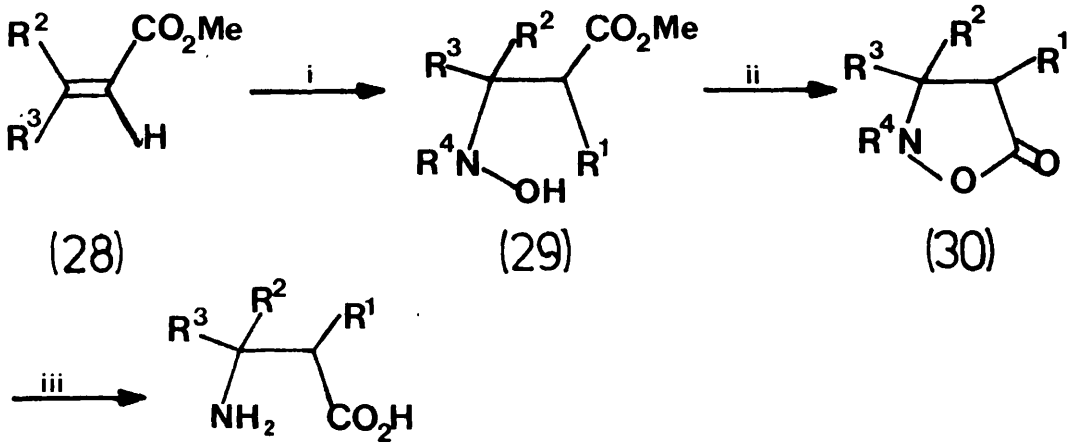




(27)

Scheme 12

Recently Baldwin[27] has reported an enantioselective approach towards α- and β-substituted β-amino acids via chiral isoxazolidinones (30). The isoxazolidinones may be prepared by conjugate addition of chiral hydroxylamine to an α,β-unsaturated ester (28), and cyclisation of the resulting adducts (29) is effected with lithium bis(trimethylsilyl)amide, the only base found to give high and reproducible yields of isoxazolidinones. Cleavage of the N-O Bond in (30) by hydrogenolysis is accompanied by removal of the benzylic nitrogen protecting group permitting direct synthesis of the β-amino acid, [Scheme 13].



(28) (29) (30)

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

	R^1	R^2	R^3	R^4
a	Me	H	H	(S)PhCHMe
b	H	CO_2Me	H	(S)PhCHMe
c	H	H	Me	(S)PhCHMe

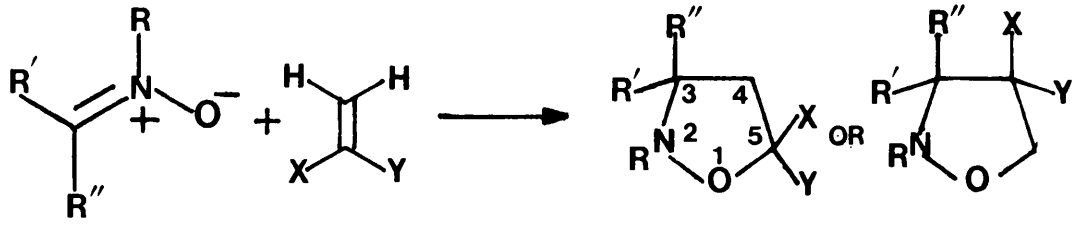
Scheme 13

Enantiomeric excesses in the range of 10-28% are obtained. In one case separation of the diastereomeric adducts (30C) was possible and this led to synthesis of β-methyl-β-alanine in 88% enantiomeric excess.

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

4.1 Background

In recent years the application of cycloaddition reactions to control the stereochemistry of acyclic systems has been an area of intense activity. The 1,3-dipolar cycloaddition of a nitrone (31) with substituted olefins to give isoxazolidines (32), [Scheme 14] has come to prominence as an extremely powerful, yet mild means of producing carbon-carbon bonds, and is particularly well suited to the construction of nitrogen-containing substances.[28]



(31) (32a) (32b)

Scheme 14

Moreover, nitrone cycloadditions frequently embody a high degree of regio- and stereochemical control, and since the N-O bond of

the isoxazolidine can, in most cases, be easily cleaved, a number of imaginative synthesis have employed isoxazolidine formation and ring opening as key steps.[29] The details of an investigation into the application of [3 + 2] nitrone-olefin cycloaddition reactions to the asymmetric syntheses of β-amino acids are discussed in Chapters 2 and 3 of this thesis.

4.2 Synthesis and Structure of Nitrones

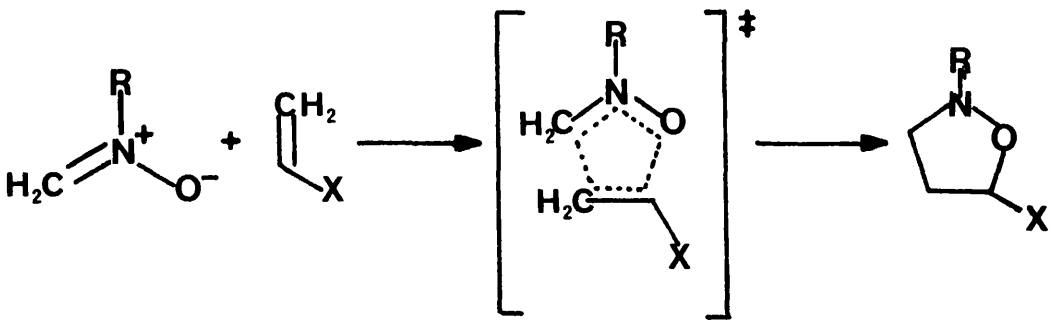
Most general procedures for the preparation of acyclic nitrones have been employed during the course of this work and are described in Chapter 1 of the Discussion section. The structure and stereochemistry of nitrones are also discussed in Chapter 1.

4.3 The Mechanism of 1,3 Dipolar Cycloaddition Reactions of Nitrones

Although current trends indicate that 1,3 dipolar cycloadditions of nitrones have become a versatile element in the synthesis of natural products such as alkaloids,[30] β-lactams[31] and amino sugars,[32,33] the reaction received little attention until the early 1960's when the brilliant work of Huisgen[34] led to an intense interest in the field of cycloaddition chemistry as a whole. The associated regio- and stereochemical control of 1,3-dipolar cycloadditions has led to much discussion and controversy over the past twenty five years in an attempt to rationalise these vital features of the reaction.

The reaction may be treated formally as an allowed [π^4S-π^2S] process, analogous to the related Diels-Alder cycloaddition. It is now

generally accepted that most 1,3-dipolar cycloadditions, including those of nitrones (eg. Scheme 15), are single step, four centre, concerted reactions in which two new σ-bonds are formed simultaneously, though not necessarily at the same rate, in agreement with the original postulate of Huisgen in 1963.[34]



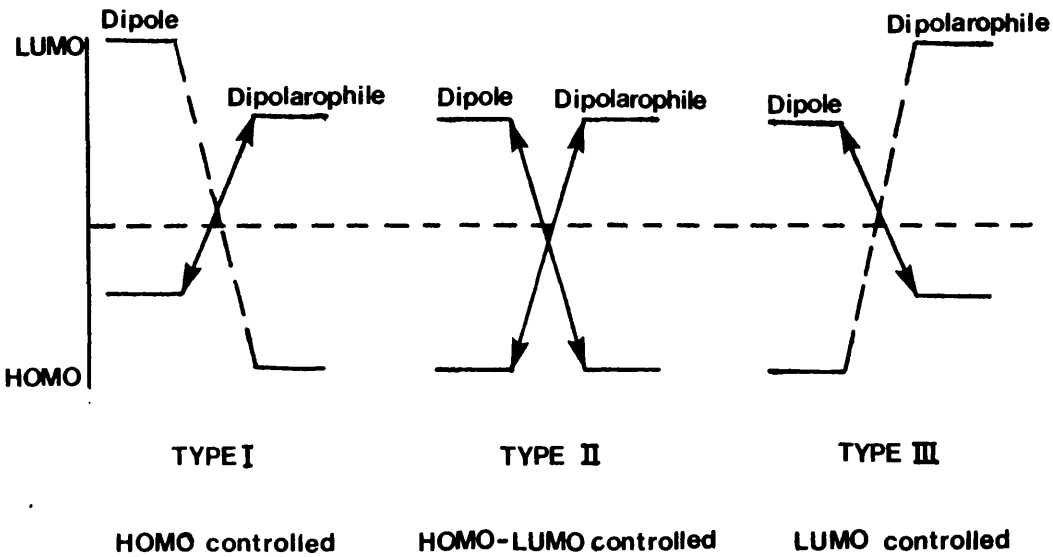
Scheme 15

One of the main arguments for a concerted mechanism employed by Huisgen[35] is the strict cis stereospecificity of the process, in that the stereochemical relationships incorporated in the dipolarophile are preserved in the product isoxazolidine. The stereochemical aspects of the reaction are covered in Section 4.4 of this Introduction.

The suggestion that diradical intermediates[36] are involved in 1,3-dipolar-additions has been severely criticized by Huisgen,[35] arguing that a diradical mechanism cannot account for the observed energetics and stereochemistry of the reaction.

Before the advent of frontier molecular orbital theory, the regiochemistry of 1,3-dipolar cycloadditions had been regarded as the biggest unsolved problem in the field. In the hands of Sustmann,[37] Houk,[38] and Bastide,[39] perturbation theory has been successfully applied to explain both the reactivity and regiochemistry of 1,3-dipolar cyclo-

additions. According to these authors, 1,3-dipolar cycloadditions can be classified into three types depending on the relative disposition of the 1,3-dipole and olefin frontier orbitals, [Scheme 16].



Scheme 16

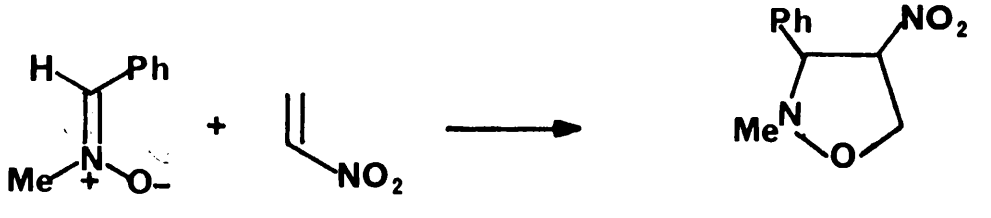
These are: type I, where the interaction of the HOMO (dipole) with LUMO (dipolarophile) is greater; type II, where both frontier orbital interactions must be taken into account; type III, where the LUMO (dipole)-HOMO (dipolarophile) interaction is greater. These are referred to more concisely as HOMO, HOMO-LUMO, and LUMO controlled cycloadditions.[37]

Qualitatively,[38] HOMO type cycloadditions are accelerated by electron-donating substituents on the dipole and electron-withdrawing substituents on the dipolarophile, as a result of decreasing the difference in energy between the reacting frontier orbitals. Conversely electron

donating substituents which raise the dipolarophile HOMO and electron withdrawing substituents which lower the dipole LUMO, accelerate LUMO controlled reactions as a result of the enhanced frontier orbital interaction. HOMO-LUMO controlled reactions are accelerated by an increase of either frontier orbital interaction.

Nitrone cycloadditions are believed to be HOMO-LUMO controlled. As such, both frontier orbital interactions may be significant, and the interaction that dominates in a particular case will depend upon the nature of dipole and dipolarophile.

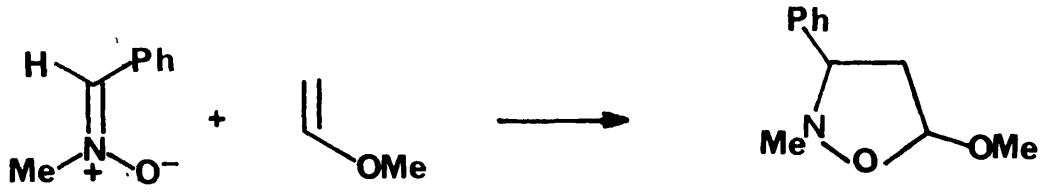
Houk[38] has employed perturbation theory to provide an explanation of the perplexing regioselectivity phenomena observed in 1,3 dipolar cycloaddition reactions. The regioselectivity for nitrone cycloadditions onto monosubstituted olefins was originally believed to proceed in a unidirectional fashion, giving 5-substituted adducts regardless of the alkene substituent. However, it was reported by Houk[40] in 1973 that very electron-deficient dipolarophiles such as nitroethylene (34) give significantly or even predominantly 4-substituted isoxazolidines (35) with N-methyl - C-phenyl nitrone (33), [Scheme 17].



(33) (34) (35)

Scheme 17

Electron-rich and moderately electron-poor monosubstituted olefins (e.g. methyl vinyl ether (36)) give exclusively 5-substituted isoxazolidines (37), [Scheme 18].



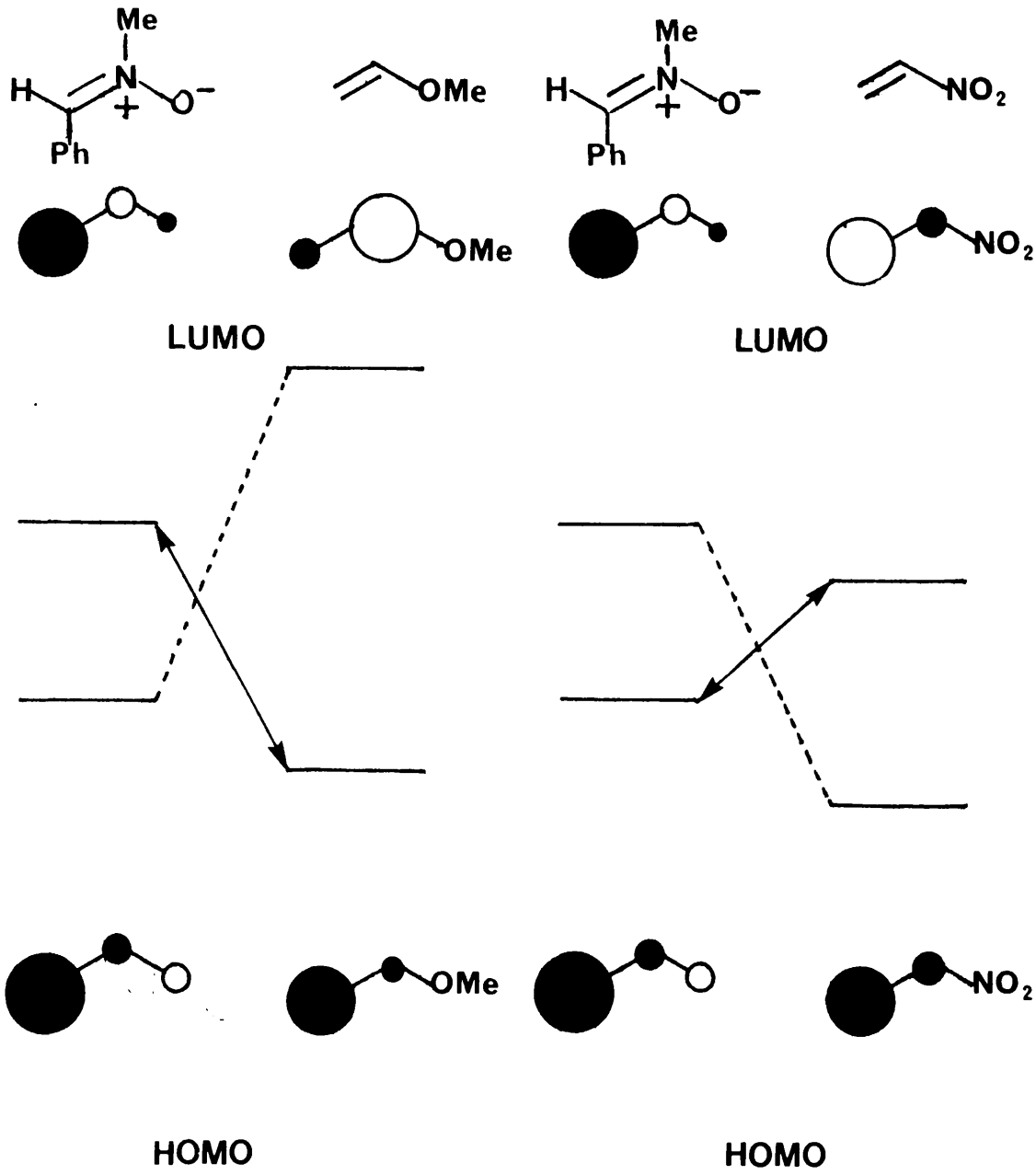
(33) (36) (37)

Scheme 18

1,1 Disubstituted olefins such as ketene acetals also form 5-substituted olefins.

Regioselectivity is determined by the relative magnitudes of the atomic orbital coefficients in the frontier molecular orbitals of both nitrone and dipolarophile. The dominant stabilizing interaction in the transition state involves the atomic orbitals of the interacting atoms with the largest coefficients (i.e. largest "size") allowing maximal FO overlap between orbitals which are closest in energy as shown in Scheme 19.

In the case of vinyl methyl ether the dominant interaction is LUMO (dipole) - HOMO (dipolarophile) in which the large AO coefficient on the carbon of the nitrone LUMO interacts with the larger coefficient associated with C-2 of the olefin HOMO, affording the 5-substituted isoxazolidine. This is in accord with experimental findings for electron-rich and moderately electron-poor olefins. For very electron-deficient dipolarophiles such as nitroethylene, the dominant interaction involves



Scheme 19

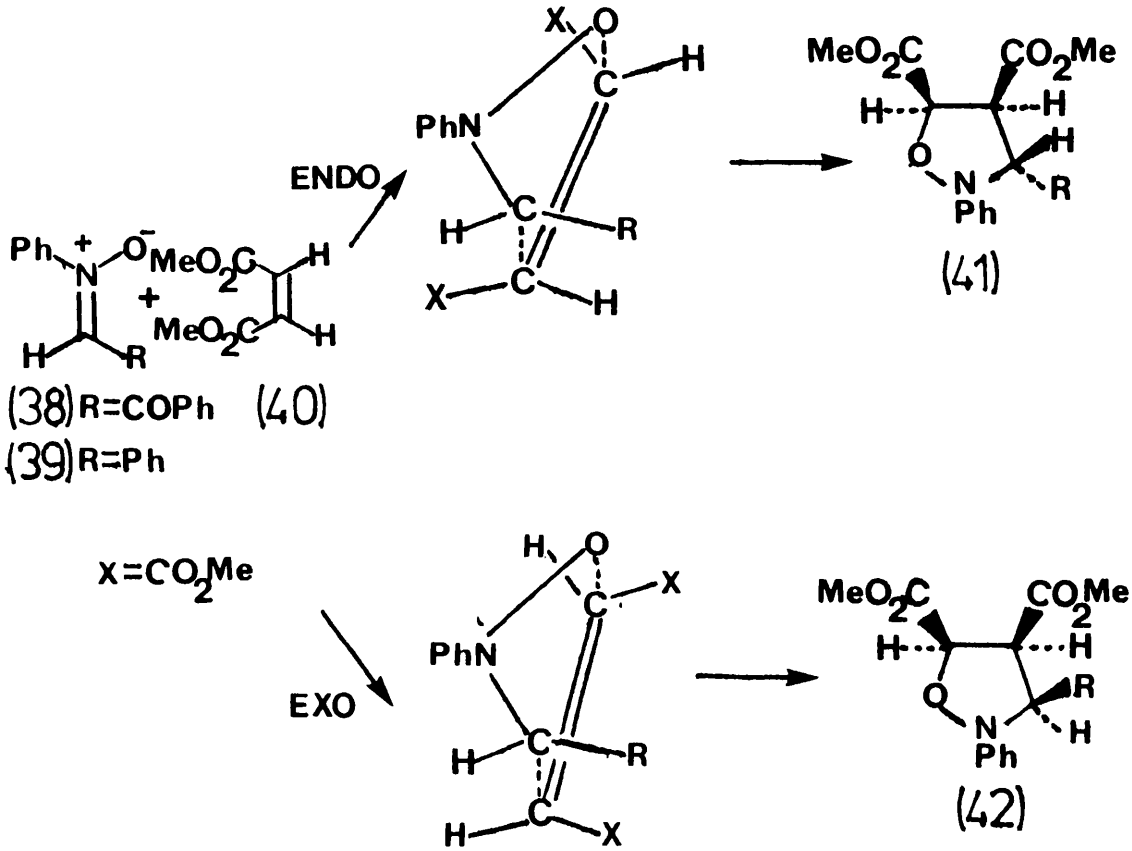
HOMO (dipole)-LUMO (dipolarophile) leading to a 4-substituted isoxazolidine. As the ionisation potential of the nitrone decreases or the electron affinity of the dipolarophile increases, a tendency towards production of 4-substituted isoxazolidines is found, i.e. a HOMO (dipole)-controlled process. At some point there must be a switch over from HOMO to LUMO control as the electron releasing power of the alkene substituent is increased. That point is apparently reached with dipolarophiles such as methyl acrylate and acrylonitrile since regioisomeric mixtures of adducts are encountered.

As regioselectivity is the result of very small energy differences (0.1-5 kcal mol^{-1}) between two transition states, the estimation of such small energy differences demonstrates the unique power of perturbation theory, in predicting the products of such reactions.

4.4 Stereochemical Aspects of Nitrone 1,3-Dipolar Cycloadditions

The stereochemical, as well as regiochemical, aspects of nitrone cycloadditions must be considered. As can be seen in Scheme 20, 1,3-cycloadditions are cis stereoselective. Cis-trans isomerism may be observed in the product isoxazolidines (41) and (42), involving the ring substituents at positions 3 and 5. This isomerism, in addition to the formation of diastereomers in the case of prochiral olefins used as dipolarophiles, is a result of the approach of reagents, i.e. nitrone of E or Z configuration and dipolarophile, in an exo- or endo-manner, comparable to the competing endo- and exo-stereoselectivities which characterise Diels-Alder reactions. These tendencies have been evaluated

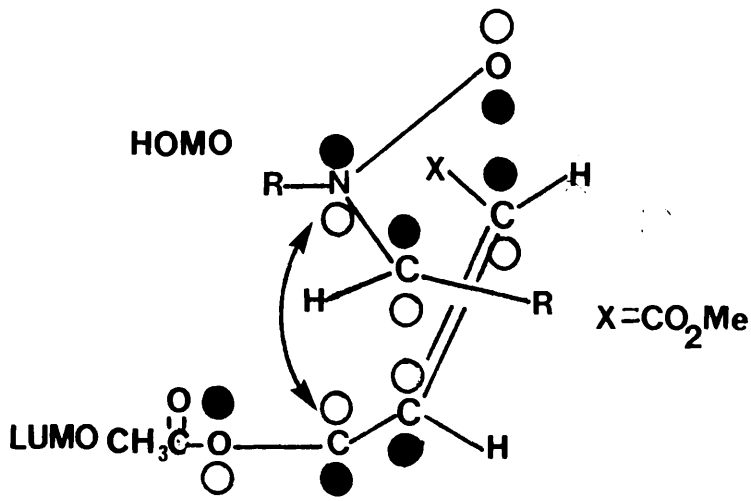
by Joucla[41] and Grée[42] in a study of the reactions of dimethyl maleate (40) with C-benzoyl-N-phenyl nitrone (38) and C,N-diphenyl nitrone (39), [Scheme 20].



Scheme 20

Determination of the stereochemistry of the product isoxazolidines makes it possible to deduce the orientation of the dipolarophile in the transition state. Nitrone (39) reacts with dimethyl maleate to afford two isoxazolidines (41) and (42) in a 9:1 ratio, indicating that the endo-process is favoured, whereas C-benzoyl-N-phenyl nitrone (38) gives isoxazolidine (41) exclusively, arising from an endo-transition state.[41]

The results may be interpreted on the basis of a study of secondary interactions of the frontier orbitals of the reactants, [Scheme 21].



(43)

Scheme 21

The dominant interaction will be of the HOMO (dipole)-LUMO (dipolarophile) type. An examination of the transition state (43) reveals a favourable secondary interaction between the N atom of the dipole and the electron attracting substituent of the olefin accounting for the predominant endo-approach. Secondary orbital interactions are therefore of considerable importance in determining the stereochemistry of the product.

Nitrones bearing chiral substituents have been synthesized and have been shown to undergo cycloaddition reactions involving transfer of chirality to appropriate dipolarophiles. However as yet there are few examples compared with the number of reported syntheses involving enantio- and diastereoselective Diels-Alder reactions.[43]

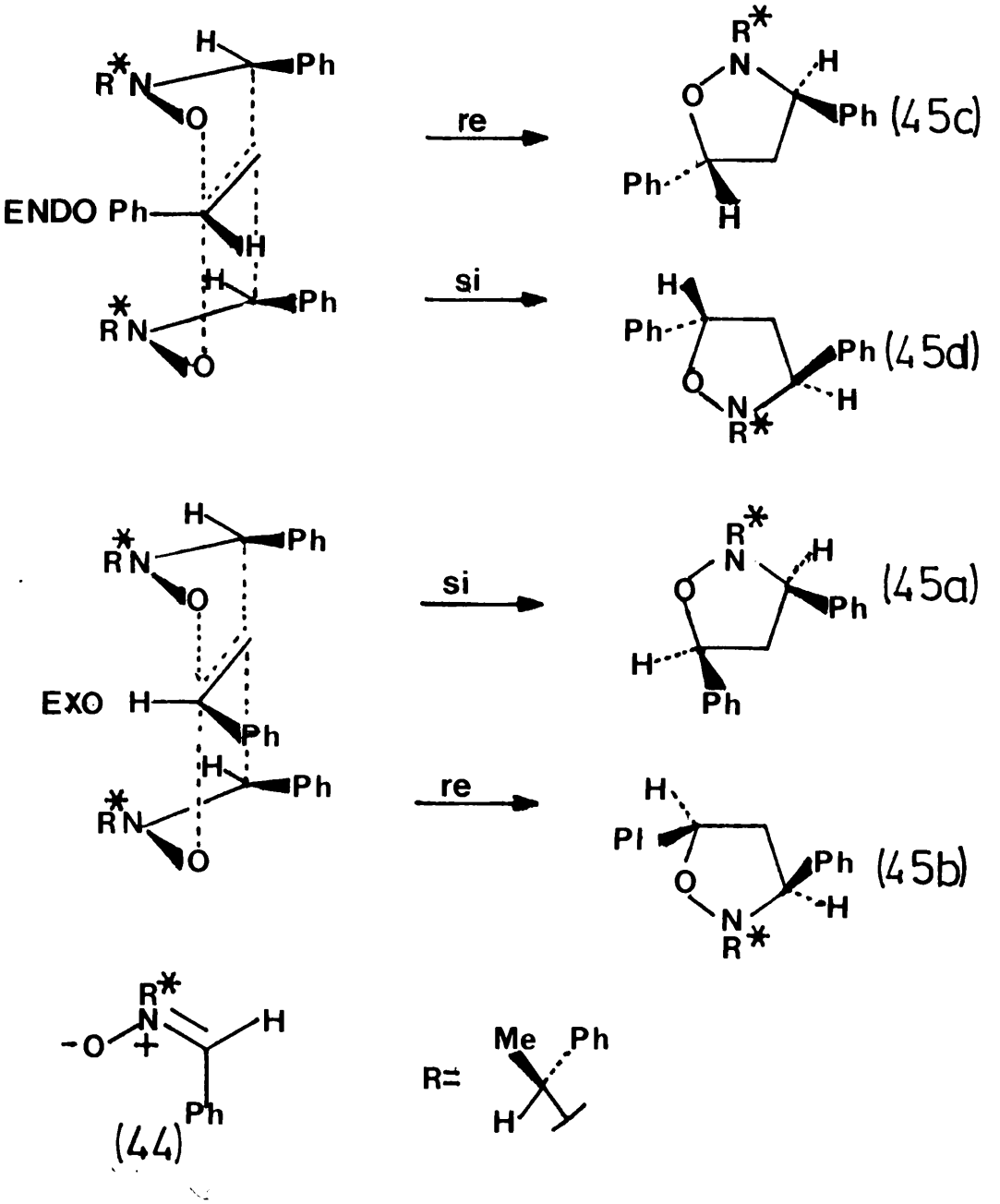
In 1979, Belzecki and Panfil[44] reported diastereoselective 1,3-cycloadditions of chiral nitrones with monosubstituted olefins. For example, chiral nitrone (44) reacts with styrene to give a mixture of four non-racemic diastereomers (45 a, b, c, d) in the proportions 76:11:8:5 respectively, [Scheme 22].

Belzecki has made the assumption that, if during the cycloaddition only the Z isomer of the nitrone is present, the diastereomers are formed as a result of the approach of reagents in an exo- or endo-manner, in addition to re or si attack at the prochiral olefin. The ratio of the sum of cis (45 a+b) isomers to the sum of trans (45 c+d) can be accepted as the measure of the stereospecificity of the cycloaddition, whereas the quantitative ratio within the pairs i.e. (a:b) and (c:d) is a measure of the diastereoselectivity of the reaction.

As the components of the diastereomeric mixture are separable, their absolute configurations can be determined, e.g. isomer (45a) was subjected to hydrogenolysis to give (S)-(-)-1,3-diphenyl propan-1-ol (46) in 92% optical purity, [Scheme 23].

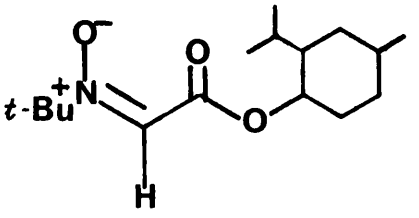
The results of this investigation indicate that monosubstituted alkenes react with chiral nitrones such as (44) to give a distinct excess of the cis isoxazolidine and a clear excess of one of the diastereomers in each cis and trans pair.

Belzecki has also investigated the cycloaddition reactions of nitrones bearing a chiral substituent at the carbon atom, e.g. C-(-) carbomenthoxy-N-tert-butyl nitrone (47).



Scheme 22

Scheme 23

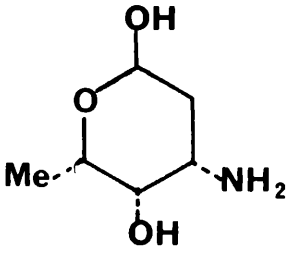


(47)

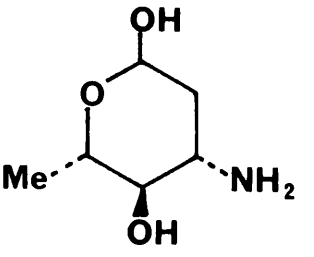
However, nitrones of this type exhibit little or no stereoselectivity with styrene and related dipolarophiles, and show Z ⇆ E interconversion at room temperature.

More recently chiral nitrones have been employed in a number of total synthesis of natural products. Wovkulich and Uskokovic[33] have achieved an elegant synthesis of the amino sugars, daunosamine (48) and acosamine (49) involving a diastereoselective intramolecular nitrone-olefin cyclisation as the key step. The chiral nitrone (50) cyclises to give two isoxazolidines (51) and (52) in an 82:18 ratio. The isoxazolidine (51) may be elaborated to (48) and (49) in only a few steps, [Scheme 24].

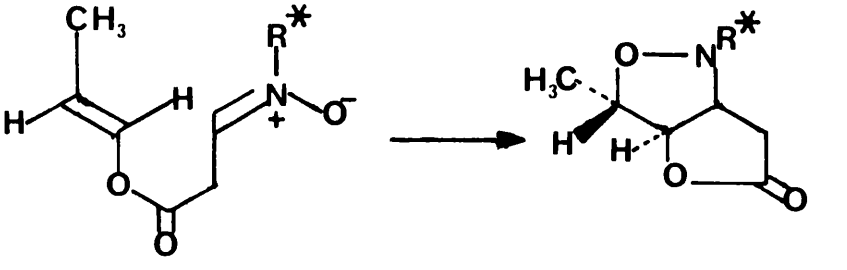
The basis for the observed stereoselection is intriguing. The authors argue that assuming cycloaddition proceeds via the Z nitrone, the rotamers (53) and (54) exhibit the smallest interaction between the incoming olefinic double bond and the N-α methyl benzyl group, [Scheme 25] and resemble their respective orientations in isoxazolidines (51) and (52).



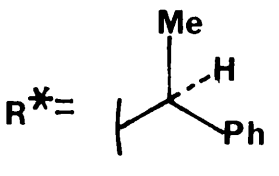
(48)

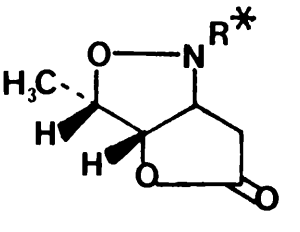


(49)



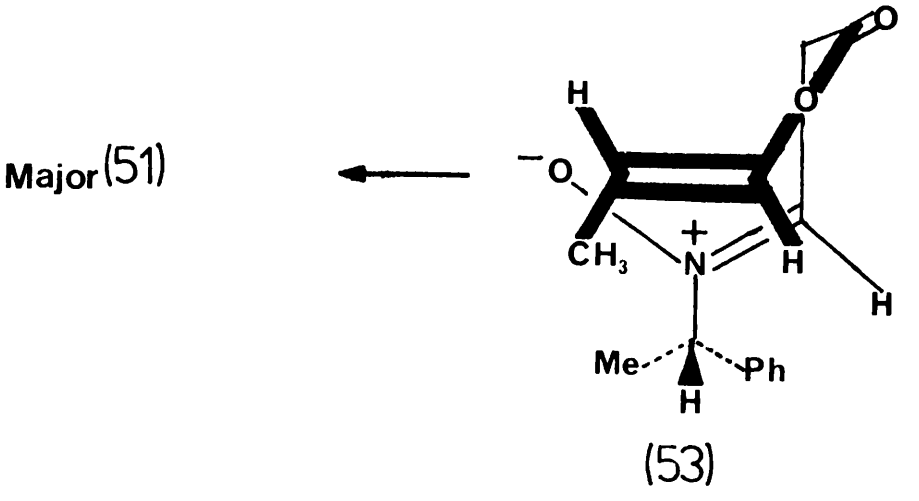
(50) (51) +





(52)

Scheme 24



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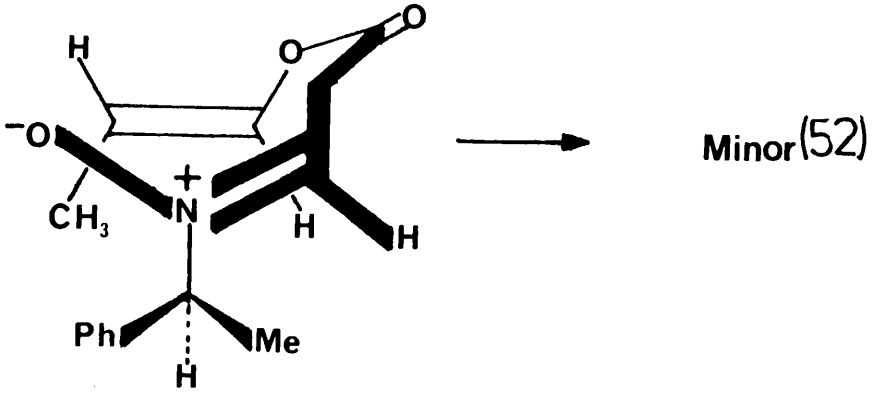
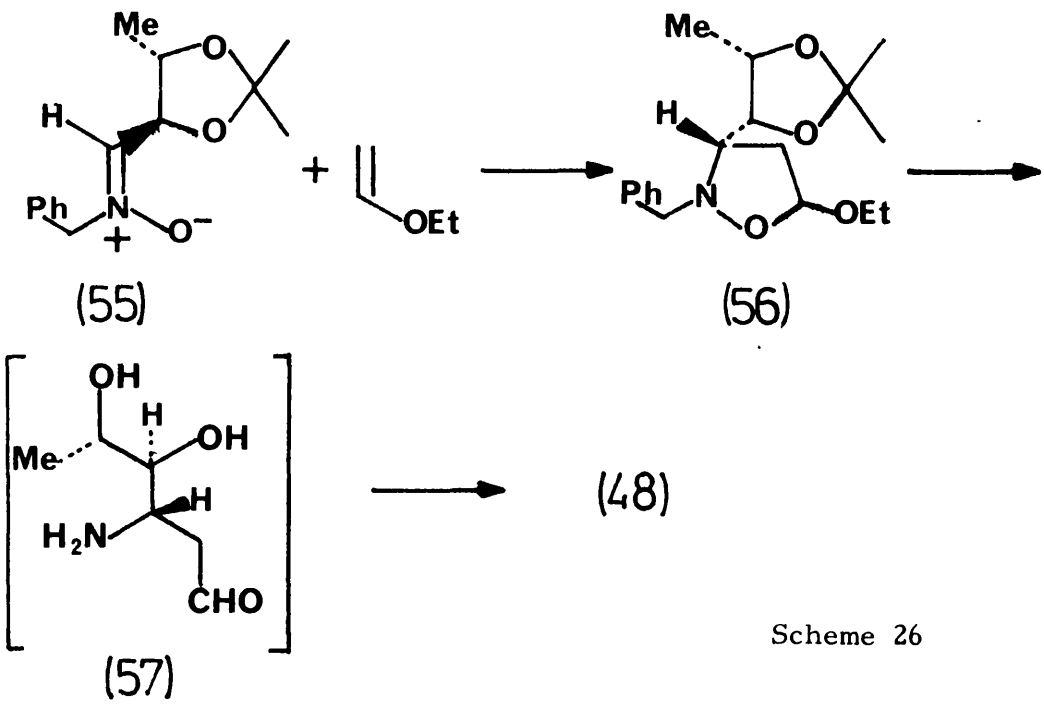


(54)

Scheme 25

Cycloaddition via (53) is the preferred route leading to major isomer (51). Rotamer (54) contains an unfavourable iteraction between the olefinic methyl group and the phenyl of the α-methyl benzyl group. This model is consistent with the diastereoselection observed for the analogous exo and endo modes of intermolecular cycloaddition reported by Belzecki and Panfil.[44]

A second synthesis of daunosamine employing a diasteeoselective cycloaddition of a nitrone has been reported by De Shong,[32] [Scheme 26].

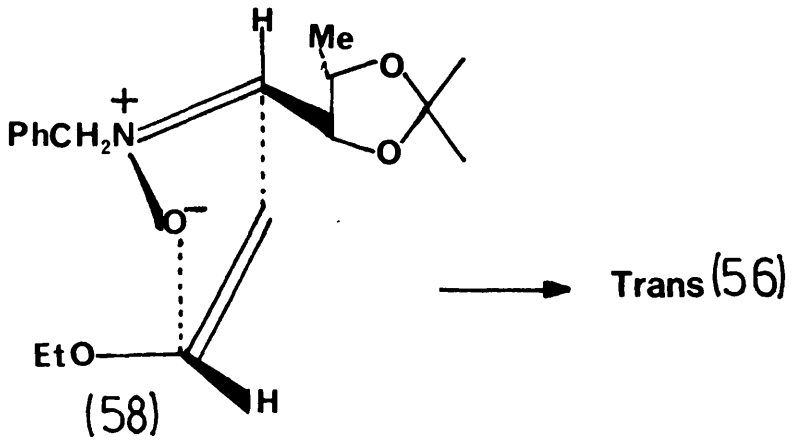


Scheme 26

Chiral nitrone (55) reacts with ethyl vinyl ether giving a single isoxazolidine (56). Subsequent reductive cleavage in acid of the N-O bond of (56) releases a β-amino aldehyde (57) as an intermediate to (48).

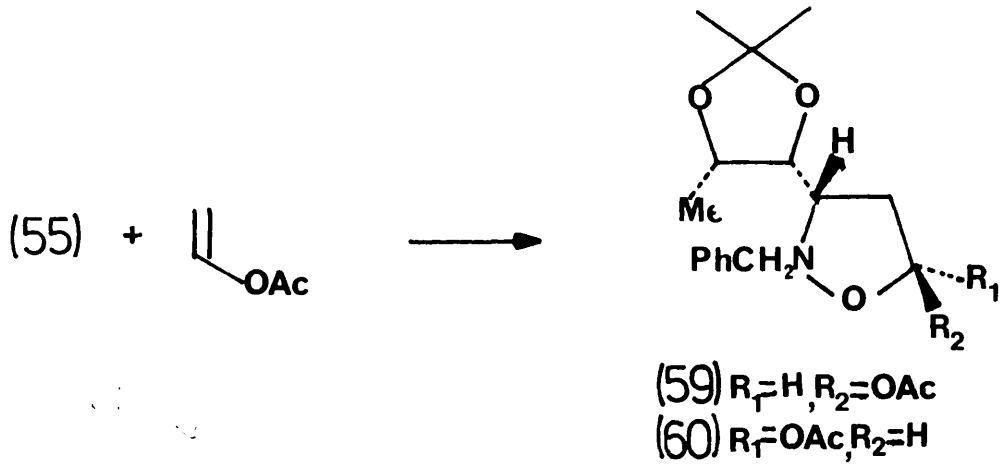
As the trans isoxazolidine (56) is only one of four possible diastereomers formed, nitrone (55) has displayed complete diastereofacial

selectivity and complete stereoselectivity for the endo transition state (58), [Scheme 27].



Scheme 27

Nitrone (55) displays diastereofacial selectivity in reactions with other dipolarophiles. Dipolar cycloaddition of (55) with vinyl acetate yields two adducts (59) and (60), differing only in their configuration at C-5, in a ratio of 1:4, [Scheme 28]



Scheme 28

Cycloaddition via the exo-transition state geometry accounts for the formation of the cis isoxazolidine (60). Chapter 2 of this thesis

describes the cycloaddition of vinyl acetate with chiral nitrones as part of an asymmetric synthesis of β-amino acids.

DISCUSSION

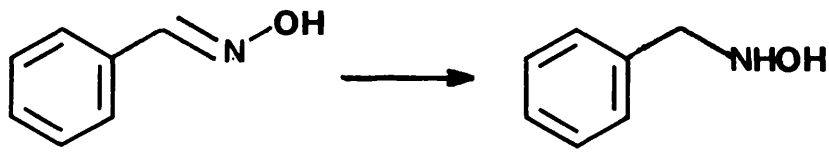
CHAPTER 1

Preparation of Nitrones and the Configuration of Aliphatic Nitrones

1:1 Preparation of Nitrones

Although acyclic nitrones are valuable intermediates in the construction of natural products, their preparation is limited to a relatively few methods. Condensation of N-monosubstituted hydroxylamines with aldehydes is the most general and efficient method.[46]

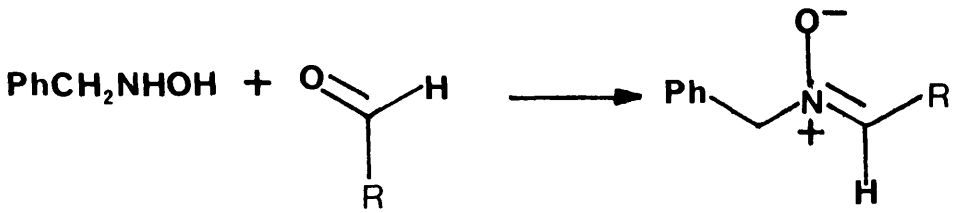
N-benzylhydroxylamine (2) was prepared by the method of Borsch,[47] involving cyanoborohydride reduction of benzaldehyde oxime (1), [Scheme 1].



(1) (2)

Scheme 1

Treatment of the appropriate aldehydes (3-5) with hydroxylamine (2) in dichloromethane at room temperature gave C-methyl (6), C-isopropyl (7) and C-tert-butyl (8), N-benzyl nitrones in good yield, [Scheme 2]. The i.r. spectra of nitrones (6-8) typically displayed C=N absorption at approximately 1600 cm^{-1}.



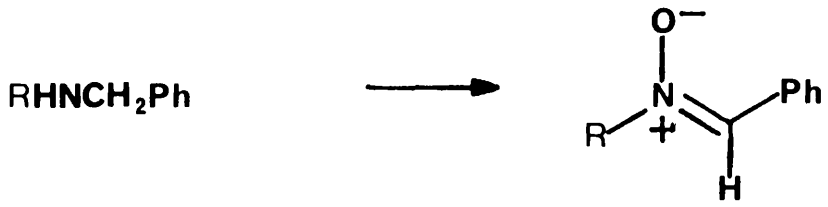
(2) (3) R=Me (6) R=Me

(4) R=*i*-Pr (7) R=*i*-Pr

(5) R=*t*-Bu (8) R=*t*-Bu

Scheme 2

C,N-diphenyl nitrone (11) and C-phenyl-N-benzyl nitrone (12) were conveniently prepared by oxidation of N-benzyl amines (9) and (10) with m-chloroperbenzoic acid in refluxing acetone, following a method described by Beckett,[48] [Scheme 3].



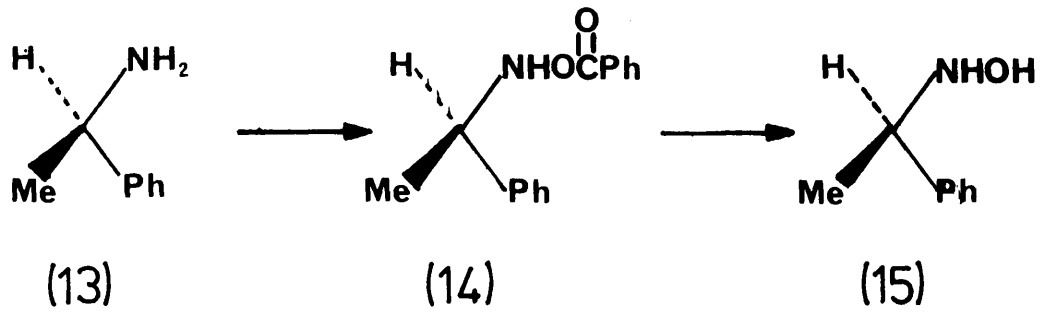
(9) R=Ph (11) R=Ph

(10) R=CH_2Ph (12) R=CH_2Ph

Scheme 3

Chiral benzylic nitrones of the type described by Belzecki,[44] required the synthesis of (R)-(+)-α-methylbenzylhydroxylamine (15). Employing the method of Zinner,[49] oxidation of the optically pure amine (13) with benzoyl peroxide, gave the benzoyloxyamine (14), which was subsequently hydrolysed under basic conditions to chiral hydroxylamine (15), [Scheme 4].

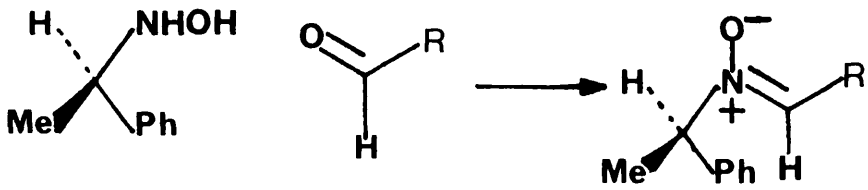
This preparation was repeated on several occasions on a 80 mmol scale (amine) but the yield never exceeded 27%. The method of Polonsky and Chimiak[50] has afforded superior yields of up to 50%. (Experiments by D. Kiers and R. Tomanek).



(13) (14) (15)

Scheme 4

The chiral nitrones (20-24) were prepared by the reaction of hydroxylamine (15) with the appropriate aldehydes (4, 16-19), [Scheme 5].



(15) (4) R=*i*-Pr (20) R=*i*-Pr

(16) R=Ph (21) R=Ph

(17) R=pMeOPh (22) R=pMeOPh

(18) R=pCl (23) R=pClPh

(19) R=α-indolyl (24) R=α-indolyl

Scheme 5

With the exception of (21) R=Ph, all the above nitrones were obtained as crystalline solids, and the i.r. spectra all showed the expected C=N absorption between 1580-1605 cm^{-1}.

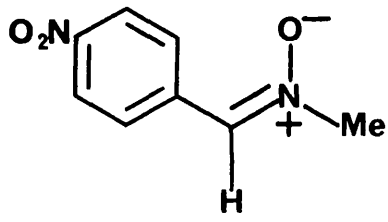
1:2 The Configuration of Aliphatic Aldonitrones

The ^{1}H nmr spectra of all the nitrones prepared indicated the formation of a single geometrical isomer, suggesting exclusive formation, presumably, of the thermodynamically more stable Z-nitrone.

The stereochemistry of acyclic nitrones is a subject that has received some attention, but although the structure and isomerisation of aromatic aldonitrones have been extensively investigated, their

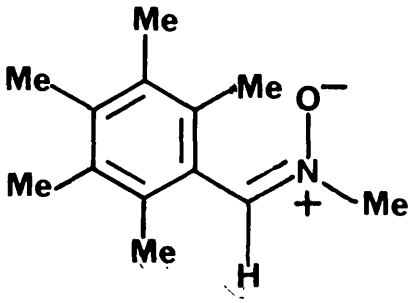
aliphatic counterparts have been largely neglected. What follows describes an investigation of the stereochemistry of several aliphatic nitrones by nuclear Overhauser difference spectroscopy (NOEDS).

The NOEDS method has previously been employed by Boyd,[51] to establish the trans stereochemistry of the aromatic nitrone (25).

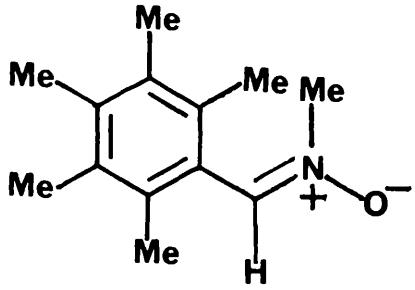


(25)

Boyd[52] has studied the phenomenon of Z⇌E isomerisation in aromatic aldonitrones and barriers for rotation about the C=N bond have been calculated and measured for several examples. Nitrone (26) was obtained as a mixture of E and Z isomers upon MCPBA oxidation of the corresponding imine.



Z-(26)

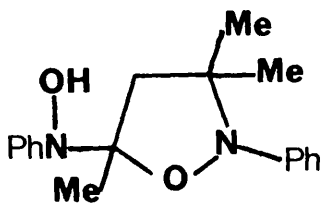


E-(26)

The proportion of E-(26) decreased from 85 to 9% upon thermal equilibration in $CDC\ell_3$. Separation of the equilibration mixture permitted the interconversion barriers of E- and Z-isomers to be determined by ^1H nmr. The values obtained ($\Delta G^{\ddagger}$ Z → E = 33.1 kcal mol^{-1}, $\Delta G^{\ddagger}$ E → Z = 34.6 kcal mol^{-1} at 147°C), indicate that E-Z aldonitrones show considerable configurational stability, comparable with that of ketonitrones. In the presence of benzoic acid, the isomerisation barriers were lowered by approximately 10 kcal mol^{-1}.

Boyd[53] has also established that the relative proportions of the E- and Z-nitrone isomers at equilibrium are both substituent- and solvent-dependent. For example N-tert-butyl-C-aryl nitrones have significantly lower barriers to isomerisations than the corresponding N-methyl compounds.

As previously stated, there have been no previous systematic investigations of the stereochemistry and ease of isomerisation of aliphatic aldonitrones. It has been assumed that they possess the Z configuration in analogy with their aromatic counterparts. One problem has been the instability of aliphatic nitrones. Thus, N-phenyl-C-dimethyl nitrone readily dimerises at room temperature to afford the dimer (27) whose constitution was a subject of controversy until it was determined by X-ray analysis.[54a] Whereas there are several examples of the rapid dimerisation of N-phenyl-C-alkyl nitrones,[54a-c] Exner[54d] has reported the synthesis of stable N-methyl-C-alkyl ketonitrones.



(27)

It was clearly important to obtain confirmation of the geometry of the aldonitrones used in dipolar additions in the course of this thesis, since in the chirally induced cycloadditions, the diastereomer ratio will depend, inter al., on the nitrone geometry.

It was fortunate, therefore, that C-alkyl-N-benzyl nitrones, unlike their N-phenyl analogues, turned out to be stable in solution at room temperature and hence amenable to study by ^{1}H nmr. Thus, the C-alkyl-N-benzyl nitrones (6-8) were chosen for analysis by NOEDS, because of their stability and the added ease of measuring NOE's between the $PhC\underline{H}_2N$ and $\underline{H}C{=}N$ protons.

The ^{1}H nmr spectrum of C-methyl-N-benzyl nitrone (6), see Fig. 1a, showed a quartet at δ6.71 (1H, J=5.8 Hz, $N{=}C\underline{H}CH_3$), a singlet at δ4.77 (2H, $PhC\underline{H}_2N$) and a doublet of triplets at δ1.87 (3H, J=1, 5.8 Hz), indicating the existence of a single isomer, and this was confirmed by the ^{13}C nmr spectrum, [Fig. 1b]. The NOEDS data for (6), contained in Table 1, showed that the nitrone double bond was exclusiv-

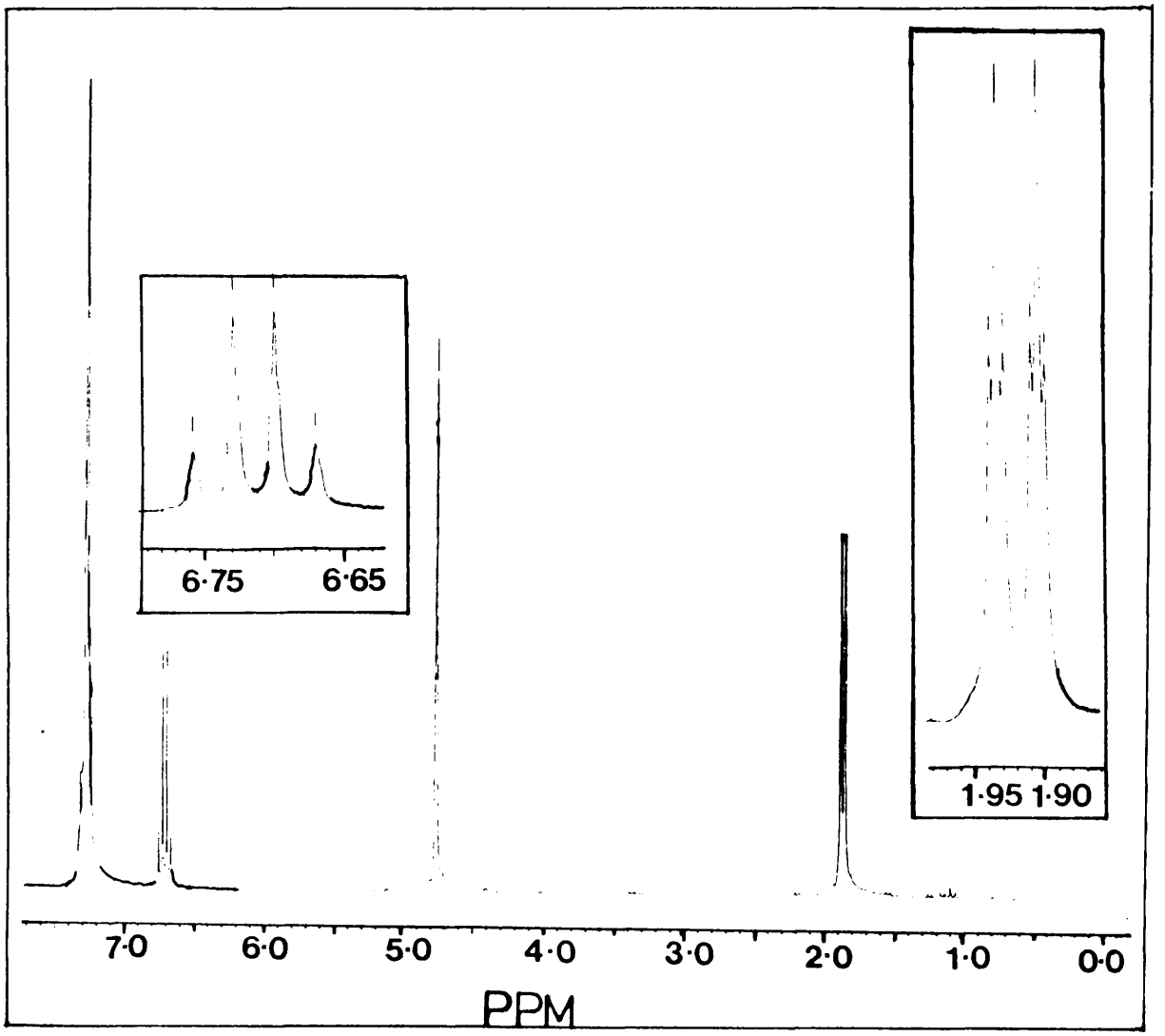


Fig. 1a ^{1}H NMR Spectrum of C-Methyl-N-Benzyl-Nitrone(6) at 200 MHz.

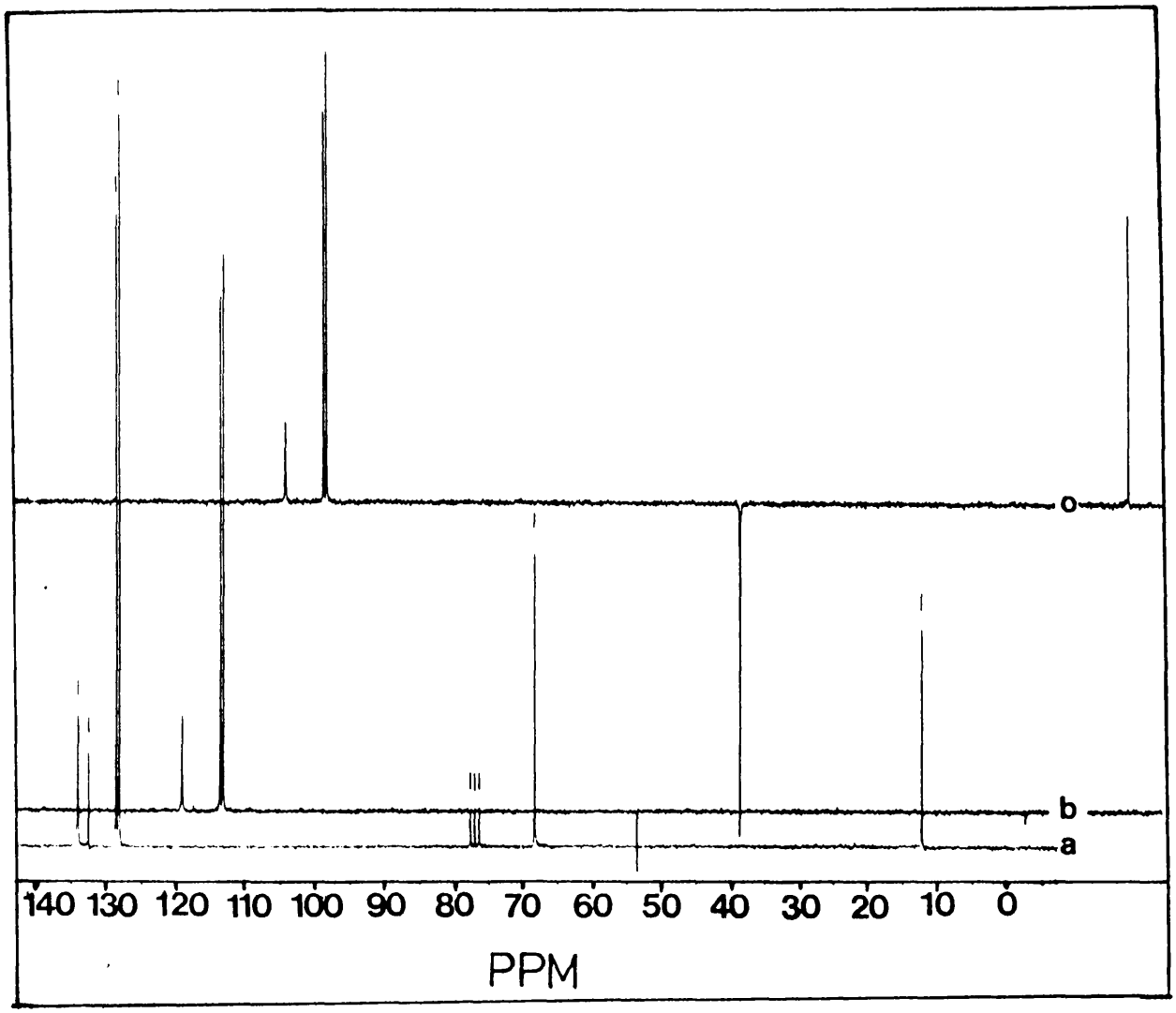
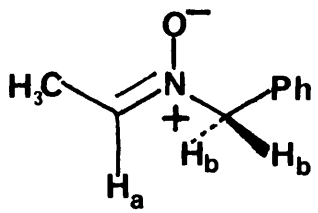


Fig. 1b (a) ^{1}H-Decoupled ^{13}C NMR Spectrum of Nitrone (6). (b) DEPT, $\theta = 90^{\circ}$, Offset -750Hz. (c) DEPT, $\theta = 135^{\circ}$, Offset -1500Hz.

ely of the Z configuration. Irradiation of the N-benzyl protons H_b resulted in a signal enhancement of 6.47% for the vinyl proton H_a, compared to an enhancement of 0.47% for the protons of the methyl group. This indicates the greater proximity of H_a to the benzyl protons H_b, and hence the Z configuration of nitrone (6). Likewise irradiation of H_a produced 1.61% enhancement at H_b, whereas irradiation at C-CH_3 gave only 0.17% enhancement.

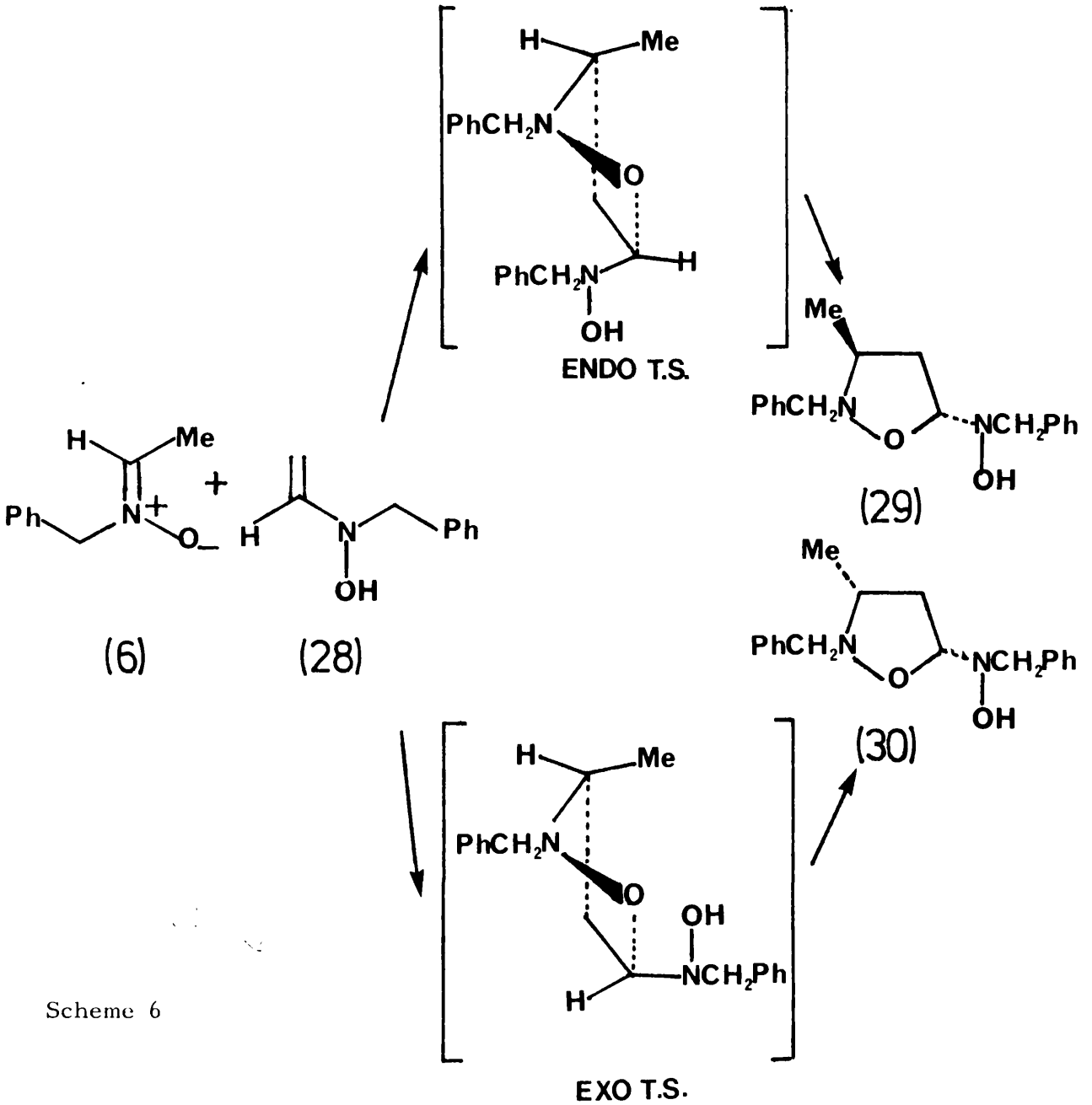
Table 1. NOE Difference Spectral Data of Nitrone (6)[a]



(6)

X[b]	6	H_a	H_b	C-CH_3	H_ϕ[c]
	H_a	-	1.61	1.35	0.11
	H_b	6.47	-	0.47	1.52
	C-CH_3	4.07	0.17	-	0.39
	H_ϕ	1.31	2.16	0.79	-

a, % increase in signal intensity; b, proton that was irradiated; c, result averaged over all protons due to signal overlap, ϕ = phenyl.


H
Me
PhCH2N
O
PhCH2N
H
OH
ENDO T.S.
Me
PhCH2N
O
NCH2Ph
OH
(29)
Me
PhCH2N
O
NCH2Ph
OH
(30)
H
Me
PhCH2N
O
OH
NCH2Ph
H
EXO T.S.
H
Me
Ph
N+
O
+
H
N
Ph
OH
(6)
(28)

Scheme 6

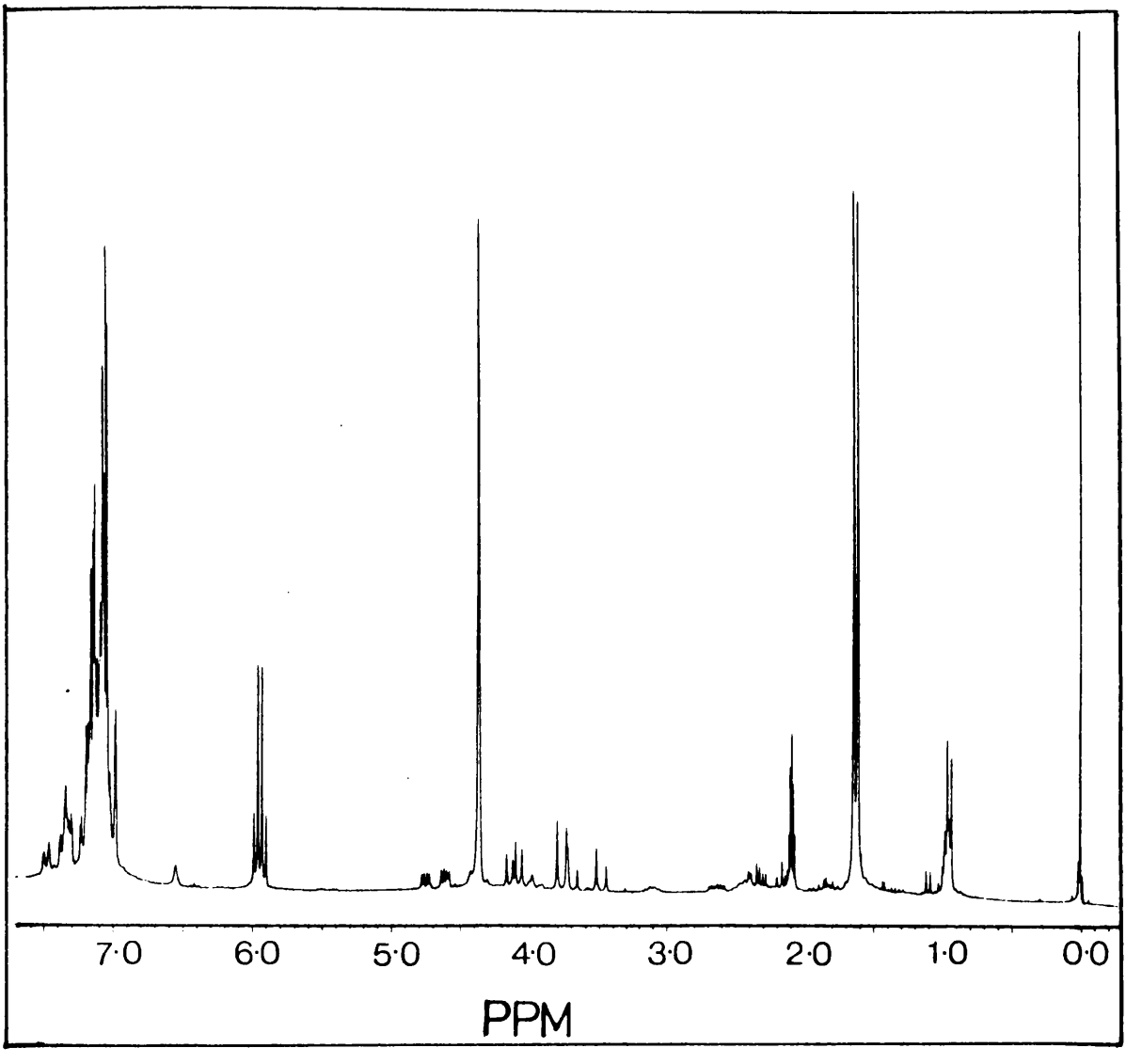


Fig. 2 ^{1}H NMR Spectrum of Isoxazolidines(29) and(30) and Nitrone(6).

Nitrone (6) was heated to +60°C in $CDC\ell_3$ containing benzoic acid, under similar conditions to those reported by Boyd[53] for the thermal equilibration of aromatic aldonitrones. The ^1H nmr spectrum showed that the nitrone double bond remained exclusively in the Z configuration, however.

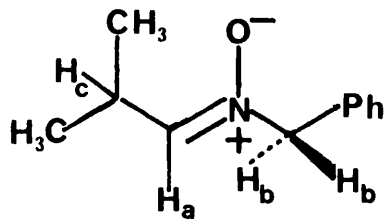
Upon standing in $CDC\ell_3$ at room temperature for approximately 48h, a new set of signals appeared in the ^1H nmr spectrum of (6). The same signals appeared on heating (6) at temperatures greater than 100°C in d^8-toluene, suggesting that dimerisation of (6) had occurred, involving [3+2]-cycloaddition of the nitrone in its Z configuration to the isomeric enamine (28), via endo- and exo-transition states to give a 1:1 mixture of diastereomers (29) and (30) respectively, [Scheme 6]. Although a similar dimerisation of aromatic aldonitrones has been reported,[55] the formation of diastereomeric dimers has not been previously discussed in the literature.

The ^1H nmr spectrum at 200 MHz, [Fig. 2] of the mixture (6), (29) and (30), showed two doublets of doublets at δ4.85 (J=3.5, 8 Hz) and δ4.61 (J=4, 8 Hz), for the ring proton at C-5, of equal intensity. The high temperature ^1H nmr experiments in d_8-toluene containing benzoic acid, did not however show any evidence for Z to E isomerisation of (6). It therefore seems that aliphatic aldonitrones such as (6) show great configurational stability, and inversion barriers must be well in excess of 30 kcal mol^{-1}.

As with nitrone (6), C-isopropyl-N-benzyl nitrone (7) was formed as a single isomer, on the evidence of ^1H and ^{13}C nmr spectra, [Figs. 3a and b]. The results of the NOEDS analysis of (7), confirmed

that the C=N bond was of the expected Z configuration. Irradiation of the N-benzyl protons produced a signal enhancement of 3.25% for the vinyl proton H_a, as opposed to an enhancement of 0.04 % for the methine proton H_c of the isopropyl group, and 0.11% for the methyl protons. The full results of the NOEDS analysis of nitrone (7) are given in Table 2.

Table 2. NOE Difference Spectral Data of Nitrone (7)[a]



(7)

X[b]	7	H_a	H_c	H_b	Pr^iMe	H_ϕ[c]
	H_a	-	0.77	1.43	0.35	0.17
	H_c	0.82	-	0.06	0.53	0.13
	H_b	3.25	0.04	-	0.11	0.58
	Pr methyl	3.40	5.69	0.51	-	1.02
	H_ϕ	0.65	0.08	0.76	0.31	-

a, % increase in signal intensity; b, proton that was irradiated; c, result averaged over all protons to signal overlap.

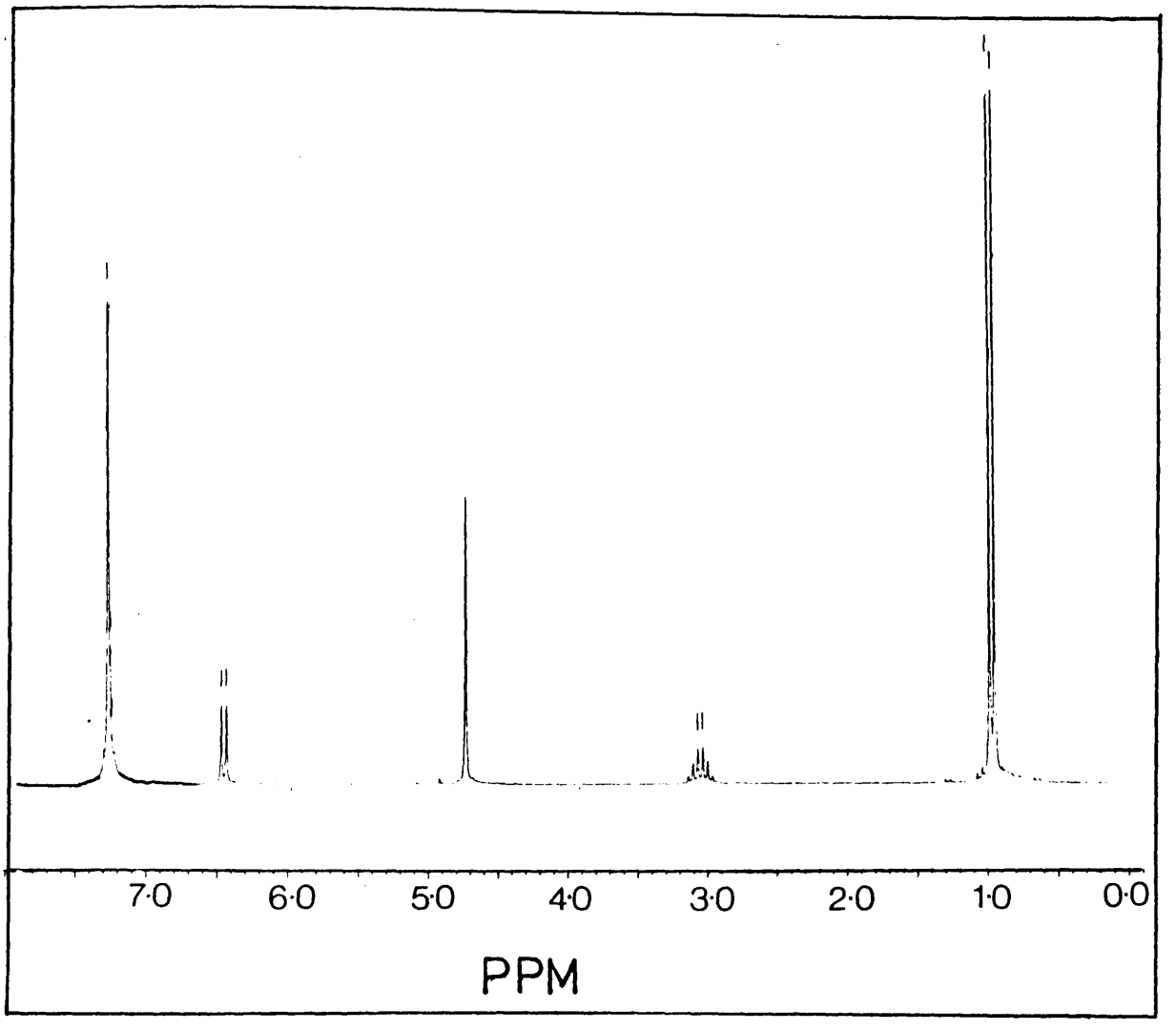


Fig.3a ^{1}H NMR Spectrum of C-Isopropyl-N-Benzyl-Nitrone(7) at 200MHz.

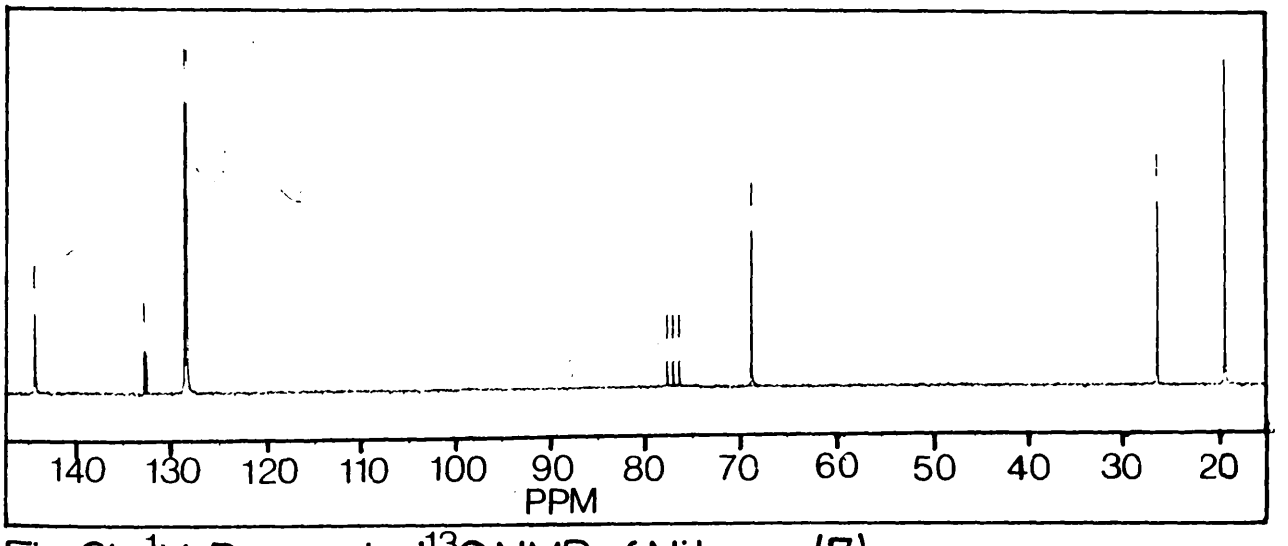


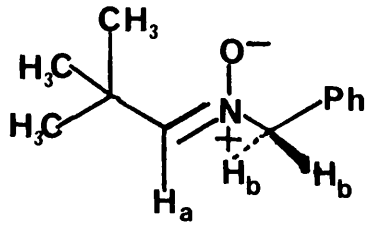
Fig.3b ^{1}H Decoupled ^{13}C NMR of Nitrone(7).

Likewise, C-tert-butyl-N-benzylnitrone (8) was also formed exclusively as the Z isomer. The ^{1}H and ^{13}C spectra of (8) [Figs. 4a and b], again showed only one isomer and the results of the NOEDS analysis confirmed the trans stereochemistry of the double bond. Irradiation of the N-benzyl protons H_b, resulted in a 10% enhancement for the signal for the vinyl proton H_a, as shown in Table 3.

Nitrone (8) was heated for 3h in d_8-toluene at 80°C. As with methyl nitrone (6) isomerisation to the E nitrone did not occur, but also dimerisation was not observed in this case, probably as a result of steric crowding of the cycloaddition transition state by the tert-butyl group of (8).

It therefore seems that aliphatic aldonitrones such as those described exhibit configurational stability at least as great as their aromatic counterparts, and that the reaction of the substituted hydroxylamine with aliphatic aldehydes is a completely selective process leading exclusively to the Z-nitrone. These conclusions considerably simplify analysis of the transition states that are relevant for the cycloadditions discussed in the following chapters.

Table 3. NOE Difference Spectral Data of Nitrone (8)[a]



(8)

X[b]	8	H_a	H_b	Bu^tMe	H_ϕ[c]
	H_a	-	3.39	0.68	0.28
	H_b	10.03	-	0.08	1.53
	Bu^tMe	8.75	0.70	-	1.21
	H_ϕ	0.30	1.97	0.28	-

a, % increase in signal intensity; b, proton that was irradiated; c, result averaged over all protons due to signal overlap.

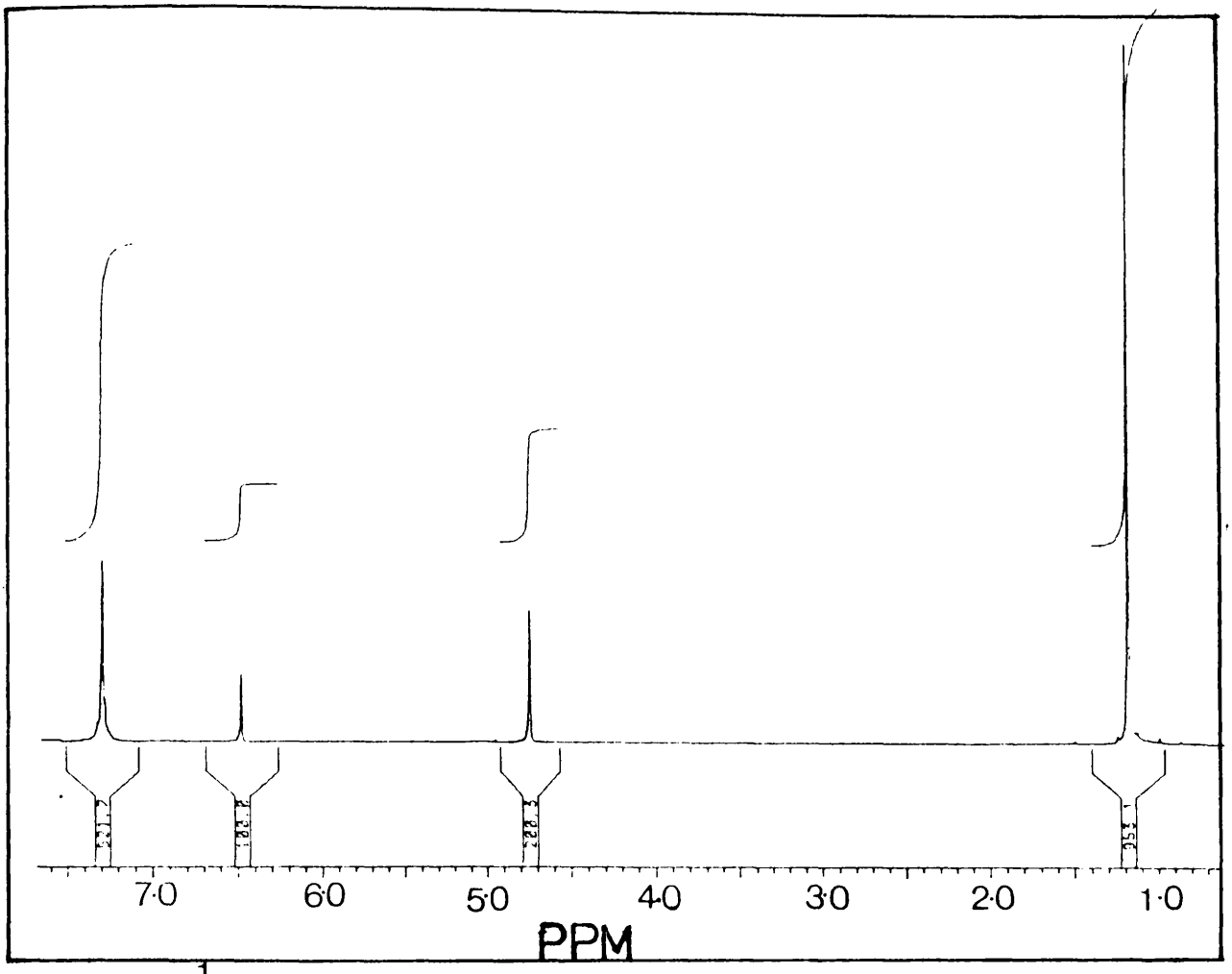


Fig.4a ^{1}H NMR Spectrum of C-t-Butyl-N-Benzyl-Nitrone (8) at 200MHz.

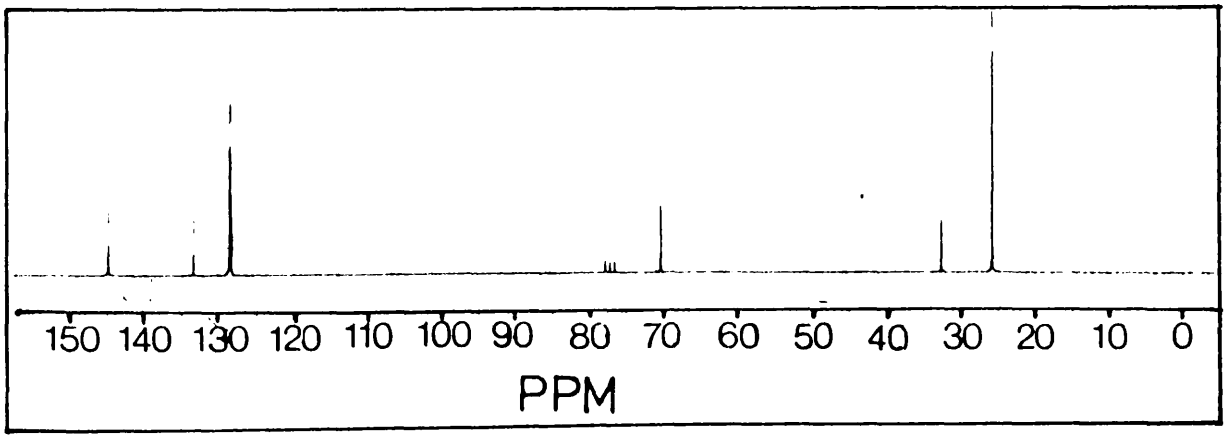


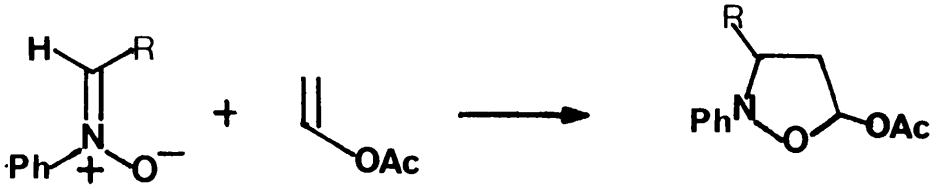
Fig.4b ^{1}H Decoupled ^{13}C NMR Spectrum of (8).

CHAPTER 2

Asymmetric Syntheses of β-Amino Acids via Nitrone Cycloadditions to Vinyl Acetate

2:1 Background

Surprisingly few examples of the cycloaddition reactions of nitrones with electron-rich dipolarophiles such as vinyl acetate (32) have been recorded. Cum[56] first reported 1,3-dipolar cycloaddition of nitrones to vinyl acetate in 1968, and performed a partial structural analysis of isoxazolidines (33) and (34) by ^{1}H nmr, [Scheme 7].

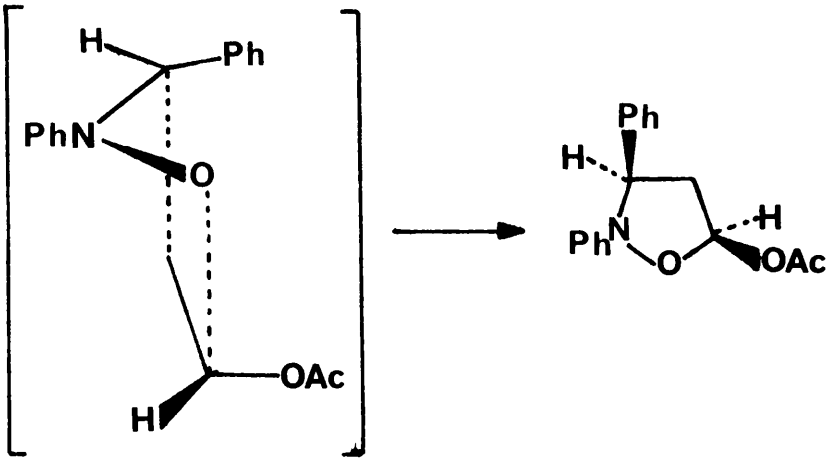


(11) R=Ph (32) (33) R=Ph

(31) R=pNO$_2$Ph (34) R=pNO$_2$Ph

Scheme 7

More recently, De Shong[57] has assigned the conformation and configuration of isoxazolidine (33) by analysis of ^{1}H nmr coupling constants and by NOEDS. The results indicated total regioselectivity as well as formation of a single diastereomer in which the ring substituents at C-3 and C-5 were syn to each other as shown in (33a). The formation of (33a) as the sole product indicated that the cycloaddition between nitrone (11) and vinyl acetate occurred exclusively via an exo-transition state (35), [Scheme 8].



(35) (33a)

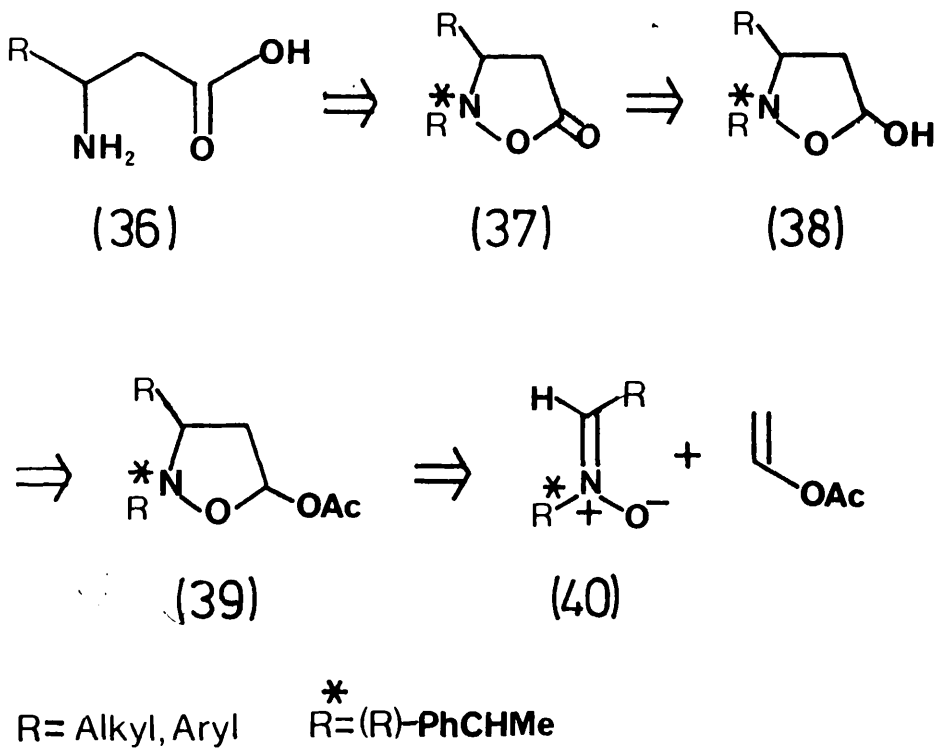
Scheme 8

De Shong[32] has also utilised stereoselective nitrone-vinyl acetate cycloadditions in the total synthesis of amino sugars, as described earlier on p31.

DISCUSSION

2:2 Introduction

Isoxazolidin-5-ones (37) have been shown to be immediate precursors of β-amino acids (36), through reductive cleavage of the N-O bond.[27] It was envisaged that (37) could be obtained from oxidation of lactol (38), which was potentially available from isoxazolidine (39). The initial aim then, was to synthesize (39) in a diastereoselective manner, employing the [3+2] dipolar cycloaddition of a chiral nitrone (40) with vinyl acetate, [Scheme 9].

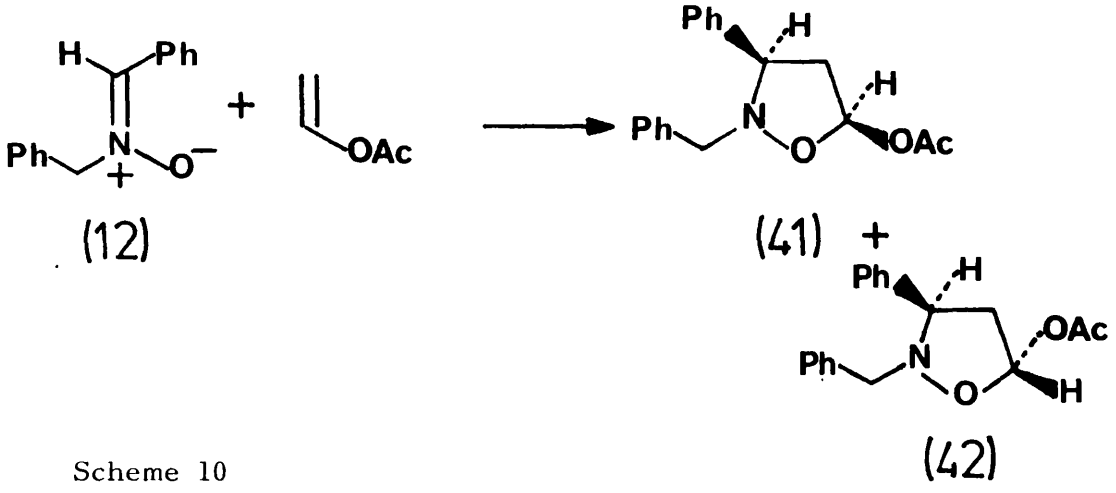


Scheme 9

Footnote: The results of Baldwin[27] appeared when the work here described was well advanced.

2:3 Cycloaddition of Achiral Nitrones to Vinyl Acetate

Initial investigations were carried out employing achiral nitrones. Cycloaddition of C-phenyl-N-benzyl nitrone (12) with vinyl acetate[32] gave a mixture of two diastereomeric isoxazolidines (41) and (42), [Scheme 10].

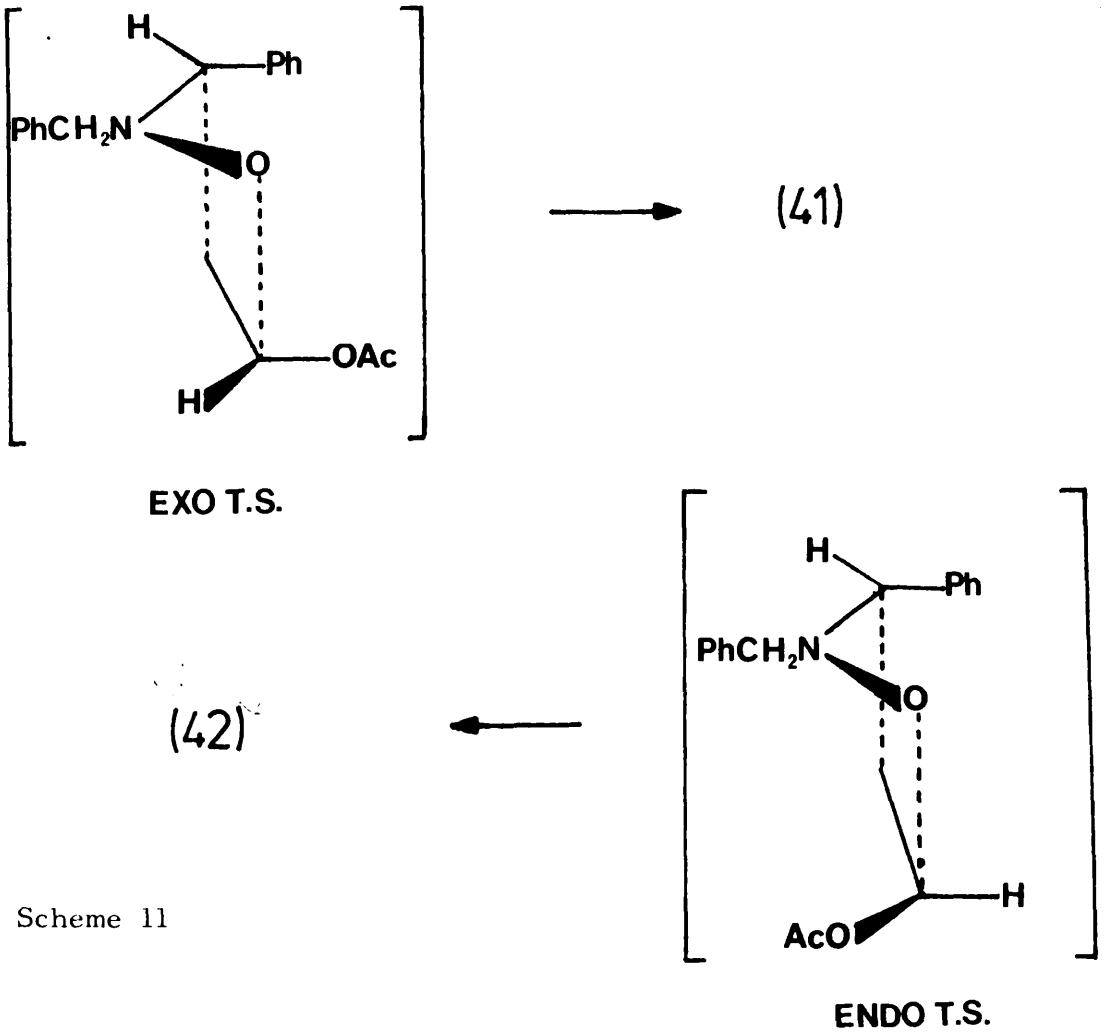


Scheme 10

The regiochemistry of this cycloaddition was assigned as shown in (41) and (42), on the basis of a one-proton multiplet at δ6.37, due to the acetal proton at C-5 in the ^{1}H nmr spectrum of the diastereomeric mixture. The ^{1}H nmr spectrum also displayed two acetoxy methyl signals at δ2.11 and 2.09 in a ratio of 3.5:1 respectively. The i.r. spectrum of mixture (41,42) displayed a broad ester carbonyl absorption at 1735 cm^{-1}.

Isoxazolidines (41) and (42) were separated by preparative t.l.c. From comparison with the results of De Shong,[57] discussed on page 52 the major isomer (41) was assigned cis stereochemistry with

regards to the ring substituents at C-3 and C-5, as the ^1H nmr spectrum showed the C-5 acetal proton as a doublet of doublets at δ6.35 (J=3, 6.5 Hz). The ^1H nmr of cis-α,N-diphenylisoxazolidine (33a) showed the corresponding proton as a doublet of doublets at δ6.57 (J=2, 6 Hz). Isomer (42) showed an unresolved multiplet at δ6.37. These results indicate that the cycloaddition reaction must have occurred preferentially via an exo-transition state to give isoxazolidine (41) as the major product, in accordance with the observations of De Shong,[57] while the corresponding endo-t.s. gave rise to (42), [Scheme 11].



Scheme 11

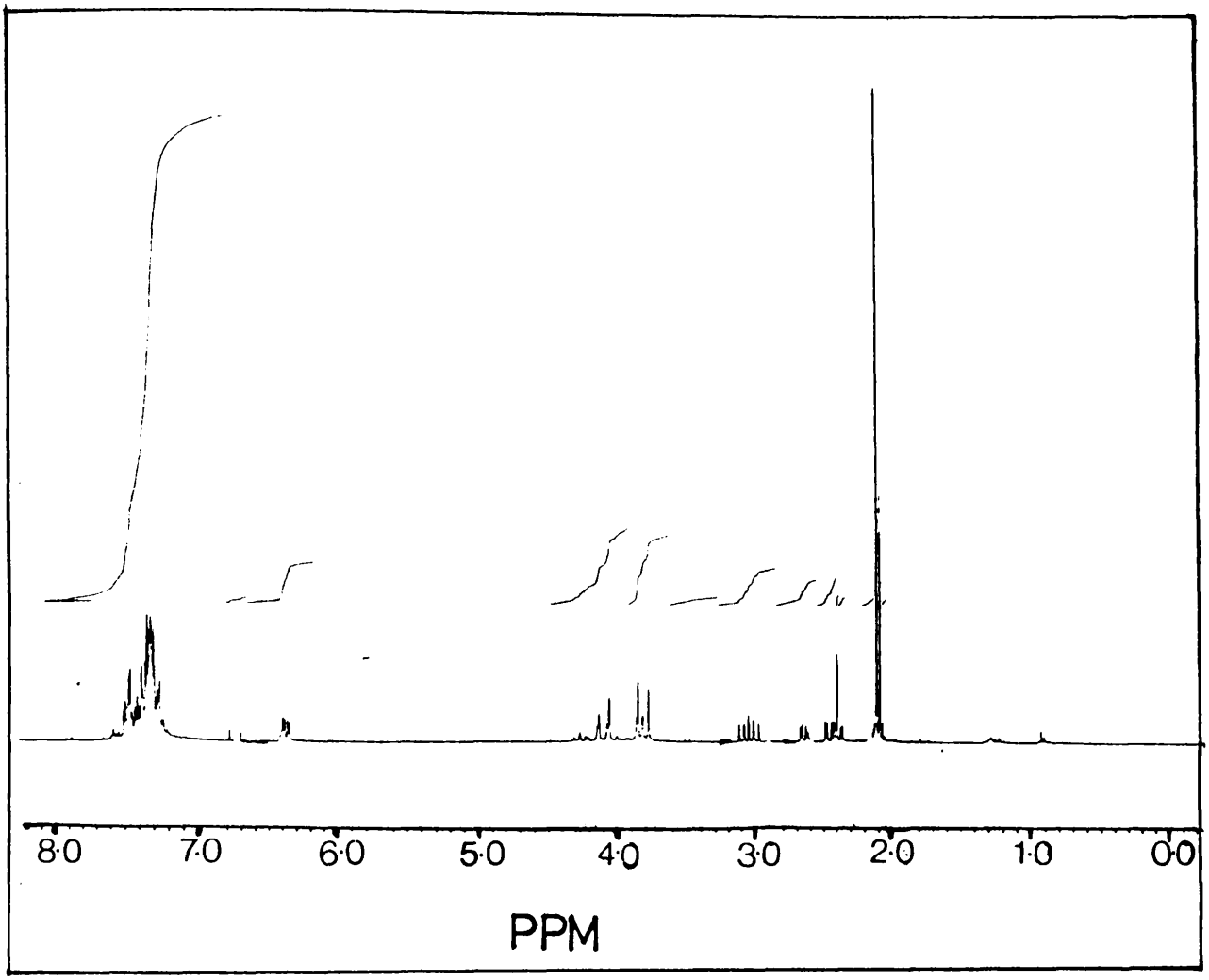


Fig. 5a ^{1}H NMR Spectrum of Isoxazolidine Mixture (41)and(42) at 200MHz.

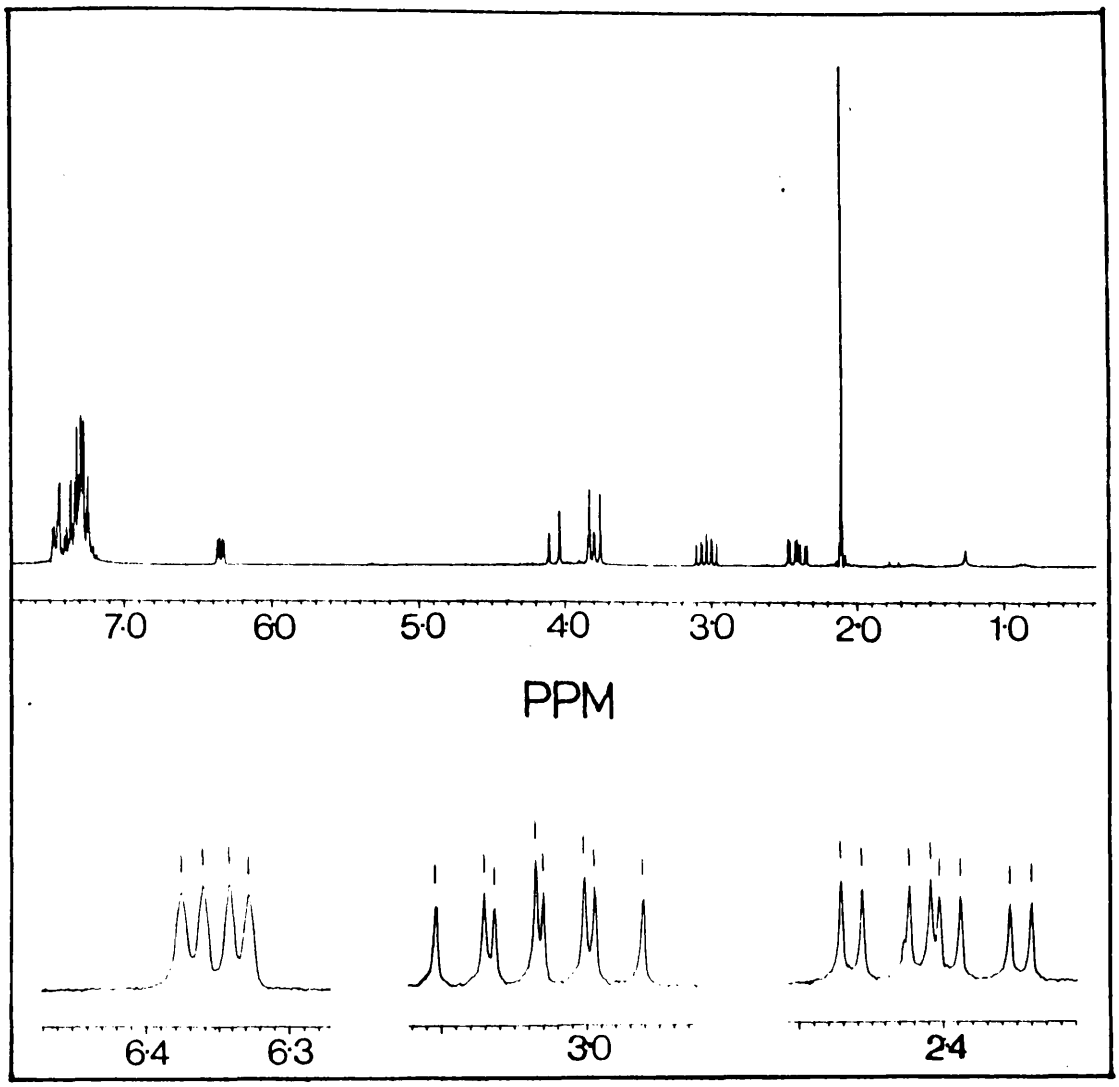


Fig. 5b ^{1}H NMR Spectrum of cis-Isoxazolidine(41) at 200MHz.

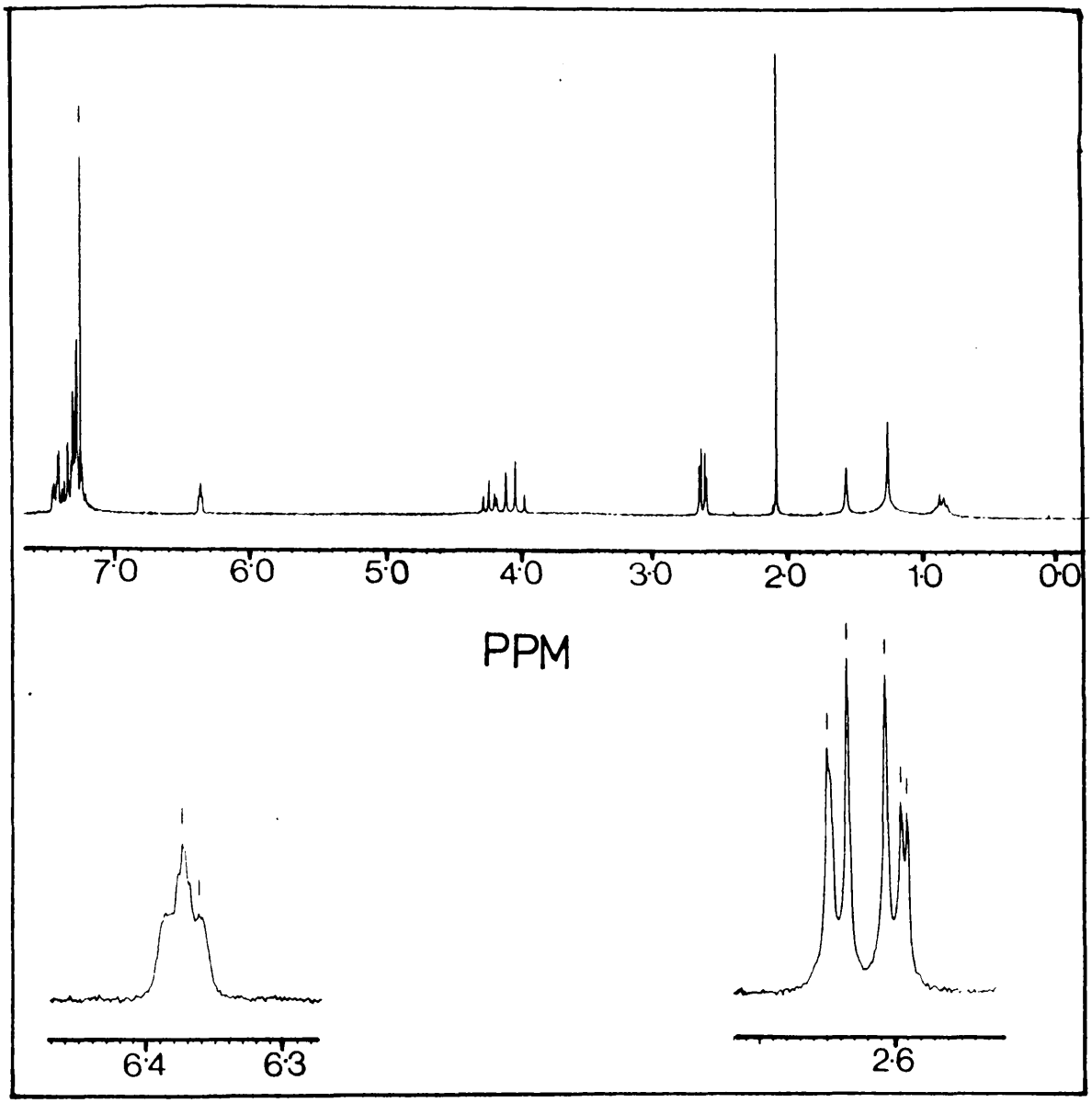
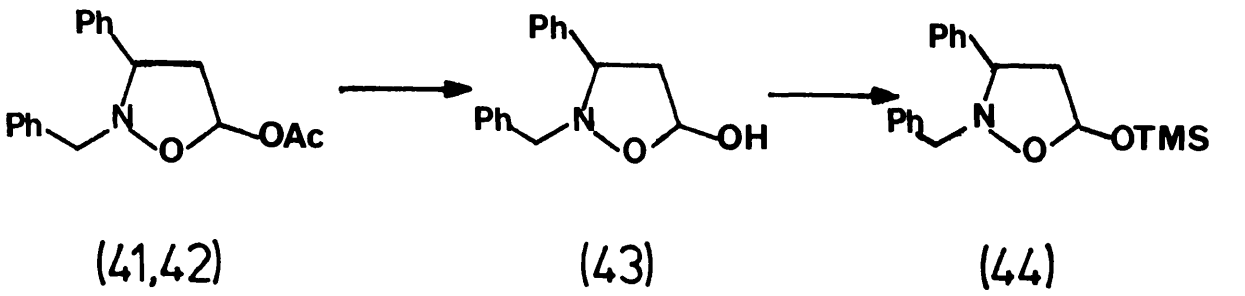


Fig. 5c ^{1}H NMR Spectrum of <u>trans</u>-Isoxazolidine (41) at 200MHz.

Isoxazolidine mixture (41,42) was hydrolysed to the lactol (43), with potassium carbonate in aqueous methanol,[58] in good yield, [Scheme 12].



(41,42) (43) (44)

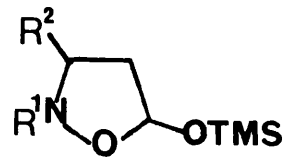
Scheme 12

The ^{1}H nmr spectrum of (43) showed a one proton multiplet at $\delta 5.50$, corresponding to the hemi-acetal proton at C-5, an upfield shift of approximately 0.9 ppm from its position in the acetate mixture (41,42). The i.r. spectrum showed both free and bonded hydroxylic absorption at 3600 and 3375 cm^{-1} respectively, and this was found to be characteristic of all the lactols synthesized in this chapter.

The trimethylsilyl ether (44) was obtained by treatment of (43) with the hexamethyldisilazane-trimethylsilyl chloride reagent. Analysis of (44) by g.c.-m.s., showed two peaks in a ratio of 1.6:1, both of which possessed m/e values of 372 corresponding to a molecular formula of $C_{19}H_{25}NO_2Si$, [Table 4]. In comparison with the 3.5:1 ratio of diastereomeric isoxazolidines (41) and (42), established by ^{1}H nmr [Fig 5a], the change in the diastereomeric ratio within TMS ether (44) indicates a

Table 4. Gas Chromatography of Isoxazolidine Trimethylsilyl Ethers

(6' 1% OV-1 Column)

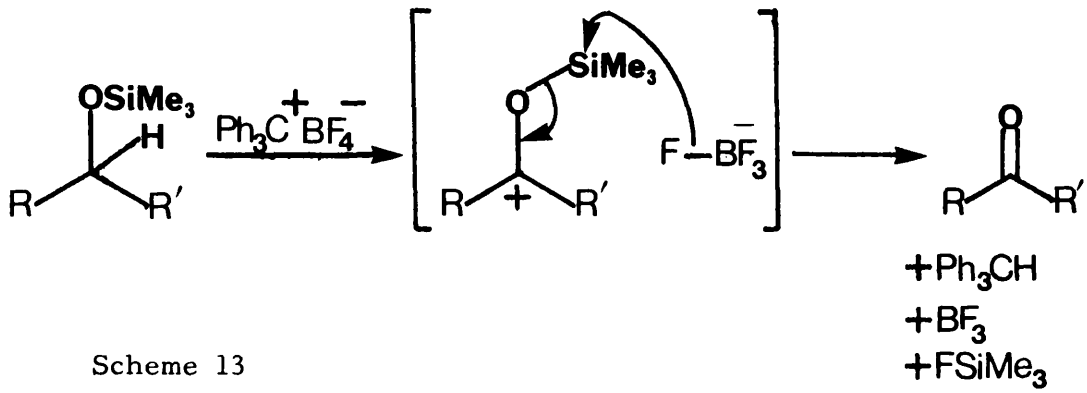


Entry	R^1	R^2	Retention Indice I_{OV-1} [a]	Temp °C	Standards
44	CH_2Ph	Ph	2030(62) 2100(38)	155	$C_{19,20,22}$
51	Me	Ph	1494(74) 1620(26)	115	$C_{14,15,16}$
55	(R)PhCHMe	Ph	2042(18) 2072(21) 2096(45) 2132(16)	155	$C_{19,20,22}$
69	(R)PhCHMe	Pr^i	1718(17) 1728(13) 1743(70)	140	$C_{17,18,19}$
78	(R)PhCHMe	pMeOPh	2170(47) 2207(53)	155	$C_{19,20,22}$

a. Figures in parentheses refer to percentage of diastereomer within the isoxazolidine mixture.

difference in the rate of hydrolysis of the acetate functionality between (41) and (42) and/or the silylation rate of the two component alcohols in the diastereomer mixture (43). However, trimethylsilyl ethers such as (44) proved valuable for establishing the diastereomeric composition of the isoxazolidine mixture formed in the initial cycloaddition reaction, particularly when such information was not readily available from the ^{1}H nmr spectra of the product acetate mixtures which were generally not separable by preparative t.l.c. The acetate mixtures were found unsuitable for g.c. analysis due to facile decomposition on the g.c. column.

Oxidation of (43) to isoxazolidinone (45), [Scheme 14] proved a difficult transformation to effect and, indeed, remains the major problem in this route to β-amino acids since the ease and cleanness of oxidation depend critically on the substituents at nitrogen and C-3. Initial attempts with mild oxidising agents were discouraging. Thus treatment of (43) with PDC[59] and PCC[60] resulted in degradation of the starting material. Oxidation of the trimethylsilyl ether (44) was attempted, employing a method described by Jung,[61] which involves hydride abstraction with triphenylcarbenium tetrafluoroborate to generate an intermediate carbocation followed by desilylation to generate a carbonyl group, [Scheme 13]. However (44) underwent simple desilylation to give parent lactol (43) under these conditions.



Scheme 13

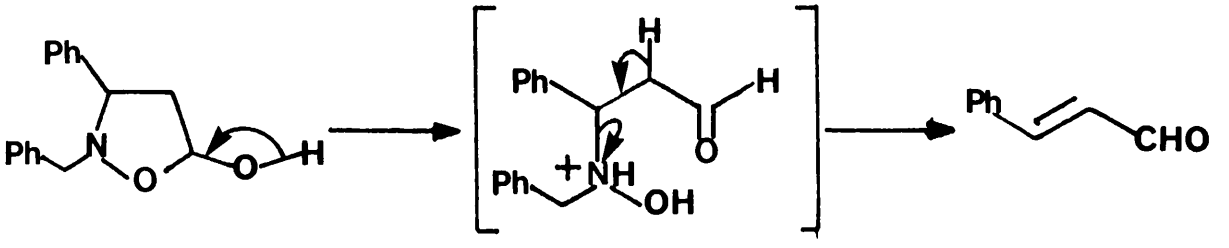
An attempted Swern[62] oxidation of (43) at -78°C with DMSO-oxalyl chloride-triethylamine yielded only starting material, as did treatment with N-chlorosuccinimide-methyl sulphide under the conditions reported by Corey.[63]

However Jones[64] oxidation of (43) at 0°C afforded the desired isoxazolidinone (45) in 36% yield. The i.r. spectrum exhibited a characteristic high frequency carbonyl band at 1780 cm^{-1} [27] and accurate mass measurement confirmed the molecular formula of $C_{16}H_{15}NO_2$. Jones oxidation of (43) at -20°C led to a slightly cleaner reaction, but without significant increase in yield.

Collins reagent[65] was employed to oxidise (43) under less harshly acidic conditions to give the isoxazolidinone in 48% yield. Cinnamaldehyde (46) was isolated as the major side product of both Jones and Collins oxidation and was presumably formed as the result of acid-catalysed ring opening and β-elimination, [Scheme 15].

(43) (45)

Scheme 14



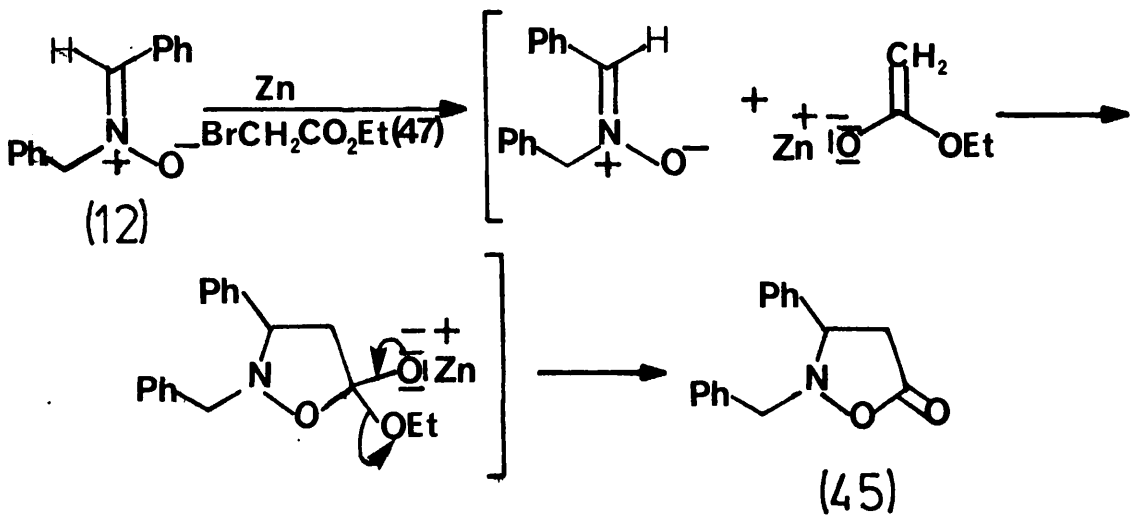
(43) (46)

+

$PhCH_2NHOH$

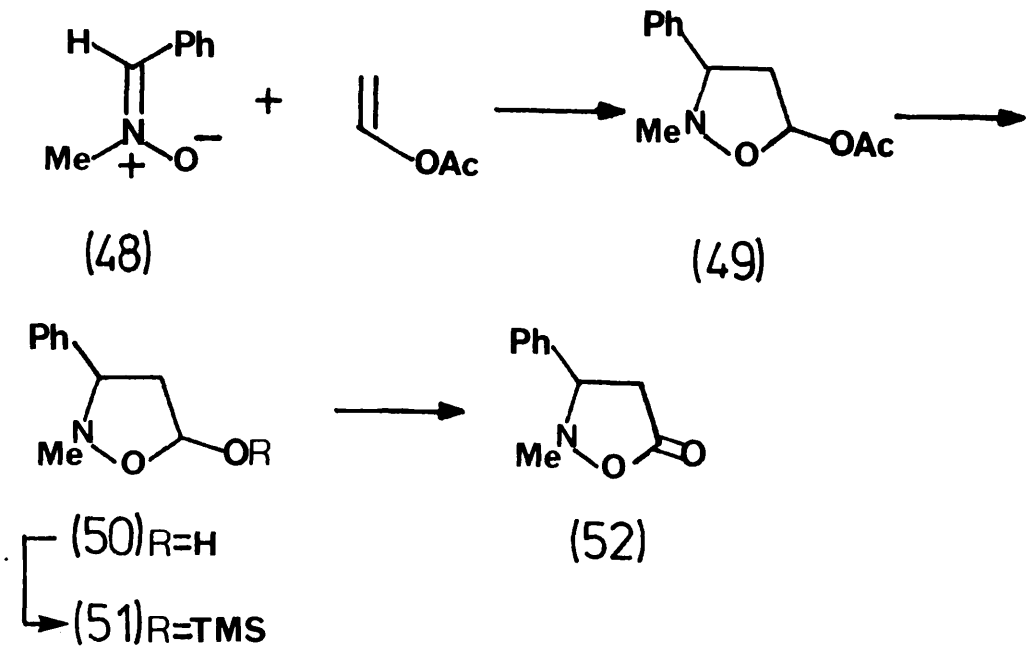
Scheme 15

The spectroscopic data for the isoxazolidinone (45) were found to be identical with those of a sample obtained independently by condensation of nitrone (12) with the Reformatski reagent from ethyl α-bromoacetate (47), [Scheme 16], via the procedure described by Stamm.[66]



Scheme 16

N-Methyl-C-phenylisoxazolidinone (52) was also synthesized employing 1,3-dipolar cycloaddition of the appropriate nitrone to vinyl acetate, [Scheme 17].



Scheme 17

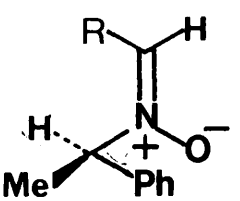
Cycloaddition of C-phenyl-N-methyl nitrone (48) with vinyl acetate[32] gave a mixture of two diastereomeric isoxazolidines (49) which were not separated. The ^{1}H nmr spectrum of mixture (49) showed a one proton multiplet at δ6.35 for the acetal proton at C-5, and two singlets at δ2.60 and 2.78, corresponding to the N-methyl groups in an approximate ratio of 2:1.

Hydrolysis of the acetate[58] mixture gave lactol (50). Analysis of TMS ether (51) by gas chromatography showed two diastereomers in a ratio of 2.9:1, [Table 4]. Oxidation of lactol (50) to isoxazolidinone (52) was again effected with Collins[65] reagent at 0°C, in 21% yield. The i.r. spectrum of (52), displayed high frequency carbonyl absorption

at 1780 cm^{-1}. The yield was disappointingly low compared with that for the N-benzylisoxazolidinone (45). In this and subsequent examples, it was found that the ring substituents at nitrogen and C-3 had a dramatic effect on the ease and cleanness of the oxidation of lactol to isoxazolidinone.

2:4 Chiral Synthesis of β-Phenyl-β-Alanine, β-Leucine, β-Tyrosine and β-Tryptophan

Having demonstrated that it is possible to secure the isoxazolidinone ring system by manipulation of the cycloadducts of nitrones with vinyl acetate,[32, 57] nitrones bearing a chiral group on nitrogen were then employed in an attempt to control the absolute stereochemistry at C-3 of the isoxazolidine acetate, viz. (39), [Scheme 9], formed in the cycloaddition process. Nitrones (20-22, 24)[44] were chosen as the required intermediates for chiral syntheses of β-leucine, β-phenyl-β-alanine, β-tyrosine and β-tryptophan.

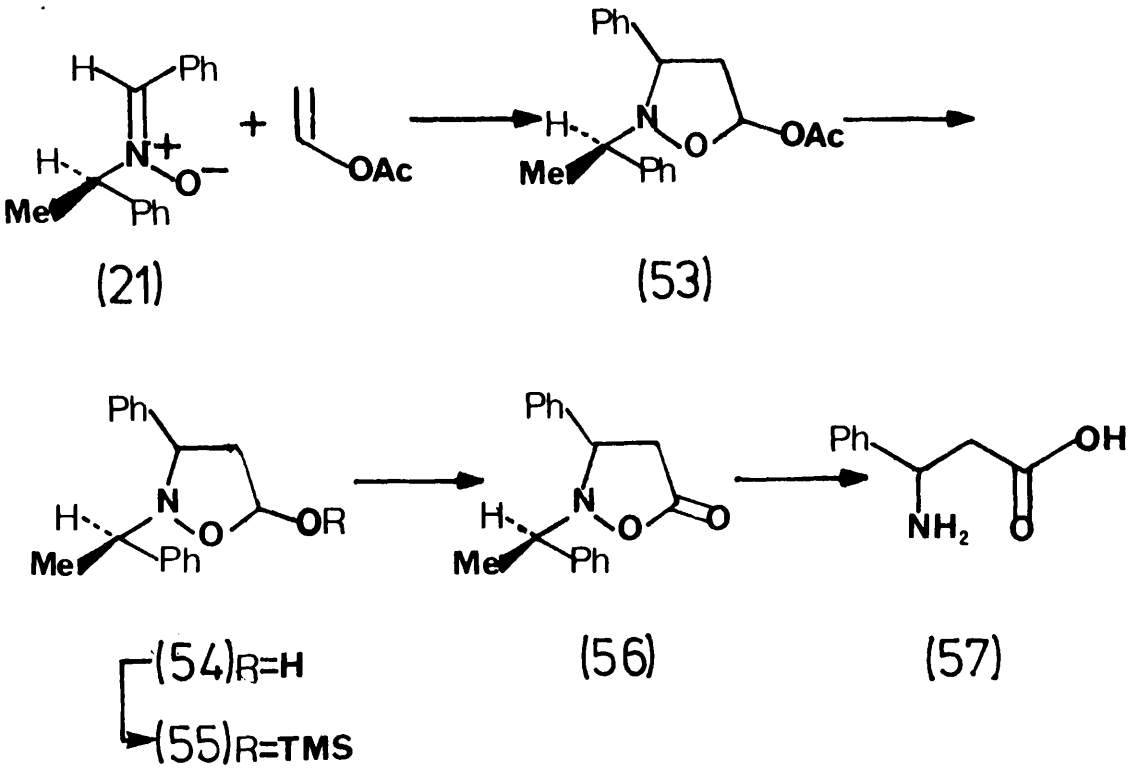


(20) R= *i* Pr
(21) R= Ph
(22) R= pMeOPh
(24) R= α-indolyl

The N-benzylic chiral auxiliary would subsequently be removable by hydrogenolysis. Belzecki[44] has previously demonstrated diastereoselectivity in cycloadditions of similar nitrones with monosubstituted olefins.

2:4:1 β-Phenyl-β-alanine

As the first step in the synthesis of β-phenyl-β-alanine (57), [Scheme 18], nitrone (21) was refluxed in neat vinyl acetate for 72h to give isoxazolidine (53), as a mixture of four diastereomers, in 69% yield.



Scheme 18

The ^1H nmr spectrum at 200 MHz [Fig. 6a] of mixture (53) showed four distinct signals for the acetal proton at C-5, δ6.51 (0.06H, dd, J=1.5, 5 Hz), δ6.42 (0.42H, dd, J=2, 6.3 Hz), and a multiplet consisting of two overlapping doublets of doublets of equal intensity centered at δ6.27, the relative intensities of the four signals being measured as 6:42:26:26 respectively, [Fig. 6b]. The i.r. spectrum of (53) showed ester carbonyl absorption at 1735 cm^{-1}, and accurate mass measurement of $[M]^+$ at m/e = 311.1523 (Calc. 311.1521) confirmed the molecular formula of $C_{19}H_{21}NO_3$.

The formation of four diastereomers was not unexpected, resulting from the approach of the reagents in an exo- or endo-manner, in addition to approach of the nitrone to the re- or si-face of the olefin, [Scheme 19]. Unfortunately in this case, the Rf values of the four diastereomers were too similar to allow complete separation by preparative t.l.c., hence a complete stereochemical analysis of the cycloaddition proved difficult. The isoxazolidine mixture (53) was observed as a single band, even upon multiple development of the plate. The band was thus divided into three regions of equal width and the region of "highest Rf" was found to contain mostly the major diastereomer of mixture (53), by the ^1H nmr spectrum at 90 MHz, which showed a doublet of doublets at δ6.41 (1H, J=2, 6.5 Hz, CHOAc), (cf ^1H nmr at 200 MHz, δ6.42 (0.42H, dd, J=2, 6.3 Hz)). The remaining two regions contained mixtures of all four isomers and further separation was not attempted.

However, Belzecki[44] demonstrated that in all cases, cycloaddition reactions of nitrones such as (21) with monosubstituted olefins proceeded preferentially via an exo-transition state resulting in the

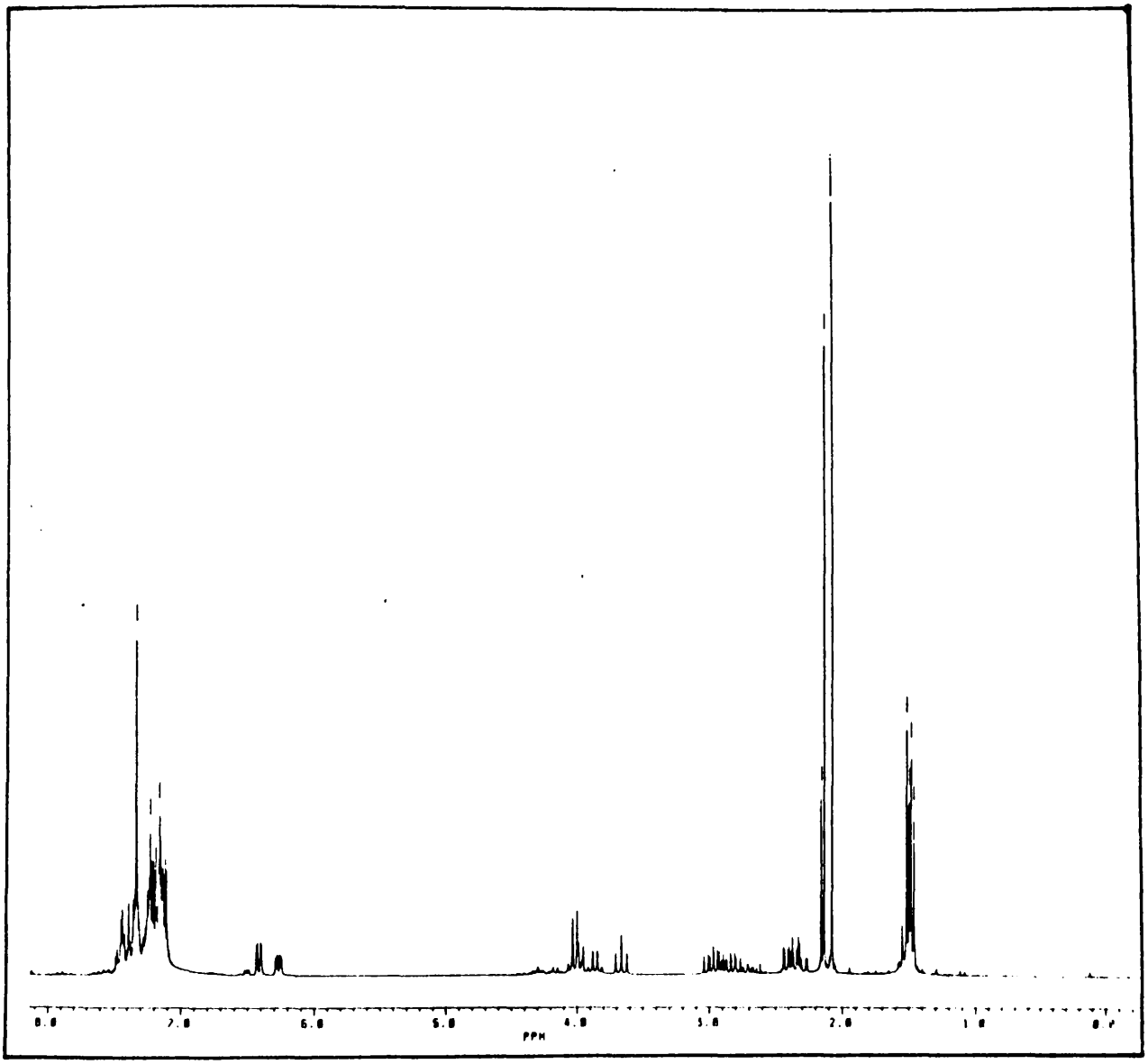
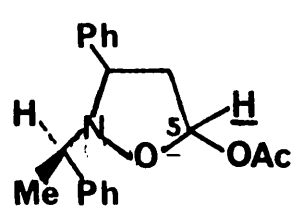
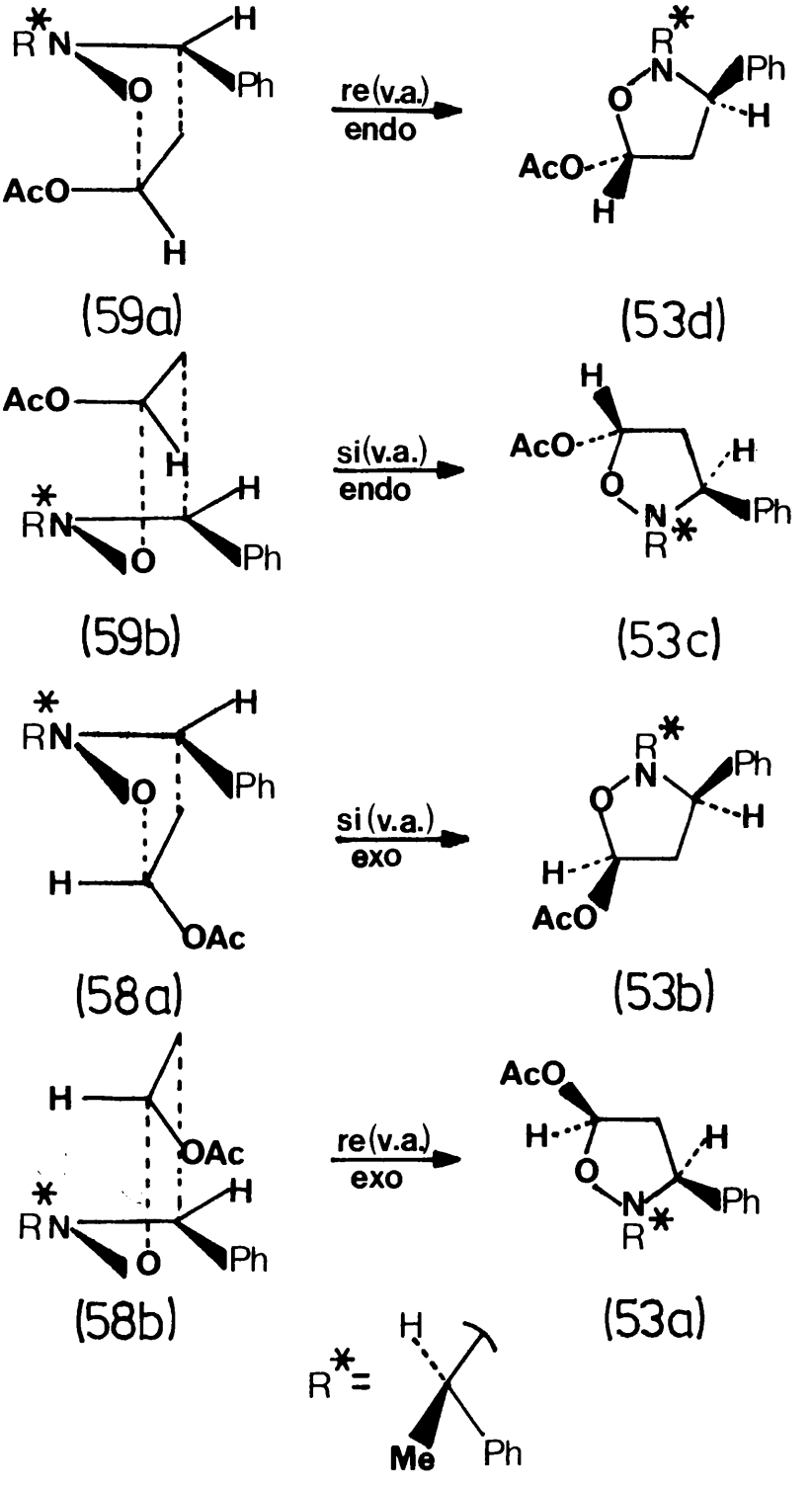


Fig 6a ^{1}H NMR Spectrum of Isoxazolidine (53) at 200 MHz



(54)

Fig 6b ^1H NMR (200 MHz) Expansion of C_5-H, Isoxazolidine (53).

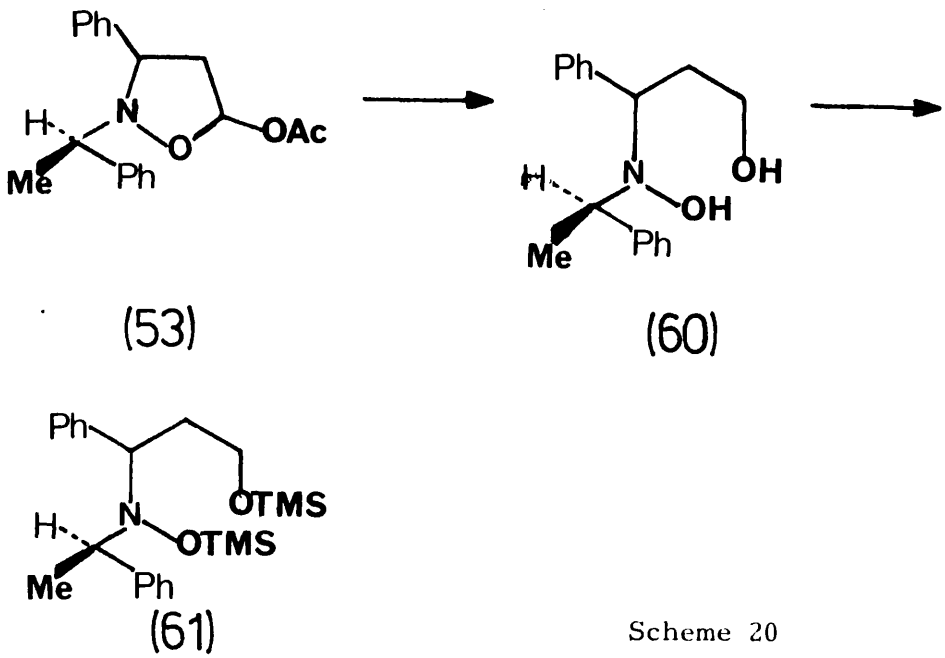

re(v.a.)
endo
si(v.a.)
endo
si(v.a.)
exo
re(v.a.)
exo
(59a)
(53d)
(59b)
(53c)
(58a)
(53b)
(58b)
(53a)
R*=
Me
Ph
AcO
OAc

Scheme 19

formation of isoxazolidines with substituents at C-3 and C-5 in a syn relationship, [Scheme 22, Introduction, p 27]. De Shong[57] has demonstrated that the cycloaddition of C,N-diphenylnitrone (11) and vinyl acetate occurred exclusively via the exo-transition state, [Scheme 8, p 53]. Therefore, from the relative intensities of the four acetal protons at C-5, i.e. (5:42:26:26), assuming the cycloaddition is highly cis stereoselective in accordance with the work of Belzecki[44] and De Shong[57] and the condensation of C-phenyl-N-benzyl nitrone (12) with vinyl acetate described above, then these figures must correspond to a cis (exo)-trans(endo) ratio of 68(42+26):32(26+6) for isoxazolidine (53). It follows from this that the overall induction arising from the cyclo-addition is also 68:32 (viz. 2:1) for the (R:S) or (S:R) ratio at C-3, on the assumption that nitrone (21) displays the same preference for the re or si face of the olefin in both the exo- and endo-transition states, [Scheme 19]. The factors responsible for diastereoselectivity in this case are not clear, since molecular models indicate that any steric repulsions are small and of a similar magnitude in exo (58a)(58b)- and endo(59a)(59b)-transition states.

As the configuration of the major diastereomer could not be established on the basis of proton coupling constants alone, and since complete separation of the isoxazolidine mixture was not feasible, it was envisaged that LAH reduction of the mixture (53) to give the hydroxyl-amine alcohol (60), [Scheme 20] would simplify analysis of the diastereo-selectivity of the cycloaddition. With the removal of the chiral centre at C-5 bearing the acetoxyl substituent, the hydroxylamine alcohol (60) consists of a mixture of two diastereomers differing only in their

configuration at C-3, and it was hoped that g.c. analysis of the bistrimethylsilyloxy ether (61) would resolve the two diastereomers and hence establish the diastereoselectivity of the cycloaddition. However, chromatography of (61) on a 6' 1% OV-1 column showed a single broad based peak of t_R = 1.2 min at 120°C.



Scheme 20

Although this result was disappointing it was hoped that a measure of the diastereoselection in the cycloaddition could be obtained from resolution of later intermediates.

Lactol (54), [Scheme 18] was obtained in 82% crude yield upon hydrolysis of (53).[58] The i.r. spectrum showed free and bonded hydroxyl absorption at 3600 and 3190 cm^{-1} respectively, while the ^1H nmr contained a complex multiplet between δ5.70 and 5.30 for the hemi-acetal proton at C-5.

The diastereomeric composition of the lactol mixture was obtained by g.c.-m.s. analysis of the trimethylsilyl ether mixture (55). Chromatography of (55) on a 6' 1% OV-1 column at 155°C showed four peaks in a ratio of 45:21:18:16, [Figure 7 and Table 4], each of which had m/e = 341 corresponding to a molecular formula of $C_{20}H_{27}NO_2Si$. This confirmed the presence of four diastereomers within the acetate mixture (53) and from these figures the C-3 (R/S or S/R) ratio within lactol (54) must lie between 1.9:1 and 1.6:1 in good agreement with the stereoselection deduced from the ^1H nmr spectrum of (53).

Isoxazolidinone (56) was obtained by Collins oxidation of lactol (54) at 0°C. The optimum yield of this reaction was disappointingly low at 16%. Among the competing side reactions, was the ring-opening and β-elimination to give cinnamaldehyde (46), [cf Scheme 15, p 64]. Isolation of the desired product proved difficult and required careful chromatography employing preparative t.l.c.

Isoxazolidinone (56) was eventually obtained as a crystalline solid, m.p. 95-98°C, upon recrystallisation of the material obtained from preparative t.l.c. The i.r. spectrum displayed the expected high frequency carbonyl absorption at 1785 cm^{-1} and the ^1H nmr spectrum, [Fig. 8a] showed an ABX system involving the benzylic methine proton at C-3, δ4.46 (1H, t, J=7.5 Hz) and the methylene protons of C-4, δ3.06 (1H, dd, J=7.5, 17.5 Hz). Only one doublet was observed at δ1.55, for the methyl signal of the α-methylbenzyl group, so that the diastereomeric composition of (56) could not be established from ^1H nmr. The ^{13}C nmr of (56), [Fig. 8b] also showed one set of signals. Analysis of (56) by g.c.-m.s. showed only one peak of m/e = 267 and chromatography by

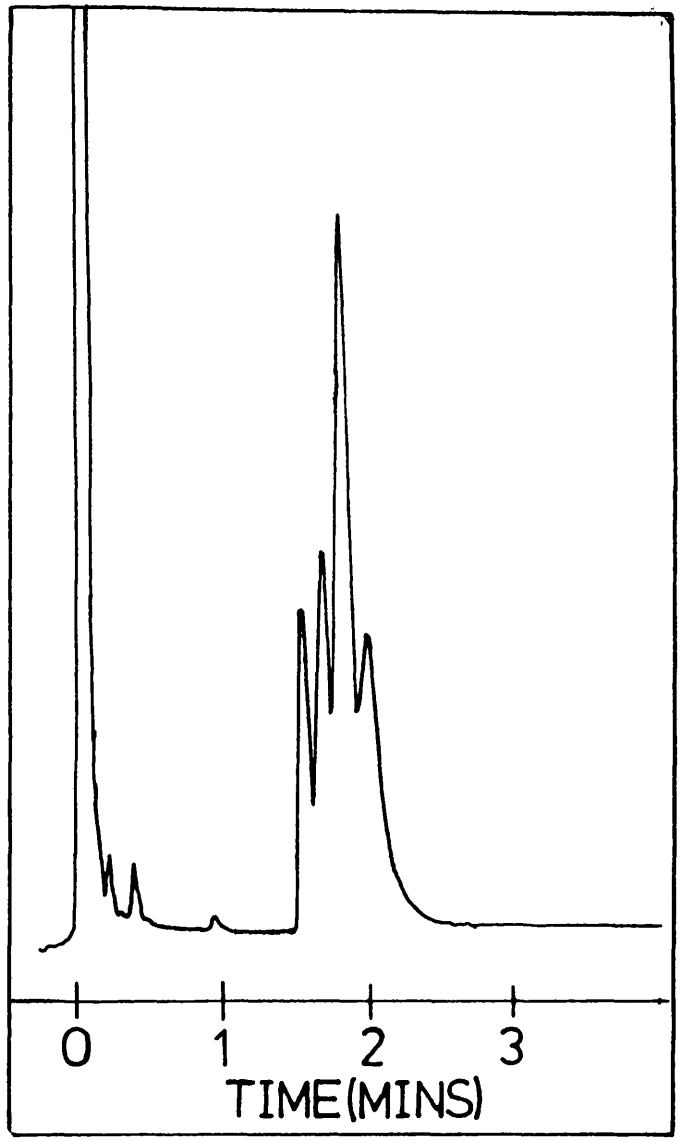


Fig.7 G.C. of Isoxazolidine TMS Ether (55) on a 6′ 1%OV-1 at 155°C.

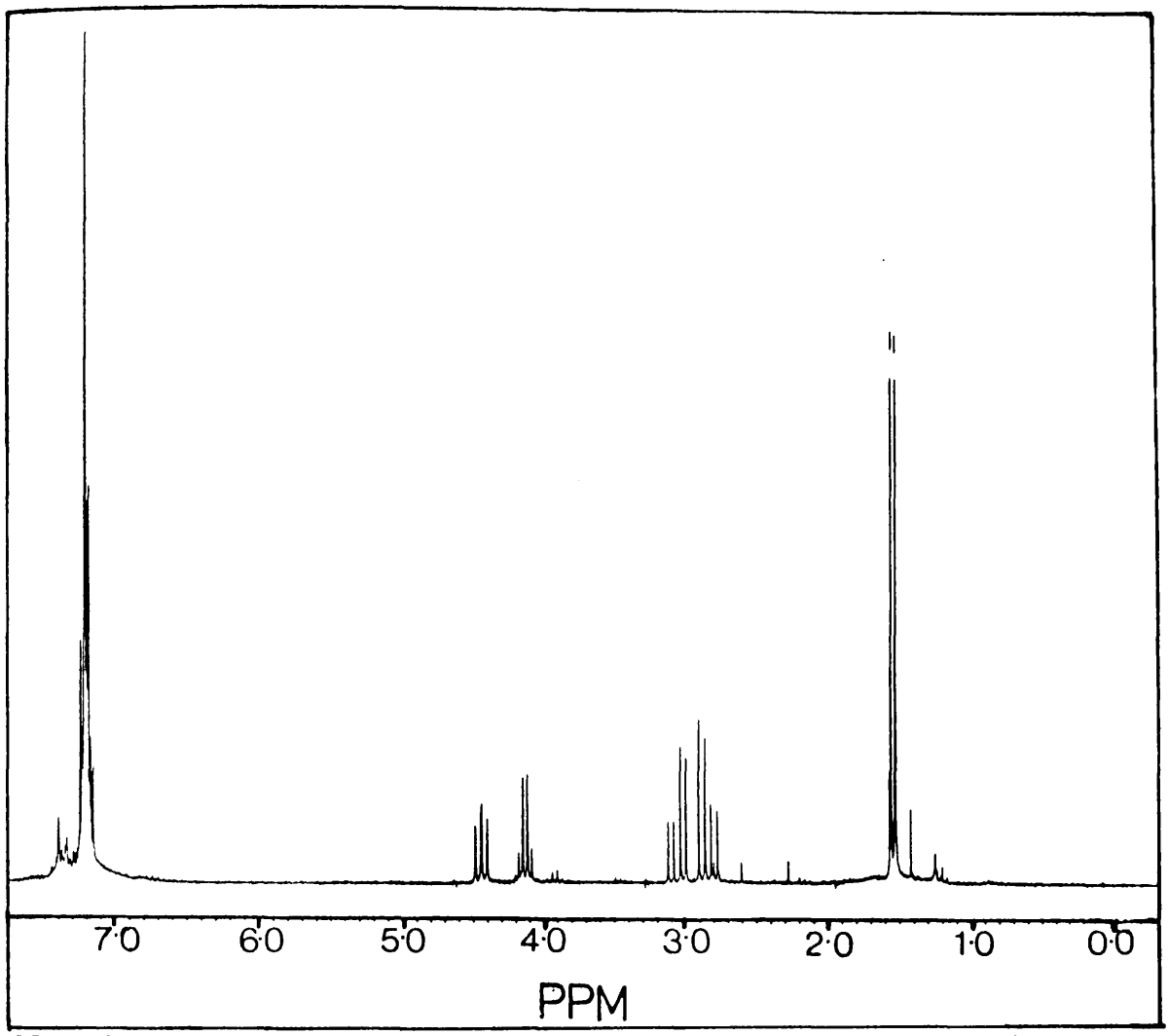


Fig.8a H NMR Spectrum of Isoxazolidinone(56) at 200MHz.

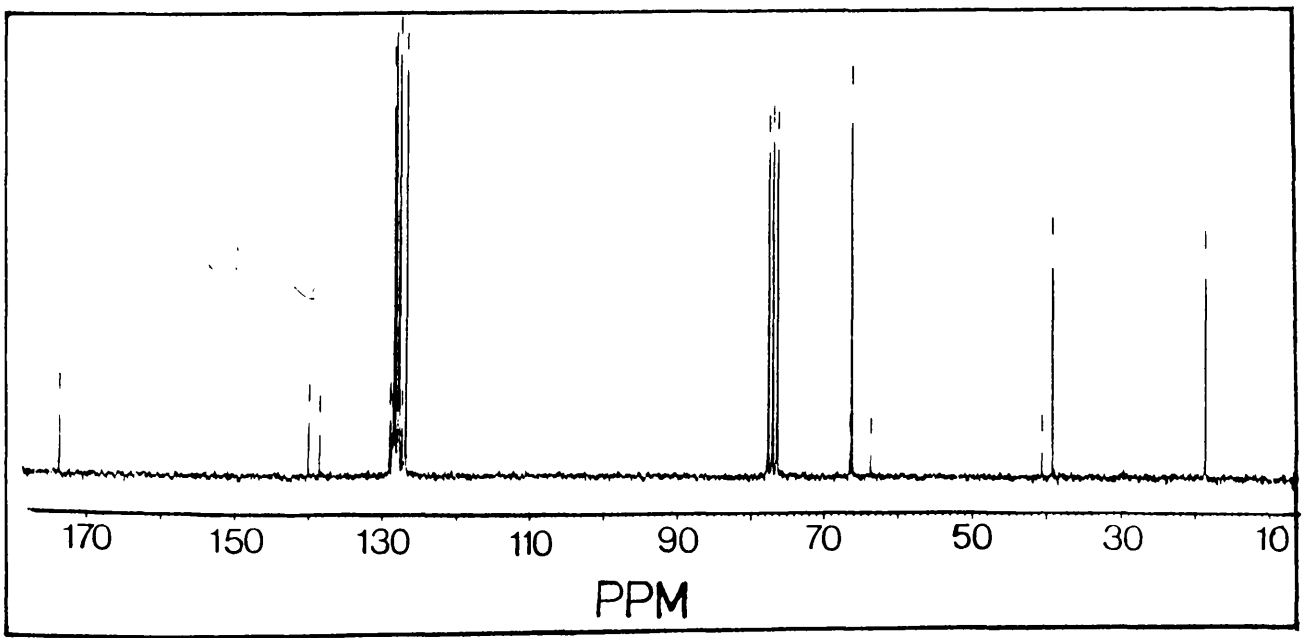


Fig.8b ^{1}H Decoupled ^{13}C NMR Spectrum of (56).

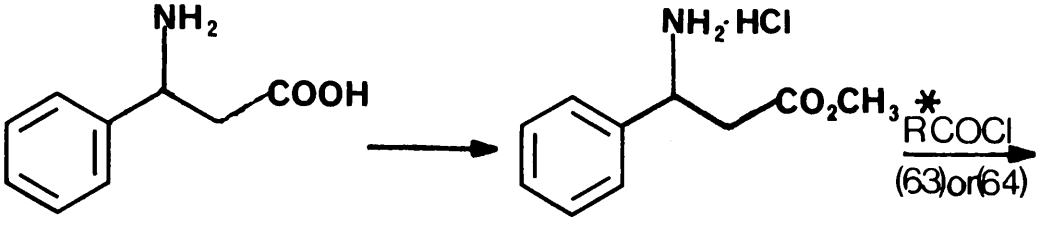
capillary g.c. on both 25m CPSil 5-CB (equivalent to 1% OV-1) and SE-54 columns also failed to resolve the diastereomers.

Hydrogenolysis of (56) with palladium hydroxide in ethanol at 70°C led directly to β-phenyl-β-alanine, in 92% yield, as a crystalline solid m.p. 231-234°C $[\alpha]_D$ -1.5°C, (lit.[67] value m.p. 236°C, $[\alpha]_D$ + 6.2° for (S)-β-phenyl-β-alanine).

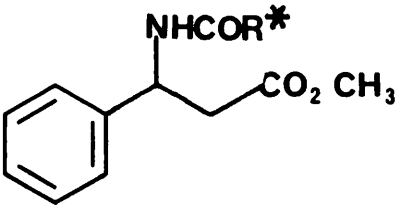
The analytical resolution of the β-phenyl-β-alanine produced was effected by gas chromatography of the N-acyl-β-phenyl-β-alanine methyl esters[68] (65) and (66). The derivatives were formed by esterification of the free amino acid in a solution of thionyl chloride and methanol, followed by the reaction of the methyl ester hydrochloride (62) with the appropriate optically active acid chloride (63) or (64), [Scheme 21].

The results which are given in Table 5 show that analytical resolution of crude β-phenyl-β-alanine was best achieved with the 'Mosher' amide[69] (66) on 25m capillary phase column SE-54, [Fig. 9] which showed two peaks of baseline separation at t_R 15.18 and 15.48 mins in a ratio of 46:54 respectively. Although the difference in retention times for the two diastereomers is greater in Column 1, the peak shapes are broad and do not show baseline separation, unlike Columns 2 and 3, preventing accurate analysis of the ratio within (66).

As the β-phenyl-β-alanine from (56) possessed a negative rotation, the major component was assigned as the (R)-amino acid, in 8% enantiomeric excess, from g.c. analysis of (66). This result is disappointingly low in comparison with the diastereoselectivity obtained from the cycloaddition step and is also lower than expected

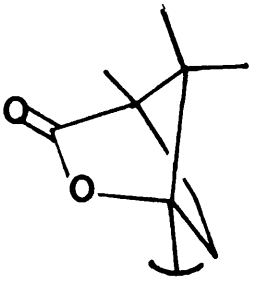


(57) (62)

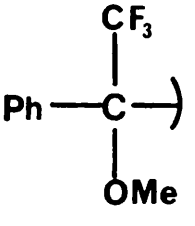


(65) or (66)

(63) and (65) R^* =



(64) and (66) R^* =



Scheme 21

Table 5

Gas Chromatography of β-Phenyl-β-Alanine Derivatives

Retention Time (t_R, mins)

Entry	Column 1	Column 2	Column 3
65	15.40	30.05	-
66	11.55,12.80	11.82,12.05	15.18,15.48

Column 1; 6' 1% QF-1 at 210°C.

Column 2; 25m x 0.32 mm i.d. fused silica capillary phase CPSil5 CB at 80°C, (rising 30°C min^{-1} to 250°C).

Column 3; 25m x 0.32 mm i.d. fused silica capillary phase SE-54 at 80°C, (rising 30°C min^{-1} to 250°C).

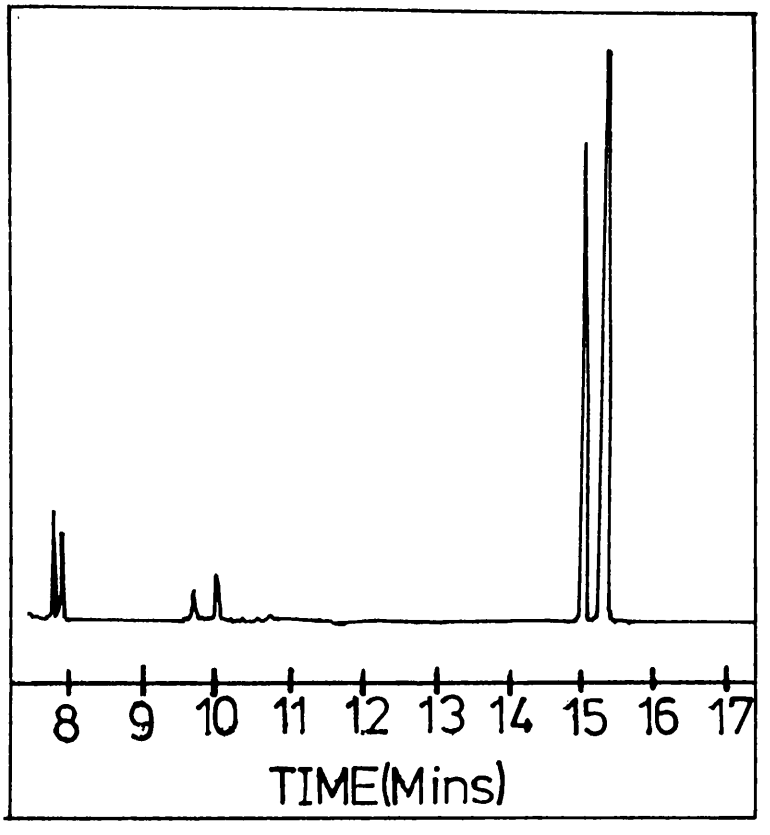
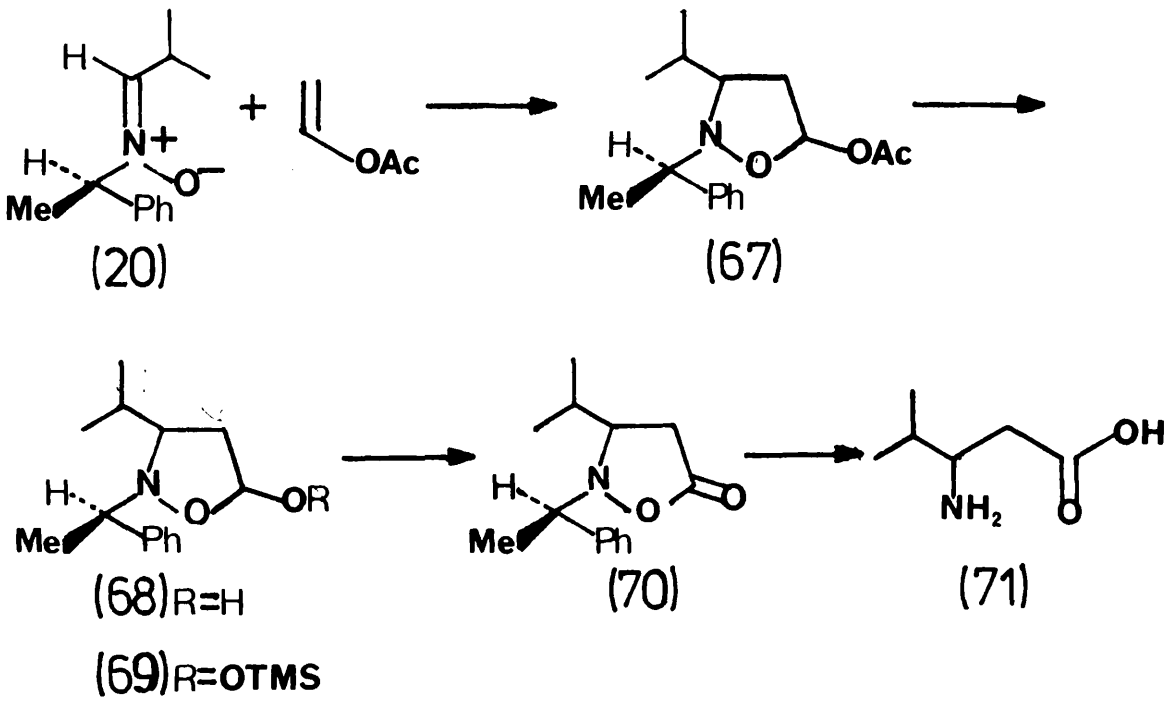


Fig. 9 Capillary G.C. of 'Mosher' Amide (66) on 25m SE-54 Column from 80°C to 250°C (Rate=30°C Min^{-1}).

compared to the diastereomeric ratio of between 1.9:1 and 1.6:1 derived from the g.c.-m.c. results of the TMS ether mixture (55), suggesting some fractionation may have occurred in the oxidation of lactol (54). Since the (R)-amino acid was produced in excess this suggests that Si attack in <u>exo</u>- and <u>endo</u>-t.s. of the olefin was preferred by nitrone (21) leading in turn to preferential formation of isoxazolidines with C-3(R) configuration and this in conjunction with the cis stereospecificity of the cycloaddition indicates (53b) as the major diastereomer. However in view of the small enantiomeric excess and the uncertainty of discrimination during oxidation it would be unwise to attach too much weight to this conclusion.

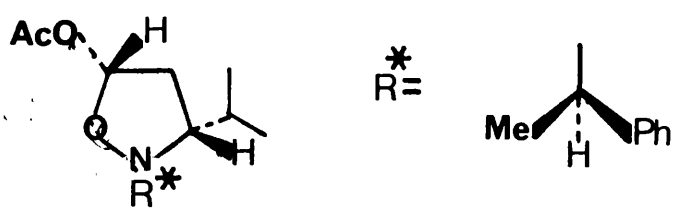
2:4:2 <u>β-Leucine</u>

β-Leucine (71) was synthesised as shown in Scheme 22.



Scheme 22

Nitrone (20) was refluxed in neat vinyl acetate for 48h to give isoxazolidine (67) in 81% yield, as a mixture of four diastereomers which could not be separated. The ^{1}H nmr spectrum, [Fig. 10a] of (67) was complex showing two sets of overlapping signals at δ6.41 (0.67H, m) and δ6.20 (0.33H, m) for the acetal proton at C-5, [Fig. 10b]. From this, it can be seen that one of the four diastereomers of (67) accounts for approximately 50% of the mixture with the other three isomers present in roughly equal amounts, i.e. [49:17:17:17]. This information suggests that if the cycloaddition is cis-stereoselective, as expected, then the cis to trans ratio of isoxazolidines in (67) must be approximately 2:1, i.e. cis (49+17) : trans (17+17). The overall diastereoselectivity of the cycloaddition reaction must also be approximately 2:1 for the R:S ratio at C-3 of (67), with the assumption that nitrone (20) shows a preference for si attack of the olefin in an exo-transition leading to cis (3(R),5(S)) isoxazolidine (67a) as the major diastereomer (c.f. Scheme 19 for phenyl nitrone (21)). Apparently there was no discrimination between the re and si faces of the olefin in the endo-transition state leading to the trans-isoxazolidines.



(67a)

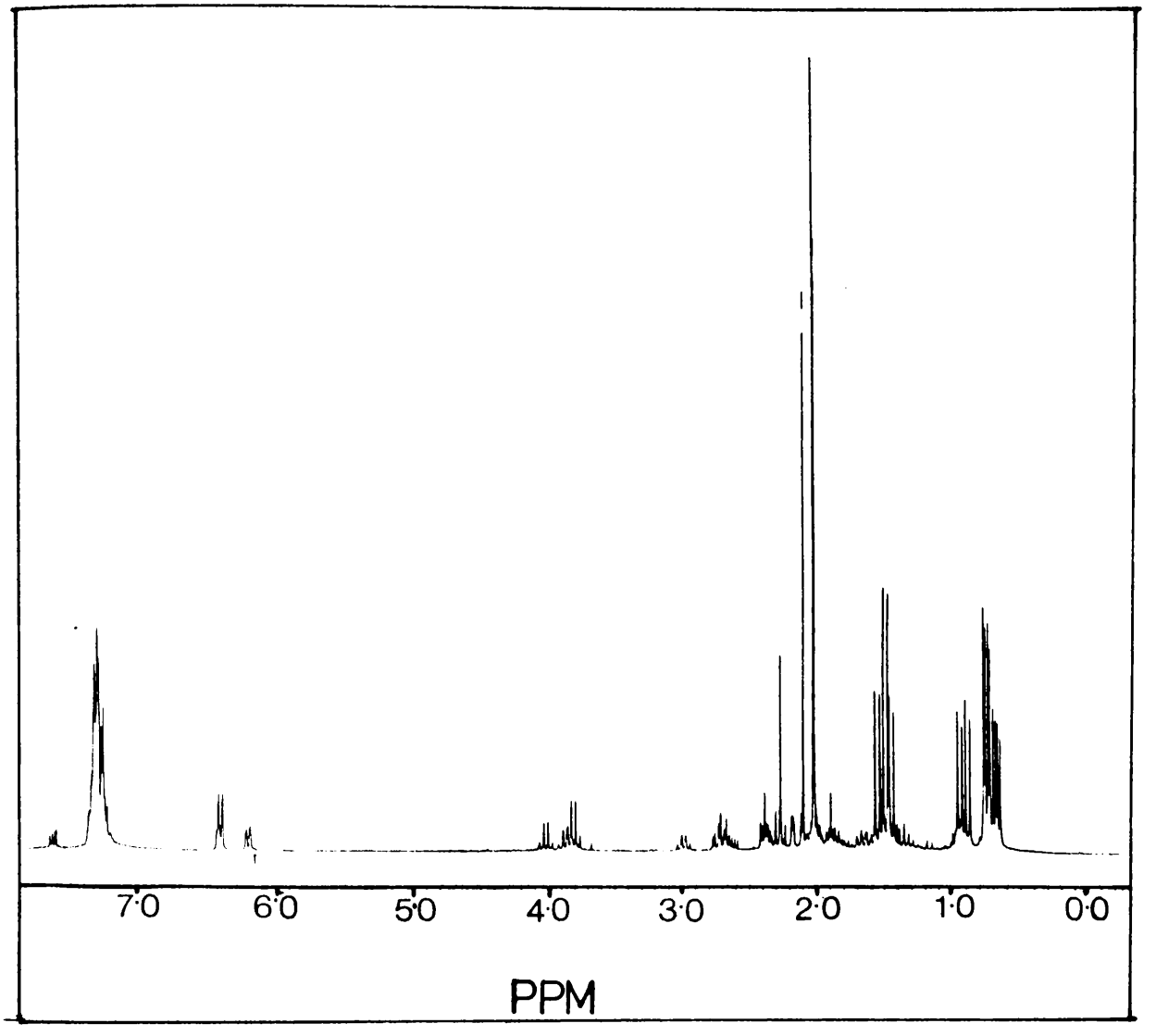


Fig. 10a ^{1}H NMR Spectrum of Isoxazolidine (67) at 200MHz.

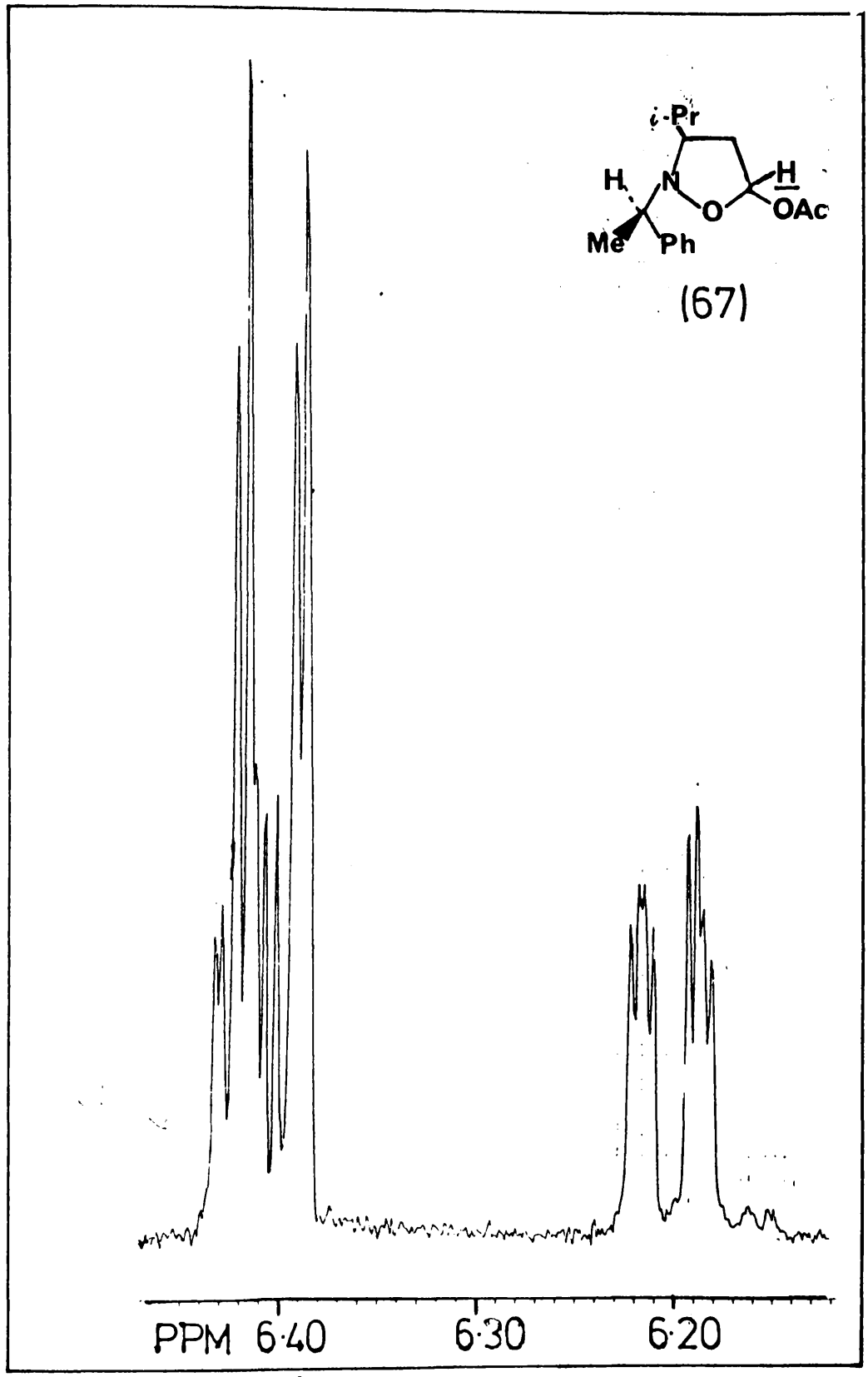


Fig.10b ^{1}H NMR(200MHz) Expansion of C_5-H, Isoxazolidine(67).

Lactol (68) was obtained in 78% yield, from hydrolysis of (67).[58] The ^{1}H nmr spectrum contained a complex multiplet between δ5.75-5.34 (1H, m, OCHOH) and the i.r. spectrum showed free and bonded hydroxyl absorption at 3600 and 3400 cm^{-1} respectively.

Analysis of trimethylsilyl ether (69) by g.c.-m.s. showed three peaks in a ratio of 70:17:13, [Fig. 11] and Table 4, each of m/e = 307, corresponding to a molecular formula of $C_{17}H_{29}NO_2Si$. The largest peak presumably arose from overlap at the two diastereomers, preventing an estimate of the diastereomeric ratio within the lactol (68).

Treatment of lactol (68) with Collins reagent proved completely deleterious. However, Swern[62] oxidation in dichloromethane at -60°C gave isoxazolidinone (70) in 14% yield. The ^{1}H nmr spectrum, [Fig. 12a] of (70) clearly showed the presence of two diastereomeric isoxazolidinones in a ratio of 4.5:1 as two signals were observed for the methyl protons of the α-methylbenzyl group at δ1.60 (0.54H, d, J=6.5 Hz) and δ1.51 (2.46H, d, J=6.5 Hz). Two distinct signals were observed for the isopropyl methyl groups at δ0.92 (1.16H, m) and δ0.75 (4.84H, m) in a similar ratio. The ^{1}H decoupled ^{13}C nmr spectrum of (70), [Fig.12b] confirmed this, for example the methylene carbon C-4 showed two signals at δ30.57 and 31.33 in a 4.5:1 ratio. This suggests that fractionation had occurred either in the hydrolysis of acetate mixture (67) or in the oxidation of (68) to the isoxazolidinone (70) resulting in an enhancement in the diastereomeric ratio within (70).

Unfortunately, under the conditions of the Swern reaction, oxidation of (68) was accompanied and sometimes precluded by the

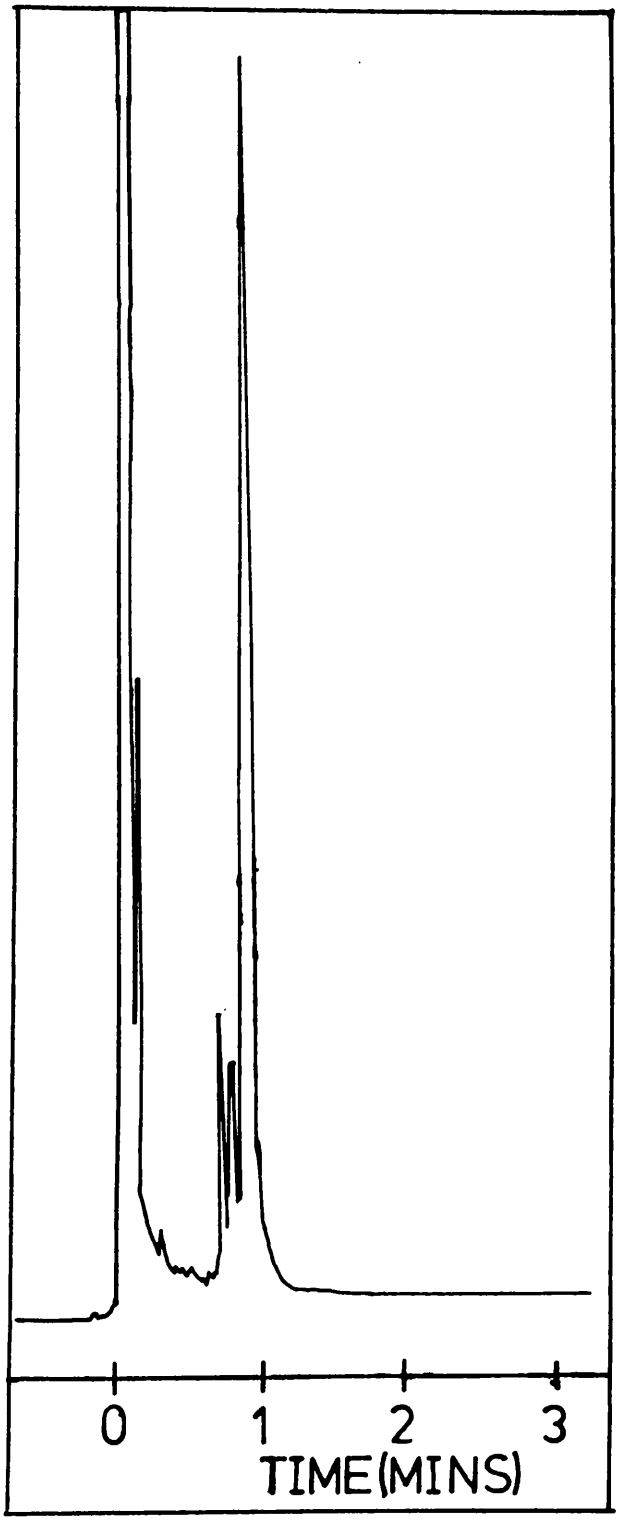


Fig.11 G.C. of Isoxazolidine TMS Ether (69)
on a 6′ 1%OV-1 at 140°C.

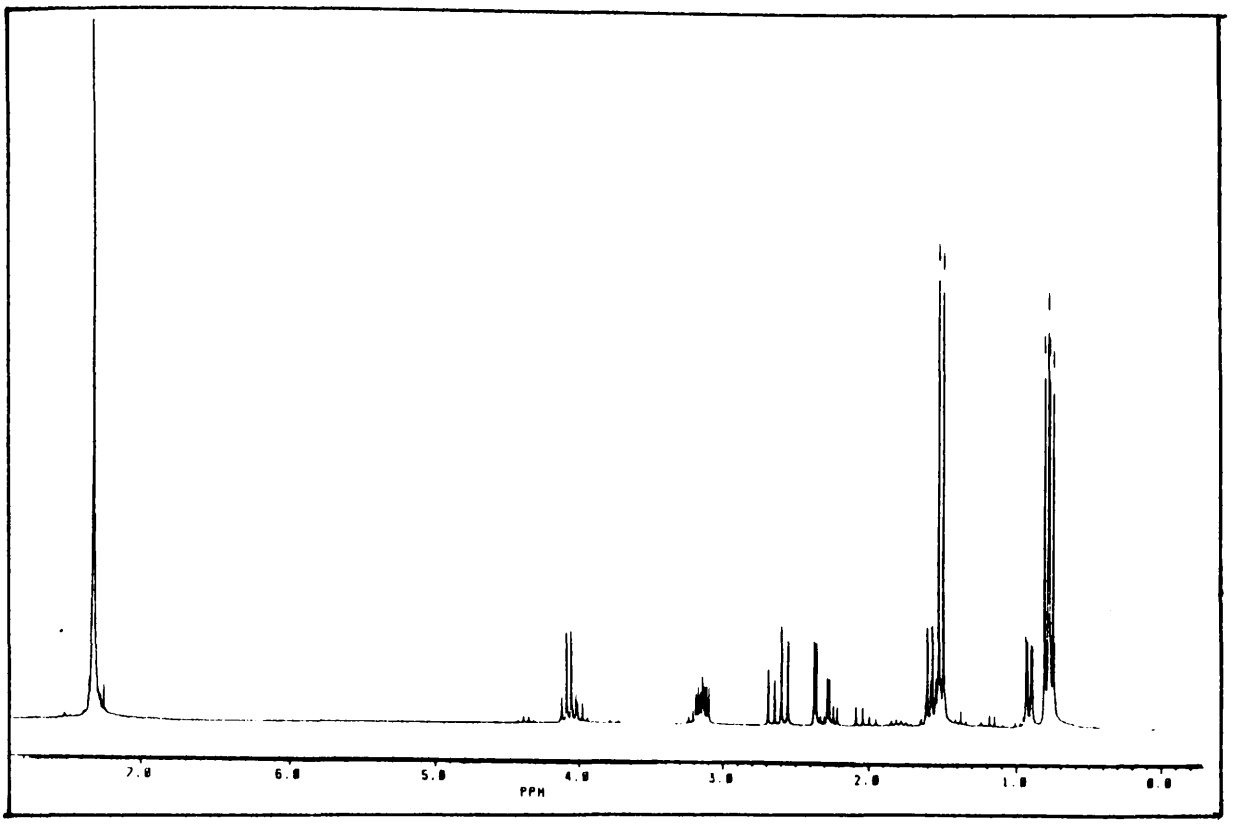


Fig.12a ^{1}H NMR Spectrum of Isoxazolidinone(70) at 200MHz.

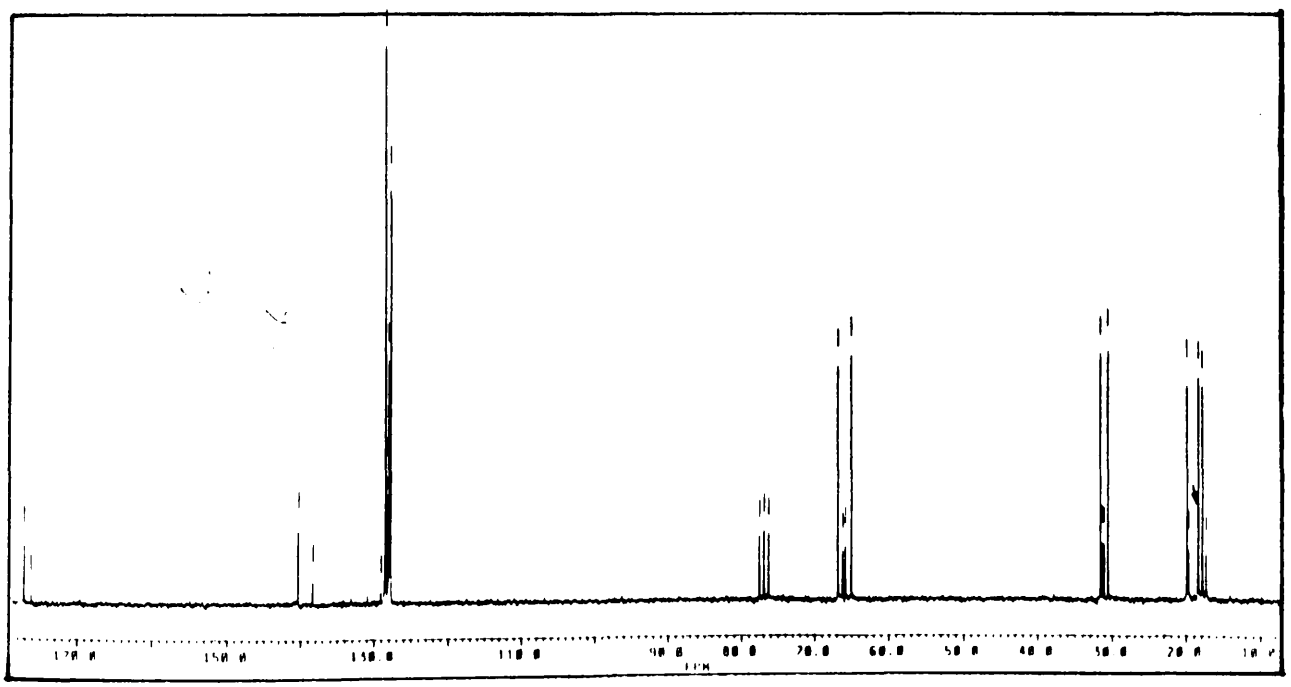
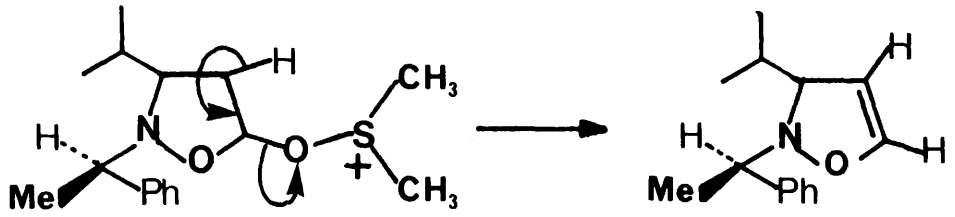


Fig.12b ^{1}H Decoupled ^{13}C NMR Spectrum of (70).

β-elimination product from intermediate (72) to give the Δ^4-isoxazolidine (73), [Scheme 23].



(72) (73)

Scheme 23

The ^{1}H nmr spectrum of (73) displayed two olefinic absorptions at δ6.39 (1H, m, CH=C<u>H</u>-O) and δ4.75 (1H, m, C<u>H</u>=CH-O), while the i.r. spectrum showed C=C absorption at 1625 cm^{-1}. Accurate mass analysis showed <u>m</u>/<u>e</u> = 217.1470, corresponding to molecular formula $C_{14}H_{19}NO$ (calc. <u>m</u>/<u>e</u> = 217.1467).

Hydrogenolysis of isoxazolidinone (70) over $Pd(OH)_2$ on charcoal at atmospheric pressure and ambient temperature gave β-leucine (71) in quantitative yield, as a colourless crystalline solid m.p. 204-207°C $[\alpha]_D$ -22.4°, (lit[67] value m.p. 201-202°C, $[\alpha]_D$ + 55.2° for (S)-β-leucine). The enantiomeric composition of β-leucine was established, employing g.c. analysis of the N-acyl methyl esters (74) and (75), see Table 6.

The best resolution was obtained from camphanamide (74) on a capillary phase SE-54, [Fig. 13]. Two peaks of baseline separation

Table 6

Gas Chromatography of β-Leucine Derivatives

Retention Time (t_R, mins)

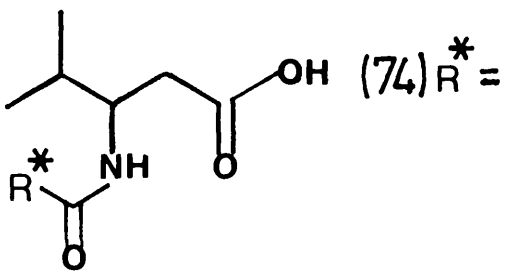
Entry	Column 1	Column 2	Column 3	Column 4
74	3.82,4.02	7.80,8.30	15.46,15.84	20.88,21.34
75	1.90	-	-	-

Column 1; 6' 1% OV-17 at 215°C (74) and 200°C (75).

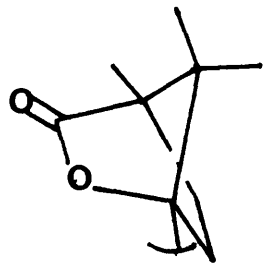
Column 2; 6' 1% QF-1 at 190°C.

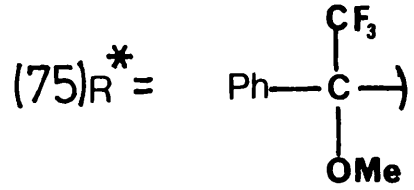
Column 3; 25m capillary phase CPSil5 at 80°C, (rising 30°C min^{-1} to 250°C).

Column 4; 25m capillary phase SE-54 at 80°C, (rising 30°C min^{-1} to 250°C).



(74) R* =





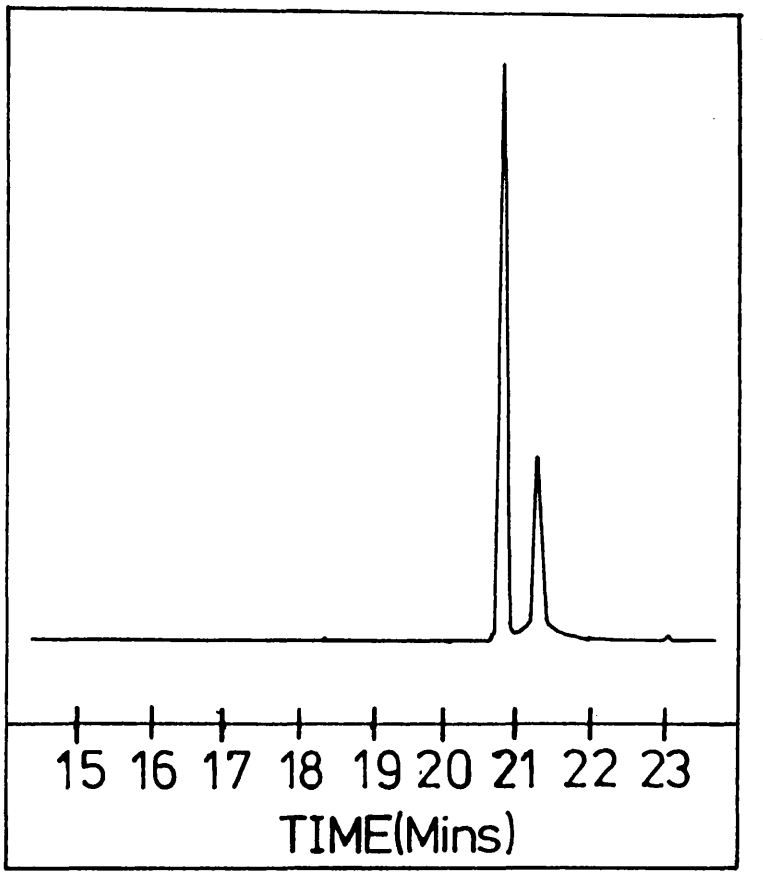


Fig.13 Capillary G.C. of Camphanamide Methyl Ester (7%) on 25m SE-54 from 80°C to 250°C (Rate=30°C Min).

were obtained at t_R 20.88 and 21.34 mins respectively in a ratio of 3.5:1. Since previous studies had shown that the camphanamide methyl ester of (3R)-β-leucine has the shorter retention time, the above analysis corresponds to an enantiomeric excess of 56% of (3R)-β-leucine. This compares with an enantiomeric excess of 40.6% from $[\alpha]_D$ measurements. The ^{19}F and ^{1}H nmr spectra of the 'Mosher' amide (75) unfortunately gave no useful information as they showed no resolution of signals.

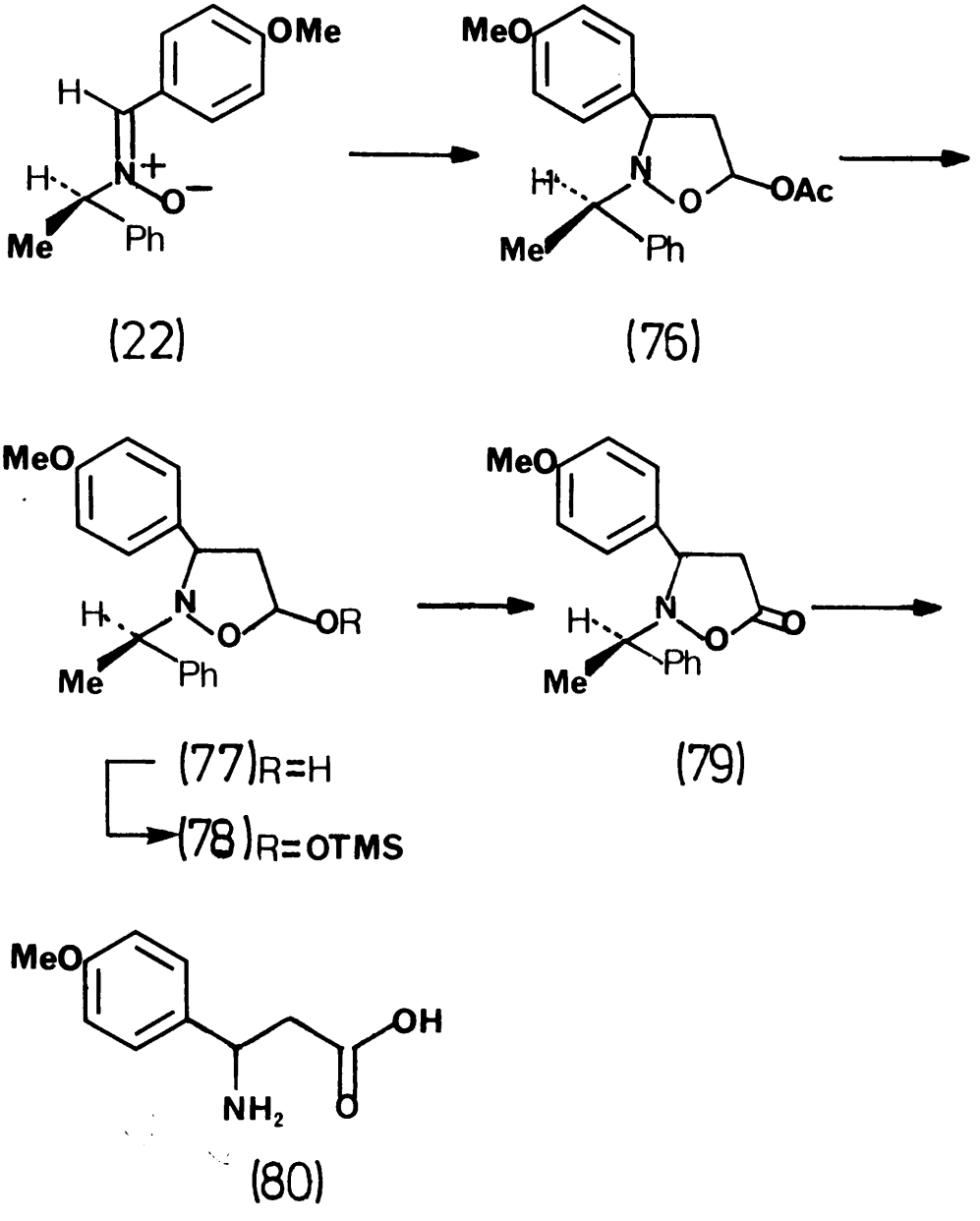
As the (R)-β-leucine was formed in excess, this confirms that nitrone (20) underwent cycloaddition with vinyl acetate with a preference for si attack in the exo-transition state, (cf. Scheme 19) to give the 3(R)-isoxazolidine (67a) as the major diastereomer.

2:4:3 β-Tyrosine

The syntheses of β-tyrosine methyl ether (80) provides a potential route to β-tyrosine, [Scheme 24].

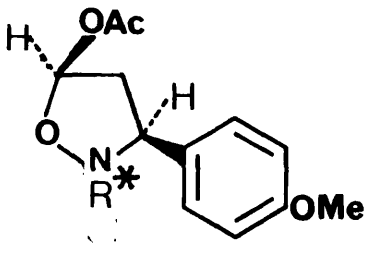
Nitrone (22) was refluxed in vinyl acetate for 96h to give isoxazolidine (76) in 60% yield. The cycloaddition proceeded at a much slower rate than those previously described, presumably because the electron releasing p-methoxyphenyl substituent increased the electron density of the C=N bond, making nitrone (22) less reactive towards electron rich dipolarophiles such as vinyl acetate.

Isoxazolidine (76) was obtained as a 1:1 mixture of two diastereomers which were not separable, as shown by its ^{1}H and ^{13}C nmr spectra, [Figs. 14a and b]. The ^{1}H nmr spectrum of (76) clearly

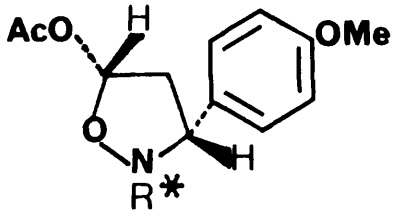

OMe
H
H
N+
O−
Me
Ph
(22)
MeO
H
N
O
OAc
Me
Ph
(76)
MeO
H
N
O
OR
Me
Ph
(77) R=H
(78) R=OTMS
MeO
H
N
O
O
Me
Ph
(79)
MeO
OH
NH2
O
(80)

Scheme 24

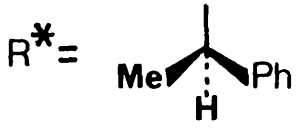
showed two acetoxyl methyl signals at δ2.07 and 2.12 of equal intensity as did the two singlets at δ3.75 and 3.82 for the p-methoxyphenyl methyl group. Two signals were also observed for the acetal proton at C-5, δ6.38 (ddd, J=0.2, 2 and 6.5 Hz) and δ6.23 (ddd, J=1, 4 and 7 Hz). In each signal a small four bond coupling (i.e. 0.2 and 1 Hz) between two protons in a 'W' configuration was observed indicating that the substituents at C-3 and C-5 were syn to each other, and hence the two diastereomers were formulated as (76a and 76b). As the reaction was completely cis stereospecific and the two diastereomers were formed in a 1:1 ratio, there could have been no discrimination shown by nitrone (22) between the re- and si-faces of vinyl acetate in the exo-transition state leading to (76a and 76b), (cf. Scheme 19, p 72). The ^{1}H decoupled ^{13}C spectrum of acetate mixture (76) confirmed the presence of two diastereomers in a 1:1 ratio, e.g. two signals of equal intensity were observed at δ46.07 and 46.57 for the methylene carbon at C-4. The i.r. spectrum of (76) displayed ester carbonyl absorption at 1735 cm^{-1}.



(76a)



(76b)



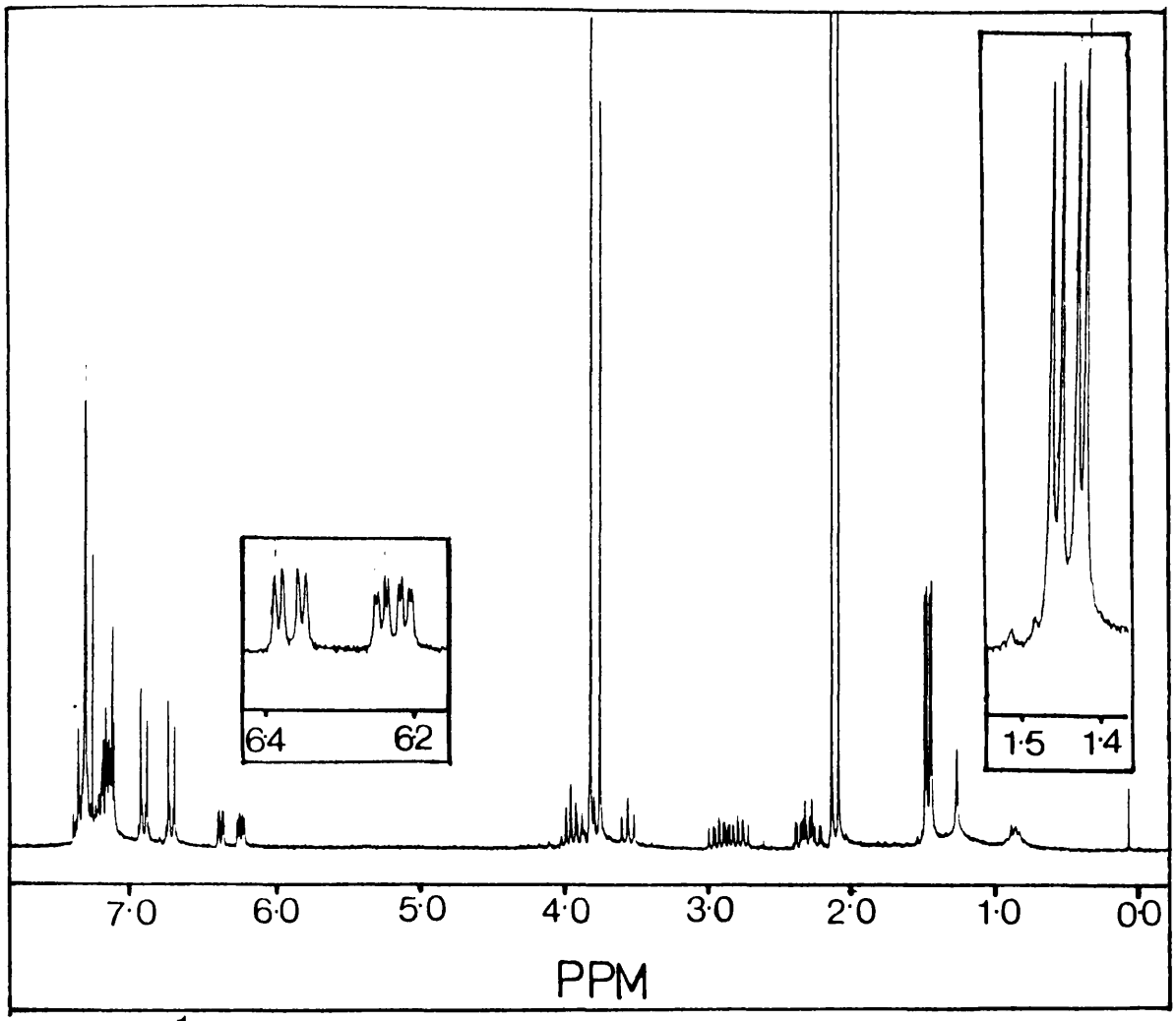


Fig.14a ^{1}H NMR Spectrum of Isoxazolidine(76) at 200 MHz.

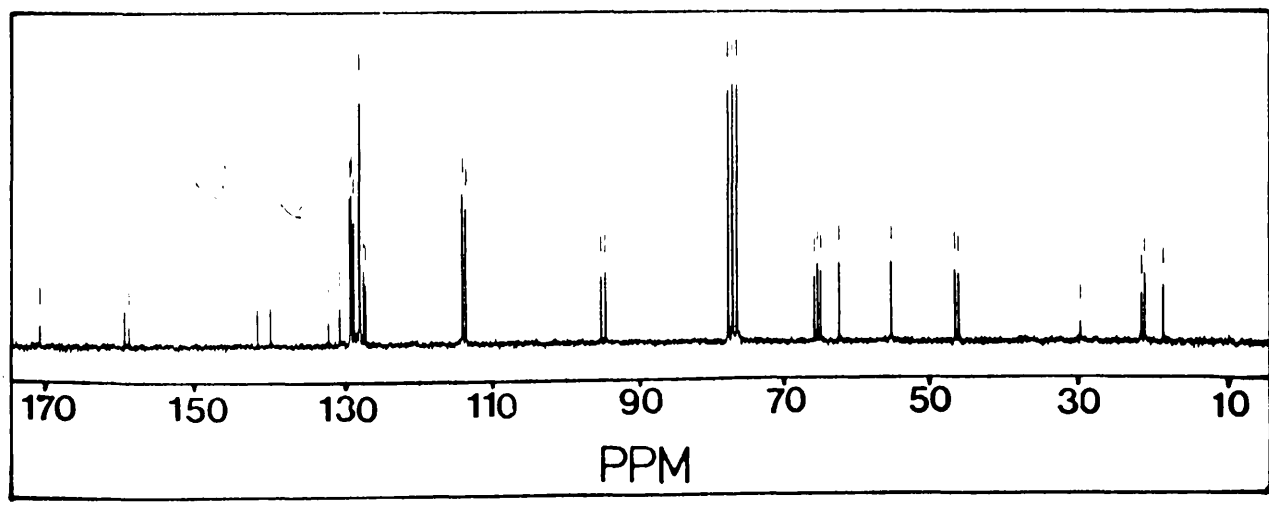


Fig.14b ^{1}H Decoupled ^{13}C NMR Spectrum of (76).

Hydrolysis of (76) in the usual manner gave lactol (77) in nearly quantitative yield. Gas chromatography of the TMS ether (78), [Fig. 15] and Table 4, showed two peaks in a 1:1 ratio as expected.

It was envisaged that oxidation of lactol (77) to isoxazolidinone (79) could be effected with Collins reagent, as with the 3-phenyl substituted lactol (54), but the reaction conditions proved detrimental to the starting material. An attempted Swern[62] oxidation also led to decomposition of (77) as did treatment with PDC and PCC. However, using a procedure described by Sharpless,[90] anhydrous N-methylmorpholine-N-oxide was found to oxidise (77) to isoxazolidinone (79) in 19% yield, under catalysis by hydrated ruthenium trichloride. The ^{1}H nmr spectrum at 90 MHz of (79) displayed two methoxymethyl signals, at δ3.77 and 3.70 of roughly equal intensity, indicating no fractionation of diastereomers had occurred during oxidation. Fortunately a single isomer (79a), m.p. 127-128°C was obtained upon recrystallisation of the diastereomeric mixture. The ^{1}H nmr spectrum of (79a), [Fig. 16a] at 200 MHz showed only one set of signals and the decoupled ^{13}C nmr spectrum, [Fig. 16b] confirmed the presence of only one isomer. Isomer (79a) showed high frequency carbonyl absorption at 1770 cm^{-1} in the i.r. spectrum.

Hydrogenolysis of (79a) with $Pd(OH)_2$ over charcoal at atmospheric pressure and 70°C gave β-tyrosine methyl ether (80) in 90% yield, as a colourless crystalline solid, m.p. 241-243°C, $[\alpha]_D$ -7.2°. On the basis that naturally-occurring (S)-β-tyrosine had $[\alpha]_D$ + 7.8°,[14] the synthetic amino acid (80a) was assigned the (R)-configuration and from this (79a) was formulated as the 3(R)-isoxazolidinone.

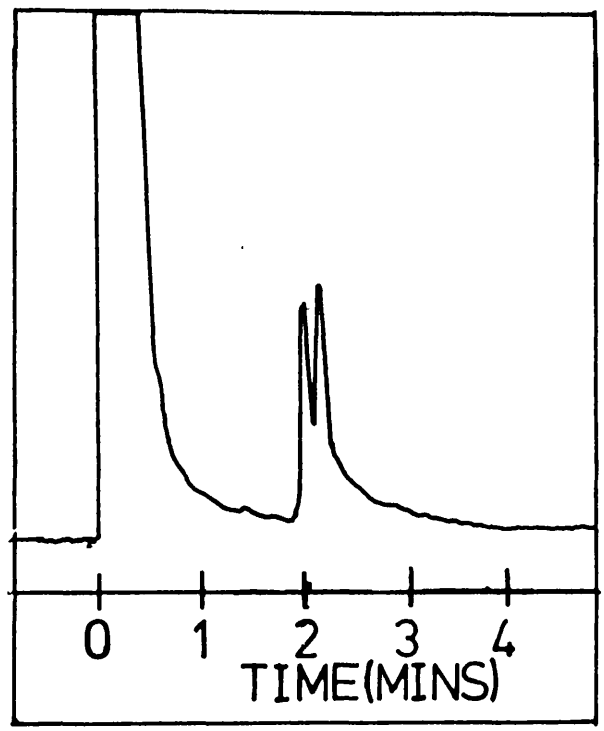


Fig.15 G.C. of Isoxazolidine TMS Ether (78) on a 6' 1% OV-1 at 155° C.

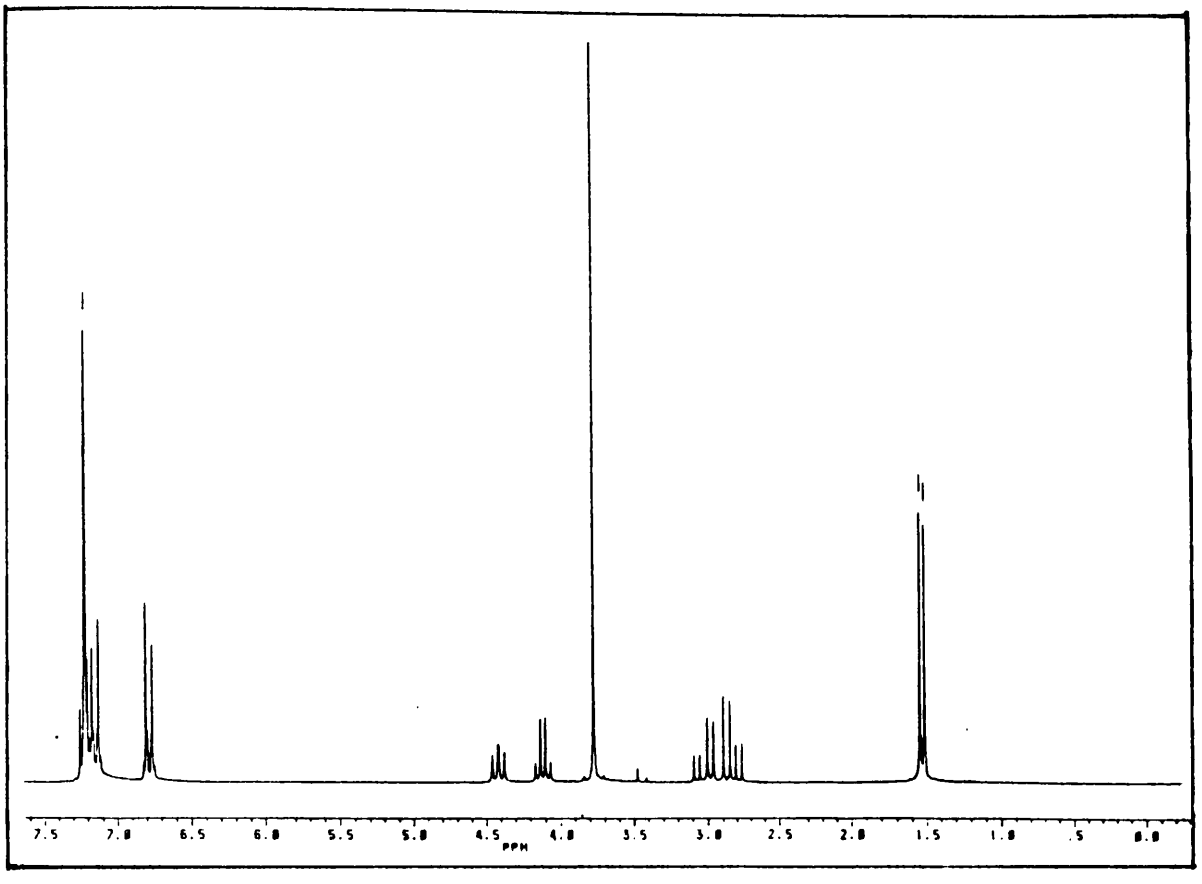


Fig.16a ^{1}H NMR Spectrum of Isoxazolidinone(79a) at 200MHz.

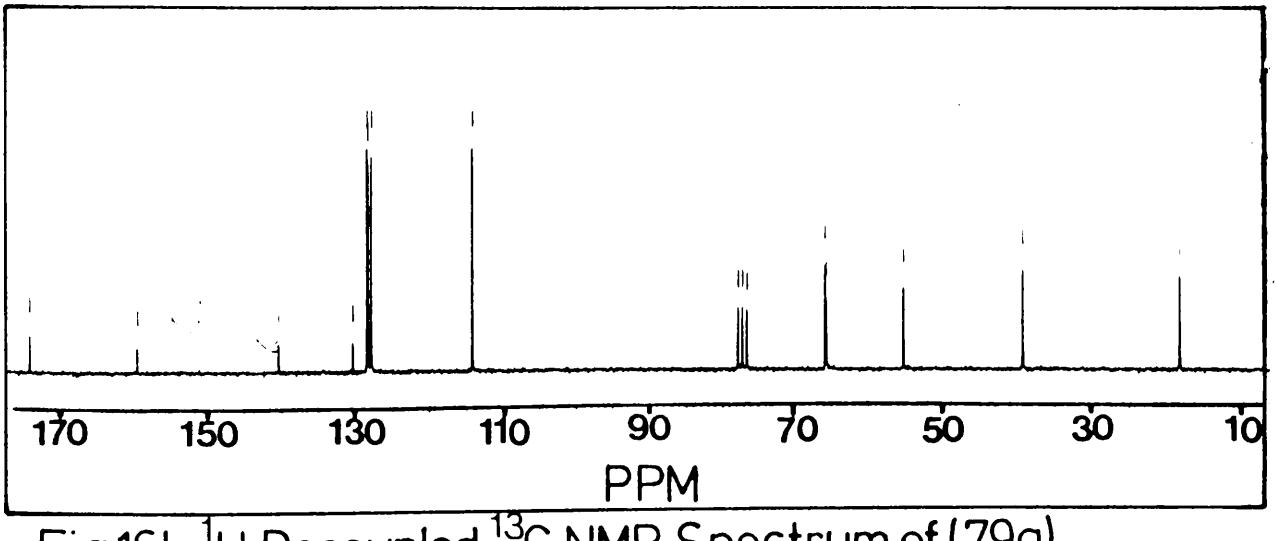
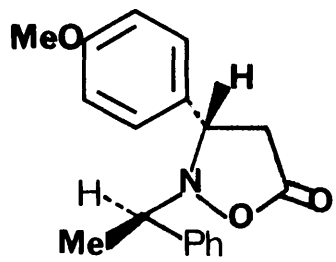
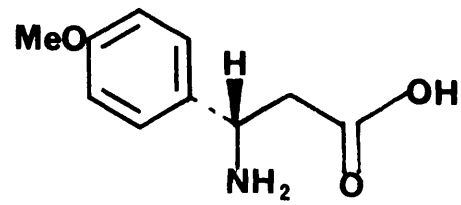


Fig.16b ^{1}H Decoupled ^{13}C NMR Spectrum of (79a).



(79a)



(80a)

The 'Mosher' amide[69] (81) was prepared from (80a). The ^{1}H nmr spectrum of the crude product displayed a single quartet at δ3.44 (3H, $^{5}J(^{1}H-\ ^{19}F)$ = 1.6 Hz, $PhCF_3\underline{C}OC\underline{H}_3$) and two singlets at δ3.78 (3H, $C\underline{H}_3OAr$) and δ3.63 (3H, $-CO_2C\underline{H}_3$), while the ^{19}F nmr spectrum showed a singlet at δ-69.35, suggesting only one diastereomer was present. This was confirmed by g.c. analysis of (81), see Table 7. In each case only one peak was observed, [Fig. 17], indicating enantiomerically pure (R)-β-tyrosine methyl ether was produced on hydrogenolysis of (79a).

2:4:4 β-Tryptophan

An asymmetric synthesis of β-tryptophan (82) was attempted. However the chiral α-indolyl-nitrone (24) did not undergo cycloaddition with vinyl acetate under the conditions used previously. As (24) is a relatively electron-rich nitrone, the difference in energy between LUMO (dipole)-HOMO(dipolarophile) may be too great to allow effective inter-

Table 7

Gas Chromatography of (R)-β-Tyrosine

Methyl Ether 'Mosher Amide' (81)

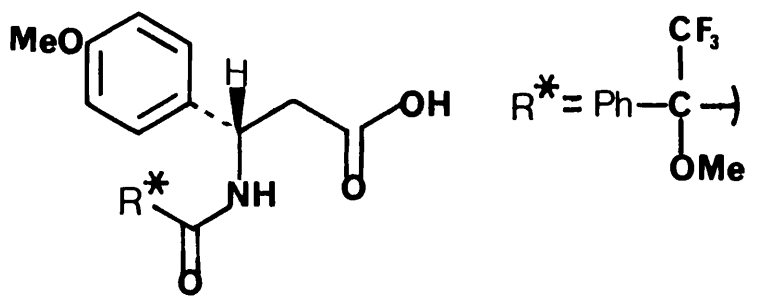
Retention Time (t_R mins)

Column 1	Column 2	Column 3
22.75	16.25	20.92

Column 1; 6' 1% QF-1 at 210°C.

Column 2; 25m CPSil5 CB at 80°C, (rising 30°C min^{-1} to 250°C).

Column 3; 25m SE 54 at 80°C, (rising 30°C min^{-1} to 250°C).



(81)

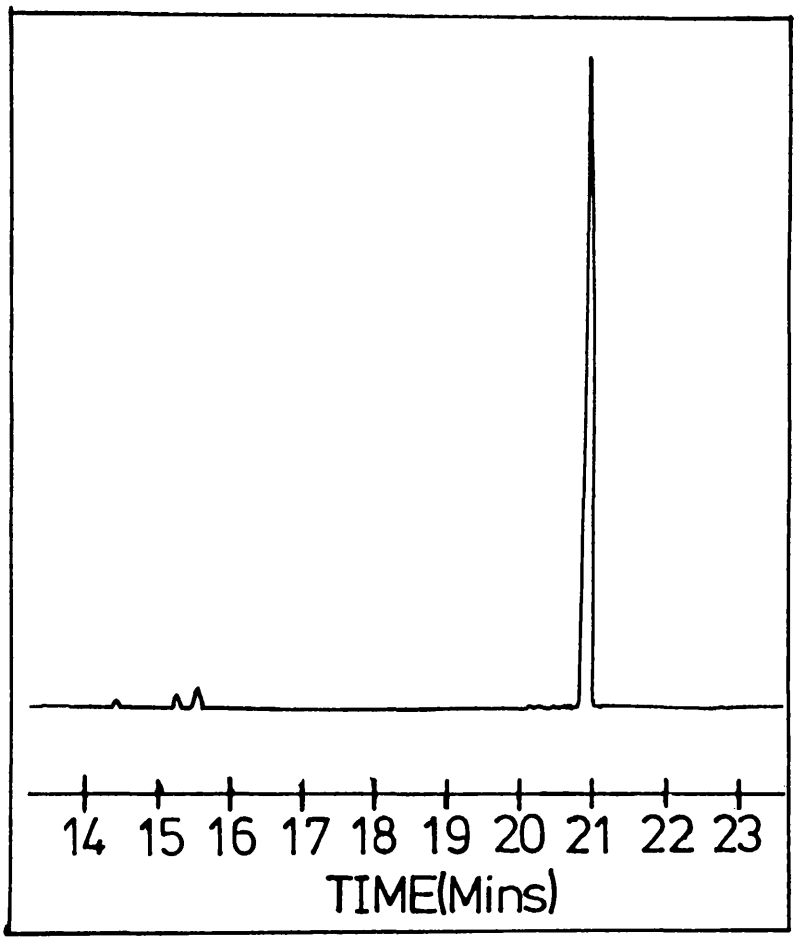
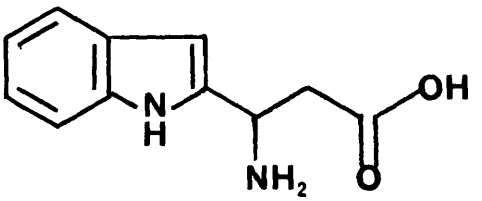
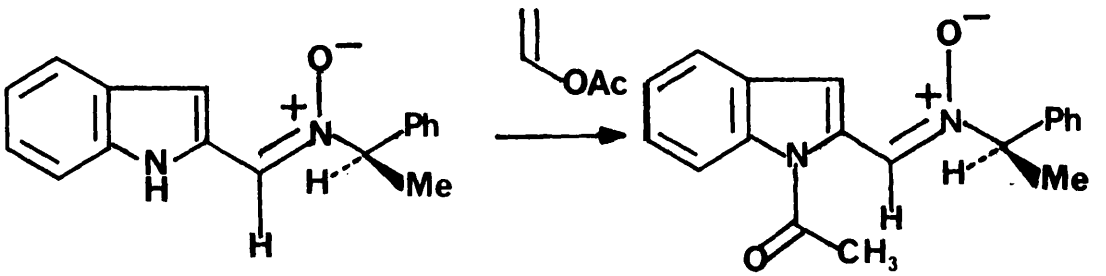


Fig.17 Capillary G.C. of 'Mosher' Amide(81) on 25m SE-54 Column from 80°C to 250°C (Rate = 30°C Min^{-1}).

action of the frontier molecular orbitals. The only product obtained was identified as the N-acyl nitrone (83) from nucleophilic attack of indolyl nitrogen on vinyl acetate. The ^{1}H nmr spectrum of (83) was similar to nitrone (24) apart from a singlet at $\delta 2.62$ corresponding to the N-acyl methyl group. The i.r. spectrum showed carbonyl absorption at 1705 cm^{-1} and the indole N-H stretching band at 3460 cm^{-1} shown for (24) was not observed.



(82)



(24) (83)

Scheme 25

Although the nucleophilic attack of nitrone (24) on vinyl acetate was not unexpected, the N-acyl nitrone also failed to undergo concomitant cycloaddition with excess vinyl acetate. This suggests that a powerful electron-withdrawing substituent on the nitrogen atom of the indole ring maybe required for chiral α-indolyl nitrones to undergo cycloaddition to electron-rich olefins. Lack of time, however, prevented further study.

2:4:5 Summary and Looking Ahead

This work establishes a new route for the synthesis of β-amino acids by cycloaddition of nitrones to a suitably oxygenated alkene such as vinyl acetate.

The route allows for control of configuration at the β-carbon atom, since highly-organised transition states for the cycloaddition should be responsive to chiral induction from a chiral substituent at nitrogen, or in the dipolarophile.

The route requires an improved method of oxidation of lactols to isoxazolidinones in order to attain higher and more reproducible yields.

Separation of the diastereomeric isoxazolidine acetate mixture formed in the cycloaddition could possibly be achieved by preparative HPLC. Such a resolution would considerably simplify the stereochemical analysis of the cycloaddition.

The method opens the way to synthesis of all β-amino acids corresponding to natural α-amino acids and to analogues.

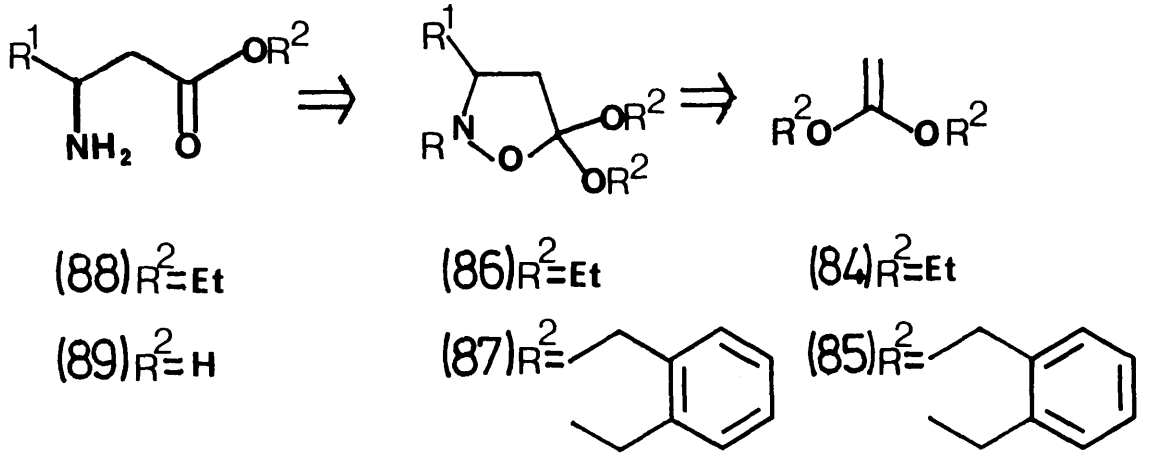
There is scope for the synthesis of nitrones containing alternative chiral inducing groups based on readily available chiral units such as α-phenylglycine[70] and carbohydrates.[71]

CHAPTER 3

1,3-Dipolar Cycloadditions of Nitrones to Ketene Acetals

3:1 Background

As part of an investigation into alternative routes to β-amino acids, the 1,3-dipolar cycloadditions of alkyl ketene acetals (84) and (85), with nitrones were studied. 1,1-Disubstituted ketene acetals are electron rich olefins, and as such undergo cycloaddition to give 5,5-substituted isoxazolidines such as (86) and (87). The cycloaddition reactions of ketene acetal (84) have previously been reported by Huisgen[72] and Scarpati,[73] the latter having established that isoxazolidines such as (86) can be hydrogenolysed to ethyl esters of β-amino acids (88), [Scheme 26]. It was therefore envisaged that hydrogenolysis of the corresponding isoxazolidine (87) would lead to the free β-amino acid (89).

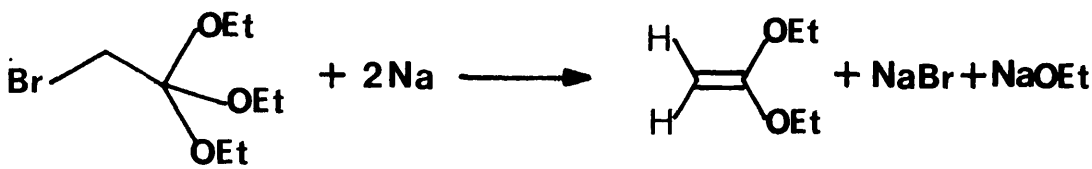


Scheme 26

Discussion

3.2 1,3-Dipolar Cycloaddition Reactions of Nitrones with Ketene Diethylacetal

Ketene diethylacetal (84) was prepared by the method of McElvain,[75] involving treatment of triethyl orthobromoacetate (90) with powdered sodium in refluxing benzene, [Scheme 27].



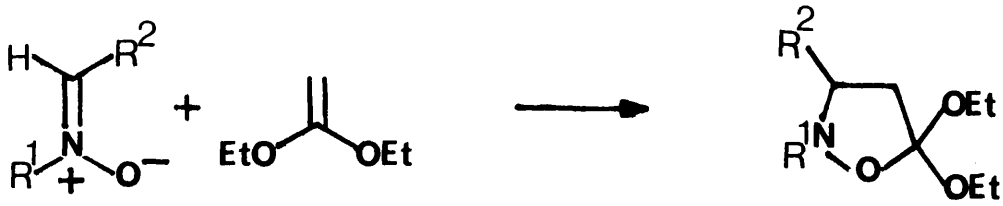
(90) (84)

Scheme 27

The 1,3-dipolar cycloaddition reactions of nitrones (11, 20 and 21) with ketene acetal (84) were investigated, [see Table 8].

Conditions A and B were previously described by Huisgen[72] and Scarpati[73] respectively for the synthesis of isoxazolidine (91) from nitrone (11). In this laboratory it was found that both sets of conditions led to (91) as a colourless oil in good yield. The spectroscopic properties were identical with those reported.[72,73] However the chiral phenyl nitrone (21) did not undergo cycloaddition with the

Table 8. Synthesis of 5,5-Diethoxyisoxazolidines

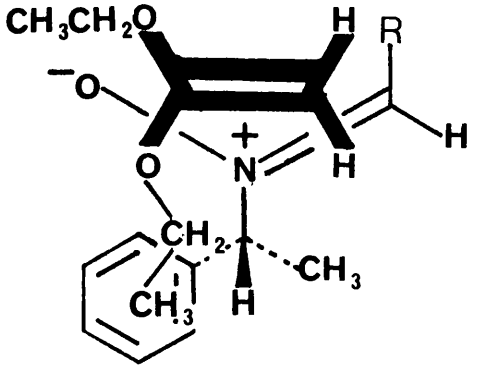


Nitrone	Isoxazolidine	R^1	R^2	Conditions[a]	Yield %
11	91	Ph	Ph	A	78
"	"	"	"	B	67
20	92	(R)PhCHMe	Pr^i	A	-
"	"	"	"	B	-
21	93	(R)PhCHMe	Ph	A	-
"	"	"	"	B	-

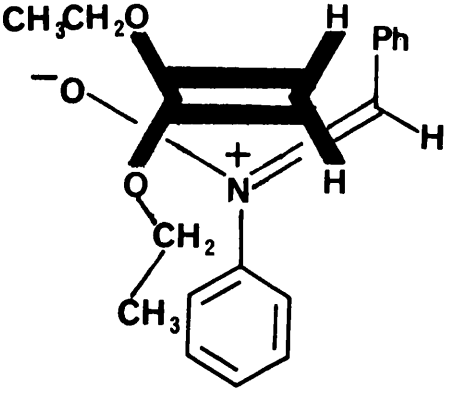
[a]Conditions: A = heating in dry toluene at 100°C for 24h, 3eq ketene acetal: leq nitrone; B = leq nitrone and 1.3eq ketene acetal, heated in sealed tube at 125°C between 1-2h.

ketene acetal under either set of conditions, from which unchanged starting material was recovered. It was thought that this may have been due to a lack of reactivity of nitrone (21) towards highly electron rich dipolarophiles such as ketene acetals, whereas the more electron-deficient diphenyl nitrone (11) underwent cycloaddition with (84) more easily. The chiral isopropyl nitrone (20) which proved the most reactive nitrone with vinyl acetate, as described previously, however also failed to undergo cycloaddition with ketene diethylacetal. The failure of nitrones (20) and (21) to undergo cycloaddition is perhaps more likely to be a result of steric congestion in the transition state, rather than electronic influences. Molecular models indicate that as the chiral nitrones approach either face of the ketene acetal a severe interaction may occur between the ethyl group of the ketene acetal and the phenyl group of the α-methylbenzyl moiety of the nitrone, as shown in (94) for one of the two possible transition states. Such interactions are greatly reduced in the transition state (95) for the reaction between the ketene acetal and C,N-diphenylnitrone (11).

As a consequence of these disappointing results, other ketene acetals were sought as potential dipolarophiles.



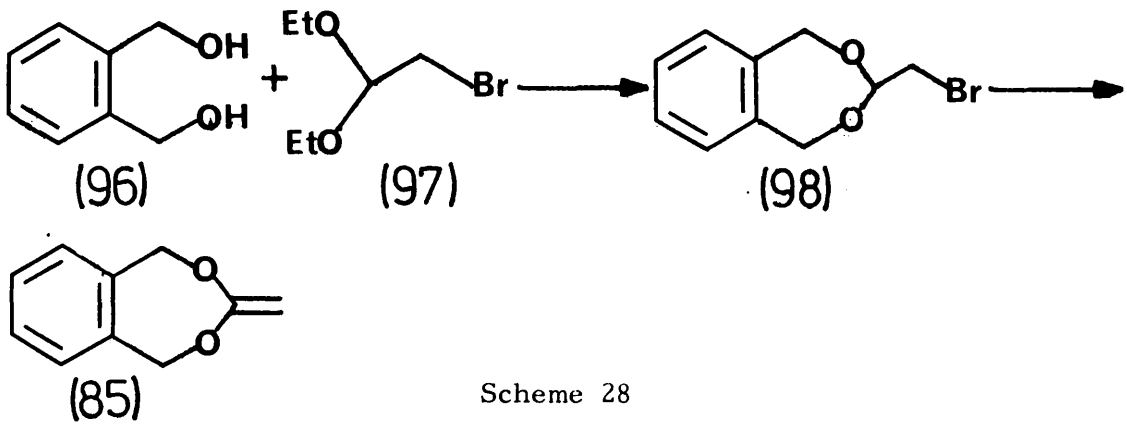
(94) R=Ph, *i*-Pr



(95)

3:3 1,3-Dipolar Cycloaddition Reactions of Nitrones with [o-Xylyl] Ketene Acetal

Ketene acetal (85) was prepared, as shown in Scheme 28, by the method of Grewe.[77] The crystalline acetal (85) was more conveniently prepared than ketene diethylacetal and could be stored for longer periods without decomposition.

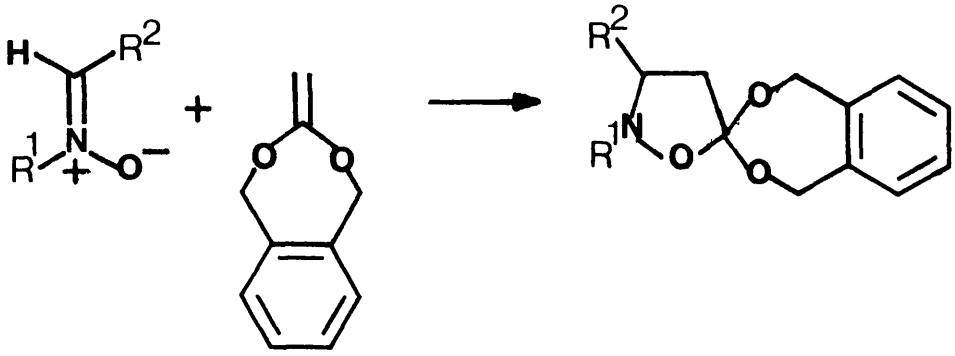


Scheme 28

The cycloaddition reactions of ketene acetal (85) with nitrones (11), (20-23) were performed in refluxing toluene, and the results are given in Table 9.

C,N-Diphenylnitrone was found to be the most reactive of the nitrones towards ketene acetal (85). N-Phenyl-3-phenylisoxazolidine (99) was obtained in 53% yield as a colourless crystalline solid, m.p. 127°C. The ^{1}H nmr spectrum of (99) showed two doublets of doublets at part of an ABX system at δ2.65 (1H, dd, J=9, 13 Hz) and δ3.02 (1H, dd, J=6, 13 Hz) while accurate mass analysis showed m/e = 359.1509 corresponding to a molecular formula of $C_{23}H_{21}NO_3$, (calc. m/e = 359.1521).

Table 9. Synthesis of 5,5-(di-o-xylyloxy)isoxazolidines



Nitrone	Isoxazolidine	R^1	R^2	Yield %	Diastereomer Ratio
11	99	Ph	Ph	53	-
20	100	(R)PhCHMe	Pr^i	4	1:1
21	101	(R)PhCHMe	Ph	12	4:1
22	102	(R)PhCHMe	pMeOPH	-	-
23	103	(R)PhCHMe	pCℓPh	28	3.5:1

Chiral nitrones (20), (21) and (23) did undergo cycloaddition with (85), unlike ketene diethylacetal, but in lower yield than with C,N-diphenylnitrone (11). However, the p-methoxynitrone (22) did not react with the xylyl ketene acetal at all. These results suggest that as the electron donating ability of the C-substituent of the C=N bond of the nitrone increases, then the electron rich nitrones become less prone to undergo cycloaddition with ketene acetal (85). The dominant FMO interaction in such cycloadditions is of the LUMO(dipole)-HOMO (dipolarophile) type. As the electron density of the nitrone is increased the energy difference between LUMO(nitrone)-HOMO(dipolarophile) becomes greater, and hence reaction between the adducts becomes more difficult, or impossible in the case of the p-methoxyphenyl nitrone. The fact that C,N-diphenyl nitrone is more reactive towards ketene acetal (85) may be due to its ability to suppress aniline-type resonance[78] and promote imminium ion character, resulting in a more electron-deficient system than the N-α-methyl benzyl nitrones. The yields of adducts are also noticeably less than those obtained from reaction of the same nitrones with vinyl acetate, described in the previous chapter.

Although the chemical yield for the cycloaddition between the chiral phenyl nitrone (21) and ketene acetal (85) was disappointingly low, the chiral induction observed in the product isoxazolidine (101) was the best obtained for any cycloaddition between a chiral nitrone and oxygenated alkene reported in this thesis. The ^{1}H nmr of (101) at 200 MHz, [Fig. 18] showed two doublets at δ1.56 (2.41H, d, J=6.5 Hz) and δ1.38 (0.59H, d, J=6.5 Hz) for the methyl protons of the N-α-methylbenzyl moiety in a ratio of 4:1 respectively. Analysis of (101)

by g.c., [Fig.19], on a 6' 1% OV-1 column at 235°C showed two peaks of t_R = 5.98 and 5.60 min in a ratio of 3.6:1 respectively, while g.c.-m.s. analysis revealed that the two compounds were isomeric, both having m/e = 387. The probable conformation of the ring system in ketene acetal (85) provides an explanation for the degree of induction observed in the formation of isoxazolidine (101). The ring conformations of 2,4-benzodioxepins similar to (85) have been studied by St. Jaques[79] and collaborators. In the absence of steric interaction between the substituents at C_7 and the axial hydrogens of C_2 and C_4, the likely conformation of the ring system is the chair form. If, as assumed, ketene acetal (85) adopts this conformation, molecular models indicate that the chiral nitrone (21) can approach the less hindered "top" face of the olefin more easily leading to preferential formation of the C-3(R) isoxazolidine (101a), [Scheme 29]. As the nitrone approaches from the "bottom" face of the olefin, a severe interaction between the N-α-methylbenzyl phenyl group and the methylene groups of the ketene acetal occurs making this mode of addition less favourable. Unfortunately the two diastereomers (101a) and (101b) were not separable so that this proposal could not be confirmed.

The chiral p-chloronitrone (23) underwent cycloaddition with (85) to give isoxazolidine (103) in 28%, reflecting the greater reactivity of more electron-deficient nitrones towards the ketene acetal. The ^1H nmr spectrum of (103) at 90 MHz contained two doublets at δ1.72 (2.35H, d, J=6 Hz) and 1.54 (0.65H, d, J=6 Hz) corresponding to the methyl protons of the α-methylbenzyl group, in a ratio of 3.5:1 respectively. Analysis of (103) by g.c. on a 6' 1% OV-1 column at 235°C showed a single broad

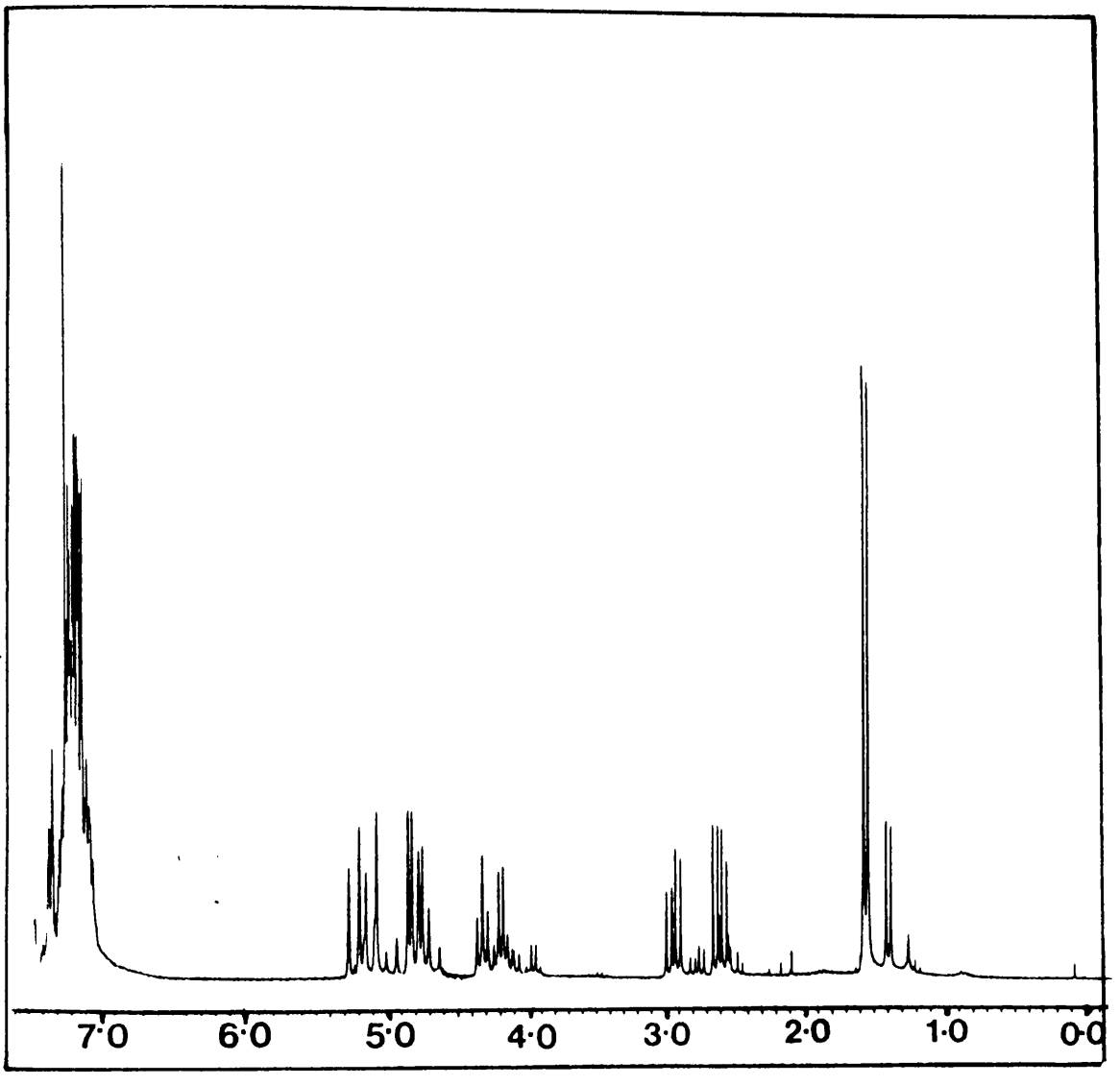
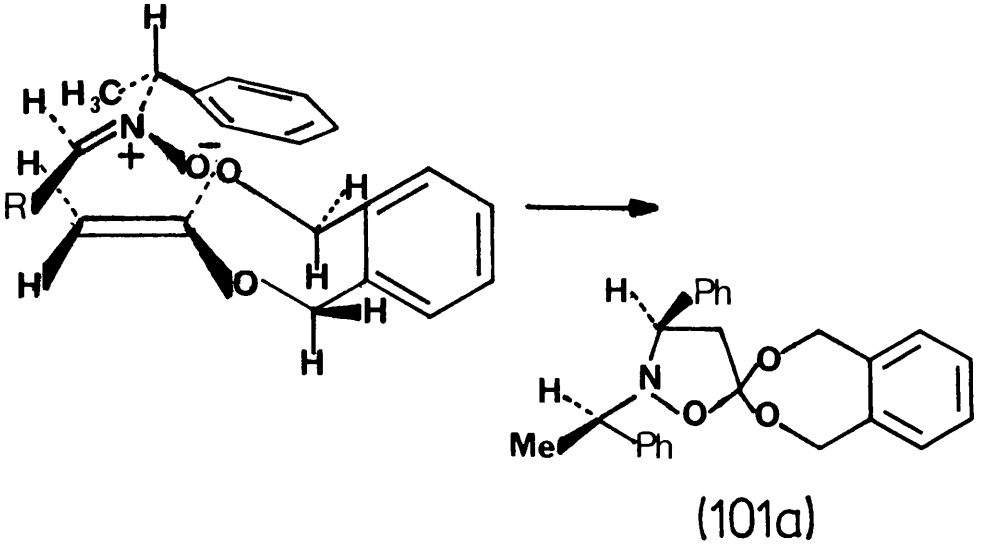
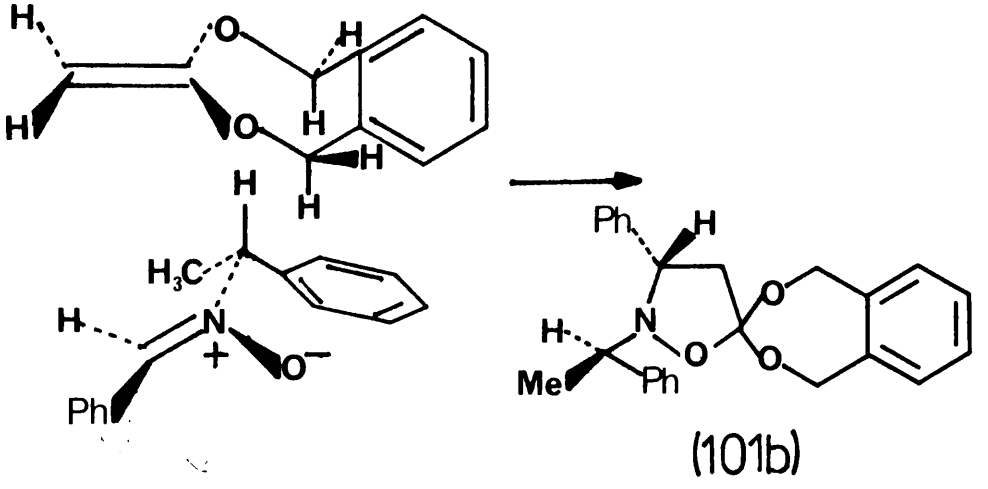


Fig. 18 ^{1}H NMR Spectrum of Isoxazolidine(101) at 200 MHz.

Fig.19 G.C. of Isoxazolidine (101) on a 6' 1% OV-1 at 225°C.



(101a)

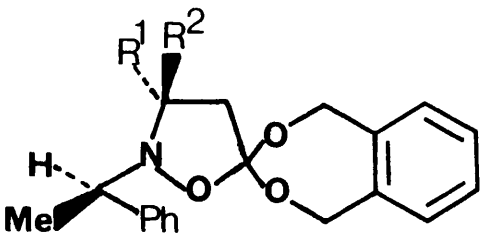


(101b)

Scheme 29

peak at t_R = 6.35 min. Analysis by g.c.-m.s. indicated two diastereomers of m/e = 421. However, the diastereomer ratio could not be measured from the g.c. trace since the peaks were not well enough resolved. Accurate mass analyses showed m/e = 421.1455 corresponding to a molecular formula of $C_{25}H_{24}NO_3C\ell$, (calc m/e = 421.1445).

Unfortunately the diastereomers of (103) were again not separable on a preparative scale. Presumably the cycloaddition of the p-chloronitrone (23) to (85) followed the same steric course as that of nitrone (21), leading preferentially to the 3(R)-substituted isoxazolidine (103a), [c.f. Scheme 29, p 116]



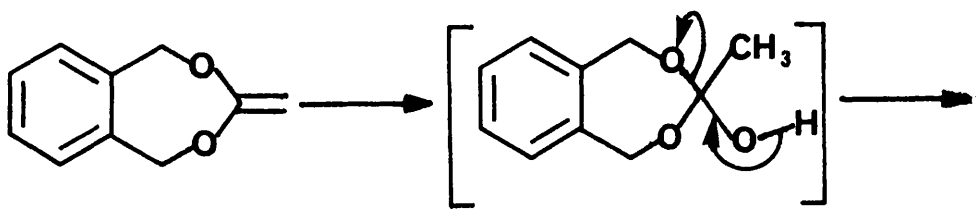
(103a) R^1=H, R^2=pClPh

(103b) R^1=pClPh, R^2=H

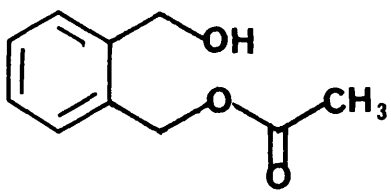
Chiral isopropyl nitrone (20) underwent cycloaddition with (85) to give isoxazolidine (100) in a miserable yield of 4%. Furthermore isoxazolidine (100) proved difficult to isolate in pure form and decomposed on repeated chromatography preventing a full characterisation. The ^1H nmr of a fraction consisting principally of (100) showed two doublets of almost equal intensity at δ1.42 (1.28H, d, J=6.5 Hz) and δ1.54 (1.72H,

d, J=6.5 Hz) indicating that no discrimination was shown by nitrone (20) between the two faces of ketene acetal (85).

The reaction conditions for the cycloadditions of (85) are required to be rigorously anhydrous. In some early experiments where conditions were evidently not completely anhydrous and where cycloaddition required prolonged refluxing, a product derived solely from (85) was isolated. The i.r. spectrum of this product showed carbonyl absorption at 1730 cm^{-1} and a sharp hydroxyl absorption at 3600 cm^{-1}. The ^{1}H nmr spectrum indicated the presence of two benzylic methylene groups at δ5.22 (2H,s) and δ4.72 (2H, s) and an acetate methyl group at δ2.05 (3H,s). From this the product was assigned the structure (104), arising from hydration of the ketene acetal double bond, [Scheme 30]. The mass spectrum had a base peak of $\underline{m}/\underline{e}$ = 120 $[M-60]^{+}$ corresponding to loss of CH_3COOH. Under anhydrous conditions unchanged ketene acetal (85) was recovered, with the appropriate isoxazolidine.



(85)



(104)

Scheme 30

Unfortunately, lack of time prevented a study of the hydrogenolysis of the (di-o-xylyloxy)isoxazolidines.

3:4 Summary and Looking Ahead

The cycloaddition of chiral nitrones to [o-xyly]ketene acetal provides a potentially new method for the asymmetric synthesis of β-amino acids. Hydrogenolysis of the resulting isoxazolidines, e.g. (101) and (103) should lead directly to the free β-amino acids. This route would circumvent the problems encountered in the oxidation step of the adducts derived from nitrones and vinyl acetate as described in the previous chapter.

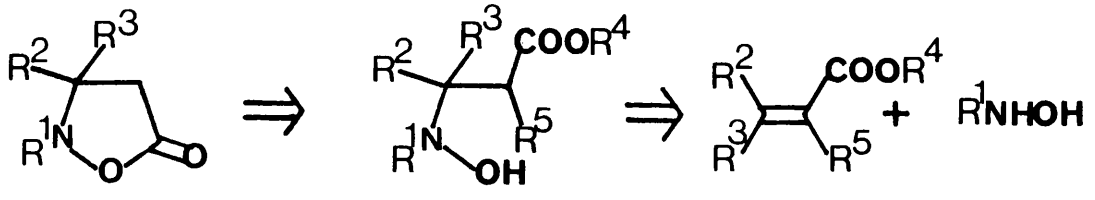
The chiral induction observed with aromatic substituted nitrones (e.g. (21)) with [o-xyly]ketene acetal is superior to that with vinyl acetate, and this route should provide enantiomeric excesses greater than those obtained in previous asymmetric syntheses of β-amino acids.[22-27]

CHAPTER 4

Synthesis of Chiral Isoxazolidin-5-ones

4:1 Background

An alternative synthesis of the isoxazolidin-5-one ring system (105), to that discussed in Chapter 3, involves the cyclisation of intermediates such as (106), formed by conjugate addition of N-substituted hydroxylamines to α,β-unsaturated esters (107), as shown retrosynthetically in Scheme 31.

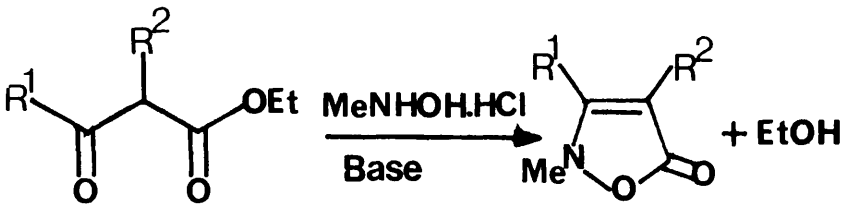


(105) (106) (107)

Scheme 31

Such an approach was first reported by Posner in 1912,[80] who described the addition of hydroxylamine to cinnamate esters to give isoxazolidin-5-ones. More recently, this approach was developed by Baldwin[27] as a general method for the synthesis of isoxazolidin-5-ones, involving isolation of the intermediate 1,4 adduct (106), and effecting cyclisation with lithium bis(trimethylsilyl)amide, as described earlier in the Introduction section, p 15. An investigation and reappraisal of the reaction of α,β-unsaturated esters with (R)-(+)-α-methylbenzylhydroxylamine (15) forms the second part of this chapter.

In addition, the reaction of β-ketoesters (108) with N-methyl-hydroxylamine hydrochloride, [Scheme 32] in the presence of base to give Δ^3-isoxazolidin-5-ones (109), is a well documented reaction.[81,82]

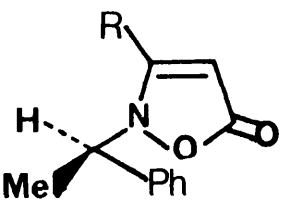


(108) (109)

R^1=H,Me,Ph R^2=H,Me,Ph

Scheme 32

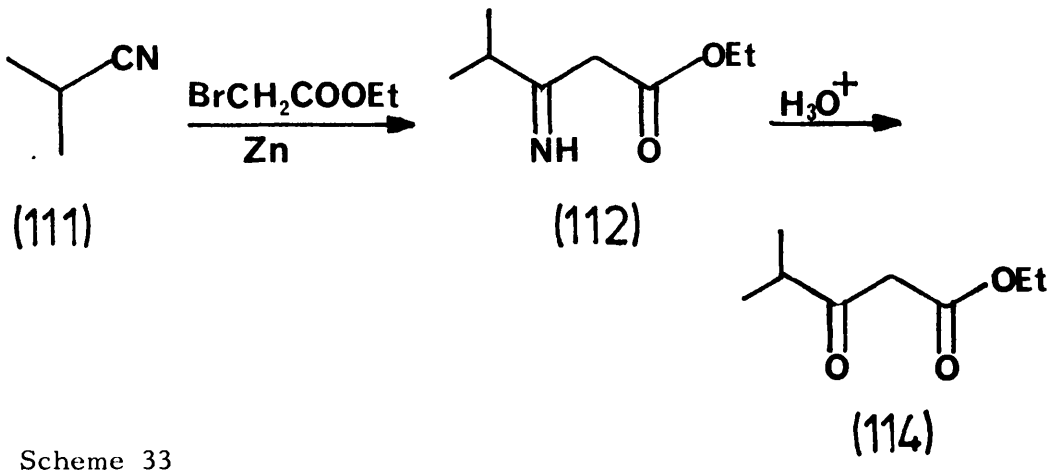
It was envisaged that chiral Δ^3-isoxazolidin-5-ones, viz. (110), could be synthesized in a similar fashion employing chiral hydroxylamine (15), and that hydrogenation and hydrogenolysis of (110) might lead to chiral β-amino acids. The results of preliminary investigations are briefly discussed below.



(110)

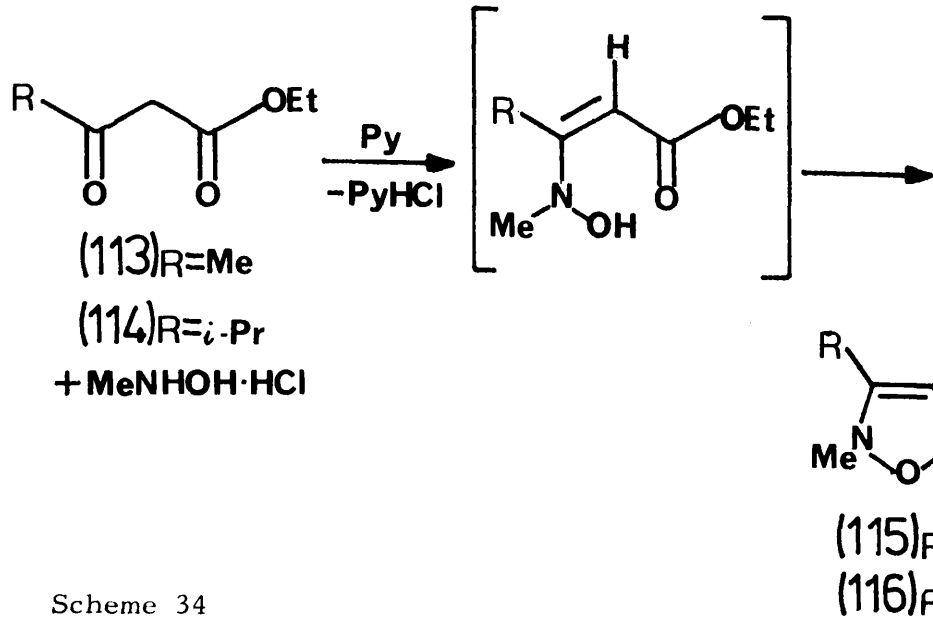
4:2 Discussion

Preliminary investigations involved the synthesis of the N-methyl-Δ^3-isoxazolidin-5-ones, (115) and (116). Ethyl isobutyryl-acetate (114) was prepared by the method of Kagan,[83] involving Reformatski reaction of isobutyronitrile (111) with ethyl α-bromoacetate, with subsequent hydrolysis of the imino moiety of the intermediate (112), [Scheme 33].



Scheme 33

The most convenient preparation of Δ^3-isoxazolidinones (115) and (116), involved the method of De Sarlo,[82] in which the appropriate β-ketoester was heated with N-methylhydroxylamine hydrochloride, in anhydrous pyridine at 100°C for 8h, [Scheme 34].



Scheme 34

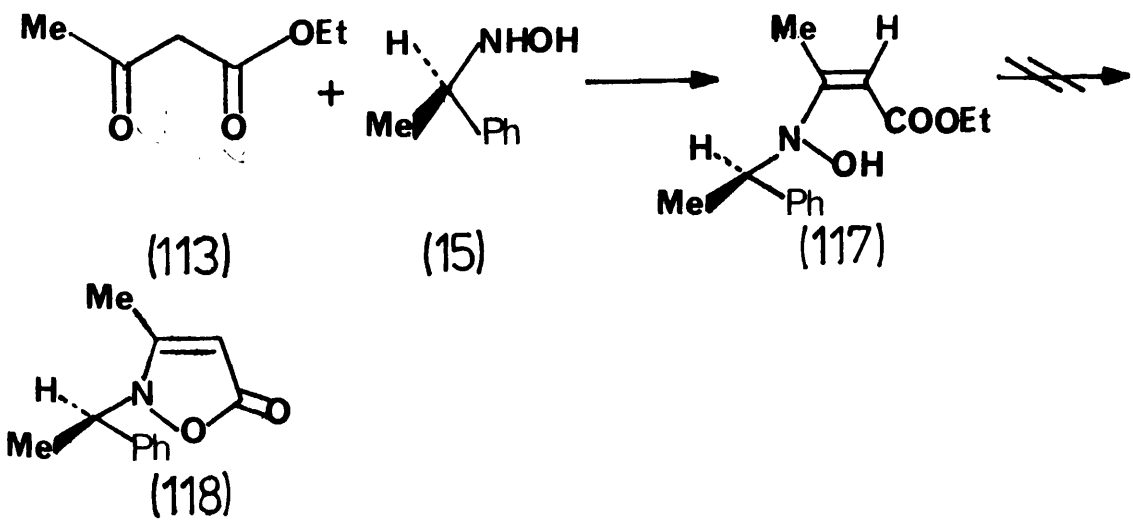
Under these conditions, the hydroxylamine adds to the β-ketoester, to give initially the "enamine" intermediate in the Z-configuration which then cyclises spontaneously to the Δ^3-isoxazolidinone (115) or (116). The cyclisation is a 5-endo-trig process and is hence favoured according to Baldwin's Rules.[84]

Isoxazolidinone (115), synthesized according to De Sarlo[82] and Katritsky,[81] showed carbonyl absorption at 1730 cm^{-1} and conjugated C=C absorption at 1585 cm^{-1} in good agreement with the literature[81] values, ($\nu_{C=O}$ 1723 cm^{-1}, $\nu_{C=C}$ 1581 cm^{-1}). The ^1H nmr spectrum showed a singlet at δ4.98 (1H, s) for the vinyl proton at C-4 which proved characteristic of such compounds.

Isopropyl isoxazolidinone (116) was obtained as a colourless oil in 54% yield. The i.r. spectrum again showed carbonyl absorption at 1730 cm^{-1} and conjugated C=C absorption at 1570 cm^{-1}, similar to (115). The ^1H nmr spectrum showed the characteristic singlet at

δ4.98 (1H, s) for the C-4 vinyl proton. Accurate mass analysis of (116) showed m/e = 141.0793 corresponding to a molecular formula of $C_7H_{11}NO_2$, (calc m/e = 141.0790).

With these encouraging results in mind, the reaction of (R)-(+)-α-methylbenzylhydroxylamine (15) and acetoacetate (113) was then investigated. On heating the two reagents in anhydrous pyridine as before, a colourless oil was obtained in 73% yield, the i.r. spectrum of which showed carbonyl absorption at 1730 cm^{-1} and what seemed to be a conjugated C=C absorption at 1670 cm^{-1}, a significantly higher frequency than that observed for isoxazolidinones (115) and (116), suggesting that the conjugate adduct (117) was the product of the reaction. The ^1H nmr spectrum of the oil, indicated the presence of an ethyl group (δ4.10 (2H, q, J=7 Hz) and δ1.14 (3H, t, J=7 Hz)) and no singlet in the region δ5.0 was observed for the C-4 vinyl proton of a Δ^3-isoxazolidinone. Accurate mass analysis revealed a molecular formula of $C_{14}H_{19}NO_3$, m/e = 249.1380, (calc m/e = 249.1365), confirming that the intermediate (117) had been formed, with no subsequent cyclisation to the isoxazolidinone (118), [Scheme 35].



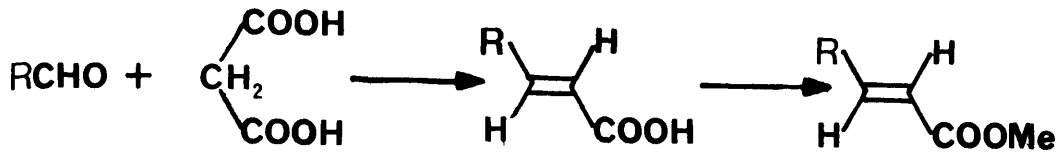
Scheme 35

Prolonged heating of (117) in pyridine for periods of up to 120h did not result in cyclisation, nor did treatment with a variety of basic reagents such as potassium tert-butoxide in benzene at 60°C, and LDA in THF at -78°C. The possibility remains that treatment of (117) with stronger bases such as lithium bis(trimethylsilyl)amide as reported by Baldwin,[27] may promote cyclisation of (117) to the Δ^3-isoxazolidinone. Lack of time, however, prevented further investigation.

It is difficult to rationalise the inability of (117) to undergo spontaneous cyclisation. Molecular models indicate that the N-α-methyl benzyl moiety of (117) should not preclude nucleophilic attack of the N-hydroxyl group on the carboethoxy carbonyl group as a result of steric hindrance. As numerous attempts were made to obtain isoxazolidinone (118) without success, this approach was eventually abandoned.

The subsequent publication of Baldwin,[27] however prompted an investigation of the reaction of chiral hydroxylamine (15) with α,β-unsaturated esters, as an independent route to the chiral saturated isoxazolidinones (56), (70) and (79), for purposes of comparison with the samples synthesised via 1,3-dipolar cycloaddition of nitrones and vinyl acetate, as described in Chapter 2.

This required the synthesis of α,β-unsaturated esters (123) and (124), by Doebner condensation of malonic acid with aldehydes[85] (119) and (120) respectively, with subsequent esterification of the resulting unsaturated acids, [Scheme 36].



(119) (121) (123)
(120) (122) (124)

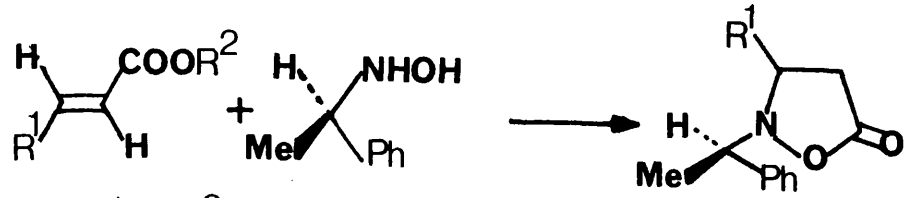
(119),(121),(123) R=*i*-Pr

(120),(122),(124) R=pMeOPh

Scheme 36

In contrast to the reaction with β-ketoesters, and the results of Baldwin,[27] chiral hydroxylamine (15) underwent conjugate addition and cyclisation with the appropriate α,β-unsaturated esters, in a one-step process to give isoxazolidinones (56), (70) and (79) in yields ranging from 53-67%, without the necessity of isolating the intermediate product of conjugate addition, [Scheme 37].

Ethyl cinnamate (125) was refluxed in benzene for 48h with chiral hydroxylamine (15) to give isoxazolidinone (56) in 59% yield, whose ^{1}H, ^{13}C nmr, i.r. and m.s. spectroscopic data was identical with that of the sample prepared via nitrone addition to vinyl acetate, as described in Chapter 2. Again no indication of the diastereomeric ratio within (56) could be obtained from these sources. However, hydrogenolysis of this sample over 20% palladium hydroxide on charcoal led to



(125) R^1=Ph, R^2=Et (15) (56) R^1=Ph

(123) R^1=*i*-Pr, R^2=Me (70) R^1=*i*-Pr

(124) R^1=pMeOPh, R^2=Me (79) R^1=pMeOPh

Scheme 37

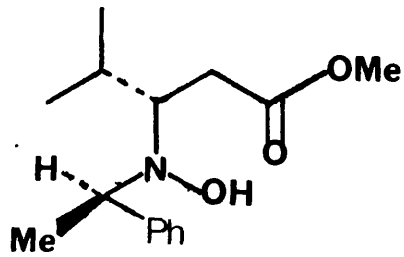
β-phenyl-β-alanine, m.p. 229-232°C, $[\alpha]_D^{23}$ +0.3° (c 1.0, H_2O), (c.f. Lit[67] m.p. 236°C, $[\alpha]_D$ +6.2), for (S)-β-phenyl-β-alanine, corresponding to an enantiomeric excess of 5%, for the (S)-amino acid. Lack of time did not permit analytical resolution of diastereomeric amides of β-phenyl-β-alanine, as described in Chapter 2. The calculation of enantiomeric excess from such small rotations is clearly unreliable but the result indicates that virtually no discrimination between the re and si faces of ethyl cinnamate is shown by chiral hydroxylamine (15) in the initial addition.

The p-methoxyphenyl isoxazolidinone (79) could also be obtained by simply refluxing hydroxylamine (15) with the α,β-unsaturated ester (124) in benzene under neutral conditions. The ^1H nmr

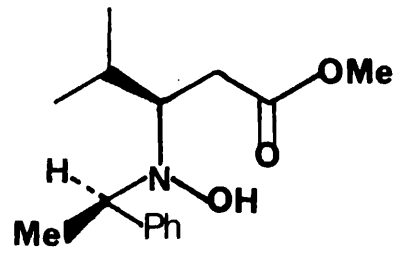
spectrum of (79) obtained by this method showed two singlets at δ3.76 (1.55H, s) and 3.70 (1.45H, s) corresponding to the p-methoxyphenyl methyl group, again indicating no discrimination was shown between the two faces of the ester (124) by hydroxylamine (15). The spectroscopic data for (79) were virtually identical with those of the diastereomeric mixture obtained via the 1,3-dipolar cycloaddition of nitrone (22) to vinyl acetate, as described in Chapter 2. Isoxazolidinone mixture (79) was not hydrogenolysed to the corresponding β-amino acid.

The spontaneous cyclisation of 1,4-adducts of cinnamate esters and hydroxylamines is a known reaction, previously described by Fountain[92] and Stamm.[93] However, Baldwin[27] reported that spontaneous cyclisation was not observed for adducts of N-benzyl-substituted hydroxylamines and methyl maleate, methyl methacrylate and methyl crotonate, [see Introduction, Scheme 13]. It was therefore surprising that 3-isopropyl isoxazolidinone (70), [Scheme 37], was obtained in 67% yield upon refluxing chiral hydroxylamine (15) with ester (123) in ether for 60h. The ^{1}H nmr spectrum at 90 MHz of (70) showed two distinct signals for the isopropyl methyl groups at δ0.92 (1.73H, m) and 0.80 (4.2H, m) in a ratio of 2.5:1. This sample of isoxazolidinone (70) was otherwise identical to that prepared by the 1,3-dipolar cycloaddition of nitrone (20) to vinyl acetate, as described previously. The apparent increase in diastereoselectivity involved in the synthesis of isoxazolidinone (70) over that observed for (56) and (79) was at first puzzling. However the i.r. spectrum of the crude reaction mixture from which (70) was obtained showed two distinct carbonyl absorptions at 1780 and 1730 cm^{-1} indicating a mixture of isoxazolidinone (70) and the inter-

mediate conjugate adduct (126) which had not undergone cyclisation. This suggests that the higher diastereomeric ratio within (70) may have arisen as a result of a difference in the rate of cyclisation of the two diastereomeric adducts (126S) and 126R) rather than preferential addition of chiral hydroxylamine to one face of the α,β-unsaturated ester (123). The enhancement of the diastereomeric ratio of isoxazolidinones as a result of the cyclisation of 1,4-adducts has been noted by Baldwin.[27]



(126R)



(126S)

Hydrogenolysis of isoxazolidinone (70), as before, yielded β-leucine in good yield as a colourless crystalline solid, m.p. 197-200°C, $[\alpha]_D^{20}$ -17.9°, (c 1.0, H_2O), (c.f. Lit[67] m.p. 201-202°C, $[\alpha]_D^{22}$ +55.2°), corresponding to an enantiomeric excess of 32% for the (R)-amino acid, suggesting that adduct (126S) underwent cyclisation at a slower rate than (126R). Lack of time did not permit a more accurate analysis of the enantiomeric excess by g.c. analysis of the camphanamide methyl ester of β-leucine, as described in Chapter 2.

4:3 Summary and Conclusions

The conjugate adducts of (R)-N-α-methylbenzylhydroxylamine (15) and the aryl- and alkyl-substituted α,β-unsaturated esters undergo spontaneous thermal cyclisation to isoxazolidin-5-ones in contrast to the findings of Baldwin.[27] The chemical yields are superior to those obtained for the corresponding isoxazolidinones obtained via 1,3-dipolar cycloadditions to vinyl acetate.

With aryl-substituted unsaturated esters no diastereoselectivity is observed in the formation of the isoxazolidinones. In the case of the 3-isopropylisoxazolidinone (70), the 2.5:1, C-3 (R:S) ratio, was probably a result of a difference in the rates of cyclisation of the two diastereomeric conjugate adducts. Although the chemical yields of the isoxazolidinones obtained by this route are superior, it is believed that the 1,3-dipolar cycloaddition of nitrones to suitably oxygenated alkenes offers the prospect of greater chiral selectivity for the synthesis of β-amino acids than any of the previously published methods.[21-27]

EXPERIMENTAL

General Experimental Procedure

All melting points (m.p.) were determined on a Kofler hot-stage apparatus, and are uncorrected. Routine infra-red spectra were recorded on a Perkin-Elmer 580 spectrophotometer. Routine ^{1}H nmr spectra were recorded in deuterochloroform (unless otherwise stated) using tetramethylsilane (TMS) as internal standard on a Perkin-Elmer R.32 (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. ^{19}F nmr were also recorded on the Bruker WP 200 SY at 188 MHz in deuterochloroform, setting the reference $CFC\ell_3$ in $CDC\ell_3$ at δ0.0, in the ^{1}H coil of the ^{13}C probe. Mass spectra were routinely recorded using a V.G./Kratos M.S.12 spectrometer; high resolution spectra were recorded on a V.G./Kratos M.S.902S spectrometer.

Analytical and preparative t.l.c. were run using the developing solvents indicated. Precoated Merck Kieselgel 60 F-254 5 x 20 cm, 0.25 mm plates were used for analytical t.l.c., and 20 x 20 cm, 0.25 mm plates for preparative t.l.c. Flash column chromatography was performed, by the method of Still,[94] over Merck Kieselgel 60 silica gel (mesh 230-400), Art 9385.

Gas chromatography was carried out on a Perkin Elmer F33 or F11 Gas Chromatograph using the column packing indicated, and the data recorded as retention time (t_R) or retention index (I^{column}_{temp}). Capillary

gas chromatography was carried out on a Hewlett Packard 5880A GC with dual capillary columns and FID detectors. The capillary columns used were fused silica capillary 25m x 0.32mm (internal diameter) SE-54 (GC^2, Northwich, Chester) and/or CP Sil 5B. The sample was injected via Grob-type injectors operated in split mode (50:1) using helium as both carrier and make-up gas (flow rates 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 I.D. (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 temp. 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.

Purification and Drying of Solvents

Solvents and reagents were dried and purified prior to use as follows: acetone (distilled from $CaSO_4 \cdot 0.5H_2O$, stored over molecular sieves (5Å)); benzene, toluene, xylene (distilled from sodium metal, stored over molecular sieves (5Å)); carbon tetrachloride, chloroform (filtered through alumina (basic, activity 1)); dichloromethane (distilled from CaH_2, and stored over molecular sieves (5Å)); ether,

tetrahydrofuran (THF) (distilled from sodium and benzophenone immediately before use); dimethylsulphoxide (DMSO) (dried over molecular sieves (4Å), distilled under reduced pressure (water-pump, b.p. 75°C/12 torr) and stored over molecular sieves (5Å) under argon); methanol (distilled from magnesium turnings); pyridine (dried and stored over anhydrous KOH).

Benzaldehyde oxime (1)

Benzaldehyde (10g, 0.09 mol) was dissolved in aqueous methanol (100 ml), to which hydroxylamine hydrochloride (6.55g, 0.09 mol) and anhydrous sodium bicarbonate (8.70g, 0.10 mol) were added. 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 150 ml). The combined organic layers were dried with anhydrous $MgSO_4$, filtered and evaporated to give an oil, which crystallised from aqueous methanol to give benzaldehyde oxime, (10.38g, 91%) as colourless crystals, m.p. 39°C, (Lit[87] m.p. 37°C).

^1H NMR $\delta(CDCl_3)$: 7.25-7.55 (5H, m), 8.15 (1H, s), 9.15-9.55 (1H, broad s).

N-Benzylhydroxylamine (2)

Benzaldehyde oxime (6g, 0.05 mol) was dissolved in methanol (50 ml) containing a trace of bromocresol green indicator, and to this 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 (10 ml) and 5N NaOH added until the pH exceeded 9. The basic solution was then extracted with chloroform (4 x 50 ml) and the combined organic layers dried with anhydrous $MgSO_4$, filtered and the solvent removed in vacuo, to give a solid residue. Recrystallisation from hexane gave N-benzylhydroxylamine (4.80g, 79%), as a white crystalline solid, m.p. 55-57°C (Lit[47] 58-59°C).

^1H NMR $\delta(CDC\ell_3)$: 4.15 (2H, s), 5.48 (2H, broad s, exchangeable in D_2O), 7.32 (5H, s).

General Preparation for N-Benzyl-C-alkylnitrones (6-8)

N-Benzylhydroxylamine and an excess (1.5 eq.) of the appropriate aldehyde were dissolved in dichloromethane and stirred, under an argon atmosphere, at room temperature for 24h. Removal of the solvent in vacuo gave a solid residue, which in each case was recrystallised to give pure nitrone.

C-Methyl-N-benzylnitrone (6)

From N-benzylhydroxylamine (1.8g, 14.6 mmol) and acetaldehyde (0.97g, 22 mmol), in dichloromethane (50 ml). Recrystallisation from ether gave nitrone (6) (1.96g, 90%) as a colourless crystalline solid, m.p. 83°C.

IR ν_{max} ($CHC\ell_3$): 1605, 1498, 1455, 1440, 1412, 1360, 1309, 1245, 1170, 1105, 1045 cm^{-1}.

^1H NMR δ($CDC\ell_3$) 200 MHz: 1.87 (3H, dt, J=1, 6 Hz), 4.77 (2H, s), 6.71 (1H, q, J=6 Hz), 7.28 (5H, m).

^{13}C NMR δ($CDC\ell_3$), ^1H decoupled: 12.13, 66.36, 128.21, 128.65, 132.51, 134.06.

[Found, 72.15, H 7.45, N 9.25; $C_9H_{10}NO$ requires C 72.45, H 7.45, N 9.4 %].

C-Isopropyl-N-benzylnitrone (7)

From N-benzylhydroxylamine (0.40g, 3.25 mmol) and isobutyraldehyde (0.26g, 3.61 mmol) in dichloromethane (10 ml). Recrystallisation from ether-hexane gave nitrone (7) (0.49g, 85%) as a colourless crystalline solid, m.p. 63°C.

IR ν_{max} ($CHC\ell_3$): 1594, 1495, 1452, 1439, 1419, 1115 cm^{-1}.

^1H NMR δ($CDC\ell_3$) 200 MHz: 0.96 (6H, s, J=7.5 Hz), 3.18 (1H, septet, J=7.5 Hz), 4.73 (2H, s), 6.44 (1H, d, J=7.5 Hz), 7.25 (5H, m).

^{13}C NMR δ($CDC\ell_3$), ^1H decoupled: 18.42, 25.56, 68.75, 128.30, 128.41, 128.59, 132.78, 144.33.

[Found, 7.45, H 8.6, N 7.75; $C_{11}H_{15}NO$ requires C 74.55, H 8.55, N 7.9 %].

C-tert-Butyl-N-benzylnitrone (8)

From N-benzylhydroxylamine (0.47g, 3.82 mmol) and trimethylacetaldehyde (0.36g, 4.19 mmol) in dichloromethane (10 ml). Recrystallisation from ether-hexane gave nitrone (8) (0.67g, 92%) as a colourless crystalline solid, m.p. 67°C.

IR ν_{max} ($CHC\ell_3$): 1595, 1498, 1482, 1455, 1420, 1052, 1030 cm^{-1}.

^1H NMR δ($CDC\ell_3$) 200 MHz: 1.22 (9H, s), 4.76 (2H, s), 6.46 (1H, s), 7.27 (5H, m).

^{13}C NMR δ($CDC\ell_3$), ^1H decoupled: 25.66, 70.17, 128.07, 128.28, 128.41, 128.48, 128.84, 133.31, 144.73.

[Found, 75.45, H 9.1, N 7.2; $C_{12}H_{17}NO$ requires C 75.34, H 9.0, N 7.3 %].

C,N-Diphenylnitrone (11)

To a stirred solution of N-phenyl-N-benzylamine (5g, 27 mmol) in dry acetone (30 ml) at 0°C, was added dropwise over a period of 15 min, a solution of m-chloroperbenzoic acid (9.40g, 55 mol) in acetone (90 ml). When addition was complete, stirring was continued at room temperature for a further 45 mins, and then the solution was refluxed for 1h. The solvent was then removed in vacuo and the residual yellow solid was partitioned between ether (100 ml) and 10% K_2CO_3 (100 ml). The ethereal layer was washed with water (2 x 100 ml), dried with anhydrous $MgSO_4$, filtered and evaporated, to give a

solid residue. Upon recrystallisation from ether-pentane nitrone (11) (3.41g, 63%) was obtained as a white crystalline solid, m.p. 108-111°C (Lit.[88] m.p. 114°C).

IR ν_{max} ($CHC\ell_3$): 1590, 1551, 1485, 1449, 1401, 1158, 1081, 1068 cm^{-1}.

^1H NMR δ($CDC\ell_3$): 7.40-7.60 (6H, m), 7.71-7.82 (2H, m), 8.32-8.45 (2H, m).

C-Phenyl-N-benzylnitrone (12)

To a stirred solution of N,N-dibenzylamine (10g, 0.05 mol) in dry acetone (50 ml) at 0°C, was added dropwise, over a 20 min period a solution of m-chloroperbenzoic acid (19.5g, 0.11 mol) in acetone (75 ml). The solution was stirred at 5°C for 2h and then heated under reflux for a further 2h during which time a yellow colour developed. Removal of solvent in vacuo gave a yellow solid which was partitioned between 10% K_2CO_3 (100 ml) and ether (200 ml). The ethereal layer was washed with water (2 x 100 ml), dried with anhydrous Na_2SO_4, filtered and evaporated to give a yellow solid. Recrystallisation from ether-pentane gave nitrone (12) (7.28g, 68%) as a white crystalline solid, m.p. 85-86°C (Lit.[48] 83-84°C).

IR ν_{max} ($CHC\ell_3$): 1730, 1660, 1605, 1585, 1515, 1488, 1455 cm^{-1}.

^1H NMR δ($CDC\ell_3$): 5.19 (2H, m), 7.40-7.70 (9H, m), 8.25-8.35 (2H, s).

(R)-(+)-α-Methylbenzylhydroxylamine (15)[49]

R-(+)-α-Methylbenzylamine (10g, 83 mmol) and benzoyl peroxide (10.36g, 48 mmol) were dissolved in benzene (50 ml), and heated on a steambath for 5 min. The exothermic reaction was cooled with a waterbath, when the benzoate salt of amine (13) precipitated. After further cooling at 0°C, ether (50 ml) was added and the salt collected by filtration. The filtrate was concentrated in vacuo to give an oil, which was dissolved in methanol (30 ml) - 5N NaOH (20 ml), and then heated on a steambath for approximately 10 mins. Methanol was removed in vacuo, when a yellow solid appeared and this was followed by addition of 5N NaOH (80 ml). After cooling at 0°C, the solid was removed by filtration and the filtrate extracted with ether (5 x 100 ml). The combined ether extracts were dried with anhydrous $MgSO_4$, filtered and evaporated to give a solid yellow residue, which was recrystallised from hexane to give hydroxylamine (15) (3.06g, 27%) as a white crystalline solid, m.p. 67-69°C (Lit.[47] 69-70°C).

^1H NMR $\delta(CDC\ell_3)$: 1.40 (3H, d, J=6.5 Hz), 4.15 (1H, q, J=6.5 Hz), 5.35-5.60 (2H, broad s, exchangeable in D_2O), 7.32 (5H, s).

(R)-(-)-C-Isopropyl-N-α-methylbenzylnitrone (20)

Nitrone (20) was prepared, following the general procedure for C-alkyl-N-benzylnitrones (6-8) described on p134, from (R)-(+)-α-methylbenzylhydroxylamine (1.96g, 14 mmol) and isobutyraldehyde (1.13g, 16 mmol) in dichloromethane (30 ml). Recrystallisation from

ether-hexane gave nitrone (20) (2.24g, 82%) as a colourless crystalline solid, m.p. 58-59°C, $[\alpha]_D^{20}$ -12°, (c 1.0, $CH_2C\ell_2$).

IR ν_{max} ($CHC\ell_3$): 1590, 1498, 1465, 1457, 1279, 1119 cm^{-1}.

^1H NMR ($CHC\ell_3$): 1.02 (3H, d, J=7 Hz), 1.05 (3H, d, J=7 Hz), 1.78 (3H, d, J=6.5 Hz), 3.20 (1H, m, J=7Hz), 4.95 (1H, q, J=6.5 Hz), 6.55 (1H, q, J=7 Hz), 7.25-7.70 (5H, m).

$[M]^+$ 191.1310; $C_{12}H_{17}NO_2$ requires 191.1310.

[Found, C 75.55, H 8.8, N 7.25; $C_{12}H_{17}NO$ requires C 75.35, H 9.0, N 7.3 %].

General Preparation if Nitrones (21-23)[44]

(R)-(+)-α-Methylbenzylhydroxylamine and the appropriate aldehyde were dissolved in benzene and heated at reflux for 5h. Removal of solvent in vacuo gave crude nitrone which was purified either by recrystallisation or flash column chromatography.

(R)-(-)-C-Phenyl-N-α-methylbenzylnitrone (21)

From hydroxylamine (15) (2.50g, 18 mmol) and belzaldehyde (1.92g, 18 mmol) in benzene (75 ml) to give a residue which was purified by flash column chromatography (ether-hexane, 1:1) to give nitrone (21) (3.65g, 86%) as a light brown oil, $[\alpha]_D^{20}$ -96°, (c 1.0, $CH_2C\ell_2$).

TLC: Rf 0.38 (silica gel-ether-hexane, 1:1).

IR ν_{max} ($CHC\ell_3$): 1580, 1495, 1455, 1295, 1280, 1140 cm^{-1}.

^1H NMR δ($CDC\ell_3$): 1.85 (3H, d, J=6.5 Hz), 5.18 (1H, q, J=6.5 Hz), 7.20-7.60 (9H, m), 8.05-8.25 (2H, m).

(R)-(-)-C-p-Methoxyphenyl-N-α-methylbenzylnitrone (22)[44]

From hydroxylamine (15) (1.80g, 13 mmol) and p-methoxybenzaldehyde (1.79g, 13 mmol) in benzene (50 ml), to give nitrone (22), (2.46g, 73%) as pale yellow crystals from hexane-ether, m.p. 97°C, $[\alpha]_D^{25}$ -104.4°, (c 1.0, $CH_2C\ell_2$).

IR ν_{max} ($CHC\ell_3$): 1605, 1509, 1458, 1255, 1172, 1145, 1040 cm^{-1}.

^1H NMR δ($CDC\ell_3$): 1.85 (3H, d, J=6.5 Hz), 3.78 (3H, s), 5.12 (1H, q, J=6.5 Hz), 6.85 (2H, d, J=8 Hz), 7.20-7.60 (5H, m), 8.28 (2H, d, J=8 Hz).

$[M^+]$ 255.1261; $C_{16}H_{17}NO_2$ requires 255.1259.

[Found, C 75.1, H 6.8, N 5.35; $C_{16}H_{17}NO_2$ requires C 75.25, H 6.7, N 5.5 %].

(R)-(-)-C-p-Chlorophenyl-N-α-methylbenzylnitrone (23)

From hydroxylamine (15) (1.50g, 11 mmol) and p-chlorobenzaldehyde (1.60g, 11 mmol) in benzene (70 ml), to give nitrone (23), (2.78g, 98%) as a colourless crystalline solid from hexane-ether, m.p. 96°C, $[\alpha]_D^{25}$ -50.4°, (c 1.0 $CH_2C\ell_2$).

IR ν_{max} ($CHC\ell_3$): 1591, 1559, 1498, 1488, 1455, 1400, 1275 cm^{-1}.

^1H NMR δ($CDC\ell_3$): 1.85 (3H, d, J=6.5 Hz), 5.16 (1H, q, J=6.5 Hz), 7.25-7.60 (7H, m), 8.15 (2H, d, J=8 Hz).

$[M]^+$ 259.0764; $C_{15}H_{15}NOC\ell$ requires 259.0764.

[Found, C 68.9, H 5.1, N 5.15; $C_{15}H_{15}NOC\ell$ requires C 69.15, H 5.4, N 5.4 %].

(R)-(-)-C-Indolyl-N-α-methylbenzylnitrone (24)

(R)-(+)-α-Methylbenzylhydroxylamine (0.5g, 3.65 mmol) and indole-3-carboxaldehyde (0.49g, 3.31 mmol) were dissolved in methanol (5 ml)-benzene (20 ml) and heated at reflux for 12h. The solvents were removed in vacuo to give a solid residue which was recrystallised from ether-chloroform to give nitrone (24) (0.89g, 93%) as a light brown crystalline solid, m.p. 174-175°C, $[\alpha]_D^{25}$ -73.7° (c 1.0, $CH_2C\ell_2$).

IR ν_{max} ($CHC\ell_3$): 3680, 3460, 1658, 1599, 1532, 1512, 1455, 1420, 1125 cm^{-1}.

^1H NMR δ($CDC\ell_3$): 1.88 (3H, d, J=6.5 Hz), 5.25 (1H, q, J=6.5 Hz), 7.65-7.01 (10H, m), 7.88 (1H, s), 8.92 (1H, broad m).

$[M]^+$ 264.1264; $C_{17}H_{16}NO$ requires 264.1257.

[Found, C 77.2, H 5.8, N 10.45; $C_{17}H_{16}N_2O$ requires C 77.25, H 6.1, N 10.6 %].

1,3-Dipolar Cycloadditions of Nitrones to Vinyl Acetate[32]

N-Benzyl-3-phenyl-5-acetoxyisoxazolidines (41) and (42)

C-Phenyl-N-benzylnitrone (12), (1.03g, 4.9 mmol) was dissolved in an excess of freshly distilled vinyl acetate (30 ml, 0.37 mol) and refluxed with exclusion of light, under an argon atmosphere for 60h. Excess vinyl acetate was removed in vacuo and the residue purified by flash column chromatography (ether-hexane, 1:1) to give isoxazolidines (41, 42) (0.98g, 67%), as a colourless oil.

TLC (41, 42): Rf 0.74 (silica gel-ether-hexane, 1:1).

IR ν_{max} ($CHC\ell_3$): 1738, 1498, 1458, 1378, 1240, 1010, 970 cm^{-1}.

$[M]^+$ 297.1360; $C_{18}H_{19}NO_3$ requires 297.1365.

Isomers (41) and (42) were separated by preparative tlc (ether-hexane, 1:4, 3 x developed).

Isoxazolidine (41)

TLC: Rf 0.58 (silica gel-ether-hexane, 2:3).

^1H NMR δ($CDC\ell_3$) 200 MHz: 2.10 (3H,s), 2.40 (1H, ddd, J=3, 9.5, 13.6 Hz), 3.03 (1H, ddd, J=6.6, 8.0, 13.6 Hz), 3.79 (1H, d, J=14.8 Hz), 3.82 (1H, dd, J=8, 9.5 Hz), 4.07 (1H, d, J=14.8 Hz), 6.35 (1H, dd, J=3, 6.5 Hz), 7.20-7.51 (10H, m).

^{13}C NMR $\delta(CDC\ell_3)$, ^{1}H decoupled: 21.37, 46.36, 59.27, 69.51, 95.05, 127.14, 127.88, 128.06, 128.14, 128.75, 128.96, 136.56, 137.86, 170.60.

Isoxazolidine (42)

TLC: Rf 0.52 (silica gel-ether-hexane, 2:3).

^{1}H NMR $\delta(CDC\ell_3)$ 200 MHz: 2.07 (3H, s), 2.62 (2H, m), 4.01 and 4.13 (2H, AB quartet, J=14 Hz), 4.24 (1H, t, J=8.5 Hz), 6.37 (1H, m), 7.20-7.45 (10H, m).

^{13}C NMR $\delta(CDC\ell_3)$, ^{1}H decoupled: 21.44, 29.69, 45.64, 62.27, 66.69, 96.54, 122.33, 127.52, 127.98, 128.18, 128.69, 129.27, 136.77, 138.34, 169.98.

General Procedure for the Hydrolysis of Isoxazolidine Acetates 10 mmol scale)[58]

The acetate (0.01 mol) was dissolved in aqueous methanol (approx. 10:1 MeOH-H_2O) containing potassium carbonate (0.005 mol) and the resulting solution stirred at room temperature for 1h. The solvent was removed in vacuo and the residue dissolved in water (50 ml). The aqueous solution was extracted with ether (3 x 50 ml) and the combined organic layers were dried with anhydrous $MgSO_4$, filtered and evaporated to give crude lactol. The lactol was generally used without purification.

General Procedure for the Silylation of Lactols[61]

Typically the lactol (2-3 mg) was dissolved in a silylating solution consisting of anhydrous pyridine (10 ml), hexamethyldisilizane (2 ml), and trimethylsilyl chloride (1 ml), and stirred for 12h at room temperature. The reaction mixture was dissolved in ether (10 ml) and washed with water (1 x 10 ml). The ethereal layer was dried with anhydrous Na_2SO_4, filtered and evaporated at the oil pump (0.01 mm Hg). The results of g.c.-m.s. analysis of trimethylsilyl ethers are given in Table 4, p61.

N-Benzyl-3-phenyl-5-hydroxyisoxazolidine (43)

Acetate mixture (41,42) (3.0g, 10 mmol) was hydrolysed with potassium carbonate (0.70g, 5 mmol) in methanol (55 ml)-water (5 ml) according to the general procedure to give the crude isoxazolidine lactol mixture (43) (2.14g, 83%) as a colourless oil.

IR ν_{max} ($CHC\ell_3$): 3600, 3450, 1500, 1460, 1068, 1032 cm^{-1}.

^1H NMR δ($CDC\ell_3$): 2.08-2.55 (1H,m), 2.75-3.30 (1H, m), 3.41-4.40 (3H, m), 5.50 (1H, m), 7.15-7.80 (10H, m).

$[M]^+$ 255.1255; $C_{16}H_{15}NO_2$ requires 255.1349.

N-Benzyl-3-phenyl-5-trimethylsilyloxyisoxazolidine (44)

Trimethylsilyl ether mixture (44) was prepared according to the general procedure on page 144 , and a solution of (44) (1 mg) in hexane (1 ml)-pyridine (0.5$\mu\ell$) was employed for analysis by g.c..

GC : I_{155}^{OV-1} = 2030, 2100, ($[M]^+$ = 327), relative to $C_{19,20,22}$ standards. The diastereomeric ratio within mixture (44) is given in Table 4 p61.

Attempted PDC Oxidation of Lactol (43)

The crude isoxazolidine lactol mixture (43) (0.1g, 0.39 mmol) was dissolved in dichloromethane (2 ml; distilled from CaH_2) containing pyridinium dichromate (0.22g, 0.59 mmol) and pyridinium trifluoroacetate (0.05g, 0.26 mmol) and the mixture stirred at room temperature for five minutes. The reaction was then diluted with ether-pentane (10 ml, 1:1) and filtered through a pad of anhydrous $MgSO_4$. The solvent was removed in vacuo to give a yellow oil (0.04g) which analytical tlc and ^1H nmr showed to be a multicomponent mixture resulting from degradation of the parent lactol.

Attempted PCC Oxidation of Lactol (43)

The crude lactol mixture (43) (0.1g, 0.39 mmol) was dissolved in dichloromethane (5 ml) containing pyridinium chlorochromate (0.13g, 0.59 mmol) and sodium acetate (0.01g, 0.12 mmol), and stirred at room temperature for 20 min. Ether (20 ml) was added and the supernatant decanted from the black gum. The insoluble residue was washed thoroughly with anhydrous ether (3 x 10 ml). The combined organic solution was passed through a pad of Celite, and the solvent removed in vacuo to give a dark brown oil (0.048g) which analytical tlc and ^1H nmr showed to be a multicomponent mixture which did not contain the desired product.

Attempted Oxidation of TMS ether (44)

Following the procedure of Jung,[60] crude silyl ether mixture (44) (0.05g, 0.15 mmol) and triphenylcarbenium tetrafluoroborate (0.075g, 0.175 mmol) were dissolved in dichloromethane (20 ml) and stirred at room temperature for 24h under an argon atmosphere. The reaction was washed with water (20 ml), dried with anhydrous Na_2SO_4, filtered and the solvent removed in vacuo to give a light yellow oil (0.03g) which was identified by tlc and ^1H nmr, as the lactol mixture (43).

Attempted NCS-Methyl Sulphide Oxidation of Lactol (43)

Following the procedure of Corey and Kim,[63] N-chlorosuccinimide (0.17g, 1.26 mmol) in toluene (5 ml) was stirred at 0°C, and to this was added dropwise methyl sulphide (0.13 ml, 1.72 mmol) under argon. A white precipitate appeared immediately after the addition of the sulphide. The mixture was cooled to -25°C ($CC\ell_4$-Dry Kold) and a solution of lactol mixture (43) (0.033g, 0.084 mmol) in toluene (2 ml) was added dropwise. The stirring was continued for 2h at -25°C, and then a solution of triethylamine (0.13g, 1.26 mmol) in toluene (1 ml) was added dropwise. The cooling bath was removed and after 5 min, ether (20 ml) was added. The combined organic solution was washed with aqueous $H C\ell$ (1 x 5 ml; 1%) and water (2 x 15 ml), dried with anhydrous $MgSO_4$, filtered and the solvent removed in vacuo, to give a light yellow oil which tlc and ^1H nmr showed to be starting lactol mixture (43).

Jones Oxidation of Lactol (43)

The crude lactol mixture (43) (0.2g, 0.78 mmol) was dissolved in dry acetone (5 ml) and stirred at 0°C for a few minutes. Jones reagent (0.2 ml of 0.8M solution, 1.5 mmol) was added and after stirring for 5 min, the solution became green. The reaction was diluted with sodium bicarbonate solution (50 ml; 10%) and extracted with ether (2 x 50 ml). The combined ether extracts were dried with anhydrous $MgSO_4$, filtered and evaporated to give a yellow oil which was chromatographed by preparative tlc, (1 x ether-hexane (1:4), 1 x ether-hexane (1:1)), to give N-benzyl-3-phenylisoxazolidin-5-one (45) as a light yellow oil, (48 mg, 36%).

TLC: Rf 0.29 (silica gel-ether-hexane, 1:1).

IR ν_{max} ($CHC\ell_3$): 3580, 3280, 1780, 1498, 1458, 1198, 1165, 705 cm^{-1}.

^1H NMR δ($CDC\ell_3$): 2.95 (2H, d, J=9 Hz), 3.95 and 4.15 (2H, AB quartet, J=15 Hz), 4.35 (1H, t, J=9 Hz), 7.30 (5H, s), 7.35-7.60 (5H, m).

$[M]^+$ = 253.1110; $C_{16}H_{15}NO_2$ requires 253.1103.

Preparation of Dipyridine Chromium(VI) Oxide, Collins Reagent[65]

A dry 500 ml 3-necked flask with sealed mechanical stirrer, thermometer and drying tube was charged with anhydrous pyridine (100 ml). The pyridine was stirred and cooled to approximately 15°C with an ice bath. The drying tube was periodically removed and

anhydrous chromium(VI) oxide (13.5g, 0.14 mol) was added in portions over 1h. The oxide was added at such a rate that the temperature did not exceed 20°C, and an intensely yellow flocculent precipitate separated from the pyridine as the viscosity of the mixture increased. When the addition was complete the mixture was allowed to warm slowly to room temperature with stirring. Within 1h, the viscosity of the mixture decreased and the initially yellow product changed to a deep red macrocrystalline form. Excess pyridine was decanted from the complex and the crystals washed several times by decantation with light petroleum (60-80). The complex was collected on a sintered glass funnel and dried at 10 mm Hg, and then stored at 0°C in the dark.

Collins Oxidation of Lactol (43)[65]

The crude lactol mixture (43) (0.1g, 0.39 mmol) was added to a solution of freshly prepared Collins reagent (0.69g, 2.35 mmol) in dry dichloromethane (15 ml). The deep red solution immediately became dark brown and reaction appeared complete after fifteen minutes (tlc) when the solution was washed with water (1 x 20 ml) and dilute $NaHCO_3$ (1 x 20 ml), dried with anhydrous Na_2SO_4 and then filtered through Celite to remove the last traces of chromium salts. Evaporation of solvent *in vacuo* gave a brown oil, which was purified by preparative tlc, (ether-hexane, 2:3), to give isoxazolidinone (45), (43 mg, 48%), as a light yellow oil. This was identical (ir, nmr, ms) with the material prepared above by Jones oxidation in somewhat inferior yield.

Synthesis of Isoxazolidinone (45) via Reformatski Reaction[66]

Powdered zinc (0.28g, 4.3 mmol) and ethyl α-bromoacetate (0.58g, 3.5 mmol) were heated together with stirring (oil bath temp. 75-80°C) in dry THF (30 ml) until boiling occurred. When the reaction started, the solution became green and boiling was continued for another 5 min. The temperature of the oil bath was then lowered sufficiently to prevent boiling. C-Phenyl-N-benzylnitrone (0.5g, 2.4 mmol) in THF (10 ml) was then added over a 5 min period. As the nitrone was added the solution began to boil slightly. After the addition was complete, the solution was brought back to boiling for a further 20 min and then left to cool. Kieselgel HF254 silica gel (1.25g) was added and the solvent removed under reduced pressure. The product was then extracted by washing the silica gel thoroughly with hot ether on a sintered glass funnel. Evaporation of the ether in vacuo gave a solid brown residue, which was chromatographed by preparative tlc (silica gel-ether-hexane, 1:1) to give N-benzyl-3-phenylisoxazolidinone (45) as a light yellow oil, (82 mg, 14%). This was essentially identical (ir, nmr, tlc) with the material obtained above by Jones and Collins oxidation of lactol (43).

C-Phenyl-N-methylnitrone (48)

N-Methylhydroxylamine hydrochloride (2.0g, 24 mmol) was dissolved in dichloromethane (50 ml) containing triethylamine (3.5 ml, 25 mmol). To this solution was added benzaldehyde (2.54g, 24 mmol) and the reaction was stirred at room temperature for 24h. The solution was washed with water (1 x 50 ml) and the organic layer dried with

anhydrous $MgSO_4$, filtered and evaporated to give a solid residue which was recrystallised from ether-hexane to give nitrone (38) (2.81g, 95%) as a colourless crystalline solid, m.p. 85-86°C, (Lit[89] 84-86°C).

IR ν_{max} ($CHC\ell_3$): 1600, 1585, 1492, 1450, 1420, 1400, 1170, 1160, 950 cm^{-1}.

^1H NMR δ($CDC\ell_3$): 3.90 (3H, s), 7.40 (4H, m), 8.25 (2H, m).

N-Methyl-3-phenyl-5-acetoxyisoxazolidine (49)

C-Phenyl-N-methylnitrone (2.10g, 17 mmol) was dissolved in an excess of vinyl acetate (50 ml, 0.62 mol) and refluxed with exclusion of light for 48h. After removal of excess vinyl acetate the residue was purified by flash column chromatography (ether-hexane, 1:4) to give isoxazolidine (49) (1.95g, 68%) as a colourless oil.

TLC: Rf 0.41 (silica gel-ether-hexane, 1:4).

IR ν_{max} ($CHC\ell_3$): 1735, 1455, 1375, 1360, 1235, 975 cm^{-1}.

^1H NMR δ($CDC\ell_3$): 2.08 (2H, m), 2.10 (3H, s), 2.60 (2H, s), 2.78 (1H, s), 3.55 (0.69H, dd, J=9, 10 Hz), 4.02 (0.31H, t, J=8 Hz), 6.35 (1H, m), 7.35 (5H, m).

$[M]^+$ 221.1041; $C_{12}H_{15}NO_3$ requires 221.1055.

N-Methyl-3-phenyl-5-hydroxyisoxazolidine (50)

Acetate (49) (0.37g, 1.67 mmol) was hydrolysed with potassium carbonate (0.12g, 0.9 mmol) in methanol (20 ml)-water (2 ml) following the general procedure, to give crude lactol (50), (0.21g, 70%) as a light yellow oil.

TLC: Rf 0.26 (silica gel-ether-hexane, 1:1).

^{1}H NMR $\delta(CDC\ell_3)$: 2.15-3.15 (2H, m), 2.60 (2.21H, s), 2.79 (0.79 H, s), 3.50 (0.76H, dd, J=9, 10 Hz), 4.10 (0.24H, t, J=9 Hz), 5.55 (1H, m), 7.32 (5H, m).

$[M]^+$ 179.0940; $C_{10}H_{13}NO_2$ requires 179.0945.

N-Methyl-3-phenyl-5-trimethylsilyloxyisoxazolidine (51)

Trimethylsilyl ether (51) was prepared according to the general procedure on page 144, and a solution of (51) (1 mg) in hexane (1 ml)-pyridine (0.5 $\mu\ell$) was employed for g.c. analysis.

GC: I_{115}^{OV-1} = 1494, 1620 relative to $C_{14,15,16}$ standards. The diastereomeric ratio within (51) is given in Table 4, p61.

N-Methyl-3-phenylisoxazolidin-5-one (52)

Crude lactol (40) (0.3g), 1.67 mmol) was added to a solution of Collins reagent (1.31g, 4.42 mmol) in dry dichloromethane (30 ml), with stirring at 0°C. The solution was then washed with water (1 x 40ml), followed by dilute $NaHCO_3$ (1 x 40 ml), dried with anhydrous Na_2SO_4,

and then filtered through Celite to remove chromium salts. Evaporation of solvent in vacuo gave a dark brown residue, which was purified by preparative tlc (ether-hexane, 2:3) to give isoxazolidininone (52) as an oil, (62 mg, 21%).

TLC: Rf 0.44 (silica gel-ether-hexane, 1:1).

IR ν_{max} ($CHC\ell_3$): 1770, 1455, 1235, 1170, 1122, 990, 915, 700 cm^{-1}.

^1H NMR δ($CDC\ell_3$): 2.88 (3H, s), 2.95 (2H, d, J=9 Hz), 4.10 (3H, t, J=9 Hz), 7.38 (5H, s).

$[M]^+$ 177.0801; $C_{10}H_{11}NO_2$ requires 177.0790.

N-(R)-α-Methylbenzyl-3-phenyl-5-acetoxyisoxazolidine (53)

R-(-)-C-Phenyl-N-α-methylbenzylnitrone (21), (2.24g, 10.7 mmol) was dissolved in vinyl acetate (75 ml, 0.93 mol) and refluxed with exclusion of light under an argon atmosphere for 72h. After removal of excess vinyl acetate in vacuo, the residue was purified by flash column chromatography (ether-hexane, 1:4) to give isoxazolidine (53) (2.14, 69%), as a colourless oil.

TLC: Rf 0.62 (silica gel-ether-hexane, 1:1).

IR ν_{max} ($CHC\ell_3$): 1735, 1495, 1455, 1378, 1365, 1240, 1011, 1000, 990, 970 cm^{-1}.

^1H NMR δ($CDC\ell_3$) 200MHz: 1.49 (3H,m), 2.07 (1.44H, s), 2.13 (1.17H,s), 2.16 (0.39H, s), 2.26-2.46 (1H, m), 2.62-3.04 (1H, m), 3.77 (0.40H,

t, J=8.5 Hz), 3.81-4.34 (1.60H, m), 6.27 (m, 0.52H), 6.42 (0.42H, dd, J=2, 8.5 Hz), 6.51 (0.06H, dd, J=1.8, 6.7 Hz), 7.10-7.50 (10H, m).

^{13}C NMR $\delta(CDC\ell_3)$ ^{1}H decoupled: 18.92, 20.82, 20.94, 21.26, 21.32, 45.19, 46.00, 46.62, 62.68, 65.38, 65.55, 65.75, 66.22, 67.74, 94.58, 95.24, 97.68, 126.88, 127.09, 127.28, 127.43, 127.74, 127.82, 127.91, 128.02, 128.32, 128.59, 128.97, 129.59, 129.67, 139.09, 138.89, 140.40, 140.91, 141.34, 141.98, 170,48, 170.56.

$[M]^+$ 311.1523; $C_{19}H_{21}NO_3$ requires 311.1521.

Isoxazolidine mixture (53) (0.15g) was partially separated by preparative tlc (3 x developed, ether-hexane, 1:4). A single band was observed (Rf 0.38) which was divided into three portions of equal width. The portion of lowest polarity was extracted with ether to give the major isomer (53b) (0.048g) as a colourless oil. The two remaining portions were found to contain a mixture of all the diastereomers of (53) which could not be further separated.

Attempted Preparation of Bistrimethylsilylether (61)

Isoxazolidine (53) (10 mg, 0.03 mmol) was added to a stirred suspension of lithium aluminium hydride (10 mg, 0.26 mmol) in ether (10 ml) and stirred for 3h at room temperature. Water was added dropwise to destroy excess hydride and dichloromethane (20 ml) was added. The solution was dried with anhydrous $MgSO_4$, filtered and evaporated in vacuo. The residue (4 mg) was dissolved in a silylating solution of pyridine (5 ml), hexamethyldisilizane (2 ml) and trimethyl-

silyl chloride (1 ml) and stirred for 24h at room temperature. The solvent was removed at the oil pump and the residue (5 mg) was dissolved in ethyl acetate (2 ml) for g.c. analysis.

GC: t_R = 1.22 mins, 6' 1% OV-1 column at 120°C.

N-(R)-α-Methylbenzyl-3-phenyl-5-hydroxyisoxazolidine (54)

Acetate (53) (2.04g, 6.6 mmol) was hydrolysed with potassium carbonate (0.45g, 3.3 mmol) in methanol (90 ml)-water (10 ml) following the general procedure to give crude lactol (44) (1.45g, 82%), as a yellow oil.

TLC: Rf 0.47, 0.40 (silica gel-ether-hexane, 1:1).

IR ν_{max} ($CHC\ell_3$): 3600, 3180, 1604, 1495, 1455, 1125, 1070 cm^{-1}.

^1H NMR δ($CDC\ell_3$): 1.18-1.58 (3H, m), 2.05-2.90 (2H, m), 3.50-4.50 (2H, m), 5.30-5.70 (1H, m), 7.00-7.70 (10H, m).

$[M]^+$ 269.1423; $C_{17}H_{19}NO_2$ requires 269.1416.

N-(R)-α-Methylbenzyl-3-phenyl-5-trimethylsilyloxyisoxazolidine (55)

Trimethylsilyl ether (55) was prepared from lactol (54) according to the general procedure on page 144, and a solution of (55) (1 mg) in hexane (1 ml)-pyridine (0.5 μℓ) was employed for g.c. analysis.

GC: I_{155}^{OV-1} = 2042, 2072, 2096 and 2132, ($[M]^+$ 341), relative to

$C_{19,20,22}$ standards. The diastereomer ratio within (55) is given in Table 4, p61.

N-(R)-α-Methylbenzyl-3-phenylisoxazolidin-5-one (56)

Crude lactol (44) (0.4g, 1.49 mmol) was added to a solution of Collins reagent (1.0g, 3.37 mmol) in dry dichloromethane (30 ml), with stirring at 0°C. The deep red solution immediately became dark brown and after 2 min stirring at 0°C, the solution was decanted from the insoluble brown gum. The gum was quickly extracted with ether (3 x 50 ml), and the ether and dichloromethane layers combined. The resulting solution was washed successively with aqueous 5% NaOH (1 x 50 ml), aqueous 5% HCℓ (1 x 20 ml), saturated $NaHCO_3$ (2 x 100 ml) and saturated NaCℓ (1 x 50 ml). The organic layer was dried with anhydrous Na_2SO_4, filtered and evaporated in vacuo to give a yellow oil, which was chromatographed using preparative tlc, (ether-hexane, 1:1) to give isoxazolidinone (56) (63 mg, 16%) as a light yellow oil. Isoxazolidinone (56) was subsequently crystallised from ether-hexane as colourless prisms, m.p. 95-98°C.

TLC: Rf 0.29 (silica gel-ether-hexane, 1:1).

IR ν_{max} ($CHCℓ_3$): 1775, 1495, 1455, 1415, 1380, 1288 cm^{-1}.

^1H NMR δ($CDCℓ_3$) 200 MHz: 1.55 (3H, d, J=6.5 Hz), 2.85 (1H, dd, J=8, 17.5 Hz), 3.06 (1H, dd, J=8, 17.5 Hz), 4.15 (1H, q, J=6.5 Hz), 4.45 (1H, t, J=8 Hz), 7.22 (10H, m).

^{13}C NMR $\delta(CDC\ell_3)$, ^{1}H decoupled: 18.60, 39.18, 66.28, 126.99, 127.49, 127.87, 127.93, 128.02, 128.12, 128.40, 128.66, 128.76, 129.07, 129.13, 138.62, 140.10, 173.85.

[Found C 76.30, H 6.45, N 5.19; $C_{17}H_{17}NO_2$ requires C 76.37, H 6.42, N 5.24 %. $[M]^+$ 267].

GC: I_{155}^{OV-1} = 2100 (relative to standards $C_{19,20,22}$).

Capillary GC: t_R = 22.33 min [25m CPsil5-CB, 80°C].

β-Phenyl-β-alanine (57)

The recrystallised isoxazolidinone (56) (0.1g, 0.37 mmol) was dissolved in dry ethanol (50 ml), containing palladium hydroxide on charcoal (20%; 10 mg) and hydrogenated at atmospheric pressure and 70°C for 5h. The solid amino acid separated during hydrogenolysis. When hydrogen uptake was complete, distilled water (100 ml) was added to dissolve the amino acid. The catalyst was removed by filtration through a pad of Celite, and was thoroughly washed with warm water (100 ml). The combined filtrate was evaporated in vacuo to give β-phenyl-β-alanine as colourless crystals, (56 mg, 92%), m.p. 231-234°C, $[\alpha]_D^{21}$ -1.5° (c 1.0, H_2O). (lit value,[67] m.p. 236°C, $[\alpha]_D$ + 6.2°, for (S)-β-phenyl-β-alanine).

General Procedure for the Preparation of β-Amino Acid Methyl Ester Hydrochlorides[68]

Typically, crude amino acid (50 mg) was dissolved in dry methanol (20 ml) to which thionyl chloride (5 ml) was added dropwise with stirring at 0°C. The reaction was allowed to warm to room temperature with continued stirring over a period of 12h, and the solvent then evaporated under reduced pressure to give crude methyl ester hydrochloride.

General Procedure for the Synthesis of N-Acyl-β-Amino Acid Methyl Esters[68]

β-Amino acid methyl ester hydrochloride (1 eq) and chiral acid chloride (1 eq) were dissolved in carbon tetrachloride and pyridine (approx. 3-4:1) and refluxed for 2h. On cooling the solution was washed with 1N HCℓ and aqueous $NaHCO_3$ (10%), dried with anhydrous Na_2SO_4, filtered and evaporated *in vacuo* to give the crude N-acyl methyl ester.

Camphanamide methyl ester (65)

From crude β-phenyl-β-alanine methyl ester hydrochloride (14 mg, 0.065 mmol) and (1R)-(-)-camphanoyl chloride (14 mg, 0.065 mmol) in a mixture of $CCℓ_4$ (20 ml) and pyridine (5 ml), following the general procedure. The crude camphanamide (65) (16 mg, 70%) was dissolved in ethyl acetate for analysis by gas chromatography (g.c. results, Table 5, p 80).

$[M]^+$ 359.1729; $C_{20}H_{25}NO_5$ requires 359.1733.

'Mosher' amide (66)[69]

From β-phenyl-β-alanine methyl ester hydrochloride (10 mg, 0.046 mmol) and (+)-α-methoxy-α-trifluoromethylphenylacetyl chloride (9 mg, 0.05 mmol) in $CC\ell_4$ (15 ml) and pyridine (5 ml) following the general procedure. The crude 'Mosher' amide (66) (13 mg, 78%) was dissolved in ethyl acetate for analysis by gas chromatography (g.c. results, Table 5, p 80)

$[M-OCH_3]^+$ = 364.1187; $C_{20}H_{20}NO_4F_3$ requires 364.1160.

N-(R)-α-Methylbenzyl-3-isopropyl-5-acetoxyisoxazolidine (67)

(R)-(-)-C-Isopropyl-N-α-methylbenzylnitrone (20) (2.24g, 11.7 mmol) was dissolved in vinyl acetate (100 ml, 1.24 mol) and refluxed with exclusion of light under an argon atmosphere for 48h. After removal of excess vinyl acetate in vacuo the residue was purified by flash column chromatography (ether-hexane, 1:4) to give isoxazolidine (67) (3.85g, 81%) as a colourless oil.

TLC: Rf 0.72 (silica gel-ether-hexane, 1:1).

IR ν_{max} ($CHC\ell_3$): 1735, 1495, 1468, 1455, 1378, 1305, 1240, 1015, 1000, 988 cm^{-1}.

^1H NMR δ($CDC\ell_3$) 200 MHz: 0.64-0.96 (6H, m), 1.28-2.41 (2H, m), 1.44 (0.75H, d, J=6.5 Hz), 1.49 (1.41H, d, J=6.5 Hz), 1.55 (0.84H,

d, J=6.5 Hz), 2.01 (0.92H, s), 2.02 (1.26H, s), 2.09 (0.82H, s), 2.61-2.87 (0.68H, m), 2.98 (0.32H, m), 3.76-4.06 (1H, m), 6.20 (0.33H, m), 6.41 (0.67H, m), 7.18-7.38 (5H, m).

^{13}C NMR $\delta(CDC\ell_3)$, ^{1}H decoupled: 17.91, 18.49, 19.43, 20.09, 20.31, 20.75, 20.85, 21.23, 21.31, 21.53, 29.77, 31.26, 35.97, 36.89, 64.93, 66.36, 67.14, 67.33, 67.63, 96.24, 96.74, 99.47, 125.84, 127.34, 127.46, 127.51, 127.65, 127.93, 127.99, 128.19, 128.25, 128.69, 128.87, 140.20, 142.13, 143.09, 170.99, 170.14, 170.35.

$[M]^+$ 277.1680; $C_{16}H_{23}NO_3$ requires 277.1678.

[Found C 69.4, H 8.4, N 5.05; $C_{16}H_{23}NO_3$ requires C 69.3, H 8.4, N 5.06 %].

N-(R)-α-Methylbenzyl-3-isopropyl-5-hydroxyisoxazolidine (68)

Acetate (67) (2.0g, 8.5 mmol) was hydrolysed with potassium carbonate (0.59g, 4.24 mmol) in methanol (90 ml)-water (5 ml) following the general procedure to give crude lactol (68) (1.53g, 91%) as a yellow oil.

TLC: Rf 0.54 (silica gel-ether-hexane, 1:1).

IR ν_{max} ($CHC\ell_3$): 3600, 3400, 1495, 1470, 1455, 1390, 1375, 1280, 1240, 1110, 1060 cm^{-1}.

^{1}H NMR $\delta(CDC\ell_3)$: 0.65-1.05 (6H, m), 1.32-1.60 (3H, m), 2.36-2.48 (2H, m), 2.95-3.45 (1H, m), 4.25 (1H, q, J=6.5 Hz), 5.35-5.75 (1H, m), 7.35 (5H, m).

$[M]^+$ 235.1561; $C_{14}H_{21}NO_2$ requires 235.1572.

N-(R)-α-Methylbenzyl-3-isopropyl-5-trimethylsilyloxyisoxazolidine(69)

Trimethylsilyl ether (69) was prepared from lactol (68) according to the general procedure on page 144, and a solution of (69) (1 mg) in hexane (1 ml)-pyridine (0.5 μℓ) was employed for g.c. analysis.

GC: I_{140}^{OV-1} = 1718, 1728, 1743, ($[M]^+$ 307), relative to $C_{17,18,19}$ standards. The diastereomer ratio within (69) is given in Table 4, p61.

N-(R)-α-Methylbenzyl-3-isopropylisoxazolidin-5-one (70)[62]

A solution of dimethyl sulphoxide (0.40 ml, 4.66 mmol) in dichloromethane (10 ml) was cooled to -60°C, and oxalyl chloride (0.54 ml, 2.92 mmol), in dichloromethane (5 ml), was added dropwise over a 5 min period. Stirring was continued at -60°C for 10 min, followed by dropwise addition of the crude lactol (68) (0.63g, 2.68 mmol) in dichloromethane (15 ml), and the reaction was stirred at -60°C for a further 15 min. After this time triethylamine (1.98 ml, 27 mmol) was added dropwise over ca. 10 min. The reaction was allowed to warm to room temperature, and then washed with 1N HCℓ (1 x 40 ml), dilute $NaHCO_3$ (1 x 40 ml), saturated NaCℓ (1 x 40 ml) and H_2O (1 x 40 ml). The organic layer was dried with anhydrous Na_2SO_4, filtered and evaporated to give a brown oil. Preparative tlc (ether-hexane, 1:1), gave isoxazolidinone (70) as a colourless oil, (98 mg, 15%).

TLC: Rf 0.61 (silica gel-ether-hexane, 1:1).

IR ν_{max} ($CHC\ell_3$): 1778, 1492, 1455, 1415, 1390, 1375, 910 cm^{-1}.

^1H NMR δ($CDC\ell_3$) 200 MHz: 0.75 (4.84H, m), 0.92 (1.16H), 1.51 (2.46H, d, J=6.5 Hz), 1.60 (0.54H, d, J=6.5 Hz), 2.02 (0.17H, dd, J=9.5, 17.5 Hz), 2.26 (0.19H, dd, J=5, 17.5 Hz), 2.31 (0.83H, dd, J=4, 19 Hz), 2.61 (0.81H, dd, J=9, 19 Hz), 3.12 (1H, m), 4.02 (1H, m), 7.32 (5H, m).

^{13}C NMR δ($CDC\ell_3$), ^1H decoupled: 17.34, 17.86, 18.42, 19.70, 19.94, 30.57, 31.07, 31.33, 31.59, 65.06, 65.85, 66.22, 66.86, 127.89, 128.04, 128.16, 128.52, 128.60, 129.17, 138.35, 140.34, 176.21, 177.20.

$[M]^+$ 233.1426; $C_{14}H_{19}NO_2$ requires 233.1416.

[Found C 71.8, H 8.2, N 5.9; $C_{14}H_{19}NO_2$ requires C 72.1, H 8.2, N 6.0 %].

Side Product (73) of Swern Oxidation

N-(R)-α-Methylbenzyl-3-isopropyl-Δ^4-isoxazolidine (73) was obtained as a side product in the oxidation of lactol (68) in 28% yield.

TLC: Rf 0.71 (silica gel-ether-hexane, 1:1).

IR ν_{max} ($CHC\ell_3$): 1625, 1492, 1455, 1122, 1052 cm^{-1}.

^1H NMR δ($CDC\ell_3$): 0.65 (6H, m), 1.42 (1.36H, d, J=6.5 Hz), 1.54 (1.64H, d, J=6.5 Hz), 3.65 (1H, m), 3.80 (1H, m), 4.75 (1H, m), 6.39 (1H, m), 7.35 (5H, m).

$[M]^+$ 217.1470; $C_{14}H_{19}NO$ requires 217.1467.

β-Leucine (71)

Isoxazolidinone (70) (98 mg, 0.42 mmol) was dissolved in methanol (50 ml) containing palladium hydroxide on charcoal (20%; 10 mg) and hydrogenated at room temperature and atmospheric pressure for 48h. The catalyst was removed by filtration through a pad of Celite, and was thoroughly washed with warm methanol. The combined filtrate and washings were evaporated in vacuo to give β-leucine as colourless crystals (51 mg, 81%), m.p. 204-207°C, $[\alpha]_D^{21}$ -22.4° (c 2.0, H_2O). Lit,[67] m.p. 201-202.5°C, $[\alpha]_D^{22}$ + 55.2°, for (S)-β-leucine).

Camphanamide Methyl Ester (74)[68]

From crude β-leucine methyl ester hydrochloride (10 mg, 0.06 mmol) and (1R)-(-)-camphanoyl chloride (13 mg, 0.06 mmol) in $CC\ell_4$ (15 ml) and pyridine (3 ml) following the general procedure. The crude camphanamide (18 mg, 95%) was dissolved in ethyl acetate for gc analysis (gc results, Table 6, p 90).

$[M]^+$ 325.1881; $C_{17}H_{27}NO_5$ requires 325.1889.

'Mosher' Amide (75)[69]

From β-leucine methyl ester hydrochloride (35 mg, 0.21 mmol) and (+)-α-methoxy-α-trifluoromethylphenylacetyl chloride (47 mg, 0.21 mmol), following the general method. The crude camphanamide was

purified by preparative tlc (silica gel-ether-hexane, 1:1) to give 'Mosher' amide (75) as a colourless oil (58 mg, 75%).

TLC: Rf 0.21 (silica gel-ether-hexane, 1:1).

^{1}H NMR δ($CDC\ell_3$) 200 MHz: 0.82 (3H, d, J=7.5 Hz), 0.86 (3H, d, J=7.5 Hz), 1.82 (1H, septet, J=7.5 Hz), 2.68 (2H, d, J= 5 Hz), 3.44 (3H, q, $^5J(^1H-^{19}F)$=1.25 Hz), 3.67 (3H, s), 4.08 (1H, m), 7.36 (5H, m).

^{19}F NMR δ($CDC\ell_3$): -69.31 (broad s).

$[M^+ - OCH_3]^+$ 330.1320; $C_{16}H_{19}NO_3F_3$ requires 329.1317.

N-(R)-α-Methylbenzyl-3-(4'-methoxy)phenyl-5-acetoxyisoxazolidine (76)

R-(-)-C-(p-Methoxy)phenyl-N-α-methylbenzylnitrone (2.30g, 8.9 mmol) was dissolved in vinyl acetate (100 ml, 1.09 mol) and refluxed with the exclusion of light under an argon atmosphere for 120h. After removal of excess vinyl acetate in vacuo, the residue was purified by flash column chromatography (ether-hexane, 1:1), to give isoxazolidine (76) (1.84g, 60%) as a light yellow oil.

TLC: Rf 0.58 (silica gel-ether-hexane, 1:1).

IR ν_{max} ($CHC\ell_3$): 1735, 1698, 1686, 1682, 1615, 1600, 1515, 1378, 1305, 1250, 1162, 1035, 985 cm^{-1}.

^{1}H NMR δ($CDC\ell_3$) 200 MHz: 1.53 (1.54H, d, J=6.5 Hz), 1.55 (1.46H, d, J=6.5 Hz), 2.08 (1.54H, s), 2.13 (1.46H, s), 2.41 (1H, m), 2.71-2.99 (1H, m), 3.50 (0.53H, t, J=9 Hz), 3.73-4.03 (1.47H, m), 3.75

(1.6H, s), 3.82 (1.4H, s), 6.32 (0.54H, ddd, J=1, 4 and 7 Hz), 6.38 (0.46H, ddd, J=0.2, 2 and 6.5 Hz), 6.71 (0.97H, d, J=9 Hz), 6.90 (0.97H, d, J=9 Hz), 7.08-7.38 (7.06H, m).

^{13}C NMR $\delta(CDC\ell_3)$, ^{1}H decoupled: 18.52, 20.99, 21.42, 21.46, 29.68, 46.07, 46.57, 55.20, 55.30, 62.37, 64.88, 65.30, 65.76, 94.66, 95.29, 113.61, 114.07, 127.10, 127.36, 127.97, 128.68, 129.01, 129.18, 130.61, 139.89, 141.60, 158.65, 159.26, 170.66, 170.75.

$[M]^+$ 341.1634; $C_{20}H_{23}NO_4$ requires 341.1627.

N-(R)-α-Methylbenzyl-3-(4'-methoxy)phenyl-5-hydroxyisoxazolidine (77)

Acetate (1.59g, 4.6 mmol) was hydrolysed with potassium carbonate (0.64g, 2.3 mmol) in methanol (50 ml) and water (5 ml), following the general procedure, to give crude lactol (77) (1.27g, 91%) as a yellow oil.

TLC: Rf 0.44 (silica gel-ether-hexane, 1:1).

IR ν_{max} ($CHC\ell_3$): 3580, 3200, 1601, 1505, 1260, 1175, 1165, 1035 cm^{-1}.

^{1}H NMR $\delta(CDC\ell_3)$: 1.49 (3H, m), 2.08-2.68 (2H, m), 3.42-4.40 (2H, m), 3.72 (1.68H, s), 3.80 (1.32H, s), 5.45-5.72 (1H, m), 6.50-7.68 (9H, m).

$[M]^+$ 299.1530; $C_{18}H_{21}NO_3$ requires 299.1528.

N-(R)-α-Methylbenzyl-3-(4'-methoxy)phenyl-5-trimethylsilyl-oxyisoxazolidine (78)

Trimethylsilyl ether (78) was prepared from lactol (77) according to the general procedure on page 144, and a solution of (78) (1 mg) in hexane (1 ml)-pyridine (0.5 μℓ) was employed for g.c. analysis.

GC: I_{155}^{Ov-1} = 2170, 2207 relative to $C_{19,20,22}$ standards.

N-(R)-α-Methylbenzyl-3-(4'-methoxy)phenylisoxazolidinone (79)[90]

A 100 ml, one-necked round bottomed flask equipped with a magnetic stirrer and drying tube was charged with dry acetone (50 ml), lactol (77) (1.2g, 4 mmol) and anhydrous N-methylmorpholine-N-oxide (0.93g, 8 mmol). To this solution, $RuC\ell_3 \cdot 3H_2O$ (2 mg, 0.08 mmol) was added, and the resulting gold coloured solution was stirred for 45 min at room temperature, after which time the reaction mixture became dark brown. The flask was attached to a rotary evaporator and most of the acetone was removed. The residue was transferred to a separatory funnel with the aid of several portions of $CH_2C\ell_2$ (100 ml total). The organic layer was washed with 2N HCℓ (2 x 50 ml) and water (1 x 100 ml), dried with anhydrous Na_2SO_4, filtered and evaporated to give a brown oil (0.93g), which was purified by flash column chromatography (hexane, hexane-ether (4:1), hexane-ether (1:1), ether), to give isoxazolidinone (79) as a pale yellow crystalline solid (0.23g, 19%).

^1H NMR δ($CDC\ell_3$): 1.50 (3H, d, J=6.5 Hz), 2.56-3.24 (2H, m), 3.70 (1.46H, s), 3.70-4.48 (2H, m), 3.77 (1.54H, s), 6.68-7.55 (9H, m).

Recrystallisation of this material from ether-hexane gave N-(R)-α-methylbenzyl-3(R)-(4'-methoxy)phenylisoxazolidin-5-one (79a) as a colourless crystalline solid, (97 mg), m.p. 127-128°C.

IR ν_{max} ($CHC\ell_3$): 1770, 1610, 1505, 1452, 1250, 1170, 1032 cm^{-1}.

^1H NMR δ($CDC\ell_3$) 200 MHz: 1.53 (3H, d, J=6.5 Hz), 2.83 (1H, dd, J=9, 17 Hz), 3.03 (1H, dd, J=9, 17 Hz), 3.77 (3H, s), 4.12 (1H, q, J=6.5 Hz), 4.42 (1H, dd, J=9, 17 Hz), 6.78 (2H, d, J=9 Hz), 7.15 (2H, d, J=9 Hz), 7.21 (5H, m).

^{13}C NMR δ($CDC\ell_3$), ^1H decoupled: 18.06, 39.15, 55.25, 65.57, 65.78, 114.05, 127.77, 128.23, 128.34, 130.28, 140.33, 159.32, 173.84.

$[M]^+$ 297.1397; $C_{18}H_{19}NO_3$ requires 297.1365.

[Found C 72.6, H 6.65, N 4.5; $C_{18}H_{19}NO_3$ requires C 72.7, H 6.45, N 4.7 %].

β-Tyrosine methyl ether (80)

Isoxazolidinone (79a), (90 mg, 0.3 mmol) was dissolved in dry ethanol (30 ml) containing palladium hydroxide on charcoal (10 mg; 20%) and hydrogenated at atmospheric pressure and 70°C for 4h. The solid amino acid separated during hydrogenolysis, and when hydrogen uptake was complete, distilled water (100 ml) was added to dissolve the amino acid. The catalyst was removed by filtration through a pad of Celite and was thoroughly washed with 100 ml warm distilled water. The combined filtrate was evaporated in vacuo to give β-tyrosine methyl ether

(53 mg, 90%) as a colourless crystalline solid, m.p. 241-244°C, $[\alpha]_D^{21}$ -7.2°, (c 1.0, H_2O).

[Found C 61.2, H 6.9, N 7.6; $C_{12}H_{13}NO_3$ requires C 61.5, H 6.7, N 7.2 %].

'Mosher' Amide (81)[69]

From β-tyrosine methyl ether (13.2 mg, 0.054 mmol) and (+)-α-methoxy-α-trifluoromethylphenylacetyl chloride (13.7 mg, 0.054 mmol), following the general method, to give crude 'Mosher' amide (81) as a light brown oil, (19.3 mg, 86%). (For gc results see Table 7, p 100).

^1H NMR δ($CDC\ell_3$) 200 MHz: 2.83 (1H, dd, J=6, 16 Hz), 2.94 (1H, dd, J=6, 16 Hz), 3.43 (3H, q, J (^{19}F- ^1H) = 1.5 Hz), 3.62 (3H, s), 3.76 (3H, s), 5.37 and 5.43 (1H, AB quartet, J=6 Hz), 6.82 (2H, d, J=8.5 Hz), 7.12 (2H, d, J=8.5 Hz), 7.31-7.68 (5H, m).

^{19}F NMR δ($CDC\ell_3$): -69.35 (broad s).

$[M]^+$ 425.1467; $C_{21}H_{22}NO_5F_3$ requires 425.1450.

Attempted cycloaddition of C-indolyl nitrone (24) to vinyl acetate

C-Indolyl nitrone (24) (1.3g, 5.2 mmol) was dissolved in excess vinyl acetate (50 ml, 0.62 mol) and refluxed with the exclusion of light under an argon atmosphere for 120h. Excess vinyl acetate was removed in vacuo and the residue purified by flash column chromatography

to give the N-acetyl nitrone (83) (1.21g, 76%), as a colourless crystalline solid, m.p. 163°C.

TLC: Rf 0.51 (silica gel-ether).

IR ν_{max} ($CHC\ell_3$): 1705, 1535, 1452, 1378, 1328, 1150 cm^{-1}.

^1H NMR δ($CDC\ell_3$): 1.92 (3H, d, J=6.5 Hz), 2.62 (3H, s), 5.26 (1H, q, J=6.5 Hz), 7.22-7.60 (8H, m), 7.82 (1H, s), 8.48 (1H, m), 9.24 (1H, s).

$[M]^+$ 306.1377; $C_{19}H_{18}N_2O_2$ requires 306.1368.

1,3-Dipolar Cycloadditions of Nitrones to Ketene Acetals

Ethyl orthobromoacetate (90)

To a stirred solution of triethyl orthoacetate (20.2g, 0.12 mol) and pyridine (10.4g, 0.14 mol), was added bromine (20.0g, 0.25 mol) dropwise over a period of 30 min. The reaction was kept at 10°C (waterbath) during the addition. The initially darkened reaction mixture changed to a pale yellow after stirring for 3h at 10°C. The brominated ester was then filtered from the precipitated pyridine hydrobromide which was washed thoroughly by triturating it several times with anhydrous ether. These washings were combined with the bromoester and the solvent was then removed under a stream of nitrogen. The crude product was distilled in vacuo to give the monobromo-orthoacetate (90) as a colourless liquid, b.p. = 92-96°C at > 10 mm Hg, (21.6g, 72%). (Lit[74] b.p. 77-79°C at 9 mm).

^{1}H NMR $\delta(CDC\ell_3)$: 1.26 (9H, t, J=8 Hz), 3.55 (2H, s), 3.65 (6H, q, J=8 Hz).

Ketene diethylacetal (84)

To a stirred suspension of powdered sodium (1.86g, 0.08 atom) in anhydrous benzene (100 ml), heated under gentle reflux, was added dropwise ethyl orthobromoacetate (10g, 0.04 mol) over a period of 40 min. After the first few drops of ester had been added the reaction mixture turned a characteristic deep blue. The reaction mixture was stirred for an additional two hours with continued refluxing. The clear supernatant

liquid was then decanted from the precipitated blue sodium salts, and the salts thoroughly washed by several triturations with anhydrous benzene. These washings were combined with the filtrate, and the benzene removed at atmospheric pressure with the heating bath temperature not exceeding 120°C. The remaining material was distilled, the main fraction being collected between 56-60°C at 95 mm Hg to give ketene acetal (84) (2.02g, 43%) as a colourless liquid. (Lit[75] b.p. 68°C at 100 mm Hg). The acetal was kept at 0°C, in a flask dusted with potassium tert-butoxide.

^{1}H NMR $\delta(CDC\ell_3)$: 1.32 (6H, t, J=7 Hz), 3.01 (2H, s), 3.85 (4H, q, J=7 Hz).

The ^{1}H nmr spectrum also contained additional signals, as follows, accounting for approximately 15% of the sample: 3.55 (q, J=6 Hz) and a multiplet overlapping with the acetal methyl signal at δ1.46-1.20.

Powdered sodium[91] was prepared by melting sodium metal (1.95g) in xylene (100 ml, distilled from sodium) at approximately 140°C (oil bath temp.), with vigorous stirring, in a 250 ml conical flask, equipped with a large magnetic stirring bar. The stirring bar was removed quickly at 130°C, the flask removed from the oil bath and then shaken vigorously until the solution had cooled to approximately 40-50°C. The sodium became a dull grey powder. The majority of the xylene was removed by decanting, and the sodium then triturated several times with anhydrous benzene, before use.

N-Phenyl-3-phenyl-5,5-diethoxyisoxazolidine, (91)[72,73]

C,N-Diphenylnitrone (0.19g, 1 mmol) and ketene acetal (84) (0.45g, 3.88 mmol) were heated together in anhydrous toluene (5 ml) at 100°C for 19h. The solvent and excess ketene acetal were removed by evaporation at the oil pump (1 mm Hg) and the residue purified by column chromatography over basic alumina grade 3 (ether-hexane, 1:4) to give isoxazolidine (91) as a colourless oil (0.24g, 78%).

TLC: Rf 0.88 (silica gel-ether-hexane, 1:1).

^{1}H NMR $\delta(CDC\ell_3)$: 1.07 (3H, t, J=7 Hz), 1.28 (3H, t, J=7 Hz), 2.53 (1H, dd, J=10, 12 Hz), 2.83 (1H, dd, J=7.6, 10 Hz), 3.74 (4H, m), 4.55 (1H, dd, J=7.6, 10 Hz), 6.88-7.56 (10H, m).

^{13}C NMR $\delta(CDC\ell_3)$, ^{1}H decoupled: 15.26, 15.87, 45.99, 54.97, 59.67, 60.75, 69.75, 117.72, 120.83, 121.81, 125.51, 126.22, 126.33, 126.73, 140.96, 151.14.

$[M]^+$ 313.1676; $C_{19}H_{23}NO_3$ requires 313.1678.

Alternatively, isoxazolidine (91) was prepared by heating C,N-diphenylnitrone (0.2g, 1.1 mmol) and ketene acetal (84) (0.15g, 1.3 mmol) in a sealed tube at 125°C for 2h. The crude product was purified by column chromatography as described above to give (91) (0.21g, 67%) as a colourless oil. This was identical (tlc, nmr) with the material prepared above.

Phthalyl alcohol (96)

Phthalic anhydride (16.8g, 0.11 mol) was placed in the thimble of a Soxhlet extractor. This was then attached to a one-litre three-necked flask containing lithium aluminium hydride (5g, 0.13 mol) in sodium-dried ether (500 ml) and the ether refluxed until extraction of the phthalic anhydride was complete (approximately 12h). The Soxhlet extractor was then replaced by a condenser and water was added dropwise to destroy excess hydride. When effervescence had stopped, the mixture was transferred to a continuous ether extractor containing additional ether (500 ml) and extracted for 24h. Upon evaporation of the ether a light yellow residue remained, which was triturated with several portions of petroleum ether, 40-60°C, to give alcohol (96) as a white solid (10.1g, 63%), m.p. 65-67°C. (Lit[76] m.p. 64°C).

^{1}H NMR δ($CDC\ell_3$): 4.20 (2H, s, exchangeable in D_2O), 4.70 (4H, s), 7.35 (4H, s).

Bromoacetaldehyde (o-xylyl)acetal (98)

Phthalyl alcohol (10g, 0.97 mol) and bromoacetaldehyde diethylacetal (14g, 0.07 mol) were stirred together in a 100 ml round-bottomed flask in the presence of toluene-p-sulphonic acid (0.05g, 0.3 mmol). The reaction was set up for distillation, and heated at an oil bath temperature of 110-120°C. As the ethanol produced by acetal exchange began to distil, a slight vacuum was applied. After 90 min, the calculated amount of ethanol (4 ml) had been collected. On cooling

the residue solidified to a dark red-brown material, which was dissolved in benzene (150 ml) and washed with sat. $NaHCO_3$ (1 x 100 ml). The benzene layer was dried with anhydrous $MgSO_4$, filtered and evaporated in vacuo. The crude product was recrystallised from cyclohexane to give acetal (98) as a pale orange crystalline material, (10.1g, 86%) m.p. 96-97°C). (Lit[77] m.p. 98°C).

(o-Xylyl)ketene acetal (85)

Bromoacetaldehyde-(o-xylyl)acetal (8.97g, 0.04 mol) was heated with potassium tert-butoxide (5.60g, 0.05 mol) in anhydrous benzene (100 ml) at 80°C for 5h. Potassium bromide formed in the reaction was removed by filtration through a pad of Celite, and the solvent removed from the filtrate in vacuo. The residue was purified by Kugelrohr distillation (0.2 mm Hg) to give ketene acetal (85) (5.3g, 91%) as a colourless crystalline solid, b.p. 140-143°C at 0.2 mm Hg, m.p. 46-47°C (Lit[77] m.p. 49°C).

^1H NMR $\delta(CDC\ell_3)$: 2.71 (2H, s), 5.31 (4H, s), 6.90-7.25 (4H, m).

General Procedure for the Synthesis of Isoxazolidinone (o-Xylyl) Acetals

The appropriate nitrone (1 eq) and (o-xylyl) ketene acetal (1.5 eq) were dissolved in anhydrous toluene and refluxed together for the specified period of time. Excess solvent was evaporated at the oil pump and the pure isoxazolidinone acetal obtained from the residue by flash column chromatography (ether-hexane, 4:1) over silica gel.

N-Phenyl-3-phenyl-5,5-(di-o-xylyloxy)isoxazolidine (99)

From C,N-diphenylnitrone (1.22g, 6.2 mmol) and ketene acetal (85) (1.10g, 6.8 mmol) in toluene (50 ml), refluxed for 48h, to give the isoxazolidine (99) (1.29g, 53%) as a colourless crystalline solid, m.p. 127°C from ether.

TLC: Rf 0.78 (silica gel-ether-hexane, 1:1).

IR ν_{max} ($CHC\ell_3$): 1598, 1496, 1450, 1315, 1298, 1275, 1258, 1095 cm^{-1}.

^1H NMR δ($CDC\ell_3$): 2.65 (1H, dd, J=9, 13 Hz), 3.02 (1H, dd, J=6, 13 Hz), 4.62-4.95 (3H, m), 5.28 (2H, d, J=14 Hz), 6.94-7.62 (14H, m).

$[M]^+$ 359.1509; $C_{23}H_{21}NO_3$ requires 359.1521.

[Found C 76.9, H 5.85, N 3.9; $C_{23}H_{21}NO_3$ requires C 76.9, H 5.9, N 3.9 %].

N-(R)-α-Methylbenzyl-3-phenyl-5,5-(di-o-xylyloxy)isoxazolidine (101)

From N-(R)-(-)-α-methylbenzyl-C-phenyl nitrone (0.50g, 2.4 mmol) and ketene acetal (83) in toluene (25 ml), refluxed for 60h, to give the isoxazolidine (101)(0.11g, 12%) as a colourless oil.

TLC: Rf 0.81 (silica gel-ether-hexane, 1:1).

IR ν_{max} ($CHC\ell_3$): 1605, 1495, 1380, 1312, 1300, 1275, 1265, 1215, 1170, 1100, 1038 cm^{-1}.

^1H NMR δ($CDC\ell_3$) 200 MHz: 1.38 (0.59H, d, J=6.5 Hz), 1.56 (2.41H, d,

J=6.5 Hz), 2.52 (0.21H, m), 2.60 (0.79H, dd, J=7.5 12.5 Hz), 2.88 (0.18H, dd, J=7.5, 12.5 Hz), 2.95 (0.82H, dd, J=7.5, 12 Hz), 3.96 (0.21H, q, J=6.5 Hz), 4.18 (0.79H, q, J=6.5 Hz), 4.32 (1H, t, J=7.5 Hz). 4.62-5.28 (4H, m), 6.98-7.56 (10H, m).

^{13}C NMR $\delta(CDC\ell_3)$, ^{1}H decoupled: 20.16, 21.36, 45.46, 47.35, 64.28, 65.96, 66.13, 66.31, 66,86, 67.17, 67.31, 67.42, 120.87, 123.49, 126.19, 126.44, 126.78, 126.87, 126.97, 127.01, 127.19, 127.27, 127.39, 127.80, 127.89, 128.11, 128.18, 128.41, 128.59, 128.93, 137.08, 137.18, 137.28, 140.79, 141.27, 142.27.

$[M]^+$ 387.1834; $C_{25}H_{25}NO_3$ requires 387.1834.

GC: t_R 5.60, 5.98 mins, $[M]^+$ 387.

N-(R)-α-Methylbenzyl-3-(4'-chloro)phenyl-5,5-(di-o-xylyloxy)-isoxazolidine (103)

From R-(-)-C-p-chlorophenyl-N-α-methylbenzylnitrone (0.5g, 1.9 mmol) and ketene acetal (83) (0.37g, 2.3 mmol) in toluene (25 ml), refluxed for 48h, to give isoxazolidine (103) (0.23g, 28%) as a light brown oil.

TLC: Rf 0.52 (silica gel-ether-hexane, 1:1).

IR γ_{max} $(CHC\ell_3)$: 1730, 1595, 1488, 1452, 1380, 1372, 1305, 1150, 1088, 1075, 1030, 1012 cm^{-1}.

^{1}H NMR $\delta(CDC\ell_3)$: 1.54 (0.65H, d, J=6 Hz), 1.72 (2.35H, d, J=6 Hz),

2.58-3.24 (2H, m), 4.09-4.52 (2H, m), 4.85-5.46 (4H, m), 7.05-7.98 (9H, m).

$[M]^+$ 421.1455; $C_{25}H_{24}NO_3C\ell$ requires 421.1445.

GC: t_R = 6.35 mins, $[M^+]$ 421.1455.

N-(R)-α-Methylbenzyl-3-isopropyl-5,5-(di-o-xylyloxy)-isoxazolidine (100)

From R-(-)-C-isopropyl-N-α-methylbenzylnitrone (0.5g, 2.6 mmol) and ketene acetal (85) (0.65g, 4.0 mmol), in toluene (25 ml), refluxed for 48h. The crude product was purified by flash column chromatography (ether-hexane, 4:1) to give a fraction containing mostly isoxazolidine (100) (53 mg, 6%) as a colourless oil. Unfortunately compound (100) decomposed during chromatography and could not be fully characterised.

^1H NMR $\delta(CDC\ell_3)$: 0.72 (3H, d, J=8 Hz), 0.78 (3H, d, J=8 Hz), 1.42 (1.28H, d, J=6.5 Hz), 1.54 (1.72H, d, J=6.5 Hz), 2.25-2.98 (3H, m), 4.24 (1H, m), 4.61-5.40 (4H, m), 6.95-7.50 (9H, m).

Phthalyl methyl ester (104)

IR ν_{max} $(CHC\ell_3)$: 3600, 1732, 1380, 1360, 1240, 1025, 1005, 908 cm^{-1}.

^1H NMR $\delta(CDC\ell_3)$: 2.05 (3H, s), 2.60 (1H, broad s, exchangeable in D_2O) 4.72 (2H,s), 5.22 (2H, s), 7.35 (4H, m).

$[M-OH]^+$ = 163.

Synthesis of Isoxazolidin-5-ones

Ethyl isobutyroacetate (114)

Ethyl α-bromoacetate (13.5 ml, 0.054 mol) was dissolved in 50 ml dry benzene and added dropwise to a refluxing solution of dry benzene (100 ml) containing isobutyronitrile (8.8 ml, 0.17 mol), acid-washed zinc wool (9.75g, 0.15 atom), and a trace of mercuric chloride. After addition of the bromoester was complete, heating was continued for 90 mins accompanied by vigorous stirring. On cooling, 2N H_2SO_4 (175 ml) was added dropwise and stirring was continued for 2h after the addition was complete. After this time, the organic and aqueous layers were separated, and the aqueous layer extracted with benzene (4 x 100 ml). The combined benzene layers were dried with anhydrous $MgSO_4$, filtered and evaporated to give a light brown liquid which was distilled *in vacuo* to give ethyl isobutyroacetate (5.93g, 69%) as a colourless liquid, b.p. 107-108°C at 20 mm Hg, (Lit[83] b.p. = 176°C at 760 mm Hg).

^{1}H NMR δ($CDC\ell_3$): 1.05 (6H, d, J=7 Hz), 1.22 (3H, t, J=8 Hz), 2.66 (1H, septet, J=7 Hz), 3.32 (2H, s), 4.14 (2H, q, J=8 Hz).

General Procedure for Δ^3-Isoxazolidin-5-ones (115) and (116)[82]

β-Keto ester (2.5 eq) and N-methylhydroxylamine hydrochloride were dissolved in anhydrous pyridine and heated at 100°C for 8h. Evaporation *in vacuo* gave a residue which was treated with saturated K_2CO_3 aq. until slightly alkaline, and then washed with ether. The

combined ether washings were dried with anhydrous $MgSO_4$, filtered and evaporated. The residue was purified by preparative t.l.c., (chloroform-methanol, 20:1) to give pure Δ^3-isoxazolidin-5-one.

N-Methyl-3-methyl-Δ^3-isoxazolidin-5-one (115)[81,82]

From ethyl acetoacetate (3.90g, 0.03 mol) and N-methylhydroxylamine (1.0g, 0.012 mol) to give isoxazolidinone (115) (0.91g, 58%), as a colourless oil. (Lit[82] m.p. = 41-42°C, from ligroin).

TLC: Rf 0.71 (silica gel-chloroform-methanol, 20:1).

IR ν_{max} ($CHC\ell_3$): 3420, 1730, 1585, 1400, 1170, 900 cm^{-1}.

^1H NMR δ($CDC\ell_3$): 2.15 (3H, s), 3.31 (3H, s), 4.98 (1H, s). $[M]^+$ 113.

N-Methyl-3-isopropyl-Δ^3-isoxazolidin-5-one (116)

From ethyl isobutyroacetate (1.25g, 8 mmol) and N-methylhydroxylamine (0.27g, 3.2 mmol) to give isoxazolidinone (116) (0.46g, 54%) as a colourless oil, (0.46g, 54%).

TLC: Rf 0.77 (silica gel-chloroform-methanol, 20:1).

IR ν_{max} ($CHC\ell_3$): 3698, 3470, 1730, 1600, 1570, 1305, 1072, 905 cm^{-1}.

^1H NMR δ($CDC\ell_3$): 1.26 (6H, d, J=7 Hz), 2.68 (1H, septet, J=7 Hz), 3.12 (3H, s), 4.98 (1H, s).

$[M]^+$ 141.0793; $C_7H_{11}NO_2$ requires 141.0790.

Attempted Synthesis of N-(R)-α-methylbenzyl-3-methyl-Δ^3-isoxazolidin-5-one (118)

(R)-(+)-α-Methylbenzylhydroxylamine (2.0g, 15 mmol) and ethyl acetoacetate (4.75g, 36 mmol) were heated together in pyridine (20 ml) at 100°C for 48h. Excess pyridine was removed at the oil pump and the residue purified by flash column chromatography (chloroform-methanol, 20:1) to give a colourless oil identified as ethyl (Z)-3-(N-hydroxy-N-(R)-α-methylbenzyl)aminobutanoate (117), (2.65g, 73%).

TLC: Rf 0.63 (silica gel-chloroform-methanol, 20:1).

IR ν_{max} ($CHC\ell_3$): 3580, 3180, 1730, 1670, 1580, 1500, 1494, 1452, 1370, 1300, 1185, 1160 cm^{-1}.

^1H NMR δ($CDC\ell_3$): 1.14 (3H, t, J=7 Hz), 1.55 (3H, d, J=6.5 Hz), 2.08 (1.64H, s), 2.12 (1.36H, s), 3.5 (1H, s), 4.10 (3H, q, J=7 Hz), 5.40 (1H, m), 7.28 (5H, m).

$[M]^+$ 249.1365; $C_{14}H_{19}NO_3$ requires 249.1380.

Attempted Cyclisation of (117) with Potassium ^{t}-Butoxide

3-(N-hydroxylamino)butanoate (117) (0.96g, 3.85 mmol) was dissolved in benzene (50 ml) containing potassium t-butoxide (0.90g, 8.0 mmol) and refluxed for 24h under an argon atmosphere. The reaction was then washed with 1N $HC\ell$ (1 x 50 ml) and water (1 x 50 ml). The benzene layer was dried with anhydrous $MgSO_4$, filtered and evaporated in vacuo to give a crude oily residue (0.71g) which was shown to be starting material (117) by ^1H nmr and t.l.c.

Attempted Cyclisation of (117) with LDA

A two-necked 50 ml round-bottomed flask flushed with argon was charged with n-butyl lithium (1.22 ml, 4 mmol of a 3.3M solution of BuLi in n-hexane) at 0°C. Di-isopropylamine (0.56 ml, 4 mmol) was added dropwise with stirring at 0°C. When addition of amine was complete, n-hexane was removed in vacuo from the resulting gel to give lithium di-isopropylamide as a white crusty solid. The flask was then reflushed with argon and the LDA dissolved in sodium-dried THF (10 ml) and cooled to -78°C. To this solution was added dropwise 3-(N-hydroxylamino)butanoate (117) (0.5g, 2 mmol) in THF (10 ml). The reaction was stirred at -78°C for 5h and then left to warm to room temperature over a period of 12h. The reaction was added to pentane (100 ml) and washed with brine (1 x 100 ml) and water (1 x 100 ml). The organic layer was dried with anhydrous $MgSO_4$, filtered and evaporated in vacuo to give an oil (0.34g) which was shown by ^1H nmr and t.l.c. to be the starting material (117).

4-Methylpent-2-enoic acid (121)

Isobutyraldehyde (25.6g, 0.2 mol) was added to a solution of malonic acid (20.8g, 0.2 mol) in anhydrous pyridine (44 ml) and piperidine (1.8 ml). The resultant solution was heated until evolution of carbon dioxide ceased (approximately 5h), and then heated at 100°C for a further 1h. The solution was then added to H_2SO_4 (75 ml, 50%) and extracted with ether (4 x 75 ml). The combined organic extracts were washed with 2N H_2SO_4 (100 ml), dried with anhydrous Na_2SO_4, filtered

and evaporated. The residue was distilled to give acid (121) (30.4g, 75%) as a colourless oil, b.p. 96-98°C, > 1 mm Hg. (Lit[85] b.p. 83-85°C at 5 mm Hg).

^{1}H NMR δ($CDC\ell_3$): 1.26 (6H, d, J=7 Hz), 2.68 (1H, m), 6.95 (1H, dd, J=1.8, 16 Hz), 7.25 (1H, dd, J=6.5, 16 Hz), 9.50 (1H, broad, s, exchangeable in D_2O).

Methyl 4-methylpent-2-enoate (123)

Acid (121) (10g, 0.087 mmol) was dissolved in methanol (125 ml) and carbon tetrachloride (125 ml) containing toluene-p-sulphonic acid monohydrate (2g, 0.01 mol), and the resulting solution heated at reflux in a Dean-Stark apparatus for 12h. After this time, the solvent was evaporated under vacuum and the residue dissolved in ether (250 ml), which was then washed with saturated $NaHCO_3$ (1 x 250 ml) and water (1 x 250 ml). The ether layer was dried with anhydrous $MgSO_4$, filtered and evaporated to give a yellow liquid which was distilled to give methyl ester (123) (10.48g, 93%), b.p. 95°C, 12 mm Hg.

^{1}H NMR δ($CDC\ell_3$): 1.04 (6H, d, J=7 Hz), 2.48 (1H, m), 3.72 (3H, s), 5.75 (1H, dd, J=1.8, 16 Hz), 6.94 (1H, dd, J=6.5, 16 Hz).

3-(4'-Methoxy)phenylpropen-2-oic acid (122)

p-Methoxybenzaldehyde (27.2g, 0.2 mol) was added to a solution of malonic acid (20.8g, 0.2 mol) in anhydrous pyridine (44 ml) and piperidine (1.8 ml). The resultant solution was heated until the evolution of

carbon dioxide ceased (approximately 5h), and then for an additional 1h at 100°C. The solution was added to H_2SO_4 (100 ml, 50%) and acid (122) was precipitated as a white solid. The acid was obtained by filtration and washed with water (100 ml). The solid was dried under vacuum for 48h to give acid (122) (30.57g, 86%) as a colourless crystalline material, m.p. 164-166°C. (Lit[86] m.p. 168°C).

Methyl 3-(4'-methoxy)phenylpropen-2-oate (124)

Acid (122) (10g, 0.056 mol) was dissolved in methanol (125 ml) and carbon tetrachloride (125 ml) containing toluene-p-sulphonic acid monohydrate (2g, 0.01 mol) and the resulting solution heated at reflux in a Dean-Stark apparatus for 12h. After this time solvent was evaporated under vacuum and the residue dissolved in ether (300 ml), which was then washed with saturated $NaHCO_3$ (1 x 250 ml) and water (1 x 250 ml). The ethereal layer was dried with anhydrous $MgSO_4$, filtered and evaporated to give a crude white solid which was recrystallised from ether-chloroform to give methyl ester (124) (10.06g, 94%) as a colourless crystalline solid, m.p. 90-92°C.

^1H NMR $\delta(CDC\ell_3)$: 4.18 (3H, s), 4.20 (3H, s), 6.56 (2H, d, J=8 Hz), 7.25 (2H, d, J=8 Hz), 7.32 (2H, d, J=8 Hz), 8.00 (2H, d, J=16 Hz).

General Procedure for the Synthesis of Isoxazolidin-5-ones (56), (79)

(R)-(+)-α-Methylbenzylhydroxylamine (1.0 eq) and the appropriate α,β-unsaturated ester (1.5 eq) were dissolved in dry benzene and heated at reflux for the specified time. The solvent was the removed

in vacuo and the crude product purified by flash column chromatography (hexane-ether used as eluent, gradually increasing the proportion of ether).

N-(R)-α-Methylbenzyl-3-phenylisoxazolidin-5-one (56)

From hydroxylamine (15), (1.0g, 7.3 mmol) and ethyl cinnamate (1.93g, 11 mmol) refluxed in benzene for 48h, to give isoxazolidinone (56) (1.14g, 59%), as a colourless crystalline solid, m.p. 97-98°C from hexane-ether. This material was identical with isoxazolidinone (56), p.155 prepared via nitrone cycloaddition.

IR ν_{max} ($CHC\ell_3$): 1775, 1498, 1458, 1415, 1380, 1278 cm^{-1}.

^1H NMR $\delta(CDC\ell_3)$ 200 MHz: 1.54 (3H, d, J=6.5 Hz), 2.85 (1H, dd, J=8, 17.5 Hz), 3.08 (1H, dd, J=8, 17.5 Hz), 4.14 (1H, q, J=6.5 Hz), 4.45 (1H, t, J=8 Hz), 7.21 (10H, m).

^{13}C NMR $\delta(CDC\ell_3)$, ^1H decoupled: 18.57, 39.11, 66.22, 125.96, 126.94, 127.44, 127.82, 127.89, 127.97, 128.36, 128.61, 128.81, 129.02, 129.07, 129.62, 130.16, 138.58, 140.07, 173.81.

[Found C 76.45, H 6.4, N 5.1; $C_{17}H_{17}NO_2$ requires C76.35, H 6.4, N 5.25 %, $[M]^+$ 267].

N-(R)-α-Methylbenzyl-3-(4'-Methoxy)phenylisoxazolidin-5-one (79)

From hydroxylamine (15) (1.0g, 7.3 mmol) and p-methoxyphenyl ester (124) (1.92g, 10.9 mmol) refluxed in benzene (30 ml) for 48h to give isoxazolidinone (79) (1.15g, 53%) as a colourless crystalline solid,

m.p. 128-131°C. This material was identical with the isoxazolidinone (79), p165 prepared via nitrone cycloaddition.

IR ν_{max} ($CHC\ell_3$): 1770, 1605, 1506, 1452, 1250, 1172, 1030 cm^{-1}.

^1H NMR δ($CDC\ell_3$): 1.48 (3H, d, J=6.5 Hz), 2.54-3.15 (2H, m), 3.70 (1.45H, s), 3.70-4.58 (2H, m), 3.76 (1.55H, s), 6.68-7.40 (9H, m).

$[M]^+$ 297.1379; $C_{18}H_{19}NO_3$ requires 297.1365.

[Found C 72.9, H 6.25, N 4.55; $C_{18}H_{19}NO_3$ requires C 72.7, H 6.45, N 4.7 %].

N-(R)-α-Methylbenzyl-3-isopropylisoxazolidin-5-one (70)

Hydroxylamine (15) (0.85g, 6.2 mmol) and ester (123) were dissolved in ether (50 ml) and heated under reflux for 96h. The solvent was removed in vacuo and the residue purified by flash column chromatography (hexane-ether, 4:1), to give isoxazolidone (70) (0.96g, 67%) as a colourless oil. This material was identical with the isoxazolidone (70), p.160, prepared via nitrone cycloaddition.

TLC: Rf 0.65 (silica gel-ether-hexane, 1:1).

IR ν_{max} ($CHC\ell_3$): 1775, 1496, 1465, 1452, 1415, 1388, 1375, 1280, 1185 cm^{-1}.

^1H NMR δ($CDC\ell_3$): 0.80 (4.27H, m), 0.92 (1.73H, d, J=7 Hz), 1.55 (3H, m), 2.08-2.81 (2H, m), 3.18 (1H, m), 4.12 (1H, q, J=6.5 Hz), 7.32 (5H, s).

$[M]^+$ 233.1419; $C_{14}H_{19}NO_2$ requires 233.1416.

β-Phenyl-β-alanine (57)

The recrystallised isoxazolidinone (56) (0.14g, 0.52 mmol) from ethyl cinnamate was dissolved in dry ethanol (50 ml) containing palladium hydroxide on charcoal (12 mg, 20%) and hydrogenated at atmospheric pressure and 70°C for 5h. The reaction work-up was as described previously on p.156 , for the β-phenyl-β-alanine derived from nitrone-vinyl acetate cycloaddition. In this case β-phenyl-β-alanine (72 mg, 83%) was obtained as colourless crystals, m.p. 229-232°C, $[\alpha]_D^{23}$ + 0.3° (c 1.0, H_2O), (c.f. Lit[67] m.p. 236°C, $[\alpha]_D$ + 6.2° for (S)-β-phenyl-β-alanine).

β-Leucine (71)

Isoxazolidine (70) (0.17g, 0.73 mmol) from ester (123) was dissolved in methanol (60 ml) containing palladium hydroxide on charcoal (20%; 16 mg) and hydrogenated at atmospheric pressure and room temperature for 48h. The reaction work-up was as described previously on p.162 , for β-leucine derived from nitrone-vinyl acetate cycloaddition. In this case crude β-leucine (83 mg, 87%) was obtained as colourless crystals, m.p. 197-200°C, $[\alpha]_D^{20}$ -17.9° (c 1.0, H_2O) (c.f. Lit[67] m.p. 201-202°C, $[\alpha]_D^{22}$ +55.2° for (S)-β-leucine).

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