A THESIS ENTITLED

"THE ASYMMETRIC SYNTHESIS 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, Dad

and my wife Rachel.

Acknowledgements.

I would like to express my sincere thanks to my supervisor, Professor Karl Overton, for his help, encouragement and advice.

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SUMMARY.

SUMMARY

Whereas the asymmetric synthesis of α-amino acids has attracted considerable attention[2] in recent years, there have been relatively few published investigations into the asymmetric synthesis of β-amino acids.[38-41, 43-49]

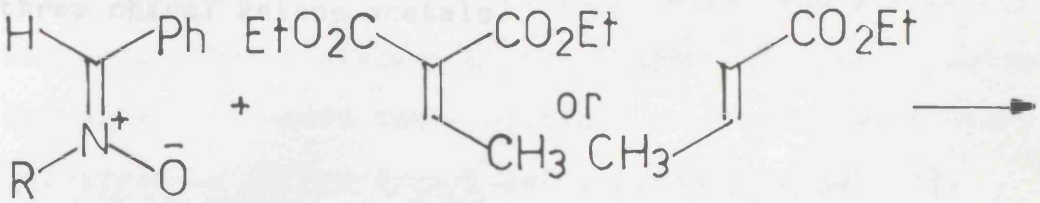
It was the aim of the work described in this thesis to devise an improved asymmetric synthesis of β-amino acids involving the construction of heterocyclic intermediates in a diastereoselective manner via the 1,3-dipolar cycloaddition reactions of chiral nitrones with suitably functionalised alkenes.

The Introduction reviews the natural occurrence of the more abundant β-amino acids, previous asymmetric syntheses of β-amino acids and the mechanism and stereochemistry of 1,3-dipolar cycloaddition reactions of nitrones.

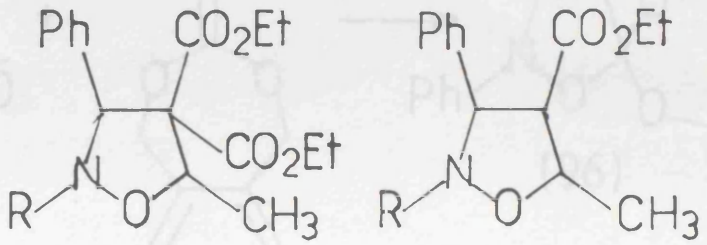
Chapter 1 describes the synthesis of the chiral and achiral nitrones used in the cycloaddition reactions described in this thesis.

Chapter 2 describes an investigation into an asymmetric synthesis of β-amino acids via, 1,3-dipolar cycloaddition reactions of nitrones with diethyl ethylidene - and methylidenemalonate. Nitrones (9), (10) and (28) have been shown to react regiospecifically with diethyl ethylidenemalonate and ethyl crotonate, while reactions between nitrones (9), (10) and (5) and diethyl methylidenemalonate afforded regioisomeric product mixtures.

The reaction between nitrone (6) and diethyl methylidenemalonate was also shown to proceed regiospecifically [Scheme I].



(9),(10),(28)

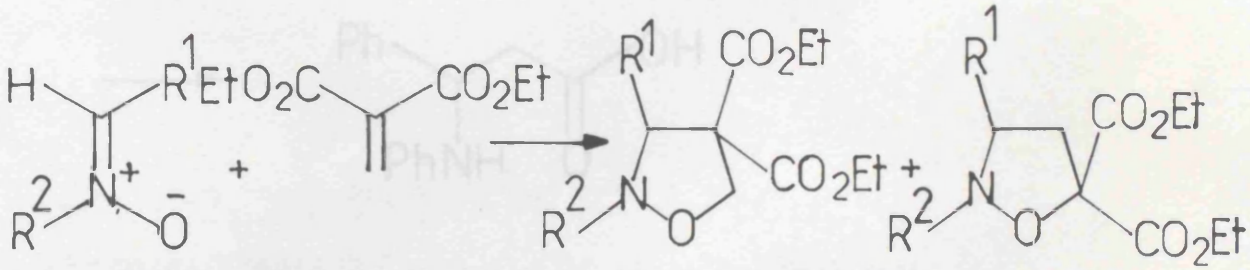


(78),(79),(80) or (69),(71),(72)

(9),(69),(78) R=Ph

(10),(79) (79) R=$PhCH_2$

(28),(72),(80) R=(R)-$PhCHCH_3$



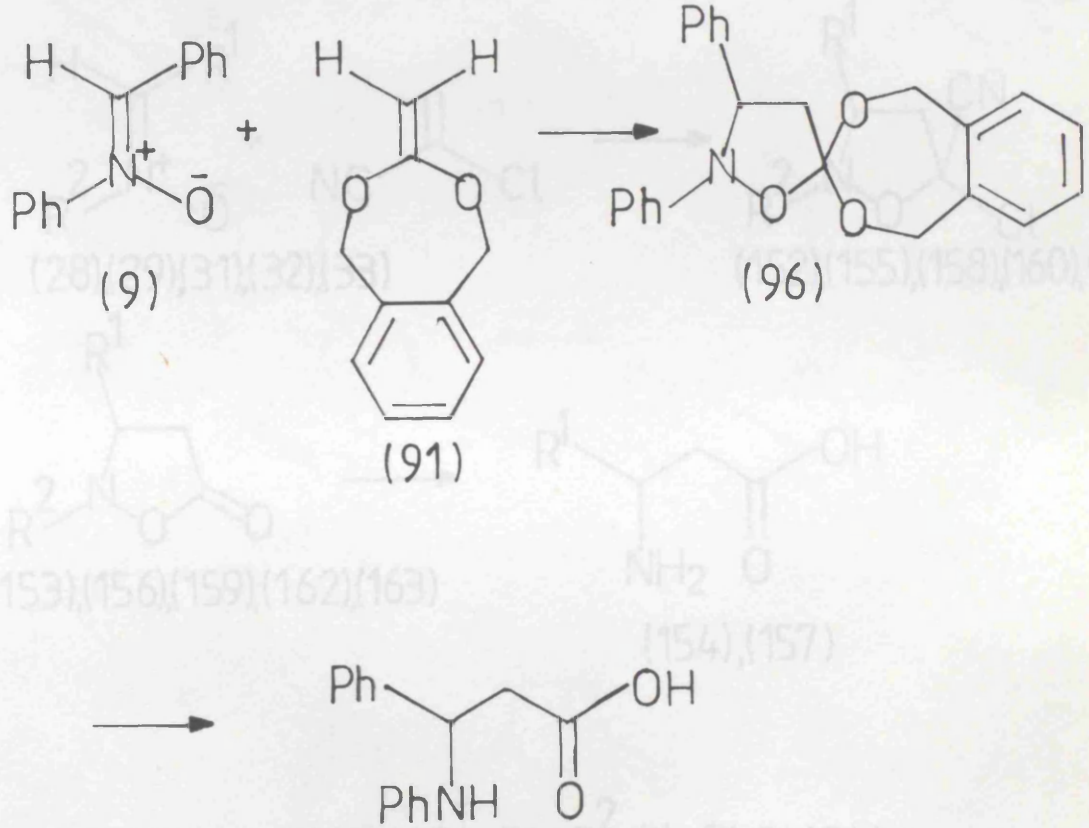
(5),(6),(9),(10) (42),(73),(74) (54),(75),(76),(77)

(5),(73),(75) R^1=Me, R^2=$PhCH_2$. (6),(76) R^1 = iPr, R^2=$PhCH_2$.

(9),(42),(54) R^1 = R^2=Ph. (10),(74),(77) R^1=Ph, R^2=$PhCH_2$.

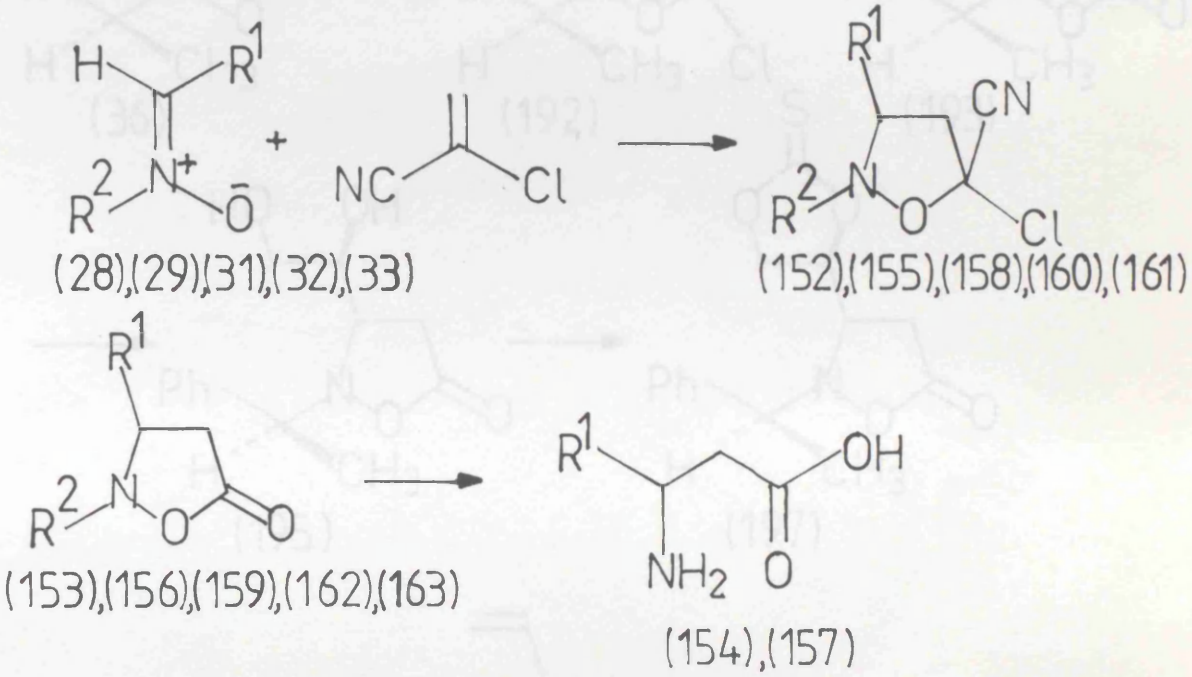
Scheme I.

Chapter 3 describes the non-asymmetric synthesis of N-phenyl-β-phenyl-β-alanine (97) via the cycloaddition of C,N-diphenylnitrone (9) with ketene acetal (91) and the subsequent hydrogenolysis of the adduct (96) thus formed [Scheme II]. Chapter 3 also describes the synthesis of three chiral ketene acetals.



Scheme II.

The asymmetric syntheses of β-phenyl-β-alanine (154), β-leucine (157) and isoxazolidinones (162,163) which may lead to β-tyrosine are described in Chapter 4. They depend upon the reaction of chiral nitrones with α-chloro-acrylonitrile to afford isoxazolidines in which the substituents have been placed in a regio- and stereoselective manner on the preriphery of the 5-membered ring. Subsequent hydrolysis afforded isoxazolidin-5-ones which were hydro-genolysed to afford free β-amino acids [Scheme III].



(28),(152),(153),(154) R^1 = Ph, R^2 = (R)-PhCHCH$_3$

(29),(160),(162) R = pMeO-Ph, R = (R)-PhCHCH$_3$

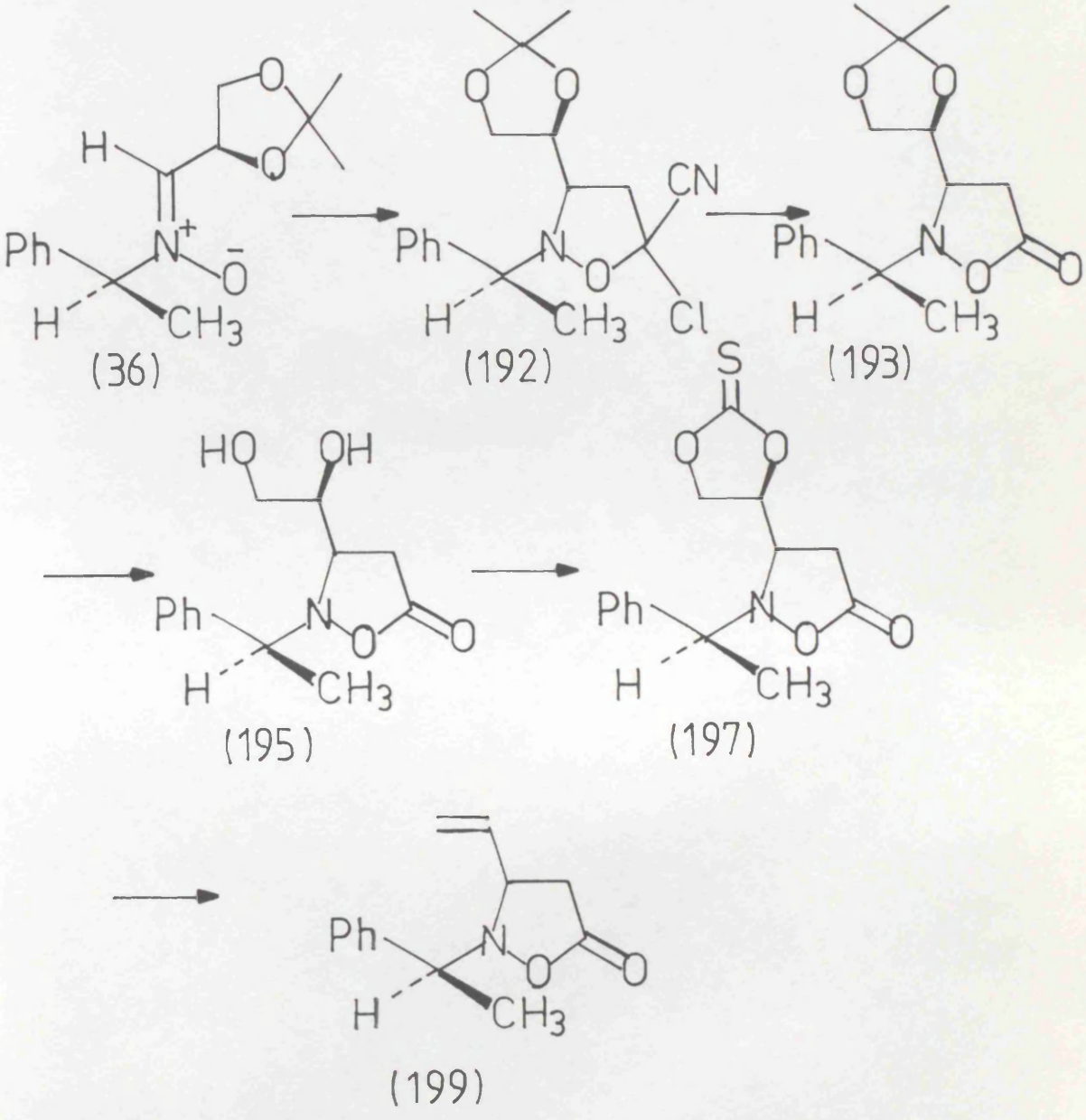
(31),(161),(163) R = pBzO-Ph, R = (R)-PhCHCH$_3$

(32),(155),(156),(157) R = iPr, R = (R)-PhCHCH$_3$

(33) (158) (159) R = iPr, R = (S)-PhCHCO$_2$CH$_3$

Scheme III

Chapter 5 describes an investigation towards an asymmetric synthesis of Thienamycin. Isoxazolidinone (193) was obtained as a single diastereomer and converted to olefin (199) via diol (195) and thionocarbonate (197) [Scheme IV].



Scheme IV.

INTRODUCTION

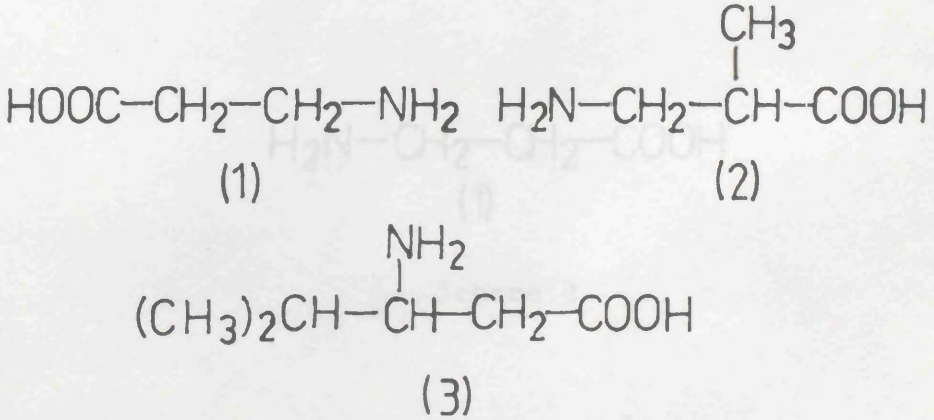
INTRODUCTION

1. Background

During the last decade asymmetric synthesis has become a major focus of activity, and many syntheses useful in the construction of optically pure natural products have been devised.[1] Although α-amino acids have been at the centre of many such investigations,[2] the asymmetric synthesis of β-amino acids has in comparison received little attention. β-Amino acids are of great current interest for several reasons, including their natural occurrences as components of biologically active antibiotics and their structural relationship to the β-lactams,[3] which are among the most biologically important functional groups. Also, β-amino acids are known to take part in several important primary metabolic pathways.[4,5]

2. The Natural Occurrence of β-Amino Acids.

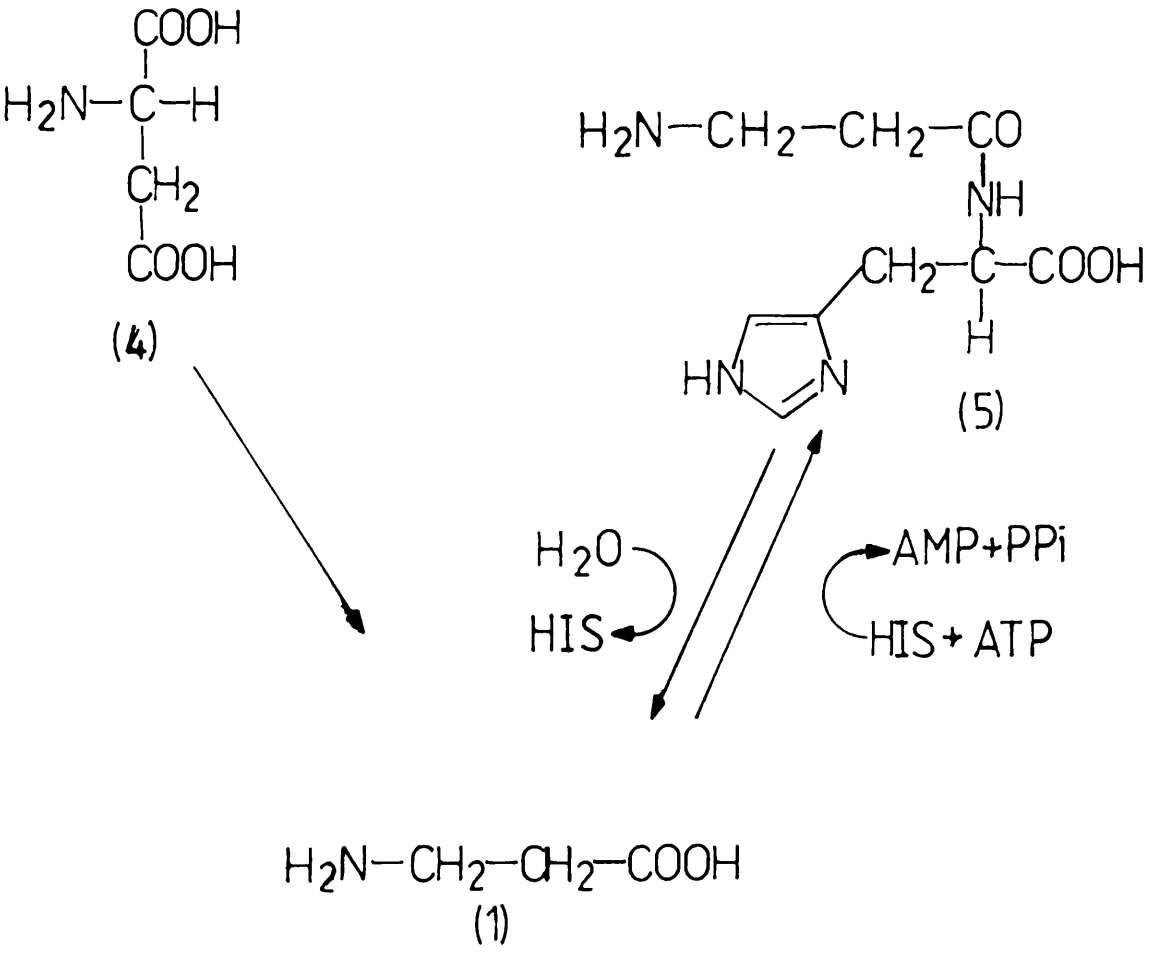
Only four β-amino acids have been shown to occur naturally in mammals, these being β-alanine (1), (R)- and (S)- β-aminoisobutyrate (2) and β-leucine (3).[5]



(1) (2)

(3)

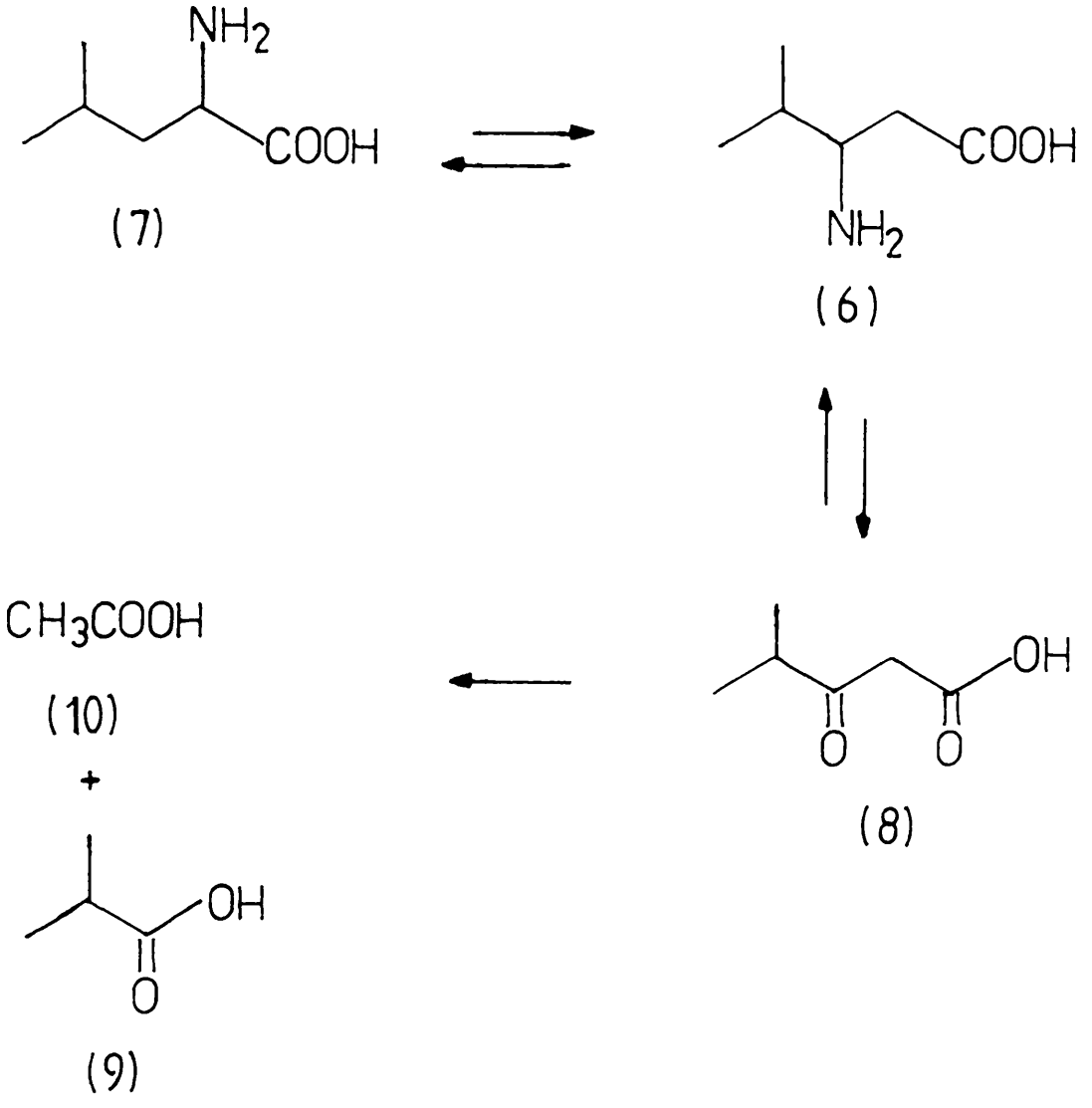
Occurrence of β-alanine, the simplest β-amino acid, as a microbial catabolite of aspartate (4) was reported as early as 1911.[6] Carnosine (5, β-alanylhistidine) which was identified in skeletal muscle in 1900,[7] represents a large endogenous store of β-alanine,[8,9] and although the physiological role of carnosine is not yet fully established, the dipeptide is known to affect muscle contraction[10] and has been implicated as a neurotransmitter,[11] [Scheme 1].



Scheme 1.

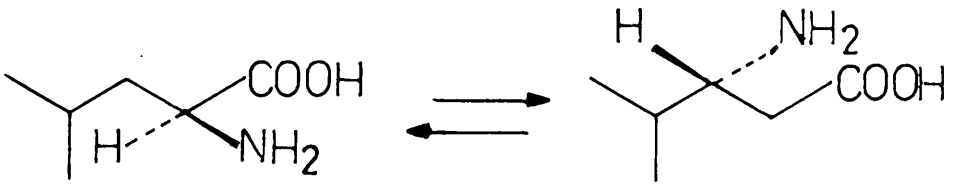
Both β-alanine and (R)-β-aminoisobutyrate were identified in the 1950's as catabolites of uracil-cytosine, and thymine respectively,[12,13] whereas (S)-β-aminoisobutyrate was shown to be a catabolite of valine.[14]

The natural occurrence of β-leucine (6) was first demonstrated by Poston in 1976,[15] who reported that extracts of Clostridia, of several mammalian tissues such as rat livers and human leukocytes, and of plants,[16] such as potatoe tubers and rye grass, catalyse the interconversion of α- to β-leucine, β-leucine being further catabolised to isobutyrate (9) and acetate (10) via β-ketoisocaproate (8). The amino group migration is catalysed by the enzyme leucine-2,3-amino mutase, is reversible and in each of the above cases it is claimed that the enzyme activity is co-enzyme B_{12} dependent.[15,16] The β-amino acid is then transaminated to β-ketoisocaproate (8) before breakdown to acetate and isobutyrate, [Scheme 2].



Scheme 2.

However, Overton[17] has reported that leucine-2,3-amino mutase activity in tissue cultures of Andrographis paniculata does not show a coenzyme B_{12} dependence, in contrast to the results of Poston, and has established that the metabolically active substances are (2S)-α-leucine (7a) and (3R)-β-leucine (6a) [Scheme 3].

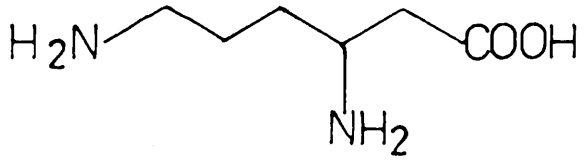


(7a) (6a)

Scheme 3.

The configuration of the β-leucine produced in mammals has not yet been established. Subsequent studies suggest that β-leucine may be formed *in vivo* from L-leucine, L-valine and terminally branched fatty acids.[5]

Among the non-mammalian β-amino acids, β-lysine (11) is by far the most extensively studied and has been identified as a constituent of numerous antibiotics. In 1952 Haskell[18] isolated a basic amino acid from the acid hydrosylate of viomycin (12), a tuberculostatic antibiotic from *Streptomyces floridae*. The new amino acid was found to be isomeric with lysine and was identical with an acid previously isolated from streptothricin hydrosylates by Carter and his associates.[19] The streptothricins (racemycins) form an homologous series of broad spectrum antibiotics produced by the *Streptomyces* species and can have up to seven β-lysine residue linked in a peptide chain.[20]



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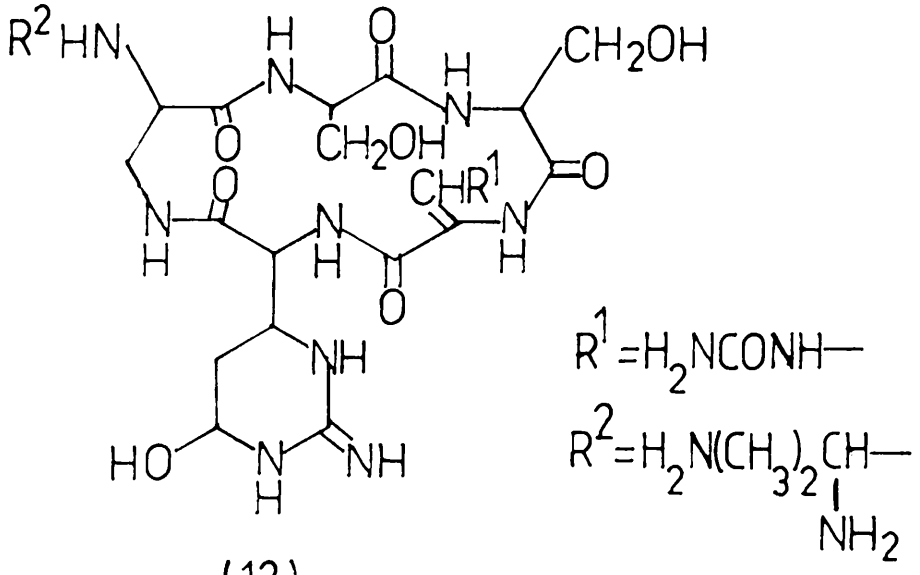

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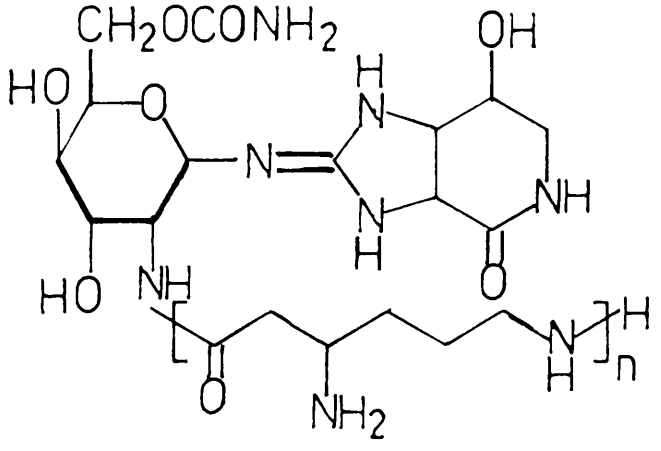
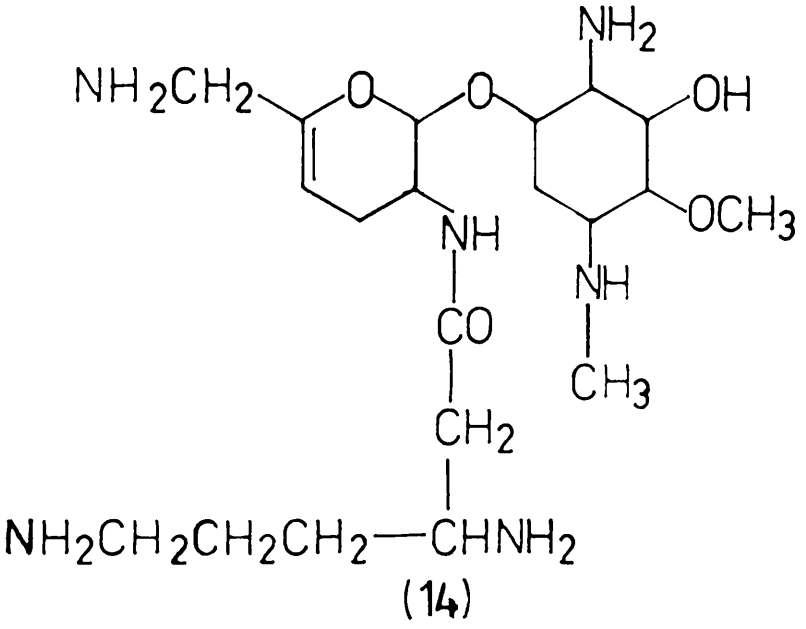


(13)

n = 1, 2, 3, 4, 5, 6 and 7 for Streptothricins FEDCBA and X.

The structure of this amino acid was confirmed by Van Tamelen[21] who synthesised (S)-β-lysine (11) by Arndt-Eisert homologation of L-ornithine, and it has since been shown by ORD that the natural form of β-lysine has the (S)-configuration.[22]

β-Lysine has been found as a constituent of several other antibiotics including myomycin,[23] roseothricin,[24] geomycin,[25] tuberactinomycin[26] and more recently as a constituent of lysinomicin[27] (14).

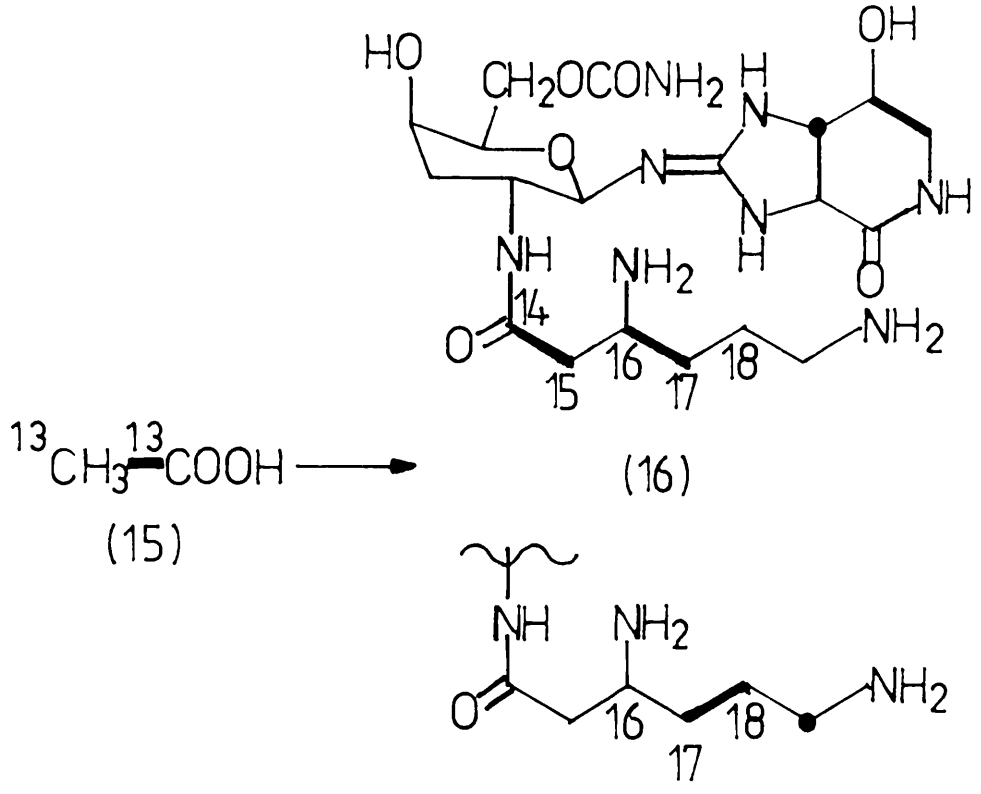


(14)

The β-lysine obtained from lysinomicin was shown to have the (S)-configuration by conversion of the amino acid to N,N'-dibenzyloxycarbonyl-(S)-β-lysine, the melting point and optical rotation of which corresponded to those reported in the literature.[28]

The biosynthesis of β-lysine has received

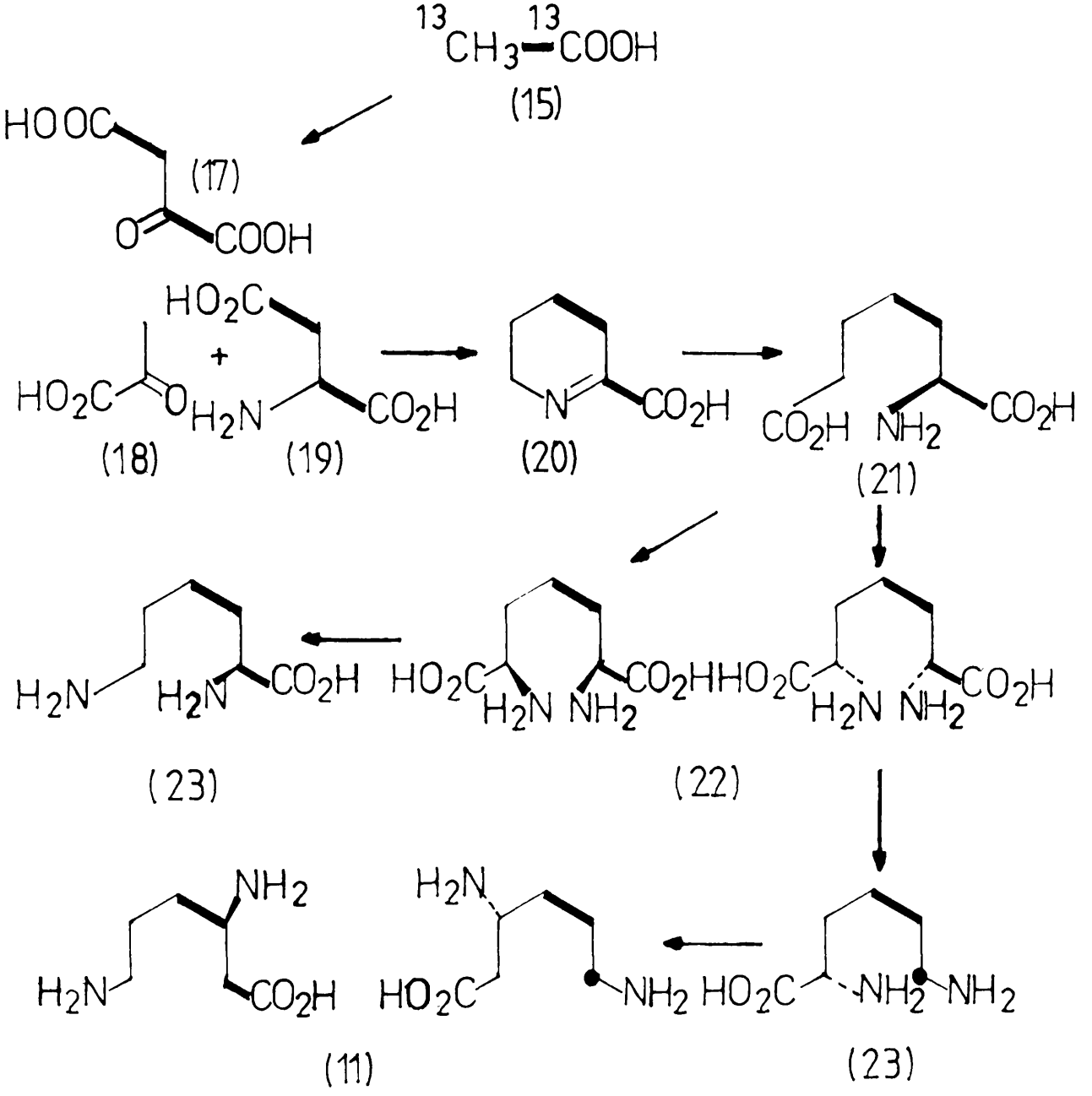
considerable attention, particularly its mode of incorporation into the streptothricin family of antibiotics. The biosynthesis of streptothricin F (16) has been extensively studied by Gould,[29] who has obtained a specific incorporation of [1,2-$^{13}C_2$] acetate into the β-lysine portion of (16) in Streptomyces L-1689-23 [Scheme 4].



Scheme 4.

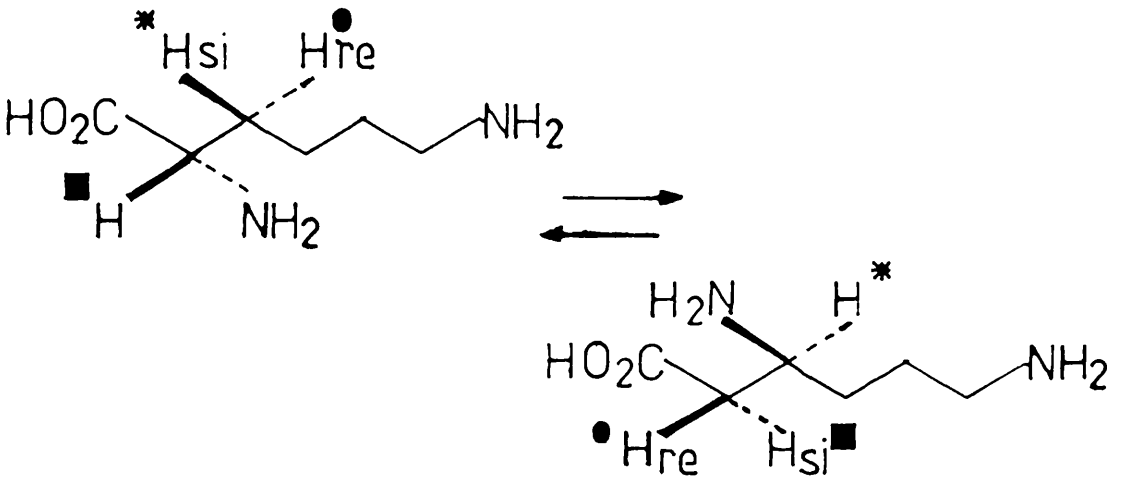
The broad band decoupled ^{13}C nmr spectrum of the derived antibiotic provided the labelling pattern shown above. The labelling pattern in the β-lysine portion showed the sample isolated to consist of some molecules in which C-16 and C-17 are derived from an acetate unit, and some in which C-17 and C-18 are so derived. This pattern is

consistent with β-lysine being derived from α-lysine (23) which was produced via the diaminopimelic (DAP) pathway shown in Scheme 5. In this pathway (2S,6S) DAP (21) derived from pyruvic acid (18) and aspartic acid (19), is epimerised to meso-DAP (22) and then decarboxylated. Aspartic acid is obtained by transamination of oxaloacetic acid, thus rationalising the specific but dichotomous labelling of β-lysine moiety of streptothricin F by acetate.



Scheme 5.

The mechanism and stereochemistry of the conversion of α- to β-lysine has been investigated in both the Streptomyces[30,31] and Clostridia species.[32,33] Aberhart[32,33] has shown by deuterium labelling and ^2H nmr that the transformation of (2*S*)-α-lysine (23) to (3*S*)-β-lysine (11) in Clostridium subterminae strain, SB4, proceeds with transfer of the 3-pro-R hydrogen of α-lysine to the 2-pro-R position of β-lysine. The 3-pro-S hydrogen of α-lysine is retained at the 2-pro-S position of β-lysine and the C-2 hydrogen of α-lysine is retained at the 2-pro-S position of β-lysine. Thus the reaction proceeds with inversion of configuration at C-2 and C-3 [Scheme 6].

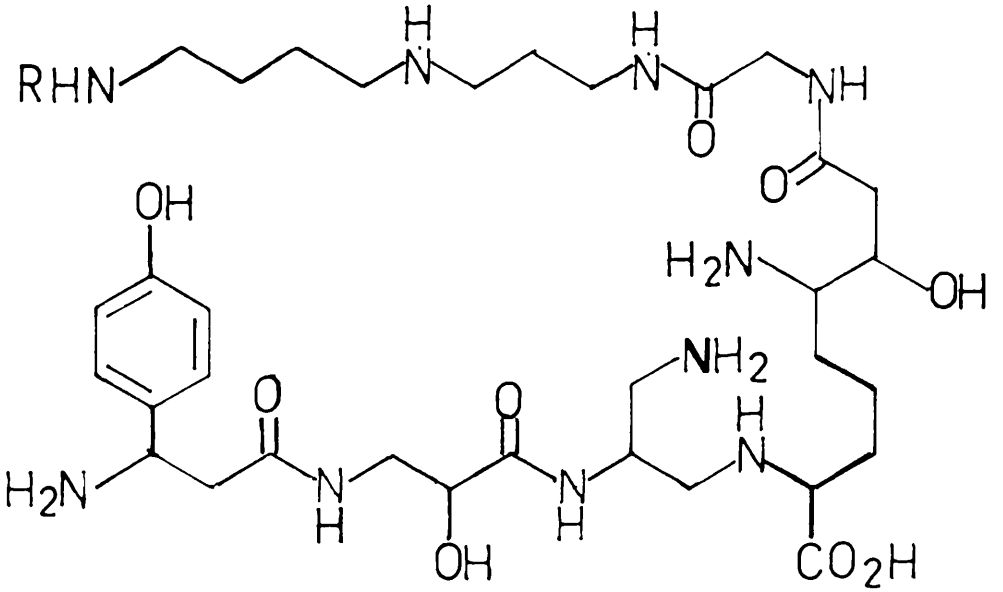


Scheme 6.

Gould and Aberhart[32,33] have also demonstrated that in C.SB4 the amino group transfer occurs completely intramolecularly, and that migration of hydrogen is substantially or completely intermolecular. The same authors have shown that the stereochemistry of the Streptomyces α-Lysine-2,3-amino mutase reaction is identical with that of the

Clostridium transformation.[31]

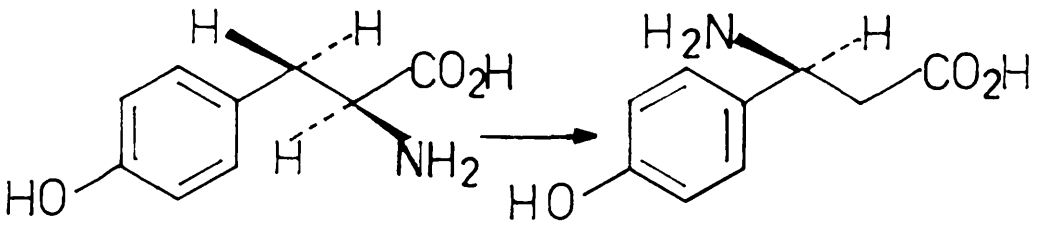
β-Tyrosine (24) has also been shown to be derived from the corresponding α-amino acid as a result of a mutase-catalysed reaction.[34] Cultures of Bacillus brevis Vm4 produce two peptide antibiotics, edeine A (25) and edeine B (26) which contain as a constituent β-tyrosine, formed by isomerisation of L-(α)-tyrosine (27) to β-tyrosine (24) by the enzyme tyrosine α,β-mutase.



(25) R=H Edeine A

(26) R= $H_2NC(=NH)$ Edeine B

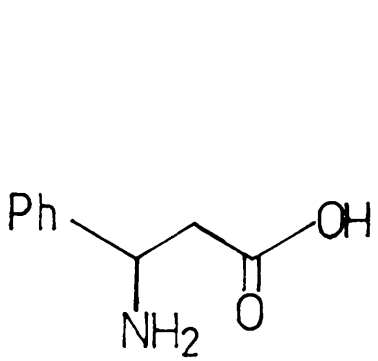
Since the β-tyrosine formed has the (S)-configuration[35], migration of the amino group of α-tyrosine occurs with inversion at C-3, [Scheme 7].

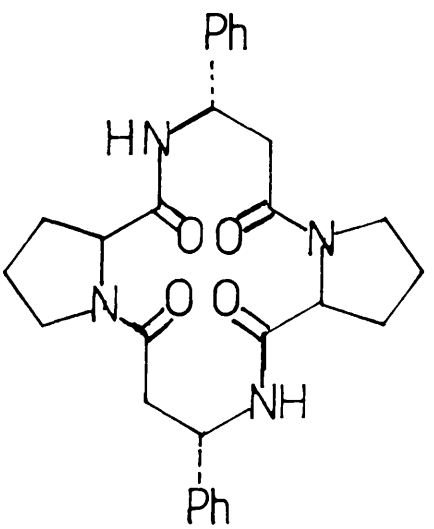


(27) (24)

Scheme 7.

(R)-β-phenyl-β-alanine (28) has been isolated from several toxic metabolites of Penicillium islandicum[36] and from the cyclic tetrapeptide roccanin (29) isolated from the lichen Rocella canarienses.[37]



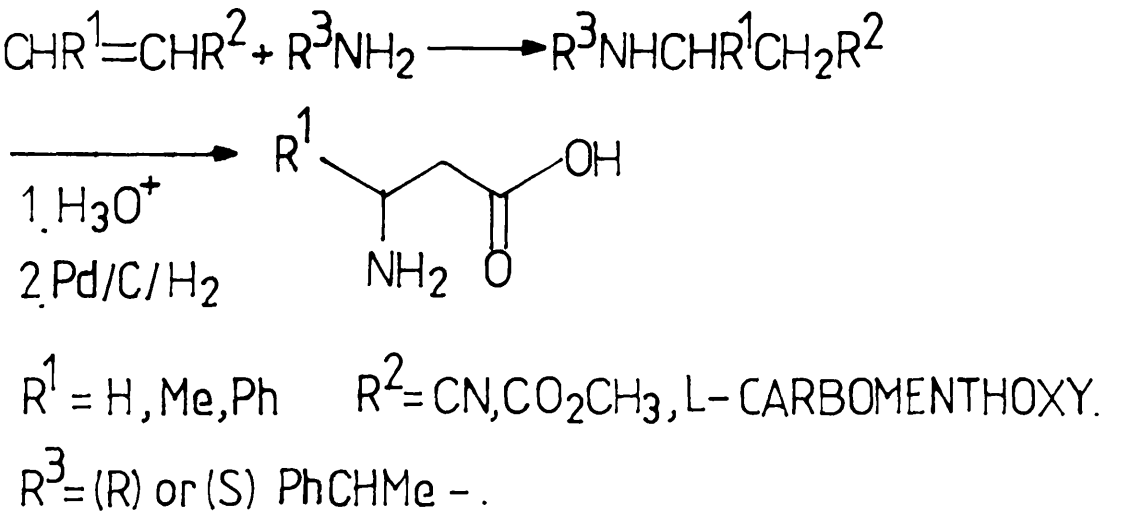


(28) (29)

The occurrence of other β-amino acids is relatively rare and has been reviewed by Drey.[5]

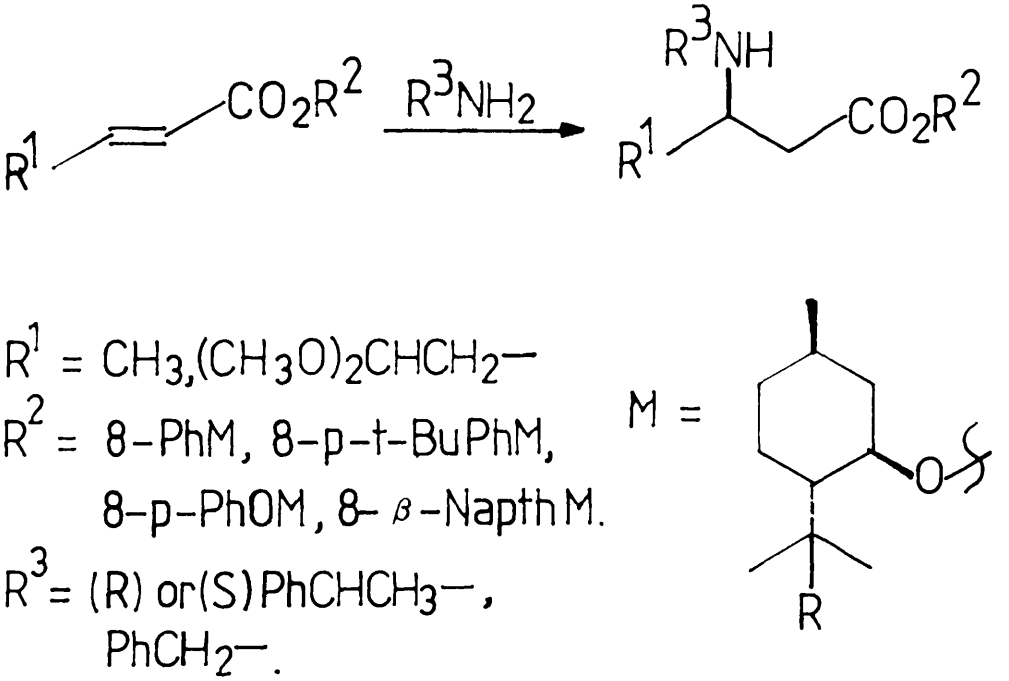
3. Asymmetric Synthesis of β-Amino Acids.

There are relatively few reports on the asymmetric synthesis of β-amino acids compared with those concerning α-amino acids. Conceptually, one of the simplest methods for the synthesis of β-amino acids is through the conjugate addition of amines to α,β- unsaturated acids or esters. In 1964, Tertentev[38] reported the first enantioselective synthesis of β-amino acids by the addition of chiral amines to crotonic acid, in poor chemical and optical yields. In 1977 Furukawa et al[39] reported an asymmetric synthesis of several β-amino acids by addition of chiral benzylic amines to 1-cyanopropenes and α,β-unsaturated esters [Scheme 8]. Hydrolysis and hydrogenolysis of the adducts formed gave β-amino acids in modest chemical yield (10-47%) and in low enantiomeric excesses (2-19%).



Scheme 8.

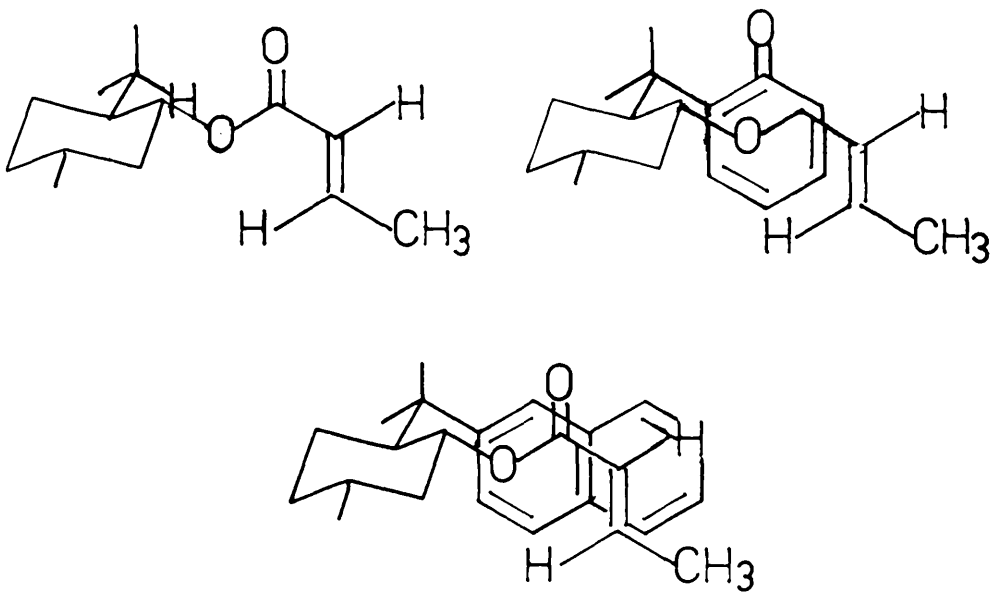
Much more recently (1986) d'Angelo[40] reported two significant modifications that confer greater synthetic utility on this reaction. While sluggish under thermal conditions,[39] the addition of primary amines to alkyl crotonates is very efficient at room temperature under 5 - 15 K bar pressures.[41] A dramatic increase in induction level (de60 - 90%) was observed by using 8-phenyl-menthyl crotonates in which the phenyl ring is substituted at the para position by bulky groups, and essentially complete diastereofacial control being achieved in the case of 8-(β-napthyl) menthyl crotonate, [Scheme 9].



Scheme 9.

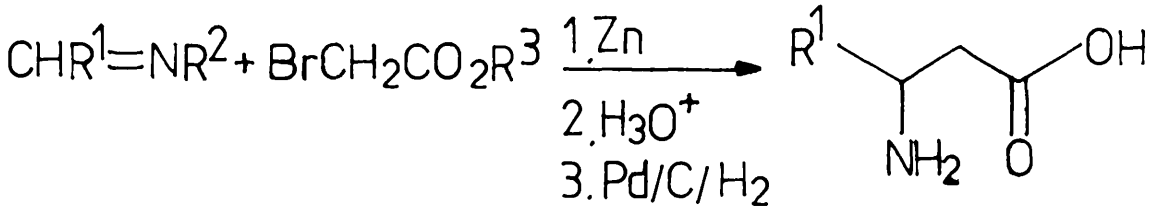
This stereochemical outcome agrees with the "π-stacking" model previously proposed by Oppolzer,[42] in which the aryl group of the inducer shields one face of the

crotonate unit, thereby directing the amine to the other face. This effect is obviously much greater for the 9-(β-napthyl)-menthyl crotonate, explaining the higher diastereoselectivity [Scheme 10].



Scheme 10

Furukawa has reported two other asymmetric syntheses of β-amino acids, one being a variation of the Reformatski reaction[43] in which a chiral Schiff base on treatment with an α-bromo ester provides β-amino acids in 2 - 28% enantiomeric excesses, [Scheme 11].



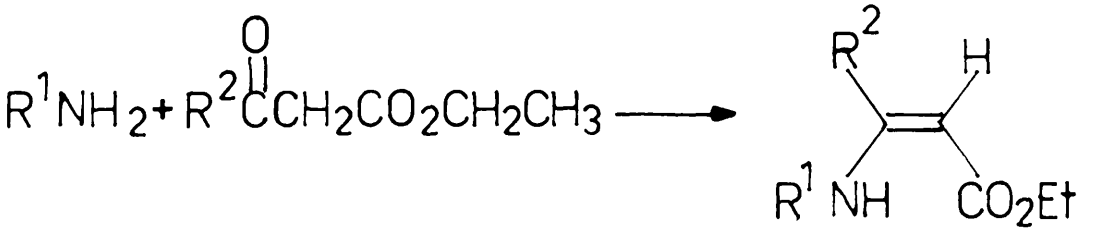
$R^1 = CH_3$, Ph.

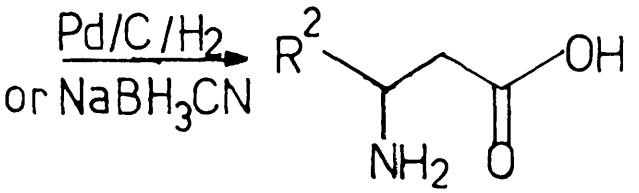
R^2 = (R) or (S) $PhCHCH_3-$.

$R^3 = CH_3CH_2$, L-MENTHYL.

Scheme 11.

The other involves the catalytic hydrogenation or hydride reduction of 3(R or S α-methylbenzyl) amino acrylates[44] which affords β-amino acids in enantiomeric excesses of 3 - 28%, [Scheme 12].



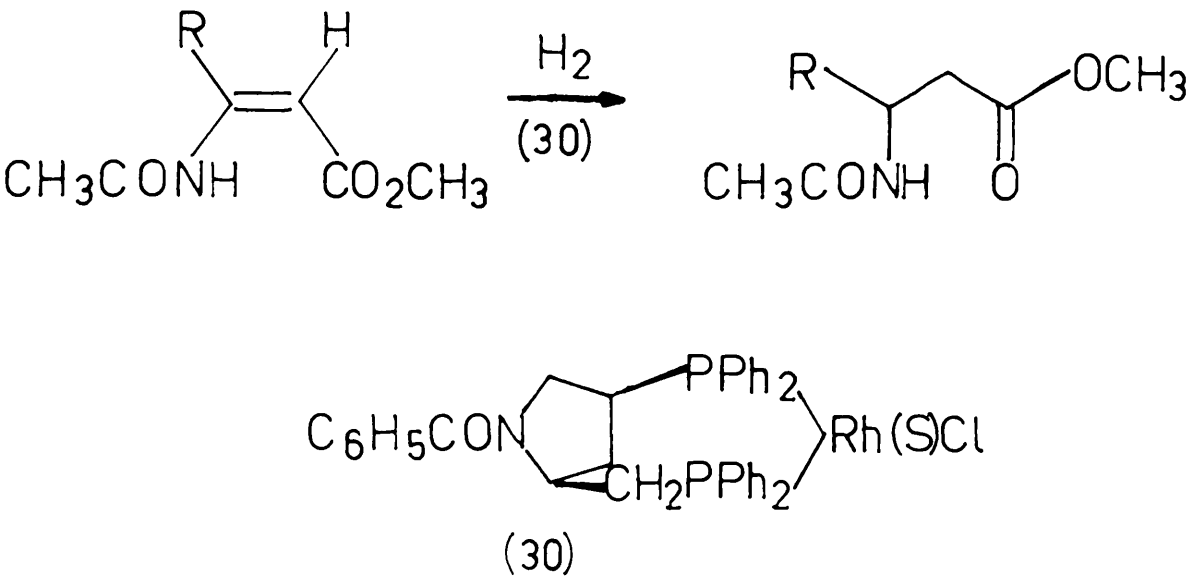


R^1 = (R) or (S) $PhCHCH_3-$.

$R^2 = Ph, CH_3$.

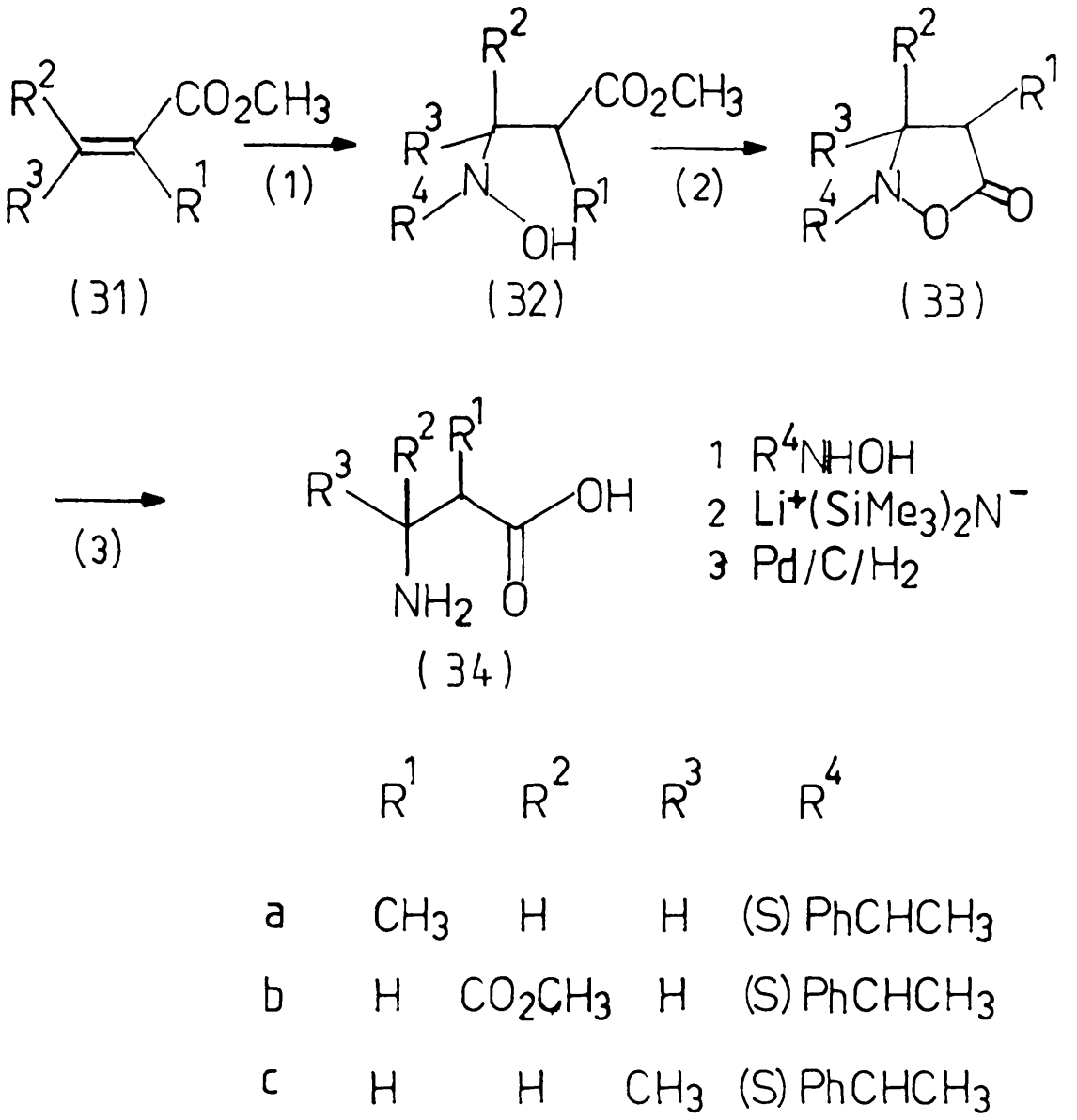
Scheme 12.

Achiwa[45] 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 13]. The chiral rhodium bisphosphine complex (30) may be prepared in situ.



Scheme 13.

In 1984 Baldwin[46] reported a general procedure for the synthesis of chiral isoxazolidinones (33) via conjugate addition of chiral hydroxylamine to α,β-unsaturated esters (31) followed by cyclization of the adducts with bis(trimethylsilyl) amide. Cleavage of the N-O bond in (33) by hydrogenolysis is accompanied by removal of the benzylic nitrogen protecting group furnishing α- and β- substituted β-amino acids, [Scheme 14].



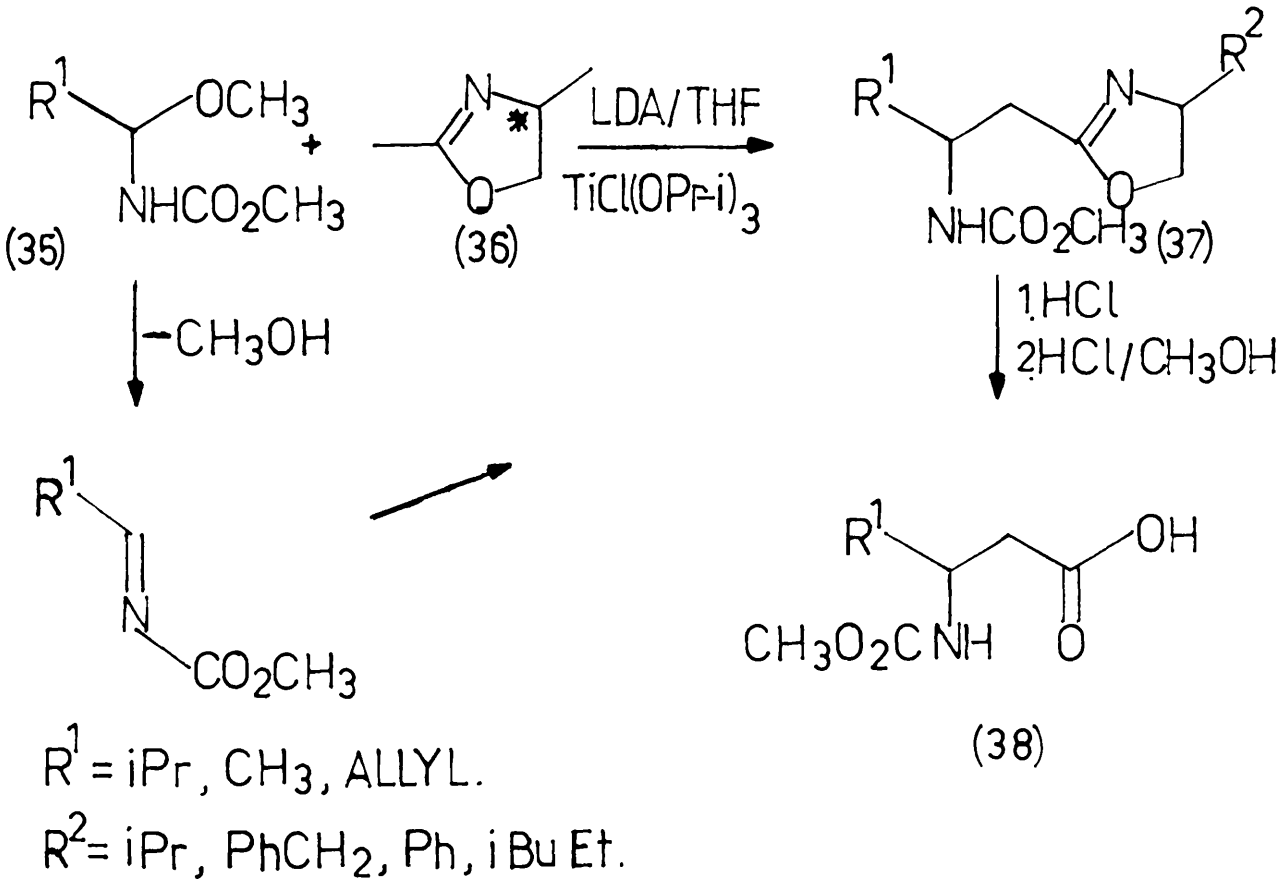
	R^1	R^2	R^3	R^4
a	CH_3	H	H	(S) $PhCHCH_3$
b	H	CO_2CH_3	H	(S) $PhCHCH_3$
c	H	H	CH_3	(S) $PhCHCH_3$

Scheme 14.

Only modest enantiomeric excesses were obtained (10 - 28%). However, in one case separation of the diastereomeric adducts (32c) was possible and led to the synthesis of β-methyl-β-alanine in 78% enantiomeric excess.

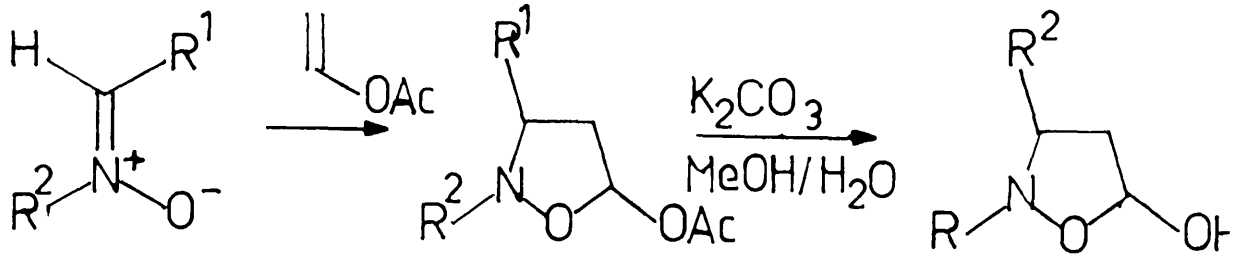
Shono et al have developed a new asymmetric synthesis of β-amino acids by nucleophilic addition of

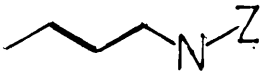
enolate anions to N-methoxycarbonylimines generated from α-methoxy carbamates.[47] The authors have shown that treatment of α-methoxylated carbamates (35) with anions generated from chiral 2-methyl oxazolines (36) in the presence of base affords, after treatment with acid, β-amino acid derivatives (38) with enantiomeric excesses of 44 - 90%. The chiral oxazoline prepared from L-valinol (R_4 = iPr) showed best selectivity (ee 72 - 90%). The mechanism of this reaction is not the common S_N2 type substitution reaction but a base-catalysed elimination of methanol followed by addition of the 2-methyloxazoline anion, [Scheme 15].



Scheme 15.

Recently, Overton et al[48] reported an enantioselective synthesis of optically pure (R)-and (S)-β-lysines (55) via cycloaddition of chiral nitrone (39) to vinyl acetate followed by facile chromatographic separation of the four resulting acetates (43) into two pairs of C-5 epimers. Both of these pairs were individually hydrolysed to the corresponding lactols (47) and oxidised to the isoxazolidinones (51), however the yield of this oxidation step was only 40%. Subsequent hydrogenolysis of isoxazolidinones (51) afforded pure (R) and (S)-β-lysine, [Scheme 16]. Moffat[49] had previously used this route to effect asymmetric syntheses of β-phenyl-β-alanine (28), β-tyrosine methylether (56) and β-leucine (6). The oxidation step in these cases afforded the corresponding isoxazolidinones (51 - 54) in low yield (15 - 19%), and the amino acids (28, 56, 6) in enantiomeric excesses of 0, 8 and 56% respectively. Fortunately, a single isomer of (53) was obtained on crystallisation of the diastereomeric mixture, ultimately leading to optically pure (R)-β-tyrosine methylether.



(39) R^1= 

(40) R^1= Ph

(41) R^1= pMeOPh

(42) R^1= iPr

(43)

(44)

(45)

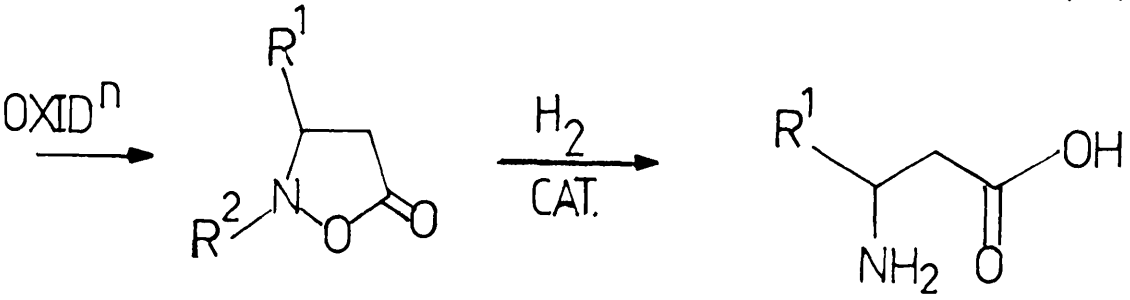
(46)

(47)

(48)

(49)

(50)

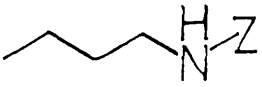


(51)

(52)

(53)

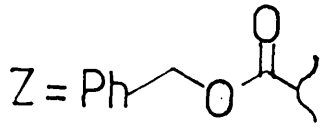
(54)

(55) R^1= 

(28) R^1=Ph

(56) R^1=pMeOPh

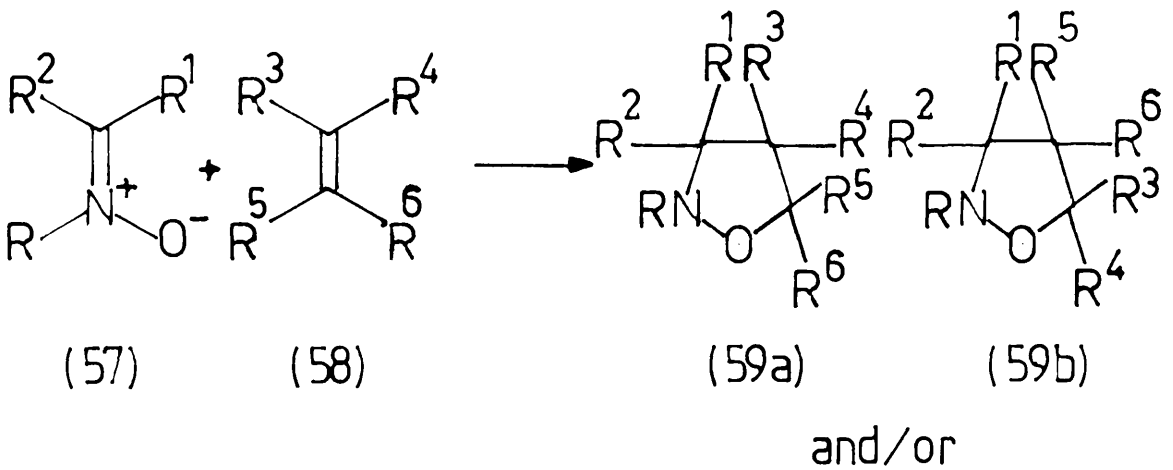
(6) R^1=iPr

$R^2 \equiv$ (R) $PhCHCH_3$— Z = 

Scheme 16.

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

In recent years the application of cycloaddition reactions in the synthesis of natural products has been an area of intense activity.[51] The 1,3-dipolar cycloaddition reactions of nitrones (57) with substituted olefins (58) gives rise to an extremely powerful yet mild means of constructing 5-membered heterocyclic ring systems (isoxazolidines, 59a,b)[50,51] [Scheme 17].



Scheme 17.

Nitrone cycloaddition reactions are normally both efficient and predictable in their outcome. The obvious advantages of carbon-carbon bond formation, carbon-oxygen bond formation and the introduction of nitrogen have been markedly enhanced by the high regio- and stereoselectivities embodied in a great many of these cycloadditions.[50,51,52] Furthermore, since the N-O bond of the isoxazolidine can in

most cases be easily cleaved, a number of imaginative syntheses have used isoxazolidine formation followed by ring opening as key steps.[51,52] The details of an investigation into the application of [3+2] nitrone-olefin cycloaddition reactions to the asymmetric synthesis of β-amino acids constitutes most of the work described in this thesis.

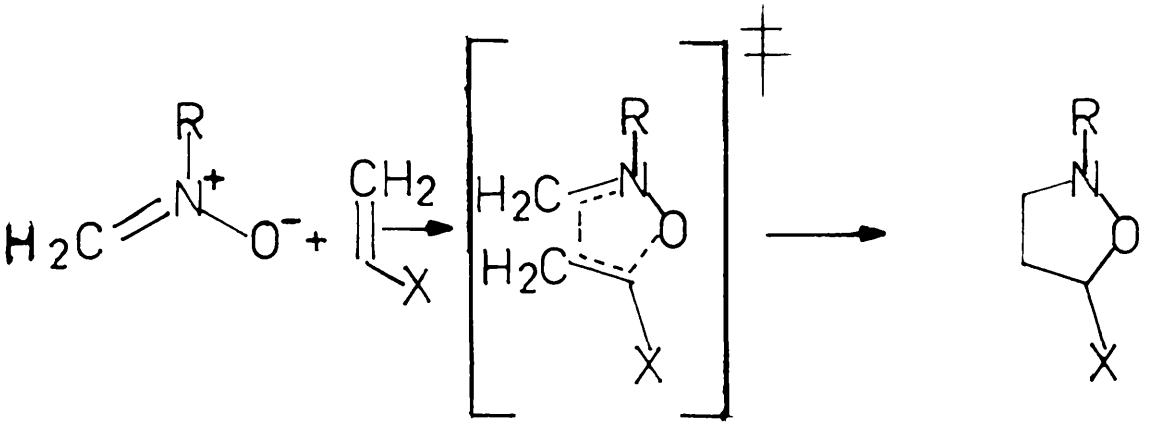
4.2 Synthesis and Structure of Nitrones.

Most of the general procedures for the preparation of acyclic nitrones have been employed during the course of this work, and along with their structure and stereochemistry are discussed in Chapter 1.

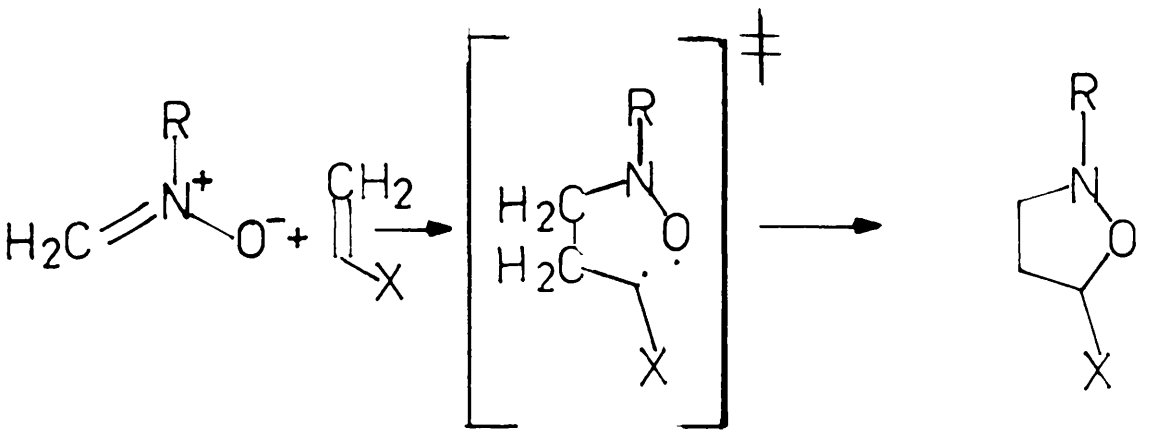
4.3 The Mechanism of 1,3-Dipolar Cycloaddition Reactions of Nitrones.

1,3-Dipolar cycloaddition reactions can in principle proceed in a single step as proposed by Huisgen[53,54] (eg. Scheme 18), or in two steps through a spin-paired diradical intermediate as suggested by Firestone[55] (eg. Scheme 19). These two alternative views of the mechanism of 1,3-dipolar cycloaddition processes have generated considerable discussion, however it is now generally accepted[51] that most 1,3-dipolar cycloadditions including those of nitrones are single-step, four-centre concerted reactions in which two new σ-bonds are formed at the same time, although not necessarily at the same rate in agreement with the

original postulate of Huisgen in 1963.[53] The reaction may be treated formally as an allowed [π^4S - π^2S], process, analogous to the related Diels-Alder cycloaddition.



Scheme 18.



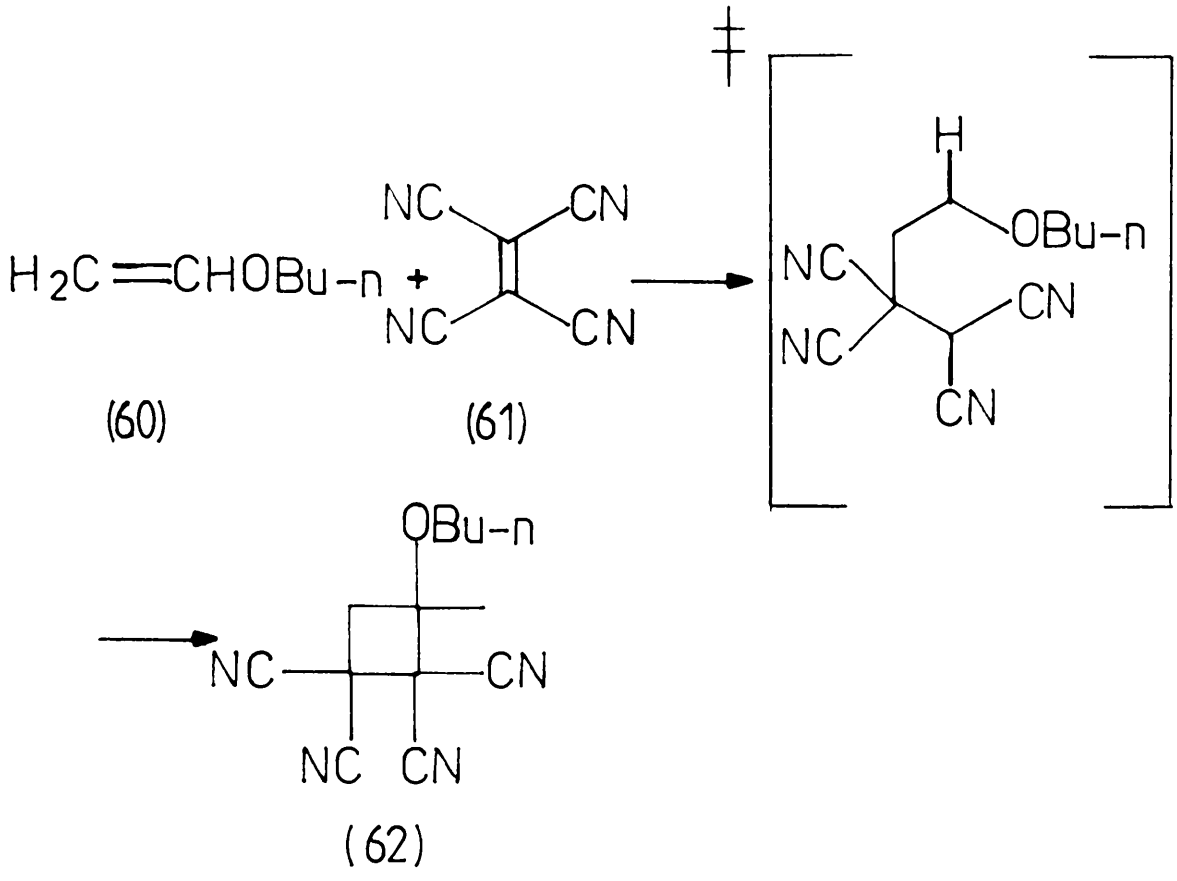
Scheme 19.

Huisgen[54] has severely criticized suggestions that diradical intermediates are involved in 1,3-dipolar cycloadditions, and has observed that the greatest obstacle for

the assumption of a diradical intermediate is the observed stereospecificity of cycloaddition reactions involving nitrones and 1,2-disubstituted olefins, in that the stereochemical relationships incorporated in the dipolarophile are preserved in the product isoxazolidine (see Section 4.4). In order for this stereospecificity to be accommodated by the diradical approach, diradicals such as in scheme 19 would be required to undergo ring closure much faster than bond rotation.

The cycloaddition reactions of nitrones with alkenes generally show little dependence on the nature of the solvent. The reaction of N-methyl-C-phenylnitrone with ethyl acrylate exhibits only a 2.6 - fold increase in rate on passing from dimethyl sulphoxide to toluene, a solvent change that spans an enormous range of dielectric constant (48.9 versus 2.4 at 25°C respectively).[56]

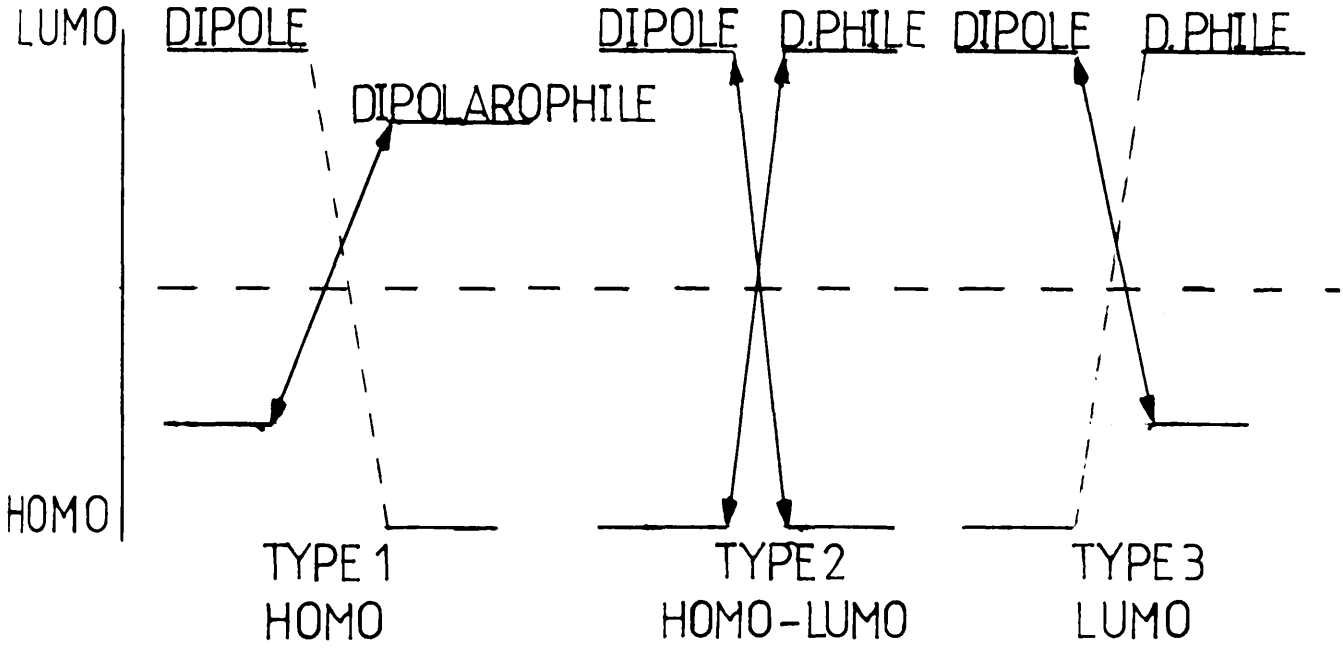
This observation mitigates strongly against the intervention of zwitterionic intermediates since cycloaddition reactions known to proceed through such intermediates experience a substantial dependence on solvent polarity. Thus, the ratio k(acetonitrile)/k(cyclohexane) is 2600 for the addition of tetracyanoethylene (61) to butyl vinyl ether (60), a reaction that proceeds through such an intermediate,[57] [Scheme 20].



Scheme 20.

Before the advent of frontier molecular orbital theory, the regiochemistry of 1,3-dipolar cycloaddition reactions had been regarded as the biggest unsolved problem in the field. Both the reactivity and regiochemistry of 1,3-dipolar cycloadditions has been spectacularly rationalised by Sustmann,[58] Houk[59] and Bastide[60] through the application of frontier molecular orbital theory to determine the relative energies of the interacting frontier molecular orbitals of the dipole and dipolarophile. Sustmann has classified reactions into three types depending on whether the dominant reaction is between the highest occupied molecular orbital (HOMO) of the dipole and the lowest unoccupied molecular orbital (LUMO) of the dipolarophile (Type 1), or the dipole LUMO and the dipolarophile HOMO (Type 3), or whether both of these interactions are of

equal significance (Type 2). These are referred to more concisely as HOMO, LUMO and HOMO-LUMO controlled cycloadditions, [Scheme 21].



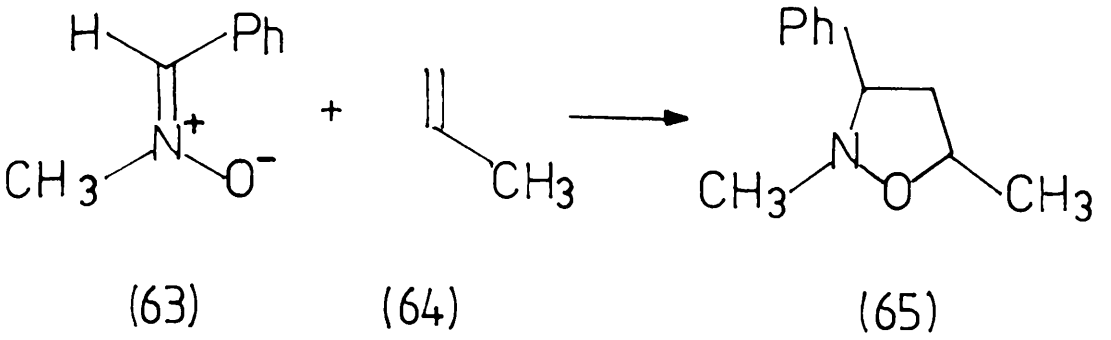
Scheme 21

According to second order perturbation theory, this interaction leads to a stabilization of the occupied molecular orbital that is inversely proportional to the energy separation between the orbitals involved.[61] That is, the more proximate the orbitals are in energy the more extensive the interaction. In general, HOMO type cycloadditions are accelerated by electron donating substituents on the dipole and electron withdrawing substituents on the dipolarophile, resulting in a decrease in the energy difference between the interacting frontier orbitals. Conversely, LUMO type cycloadditions are accelerated by

electron donating substituents on the dipolarophile and electron withdrawing substituents on the dipole. HOMO-LUMO controlled reactions are accelerated by an increase in either frontier molecular orbital interaction. Nitrone cyclo-additions are believed to be Type 2 processes and as such both frontier orbital interactions may be important. The interaction that dominates in a particular case will depend on the nature of both the dipole and dipolarophile.

In the addition of an unsymmetrical dipolarophile to a nitrone two orientations are possible, and it has been found[62] that cycloadditions can be reversible and are therefore subject to both kinetic and thermodynamic control (see Chapter 2),. Although the focus thus far has been on the energies of the frontier orbitals, attention must now be turned to the coefficients associated with the atomic orbitals in each of the frontier molecular orbitals in order to explain the regio-selectivity observed in 1,3-dipolar cycloadditions.

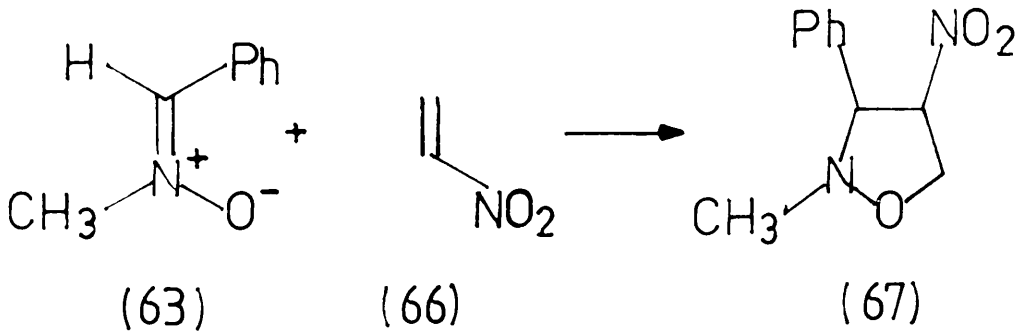
1,3-Dipolar cycloaddition reactions of nitrones with monosubstituted olefins bearing a variety of functional groups afford 5-substituted isoxazolidines.[50] Electron-rich olefins give exclusively 5-substituted isoxazolidines (65) as in the reaction of C-phenyl-N-methylnitrone (63) with propene[51] (64), [Scheme 22].



(63) (64) (65)

Scheme 22.

However, it has been found that very electron-deficient dipolarophiles such as nitroethylene (66) give significantly or exclusively 4-substituted isoxazolidines (67) with nitrone[63] (63), [Scheme 23].



(63) (66) (67)

Scheme 23.

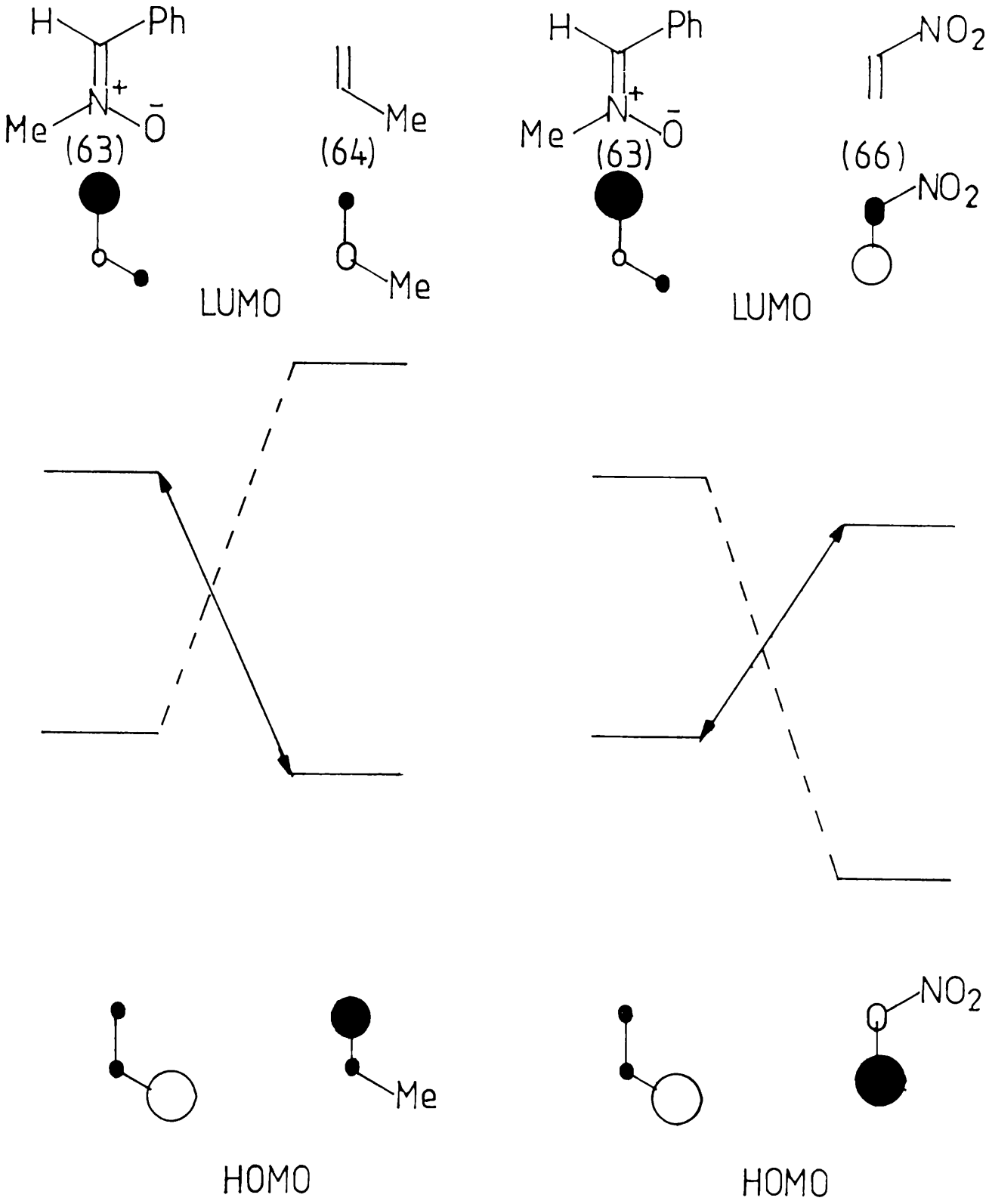
1,1-Disubstituted olefins such as diethylmethylene malonate are also known to form 4-substituted isoxazolidines (see Chapter 2).

Regioselectivity is determined by the relative

magnitudes of the atomic orbital coefficients in the frontier orbitals of both the nitrone and the dipolarophile. The dominant stabilizing interaction in the transition state involves those atomic orbitals at the interacting atoms with the largest coefficients,[64] allowing maximum frontier orbital overlap. Scheme 24 summarises the interactions between both a moderately electron rich olefin (64) and an electron deficient olefin (66) with C-phenyl-N-methylnitrone (63).

In the case of propene, the dominant interaction involves LUMO(dipole)-HOMO(dipolarophile) in which the large AO coefficient on the carbon of the nitrone LUMO interacts with the larger coefficient associated with the unsubstituted carbon of the olefin HOMO, affording the 5-substituted isoxazolidine which is in accordance with the experimental finding. For very electron deficient dipolarophiles such as nitroethylene (66), the HOMO and LUMO levels are lowered in energy so that the cycloaddition resembles a Type 1 process. The dominant interaction involves HOMO(dipole)-LUMO(dipolarophile) and leads to a 4-substituted isoxazolidine again in accordance with experimental results. Clearly at some point there must be a switchover from HOMO to LUMO control as the electron-withdrawing power of the substituent on the dipolarophile increases. This point is apparently approached for substituents such as ester and cyano moieties since regioisomeric mixtures of adducts are obtained (see Chapter 2).

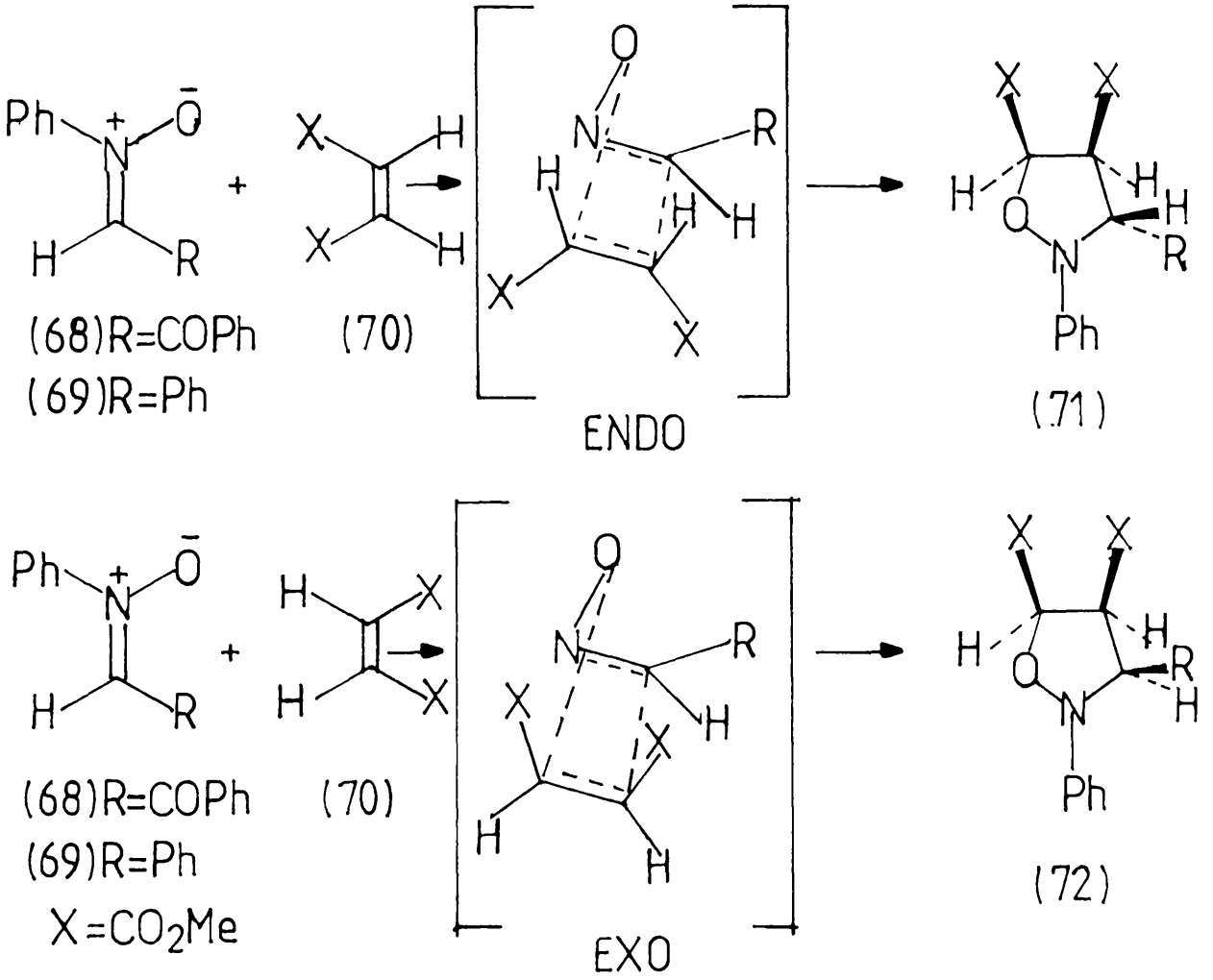
The fact that the above results were predicted by frontier molecular orbital considerations presents an impressive demonstration of their power.


H
Ph
N+
Me
O
(63)
Me
(64)
LUMO
Me
HOMO
H
Ph
N+
Me
O
(63)
NO2
(66)
NO2
LUMO
NO2
HOMO

Scheme 24.

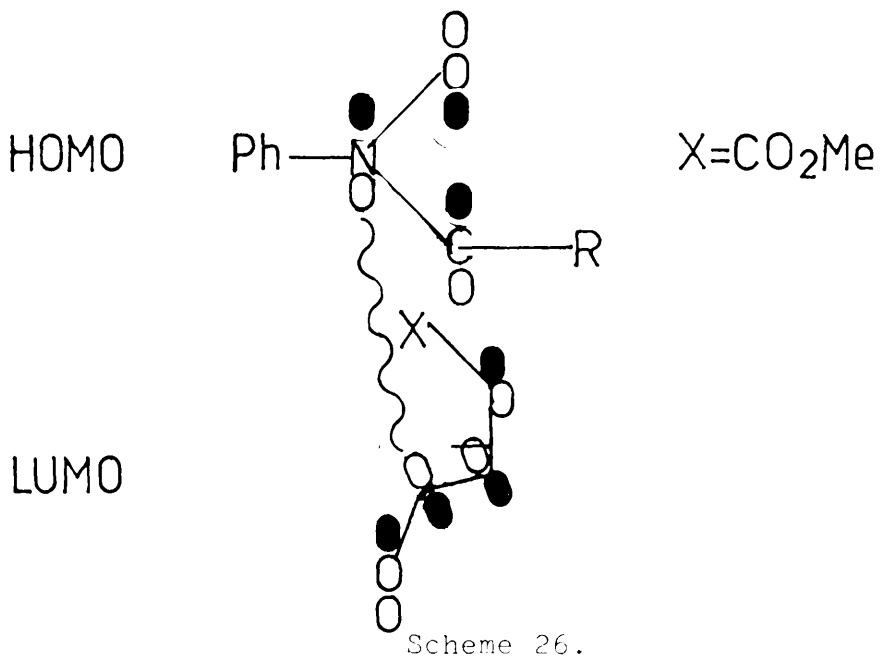
4.4 Stereochemical Aspects of Nitrone 1,3-Dipolar Cycloadditions.

The stereochemical as well as regiochemical aspects of nitrone cycloadditions must be considered. Nitrone cycloaddition reactions can give rise to the formation of diastereomeric or enantiomeric adducts as a result of the different possible modes of approach of the reagents, ie. nitrone of E or Z configuration (see Chapter 1) can approach either face of the dipolarophile in an exo- or endo- manner, comparable to the competing endo- and exo- stereoslectivities which characterise Diels-Alder reactions. These tendencies have been evaluated by studying the reactions of dimethyl maleate (70) with C-benzoyl-N-phenylnitrone (68) and C,N-diphenylnitrone (69),[65,66] [Scheme 25].



Scheme 25

Both of these reactions are cis-stereospecific in that the stereochemical relationship of the carbomethoxyl groups in dipolarophile is preserved in the product isoxazolidines. Nitrone (69) reacts with dimethylmaleate to afford two isoxazolidines (71) and (72) in a 9:1 ratio, indicating the endo transition state is favoured, whereas nitrone (68) gives only isoxazolidine (71), arising exclusively from an endo transition state. The results can be interpreted by an examination of the transition state involved in these reactions in terms of frontier molecular orbital interactions, [Scheme 26].

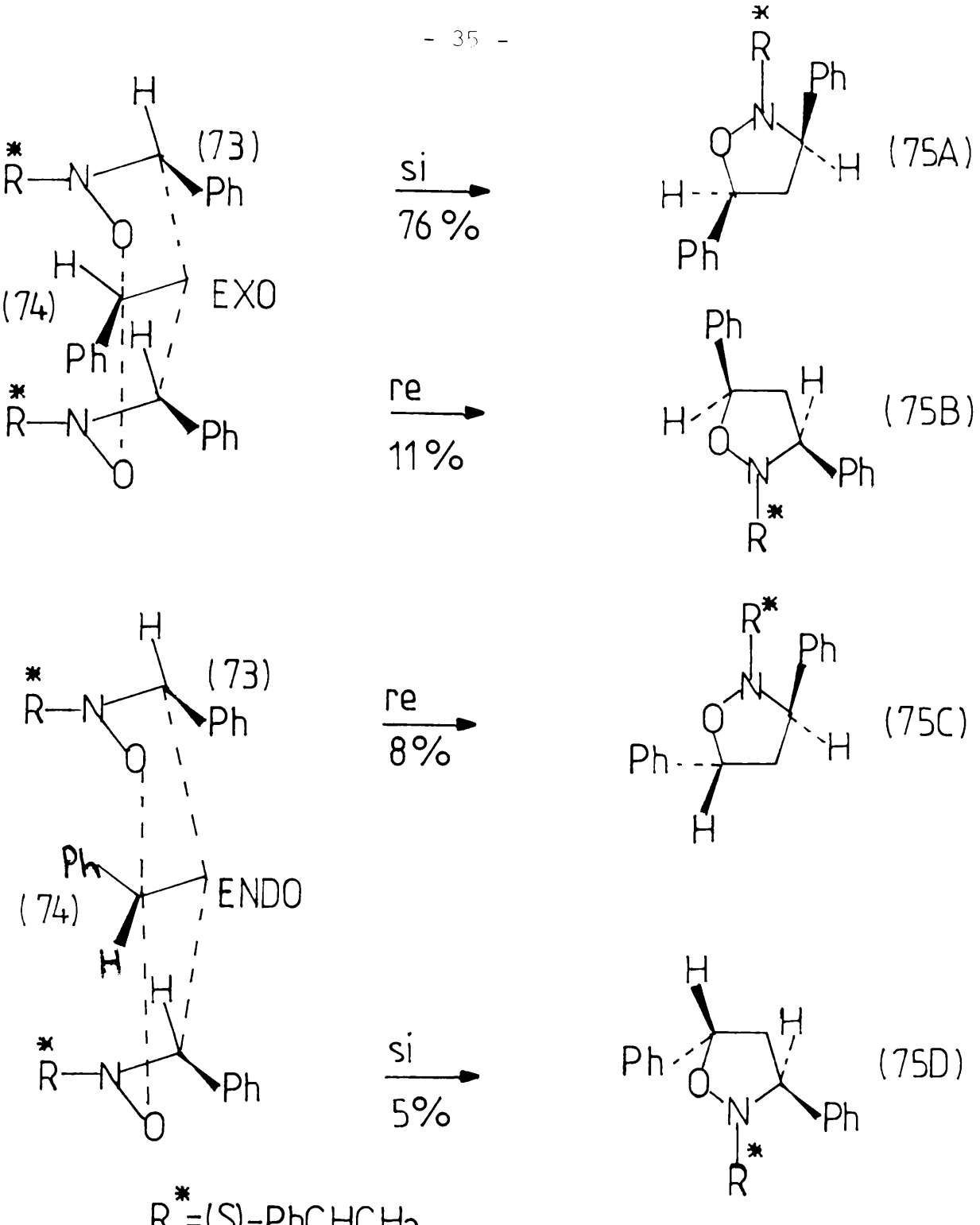


Scheme 26.

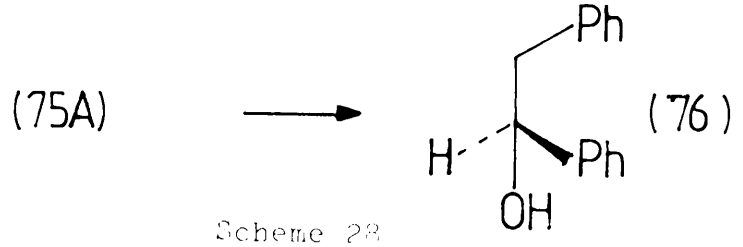
The dominant interaction for substantially electron deficient dipolarophiles with a nitrone should be HOMO (dipole)-LUMO (dipolarophile). An examination of the endo transition state in these terms reveals a favourable secondary orbital interaction between the N atom of the dipole and the carbonyl moiety of the olefin, thus explaining the preference for the

endo transition state. Interestingly, the reaction of C,N-diphenylnitrone and methyl acrylate[67] gives rise to 4 adducts, diastereomeric pairs of both the 4- and 5-carbomethoxyl substituted isoxazolidines. In comparison to the above, the relative difference in energy separation between HOMO (dipole) - LUMO (dipolarophile) and HOMO (dipolarophile) - LUMO (dipole) may be expected to be less when dealing with methyl acrylate, therefore increased competition between these two interactions, while opposing secondary orbital effects may explain the observed lack of stereochemical control.[51] Secondary orbital interactions should therefore be seen to be of considerable importance in determining the stereochemical course of nitrone cycloaddition reactions.

Nitrones bearing chiral substituents (R^*) have been shown to undergo cycloaddition reactions involving a transfer of chirality to appropriate dipolarophiles. For example, Belzecki and Panfil[68] have shown that nitrone (73) reacts with styrene (74) to give two diastereomeric pairs (cis and trans) of isoxazolidines (75 A,B,C,D) in a 76:11:8:5 ratio. If during the cycloaddition only the Z isomer of the nitrone is present, the diastereomers are formed as a result of the approach of the nitrone to the re or si prochiral faces of the olefin in an exo or endo manner, [Scheme 27]. As the components of the diastereomeric mixture are separable their absolute configurations were determined, e.g. isomer (75A) was subjected to hydrogenolysis to give (S) - (-) - 1,3 diphenyl propan-1-ol (76) in 92% optical purity, [Scheme 28].



Scheme27

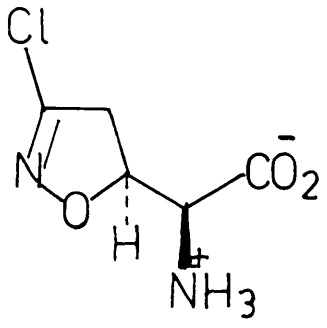


Scheme 28

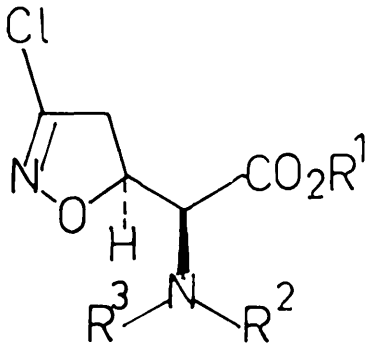
These results indicate that styrene reacts with nitrone (73) preferentially via the endo transition state to give an excess of the cis isoxazolidine and an excess of one of the diastereomers in each cis and trans pair. Other mono substituted dipolarophiles have been shown to exhibit similar behaviour.[68]

Chiral nitrones have been employed in a number of total synthesis of natural products, the subject of which has been reviewed.[51,52] One instructive example will be discussed here in detail. Whitney et al have recently reported a short, highly stereoselective total synthesis of acivicin[69] (77), an antibiotic produced by Streptomyces sviceus and noted for its antitumor properties. Nitrones (78a-c) used in this work were generated in situ from 5-hydroxypentanal oxime,[70] 2,3:5,6 di-O-isopropylidene-D-mannose oxime[71] and 2,3-O-isopropylidene-5-O-trityl-D-ribose oxime respectively, by reaction with paraformaldehyde. The N- substituted isoxazolidines isolated from these reactions were converted to N-unsubstituted isoxazolidines by acid hydrolysis and thence to isoxazolines (80,81) by oxidation with N-chlorosuccinimide. The diastereoselectivity in the cyclo-addition was assessed by ^{1}H nmr at this stage by integration of the signals for the proton at C-3 of the isoxazolines, (Table 1). In all cases the slightly broadened singlets observed for (80) and (81) were located near δ7.2 with the 5S-isomer giving the higher field signal. The final conversion of (80) to acivicin required chlorination at C-3 to give (82), and deprotection of (82) giving synthetic material which was

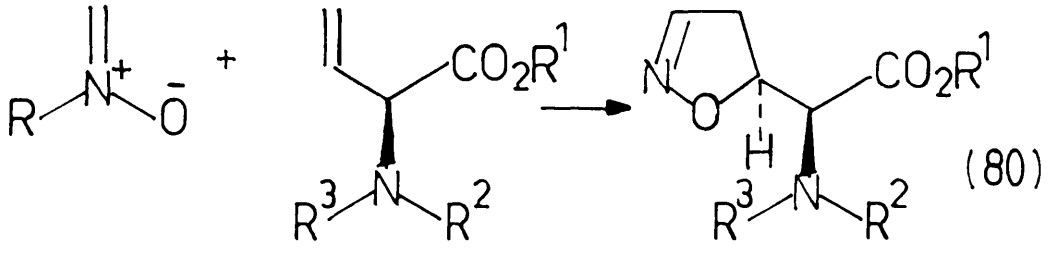
identical in all respects with the natural product, [Scheme 29].



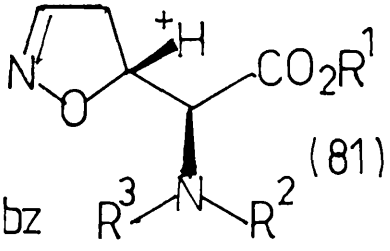
(77)



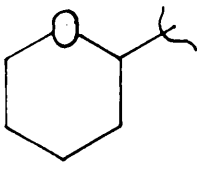
(82)



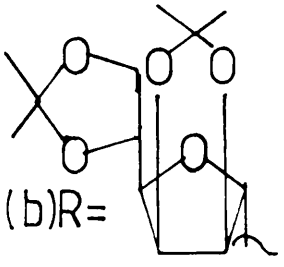
(78) (79) (80)



(81)

(a)R= 

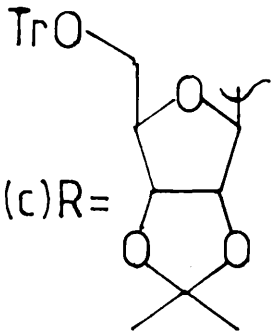
(d)R^1 =Me, R^2=H, R^3=Cbz



(b)R=

(e)$R^1 + R^2$=CH_2, R^3=Cbz

(f)$R^1 + R^2$=CH_2, R^3=CH_3CH_2OC(=O)–



(c)R=

(g)$R^1 + R^2$=CH_2, R^3=CH_3OC(=O)–

Scheme 29.

Table 1.

NITRONE	ALKENE	PROD.RATIO 80:81	YIELD %
78a	79d	2:3	71
78b	79d	1:2	72
78c	79d	2:1	77
78a	79e	2:1	45
78b	79e	3:1	60
78c	79e	>19:1	74
78c	79f	>19:1	74
78c	79g	>19:1	80

The methylidene-protected L-vinylglycines (79e-g) exhibited selectivity for the desired 5-(S)-stereoisomer (80) with all three nitrones (77a-c). The selectivity in the reaction of (78c) with (79e-g) was sufficiently great that the minor isomer could not be detected by ^{1}H nmr. It would appear that these last three combinations constitute matched pairs of asymmetric reactants for double asymmetric induction[72] (see Chapter 5).

Chapter 4 of this thesis describes the cycloaddition of α-chloroacrylonitrile with chiral nitrones as part of an asymmetric synthesis of β-amino acids.

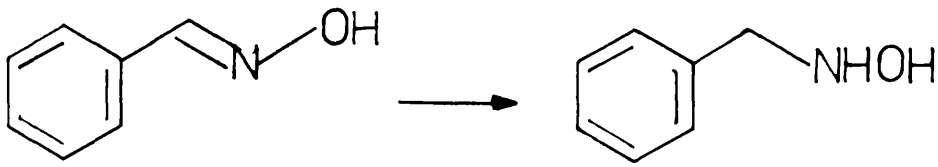
DISCUSSION.

CHAPTER 1.

Preparation and Configuration of Nitrones.

1.1 Preparation of Nitrones.

The most general and efficient method of preparing acyclic nitrones involves the condensation of N-monosubstituted hydroxylamines with aldehydes.[73] N-benzylhydroxylamine (2) was prepared by the method of Borch[74] which involves cyanoborohydride reduction of benzaldehyde oxime (1), [Scheme 1].

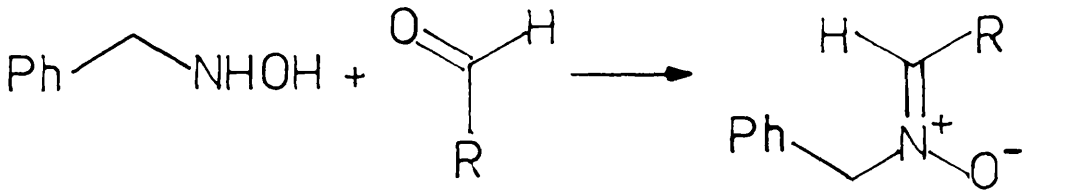


(1) (2)

Scheme 1.

Treatment of the appropriate aldehydes (3,4) with hydroxylamine (2) in dichloromethane at room temperature gave C-methyl and C-iso-propyl-N-benzylnitrones in good yield, [Scheme 2].

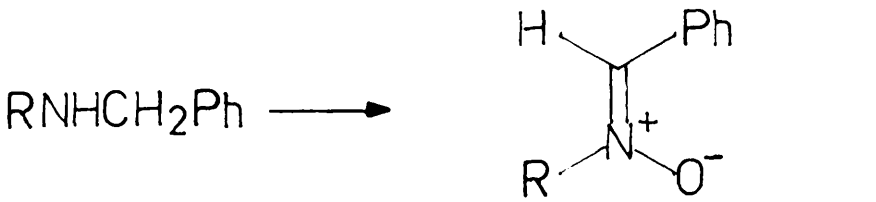
The spectroscopic properties of these nitrones were identical to those described by Moffat,[49] the i.r. spectra of which typically displayed C=N absorption at approximately 1600cm^{-1}.



(2) (3) R= Me (4) R= iPr (5) R=Me (6) R=iPr

Scheme 2.

C,N-diphenylnitrone (9) and C-phenyl-N-benzylnitrone (10) were conveniently prepared by oxidation of N-benzylamines (7) and (8) with m-chloroperbenzoic acid in refluxing acetone, following the method described by Beckett,[75] [Scheme 3].

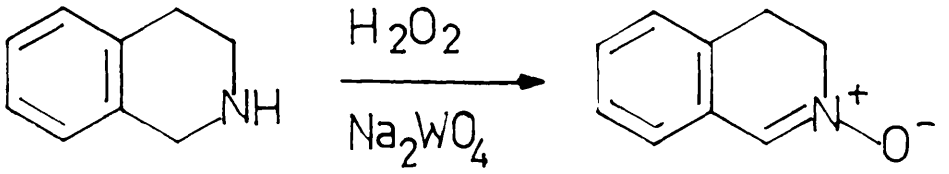


(7) R = Ph (8) R = $PhCH_2$ (9) R=Ph (10) R = $PhCH_2$

Scheme 3.

3,4-Dihydroisoquinoline N-oxide (12) was prepared by the method of Murahashi,[76] and involved the tungstate catalysed oxidation of tetrahydroisoquinoline (11) with

hydrogen peroxide, [Scheme 4].

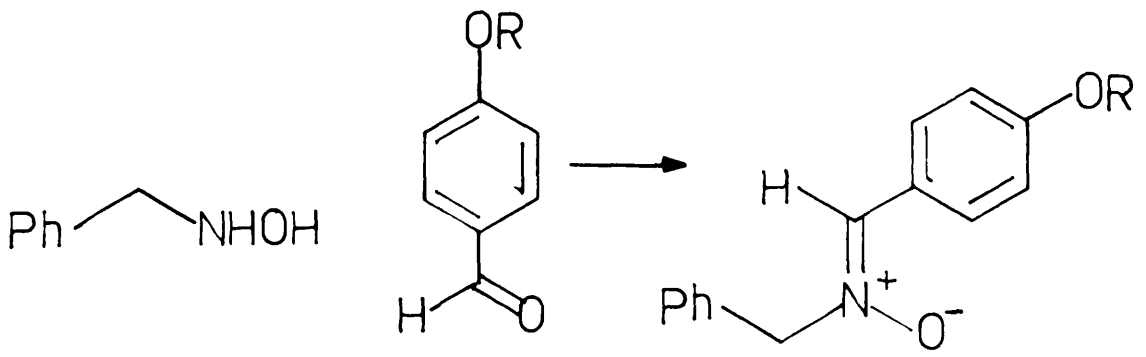


(11) (12)

Scheme 4.

The i.r of nitrone (12) displayed C=N absorption at 1595cm^{-1}.

Treatment of hydroxylamine (2) with p-methoxy-benzaldehyde (13) in refluxing benzene, and p-hydroxy-benzaldehyde (14) in refluxing methanol-benzene afforded nitrones (15) and (16), again in good yield, [Scheme 5].

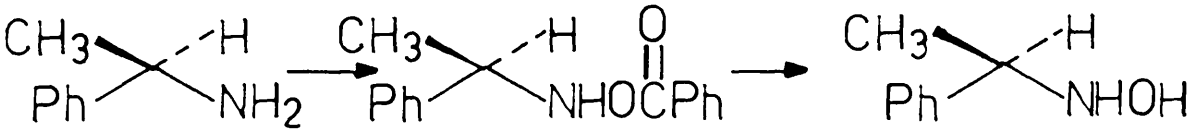


(2) (13) R=Me (14) R=H (15) R=Me (16) R=H

SCheme 5.

The i.r. spectra of nitrones (15) and (16) displayed C=N absorption at 1605 and 1600 cm^{-1} respectively.

Chiral benzylic nitrones of the type described by Belzecki[68] required the synthesis of (R)-(+)-α-methylbenzylhydroxylamine (19). This can be achieved by employing the method of Zinner[77] in which oxidation of the optically pure amine (17) with benzoylperoxide gives initially the benzoylhydroxylamine (18) which is subsequently hydrolysed under basic conditions to yield hydroxylamine (19), [Scheme 6]. However, the optimum yield of this reaction is approximately 30% overall.

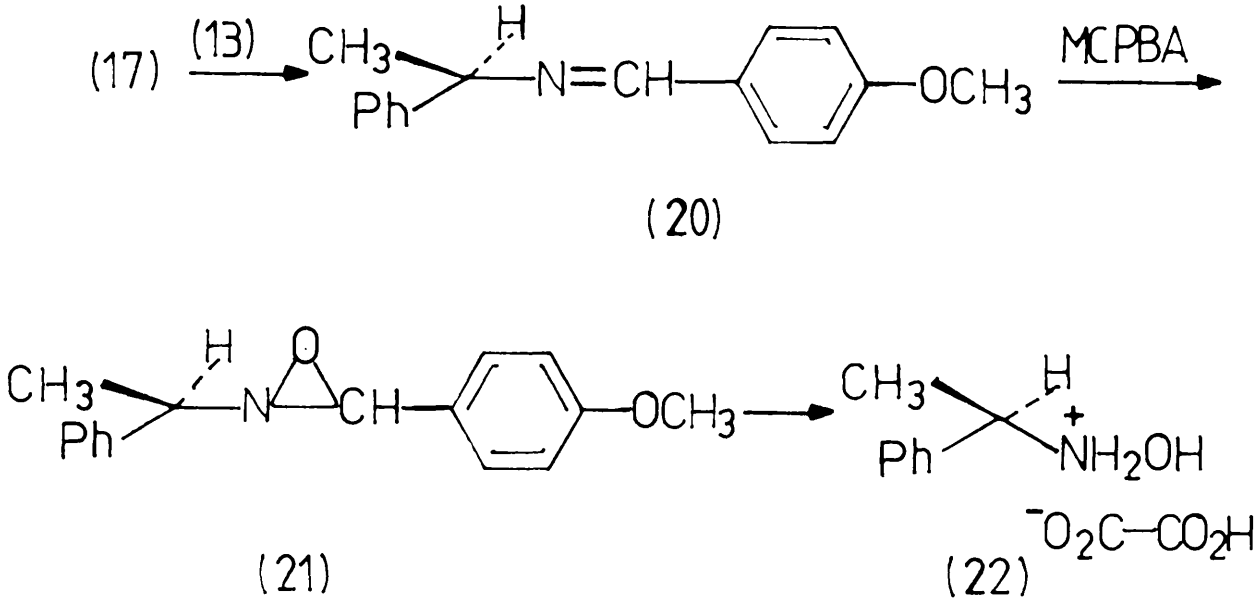


(17) (18) (19)

Scheme 6.

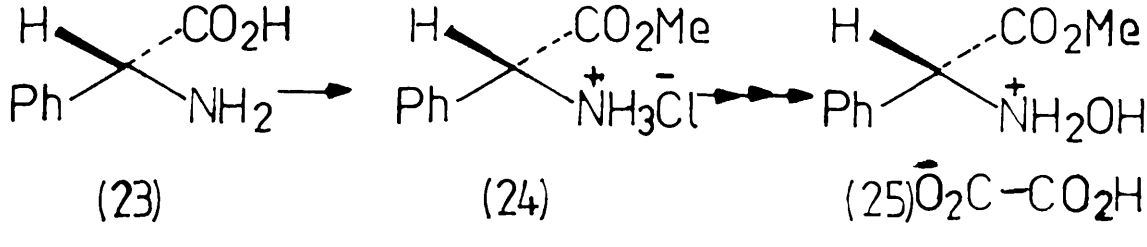
The method employed during the course of the work described in this thesis is that of Polonsky and Chimiak[78] in which optically pure amine (17) is converted into chiral hydroxylamine oxalate (22) in three simple steps via the

imine (20) and the oxaziridine (21), and has afforded superior yields of up to 50%, [Scheme 7].



Scheme 7.

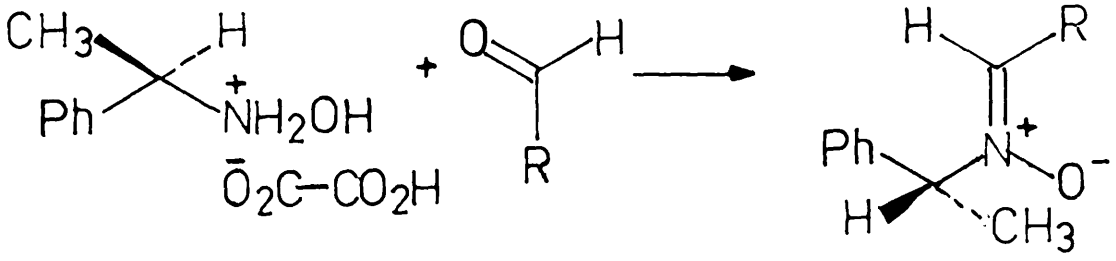
(R)-(+)-α-Carbomethoxybenzylhydroxylamine oxalate (25) was synthesised using the same general method starting from (D)-α-phenylglycine (23) which was first converted to the corresponding methylester hydrochloride (24), however the optimum yield of this process was only about 16%, [Scheme 8].



Scheme 8.

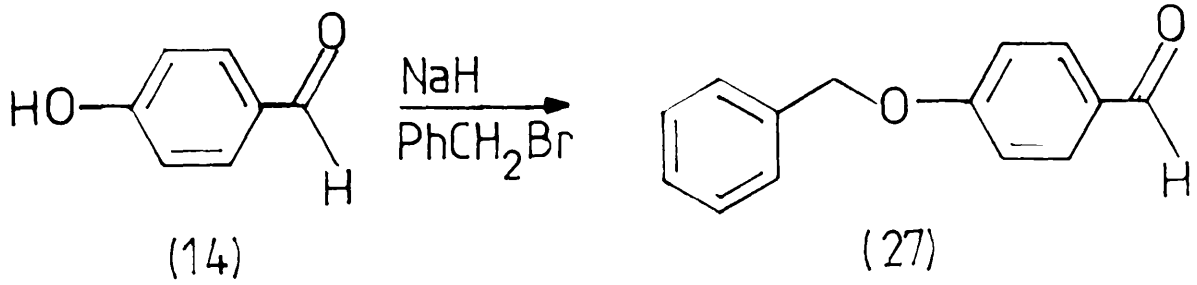
Satisfactory spectroscopic date were obtained for oxalate (25) but the microanalytical data were unsatisfactory in separate runs.

The chiral nitrones (28-31) were prepared by treatment of oxalate (22) with triethylamine (1.1 equiv.) and the appropriate aldehydes (13,14,26,27) in either refluxing benzene or benzene-methanol. Aldehyde (27) was prepared by treatment of p-hydroxybenzaldehyde (14) in DMF with sodium hydride in the presence of benzylbromide, [Scheme 9].



(22)

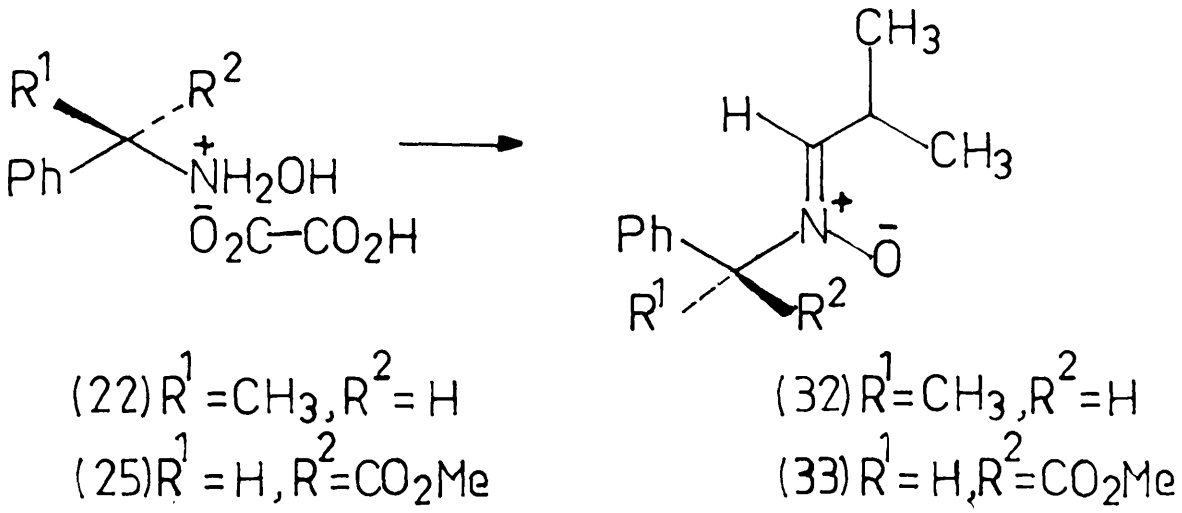
(26) R=Ph (28) R=Ph
(13) R=pMeOPh (29) R=pMePh
(14) R=pHOPh (30) R=pHOPh
(27) R=pBzOPh (31) R=pBzOPh



(14) (27)

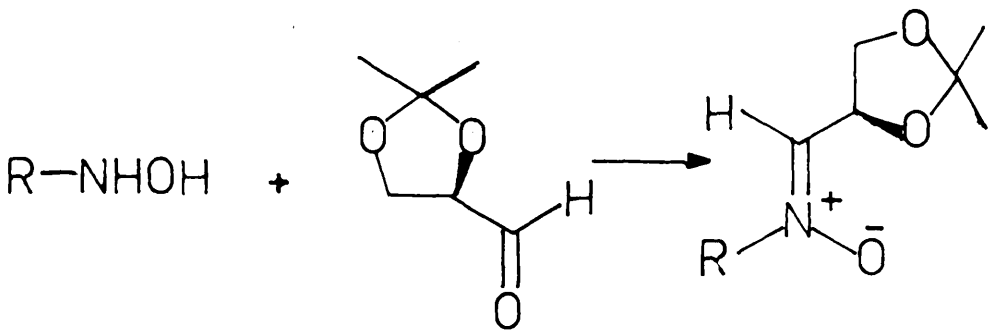
Scheme 9.

Similarily, nitrones (32) and 33) were prepared by treatment of the appropriate hydroxylamine oxalate with triethylamine in the presence of iso-butyraldehyde 4) in dichloromethane at room temperature, [Scheme 10].



Scheme 10.

Nitrones (35) and (36) were readily prepared by condensation of the appropriate hydroxylamine with 2,3-O-isopropylidene-D-glyceraldehyde (34) following the general procedure of DeShong.[79] Aldehyde (34) was synthesised in two steps from (D)-mannitol following the procedures of Baer and Fischer,[80,81] [Scheme 11].



(2) R=PhCH$_2$ (34) (35) R=PhCH$_2$

(22) R=(R)-PhCHCH$_3$ (36) R=(R)-PhCHCH$_3$

Scheme 11.

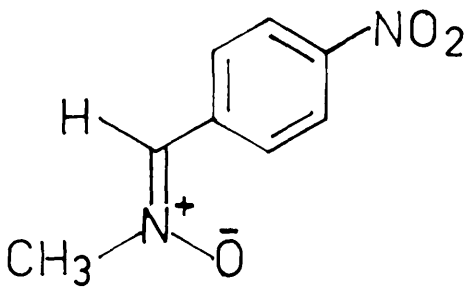
The i.r. spectra of the aforementioned chiral nitrones typically displayed the expected C=N absorption at around 1600cm^{-1}. With the exception of compounds (12), (28) and (33), all of the nitrones described above were obtained as crystalline solids.

1.2 Configuration of Acyclic Nitrones.

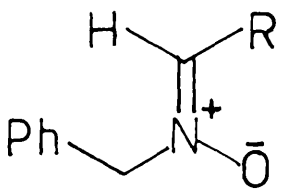
The stereochemistry of acyclic nitrones, particularly of aromatic aldonitrones, is a subject that has received some attention, and indeed a knowledge of double bond geometry is essential for predicting and interpreting the outcome of cycloadditions with nitrones.

In general, aldonitrones have been observed as single geometric isomers, presumably in the thermodynamically more stable Z- configuration. For instance, Boyd[82] has

established the Z- configuration of aromatic nitrone (37), and Moffat[49] has established the Z- configuration of nitrones (5), (6) and (38), both by employing NOEDS studies.



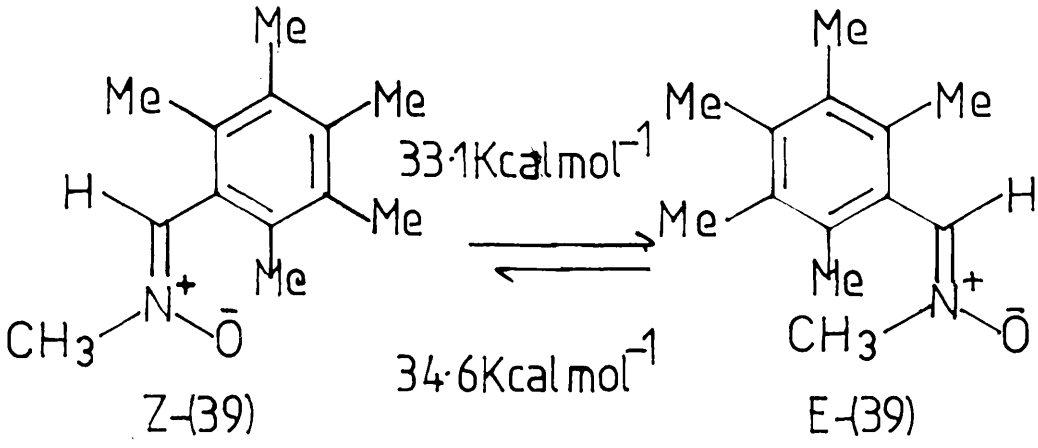
(37)



(5) R = Me
(6) R = iPr
(38) R = tBu

Furthermore, when nitrones (5) and (38) were heated in $CDCl_3$ in the presence of benzoic acid no trace of the isomeric E-nitrones was observed, howver nitrone (5) was seen to dimerise on heating at temperatures greater than 100°C in d^8-toluene.[49] Whereas there are several examples of the rapid dimerisation of N-phenyl-C-alkylnitrones,[83] this is evidently not a characteristic shared by their N-benzyl analogues.

Boyd[84] has also studied the E⇌Z isomerisation of certain aromatic aldonitrones such as (39), and has established by calculating the barrier for rotation about the C=N bond that such nitrones show considerable configurational stability [Scheme 12].



Scheme 12.

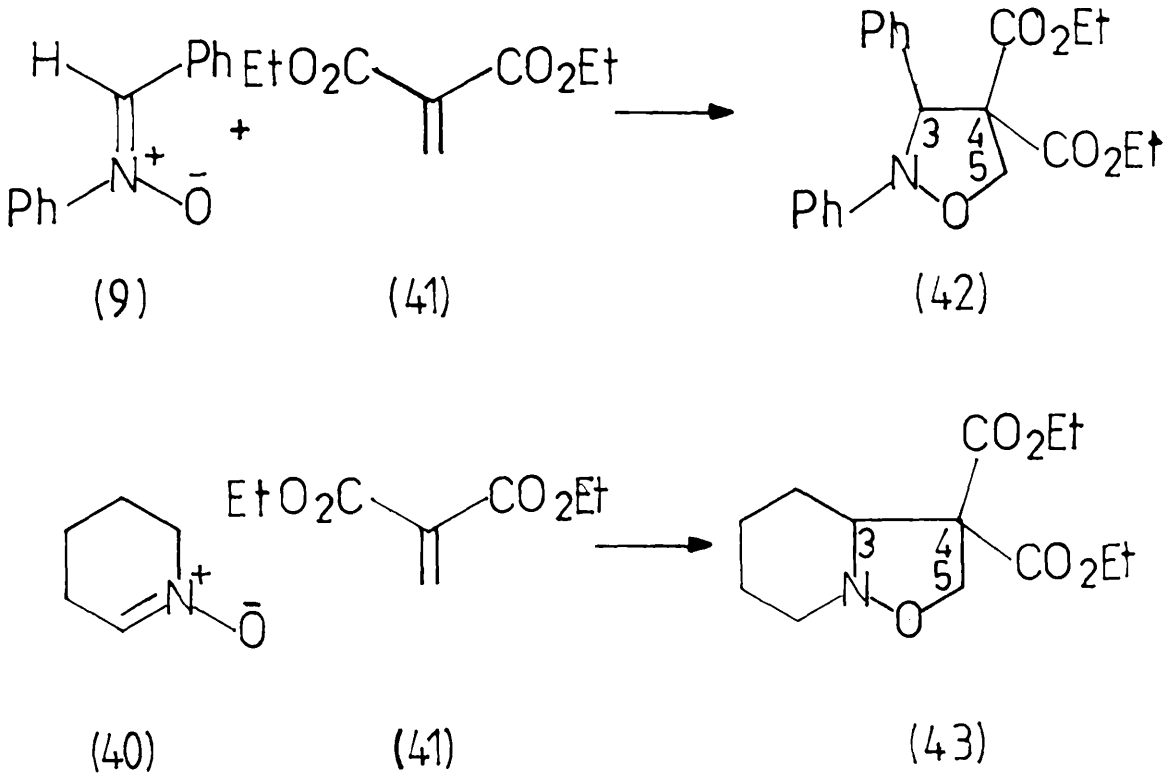
The ^{1}H nmr spectra of all the nitrones previously described in this chapter also indicate the formation of a single geometrical isomer, suggesting exclusive formation of the thermodynamically more stable Z-nitrone. This apparent configurational stability considerably simplifies the analysis of the transition states that are relevant for the cyclo-additions discussed in the following chapters.

CHAPTER 2.

1,3-Dipolar Cycloaddition Reactions of Nitrones with Diethyl Methylidenemalonate, Diethyl Ethylidenemalonate and Ethyl Crotonate.

2.1 Background and Introduction.

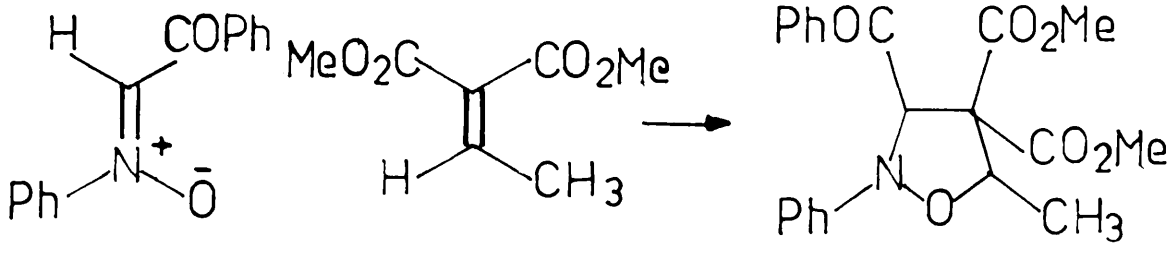
In 1979 Tufariello[85] reported that both C,N-diphenylnitrone (9) and 3,4,5,6-tetrahydropyridine oxide (40) undergo cycloaddition with diethyl methylenemalonate (41) to give the 4,4' - disubstituted isoxazolidines (42) and (43) respectively, [Scheme 13].



Scheme 13.

It has also been shown that C-benzoyl-N-phenyl-nitrone (44) reacts regiospecifically with dimethyl ethyl-idenemalonate (45) to afford only the 4,4'-disubstituted

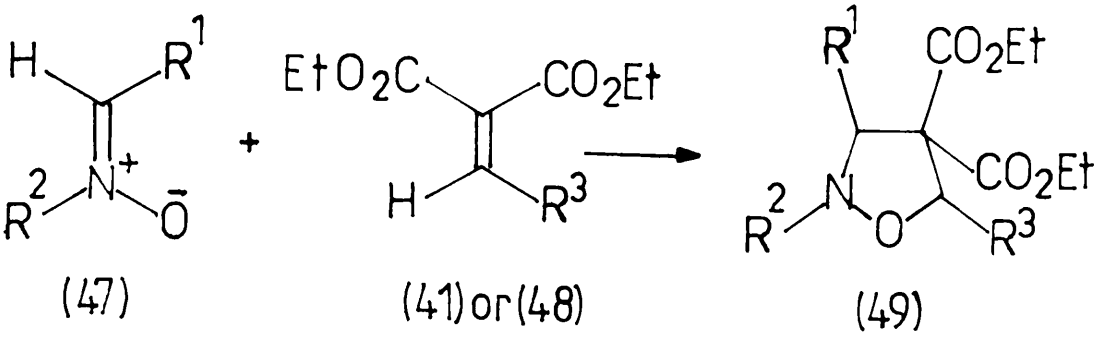
isoxazolidine (46),[86] [Scheme 14].



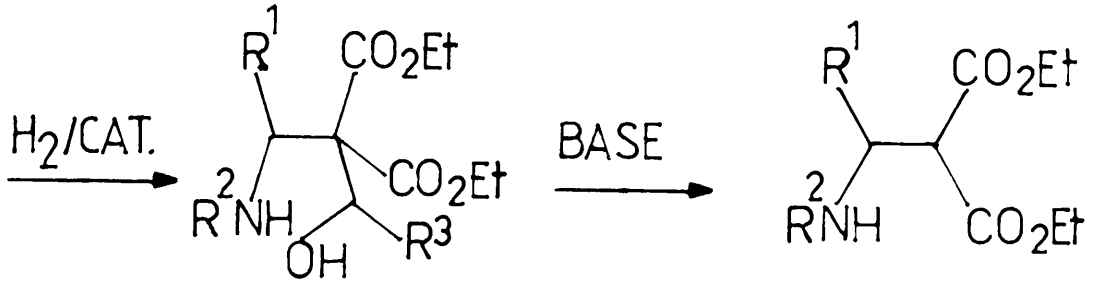
(44) (45) (46)

Scheme 14.

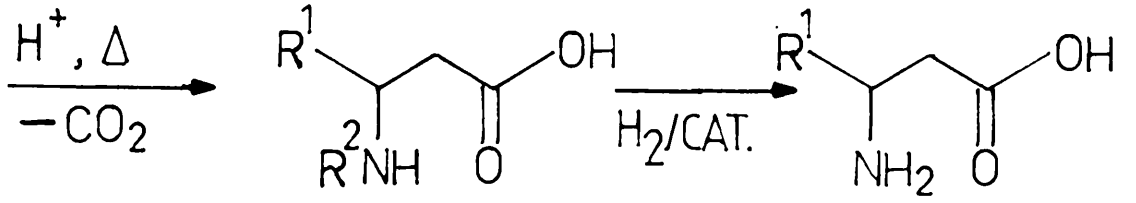
In the light of this apparent regiospecificity, it was envisaged that [3 + 2] cycloaddition reactions of chiral nitrones with diethyl methylidene- or ethylidene-malonate could constitute the first step in an asymmetric synthesis of β-amino acids, [Scheme 15]. After hydrogenolysis of the cycloadduct (49), the aim was to de-formylate or de-acetylate the aminol (50) using the two carboethoxyl groups as the driving force in this step, and then to hydrolyse and de-carboxylate (51) to give the N-protected β-amino acid (52) which could be deprotected by hydrogenolysis to yield the free β-amino acid (53).



(47) (41) or (48) (49)



(50) (51)



(52) (53)

R^1 = ALKYL or ARYL

R^2 = $PhCH_2-$, (R)−$PhCHCH_3$

R^3 = H, CH_3

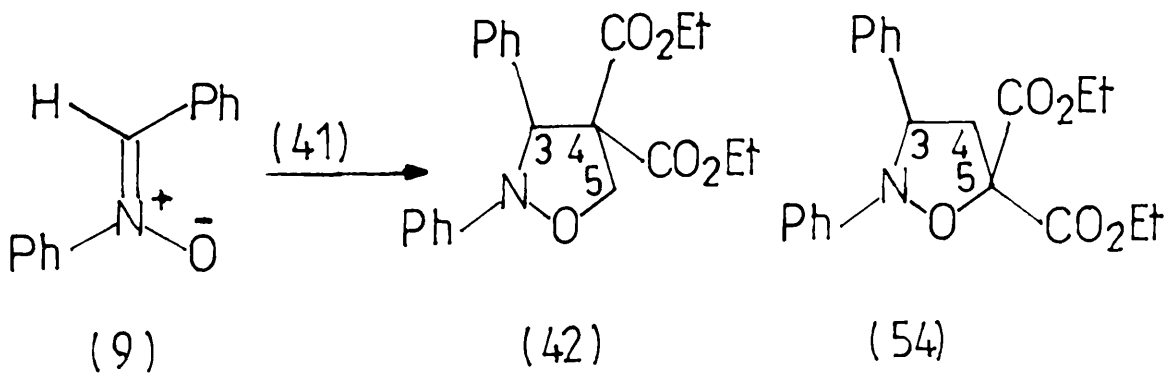
Scheme 15.

Discussion

2.2 1,3-Dipolar Cycloaddition Reactions of Nitrones with Diethyl Methylidenemalonate, Diethyl Ethylidenemalonate and Ethyl Crotonate.

Initial investigations were carried out employing achiral nitrones. Diethyl methylidenemalonate (41) was prepared by the method of Bachman[87] by refluxing diethylmalonate in glacial acetic acid in the presence of paraformaldehyde and catalytic amounts of potassium and copper acetates. Diethyl methylidenemalonate is known[87] and was found to polymerise quite rapidly on standing, and was therefore used immediately after distillation in each of the following cycloadditions.

Cycloaddition of C,N-diphenylnitrone (9) with (41) in refluxing toluene under an argon atmosphere gave a mixture of the two regio-isomeric isoxazolidines (42) and (54) which are separable by chromatography, the relative ratio of which was seen to vary with reaction time, [Scheme 16, Table 1].



(9) (42) (54)

Scheme 16

Table 1.

Reaction Time(h)	Ratio 42:54	Chemical Yield[a]
2	5:1	82%
4	2:1	72%
16	1:1	72%

a - Total yield after chromatography

Figure 1 shows the 90MHz ^1H nmr spectrum of (42) the regiochemistry of which was easily assigned by the one proton singlet at δ5.56 corresponding to the C-3 proton, and the AB quartet (J = 10 Hz) centred at δ4.7 corresponding to the two C-5 protons. As expected, separate signals appear for each of the diastereotopic - CH_3 and -CH_2- groups of the two carboethoxyl moieties. Each of the -CH_2- groups should give rise to 16 lines due to the diastereotopic nature of the protons within each -CH_2- group. The lower field -CH_2- multiplet centred at δ4.16 appears as two overlapping quartets, while the higher field -CH_2- multiplet centred at δ3.6 clearly shows 16 lines reflecting the non-equivalence of each of the protons within each -CH_2- group. The two -CH_3 triplets (J = 7.6 Hz) appear at δ0.8 and 1.15 respectively.

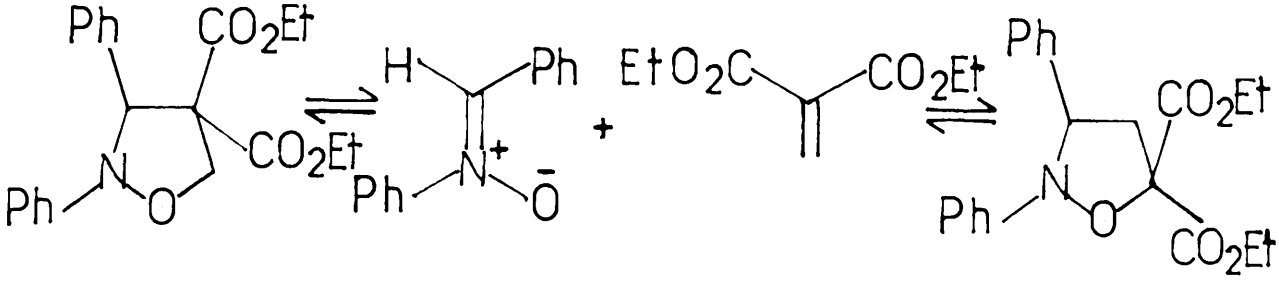
Figure 2 shows the ^1H nmr spectrum of the regio-isomeric isoxazolidine 54) which clearly shows the expected ABX pattern for the three-proton system at C-3 and C-4. The two C-4 protons correspond to the doublets of doublets

at δ2.99 (J = 7.9, 13.8 Hz) and δ3.34 (J = 7.9, 13.8 Hz) respectively. The C-3 proton corresponds to the triplet at δ4.65, (J = 7.9 Hz). In contrast to the ^{1}H nmr spectrum of the regio-isomeric isoxazolidine (42), the two $-O\underline{CH}_2CH_3$ groups appear as a single multiplet centred at δ4.21 and both $-OCH_2\underline{CH}_3$ groups appear as a slightly broadened triplet at δ1.2, (J = 7.8 Hz). Thus, the non-equivalence of the two carboethoxyl moieties is apparently much greater in isoxazolidine (42) than in (54), presumably due to the proximity of the C-3 phenyl substituent.

Both of these isoxazolidines were obtained as oils after chromatography, and accurate mass analysis showed $[M]^+$ = 369.1583 for (42) and $[M]^+$ = 369.1572 for (54), corresponding to a molecular formula of $C_{21}H_{23}NO_5$ (calc.m/e = 369.1576). The i.r. spectra of (42) and (54) show strong carbonyl absorptions at 1735 and 1743 cm^{-1} respectively.

As discussed in the introduction, the dominant interaction between a nitrone and a highly electron-deficient dipolarophile such as diethyl methylenemalonate should be HOMO(dipole) - LUMO(dipolarophile), and one would consequently expect the 4,4'-disubstituted isoxazolidine to be the dominant product (by analogy with nitroethylene). The time-course data in Table 1 suggests that isoxazolidine (42) is indeed the kinetic product, however the relative amount of (54) increases with time suggesting that this cycloaddition is reversible and that isoxazolidine (54) is the thermodynamically

more stable product, [Scheme 17].



(42) (54)

Scheme 17

Isoxazolidines which have groups at C-4 or C-5 capable of conjugative stabilization of the developing dipolarophile double bond in the transition state for the cycloreversion process, are known to undergo this reversal with relative ease. For example, nitrone (55) is known to give isoxazolidine (56) on treatment with ethyl acrylate under conditions of kinetic control,[51,88] [Scheme 18]. However, when the reaction is run for several days an approximately equimolar amount of the two isomeric isoxazolidines is obtained at equilibrium.

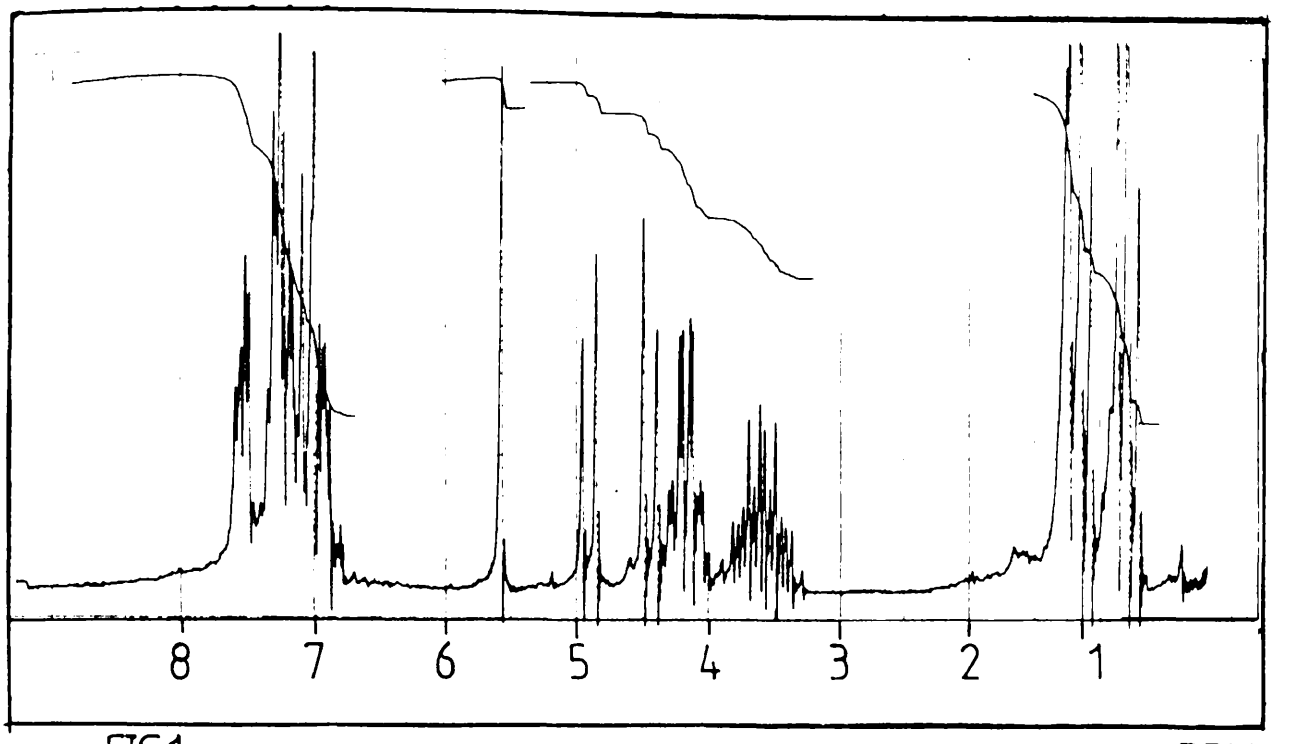


FIG.1

^1H NMR SPECTRUM OF ISOXAZOLIDINE (42) AT 90MHz.

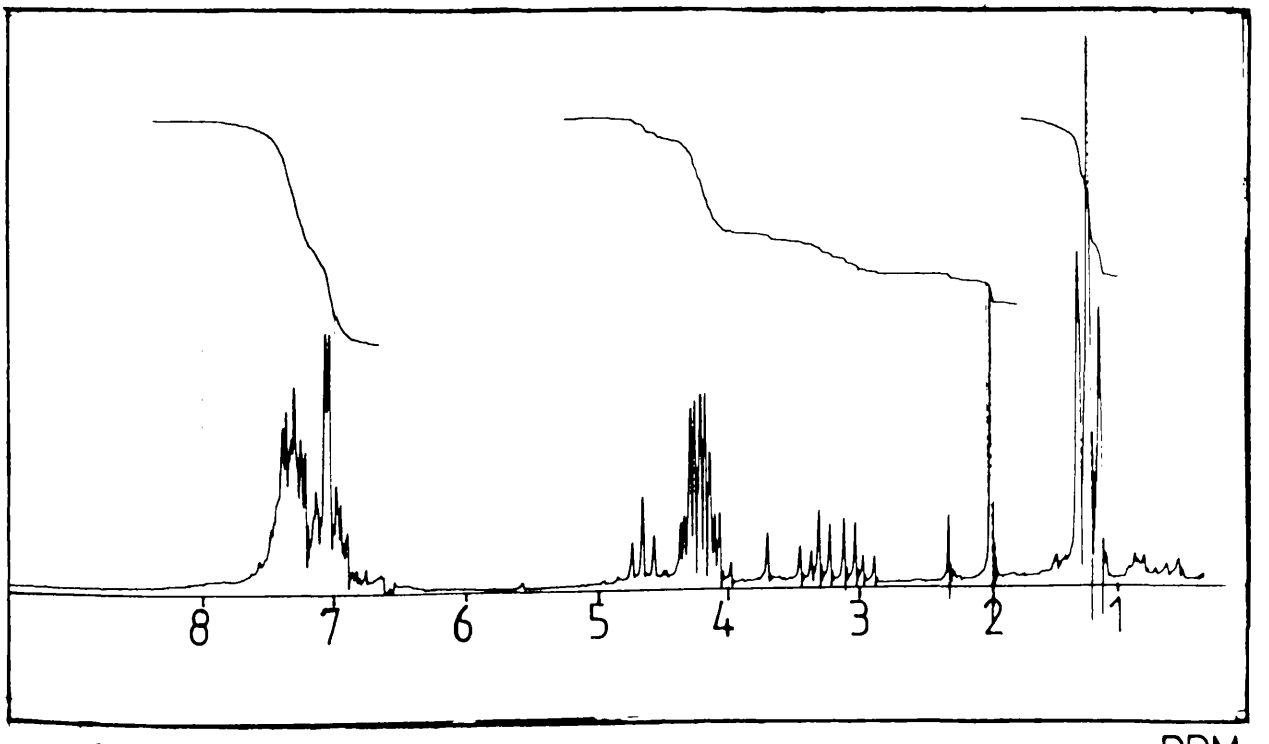
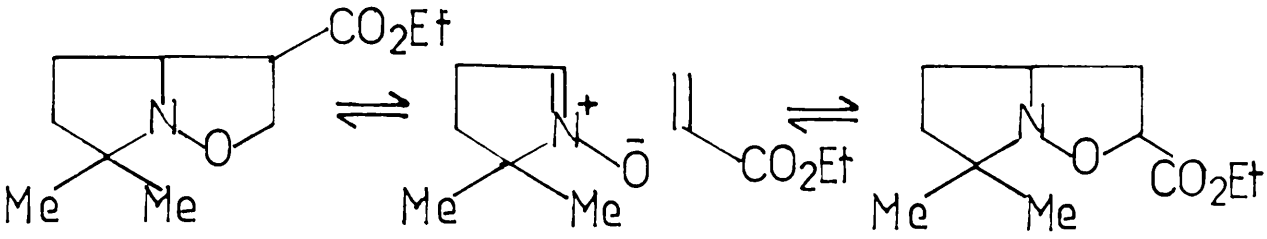


FIG.2

^1H NMR SPECTRUM OF ISOXAZOLIDINE(54) AT 90MHz.

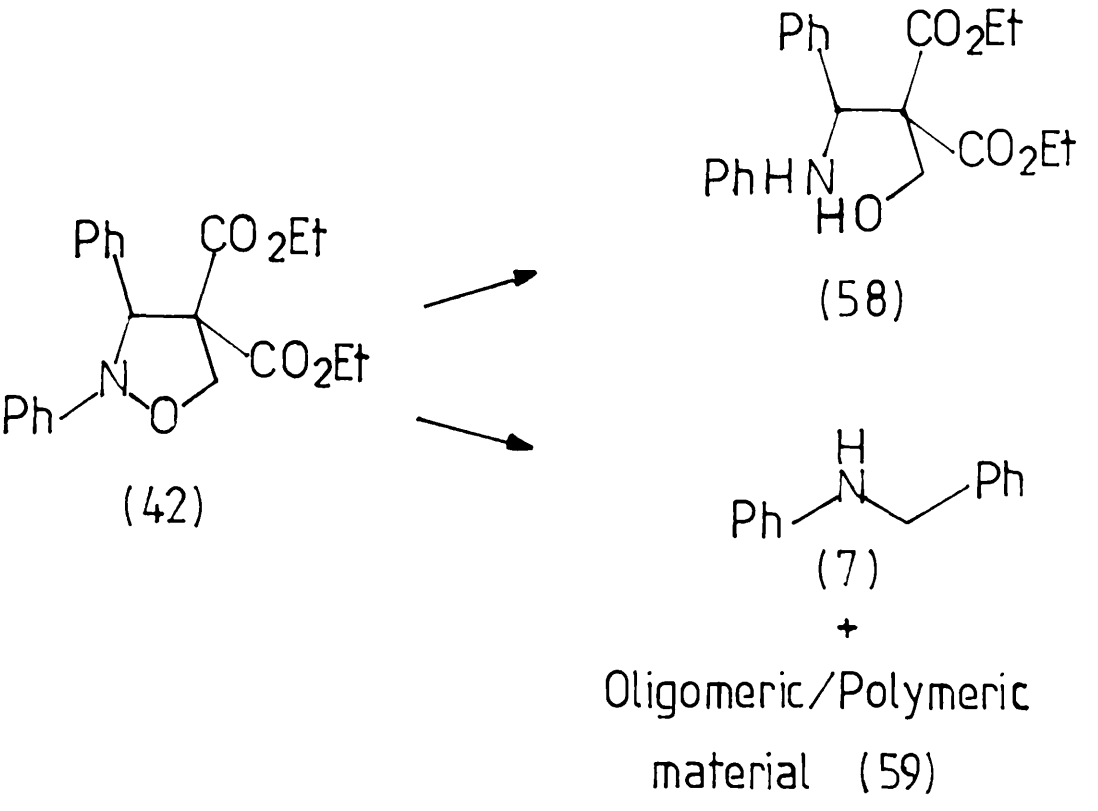


(57) (55) (56)

Scheme 18

The attempted hydrogenolysis of isoxazolidine (42) proved to much more complicated than expected. Instead of the desired aminol (58), a complicated mixture of products was obtained on attempted hydrogenolysis in ethanol at room temperature in the presence of catalytic amounts of Pd/C, PtO_2/C or Ni. In each of these cases the same result was observed:

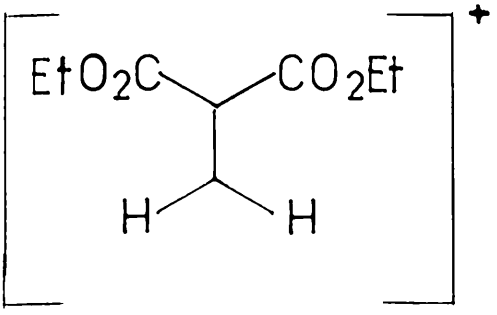
Instead of aminol (58), fragments whose ^1H nmr spectra displayed a lack of either carboethoxyl or aromatic signals were isolated after chromatography. From these fragments, N-phenylbenzylamine (59) was recovered along with oligomeric or polymeric material derived from the malonyl portion of adduct (42), [Scheme 19].



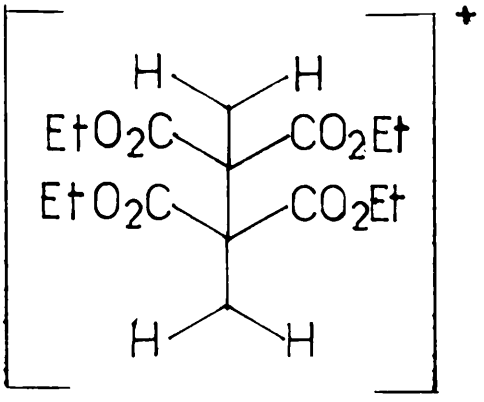
Scheme 19

The i.r. spectrum of the latter shows a strong carbonyl absorption at 1730 cm^{-1}, while accurate mass analysis showed m/e = 346.1616 as the highest mass ion corresponding to a molecular formula of $C_{16}H_{26}O_2$ (calc. m/e = 346.1627), and m/e = 173.0816 as the base peak (100%) corresponding to a molecular formula of $C_8H_{13}O_4$ (calc. m/e = 173.08138). The ion of composition $C_8H_{13}O_4^+$ may correspond to (60) shown below, while the ion of composition $C_{16}H_{26}O_2^+$ may be accounted for by a dimeric ion such as (61) or (62). Accurate mass analysis also showed m/e = 174.0962 corresponding to a molecular formula of $C_8H_{14}O_4$ (calc. m/e = 174.0962) which could be accounted for by the presence of methyl diethyl-malonate (63). The ion represented by (60) may have been

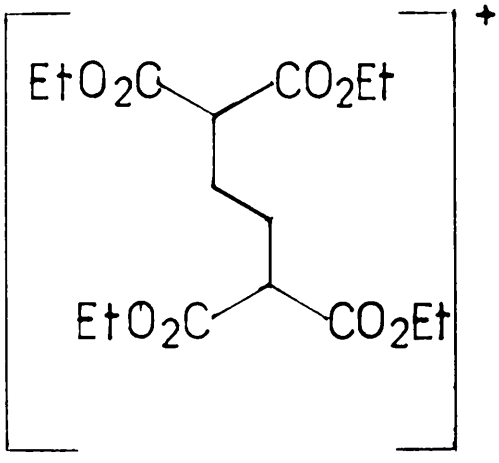
derived from oligomeric or polymeric material or from (63).



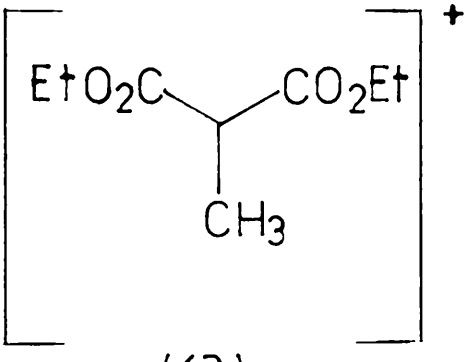
(60)



(61)



(62)

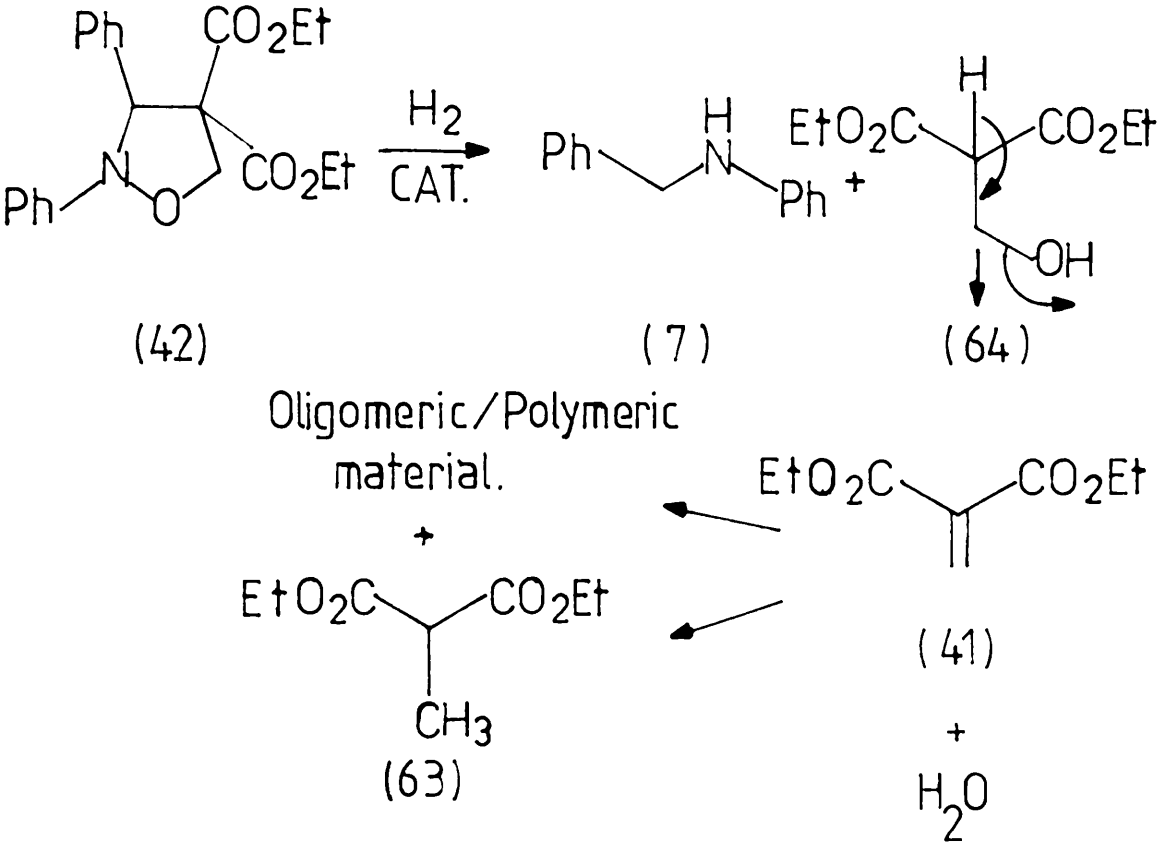


(63)

This material was still a mixture of compounds as indicated by TLC analysis which showed two or more overlapping spots. The only useful information to be drawn from the ^1H nmr spectrum of this mixture is that the carboethoxyl moieties that originated in cycloadduct (42) are substituents in this material as can be seen by the triplet at $\delta 1.2$ (J = 7.8 Hz) and the quartet at $\delta 4.15$ (J = 7.8 Hz).

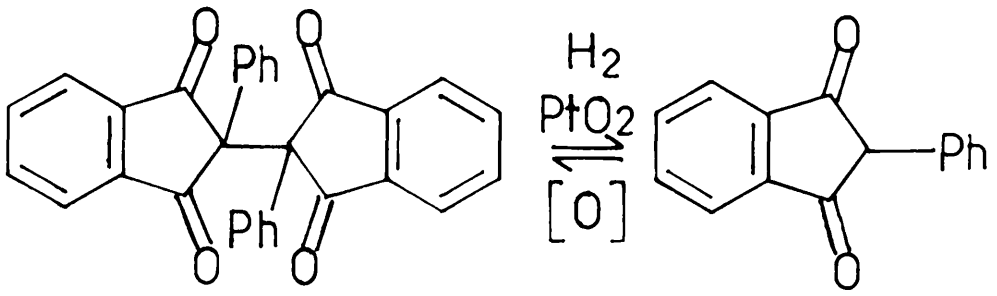
The evidence presented here suggests that during hydrogenolysis the C_3 - C_4 as well as the N-O bond has been cleaved, and that the malonyl alcohol (64) so produced has

after elimination of H_2O, oligomerised or polymerised under the conditions of hydrogenolysis. In addition to this some of the diethyl methylenemalonate (41) produced after elimination of H_2O may have been hydrogenated to afford methyl diethylmalonate (63), [Scheme 20].



Scheme 20

Benzylic carbon-carbon bonds are not easily cleaved under mild hydrogenolytic conditions unless the bond is part of a strained system or is weakened by other structural features, as in the example shown below,[29] [Scheme 21].

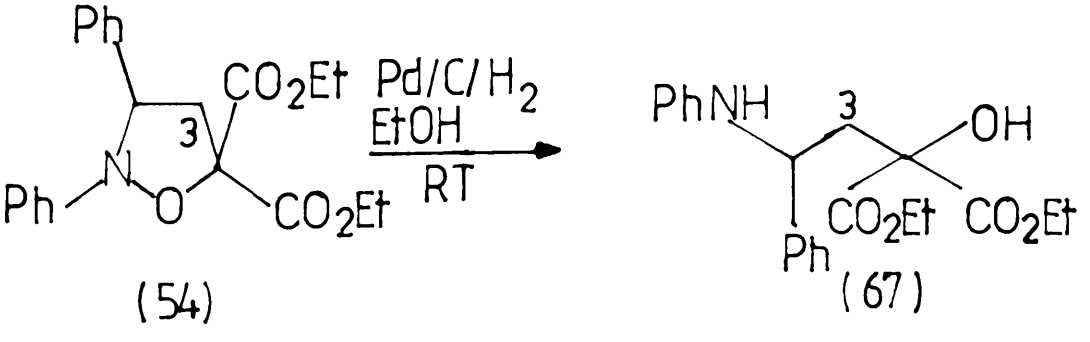


(65) (66)

Scheme 21

Presumably the C_3 - C_4 bond in isoxazolidine (42) is weakened by the electron-withdrawing effect of the two carboethoxyl groups at C_4, in a manner similar to the effect seen in the tetrone (65).

This hypothesis is supported by the observation that in contrast to the above, isoxazolidine (54) undergoes smooth hydrogenolysis at room temperature to afford the expected aminol (67) as a colourless oil in [illegible] yield after chromatography, [Scheme 22].

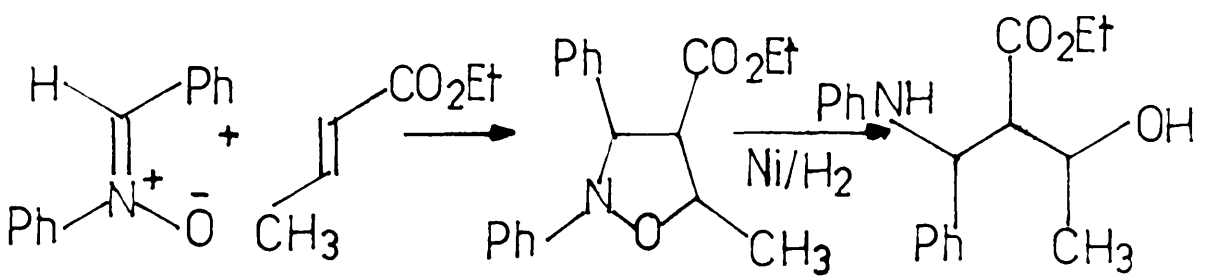


(54) (67)

Scheme 22

The ^1H nmr of the aminol (67) shows the two C-3 protons as a doublet at δ2.55 (J = 6.9 Hz), the C-4 proton as a triplet at δ4.68 (J = 6.9 Hz), and a broad singlet at δ4.35 corresponding to two D_2O- exchangeable protons [Figure 3]. The i.r. spectrum of (67) shows hydrogen bonded -OH at 3500 cm^{-1} and a strong carbonyl band at 1740 cm^{-1}. Accurate mass analysis showed $[M]^+$ = 371.1737 corresponding to a molecular formula of $C_{21}H_{25}NO_5$ (calc. m/e ; 371.1733).

The foregoing hypothesis is also supported by an observation by Huisgen[90] that isoxazolidine (69) obtained regiospecifically by the cycloaddition of C,N-diphenylnitrone (9) with ethyl crotonate (68), undergoes hydrogenolysis in the presence of Raney nickel to afford the corresponding aminol (70). When this was repeated, aminol (70) was obtained as a crystalline solid in 61% yield, m.p. 133-134°C (Lit. m.p. [90] 134.5 - 135°C), [Scheme 23].



(9) (68) (69) (70)

Scheme 23

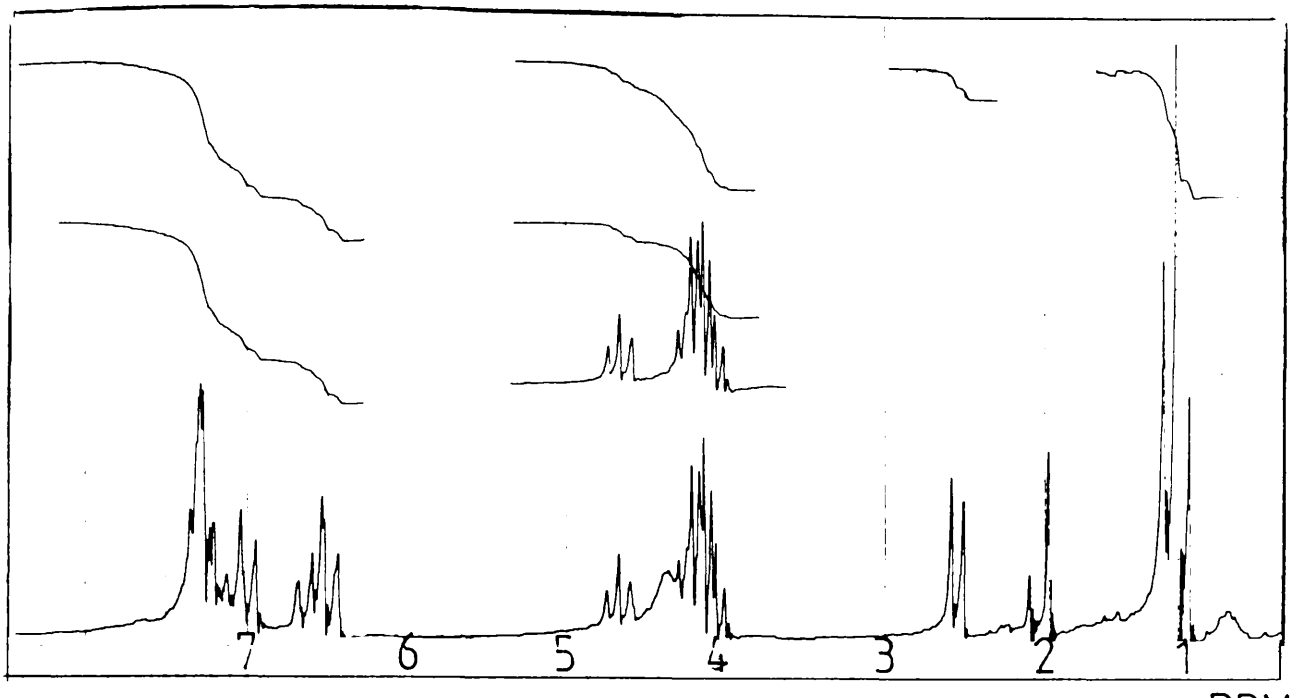


FIG 3.

^{1}H NMR OF AMINOL(67) AT 90MHz

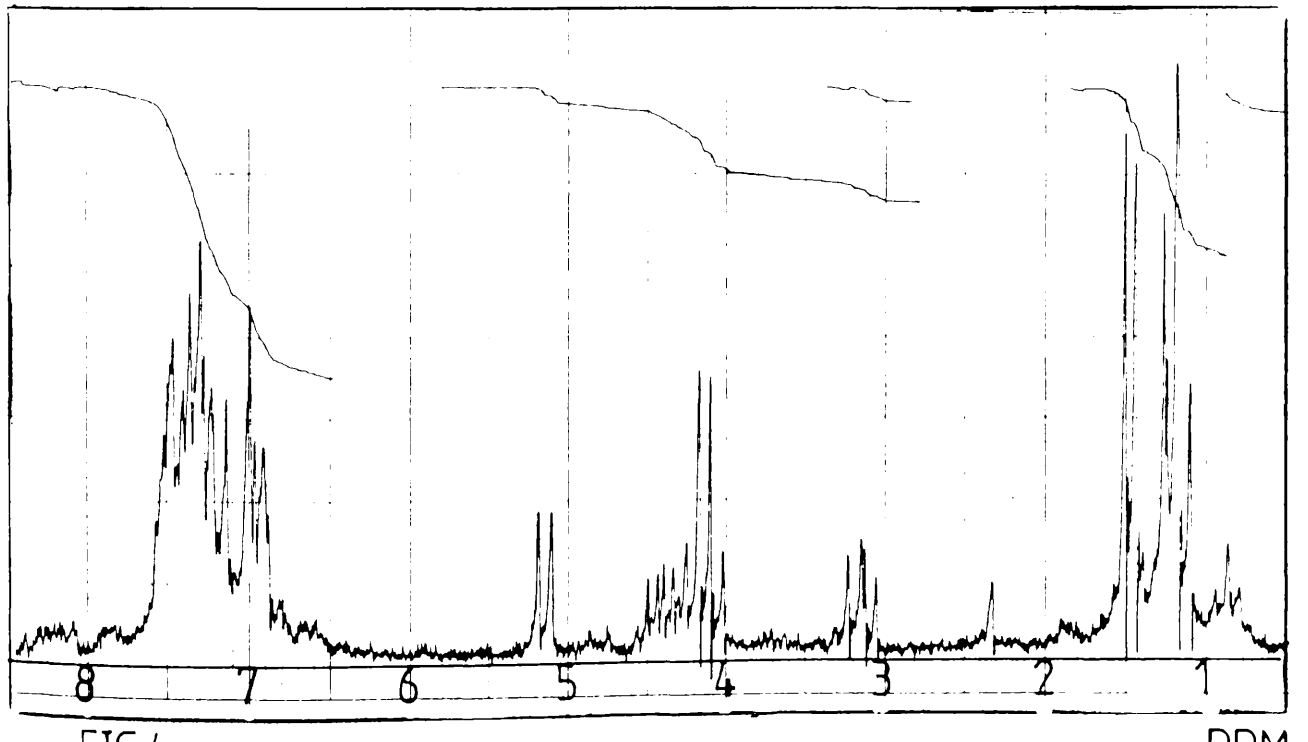


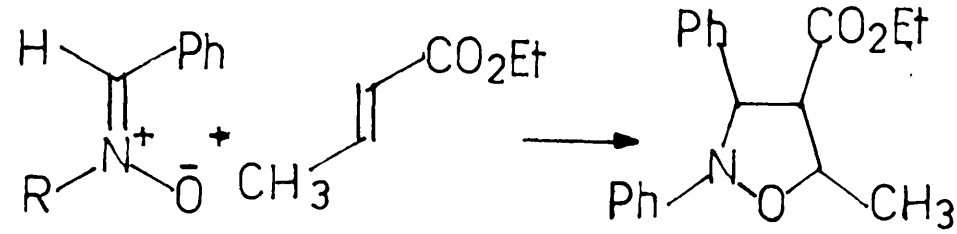
FIG.4

^{1}H NMR SPECTRUM OF ISOXAZOLIDINE (69) AT 90MHz.

The regiochemistry of this cycloaddition was easily assigned on the basis of the position of the doublet of doublets at δ3.15 ($J_{3,4}$ = 7.8 Hz, $J_{4,5}$ = 9 Hz) corresponding to the C-4 proton in the ^{1}H nmr spectrum of (69), [Figure 4]. If the carboethoxyl group were located at C-5, the signal corresponding to the proton at C-4 would appear as a multiplet at significantly higher field. The ^{1}H nmr spectrum of aminol (70) is almost identical to that of isoxazolidine (69), except for small differences in the chemical shift values of the signals.

The observation that isoxazolidine (69) readily undergoes hydrogenolysis to afford aminol (70) indicates that in comparison to the case of (42), one carboethoxyl group at C-4 is not sufficient to facilitate hydrogenolysis of the C_3 - C_4 bond.

Both C-phenyl-N-benzyl and C-phenyl-N-α-methyl-benzylnitrone (10,28) were also shown to react regiospecifically with ethylcrotonate under the same conditions as described by Huisgen,[90] and afforded isoxazolidines (71) and (72) respectively, [Scheme 24].



(10) R = $PhCH_2$ (71) R = $PhCH_2$

(28) R = (R)-$PhCHCH_3$ (72) R = (R)-$PhCHCH_3$

Scheme 24

The regiochemistry of these cycloadditions was readily assessed by comparison with isoxazolidine (69). The ^1H nmr spectra of cycloadducts (71) and (72) show signals corresponding to the C-4 proton at δ3.08 and δ2.99 respectively, the former as a broadened triplet (J = 7.8 Hz, Figure 5) and the latter as a doublet of doublets ($J_{3,4}$ = 6.2 Hz, $J_{4,5}$ = 9 Hz, Figure 6). Also, as reported by Huisgen[90] Figure 4 shows an additional triplet at δ0.87 (J = 7 Hz) associated with the carboethoxyl group of another minor stereoisomer of isoxazolidine (69), these stereoisomers presumably differing in the relative stereochemistry of the C-3 and C-4 substituents. Similarily, an additional triplet can be clearly seen in Figure 5 at δ0.75 (J = 7.2 Hz). Isoxazolidines (64), (71)

and (72) were all obtained as oils after chromatography, the i.r.spectra of which show strong carbonyl absorptions at approximately 1725 cm^{-1}, [Table 2].

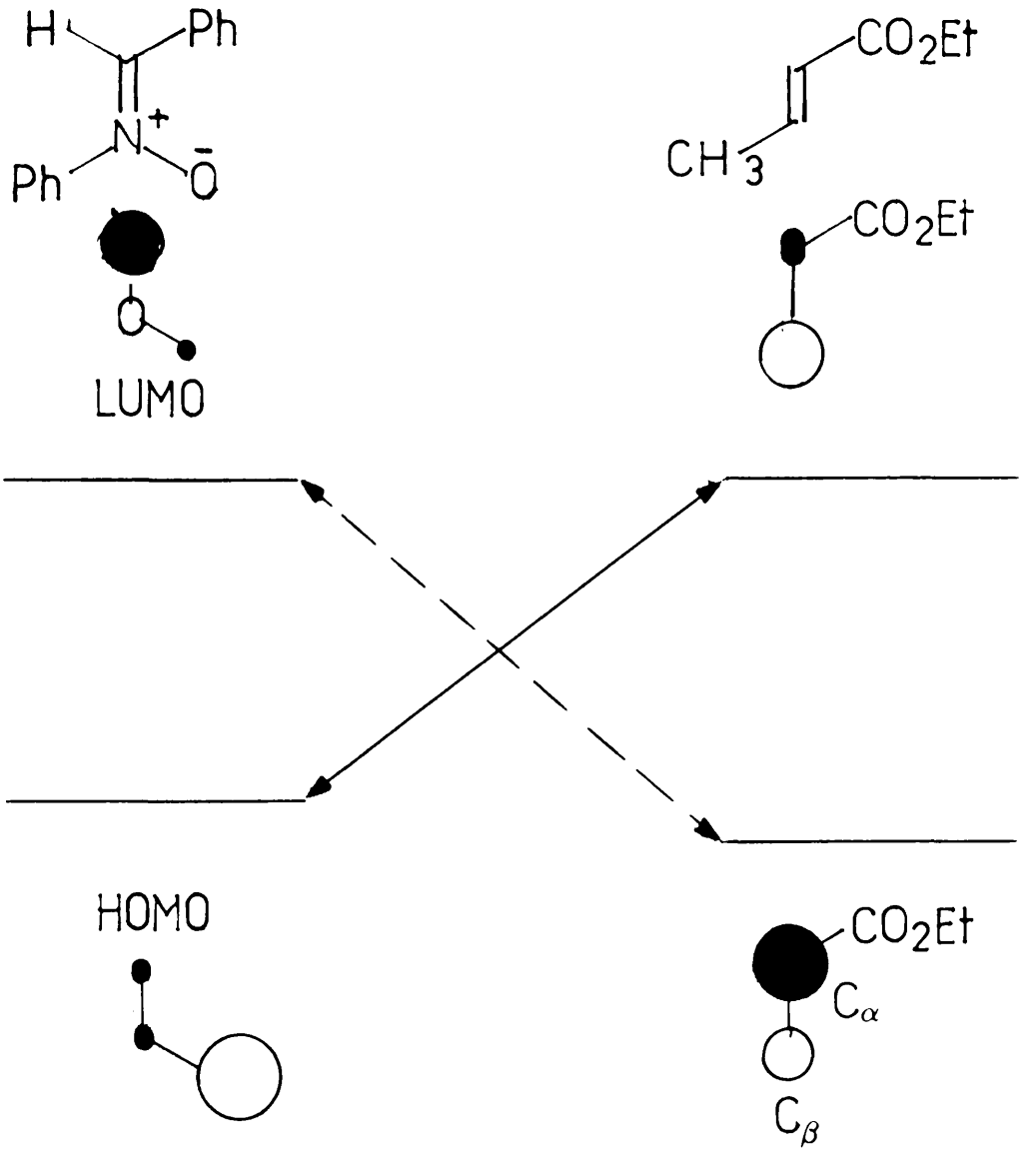
Table 2.

Isoxazolidine	$[M]^+$	Molecular Formula	m/e calc.	Yield[a]
69	311.1514	$C_{19}H_{21}NO_3$	311.1521	95%
71	325.1670	$C_{20}H_{23}NO_3$	325.1678	92%
72	339.1836	$C_{21}H_{25}NO_3$	339.1841	82%

(a) Yield after chromatography.

Huisgen[91] has explained this tendancy of nitrones to undergo cycloaddition reactions with alkyl crotonates to afford C-4 carboxylic ester-substituted isoxazolidines in terms of frontier molecular orbital interactions. In comparison to very electron deficient dipolarophiles such as nitroethylene (see Introduction) the atomic orbital coefficient at C_α in the HOMO of alkyl crotonates is slightly larger than the atomic orbital coefficient at C_β. Thus, both HUMO-LUMO interactions now favour formation of the C-4 carboxylic ester substituted isoxazolidine, [Scheme 25]. Presumably the energetically most favourable interaction is HOMO(dipole)-LUMO(dipolarophile), however the relative difference in energy between the respective HOMO-LUMO interactions may be expected to be less than in the case of a highly electron-deficient

dipolarophile such as nitroethylene.



Scheme 25

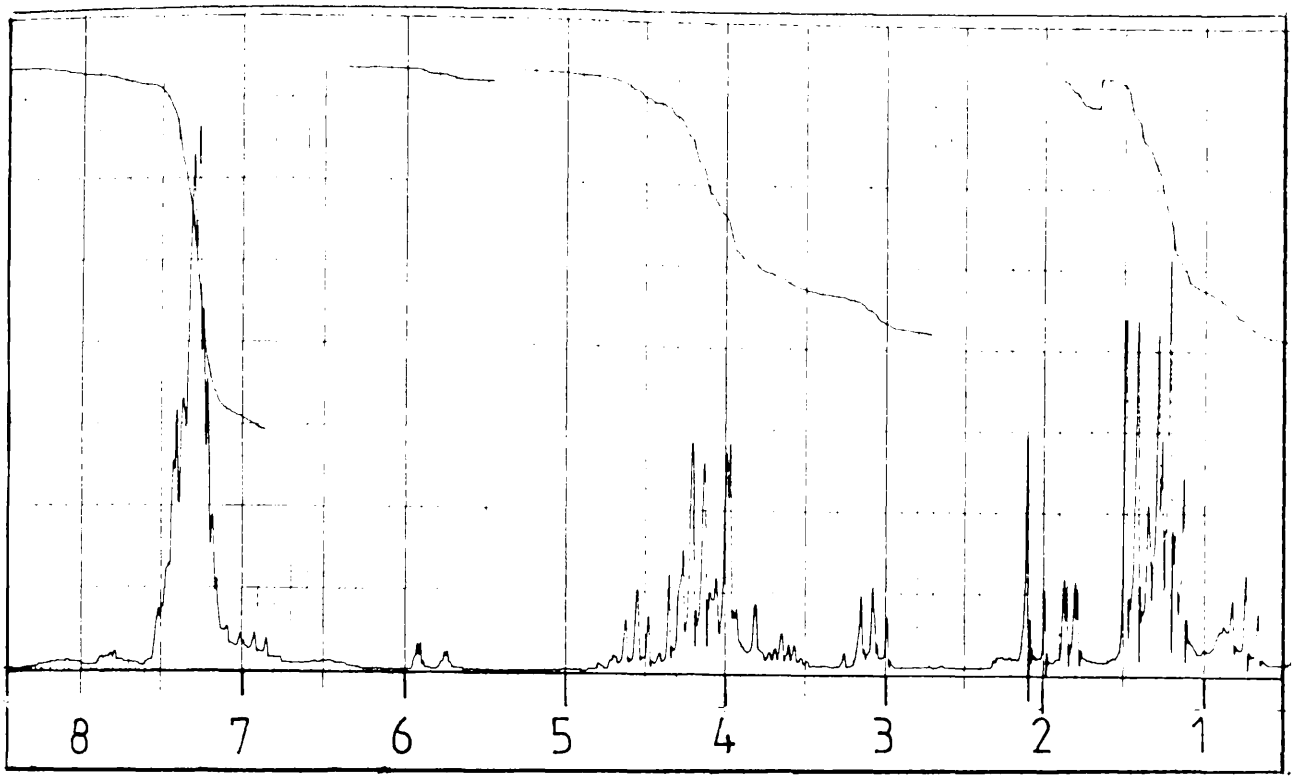


FIG.5

H NMR SPECTRUM OF ISOXAZOLIDINE(71)AT 90MHz.

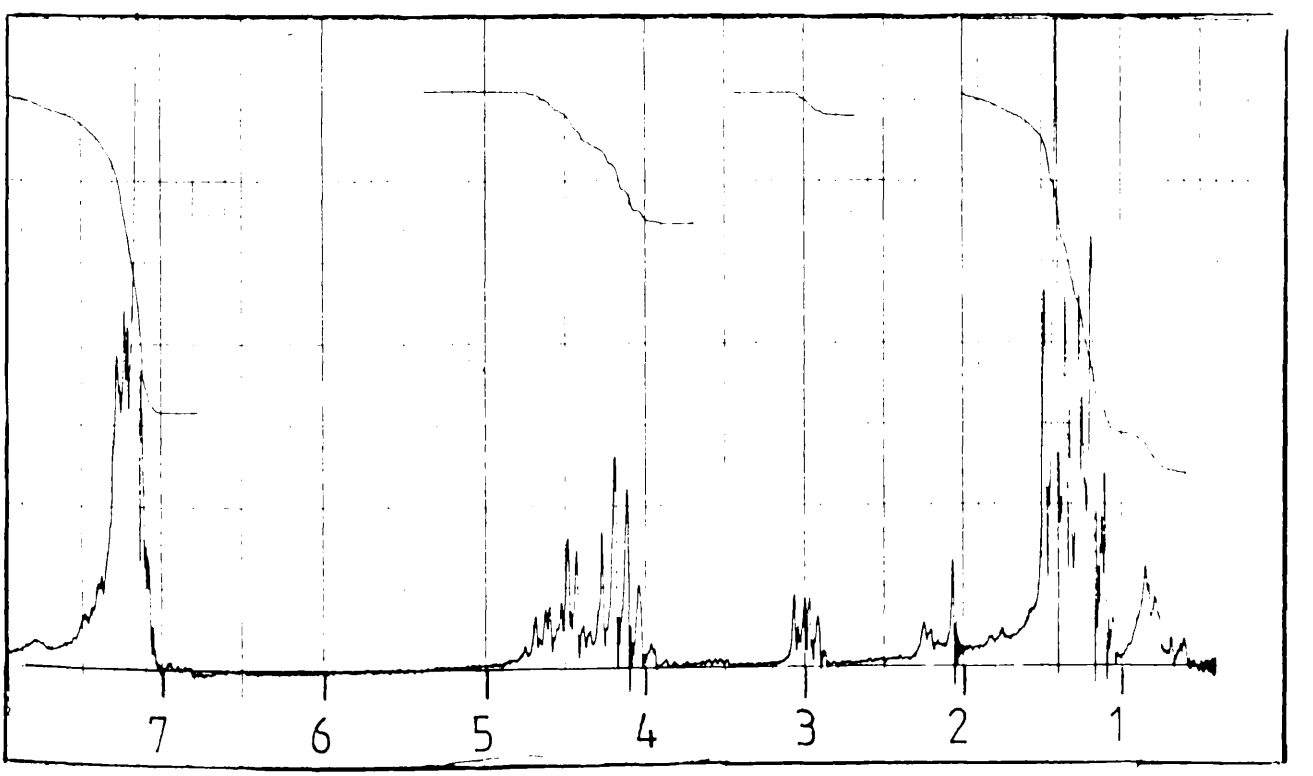
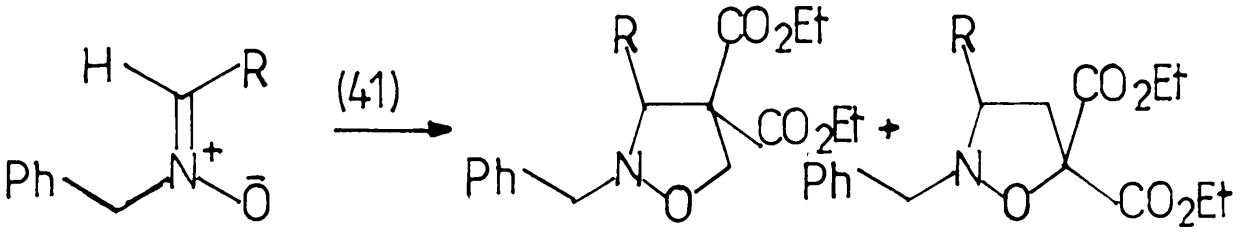


FIG. 6

^{1}H NMR SPECTRUM OFISOXAZOLIDINE(72)AT 90MHz

Cycloadditions between diethyl methylidenemalonate and nitrones (5), (6) and (10) were also carried out under the same conditions as described for the reaction with nitrone (9). Both C-phenyl-N-benzylnitrone and C-methyl-N-benzylnitrone afforded regioisomeric mixtures whereas C-isopropyl-N-benzyl-nitrone afforded only the 5,5'-disubstituted isoxazolidine. Each of the cycloadditions was run over a period of 16 h.



(5) R=Me
(6) R=iPr
(10) R=Ph

(73) R=Me
(74) R=Ph

(75) R=Me
(76) R=iPr
(77) R=Ph

Scheme 26

Table 3.

R	Ratio A:B[a]	Yield[b]
Me	1:8.5	62.4%
iPr	0:100	66.4%
Ph	1:1	73%

(a) Product ratio after chromatography

(b) Yield after chromatography

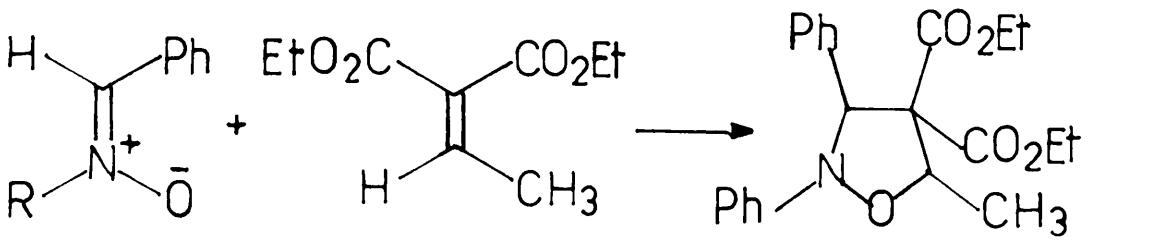
The regiochemistry of these isoxazolidines was readily assigned by comparison of their ^1H nmr spectra with those of compounds (42) and (54). The ^1H nmr spectra of the 5,5'-disubstituted isoxazolidines (75), (76) and (77) characteristically display signals in the region δ2.5 - δ3.0 corresponding to the two C-4 protons as part of an ABX system, while those of the 4,4'-disubstituted isoxazolidines (73) and (74) characteristically display separate signals for each of the diastereotopic $-CH_2-$ and $-CH_3$ groups of the two carboethoxyl moieties, although in the ^1H nmr spectrum of (73) these signals overlap, [Figures 7,8,9,10,11]. All of these compounds were obtained as oils after chromatography, the i.r. spectra of which showed strong carbonyl absorptions in the region 1729 to 1741 cm^{-1}, [Table 4].

Table 4.

Isoxazolidine	$[M]^+$	Molecular Formula	calc. m/e
73	321.1569	$C_{17}H_{23}NO_5$	321.1576
74	383.1739	$C_{22}H_{25}NO_5$	383.1733
75	321.1571	$C_{17}H_{23}NO_5$	321.1576
76	349.1891	$C_{19}H_{27}NO_5$	349.1889
77	383.1723	$C_{22}H_{25}NO_5$	383.1733

In contrast to the above, cycloadditions of nitrones (9), (10) and (28) with diethyl ethylidenemalonate (48) in refluxing benzene under a nitrogen atmosphere afforded regiospecifically the 4,4'-dicarboethoxyl substituted isoxazolidines shown in Scheme 27. Diethyl ethylidenemalonate was prepared

by the method of Fones,[92] and is much more resistant to polymerisation than diethyl methylidenemalonate.



(9) R=Ph (48) (78) R=Ph
(10) R=PhCH$_2$ (79) R=PhCH$_2$
(28) R=(R)-PhCHCH$_3$ (80) R=(R)-PhCHCH$_3$

Scheme 27

Isoxazolidines (78) and (80) were obtained as oils after chromatography, whereas isoxazolidine (79) was obtained as a crystalline solid, m.p. 94-95°C. The regiochemistry of these isoxazolidines was again easily determined by comparison with compound (42). The ^{1}H nmr spectra of these isoxazolidines clearly show a one proton singlet corresponding to the C-3 proton as does the ^{1}H nmr spectrum of isoxazolidine (42), while the i.r. spectra show carbonyl absorptions at approximately 1725 cm^{-1}, [Table 5, Figures 12,13,14].

Table 5.

Isoxazolidine	δC-3H (ppm)	$[M]^+$	Molecular Formula	Calc. m/e.	Micro. Analysis
78	5.34	383.1737	$C_{22}H_{25}NO_5$	383.1733	-
79	4.81	-	$C_{23}H_{27}NO_5$	-	Found C69.5 , H6.8, N3.5%; Requires C69.49, H6.85, N3.5%
80	4.76	411.2048	$C_{24}H_{29}NO_5$	411.2046	-

Table 6.

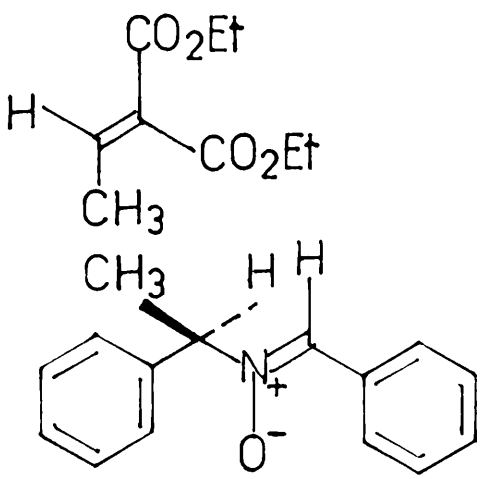
Isoxazolidine	Yield[a]	Reaction Time
76	83%	3 hr[b]
77	61%	16 hr[c]
78	2%	16 hr[c]

(a) After chromatography

(b) Time to completion as judged by TLC.

(c) Reaction incomplete after this time as judged by TLC.

Table 6 shows a marked decrease in yield on progressing from nitrone (9) to nitrone (28), indicating a substantial decrease in reaction rate. This is probably due in part to an increase in steric congestion in the transition states leading to the formation of the above isoxazolidines, i.e. as the size of the N- substituent increases this may lead to an increasingly unfavourable interaction between this and the vinyl methyl of diethyl ethylidenemalonate.



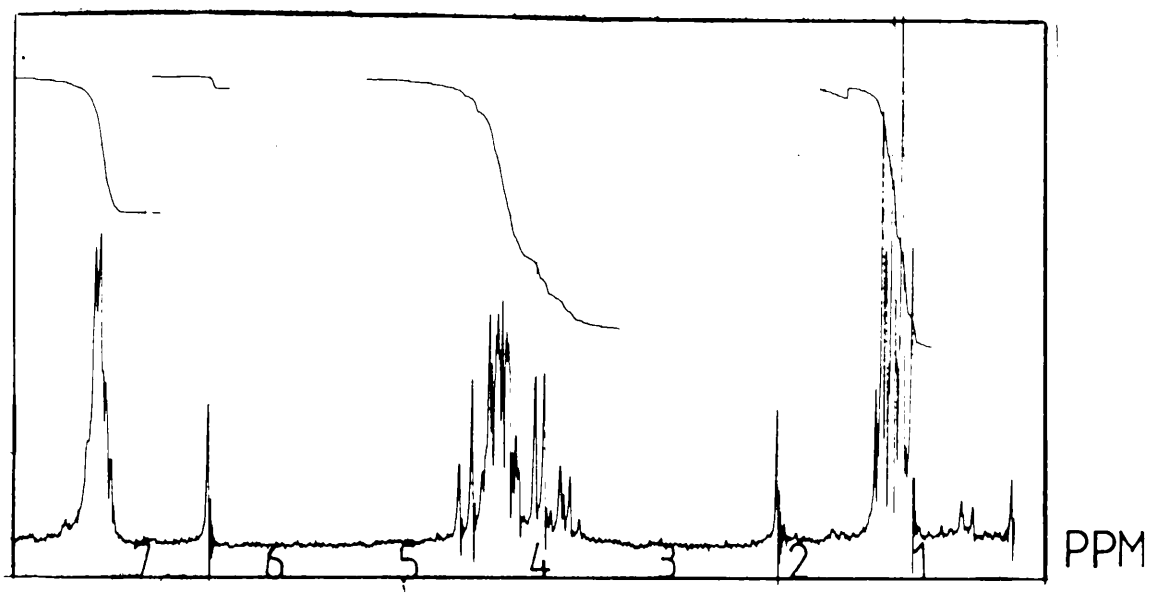


FIG. 7
^{1}H NMR SPECTRUM OF ISOXAZOLIDINE(73) AT 90MHz.

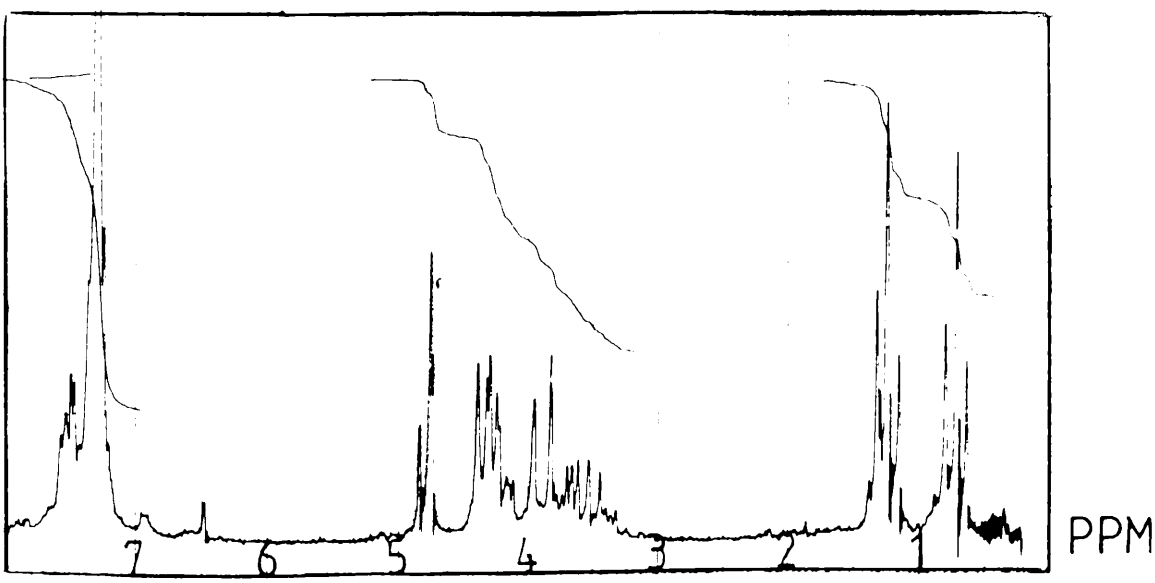


FIG. 8
^{1}H NMR SPECTRUM OF ISOXAZOLIDINE(74) AT 90 MHz.

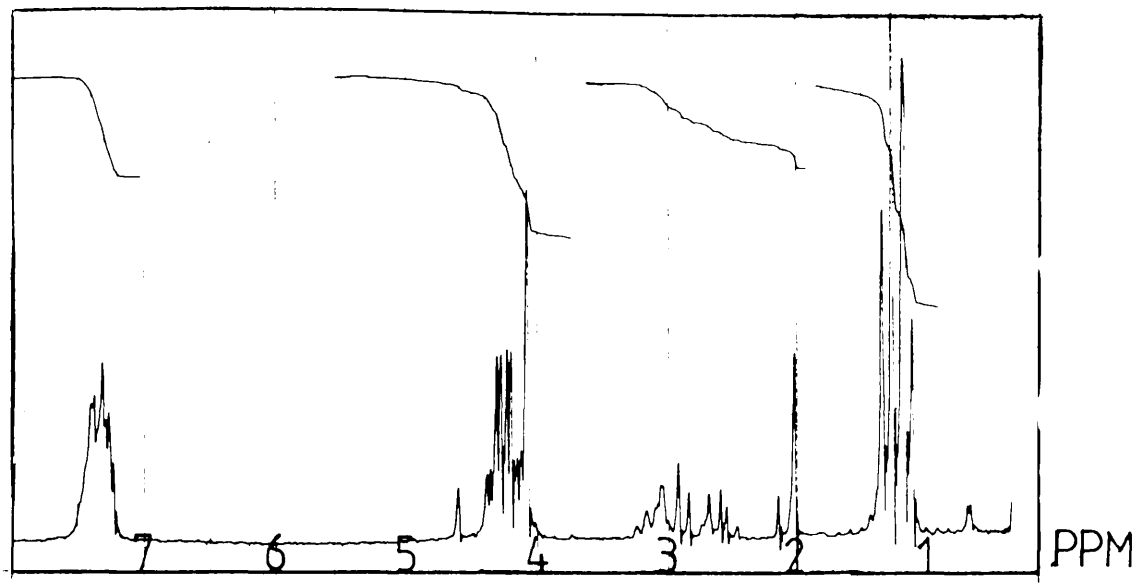


FIG.9

^{1}H NMR SPECTRUM OF ISOXAZOLIDINE(75) AT 90MHz.

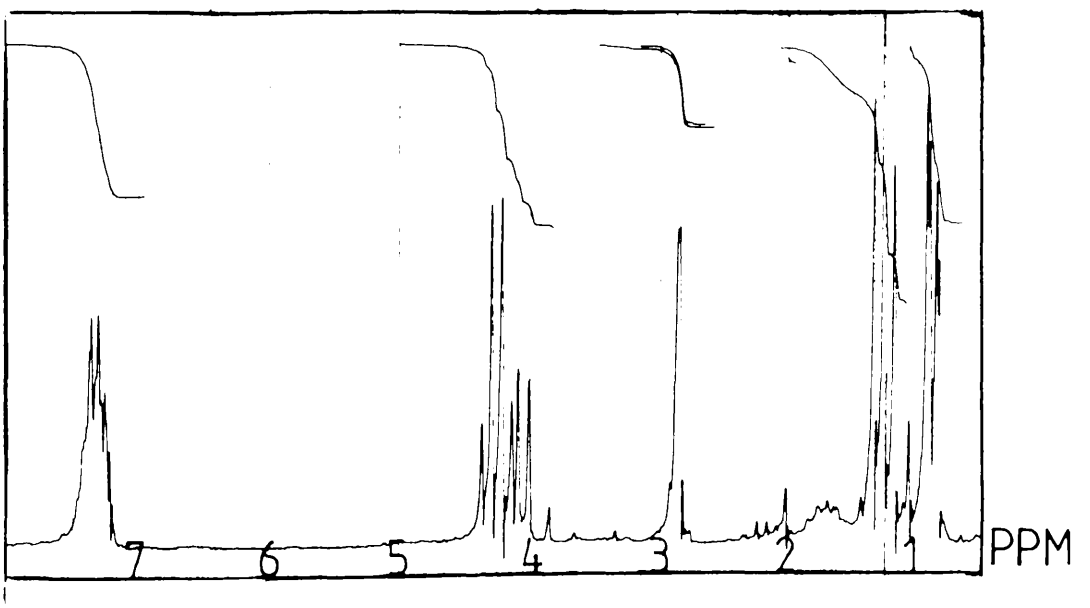


FIG.10

^{1}H NMR SPECTRUM OF ISOXAZOLIDINE(76) AT 90MHz.

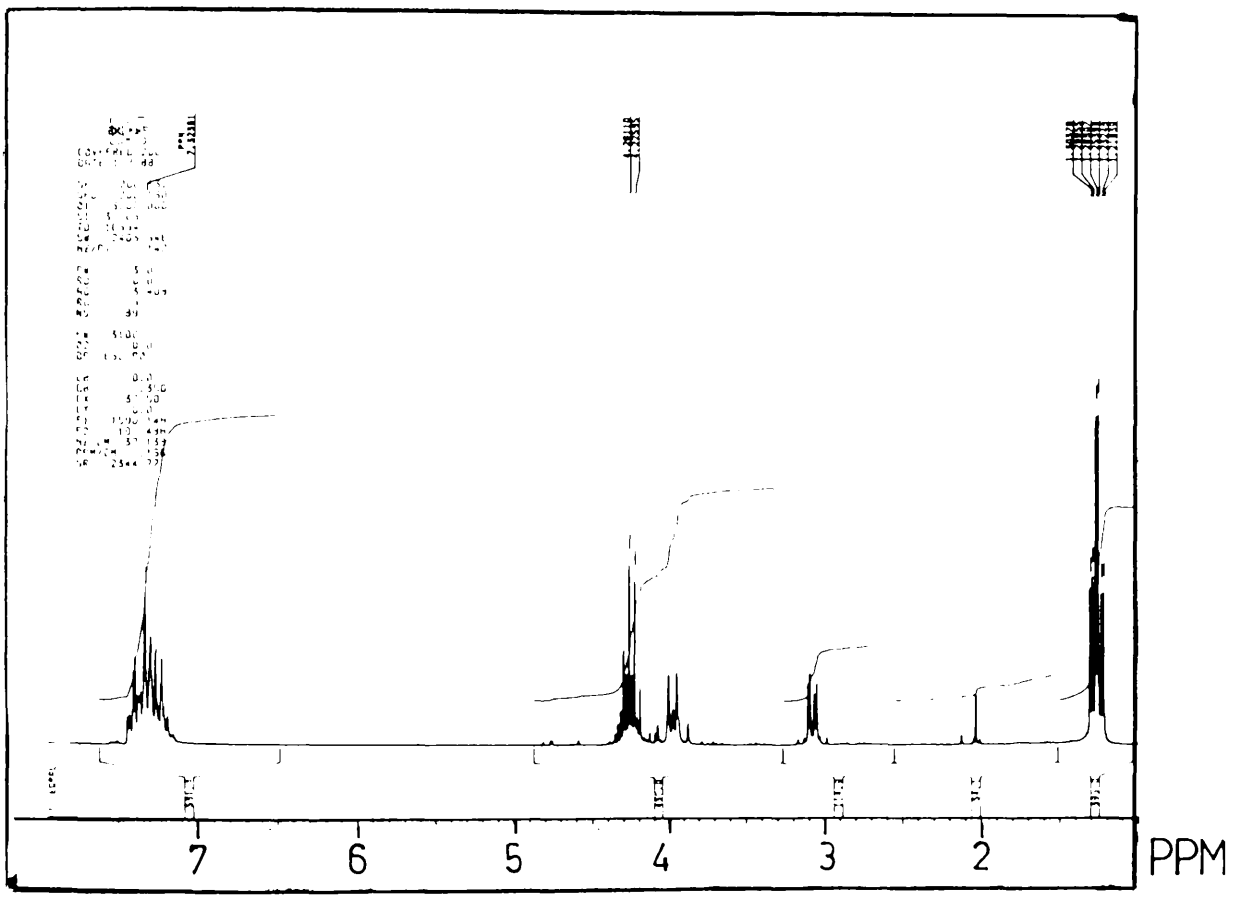


FIG.11

^{1}H NMR SPECTRUM OF ISOXAZOLIDINE(77) AT 200MHz.

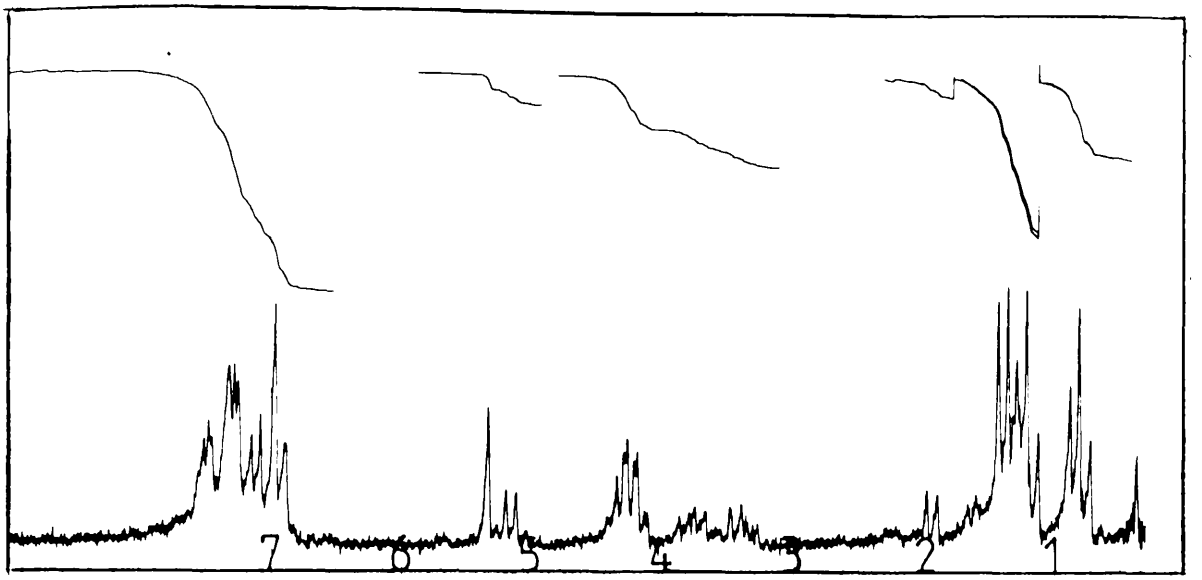


FIG.12

^{1}H NMR SPECTRUM OF ISOXAZOLIDINE(78) AT 90MHz.

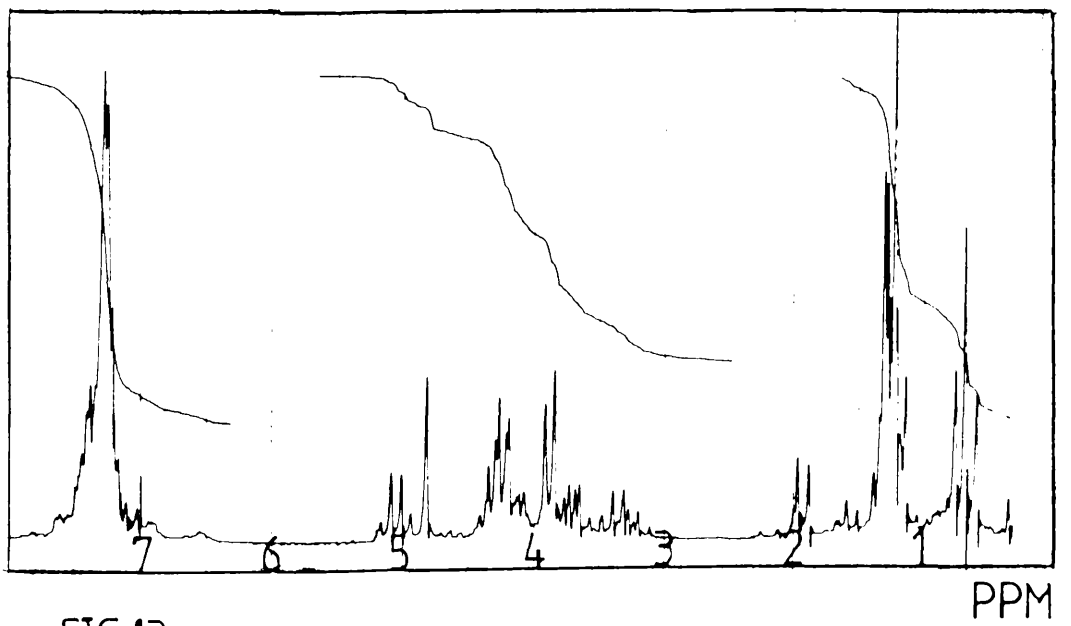


FIG.13

^{1}H NMR SPECTRUM OF ISOXAZOLIDINE(79) AT 90MHz.

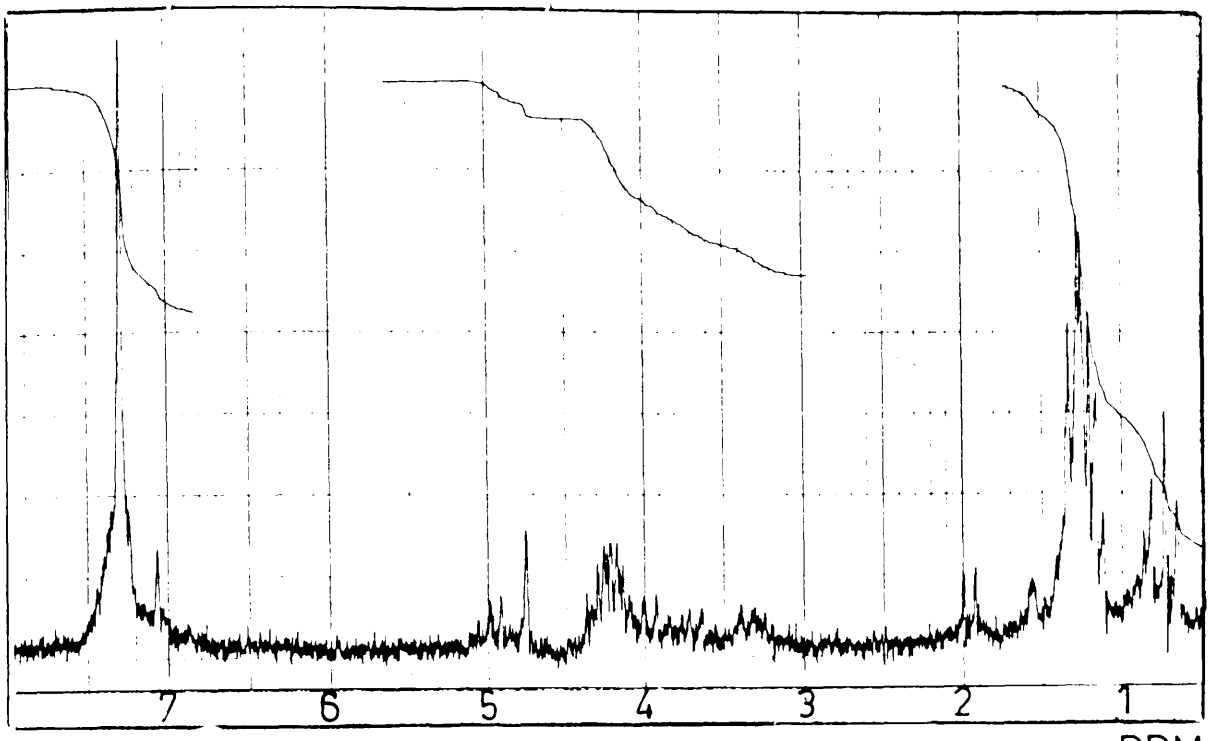


FIG.14

^1H NMR SPECTRUM OF ISOXAZOLIDINE(80) AT 90MHz.

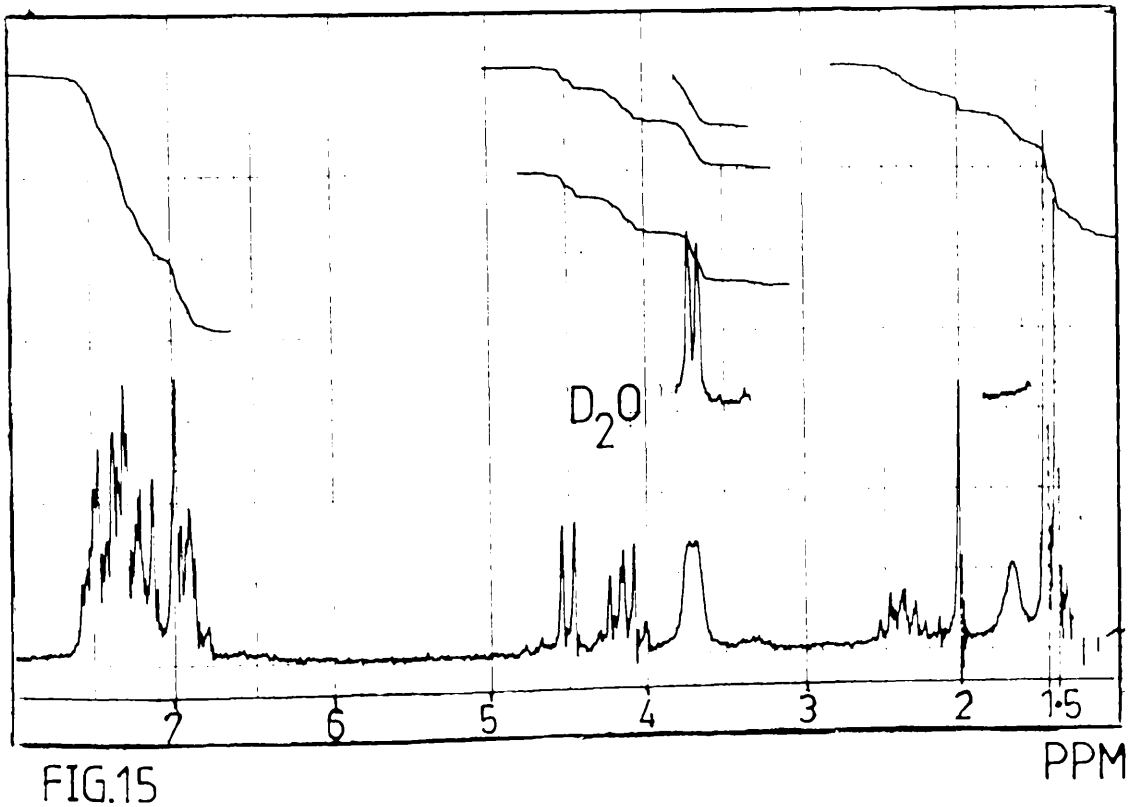
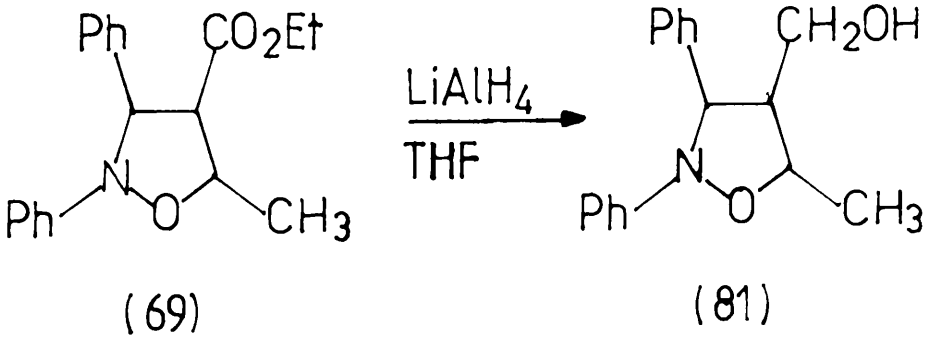


FIG.15

^1H NMR SPECTRUM OF ISOXAZOLIDINE(81) AT 90MHz.

The regiospecificity observed in these cycloadditions is in contrast to what has been observed in cycloadditions with diethyl methylidenemalonate, and may possibly be explained using the same argument as for ethyl crotonate, i.e. the introduction of the vinylic methyl group may change the relative sizes of the atomic orbital coefficients in the HOMO of the olefin, thus making both HOMO-LUMO interactions favour formation of the 4,4'-disubstituted isoxazolidine. Attenpted hydrogenolysis of isoxazolidines (78) and (79) using various catalysts (PtO_2/C, Pd/C, Ni) at temperatures from room temperature to 100°C at moderate pressures (up to 7.1 ATM) were unsuccessful, with the isoxazolidines being recovered unchanged. Reagents such as aluminium amalgam, sodium amalgam, Zn-acetic acid and lithium aluminium hydride are also known to effect N-O bond cleavage.[93,94] As a model study, attempted reduction of the N-O bond in isoxazolidine (69) by prolonged treatment with $LiAlH_4$ in refluxing THF afforded only the alcohol (81), isolated as a colourless oil in 81% yield after chromatography [Scheme 28].

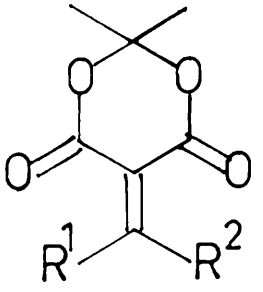


(69) (81)

Scheme 28

The ^1H nmr spectrum of (81) [Figure 15] clearly shows a doublet corresponding to the newly introduced $-CH_2-$ group at C-4 at δ3.72 (J = 6 Hz), and a one proton D_2O-exchangeable signal at δ1.18. The i.r. spectrum of (81) shows a strong hydroxyl adsorption at 3600 cm^{-1}, while accurate mass analysis showed $[M]^+$ = 269.1413 corresponding to a molecular formula of $C_{17}H_{19}NO_2$ (calc. m/e = 269.1416).

Following the same general strategy, attempts were made to carry out cycloadditions between nitrones (9) and (10) with derivatives of Meldrum's acid as shown below.[95] However, no cycloadducts were isolated.



(82) $R^1 = R^2 = Me$
(83) $R^1 = H, R^2 = Me$
(84) $R^1 = H, R^2 = OMe$
(85) $R^1 = H, R^2 = OEt$

Summary and Conclusions.

The evidence presented makes the route to β-amino acids here explored unlikely, for three reasons:-

1) the lack of regiospecificity in nitrone cycloadditions

with diethyl methylidenemalonate; (2) the sluggish nature of the cycloaddition of nitrone (28) with diethyl ethylidenemalonate and (3) the increased resistance of isoxazolidines derived from diethyl ethylidenemalonate to catalytic hydrogenation.

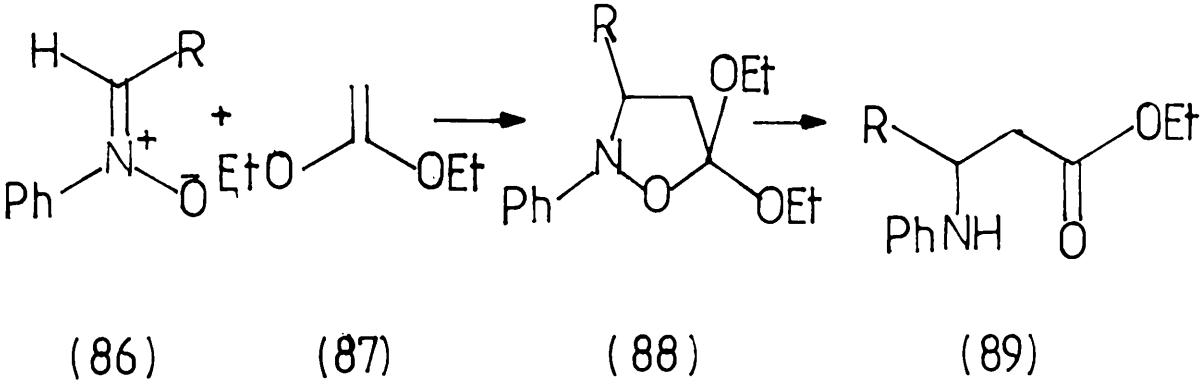
CHAPTER 3.

1,3-Dipolar Cycloaddition Reactions of Nitrones to Ketene Acetals and the Synthesis of Chiral Ketene Acetals.

3.1 Background and Introduction.

Ketene acetals are electron rich dipolarophiles and as such undergo cycloaddition reactions with nitrones to give 5,5' - substituted isoxazolidines such as (88) and (92) shown below. The cycloaddition reactions of diethyl ketene acetal (87) have been investigated by Huisgen,[96] Scarpati[97] and Moffat,[49] while Scarpati has further established that isoxazolidines such as (88) can be hydrogenolysed to afford ethyl esters of β-amino acids, [Scheme 29]. Moffat[49] has studied the cycloaddition reactions of ketene acetal (91), however cycloadditions with N- phenethyl nitrones (R_2=(R)-PhCHMe) were extremely sluggish, affording isoxazolidines in yields between 0 and 28%, [Scheme 30]. In spite of the low yields, chiral induction at C-3 of the isoxazolidines formed of the order of 3:1 was observed. Also, Moffat[49] was unable to cyclo-add chiral phenethylnitrones to diethyl ketene acetal, presumably due to unfavourable steric interactions.

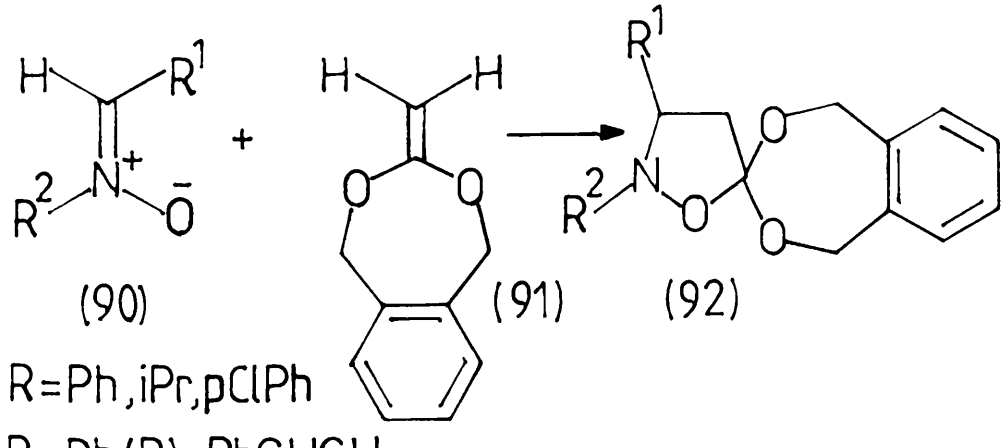
As part of an investigation into alternative asymmetric routes to β-amino acids, chiral ketene acetals were synthesised as described in Section 3.2 with a view to using these in cycloaddition reactions with nitrones as the first step in an asymmetric synthesis of β-amino acids. Section 3.1 describes the synthesis of racemic N-phenyl-β-phenyl-β-alanine (97) by this route.



(86) (87) (88) (89)

R = Ph, pClPh

Scheme 29.



(90) (91) (92)

R=Ph, iPr, pClPh

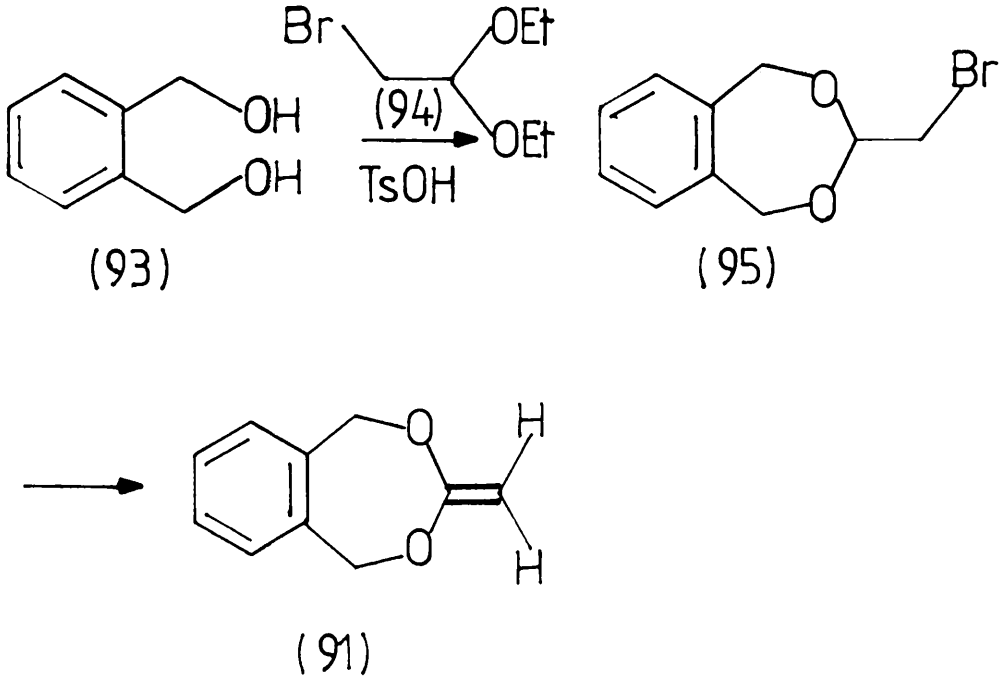
R=Ph, (R)-PhCHCH$_3$

Scheme 30.

Discussion

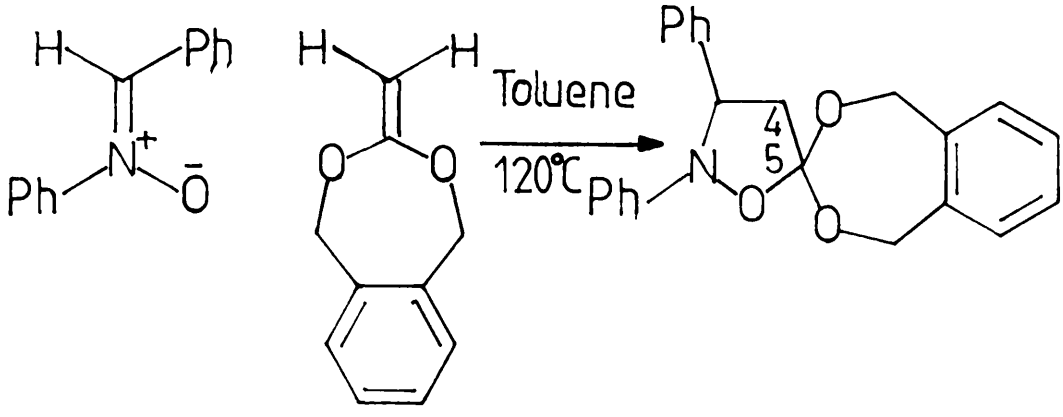
3.2 Non-asymmetric Synthesis of N-Phenyl-β-Phenyl-β-Alanine.

Ketene acetal (91) was prepared by the method of Grewe [98] as shown in Scheme 31, and was obtained as a stable crystalline solid after distillation, m.p. 47-48°C (Lit[98] m.p. 49°C).



Scheme 31.

Cycloaddition of C,N-diphenylnitrone (9) with ketene acetal (91) as described by Moffat[40] afforded isoxazolidine (96) as a crystalline solid after chromatography in 63% yield, m.p. 130-131°C (Lit[40] m.p. 127°C), [Scheme 32].



(9) (91) (96)

Scheme 32.

The ^{1}H nmr spectrum of (96) shows two doublets of doublets as part of an ABX system at δ2.65 (1H, dd, J = 9, 13 Hz) and at δ3.02 (1H, dd, J = 7, 13 Hz) corresponding to the two C-4 protons [Figure 16], while accurate mass analysis showed $[M]^+$ = 359.1516 corresponding to a molecular formula of $C_{23}H_{21}NO_3$, (calc. m/e = 359.1521).

Hydrogenolysis of (96) at room temperature in ethylacetate afforded N-phenyl-β-phenyl-β-alanine (97) as a crystalline solid, m.p. 118-120°C, in 80% yield after chromatography, [Scheme 33].

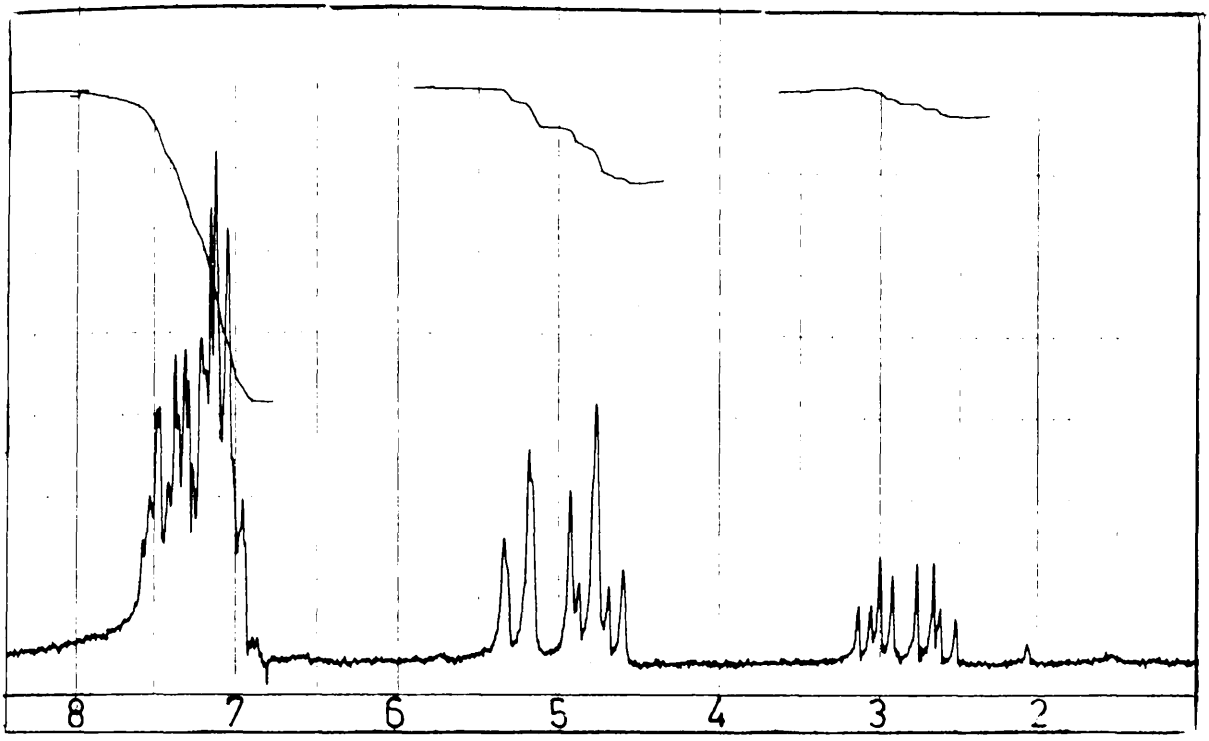


FIG.16

^1H NMR SPECTRUM OF ISOXAZOLIDINE(96) AT 90 MHz.

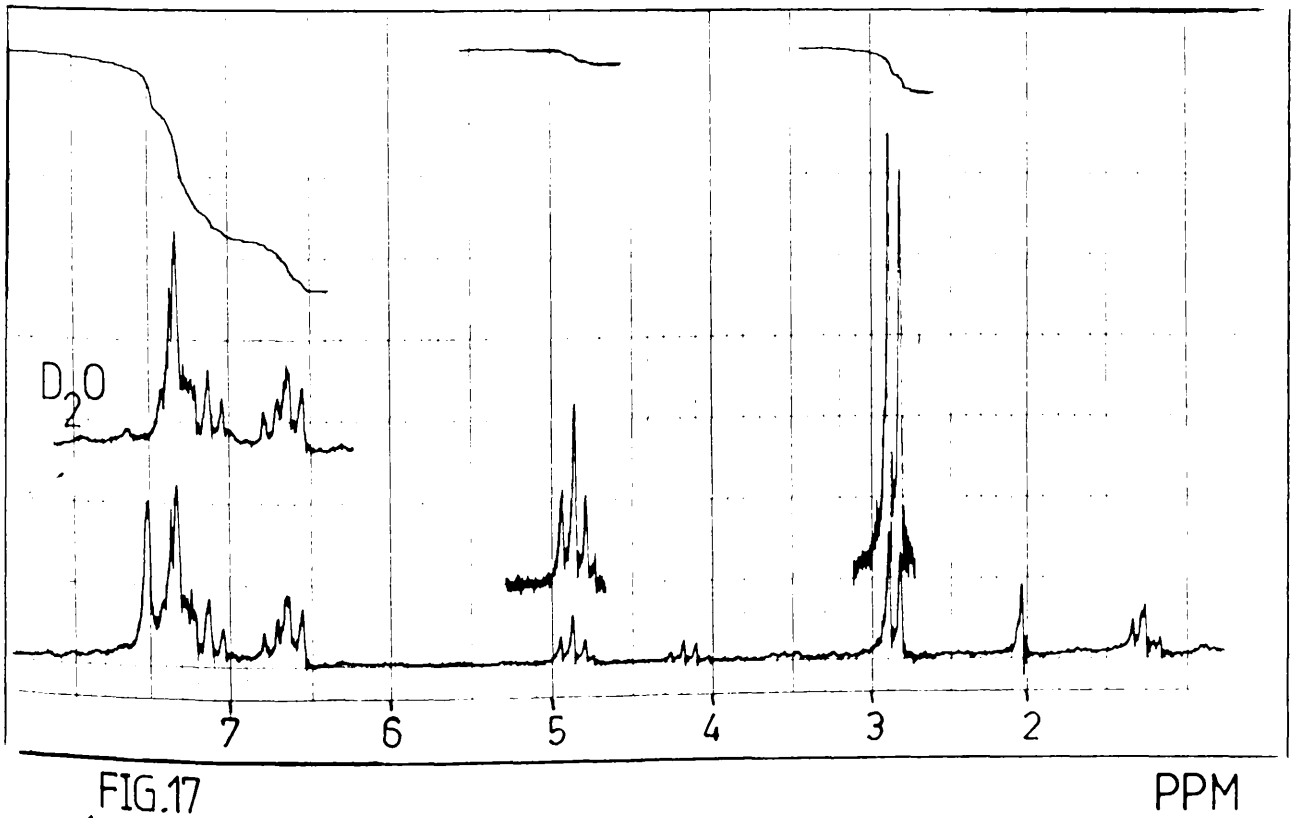
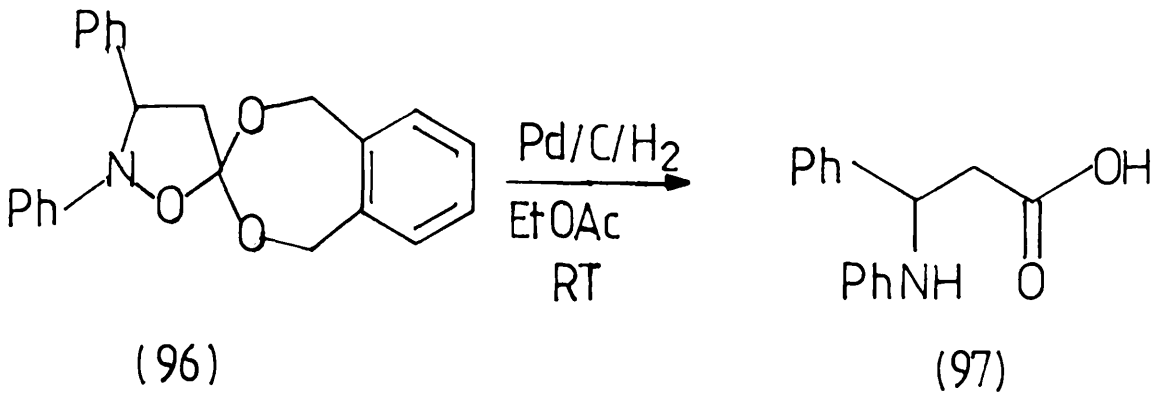


FIG.17

^1H NMR SPECTRUM OF(97) AT 90MHz.



(96) (97)

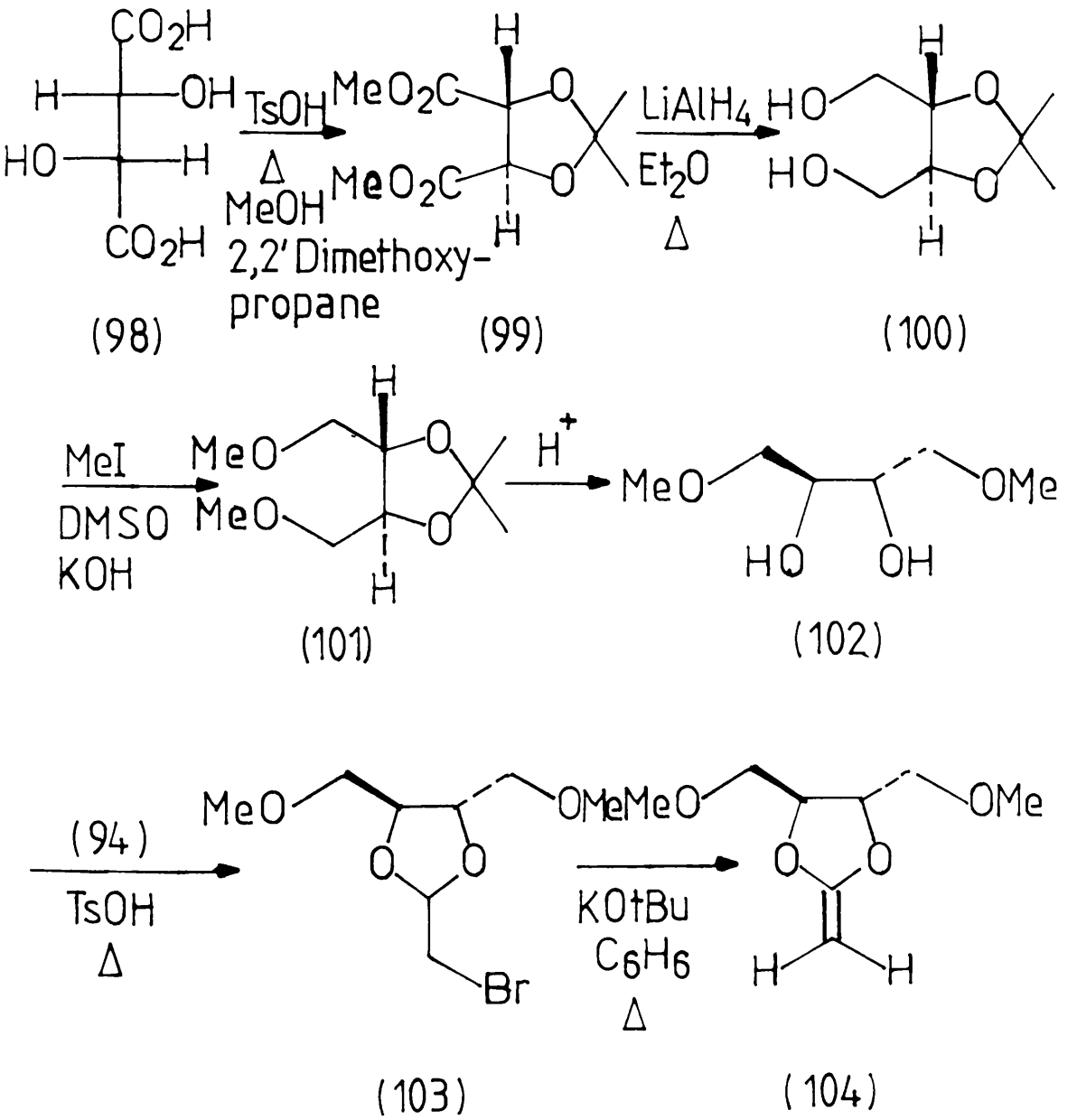
Scheme 33.

Figure 17 shows the ^1H nmr spectrum of (97) in which the C-2 protons appear as a doublet at δ2.86 (J = 7 Hz), and the C-3 proton as a triplet at δ4.88 (J = 7 Hz). The i.r. spectrum of (97) shows both hydrogen-bonded and free hydroxyl absorption in the region 3400-3600 cm^{-1}, while accurate mass analysis showed $[M]^+$ = 241.1103 corresponding to a molecular formula of $C_{15}H_{15}NO_2$, (calc. m/e = 241.1106).

3.3 The Synthesis of Chiral Ketene Acetals.

Chiral ketene acetal (104) was synthesised in two steps from (-) - (2S,3S)-1,4-dimethoxy-2,3-butandiol (102) following the same general procedure as used by Grewe in the preparation of ketene acetal (91), i.e. acetal exchange of diol (102) with bromoacetaldehyde diethyl acetal followed by elimination of HBr using potassium-t-butoxide. Diol (102)

was prepared in four steps from (+)-tartaric acid following the procedure outlined by Tamera,[99] the utility of which as a chiral auxilliary has been recognised by its application to the synthesis of (R)- and (S)- mevalolactone ,[99] [Scheme 34].



Scheme 34

Diol (102) was isolated as an oil from acid hydrolysis of ketal (101) in 87% yield and was used without further purification. The ^{1}H nmr spectrum of diol (102) shows a two proton D_2O-exchangeable signal at δ2.66, a singlet corresponding to the methoxyl methyls at δ3.4, a doublet at δ3.51 (J = 4.6 Hz) and a multiplet at δ3.81 corresponding to the four -$\underline{CH_2}$- and two -$\underline{CH}$- protons respectively, [Figure 18].

The bromo-acetal (103) was obtained as a colourless liquid after distillation in 70% yield, b.p. 110°C at 2mmHg, $[\alpha]_D^{22}$ = -9.3° ($CHCl_3$, C = 1.6). Figure 19 shows the ^{1}H nmr spectrum of (103) in which the acetal proton appears as a triplet at δ5.31 (J = 4.2 Hz). Interestingly, the ^{13}C proton-decoupled nmr spectrum of (103) displays two separate signals at δ77.87 and δ78.1 for the secondary carbons at the two chiral centres, the assignment of which follows from comparison with the off-resonance proton-decoupled spectrum, [Figures 20,21]. Accurate mass analysis of compound (103) showed $[M-CH_2Br]^+$ = 161.0816 corresponding to a molecular formula of $C_7H_{13}O_4$ (calc. m/e = 161.0814).

The dehydrobromination of acetal (103) proved to be problematic, and in fact ketene acetal (104) was only isolated on two separate occasions. Figure 22 shows the ^{1}H nmr of (104) and clearly displays a two proton singlet attributable to the olefinic protons at δ3.2. This compares well with the chemical shift observed for the same protons in

diethyl ketene acetal at δ3.01.[49] Accurate mass analysis immediately after isolation showed $[M]^+$ = 174.0892 corresponding to a molecular formula of $C_8H_{14}O_2$ (calc. m/e = 174.0892). Generally, however ketene acetal (104) had polymerised before or during work-up, and on one of the occasions when it was isolated, on standing at 0°C in $CDCl_3$ solution overnight. The use of alkali-washed glassware did not prevent this polymerisation.

The instability of ketene acetals derived from 1,3-dioxalanes has previously been reported by McElvain[100] who carried out an extensive study of the synthesis of such compounds. McElvain noted that the most striking property of these cyclic ketene acetals is their marked tendency to undergo spontaneous polymerisation, and that only those containing bulky substituents such as chlorine (107) or phenyl (110) in the methylene group were relatively resistant to polymerisation. It was therefore decided to try and use ketene acetals (107) and (110) as model compounds in cycloadditions with nitrones.

Both of these ketene acetals were prepared using the general procedures outlined by McElvain[100] starting from ethylene glycol (105), however the dehydrohalogenations were carried out on the pure acetals (106) and (109) in sodium dried benzene rather than tert-butyl-alcohol, and afforded ketene acetals which required no further purification after isolation, [Scheme 35].

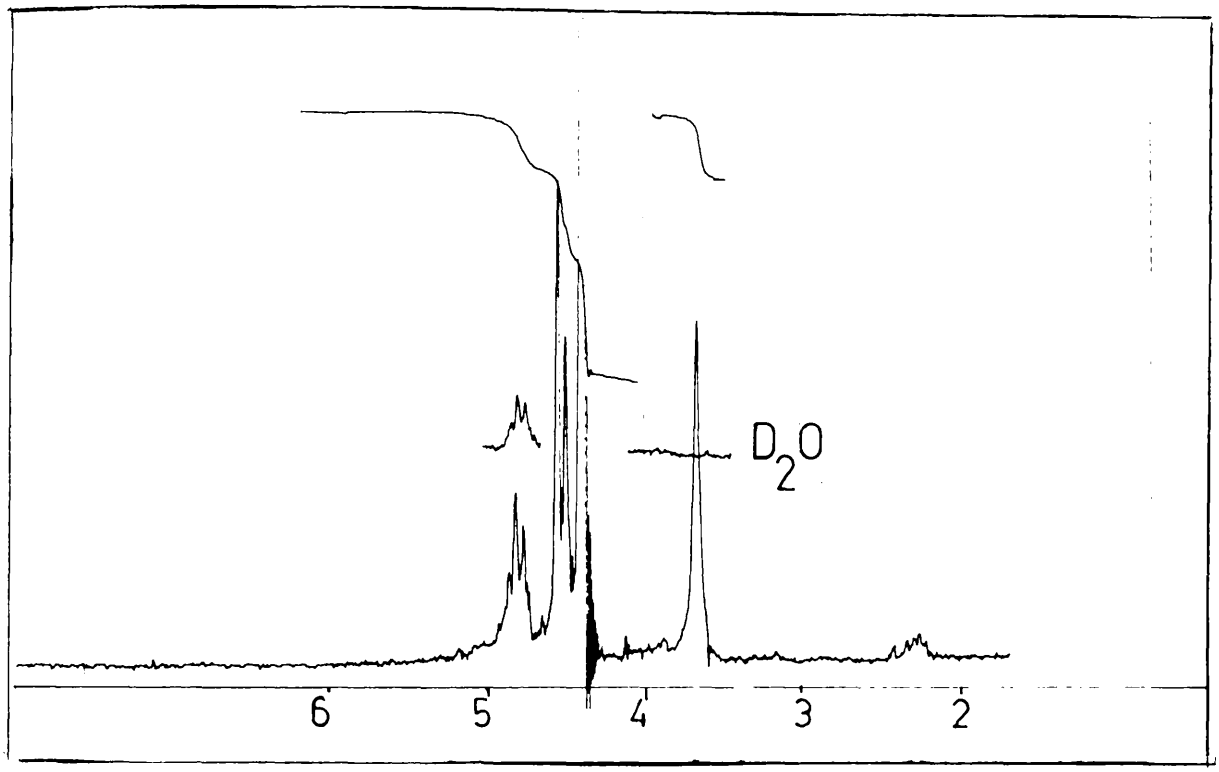


FIG.18

^1H NMR SPECTRUM OF DIOL(102) AT 90MHz.

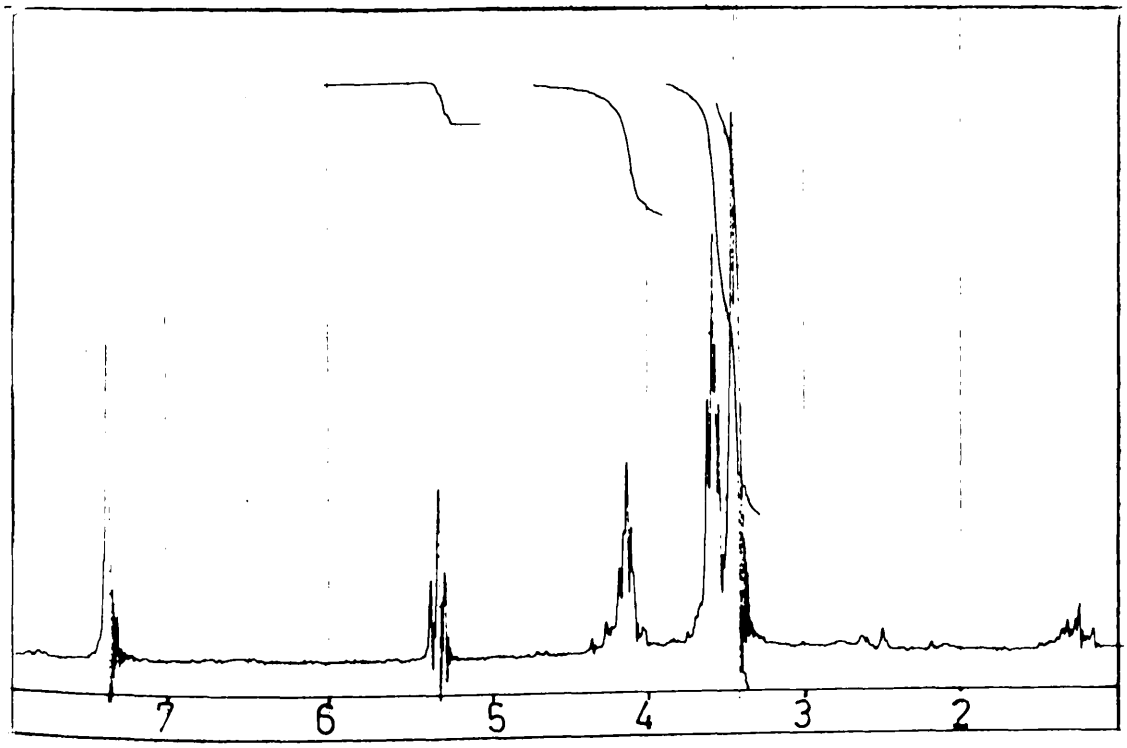


FIG.19

^1H NMR SPECTRUM OF ACETAL(103) AT 90MHz.

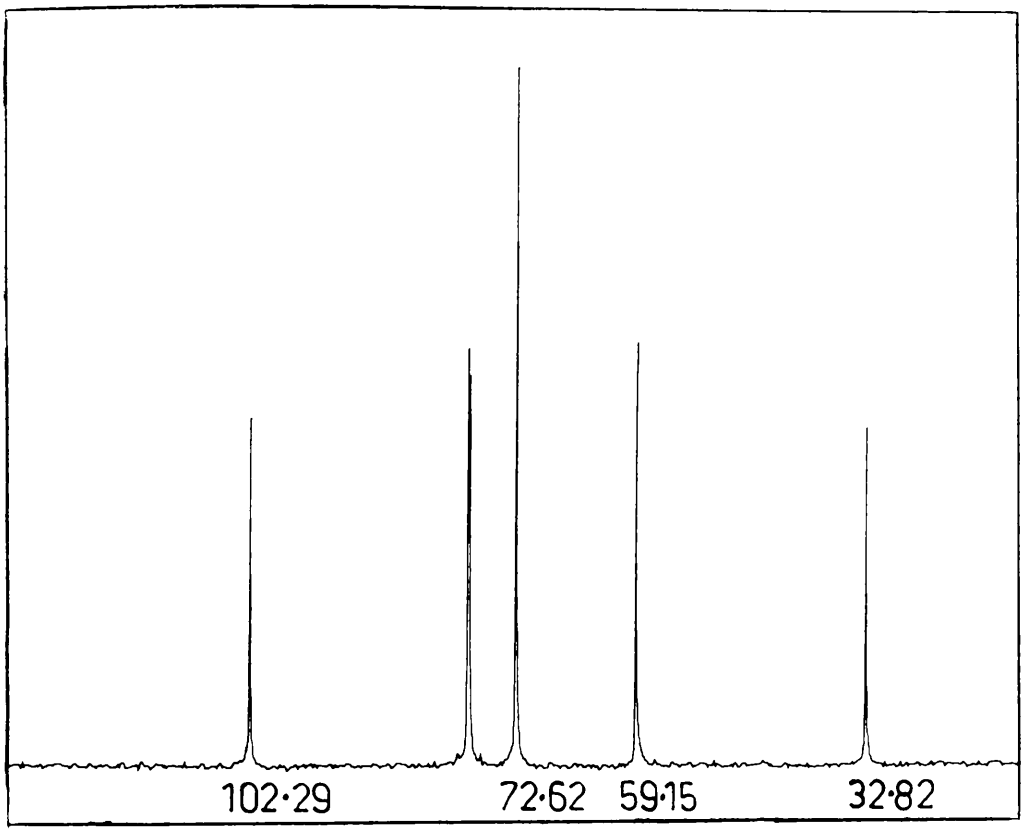


FIG.20

^{1}H-DECOUPLED ^{13}C NMR SPECTRUM OF ACETAL(103) AT 25·2 MHz

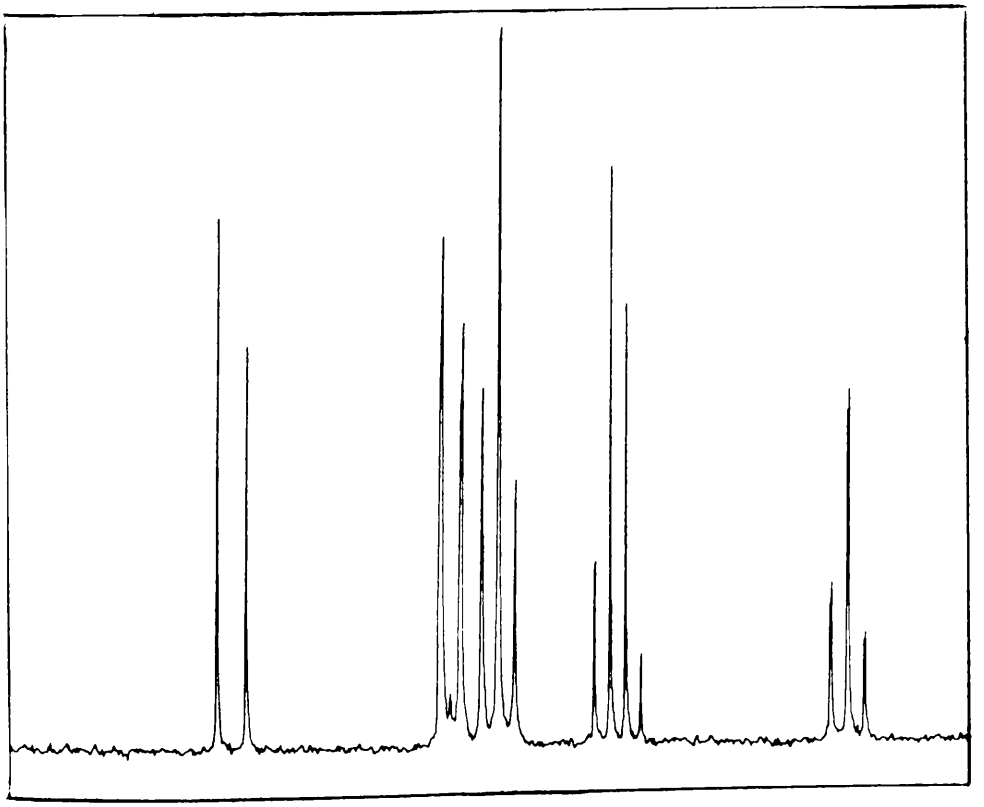


FIG.21

OFF-RESONANCE ^{1}H-DECOUPLED ^{13}C NMR OF (103)

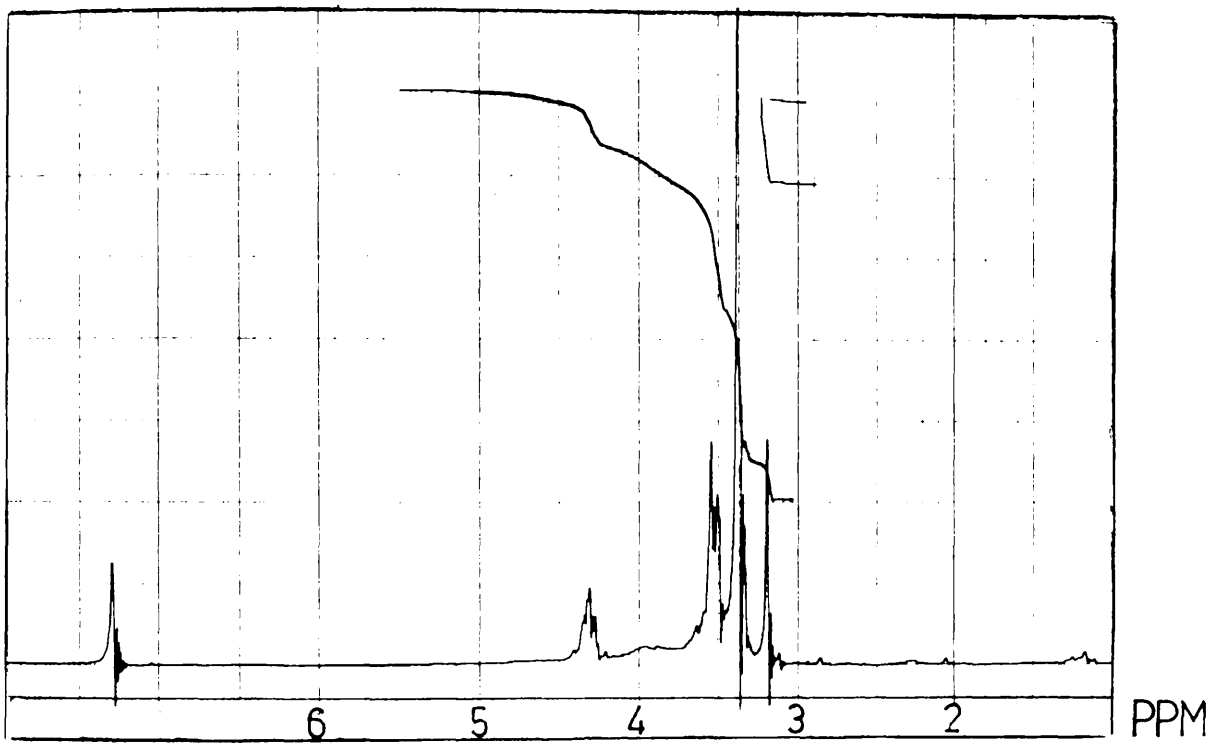
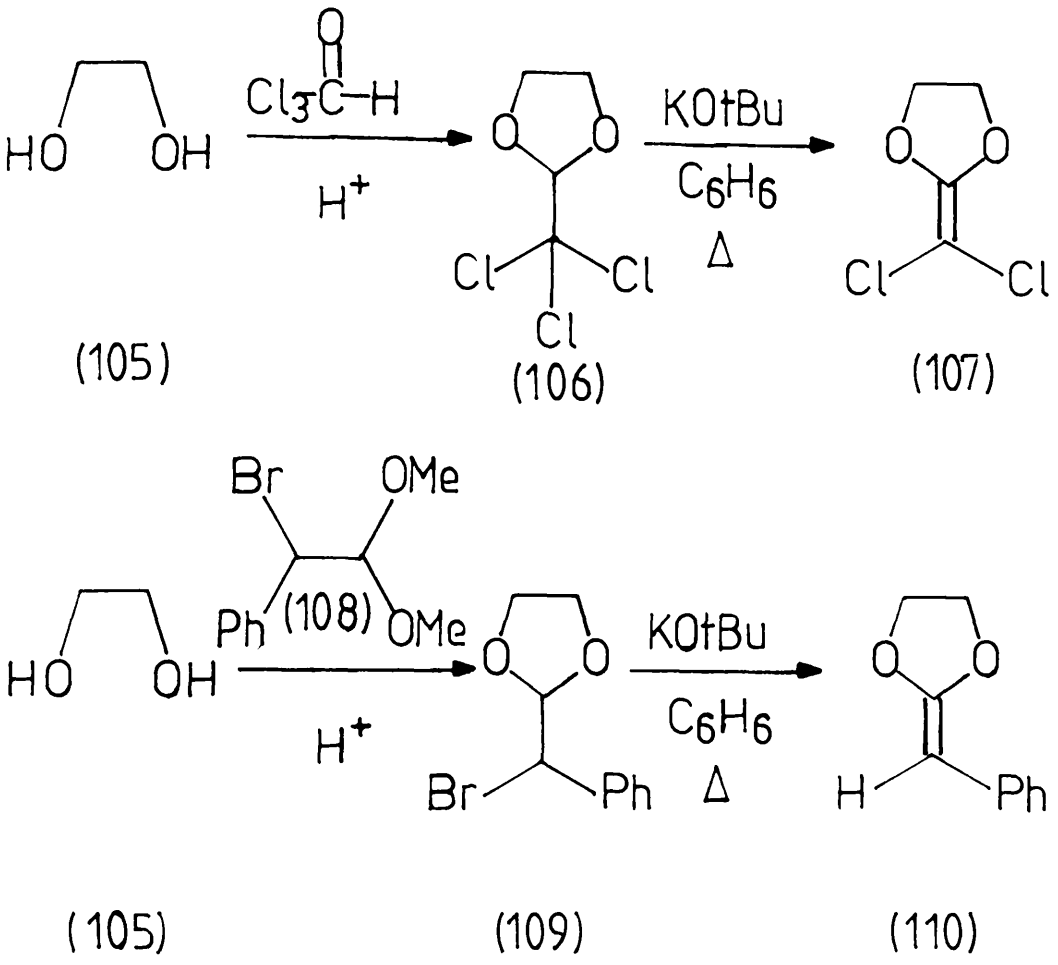


FIG.22

^{1}H NMR SPECTRUM OF KETENE ACETAL (104) AT 90MHz.



Scheme 35

The ^{1}H nmr of ketene acetal (107) shows only a broad singlet at δ4.42, while that of (110) clearly shows a one proton singlet at δ4.99 corresponding to the olefinic proton in addition to a multiplet centred at δ3.36 (4H) and an aromatic multiplet centred at δ7.25 (5H). As a test of the thermal stability of ketene acetal (110), a sample was heated in an nmr tube in d^{8}-toluene at 120°C for a period of 2h. As can be seen in Figures 23a and 23b, there was no detectable

change by ^{1}H nmr during this time.

Attempts were made to cyclo-add ketene acetals (107) and (110) with both C,N-diphenylnitrone (9) and the much more reactive[51] 3,4-dihydroisoquinoline-N-oxide (12) in refluxing toluene under an argon atmosphere over periods of up to 24h, however in neither case was any reaction observed and nitrone was recovered unchanged after chromatography. Presumably the bulky substituents provide sufficient steric hinderance to inhibit cycloaddition at atmospheric pressure. Also, since cycloadditions of nitrones with electron-rich olefins such as ketene acetals are thought to be LUMO controlled, perhaps the inductive effect of the two chlorine substituents in (107) may make the energy difference between LUMO(dipole)-HOMO(dipolarophile) larger in this case, hence rendering the attempted cycloaddition energetically unfavourable.

In an attempt to decide whether the size of the acetal ring in ketene acetal (91) plays a significant role in determining its stability, cyclic bromo-acetal (112) was prepared by acetal exchange of 1,4-butanediol (111) with bromoacetaldehyde diethyl acetal as a colourless liquid in 69% yield, b.p. 120 - 125^{o}C at 1mmHg, [Scheme 36].

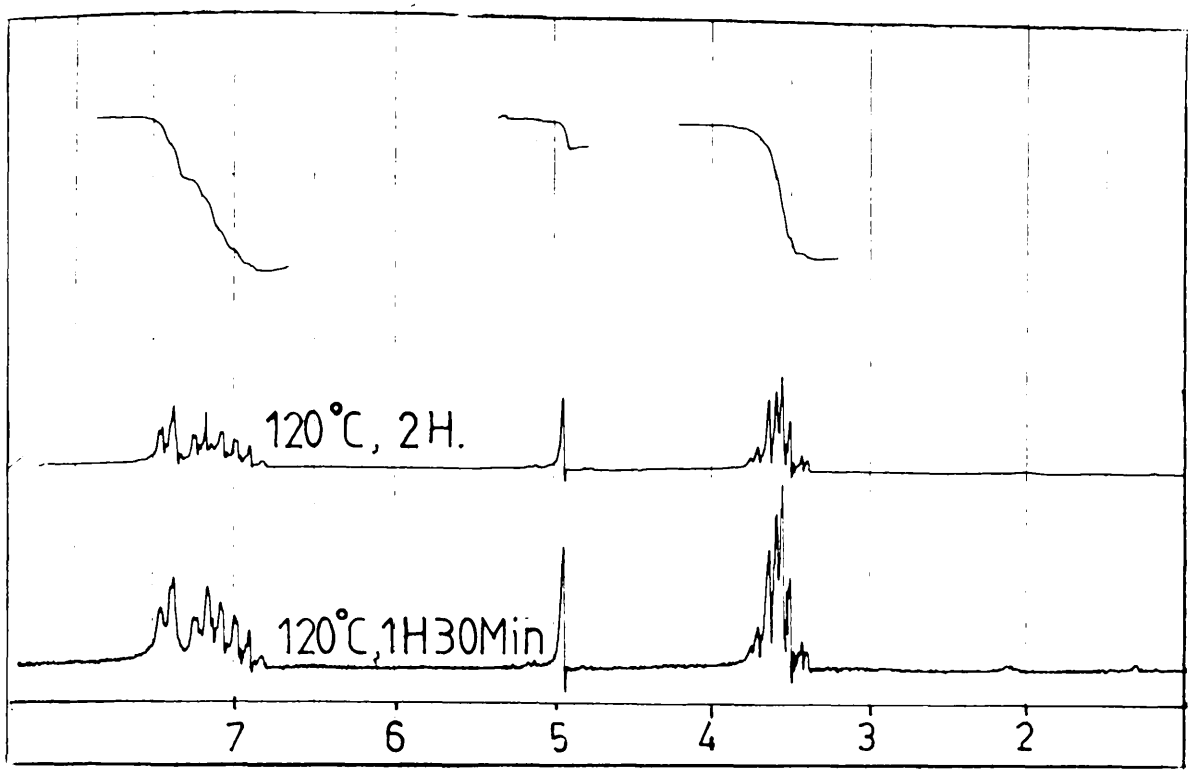


FIG. 23b

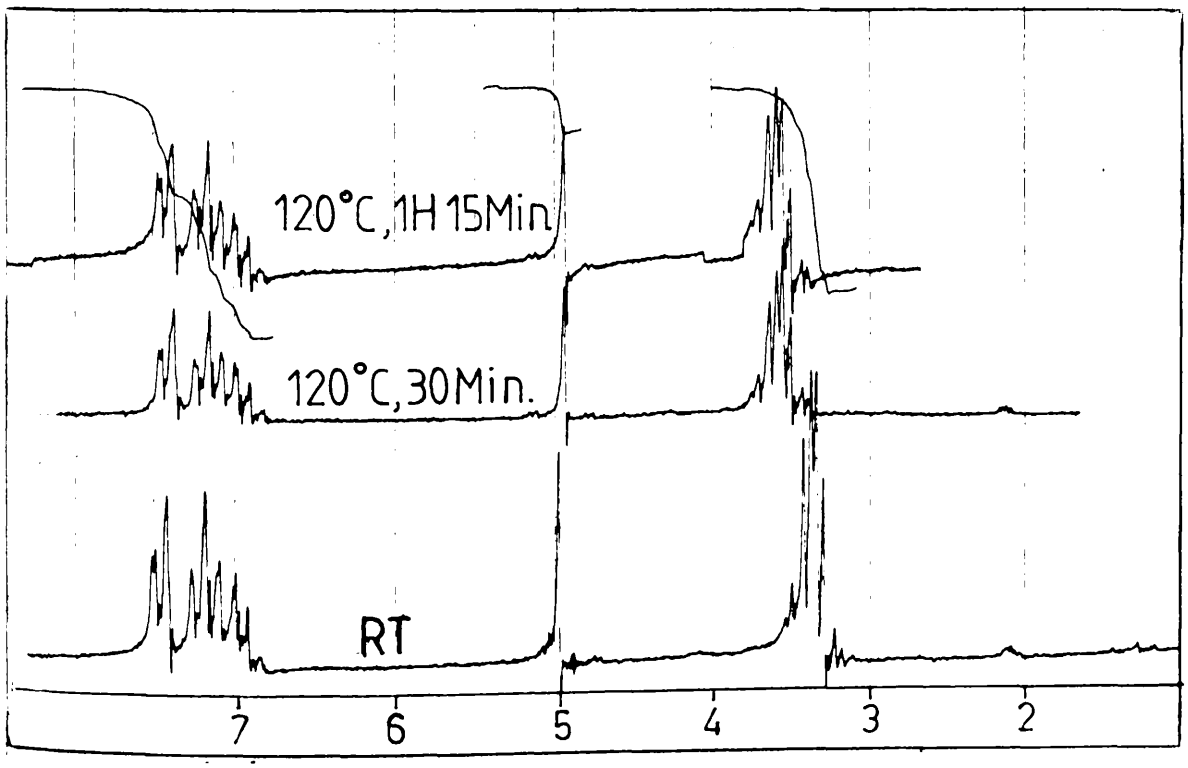
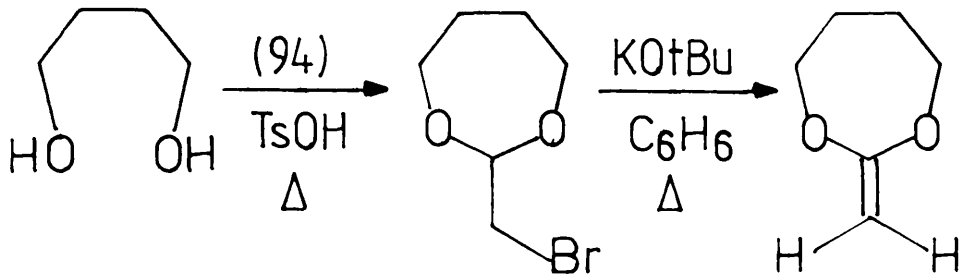


FIG. 23a

^{1}H NMR SPECTRUM OF KETENE ACETAL(110) AT 90MHz.



(111) (112) (113)

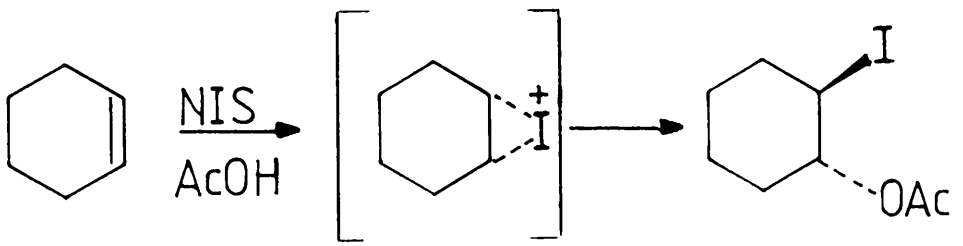
Scheme 36.

The ^{1}H nmr spectrum of bromo-acetal (112) displays a characteristic triplet at δ4.9 (J = 5 Hz) corresponding to the acetal methine proton, and a doublet at δ3.32 (J = 5 Hz) corresponding to the -$\underline{CH_2}$-Br protons. Accurate mass analysis showed $[M-CH_2Br]^+$ = 101.0601 corresponding to a molecular formula of $C_5H_9O_2$ (calc. m/e = 101.0604). Several attempts were made in an effort to isolate the corresponding ketene acetal (113) after dehydrobromination, however only polymeric material was recovered. Thus it appears that the stability of ketene acetal (91) cannot be attributed solely to the size of the acetal ring.

All of the dehydrohalogenations described above

required heat to facilitate reaction. It was therefore envisaged that α-iodo acetals may undergo elimination to afford ketene acetals under much milder conditions since iodine should be a superior leaving group.

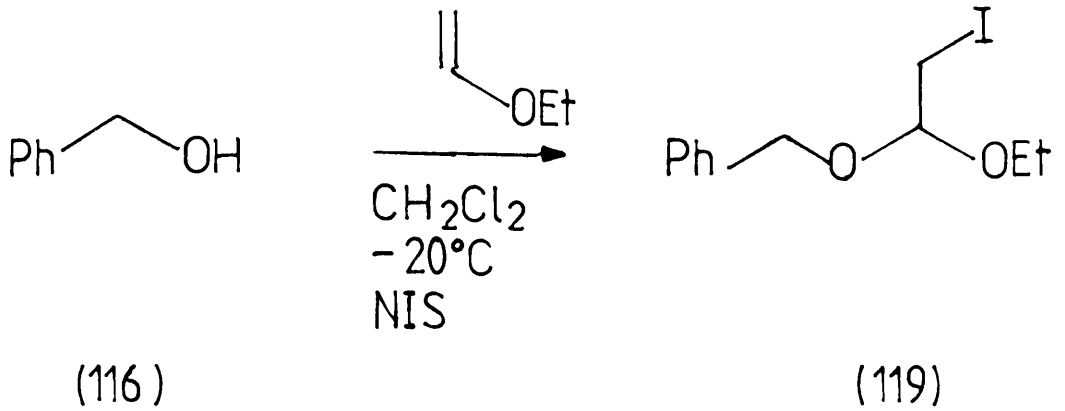
Adinolfi[101] has established that N-iodo-succinimide (NIS) can act as a convenient alternative to the I_2/KIO_3 system as a source of I^+, and has demonstrated this by the addition of carboxylic acids to alkenes in the presence of NIS as in the example shown in Scheme 37.



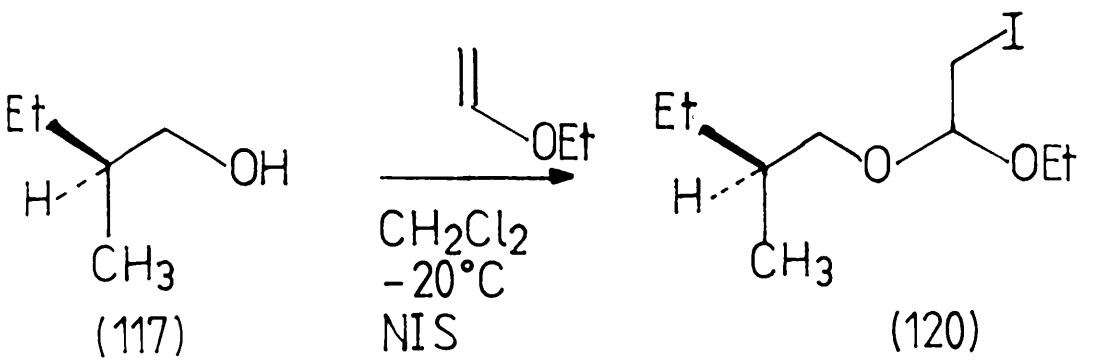
(114) (115)

Scheme 37.

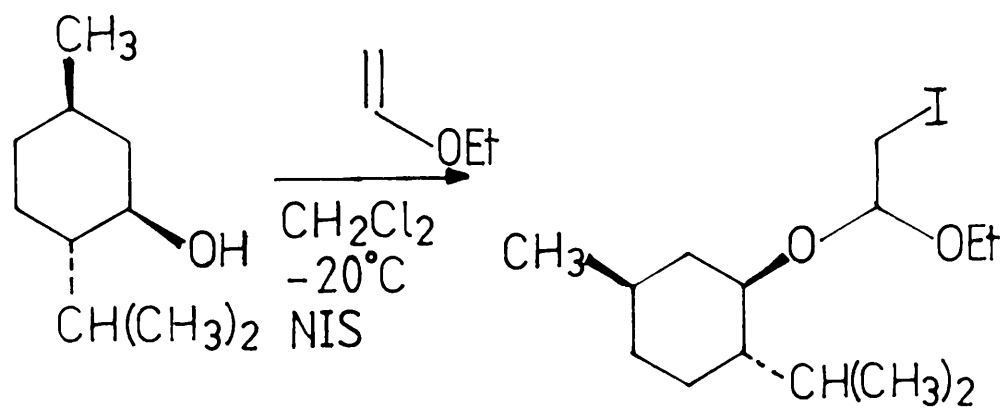
Using the same strategy, α-iodo-acetals have been prepared by the addition of alcohols or thiols to ethylvinyl-ether in the presence of NIS.[102] Thus, α-iodo-acetals (119 to 121) were prepared by addition of alcohols (116 to 118) to ethyl vinyl ether in dichloromethane at -20°C in the presence of NIS, [Scheme 38].



(116) (119)



(117) (120)



(118) (121)

Scheme 38

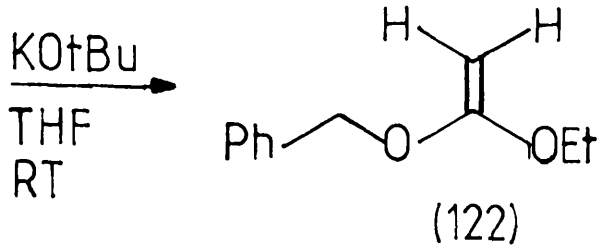
The ^{1}H nmr spectra of acetals (119 to 121) characteristically show a doublet at approximately δ3.2 corresponding to the -$\underline{CH_2}$-I protons, and a triplet, or as in (121) two overlapping triplets in the region δ4.6 - δ4.75 corresponding to the acetal methine proton, [Figures 24,25,26]. Acetals (120) and (121) are formed as a mixture of diastereomers accounting for the overlapping triplets and broad doublet seen in Figure 26. Also, the ^{13}C proton-decoupled nmr spectrum of (121) clearly displays a set of signals for both diastereomers. Accurate mass analysis showed a parent ion for (119) only, whereas (116) and (117) showed $[M-CH_2I]^+$ or $[M-OEt]^+$ respectively as highest mass ions, [Table 7]. These acetals were obtained as liquids after purification by distillation (119,120) or by chromatography (121), however satisfactory microanalyses were not obtained.

Acetals (119) and (120) underwent dehydroiodination at room temperature in sodium dried THF to afford the corresponding ketene acetals, whereas acetal (121) required heating, [Scheme 39]. The ^{1}H nmr spectra of ketene acetals (122 to 124) display either a singlet or an AB quartet in the region δ3.1 - δ3.2 attributable to the olefinic protons, [Figures 27,28,29]. Accurate mass analysis of ketene acetals (122) and (123) immediately after isolation showed parent molecular ions, while both (123) and (124) showed ions corresponding to $[M+1]^+$; (124) did not show a parent ion, [Table 8].

Table 7.

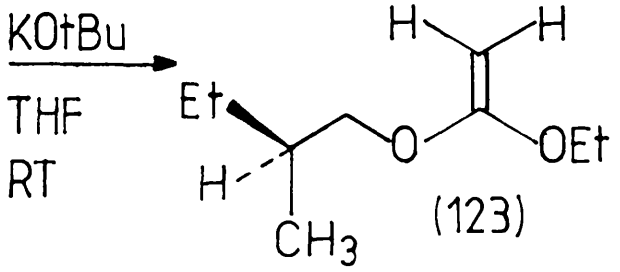
	m/e	molecular formula	calc. m/e	
Acetal 119				
$[M]^+$	306.0114	$C_{11}H_{15}O_2I$	306.0115	Obtained in 74% yield, b.p. 160-165°C at 2mmHg
$[M-CH_2I]^+$	165.0915	$C_{10}H_{13}O_2$	165.0919	
Acetal 120				
$[M-OEt]^+$	241.0086	$C_7H_{14}OI$	241.0088	Obtained in 73% yield, b.p.150-154°C at 9mmHg
$[M-CH_2I]^+$	145.1230	$C_8H_{17}O_2$	145.1228	
Acetal 121				
$[M-CH_2I]^+$	213.1874	$C_{13}H_{25}O_2$	213.1854	Obtained in 78% yield after chromatography

(119)



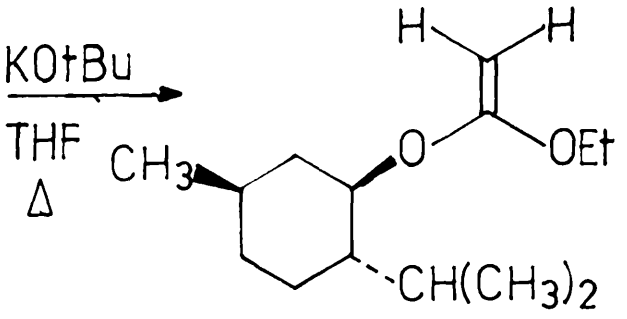
(122)

(120)



(123)

(121)



(124)

Scheme 39.

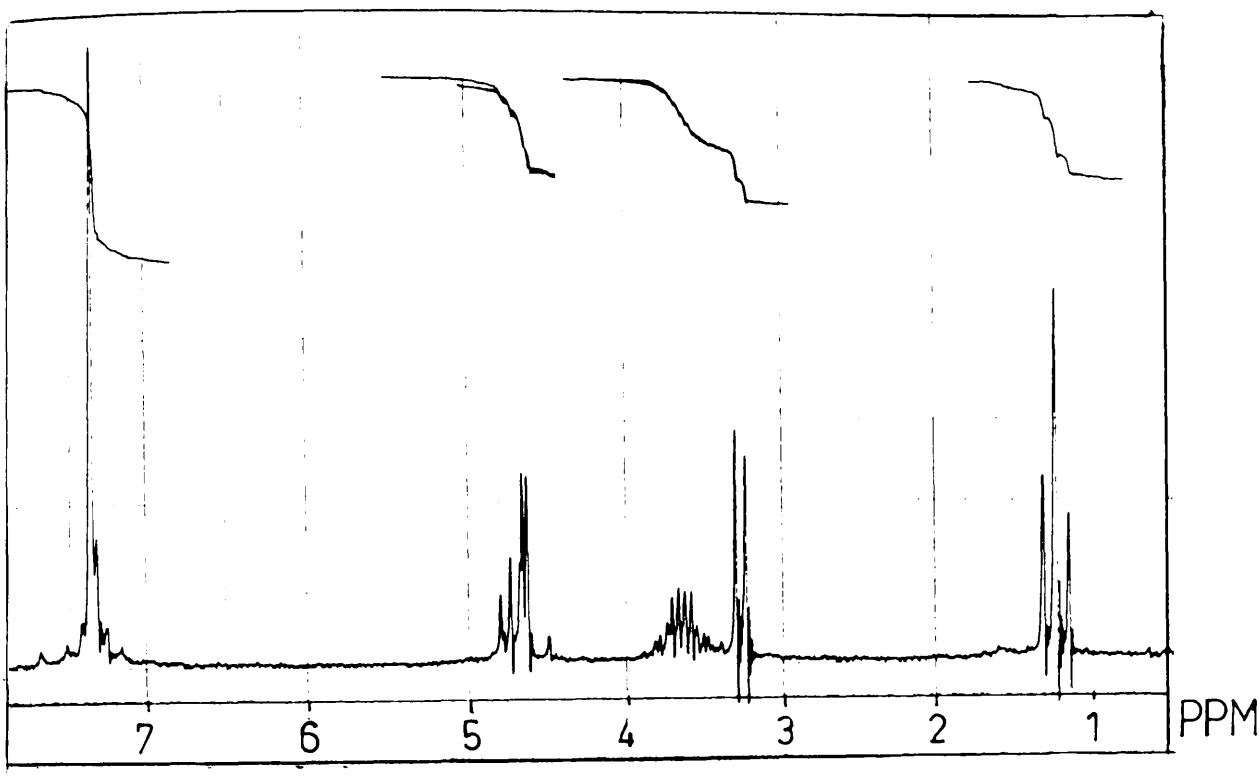


FIG. 24
^{1}H NMR SPECTRUM OF ACETAL(119) AT 90MHz.

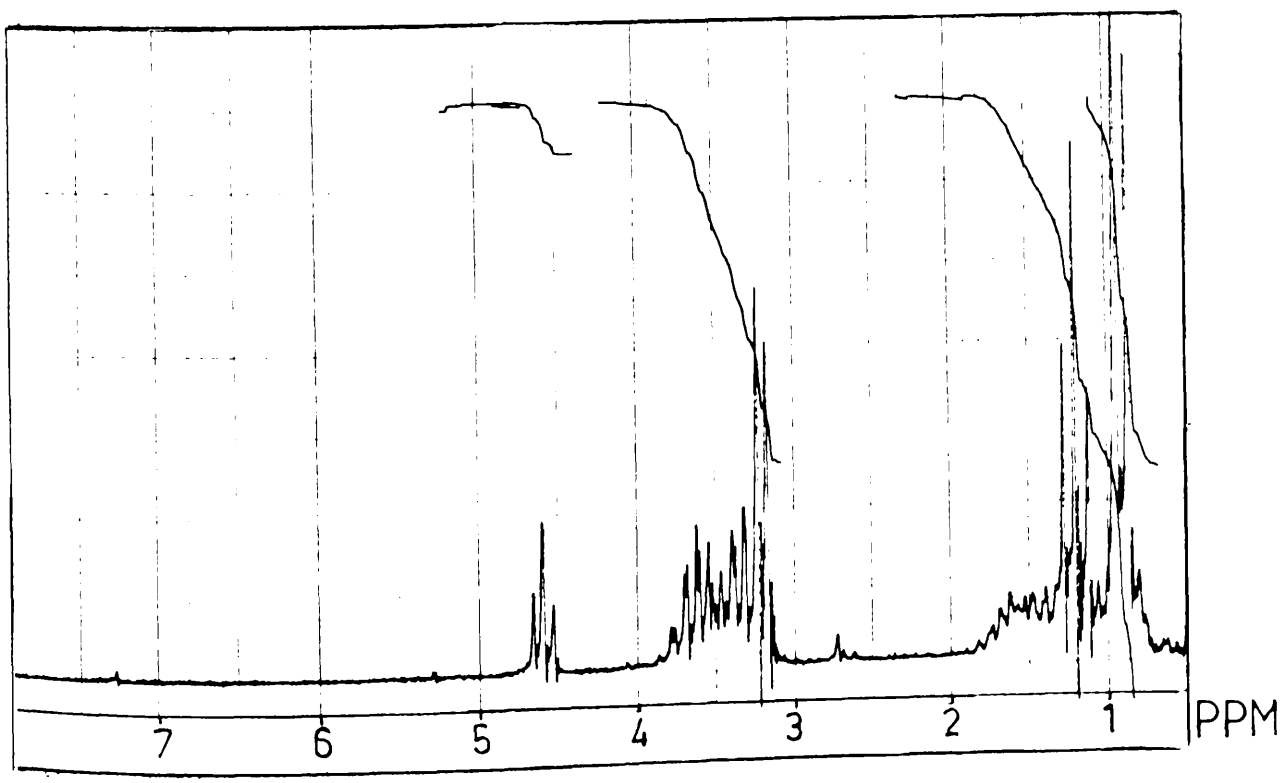


FIG. 25
^{1}H NMR SPECTRUM OF ACETAL(120) AT 90MHz.

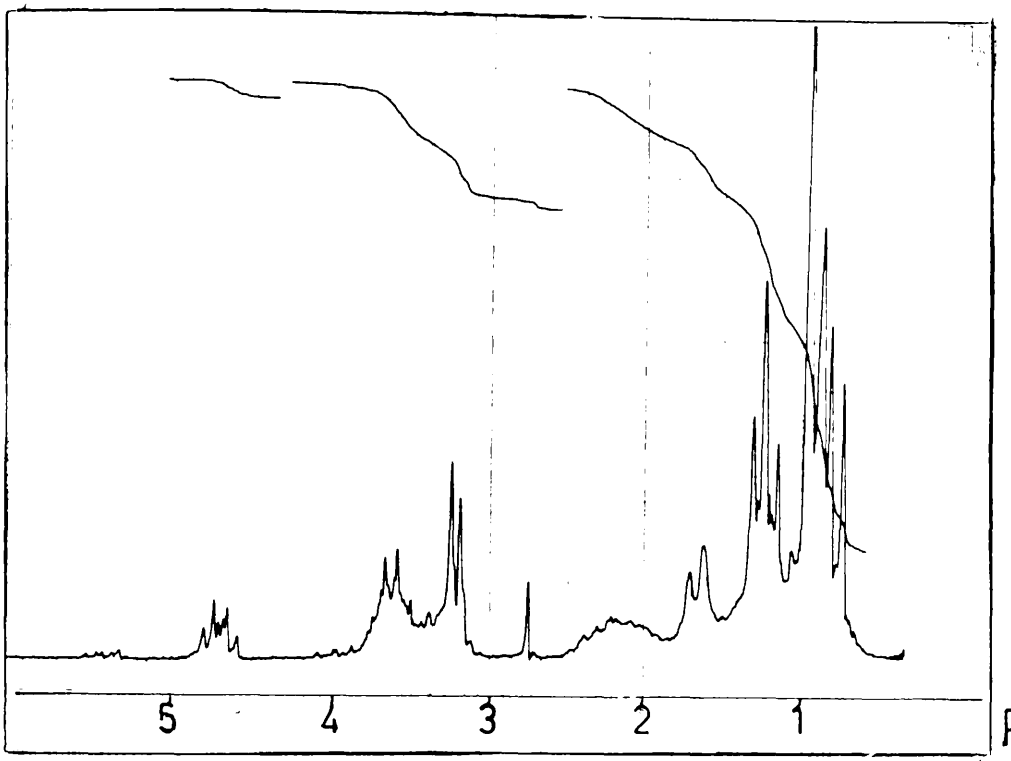


FIG. 26

^{1}H NMR SPECTRUM OF ACETAL (121) AT 90 MHz.

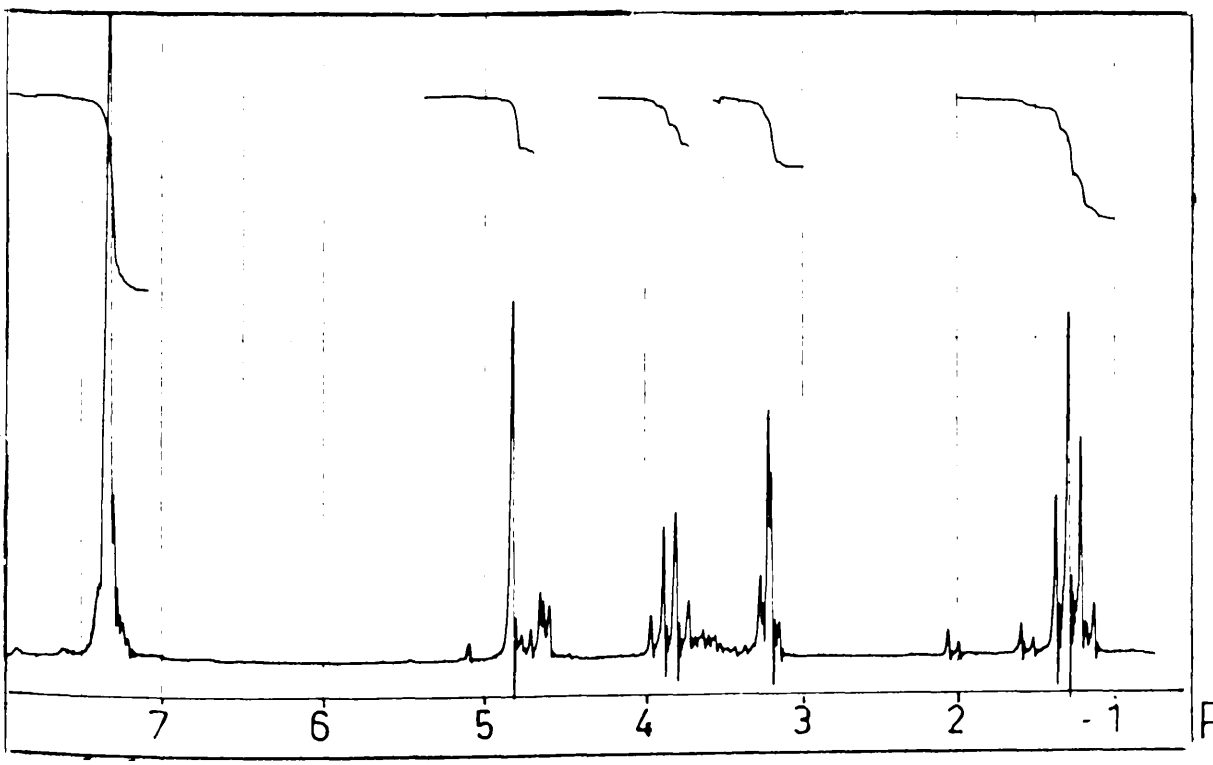


FIG. 27

^{1}H NMR SPECTRUM OF KETENE ACETAL (122) AT 90 MHz.

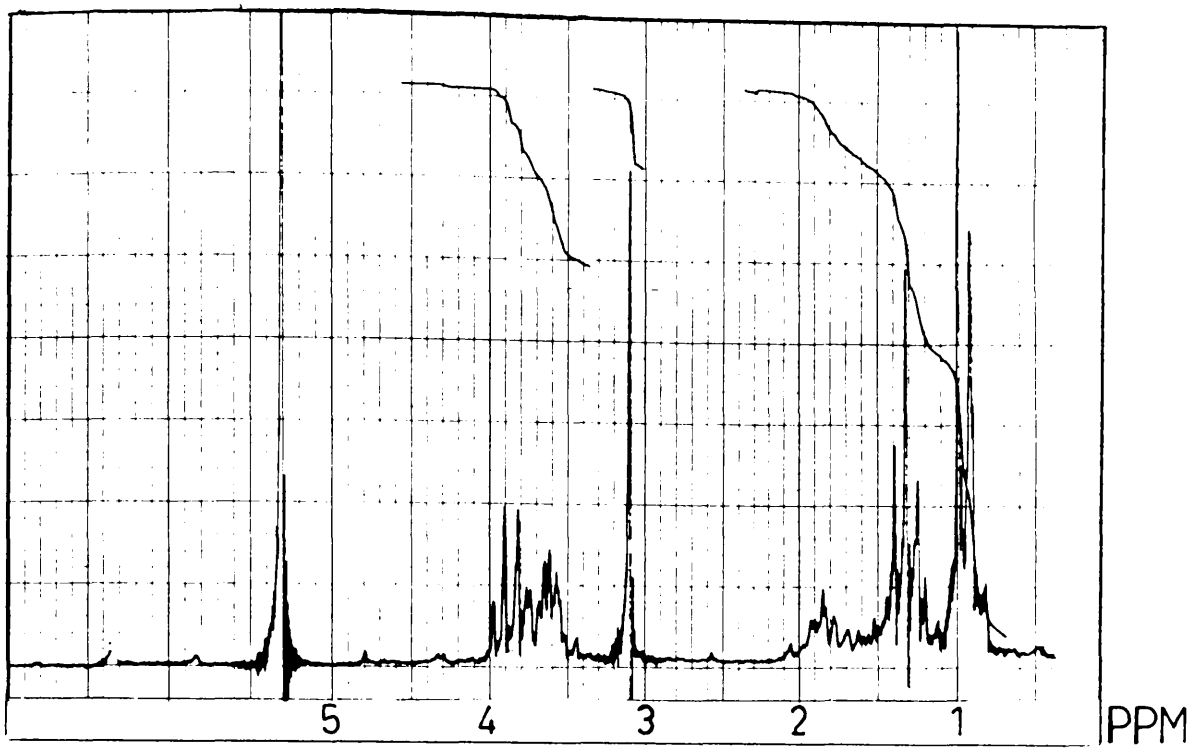


FIG. 28

^1H NMR SPECTRUM OF KETENE ACETAL(123) AT 90MHz.

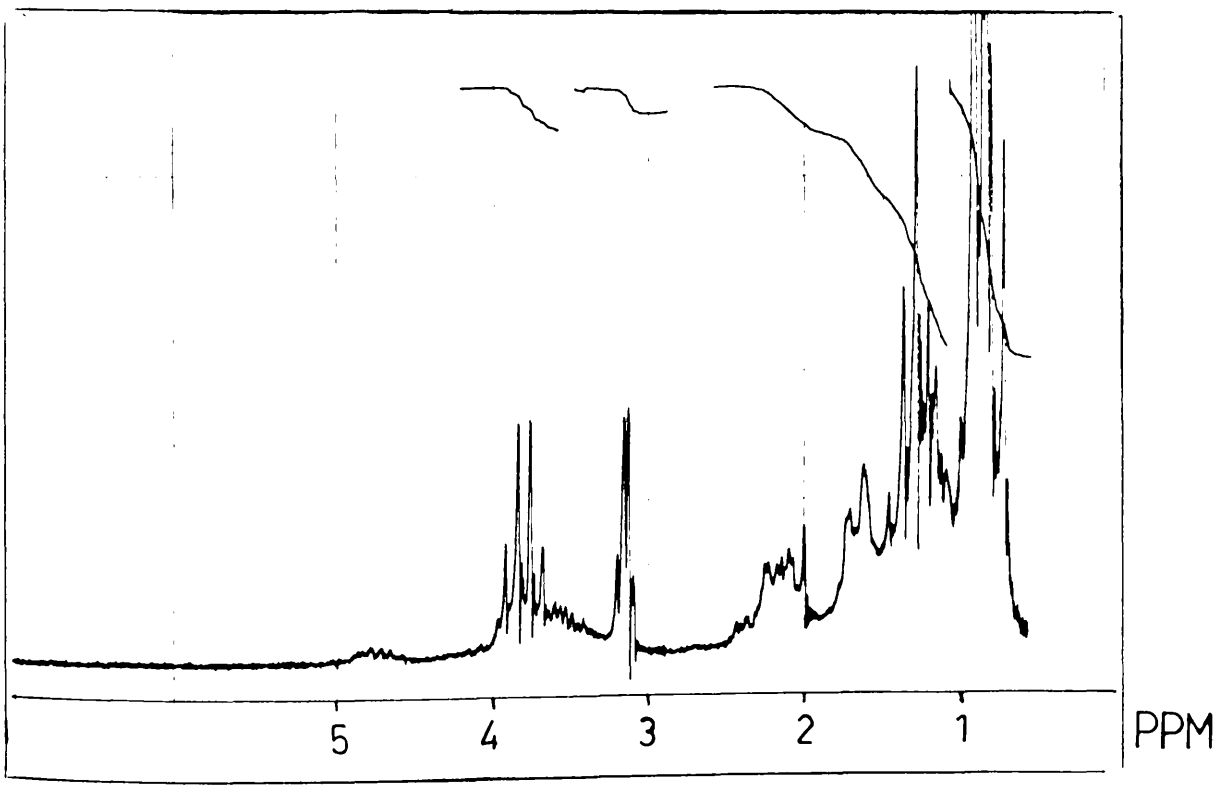


FIG. 29

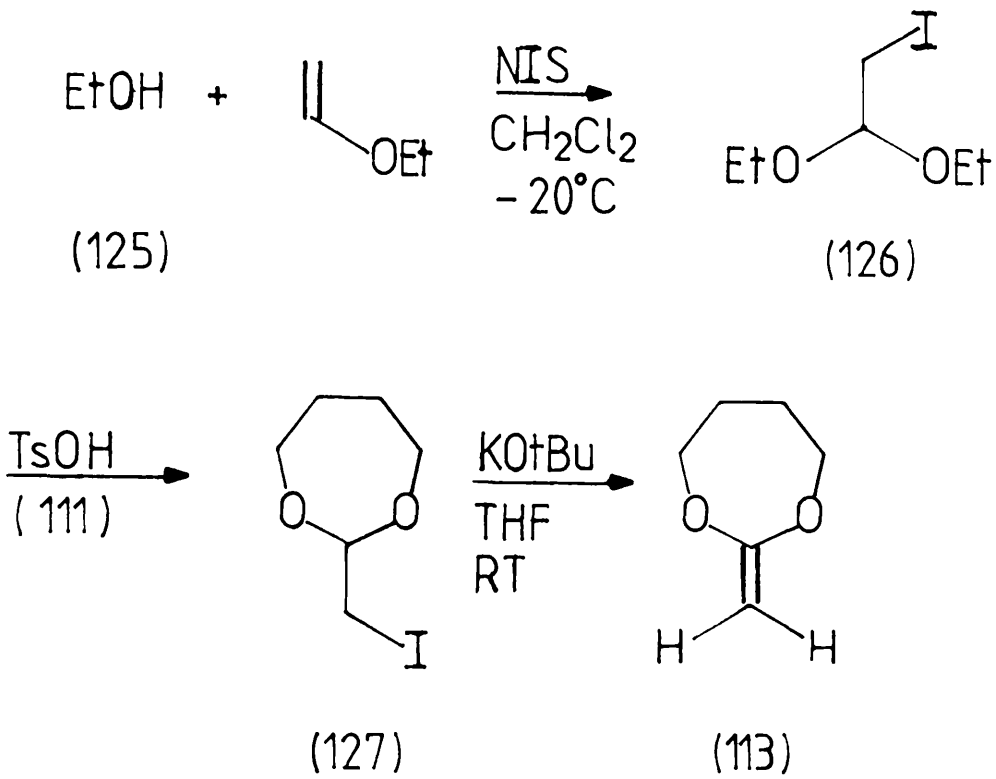
^1H NMR SPECTRUM OF KETENE ACETAL(124) AT 90MHz.

Table 8.

	m/e	molecular formula	calc. m/e.	Yield.
122 $[M]^+$	178.0991	$C_{11}H_{14}O_2$	178.0994	89%
123 $[M^+]$	158.1310	$C_9H_{18}O_2$	158.1307	91%
$[M+1]^+$	159.1386	$C_9H_{19}O_2$	159.1385	
124 $[M+1]^+$	227.2008	$C_{14}H_{27}O_2$	227.2001	90%

The accurate mass data indicates that ketene acetals (123) and (124) are not as stable as (122) under the conditions used for analysis. These ketene acetals were isolated as oils after work-up and were not further purified.

In a preliminary series of experiments iodo acetaldehyde diethyl acetal (126) was prepared using the same method as for the α-iodo-acetals described above, and used without purification in an acetal exchange reaction with butan-1,4-diol (111) to afford the cyclic α-iodo-acetal (127) as a colourless oil after chromatography. However, the yield of this cyclisation was disappointingly low (30%), [Scheme 40].



Scheme 40

The ^1H nmr spectrum of acetal (126) characteristically displays a triplet at δ4.61 (J = [illegible] Hz) and a doublet at δ3.2 (J = [illegible] Hz) corresponding to the acetal methine proton and the $\underline{CH_2}$-I protons respectively. Accurate mass analysis showed $[M-C_2H_5O]^+$ = 198.9638 corresponding to a molecular formula of C_4H_8OI (calc. m/e = 198.9619) as highest mass ion and $[M-CH_2I]^+$ = 103.0752 corresponding to $C_6H_{11}O_2$ (calc. m/e = 103.0759) as the base peak. The ^1H nmr spectrum of cyclic

acetal (127) is almost identical to that of the corresponding α-bromo-acetal (112) and shows a triplet at δ4.6 (J = 5.8 Hz) and a doublet at δ3.2 (J = 5.8 Hz). Accurate mass analysis showed $[M]^+$ = 241.9789 corresponding to a molecular formula of $C_6H_{11}O_2I$ (calc. m/e = 241.98025) and $[M-CH_2I]^+$ = 101.0602 corresponding to $C_5H_9O_2$ (calc. m/e = 101.0602).

Attempted dehydroiodination of acetal (127) afforded a sample of ketene acetal (128) which had already undergone substantial polymerisation, however the ^1H nmr spectrum of which clearly shows a singlet at δ3.09 attributable to the olefinic protons.

Summary and Conclusions.

The simplicity of the hydrogenolysis of isoxazolidine (96) in which the N-O bond and both benzyl-oxygen bonds are cleaved at the same time under mild conditions, confers great synthetic utility on this route as a means to synthesising β-amino acids. However, the problems encountered in cyclo-additions of (91) with chiral phenethyl nitrones[49] prevent this route from being adapted to form a general asymmetric synthesis of β-amino acids. An investigation into the use of pressure in these cycloadditions may prove useful.

Cyclic ketene acetals such as (104) and (113) appear to lack the stability required to be used in cycloadditions with nitrones as part of a general synthesis of β-amino acids.

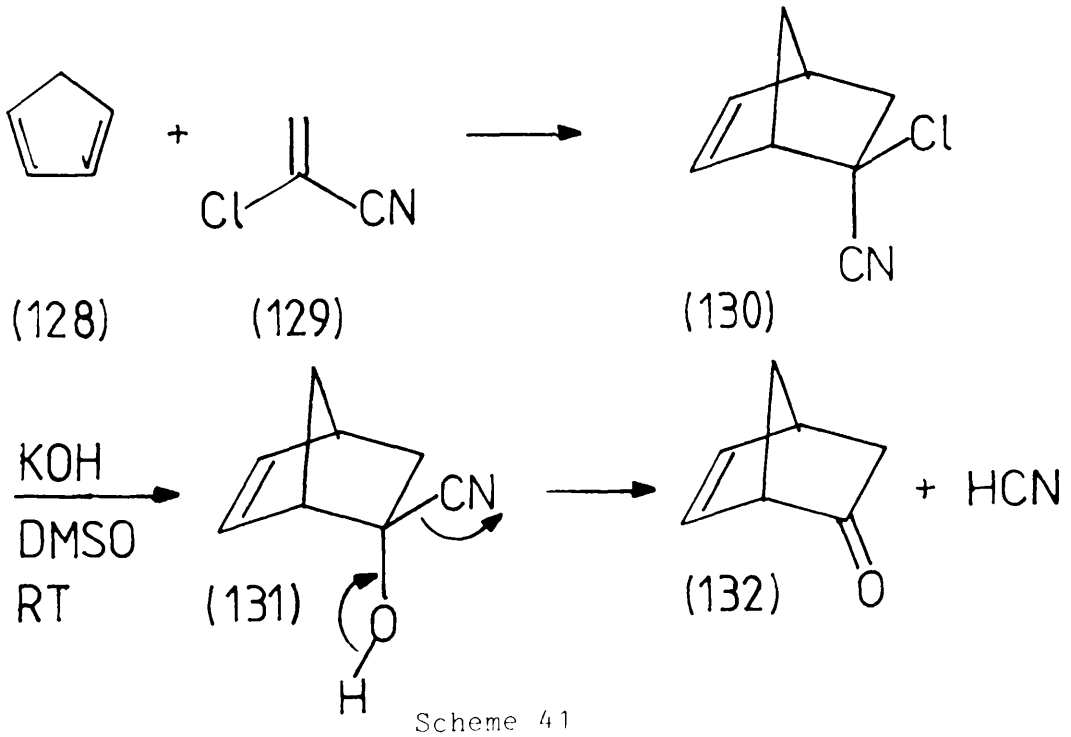
α-Iodo-acetals appear to undergo elimination reactions to afford ketene acetals under much milder conditions than their α-bromo counterparts. If cyclic α-iodo-acetals can be prepared in higher yields than acetal (127), this appraoch may be extended to allow easier isolation of cyclic ketene acetals such as (104). Lack of time prevented an investigation into the use of ketene acetals (122-124) in cycloaddition reactions with nitrones.

CHAPTER FOUR

The Asymmetric Synthesis of β-Amino Acids via Nitrone Cycloaddition to α-Chloroacrylonitrile.

4.1 Background and Introduction

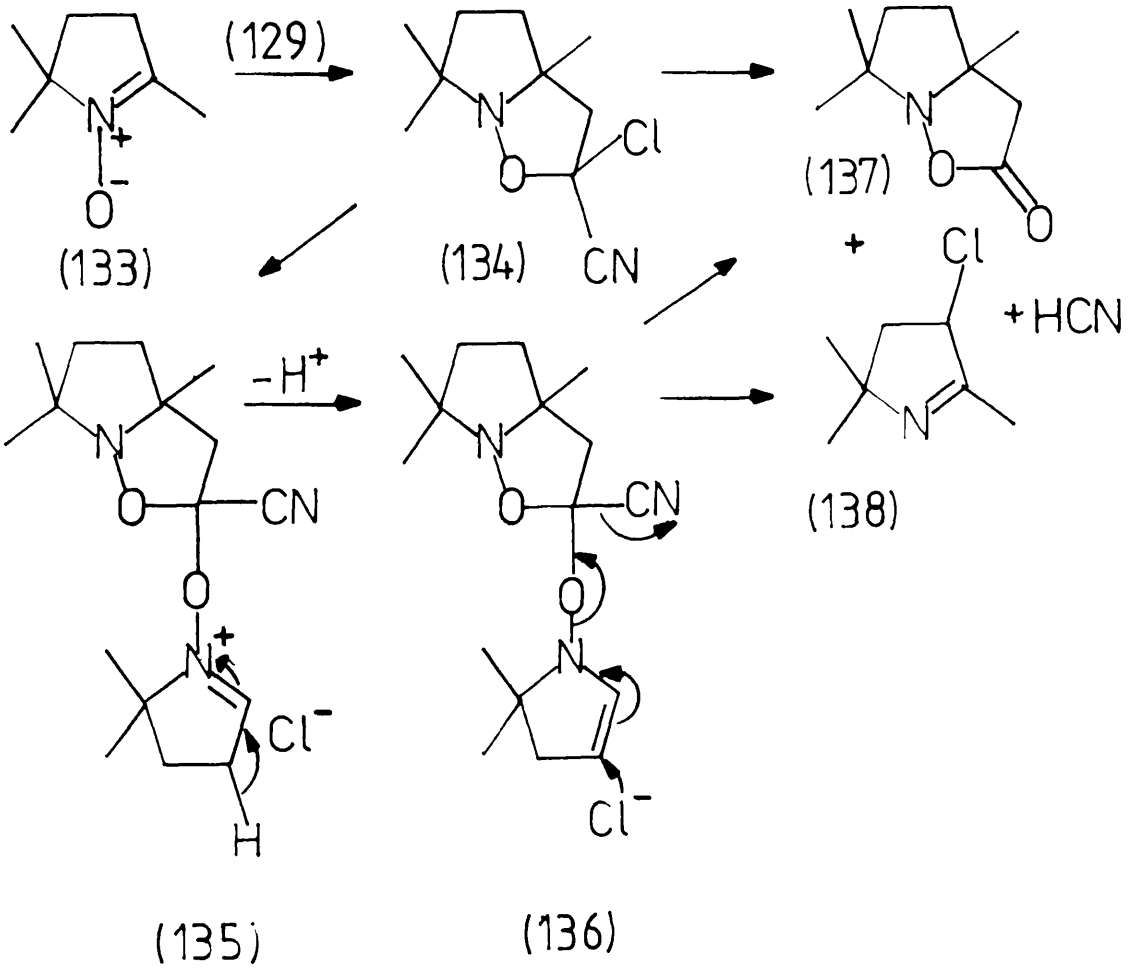
α-Chloroacrylonitrile (129) is recognised[103] as an efficient ketene equivalent and has been successfully employed in a number of Diels Alder [4+2] cycloaddition reactions such as that shown in Scheme 41. Hydrolysis of the newly formed cycloadduct (130) which presumably involves S_N2 displacement of CL^- by OH^- results in the formation of the cyano-hydrin (131) which undergoes elimination of HCN to yield the ketone[103] (132).



Scheme 41

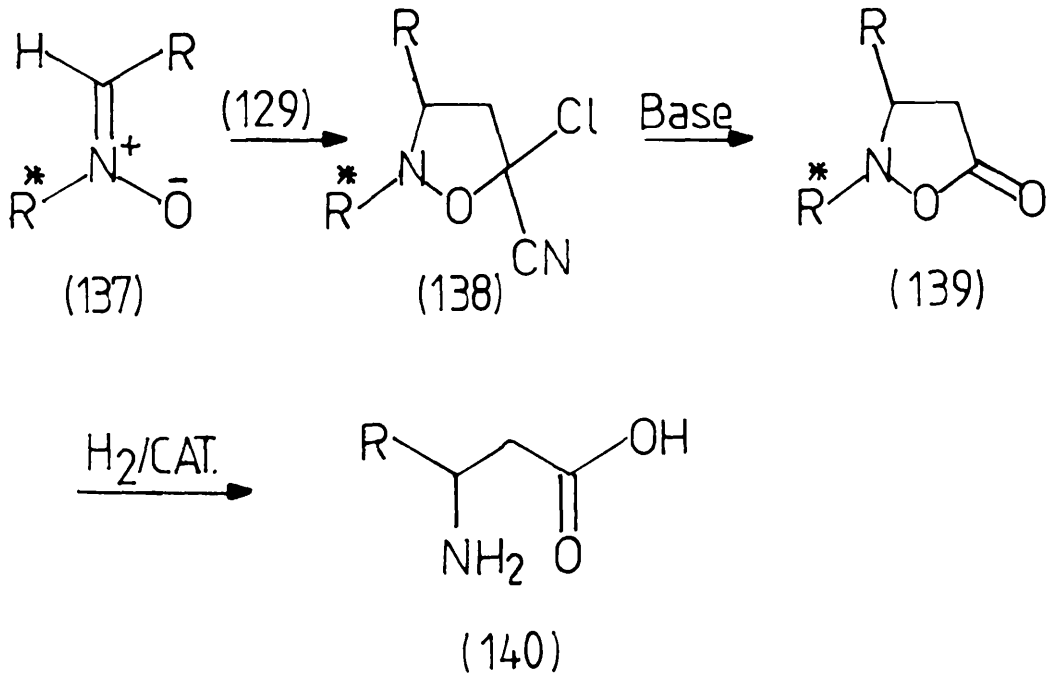
There has been only one previous reported example of the cycloaddition of a nitrone with α-chloroacrylonitrile as shown in Scheme 42. Schneider[104] reports that the

cycloaddition of nitrone (133) with α-chloroacrylonitrile results in the formation of isoxazolidinone(137) and the α-chloroimine (138). Schneider accounts for the formation of these products by the mechanism shown in Scheme 42, in which nucleophilic attack of nitrone on newly formed cyclo-adduct is followed by isomerisation of the double bond in (135) and Michael-type attack of CL^- on (136). Compounds (137) and (138) were isolated in a relative ratio of approximately 2.5:1 following distillation of the total product.



Scheme 42.

In the light of this apparent regiospecificity of addition, it was envisaged that cycloaddition reactions of chiral benzylic nitrones with α-chlorocrylonitrile may after hydrolysis of the cycloadducts thus formed, lead to the formation of isoxazolidinones such as (139) shown in Scheme 43. Baldwin[46] and Overton[48] have shown independently that isoxazolidinones of this type can be hydrogenolysed to afford free β-amino acids, therefore the cycloaddition of nitrones to α-chloroacrylonitrile may form the first step in an asymmetric synthesis of β-amino acids.



Scheme 43.

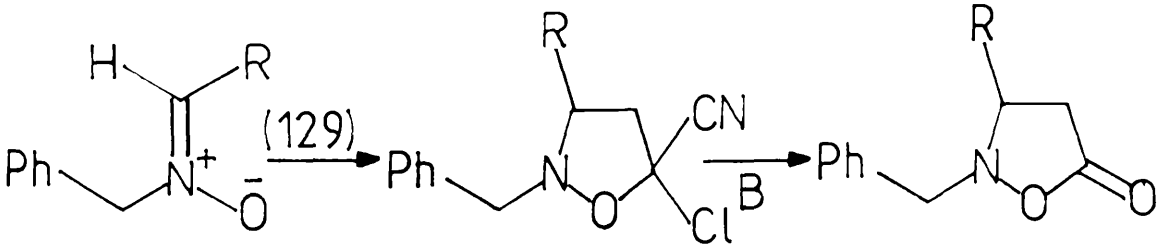
In the route developed by Overton et al[49,50] in which the isoxazolidinone system was arrived at via cyclo-addition reactions of nitrones with vinyl acetate (see

Introduction) followed by subsequent hydrolysis and oxidation of the diastereomeric acetates thus formed, the oxidation step proved troublesome and afforded isoxazolidinones in yields of only 15-40%.

Discussion

4.2 Cycloaddition of Achiral Nitrones to α-Chloroacrylonitrile.

Initial investigations were carried out employing achiral nitrones. Nitrones (10) and (15) were refluxed in neat α-chloroacrylonitrile for approximately 1 hour and the product mixtures from the respective cycloadditions were purified by flash column chromatography. Thin layer chromatographic analysis of both of these mixtures showed several spots of very similar RF value. Attempts to hydrolyse these mixtures using KOH/DMSO were unsuccessful. However, it was found that both pyridine and triethylamine (1.5 equiv) in aqueous THF solution facilitate the conversion of the cycloadducts to the corresponding isoxazolidinones (143) and (144), [Scheme 44].



(10) R=Ph (141) (143) R=Ph

(15) R=PhCH$_2$ (142) (144) R=PhCH$_2$

B = Py, Et$_3$N/THF/H$_2$O

Scheme 44.

Isoxazolidinones (143) and (144) were both obtained as oils in yields of 50% and 42% respectively using Et_3N as the base, while (144) was obtained in only 26% yield using pyridine. The ^1H nmr spectra of these compounds are almost identical as can be seen in Figures 31 and 32. Both display a doublet at approximately δ2.95 (J = 9Hz) corresponding to the two C-4 protons, a triplet at approximately δ4.3 (J = 9Hz) corresponding to the C-3 methine proton, and an AB quartet at δ4.0 (J = 14.2Hz) corresponding to the N-benzylic protons. The i.r. spectra show a strong carbonyl band at approximately 1769 cm^{-1} while accurate mass analysis showed $[M]^+$ = 253.1098 corresponding to a molecular formula of $C_{16}H_{15}NO_2$ (calc. m/e = 253.1103) for compound (143), and $[M]^+$ = 283.1221 corresponding to a molecular formula of $C_{17}H_{17}NO_3$ (calc. m/e = 283.1208) for compound (144). The spectral characteristics of compound (143) are identical to those previously recorded by Moffat.[49]

The material recovered in addition to these isoxazolidinones was shown to be a mixture of compounds of very similar Rf value by TLC analysis. The 90 MHz ^1H nmr spectra of the initial cycloadduct mixtures provide little information on their composition, however the 200MHz ^1H nmr spectrum of the mixture formed from nitrone (15) and α-chloroacrylonitrile shows the presence of at least four methoxyl methyl singlets and indicates that this is a more complex mixture of compounds than at first thought, [Figure 30].

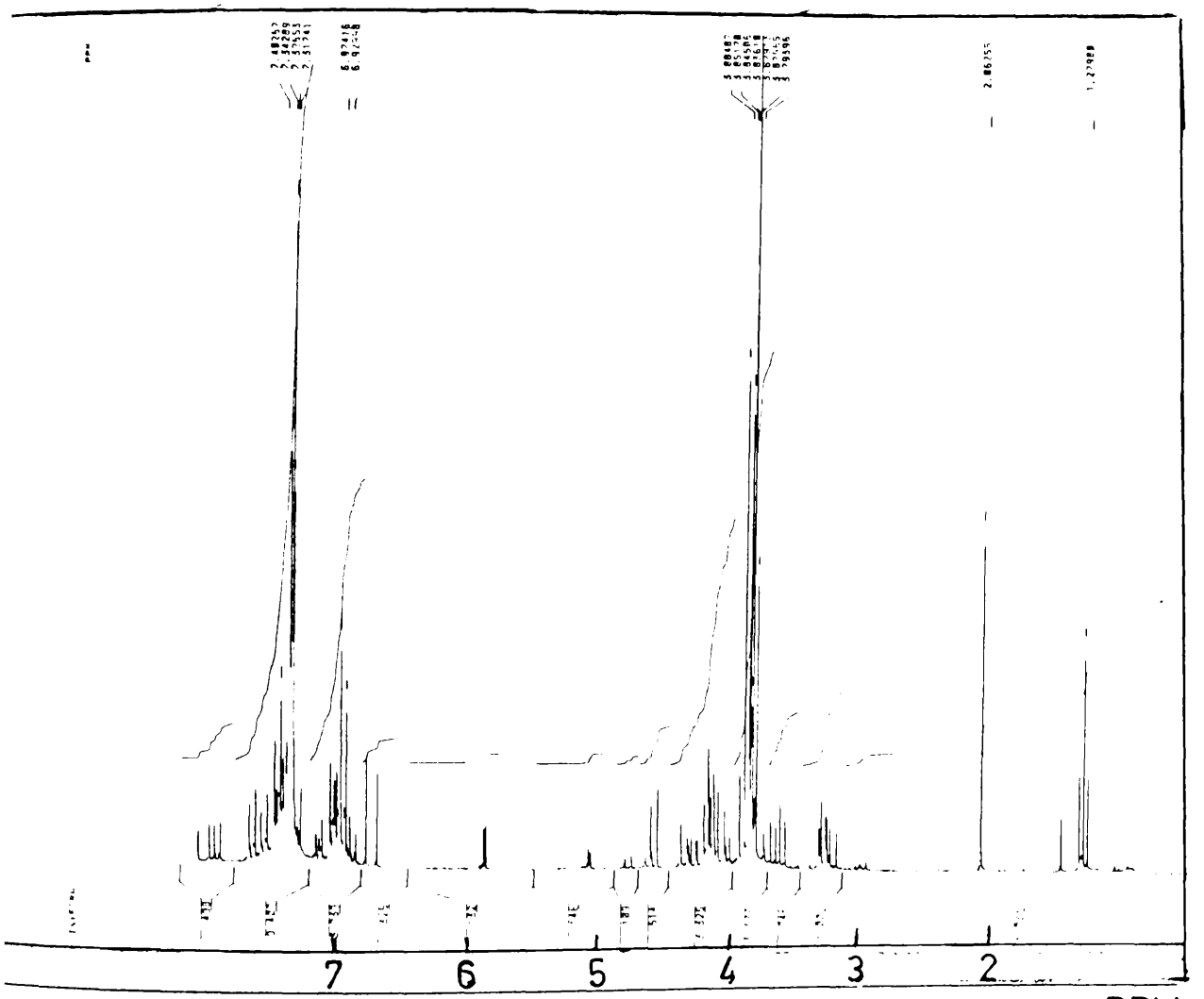


FIG. 30

^{1}H NMR SPECTRUM OF(142) AT 200MHz.

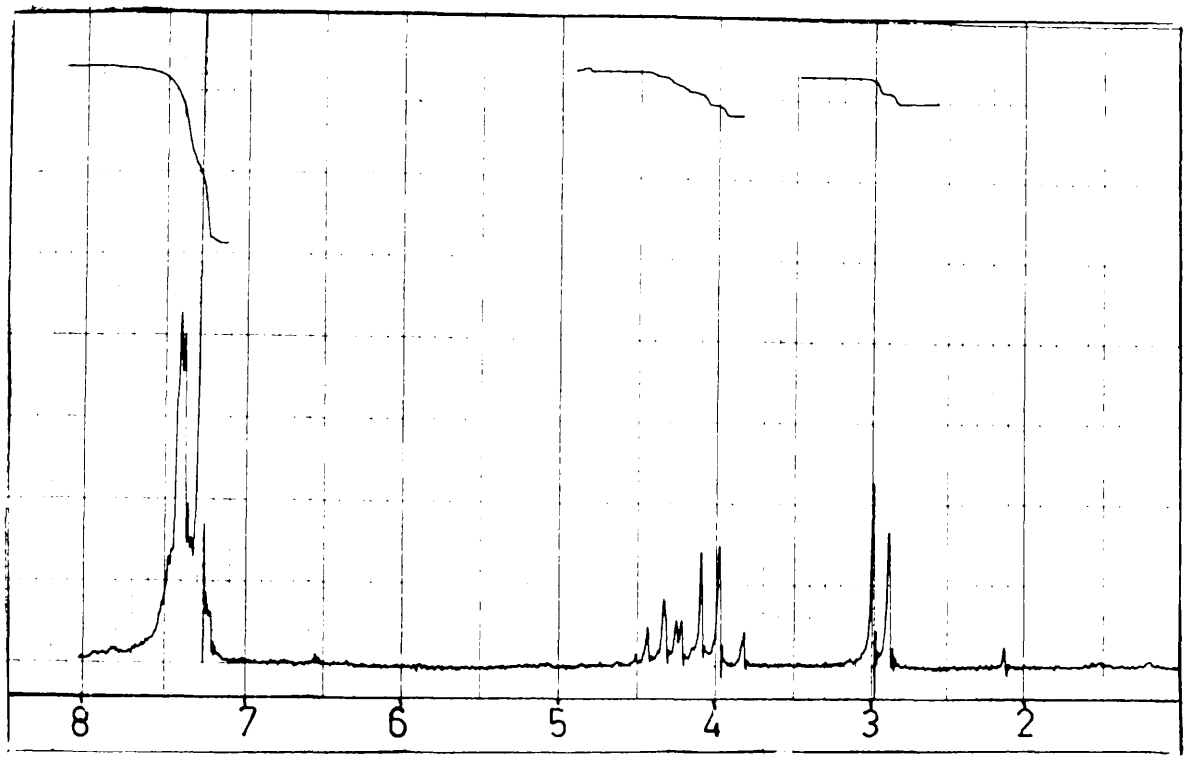


FIG.31

^1H NMR SPECTRUM OF ISOXAZOLIDINONE(143) AT 90MHz.

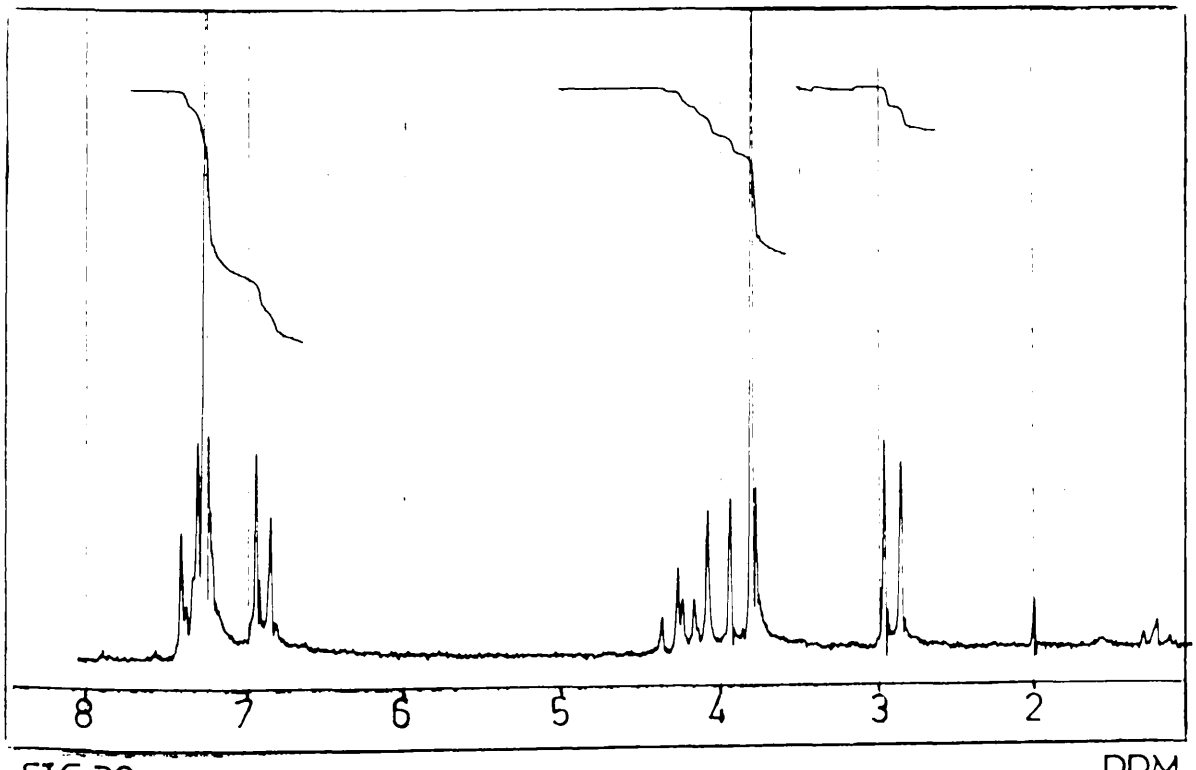
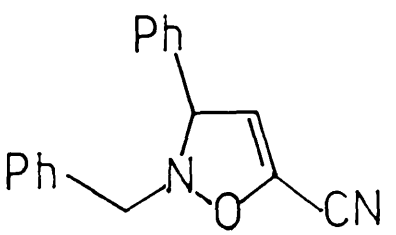


FIG.32

^1H NMR SPECTRUM OF ISOXAZOLIDINONE(144) AT 90MHz.

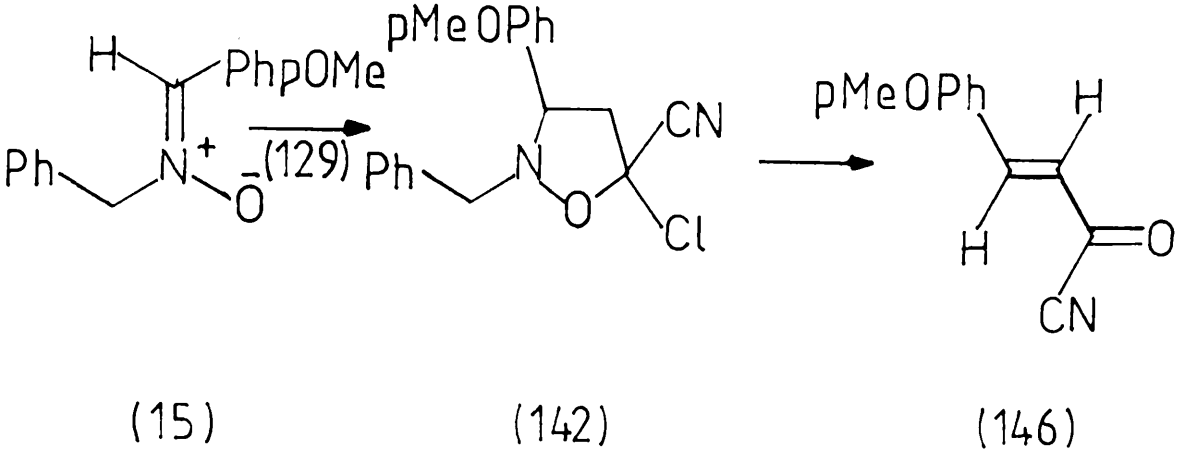
Assuming that the cycloaddition regiospecifically gave rise to the formation of the two possible diastereomeric 5,5'-disubstituted isoxazolidines, one would expect to see only two such methoxyl methyl singlets. A partial separation of the total product from cycloaddition of nitrone (10) with α-chloroacrylonitrile gave rise to a colourless oil whose ^{1}H nmr spectrum [Figure 33] suggests that it is the isoxazoline (145) formed by elimination of HCl from the initial cyclo-adduct. This spectrum clearly shows an AB quartet centred at δ4.15 (J = 13Hz) corresponding to the N-benzylic protons and two doublets at δ5.08 and δ5.85 (J = 4.5Hz) presumably attributable to the C-3 and C-4 protons. Accurate mass analysis showed $[M]^+$ = 262.1108 corresponding to a molecular formula of $C_{17}H_{14}N_2O$ (calc. m/e = 262.1106).



(145)

The hypothesis that the cycloadditions of nitrones (10) and (15) with α-chloroacrylonitrile may be complicated by elimination of HCl during the cycloaddition was verified by the observation that on refluxing nitrone (15) in neat α-chloroacrylonitrile for 24h, the α,β-unsaturated keto nitrile

(146) shown in Scheme 45 was recovered in 75% yield after chromatography as a crystalline solid, m.p. 125-126°C.

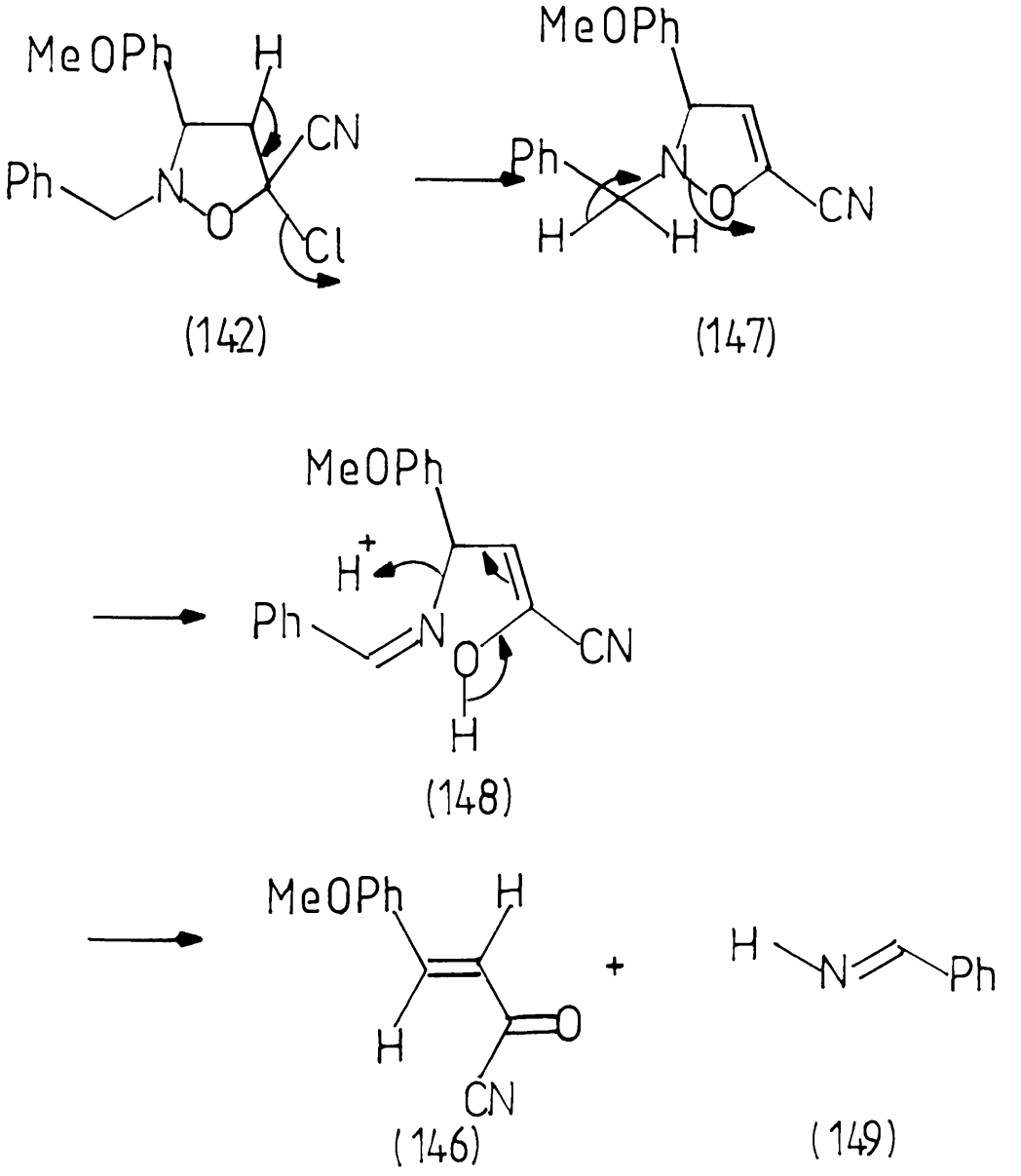


(15) (142) (146)

Scheme 45.

The ^{1}H nmr spectrum of (146) [Figure 34] shows doublets at δ6.75 (J = 16Hz) and δ7.95 (J = 16Hz) corresponding to the olefinic protons, doublets at δ7.0 (J = 8.4Hz) and δ7.6 (J = 8.4Hz) corresponding to the aromatic protons and a singlet at δ3.91 associated with the methoxyl methyl group. The proton-decoupled ^{13}C nmr spectrum shows signals at δ175.6 and δ112.63 corresponding to the carbonyl and nitrile carbon atoms respectively. The i.r. spectrum shows carbonyl and nitrile absorptions at 1659 and 2230 cm^{-1} respectively, while accurate mass analysis showed $[M]^{+}$ = 187.0632 corresponding to a molecular formula of $C_{11}H_9NO_2$ (calc. m/e = 187.0633). The

formation of compound(146) may be accounted for by a fragmentation process such as that shown in Scheme 46.



Scheme 46.

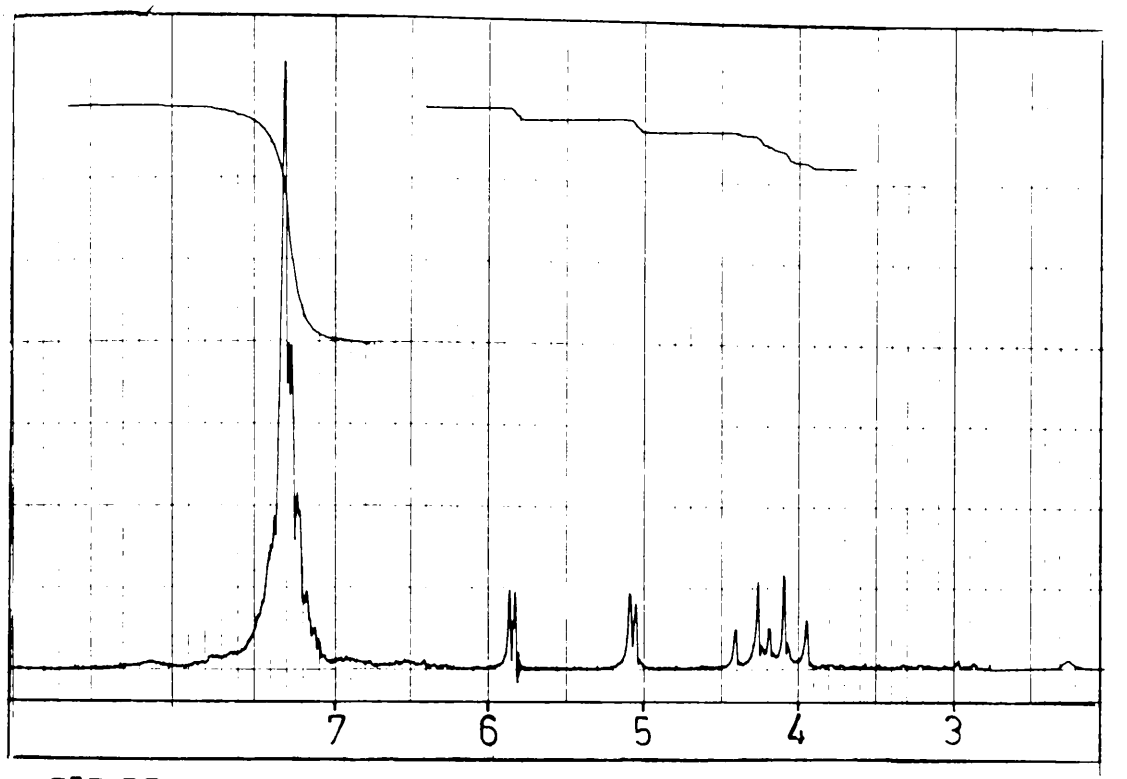


FIG. 33

^{1}H NMR SPECTRUM OF(145) AT 90 MHz.

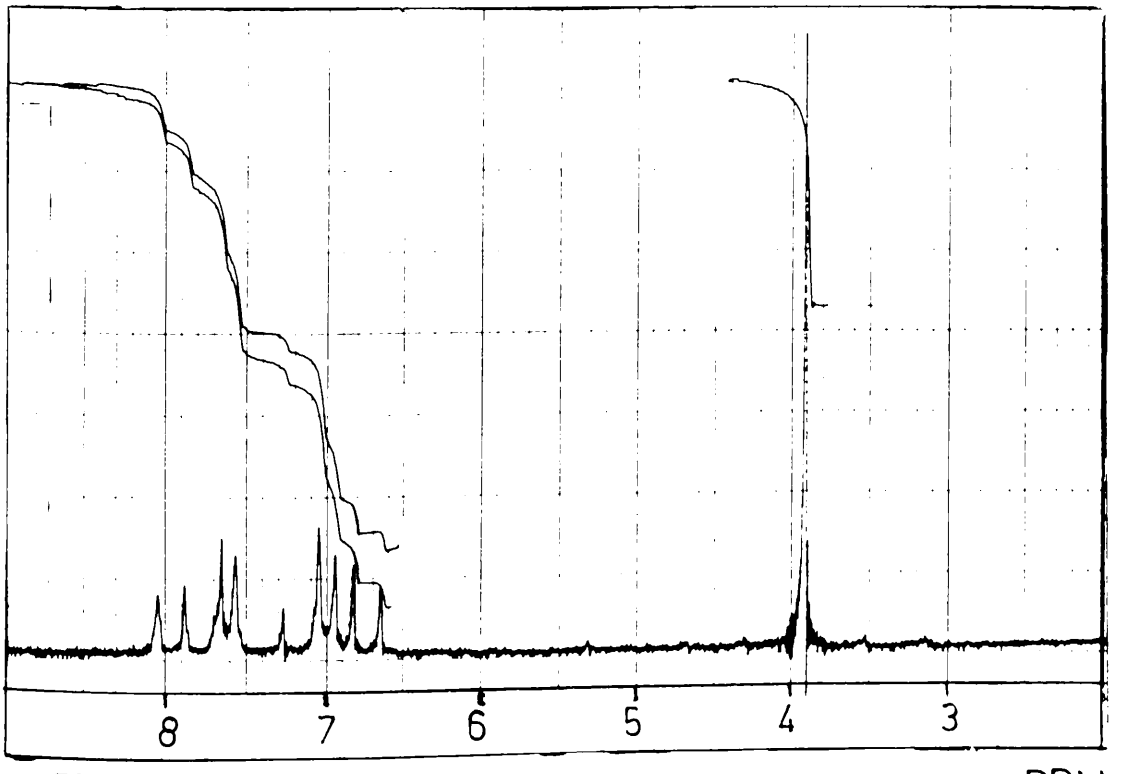
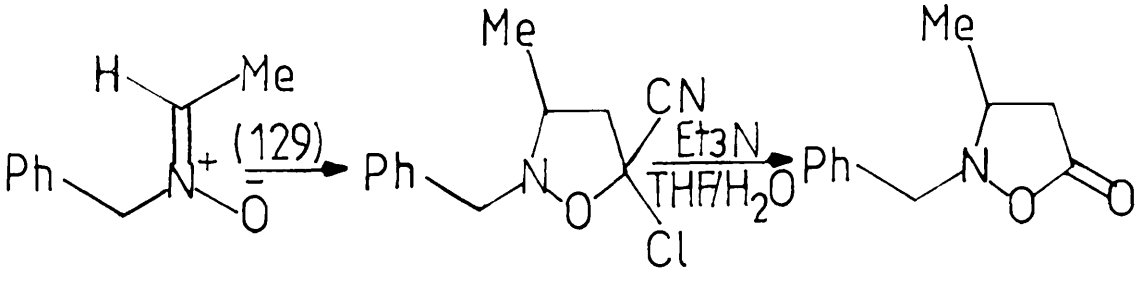


FIG. 34

^{1}H NMR SPECTRUM OF(146) AT 90MHz.

It would appear that the product mixture isolated from the cycloadditions of nitrones (10) and (15) with α-chloroacrylonitrile may consist of the two diastereomeric cycloadducts, the HCl-eliminated adduct and the products of a fragmentation process such as that shown in Scheme 46. This would explain the modest conversion (40-50%) of these mixtures to isoxazolidinones (143) and (144). However, in contrast to these two cases cycloaddition of nitrone (5) with α-chloroacrylonitrile afforded cycloadduct mixture (150) in 74% yield after only 10 minutes reflux. This material was immediately hydrolysed using triethylamine in aqueous THF and afforded isoxazolidinone (151) as a colourless oil in 74% yield after chromatography, [Scheme 47].



(5) (150) (151)

Scheme 47.

The ^1H nmr spectrum of isoxazolidinone (151) displays two doublets of doublets as part of the expected ABX system

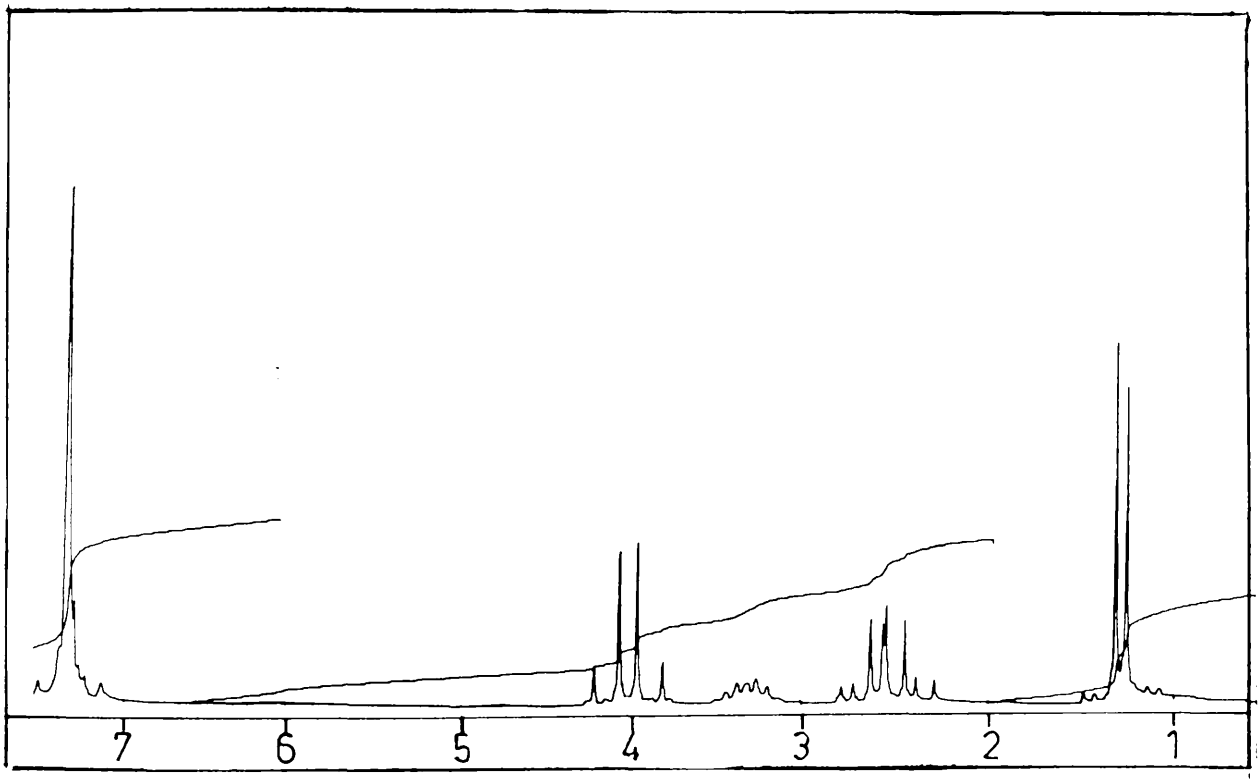


FIG. 35

^1H NMR SPECTRUM OF ISOXAZOLIDINONE(151) AT 100MHz.

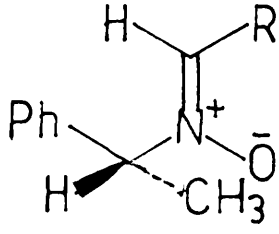
at δ2.4 (J = 11,17Hz) and δ2.68 (J = 7, 17Hz) corresponding to the C-4 protons, a multiplet centred at δ3.35 corresponding to the C-3 proton and an AB quartet centred at δ4.0 (J = 13.8 Hz) attributable to the two benzylic protons, [Figure 35]. The i.r. spectrum of (151) shows a strong carbonyl absorption at 1770 cm^{-1}, while accurate mass analysis showed $[M]^+$ = 191.0961 corresponding to a molecular formula of $C_{11}H_{13}NO_2$ (calc. m/e = 191.0946).

Isolation of isoxazolidinone (151) in significantly higher yield than isoxazolidinones (143) and (141) is probably attributable to two factors:- (1) the apparent increase in reactivity of nitrone (5) with α-chloroacrylonitrile allowing isolation of the cycloadducts before significant elimination or fragmentation occurs (2) the C-3 aromatic substituent in isoxazolidines (143) and (144) may stabilise any developing double bond between C-3 and C-4 leading to (146).

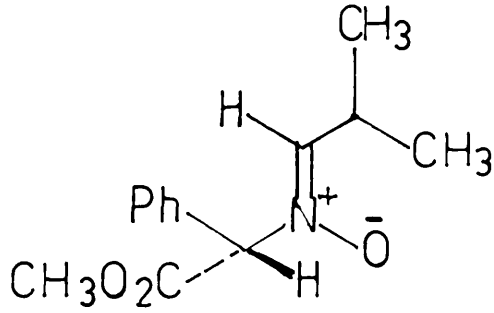
4.3 The Asymmetric Synthesis of β-Phenyl-β-Alanine, β-Leucine and β-Tyrosine.

Having demonstrated that it is possible to derive the isoxazolidinone ring system by manipulation of the cycloadducts of nitrones with α-chloroacrylonitrile, nitrones bearing a chiral group on nitrogen were then employed in an attempt to control the absolute stereochemistry at C-4 of

the isoxazolidine formed in the cycloaddition process. Nitrones (28-33) were chosen as intermediates for the asymmetric syntheses of β-phenyl-β-alanine, β-tyrosine and β-leucine.



(28) R=Ph
(29) R=p-MeOPh
(30) R=p-HOPh
(31) R=p-BzOPh
(32) R=iPr

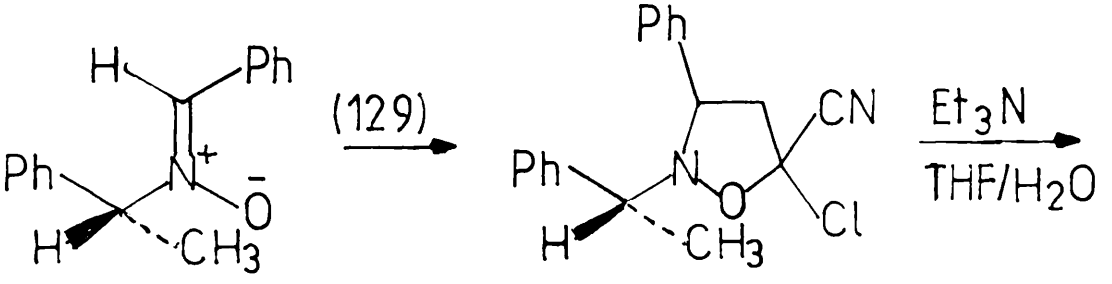


(33)

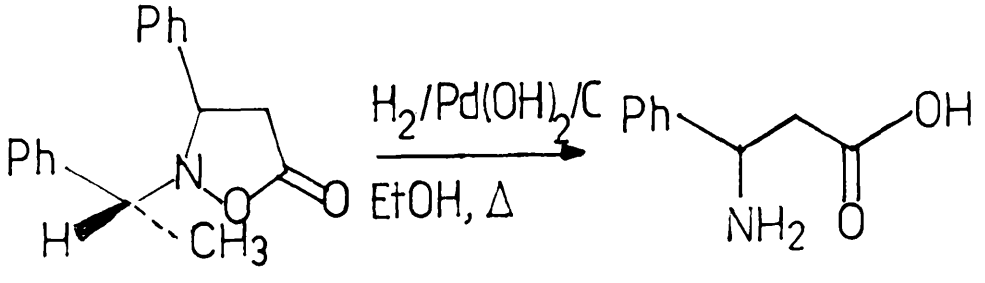
The N-benzylic chiral auxiliary would subsequently be removable by hydrogenolysis. Moffat[46] had previously demonstrated diastereoselectivity in cycloadditions of nitrones (28), (29) and (32) with vinyl acetate.

4.3.1 β-Phenyl-β-Alanine.

As the first step in the asymmetric synthesis of β-phenyl-β-alanine (154), nitrone (28) was refluxed in neat α-chloroacrylonitrile for 1 hour to give a product mixture in 60% yield after column chromatography. Hydrolysis of this material with triethylamine in aqueous THF for 24 hours afforded isoxazolidinone (153) as a light yellow oil which solidified on standing in 34% yield, m.p. 93-96°C (lit.[49] m.p. 95-98°C), [Scheme 48].



(28) (152)



(153) (154)

Scheme 48

The ^1H nmr spectrum of isoxazolidinone (153) shows the expected ABX system involving the benzylic methine proton at C-3, δ4.55(1H,t, J = 8Hz) and the methylene protons at C-4 as two doublets of doublets at δ3.15(1H,dd, J = 8, 17.8 Hz) and at δ2.86 (1H,dd, J = 8, 17.8 Hz), [Figure 46]. Only one doublet can be seen at δ1.6 (J = 7 Hz) for the methyl signal of the α-methylbenzyl group, and would seem to indicate the presence of only one of the two possible diastereomeric isoxazolidinones. However, Moffat[49] has found that both the ^1H nmr spectrum and the proton-decoupled ^{13}C nmr spectrum of a diastereomeric mixture of isoxazolidinones (153) (approximately 1:1) misleadingly indicate the presence of only one compound, i.e. the diastereomeric composition cannot be determined by analysis of these spectra. The i.r. spectrum of compound (153) shows a strong carbonyl absorption at 1765 cm^{-1} while accurate mass analysis showed $[M]^+$ = 267.1265 corresponding to a molecular formula of $C_{17}H_{17}NO_2$ (calc m/e = 267.1259). Hydrogenolysis of isoxazolidinone (152) with palladium hydroxide in ethanol at 70°C as described by Moffat[49] led directly to β-phenyl-β-alanine in quantitative yield as a crystalline solid m.p. 231-233°C $[\alpha]_D$ + 5.4° (c1.16, H_2O) (Lit.[105] value m.p. 236°C, $[\alpha]_D$ + 6.2° for (S)-β-phenyl-β-alanine). This $[\alpha]_D$ measurement indicates an enantiomeric excess of 87% of (S)-β-phenyl-β-alanine. However, due to the small size of the $[\alpha]_D$ measured, an error of 0.1° would mean the difference of approximately 2% in the calculated enantiomeric excess.

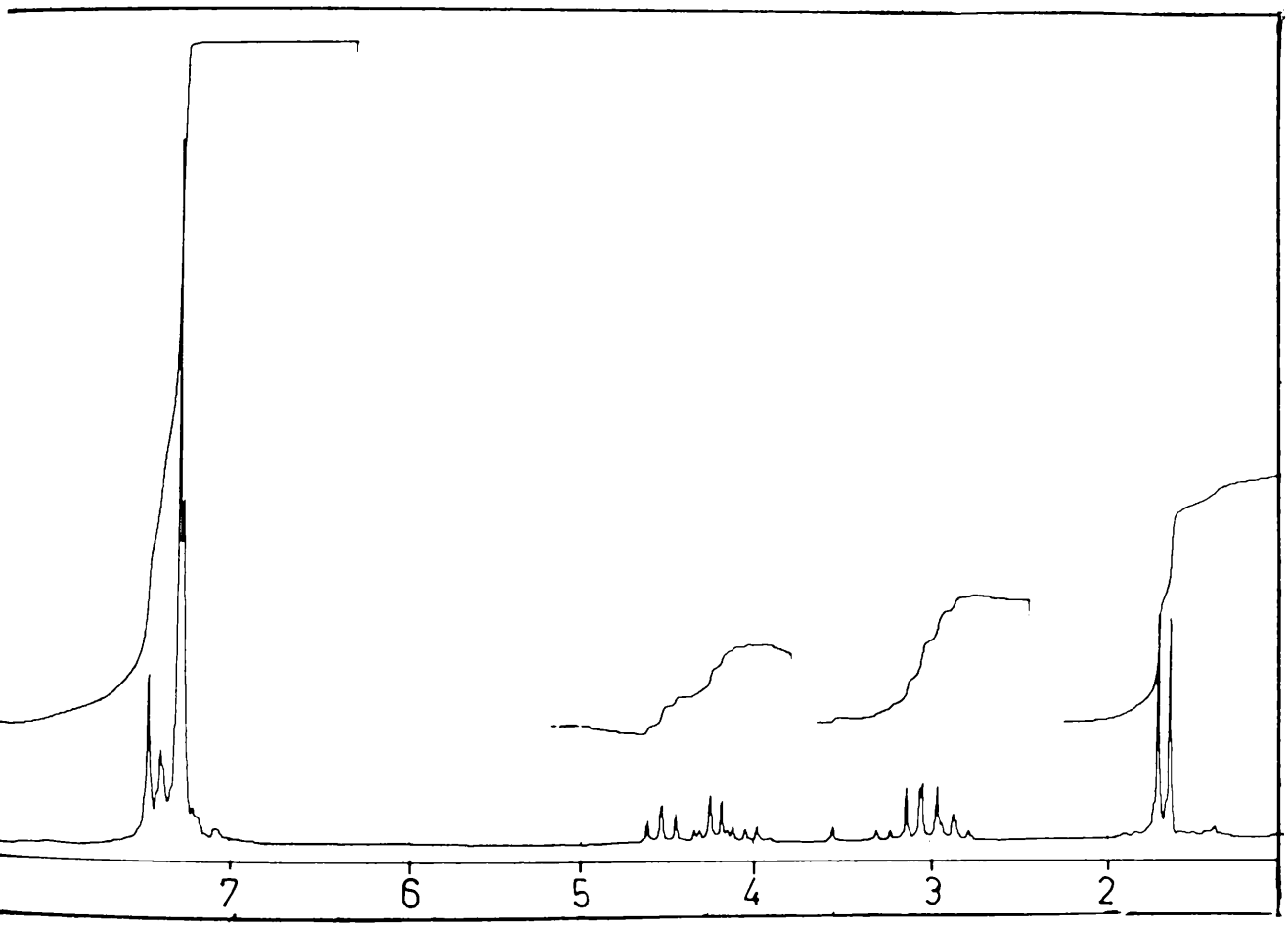
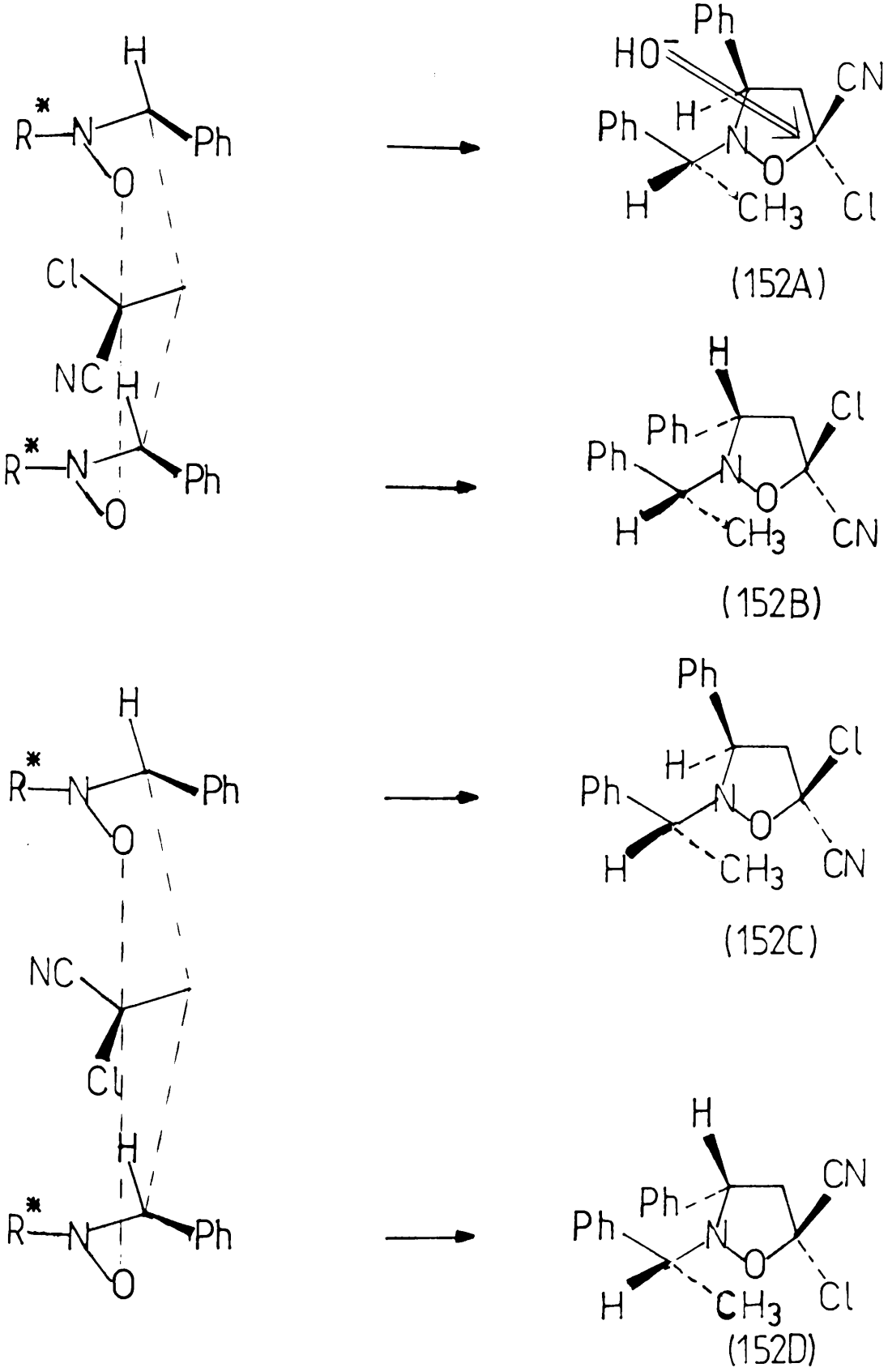


FIG. 36

^{1}H NMR SPECTRUM OF ISOXAZOLIDINONE (153) AT 100 MHz.

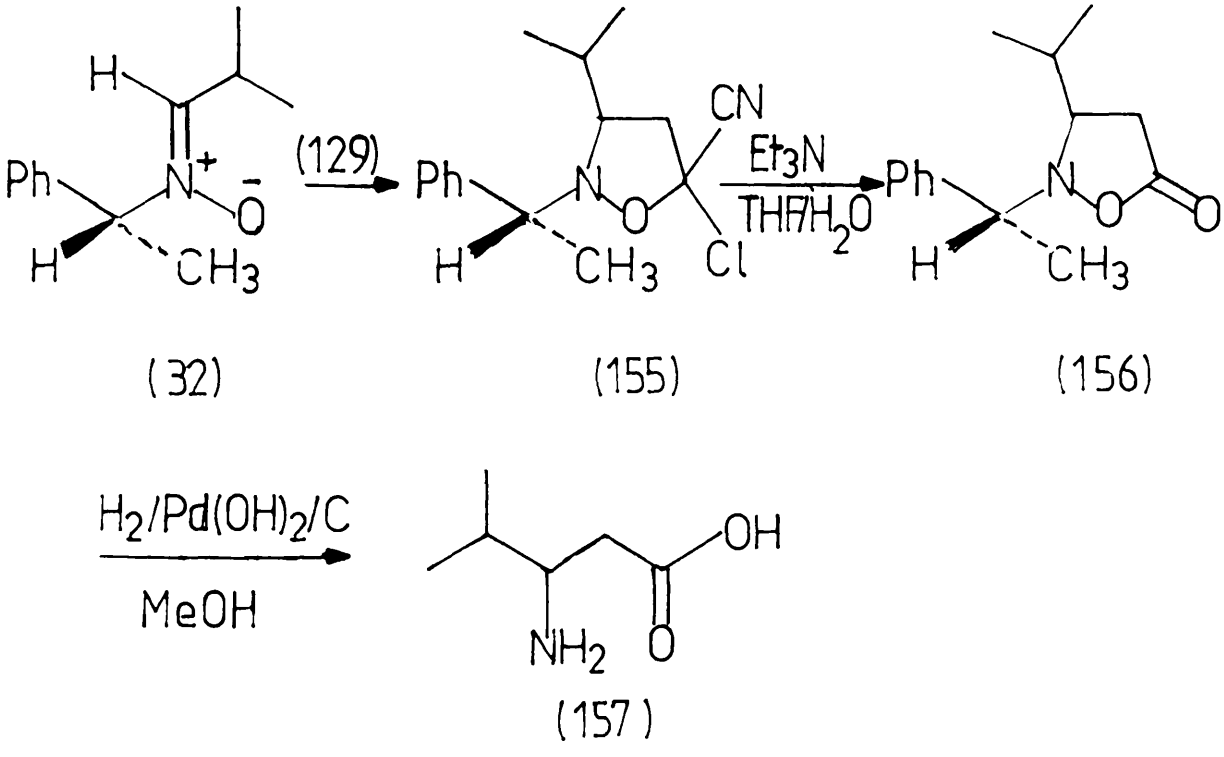
As in the previously described cases involving cycloadditions of C-aryl nitrones with α-chloroacrylonitrile, in addition to isoxazolidinone (153) other material was recovered after hydrolysis, presumably a mixture of elimination and fragmentation products, and some unhydrolysed chloro-nitrile. Therefore it would be unwise to attach too much weight to the observation that the ß-amino acid obtained following hydrogenolysis of compound (153) is predominantly of the (S)-configuration. It would be equally unwise to assume that only isoxazolidines with the (R)- configuration at C-3 can undergo elimination and fragmentation processes. However, molecular models suggest that S_N2 displacement of CL^- by OH^- may be sterically less favourable when the C-3 aryl and C-5 chlorine substituents are trans to each other than when they are cis. This would imply that isoxazolidinone (153) originated almost entirely from the isoxazolidine (152D) in which the configuration at C-3 is S and C-5 is (R). This would also imply that any unhydrolysed chloro-nitrile present in the material recovered along with compound (153) may consist predominantly of isoxazolidines in which the C-3 aryl and C-5 chlorine substituents are trans to each other (152A, 152B), [Scheme 49]. As in the cases described in Section 4.2, TLC analysis of this additional material showed a mixture of compounds with very similar RF values, the ^1H nmr spectrum of which gave little information as to its composition.


H
R*
N
O
Ph
Cl
NC
H
R*
N
O
Ph
HO⁻
Ph
H
CN
Ph
N
O
H
CH3
Cl
(152A)
H
Ph
Cl
Ph
N
O
H
CH3
CN
(152B)
H
R*
N
O
Ph
NC
Cl
H
R*
N
O
Ph
Ph
H
Cl
Ph
N
O
H
CH3
CN
(152C)
H
Ph
CN
Ph
N
O
H
CH3
Cl
(152D)

Scheme 49.

4.3.2 β-Leucine.

β-Leucine (157) was synthesised as shown in Scheme 50. Nitrone (32) was refluxed in neat α-chloroacrylonitrile for approximately 25 minutes, after which the material recovered in 71% yield following column chromatography was hydrolysed with triethylamine in aqueous THF and afforded isoxazolidinone (156) as a colourless oil in 66% yield.

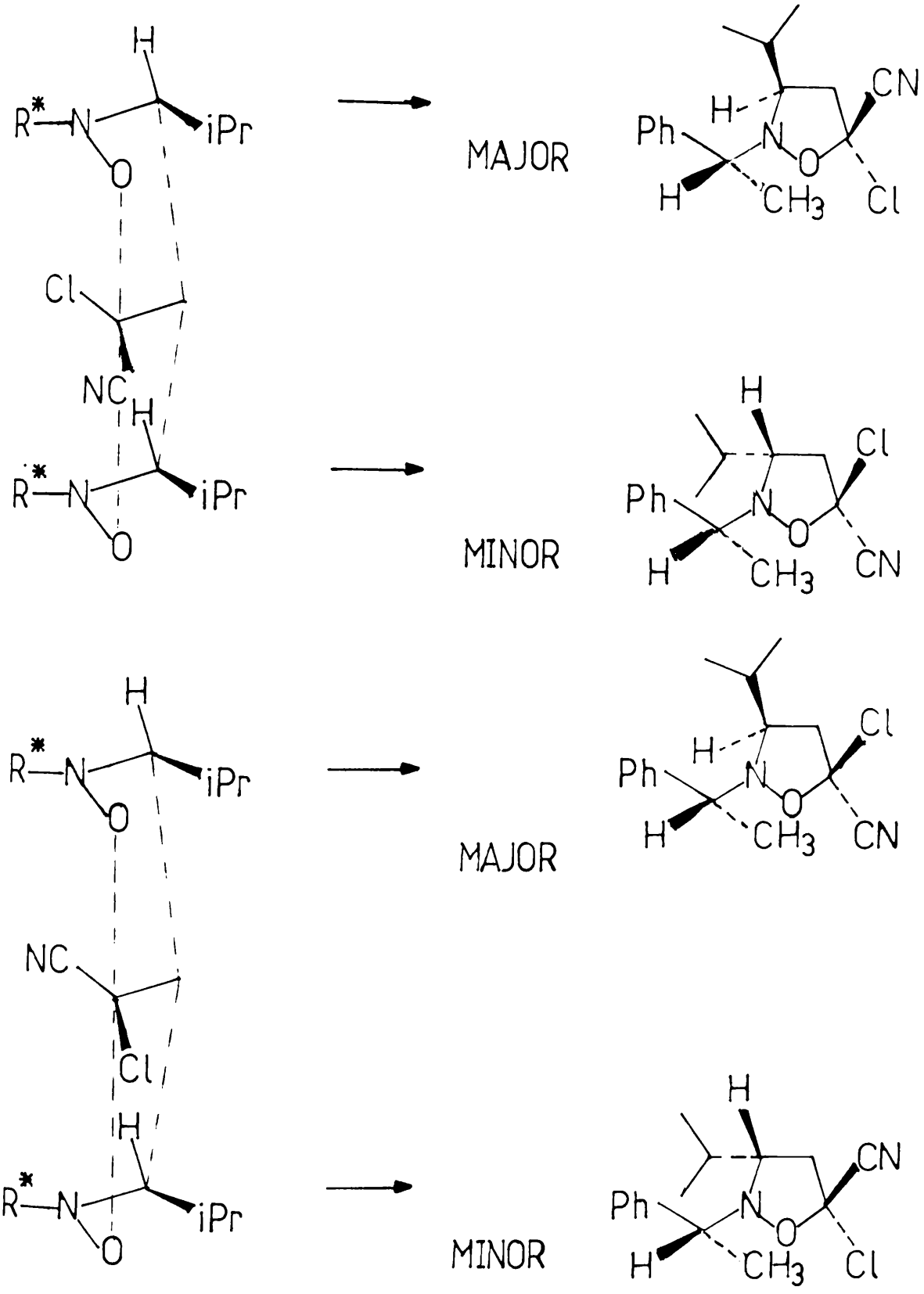


Scheme 50.

The ^1H nmr spectrum of (156) clearly shows the presence of two diastereomeric isoxazolidinones in a ratio

of approximately 2.2:1 as two signals are observed for the α-methylbenzyl methyl group at δ1.6 (0.94H,d, J = 6.9Hz) and δ1.52 (2.06H, d, J = 6.6Hz). Two distinct sets of signals are also observed for the isopropyl methyls centred at δ0.92 and δ0.75 in a similar ratio, [Figures 37A,B]. The proton-decoupled ^{13}C nmr spectrum of (156) shows, for example, two signals at δ30.6 and δ31.1 in a ratio of approximately 2.4:1 corresponding to the C-4 methylene carbon, [Figure 37C]. The i.r. spectrum of isoxazolidinone (156) shows a strong carbonyl absorption at 1770 cm^{-1} while accurate mass analysis showed $[M]^+$ = 233.1413 corresponding to a molecular formula of $C_{14}H_{19}NO_2$ (calc. m/e = 233.1416). Hydrogenolysis of isoxazolidinone (156) with palladium hydroxide in methanol at room temperature as described by Moffat[49] led directly to β-leucine in quantitative yield as a colourless crystalline solid, m.p. 197-200°C $[\alpha]_D$ -15.1 (c 0.81, H_2O) (Lit.[105] value m.p. 201-202°C, $[\alpha]_D$ + 55.2° for (S)- -leucine). The $[\alpha]_D$ measurement indicates an enationmeric excess of 27% of (R)-β -leucine, which compares reasonably well with that obtained from the ^1H nmr spectrum of isoxazolidinone (156), i.e. 37%.

The excess of (R)-β-leucine obtained from isoxazolidine (156) implies that α-chloroacrylonitrile approached the nitrone preferentially from the less hindered C-re N-si face as shown in Scheme 51. Isoxazolidinone (156) was obtained in significantly higher yield than (152) and this is in line



Scheme 51.

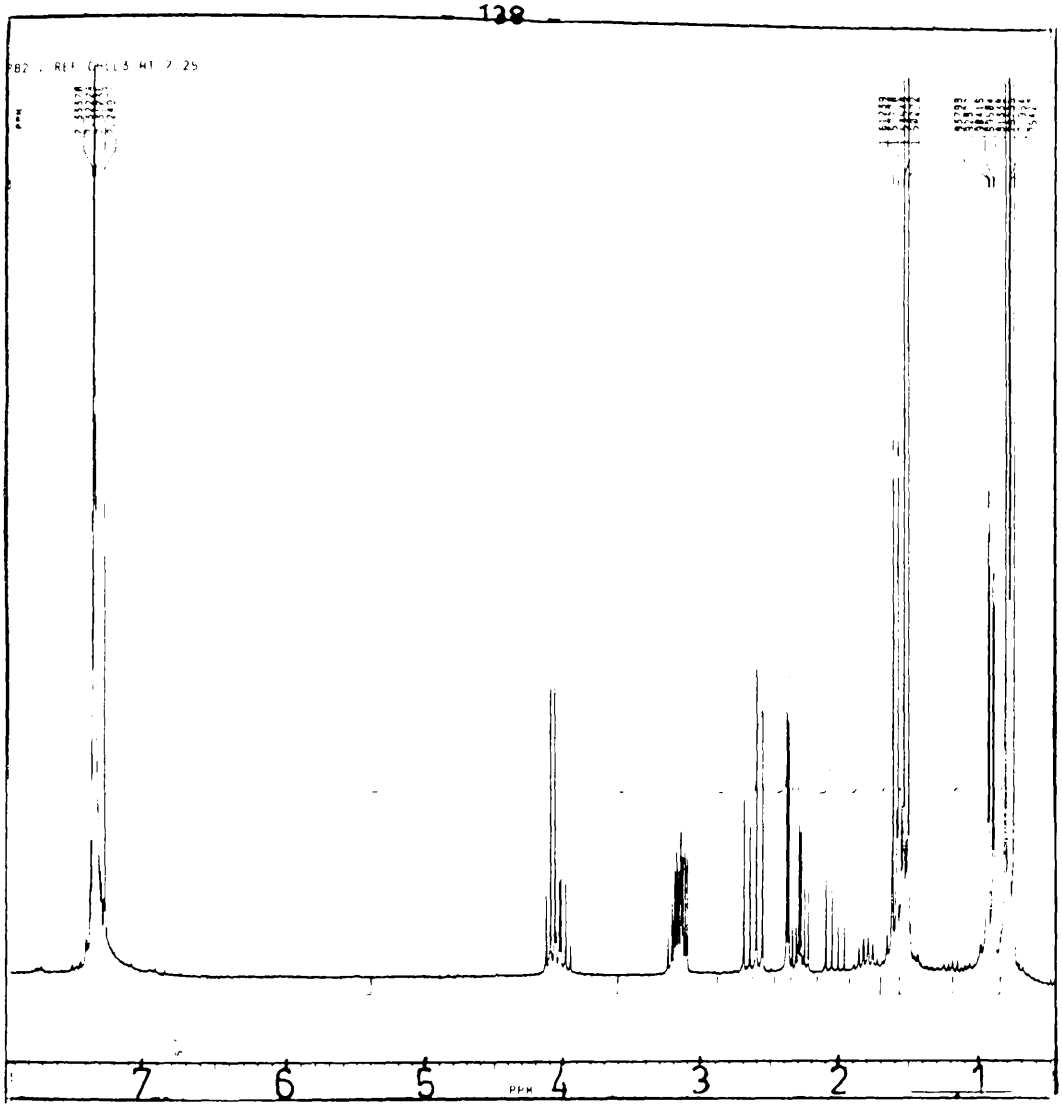


FIG. 37A

^{1}H NMR SPECTRUM OF ISOXAZOLIDINONE(156) AT 200MHz.

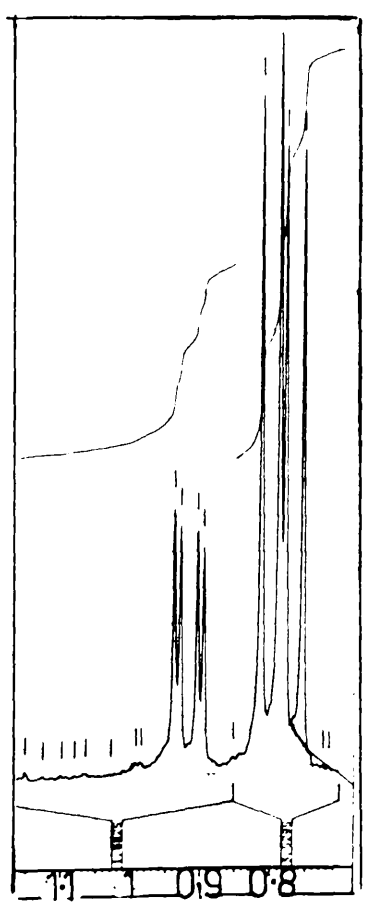


FIG. 37B

EXPANSION BETWEEN 0·7&1·1

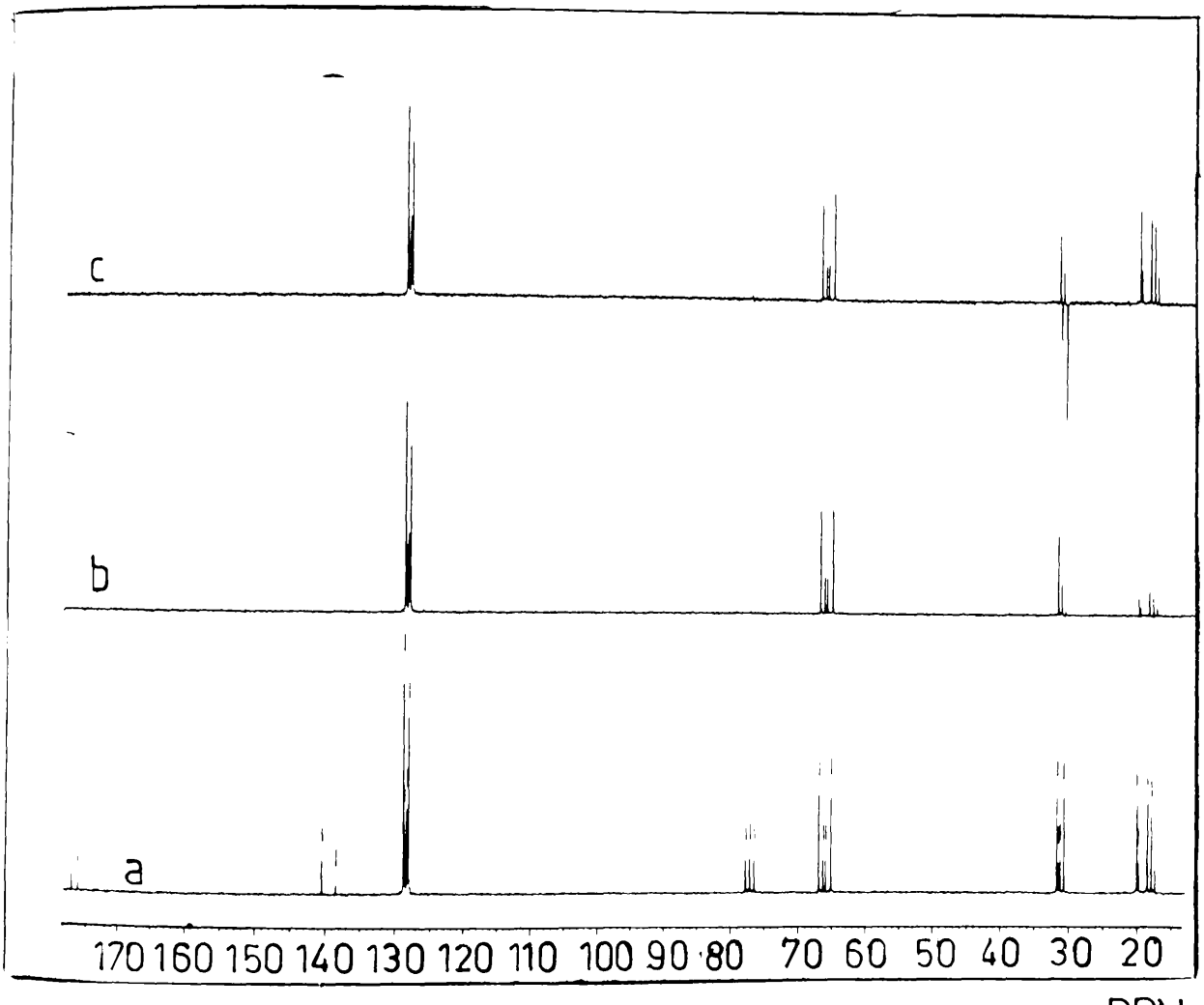


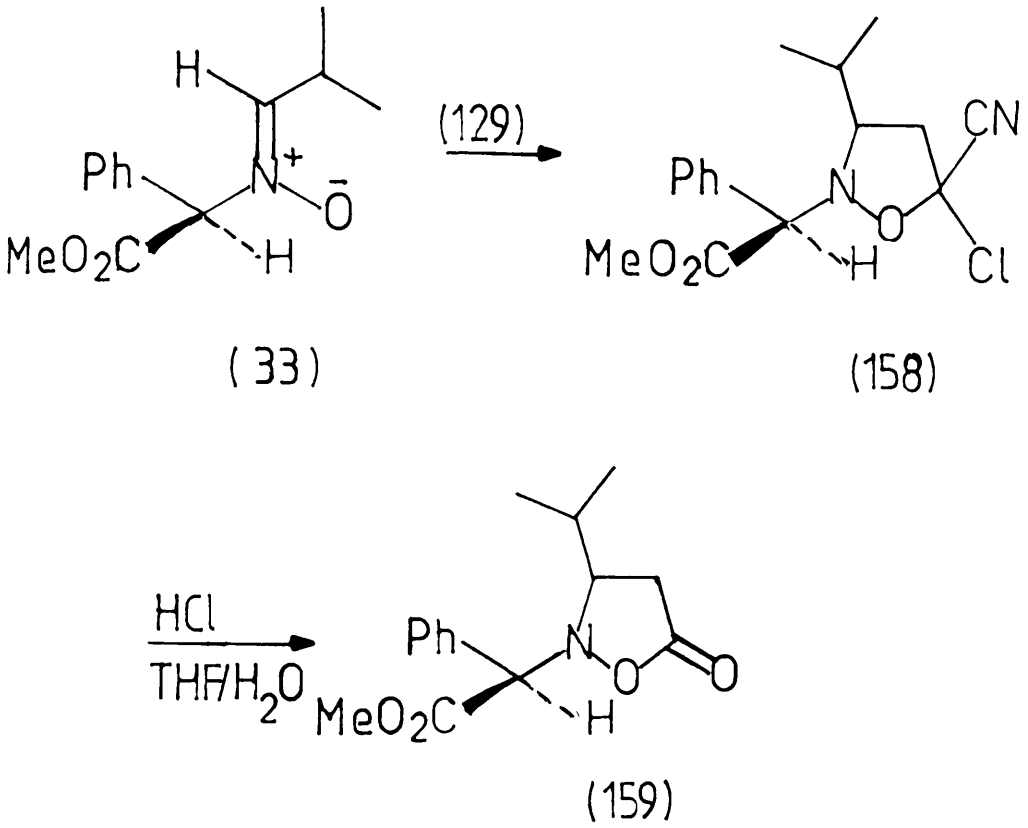
FIG. 37C

(a) ^{1}H-DECOUPLED ^{13}C NMR OF (156) AT 55 MHz (b) DEPT, $\theta = 90^{\circ}$.

(c) DEPT, $\theta = 135^{\circ}$.

with what was previously observed with C-methyl-N-benzyl-nitrone, i.e. C-alkyl nitrones tend to react faster with α-chloroacrylonitrile than their C-aryl counterparts and lead to higher yields of the desired isoxazolidinones. Following the argument outlined in Section 4.3.1, this may mean that cycloadditions of C-alkyl nitrones with α-chloroacrylonitrile preferentially lead to the formation of isoxazolidines in which the C-3 and C-5 chlorine substituents are cis to each other, allowing easier S_N2 displacement of Cl^- by OH^-, or it may simply mean that the C-3 aryl group provides more steric hindrance to this displacement when these substituents are trans, than do methyl or iso-propyl groups.

In a preliminary experiment nitrone (33) was refluxed in neat α-chloroacrylonitrile for approximately 30 minutes and afforded a cycloadduct mixture in 59% yield after chromatography. As a precautionary measure against racemisation of the N-benzylic chiral centre, it was envisaged that hydrolysis of this mixture may be achieved by using aqueous HCl (0.4 equiv)/THF instead of Et_3N/THF. Using this method isoxazolidinone (159) was obtained as a light yellow oil in 52% yield after chromatography, [Scheme 52].



(33) (158) (159)

Scheme 52.

The ^{1}H nmr spectrum of isoxazolidinone (159) clearly shows two sets of signals centred at δ0.76 and δ0.95 corresponding to the iso-propyl methyl groups in a ratio of approximately 11:1. Two distinct singlets are also observed for the N-benzylic methine proton in a similar ratio, [Figure 38A]. The proton-decoupled ^{13}C nmr spectrum shows only very minor signals corresponding to the minor diastereomer, and clearly displays two carbonyl carbon signals at δ176.11 and δ169.13 attributable to the methyl ester and isoxazolidinone carbonyl carbon atoms respectively,

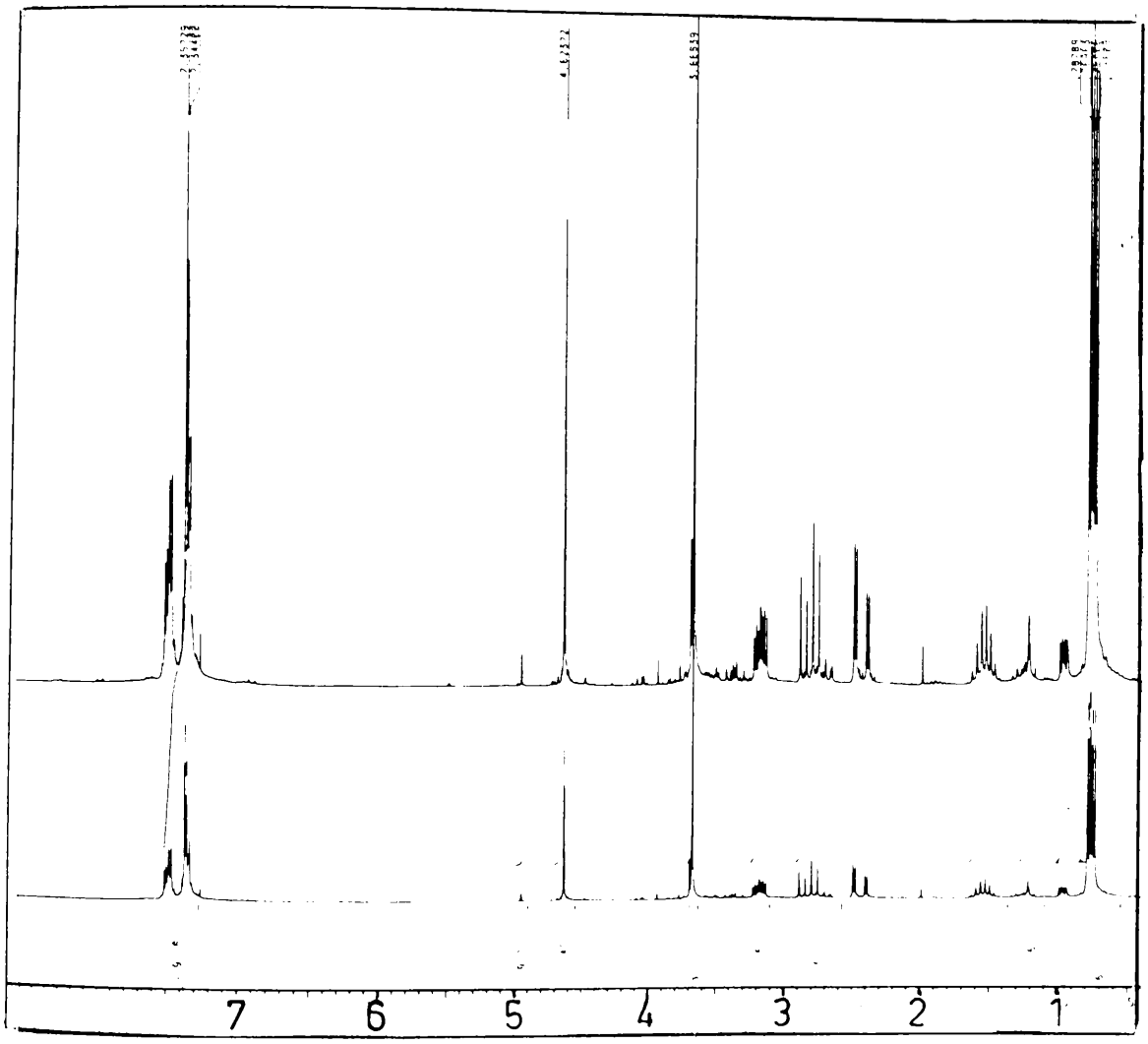


FIG. 38A

^{1}H NMR SPECTRUM OF ISOXAZOLIDINONE(159) AT 200 MHz.

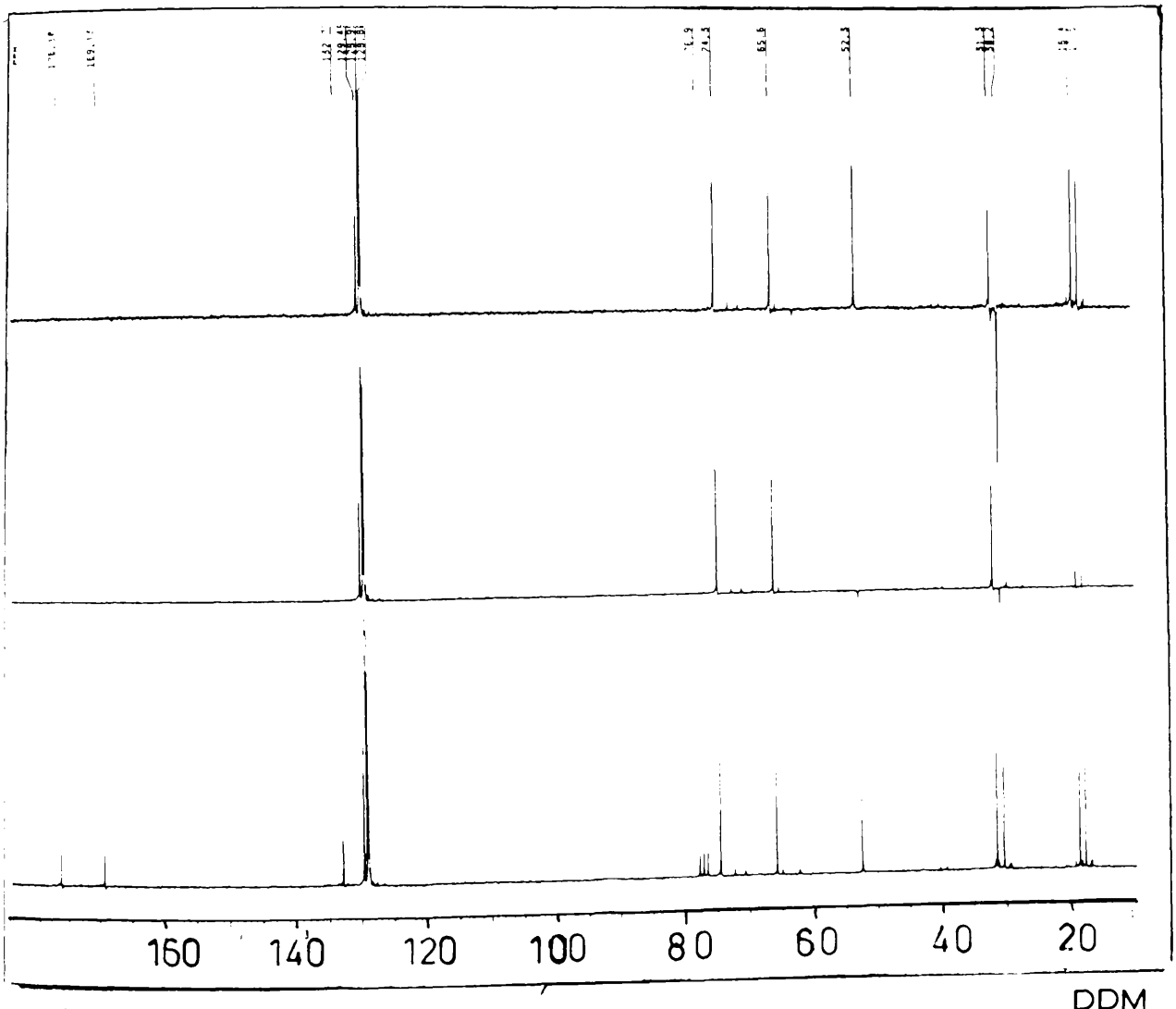


FIG. 38B

(a) ^{1}H– DECOUPLED ^{13}C NMR OF(159)(b)DEPT, $\theta = 135^{\circ}$.

(c) DEPT, $\theta = 90^{\circ}$.

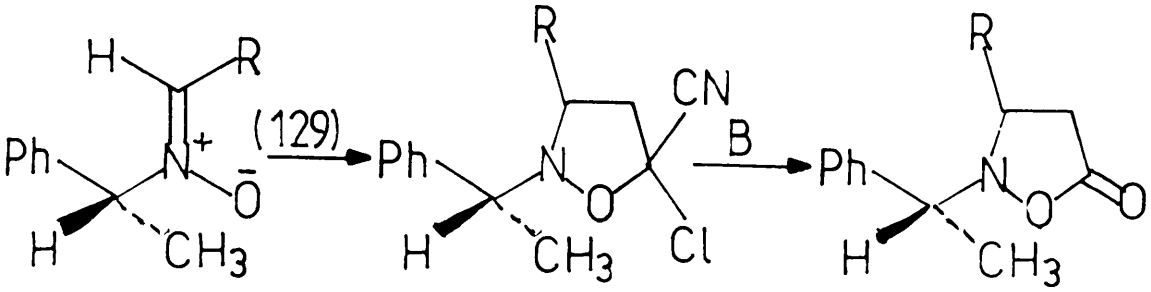
[Figure 38B]. The i.r. spectrum of isoxazolidinone (159) shows two strong carbonyl absorptions at 1731 and 1685 cm^{-1} respectively, while accurate mass analysis showed $[M]^+$ = 277.1321 corresponding to a molecular formula of $C_{15}H_{19}NO_4$ (calc. m/e = 277.1314).

Lack of time prevented hydrogenolysis of isoxazolidinone (159) in order to establish the absolute configuration at C-3, however comparison of the signals corresponding to the iso-propyl methyl groups in the ^1H nmr spectra of compounds (156) and (159) [Figures 37A, 38A] suggest that isoxazolidinone (159) may lead almost exclusively to (R)-β-leucine.

Therefore, the cycloaddition of nitrone (33) with α-chloroacrylonitrile may potentially lead to the synthesis of (R)-β-leucine of high enantiomeric purity (ee 83%) in reasonable yield.

4.3.3 β-Tyrosine.

The syntheses of isoxazolidinones (162) and (163) as shown in Scheme 53 provides potential routes to β-tyrosine.



(29) R=p-MeOPh (160) (162)

(31) R=p-BzOPh (161) (163)

B = Py, Et_3N/THF/H_2O

Scheme 53

Nitrone (29) was refluxed in neat α-chloroacrylonitrile for 1h, after which the material recovered in 7[illegible]% yield following column chromatography was hydrolysed using aqueous pyridine/THF, and afforded isoxazolidinone (162) as a crystalline solid in 1[illegible]% yield, m.p. 125-127°C (Lit.[49] m.p. 127-128°C). The ^{1}H nmr spectrum of isoxazolidinone (162) shows only one methoxyl methyl group singlet at δ3.77 and one doublet at δ1.55 (J = 6.6Hz) corresponding to the α-methylbenzyl methyl group, [Figure 3:A]. The C-4

methylene protons appear as two doublets of doublets centred at δ3.03 (1H,dd, J = 7.7, 17.3Hz) and δ2.82 (1H,dd, J = 9.1, 17.3Hz), while the C-3 methine proton appears as a triplet at δ4.42 (J = 7.9Hz), these signals corresponding to the expected ABX system. The benzylic methine proton appears as a quartet at δ4.12 (J = 6.6Hz). The proton-decoupled ^{13}C nmr spectrum also indicates the presence of only one of the two possible diastereomeric isoxazolidinones, [Figure 39C]. Both of these spectra are identical to those described by Moffat[49] for a single diastereomer of (162) which led to enantiomerically pure (R)-β-tyrosine methyl ether. The i.r. spectrum of isoxazolidinone (162) shows a strong carbonyl absorption at 1775 cm^{-1}, while accurate mass analysis showed $[M]^+$ = 297.1387 corresponding to a molecular formula of $C_{18}H_{19}NO_3$ (calc. m/e = 297.1365).

When the above reaction sequence was repeated using Et_3N as the base in the hydrolysis step, isoxazolidinone (162) was obtained in 26% yield after chromatography as an approximately 2:1 mixture of diastereomers as can be seen by the ratio of the two methoxyl methyl group singlets in Figure 39B. By comparison of Figures 39A and 39B it can be said that the isoxazolidinone which has the (R)-configuration at C-3 is the major product in this mixture. As in the case of nitrone (29) discussed in Section 4.3.1, only a modest conversion to the desired isoxazolidinone was observed. Presumably this is also partly due to

the cycloaddition reaction between nitrone (29) and α-chloroacrylonitrile being complicated by elimination and fragmentation processes as discussed in Section 4.2.

Nitrone (31) was also refluxed in neat α-chloroacrylonitrile for 1 hour to afford a product mixture which after hydrolysis afforded isoxazolidinone (163) in 47% yield. Isoxazolidinone (163) was obtained as a 1:1 mixture of diastereomers, however a partial separation was achieved by column chromatography [Figures 40A and 40B]. The ^1H nmr spectrum shown in Figure 40A clearly shows only one singlet at δ5.0 corresponding to the O-benzylic protons, while that in Figure 40B shows two such singlets at δ5.06 and δ5.0 in a ratio of approximately 6:1. The i.r. spectra of these compounds show strong carbonyl absorptions at approximately 1770 cm^{-1}, while accurate mass analysis showed $[M]^+$ = 373.1680 and 373.1665 respectively, corresponding to a molecular formula of $C_{24}H_{23}NO_3$ (calc. m/e = 373.1678). Attempted hydrogenolysis of a 1:1 mixture of these isoxazolidinones with palladium hydroxide in ethanol at 70°C for 24h led only to the N-protected β-amino acid (164) shown in Scheme 54.

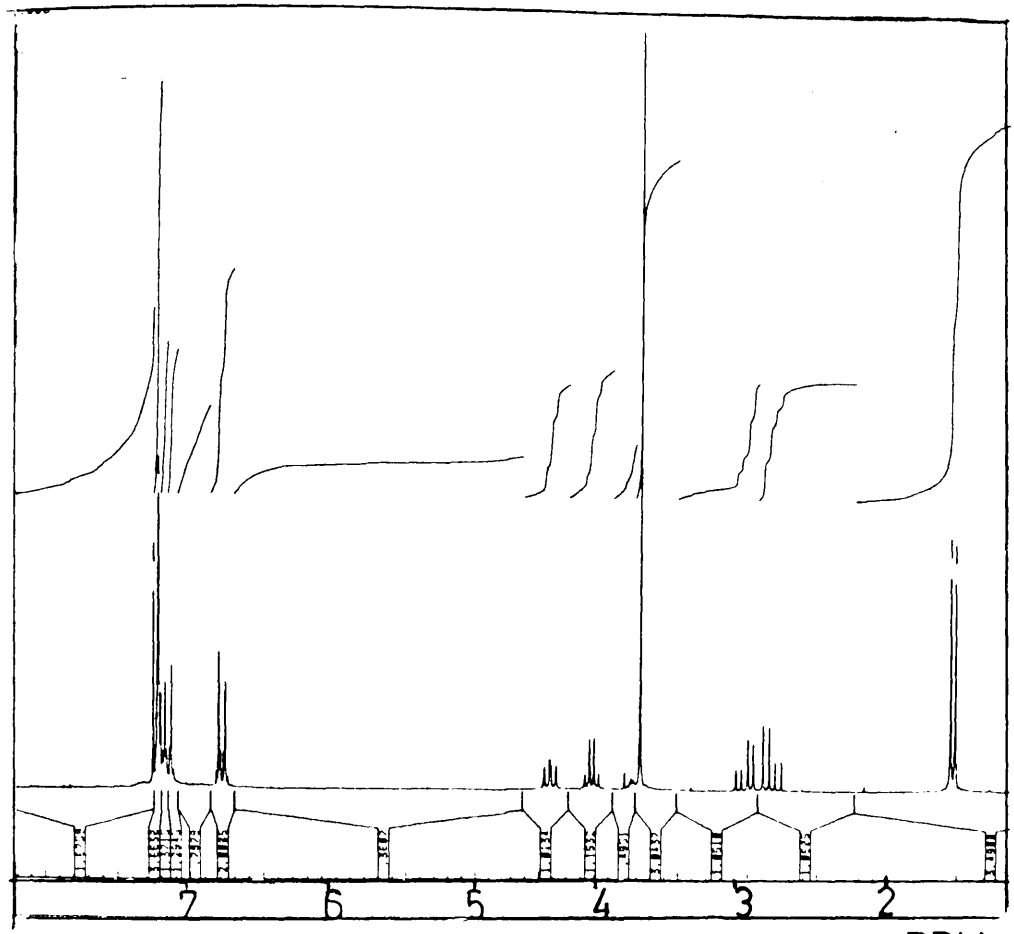


FIG.39A

^{1}H NMR SPECTRUM OF ISOXAZOLIDINONE(162) AT 200MHz.

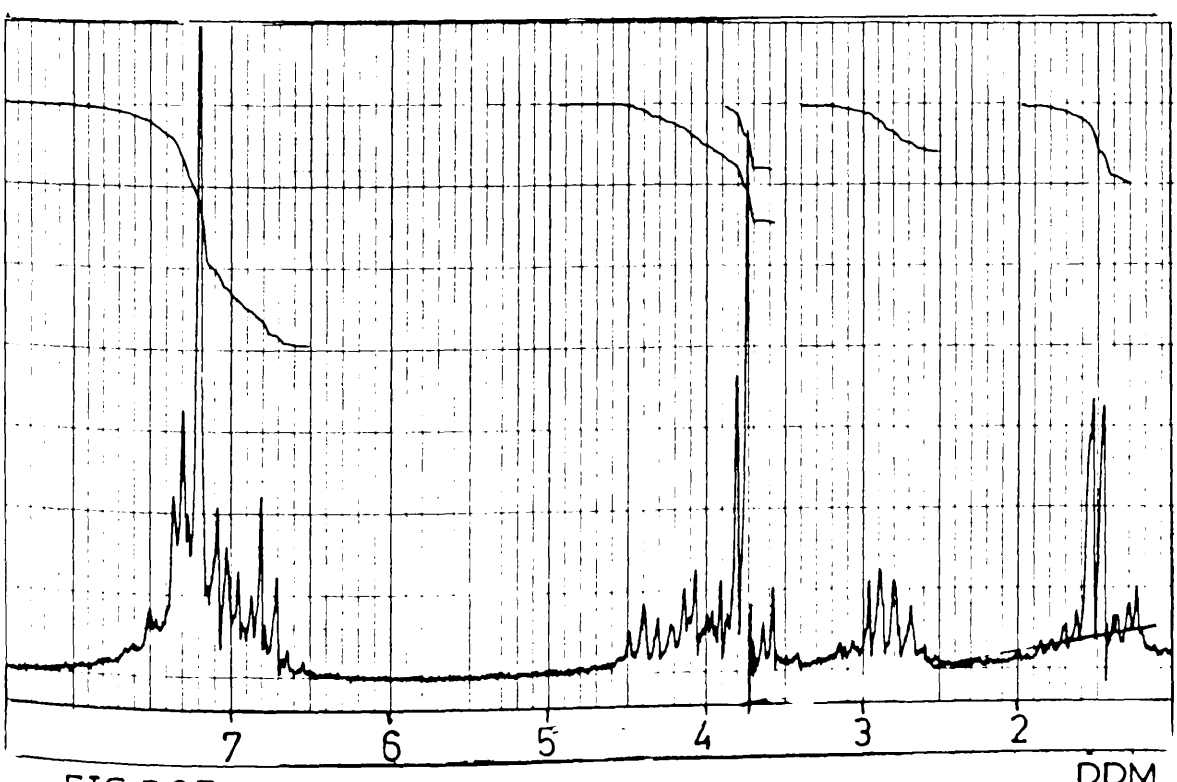


FIG.39B

^{1}H NMR SPECTRUM OF(162) AT 90MHz.

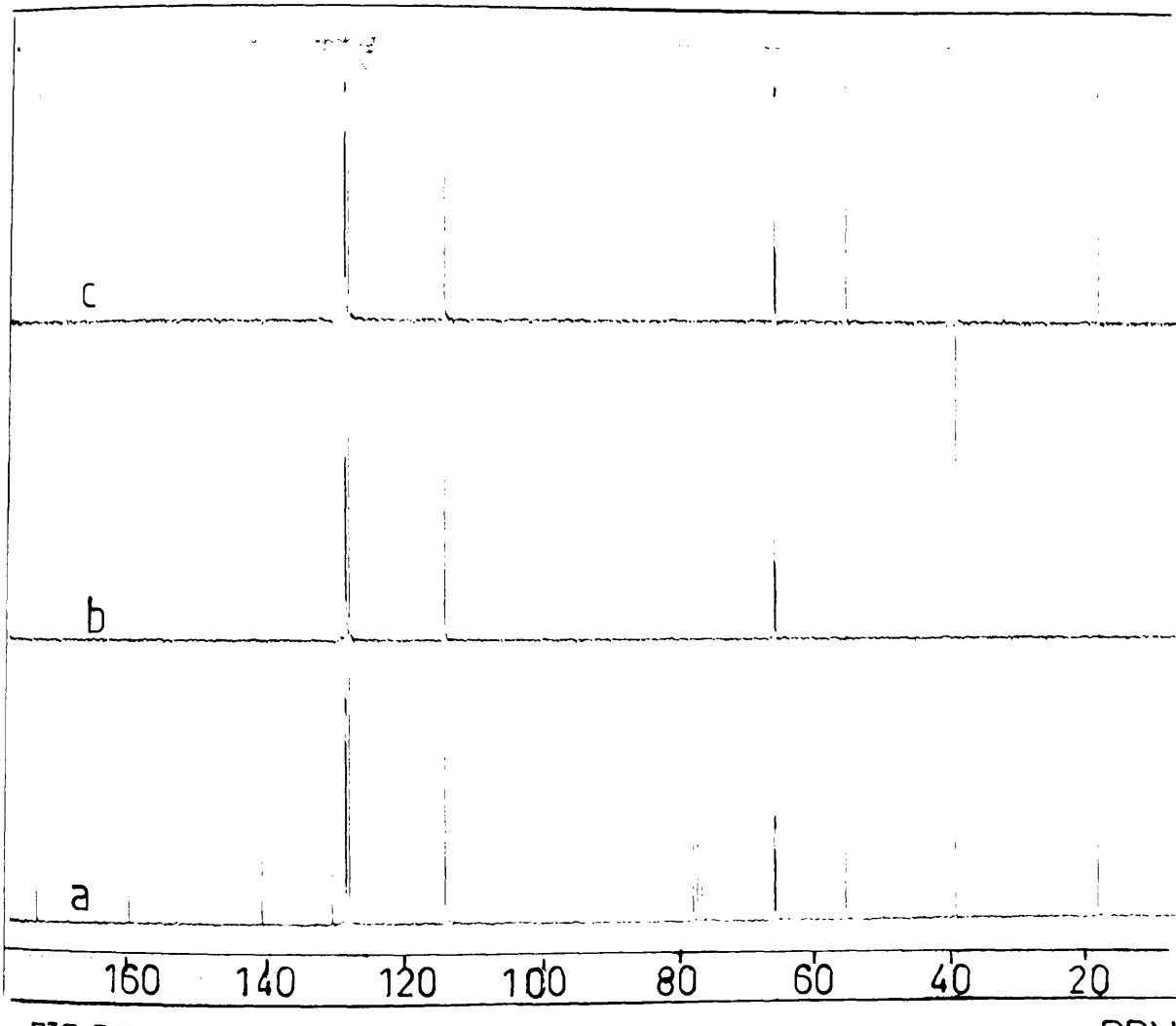


FIG. 39C

(a) ^{1}H-DECOUPLED ^{13}C NMR SPECTRUM OF(162) AT 55MHz.

(b) DEPT, $\theta = 90^{\circ}$, (c) DEPT, $\theta = 135^{\circ}$.

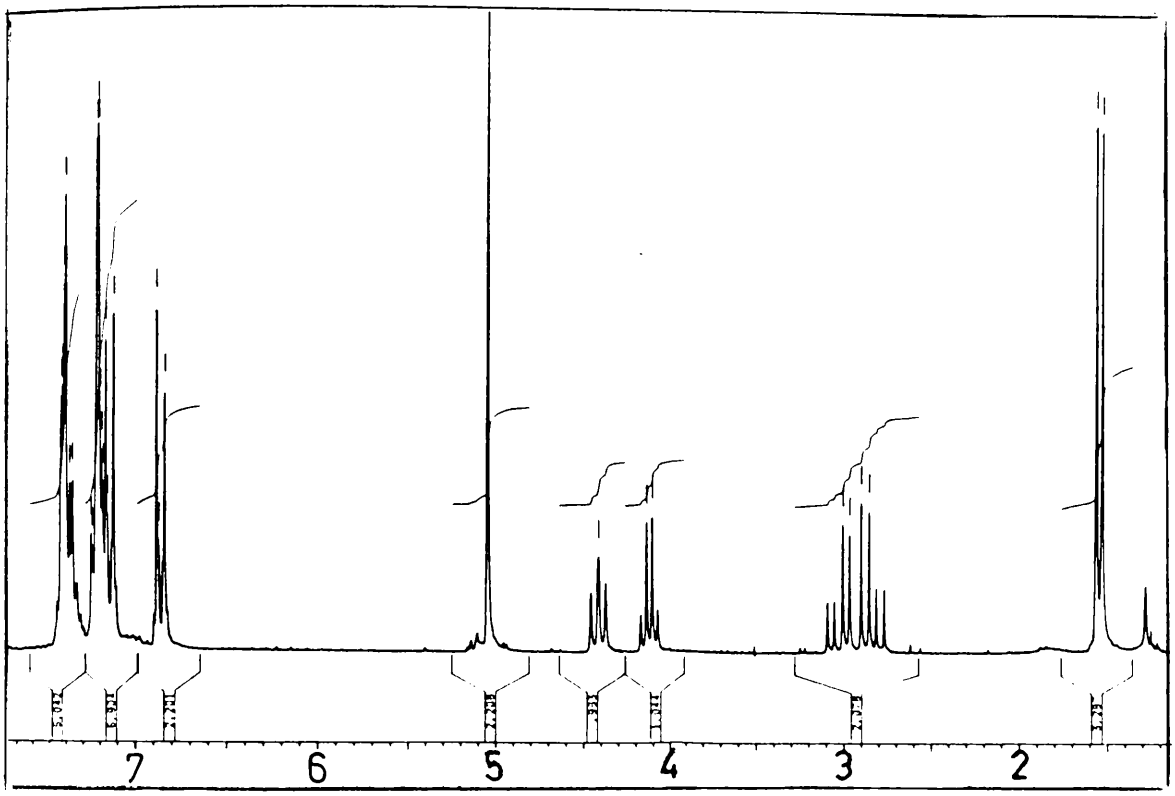


FIG. 40A

^{1}H NMR SPECTRUM OF ISOXAZOLIDINONE (163) AT 200MHz.

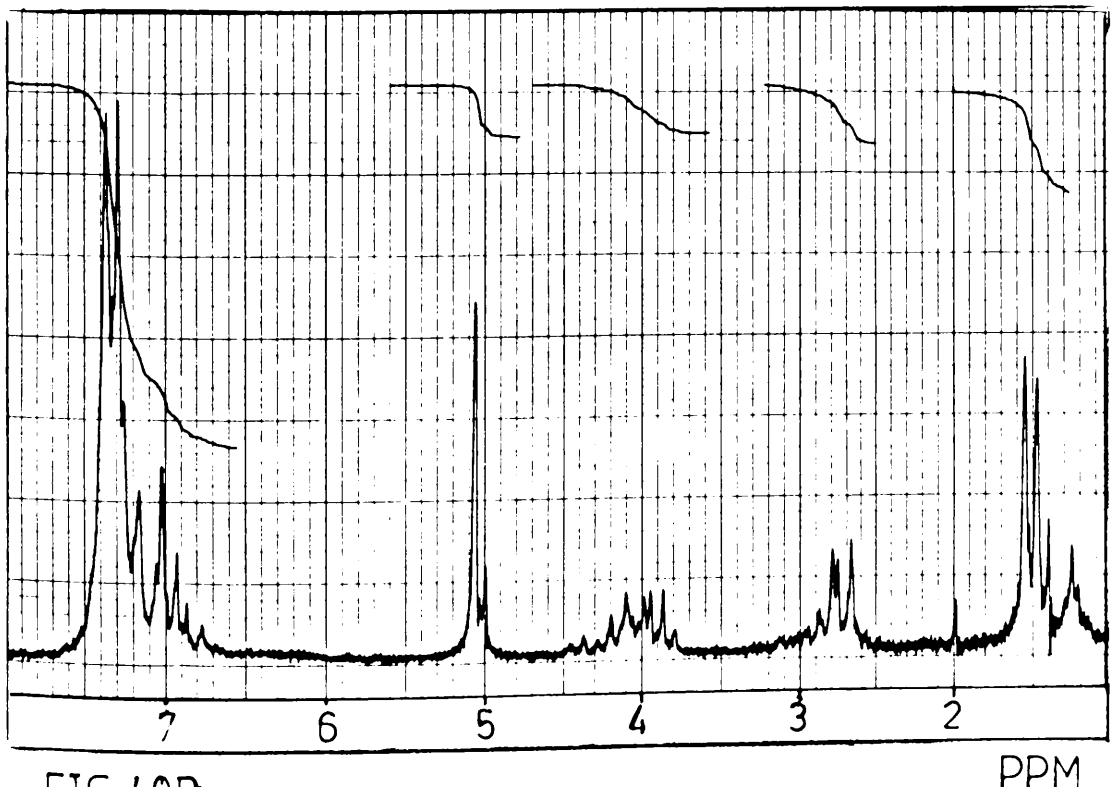
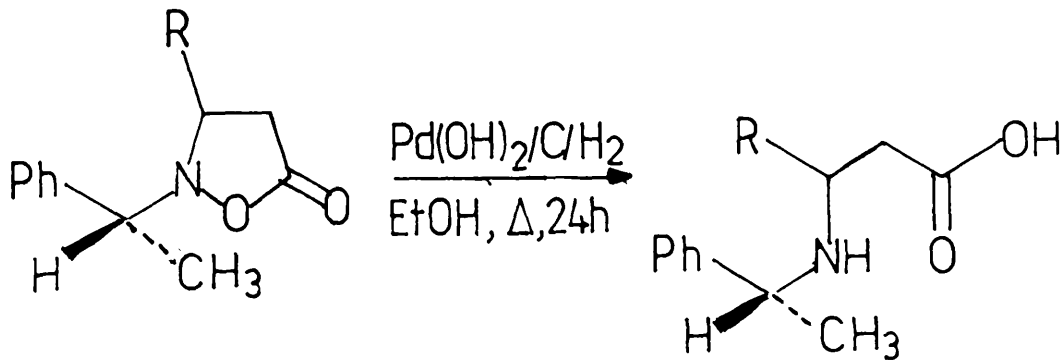


FIG. 40B

^{1}H NMR SPECTRUM OF (163) AT 90MHz.



(163)

R=p-BzOPh

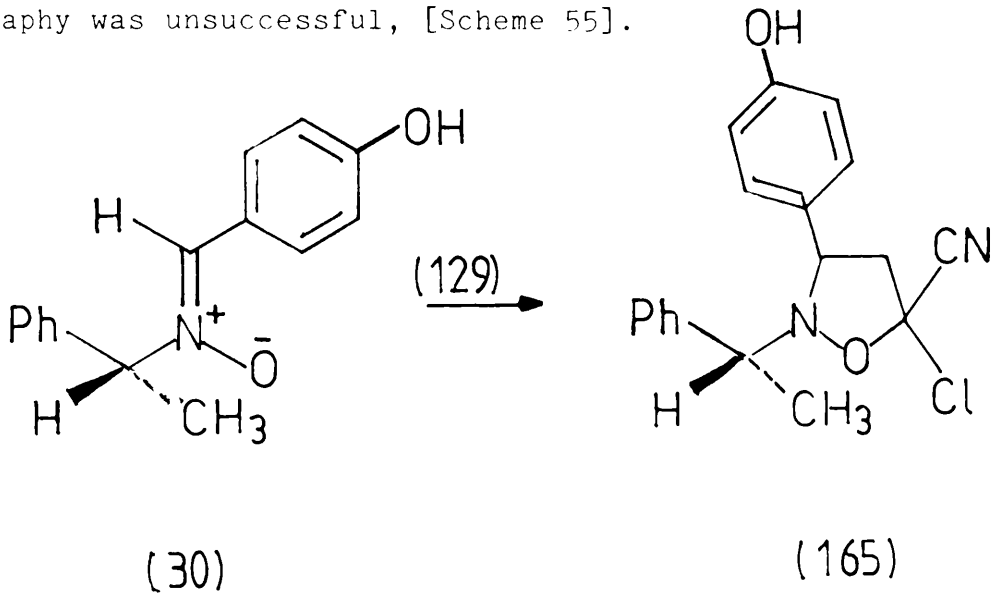
(164)

Scheme 54.

The ^1H nmr spectrum of (164) shows the presence of both the α-methyl-benzyl group and the benzyl-O $-CH_2-$ protons, while accurate mass analysis showed $[M-CH_2CO_2H]^+$ = 316.1715 corresponding to a molecular formula of $C_{22}H_{22}NO$ (calc. m/e = 316.1701). It was envisaged that hydrogenolysis of isoxazolidinone (163) would lead directly to free β-tyrosine, however lack of time prevented an investigation into the use of pressure in this hydrogenolysis. Although only a modest conversion of nitrone (31) to the corresponding isoxazolidinone was obtained, the chroma-

tographic separation of the two diastereomeric isoxazolidinones provides a potential route to both (R)- and (S)-β-tyrosine of high enantiomeric purity.

Following the successful synthesis of nitrone (16), nitrone (30) was prepared and refluxed in neat α-chloroacrylonitrile. Attempted hydrolysis of the product mixture obtained in 60% yield following column chromatography was unsuccessful, [Scheme 55].



(30) (165)

Scheme 55.

The ^{1}H nmr spectrum of the material recovered after attempted hydrolysis was almost identical with that of the cycloaddition product, and gave little information as to its exact composition. As with all of the other cycloaddition products described in this chapter, accurate

mass analysis showed parent ions corresponding to the two naturally occuring isotopes of chlorine, i.e. $[M]^+$ = 328.0971 corresponding to a molecular formula of $C_{18}H_{17}N_2O_2{}^{35}Cl$ (calc. m/e = 328.0978) and $[M]^+$ = 330.0978 corresponding to a molecular formula of $C_{18}H_{17}N_2O_2{}^{37}Cl$ (calc. m/e = 330.0978).

Again following the same arguments as outlined in Sections 4.2 and 4.3.1, it may be that the product of the cycloaddition consists almost entirely of isoxazolidine in which the C-3 and C-5 chlorine substituents are trans to each other and material derived from elimination and fragmentation processes, thus accouuting for the fact that no isoxazolidinone was obtained on attempted hydrolysis.

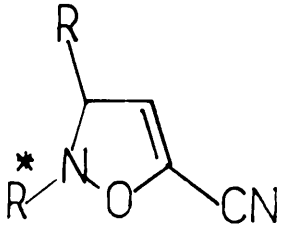
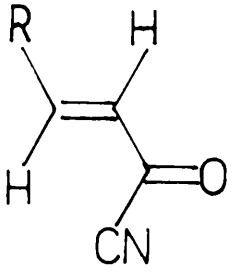
Summary and Conclusions

In general, the cycloaddition reactions of nitrones with α-chloroacrylonitrile have thus been shown to provide an efficient and relatively simple entry to the isoxazolidinone ring system, affording isoxazolidinones (153), (156) and (162) in much higher yields than previously described by Moffat.[49] Therefore, a large variety of β-amino acid systems may potentially be synthesised using this method (see Chapter 5).

The cycloaddition reactions are however much more complicated than envisaged, especially in the case of C-aryl nitrones. The cycloaddition reactions of nitrones (19) and

(15) have been shown to be accompanied by elimination and fragmentation processes. Accurate mass analysis of the total cycloaddition product of the C-aryl-N- α'-methylbenzyl nitrones with the exception of nitrone (30), show ions corresponding to $[M-HCl]^+$ and in most cases an ion corresponding to a fragmentation product analogous to that described in Section 4.2, [Table 9].

Table 9.

NITRONE	(28) R=Ph	(29) R=p-MeOPh	(31) R=p-BzOPh
	277.1329, corresponds to $C_{18}H_{17}N_2O$ (requires m/e = 277.1341)	306.1367, corresponds to $C_{19}H_{18}N_2O_2$ (requires m/e = 306.1368)	382.1686, corresponds to $C_{25}H_{22}N_2O_2$ (requires m/e = 382.1681)
	157.0528 corresponds to $C_{10}H_7NO$ (requires m/e = 157.0528)	187.0629 corresponds to $C_{11}H_9NO_2$ (requires m/e = 187.0633)	———

R* = (R)-PhCHCH$_3$

Accurate mass analysis of the cycloaddition products of the C-alkyl nitrones used in this work showed no

sign of either of these ions, and the isoxazolidinones so derived were generally obtained in significantly higher yield than their C-3 aryl substituted counterparts. As already indicated, isoxazolidines bearing a C-3 aryl substituent may undergo fragmentation much more readily than those bearing a C-3 alkyl substituent due to the ability of an aryl group to help stabilise any developing double bond. However, considering the mostly short reaction times in these cycloadditions one would not expect elimination and fragmentation processes to account for all of the additional material recovered in addition to isoxazolidinones. Indeed, it may be reasonable to assume that some isoxazolidines are more readily hydrolysed under the conditions used than others, depending on the relative configuration of the C-3 and C-5 chlorine substituents. Apparently this hydrolysis may be less hindered when these substituents are cis to each other.

This route to β-amino acids allows for control of configuration at the β- carbon atom, since the transition states for the cycloaddition should be responsive to chiral induction from a chiral substituent on the nitrogen atom. There is scope for a further investigation into the use of the chiral inducing group based on α-phenylglycine and for an investigation into the use of other inducing groups such as carbohydrates.[106]

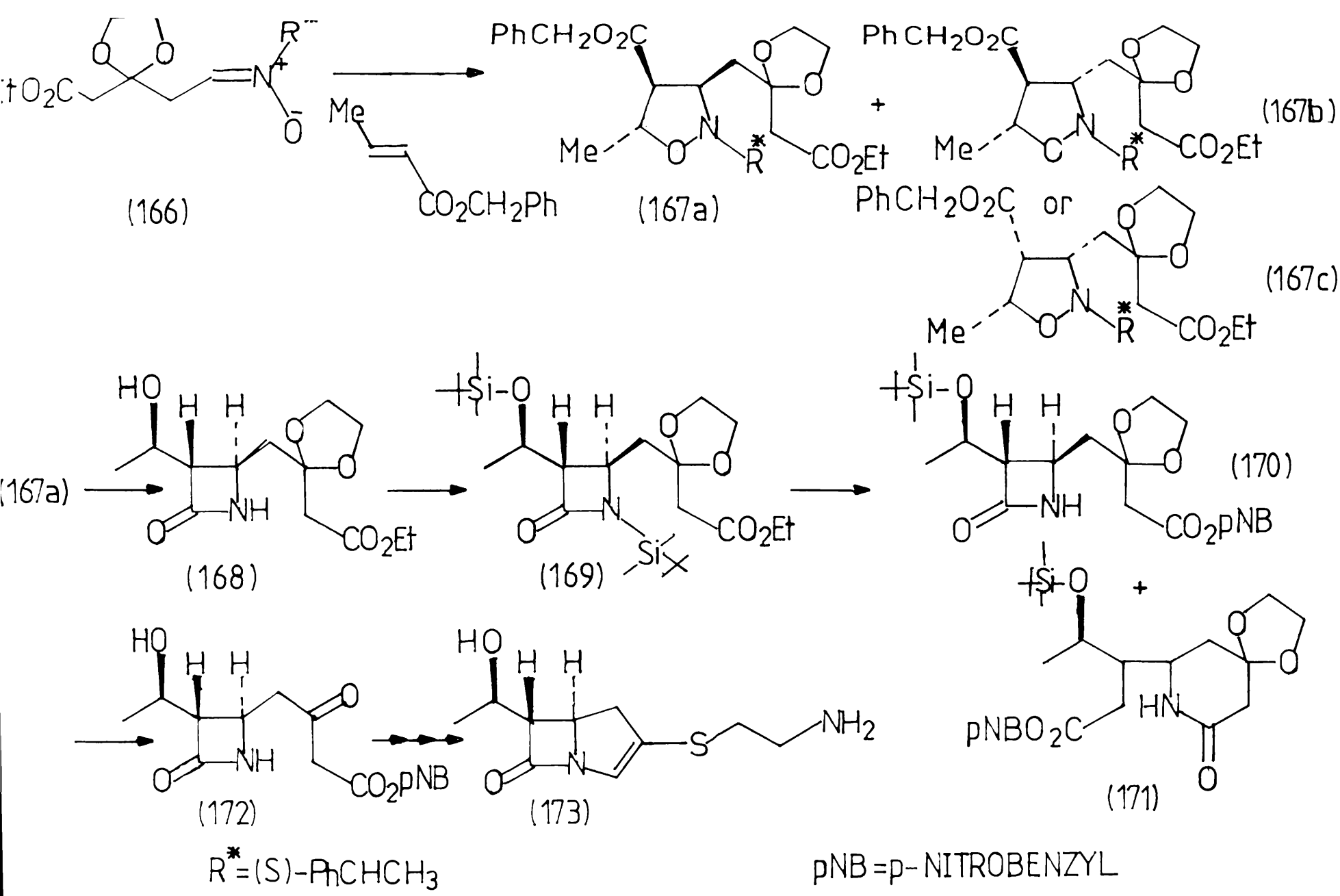
CHAPTER FIVE

Towards an Asymmetric Synthesis of Thienamycin.

5.1 Background and Introduction

The discovery [107] of the potent antibiotic thienamycin (173) and its relatives has provided impetus to design general strategies for the synthesis of these naturally occurring carbapenem antibiotics. Consequently, a number of enantiospecific syntheses of the natural (+) enantiomer of thienamycin have appeared by elaboration of a chiral substrate such as L-aspartic acid[108] and D-glucose.[109]

Kametami[110] has reported the synthesis of the optically active β-keto ester (172) which has previously been transformed into (+) - thienamycin by the Merck group, [109] [Scheme 56]. The key reaction in this synthesis involved the cycloaddition of nitrone (166) with benzyl crotonate, however the desired isoxazolidine (167a) was obtained in only 23% yield following chromatographic separation from the other diastereomeric isoxazolidines formed in the cycloaddition process. Hydrogenolysis of the desired cycloadduct (167a) followed by lactamisation provided β-keto ester (172) after further manipulation as shown below. Conversion of the bis-silylated azetidinone (169) to the p-nitrobenzyl ester (170) was accompanied by formation of the δ-lactam (171), these compounds being formed in a relative ratio of 3:1. (-)-Thienamycin is reported as having been synthesised in the same manner starting from the (R)-α-methylbenzyl nitrone as opposed to the (S).

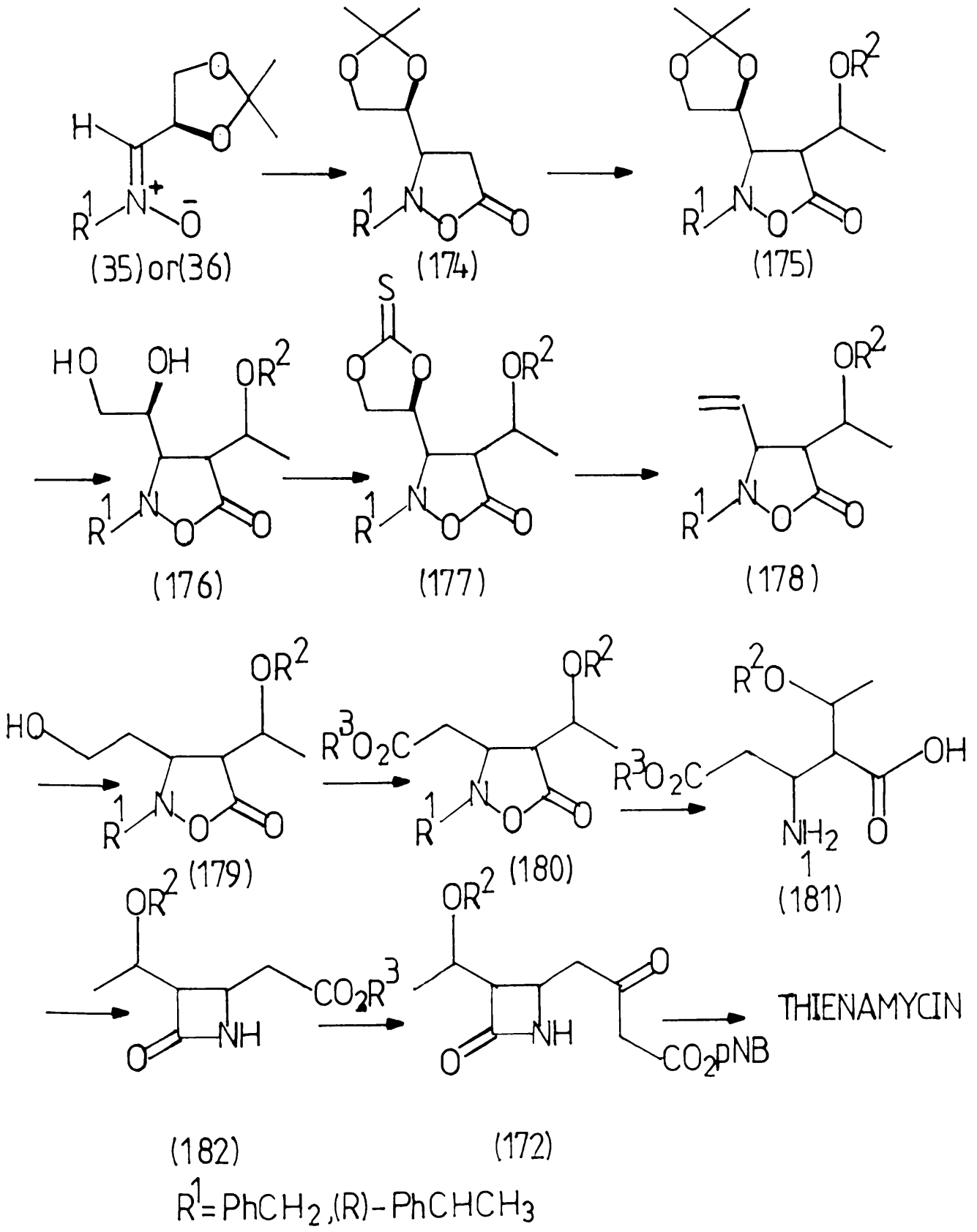

(166)
(167a)
(167b)
(167c)
(168)
(169)
(170)
(171)
(172)
(173)
R*=(S)-PhCHCH3
pNB=p-NITROBENZYL

Scheme 56.

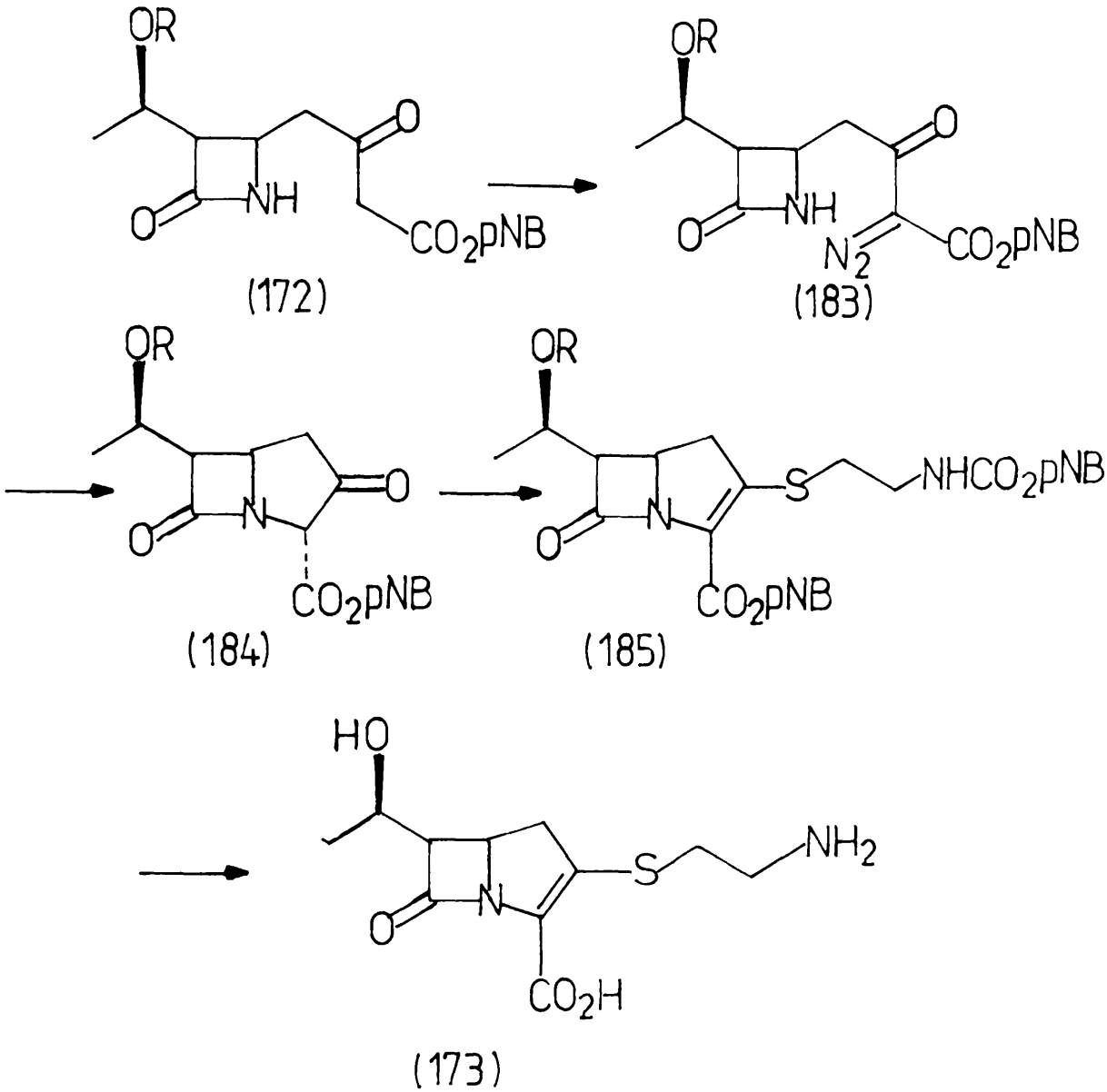
It was envisaged that as an extension of the route to β-amino acids described in the previous chapter, β-keto ester (172) could be synthesised via the cycloaddition reaction of either nitrone (35) or (36) with α-chloroacrylonitrile as shown in Scheme 57.

It was hoped that if a single diastereomerically pure isoxazolidinone (174) could be obtained, that the chiral 2,3,-O-isopropylidene moiety at C-3 would act as an efficient chiral auxilliary in the subsequent alkylation at C-4. Corey[111] has developed a mild procedure for the conversion of 1,2-diols to olefins via the appropriate thionocarbonate (177) which should afford the desired olefin (178) in good yield. Subsequent hydroboration, oxidation and esterification should afford isoxazolidinone (180), following which hydrogenolysis and lactamisation[3,110] should lead to azetidinone (182) which can be readily converted into the desired p-nitrobenzyl ester[112] (172).

Azetidinone (172) has as already stated been previously converted into (+)-thienamycin[109] as shown in Scheme 58.


(35) or (36)
(174)
(175)
(176)
(177)
(178)
(179)
(180)
(181)
(182)
(172)
THIENAMYCIN
R1 = PhCH2, (R)-PhCHCH3

Scheme 57.

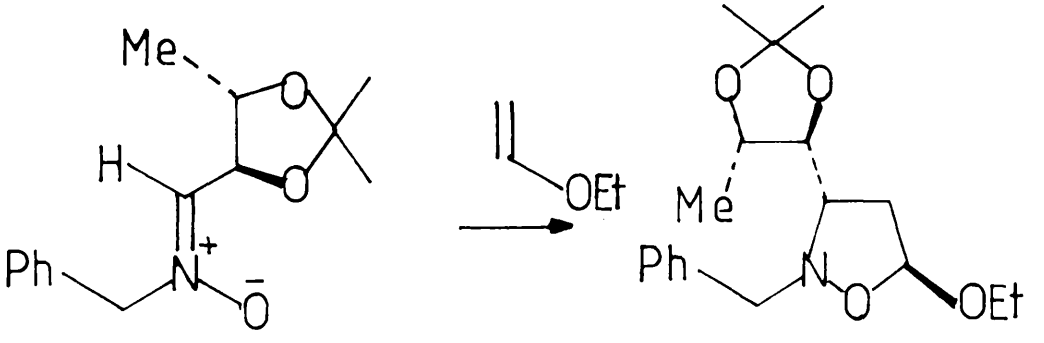


Scheme 58

Cyclisation of (183) prepared by diazo exchange with p-carboxybenzenesulphonyl azide [illegible] ester (184) which when treated with N-p-nitrobenzyloxy carbonyl cysteamine provided the bisprotected thienamycin derivative (185). Catalytic hydrogenation of (185)

afforded thienamycin which was identical to natural thienamycin.

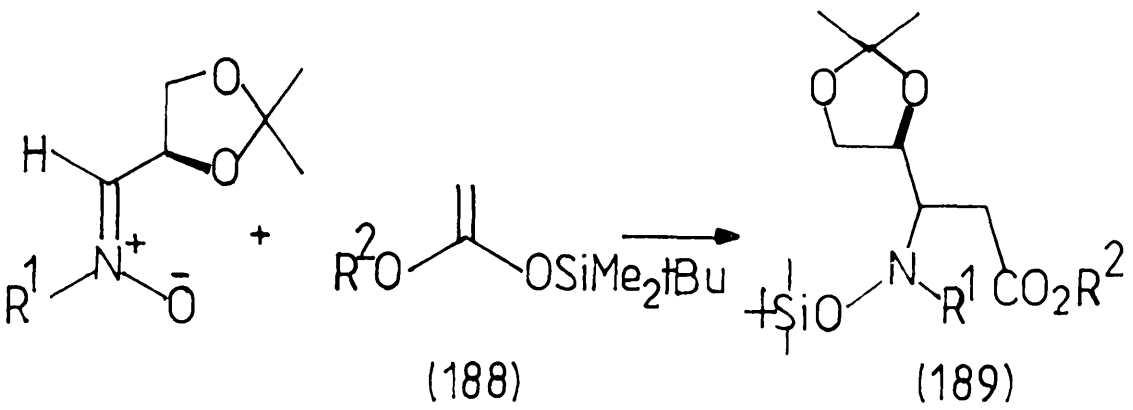
DeShong[79] has previously used nitrone (35) in a cycloaddition reaction with maleic anhydride, however diastereofacial selectivity of only 2:1 was observed. In contrast to this, cycloaddition of nitrone (186) with ethyl vinyl ether afforded only one out of four possible diastereomeric isoxazolidines, the nitrone having displayed complete diastereoselectivity,[79] [Scheme 59].



(186) (187)

Scheme 59.

More recently nitrones (35) and (36) have displayed diastereoselectivity in 1,3-addition reactions involving silyl group transfer with silyl ketene acetals,[112] [Scheme 60].



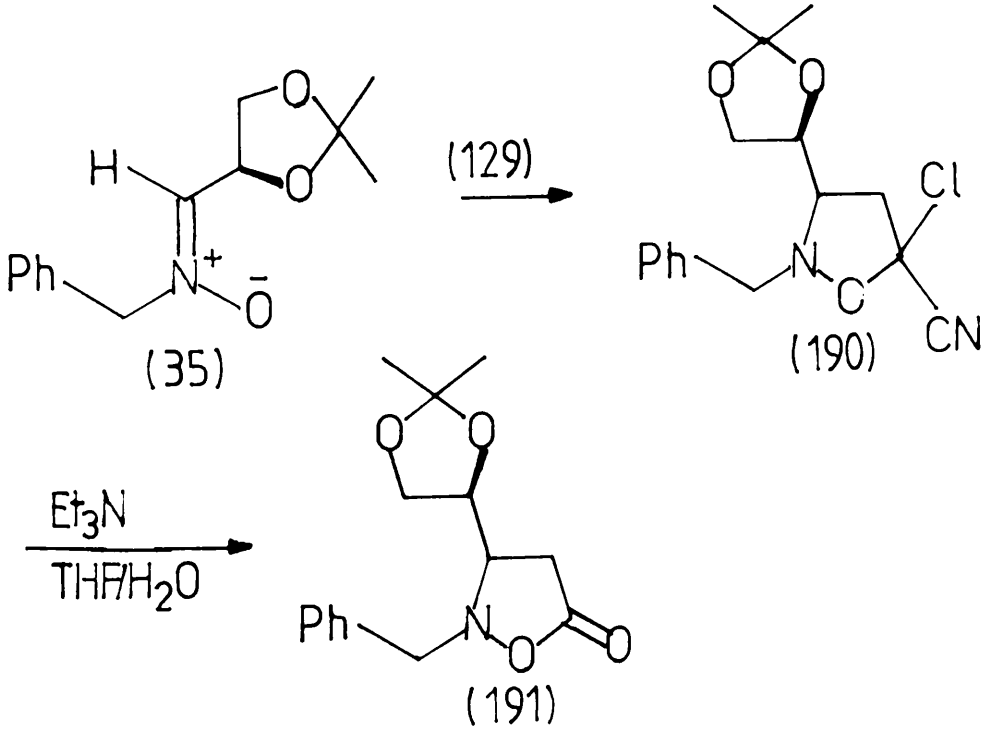
Scheme 60.

Nitrones (35) and (36) were prepared from (R)-2,3-O-isopropylidene glyceraldehyde,[79] the utility of which along with the (S)- enantiomer as chiral substrates in stereoselective synthesis is well recognised and has been reviewed.[114]

Discussion.

5.2 Towards an Asymmetric Synthesis of Thienamycin.

Both nitrones (35) and (36) were prepared in good yield following the general procedure outlined by DeShong.[79] Nitrone (35) was refluxed in neat α-chloroacrylonitrile for approximately 30 minutes to afford a diastereomeric mixture in 73% yield after chromatography. As with the cyclo-addition products described in Chapter 4, the ^{1}H nmr spectrum of this mixture gave little information as to its composition. Hydrolysis with triethylamine in aqueous THF afforded isoxazolidinone (191) as a colourless oil in 80% after chromatography, [Scheme 61].



Scheme 61.

The ^{1}H nmr spectrum of (191) indicates the formation of the two possible diastereomeric isoxazolidinones by the two sets of signals for the O-isopropylidene methyl groups in the region δ1.2 - δ1.45, in a ratio of approximately 6:1, [Figures 41 A,B]. Two multiplets centred at δ2.62 and δ2.75 corresponding to the C-4 methylene protons can be seen in a similar ratio. The proton-decoupled ^{13}C nmr spectrum shows, for example, two signals at δ32.16 and δ30.08 attributable to the C-4 carbon atom again in a ratio of approximately 6:1, in addition to two carbonyl carbon signals at δ175.49 and δ173.28,[Figure 41C]. Gas chromatographic analysis of this mixture on a fused-silica capillary column (SE-54) showed two peaks at t_R 26.1 and 27.63 minutes respectviely in a ratio of approximately 10:1, [Figure 42]. GC/MS analysis on a 60m DB-1 column at 190°C showed $[M-CH_3]^+$ = 262 for both of these peaks, while accurate mass analysis showed $[M]^+$ = 277.1307 corresponding to a molecular formula of $C_{15}H_{19}NO_4$ (calc. m/e = 277.1314). The i.r. spectrum of isoxazolidinone (191) shows a strong carbonyl absorption at 1779 cm^{-1}.

In an attempt to obtain a diastereomerically pure isoxazolidinone, nitrone (36) was also reacted with α-chloro-acrylonitrile to afford a diastereomeric mixture (192) in 91% yield. Hydrolysis of this mixture using triethylamine in aqueous THF afforded isoxazolidinone (193) as a colourless oil in 79% yield after chromatography, $[\alpha]_D$ -15.2° (C1.95, $CHCl_3$), [Scheme 62].

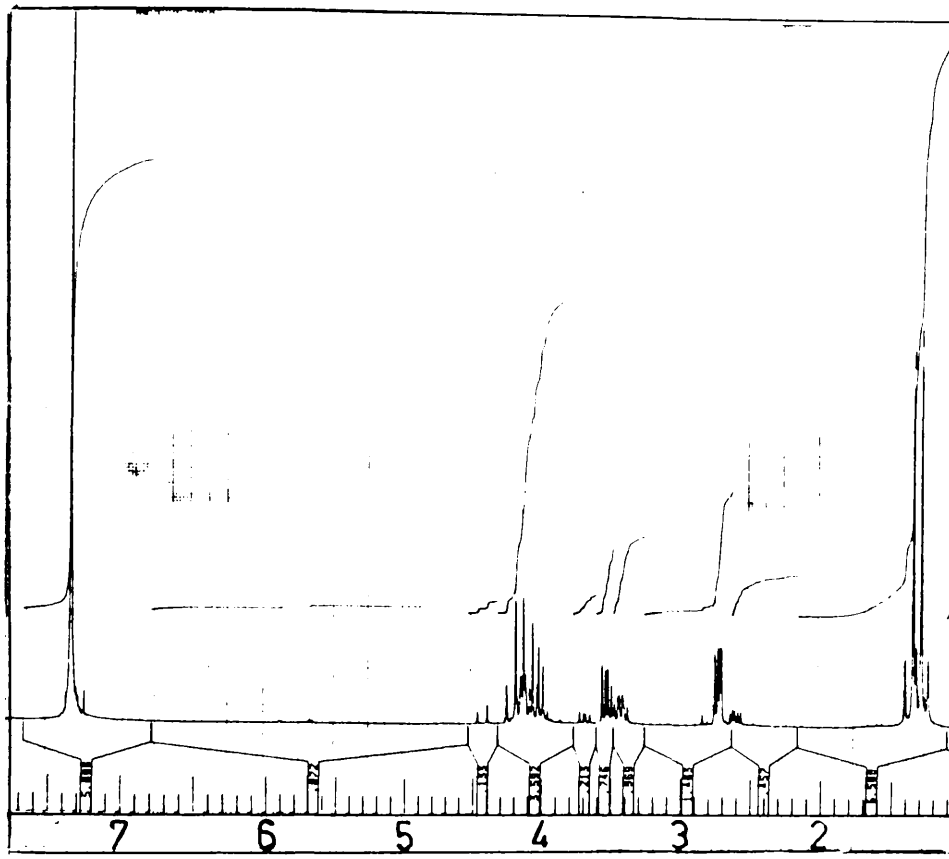


FIG. 41 A

H NMR OF ISOXAZOLIDINONE(191) AT 200MHz.

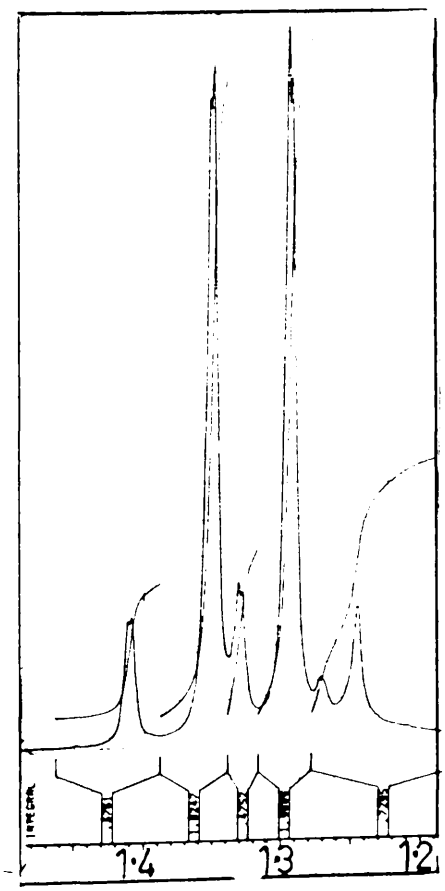


FIG. 41 B

EXPANSION

BETWEEN 1·2 – 1·5PPM

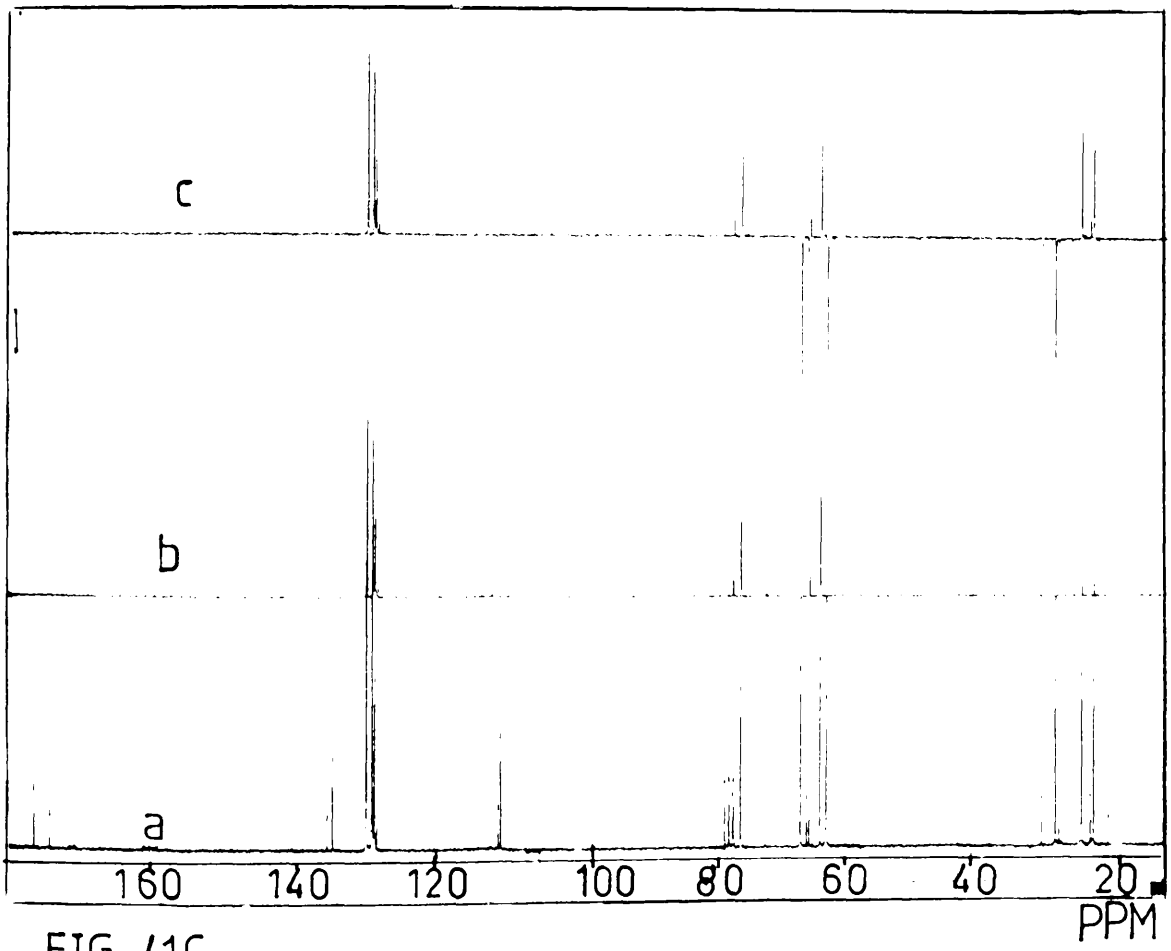


FIG. 41C

(a) ^{1}H-DECOUPLED ^{13}C NMR SPECTRUM OF(191) AT 55MHz

(b) DEPT, $\theta = 90^{\circ}$. (c) DEPT, $\theta = 135^{\circ}$.

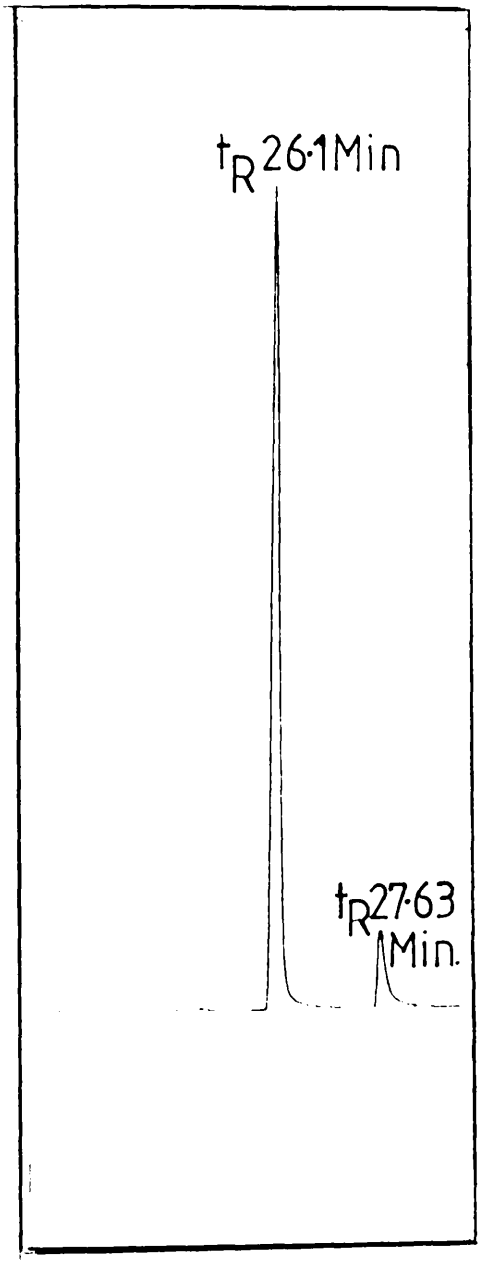
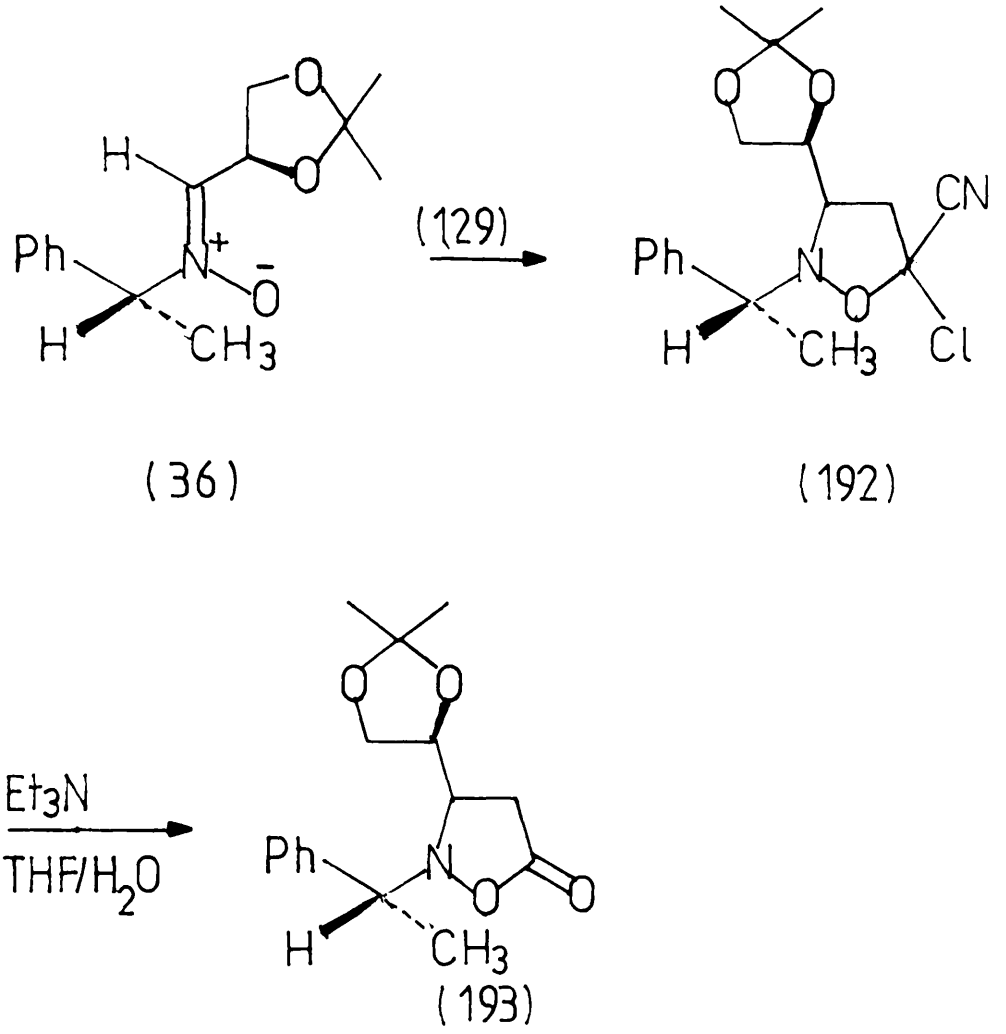


FIG. 42
CAPILLARY G.C. OF(191) ON A 25M SE -54 COLUMN FROM 80°C TO 250°C AT 30°C MIN.$^{-1}$



(36) (192) (193)

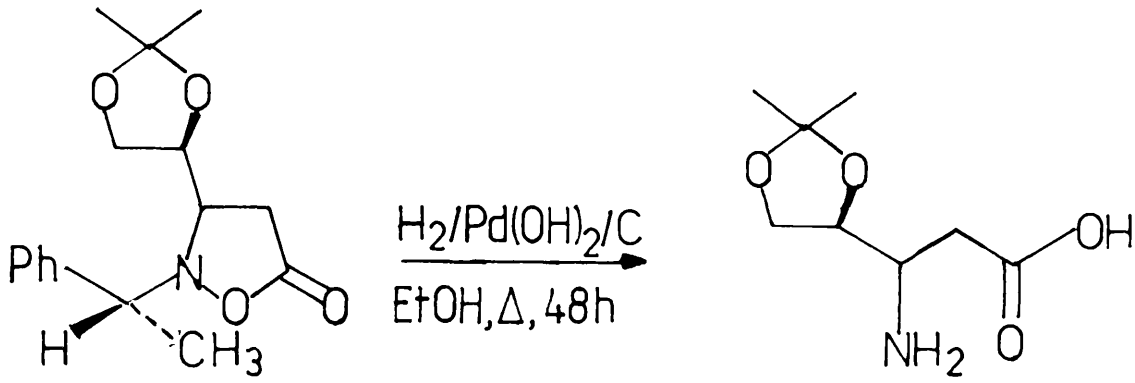
Scheme 62.

In contrast to the previous case, the ^{1}H nmr spectrum of isoxazolidinone (193) indicates the presence of only one compound. Only one α-methylbenzyl methyl group doublet at δ1.53 (J = 6.48Hz) and one set of two doublets of doublets at δ2.59 (J = 2.6, 18.1Hz) and δ2.71 (J = 7.7, 18.1Hz) corresponding to the C-4 methylene protons can be seen in Figure 43A. The acetonide methylene protons appear as a multiplet centred at δ3.32, while signals corresponding to the benzylic, C-3 and acetonide methine protons appear as part of a multiplet centred at δ4.05. In contrast to the proton-decoupled

^{13}C nmr spectrum of isoxazolidinone (191), that of (193) shows the presence of only one compound, [Figure 43B]. Gas chromatographic analysis on a fused silica capillary column (CP Sil5 CB) showed one peak at t_R 18.95 minutes, while GC/MS analysis showed $[M]^+$ = 291 for this peak, [Figure 44]. Accurate mass analysis showed $[M]^+$ = 291.1473 corresponding to a molecular formula of $C_{16}H_{21}NO_4$ (calc. m/e = 291.1471), while the i.r. spectrum of compound (193) shows a strong carbonyl absorption at 1782cm^{-1}.

The spectroscopic and chromatographic evidence presented here indicates that the cycloaddition between nitrone (36) and α-chloroacrylonitrile has diastereoselectively afforded two isoxazolidines which have the same configuration at C-3, however the absolute configuration at this centre cannot be determined at this stage. This implies that the nitrone has displayed complete diastereofacial selectivity in this cycloaddition and that the combination of the O-iso-propylidene and (R)-α-methylbenzyl moieties constitutes a matched pair of asymmetric reactants for double asymmetric induction.[72]

In a preliminary experiment, hydrogenolysis of isoxazolidinone (193) with palladium hydroxide in absolute ethanol at 70°C for 48h afforded the expected β-amino acid (194) as an oil in 84% yield, $[\alpha]_D$ -27.5° (c 0.8, MeOH), [Scheme 63].



(193) (194)

Scheme 63.

The ^{1}H nmr spectrum of (194) shows singlets at δ1.36 and δ1.48 corresponding to the [illegible], a broad signal at δ2.6(2H) corresponding to the C-2 methylene protons and a broad multiplet in the region δ3.4- δ4.5(4H) corresponding to the remaining methylene and methine protons [Figure 45]. The proton-decoupled ^{13}C nmr spectrum shows a signal at δ177 corresponding to the carbonyl carbon atom, while accurate mass analysis showed $[M-CH_3]^+$ = 174.0762 corresponding to a molecular formula of $C_7H_{12}NO_4$ (calc. m/e = 174.0766).

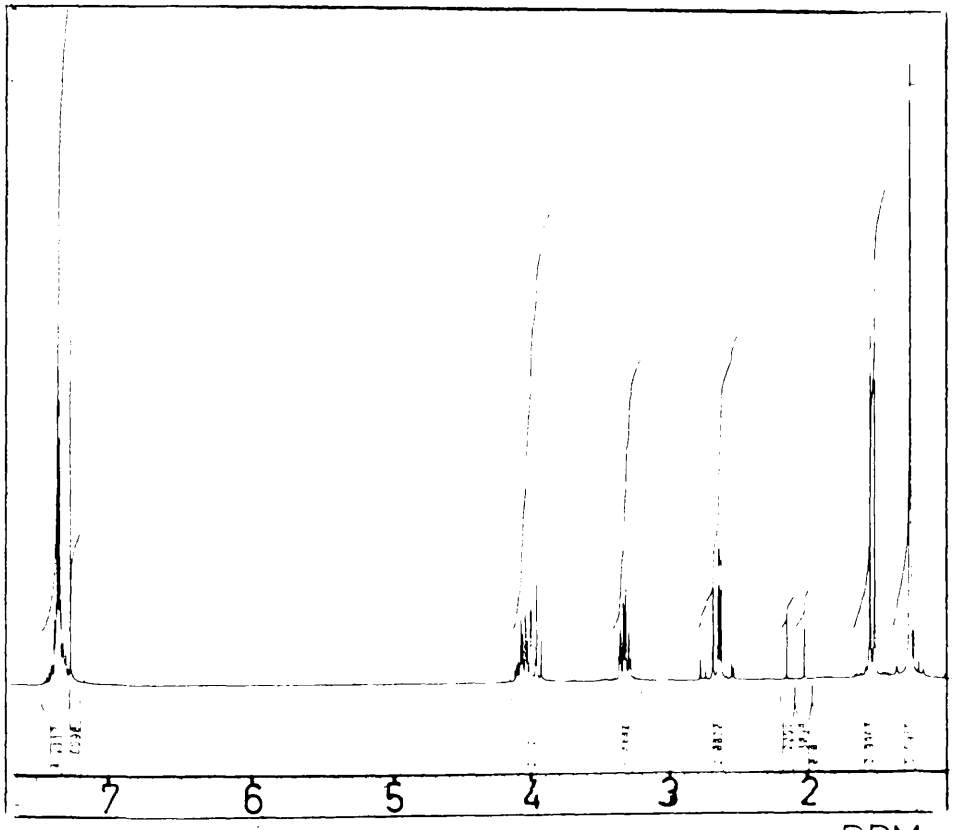


FIG. 43A

^{1}H NMR SPECTRUM OF ISOXAZOLIDINONE(193)

AT 200 MHz.

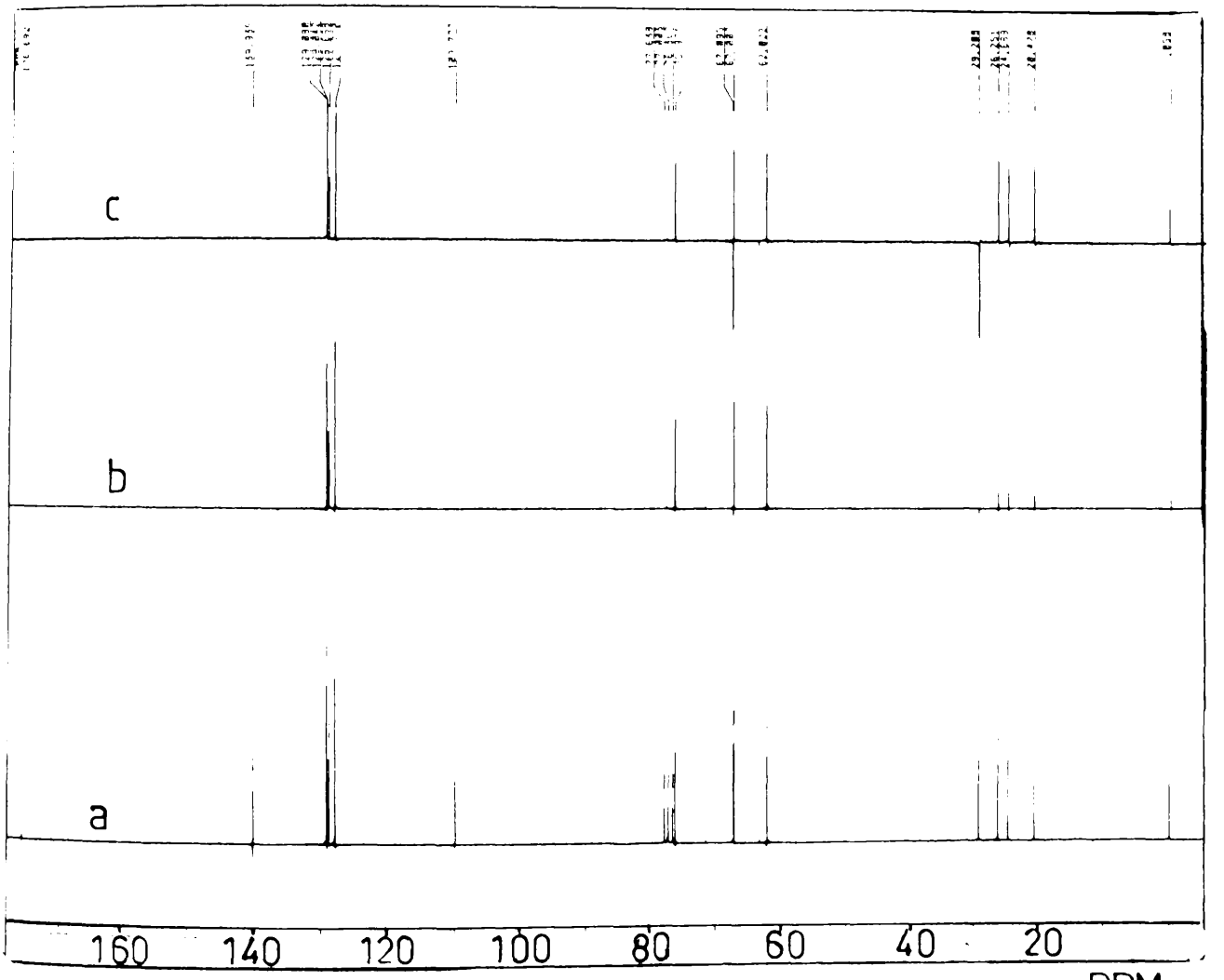


FIG. 43B

(a) ^{1}H-DECOUPLED ^{13}C NMR SPECTRUM OF (193) AT 55MHz.

(b) DEPT, $\theta = 90^{\circ}$. (c) DEPT, $\theta = 135^{\circ}$.

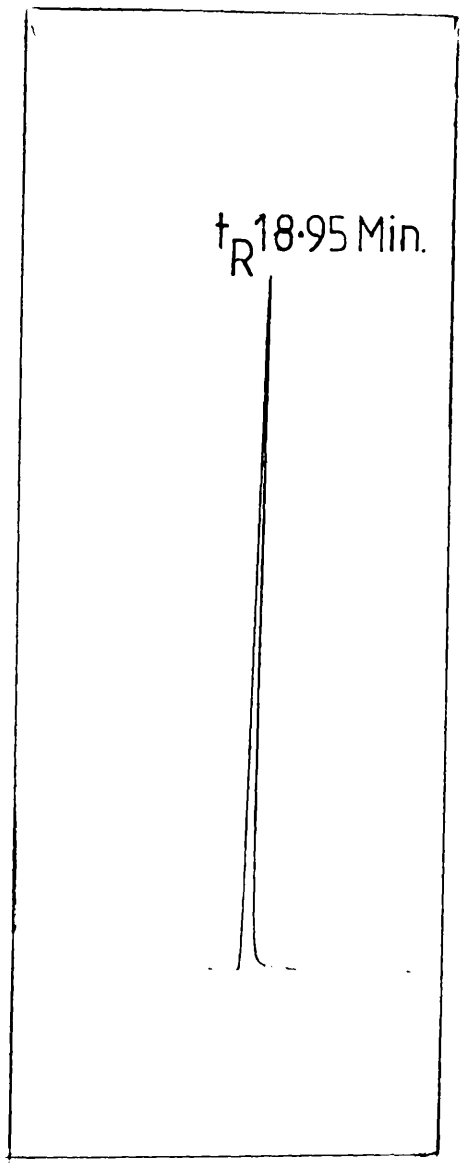


FIG. 44
CAPILLARY G.C. OF (193) ON A 25M CP SIL 5 CB COLUMN FROM 80°C TO 250°C AT 30 °C MIN.$^{-1}$

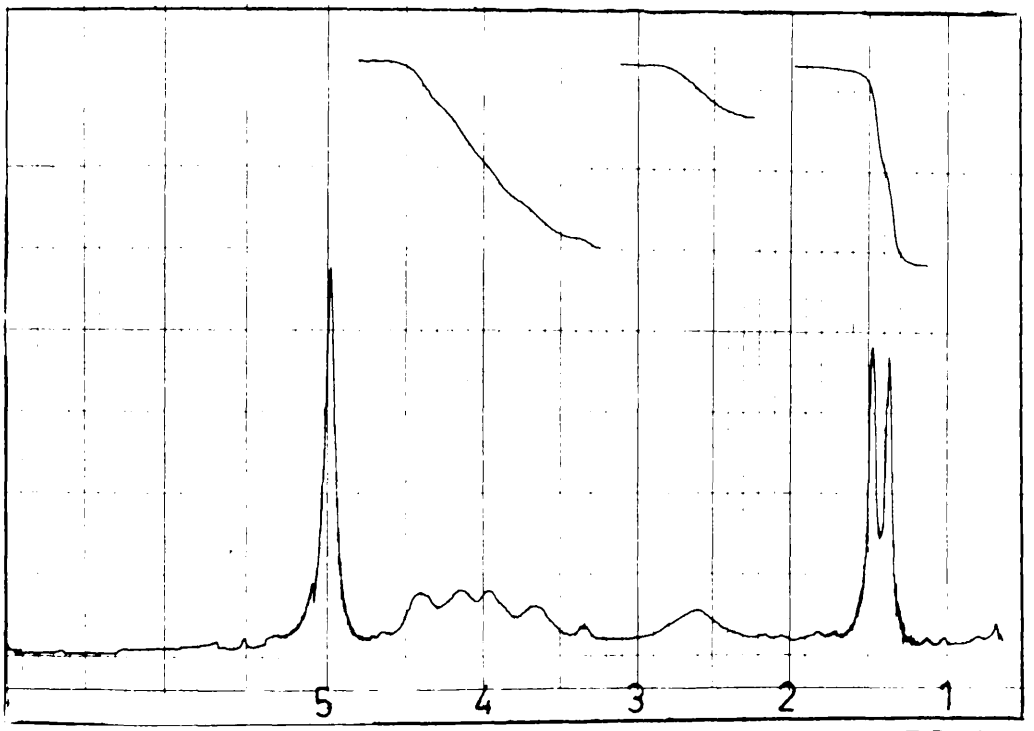
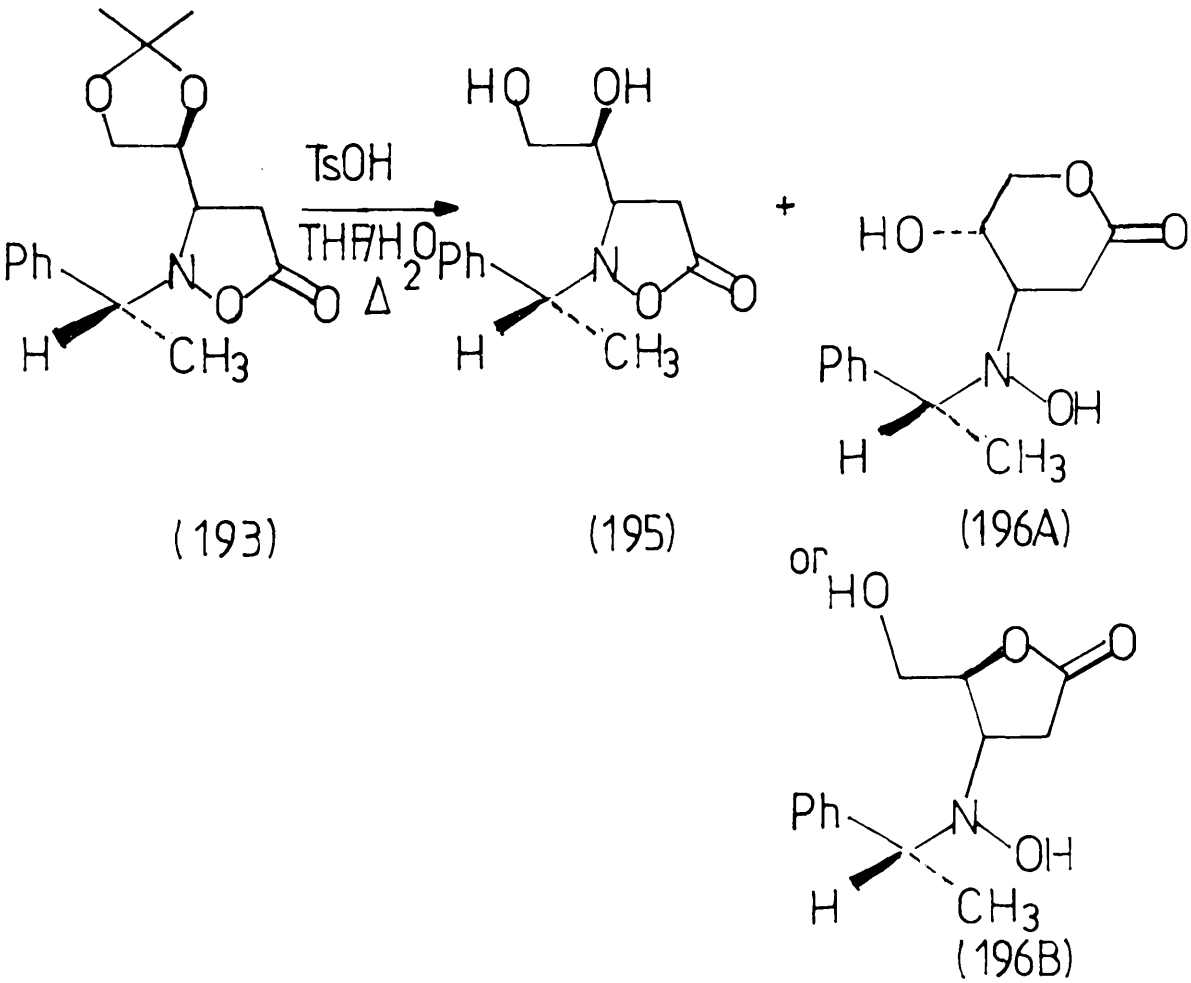


FIG.45

^{1}H NMR SPECTRUM OF(194) AT 90 MHz.

Deprotection of the acetonide of isoxazolidinone (193) using a catalytic amount of p-toluenesulphonic acid in aqueous THF following the method of Hubschwerlen[115] afforded a mixture of both the desired diol (195) and the isomeric lactone (196) in a total yield of 70%, [Scheme 64]. These compounds have very similar RF values and are therefore difficult to separate by chromatography. The ^{1}H nmr spectrum of the total product mixture of this reaction indicates that compounds (195) and (196) are formed in a relative ratio of approximately 4:1 as can be seen by the two overlapping α-methylbenzyl methyl group doublets in the region δ1.4- δ1.7, [Figure 46A].



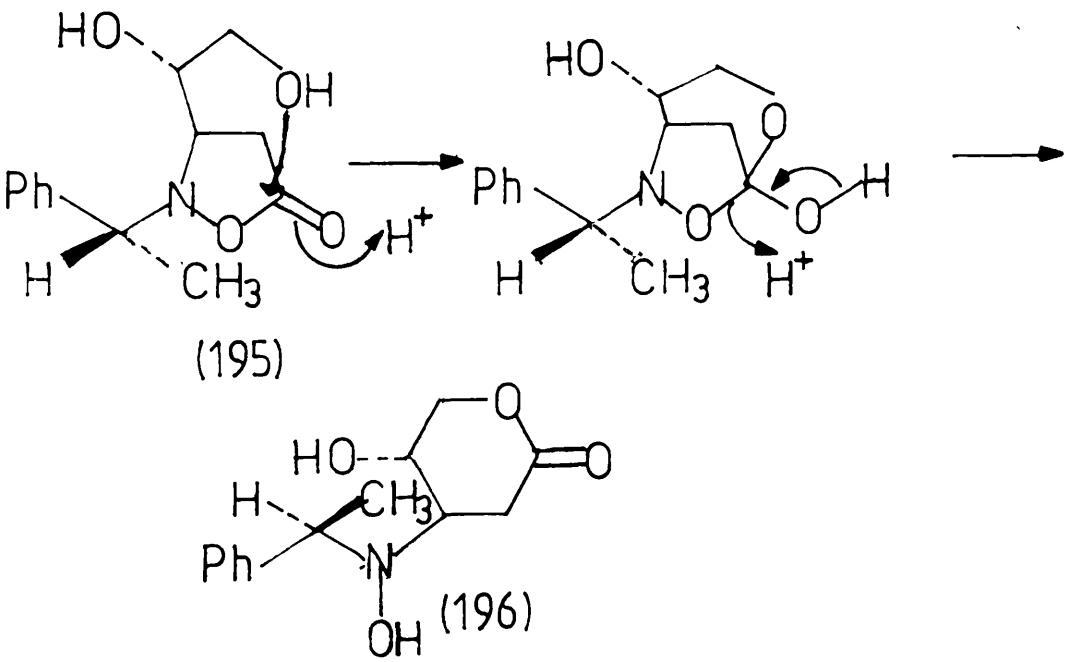
Scheme 64.

Deprotection of the acetonide at room temperature in HCl/MeOH[116] also afforded a mixture of these compounds, however in a less favourable ratio of approximately 2:1 as can be seen in the ^{1}H nmr spectrum of this material, [Figure 46B].

Partial separation of the mixture obtained from p-toluenesulphonic acid catalysed deprotection by column chromatography provided diol whose ^{1}H nmr spectrum shows two α-methylbenzyl methyl group doublets at δ1.53 (J = 6.5Hz) and δ1.42 (J = 6.5Hz) in a relative ratio of approximately 7:1, and whose proton-decoupled ^{13}C nmr spectrum shows essentially one compound, [Figures 47A,B,C]. The i.r. spectrum of diol (195) shows both free and hydrogen bonded -OH absorptions in the region 3200-3650 cm^{-1} in addition to a strong carbonyl absorption at 1780 cm^{-1}, while accurate mass analysis showed $[M]^{+}$ = 251.1145 corresponding to a molecular formula of $C_{13}H_{17}NO_4$ (calc. m/e = 251.1158).

The isomeric lactone (196) was obtained as a colourless crystalline solid, m.p. 140-142°C $[\alpha]_D$ + 112.4° (c2.1, MeOH). The ^{1}H nmr spectrum of lactone (196) clearly shows one doublet at δ1.42 (J = 6.45Hz) corresponding to the α-methylbenzyl methyl group, and two doublets of doublets at δ2.86 (J = 3.9,17.9Hz) and δ2.4 (J = 8.9, 17.9Hz) corresponding to the methylene protons α to the carbonyl moiety, [Figure 48A]. The benzylic methine proton appears as a quartet at δ3.7 (J = 6.45Hz), while the remaining non-aromatic protons can be

accounted for by the multiplets centred at δ4.6(1H), δ3.66(1H), and δ3.46(2H). The proton-decoupled ^{13}C nmr spectrum [Figure 48B] shows only one carbonyl carbon signal at δ179.6, and in addition to the ^{1}H nmr spectrum indicates the formation of only one of the two possible 5- or 6- membered ring lactones (196A or 196B). Indeed, molecular models suggest that formation of the 6-membered ring lactone via attack of the terminal hydroxyl group on the isoxazolidinone carbonyl group, regardless of the absolute stereochemistry at C-3, is by far the more favourable process, [Scheme 65].



Scheme 65

The i.r. spectrum of lactone (196) shows strong hydroxyl absorption in the region 3200-3500 cm^{-1} and a strong

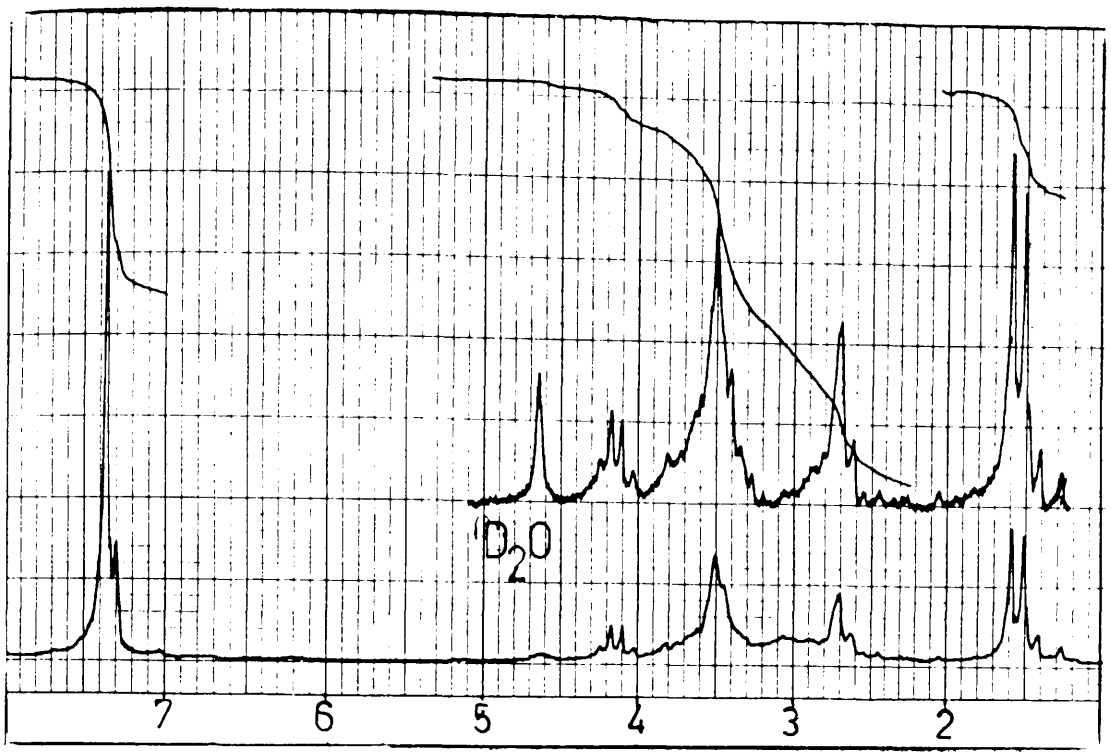


FIG. 46A

^{1}H NMR SPECTRUM OF MIXTURE (195) + (196) AT 90 MHz.
(From TsOH deprotection)

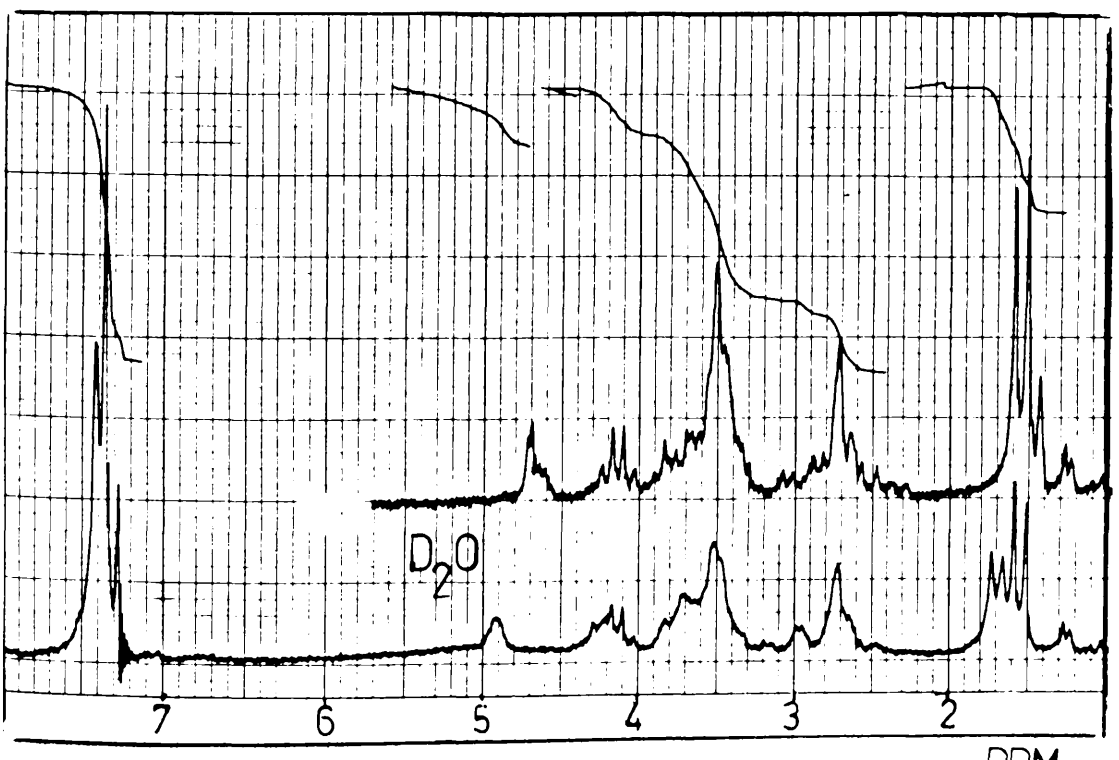


FIG. 46B.
(From MeOH/HCl deprotection)

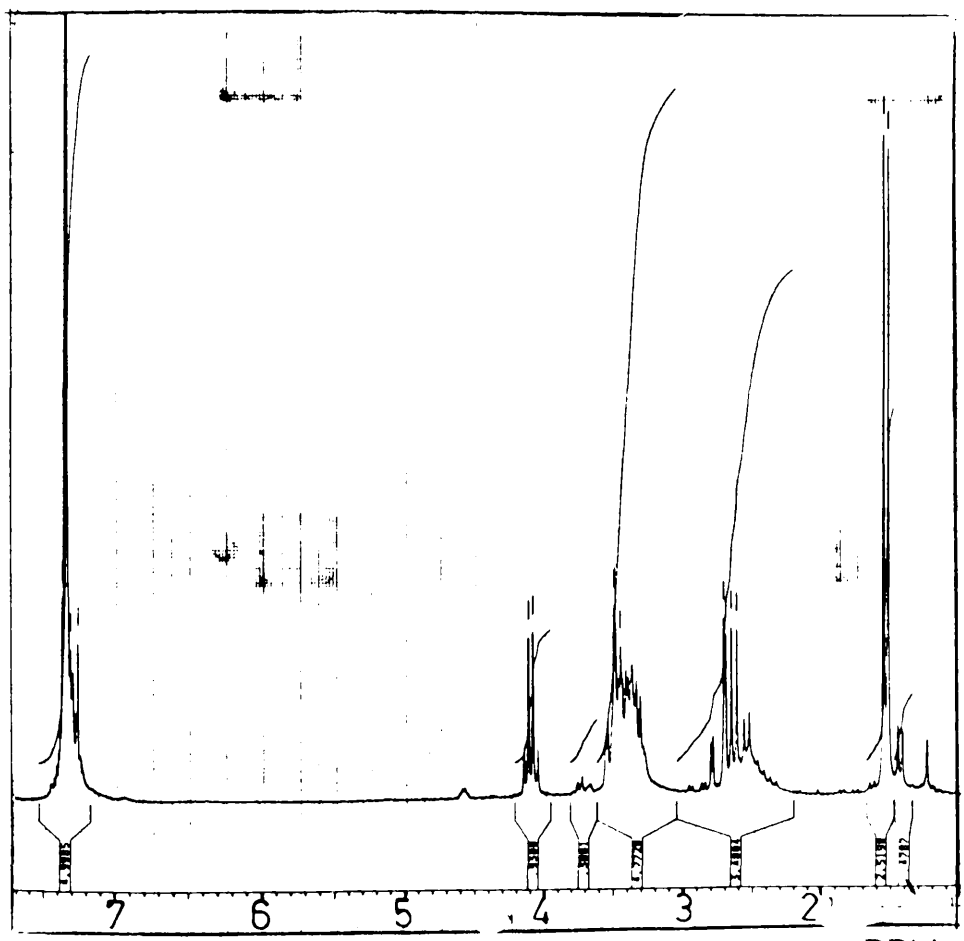


FIG. 47A

^{1}H NMR SPECTRUM OF DIOL(195) AT 200MHz.

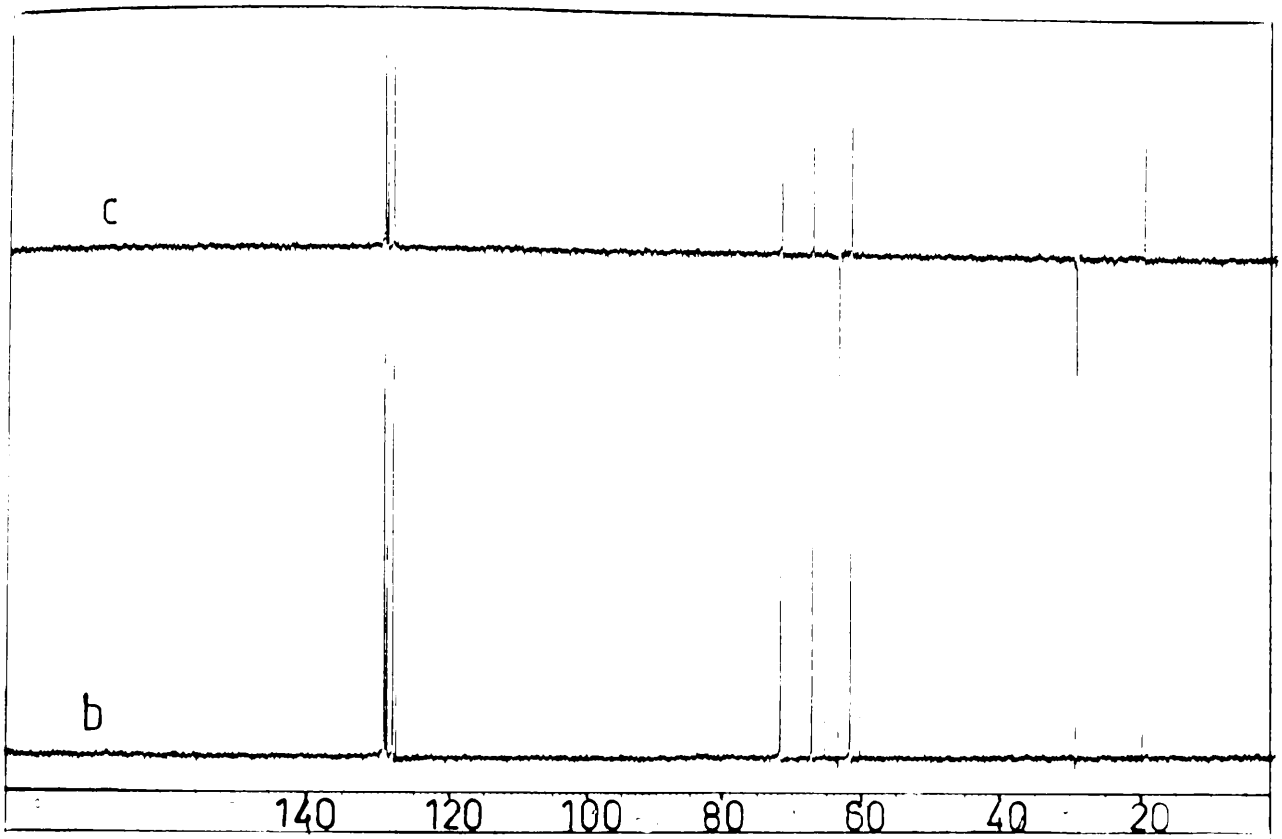


FIG. 47 C
(b) DEPT, $\theta = 90^{\circ}$. (c) DEPT, $\theta = 135^{\circ}$.

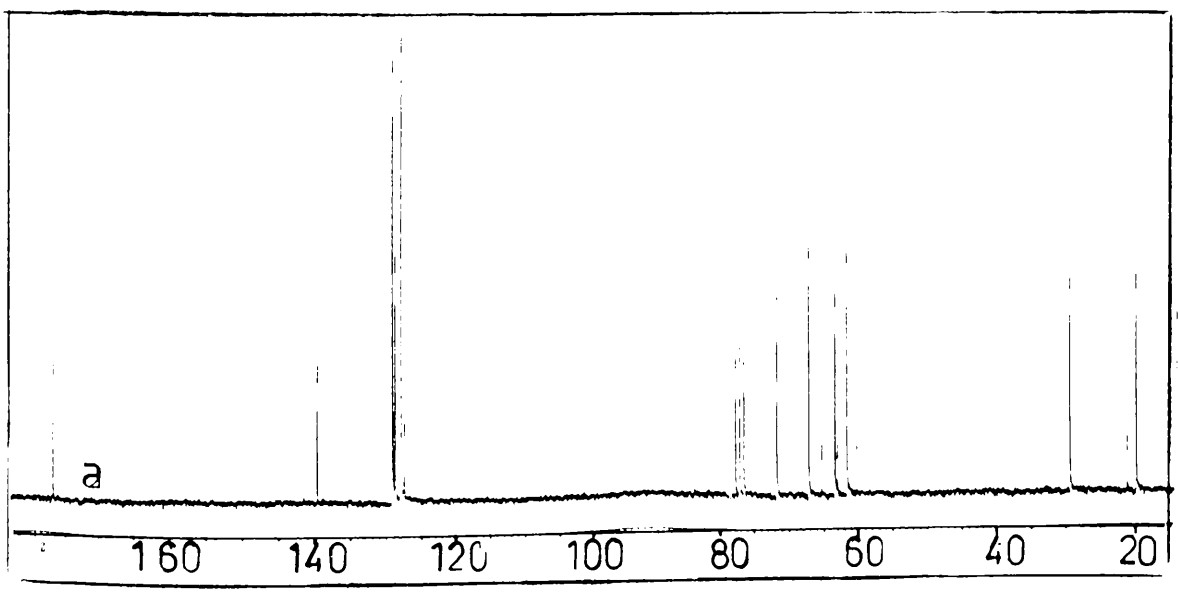


FIG. 47
(a) ^{1}H-DECOUPLED ^{13}C NMR SPECTRUM OF(195) AT 55 MHz.

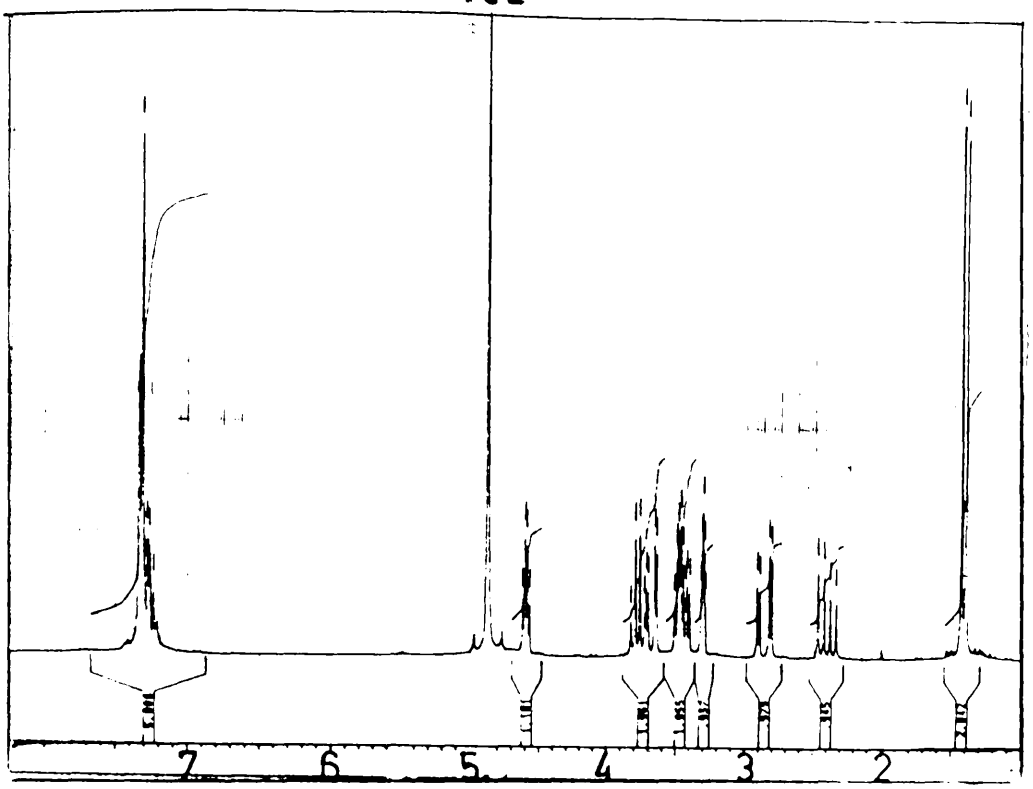


FIG. 48A
^{1}H NMR SPECTRUM OF LACTONE (196) AT 200MHz.

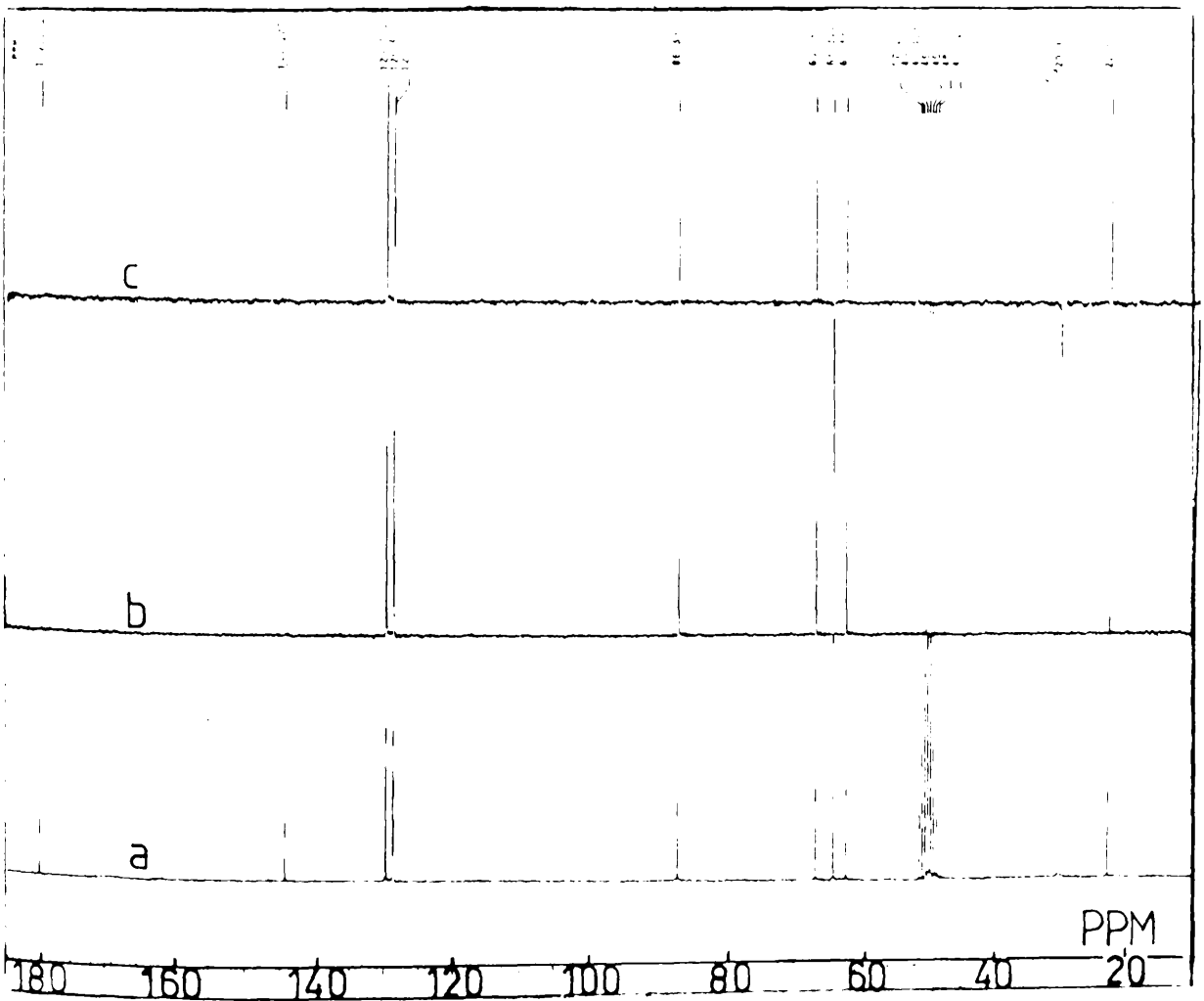
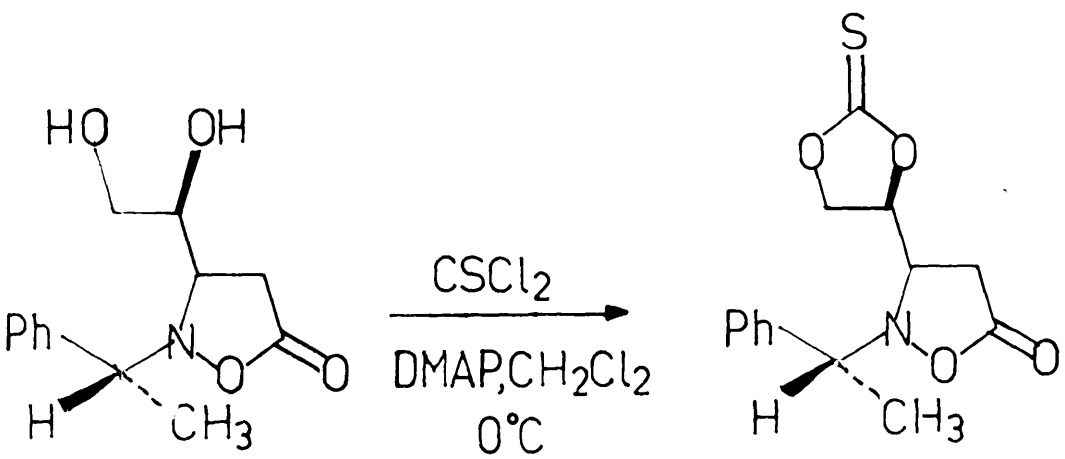


FIG. 48B (a) ^{1}H-DECOUPLED ^{13}C NMR SPECTRUM OF (196) AT 55MHz. (b) DEPT, $\theta = 90°$. (c) DEPT, $\theta = 135°$.

carbonyl absorption at 1731 cm^{-1}, while accurate mass analysis showed $[M]^+$ = 251.1149 corresponding to a molecular formula of $C_{13}H_{17}NO_4$ (calc. m/e = 251.1158).

The substantially purified diol was treated with thiophosgene in the presence of 4-dimethylaminopyridine in dichloromethane following the procedure of Corey,[111] and afforded thionocarbonate (197) as a pale yellow crystalline solid, m.p. 174-175 $[\alpha]_D$ -10.89° (c 1.91, $CHCl_3$), in 66% yield after chromatography, [Scheme 66].



(195) (197)

Scheme 66

The ^1H nmr spectrum of thionocarbonate (197) clearly shows one α-methylbenzyl methyl group doublet at δ1.56 (J = 6.5Hz) and a quartet at δ4.13 (J = 6.5Hz) corresponding

to the benzylic methine proton, [Figure 49A]. An expansion of the region between δ2.5 and δ3.0 shows one major set of two doublets of doublets at δ2.88 (J = 8.2, 18.6Hz) and δ2.65 (J = 1.6, 18.6Hz) corresponding to the C-4 methylene protons, [Figure 49B]. In addition to this one can see a very minor set of two doublets of doublets. It is possible that the small amount of lactone (196) which was present in the sample of diol (194) used in this reaction has also been converted to its corresponding thionocarbonate, thus accounting for these very minor extra signals. The remaining non-aromatic protons can be seen as multiplets centred at δ3.65(1H), δ4.05(1H) and δ4.75(2H). The proton-decoupled ^{13}C nmr spectrum of thionocarbonate (197) shows a signal at δ190.4 corresponding to the thiocarbonyl carbon atom and a signal at δ175.1 corresponding to the carbonyl carbon atom, [Figure 49C]. The i.r spectrum of (197) shows a strong carbonyl absorption at 1781 cm^{-1} and a band at 1300 cm^{-1} associated with the thiocarbonyl group,[111] while accurate mass analysis showed $[M]^+$ = 293.0724 corresponding to a molecular formula of $C_{14}H_{15}NO_4S$ (calc. m/e = 293.0722). The thionocarbonate (197) proved not to be suitable for gas chromatographic analysis and gave rise to a trace which indicated that it may be decomposing during analysis.

In a preliminary experiment, thionocarbonate (197) was treated with 1,3-dimethyl-2-phenyl-1,3,2-diazaphospholidine (198) (conveniently prepared in one step (70%) from sym-dimethylenediamine and dichlorophosphine)[117] following

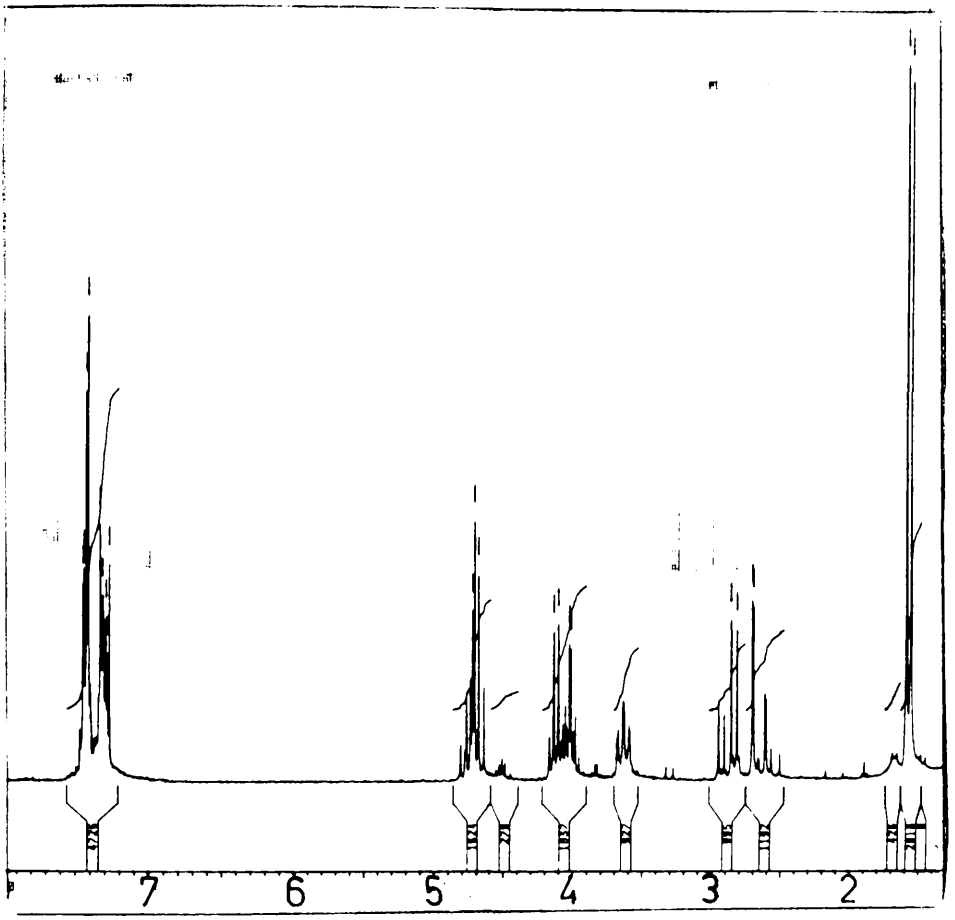


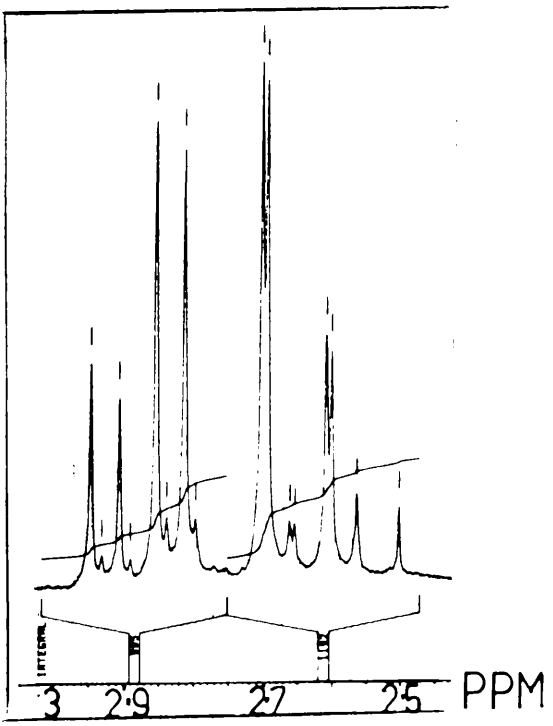
FIG. 49A

^{1}H NMR SPECTRUM OF THIONOCARBONATE (197) AT 200MHz.

FIG. 49B

EXPANSION BETWEEN

2·5 – 3 PPM.



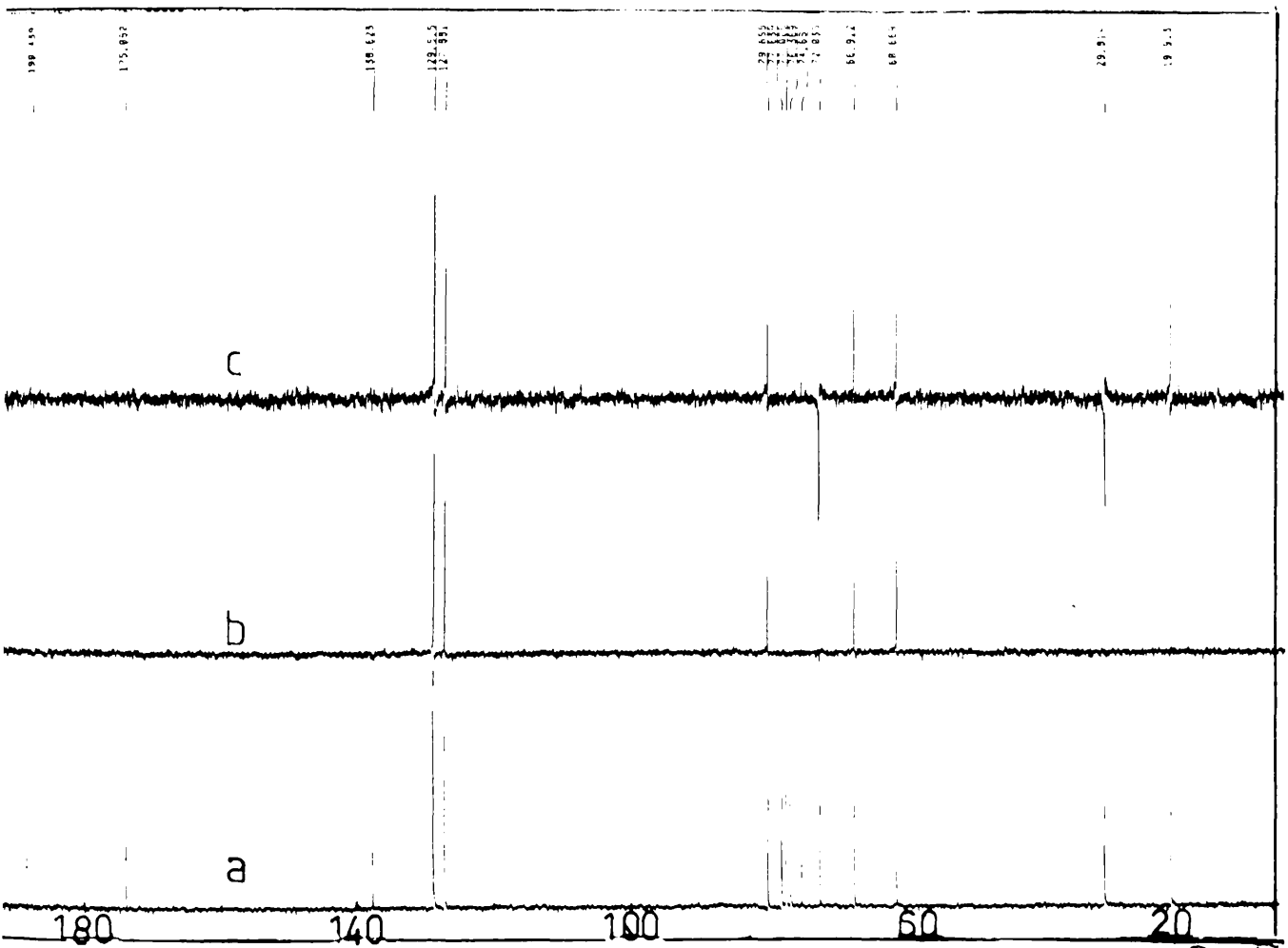
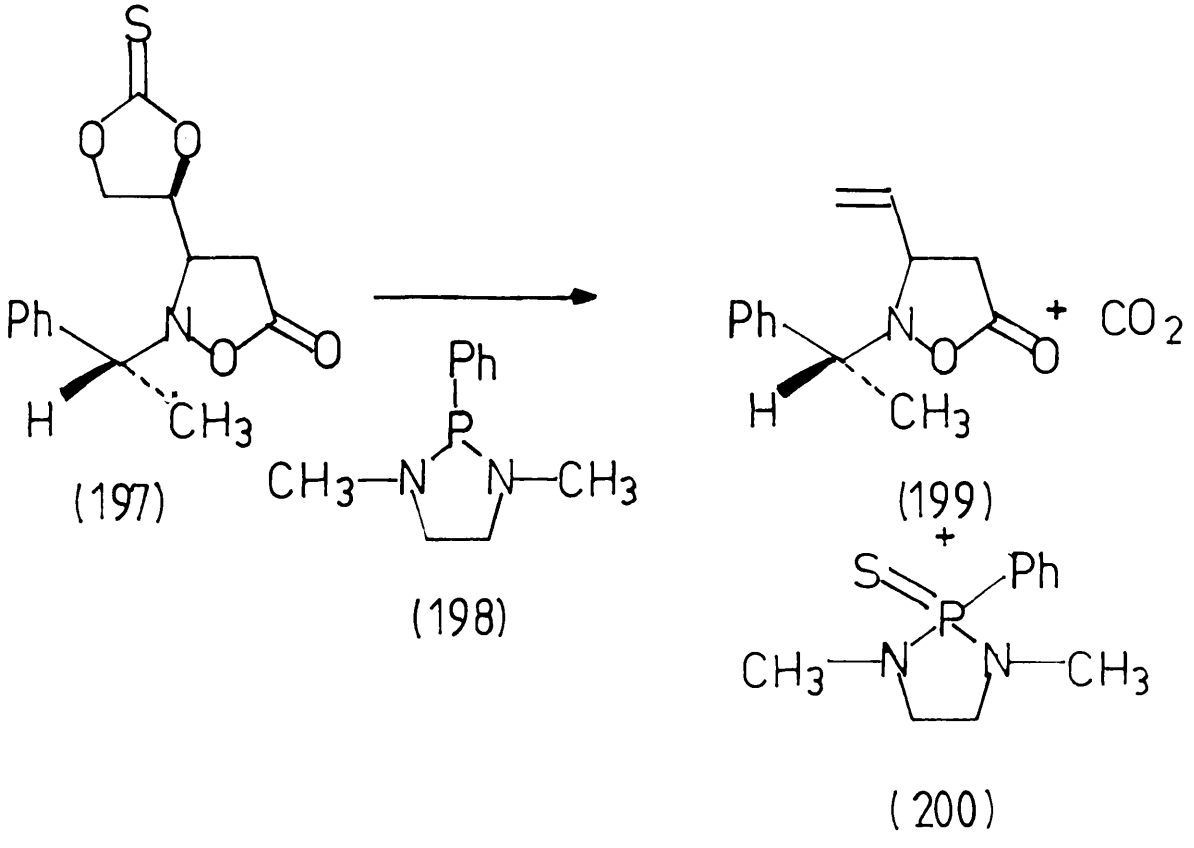


FIG. 49C

(a) ^{1}H-DECOUPLED ^{13}C NMR SPECTRUM OF (197) AT 55MHz.

(b) DEPT, $\theta = 90^{\circ}$. (c) DEPT, $\theta = 135^{\circ}$.

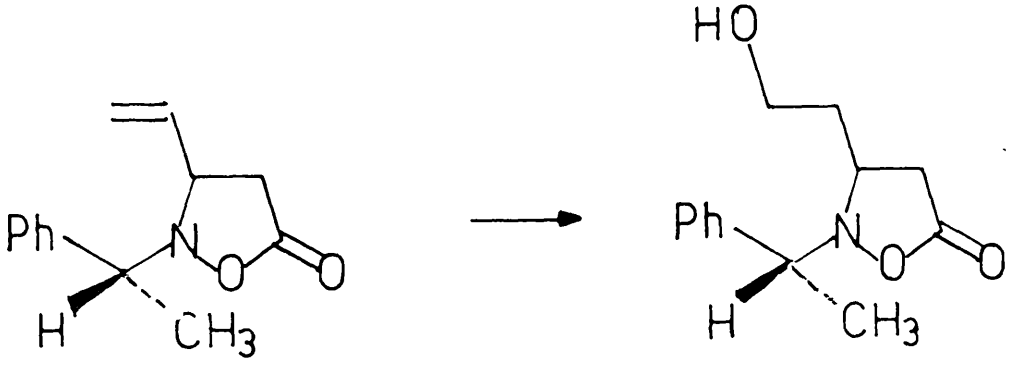
the procedure of Corey,[111] and afforded after chromatography a partially purified sample of the desired olefin (199) [Scheme 67].



Scheme 67

The ^{1}H nmr spectrum of (199) clearly shows the expected three proton olefinic system in the region δ4.9 - δ5.9, a multiplet centred at δ4.1 corresponding to the benzylic and C-3 methine protons and a doublet at δ1.55 (J = 7Hz) corresponding to the α-methylbenzyl methyl group. The signal associated with the C-4 methylene protons is masked by a doublet in the region δ2.4 - δ3.0 arising from contaminant material derived from compound (198) during the reaction,

presumably compound (200). The i.r. spectrum of this material shows a strong carbonyl absorption at 1775 cm^{-1}, while accurate mass analysis showed $[M]^+$ = 217.1105 corresponding to a molecular formula of $C_{13}H_{15}NO_2$ (calc. m/e = 217.1103). Accurate mass analysis also showed $[M]^+$ = 226.069 corresponding to a molecular formula of $C_{10}H_{15}N_2PS$ (calc. m/e = 226.06936) due to the presence of compound (200). Thin layer chromatographic analysis of this material showed only one spot, however subsequent hydroboration may allow easier purification, [Scheme 68].



(199) (201)

Scheme 68.

Lack of time prevented any further investigation as to the utility of this approach to the asymmetric synthesis of thienamycin.

Summary and Conclusions.

The diastereomerically pure isoxazolidinone (193) was obtained in two operationally simple steps from nitrone (36) in high yield, and may prove to be a useful intermediate in the asymmetric synthesis of carbapenem type antibiotics.

The generally high yielding conversion of the C-alkyl nitrones as described in Chapter 4 and nitrones (35) and (36) described above to the corresponding isoxazolidinones, confers great synthetic utility on the cycloaddition reactions of non C-aromatic nitrones with α-chloroacrylonitrile as means of entry to this class of compounds. Furthermore, hydrogenolysis of isoxazolidinones followed by re-cyclisation constitutes an efficient synthesis of the β-lactam nucleus.[110]

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 n.m.r spectra were recorded in deuterochloroform (unless otherwise stated) using tetramethylsilane (TMS) as internal standard on a Perkin-Elmer R.32 (90MHz) spectrometer. ^{1}H n.m.r spectra were also recorded at 100MHz on a Varian XL 100 spectrometer and at 200MHz on a Bruker WP 200 SY spectrometer, both employing a deuterium lock system setting either chloroform ($\underline{CH}Cl_3$) in $CDCl_3$ at δ7.25 or methanol ($\underline{CH_3}OH$) in CD_3OD at δ3.35 as internal standard.

^{13}C n.m.r spectra were recorded either at 25.2MHz on the Varian XL 100 spectrometer or at 55MHz on the Bruker WP 200 SY spectrometer, either in deuterochloroform setting the reference $CDCl_3$ signal at δ77.0, in deuteromethanol setting the reference CD_3OD signal at δ49.0, or in deuterodimethylsulphoxide setting the reference $(CD_3)_2SO$ signal at δ40.0. 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. 9025 spectrometer.

Analytical and preparative t.l.c were run using the developing solvents indicated. Pre-coated Merck Kieselgel 60-F254 20 x 20cm, 0.2mm plates were used for analytical

t.l.c., and 20 x 20cm, 0.25mm plates for preparative t.l.c. Flash column chromatography was performed by the method of Harwood,[124] over Fluka Kieselgel GF-254 silica gel.

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) or CP Sil5B. The sample was injected via Grob-type injectors in split mode (50:1) using helium as both carrier and make up gas (flow rates $3mlmin^{-1}$ and $25mlmin^{-1}$, respectively).

GC-MS was performed with an LKB 9000 instrument fitted with DB-1 fused silica capillary columns, 60m x 0.3mm I.D. (J. and W. Scientific, Rancho Cordova, CA, USA) and a falling needle injector. Helium was used as both carrier and make-up gas (flow rates $7mlmin^{-1}$ and $25mlmin^{-1}$ respectively, measured at ambient temperature). Mass spectra were recorded under electron impact conditions (20eV); accelerating voltage 3.5kV; trap current 60μA; source and separator temperatures $260^{o}C$.

Optical rotations were measured at ambient temperature on an Optical Acivity AA-100 polarimeter.

Purification and Drying of Solvents.

Solvents were dried and purified prior to use as follows: acetone distilled from K_2CO_3, stored over molecular

sieves (4Å)); benzene, toluene (dried and stored over sodium metal); carbon tetrachloride (filtered through alumina (basic, activity 1); dichloromethane (distilled from P_2O_5, stored over molecular sieves (4Å)); ether and tetrahydrofuran (THF) (distilled from sodium and benzophenone immediately before use); dimethylformamide (distilled from blue silica gel, stored over molecular sieves (4Å)); dimethylsulphoxide (dried and stored over molecular sieves (4Å)); triethylamine (distilled from anhydrous KOH, stored over molecular sieves (4Å)).

Benzaldehyde oxime (1)[73]

Benzaldehyde (20g, 0.19 mol) was dissolved in aqueous methanol (200ml; 50ml H_2O 150ml MeOH), and to this were added hydroxylamine hydrochloride (13.2g, 0.19 mol) and anhydrous sodium bicarbonate (17.4g, 0.2 mol). The resulting solution was heated with stirring at 80°C for 3h. The solution was reduced in volume to approximately 100ml, added to water (100ml), and then extracted with ethyl acetate (3 x 150ml). The combined organic layers were dried with anhydrous $MgSO_4$, filtered and evaporated to give benzaldehyde oxime (20.1g, 88%) as a colourless oil. ^1H NMR ($CDCl_3$) δ7.25 - 7.55 (m, 5H), 8.15 (s, 1H), 9.15 - 9.55 (bs, 1H).

N-Benzylhydroxylamine (2)

To benzaldehyde oxime (20g, 0.16 mol) dissolved in methanol (200ml) and sodium cyanoborohydride[74] (6.8g, 0.11 mol), a solution of 2N HCl-MeOH was added slowly until the pH of the solution reached 2-3 (as judged by universal indicator paper), and additional MeOH - HCl was added as required to maintain this pH. After 2h, the methanol was removed *in vacuo*. The residue was dissolved in water (50ml) and 5N NaOH was added until the pH exceeded 9. The basic solution was then extracted with chloroform (3 x 100ml) and the combined organic layers dried with anhydrous $MgSO_4$, filtered and the solvent removed *in vacuo*

to give N-benzylhydroxylamine (17.2g, 85%), as a white crystalline solid from hexane, m.p. 56-57°C (Lit.[74] 58-59°C). ^{1}H NMR ($CDCl_3$) δ3.98 (s, 2H), 6.3 (broad s exchangeable in D_2O, 2H), 7.3 (s, 5H).

General Preparation of N-Benzyl-C-alkylnitrones (5,6).

N-Benzylhydroxylamine and an excess (1.5 equiv) 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 (5)

From N-benzylhydroxylamine (3g, 24.4mmol) and acetaldehyde (1.61g, 36.6mmol), in dichloromethane (75ml). Recrystallisation from ether-hexane gave nitrone (5) (3g, 83%) as a colourless crystalline solid, m.p 82-83°C (Lit.[47] 83°C). IR ($CHCl_3$) 1602, 1491, 1450, 1436, 1410, 1356, 1306, 1235, 1164, 1100, 1040 cm^{-1}.
^{1}H NMR ($CDCl_3$) δ1.99 (d J = 5.9Hz, 3H), 4.9 (s,2H), 6.73 (q J = 5.9Hz, 1H), 7.39 (s,5H).

C-Isopropyl-N-benzylnitrone (6)

From N-benzylhydroxylamine (2.4g, 17.4mmol) and isobutyraldehyde (2.11g, 29.3mmol) in dichloromethane (50ml).

Recrystallisation from ether-hexane gave nitrone (6) (2.9g, 84%) as a colourless crystalline solid, m.p. 63°C Lit.[49] 63°C).
IR ($CHCl_3$) 1593, 1493, 1451, 1418, 1114 cm^{-1}.
^1H NMR ($CDCl_3$) δ1.08 (d J = 7.4Hz, 6H), 3.18 (m,1H), 4.86 (s,2H), 6.49 (d J = 7.4Hz, 1H), 7.4 (s,5H).

C,N-Diphenylnitrone (9)

To a stirred solution of N-phenyl-N-benzylamine (5g, 27.3mmol) in dry acetone (30ml) at 0°C, was added dropwise over a period of 15 min, a solution of m-chloroperbenzoic acid (9.5g, 55mmol) in acetone (90ml). When addition was complete, stirring was continued at room temperature for a further 45 min, and then the solution was refluxed for 1h. The solvent was then removed in vacuo and the residual yellow solid partitioned between ether (100ml) and 10% K_2CO_3 (100ml). The ethereal layer was washed with water (2 x 100ml), dried over anhydrous $MgSO_4$, filtered and evaporated to give a solid residue. Upon recrystallisation from ether-hexane, nitrone (9) (3.21g, 60%) was obtained as a pale yellow crystalline solid, m.p. 111-113°C (Lit.[118] 114°C).
IR ($CHCl_3$) 1595, 1575, 1480, 1435, 1409, 1285, 1260, 1140, 1085, 1070 cm^{-1}.
^1H NMR ($CDCl_3$) δ7.3 - 7.6 (m,6H), 7.7 - 7.84 (m,2H), 7.99 (s,1H), 8.3 - 8.45 (m,2H).

C-Phenyl-N-benzylnitrone (10)

To a stirred solution of N,N-dibenzylamine (6g, 30.4mmol) in dry acetone (50ml) at 0°C was added dropwise over a period of 15 min, a solution of m-chloroperbenzoic acid (11.4g, 66.1mmol) in acetone (75ml). The solution was stirred at 5°C for 2h and then heated under reflux for 2h. Removal of solvent in vacuo gave a yellow solid which was partitiioned between 10% K_2CO_3 (100ml) and ether (200ml). The ethereal layer was washed with water (2 x 100ml), dried with anhydrous $MgSO_4$, filtered and evaporated in vacuo to give a yellow solid. Recrystallisation from ether-hexane gave nitrone (10) (4.05g, 63.) as a pale yellow crystalline solid, m.p. 84 - 85°C (Lit.[75] 83 - 84°C).

IR ($CHCl_3$) 1586, 1570, 1501, 1461, 1455, 1325, 1165, 1150 1030, 710 cm^{-1}.

^1H NMR ($CDCl_3$) δ5.08 (s,2H), 7.1 - 7.7 (m,9H), 8.2 - 8.4(m,2H).

3,4-Dihydroisoquinoline N-oxide (12)

To a stirred solution of tetrahydroisoquinoline (5g, 37.6mmol) and sodium tungstate dihydrate (0.5g, 1.5mmol) in methanol (30ml) at 0°C was added a 30% solution of hydrogen peroxide (9.3g, 80mmol) over a period of 15 min. After stirring at room temperature for 2h, water (50ml) followed by sodium bisulphite (2g) and sodium chloride (2g) was added. The resulting solution was extracted with chloroform (2 x 100ml) and the organic extracts dried over

anhydrous Na_2SO_4, filtered and evaporated in vacuo. The residue was chromatographed over silica gel (10% methanol - dichloromethane) to afford nitrone (12) as a light brown oil in 60% yield.[76]

TLC: Rf 0.5 (silica gel, 10% methanol - dichloromethane).

IR ($CHCl_3$) 1595, 1565, 1492, 1449, 1430, 1309, 1288, 1265, 1175, 1110 cm^{-1}.

^1H NMR ($CDCl_3$) δ3.12 (t J = 8Hz, 2H), 4.09 (t J = 8Hz, 2H), 7 - 7.4 (m,4H), 7.75 (s,1H).

$[M]^+$ 147.0678. C_9H_9NO requires 147.0684.

General Preparation of Nitrones (15) and (16).

N-Benzylhydroxylamine and the appropriate aldehyde (1 equiv) were dissolved in benzene or methanol-benzene and heated at reflux with stirring for 3h. Removal of the solvent in vacuo gave a solid residue, which in each case was recrystallised to give pure nitrone.

C-p-Methoxyphenyl-N-benzylnitrone (15).

From N-benzylhydroxylamine (3g, 24.4mmol) and p-methoxybenzaldehyde (3.32g, 24.4mmol) in benzene (100ml). Recrystallisation from ether-hexane gave nitrone (15) (4.6g, 78%) as a colourless crystalline solid, m.p. 115 - 116°C.

IR ($CHCl_3$) 1605, 1569, 1505, 1451, 1439, 1425, 1320, 1304, 1260, 1170, 1141, 1032, 841, 705 cm^{-1}.

^{1}H NMR ($CDCl_3$) δ3.84 (s,3H), 5.02 (s,2H), 6.9 (d J = 9Hz, 2H), 7.31 (s,1H), 7.35-7.6 (m,5H), 8.2 (d J = 9Hz,2H).
^{13}C NMR (25.2MHz, $CDCl_3$) δ53.62 (O<u>Me</u>), 68.96 (Ph<u>CH</u>$_2$), 119.16 (<u>HC</u> = $\overset{+}{N}$), 121.9 (<u>Ar</u>), 127.2 (<u>Ar</u>-H), 127.45 (<u>Ar</u>-H), 128.96 (<u>Ar</u>-H), 132.04 (<u>Ar</u>) 132.3 (<u>Ar</u>-H), 159.4 (<u>Ar</u>)
$[M]^+$ 241.1103. $C_{15}H_{15}NO_2$ requires 241.11027.
[Found C 74.65, H 6.35, N 5.9; $C_{15}H_{15}NO_2$ requires C 74.65, H 6.25, N 5.8%].

<u>C-p-Hydroxyphenyl-N-benzylnitrone (16)</u>

From N-benzylhydroxylamine (3g, 24.4mmol) and p-hydroxybenzaldehyde (2.98g, 24.4 mol) in methanol (20ml)-benzene (80ml). Recrystallisation from methanol-ether gave <u>nitrone</u> (<u>16</u>) (3.9g, 71%) as a pale orange crystalline solid, m.p. 192-195°C.
IR (KBr disc) 3500-2500, 1600, 1510, 1451, 1415, 1379, 1315, 1285, 1250, 1220, 1170, 1135, 940, 860, 840, 760, 700 cm^{-1}.
^{1}H NMR (CD_3OD) δ5.03 (s,2H), 6.85 (d J = 9Hz,2H), 7.3 - 7.6 (m,5H), 7.85 (s,1H), 8.14 (d J = 9Hz,2H).
^{13}C NMR (25.2MHz, CD_3OD) δ70.55 (Ph<u>CH</u>$_2$), 116.45 (<u>CH</u> = $\overset{+}{N}$), 122.84 (<u>Ar</u>), 129.8 (<u>Ar</u>-H), 130.06 (<u>Ar</u>-H), 133.16 (<u>Ar</u>-H), 135.31 (<u>Ar</u>), 139.65 (<u>Ar</u>-H), 162.05 (<u>Ar</u>).
$[M]^+$ 227.0943. $C_{14}H_{13}O_2$ requires 227.0946.
[Found C 74.0, H 5.75, N 5.7; $C_{14}H_{13}NO_2$ requires C 74.0, H 5.75, N 6.15%].

(R)-(+)-α-Methylbenzylhydroxylamine oxalate (22).

A mixture of anhydrous $MgSO_4$, (R)-(+)-α-methylbenzylamine (20g, 0.165 mol) and p-methoxybenzaldehyde (22ml, 0.18 mol) in dichloromethane (200ml) was stirred under argon at room temperature overnight. The mixture was then filtered through a pad of $MgSO_4$ washing with dichloromethane (100ml). The filtrate was cooled to 0°C under argon and m-chloroperbenzoic acid (41.6g, 0.24 mol) slurried in dichloromethane (100ml) was added. The resulting mixture was stirred at 0°C for 1.5h and at room temperature for 2.5h. The mixture was then filtered and the solid washed with dichloromethane (100ml). The filtrate was washed successively with 0.5M Na_2SO_3 (100ml), 0.5M K_2CO_3 (100ml) and H_2O (50ml), and the organic layer dried over Na_2SO_4, filtered and evaporated in vacuo. The residual oil was dissolved in absolute ethanol (100ml) and cooled to 0°C. With stirring the solution was treated with hydroxylamine hydrochloride (15.2g, 0.22 mol) and the mixture stirred overnight under argon, the cooling bath being allowed to warm to room temperature. Chloroform (100ml) was added to precipitate excess hydroxylamine hydrochloride, and after stirring for a further 2h the mixture was filtered and the solvents removed in vacuo. The residue was taken up in water (100ml) and extracted with diethyl ether (2 x 100ml). The aqueous phase was treated with saturated $NaHCO_3$ solution (50ml) and extracted with diethyl

ether (4 x 50ml). The combined extracts were dried over Na_2SO_4 and filtered into a flask containing oxalic acid (18.8g, 0.21 mol) dissolved in diethyl ether (150ml). The oxalate salt precipitated immediately, was filtered and recrystallised from methanol-ethanol to give oxalate (22) (18.1g, 48%) as a colourless crystalline solid, m.p. 179 - 183°C (Lit.[78] m.p. 177 - 180°C for (S)-oxalate).
^{1}H NMR (CD_3OD) δ1.68 (d J = 6.8Hz,3H), 4.55 (q J = 6.8Hz,1H), 7.46 (m,5H).

(R)-(+)-α-Carbomethoxybenzylhydroxylamine oxalate (25).

To a solution of thionyl chloride (16ml) in methanol (200ml) at 0°C was added (S)-α-phenylglycine (21.3g, 0.14 mol) portionwise over a period of 10 min. The mixture was then allowed to warm to room temperature and was heated at 60°C for 2h. The solvent was removed in vacuo and the remaining solid heated at 100°C in vacuo (water aspirator) for 1h, to give hydrochloride (24) in quantitative yield as a colourless crystalline solid, m.p. 216 - 217°C.
^{1}H NMR ($CDCl_3$) δ3.82 (s,3H), 5.25 (s,1H), 7.5 (s,5H).

A mixture of hydrochloride (24) (28g, 0.14 mol), anhydrous $MgSO_4$ (40g) and triethylamine (15.4g, 0.15 mol) in dichloromethane (300ml) was stirred at room temperature under argon overnight. The mixture was then filtered through a pad of $MgSO_4$ washing with dichloromethane (100ml). The

filtrate was cooled to 0°C under argon and m-chloroperbenzoic acid (32.5g, 0.19 mol) slurried in dichloromethane (100ml) was added. The resulting mixture was stirred at 0°C for 1.5h and at room temperature for 2.5h. The mixture was then filtered, and the solid washed with dichloromethane (50ml). The filtrate was washed with 0.5M Na_2SO_3 (100ml), 0.5M K_2CO_3 (100ml) and H_2O (50ml), and the organic layer dried over Na_2SO_4, filtered and evaporated *in vacuo*. The residual oil was dissolved in absolute ethanol (100ml) and cooled to 0°C. With stirring, the solution was treated with hydroxylamine hydrochloride (12g, 0.17 mol) and the mixture stirred overnight under argon, the cooling bath being allowed to warm to room temperature.

Work-up as described for oxalate (22) (14.6g oxalic acid; recrystallisation from methanol-ethanol) afforded *oxalate* (25) (6.1g, 16%) as a colourless crystalline solid m.p. 188-190°C $[\alpha]_D$ + 1.6 (c0.81, MeOH).
IR (KBr disc) 3500-2500, 1790, 1620, 1515, 1455, 1440, 1400, 1230, 1200, 720, 700 cm^{-1}.
^1H NMR (CD_3OD) δ3.81 (s,3H), 5.2 (s,1H), 7.49 (s,5H).
^{13}C NMR (25.2MHz, $(CD_3)_2SO$) δ52.98 ($CO_2\underline{Me}$), 55.73 (Ph$\underline{CH}$), 128.12 (*Ar*-H), 128.98 (*Ar*-H), 129.34 (*Ar*-H), 133.45 (*Ar*), 164.57 ($\underline{CO}_2H$), 169.38 ($\underline{CO}_2Me$). [Found C 49.5, 51.5, H 5.0, 5.3, N 6.95, 5.5; $C_{11}H_{13}NO_7$ requires C 49, H 4.86, N 5.15].

p-Benzoxybenzaldehyde (27).

To a stirred suspension of sodium hydride (1.1g, 45.8mmol) in dry DMF (100ml) was added a solution of p-hydroxybenzaldehyde (5g, 41mmol) in DMF (30ml) over a period of 10 minutes, followed by benzylbromide (7g, 41mmol). The resulting mixture was heated at 100°C for 3h, allowed to cool and poured into water (50ml). This mixture was extracted with dichloromethane (2 x 100ml), the organic layers combined and washed with water (4 x 50ml), dried over $MgSO_4$, filtered and evaporated *in vacuo*. The residue was purified by column chromatography (silica gel, ethylacetate-hexane, 2:3) to give aldehyde (27) (7.1g, 82%) as a colourless crystalline solid, m.p. 74 - 75°C.
TLC. Rf 0.6 (silica gel, ethylacetate-hexane 2:3).
IR ($CHCl_3$) 1685, 1600, 1568, 1506, 1450, 1429, 1379, 1311, 1256, 1225, 1155, 1106, 1009, 915, 860, 829, 698 cm^{-1}.
^1H NMR ($CDCl_3$) δ5.06 (s,2H), 7.0 (d J = 9.2Hz,2H), 7.2 - 7.5 (m,5H), 7.85 (d J = 9.2Hz,2H), 9.78 (s,1H).
$[M]^+$ 212.0840 $C_{14}H_{12}O_2$ requires 212.0837. [Found C 79.0, H 5.8; $C_{14}H_{12}O_2$ requires C 79.2, H 5.7%].

General Preparation of N-(R)-α-methylbenzylnitrones (28-31).

A mixture of (R)-(+)-α-methylbenzylhydroxylamine oxalate (22) and the appropriate aldehyde (1 equiv) in benzene or methanol-benzene was treated with triethylamine (1.1 equiv) and heated at reflux for approximately 4h.

The solvent was removed in vacuo, the residue taken up in chloroform and washed with water. The organic layer was separated, dried over anhydrous Na_2SO_4, filtered and evaporated in vacuo to give crude nitrone which was purified either by recrystallisation or column chromatography.

R-(-)-C-Phenyl-N-α-methylbenzylnitrone (28).

From oxalate (22) (3g, 13.2mmol) benzaldehyde (1.4g, 13.2mmol) and triethylamine (1.47g, 14.5mmol) in benzene (100ml) to give a residue which was purified by column chromatography (silica gel, ether-hexane 1:1) to give nitrone (28) (2.8g, 94%) as a light yellow oil.[49]
TLC Rf 0.41 (silica gel, ether-hexane 1:1).
^{1}H NMR ($CDCl_3$) δ1.86 (d J = 6.5Hz,3H), 5.21 (q J = 6.5Hz,1H), 7.25-7.6 (m,9H), 8.1-8.3 (m,2H).

(R)-(-)-C-p-Methoxyphenyl-N-α-methylbenzylnitrone (29).

From oxalate (22) (3g, 13.2mmol), p-methoxybenzaldehyde (1.7g, 13.2mmol) and triethylamine (1.47g, 14.5mmol) in benzene (100ml) to give nitrone (29) (2.6g, 77%) as pale yellow crystals from hexane-ether, m.p. 96-97°C (Lit.[49] 97°C).
^{1}H NMR ($CDCl_3$) δ1.86 (d J = 6.5Hz,3H), 3.79 (s,3H), 5.14 (q J = 6.5Hz,1H), 6.9 (d J = 8.2Hz,2H), 7.2-7.6 (m,5H), 8.22 (d J = 8.2Hz,2H).

(R)-(-)-C-p-Hydroxyphenyl-N-α-methylbenzylnitrone (30).

From oxalate (22) (2.5g, 11 mmol), p-hydroxybenzaldehyde (1.34g, 11 mmol) and triethylamine (1.22g, 12.1 mmol) in methanol (20ml)-benzene (80ml) to give nitrone (30) (1.8g, 68%) as pale orange crystals from methanol-ether, m.p. 178 - 180°C $[\alpha]_D$ - 51.9° (c1.7, MeOH).

IR (KBr disc) 3500-2200, 1602, 1575, 1509, 1451, 1381, 1315, 1285, 1245, 1169, 1135, 1055, 905, 835, 701 cm^{-1}.

^1H NMR (CD_3OD) δ1.86 (d J = 6.4Hz,3H), 5.35 (q J = 6.4Hz,1H), 6.9 (d J = 8.4Hz,2H), 7.3-7.65 (m,5H), 7.92 (s,1H), 8.2 (d J = 8.4Hz,2H).

^{13}C NMR (25.2MHz, CD_3OD) δ19.49 ($PhCH\underline{C}H_3$), 75.3 ($Ph\underline{C}H$), 117.07 ($\underline{C}H = \overset{+}{N}$), 123.55 (Ar), 129.07 (Ar-H), 130.31 (Ar-H), 133.74 (Ar-H), 138.77 (Ar-H), 140.64 (Ar), 162.5 (Ar).

$[M]^+$ 241.1108. $C_{15}H_{15}NO_2$ requires 241.1103.

[Found C 74.55, H 6.25, N 5.8; $C_{15}H_{15}NO_2$ requires C 74.65, H 6.25, N 5.8%].

(R)-(-)-C-p-Benzyloxyphenyl-N-α-methylbenzylnitrone (31).

From oxalate (22) (4.14g, 18.2mmol), p-benzyloxybenzaldehyde (3.87g, 18.2mmol) and triethylamine (2.03g, 20.1mmol) in benzene (100ml) to give nitrone (31) (4.9g, 81%) as a colourless crystalline solid from dichloromethane-hexane, m.p. 115 - 116°C $[\alpha]_D$ -51.98° (c1.56, $CHCl_3$).

IR ($CHCl_3$) 1601, 1566, 1502, 1450, 1325, 1331, 1305, 1250, 1165, 1135, 1020, 912, 840, 700 cm^{-1}.

^{1}H NMR ($CDCl_3$) δ1.85 (d J = 6.45Hz,3H), 5.07 (s,2H), 5.11 (q J = 6.45Hz, 1H), 6.95 (d J = 9Hz,2H), 7.2-7.6 (m,10H), 8.2 (d J = 9Hz,2H).

^{13}C NMR (25.2MHz,$CDCl_3$) δ19.01 ($PhCH\underline{C}H_3$), 69.87 ($O\underline{C}H_2$), 74.41 ($Ph\underline{C}H$), 114.58 ($\underline{C}H = \overset{+}{N}$), 123.76 (Ar), 128.51 (Ar-H), 130.51 (Ar-H), 132.5 (Ar-H), 136.37 (Ar), 138.68 (Ar), 159.99 (Ar).

$[M]^+$ 331.1584. $C_{22}H_{21}NO_2$ requires 331.1572 [Found C 79.75, H 6.4, N 4.2; $C_{22}H_{21}NO_2$ requires C 79.7, H 6.4, N 4.25%].

General Preparation of Nitrones (32) and (33)

A mixture of either oxalate (22) or oxalate (25) and isobutyraldehyde (1.5 equiv) in dichloromethane was treated with triethylamine (1.1 equiv) and stirred at room temperature under an argon atmosphere for 24h. The solvent was removed in vacuo, the residue taken up in chloroform and washed with water. The organic layer was separated, dried over anhydrous Na_2SO_4, filtered and evaporated to give nitrone (32) as a solid after crystallisation and nitrone (33) as an oil which was used without further purification.

(R)-(-)-C-Isopropyl-N-α-methylbenzylnitrone (32).

From oxalate (22) (2.3g, 10.1mmol), isobutyraldehyde (1.1g, 15.3mmol) and triethylamine (1.13g, 11.2mmol) in dichloromethane (50ml) to give nitrone (32) (1.7g, 88%) as

a colourless crystalline solid from ether-hexane, m.p. 57 - 58°C (Lit.[49] 58-59°C).

^{1}H NMR ($CDCl_3$) δ1.05 (d J = 7Hz,3H), 1.07 (d J = 7Hz,3H), 1.79 (d J = 6.5Hz,3H), 3.2 (m,1H), 4.97 (q J = 6.5Hz,1H), 6.55 (d J = 7Hz,1H), 7.25-7.7 (m,5H).

(R)-C-Isopropyl-N-α-carbomethoxybenzylnitrone (33).

From oxalate (25) (1.08g, 3.98mmol), isobutyraldehyde (0.43g, 5.98mmol) and triethylamine (0.44g, 4.38mmol) in dichloromethane (20ml) to give nitrone (33) (0.8g, 85%) as a light yellow oil.

IR ($CHCl_3$) 1755, 1651, 1600, 1501, 1461, 1441, 1410, 1230, 1175, 1110, 1021, 975, 701 cm^{-1}.

^{1}H NMR ($CDCl_3$) δ1.05 (m,6H), 3.18 (m,1H), 3.81 (s,3H), 5.65 (s,1H), 6.33 (d J = 7.9Hz,1H), 7.41 (s,5H).

$[M]^+$ 235.1211 $C_{13}H_{17}NO_3$ requires 235.1208.

(R)-2,3-O-Isopropylidene-glyceraldehyde (34).[81]

Zinc chloride (80g, 0.59 mol) was added to dry acetone (400ml) in a 500ml conical flask. The stoppered flask was swirled until the zinc chloride had dissolved (heat is evolved), leaving only a small amount of insoluble material. The zinc chloride-acetone solution was set aside to cool and to allow most of the insoluble material to settle out.

In a 2-L three-neck flask equipped with a mechanical

stirrer was placed finely powdered D-mannitol (50g, 0.27 mol), and the still slightly turbid zinc chloride-acetone solution was added by decantation, care being taken that most of the insoluble material remained behind. The mixture was stirred vigorously until the greater part of the mannitol had dissolved (approximately 2h). The solution was filtered to remove unreacted mannitol and the filtrate processed immediately as follows.

In a 3-L three-neck flask equipped with an efficient mechanical stirrer, a solution of potassium carbonate (100g) in water (100ml) was prepared and covered with diethyl ether (400ml). The mixture was stirred vigorously while the filtered acetone solution was added as rapidly as possible. The vigorous stirring was continued for a period of 30-40 minutes, after which the ether-acetone solution was decanted and the zinc carbonate pellets washed with several portions of a 1:1 acetone-ether mixture (totaling 200ml). The combined solutions were dried by stirring with anhydrous potassium carbonate (100g) for 30 minutes. The solution was filtered, and the carbonate washed with several portions of a 1:1 acetone-ether mixture (totaling 200ml). The combined filtrates and washings were evaporated <u>in vacuo</u>, and the residue thoroughly dried <u>in vacuo</u> at 70°C for 2 hours.

The solid residue was dissolved in hot n-butyl ether (120ml) and filtered rapidly on a hot sinter-funnel, a 50ml portion of hot butyl ether being used to rinse the flask and

funnel. The filtrate, which solidified immediately, was kept in the cold for 2 hours. The precipitate was then filtered with suction, washed on a filter funnel with low boiling petroleum ether (40-60°C), and dried *in vacuo* to give 1,2:5,6-di-O-isopropylidene-D-mannitol (25g, 35%) as a colourless crystalline solid, m.p. 120-122°C (Lit.[80] m.p. 117-119°C).

To a solution of 1,2:5,6-di-O-isopropylidene-D-mannitol (10g, 38.2mmol) in sodium dried benzene (100ml) was added fresh lead tetraacetate (Aldrich, 20g, 45.1mmol), slowly with stirring. After stirring for 3h at room temperature the mixture was filtered, and the filtrate was evaporated *in vacuo* below 25°C to give a syrup from which four 20ml quantities of carbon tetrachloride were evaporated, again the temperature kept below 25°C. The syrup was then distilled *in vacuo* to give (R)-2,3-O-isopropylidene glyceraldehyde (34) (7.2g, 73%) as a colourless liquid, b.p. 95°C (water aspirator) (Lit.[81] b.p. 31°C at 5mm Hg).

^{1}H NMR ($CDCl_3$) δ1.42 (s,3H), 1.49 (s,3H), 4.15 (m,2H), 4.28 (m,1H), 9.69 (d J = 1.9Hz,1H).

(R)-(+)-C-2,3-O-Isopropylidene glyceraldehydo-N-benzylnitrone (35)

To a cooled(0°C) mixture of N-benzylhydroxylamine (4.9g, 40mmol) and $CaCl_2$ (2g) in sodium dried either (50ml) was added an ethereal solution (10ml) of freshly distilled aldehyde (34) (5.2g, 40mmol) and the resulting mixture stirred

at 0°C under argon for 3h. The mixture was filtered and the filtrate evaporated in vacuo to give a residue which was purified by column chromatography (silica gel, 8% methanol-ethylacetate) to give nitrone (35) (5.9g, 63%) as a colourless crystalline solid, m.p. 89-90°C $[\alpha]_D$ + 132.4° (c1.84, $CHCl_3$).[79]
TLC Rf 0.5 (silica gel, 8% methanol-ethylacetate).
IR ($CHCl_3$) 1600, 1491, 1380, 1371, 1225, 1140, 1060, 840 700 cm^{-1}.
^1H NMR (200 MHz, $CDCl_3$) δ1.33 (s,3H), 1.36 (s,3H), 3.84 (dd J = 5.8, 8.7Hz,1H), 4.35 (dd J = 7.02, 8.7Hz,1H), 4.83 (s,2H), 5.12 (m,1H), 6.82 (d J = 4.7Hz,1H), 7.36 (s,5H).
^{13}C NMR (50MHz, $CDCl_3$) δ24.79 ($\underline{C}H_3$), 26.1($\underline{C}H_3$), 67.73 ($\underline{C}H_2O$), 68.86 ($Ph\underline{C}H_2$), 71.9 ($\underline{C}HO$), 109.27 ($\underline{C}(Me)_2$), 128.94 ($\underline{Ar}$-H), 129.1 ($\underline{Ar}$-H), 129.29 ($\underline{Ar}$-H), 132.06 ($\underline{Ar}$), 138.99 ($\underline{C}H = N$).
$[M-CH_3]^+$ 220.0977. $C_{12}H_{14}NO_3$ requires 220.0974.
[Found C 66.3, H 7.2, N 5.9; $C_{13}H_{17}NO_3$ requires C 66.35, H 7.3, N 5.95%]
Note - No spectroscopic, analytical or physical data given in Ref. 79.

(R)-(+)-2,3-O-Isopropylidene glyceraldehydo-N-(R)-α-methylbenzylnitrone (36).

To a cooled (0°C) mixture of oxalate (22) (6.5g, 28.6mmol), $CaCl_2$ (2g) and triethylamine (3.2g, 31.9mmol) in sodium dried diethyl ether (100ml) was added an ethereal solution (10ml) of freshly distilled aldehyde 34 (3.72g, 28.6mmol) and the resulting mixture stirred at 0°C under

argon for 3h. The mixture was filtered and the ethereal solution washed with water (50ml), dried over anhydrous Na_2SO_4, filtered and evaporated *in vacuo* to give a residue which was purified by column chromatography (silica gel, ethyl acetate-hexane 4:1) to give nitrone (36) (5.1g, 72%) as a pale yellow crystalline solid, m.p. 54-55°C $[\alpha]_D$ + 127.4° (c4.0, $CHCl_3$).[113]

TLC Rf 0.53 (silica gel, ethyl acetate).

IR ($CHCl_3$) 1595, 1491, 1450, 1381, 1372, 1250, 1140, 1061, 840, 701 cm^{-1}.

^1H NMR (200MHz, $CDCl_3$) δ1.26 (s,3H), 1.3 (s,3H), 1.65 (d J = 6.9Hz,3H), 3.68 (dd J = 5.9, 8.7Hz,1H), 4.27 (dd J = 7.1,8.7,1H) 4.92 (q J = 6.9Hz,1H), 5.05 (m,1H), 6.86 (d J=4.7Hz,1H), 7.2-7.5(m,5H

^{13}C NMR (50MHz, $CDCl_3$) δ18.8 ($PhCH\underline{C}H_3$), 24.73 ($\underline{C}H_3$), 26.07 ($\underline{C}H_3$), 67.78 ($\underline{C}H_2O$), 71.84 ($\underline{C}HO$), 73.03 ($Ph\underline{C}H$), 109.61 ($\underline{C}(Me)_2$), 127.07 ($\underline{Ar}$-H), 128.72 ($\underline{Ar}$-H), 137.41 ($\underline{C}H = \overset{+}{N}$), 137.63 ($\underline{Ar}$).

$[M]^+$ 249.1362. $C_{14}H_{19}NO_3$ requires 249.1365.

[Found C 76.5, H 7.6, N 5.7; $C_{14}H_{19}NO_3$ requires C 67.45, H 7.7 N 5.6%]

Note: No spectroscopic, analytical or physical data given in Ref. 114.

1,3-Dipolar Cycloaddition Reactions of Nitrones with Diethyl Methylidenemalonate, Diethyl Ethylidenemalonate and Ethyl Crotonate.

Diethyl methylidenemalonate (41)

A mixture of diethyl malonate (40g, 0.25 mol),

paraformaldehyde (15g), copper acetate (2.5g) and potassium acetate (2.5g) in glacial acetic acid (100ml) was refluxed for 3h. The glacial acetic acid was distilled from the reaction flask (water aspirator) and the residue distilled at reduced pressure to afford diethyl methylidenemalonate (41) (15.2g, 35%) as a colourless liquid, b.p. 120-125°C at approximately 5mm Hg (Lit.[87] b.p. 230°C at 760 mm Hg).
^{1}H NMR ($CDCl_3$) δ1.3 (t J = 7.4Hz,6H), 4.29 (q J = 7.4Hz,4H), 6.49 (s,2H).

N-Phenyl-3-phenyl-4,4' and 5,5'-dicarboethoxylisoxazolidines (42) and (54).

C,N-Diphenylnitrone (1.8g, 9.14mmol) and freshly distilled diethyl methylidenemalonate (1.73g, 10.1mmol) were refluxed in analar toluene (30ml) under an argon atmosphere for 2h. The solvent was removed in vacuo and the residue chromatographed over silica gel (hexane-ethylacetate 4:1) to afford isoxazolidines (42) (2.31g, 6.2mmol) and (54) (0.44g, 1.2 mmol) in a relative ratio of 5:1 and in a combined yield of 82%. Both isoxazolidines were obtained as oils.

Isoxazolidine (42).

TLC Rf 0.7 (silica gel, hexane-ethylacetate, 1:1).
IR ($CHCl_3$) 1790, 1735, 1600, 1569, 1492, 1455, 1370, 1260, 1230, 1205, 1100, 1030, 700 cm^{-1}.
^{1}H NMR ($CDCl_3$) δ0.8 (t J = 7.6Hz,3H), 1.15 (t J = 7.6Hz,3H), 3.6 (m,2H), 4.16 (m,2H), 4.45 (d J = 10Hz,1H), 4.[illegible] (d J = 10Hz,

1H), 5.56 (s,1H), 6.9-7.7 (m,10H).

^{13}C NMR (25.2MHz, $CDCl_3$) δ13.39 ($CO_2CH_2\underline{C}H_3$), 13.88 ($CO_2CH_2\underline{C}H_3$), 61.71 ($CO_2\underline{C}H_2CH_3$), 62.34 ($CO_2\underline{C}H_2CH_3$), 71.53 ($\underline{C}(CO_2Et)_2$), 72.25 ($\underline{C}H_2O$), 73.78 (Ph$\underline{C}$H), 115.95 ($\underline{Ar}$-H), 122.52 ($\underline{Ar}$-H), 128.28 ($\underline{Ar}$-H), 128.7 ($\underline{Ar}$-H), 149.65 ($\underline{Ar}$), 166.68 ($\underline{C}O_2Et$), 169.04 ($\underline{C}O_2Et$).

$[M]^+$ 369.1583. $C_{21}H_{23}NO_5$ requires 369.1576.

Isoxazolidine (54).

TLC Rf 0.5 (silica gel, hexane-ethyl acetate 1:1).

IR ($CHCl_3$) 1743, 1600, 1491, 1455, 1370, 1301, 1250, 1190, 1096, 1065, 915, 860, 700 cm^{-1}.

^1H NMR ($CDCl_3$) δ1.2 (t J = 7.8Hz,6H), 2.99 (dd J = 7.9, 13.8Hz, 1H), 3.34 (dd J = 7.9, 13.8Hz,1H), 4.21 (m,4H), 4.65 (t J = 7.9Hz,1H), 6.9-7.6 (m,10H).

^{13}C NMR (25.2MHz, $CDCl_3$) δ18.89 ($CO_2CH_2\underline{C}H_3$), 46.21 (PhCH$\underline{C}H_2$), 62.23 ($CO_2\underline{C}H_2CH_3$), 62.33 ($CO_2\underline{C}H_2CH_3$), 69.68 (Ph$\underline{C}$H), 84.84 ($\underline{C}(CO_2Et)_2$), 117.14 ($\underline{Ar}$-H), 123.33 ($\underline{Ar}$-H), 127.1 ($\underline{Ar}$-H), 127.95 ($\underline{Ar}$-H), 128.45 ($\underline{Ar}$-H), 128.78 ($\underline{Ar}$-H), 139.27 ($\underline{Ar}$), 149.67 ($\underline{Ar}$-H), 167.64 ($\underline{C}O_2Et$), 167.95 ($\underline{C}O_2Et$).

$[M]^+$ 369.1572. $C_{21}H_{23}NO_5$ requires 369.1576.

This cycloaddition reaction was also carried out for periods of 4 and 16h, with isoxazolidines (42) and (54) being isolated after chromatography in the relative ratios shown in Table 1 in Chapter 2.

Attempted hydrogenolysis of 3-phenyl-4,4'-di-carboethoxy-isoxazolidine (42).

Isoxazolidine (42) (1.91g, 5.2mmol) was dissolved in absolute ethanol (30ml), containing palladium on charcoal (20%; 0.2g) and hydrogenated at atmospheric pressure and room temperature until hydrogen uptake was complete (approximately 1.8 equiv. of hydrogen absorbed). The catalyst was removed by filtration through a pad of Celite, and was washed with ethanol (50ml). The combined filtrate was evaporated *in vacuo* and the residue (1.75g) chromatographed over silica gel (hexane-ethylacetate, 3:2).

Least polar material.

TLC Rf range 0.5-0.7 (silica gel, hexane-ethylacetate 3:2), from which was isolated N-phenylbenzylamine (0.3g, 1.6mmol).

TLC Rf 0.5 (silica gel, hexane-ethylacetate, 2:3).

^{1}H NMR ($CDCl_3$) δ4.3 (s,2H), 6.5-7.5 (m,10H).

$[M]^+$ 183.1032. $C_{13}H_{13}N$ requires 183.1048.

More polar material (0.8g).

TLC Rf range 0.2-0.4

IR ($CHCl_3$) 1730, 1603, 1510, 1370, 1235, 1160, 1098, 1025 cm^{-1}.

^{1}H NMR ($CDCl_3$) δ1.2 (t J = 7.8Hz,6H), 2.9 (broad s,1H), 4.1 (m,2H), 4.15 (q J = 7.8Hz,4H). This spectrum also shows weak aromatic signals in the region δ7.2 - δ7.5.

Accurate mass analysis.

Table 10.

Ion.	Measured m/e	Calculated m/e	%Int.
$C_{16}H_{26}O_2$	346.1616	346.1627	0.4
$C_8H_{13}O_4$	173.0816	173.0814	100%
$C_{18}H_{13}O_4$	174.0862	174.0862	14%

The same result was observed when platinum oxide on charcoal and Raney nickel were used as catalysts. When the hydrogenation was stopped after the absorption of 1 equivalent of hydrogen, the same complicated mixture of products was observed in addition to some unchanged starting isoxazolidine.

Hydrogenolysis of isoxazolidine (54).

Isoxazolidine (54) (0.44g, 1.2mmol) was dissolved in absolute ethanol (20ml) containing palladium on charcoal (20%;40mg) and hydrogenated at atmospheric pressure and room temperature until hydrogen uptake was complete (1.1 equiv). The catalyst was removed by filtration through a pad of Celite, and was washed with ethanol (50ml). The combined filtrate was evaporated *in vacuo* and the residue chromatographed over silica gel (petroleum ether (40/60°) - ethyl acetate, 3:2) to give aminol (67) (0.34g, 77%) as a colourless oil.

TLC Rf 0.73 (silica gel, pet. ether (60/40) - ethyl acetate 3:2).

IR ($CHCl_3$) 3500-3400, 1740, 1601, 1510, 1455, 1370, 1300-1230, 1195, 1135, 1029, 915, 860, 701 cm^{-1}.

^1H NMR ($CDCl_3$) δ1.18 (t J = 7.8Hz,6H), 2.55 (d J = 6.9Hz,2H), 4.15 (m,4H), 4.35 (broad s, D_2O exchangeable,2H), 4.68 (t J = 6.9Hz,1H), 6.4-7.4 (m,10H).

$[M]^+$ 371.1737. $C_{21}H_{25}NO_5$ requires 371.1733.

N-Phenyl-3-phenyl-4-carboethoxyl-5-methyl-isoxazolidine (69)

C,N-Diphenylnitrone (1g, 5.1mmol) was refluxed in ethyl crotonate (15ml) overnight under an argon atmosphere. Excess ethyl crotonate was distilled out under reduced pressure and the residue chromatographed over silica gel (hexane - ethyl acetate, 1:1) to afford isoxazolidine (69) (1.5g, 95%) as a light orange oil.[90]

TLC Rf 0.75 (silica gel, hexane - ethyl acetate, 1:1).

IR ($CHCl_3$) 1730, 1600, 1490, 1455, 1369, 1225, 1190, 1140, 1030, 700 cm^{-1}.

^1H NMR ($CDCl_3$) δ1.18 (t J = 7.6Hz,3H), 1.48 (d J = 5.9Hz,3H), 3.15 (dd $J_{3,4}$ 7.8Hz, $J_{4,5}$ 9Hz,1H), 4.15 (q J = 7.6Hz,2H), 4.4 (m,1H), 5.15 (d J = 7.8Hz,1H), 6.9-7.6 (m,10H).

$[M]^+$ 311.1514. $C_{19}H_{21}NO_3$ requires 311.1521.

Preparation of Raney Nickel.[119]

Sodium hydroxide (100g) was dissolved in distilled

water (400ml) and stirred mechanically. The beaker was cooled in an ice bath, and then nickel-aluminium catalyst powder (75g) was added in small portions so as to keep the temperature of the mixture below 25°C. When all the alloy had been added the stirrer was removed and the beaker heated at 100°C until hydrogen evolution became slow (6h), adding distilled water as required to maintain the volume. The beaker was then cooled and the contents allowed to settle. The supernatant liquid was decanted, distilled water added up to the original volume, the nickel stirred, allowed to settle and decanted again. The catalyst was then washed into another beaker (500ml) and the water decanted. Sodium hydroxide solution (10%, 100ml) was added, the nickel stirred for a few minutes, allowed to settle and the alkali decanted. More distilled water was added (250ml) and the nickel stirred continuously for 5 minutes, allowed to settle and decanted. This procedure was repeated until the water wash was neutral to litmus paper. The catalyst was washed by decantation with 95% ethanol (3 x 100ml) and absolute ethanol (3 x 100ml), and stored in a glass jar which is full to the top with absolute ethanol and kept in a refrigerator.

Hydrogenolysis of isoxazolidine (69)

To isoxazolidine (69) (0.36g, 1.16mmol) dissolved in absolute ethanol (20ml) was added Raney nickel (approximately 0.1g). Isoxazolidine (69) was then

hydrogenated at room temperature and atmospheric pressure overnight (1.1 equiv. hydrogen absorbed). The ethanol solution was decanted, the catalyst washed with absolute ethanol (3 x 20ml), and the combined washings filtered through a pad of Celite and evaporated in vacuo to give aminol (70) (0.22g, 61%) as a colourless crystalline solid after trituration with diethyl ether, m.p. 133-134°C (Lit.[90] 134.5 - 135°C).

IR (KBr disc) 3460, 3380, 1705, 1605, 1515, 1545, 1380, 1310, 1285, 1240, 1195, 1120, 1020, 930, 750, 700 cm^{-1}.

^1H NMR (CD_3OD) δ0.94 (t J = 7.6Hz, 3H), 1.25 (d J = 6.2Hz,3H), 2.97 (dd J = 8, 9.2Hz,1H), 3.45 (q J = 7.6Hz,2H), 4.25 (m,1H), 4.71 (d J = 8Hz), 6.55-7.4 (m,10H).

$[M]^+$ 313.1679. $C_{19}H_{23}NO_3$ requires 313.1678.

General Preparation of Isoxazolidines (71) and (72).

The appropriate nitrone (10 or 28) was refluxed in excess ethyl crotonate for approximately 5h under an argon atmosphere. Unreacted ethyl crotonate was distilled out under reduced pressure and the residue chromatographed over silica gel to afford isoxazolidines (71) and (72) as oils.

N-Benzyl-3-phenyl-4-carboethoxyl-5-methylisoxazolidine (71).

From C-phenyl-N-benzylnitrone (1g, 4.74 mol) to afford isoxazolidine (71) (1.41g, 92%) as a light yellow

oil after chromatography (silica gel, hexane - ethyl acetate 1:1).

TLC Rf 0.55 (silica gel, hexane - ethyl acetate 1:1).

IR ($CHCl_3$) 1728, 1495, 1455, 1379, 1280, 1230, 1185, 1100, 1030, 910, 700 cm^{-1}.

NMR ($CDCl_3$) δ1.21 (t J = 7.6Hz,3H), 1.45 (d J = 6.2Hz,3H), 3.08 (t J = 7.8Hz,1H), 3.9-4.25 (m,4H), 4.3 (d J = 7.8Hz,1H), 4.55 (t J = 7Hz,1H), 7.1-7.5 (m,10H).

$[M]^+$ 325.1670. $C_{20}H_{23}NO_3$ requires 325.1678.

(R)-N-α-methylbenzyl-3-phenyl-4-carboethoxyl-5-methyl-isoxazolidine (72).

From (R)-(-)-C-phenyl-N-α-methylbenzyl nitrone (1.25g, 5.6mmol) to afford isoxazolidine (72) (1.54g, 82%) as a light yellow oil after chromatography (silica gel, hexane - ethyl acetate, 1:1).

TLC Rf 0.7 (silica gel, hexane - ethyl acetate, 1:1).

IR ($CHCl_3$) 1726, 1495, 1455, 1378, 1230, 1185, 1030, 905, 701 cm^{-1}.

^1H NMR ($CDCl_3$) δ1.1-1.5 (m,9H), 2.99 (dd J = 6.2,9Hz,1H), 4.15-4.7 (m,5H), 7.0-7.5 (m,5H).

$[M]^+$ 339.1836. $C_{21}H_{25}NO_3$ requires 339.1841.

General Procedure for Preparation of Isoxazolidines (73 - 77).

The appropriate nitrone (3,4 or 10) and freshly distilled diethyl methylidenemalonate (1.1 equiv) were

refluxed in toluene under an argon atmosphere for 16h. The solvent was removed in vacuo and the residue chromatographed over silica gel to afford isoxazolidines (73 - 77) as oils.

N-Benzyl-3-methyl-4,4' and 5,5'-dicarboethoxylisoxazolidines (73,75).

From C-methyl-N-benzylnitrone (1.14g, 7.65mmol) and freshly distilled diethyl methylidene malonate (1.45g, 8.4mmol) to afford isoxazolidines (73) (0.16g, 0.5mmol) and (75) (1.37g, 4.27mmol) in a relative ratio of 1:8.5 and in a combined yield of 62% after chromatography (silica gel, hexane - ethyl acetate, 4:1). Both isoxazolidines were obtained as oils.

Isoxazolidine (73)

TLC Rf 0.5 (silica gel, hexane - ethyl acetate 2:1).
IR ($CHCl_3$) 1731, 1455, 1370, 1270, 1110, 1020, 855, 700 cm^{-1}.
^1H NMR ($CDCl_3$) δ1.1-1.4 (m,9H), 3.3-4.6 (m,9H), 7.2-7.5 (m,10H).
$[M]^+$ 321.1569. $C_{17}H_{23}NO_5$ requires 321.1576.

Isoxazolidine (75).

TLC Rf 0.4 (silica gel, hexane - ethyl acetate, 2:1).
IR ($CHCl_3$) 1741, 1455, 1370, 1301, 1275, 1240, 1200, 1140, 1108, 905, 860 cm^{-1}.
^1H NMR ($CDCl_3$) δ1.1-1.35 (m,9H), 2.5-3.2 (m,3H), 4.09 (s,2H), 4.25 (m,4H), 7.2-7.5 (m,5H).

^{13}C NMR (25.2MHz, $CDCl_3$) δ13.93 ($CO_2CH_2\underline{C}H_3$), 17.01 ($\underline{C}H_3CH$), 43.93 ($\underline{C}H_2O$), 59.75 ($CH_3\underline{C}H$), 60.76 ($Ph\underline{C}H_2$), 61.84 ($CO_2\underline{C}H_2CH_3$), 62.03 ($CO_2\underline{C}H_2CH_3$), 84.22 ($\underline{C}(CO_2Et)_2$), 127.03 (Ar-H), 128.09 (Ar-H), 128.64 (Ar-H), 137.16 (Ar), 168.34 ($\underline{C}O_2Et$), 169.15 ($\underline{C}O_2Et$).

$[M]^+$ 321.1571. $C_{17}H_{23}NO_5$ requires 321.1576.

N-Benzyl-3-phenyl-4,4' and 5,5'-dicarboethoxyl-isoxazolidines (74,77).

From C-phenyl-N-benzylnitrone (1.41g, 7.1mmol) and freshly distilled diethyl methylidenemalonate (1.26g, 7.35mmol) to afford isoxazolidines (74) (0.23g, 0.6mmol) and (77) (1.64g, 4.3mmol) in a relative ratio of 1:7 and in a combined yield of 73% after chromatography (silica gel, hexane - ethyl acetate 4:1). Both isoxazolidines were obtained as oils.

Isoxazolidine (74).

TLC Rf 0.75 (silica gel, hexane - ethyl acetate 1:1).

IR ($CHCl_3$) 1729, 1495, 1455, 1370, 1270, 1230, 1200, 1100, 1041, 905, 860, 700 cm^{-1}.

^1H NMR ($CDCl_3$) δ0.71 (t J = 7.8H,3H), 1.24 (t J = 7.8Hz,3H), 3.4-3.7 (m,2H), 3.9 (d J = 12Hz,2H), 4.25 (m,2H), 4.39 (s,1H), 4.75 (s,2H), 7.1-7.7 (m,10H).

$[M]^+$ 383.1739. $C_{22}H_{25}NO_5$ requires 383.1733.

Isoxazolidine (74).

TLC Rf 0.67 (silica gel, hexane - ethyl acetate 1:1).

IR ($CHCl_3$) 1740, 1495, 1455, 1370, 1300, 1260, 1189, 1095, 1030, 905, 860, 700 cm^{-1}.

^1H NMR (200MHz, $CDCl_3$) δ1.25 (t J = 7.13Hz,3H), 1.27 (t J = 7.13Hz,3H), 3.03 (dd J = 8.9, 13Hz,1H), 3.12 (dd J = 7.7, 13Hz,1H), 3.85-4.1 (m,3H), 4.15-4.4 (m,4H), 7.1-7.5 (m,10H).

^{13}C NMR (25.2MHz, $CDCl_3$) δ13.92 ($CO_2CH_2\underline{C}H_3$), 45.76 ($\underline{C}H_2O$), 58.9 ($Ph\underline{C}H_2$), 61.89 ($CO_2\underline{C}H_2CH_3$), 62.14 ($CO_2\underline{C}H_2CH_3$), 69.74 ($Ph\underline{C}H$), 84.29 ($\underline{C}(CO_2Et)_2$), 126.91 (Ar-H), 127.92 (Ar-H), 128.15 (Ar-H), 128.43 (Ar-H), 128.7 (Ar-H), 137.1 (Ar), 137.69 (Ar), 167.74 ($\underline{C}O_2Et$), 169.11 ($\underline{C}O_2Et$).

$[M]^+$ 383.1723. $C_{22}H_{22}NO_5$ requires 383.1733.

N-Benzyl-3-isopropyl-5,5'-dicarboethoxylisoxazolidine (76).

From C-isopropyl-N-benzylnitrone (1g, 5.6mmol) and freshly distilled diethyl methylidenemalonate (1.1g, 6.4 mmol) to afford isoxazolidine (76) (1.31g, 66%) as a colourless oil after chromatography (silica gel, 10% ethyl acetate - hexane).

TLC Rf 0.43 (silica gel, 30% ethyl acetate - hexane).

IR ($CHCl_3$) 1741, 1498, 1465, 1390, 1370, 1300, 1265, 1209, 1115, 1050, 910, 860, 700 cm^{-1}.

^1H NMR ($CDCl_3$) δ0.85 (d J = 2.4Hz,3H), 0.91 (d J = 2.4,3H), 1.25 (t J = 7.8Hz,3H), 1.7 (m,1H), 2.85(broad s,3H), 4.05 (AB q J = 13Hz,2H), 4.25 (q J = 7.8Hz,4H), 7.2-7.5 (m,5H).

Diethyl ethylidenemalonate (48)

In a 100ml three-necked flask equipped with a thermometer and a reflux condenser, were placed paraldehyde (12g, 0.09 mol, equivalent to 0.27 mol of acetaldehyde) and acetic anhydride (20ml, 0.2 mol). The temperature of the mixture was raised to 125°C, at which point diethyl malonate (20g, 0.12 mol) was added portionwise over 10 minutes. During the addition of diethylmalonate the temperature dropped to about 100°C, and the mixture was heated so as to maintain a reflux rate of 30-60 drops per minute. After the addition was complete, the reaction mixture was heated under reflux for 4 hours.

The reflux condenser was replaced by a Claisen distillation head, and the reaction mixture distilled until the vapour temperature reached 140°C. The residue was transferred to a smaller flask and fractionated through a 30cm column packed with glass balls to afford diethyl ethylidenemalonate (48) (10.1g, 43%) as a colourless liquid b.p. 100-106 at 10mm Hg (Lit.[92] b.p. 102-106 at 10 mm Hg). ^{1}H NMR ($CDCl_3$) δ1.38 (m,6H), 1.95 (d J = 7Hz,3H), 4.25 (m,4H), 7.09 (q J = 7Hz,1H).

General Preparation of Isoxazolidines (78 - 80).

The appropriate nitrone (3,4 or 10) and diethyl ethylidenemalonate 1.1 equiv.) were refluxed in dry benzene under an argon atmosphere for the specified length of time.

The solvent was removed in vacuo and the residue chromatographed over silica gel.

N-Phenyl-3-phenyl-4,4'-dicarboethoxyl-5-methylisoxazolidine (78).

From C,N-diphenylnitrone (0.53g, 2.7mmol) and diethyl ethylidenemalonate (0.55g, 2.96mmol) in benzene (20ml) for 3h to afford isoxazolidine (78) (0.86g, 83%) as a light yellow oil after chromatography (silica gel, pet.-ether (40/60) - ethyl acetate, 4:1).

TLC Rf 0.7 (silica gel, pet.ether - ethyl acetate, 4:1).

IR ($CHCl_3$) 1728, 1600, 1490, 1450, 1385, 1370, 1350, 1265, 1225, 1205, 1125, 1060, 1030, 790, 720, 700 cm^{-1}.

^1H NMR ($CDCl_3$) δ0.8 (t J = 7.4Hz,3H), 1.2 (t J = 7.4Hz,3H), 1.4 (d J = 7Hz,3H), 3.2-3.9 (m,2H), 4.24 (m,2H), 5.15 (q J = 7Hz,1H), 5.34 (s,1H), 6.9-7.6 (m,10H).

$[M]^+$ 383.1737. $C_{22}H_{25}NO_5$ requires 383.1733.

N-Benzyl-3-phenyl-4,4'-dicarboethoxyl-5-methylisoxazolidine (79)

From C-phenyl-N-benzylnitrone (0.65g, 3.1mmol) and diethyl ethylidenemalonate (0.63g, 3.4mmol) in benzene (20ml) for 16h to afford isoxazolidine (79) (0.74g, 61%) as a colourless crystalline solid after chromatography (silica gel, pet.ether (40/60)-ethyl acetate, 4:1), m.p. 94 - 95°C.

TLC Rf 0.7 (silica gel, pet.ether (40/60)-ethyl acetate, 4:1).

IR ($CHCl_3$) 1725, 1599, 1446, 1385, 1370, 1265, 1200, 1125, 1085, 1070, 1030, 925, 860, 701 cm^{-1}.

^1H NMR ($CDCl_3$) δ0.69 (t J = 7,4Hz,3H), 1.21 (m,6H), 3.2-3.8 (m,2H), 3.88 (d J = 7.8Hz,2H), 4.25 (m,2H), 4.81 (s,1H), 5.05 (q J = 6.4Hz,1H), 7.1-7.6 (m,10H).

[Found C 69.5, H 6.8, N 3.5; $C_{23}H_{27}NO_5$ requires C 69.5, H 6.85, N 3.5%]

(R)-N-α-methylbenzyl-3-phenyl-4,4'-dicarboethoxyl-5-methyl-isoxazolidine (80).

From (R)-(-)-C-phenyl-N-α-methyl-benzylnitrone (0.82g, 3.6mmol) and diethyl ethylidenemalonate (0.74g, 3.98mmol) in benzene (50ml) for 16h to afford isoxazolidine (80) (30mg, 2%) as a light yellow oil after column chromatography followed by preparative TLC (silica gel, hexane - ethyl acetate 3:2).

TLC Rf 0.85 (silica gel, hexane - ethyl acetate, 3.2).

IR ($CHCl_3$) 1726, 1495, 1458, 1375, 1265, 1225, 1205, 1120, 1090, 1030, 910, 701 cm^{-1}.

^1H NMR ($CDCl_3$) δ0.74 (t J = 7.8Hz,3H), 1.25 (m,6H), 3.2-3.8 (m,2H), 4.2 (m,2H), 4.76 (s,1H), 4.95 (q J = 6.8Hz,1H), 7.2-7.5 (m,10H).

$[M]^+$ 411.2048. $C_{24}H_{29}NO_5$ requires 411.2046.

Lithium aluminium hydride reduction of isoxazolidine (69).

To a stirred suspension of lithium aluminium hydride (0.11g, 3mmol) in sodium dried ether (30ml) at room temperature was added an ethereal solution (10ml) of isoxazolidine (69) (0.5g, 1.6mmol) dropwise over a period of 15 minutes. The mixture was then heated at reflux for 8h. The flask was allowed to cool, and then ethyl acetate (1ml) followed by water (5ml) was added to destroy excess hydride. The mixture was stirred at room temperature for 1h then filtered, the solid being washed with several portions of warm ethyl acetate (3 x 50ml). The filtrate was dried over anhydrous Na_2SO_4, filtered and evaporated *in vacuo*, the residue being chromatographed over silica gel (hexane - ethyl acetate, 3:2) to afford alcohol (81) (0.35g, 81%) as a colourless oil.

TLC Rf 0.45 (silica gel, hexane - ethyl acetate, 3:2).

IR ($CHCl_3$) 3600, 1600, 1490, 1455, 1230, 1075, 1030, 910, 700 cm^{-1}.

^1H NMR ($CDCl_3$) δ1.42 (d J = 6Hz,3H), 1.65 (broad s, D_2O exchangeable,1H), 2.4 (m,1H), 3.72 (d J = 6Hz,2H), 4.15 (m,1H), 4.5 (d J = 7Hz), 6.9-7.6 (m,10H).

$[M]^+$ 269.1413. $C_{17}H_{19}NO_2$ requires 269.1416.

Preparation of Meldrum's Acid

To a suspension of powdered malonic acid (26g, 0.25 mol) in acetic anhydride (30ml, 0.3 mol) was added with stirring, concentrated sulphuric acid (0.75ml). Most of

the malonic acid dissolved with spontaneous cooling. Acetone (20ml, 0.27 mol) was added to the resulting solution while cooling to maintain the temperature at 20-25°C. The reaction mixture was allowed to stand overnight in the refrigerator and the resulting crystals filtered and washed with ice water (3 x 100ml). Recrystallisation by dissolving the solid in acetone (30ml) filtering and adding water (50ml) afforded Meldrum's acid (11g, 30%) as a colourless crystalline solid, m.p. 93-94°C (Lit.[95] m.p. 94-95°C). IR ($CHCl_3$) 1755, 1395, 1305, 1220, 1080, 1010, 975, 840 cm^{-1}. ^1H NMR ($CDCl_3$) δ1.8 (s,6H), 3.65 (s,2H).

Isopropylidene-isopropylidenemalonate (82).

Meldrum's acid (3,5g, 24.3mmol), dry acetone (2ml, 27.2mmol) dry pyridine (5ml) and 4Å molecular sieves (0.4g) were stirred together at room temperature for 5 days. Pyridine was removed in vacuo, and the residue crystallised from diethyl ether. Recrystallisation from water-methanol afforded (82) (1.05g, 25%) as a crystalline solid, m.p. 72-74°C (Lit.[95] 74.5-76°C).
^1H NMR ($CDCl_3$) δ1.2 (s,6H), 2.5 (s,6H).

Ethylidene - isopropylidenemalonate (83).

To the sodium salt of Meldrum's acid (1.05g, 6.3mmol) in dry methanol (10ml) was added acetaldehyde (1ml) in methanol (5ml) dropwise over 5 minutes, and repeated 10 minutes later. The solvent was removed in vacuo, the

residue taken up in dichloromethane and acidified with 1M HCl. The organic layer was separated, dried over anhydrous Na_2SO_4, filtered and the solvent removed in vacuo to give (83) (0.65g, 61%) a colourless oil which was used without further purification.[95]

^1H NMR ($CDCl_3$) δ1.8 (s,6H), 2.48 (d J = 8Hz,3H), 8.0 (q J = 8Hz,1H).

General Preparation of Ethoxymethylidene- and Methoxymethylidene- isopropylidenemalonate (84,85).

Meldrum's acid was heated in neat triethyl or trimethyl orthoformate at 90°C for 3h. After cooling, compounds (84) and (85) were precipitated from the reaction mixtures by addition of petroleum ether (40/60), filtered and recrystallised.

Methoxymethylidene-isopropylidenemalonate (84).

From Meldrum's acid (4g, 27.8mmol) in trimethylorthoformate (10ml) to afford compound (84) (3.8g, 74%) after recrystallisation from chloroform-petroleum ether (40/60), m.p. 136-137°C (Lit.[95] m.p. 136-137°C).

^1H NMR ($CDCl_3$) δ1.7 (s,6H), 4.27 (s,3H), 8.12 (s,1H).

Ethoxymethylidene-isopropylidenemalonate (85).

From Meldrum's acid (1g, 6.9mmol) in triethylorthoformate (5ml) to afford compound (85) (0.69g, 49%)

after recrystallisation from chloroform-petroleum ether (40/60) m.p. 87-88°C (Lit.[95] m.p. 87-88°C).
^{1}H NMR ($CDCl_3$) δ1.45 (t J = 7Hz,3H), 1.7 (s,6H), 4.45 (q J = 7Hz,2H), 8.15 (s,1H).

1,3-Dipolar Cycloadditions Reactions of Nitrones to Ketene Acetals and the Synthesis of Chiral Ketene Acetals.

Pthalyl alcohol (93)

Pthalic anhydride (10g, 68mmol) was placed in the thimble of a Soxhlet extractor. This was attached to a 500ml three-necked flask containing lithium aluminium hydride (3g, 79mmol) in sodium dried diethyl ether (300ml) and the ether refluxed until extraction of the pthalic anhydride was complete (overnight). 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 (250ml) and extracted for 24h. Upon evaporation of the ether *in vacuo* a light yellow residue remained, which was triturated with several portions of light petroleum (40-60°C), to give alcohol (93) (5.9g, 64%) as a white crystalline solid, m.p. 65-66°C (Lit.[98] m.p. 64°C).
^{1}H NMR ($CDCl_3$) δ3.82 (s,D_2O exchangeable,2H), 4.6 (s,4H), 7.28 (s,4H).

Bromoacetaldehyde (o-xylyl)acetal (95).

Pthalyl alcohol (3.8g, 27mmol) and bromoacetaldehyde diethyl acetal 5.5g, 27mmol) were stirred together in a 50ml round bottomed flask in the presence of toluene-p-sulphonic acid (0.02g, 0.12mmol). 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 1h no more ethanol distilled. On cooling the residue solidified to a dark red-brown material, which was dissolved in benzene (100ml) and washed with sat. $NaHCO_3$ (100ml). The benzene layer was dried over anhydrous $MgSO_4$, filtered and evaporated *in vacuo*. The crude product was recrystallised from cyclohexane to give acetal (95) (5.1g, 76%) as a pale orange crystalline solid, m.p. 97-98°C (Lit.[98] m.p. 98°C) ^1H NMR ($CDCl_3$) δ3.46 (d J = 5.8Hz,2H), 4.92 (s,4H), 5.13 (t J = 5.8Hz,1H), 7.18-7.4 (m,10H).

(O-Xylyl)ketene acetal (91).

Bromoacetaldehyde-(O-xylyl)acetal (4.45g, 18mmol) was heated with potassium tert-butoxide (3.1g, 29mmol) in sodium-dried benzene at 80°C for 5h. Potassium bromide formed in the reaction was removed by filtration through a pad of Celite, this being washed with benzene (100ml), and the solvent removed from the filtrate *in vacuo*. The residue was purified by Kugelrohr distillation (0.2mm Hg)

to give ketene acetal (91) (2.47g, 85%) as a colourless crystalline solid, b.p. 140-143°C at 0.2mm Hg, m.p. 46-47°C (Lit.[98] m.p. 49°C).
^{1}H NMR ($CDCl_3$) δ3.7 (s,2H), 5.02 (s,4H), 6.98-7.4 (m,4H).

N-Phenyl-3-phenyl-5,5'-(di-O-xylyloxy)isoxazolidine (96).

C,N-Diphenylnitrone (1.3g, 6.6mmol) and ketene acetal (96) (2.2g, 13.5mmol) were refluxed in anhydrous toluene (50ml) under an argon atmosphere for 24h. Solvent was removed in vacuo and the residue chromatographed over silica gel (ether-hexane, 4:1) to afford isoxazolidine (96) (1.5g, 63%) as a colourless crystalline solid from ether, m.p. 130-131°C (Lit.[49] m.p. 127°C).
^{1}H NMR ($CDCl_3$) δ2.65 (dd J = 9,13Hz,1H), 3.02 (dd, J = 7, 13Hz,1H), 4.6-4.95 (m,4H), 5.25 (d J = 14Hz,2H), 6.9-7.6 (m,14H).
$[M]^+$ 359.1516. $C_{23}H_{21}NO_3$ requires 359.1521.

N-Phenyl-β-phenyl-β-alanine (97).

Isoxazolidine (96) (0.15g, 0.42mmol) was dissolved in ethyl acetate (40ml)-ethanol (10ml) containing palladium on charcoal (20%;40mg) at atmospheric pressure and room temperature until hydrogen uptake was complete (3 equiv,3h). The catalyst was removed by filtration through a pad of Celite, and washed with ethanol (20ml). The filtrate was evaporated in vacuo and the residue chromatographed over silica gel (hexane-ethylacetate, 2:3) to afford β-amino acid

(97) (80mg, 80%) as a crystalline solid after trituration with petroleum ether (40/60), m.p. 118-120°C.
TLC Rf 0.27 (silica gel, hexane-ethylacetate 2:3).
IR ($CHCl_3$) 3400-2500, 1709, 1601, 1501, 1450, 1420, 1315, 1265, 1225, 701 cm^{-1}.
^1H NMR ($CDCl_3$) δ2.86 (d J = 7Hz,2H), 4.88 (t J = 7Hz,1H), 6.5-7.4 (m,10H), 7.5 (broad s, D_2O exchangeable,2H).
^{13}C NMR (25.2MHz, $CDCl_3$) δ42.17 ($\underline{CH_2}CO_2H$), 55.3 (Ph$\underline{CH}$), 114.51 ($\underline{Ar}$-H), 118.74 ($\underline{Ar}$-H), 128.79 ($\underline{Ar}$-H), 129.15 ($\underline{Ar}$-H), 141.245 ($\underline{Ar}$), 145.81 ($\underline{Ar}$), 176.7 ($\underline{CO_2}H$).
$[M]^+$ 241.1103. $C_{15}H_{15}NO_2$ requires 241.1106.
[Found C 74.6, H 6.2, N 5.8; $C_{15}H_{15}NO_2$ requires C 74.65, H 6.25, N 5.8%].

Dimethyl-2,3-O-isopropylidene-L-tartarate (99).

A mixture of powdered L-(+)-tartaric acid (10.1g, 67mmol), 2,2-dimethoxypropane (16g, 0.15mol), methanol (4ml) and p-toluenesulphonic acid monohydrate (0.04g, 0.2mmol) was heated with stirring at 60°C in a flask equipped with a reflux condenser for 1.5h. To the dark red homogeneous solution was added additional 2,2-dimethoxypropane (8g, 77mmol) and cyclohexane (45ml). The resulting two-layer solution was refluxed with stirring while the acetone-cyclohexane (observed b.p. 53°C) and the methanol-cyclohexane (observed b.p. 55°C) azetropes were slowly removed at the head of a 30cm Vigreux column. After 4h when the vapour temperature had reached 79°C, the flask was cooled

and anhydrous K_2CO_3 was added to neutralise the catalyst. The remaining solvent and unreacted 2,2-dimethoxypropane were removed in vacuo and the residue distilled to afford ketal (99) (9.98g, 68%) as a light yellow liquid, b.p. 130-135°C at approximately 1mm Hg (Lit.[120] b.p. 82-90°C at 0.02 mm Hg). ^1H NMR ($CDCl_3$) δ1.5 (s,6H), 3.8 (s,6H), 4.82 (s,2H).

Diol (100)

To lithium aluminium hydride (1g, 26mmol) suspended in sodium dried ether (100ml) was added a solution of dimethyl-2,3-O-isopropylidene-L-tartarate (2g, 10mmol) in dry ether (20ml) with stirring at room temperature over a period of 20 minutes. The resulting mixture was refluxed for 4h after which the flask was cooled to 0°C in an ice bath. Ethyl acetate (2ml) followed by water (8ml) was added to the mixture which was left stirring for 30 minutes. The ethereal solution was filtered and the solid washed with several portions of warm ether (4 x 100ml). The combined filtrate was dried over anhydrous Na_2SO_4, filtered and evaporated in vacuo to give diol (100) (1.24g, 83%) as a pale yellow oil which was used without further purification.

^1H NMR ($CDCl_3$) δ1.43 (s,6H), 2.8 (s, D_2O exchangeable,2H) 3.78 (m,4H), 4.0 (m,2H).

Di-O-methyl ether (101)

To DMSO (30ml) was added powdered KOH (6.3g, 0.11 mol). After stirring for 5 minutes, a solution of diol (100) (2.3g, 14mmol) in DMSO (5ml) was added, followed immediately by methyl iodide (8.05g, 57mmol). Stirring was continued for 1h after which the mixture was poured into water (50ml) and extracted with dichloromethane (4 x 50ml). The combined organic extracts were washed with water (5 x 25ml), dried over anhydrous sodium sulphate, filtered and evaporated *in vacuo* to give compound (101) (2.23g, 83%) as a light yellow liquid which was used without further purification.

^{1}H NMR ($CDCl_3$) δ1.42 (s,6H), 3.42 (s,6H), 3.55 (m,4H), 4.0 (m,2H).

Ref. 121 for general procedure.

(-)-(2S,3S)-1,4-Dimethoxy-2,3-butandiol (102)[121]

Di-O-methyl ether (101) (4.23g, 22.3mmol) was stirred in N H_2SO_4 (30ml) at room temperature for 24h and then refluxed for 1h, neutralised with sodium hydrogencarbonate and extracted continuously with chloroform for 48h. The chloroform solution was dried over anhydrous $MgSO_4$, filtered and evaporated *in vacuo* to give diol (102) (2.91g, 87%) as a light brown oil which was used without further purification.

^{1}H NMR ($CDCl_3$) δ2.66 (broad s, D_2O exchangeable,2H), 3.4 (s,6H), 3.51 (d J = 4.6Hz), 3.8 (m,2H).

Bromo-acetal (103)

Diol (102) (1.9g, 12.7mmol) and bromoacetaldehyde diethyl acetal (2.49g, 12.7mmol) were stirred together in a 10ml round bottomed flask in the presence of a few drops of concentrated sulphuric acid. The reaction was set up for distillation, and heated at an oil bath temperature of 120°C. As the ethanol produced by acetal exchange began to distil a slight vacuum was applied. When no more ethanol was being distilled, solid K_2CO_3 (0.1g) was added to neutralise the catalyst. The residue was then distilled at reduced pressure to afford bromo-acetal (103) (2.25g, 70%) as a colourless liquid, b.p. 110-112°C at 2mm Hg, $[\alpha]_D$ -9.3° (c1.6, $CHCl_3$).

^1H NMR ($CDCl_3$) δ3.42 (s,6H), 3.59 (m,6H), 4.12 (m,2H), 5.31 (t J = 4.2Hz,1H).

^{13}C NMR (25.2MHz, $CDCl_3$) δ32.82 ($\underline{C}H_2Br$), 59.15 (O$\underline{Me}$), 72.62 ($\underline{C}H_2O$), 77.86 ($\underline{C}HO$), 78.06 ($\underline{C}HO$), 102.29 ($\underline{C}HO_2$).

$[M-CH_2Br]^+$ 161.0816. $C_7H_{13}O_4$ requires 161.0814.

Ketene Acetal (104)

Bromo-acetal (103) (1g, 3.9mmol) and potassium tert-butoxide (0.66g, 5.9mmol) were heated at 60°C with stirring in sodium dried benzene (25ml) under an argon atmosphere for 3h. The mixture was filtered through a pad of Celite, this being washed with dry benzene (50ml). The combined filtrate was evaporated *in vacuo* to afford ketene

acetal (104) (0.62g, 91%) as a colourless oil.
^{1}H NMR ($CDCl_3$) δ3.2 (s,2H), 3.39 (s,6H), 3.52 (m,4H), 4.3 (m,2H).
$[M]^+$ 174.0895. $C_8H_{14}O_4$ requires 174.0892.

2-Trichloromethyl-1,3-dioxolane (106).

A mixture of chloral (3.8g, 26mmol), ethylene glycol (1.6g, 26mmol) and 2.5ml of concentrated sulphuric acid was heated at 70°C for 2 hours. After cooling, the black solution was poured into a mixture of ice and water, this being extracted with chloroform (2 x 100ml). The chloroform extract was washed with water, dried over anhydrous sodium sulphate and evaporated in vacuo. The residue was purified by distillation to give acetal (106) (2.64g, 53%) as a colourless crystalline solid, b.p. 120-125°C (water aspirator), m.p. 40-41°C (Lit.[100] m.p. 41-42°C).
^{1}H NMR ($CDCl_3$) δ4.25 (m,4H), 5.35 (s,1H),

Ketene Acetal (107).

Trichloro-acetal (103) (1g, 5.2mmol) and potassium tert-butoxide (0.88g, 7.8mmol) were heated at 60°C with stirring in sodium dried benzene (30ml) under an argon atmosphere for 2h. The mixture was filtered through a pad of Celite, this being washed with dry benzene (50ml). The combined filtrate was evaporated in vacuo to afford ketene acetal (107) (0.8g, 99%) as a colourless oil which was used

without further purification.

^{1}H NMR ($CDCl_3$) δ4.42 (broad s).

$[M]^+$ 153.9574. $C_4H_4O_2{}^{35}Cl_2$ requires 153.9588.

$[M]^+$ 155.9551. $C_4H_4O_2{}^{35}Cl^{37}Cl$ requires 155.9559.

α-Bromophenylacetaldehyde dimethyl acetal (108)

A mixture of phenylacetaldehyde (4.8g, 0.4 mol) acetic anhydride (7.2g, 0.7 mol) and potassium acetate (7.35g, 0.075 mol) was refluxed in an oil bath kept at 160°C for 2h. The reaction mixture was then allowed to cool, taken up in diethyl ether (100ml), and excess acid washed out with water (3 x 20ml) and 5% Na_2CO_3 solution (20ml). The ethereal solution was dried over anhydrous $MgSO_4$, filtered and evaporated *in vacuo*. The residue was purified by distillation to afford phenylacetaldehyde enol acetate (3.92g, 60%) as a pale orange liquid, b.p. 130-135 (water aspirator) (Lit.[123] b.p. 119-121 at 10mm Hg).

A solution of phenylacetaldehyde enol acetate (3.92g, 0.024 mol) in carbon tetrachloride (50ml) was cooled in an ice bath and bromine (4.35g, 0.024 mol) diluted with an equal volume of carbon tetrachloride was added slowly with constant shaking over a period of 30 minutes, care being taken not to allow the temperature to rise above 10°C.

To the above brominated mixture was added analar methanol (10ml) and the mixture allowed to stand for 2 days with occasional shaking. The mixture was then diluted with

water (250ml) and extracted with diethyl ether (2 x 100ml), the combined ether extracts dried over anhydrous Na_2SO_4, filtered and evaporated *in vacuo*. The residue was purified by distillation in the presence of a small amount of K_2CO_3, and afforded acetal (108) (4.74g, 80%) as a pale orange liquid, b.p. 150-155°C (water aspirator), (Lit.[123] b.p. 130-135°C at 10mm Hg).

^1H NMR ($CDCl_3$) δ3.25 (s,3H), 3.46 (s,3H), 4.81 (AB q J = 7.8Hz,2H), 7.2-7.6 (m,10H).

2-α-Bromobenzyl-1,3-dioxalane (109).

Ethylene glycol (1.52g, 24.5mmol) and acetal (108) (6g, 24.5mmol) were stirred together in a 25ml round bottomed flask in the presence of a few drops of concentrated sulphuric acid. The reaction was set up for distillation, and heated at an oil bath temperature of 80°C. As the methanol produced by acetal exchange began to distil a slight vacuum was applied. When no more methanol was being distilled, solid K_2CO_3 (0.1g) was added to neutralise the catalyst. The residue was distilled at reduced pressure to afford acetal (109) (4.52g, 76%) as a pale orange liquid, b.p. 140-142°C at approximately 2mm Hg (Lit.[100] b.p. 162-165°C at 9mm Hg).

^1H NMR ($CDCl_3$) δ3.91 (s,4H), 4.9 (d J = 5Hz,1H), 5.3 (d J = 5Hz,1H), 5.2-5.6 (m,5H).

Ketene Acetal (110)

Bromo-acetal (109) (1g, 4.1mmol) and potassium tert-butoxide (0.69g, 6.1mmol) were heated at 60°C with stirring in sodium dried benzene (30ml) under an argon atmosphere for 30 minutes. The mixture was filtered through a pad of Celite, this being washed with dry benzene (50ml). The combined filtrate was evaporated in vacuo to afford ketene acetal (110) (0.57g, 85%) as a colourless oil which was used without further purification.
^{1}H NMR (D_8-Toluene) δ3.36 (m,4H), 4.99 (s,1H), 6.9-7.6 (m,5H).

Bromo-acetal (112)

Butan-1,4-diol (10g, 0.11 mol) and bromoacetaldehyde diethyl acetal (21.88g, 0.11 mol) were stirred together in a 50ml round bottomed flask in the presence of a few drops of concentrated sulphuric acid. The reaction was set up for distillation, and heated at an oil bath temperature of 120°C. As the ethanol produced by acetal exchange began to distil a slight vacuum was applied. When no more ethanol was being distilled, solid K_2CO_3 (0.1g) was added to neutralise the catalyst. The residue was distilled at reduced pressure to afford acetal (112) (15g, 69%) as a colourless liquid, b.p. 120-125°C at 1mm Hg.
^{1}H NMR ($CDCl_3$) δ1.71 (m,4H), 3.32 (d J = 5Hz,2H), 3.8 (m,4H), 4.9 (t J = 5Hz,1H).
$[M-CH_2Br]^+$ 101.0601. C_5H_9O requires 101.0604.

[Found C 36.45, H 5.6, Br 40.25; $C_6H_{11}BrO_2$ requires C 36.05, H 5.7, Br 41%].

General Preparation of Iodo acetals (119-121).

To a mixture of the appropriate alcohol and ethyl vinyl ether (1.4 equiv.) in dichloromethane at -20°C was added N-iodo-succinimide (1.05 equiv.) The mixture was allowed to stir for the specified time under an argon atmosphere and then allowed to warm to room temperature. The mixture was then diluted with an equal volume of diethyl ether and washed with saturated sodium bicarbonate solution (2 x 20ml), followed by saturated brine (20ml) and sodium thiosulphate solution (40ml). The organic phase was then dried over anhydrous $MgSO_4$, filtered and evaporated in vacuo to give a residue which was purified by Kugelrohr distillation or column chromatography.

Iodoacetaldehyde ethylbenzyl acetal (119).

From benzyl alcohol (1g, 9.25mmol), ethyl vinyl ether (0.93g, 12.9mmol) and N-iodosuccinimide (2.18g, 9.69 mmol) in dichloromethane (30ml) for 30 minutes to afford acetal (119) (2.1g, 74%) as a colourless liquid, b.p. 160-165 at 2mm Hg.

^1H NMR ($CDCl_3$) δ1.22 (t J = 7Hz,3H), 3.28 (d J = 6Hz), 3.65 (m,2H), 4.63 (AB q J = 11.8Hz,2H), 4.72 (t J = 6Hz,1H), 7.35(s,5H).

^{13}C NMR (25.2MHz, $CDCl_3$) δ5.18 ($\underline{CH_2}I$), 15.04 ($\underline{CH_3}CH_2O$), 62.01 ($CH_3\underline{CH_2}O$), 68.06 ($Ph\underline{CH_2}$), 100.99 ($\underline{CHO_2}$), 127.74 (Ar-H), 128.36 (Ar-H), 137.44 (Ar).

$[M]^+$ 306.0114. $C_{11}H_{15}O_2I$ requires 306.0115.

$[M-CH_2I]^+$ 165.0915 $C_{10}H_{13}O_2$ requires 165.0919

[Found C 43.1, H 5.0, I 42.65; $C_{11}H_{15}O_2I$ requires C 43.15, H 4.95, I 41.45%].

Iodoacetaldehyde ethyl-2-methylbutyl acetal (120)

From (S)-(-)-2-methyl butanol (2g, 22.7mmol) ethyl vinyl ether (2.29g, 31.76mmol) and N-iodo succinimide (5.36g, 23.82mmol) in dichloromethane (50ml) for 30 minutes to afford acetal (120) (4.71g, 73%) as a pale orange liquid, b.p. 150-152°C at 9mm Hg.

^1H NMR ($CDCl_3$) δ0.7-1.0 (m,6H), 1.05-1.8 (m,6H), 3.2 (d J = 6Hz,2H), 3.25-3.8 (m,4H), 4.6 (t J = 6Hz,1H).

^{13}C NMR ($CDCl_3$) δ5.3 ($\underline{CH_2}I$), 11.15 ($\underline{CH_3}CH_2CH$), 15.03 ($\underline{CH_3}CH_2O$) 16.49 ($\underline{CH_3}CHCH_2$), 25.99 ($CH_3\underline{CH_2}CH$), 34.91 ($\underline{CH}CH_2O$), 61.91 ($EtCH(CH_3)\underline{CH_2}O$), 71.48 ($CH_3\underline{CH_2}O$), 101.81 ($\underline{CHO_2}$).

$[M-OEt]^+$ 241.0086 $C_7H_{14}OI$ requires 241.0088

$[M-CH_2I]^+$ 145.1230 $C_8H_{17}O_2$ requires 145.1228.

[Found C 36.5, H 6.7, I 44.6; $C_9H_{19}O_2I$ requires C 37.75, H 6.7, I 44.35%]

Iodoacetaldehyde ethylmenthyl acetal (121)

From (-)-methol (2.8g, 17.9mmol), ethyl vinyl ether (1.81g, 25.1mmol) and N-iodo succinimide (4.23g, 18.8 mmol) in dichloromethane (50ml) for 1h to afford acetal (121) (4.95g, 78%) as a pale orange liquid after chromatography (silica gel, 10% ethyl acetate-hexane).

TLC Rf 0.64 (silica gel, 10% ethyl acetate-hexane)

^{1}H NMR ($CDCl_3$) δ0.75-2.5 (m,21H), 3.21 (d J = 5.6Hz,2H), 3.35-3.8 (m,3H), 4.65 (t J = 5.6Hz,0.5H), 4.74 (t J = 5.6Hz, 0.5H).

^{13}C NMR (25.2MHz,$CDCl_3$) δ6.15,6.8 ($\underline{CH_2}I$), 40.82,42.31 ($\underline{CH_2}CHO$), 48.1,48.47 ($\underline{CH}CHO$), 61.25,61.53 ($\underline{CH_2}O$), 76.15,78.6 ($\underline{CH}O$), 99.51,101.88 ($\underline{CH}O_2$).

The remaining signals in the region δ15 - δ35 can not be readily assigned from the 25.2MHz proton-decoupled and off-resonance decoupled spectra.

$[M-CH_2I]^+$ 213.1874. $C_{13}H_{25}O_2$ requires 213.1854.

[Found C 47.8, H 7.6, I 34.65; $C_{14}H_{27}O_2I$ requires C 47.45, H 7.8, I 35.85%]

General Preparation of Ketene Acetals (122-124)

The appropriate acetal and potassium tert-butoxide (1.5 equiv.) in dry THF was stirred at room temperature or with heating as specified under an argon atmosphere until reaction was complete as judged by TLC analysis. The mixture was then diluted with petroleum

ether (40/60) and filtered through Celite, this being washed with additional THF. Evaporation of the solvent *in vacuo* afforded ketene acetals (122-124).

Ketene acetal (122)

From acetal (119) (0.27g, 0.88mmol) and potassium tert-butoxide (0.15g, 13.4mmol) in THF (20ml) at room temperature for 5 minutes to afford ketene acetal (122) (0.14g, 89%) as a colourless oil.

^{1}H NMR ($CDCl_3$) δ1.3 (t J = 7.2Hz,3H), 3.2 (AB q J = 4.4Hz,2H), 3.85 (q J = 7.2Hz,3H), 4.82 (s,2H), 7.32 (s,5H).

$[M]^+$ 178.0991. $C_{11}H_{14}O_2$ requires 178.0994.

Ketene acetal (123)

From acetal (120) (0.5g, 1.75mmol) and potassium tert-butoxide (0.29g, 2.58mmol) in THF (30ml) at room temperature for 15 minutes to afford ketene acetal (123) (0.25g, 91%) as a colourless oil.

^{1}H NMR ($CDCl_3$) δ0.8-1.1 (m,6H), 1.15-1.9 (m,6H), 3.08 (s,2H), 3.58 (m,2H), 3.84 (q J = 7.2Hz,2H).

$[M]^+$ 158.1310. $C_9H_{18})_2$ requires 158.1307.

$[M]^+$ 159.1386. $C_9H_{19}O_2$ requires 159.1385.

Ketene acetal (124)

From acetal (121) (0.3g, 0.85 mmol) and potassium tert-butoxide (0.14g, 1.25mmol) in THF (30ml) at 80°C for 1h

to afford ketene acetal (124) (0.18g, 95%) as a colourless oil.

^{1}H NMR ($CDCl_3$) δ0.7-2.4 (m,21H), 3.15 (AB q J = 4.2Hz,2H), 3.6 (m,1H), 3.8 (q J = 7.8Hz, 2H).

$[M+1]^+$ 227.2008. $C_{14}H_{27}O_2$ requires 227.2001.

Iodoacetaldehyde diethyl acetal (126).

Prepared by the same method as acetals (119-121) from absolute ethanol (1g, 21.7mmol), ethyl vinyl ether (2.1g, 30.4mmol) and N-iodo succinimide (5.13g, 22.8mmol) in dichloromethane (30ml) for 30 minutes to afford acetal (126) (4.63g, 87%) as a pale orange liquid which was used without further purification.

^{1}H NMR ($CDCl_3$) δ1.2 (t J = 7Hz,6H), 3.2 (d J = 5.2Hz,2H), 3.6 (m,4H), 4.11 (t J = 5.2Hz,1H).

^{13}C NMR (25.2MHz,$CDCl_3$) δ5.45 ($\underline{C}H_2I$), 15.06 ($\underline{C}H_3CH_2O$), 62.05 ($CH_3\underline{C}H_2O$), 101.66 ($\underline{C}H_2I$).

$[M-C_2H_5O]^+$ 198.9638. C_4H_8OI requires 198.9619.

$[M-CH_2I]^+$ 103.0752. $C_5H_{11}O_2$ requires 103.0759.

Acetal (127).

Butan-1,4-diol (1g, 11.1mmol) and iodoacetaldehyde diethyl acetal (2.7g, 11.1mmol) were stirred together in a 10ml round bottomed flask in the presence of a few drops of concentrated sulphuric acid. The reaction was set up for distillation, and heated at an oil bath temperature of 120°C. As the ethanol produced by acetal exchange began to distil a

slight vacuum was applied. When no more ethanol was being distilled, the dark brown residue was dissolved in chloroform (50ml) and washed with saturated $NaHCO_3$ solution. The organic layer was dried over anhydrous Na_2SO_4, filtered and evaporated in vacuo. The residue was chromatogrphed over silica gel (hexane-ethylacetate 1:1) and afforded acetal (127) (0.8g, 30%) as a pale yellow oil.

TLC Rf 0.5 (silica gel, hexane-ethyl acetate 1:1).

^1H NMR ($CDCl_3$) δ1.68 (m,4H), 3.2 (d J = 5.8Hz,2H), 3.6 (m,4H), 4.6 (t J = 5.8Hz,1H).

$[M]^+$ 241.9789. $C_6H_{11}O_2I$ requires 241.98025

$[M-CH_2I]^+$ 101.0602. $C_5H_9O_2$ requires 101.0602

Attempted dehydroiodination of acetal (127).

Acetal (127) (0.3g, 1.24mmol) and potassium tert-butoxide (0.21g, 1.87mmol) were stirred in dry THF (20ml) for 10 minutes under an argon atmosphere. The mixture was then diluted with petroleum ether (40/60) and filtered through a pad of Celite, this being washed with additional THF (30ml). Evaporation of solvent in vacuo gave a substantially polymerised sample of ketene acetal (113).

^1H NMR ($CDCl_3$) δ1.69 (m,9H), 3.09 (s,1H), 3.75 (m,9H).

1,3-Dipolar Cycloaddition Reactions of Nitrones with α-Chloroacrylonitrile.

Note: The α-chloroacrylonitrile used in these cycloadditions was supplied by Aldrich and re-distilled before use. The nitrones were refluxed in neat α-chloroacrylonitrile until the reactions were complete as judged by TLC analysis.

N-Benzyl-3-phenylisoxazolidin-5-one (143)

C-Phenyl-N-benzylnitrone (1.6g, 7.58mmol) was refluxed in neat α-chloroacrylonitrile (20ml) under an argon atmosphere for 1h. Excess α-chloroacrylonitrile was evaporated *in vacuo* and the dark orange residue chromatographed over silica gel (ethyl acetate - petroleum ether (40/60), 2:3) to give the cycloaddition product mixture as an orange oil (1.68g, 74%).

TLC Rf approximately 0.55 (silica gel, ethyl acetate - petroleum ether (40/60), 2:3).

$[M]^+$ 298.0859. $C_{17}H_{15}N_2O^{35}Cl$ requires 298.0873, relative intensity 5.83%.

$[M]^+$ 300.0839. $C_{17}H_{15}N_2O^{37}Cl$ requires 300.0843, relative intensity 1.99%.

A partial chromatographic separation of the above mixture afforded isoxazoline (145) (0.2g, 0.76mmol) as a colourless oil.

TLC Rf 0.48 (silica gel, diethyl ether - petroleum ether (40/60), 2:3).

^{1}H NMR ($CDCl_3$) δ4.15 (AB q J = 13Hz,2H), 5.08 (d J = 4.5Hz, 1H), 5.85 (d J = 4.5Hz,1H), 7.1-7.6 (m,10H).

$[M]^+$ 262.1108. $C_{17}H_{14}N_2O$ requires 262.1106.

To a portion of the cycloadduct mixture (0.2g, 0.67mmol, assuming only isoxazolidine (141) present) dissolved in aqueous THF (5ml H_2O, 20ml THF) was added triethylamine (0.1g, 1mmol, 1.5 equiv) and the resulting mixture stirred at room temperature overnight. The THF was then evaporated in vacuo and the residue taken up in chloroform (50ml). The organic layer was washed with water (20ml), dried over anhydrous Na_2SO_4, filtered and evaporated in vacuo to give a residue which was chromatographed over silica gel (ethyl acetate - petroleum ether (40/60), 1:7) to afford isoxazolidinone (143) (0.085g, 50%) as a colourless oil.[49]

TLC Rf 0.72 (silica gel, ethyl acetate - petroleum ether, 1:1).

IR ($CHCl_3$) 1769, 1630, 1490, 1449, 1410, 1250, 1190, 1110, 912, 890, 699 cm^{-1}.

^{1}H NMR ($CDCl_3$) δ2.95 (d J = 9Hz,2H), 4.02 (AB q J = 14.2Hz,2H), 4.32 (t J = 9Hz,1H), 7.2-7.6 (m,10H).

$[M]^+$ 253.1098. $C_{16}H_{15}NO_2$ requires 253.1103.

In addition to isoxazolidinone (143), material (50mg) in the same Rf range as the cycloaddition product was recovered.

N-Benzyl-3-p-methoxyphenylisoxazolidin-5-one (144).

C-p-Methoxyphenyl-N-benzylnitrone (0.9g, 3.73mmol) was refluxed in neat α-chloroacrylonitrile (20ml) under an argon atmosphere for 1h. Excess α-chloroacrylonitrile was evaporated in vacuo and the light brown residue chromatographed over silica gel (ethyl acetate - petroleum ether (40/60), 1:4) to give the cycloaddition product mixture as a pale yellow oil (0.95g, 77%).
TLC Rf approximately 0.73 (silica gel, ethyl acetate - petroleum ether 1:1).
$[M]^+$ 328.0990. $C_{18}H_{17}N_2O_2{}^{35}Cl$ requires 328.0978, relative intensity 4.45%.
$[M]^+$ 330.0949. $C_{18}H_{17}N_2O_2{}^{37}Cl$ requires 330.0949, relative intensity 1.47%.

To a portion of the cycloadduct mixture (0.4g, 1.2mmol, assuming only isoxazolidine (142) present) dissolved in aqueous THF (10ml H_2O, 20ml THF) was added triethylamine (0.18g, 1.8mmol, 1.5 equiv) and the resulting mixture stirred at room temperature overnight. The THF was then evaporated in vacuo, and the residue taken up in chloroform (50ml). The organic layer was washed with water, dried over anhydrous Na_2SO_4, filtered and evaporated in vacuo to give a residue which was chromatographed over silica gel (ethyl acetate - petroleum ether (40/60), 1:5) to afford isoxazolidinone (144) (0.145g, 42%) as a pale yellow oil.

TLC Rf 0.51 (silica gel, ethyl acetate - petroleum ether (40/60), 2:3).

IR ($CHCl_3$) 1769, 1610, 1510, 1400, 1300, 1250, 1105, 1030, 920, 895, 830 cm^{-1}.

^1H NMR ($CDCl_3$) δ2.91 (d J = 9Hz,2H), 3.8 (s,3H), 4.0 (AB q J = 14.2Hz,2H), 4.28 (t J = 9Hz,1H), 6.9 (d J = 9Hz,2H), 7.26 (s,5H), 7.38 (d J = 9Hz,2H).

$[M]^+$ 283.1221. $C_{17}H_{17}NO_3$ requires 283.1208.

In addition to isoxazolidinone (144), material (95mg) in the same Rf range as the cycloaddition product was recovered. This hydrolysis was initially carried out using pyridine (1.5 equiv) as the base, affording isoxazolidinone (144) in 26% yield.

Keto nitrile (146)

C-p-Methoxyphenyl-N-benzylnitrone (1g, 4.15mmol) was refluxed in neat α-chloroacrylonitrile (20ml) under an argon atmosphere for 24h. Excess α-chloroacrylonitrile was evaporated in vacuo, and the dark brown residue chromatographed over silica gel (hexane - ethyl acetate, 3:2) to afford keto nitrile (146) (0.58g, 75%) as a pale yellow crystalline solid, m.p. 125-126°C.

TLC Rf 0.65 (silica gel, hexane - ethyl acetate 3:2).

IR ($CHCl_3$) 2230, 1659, 1595, 1570, 1510, 1430, 1340, 1310, 1260, 1239, 1200, 1171, 1031, 979, 835 cm^{-1}.

^1H NMR ($CDCl_3$) δ3.91 (s,3H), 6.75 (d J = 16Hz,1H), 7.0 (d J = 8.4Hz,1H), 7.6 (d J = 8.4Hz,1H), 7.95 (d J = 16Hz,1H).

^{13}C NMR (25.2MHz,$CDCl_3$) δ55.53 (MeO), 112.63 (CN), 114.96 (CH=CH-CO), 122.95 (Ar-H), 125.58 (Ar), 131.7 (Ar-H), 154.72 (Ar-CH=CH), 163.74 (Ar-H), 175.59 (C=O).

$[M]^+$ 187.0632. $C_{11}H_9NO_2$ requires 187.0633.

[Found C 70.35, H 4.7, N 7.3; $C_{11}H_9NO_2$ requires C 70.55, H 4.85, N 7.5%]

N-Benzyl-3-methylisoxazolidin-5-one (151).

C-methyl-N-benzylnitrone (1.2g, 8.05mmol) was refluxed in neat α-chloroacrylonitrile (30ml) under an argon atmosphere for 10 minutes. Excess α-chloroacrylonitrile was evaporated *in vacuo* and the light brown residue chromatographed over silica gel (hexane - ethyl acetate 2:3) to give the cycloaddition product mixture as a pale yellow oil (1.41g, 74%).

TLC Rf 0.56 (silica gel, ethyl acetate - hexane, 2:3).

$[M]^+$ 236.0732. $C_{12}H_{13}N_2O^{35}Cl$ requires 236.0716, relative intensity 2.33%.

$[M]^+$ 238.0699. $C_{12}H_{13}N_2O^{37}Cl$ requires 238.0687.[0.7%]

To a portion of the cycloadduct mixture (0.8g, 3.38 mmol, assuming only isoxazolidine (150) present) dissolved in aqueous THF (10ml H_2O, 30ml THF) was added triethylamine (0.5g, 4.95mmol, 1.5 equiv) and the resulting mixture left stirring at room temperature overnight. Work-up as for isoxazolidinone (143) gave a residue which was chromatographed over silica gel (ethyl acetate - hexane, 1:4) to afford isoxazolidinone (151) (0.48g, 74%) as a light yellow oil.

TLC Rf 0.65 (ethyl acetate - hexane, 2:3).

IR ($CHCl_3$) 1770, 1490, 1410, 1380, 1320, 1255, 1220, 1170, 1045, 1025, 910, 900, 700 cm^{-1}.

^1H NMR (100MHz, $CDCl_3$) δ1.16 (d J = 6.2Hz,3H), 2.4(dd J = 11, 17Hz,1H), 2.68 (dd J = 7,17Hz,1H), 3.35 (m,1H), 4.0 (AB q J = 13.8Hz,2H), 7.2-7.5 (m,5H).

^{13}C NMR (25.2MHz,$CDCl_3$) δ17.06 (Me), 37.81 (CH_2CHCO), 61.084 (CHN and $PhCH_2$), 127.48 (Ar-H), 128.17 (Ar-H), 128.73 (Ar-H), 135.35 (Ar), 173.31 (C=O).

$[M]^+$ 191.0961. $C_{11}H_{13}NO_2$ requires 191.0946.

In addition to isoxazolidinone (151), additional material (60mg) in the same Rf range as the cycloaddition product was recovered.

N-(R)-α-Methylbenzyl-3-phenylisoxazolidin-5-one (153).

(R)-(-)-C-phenyl-N-α-methyl-benzylnitrone (2.5g, 11.1mmol) was refluxed in neat α-chloroacrylonitrile (40ml) under an argon atmosphere for 1h. Excess α-chloroacrylonitrile was evaporated *in vacuo* and the pale brown residue chromatographed over silica gel (ethyl acetate - hexane 1:2) to give the cycloaddition product mixture (2.1g, 60%) as a pale yellow oil.

TLC Rf approximately 0.57 (silica gel, ethyl acetate - hexane, 1:1).

$[M]^+$ 312.1037. $C_{18}H_{17}N_2O^{35}Cl$ requires 312.1029 [1·13%]

$[M]^+$ 314.1020. $C_{18}H_{17}N_2O^{37}Cl$ requires 314.0999. [0·41%]

To a portion of the cycloadduct mixture (1.5g, 4.8 mmol, assuming only isoxazolidine (152) present) dissolved in aqueous THF (10ml H_2O, 20ml THF) was added triethylamine (0.73g, 7.2mmol, 1.5 equiv) and the resulting mixture left stirring at room temperature overnight. Work-up as for isoxazolidinone (143) gave a residue which was chromatographed over silica gel (hexane - ethyl acetate, 5:1) to afford isoxazolidinone (153) (0.43g, 34%) as a pale yellow crystalline solid, m.p. 93-96°C (Lit.[49] m.p. 95-98°C).
TLC Rf 0.55 (silica gel, ethyl acetate - hexane 2:3).
IR ($CHCl_3$) 1765, 1600, 1489, 1449, 1410, 1371, 1281, 1225, 1195, 1160, 1030, 905, 700 cm^{-1}.
^1H NMR (100MHz, $CDCl_3$) δ1.6 (d J = 7Hz,3H), 2.86 (dd J = 8, 17.8Hz,1H), 3.15 (dd J = 8,17.8Hz,1H), 4.21 (q J = 7Hz,1H), 4.55 (t J = 8Hz,1H), 7.2-7.6 (m,10H).
$[M]^+$ 267.1265. $C_{17}H_{17}NO_2$ requires 267.1259.

In addition to isoxazolidinone (153), material (400mg) in the same Rf range as the cycloaddition product was recovered.

β-Phenyl-β-alanine (154).

To isoxazolidinone (153) (0.3g, 1.12mmol) dissolved in absolute ethanol (50ml) was added palladium hydroxide on charcoal (20%; 30mg) and the mixture hydrogenated at atmospheric pressure and 70°C overnight. The solid amino acid separated during hydrogenolysis. Distilled water (50ml) was added to dissolve the amino acid, and the catalyst was removed by

filtration through a pad of Celite, this being thoroughly washed with warm water (100ml). The combined filtrate was evaporated in vacuo to give β-phenyl-β-alanine (154) as colourless crystals, (0.18g, 97%), m.p. 231-233°C, $[\alpha]_D$+ 5.43° (c1.16, H_2O) [Lit.[105] m.p. 236°C, $[\alpha]_D$+ 6.2° for (S)-β-phenyl-β-alanine.

N-(R)-α-Methylbenzyl-3-isopropylisoxazolidin-5-one (156).

(R)-(-)-C-Isopropyl-N-α-methylbenzylnitrone (0.5g, 2.62mmol) was refluxed in neat α-chloroacrylonitrile under an argon atmosphere for 25 minutes. Excess α-chloroacrylonitrile was evaporated in vacuo and the residue chromatographed over silica gel (ethyl acetate - petroleum ether (40/60) 2:3) to give the cycloaddition product mixture a light brown oil (0.52g, 71%).

TLC Rf approximately 0.7 (silica gel, ethyl acetate - petroleum ether (40/60), 2:3).

$[M]^+$ 278.1190. $C_{15}H_{19}N_2O^{35}Cl$ requires 278.1186, relative intensity 0.34%.

$[M]^+$ 280.1160. $C_{15}H_{19}N_2O^{37}Cl$ requires 280.1156, relative intensity 0.16%.

To cycloadduct mixture (155) (0.51g, 1.83mmol, assuming only isoxazolidine (155) present) dissolved in aqueous THF (10ml H_2O, 20ml THF) was added triethylamine (0.28g, 2.8mmol) and the resulting mixture left stirring at room temperature overnight. Work-up as for isoxazolidin-one (143) gave a residue which was chromatographed over silica

gel (ethyl acetate - petroleum ether, 1:4) to afford isoxazolidinone (156) (0.28g, 66%) as a colourless oil.
TLC Rf 0.48 (silica gel, ethyl acetate - petroleum ether (40/60), 1:2).
IR ($CHCl_3$) 1770, 1630, 1488, 1445, 1390, 1280, 1225, 1180, 1100, 915, 870, 700 cm^{-1}.
^1H NMR (200MHz, $CDCl_3$) δ0.75 (m,4.125H), 0.92 (m,1.875H), 1.52 (d J = 6.6Hz,2.06H), 1.6 (d J = 6.9Hz, 0.94H), 1.7 (m,0.31H), 2.03 (dd J = 8.9, 17.7Hz,).31H), 2.28 (dd J = 5.5, 18.3Hz, 0.31H), 2.26 (dd J = 3.1, 17.9Hz,0.69H), 2.62(dd J = 8.8, 17.95Hz, 0.69H), 3.15 (m,1H), 4.04 (m,1H), 7.32 (m,5H).
^{13}C NMR (50MHz, $CDCl_3$) δ17.34 ($(\underline{Me})_2CH$), 17.86 ($(\underline{Me})_2CH$), 18.43 ($(\underline{Me})_2CH$), 19.71 ($PhCH\underline{C}H_3$), 19.95 ($PhCH\underline{C}H_3$), 30.58 ($\underline{C}H_2CO$), 31.07 ($(Me)_2\underline{C}H$), 31.34 ($\underline{C}H_2CO$), 31.59 ($(Me)_2\underline{C}H$), 65.07 ($\underline{C}HN$), 65.86 ($\underline{C}HN$), 66.23 ($Ph\underline{C}H$), 66.88 ($Ph\underline{C}H$), 127.89 ($\underline{Ar}$-H), 128.05 ($\underline{Ar}$-H), 128.16 ($\underline{Ar}$-H), 128.53 ($\underline{Ar}$-H), 128.61 ($\underline{Ar}$-H), 138.35 ($\underline{Ar}$), 140.34 ($\underline{Ar}$), 176.19 ($\underline{C}$=O), 177.19 ($\underline{C}$=O).
$[M]^+$ 233.1413. $C_{14}H_{19}NO_2$ requires 233.1416.

In addition to isoxazolidinone (156), material (70mg) in the same Rf range as the cycloaddition product was recovered.

β-Leucine (157).

To isoxazolidinone (157) (0.13g, 0.56mmol) dissolved in methanol (50ml) was added palladium hydroxide on charcoal

(20%; 20mg) and the resulting mixture hydrogenated at atmospheric pressure and room temperature for 48h. The catalyst was removed by filtration through a pad of Celite, this being thoroughly washed with warm methanol (100ml). The combined filtrate was evaporated in vacuo to give β-leucine as colourless crystals (69mg, 94%), m.p. 197-200°C, $[\alpha]_D$ -15.1° (c0.81, H_2O) [Lit.[105] m.p. 201-202°C, $[\alpha]_D$ + 55.2 for (S)-β-leucine].

N-(S)-α-Carbomethoxyl-3-isopropylisoxazolidin-5-one (159).

C-Isopropyl-N-(S)-α-carbomethoxylbenzylnitrone (1g, 4.25mmol) was refluxed in neat α-chloroacrylonitrile (20ml) under an argon atmosphere for 30 minutes. Excess α-chloroacrylonitrile was evaporated in vacuo and the residue chromatographed over silica gel (hexane - ethyl acetate, 3:2) to give the cycloaddition product mixture as a pale yellow oil (0.81g, 59%).
TLC Rf approximately 0.48 (silica gel, hexane - ethyl acetate 3:2).

To a portion of the cycloadduct mixture (0.6g, 1.86 mmol, assuming only isoxazolidine (158) present) was added aqueous HCl (0.4 equiv) and the mixture stirred at room temperature overnight. Work-up as for isoxazolidinone (143) gave a residue which was chromatographed over silica gel (ethyl acetate - hexane, 2:3) to afford isoxazolidinone (159) (0.27g, 52%) as a pale yellow oil.

TLC Rf 0.25 (silica gel, ethyl acetate - hexane, 2:3).
IR ($CHCl_3$) 1731, 1658, 1600, 1575, 1504, 1475, 1430, 1355, 1259, 1195, 1165, 1005, 830, 690 cm^{-1}.
^1H NMR (200MHz, $CDCl_3$) δ0.76 (m,5.5H), 0.95 (m,0.5H), 1.55 (m,1H), 2.45 (m,1H), 2.7 (m,1H), 3.16 (m,1H), 3.67 (s,2.75H), 3.68 (s,0.5H), 4.62 (s,0.92H), 4.95 (s,0.08H), 7.3-7.6 (m,5H).
^{13}C NMR(50MHz, $CDCl_3$)δ17.51 ($(\underline{CH_3})_2CH$), 18.44 ($PhCH\underline{CH_3}$), 30.28 ($\underline{CH_2}CO$), 31.34 ($(CH_3)_2\underline{CH}$), 52.34 ($CO_2\underline{CH_3}$), 65.64 ($\underline{CH}N$), 77.0 ($Ph\underline{CH}CO_2CH_3$), 128.8 ($\underline{Ar}$-H), 128.99 ($\underline{Ar}$-H), 129.5 ($\underline{Ar}$-H), 132.78 ($\underline{Ar}$), 169.13 ($CH_2\underline{C}=O$), 176.11 ($\underline{CO_2}CH_3$).
$[M]^+$ 277.1321. $C_{15}H_{19}NO_4$ requires 277.1314.

In addition to isoxazolidinone (159), material (110mg) in the same Rf range as the cycloaddition product was recovered.

N-(R)-α-Methylbenzyl-C-P-methoxyphenylisoxazolidin-5-one (162)

(R)-C-(-)-p-Methoxyphenyl-N-α-methylbenzylnitrone (0.2g, 0.78mmol) was refluxed in neat α-chloroacrylonitrile (15ml) under an argon atmosphere for 1h. Excess α-chloronitrile was evaporated in vacuo and the residue chromatographed over silica gel (hexane - ethyl acetate, 4:1) to give the cycloaddition product mixture as a yellow oil (0.2g, 75%).
TLC Rf approximately 0.72 (silica gel, hexane - ethyl acetate, 1:1).
$[M]^+$ 342.1145. $C_{19}H_{19}N_2O_2{}^{35}Cl$ requires 342.1135, relative intensity 0.87%.
$[M]^+$ 344.1124. $C_{19}H_{19}N_2O_2{}^{37}Cl$ requires 344.1105, relative intensity 0.42%.

To cycloadduct mixture (160) (0.2g, 0.58mmol, assuming only isoxazolidine (160) present), dissolved in aqueous THF (5ml H_2O, 20ml THF) was added pyridine (0.07g, 0.89mmol, 1.5 equiv) and the resulting mixture stirred at room temperature overnight. Work-up as for isoxazolidinone (143) gave a residue which was chromatographed over silica gel (ethyl acetate - hexane, 1:4) to afford isoxazolidinone (162) (30mg, 17%) as a pale yellow crystalline solid, m.p. 125-127°C (Lit.[49] m.p. 127-128°C).

TLC Rf 0.7 (silica gel, ethyl acetate - hexane 1:1)

IR ($CHCl_3$) 1775, 1615, 1515, 1455, 1410, 1300, 1251, 1210, 1175, 1160, 1035, 912, 885, 701 cm^{-1}.

^1H NMR (200MHz, $CDCl_3$) δ1.55 (d J = 6.6Hz,3H), 2.82 (dd J = 9.1, 17.3Hz,1H), 3.03 (dd J = 7.7, 17.3Hz,1H), 3.77 (s,3H), 4.12 (q J = 6.6Hz,1H), 4.42 (t J = 7.9Hz,1H), 6.78 (d J = 9.4Hz,1H), 7.15 (d J = 9.4Hz,1H), 7.21 (m,10H).

^{13}C NMR (50MHz, $CDCl_3$) δ18.06 ($PhCH\underline{C}H_3$), 39.12 ($\underline{C}H_2CO$), 55.23 ($O\underline{C}H_3$), 65.56 ($PhCHCH_3$), 65.75 (pMeOPhCH), 14.04 (Ar-H), 127.76 (Ar-H), 128.22 (Ar-H), 128.33 (Ar-H), 130.29 (Ar), 140.34 (Ar), 159.32 (Ar), 173.82 (C=O).

$[M]^+$ 297.1387. $C_{18}H_{19}NO_3$ requires 297.1365.

In addition to isoxazolidinone (162), material (60mg) in the same Rf range as the cycloaddition product was recovered.

The above was repeated starting from 1g (3.9mmol) of nitrone to give the same cycloadduct mixture (0.95g, 75%)

0.8g (2.3mmol) of which was hydrolysed using triethylamine (0.35g, 3.5mmol, 1.5 equiv) as the base and afforded isoxazolidinone (162) (0.18g, 26%) as a 2:1 mixture of diastereomers.

TLC Rf 0.7 (silica gel, hexane ethyl acetate 1:1).

^{1}H NMR ($CDCl_3$) δ1.5 (m,3H), 2.9 (m,2H), 3.75 (s,2H), 3.81 (s,1H), 3.9-4.5 (m,2H), 6.7-7.5 (m,10H).

N-(R)-α-Methylbenzyl-3-p-benzyloxyphenylisoxazolidin-5-one (163)

(R)-(-)-C-p-Benzyloxyphenyl-N-α-methylbenzylnitrone (1g, 3.02mmol) was refluxed in neat α-chloroacrylonitrile (20ml) under an argon atmosphere for 1h. Excess α-chloroacrylonitrile was evaporated in vacuo and the residue chromatographed over silica gel (ethyl acetate - hexane, 2:3) to give the cycloaddition product mixture as a yellow oil (0.95g, 75%).

TLC Rf approximately 0.76 (ethyl acetate - hexane, 2:3).

$[M]^+$ 418.1449 $C_{25}H_{23}N_2O_2{}^{35}Cl$ requires 418.1448, relative intensity 0.9%.

$[M]^+$ 420.1418. $C_{25}H_{23}N_2O_2{}^{37}Cl$ requires 420.1418, relative intensity 0.4%.

To a portion of the cycloadduct mixture (0.6g, 1.43 mmol) dissolved in aqueous THF (10ml H_2O, 30ml THF) was added triethylamine (0.22g, 2.2mmol) and the resulting mixture stirred at room temperature overnight. Work-up as for isoxazolidinone (143) afforded a residue which was chromato-

graphed over silica gel (ethyl acetate - hexane, 1:6). A partial separation was achieved and afforded the diastereomeric isoxazolidinones in a combined yield of 47% (0.25g), both as pale yellow oils.

Least polar isoxazolidinone mixture.

TLC Rf approximately 0.65 (silica gel, ethyl acetate - hexane, 1:1).

IR ($CHCl_3$) 1765, 1609, 1509, 1449, 1375, 1295, 1230, 1195, 1170, 1030, 905, 831, 701 cm^{-1}.

^1H NMR ($CDCl_3$) δ1.5 (m,3H), 2.7 (m,2H), 4.0 (m,2H), 5.0 (s,0.29H), 5.06 (s, 1.71H), 6.9-7.5 (m,10H).

^{13}C NMR (25.2MHz, $CDCl_3$) δ18.32 ($PhCH\underline{C}H_3$), 20.63 ($PhCH\underline{C}H_3$), 39.13 ($\underline{C}H_2CO$), 40.44 ($\underline{C}H_2CO$), 63.36 ($Ph\underline{C}HCH_3$), 65.98 (pBzoPh$\underline{C}$H), 70.06 ($Ph\underline{C}H_2O$), 115.34 (Ar), 115.34 (Ar-H), 127.43 (Ar-H), 127.86 (Ar-H), 128.07 (Ar-H), 128.39 (Ar-H), 128.62 (Ar-H), 129.14 (Ar-H), 136.73 (Ar), 138.1 (Ar), 159.1 (Ar), 172.55 ($\underline{C}$=O).

$[M]^+$ 373.1665. $C_{24}H_{23}NO_3$ requires 373.1678.

More polar isoxazolidinone

TLC Rf 0.63 (silica gel, hexane - ethyl acetate, 1:1).

IR ($CHCl_3$) 1770, 1611, 1510, 1450, 1376, 1295, 1230, 1200, 1171, 1030, 910, 831, 705 cm^{-1}.

^1H NMR (200MHz, $CDCl_3$) δ1.54 (d J = 6.6Hz, 3H), 2.83 (dd J = 9.1, 17.3Hz,1H), 3.03 (dd J = 7.7, 17.3Hz,1H), 4.13 (q J =

6.6Nz,1H), 4.42 (t J = 8.1Hz,1H), 6.85 (d J = 8.8Hz,2H), 7.1-7.5 (m,12H).

^{13}C NMR (25.2MHz, $CDCl_3$) δ18.27 ($PhCHCH_3$), 39.07 (CH_2CO), 65.79 ($PhCHCH_3$ and pBzoPhCH), 69.91 ($PhCH_2$), 114.99 (Ar-H), 127.32 (Ar-H), 127.79 (Ar-H), 128.28 (Ar-H), 128.52 (Ar-H), 130.65 (Ar), 136.78 (Ar), 140.32 (Ar), 158.46 (Ar), 173.81 (C=O).

$[M]^+$ 373.1680. $C_{24}H_{23}NO_3$ requires 373.1678.

In addition to isoxazolidinone (163), material (0.3g) in the same Rf range as the cycloaddition product was recovered.

Hydrogenolysis of isoxazolidinone (163).

To a 1:1 diastereomeric mixture of isoxazolidinone (163) (0.1g, 0.27mmol) dissolved in absolute ethanol (30ml) was added palladium hydroxide (20%, 20mg) and the resulting mixture hydrogenated at atmospheric pressure and 70°C for 24h. The catalyst was removed by filtration through a pad of Celite, this being thoroughly washed with warm ethanol (50ml). The combined filtrate was evaporated *in vacuo* to give β-amino acid (164) (80mg, 80%) as a colourless oil.

^1H NMR (CD_3OD) δ1.6 (m,3H), 2.7 (m,2H), 4.0 (m,2H), 5.1 (s,2H), 6.9-7.5 (m,14H).

$[M-CH_2CO_2H]^+$ 316.175. $C_{22}H_{22}NO$ requires 316.1701.

Attempted synthesis of N-(R)-α-methylbenzyl-3-p-hydroxyphenylisoxazolidin-5-one

(R)-(-)-C-p-Hydroxylphenyl-N-α-methylbenzylnitrone (1g, 4.15mmol) was refluxed in neat α-chloroacrylonitrile under an argon atmosphere for 1h. Excess α-chloroacrylonitrile was evaporated *in vacuo* and the residue chromatographed over silica gel (ethyl acetate - hexane, 2:3) to give the cycloaddition product mixture as a light brown oil (0.81g, 60%).

TLC Rf 0.53 (silica gel, ethyl acetate - hexane 2:3).

$[M]^+$ 328.0971. $C_{18}H_{17}N_2O_2{}^{35}Cl$ requires 328.0978, relative intensity 0.89%.

$[M]^+$ 330.0978. $C_{18}H_{17}N_2O_2{}^{37}Cl$ requires 330.0978, relative intensity 0.33%.

Attempted hydrolysis in the usual manner with triethylamine (3 equiv.) in aqueous THF was unsuccessful. Work-up afforded quantitative recovery of the cycloaddition product mixture.

Isoxazolidinone (191)

(+)-C-2,3-O-Isopropylidene glyceraldehydo-N-benzylnitrone (0.35g, 1.5mmol) was refluxed in neat α-chloroacrylonitrile under an argon atmosphere for 30 minutes. Excess α-chloroacrylonitrile was evaporated *in vacuo* and the residue chromatographed over silica gel (ethyl acetate - hexane, 2:3) to give isoxazolidine (190) (0.36g, 73%) as a

yeloow oil.

TLC Rf 0.54 (silica gel, ethyl acetate - hexane 2:3).

To isoxazolidine (190) (0.22g, 0.67mmol) dissolved in aqueous THF (5ml H_2O, 20ml THF) was added triethylamine (0.1g, 1mmol) and the resulting mixture stirred at room temperature overnight. Work-up as for isoxazolidinone (143) gave a residue which was chromtographed over silica gel (ethyl acetate - hexane 2:3), to afford isoxazolidinone (191) (0.15g, 80%) as a 6:1 diastereomeric mixture, and as a colourless oil.

TLC Rf 0.51 (silica gel, ethyl acetate - hexane 2:3).

IR ($CHCl_3$) 1779, 1449, 1410, 1378, 1369, 1250, 1220, 1165, 1071, 905, 845, 699 cm^{-1}.

^1H NMR (200MHz, $CDCl_3$) δ1.31 (m,5.14H), 1.38 (m,0.86H), 2.62 (m,0.28H), 2.75 (m,1.72H), 3.5 (m,2H), 4.15 (m,4H), 7.34 (m,5H).

^{13}C NMR (50MHz, $CDCl_3$) δ22.53 ($(\underline{CH_3})_2C$), 24.64 ($(\underline{CH_3})_2C$), 26.3 ($(\underline{CH_3})_2C$), 30.08 ($\underline{CH_2}CO$), 32.16 ($\underline{CH_2}CO$), 63.05 ($\underline{CH_2}O$), 63.99 ($\underline{CH}N$), 65.53 ($\underline{CH}N$), 65.88 ($\underline{CH_2}Ph$), 66.79 ($\underline{CH_2}Ph$), 75.36 ($\underline{CH}O$), 76.36 ($\underline{CH}O$), 109.8 ($(CH_3)_2\underline{C}$), 110.17 ($(CH_3)_2\underline{C}$), 127.9 (Ar-H), 128.27 (Ar-H), 128.42 (Ar-H), 128.64 (Ar-H), 129.37 (Ar-H), 129.44 (Ar-H), 134.1 (Ar), 134.82 (Ar), 173.28 ($\underline{C}=O$), 175.49 ($\underline{C}=O$)

$[M]^+$ 277.1307. $C_{15}H_{19}NO_4$ requires 277.1314.

Isoxazolidinone (193).

(R)-(+)-C-2,3-O-Isopropylidene glyceraldehydo-N-α-methylbenzylnitrone (0.6g, 2.41mmol) was refluxed in neat α-chloroacrylonitrile (20ml) for 15 minutes. Excess α-chloroacrylonitrile was evaporated in vacuo and the residue chromatographed over silica gel (ethyl acetate - hexane, 2:3) to give isoxazolidine (192) (0.74g, 91%) as a yellow oil.
TLC Rf 0.75 (silica gel, ethyl acetate - hexane, 2:3).

To isoxazolidine (192) (0.7g, 2.1mmol) dissolved in aqueous THF (10ml H_2O, 30ml THF) was added triethylamine (0.32g, 3.2mmol) and the resulting mixture stirred at room temperature overnight. Work-up as for isoxazolidinone (143) gave a residue which was chromtographed over silica gel (ethyl acetate - hexane, 1:4) to afford isoxazolidinone (193) (0.48g, 79%) as a colourless oil, $[\alpha]_D$ -16.2° (c1.95, $CHCl_3$).
TLC Rf 0.52 (silica gel, ethyl acetate - hexane, 2:3).
IR ($CHCl_3$) 1782, 1490, 1451, 1429, 1382, 1375, 1220, 1170, 1089, 1071, 875, 849, 705 cm^{-1}.

^1H NMR (200MHz, $CDCl_3$) δ1.26 (s,6H), 1.53 (d J = 6.48Hz,3H), 2.59 (dd J = 2.6, 18.1Hz), 2.71 (dd J = 7.7, 18.1Hz), 3.32 (m2H), 4.05 (m,3H), 7.2-7.5 (m,5H).

^{13}C NMR (50MHz, $CDCl_3$) δ20.48 ($PhCH\underline{C}H_3$), 24.69 ($(\underline{C}H_3)_2C$), 26.25 ($(\underline{C}H_3)_2C$), 29.21 ($\underline{C}H_2CO$), 62.02 ($\underline{C}HN$), 67.01 ($\underline{C}HO$), 67.09 ($\underline{C}H_2O$), 75.97 ($Ph\underline{C}HCH_3N$), 109.78 ($(CH_3)_2\underline{C}$), 127.77 (Ar-H), 128.69 (Ar-H), 129.08 (Ar-H), 139.935 (Ar), 176.69 (C=O).

$[M]^+$ 291.1473. $C_{16}H_{21}NO_4$ requires 291.1471.

β-Amino acid (194)

To isoxazolidinone (193) (0.86g, 2.95mmol) dissolved in absolute ethanol (50ml) was added palladium hydroxide on charcoal (20%; 80mg) and the resulting mixture hydrogenated at atmospheric pressure and room temperature for 48h. The catalyst was removed by filtration through a pad of Celite, this being thoroughly washed with warm ethanol (100ml). The combined filtrate was evaporated in vacuo to give β-amino acid (194) (0.47g, 84%) as a colourless oil, $[\alpha]_D$ -27.5° (c0.8, MeOH).

^1H NMR (CD_3OD) δ1.36 (s,3H), 1.48 (s,3H), 2.6 (bs,2H), 3.4-4.5 (m,4H).

^{13}C NMR (50MHz, CD_3OD) 24.81 ($(\underline{C}H_3)_2C$), 26.34 ($(\underline{C}H_3)_2C$), 34.02 ($\underline{C}H_2CO_2H$), 52.07 ($\underline{C}HN$), 66.39 ($\underline{C}H_2O$), 75.91 ($\underline{C}HO$), 111.28 ($(CH_3)_2\underline{C}$), 177 ($\underline{C}$=O).

$[M-CH_3]^+$ 174.0762. $C_7H_{12}NO_4$ requires 174.0766.

Deprotection of isoxazolidinone (193).

Isoxazolidinone (193) (0.58g, 2mmol) was refluxed in aqueous THF (5ml H_2O, 20ml THF) in the presence of p-toluenesulphonic acid (0.06g, 0.3nmmol) for 1h. The THF was evaporated in vacuo, the residue taken up in chloroform (50ml) and washed with dilute $NaHCO_3$ solution. The organic layer was dried over anhydrous Na_2SO_4, filtered and

evaporated in vacuo to give a (4:1) mixture of diol (195) and lactone (196) (0.35g, 70%).

^{1}H NMR ($CDCl_3$) δ1.45 (d J = 7.2Hz, 0.6H), 1.53 (d J = 7.2Hz, 2.4H), 2.7 (m,2H), 3.5 (m,4H), 4.15 (m,1H), 7.2-7.5 (m,5H).

Deprotection of isoxazolidinone (193) (0.3g, 1mmol) using aqueous HCl (0.5 equiv) in methanol (20ml) at room temperature overnight followed by the same work up as above afforded a 2:1 mixture of compounds (195) and (196) (0.18g, 72%).

^{1}H NMR ($CDCl_3$) δ1.45 (d J = 7.2Hz,1H), 1.53 (d J = 7.2Hz,2H), 2.7 (m,2H), 3.5 (m,4H), 4.15 (m,4H), 7.2-7.5 (m,10H).

A partial separation of the product obtained from p-toluenesulphonic acid catalysed deprotection was achieved by column chromatography over silica gel (10% methanol - ethyl acetate).

Lactone (196) (50mg), m.p. 140-142°C $[\alpha]_D$ + 112.4° (c2.1,MeOH).
TLC Rf 0.9 (silica gel, 10% methanol - ethyl acetate).
IR (KBr disc) 3500-3200, 1731, 1491, 1451, 1399, 1361, 1265, 1208, 1070, 1039, 980, 965, 915, 771, 755, 705 cm^{-1}.

^{1}H NMR (200MHz, CD_3OD) 1.42 (d J = 6.45Hz,3H), 2.4 (dd J = 8.9, 17.9Hz,1H), 2.86 (dd J = 3.9, 17.9Hz,1H), 3.46 (m,2H), 3.66 (m,1H), 3.78 (q J = 6.45Hz,1H), 4.6 (m,1H), 7.2-7.4 (m,5H).

^{13}C NMR (50MHz, CD_3OD) 22.14 ($PhCH\underline{C}H_3$), 29.43 ($\underline{C}H_2CO$), 61.39 ($\underline{C}HN$), 63.32 ($\underline{C}H_2O$), 65.97 ($\underline{C}HO$), 86.36 ($PhC\underline{H}CH_3$), 128.58 ($\underline{Ar}$-H), 128.68 ($\underline{Ar}$-H), 129.7 ($\underline{Ar}$-H), 144.21 ($\underline{Ar}$), 179.57 ($\underline{C}$=O).

$[M]^+$ 251.1149. $C_{153}H_{17}NO_4$ requires 251.1158.

[Found C 62.1, H 6.85, N 5.65; $C_{13}H_{14}NO_4$ requires C 62.1, H 6.8, N 5.6%].

Partially purified diol (195) (300mg).

TLC Rf 0.77 (silica gel, 10% methanol - ethyl acetate).

IR ($CHCl_3$) 3650-3200, 1780, 1489, 1450, 1415, 1375, 1280, 1225, 1175, 1085, 1035, 920, 870, 705 cm^{-1}.

^1H NMR (200MHz, $CDCl_3$) δ1.42 (d J = 6.5Hz, 0.375H), 1.53 (d J = 6.5Hz, 2.625H), 2.65 (m,3H), 3.4 (m,5H), 4.1 (q J = 6.5Hz,1H), 7.2-7.5 (m,5H).

^{13}C NMR (50MHz, $CDCl_3$) δ17.79 ($PhCH\underline{C}H_3$), 29.24 ($\underline{C}H_2CO$). 60.17 ($\underline{C}HN$), 63.32 ($\underline{C}H_2O$), 67.06 ($\underline{C}HO$), 71.61 ($PhC\underline{H}CH_3$) 127.85 ($\underline{Ar}$-H), 128.68 ($\underline{Ar}$-H), 129.05 ($\underline{Ar}$-H), 139.62 ($\underline{Ar}$), 177.01 ($\underline{C}$=O).

$[M]^+$ 251.1145. $C_{13}H_{17}NO_4$ requires 251.1158

Thionocarbonate (197)[111]

To a stirred solution of diol (0.26g, 1.04mmol) and 4-dimethyl-aminopyridine (0.3g, 2.45mmol, 2.4 equiv. , in dry dichloromethane (10ml) at 0°C under argon was added

thiophosgene (0.14g, 1.22mmol, 1.2 equiv) and the resulting mixture stirred at 0°C for 1h. Silica gel (2g, Merck) was added and the mixture was allowed to warm to room temperature. After removal of the dichloromethane in vacuo, the remaining solid was loaded onto a short silica gel column and eluted with 50% ethyl acetate-hexane. Concentration in vacuo afforded thionocarbonate (197) (0.201g, 66%) as a pale yellow solid, m.p. 174-175°C, $[\alpha]_D$ -10.89° (c1.91, $CHCl_3$).

TLC Rf 0.46 (silica gel, 50% ethyl acetate - hexane).

IR ($CHCl_3$) 1781, 1431, 1300, 1280, 1155, 1075, 965, 897, 860, 695 cm^{-1}.

^1H NMR (200MHz, $CDCl_3$) 1.56 (d J = 6.5Hz,3H), 2.65 (dd J = 1.6, 18.6Hz,1H), 2.88 (dd, J = 8.2, 18.6Hz,1H), 3.65 m,1H), 4.05 (m,1H), 4.13 (q J = 6.5Hz,1H), 4.75 (m,2H), 7.1-7.5 (m,5H).

^{13}C NMR (50MHz, $CDCl_3$) 19.95 ($\underline{C}H_3$), 29.81 ($\underline{C}H_2CO$), 60.67 ($\underline{C}H_2$) 66.9 ($\underline{C}HO$), 72.03 ($\underline{C}H_2O$), 79.66 ($PhCHCH_3$), 127.88 ($\underline{Ar}$-H), 129.51 ($\underline{Ar}$-H), 138.62 ($\underline{Ar}$), 175.08 ($\underline{C}$=O), 190.45 ($\underline{C}$=S).

$[M]^+$ 293.0724. $C_{14}H_{15}NO_4S$ requires 293.0722.

[Found C 57.3, H 5.15, N 4.6, S 11.05; $C_{14}H_{15}NO_4S$ requires C 57.3, H 5.15, N 4.5, S 10.9%].

1,3-Dimethyl-2-phenyl-1,3,2-diazaphospholidine (198).

N,N'-Dimethylenediamine (8.82g, 0.1 mol) was dissolved in benzene (200ml) in a 500ml three-necked flask

fitted with a reflux condenser and a dropping funnel. Triethylamine (22.2g, 0.22 mol) was then added with stirring. Dichlorophenylphosphine (17.9g, 0.1 mol) dissolved in benzene (25ml) was added dropwise with stirring. When the addition of dichlorophenylphosphine was complete the mixture was stirred at room temperature overnight. The solution was filtered and the precipitate of triethylamine hydrochloride washed with benzene (50ml). The solvent was removed in vacuo and the residue distilled to afford phospholidine (198) (12.2g, 63%) as a colourless liquid, b.p. 89-93°C at 1mm Hg (Lit.[117] b.p. 95°C, 0.7mm Hg).

^{1}H NMR ($CDCl_3$) 2.65 (d J = 16Hz, 6H), 3.06 (m,4H), 7.3-7.7 (m,5H).

Olefin (199)[111]

A suspension of thionocarbonate (197) (0.2g, 0.68 mmol) in 0.4ml (0.4g, 2mmol) of (198) under argon was stirred at room temperature overnight. The mixture was directly chromatographed on a column of 20g of silica gel (elution with diethylether-hexane, 3:2) to afford a partially purified sample of olefin 199 (total recovery 0.2g).

TLC Rf 0.4 (silica gel, diethylether-hexane, 3:2).

IR ($CHCl_3$) 1775, 1471, 1450, 1435, 1230, 1155, 1105, 1035, 940, 710 cm^{-1}.

^{1}H NMR ($CDCl_3$) 1.55 (d J = 7Hz,3H), 2.4-3.0 (m,9H), 3.3 (d J = 10.2Hz,6H), 4.1 (m,2H), 5.05 (m, H), 5.65 (m,1H),

7.2 - 8 (m,9H).

$[M]^+$ 217.1105. $C_{13}H_{15}NO_2$ requires 217.1103.

$[M]^+$ 226.069. $C_{10}H_{15}N_2PS$ requires 226.06936.

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