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Asymmetric synthesis of conformationally restricted amino acids

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ASYMMETRIC SYNTHESIS of CONFORMATIONALLY RESTRICTED AMINO ACIDS

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by

Javad Safaei Ghomi (M.Sc.)

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In the Name of God, the Compassionate and the Merciful

Publications

Some of the work described in this thesis has been reported in the following publications:

"*Exo*-Diastereoselective Diels-Alder Reactions of (2*R*)-3-Benzoyl-4-methylene-2-phenyloxazolidin-5-one" Stephen G. Pyne, Javad Safaei-G., David C. R. Hockless, Brian W. Skelton, Alexander N. Sobolev and Allan H. White, *Tetrahedron*, **1994**, *50*, 941-956.

"*Exo*-Diastereoselective 1,3-Dipolar Cycloadditions of Azomethine Ylides to (2*R*)-3-Benzoyl-4-methylene-2-phenyloxazolidin-5-one" Stephen G. Pyne, Javad Safaei-G. and Fiona Koller (in part), *Tetrahedron Lett.*, **1995**, *36*, 2511-2514.

"1,3-Dipolar Cycloadditions of a Chiral Oxazolidinone with Nitrones and Nitrile Oxides" Stephen G. Pyne, Javad Safaei-G., Brian W. Skelton and Allan H. White, *Aust. J. Chem.*, **1995**. (accepted)

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ABBREVIATIONS

The following abbreviations have been used throughout this thesis.

[α]	specific rotation
AACB	amino acid of cyclobutane series
Ac	acetyl
ACC	1-aminocyclopropanecarboxylic acid
ACE	angiotension converting enzyme
AO	atomic orbital
Ar	aryl
atm	atmosphere
Bn	benzyl
b.p.	boiling point
Bu	butyl
Bu^t	*tert*-butyl
°C	degrees Celsius
calcd	calculated
CH_2Cl_2	dichloromethane
CI	chemical ionization
cm	centimetre
COSY	correlation spectroscopy
CPD	cyclopentadiene
δ	chemical shift in parts per million downfield from tetramethylsilane
d	doublet
1D	1 dimensional
2D	2 dimensional
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
d.e.	diastereomeric excess
dec	decomposes
DHAA	dehydroamino acid
DMF	dimethylformamide
d.r.	diastereomeric ratio
e.e.	enantiomeric excess
EI	electron impact
ent	enantiomer
epi	epimer

eq.	equation
equiv.	(molar) equivalents
ES	electrospray
Et	ethyl
FAB	fast atom bombardment
FMO	frontier molecular orbital
FT	Fourier transform
g	gram
GPI	guinea pig ileum
HETCOR	heteronuclear correlation spectroscopy
HIV	human immunodeficiency virus
HOMO	highest occupied molecular orbital
HPLC	high-performance liquid chromatography
hr	hours
HRMS	high-resolution mass spectrum
Hz	hertz
IR	infrared
J	coupling constant
k	kilo
L	litre(s)
LAH	lithium aluminium hydride
lit.	literature
LDA	lithium diisopropylamide
Leu	leucine
LUMO	lowest unoccupied molecular orbital
μ	micro
m	multiplet (spectral), milli
M	mols per litre
Me	methyl
MHz	megahertz
min	minutes
MNDO	modified neglect of differential overlap
mol	mole(s)
m.p.	melting point
MTPA	α-methoxy-α-trifluoromethylphenylacetate
MS	mass spectrometry
m/z	mass to charge ratio
NCS	*N*-chlorosuccinimide
ND	not determined

NMR	nuclear magnetic resonance
NOESY	nuclear Overhauser effect spectroscopy
NPAA	non-proteinogenic amino acid
NR	no reaction
Ph	phenyl
Phe	phenylalanine
ppm	parts per million
Pr	propyl
Pr^i	isopropyl
Pro	proline
PTLC	preparative thin layer chromatography
q	quartet
r.t.	room temperature
s	singlet
t	triplet
tert	tertiary
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	tetramethylsilane
Tyr	tyrosine

ABSTRACT

This thesis describes new approaches to the asymmetric synthesis of cyclic non-proteinogenic α-amino acids (NPAAs) and amino acid derivatives from (2*R*)-3-benzoyl-4-methylene-2-phenyloxazolidin-5-one. In the first Chapter, an overview of the strategies used for the synthesis of these compounds and also their biological activities was provided. It was found that for the preparation of cyclic α-amino acids in high enantiomeric purity, starting materials with a chiral auxiliary have generally been employed.

In Chapter Two, the synthesis of cyclic NPAAs, through the thermally induced Diels-Alder reactions of (2*R*)-3-benzoyl-4-methylene-2-phenyloxazolidin-5-one (8) and substituted 1,3-butadienes and substituted 1,3-cyclohexadienes was explored. In general, the reactions were found to be highly regioselective and *exo*-diastereoselective. The *exo* selectivity of these reactions was explained by a secondary orbital interaction between the *N*-donor group of the oxazolidinone ring of (8) (a captodative alkene) and the diene. The NPAA, (2*S*,4*S*)-2-aminobicyclo[2.2.2]octane-2-carboxylic acid, was prepared in optically active form starting with (8) and cyclohexadiene.

In Chapter Three, the 1,3-dipolar cycloaddition reactions of (2*R*)-3-benzoyl-4-methylene-2-phenyloxazolidin-5-one (14) with nitrones and nitrile oxides are reported. In general the nitrone reactions occur under equilibrating conditions to give the more stable adducts that result from addition to the *exo*-cyclic methylene of (14) from the sterically more hindered π-face. The major adducts from the reaction of (14) and nitrile oxides (2) and (37) had the expected stereochemistry, addition of the 1,3-dipole occurred from the least hindered π-face of the *exo*-cyclic methylene

of (14). Hydrogenation / hydrolysis of the cycloadduct of (14) and *C,N*-diphenylnitrone gave the novel compound, *cis*-(2*R*,4*S*)-1,4-diphenyl-2-benzoylazethane (58).

In Chapter Four, a new method for the synthesis of polyfunctional prolines was established through *exo*-diastereoselective 1,3-dipolar cycloaddition reaction of (2*R*)-3-benzoyl-4-methylene-2-phenyloxazolidin-5-one (22) and *N*-benzylidene α-amino acid esters. The proline derivatives (49) and (50) were synthesised in high enantiomeric purity (92% e.e.) by methanolysis of the oxazolidinone moiety of their respective cycloadducts. In the case of ethyl *N*-benzylidene glycinate, a Michael addition product (35) and two novel tricyclic compounds (30a) and (30b) were also isolated and characterized.

In each Chapter, the stereochemistry of the products was determined by a combination of single crystal X-ray structural analysis, 1D and 2D NMR spectroscopy and molecular modelling.

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CHAPTER ONE

INTRODUCTION

1-1. Non-Proteinogenic α-Amino Acids (NPAAs)

The α-amino acids form one of the five major classes of natural products and they exhibit an important and diverse range of biological properties. Historically, the α-amino acids have been subdivided into the 20 proteinogenic and the non-proteinogenic (NPAA) representatives. The number of known naturally occurring non-proteinogenic examples is constantly increasing and had reached 1000 when counting was discontinued in 1989.[1] These compounds are mainly produced by various micro-organisms and many of them are the end products of secondary metabolism, which have evolved to interfere with the biochemical pathways of other organisms.[1a] The number of non-natural or totally synthetic amino acids could in principle be almost infinite. The NPAAs possess enormous structural diversity and a broad range of biological activity including medicinal properties,[2] and the ability to act as enzyme inhibitors.[3] Some NPAAs, are important intermediates in biosynthesis,[4] while others have found application in the investigation of enzymatic mechanisms.[5]

New peptide pharmaceuticals have been developed by incorporating one or more conformationally restricted NPAAs into bioactive peptides, including peptide hormone analogues and enzyme (protease) inhibitors.[6a] This incorporation constitutes an important approach to the systematic study of the structure-activity relationships of peptides and also offers the potential to discover analogues with improved stability, bioselectivity and bioavailibility. *N*-methyl amino acids, α,α-disubstituted amino acids, proline analogues and dipeptide lactam derivatives are common examples of moieties that may be incorporated to influence the local conformation of peptides.[6b]

Like proteinogenic amino acids, NPAAs can also be used as chiral starting materials in organic synthesis and for the preparation of chiral auxiliaries for use in asymmetric synthesis.[7]

1-1-1. Cyclic Non-Proteinogenic Amino Acids

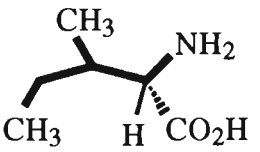
Conformationally rigid cyclic α-amino acids are useful for probing the structure and steric requirements of the receptor sites by which amino acids are transported or stimulate hormonal secretion.[8] Since many of these cyclic α-amino acids are α',α''-disubstituted amino acids, conventional enzymic optical resolution technology cannot be applied effectively to their asymmetric synthesis. While various synthetic methods have been reported for the synthesis of cyclic amino acids, no general method has been developed for the asymmetric synthesis of these compounds.

1-1-1-1. Bicyclic Amino Acids

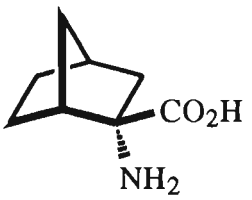
(2*S*)-2-Aminonorbornane-2-carboxylic acids (1) and (2) are cyclic amino acids in which rigidly specified positions are taken by carbon atoms corresponding to those of the ordinary branched chain amino acids (*S*)-isoleucine (3) and (*S*)-valine (4), respectively. Amino acids (1) and (2) are transported by the same system operating for amino acids with branched, hydrophobic side chains (eg. (3) and (4)) in some cells and tissues.[9] Evidently, several of the carbon atoms in (1) and (2) take critical positions in space which meet the site-fitting requirements that are met so well by the branched chains of leucine and isoleucine (3), less well in the case of valine (4). For the species in which the transport system shows the narrowest specificity to such amino acids, namely that in *Escherichia coli*, the restriction to one of the two stereoisomers (1) appears complete.[8a] The compounds (1) and (2) have also been used as

stimulators for the release of insulin from the rat pancreas.[9a] These results bear significantly on the character of the receptor site at which administered leucine and other amino acids produce their hypoglycaemic action and their stimulation of insulin release.[9b]

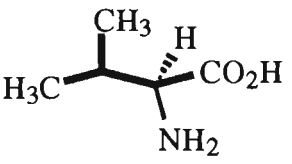
(2*S*)-*endo* (**1**)



(*S*)-Isoleucine (**3**)

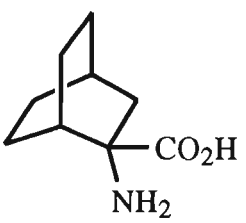


(2*S*)-*exo* (**2**)



(*S*)-Valine (**4**)

A similar study on 2-aminobicyclo[2.2.2]octane-2-carboxylic acid (5) has been reported.[8b] In this study the effect of this compound on the levels of the neutral and aromatic amino acids of the rat cerebral cortex was examined. Compound (5) caused an elevation in the levels of isoleucine and leucine. The level of methionine, on the other hand, was depressed by this compound. The observed effects of this bicyclic amino acid and other cyclic amino acids as selective perturbators of the cerebral free amino acid pool, provide new avenues of entry for the study of amino acid-dependent dysfunctions of the brain. Foremost among these is the capability they afford to experimentally manipulate cerebral amino acid levels where they are abnormal.[8b]

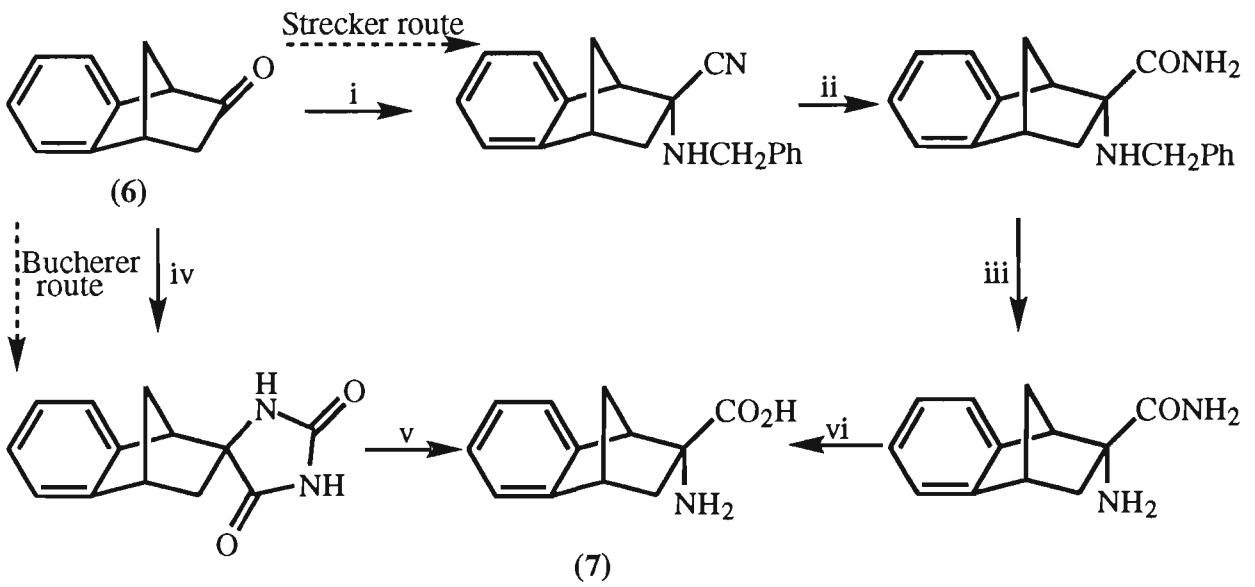


(**5**)

Amino acids with the norbornane skeleton have been prepared by two different routes: Strecker or Bucherer synthesis from the corresponding carbonyl compounds (Scheme 1.1),[10] and the Diels-Alder reaction with cyclopentadiene and α,β-dehydroamino acids (DHAAs). The latter synthetic approach has also been used for the asymmetric synthesis of 2-aminonorbornane-2-carboxylic acids (Scheme 1.2).[11]

2-Amino-1,2,3,4-tetrahydro-1,4-methanonaphthalene-2-carboxylic acid (7), of unknown stereochemistry, was obtained as the sole amino acid product from 1,2,3,4-tetrahydro-1,4-methanonaphthalene-2-one (6) using the Strecker or Bucherer method of synthesis.[10] Compound (5) was prepared by Zand *et al.* via a similar procedure.[8b]

Scheme 1.1

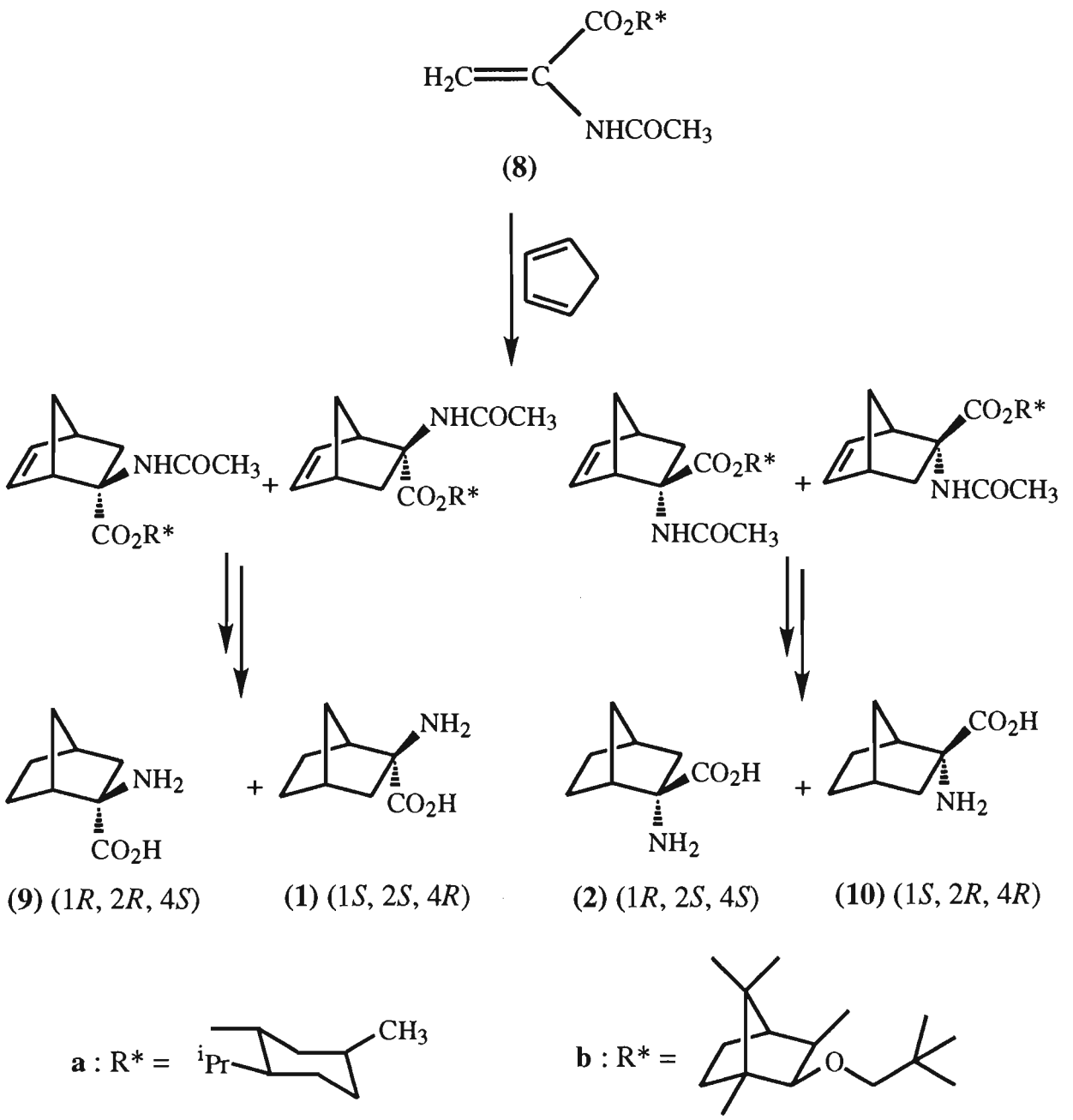


i, $PhCH_2NH_2$, KCN; ii, H_2SO_4; iii, Pd-C 5%, EtOH; iv, $(NH_4)_2CO_3$, KCN; v, $Ba(OH)_2$, vi, 10% H_2SO_4

Cativiela *et al.*[11(b-e)] reported that the Diels-Alder reaction between cyclopentadiene (CPD) and (-)-menthyl *N*-acetyl-α,β-dehydroalaninate (8a) is an excellent method for the asymmetric synthesis of 2-*endo*-aminonorbornane-2-*exo*-carboxylic acids (2) and (10), whereas the use of the *N*-acetyl-α,β-dehydroalaninate of (-)-*cis*-3-hydroxyisobornylneo-

pentyl ether (8b) as a dienophile is a better method for the asymmetric synthesis of 2-*exo*-aminonorbornane-2-*endo*-carboxylic acids (9) and (1) (Scheme 1.2).

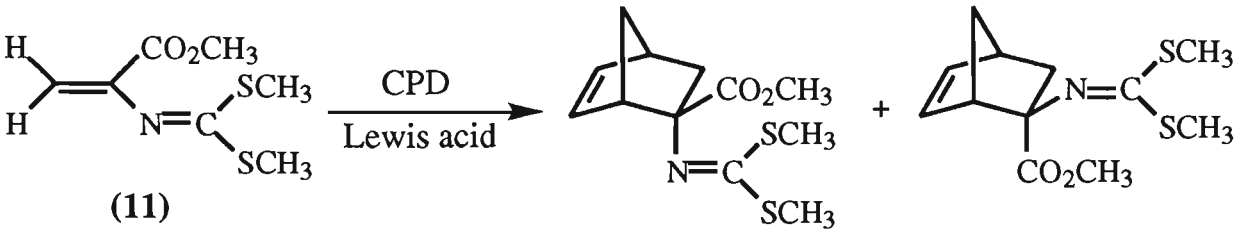
Scheme 1.2



In the above reactions the (2*S*) stereoisomers (1) or (2) are produced predominantly. In 1993, E. Bunuel *et al.*[12] introduced *N*-[bis (methylthio)methylene]-dehydroalanine methyl ester (11) (a stable derivative of α,β-dehydroalanine) as a new excellent dienophile for this type of reaction (Scheme 1.3). In this reaction the ratio of the *exo*

carboxylic acid to the *endo* one can be changed by changing the Lewis acid catalyst from $TiCl_4$ to $EtAlCl_2$.

Scheme 1.3

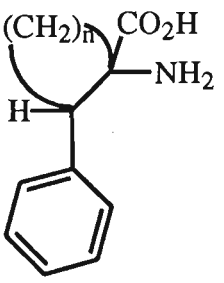


(11)

The use of the Diels-Alder reactions of 1,3-cyclohexadienes with a chiral DHAA to prepare some NPAAs with the norbornane skeleton will be considered in Chapter Two.

1-1-1-2. Cyclic Phenylalanine Analogues

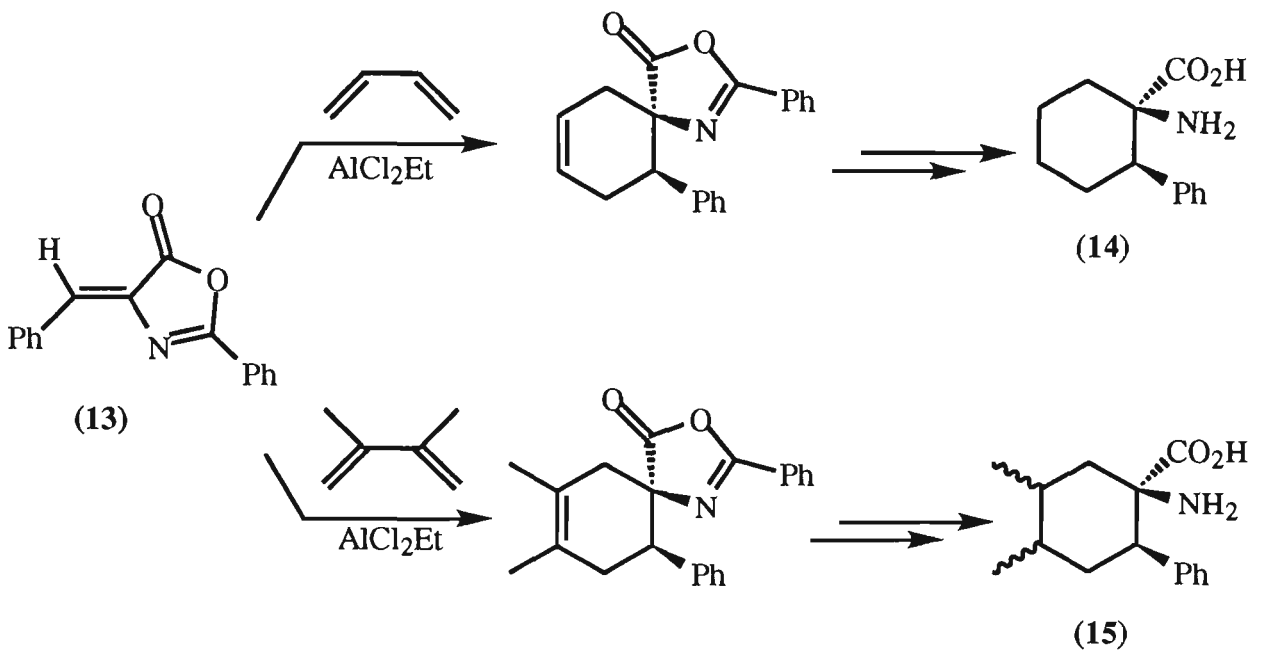
The conformationally restricted cyclic amino acid analogues of phenylalanine, as shown in the general structure (12), have proven useful for determining the importance of tyrosine conformation in the enkephalins on analgesic activity and receptor recognition.[13]



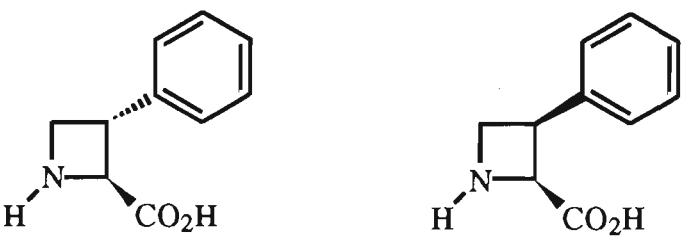
(12)

These series of compounds have been prepared[13] by the Diels-Alder reactions of 1,3-butadiene and 2,3-dimethyl-1,3-butadiene with (Z)-2-phenyl-4-benzylidene-5(4H)-oxazolone (13), to give the 1-amino-2-phenylcyclohexanecarboxylic acid derivatives (14) and (15) (Scheme 1.4).

Scheme 1.4



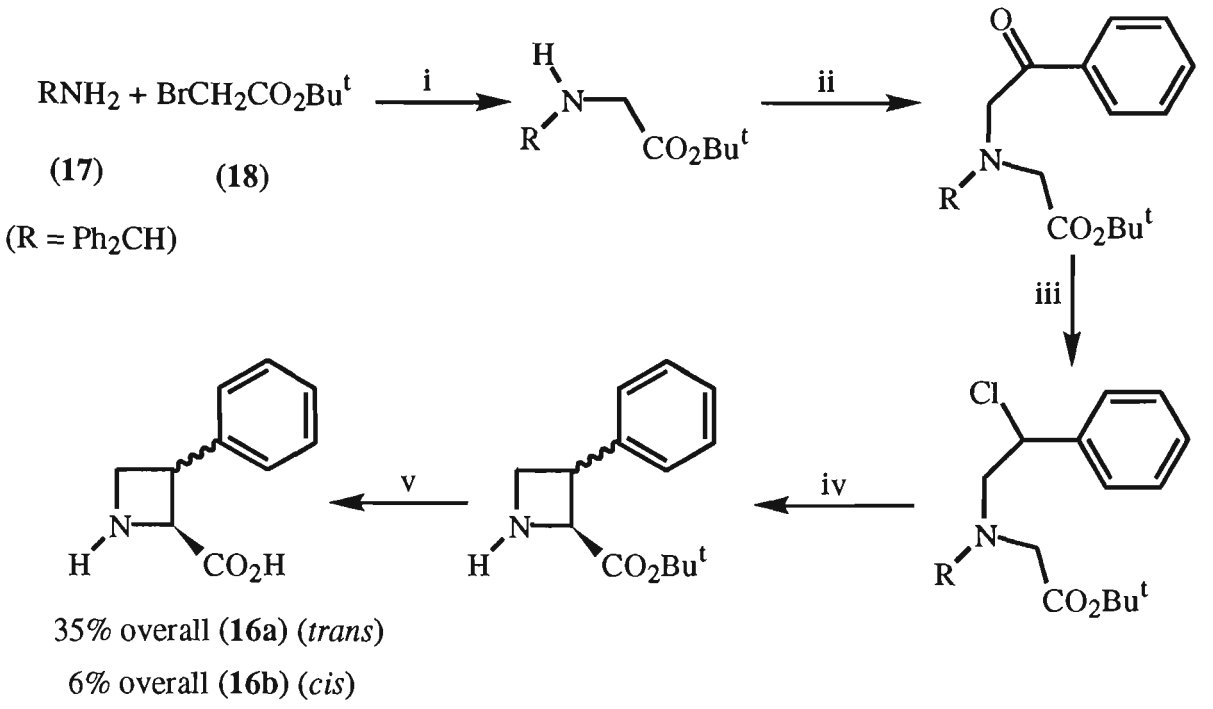
The azetidine-based analogues (16a) and (16b) have structural features that may prove useful when incorporated into peptides as phenylalanine mimics.[14a] For example, they should have improved metabolic stability since tertiary amide bonds are resistant to proteolysis.[14b,c] The conformationally restricted analogues (16a) or (16b) may also be useful in the design of novel peptide-based enzyme inhibitors.[15]



(16a) (16b)

The efficient method[15] for the synthesis of this ring system starts from the alkylation of benzhydrylamine (17) with *tert*-butyl bromoacetate (18), and after 4 steps a mixture of the *trans* isomer (16a) and the *cis* isomer (16b) were obtained. The *trans* isomer (16a) was the major product (Scheme 1.5).

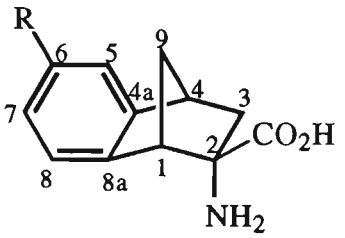
Scheme 1.5



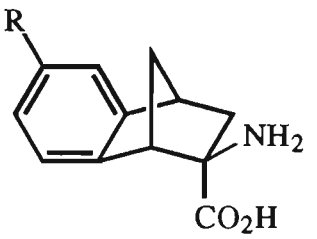
i, K_2CO_3, KI, DMF; ii, Hunig's base, $PhCOCH_2Br$, acetone; iii, 1. $NaBH_4$, $CeCl_3$, 2. $SOCl_2$, $CHCl_3$; iv, 1. $NaN(Si(CH_3)_3)_2$, THF, -78 °C, 2. $Pd(OH)_2$, H_2, HCl-MeOH; v, HCO_2H (88%), 80 °C.

The synthetic method for the preparation of (16a) and (16b) may also be applicable to the synthesis of similar conformationally restricted analogues of other amino acids, such as tryptophan, tyrosine, methionine, lysine, leucine, and histidine.

The 2-amino substituted 1,2,3,4-tetrahydro-1,4-methanonaphthalenes (19) and (20) represent rigid, pharmaceutically interesting analogues of more conformationally flexible phenylamino compounds such as amphetamine, dopamine, and noradrenaline, which may provide useful information about the nature of agonist-receptor interactions in these phenylethylamine systems.[10]



(19)

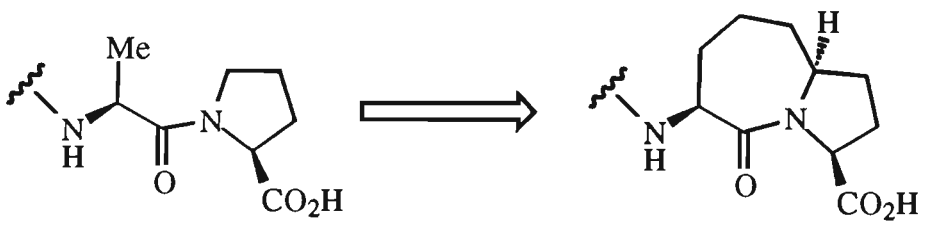


(20)

Replacement of the 1-tyrosyl moiety in Leu-enkephalin methyl ester with one of these two amino acids led to a 7 to 8 times higher agonist activity at the analgesic μ-receptor subtype in guinea pig ileum (GPI), when compare to Leu-enkephalin.[16]

1-1-1-3. Cyclic Alanine Analogues

Replacement of the alanyl-proline portion of a peptide with the bicyclic moiety (21) has been used to generate novel metalloprotease inhibitors for the treatment of hypertension and congestive heart failure[17] (eq 1.1). The alanine methyl group is joined to the C-5 position of proline ring by a ethylene linker to make the fused bicyclic lactam (21).



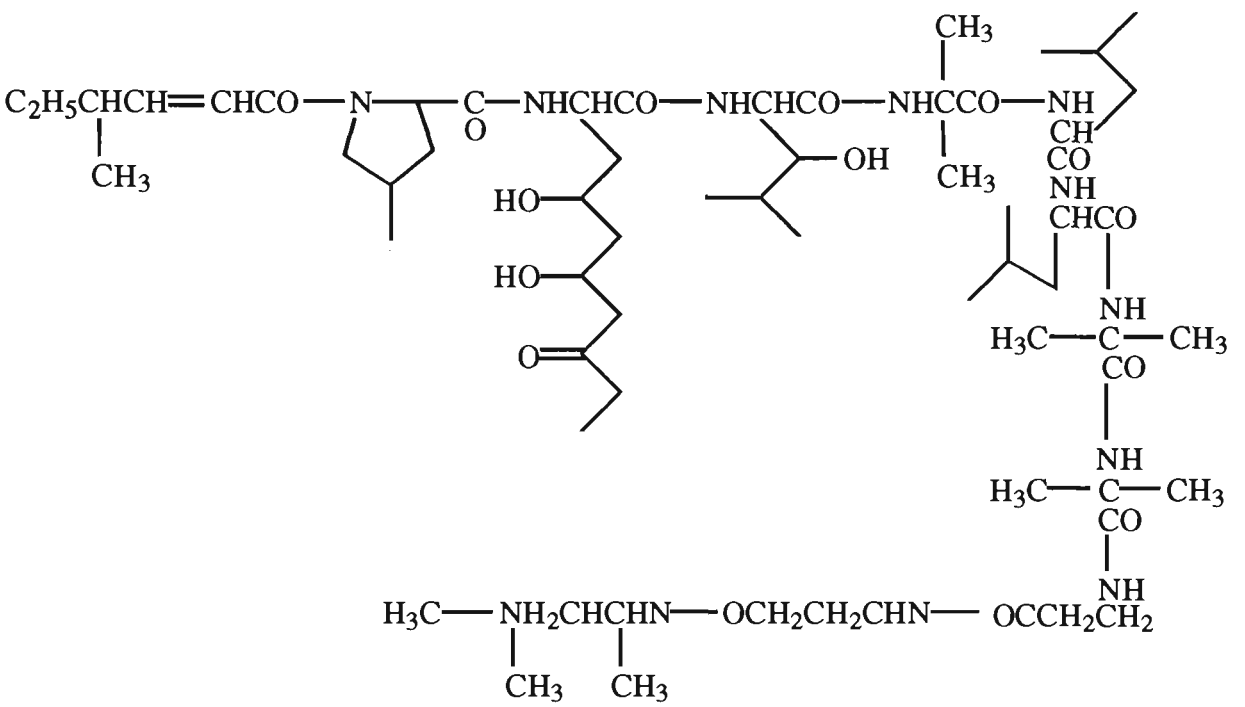
(eq 1.1)

(21)

1-1-1-4. Prolines

Proline is an amino acid that plays a significant role in the biochemistry of proteins, including preference for secondary structural motifs. Several proline analogues are rare naturally occurring amino acids, they are constituent amino acids in antibiotics, and recently they have gained interest in the development of novel Angiotension Converting Enzyme (ACE) inhibitors as a target of therapeutic agents designed to lower blood pressure in man.[18] The antibiotic P 168 (22) was isolated from a culture

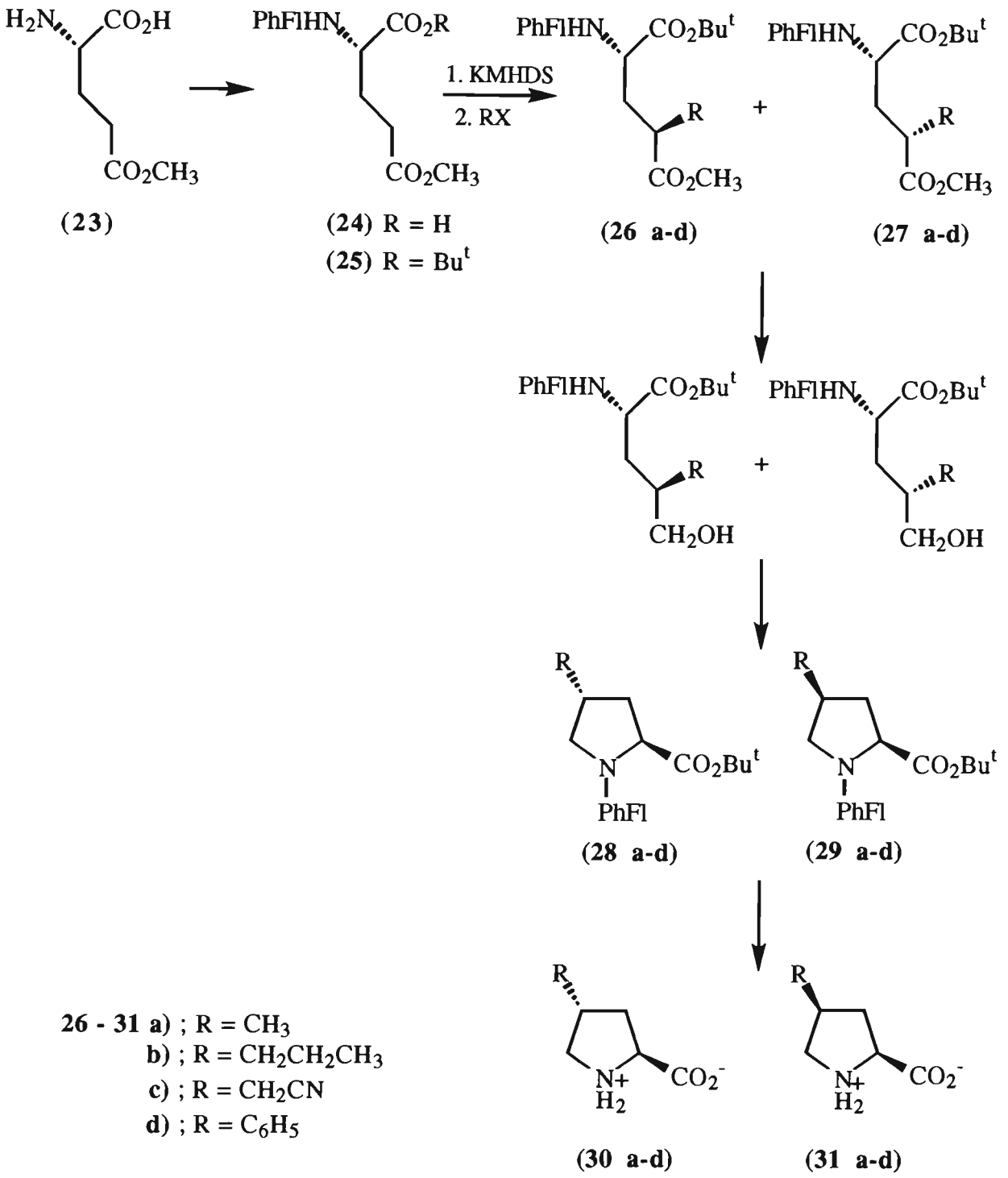
filtrate of *paecilomyces lilacinus* and has 4-methyl proline as one of its amino acids.[19a] This antibiotic was found to possess a wide antimicrobial spectrum against fungi, yeasts, and gram-positive bacteria.[19b]



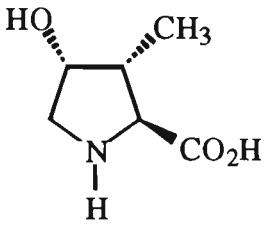
(22)

Substituted prolines provide a new type of simple conformational constraint. 4-Substituted prolines have been synthesised by chirospecific transformations of glutamic acid (23), in four steps as shown in Scheme 1.6.[18] A suitably protected glutamic acid derivative (25) (9-[9-phenylfluorenyl] is the nitrogen protecting group) was alkylated and selective reduction of the distal esters of (26) and (27) was achieved by the proper choice of ester protecting groups. Finally ring closure to prolines (28) and (29) completed the synthesis (Scheme 1.6). The optical integrity of the final proline derivatives was shown to be >99%.

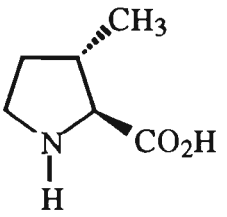
Scheme 1.6



Other examples of non-proteinogenic proline derivatives are compounds (32) and (33). They have recently been detected in a novel cyclic peptide, scytonemin A, a metabolite of cultured *cyanophyte Scytonema sp.*, which possesses potent calcium antagonistic properties.[20]

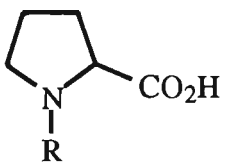


(32)



(33)

Several other structurally novel proline derivatives are potent ACE inhibitors (34 a-e) and contain L-proline as the C-terminal portion.[21a] Captopril (34 a) is the first ACE inhibitor to have been approved as a drug. It is used in the treatment of essential hypertension and congestive heart failure.[21b] Captopril and its analogues have several advantages over conventional antihypertensive therapeutics including the lack of interaction with the central and automatic nervous systems.

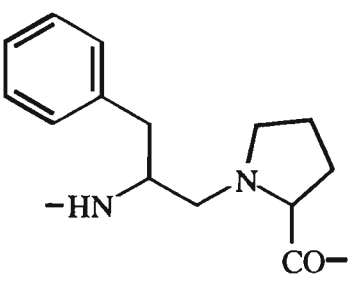


(**34 a**) ; R = $HSCH_2CH(CH_3)CO$
(**b**) ; R = $HSCH_2CH_2CO$
(**c**) ; R = $PhCH_2CH_2CH(CO_2Et)NHCH(CH_3)CO$
(**d**) ; R = $PhCH_2CH_2CH(CO_2H)NHCH(CH_3)CO$
(**e**) ; R = $PhCH_2CH(NHCOPh)COCH_2CH_2CO$

The introduction of conformationally constrained analogues of proline into peptides by incorporating 3-substituted derivatives is an important tool in developing peptide-derived pharmaceutical agents.[22] The replacement of appropriate residues in biologically active peptides with these analogues could lead to important conformational information and offer the potential to discover peptide analogues with improved selectivity, stability, or bioavailability. Due to motional restrictions inherent to the pyrrolidine ring, the presence of a proline residue greatly reduces the available conformational space of a peptide and gives rise to conformers separated by relatively high interconversion barriers. Thus,

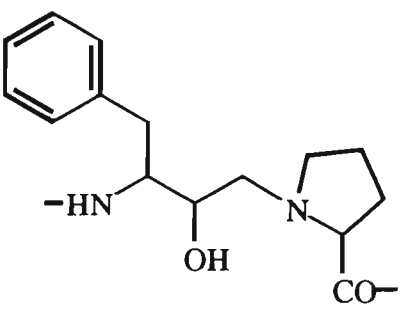
information can be obtained about the bioactive conformation of a peptide, and the biological potency may be increased by incorporation of a proline residue.[23]

Replacement of proline by its higher homologue is reported to dramatically improve pharmaceutical potency in peptide-based HIV proteinase inhibitors.[24] Since the amide bonds of proline residues (35) and (36) are not susceptible to cleavage by mammalian endopeptidases, these compounds can provide a basis for the rational design of HIV proteinase inhibitors selective for the viral enzyme.



Reduced amide

(35)



Hydroxyethylamine

(36)

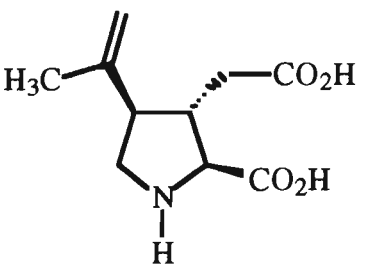
The reduced amide (35) and the hydroxyethylamine (36) structures most readily accommodate the amino acid moiety characteristic of Phe-Pro and Tyr-Pro in retroviral substrates. Although the compounds containing the reduced amide function are relatively poor inhibitors, the compounds incorporating the hydroxyethylamine moiety are very potent and highly selective inhibitors of HIV proteinase.[24]

The 1,3-dipolar cycloaddition reactions of azomethine ylides from *N*-alkylidene α-amino acid esters to electron deficient alkenes is an extremely powerful method for the asymmetric synthesis of polyfunctional prolines.[1b] In this synthetic method, that will be outlined in Chapter 4, a chiral DHAA will be employed as a dipolarophile for the asymmetric synthesis of proline derivatives.

1-1-1-5. Cyclic Glutamate Analogues

L-Glutamate is the major excitatory neurotransmitter in the mammalian central nervous system.[25] In this role glutamate binds to a number of different proteins, including several distinct receptors, transport systems, and enzymes. In addition, abnormal levels of glutamate have been linked to a wide spectrum of neurological disorders, including ischaemia, anoxia, hypoglycaemia, epilepsy, and Huntington's, Parkinson's, and Alzheimer's diseases.[26] In particular, structure-activity studies with conformationally restricted glutamate analogues have provided valuable new information about the structural requirements for binding to the various glutamate receptors, and to the high-affinity glutamate uptake system responsible for removing glutamate from the synaptic cleft.

Kainic acid (37) occurs naturally in red algae and exerts a powerful neuroexitatory effect on glutamate receptors.[27] This compound exhibits neurotoxic activity and has a role in the treatment of Huntington's disease (a rare hereditary disease of the nervous system).

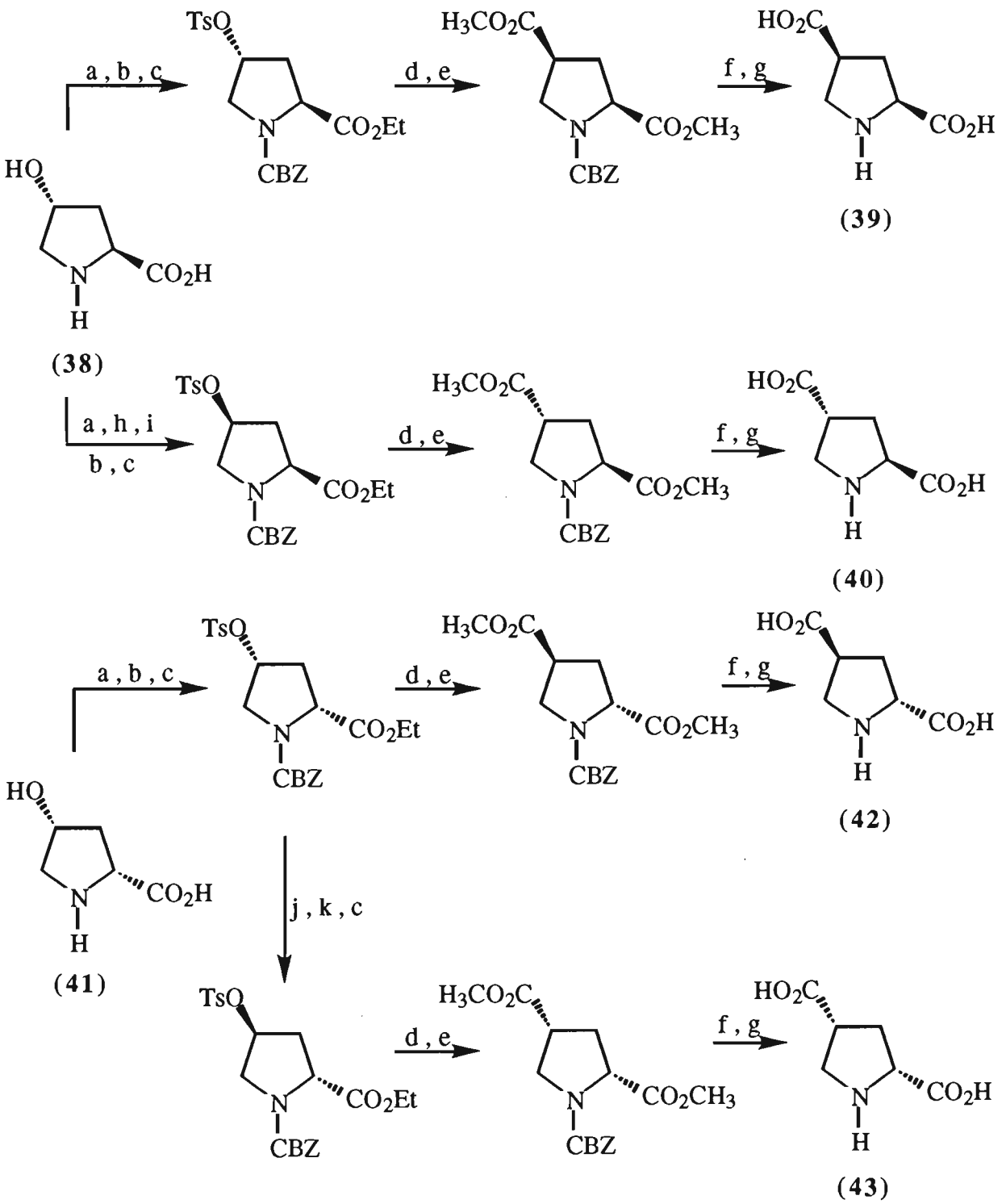


(37)

In Scheme 1.7 the enantioselective synthesis of the four diastereomeric pyrrolidine-2,4-dicarboxylates (39, 40, 42, 43) from commercially available *trans*-4-hydroxy-L-proline (38) and *cis*-4-hydroxy-D-proline (40) is outlined.[28] These rigid analogues contain an embedded glutamate moiety. While none of the four analogues binds effectively to the

excitatory receptors, the L-*trans*-isomer (40) is a potent and selective competitive inhibitor of L-glutamate transport.[28]

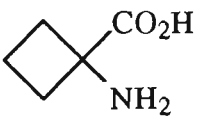
Scheme 1.7



(a) $ClCO_2CH_2Ph$, $NaHCO_3$, H_2O, $PhCH_3$; (b) EtOH, *p*-TsOH; (c) TsCl, py; (d) NaCN, DMSO; (e) HCl, wet CH_3OH; (f) NaOH, THF-H_2O 1:1; (g) H_2 (48 psi) / 10% Pd-C, CH_3OH; (h) Jones oxidation; (i) $NaBH_4$, CH_3OH; (j) *n*-Bu_4NOAc, acetone; (k) NaOEt, EtOH

1-1-1-6. Aminocyclobutanecarboxylic Acids

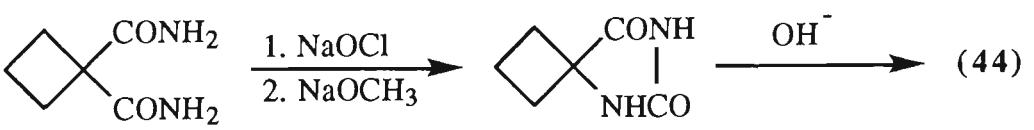
Amino acids of the cyclobutane series (AACB) are compounds which have been relatively little investigated. These compounds were almost the only type of amino acids which have not been detected in natural sources until 1980 when Bell *et al.*[29] isolated them from *Atelia Herbert Smithii (Sophoreae, Leguminosae)*. Since biologically active substances with antiviral, neurotropic, analgesic, depressant, antimicrobial, and other activities have been found among AACB derivatives, these compounds have attracted the attention of chemists during the recent decades.[30] 1-Aminocyclobutanecarboxylic acid (44) is an inhibitor of the growth of tumours and a selective antagonist of *N*-methyl-*D*-aspartic acid in relation to the [^{2}H]-receptors of histamine and [^{3}H]-receptor of glycine. The 2-(3-methoxyphenyl) derivative of (44) inhibits aminooxidases in rat liver mitochondria.[30]



(44)

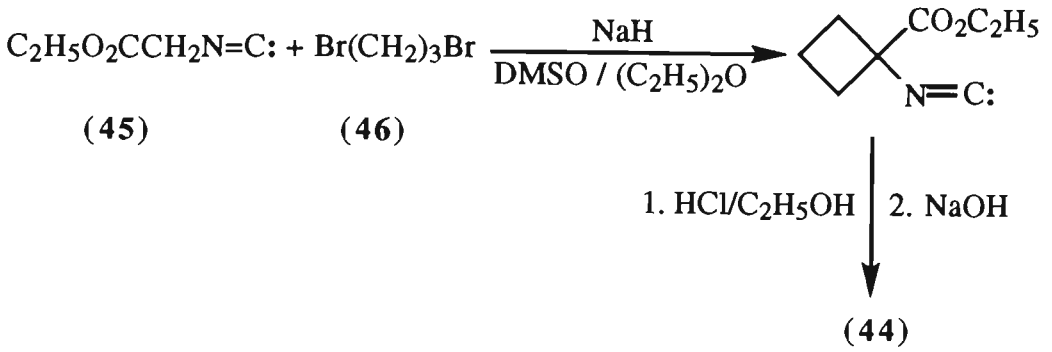
A successful preparative method for the synthesis of compound (44) is the classical hydantoin synthesis of amino acids (Scheme 1.8).[31]

Scheme 1.8



In 1986, M. Jouda *et al.*[32] reported the use of ethyl isocyanoacetate (45) and 1,3-dibromopropane (46) for the preparative synthesis of compound (44) in 98% yield (Scheme 1.9).

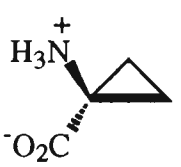
Scheme 1.9



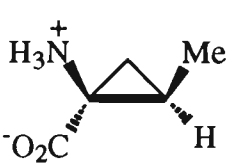
(45) (46) (44)

1-1-1-7. Cyclopropane Amino Acids

Among conformationally restricted amino acids, 1-aminocyclopropane carboxylic acid (ACC) derivatives constitute a wide family of naturally occurring or synthetic compounds which have attracted special attention due to their biological activities as phytochemical agents, enzyme inhibitors and probes in metabolism studies.[33] These sterically rigid cyclopropane amino acids were found to be a key constituent not only as conformational constraint but also as a structural element to avoid enzymatic degradation.[34] For instance, the parent compound (47), isolated from several fruits (cider apples and perry pears), has been found to be the biosynthetic precursor to the plant hormone ethylene.[35] It has also been shown that allonorcoronamic acid (47) is a substrate and the strongest known competitive inhibitor of the ethylene-forming enzyme in mung bean hypocotyls.[40]



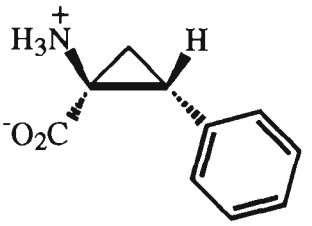
(47)



(48)

Incorporation of cyclopropane amino acids into several peptides has been achieved for some neuropeptides, hormones, and enzyme inhibitors.[34] Two interesting examples that involve the use of methanophenylalanine (49) include novel enkephalin and aspartam analogues. Enkephalin

analogues showed reduced activity in the mouse vas defens and GPI muscle assays, the peptides showing a strong preference for the δ-receptor of the GPI.[37]



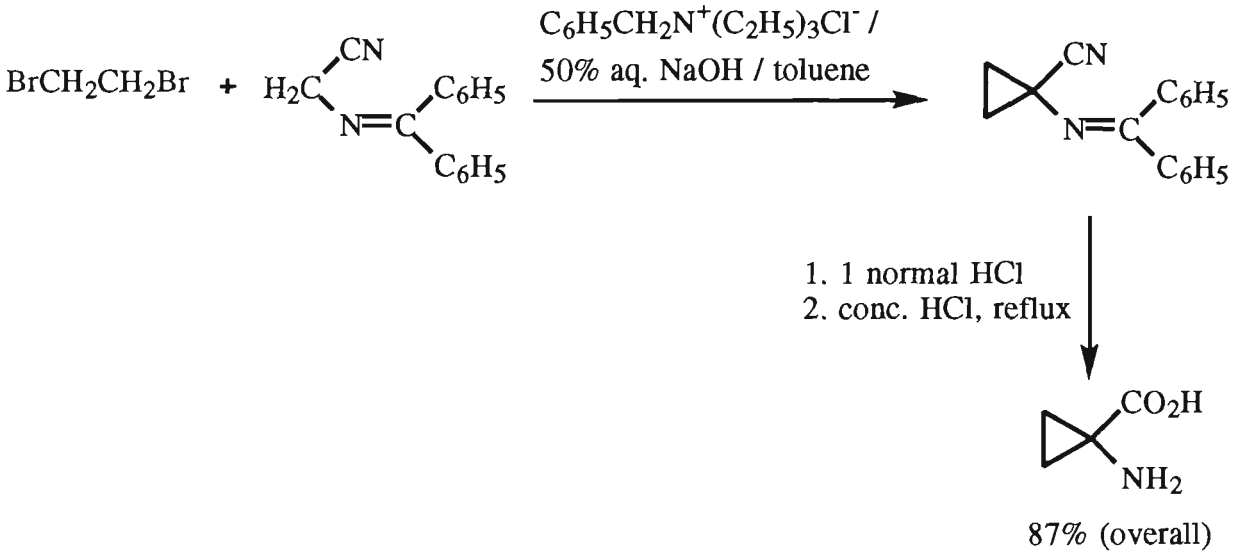
(49)

These studies illustrate the potential medicinal utility of peptides incorporating ACC derivatives.

Mono- and disubstituted ACCs have been synthesised through the following routes:

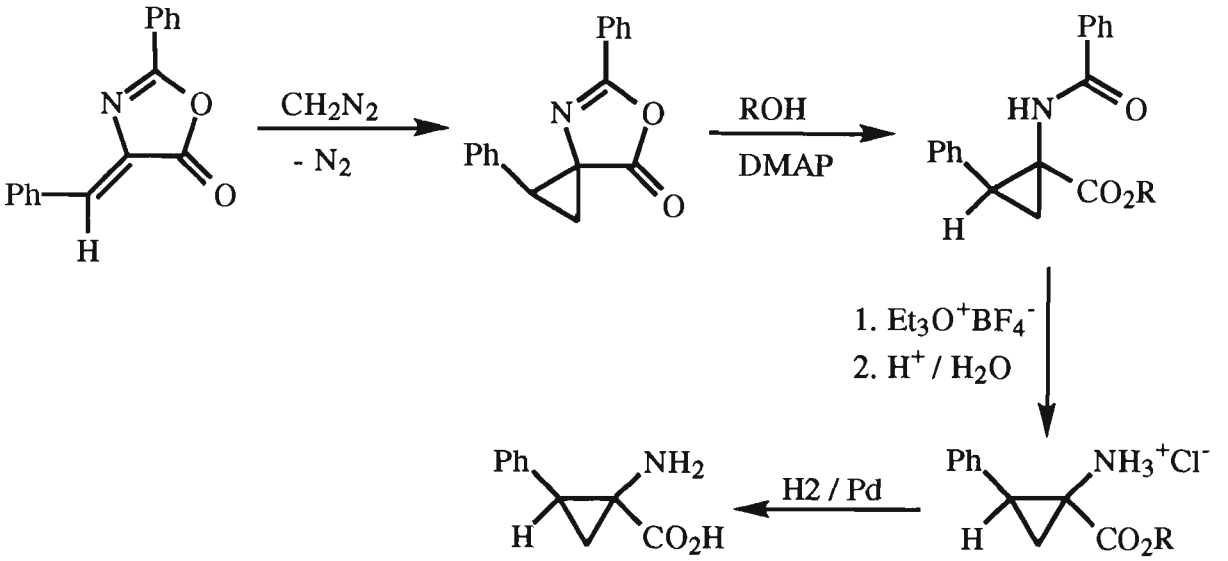
1) Tandem dialkylation of a glycine equivalent with a 1,2-dibromoalkane (Scheme 1.10)[38a] or a similar 1,2-disubstituted electrophile.[38b]

Scheme 1.10



2) Diazoalkane or dimethylsulfoxonium methylide addition to dehydroamino acid derivatives, followed by extrusion of N_2 gas[39a] (Scheme 1.11) or elimination of DMSO[39b], respectively.

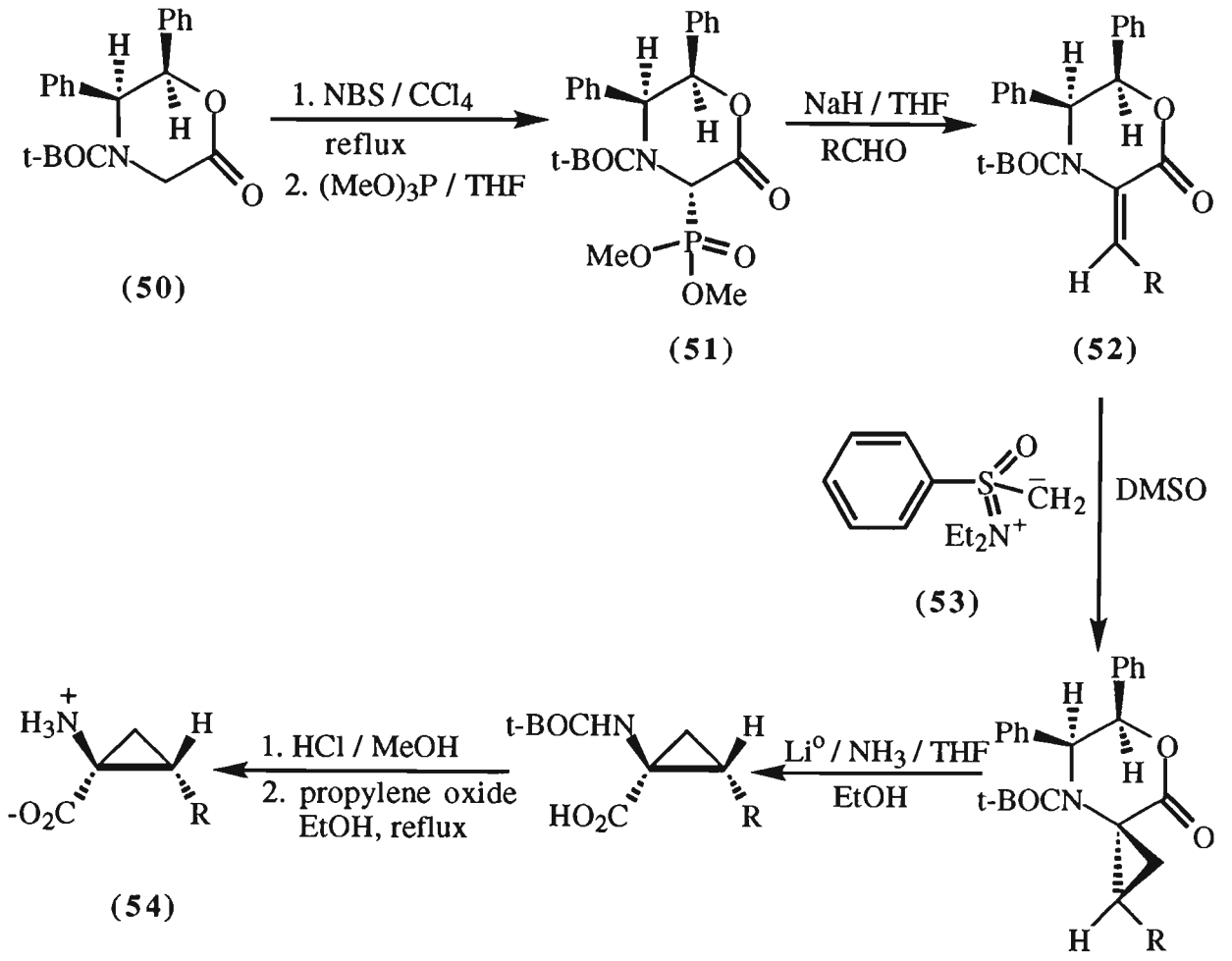
Scheme 1.11



In the above synthetic methods there is no single, general stereocontrolled approach to differentially substituted ACC derivatives in optically pure form.

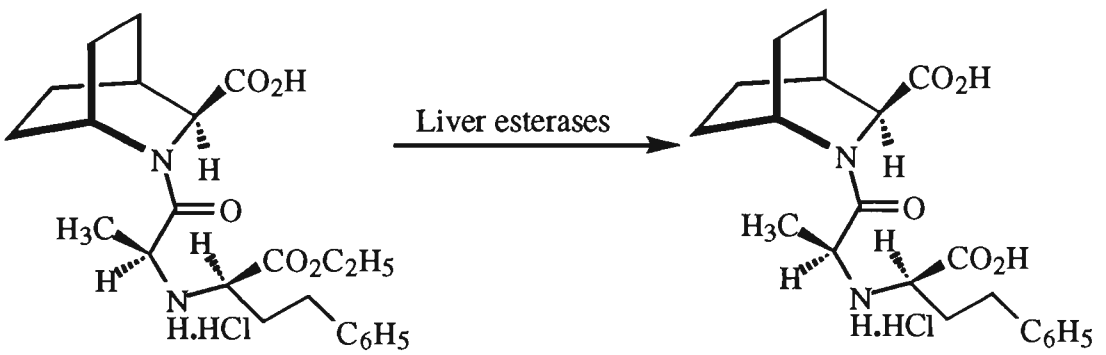
Williams *et al.*[37] prepared (*E*)-2-alkyl ACCs (54) in high enantiomeric purity. This approach employs the phosphonate ester (51) which is produced by bromination of the lactone (50) and then treatment with trimethyl phosphite under reflux (Scheme 1.12). Subsequent treatment of (51) with base and aldehyde through the Wittig reaction provided the cyclic (*E*)-α,β-dehydroamino acid derivative (52). The cyclopropanation reaction product was obtained upon treatment of the DHAA (52) with the NaH-derived dimethyloxosulfonium methylide (53).

Scheme 1.12



1-1-1-8. Other Cyclic Amino Acids

The clinical studies of Zabicipril (55) (alanine analogue) suggest that this compound is a well tolerated, powerful and long acting inhibitor of ACE, with maximal inhibitory effect at 2.5 mg per day when given *via* the oral route.[40a] Compound (55) is an acid-ester, devoid of activity *per se*, which is transformed by liver esterases into its active diacid form Zabiciprilate (56) (eq 1.2). *In vitro*, (56) is a very active compound (IC_{50}=1.8 nmol, substrate: hippuryl-histidyl-leucine).[40b] It is believed that the two carboxylic groups of (56) bind to the positive sites of ACE, which suggests the spatial disposition of these charged groups in the enzyme.

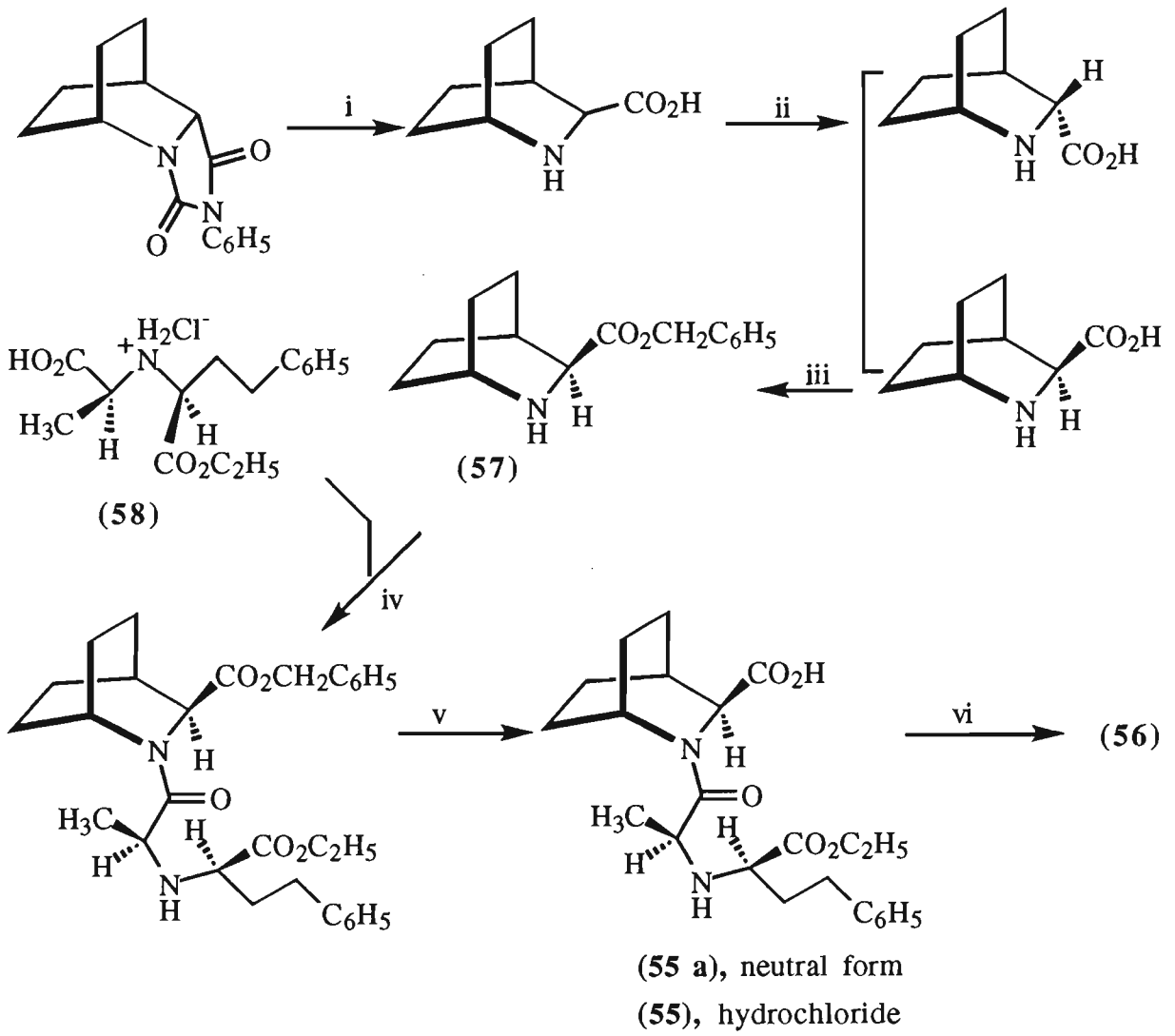


(eq 1.2)

(55) Zabicipril **(56) Zabiciprilate**

The synthesis of (55) and (56) was performed *via* coupling of the two intermediates (57) and (58) following the route outlined in Scheme 1.13.[40]

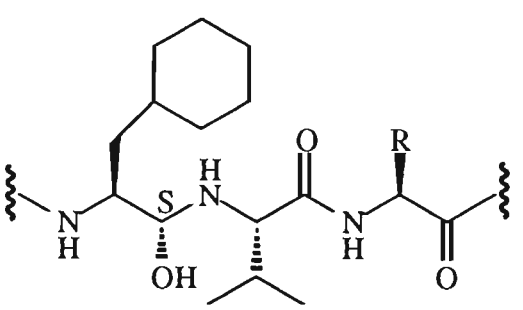
Scheme 1.13



i, NaOH; ii, resolution by (-)-tartaric acid; iii, $C_6H_5CH_2OH$, PTSH; iv, coupling; v, H_2 cat Pd / C; vi, NaOH

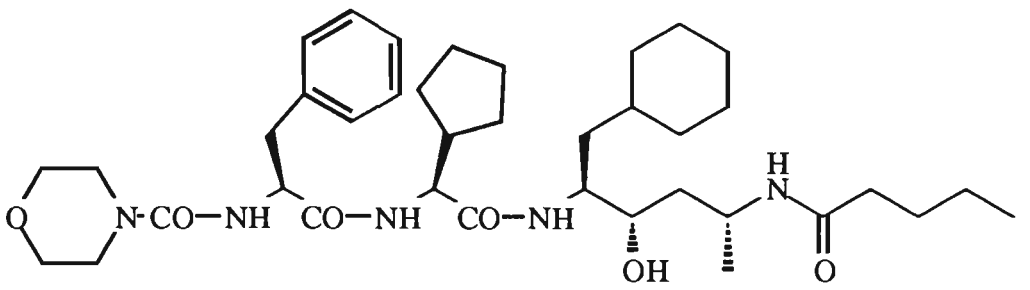
Cyclopentylglycine is an excellent inhibitory analogue of isoleucine in that the toxicity of the analogue for *E. coli* is prevented in a competitive manner over a broad range of concentrations at a relatively low inhibition index. A study of the effects of the metabolites on the toxicity of cyclopentylglycine has revealed that certain metabolites, particularly threonine, allow *E. coli* to synthesise increased concentrations of isoleucine. The keto analogue of isoleucine, α-keto-β-methylvaleric acid, is very effective in preventing the toxicity of cyclopentylglycine, and this activity can be accounted for only in part by its conversion to isoleucine.[41]

Introduction of a cycloalkyl group to the β-position of an α-amino acid and incorporation of the so-obtained cycloalkylglycine into peptides provides novel renin-inhibitors.[42a] The renin-angiotension system plays a central role in the pathogenesis of hypertension, mostly via the circulating vasoconstrictor angiotensin II. The most important reaction of renin is the proteolysis of the *N*-terminus of the globular protein angiotensinogen to the decapeptide angiotensin I. Replacement of the Leu-Val peptide bond that is cleaved in this reaction, with a cyclic substituted (*S*)-hydroxyethylene amide bond surrogate, renin-inhibitors of the type (59) are obtained.[42b] Since these molecules resemble the transition state for cleavage by aspartyl proteases they possess a high affinity for renin but are not cleaved by the enzyme.[42a]



(59)

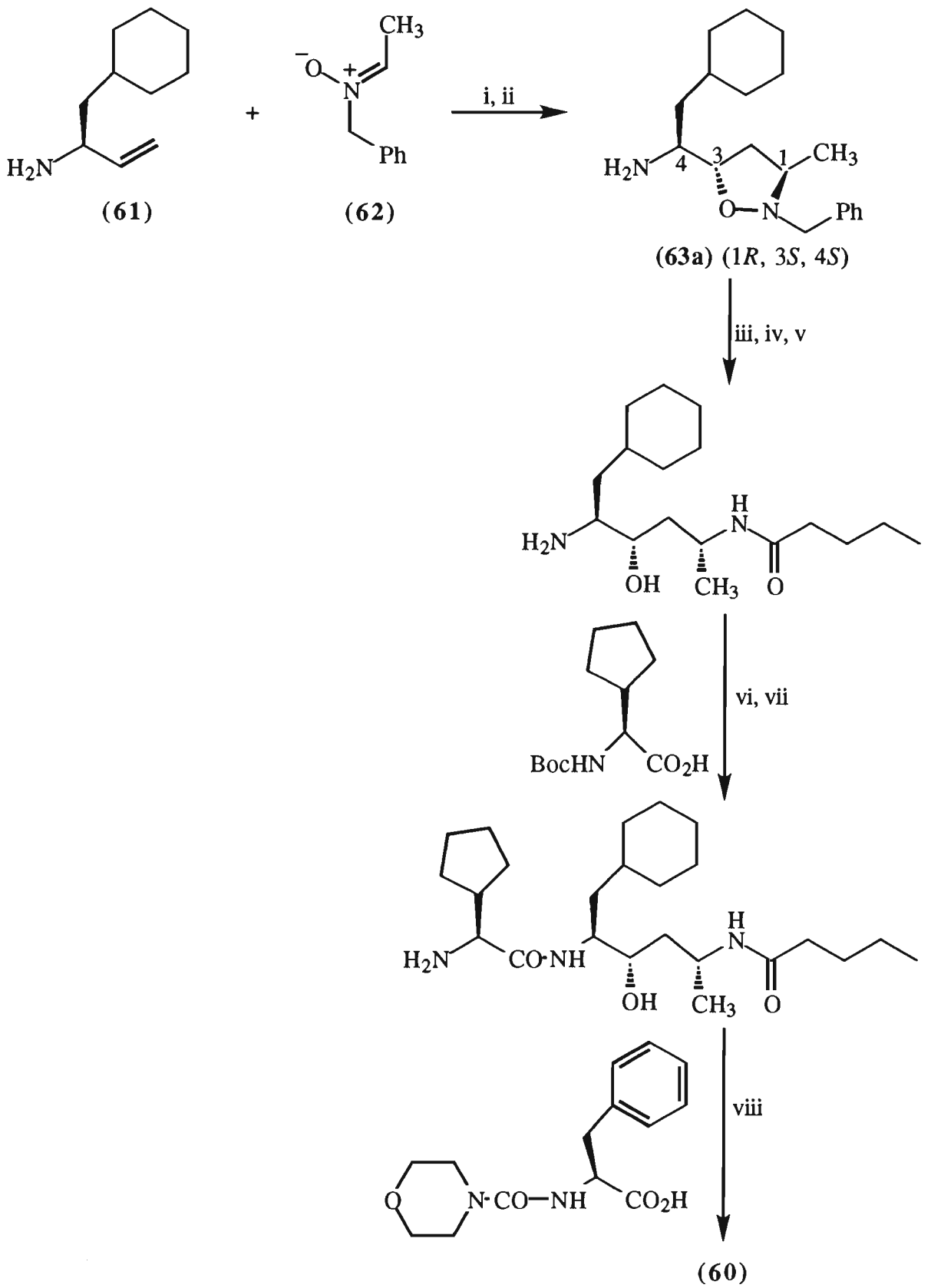
The enzyme inhibitory activity against endogenous renin from human plasma of the renin-inhibitor (60) that incorporates a cyclopentylglycine had an IC_{50}=1.3 nmol L^{-1}.[42a]



(60)

The 1,3-dipolar cycloaddition of allylamines (61) with *N*-benzylnitrones (62) provides an easy access to this type of structure. The stereochemistry of the product can be influenced either by employing chiral nitrones or chiral allylamines. The synthesis of the renin inhibitor (60) via the chiral and enantiomerically pure isoxazolidine (63a) is shown in Scheme 1.14.[42a]

Scheme 1.14



(61) (62) (63a) (1*R*, 3*S*, 4*S*) (60)

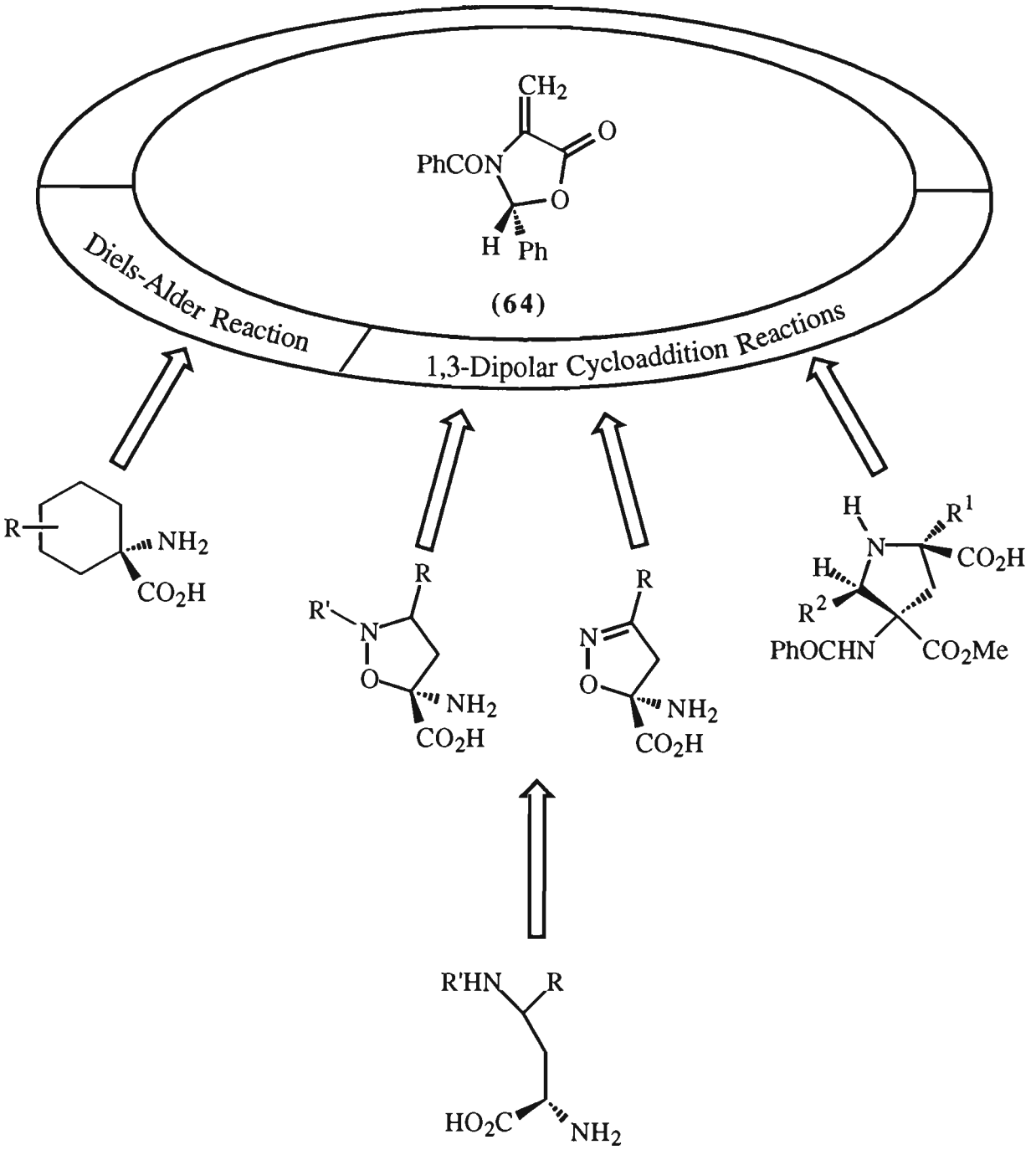
i, Mesitylene; ii, SiO_2, chromatography, *n*-hexane/ether 7:3; iii, $NH_4^+HCO_2^-$, 10% Pd/C, CH_3OH, reflux; iv, $(n\text{-}C_4H_9CO)_2O$, NEt_3, CH_3OH; v, 4N HCl, dioxane; vi, dicyclohexylcarbodiimide (DCC), hydroxybenzotriazole (HOBT), diisopropylethyl amine (DIPEA); vii, 4N HCl, dioxane; viii, DCC, HOBT, DIPEA

1-1-2. Asymmetric Synthesis of Chiral Amino Acids

While a number of methods have been reported for the synthesis of biological active cyclic amino acids, these approaches have their individual strengths and weaknesses. Some of them were not stereoselective and gave the target molecules with no defined stereochemistry. Others were racemic in design, and incorporated enzymatic or chemical resolutions as the final step. While in others, although the target compounds have been prepared in enantiomerically pure form, they involved lengthy synthetic procedures using many reagents.

In this thesis the asymmetric synthesis of some NPAAs through cycloaddition reactions, starting with the chiral DHAA, (2*R*)-3-benzoyl-4-methylene-2-phenyloxazolidin-5-one (64) will be developed (Scheme 1.15). In principle theses approaches would allow access to the target molecules with high enantiomeric purity and achieve the rapid assembly of the NPAAs in a minimal number of synthetic steps.

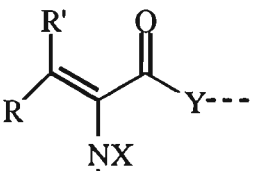
Scheme 1.15



In Chapter Two, the development of asymmetric synthesis of NPAAs through the Diels-Alder reactions of substituted 1,3-cyclohexadienes and substituted 1,3-butadienes with compound (64) will be considered. The 1,3-dipolar cycloaddition reactions of chiral oxazolidinone (64) with nitrones and nitrile oxides will be explored in Chapter Three. The asymmetric synthesis of polyfunctional prolines through the 1,3-dipolar cycloaddition reaction of azomethine ylides derived from *N*-alkylidene α-amino acid esters with compound (64) will be described in Chapter Four.

1-2. α,β-Dehydroamino Acids (DHAAs)

DHAAs are recognised to be intermediates of extensive value in both organic synthesis and biological transformations.[43] These compounds are extremely useful substrates for preparing both natural and non-proteinogenic amino acids (NPAAs). These substrates have the following structural unit (65):[44]



(65)

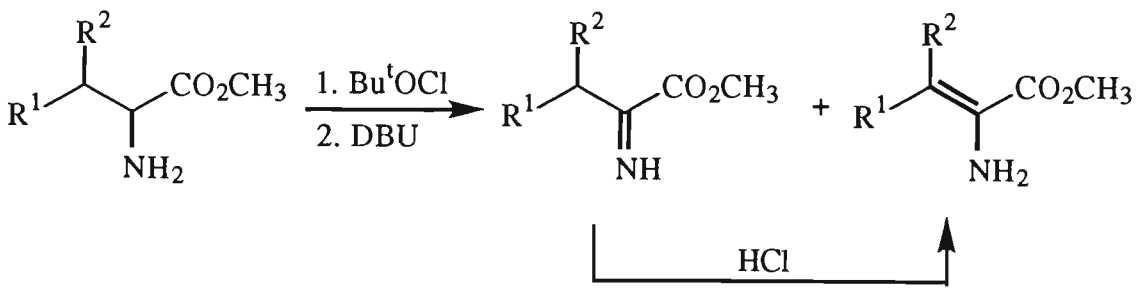
Y = O, N

X = HCO, CH_3CO, ArCO, alkylO_2C, aralkylO_2C, α-aminoacyl

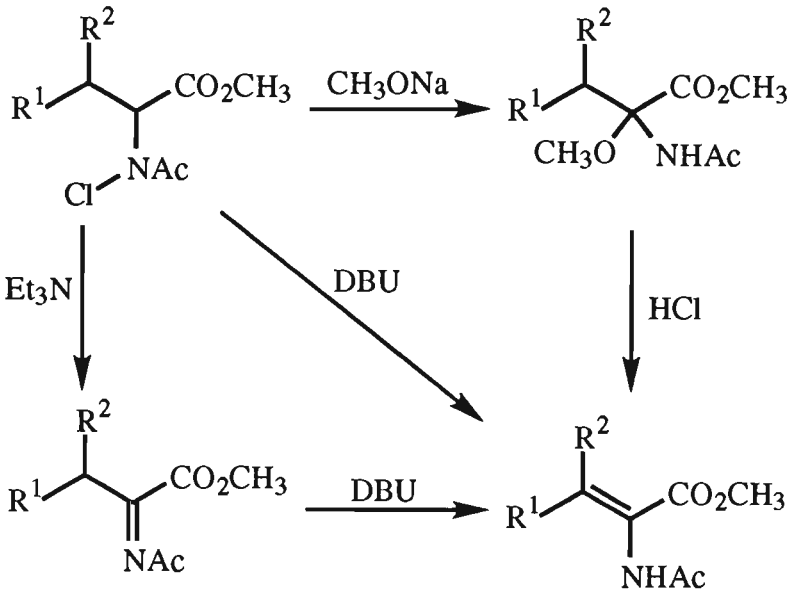
R, R' = H, alkyl, aryl, heterocycle

DHAAs have been prepared by various synthetic methods. These methods involve syntheses via elimination reactions or via C-C double bond forming reactions.[44] The *N*-chlorination and then dehydrochlorination of α-amino acid esters (Scheme 1.16) and α-*N*-acyl amino esters (Scheme 1.17) are examples of the former synthetic method.

Scheme 1.16

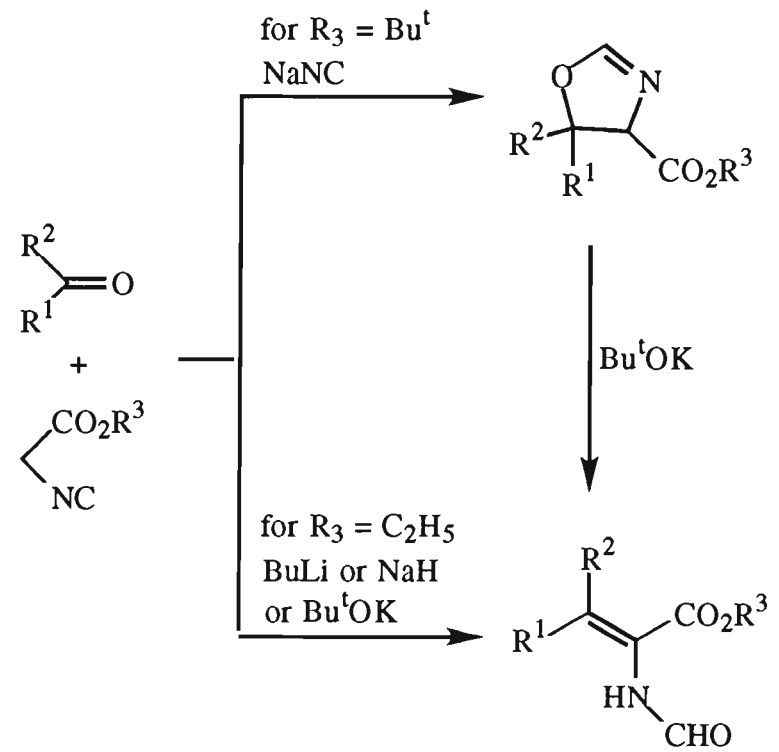


Scheme 1.17



The condensation of aldehydes and ketones with isocyanoacetates is an example of the synthesis of DHAAs through the later synthetic method (Scheme 1.18).

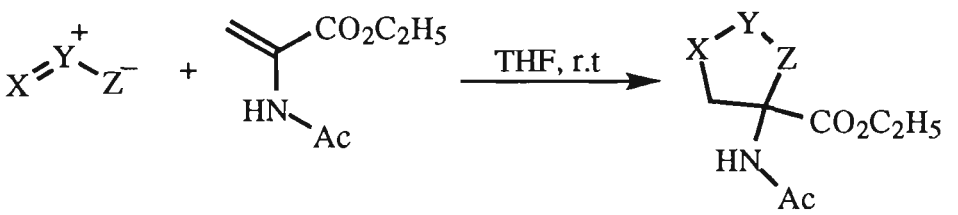
Scheme 1.18

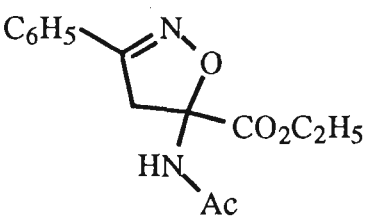
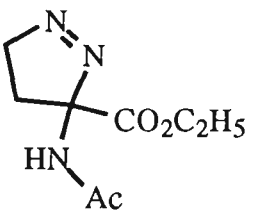
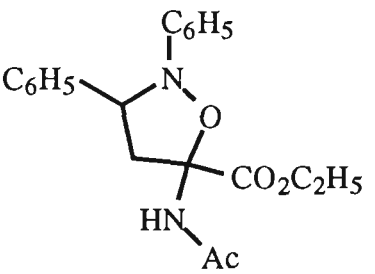
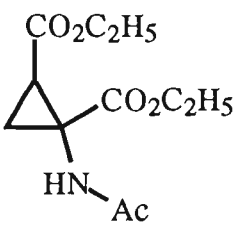


The vast majority of the literature dealing with the chemistry of DHAAs involves nucleophilic and electrophilic addition reactions to give β and α substituted amino acids, respectively. Relatively few applications of

cycloaddition reactions of DHAAs to the synthesis of geminally functionalized cyclic amino acids have been described to date.[43] Racemic α-amino acids have been prepared from the conjugate addition of nucleophilic reagents to DHAAs.[44] These substrates (DHAAs) have been employed as dienophiles in Diels-Alder reactions[11-13] and as dipolarophiles in 1,3-dipolar cycloaddition reactions (Scheme 1.19)[43] for the synthesis of cyclic amino acids.

Scheme 1.19



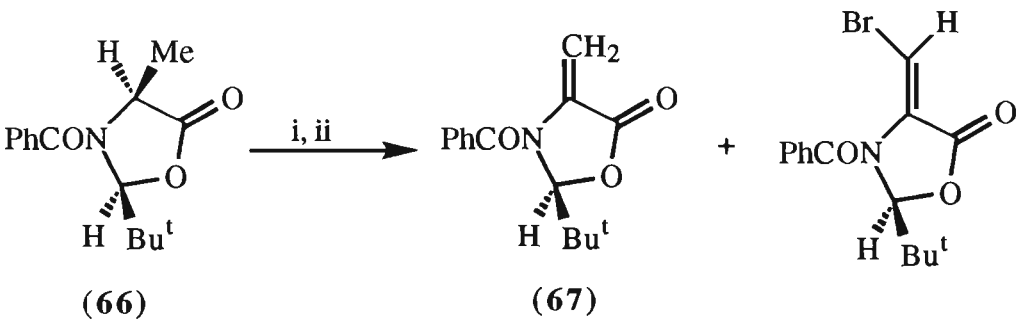
X=Y⁺–Z⁻	Product	Yield(%)
$C_6H_5—C\equiv N^+—O^-$		85
CH_2N_2		95
$C_6H_5—C(H)=N^+(O^-)—C_6H_5$		75
$N_2CHCO_2C_2H_5$		12.5

To prepare the cyclic α-amino acids in high enantiomeric purity chiral DHAA have to be employed. The chiral DHAA that we have chosen is the chiral 1,3-oxazolidinone derivative (64).

1-2-1. 1,3-Oxazolidinones as the Chiral Auxiliary.

In 1987, Seebach *et al.*[45] reported the synthesis of the DHAA, (2*S*)-3-benzoyl-2-*tert*-butyl-4-methyleneoxazolidin-5-one (67) from the bromination and then dehydrobromination of the oxazolidinone (66),[46] derived from (*S*)-alanine (Scheme 1.20). In 1990, a modified synthesis of (67) was reported by Beckwith *et al.*[47] The latter author has employed this compound as a useful Michael acceptor for alkyl radicals to produce α-amino acids in high enantiomeric purity.

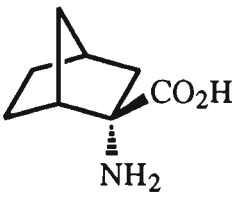
Scheme 1.20



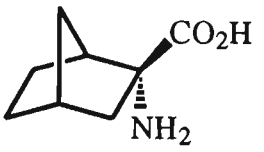
(66) **(67)**

i, N-bromosuccinimide (2 eqiv.), hν, $(PhCO_2)O$; ii, NaI, acetone, heat

More recently, Pyne *et al.*[48a,b] reported a new method for the synthesis of (67) and its (2*R*) analogues (64), (68a) and (68c) from (*S*)-*S*-methylcysteine (Scheme 1.21). These compounds have been employed as dienophiles in Diels-Alder reactions with cyclopentadiene and 1,3-cyclohexadiene[48] and the resulting adducts were used to prepare cyclic NPAAs (2) and (9) in high enanatiomeric purity.



(2)

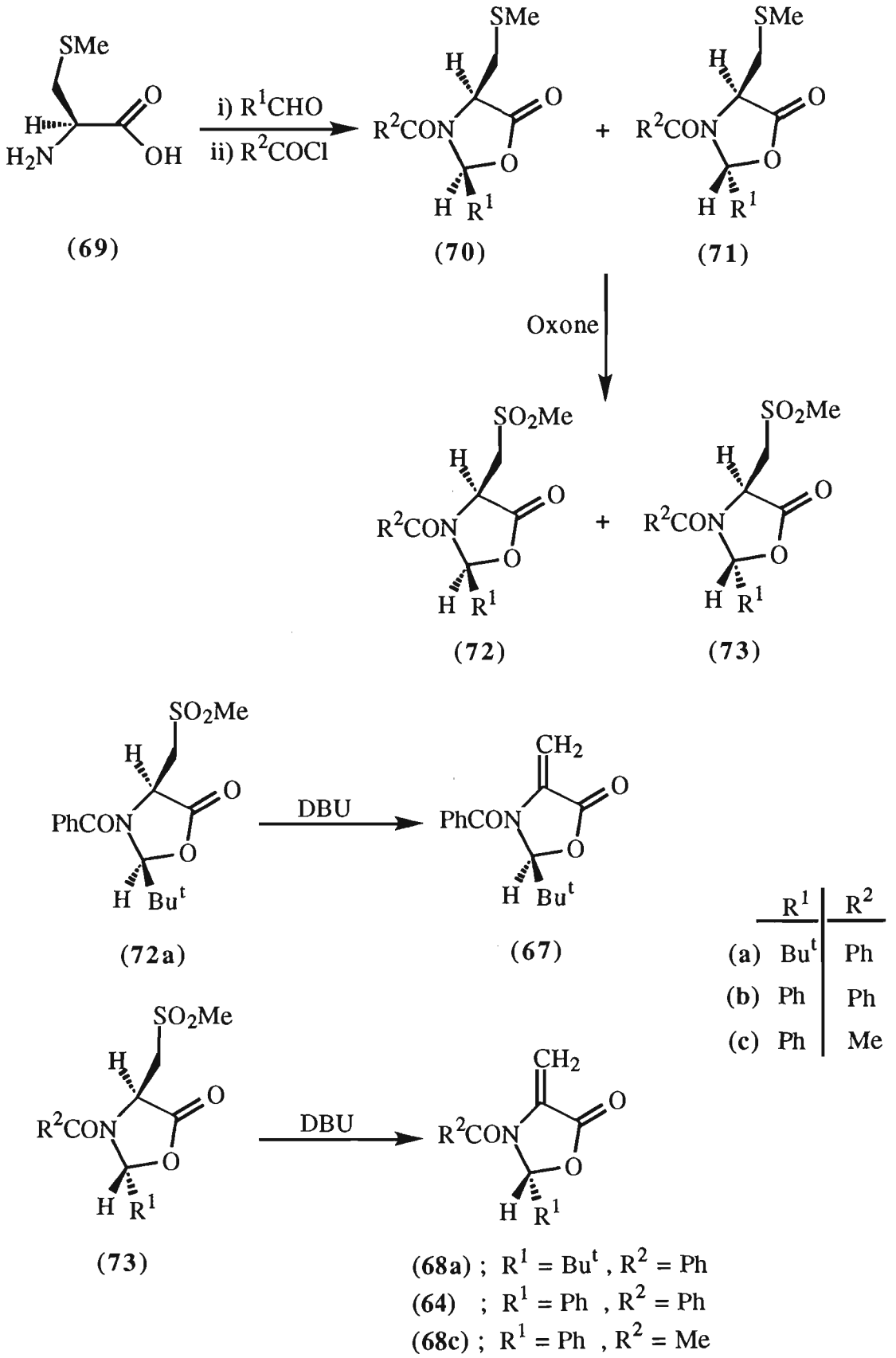


(9)

1-2-2. Synthesis of (2*S*) and (2*R*)-4-Methylene oxazolidin-5-ones

The reaction of (2*S*)-*S*-methylcysteine (69) with benzaldehyde or pivaldehyde and then treatment with benzoyl chloride or acetyl chloride gave a mixture of *cis* and *trans* oxazolidin-5-ones (70) and (71). This mixture was converted into a mixture of sulfones (72) and (73) by oxidation with Oxone in acetonitrile in good yield. Treatment of diastereomerically pure (72a) or (73a-c) with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) smoothly yielded (67), (68a), (64) and (68c) respectively, in high enantiomeric purity (Scheme 1.21).

Scheme 1.21



	R^1	R^2
(a)	Bu^t	Ph
(b)	Ph	Ph
(c)	Ph	Me

In the first reaction, the ratio of *cis* and *trans* isomers (70) and (71), was dependent upon the nature of the substituents R^1 and R^2 as shown in Table 1.1.

Table 1.1. Diastereomeric ratio of the *cis/trans* oxazolidin-5-ones (70) : (71).[48]

Product(s) from (69)	Diastereoselection (70) : (71)	Yields(%)
(70a) / (71a)	81 : 19	49
(70b) / (71b)	6 : 94	28
(70c) / (71c)	8 : 92	23

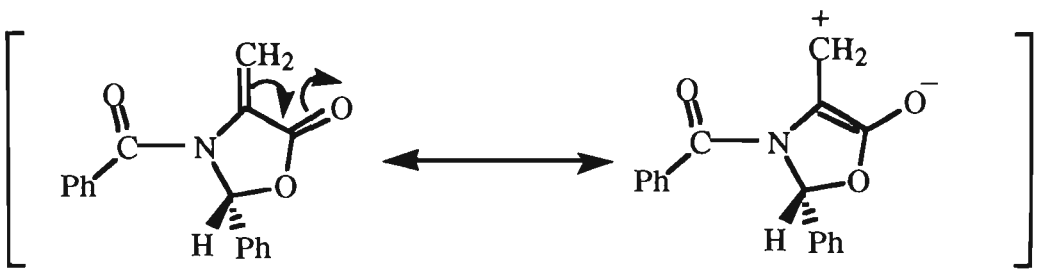
While the purified yields of (71b) and (71c) were poor, these latter reactions were much more diastereoselective than that leading to (70a) and (71a). Furthermore, these syntheses avoid the use of expensive pivaldehyde. Since (71b) can be more easily obtained diastereomerically pure than (70a) or (71c), it was decided to study the cycloaddition chemistry of the (2*R*)-oxazolidinone (64).

1-2-3. The Structural and Electronic Properties of the Oxazolidinone (64).

The delocalisation of the electrons around the methylene, amide and lactone groups of (64) are responsible for the electron deficient character of the 4-methylene moiety of this compound. The lactone carbonyl group in (64) withdraws electron density from the *exo*-cyclic methylene group by resonance (Figure 1.1a), while the nitrogen of the amide group reduces the electron density by induction as outlined in Figure 1.1b. The nitrogen of the amide group would also be expected to donate electron density into the *exo*-cyclic group by resonance. X-ray studies[48] have shown that the nitrogen of the amide group is intermediate in character between sp^2 and sp^3 hybridisation. Alkenes like (64) which are geminally substituted by both an electron-withdrawing (captor) and an electron-releasing (donor) groups are classified as "captodative" alkenes.[49]

However, overall the *exo*-cyclic methylene group in (64) would be expected to be an electron deficient double bond.

a)



b)

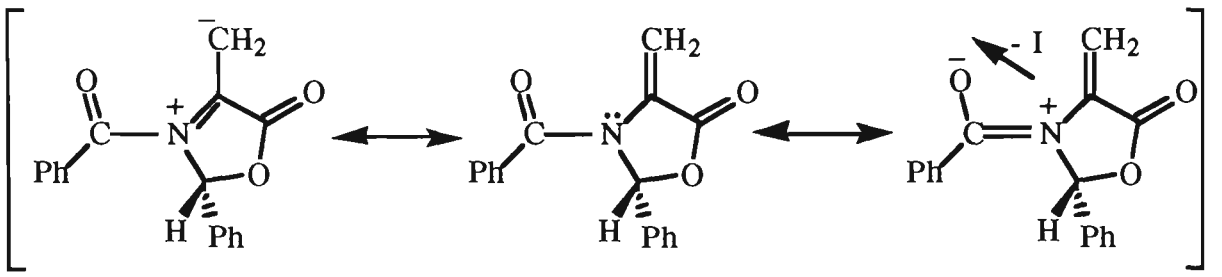
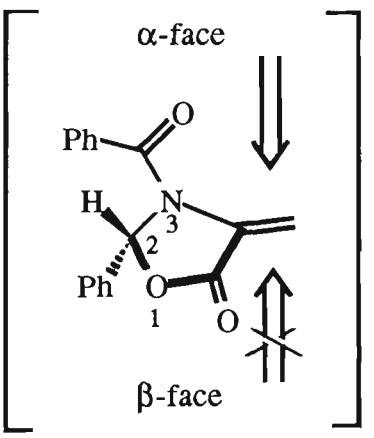


Figure 1.1. The resonance structures for the carbonyl and benzamido groups in oxazolidinone (64).

The phenyl group at the C-2 position in (64) is a bulky group which effectively shields the β-face of the *exo*-cyclic methylene group to attack by reagents.



The steric and electronic features of the molecule are summarised in Figure 1.2. The lactone and amide groups control the electronic properties of (64) while the C-2 phenyl group is responsible for the steric properties of this compound. These electronic and steric features will

determine the direction of approach and the selectivity of reactions involving compound (64).

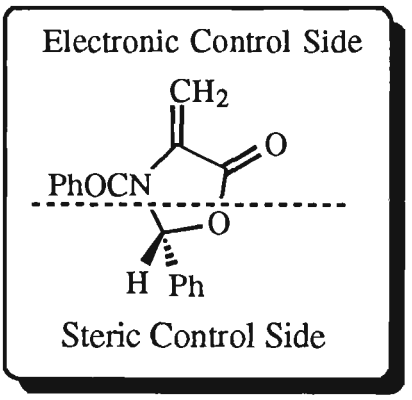


Figure 1.2. The overall electronic and structural factors of the oxazolidinone (64).

CHAPTER TWO

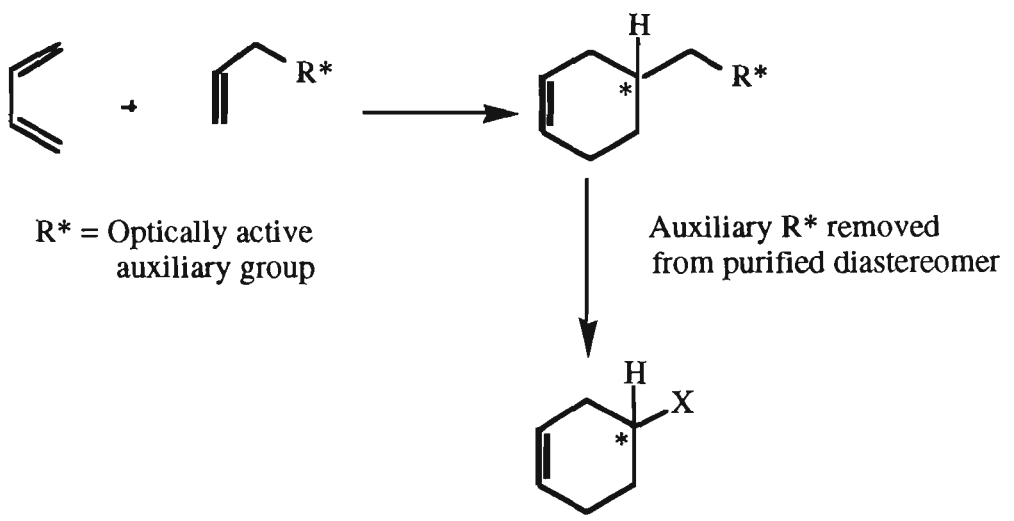
Asymmetric Synthesis of Cyclic Amino Acids via *Exo*-Diastereoselective Diels-Alder Reactions

2-1. Asymmetric Diels-Alder Reaction

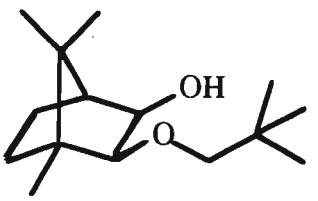
Diels-Alder cycloadditions, which have been discovered over seven decades ago, play an ever increasing role in contemporary organic synthesis.[50] In particular, asymmetric Diels-Alder reactions have become of prime interest during the present decade, this being in great part due to the fact that modern pharmacopoeia requires enantiomerically pure drugs, with the potential advantage of a lower dose and a greater safety, as compared to the corresponding racemates.

The usefulness of the Diels-Alder reaction in synthesis arises from its versatility and its high regio- and stereoselectivity. In addition, this type of reaction can be used in asymmetric synthesis, with a non-statistical mixture of optically active diastereomeric products resulting when either the diene or dienophile is chiral, enantiomerically enriched and facially selective. One type of asymmetric Diels-Alder reactions has been realized by temporarily attaching to the diene or dienophile an optically active auxiliary group. This auxiliary can then be removed from the diastereomerically pure adduct to give an enantiomerically pure product (Scheme 2.1).[51]

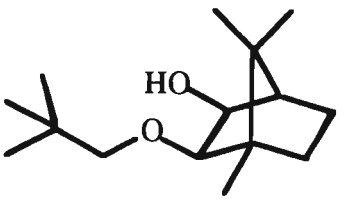
Scheme 2.1



A number of optically active alcohols have been employed as auxiliary groups in this sequence, including menthol and, better, (-)-8-phenylmenthol or neopentyl alcohols (1) and (2).[52]



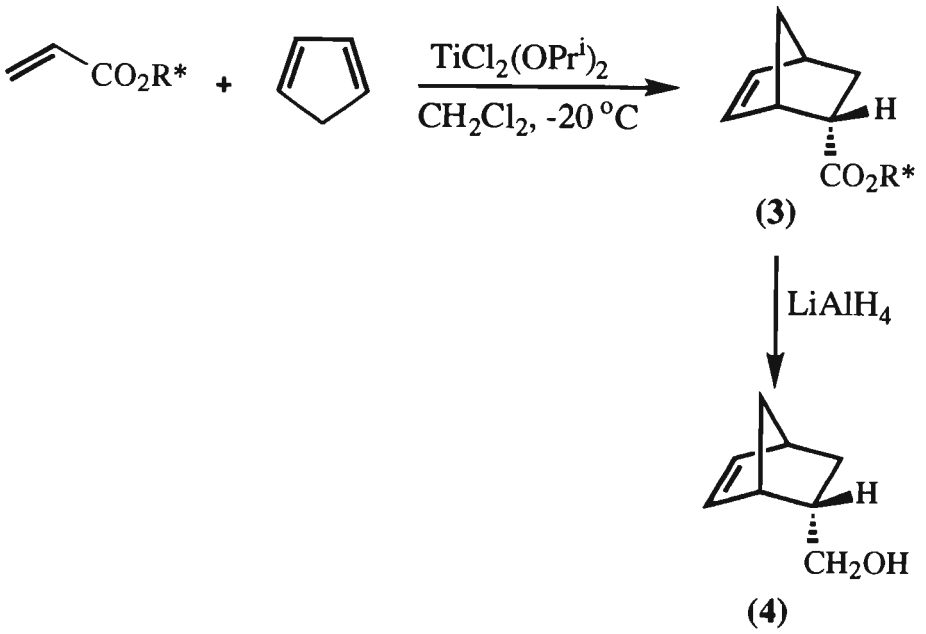
(1)



(2)

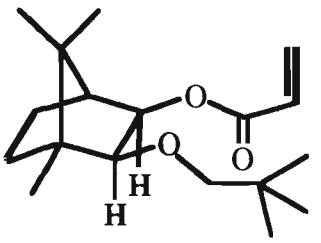
In Lewis acid catalysed Diels-Alder reactions of the acrylate ester of alcohol (1) with cyclopentadiene, the adduct (3) was obtained with almost complete diastereomeric selectivity. Reduction of the purified product with lithium aluminium hydride regenerated the auxiliary alcohol and gave the optically pure *endo* alcohol (4) (Scheme 2.2).[51a]

Scheme 2.2



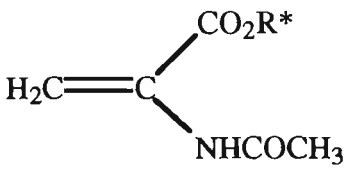
This reaction is believed to take place by addition of the diene to the ester in the conformation (5) in which access to the front face of the double bond is hindered by the neopentyl group. Other chiral auxiliaries and chiral Lewis acid catalysts have also been employed in asymmetric Diels-Alder

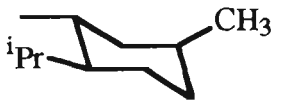
reactions, however these have been recently reviewed[51b] and will not be discussed in this thesis.

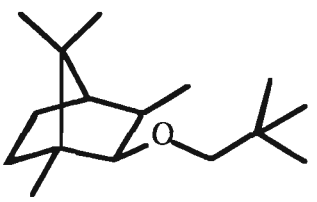


(5)

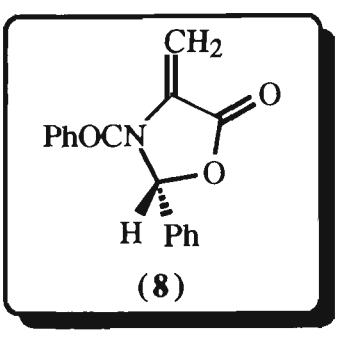
The chiral DHAAs (6) and (7) have been employed as a dienophile in Diels-Alder reactions by C. Cativiela *et al.*[11b-e] to prepare *exo* or *endo* diastereofacial selective adducts in high enantiomeric purity (Scheme 2.1, Chapter 1).



(6) R* =  (*exo* diastereofacial selective)

(7) R* =  (*endo* diestereofacial selective)

In this Chapter, the asymmetric Diels-Alder reactions of oxazolidinone (8) as a chiral DHAA, with substituted 1,3-butadienes and substituted 1,3-cyclohexadienes is reported as a method for the asymmetric synthesis of novel cyclic amino acids. The regioselectivity and stereoselectivity of these reactions is also addressed.

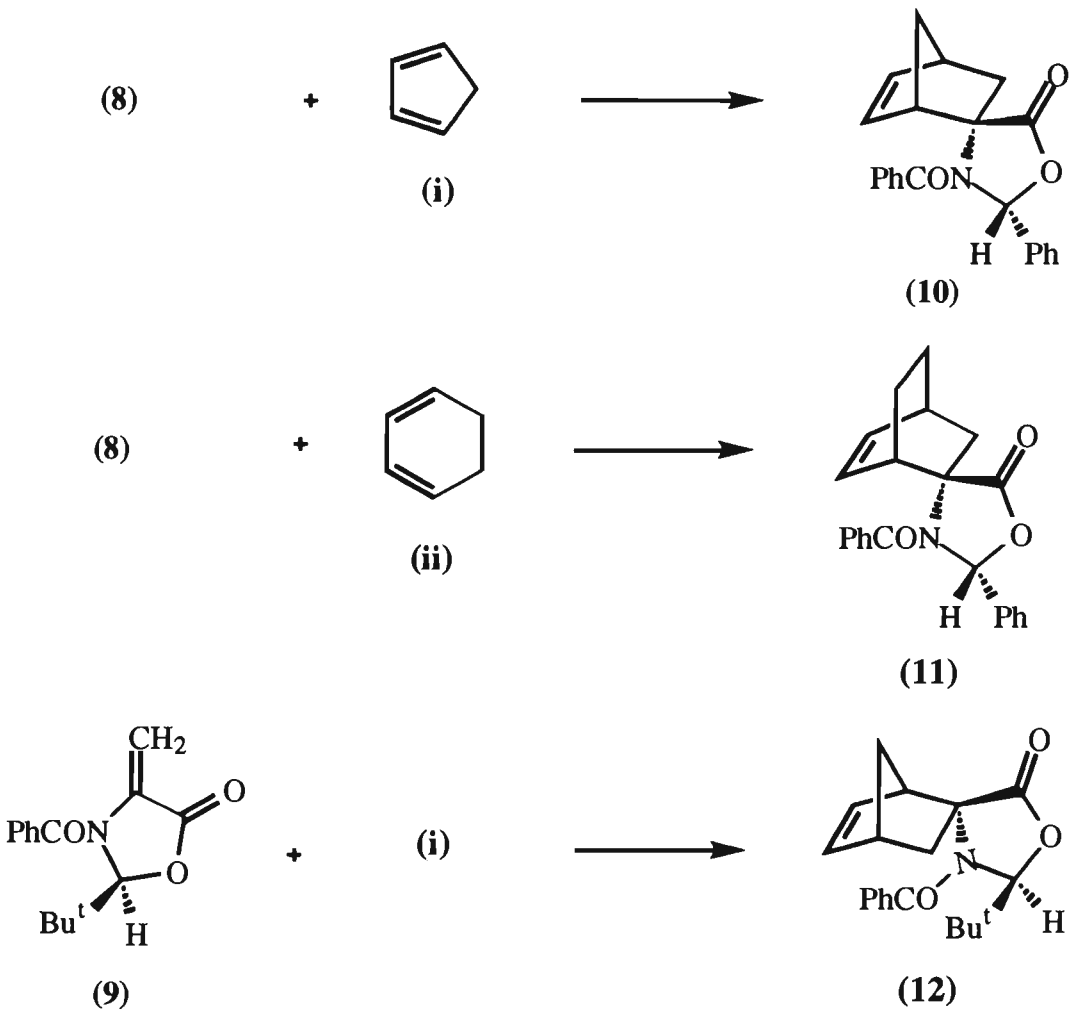


(8)

2-2. Synthesis of Cyclic NPAAs by Asymmetric Diels-Alder Reactions of (2S)- and (2*R*)-2-Substituted 3-Benzoyl-4-methyleneoxazolidin-5-ones

In 1993, Pyne *et al.*[48,49] reported a new method for the synthesis of either (*R*) or (*S*) cyclic NPAAs. In this synthetic method, (2*S*)-3-benzoyl-2-*tert*-butyl-4-methylene-oxazolidin-5-one (9) and (2*R*)-3-benzoyl-4-methylene-2-phenyl-oxazolidin-5-one (8) were used as chiral dienophiles in Diels-Alder reactions with cyclopentadiene (i) at room temperature and with 1,3-cyclohexadiene (ii) at 130 °C (Scheme 2.3).

Scheme 2.3



Scheme 2.3 (cont'd)

(13)

While (8) appeared to be more reactive than (9) as a dienophile towards cyclopentadiene, the diastereoselectivity in both cases was the same. However the diastereoselectivity in the case of (8) toward 1,3-cyclohexadiene was less favourable (Table 2.1).

Table 2.1. Diels-Alder reactions of (8) and (9) with cyclopentadiene (i) and 1,3-cyclohexadiene (ii).[48]

Dienophile	Diene	Temp. (°C)	Time (days)	Yield (%)	Diastereoselection (products)
(8)	(i)	25	5	100	>97 (10) : <3 (others)
(8)	(ii)	130	16	63	67 (11) : 33 (isomer)
(9)	(i)	25	5	70	>97 (12) : <3 (others)
(9)	(ii)	130	16	62	>97 (13) : <3 (others)

The *exo* stereochemistry of (10), (12) and (13) was established by a single crystal X-ray structure analyses. In these reactions the diene had added to the face of the 4-methylene group of (8) and (9) that was *anti* to the bulky C-2 substituent as shown in Figure 2.1.

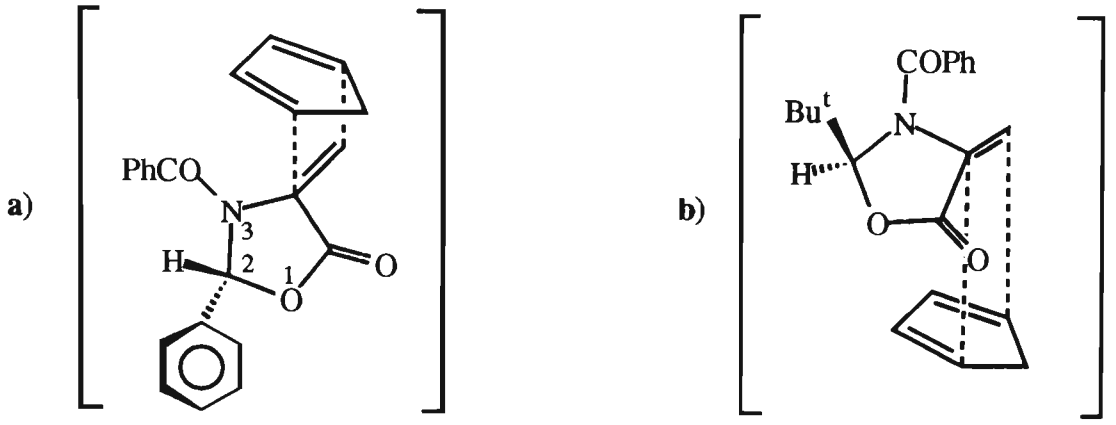
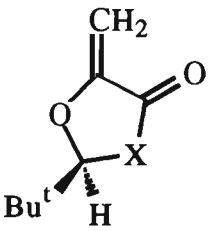


Figure 2.1. *Exo* transition states for the addition of cyclopentadiene to **a)** (8) and **b)** (9), addition of the diene occurs *anti* to the C-2 substituent.

The high *exo*-diastereoselectivity in these reactions is in accord with the work of Mattay[53] and Roush[54] who reported high *exo*-diastereoselectivity for the thermally induced reactions of 2-*tert*-butyl-5-methylene-1,3-dioxolan-4-one (14a) and the related oxazolidinone (14b), respectively, with cyclopentadiene.

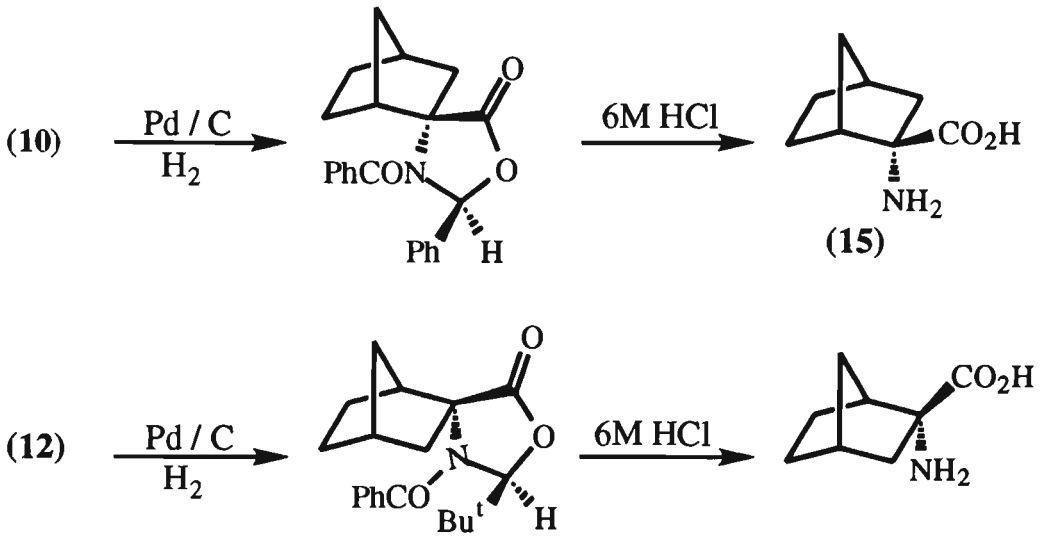


(14a) ; X = O

(14b) ; X = NAc

The Diels-Alder adducts (10) and (12) were converted into related amino acids, by first hydrogenation over palladium on carbon and then acid-catalysed hydrolysis of the oxazolidinone moiety. (1*R*,2*S*,4*S*)-2-*endo*-aminobicyclo[2.2.1]heptane-2-*exo*-carboxylic acid (15) was obtained in high enantiomeric purity (e.e. 92%) via the above procedure (Scheme 2.4).[48]

Scheme 2.4



The oxazolidinone (8) is extremely valuable since it gives cyclic amino acids with the natural (2*S*)-configuration, which have been used to study the transport of amino acids with hydrophobic side chains such as leucine, isoleucine and valine.[9]

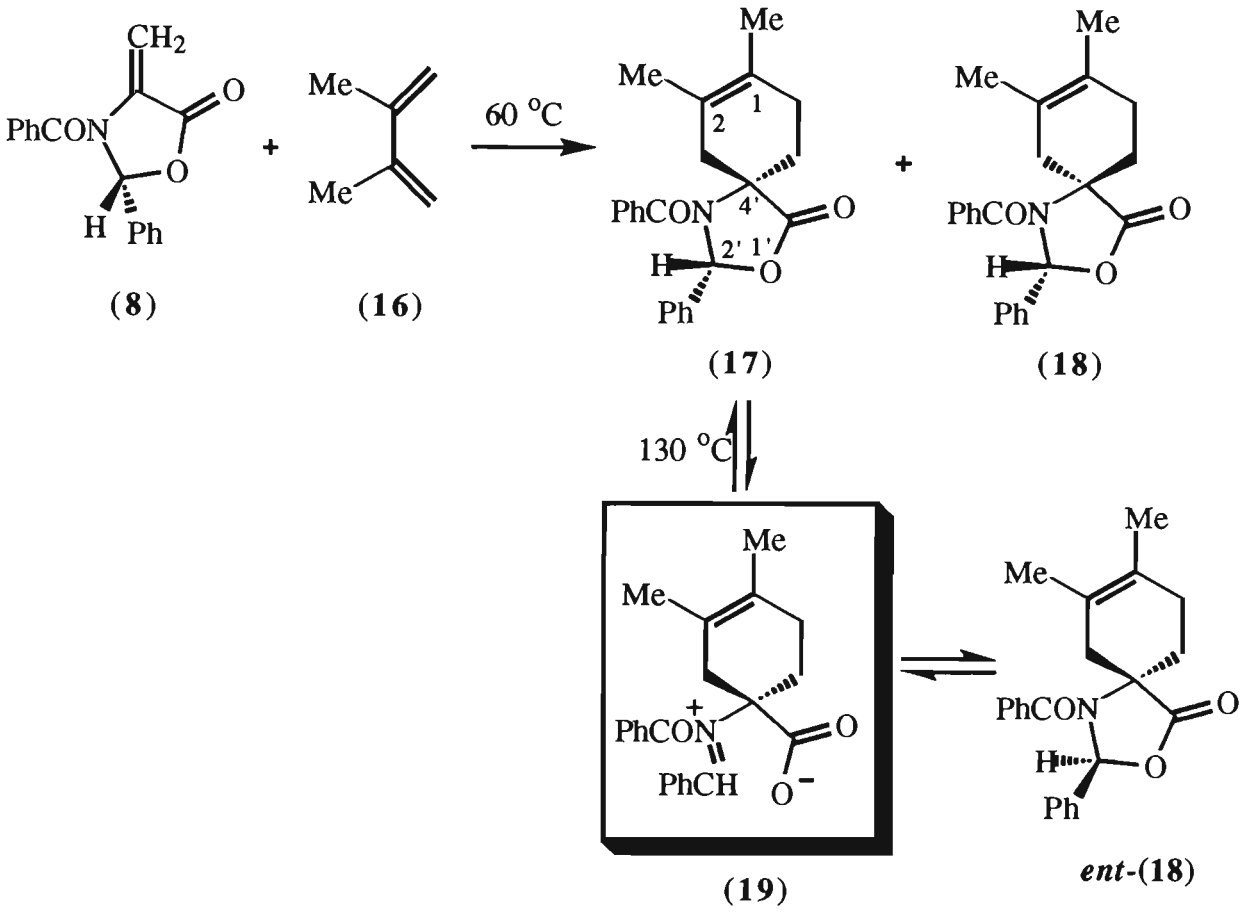
2-3. Diels-Alder Reactions of (8) and Substituted 1,3-Butadienes

2-3-1. Diels-Alder Reactions of (8) and 2,3-Dimethyl-1,3-Butadiene (16)

The thermally induced reaction of (8) and 2,3-dimethyl-1,3-butadiene in CH_2Cl_2 gave two diastereomeric products. The diastereomeric ratio of these products was dependent upon the reaction temperature (Table 2.2, page 47). The reaction at 130 °C for 24 hr, resulted in a 50 : 50 mixture of diastereoisomeric cycloaddition products, while at 60 °C over a period of 9 days the diastereomeric ratio was 97 : 3. The ratio of the diastereoisomeric cycloadducts was determined by ^1H NMR spectroscopy on the crude reaction mixtures. The major diastereomeric adduct (17) from the above reaction at 60 °C could be obtained diastereomerically pure by recrystallization. The structure and stereochemistry of this compound was secured by a single crystal X-ray structural determination (Figure 2.2). This analysis showed that the 2,3-dimethyl-1,3-butadiene had, as expected, added to the least hindered diastereotopic face of the 4-methylene group of (8). This solid state structure revealed the *N*-benzoyl group of the oxazolidinone ring was pseudo-equatorial with respect to the cyclohexene ring moiety of (17). This structure is concordant with the solution structure of (17) from ^1H NMR analysis that showed both H3β and H5β are strongly deshielded (δ 3.36 and δ 3.15), compared to H3α (δ 2.24) and H5α (δ 2.12) respectively, which is consistent with the close disposition of these former two protons and the benzoyl carbonyl group in the solid state structure (Figure 2.2). This solid state structure proved extremely useful for assigning the stereochemistry of other Diels-Alder adducts of (8) and 1-substituted-1,3-butadienes that are discussed later in this Chapter. The optimised temperature for these series of reactions was

60 °C because of the high diastereoselectivity of cycloadducts. Heating a solution of (17) at 130 °C for 24 hr gave a 50 : 50 mixture of the above two diastereoisomers (Scheme 2.5).

Scheme 2.5



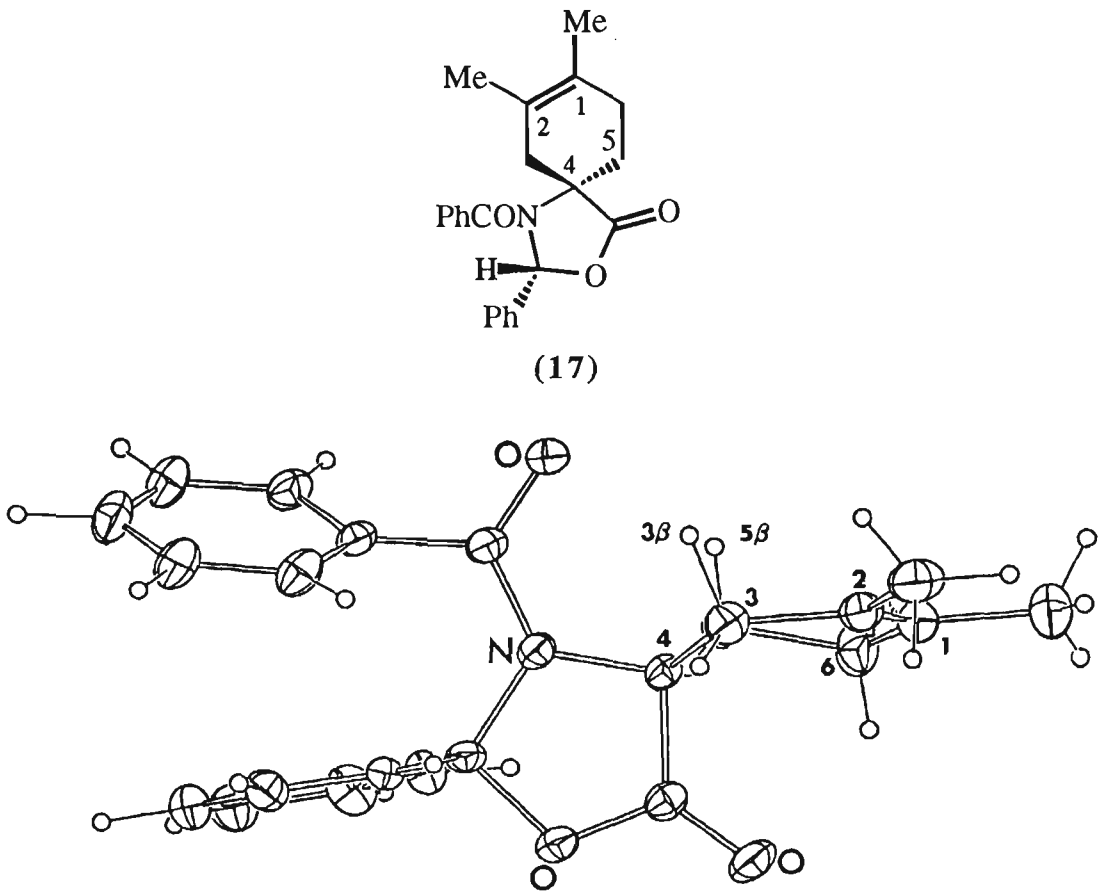
The minor diastereoisomeric adduct formed at 60 °C could be either compound (18) or *ent*-(18) or a mixture of these compounds. Compound (18) could arise from addition of the diene to the more hindered π-face of the 4-methylene group of (8), while *ent*-(18) could arise from the epimerization of (17) at C2' during the course of the Diels-Alder reaction. The thermally induced ring opening of the oxazolidinone ring of (17) to give an intermediate iminium ion (19), which could ring close to give either (17) or *ent*-(18), would be facilitated by the C2' phenyl group which can stabilize the incipient carbocation ring-opened intermediate (19) (Scheme 2.5). Unfortunately the minor adduct could not be separated from the major diastereomeric product and we were therefore unable to quantify

the enantiomeric purity or determine the absolute stereochemistry of this compound.

Table 2.2. Diels-Alder products from the reactions of (8) and dienes at 60 °C.

Entry	Diene	Time (days)	Yield (%)[a]	Diastereoselection[b] (products)
1	2,3-dimethyl-1,3-butadiene (16)	1 (130 °C)	ND	50 : 50 (17, 18)
2		1 (100 °C)	52	86 : 14 (17, 18)
3		2 (80 °C)	59	91 : 9 (17, 18)
4		9	81	97 : 3 (17, 18)
5	1-methyl-1,3-butadiene (23)	15	50	94 : 6 (25a, 25b)
6	1-methoxy-1,3-butadiene (24)	10	51	82 : 18 (26a, 26b)
7	1-methoxy-3-(trimethylsilyloxy)-1,3-butadiene (27)	2	40[d]	50 : 50 (28a, 28b)
8	2-methyl-1,3-butadiene	10	96	66 : 31 : 3 (29, 30, 31)
9	1,3-cyclohexadiene	15	60	74 : 26 (11, 32)
10	1-methoxy-1,3-cyclohexadiene (35)	8	81	89 : 11 (37, c)
11	1-(trimethylsilyloxy)-1,3-cyclohexadiene (36)	15	84	97 : 3 (38, c)
12	2-(trimethylsilyloxy)-1,3-cyclohexadiene (39)	25	37[d]	50 : 26 : 12 : 12 (40a, 40c, 40b, c)
13		8 (80 °C)	45[d]	19 : 24 : 47 : 10 (40a, 40c, 40b, c)

[a] After purification. [b] Determined on the crude reaction mixture by ^{1}H NMR (400 MHz). [c] The structure of the minor isomer is uncertain. [d] Yield after acid hydrolysis.

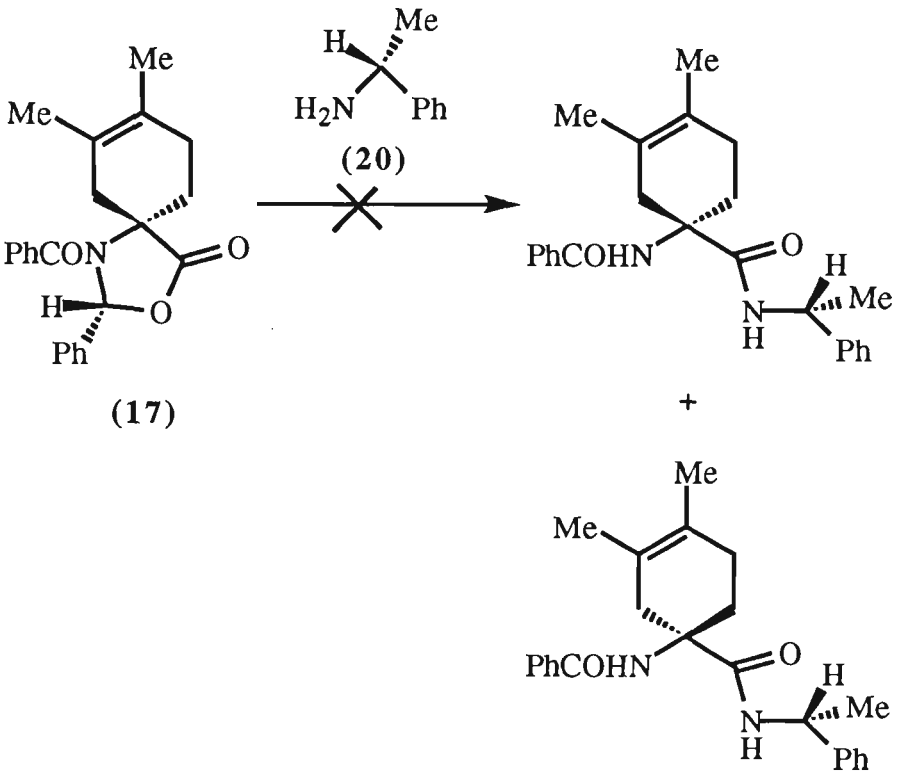


(17)

Figure 2.2. Molecular projection of (17) normal to the plane of the five-membered ring. 20% thermal ellipsoids are shown for the non-hydrogen atoms; hydrogen atoms have an arbitrary radii of 0.1 Å.

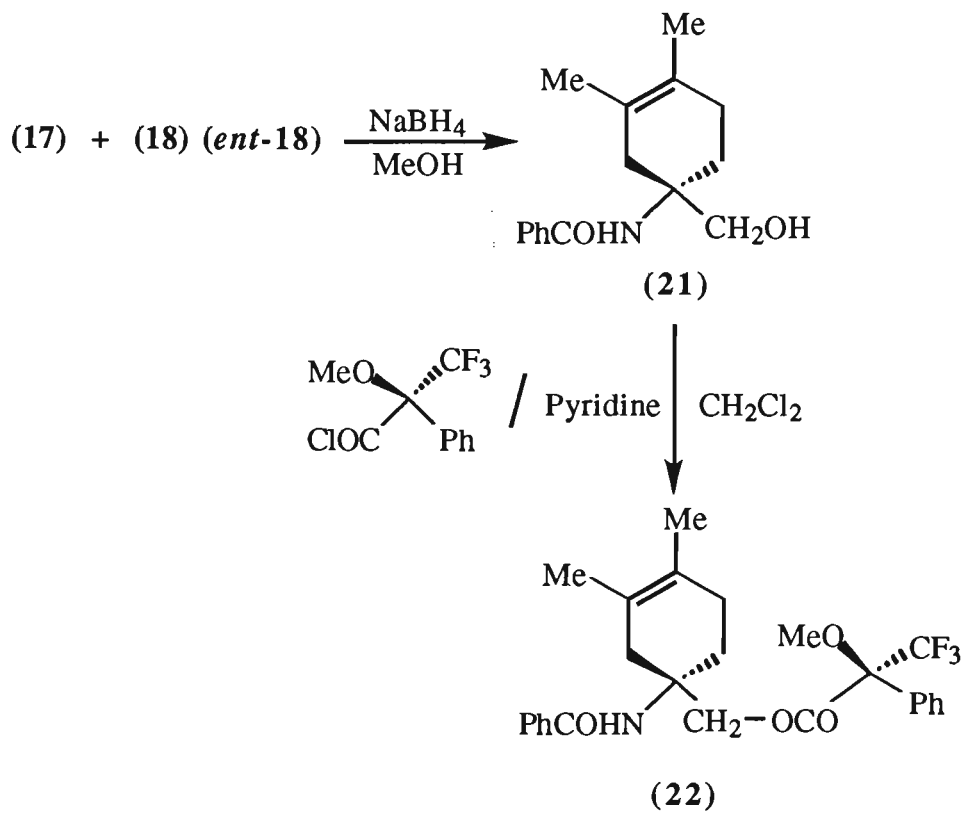
In order to determine the enantiomeric purity of the reaction product (17), the condensation reaction of (17) with (*R*)-(+)-α-methylbenzyl amine (20) was attempted (Scheme 2.6). Attempts to do this reaction thermally in CH_2Cl_2 or DMF at 60 °C were not successful and only starting materials were isolated. The reaction of (17) with the lithium salt of (20) (prepared from (20) and n-BuLi at -78 °C) in THF at -78 °C to 0 °C was also unsuccessful, with starting material being recovered along with some impurities.

Scheme 2.6



However, reduction of the 97 : 3 mixture of diastereoisomers that was obtained from the above Diels-Alder reaction at 60 °C, with sodium borohydride ($NaBH_4$)[55] gave the alcohol (21) (Scheme 2.7). The enantiomeric purity of (21) was determined to be 94% from ^1H NMR analysis of its Mosher ester (22) prepared from the reaction of (21) and (*R*)-(-)-α-methoxy-α-trifluoromethylphenylacetyl chloride.[56] Integration of the resonances for the diastereotopic methylene protons ($C\underline{H_A}\underline{H_B}OCOC(Ph)(CF_3)OMe$) for the major and minor diastereoisomers of (22) allowed the enantiomeric purity of (21) to be calculated (97 : 3 mixture of diastereoisomers, Figure 2.3).

Scheme 2.7



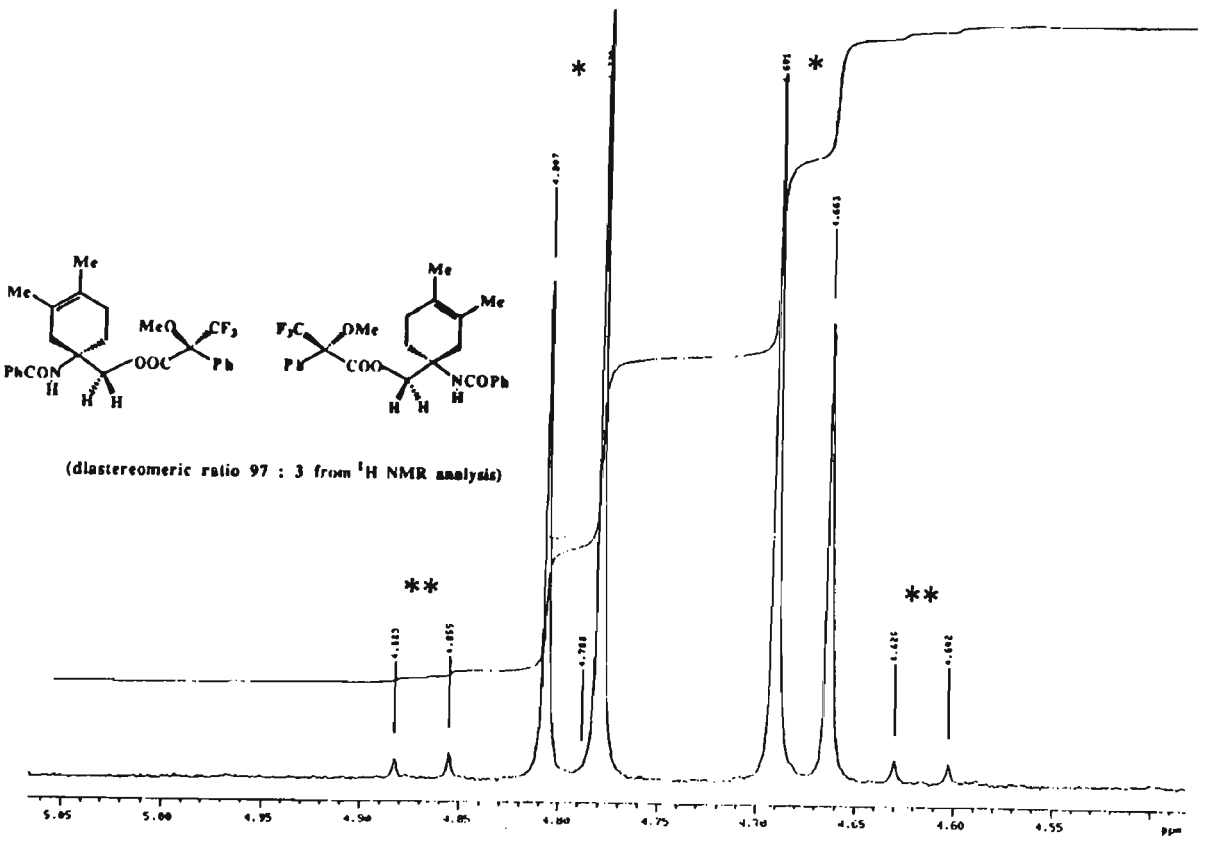


Figure 2.3. Expanded section of the ^{1}H NMR (400 MHz) spectrum of the Mosher ester (22) showing the diastereotopic methylene protons for the two diastereomeric products (ratio 97 : 3). * major diastereoisomer; ** minor diastereoisomer.

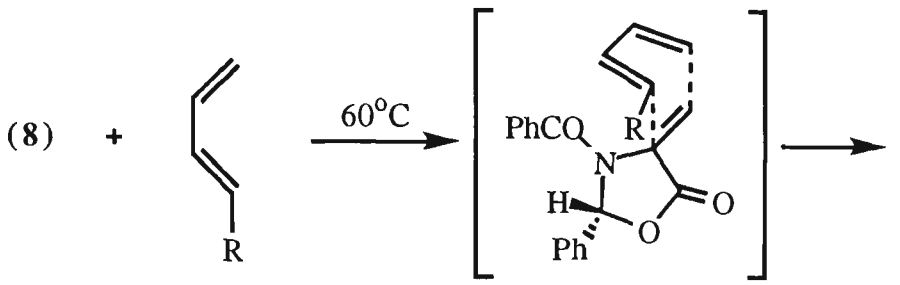
2-3-2. Diels-Alder Reactions of (8) and 1-Substituted-1,3-Butadienes

The high regio- and stereoselectivity of the Diels-Alder reaction has led to its widespread application in the synthesis of complex natural products. In principle two regioisomeric adducts are produced from the reaction of an unsymmetrical diene with an unsymmetrical dienophile, but in practice one product generally predominates.[51a,57] Generally in Diels-Alder reaction of a 1-substituted-1,3-butadiene with an electron deficient dienophile the 'ortho' adduct is favoured, while with 2-substituted-1,3-butadienes the 'para' isomer predominates.[51a]

2-3-2-1. Diels-Alder Reactions of (8) with 1-Methyl-1,3-Butadiene (23) and 1-Methoxy-1,3-Butadiene (24)

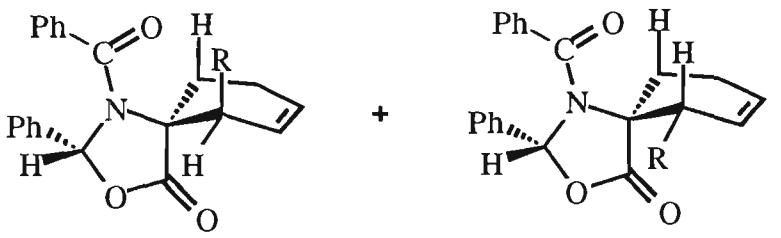
The Diels-Alder reaction of (8) and 1-methyl-1,3-butadiene (23) at 60 °C for 15 days was highly diastereoselective (d.r. 94 : 6) and gave a mixture of the *exo* and *endo* adducts (25a) and (25b) respectively, in 50% yield. The major adduct could be isolated pure by semi-preparative HPLC. The major and minor diastereomeric adducts were assigned to be the *exo* and *endo* diastereoisomers, (25a) and (25b), respectively, from a combination of COSY and NOESY ^{1}H NMR and molecular modelling (PC MODEL, using the MMX force field) studies (Scheme 2.8).

Scheme 2.8



(23) ; R = Me
(24) ; R = OMe

(*exo* transition state)



exo **(25a)** ; R = Me
(26a) ; R = OMe

endo **(25b)** ; R = Me
(26b) ; R = OMe

The energy minimized structures for (25a) and (25b) are shown in Figure 2.4, along with the calculated proton-proton bond distances and observed NOE cross peaks in the NOESY NMR spectrum for each diastereoisomer. These energy minimized conformations showed close correlation to the solid state structure of (17) (Figure 2.2). The ^{1}H NMR spectrum of (25a) showed H5β was highly deshielded (δ 2.76, compared to H5α, δ 2.30), as expected from the close proximity of this proton to the *N*-benzoyl carbonyl group. The stereochemistry of (25a) was evident from the strong NOE cross peaks between H5β and the C3 Me group and between H2' and H3α. In contrast, the minor diastereoisomer (25b) showed a significant NOE cross peak between H2' and the C3 Me, consistent with the *endo* stereochemistry.

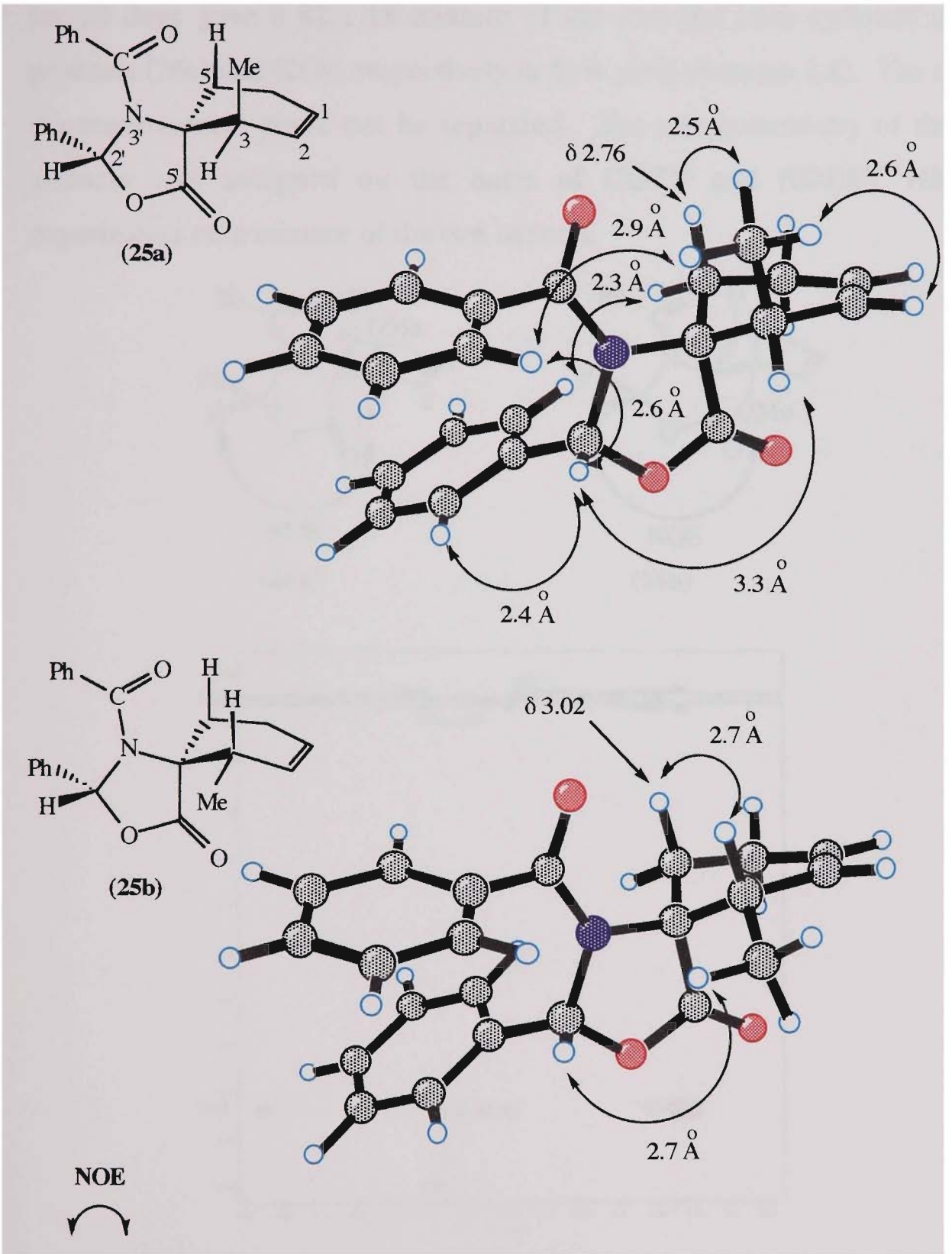
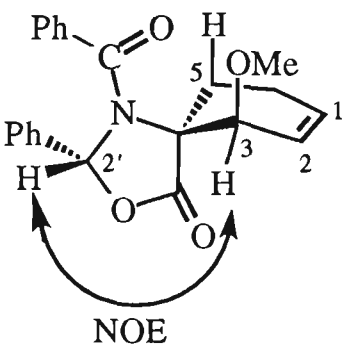
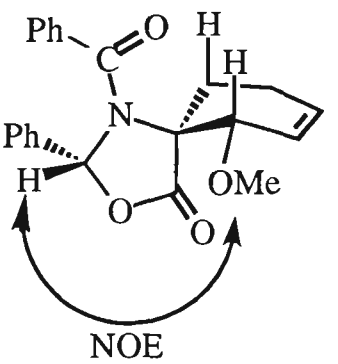


Figure 2.4. Energy minimized structures for (25a) and (25b) showing interatomic distances calculated using PC MODEL and the MMX force field parameters. Double headed arrows indicate observed NOE cross peaks in the 2D ^{1}H NMR NOESY spectrum of these compounds.

The Diels-Alder reaction of (8) and 1-methoxy-1,3-butadiene (24) at 60 °C for 10 days gave a 82 : 18 mixture of the *exo* and *endo* cycloaddition products (26a) and (26b), respectively in 51% yield (Scheme 2.8). The two diastereoisomers could not be separated. The stereochemistry of these adducts was assigned on the basis of COSY and NOESY NMR experiments on a mixture of the two isomers.



(26a)



(26b)

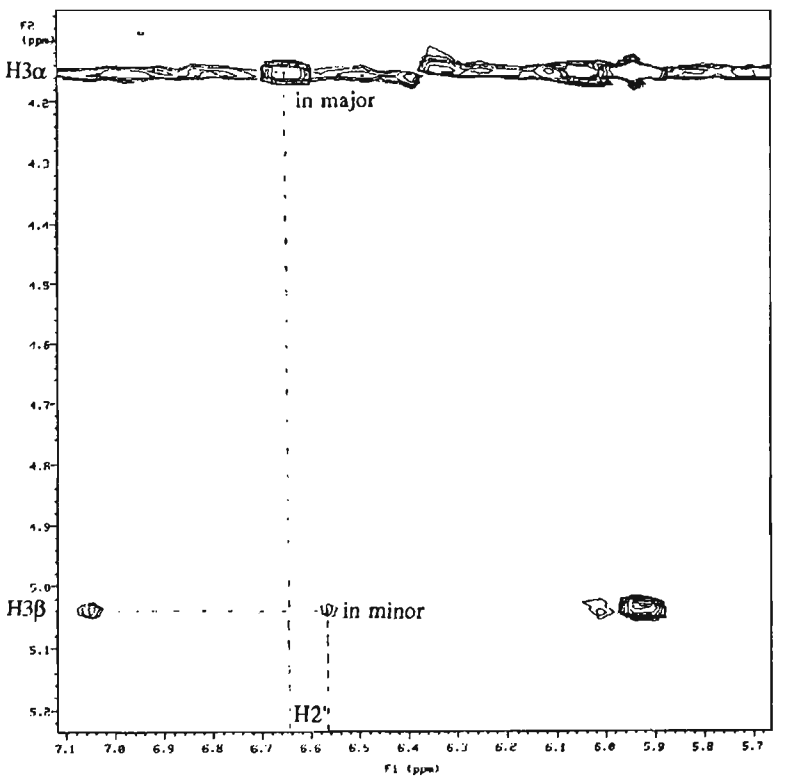


Figure 2.5. Expanded section of the NOESY NMR spectrum (400 MHz, $CDCl_3$) of the adducts (26a) and (26b). (Note: The referencing of the F1 scale offset by 0.2 ppm).

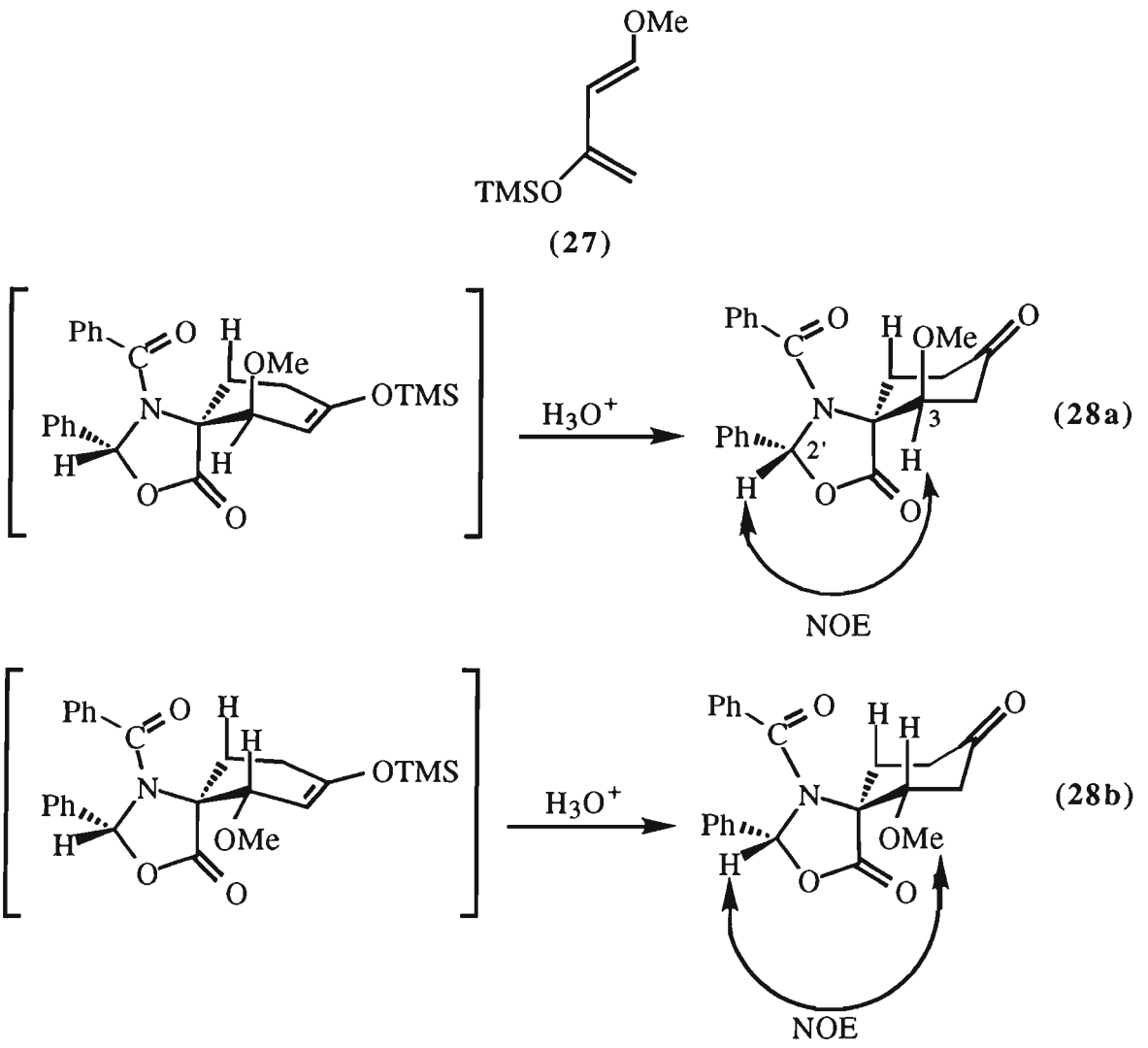
The major diastereoisomer (26a) showed a NOE cross peak between H2' (δ 6.61) and H3α (δ 4.15). While in the minor diastereoisomer (26b), a weak

NOE cross peak was observed between H2' (δ 6.52) and H3β (δ 5.03) (Figure 2.5) and a NOE cross peak was observed between H2' and the OMe (δ 3.62) group.

2-3-2-2. Diels-Alder Reaction of (8) and 1-Methoxy-3-(trimethylsilyloxy)-1,3-Butadiene (27)

The Diels-Alder reaction of 1-methoxy-3-(trimethylsilyloxy)-1,3-butadiene (Danishefsky's diene) (27) at 60 °C for two days gave a 1 : 1 mixture of two diastereoisomers. The crude reaction product was hydrolysed with dilute hydrochloride acid[58] to give a 50 : 50 mixture of the *exo* and *endo* cycloaddition products (28a) and (28b), respectively (Scheme 2.9).

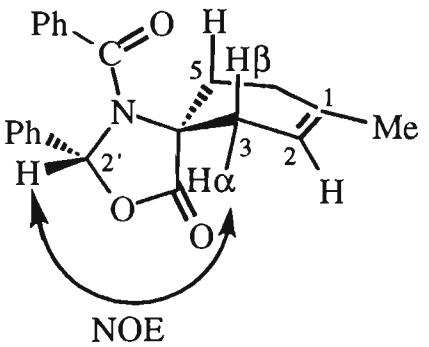
Scheme 2.9



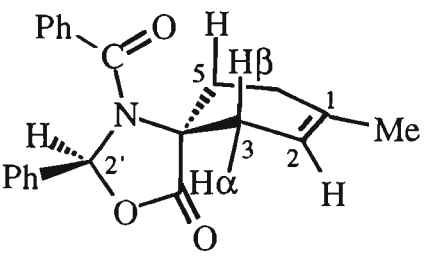
The stereochemistry of these adducts was assigned on the basis of a NOESY experiment. The H2' proton (δ 6.55) in the *exo* isomer (28a) showed a strong NOE cross peak to the H3α (δ 4.14), while in the *endo* isomer (28b) a cross peak was observed between H2' (δ 6.54) and the methoxy group at δ 3.53. Attempts to convert (28a) and (28b) to the same α,β-unsaturated ketone by treating these compound with base (eg. DBU or LDA) were unsuccessful.

2-3-2. Diels-Alder Reactions of (8) and 2-Substituted-1,3-Butadienes

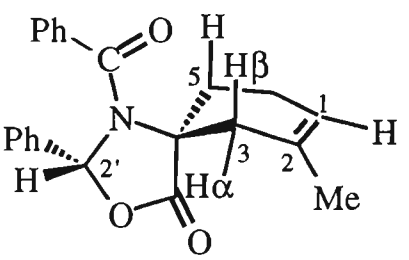
The Diels-Alder reaction of (8) and 2-methyl-1,3-butadiene at 60 °C for 10 days gave a 66:31:3 mixture of three diastereomeric adducts in excellent yield (96%). The two major diastereomeric adducts could be obtained pure after separation by semi-preparative HPLC. The predominant and second most predominant adducts were assigned the 'para' (29) and '*epi*-C2'-para' (30) structures respectively, on the basis of the following NMR and chemical experiments.



(29)



(30)



(31)

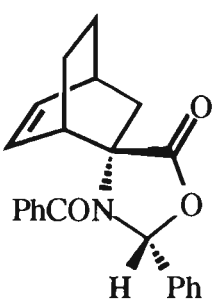
A COSY NMR experiment on (29) showed the alkene proton H2 (δ 5.37) was strongly coupled with H3α (δ 2.38), consistent with a 'para' structure. The same cross peak was observed between H2 (δ 5.58) and H3α (δ 2.24) in minor isomer (30). In a NOESY experiment of the major isomer (29) a strong cross peak was observed between H2' (δ 6.61) and H3α (2.38) but in the minor isomer this cross peak could not be observed. Another experiment which established the stereochemistry of the minor isomer (30) involved heating the major isomer (29) at 100 °C for 24 hr. This experiment resulted in a 86 : 14 mixture of the compounds (29) and (30), respectively. The third isomer could not be isolated in pure form and was possibly the 'meta' product (31).

Attempts to increase the rate of these reactions of (8) with substituted 1,3-butadienes by the addition of a Lewis acid (e.g. $BF_3(C_2H_5)_2O$ and $TiCl_2(OPr^i)_2$) were unsuccessful. These experiments resulted in either no enhancement of the rate or in the destruction of the dienophile (8).

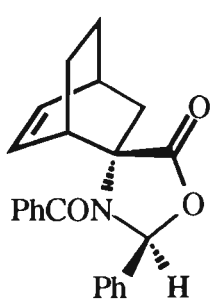
2-4. Diels-Alder Reactions of (8) and Substituted-1,3-Cyclohexadienes

2-4-1. Diels-Alder Reactions of (8) and 1,3-Cyclohexadiene

It has been reported that the thermally induced reaction of (8) and 1,3-cyclohexadiene gave two diastereomeric products.[48] The ratio of these products was dependent upon the reaction temperature. When this reaction was performed at 130 °C, the two diastereomeric adducts were obtained in a ratio of 67 : 33.[48] In this study it was found that the diastereomeric ratio was more favourable (74 : 26) at 60 °C, although the reaction time for complete consumption of (8) was dramatically increased (15 days, Table 2.2, page 47). These two diastereomeric adducts could be obtained diastereomerically pure after purification of the reaction mixture by semi-preparative HPLC or by fractional crystallization from ethyl acetate / hexane. The stereochemistry of these isomers was determined to be (11) and (32).

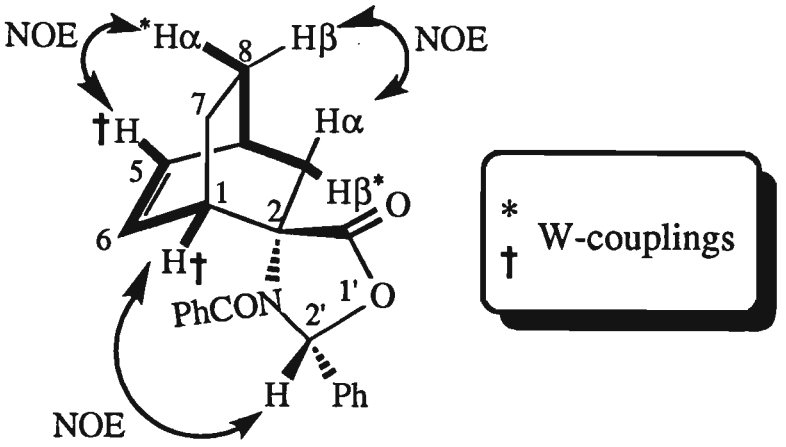


(11)



(32)

The major adduct was confirmed to have the *exo*-stereochemistry by comparison of its ^{1}H NMR with that of the compound (10)[48] which was established by a single crystal X-ray structural determination. The aromatic proton resonances for the two structures (10) and (11) were almost identical, as were the signals for H2' in (10) (δ 6.56) and (11) (δ 6.57). COSY and NOESY NMR experiments also established the stereochemistry of the major isomer as shown in (11) (Figure 2.6).



(11)

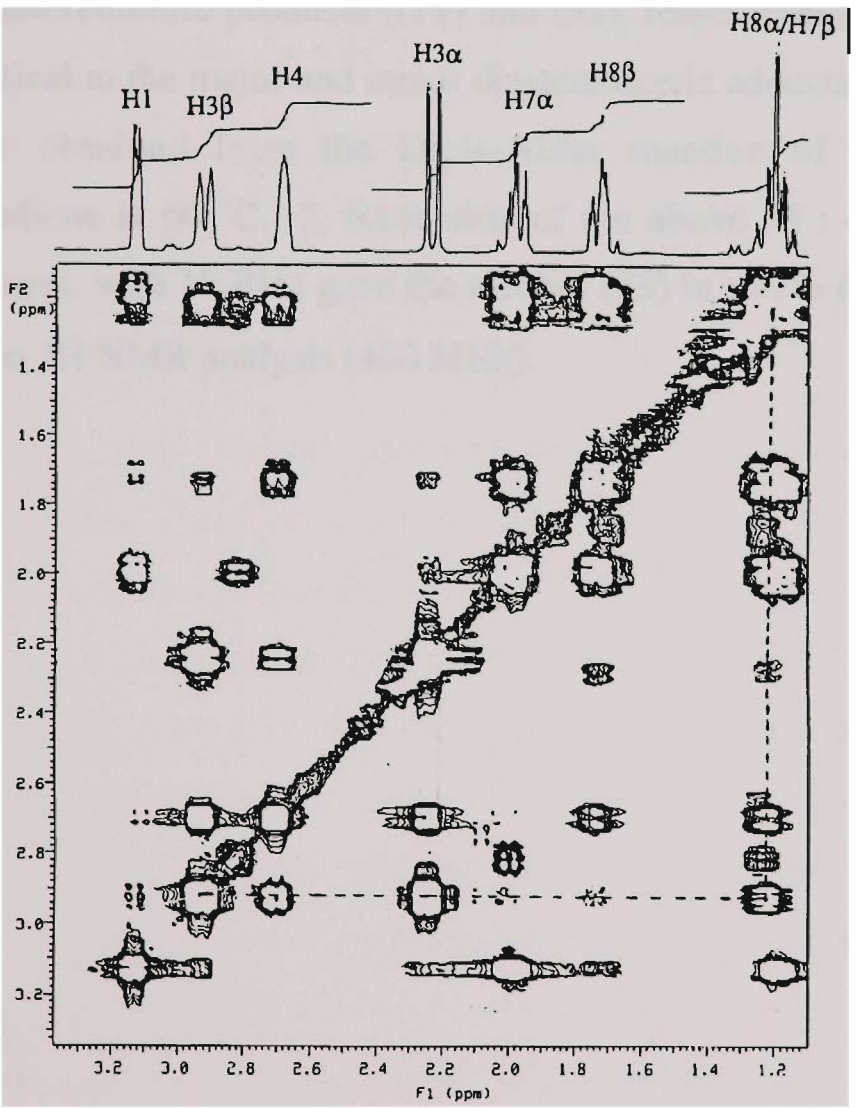
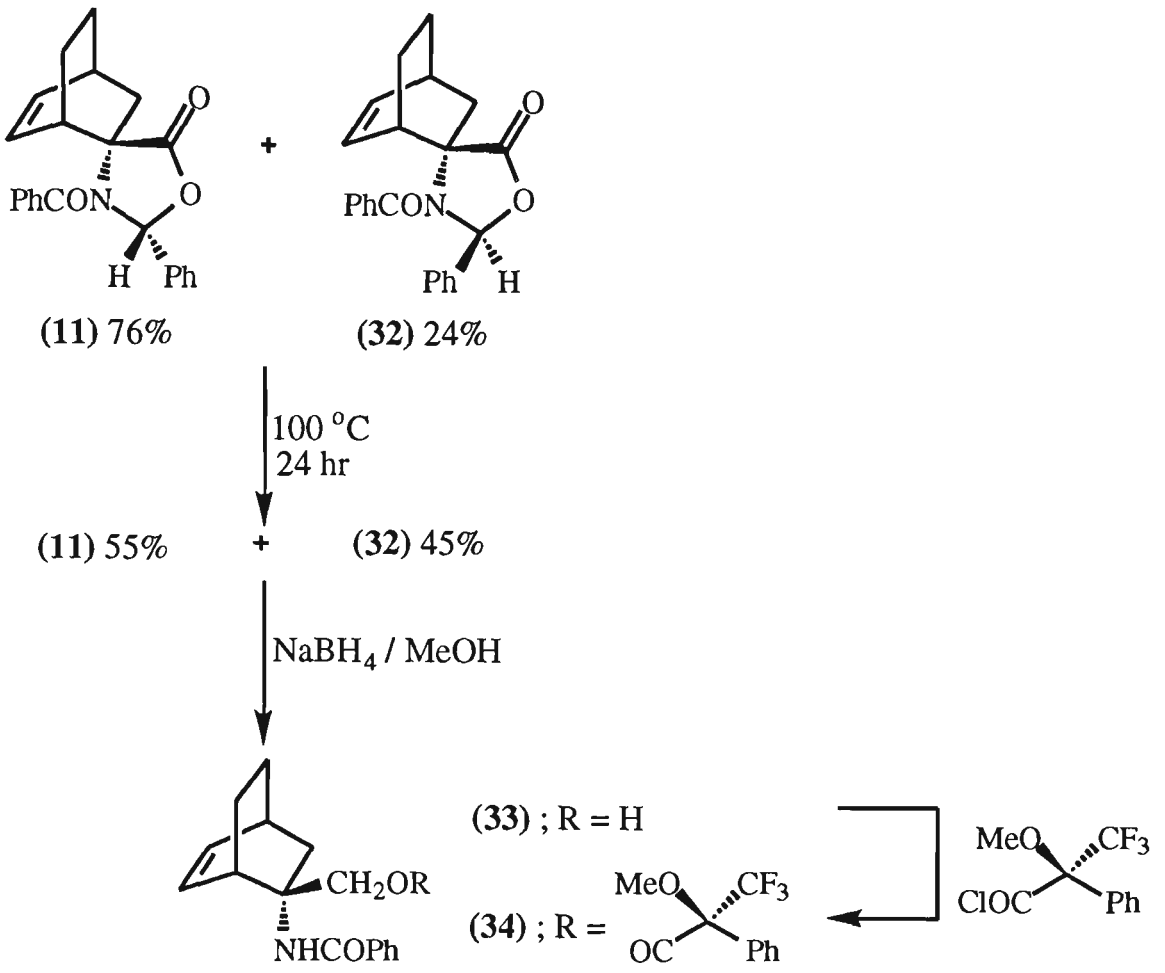


Figure 2.6. Expanded section of the COSY NMR spectrum (400 MHz, $CDCl_3$) of the adduct (11). (W-coupling between H3β and H8α indicated by ------- line).

In the COSY spectrum of (11), strong cross peaks were observed between H5 (δ 6.16) and H1 (δ 3.12) and between H3β (δ 2.90) and H8α (δ 1.22) due to W-coupling (Figure 2.6). The NOESY spectrum showed strong cross peaks between H2' (δ 6.57) and H1 (δ 3.12) and between H8β (δ 1.72) and H3α (δ 2.23) and also between H5 (δ 6.16) and H8α (δ 1.22).

The stereochemistry of the minor isomer was assigned on the basis of the following experiments that were performed on a 76 : 24 mixture of the diastereoisomers (11) and (32) (Scheme 2.10). 1. When a solution of these diastereomers was heated at 100 °C or 130 °C for 24 hr, a 55 : 45 mixture of two diastereomeric products ((11) and (32), respectively) resulted that were identical to the major and minor diastereomeric adducts, respectively, that were obtained from the Diels-Alder reaction of (8) and 1,3-cyclohexadiene at 60 °C. 2. Reduction of the above 55 : 45 mixture of diastereomers, with $NaBH_4$ gave the alcohol (33) in >97% diastereomeric purity from ^1H NMR analysis (400 MHz).

Scheme 2.10



The above experiments clearly demonstrate that the two diastereomeric Diels-Alder adducts had the same configuration at C2 (C4') and were epimeric at the amino-acetal carbon C2'. The major and minor diastereomeric Diels-Alder adducts are therefore structures (11) and (32), respectively. The poor diastereoselectivity in the Diels-Alder reaction of (8) and 1,3-cyclohexadiene is hence the consequence of a thermally induced epimerization, at C2', of the initially formed *exo* adduct (11) and is not due to the formation of the diastereomeric *endo* adduct as previously reported.[48] The diastereoisomer (32) is formed from the epimerization of (11) at C2' through a thermally induced ring opening of the oxazolidinone ring during the course of the Diels-Alder reaction similar to that observed in the case of compounds (17). The enantiomeric purity of the alcohol (33) was determined to be 90% from ^{1}H NMR analysis of its Mosher ester (34)

(95 : 5 mixture of diastereoisomers, Figure 2.7). The enantiomeric purity of the alcohol (33) indicates that the extent of epimerization at C2 in the starting dienophile (8) is about 3-4% at 60 °C over 15 days since the enantiomeric purity of (8) prior to the Diels-Alder reaction was > 97%.[48]

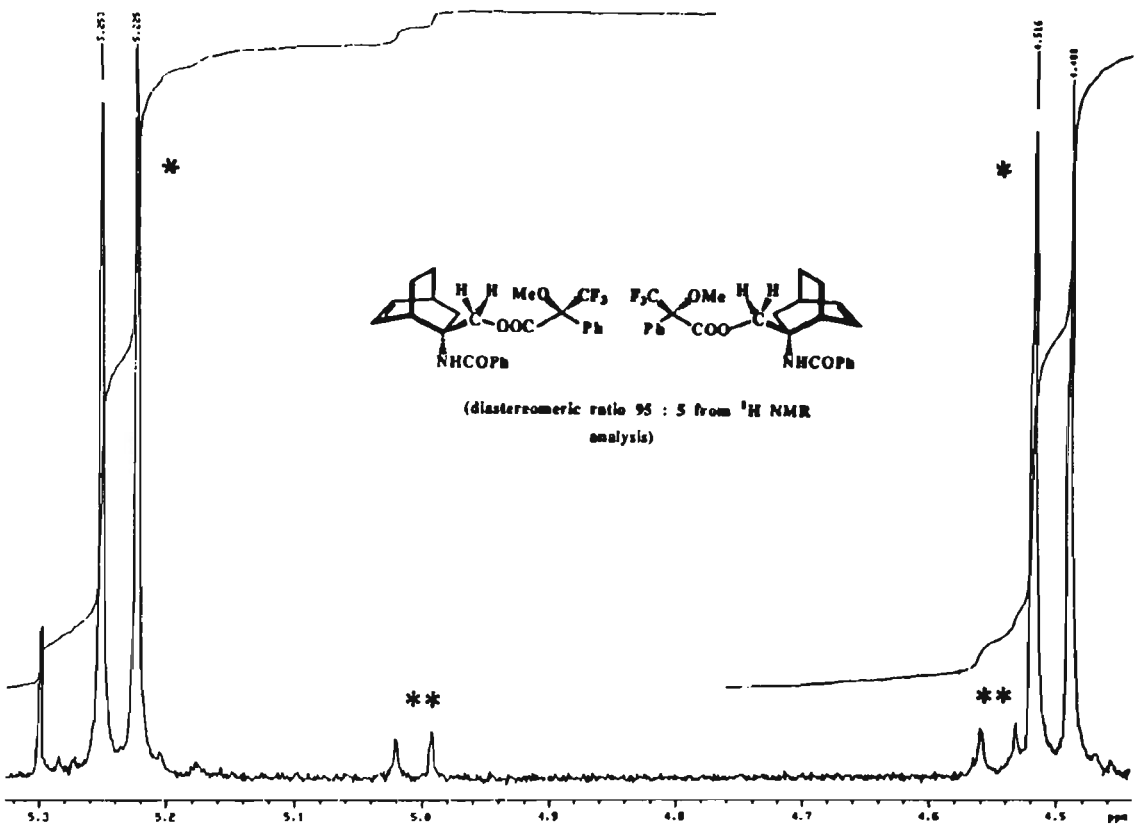
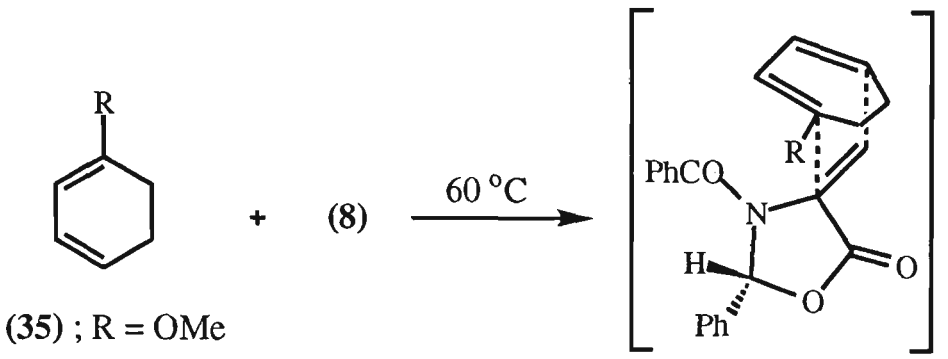


Figure 2.7. Expanded section of the ^{1}H NMR (400 MHz) spectrum of the Mosher ester (34) showing the diastereotopic methylene protons for the two diastereomeric products (ratio 95 : 5). * major diastereoisomer; ** minor diastereoisomer.

2-4-2. Diels-Alder reactions of (8) and 1-Substituted-1,3-Cyclohexadienes

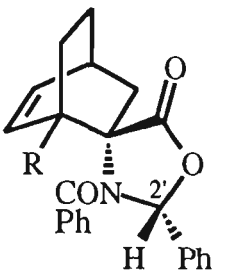
The Diels-Alder reactions of (8) and 1-methoxy- or 1-(trimethylsilyloxy)-1,3-cyclohexadiene (35) and (36) at 60 °C were highly regioselective and diastereoselective and gave (37) and (38), respectively, as the major diastereomeric adducts (Scheme 2.11). The diastereoselectivity of the latter reaction (d.r. 97 : 3) was greater than that of the former reaction (d.r. 89 : 11) (Table 2.2, page 47).

Scheme 2.11



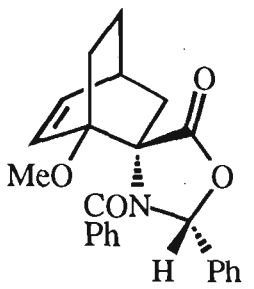
(35) ; R = OMe
(36) ; R = OTMS

(*exo* transition state)



(37) ; R = OMe (d.r. = 89 : 11)
(38) ; R = OTMS (d.r. = 97 :3)

The structure and stereochemistry of the major diastereomeric adduct (37), from 1-methoxy-1,3-cyclohexadiene and (8), was established by a single crystal X-ray structural determination (Figure 2.8). The structural analysis showed that the diene had added to the face of the 4-methylene group which was *anti* to the C2' phenyl group and that the 'ortho' regioisomer had been obtained. The structure determination also showed that the oxazolidinone carbonyl group in (37) was *exo* to the ethano bridge of the bicyclo[2.2.2]octenyl ring system (Figure 2.8). The stereochemistry assigned to (38) was based on the similarity between its ^{1}H NMR spectra and that of (37) (Experimental Section, Chapter Two).



(37)

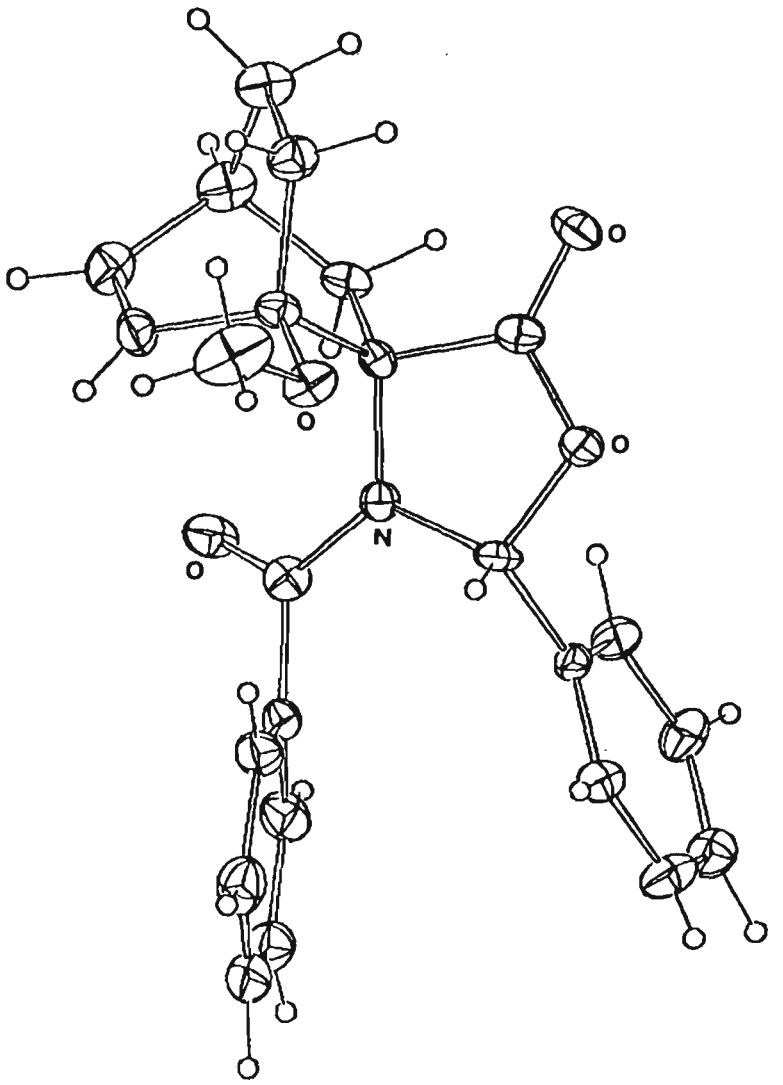


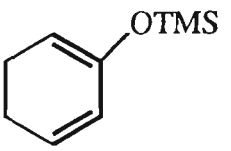
Figure 2.8. Molecular projection of (37), normal to the plane of the five-membered ring. 20% thermal ellipsoids are shown for the non-hydrogen atoms; hydrogen atoms have an arbitrary radii of 0.1 Å.

In contrast to (11), heating a solution of (37) at 100 °C for 24 hr resulted in the recovery of only diastereomerically pure starting material and no products that would result from epimerization at C2' could be detected. It seems likely the bridgehead MeO or TMSO in (37) and (38) respectively is

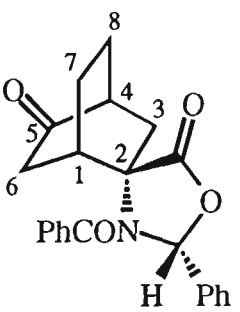
responsible for an increase in the energy barrier for ring opening of the oxazolidinone ring in these compounds. This could be possibly due to an increase in steric interactions between the bridgehead substituent and the Ph and PhCO substituents about the developing iminium ion that would be required for ring opening (cf (19), Scheme 2.5). The minor cycloadducts from the above two reactions could not be isolated diastereomerically pure and therefore their structures could not be unequivocally determined.

2-4-3. Diels-Alder Reaction of (8) and 2-Substituted-1,3-Cyclohexadiene

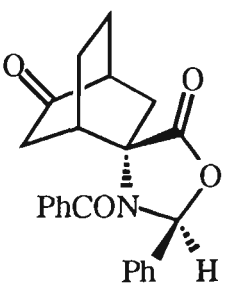
The Diels-Alder reaction of 2-(trimethylsilyloxy)-1,3-cyclohexadiene (39) and (8) at 60 °C, followed by hydrolysis of the crude reaction products with dilute acid, gave a mixture of four diastereomeric adducts (d.r. 50 : 26 : 12 : 12; Table 2.2, page 47). Three of the adducts have been identified as (40a), (40b) and (40c). The fourth diastereomeric adduct could not be isolated pure and its structure could not be determined. From COSY and NOESY NMR experiments the structure of the major diastereoisomer was determined to be the 'para' *exo* adduct (40a).



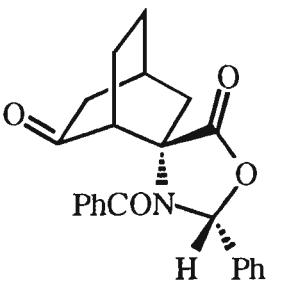
(39)



(40a)



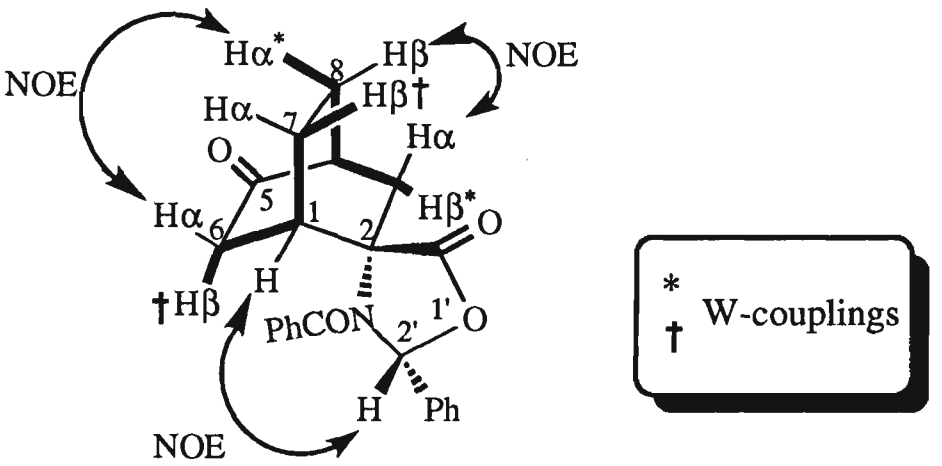
(40b)



(40c)

Two strong cross peaks were observed in the COSY spectrum of (40a) due to W-coupling (Figure 2.9) between H3β (δ 2.85) and H8α (δ 2.50) and

between H7β (δ 1.88) and H6β (δ 3.63). The NOESY spectrum showed strong cross peaks between H2' (δ 6.54) and H1 (δ 2.72) and between H3α (δ 2.29) and H8β (δ 1.64) and between H6α (δ 2.57) and H7α (δ 2.14).



(40a)

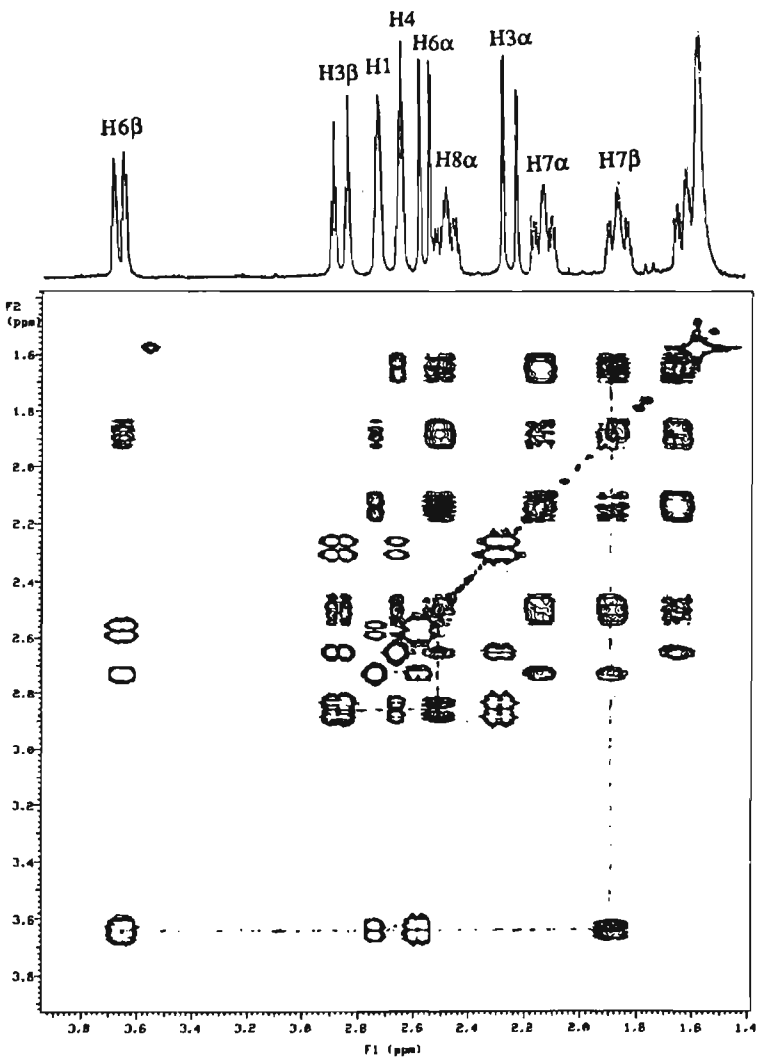
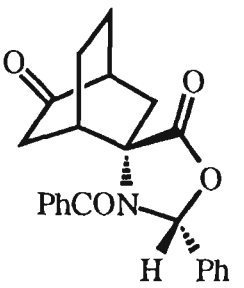


Figure 2.9. Expanded section of the COSY NMR spectrum (400 MHz, $CDCl_3$) of adduct (40a). (W-couplings indicated by -----line).

The structure of compound (40a) was unequivocally established by a single crystal X-ray structure determination (Figure 2.10).



(40a)

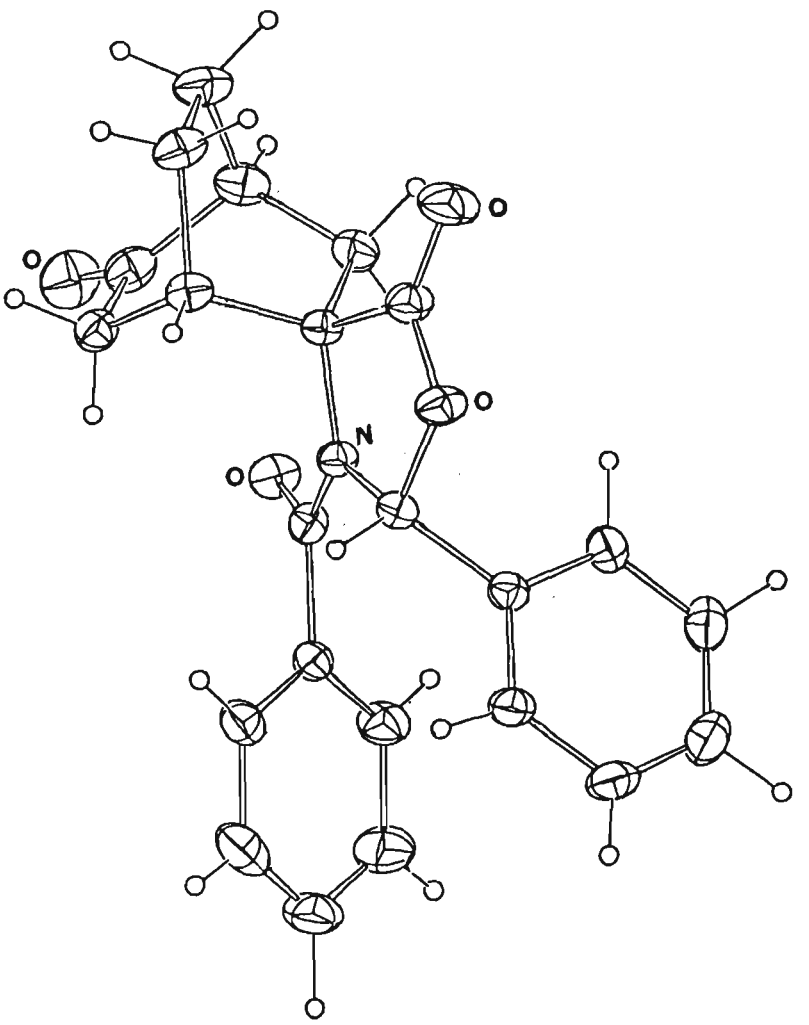
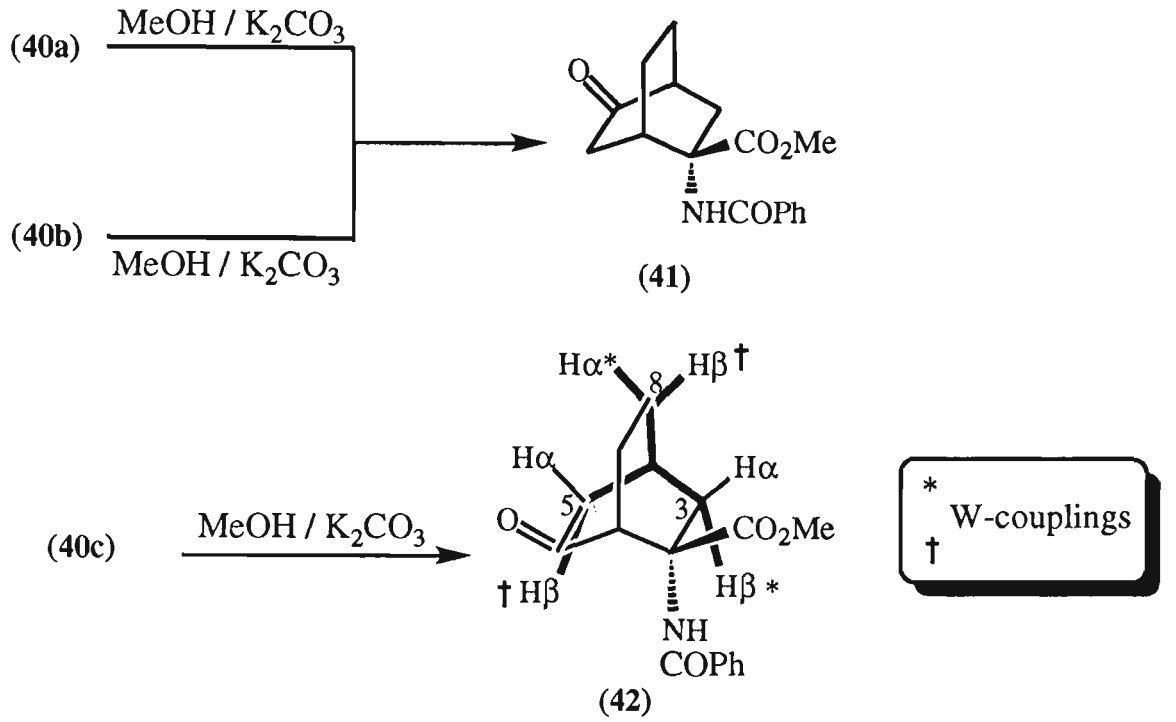


Figure 2.10. Molecular projection of (40a) normal to the plane of the five-membered ring. 20% thermal ellipsoids are shown for the non-hydrogen atoms; hydrogen atoms have an arbitrary radii of 0.1 Å.

The stereochemistry of one of the minor isomers (40b) was determined to be the *exo* diastereoisomer (40b) in which epimerization had occurred at

C2', by the conversion of both isomers (40a) and (40b) with MeOH / K_2CO_3 to the same methyl ester (41) (Scheme 2.12).

Scheme 2.12



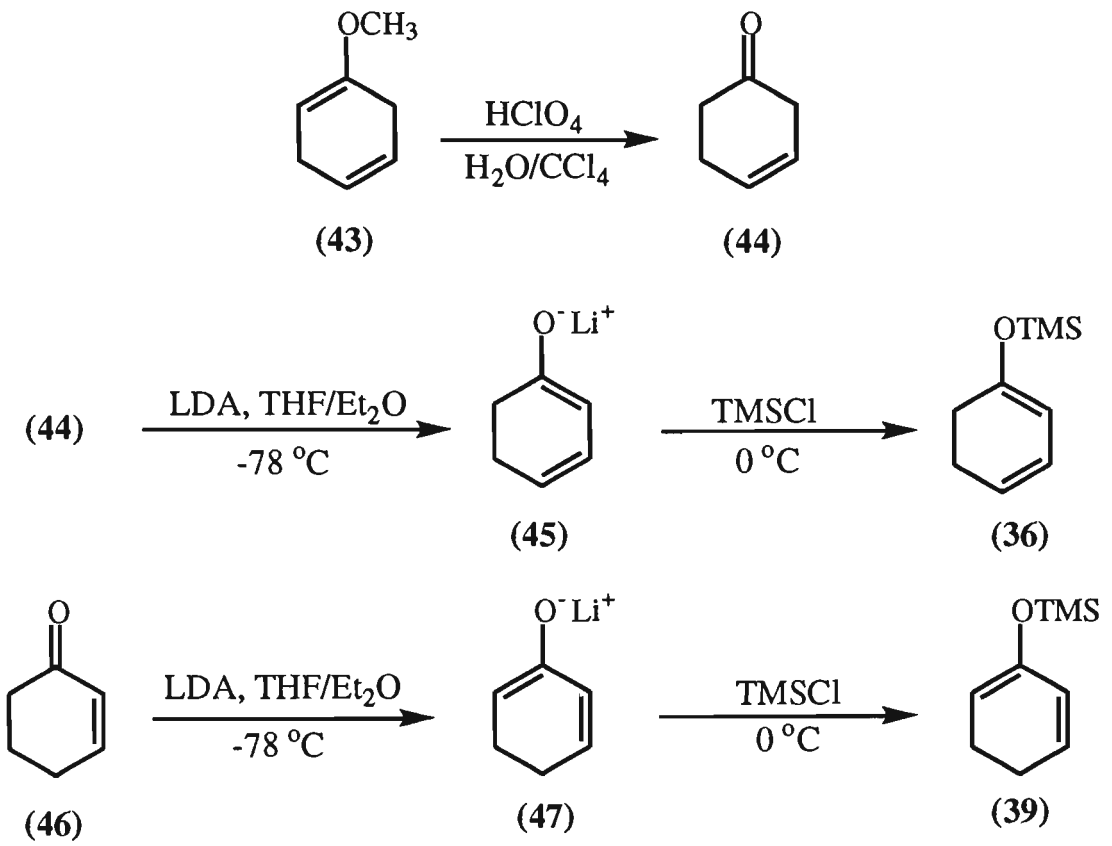
The methyl ester (42) was prepared using the above reaction conditions from minor isomer (40c) (Scheme 2.12). This compound (40c) was determined to be the 'meta' regioisomer from COSY NMR analysis of its ester derivative (42). Two strong cross peaks were observed between H5β (δ 3.20) and H8β (δ 2.00) and between H3β (δ 2.38) and H8α (δ 2.20) (W-couplings) in the COSY spectrum of compound (42).

2-4-4. Preparation of the Dienes (36) and (39)

The diene (36) was prepared from 3-cyclohexene-1-one (44), which was available from the hydrolysis of 1-methoxycyclohexa-1,4-diene (43) with perchloric acid in carbon tetrachloride and water (Scheme 2.13).[59] The enolates (45) and (47) were prepared from treatment of ketones (44) and (46), respectively, with lithium diisopropylamide in THF-Et_2O at -78 °C. The resulting enolates (45) and (47) were treated with trimethylsilyl

chloride to give exclusively the dienes (36)[60] and (39)[61], respectively (Scheme 2.13).

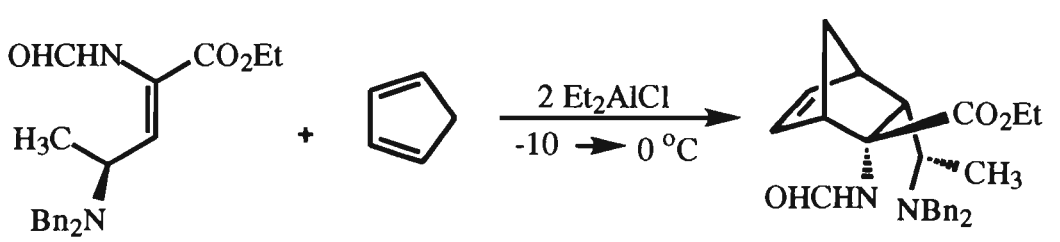
Scheme 2.13



2.5. *Exo*-Diastereoselectivity of the Diels-Alder Reactions

Diels-Alder reactions often display a preference for *endo* cycloadducts.[50,57,62] Numerous attempts have been undertaken to explain this phenomenon. In 1937, Alder *et al.* suggested the maximum accumulation of unsaturation in the transition state as a heuristic principle.[63] The Alder rule stimulated a number of rationalizations including stabilization of the *endo* transition state by: (1) inductive (van der Waals or dipolar) forces,[64] (2) charge transfer,[65] (3) favourable geometry for overlap,[66] (4) secondary bonding forces,[67] (5) secondary orbital interactions.[68] It should be noted that the *endo* rule applies only to the kinetic products of Diels-Alder reactions, and that its application to intramolecular cycloadditions is more uncertain.[51] In some cases a destabilizing steric interaction was considered for the *endo* transition state, in the reactions of cyclic dienes.[69-71] *Exo* selective Diels-Alder reactions of cyclic dienes and DHAAs[11,69] and related dienophiles[70,54,71] are well documented. Diels-Alder reaction of the γ-*N*,*N*-dibenzylamino dehydroamino acid ester (48) and cyclopentadiene produced the *exo* cycloadduct (49), in high diastereomeric excess (d.e. 96%) (Scheme 2.14).[69a]

Scheme 2.14

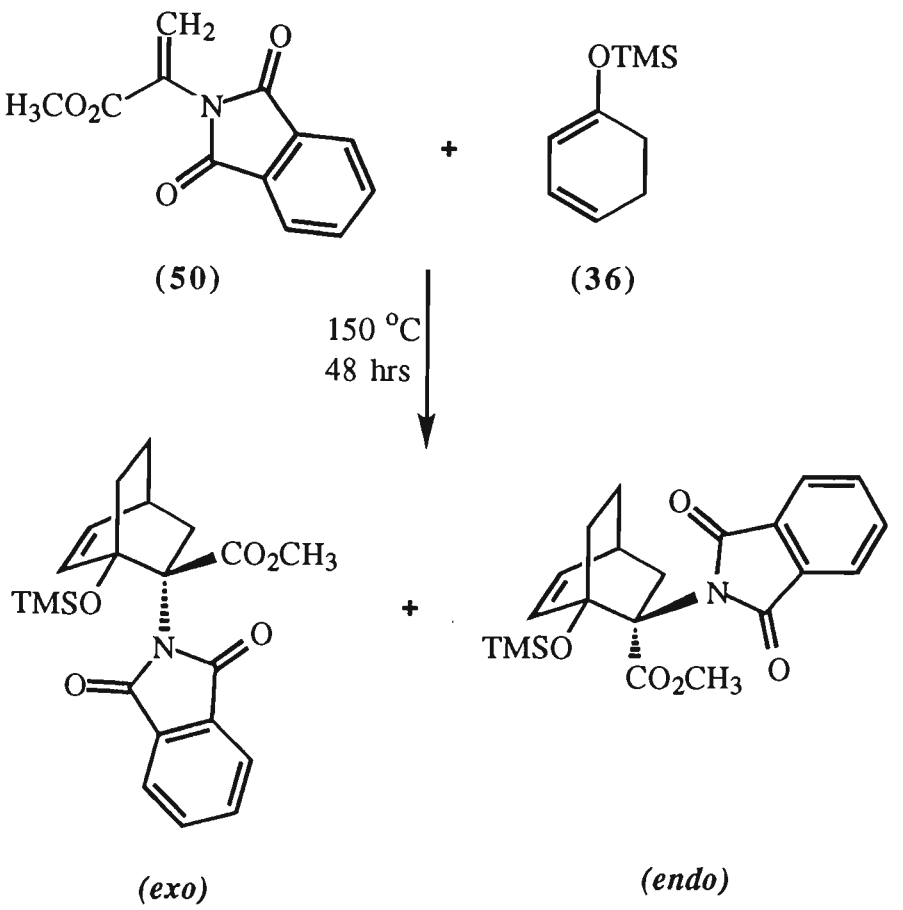


(48) **(49)**

The cycloaddition reaction of the DHAA (50) with 1-(trimethylsilyloxy)-1,3-cyclohexadiene (36) gave the *exo* and *endo* cycloadducts in a ratio of

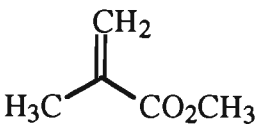
62 : 38 (Scheme 2.15).[69b] It was not clear, however, if these adducts were formed under kinetically or thermodynamically controlled conditions.

Scheme 2.15



(exo) *(endo)*

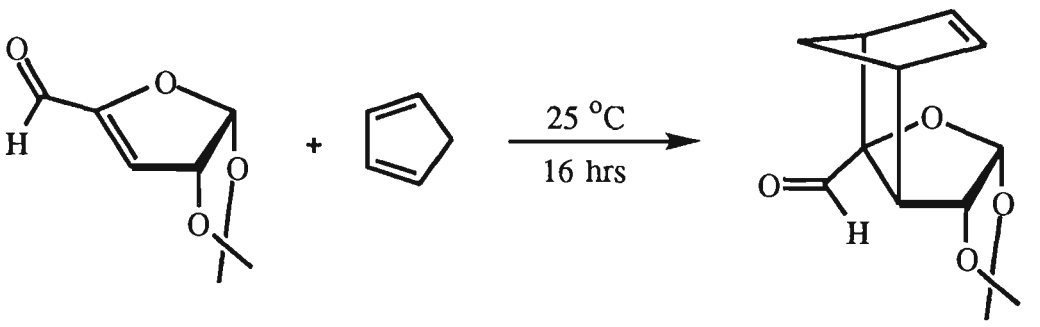
Other α-substituted acrylate esters such as methyl methacrylate (51) also give *exo* cycloadducts with cyclopentadiene.[72]



(51)

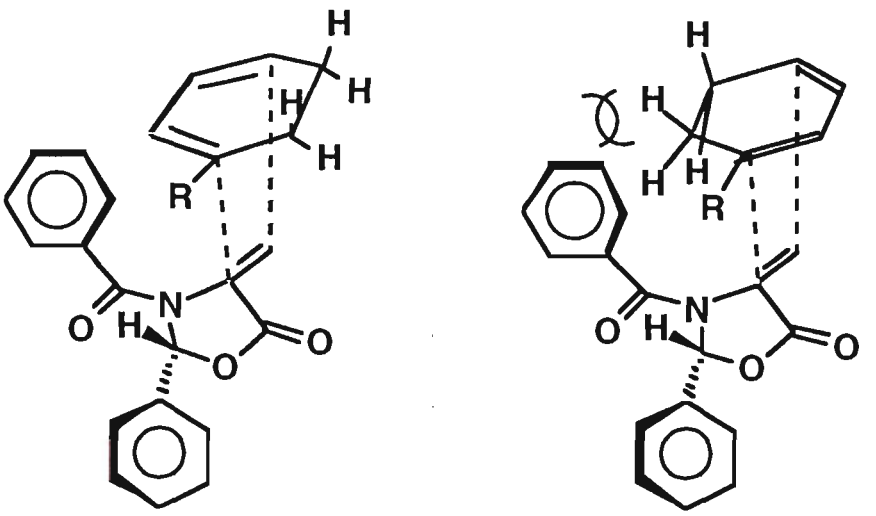
The related cyclic dienophile (52) reacted with 1.2 equivalents of cyclopentadiene in methylene chloride to give the *exo* adduct (53) as a single stereoisomer in 90% yield (Scheme 2.16).[70a]

Scheme 2.16



(52) (53)

For the Diels-Alder reactions of dienes with our dienophile (8), and related α-substituted acrylates, the *endo* transition state (54b) would be expected to be destabilized due to an unfavourable steric interaction between the α-substituent (the stericaly demanding PhCON group in our reactions) and the methylene proton(s) on the cyclic diene and thus the *exo* transition state (54a) would be expected to be favoured.

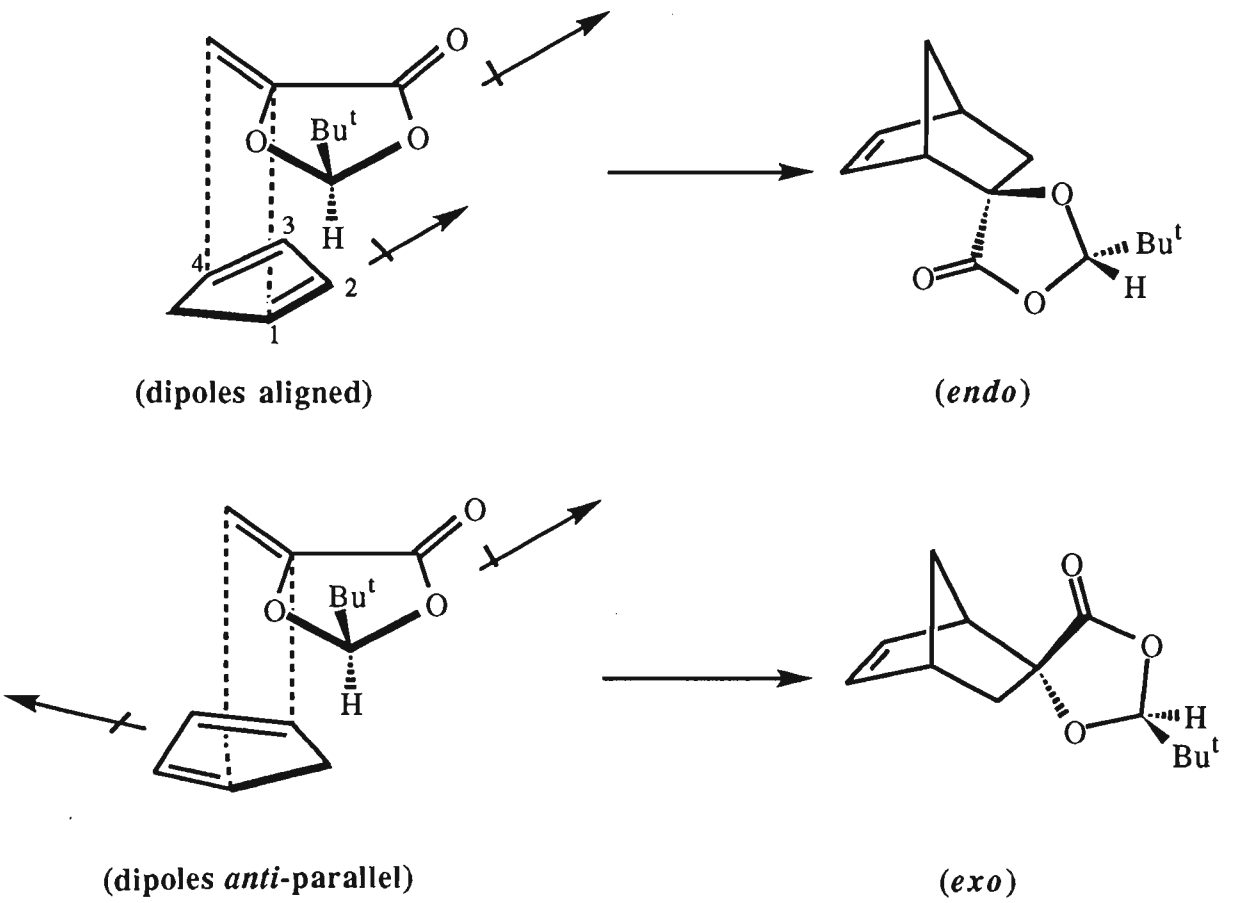


(54a) (54b)

Using this stereochemical argument however, one would expect that the reaction of (8) with 1-substituted-1,3-butadienes to give *endo* cycloaddition products rather than the observed *exo* cycloadducts, since there is now no significant destabilizing steric interaction between the α-substituent and the diene in the *endo* transition state. It appears that electronic factors rather than steric factors are responsible for the high *exo* selectivity in the Diels-Alder reactions of (8) and related dienophiles. It has been recently

suggested by Roush *et al.*[71a] that dipole-dipole interactions between the diene and dienophile are responsible for the *exo* selectivity in the Diels-Alder reactions of *exo* cyclic-methylene dienophiles like (8). Roush suggests that the *exo* transition state for the reaction between dioxolan-one (14a) and cyclopentadiene is favoured because this transition state structure has the smallest permanent dipole moment (Scheme 2.17). The dipole of the diene must have its negative end bisecting C2 and C3 of the cyclopentadiene ring and its positive end toward the saturated methylene group because the electronegativity of a sp^2 carbon is greater than that of a sp^3 carbon.[72] The negative end of the dipole due to the dienophile must lie toward the carboxy function. Although some change in the magnitudes of the two dipole moments might be expected in passing from the reactants to the transition state, the directions are expected to remain qualitatively the same (Scheme 2.17).

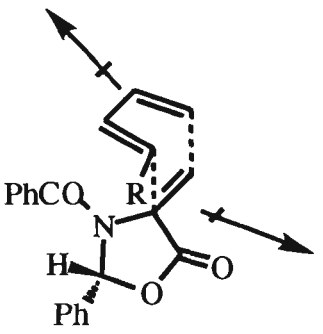
Scheme 2.17



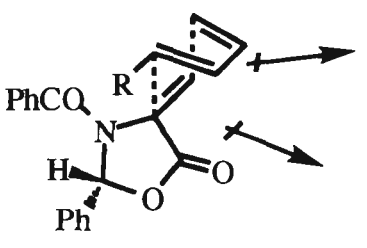
In the *endo* transition state, the component dipoles point in roughly the same direction and, consequently, the net dipole moment is expected to be greater than that of the *exo* transition state, where the component dipoles point in roughly opposite directions (Scheme 2.17).

Berson and co-workers have suggested that "the permanent dipole moment of the *endo* transition state is greater than that of the *exo*".[72] This suggestion resulted from the analysis of the stereoselectivity and solvent dependence of the Diels-Alder reactions of cyclopentadiene and methyl acrylate, methyl methacrylate, and methyl crotonate. They established a new solvent polarity constant based on the solvent dependence of the *exo/endo* ratio (increased *exo* selectivity in low polarity media). In the cycloaddition reaction of cyclopentadiene and methyl methacrylate (51) in 1,2-dichloroethane at 30 °C they found a ratio 70 : 30 for the *exo* and *endo* adducts, while in the more polar solvent such as ethanol the *exo/endo* ratio was 64 : 36.

The explanation of Roush can be used to explain why the transition state (55a) is favoured over (55b) in our study based on dipolar considerations.



(55a)



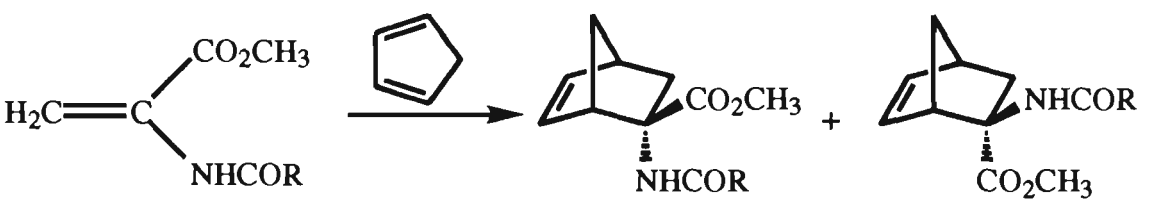
(55b)

Our reactions however, showed no rate enhancement, or change in *exo/endo* selectivity, when the reaction solvent was changed from CH_2Cl_2 to benzene or acetonitrile. This lack of a solvent effect suggests the dipole-dipole interactions in the transition state are not responsible for the *exo*-diastereoselectivity in our reactions. It seems likely that electronic factors

are responsible for the *exo*-diastereoselectivity and that more sophisticated theoretical calculations are required to understand the diastereoselectivity in these reaction.

Bueno *et al.* in 1987[73] introduced a system in which secondary orbital interactions from the donor group of captodative dienophiles might stabilize the *exo* transition state. In this study *N*-acyl-α,β-dehydroalaninates (56) were treated with cyclopentadiene under several conditions (Scheme 2.18). Complete consumption of (56) was achieved by using a moderate excess of cyclopentadiene, $TiCl_4$ as a catalyst, or high reaction temperatures in various solvents (Table 2.3). In all cases the *exo* stereoisomer was favoured over the *endo* one.

Scheme 2.18



(56)
a ; R = CH_3
b ; R = C_6H_5

(exo) ***(endo)***

Table 2.3. Diels-alder reactions of *N*-acyl-α,β-dehydroalaninates (56) with cyclopentadiene.[73]

Substrate	Temperature (°C)	Time (hr)	Solvent	Lewis acid	Reagents ratio[a]	Yield (%)	Adducts *exo/endo*
(56a)	90-100	5	Toluene	-	1 : 6	100	6.9 : 3.1
(56a)	90-100	5	Toluene	-	1 : 9	100	7.1 : 2.9
(56a)	130-140	5	Xylene	-	1 : 3	100	7.2 : 2.8
(56a)	80-90	5	EtOH	-	1 : 3	78	6.4 : 3.6
(56a)	25-30	5	CH_2Cl_2	$TiCl_4$	1 : 3	100	5.7 : 4.3
(56a)	-10	5	CH_2Cl_2	$TiCl_4$	1 : 6	NR[b]	-
(56b)	130-140	5	Xylene	-	1 : 9	25	-

[a]dienophile/diene. [b] No reaction.

Perturbation MO calculations, using wave functions generated by the MNDO method, were used to rationalize the relative reactivity of these captodative dienophiles[74] and stereoselectivity observed. Bueno explained the *exo/endo* selectivity of Diels-Alder reaction of the captodative alkene (56) with cyclopentadiene, by secondary orbital interactions. He focused his attention on the nitrogen atom in the acylamino group and on the carbonyl carbon in the ester moiety. Bueno explained if the $HOMO_{diene}$-$LUMO_{dienophile}$ pair was considered, the only relevant secondary interaction occurred between C3 of both diene and dienophile, leading to preference for the *endo* stereoisomer. However, if one considered the $LUMO_{diene}$-$HOMO_{dienophile}$ pair, the only relevant secondary interaction occurred between C3-diene and N4-dienophile and this orbital pair favoured the formation of the *exo* adduct (Figure 2.11).

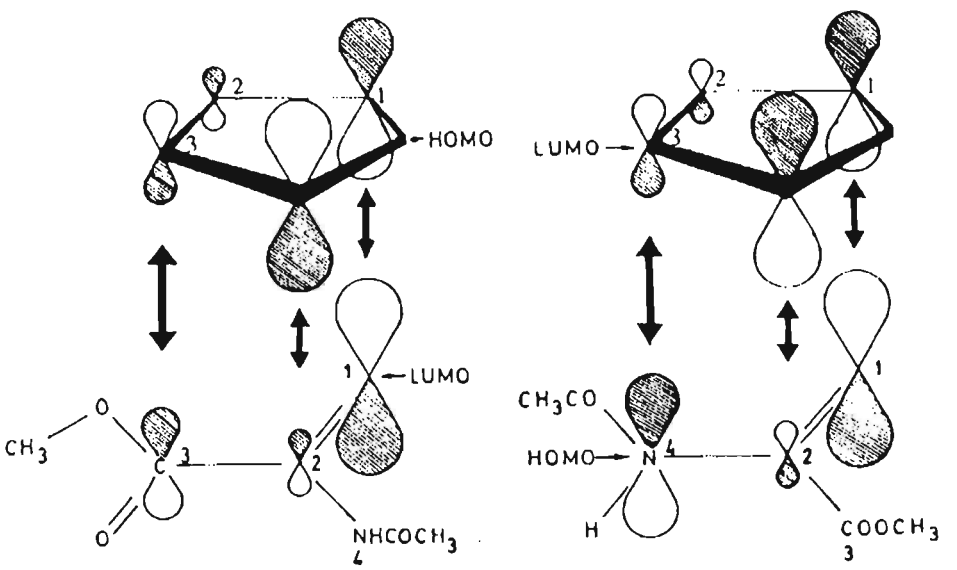


Figure 2.11. *Endo* and *exo* orbital interactions between (56a) and cyclopentadiene.

He obtained a ΔE_{endo} = -0.082 β_c^2 and a ΔE_{exo} = -0.089 β_c^2 by introducing the atomic coefficients and MO energies for cyclopentadiene and dienophile (56a), and taking the resonance integrals. From these values he inferred that the *exo* isomer was slightly favoured over the *endo*, being in qualitative agreement with the experimentally observed preference

for the *exo* over the *endo* isomer. From a consideration of the HOMO-LUMO energy gaps from cyclopentadiene and dienophile (56b) he found E^{HOMO}_{diene} - $E^{LUMO}_{dienophile}$ = -8.605 eV and $E^{HOMO}_{dienophile}$-E^{LUMO}_{diene} = -9.634 eV and also ΔE_{endo} = -0.040 β_c^2 and ΔE_{exo} = -0.054 β_c^2. He calculated the only important secondary interactions were those coming from the nitrogen atom of the benzamido group, since the carbonyl carbon of the ester moiety had no significant coefficients at all. Consequently the *exo* stereoisomer was favoured.

A similar explanation can be used to understand the *exo* selectivity in the Diels-Alder reactions of dienophile (8). The lactone carbonyl group in dienophile (8) is a withdrawing group and the benzamido group is a electron releasing group giving the alkene its captodative properties.[49] If we consider the frontier orbitals of the alkene (8) and 1,3-diene we would expect a secondary interaction between C3-diene and N3-dienophile in the $HOMO_{dienophile}$-$LUMO_{diene}$ pair (Figure 2.12), thus stabilizing the *exo* transition state.

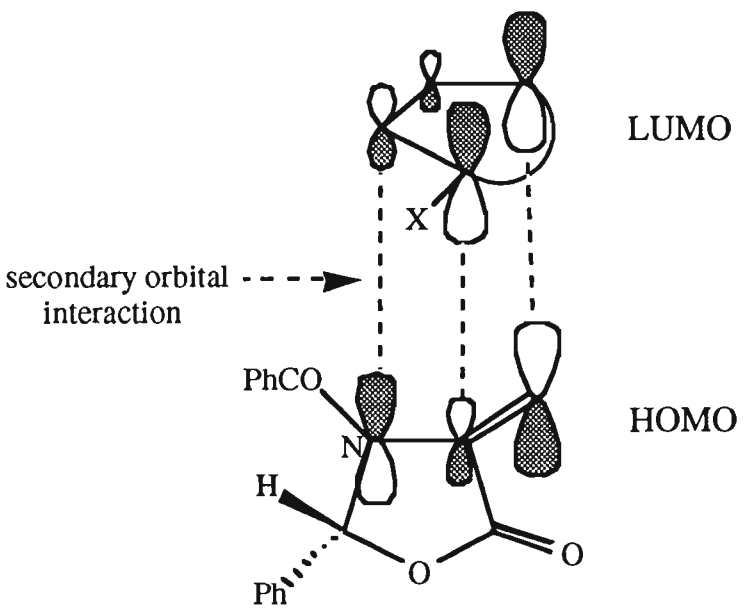
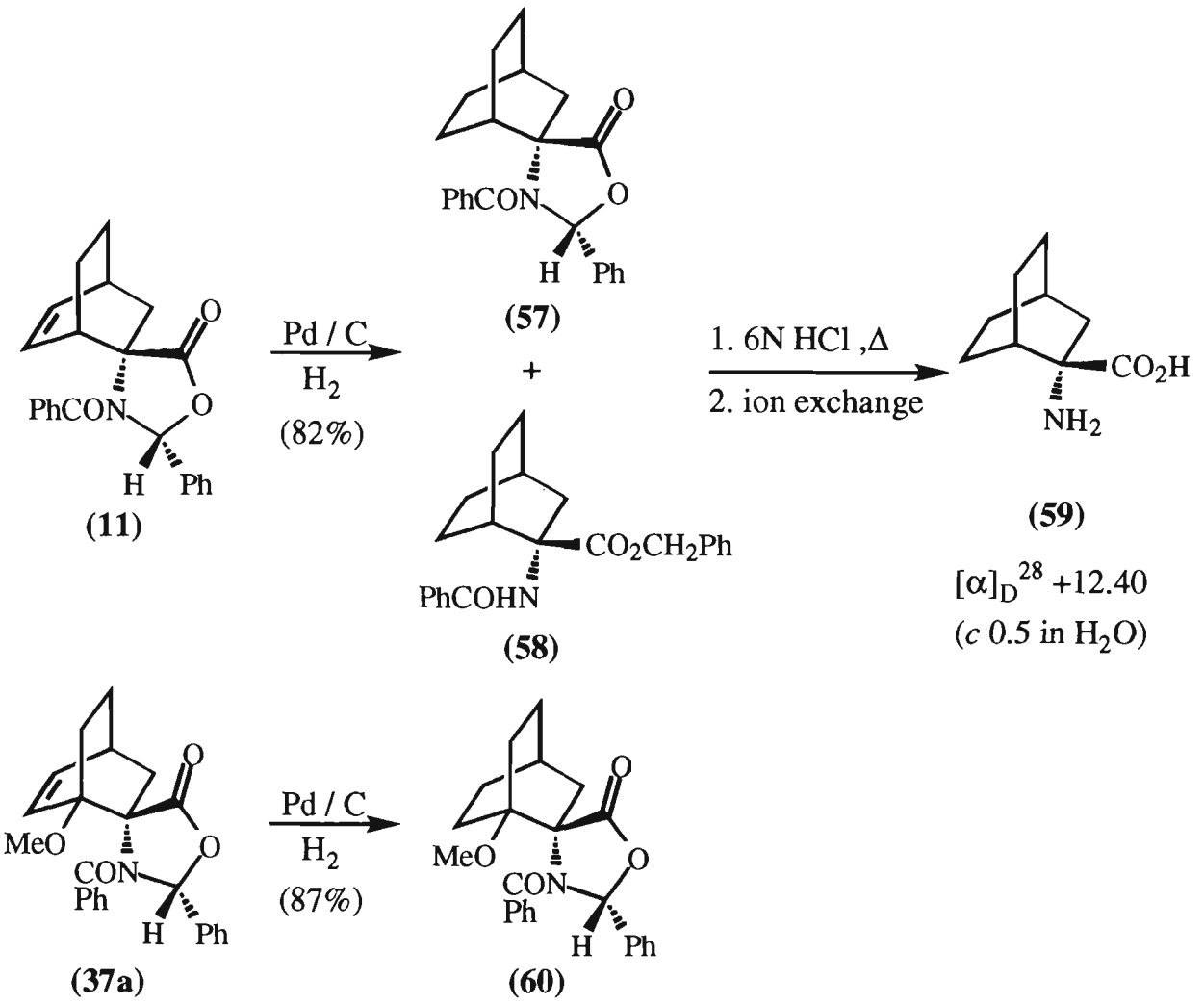


Figure 2.12. Orbital interactions between dienophile (8) and 1,3-dienes in the *exo* transition state.

2-6. Synthesis of 2-Aminobicyclo[2.2.2]octane-2-carboxylic Acids

The amino acid (59) with the bicyclo[2.2.2]octane skeleton was prepared by first catalytic hydrogenation of the double bond over palladium on carbon and then acid-catalysed hydrolysis of the oxazolidinone moiety of the Diels-Alder adduct (11) (Scheme 2.19). Catalytic hydrogenation of (11) gave a mixture of (57) and (58). The ratio of (57) to (58) depended upon the amount of catalyst and the reaction time. Compound (57) was favoured when the catalyst loading was small (5-10%) and shorter reaction times were used. Acid hydrolysis of the mixture of (57) and (58) in refluxing 6 M hydrochloric acid[11,48,74] followed by purification by ion exchange column chromatography over Dowex 50-X8 gave the free amino acid (59), $[\alpha]_D^{28}$ +5.40 (*c* 1.0 in $CHCl_3$). The structure of (59) was evident from its spectral analysis. This compound was previously prepared in racemic form with undefined stereochemistry at C2 by Zand *et al.*[8b] via the Strecker synthetic method (Chapter One, page 5). Attempts to prepare the 1-methoxy analogue of (59) from the hydrolysis of (60) gave a mixture of two diastereomeric amino acids. Unfortunately there was not sufficient time to determine the structure of these compounds.

Scheme 2.19



2-7. Conclusions

In this Chapter, a new method for the synthesis of cyclic NPAAs, through the thermally induced Diels-Alder reactions of chiral oxazolidinone (8) and substituted 1,3-butadienes and substituted 1,3-cyclohexadienes has been presented. It was found that the *exo* cycloadduct was favoured in all of these reactions. A secondary orbital interaction of the donor group of the oxazolidinone ring seems to be responsible for the *exo* selectivity of the Diels-Alder reactions of the captodative alkene (8). In some cases the initially formed adducts undergo epimerization at the amino-acetal carbon (C2'), however the stereochemical integrity of the quaternary α-amino acid stereogenic centre is maintained and Diels-Alder adducts can be obtained in high enantiomeric purity (>90% e.e.). The stereochemistry of these

adducts has been elucidated by single crystal X-ray structure determinations and 2D ^{1}H NMR analysis. The optically active bicyclic amino acid (59) was synthesised for the first time by first hydrogenation and then hydrolysis of the oxazolidinone moiety.

EXPERIMENTAL

CHAPTER TWO

GENERAL PROCEDURES

(a) Melting Point (m.p.)

Melting points were determined on a Gallenkamp hot-stage apparatus and are uncorrected.

(b) Infrared (IR) Spectra

Infrared spectra were recorded on a Bio Rad Fourier Transform Infrared Spectrometer model FTS-7 or Perkin-Elmer 783 Infrared Spectrometer as mulls in nujol unless otherwise stated.

(c) Optical Rotation $[\alpha]_D$

All optical rotations were recorded with a JASCO, DIP-370, Digital Polarimeter in analytical reagent (AR) grade chloroform unless otherwise stated.

(d) ^1H Nuclear Magnetic Resonance (NMR) Spectra

^1H NMR spectra were recorded on the following instruments: JEOL FX 90Q F. T. NMR Spectrometer operating at 90 MHz, Varian Unity 400 F. T. NMR Spectrometer operating at 400 MHz, and Varian Unity 300 F. T. NMR Spectrometer operating at 300 MHz. Chemical shifts are reported as δ values in parts per million (ppm). Tetramethylsilane (TMS) was used as nominal standard for all recorded spectra (0.00 ppm). Data are recorded as follows: chemical shift (δ), multiplicity (**s**: singlet, **d**: doublet, **t**: triplet, **q**: quartet, **m**: multiplet, **dd**: doublet of doublets, **b**: indicates some degrees of broadening in the signal, coupling constant (Hz), integrated intensity and assignment (first order analyses of spectra were attempted where possible and, consequently, chemical shifts and coupling constants for multiplets may only be approximate). Two dimensional NMR experiments were

carried out using the following instruments: Varian Unity 400 F.T. and Varian Unity 300 F.T. The pulse sequences used were homonuclear ($^1H/^1H$) correlation spectroscopy (COSY), Nuclear Overhauser and exchange spectroscopy (NOESY) and heteronuclear ($^1H/^{13}C$) correlation spectroscopy (HETCOR).

(e) ^{13}C Nuclear Magnetic Resonance (NMR) spectra

^{13}C NMR were recorded on a Varian Unity 400 F.T. NMR Spectrometer (100 MHz) or Varian Unity 300 F.T. NMR Spectrometer (75 MHz). The internal reference was the central peak of $CDCl_3$ (δ 77.0 ppm). Distortionless enhancement by polarisation transfer (DEPT) was used in the assignment of carbon spectra.

(f) Mass spectra (MS)

Low resolution mass spectra were recorded on a vacuum Generator VG 12-12 mass Spectrometer. The protonated molecular ion (MH^+), if present, significantly high mass ions and the more intense low mass ions are reported. Data are presented in the following order: *m/z* value; relative intensity as a percentage of the base peak.

g) Microanalyses were performed by the Microanalytical Service Unit, Australian National University, Canberra or the Microanalytical Service Unit, the Queensland University, Queensland.

(h) Chromatography

Analytical thin layer chromatography (TLC) was conducted on plastic sheet coated with Merck Kieselgel KG60F-254. The developed plates were visualised under shortwave ultraviolet light. Column chromatography was conducted on silica gel absorbent using Fluka

Kieselgel 60 (0.063-0.2 mm) as the absorbent and analytical reagent (AR) grade solvents as indicated.

The High Performance Liquid Chromatography (HPLC) was carried out using a Waters pump model 510 and a Waters μ porasil column, (particle size 10 μm, pore size 125 Å, dimensions 7.8 mm / 300 mm). The U.V. detector was a Waters series R-400 detector at 254 nm.

(i) Solvents and reagents used in these reactions were purified according to well established procedures.[75] Tetrahydrofuran (THF) and diethyl ether were dried over sodium metal and purified by distillation from a purple suspension of sodium / benzophenone ketyl under nitrogen. Dichloromethane (CH_2Cl_2), chloroform, *N,N*-dimethylformamide (DMF) and acetonitrile were distilled from calcium hydride and stored over molecular sieves (4Å) under nitrogen. Methanol was purified by distillation from magnesium methoxide.

(j) Unless otherwise stated, all reactions, particularly reactions involving n-BuLi, LDA or sodium borohydride, were performed in glassware that had been oven-dried and cooled in a desiccator prior to use and under a dry nitrogen atmosphere. All organic extracts were dried with anhydrous $MgSO_4$ and after filtration of these solutions, the bulk of the solvent was removed on a Buchi rotary evaporator. The last traces of solvent were removed under high vacuum.

k) Molecular modelling was performed using PC MODEL (Serena Software, Box 3076, Bloomington, Indiana) using the MMX force field parameters or Insight II, Version 2.3.0., Biosym Tecnologies, San Diego, C.A.

The dienes, 1-(trimethylsilyloxy)-1,3-cyclohexadiene (36) and 2-(trimethylsilyloxy)-1,3-cyclohexadiene (39) were prepared according to the literature.[60,61] For compounds (17), (18), (21), (22), (25), (26), (28), (29)-(31) the carbons have been numbered as shown for (25a) in Figure 2.4. For compounds (11), (32)-(34), (37), (38), (40)-(42) and (57)-(60) the carbons have been numbered as shown for (11) in Figure 2.6. In the ^{1}H NMR analysis of these compounds the protons have been assigned α or β as indicated in the structure (24a) and (11). In the ^{1}H NMR spectrum protons like H3β are observed as a ddd due to W-coupling (to H8α). All crystalline compounds were recrystallized from ethyl acetate/hexane.

X-ray Structure Determinations.

The single crystal X-ray structural determinations were performed by Brian W. Skelton and Allan H. White at the University of Western Australia.

The room temperature (~295K) single crystal X-ray structure determinations are derivative of unique diffractometer data sets (2r/r scan mode; monochromatic Mo Kα radiation, $\lambda = 0.7109_3$ Å) yielding N independent reflections, N_o of these with $I > 3\sigma(I)$ being considered 'observed' and used in the full matrix least squares refinement without absorption correction after solution by direct methods. Anisotropic thermal parameters were refined for C, N, O; (x, y, z, U_{iso})$_H$ were also refined. Conventional residuals R, R_w on $|F|$ are quoted at convergence, statistical weights derivative of $\sigma^2(I) = \sigma^2(I_{diff}) + 0.0004\ \sigma^4(I_{diff})$ being used; chiralities were adopted from the chemistry. Neutral atom complex scattering factors were employed, computation using the XTAL 3.0 program system implemented by S. R. Hall. Derivative connectivities, conformation and stereochemistries are shown pictorially in the Figures, geometries being essentially as expected. Full tabulations of atom

coordinates and thermal parameters, molecular geometries and structure factor amplitudes have been deposited with the Cambridge Crystallographic Data Centre. Details of the specimens and refinement are as follows:

(17). $C_{23}H_{23}NO_3$, M = 361.4. Orthorhombic, space group $P2_12_12_1$, a = 22.225(9), b = 9.635(4), c = 9.181(6) Å, V = 1966(3) Å^3. D_c(Z = 4) = 1.22 g. cm.$^{-3}$; F(000) = 864. μ_{Mo} = 0.8 cm.$^{-1}$; specimen: 0.90 x 0.60 x 0.38 mm. $2r_{max}$ = 50°; N = 1853, N_o =1510, R = 0.037, R_w = 0.044.

(37). $C_{24}H_{23}NO_4$, M = 389.5. Orthorhombic, space group $P2_12_12_1$ (D_2^4, No. 19), a = 22.094(5), b = 12.588(5), c = 7.211(2) Å, V = 2005(1) Å^3. D_c(Z = 4) = 1.29 g. cm.$^{-3}$; F(000) = 824. μ_{Mo} = 0.9 cm.$^{-1}$; specimen: 0.17 x 0.24 x 0.28 mm. $2r_{max}$ = 50°; N = 2045, N_o =1024; R = 0.051, R_w = 0.049.

(40a). $C_{23}H_{21}NO_4$, M = 375.4. Monoclinic, space group $P2_1$ (C_2^2, No. 4), a = 8.125(1), b = 10.703(2), c = 11.337(2) Å, β = 103.40(1)°, V = 959.0(3) Å^3. D_c(Z = 2) = 1.30 g. cm.$^{-3}$; F(000) = 396. μ_{Mo} = 0.9 cm.$^{-1}$; specimen: 0.58 x 0.48 x 0.40 mm. $2r_{max}$ = 55°; N = 2316, N_o =1922; R = 0.037, R_w = 0.036.

3-Cyclohexene-1-One (44).[59]

Four drops of 70% perchloric acid were added to a mixture of 1-methoxycyclohexa-1,4-diene (43) (8 g, 73 mmol) in carbon tetrachloride (20 mL) and water (50 mL). The two-phase system was shaken vigorously. The reaction was monitored by NMR sampling aliquots from the carbon tetrachloride layer (the disappearance of the ether methyl absorbance was particularly apparent). After 12 hr the organic layer was separated, dried ($MgSO_4$) and filtered. Partial removal of the solvent on a

rotary evaporator gave 5 g (74%) of (44) as an oil. ^{1}H NMR δ 5.58 (m, 2H), 2.89 (m, 2H), 2.5 (m, 4H).

Preparation of 1-Trimethylsilyloxy- and 2-Trimethylsilyloxy-1,3-cyclohexadienes (36) and (39).

A solution of diisopropylamine (3 mL, 22 mmol) in THF (5 mL) and ether (5 mL) at 0 °C was treated with n-butyl lithium (12.5 mL, 20 mmol, solution in hexane). The resulting solution was cooled to -78 °C and treated with cyclohexenone (44) or (46) (1.44 g, 15 mmol) dropwise under nitrogen. The solution was stirred for 1 hr. Meanwhile a quenching solution was prepared from triethylamine (1.4 mL, 10 mmol) and chlorotrimethylsilane (4 mL, 32 mmol) which was centrifuged to remove any of the insoluble triethylamine hydrochloride. The chlorotrimethylsilylane solution was added rapidly and with stirring, to a cooled (0 °C) solution of the above lithium enolate. After the addition was complete, a white solid (LiCl) began to separate after 5 min. The resulting mixture was stirred at room temperature for 10 min. and then partitioned between hexane and a cold solution of 5% aqueous $NaHCO_3$ (20 mL). The organic layer was dried and concentrated to leave a residual liquid containing the crude silyl ether. Fractional distillation through a short Vigreux column produced exclusively the silyl ether.

(36) 800 mg (36%). B.p. 40-44 °C / 1 mm. ^{1}H NMR δ 5.80 (m, 1H), 5.40 (m, 1H), 5.09 (d, J = 4.2 Hz, 1H), 2.22 (m, 4H), 0.21 (s, 9H, $SiMe_3$).

(39) 1500 mg (60%). B.p. 55-59 °C / 1 mm (Lit.[61a] 33-37 °C / 10^{-2} mm). ^{1}H NMR δ 5.60 (m, 1H), 5.50 (m, 1H), 4.71 (m, 1H), 0.32 (s, 9H, $SiMe_3$).

Diels-Alder Reactions of (8) and Dienes, A General Procedure:

A solution of (8) (225 mg, 0.8 mmol) and the diene (10 molar equiv.) in CH_2Cl_2 (3 mL) under nitrogen was heated at 60 °C in a sealed tube for

several days, as reported in the Table 2.2. The solution was then cooled and evaporated to dryness. The crude products were purified by column chromatography on silica gel using ethyl acetate/hexane as the eluent. The diastereoselection of these reactions were determined from ^{1}H NMR (400 MHz) analysis of the crude reaction product. The adducts (28a), (28b) and (40 a-c) were obtained by hydrolysis of the crude reaction product in a two phase system using hydrochloric acid solution (5%) and ether for 30 min,[58] followed by purification of the crude reaction mixture by column chromatography on silica gel.

(2'*R*,4*S*)-3'-Benzoyl-1,2-dimethyl-2'-phenylspiro[cyclohex-1-ene-4,4'-oxazolidin]-5'-one (17).

M.p. 166-8 °C; $[\alpha]_D^{25}$ (on 97 : 3 mixture) +188.6 (*c* 0.5 in $CHCl_3$). ^{1}H NMR (of mixture, in part) δ 7.38-6.97 (m, 10H), 6.60 (s, 1H, H2') [minor isomer, 6.55 (s, 1H, H2')]; 3.36 (d, J = 17.2 Hz, 1H, H3β), 3.15 (m, 1H, H5β), 2.60 (m, 1H, H6α), 2.24 (d, J = 17.2 Hz, 1H, H3α), 2.16 (m, 1H, H6β), 2.12 (m, 1H, H5α), 1.72 (s, 3H), 1.68 (s, 3H). ^{13}C NMR δ 172.5 (CO); 169.3 (CO), 136.6, 136.3, 130.0, 129.7, 128.5, 128.4, 126.6, 126.2, 125.6 (C), 120.8 (C), 89.2 (CH), 61.1 (C), 35.8 (CH_2), 29.0 (CH_2), 28.6 (CH_2), 18.9 (CH_3), 18.7 (CH_3). IR (nujol) 1770, 1638, 1158, 1032, 731, 639 cm^{-1}. MS (CI) *m/z* 362 (100%, MH^+). Anal. Calcd for $C_{23}H_{23}NO_3$: C, 76.43; H, 6.41; N, 3.88%. Found: C, 76.87; H, 6.81; N, 3.72%.

(2'*R*,3*R*,4*R*)-3'-Benzoyl-3-methyl-2'-phenylspiro[cyclohex-1-ene-4,4'-oxazolidin]-5'-one (25a).

M.p. 155-6 °C; $[\alpha]_D^{27}$ +79.1 (*c* 0.30 in $CHCl_3$). ^{1}H NMR δ 7.32-6.98 (m, 10H), 6.60 (s, 1H, H2'), 5.92 (m, 1H, H1), 5.67 (m, 1H, H2), 3.01 (m, 1H, H3α), 2.76 (m, J = 6.4, 14 Hz, 1H, H5α), 2.50 (m, 1H, H6α), 2.41 (m, 1H, H6β), 2.30 (m, J = 6.4, 14 Hz, 1H, H5α), 1.30 (d, J = 7.2 Hz, 3H). [minor isomer (from NMR on the mixture) 6.75 (s, 1H, H2'), 5.82 (m, 1H, $=CH_2$),

5.48 (m, 1H, $=CH_2$), 1.25 (d, J = 7.6 Hz, 3H)]. ^{13}C NMR δ 174.4 (CO), 169.93 (CO), 137.0, 136.8, 130.0, 129.6, 129.4, 128.6, 128.4, 126.5, 126.2 (=CH), 126.1 (=CH), 89.8 (CH), 65.4 (C), 38.0 (CH), 30.2 (CH_2), 23.0 (CH_2), 16.4 (CH_3). IR (nujol) 1798, 1647, 1223, 1165, 1051, 729, 700 cm^{-1}. MS (CI) *m/z* 348 (14%, MH^+), 302 (33), 242 (33), 210 (38), 197 (100), 182 (82). Anal. Calcd for $C_{22}H_{21}NO_3$: C, 76.06; H, 6.09; N, 4.03%. Found: C, 76.37; H, 6.06; N, 3.94%.

(2'*R*,3*R*,4*R*)-3'-Benzoyl-3-methoxy-2'-phenylspiro[cyclohex-1-ene-4,4'-oxazolidin]-5'-one (26a).

M.p. 118-20 °C; $[\alpha]_D^{25}$ (on 82 : 18 mixture) +56.6 (*c* 0.45 in $CHCl_3$). ^1H NMR (on mixture) δ 7.32-6.89 (m, 10H), 6.61 (s, 1H, H2') [minor isomer, 6.52 (s, 1H, H2')], 5.97 (m, 1H, H1), 5.90 (m, 1H, H2), 4.15 (bs, 1H, H3α), [minor isomer, 5.03 (bs, 1H, H3β)], 3.55 (s, 3H, OCH_3) [minor isomer, 3.62 (s, 3H, OCH_3)], 2.50 (m, 2H, H5β/6α), 2.34 (m, 2H, H5α/H6β). ^{13}C NMR (of mixture, in part) δ 172.4 (CO), 170.4 (CO), 137.5, 136.6, 130.1, 129.7, 128.5, 128.0, 127.2, 126.8, 123.2 (=CH), 122.5 (=CH), 90.4 (CH), 75.2 (CH), 65.5 (C), 57.7 (CH_3), 28.8 (CH_2), 23.1 (CH_2). IR (nujol) 1775, 1636, 1395, 1335, 1168, 1083, 680 cm^{-1}. MS (CI) *m/z* 364 (100%, MH^+), 332 (37). Anal. Calcd for $C_{22}H_{21}NO_4$: C, 72.71; H, 5.82; N, 3.85%. Found: C, 72.54; H, 6.12; N, 3.95%.

(2'*R*,3*R*,4*R*) and (2'*R*,3*S*,4*R*)-3'-Benzoyl-3-methoxy-2'-phenylspiro [cyclohexan-1-one-4,4'-oxazolidin]-5'-one (28a) and (28b).

The two diastereoisomers were separated by fractional recrystallization from ethyl acetate / hexane.

(28a): M.p. 205-8 °C; $[\alpha]_D^{20}$ +127.7 (*c* 0.23 in $CHCl_3$). ^1H NMR δ 7.32-6.89 (m, 10H), 6.54 (s, 1H, H2'), 4.79 (dd, J = 5.2, 11.6 Hz, 1H, H3β), 3.53 (s, 3H, OCH_3), 3.36, (dd, J = 5.2, 11.6 Hz, 1H, H2α), 3.18 (m, 1H, H2β),

3.14 (dd, J = 5.2, 11.6 Hz, 1H, H6α), 2.97 (m, 1H, H6β), 2.59 (m, 1H, H5β), 2.44 (m, 1H, H5α). [NOE cross peak was observed between H2' and OCH_3]. ^{13}C NMR δ 206.5 (CO), 170.7 (CO), 169.8 (CO), 136.1, 136.1, 129.99, 129.96, 128.7, 128.6, 126.9, 125.7, 90.8 (CH), 75.2 (CH), 65.5 (C), 57.3 (CH_3), 41.7 (CH_2), 36.7 (CH_2), 27.9 (CH_2). MS (FAB) *m/z* 380 (34%, MH^+), 348 (54), 316 (39), 288 (100).

(28b): M.p. 135-8 °C; $[\alpha]_D^{20}$ +80.0 (*c* 0.3 in $CHCl_3$). ^1H NMR δ 7.3-6.88 (m, 10H), 6.55 (s, 1H, H2'), 4.14 (dd, J = 5.6, 12 Hz, 1H, H3α), 3.52 (s, 3H, OCH_3), 3.00 (m, 4H), 2.65 (m, 2H). [NOE cross peak was observed between H2' and H3α]. ^{13}C NMR δ 207.3 (CO), 174.5 (CO), 171.3 (CO), 136.6, 136.1, 130.2, 129.9, 128.7, 128.4, 127.0, 126.1, 91.4 (CH), 80.8 (CH), 64.9 (C), 57.8 (CH_3), 42.3 (CH_2), 36.51 (CH_2), 28.84 (CH_2). IR (nujol) 1790, 1705, 1648, 1300, 1222, 1162, 1100, 1025, 695 cm^{-1}. MS (CI) *m/z* 380 (10%, MH^+), 348 (14), 229 (33), 198 (75), 122 (100). Anal. Calcd for $C_{22}H_{21}NO_5$: C, 69.65; H, 5.58, N, 3.69%. Found: C, 69.18; H, 5.77, N, 3.44%.

(2'*R*,4*S*) and (2'*S*,4*S*)-3'-Benzoyl-1-methyl-2'-phenylspiro[cyclohex-1-ene-4,4'-oxazolidin]-5'-one (29) and (30).

(29): M.p. 182-3 °C; $[\alpha]_D^{27}$ +177.6 (*c* 0.5 in $CHCl_3$). ^1H NMR δ 7.33-6.98 (m, 10H), 6.61 (s, 1H, H2'), 5.37 (m, 1H, H2), 3.38 (dd, J = 2.4, 17 Hz, 1H, H3β), 3.21 (ddd, J = 5.6, 12.8, 18 Hz, 1H, H6β), 2.58 (m, 1H, H6α), 2.38 (bd, J = 18 Hz, 1H, H3α), 2.14 (m, 2H, H5α/5β), 1.77 (s, 3H, CH_3). ^{13}C NMR δ 172.4 (CO), 169.3 (CO), 136.7, 136.4, 133.9 (CH), 130.1, 129.7, 128.6, 128.5, 126.7, 122.2, 116.2 (C), 89.2 (CH), 60.1 (C), 30.4 (CH_2), 28.5 (CH_2), 27.6 (CH_2), 23.2 (CH_3). IR (nujol) 1782, 1650, 1401, 1175, 1036 cm^{-1}. MS (CI) *m/z* 348 (MH^+, 92%), 210 (49), 198 (29), 105 (100). Anal. Calcd for $C_{22}H_{21}NO_3$: C, 76.06; H, 6.09; N, 4.03%. Found: C, 76.14; H, 6.14; N, 3.87%.

(30): ^{1}H NMR δ 7.35-6.98 (m, 10H), 6.62 (s, 1H, H2'), 5.58 (m, 1H, H2), 3.34 (bd, 1H, H3β), 3.10 (ddd, J = 5.2, 12, 17.8 Hz, 1H, H6β), 2.56 (m, 1H, H6α), 2.29 (m, 1H, H5α), 2.24 (bd, 1H, H3α), 2.12 (m, 1H, H5β), 1.57 (s, 3H, CH_3).

(1*S*,2*S*,2'*R*,4*S*)-3'-Benzoyl-2'-phenylspiro[bicyclo[2.2.2]oct-5-ene-2,4'-oxazolidin]-5'-one (11).

The two isomers (11) and (32) were separated by semi-preparative HPLC (silica gel, 1% ethyl acetate / hexane as eluent) or fractional crystallization from ethyl acetate / hexane.

(11): M.p. 123-5 °C; $[\alpha]_D^{23}$ -92.0 (*c* 0.25 in $CHCl_3$). ^{1}H NMR δ 7.38-7.14 (m, 10H), 6.57 (s, 1H, H2'), 6.25 (dd, J = 7.6, 8 Hz, 1H, H6), 6.16 (dd, J = 7.4, 8 Hz, 1H, H5), 3.12 (m, 1H, H1), 2.90 (m, 1H, H3β), 2.69 (m, 1H, H4), 2.23 (m, 1H, H3α), 1.98 (m, 1H, H7α), 1.72 (m, 1H, H8β), 1.22 (m, 2H, H7β/8α). ^{13}C NMR δ 173.5 (CO), 173.1 (CO), 138.7, 138.2, 137.3, 136.2, 130.7, 129.7, 129.2, 128.5, 127.9, 127.4, 89.7, 68.2, 37.4, 35.4, 30.2, 23.6, 21.1. IR (nujol) 1790, 1642, 1334, 1209, 1174, 1016, 714, 694 cm^{-1}. MS (FAB) *m/z* 360 (11%, MH^+), 226 (31), 210 (47), 165 (53), 148 (78), 127 (100). Anal. Calcd for $C_{23}H_{21}NO_3$: 76.86; H, 5.89; N, 3.90%. Found: C, 77.06; H, 6.25; N, 3.78%.

(1*S*,2*S*,2'*S*,4*S*)-3'-Benzoyl-2'-phenylspiro[bicyclo[2.2.2]oct-5-ene-2,4'-oxazolidin]-5'-ene (32).

M.p. 40 °C; $[\alpha]_D^{23}$ -102 (*c* 0.3 $CHCl_3$). ^{1}H NMR δ 7.4-7.26 (m, 10H), 6.78 (s, 1H, H2'), 6.58 (dd, J = 7.2, 7.6 Hz, 1H, H6), 6.24 (dd, J = 7.2, 7.4 Hz, 1H, H5), 2.80 (m, 2H, H1/3β), 2.43 (m, 1H, H4), 1.98 (m, 1H, H3α), 1.86 (m, 1H, H7α), 1.70 (m, 1H, H8α), 1.25 (m, 1H, H7β), 0.90 (m, 1H, H8β). ^{13}C NMR δ 173.8 (CO), 168.5 (CO), 137.6, 137.4, 136.8, 136.23, 129.9, 129.4, 123.6, 128.6, 126.4, 125.7, 88.0, 66.9, 37.5, 34.1, 29.7, 24.3,

20.3. IR (nujol) 1796, 1675, 1333, 1146, 1029 cm^{-1}. MS (ES) *m/z* 398 (13%, MK^+), 382 (15, MNa^+) 360 (100, MH^+).

(1*R*,2*S*,2'*R*,4*S*)-3'-Benzoyl-1-methoxy-2'-phenylspiro[bicyclo[2.2.2.] oct-5-ene-2,4'-oxazolidin]-5'-one (37).

M.p. 159-60 °C; $[\alpha]_D^{30}$ (on 90 : 10 mixture) +99.8 (*c* 0.54 in $CHCl_3$). ^1H NMR (of mixture, in part) δ 7.26-6.80 (m, 10H), 6.54 (s, 1H, H2'), [minor isomer: 6.51(s, 1H, H2')] 6.39 (m, 2H, H5/6), 3.57 (m, 4H, OCH_3 and H4), [minor isomer 3.56 (s, 3H, OCH_3)], 2.88 (m, 1H, H3β), 2.34 (m, 1H, H3α), 2.07 (m, 1H, H7α), 1.99 (m, 1H, H7β), 1.62 (m, 1H, H8β), 1.47 (m, 1H, H8α). ^{13}C NMR δ 173.3 (CO), 171.8 (CO), 138.8, 137.7, 137.1, 135.8, 130.1, 129.3, 128.4, 128.2, 127.3, 126.3, 92.2, 84.9, 71.0, 51.8, 37.5, 30.7, 25.1, 23.5. IR (nujol) 1780, 1664, 1178, 1101, 1026, 769, 693 cm^{-1}. MS (CI) *m/z* 390 (15%, MH^+), 280 (12), 256 (19), 240 (30), 174 (28), 135 (93), 121 (100). Anal. Calcd for $C_{24}H_{23}NO_4$: C, 74.02; H, 5.95; N, 3.60%. Found: C, 74.00; H, 6.00; N, 3.64%.

(1*R*,2*S*,2'*R*,4*S*)-3'-Benzoyl-2-trimethylsilyloxy-2'-phenylspiro[bicyclo [2.2.2.]oct-5-ene-2,4'-oxazolidin]-5'-one (38).

M.p. 135-6 °C; $[\alpha]_D^{26}$ (on 93 : 7 mixture) +96.1 (*c* 0.52 in $CHCl_3$). ^1H NMR (of mixture) δ 7.2-6.8 (m, 10H), 6.51 (s, 1H, H2') [minor isomer, 6.47 (s, 1H, H2')], 6.30 (m, J = 3.2, 8.8 Hz, 1H, H5), 6.22 (d, J = 8.8 Hz, 1H, H6), 3.56 (m, 1H, H4), 2.85 (bs, 1H, H3β), 2.35 (m, 1H, H7β), 2.31 (dd, J = 2,13.2 Hz, 1H, H3α), 1.97 (m, 1H, H7α), 1.46 (m, 2H, H8α/8β), 0.22 (s, 9H). ^{13}C NMR δ 173.3 (CO), 171.8 (CO), 138.8, 137.1, 136.3, 134.4, 130.1, 129.3, 128.4, 128.2, 127.3, 126.3, 92.4, 82.4, 72.3, 36.9, 30.6, 29.4, 25.8, 2.34. IR (nujol) 1786, 1667, 1251, 1217, 1134, 1099, 754, 704. MS (CI) *m/z* 447 (42%, M^+), 279 (73), 235 (29), 121 (26), 100 (100). Anal. Calcd for $C_{26}H_{29}NO_4Si$: C, 69.77; H, 6.53; N, 3.13%. Found: 69.56; H, 6.59; N, 2.99%.

(1*S*,2*S*,2'*R*,4*S*)-3'-Benzoyl-2'-phenylspiro[bicyclo[2.2.2.]oct-5-one-2-4'-oxazolidin]-5'-one (40a).

Separation of the crude reaction mixture by column chromatography gave pure (40a) and an inseparable mixture of three minor diastereoisomers. Fractional crystallization of this mixture from ethyl acetate/hexane gave a mixture (about 1 : 1) of (40a) and (40c), which could not be separated by further crystallizations.

(40a): M.p. 212-14 °C; $[\alpha]_D^{22}$ +174.3 (*c* 0.35 in $CHCl_3$). ^1H NMR δ 7.26-6.76 (m, 10H), 6.54 (s, 1H, H2'), 3.63 (ddd, J = 2.4, 6, 14 Hz, 1H, H6β), 2.85 (ddd, J = 3, 6, 17 Hz, 1H, H3β), 2.72 (m, 1H, H1), 2.65 (m, 1H, H4), 2.57 (dd, J = 2.4, 14 Hz, 1H, H6α), 2.50 (m, 1H, H8α), 2.29 (dd, J = 2.4, 17 Hz, 1H, H3α), 2.14 (m, 1H, H7α), 1.88 (m, 1H, H7β), 1.64 (m, 1H, H8β). ^{13}C NMR δ 211.4 (CO), 172.9 (CO), 171.3 (CO), 137.0, 136.7, 130.3, 129.8, 128.7, 128.4, 126.6, 125.9, 90.3, 63.3, 43.0, 41.4, 39.9, 33.8, 22.4, 21.2. IR (nujol) 1780, 1718, 1660, 1205, 1170, 933, 871, 725 cm^{-1}. MS (FAB) *m/z* 376 (15%, MH^+), 242 (40), 165 (47), 154 (100). Anal. Calcd for $C_{23}H_{21}NO_4$: C, 73.58; H, 5.64; N, 3.73%. Found: C, 73.35; H, 5.77; N, 3.35%.

(40b): ^1H NMR (in part) δ 6.86 (s, 1H, H2')

(40c): ^1H NMR (in part) δ 6.51 (s, 1H, H2').

(1*S*)-1-(1-Benzenecarboxamido-3,4-dimethyl-cyclohex-3-enyl)methanol (21).

A mixture (97 : 3) of (17) and (18) (100 mg, 0.3 mmol) in dry methanol (10 mL) was treated with $NaBH_4$ (20 mg). After 16 hr at room temperature the solution was then treated with acetone (2 mL) at 0 °C for 10 min. The solvent was then evaporated and water was added and the alcohol was extracted into CH_2Cl_2 (2x). Short-path column chromatography on silica gel gave (21) (32 mg, 41%). ^1H NMR δ 7.72-

7.41 (m, 5H), 6.17 (bs, 1H, OH), 5.14 (bs, 1H, NH), 3.79 (m, 2H, $C\underline{H}_B\underline{H}_AOH$), 2.22-2.00 (m, 5H), 1.78 (m, 1H), 1.67 (bs, 6H). MS (CI) *m/z* 260 (53%, MH^+), 138 (100), 122 (95), 105 (63).

MTPA ester of (21).

A solution of (21) (25 mg, 0.096 mmol) in CH_2Cl_2 and two drops of dry pyridine at 0 °C was treated with (*R*)-(-)-α-methoxy-α-trifluoromethyl-phenylacetyl chloride (34 mg, 0.13 mmol). The solution was stirred for 3 hr at room temperature and then the solvent was evaporated. The solid residue was dissolved in CH_2Cl_2 (10 mL) and the solution was washed with 5% aqueous HCl, 10% aqueous NaOH, and then water. The CH_2Cl_2 solution was then dried over $MgSO_4$, filtered and evaporated in vacuo to give (22) as an oil (20 mg, 44%). The ^1H NMR spectrum was taken on this oil. $[\alpha]_D^{25}$ -8.5 (*c* 0.2 in $CHCl_3$). ^1H NMR δ 7.6-7.22 (m, 10H), 5.73 (s, 1H, NH), 4.79 (d, J=11.2 Hz, 1H) [minor isomer, 4.87 (d J=11.2 Hz, 1H)], 4.68 (d, J=11.2 Hz, 1H) [minor isomer, 4.63 (d, J=11.2 Hz, 1H)], 3.47 (s, 3H), 2.45-2 (m, 5H), 1.70 (m, 1H), 1.62 (bs, 6H). MS (CI) *m/z* 476 (9%, MH^+) 445 (100). An expanded section of the ^1H NMR spectrum of (22) is shown in Figure 2.3.

(1*S*,2*S*,4*S*)-2-(2-Benzenecarboxamidobicyclo[2.2.2]oct-5-enyl) methanol (33).

This compound was prepared from a mixture (76 : 24) of (11) and (32) (200 mg, 0.6 mmol) by treatment with $NaBH_4$ as described in the preparation of (21). Purification of the crude reaction product by column chromatography gave (33) (40 mg, 50%). ^1H NMR δ 7.68-7.4 (m, 5H), 6.45 (t, J = 7.2 Hz, 1H, H6), 6.32 (t, J = 7.2 Hz, 1H, H5), 5.94 (bs, 1H, NH), 5.64 (dd, J = 2.4, 9.2 Hz, 1H, OH), 4.10 (dd, J = 2.4, 12, Hz, 1H, $C\underline{H}_ACH_BOH$), 3.68 (dd, J = 9.2, 12 Hz, 1H, $CH_AC\underline{H}_BOH$), 3.32 (m, 1H, H1), 2.68 (m, 1H, H3β), 1.94 (m, 1H, H4), 1.71-1.23 (m, 5H). ^{13}C NMR δ

168.1 (CO), 135.7, 134.8, 132.9, 131.7, 128.7, 126.9, 68.9, 62.6, 42.3, 34.4, 30.0, 23.4, 20.6.

MTPA ester of (33).

This compound was prepared from (33) (10 mg, 0.04 mmol) as described in the preparation of (22). Short-path column chromatography gave (34) (8 mg, 46%). $[\alpha]_D^{26}$ -39.0 (*c* 0.2 in $CHCl_3$). ^1H NMR δ 7.53-7.22 (m, 10H), 6.42 (t, J = 7.2 Hz, 1H, H6), 6.24 (t, J = 7.2 Hz, 1H, H5), 5,63 (bs, 1H, NH), 5.24 (d, J = 11.2 Hz, 1H) [minor isomer, 5.05 (d, J = 11.2 Hz, 1H)], 4.50 (d, J = 11.2 Hz, 1H) [minor isomer, 4.56 (d, J = 11.2 Hz, 1H)], 3.47 (s, 3H, OCH_3), 2.94 (m, 1H, H1), 2.66 (m, 1H, H3β), 1.75 (m, 3H), 1.5-1.26 (m, 3H). MS (CI) *m/z* 474 (37%, MH^+), 394 (11), 240 (100). An expanded section of the ^1H NMR spectrum of (34) is shown in Figure 2.7.

Methyl (1*S*,2*S*,4*S*)-2-benzamido-5-oxo-bicyclo[2.2.2]octane-2-carboxylate (41) and Methyl (1*S*,2*S*,4*R*)-2-benzamido-6-oxo-bicyclo[2.2.2]octane-2-carboxylate (42).

To a solution of (40a) or a mixture (1 : 1) of (40b) and (40c) (50 mg, 0.13 mmol) in dry methanol (10 mL) under nitrogen was added powdered anhydrous potassium carbonate (20 mg, 0.14 mmol). The mixture was stirred at room temperature for 16 hr. The mixture was then diluted with ethyl acetate (20 mL) and washed with an aqueous solution of saturated ammonium chloride. The aqueous layer was separated and extracted with ethyl acetate (2 x 10 mL). The combined extracts were washed with water, brine, dried ($MgSO_4$) and concentrated in vacuo. Starting from pure (40a), the ester (41) was obtained in nearly quantitative yield. Starting with a mixture of (40b) and (40c), then a 1 : 1 mixture of (41) and (42) was obtained, these could be separated by preparative TLC using 40% ethyl acetate / hexane as eluent. In one experiment a mixture of (40b) and a small amount of the fourth unidentified Diels-Alder diastereomeric product

was converted to mainly (41). The unidentified Diels-Alder diastereomeric product gave an ester that was different to both (41) and (42), but could not be obtained in sufficient quantity or diastereomeric purity for structural elucidation studies.

(41): ^{1}H NMR δ 7.75-7.42 (m, 5H), 6.47 (bs, 1H, NH), 3.77 (s, 3H, OCH_3), 3.32 (dd, J = 2.8, 15 Hz, 1H, H6α), 2.70 (ddd, J = 2.8, 5.6, 18.8 Hz, 1H, H3β), 2.50 (m, 1H, H1), 2.46 (m, 1H, H4), 2.30 (dd, J = 2.8,18.8 Hz, 1H, H3α), 2.04 (m, 1H, H8α), 2.00 (ddd, J = 2.8, 12.8, 15 Hz, 1H, H6β), 1.80 (m, 1H, H7α), 1.78 (m, 1H, H7β), 1.64 (m, 1H, H8β). MS (ES) *m/z* 302 (100%, MH^+).

(42): ^{1}H NMR δ 7.8-7.45 (m, 5 H), 6.68 (bs, 1H, NH), 3.74 (s, 3H, OCH_3), 3.20 (ddd, J = 2.6, 5.6, 15 Hz, 1H, H5β), 2.50 (t, J = 2.8 Hz, 1H, H1), 2.46 (m, 1H, H4), 2.38 (ddd, J = 2.8, 3.2, 19 Hz, 1H, H3β), 2.32 (m, 1H, H7α), 2.26 (dt, J = 2.8, 19 Hz, 1H, H3α), 2.20 (m, 1H, H8α), 2.00 (m, 1H, H8β), 1.97 (dd, J = 2.6, 15 Hz, 1H, H5α), 1.70 (m, 1H, H7β). MS (ES) *m/z* 302 (100%, MH^+).

(2*S*,2'*R*,4*S*)-3'-Benzoyl-2'-phenylspiro[2.2.2]octane-2,4'-oxazolidin]-5'-one (57) and Benzyl (2*S*,4*S*)-2-benzamido-bicyclo[2.2.2]octane-2-carboxylate (58).

A solution of (11) (1.8 g, 5 mmol) in ethyl acetate (30 mL) was hydrogenated over 10% palladium on carbon (360 mg) for 10 hr at room temperature under a hydrogen atmosphere (1 atm). The mixture was filtered through celite, and the filtrate was evaporated to dryness under reduced pressure to furnish a 80 : 20 mixture of (57) and (58) (1.5 g).
(57): ^{1}H NMR (of mixture, in part) δ 7.36-6.81 (m, 10H), 6.44 (s, 1H, H2'), 3.60 (dt, J = 3, 5.4, 13.8 Hz, 1H, H3β), 2.20 (dt, J = 2.4, 4.8, 13.8 Hz, 1H, H3α), 2.09-1.43 (m, 10H).

Compound (58) was obtained in >95% purity after purification by column chromatography on silica gel with ethyl acetate / hexane as the eluent.
(58): M.p. 125-7 °C; $[\alpha]_D^{24}$ +24.7 (*c* 0.15 in $CHCl_3$). ^1H NMR δ 6.91-7.80 (m, 10H), 6.36 (bs, 1H, NH), 4.75 (d, J = 15.2 Hz, 1H, $C\underline{H}_AH_BPh$), 4.61 (d, J = 15.2 Hz, 1H, $CH_A\underline{H}_BPh$), 3.04 (bs, 2H, H1/H3α), 2.66 (bd, 1H, H3β), 2.54 (bs, 1H, H4), 2.08 (bd 1H, H8α), 1.87 (bd, 1H, H8β), 1.76 (m, 2H, H7α/H7β), 1.68-1.40 (m, 4H, H5α/H5β/H6α/H6β). ^{13}C NMR δ 174.8 (CO), 169.6(CO), 145.2, 143.1, 132.5, 132.1, 128.9, 128.8, 127.3, 127.2, 88.0, 62.3, 37.7, 29.7, 24.7, 24.0, 23.5, 21.6, 20.8. IR (nujol) 1712, 1600, 1505, 1290, 1206, 1160, 1061, 1028, 792, 712 cm^{-1}. MS (ES) *m/z* 364 (10%, MH^+), 296 (25), 274 (100).

(2*S*,4*S*)-2-Aminobicyclo[2.2.2]octane-2-carboxylic Acid (59)

A 90 : 10 mixture of (57) and (58) (250 mg, 0.69 mmol) in 6 N hydrochloric acid (20 mL) was heated to reflux for 24 hr. The solution was then cooled, and extracted with CH_2Cl_2 (50 mL). The aqueous layer was purified on a Dowex 50-X8 ion exchange column that had been previously conditioned with 1 M hydrochloric acid. The column was eluted with water until the eluent became neutral. The free amino acid was then obtained by eluting with 1.6 M aqueous ammonia. Pure (59) (115 mg, 99%) was obtained as a white solid.
M.p. 280-2 °C; $[\alpha]_D^{28}$ +12.40 (*c* 0.5 in H_2O). ^1H NMR (D_2O) δ 2.42 (bd, J = 14.4 Hz, 1H, H3β) 1.90 (bt, J = 2.8, 5.6 Hz, 1H), 1.75 (bt, J = 2.4, 5.6 Hz, 1H, H4), 1.67-1.60 (m, 3H), 1.53 (m, 4H), 1.47 (m, 2H), 1.46 (bs, 1H, H3α). ^{13}C NMR (D_2O) δ 174.2 (CO), 61.3 (C), 33.6 (CH_2), 31.1 (CH), 23.5 (CH_2), 23.4 (CH), 22.9 (CH_2), 22.1 (CH_2), 19.8 (CH_2). MS (ES) *m/z* 170 (100%, MH^+).

(2*S*,2'*R*,4*S*)-2-Methoxy-3'-benzoyl-2'-phenylspiro[2.2.2]octane-2,4'-oxazolidin]-5'-one (60).

A solution of (37a) (85 mg, 0.22 mmol) in ethyl acetate (7 mL) was hydrogenated at atmospheric pressure over 10% palladium on carbon (17 mg) for 10 hr. A similar work up procedure to that described for (57) and (58) gave (60) (75 mg, 87%) which was pure by ^{1}H NMR and TLC analysis. Recrystallization from ethyl acetate / hexane gave clear needles. M.p. 164-5 °C; $[\alpha]_D^{24}$ +188.3 (*c* 0.86 in $CHCl_3$). ^{1}H NMR δ 7.26-6.78 (m, 10H), 6.45 (s, 1H, H2'), 3.78 (bd, 1H, H3β), 3.36 (s, 3H, OCH_3), 2.38 (m, 1H, H4), 2.32 (dt, J = 2.8, 5.2, 13.6 Hz, 1H, H3α), 2.06 (m, 2H), 1.95-1.82 (m, 4H), 1.73 (m, 2H). ^{13}C NMR δ 173.9 (CO), 172.0 (CO), 138.4, 137.2, 129.8, 129.1, 128.3, 128.2, 127.1, 125.9, 91.8 (CH), 80.9 (C), 69.3 (C), 49.4 (CH_3), 34.5 (CH_2), 27.2 (CH_2), 25.3 (CH), 25,.2 (CH_2), 25.1 (CH_2), 24.3 (CH_2). IR (nujol) 1750, 1628, 1325, 1262, 1198, 1155, 1086, 1033, 989, 752, 718, 688 cm^{-1}. MS (CI) *m/z* 392 (10%, MH^+), 286 (30), 242 (85), 226 (80), 181 (90), 123 (86), 110 (100). Anal. Calcd for $C_{24}H_{25}NO_4$: C, 73.66; H, 6.39; N, 3.58%. Found: C, 73.76; H, 6.50; N, 3.41%.

CHAPTER THREE

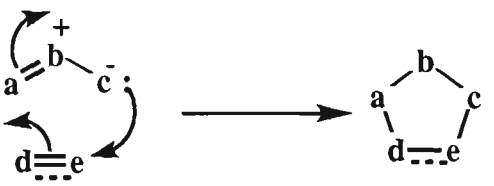
Asymmetric Synthesis of Amino Acids Derivatives via 1,3-Dipolar Cycloaddition Reactions of Nitrones and Nitrile Oxides

3-1. Introduction

A general principle for the synthesis of five-membered rings via 1,3-dipolar cycloaddition was introduced by the monumental work of Huisgen and coworkers in the early 1960s.[76] The 1,3-dipole with 4π electrons is defined as a species that is represented by zwitterionic octet structures and undergoes 1,3-cycloadditions to a multiple-bond system, the dipolarophile with 2π electrons (eq 3.1).[77]

1,3-Dipole (4πe)

Dipolarophile (2πe)

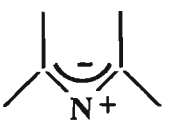


(eq 3.1)

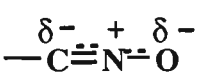
A considerable number of 1,3-dipoles containing various combinations of carbon and hetero atoms is theoretically possible and many have been made and their reactions with dipolarophiles studied.[77] Huisgen has classified the eighteen possibilities, six of the propargyl-allene type such as nitrile oxides and twelve of the allyl type such as nitrones and azomethine ylides.[77]

Nitrones

Azomethine Ylides



Nitrile Oxides

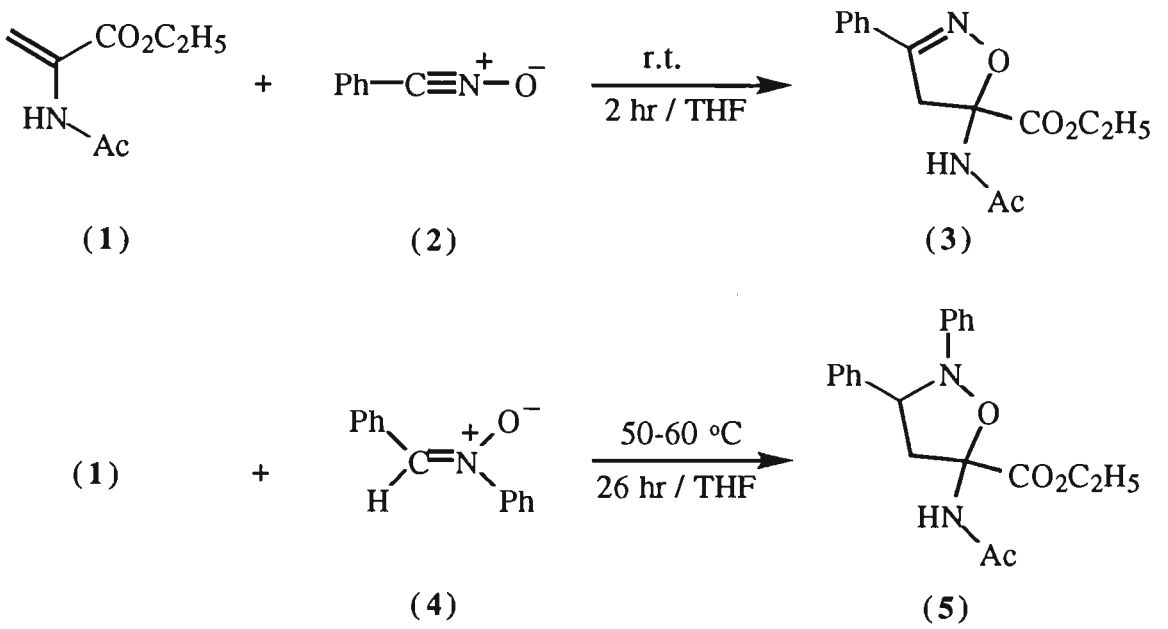


Generally, it is agreed that 1,3-dipolar cycloadditions are concerted, making them of great value in synthesis that require high degrees of regio- and stereoselectivities.[76-78] In most reactions the 1,3-dipole is not isolated but is generated *in situ* in the presence of the dienophile, which is generally an alkene or alkyne. Reactions generally classified as 1,3-dipolar

cycloadditions have been extensively employed in the synthesis of a diverse array of heterocyclic compounds, including natural products.[77-79]

Nitrones and nitrile oxides react with DHAAs to produce geminally functionalized heterocyclic amino acids.[43] The 1,3-dipolar cycloaddition of ethyl *N*-acetyl-α,β-dehydroalaninate (1) with nitrones and nitrile oxides generally proceeded with remarkably high regioselectivity (Scheme 3.1). Compound (1) reacted with phenylnitrile oxide (2) to produce a single regioisomer, Δ^2-isoxazoline (3) (herein-after referred to as isoxazoline) in 85% yield. Treatment of (1) with *C,N*-diphenylnitrone (4) provided a mixture of two stereoisomers of the isoxazolidine (5).

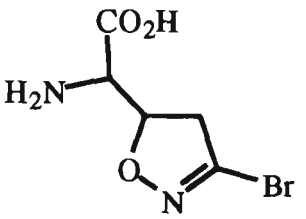
Scheme 3.1



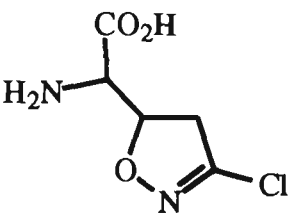
Since 1987 more than two hundred papers have been published on the reaction of nitrile oxides with alkenes,[80] thus highlighting the importance of these types of reactions in organic synthesis.

Another application of the 1,3-dipolar cycloaddition of nitrile oxides is in medicinal chemistry.[81] Bromonitrile oxide (BrCNO) undergoes cycloaddition with alkenes and alkynes with high regioselectivity to give the 3-bromo-4,5-dihydroisoxazole ring system (6a) in good yield.[81a] This

compound is an analogue of the amino acid antimetabolite antibiotic *Acivicin* (6b).



(6a)



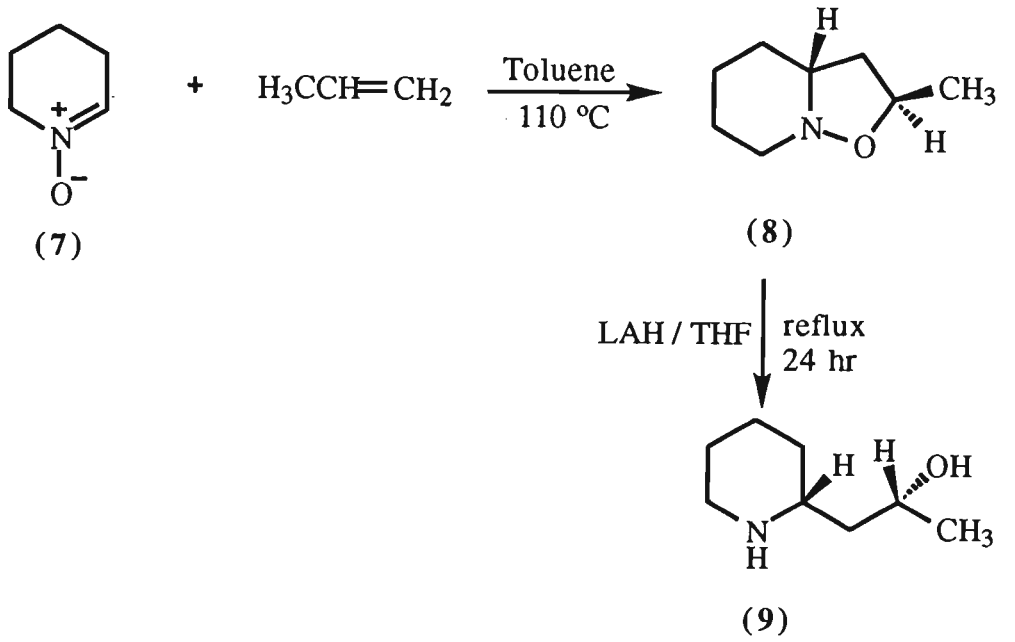
(6b)

Some of the heterocyclic systems produced through 1,3-dipolar additions with dipolarophiles that contain hetero multiple bonds can be readily converted into other synthetically useful compounds; ring-opening reactions which result in the stereocontrolled formation of acyclic compounds are particularly valuable.[82] Nitrones, nitrile oxides and azomethine ylides have been most widely used and the present Chapter will be concerned with the reactions of two former compounds. In the next Chapter the reactions of the latter compounds will be considered.

Nitrones are reactive 1,3-dipoles and with alkenes form isoxazolidines. Reactions with alkenes are stereospecific as regards to the disposition of substituents on the olefinic bond. These reactions are valuable in synthesis because the nitrogen-oxygen bond of the adducts is easily cleaved and the sequence of cycloaddition followed by ring cleavage provides a route for the stereocontrolled synthesis of a variety of acyclic and substituted cyclic compounds. These reactions have been extensively utilized as the key feature in total synthesis of structurally diverse natural products, particularly alkaloids.[77-79, 83-86] There are some examples of ring opening of nitrone cycloadducts to γ-amino alcohols via reductive cleavage of the nitrogen-oxygen bond. The isoxazolidine (8), which was produced by cycloaddition reaction of nitrone (7) and propylene, was reduced with

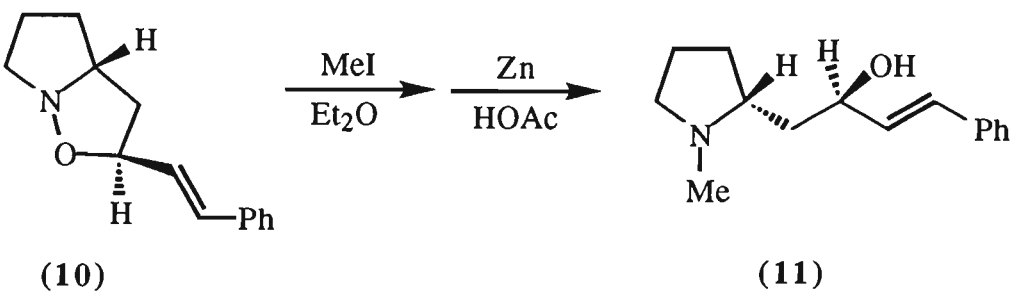
lithium aluminium hydride (LAH) in refluxing THF for 24 hr to give the alkaloid *dl*-sedridine (9) in quantitative yield (Scheme 3.2).[84]

Scheme 3.2



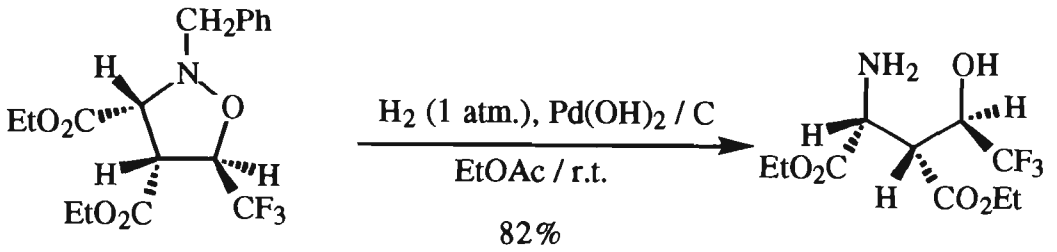
The nitrogen-oxygen bond cleavage in the methiodide salt derived from isoxazolidine (10) with zinc in the presence of acetic acid, afforded the alkaloid darlinine (11) (Scheme 3.3).[85]

Scheme 3.3



Cleavage of the nitrogen-oxygen bond of isoxazolidines by hydrogenation over palladium hydroxide (Perlmann's catalyst) has been used to prepare natural products, including alkaloids[79] and amino sugars.[87] More recently Bravo *et al.*[88] reported that the hydrogenation of isoxazolidine (12) over palladium hydroxide as a catalyst, afforded in 5 hr, the corresponding γ-amino alcohol (13) in high yield (Scheme 3.4).

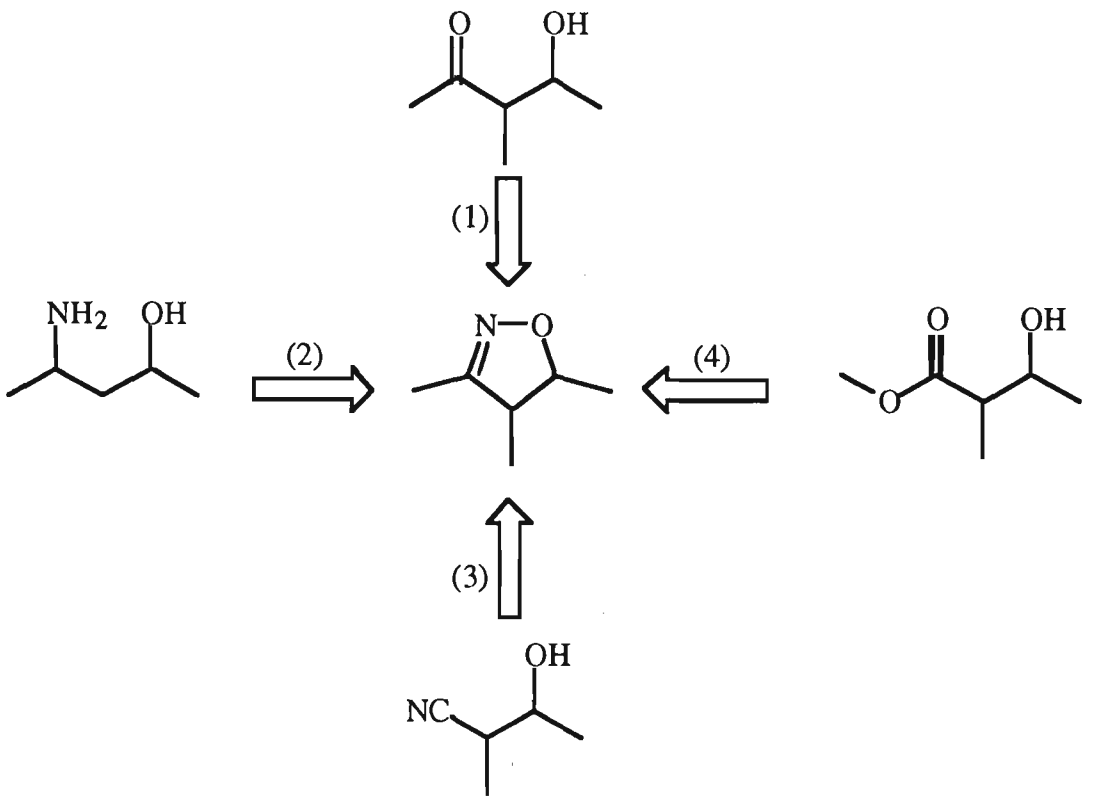
Scheme 3.4



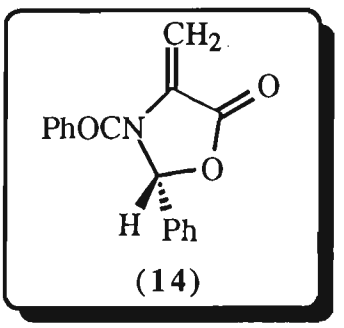
(12) **(13)**

Some of the known transformations of isoxazoline rings, which were prepared from nitrile oxides, are summarized in Scheme 3.5. 1) Reductive cleavage of the nitrogen-oxygen bond of isoxazolines followed by acid hydrolysis leads to β-hydroxy ketones which are important in organic synthesis because this functional group, called an aldol, can be further transformed into a variety of related functionalities such as α,β-unsaturated ketones, 1,3-diols and 1,3-dienes. Catalytic hydrogenation over Raney Ni in aqueous methanol,[89] in the presence of boric acid[90] or aluminium chloride,[91] is most commonly employed for this purpose. 2) Reduction of isoxazolines under severe conditions leads to a γ-amino alcohol functionality. In most cases LAH is employed as the reducing agent for this purpose.[92] 3) β-Hydroxy nitriles are formed through a novel ring opening reaction of 3-unsubstituted isoxazolines by the action of a base such as sodium methoxide.[93] 4) β-Hydroxy acids and derivatives are produced by catalytic hydrogenation over Raney Ni in the presence of acetic acid.[94]

Scheme 3.5



In this Chapter, the 1,3-dipolar cycloaddition reaction of nitrones and nitrile oxides with the chiral oxazolidinone (14) is described and the structure and stereochemistry of the cycloadducts is reported. Our attempts to affect ring opening of some cycloadducts by catalytic hydrogenation with the aim of preparing novel chiral amino acids will also be described.



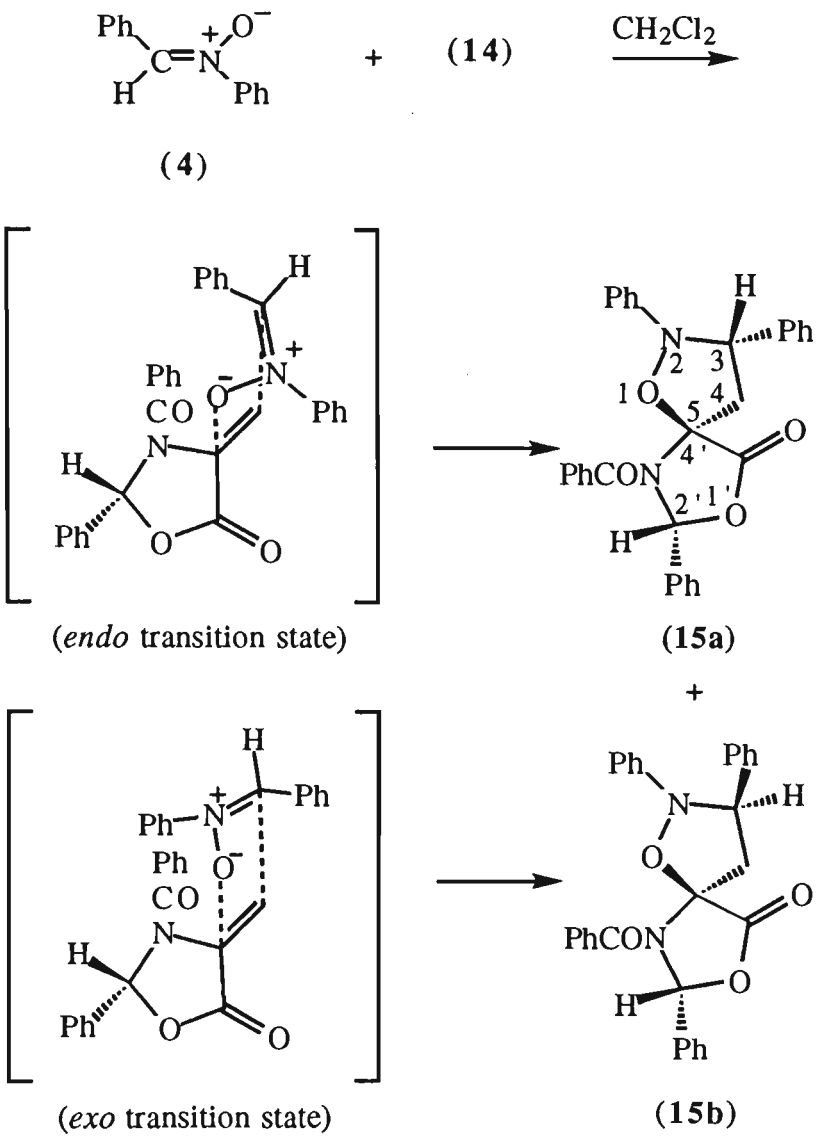
(14)

3-2. 1,3-Dipolar Cycloaddition Reactions of (14) and Nitrones

3-2-1. 1,3-Dipolar Cycloaddition Reactions of (14) and *C,N*-Diphenylnitrone (4)

When a solution of oxazolidinone (14) and nitrone (4) (1.1 molar equivalents) in CH_2Cl_2 was stirred at room temperature for 7 days, then a 70 : 30 mixture of two diastereomeric cycloaddition products, (15a) and (15b) was formed in 94% yield (Scheme 3.6). The same two diastereomeric products were produced in a ratio of 62 : 38 when this reaction was performed at 60 °C over 3 days (Table 3.1, page 110). The diastereoisomers could be readily separated by fractional crystallization. ^1H NMR analysis of both diastereoisomers indicated that these reactions were highly regioselective and that both diastereoisomers had the 5,5-disubstituted isoxazolidine rather than the 4,4-disubstituted isoxazolidine structure. The relative stereochemistry of these compounds however, could not be determined from NMR experiments. The stereochemistry of the major diastereoisomer (15a) was unequivocally determined by a single crystal X-ray structural determination (Figure 3.1). The X-ray structural analysis indicated that the stereochemistry of (15a) arises from addition of nitrone (4) to the π-face of the *exo*-cyclic 4-methylene group of (14) that is *anti* to the C-2 phenyl substituent, via an *endo* type transition state.

Scheme 3.6



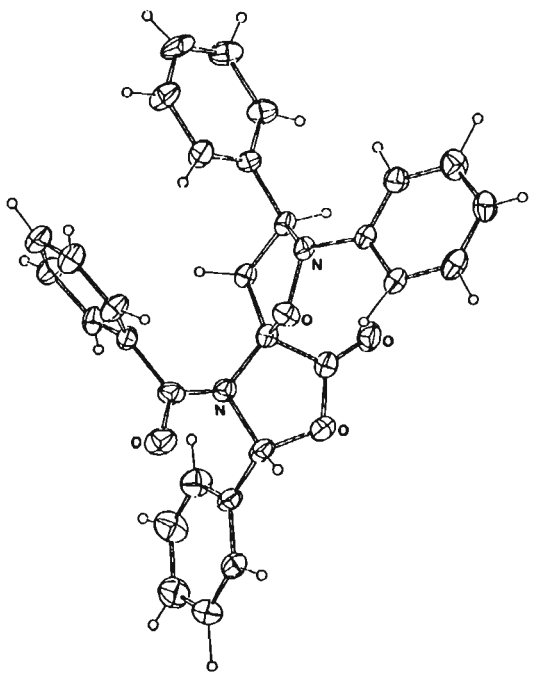


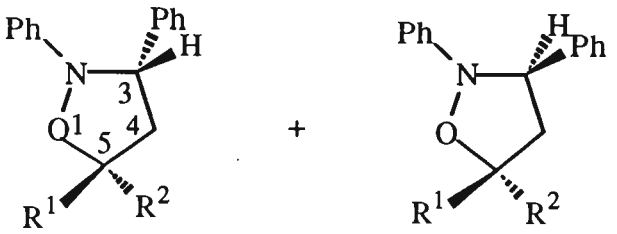
Figure 3.1. Molecular projection of **(15a)** normal to the plane of the five membered ring.

To determine the stereochemistry at C-3 of the minor diastereoisomer, a 73 : 27 mixture of the minor (15b) and major (15a) diastereoisomers respectively, was reduced with sodium borohydride[55] to give a 72 : 28 mixture of diastereomeric alcohols (Scheme 3.7). Treatment of this mixture with (-)-(*R*)-α-methoxy-α-trifluoromethylphenylacetyl chloride (MTPACl)[56] and pyridine gave a mixture of four diastereomeric α-methoxy-α-trifluoromethylphenylacetates (MTPA) (18), (19), (20) and (21). The ratio of (20) + (21) : (18) + (19) was 70 : 30 (see Experimental section for details). Clearly the above reduction reaction had produced a mixture of (16) and its enantiomer *ent*-(16), and (17) and its enantiomer *ent*-(17). Thus epimerization at C-5 had occurred in the alcohol products. When this sequence of reactions was performed on diastereomerically pure (15a) then only MTPA's (18) and (19) were formed, not necessarily respectively, in a 55 : 45 ratio (Scheme 3.7). These experiments clearly establish the stereochemistries at C-3 in the major (15a) and minor (15b) diastereoisomers to be opposite. We therefore suggest that the structure of the minor diastereoisomer is (15b). The above experiments also show that (15a) was obtained in high enantiomeric purity (e.e. > 98%).

Scheme 3.7

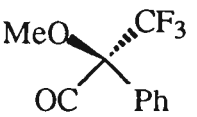
(15a) + **(15b)**

1. $NaBH_4$, MeOH
2. MTPACl, pyridine



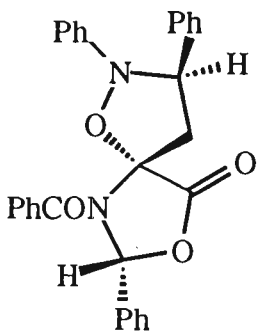
(16) ; R^1 = PhCONH, R^2 = CH_2OH ***ent*-(16)** ; R^1 = CH_2OH, R^2 = PhCONH
(17) ; R^1 = CH_2OH, R^2 = PhCONH ***ent*-(17)** ; R^1 = PhCONH, R^2 = CH_2OH
(18) ; R^1 = PhCONH, R^2 = CH_2OMTPA **(20)** ; R^1 = CH_2OMTPA, R^2 = PhCONH
(19) ; R^1 = CH_2OMTPA, R^2 = PhCONH **(21)** ; R^1 = PhCONH, R^2 = CH_2OMTPA

MTPA =



(15a) —(1. $NaBH_4$, MeOH; 2. MTPACl, pyridine)→ **(18)** + **(19)**

Although the structure (15c), which could arise from an *endo* type transition state, and addition of the nitrone to the more hindered side of the *exo*-cyclic methylene group of (14), could not be ruled out for the minor isomer, the ^1H NMR of this compound was significantly different to that of (23b) (Scheme 3.8, page 112), the structure of which was established by single crystal X-ray structural analysis.



(15c)

Table 3.1. 1,3-Dipolar cycloaddition products from the reactions of (14) with nitrones and nitrile oxides.

Entry	Dipole	Time (days) / Temp. (°C)	Yield (%)[a]	(Products) Diastereoselection [b]
1	*C,N*-Diphenylnitrone (4)			(15a), (15b)
		7 / r.t.	94	70 : 30
		3 / 60	99	62 : 38
2	*C*-Phenyl-*N*-*tert*-butylnitrone (22)			(23a), (23b)
		10 / r.t.	36	88 : 12
		22 / r.t.	52	88 : 12
		31 / r.t.	69	89 : 11
		3 / 60	42	72 : 28
		10 / 60	49	55 : 45
		22 / 60	66	33 : 67
3	*C*-Phenyl-*N*-methylnitrone (24)			(25a),(25b),(25c),(25d)
		15 / r.t.	50	28 : 44 : 22 : 6
		8 / 60	53	11 : 30 : 39 : 20
4	Pyrolidine nitrone (28)			(30), minor isomer
		2 / r.t.	27	>98 : <2
		2 / 40	33	92 : 8
5	Piperidine nitrone (29)			(31), minor isomers
		1.5 / r.t.	25	85 : 15
		1.5 / 40	30	70 : 15 : 15
6	Phenylnitrile oxide (2)	2 hr / r.t.	94	(38a), (39a) 85 : 15
7	Methylnitrile oxide (37)	2 hr / r.t.	41[c]	(38b), (39b) 83 : 17

[a] After purification. [b] Determined on the crude reaction mixture by ^{1}H NMR (400 MHz). [c] Yield of pure major diastereoisomer.

When a solution of diastereomerically pure (15a) in CH_2Cl_2 was heated at 60 °C for 3 days no interconversion of (15a) to (15b) or the formation of (4) and (14) was observed. Thus (15a) appears to be formed under kinetically controlled conditions with no interconversion of (15a) to (15b) occurring under the reaction conditions. In contrast, the cycloaddition reactions of (14) and nitrones (22) and (24) were found to be reversible at 60 °C and furthermore, the starting compounds (14) and (22 or 24) were always observed in the crude reaction mixtures.

3-2-2. 1,3-Dipolar Cycloaddition Reactions of (14) and *C*-Phenyl-*N-tert*-butylnitrone (22)

When a solution of (14) and nitrone (22) in CH_2Cl_2 was stirred at room temperature then a 88 : 12 mixture of (23a) and (23b) was obtained (Scheme 3.8). The diastereomeric ratio of (23a) : (23b) remained essentially unchanged over 31 days (Table 3.1, page 110). The structures of (23a) and (23b) were elucidated by single crystal X-ray structural determinations (Figure 3.2). The major diastereomeric product (23a) had the same relative stereochemistry as (15a) and was the expected '*endo*' product. The minor diastereoisomer (23b) had the unexpected stereochemistry at C-4' of the oxazolidinone ring. This isomer arises from addition of the nitrone (22) to the more sterically hindered π-face of the *exo*-cyclic 4-methylene group of (14), via an *endo* type transition state. When this reaction was performed at 60 °C however, the ratio of (23a) : (23b) changed with the reaction time and after 22 days, (23b) was the major diastereomeric product (Table 3.1, page 110). When a solution of diastereomerically pure (23a) was heated at 60 °C for 10 days then a 32 : 12 : 56 mixture of (23a), (23b) and (14) was obtained along with some nitrone (22).

Scheme 3.8

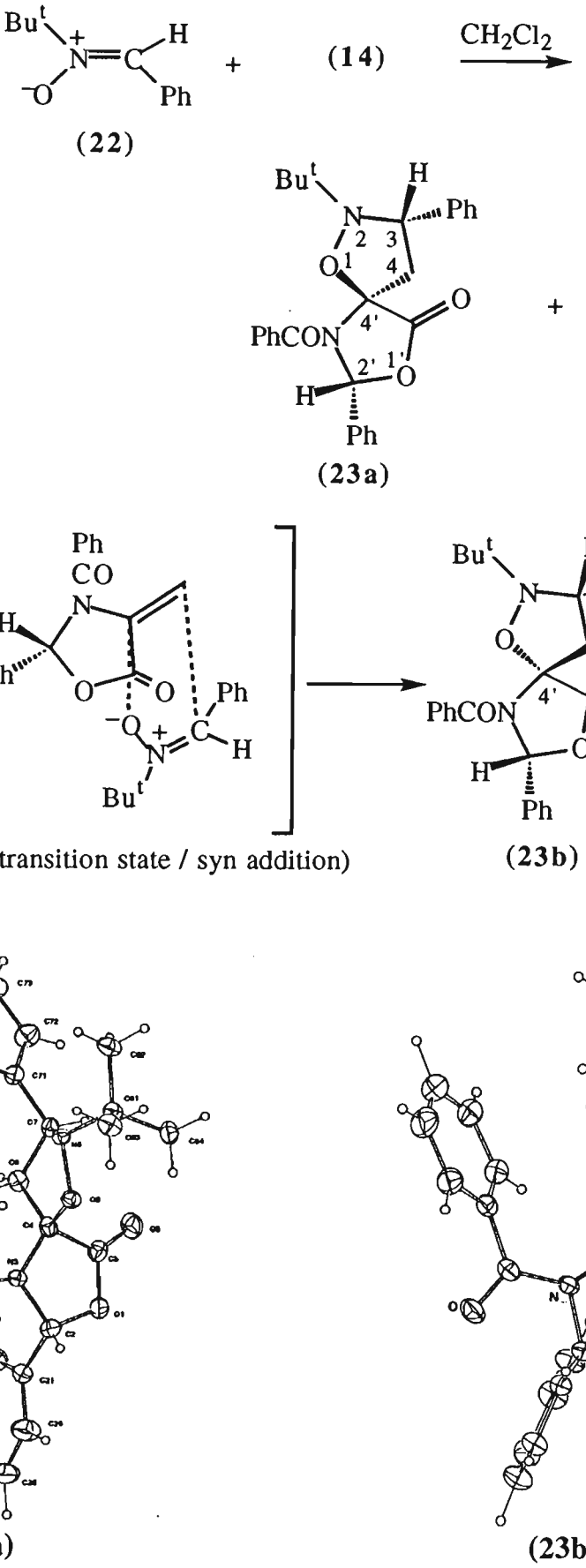
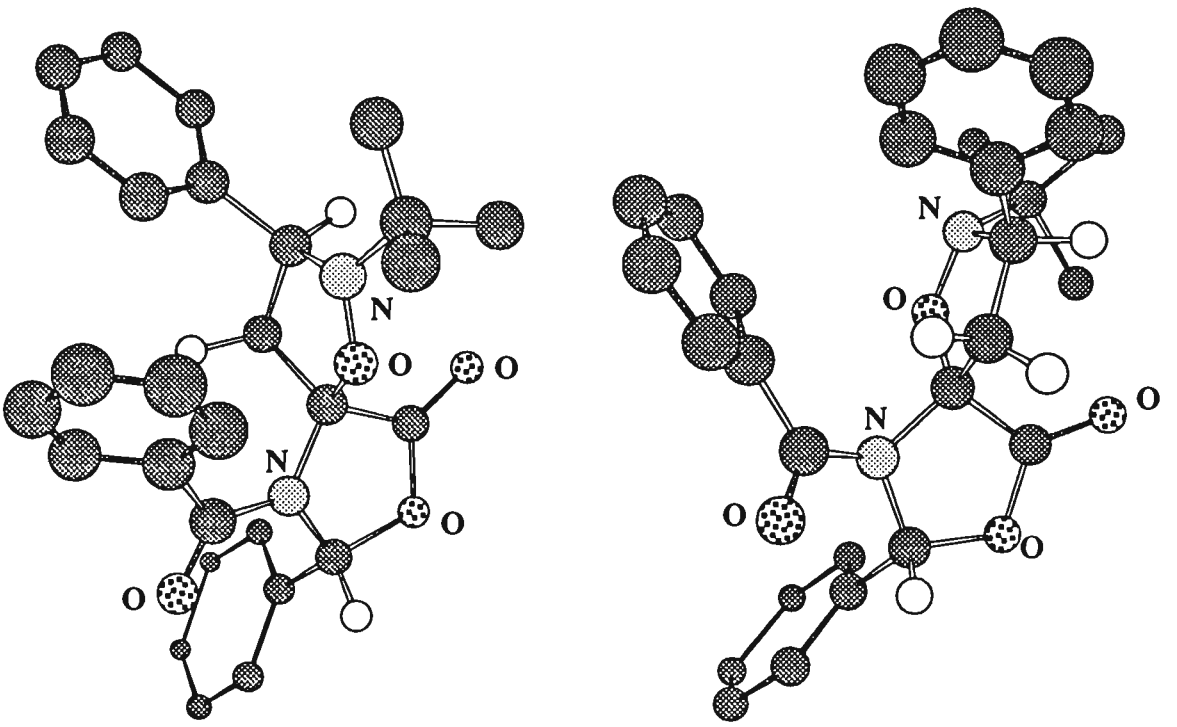


Figure 3.2. Molecular projection of (23a) and (23b) normal to the plane of five membered ring.

The above experiments clearly indicate that while diastereoisomer (23a) is favoured kinetically, diastereoisomer (23b) is thermodynamically more stable. Indeed molecular modelling of these diastereomeric molecules, using the BIOSYM molecular modelling program and the INSIGHT II force field, indicated that (23b) should be thermodynamically favoured over (23a) by about 3 kcal mol^{-1}.



(23a) Total Energy = 103 kcal / mol **(23b)** Total Energy = 100 kcal / mol

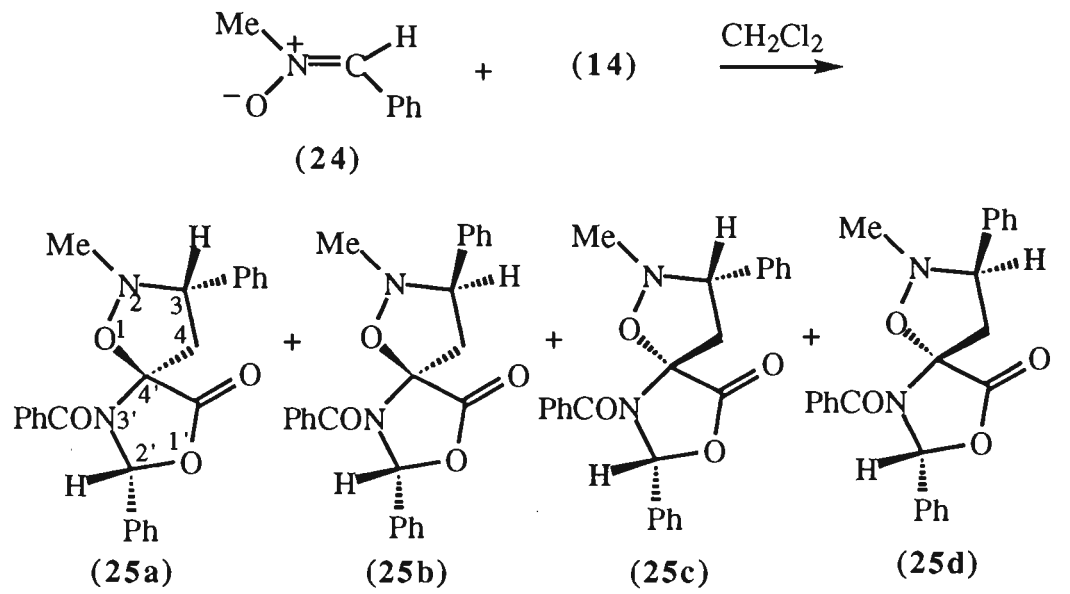
Figure 3.3. Energy minimized structures of (23a) and (23b) using the INSIGHT II force field of BIOSYM.

3-2-3. 1,3-Dipolar Cycloaddition Reactions of (14) and *C*-Phenyl-*N*-methylnitrone (24)

When a solution of (14) and nitrone (24) in CH_2Cl_2 was stirred at room temperature for 15 days, then four diastereomeric 5,5-disubstituted isoxazolidine products (25a), (25b), (25c) and (25d) were formed in 50% yield (Scheme 3.9). The ratio of these adducts remained essentially unchanged throughout the course of the reaction (Table 3.1, page 110). The two major diastereoisomers could not be obtained diastereomerically

pure, however the two minor diastereoisomers (25c) and (25d) could be isolated diastereomerically pure after partial separation by column chromatography and then selective crystallisations. The single crystal X-ray structures of (25c) and (25d) are shown in Figure 3.4.

Scheme 3.9



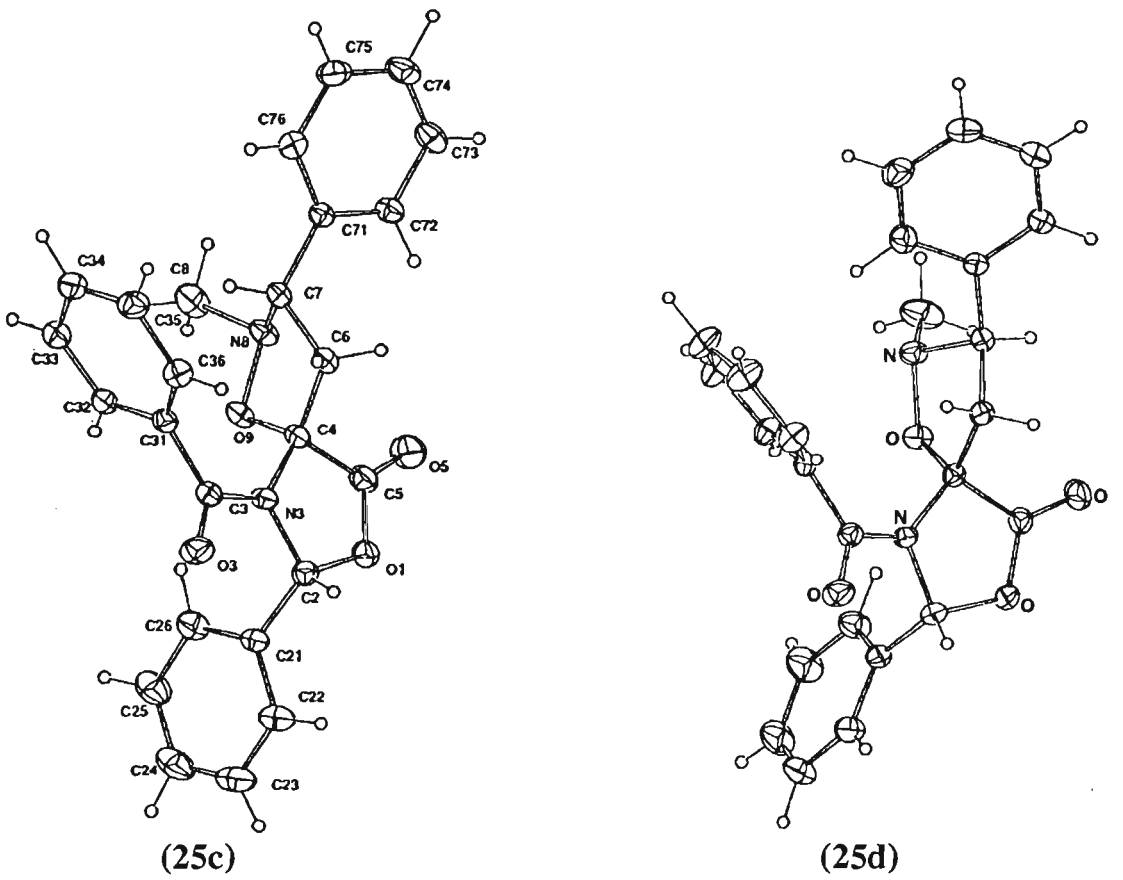
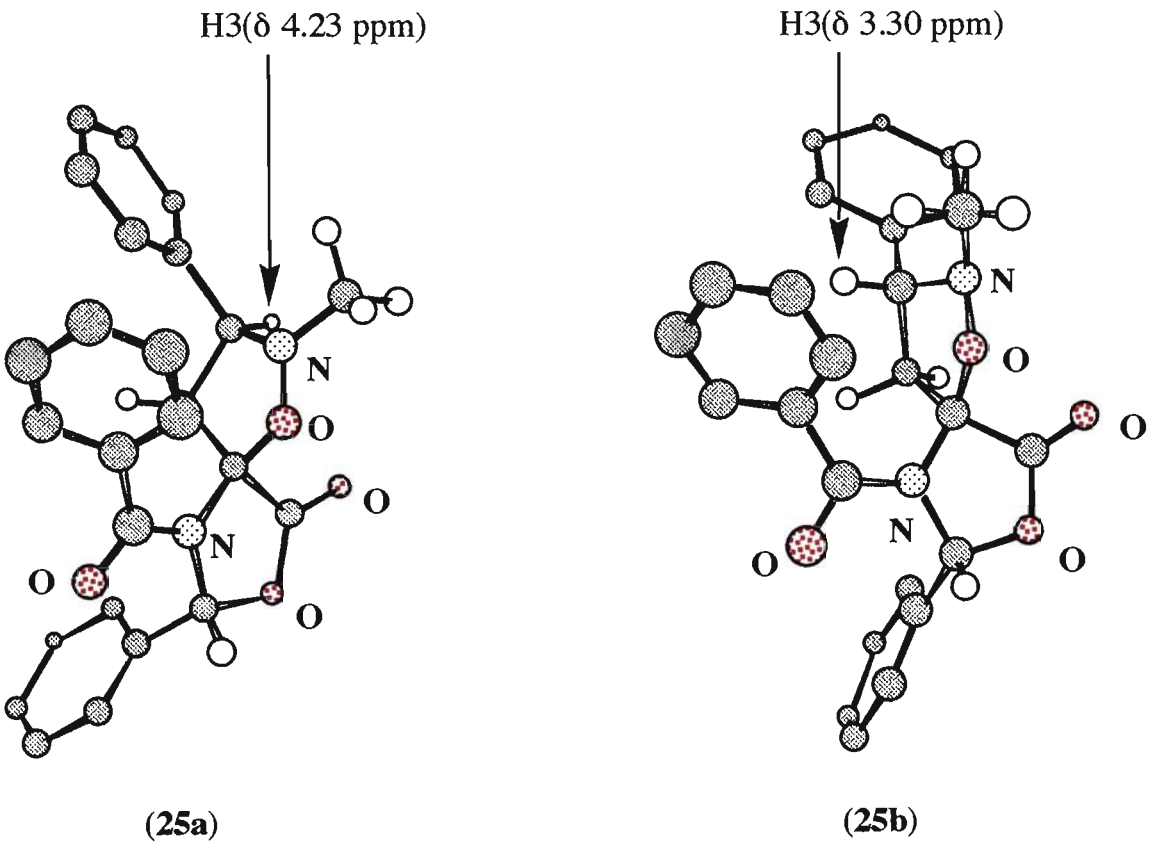


Figure 3.4. Molecular projection of (25c) and (25d) normal to the plane of five membered ring.

Both structures have the same stereochemistry at C-4' of the oxazolidinone ring as (23b). Consequently (25a) and (25b) must have the same stereochemistry at C-4' as the adducts (15a) and (23a). The stereochemistry of (25a) and (25b) was based upon ^{1}H NMR analysis and molecular modelling studies (Figure 3.5). The ^{1}H NMR spectrum of (25b) showed that H3 was highly shielded (δ 3.30) compared to H3 in the ^{1}H NMR spectrum of (25a) (δ 4.23). Molecular modelling (Figure 3.5) of these compounds showed that H3 in (25b) is in the shielding region of the phenyl ring of the *N*-benzoyl group, while H3 in (25a) is remote from such influences. Thus based on these considerations we tentatively assign the structures (25a) and (25b). When the reaction of (14) and (24) was performed at 60 °C the ratio of the diastereomeric products favoured the adducts (25c) and (25d) over (25a) and (25b) (Table 3.1, page 110).



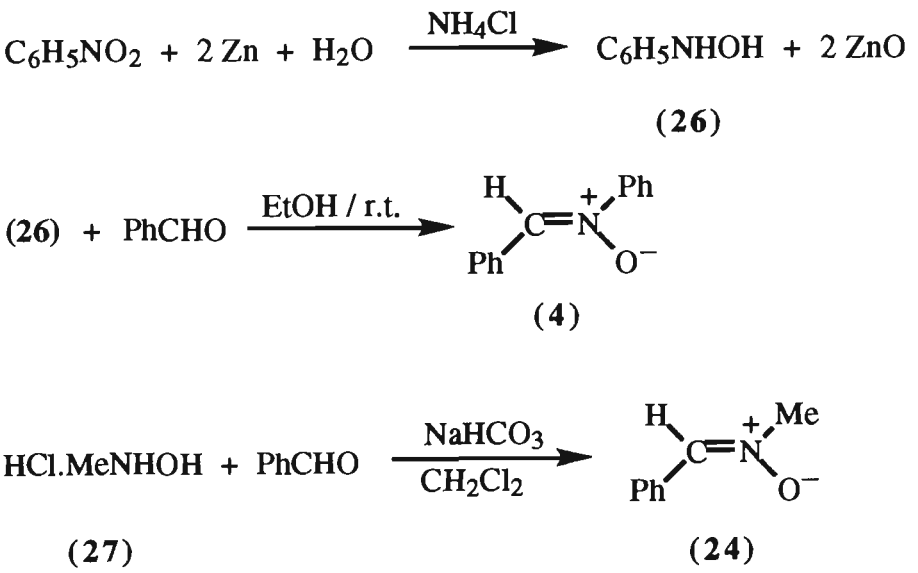
(25a) **(25b)**

Figure 3.5. Energy minimised structures of (25a) and (25b) using the INSIGHT II force field of BIOSYM.

3-2-4. Preparation of the Nitrones (4) and (24)

Nitrones are highly versatile synthetic intermediates and excellent spin trapping reagents.[95] Nitrones have been prepared by either condensation of an aldehyde or ketone with a hydroxylamine,[96] by the oxidation of hydroxylamines,[97] and by the direct and catalytic oxidation of secondary amines.[98] The oxidation methods have been routinely used for the preparation of cyclic nitrones.[98,99] The *C,N*-diphenylnitrone (4) and *C*-phenyl-*N*-methylnitrone (24) were prepared by condensation of benzaldehyde with the appropriate *N*-hydroxylamines.[100,101] The *N*-phenylhydroxylamine (26) was produced by reduction of nitrobenzene with zinc dust in a solution of ammonium chloride in water. Treatment of the compound (26) with benzaldehyde in ethanol at room temperature produced the nitrone (4) with 85% yield (Scheme 3.10). The nitrone (24) was prepared by treatment of *N*-methyl hydroxylamine hydrochloride (27) with benzaldehyde in CH_2Cl_2 and in the presence of sodium bicarbonate (Scheme 3.10).

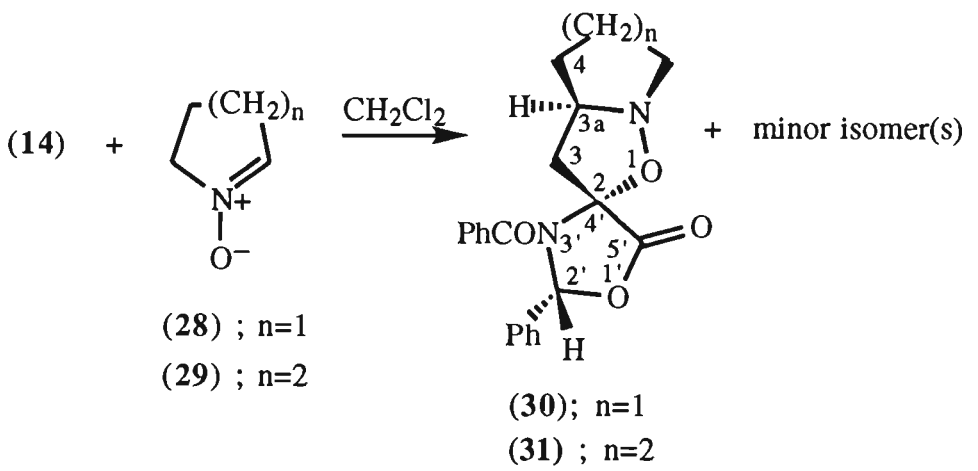
Scheme 3.10



3-2-5. 1,3-Dipolar Cycloaddition Reactions of (14) and Cyclic Nitrones

The reactions of (14) and the pyrrolidine nitrone (28) (Scheme 3.11) were highly diastereoselective at room temperature to 40 °C, but the isolated yields of the major diastereomeric product were low (Table 3.1, page 110). The reactions of (14) with the homologous (cyclic) piperidine nitrone (29) (Scheme 3.11) were less diastereoselective and again the isolated yields of the major diastereomeric product were low (Table 3.1, page 110). In contrast, the reaction of (14) and (29) at 40 °C apparently gave three diastereomeric adducts, however the stereochemistry of the two minor adducts could not be determined. The single crystal X-ray structures of the major diastereomeric adducts (30) and (31) from the reactions of (28) and (29) respectively, are shown in Figure 3.6.

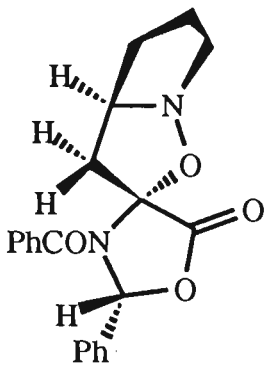
Scheme 3.11



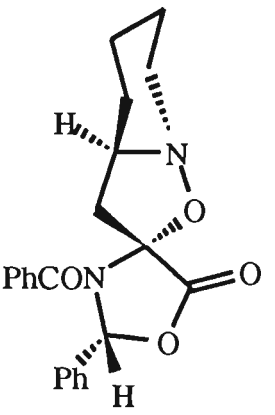
(28) ; n=1
(29) ; n=2

(30); n=1
(31) ; n=2

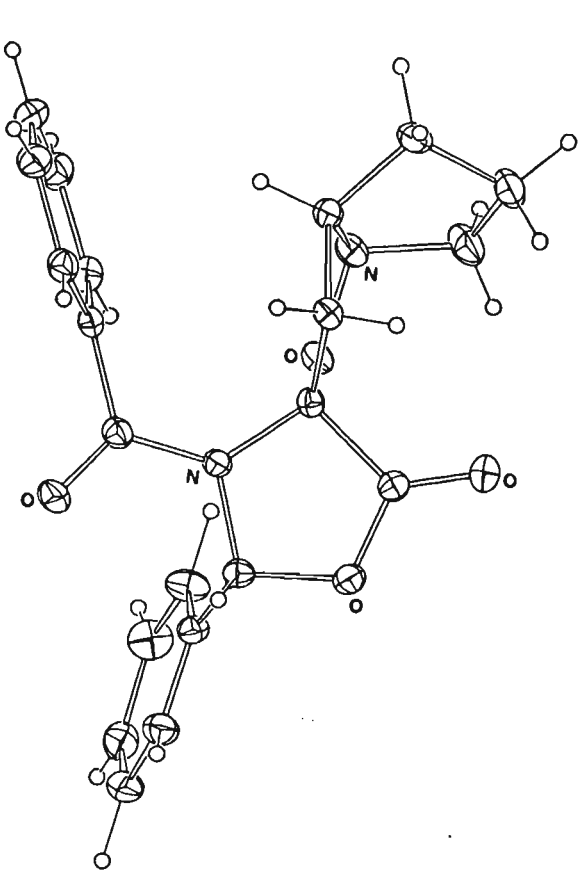
Both adducts (30) and (31) have the same relative stereochemistry. The stereochemistry at C-4' of the oxazolidinone ring of these adducts suggests that they are the thermodynamically favoured products that have been formed from a reversible cycloaddition reaction. Both adducts arise from an *endo*-like transition state.



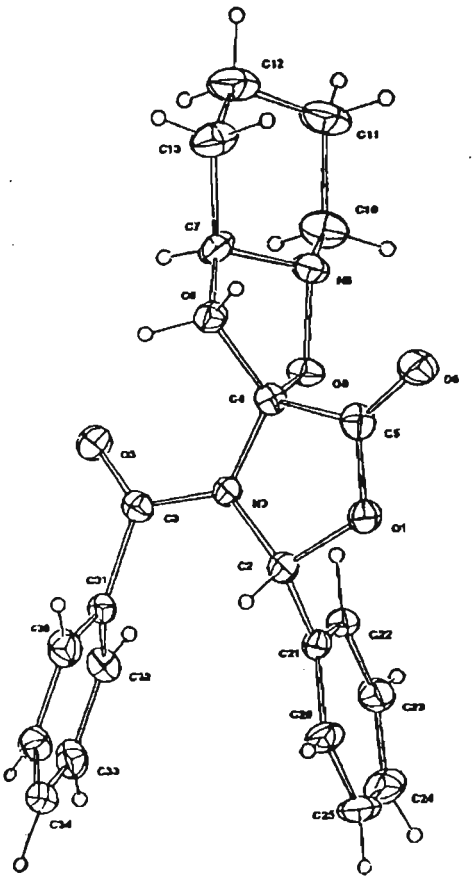
(30)



(31)



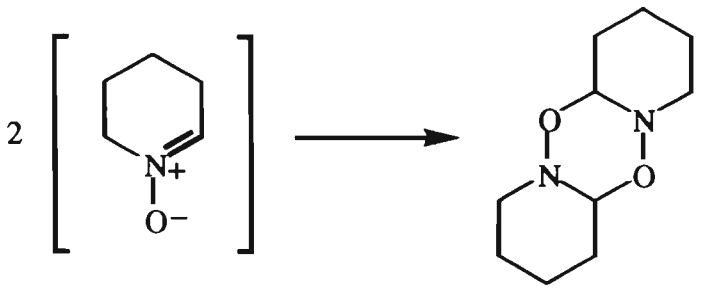
(30)



(31)

Figure 3.6. Molecular projection of (30) and (31) normal to the plane of five membered ring.

The yields of these reactions were low (25-33 %) with the recovery of some of the alkene (14) because of the competitive dimerisation of the nitrones as shown in (eq 3.2).[102]

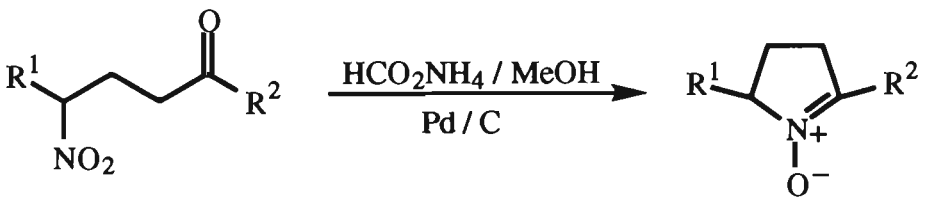


(29) (32) (eq 3.2)

3-2-6. Preparation of the Cyclic Nitrones (28) and (29)

The preparation of cyclic nitrones have been performed by reduction or oxidation reactions. An efficient synthesis of 5-membered cyclic nitrones from γ-nitro ketones (33) was introduced by R. Zschiesche *et al.* in 1988.[103] In these reactions, substituted and functionalized pyrrolidine nitrones (34) were obtained from α-nitro ketones by hydrogenation over Pd / C in the presence of ammonium formate (Scheme 3.12).

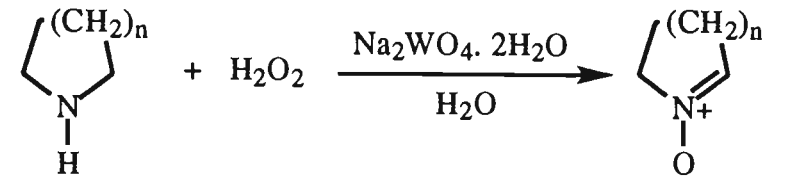
Scheme 3.12



(33) (34)

Recently Murahashi *et al.*[99] reported the preparation of cyclic nitrones such as pyrrolidine and piperidine nitrones in high yields from the oxidation of secondary amines. We have prepared nitrones (28) and (29) by oxidation of the secondary amines (35) and (36) respectively, with hydrogen peroxide in the presence of sodium tungstate as a catalyst following the Murahashi procedure (Scheme 3.13)[99].

Scheme 3.13



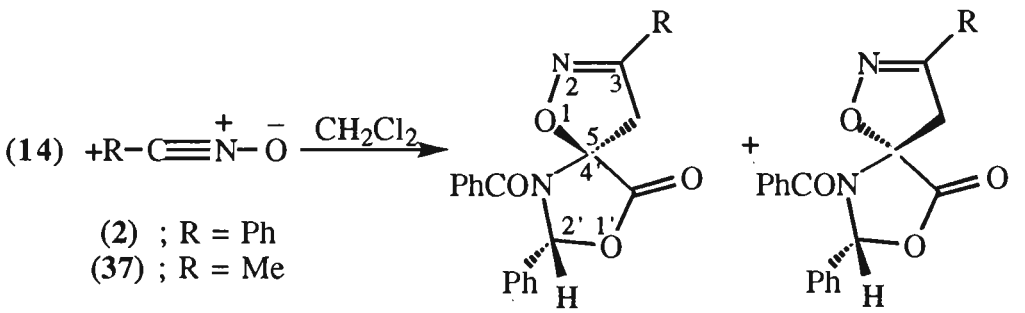
n =1 ; (35)
n =2 ; (36)

n =1 ; (28)
n =2 ; (29)

3-3. 1,3-Dipolar Cycloaddition Reactions of (14) and Nitrile Oxides

Treatment of (14) with phenylnitrile oxide (2) (Scheme 3.14) in CH_2Cl_2 at room temperature for 2 hr gave an 85 : 15 mixture of two diastereomeric adducts (38a) and (39a) in excellent yield (94%) (Table 3.1, page 110). The analogous reaction of (14) with methylnitrile oxide (37) (Scheme 3.14) proceeded with a similar diastereoselectivity, however, the isolated yield of the major diastereomerically pure product (38b) was low (41%) (Table 3.1, page 110). The structure of the diastereoisomeric products (38a), (39a) and (38b) were determined by single crystal X-ray structure determinations (Figure 3.7) and (Figure 3.8).

Scheme 3.14

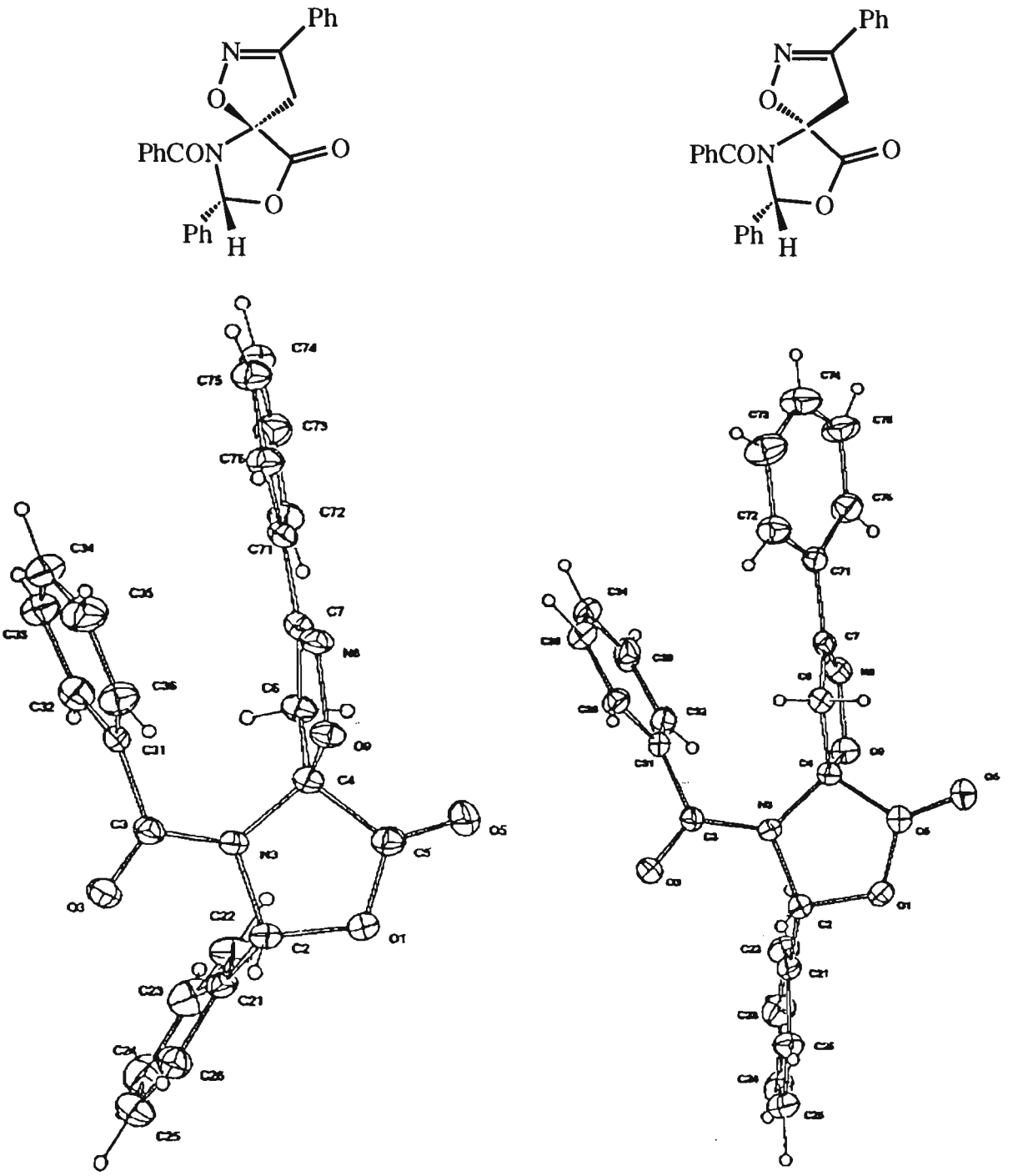


(2) ; R = Ph
(37) ; R = Me

a ; R = Ph
b ; R = Me

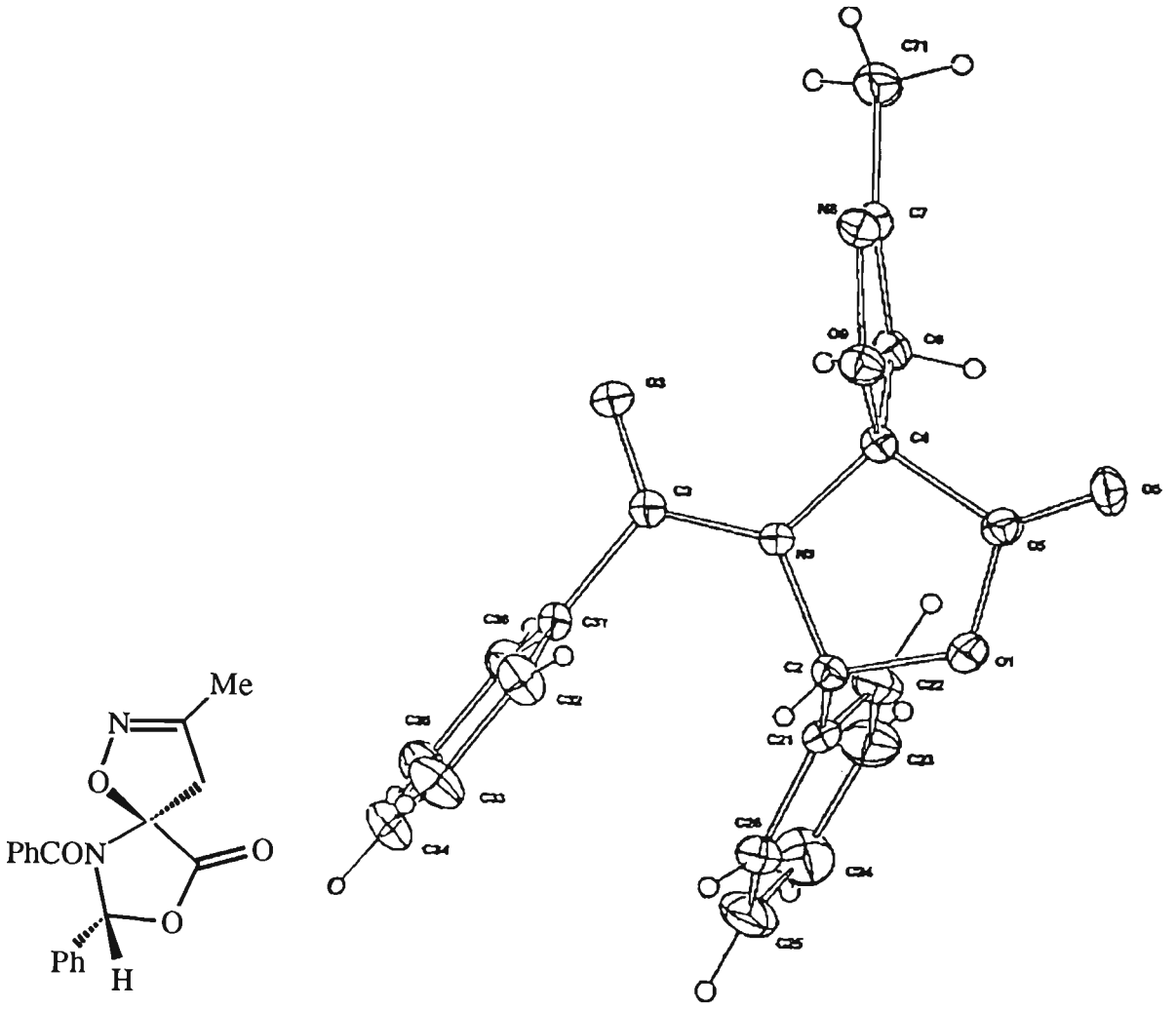
Both the major diastereomeric adducts (38a) and(38b) had the expected regiochemistry and stereochemistry at C-4'. These adducts arise from addition of the nitrile oxides to the π-face of the *exo*-cyclic methylene

group of (14) that is *anti* to the C2'-Ph substituent of the oxazolidinone ring of (14). The minor isomers (39a) and(39b) were formed via addition of the nitrile oxides to the more hindered π-face of the *exo*-cyclic methylene group of (14).



(38a) (39a)

Figure 3.7. Molecular projection of (38a) and (39a) normal to the plane of five membered ring.

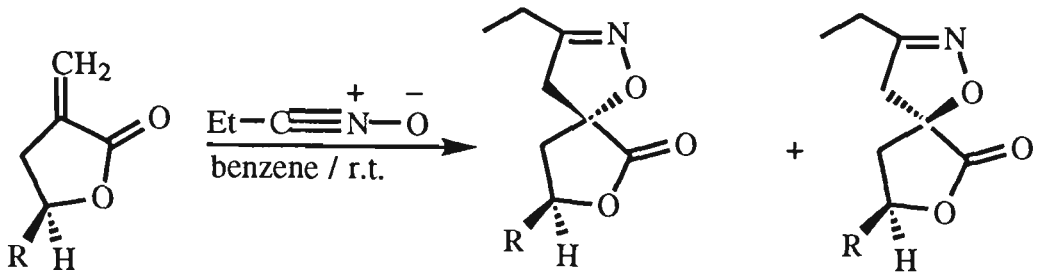


(38b)

Figure 3.8. Molecular projection of (38b) normal to the plane of five membered ring.

Analogous results have been reported by Pereira *et al.*[104] in 1993 for the addition of propionitrile oxide to the structurally related α-methylene-γ-butyrolactones (40a-h) (Scheme 3.15). In this series of reactions the product mixture contained two diastereoisomers, the major cycloadduct (41) was formed by addition *anti* to the bulky *R* substituent, and the minor cycloadduct (42) was formed from *syn* addition.

Scheme 3.15



(40) (41) (42)

a ; R = methyl
b ; R = heptyl
c ; R = phenyl
d ; R = t-butyl
e ; R = 2-naphthyl
f ; R = 2-methoxyphenyl
g ; R = 4-methoxyphenyl
h ; R = 2,6-dichlorophenyl

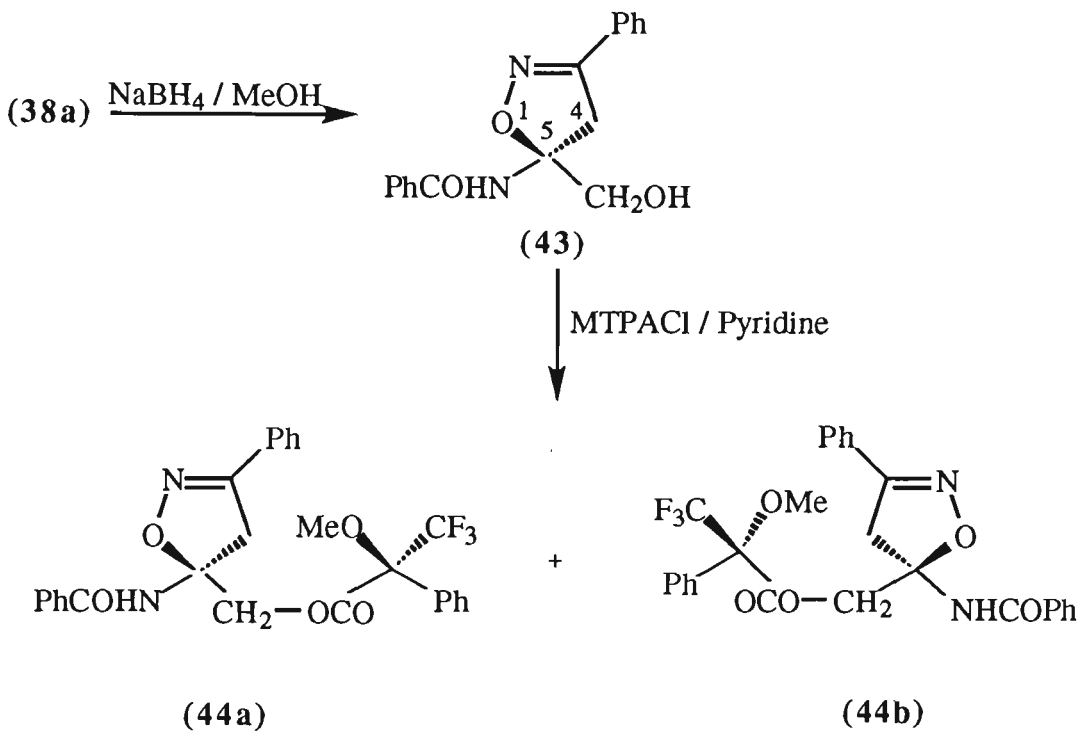
Table 3.2. Relative proportions of *syn* and *anti* additions of propionitrile oxide to γ-substituted α-methylene-γ-butyrolactones (40a) to (40h).[104]

Dienophile (40)	*Anti* addition	*Syn* addition	Total yield (%)
(a)	81	19	54
(b)	86	14	72
(c)	89	11	86
(d)	90	10	80
(e)	87	13	79
(f)	82	18	83
(g)	86	14	66
(h)	100	0	65

To determine the enantiomeric purity of the nitrile oxide cycloadducts, compound (38a) was reduced with sodium borohydride in methanol to give the alcohol (43). Treatment of this alcohol with (-)-*R*-α-methoxy-α-trifluoromethylphenylacetyl chloride (MTPACl)[56] and pyridine gave two diastereoisomeric esters (44a) and (44b) in a ratio of 88 : 12 (Scheme 3.16). This experiment indicated that the enantiomeric purity of the (38a)

was 76% and showed that ring opening of (43) is much less facile than that in (16) and (17). This was not surprising since the extra double bond (C=N) in (43) would be expected to retard the rate of ring opening.

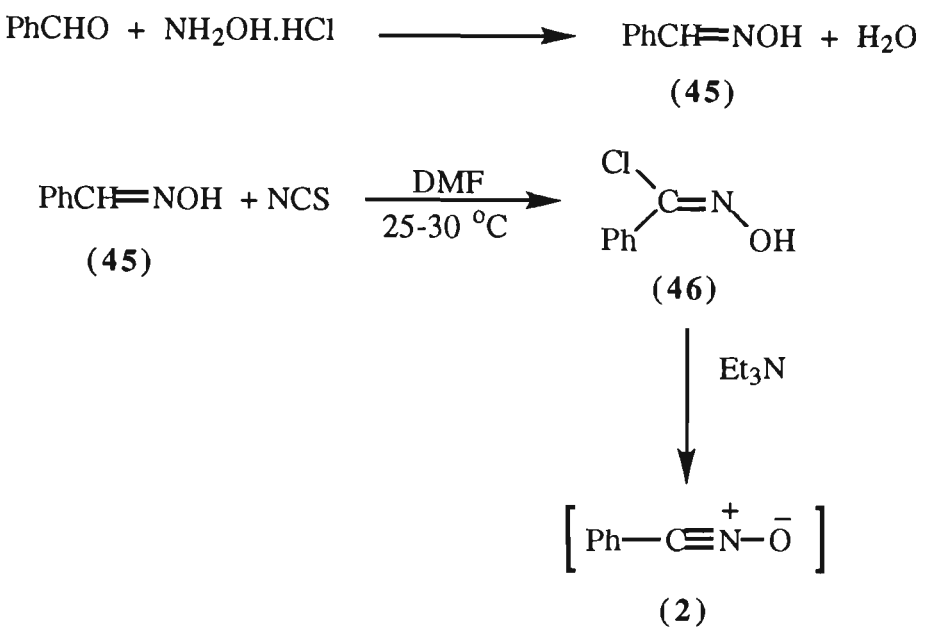
Scheme 3.16



3-3-1. Preparation of Nitrile Oxides

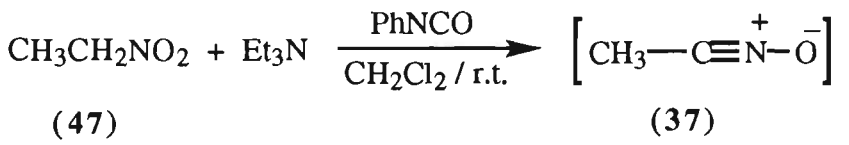
Nitrile oxides are usually prepared *in situ* and not isolated. Generated in the presence of a dipolarophile they form the cycloadduct directly, often in high yield.[51] Two general methods that have been used for their preparation are dehydrochlorination of hydroxamoyl chlorides with triethyl amine[76] and dehydration of primary nitro compounds with an aryl isocyanate.[104,105] They have also been conveniently obtained by oxidation of aldoximes.[90,106] The phenylnitrile oxide (2) was prepared *in situ* from benzohydroxamoyl chloride (46) which was available from the chlorination of *syn*-benzaldoxime (45) with *N*-chlorosucinimide (NCS) in DMF (Scheme 3.17).[107]

Scheme 3.17



Methylnitrile oxide (37) was prepared *in situ* from the dehydration of nitroethane (47) with triethylamine in the presence of phenyl isocyanate in CH_2Cl_2 (Scheme 3.18).[105a]

Scheme 3.18



3-4. Regioselectivity of 1,3-Dipolar Cycloaddition Reactions of Nitrones and Nitrile Oxides

1,3-Dipolar cycloadditions of nitrones and nitrile oxides are reversible and therefore subject to both thermodynamic and kinetic control. Both electronic and steric factors are of importance in determining the regiochemistry of these reactions. In general, in the reaction with the 1,1-disubstituted electron deficient dienophiles with nitrones and nitrile oxides, the oxygen of the dipole becomes attached to the more sterically hindered end of the dienophile and therefore usually 5,5-disubstituted isoxazolidines or isoxazoles are formed.[80,108] The regiochemistry of 1,3-dipolar

additions is controlled by the magnitudes of the atomic orbital coefficients in the participating frontier orbitals.[109] From these generalizations and the coefficient magnitudes, Houk[110] has rationalised the regioselectivity of all 1,3-dipolar cycloadditions based on the model shown in Figure 3.9. In his rationale, one frontier orbital interaction generally favours one regioisomer while the other favours the opposite regioisomer. This is because the larger HOMO coefficient is on "z", while the larger LUMO coefficient is on "x" of the dipolarophile.

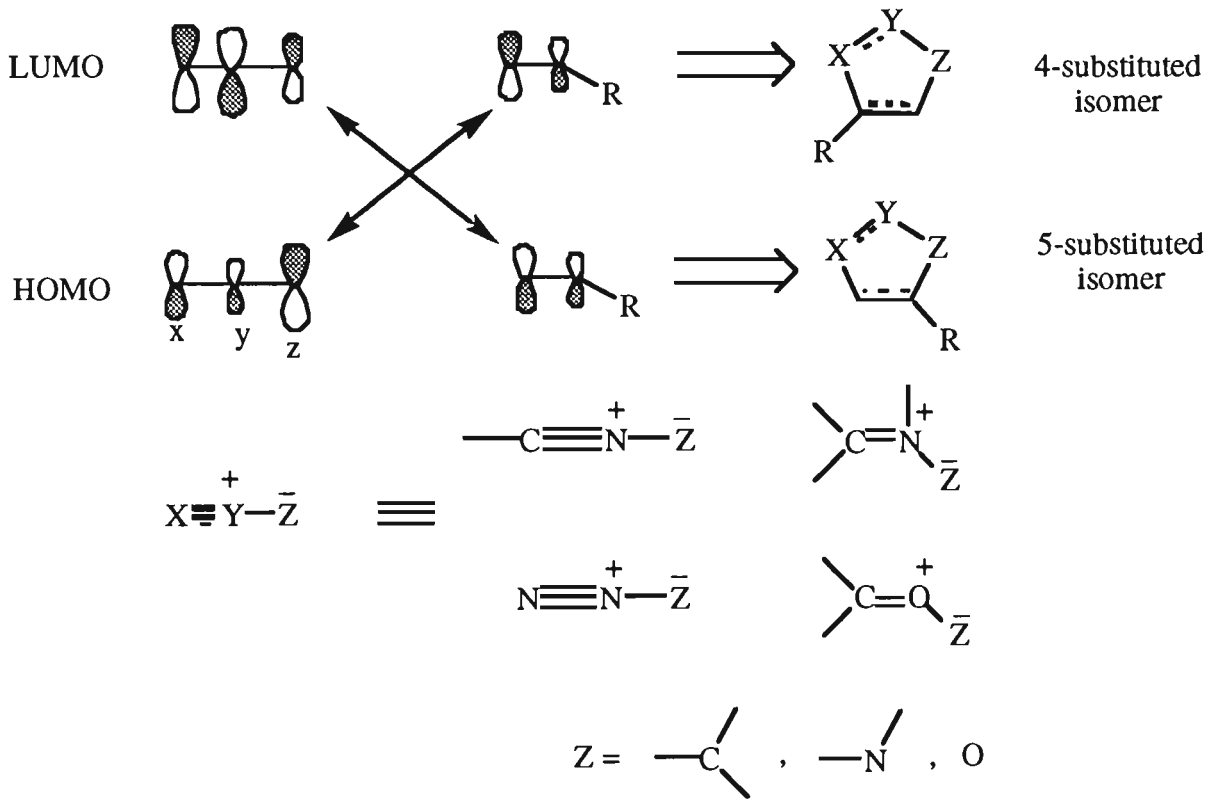
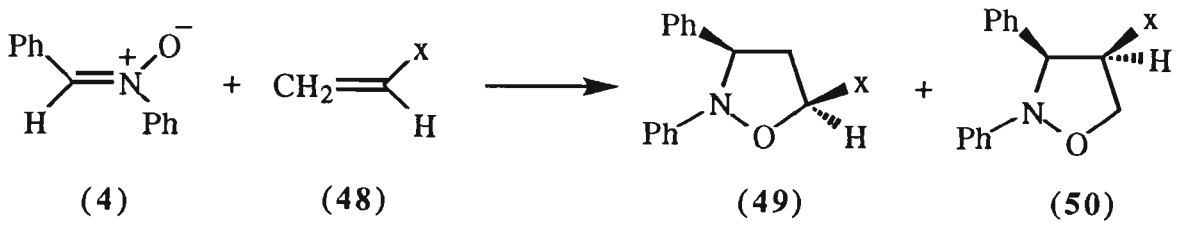


Figure 3.9. Frontier orbital interaction in 1,3-dipolar cycloadditions

The degree of regioselectivity in the cycloaddition of nitrones to electron deficient alkenes has been investigated by Ali *et al.*[111a] and Bimanand and Houk.[111b] Ali *et al.* have reported the formation of 4- and 5-substituted isoxazolidines (49) and (50) from the 1,3-disubstituted alkenes (48a-f) as are shown in Scheme 3.19.

Scheme 3.19



(4) (48) (49) (50)

a ; x = Me d ; x = CO_2Et
b ; x = Ph e ; x = CO_2Me
c ; x = CN f ; x = CHO

Table 3.3. Reaction of *C,N*-diphenyl nitrone (4) with dipolarophile (48).[111a]

Dipolarophile (48)	5-Substituted isomer (49) (%)	4-Substituted isomer (50) (%)
a	98.4	1.6
b	~100	~0
c	91	9
d	70	30
e	83	17
f	82	18

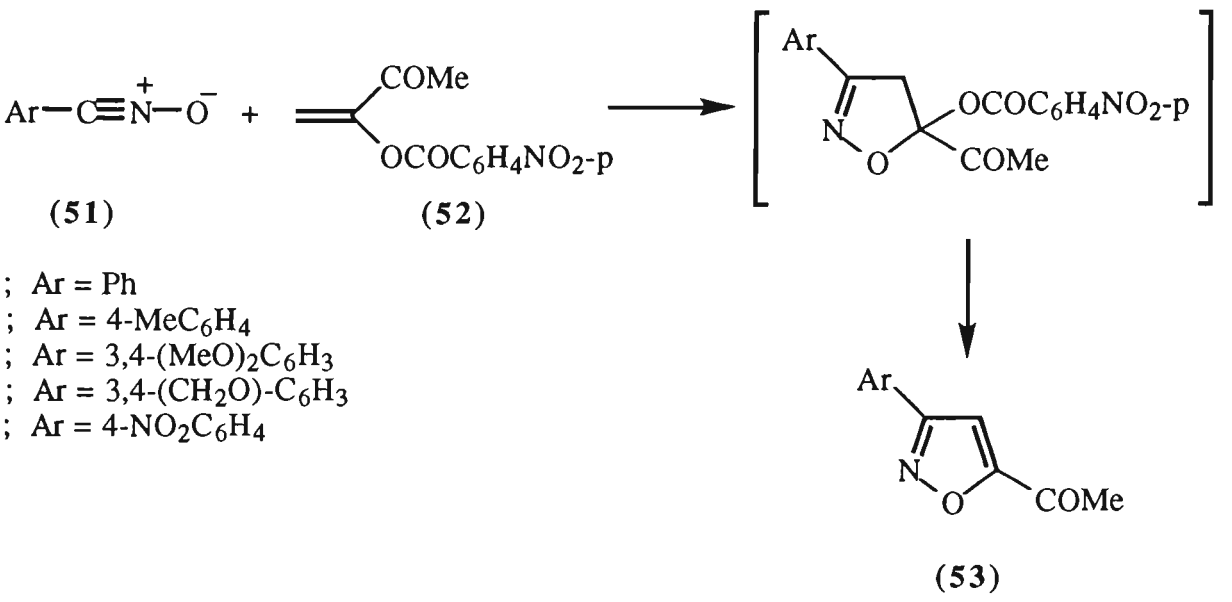
It was observed that the ratio of 4-substituted to 5-substituted products increased roughly with electron-deficiency of the dienophile (Table 3.3). This is in general accord with the frontier orbital treatment of nitrone cycloadditions.[112,113] According to this view most dipolarophiles should undergo cycloaddition to afford predominantly 5-substituted adducts. However, as the ionisation potential of the dipolarophile increase, i.e. as its HOMO decreases in energy, an increasing tendency is expected towards production of 4-substituted isoxazolidines. This is a consequence of the $HOMO_{dipole}$-$LUMO_{dipolarophile}$ interaction becoming more important than the $HOMO_{dipolarophile}$-$LUMO_{dipole}$ interaction in the generation of 4-substituted adducts.

Following the above explanations it can be appreciated that the 1,3-dipolar cycloaddition reactions of dipolarophile (14) with nitrones (4), (22), (24),

(28) and (29) produces 5,5-disubstituted isoxazolidinone adducts with high (100%) regioselectivity. The dienophile (14) with one electron withdrawing group (lactone carbonyl group) and one electron releasing / withdrawing group (benzamido group) would be expected to be moderately electron deficient and therefore shows a similar regioselectivity in its reactions as (48a) and (48b). Our observations are comparable with what were observed by Ali *et al.*[111a] in the reaction of (48b) with *C,N*-diphenylnitrone.

The regiochemistry of nitrile oxides cycloadditions can be explained by the FMO theory as mentioned above. In the majority of cases with 1,1-disubstituted and trisubstituted alkenes, the more hindered end of the dipolarophile adds to the nitrile oxide oxygen.[114] The 1,3-dipolar cycloaddition of captodative alkenes with arylnitrile oxides was considered for the first time by Jiménez *et al.* in 1993.[115] They observed the 5-substituted isoxazoline adducts as the only regioisomer in their reactions. Treatment of aryl nitrile oxides (51a-e) with alkenes (52) in dry benzene gave the expected 5-acetyl-3-arylisoxazoles (53) in moderate to good yields (66-96%) (Scheme 3.20).

Scheme 3.20



(51) (52) (53)

a ; Ar = Ph
b ; Ar = 4-MeC_6H_4
c ; Ar = 3,4-$(MeO)_2C_6H_3$
d ; Ar = 3,4-(CH_2O)-C_6H_3
e ; Ar = 4-$NO_2C_6H_4$

Jiménez *et al.*[115] explained the regioselectivity of their reactions by invoking a radicaloid transition state. They have considered the substituent effects that could stabilize the transition state that leads to the major regioisomer (53). The most likely transition state was the one in which allylic conjugative and captodative stabilizing effects were maximized, as shown in Figure 3.10.

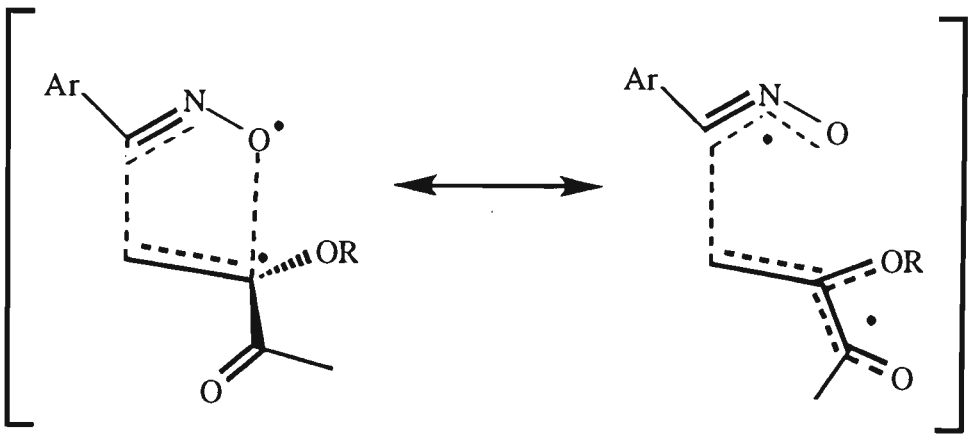


Figure 3.10. Conjugate and captodative effect in 1,3-dipolar addition of arylnitrile oxides with alkene (52).

A similar explanation can be used to understand the regioselectivity of 1,3-dipolar additions of nitrile oxides (2) and (37) with dienophile (14). As it was explained in Chapter Two, the alkene (14) has captodative properties. The transition state that lead to the major regioisomers observed in our reactions could be stabilized by similar allylic conjugative and captodative effects as described by Jiménez *et al.*[115] (Figure 3.11).

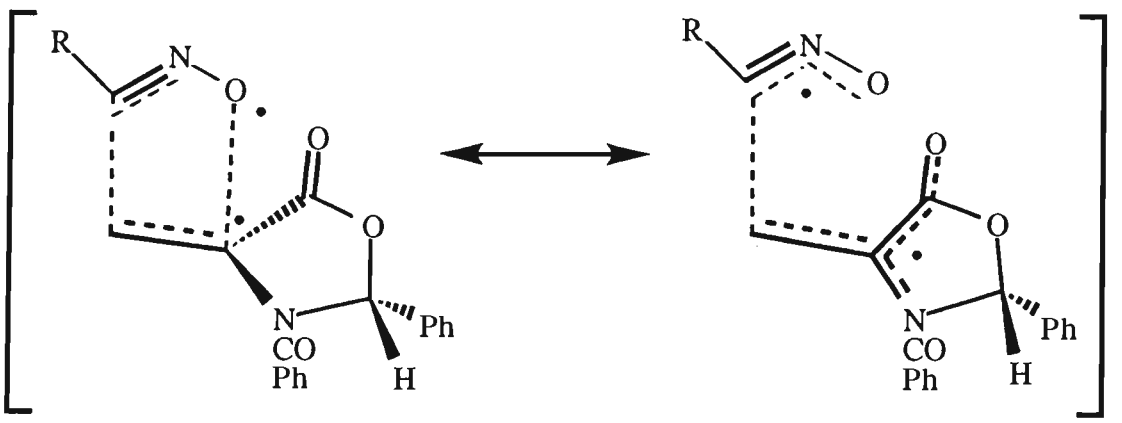


Figure 3.11. Conjugative and captodative effect in 1,3-dipolar addition of nitrile oxides (2) and (37) with alkene (14).

Additionally, the regiochemistry of 1,3-dipolar cycloaddition may be influenced by steric effects. Steric factors have been discussed by Pereira *et al.*[104] (Section 3.3) and others.[116] Martin *et al.*[116a] stated that "the regiochemical course of the 1,3-dipolar cycloadditions of nitrile oxides with unactivated and unsymmetrical alkenes was subject to steric effects alone".

Besides the electronic factors the steric interaction can be considered to explain the regioselectivity of our 1,3-dipolar cycloadditions with nitrones and nitrile oxides. The repulsion between the C-substituent on carbon in nitrones or nitrile oxides with the bulky benzamido group of (14) could be responsible for the non-existence of 4-substituted isoxazolidine or isoxazoline adducts (Figure 3.12).

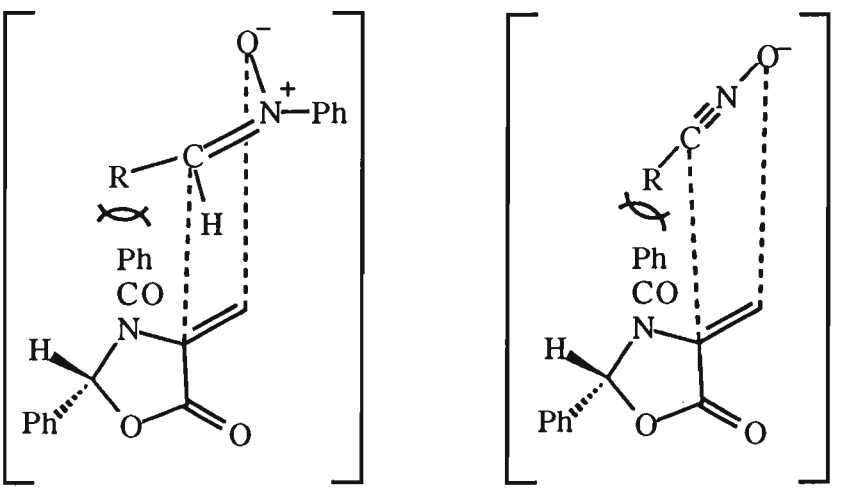


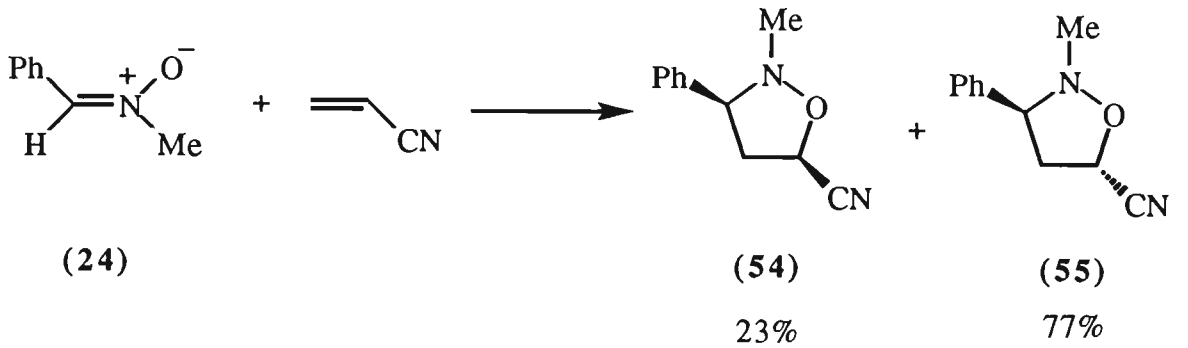
Figure 3.12. Steric interactions between the *C*-substituent on carbon in nitrones or nitrile oxides with the benzamido group in alkene (14).

3-5. Stereoselectivity of the 1,3-Dipolar Cycloaddition of Nitrones

Dipolar cycloadditions of nitrones, like the Diels-Alder reactions, proceed through *exo* or *endo* transition states. In most cases the *endo* cycloadduct is favoured due to a stabilizing secondary orbital interaction. This was explained by Padwa *et al.*[117] in the reaction of *C*-phenyl-*N*-methylnitrone (24) with acrylonitrile to produce a mixture of *cis* (23%) and *trans* (77%)

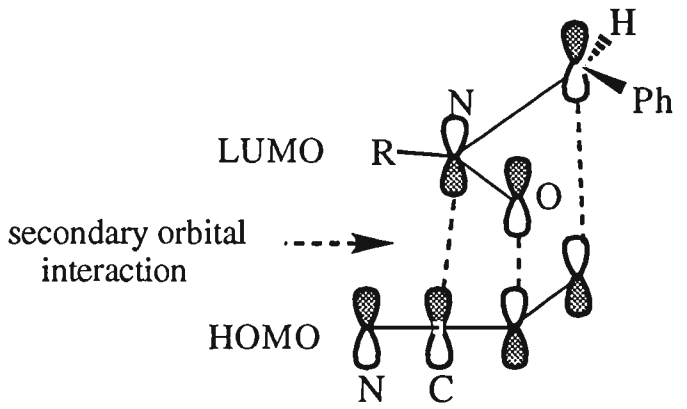
5-cyano-substituted isoxazolidines (54) and (55) respectively (Scheme 3.21).

Scheme 3.21



(24) (54) 23% (55) 77%

The *endo* transition state was suggested to be favoured because of a stabilizing secondary orbital interaction in the participating $HOMO_{dipolarophile}$-$LUMO_{nitrone}$ frontier molecular orbitals to produce the *trans* isomer (55) (Figure 3.13).



(*endo* transition state)

Figure 3.13. Secondary orbital interaction in the *endo* transition state of *C*-phenyl-*N*-methylnitrone and acrylonitrile.

A similar secondary orbital interaction in the *endo* transition state is possible for the dipolar cycloaddition of dienophile (14) with nitrones (Figure 3.14a). An alternate possibility is that steric repulsion between the alkyl group on nitrogen of the nitrone and the benzamido substituent on the dipolarophile destabilize the *exo* transition state (Figure 3.14b) and therefore the *endo* adduct is favoured.

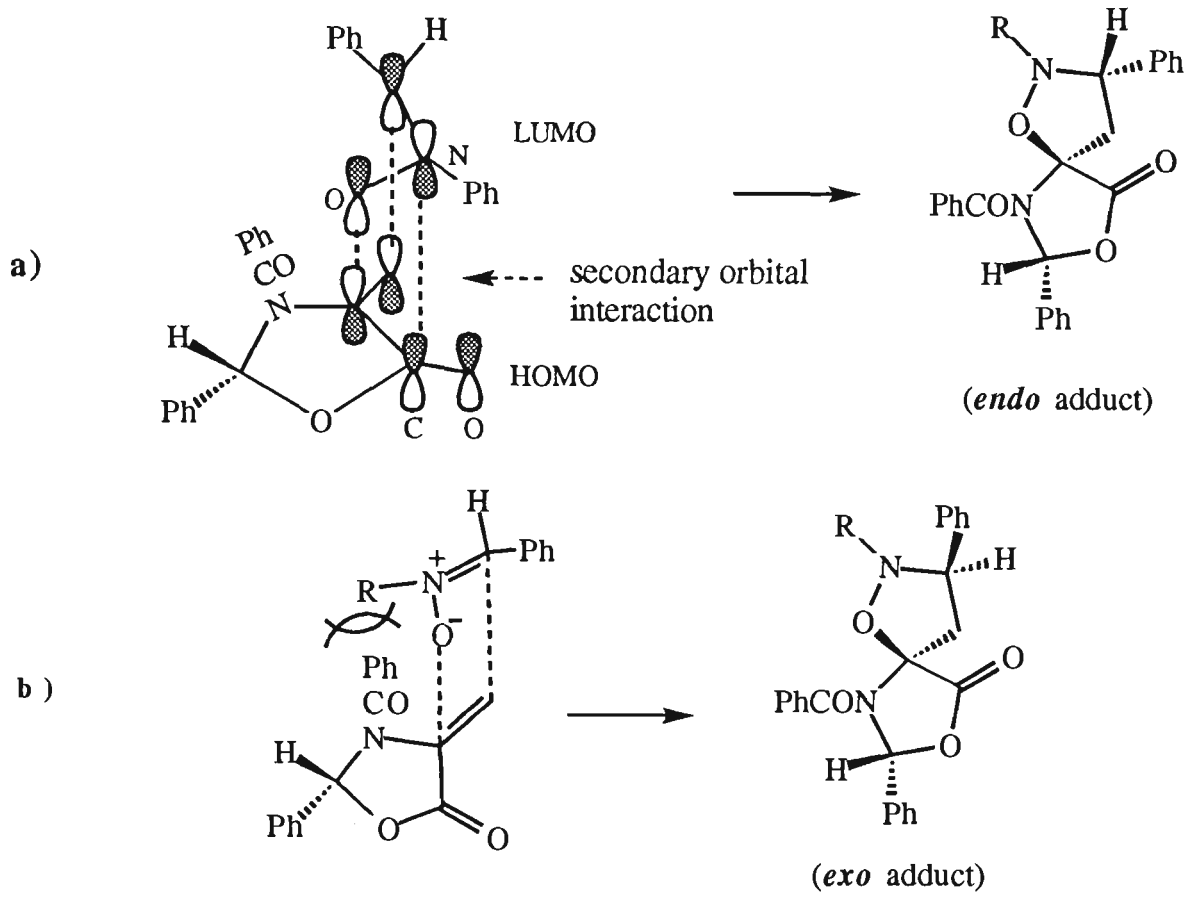
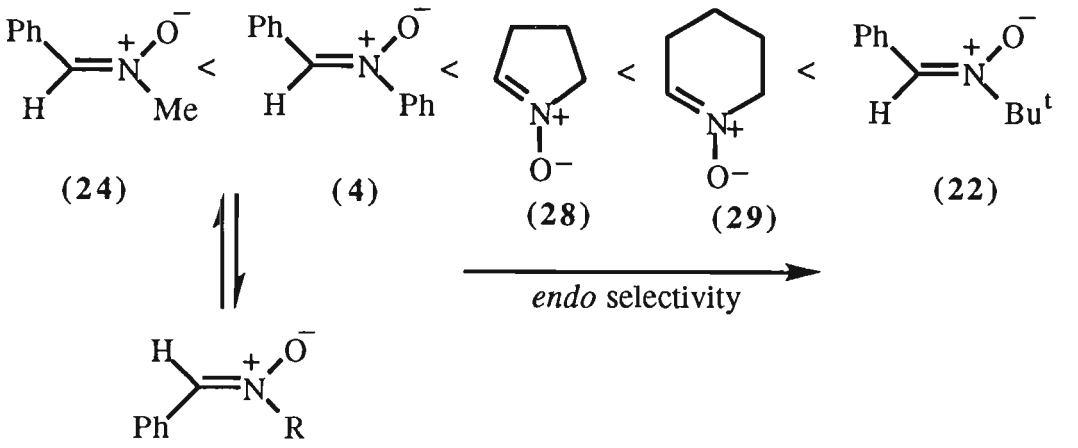


Figure 3.14. **a)** *Endo* and **b)** *exo* transition state structures for the reaction of (14) and nitrones.

While steric and orbital interactions can explain the preference for *endo* type cycloadducts in the reactions of (14) with 1,3-dipoles, some of the major (eg.(30) and(31)) and most of the minor adducts appear to be formed under reversible, thermodynamically controlled conditions.

The formation of the *exo* adducts (25b) and (25c) from the reaction of (14) with *C*-phenyl-*N*-methyl nitrone (24) may be due to the possibility that the more stable (*Z*)-form of the nitrone is in equilibrium with a small amount of the less stable (*E*)-isomer.[108] Adducts (25b) and (25c) may be derived from the reaction of the (*E*)-form of the nitrone with (14) via an *endo* transition state. (*Z*) to (*E*) isomerization of the nitrones (4) and (22) would be expected to be less likely for steric reasons, while such an isomerization is not possible for cyclic nitrones (28) and (29).

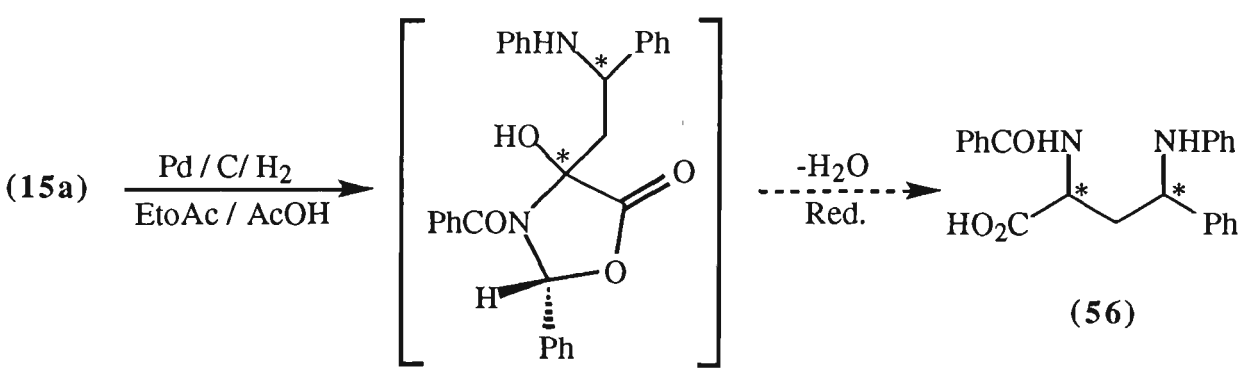
From the above considerations, the *endo / exo* ratio of dipolar cycloadducts with our nitrones would be expected to vary according to the following series, which is consistent with our experimental findings.



3-6. Attempted Synthesis of γ-Amino-α-Amino Acids

As it was mentioned in Section 3-1. there are various methods to reduce the nitrogen-oxygen bond in isoxazolidines to give synthetically useful compounds. Catalytic hydrogenation of the cycloadduct (15a) was carried out over palladium on carbon in acetic acid and ethyl acetate solution under an atmosphere of hydrogen with the aim of preparing γ-amino-α-amino acid (56) (Scheme 3.22). Unfortunately these reaction conditions gave a mixture of compounds that were difficult to separate and characterise.

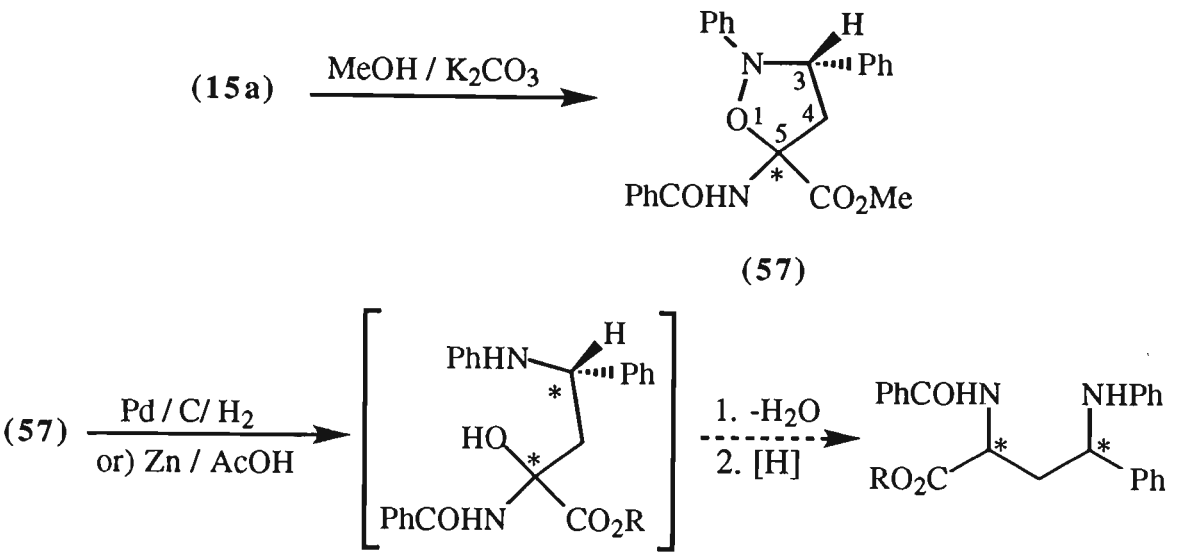
Scheme 3.22



The reaction of (15a) with methanol and potassium carbonate produced the methyl ester (57) (Scheme 3.23) as a mixture of two diastereoisomers.

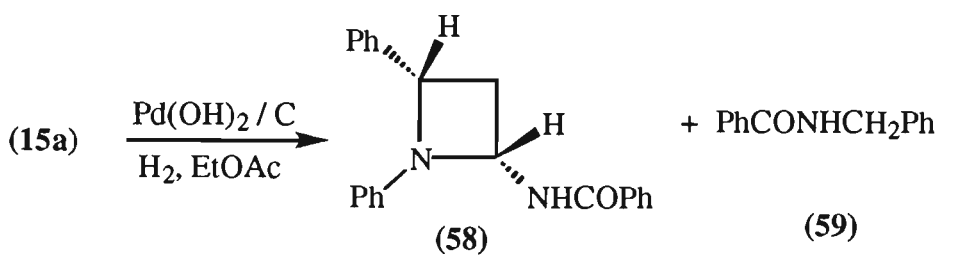
Catalytic hydrogenation of compound (57) over palladium on carbon or with zinc in the presence of acetic acid with the purpose of preparing a γ-amino-α-amino acid (Scheme 3.23) was also disappointing. Likewise, hydrogenation of a mixture of (16) and (17) gave a complex mixture of products.

Scheme 3.23



However, treatment of (15a) under catalytic hydrogenation / hydrogenolysis conditions with palladium hydroxide on carbon under an atmosphere of hydrogen gave the unexpected *cis*-1,4-diphenyl-2-benzoylazethane (58) in 30% yield and *N*-benzylbenzamide (59) in 47% yield (Scheme 3.24).

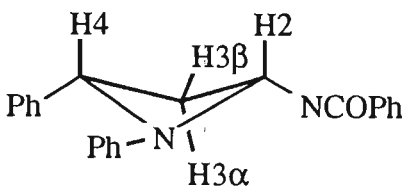
Scheme 3.24



The structure of (58) was evident from ^{1}H and ^{13}C NMR and MS and HRMS spectral analysis. The *cis*-stereochemistry of (58) was determined by analysis of the coupling constants for H2, H3α, H3β, H4 in the ^{1}H

NMR spectrum of (58) using the known coupling constants of *cis*- and *trans*-2,3-dimethyloxetanes as reference compounds.[118] In these heterocyclic 4-membered ring compounds vicinal coupling constants for *cis* protons are generally larger (7.25-8.65 Hz) than those for *trans* protons (5.61-6.65 Hz). The geminal coupling constant $J_{3\alpha,3\beta}$ in (58) is consistent with that typically found oxetanes (10.77-11.15 Hz).[118] The selected ^1H NMR data for (58) in $CDCl_3$ solution are outlined in Scheme 3.25.

Scheme 3.25

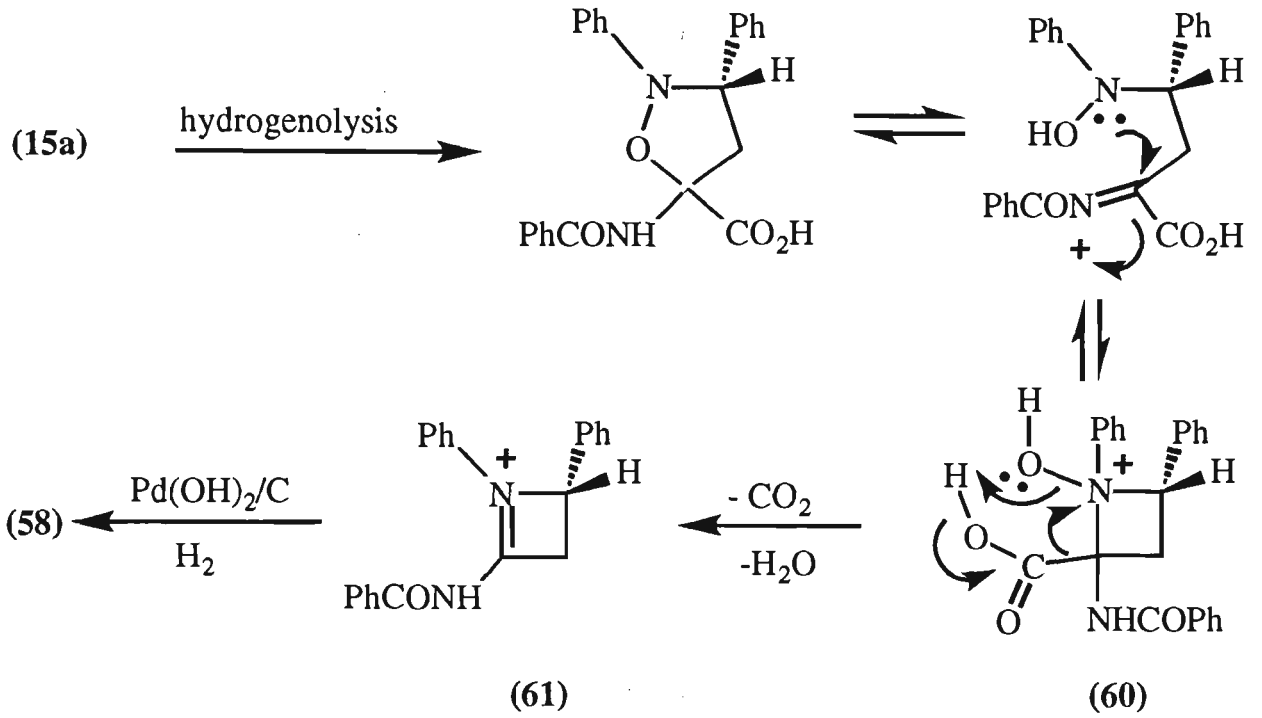


(58)

chemical shift δ	coupling constant (Hz)
H2, 5.27	$J_{2,3\alpha}$ 6.4
H3α, 3.30	$J_{2,3\beta}$ 9.6
H3β, 2.00	$J_{3\alpha,3\beta}$ 12.8
H4, 4.27	$J_{3\alpha,4}$ 7.6
	$J_{3\beta,4}$ 10.4

A possible mechanism for the formation of (58) is given in Scheme 3.26. The proposed mechanism involves, hydrogenolysis of (15a), followed by ring closure to the azethanium ion (60). Carboxy-hydroxy-elimination[119] then gives the azethenium ion (61) which undergoes addition of hydrogen from the least hindered π-face of the iminium group of (61) to give the *cis*-1,4-disubstituted product (21) (Scheme 2.26). Unfortunately related azethane products could not be isolated upon hydrogenolysis / hydrogenation of the adducts (23a) and (30).

Scheme 2.26



3-7. Conclusions

The 1,3-dipolar cycloaddition reactions of (14) and nitrones generally occur under equilibrating conditions to give the more stable adducts that result from addition to the *exo*-cyclic methylene of (14) from the sterically more hindered π-face. These reactions are highly regioselective and only 5,5-disubstituted isoxazolidines are formed. The regiochemistry of these reactions can be explained by electronic and steric factors. The *endo* adducts are generally kinetically and thermodynamically favoured. In one case the novel azethane (58) was formed from the treatment of the adduct (15a) with palladium hydroxide on carbon under a hydrogen atmosphere. The major adducts from the reaction of (14) and nitrile oxides (2) and (37) had the expected stereochemistry, addition of the 1,3-dipole occurred from the least hindered π-face of the *exo*-cyclic methylene of (14).

EXPERIMENTAL

CHAPTER THREE

General experimental procedures were as described in the Experimental Section of Chapter Two.

The nitrones (4) and (24) were prepared by condensation of benzaldehyde with the appropriate *N*-hydroxyl amine.[100,101] *N*-Phenylhydroxylamine (26) and *syn*-benzaldoxime (45) were prepared following the procedures from *'Vogel's Practical Organic Chemistry'*.[107a] Pyrrolidine and piperidine nitrones (28, 29) were prepared by oxidation of their related secondary cyclic amines with hydrogen peroxide.[99] All NMR spectra were measured in $CDCl_3$ solution. ^1H NMR of some of compounds have been run at high temperature because at ambient temperature the NMR signals were very broad due to restricted rotation about the amide C-N bond. All crystalline compounds were crystallized from ethyl acetate / hexane unless otherwise stated.

X-ray Structure Determinations.

Unique diffractometer data sets were measured at ~ 295 K; ($2\theta_{max}$, as specified; $2\theta/\theta$ scan mode; monochromatic Mo Kα radiation, $\lambda = 0.71073$ Å) yielding *N* independent reflections, N_o of these with $I > 3\sigma(I)$ being considered 'observed' and used in the full matrix least squares refinement without absorption correction. Anisotropic thermal parameters were refined for the non-hydrogen atoms; $(x, y, z, U_{iso})_H$ were included constrained at estimated values. Conventional residuals R, R_w on $|F|$ at convergence are given (statistical weights, derivative of $\sigma^2(I) = \sigma^2(I_{diff}) + 0.0004\ \sigma^4(I_{diff})$. Neutral atom complex scattering factors were used; computation used the XTAL 3.2 program system, implemented by S. R. Hall. Individual variations in procedure or anomalous features are noted where applicable ('variata'). Pertinent results are given in the Figures (20% thermal ellipsoids for the non-hydrogen atoms; arbitrary radii of 0.1 Å for H). The common (crystallographic) numbering adopted for the molecular

core is as follows, with a common chirality for the oxazolidinone ring and substituents, the 2-Ph substituent lying away from the reader. Where the material is optically active, the chirality adopted is drawn from the chemistry.

Crystal / refinement data.

(15a). $C_{30}H_{24}N_2O_4$, M = 476.5. Monoclinic, space group $P2_1$ (C_2^2, No.4); a = 10.06(1), b = 5.79(1), c = 21.398(7) Å, β = 95.42(7)°, V = 1241 Å^3. D_c (Z = 2) = 1.28 g.cm.$^{-3}$; F(000) = 500. μ_{Mo} = 0.9 cm^{-1}; specimen: 0.25 x 0.85 x 0.42 mm, $2\theta_{max}$ = 50°; N = 2401, N_o = 1633; R = 0.065, R_w = 0.067.

'*Variata*'. -Linewidths were very broad, and the optimum specimen from recrystallized material was used without cutting.

(23a). $C_{28}H_{28}N_2O_4$. 1/3 $CH_3CO_2C_2H_5$, M = 485.9. Trigonal, space group $P3_2$ (C_3^3, (No.145); a = 15.023(6), c=10.656(6) Å, V = 2084 Å^3. D_c (Z = 3) = 1.16 g.cm.$^{-3}$; F(000) = 774. μ_{Mo} = 0.8 cm^{-1}; specimen: 0.80 x 0.50 x 0.38 mm. $2\theta_{max}$ = 45°; N = 3193, N_o = 1908; R = 0.055, R_w = 0.052.

'*Variata*'. - Steady deterioration of the periodic standards of, ultimately, ~6% was compensated for by appropriate scaling. The solvent comprises a disordered array about the symmetry axis.

(23b). $C_{28}H_{28}N_2O_4$, M = 456.6. Monoclinic, space group $P2_1/c$ (C_{2h}^5, No.14); a = 12.005(6), b = 7.906(6), c = 26.73(1) Å, β = 105.08(4)°, V = 2450 Å^3. D_c (Z = 4) = 1.24 g.cm.$^{-3}$; F(000) = 968. μ_{Mo} = 0.8 cm^{-1}; specimen: 0.75 x 0.38 x 0.21 mm. $2\theta_{max}$ = 50°; N = 4311, N_o = 2619; R = 0.041, R_w = 0.042.

'*Variata*'. -(x, y, z, U_{iso})$_H$ were all refined.

(25c). $C_{25}H_{22}N_2O_4$, M = 414.5 Orthorhombic, space group $P2_12_12_1$ (D_2^4, No.19); a = 16.215(6), b = 12.913(5), c = 10.198(5) Å, V = 2135 Å^3. D_c (Z = 4) = 1.29 g.cm.$^{-3}$; F(000) = 872. μ_{Mo} = 0.9 cm^{-1}; specimen: 0.60 x 0.45 x 0.40 mm. $2\theta_{max}$ = 60°; N = 3477, N_o = 1647; R = 0.039, R_w = 0.036. '*Variata*'.-(x, y, z, U_{iso})$_H$ were all refined.

(25d). $C_{25}H_{22}N_2O_4$, M = 414.5. Triclinic, space group $P\bar{1}$ (C_i^1, No.2); a = 12.11(1), b = 10.361(4), c = 10.133(4) Å, α = 94.91(3), β = 108.24(5)°, γ = 112.26(5)°, V = 1087 Å^3. D_c (Z = 2) = 1.27 g.cm.$^{-3}$; F(000) = 436. μ_{Mo} = 0.8 cm^{-1}; specimen: 0.30 x 0.32 x 0.40 mm. $2\theta_{max}$ = 50°; N = 3810, N_o = 2424; R = 0.041, R_w = 0.042.
'Variata'. -(x, y, z, Ui_{so})$_H$ were all refined.

(30). $C_{21}H_{20}N_2O_4$, M = 364.4. Orthorhombic, space group $P2_12_12_1$; a = 16.868(4), b = 13.294(2), c = 8.006(2) Å, V = 1795 Å^3. D_c (Z = 4) = 1.35 g.cm^{-3}; F(000) = 768. μ_{Mo} = 0.9 cm^{-1}; specimen: 0.065 x 0.60 x 0.27 mm. $2\theta_{max}$ = 60°; N = 2963, N_o = 2342; R = 0.038, R_w = 0.040.
'*Variata*'.-(x, y, z, Ui_{so})$_H$ were all refined.

(31). $C_{22}H_{22}N_2O_4$, M = 378.4. Monoclinic, space group $P2_1$; a = 9.408(4), b = 8.610(3), c = 11.720(2) Å, β = 90.19(2)°, V = 949.2 A3. D_c (Z = 2) = 1.32 g.cm.$^{-3}$; F(000) = 400. μ_{Mo} = 0.9 cm^{-1}; specimen: 0.38 x 0.27 x 0.08 mm. $2\theta_{max}$ = 45°; N = 1348, N_o = 951; R = 0.045, R_w = 0.033. '*Variata*'.-Distinction between the nitrogen atom at N(8) and possible alternative sites was made on the basis of refinement behaviour. 'Observed' criterion : $I > 2\sigma(I)$.

(38a). $C_{24}H_{18}N_2O_4$, M = 398.4. Monoclinic, space group $P2_1$; a = 12.820(4), b = 7.994 (5), c = 10.111 (7) A, β = 102.17 (4)°, V = 1013 Å^3. D_c (Z = 2) = 1.31 g.cm.$^{-3}$; F (000) = 416. μ_{Mo} = 0.9 cm^{-1}; specimen: 0.45

x 0.27 x 0.15 mm. $2\theta_{max}$ = 50°; N = 1992, N_o = 1236; R = 0.039, R_w = 0.037.
'*Variata*'.-(x, y, z, Ui_{so})$_H$ were all refined.

(39b). $C_{24}H_{18}N_2O_4$, M = 398.4. Orthorhombic, space group $P2_12_12_1$; a = 16.38 (1), b = 15989 (7), c = 7.631 (3) Å, V = 1998 Å^3. D_c (Z = 4) = 1.32 g.cm.$^{-3}$; F(000) = 832. μ_{Mo} = 0.9 cm^{-1}; specimen: 0.40 x 0.11 x 0.75 mm. $2\theta_{max}$ = 50°; N = 2018, N_o = 1361; R = 0.042, R_w = 0.043.
'*Variata*'.-(x, y, z, Ui_{so})$_H$ were all refined.

(38b). $C_{19}H_{16}N_2O_4$, M = 336.4. Orthorhombic, space group $P2_12_12_1$; a = 12.298 (5) , b = 12.274 (4), c = 10.824 (5) Å, V = 1634 Å^3. D_c (Z = 4) = 1.37 g.cm.$^{-3}$; F(000) = 704. μ_{Mo} = 1.0 cm^{-1}; specimen: 0.35 x 0.32 x 0.18 mm. $2\theta_{max}$ = 50°; N = 1656, N_o = 1262; R = 0.049, R_w = 0.051.
'*Variata*'.-(x, y, z, Ui_{so})$_H$ were all refined.

Structural commentary. The results of the room temperature single crystal X-ray studies are presented above, and in summary in Figures 3.1, 3.2, 3.4, 3.6 and 3.7. In all cases, the asymmetric unit is a single molecule, with stoichiometries and connectivities consistent with the above formulations; in most cases hydrogen atoms have been located and refined in (x, y, z, U_{iso}). The crystals of (23b) and (25d), belonging to centro symmetric space groups are racemic, presumably consequent of relative insolubility and less than 100% optical purity of the sample; the remainder crystallize in polar space groups, so that, at least within the single crystal studied, all molecules have the same chirality. Presentation of the results follows adoption of the common chirality of the parent oxazolidinone (14) with the *ad hoc* common numbering scheme for the common bicyclic core given above; in cases, ring 21 lies away from the reader and is assigned a negative sign in the description of deviations from the associated

heterocycle, while substituents of the other fused ring are assigned positive deviations if directed toward O(5). The following comments may be made:

The parent oxazolidinone ring is effectively planar throughout the series of compounds studied, the higher χ^2 values lying generally among the more precisely determined members; in no case does the deviation of any defining atom from the ring plane exceed 0.065 Å. Distances within the ring do not vary non-trivially although it may be no accident that C(2)-N (3) in (38a,b) and (39a) exhibit the longest values associated with this parameter; the endocyclic angles are similarly uniform. The exocyclic angles at N(3) are essentially equivalent in (31) and (38a); in the remainder, in which the carbonyl disposition is reversed, they become quite unsymmetrical, C(4)-N(3)-C(3) being much the larger. At C(5), the exocyclic angle C(4)-C(5)-O(5) is slightly larger than O(1)-C(5)-O(5) throughout the series. C(6)-C(4)-O(9) varies over a range of about 3°, being smallest in (38a,b) and (39a) (and, perhaps, (15a)); variations of similar magnitude are found among the other exocyclic angles at C(4). Some variation is observed in the deviation of O(5) from the ring plane, also in that for C(21); the plane of phenyl 2 lies effectively to the ring throughout the series. Carbonyl 3 plane lies quasi-coplanar with the ring, while the associated phenyl ring lies quasi-normal and quasi-parallel to the fused ring ((31) and (39a) excepted). Angles about C(3) vary only slightly throughout the series N(3)-C(3)-C(37) being consistently just less than 120°, as might be expected from electron pair repulsion theory, while the others are slightly greater.

The other ring plane lies quasi-normal to the first, as might be expected, in most cases (excluding (38a,b) and (39a)) adopting a quasi 'envelope' conformation with C(7) the deviant atom; the fused ring in 31 is a chair, while in 30 it is a pseudo envelope, with C(10) deviant. About C(7), the

non-hydrogen angle sum is generally close to 326°, as also N(8), where (excepting 38a,b, 39a) the spread is rather greater (323-331°).

C, N-Diphenylnitrone (4)

A solution of *N*-phenylhydroxylamine (19.85 g, 0.18 mol) and benzaldehyde (18.3 g, 0.18 mol) in the minimum amount of ethanol was allowed to stand at room temperature overnight. The crystalline precipitates were filtered and recrystallized from benzene to afforded the nitrone (4) (32 g, 90%), as white crystals. M.p. 114 °C (lit.[100a,b] 114-115 °C).

***C*-Phenyl-*N*-methylnitrone (24)**

Freshly distilled benzaldehyde (5 g, 47.1 mmol) was added to a solution of *N*-methyl hydroxylamine hydrochloride (27) (4.97 g, 59.5 mmol) in CH_2Cl_2 (60 mL). Sodium bicarbonate (12.43 g) was added and the reaction mixture was refluxed at 80 °C for 10 hr. The mixture was cooled, filtered and washed with CH_2Cl_2 (10 mL). After evaporating the solvent the yellow crystals that remained were recrystallized from ethyl acetate / hexane (4.5 g, 71%). M.p. 83-85 °C (lit.[101] 84-86 °C). ^{1}H NMR δ 8.21 (dd, J = 3.6, 7.6 Hz, 2H), 7.42 (m, 3H), 7.37 (s, 1H, CH=N), 3.9 (s, 3H, CH_3).

Preparation of Pyrolidine nitrone (28) and Piperidine nitrone (29).[99]

The secondary cyclic amine (100 mmol) was added to a solution of sodium tungstate dihydrate (1.32 g, 4 mmol) in water (20 mL) under nitrogen. The mixture was then cooled to -5 °C and a solution of aqueous hydrogen peroxide (34%, 20 mL, 200 mmol) was added dropwise over a period of 60 min. During the period of addition the reaction mixture was kept below 20 °C. The mixture was stirred at room temperature for 3 hr. Excess

hydrogen peroxide was decomposed by addition of sodium hydrogen sulfite (1.5 g) with ice cooling. (The presence of hydrogen peroxide was detected with potassium iodide-starch test paper). The solution was saturated by sodium chloride (15 g) and extracted with ten portions (100 mL) of CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$. The drying agent was removed by filtration, and the solvent was removed by a rotatory evaporator keeping the temperature at 40 °C to give a pale yellow oil.

(28): 3.5 g (41%), ^{1}H NMR δ 6.93 (s, 1H, CH=N), 3.95 (m, 2H), 3.41 (m, 4H).

(29): 4.5 g (45%), ^{1}H NMR δ 7.29 (s, 1H, CH=N), 3.81 (m, 2H), 3.42 (m, 2H), 2.50 (m, 4H).

1,3-Dipolar Cycloaddition Reactions of (14) and Nitrones, A General Procedure:

A solution of (14) (225 mg, 0.8 mmol) and the nitrone (0.88 mmol) in dichloromethane (3 mL) under nitrogen was stirred at room temperature or 60 °C in a sealed tube under an atmosphere of nitrogen for several days, as reported in Table 3.1, page 110. The solution was then cooled and evaporated to dryness. The crude products were purified by column chromatography on silica gel using ethyl acetate / hexane (10-20 / 90-80) as the eluent or by fractional crystallisation. The diastereoselection of these reactions were determined from ^{1}H NMR (400 MHz) analysis of the crude reaction product.

(2'*R*,3*S*,5*S*) and (2'*R*,3*R*,5*S*)-2,3-Diphenylisoxazolidine-5-spiro-4'-(3'-benzoyl-2'-phenyl)oxazolidin-5'-one (15a) and (15b).

The two diastereoisomers were separated by fractional crystallization from ethyl acetate / hexane.

(15a): M.p. 160-1 °C dec; $[\alpha]_D^{27}$ -44.6 (*c* 0.55 in $CHCl_3$). ^1H NMR δ 7.53-6.97 (m, 20H), 6.95 (s, 1H, H2'), 4.93 (dd, 1H, J = 6.0, 11.4 Hz, H3), 3.32 (1H, bt, J = 11.4, 12.6 Hz, H4), 2.99 (dd, 1H, J = 6.0, 12.6 Hz, H4). ^{13}C NMR δ 170.5 (CO), 170.1 (CO), 149.2, 137, 135.9, 135.7, 130.2, 130.1, 128.9, 128.7, 128.6, 128.4, 128.3, 127.5, 127.4, 126.4, 125, 119.6, 89.6 (C2'), 88.8 (C5), 72.1 (C3), 47.5 (C4). IR (nujol) 1765, 1660, 1580, 1470, 1338, 1283, 1178, 1135, 1075, 1003, 743, 690 cm^{-1}. MS (ES) *m/z* 477 (16%, MH^+), 268 (100). Anal. Calcd for $C_{30}H_{24}N_2O_4$: C, 75.6; H, 5.1; N, 5.9%. Found: C, 75.85; H, 4.95; N, 5.65%.

(15b): M.p. 145-6 °C dec; $[\alpha]_D^{27}$ +198.7 (*c* 0.23 in $CHCl_3$). ^1H NMR δ (at 55 °C) 7.46-6.96 (m, 15H), 6.77 (s, 1H, H2'), 4.29 (bt, J = 8.4 Hz, 1H, H3), 3.53 (dd, J = 7.6, 12.8 Hz, 1H, H4), 3.23 (dd, J = 9.6, 12.8 Hz, 1H, H4). ^{13}C NMR δ 170 (CO), 169.7 (CO), 148.1, 138.3, 135.7, 135.5, 130.6, 130.1, 128.84, 128.8, 128.44, 128.4, 128.2, 127.9, 126.7, 126.6, 124.8, 119.7, 89.5 (C2'), 87.7 (C5), 69.4 (C3), 47.4 (C4). IR (nujol) 1778, 1655, 1580, 1482, 1333, 1160, 1010, 758, 687 cm^{-1}. MS (ES) *m/z* 477 (70%, MH^+), 314 (37), 268 (100).

(2'*R*,3*S*,5*S*) and (2'*S*,3*S*,5*S*)-2-*tert*-Butyl-3-phenylisoxazolidine-5-spiro-4'-(3'-benzoyl-2'-phenyl)oxazolidin-5'-one (23a) and (23b).

(23a): M.p. 112 °C; $[\alpha]_D^{24}$ -84.6 (*c* 1.0 in $CHCl_3$). ^1H NMR δ 7.61-6.84 (m, 15H), 6.95 (s, 1H, H2'), 4.67 (dd, J = 6.0, 11.6 Hz, 1H, H3), 2.94 (bt, J = 11.6, 12.6 Hz, 1H, H4), 2.78 (dd, J = 6.0, 12.6 Hz, 1H, H4), 0.95 (s, 9H, $3CH_3$). ^{13}C NMR δ 170.8 (CO), 170.3 (CO), 140, 136.3, 135.7, 130, 129.9, 128.9, 128.33, 128.27, 127.9, 127.6, 127.2, 126.3, 89.0 (C2'), 87.8 (C5), 64.7 (C3), 60.0 ($\underline{C}(CH_3)_3$), 50.0 (C4), 26.4 ($C(\underline{C}H_3)_3$). IR (nujol) 1785, 1642, 1368, 1342, 1251, 1222, 1140, 1012, 761, 732, 692 cm^{-1}. MS (ES) *m/z* 457 (100%, MH^+). Anal. Calcd for $C_{28}H_{28}N_2O_4$: C, 73.7; H, 6.2; N, 6.1%. Found: C, 74.0; H, 6.2; N, 5.8%.

(23b): M.p. 146-7 °C; $[\alpha]_D^{24}$ -4.0 (*c* 0.4 in $CHCl_3$). ^1H NMR δ (at 55 °C) 7.84-6.81 (m, 15H), 6.93 (s, 1H, H2'), 4.73 (dd, J = 6.0, 11.0 Hz, 1H, H3), 2.65 (dd, J = 11, 13.2 Hz, 1H, H4), 2.56 (dd, J = 6.0, 13.2 Hz, 1H, H4), 1.05 (s, 9H, $3CH_3$). ^{13}C NMR δ 170.2 (CO), 170.1 (CO), 139.6, 135.9, 134.8, 131.6, 130, 129.5, 128.7, 128.5, 128.3, 127.6, 127.2, 127.1, 88.9 (C2'), 87.5 (C5), 64.6 (C3), 60.0 ($\underline{C}(CH_3)_3$), 48.5 (C4), 26.4 ($C(\underline{C}H_3)_3$). IR (nujol) 1768, 1627, 1446, 1350, 1255, 1226, 1142, 1025, 721, 687 cm^{-1}. MS (ES) *m/z* 457 (100%, MH^+), 284 (14).

(2'*R*,3*S*,5*S*), (2'*R*,3*R*,5*S*), (2'*R*,3*S*,5*R*) and (2'*R*,3*R*,5*R*)-2-Methyl-3-phenylisoxazolidine-5-spiro-4'-(3'-benzoyl-2'-phenyl)oxazolidin-5'-one (25a), (25b), (25c) and (25d).

(25a): ^1H NMR δ (in part) 7.72-6.96 (15H, m), 6.82 (s, 1H, H2'), 4.23 (dd, J = 5.6, 11.2 Hz, 1H, H3), 3.45 (bt, J = 12.6 Hz, 1H, H4), 2.87 (dd, J = 5.6, 12.8 Hz, 1H, H4), 2.63 (s, 3H, CH_3).

(25b): ^1H NMR δ (in part) 7.72-6.96 (15H, m), 6.77 (s, 1H, H2'), 3.30 (dd, J = 6.0, 12.0 Hz, 1H, H3), 3.1.0 (bt, J = 12.0 Hz, 1H, H4), 2.90 (m, 1H, H4), 2.56 (s, 3H, CH_3).

(25c): M.p. 166-8 °C; $[\alpha]_D^{25}$ +30.2 (*c* 0.42 in $CHCl_3$). ^1H NMR (at 60 °C) δ 7.53-7.24 (m, 15H), 6.75 (s, 1H, H2'), 3.38 (bs, 1H, H3), 2.94 (dd, J = 10.4, 13.0 Hz, 1H, H4), 2.84 (dd, J = 6.8, 13.0 Hz, 1H, H4), 2.68 (s, 3H, CH_3). ^{13}C NMR δ 170.2 (CO), 169.6 (CO), 137, 135.5, 135.1, 131.2, 130.1, 128.7, 128.6, 128.42, 128.41, 128.1, 127.8, 127.2, 89.1 (C2'), 86.7 (C5), 72.4 (C3), 46.2 (C4), 42.8 (CH_3). IR (nujol) 1780, 1648, 1475, 1350, 1268, 1145, 1035, 697 cm^{-1}. MS (ES) *m/z* 415 (100%, MH^+), 288 (37), 210 (75). Anal. Calcd for $C_{25}H_{22}N_2O_4$: C, 72.5; H, 5.35; N, 6.8%. Found: C, 72.9; H, 5.4; N, 6.5%.

(25d): M.p. 150-2 °C; $[\alpha]_D^{26}$ -16.7 (*c* 0.15 in $CHCl_3$). ^1H NMR (at 55 °C) δ 7.72-6.96 (m, 15H), 6.88 (s, 1H, H2'), 4.28 (dd, J = 6.0, 11.8 Hz, 1H, H3), 2.92 (bt, J = 11.8, 12.6 Hz, 1H, H4), 2.71 (s, 3H, CH_3), 2.64 (dd, J 6.0, 12.8 Hz, 1H, H4). ^{13}C NMR δ 170.7 (CO), 170.0 (CO), 136.0, 135.7, 134.8, 131.45, 130.1, 128.72, 128.71, 128.6, 128.5, 128.4, 127.8, 127.2, 89.5 (C2'), 88.8 (C5), 73.8 (C3), 46.1 (C4), 44.3 (CH_3). IR (nujol) 1779, 1635, 1480, 1345, 1315, 1268, 1145, 1035, 692 cm^{-1}. MS (ES) *m/z* 415 (100%, MH^+), 341 (9), 288 (8), 136 (20).

(2*R*,3a*R*,2'*R*)2,3,3a,4,5,6,-Hexahydropyrrolo[1,2-b]isoxazole-2-spiro-4'-(3'-benzoyl-2'-phenyl)oxazolidin-5'-one (30).

M.p. 142-4 °C dec.; $[\alpha]_D^{25}$ +35.5 (*c* 0.2 $CHCl_3$). ^1H NMR (at 55 °C) δ 7.42-7.25 (m, 10H), 6.67 (s, 1H, H2'), 3.70 (bs, 1H, H3a), 3.51 (m, 1H, H6), 3.25 (m, 1H, H6), 2.87 (dd, J = 8.0, 13.6 Hz, 1H, H3), 2.66 (dd, J = 7.6, 13.6 Hz, 1H, H3), 2.12 (m, 1H, H4), 1.90 (m, 2H, H5), 1.71 (m, 1H, H4). ^{13}C NMR δ 171.2 (CO), 169.3 (CO), 135.4, 135.1, 131.1, 130.1, 128.7, 128.5, 127.3, 127.2, 92.7 (C2), 89.7 (C2'), 65.9 (C3a), 56.5 (CH_2), 45.3 (CH_2), 29.3 (CH_2), 22.0 (CH_2). IR (nujol) 1772, 1646, 1380, 1268, 1150, 1025, 718, 692 cm^{-1}. MS (ES) *m/z* 365 (100%, MH^+), 86 (20). Anal. Calcd for $C_{21}H_{20}N_2O_4$: C, 69.2; H, 5.5; N, 7.7%. Found: C, 68.8; H, 5.6; N, 7.5%.

(2*R*,3a*R*,2'*R*)3,3a,4,5,6,7-Hexahydro-2H-isoxazolo[2,3-a]-pyridine-2-spiro-4'-(3'-benzoyl-2'-phenyl)oxazolidin-5'-one (31) and minor isomer.

The two diastereoisomers were separated by fractional crystallisation from ethyl acetate / hexane and or by column chromatography on silica gel using ethyl acetate / hexane as eluent.

(30): M.p. 155-7 °C dec; $[\alpha]_D^{27}$ +77.7 (*c* 0.3 in $CHCl_3$). ^1H NMR (at 55 °C) δ 7.41-7.25 (m, 10H), 6.63 (s, 1H, H2'), 3.52 (m, 1 H), 2.7 (m, 2H),

2.57 (bs, 1H), 1.9-1.6 (m, 6H), 1.25 (t, J = 7.2 Hz, 1H). ^{13}C NMR (broad signals were observed) δ 170.1 (CO), 169.5 (CO), 135.9, 135.5, 130.2, 130.1, 128, 127.9, 127.5, 127.4, 89.0, 86.1, 66.0, 55.2, 42.0, 28.8, 24.0, 23.8. IR (nujol) 1770, 1658, 1340, 1285, 1160, 1021, 758, 690 cm^{-1}. MS (ES) *m/z* 379 (100%, MH^+), 288 (16), 209 (11). Anal. Calcd for $C_{22}H_{22}N_2O_4$: C, 69.8; H, 5.9; N, 7.4%. Found: C, 69.5; H, 5.85; N, 7.1%.

minor isomer: M.p. 46-8 °C; $[\alpha]_D^{29}$ -10.0 (*c* 0.15 in $CHCl_3$). ^1H NMR (at 55 °C) δ 7.35-7.00 (m, 10H), 6.67 (s, 1H, H2'), 3.43 (m, 1H), 2.93 (dd, J = 6.0, 12.0 Hz, 1H), 2.68 (bs, 1H), 2.58 (m, 1H), 2.41 (m, 1H), 1.87 (m, 1H), 1.71 (m, 4H), 1.27 (bs, 1H). ^{13}C NMR (broad signals were observed) δ 170.1 (CO), 169.4 (CO), 136.3, 135.4, 129.9, 128.7, 128.6, 128.3, 127.3, 126.7, 103.4, 89.3 (CH), 65.8, 54.9, 42.1, 28.9, 24.6, 23.6. IR (nujol) 1780, 1660, 1320, 1240, 1155, 1080, 1015, 770, 680 cm^{-1}. MS (FAB) *m/z* 379 (15%, MH^+), 247 (80), 230 (71), 188 (90).

(3*S*,5*S*) and (3*S*,5*R*)-5-Benzamido-5-hydroxymethyl-2,3-diphenylisoxazolidine (16) and (17).

To a solution of (25a) (80 mg, 0.17 mmol) in dry methanol (10 mL) and dichloromethane (2 mL) was added sodium borohydride (20 mg). After stirring 16 hr at room temperature the solution was then treated with acetone (3 mL) at 0 °C for 10 min. The solvent was then evaporated. Water (10 mL) was added and the products were extracted into dichloromethane (2 x 10 mL). The extracts were dried ($MgSO_4$) and evaporated. Short-path column chromatography on silica gel gave a 61 : 39 mixture of diastereoisomers (16) and (17) (40 mg, 60%).

^1H NMR (major isomer, in part) δ 7.65-6.98 (m, 15H), 6.66 (bs, 1H, NH), 4.91 (dd, J = 7.2, 9.6 Hz, 1H, H3'), 4.20 (m, 1H, CH_AH_BOH), 4.01 (m, 1H, CH_AH_BOH), 3.68 (bs, 1H, OH), 3.65 (dd, J = 7.6, 12.8 Hz, 1H, H4'), 2.60

(dd, J = 9.6, 12.8 Hz, 1H, H4'). (minor isomer, in part) δ 7.65-6.98 (m, 15H), 6.89 (bs, 1H, NH), 4.63 (dd, J = 6.0, 8.8 Hz, 1H, H3'), 4.18 (m, 1H, $C\underline{H}_AH_BOH$), 4.02 (m, 1H, $CH_A\underline{H}_BOH$), 3.27 (dd, J = 8.8, 13.6 Hz, 1H, H4'), 3.08 (bs, 1H, OH), 2.98 (dd, J = 6.4, 13.6 Hz, 1H, H4'). ^{13}C NMR δ (major isomer, in part) 167.19 (CO), 151.9, 140.3, 133.7, 132, 129.05, 128.9, 128.6, 127.8, 126.9, 126.7, 122.6, 115.3, 94.5, 69.5, 65.4, 45.8. (minor isomer, in part) δ 167.23 (CO), 149.4, 140.1, 133.7, 132.0, 129.02, 128.7, 128.6, 127.8, 126.9, 126.8, 123.5, 117.0, 93.7, 69.8, 65.6, 47.2. MS (ES) *m/z* 375 (35%, MH^+), 254 (100), 180 (25).

MTPA esters (18) and (19) of alcohols (16) and (17).

A solution of (16) and (17) (10 mg, 0.03 mmol) in dichloromethane (0.5 mL) and two drops of dry pyridine at 0 °C was treated with *R*-(-)-α-methoxy-α-trifluoromethylphenylacetylchloride (12 mg, 0.04 mmol). The solution was stirred for 2 hr at room temperature and then the solvent was evaporated. The residue was dissolved in dichloromethane (10 mL) and the solution was washed with 5% aqueous hydrochloric acid, 10% aqueous sodium hydroxide, and then water. The organic layer was dried over $MgSO_4$, filtered and evaporated under reduced pressure to leave an oil. Short-path column chromatography on silica gel gave a 55 : 45 mixture of two diastereoisomers (18) and (19) (10 mg, 61%).

^1H NMR (major isomer, in part) 7.68-6.87 δ (m, 15H), 6.28 (s, 1H, NH), 4.99 (d, J = 12.0 Hz, 1H, $C\underline{H}_AH_BOR$), 4.88 (d, J = 12.0 Hz, 1H, $CH_A\underline{H}_BOR$), 4.23 (t, J = 8.8 Hz, 1H, H3'), 3.54 (s, 3H, OCH_3), 3.09 (bd, J = 8.0 Hz, 2H, H4'/H4'); (minor isomer, in part) δ 7.68-6.87 (m, 15H), 6.73 (s, 1H, NH), 5.05 (d, J = 11.6 Hz, 1H, $C\underline{H}_AH_BOR$), 4.87 (d, J = 12.0 Hz, 1H, H3'), 4.79 (d, J = 11.6 Hz, 1H, $CH_A\underline{H}_BOR$), 3.72 (dd, J = 7.2, 13.0 Hz, 1H, H4'), 3.56 (s, 3H, OCH_3), 2.53 (dd, J = 10.0 Hz, 13.0 Hz, 1H, H4').

(3*S*,5*S*), (3*R*,5*R*), (3*S*,5*R*) and (3*R*,5*R*)-5-Benzamido-5-hydroxymethyl-2,3-diphenylisoxazolidine (16), *ent*-(16), (17), *ent*-(17).

The title compounds were prepared from a 73 : 27 mixture of (15b) and (15a) (50 mg, 0.1 mmol) by treatment with sodium borohydride as described above. Purification of the crude reaction product by column chromatography gave 25 mg (64%) of a 72 : 28 mixture of diastereoisomers that were identical by ^{1}H NMR to the major and minor diastereoisomers, respectively as described above from (15a).

MTPA esters (18), (19), (20) and (21) of alcohols (16), *ent*-(16), (17) and *ent*-(17).

The title compounds were prepared from the mixture of alcohols (16), *ent*-(16), (17) and *ent*-(17) (15 mg, 0.04 mmol) as described above. Purification of the crude reaction mixture by column chromatography gave a mixture of four diastereoisomers (15 mg, 69%).

^{1}H NMR (major isomer, in part) δ 5.08 (d, J = 11.6 Hz, 1H, C$\underline{H}_A$H$_B$OR), 4.80 (d, J = 11.6 Hz, 1H, CH$_A$$\underline{H}_B$OR), 4.36 (t, J = 8.0 Hz, 1H) 3.56 (s, 3H, OCH_3). (second most prominent diastereoisomer, in part) δ 4.95 (d, J = 11.6 Hz, 1H, C$\underline{H}_A$H$_B$OR), 4.86 (d, J = 11.6 Hz, 1H, CH$_A$$\underline{H}_B$OR). MS (ES) *m/z* 591.7 (35%, MH$^+$), 470.5 (23), 102.3 (100). The other two diastereoisomers were (18) and (19).

Preparation of Benzohydroxamoyl Chloride (46).[107b,c]

To a stirred solution of *syn*-benzaldoxime (45) (19g, 0.16 mol) in DMF (150 mL) at 25-30 °C was added about one-tenth of 21.3 g (0.16 mol) of solid NCS. The initial NCS addition resulted in a slight temperature decrease. Because the reaction did not self initiate within 10 min. (It should be initiated with a slight temperature rise) 10 mL of gas from the head space of a concentrated hydrochloric acid reagent bottle was collected

in a syringe and then bubbled into the DMF solution. The reaction initiated after 5 min. The rest of the NCS was added at 25-30 °C by cooling in ice bath. Completion of the reaction was indicated by cessation of the exotherm. The solution was poured into four volume of ice water. The mixture was extracted twice with ether. The combined ether extracts were washed three times with water, dried ($MgSO_4$), concentrated under reduced pressure. The almost colourless residual liquid was dissolved in hexane (100 mL) and cooled in an ice-acetone bath, whereupon a colourless crystalline solid started separating. The cooling was continued for 30 min and the solid was then filtered and washed with cold hexane. The residual solid was dried in desiccator. The yield of benzohydroxamoyl chloride (46) was 12.5 g (50%) with m.p. 48-50 °C (lit.[107c] m.p. 48-52 °C). ^1H NMR δ 9.25 (bs, 1H NOH), 7.7-6.83 (m, 5H). MS (FAB) *m/z* 156 (95%, M^+).

(2'*R*,5*S*) and (2'*R*,5*R*)-3-Phenyl-Δ^2-isoxazolidine-5-spiro-4'-(3'-benzoyl-2'-phenyl)oxazolidin-5'-one (38a) and (39a).

To a solution of (14) (225 mg, 0.8 mmol) and triethylamine (0.11 mL, 0.8 mmol) in dry CH_2Cl_2 (10 mL) was added dropwise a solution of benzohydroxamoyl chloride (128 mg, 0.8 mmol) in CH_2Cl_2 (5 mL) under nitrogen at room temperature. After stirring for 2 hr the solution was washed with water (2 x 20 mL), the organic layer was dried over $MgSO_4$, and the solvent was removed under reduced pressure. ^1H NMR analysis of the crude product revealed a 85 : 15 mixture of diastereoisomers that were separated by column chromatography on silica gel (20% ethyl acetate / hexane) to furnish a mixture of (38a) and (39a) (300 mg, 94%).

(38a): M.p. 130-2 °C; $[\alpha]_D^{26}$ +30.2 (*c* 0.5 in $CHCl_3$). ^1H NMR δ 7.6-7.05 (m, 15H), 6.83 (s, 1H, H2'), 4.13 (d, J = 17.0 Hz, 1H, H4), 4.04 (d, J = 17.0 Hz , 1H, H4). ^{13}C NMR δ 169.9 (CO), 168.5(CO), 155.5 (CN), 135.2,

134.8, 130.7, 130.5, 130.4, 128.9, 128.7, 128.4, 127.9, 127.0, 126.6, 126.2, 91.9 (C5), 89.9 (C2), 43.6 (C4). IR (nujol) 1768, 1655, 1385, 1305, 1255, 1020, 880, 855, 685 cm^{-1}. MS (ES) *m/z* 399 (100%, MH^+), 277 (15), 210 (49), 130 (53). Anal. Calcd for $C_{24}H_{18}N_2O_4$: C, 72.3; H, 4.6; N, 7.0%. Found: C, 72.6; H, 4.7; N, 7.0%.

(39a): M.p. 222-3 °C; $[\alpha]_D^{26}$ +89.5 (*c*, 0.45 in $CHCl_3$). ^1H NMR 7.50-7.20 δ (m, 15H), 6.87 (s, 1H, H2'), 3.86 (d, J = 17.6 Hz, 1H, H4), 3.54 (d, J = 17.6 Hz, 1H, H4). ^{13}C NMR δ 169.1 (CO), 168.4 (CO), 150.6 (CN), 134.8, 134.7, 134.1, 132.3, 131.5, 131.2, 129.5, 128.1, 127.8, 126.5, 126.2, 126.0, 91.6 (C5), 89.3 (C2'), 42.5 (C4). IR (nujol) 1775, 1640, 1580, 1370, 1340, 1265, 1010, 880, 850, 694 cm^{-1}. MS (ES) *m/z* 399 (45%, MH^+), 316 (44), 288 (100).

(5*S*)-5-Benzamido-5-hydroxymethyl-3-phenyl-Δ^2-isoxazoline (43).

The title compound was prepared from (38a) (150 mg, 0.37 mmol) by treatment with sodium borohydride as described for the preparation of (16) and (17). Purification of the crude reaction product by column chromatography gave (43) (120 mg, 51%).

M.p. 72-3 °C; $[\alpha]_D^{28}$ -111.2 (*c* 0.2 in $CHCl_3$). ^1H NMR δ 7.77-7.34 (m, 10H), 7.15 (s, 1H, NH), 4.14 (d, J = 11.1 Hz, 1H, H4'), 4.00 (d, J = 17.4 Hz, 1H, $C\underline{H}_AH_BOH$), 3.92 (bd, 1H, H4'), 3.55 (d, J = 17.4 Hz, 1H, $CH_A\underline{H}_BOH$), 3.44 (bs, 1H, OH). ^{13}C NMR δ 167.3 (CO), 158.2 (CN), 132.1, 130.5, 128.7, 128.6, 128.5, 127.2, 126.9, 126.8, 96.2, (C5'), 65.4 (C4'), 41.2 (C1). MS (ES) *m/z* 319 (83%, MNa^+), 297 (27%, MH^+), 176 (100). Anal. Calcd for $C_{17}H_{16}N_2O_3$: C, 68.92; H, 5.40; N, 9.46%. Found: C, 68.61; H, 5.59; N, 9.06%.

MTPA ester (44) of alcohol (43).

The title compound was prepared from (43) (10 mg, 0.034 mmol) as described for the preparation of (18) and (19). Short-path column chromatography gave a 88 : 12 mixture of two diastereoisomeric MTPA esters (15 mg, 86%).

$[\alpha]_D^{23}$ -48 (*c* 0.2 in $CHCl_3$). ^1H NMR (major isomer, in part) δ 7.71-7.26 (m, 15H), 6.71 (bs, 1H, NH), 4.97 (d, J = 11.6 Hz, 1H, $C\underline{H}_AH_BOR$), 4.83 (d, J = 12 Hz, 1H, $CH_A\underline{H}_BOR$), 4.38 (d, J = 18.0 Hz, 1H, H4'), 3.53 (d, J = 18.0 Hz, 1H, H4'), 3.53 (s, 3H, OCH_3). (minor isomer, in part) 7.71-7.26 δ (m, 15H), 6.73 (bs, 1H, NH), 4.90 (d, J = 11.2 Hz, 1H, $C\underline{H}_AH_BOR$), 4.82 (bd, 1H, $CH_A\underline{H}_BOR$), 4.00 (d, J = 17.6 Hz, 1H, H4'), 3.52 (m, 4H, H4', OCH_3). MS (ES) *m/z* 535 (100%, MNa^+)

(2'*R*,5*S*)-3-Methyl-Δ^2-isoxazolidine-5-spiro-4'-(3'-benzoyl-2'-phenyl)oxazolidin-5'-one (38b).

To a solution of (14) (225 mg, 0.8 mmol), nitroethane (150 mg, 2 mmol), and triethylamine (0.11 mL, 0.8 mmol) in of dry CH_2Cl_2 (5 mL) at room temperature under nitrogen was added a solution of phenyl isocyanate (380 mg, 3.2 mmol) in dichloromethane (3 mL) by syringe over a 2.5 hr period. The reaction mixture was stirred for an additional 2 hr. Water (6 mL) was then added and the mixture was stirred for 3 hr, and then filtered. The layers were separated and the aqueous phase was extracted with dichloromethane. The combined extracts were dried over $MgSO_4$ and concentrated. ^1H NMR analysis of the crude product revealed a 83 : 17 mixture of diastereoisomers. Purification of the mixture by column chromatography on silica gel (30% ethyl acetate / hexane) furnished diastereomerically pure (38b) (110 mg, 41%).

(38b): M.p. 182-3 °C; $[\alpha]_D^{27}$ +52.0 (*c* 0.2 in $CHCl_3$). ^1H NMR δ 7.39-7.00 (m, 10H), 6.75 (s, 1H, H2'), 3.71 (d, J = 17.6 Hz, 1H, H4), 3.61 (d, J = 17.6 Hz, 1H, H4), 1.94 (s, 3H, CH_3). ^{13}C NMR δ 169.8 (CO), 168.6 (CO), 154.3 (CN), 135.2, 134.9, 130.5, 130.3, 128.8, 128.4, 126.6, 126.2, 91.2 (C5), 89.8 (C2'), 46.6 (C4), 12.4 (CH_3). IR (nujol) 1777, 1657, 1408, 1345, 1320, 1241, 1155, 1005, 740, 685 cm^{-1}. MS (ES) 337 (100%, MH^+), 288 (40), 210 (28). Anal. Calcd for $C_{19}H_{16}N_2O_4$: C, 67.85; H, 4.8; N, 8.3%. Found : C, 67.5; H, 4.9; N, 7.95%.

(39b) (in part): ^1H NMR δ 7.39-7.00 (m, 10H), 6.8 (s, 1H, H2'), 3.85 (d, J = 17.6 Hz, 1H, H4), 3.61 (d, J = 17.6 Hz, 1H, H4), 2.08 (s, 3H, CH_3).

Methyl (3*S*,5*S*)-5-benzamido-2,3-diphenylisoxazolidine-5-carboxylate (57a) and Methyl (3*S*,5*R*)-2-benzamido-2,3-diphenylisoxazolidine)-5-carboxylate (57b) .

To a 0 °C solution of (15a) (150 mg, 0.31 mmol) in dry methanol (10 mL) under nitrogen was added powdered anhydrous potassium carbonate (43.5 mg, 0.31 mmol). The mixture was stirred at room temperature for 13 hr. The mixture was then diluted with ethyl acetate (20 mL) and washed with an aqueous solution of saturated ammonium chloride. The aqueous layer was separated and extracted with ethyl acetate (2 x 10 mL). The combined extracts were washed with water, brine, dried ($MgSO_4$) and concentrated in vacuo to give 100 mg (83%) of the two isomers (57a) and (57b) in a ratio of 56 : 44.

^1H NMR (major isomer, in part) δ 7.91-6.92 (m, 15H), 4.94 (dd, J = 7.6, 9.6 Hz, 1H, H3'), 3.91 (s, 3H, CH_3), 3.51 (dd, J = 7.2, 13.2 Hz, 1H, H4'), 3.2 (dd, J = 9.8, 13.2 Hz, 1H, H4'); (minor isomer, in part) δ 7.91-6.92 (m, 15H), 4.81 (bt, J = 7.6 Hz, 1H, H3'), 3.83 (s, 3H, CH_3), 3.68 (dd, J = 7.6, 13.2 Hz, 1H, H4'), 3.02 (dd, J = 9.8, 13.2 Hz, 1H, H4'). MS (ES) *m/z* 403 (19%, MH^+), 282 (100).

(2*R*,4*S*)-1,4-Diphenyl-2-benzoylazethane (58).

A solution of (15a) (150 mg, 0.3 mmol) in ethyl acetate (10 mL) was stirred at room temperature under an atmosphere of hydrogen (1 atm.) for 5 hr in the presence of 20% palladium hydroxide on carbon (50% water) (100 mg). The catalyst was removed by filtration through celite and the solvent was evaporated under reduced pressure. Purification of the crude reaction mixture by column chromatography (silica gel, 20% ethyl acetate / hexane) afforded 1,4-diphenyl-2-benzoylazethane (58) (30 mg, 30%) and *N*-benzylbenzamide (59) (30 mg, 47%).

(58): M.p. 175-7 °C; $[\alpha]_D^{26}$ +71.1 (*c* 0.18 in $CHCl_3$). ^1H NMR δ 7.38-7.00 (m, 15H), 5.27 (dd, J = 6.4 Hz, 1H, 9.6, H2), 4.73 (bs, 1H, NH), 4.27 (dd, J = 7.6 ,10.4 Hz, 1H, H4), 3.30 (ddd, J = 6.4, 7.6, 12.8 Hz, 1H, H3α), 2.00 (ddd, J = 9.6, 10.4, 12.8 Hz, 1H, H3β). ^{13}C NMR δ 173.1 (CO), 147.3, 139.8, 137.1, 129.3, 128.8, 128.6, 128, 126.7, 125.6, 123.3, 118.6, 113.8, 60.8 (C2), 55.9 (C4), 40.7 (C3). MS (ES) *m/z* 329 (100%, MH^+), 182 (15). HRMS found: 329.1647 +/- 0.007. Calcd for $C_{22}H_{20}N_2O$+H: 329.1653.

(59): M.p. 97-100 °C dec (lit.[120] 105-6 °C). ^1H NMR δ 7.80-7.30 (m, 10H), 6.48 (bs, 1H, NH), 4.66 (d, J = 5.2 Hz, 2H, CH_2). ^{13}C NMR δ 167.3 (CO), 138.1, 134.3, 131.5, 128.8, 128.6, 127.9, 127.6, 126.9, 44.1. MS (ES) *m/z* 212 (3%, MH^+), 182 (12), 91 (100).

CHAPTER FOUR

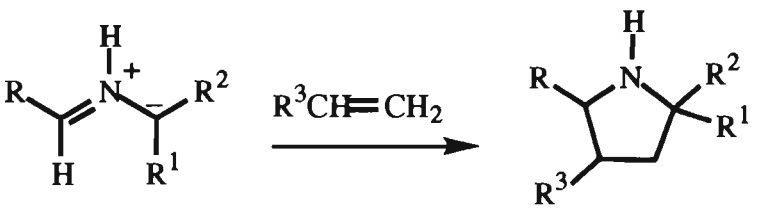
Asymmetric Synthesis of Proline Derivatives via *Exo*-Diastereoselective 1,3-Dipolar Cycloaddition Reactions of Azomethine Ylides

4-1. Introduction

1,3-Dipolar cycloaddition reactions to alkenes have found wide synthetic application in organic chemistry, as they open access to polyfunctionalized five membered heterocyclic rings, often in a highly regio- and stereoselective fashion.[77] Among the variety of 1,3-dipoles available, the chemistry and stereochemistry of nitrone and nitrile oxide cycloadditions has been more intensively investigated, with particular focus on the variant of these reactions that secures control of the absolute stereochemistry of the products (Chapter Three).

1,3-Dipolar cycloaddition reaction of azomethine ylides (1) to alkenes has become a powerful method for constructing the pyrrolidine ring system (2). (Scheme 4.1).[77,121] Several natural products with highly substituted pyrrolidine ring systems have been synthesised by utilization of the 1,3-dipolar ring forming reaction as a key step.[122]

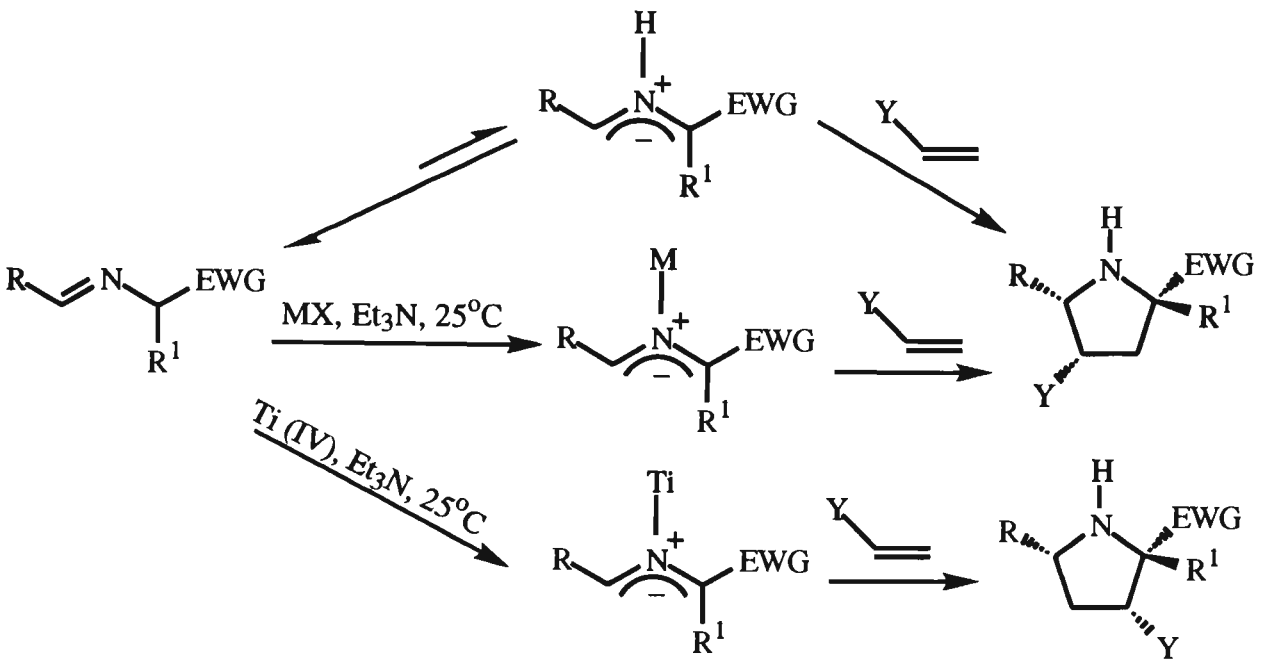
Scheme 4.1



(1) (2)

Azomethine ylides are generated *in situ* and not isolated. The preparation of stabilized azomethine ylides with a wide range of electron withdrawing substituents on the carbon atom bearing the negative charge was first described by Grigg *et al.*[123] in 1978. These intermediates undergo 1,3-dipolar cycloaddition reactions to give a wide range of novel polyfunctionalized pyrrolidines (Scheme 4.2).[124]

Scheme 4.2



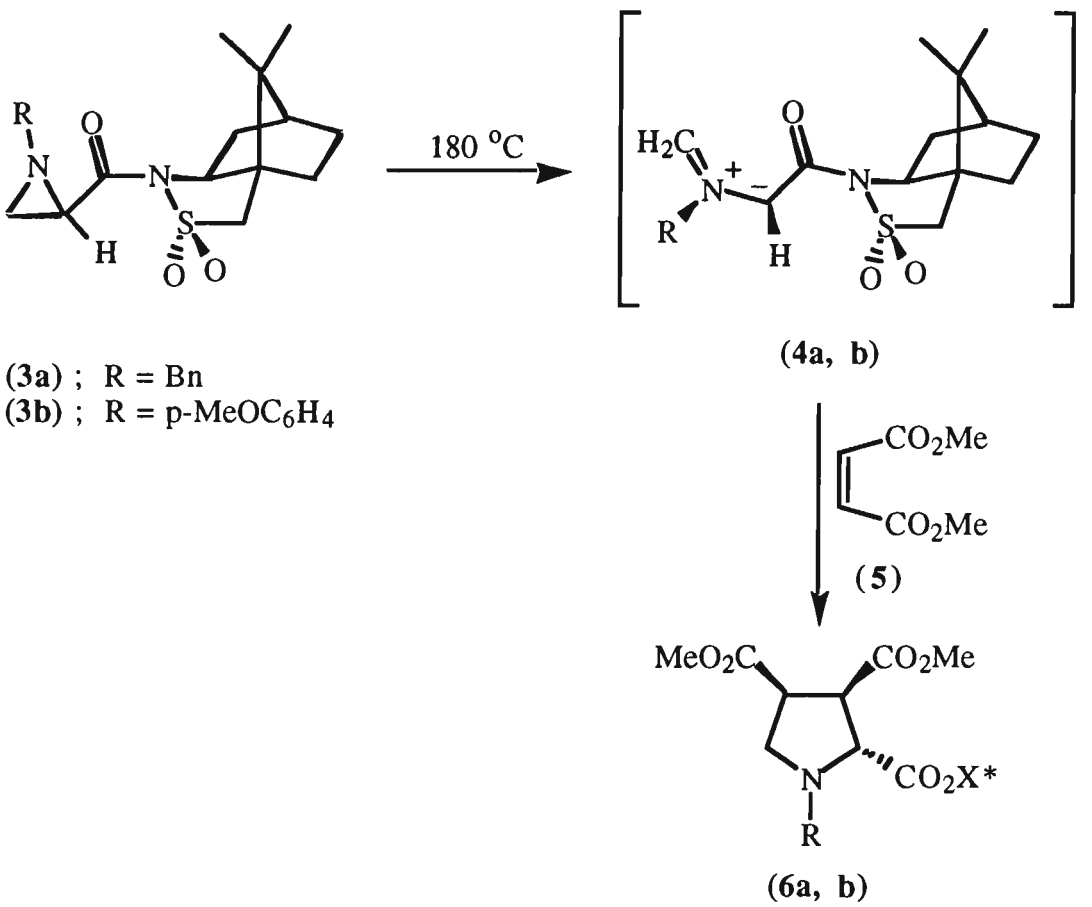
M = Ag(I), Tl(I) , Mg(II), Mn(II)

EWG = CO_2R, C(O)R, CN, P(O)$(OEt)_2$, 2-pyridyl, 2-thiazolyl, Y=CO_2R, C(O)R

1,3-Dipolar cycloaddition reaction of azomethine ylides derived from *N*-arylidene α-amino acids[125] and α-amino acid esters to electron deficient alkenes is an extremely powerful method for the synthesis of polyfunctional prolines.[126-130] Recent attention in this area has focused on devising methods for preparing optically active 1,3-dipolar cycloaddition products from azomethine ylides.[128-130] Three general approaches for the asymmetric version of these reactions have been realized by employing a chiral auxiliary attached to either the azomethine ylide[128] or the dipolarophile[129] or by utilization of a chiral metal complex as catalyst.[130] Besides these three approaches there is another report in which a chiral azomethine ylide and a chiral dipolarophile reacted to give chiral adducts with double asymmetric induction.[131] There are five issues which need to be considered when evaluating the utility of such systems for asymmetric synthesis: 1) availability of the auxiliary; 2) diastereofacial selectivity; 3) *endo/exo* selectivity; 4) geometry of 1,3-disubstituted ylides and 5) auxiliary removal / recovery.

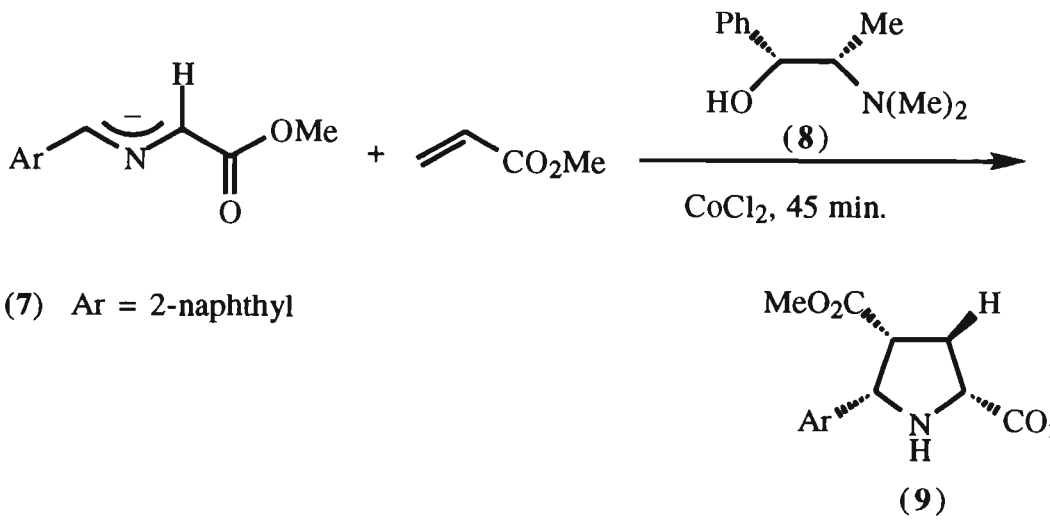
Suffice it to say none of the chiral systems reported so far appears to satisfy all of these requirements. While good stereocontrol has been achieved in the asymmetric version of these reactions by attaching chiral auxiliaries to the dipolarophile component, the development of a general chiral auxiliary for azomethine ylides is ongoing.[128] In 1994 Garner *et al.*[128h] demonstrated that Oppolzer's sultam could serve as an effective recoverable chiral auxiliary for 1,3-dipolar cycloadditions of carbonyl-stabilized azomethine ylides. Thermolysis of aziridine (3a,b) produced the corresponding *N*-substituted azomethine ylides (4a,b) which underwent 1,3-dipolar cycloaddition to dimethyl maleate (5) as a dipolarophile. Cycloadducts (6a,b) (proline derivatives) were obtained as the major products, with facial selectivity of 9 : 1 and 11 : 1 respectively, and arose via the exclusive *endo* cycloaddition to the Z-ylide (4a,b) (Scheme 4.3).

Scheme 4.3



Utilization of a chiral metal complex in 1,3-dipolar cycloadditions of azomethine ylides was reported for the first time by Allway *et al.*[130] in 1991. They explored the use of anhydrous $CoCl_2$ in the presence of (1*R*, 2*S*)-*N*-methylephedrine (8) for the reaction of (7) with methyl acrylate to give (9) (Scheme 4.4). The best results (84% yield, 96% e.e.) were reported with a mole equivalent of $CoCl_2$ and a 1 : 2 metal salt to ligand ratio.

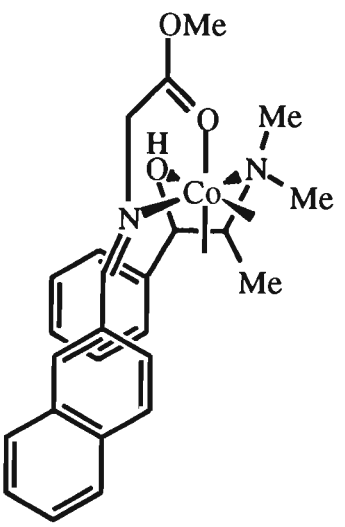
Scheme 4.4



(7) Ar = 2-naphthyl

(9)

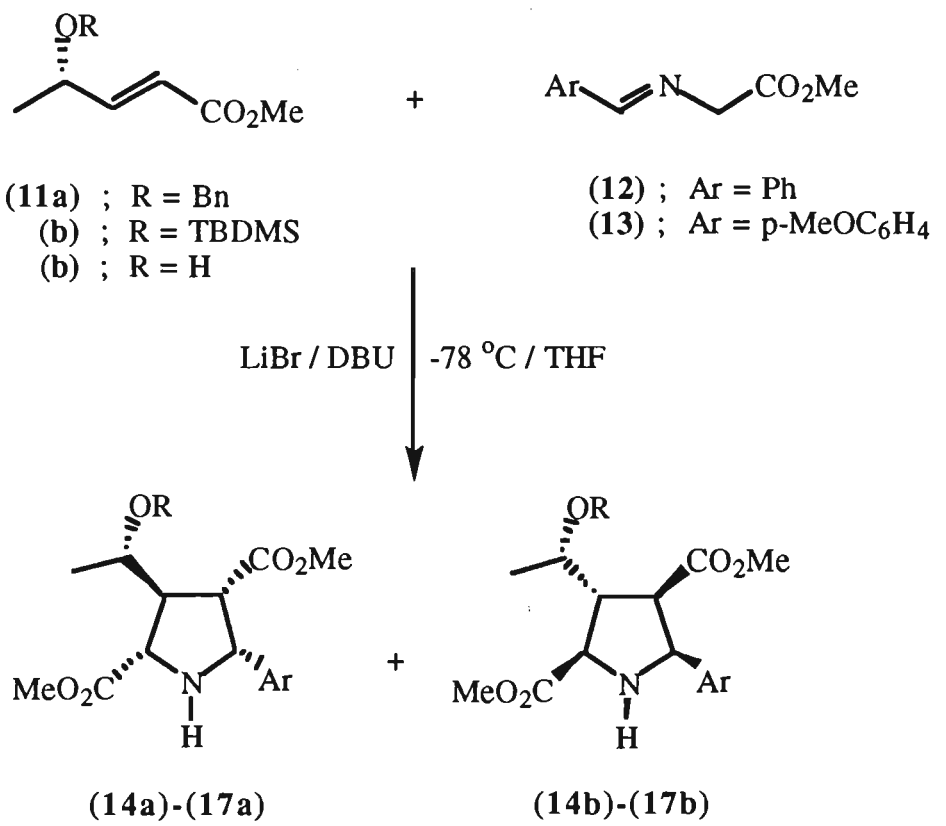
The suggested model (10) for the asymmetric induction shows that the *cis*-arrangement of the methyl and phenyl groups of the chiral ligand results in a pseudo-equatorial conformation for the phenyl group and effective blockade of one π-face of the imine of the dipole.



(10)

In 1991, Annunziata *et al.*[129e] reported the cycloaddition of enantiomerically pure (*E*)-γ-alkoxy-α,β-unsaturated esters (11a-c) and azomethine ylides derived from the glycine imines (12) and (13) in the presence of LiBr and DBU (Scheme 4.5). From these reactions proline derivatives (14)-(17) were prepared. These reactions were highly regioselective and only two diastereoisomers were obtained (Table 4.1). The major diastereoisomers (14a)-(17a) arose from addition of the ylide to the π-face of the dipolarophile that was *anti* to the γ-alkoxy or γ-hydroxy substituent via an *endo* type transition state.

Scheme 4.5



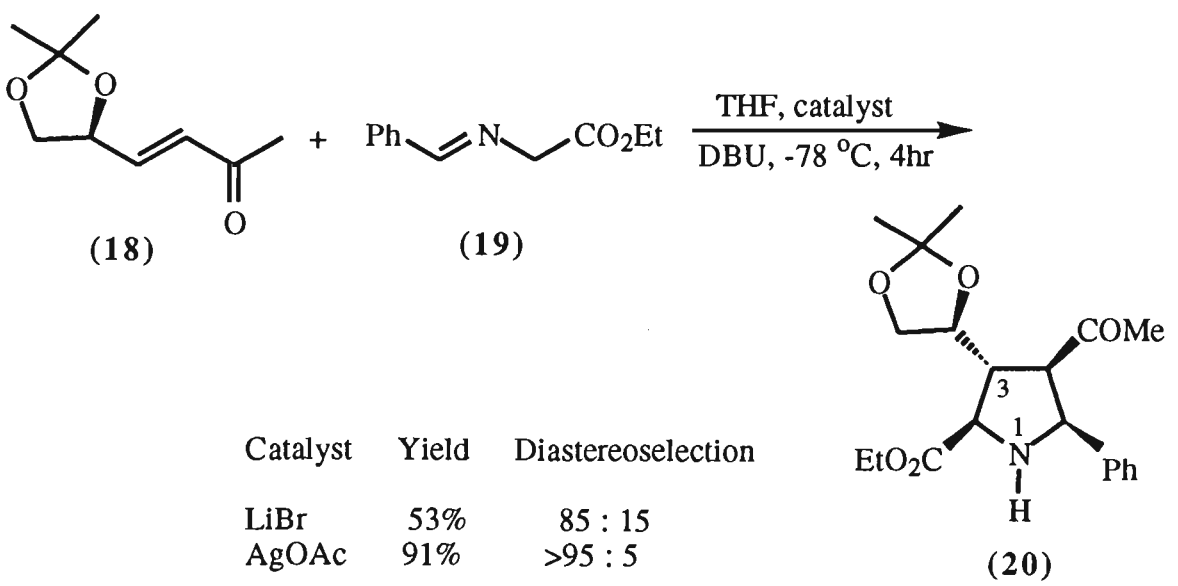
(14a)-(17a) **(14b)-(17b)**

Table 4.1. Diastereoselective synthesis of pyrrolidines (14)-(17) from esters (11a-c).[128e]

Entry	Ester (11)	Imine	Dipole : Alkene ratio	Yield%	(Products) Diastereoselection
1	a	(12)	1 : 1	40	(14a) : (14b) 78 : 22
2	a	(12)	3 : 1	58	(14a) : (14b) 77 : 23
3	b	(12)	1 : 1	65	(15a) : (15b) 90 : 10
4	b	(12)	3 : 1	77	(15a) : (15b) 88 : 12
5	c	(12)	1 : 1	24	(16a) : (16b) 96 : 4
6	a	(13)	1 : 1	52	(17a) : (17b) 79 : 21

Similar observations were reported by Pätzel *et al.*[129f] in 1993 with different α,β-unsaturated ketones (enones) (18) bearing a chiral alkoxy or amino substituent in the γ-position (Scheme 4.6). Again the major diastereoisomer (20) arose from addition of the ylide to the π-face of (18) that was *anti* to the γ-oxygen substituent via an *endo* type transition state.

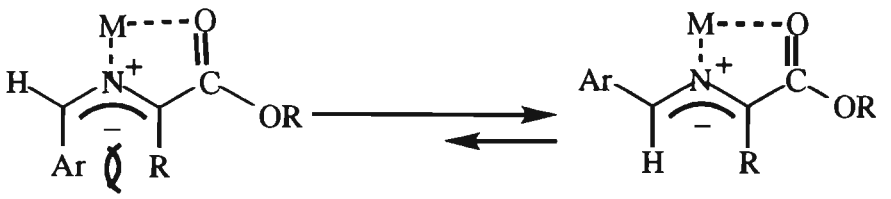
Scheme 4.6



Catalyst	Yield	Diastereoselection
LiBr	53%	85 : 15
AgOAc	91%	>95 : 5

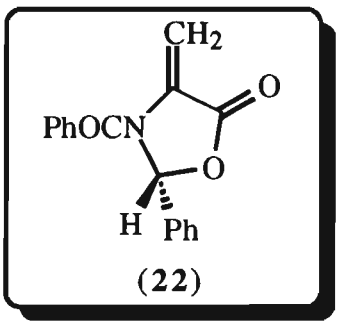
Compared with LiBr / DBU, the use of AgOAc / DBU gave higher stereoselectivity.[129f]

In all of the above series of reactions the geometry of the azomethine ylides has been proposed to be (21b), for the following two reasons: 1) Intramolecular chelation of the metal ion would favour structures (21a) and (21b)[132] and 2) Steric effects favour (21b), because of an unfavourable steric interaction between Ar and R in (21a)[133] (eq 4.1).



(21a) **(21b)** **eq (4.1)**

In this Chapter, the 1,3-dipolar cycloaddition reaction of azomethine ylides with the chiral oxazolidinone (22) is described as a method for the asymmetric synthesis of polyfunctional proline derivatives. The structure and stereochemistry of the cycloadducts will also be considered.

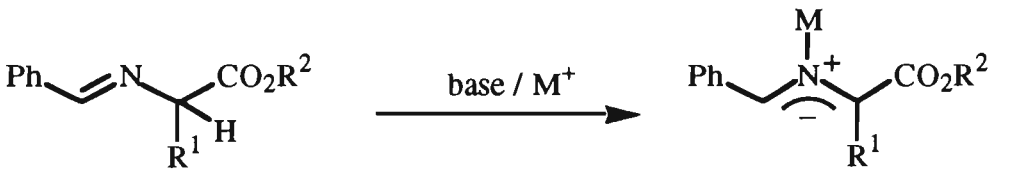


(22)

4-2. 1,3-Dipolar Cycloaddition Reactions of (22) and Azomethine Ylides

In this study the azomethine ylides (24a-e) were generated *in situ* from (23a-e) in the presence of (22) by treating a THF or CH_3CN solution of (23) with a metal salt (LiBr or AgOAc) and a base (DBU or Et_3N) at -78 °C. The reactions were performed via three different methods that are indicated in Scheme 4.7. Methods I, II, III involved the salt, base, solvent combinations (LiBr / DBU / THF), (LiBr / Et_3N / CH_3CN) and (AgOAc / DBU / THF), respectively. The reaction mixtures were maintained at -78 °C for several hours or warmed to the temperature specified in Table 4.2 (page 171) before being quenched with saturated aqueous NH_4Cl solution.

Scheme 4.7



(23a) ; $R^1 = CH_2CH(CH_3)_2$, $R^2 = CH_3$
(b) ; $R^1 = CH_2Ph$, $R^2 = CH_2CH_3$
(c) ; $R^1 = Ph$, $R^2 = CH_3$
(d) ; $R^1 = CH_3$, $R^2 = CH_3$
(e) ; $R^1 = H$, $R^2 = CH_2CH_3$

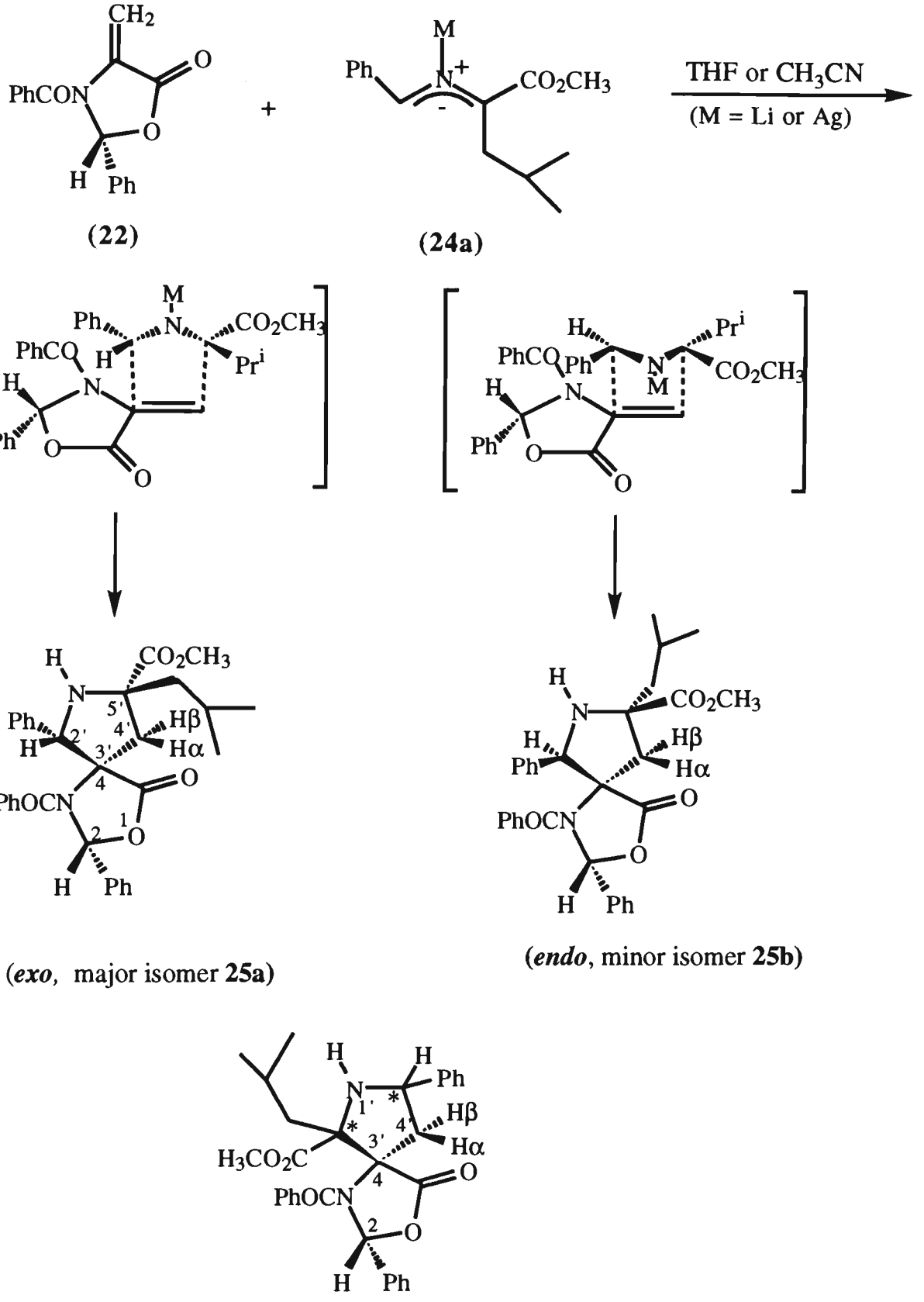
(24a-e) ; M = Li, Ag

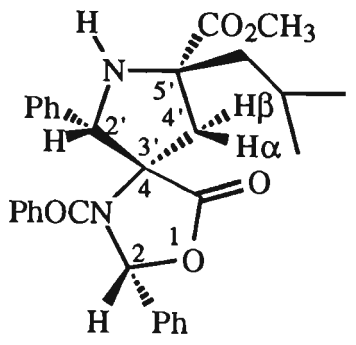
method I : LiBr / DBU / THF
method II : LiBr / Et_3N / CH_3CN
method III : AgOAc / DBU / THF

4-2-1. 1,3-Dipolar Cycloaddition Reactions of (22) and Methyl *N*-Benzylidene Leucinate (23a)

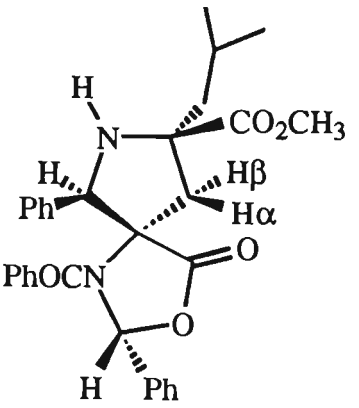
When a solution of oxazolidinone (22) and methyl *N*-benzylidene leucinate (23a) was treated according to Method I, at -78 °C for 2 hr and then at -20 °C for 30 hr, a 94 : 6 mixture of two diastereomeric cycloaddition products (25a) and (25b) was formed in 61% yield (Scheme 4.8). The same two diastereomeric products were produced in a ratio of 88 : 18 when this reaction was performed according to Method II at 0 °C for 10 hr. When this reaction was performed using Method III, at -78 °C for 2 hr and then at to room temperature for 30 hr, the reaction proceeded with a poorer diastereoselectivity and a small amount of the regioisomer (25c) was also obtained. The ratio of diastereoisomers (25a) : (25b) : (25c) was 58 : 37 : 5 as determined by ^{1}H NMR on the crude reaction mixture (Table 4.2, page 170). The diastereoisomers were readily separated by column chromatography. The structures of (25a) and (25b) were elucidated by single X-ray structural determinations (Figure 4.1). The X-ray structural analysis indicated that the stereochemistry of (25a) and (25b) arose from addition of the azomethine ylide (24a) to the π-face of the *exo*-cyclic 4-methylene group of (22) that is *anti* to the C-2 phenyl substituent, via an *exo* and *endo* type transition state, respectively.

Scheme 4.8

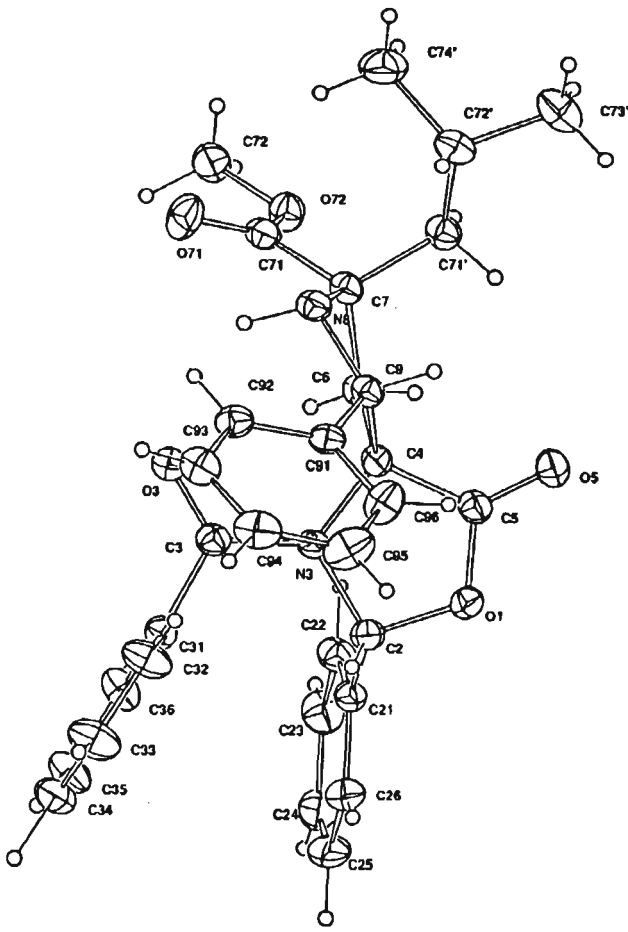

CH2
PhCON
O
O
H Ph
(22)
+
M
Ph
N+
-
CO2CH3
(24a)
THF or CH3CN
(M = Li or Ag)
M
Ph
N
CO2CH3
PhCO
H
Pri
H
N
Ph
O
O
H
Pri
PhCO
Ph
N
CO2CH3
H
N
M
Ph
O
O
H
N
CO2CH3
Ph
H
5'
4'
Hβ
2'
3'
Hα
4
O
PhOCN
1
2
O
H Ph
(exo, major isomer 25a)
H
N
CO2CH3
H
Ph
Hβ
Hα
O
PhOCN
O
H Ph
(endo, minor isomer 25b)
H
H
N
Ph
1'
*
*
4'
Hβ
3'
Hα
H3CO2C
4
O
PhOCN
2
O
H Ph
(regioisomer 25c)



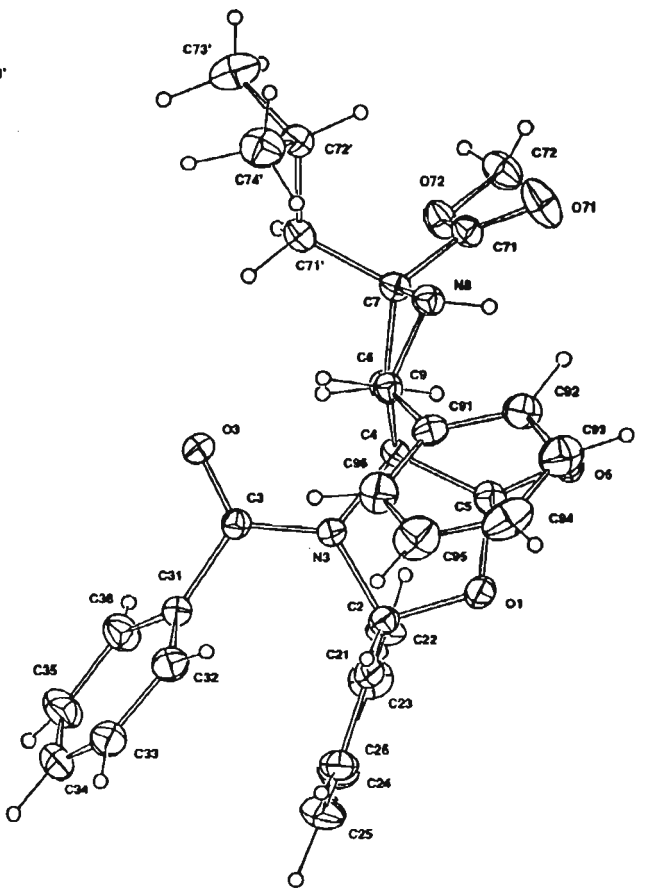
(25a)



(25b)



(25a)



(25b)

Figure 4.1. Molecular projection of (25a) and (25b) normal to the plane of five-membered ring.

COSY and NOESY NMR experiments were used to assign the ^{1}H NMR spectra of the cycloadducts. In the NOESY spectrum of the major isomer (25a), strong cross peaks between H2' (δ 4.91) and the signal at δ 2.79 (d, J = 14 Hz) identified this resonance as being associated with H4'α rather than H4'β (δ 3.54, d, J = 14 Hz) in (25a). Similar cross peaks in the

NOESY spectrum of the minor isomer (25b) were observed between H2' (δ 5.45) and the resonance at δ 3.57 (d, J = 13.2 Hz), which identified this resonance as being associated with H4'β rather than H4'α (δ 2.90, d, J = 13.2 Hz). These observed NOESY cross peaks were consistent with the close proximity of H2' and H4'α and also H2' and H4'β in (25a) and (25b) respectively, from the energy minimized structure of these compounds (Figure 4.2).

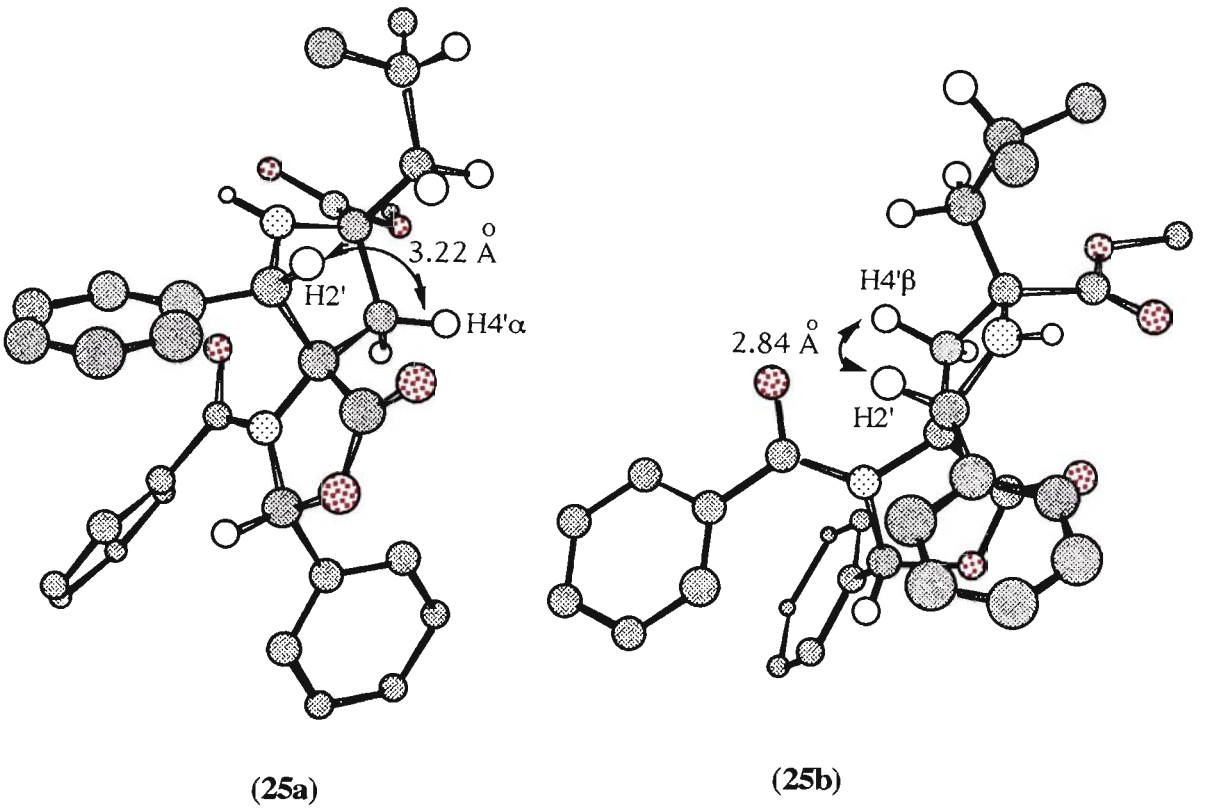


Figure 4.2. Energy minimized structures of (25a) and (25b) using the INSIGHT II force field of BIOSYM.

The ^{1}H NMR of these two diastereoisomers were useful in determining the stereochemistry of the other cycloadducts in this study. As it is shown in Figure 4.3, the H2 signal in the *exo* isomer (25a) is observed upfield (δ 5.80) of the H2 signal in the *endo* isomer (25b) (δ 6.04) (Table 4.3, page 173). In the *exo* isomer (25a), two relatively upfield 'ortho'-aromatic proton signals are observed at δ 6.60 and δ 6.08. While in the *endo* isomer (25b) only one upfield aromatic signal is observed at δ 6.71 (Figure 4.3).

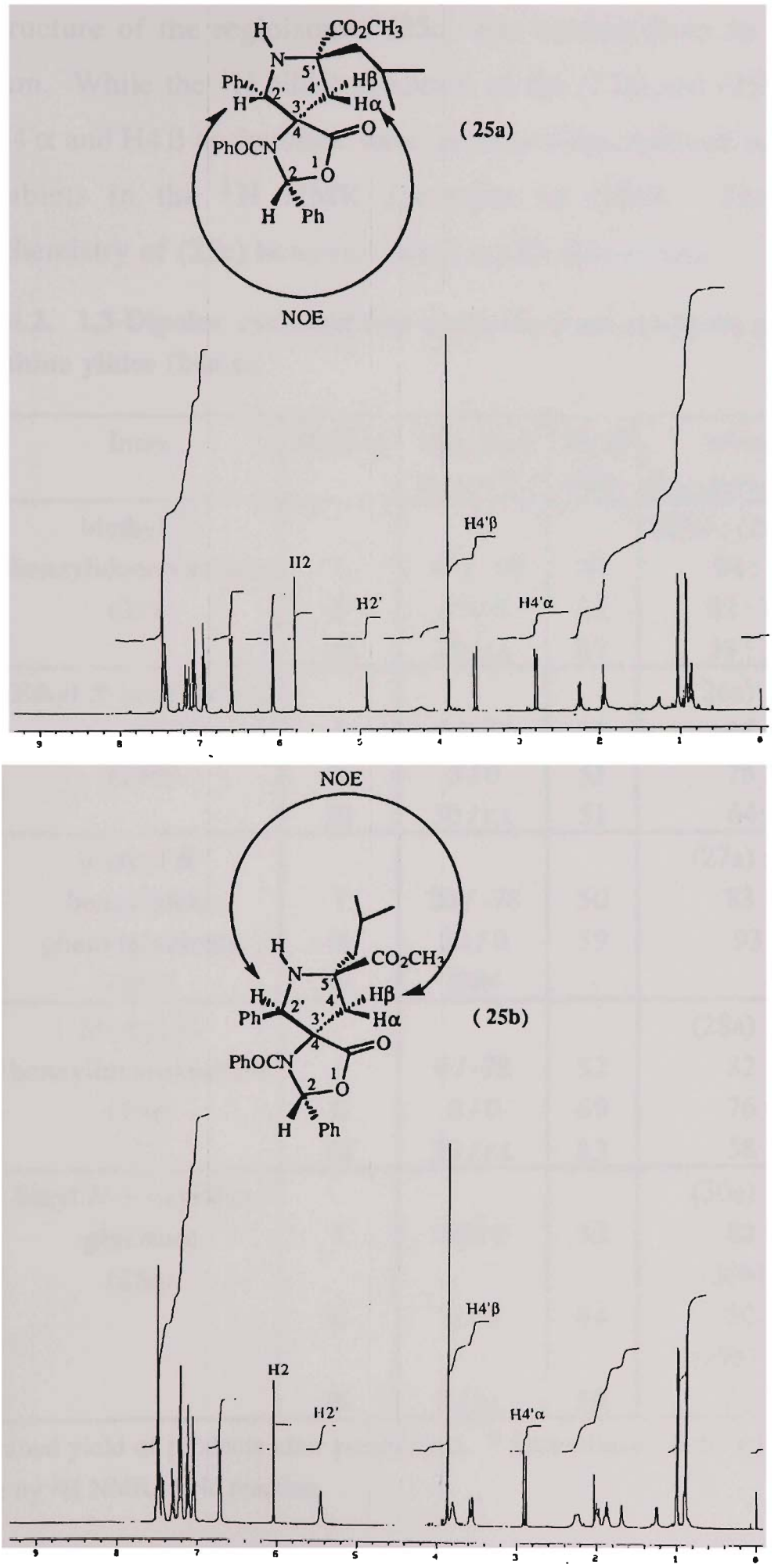


Figure 4.3. 400 MHz ^1H NMR spectrum of (25a) and (25b) in $CDCl_3$.

The structure of the regioisomer (25c) was evident from its ^{1}H NMR spectrum. While the ^{1}H NMR spectrum of the (25a) and (25b) showed both H4'α and H4'β as doublets, these protons were observed as a doublet of doublets in the ^{1}H NMR spectrum of (25c). The relative stereochemistry of (25c) however, could not be determined.

Table 4.2. 1,3-Dipolar cycloaddition products from reactions of (22) and azomethine ylides (24a-e).

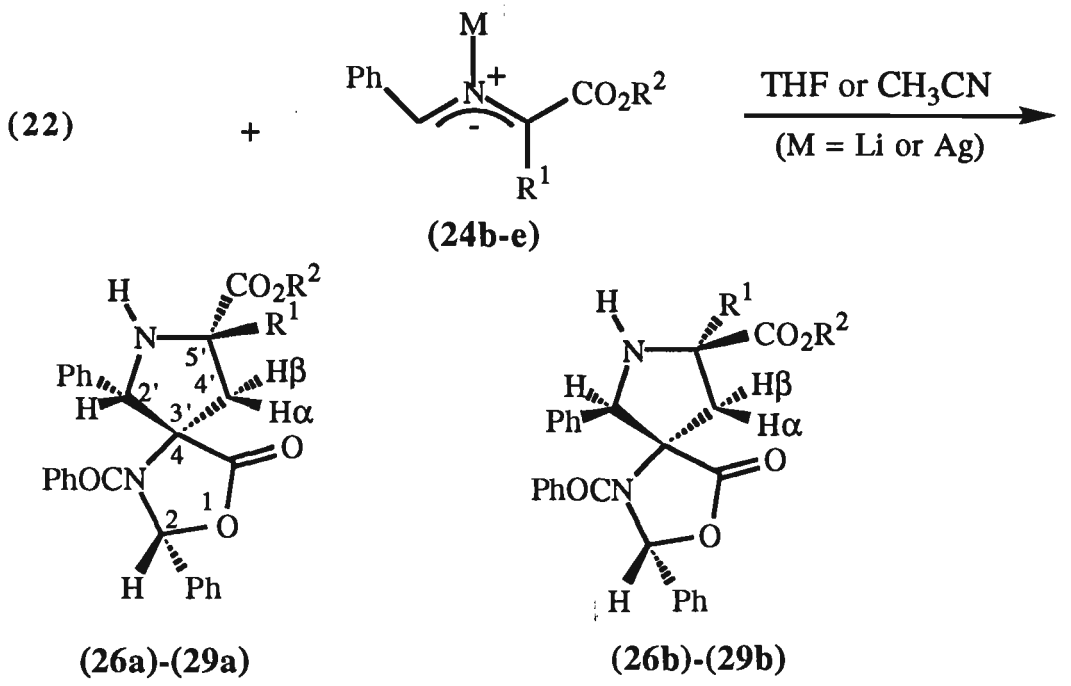
Entry	Imine	Method	Time (hr) / Temp (°C)	Yield (%)[a]	(Products) Diastereoselection[b]
1	Methyl *N*-benzylideneleucinate (23a)				(25a) : (25b) : (25c)
		I	30 / -20	61	94 : 6 : 0
		II	10 / 0	62	82 : 18 : 0
		III	30 / r.t.	67	58 : 37 : 5
2	Ethyl *N*-benzylidene alaninate (23b)				(26a) : (26b)
		I	9 / -78	45	85 : 15
		II	3 / 0	51	78 : 22
		III	30 / r.t.	51	64: 36
3	Methyl *N*-benzylidene phenylglycinate (23c)				(27a) : (27b)
		I	20 / -78	50	83 : 17
		II	20 / 0	59	93 : 7
		III	NR[c]	-	-
4	Methyl *N*-benzylidenealaninate (23d)				(28a) : (28b)
		I	6 / -78	52	82 : 18
		II	8 / 0	69	76 : 24
		III	20 / r.t.	83	58 : 42
5	Ethyl *N*-benzylidene glycinate (23e)				(30a) : (29b)
		I	15 / 0	32	82 : 18
					(30b) : (31)
		II	6 / 0	44	50 : 50
					(29b) : (29a)
		III	6 / r.t.	88	55 : 45

[a] Combined yield of products after purification. [b] Determined on the crude reaction mixture by ^{1}H NMR. [c] No reaction.

4-2-2. 1,3-Dipolar Cycloaddition Reactions of (22) and *N*-Benzylidene α-Amino Acid Esters (23b)-(23e)

The 1,3-dipolar cycloaddition reactions of (22) and *N*-benzylidene α-amino acid esters (23b)-(23e) were performed via Methods I, II and III, for the period of time and reaction temperature indicated in Table 4.2, page 170 (Scheme 4.9). The diastereomeric adducts were separated by column chromatography. The cycloadducts (26a)-(29a) and (26b)-(29b) were determined to have the *exo* and *endo* stereochemistry respectively, by comparison of their ^{1}H NMR spectra with that of the compounds (25a) and (25b) respectively, whose stereochemistry was established by single crystal X-ray structural determinations (Figure 4.1). The chemical shifts for the two upfield aromatic protons in the ^{1}H NMR spectra of compounds (25a) and (26a)-(29a) were almost identical (Table 4.3, page 173). Likewise, the chemical shifts for the single upfield aromatic proton in compound (25b) and (26b)-(29b) were essentially the same. In addition, the signals for H2 in compounds (26a)-(29a) were observed upfield of H2 in compounds (26b)-(29b), similar to what was observed in (25a) and (25b) respectively (Table 4.3, page 173). The stereochemistry of (26a) was further evident from a single crystal X-ray structure determination of its proline derivative (50) that is described later in this Chapter (Figure 4.7). The structure of compound (26b) was unequivocally established by a single crystal X-ray structure determination (Figure 4.4). This X-ray structure confirmed what was deduced about the stereochemistry of (26b) from ^{1}H NMR analysis.

Scheme 4.9



(26) :	$R^1 = CH_2Ph$	, $R^2 = CH_2CH_3$
(27) :	$R^1 = Ph$	, $R^2 = CH_3$
(28) :	$R^1 = CH_3$	, $R^2 = CH_3$
(29) :	$R^1 = H$	, $R^2 = CH_2CH_3$

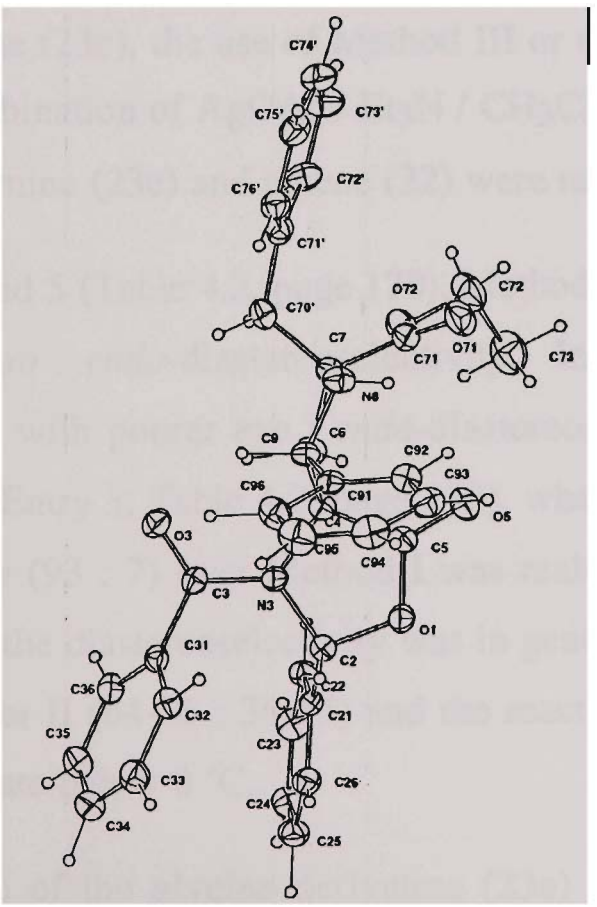


Figure 4.4. Molecular projection of **(26b)** normal to the plane of five-membered ring.

The assignment of the ^1H NMR spectra of (26a)-(29a) and (26b)-(29b) were aided by COSY and NOESY NMR experiments. In the NOESY spectra strong cross peaks were observed between H2' and H4'α in (26a)-(29a) and between H2' and H4'β in (26b)-(29b) (Table 4.3).

Table 4.3. Chemical shifts δ (ppm) of H2α, H4'α, H4'β and 'ortho-aromatic' protons ('ortho'-ArH) of the cycloaddition adducts (25)-(29).

Cycloadduct	*Exo* isomer (**a**)				*Endo* isomer (**b**)			
	H4'α	H4'β	H2	o-ArH[a]	H4'α	H4'β	H2	o-ArH[a]
(25)	2.79	3.54	5.80	6.60, 6.08	2.90	3.57	6.04	6.71
(26)	3.02	3.67	5.80	6.62, 6.12	3.31	3.51	6.04	6.73
(27)	3.53	4.18	5.76	6.64, 6.21	3.19	3.78	6.35	6.78
(28)	2.85	3.65	5.80	6.61, 6.11	2.98	3.59	6.06	6.71
(29)	3.10	3.41	5.88	6.64, 6.10	2.70	3.57	6.25	6.72

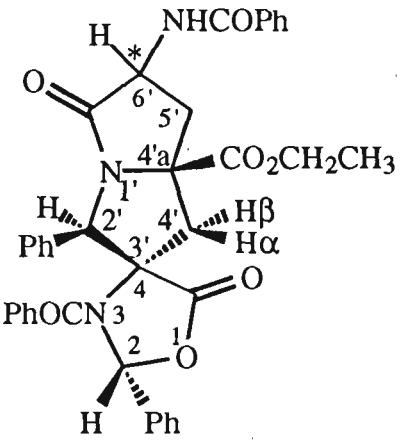
[a] 'ortho'-aromatic protons

In the case of imine (23c), the use of Method III or using the metal salt / base / solvent combination of AgOAc / Et_3N / CH_3CN were unsuccessful and only starting imine (23e) and alkene (22) were recovered.

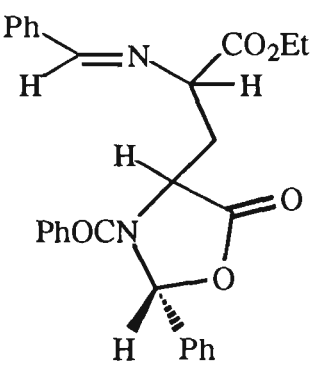
For entries 1,2,4 and 5 (Table 4.2, page 170), Method I gave cycloadducts with the highest *exo* : *endo*-diastereoselectivity. In general, Method II gave cycloadducts with poorer *exo* : *endo*-diastereoselectivity except in the case of (23c) (Entry 3, Table 4.2, page 170), where an enhanced *exo*-diastereoselectivity (93 : 7) over Method I was realised. When Method III was employed, the diastereoselectivity was in general much lower than that for Method I or II (64-55 : 36-45) and the reactions did not proceed at an appreciable rate below 0 °C.

When the reaction of the glycine derivative (23e) (Entry 5, Table 4.2, page 170) was performed using Method I, at -78 °C for 15 hr and then 0

°C for 8 hr, the cycloadduct (29b) and the tricyclic product (30a) were obtained, in 10 and 25% yields, respectively. The structure of (30a) was determined from ^{1}H, ^{13}C NMR, COSY and HETCOR NMR and mass spectrometric analysis. The details of the ^{1}H and ^{13}C NMR spectra of (30a) are outlined in the Experimental Section of Chapter Four.** The similarity of the proton resonances for the aromatic and H2 (δ 6.45) protons in the ^{1}H NMR of (30a) with those of (29b) showed this compound had the stereochemistry at C2' and C4'a indicated in structure (30a). In the COSY experiment, H6' (δ 5.26) had a strong cross peak with two hydrogens at (δ 3.41) and (δ 2.42). This showed that H6' is next to two hydrogens on C5'. A HETCOR experiment showed that H2 (δ 6.45), H2' (δ 6.08) and H6' (δ 5.26) are on C2, C2' and C6', respectively. Also from this experiment it was found that there are two hydrogens on C4' (H4'α (δ 3.35, d, J = 12.8 Hz) and H4'β (δ 3.76, d, J = 12.8 Hz)) and two hydrogens on C5' (H5α (δ 3.41) and H5β (δ 2.42)) (Figure 4.5).



(30a) ; (Stereochemistry at C-6' unknown)
(30b) ; (Stereochemistry at C-6' opposite to that of (30a))



(31)

**The numbering used here for compounds (30a) and (30b) is not systematic. This numbering scheme has been used to allow a direct comparison of the structural and stereochemical features of (30a) and (30b) with those of the related compounds (25-29a,b). The systematic number system is used in the Experimental Section, Chapter Four.

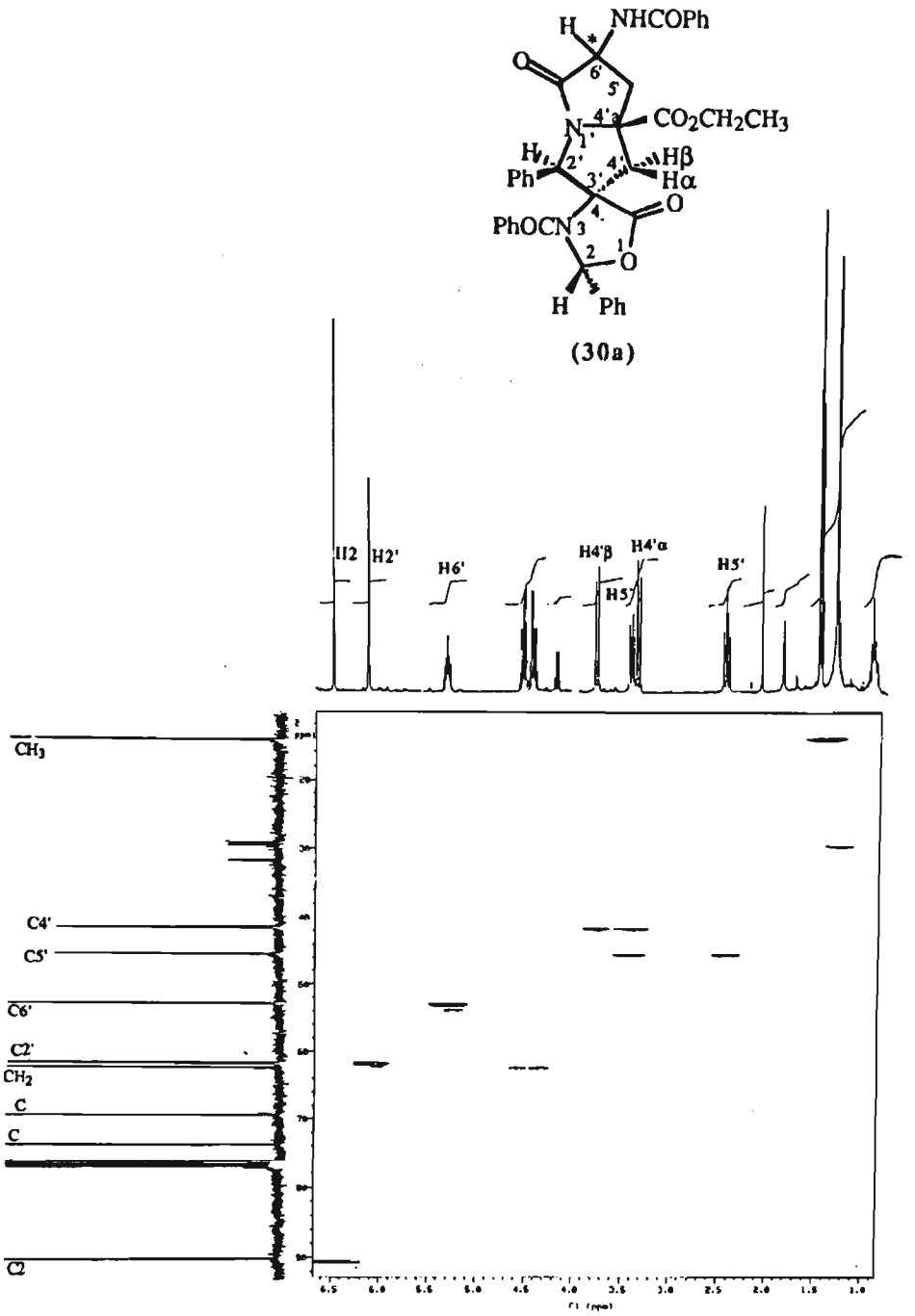
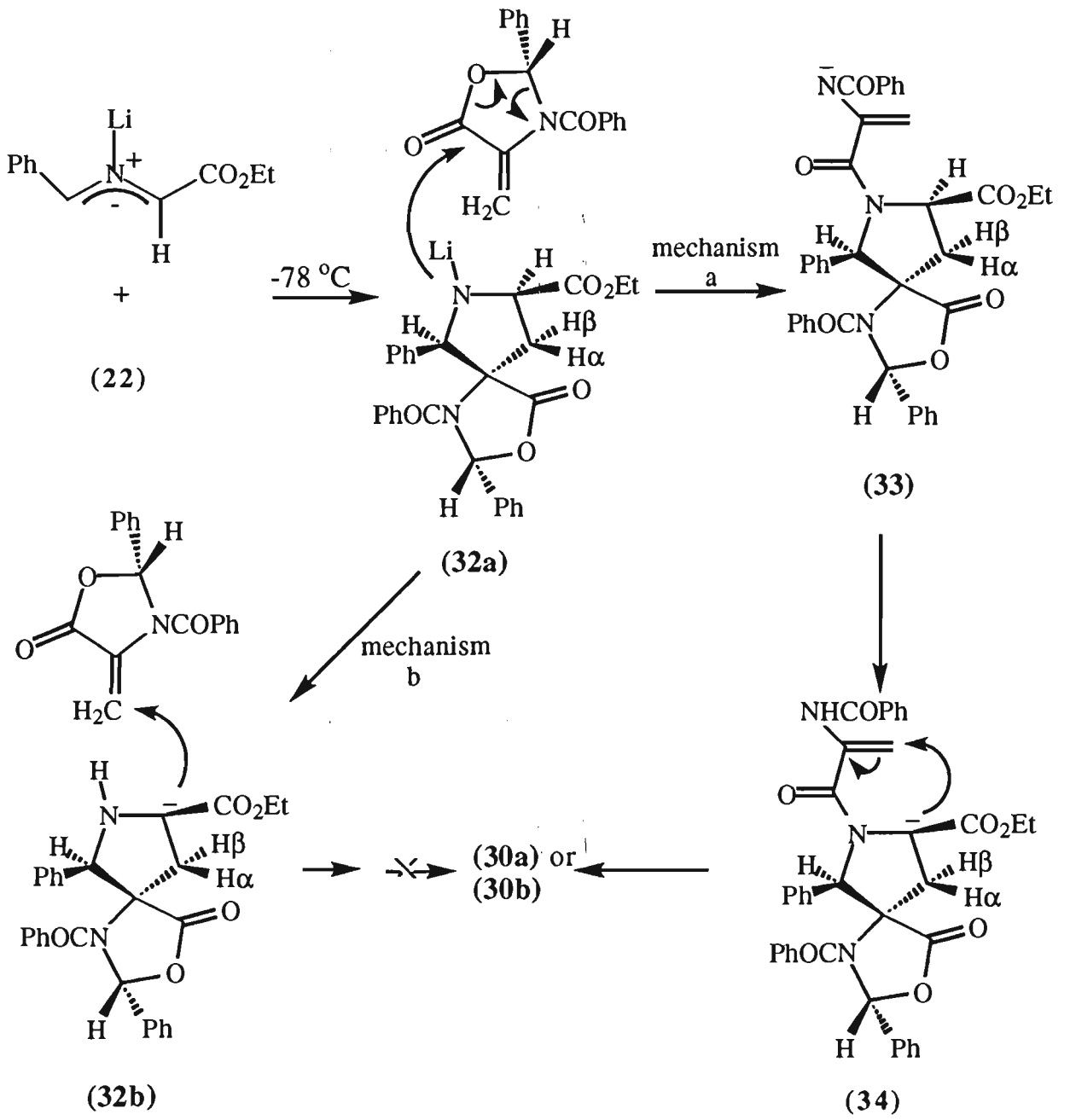


Figure 4.5. The HETCOR spectrum of tricyclic (30a).

When the reaction of (22) and (23e) was performed using Method II, at 0 °C for 6 hr, then compound (30b) and the Michael adduct (31) were obtained. ^{1}H NMR analysis showed compound (30b) is the C6' epimer of (30a) (Experimental Section, Chapter Four). A possible mechanisms for the formation of the tricyclic compounds (30a) and (30b) is given in Scheme 4.13. The proposed mechanism (mechanism a) involves, nucleophilic attack of the initially formed lithiated cycloadduct (32a) to the carbonyl lactone of (22), followed by ring opening of the

oxazolidinone ring to release PhCHO and to generate intermediate (33). Anion (34), which may be formed from intramolecular or intermolecular deprotonation of compound (33), undergoes a Michael type addition to produce the tricyclic compound (30a) or (30b) (Scheme 4.10). Another possible mechanism for the formation of the tricyclic compounds (30a) and (30b) involves first Michael addition of (32b) to (22) and then nucleophilic attack on the lactone carbonyl group (mechanism b). Compounds (30a) and (30b) may also be interconverted, by epimerization at C6', by base.

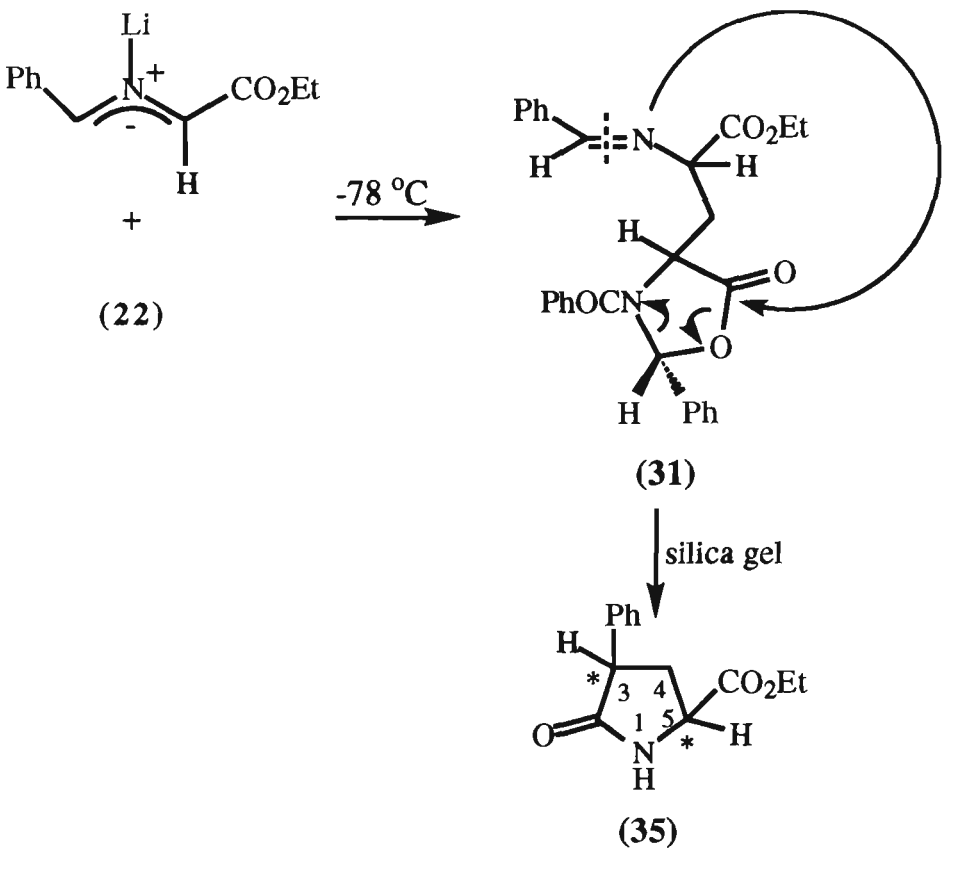
Scheme 4.10



Mechanism b would seem unlikely since, treatment of a mixture of the cycloadducts (29a) or (29b) and alkene (22) with DBU / LiBr, at -78 °C to room temperature, resulted only in the recovery of unreacted starting materials and the products (30a) and (30b) could not be detected.

Another compound formed from the reaction of (22) and (23e) using Method II was the Michael adduct (31). Unfortunately isolation of this compound after purification by column chromatography was unsuccessful. Compound (31) was converted to the lactam (35) when the crude reaction products were separated on silica gel (Scheme 4.11). This conversion most likely occurs via first hydrolysis of the C=N bond and then cyclization by nucleophilic attack of nitrogen to the lactone carbonyl of the oxazolidinone ring. Lactam (35) was a single diastereoisomer and the structure of this compound was evident from ^{1}H, ^{13}C, COSY NMR and mass spectroscopic analyses (Experimental Section, Chapter Four). The stereochemistry of (35) was not determined.

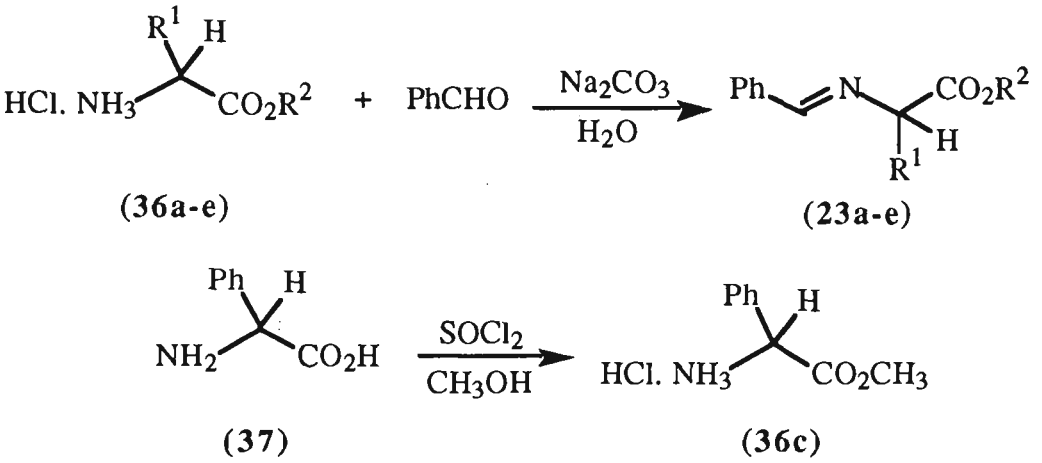
Scheme 4.11



4-2-3. Preparation of Imines (23a)-(23e)

The *N*-benzylidene-α-amino acid esters (23a)-(23e) were prepared by condensation of benzaldehyde with the appropriate α-amino acid ester hydrochloride (36a-e) in the presence of sodium carbonate[132a] (Scheme 4.14). These reactions were performed in water initially at 40 °C and then at room temperature overnight. Compound (36c) was prepared by treatment of 2-phenylglycine (37) with thionyl chloride in dry methanol (Scheme 4.12).

Scheme 4.12



4-3. Cycloaddition vs. Michael Addition in the Reactions of (22) with Azomethine Ylides

Imines of α-amino esters undergo regio- and stereospecific cycloaddition to electron deficient alkenes in THF, CH_3CN or other polar solvents in the presence of a metal salt (silver, lithium or zinc) and DBU or Et_3N.[126-130] They also undergo regiospecific Michael addition to electron deficient alkenes in the presence of a suitable base.[134] Barr *et al.*[135] presented evidence which indicated there was a fine balance between Michael addition and cycloaddition of the species generated from imines in the presence of metal salts and base. Reaction of methyl *N*-benzylidene alaninate (23d) with methyl acrylate under various conditions

gave different ratios of cycloadduct (41) and Michael adduct (40) (Table 4.4, page 180).[127e] The proposed transition state for these reactions is shown in structure (38a) in which the metal ion is chelated to the oxygen and nitrogen atoms of both reaction partners (Scheme 4.13). Bond formation at the β-carbon of the acrylate precedes that at the α-carbon to give (38b). Quenching of (38b) with a proton source, presumably triethylammonium bromide, leading to the Michael adduct (40) competes with intramolecular cyclization producing the metal amide cycloadduct (39). Ready quenching of (39) with the ammonium salt produces cycloadduct (41). The direct formation of (39) from (38a) via a concerted cycloaddition may also be involved.

Scheme 4.13

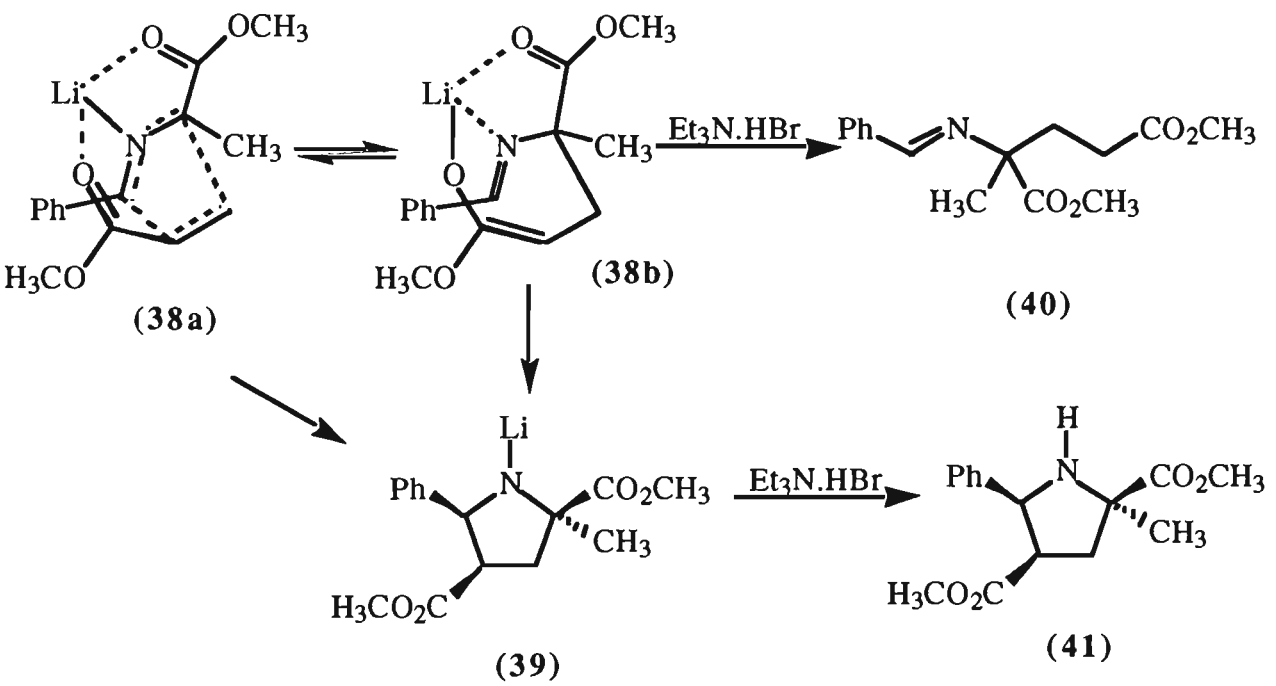


Table 4.4. Metal halide / amine-induced reactions of imine (23d) with methyl acrylate at room temperature.[127e]

Entry	Metal halide (equivalent)	Et_3N	DBU	Time (hr)	Solvent	Yield(%) (40)+(41)	Ratio (40) : (41)
1	LiBr, 1.5	1.2	-	49	THF	95	1 : 5
2	LiBr, 1.5	1.2	-	1	CH_3CN	79	1.4 : 1
3	LiBr, 1.5	1.2	-	3	CH_2Cl_2	92	3.3 : 1
4	LiBr, 1.5	-	1	1 min	THF	96	1 : 1.8
5	$MgBr_2$, 1.5	1.2	-	7	THF	99	0 : 1

The ratio of cycloadduct (40) to Michael adduct (41) was dependent upon the reaction conditions (Table 4.4). Replacement of THF by CH_3CN or CH_2Cl_2 favoured the Michael addition product (40) (Entries 2,3). The polar solvent (CH_3CN) would be expected to stabilize the polar Michael addition transition state more effectively than the relatively non-polar cycloaddition transition state, thus favouring the formation of Michael adduct (40).[136] The effect of CH_2Cl_2 on the product ratio is more difficult to rationalize since reactions in this solvent are heterogeneous and probably occur at a solid-liquid interface. When DBU was employed as a stronger base, the reaction was complete within 1 min at room temperature, indicating high acceleration of the deprotonation step leading to the lithiated anion intermediate (Entry 4). With DBU as base, the relative amount of Michael product (40) increased relative to that of the cycloadduct (41) (compare Entries 1 and 4 in Table 4.4). When a magnesium salt was employed the cycloadduct was the only identified product (Entry 5). The tendency of the small 'hard' lithium cation to complex with oxygen donor groups and of the 'soft' (magnesium, aluminium, silver) cation to complex with nitrogen donor groups may form the basis for the differences observed.[135]

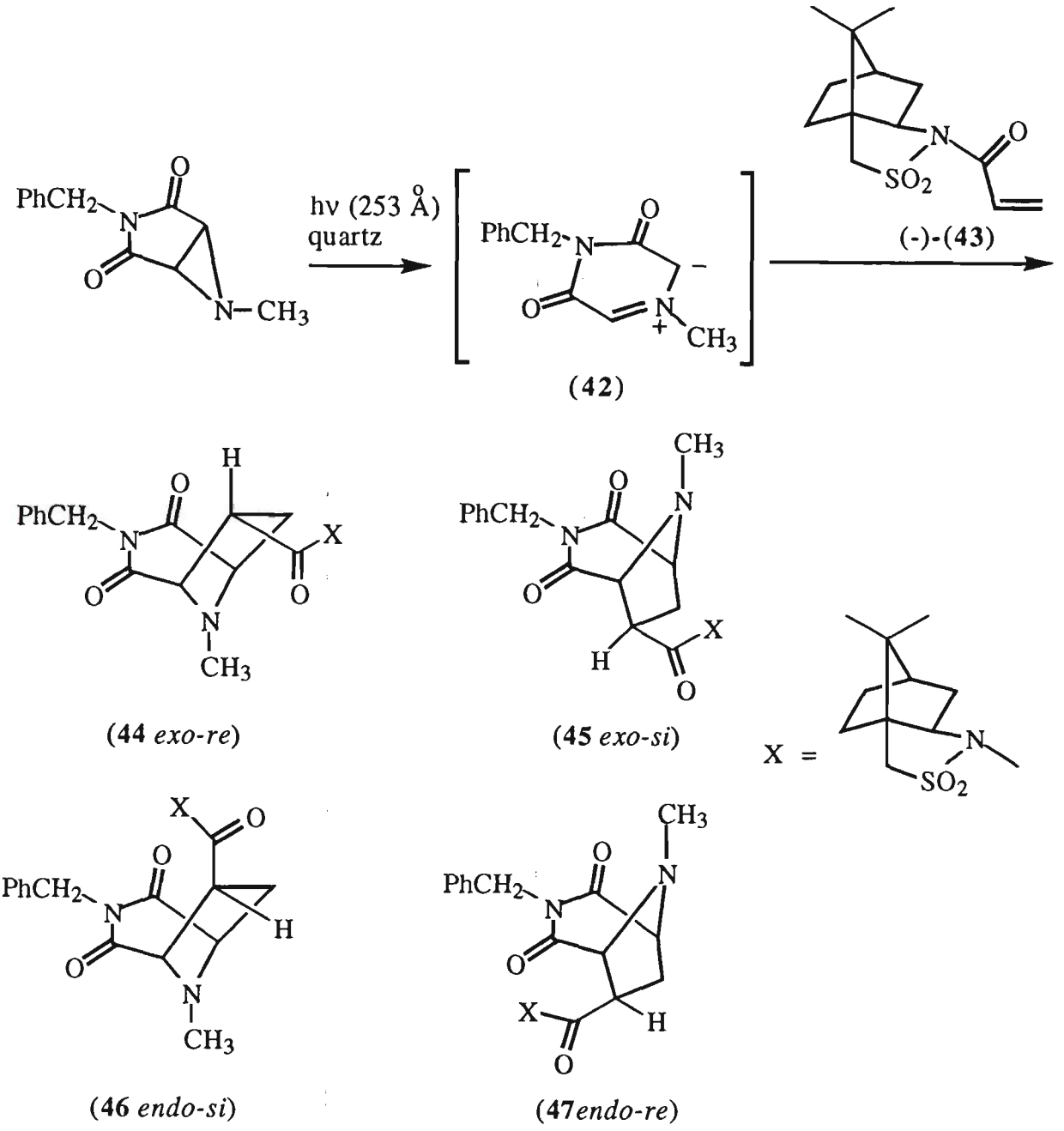
In contrast, the analogous reactions of (23a-e) and (22) produced only cycloadducts, except in the reaction of (23e) and (22) in the presence of LiBr / Et_3N. This reaction gave the tricyclic compound (30b) and the Michael adduct (31) in a 1 : 1 ratio.

4-4. Regio- and Stereoselectivity of 1,3-Dipolar Cycloaddition Reactions of (22) and Azomethine Ylides

It has been observed experimentally that azomethine ylides show a high regioselectivity in their reactions with electron deficient alkenes.[126-130] Calculation of the energies of the various orbitals involved for different types of cycloadditions by Houk[137] and Padwa *et al.*[77] revealed that the azomethine ylides are all electron rich species characterized by relatively high energy HOMOs and LUMOs. From these calculations it has been concluded that such species react preferentially with electron deficient alkenes to give products via a transition state that favours 4-substituted adducts because of a more favourable $HOMO_{dipole}$-$LUMO_{dipolarophile}$ interaction. This explanation can be used to explain the regiochemistry of the 1,3-dipolar cycloaddition of alkene (22) and azomethine ylides (24a-e). In all cases we observed exclusively 2',3',3',5',5'-pentasubstituted pyrrolidine cycloadducts except in the case of (23a) using Method III where a small amount (5%) of the 2',2',3',3',5'-pentasubstituted pyrrolidine cycloadduct (25c) was observed.

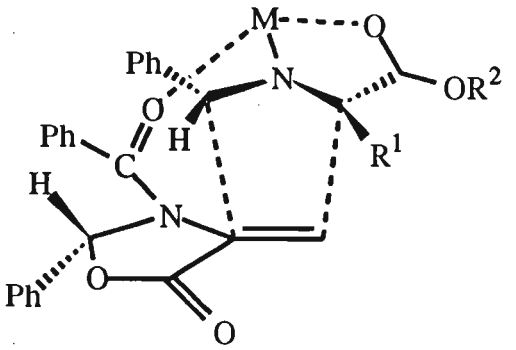
While *endo* cycloaddition adducts are generally favoured in 1,3-dipolar cycloaddition reactions of azomethine ylides,[126,127(a,e,g),128(a,c-e,g),129(b,c,g,h)] *exo*-diastereoselective azomethine ylide cycloadditions are not uncommon.[129e,138] Garner *et al.*[138] reported the intermolecular cycloaddition of azomethine ylide (42) to Oppolzer's chiral acryloyl sultam (43) gave cycloadducts (44)-(47) with high *exo*-diastereoselectivity (Scheme 4.14).

Scheme 4.14



(44) + (45) : (46) + (47) = 5:1

The preference for *exo* cycloaddition adducts in the reaction of (22) and azomethine ylides (24a)-(24d) can be rationalized by assuming chelation between the metal cation and *N*-benzoyl carbonyl group in alkene (22) and the azomethine ylide, as shown in the possible transition state structure (48).



(48)

A secondary orbital interaction between the nitrogen of the azomethine ylide and the benzamido nitrogen in the alkene (22) in the $HOMO_{dipole}$-$LUMO_{dipolarophile}$ pair (Figure 4.6) is another possible reason for the formation of *exo* cycloadducts in these series of reactions.

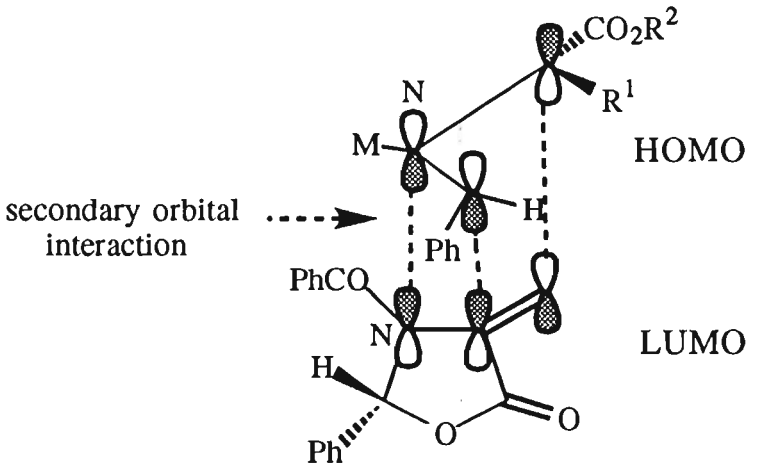


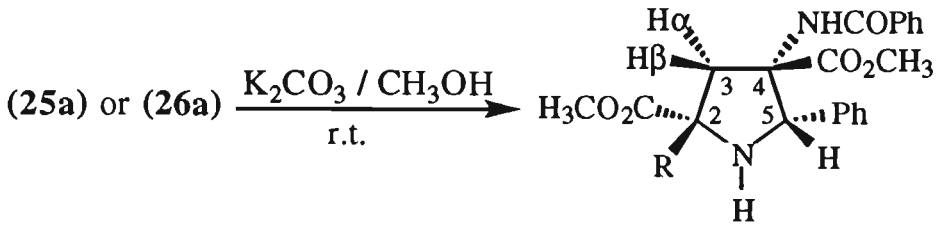
Figure 4.6. Orbital interactions between dipolarophile (22) and azomethine ylides in *exo* transition state.

4-5. Synthesis of Proline Derivatives

The polyfunctional proline derivatives (49) and (50) were prepared by based catalysed methanolysis of the oxazolidinone moiety of the major dipolar cycloadducts (25a) and (26a), respectively (Scheme 4.15). Treatment of the cycloadducts (40) and (50) in methanol solution with anhydrous potassium carbonate at room temperature for 13 hr and then purification of the products by column chromatography gave the proline derivatives (49) and (50) in high yields (86-95%). The structures of (49)

and (50) were evident from their spectral analysis and both compounds were a single diastereoisomer. The structure of (50) was elucidated by a single crystal X-ray structural determination (Figure 4.7). This X-ray structure also confirmed the stereochemistry of the cycloadduct (26a) as being *exo*.

Scheme 4.15



(49); R = CH_2Pr^i ($[\alpha]_D^{25}$ + 69.0, *c* 0.3 in $CHCl_3$)
(50); R = CH_2Ph ($[\alpha]_D^{28}$ + 82.8, *c* 0.6 in $CHCl_3$)

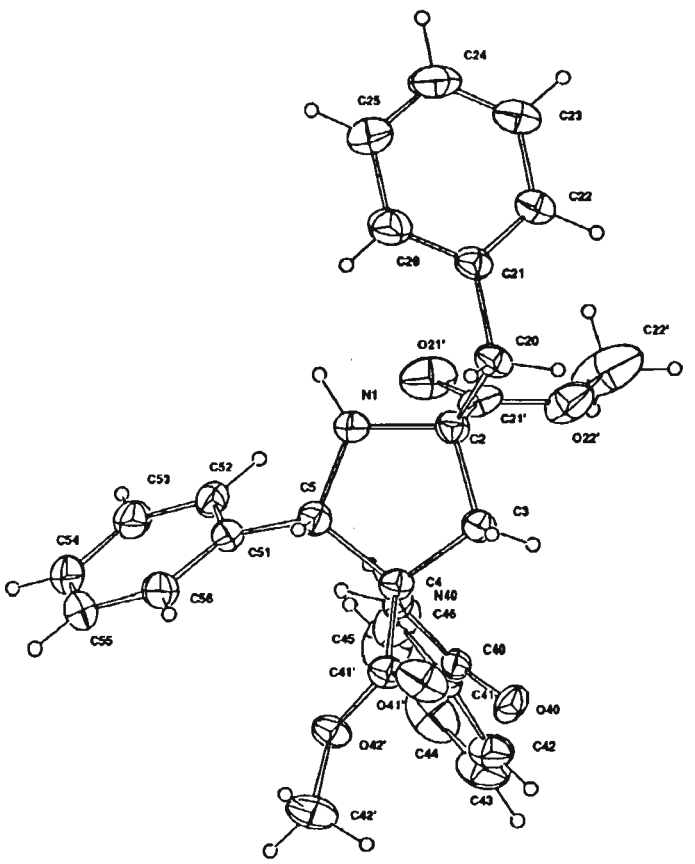
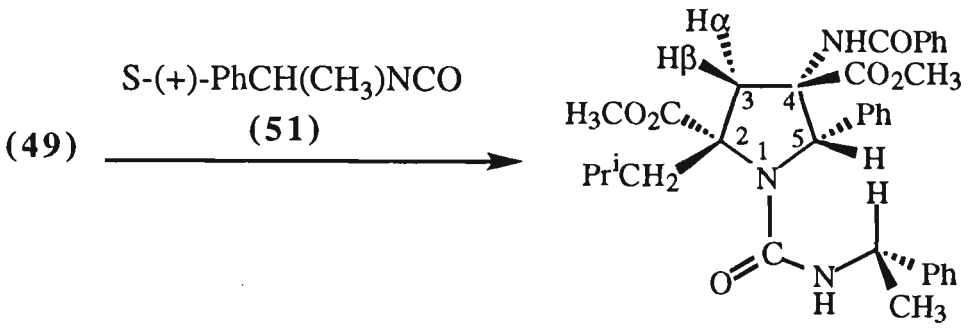


Figure 4.7. Molecular projection of **(50)** normal to the plane of five-membered ring.

The enantiomeric purity of (25a) was determined to be 92% based on ^1H NMR analysis of its diastereomeric carbamate derivatives (52) from treatment with (*S*)-(+)-1-phenylethylisocyanate (51) (Scheme 4.16).

Integration of the resonances for the diastereotopic methylene protons H3α and H3β for the major and the minor diastereoisomers of (52) showed that these diastereoisomers were in a ratio of 96 : 4. This allowed the enantiomeric purity of (25a) to be calculated as 92%.

Scheme 4.16



(52)

4-6. Conclusions

In this Chapter, a new method for the synthesis of polyfunctional prolines, through the 1,3-dipolar cycloaddition reactions of the chiral dipolarophile (22) and *N*-benzylidene amino acid esters have been presented. The cycloadducts resulted from addition to the *exo*-cyclic methylene of (22) from the less hindered π-face. It was found that these reactions proceeded with good to high *exo*-diastereoselectivity and they were highly regioselective to produce only 2',3',3',5',5'-pentasubstituted pyrrolidines. When Method I (LiBr / DBU / THF) was employed the diastereoselectivities were much higher than that for Method II (LiBr / Et_3N / CH_3CN) or Method III (AgOAc / DBU / THF). The regio- and stereoselectivity of these reactions can be explained by frontier molecular orbital theory. The stereochemistry of the cycloadducts has been elucidated by single crystal X-ray structural determinations and 1D and 2D ^1H NMR analysis. The highly functionalized prolines (49) and (50) of cycloadducts (25a) and (26a) were synthesised in high enantiomeric purity (92% e.e.) by methanolysis of the oxazolidinone moiety.

EXPERIMENTAL

CHAPTER FOUR

For general experimental procedures see the Experimental Section of Chapter Two.

Crystal / refinement data.

(25a). $C_{31}H_{32}N_2O_5$, M = 512.6. Monoclinic, space group $P2_1$; *a* = 11.605 (5), *b* = 10.422 (9), *c* = 11.286 (8) Å, β = 100.38 (5)°, *V* = 1343 (2) Å^3. D_c (Z = 2) = 1.27 g.Cm.$^{-3}$; F (000) = 544

(25b). $C_{31}H_{32}N_2O_5$, M = 512.6. Orthorhombic, space group $P2_12_12_1$ (D_2 4, No. 19), *a* = 17.43 (2), *b* = 13.988 (4), *c* = 11.278 (4) Å, *V* = 2750 (3) Å^3. D_c (Z = 4) = 1.24 g.Cm.$^{-3}$; F (000) = 1088.

(26b). $C_{35}H_{32}N_2O_5$, M = 560.7. Monoclinic, space group $P2_1$, *a* = 9.627 (6), *b* = 9.06 (1), *c* = 16.76 (1) Å, β = 90.39 (6)°, *V* = 1461 (2) Å^3. Dc (Z = 2) = 1.27 g.cm.$^{-3}$; F (000) 592.

(49). $C_{28}H_{28}N_2O_5$, M = 472.6. Monoclinic, space group $P2_1$, (C_2^2, No. 4) *a* = 10.612 (4), *b* = 9.384 (s), *c* = 13.134 (9) Å, β = 91.83 (4)°, *V* = 1307 (1) A^3. D_c (Z = 2) = 1.20 g.cm.$^{-3}$; F (000) 500.

Preparation of 2-Phenylglycine methyl ester hydrochloride (36c).

To a magnetically stirred solution of 2-phenylglycine (37) (3.4 g, 22.5 mmol) in dry methanol (20 mL) at 0 °C was slowly added thionyl chloride (3.0 g, 2.5 mmol). The homogeneous solution was left to stand for 16 hr. The methanol was then evaporated in vacuo to furnish a white solid, 4.3 g (95%). ^{1}H NMR δ 7.52-7.46 (m, 5H), 5.27 (s, 1H, C<u>H</u>Ph), 3.78 (s, 3H, CH_3).

General Method for the Preparation of Imines (23a-e).[132a]

The amino acid ester hydrochloride (9.25 mmol) and sodium carbonate (9.25 mmol) were dissolved in water (25 mL). Benzaldehyde (1 g, 9.25

mmol) was added to the clear solution while stirring. The reaction mixture was heated to 40 °C and stirred for 1 hr and then at room temperature for a further 20 hr. The mixture was then extracted with chloroform (3 x 100 mL) and the combined chloroform extracts were washed with water (2 x 100 mL), dried ($MgSO_4$) and evaporated under reduced pressure to afford the crude imine.

Methyl *N*-benzylideneleucinate (23a). (70%) Colourless liquid. ^1H NMR δ 8.29 (s, 1H, CH=N), 7.87-7.38 (m, 5H), 4.09 (dd, J = 6, 8.8 Hz, 1H, C<u>H</u>CO_2CH_3), 3.73 (s, 3H, CO_2CH_3), 1.85 (m, 2H, CH_2), 1.58 (m, 1H, C<u>H</u>$(CH_3)_2$), 0.95 (d, J = 6.8 Hz, 3H, CH_3), 0.9 (d, J = 6.6 Hz, 3H, CH_3). MS (CI) *m/z* 234 (24%, MH^+), 174 (43), 131 (65), 105 (100).

Ethyl *N*-benzylidenephenylalaninate (23b). (85%) Colourless semisolid. ^1H NMR δ 7.92 (s, 1H, CH=N), 7.69-7.15 (m, 10H), 4.17 (m, 3H, C<u>H</u>$CO_2C\underline{H}_2CH_3$), 3.36 (dd, J = 5.6, 13.6 Hz, 1H, C<u>H$_A$H$_B$</u>Ph), 3.14 (dd, J = 8.8, 13.6 Hz, 1H, $CH_A\underline{H_B}$Ph), 1.22 (t, J = 7.2 Hz, 3H, CH_3). MS (CI) *m/z* 282 (8%, MH^+), 208 (55), 190 (65), 116 (100).

Methyl *N*-benzylidenephenylglycinate (23c). (80%) Colourless solid, m.p. 47-8 °C. ^1H NMR δ 8.32 (s, 1H, CH=N), 7.82-7.80 (m, 10H), 5.20 (s, 1H, C<u>H</u>CO_2CH_3), 3.71 (s, 3H, CH_3). MS (CI) *m/z* 254 (17%, MH^+), 194 (100).

Methyl *N*-benzylidenealaninate (23d). (80%) Colourless liquid. ^1H NMR δ 8.30 (s, 1H, CH=N), 7.89-7.39 (m, 5H), 4.15 (q, J = 6.6, 13.5 Hz, 1H, C<u>H</u>CO_2CH_3), 3.73 (s, 3H, CO_2CH_3), 1.52 (d, J = 6.6 Hz, 3H, CH_3). MS (CI) *m/z* 192 (29%, MH^+), 132 (100).

Ethyl N-benzylideneglycinate (23e). (83%) Colourless liquid. ^1H NMR δ 8.29 (s, 1H, CH=N), 7.89-7.39 (m, 5H), 4.40 (s, 2H,

$C\underline{H}_2CO_2CH_2CH_3$), 4.23 (q, J = 7.2 Hz, 2H, $C\underline{H}_2CH_3$), 1.30 (t, J = 7.2 Hz, 3H, $CH_2C\underline{H}_3$). MS (CI) *m/z* 192 (90%, MH^+), 116 (100).

General Procedure for Preparing Cycloadducts:

To a solution of the imine (0.91 mmol) and metal salt (AgOAc or LiBr, 0.91 mmol) in either dry THF or CH_3CN (10 mL) was slowly added, by the aid of syringe at -78 °C under N_2, a solution of the alkene (22) (0.225 mg, 0.8 mmol) in the same solvent as the imine / metal salt (5 mL) and then DBU or Et_3N (0.91 mmol). The mixture was stirred at the temperature and for the period of time as reported in Table 4.2, page 170 (the progress of the reaction was monitored by TLC). The mixture was quenched with a solution of saturated aqueous ammonium chloride (20 mL) and the products were extracted into diethyl ether (3 x 20 mL). The combined extracts were dried ($MgSO_4$) and evaporated in vacuo. The residue was chromatographed over silica gel using ethyl acetate / hexane (20-30 / 80-70) as an eluent to give the products. The diastereoselection of these reactions were determined from ^1H NMR analysis of the crude reaction mixture.

(2*R*,2'*S*,4*S*,5'*S*) and (2*R*,2'*R*,4*S*,5'*R*)-3-Benzoyl-2-phenyl-oxazolidin-5-one-4-spiro-3'-[5'-methoxycarbonyl-5'-(2-methyl-1-propyl)-2'-phenyl]pyrrolidine (25a) and (25b).

(25a): M.p. 142-3 °C; $[\alpha]_D^{20}$ +166.5 (*c* 0.8 in $CHCl_3$). ^1H NMR δ 7.46-6.07 (m, 15H), 5.80 (s, 1H, H2), 4.91 (s, 1H, H2'), 4.23 (bs, 1H, NH), 3.88 (s, 3H, CO_2CH_3), 3.54 (d, J = 14 Hz, 1H, H4'β), 2.79 (d, J = 14 Hz, 1H, H4'α), 2.25 (dd, J = 8, 17.4 Hz, 1H, $C\underline{H}_AH_BCH(CH_3)_2$), 1.98 (m, 2H, $CH_A\underline{H}_BCH(CH_3)_2$), 1.02 (d, J = 6.4 Hz, 3H, CH_3), 0.91 (d, J = 6 Hz, 3H, CH_3). ^{13}C NMR δ 175.2 (CO), 174.6 (CO), 169.8 (CO), 136.2, 136.1, 136.0, 129.8, 129.7, 128.8, 128.5, 128.1, 128, 126.3, 126.2, 125.4, 90.6 (C2), 73.7 (C4), 72.9 (C5'), 70.7 (C2'), 52.4 ($CO_2\underline{C}H_3$), 50.8 (C4'), 46.5

($\underline{C}H_2CH(CH_3)_2$), 24.8 ($CH_2\underline{C}H(CH_3)_2$), 24.4 ($CH_3$), 22.7 ($CH_3$). IR (nujol) 3250 1747, 1705, 1631, 1306, 1213, 1192, 1151, 1134, 1018, 1007, 851, 690 Cm^{-1}. MS (ES) *m/z* 513 (100%, MH^+). Anal. Calcd for $C_{31}H_{32}N_2O_5$: C, 72.66; H, 6.25; N, 5.45%. Found: C, 72.87; H, 6.35; N, 5.32%.

(25b): M.p. 220 °C; $[\alpha]_D^{24}$ +189.6 (*c* 0.5 in $CHCl_3$). ^1H NMR δ 7.51-6.70 (m, 15H), 6.04 (s, 1H, H2), 5.45 (s, 1H, H2'), 3.86 (s, 3H, CO_2CH_3), 3.80 (bs, 1H, NH), 3.57 (d, J = 13.2 Hz, 1H, H4'β), 2.90 (d, J = 13.2 Hz, 1H, H4'α), 2.24 (dd, J = 6.4, 13.6 Hz, 1H, $C\underline{H}_AH_BCH(CH_3)_2$), 1.99 (dd, J = 6.8, 13.6 Hz, 1H, $CH_A\underline{H}_BCH(CH_3)_2$), 1.87 (m, 1H, $CH_2C\underline{H}(CH_3)_2$), 1.02 (d, J = 6.8 Hz, 3H, CH_3), 0.89 (d, J=6.8 Hz, 3H, CH_3). ^{13}C NMR δ 175.6 (CO), 172.1 (CO), 169.2 (CO), 136.2, 135.9, 135.0, 130.2, 129.9, 128.9, 128.8, 128.7, 128.6, 127.3, 126.2, 125.9, 90.0 (C2), 72.1 (C4), 67.5 (C5'), 62.9 (C2'), 52.5 ($CO_2\underline{C}H_3$), 49.0 (C4'), 44.4 ($\underline{C}H_2CH(CH_3)_2$), 25.3 ($CH_2\underline{C}H(CH_3)_2$), 24.5 ($CH_3$), 22.9 ($CH_3$). IR (nujol) 3258 1770, 1701, 1625, 1318, 1257, 1209, 1150, 1128, 1021, 818, 770, 731, 690 cm^{-1}. MS (ES) *m/z* 513 (100%, MH^+). Anal. Calcd for $C_{31}H_{32}N_2O_5$: C, 72.66; H, 6.25; N, 5.45%. Found: C, 73.05; H, 6.31; N, 5.47%.

3-Benzoyl-2-phenyl-oxazolidin-5-one-4-spiro-3'-[2'-methoxy carbonyl-2'-(2-methyl-1-propyl)-5'-phenyl]pyrrolidine (25c).

M.p. 149-51 °C dec; $[\alpha]_D^{24}$ +93.3 (*c* 0.12 in $CHCl_3$). ^1H NMR δ 7.58-6.8 (m, 15H), 6.63 (s, 1H, H2), 4.91 (bs, 1H, H5'), 3.96 (dd, J = 6.8, 12.8 Hz, 1H, H4'), 3.84 (s, 3H, CO_2CH_3), 3.12 (bs, 1H, NH), 2.54 (dd, J = 10, 12.8 Hz, 1H, H4'), 2.35 (dd, J = 6.4, 13.6 Hz, 1H, $C\underline{H}_AH_BCH(CH_3)_2$), 2.06 (dd, J = 5.2, 13.6 Hz, 1H, $CH_A\underline{H}_BCH(CH_3)_2$), 1.79 (m, 1H, $CH_2C\underline{H}(CH_3)_2$), 1.04 (d, J = 6.8 Hz, 3H, CH_3), 0.88 (d, J = 6.8 Hz, 3H, CH_3). ^{13}C NMR δ 175.4 (CO), 173.6 (CO), 171.4 (CO), 140.9, 137.3, 136.6, 130.5, 129.7, 128.7, 128.6, 128.59, 127.7, 127.1, 126.9, 126.2,

91.7 (C-2), 81.7 (C-4), 75.4 (C2'), 60.6 (C5'), 52.8 ($CO_2\underline{C}H_3$), 44.0 (C4'), 41.3 ($\underline{C}H_2CH(CH_3)_2$), 25.5 ($CH_2\underline{C}H(CH_3)_2$), 24.4 ($CH_3$), 23.8 ($CH_3$). IR (nujol) 3250 1750, 1717, 1632, 1129, 1208, 1153, 1020, 745, 690 cm^{-1}. MS (ES) *m/z* 513 (100%, MH^+), 71 (94).

(2*R*,2'*S*,4*S*,5'*S*) and (2*R*,2'*R*,4*S*,5'*R*)-3-Benzoyl-2-phenyl-oxazolidin-5-one-4-spiro-3'-(5'-benzyl-5'-ethoxycarbonyl-2'-phenyl)pyrrolidine (26a) and (26b).

(26a): M.p. 201-2 °C; $[\alpha]_D^{24}$ +191.4 (*c* 1.3 in $CHCl_3$). ^1H NMR δ 7.5-6.1 (m, 20H), 5.8 (s, 1H, H2), 5.1 (d, J = 12.4 Hz, 1H, H2'), 4.24 (m, 2H, $CO_2C\underline{H}_2CH_3$), 4.11 (d, J = 12.4 Hz, 1H, NH), 3.67 (d, J = 14 Hz, 1H, H4'β), 3.52 (d, J = 13.6 Hz, 1H, $C\underline{H}_AH_BPh$), 3.26 (d, J = 13.6 Hz, 1H, $CH_A\underline{H}_BPh$), 3.02 (d, J = 14.4 Hz, 1H, H4'α), 1.22 (t, J = 7.2 Hz, 3H, CH_3). ^{13}C NMR δ 174.6 (CO), 173.6 (CO), 169.8(CO), 136.7, 136, 135.6, 135.5, 130.4, 129.85, 129.81, 128.9, 128.6, 128.2, 128.1, 128.0, 126.7, 126.5, 126.4, 125.5, 90.7 (C2), 74.0 (C4), 72.9 (C2'), 72.6 (C5'), 61.4 ($CO_2\underline{C}H_2CH_3$), 49.0 ($\underline{C}H_2Ph$), 44.1 (C4'), 14.1 (CH_3). IR (nujol) 3278 1750, 1716, 1639, 1335, 1310, 1175, 1155, 1073, 1020, 689 cm^{-1}. MS (ES) *m/z* 561 (100%, MH^+). Anal. Calcd for $C_{35}H_{32}N_2O_5$: C, 75.00; H, 5.71; N, 5.00%. Found: C, 74.74; H, 5.81; N, 4.91%.

(26b): M.p. 212-13 °C; $[\alpha]_D^{24}$ +173.7 (*c* 0.27 in $CHCl_3$). ^1H NMR δ 7.52-6.72 (m, 20H), 6.04 (s, 1H, H2), 5.58 (d, J = 9.6 Hz, 1H, H2'), 4.19 (m, 2H, $CO_2C\underline{H}_2CH_3$), 3.76 (d, J = 13.6 Hz, 1H, $C\underline{H}_AH_BPh$), 3.61 (d, J = 10.8 Hz, 1H, NH), 3.51 (d, J=14 Hz, 1H, H4'β), 3.31 (d, J=13.6 Hz, 1H, H4'α), 3.01 (d, J = 13.6 Hz, 1H, $CH_A\underline{H}_BPh$), 1.24 (t, J = 7.0 Hz, 3H, CH_3). ^{13}C NMR δ 173.8 (CO), 171.9 (CO), 169.3 (CO), 137.0, 136.2, 136.0, 135.2, 130.3, 130.2, 129.9, 128.93, 128.9, 128.7, 128.6, 127.9, 127.4, 126.7, 126.4, 125.8, 90.0 (C2), 72.2 (C4), 69.0 (C5'), 62.9 (C2'), 61.5 ($CO_2\underline{C}H_2CH_3$), 46.4 ($\underline{C}H_2Ph$), 42.9 (C4'), 14.1 (CH_3). IR (nujol)

3280 1765, 1708, 1639, 1359, 1337, 1324, 1210, 1180, 1151, 1109, 1021, 721, 692 cm^{-1}. MS (ES) *m/z* 561 (100%, MH^+), 288 (15).

(2*R*,2'*S*,4*S*,5'*R*) and (2*R*,2'*R*,4*S*,5'*S*)-3-Benzoyl-2-phenyl-oxazolidin-5-one-4-spiro-3'-(5'-methoxycarbonyl-2',5'-diphenyl)pyrrolidine (27a) and (27b).

(27a): M.p. 100-101 °C, $[\alpha]_D^{26}$ +178.3 (*c* 0.6 in $CHCl_3$). ^1H NMR δ 7.91-6.20 (m, 20H), 5.76 (s, 1H, H2), 4.76 (bd, J = 9.9 Hz, 1H, H2'), 4.54 (bs, 1H, NH), 4.18 (d, J = 14.4 Hz, 1H, H4'β), 3.80 (s, 3H, CH_3), 3.53 (d, J = 14.4 Hz, 1H, H4'α). ^{13}C NMR δ 173.8 (CO), 173.5 (CO), 170.5 (CO), 141.4, 135.9, 135.5, 135.4, 129.9, 129.8, 128.9, 128.6, 128.5, 128.3, 128.2, 127.9, 126.5, 126.4, 126.2, 125.5, 90.5 (C2), 74.5 (C4), 73.8 (C2'), 73.1 (C5'), 53.1 (CH_3), 51.3 (C4'). IR (nujol) 3275, 1742, 1710, 1616, 1340, 1225, 1195, 1155, 1010, 685 cm^{-1}. MS (CI) *m/z* 533 (7%, MH^+), 323 (18), 253 (100). Anal. Calcd for $C_{33}H_{28}N_2O_5$: C, 74.44; H, 5.26; N, 5.26%. Found: C, 74.40; H, 5.40; N, 4.97%.

(27b): M.p. 70-2 °C; $[\alpha]_D^{23}$ +40.95 (*c* 0.4 in $CHCl_3$). ^1H NMR δ 7.91-6.76 (m, 20H), 6.35 (s, 1H, H2), 6.21 (bs, 1H, H2'), 5.17 (bs, 1H, NH), 3.78 (d, J = 11.7 Hz, 1H, H4'β), 3,70 (s, 3H, CH_3), 3.19 (d, J = 12.3 Hz, 1H, H4'α). ^{13}C NMR δ 174 (CO), 172.3 (CO), 171.0 (CO), 136.7, 135.5, 135.1, 134.4, 129.4, 129.2, 129.1, 128.9, 128.7, 128.6, 128.3, 127.4, 127.1, 127.0, 126.8, 126.3, 91.3 (C2), 77.1 (C2'), 73.5 (C4), 70.1, (C5'), 52.5 (CH_3), 41.6 (C4'). IR (nujol) 3277, 1750, 1705, 1619, 1350, 1250, 1180, 1140, 1020, 689 cm^{-1}. MS (ES) *m/z* 533 (90%, MH^+), 339 (100).

(2*R*,2'*S*,4*S*,5'*S*) and (2*R*,2'*R*,4*S*,5'*R*)-3-Benzoyl-2-phenyl-oxazolidin-5-one-4-spiro-3'-(5'-methoxycarbonyl-5'-methyl-2'-phenyl)pyrrolidine (28a) and (28b).

(28a): M.p. 156-7 °C; $[\alpha]_D^{26}$ +158.8 (*c* 1 in $CHCl_3$). ^1H NMR δ 7.48-6.10 (m, 15H), 5.80 (s, 1H, H2), 5.03 (s, 1H, H2'), 4.36 (bs, 1H, NH), 3.90 (s, 3H, CO_2CH_3), 3.65 (d, J = 13.8 Hz, 1H, H4'β), 2.85 (d, J = 14.1 Hz, 1H, H4'α), 1.78 (s, 3H, CH_3). ^{13}C NMR δ 175.3 (CO), 174.4 (CO), 170.0 (CO), 135.9, 135.5, 135.4, 129.8, 128.8, 128.5, 128.2, 128.1, 126.4, 126.2, 126.1, 125.4, 90.6 (C2), 74.0 (C4), 72.6 (C2'), 67.5 (C5'), 52.6 ($CO_2\underline{C}H_3$), 46.6 (C4'), 25.9 (CH_3). IR (nujol) 3245, 1751, 1701, 1625, 1310, 1200, 1117, 1010, 738, 685 cm^{-1}. MS (CI) *m/z* 471 (20%, MH^+), 321 (10), 261 (60), 202 (55), 191 (100). Anal. Calcd for $C_{28}H_{26}N_2O_5$: C, 71.49; H, 5.53; N, 5.96%. Found: C, 71.66; H, 5.61: N, 5.72%.

(28b): M.p. 168-9 °C; $[\alpha]_D^{28}$ +204.2 (*c* 0.8 in $CHCl_3$). ^1H NMR δ 7.48-6.7 (m, 15H), 6.06 (s, 1H, H2), 5.59 (s, 1H, H2'), 3.88 (s, 4H, NH, CO_2CH_3), 3.59 (d, J = 12.8 Hz, 1H, H4'β), 2.98 (d, J = 12.8 Hz, 1H, H4'α), 1.84 (s, 3H, CH_3). ^{13}C NMR δ 175.6 (CO), 171.9 (CO), 169.1 (CO), 136.1, 135.8, 134.7, 130.2, 129.8, 128.8, 128.7, 128.6, 128.5, 127.1, 126.3, 125.8, 90.0 (C2), 72.3 (C4), 64.2 (C5'), 62.6 (C2'), 52.7 ($CO_2\underline{C}H_3$), 43.6 (C4'), 28.1 (CH_3). IR (nujol) 3245, 1760, 1770, 1628, 1330, 1210, 1190, 1120, 730, 689 cm^{-1}. MS (CI) *m/z* 471 (10%, MH^+) 321 (10), 261 (50), 202 (62), 191 (100). Anal. Calcd for $C_{28}H_{26}N_2O_5$: C, 71.49; H, 5.53; N, 5.96%. Found: C, 71.30; H, 5.55: N, 5.77%.

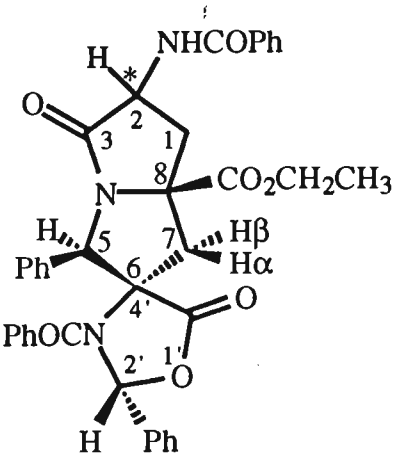
(2*R*,2'*S*,4*S*,5'*S*) and (2*R*,2'*R*,4*S*,5'*R*)-3-Benzoyl-2-phenyl-oxazolidin-5-one-4-spiro-3'-(5'-ethoxycarbonyl-2'-phenyl) pyrrolidine (29a) and (29b).

(29a): M. p. 154-6 °C; $[\alpha]_D^{24}$ +257.7 (*c* 0.3 in $CHCl_3$). ^1H NMR δ 7.47-6.09 (m, 15H), 5.88 (s, 1H, H2), 4.81 (d, J = 9.6 Hz, 1H, H2'), 4.36 (m, 3H, H5', $CO_2C\underline{H}_2CH_3$), 4.05 (bs, 1H, NH), 3.41 (dd, J = 9.6, 13.2 Hz, 1H, H4'β), 3.10 (dd, J = 8.8, 13.6 Hz, 1H, H4'α), 1.38 (t, J = 7.2 Hz, 3H,

CH_3). ^{13}C NMR δ 174.5 (CO), 171.2 (CO), 169.9 (CO), 135.9, 135.5, 135.3, 129.9, 129.8, 128.8, 128.6, 128.2, 128.1, 126.3, 126.2, 125.3, 90.6 (C2), 74.4 (C5'), 72.8 (C4), 61.9 (C2'), 61.4 ($CO_2\underline{C}H_2CH_3$), 42.8 (C4'), 14.2 (CH_3). IR (nujol) 3300, 1752, 1711, 1621, 1218, 1193, 1151, 1020, 690 cm^{-1}. MS (ES) *m/z* 471 (100%, MH^+), 153 (7), 102 (10).

(29b): M.p. 53.5 °C; $[\alpha]_D^{24}$ +144.4 (*c* 0.9 in $CHCl_3$). ^1H NMR δ 7.49-6.71 (m, 15H), 6.25 (s, 1H, H2), 5.20 (s, 1H, H2'), 4.60 (bs, 1H, H5'), 4.32 (m, 2H, $CO_2C\underline{H}_2CH_3$), 3.57 (dd, J = 8.4, 12.4 Hz, 1H, H4'β), 3.27 (bs, 1H, NH), 2.70 (dd, J = 8.4, 12.8 Hz, 1H, H4'α), 1.36 (t, J = 7.2 Hz, 3H, CH_3). ^{13}C NMR δ 172.4 (CO), 171.9 (CO), 168.9 (CO), 136.2, 135.8, 135.1, 130.3, 129.9, 128.8, 128.7, 128.5, 128.4, 126.9, 126.4, 125.9, 90.1 (C2), 71.4 (C4), 66.5 (C5'), 61.4 ($CO_2\underline{C}H_2CH_3$), 58.9 (C2'), 39.6 (C4'), 14.2 (CH_3). IR (nujol) 3250 1761, 1691, 1628, 1325, 1210, 1148, 1022, 848, 725, 690 cm^{-1}. MS (ES) *m/z* 493 (95%, MNa^+), 471 (100, MH^+), 316 (15), 288 (38). Anal. Calcd for $C_{28}H_{26}N_2O_5$: C, 71.50; H, 5.53; N, 5.96%. Found: C, 71.71; H, 5.89; N, 5.61%.

(5*S*,6*S*,8*S*,2'*R*)-2-Benzamido-8-ethoxycarbonyl-hexahydro-3H-pyrrolizin-3-one-6-spiro-4'-(3'-benzoyl-2'-phenyl)oxazolidin-5'-one (30a) and (30b).



(30a) and (30b)

(30a): M.p. 103-5 °C; $[\alpha]_D^{26}$ +108.7 (*c* 0.45 in $CHCl_3$). ^1H NMR δ 7.82-6.77 (m, 20H), 6.45 (s, 1H, H2'), 6.08 (s, 1H, H5), 5.26 (m, 1H, H2),

4.47 (q, J = 7.2, 10.8 Hz, 1H, $CO_2CH_AH_BCH_3$), 4.36 (q, J = 7.2, 10.8 Hz, 1H, $CO_2CH_AH_BCH_3$), 3.76 (d, J = 12.8 Hz, 1H, 7β), 3.41 (dd, J = 7.6, 12.8 Hz, 1H, H1), 3.35 (d, J = 12.8 Hz, 1H, H7α), 2.42 (t, J = 12.4 Hz, 1H, H1), 1.43 (t, J = 7.2 Hz, 3H, CH_3). ^{13}C NMR δ 174.4 (CO), 171.8 (CO), 169.3 (CO), 169.1 (CO), 167.5 (CO), 135.4, 135.15, 135.1, 133.3, 131.6, 130.5, 130,1, 128.7, 128.68, 128.6, 128.4, 128.38, 127.0, 126.3, 126.1, 125.6, 90.5 (C2'), 74.0 (C), 69.5(C), 62.5 ($CO_2CH_2CH_3$), 61.8 (C5), 53.0 (C2), 45.7 (C1), 41.7 (C7), 14.0 (CH_3). MS (ES) *m/z* 666 (21%, MNa^+), 644 (91, MH^+), 281 (56), 195 (100), 142 (86).

(30b): M.p. 110-113 °C; $[\alpha]_D^{29}$ +33.0 (*c* 0.1 in $CHCl_3$). ^1H NMR δ 7.87-6.80 (m, 20H), 6.49 (s, 1H, H2'), 6.00 (s, 1H, H5), 5.21 (bt, J = 8.1 Hz, 1H, H2), 4.40 (dd, J = 7.2, 10.8, Hz, 1H, $CO_2CH_AH_BCH_3$), 4.29 (dd, J = 7.5, 10.5 Hz, 1H, $CO_2CH_AH_BCH_3$), 3.82 (d, J = 12.6, Hz, 1H, H7β), 3.29 (d, J = 12.3 Hz, 1H, H7α), 2.8 (dd, J = 8.1, 14.4 Hz, 1H, H1), 2.53 (d, J = 14.1 Hz, 1H, H1), 1.29 (t, J = 7.2 Hz, 3H, CH_3). ^{13}C NMR δ 174.5 (CO), 173.7 (CO), 169.7 (CO), 169 (CO), 166.5 (CO), 135.6, 135.2, 135.0, 133.3, 131.7, 130.6, 130.2, 128.9, 128.8, 128.7, 128.5, 127.0, 126.4, 126.3, 125.8, 90.7 (C2'), 78.8 (C), 71.3 (C), 62.8 ($CO_2CH_2CH_3$), 62.3 (C5), 53.9 (C2), 43.3 (C1), 41.2 (C4), 13.9 (CH_3). MS (ES) *m/z* 644 (33%, MH^+), 2.11 (25), 193 (30), 192 (100).

5-Ethoxycarbonyl-3-phenylpyrrolidin-2-one (35).

M.p. 135-6 °C; $[\alpha]_D^{29}$ -12.0 (*c* 0.15 in $CHCl_3$). ^1H NMR δ 7.80-7.37 (m, 5H), 7.06 (d, J = 4.8 Hz, 1H, NH), 6.65 (bs, 1H, NH), 4.56 (m, 1H), 4.25 (m, 3H), 2.98 (m, 1H, H4), 2.42 (m, 1H, H4), 1.31 (t, J = 7.2, 3H, CH_3). ^{13}C NMR δ 175.7 (CO), 171.8 (CO), 167.8 (CO), 133.2, 131.8, 128.4, 127.1, 62.0 (CH_2), 53.2 (CH), 49.8 (CH), 32.9 (CH2), 14.1 (CH_3). MS (ES) *m/z* 299 (47%, MNa^+), 277 (55, MH^+), 141 (57).

Preparation of Proline Derivatives, A General Procedure:

To a solution of (25a) or (26a) (117 mmol) in dry methanol (10 mL) under nitrogen was added powdered anhydrous potassium carbonate (17 mg, 117 mmol). The mixture was stirred at room temperature for 13 hr. The mixture was then diluted with ethyl acetate (20 mL) and washed with a saturated aqueous solution of ammonium chloride. The aqueous layer was extracted with ethyl acetate (2 x 10 mL). The combined organic extracts were washed with water and brine, then dried over $MgSO_4$ and concentrated in vacuo. Short path column chromatography on silica gel using ethyl acetate / hexane (20 / 80) as eluent gave the proline derivatives (49) or (50).

Methyl (2*S*,3*S*,5*S*)-2-(2-methyl-1-propyl)-4-benzamido-4-methoxy carbonyl-5-phenylprolinate (49).

White solid (86%). M.p. 75-6 °C; $[\alpha]_D^{25}$ +69.0 (*c* 0.3 in $CHCl_3$). ^1H NMR δ 7.57-7.35 (m, 10H), 6.14 (s, 1H, N<u>H</u>COPh), 4.78 (s, 1H, H5), 3.71 (s, 3H, CO_2CH_3), 3.52 (d, J = 14 Hz, 1H, H3β), 3.46 (s, 3H, CO_2CH_3), 3.1 (bs, 1H, NH), 2.92 (d, J = 14 Hz, 1H, H3α), 1.92 (dd, J = 6, 13.2 Hz, 1H, C<u>H</u>$_A$H$_B$CH(CH$_3$)$_2$), 1.70 (m, 2H, CH$_A$<u>H</u>$_B$C<u>H</u>(CH$_3$)$_2$), 0.96 (d, J = 6.4 Hz, 3H, CH_3), 0.88 (d, J = 6.4 Hz, 3H, CH_3). ^{13}C NMR δ 178.3 (CO), 171.3 (CO), 167.0 (CO), 135.7, 133.9, 131.7, 129.2, 129.1, 128.5, 127.1, 126.8, 70.3 (C-4), 67.7 (C2), 66.9 (C5), 52.6 ($CO_2\underline{C}H_3$), 52.3 ($CO_2\underline{C}H_3$), 48.9 (C3), 46.0 ($\underline{C}H_2CH(CH_3)_2$), 25.5 ($CH_2\underline{C}H(CH_3)_2$), 23.9 ($CH_3$), 23.3 ($CH_3$). IR (nujol) 3355, 3310, 1698, 1640, 1572, 1550, 1490, 1460, 1270, 1240, 1200, 1140, 1112, 1060, 710, 693 cm^{-1}. MS (CI) *m/z* 349 (100%, MH^+), 258 (6), 233 (100). Anal. Calcd for $C_{25}H_{30}N_2O_5$: C, 68.49; H, 6.84; N, 6.39%. Found: C, 68.08; H, 6.95; N, 5.97%.

Methyl (2*S*,4*S*,5*S*)-2-benzyl-4-benzamido-4-methoxycarbonyl-5-phenylprolinate (50).

White solid (95%). M.p. 140-2 °C; $[\alpha]_D^{28}$ +82.8 (*c* 0.6 in $CHCl_3$). ^1H NMR δ 7.53-7.20 (m, 15H), 6.11 (bs, 1H, NHCOPh), 4.74 (s, 1H, H5), 3.71 (s, 3H, CO_2CH_3), 3.54 (d, J = 13.8 Hz, 1H, H3β), 3.43 (s, 3H, CO_2CH_3), 3.23 (d, J = 13.2 Hz, 1H, H3α), 3.10 (m, 3H, CH_2Ph, NH). ^{13}C NMR δ 177.0 (CO), 171.1 (CO), 166.9 (CO), 136.5, 135.7, 133.9, 131.7, 129.8, 129.2, 129.1, 128.5, 128.2, 127.2, 126.9, 126.8, 70.1 (C5), 68.9 (C4), 67.0 (C2), 52.6 (CO_2CH_3), 52.2 (CO_2CH_3), 45.4 (C3), 44.6 (CH_2Ph). IR (nujol) 3352, 1695, 1640, 1572, 1550, 1480, 1240, 1178, 1080, 1030, 690 cm^{-1}. MS (ES) *m/z* 473 (100%, MH^+). Anal. Calcd for $C_{28}H_{28}N_2O_5$: C, 71.18; H, 5.93; N, 5.93%. Found: C, 70,78; H, 6.05; N, 5.59%.

Synthesis of Urea (52) to determine the enantiomeric purity of proline methyl ester (49).

A solution of the proline methyl ester (49) (18 mg, 0.041 mmol) in CH_2Cl_2 (2 mL) was treated with (*S*)-(+)-1-phenylethylisocyanate (0.082 mmol, 0.012 mL) and the mixture was heated at reflux for 2 hr. Removal of the volatiles under vacuum left a mixture of the two diastereoisomers of urea (52) in a ratio of 96 : 4 from ^1H NMR analysis. After purification on a 0.2-mm PTLC plate (silica gel) pure urea (52) was isolated (16 mg, (63%)). ^1H NMR δ 7.50-7.12 (m, 15H), 6.44 (s, 1H, NHCOPh), 5.40 (s, 1H, H5), 4.76 (q, J = 6.9 Hz, 1H, $PhCHCH_3$), 4.50 (bs, 1H, NH), 3.75 (s, 3H, CO_2CH_3), 3.58 (d, J = 14.4 Hz, 1H, H3β), 3.45 (s, 3H, CO_2CH_3), 3.08 (d, J = 13.8 Hz, 1H, H3α), 2.17 (m, 2H, $CH_2CH(CH_3)_2$), 1.83 (m, 1H, $CH_2CH(CH_3)_2$), 1.40 (d, J = 6.9 Hz, 1H, $PhCHCH_3$), 0.99 (d, J = 6.6 Hz, 3H, $CH_2CH(CH_3)_2$), 0.98 (d, J = 6.9 Hz, 3H, $CH_2CH(CH_3)_2$). MS (ES) *m/z* 586 (100%, MH^+), 439 (10), 291 (20), 269 (80).

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