Synthetic Studies Using Chiral Stabilised Azomethine Ylids

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Abstract

SYNTHETIC STUDIES USING CHIRAL STABILISED AZOMETHINE YLIDS

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St. John's College, Oxford **Michaelmas Term 1995**

The work described herein is concerned with the [3+2] dipolar cycloaddition of amino acid derived azomethine ylids. Such cycloadditions are a highly efficient technique for the construction of proline derivatives, and may potentially be employed in other areas of asymmetric synthesis.

Chapter 1 commences with a brief review of natural and synthetic, proline containing, molecules. Approaches to the synthesis of the proline moiety are described, focusing on previously developed methods for performing the [3+2] dipolar cycloaddition in a chiral manner. The methodology employed in this thesis is subsequently detailed, along with a brief description of the aims of the work. This is followed by a review of α-amino acid synthesis *via* chiral template technology. The potential application of chiral [3+2] dipolar cycloadditions to such syntheses is introduced.

Chapter 2 describes the cycloaddition of carboxylate substituted chiral azomethine ylids with a range of dipolarophiles under both thermal and Lewis acid catalysed conditions. The effect on the stereoselectivity and yield caused by changing the conditions is discussed. Subsequent removal of the chiral template allows the synthesis of some tetra-substituted proline derivatives.

Chapter 3 details the intramolecular variant of the cycloaddition. Further functionalisation of the cycloadducts *via* insertion of alternative chain links and sulfone alkylation was attempted. The Pummerer rearrangement of the related sulfoxide was shown to proceed smoothly and with total regio- and stereocontrol. Application of the methodology to the synthesis of a simple proline derivative and a symmetric pyrrolidine is described.

Chapter 4 reports the attempted application of [3+2] dipolar cycloadditions to the synthesis of α- amino acids. The synthesis and subsequent cycloaddition of a new, α- amino acid derived, chiral template is described. Subsequent deprotection of the cycloadducts generated allows the synthesis of some α-phenyl substituted prolines. Unsuccessful attempts to incorporate additional substituents and perform the cycloaddition in an intramolecular manner are described.

Chapter 5 contains a description of the techniques employed, together with spectroscopic data for the compounds described in this thesis.

To Lara, for her love, support

and much much more.

Acknowledgements

I would like to thank my supervisor, Laurence, for keeping me more than busy over the last three years. I'd also like to thank George for giving me such a good start, Richard for the same and the barbies, Luet for saving the day, and the Doc for getting me into chemistry in the first place.

The D.P. technical staff have done a sterling job over the last three years, for which I would like to thank them. Special thanks go to Mrs Elizabeth McGuinness for the countless n.O.e. experiments, COSY experiments etc. she has run for me.

The Harwood group past and present have helped provide a sound working atmosphere. A big thank you, especially to the many occupants of lab 52 Jase, Jane, Gordon, Antonio, Lucia, Mark, Andy, Catherine, Ade and the Prof. Jase (long time since physics practicals), Jane and Eleri deserve a particular mention for their long service, while Toby, Gordon, Geoff and Angela have all brought much needed new life to the group. Thanks to Jane, Eleri, Emma and Angela for the many, much appreciated, Linacre lunches.

Aside from work Dave, Fez, Ken, Joe, Neil, Andy and Mark have made 6X (hmm!) and "cheeky" chicken tikka massala the backbone of many a long winter evening. Thanks particularly to Dave for being the "more experienced" half of the best doubles pair in Oxford. A quick mention also for the worst house in the world and the Osberton Road crew - Jase, Danny, Joe, Neil and Chris - central heating, who needs it ? Outside the lab, life without Stu, Jules, Grant, Dave and Neil would have been cheaper, healthier and a lot more dull. La Clusaz, Barcelona, Stockholm (where we learned to count to ten!) and even ferries will never be forgotten.

My Mum and Dad have helped me immeasurably over the last 25 years, - what I owe you can never be repaid. Katharine has helped me keep things in perspective, especially this year (even from Oz!), while for 7 years of postal football reports deepest respect to my GREAT Aunt. I will also always cherish many fond memories of my Grandfather.

Last, and most definitely most, I want to thank Lara. For two and a half years of memories, and many more yet to be made.

Contents

Abbreviations

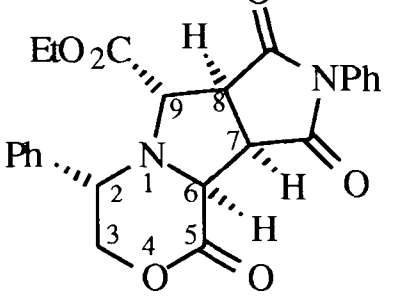
Ac	acetyl
AIBN	2, 2'-azobis*iso*butyronitrile
aq	aqueous
Ar	aryl
BINAP	binaphthol
Boc	*tert*-butoxycarbonyl
Bu	butyl
cat.	catalytic quantity
CI	chemical ionisation
D	deuterium (^2H)
dec	decomposed
DCM	dichloromethane
DIBAL	di-*iso*butyl aluminium hydride
DMF	*N*,*N*-dimethylformamide
E-	entgegen
equiv	equivalent
EWG	electron withdrawing group
fod	6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionatyl
His	histidine
HOMO	highest occupied molecular orbital
i	iso
LDA	lithium di-*iso*propylamide
LHMDS	lithium *bis*(trimethylsilyl)amide
LUMO	lowest unoccupied molecular orbital
*m*CPBA	*meta*-chloroperbenzoic acid
ACE	angiotensin converting enzyme
AIDS	acquired immune deficiency syndrome
Arg	arginine
Bn	benzyl
b.p.	boiling point
C_{60}	buckminsterfullerene
CBz	benzyloxycarbonyl
COSY	COrrelated SpectroscopY
d.e.	diastereomeric excess
DBU	1,8-diazabicyclo[5.4.0]un-dec-7-ene
DMAP	dimethylamino pyridine
DMSO	dimethyl sulfoxide
e.e.	enantiomeric excess
Et	ethyl
FMoc	9-fluorenylmethoxycarbonyl
Fu	furyl
HIV	human immunodeficiency virus
HMPA	hexamethylphosphoramide
hν	photochemical irradiation
KHMDS	potassium *bis*(trimethylsilyl)amide
Leu	leucine
lit	literature value
m	meta
$^m/_z$	mass to charge ratio
Me	methyl

m.p.	melting point	Ms	methane sulfonyl
n	normal	NaHMDS	sodium *bis*(trimethylsilyl)amide
Naphth	Naphthyl	n.m.r.	nuclear magnetic resonance
n.O.e.	nuclear Overhauser effect	P	protecting group
PCC	pyridinium chlorochromate	Ph	phenyl
Phe	phenyl alanine	PhFl	9-phenylfluorenyl
PMB	*para*-methoxybenzyl	PMP	*para*-methoxyphenyl
Pr	propyl	Pro	proline
*p*TSA	*para*-toluenesulfonic acid	quant	quantitative
R	R configuration according to the Cahn-Ingold Prelog rules	r.t.	room temperature
		S	S configuration according to the Cahn-Ingold Prelog rules
Ser	serine		
t or *tert*	tertiary	TBDMS	*tert*-butyldimethylsilyl
TBDPS	*tert*-butyldiphenylsilyl	TBS	tributylsilyl
TFAA	trifluoroacetic anhydride	TFA	trifluoroacetic acid
Tf	trifluoromethanesulfonyl	tfc	3-(trifluoromethyl hydroxymethylene)camphoratyl
THF	tetrahydrofuran		
t.l.c.	thin layer chromatography	TMS	trimethylsilyl
Ts	(tosyl) = *para*-toluenesulfonyl	X	unspecified substituent
Y	unspecified substituent	Z	unspecified substituent
Z-	zusammen		

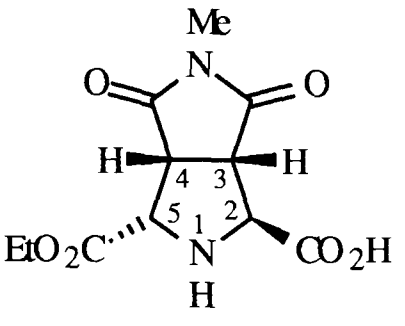
Nomenclature

The nomenclature used to describe the compounds in this thesis is in accordance with the IUPAC convention as detailed in "Nomenclature of Organic Chemistry. Sections A and B", Pergamon Press, Oxford, 1979. In addition, the trivial "morpholinone" nomenclature is used to describe the 2,3,5,6-tetrahydro-*4H*-oxazinone ring system. A broken, wedged line is used to denote the α-configuration where the substituent lies behind the general plane of the ring system and a solid, wedged line denotes the β-configuration where the substituent lies in front of the plane. Representative examples of the three basic ring systems encountered in this thesis are shown below, together with the numbering systems which have been used throughout.

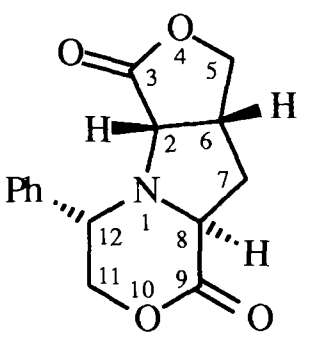
(2S,6S,7R,8S,9S)-N-*Phenyl-1-aza-9-carboethoxy-4-oxa-2-phenyl[4.3.0^{1,6}]bicyclononan-5-one-7,8-dicarboximide.*



*(2S,3S,4R,5S)-5-Carboethoxy-3,4-(*N-*methyl-dicarboximido)-pyrrolidine-2-carboxylic acid.*



(2S,6R,8S,12S)-1-Aza-4,10-dioxa-12-phenyl[6.4.0^{1,8}.0^{2,6}]tricyclododecan-3,9-dione.



CHAPTER ONE

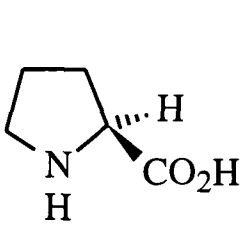
Introduction

CHAPTER ONE

Introduction

1.1 Chemotherapeutic and Biological Properties of some Proline Derivatives.

The proline ring is a structural component of a wide range of both naturally occurring and synthetic compounds. As one of twenty three proteinogenic amino acids (*S*)-proline (**1.1**) is a constituent of many proteins and enzymes. The first identification of a proline derivative in a natural product was that of 4-hydroxy-(*S*)-proline (**1.2**), isolated from gelatin hydrosylate by Fischer in 1902.[1] Since then proline derivatives have been isolated from a wide range of different sources including alfalfa protein,[2] sugar beet protein[3] and dentine protein.[4] (*S*)-Proline (**1.1**) and 4-hydroxy-(*S*)-proline (**1.2**) are major components of collagen, the protein of connective tissue, which accounts for one-third of the total protein content of the body.



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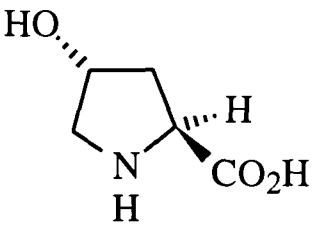
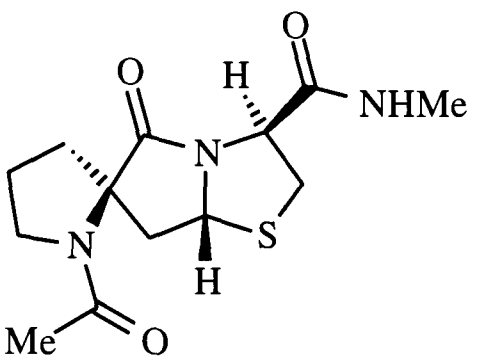


(1.2)

Proline and 4-hydroxy-proline have a profound effect on the folding of a polypeptide chain, and hence the secondary structure. Because of the rigidity of the C-N bond, the incorporation of a proline residue induces a number of secondary structural features, for example β-turns and kinks in α-helices.[5] Analogues of proline, for example (**1.3**) and (**1.4**), have been used as β-turn mimics, and in conformationally constrained peptides to develop peptide derived drugs.[6]



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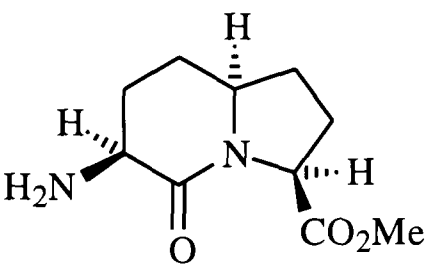
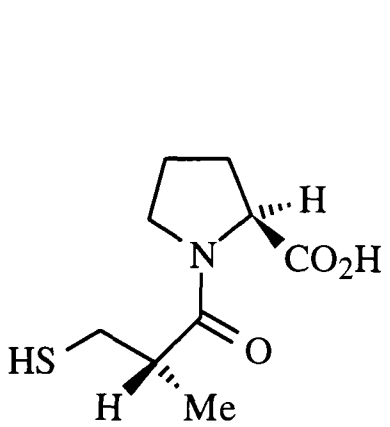


(1.4)

1.1.1 Proline Derivatives as Angiotensin Converting Enzyme Inhibitors.

The discovery of the drug Captopril (**1.5**) in 1977[7] led to a surge of interest in the synthesis of substituted prolines, and resulted in the identification of Zofenopril (**1.6**)[8] and Fosinopril (**1.7**)[9] as similarly active molecules. These compounds all act as inhibitors of Angiotensin Converting Enzyme (ACE). ACE catalyses cleavage of the His-Leu sequence from the C-terminus of Angiotensin I leading to the formation of Angiotensin II, a powerful vasopressor. It also catalyses sequential hydrolysis of the Phe-Arg and Ser-Pro residues from bradykinin, thus deactivating this vasodepressor.[10] Captopril (**1.5**) has therefore been used in the treatment of hypertension and heart failure. Given orally it has been shown to lower blood pressure while having few unpleasant side effects.



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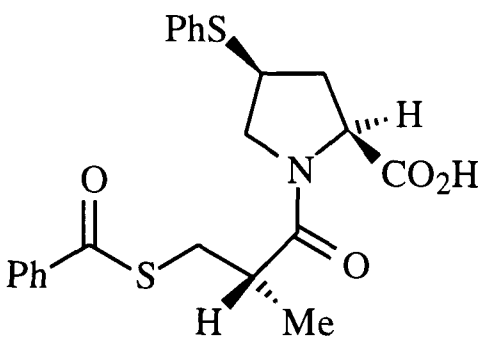

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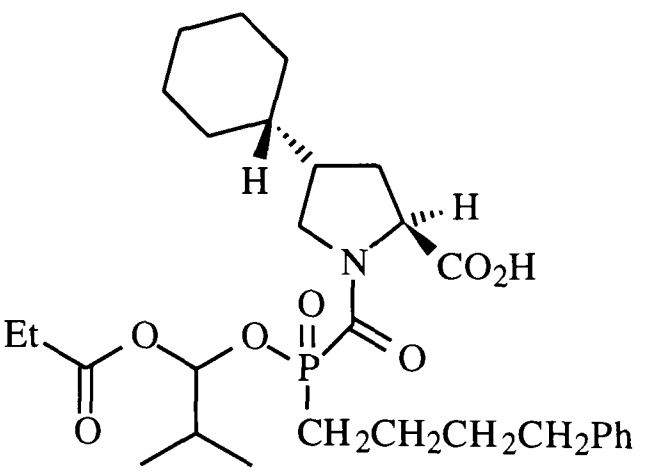
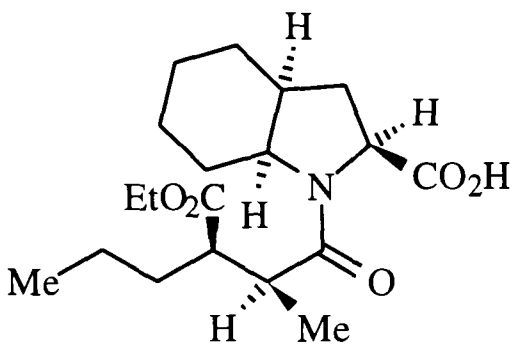


(1.7)

The observation that analogues of Captopril with hydrophobic and lipophilic groups at the 4- position showed particularly high activity, led to a second series of ACE inhibitors based on bicyclic proline derivatives. Compounds such as Perinopril (**1.8**), Trandolapril (**1.9**) and Ramipril (**1.10**) have all shown increased activity and exhibit even fewer side effects.



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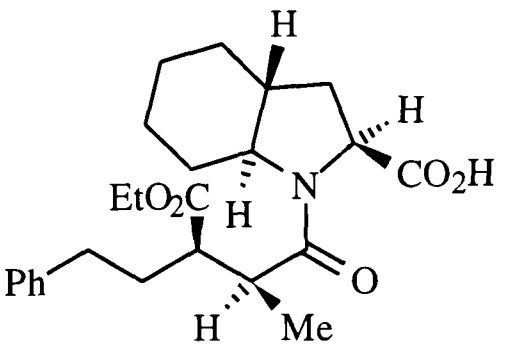

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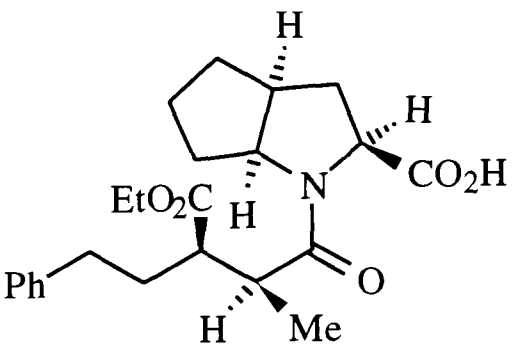
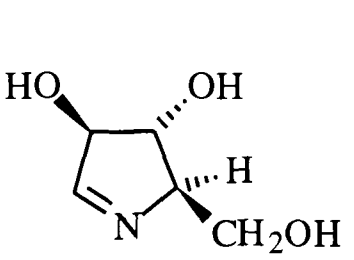


(1.10)

1.1.2 Hydroxylated Proline Derivatives as Glycosidase Inhibitors.

Polyhydroxylated proline derivatives have received much attention in recent years due to their frequent display of often quite specific glycosidase inhibition.[11] The activity of these derivatives is due to their ability to act as sugar analogues - so called amino-sugars. With the discovery of HIV and the observation that HIV causes AIDS, polyhydroxylated proline derivatives were extensively screened as potential inhibitors of HIV. The fungal metabolite FR900483 (**1.11**), isolated from *Nectria lucida* has been shown to reverse immunosupression,[12] while LAB-1 (**1.12**) was demonstrated to be a non-cytotoxic inhibitor of the cytopathic effect of HIV.[13] Similiarly Castanospermine (**1.13**), isolated from the Australian legume *Castanospermine australe*, has been shown to inhibit enzymes that are essential for the glycosidation of viral glycoproteins.[14] Inhibition of the glycosidation process prevents viral entry into the cell, and led to the postulation of Castanospermine (**1.13**) as an HIV inhibitor.[15]



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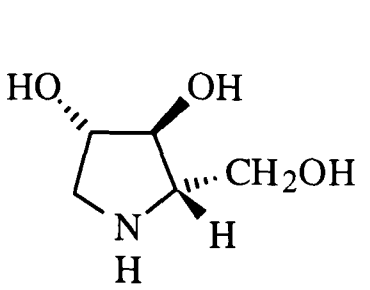

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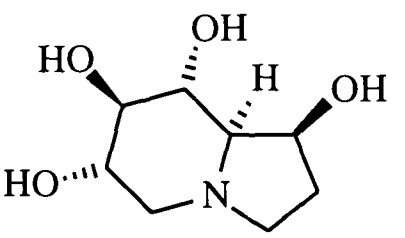
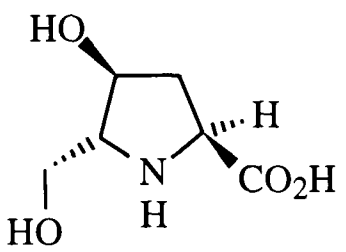


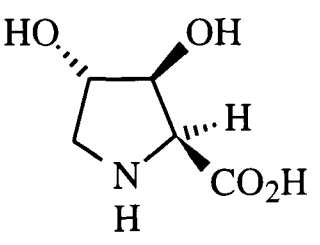
(1.13)

Natural products have been the source of a significant number of simple hydroxylated prolines. For example, Bulgecinine (**1.14**) was isolated from *Pseudomonas mesoaidophila*,[16] while (2*S*,3*S*,4*S*)-3,4-dihydroxyproline (**1.15**) and (2*S*,3*R*,4*R*)-3,4-dihydroxyproline (**1.16**) were isolated from diatom cell walls and a toxic mushroom peptide respectively. Recently the

naturally occurring proline derivative (2*S*,3*R*,4*S*)-3,4-dihydroxyproline (**1.17**) was isolated from the adhesive protein of the mussel *Mytilus edulis*.[17]



(**1.14**)



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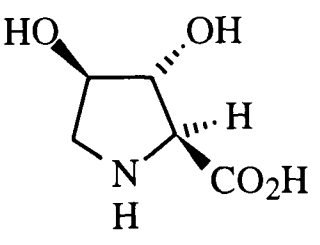

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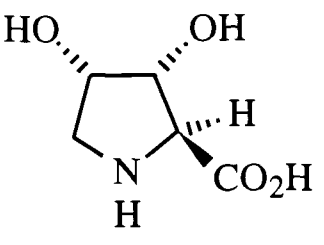
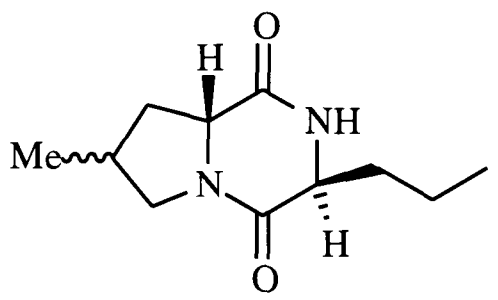


(**1.17**)

1.1.3 Poly-Substituted Proline Derivatives.

Many other highly complicated natural products also contain a proline nucleus. The diketopiperazine cyclo-(4-methyl)-(*R*)-proline-(*S*)-norvaline (**1.18**) was isolated from the sponge *Calyx podatypa*,[18] while the diketopiperazine antibiotic TAN1496A (**1.19**) was isolated from the Japanese sponge *Microsphaeropsis sp.*[19] Plakoridine A (**1.20**), isolated from the marine sponge *Plakortis sp.*, contains a fully substituted pyrrolidine ring,[20] as does Pranamycin (**1.21**), a recently reported anti-microbial agent isolated from fungal fermentations.[21]



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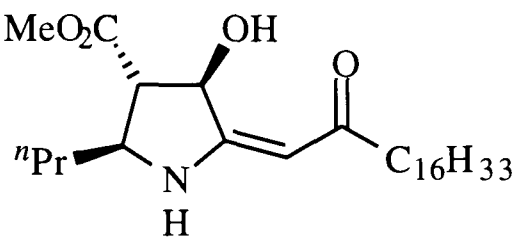

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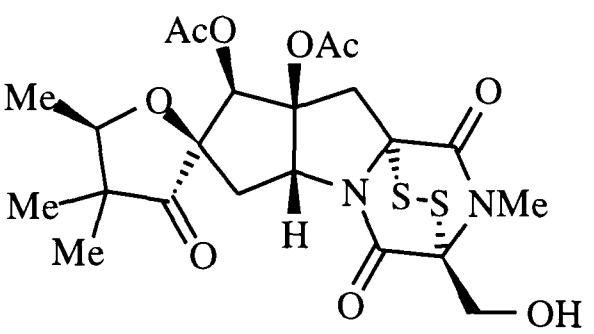

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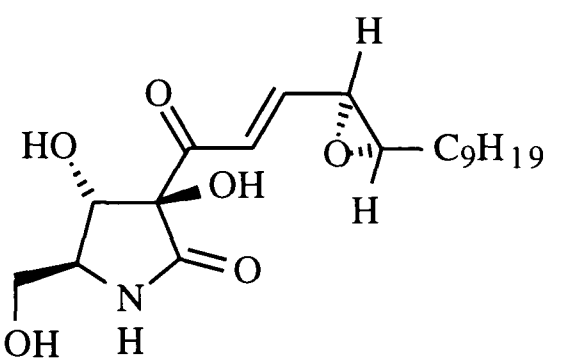
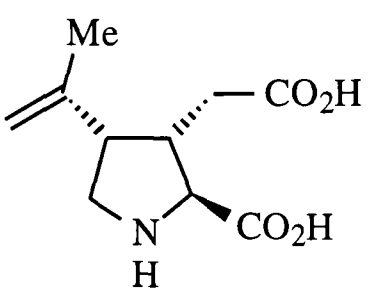


(**1.21**)

1.1.4 The Kainic Acids.

The kainoid amino acids are a class of non-proteinogenic pyrrolidine dicarboxylic acids. The parent kainic acid (**1.22**) and the C_4 epimer allokainic acid (**1.23**) were first isolated in 1953 from the alga *Digenea simplex*.[22] Kainic acid itself displays a range of neuroexcitatory,[23] antihelmintic[22] and insecticidal[24] properties. Domoic acid (**1.24**) was isolated by Daigo[25] from the alga *Chondria armata* in 1958, and later demonstrated to be a potent insecticide against the American cockroach.[26] Acromelic acids A (**1.25**) and B (**1.26**) were isolated in 1983 from the Japanese mushroom *Clitocybe acromelalga*, and shown to have even greater neuroexcitatory properties than the parent.[27]



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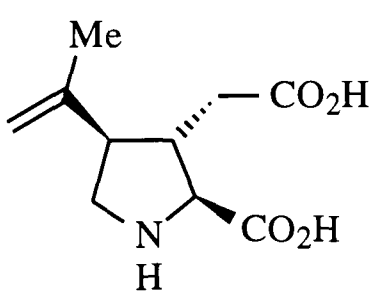

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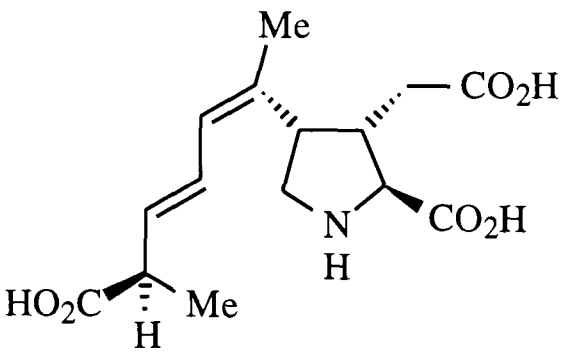

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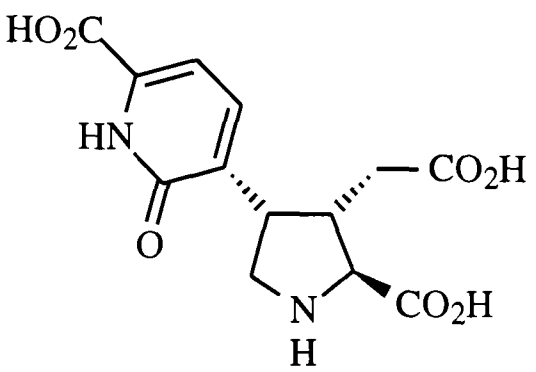

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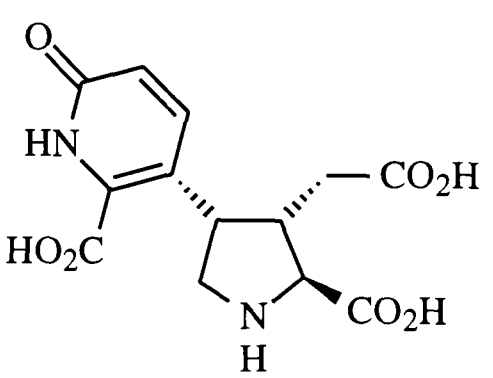
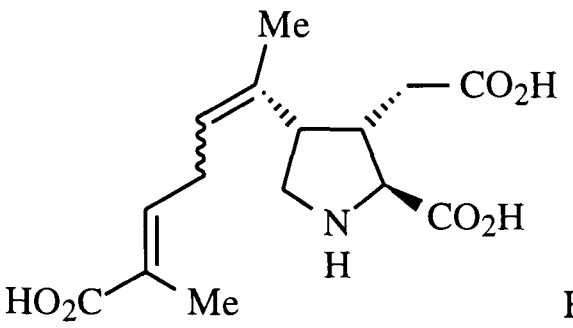


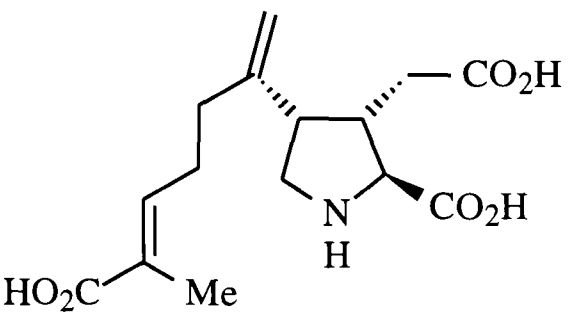
(1.26)

The neuroexcitatory properties of the kainoids have prompted extensive studies into the properties of both the natural products and synthetic analogues. They exhibit extremely potent depolarising activity on neurotransmission and as such have been used as a tool to investigate neurofunction. The physiological effect of kainoid injection is to mimic the symptoms experienced by patients suffering from epilepsy, Alzheimer's disease and Huntingdon's disease.[28]

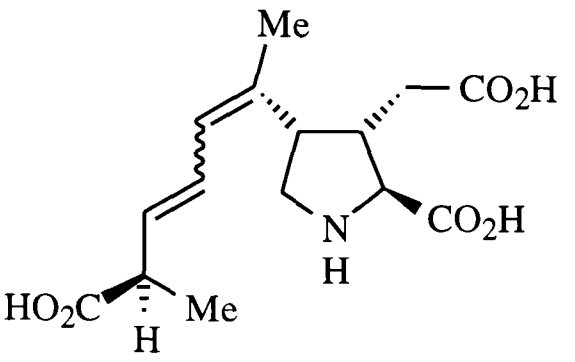
A number of higher homologues of kainic acid have also been isolated. These include the isodomoic acids A-F (**1.27** to **1.32**) and domiolactones A (**1.33**) and B (**1.34**), all of which were isolated from the same alga, *Chondria armata*.[29] These analogues all display the same relative and absolute stereochemistry at C_2, C_3 and C_4, differing only in the nature of the side chain at C_4. These changes in the side chain impart radically different properties to the kainoids.[27]



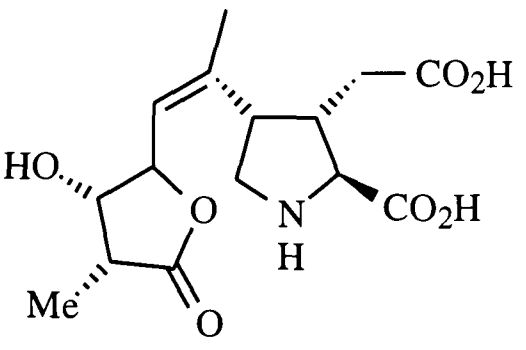
(*Z*,*E*)-Isodomoic acid A (**1.27**)
(*E*,*E*)-Isodomoic acid B (**1.28**)



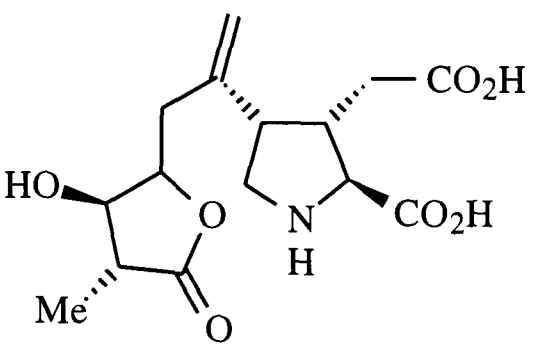
Isodomoic acid C (**1.29**)



(*Z*,*Z*)-Isodomoic acid D (**1.30**)
(*E*,*E*)-Isodomoic acid E (**1.31**)
(*E*,*Z*)-Isodomoic acid F (**1.32**)



Domiolactone A (**1.33**)



Domiolactone B (**1.34**)

The neuroexcitatory properties of the kainic acids are considered to be derived from their ability to act as conformationally restricted analogues of glutamic acid. The availability of a large number of analogues, both natural and synthetic, has allowed detailed investigation into the relationship between structure and activity of the kainoids.[30] These have shown that the (2*S*,3*S*) stereochemistry is vital due to the importance of the carboxylic acid groups in binding to the receptor site. The *cis*- relationship between the substituents at C_3 and C_4 is highly important since the activity of the *trans*- substituted allokainic acid is some 200 times less than kainic acid. The amino acid functionality is also important in binding, with the activity being dramatically reduced on *N*-alkylation or esterification of the acid. The sp^2 hybridised centre of the C_4 substituent also plays a crucial role as demonstrated by the observation that the saturated analogue dihydrokainic acid is approximately 130 times less active than unsaturated kainic acid.

1.2 Synthesis of Proline Derivatives.

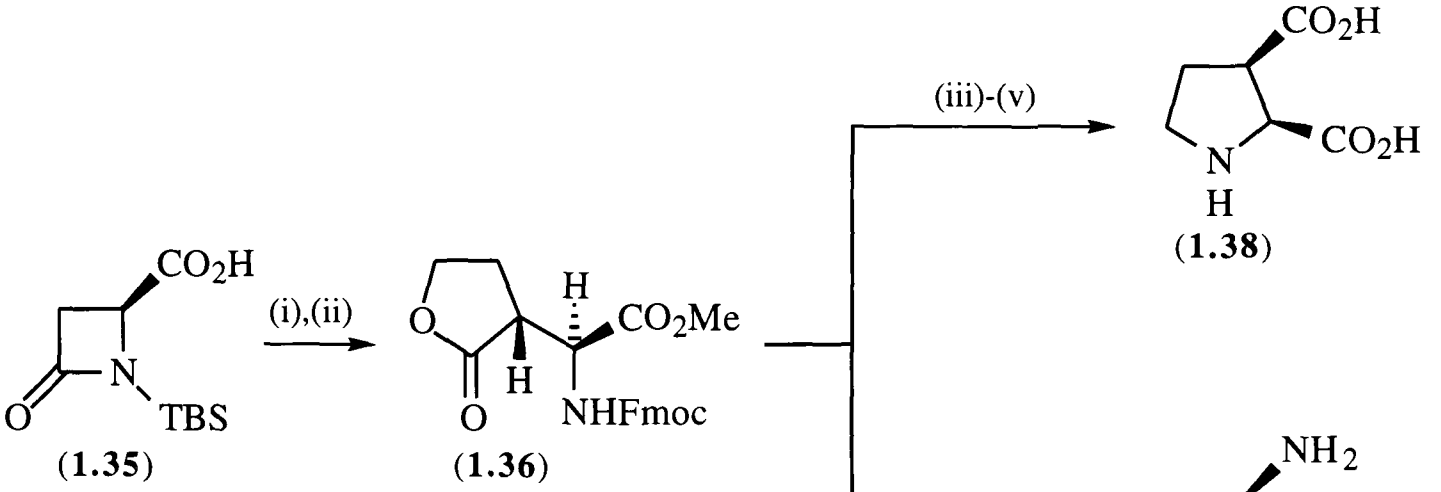
In 1966 the synthesis of proline derivatives was reviewed in detail by Mauger and Witkop.[31] However these early syntheses tended to be non-diastereoselective. General strategies included the Gabriel condensation of an acyclic precursor and the Favorski ring contraction of higher homologues. Subsequent elaboration of the proline assembled *via* one of these routes furnished the desired derivative.

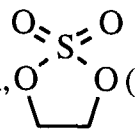
Since this review, a large number of methods have been devised for both the diastereo- and enantioselective synthesis of a wide range of proline derivatives. Elaboration of an existing proline derivative, for example pyroglutamic acid, has been the basis of a substantial quantity of research effort,[32] however this review will concentrate solely on those methods which involve proline ring formation. These methods can be loosely divided into those in which formation of a single bond generates the ring (step-wise methods), and those in which two bonds are formed simultaneously in the ring generating step (concerted methods).

1.2.1 Step-wise Methods.

Nucleophilic Ring Closure.

Ring closure using the nucleophilic nitrogen atom is the basis of the synthesis of a large number of proline derivatives. The ring substituents are generally introduced before ring closure through diastereoselective functionalisation of a chiral precursor. The neurotransmitter mimic *cis*-3-carboxyproline (**1.38**) was synthesised by Baldwin from the homochiral β-lactam (**1.35**).[33] Initial diastereoselective alkylation with 2,2-dioxo-1,3-dioxathiolane (**1.37**) was accompanied by concomitant β-lactam hydrolysis, and subsequent protection gave the γ-lactone (**1.36**). Hydrobromic acid hydrolysis of the lactone and base catalysed cyclisation was followed by deprotection to give the desired derivative (**1.38**). Alternatively cyclisation followed by Curtius rearrangement and deprotection gave the amino proline (**1.39**), a non proteinogenic amino acid isolated from the mushroom *Morchella esculenta* (**Scheme 1.1**).



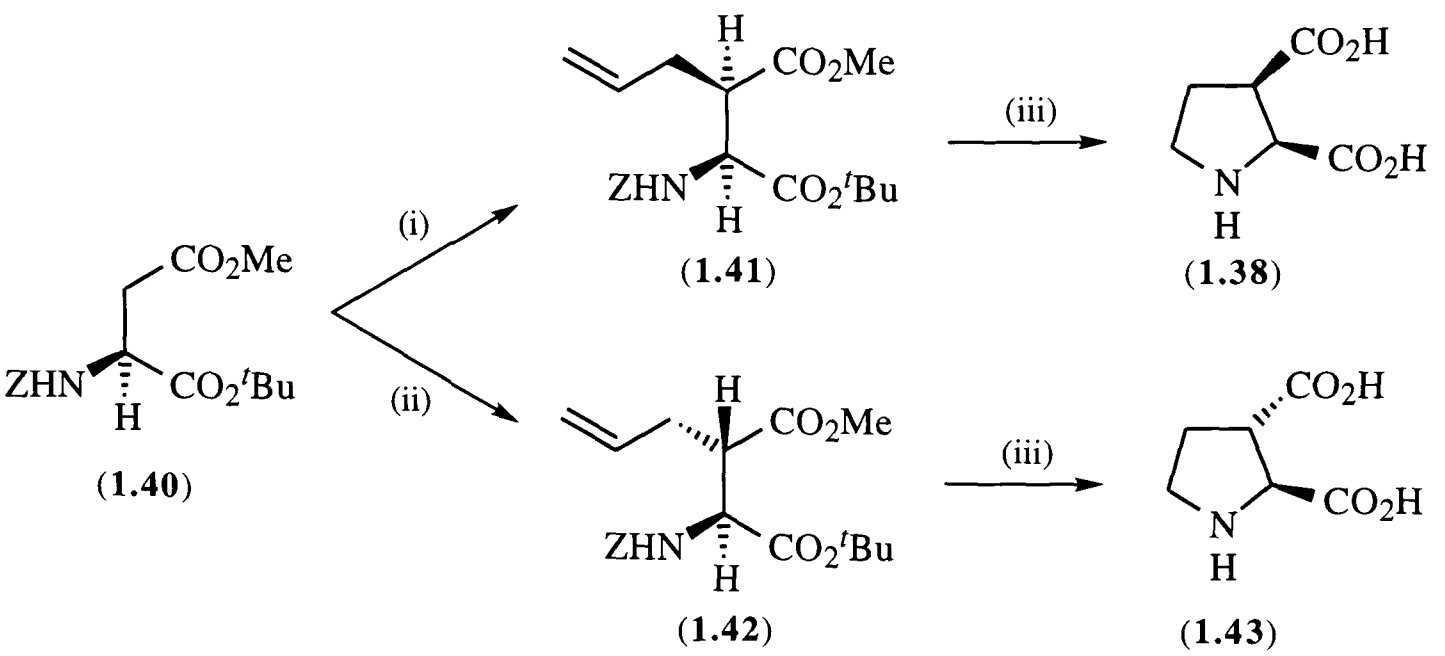
(i) LDA,  (**1.37**), THF, -78°C, (ii) Fmoc protection, esterification

(iii) HBr, AcOH, (iv) piperidine, DMF, (v) deprotection
(vi) Curtius rearrangement, (vii) deprotection.

Scheme 1.1

Cis-3-carboxyproline (**1.38**), along with the C_3 epimer (**1.43**), has also been prepared by chelation controlled alkylation of the protected aspartic acid (**1.40**).[34] Use of lithium bis(trimethylsilyl)amide as base in the alkylation gave a 23 : 1 excess of the precursor (**1.41**)

to *cis*-3-carboxyproline (**1.38**), while use of potassium bis(trimethylsilyl)amide gave a 10 : 1 excess of the precursor (**1.42**) to *trans*-3-carboxyproline (**1.43**) (**Scheme 1.2**). Subsequent reductive ozonolysis, followed by hydrogenolysis with concomitant cyclisation and ester hydrolysis gave the required proline derivatives (**1.38**) and (**1.43**).

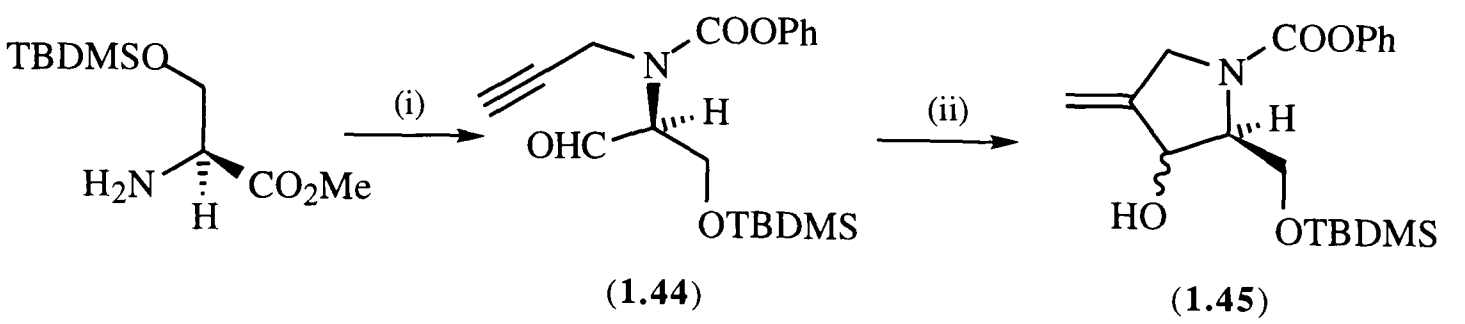


(i) LHMDS, allyl iodide, (ii) KHMDS, allyl iodide, (iii) several steps.

Scheme 1.2

Radical Ring Closure.

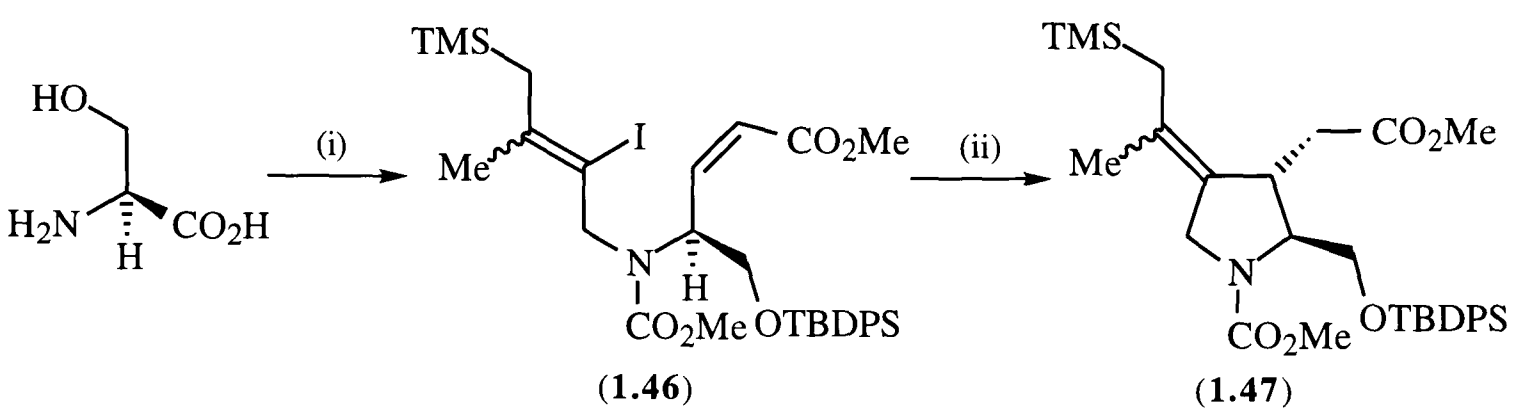
As part of an approach to kainic acid analogues Baldwin used samarium iodide to form radicals from the functionalised serine derivative (**1.44**).[35] The samarium (II) species promotes reaction *via* two sequential one-electron reductions. The radicals generated underwent efficient intramolecular cyclisation to give a 70% yield of the proline derivative (**1.45**) as a mixture of C_3 epimers (**Scheme 1.3**).



(i) several steps, (ii) SmI_2.

Scheme 1.3

Tributyltin hydride generated radicals have been used by Takano as part of an approach to advanced kainoid intermediates.[36] Simple elaboration of serine gave a precursor (**1.46**) possessing appropriate functionality both for cyclisation and subsequent elaboration. Initiation with AIBN followed by iodide abstraction generated an alkene radical which cyclised smoothly onto the conjugated olefin to generate the advanced intermediate (**1.47**) in 86% yield (**Scheme 1.4**). This cyclisation exclusively set up the required *trans*- relationship between the substituents at C_2 and C_3.

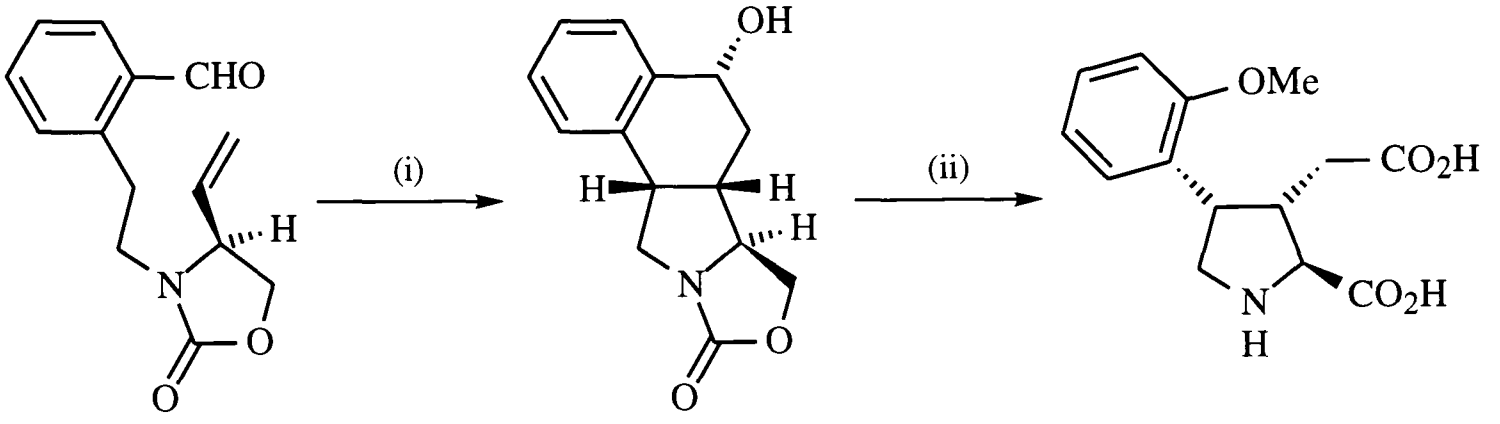


(i) several steps, (ii) Bu_3SnH, AIBN (cat.), benzene, reflux.

Scheme 1.4

Electrocyclic Reactions.

The transition state requirements of electrocyclic reactions, dictated by the Woodward-Hoffman rules,[37] offer an excellent method of controlling the stereochemistry of both newly generated stereocentres. These constraints were elegantly utilised by Shirahama in the synthesis of some analogues of acromelic acid (**Scheme 1.5**).[38] The functionalised vinyl glycinol (**1.48**) was irradiated in toluene and underwent photoinduced intramolecular Diels-Alder reaction generating the tetracycle (**1.49**) in 64% yield. This dictated the *cis*- relationship between the C_3 and C_4 substituents with a diastereomeric excess of >99%. Subsequent elaboration furnished the acromelic acid analogue (**1.50**), the most potent neuroexcitatory member of the kainic acid family yet discovered.

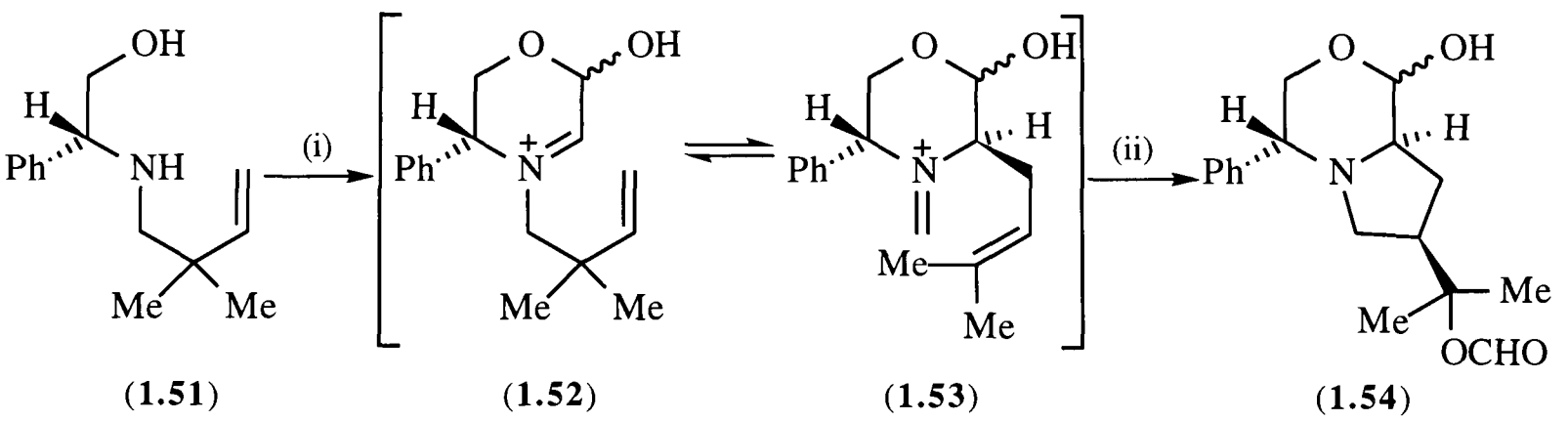


(1.48) **(1.49)** **(1.50)**

(i) hν, toluene, (ii) several steps.

Scheme 1.5

The assembly of 4-substituted proline derivatives was also efficiently achieved by Agami *via* consecutive stereoselective *aza*-Cope rearrangement and ene-iminium cyclisation (**Scheme 1.6**).[39] The amine (**1.51**), derived from phenyl glycinol, was condensed with glyoxal to form the intermediate iminium ion (**1.52**), which underwent reversible *aza*-Cope rearrangement to furnish the iminium ion (**1.53**). The stereochemistry at C_2 was a consequence of axial attack on the iminium double bond during this [3,3] sigmatropic rearrangement. Subsequent cyclisation to the proline (**1.54**) occurred to give a single C_4 stereochemistry, derived exclusively from cyclisation of the conformer shown. The conformation of the double bonds in tautomer (**1.53**) has greater reactivity due to their *synclinal* arrangement, in agreement with the general topographical rule proposed by Seebach for the reaction of such trigonal centres.[40]



(1.51) **(1.52)** **(1.53)** **(1.54)**

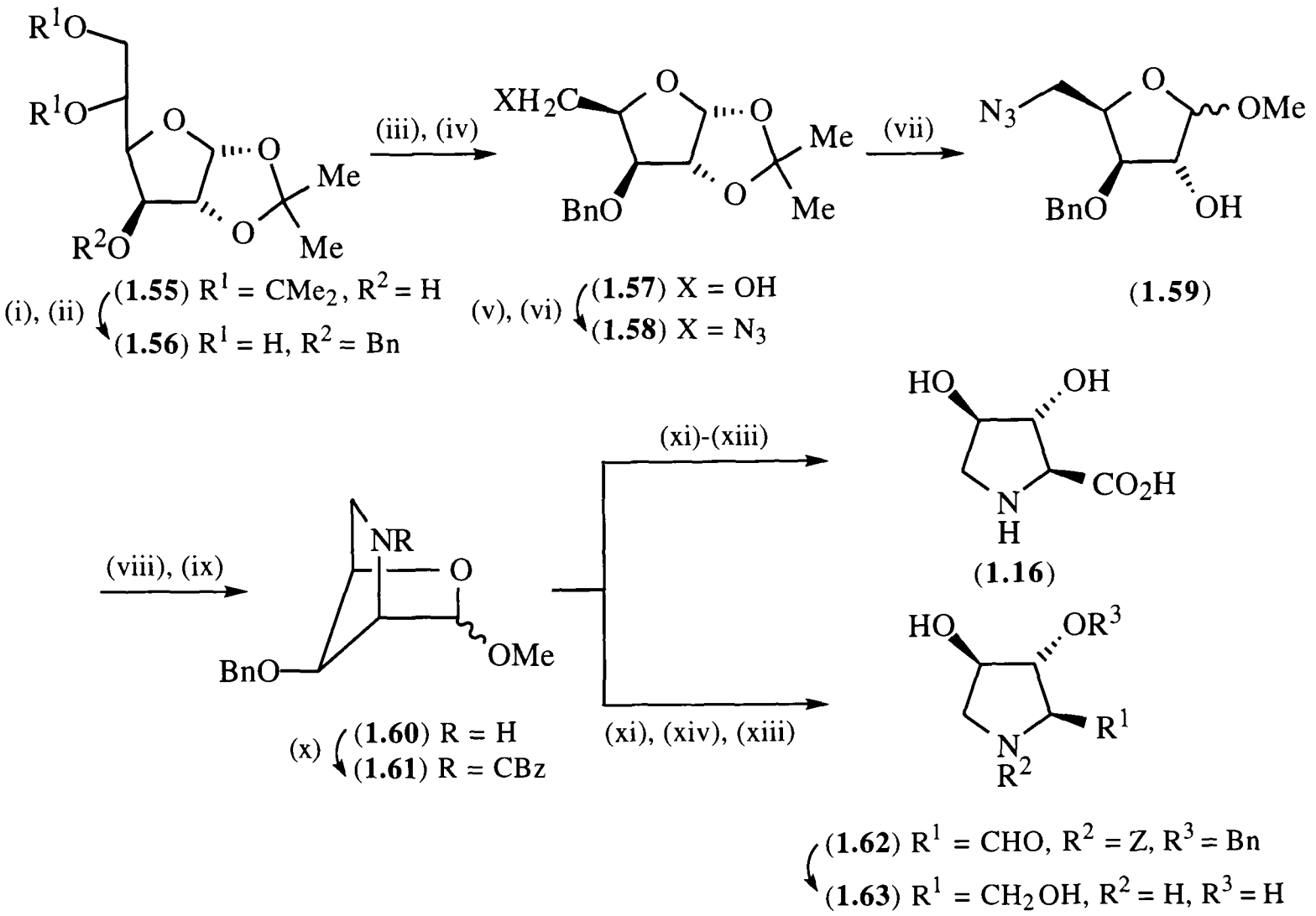
(i) glyoxal, (ii) formic acid.

Scheme 1.6

Synthesis from Carbohydrates.

Carbohydrates provide highly functionalised starting materials, the absolute and relative stereochemistry of which can be specified by appropriate choice of carbohydrate. In the search for effective and selective glycosidase inhibitors Fleet and co-workers have made extensive use of carbohydrates in the synthesis of a large number of hydroxylated prolines.[11] The general procedure involves identification of the carbohydrate required to set up the relative and absolute stereochemistry in the product followed by selective protection of this sugar in a suitable form for elaboration. Nitrogen is then introduced through nucleophilic displacement of an activated hydroxyl followed by cyclisation through displacement of a second activated hydroxyl. Deprotection is then performed to furnish the required target.

This approach is exemplified by the synthesis of (2*S*,3*R*,4*R*)-3,4-dihydroxyproline (**1.16**) (**Scheme 1.7**). Diacetone glucose (**1.55**) was first benzylated at C_3 then the primary acetonide removed to give the diol (**1.56**). Removal of one carbon was achieved by periodate cleavage and the aldehyde generated reduced with sodium borohydride to the alcohol (**1.57**). Subsequent activation of the newly generated, unprotected, hydroxyl with mesyl chloride followed by displacement with sodium azide gave the azide (**1.58**). Removal of the second acetonide in methanolic hydrogen chloride resulted in a mixture of anomers (**1.59**) however both of these could be elaborated to the desired product. Activation of the free hydroxyl followed by hydrogenation of the azide resulted in concomitant cyclisation to the bicyclic system (**1.60**), the amine of which was immediately protected, for ease of handling, to give the carbamate (**1.61**). Bromine oxidation of the aldehyde (**1.62**), generated by acidic ring opening of the methyl furanoside (**1.61**), followed by deprotection gave the required (2*S*,3*R*,4*R*)-3,4-dihydroxyproline (**1.16**) in 18% overall yield from diacetone glucose (**1.55**). Alternatively sodium borohydride reduction of the aldehyde followed by deprotection gave DAB-1 (**1.63**), the enantiomer of LAB-1 (**1.12**) in 33% overall yield from diacetone glucose (**1.55**). Other hydroxylated proline derivatives prepared in this way include the immunomodulator FR900483 (**1.11**) and the anti-HIV agent LAB-1 (**1.12**).

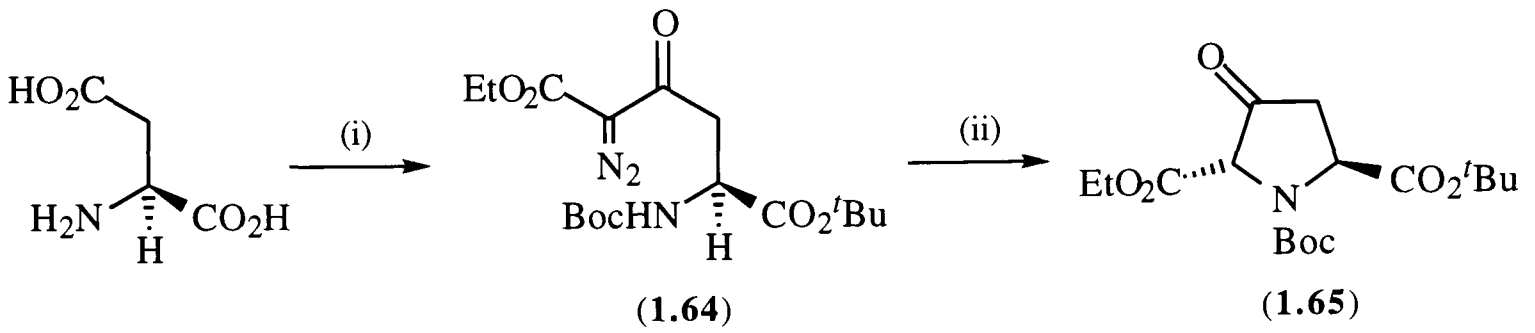


(i) NaH, BnBr, THF, (ii) AcOH, dioxan (aq), (iii) $NaIO_4$, AcOH, H_2O, (iv) $NaBH_4$, EtOH (aq), (v) MsCl, pyridine, (vi) NaN_3, DMF, (vii) MeOH, AcCl, (viii) Tf_2O, pyridine, DCM, (ix) H_2, Pd/ C, EtOAc, NaOAc, (x) CBz-Cl, Et_2O, Na_2CO_3, (xi) TFA (aq), (xii) Br_2, dioxan (aq), (xiii) H_2, Pd black, AcOH, (xiv) $NaBH_4$, EtOH (aq).

Scheme 1.7

Carbene Insertion.

The dicarboxyl-pyrrolidinone (**1.65**) was prepared from aspartic acid by Honma as an advanced intermediate for studies on the chemical modification of the potent ACE inhibitor Enalapril (**Scheme 1.8**).[41] The key cyclisation step was a rhodium acetate catalysed N-H insertion by the metallo carbene derived from the elaborated aspartic acid diazo precursor (**1.64**). This cyclisation proceeded with a diastereomeric excess of >90% to give an 85% yield of the 2,5-*trans*- substituted proline (**1.65**).

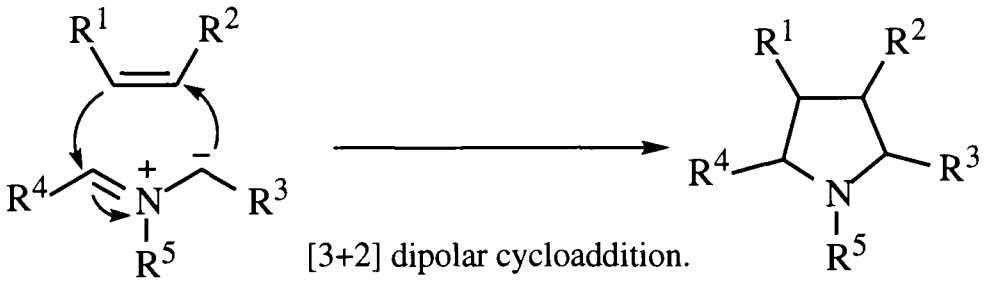


(i) several steps, (ii) $Rh_2(OAc)_4$.

Scheme 1.8

1.2.2 Concerted Methods.

Despite the many chiral methods developed for the synthesis of proline derivatives, the [3+2] dipolar cycloaddition reaction of azomethine ylids continues to provide the organic chemist with a most versatile and general method of constructing this common ring system.[42] The reaction of azomethine ylids with substituted alkenes allows the simultaneous generation of up to four stereocentres, and thus permits rapid access to highly functionalised pyrrolidines (**Scheme 1.9**).



Scheme 1.9

Azomethine ylids may be generated by a variety of routes including prototropic shifts, desilylation processes, thermal opening of aziridines, base treatment of *N*-oxides, decarboxylation of oxazolidinones or from the iminium salt of an amino acid precursor.[42] They may be divided into those bearing an electron withdrawing group on the carbon adjacent to nitrogen and are stabilised (X = CO_2R), and those which do not and are therefore non-stabilised (X = H) (**Figure 1.1**).

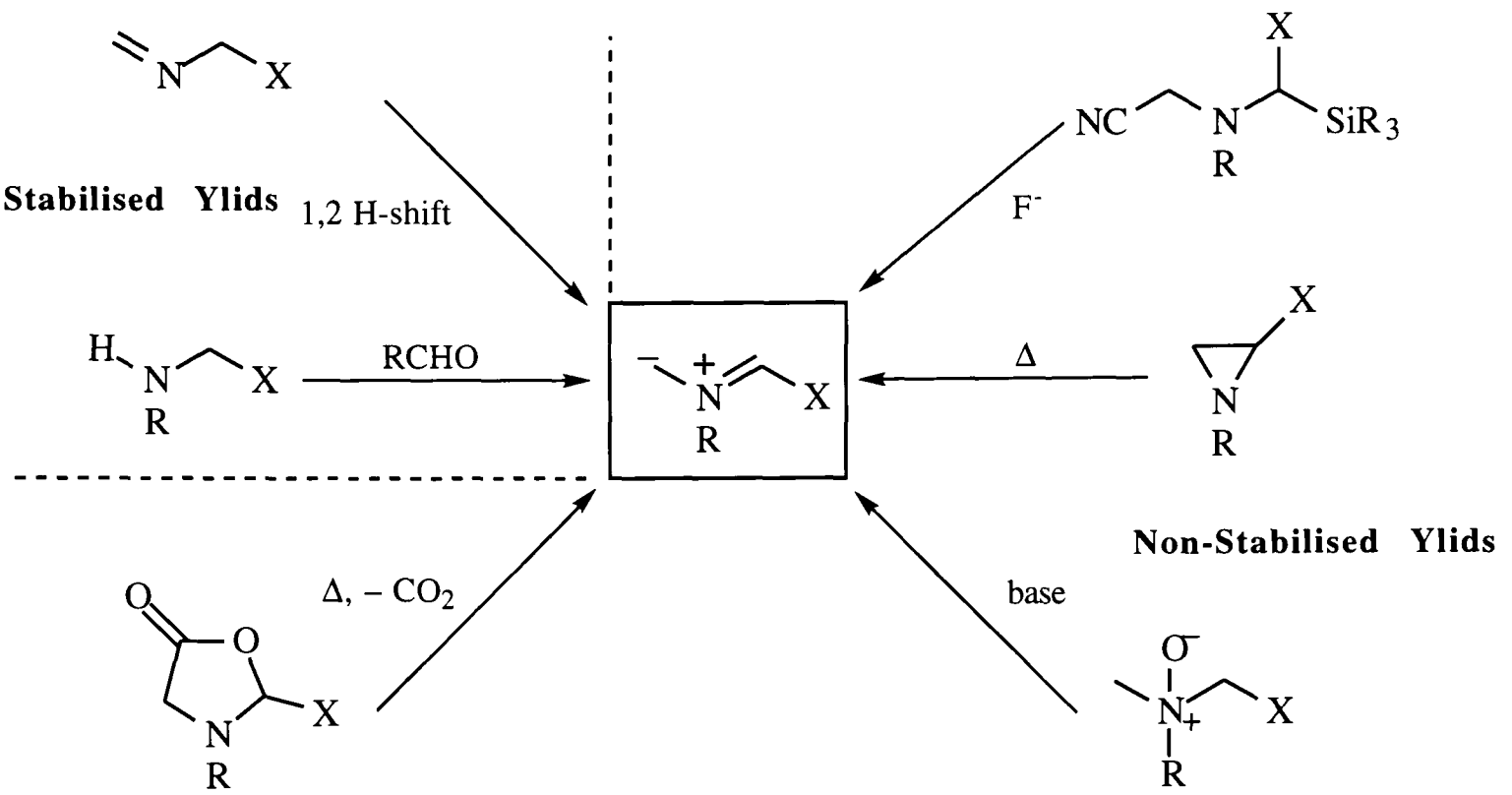
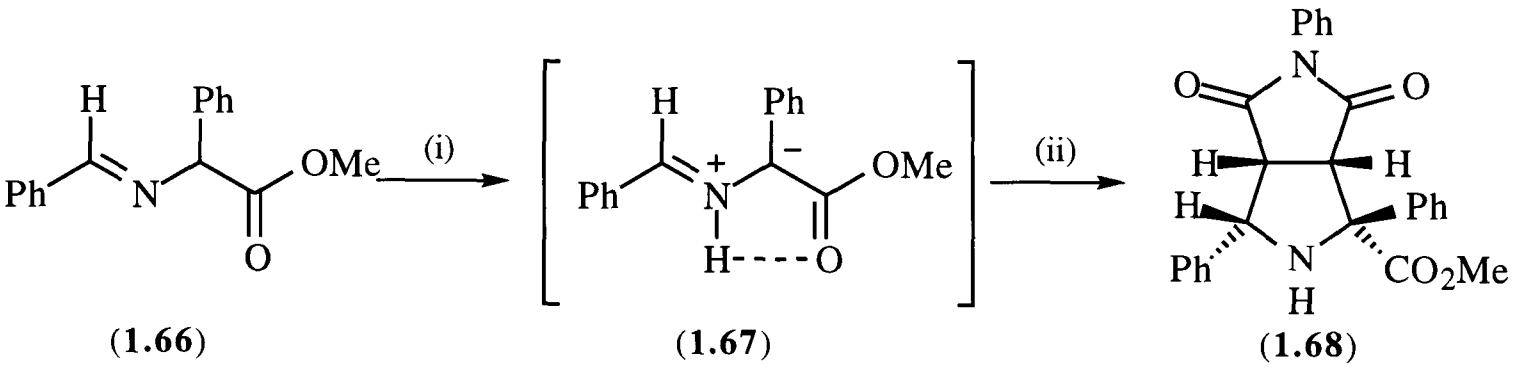


Figure 1.1

Early azomethine ylid cycloadditions were non-enantioselective, although many displayed a high degree of diastereocontrol. For example thermal or acid catalysed cycloaddition with *N*-phenylmaleimide of the ylid derived from imine (**1.66**) gave a single cycloadduct (**1.68**) resulting from *endo*- addition to the dipolarophile (**Scheme 1.10**).[43] This was proposed by Grigg to be a consequence of intramolecular hydrogen bonding which resulted in the ylid (**1.67**) being favoured.

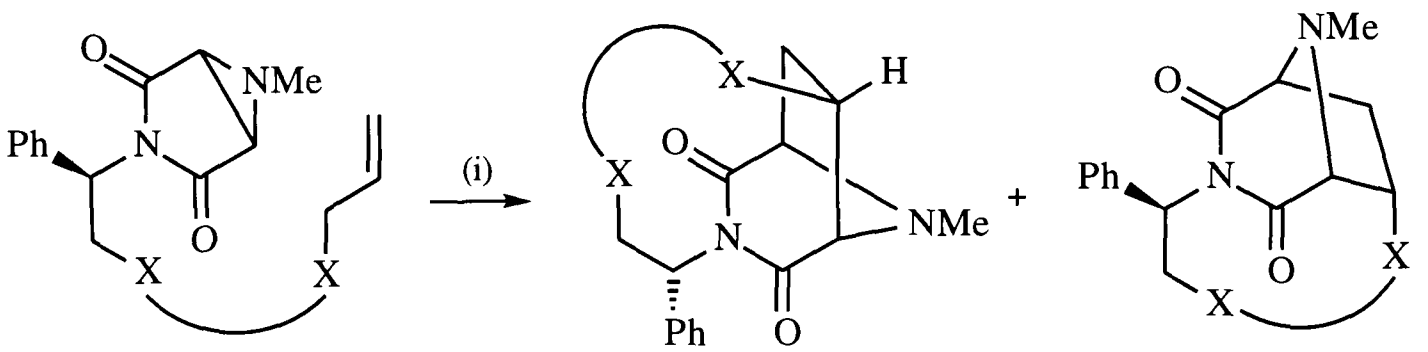


(i) toluene, 105°C, or AcOH, r.t., (ii) *N*-phenylmaleimide.

Scheme 1.10

The additional stereochemical requirements imposed by performing the reaction in an intramolecular manner have also been used to control the stereochemical outcome of cycloaddition. In studies on the synthesis of naphthryidinomycin and cyanocycline, Garner has demonstrated that varying the length of tether between the ylid and dipolarophile can be used to control which of two possible diastereomers is formed (**Scheme 1.11**).[44] Hence use of a long

allylsilicone tethered aziridine (**1.69**) resulted in *endo-si* addition to form a 12 : 1 excess of the incorrect diastereomer (**1.71**) for the natural product, while use of a short acetal tether (**1.70**) resulted in exclusive *endo-re* addition to furnish the correct diastereomer (**1.72**) in 35% yield. Chiral [3+2] dipolar cycloadditions of azomethine ylids will be discussed in the next section



(**1.69**) X–X = $OSi(Ph)_2OCH_2CH_2OCO$
(**1.70**) X–X = OCH(OMe)O

(**1.71**)

(**1.72**)

(i) hν, MeCN, isoprene.

Scheme 1.11

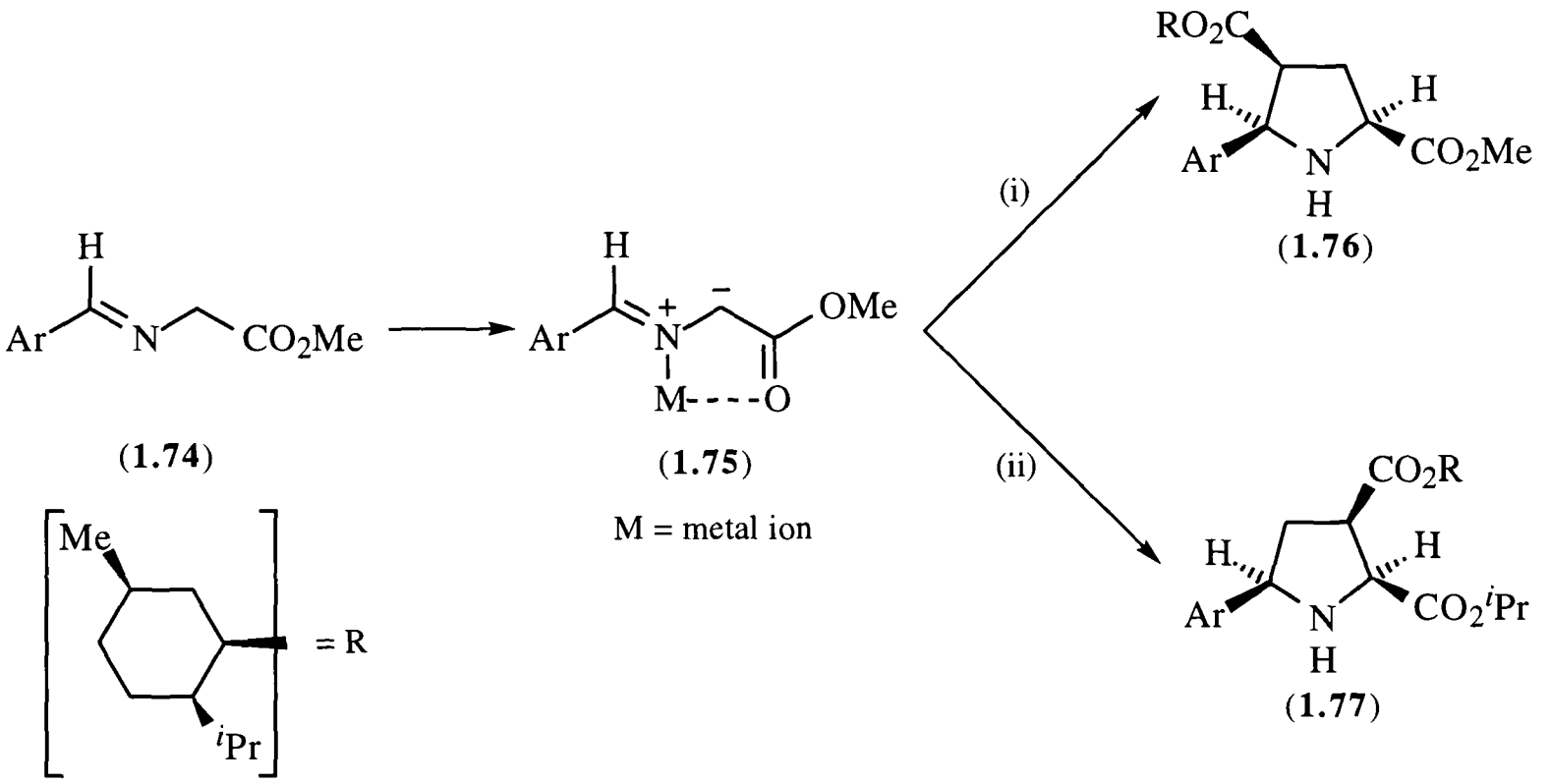
1.2.3 Chiral [3+2] Dipolar Cycloadditions of Azomethine Ylids.

The [3+2] dipolar cycloaddition of azomethine ylids has therefore been demonstrated to proceed with high diastereocontrol under certain circumstances. However, in order for the reaction to be synthetically useful in constructing the pyrrolidine ring of biologically active natural products, enantioselective methods for performing the cycloaddition are necessary. As a consequence the development of such chiral control has been the focus of much research activity in recent years. Chiral control may conceivably be incorporated in one of three ways; through the use of chiral dipolarophiles, catalysts or dipoles, and all of these areas have been extensively studied.

Chiral Dipolarophiles.

The coupling of a chiral auxiliary to the dipolarophile provides a ready method of introducing a chiral component into the reaction, and a number of chiral esters and amides of acrylic acid have been particularly exploited. The menthyl ester of acrylic acid (**1.73**) was used by Grigg in the metal catalysed cycloaddition of ylids (**1.75**) derived from the imines of

α-amino esters such as (**1.74**) (**Scheme 1.12**).[45] The reaction was observed to give the homochiral cycloadduct (**1.76**) using the Lewis acid catalysts AgOAc (50% yield), $TlNO_3$ (quantitative yield) and LiBr (90% yield). Use of $Ti(^iPrO)_3Cl$ however resulted in a reversal of regiochemistry coupled with transesterification to furnish the homochiral cycloadduct (**1.77**) in 75% yield. This reversal of regiochemistry under $Ti(^iPrO)_3Cl$ catalysis was attributed to the ability of titanium to form a six co-ordinate octahedral complex through complexation to the ester carbonyl of both the ylid and the dipolarophile.



(i) AgOAc or $TlNO_3$ or LiBr, NEt_3, menthyl acrylate (**1.73**), MeCN, r.t.

(ii) $Ti(^iPrO)_3Cl$, NEt_3, menthyl acrylate (**1.73**), MeCN, r.t.

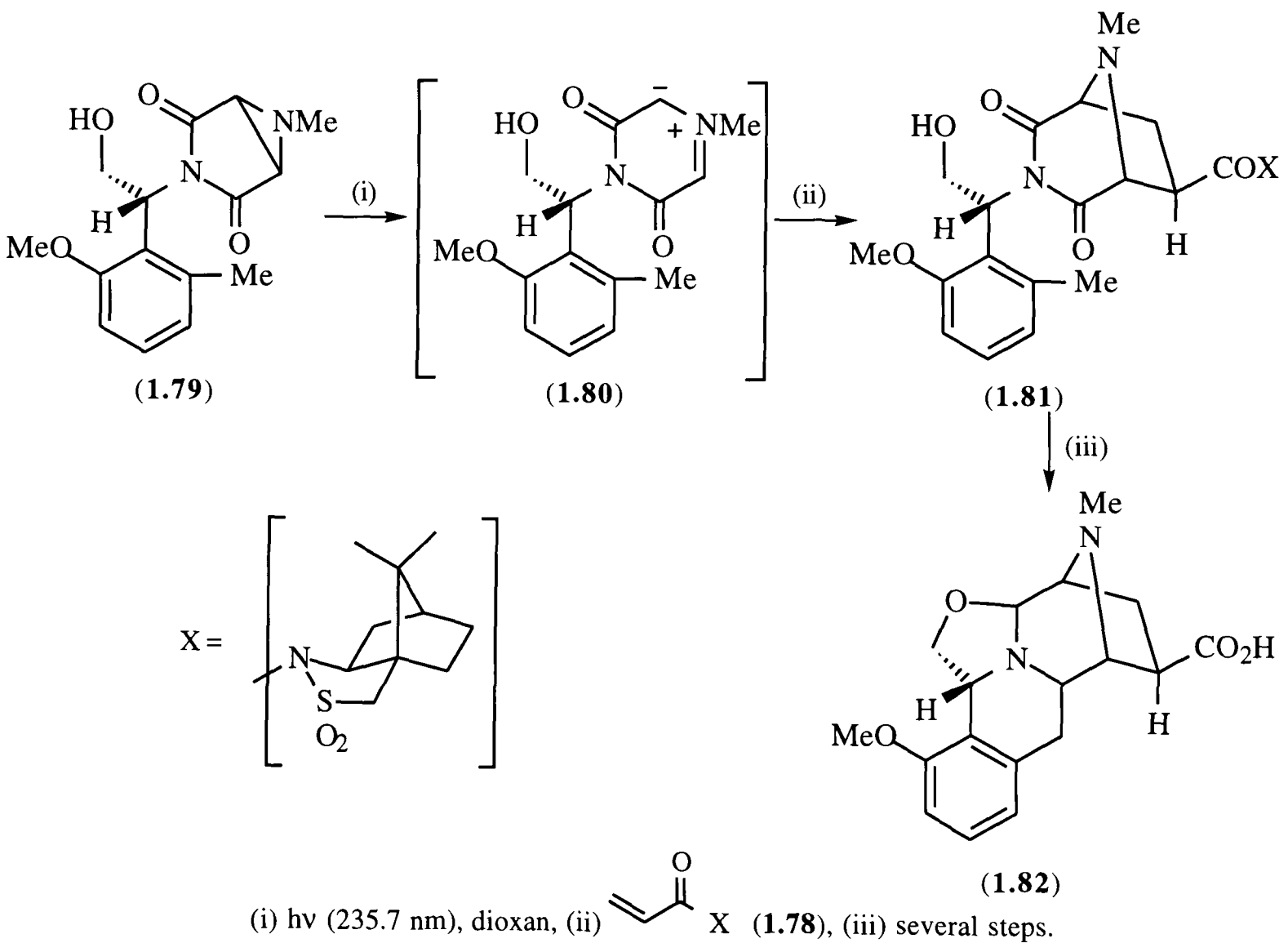
Scheme 1.12

The use of bulky ester groups such as menthyl led to a reduction in rate and yield compared with the cycloaddition using methyl acrylate. Complexation of the metal to the nitrogen facilitates imine hydrolysis and, as the rate of cycloaddition drops, this hydrolysis begins to compete. It was reasoned that use of a stronger base would increase the rate of deprotonation of the iminium salt to form the ylid and therefore increase the rate of cycloaddition. Initial use of DBU bore out this theory, while the highest rate of deprotonation, and therefore of cycloaddition, was achieved with 2-*tert*-butyl-1,1,3,3-tetramethylguanidine.

Proline itself has been used as a chiral auxiliary in azomethine ylid cycloadditions, with results matching those observed with menthyl acrylate.[46] Hence the acrylamide derived from

the benzyl ester of proline typically gave enantiomeric excesses of >99%, and an *endo- /exo-* ratio of 99 : 1. The observed yields were generally lower than those observed by Grigg, however this may be a consequence of the weaker bases used.

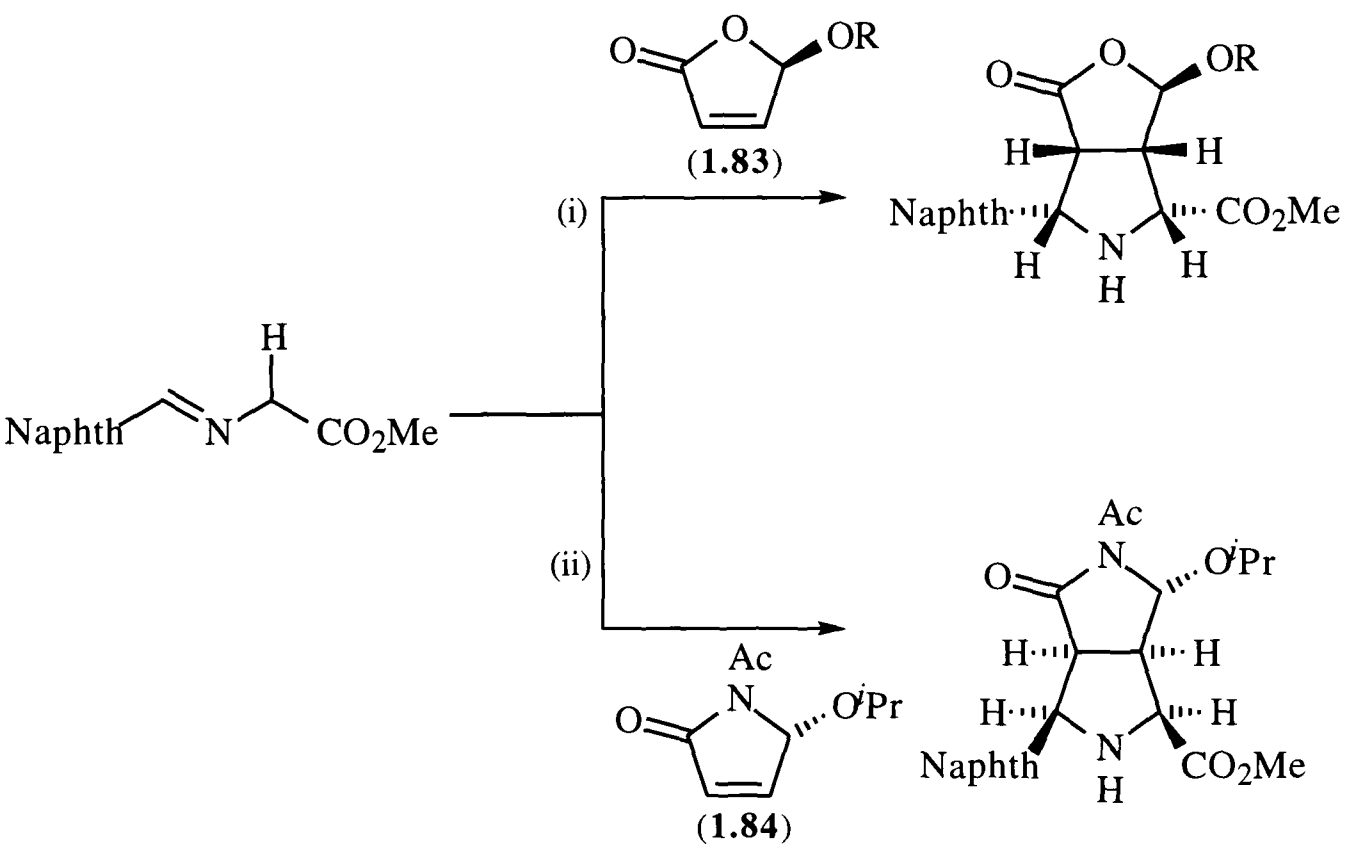
Garner utilised the acrylamide of Oppolzer's camphor sultam (**1.78**) as a chiral dipolarophile in the synthesis of quinocarcin (**1.82**), an antitumour antibiotic isolated from *Streptomyces melanovinaceus*.[47] The key step assembled the 3,8-diazabicyclo[3.2.1]octane unit through the cycloaddition of azomethine ylid (**1.80**) derived from photolysis of aziridine (**1.79**) with the acrylamide (**1.78**) (**Scheme 1.13**). Provided the concentration of dipolarophile was kept low (to avoid absorption of the incident radiation by the dipolarophile) the cycloaddition proceeded efficiently to give a single product (**1.81**), in 61% yield, which could be readily elaborated to quinocarcin (**1.82**).



Scheme 1.13

Cyclic dipolarophiles have the advantage that the conformation of the double bond is fixed, and hence stereocontrol may be expected to be improved. Additionally relief of angle

strain gives these dipolarophiles greater reactivity. Both the furanone menthyl ether (**1.83**) and the pyrrolone (**1.84**) have been employed by Grigg in azomethine ylid cycloadditions (**Scheme 1.14**).[48] Results with both dipolarophiles were similar, in each case generating a single diastereomer with enantiomeric excesses >99% and yields, although dependent on the ylid substituents, of up to 90%.

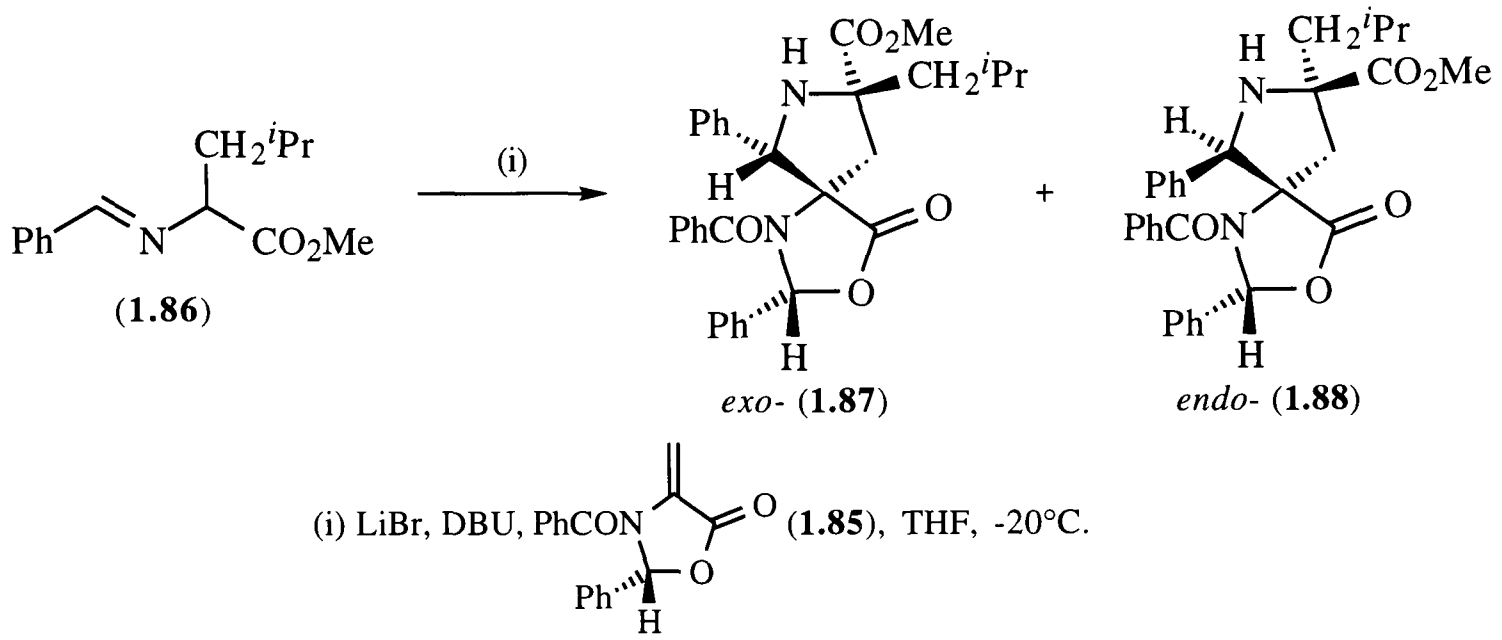


(i) AgOAc, ^{t}BuN (Me_2N, NMe_2), MeCN, r.t., (ii) AgOTf, DBU, DCM, r.t.

Scheme 1.14

Geminally disubstituted proline derivatives have also been accessed through the dipolar cycloaddition of an azomethine ylid to a chiral dipolarophile. The methylene oxazolidinone (**1.85**), readily accessible from alanine *via* an adaptation of the Seebach "self replication of chirality" system (*vide infra*), undergoes highly diastereoselective *exo*- cycloaddition with a range of stabilised ylids (**Scheme 1.15**).[49] The ylid derived from imino ester (**1.86**) therefore underwent efficient cycloaddition with the methylene oxazolidinone (**1.85**) to furnish a combined 61% yield of two cycloadducts with a 94 : 6 excess of the *exo*- isomer (**1.87**) over the *endo*- isomer (**1.88**). Subsequent hydrolysis under mildly basic conditions readily liberated the geminally disubstituted proline derivative. The enantiomeric excesses, determined by formation of the carbamate with (*S*)-1-phenylethylisocyanate, were found to be typically in

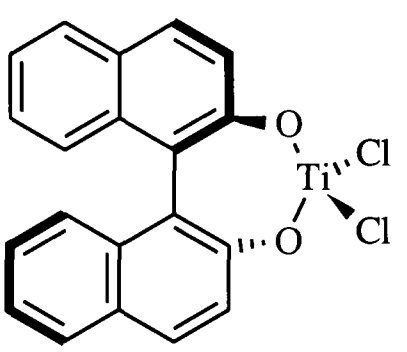
excess of 92%. The preference for *exo-* cycloaddition was rationalised by considering chelation to occur between the lithium cation and the *N*- benzoyl carbonyl group of the ylid.



Scheme 1.15

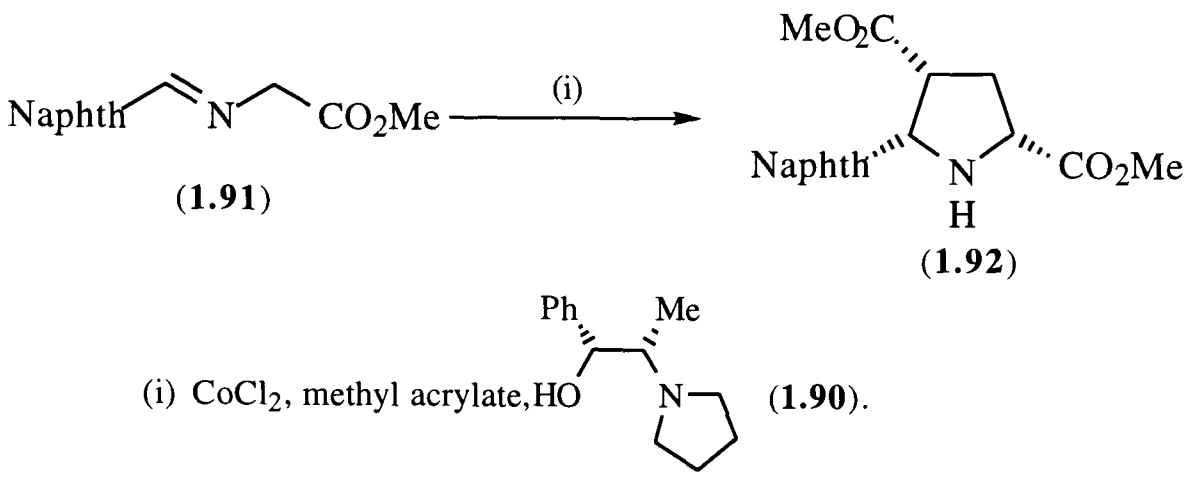
Chiral Catalysts.

Use of chiral catalysts offers possibly the most challenging and attractive method of introducing chirality into the cycloaddition. This method has been widely employed in the Diels-Alder reaction,[50] although application to the [3+2] cycloaddition reaction of azomethine ylids has been rarer. Generation of the azomethine ylid is often achieved through the use of Lewis acids. Therefore chiral ligands attached to the catalyst should furnish an asymmetric environment, and thereby allow chiral induction. However Lewis acids such as binaphthol titanium dichloride (**1.89**) failed to promote cycloaddition. It was similarly expected that use of chiral bases to effect deprotonation of the imine salt would induce chirality, disappointingly however enantiomeric excesses of only 10-20% were achieved.[51]



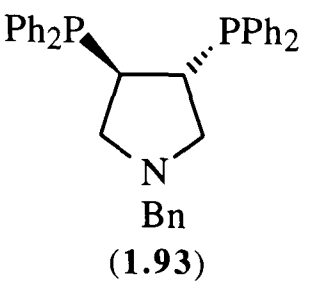
(1.89)

Recent work by Grigg has shown the possibility of chiral induction using ephedrine ligands with complexation between the metal, ligand and ylid (**Scheme 1.16**).[52] Manganese bromide and cobalt chloride were investigated as catalysts, with the best results being obtained with cobalt chloride. Hence stirring imine (**1.91**) with 1 mole equivalent of cobalt chloride and 2 mole equivalents of ligand (**1.90**) in methyl acrylate gave 84% yield of a single adduct (**1.92**), with an enantiomeric excess of >96%. The high degree of steric control was attributed to formation of an octahedral cobalt complex containing one equivalent of imine and one of ligand. Use of more than two equivalents of ligand led to a reduction in rate due to complexation of extra ligand to the catalyst preventing substrate complexation. Alternatively use of lower quantities of ligand reduced the enantiomeric excess.



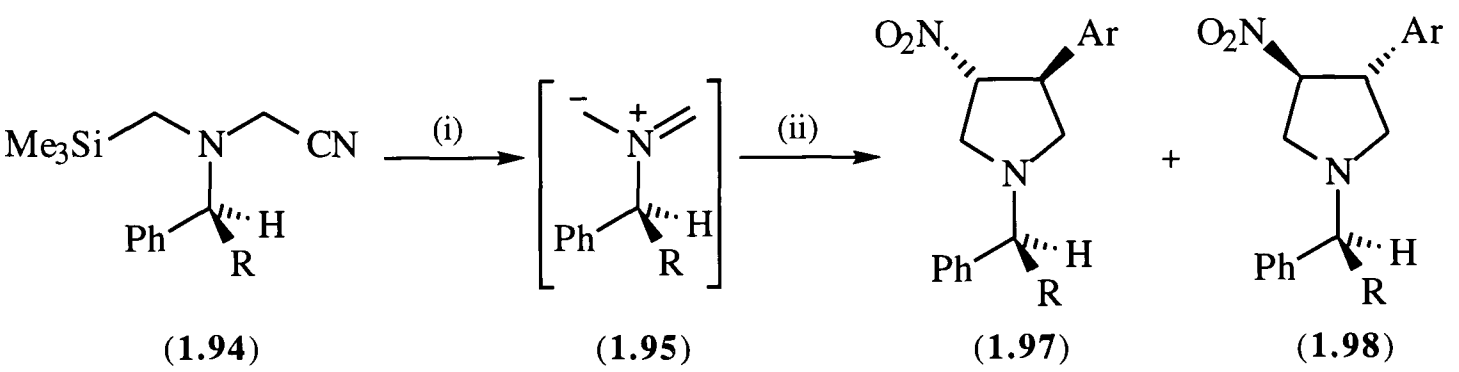
Scheme 1.16

Disappointingly the catalytic system proved to be non-general, leading to the necessity of tuning the system for each combination of dipolarophile and ylid. More recent developments have focused on the use of silver mediated ylid formation using chiral diphosphine ligands, for example (**1.93**), to control the chirality. However these systems have again suffered from problems of non-generality.[51]

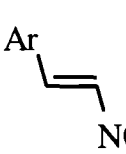


Chiral Dipoles.

The final possibility for asymmetric induction is through the use of a chiral azomethine ylid. The first chiral ylid (**1.95**), reported by Padwa in 1985, was generated by desilylation of the phenylethylamine derivative (**1.94**) (**Scheme 1.17**).[53] The degree of stereocontrol observed in the cycloaddition was found to be dependent on the size of the substituents around nitrogen. With R = Me cycloaddition with the activated alkene (**1.96**) gave a 3 : 2 excess of (**1.97**) over (**1.98**), while with R = CH_2OCH_3 the diastereoselectivity was increased to a 4 : 1 excess.

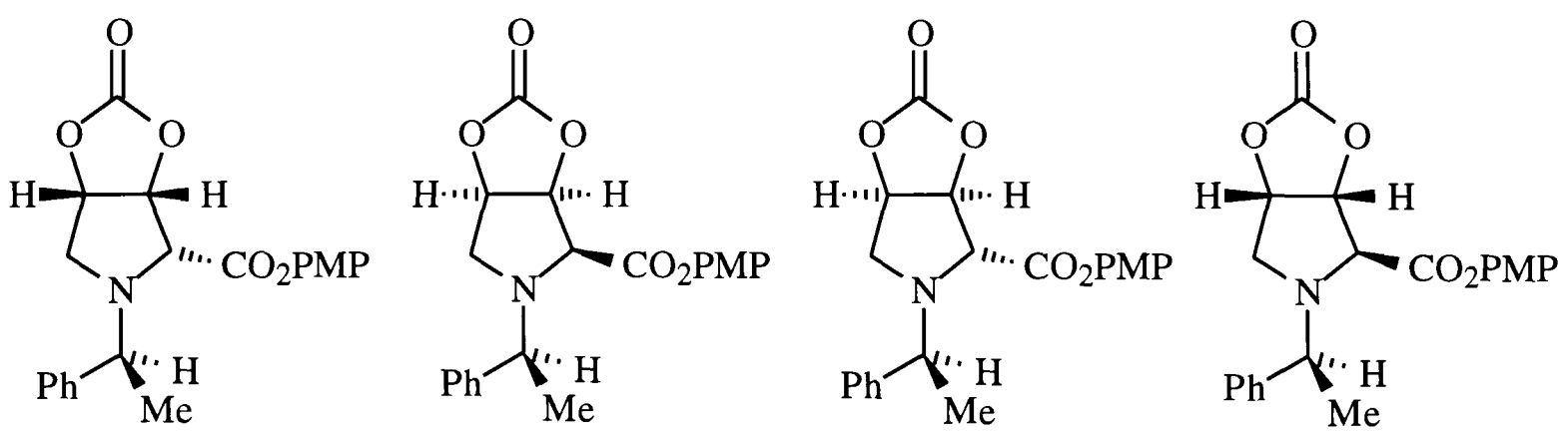


(**1.94**) (**1.95**) (**1.97**) (**1.98**)

(i) AgF, MeCN, (ii)  (**1.96**).

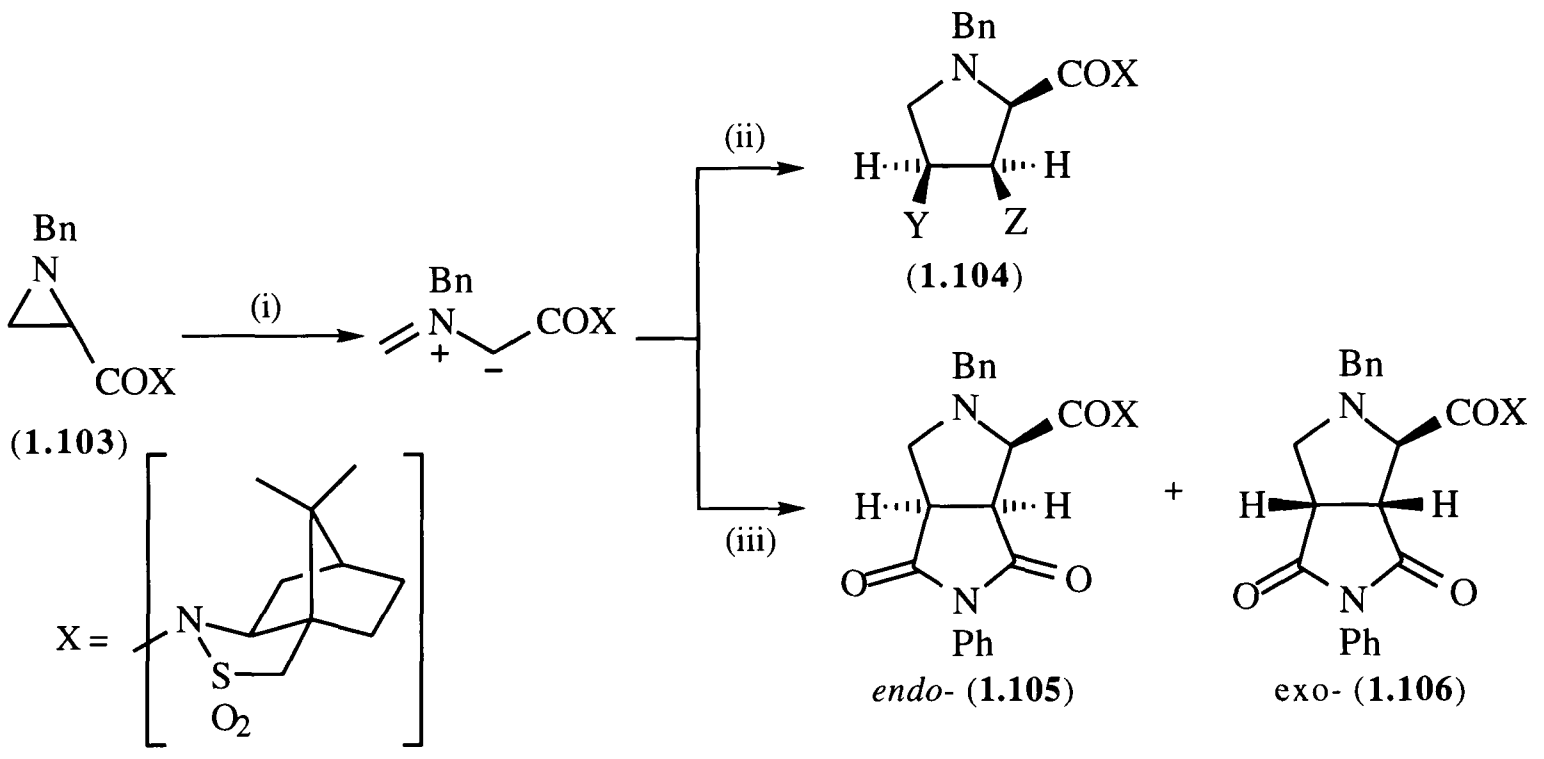
Scheme 1.17

Despite these limitations this methodology was used by Takano in the synthesis of precursors to the four possible isomers of *cis*-3,4-dihydroxyproline as potential glycosidase inhibitors.[54] The cycloaddition was found to display a 3 : 1 bias in favour of the all *cis*-products (**1.99**) and (**1.100**) over the *trans*- products (**1.101**) and (**1.102**), however no facial selectivity was observed, leading to roughly equimolar mixtures of the *cis*- and *trans*-diastereomers. These were however readily separable, and the aim of accessing the hydroxylated pyrrolidines was therefore achieved.



(**1.99**)-30% (**1.100**)-33% (**1.101**)-11% (**1.102**)-10%

The stereoselectivity of this type of simple ylid can be rapidly improved through attaching the auxiliary to the acid rather than amine functionality. Garner employed Oppolzer's camphor sultam as the chiral auxiliary in the thermolysis of aziridine (**1.103**) (**Scheme 1.18**).[55] Enantiomeric excesses were in all cases >95%, however diastereo- and regioselectivity was variable. Dimethyl maleate furnished a single cycloadduct (**1.104**, Y = Z = CO_2Me) derived from *endo*- addition to the ylid, while *N*-phenylmaleimide gave a 2 : 1 excess of *endo*- (**1.105**) over *exo*- (**1.106**). Methyl acrylate similarly gave a 2 : 1 mixture of regioisomers (**1.104**, Y = H, Z = CO_2Me : **1.104** , Y = CO_2Me, Z = H).



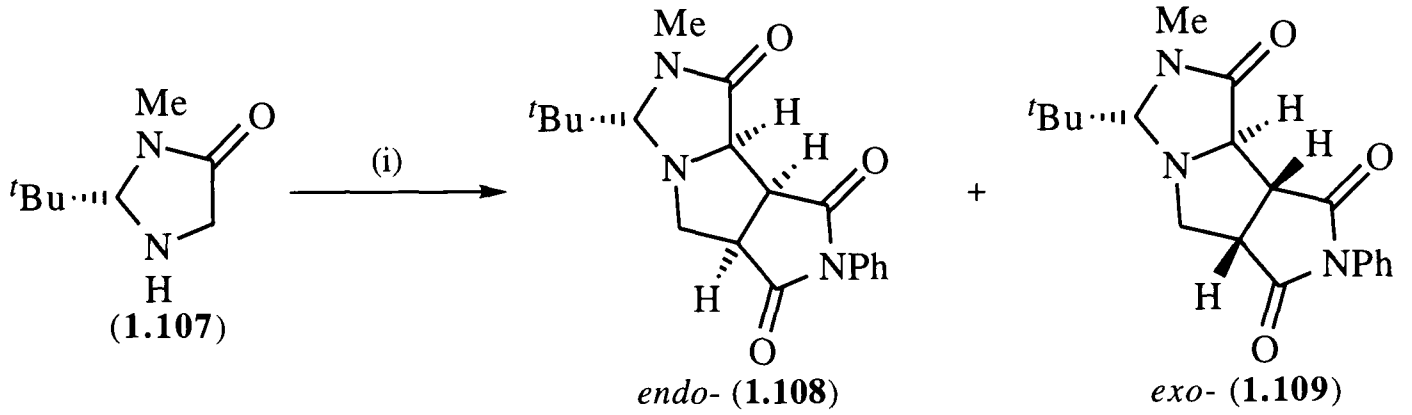
(i) thermolysis, 180°C, (ii) dimethyl maleate or methyl acrylate, (iii) *N*-phenylmaleimide.

Scheme 1.18

The stereocontrol obtained in cycloaddition reactions with the acyclic chiral ylids so far described has been good, however it was considered that incorporation of the ylid into a cyclic structure would increase the selectivity for two reasons. Firstly the geometry of the ylid would be fixed due to the cyclic nature, and secondly the additional steric hindrance of the ring should increase the potential for facial and therefore enantioselectivity.

The imidazolidinone (**1.107**), introduced by Seebach as a chiral glycine equivalent,[56] has also been exploited as a chiral ylid precursor.[57] Generation of the ylid through condensation with paraformaldehyde was followed by highly efficient cycloaddition with a range of electron deficient dipolarophiles to give enantiomerically pure cycloadducts. For

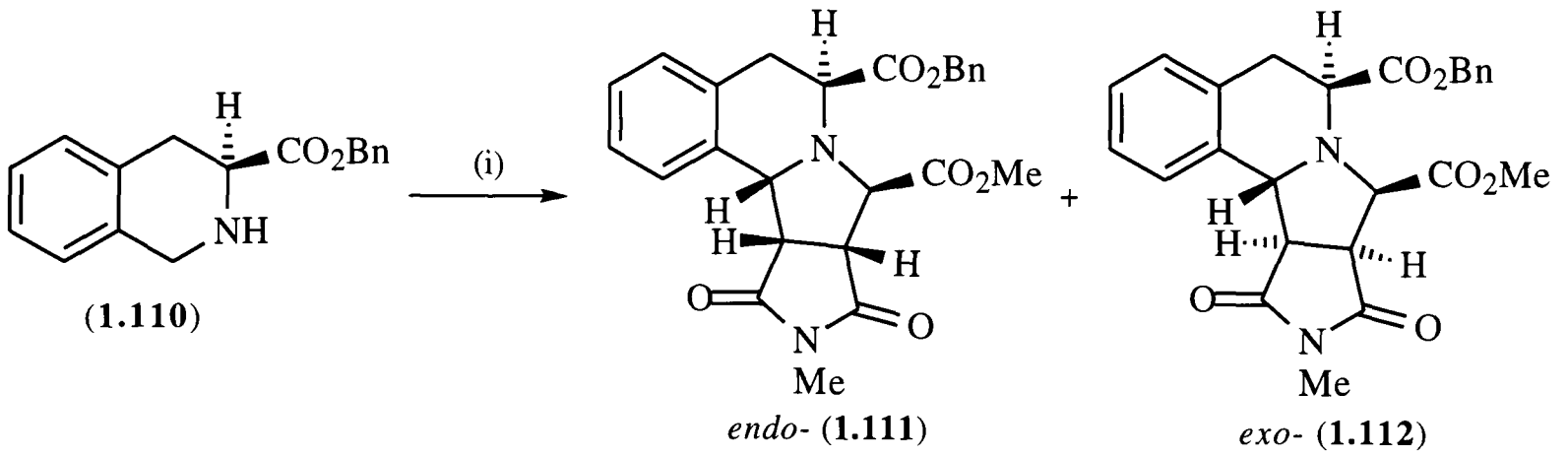
example, generation of the ylid in the presence of *N*-phenylmaleimide resulted in the isolation of two cycloadducts in a combined yield of 71%, with the *endo*- adduct (**1.108**) predominating over the *exo*- adduct (**1.109**) by a 4 : 1 ratio (**Scheme 1.19**).



(i) $(HCHO)_n$, *N*-phenylmaleimide, reflux toluene.

Scheme 1.19

Grigg has observed unusual enantiocontrol in cycloadditions of the cyclic ylid derived from amino acid (**1.110**).[58] Condensation with methyl glyoxylate was followed by regiospecific deprotonation, not from the more acidic α-amino acid carbon, but from the benzylic carbon. This preserved the chirality of the amino acid (no adducts derived from the regio- ylid were observed) leading to enantiopure products (**Scheme 1.20**). The diastereoselectivity was also good with the observation of a 5 : 1 excess of *endo*- (**1.111**) over *exo*- (**1.112**) in an overall yield of 73%.

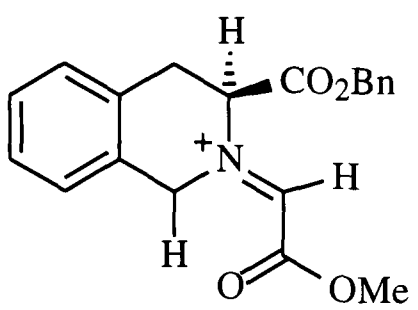


(i) $CHOCO_2Me$, *N*-methylmaleimide, DMF, 110°C.

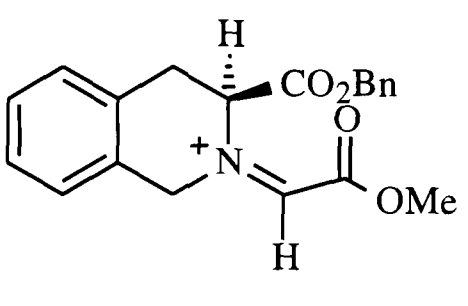
Scheme 1.20

The origin of the regiospecific deprotonation was attributed to two complementary effects. Initial formation of the *E*-iminium ion (**1.113**) over the *Z*-iminium ion (**1.114**) is

favoured due to steric hindrance between the two ester substituents. Subsequent anchimeric assistance rendered by the glyoxal ester carbonyl results in exclusive deprotonation of the benzylic hydrogen. Regiospecific deprotonation was observed as long as the C-H bond was slightly activated e.g. benzylic.

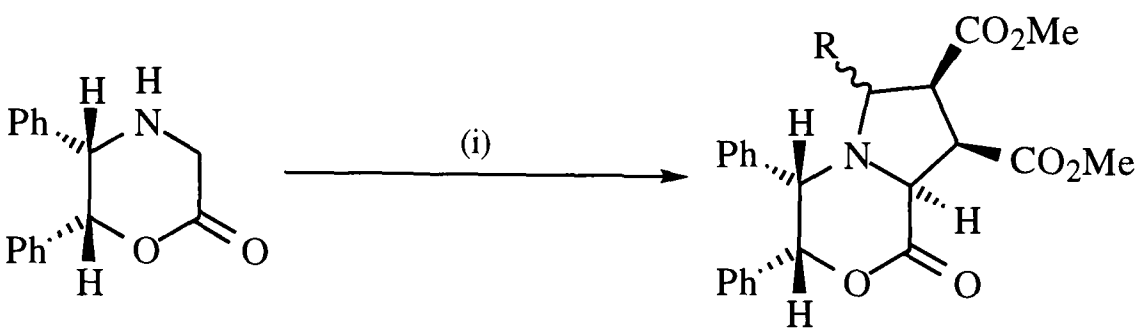


(1.113)



(1.114)

Williams has conducted a limited investigation into the potential of template (**1.115**) as a chiral azomethine ylid precursor (**Scheme 1.21**).[59] Ylid generation with a range of aldehydes followed by cycloaddition with dimethyl maleate furnished a range of cycloadducts (**1.116**). In all cases exclusive *endo*- addition to the least hindered face of the ylid gave the unique stereochemistry observed at C_2, C_3 and C_4, with enantiomeric excesses of >99%. The control of stereochemistry at C_5 was poor however, and generally an equimolar mixture of epimers was observation. The exception was the ylid derived from *iso*-butyraldehyde, which gave a single diastereomer in 52% yield. Although this template is structurally very similar to the templates used in the work described in this thesis, it suffers from the disadvantage that it can not be prepared from an optically pure amino acid. In addition it is not suitable for the chiral memory system previously developed within the group and further elaborated in this thesis.

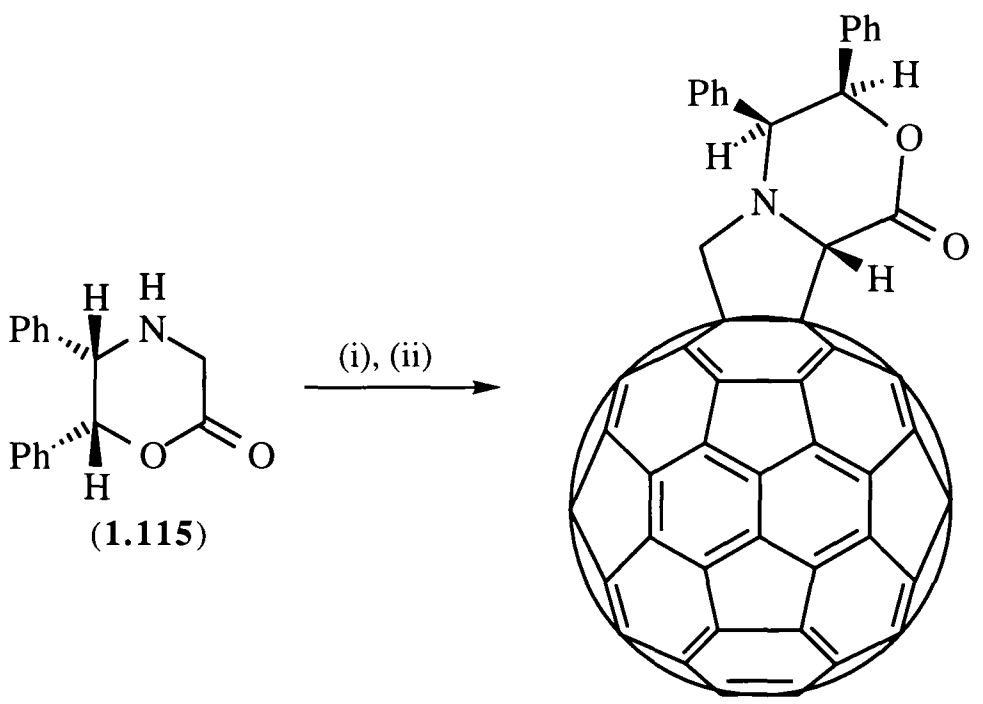


(1.115) **(1.116)**

(i) RCHO, dimethyl maleate, *p*TSA, reflux benzene.

Scheme 1.21

The methodology developed by Williams has been exploited by Maggini in the synthesis of optically active fulleroprolines.[60] Water soluble derivatives of C_{60} have been recently shown to interact with the active site of HIV-1 protease, demonstrating their potential therapeutic use.[61] Treatment of C_{60} with the ylid derived from the diphenyl substituted morpholinone (**1.115**) resulted in the isolation of a single product (**1.117**) in 46% yield (**Scheme 1.22**). The deprotection of this cycloadduct should allow access to fulleroproline, a synthetic precursor for C_{60} containing peptides that may show HIV-1 protease inhibitory properties.



(1.115) **(1.117)**

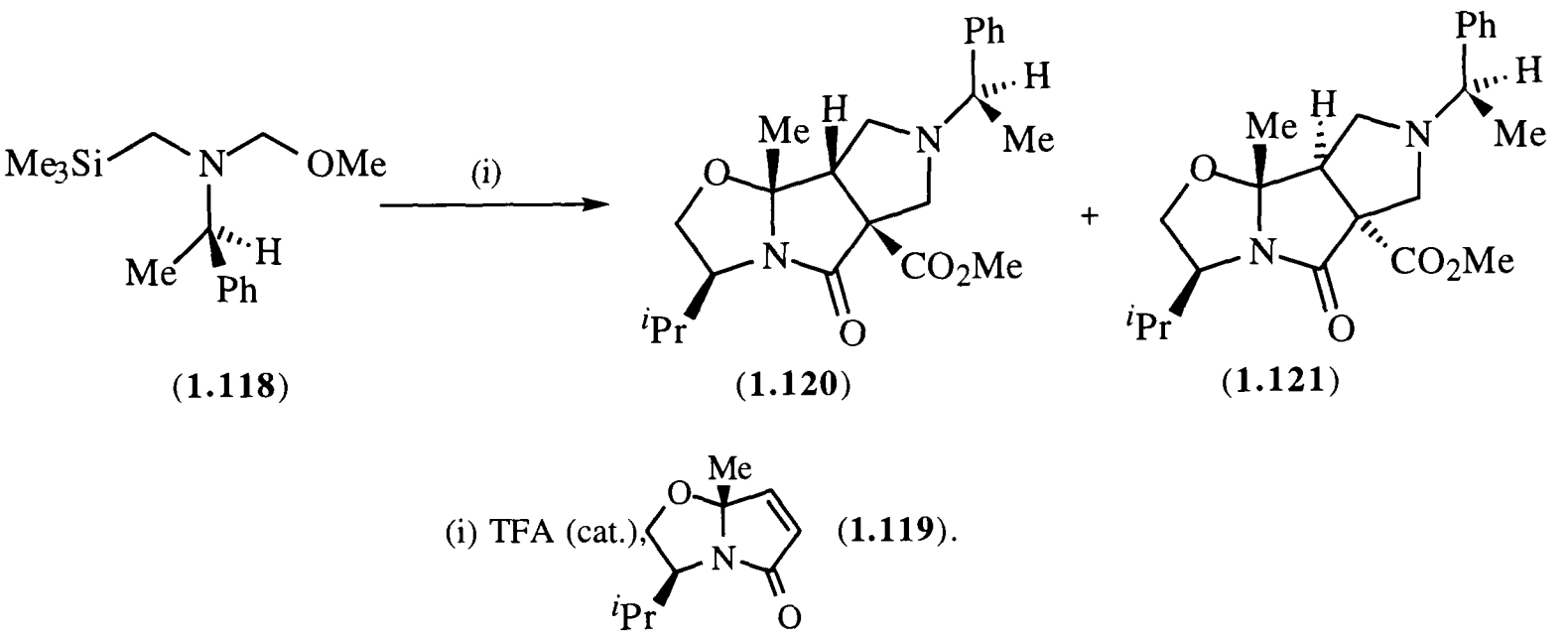
(i) $ClCH_2OC_8H_{17}$, NEt_3, Δ, (ii) C_{60}, *p*TSA.

Scheme 1.22

Double Asymmetric Induction.

Despite the possibility of combining two or more of the potential methods of chiral induction, very little research effort has been so directed. In studies on the synthesis of quinocarcin, Garner investigated the combination of a Padwa type chiral ylid with chiral acrylamide and acrylate dipolarophiles.[62] However chiral induction was only achieved when using the acrylamide derived from Oppolzer's camphor sultam, an effect later shown to be due exclusively to the dipolarophile. Meyers however obtained greater success when investigating the cycloaddition between chiral ylids (**1.118**) of the Padwa type and chiral bicyclic lactams (**1.119**) (**Scheme 1.23**).[63] When using the matched pair of reagents an 84% diastereomeric

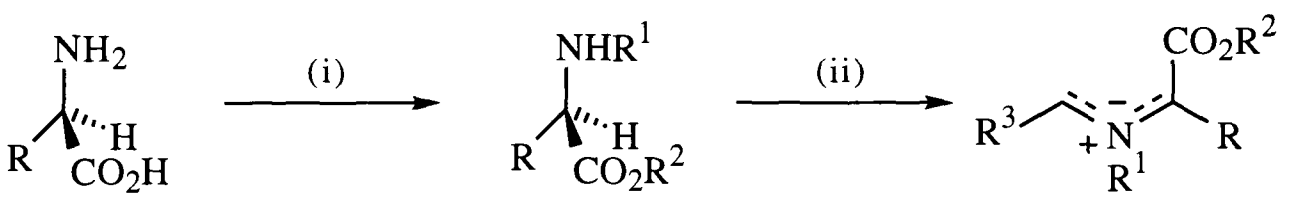
excess of the α- diastereomer (**1.120**) over the β- diastereomer (**1.121**) was observed. By contrast the achiral dipole gave a diastereomeric excess of 44%, while the mismatched pair gave a diastereomeric excess of only 2%.



Scheme 1.23

1.3 Morpholinone Systems as Chiral Azomethine Ylid Precursors.

Azomethine ylids are readily generated from α-amino acids through condensation of an aldehyde with a suitably protected derivative. The chirality of the α- centre is however necessarily lost on generation of the planar ylid (**Scheme 1.24**). Consequently, in order for cycloaddition to proceed in a stereocontrolled manner, additional chirality must be incorporated into the ylid precursor.

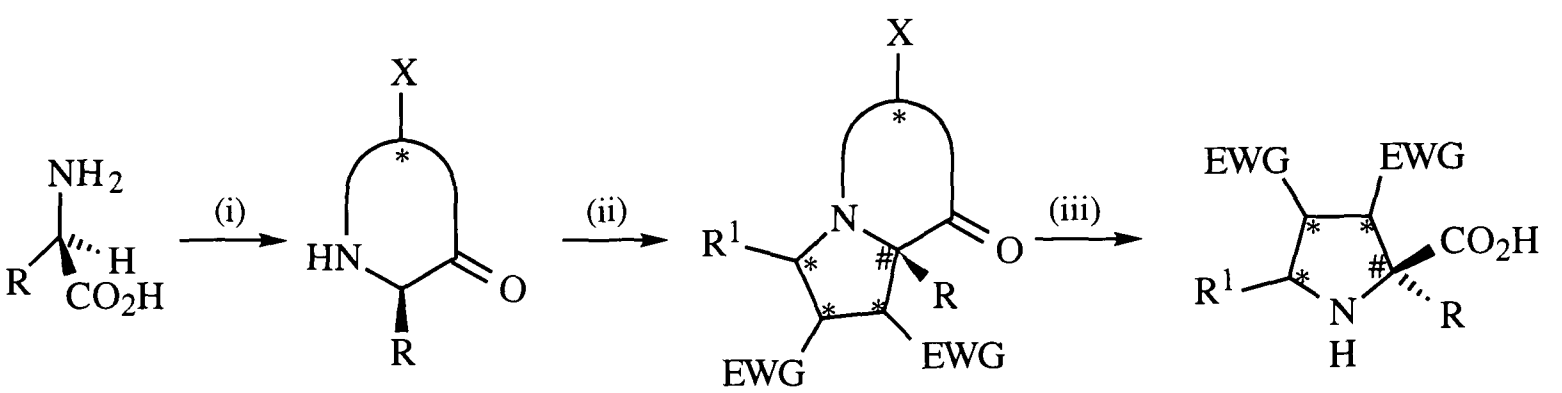


(i) protection, (ii) R^3CHO, $-H_2O$.

Scheme 1.24

The approach proposed by Harwood and co-workers was to incorporate the amino acid into a chiral template which, following ylid generation and cycloaddition, could be readily removed. In order to make most efficient use of the chirality of the starting material the amino

acid (**1.122**) was initially to be functionalised with a prochiral auxiliary. Chirality transfer would generate a second chiral centre (**1.123**) which would then be used to control the stereochemical outcome of the cycloaddition. The cycloadduct (**1.124**) generated would have up to four new chiral centres and, in addition to regeneration of the original amino acid centre, a degree of stereocontrol over the other three was anticipated. Subsequent removal of the template would generate the free proline derivative (**1.125**) (**Scheme 1.25**). In order for the proposed chiral relay system to operate effectively, chiral transfer and later auxiliary removal would need to be highly efficient.



(1.122) **(1.123)** **(1.124)** **(1.125)**

* induced chiral centre # remembered chiral centre

(i) prochiral auxiliary, chirality transfer, (ii) ylid generation, cycloaddition, (iii) auxiliary removal.

Scheme 1.25

The synthesis of disubstituted morpholinones (**Figure 1.2**) through highly diastereoselective hydrogenation of the corresponding morpholinone imines had previously been reported by Sunjic.[64] The imines were derived from α- amino acids, and this method would therefore allow highly selective functionalisation of a prochiral auxiliary. The second requirement, that of template removal, would be possible through hydrogenolysis of the *N*-aryl bond and hydrolysis of the lactone. The morpholinone system therefore appeared to fulfil all the requirements of the chiral relay system.

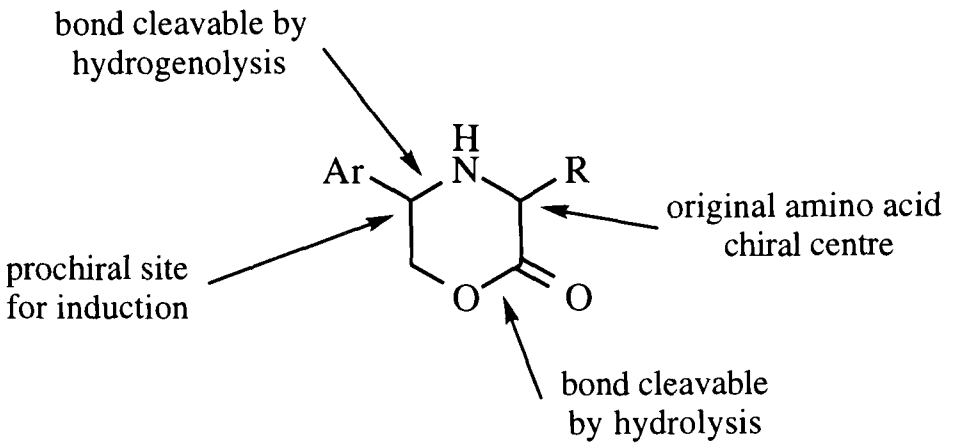
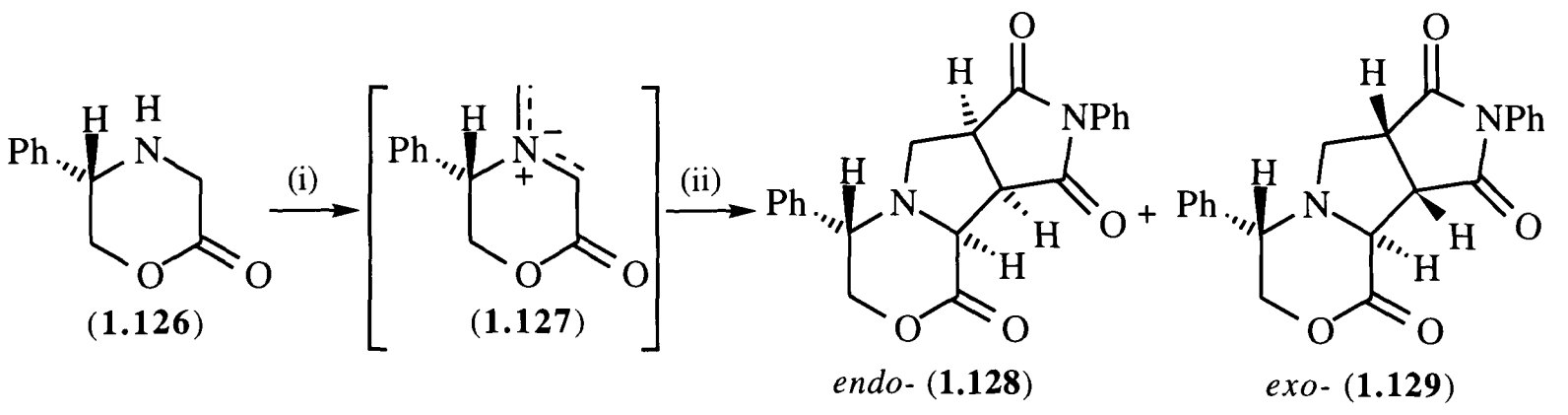


Figure 1.2

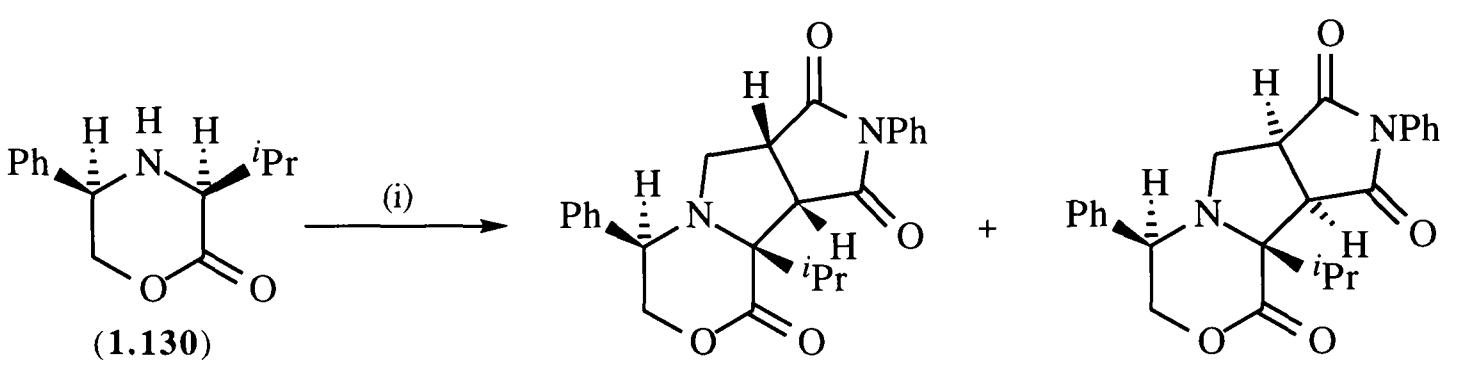
As a preliminary study the effect of the C_5 substituent on the stereochemical outcome was demonstrated using the known analogue (**1.126**), previously employed by Santarsiero as a chiral glycine equivalent.[65] Generation of the ylid (**1.127**) through condensation with paraformaldehyde followed by cycloaddition with a range of electron deficient dipolarophiles furnished enantiomerically pure cycloadducts with good stereocontrol.[66] Generation of the ylid in the presence of *N*-phenylmaleimide therefore resulted in the isolation of two cycloadducts, derived exclusively from addition to the least hindered face of the ylid, in a combined yield of 58% (**Scheme 1.26**). The *endo*- adduct (**1.128**) was observed to predominate over the *exo*-adduct (**1.129**) by a 3.5 : 1 ratio, possibly due to non-bonding interactions of the frontier orbitals in a manner akin to the Diels-Alder reaction. The excellent stereocontrol observed in cycloadditions with ylids derived from phenylmorpholinone (**1.126**) has resulted in this method being employed in the synthesis of kainic acid precursors,[67] bicyclic proline derivatives[68] and β-hydroxy-α-amino acids.[69]



(i) $(HCHO)_n$, molecular sieves, reflux benzene, (ii) *N*-phenylmaleimide.

Scheme 1.26

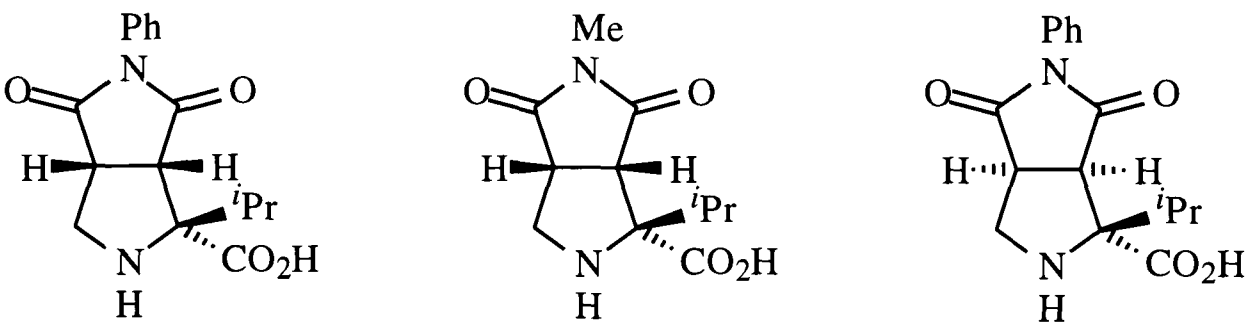
The disubstituted template (**1.130**) required for the chiral relay system was constructed from (*S*)-valine using the method of Sunjic,[64] then subjected to cycloaddition with a range of dipolarophiles. A slight reduction in yield was observed in all cases, although this was accompanied by an increase in the *endo-*/ *exo-* selectivity. Both of these effects were attributed to the steric bulk of the *iso*-propyl group. *N*-phenylmaleimide was observed to give a 5 : 1 excess of the *endo-* adduct (**1.131**) over the *exo-* adduct (**1.132**) in an overall yield of 41% (**Scheme 1.27**),[70] compared with the 3.5 : 1 *endo-* : *exo-* excess, and overall yield of 58% observed in the monosubstituted case above.



(i) $(HCHO)_n$, *N*-phenylmaleimide, molecular sieves, reflux toluene.

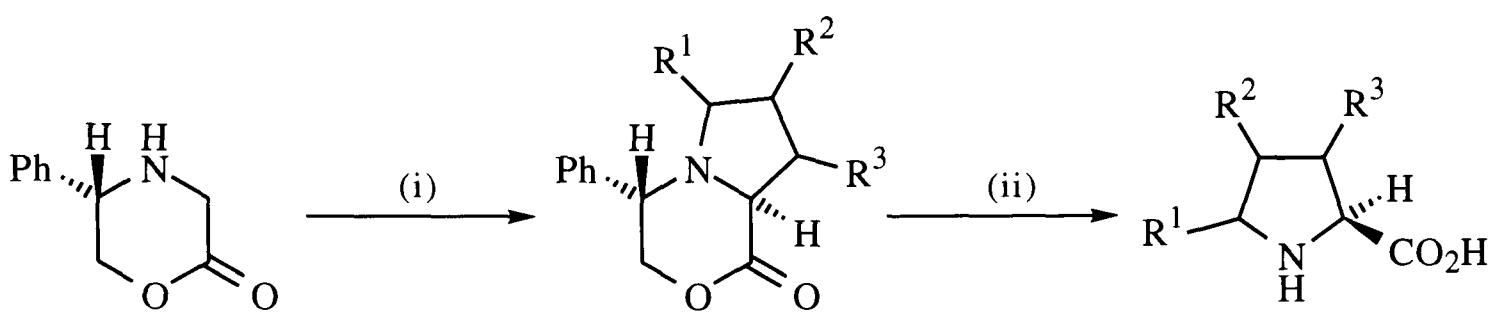
Scheme 1.27

Completion of the relay system was achieved through removal of the chiral template to release the free proline. Efficient hydrogenolysis of the *N*-benzyl bond with Pearlman's catalyst in acidic methanol was accompanied by concomitant ester hydrolysis to generate a number of novel proline derivatives (**1.133-1.135**).[70]



The [3+2] dipolar cycloaddition reaction of chiral azomethine ylids derived from substituted morpholinones has therefore been demonstrated to proceed in a highly diastereocontrolled manner, generating cycloadducts from which α- substituted and α-unsubstituted proline derivatives can be readily obtained. Recent studies have also shown that

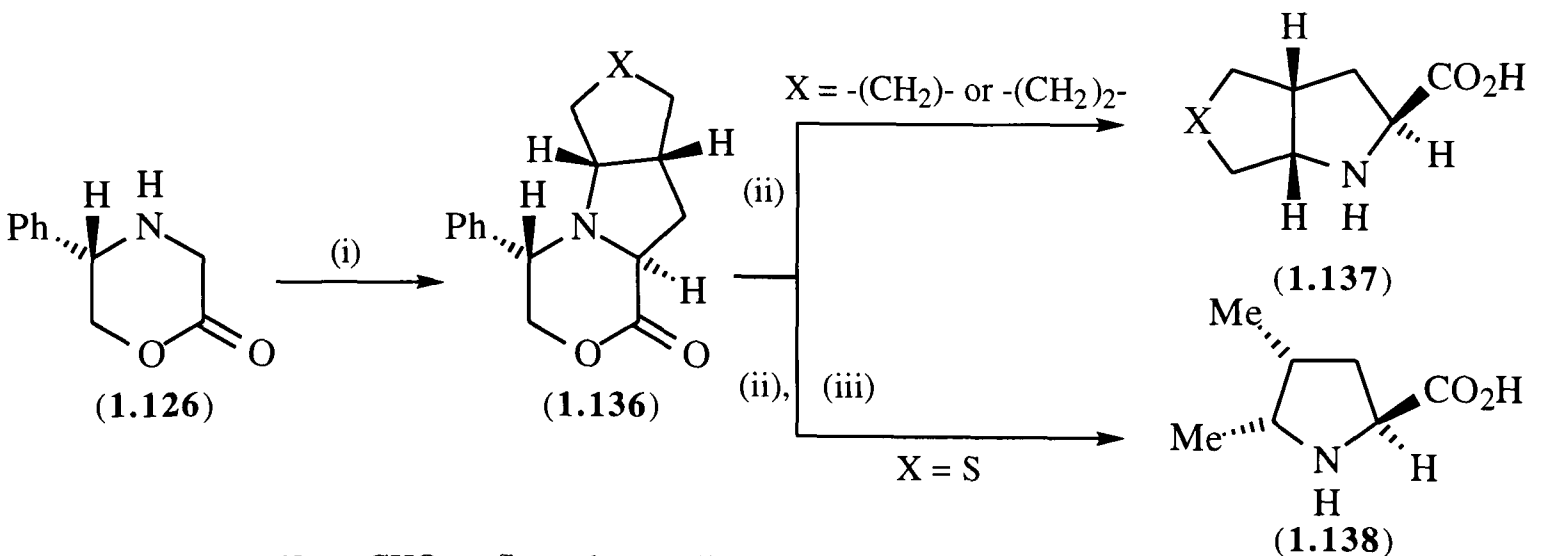
the regio- and stereochemical outcome of the cycloaddition can be dramatically altered under the influence of Lewis acid catalysis.[71] Such catalysis offers the potential for controlling the introduction of a substituent at the 5- position through the use of an aldehyde to which the catalyst may co-ordinate. Full extension of this methodology should therefore allow the synthesis of tetra-substituted prolines from a simple amino acid precursor (**Scheme 1.28**).



(i) R^1CHO, R^2 R^3, (ii) template removal.

Scheme 1.28

Harwood has also demonstrated that the intramolecular cycloaddition reaction proceeds efficiently to generate tricyclic cycloadducts (**1.136**). Removal of the template generates bicyclic (**1.137**) proline derivatives, while heteroatom removal allows 4,5- disubstituted (**1.138**) derivatives to be obtained (**Scheme 1.29**).[68] Introduction of heteroatoms has so far been limited to the incorporation of sulfur, however the introduction of alternative linkages may allow further elaboration of the cycloadduct. Such elaboration may potentially take place in a highly stereocontrolled manner due to the rigid tricyclic structure of the cycloadduct, and allow access to a range of pyrrolidines not readily synthesised by other means.



(i) X CHO , reflux toluene, (ii) template removal, (iii) sulfur removal.

Scheme 1.29

1.4 Synthesis of α-Amino Acids.

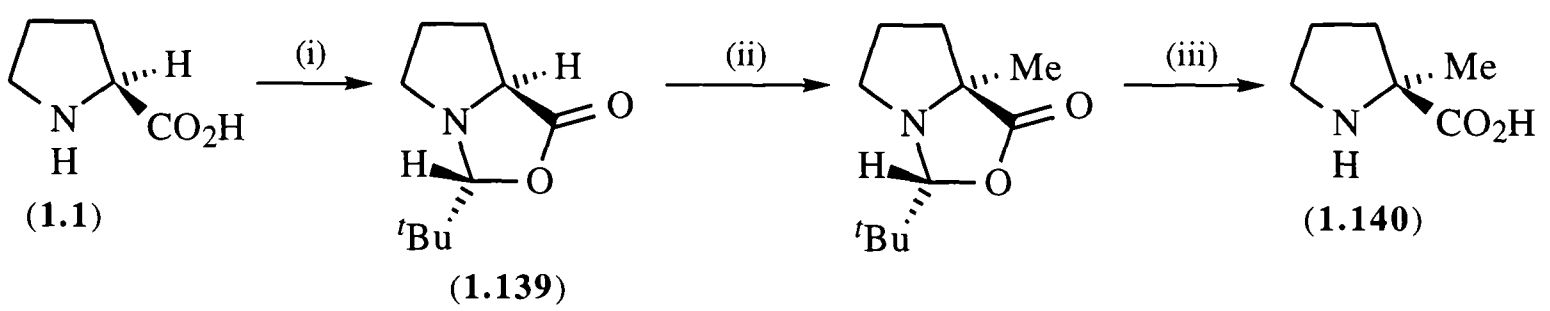
α-Amino acids as the constituent of proteins serve a fundamental role in both biology and chemistry. In nature they are the raw materials for a range of primary and secondary metabolites,[72] and have been used synthetically as chiral starting materials in a number of syntheses.[73] Non-proteinogenic amino acids have been incorporated into peptides to induce a range of properties from protease resistance to enzyme inhibition. The potential application of these unnatural and non-proteinogenic amino acids has therefore led to a great deal of interest in their synthesis. The classical method of obtaining optically pure amino acids involved the resolution of a racemate by derivatisation with a chiral agent. This process produced a mixture of diastereomers which could then be separated by conventional methods. More recent methods of resolution have included the use of enzymes to selectively functionalise a single enantiomer,[74] or kinetic resolution *via* chemical means for example the Sharpless epoxidation.[75] However the homochiral requirements of drug regulatory legislation[76] have led to increased interest in the asymmetric synthesis of amino acids. These syntheses can be categorised according to which bond is formed in the asymmetric step.

Introduction of hydrogen can be accomplished by asymmetric hydrogenation of α,β-didehydro amino acids,[77] reductive amination of α-keto acids[78] or by asymmetric protonation of enolates.[79] Nitrogen may be introduced through the electrophilic amination of enolates[80] or through nucleophilic amination, when the chirality required is generally already present.[81] Alternatively the carboxylate moiety may be added through an asymmetric Strecker synthesis with cyanide ion, or an asymmetric Ugi reaction using an isocyanide.[82] These methods were reviewed in detail by Duthaler in 1994.[83]

The final possible disconnection is removal of the side chain. A wide variety of techniques have been developed for the introduction of this group by electrophilic, nucleophilic and radical means. The general strategy involves a chiral template, which is used to induce chirality in the introduction of the side chain, then removed to afford the pure amino acid. A number of these templates have been devised, commonly utilising a readily available amino acid as the source of chirality.

1.4.1 Chiral Templates in Amino Acid Synthesis.

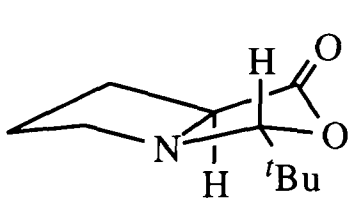
The first system for amino acid synthesis was introduced by Seebach in 1981, initially for the synthesis of α-substituted prolines.[84] Proline (**1.1**) was condensed with excess pivaldehyde to afford a single diastereomer of the bicyclic derivative (**1.139**). This could then be deprotonated and subsequently alkylated with complete stereocontrol to furnish, after template removal, the α-substituted proline (**1.140**) in an overall yield of 68% (**Scheme 1.30**).



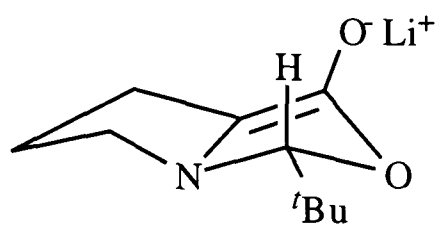
(i) ^{t}BuCHO, TFA (cat.), pentane, Δ, (ii) LDA, MeI, THF, -78°C, (iii) 15% aqueous HBr.

Scheme 1.30

In this process, which Seebach dubbed "self-replication of chirality", the chirality of the proline is used to dictate the stereochemistry of the chiral centre formed on condensation with pivaldehyde. This centre is generated under thermodynamic control so as to place the bulky *tert*-butyl group in a pseudo equatorial configuration (**1.139**). The α-stereocentre is then destroyed on enolate formation and the new stereocentre acts as a chiral memory. Subsequent alkylation of the enolate (**1.141**) occurs from the lower convex, and therefore less hindered, face, rather than the upper concave face. Additional steric hindrance may be provided by the lithium cation, however the instability of the anion above -30°C precludes any investigation of this possibility.



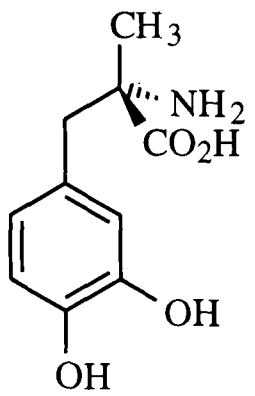
(1.139)



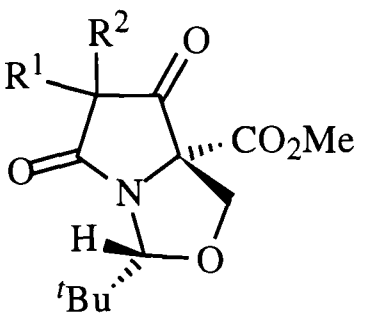
(1.141)

This methodology has been used by Seebach in the synthesis of both enantiomers of methyldopa (**1.142**) from alanine,[85] and has also been applied to the synthesis of tetramic and

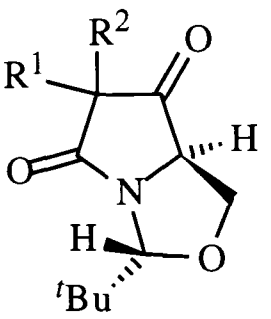
kainic acid precursors (**1.143**) and (**1.144**) from serine.[86] This Seebach methodology is generally however only applicable to the synthesis of amino acids with a quaternary α-carbon.



(**1.142**)

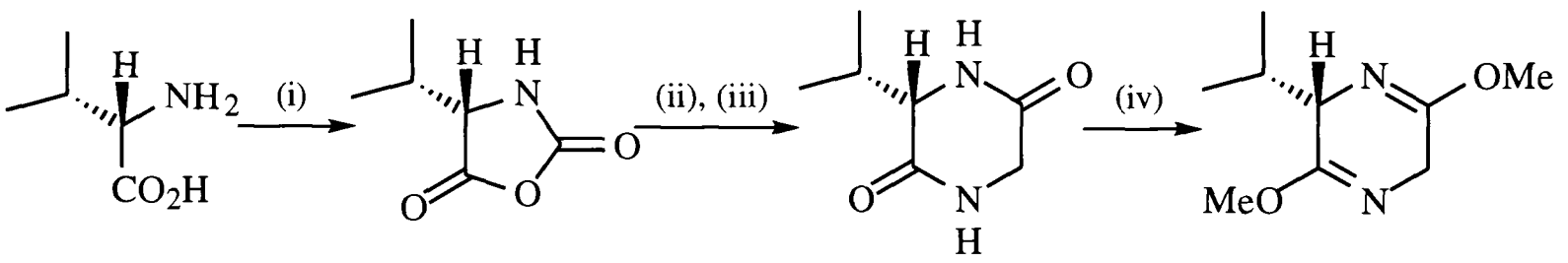


(**1.143**)



(**1.144**)

At the same time as the Seebach approach a second template, the dihydropyrazine (**1.147**), was introduced by Scholkopf (**Scheme 1.31**).[87] Treatment of (*S*)-valine with phosgene in tetrahydrofuran afforded oxazinone (**1.145**). Condensation of this oxazinone with glycine methyl ester followed by decarboxylation and cyclisation in refluxing toluene furnished the *bis*- lactam (**1.146**). Subsequent treatment with trimethyloxonium tetrafluoroborate furnished the homochiral template (**1.147**) in an overall yield of 75%.



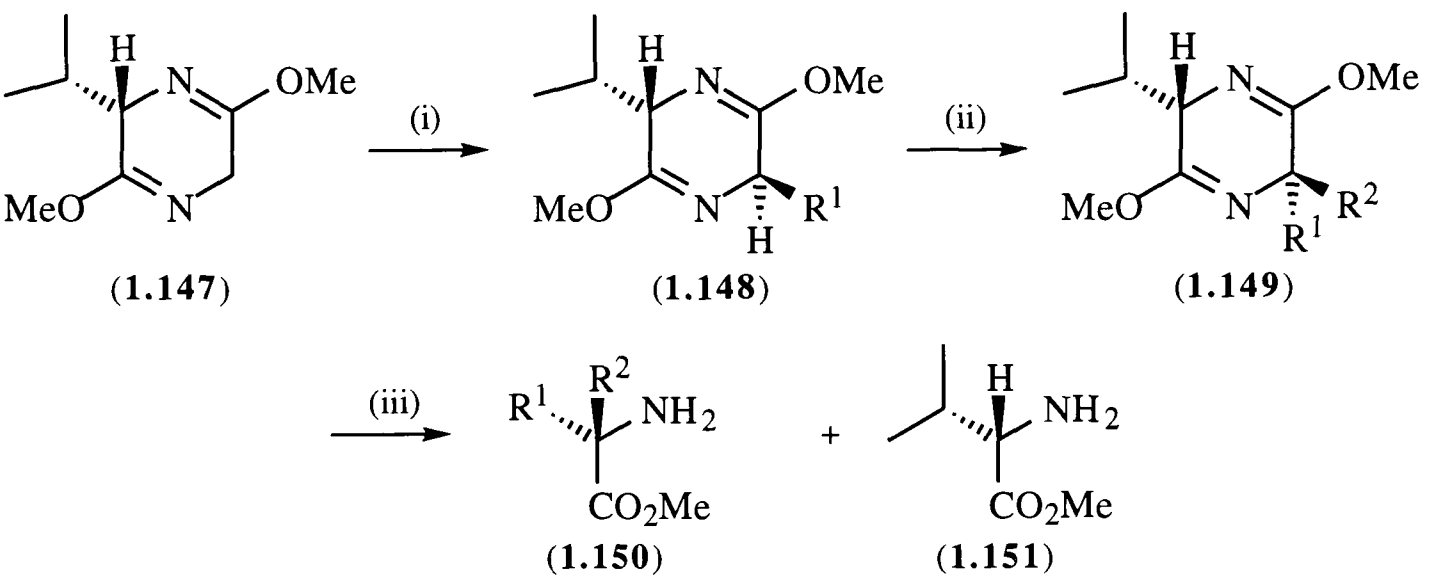
(**1.145**) (**1.146**) (**1.147**)

(i) $COCl_2$, THF, (ii) $H_2NCH_2CO_2Me$, (iii) reflux toluene, (iv) $Me_3O^+BF_4^-$.

Scheme 1.31

Deprotonation of the template (**1.147**) with *n*-butyl lithium followed by treatment with the required electrophile afforded the mono-functionalised template (**1.148**). The stereochemistry of the new chiral centre was dictated by approach of the electrophile from the least hindered face of the planar anion. This defined the *trans*- relationship between the new substituent and the *iso*-propyl group with a typical diasteromeric excess of >90%. Repetition of the sequence of anion formation / electrophilic quench allowed the synthesis of quaternary α-amino acid precursors (**1.149**). Template removal to furnish the amino acid (**1.150**) was

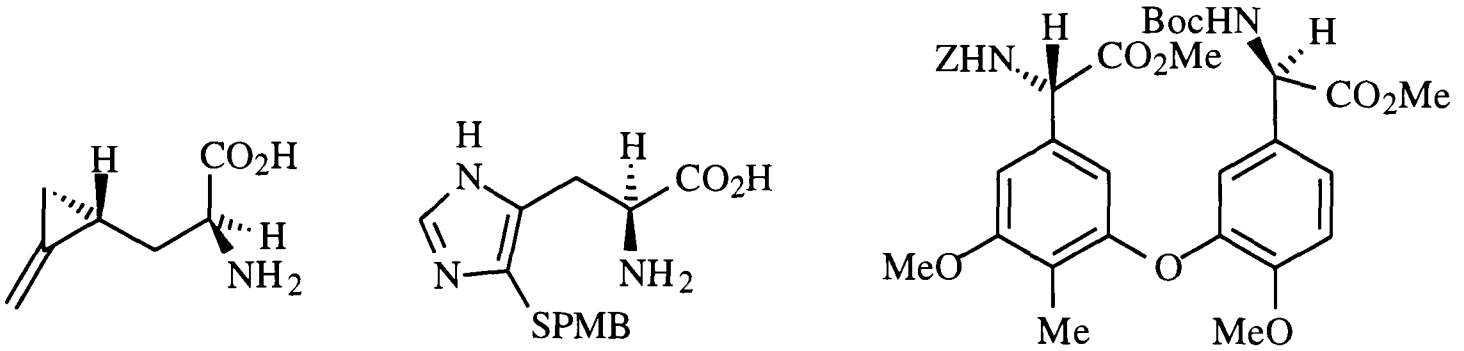
originally effected with aqueous hydrogen chloride however, depending on the system, the optimal conditions for cleavage must be devised (**Scheme 1.32**).



(i) *n*-BuLi, R^1X, (ii) *n*-BuLi, R^2X, (iii) HCl.

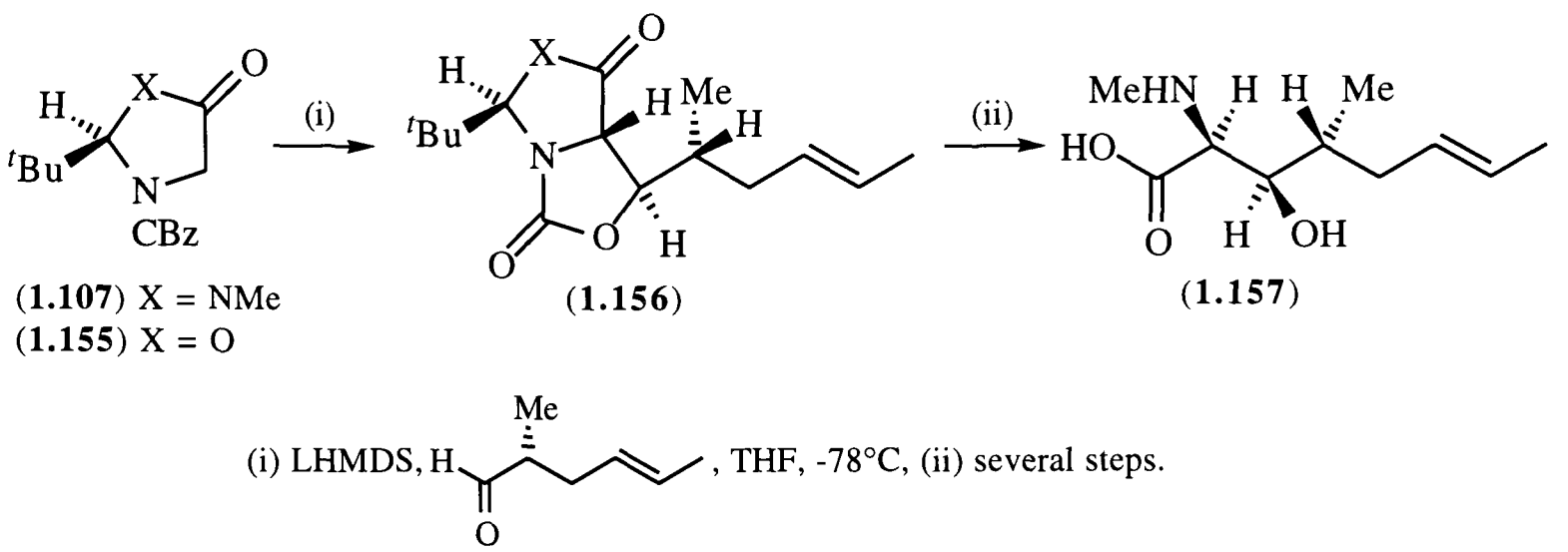
Scheme 1.32

One inherent complication with the Scholkopf method is the necessity of removing (*S*)-valine methyl ester (**1.151**) from the required amino acid methyl ester (**1.150**). Despite this drawback this method has been used for the synthesis of a wide variety of amino acid containing molecules including hypoglycin A (**1.152**),[88] ovothiol A (**1.153**)[89] and ristomycinic acid derivatives (**1.154**).[90]



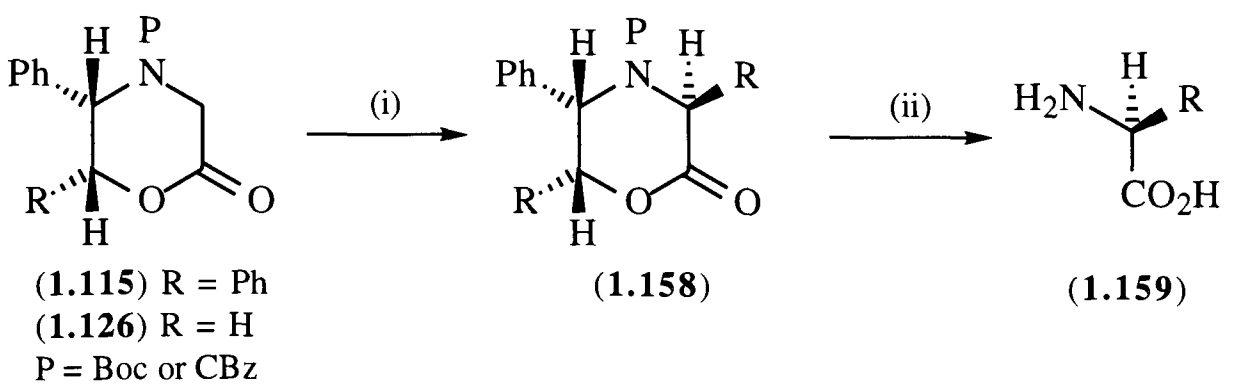
A second chiral glycine template, introduced by Seebach, was the imidazolidinone (**1.107**). This demonstrated excellent selectivity in the alkylation stage, however the harsh conditions necessary for removal (reflux 6 M hydrogen chloride) reduced the synthetic usefulness. The oxazolidinone (**1.155**) was more labile, and was exploited by Seebach in the synthesis of MeBmt (**1.157**), a structural component of the immunosupressant undecapeptide cyclosporin.[56] Formation of the anion with lithium bis(trimethylsilyl)amide was followed by alkylation and concomitant lactonisation to form the *bis*- lactone (**1.156**) as a single

diastereomer (**Scheme 1.33**). Elaboration of this intermediate furnished the target compound (**1.157**).



Scheme 1.33

Two final examples of templates for amino acid synthesis are the substituted oxazinones (**1.115**, R = Ph) and (**1.126**, R = H), introduced almost simultaneously by Williams[91] and Santarsiero[65] respectively. In common with the Scholkopf procedure, enolate formation was followed by addition of the electrophile from the least hindered face to furnish the substituted oxazinone (**1.158**) in excellent diastereomeric excess (>99%). Subsequent removal of the template could be efficiently achieved using hydrogenolysis to furnish the free amino acid (**1.159**), or dissolving metal reduction to afford the protected version (**Scheme 1.34**). These oxazinone templates possess the advantage over alternative methodologies in that the byproducts of template removal (2-phenyl ethanol and 1,2-diphenyl ethane) have very different properties to the required amino acid, and can therefore be readily removed through trituration or extraction.

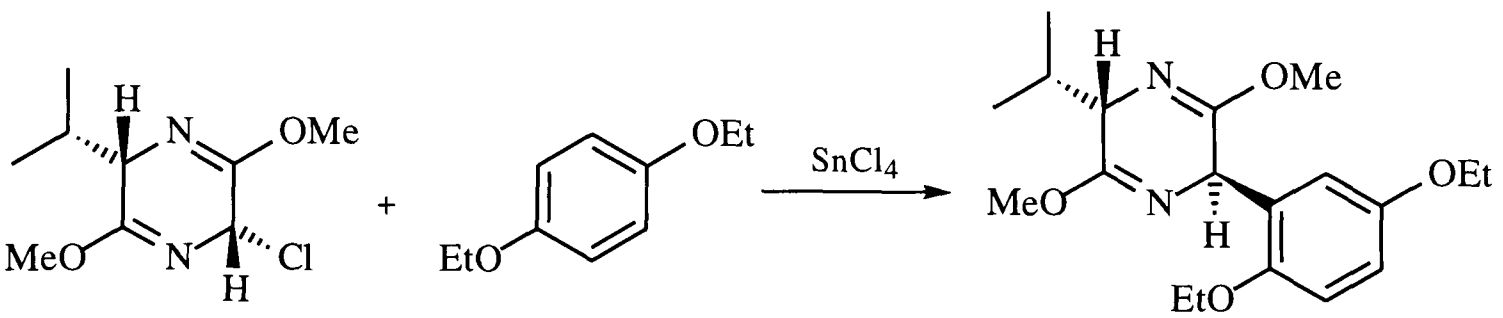


(i) NaHMDS, THF, RX, (ii) H_2, $PdCl_2$.

Scheme 1.34

Initial reports of the utility of these systems were however marred by the observation that unactivated electrophiles were unreactive under the standard conditions. In order to effect alkylation it was necessary to add the base to a solution of the oxazinone and electrophile in tetrahydrofuran and hexamethylphosphoramide. However a recent report by Baldwin has shown that addition of up to 6 equivalents of 15-crown-5 to a tetrahydrofuran solution of the reactants allowed the generation and efficient trapping of the enolate with unactivated electrophiles.[92] This extension of the methodology also allowed access to α-disubstituted amino acids, and was utilised by Baldwin in the synthesis of some conformationally restricted analogues of the Phe-Pro and Tyr-Pro dipeptide. These are cleavage sites for HIV protease, and it was hoped that analogues would act as inhibitors of that enzyme, and consequently have anti- HIV properties.[93]

In these examples the chiral templates have, with the exception of the Seebach system, acted as chiral glycine anion equivalents. However, through oxidation to the halide or alcohol, the polarity of these systems can be reversed and enable their use as chiral glycine cation equivalents. Thus the chlorinated *bis*-lactim ether (**1.160**) undergoes efficient tin (IV) chloride catalysed Friedel-Crafts type alkylation with electron rich aromatics (**Scheme 1.35**).[94] The substitution was found to proceed with inversion leading to the *trans*- aryl glycine derivative (**1.161**).

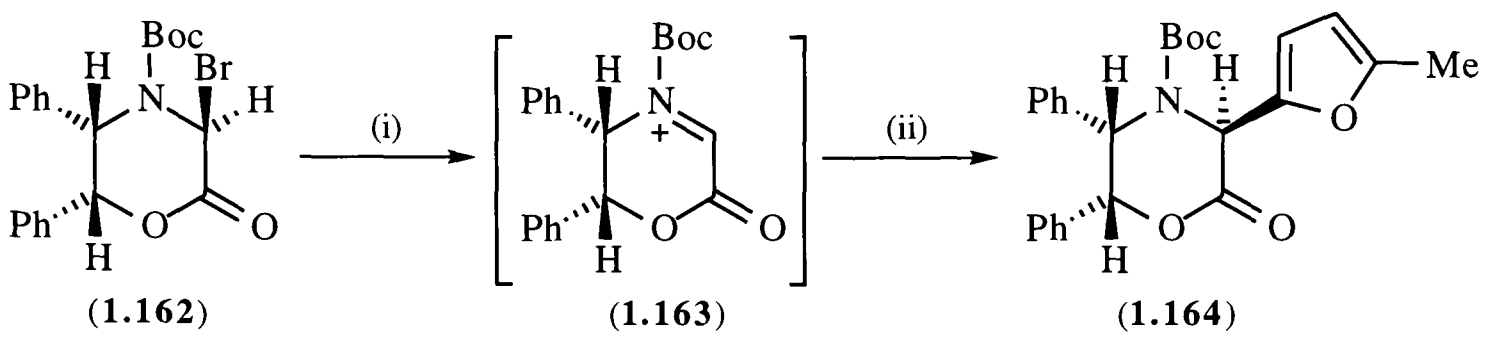


(**1.160**) (**1.161**)

Scheme 1.35

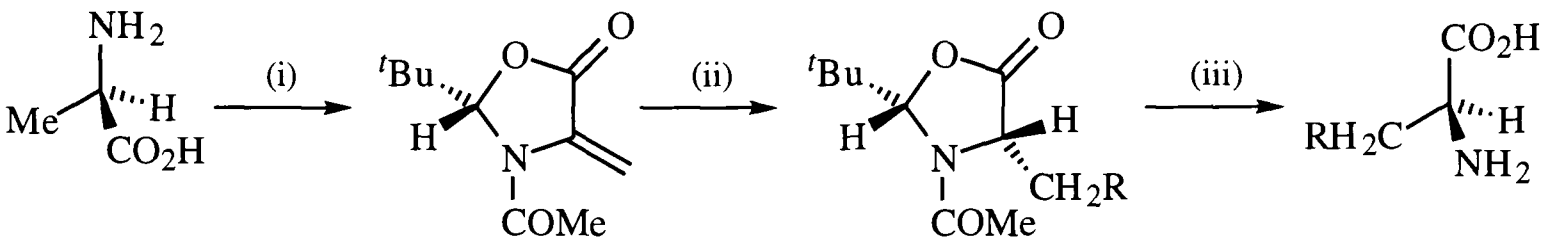
The bromo-oxazinone (**1.162**), readily prepared as a single diastereomer by *N*-bromosuccinimide treatment of the parent oxazinone, has been extensively studied as a chiral glycine cation equivalent.[95] Direct substitution is possible with alkyl thiolates, malonates, alkyl zinc halides and alkyl cuprates, while under Lewis acid catalysis the template will couple with allyl silanes, silyl enol ethers and also undergo Friedel-Crafts alkylations to furnish aryl glycine

derivatives (**1.164**) (**Scheme 1.36**). Substitution occured with retention of configuration, suggesting that alkylation from the least hindered face of an intermediate iminium species (**1.163**) is taking place. Subsequent deprotection following the standard method, allowed the preparation of a range of amino acids inaccessible *via* the enolate alkylation strategy.



Scheme 1.36

A very recent report has applied the methodology of Seebach, to achieve a highly diastereoselective method of amino acid synthesis *via* radical addition to methyleneoxazolidinones (**Scheme 1.37**).[96] In an analogous manner to Seebach, alanine was treated with pivaldehyde to afford a mixture of the C_2 epimers. Separation followed by dehydrogenation allowed the isolation of both enantiomers of the required methyleneoxazolidinone (**1.165**). Radical addition could be achieved under a variety of conditions, and was followed by hydrogenolysis to furnish the desired amino acid (**1.167**). Interestingly, the orientation and degree of diastereoselectivity was highly dependent on the nature of the nitrogen protecting group. *N*-benzoyl protecting groups showed a preference for inducing a *trans*- relationship between the substituents with a typical d.e. of 60%, while carbamate and acetamide (**1.166**) protecting groups gave the alternative *cis*- relationship with excellent diastereocontrol (d.e. >95%). An analogous effect was observed by Williams in the alkylation of enolates of oxazinone (**1.115**), where carbamate protecting groups gave better and opposite diastereocontrol to the benzyl protecting group.[91] This method has been used to prepare α-D-glucose-(*R*)-alanine and α-D-galactose-(*R*)-alanine, however it suffers from the inherent disadvantage that only mono substitution at the β-centre is possible.



(1.165) **(1.166)** **(1.167)**

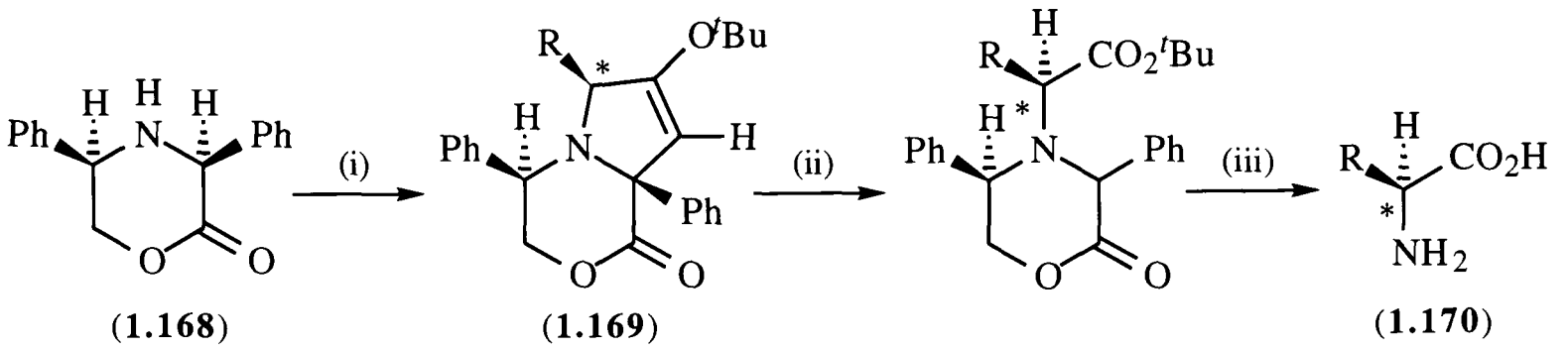
(i) ^{t}BuCHO, dehydrogenate, (ii) RI, AIBN, Bu_3SnH, (iii) H_2, Pd/ C.

Scheme 1.37

1.4.2 Application of Morpholinone Templates to α-Amino Acid Synthesis.

The [3+2] dipolar cycloaddition of morpholinone derived ylids has been shown to proceed with a high degree of stereocontrol while displaying low substrate dependence. Although ideal for the synthesis of proline derivatives, this methodology may potentially be applied to the synthesis of acyclic α-amino acids. Current amino acid syntheses using chiral templates commonly employ esoteric conditions, where choice of base, solvent and reaction temperature can all play a role in determining the stereochemical outcome. The simple conditions required for effecting cycloaddition therefore render this method attractive for α-amino acid synthesis

The strategy to be adopted envisaged the use of a template which, following ylid generation with an aldehyde, would undergo stereocontrolled cycloaddition with butoxyethyne to furnish cycloadducts (**1.169**). Elaboration of these cycloadducts, including complete removal of the chiral template, would allow access to a range of amino acids (**1.170**) in optically pure form. The template chosen was (3*S*,5*R*)-diphenylmorpholinone (**1.168**), a disubstituted analogue of the (5*S*)-phenylmorpholinone template (**1.126**), which should allow complete template removal *via* hydrogenolysis of both the *N*-benzyl bonds (**Scheme 1.38**). This approach would effectively result in the simultaneous enantioselective amination and carboxylation of an appropriate aldehyde, an asymmetric Strecker synthesis. Successful implementation of this procedure would therefore avoid the difficulties associated with enolate alkylation chemistry.



(1.168) **(1.169)** **(1.170)**

* induced chiral centre

(i) RCHO, HC≡ CO^{t}Bu , molecular sieves, reflux xylene, (ii) oxidative cleavage, decarboxylation, (iii) template removal, hydrolysis.

Scheme 1.38

CHAPTER ONE

References

CHAPTER ONE

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CHAPTER TWO

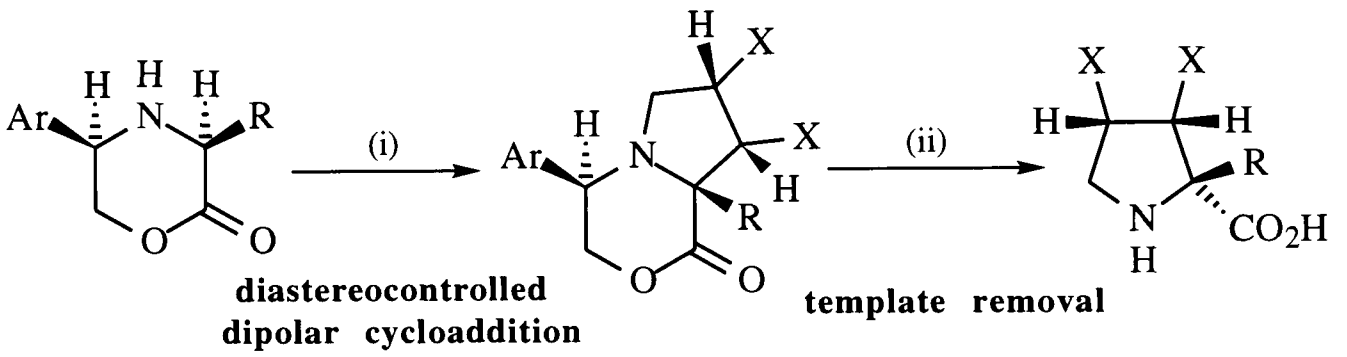
Results and Discussion

CHAPTER TWO

Intermolecular Cycloadditions Of (5*S*)-Phenylmorpholinone

2.1 Introduction of Substituents α- to Nitrogen.

The development of the chiral memory system within the group has concentrated on the [3+2] dipolar cycloaddition of azomethine ylids derived from the condensation of both mono- and di-substituted morpholinones with paraformaldehyde. The cycloaddition has been shown to proceed in a highly diastereocontrolled manner, generating predominantly the *endo*- adduct, from which the corresponding 2,3,4-trisubstituted proline can be readily obtained on hydrogenolytic cleavage of the chiral template (**Scheme 2.1**).

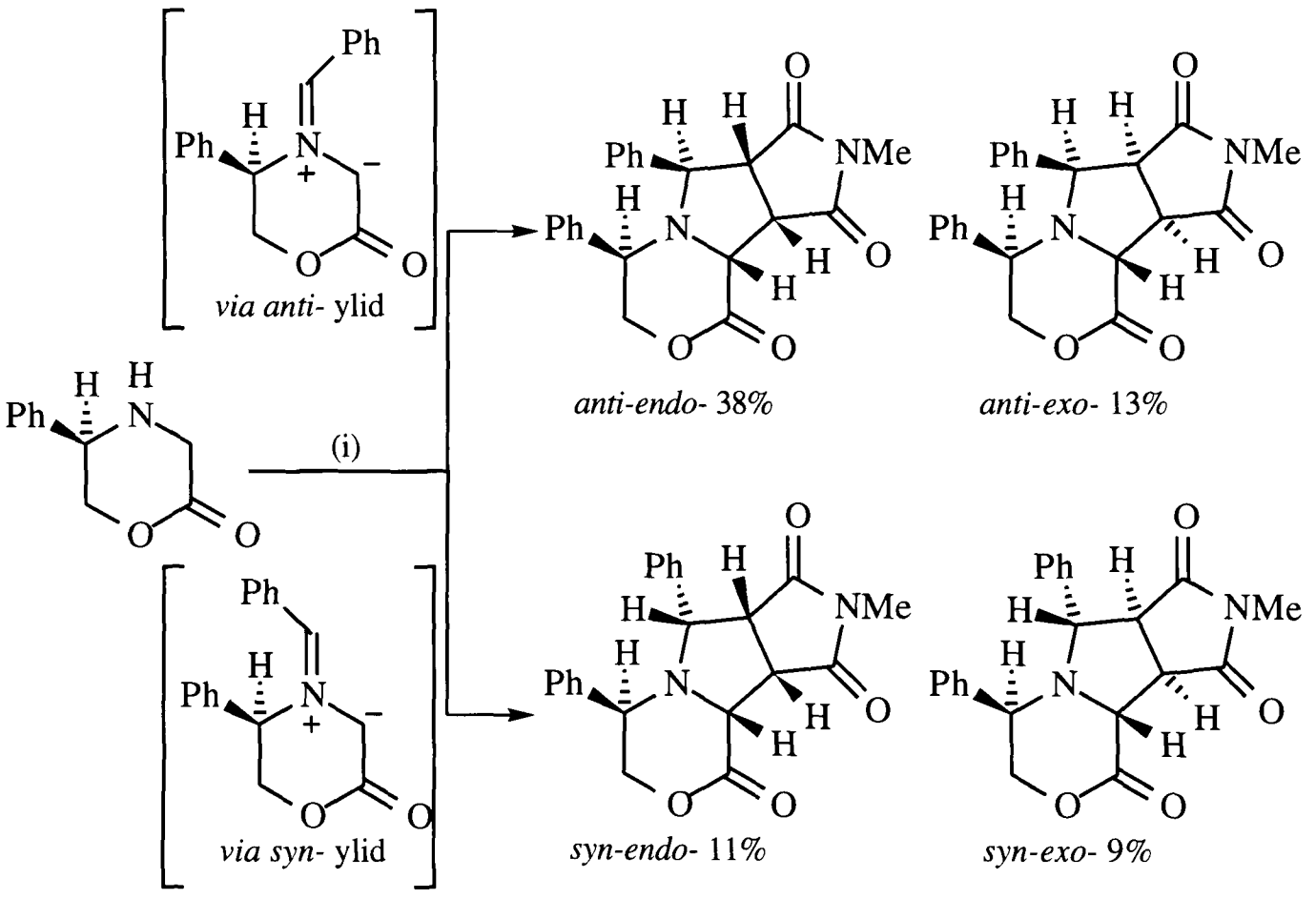


(i) $(HCHO)_n$, reflux toluene, molecular sieves, dipolarophile.
(ii) H_2 5 bar, $Pd(OH)_2$/ C, TFA, wet methanol, stir r.t.

Scheme 2.1

It was considered that the introduction of substituents α- to nitrogen on the proline ring could be achieved by generating the ylid with an aldehyde possessing appropriate functionality, followed by [3+2] dipolar cycloaddition in the usual fashion. A preliminary investigation of this route, undertaken by Anslow, has demonstrated the feasibility of introducing a phenyl or methyl substituent α- to nitrogen through the use of benzaldehyde or acetaldehyde in the ylid forming step.[1] The subsequent cycloaddition of the ylid can conceivably generate a total of eight diastereoisomers, arising from attack on either face of a *syn*- or *anti*- ylid in either an *exo*-

or *endo-* manner. However it was anticipated that attack, in common with the unsubstituted ylid, would occur in an axial manner exclusively on the least hindered face of the ylid. This assumption was demonstrated to be accurate as use of benzaldehyde in the ylid generation step, followed by reaction with *N*-methylmaleimide, resulted in the formation of four α-phenyl substituted cycloadducts in an overall material yield of 71% (**Scheme 2.2**). Disappointingly when dimethyl maleate was employed as dipolarophile only 4% of a single adduct, derived from *endo-* addition to the *anti-* ylid, was obtained. Use of acetaldehyde similarly resulted in the isolation of only 4% of the *anti-/ endo-* adduct. This may be a result of the fact that as acetaldehyde has a low boiling point the reaction was performed at 0°C with monomeric formaldehyde. It has been observed that adduct yields increase on increasing the reaction temperature,[2] and therefore the lack of thermal activation may account for the low yield observed.



(i) PhCHO, reflux toluene, molecular sieves, *N*-methylmaleimide.

Scheme 2.2

The initial cycloaddition reaction of a substituted ylid therefore demonstrated lower diastereoselectivity, with the generation of all four predicted cycloadducts. The yield was

observed to be greater than that in the unsubstituted case, while the ratio of total *endo-* to total *exo-* adduct was identical (2 : 1 *endo-* : *exo-*). The product distribution in the cycloaddition was rationalised by considering the steric and electronic demands imposed on the transition state by both the substituent and dipolarophile (**Figure 2.1**). The ylid may adopt either a *syn-* or *anti-* configuration, with the *anti-* form expected to be favoured on steric grounds. Attack may then occur in either an *exo-* or *endo-* manner, with the *endo-* transition state being favoured due to secondary orbital interactions. This consideration rationalises the predominance of the *anti-*/ *endo-* product in the reaction mixture. However it cannot be concluded whether this combination is intrinsically more reactive, or whether, due to the greater thermodynamic stability of this combination, it has a greater population in the reaction mixture.

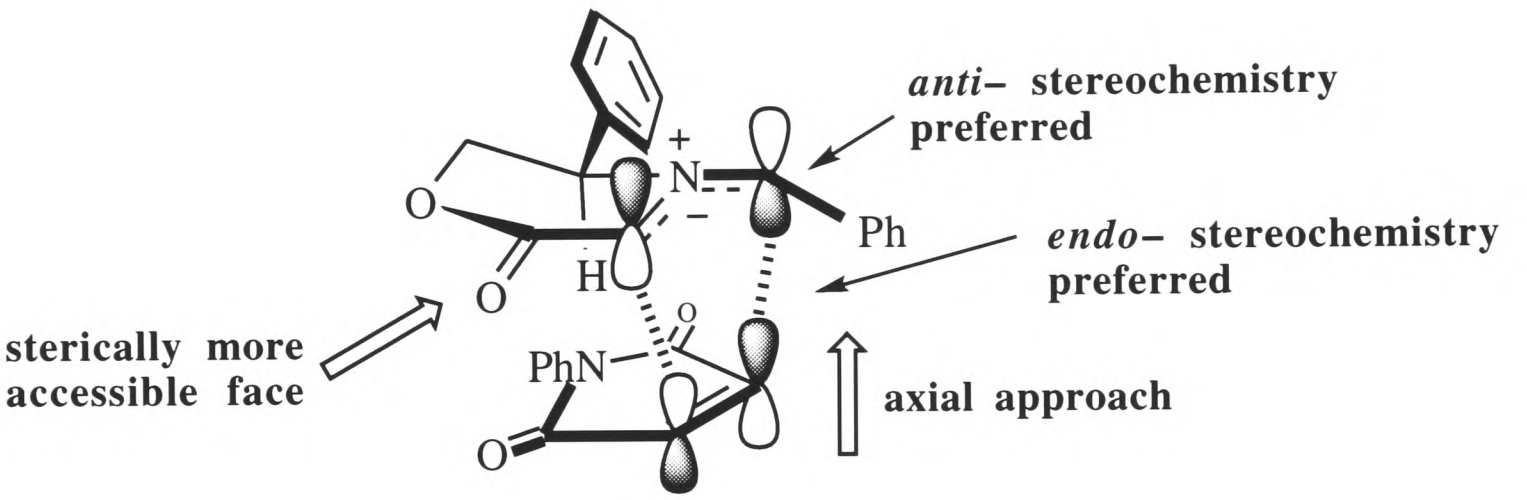
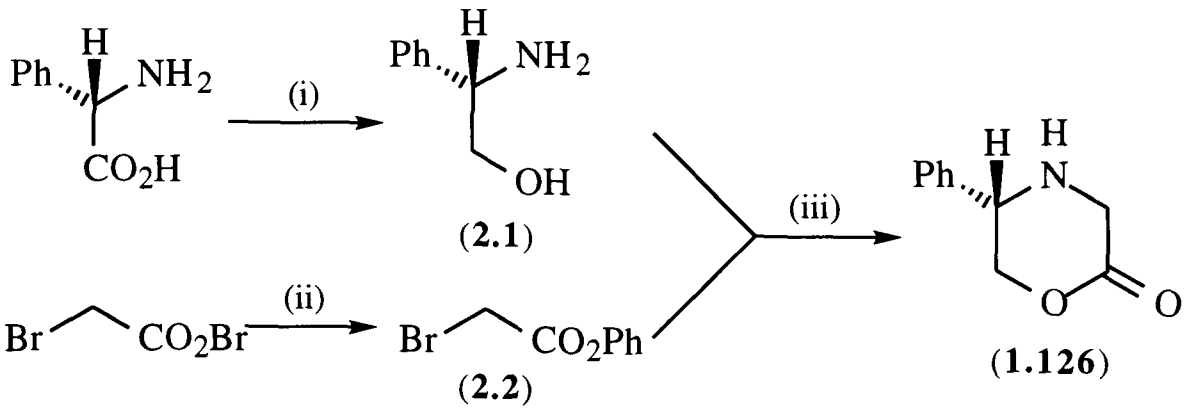


Figure 2.1

The phenyl substituent was expected to have the effect of stabilising the ylid due to the possibility of charge delocalisation into the aromatic ring, and thus alter the energy gap between the molecular orbitals responsible for the stabilising secondary interactions. This would therefore alter the ratio of *endo-* to *exo-* adduct. The increase in steric hindrance for the transition state leading to the *exo-* adduct caused by the phenyl substituent would be expected to increase the proportion of *endo-* addition. The almost identical *endo-*/ *exo-* ratio observed in both unsubstituted and phenyl substituted ylids indicates that these two effects are either not significant or have equal and opposite effects. The ratio between *anti-* and *syn-* conformations should be governed by the steric interactions between the two groups. The ratio observed (2.5 : 1 *anti*-adducts : *syn-* adducts), although not exceptional, was better than that generally observed by Williams using the disubstituted morpholinone template (**1.115**).[3]

Use of an aldehyde which could stabilise the derived ylid may permit the secondary orbital interactions to exert a greater effect on the transition state and thus allow the cycloaddition to proceed with greater diastereoselectivity. Similarly it would be anticipated that use of an aldehyde with a more sterically demanding substituent would cause an increase in the proportion of adducts derived from the less hindered *anti*- ylid. As a first step it was decided to introduce an electron withdrawing carboxylate group into the ylid in the form of an ethyl ester. This functionality would not only potentially stabilise the ylid, and thus hopefully alter the diasteroselectivity, but also introduce a more synthetically useful group for further manipulation. It was hoped that this approach would allow the synthesis of some tetracarboxylate substituted pyrrolidines, not previously synthesised in a stereocontrolled manner.[4]

The starting morpholinone template (**1.126**) was prepared in three steps starting from (*S*)-phenylglycine using the previously developed methodology. Reduction of phenylglycine with lithium aluminium hydride in refluxing tetrahydrofuran afforded (*S*)-phenylglycinol (**2.1**) in 72% yield,[2] while heating bromoacetyl bromide with phenol followed by vacuum distillation afforded phenyl bromoacetate (**2.2**) in 79% yield.[5] Subsequent treatment of (*S*)-phenylglycinol (**2.1**) and phenyl bromoacetate (**2.2**) with diisopropylethylamine in acetonitrile followed by column chromatography afforded the required morpholinone (**1.26**) in 55% yield (**Scheme 2.3**).[5] Ethyl glyoxylate trimer was donated by SmithKline Beecham, and so an extensive survey of the reactivity of this system was undertaken.



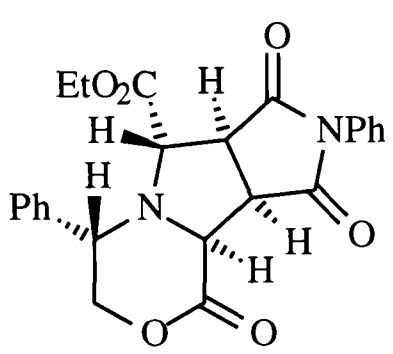
(i) $LiAlH_4$, reflux THF, 72%, (ii) phenol, 65°C, 79%, (iii) $EtN(^iPr)_2$, MeCN, stir r.t., 55%.

Scheme 2.3

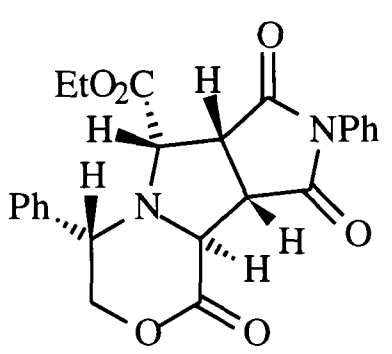
2.2 Thermal Cycloadditions with Ethyl Glyoxylate Trimer.

2.2.1 Alkene Dipolarophiles.

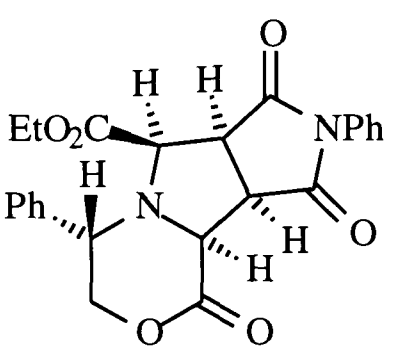
Following the previously established methodology[6] morpholinone (**1.126**), ethyl glyoxylate trimer, and *N*-phenylmaleimide were refluxed in toluene using molecular sieves placed in a soxhlet extractor to remove the water produced in the ylid generation step. After 18 hours t.l.c. analysis indicated the absence of starting material and the formation of three new products. Removal of the solvent followed by gradient column chromatography permitted the isolation of these products, the ^1H n.m.r. and mass spectrometric data of which were consistent with that expected for cycloadduct material. Two dimensional n.m.r. coupled with the use of n.O.e. difference experiments enabled the total structural and stereochemical assignment of the three cycloadducts (**2.3**), (**2.4**) and (**2.5**).



anti-endo (**2.3**)-28%



anti-exo (**2.4**)-1%



syn-endo (**2.5**)-9%

The n.O.e. experiment for the major cycloadduct (**2.3**), obtained in 28% yield, showed an enhancement (6.4%) of the proton at C_2 on irradiation of the proton at C_9 (**Figure 2.2**). The proton at C_2 is known to be on the β- face and this indicated therefore that the proton at C_9 was also on the β- face. Irradiation of the proton at C_6 gave a strong enhancement (12.3%) to the proton at C_7, and a small enhancement (4.2%) to one of the protons at C_3. This proton appeared as a triplet, and on the basis of the Karplus equation[7] was assigned to the α- face, thus indicating that the C_6 and C_7 protons were also on this face. Irradiation of the proton at C_7 gave a strong enhancement (7.6%) to the proton at C_8, indicating the ring junction to be *cis*-, while irradiation of the proton at C_8 gave only a small enhancement

(3.1%) to the proton at C_9, confirming the assignment of β- face stereochemistry to this proton.

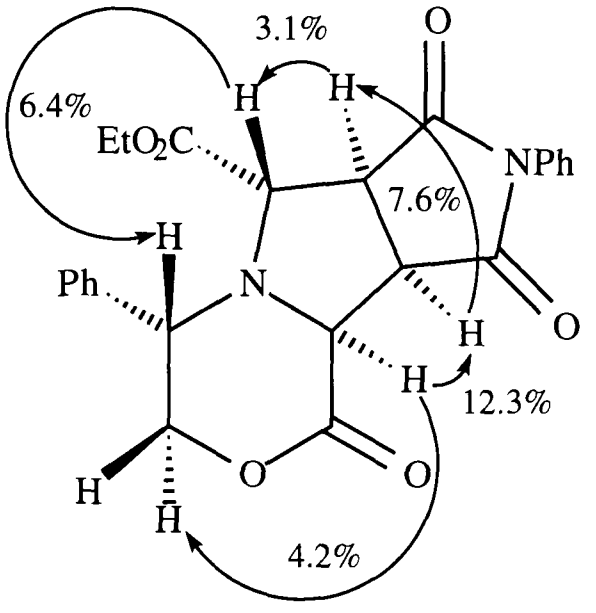


Figure 2.2

The minor cycloadduct (**2.4**), obtained in 1% yield, showed a strong enhancement (10.4%) of the proton at C_9 on irradiation of the proton at C_2 (**Figure 2.3**) This indicated that the proton at C_9 was on the β- face. Irradiation of the proton at C_6 gave a strong enhancement (16.5%) to one of the protons at C_3, and no enhancement to the proton at C_7. Irradiation of the opposite proton at C_3 gave a strong enhancement (9.2%) to the proton at C_2, indicating it to be on the β- face, and therefore showing the proton at C_6 to be on the α- face. Irradiation of the proton at C_9 gave an enhancement (6.5%) to the proton at C_8, indicating that this proton, and therefore the proton at C_7 both lay on the β- face.

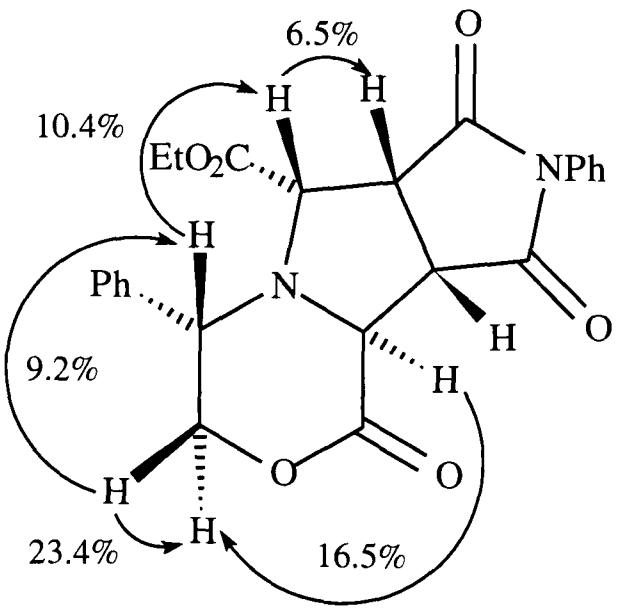


Figure 2.3

The third cycloadduct (**2.5**), obtained in 9% yield, showed a strong enhancement (10%) of the proton at C_7 on irradiation of the proton at C_6 (**Figure 2.4**). The proton at C_6 was assigned as being on the α- face in common with all previous observations and this therefore indicated that the proton at C_7 was also on the α- face. Irradiation of the proton at C_6 also showed an enhancement to the proton at C_9, indicating that this proton was also on the α- face. Irradiation of the proton at C_8 gave a strong enhancement (10%) to the proton at C_7, and a strong enhancement (10%) to the proton at C_9. This indicated the ring junction to be *cis*- as expected, and also confirmed the assignment of α- face stereochemistry to the proton at C_9.

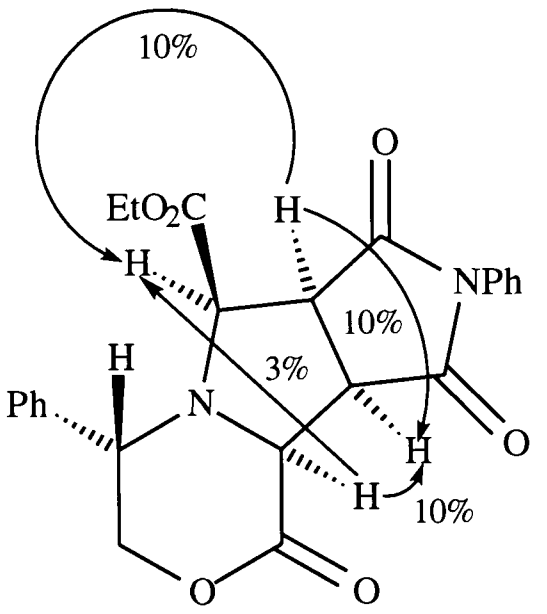


Figure 2.4

The stereochemistry of each adduct can be rationalised by considering the potential formation of both *syn*- and *anti*- ylids followed by cycloaddition in either an *endo*- or *exo*- manner, with the major product being derived from reaction of the *anti*- ylid (least hindered) in an *endo*- (most electronically favoured) manner (**Figure 2.5**). The proportion of *endo*- adduct was observed to be significantly greater than had previously been observed in any cycloaddition involving *N*-phenylmaleimide, while the proportion of *anti*- adduct was greater than that observed with the phenyl substituted ylid. These two observations are complementary and can both be rationalised in terms of a greater population of the *anti*- ylid. The ethyl ester functionality can be considered to be a more bulky substituent than the planar phenyl group, and therefore prefer an *anti*- orientation on steric grounds. While in this position the greater steric bulk allows it to exert more of an influence on the balance between *endo*- and *exo*- approach of the dipolarophile. The substituent α- to nitrogen imposes greater steric hindrance

on the *exo-* transition state due to the interaction between this substituent and the dipolarophile. The balance between secondary orbital interactions against relief of steric hindrance usually obtained in the *exo-* transition state is therefore shifted in favour of the secondary orbital interactions, accounting for the increased proportion of *endo-* adducts. In common with the benzaldehyde derived ylid system however it can not be concluded whether the *anti-/ endo-* combination is intrinsically more reactive than the other potential combinations, or whether it has a greater thermodynamic stability and hence has a greater population in the reaction mixture.

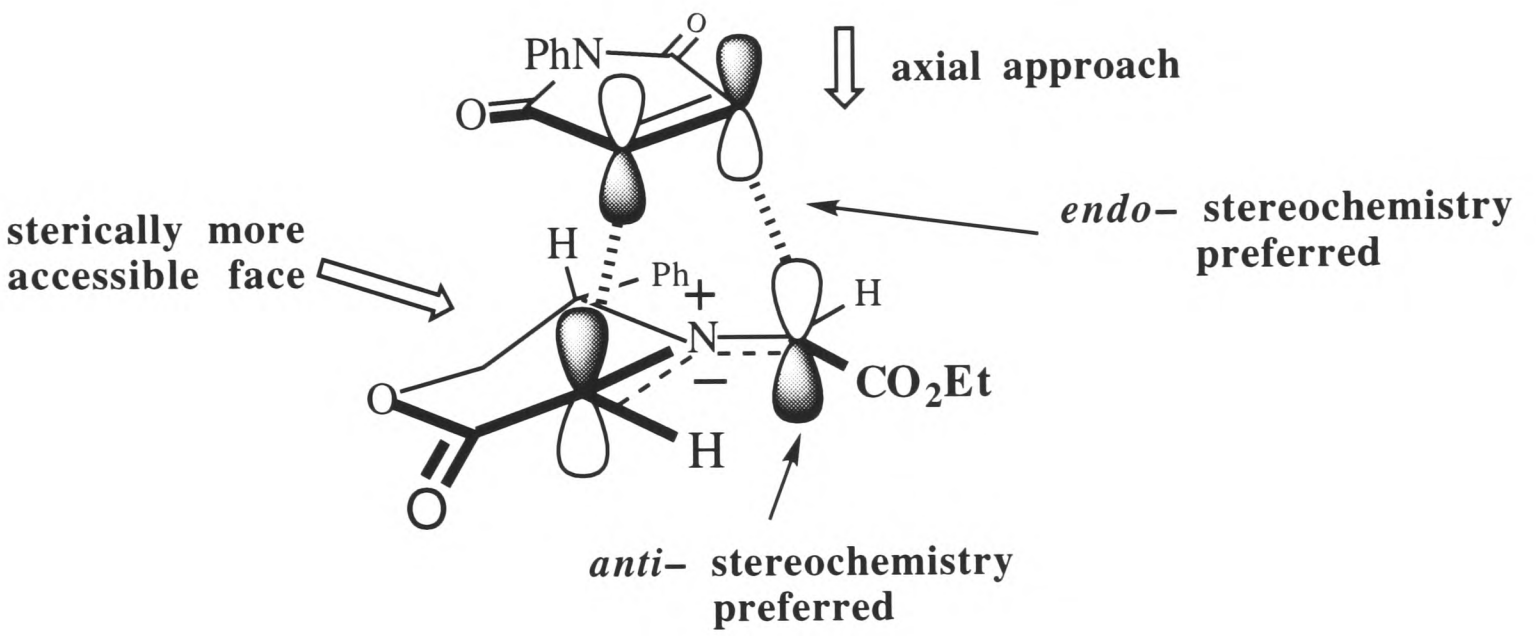
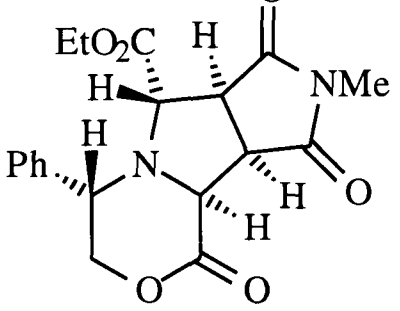


Figure 2.5

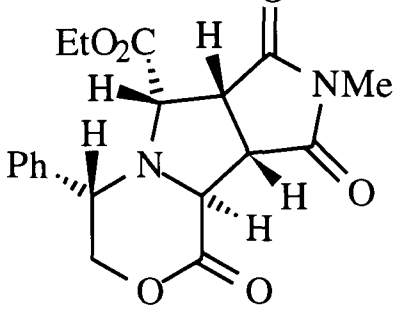
Although the diastereoselectivity using ethyl glyoxylate trimer was improved, the overall material yield of cycloadduct was disappointingly lower than that observed in the case of the ylid derived from benzaldehyde. This may be the result of the ylid now having too great a stability, through the electron withdrawing effect of the carboxylate substituent, with the result that the HOMO/ LUMO interaction is now not as favourable. Repetition of the reaction in refluxing tetrahydrofuran gave the same three cycloadducts with lower diastereoselectivity (3.4 : 1 : 1.4 *c.f.* 28 : 1 : 9), and in a lower overall yield. These results were consistent with previous work within the group, where a lower overall yield was observed at lower temperatures (benzene *vs.* toluene) in the reaction of ylids with the aldehyde from which they were derived.[8] The enhancement of yield in higher boiling solvents resulted in toluene being used as the solvent of choice in thermal cycloaddition reactions.

Following the successful observation of cycloaddition between a carboxylate substituted ylid and *N*-phenylmaleimide it was decided to investigate a range of other potential dipolarophiles previously employed in [3+2] dipolar cycloadditions. Morpholinone (**1.126**), ethyl glyoxylate trimer, and *N*-methylmaleimide were therefore refluxed in toluene following the previous method. After 18 hours t.l.c. analysis indicated the absence of starting material and the formation of two new products. Removal of the solvent followed by gradient column chromatography resulted in the isolation of these products, the ^1H n.m.r. and mass spectrometric data of which were consistent with that expected for cycloadduct material.

Two dimensional n.m.r. experiments coupled with n.O.e. difference experiments enabled the total structural and stereochemical assignment of the two cycloadducts (**2.6**) and (**2.7**). Both products are derived from formation of the *anti*- ylid followed by either *endo*- or *exo*- addition of the dipolarophile, which can be rationalised in an analogous manner to the cycloaddition with *N*-phenylmaleimide.



anti-endo (**2.6**)-25%



anti-exo (**2.7**)-6%

The n.O.e. difference experiment for the major cycloadduct (**2.6**), obtained in 25% yield, showed an enhancement (5.9%) of the proton at C_9 on irradiation of the proton at C_2 (**Figure 2.6**). This indicated that the proton at C_9 was on the β- face. Irradiation of the proton at C_6 gave a strong enhancement (11%) to the proton at C_7. The proton at C_6 was assigned as being on the α- face in common with all previous observations and this therefore indicated that the proton at C_7 was also on the α- face. Irradiation of the proton at C_7 gave a strong enhancement (7.6%) to the proton at C_8, indicating the ring junction to be *cis*-, while irradiation of the proton at C_9 gave only a small enhancement (1%) to the proton at C_8, confirming the assignment of β- face stereochemistry to the proton at C_9, and α- face stereochemistry to the protons at C_6, C_7 and C_8.

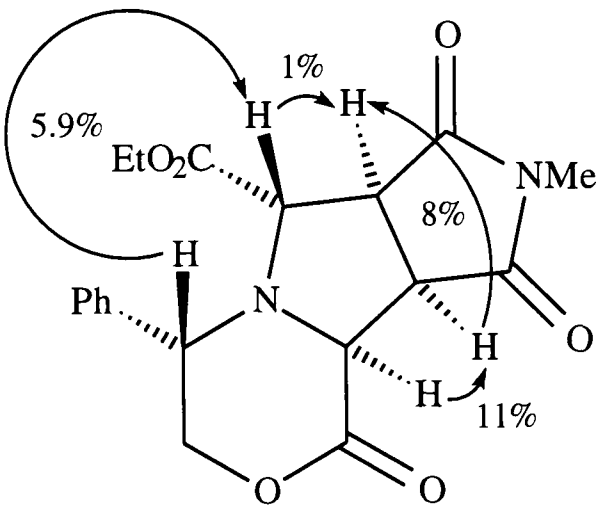


Figure 2.6

The minor cycloadduct (**2.7**), obtained in 6% yield, showed an enhancement (9.1%) of the proton at C_9 on irradiation of the proton at C_2 (**Figure 2.7**), indicating that the proton at C_9 was on the β- face. Irradiation of the proton at C_6 gave a strong enhancement (12.4%) to one of the protons at C_3, while irradiation of the other proton at C_3 gave a strong enhancement (7.7%) to the proton at C_2. The proton at C_6 was therefore assigned as being on the α- face. Irradiation of the proton at C_8 gave a strong enhancement (9.7%) to the proton at C_7, indicating the ring junction to be *cis*-, and a strong enhancement (8.2%) to the proton at C_9. This indicated that the protons at both C_8 and C_7 were on the β- face, and was further confirmed by the observation of a small enhancement (4%) between the protons at C_6 and C_7.

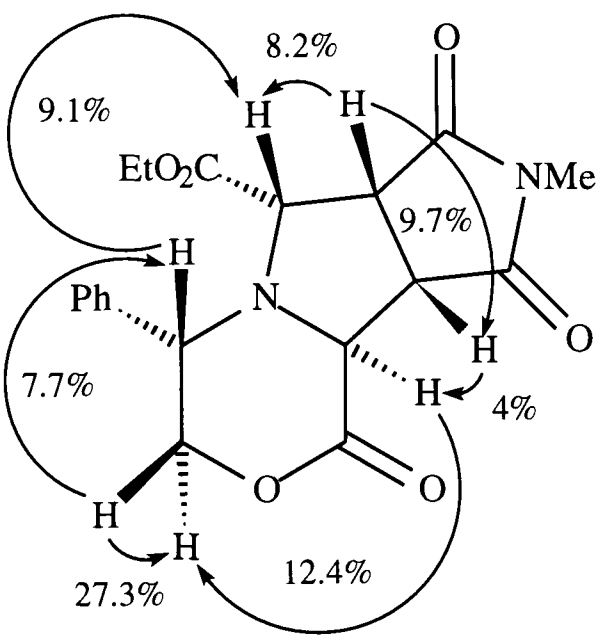
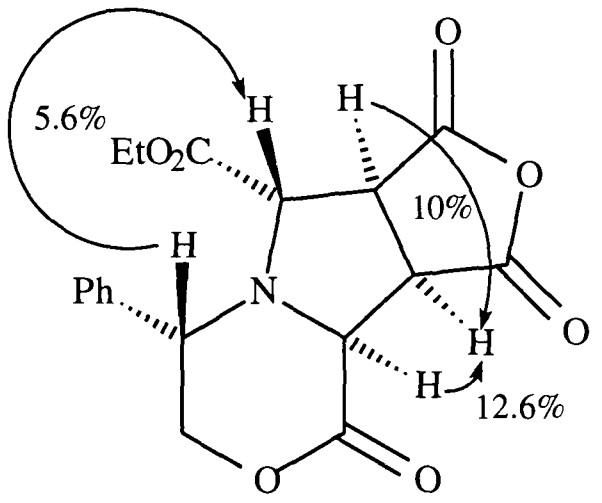


Figure 2.7

Maleic anhydride has also been demonstrated to undergo efficient cycloaddition reaction with morpholinone derived ylids.[9] However refluxing morpholinone (**1.126**), ethyl glyoxylate trimer, and maleic anhydride in toluene under the usual conditions resulted in extensive

polymerisation. Removal of the solvent furnished a viscous oil from which column chromatography furnished only 2% yield of a highly polar product, the ^1H n.m.r. and mass spectrometric data of which was consistent with that expected for the cycloadduct (**2.8**).

The stereochemistry of this adduct (**2.8**) was assigned through the use of two dimensional n.m.r. and n.O.e. difference experiments (**Figure 2.8**). Irradiation of the proton at C_2 showed an enhancement (5.6%) of the proton at C_9 indicating that the proton at C_9 was on the β- face. Irradiation of the proton at C_6 gave a strong enhancement (12.6%) of the proton at C_7. The proton at C_6 was assigned as being on the α- face in common with all previous observations and this therefore indicated that the proton at C_7 was also on the α- face. Irradiation of the proton at C_8 gave a strong enhancement (9.7%) to the proton at C_7, and no enhancement to the proton at C_9. This indicated that the proton at C_8 was on the α- face, with a *cis*- ring junction, and also provided supporting evidence for the proton at C_9 being on the β- face.

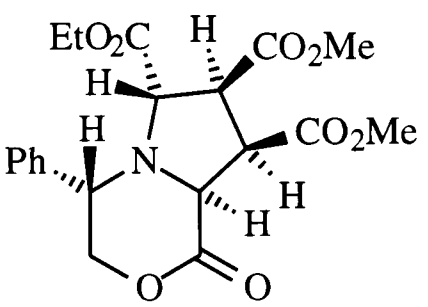


(**2.8**)-2%

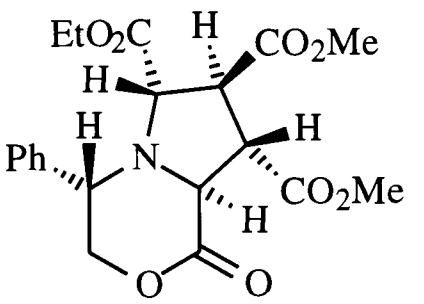
Figure 2.8

Non-cyclic dipolarophiles, for example dimethyl maleate and dimethyl fumarate, have also been employed in cycloaddition reactions with morpholinone derived ylids. However, the yields have been lower, with dimethyl fumarate observed to be unreactive in the simplest case of the paraformaldehyde derived ylid.[9] Nevertheless it was decided to attempt the cycloaddition using these potential traps. Accordingly morpholinone (**1.126**) and ethyl glyoxylate trimer were refluxed in toluene with dimethyl maleate or dimethyl fumarate under standard conditions. Removal of the solvent followed by column chromatography furnished in both cases a single product, having ^1H n.m.r. and mass spectrometric data consistent with that of a cycloadduct.

Two dimensional n.m.r. experiments and n.O.e. difference experiments enabled the total structural and stereochemical assignment of the two cycloadducts (**2.9**) and (**2.10**) derived from dimethyl maleate and dimethyl fumarate respectively.



anti-endo (**2.9**)-37%



anti-endo (**2.10**)-44%

The n.O.e. experiment of the dimethyl maleate derived adduct (**2.9**) showed an enhancement (8.3%) of the proton at C_2 on irradiation of the proton at C_9, indicating that the proton at C_9 was on the β- face (**Figure 2.9**). Irradiation of the proton at C_6 gave a strong enhancement (13.2%) to the proton at C_7, and a weaker enhancement (5.6%) to the proton at C_8. The proton at C_6 was assigned as being on the α- face in common with all previous observations and this therefore indicated that the protons at C_7 and C_8 were also on the α- face. Irradiation of the proton at C_9 gave only a weak enhancement (1%) to the proton at C_8 providing supporting evidence for the given stereochemical assignment.

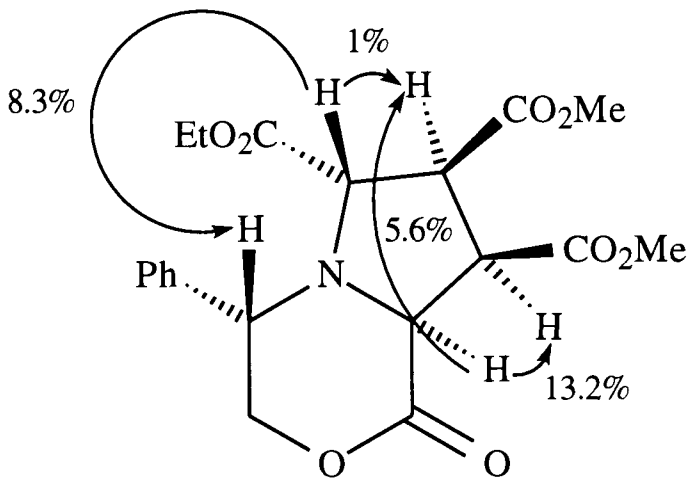


Figure 2.9

The n.O.e. experiment of the adduct derived from dimethyl fumarate (**2.10**) showed an enhancement (6.7%) of the proton at C_9 on irradiation of the proton at C_2, indicating that the proton at C_9 was on the β- face (**Figure 2.10**). Irradiation of the proton at C_6 gave a weak enhancement (4%) to one of the protons on C_3, and a weaker enhancement (1.2%) to the proton at C_8. The opposite proton at C_3 was enhanced on irradiation of the proton at C_2, and

the proton at C_6 was therefore assigned as being on the α- face. This therefore indicated that the proton at C_8 was also on the α- face. Irradiation of the proton at C_9 gave a weak enhancement (2.2%) to the proton at C_7 providing further supporting evidence for the assigned stereochemistry.

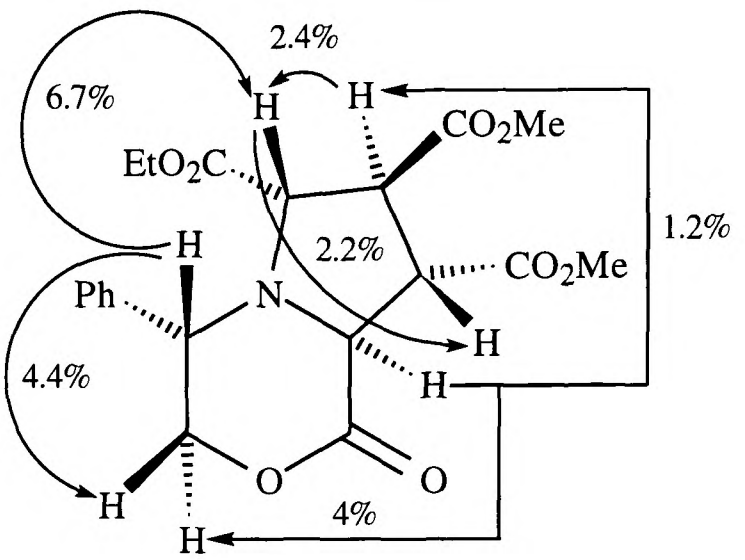


Figure 2.10

The adducts from dimethyl maleate (**2.9**) and dimethyl fumarate (**2.10**) are both derived from exclusive addition of the dipolarophile to the *anti-* ylid (**Figure 2.11**). The adduct derived from dimethyl maleate can be considered as arising from a transition state in which steric hindrance to the substituent α- to nitrogen is minimised, at the same time as offering stabilising secondary orbital overlap. The adduct derived from dimethyl fumarate however is that in which steric hindrance is reduced to a minimum at the cost of the loss of secondary orbital overlap. The overall result of the cycloadditions with dimethyl maleate and dimethyl fumarate was especially gratifying, as all four centres on the pyrrolidine ring had been specifically generated in higher yields than in the unsubstituted case.

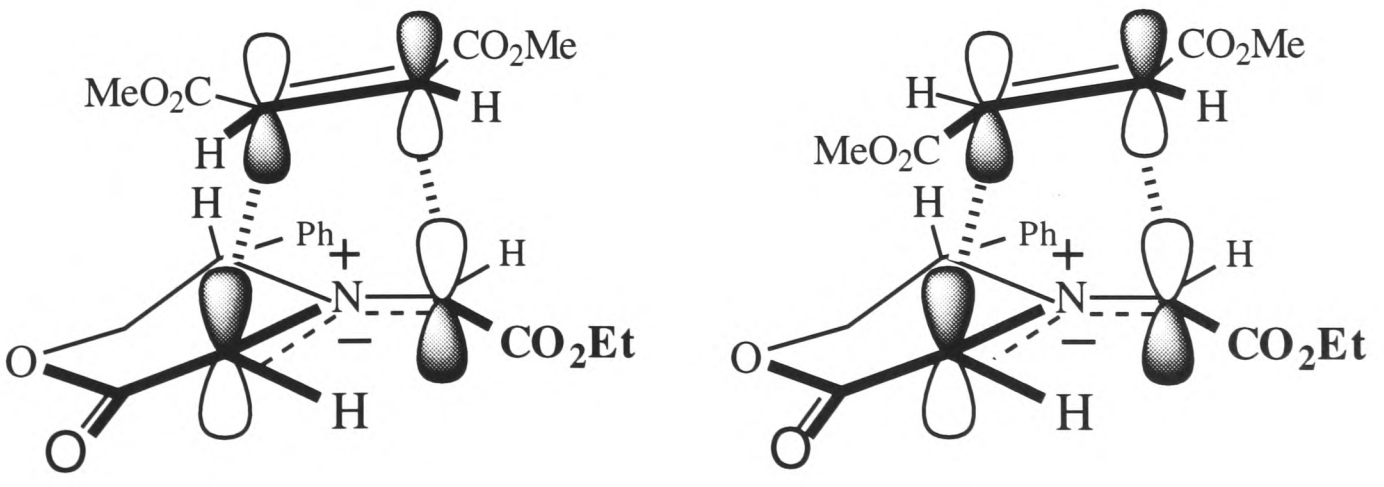
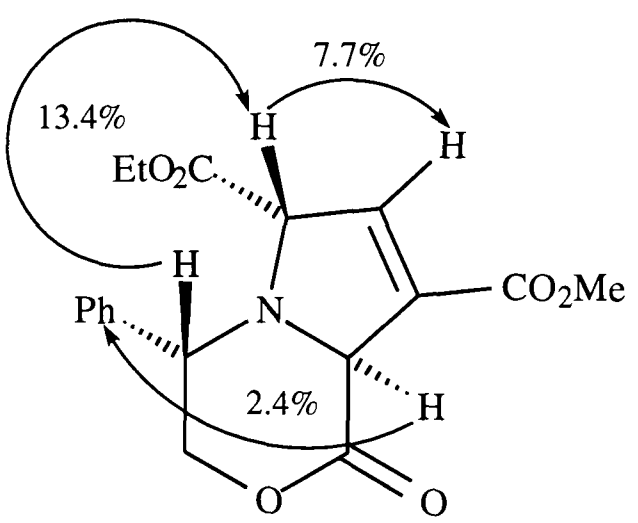


Figure 2.11

2.2.2 Alkyne Dipolarophiles.

Having demonstrated the ability of ylids derived from ethyl glyoxylate to undergo cycloaddition reaction with activated alkenes, it was decided to investigate the use of alkynes as potential traps. Adducts derived from these dipolarophiles would have the additional advantage of being free from stereochemical complications arising from *exo*- or *endo*- cycloaddition.

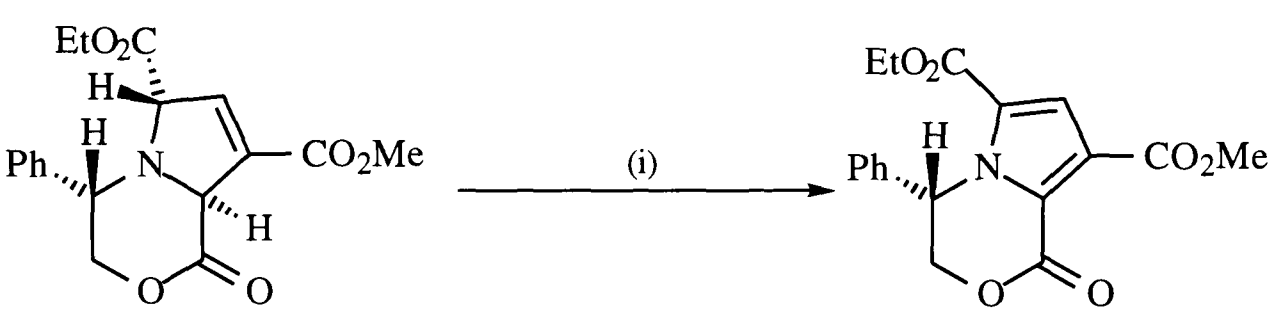
Accordingly morpholinone (**1.126**), ethyl glyoxylate trimer and dimethyl acetylenedicarboxylate were refluxed in toluene following the standard procedure. However following 48 hour reflux and work up ^{1}H n.m.r. spectroscopic analysis disappointingly indicated only the presence of starting material. It has been previously demonstrated that alkyne dipolarophiles are lower in reactivity than their alkene counterparts,[9] and this may explain the failure to obtain a cycloadduct. Despite this, morpholinone (**1.126**), ethyl glyoxylate trimer and methyl propiolate were refluxed in toluene following the previously described procedure. Work up and column chromatography afforded two novel compounds, of which one, obtained in 21% yield, had ^{1}H n.m.r. and mass spectrometric data consistent with that of a cycloadduct. Two dimensional n.m.r. coupled with n.O.e. difference experiments enabled the total regio- and stereochemical assignation of the cycloadduct (**2.11**) (**Figure 2.12**). Irradiation of the proton at C_2 showed an enhancement (13.4%) of the proton at C_9, indicating that this proton was also on the β- face. Irradiation of the proton at C_9 gave an enhancement (7.7%) to the alkene proton, indicating that it lay on C_8. Irradiation of the proton at C_6 enhanced the phenyl ring protons (1.2%), and this proton was therefore assigned as being on the α- face.



(**2.11**)-21%

Figure 2.12

The ^1H n.m.r. data of the second product (**2.12**), obtained in 23% yield, indicated it to have two protons less than would be expected for a cycloadduct. This was confirmed by mass spectrometric analysis which showed the product to have an MH^+ peak at 346. This was consistent with previous observations in the intramolecular reaction, where cycloadducts with a double bond in the ring were observed to dehydrogenate to the corresponding pyrrole.[10] N.O.e. experiments could not confirm unequivocally the regiochemistry of this adduct, and so chemical means were employed. The cycloadduct (**2.11**) was refluxed with 5% palladium on carbon in ethyl acetate in order to effect dehydrogenation (**Scheme 2.4**). One hour reflux followed by filtration and removal of the solvent afforded the previously observed product (**2.12**) in quantitative yield, demonstrating the regiochemistry to be as shown.



(2.11) **(2.12)**

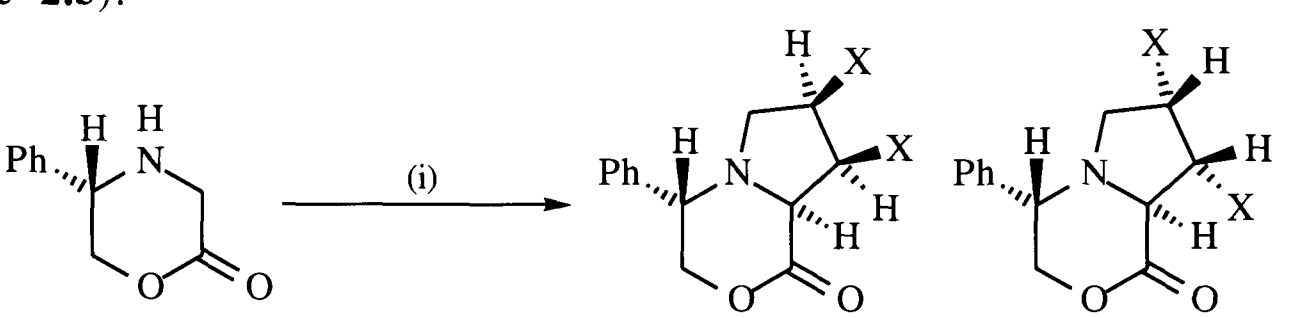
(i) 5% Pd/ C, reflux EtOAc, quantitative.

Scheme 2.4

2.3 Catalysed Cycloadditions with Ethyl Glyoxylate Trimer.

2.3.1 Alkene Dipolarophiles.

Having demonstrated the possibility of cycloaddition between ethyl glyoxylate derived morpholinone ylids and a range of dipolarophiles, attention turned to the possibility of using Lewis acids to catalyse the reaction. An extensive survey of potential catalysts, previously performed within the group, had identified magnesium bromide-etherate as the most effective catalyst for the cycloaddition of paraformaldehyde derived ylids with a range of dipolarophiles (**Scheme 2.5**).[11]



Dipolarophile	8-*endo*	8-*exo*
N-Methylmaleimide	0%	80%
N-Phenylmaleimide	9%	54%
Dimethyl maleate	20%	40%

(i) $(HCHO)_n$, dipolarophile, $MgBr_2.Et_2O$, molecular sieves, stir THF, r.t.

Scheme 2.5

The effect of the catalyst was to increase the yield of the cycloaddition, while also promoting a shift in stereocontrol from predominantly *endo-* material to predominantly *exo-* material. This was especially dramatic in the case of *N*-methylmaleimide where the *exo-* product was formed exclusively under catalytic conditions. The change in stereocontrol has been rationalised by considering the catalyst to co-ordinate to the lactone carbonyl of the ylid. This has the effect of increasing the bulk of the reaction centre and thus favours the less hindered *exo-* transition state. The co-ordination will also reduce the energy of the ylid orbitals (**Figure 2.13**), and thus may change the dominant frontier molecular orbital interaction from ylid HOMO-dipolarophile LUMO to ylid LUMO-dipolarophile HOMO. This change alters the possibility of secondary orbital interaction, and therefore influences the *endo-*/ *exo-* ratio. Evidence for this change in interaction is provided by the observation of a change in

regiocontrol when non-symmetrical dipolarophiles are used (*e.g.* acrylonitrile and phenyl vinylsulfone).[11]

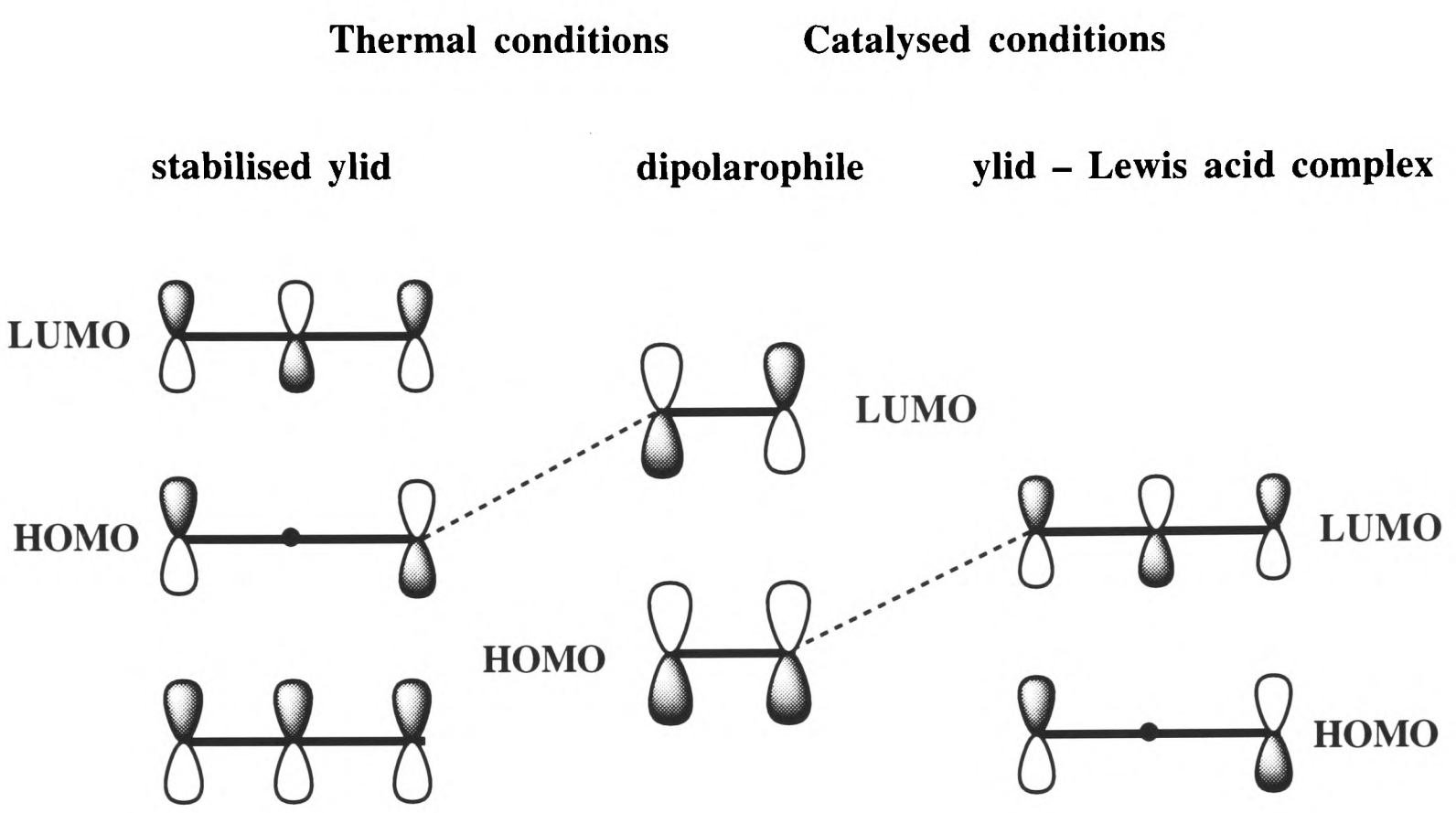


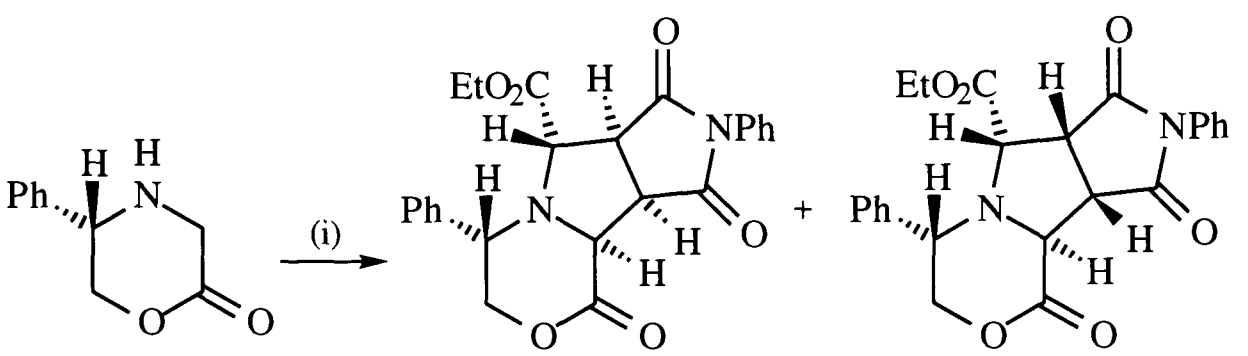
Figure 2.13

In the case of the substituted ylid there is the possibility of influencing the stereochemistry α- to nitrogen by altering the ratio of *syn*- to *anti*- ylid, as well as the ratio of *exo*- to *endo*- cycloadduct. It was therefore decided to attempt catalysis of the ethyl glyoxylate derived ylid system.

Magnesium bromide-etherate was prepared by the slow addition of dibromoethane to a suspension of magnesium turnings in diethyl ether under a nitrogen atmosphere. The catalyst appeared as a dark brown solution beneath a colourless ether layer and, provided the ether was regularly replenished, was observed to retain activity over a period of several months.

Morpholinone (**1.126**), ethyl glyoxylate trimer and *N*-phenylmaleimide were stirred with molecular sieves and magnesium bromide-etherate in tetrahydrofuran at room temperature (**Scheme 2.6**). After 4 hours t.l.c. analysis indicated the absence of starting material, and the

appearance of two new products. The reaction was worked up by filtration through silica to remove the catalyst followed by column chromatography. This resulted in the isolation of two cycloadducts, the ^1H n.m.r. spectroscopic data and optical rotation of which were identical with the cycloadducts (**2.3**) and (**2.4**) previously prepared *via* the thermal reaction.



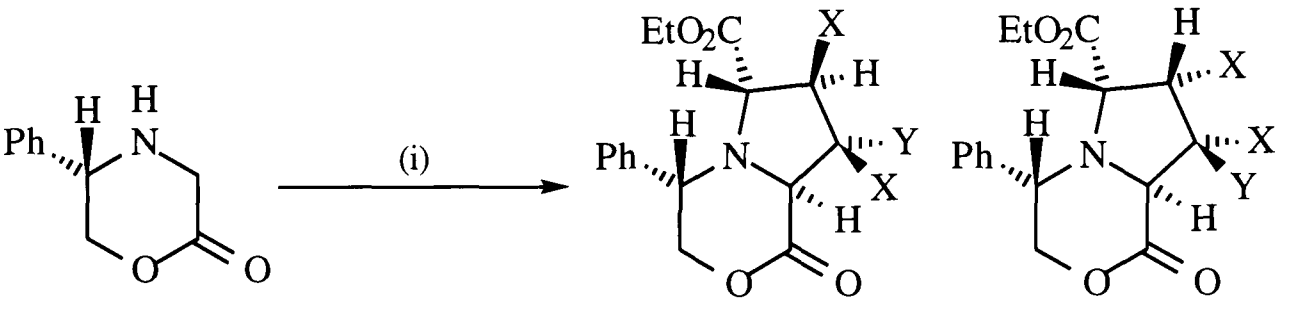
(**1.126**) (**2.3**)-32% (**2.4**)-17%

(i) ethyl glyoxylate trimer, *N*-phenylmaleimide, $MgBr_2.Et_2O$, molecular sieves, stir THF, r.t.

Scheme 2.6

The overall material yield in the catalysed reaction was greater than that observed in the thermal reaction, while the cycloadducts were derived exclusively from the *anti*- ylid. The ratio of *endo*- to *exo*- product was shifted in favour of the *exo*- cycloadduct, although not as dramatically as in the case of the unsubstituted ylid (1 : 2 *vs.* 6 : 1 *exo*- : *endo*).[11] Both of these effects can be rationalised by considering the catalyst to co-ordinate to the ester carbonyl rather than that of the lactone. Such co-ordination would cause an increase in the steric demands of the α- substituent, increasing the steric interaction with the phenyl group, and therefore increasing the proportion of the *anti* - ylid. Co-ordination to the carbonyl of the ester group rather than that of the lactone would also increase the steric hindrance associated with the transition state for *exo*- addition. This would therefore invert the steric influence of catalyst co-ordination.

Following the success of the catalysed reaction in the case of *N*-phenylmaleimide, the reaction was repeated using the alkene dipolarophiles previously employed in the thermal cycloaddition. Usual work up followed by column chromatography resulted in the isolation of the cycloadducts previously observed in the thermal reaction, with the exception of maleic anhydride where a second product (**2.13**) having ^1H n.m.r. and mass spectrometric data consistent with that of a cycloadduct was observed (**Scheme 2.7**).

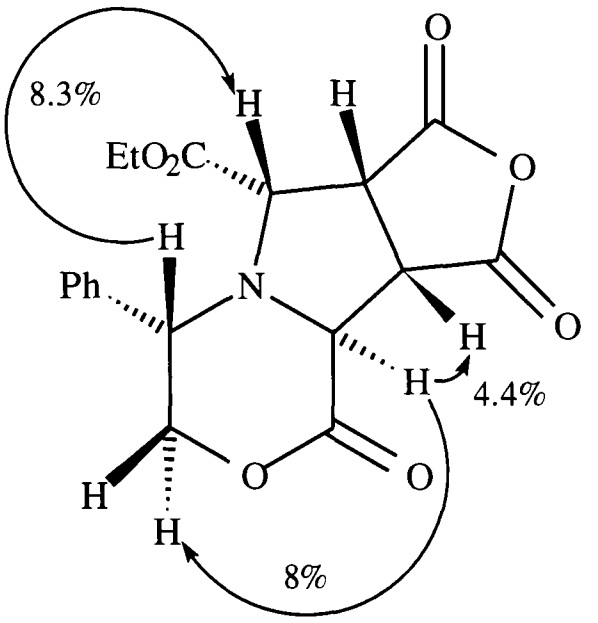


Dipolarophile	8-*endo*	8-*exo*
N-Methylmaleimide	23%	33%
Dimethyl fumarate	65%	0%
Dimethyl maleate	44%	0%
Maleic anhydride	3%	1%

(i) ethyl glyoxylate trimer, dipolarophile, $MgBr_2.Et_2O$, molecular sieves, stir THF, r.t.

Scheme 2.7

Two dimensional n.m.r. experiments coupled with the use of n.O.e. difference experiments enabled the total stereochemical assignment of the second cycloadduct (**2.13**) derived from maleic anhydride (**Figure 2.14**). Irradiation of the proton at C_2 showed an enhancement (8.3%) of the proton at C_9, indicating that the proton at C_9 was on the β- face. Irradiation of the proton at C_6 enhanced 8% one of the protons at C_3 and, in common with all previous observations, this proton was assigned as being on the α- face. Irradiation of the proton at C_6 showed a small enhancement (4.4%) to the proton at C_7, and this proton was therefore assigned as being on the β- face.



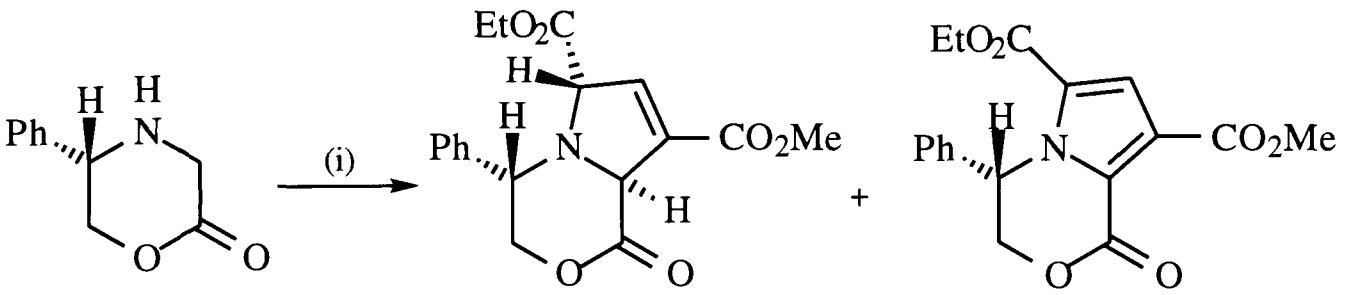
(**2.13**)-1.4%

Figure 2.14

In all the catalysed cycloadditions an increase in material yield over the thermal reaction was observed. The cyclic dipolarophiles (maleic anhydride and *N*-methylmaleimide) both showed an increase, comparable to that observed with *N*-phenylmaleimide, in the proportion of *exo*- adduct. This can again be rationalised by considering the catalyst to co-ordinate to the carbonyl group of the ester. The acyclic dipolarophiles (dimethyl maleate and dimethyl fumarate) showed no shift in stereocontrol with again only a single adduct observed. In the transition state required to form these two cycloadducts, the steric hindrance with the substituent α- to nitrogen is minimised, and therefore a shift to the alternative transition state leading to the *exo*- adducts is disfavoured.

2.3.2 Alkyne Dipolarophiles.

Having succeeded in performing the cycloaddition in a catalysed manner with alkene dipolarophiles attention turned to the catalysed cycloaddition of alkyne dipolarophiles. Accordingly morpholinone (**1.126**), ethyl glyoxylate trimer and methyl propiolate were stirred with magnesium bromide-etherate under the usual conditions. Usual work up followed by column chromatography afforded the same cycloadduct (**2.11**) and dehydrogenated cycloadduct (**2.12**) as in the thermal reaction (**Scheme 2.8**). The increase in overall yield of cycloadduct (**2.11**) (from 21% to 40%) was consistent with previous observations, while the reduction (from 23% to 12%) in the proportion of oxidised product (**2.12**) suggested that the original cycloadduct (**2.11**) was thermally unstable with respect to dehydrogenation.

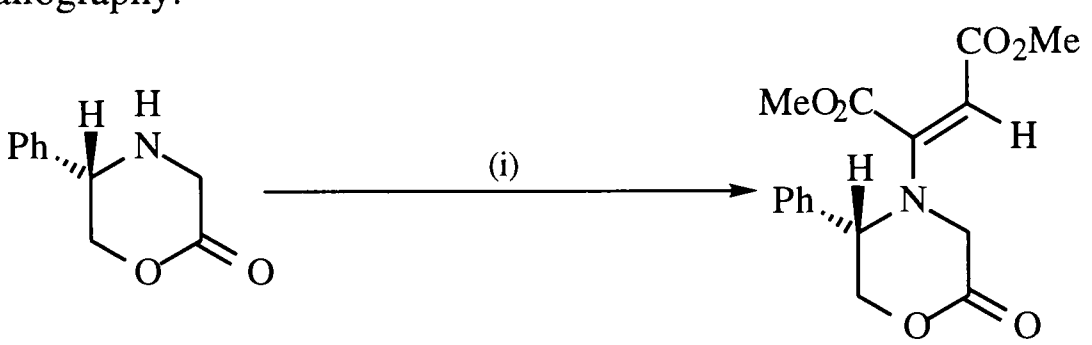


(**1.126**) (**2.11**)-40% (**2.12**)-12%

(i) ethyl glyoxylate trimer, methyl propiolate, $MgBr_2.Et_2O$, molecular sieves, stir THF, r.t.

Scheme 2.8

Despite the failure to observe a cycloadduct with dimethyl acetylenedicarboxylate under thermal conditions it was decided, due to the enhancement in yields observed in other cycloadditions, to attempt the reaction under catalysed conditions. Accordingly morpholinone (**1.126**), ethyl glyoxylate trimer and dimethyl acetylenedicarboxylate were stirred with magnesium bromide-etherate under the usual conditions (**Scheme 2.9**). Usual work up followed by column chromatography afforded a product whose ^{1}H n.m.r. and mass spectrometric data were consistent with a Michael type adduct (**2.14**). The double bond was initially assigned the *E*- configuration on the basis of n.O.e. experiments, and later confirmed by X-ray crystallography.[12]



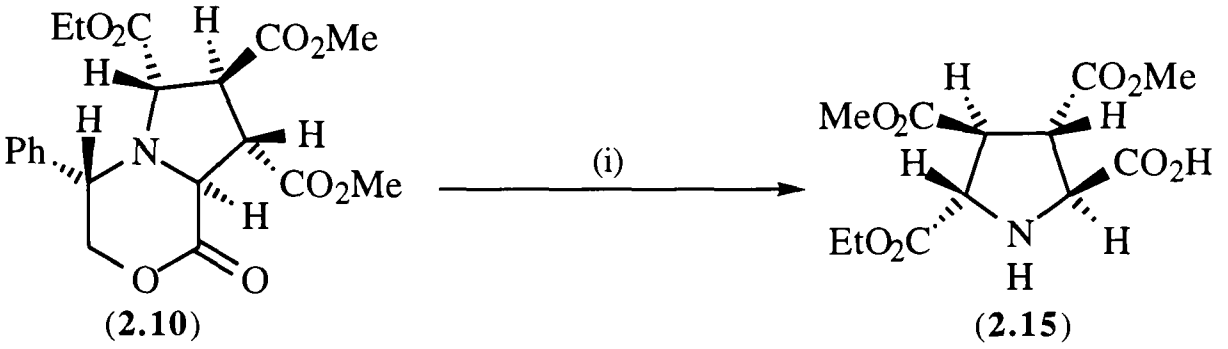
(1.126) **(2.14)**

(i) ethyl glyoxylate trimer, dimethyl acetylenedicarboxylate, $MgBr_2.Et_2O$, molecular sieves, stir THF, r.t., 25%.

Scheme 2.9

2.4 Hydrogenolysis of Cycloadducts: Generation of Proline Derivatives.

Having demonstrated that the ylid derived from ethyl glyoxylate and morpholinone (**1.126**) will react with a range of dipolarophiles under both thermal and Lewis acid catalysed conditions, it was decided to attempt the liberation of a representative sample of the free prolines. Accordingly, following the previously established methodology,[13] the cycloadduct derived from dimethyl fumarate (**2.10**) was stirred in wet methanol with Pearlman's catalyst and trifluoroacetic acid under a 5 bar atmosphere of hydrogen (**Scheme 2.10**). Filtration through Celite® to remove the catalyst, followed by removal of the solvent and trituration with ether afforded a colourless powder whose ^{1}H n.m.r. and mass spectrometric data were consistent with the amino acid (**2.15**). The stereochemistry was inferred from that of the starting cycloadduct (**2.10**).

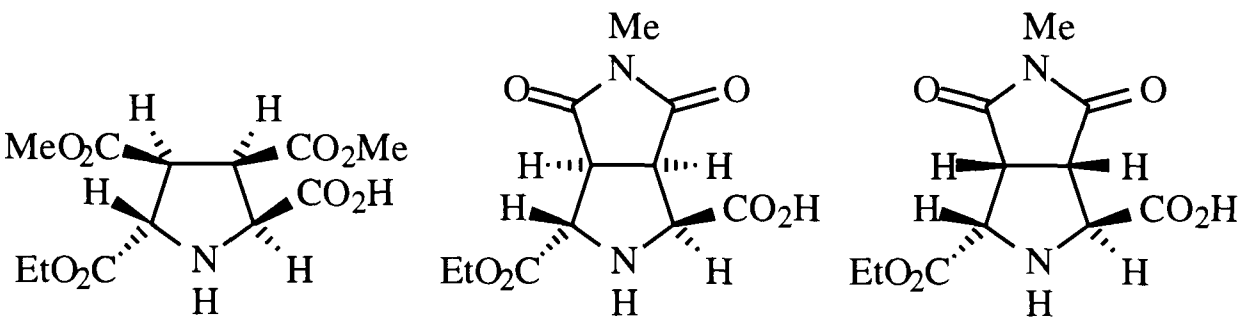


(2.10) **(2.15)**

(i) H_2 5 bar, $Pd(OH)_2$/ C, TFA, wet methanol, 92%.

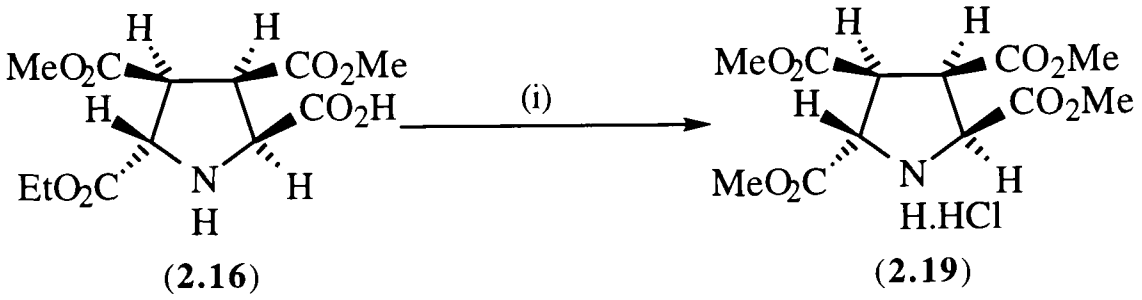
Scheme 2.10

Similarly treatment of the cycloadduct derived from dimethyl maleate (**2.9**) afforded the amino acid (**2.16**) in 92% yield, while subjecting the cycloadducts (**2.6**) and (**2.7**) derived from *N*-methylmaleimide to the hydrogenolysis conditions afforded the corresponding amino acids (**2.17**) and (**2.18**) in 89% and 85% yield respectively.



(2.16)-92% **(2.17)**-89% **(2.18)**-85%

It was decided to further demonstrate the relative stereochemistry of the amino acids derived from dimethyl maleate and dimethyl fumarate by exploiting their differing symmetry. Formation of the fully methylated ester derivative would furnish a C_2 symmetric molecule in one case, while in the other, the derivative would remain asymmetric. The amino acid (**2.16**) was therefore heated in methanol saturated with hydrogen chloride (**Scheme 2.11**). The solvent was removed, the residue taken up in concentrated hydrogen chloride solution, then washed with dichloromethane. Removal of the solvent gave a colourless powder, the ^{1}H n.m.r. spectroscopic data of which indicated that the desired tetramethylated product had been formed. The insolubility of the powder in organic solvents indicated it to be the hydrogen chloride salt (**2.19**), obtained in 76% yield.



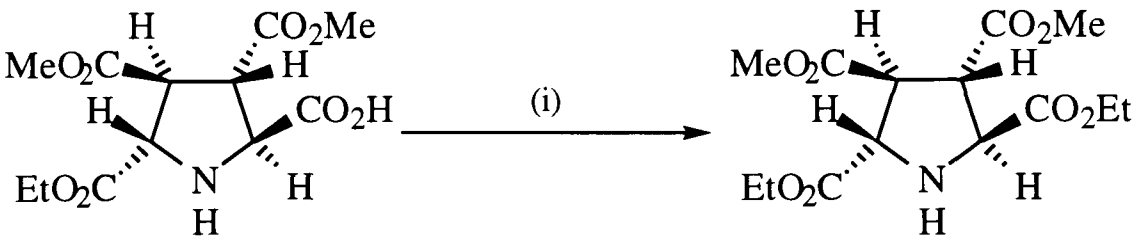
(2.16) **(2.19)**

(i) methanolic HCl, 50°C, 76%.

Scheme 2.11

Similar treatment and work up of the dimethyl fumarate derived amino acid (**2.15**) again resulted in the formation of a colourless powder. ^{1}H n.m.r. analysis initially indicated the presence of only the two expected methyl singlets, however over time the spectra became complicated by the appearance of a number of methyl singlets. This suggested that hydrolysis of one or more of the ester groups was resulting in the generation of a number of different substitution patterns around the pyrrolidine ring, and consequently loss of symmetry.

Having failed to form the tetramethyl ester of both amino acids an alternative approach was adopted. The acid could be converted to the ethyl ester, thus generating a C_2 axis of symmetry, and accordingly the dimethyl fumarate derived amino acid (**2.15**) was stirred in acetone with ethyl iodide and potassium carbonate (**Scheme 2.12**). Removal of the solvent followed by column chromatography on alumina afforded a colourless oil in 86% yield. The mass spectrometric data indicated that ethylation had occurred, while the ^{1}H and ^{13}C n.m.r. data (**Spectra 2.1**) showed the expected reduction in the number of signals due to the imposition of magnetic equivalence. The product was therefore assigned as the tetra-ester (**2.20**).

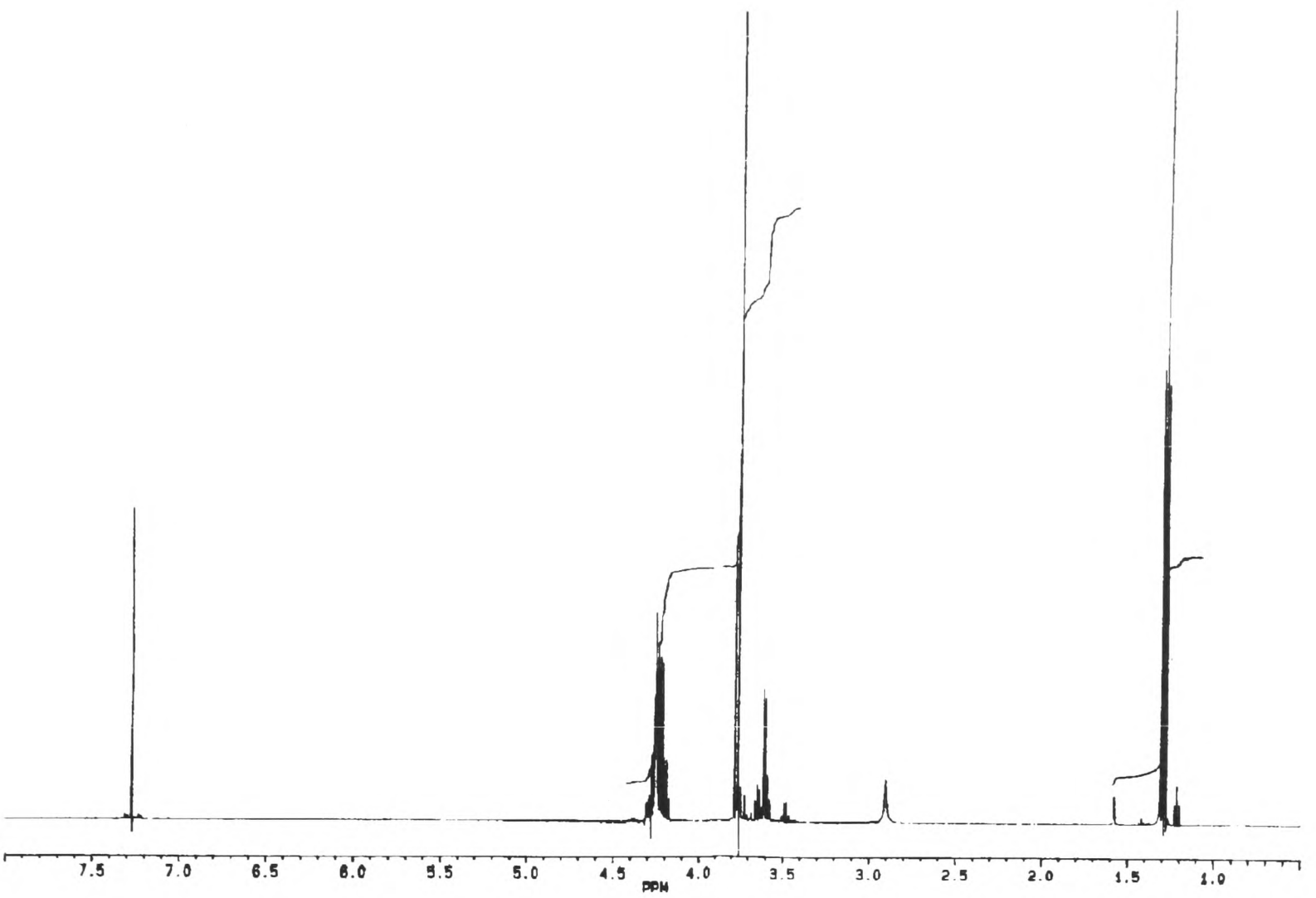


(2.15) **(2.20)**

(i) K_2CO_3, EtI, acetone, r.t., 86%.

Scheme 2.12

Similar treatment of the dimethyl maleate derived amino acid (**2.16**) again afforded a colourless oil, in 56% yield, the ^{1}H n.m.r. and mass spectrometric data of which indicated that


7.5
7.0
6.5
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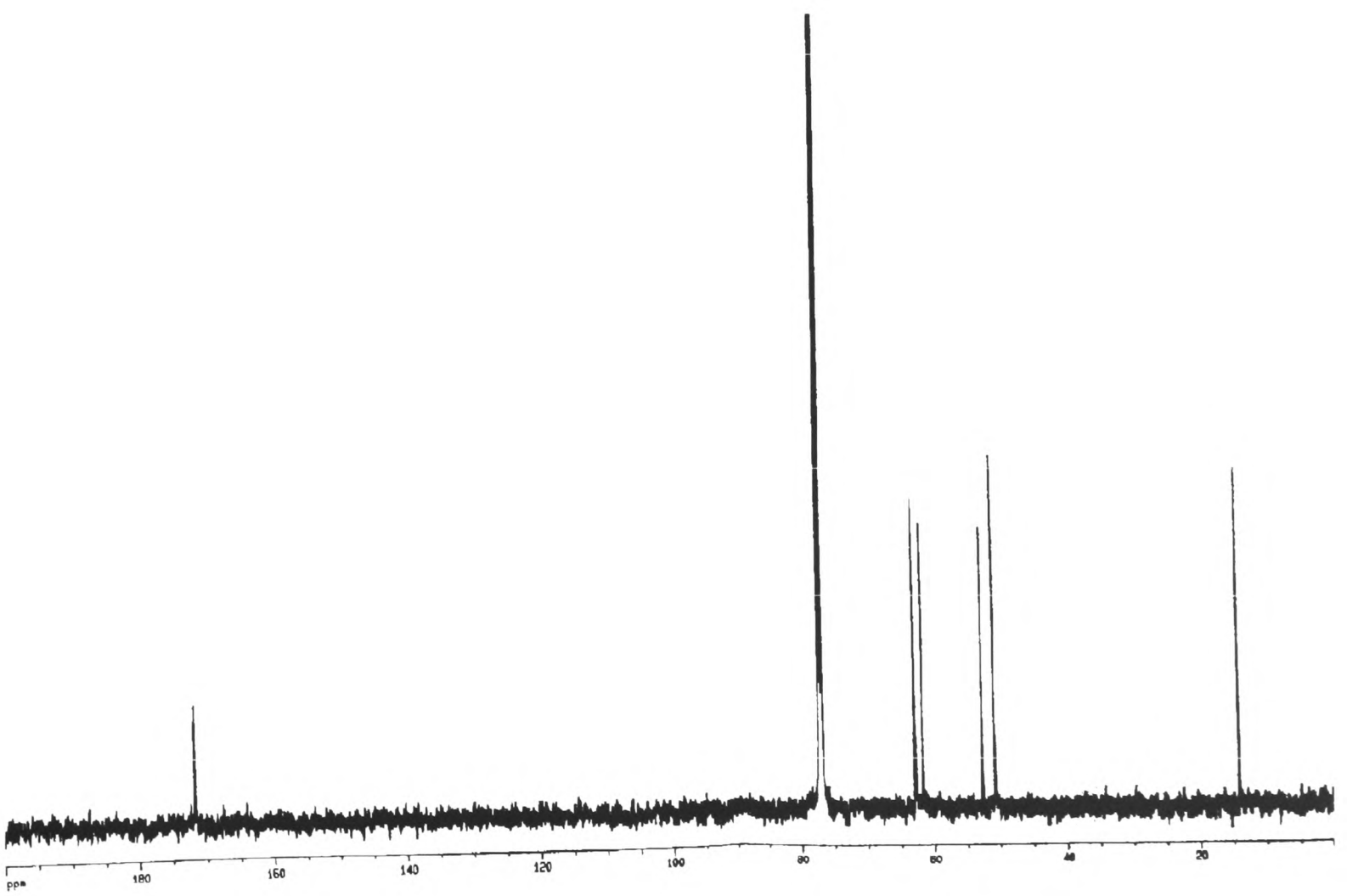
ppm
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160
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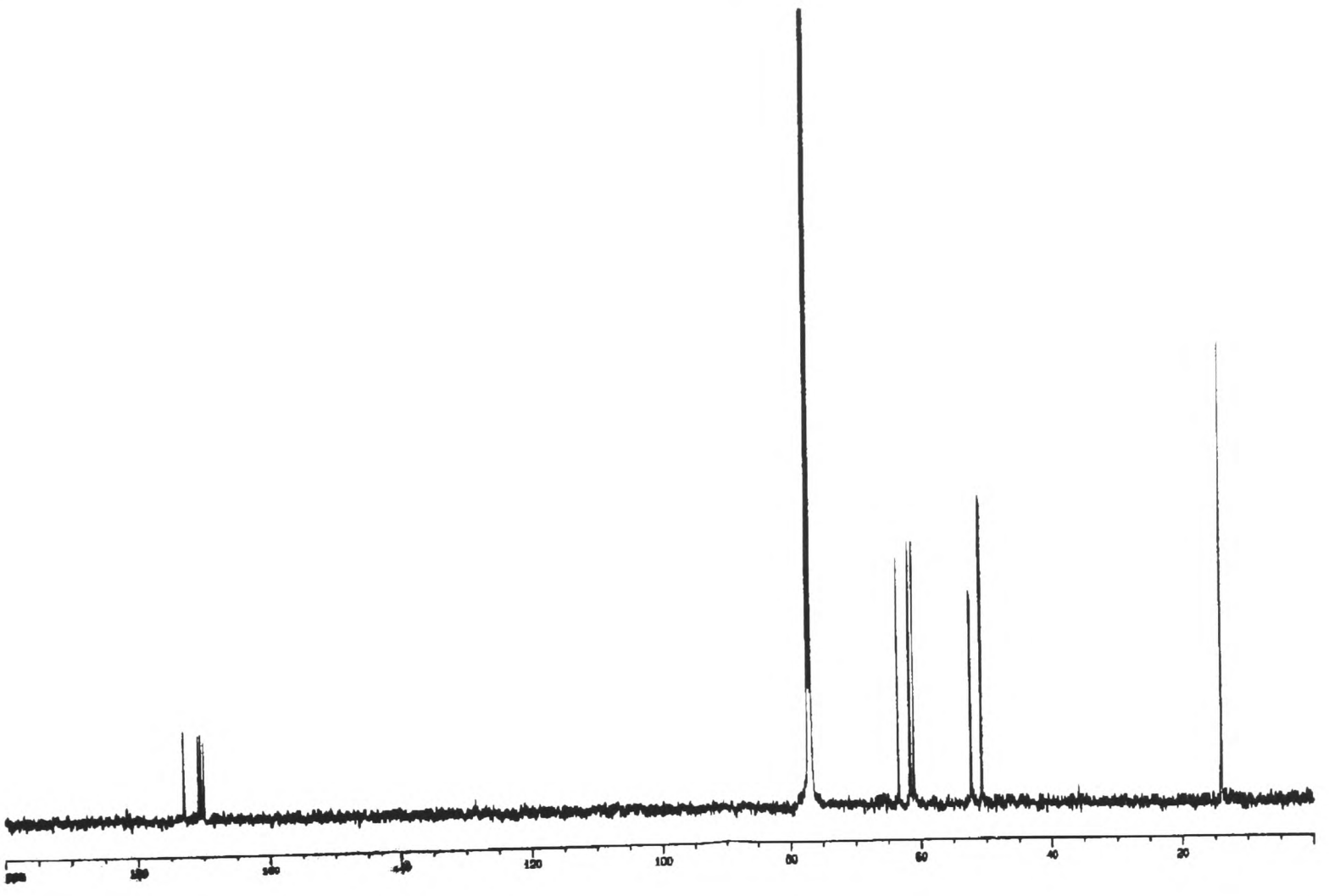
20

Spectra 2.1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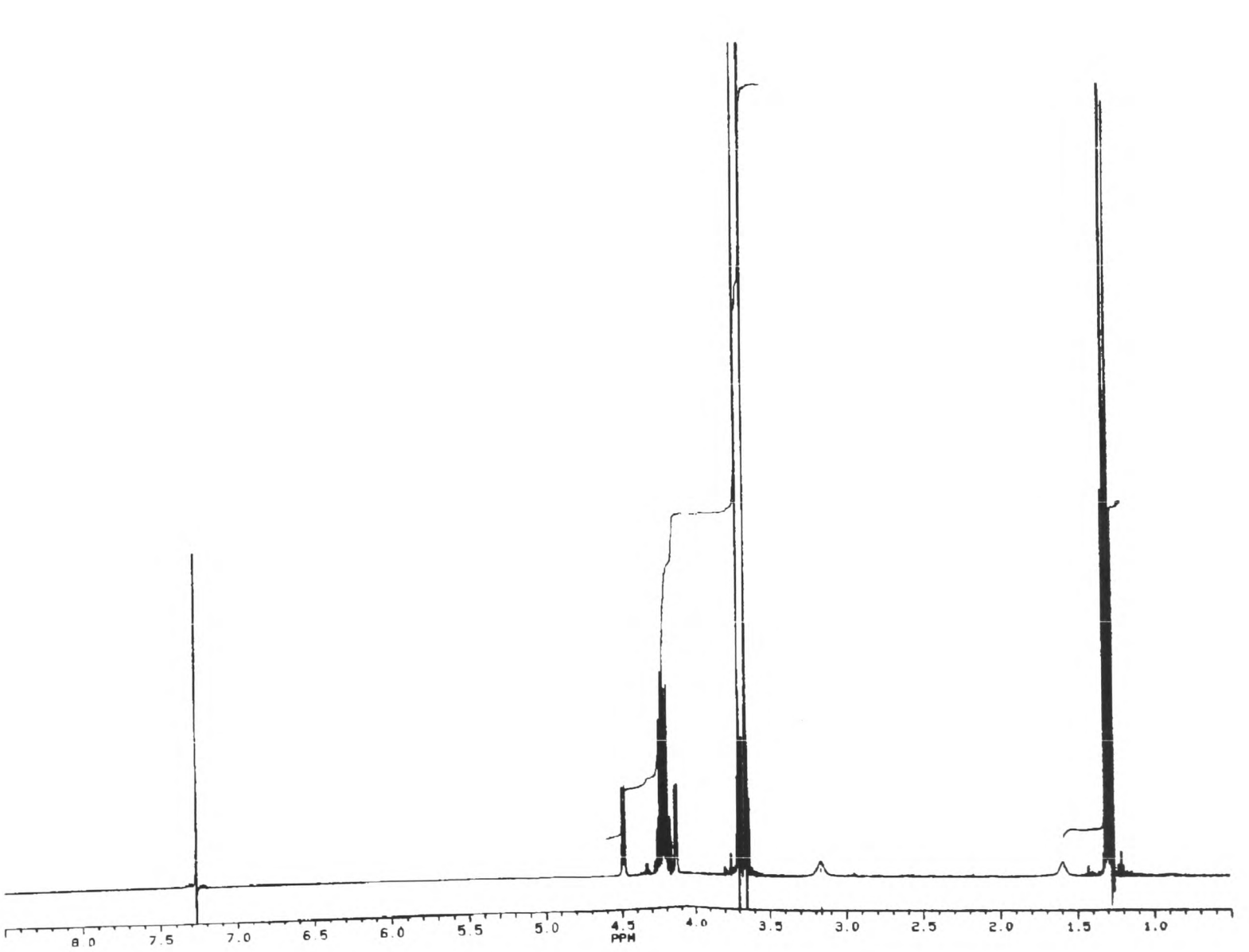
8.0
7.5
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5.0
4.5
PPM
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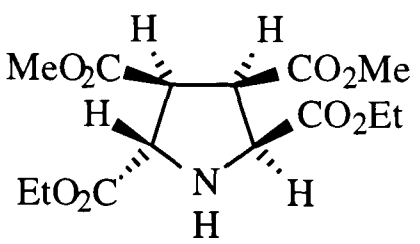
2.5
2.0
1.5
1.0

Spectra 2.2

the ethyl ester (**2.21**) had been formed. Due to the lack of symmetry of this system both the ^{1}H and ^{13}C n.m.r. spectra showed the expected multiplicity of signals (**Spectra 2.2**).



(**2.21**)-56%

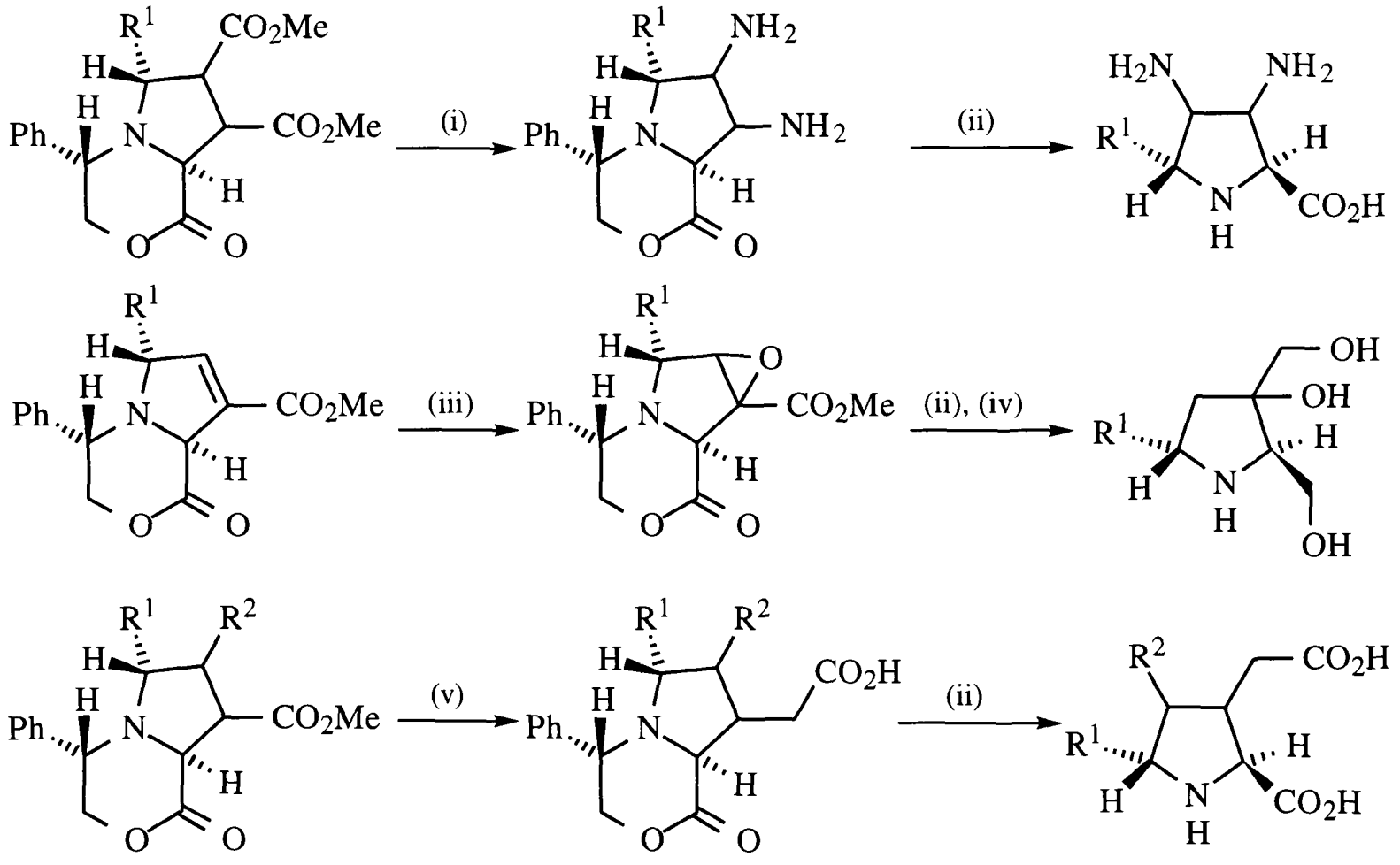
2.5 Summary.

It has been demonstrated that (5*S*)-phenylmorpholinone (**1.126**) reacts with ethyl glyoxylate to efficiently generate an azomethine ylid. This ylid undergoes cycloaddition with a range of activated dipolarophiles under both thermal and Lewis acid catalysed conditions generating cycloadducts. The cycloadditions proceed with a high degree of stereocontrol, with dimethyl fumarate and dimethyl maleate observed to form a single adduct. The *anti-* ylid is observed to be formed preferentially under thermal control, while catalysis results in exclusive formation of adducts derived from this ylid. The catalysed reaction additionally proceeds in a higher yield (typically 10-20% higher), while also increasing the proportion of *exo-* adduct in the case of cyclic dipolarophiles.

The chiral template can be efficiently removed by high pressure catalytic hydrogenolysis to furnish a number of proline derivatives of varied, defined stereochemistry. The relative stereochemistry of the amino acids derived from dimethyl fumarate and dimethyl maleate was further demonstrated by forming the ethyl esters. In the case of the amino acid derived from dimethyl fumarate a C_2 symmetric molecule is generated, while no such symmetry is created with the amino acid derived from dimethyl maleate.

2.6 Future Work.

The [3+2] cycloaddition of the azomethine ylid derived from condensation of aldehydes with (5*S*)-phenylmorpholinone (**1.126**) can be used to rapidly assemble the proline ring. Variation of the conditions employed in the cycloaddition can be exploited to alter the stereochemical outcome and therefore provide access to a range of substitution patterns. Use of alternative aldehydes in the ylid generation step may allow the cycloaddition to proceed with greater stereochemical control, while allowing the introduction of alternative substituents. Elaboration of cycloadducts so generated *via* for example Curtius rearrangement, Arndt-Eistert homologation or Darzens chemistry should allow access to a wide range of proline derivatives with excellent stereocontrol (**Scheme 2.13**).



(i) Curtius rearangement, (ii) deprotection, (iii) epoxidation, (iv) reduction, (v) Arndt-Eistert.

Scheme 2.13

CHAPTER TWO

References

CHAPTER TWO

References

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CHAPTER THREE

Results and Discussion

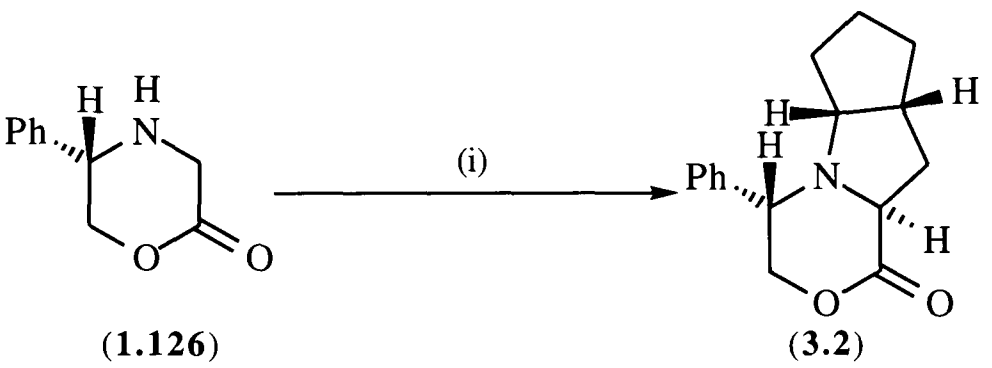
CHAPTER THREE

Intramolecular Cycloadditions of (5*S*)-Phenylmorpholinone

3.1 Catalysed Intramolecular Cycloadditions.

The (5*S*)-phenylmorpholinone template (**1.126**) has previously been shown to undergo efficient intramolecular cycloaddition with long chain aldehydes having a terminal alkene or alkyne functionality. It has also been demonstrated that the inclusion of a sulfur atom in the connecting chain, leading to sulfur containing cycloadducts, is possible.[1] These cycloadditions were performed under thermal conditions, and it was therefore decided to attempt the reaction under the more experimentally convenient conditions of Lewis acid catalysis. This has been shown to alter the stereochemical outcome of intermolecular cycloadditions, however it was considered that the more rigid requirements of the transition state for intramolecular cycloaddition would continue to dictate the stereochemistry.

Accordingly morpholinone (**1.126**) and 5-hexenal (**3.1**) were stirred in tetrahydrofuran with molecular sieves and magnesium bromide-etherate until t.l.c. analysis indicated the absence of starting material (**Scheme 3.1**). Filtration through silica to remove the catalyst followed by column chromatography furnished a single product (**3.2**), whose ^{1}H n.m.r. spectroscopic data and optical rotation were identical with that isolated from the thermal reaction. Disappointingly however, the cycloadduct was obtained in only 15% yield, as opposed to the near quantitative yield observed under thermal conditions.[1] Repetition of the reaction using 5-hexynal resulted in no cycloaddition, only starting material being recovered after 48 hours reaction time.



(1.126) **(3.2)**

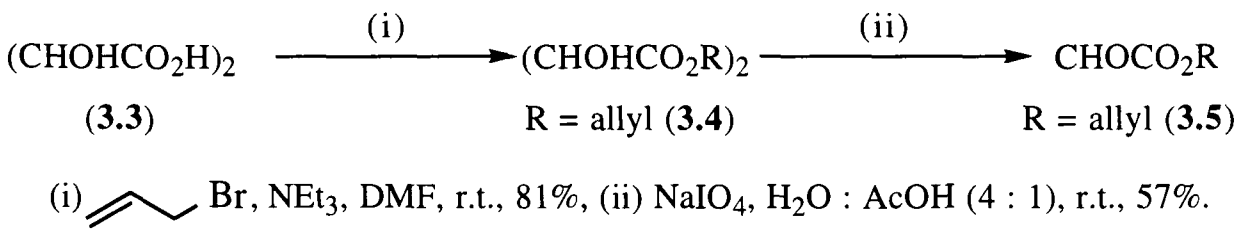
(i) CHO (**3.1**), $MgBr_2.Et_2O$, molecular sieves, stir THF, r.t., 15%.

Scheme 3.1

It is likely that a higher activation energy is required for reaction with the inactivated dipolarophiles used in the intramolecular reaction. Although the catalyst results in a lowering of this activation energy it is unable to overcome the effect of the reduction in temperature, and therefore the yield is substantially reduced. Alkene dipolarophiles have been demonstrated to be more reactive than alkyne dipolarophiles under the same conditions,[2] accounting for the observation of a small amount of cycloadduct when 5-hexenal (**3.1**) is used. Following the disappointing result using the dipolarophiles which were most reactive in the thermal reaction, it was decided that catalysis of the intramolecular reaction was not viable. Attention therefore turned to the introduction of alternative heteroatoms into the second ring.

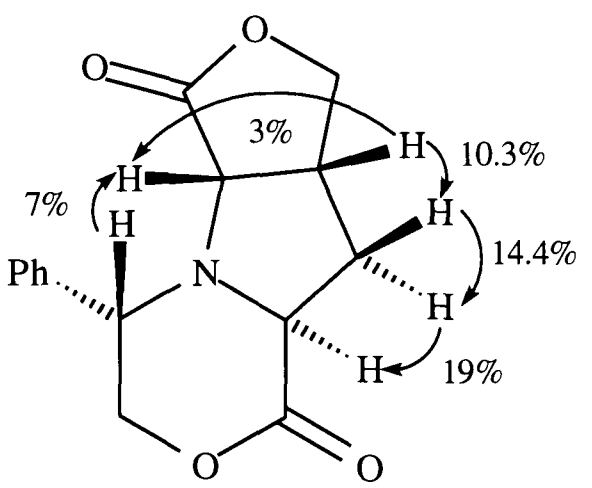
3.2 Introduction of a Carboxylic Ester Chain Link.

It has been previously demonstrated that sulfur may be efficiently incorporated into the tricyclic structure of the intramolecular cycloadducts through the use of a sulfur containing aldehyde. The introduction of an ester functionality would offer the possibility of further elaboration of the resultant cycloadduct, and it was therefore decided to attempt the introduction of such a moiety. The required aldehyde, allyl glyoxylate (**3.5**), was prepared from tartaric acid (**3.3**) in two steps following the method of Woodward.[3] Allylation of the carboxylic acid with allyl bromide in dimethylformamide gave the diester (**3.4**) in 81% yield. Subsequent oxidative cleavage with sodium metaperiodate in aqueous acetic acid gave allyl glyoxylate (**3.5**) in 57% yield (**Scheme 3.2**).



Scheme 3.2

Morpholinone (**1.126**) and allyl glyoxylate (**3.5**) were subsequently refluxed in toluene under the usual conditions. After 18 hours reflux, t.l.c. analysis indicated the absence of starting material and the presence of a number of new products. ^{1}H n.m.r. analysis of the crude material suggested the presence of material having spectroscopic data consistent with that of a cycloadduct. However the data also showed signals consistent with the addition of a second molecule of aldehyde to the initially formed ylid, a process that had previously been observed in cases where no dipolarophile was added to the reaction mixture.[4] Column chromatography permitted the isolation of material which, through the use of two dimensional n.m.r. and n.O.e. experiments, was unambiguously assigned as the desired cycloadduct (**3.6**), although in a disappointing 23% yield. Irradiation of the proton at C_{12} gave an enhancement (7%) to the proton at C_2 indicating that this proton was also on the β- face (**Figure 3.1**). The proton at C_2 was also enhanced (3%) on irradiation of the proton at C_6, showing that the proton at C_6 was also on the β- face. Irradiation of this proton also gave a strong enhancement (10.3%) to one of the protons at C_7. Irradiation of the other proton at C_7 gave a strong enhancement (19%) to the proton at C_8 indicating this proton to be on the α- face.

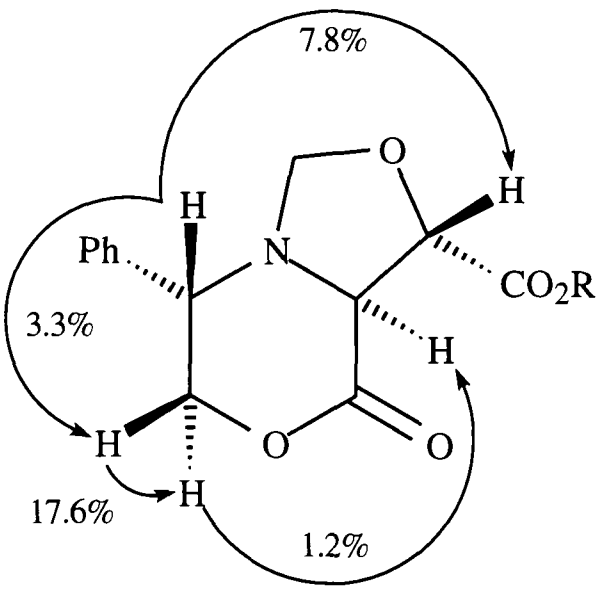


(**3.6**)-23%

Figure 3.1

The observation in the crude ^1H n.m.r. spectra of products derived from sequential addition of two molecules of aldehyde prompted the suggestion of adding the allyl glyoxylate (**3.5**) slowly to a solution of the morpholinone (**1.126**) in refluxing toluene. This would lower the concentration of allyl glyoxylate (**3.5**) present in the reaction mixture, thus hopefully promoting intramolecular cycloaddition over intermolecular cycloaddition.

Accordingly morpholinone (**1.126**) was refluxed in toluene under the usual conditions, while allyl glyoxylate (**3.5**) was added over 14 hours *via* a syringe pump. After 18 hours t.l.c. analysis indicated the absence of starting material and the presence of a new product. Usual work up followed by column chromatography furnished a 4.3% yield of a novel compound, which by ^1H n.m.r. analysis was not the expected, previously isolated, cycloadduct (**3.6**). Two dimensional n.m.r. coupled with the use of n.O.e. experiments enabled the structural and stereochemical elucidation of the material as the adduct (**3.7**). Irradiation of the proton at C_2 gave a strong enhancement (7.8%) to the proton at C_7 indicating it to be on the β- face, and also an enhancement (3.3%) to one of the protons at C_3. Irradiation of the other proton at C_3 gave an enhancement to the proton at C_6 indicating it to be on the α-face (**Figure 3.2**).

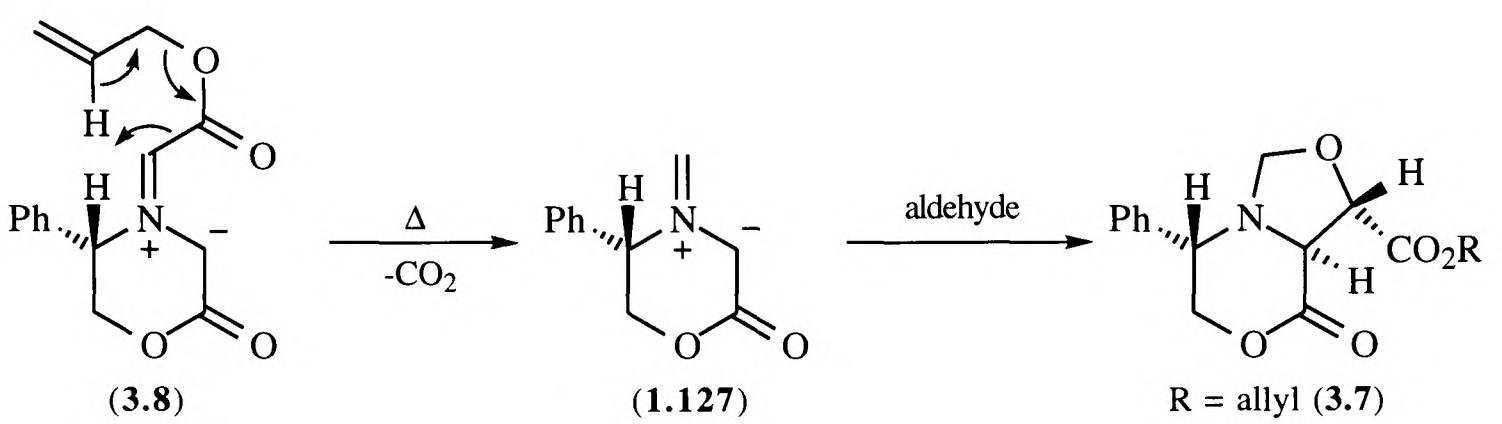


R = allyl (**3.7**)

Figure 3.2

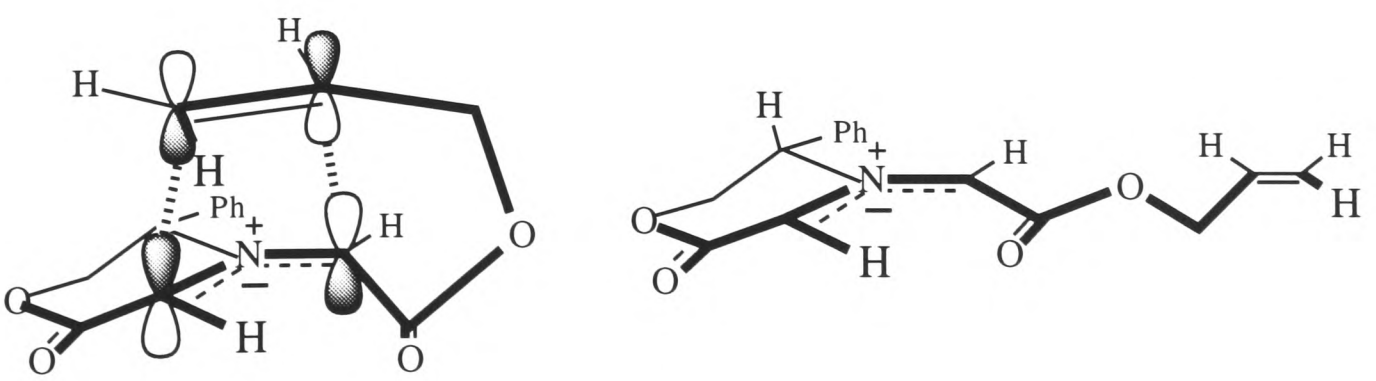
The product is seemingly the result of exclusive *exo*- addition of the ylid (**1.127**) derived from the condensation of paraformaldehyde with phenylmorpholinone to another molecule of the aldehyde. Formation of the unsubstituted ylid (**1.127**) can be rationalised by

considering decarboxylation of the ylid (**3.8**), formed from condensation with allyl glyoxylate (**3.5**), under the high temperature conditions (**Scheme 3.3**). The nature of the mechanism of this decarboxylation is not known, however an entropically favoured fragmentation can be envisaged to generate the required ylid. Subsequently the ylid is trapped by a second molecule of aldehyde as has been demonstrated previously.[4] Further observations of this apparent decarboxylation will be given later.



Scheme 3.3

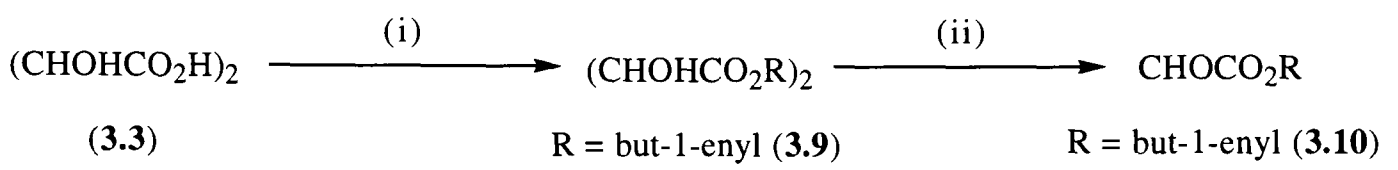
The low yield in the cycloaddition can be rationalised by considering the conformation adopted by the ylid. In order for cycloaddition to occur, the ylid must be in a *cisoid-* conformation to allow efficient molecular orbital overlap (**Figure 3.3**). However the preferred conformation is the electronically favoured[5] *transoid-* conformation in which the double bond is positioned away from the dipole. The slow rate of cycloaddition allows decarboxylation to occur, and following this there is a low concentration of potential dipolarophile. The paraformaldehyde derived ylid is known to be unstable and the low probability of being trapped before undergoing decomposition accounts for the low observed yield.



cisoid- conformation *transoid-* conformation

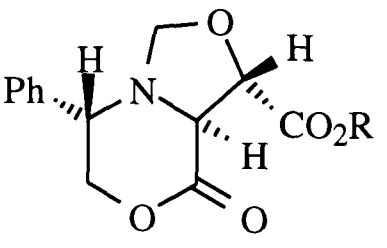
Figure 3.3

Following the poor yield observed in the attempted cycloadditions with allyl glyoxylate (**3.5**) it was decided to attempt the same reaction using the higher homologue in the hope that this would allow the ylid to adopt a more favourable geometry for reaction. But-1-enyl glyoxylate (**3.10**) was therefore prepared in an analogous manner to that previously employed for allyl glyoxylate (**3.5**). Alkylation of tartaric acid (**3.3**) gave a 50% yield of the dibut-1-enyl ester (**3.9**), which was subsequently oxidatively cleaved to give the required but-1-enyl glyoxylate (**3.10**) in 58% yield (**Scheme 3.4**).



Scheme 3.4

Morpholinone (**1.126**) and but-1-enyl glyoxylate (**3.10**) were refluxed in toluene, under the usual conditions, until t.l.c. analysis indicated the absence of starting material. Usual work up followed by column chromatography permitted the isolation of a single product in 17% yield. The ^{1}H n.m.r. and mass spectrometric data were consistent with that of an adduct (**3.11**) derived from cycloaddition of the paraformaldehyde derived ylid (**1.127**) with a second molecule of aldehyde and, by comparison with the previously observed cycloadduct, the product was initially assigned the (2*S*,6*S*,7*S*) stereochemistry. This assignment was subsequently confirmed by the observation of an n.O.e. enhancement (6%) between the protons at C_2 and C_7.



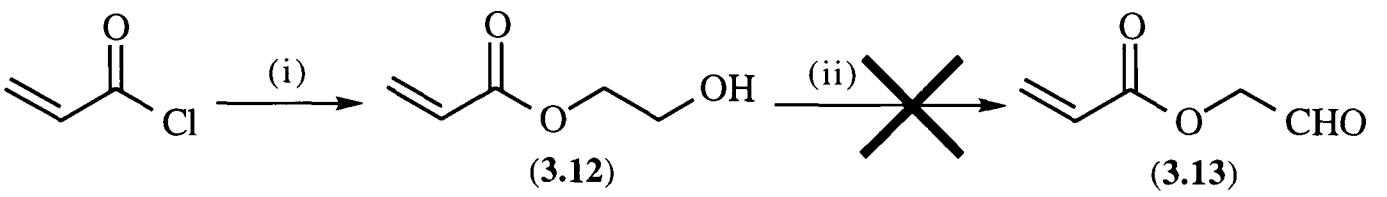
R = but-1-enyl (**3.11**)-17%

The formation of the observed cycloadduct (**3.11**) can be rationalised in an analogous manner to the formation of the homologue (**3.7**). Decarboxylation of the initially formed but-1-enyl derived ylid generates the ylid (**1.127**) derived from condensation with

paraformaldehyde. This can subsequently be trapped by a second molecule of aldehyde in an exclusive *exo*- manner to generate the required cycloadduct (**3.11**). The increase in yield over the homologue can be ascribed to the fact that as the aldehyde was not added over a period of time, the concentration of aldehyde was greater, and therefore the ylid has a greater probability of being trapped before undergoing decomposition.

The problems encountered in attempting to incorporate the ester linkage with the carbonyl at C_3 led to the suggestion that more success would be achieved using the regiomeric ester (**3.13**). This would hopefully allow the ylid to achieve a geometry more favourable for orbital overlap and in addition, due to activation of the double bond by the ester, favour the cycloaddition.

The mono-acrylate ester of ethylene glycol (**3.12**) was therefore prepared in 22% yield, according to the method of Burtle, by addition of acryloyl chloride to a chloroform solution of ethylene glycol.[6] However attempted oxidation using either pyridinium chlorochromate or the method of Swern,[7] resulted in the destruction of starting material and no isolation of the required aldehyde (**3.13**) (**Scheme 3.5**). An alternative method of synthesising the aldehyde was therefore required.



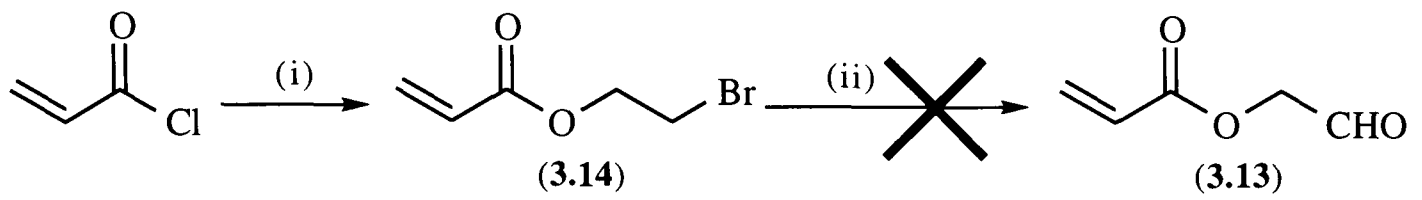
(3.12) **(3.13)**

(i) $HOCH_2CH_2OH$, Na_2SO_4, Na_2SO_3, CuCl, $CHCl_3$, 30-40°C, 22%, (ii) oxidation.

Scheme 3.5

It has been reported that aldehydes may be prepared from the corresponding alkyl bromide by nucleophilic displacement followed by α-oxidation, and it was therefore decided to attempt preparation of the bromide (**3.14**). Treatment of acryloyl chloride with bromoethanol, in an adaptation of the procedure of Burtle,[6] afforded the required alkyl bromide (**3.14**), in 25% yield. However treatment with trimethylamine *N*-oxide,[8] pyridine *N*-oxide[9] or dimethyl sulfoxide[10] resulted only in the isolation of small quantities of starting material (**Scheme 3.6**). Alkyl acrylates have been extensively studied as copolymers in the development of acrylic

rubbers,[11] and their ready polymerisation renders efficient chemical modification difficult. For this reason attempted synthesis of the aldehyde (**3.13**) was abandoned.



(i) $HOCH_2CH_2Br$, Na_2SO_4, Na_2SO_3, CuCl, $CHCl_3$, 30-40°C, 25%, (ii) oxidation.

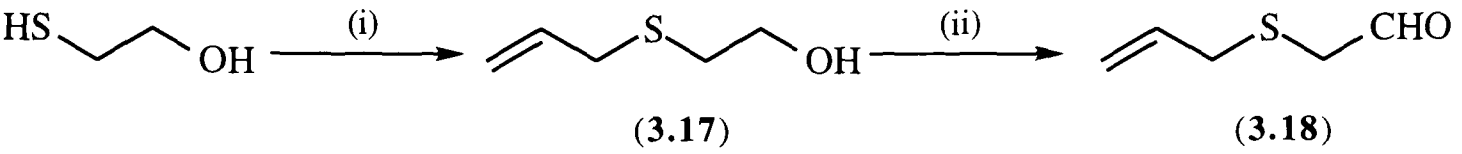
Scheme 3.6

3.3 Elaboration of Intramolecular Cycloadducts.

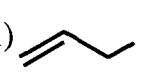
3.3.1 Alkylation of Sulfones.

Following the disappointing results observed on attempting to incorporate an ester linkage into the second ring, it was decided to attempt additional modification of the sulfur cycloadduct (**3.15**) previously prepared within the group.[1] Due to the rigid tricyclic structure of the intramolecular cycloadducts, such transformations may potentially be carried out in a highly diastereoselective manner. The deprotonation of sulfones and subsequent reaction of the anion with electrophiles has been extensively studied.[12] Therefore it was decided to employ this technique to attempt further functionalisation of the adduct generated by intramolecular cycloaddition. This required the synthesis of the sulfone (**3.16**), and it was envisaged that this could be achieved *via* oxidation of the previously prepared cycloadduct (**3.15**).

Stirring mercaptoethanol with allyl bromide and potassium carbonate in dimethylformamide followed by extraction and distillation furnished the thio alcohol (**3.17**) in 67% yield. Subsequent oxidation to the aldehyde (**3.18**) was effected in 22% yield by stirring with pyridinium chlorochromate and powdered molecular sieves in dichloromethane, followed by filtration through silica and distillation (**Scheme 3.7**). The disappointing yield in the oxidation led to the investigation of alternative oxidation systems, however attempted Swern[7] or modified Collins[13] oxidation resulted in the recovery of starting material or even lower yields respectively.

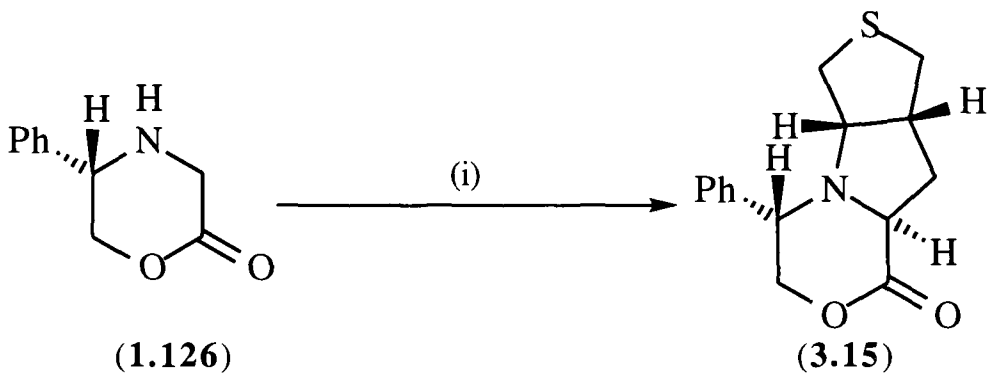


(3.17) **(3.18)**

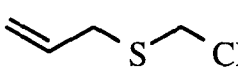
(i)  , K_2CO_3, DMF, r.t., 67%, (ii) PCC, powdered molecular sieves, DCM, r.t., 22%.

Scheme 3.7

The thio aldehyde (**3.18**) was subsequently refluxed with morpholinone (**1.126**), under the usual conditions, until t.l.c. analysis indicated the absence of starting material (**Scheme 3.8**). Usual work up followed by column chromatography furnished a single adduct (**3.15**), in 74% yield, whose ^1H n.m.r. data and optical rotation were identical to that of the sample previously prepared.[1] The stereochemistry, previously assigned using n.O.e. experiments, was confirmed by X-ray crystal structure analysis (**Figure 3.4**).

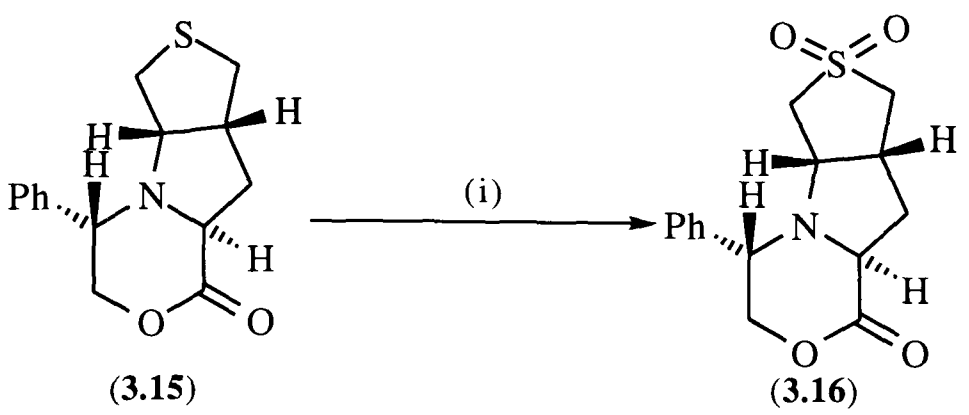


(1.126) **(3.15)**

(i)  CHO (**3.18**), molecular sieves, reflux toluene, 74%.

Scheme 3.8

The cycloadduct (**3.15**) was dissolved in dichloromethane and refluxed with *meta*-chloroperbenzoic acid, following the procedure of Larcheveque,[14] until t.l.c. analysis indicated the absence of starting material (**Scheme 3.9**). Removal of solvent followed by column chromatography furnished a single product, in 78% yield, whose mass spectrometric data was consistent with that of the sulfone (**3.16**). Confirmation was provided by the appearance of characteristic sulfone absorptions in the infra-red spectrum.

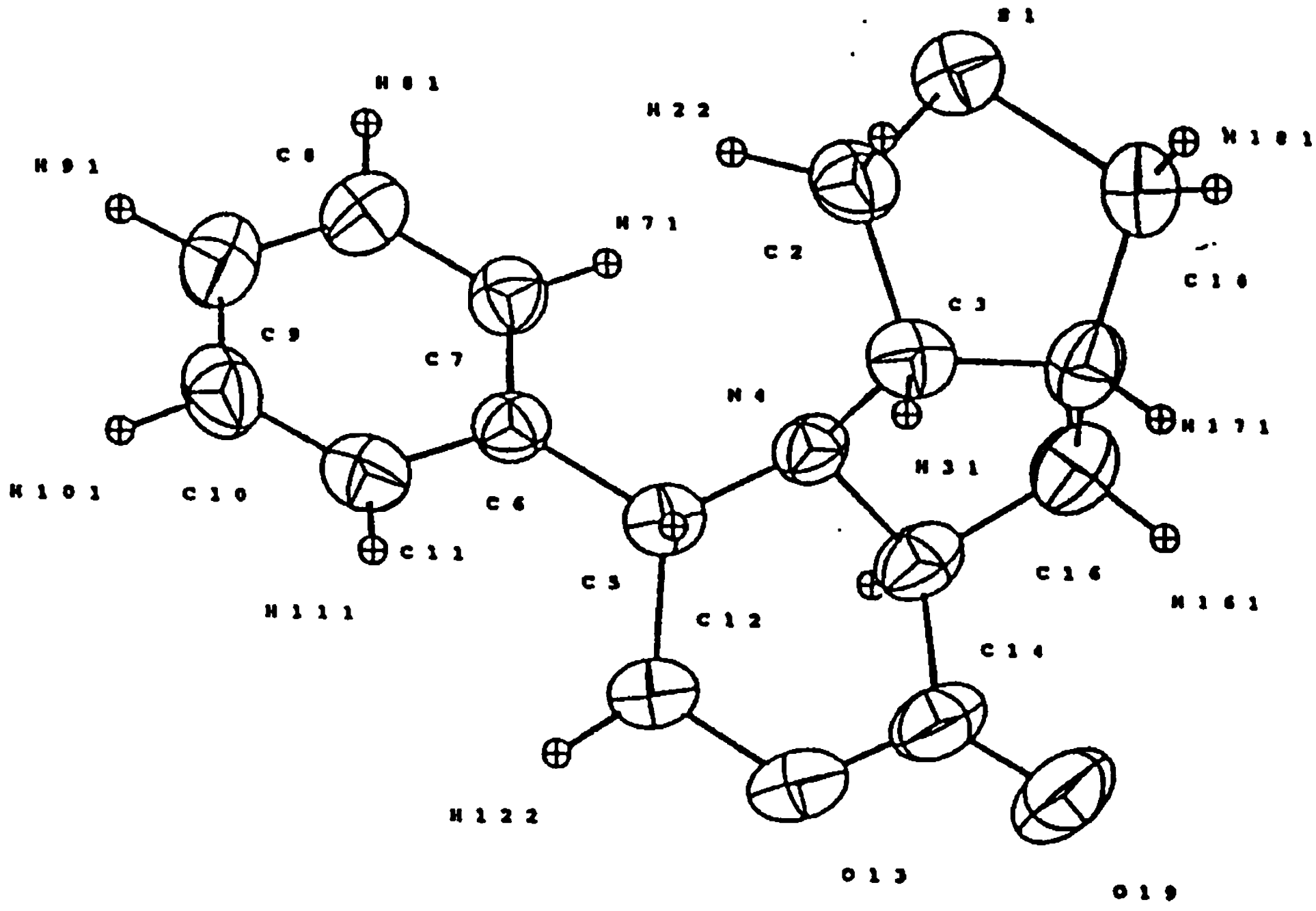


(3.15) **(3.16)**

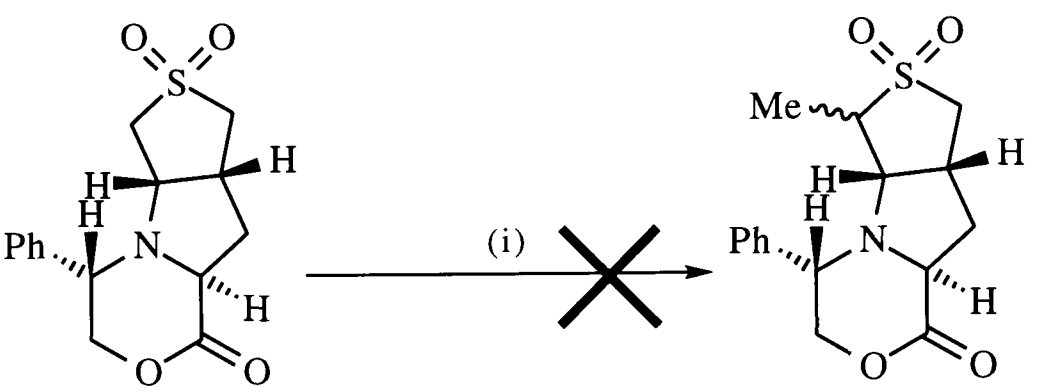
(i) *m*CPBA, reflux DCM, 78%.

Scheme 3.9

Figure 3.4
Crystal Structure for Compound (3.15)



In order to effect alkylation a solution of the sulfone (**3.16**) in tetrahydrofuran was added *via* cannula to a solution of lithium diisopropylamide, then stirred for 1 hour in order to effect anion generation. Methyl iodide was added, the solution stirred for 4 hours, then quenched by the addition of ammonium chloride solution (**Scheme 3.10**). However following work up, ^{1}H n.m.r. spectroscopic analysis indicated only the presence of the starting material.



(i) LDA, MeI, THF, -78°C.

Scheme 3.10

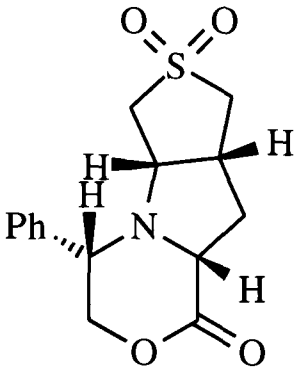
Subsequently the alkylation was attempted using different bases at a range of temperatures, in both tetrahydrofuran and the more polar hexamethylphosphoramide. However no alkylated product (**3.19**) was detected and, with the exception of *n*-butyl lithium, only starting material (**3.16**) was recovered on extraction with diethyl ether (**Table 3.1**).

BASE	SOLVENT	TEMPERATURE	RESULT
NaH	THF	-78°C	Starting Material
KO^{t}Bu	HMPA	0°C	Starting Material
LHMDS	HMPA	0°C	Starting Material
LDA	THF	-78°C	Starting Material
LDA	THF	0°C	Starting Material
LDA	HMPA	0°C	Starting Material
^{n}BuLi	THF	-78°C	Decomposition

Table 3.1

It was not clear as a result of these studies whether deprotonation was occurring, despite the appearance of the yellow colour characteristic of such deprotonations. It was

therefore decided to attempt deprotonation with sodium bis(trimethylsilyl)amide, known to deprotonate α- to nitrogen in the *N*-protected (5*S*)-phenylmorpholinone,[15] then quench with a source of deuterium. Accordingly, sodium bis(trimethylsilyl)amide in tetrahydrofuran was added to a solution of the sulfone (**3.16**) in tetrahydrofuran at -78°C, the solution stirred for 1 hour to effect deprotonation, then quenched by the addition of MeOD. Infra-red spectroscopy indicated the presence of the sulfone functionality, however ^{1}H n.m.r. analysis indicated that the material recovered was not the starting sulfone (**3.16**). The integration of the proton n.m.r. indicated that the molecule still contained 12 protons, and therefore that deuterium incorporation had not occurred. Mass spectral analysis was not conclusive, showing only a small MH^+ peak at 308 mass units corresponding to fully protonated material. This data suggested that the material was the C_8 epimer (**3.20**) of the starting sulfone. Further evidence was provided by the observation of n.O.e enhancements between the proton at C_8 and both the proton at C_{12} (0.9%), and the proton on the β- face of C_{11} (4.6%).



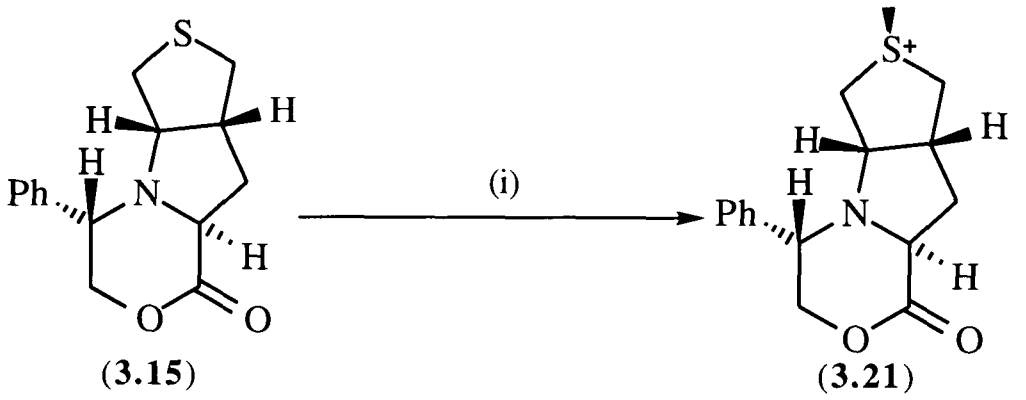
(**3.20**)

In order to produce the C_8 epimer deprotonation must have occurred at this site followed by protonation from the opposite face, protonation rather than deuteration presumably occurring as a result of water in the quenching solvent. Reprotonation from the opposite face allows both substituents on the morpholinone ring to lie in the energetically favoured equatorial position with the morpholinone ring in the most favoured chair conformation. As deprotonation had occurred from the incorrect site for elaboration, the attempted alkylation of the sulfone was abandoned.

3.3.2 Pummerer Rearrangements of Sulfoxides.

Having failed to effect alkylation of the sulfone, it was decided to investigate the regio- and stereoselectivity of the Pummerer rearrangement of the corresponding sulfoxide. Initial elimination from either C_3 or C_5 can be followed by trapping from either the α- or β- face, giving a total of four possible products. However the hindered nature of the tricyclic system suggested that a degree of stereoselectivity would be possible. Preparation of the required sulfoxide (**3.21**) was envisaged *via* mild oxidation of the sulfur cycloadduct (**3.15**).

According to the procedure of Leonard,[16] a methanolic solution of the cycloadduct (**3.15**) was added to a solution of sodium metaperiodate in aqueous methanol at -5°C, then stirred overnight (**Scheme 3.11**). Filtration followed by extraction with dichloromethane and recrystallisation from ethyl acetate furnished a colourless solid, in near quantitative yield, whose mass spectrometric data was consistent with the required sulfoxide (**3.21**). Further confirmation was provided by the appearance of characteristic sulfoxide absorptions in the infra-red spectrum.



(3.15) **(3.21)**

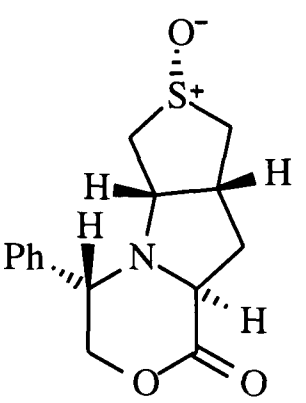
(i) $NaIO_4$, MeOH, H_2O, -5°C, 97%.

Scheme 3.11

Interestingly the ^1H n.m.r. spectroscopic data indicated that only a single diastereoisomer of the sulfoxide had been formed, however n.O.e experiments were unable to determine the configuration. The stereochemistry of sulfoxides has been assigned on the basis of perturbations of hydrogen bonding,[17] however the lack of hydrogen bonding in this system prevented this technique being applied. The β- face or *S* stereochemistry was therefore initially assigned on the basis that this would be both the thermodynamic and kinetic product. Further

evidence for this assignment was later provided on the basis of proton chemical shifts on the α- and β- faces of the sulfoxide.

The Pummerer rearrangement involves initial attack by sulphur on a highly electrophilic species followed by elimination and subsequent trapping by a nucleophile. The sulfoxide (**3.21**) was therefore stirred in dichloromethane with trifluoromethanesulfonic anhydride then quenched by the addition of 2 M hydrogen chloride solution. However following extraction the only isolable product had mass spectrometric data showing a molecular ion of the same mass as the starting material and characteristic sulfoxide absorptions in the infra-red spectrum. The ^1H n.m.r. data was different to the original sulfoxide (**3.21**) however, and this suggested that the isolated product was the epimeric sulfoxide (**3.22**), isolated in 6.4% yield.



(**3.22**)-6.4%

Two dimensional n.m.r. coupled with the use of n.O.e. experiments allowed the total assignment of the ^1H n.m.r. spectra of the isolated product (**3.22**). The proton resonances were all observed to have shifted down field, however the α- face protons showed a greater shift than the β- face protons (**Table 3.2**). By comparison with the work of Cooper,[17] this indicated that the oxygen of the sulfoxide was now on the α- face. The low yield of recovery of the epimeric sulfoxide (**3.22**) meant however that it could not be concluded whether epimerisation had occurred during the reaction or whether the epimeric sulfoxide were already present. If a small quantity of the epimeric sulfoxide (**3.22**), undetectable by ^1H n.m.r., were present as an impurity then this may be unchanged under the reaction conditions whilst the major component is destroyed. The β-sulfoxide (**3.21**) would be expected to be more readily formed in the initial oxidation due to the β- face being more accessible. The resultant sulfoxide would also be the least hindered, and therefore the most thermodynamically stable. This would

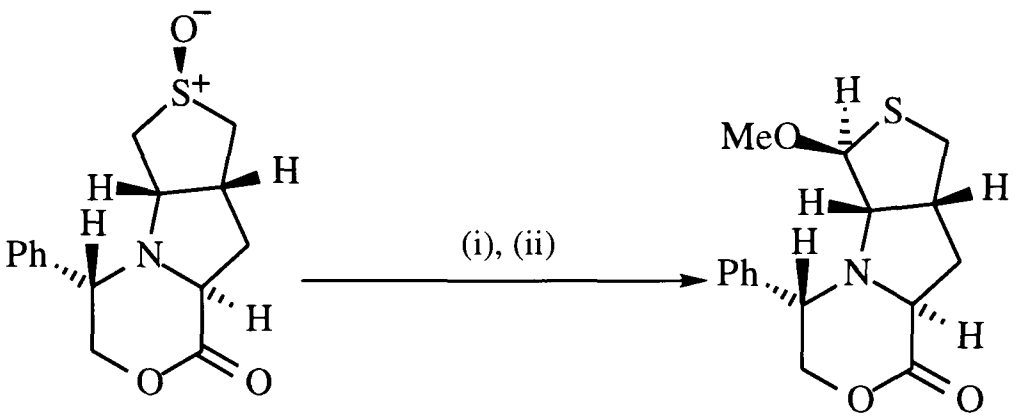
mean that the β- sulfoxide (**3.21**) was both the kinetic and thermodynamic product and thus account for the seemingly exclusive formation of this epimer. If the sulfoxide (**3.21**) is both the kinetic and thermodynamic epimer then it seems unlikely that epimerisation to the least favourable sulfoxide (**3.22**) would occur. This therefore suggests that trifluoromethanesulfonic anhydride causes degradation of the β- sulfoxide (**3.21**) while leaving the α- sulfoxide (**3.22**) intact. This assumption therefore gives a diastereomeric excess of at least 87% in the original oxidation to the sulfoxide. For the purposes of the Pummerer rearrangement, the mixture of epimers at this centre is unimportant as the stereocentre is destroyed in the course of reaction.

Proton	**Chemical Shift (3.21)**	**Chemical Shift (3.22)**	**Change in δ (3.22)-(3.21)**
2β-H	3.30	3.85	+0.55
3α-H	2.11	2.97	+0.86
3β-H	2.20	2.63	+0.43
5α-H	1.87	3.16	+1.29
5β-H	2.42	2.81	+0.39
6β-H	2.98	3.27	+0.29
7α-H	1.34	2.64	+1.30
7β-H	2.42	2.81	+0.39
8α-H	3.34	4.50	+1.16

Table 3.2

Pummerer rearrangements have been effected under milder conditions using trifluoroacetic anhydride.[18] The sulfoxide (**3.21**) was therefore stirred in dichloromethane with trifluoroacetic anhydride for four hours before quenching with methanol (**Scheme 3.12**). Removal of the solvent followed by column chromatography furnished a single product whose ^{1}H n.m.r. and mass spectrometric data were consistent with that of the required rearranged product. The absence of characteristic sulfoxide absorptions in the infra-red spectrum provided

further evidence, and two dimensional n.m.r. coupled with the use of n.O.e. experiments allowed total structural and stereochemical assignment of the product as the rearranged sulfoxide (**3.23**), isolated in 57% yield.



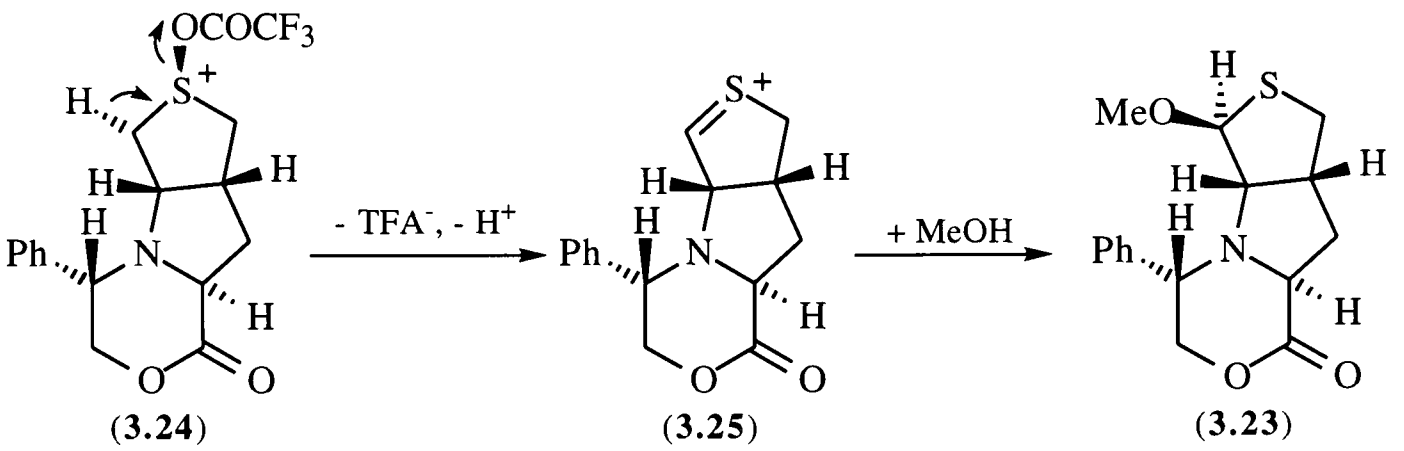
(3.21) **(3.23)**

(i) TFAA, DCM, r.t., (ii) MeOH, 57%.

Scheme 3.12

The initial assignment of the stereochemistry at C_3 was on the basis of the lack of a coupling constant between the protons at C_2 and C_3. According to the Karplus equation this suggests a dihedral angle of 90° which is only possible if the proton at C_3 is on the α- face.[19] Further evidence for this stereochemistry was provided by an observed n.O.e. enhancement (1.2%) between the proton on the α- face at C_5 and the proton at C_3, and a small enhancement (2.9%) between the proton at C_3 and the proton at C_2.

Gratifyingly, although the rearrangement proceeded in low yield, only a single regio- and stereoisomer was produced. The formation of a single isomer can be rationalised by considering initial formation of the trifluoroacetate of the sulfoxide (**3.24**) followed by elimination from C_3 to give the sulfinium ion (**3.25**). This can then be trapped by methanol from the least hindered β- face to give the observed product (**3.23**) (**Scheme 3.13**). The origin of the formation of a single sulfinium ion is however not known. It is possible that a greater relief of steric hindrance is associated with the formation of an sp^2 centre at C_3 than at C_5. Alternatively the nitrogen may act as an internal base, thus promoting proton loss from the more proximate carbon.

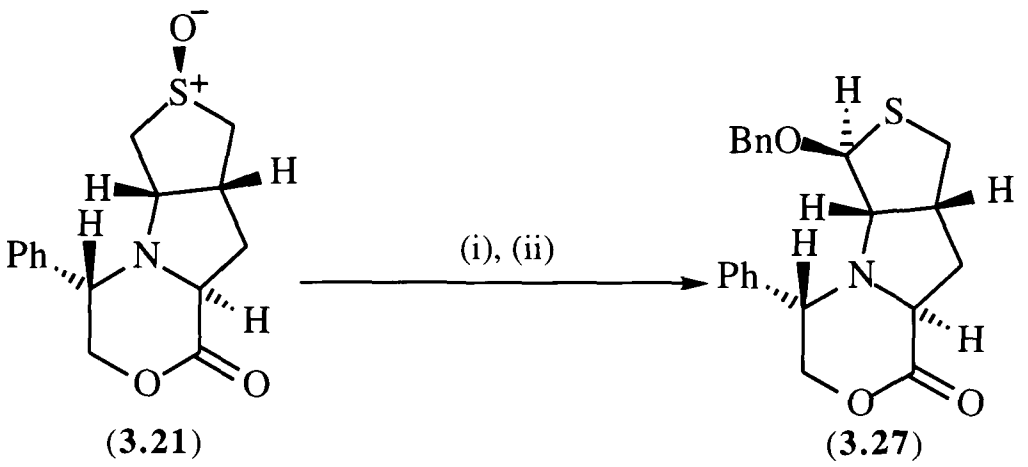


(3.24) (3.25) (3.23)

Scheme 3.13

Following the successful observation of a Pummerer rearrangement with total control over both the regio- and stereochemistry of the product, it was decided to apply this to the synthesis of a hydroxymethyl proline derivative (**3.26**). This would require the intermediate sulfinium ion (**3.25**) to be trapped by an oxygen nucleophile capable of subsequent ready deprotection. With regard to the conditions used for removing the chiral template it was decided to use benzyl alcohol as the trapping nucleophile, the benzyl group of which would be removed under the hydrogenolysis conditions employed.

The sulfoxide (**3.21**) was therefore stirred for four hours in dichloromethane with trifluoroacetic anhydride before quenching with benzyl alcohol (**Scheme 3.14**). Removal of the solvent followed by column chromatography furnished a single product, in 38% yield, whose ^1H n.m.r. and mass spectrometric data were consistent with that of the required rearranged product. The absence of infra-red absorptions characteristic of a sulfoxide provided further evidence, and two dimensional n.m.r. coupled with the use of n.O.e. experiments allowed total structural and stereochemical assignment of the product as that of the rearranged sulfoxide (**3.27**). The stereochemistry at C_3 was initially inferred from the analogous methyl compound, with further evidence being provided by the lack of coupling between the protons at C_2 and C_3, and the small enhancement (3.7%) of the C_3 proton on irradiation of the proton at C_2.

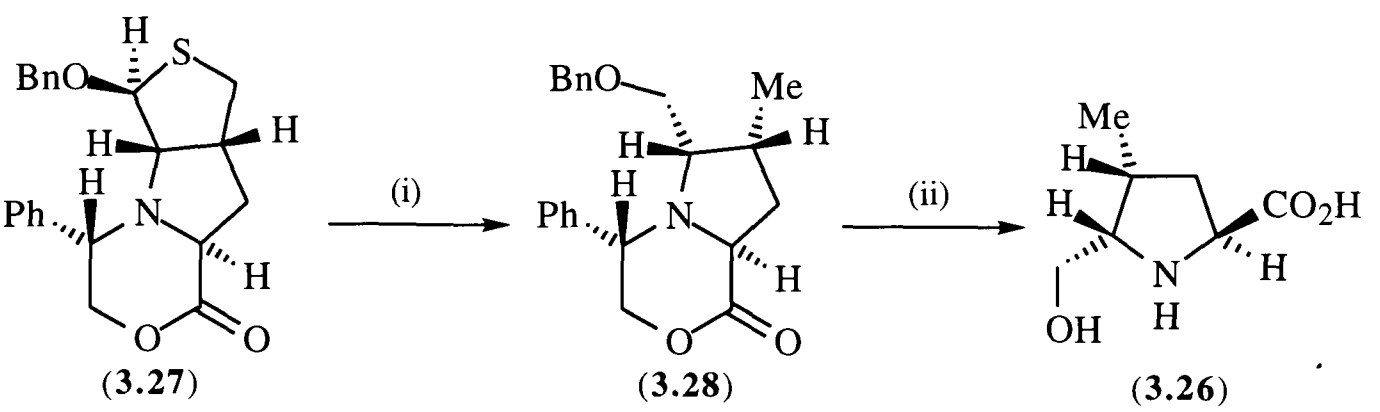


(3.21) (3.27)

(i) TFAA, DCM, r.t., (ii) BnOH, 38%.

Scheme 3.14

The rearranged cycloadduct (**3.27**) was then treated with Raney® nickel in refluxing acetone in order to remove the sulfur atom (**Scheme 3.15**). Thus a 12 hour reflux followed by filtration and column chromatography furnished a colourless oil whose ^1H n.m.r. and mass spectrometric data were consistent with the desulfurised product (**3.28**), isolated in 57% yield. Removal of the template and *O*-benzyl group was achieved simultaneously, as expected, using the standard conditions for template removal. Filtration to remove the catalyst and evaporation of the solvent was followed by trituration with diethyl ether to furnish a colourless powder, in 79% yield, whose ^1H n.m.r. and mass spectrometric data were consistent with the required proline derivative (**3.26**) (**Scheme 3.15**).



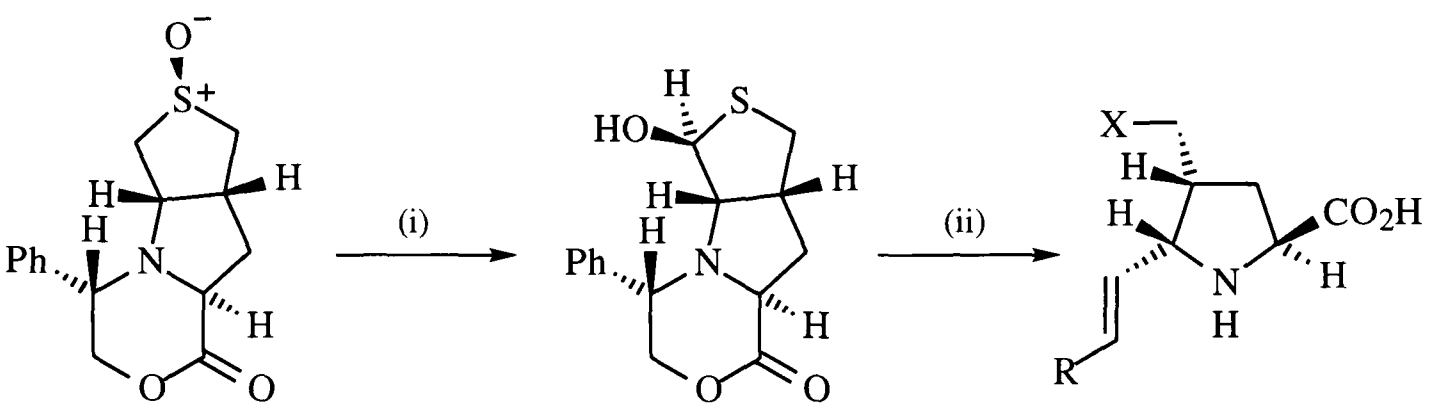
(3.27) (3.28) (3.26)

(i) Raney® nickel, reflux acetone, 38%, (ii) H_2 5 bar, $Pd(OH)_2$/ C, TFA, wet methanol, 79%.

Scheme 3.15

The intramolecular cycloaddition coupled with the Pummerer rearrangement therefore provides a convenient method of rapidly assembling functionalised stereocentres around the proline ring. Although the observed yield is low, optimisation of the conditions should allow this to be increased. Suitable variation of the nucleophile would allow this method to be applied

to the synthesis of a range of proline derivatives. Subsequent further elaboration of the rearrangement product *via* for example Wittig reaction (**Scheme 3.16**) would allow rapid access to highly functionalised prolines. Similarly use of substituted alkenes in the original generation of the cycloadduct would allow the introduction of substituents at the 3- position of the proline ring.

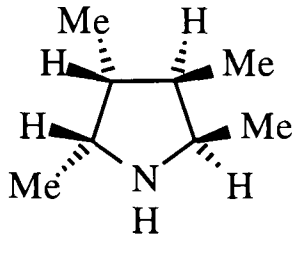


(i) Pummerer rearrangement, (ii) Wittig reaction (iii) deprotection.

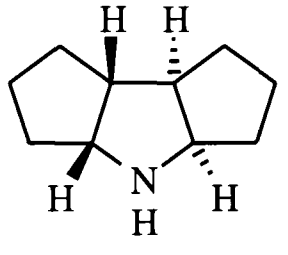
Scheme 3.16

3.4 Synthesis of a C_2-Symmetric Pyrrolidine.

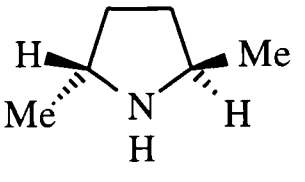
Having applied the Pummerer rearrangement to the synthesis of the hydroxymethyl proline derivative (**3.26**) it was decided to attempt the synthesis of the C_2 symmetric pyrrolidine derivative (**3.29**). C_2 symmetric derivatives of this type, for example (**3.30**) and (**3.31**), have had a number of applications as both chiral bases and auxiliaries.[20] However the syntheses of many of these pyrrolidines are long, thus limiting their availability and therefore their use. It was considered that the intramolecular cycloaddition methodology would be particularly amenable to the rapid construction of a derivative of this type.



(3.29)

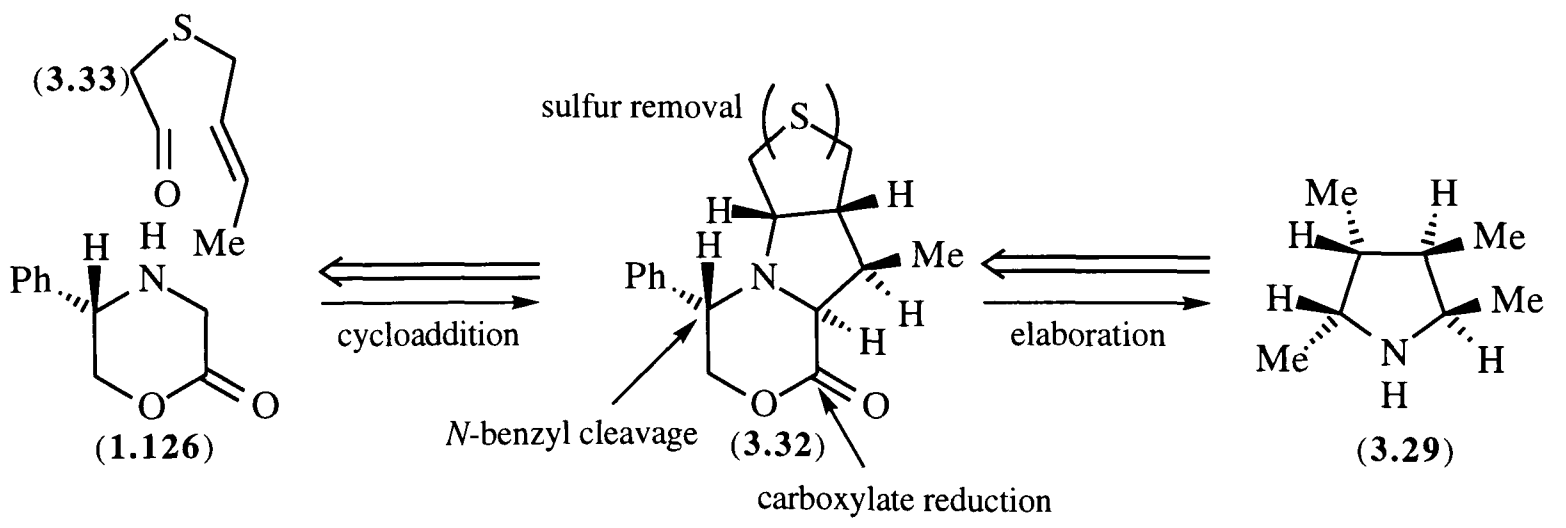


(3.30)



(3.31)

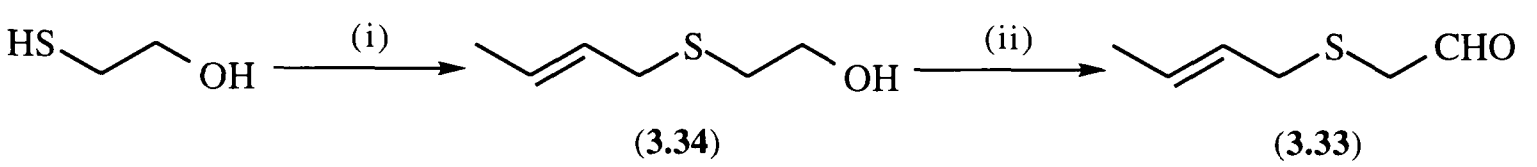
Analysis of the relative stereochemistry of the pyrrolidine (**3.29**) showed that the required *syn*- relationship between the methyl substituents at C_4 and C_5 would automatically be adopted on formation of the *cis*- fused ring junction in the cycloadduct (**3.32**). The transition state for cycloaddition showed that the C_3 methyl group would be positioned on the β- face of the cycloadduct if the double bond of the aldehyde precursor (**3.33**) had an *E*- relationship. The C_2 methyl group would be derived from reduction of the lactone carbon (**Scheme 3.17**).



Scheme 3.17

Following cycloaddition it was envisaged that diisobutylaluminium hydride reduction of the lactone, followed by formation of a dithiane, would result in a precursor that could be fully deprotected using Raney® nickel. It was therefore decided to synthesise the required aldehyde (**3.33**) using the methodology adopted for the unsubstituted aldehyde (**3.18**).

Stirring mercaptoethanol with crotyl bromide and potassium carbonate in dimethylformamide, followed by extraction and distillation furnished the thio alcohol (**3.34**) in 71% yield. Subsequent oxidation to the aldehyde (**3.33**) was effected in 27% yield by stirring with pyridinium chlorochromate and powdered molecular sieves in dichloromethane, followed by filtration through silica and distillation (**Scheme 3.18**). The yield of the oxidation was again disappointing, however investigation of alternative oxidation systems showed no enhancement in yield.

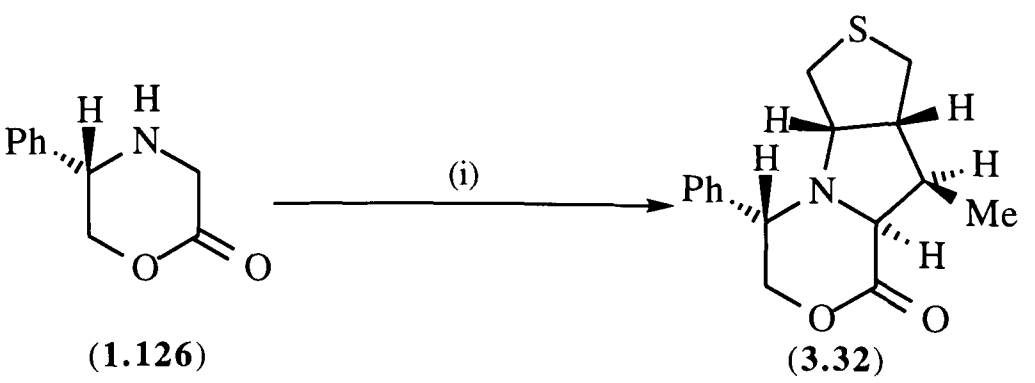


(3.34) **(3.33)**

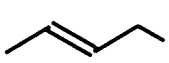
(i) Br, K_2CO_3, DMF, r.t., 71%, (ii) PCC, powdered molecular sieves, DCM, r.t., 27%.

Scheme 3.18

The thio aldehyde (**3.33**) was then refluxed with morpholinone (**1.126**), under the usual conditions, until t.l.c. analysis indicated the absence of starting material (**Scheme 3.19**). Usual work up followed by column chromatography furnished a single adduct (**3.32**) in 70% yield whose ^1H n.m.r. and mass spectrometric data were consistent with that of the required cycloadduct. The stereochemistry was assigned on the basis of n.O.e. experiments, and subsequently confirmed by X-ray crystallography (**Figure 3.5**).

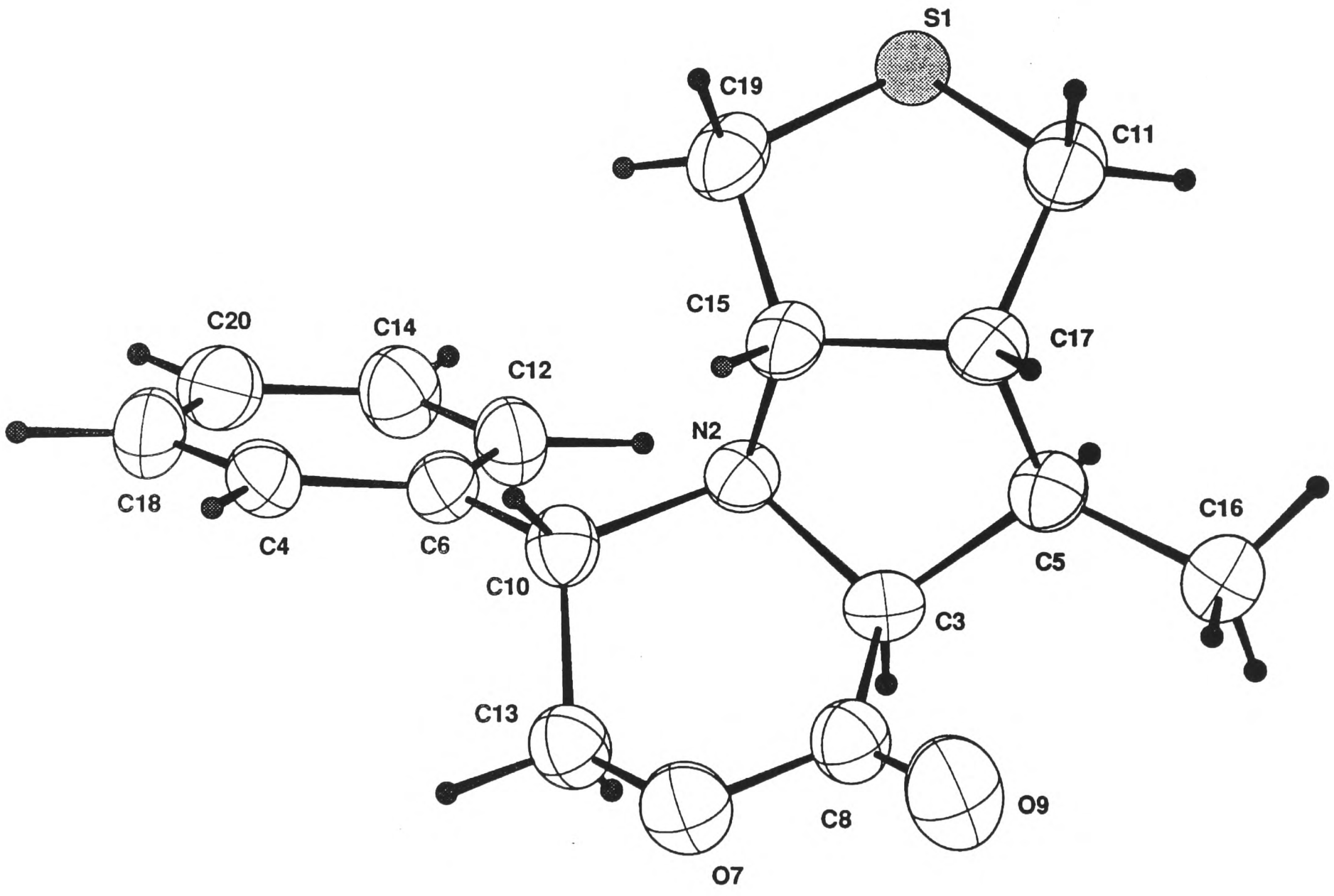


(1.126) **(3.32)**

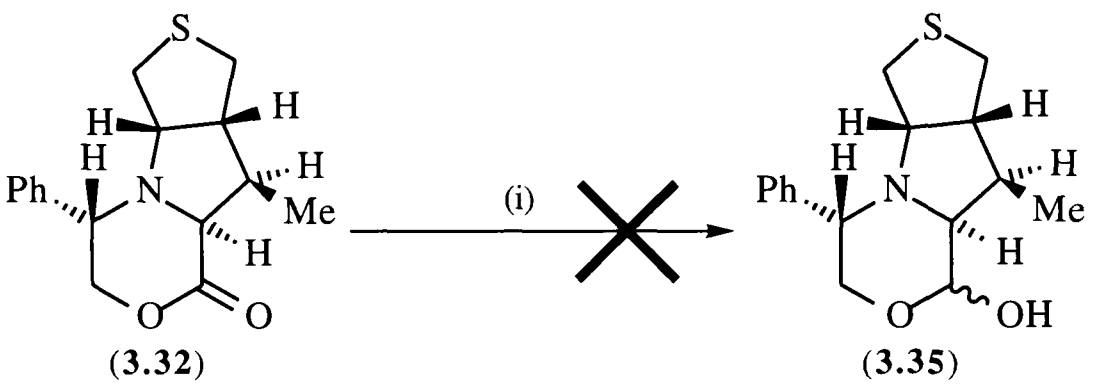
(i)  CHO(**3.33**), molecular sieves, reflux toluene, 70%.

Scheme 3.19

Figure 3.5
Crystal Structure for Compound (3.32)



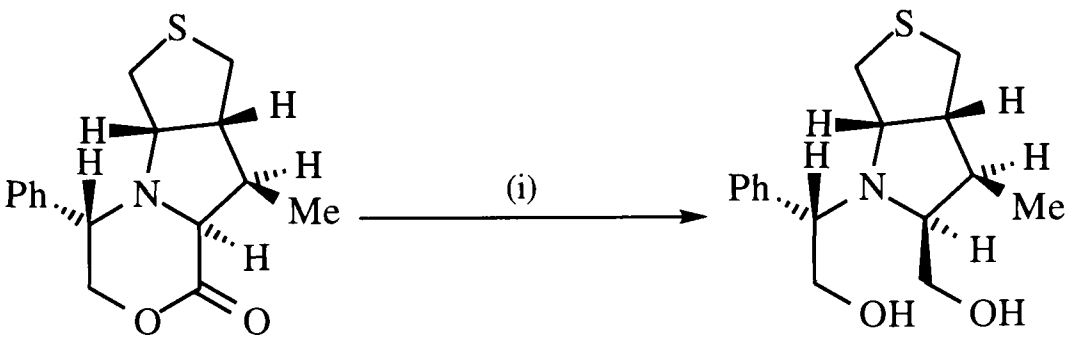
Having achieved the synthesis of the required cycloadduct (**3.32**), and unequivocally demonstrated the stereochemistry, attempted elaboration to the pyrrolidine (**3.29**) was begun. The cycloadduct (**3.32**) was therefore stirred with diisobutylaluminium hydride in tetrahydrofuran in order to effect conversion to the lactol (**3.35**) (**Scheme 3.20**). Disappointingly however, t.l.c. analysis after 12 hours indicated only the presence of starting material, which was confirmed by work up and ^{1}H n.m.r. spectroscopic analysis.



(i) DIBAL, stir THF, -78°C.

Scheme 3.20

It has been previously demonstrated that the cycloadduct (**3.15**), lacking the C_7 methyl group, can be desulfurised and debenzylated simultaneously, although in low yield, by refluxing with Raney® nickel in ethanol.[1] The low yield was attributed to complexation of the resultant amino acid to the nickel catalyst,[21] and it was considered that this effect could be diminished by reduction of the acid to the corresponding alcohol. The cycloadduct (**3.32**) was therefore refluxed with lithium aluminium hydride in diethyl ether until t.l.c. analysis indicated the absence of starting material. The reaction was quenched, extracted, and the solvent removed to furnish a colourless oil, in an excellent 97% yield, whose ^{1}H n.m.r. and mass spectrometric data were consistent with that of the required diol (**3.36**) (**Scheme 3.21**). The infra-red spectrum additionally indicated the lack of any carbonyl absorptions and the presence only of absorptions attributable to the hydroxyl groups.

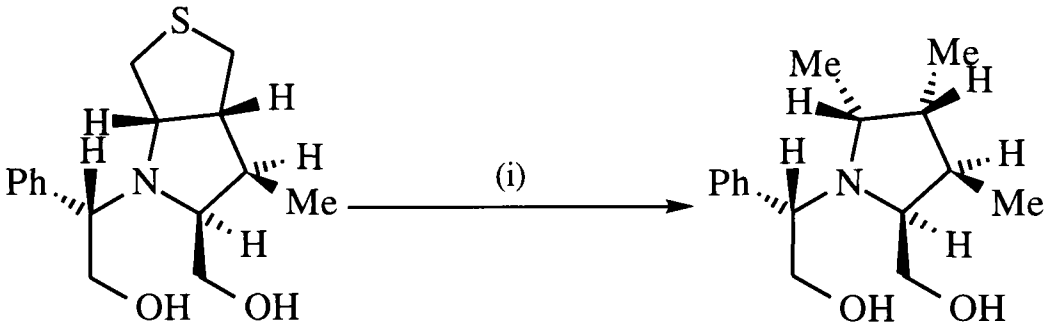


(3.32) **(3.36)**

(i) $LiAlH_4$, reflux Et_2O, 97%.

Scheme 3.21

The diol (**3.36**) was then treated with Raney® nickel in refluxing ethanol until t.l.c. analysis indicated the absence of starting material (**Scheme 3.22**). Usual work up afforded a colourless solid whose ^1H n.m.r. and mass spectrometric data indicated that the *N*-benzyl group was still present. The data was however consistent with that of the desulfurised diol (**3.37**), isolated in a disappointing 45% yield. The low yield may be a result of efficient complexation to nickel of any aminol formed, although hydrolysis of the Raney® nickel used in the reaction followed by extraction failed to isolate any of this product.[21]



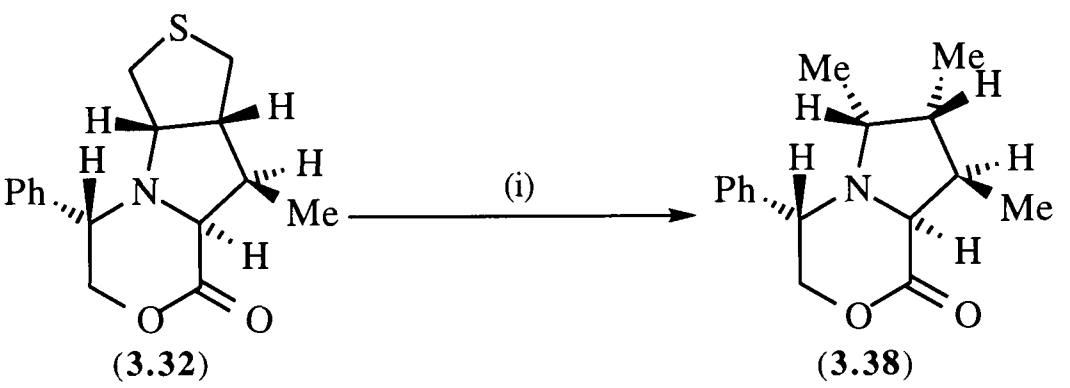
(3.36) **(3.37)**

(i) Raney® nickel, reflux ethanol, 45%.

Scheme 3.22

The low yield in the desulfurisation, coupled with the lack of debenzylation, meant that another route was required. If complexation to the nickel were causing the low yield then performing the reaction in the absence of groups capable of complexing to the nickel should result in an increased yield. Accordingly, the cycloadduct (**3.32**) was refluxed in acetone with Raney® nickel until t.l.c. analysis indicated the absence of starting material (**Scheme 3.23**). Usual work up followed by column chromatography afforded a 75% yield of a colourless solid whose ^1H n.m.r. and mass spectrometric data were consistent with that of the desulfurised

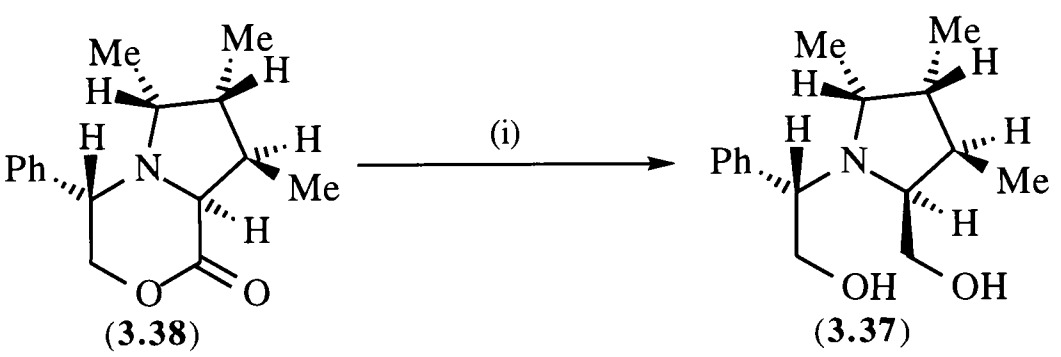
adduct (**3.38**). The stereochemistry of this adduct was initially inferred from the stereochemistry of the cycloadduct (**3.32**), then confirmed through n.O.e. experiments.



(i) Raney® nickel, reflux acetone, 75%.

Scheme 3.23

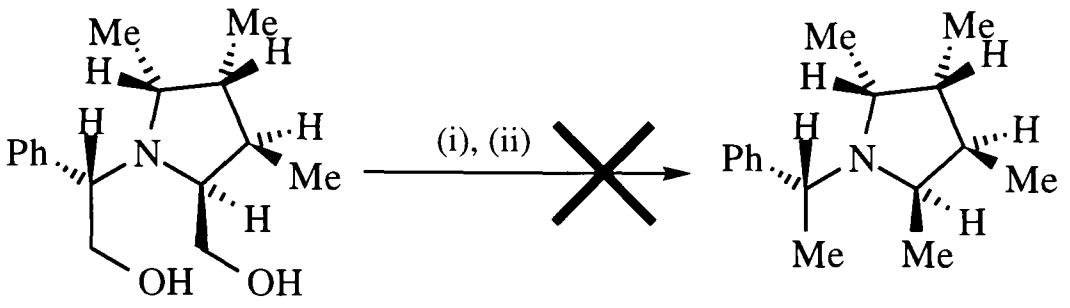
Reduction to the diol was achieved by refluxing the desulfurised adduct (**3.38**) with lithium aluminium hydride in diethyl ether until t.l.c. analysis indicated the absence of starting material (**Scheme 3.24**). The reaction was quenched, extracted and the solvent removed to furnish a colourless solid, in quantitative yield, whose spectroscopic data was consistent with that of the previously prepared diol (**3.37**).



(i) $LiAlH_4$, reflux Et_2O, quant.

Scheme 3.24

The remaining required steps were to effect deoxygenation and debenzylate the nitrogen, and it was decided to attempt initial double deoxygenation of the diol (**3.37**) to give the phenylethylamine derivative (**3.39**). According to the method of Morita,[22] the diol (**3.37**) was refluxed in acetonitrile with trimethylsilylchloride and sodium iodide for 1 hour. Activated zinc and acetic acid were then added, and the suspension refluxed for a further 4 hours (**Scheme 3.25**). Work up however resulted only in recovery of starting material.

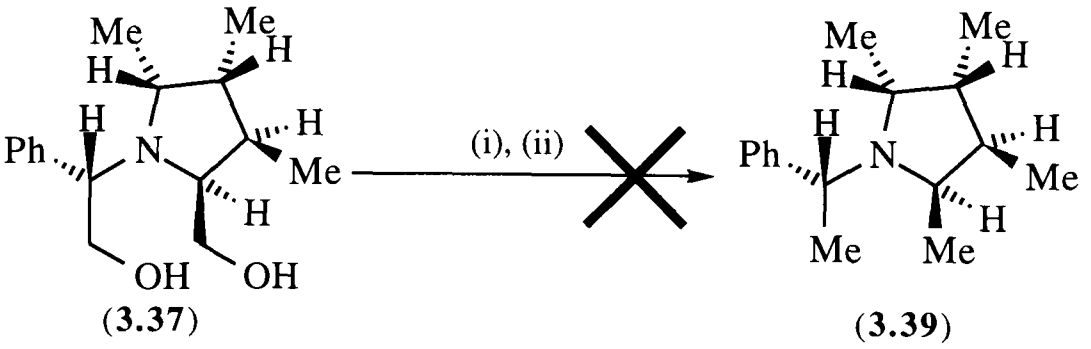


(3.37) **(3.39)**

(i) TMSCl, NaI, reflux MeCN, (ii) Zn, AcOH, reflux MeCN.

Scheme 3.25

A wide variety of radical methods exist for alcohol deoxygenation. These commonly involve coupling the alcohol to a thiocarbonyl derivative followed by treatment with tributyltin hydride.[23] Accordingly the diol (**3.37**) was stirred in dichloromethane with phenyl thionochloroformate and dimethylaminopyridine until t.l.c. analysis indicated the absence of starting material. Usual work up however failed to isolate the coupled product, and therefore it was decided to attempt deoxygenation on the crude material. The diol was therefore again stirred in dichloromethane with phenyl thionochloroformate and dimethylaminopyridine, and the solvent then removed *in vacuo*. The residue was dissolved in toluene, AIBN and tributyltin hydride added, and the resultant solution refluxed for 12 hours (**Scheme 3.26**). However, following usual work up neither starting material (**3.37**) or the desired phenylethylamine derivative (**3.39**) could be isolated.



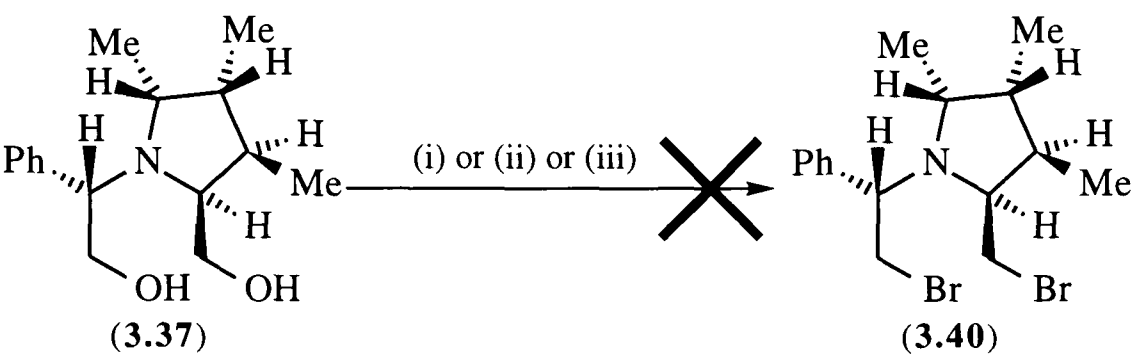
(3.37) **(3.39)**

(i) PhOC(=S)Cl, DMAP, stir DCM r.t., (ii) AIBN, $HSnBu_3$, reflux toluene.

Scheme 3.26

Alternative alkyl radical precursors are the corresponding bromides, and it was therefore decided to attempt the synthesis of the dibromo species (**3.40**). The diol (**3.37**) was therefore stirred with carbon tetrabromide and triphenylphosphine in acetonitrile for 12 hours,[24] however no bromination was observed with only starting material being recovered. This was

assumed to be a result of the low reactivity of the brominating reagent, and the diol (**3.37**) was therefore stirred in toluene with the more reactive phosphorus tribromide and pyridine.[25] Aqueous quench followed by extraction with diethyl ether however furnished only degraded material. Similar results were observed on refluxing the diol (**3.37**) with refluxing hydrobromic acid (**Scheme 3.27**).

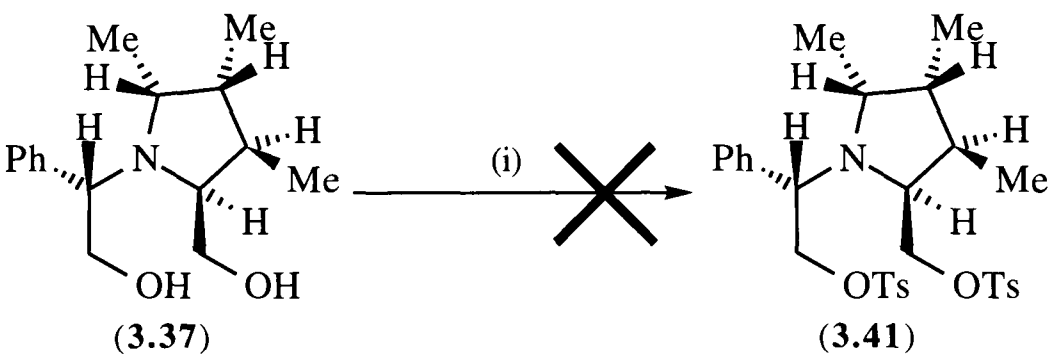


(3.37) **(3.40)**

(i) CBr_4, PPh_3, stir MeCN r.t., (ii) PBr_3, pyridine, stir toluene r.t., (iii) reflux 48% HBr.

Scheme 3.27

As a final method it was decided to attempt to activate the alcohol generating a better leaving group, which could be removed on treatment with lithium aluminium hydride. The diol (**3.37**) was accordingly stirred with tosyl chloride and pyridine in dichloromethane (**Scheme 3.28**), however following work up neither the tosylated alcohol (**3.41**) or the starting material (**3.37**) could be identified.



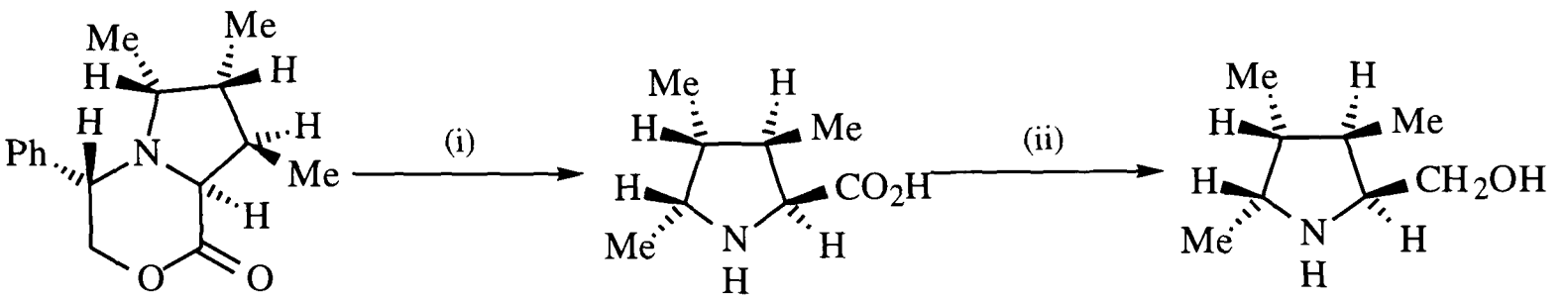
(3.37) **(3.41)**

(i) TsCl, pyridine, stir DCM r.t.

Scheme 3.28

The problems encountered in attempting deoxygenation were ascribed to the diol system, and it was therefore decided to remove one of the hydroxyl groups before attempting the deoxygenation step. Removal of the benzyl group from the diol (**3.37**) would generate the problem of separating the resulting aminol (**3.43**) from the 2-phenyl ethanol produced. It was therefore decided to attempt initial debenzylation of the desulfurised cycloadduct to give the

amino acid (**3.42**). The desulfurised cycloadduct (**3.38**) was therefore stirred in wet methanol with Pearlman's catalyst and trifluoroacetic acid under a 5 bar atmosphere of hydrogen (**Scheme 3.29**). Usual work up followed by recrystallisation from diethyl ether gave a colourless solid, in 90% yield, whose ^1H n.m.r. and mass spectrometric data were consistent with the required amino acid (**3.42**), isolated in 90% yield. The amino acid (**3.42**) was then refluxed in tetrahydrofuran with boron trifluoride-etherate and borane-dimethyl sulfide complex according to the procedure previously reported by Evans (**Scheme 3.29**).[26] The reaction was quenched, then extracted to furnish a colourless oil whose ^1H n.m.r. and mass spectrometric data were consistent with the required aminol (**3.43**), isolated also in 90% yield.

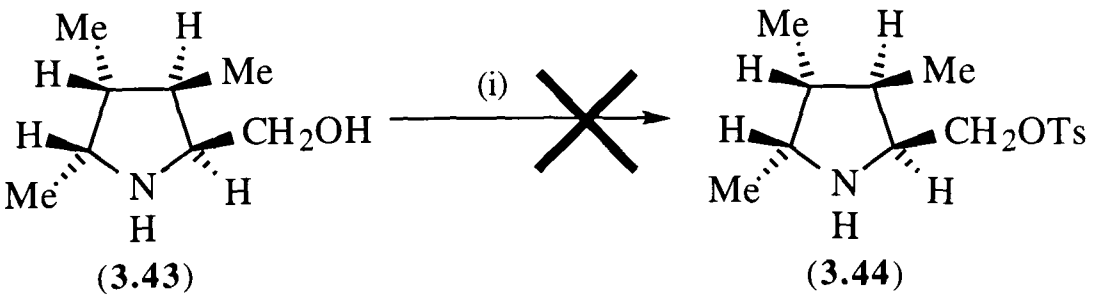


(3.38) **(3.42)** **(3.43)**

(i) H_2 5 bar, $Pd(OH)_2$/ C, TFA, wet methanol, 90%, (ii) $BF_3.Et_2O$, $BH_3.SMe_2$, reflux THF, 90%.

Scheme 3.29

Having eliminated the potential problem caused by the diol system the final deoxygenation was attempted. Although treatment with tosyl chloride may result in *N*- rather than *O*- tosylation it was nevertheless decided to attempt this route. Accordingly the aminol (**3.43**) was treated with 1 equivalent of tosyl chloride and pyridine in dichloromethane. However, following usual work up neither the tosylated alcohol (**3.44**) or the starting material (**3.43**) could be identified (**Scheme 3.30**).



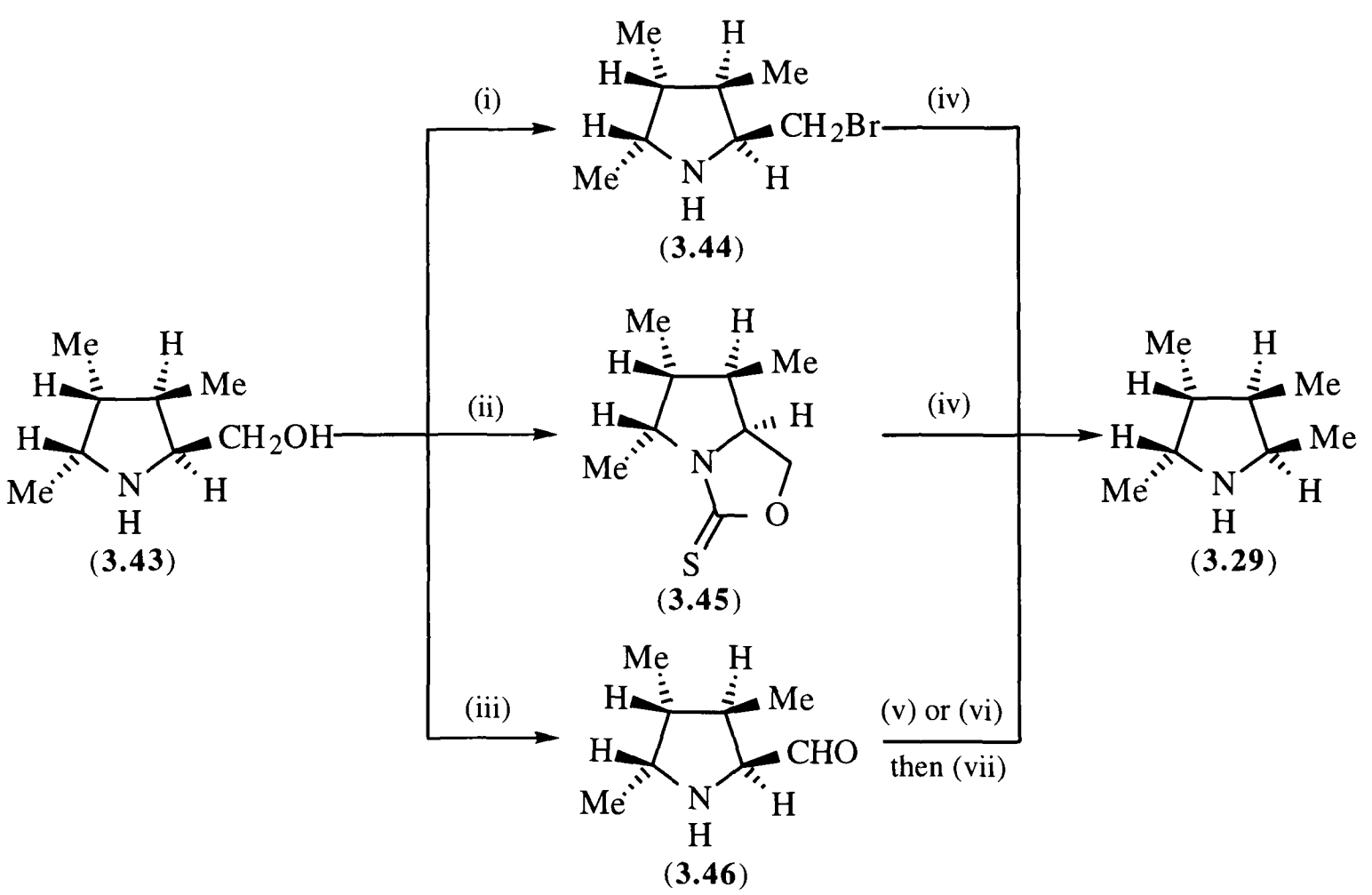
(3.43) **(3.44)**

(i) TsCl, pyridine, DCM.

Scheme 3.30

Unfortunately, due to time constraints and unanticipated problems encountered in this synthesis it has not proved possible to complete the important final step. The synthesis of a precursor to the tetramethyl-pyrrolidine (**3.29**), aminol (**3.43**), has been achieved in an overall yield of 43% from (5*S*)-phenylmorpholinone (**1.126**). Although the majority of the synthesis has proceeded as anticipated, the final step, namely deoxygenation of the primary alcohol, has proved to be significantly more difficult than originally expected.

In order to optimise conditions for this final, crucial step, it is proposed that commercially available pyrrolidine methanol should be used as a model system. Direct methods of oxygen removal include conversion to the bromide (**3.44**) followed by radical debromination or radical reduction of the thione (**3.45**). Alternatively conversion to the aldehyde (**3.46**) followed by either dithiane or thio-aldehyde formation should allow Raney® nickel desulfurisation (**Scheme 3.31**).



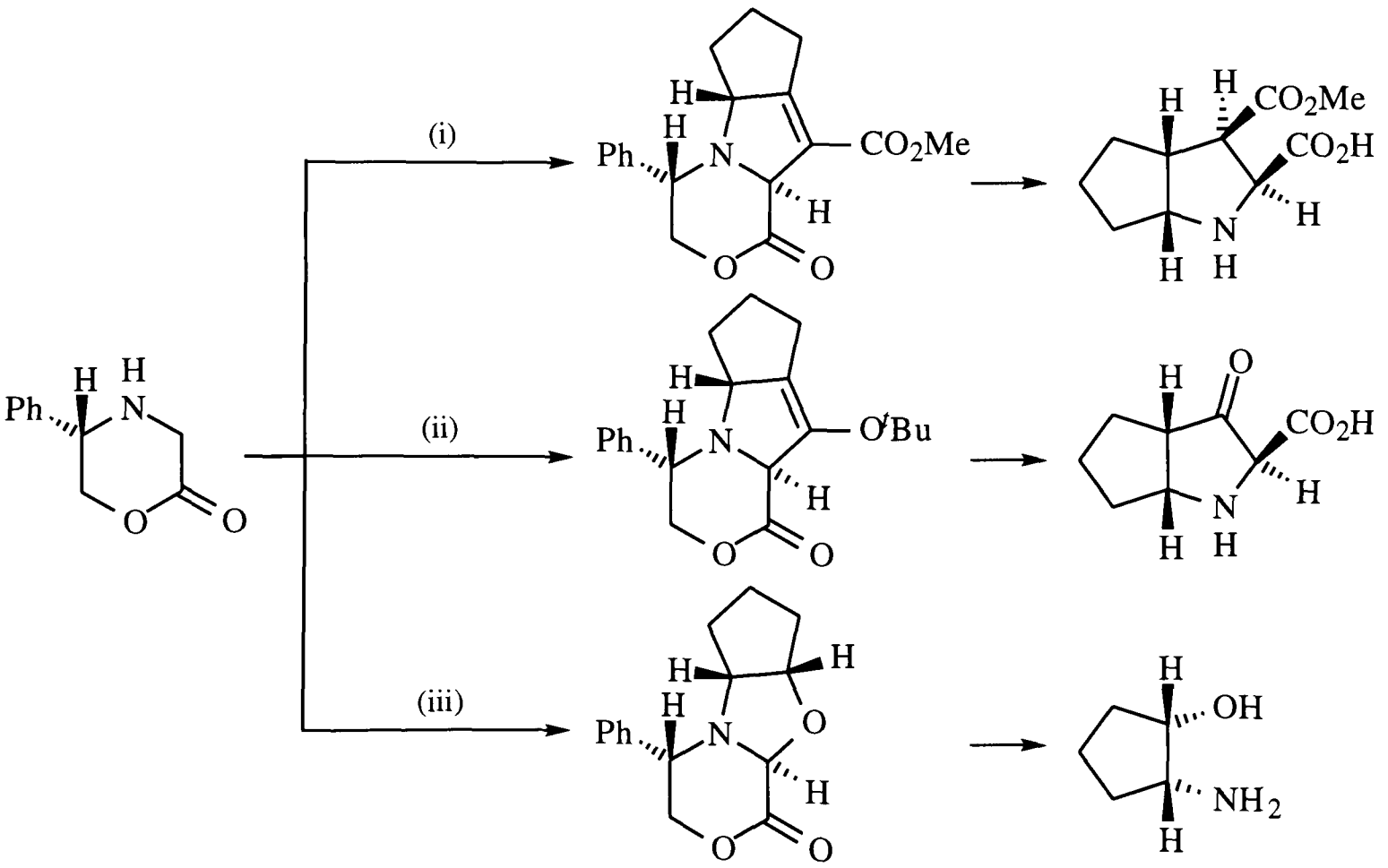
(i) bromination, (ii) $Cl_2C{=}S$, (iii) oxidation, (iv) AIBN, Bu_3SnH,
(v) Lawesson's reagent, (vi) $HSCH_2CH_2SH$, $BF_3.Et_2O$, (vii) Raney® nickel.

Scheme 3.31

3.4 Summary and Future Work.

The intramolecular cycloaddition of (5*S*)-phenylmorpholinone (**1.126**) has been shown to proceed efficiently to furnish cycloadducts with total stereocontrol. Heteroatom and non-carbocyclic chains may be used to link the aldehyde and the dipolarophile. However, the conformation of the linking chain plays a significant role in determining the efficiency of the reaction. The cycloadducts generated may be further elaborated, with the rigid structure allowing such operations to be carried out in a stereocontrolled manner, for example the Pummerer rearrangement. Attempts to exploit the methodology in the synthesis of a C_2 symmetric pyrrolidine were frustrated by the difficulty of achieving the final step.

Further investigation of the intramolecular cycloaddition may look at the use of alternative functionalised long chain aldehydes (**Scheme 3.32**). Such cycloaddition should generate cycloadducts from which a range of substituted bicyclic amino acids, not readily accessible by other routes, may be rapidly obtained. Such amino acids may be of use in investigating structure activity relationships for the ACE inhibitors referred to in Chapter One. Similarly use of dialdehydes may allow the synthesis of a range of β- amino alcohols.



Scheme 3.32

CHAPTER FOUR

Results and Discussion

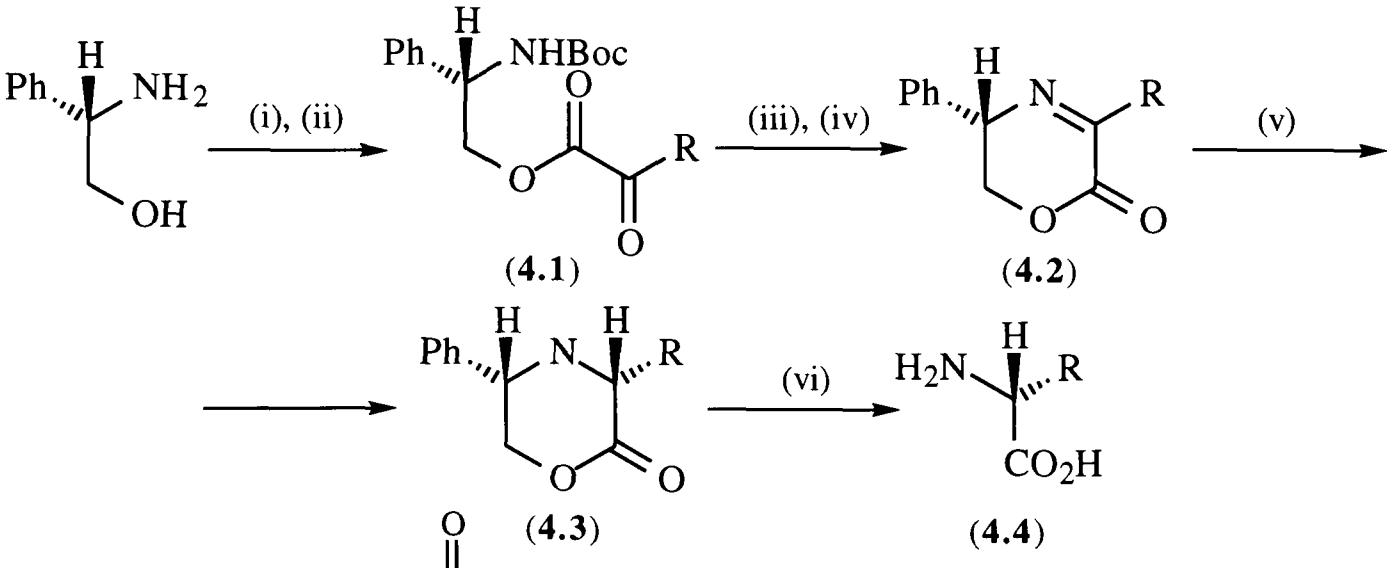
CHAPTER FOUR

[3+2] Dipolar Cycloadditions of (3*S*,5*R*)-Diphenylmorpholinone

4.1 Asymmetric Synthesis of α-Amino Acids.

The increasing importance of proteinogenic and non-proteinogenic α-amino acids has resulted in significant research effort being directed towards their synthesis in an optically pure form. Approaches have included asymmetric hydrogenation and amination, alkylation of chiral glycine equivalents and asymmetric Strecker reactions (See Introduction).

Within Harwood's group in Oxford two major strategies have been considered. The first exploited the stereoselective hydrogenation of morpholinone imines (**4.2**), formed *via* the condensation of esters (**4.1**), in an analogous fashion to the method of Sunjic.[1] Hydrogenation of the imine (**4.2**) gave excellent diastereoselectivity, generating the *syn*- substituted morpholinone (**4.3**) with a diastereomeric excess of 15 : 1. Subsequent hydrogenolysis of the *N*-benzyl bond was accompanied by ester hydrolysis to furnish the free amino acid (**4.4**) (**Scheme 4.1**). However this approach has not proved widely applicable with problems arising in both the esterification and cyclisation stages, and thus far has only allowed the synthesis of (2*S*)-2-amino butanoic acid (**4.4**, R = Et).[2]



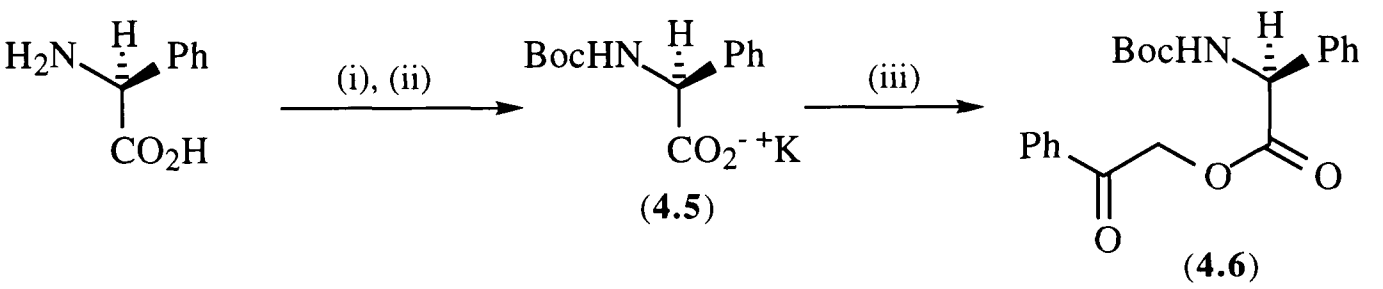
(i) Boc_2O, (ii) R CO_2H, (iii) 33% HBr/ AcOH, (iv) K_2CO_3, DCM,
(v) H_2, PtO_2, EtOAc, (vi) H_2 5bar, $Pd(OH)_2$/ C, TFA, wet methanol.

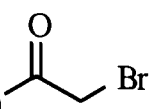
Scheme 4.1

The second approach to be examined, described in the introduction, was based on the application of the [3+2] dipolar cycloaddition of chiral azomethine ylids. Previous work had demonstrated the synthesis of the required diphenyl substituted template (**1.168**) using the method of Sunjic,[1] and also the possibility of subsequent cycloaddition.[3] It was decided to build on this result as the start of an investigation into the cycloaddition profile of the (3*S*,5*R*)-diphenylmorpholinone template (**1.168**).

4.2 Preparation of the (3*S*,5*R*)-Diphenylmorpholin-2-one Template (1.168).

The required template was conveniently prepared on a multigram scale *via* a high yielding six step sequence. (*S*)-Phenyl glycine was *N*- protected by standard methods with di-*tert*-butyldicarbonate and sodium hydroxide in 50% aqueous dioxan,[4] then immediately converted to the potassium salt (**4.5**) by stirring with potassium hydroxide in methanol. Subsequent alkylation with α-bromoacetophenone in dimethylformamide followed by column chromatography furnished the ester (**4.6**) in 66% overall yield from phenyl glycine (**Scheme 4.2**).



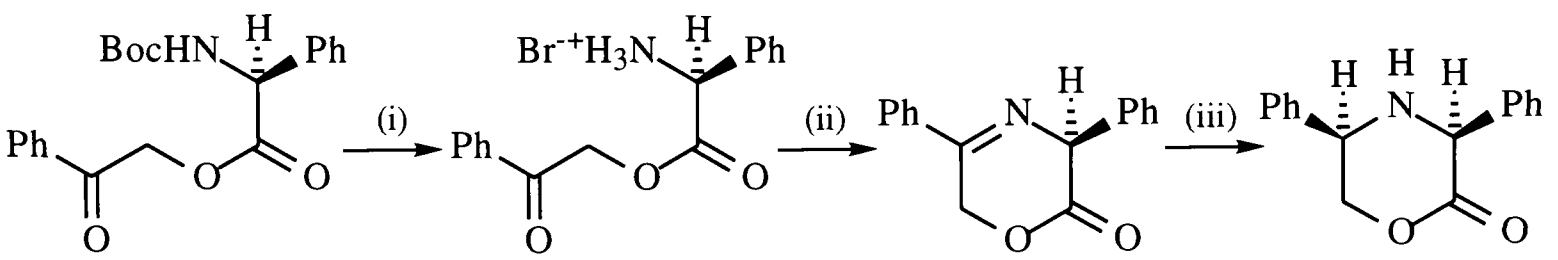
(i) Boc_2O, NaOH, 50% dioxan/ H_2O, (ii) KOH, methanol, 89%, (iii) 

, DMF, 74%.

Scheme 4.2

In order to effect deprotection of the amine functionality the ester (**4.6**) was dissolved in 33% HBr in acetic acid and stirred until evolution of carbon dioxide ceased. The hydrobromide salt (**4.7**) was precipitated by the addition of diethyl ether and light petroleum, filtered, then added without further purification to a 0.2 M sodium acetate/ acetic acid buffer solution. The imine (**4.8**) precipitated as a pale yellow solid, and was removed by filtration. Hydrogenation of the unpurified imine furnished, after column chromatography,

diphenylmorpholinone (**1.168**) in 41% overall yield from (*S*)-phenyl glycine (**Scheme 4.3**). In contrast to the observation of Sunjic that hydrogenation of the imine (**4.8**) resulted in concomitant hydrogenolysis,[1] we have only ever observed clean stereoselective hydrogenation to furnish diphenylmorpholinone (**1.168**).



(4.6) **(4.7)** **(4.8)** **(1.168)**

(i) 33% HBr in acetic acid, 81%, (ii) 0.2 M NaOAc/AcOH, 89%, (iii) H_2, Pd/ C, EtOAc, 86%.

Scheme 4.3

Spectroscopic data for the diphenylmorpholinone (**1.168**) was in accordance with the previously prepared sample, with the exception of the optical rotation which was significantly greater than the previously measured value ($[\alpha]_D^{20}$ +80, c 0.88 $CHCl_3$, lit (enantiomer) $[\alpha]_D^{20}$ -5, c 0.88 $CHCl_3$).[3] As the optical rotation was our criterion of enantiomeric purity this was a cause for concern, and an alternative assessment method was therefore required.

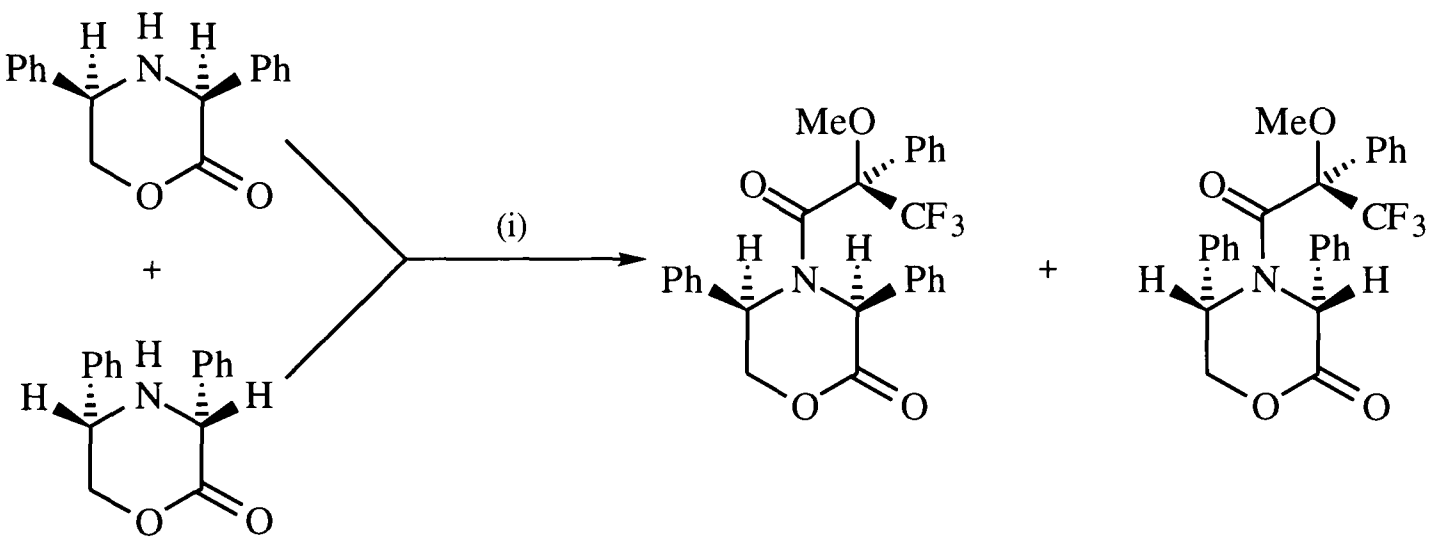
4.3 Enantiomeric Purity Determination for Diphenylmorpholinone (1.168).

A wide variety of methods exist for the determination of enantiomeric purity although most rely on the same principle, that of converting the indistinguishable enantiomeric mixture to a distinguishable diastereomeric mixture. Chiral shift n.m.r. reagents complex to the compound under investigation, thus converting the enantiomers into a pair of diastereomers, and thereby splitting signals in the n.m.r. spectrum.[5] $Er(fod)_3$, $Eu(fod)_3$ and Eu(tfc) were therefore added to solutions of diphenylmorpholinone (**1.168**) in deuterochloroform and deuterobenzene, however no useful shift was obtained before excessive peak broadening occurred.

An alternative method for determining the enantiomeric purity of a substance involves physical coupling of the substrate to a chiral auxiliary, again producing a mixture of

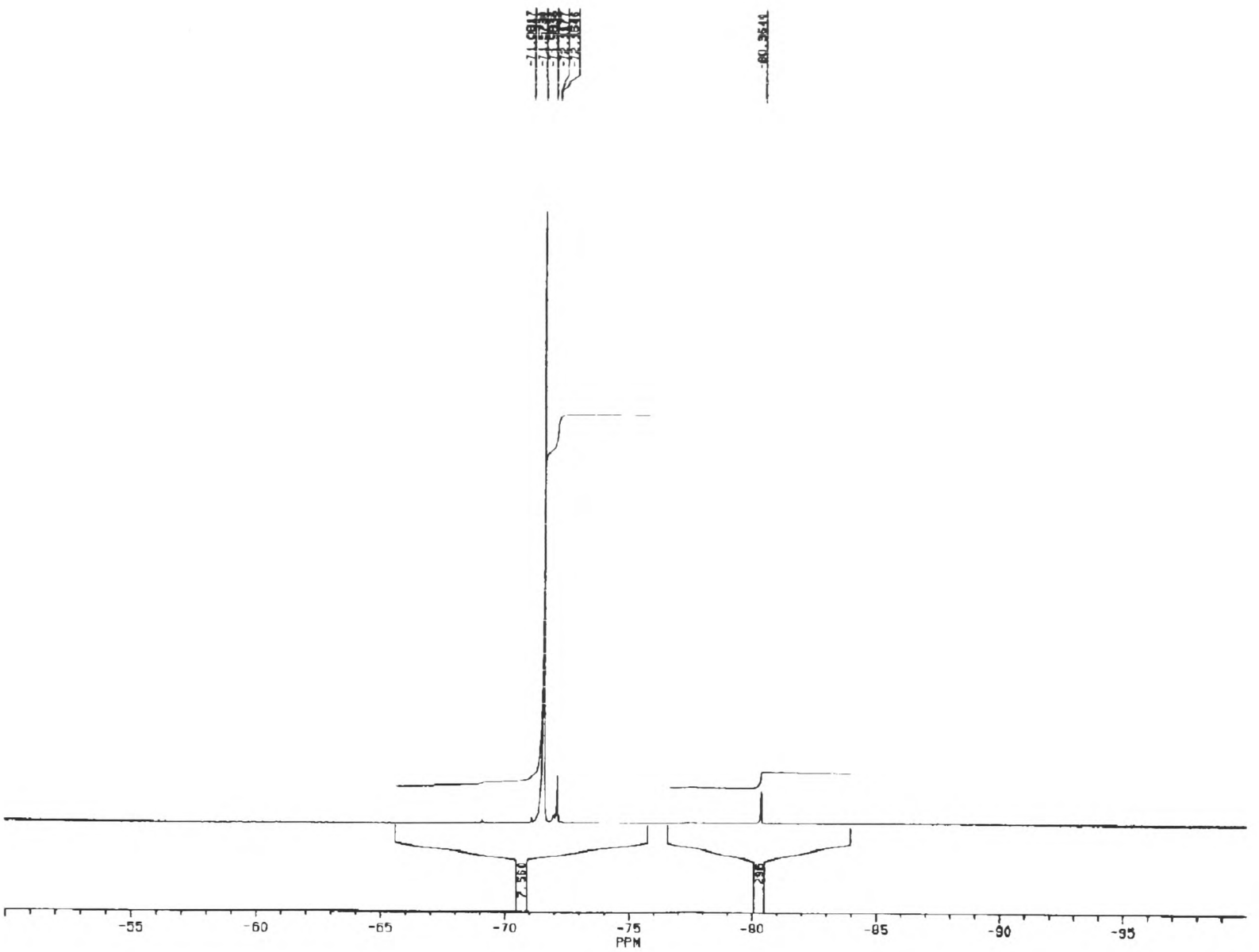
diastereomers. The n.m.r. spectra are therefore no longer identical, and measurement of the integral ratio from the n.m.r. spectra gives a measurement of the optical purity of the sample.[5] The chiral auxiliary chosen was Mosher's acid in which the ^{19}F spectra was observed.[6] In order to determine whether splitting is due to formation of diastereomers or some alternative feature, it is necessary to have a standard with which to compare the observed result. Formation of the Mosher's derivative with either racemic sample or racemic Mosher's acid should produce an equimolar mixture of diastereomers, and thus the integrals in the ^{19}F spectra should be equal.

Two sets of Mosher's derivatives were therefore prepared. The first was prepared from the sample of diphenylmorpholinone (**1.168**), of unknown optical purity, and racemic Mosher's acid chloride by stirring with pyridine in carbon tetrachloride. This would produce an equimolar mixture of diastereomers, and therefore provide a standard. The second was prepared from the diphenylmorpholinone (**1.168**) and chiral Mosher's acid chloride, to produce an unequal mixture of diastereomers, and allow the optical purity to be calculated (**Scheme 4.4**). The crude ^{19}F n.m.r. of the racemic sample showed three singlets, and these were assigned as being due to Mosher's acid and the two diastereomeric Mosher's amides (**Spectra 4.1**). The chiral sample displayed the same three signals in the ^{19}F n.m.r., although with differing intensities (**Spectra 4.2**). Subsequent analysis of the signal integrals suggested an enantiomeric excess of >80%.

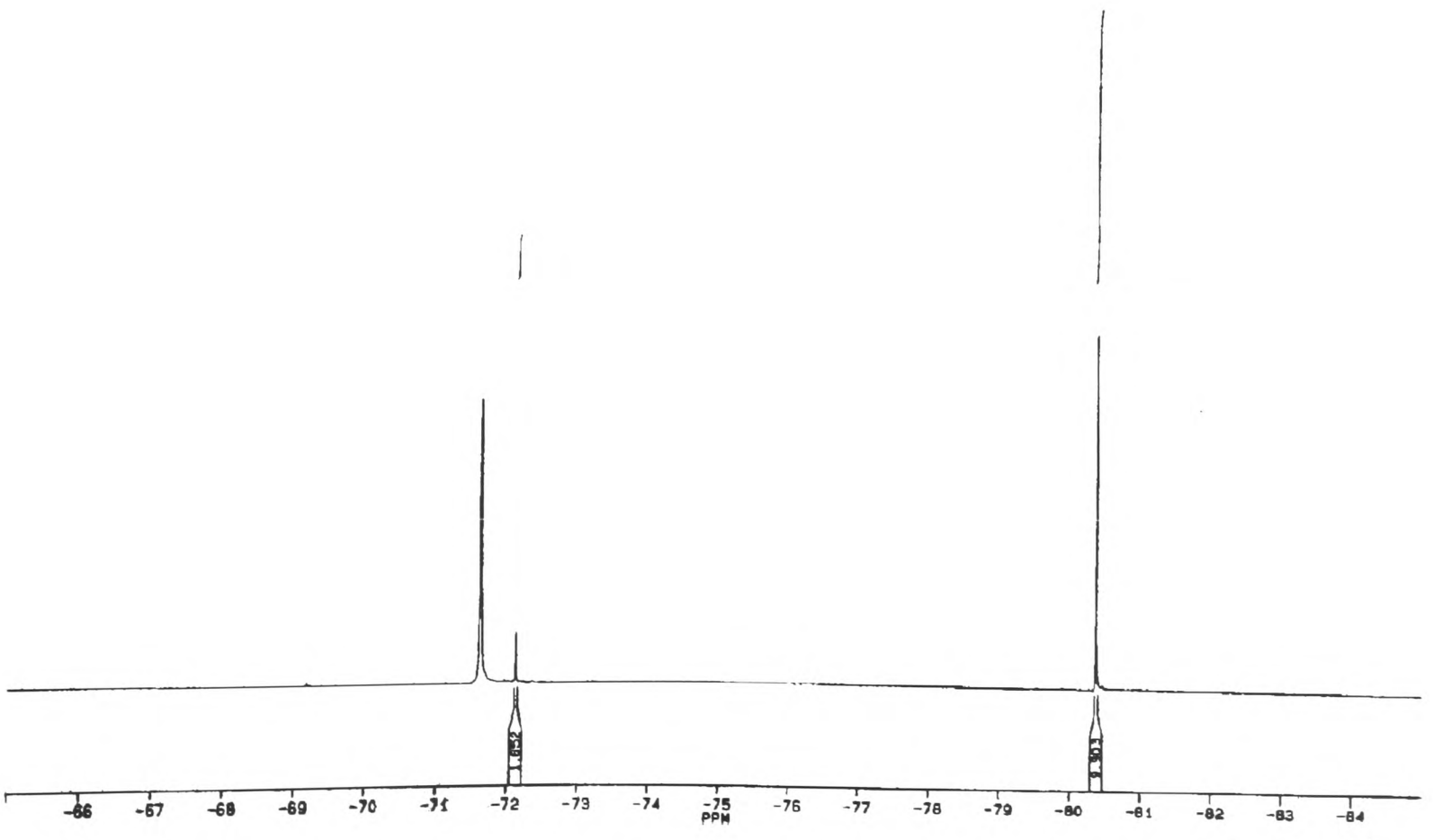


(i) (*R*)-Mosher's acid chloride or (±)-Mosher's acid chloride, pyridine, carbon tetrachloride, r.t.

Scheme 4.4

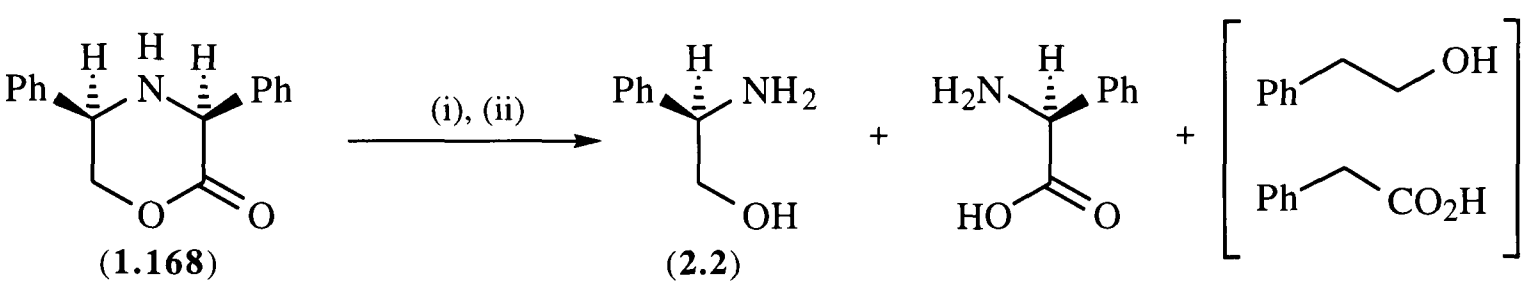


Spectra 4.1



Spectra 4.2

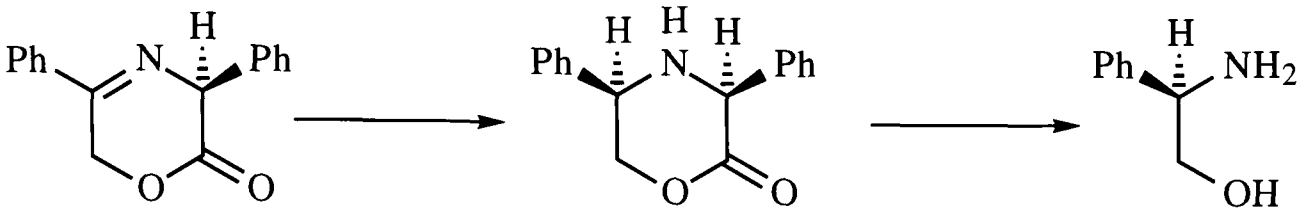
In order to unambiguously assign the ^{19}F n.m.r. spectra, purification of the crude reaction mixture was attempted. Unfortunately all such attempts resulted only in isolation of diphenylmorpholinone (**1.168**), suggesting that hydrolysis of the Mosher's amide was taking place. However a parallel study performed within this group by Diaz, using a different technique, corroborated the value for the enantiomeric excess.[7] This method involved the hydrogenolysis of the chiral (3*S*,5*R*)-diphenylmorpholinone (**1.168**) to the parent phenyl glycine and phenyl glycinol (**2.2**). These were separated by ion exchange then the optical rotation measured (**Scheme 4.5**).



(i) H_2 5 bar, $Pd(OH)_2$/ C, TFA, wet methanol, (ii) ion exchange.

Scheme 4.5

The origin of the loss of optical purity has been investigated, and shown to arise on hydrogenation of the imine (**4.8**).[7] If the catalyst promotes double bond migration before hydrogenation then the chirality at C_3 is lost. Subsequent hydrogenation, although still highly diasteroselective, produces a mixture of enantiomers. A range of other catalysts and reduction methods have been surveyed by Diaz,[7] however none of these showed any advantage in terms of optical purity or *syn-*/ *anti-* ratio (**Table 4.1**). The quality of the palladium on carbon catalyst was also found to have an effect on the stereochemical outcome, with older, less active, catalysts giving the best results. These observations may have prompted the original suggestion of Sunjic that the result of this hydrogenation was degradation of the morpholinone.[1] Despite the lack of enantiomeric purity in the prepared sample, it was decided to commence an investigation into the cycloaddition profile of the template.



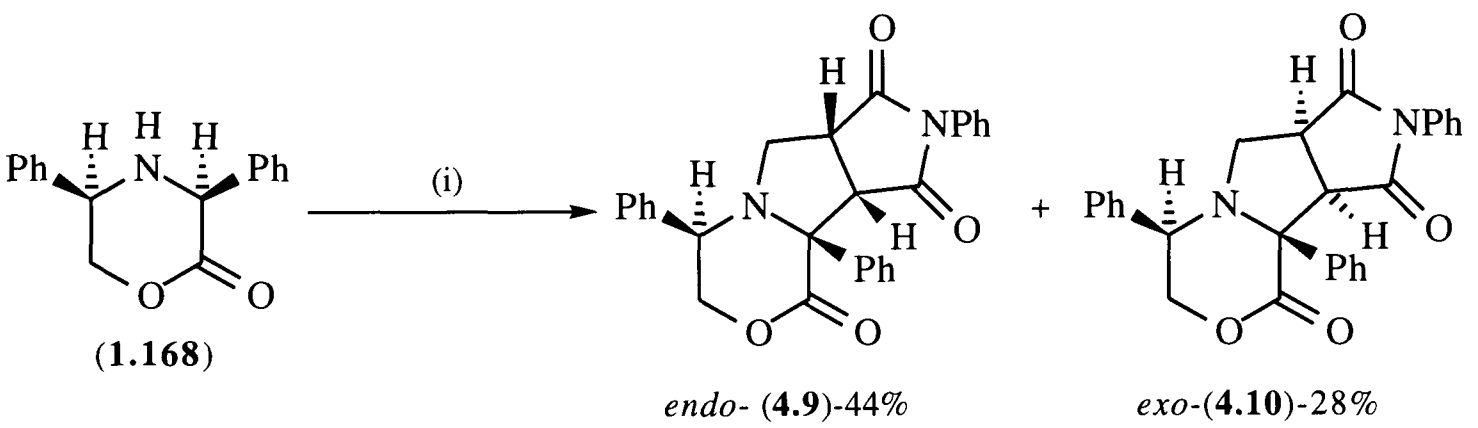
Reduction Method	Optical Rotation / d.e.	Optical Rotation / e.e.
H_2, Pd/ C, EtOAc	$[\alpha]_D$ +85.5/ d.e. >20:1	$[\alpha]_D$ -25.3/ e.e. 80%
H_2, PtO_2, EtOAc	$[\alpha]_D$ +14.5/ d.e. 10:1	$[\alpha]_D$ -5.9/ e.e. 18%
$NaBH_3CN$, THF	$[\alpha]_D$ 0/ d.e. >4:1	$[\alpha]_D$ 0/ e.e. 0%

Table 4.1

4.4 Thermal Cycloadditions with (3*S*,5*R*)-Diphenylmorpholin-2-one (1.168).

4.4.1 Alkene Dipolarophiles.

Previous work within the group has shown that diphenylmorpholinone (**1.168**) would react with paraformaldehyde in refluxing xylene, to generate an ylid capable of subsequent cycloaddition. Repetition of the trial reaction in xylene using the standard cycloaddition method resulted in the isolation of the cycloadducts (**4.9**) and (**4.10**), previously synthesised by Anslow, but in a higher overall yield (72% *cf* 50%) (**Scheme 4.6**).[3]



(**1.168**)

endo- (**4.9**)-44% *exo*-(**4.10**)-28%

(i) $(HCHO)_n$, *N*-phenylmaleimide, molecular sieves, reflux, xylene.

Scheme 4.6

The overall yield of the cycloaddition was found to be greater than in the monosubstituted (5*S*)-phenylmorpholinone case, with the *endo*- adduct (**4.9**) again observed

to be the major product. The proportion of the *exo*- (**4.10**) adduct was however significantly greater than in the simplest case. It might be expected however that the proportion of *endo*-adduct (**4.9**) would be increased due to the additional steric hindrance in the transition state leading to the *exo*- adduct (**4.10**) caused by the substituent at C-3 (**Figure 4.1**). These observations can both be rationalised by considering the increase in stability of the ylid imparted by the phenyl substituent. The additional stability means that the ylid has a longer lifetime in the reaction mixture, giving a greater probability of being trapped before undergoing decomposition, and therefore an increase in yield. The additional stability may also cause a reduction in the influence of the stabilising secondary orbital interactions, which favour the *endo*- product, thus leading to a reduction in the proportion of this product.

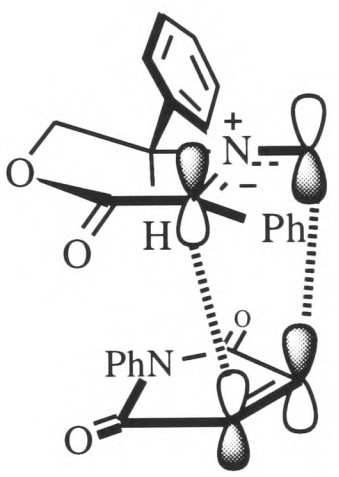
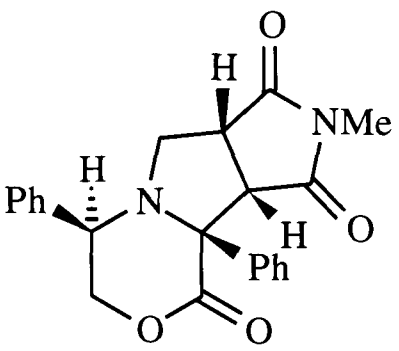
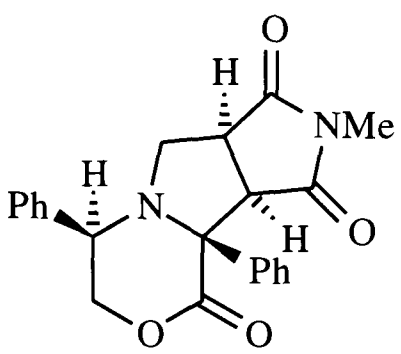


Figure 4.1

Following the observation of successful cycloaddition it was decided to investigate the effect of the dipolarophile on the yield and stereochemical outcome. Diphenylmorpholinone (**1.168**), paraformaldehyde and *N*-methylmaleimide were therefore refluxed in xylene following the standard method. After 18 hours t.l.c. analysis indicated the absence of starting material and the presence of two new products. Removal of the solvent followed by column chromatography afforded two products whose ^{1}H n.m.r. and mass spectrometric data were consistent with the gross structure of cycloadducts. Two dimensional n.m.r. coupled with the use of n.O.e. difference experiments enabled the total structural and stereochemical assignment of the two cycloadducts (**4.11**) and (**4.12**).



endo- (**4.11**)-53%



exo- (**4.12**)-29%

The stereochemistry of the major cycloadduct (**4.11**), obtained in 53% yield, was initially assigned on the basis of n.O.e. experiments, an assignment that was subsequently confirmed by X-ray crystallography (**Figure 4.2**).

The stereochemistry of the minor component (**4.12**), obtained in 29% yield, was assigned on the basis of n.O.e. experiments (**Figure 4.3**). Irradiation of the proton at C_7 gave an enhancement (6.6%) to the proton at C_8 showing the ring junction to be *cis*. Irradiation of one of the protons at C_9 gave an enhancement (10%) to the proton at C_2, and also an enhancement (4%) to the proton at C_8. This showed that the proton at C_9, the proton at C_8 and therefore the proton at C_7 were all on the α- face. The phenyl group at C_6 was assigned as being on the β- face on the basis of all previous observations of cycloadditions in both the mono- and di-substituted morpholinone series.

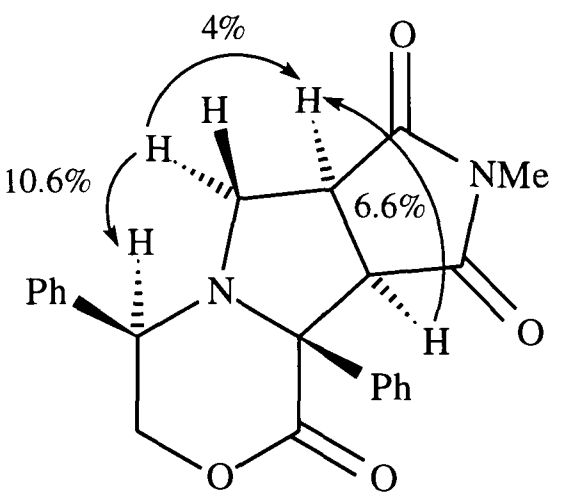
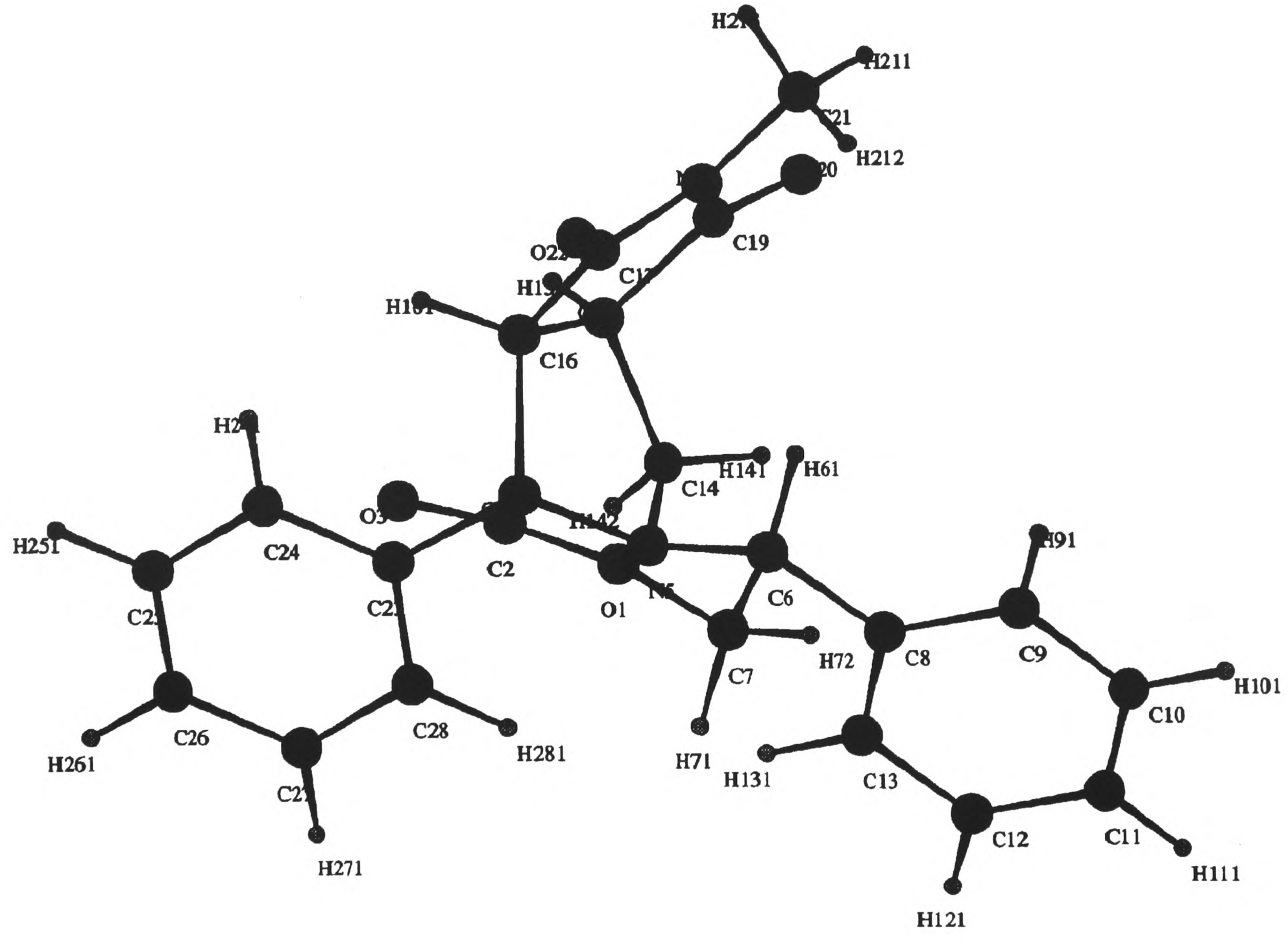


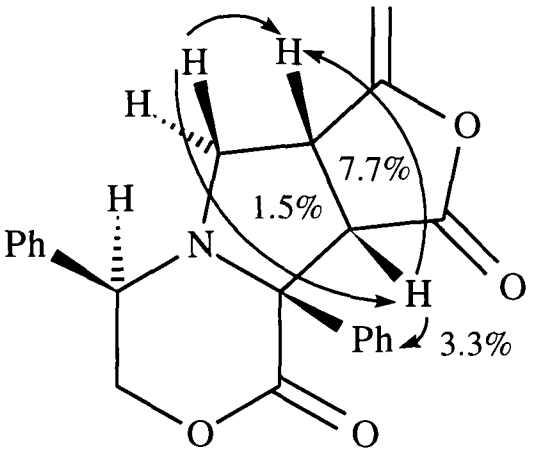
Figure 4.3

The slight increase in the proportion of the *endo-* adduct (**4.11**) with *N*-methylmaleimide was predictable on the basis of the lower steric demands of the *N*-methyl group compared with the *N*-phenyl substituent. This trend was further supported on using maleic anhydride as the dipolarophile in the cycloaddition. Considerable polymerisation

Figure 4.2
Crystal Structure for Compound (4.11)



occurred under the high temperature conditions, however usual work up followed by column chromatography resulted in the isolation, in 17% yield, of a single product whose ^1H n.m.r. and mass spectrometric data were consistent with that of a cycloadduct. Two dimensional n.m.r. coupled with the use of n.O.e. difference experiments enabled the total structural and stereochemical assignment of the cycloadduct (**4.13**). Irradiation of the proton at C_7 showed an enhancement (7.7%) to the proton at C_8 indicating the ring junction to be *cis*- (**Figure 4.4**). An enhancement (3.3%) was also observed to the phenyl ring showing the proton at C_7 to be on the same β- face as the phenyl ring. Irradiation of one of the protons at C_9 showed a strong enhancement (11.5%) to the proton at C_8 and a small enhancement (1.5%) to the proton at C_7 indicating that these protons all resided on the β- face. Further evidence for the assignment as shown was provided by the fact that no enhancement was observed to the proton at C_2, which is known to lie on the α- face.



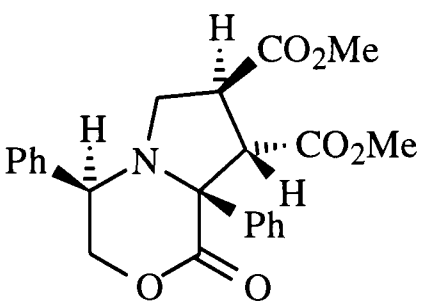
(**4.13**)-17%

Figure 4.4

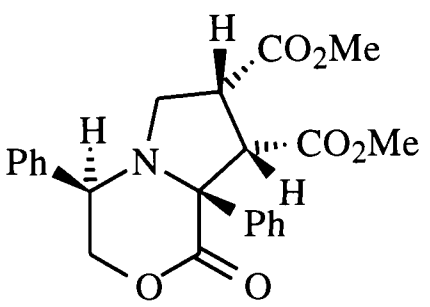
Dimethyl fumarate and dimethyl maleate have also been employed as dipolarophiles with morpholinone derived ylids, although yields have generally been lower than those observed with the cyclic maleimide type dipolarophile.[8] Nevertheless it was decided to attempt the cycloaddition with the acyclic dipolarophiles.

Accordingly diphenylmorpholinone and paraformaldehyde were refluxed in xylene with dimethyl fumarate or dimethyl maleate under the usual conditions. Removal of solvent followed by column chromatography furnished in both cases a single product whose ^1H n.m.r. and mass spectrometric data were consistent with that of a cycloadduct. Two dimensional

n.m.r. coupled with n.O.e. difference experiments allowed the total structural and stereochemical assignment of the cycloadducts (**4.14**) and (**4.15**), derived from dimethyl fumarate and dimethyl maleate respectively. The stereochemistry of both the cycloadducts can be rationalised in the usual manner by considering the dipolarophile to attack in an *endo*-fashion from the least hindered face of the ylid.



(**4.14**)-95%



(**4.15**)-89%

N.O.e studies on the adduct derived from dimethyl fumarate (**4.14**) showed a strong enhancement (10.9%) of the proton at C_2 on irradiation of one of the protons at C_9, indicating that this proton was also on the α- face (**Figure 4.5**). Irradiation of this proton also showed a strong enhancement (12%) to the proton at C_8 indicating that this proton was also on the α- face. The β- face stereochemistry of the proton at C_7 was inferred from the initial geometry of the double bond, while the phenyl substituent at C_6 was assigned as being on the β- face on the basis of all previous observations.

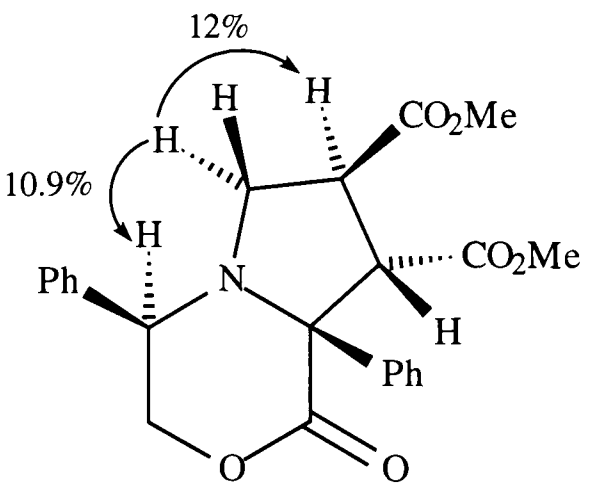
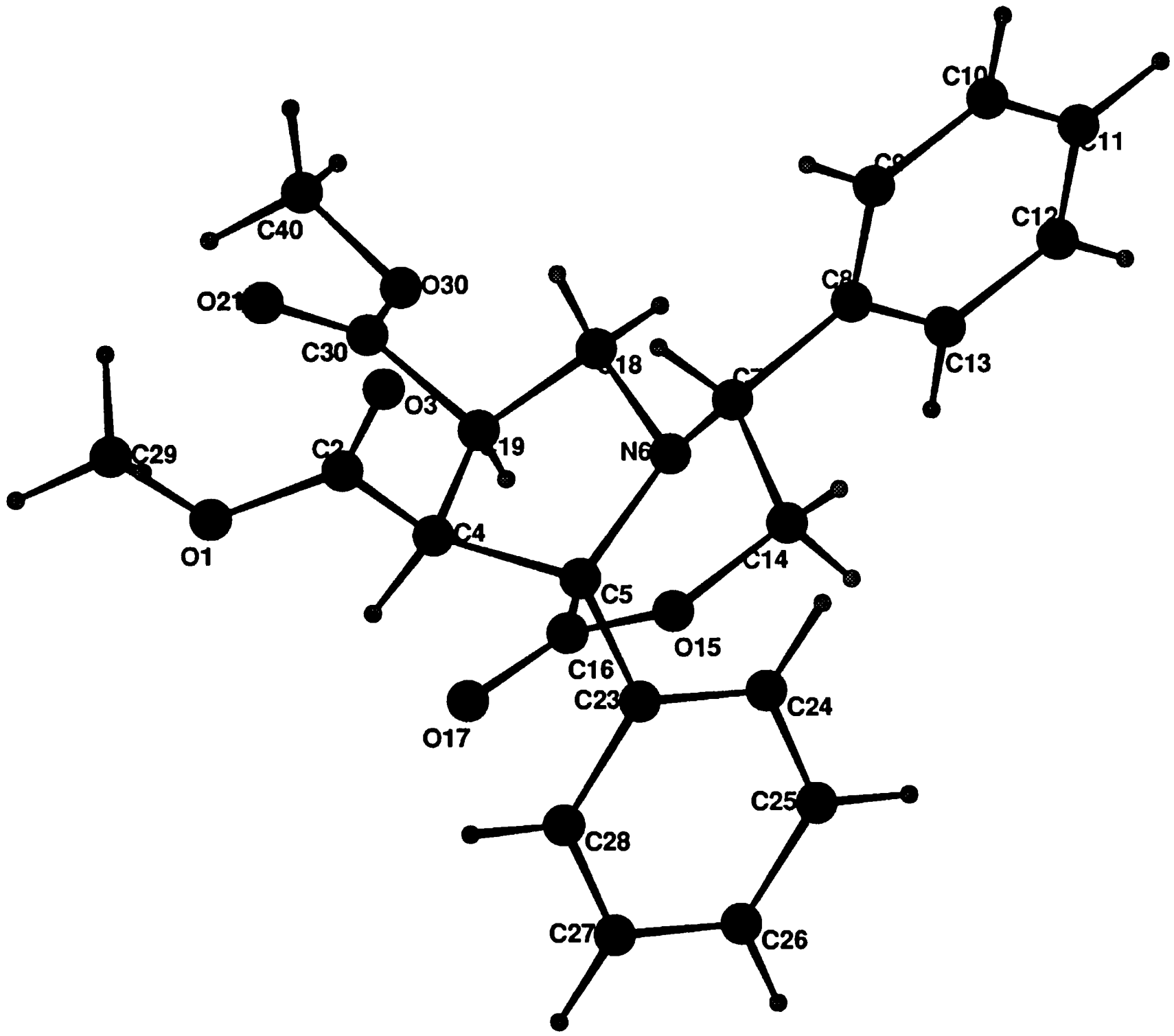


Figure 4.5

The stereochemistry of the adduct derived from dimethyl maleate (**4.15**) was initially assigned on the basis of n.O.e. experiments, and later confirmed by X-ray crystallography (**Figure 4.6**).

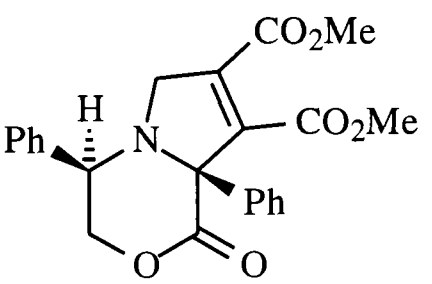
Figure 4.6

Crystal Structure for Compound (4.15)



4.4.2 Alkyne Dipolarophiles.

Attention was then turned to cycloadditions involving alkyne dipolarophiles, the cycloadducts of which would be free of stereochemical complications arising from *endo-/ exo-* addition. Diphenylmorpholinone (**1.168**) was accordingly refluxed in xylene with paraformaldehyde and dimethyl acetylenedicarboxylate under the usual conditions. Work up followed by column chromatography afforded a single product whose ^1H n.m.r. and mass spectrometric data was consistent with that of the cycloadduct (**4.16**), isolated in 79% yield. The structural and stereochemical assignment was confirmed through the use of two dimensional n.m.r. and n.O.e. difference experiments.



(**4.16**)-79%

Similar treatment of diphenylmorpholinone (**1.168**) with paraformaldehyde and methyl propiolate, followed by work up and column chromatography afforded a roughly equimolar mixture of two products. The ^1H n.m.r. and mass spectrometric data were consistent with that of cycloadducts, and two dimensional n.m.r. coupled with the use of n.O.e. difference experiments enabled the assignment of the products as the regiomeric cycloadducts (**4.17**) and (**4.18**).

Irradiation of the alkene proton in the major isomer (**4.17**) gave an enhancement (1.2%) to the phenyl group, while irradiation of the β-face proton at C_9 gave an enhancement (6%) to the methyl group of the ester (**Figure 4.7**). This indicated that the alkene proton was on C_7. Similar irradiation of the alkene proton of the minor cycloadduct (**4.18**) gave enhancements to the protons at C_9 on the α- face (3.4%), and the β- face (4.8%). This indicated the alkene proton to be on C_8. In the cycloaddition reaction of phenylmorpholinone (**1.126**) only a single regioisomer was observed.[8] The observation of two regioisomers in the case of the diphenylmorpholinone (**1.168**) suggests that the balance between the transition

state energies leading to the different products is closer.

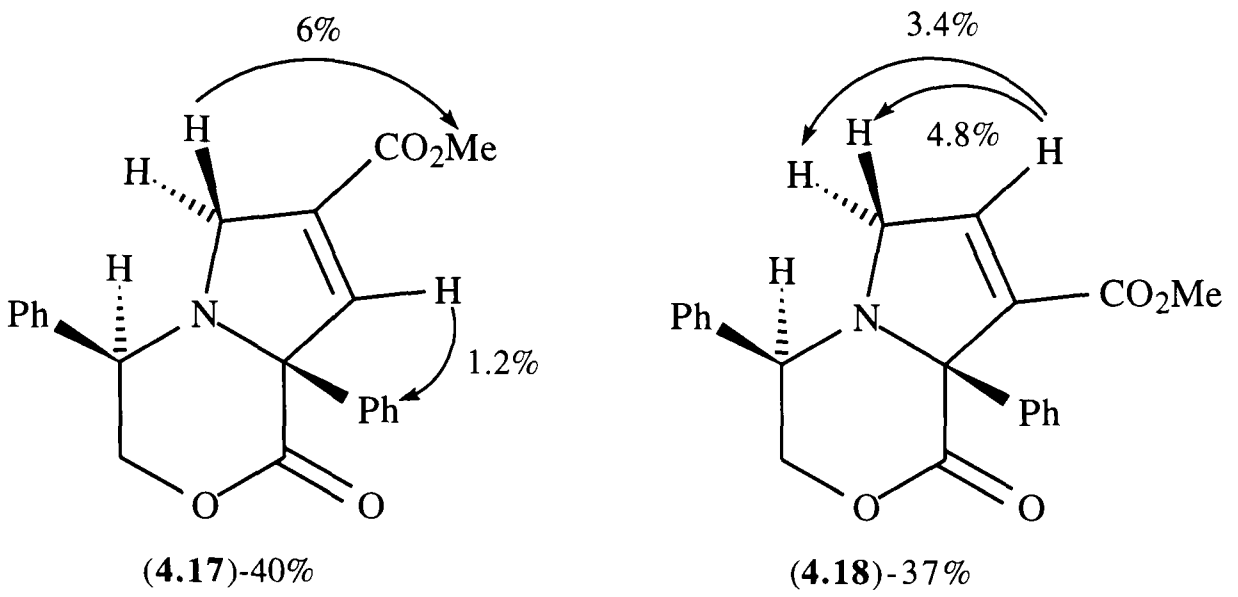


Figure 4.7

The overall yield of cycloadduct is, with the exception of maleic anhydride, greater in cycloadditions involving the di-substituted rather than mono-substituted ylid (**Table 4.2**). This can be rationalised in terms of the increase in stability of the ylid caused by the additional phenyl substituent. This results in the ylid having a greater lifetime in the reaction mixture, and therefore a greater probability of being trapped before undergoing decomposition. The degree of stereocontrol varied however with better control being obtained with acyclic dipolarophiles for diphenylmorpholinone (**1.168**) and maleimide dipolarophiles for phenylmorpholinone (**1.126**).

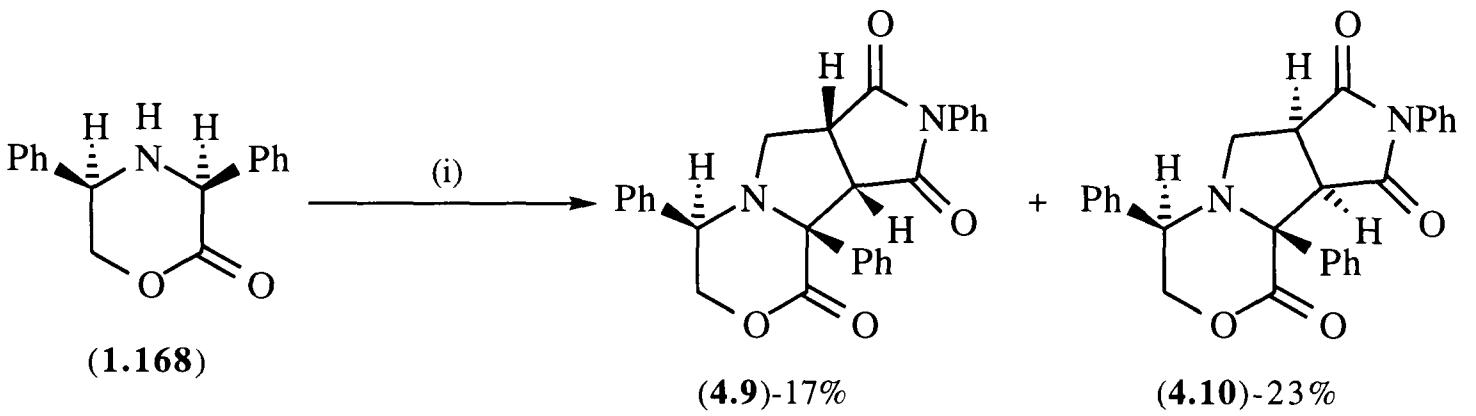
Dipolarophile	Diphenylmorpholinone: Yield	Phenylmorpholinone: Yield[9]
N-phenyl maleimide	*endo*- 44%, *exo*- 28%	*endo*- 45%, *exo*- 13%
N-methyl maleimide	*endo*- 53%, *exo*- 29%	*endo*- 41%, *exo*- 19%
maleic anhydride	*endo*- 17%	*endo*- 49%
dimethyl maleate	*endo*- 89%	*endo*- 20%, *exo*- 6%
dimethyl fumarate	*endo*- 95%	0%
methyl propiolate	40% + 37%	30%
dimethyl acetylenedicarboxylate	79%	29%

Table 4.2

4.5 Catalysed Cycloadditions with (3*S*,5*R*)-Diphenylmorpholinone (1.168).

4.5.1 Alkene Dipolarophiles.

The high yields and excellent stereocontrol observed in the thermal cycloaddition reaction of ylids derived from diphenylmorpholinone (**1.168**) were extremely promising as regards applying the method to the synthesis of α-amino acids. It was decided therefore to attempt the reactions under the more experimentally convenient catalytic conditions. Diphenylmorpholinone (**1.168**), paraformaldehyde and *N*-phenylmaleimide were accordingly sonicated in tetrahydrofuran with molecular sieves and magnesium bromide-etherate (**Scheme 4.7**). After 4 hours t.l.c. analysis indicated the absence of starting material, and the appearance of two new products. The reaction was worked up by filtration through silica to remove the catalyst followed by column chromatography. This resulted in the isolation of two products, the spectroscopic data of which were consistent with the cycloadducts (**4.9**) and (**4.10**) previously prepared *via* the thermal cycloaddition reaction.



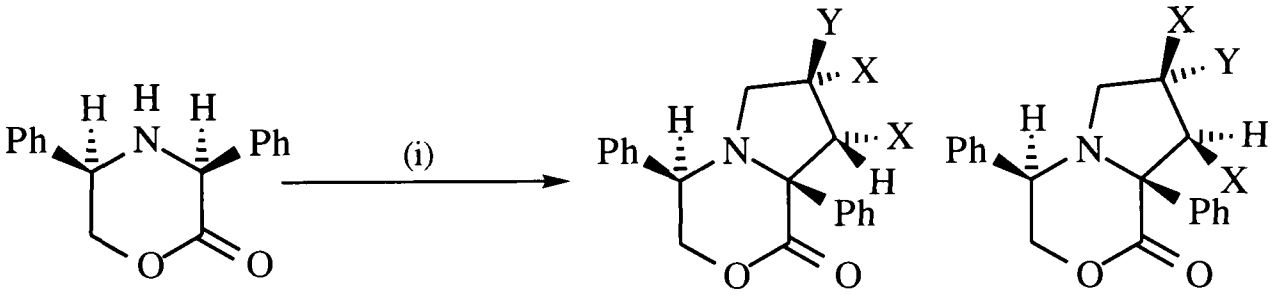
(i) $(HCHO)_n$, *N*-phenylmaleimide, molecular sieves, $MgBr_2.Et_2O$, sonicate, THF.

Scheme 4.7

The overall yield, in contrast to the results of previous catalysed cycloadditions, was observed to be lower than in the thermal reaction, while the proportion of *exo*- adduct was observed to have increased in line with previous results. The higher temperature required for reaction to occur has demonstrated that diphenylmorpholinone (**1.168**) is less reactive than phenylmorpholinone (**1.126**). The lack of thermal activation in the sonicated reaction may therefore account for the lower observed yield. The increase in proportion of *exo*- adduct was

rationalised, as before, by considering the additional steric hindrance imposed on the transition state leading to the *endo*- adduct caused by co-ordination of the Lewis acid catalyst to the lactone carbonyl.

The reaction was subsequently repeated using the alkene dipolarophiles previously used in the thermal cycloaddition. Solvent removal and column chromatography resulted in the isolation of the cycloadducts previously observed in the thermal reaction, in all cases in reduced overall yield (**Scheme 4.8**). In common with previous observations, *N*-methylmaleimide was observed to give an increase in the proportion of the *exo*- adduct, although not as dramatically as in the simplest phenylmorpholinone (**1.126**).[9] The remaining dipolarophiles however all showed continued exclusive formation of the *endo*- cycloadduct, which may be a consequence of the lack of thermal activation. This results in the stabilising effect of the secondary orbital interactions continuing to provide a lower energy pathway for cycloaddition, and thus with the lower energy of the reactants a continued predominance of the *endo*- cycloadduct.



Dipolarophile	7-*endo*	7-*exo*
N-Methylmaleimide	36%	25%
Dimethyl fumarate	65%	0%
Dimethyl maleate	56%	0%
Maleic anhydride	4%	0%

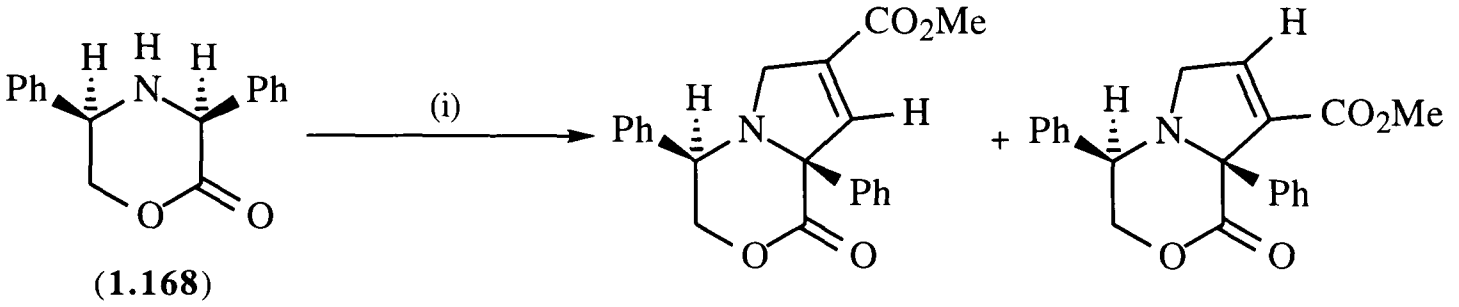
(i) $(HCHO)_n$, dipolarophile, $MgBr_2.Et_2O$, molecular sieves, sonicate, THF.

Scheme 4.8

4.5.2 Alkyne Dipolarophiles.

Following successful cycloaddition under catalysed conditions between the paraformaldehyde derived diphenylmorpholinone ylid and a range of alkene dipolarophiles, attention turned to the use of alkyne dipolarophiles. Accordingly diphenylmorpholinone

(**1.168**), paraformaldehyde and methyl propiolate were sonicated in tetrahydrofuran with molecular sieves and magnesium bromide-etherate (**Scheme 4.9**). After 4 hours t.l.c. analysis indicated the absence of starting material, and the appearance of two new products. Usual work up followed by column chromatography resulted in the isolation of two cycloadducts, the ^1H n.m.r. data and optical rotation of which were identical with the cycloadducts (**4.17**) and (**4.18**) previously prepared *via* the thermal cycloaddition reaction. Similar treatment of diphenylmorpholinone, paraformaldehyde and dimethyl acetylene dicarboxylate however resulted only in the isolation of starting materials, even after 24 hours of sonication. The lower yields are consistent with the theory that the activation energy for the reaction is such that high temperatures are required to effect reaction. The alteration in regiocontrol observed with methyl propiolate parallels previous observations, and is consistent with a shift in the dominant interaction from ylid HOMO-dipolarophile LUMO to ylid LUMO-dipolarophile HOMO.[10]



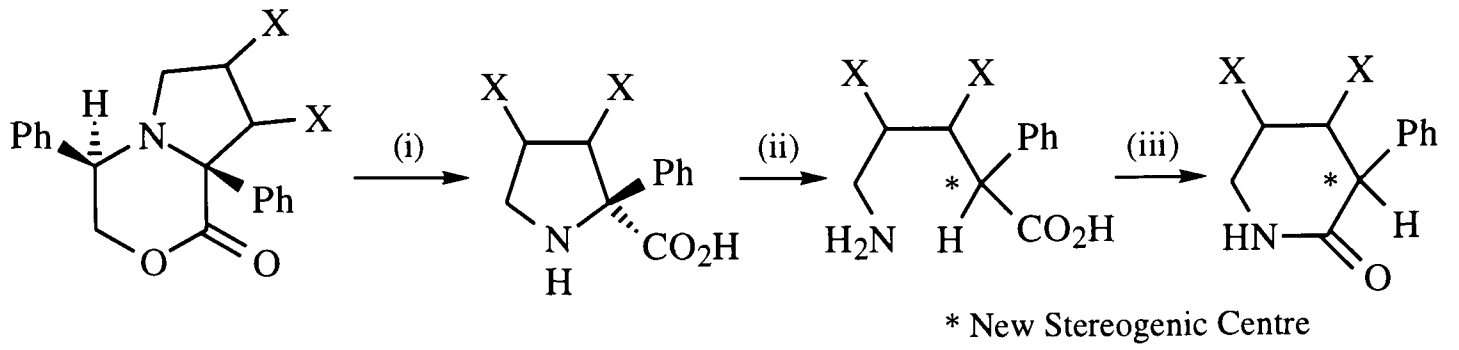
(i) $(HCHO)_n$, methyl propiolate, molecular sieves, $MgBr_2.Et_2O$, sonicate, THF.

Scheme 4.9

4.6 Hydrogenolysis of Cycloadducts: Generation of Proline Derivatives.

Having generated a number of cycloadducts using the ylid derived from the condensation of diphenylmorpholinone (**1.168**) and paraformaldehyde, it was decided to attempt the removal of the template. It was envisaged that the hydrogenolysis could generate a number of products (**Scheme 4.10**), and it was hoped that following hydrogenolysis of the second *N*-benzyl bond cyclisation would occur under the acidic conditions. This would allow the stereochemistry at C_3 to be determined, and thus the degree of any stereocontrol in the

hydrogenolysis of the second *N*-benzyl bond.

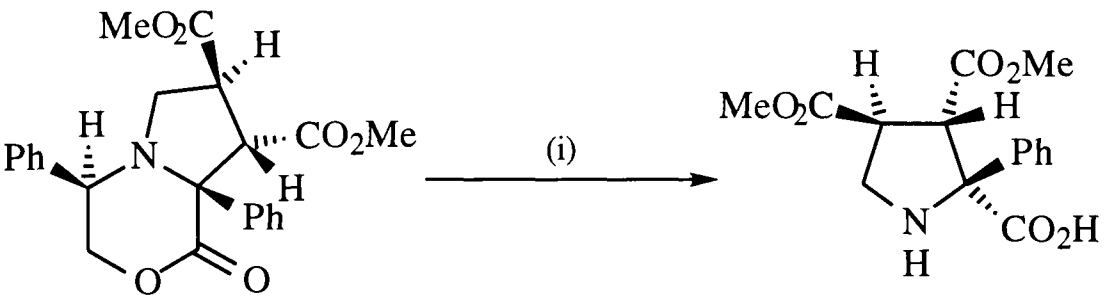


(i) hydrogenolysis of first *N*-benzyl bond, (ii) hydrogenolysis of second *N*-benzyl bond, (iii) cyclisation.

Scheme 4.10

Previous work had shown that one of the adducts derived from *N*-phenylmaleimide would undergo cleavage of one *N*-benzyl bond under one atmosphere of hydrogen, and it was hoped that higher pressure would allow the second hydrogenolysis to occur.

Accordingly, the adduct derived from dimethyl fumarate (**4.14**) was dissolved in methanol, catalytic quantities of trifluoroacetic acid and Pearlman's catalyst added, and the resultant suspension stirred under a 5 bar atmosphere of hydrogen for 18 hours (**Scheme 4.11**). Release of pressure followed by removal of the catalyst and trituration with diethyl ether afforded a colourless powder whose ^{1}H n.m.r. and mass spectrometric data were consistent with that of the amino acid (**4.19**). Disappointingly, cleavage of the second *N*-benzyl bond had not occured, and even prolonged exposure to the hydrogenolysis conditions failed to effect this transformation. It has recently been reported that the use of very high pressures (>150 atmospheres) was necessary to effect hydrogenolysis of a very similar system,[11] and therefore application of such pressure may allow this hydrogenolysis to occur.

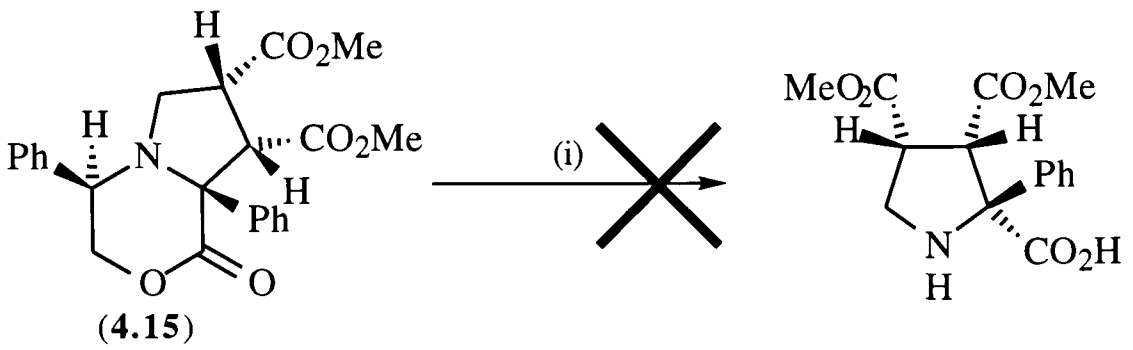


(i) H_2 5 bar, $Pd(OH)_2$/ C, trifluoroacetic acid, wet methanol, stir r.t.

Scheme 4.11

Despite the failure to effect the second hydrogenolysis with cycloadduct (**4.14**), it was decided to subject a range of other cycloadducts to the hydrogenolysis conditions. The adduct

derived from dimethyl maleate (**4.15**) was therefore stirred with trifluoroacetic acid and Pearlman's catalyst under a 5 bar atmosphere of hydrogen for 18 hours (**Scheme 4.12**). However usual work up resulted only in the quantitative recovery of starting material, an observation which was unchanged following prolonged exposure to the hydrogenolysis conditions.

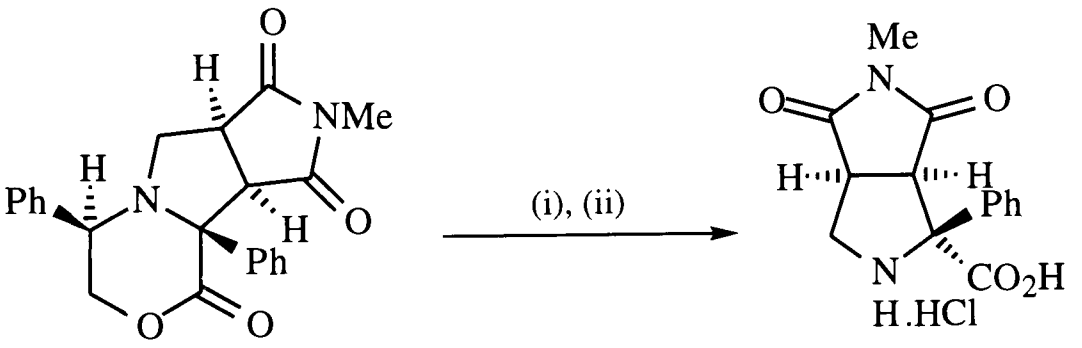


(4.15)

(i) H_2 5 bar, $Pd(OH)_2$/ C, trifluoroacetic acid, wet methanol, stir r.t.

Scheme 4.12

Similar treatment of the *endo*- cycloadduct derived from *N*-methylmaleimide (**4.11**) again resulted only in the recovery of starting material. However, treatment of the *exo*- adduct (**4.12**) with hydrogen, trifluoroacetic acid and Pearlman's catalyst resulted in the formation of a grey suspension which was attributed to the formation of a highly insoluble amino acid. Treatment of the grey suspension with a few drops of concentrated hydrochloric acid, followed by filtration to remove the catalyst, furnished an orange powder (**Scheme 4.13**). Recrystallisation from water gave a colourless powder whose ^1H n.m.r. and mass spectrometric data were consistent with quantitative formation of the amino acid hydrochloride (**4.20**). The stereochemistry was again assigned on the basis of the parent cycloadduct.

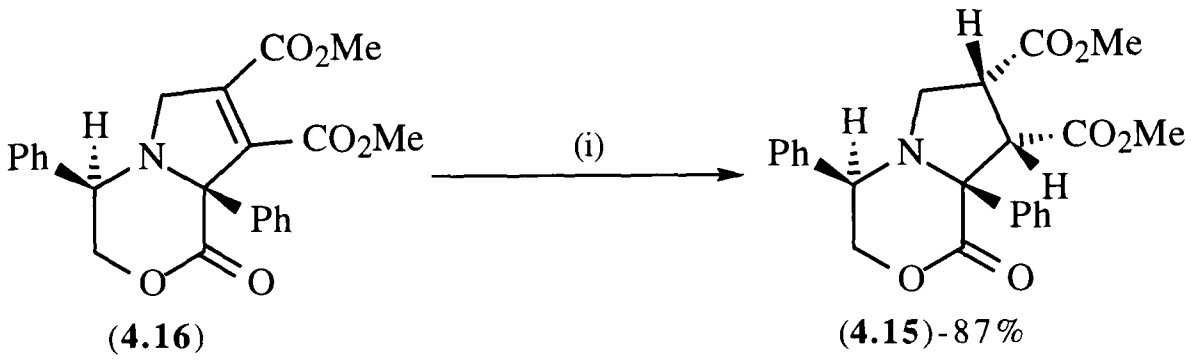


(4.12) **(4.20)**-quant

(i) H_2 5 bar, $Pd(OH)_2$/ C, trifluoroacetic acid, wet methanol, stir r.t., (ii) 35% HCl.

Scheme 4.13

Before attempting to remove the template from the adduct derived from dimethyl acetylenedicarboxylate (**4.16**) it was decided to attempt hydrogenation of the double bond. This could conceivably generate either cycloadduct (**4.15**), or the C_7 epimer of cycloadduct (**4.14**). The cycloadduct (**4.16**) was therefore stirred in ethyl acetate with 10% palladium on carbon under an atmosphere of hydrogen. However following removal of the catalyst and solvent only starting material was recovered. Use of platinum (IV) oxide, platinum on carbon, Pearlman's catalyst or Wilkinson's catalyst under the same conditions similarly resulted in recovery of starting material, and so it was decided to effect template removal. Accordingly the cycloadduct was stirred with trifluoroacetic acid and Pearlman's catalyst under a 5 bar atmosphere of hydrogen (**Scheme 4.14**). Removal of the catalyst and solvent however resulted in the exclusive isolation of an 87% yield of the cycloadduct derived from dimethyl maleate (**4.15**), previously shown to be inert to template cleavage.



(**4.16**) (**4.15**)-87%

(i) H_2 5 bar, $Pd(OH)_2$/ C, trifluoroacetic acid, wet methanol, stir r.t.

Scheme 4.14

The stereochemistry of the hydrogenation can be rationalised by considering the conformation of the cycloadduct (**4.16**). The crystal structure of the hydrogenated cycloadduct (**4.15**) shows the morpholinone ring to be largely planar, with the methylene group adjacent to oxygen raised above the plane, and the conformation of the dehydrogenated cycloadduct (**4.16**) can be assumed to be similar (**Figure 4.8**). This shows that hydrogenation from the α- face, leading to the *exo-* adduct, is hindered by the morpholinone ring. Therefore hydrogenation occurs from the β- face, hindered only by the phenyl ring, leading to formation of the *endo-* cycloadduct (**4.15**).

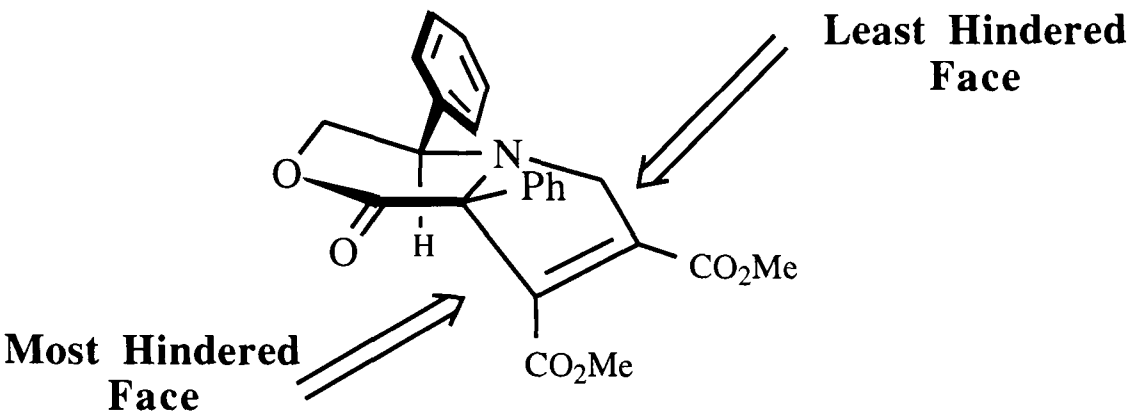


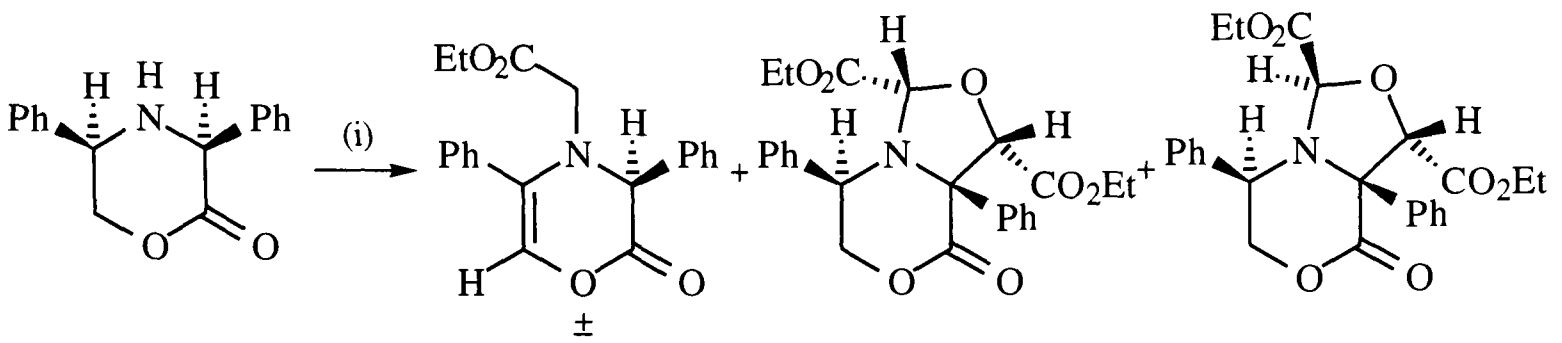
Figure 4.8

Following the failure to remove the template using catalytic hydrogenation it was decided to employ a dissolving metal reduction to effect this transformation. Cycloadducts (**4.11**), (**4.12**), (**4.14**) and (**4.15**) were therefore dissolved in liquid ammonia, and sodium metal added until a blue colour persisted.[4] The reactions were quenched, neutralised, then extracted, however following removal of the solvent ^{1}H n.m.r. spectroscopic analysis indicated that in all cases degradation of the starting material had occurred.

Despite the failure to effect total template removal, it was decided to attempt the introduction of a substituent α- to nitrogen. This would require the use of a substituted aldehyde and, following the success of cycloadditions using ethyl glyoxylate trimer as the ylid generating aldehyde, it was decided to commence with that.

4.7 Introduction of Substituents α- to Nitrogen.

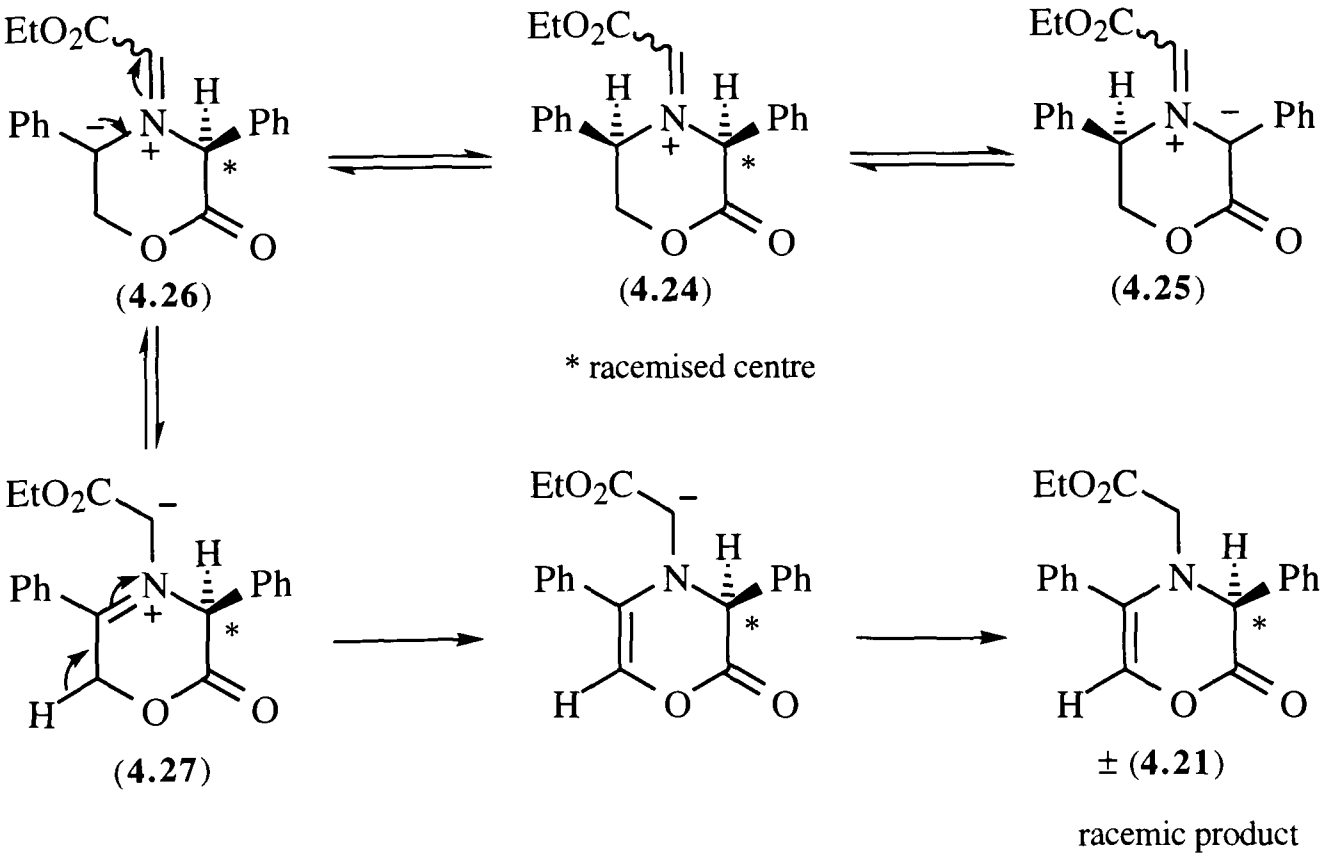
Following the usual procedure, diphenylmorpholinone (**1.168**), ethyl glyoxylate trimer and *N*-phenylmaleimide were refluxed in xylene. After 18 hours t.l.c. analysis indicated the absence of starting material and the appearance of three new products. Column chromatography followed by recrystallisation allowed the isolation of these materials, none of which had ^{1}H n.m.r. and mass spectrometric data consistent with that of the desired cycloadducts. Two dimensional n.m.r. coupled with the use of n.O.e. difference experiments allowed the total structural and stereochemical assignment of the products (**Scheme 4.15**).



(i) *N*-phenylmaleimide, $CHOCO_2Et$, molecular sieves, reflux xylene.

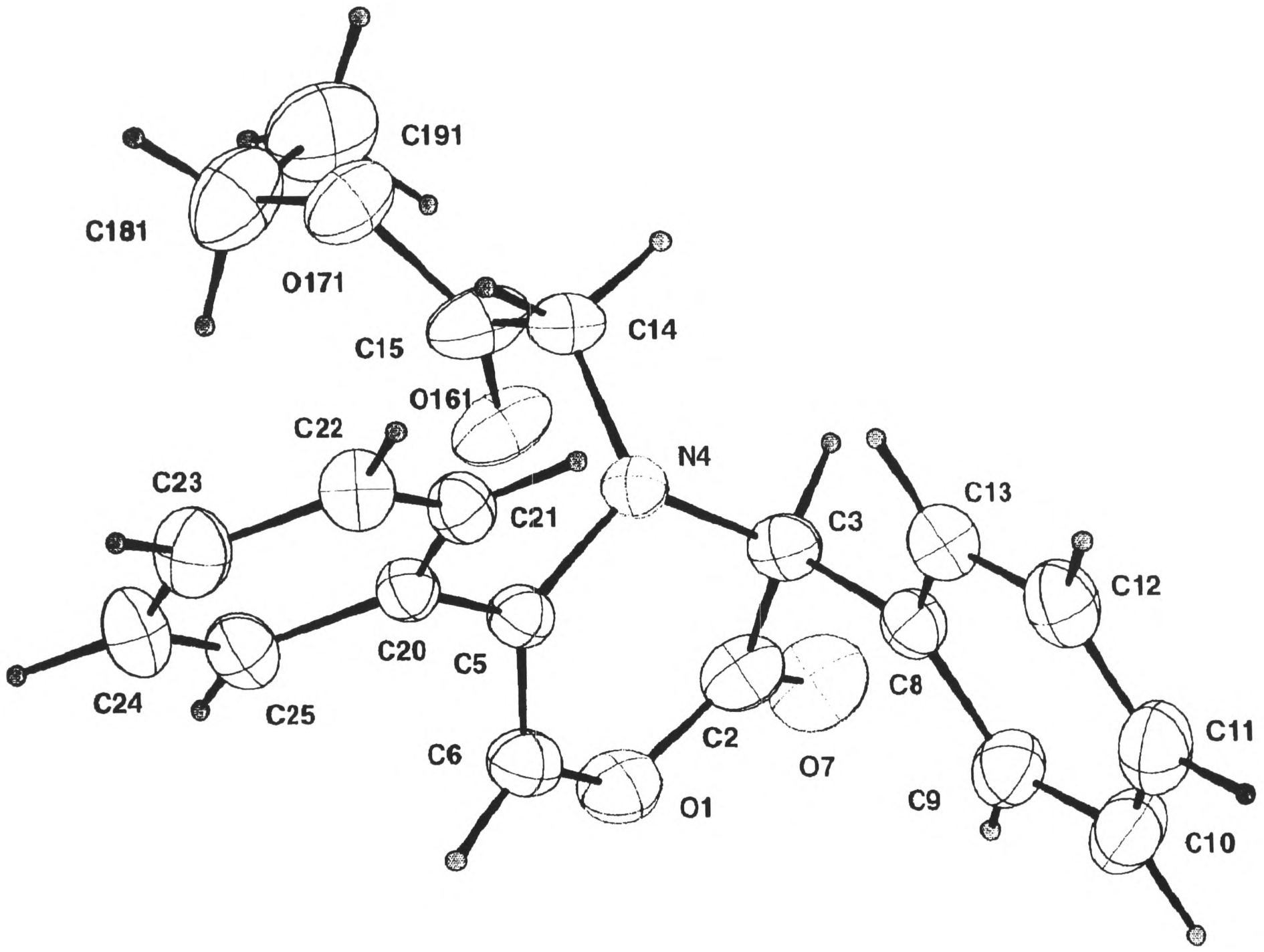
Scheme 4.15

Structural assignment of the first product (**4.21**), which was observed to be racemic, caused initial difficulty but was confirmed on obtaining an X-ray crystal structure (**Figure 4.9**). Initial formation of the iminium ion (**4.24**) is followed by generation of the more stable ylid (**4.25**) (**Scheme 4.16**). The stability of this ylid due to the two electron withdrawing groups is such as to make cycloaddition slow. Reprotonation can therefore occur, reforming the iminium ion (**4.24**) and scrambling the chiral centre at C_3. Due to the electron withdrawing substituent α- to nitrogen, the regio ylid (**4.26**) may be formed, and subsequently isomerise to the alternative tautomer (**4.27**). Loss of a proton from this tautomer of the regio ylid is irreversible, and subsequent reprotonation on the carbon α- to nitrogen gives the racemic product.



Scheme 4.16

Figure 4.9
Crystal Structure for Compound (4.21)



The two remaining products are derived from the cycloaddition of the initially formed ylid onto a second molecule of aldehyde. Irradiation of the proton at C_9 of the major isomer (**4.22**) gave a strong enhancement (6.7%) to the phenyl group on C_2, and a strong enhancement (12%) to the proton at C_7 (**Figure 4.10**). This showed that the protons at C_7 and C_9 were both on the β- face. Irradiation of the proton at C_7 showed an enhancement (2.5%) to the phenyl group on C_6, showing that this phenyl group was also on the β- face. Irradiation of the proton at C_2 of the minor isomer (**4.23**) gave an enhancement (3.8%) to the proton on C_9, indicating that these protons were on the same α- face. No enhancement was observed between the protons at C_7 and C_9, and this indicated that they were on opposite faces, and thus the proton at C_7 was on the β- face.

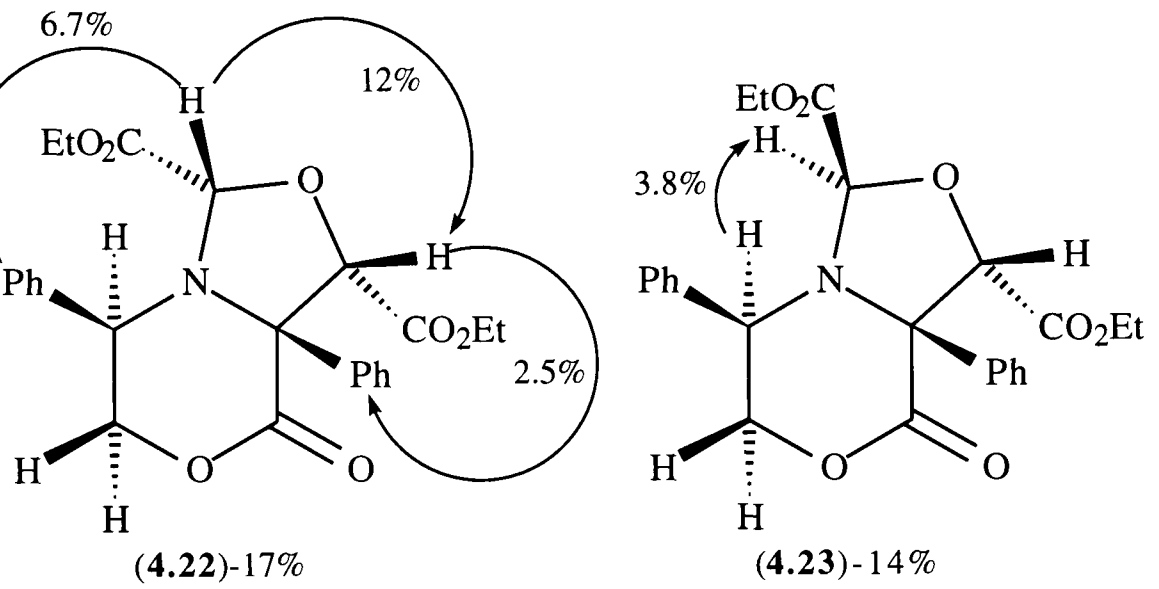
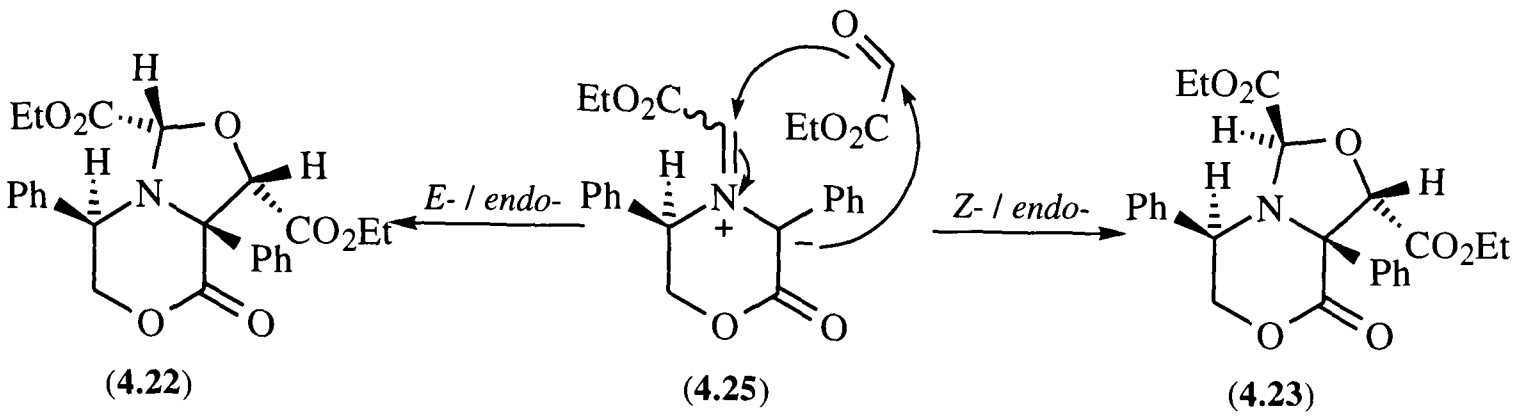


Figure 4.10

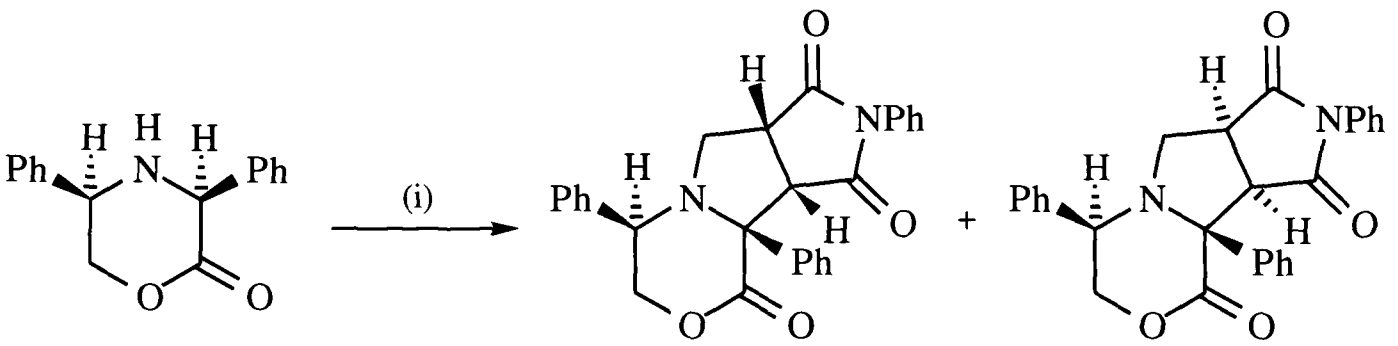
Due to the steric hindrance provided by both phenyl groups, there is little energy and therefore population difference between the *E*- and *Z*- ylids (**4.25**), which rationalises the formation of equal quantities of the C_9 epimer. Subsequent *endo*- cycloaddition occurs exclusively to give a single stereoisomer at C_7 (**Scheme 4.17**). Previous work on the cycloaddition reaction of substituted ylids with the aldehyde from which they were derived had shown exclusive formation of the *exo*- adduct.[12] The lower reactivity of the diphenylmorpholinone however results in secondary orbital interactions continuing to dictate the stereochemical outcome of cycloaddition, thus favouring *endo*- cycloaddition.



(**4.22**) (**4.25**) (**4.23**)

Scheme 4.17

The observation of cycloadducts (**4.22**) and (**4.23**) derived from the addition of two molecules of aldehyde prompted the idea of generating the ylid in the absence of ethyl glyoxylate trimer, thus hopefully forcing cycloaddition to occur with the desired dipolarophile. Accordingly diphenylmorpholinone (**1.168**) and *N*-phenylmaleimide were refluxed in xylene, and ethyl glyoxylate trimer added over a 14 hour period using a syringe pump. Following usual work up and column chromatography two products were isolated with ^{1}H n.m.r. and mass spectrometric data consistent with the cycloadducts (**4.09**) and (**4.10**) previously isolated from the cycloaddition of the paraformaldehyde derived ylid with *N*-phenylmaleimide (**Scheme 4.18**).



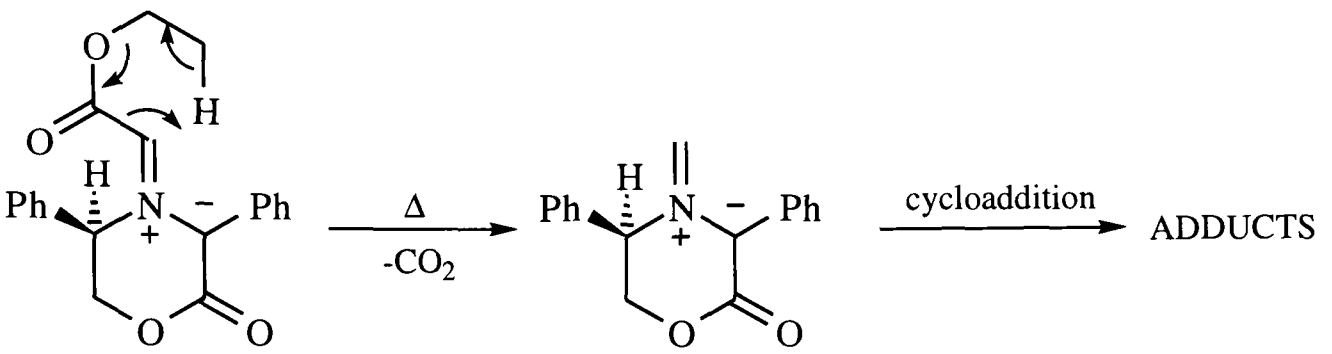
(**1.168**) (**4.9**)-11% (**4.10**)-7%

(i) *N*-phenylmaleimide, $CHOCO_2Et$ added slowly, molecular sieves, reflux xylene.

Scheme 4.18

The formation of cycloadducts from the paraformaldehyde derived ylid (**4.28**) suggests that this ylid is formed in the reaction. This can be rationalised by considering entropically favoured fragmentation of the ethyl glyoxylate trimer derived ylid (**4.25**) under the high temperature conditions (**Scheme 4.19**), in an analogous manner to that observed with allyl glyoxylate and phenylmorpholinone (see Chapter Three). The ratio of cycloadducts was

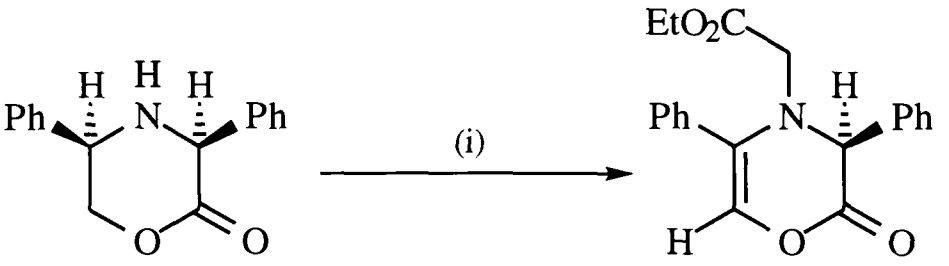
identical (*endo-/ exo-*, 1.6 : 1) to that previously observed, indicating that it is indeed the paraformaldehyde derived ylid (**4.28**) that undergoes cycloaddition, however the yield was reduced (from 72% to 18%). The difficulty of the decarboxylation stage results in the production of only a small quantity of the ylid, and therefore the observed yield is lower.



(4.25) **(4.28)**

Scheme 4.19

Following the lack of cycloaddition between the ylid derived from ethyl glyoxylate and *N*-phenylmaleimide, it was decided to alter the dipolarophile employed in the reaction in order to attempt to change the molecular orbital interactions in favour of cycloaddition with the desired dipolarophile. Diphenylmorpholinone (**1.168**), ethyl glyoxylate trimer and a selection of dipolarophiles were therefore refluxed in xylene under the usual conditions. However following usual work up and column chromatography only the racemic product (**4.21**) was isolated in varying yield (**Scheme 4.20**).



(1.168) **± (4.21)**

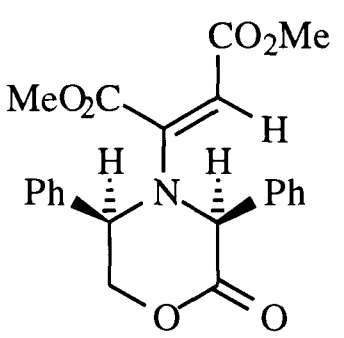
Dipolarophile	Yield
Maleic anhydride	18%
Dimethyl fumarate	16%
Dimethyl maleate	14%
Methyl propiolate	10%

(i) $CHOCO_2Et$, dipolarophile, molecular sieves, reflux xylene.

Scheme 4.20

By contrast, when dimethyl acetylenedicarboxylate was refluxed in xylene with diphenylmorpholinone (**1.168**) and ethyl glyoxylate trimer, under the usual conditions, a new

product was observed after 18 hours. Usual work up followed by column chromatography permitted the isolation, in 80% yield, of a compound having ^{1}H n.m.r. and mass spectrometric data consistent with the Michael adduct (**4.29**). The stereochemistry of the double bond was initially assigned as *E*- by analogy with the Michael adduct observed between dimethyl acetylenedicarboxylate and (5*S*)-phenylmorpholinone. This was confirmed by the observation of an n.O.e. enhancement (13.2%) between the proton on the double bond and the proton at C_3. The formation of the Michael adduct can be rationalised by considering the greater electrophilicity of dimethyl acetylenedicarboxylate over ethyl glyoxylate trimer, which results in initial nucleophilic attack on the dipolarophile rather than on the aldehyde.



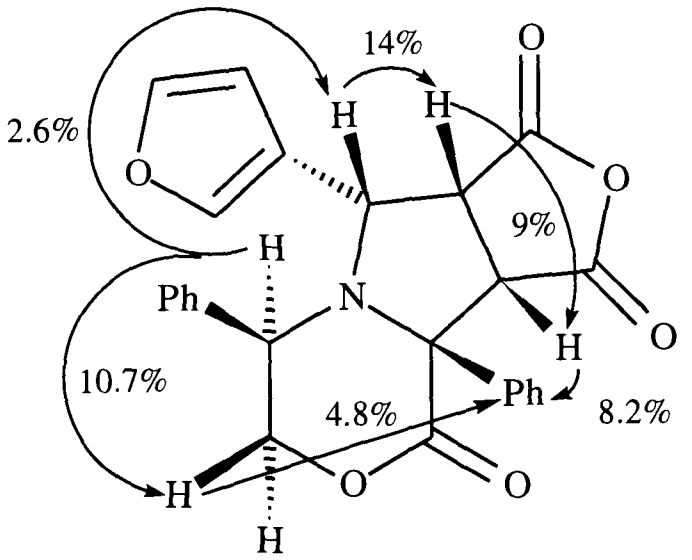
(**4.29**)-80%

The lack of any cycloaddition was attributed to a combination of the additional stabilising influence and the increased steric hindrance of the phenyl and carboxylate substituents. In order to circumvent this problem it was decided to attempt to reduce the stability of the ylid. Cycloadditions have previously been observed with the ylid derived from the condensation of phenylmorpholinone (**1.126**) with benzaldehyde,[8] and so it was decided to attempt the cycloaddition using this aldehyde. Diphenylmorpholinone (**1.168**), benzaldehyde and *N*-phenylmaleimide were therefore refluxed in xylene under the usual conditions. However following 18 hour reflux t.l.c. and ^{1}H n.m.r. analysis indicated only the presence of starting material. Similar use of *N*-methylmaleimide, maleic anhydride, dimethyl fumarate, dimethyl maleate and methyl propiolate gave the same result. Dimethyl acetylenedicarboxylate by contrast, furnished the Michael adduct (**4.29**) in 56% yield.

It was decided that either the ylid was not being formed, or that the ylid was still too unreactive to undergo cycloaddition. In order to further increase the electron density on the ylid it was decided to attempt ylid generation using furfuraldehyde. This would have the additional

advantage that subsequent oxidative cleavage to the carboxylic acid would generate an α- amino acid. The cycloaddition reaction was therefore repeated with furfuraldehyde and a selection of dipolarophiles. *N*-phenylmaleimide, *N*-methylmaleimide, dimethyl fumarate, dimethyl maleate and methyl propiolate all proved unsuccessful, with the recovery of starting material, while dimethyl acetylenedicarboxylate furnished a 90% yield of the Michael adduct (**4.29**).

However when diphenylmorpholinone (**1.168**), furfuraldehyde and maleic anhydride were refluxed in xylene t.l.c. analysis after 18 hours indicated the absence of starting material, and the appearance of a new product. Usual work up followed by column chromatography allowed the isolation of a new product, having ^1H n.m.r. and mass spectrometric data consistent with that of a cycloadduct. Two dimensional n.m.r. coupled with the use of n.O.e. difference experiments allowed the total structural and stereochemical assignment of the cycloadduct (**4.30**), isolated in 14% yield. Irradiation of the proton at C_2 showed only a small enhancement (2.6%) to the proton at C_9, indicating this proton to be on the opposite β- face (**Figure 4.11**). Irradiation of the proton at C_9 showed a strong enhancement (14%) to the proton at C_8, which on irradiation gave a strong enhancement (9%) to the proton at C_7. This indicated that the protons at C_7 and C_8 were also on the β- face. Irradiation of the proton at C_7 showed a strong enhancement (8.2%) to the phenyl group at C_6, which was also enhanced (4.8%) on irradiation of the proton on the β- face of C_3. This indicated that the phenyl group at C_6 was on the β- face, and also confirmed the assignment of the protons at C_7, C_8 and C_9 as being on the β- face.



(**4.30**)-14%

Figure 4.11

The cycloadduct isolated was again derived from exclusive *endo*- addition to the least hindered face of the ylid. The unique stereochemistry observed at C_9 is a result of exclusive addition to the *E*- ylid (**Figure 4.12**). This observation of a single epimer is of particular importance in the potential application of the cycloaddition reaction to the synthesis of α-amino acids, as it should allow synthesis of a single enantiomer of the amino acid. This result was surprising in the light of some concurrent work on the alkylation of diphenylmorpholinone imines with alkyl boronic acids.[13] These had given an equimolar mixture of diastereomers, showing that the population of each imine was equal due to the similarities in steric interactions. The origin of the formation of a single diastereomer in the cycloaddition may be a result of the furyl group imposing additional steric hindrance on the cycloaddition when in the *Z*- conformation. Due to the low reactivity of the substituted diphenylmorpholinone ylid this may result in this reaction pathway being too disfavoured, and therefore exclusive reaction with the *E*- ylid occurs.

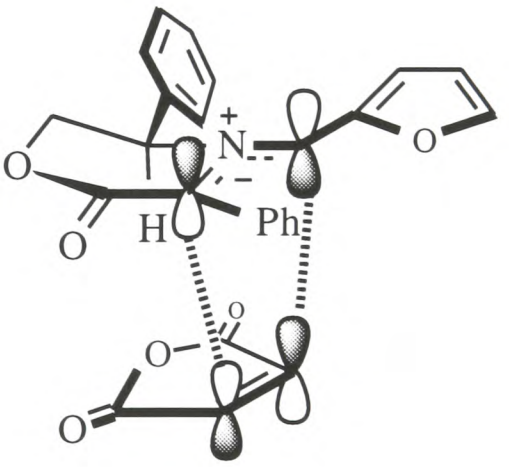
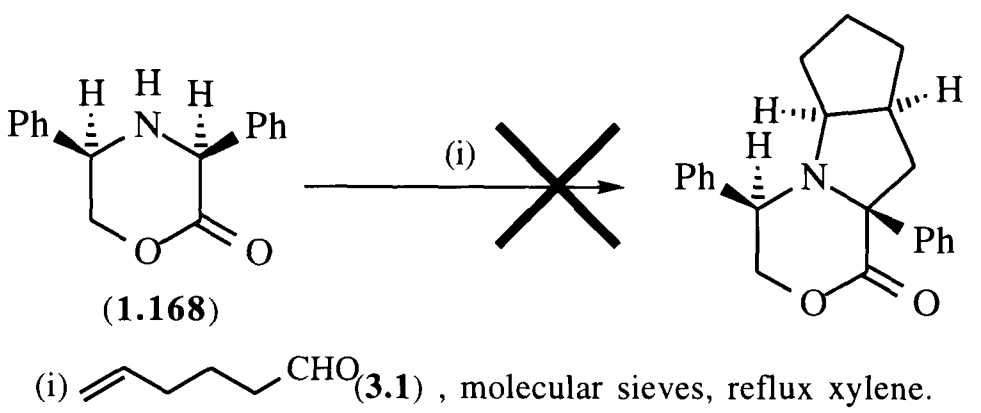


Figure 4.12

This extensive survey of potential ylid precursors and dipolarophiles has shown that cycloaddition could only be achieved when the dipolarophile was highly activated, and the ylid destabilised through the addition of an electron donating group. This indicated that cycloadditions using the dipolarophiles necessary to effect cleavage of the pyrrolidine would be highly unlikely due to their deactivated nature. It was therefore decided that this problem, coupled with the difficulties previously encountered in effecting cleavage of the two *N*-benzyl bonds, meant that the use of this template as a simple general synthetic tool for α-amino acid synthesis was disappointingly unlikely.

4.8 Intramolecular Cycloadditions of (3*S*,5*R*)-Diphenylmorpholinone (1.168).

In order to complete the investigation into the cycloaddition profile of the diphenylmorpholinone template, it was decided to attempt to perform the cycloaddition reaction in an intramolecular fashion. This has previously been shown to allow cycloaddition to proceed in high yield with unactivated dipolarophiles.[14] Accordingly, diphenylmorpholinone (**1.168**) was refluxed with 5-hexenal (**3.1**) in xylene under the usual conditions (**Scheme 4.21**). After 18 hours however t.l.c. and ^{1}H n.m.r. spectroscopic analysis indicated only the presence of starting material.



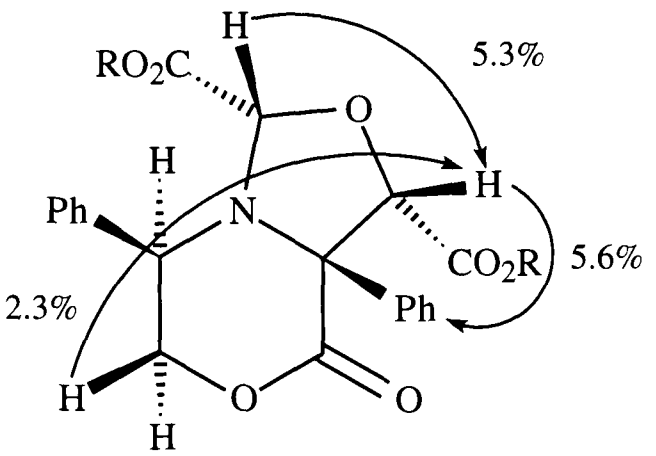
(1.168)

(i) CHO **(3.1)** , molecular sieves, reflux xylene.

Scheme 4.21

By contrast when diphenylmorpholinone (**1.168**) was refluxed in xylene, under the usual conditions, with allyl glyoxylate (**3.5**) (prepared as in Chapter Three), t.l.c. analysis after 18 hours indicated the presence of a new product, which was isolated by column chromatography. The ^{1}H n.m.r. and mass spectrometric data were consistent however, not with that of the required cycloadduct, but instead with that of the adduct derived from the addition of a second mole of aldehyde to the initially formed ylid. Two dimensional n.m.r. coupled with the use of n.O.e. experiments allowed the total structural and stereochemical assignation as that of the cycloadduct (**4.31**), obtained in 24% yield. Irradiation of the proton on the β- face of C_3 gave an enhancement (2.3%) to the proton at C_7, indicating that this proton was also on the β- face (**Figure 4.13**). Irradiation of the proton at C_7 gave a strong enhancement to the protons on the phenyl group at C_6, indicating that this was also on the β- face. Similarly irradiation of the proton at C_9 gave an enhancement to the proton at C_7, showing that the C_9 proton was also on the β- face. No enhancement was observed between the proton at C_2 and C_9, providing further evidence for the given assignment. Use of the

homologue of allyl glyoxylate, but-1-enyl glyoxylate (**3.10**) under the same conditions resulted only in the recovery of starting material after 18 hour reflux.



R = $CH_2CH{=}CH_2$, (**4.31**)-24%

Figure 4.13

Attempts at performing the cycloaddition in an intramolecular fashion with diphenylmorpholinone (**1.168**) suffer from two problems; firstly, steric hindrance due to the substituent α- to nitrogen renders the cycloaddition extremely difficult; secondly, the dipolarophile used in the intramolecular cycloaddition is a simple unactivated double bond, while the highly activated dipolarophile maleic anhydride was necessary to effect cycloaddition with a substituted ylid. The combined effect of the two factors is to prohibit cycloaddition.

4.9 Summary and Future Work.

(3*S*,5*R*)-diphenylmorpholinone (**1.168**) has been shown to readily condense with paraformaldehyde, forming an ylid which undergoes cycloaddition with a range of dipolarophiles to generate cycloadducts in high yield and with good stereocontrol. The higher yield has been rationalised by considering the greater stability of this ylid over the equivalent ylid derived from the simple (5*S*)-phenylmorpholinone (**1.126**) template. Unfortunately, on attempting to introduce substituents α- to nitrogen cycloaddition became extremely disfavoured due to a combination of the additional stability imparted by the phenyl substituent and the steric hindrance of the aldehyde and phenyl substituents. As a result of these two factors attempted intramolecular cycloaddition was also unsuccessful. A second problem arose on attempting to effect complete cleavage of the chiral template. Initial cleavage of the oxazinone ring proceeded

reluctantly, while subsequent hydrogenolysis to furnish the free amino group was not observed. In order to fully exploit this template as a synthetic tool, methods to circumvent these problems must be developed.

4.9.1 High Pressure Mediated Cycloadditions.

It has been widely reported that cycloaddition reactions are promoted by the application of high pressure.[15] The relationship between equilibrium constant and activation volume is given by the equation below, where $\Delta V^{\ddagger}$ is the volume of activation. The transition state for cycloaddition occupies a lower volume than the reactants, and so by Le Chatelier's principle, high pressure may be used to promote the forward reaction.

$$\frac{\delta \ln k}{\delta p} = -\frac{\Delta V^{\ddagger}}{RT}$$

The application of high pressure has been widely applied to the Diels-Alder cycloaddition of unreactive dienes with even the highly deactivated furan ring participating in both intermolecular and intramolecular cycloaddition reactions.[16] Application to [3+2] dipolar cycloadditions has however been much rarer.[17] Theoretically application of high pressure would promote cycloaddition in three separate ways. Initial formation of the ylid would be favoured due to the reduction in molecularity of the reaction. The formation of ionic species would also be favoured due to the increase in solvation energy caused by contraction of the solvation shell. Subsequent cycloaddition would again be favoured on the grounds of molecularity. The Diels-Alder reaction suffers from the problem of cyclo-reversion due to the continued presence of the double bond in the system, however this would not apply to azomethine ylid derived adducts. The reluctant cycloadditions of diphenylmorpholinone (**1.168**) may therefore be attempted under conditions of high pressure. Ylid formation is observed in both inter- and intramolecular cycloaddition, however subsequent cycloaddition has a greater negative activation volume in the intermolecular reaction. The application of pressure is therefore more likely to promote intermolecular cycloaddition.

4.8.2 Template Cleavage.

The second problem arising from the use of (3*S*,5*R*)-diphenylmorpholinone (**1.168**) in cycloadditions is the difficulty in removal of the template following cycloaddition. It was originally envisaged that cleavage of both benzylic nitrogen bonds would occur readily, thus allowing the template to be used as a source of chiral nitrogen. However the observation of reluctant hydrogenation and consequential cleavage of even one *N*-benzyl bond in the case of cycloadducts (**4.12**) and (**4.15**) meant that this aim was far from achieved. As previously stated, the application of very high pressures of hydrogen (>150 atmospheres) has been shown to effect cleavage of the *N*-benzyl bond of a very similar system,[11] and it is therefore conceivable that these conditions would enable template cleavage. In the event of hydrogenolysis being a non-viable method for effecting total template cleavage alternative non-hydrogenolytic methods may prove more successful. Such methods are under investigation within the group.[13]

CHAPTER FOUR

References

CHAPTER FOUR

References

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CHAPTER FIVE

Experimental

CHAPTER FIVE

Experimental

5.1 Experimental Techniques.

^{1}H n.m.r. spectra were recorded in $CDCl_3$, CD_3CN, C_6D_6, D_2O or CD_3OD as stated and referenced to the solvent peak. Instruments used were a Varian Gemini (200 MHz) a Bruker AC200 (200 MHz) and a Bruker AM500 (500 MHz). Peak positions were recorded in δ p.p.m. with the abbreviations s, d, t, q, dd, ddd, qu, dt, se and m denoting singlet, doublet, triplet, quartet, double doublet, double double doublet, quintet, double triplet, sextet and multiplet respectively. Two dimensional COSY spectra and nuclear Overhauser experiments were recorded on the 500 MHz spectrometer and performed in the Dyson-Perrins laboratory by Mrs E. McGuinness. N.O.e. difference data are quoted in the format: irradiation position (δ) **irradiated proton**–enhanced proton (% enhancement).

Infra-red spectra were recorded on a Perkin Elmer 1750 FT-IR spectrometer as thin films or KBr discs as stated.

Mass-spectrometric data was recorded on a TRIO 1 G.C. or ZAB1F mass spectrometer under conditions of chemical ionisation (C.I.), using ammonia as the ionising source. Mass spectra are quoted in the form $^m/_z$ (relative intensity).

Microanalyses were performed on a Carlo Erba 1106 elemental analyser in the Dyson-Perrins laboratory by Mrs V. Lamburn.

Optical rotations were recorded at the sodium D line using a Perkin-Elmer 241 polarimeter.

Melting points were recorded using a Koffler heated-stage microscope and are uncorrected.

Sonications were performed by clamping the flask and placing in a Decon F5 minor sonication bath.

T.l.c. analysis refers to analytical thin layer chromatography using Merck plastic backed plates precoated with 0.2 mm silica 60 F_{254}. Product spots were visualised either by the quenching of u.v. fluorescence, by staining with iodine vapour or by staining with 2% aqueous potassium permanganate solution.

Column chromatography refers to chromatography with Kieselgel 60, using head pressure by means of compressed air.

Short-path distillation (bulb-to-bulb) was performed using a horizontal Kugelrohr apparatus, recording the uncorrected oven temperature.

Solvents and reagents were purified according to procedures detailed in Perrin and Armarego.[1] Acetonitrile and dichloromethane were dried by refluxing over and distilling from calcium hydride. Diethyl ether and tetrahydrofuran were dried by distilling from sodium benzophenone ketyl under nitrogen. Toluene and xylene were dried by standing over sodium. Light petroleum referring to the petroleum ether fraction boiling between 30 and 40°C, and was fractionally distilled before use.

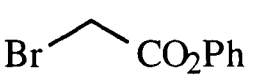
Magnesium bromide-etherate was prepared according to the method of Harwood[2] and stored under an atmosphere of argon. Regular replenishment of the upper diethyl ether layer resulted in the catalyst retaining activity over a period of several months.

Compounds whose preparation is not described below were obtained commercially from Aldrich Fine Chemicals, with the exception of ethyl glyoxylate trimer which was donated by SmithKline Beecham.

5.2 Preparation of Chiral Templates.

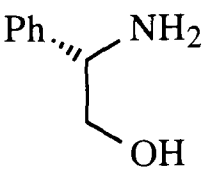
5.2.1 Preparation of (5*S*)-5-Phenyl-morpholin-2-one (1.126).[3]

Phenyl bromoacetate (**2.2**).



Bromoacetyl bromide (9.0 ml, 20.85 g, 103 mmol) was stirred with phenol (9.36 g, 99.6 mmol) at 65°C under nitrogen for 2 hours. The outlet was fitted with a sodium thiosulphate wash bottle to scrub the hydrogen bromide produced during reaction. The mixture was then cooled to room temperature and distilled under vacuum to give a colourless oil which solidified on cooling (16.9 g, 79%). B.p. 91-92°C / 0.1 mmHg, lit[3] 112°C / 2 mmHg; ν_{max} (Film) 1780, 1600, 1495, 1285, 1160 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 7.10-7.46 (5H, m, Ph), 4.07 (2H, s, $BrCH_2$).

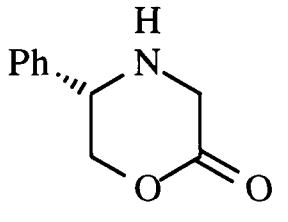
(S)-(+)-2-phenylglycinol (**2.1**).[4]



Lithium aluminium hydride (20.7 g, 0.545 mol, 2 equiv) was suspended in dry tetrahydrofuran (800 ml) in a 2 L round bottom flask fitted with a condenser and nitrogen bubbler. (*S*)-(+)-α-Phenylglycine (40.0 g, 0.265 mol, 1 equiv) was added to the suspension in small portions over 1.5 hours and the resultant green suspension refluxed for 12 hours. The reaction was quenched by dropwise addition of water (20 ml), followed by 4 M sodium hydroxide solution (20 ml) and water (60 ml). The mixture was stirred for 1 hour, filtered through a 4 cm pad of silica and the silica washed with warm tetrahydrofuran (1 l). The tetrahydrofuran was removed under reduced pressure, the residue dissolved in

dichloromethane (400 ml) and the solution washed with brine (2 x 400 ml). The organic phase was dried ($MgSO_4$), filtered and the solvent removed under reduced pressure to yield a yellow solid. The solid was triturated with ether and the title compound isolated by filtration as a colourless solid (26.01 g, 72%). M.p. 75-78°C, lit[5] 75-78°C; δ_H (200 MHz, $CDCl_3$) 7.20-7.47 (5H, m, Ph), 4.08 (1H, dd, *J* 8.4, *J'* 4.1 Hz, PhCH), 3.75 (1H, dd, *J* 10.9, *J'* 4.1 Hz, CH_2OH), 3.57 (1H, dd, *J* 10.9, *J'* 8.4 Hz, CH_2OH), 2.61 (3H, bs, CH_2OH and NH_2); $[\alpha]_D^{23}$ +56.0 (c 1.0, $CHCl_3$), lit[5] $[\alpha]_D^{19}$ +33.0 (c 0.75, 1M HCl).

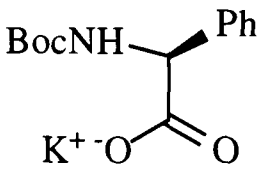
(5S)-3,4,5,6-Tetrahydro-5-phenyl-2H-1,4-oxazin-2-one (**1.126**).



A solution of (*S*)-(+)-2-phenylglycinol (**2.1**) (7.37 g, 53.7 mmol, 1 equiv) and diisopropylethylamine (28 ml, 160 mmol, 2.6 equiv) in dry acetonitrile (250 ml) was added to a stirred solution of phenyl bromoacetate (**2.2**) (12.69 g, 59 mmol, 1.1 equiv) in dry acetonitrile (100 ml) over a period of 1 hour. The mixture was stirred for 16 hours at room temperature, then the solvent removed *in vacuo* to give a yellow oil. Column chromatography using a pre-column pad of Na_2CO_3 (2 cm) and eluting with 1 : 1 ethyl acetate : light petroleum furnished the title compound as a pale yellow solid (5.05 g, 55%). M.p. 53-55°C, lit[3] 53.5-54°C; ν_{max} (KBr disc), 3450, 1740, 1450, 1220 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 7.35-7.45 (5H, m, Ph), 4.15-4.46 (3H, m, PhCH and OCH_2), 4.01 (1H, d, *J* 18.0 Hz, $HNCH_2$), 3.85 (1H, d, *J* 18.0 Hz, $HNCH_2$), 2.10 (1H, bs, NH); $[\alpha]_D^{22}$ +100.4 (c 1.0, $CHCl_3$), lit[6] $[\alpha]_D^{20}$ +95.9 (c 1.0, $CHCl_3$).

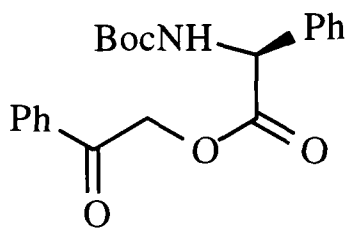
5.2.2 Preparation of (3*S*,5*R*)-3,5-Diphenyl-morpholin-2-one (1.168).[6]

Potassium N-(tert-*butoxycarbonyl)-(*S*)-(+)-2-phenylglycinate* (**4.5**).



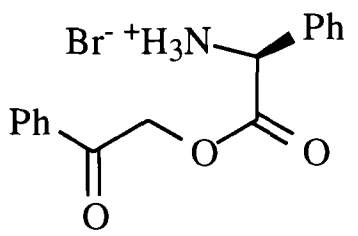
(*S*)-(+)-2-Phenylglycine (15.01 g, 99.3 mmol, 1 equiv) was suspended in 50% aqueous dioxan (220 ml) and 1 M aqueous sodium hydroxide (100 ml, 100 mmol, 1 equiv) added. The solution was cooled in an ice bath, a solution of di-*tert*-butyldicarbonate (23.8 g, 109 mmol, 1.1 equiv) in dioxan (20 ml) added dropwise over 10 minutes, then warmed to room temperature and stirred for 24 hours. The solution was concentrated *in vacuo* to approximately a third of its initial volume, diluted with ethyl acetate (200 ml), and brought to pH 5 (indicator paper) with potassium hydrogen sulphate solution. The aqueous phase was extracted with ethyl acetate (2 x 200 ml), dried ($MgSO_4$) and concentrated *in vacuo* to give a colourless oil. The oil was redissolved in methanol (50 ml) and potassium hydroxide (5.61 g, 100 mmol, 1 equiv) in methanol (150 ml) added. This solution was concentrated *in vacuo* to afford the title compound as a colourless gummy solid which was used in the next stage without further purification (25.58 g, 89%). ν_{max} (KBr disc) 3414, 2979, 1694, 1605, 1368, 1171 cm^{-1}; δ_H (200 MHz, CD_3OD) 7.40-7.43 (2H, m, Ph), 7.20-7.31 (3H, m, Ph), 4.96 (1H, s, NCH), 1.41 (9H, s, ^{t}Bu).

Phenacyl N-(tert-*butoxycarbonyl)-(*S*)-(+)-2-phenylglycinate* (**4.6**).



α-Bromoacetophenone (17.55 g, 88.2 mmol, 1 equiv) in dimethylformamide (20 ml) was added, over 15 minutes, *via* a syringe to a solution of potassium *N*-(*tert*-butoxycarbonyl)-(*S*)-(+)-2-phenylglycinate (**4.5**) (25.58 g, 88.1 mmol, 1 equiv) in dimethylformamide (100 ml). The solution was stirred for 18 hours, diluted with water (200 ml) then extracted with ether (4 x 100 ml). The ether extracts were washed with water (2 x 200 ml), dried ($MgSO_4$), and concentrated *in vacuo* to afford a pale yellow oil. Purification by column chromatography, eluting with 1 : 2 diethyl ether : light petroleum, afforded the title compound as a colourless gum which was used in the next stage without further purification (23.01 g, 74%). δ_H (500 MHz, $CDCl_3$) 7.85-7.87 (2H, m, Ph), 7.60 (1H, t, *J* 7.5 Hz, Ph), 7.34-7.52 (7H, m, Ph), 5.50-5.60 (2H, m), 5.30-5.42 (2H, m), 1.47 (9H, s, ^tBu).

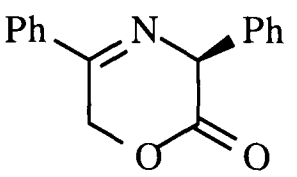
(S)-Phenacyl phenylglycinate, hydrobromide (**4.7**).



Hydrobromic acid (140 ml, 33% w/w solution in acetic acid) was added to phenacyl *N*-(*tert*-butoxycarbonyl)-(*S*)-(+)-2-phenylglycinate (**4.6**) (23.01 g, 65.2 mmol, 1 equiv). The reaction mixture was stirred until evolution of carbon dioxide ceased (16 hours) then diluted with diethyl ether (250 ml) and light petroleum (250 ml). The resulting precipitate was filtered, washed with diethyl ether (2 x 250 ml) and dried *in vacuo* to furnish the title compound as a colourless powder which was used in the next stage without further purification (18.48 g,

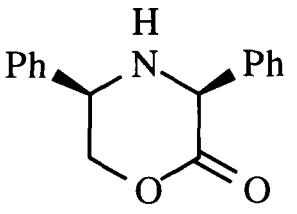
81%). M.p. 162-164°C, lit[6] 170-174°C (dec); ν_{max} (KBr disc) 2962, 2884, 2610, 1754, 1693, 1491, 1219 cm^{-1}; δ_H (200 MHz, CD_3OD) 7.40-8.10 (10H, m, Ph), 5.60 (2H, bs, CH_2O), 5.40 (1H, s, CHPh); $^m/_z$ (CI, NH_3) 270 ($[MH-Br]^+$, 70%), 252 (60%), 106 (100%); $[\alpha]_D^{20}$ +101 (c 1.10, MeOH), lit[6] (enantiomer) $[\alpha]_D^{20}$ -102.5 (c 1.13, MeOH).

(3S)-3,5-Diphenyl-3,6-dihydro-oxazin-2-one (**4.8**).



(*S*)-Phenacyl phenylglycinate hydrobromide (**4.7**) (18.48 g, 52.8 mmol, 1 equiv) was added to 500 ml of a 0.2 M buffer solution [prepared by dissolving sodium acetate trihydrate (13.6 g, 100 mmol) and acetic acid (5.72 ml, 100 mmol) in water (500 ml)]. Precipitation commenced almost immediately. The suspension was stirred for a further 2 hours before being filtered, washed with cold water (500 ml) and dried *in vacuo* to afford the title compound as a pale yellow solid which was used in the next stage without further purification (11.80 g, 89%). M.p. 116-117°C; ν_{max} (KBr) 3061, 2908, 1735, 1655, 1223 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.87-7.88 (2H, m, Ph), 7.35-7.57 (8H, m, Ph), 5.72 (1H, s, NCH), 5.49 (1H, dd, *J* 16.3 Hz, *J'* 2.1 Hz, CH_2O), 5.35 (1H, dd, *J* 16.3 Hz, *J'* 1.1 Hz, CH_2O); $[\alpha]_D^{20}$ +184.9 (c 1.0, MeOH).

(3S,5R)-3,4,5,6-Tetrahydro-3,5-diphenyl-2H-1,4-oxazin-2-one (**1.168**).



(3*S*)-3,5-diphenyl-4,5-dehydromorpholin-2-one (**4.8**) (11.80 g, 47 mmol) was dissolved in ethyl acetate (180 ml) and 5% palladium on carbon (200 mg) added. The

suspension was stirred under an atmosphere of hydrogen until t.l.c. analysis (1 : 1 diethyl ether : light petroleum) demonstrated the absence of starting material, then filtered through Celite® to remove the catalyst and concentrated *in vacuo* to afford a pale yellow oil. Column chromatography eluting with 1 : 1 diethyl ether : light petroleum, followed by recrystallisation from diethyl ether furnished the title compound as colourless cubes (10.22 g, 86%). M.p. 93-96°C, lit[6] 93-95°C; ν_{max} (KBr disc) 3301, 2950, 1733, 1201, 701 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 7.65-7.36 (10H, m, Ph), 4.96 (1H, s, NCHCO), 4.39-4.52 (3H, m, NCH and CH_2O), 2.28 (1H, s, NH); $^m/_z$ (CI, NH_3) 254 (100%, MH^+), 209 (75%), 104 (75%); $[\alpha]_D^{25}$ +85.5 (c 1.0, $CHCl_3$), lit[6] (enantiomer) $[\alpha]_D^{20}$ -5 (c 0.88, $CHCl_3$).

5.3 Chapter Two Experimental.

5.3.1 General Methods for the Preparation of Cycloadducts (2.3-2.14).

Cycloaddition Method A.[6]

(5*S*)-Phenylmorpholin-2-one (**1.126**) (177 mg, 1 mmol, 1 equiv), dipolarophile (2 equiv) and ethyl glyoxylate trimer (204 mg, 2 mmol, 2 equiv) were dissolved in sodium dried toluene (80 ml). The flask was fitted with a condenser and a soxhlet extractor containing activated 4A molecular sieves and the reaction mixture refluxed for 18 hours. The solution was allowed to cool to room temperature and the solvent removed *in vacuo* to afford the crude material. Purification by gradient column chromatography eluting with 1 : 4 diethyl ether : light petroleum to 1 : 1 diethyl ether : light petroleum followed by recrystallisation furnished the pure cycloadducts.

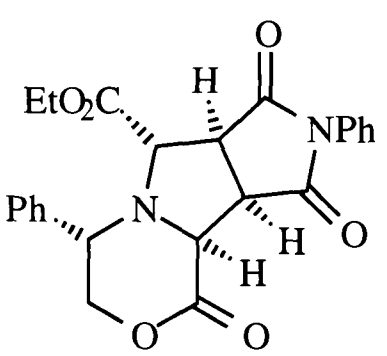
Cycloaddition Method B.[2]

(5*S*)-Phenylmorpholin-2-one (**1.126**) (177 mg, 1 mmol, 1 equiv), dipolarophile (2 equiv) and ethyl glyoxylate trimer (204 mg, 2 mmol, 2 equiv) were dissolved in dry tetrahydrofuran (50 ml) and activated 4A molecular sieves added. $MgBr_2.Et_2O$ (0.5 ml) was added *via* syringe and the solution stirred at room temperature for 4 hours. The reaction

mixture was filtered through silica to remove the sieves and catalyst, the silica washed with ethyl acetate (3 x 20 ml), then the solvent removed *in vacuo* to afford the crude material. Purification by gradient column chromatography eluting with 1 : 4 diethyl ether : light petroleum to 1 : 1 diethyl ether : light petroleum followed by recrystallisation furnished the pure cycloadducts.

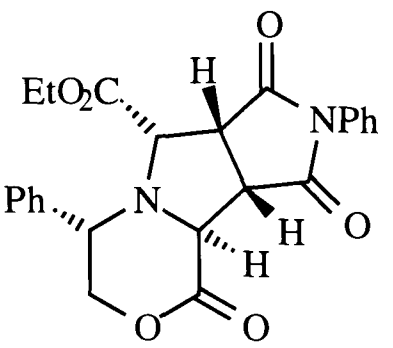
5.3.2 Preparation of Cycloadducts.

(2S,6S,7R,8S,9S)-N-Phenyl-1-aza-9-carboethoxy-4-oxa-2-phenyl[4.3.0^{1,6}]bicyclononan-5-one-7,8-dicarboximide (**2.3**).



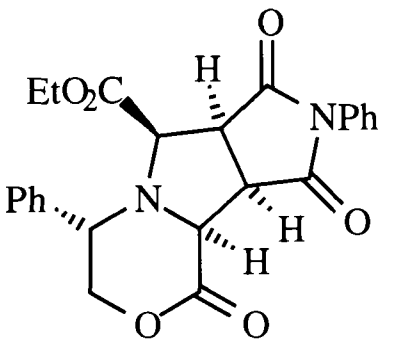
Recrystallised from diethyl ether as colourless needles. Yield: Method A (122 mg, 28%), method B (139 mg, 32%). M.p. 175-179°C; Found C 66.17, H 5.22, N 6.45%, $C_{24}H_{22}N_2O_6$ requires C 66.35, H 5.10, N 6.44%; ν_{max} (KBr disc) 3033, 2979, 1780, 1750, 1720, 1496, 1386, 1234, 1197, 697 cm^{-1}; δ_H (500 MHz, C_6D_6) 7.57-7.60 (2H, m, Ph), 7.15-7.22 (4H, m, Ph), 6.95-7.08 (4H, m, Ph), 4.19 (1H, d, *J* 8.1 Hz, 6α-H), 3.90 (1H, d, *J* 4.0 Hz, 9β-H), 3.55-3.69 (5H, m, CH_2CH_3, 3α-H, 3β-H and 2β-H), 3.48 (1H, dd, *J* 9.5, *J'* 4.0 Hz, 8α-H), 3.39 (1H, dd, *J* 9.5, *J'* 8.0 Hz, 7α-H), 0.69 (3H, t, *J* 7.1 Hz, CH_2CH_3); n.O.e. expt: (δ, %), 4.20 **6α-H**-7α-H (12.3%), -3α-H (4.2%), 3.90 **9β-H**-2β-H (6.4%), -8α-H (3.8%), -Ph (2%), 3.50 **8α-H**-7α-H (4.6%), -9α-H (3.1%), 3.40 **7α-H**-6α-H (12.6%), -8α-H (7.6%); $^m/_z$ (CI, NH_3) 452 (15%, MNH_4^+), 435 (100%, MH^+), 361 (20%), 104 (20%), 94 (20%); $[\alpha]_D^{21}$ +58.2 (c 0.71, $CHCl_3$).

(2S,6S,7S,8R,9S)-N-*Phenyl-1-aza-9-carboethoxy-4-oxa-2-phenyl[4.3.0^{1,6}]bicyclononan-5-one-7,8-dicarboximide* (**2.4**).



Recrystallised from diethyl ether as colourless spines. Yield: Method A (6 mg, 1.4%), method B (74 mg, 17%). M.p. 184.5-186°C; Found C 66.25, H 4.93, N 6.40%, $C_{24}H_{22}N_2O_6$ requires C 66.35, H 5.10, N 6.44%; ν_{max} (KBr disc) 3065, 2982, 1752, 1719, 1494, 1177, 1142, 1046, 703 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.30-7.55 (10H, m, Ph), 4.75 (1H, s, 6α-H), 4.44 (1H, dd, *J* 12.4, *J'* 5.4 Hz, 3β-H), 4.22-4.29 (2H, m, 7β-H + 3α-H), 4.01 (dd, *J* 11.5, *J'* 5.4 Hz, 2β-H), 3.90 (1H, d, *J* 9.1 Hz, 9β-H), 3.78-3.88 (3H, m, CH_2CH_3 + 8β-H), 0.89 (3H, t, *J* 7.2 Hz, CH_2CH_3); n.O.e. expt: (δ, %), 4.75 **6α-H**-3α-H (16.5%), -Ph (3%), 4.40 **3β-H**-3α-H (23.4%), -2β-H (9.2%), 4.0 **2β-H**-3β-H (11%), -9β-H (10.4%), -Ph (10.7%), 3.90 **9β-H**-8β-H (6.5%), -2β-H (4.8%); $^m/_z$ (CI, NH_3) 435 (100%, MH^+), 361 (30%), 104 (30%); $[\alpha]_D^{21}$ -58.4 (c 0.26, $CHCl_3$).

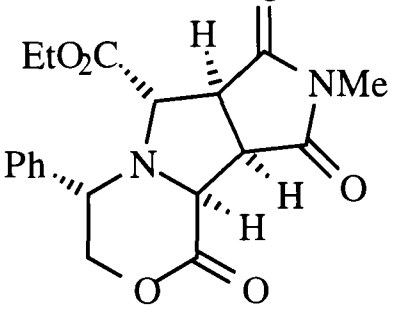
(2S,6S,7R,8S,9R)-N-*Phenyl-1-aza-9-carboethoxy-4-oxa-2-phenyl[4.3.0^{1,6}]bicyclononan-5-one-7,8-dicarboximide* (**2.5**).



Recrystallised from diethyl ether as colourless needles. Yield: Method A (37 mg, 8.6%), method B (0%). M.p. 205-210°C; Found C 66.4, H 4.79, N 6.39%, $C_{24}H_{22}N_2O_6$

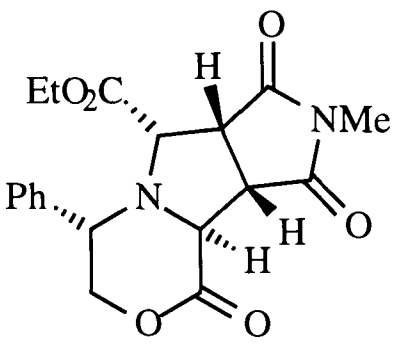
requires C 66.35, H 5.10, N 6.44%; ν_{max} (KBr disc) 3001, 2907, 1765, 1738 , 1709, 1391, 1189, 708 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.32-7.55 (10H, m, Ph), 4.89 (1H, dd, *J* 11.4, *J'* 4.6 Hz, 3β-H), 4.70 (1H, dd, *J* 11.4, *J'* 2.4 Hz, 3α-H), 4.38 (1H, m, 2β-H), 4.36 (2H, q, *J* 7.2 Hz, CH_2CH_3), 3.81 (1H, dd, *J* 7.9, *J'* 6.3 Hz, 8α-H), 3.53 (1H, dd, *J* 8.9, *J'* 7.9 Hz, 7α-H), 3.49 (1H, d, *J* 6.3 Hz, 9α-H), 3.41 (1H, d, *J* 8.9 Hz, 6α-H), 1.38 (3H, t, *J* 7.2 Hz, CH_2CH_3); n.O.e. expt: (δ, %), 4.90 **3β-H**-3α-H (12%), -2β-H (7%), 4.70 **3α-H**-3β-H (24%), -Ph (7%), 3.80 **8α-H**-9α-H (10%), -7α-H (10%), 3.40 **6α-H**-7α-H (10%), -9α-H (3%); $^m/_z$ (CI, NH_3) 452 (10%, MNH_4^+), 435 (100%, MH^+), 361 (20%), 104 (30%); $[\alpha]_D^{21}$ +56.4 (c 0.28, $CHCl_3$).

(2S,6S,7R,8S,9S)-N-*Methyl-1-aza-9-carboethoxy-4-oxa-2-phenyl[4.3.0^{1,6}]bicyclononan-5-one-7,8-dicarboximide* (**2.6**).



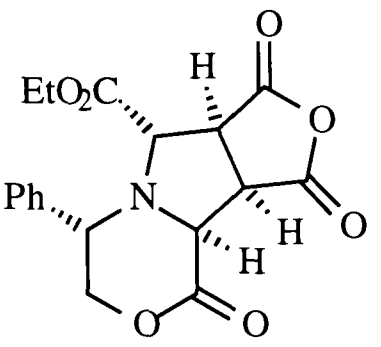
Colourless powder. Yield: Method A (93 mg, 25%), method B (86 mg, 23%). M.p. 65-67°C; Found C 61.39, H 5.14, N 7.71%, $C_{19}H_{20}N_2O_6$ requires C 61.28, H 5.41, N 7.52%; ν_{max} (KBr disc) 2982, 1780, 1751, 1705, 1436, 1383, 1282, 1234, 701 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.37-7.39 (3H, m, Ph), 7.25-7.28 (2H, m, Ph), 4.55 (1H, d, *J* 8.2 Hz, 6α-H), 4.21-4.29 (2H, m, 3α-H and 3β-H), 4.08-4.14 (2H, m, CH_2CH_3), 3.98 (1H, d, *J* 3.5 Hz, 9β-H), 3.91 (1H, t, *J* 8.5 Hz, 7α-H), 3.72 (1H, dd, *J* 8.5, *J'* 2.5 Hz, 8α-H), 3.64 (1H, dd, *J* 10.0, *J'* 4.1 Hz, 2β-H), 3.08 (3H, s, NMe), 1.22 (3H, t, *J* 7.1 Hz, CH_2CH_3); n.O.e. expt: (δ, %), 4.55 **6α-H**-7α-H (11%), 4.00 **9β-H**-2β-H (2.8%), -8α-H (1%), 3.90 **7α-H**-6α-H (11%), -8α-H (8%), 3.75 **8α-H**-7α-H (8.3%), -9β-H (4.1%), 3.65 **2β-H**-Ph (11.2%), -9β-H (5.9%), -3α/β-H (3.1%); $^m/_z$ (CI, NH_3) 373 (100%, MH^+), 299 (15%), 104 (45%); $[\alpha]_D^{25}$ -40.7 (c 0.29, $CHCl_3$).

(2S,6S,7S,8R,9S)-N-Methyl-1-aza-9-carboethoxy-4-oxa-2-phenyl[4.3.0^{1,6}]bicyclononan-5-one-7,8-dicarboximide (**2.7**).



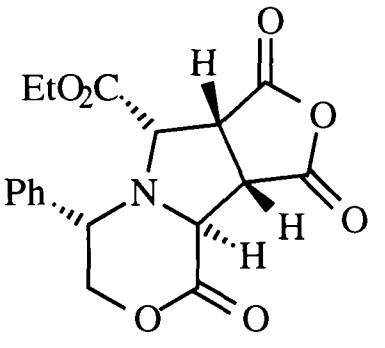
Recrystallised from diethyl ether / light petroleum as colourless needles. Yield: Method A (23 mg, 6.3%), method B (123 mg, 33%). M.p. 161-162°C; Found C 61.55, H 5.73, N 7.61%, $C_{19}H_{20}N_2O_6$ requires C 61.28, H 5.41, N 7.52%; ν_{max} (KBr disc) 2990, 1758, 1737, 1700, 1438, 1293, 1026, 697 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.28-7.35 (5H, m, Ph), 4.63 (1H, s, 6α-H), 4.40 (1H, dd, *J* 12.4, *J'* 5.3 Hz, 3β-H), 4.21 (1H, t, *J* 11.9 Hz, 3α-H), 4.10 (1H, d, *J* 8.5 Hz, 7β-H), 3.93 (1H, dd, *J* 11.4, *J'* 5.3 Hz, 2β-H), 3.77-3.85 (3H, m, CH_2CH_3 and 9β-H), 3.64 (1H, t, *J* 8.8 Hz, 8β-H), 3.06 (3H, s, NMe), 0.93 (3H, t, *J* 7.2 Hz, CH_2CH_3); n.O.e. expt: (δ, %), 4.65 **6α-H**-3α-H (7.1%), -7β-H (5.2%), -Ph (3.6%), 4.40 **3β-H**-3α-H (27.3%), -2β-H (7.7%), -Ph (3.6%), 4.25 **3α-H**-3β-H (20%), -6α-H (12.4%), -Ph (4.2%), 4.10 **7β-H**-8β-H (8%), -6α-H (4%), 3.95 **2β-H**-Ph (9.4%), -9β-H (9.1%), -3β-H (7.1%), 3.70 **8β-H**-7β-H (9.7%), -9β-H (8.2%); $^m/_z$ (CI, NH_3) 373 (100%, MH^+), 299 (25%), 104 (30%); $[\alpha]_D^{20}$ -43.6 (c 0.28, $CHCl_3$).

(2S,6S,7R,8S,9S)-1-Aza-9-carboethoxy-4-oxa-2-phenyl[4.3.0^{1,6}]bicyclononan-5-one-7,8-dicarboxylic anhydride (**2.8**).



Recrystallised from ethyl acetate as a colourless powder. Yield: Method A (7 mg, 2%), method B (9 mg, 2.6%). M.p. 165-167°C; Found C 60.32, H 4.53, N 3.66%, $C_{18}H_{17}NO_7$ requires C 60.16, H 4.77, N 3.90%; ν_{max} (KBr disc) 3035, 2973, 1860, 1798, 1781, 1456, 1242, 1115, 700 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.31-7.48 (5H, m, Ph), 4.62 (1H, d, *J* 8.4 Hz, 6α-H), 4.28-4.35 (2H, m, 3α-H and 3β-H), 4.17 (1H, d, *J* 2.3 Hz, 9β-H), 4.13-4.17 (3H, m, 7α-H and CH_2CH_3), 4.02 (1H, dd, *J* 9.4, *J'* 2.1 Hz, 8α-H), 3.82 (1H, dd, *J* 9.6, *J'* 4.4 Hz, 2β-H), 1.24 (3H, t, *J* 7.1 Hz, CH_2CH_3); n.O.e. expt: (δ, %), 4.60 **6α-H**-7α-H (12.6%), 4.05 **8α-H**-7α-H (10%), 3.85 **2β-H**-Ph (12.3%), -3β-H (5.6%), -9β-H (5.6%); $^m/_z$ (CI, NH_3) 377 (90%, MNH_4^+), 360 (100%, MH^+), 288 (40%), 264 (25%), 104 (30%); $[\alpha]_D^{25}$ -56 (c 0.25, $CHCl_3$).

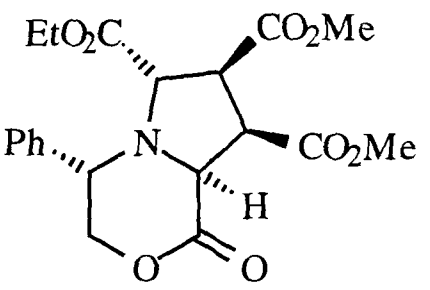
(2S,6S,7S,8R,9S)-1-Aza-9-carboethoxy-4-oxa-2-phenyl[4.3.0^{1,6}]bicyclononan-5-one-7,8-dicarboxylic anhydride (**2.13**).



Recrystallised from ethyl acetate as a colourless powder. Yield: Method A (0%), method B (5 mg, 1.4%). M.p. 141.5-143°C; Found C 60.39, H 4.55, N 3.86%, $C_{18}H_{17}NO_7$

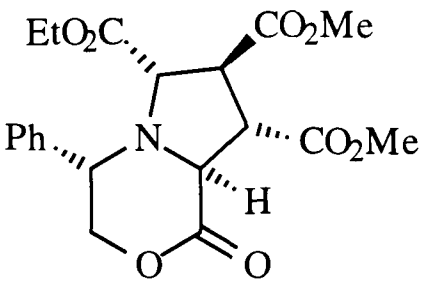
requires C 60.16, H 4.77, N 3.90%; ν_{max} (KBr disc) 2999, 1861, 1783, 1745, 1742, 1285, 1039, 702 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.28-7.48 (5H, m, Ph), 4.72 (1H, s, 6α-H), 4.45 (1H, dd, *J* 12.5, *J'* 5.4 Hz, 3β-H), 4.38-4.43 (1H, m, 7β-H), 4.24 (1H, t, *J* 11.5 Hz, 3α-H), 4.00 (1H, dd, *J* 11.4, *J'* 5.4 Hz, 2β-H), 3.80-3.90 (2H, m, 8β-H and 9β-H), 3.85 (2H, q, *J* 7.2 Hz, CH_2CH_3), 0.93 (3H, t, *J* 7.2 Hz, CH_2CH_3); n.O.e. expt: (δ, %), 4.70 **6α-H**-3α-H (8%), -Ph (4.8%), -7β-H (4.4%), 4.25 **3α-H**-3β-H (22.2%), -6α-H (13.4%), -Ph (2%), 4.00 **2β-H**-Ph (10.2%), -9β-H (8.3%), -3β-H (7.2%); $^m/_z$ (CI, NH_3) 377 (50%, MNH_4^+), 360 (100%, MH^+), 286 (25%), 164 (25%), 104 (25%); $[\alpha]_D^{25}$ -50.1 (c 0.29, $CHCl_3$).

(2S,6S,7R,8S,9S)-1-Aza-9-carboethoxy-7,8-di(carbomethoxy)-4-oxa-2-phenyl[4.3.0^{1,6}]bicyclononan-5-one (**2.9**).



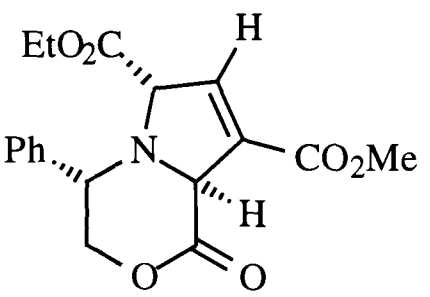
Recrystallised from diethyl ether as colourless needles. Yield: Method A (150 mg, 37%), method B (178 mg, 44%). M.p. 179-180°C; Found C 58.24, H 6.13, N 3.56%, $C_{20}H_{23}NO_8$ requires C 58.01, H 5.89, N 3.56%; ν_{max} (KBr disc) 2994, 1758, 1740, 1732, 1719, 1277, 1202, 1173, 708 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.29-7.39 (5H, m, Ph), 4.68 (1H, d, *J* 6.2 Hz, 6α-H), 4.40 (1H, dd, *J* 10.7, *J'* 2.4 Hz, 2β-H), 4.35 (1H, t, *J* 10.7 Hz, 3α-H), 4.25 (1H, dd, *J* 10.7, *J'* 2.4 Hz, 3β-H), 4.02 (1H, d, *J* 10.2 Hz, 9β-H), 3.83 (1H, t, *J* 6.7 Hz, 7α-H), 3.73-3.79 (1H, m, CH_2CH_3), 3.75 (3H, s, OMe), 3.67 (3H, s, OMe), 3.57 (1H, dd, *J* 10.2, *J'* 7.1 Hz, 8α-H), 3.35-3.42 (1H, m, CH_2CH_3), 0.88 (3H, t, *J* 7.1 Hz, CH_2CH_3); n.O.e. expt: (δ, %), 4.70 **6α-H**-7α-H (13.2%), -8α-H (5.6%), 4.25 **3β-H**-2β-H + 3α-H (27%), 4.00 **9β-H**-2β-H (8.3%), -8α-H (1%), 3.85 **7α-H**-6α-H (11.4%), -8α-H (10%), 3.60 **8α-H**-7α-H (9.5%), -6α-H (4.2%), -9β-H (2%); $^m/_z$ (CI, NH_3) 406 (100%, MH^+), 332 (15%), 104 (15%); $[\alpha]_D^{25}$ +68.1 (c 0.31, $CHCl_3$).

(2S,6S,7S,8S,9S)-1-Aza-9-carboethoxy-7,8-di(carbomethoxy)-4-oxa-2-phenyl[4.3.0^{1,6}]bicyclononan-5-one (**2.10**).



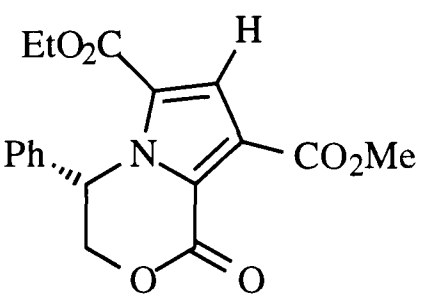
Recrystallised from diethyl ether as colourless needles. Yield: Method A (178 mg, 44%), method B (263 mg, 65%). M.p. 99-100°C; Found C 58.18, H 5.69, N 3.27%, $C_{20}H_{23}NO_8$ requires C 58.01, H 5.89, N 3.56%; ν_{max} (KBr disc) 3030, 2959, 1762, 1740 , 1728, 1280, 1220, 1196, 698 cm^{-1}; δ_H (500 MHz, C_6D_6) 6.98-7.15 (5H, m, Ph), 4.69 (1H, d, *J* 5.0 Hz, 6α-H), 4.33 (1H, dd, *J* 6.9, *J'* 5.0 Hz, 7β-H), 4.03 (1H, t, *J* 6.8 Hz, 8α-H), 3.79 (1H, d, *J* 6.7 Hz, 9β-H), 3.72 (1H, dd, *J* 10.9, *J'* 4.0 Hz, 2β-H), 3.51-3.60 (3H, m, 3α-H, 3β-H and CH_2CH_3), 3.36 (3H, s, OMe), 3.32-3.38 (1H, m, CH_2CH_3), 3.26 (3H, s, OMe), 0.63 (3H, t, *J* 7.1 Hz, CH_2CH_3); n.O.e. expt: (δ, %), 4.70 **6α-H**-3α-H (4%), -7β-H (3.3%), -8α-H (1.2%), 4.35 **7β-H**-8α-H (2.5%), -6α-H (2.3%), -9β-H (1.5%), 4.05 **8α-H**-9β-H (2.4%), -7β-H (2.1%), -6α-H (1%), 3.80 **9β-H**-2β-H (5.4%), -8α-H (4.7%), -7β-H (2.2%), 3.70 **2β-H**-Ph (10.4%), -9β-H (6.7%), -3β-H (4.4%); $^m/_z$ (CI, NH_3) 406 (100%, MH^+), 104 (25%); $[\alpha]_D^{25}$ -27.9 (c 0.61, $CHCl_3$).

(2S,6S,9S)-1-Aza-9-carboethoxy-7-carbomethoxy-4-oxa-2-phenyl[4.3.0^{1,6}]bicyclononan-7-en-5-one (**2.11**).



Recrystallised from diethyl ether / light petroleum as a colourless powder. Yield: Method A (72 mg, 21%), method B (138 mg, 40%). M.p. 120-123°C; Found C 62.84, H 5.32, N 3.80%, $C_{18}H_{19}NO_6$ requires C 62.60, H 5.55, N 4.06%; ν_{max} (KBr disc) 3032, 2987, 1757, 1751, 1724, 1646, 1265, 1182, 1032, 700 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.29-7.49 (5H, m, Ph), 6.72 (1H, t, *J* 1.7 Hz, 8-H), 5.30 (1H, dd, *J* 5.9, *J'* 1.6 Hz, 6α-H), 4.42 (1H, dd, *J* 5.9, *J'* 1.9 Hz, 9β-H), 4.25-4.37 (2H, m, 3α-H and 3β-H), 4.05 (1H, dd, *J* 10.8, *J'* 3.9 Hz, 2β-H), 3.85 (3H, s, OMe), 3.78-3.85 (1H, m, CH_2CH_3), 3.64-3.70 (1H, m, CH_2CH_3), 0.90 (3H, t, *J* 7.1 Hz, CH_2CH_3); n.O.e. expt: (δ, %), 6.70 **8-H**-9β-H (7%), 5.30 **6α-H**-3α-H (4.8%), -Ph (2.4%), 4.40 **9β-H**-2β-H (10%), -8-H (7.7%), 4.05 2β-H-Ph (13.8%), -9β-H (13.4%); $^m/_z$ (CI, NH_3) 346 (100%, MH^+), 344 (20%), 272 (20%), 104 (20%); $[\alpha]_D^{25}$ -136 (c 0.29, $CHCl_3$).

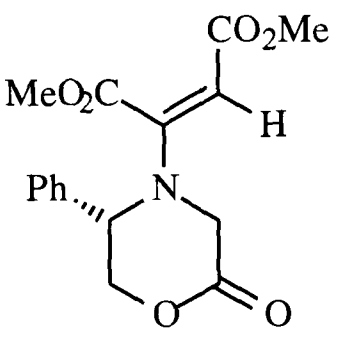
(2S)-1-Aza-9-carboethoxy-7-carbomethoxy-4-oxa-2-phenyl[4.3.0^{1,6}]bicyclononan-6,8-dien-5-one (**2.12**).



Recrystallised from diethyl ether as colourless needles. Yield: Method A (80 mg, 23%), method B (41 mg, 12%). M.p. 204-205°C; Found C 62.76, H 4.82, N 3.91%, $C_{18}H_{17}NO_6$

requires C 62.97, H 4.99, N 4.08%; ν_{max} (KBr disc) 3128, 2989, 1734, 1720, 1707, 1548, 1446, 1281, 1216, 1117, 710 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.47 (1H, s, 8-H), 7.32-7.35 (3H, m, Ph), 6.90-6.92 (2H, m, Ph), 6.45 (1H, d, *J* 2.5 Hz, 2β-H), 4.93 (1H, dd, *J* 11.8, *J'* 3.3 Hz, 3β-H), 4.67 (1H, dd, *J* 11.8, *J'* 1.3 Hz, 3α-H), 4.19-4.30 (2H, m, CH_2CH_3), 3.95 (3H, s, OMe), 1.29 (3H, t, *J* 7.1 Hz, CH_2CH_3); n.O.e. expt: (δ, %), 6.50 **2β-H**-Ph (8.8%), -3β-H (5.8%), -3α-H (3.5%), 4.95 **3β-H**-3α-H (28%), -2β-H (11%), 4.7 **3α-H**-3β-H (30.2%), -2β-H (6.6%), -Ph (5.8%); $^m/_z$ (CI, NH_3) 344 (100%, MH^+), 91 (30%); $[\alpha]_D^{22}$ -189 (c 0.25, $CHCl_3$).

Attempted preparation of *(2S,6S,9S)-1-Aza-9-carboethoxy-7,8-di(carbomethoxy)-2-phenyl-4-oxa[4.3.0^{1,6}]bicyclonon-7-en-5-one*, preparation of *(5S)*-N-(E-*Dimethyl-butenedioate)-5-phenyl-morpholin-2-one* (**2.14**).



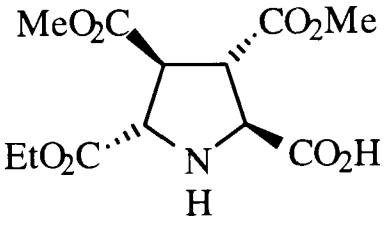
Recrystallised from diethyl ether as a colourless powder. Yield: Method A (0%), method B (80 mg, 25%). M.p. 139-143°C; Found C 60.34, H 5.50, N 4.48%, $C_{16}H_{17}NO_6$ requires C 60.18, H 5.37, N 4.39%; ν_{max} (KBr disc) 3027, 2953, 1770, 1742, 1697, 1581, 1164, 698 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.22-7.42 (5H, m, Ph), 4.76 (1H, t, *J* 4.2 Hz, 6α-H), 4.71 (1H, dd, *J* 12.1, *J'* 4.2 Hz, 6β-H), 4.67 (1H, s, C=CH), 4.55 (1H, dd, *J* 12.1, *J'* 4.2 Hz, 5β-H), 4.19 (1H, d, *J* 17.3 Hz, 3β-H), 4.15 (1H, d, *J* 17.3 Hz, 3α-H), 3.83 (3H, s, OMe_1), 3.62 (3H, s, OMe_2); n.O.e. expt: (δ, %), 4.55 **5β-H**-C=CH (15.9%), -6α-H (8%), -Ph (7.8%), -6β-H (5.8%), -3β-H (3.7%), -Me_1 (3%); $^m/_z$ (CI, NH_3) 320 (100%, MH^+), 104 (20%); $[\alpha]_D^{24}$ +114 (c 0.30, $CHCl_3$).

5.3.3 Preparation of Proline Derivatives (2.15-2.18).

General Method For Hydrogenolysis of Cycloadducts.[7]

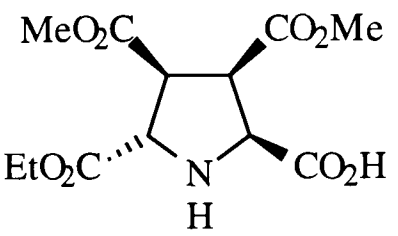
The cycloadduct (0.5 mmol) was dissolved in methanol (25 ml), and placed in a Fischer-Porter bottle. Pearlman's catalyst (50 mg), trifluoroacetic acid (0.1 ml), and water (0.1 ml) were added, and the bottle pressurised with hydrogen to 4 bar behind a safety shield. The suspension was stirred for 18 hours then depressurised and filtered through Celite® to remove the catalyst. Removal of the solvent *in vacuo* afforded a yellow oil, which was precipitated as a gummy solid by the addition of diethyl ether. The solid was washed with diethyl ether (3 x 10 ml), then centrifuged to afford the pure amino acid as a colourless powder.

(2S,3S,4S,5S)-5-Carboethoxy-3,4-di(carbomethoxy)pyrrolidine-2-carboxylic acid (**2.15**).



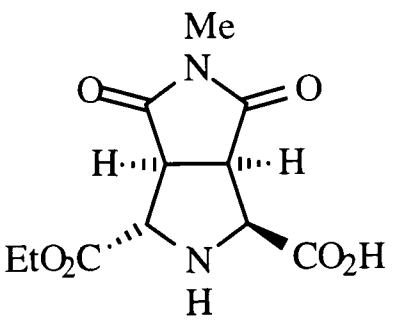
The amino acid was prepared according to the general procedure for proline preparation previously described then recrystallised from diethyl ether as a colourless powder (139 mg, 92%). M.p. 125-127°C; Found C 47.49, H 5.42, N 4.67%, $C_{12}H_{17}NO_8$ requires C 47.55, H 5.65, N 4.62%; ν_{max} (KBr disc) 3750-2600, 3440, 2961, 1747, 1687, 1652, 1442, 1265, 1205 cm^{-1}; δ_H (500 MHz, CD_3OD) 4.52-4.61 (1H, bs, 2α-H), 4.35-4.44 (1H, bs, 5β-H), 4.20-4.35 (2H, m, $C\underline{H}_2CH_3$), 3.76 (6H, s, 2 x O<u>Me</u>), 3.65-3.73 (2H, m, 3β-H and 4α-H), 1.30 (t, *J* 7.1 Hz, $CH_2C\underline{H}_3$); δ_C (125 MHz, CD_3OD) 172.60, 172.00, 170.74, 153.17, 64.17, 63.64, 63.51, 53.49, 53.45, 51.74, 51.63, 14.31; $^m/_z$ (CI, NH_3) 304 (100%, MH^+), 260 (25%), 258 (85%), 226 (30%); $[\alpha]_D^{25}$ +14 (c 0.3, MeOH).

(2S,3R,4S,5S)-5-Carboethoxy-3,4-di(carbomethoxy)pyrrolidine-2-carboxylic acid (**2.16**).



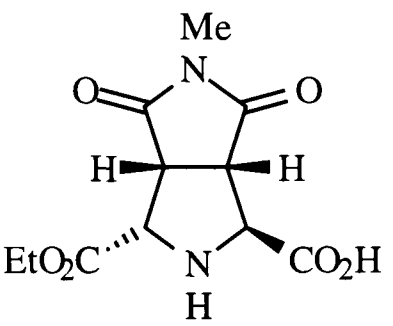
The amino acid was prepared according to the general procedure for proline preparation previously described then recrystallised from diethyl ether as a colourless powder (140 mg, 92%). M.p. 120-125°C; Found C 47.26, H 5.65, N 4.65%, $C_{12}H_{17}NO_8$ requires C 47.55, H 5.65, N 4.62%; ν_{max} (KBr disc) 2400-3600, 3467, 2991, 1752, 1642, 1290, 1240, 1207 cm^{-1}; δ_H (500 MHz, CD_3OD), 4.78 (1H, d, *J* 9.0 Hz, 2α-H), 4.49 (1H, bs, 5β-H), 4.21 (2H, m, $C\underline{H}_2CH_3$), 3.81-3.95 (2H, m, 3α-H and 4α-H), 3.74 (3H, s, O<u>Me</u>), 3.68 (3H, s, O<u>Me</u>), 1.29 (3H, t, *J* 7.0 Hz, $CH_2C\underline{H}_3$); δ_C (125 MHz, CD_3OD) 171.98, 170.34, 169.82, 65.00, 63.95, 61.45, 53.32, 53.14, 50.92, 50.63, 14.24; $^m/_z$ (CI, NH_3) 304 (100%, MH^+), 259 (60%), 258 (100%); $[\alpha]_D^{25}$ +20.6 (c 1.0, MeOH).

(2S,3R,4S,5S)-5-Carboethoxy-3,4-(N-methyl-dicarboximido)-pyrrolidine-2-carboxylic acid (**2.17**).



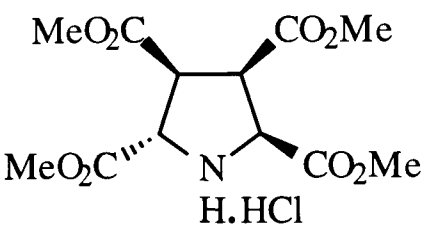
The amino acid was prepared according to the general procedure for proline preparation previously described then recrystallised from methanol as a colourless powder (120 mg, 89%). M.p. 164-168°C; ν_{max} (KBr disc) 2600-3680, 3446, 2989, 1780, 1708, 1445, 1388, 1207, 1137 cm^{-1}; δ_H (500 MHz, CD_3OD) 4.23-4.36 (4H, m, $C\underline{H}_2CH_3$, 2α-H and 5β-H), 3.73-3.75 (2H, m, 3α–H and 4α-H), 2.94 (3H, s, N<u>Me</u>), 1.33 (3H, t, *J* 7.1 Hz, $CH_2C\underline{H}_3$); δ_C (125 MHz, CD_3OD) 177.67, 176.39, 171.39, 171.14, 63.53, 62.84, 50.15, 48.06, 25.58, 14.32; $^m/_z$ (CI, NH_3) 271 (100%, MH^+), 225 (55%), 94 (25%); $[\alpha]_D^{25}$ -6.4 (c 0.25, MeOH).

(2S,3S,4R,5S)-5-Carboethoxy-3,4-(N-methyl-dicarboximido)-pyrrolidine-2-carboxylic acid (**2.18**).



The amino acid was prepared according to the general procedure for proline preparation previously described then recrystallised from diethyl ether as a colourless powder (115 mg, 85%). M.p. 160-165°C (dec); ν_{max} (KBr disc) 2510-3800, 3457, 2991, 1780, 1740, 1708, 1387, 1207, 1138 cm^{-1}; δ_H (500 MHz, CD_3CN) 4.18-4.24 (2H, m, $C\underline{H}_2CH_3$), 4.16 (1H, s, 2α-H), 4.01 (1H, d, *J* 7.9 Hz, 5β-H), 3.63 (1H, d, *J* 7.8 Hz, 3β-H), 3.56 (1H, t, *J* 7.9 Hz, 4β-H), 2.86 (3H, s, N<u>Me</u>), 1.29 (3H, t, *J* 7.1 Hz, $CH_2C\underline{H}_3$); δ_C (125 MHz, CD_3CN) 177.88, 176.61, 173.19, 170.28, 63.33, 62.66, 62.11, 50.38, 50.08, 25.42, 14.30; $^m/_z$ (CI, NH_3) 271 (100%, MH^+), 225 (30%), 197 (25%), 94 (15%); $[\alpha]_D^{25}$ -12 (c 0.25, MeOH).

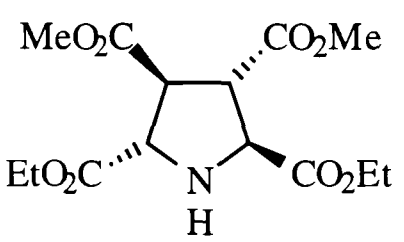
(2S,3R,4S,5S)-2,3,4,5-Tetra(carbomethoxy)pyrrolidine hydrochloride (**2.19**).



A saturated solution of hydrogen chloride in methanol (50 ml) was prepared by bubbling hydrogen chloride gas through the dry solvent for 1 hour. The amino acid (**2.16**) (127 mg, 0.41 mmol, 1 equiv) was dissolved in methanol (5 ml) and added to the stirred solution which was heated to 50°C for 4 hours. After this time the solvent was removed *in vacuo*, the resultant oil dissolved in 5 M HCl solution (50 ml), washed with dichloromethane (3 x 20 ml), and then the solvent removed *in vacuo* to afford the title compound as a colourless powder (105 mg, 76%). M.p. >310°C; ν_{max} 3436, 2925, 1748, 1635, 1156 cm^{-1}; δ_H (500

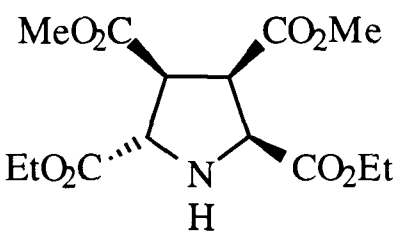
MHz, D_2O) 4.99 (1H, s, 5β-H), 4.97 (1H, d, *J* 4.7 Hz, 2α-H), 4.17 (1H, t, *J* 7.0 Hz, 4α-H), 4.09 (1H, dd, *J* 9.9, *J'* 7.6 Hz, 3α-H), 3.80 (3H, s, OMe), 3.79 (3H, s, OMe), 3.75 (3H, s, OMe), 3.69 (3H, s, OMe); δ_C (125 MHz, D_2O) 171.04, 169.83, 167.89, 166.90, 62.19, 60.00, 54.78, 54.61, 54.19, 48.94, 48.58; $^m/_z$ (CI, NH_3) 304 (100%, $[MH\text{-}Cl]^+$), 244 (10%), 80 (15%); $[\alpha]_D^{25}$ +4.1 (c 0.27, MeOH).

(2S,3S,4S,5S)-2,5-Di(carboethoxy)-3,4-di(carbomethoxy)pyrrolidine (**2.20**).



The amino acid (**2.15**) (150 mg, 0.49 mmol, 1 equiv) was dissolved in acetone (5 ml) and added to a stirred suspension of potassium carbonate (138 mg, 1 mmol, 2 equiv) in acetone (30 ml). Ethyl iodide (0.5 ml, 6.2 mmol, 12 equiv) was added *via* a syringe, and the solution stirred at room temperature for 12 hours. The solvent was removed *in vacuo*, and the resultant solid residue extracted with diethyl ether (3 x 5 ml). The ether extracts were combined and the solvent removed *in vacuo* to afford the crude product which was further purified by column chromatography on alumina, eluting with 1 : 1 diethyl ether : light petroleum, to furnish the title compound as a colourless oil (135 mg, 86%). Found 332.1345, $C_{14}H_{22}NO_8$ (MH^+) requires 332.1346; ν_{max} (film) 3341, 2985, 1739, 1439, 1217, 1024 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 4.19-4.27 (6H, m, $C\underline{H}_2CH_3$ and $C\underline{H}CO_2Et$), 3.76 (6H, s, OMe), 3.60 (2H, dd, *J* 4.3, *J'* 1.8 Hz, $C\underline{H}CO_2Me$), 2.90 (1H, bs, N<u>H</u>), 1.29 (6H, t, *J* 7.1 Hz, $CH_2C\underline{H}_3$); δ_C (125 MHz, $CDCl_3$) 171.85, 171.72, 62.92, 61.71, 52.71, 50.90, 14.10; $^m/_z$ (CI, NH_3) 332 (100%, MH^+), 318 (30%), 226 (20%); $[\alpha]_D^{22}$ +10.8 (c 0.74, $CHCl_3$).

(2S,3R,4S,5S)-2,5-Di(carboethoxy)-3,4-di(carbomethoxy)pyrrolidine (**2.21**).

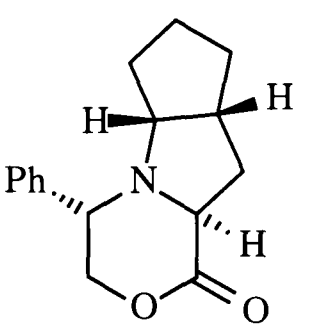


The amino acid (**2.16**) (155 mg, 0.52 mmol, 1 equiv) was dissolved in acetone (5 ml) and added to a stirred suspension of potassium carbonate (168 mg, 1.2 mmol, 2.3 equiv) in acetone (30 ml). Ethyl iodide (0.5 ml, 6.2 mmol, 12 equiv) was added *via* a syringe, and the solution stirred at room temperature for 12 hours. The solvent was removed *in vacuo*, and the resultant solid residue extracted with diethyl ether (3 x 5 ml). The ether extracts were combined and the solvent removed *in vacuo* to afford the crude product which was further purified by column chromatography on alumina, eluting with 1 : 1 diethyl ether : light petroleum, to furnish the title compound as a colourless oil (96 mg, 56%). Found 332.1345, $C_{14}H_{22}NO_8$ (MH^+) requires 332.1346; ν_{max} (film) 3346, 2982, 2909, 1743, 1739, 1730, 1441, 1207, 1030 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 4.49 (1H, d, *J* 8.0 Hz, 5β-H), 4.17-4.26 (4H, m, 2 x $C\underline{H}_2CH_3$), 4.13 (1H, d, *J* 5.8 Hz, 2α-H), 3.70 (3H, s, O<u>Me</u>), 3.68-3.72 (1H, m, 4α-H), 3.65 (3H, s, O<u>Me</u>), 3.64 (1H, dd, *J* 7.3, *J'* 5.8 Hz, 3α-H), 3.16 (1H, bs, N<u>H</u>), 1.30 (3H, t, *J* 7.2 Hz, $CH_2C\underline{H}_3$), 1.28 (3H, t, *J* 7.1 Hz, $CH_2C\underline{H}_3$); δ_C (125 MHz, $CDCl_3$) 172.97, 170.77, 170.36, 169.92, 63.41, 61.66, 61.59, 61.03, 52.40, 52.23, 50.78, 50.64, 14.08; $^m/_z$ (CI, NH_3) 332 (100%, MH^+), 258 (10%); $[\alpha]_D^{18.5}$ -1.3 (c 0.83, $CHCl_3$).

5.4 Chapter Three Experimental.

5.4.1 Catalysed Intramolecular Cycloadditions.

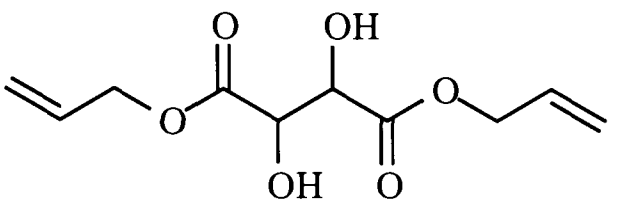
(2R,6R,8S,12S)-1-Aza-10-oxa-12-phenyl[6.4.0^{1,8}.0^{2,6}]tricyclododecan-9-one (**3.2**).



(5*S*)-Phenylmorpholin-2-one (**1.126**) (88 mg, 0.49 mmol, 1 equiv) and 5-hexenal (**3.1**) (120 mg, 1.22 mmol, 2.5 equiv) were dissolved in dry tetrahydrofuran and 4A molecular sieves added. $MgBr_2.Et_2O$ (0.5 ml) was added *via* syringe and the solution stirred at room temperature for 4 hours. The reaction mixture was filtered through silica to remove the sieves and catalyst, then the solvent removed *in vacuo* to afford the crude material. Purification by column chromatography eluting with 1 : 4 diethyl ether : light petroleum afforded the title compound as a colourless solid (19 mg, 15%). M.p. 113-115°C, lit[8] M.p. 114.5-115.5°C; ν_{max} (KBr disc) 2978, 1750, 1460, 1240, 1078, 705 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.29-7.45 (5H, m, Ph), 4.29 (1H, dd, *J* 11.6, *J'* 4.6 Hz, 11β-H), 4.13 (1H, t, *J* 11.6 Hz, 11α-H), 4.11 (1H, dd, *J* 7.3, *J'* 3.3 Hz, 8α-H), 3.95 (1H, dd, *J* 11.6, *J'* 4.6 Hz, 12β-H), 3.25-3.30 (1H, m, 2β-H), 2.61-2.67 (2H, m, 6β-H and 7α-H), 1.77-1.87 (1H, m, 7β-H), 1.58-1.68 (2H, m, 5β-H and 4α-H), 1.42-1.47 (1H, m, 5α-H), 1.37-1.42 (1H, m, 4β-H), 1.30-1.35 (2H, m, 3α-H and 3β-H); $^m/_z$ (CI, NH_3) 258 (100%, MH^+), 213 (15%), 104 (35%); $[\alpha]_D^{22}$ -38.2 (c 0.79, $CHCl_3$), lit[8] $[\alpha]_D^{20}$ -44 (c 0.55, $CHCl_3$).

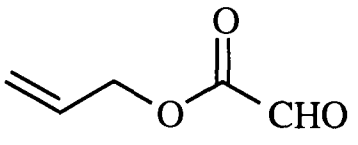
5.4.2 Introduction of Carboxylic Ester Chain Links.

Diallyl tartrate (**3.4**).



Allyl bromide (3.5 ml, 40 mmol, 2 equiv) was added dropwise *via* a syringe to a stirred solution of triethylamine (5.5 ml, 40 mmol, 2 equiv) and tartaric acid (**3.3**) (3.00 g, 20 mmol, 1 equiv) in dimethylformamide (20 ml). The solution was stirred at room temperature for 15 hours then diluted with water (200 ml) and extracted with diethyl ether (3 x 200 ml). The ether extracts were washed with water (2 x 200 ml), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resultant pale yellow oil was distilled using a Kugelrohr apparatus to afford the title compound as a colourless oil (3.71 g, 81%). B.p. 125°C / 20 mmHg); ν_{max} (film) 3490, 2950, 1747, 1650, 1365, 1130, 1092 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 5.84-6.01 (2H, m, C<u>H</u>=CH_2), 5.26-5.42 (4H, m, $C\underline{H}_2$=CH), 4.74 (4H, d, *J* 5.8 Hz, $CO_2C\underline{H}_2$), 4.62 (2H, s, C<u>H</u>OH), 3.42-3.85 (2H, b, O<u>H</u>); $^m/_z$ (CI, NH_3) 248 (100%, MNH_4^+), 231 (45%, MH^+), 58 (20%).

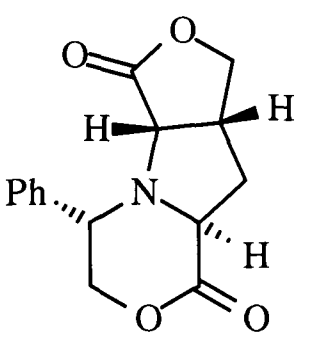
Allyl glyoxylate (**3.5**).



Diallyl tartrate (**3.4**) (456 mg, 2 mmol, 1 equiv) was added dropwise *via* a syringe to a stirred solution of sodium metaperiodate (2.58 g, 12 mmol, 6 equiv) in 4 : 1 water : acetic acid (30 ml) The solution was stirred at room temperature for 15 hours then diluted with water (100 ml) and extracted with ethyl acetate (3 x 100 ml). The ethyl acetate extracts were washed with sat Na_2CO_3 solution (2 x 100 ml), dried ($MgSO_4$), then concentrated *in vacuo*. The resultant

pale yellow oil was distilled using a Kugelrohr apparatus to afford the title compound as a colourless oil (258 mg, 57%). B.p. 75°C / 15 mmHg); ν_{max} (film) 2953, 1746, 1650, 1218, 1098, 1049 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 9.43 (1H, s, C<u>H</u>O), 5.84-6.03 (1H, m, C<u>H</u>=CH_2), 5.28-5.49 (2H, m, CH=C<u>H</u>$_2$), 4.74 (2H, d, *J* 5.7 Hz, $CO_2C\underline{H}_2$); $^m/_z$ (CI, NH_3) 114 (100%, M^+), 58 (100%).

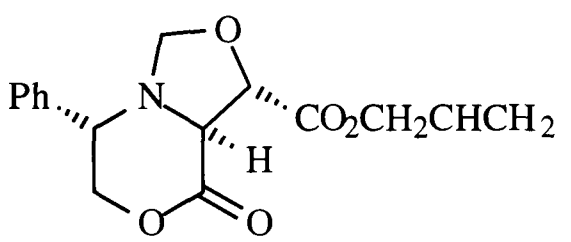
(2S,6R,8S,12S)-1-Aza-4,10-dioxa-12-phenyl[6.4.0^{1,8}.0^{2,6}]tricyclododecan-3,9-dione (**3.6**).



(5*S*)-Phenylmorpholin-2-one (**1.126**) (223 mg, 1.26 mmol, 1 equiv) and allyl glyoxylate (**3.5**) (379 mg, 2.86 mmol, 2.3 equiv) were dissolved in sodium dried toluene (80 ml). The flask was fitted with a condenser and a soxhlet extractor containing activated 4A molecular sieves and the reaction mixture heated to reflux with stirring. After 24 hours the flask was cooled and the reaction mixture concentrated *in vacuo* to afford a pale yellow oil. Column chromatography eluting with 1 : 1 diethyl ether : light petroleum to diethyl ether furnished the title compound as a colourless solid (78 mg, 23%). M.p. 192-193°C; Found C 65.9, H 5.25, N 5.11%, $C_{15}H_{15}NO_4$ requires C 65.93, H 5.53, N 5.13%; ν_{max} (KBr disc) 3031, 2983, 1776, 1738, 1172, 1027, 768, 703 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.51-7.53 (2H, m, <u>Ph</u>), 7.34-7.43 (3H, m, <u>Ph</u>), 4.40 (1H, dd, *J* 9.7, *J'* 7.1 Hz, 5β-H), 4.29-4.31 (2H, m, 11α-H and 11β-H), 4.18-4.24 (2H, m, 5α-H and 8α-H), 4.00 (1H, dd, *J* 6.5, *J'* 2.6 Hz, 12β-H), 3.71 (1H, d, *J* 8.3 Hz, 2β-H), 3.09-3.14 (1H, m, 6β-H), 2.79-2.85 (1H, m, 7β-H), 2.20-2.26 (1H, m, 7α-H); n.O.e. expt: (δ, %) 4.4 **5β-H**-5α-H (14.8%), -6β-H (5.2%), 4.3 **11α-H and 11β-H**-12β-H (2%), -Ph (1%), 4.2 **5α-H and 8α-H**-5β-H (8.7%), 4.0 **12β-H**-11α-H and 11β-H (7.0%), -2β-H (7.0%), 3.7 **2β-H**-12β-H (3.5%), -6β-H (2.6%), 3.1 **6β-H**-2β-H (3.0%), -5β-H (6.7%), -7β-H (10.3%), 2.8 **7β-H**-7α-H (14.4%), -6β-H (3.0%),

2.25 **7α-H**-7β-H (20%), -8α-H (19%); $^{m}/_{z}$ (CI, NH_3) 274 (55%, MH^+), 229 (15%), 104 (100%); $[\alpha]_D^{20}$ +31.5 (c 0.27, $CHCl_3$).

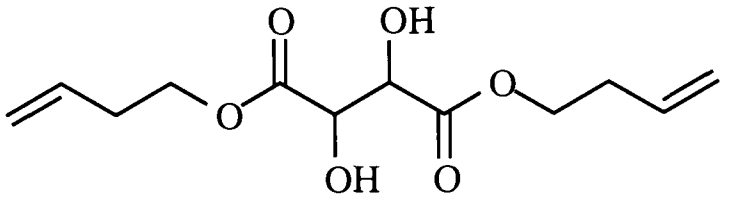
Attempted preparation of *(2S,6R,8S,12S)-1-Aza-4,10-dioxa-12-phenyl[6.4.0^{1,8}.0^{2,6}]tricyclododecan-3,9-dione* (**3.6**), preparation of *(2S,6S,7S)-1-Aza-7-carboallyloxy-4,8-dioxa-2-phenyl[4.3.0^{1,6}]bicyclononan-5-one* (**3.7**).



(5*S*)-Phenylmorpholin-2-one (**1.126**) (188 mg, 1.06 mmol, 1 equiv) was dissolved in sodium dried toluene (80 ml), the flask fitted with a condenser and a soxhlet extractor containing activated 4A molecular sieves and the reaction mixture heated to reflux with stirring. Allyl glyoxylate (**3.5**) (198 mg, 1.74 mmol, 1.6 equiv) was dissolved in toluene and added to the refluxing solution over 10 hours using a syringe pump. After 24 hours the flask was cooled and the reaction mixture concentrated *in vacuo* to afford a pale yellow oil. Column chromatography eluting with 1 : 4 diethyl ether : light petroleum to 4 : 1 diethyl ether : light petroleum furnished the title compound as a colourless solid (14 mg, 4.3%). M.p. 103-105°C; Found C 63.1, H 5.43, N 4.26%, $C_{16}H_{17}NO_5$ requires C 63.36, H 5.65, N 4.61%; ν_{max} (KBr disc) 3087, 2961, 1752, 1748, 1203, 1087, 1018 cm^{-1}; δ_H (500 MHz, C_6D_6) 7.00-7.07 (3H, m, Ph), 6.87-6.91 (2H, m, Ph), 5.61-5.69 (1H, m, C<u>H</u>=CH_2), 5.17 (1H, dt, *J* 17.2 , *J'* 1.6 Hz, CH=C<u>H</u>$_2$), 4.95 (1H, dt, *J* 11.8, *J'* 1.6 Hz, CH=C<u>H</u>$_2$), 4.68 (1H, d, *J* 6.7 Hz, 7β-H), 4.38-4.50 (2H, m, C<u>H</u>$_2$CH=CH_2), 4.35 (1H, d, *J* 6.7 Hz, 6α-H), 4.30 (1H, d, *J* 7.0 Hz, 9α-H), 4.18 (1H, d, *J* 7.0 Hz, 9β-H), 3.67 (1H, t, *J* 11.0 Hz, 3α-H), 3.53 (1H, dd, *J* 11.0, *J'* 3.2 Hz, 3β-H), 3.35 (1H, dd, *J* 11.0, *J'* 3.2 Hz, 2β-H); n.O.e. expt: (δ, %) 4.70 **7β-H**-2β-H (4%), 4.30 **9α-H**-9β-H (28.3%), 4.20 **9β-H**-9α-H (23.2%), -2β-H (4.2%), 3.70 **3α-H**-3β-H (21.1%), -2β-H (2%), -6α-H (1.2%), 3.53 **3β-H**-3α-H (17.6%), -2β-H (4.6%), 3.35 **2β-H**-Ph (7.8%), -7β-H (5%), -3β-H (3.3%), -3α-H (2.1%), -9β-H (1.5%);

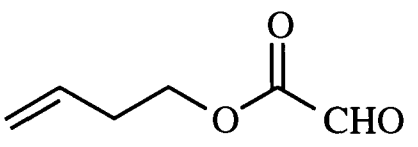
$^{m}/_{z}$ (CI, NH_3), 304 (25%, MH^+), 227 (35%), 137 (70%), 106 (95%), 95 (55%), 81 (100%), 74 (55%); $[\alpha]_D^{23}$ +44.4 (c 0.25, $CHCl_3$).

Di(but-3-enyl) tartrate (**3.9**).



4-Bromo-1-butene (4.7 ml, 46.3 mmol, 2 equiv) was added dropwise *via* a syringe to a stirred solution of triethylamine (6.4 ml, 46 mmol, 2 equiv) and tartaric acid (**3.3**) (3.47 g, 23.1 mmol, 1 equiv) in dimethylformamide (20 ml). The solution was stirred at room temperature for 15 hours then diluted with water (200 ml) and extracted with diethyl ether (3 x 200 ml). The ether extracts were washed with water (2 x 200 ml), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resultant pale yellow oil was distilled using a Kugelrohr apparatus to afford the title compound as a colourless oil (2.98 g, 50%). B.p. 125°C / 20 mmHg; ν_{max} (film) 3490, 3081, 2963, 1746, 1643, 1273, 1128, 1091 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 5.69-5.86 (2H, m, C<u>H</u>=CH_2), 5.09-5.19 (4H, m, C<u>H</u>$_2$=CH), 4.53 (2H, s, C<u>H</u>OH), 4.32 (4H, t, *J* 6.7 Hz, $CO_2C\underline{H}_2$), 2.60-3.00 (2H, b, O<u>H</u>), 2.47 (4H, qu, *J* 6.7 Hz, C<u>H</u>$_2$CH=CH_2); $^{m}/_{z}$ (CI, NH_3) 276 (70%, MNH_4^+), 259 (100%, MH^+), 55 (80%).

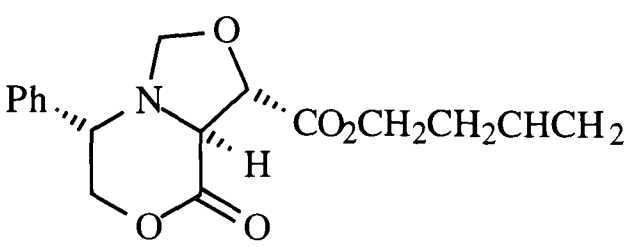
But-3-enyl glyoxylate (**3.10**).



Di(but-3-enyl) tartrate (**3.9**) (417 mg, 1.62 mmol, 1 equiv) was added dropwise *via* a syringe to a stirred solution of sodium metaperiodate (746 mg, 3.5 mmol, 2 equiv) in 4 : 1 water : acetic acid (50 ml). The solution was stirred at room temperature for 15 hours then diluted with water (100 ml) and extracted with ethyl acetate (3 x 100 ml). The ethyl acetate

extracts were washed with saturated Na_2CO_3 solution (2 x 100 ml), dried ($MgSO_4$), then concentrated *in vacuo*. The resultant pale yellow oil was distilled using a Kugelrohr apparatus to afford the title compound as a colourless oil (241 mg, 58%). B.p. 70°C / 15 mmHg; ν_{max} (film) 3082, 2982, 1742, 1643, 1216, 1098 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 9.42 (1H, s, C<u>H</u>O), 5.77-5.95 (1H, m, C<u>H</u>=CH_2), 5.05-5.40 (2H, m, CH=C<u>H</u>$_2$), 4.20-4.40 (2H, m, CO_2C<u>H</u>$_2$), 2.40-2.60 (2H, m, C<u>H</u>$_2$CH=CH_2); $^m/_z$ (CI, NH_3) 146 (30%, MNH_4^+), 128 (100%, M^+), 96 (45%), 58 (45%), 54 (55%).

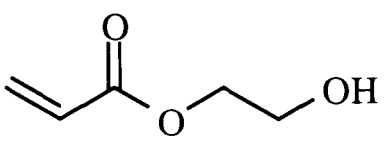
Attempted preparation of *(2S,7R,9S,13S)-1-Aza-4,11-dioxa-13-phenyl[6.4.0^{1,9}.0^{2,7}]tricyclotridecan-3,10-dione*, preparation of *(2S,6S,7S)-1-Aza-7-(carbobut-3-enyloxy)-4,8-dioxa-2-phenyl[4.3.0^{1,6}]bicyclononan-5-one* (**3.11**).



(5*S*)-Phenylmorpholin-2-one (**1.126**) (150 mg, 0.85 mmol, 1 equiv) and but-3-enyl glyoxylate (**3.10**) (166 mg, 1.3 mmol, 1.5 equiv) were dissolved in sodium dried toluene (80 ml). The flask was fitted with a condenser and a soxhlet extractor containing activated 4A molecular sieves and the reaction mixture heated to reflux with stirring. After 24 hours the flask was cooled and the reaction mixture concentrated *in vacuo* to afford a pale yellow oil. Column chromatography eluting with 1 : 1 diethyl ether : light petroleum to diethyl ether furnished the title compound as a colourless solid (38 mg, 17%). M.p. 105-106°C; Found C 64.2, H 5.73, N 4.29%, $C_{17}H_{19}NO_5$ requires C 64.34, H 6.03, N 4.41%; ν_{max} (KBr disc) 3003, 2899, 1751, 1740, 1249, 1094, 706 cm^{-1}; δ_H (500 MHz, C_6D_6) 6.80-7.15 (5H, m, <u>Ph</u>), 5.50-5.58 (1H, m, C<u>H</u>=CH_2), 4.87-4.93 (2H, m, CH=C<u>H</u>$_2$), 4.61 (1H, d, *J* 6.7 Hz, 7β-H), 4.33 (1H, d, *J* 6.7 Hz, 6α-H), 4.27 (1H, d, *J* 6.9 Hz, 9α-H or 9β-H), 4.15 (1H, d, *J* 6.9 Hz, 9β-H or 9α-H), 3.90-4.00 (2H, m, OC<u>H</u>$_2$), 3.64 (1H, t, *J* 11.0 Hz, 3α-H), 3.48 (1H, dd, *J* 11.0, *J'* 3.0 Hz, 3β-H), 3.31 (1H, dd, *J* 11.0, *J'* 3.0 Hz, 2β-H), 2.04-2.08 (2H, m, C<u>H</u>$_2$CHCH_2);

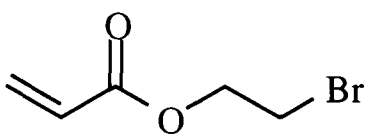
n.O.e. expt: (δ, %) 4.65 **7β-H**-2β-H (5%), -6α-H (2%), 3.70 **3α-H**-3β-H (18%), 3.55 **3β-H**-3α-H (21%), -2β-H (4%), 3.35 **2β-H**-7β-H (6%), -3β-H (5%); $^{m}/_{z}$ (CI, NH_3) 318 (100%, MH^+), 218 (15%), 104 (50%); $[\alpha]_D^{21}$ +56.1 (c 0.29, $CHCl_3$).

2-Hydroxyethyl acrylate (**3.12**).[9]



Ethanediol (1.1 ml, 20 mmol, 1 equiv), sodium sulfate (2.84 g, 20 mmol, 1 equiv), sodium sulfite (2.52 g, 20 mmol, 1 equiv), and cuprous chloride (100 mg, 1 mmol, 0.05 equiv) were suspended in chloroform (20 ml) and the suspension cooled to 0°C. Freshly distilled acryloyl chloride (2.4 ml, 30 mmol, 1.5 equiv) was dissolved in chloroform (10 ml) and added over 30 minutes, *via* a syringe, to the vigorously stirred suspension. The suspension was stirred for a further 2 hours then slurried with water and extracted with chloroform (3 x 50 ml). The chloroform extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford a yellow oil. Vacuum distillation using a Kugelrohr apparatus, inhibiting polymerisation with 1,2,3-trihydroxy-benzene, furnished the title compound as a colourless oil (464 mg, 22%). B.p. 100°C / 20 mmHg, lit[9] 61-65°C / 1 mmHg; ν_{max} (film) 3427, 2957, 1724, 1637, 1619, 1411, 1299, 1149 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 6.47 (1H, dd, *J* 17.3, *J'* 1.6 Hz, CH=C$\underline{H}_2$), 6.17 (1H, dd, *J* 17.3, *J'* 10.3 Hz, C$\underline{H}$=CH_2), 5.88 (1H, dd, *J* 10.3, *J'* 1.6 Hz, CH=C$\underline{H}_2$), 4.32 (2H, t, *J* 4.6 Hz, $CO_2C\underline{H}_2$), 3.89 (2H, t, *J* 4.6 Hz, C$\underline{H}_2$OH), 3.50 (bs, O$\underline{H}$). $^{m}/_{z}$ (CI, NH_3) 134 (95%, MNH_4^+), 117 (100%, MH^+), 99 (55%), 55 (60%).

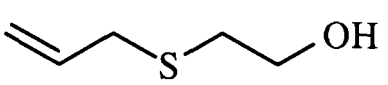
2-Bromoethyl acrylate (**3.14**).[9]



Bromoethanol (1.4 ml, 20 mmol, 1 equiv), sodium sulfate (2.84 g, 20 mmol, 1 equiv), sodium sulfite (2.52 g, 20 mmol, 1 equiv), and cuprous chloride (100 mg, 1 mmol, 0.05 equiv) were suspended in chloroform (20 ml) and the suspension cooled to 0°C. Freshly distilled acryloyl chloride (1.6 ml, 20 mmol, 1 equiv) was dissolved in chloroform (10 ml) and added over 30 minutes, *via* a syringe, to the vigorously stirred suspension. The suspension was stirred for a further 2 hours then slurried with water and extracted with chloroform (3 x 50 ml). The chloroform extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford a yellow oil. Vacuum distillation using a Kugelrohr apparatus, inhibiting polymerisation with 1,2,3-trihydroxy-benzene, furnished the title compound as a colourless oil (895 mg, 25%). B.p. 65°C / 20 mmHg, lit[10] 53°C / 5 mmHg; ν_{max} (film) 2928, 1729, 1636, 1620, 1408, 1297, 1267, 1191 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 6.48 (1H, dd, *J* 17.2, *J'* 1.6 Hz, CH=C$\underline{H}_2$), 6.16 (1H, dd, *J* 17.2, *J'* 10.4 Hz, C$\underline{H}$=CH_2), 5.90 (1H, dd, *J* 10.4, *J'* 1.6 Hz, CH=C$\underline{H}_2$), 4.48 (2H, t, *J* 6.1 Hz, $CO_2C\underline{H}_2$), 3.89 (2H, t, *J* 6.1 Hz, $C\underline{H}_2OH$); $^m/_z$ (CI, NH_3) 198 (10%, MNH_4^+), 196 (10%, MNH_4^+), 126 (10%), 124 (10%), 99 (20%), 72 (10%), 55 (100%).

5.4.3 Elaboration of Intramolecular Cycloadducts.

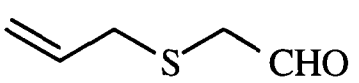
2-(Prop-2-enylthio)ethanol (**3.17**).



Mercaptoethanol (2.1 ml, 29.9 mmol, 1 equiv) was added *via* a syringe to a stirred suspension of potassium carbonate (4.10 g, 29.7 mmol, 1 equiv) in dimethylformamide (25 ml). Allyl bromide (2.6 ml, 30 mmol, 1 equiv) was added dropwise *via* a syringe, and the

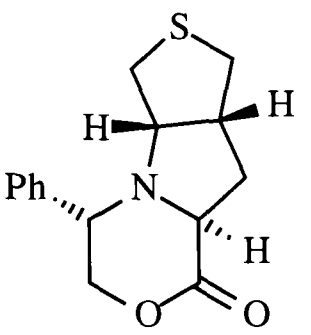
solution stirred at room temperature for 15 hours. The reaction mixture was then diluted with water (200 ml) and extracted with diethyl ether (3 x 150 ml). The ether extracts were washed with water (3 x 100 ml), dried ($MgSO_4$), then concentrated *in vacuo*. The resultant pale yellow oil was distilled using a Kugelrohr apparatus to afford the title compound as a colourless oil (2.38 g, 67%). B.p. 100°C / 15 mmHg; Found C 50.3, H 8.6%, $C_5H_{10}OS$ requires C 50.1, H 8.3%; ν_{max}/cm^{-1} (film) 3369, 3081, 2917, 1635, 1428, 1046, 920; δ_H (200 MHz, $CDCl_3$) 5.71-5.91 (1H, m, CH_2=C<u>H</u>), 5.01-5.16 (2H, m, C<u>H</u>$_2$=CH), 3.72 (2H, t, *J* 6.0 Hz, C<u>H</u>$_2$OH), 3.15 (2H, d, *J* 7.2 Hz, CHC<u>H</u>$_2$), 2.70 (2H, t, *J* 6.0 Hz, SC<u>H</u>$_2$), 2.1 (1H, bs, O<u>H</u>); $^m/_z$ (CI, NH_3) 136 (40%, MNH_4^+), 119 (100%, MH^+), 118 (30%), 101 (40%).

2-(Prop-2-enylthio)ethanal (**3.18**).



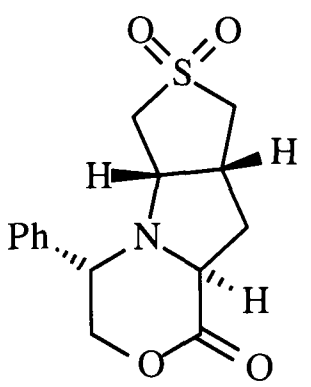
2-(Prop-2-enylthio)ethanol (**3.17**) (2.31 g, 19.6 mmol, 1 equiv) was dissolved in dichloromethane (10 ml), and added rapidly to a stirred suspension of pyridinium chlorochromate (5.15 g, 23.9 mmol, 1.2 equiv), and powdered molecular sieves (11.1 g, 2 mass equiv), in dichloromethane (100 ml). The mixture was stirred at room temperature for 15 hours, then diluted with diethyl ether (100 ml) and filtered through a silica plug to remove chromium residues. The solvent was removed *in vacuo* to afford the crude product as a light green oil, which was purified by Kugelrohr distillation to afford the title compound as a colourless oil (504 mg, 22%). B.p. 70°C / 20 mmHg; Found C 51.74, H 7.28%, C_5H_8OS requires C 51.69, H 6.94%; ν_{max} (film) 1720, 1635, 1441, 1428 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 9.50 (1H, t, *J* 4.0 Hz, C<u>H</u>O), 5.65-5.95 (1H, m, CH_2=C<u>H</u>), 5.15-5.25 (2H, m, C<u>H</u>$_2$=CH), 3.17 (2H, d, *J* 4.0 Hz, SC<u>H</u>$_2$), 3.08 (2H, d, *J* 6.9 Hz, CHC<u>H</u>$_2$); $^m/_z$ (CI, NH_3) 134 (15%, MNH_4^+), 117 (MH^+, 30%), 116 (40%), 102 (40%), 84 (50%), 58 (100%), 56 (45%).

(2S,6R,8S,12S)-1-Aza-10-oxa-12-phenyl-4-thia[6.4.0^{1,8}.0^{2,6}]tricyclododecan-9-one (**3.15**).



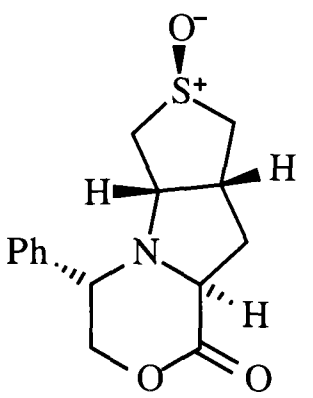
(5*S*)-Phenylmorpholin-2-one (**1.126**) (340 mg, 1.92 mmol, 1 equiv) and 2-(prop-2-enylthio)ethanal (**3.17**) (500 mg, 4.3 mmol, 2.2 equiv) were dissolved in sodium dried toluene (80 ml). The flask was fitted with a condenser and a soxhlet extractor containing activated 4A molecular sieves and the reaction mixture heated to reflux with stirring. After 24 hours the flask was cooled and the reaction mixture concentrated *in vacuo* to afford a pale yellow oil. Column chromatography eluting with 4 : 1 diethyl ether : light petroleum to 1 : 1 diethyl ether : light petroleum furnished the title compound as colourless needles (389 mg, 74%). M.p. 109-110°C, lit[8] 109-110°C; ν_{max} (KBr disc) 3029, 2985, 1758, 1157, 1147, 1085, cm^{-1}; $\delta_{H\ (500\ MHz,\ CDCl_3)}$ 7.30-7.50 (5H, m, Ph), 4.25-4.30 (2H, m, 11β-H and 8α-H), 4.18 (1H, t, *J* 11.5 Hz, 11α-H), 4.00 (1H, dd, *J* 11.5 J' 4.6 Hz, 12β-H), 3.56-3.59 (1H, m, 2β-H), 2.95-3.05 (1H, m, 6β-H), 2.85-2.95 (1H, m, 5α-H), 2.65-2.75 (2H, m, 5β-H and 7β-H), 2.55-2.65 (1H, m, 3β-H), 2.35-2.45 (1H, m, 3α-H), 2.05-2.15 (1H, m, 7α-H); $^{m}/_{z}$ (CI, NH_3) 276 (100%, MH^+), 142 (20%), 104 (25%), 80 (15%); $[\alpha]_D^{20}$ -32 (c 0.27, $CHCl_3$), lit[8] $[\alpha]_D^{20}$ -33 (c 0.27, $CHCl_3$).

(2S,6R,8S,12S)-1-Aza-10-oxa-12-phenyl-4-dioxythia[6.4.0^{1,8}.0^{2,6}]tricyclododecan-9-one (**3.16**).



Cycloadduct (**3.15**) (630 mg, 2.29 mmol, 1 equiv) and 50% by weight wet *meta*-chloroperbenzoic acid (1.57 g, 4.6 mmol, 2 equiv) were dissolved in dichloromethane (80 ml) and the reaction mixture refluxed for 1 hour. Silica (2 g) was added, and the solvent removed *in vacuo*. Column chromatography eluting with diethyl ether furnished the title compound as colourless needles (703 mg, 78%). M.p. 162-164°C; Found C 58.71, H 5.07, N 4.52, S 10.51%, $C_{15}H_{17}NO_4S$ requires C 58.62, H 5.57, N 4.56, S 10.43%; ν_{max} (KBr disc) 3009, 2920, 1755, 1303, 1151, 1127 706 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.36-7.59 (5H, m, Ph), 4.33 (1H, dd, *J* 7.9, *J'* 4.4 Hz, 8α-H), 4.24-4.30 (2H, m, 11α-H and 11β-H), 3.95 (1H, dd, *J* 9.7 Hz, *J'* 5.7 Hz, 12β-H), 3.69 (dt, *J* 7.4 Hz, *J'* 4.0 Hz, 2β-H), 3.28 (ddd, *J* 13.2, *J'* 8.2, *J''* 1.3 Hz, 5α-H), 3.15 (1H, dt, *J* 8.1, *J'* 5.7 Hz, 6β-H), 3.00 (1H, dd, *J* 13.2 Hz, *J'* 8.2 Hz, 5β-H), 2.84-2.93 (2H, m, 3α-H and 7β-H), 2.78 (1H, dd, *J* 14.1, *J'* 4.0 Hz, 3β-H), 2.27 (1H, m, 7α-H); n.O.e. expt: (δ, %), 4.0 **12β-H**-2β-H (9.6%), -Ph (8.6%), -11β-H (4.6%), 3.7 **2β-H**-3β-H (9.0%), -6β-H (8.8%), -12β-H (8.1%), 3.3 **5α-H**-5β-H (16.5%), 3.15 **6β-H**-2β-H (6%), -7β-H (4.3%), -7α-H (1.5%), 3.0 **5β-H**-5α-H (12%), 2.8 **3α-H**-3β-H (17%), 2.3 **7α-H**-7β-H (25%), -8α-H (8%); $^m/_z$ (CI, NH_3) 308 (100%, MH^+), 104 (30%); $[\alpha]_D^{24}$ -36 (c 0.25, $CHCl_3$).

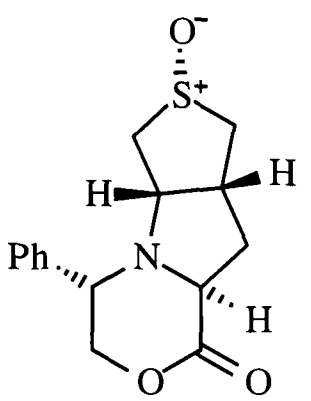
(2S,4S,6R,8S,12S)-1-Aza-10-oxa-12-phenyl-4-oxythia[6.4.0^{1,8}.0^{2,6}]tricyclododecan-9-one (**3.21**).



Sodium metaperiodate (173 mg, 0.81 mmol, 1 equiv) was dissolved in 1 : 1 methanol : water (30 ml) and cooled to -5°C. Cycloadduct (**3.15**) (214 mg, 0.78 mmol, 1 equiv) was dissolved in methanol (30 ml) and added to the solution. A colourless precipitate appeared immediately, and this suspension was stirred at -5°C for 15 hours. The suspension was filtered, the filter cake washed with dichloromethane (3 x 20 ml), and the volatile solvent removed *in vacuo*. The residue was diluted with water, extracted with dichloromethane (3 x 50 ml), the organic layer dried ($MgSO_4$), and the solvent removed *in vacuo*. Recrystallisation from ethyl acetate furnished the title compound as colourless needles (220 mg, 97%). M.p. 138-142°C; Found C 61.51, H 6.17, N 4.97, S 10.79%, $C_{15}H_{17}NO_3S$ requires C 61.83, H 5.88, N 4.81, S 11.01%; ν_{max} 3006, 2978, 1746, 1326, 1236, 1050, 766, 704 cm^{-1}; δ_H (500 MHz, C_6D_6) 7.03-7.13 (3H, m, Ph), 6.83-6.86 (2H, m, Ph), 3.57 (1H, dd, *J* 11.7, *J'* 4.2 Hz, 11β-H), 3.47 (1H, t, *J* 11.4 Hz, 11α-H), 3.34 (1H, dd, *J* 7.8, *J'* 5.4 Hz, 8α-H), 3.28-3.32 (1H, m, 2β-H), 3.15 (1H, dd, *J* 11.0, *J'* 4.2 Hz, 12β-H), 2.95-3.01 (1H, m, 6β-H), 2.37-2.47 (2H, m, 5β-H and 7β-H), 2.20 (1H, ddd, *J* 12.1, *J'* 6.2, *J''* 1.9 Hz, 3β-H), 2.11 (1H, dd, *J* 14.0, *J'* 4.6 Hz, 3α-H), 1.87 (1H, dd, *J* 13.4, *J'* 9.2 Hz, 5α-H), 1.34 (1H, ddd, *J* 9.0, *J'* 7.9, *J''* 4.3 Hz, 7α-H); n.O.e. expt: (δ, %), 3.15 **12β-H**-Ph (9.1%), -11β-H (5.7%), -2β-H (5%), -7β-H (2.3%), 3.0 **6β-H**-7β-H and 5β-H (7.2%), -2β-H (4%), 2.20 **3β-H**-3α-H (7.4%), -2β-H (4.8%), 2.10 **3α-H**-3β-H (7.1%), -Ph (2.2%), 1.85 **5α-H**-5β-H (17.2%), -7α-H (2.5%), -8α-H (2%), 1.35 **7α-H**-7β-H (16.5%), -8α-H (5.7%), -5α-H (2%); $^m/_z$

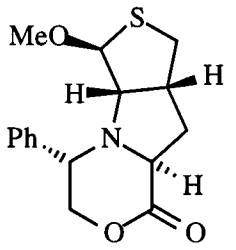
(CI, NH_3) 292 (20%, MH^+), 276 (100%), 147 (20%), 104 (55%), 80 (20%); $[\alpha]_D^{22}$ +39.2 (c 0.25, $CHCl_3$).

(2S,4R,6R,8S,12S)-1-Aza-10-oxa-12-phenyl-4-oxythia[6.4.0^{1,8}.0^{2,6}]tricyclododecan-9-one (**3.22**).



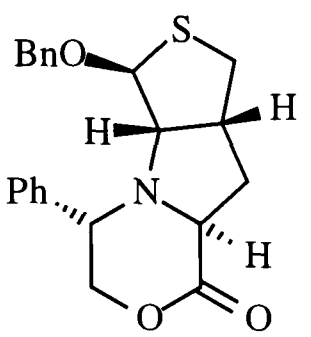
The sulfoxide (**3.21**) (58 mg, 0.20 mmol, 1 equiv), was dissolved in dichloromethane (5 ml), and trifluoromethanesulfonic anhydride (0.1 ml, 0.53 mmol, 2.5 equiv) added. The solution was stirred at room temperature for 4 hours, then quenched by the addition of 2 M HCl (10 ml). The solution was extracted with diethyl ether (3 x 30 ml), the organic layer dried ($MgSO_4$), and concentrated *in vacuo* to afford the title compound as a pale yellow solid (4 mg, 6.4%). M.p. 153-156°C; ν_{max} 2958, 1751, 1188, 1089, 1070, 1024, 704 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.34-7.51 (5H, m, Ph), 4.50 (1H, dd, *J* 7.4, *J'* 4.6 Hz, 8α-H), 4.22-4.29 (2H, m, 11α-H and 11β-H), 3.98 (1H, dd, *J* 9.9, *J'* 5.5 Hz, 12β-H), 3.85 (1H, dt, *J* 7.8, *J'* 2.4 Hz, 2β-H), 3.23-3.30 (1H, m, 6β-H), 3.14-3.18 (1H, m, 5α-H), 2.97 (1H, dt, *J* 12.2, *J'* 2.3 Hz, 3α-H), 2.77-2.86 (2H, m, 5β-H and 7β-H), 2.59-2.68 (2H, m, 3β-H and 7α-H); n.O.e. expt: (δ, %) 4.50 **8α-H**-7α-H (7.2%), -11α-H (3.9%), 4.0 **12β-H**-Ph (8.9%), -2β-H (6.8%), -11β-H (5.5%), 3.85 **2β-H**-3β-H (8%), -6β-H (8.3%), 3.30 **6β-H**-5β-H and 7β-H (9.6%), -2β-H (7%), 3.15 **5α-H**-5β-H (17%), -7α-H (2.8%), 3.0 **3α-H**-3β-H (19.8%), -Ph (3.3%), -2β-H (1.6%); $^m/_z$ (CI, NH_3) 292 (25%, MH^+), 276 (100%), 274 (20%), 104 (20%); $[\alpha]_D^{22}$ -28.9 (c 0.28, $CHCl_3$).

(2S,3S,6R,8S,12S)-1-Aza-3-methoxy-10-oxa-12-phenyl-4-thia[6.4.0^{1,8}.0^{2,6}]tricyclododecan-9-one (**3.23**).



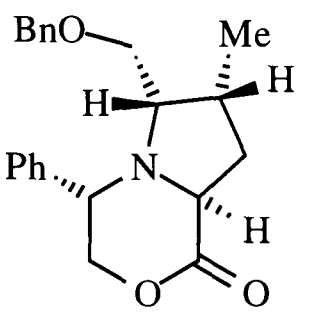
The cycloadduct (**3.21**) (55 mg, 0.19 mmol, 1 equiv) was dissolved in dichloromethane (2 ml), and trifluoroacetic anhydride (0.1 ml, 0.7 mmol, 3.5 equiv) added dropwise *via* a syringe. The resultant dark solution was stirred at room temperature for 4 hours then quenched by the addition of methanol (5 ml). Removal of the solvent *in vacuo* followed by column chromatography eluting with 2 : 3 diethyl ether : light petroleum afforded the title compound as colourless needles (33 mg, 57%). M.p. 119-121°C; Found C 62.90, H 5.98, N 4.34, S 10.39%, $C_{16}H_{19}NO_3S$ requires C 62.93, H 6.27, N 4.59, S 10.50%; ν_{max} 3028, 2993, 1758, 1159, 1095, 1080, 698 cm^{-1}; δ_H (500 MHz, C_6D_6) 7.02-7.14 (5H, m, Ph), 4.27 (1H, s, 3α-H), 3.66 (1H, dd, *J* 11.1, *J'* 4.2 Hz, 11β-H), 3.57 (1H, dd, *J* 11.3, *J'* 4.2 Hz, 12β–H), 3.48-3.53 (2H, m, 11α-H and 8α-H), 3.35 (1H, d, *J* 7.5 Hz, 2β-H), 2.86-2.93 (1H, m, 6β-H), 2.78 (1H, dd, *J* 11.6, *J'* 6.6 Hz, 5α-H), 2.75 (3H, s, OMe), 2.53 (1H, ddd, *J* 13.5, *J'* 8.9, *J''* 2.7 Hz, 7α-H), 2.10 (1H, dd, *J* 11.6, *J'* 1.4 Hz, 5β-H), 1.78 (1H, dt, *J* 12.6, *J'* 7.8 Hz, 7β-H); n.O.e. expt: (δ, %) 4.30 **3α-H**-Me (6.2%), -Ph (4.5%), -2β-H (3.8%), -8α-H (1.8%), 3.35 **2β-H**-12β-H (8.8%), -6β-H (5.7%), -3α-H (2.9%), 2.80 **5α-H**-5β-H (13%), -6β-H (1.3%), -3α-H (1.2%), 2.55 **7α-H**-7β-H (22.8%), -6β-H (5.3%), 8α-H (2.8%), -5β-H (1%), 2.10 **5β-H**-5α-H (19.3%), -7β-H (3%), -6β-H (2.6%); $^m/_z$ (CI, NH_3) 306 (100%, MH^+), 229 (20%), 104 (40%); $[\alpha]_D^{22}$ +167.7 (c 0.26, $CHCl_3$).

(2S,3S,6R,8S,12S)-1-Aza-3-benzyloxy-10-oxa-12-phenyl-4-thia[6.4.0^{1,8}.0^{2,6}]tricyclododecan-9-one (**3.27**).



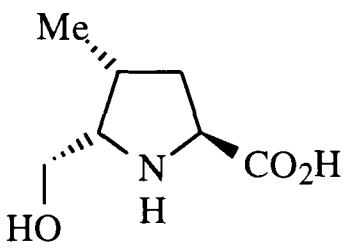
The cycloadduct (**3.21**) (110 mg, 0.38 mmol, 1 equiv) was dissolved in dichloromethane (2 ml), and trifluoroacetic anhydride (0.1 ml, 0.7 mmol, 2 equiv) added dropwise *via* a syringe. The resultant dark solution was stirred at room temperature for 4 hours then quenched by the addition of benzyl alcohol (1 ml, 1 mmol, 2.75 equiv). Removal of the solvent *in vacuo* followed by column chromatography eluting with 1 : 4 diethyl ether : light petroleum afforded the title compound as colourless needles (55 mg, 38%). M.p. 116-119°C; Found C 69.36, H 6.10, N 3.68, S 8.41%, $C_{22}H_{23}NO_3S$ requires C 69.27, H 6.08, N 3.67, S 8.11%; ν_{max} 3028, 2980, 1748, 1737, 1163, 1087, 703 cm^{-1}; δ_H (500 MHz, C_6D_6) 6.96-7.09 (10H, m, Ph), 4.48 (1H, s, 3α-H), 4.40 (1H, d, *J* 12.0 Hz, OC$\underline{H}_2$), 3.85 (1H, d, *J* 12.0 Hz, OC$\underline{H}_2$), 3.65 (1H, dd, *J* 9.3, *J'* 2.3 Hz, 11β-H), 3.48-3.55 (3H, m, 12β-H, 11α-H and 8α-H), 3.38 (1H, d, *J* 7.4 Hz, 2β-H), 2.89-2.95 (1H, m, 6β-H), 2.85 (dd, *J* 11.5, *J'* 6.6 Hz, 5β-H), 2.54 (1H, ddd, *J* 10.2, *J'* 8.3, *J''* 2.4 Hz, 7β-H), 2.14 (1H, dd, *J* 11.5, *J'* 1.5 Hz, 5α-H), 1.80 (1H, dt, *J* 12.6, *J'* 7.7 Hz, 7α-H); n.O.e. expt: (δ, %) 3.4 **2β-H**-6β-H (7.3%), -12β-H (6.4%), -3α-H (3.7%), 2.55 **7β-H**-7α-H (23.1%), -6β-H (5.2%), -8α-H (1.3%), 2.15 **5α-H**-5β-H (28.6%), -7α-H (3.3%), 1.80 **7α-H**-7β-H (21%), -8α-H (7.7%), -5α-H (2.4%); $^m/_z$ (CI, NH_3) 382 (100%, MH^+), 290 (10%), 275 (10%), 104 (10%), 91 (10%); $[\alpha]_D^{22}$ +183.6 (c 0.25, $CHCl_3$).

(2S,6S,8R,9S)-1-Aza-9-benzyloxymethyl-8-methyl-4-oxa-2-phenyl[4.3.0^{1,6}]bicyclononan-5-one (**3.28**).



Raney® nickel was added to a vigorously stirred solution of cycloadduct (**3.27**) (28 mg, 0.07 mmol, 1 equiv) in acetone (50 ml). The flask was fitted with a condenser and the reaction mixture refluxed with vigorous stirring for 15 hours. The solution was allowed to cool, filtered through Celite® to remove the Raney® nickel, then concentrated *in vacuo*. Column chromatography eluting with 1 : 4 diethyl ether : light petroleum afforded the title compound as a colourless oil (14.0 mg, 57%). Found 352.1910, $C_{22}H_{26}NO_3$ (MH^+) requires 352.1913 ν_{max} 3030, 2963, 1752, 1454, 1162, 1072, 700 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.40-7.42 (2H, m, Ph), 7.25-7.35 (6H, m, Ph), 7.14-7.16 (2H, m, Ph), 4.11-4.23 (5H, m, 3α-H, 3β-H, 6α-H and PhCH_2O), 4.01 (1H, dd, *J* 9.5, *J'* 5.6 Hz, 2β-H), 3.17 (1H, dd, *J* 9.6, *J'* 6.1 Hz, OCH_2), 3.05 (1H, dd, *J* 9.6, *J'* 4.5 Hz, OCH_2), 2.99 (1H, dt, *J* 6.4, *J'* 4.7 Hz, 9β-H), 2.57 (1H, ddd, *J* 12.9, *J'* 7.2, *J''* 4.0 Hz, 7β-H), 2.36 (1H, qu, *J* 7.0 Hz, 8β-H), 1.94 (1H, dt, *J* 12.8, *J'* 7.5 Hz, 7α-H), 1.05 (3H, d, *J* 6.9 Hz, Me); n.O.e. expt: (δ, %) 3.0 **9β-H**-2β-H (8.7%), -8β-H (7.9%), -OCH_2 (2.4%), -7β-H (1%), 2.6 **7β-H**-7α-H (19.9%), -8β-H (3.3%), 2.4 **8β-H**-9β-H (6.0%), -Me (3%), -7β-H (2.7%), 1.95 **7α-H**-7β-H (26.1%), -6α-H (8.9%), -Me (2.2%); δ_C (125 MHz, $CDCl_3$) 173.47, 139.85, 138.16, 128.48, 128.19, 127.97, 127.45, 127.38, 127.29, 72.98, 70.94, 70.71, 68.06, 63.60, 58.28, 34.38, 33.77, 14.64; $^m/_z$ (CI, NH_3) 352 (100%, MH^+), 230 (30%); $[\alpha]_D^{22}$ -24.8 (c 1.17, $CHCl_3$).

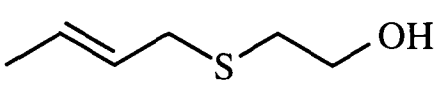
(2S,4R,5R)-5-hydroxymethyl-4-methyl-pyrrolidine-2-carboxylic acid **3.26**).



The desulfurised cycloadduct (**3.28**) (58 mg, 0.16 mmol, 1 equiv) was dissolved in methanol (20 ml), and placed in a Fischer-Porter bottle. Pearlman's catalyst (20 mg), trifluoroacetic acid (0.1 ml), and water (0.1 ml) were added, and the bottle pressurised with hydrogen to 4 bar behind a safety shield. The suspension was stirred for 18 hours then depressurised and filtered through Celite® to remove the catalyst. Removal of the solvent *in vacuo* afforded a pale yellow oil, which was precipitated with diethyl ether. The resultant gummy solid was washed with diethyl ether (3 x 10 ml) then centrifuged to afford the title compound as a colourless powder (21 mg, 79%). M.p. 200°C (dec); ν_{max} 2800-3700, 3436, 2927, 1632, 1426, 1142 cm^{-1}; δ_H (500 MHz, CD_3OD) 3.82-3.85 (2H, m, C<u>H</u>$_2$OH), 3.73-3.76 (1H, m, 2α-H), 2.52-2.55 (1H, m, 5β-H), 2.29-2.46 (1H, m, 3α-H or 3β-H), 2.17-2.23 (1H, m, 3α-H or 3β-H), 1.70-1.74 (1H, m, 4β-H), 1.09 (3H, d, *J* 6.8 Hz, <u>Me</u>); δ_H (125 MHz, CD_3OD) 170.60, 65.41, 65.30, 58.90, 34.17, 27.24, 13.32; $^m/_z$ (ES^+) 160 (100%, MH^+), 144 (30%), 114 (40%); $[\alpha]_D^{23}$ -11.6 (c 0.48, H_2O).

5.4.4 Preparation of a C_2 Symmetric Pyrrolidine.

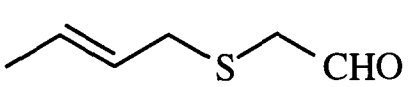
*2-(*E*-But-2-enylthio)ethanol* (**3.34**).



Mercaptoethanol (2.30 ml, 32.4 mmol, 1 equiv) was added *via* a syringe to a stirred suspension of potassium carbonate (4.50 g, 32.6 mmol, 1 equiv) in dimethylformamide (50 ml). Crotyl bromide (4.0 ml, 38.9 mmol, 1.2 equiv) was added dropwise *via* a syringe, and

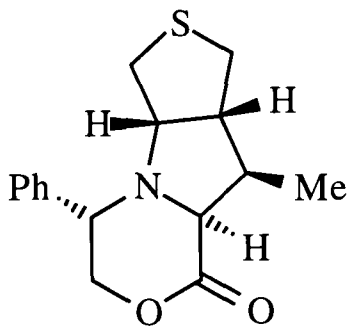
the solution stirred at room temperature for 15 hours. The reaction mixture was then diluted with water (200 ml) and extracted with diethyl ether (3 x 200 ml). The ether extracts were washed with water (3 x 100 ml), dried ($MgSO_4$), then concentrated *in vacuo*. The resultant pale yellow oil was distilled using a Kugelrohr apparatus to afford the title compound as a colourless oil (3.03 g, 71%). B.p. 100°C / 10 mmHg; Found C 54.74, H 9.41, S 24.32%, $C_6H_{12}OS$ requires C 54.50, H 9.15, S 24.25%; ν_{max} (film) 3369, 3021, 2918, 1666, 1451, 1046 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 5.32-5.65 (2H, m, C<u>H</u>=C<u>H</u>), 3.72 (2H, t, *J* 5.9 Hz, C<u>H</u>$_2$OH), 3.12 (2H, d, *J* 6.9 Hz, SC<u>H</u>$_2$CH), 2.71 (2H, d, *J* 5.9 Hz, SC<u>H</u>$_2$CH$_2$), 1.73 (3H, d, *J* 5.9 Hz, <u>Me</u>); $^m/_z$ (CI, NH_3) 150 (15%, MNH_4^+), 133 (100%, MH^+).

*2-(*E*-But-2-enylthio)ethanal* (**3.33**).



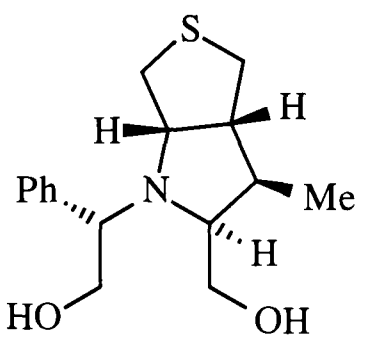
2-(*E*-But-2-enylthio)ethanol (**3.34**) (2.40 g, 18.2 mmol, 1 equiv) was dissolved in dichloromethane (10 ml), and added rapidly to a stirred suspension of pyridinium chlorochromate (4.86 g, 22.6 mmol, 1.2 equiv) and powdered molecular sieves (9.6 g, 2 mass equiv) in dichloromethane (100 ml). The mixture was stirred at room temperature for 15 hours, then diluted with diethyl ether (200 ml), filtered through a silica plug to remove chromium residues, and concentrated *in vacuo* to afford the crude product as a light green oil. Kugelrohr distillation afforded the title compound as a colourless oil (646 mg, 27%); B.p. 90°C / 20 mmHg; ν_{max} (film) 3023, 2967, 1719, 1670, 1031, 967 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 9.48 (1H, t, *J* 3.6 Hz, C<u>H</u>O), 5.40-5.62 (2H, m, C<u>H</u>=C<u>H</u>), 3.17 (2H, d, *J* 3.6 Hz, C<u>H</u>$_2$CHO), 3.04 (2H, d, *J* 7.4 Hz, C<u>H</u>$_2$CH), 1.72 (3H, d, *J* 5.6 Hz, <u>Me</u>); $^m/_z$ (CI, NH_3) 148 (15%, MNH_4^+), 131 (100%, MH^+), 130 (40%), 86 (40%).

(2S,6R,7R,8S,12S)-1-Aza-7-methyl-10-oxa-12-phenyl-4-thia[6.4.0^{1,8}.0^{2,6}]tricyclododecan-9-one (**3.32**).



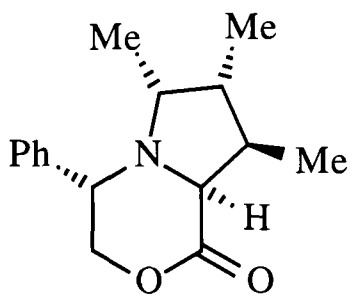
(5*S*)-Phenylmorpholin-2-one (**1.126**) (307 mg, 1.73 mmol, 1 equiv) and 2-(*E*-but-2-enylthio)ethanal (**3.33**) (600 mg, 4.6 mmol, 2.65 equiv) were dissolved in sodium dried toluene (80 ml). The flask was fitted with a condenser and a soxhlet extractor containing activated 4A molecular sieves and the reaction mixture heated to reflux with stirring. After 24 hours the flask was cooled and the reaction mixture concentrated *in vacuo* to afford a pale yellow oil. Column chromatography eluting with 4 : 1 diethyl ether : light petroleum to 1 : 1 diethyl ether : light petroleum furnished the title compound as colourless needles (350 mg, 70%). M.p. 130.5-131.5°C; Found C 66.71, H 6.72, N 4.75, S 11.36%, $C_{16}H_{19}NO_2S$ requires C 66.41, H 6.62, N 4.84, S 11.08%; ν_{max} (KBr disc) 3001, 2977, 1761, 1453, 1132 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.31-7.44 (5H, m, Ph), 4.21-4.30 (3H, m, 11α-H, 11β-H and 8α-H), 4.04 (1H, dd, *J* 10.4, J' 4.6 Hz, 12β-H), 3.76 (1H, m, 2β-H), 2.90 (1H, dd, *J* 11.7, J' 7.4 Hz, 3α-H), 2.67-2.71 (1H, m, 6β-H), 2.62 (1H, dd, *J* 11.7, J' 7.4 Hz, 3β-H), 2.55-2.60 (2H, m, 7α-H and 5α-H), 2.43 (1H, dd, *J* 12.2, J' 2.2 Hz, 5β-H), 1.32 (3H, d, *J* 7.2 Hz, Me); n.O.e. expt: (δ, %), 4.2 **8α-H**-7α-H (6%), 4.0 **12β-H**-Ph (9.6%), -11α-H and 11β-H (7.1%), -2β-H (6%), 3.75 **2β-H**-12β-H (7.6%), -6β-H (6.5%), -3β-H (4%), 2.9 **5β-H**-5α-H (24%), 2.7 **6β-H**-2β-H (5.7%), 2.4 **3α-H**-3β-H (12.8%), -2β-H (2%), 1.3 **Me**-7α-H (13%), -6β-H (9%), -12β-H (5.8%), -8α-H (3.8%); $^m/_z$ (CI, NH_3) 290 (100%, MH^+), 104 (15%); $[\alpha]_D^{24}$ -33.8 (c 0.29, $CHCl_3$).

(2S,6R,7R,8S)-N-((1S)-2-Hydroxy-1-phenylethane)-1-aza-8-hydroxymethyl-7-methyl-4-thia[3.3.0^{2,6}]bicyclooctane (**3.36**).



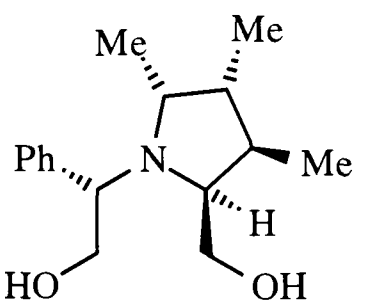
Lithium aluminium hydride (86 mg, 2.25 mmol, 3.9 equiv) was suspended in dry diethyl ether (30 ml), the flask fitted with a condenser, and the reaction mixture brought to reflux under an atmosphere of nitrogen. Cycloadduct (**3.32**) (168 mg, 0.58 mmol, 1 equiv) was dissolved in dry diethyl ether (25 ml) and added dropwise *via* a syringe. The suspension was refluxed for 4 hours after which time t.l.c. analysis (1 : 1 diethyl ether : light petroleum) indicated the absence of starting material. The reaction was quenched by the dropwise addition of concentrated sodium hydroxide solution (5 ml) and water (50 ml), and the residue extracted with diethyl ether (4 x 100 ml). The ether extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo* to furnish the title compound as a colourless oil (169 mg, 98%). Found C 65.34, H 7.88, N 4.39, S 10.61%, $C_{16}H_{23}NO_2S$ requires C 65.49, H 7.90, N 4.77, S 10.93%; ν_{max} (film) 3392, 3029, 2928, 1455, 1054, 1030, 704 cm^{-1}; δ_H (500 MHz, $CDCl_3$), 7.10-7.42 (5H, m, Ph), 4.15 (1H, t, *J* 6.9 Hz, PhCH), 4.00-4.05 (2H, m, 2β-H and $PhCHCH_2$), 3.93 (1H, dd, *J* 10.9, J' 7.2 Hz, $PhCHCH_2$), 3.50 (1H, dd, *J* 11.8, J' 1.0 Hz, 9-H), 3.34 (1H, dd, *J* 11.8, J' 3.4 Hz, 9-H), 3.20 (1H, dd, *J* 8.1, J' 2.8 Hz, 8α-H), 2.86 (1H, dd, *J* 11.5, J' 6.6 Hz, 5β-H), 2.69 (2H, d, *J* 6.2 Hz, 3α-H and 3β-H), 2.56-2.62 (2H, m, 6β-H and 5α-H), 2.22-2.31 (1H, m, 7α-H), 1.05 (3H, d, *J* 7.0 Hz, Me); n.O.e. expt: (δ, %), 3.20 **8α-H**-7α-H (15%), 2.85 **5β-H**-5α-H and 6β-H (27%), 2.70 **3α-H and 3β-H**-2β-H (6.1%), 2.60 **6β-H and 5α-H**-5β-H (18%), -Me (5%), -2β-H (4%), **Me**-7α-H (16%), -6β-H (12%), -9-H (10.3%), -8α-H (4%); $^m/_z$ (CI, NH_3) 294 (100%, MH^+), 262 (45%); $[\alpha]_D^{24}$ -15.4 (c 0.78, $CHCl_3$).

(2S,6S,7R,8R,9R)-1-Aza-4-oxa-2-phenyl-7,8,9-trimethyl[4.3.0^{1,6}]bicyclononan-5-one (**3.38**).



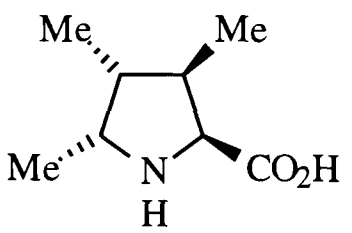
Raney® nickel was added to a vigorously stirred solution of cycloadduct (**3.32**) (180 mg, 0.63 mmol, 1 equiv) in acetone (50 ml). The flask was fitted with a condenser and the reaction mixture refluxed with vigorous stirring for 15 hours. The solution was allowed to cool, filtered through Celite® to remove the Raney® nickel, then concentrated *in vacuo*. Column chromatography eluting with 1 : 4 diethyl ether : light petroleum afforded the title compound as a clumpy colourless solid (122 mg, 75%). M.p. 90-93°C; Found C 74.40, H 8.43, N 5.48%, $C_{16}H_{21}NO_2$ requires C 74.10, H 8.16, N 5.40%; ν_{max} (KBr disc) 2961, 1751, 1383, 1136, 1037, 699 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.29-7.43 (5H, m, Ph), 4.26-4.23 (2H, m, 3α-H and 3β-H), 4.21 (1H, d, *J* 7.0 Hz, 6α-H), 3.94 (1H, dd, *J* 8.9, *J'* 4.2 Hz, 2β-H), 3.18 (1H, qu, *J* 6.7 Hz, 9β-H), 2.27 (1H, qu, *J* 7.2 Hz, 7α-H), 1.98 (1H, qu, *J* 7.0 Hz, 8β-H), 1.21 (3H, d, *J* 7.2 Hz, 7-Me), 0.96 (3H, d, *J* 7.0 Hz, 8-Me), 0.75 (3H, d, *J* 6.7 Hz, 9-Me); n.O.e. expt: (δ, %), 3.95 **2β-H**-Ph (10.7%), -9β-H (7.9%), -3α-H and 3β-H (6.6%), -8β-H (3.2%), -7-Me (2.5%), -9-Me (2%), 3.20 **9β-H**-8β-H (7.7%), -9-Me (6.8%), -2β-H (6.3%), -7-Me (3.2%), -Ph (3%), 2.25 **7α-H**-6α-H (9.4%), -7-Me (5.8%), -8-Me (3.4%), -9-Me (1.8%), 1.95 **8β-H**-9β-H (6.6%), -8-Me (5.4%), -7-Me (3.7%), -2β-H (2.8%); $^{m}/_{z}$ (CI, NH_3) 260 (100%, MH^+), 258 (20%), 215 (15%), 157 (20%), 104 (10%); $[\alpha]_D^{24}$ -26.1 (c 0.33, $CHCl_3$).

(2S,3R,4R,5R)-N-((1S)-2-Hydroxy-1-phenylethane)-2-hydroxymethyl-3,4,5-trimethyl-pyrrolidine (**3.37**).



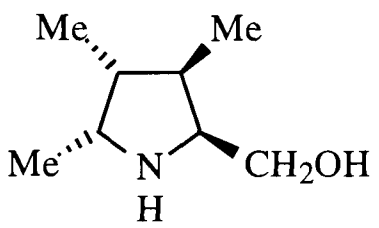
Lithium aluminium hydride (160 mg, 4.2 mmol, 4 equiv) was suspended in dry diethyl ether (30 ml), the flask was fitted with a condenser, and the reaction mixture brought to reflux under an atmosphere of nitrogen. Cycloadduct (**3.38**) (288 mg, 1.1 mmol, 1 equiv) was dissolved in dry diethyl ether (25 ml) and added dropwise *via* a syringe. The suspension was refluxed for 4 hours after which time t.l.c. analysis (1 : 1 diethyl ether : light petroleum) indicated the absence of starting material. The reaction was quenched by the dropwise addition of concentrated sodium hydroxide solution and water (50 ml), and the residue extracted with diethyl ether (4 x 100 ml). The ether extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo* to furnish the title compound as a colourless solid (295 mg, quant). M.p. 106-109°C; Found C 72.85, H 9.88, N 5.04%, $C_{16}H_{25}NO_2$ requires C 72.97, H 9.58, N 5.32%; ν_{max} (KBr disc) 3490, 3027, 2982, 1395, 1040, 1014, 708 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.30-7.42 (5H, m, Ph), 4.03 (2H, m, PhCHCH_2), 3.94-3.99 (1H, m, PhCH), 3.44 (1H, qu, *J* 6.2 Hz, 5β-H), 3.23 (1H, d, *J* 11.2 Hz, CH_2OH), 2.91 (1H, dd, *J* 10.3, *J'* 3.6 Hz, 2α-H) 2.55 (1H, dd, *J* 11.2, *J'* 3.6 Hz, 1H, CH_2OH), 1.86-1.93 (2H, m, 3α-H and 4β-H), 1.50-1.70 (2H, bs, OH), 1.03 (3H, d, *J* 6.4 Hz, 5-Me), 0.97 (3H, d, *J* 6.4 Hz, 3-Me), 0.89 (3H, d, *J* 6.3 Hz, 4-Me); n.O.e. expt: (δ, %), 3.5 **5β-H**-4β-H (5.4%), -5-Me (5%), 3.2 **CH_2OH**-CH_2OH (14.7%), -3-Me (5%), -2α-H (2.5%), 2.95 **2α-H**-3α-H (5.2%), -CH_2OH (2%, 1.9%), 2.6 **CH_2OH**-CH_2OH (16.6%), -2α-H (2%); $^m/_z$ (CI, NH_3) 264 (100%, MH^+), 262 (30%), 232 (30%), 144 (30%), 142 (25%), 112 (30%), 104 (15%); $[\alpha]_D^{24}$ +80.4 (c 0.27, $CHCl_3$).

(2S,3R,4R,5R)-3,4,5-Trimethylpyrrolidine-2-carboxylic acid (**3.42**).



The amino acid was prepared according to the general procedure for proline preparation previously described then recrystallised from diethyl ether to furnish the title compound as a colourless powder (82 mg, 90%). M.p. 114-117°C; ν_{max} 2400-3600, 3432, 2984, 1730, 1678, 1201, 1137, 692 cm^{-1}; δ_H (500 MHz, CD_3OD) 4.41 (1H, d, *J* 8.8 Hz, 2α-H), 3.99 (1H, qu, *J* 7.0 Hz, 5β-H), 2.42 (1H, se, *J* 7.1 Hz, 3α-H), 2.09 (1H, se, *J* 7.1 Hz, 4β-H), 1.28 (3H, d, *J* 7.1 Hz, 5-Me), 1.11 (3H, d, *J* 7.1 Hz, 3-Me), 1.05 (3H, d, *J* 7.1 Hz, 4-Me); δ_H (125 MHz, CD_3OD) 170.10, 62.67, 59.06, 43.83, 41.79, 14.68, 13.23, 12.98; $^m/_z$ (CI, NH_3) 158 (100%, MH^+), 112 (30%); $[\alpha]_D^{22}$ +9.2 (c 0.26, MeOH).

(2S,3R,4R,5R)-3,4,5-Trimethylpyrrolidinemethanol (**3.43**).



The amino acid (**3.42**) (76 mg, 0.5 mmol, 1 equiv) was dissolved in tetrahydrofuran (50 ml), the flask fitted with a condenser, and the solution brought to vigorous reflux. Boron trifluoride etherate (69 µl, 0.5 mmol, 1 equiv) was added dropwise over 30 minutes, the solution refluxed for a further 2 hours, then borane-dimethyl sulfide complex (2.0 M in tetrahydrofuran, 28 µl, 0.56 mmol, 1.15 equiv) added over 45 minutes. The solution was refluxed for 4 hours, 5 M NaOH (25 ml) added, then refluxed for a further 12 hours. The tetrahydrofuran was removed *in vacuo* then the solution extracted with dichloromethane (3 x 30 ml). The organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* to afford the title compound as a colourless oil (62 mg, 90%). ν_{max} 3350, 2964, 1460, 1412, 1052, 732 cm^{-1};

δ_H (500 MHz, $CDCl_3$) 4.08 (2H, bs, O<u>H</u> and N<u>H</u>), 3.65-3.88 (4H, m, C<u>H</u>$_2$OH, 3α-H and 5β-H), 1.99-2.02 (2H, m, 3α-H and 4β-H), 1.20 (3H, d, *J* 7.0 Hz, 5-<u>Me</u>), 1.03 (3H, d, *J* 6.6 Hz, 3-<u>Me</u>), 0.96 (3H, d, *J* 6.5 Hz, 4-<u>Me</u>); δ_H (125 MHz, CD_3OD) 61.11, 60.03, 56.19, 42.54, 39.89, 15.16, 13.02, 12.57; $^m/_z$ (CI, NH_3) 144 (100%, MH^+), 126 (10%), 112 (30%); $[\alpha]_D^{22}$ +60 (c 0.36, MeOH).

5.5 Chapter Four Experimental.

5.5.1 General Methods for the Preparation of Cycloadducts (4.9-4.18).

<u>Cycloaddition method C.</u>

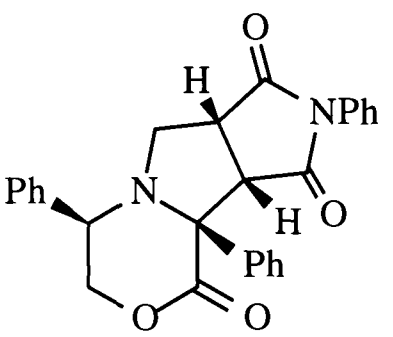
Diphenylmorpholinone (**1.168**) (253 mg, 1 mmol, 1 equiv), dipolarophile (5 equiv), and paraformaldehyde (300 mg, 10 mmol, 10 equiv), were dissolved in sodium dried xylene (80 ml). The flask was fitted with a condenser and a soxhlet extractor containing activated 4A molecular sieves and the reaction mixture refluxed for 18 hours. The reaction mixture was allowed to cool to room temperature and the solvent removed *in vacuo* to afford the crude material. Purification by gradient column chromatography eluting with 1 : 9 diethyl ether : light petroleum to 1 : 1 diethyl ether : light petroleum followed by recrystallisation afforded the pure cycloadducts.

<u>Cycloaddition method D.</u>

Diphenylmorpholinone (**1.168**) (253 mg, 1 mmol, 1 equiv), dipolarophile (5 equiv), and paraformaldehyde (150 mg, 5 mmol, 5 equiv) were dissolved in dry tetrahydrofuran (50 ml) and activated 4A molecular sieves added. $MgBr_2.Et_2O$ (0.5 ml) was added *via* a syringe and the solution sonicated for 4 hours. The reaction mixture was filtered through silica to remove the sieves and catalyst, the silica washed with ethyl acetate (3 x 20 ml), then the solvent removed *in vacuo* to afford the crude material. Purification by gradient column chromatography eluting with 1 : 9 diethyl ether : light petroleum to 1 : 1 diethyl ether : light petroleum followed by recrystallisation afforded the pure cycloadducts.

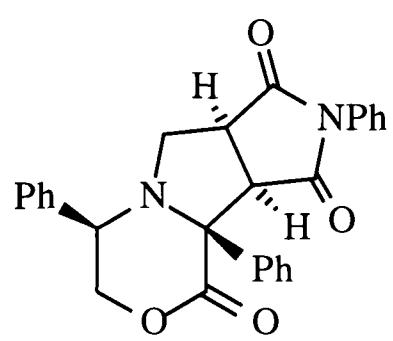
5.5.2 Preparation of Cycloadducts.

(2R,6R,7S,8R)-N–*Phenyl-1-aza-2,6-diphenyl-4-oxa[4.3.0^{1,6}]bicyclononan-5-one-7,8-dicarboximide* (**4.9**).



Recrystallised from diethyl ether / light petroleum as colourless needles. Yield: Method C (193 mg, 44%), method D (75 mg, 17%). M.p. 228-230°C, lit[6] 228-231°C; ν_{max} (KBr disc) 1747, 1713, 1381, 1223, 1183 cm^{-1}; δ_H (500 MHz, $CDCl_3$), 7.27-7.87 (15H, m, Ph), 4.22-4.30 (2H, m, 3α-H and 3β-H), 4.13 (1H, dd, *J* 9.9, *J'* 5.3 Hz, 2β–H), 4.10 (1H, d, *J* 8.9 Hz, 7α-H), 3.65 (1H, dd, *J* 12.5, *J'* 9.9 Hz, 9α-H), 3.40 (1H, ddd, *J* 9.9, *J'* 8.9, *J''* 4.5 Hz, 8α-H), 3.29 (1H, dd, *J* 12.5, *J'* 4.5 Hz, 9β-H); $^m/_z$ (CI, NH_3) 456 (40%, MNH_4^+), 439 (100%, MH^+), 104 (80%); $[\alpha]_D^{20}$ +45 (c 1.10, $CHCl_3$), lit[6] (enantiomer) $[\alpha]_D^{20}$ -43.1 (c 1.10, $CHCl_3$).

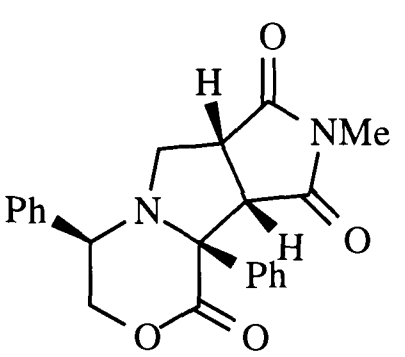
(2R,6R,7R,8S)-N–*Phenyl-1-aza-2,6-diphenyl-4-oxa[4.3.0^{1,6}]bicyclononan-5-one-7,8-dicarboximide* (**4.10**).



Recrystallised from diethyl ether / light petroleum as colourless needles. Yield: Method C (123 mg, 28%), method D (101 mg, 23%). M.p. 199-203°C, lit[6] 200-204°C; ν_{max} (KBr

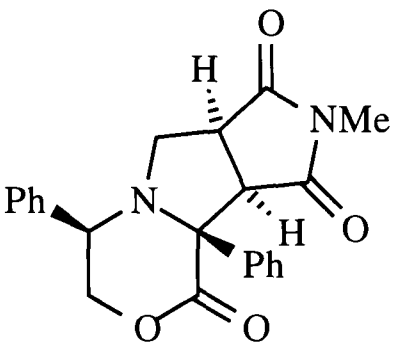
disc) 1748, 1712, 1213 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.33-7.83 (15H, m, Ph) 4.69 (1H, d, *J* 8.6 Hz, 7β-H), 4.18 (1H, dd, *J* 11.6, *J'* 4.4 Hz, 2β-H or 3β-H), 4.13 (1H, d, *J* 10.0 Hz, 9α-H), 4.05 (1H, dd, *J* 11.9, *J'* 4.4 Hz, 2β-H or 3β-H), 3.95 (1H, t, *J* 11.7 Hz, 3α-H), 3.54 (1H, dd, *J* 8.4, *J'* 7.0 Hz, 8β-H), 3.05 (1H, dd, *J* 10.0, *J'* 6.9 Hz, 9β-H); $^m/_z$ (CI, NH_3) 456 (5%, MNH_4^+), 439 (100%, MH^+), 104 (40%); $[\alpha]_D^{20}$ +3.8 (c 1.10, $CHCl_3$), lit[6] (enantiomer) $[\alpha]_D^{20}$ -3.0 (c 1.10, $CDCl_3$).

(2R,6R,7S,8R)-N-*Methyl-1-aza-2,6-diphenyl-4-oxa[4.3.0^{1,6}]bicyclononan-5-one-7,8-dicarboximide* (**4.11**).



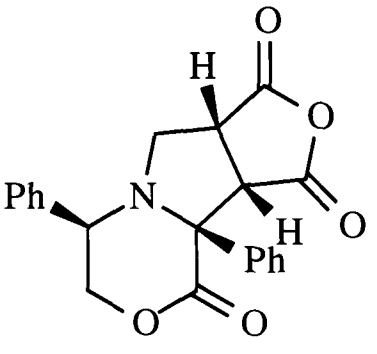
Recrystallised from diethyl ether / light petroleum as colourless needles. Yield: Method C (199 mg, 53%), method D (135 mg, 36%). M.p. 106-109°C; Found C 70.27, H 5.15, N 7.29%, $C_{22}H_{20}N_2O_4$ requires C 70.20, H 5.35, N 7.44%; ν_{max} (KBr disc) 3027, 2946, 1781, 1750, 1703, 1434, 1282, 748 cm^{-1}; δ_H (500 MHz, C_6D_6) 7.70-7.72 (2H, m, Ph), 7.12-7.15 (3H, m, Ph), 7.02-7.06 (3H, m, Ph), 6.92-6.94 (2H, m, Ph), 3.73 (1H, t, *J* 11.3 Hz, 3β-H), 3.58 (1H, dd, *J* 11.3, *J'* 4.2 Hz, 3α-H), 3.53 (1H, dd, *J* 11.3, *J'* 4.2 Hz, 2α-H), 3.27 (1H, d, *J* 8.9 Hz, 7β-H), 3.00 (1H, dd, *J* 12.2, *J'* 9.9 Hz, 9β-H), 2.86 (1H, dd, *J* 12.2, *J'* 4.8 Hz, 9α-H), 2.80 (3H, s, NMe), 2.31-2.36 (1H, m, 8β-H); n.O.e. expt: (δ, %), 3.70 **3β-H**-3α-H (26.6%), -Ph (5.2%), -Ph (3.8%), 3.30 **7β-H**-Ph (13%), -8β-H (7.2%), 3.00 **9β-H**-9α-H (25%), -8β-H (13.2%), -Ph (4%), -Ph (1.6%), 2.90 **8α-H**-9β-H (19%), -2β-H (6.8%), 2.30 **8β-H**-7β-H (8.1%), -9β-H (4.4%); $^m/_z$ (CI, NH_3) 394 (50%, MNH_4^+), 377 (100%, MH^+), 332 (20%), 104 (50%); $[\alpha]_D^{20}$ +64.4 (c 0.25, $CHCl_3$).

(2R,6R,7R,8S)-N-Methyl-1-aza-2,6-diphenyl-4-oxa[4.3.0^{1,6}]bicyclononan-5-one-7,8-dicarboximide (**4.12**).



Recrystallised from diethyl ether / light petroleum as colourless needles. Yield: Method C (109 mg, 29%), method D (94 mg, 25%). M.p. 83-87°C; Found C 70.01, H 5.59, N 7.39%, $C_{22}H_{20}N_2O_4$ requires C 70.20, H 5.35, N 7.44%; ν_{max} (KBr disc) 1782, 1748, 1705, 1184, 701 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.27-7.48 (10H, m, Ph), 4.54 (1H, d, *J* 8.4 Hz, 7α-H), 4.16 (1H, dd, *J* 11.5, J' 4.4 Hz, 3α-H), 3.98-4.04 (2H, m, 2α-H and 9β-H), 3.91 (1H, t, *J* 12.7 Hz, 3β-H), 3.36 (1H, t, *J* 7.7 Hz, 8α-H), 2.99 (1H, dd, *J* 10.0, J' 7.1 Hz, 9α-H), 2.72 (3H, s, NMe); n.O.e. expt: (δ, %), 4.6 **7α-H**-8α-H (6.6%), 4.2 **3α-H**-3β-H (24%), -2α-H (10%), 3.90 **3β-H**-3α-H (24%), 3.40 **8α-H**-7α-H (12%), -9α-H (5.2%), -9β-H (1.8%), 3.0 **9α-H**-9β-H (25.6%), -8α-H (10.6%), -2α-H (4%); $^m/_z$ (CI, NH_3) 377 (100%, MH^+), 104 (35%); $[\alpha]_D^{20}$ -3.5 (c 0.26, $CHCl_3$).

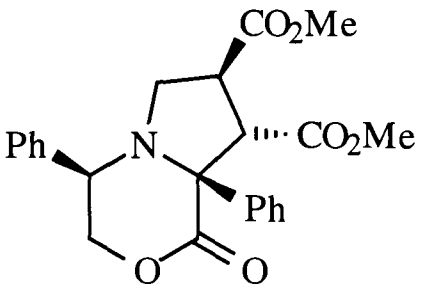
(2R,6R,7S,8R)-1-Aza-2,6-diphenyl-4-oxa[4.3.0^{1,6}]bicyclononan-5-one-7,8-dicarboxylic anhydride (**4.13**).



Recrystallised from ethyl acetate as pale cream needles. Yield: Method C (62 mg, 17%), method D (15 mg, 4%). M.p. 285-290°C (dec); Found C 69.71, H 4.51, N 3.65%,

$C_{21}H_{17}NO_5$ requires C 69.41, H 4.72, N 3.85%; ν_{max} (KBr disc) 2961, 1862, 1792, 1739, 1191, 1054, 702 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.32-7.53 (10H, m, Ph), 4.81 (1H, d, *J* 9.1 Hz, 7β-H), 4.23 (1H, dd, *J* 11.6, *J'* 4.6 Hz, 3α-H), 4.03-4.08 (2H, m, 2α-H and 9α-H), 3.96 (1H, t, *J* 11.8 Hz, 3β-H), 3.66 (1H, dd, *J* 9.1, *J'* 6.7 Hz, 8β-H), 3.09 (1H, dd, *J* 10.2, *J'* 6.7 Hz, 9β-H); n.O.e. expt: (δ, %), 4.80 **7β-H**-8β-H (7.7%), -Ph (3.3%), 4.25 **3α-H**-3β-H (28.7%), -2α-H (10%), -Ph (2.5%), 3.95 **3β-H**-3α-H (25.6%), -Ph (5.3%), -Ph (4.2%), 3.70 **8β-H**-7β-H (10%), -9β-H (5.5%), -9α-H (2%), 3.10 **9β-H**-9α-H (30%), -8β-H (11.5%), -7β-H (1.5%); $^m/_z$ (CI, NH_3) 364 (100%, MH^+), 319 (10%), 104 (80%); $[\alpha]_D^{22}$ -5.1 (c 0.47, MeOH).

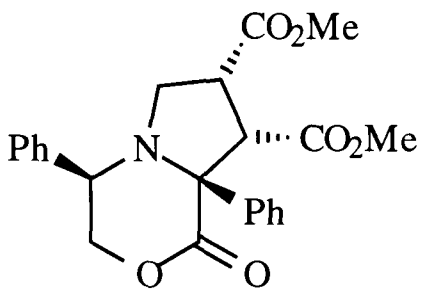
(2R,6R,7S,8S)-1-Aza-7,8-di(carbomethoxy)-2,6-diphenyl-4-oxa[4.3.0^{1,6}]bicyclononan-5-one (**4.14**).



Recrystallised from diethyl ether / light petroleum as colourless needles. Yield: Method C (389 mg, 95%), method D (266 mg, 65%). M.p. 203-206°C; Found C 67.53, H 5.50, N 3.26%, $C_{23}H_{23}NO_6$ requires C 67.47, H 5.66, N 3.42%; ν_{max} (KBr disc) 3035, 2952, 1741, 1725, 1720, 1230, 1209, 1174, 700 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.97-7.99 (2H, m, Ph), 7.61-7.63 (2H, m, Ph), 7.29-7.48 (6H, m, Ph), 4.41 (1H, dd, *J* 10.7, *J'* 3.5 Hz, 2α-H), 4.09-4.18 (3H, m, 7β-H, 3β-H and 3α-H), 3.81 (3H, s, OMe), 3.79 (1H, dd, *J* 10.0, *J'* 2.4 Hz, 9β-H), 3.19 (3H, s, OMe), 3.11 (1H, dd, *J* 10.0, *J'* 7.0, 9α-H), 2.99-3.01 (1H, m, 8α-H); n.O.e. expt: (δ, %), 4.4 **2α-H**-Ph (9.9%), -9α-H (6%), -3β-H and 3α-H (5.0%), 3.8 **9β-H**-9α-H (18.5%), -8α-H (3.3%), -Ph (3.4%), -Ph (1.9%), 3.1 **9α-H**-9β-H (28.9%), -2α-H (9.9%), -8α-H (9.6%), 3.0 **8α-H**-7β-H (5.2%), -9α-H (3.5%), -9β-H (2.1%), -2α-H (1.0%); δ_H (500 MHz, C_6D_6) 8.11-8.13 (2H, m, Ph), 7.31-7.33 (2H, m, Ph), 6.96-7.13

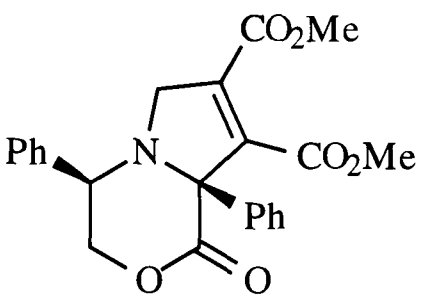
(6H, m, Ph), 4.29 (1H, dd, *J* 11.3, J' 3.4 Hz, 2α-H), 4.27 (1H, d, *J* 2.7 Hz, 7β-H), 3.81 (1H, dd, *J* 9.8, *J'* 2.6 Hz, 9β-H), 3.80 (1H, t, *J* 11.3 Hz, 3β-H), 3.64 (1H, dd, *J* 11.3, *J'* 3.4 Hz, 3α-H), 3.44 (3H, s, OMe), 2.97 (1H, dd, *J* 9.8, *J'* 7.0, 9α-H), 2.85 (3H, s, OMe), 2.59-2.84 (1H, m, 8α-H); n.O.e. expt: (δ, %) 3.8 **3β-H and 9β-H**-9α-H (29%), -3α-H (24.7%), -8α-H (4.3%), -Ph (10%), -Ph (6%), 3.6 **3α-H**-3β-H (29.5%), -2α-H (4.3%), 2.9 **9α-H**-9β-H (29.8%), -8α-H (12%), -2α-H (10.9%), 2.6 **8α-H**-7β-H (6.7%), -9α-H (6.2%); $^{m}/_{z}$ (CI, NH_3) 410 (100%, MH^+), 137 (35%), 104 (40%), 81 (45%), 61 (30%); $[\alpha]_D^{23}$ -27.8 (c 0.32, $CHCl_3$).

(2R,6R,7S,8R)-1-Aza-7,8-di(carbomethoxy)-2,6-diphenyl-4-oxa[4.3.0^{1,6}]bicyclononan-5-one (**4.15**).



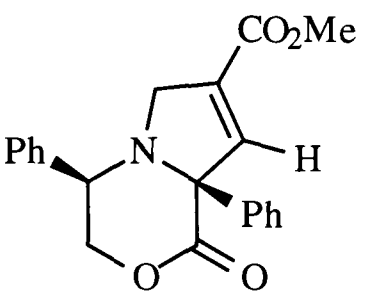
Recrystallised from ethyl acetate as colourless cubes. Yield: Method C (364 mg, 89%), method D (229 mg, 56%). M.p. 110-114°C; Found C 67.47 H 5.63, N 3.40%, $C_{23}H_{23}NO_6$ requires C 67.47, H 5.66, N 3.42%; ν_{max} (KBr disc) 2954, 1750, 1742, 1720, 1250, 1216, 1172, 702 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 8.04-8.06 (2H, m, Ph), 7.60-7.62 (2H, m, Ph), 7.37-7.50 (6H, m, Ph), 4.54 (1H, dd, *J* 10.6, *J'* 3.3 Hz, 2α-H), 4.10-4.19 (2H, m, 3α-H and 3β-H), 3.81 (3H, s, OMe), 3.66 (1H, d, *J* 6.5 Hz, 7β-H), 3.62 (3H, s, OMe), 3.41 (1H, dd, *J* 9.2, *J'* 7.5 Hz, 9β-H), 3.33 (1H, dd, *J* 11.9, *J'* 9.2 Hz, 9α-H), 3.06-3.11 (1H, m, 8β-H); n.O.e. expt: (δ, %), 4.55 **2α-H**-Ph (10.5%), -9α-H (6.1%), -3β-H and 3α-H (5.6%), 3.4 **9β-H**-9α-H (21.7%), -8β-H (13.4%), -Ph (3.9%), -Ph (2.2%), 3.3 **9α-H**-9β-H (12.8%), -2α-H (10.7%), 3.1 **8β-H**-7β-H (10.9%), -9β-H (6.2%), -Ph (3.1%); $^{m}/_{z}$ (CI, NH_3) 410 (100%, MH^+), 378 (10%), 365 (10%), 104 (15%); $[\alpha]_D^{22}$ -27.6 (c 0.25, $CHCl_3$).

(2R,6R)-1-Aza-7,8-di(carbomethoxy)-2,6-diphenyl-4-oxa[4.3.0^{1,6}]bicyclonon-7-en-5-one (**4.16**).



Recrystallised from diethyl ether as a colourless powder. Yield: Method C (322 mg, 79%), method D (0%). M.p. 170-172°C; Found C 67.80, H 4.84, N 3.15%, $C_{23}H_{21}NO_6$ requires C 67.81, H 5.19, N 3.44%; ν_{max} (KBr disc) 3008, 2953, 1746, 1667, 1391, 1371, 1197, 701 cm^{-1}; δ_H (500 MHz, C_6D_6) 6.97-7.67 (10H, m, Ph), 3.92 (1H, d, *J* 15.9 Hz, 9β-H), 3.61 (1H, t, *J* 11.4 Hz, 2α-H), 3.43 (1H, dd, *J* 11.4, *J'* 3.5 Hz, 3β-H or 3α-H), 3.42 (3H, s, OMe$_1$), 3.40 (1H, d, *J* 15.9 Hz, 9α-H), 3.39 (1H, dd, *J* 11.4, *J'* 3.5 Hz, 3α-H or 3β-H), 3.30 (3H, s, OMe$_2$); n.O.e. expt: (δ, %), 3.9 **9β-H**-9α-H (27%), -Ph (3.8%), 3.6 **2α-H**-3α-H and 9α-H (20%), -Ph (2.8%), 3.3 Me$_2$-9β-H (2%); $^m/_z$ (CI, NH_3) 408 (100%, MH^+), 396 (25%), 104 (30%); $[\alpha]_D^{24}$ -32.3 (c 0.26, $CHCl_3$).

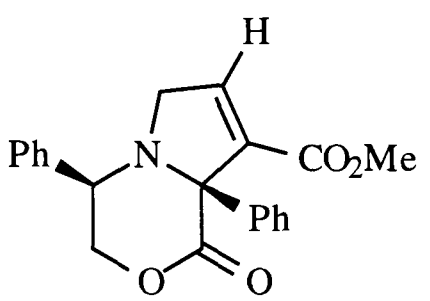
(2R,6R)-1-Aza-8-carbomethoxy-2,6-diphenyl-4-oxa[4.3.0^{1,6}]bicyclonon-7-en-5-one (**4.17**).



Recrystallised from diethyl ether / light petroleum as a pale yellow powder. Yield: Method C (140 mg, 40%), method D (56 mg, 16%). M.p. 55-59°C; Found C 71.89, H 5.27, N 3.85%, $C_{21}H_{19}NO_4$ requires C 72.19, H 5.48, N 4.01%; ν_{max} (KBr disc) 3002, 2951, 1747, 1723, 1650, 1164, 700 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.75-7.77 (2H, m, Ph), 7.34-7.50 (8H, m, Ph), 6.84 (1H, t, *J* 2.1 Hz, 7-H), 4.31 (dd, *J* 12.8, *J'* 2.1 Hz, 9β-H), 4.18 (1H, dd,

J 11.4, *J'* 3.4 Hz, 2α-H), 4.12 (1H, dd, *J* 11.4, *J'* 3.4 Hz, 3α-H), 4.04 (1H, t, *J* 11.4 Hz, 3β-H), 3.74 (1H, dd, *J* 12.8, *J'* 2.1 Hz, 9α-H), 3.72 (3H, s, OMe); n.O.e. expt: (δ, %), 6.88 **7-H**-Ph (1.2%), 4.32 **9β-H**-9α-H (9.6%), -Me (6%), 3.75 **9α-H**-9β-H (5%), -2α-H (1.2%); $^{m}/_{z}$ (CI, NH_3) 350 (100%, MH^+), 104 (20%); $[\alpha]_D^{20}$ -109 (c 0.25, $CHCl_3$).

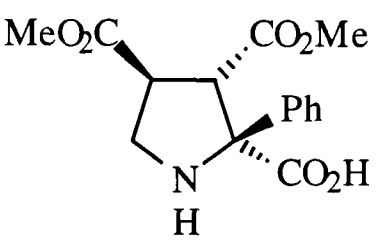
(2R,6R)-1-Aza-7-carbomethoxy-2,6-diphenyl-4-oxa[4.3.0^{1,6}]bicyclonon-7-en-5-one (**4.18**).



Recrystallised from diethyl ether / light petroleum as a pale yellow powder. Yield: Method C (129 mg, 37%), method D (94 mg, 27%). M.p. 48-52°C; Found C 72.08, H 5.47, N 3.78%, $C_{21}H_{19}NO_4$ requires C 72.19, H 5.48, N 4.01%; ν_{max} (KBr disc) 2925, 1756, 1746, 1640, 1164, 699 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.62-7.64 (2H, m, Ph), 7.28-7.51 (8H, m, Ph), 6.98 (1H, t, *J* 2.2 Hz, 8-H), 4.26 (1H, dd, *J* 17.2, *J'* 2.2 Hz, 9β-H), 4.12 (1H, dd, *J* 11.6, *J'* 4.0 Hz, 2α-H), 4.04 (1H, dd, *J* 11.6, *J'* 4.0 Hz, 3α-H), 3.96 (1H, t, *J* 11.6 Hz, 3β-H), 3.62 (3H, s, OMe), 3.61 (1H, dd, *J* 17.2, *J'* 2.2 Hz, 9α-H); n.O.e. expt: (δ, %), 7.0 **8-H**-9β-H (4.8%), -9α-H (3.4%), 4.30 **9β-H**-9α-H (17%), -8-H (5.3%), 4.15 **2α-H**-Ph (9.6%), -9α-H (6%), 3.60 **9α-H**-9β-H (27%), -2α-H (9.9%), -8-H (1%); $^{m}/_{z}$ (CI, NH_3) 350 (100%, MH^+), 296 (50%), 104 (25%); $[\alpha]_D^{21}$ -120 (c 0.28, $CHCl_3$).

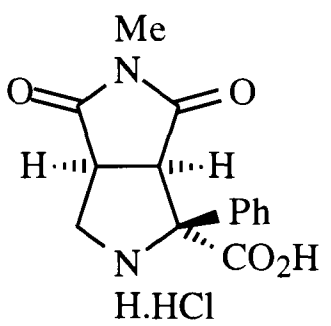
5.5.3 Preparation of Proline Derivatives (4.19 and 4.20).

(2R,3R,4S)-3,4-Di(carbomethoxy)-2-phenyl-pyrrolidine-2-carboxylic acid (**4.19**).



The amino acid was prepared according to the general procedure for proline preparation previously described then recrystallised from methanol to give the title compound as a colourless powder (130 mg, 85%). M.p. 181-185°C; ν_{max} 2600-3700, 3439, 2957, 1741, 1680, 1640, 1439, 1207, 1180, 698 cm^{-1}; δ_H (500 MHz, CD_3OD) 7.68-7.69 (2H, m, Ph), 7.40-7.44 (3H, m, Ph), 4.06-4.15 (1H, bs, 3β-H), 3.76-3.87 (3H, m, 4α-H, 5α-H and 5β-H), 3.72 (3H, s, OMe), 3.67 (3H, s, OMe); δ_C (125 MHz, CD_3OD) 172.50, 171.70, 171.50, 130.28, 129.90, 128.98, 128.79, 128.60, 128.16, 53.29, 53.13, 46.13; $^m/_z$ (CI, NH_3) 308 (100%, MH^+), 276 (70%), 262 (70%), 144 (30%); $[\alpha]_D^{25}$ +46 (c 0.25, MeOH).

(2R,3S,4S)-3,4-(N-Methyl-dicarboximido)-2-phenyl-pyrrolidine-2-carboxylic acid hydrogen chloride (**4.20**).

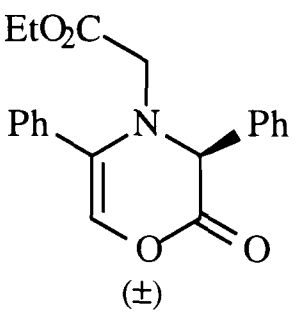


The cycloadduct (188 mg, 0.5 mmol, 1 equiv) was dissolved in methanol (25 ml), and placed in a Fischer-Porter bottle. Pearlman's catalyst (50 mg), trifluoroacetic acid (0.1 ml), and water (0.1 ml) were added, and the bottle pressurised with hydrogen to 4 bar behind a safety shield. The suspension was stirred for 18 hours then depressurised. 35% Hydrogen chloride

solution (0.25 ml) was added to the resultant grey suspension, which was stirred for 5 minutes then filtered through Celite® to remove the catalyst. Removal of the solvent *in vacuo* afforded an orange powder, which was washed with diethyl ether (3 x 10 ml), then recrystallised from H_2O to afford the pure amino acid as a colourless powder (154 mg, quant). M.p. 210-215°C; Found C 48.46, H 4.17, N 8.02%, $C_{14}H_{15}N_2O_4Cl.2H_2O$ requires C 48.49, H 4.36, N 8.09%; ν_{max} (KBr disc) 2300-3700, 2949, 1783, 1703, 1443, 1291, 695 cm^{-1}; δ_H (500 MHz, CD_3OD) 7.57-7.58 (2H, m, Ph), 7.45-7.46 (3H, m, Ph), 4.72 (1H, d, *J* 6.1 Hz, 3α-H), 3.77-3.93 (3H, m, 4α-H, 5α-H and 5β-H), 2.84 (3H, s, NMe); δ_C (125 MHz, CD_3OD), 176.85, 173.46, 169.37, 132.07, 130.77, 129.62, 127.78, 78.34, 50.31, 47.40, 44.18, 25.80; $^m/_z$ (CI, NH_3) 274 ($[M-Cl]^+$, 5%), 229 ($[MH-CO_2-Cl]^+$, 100%), 125 (55%), 117 (40%); $[\alpha]_D^{22}$ -154.4 (c 0.34, MeOH).

5.5.4 Cycloadditions with Substituted Aldehydes.

Attempted preparation of 9-carboethoxy substituted diphenylmorpholinone cycloadducts, preparation of N-*(carboethoxymethyl)-3,5-diphenyl-5,6-dehydromorpholin-2-one* (**4.21**).

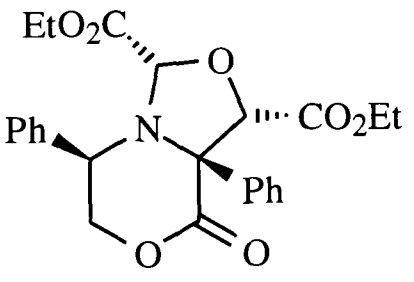


(±)

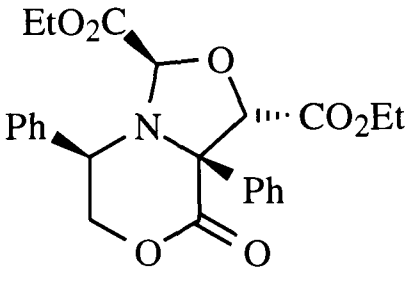
Diphenylmorpholinone (**1.168**) (126 mg, 0.5 mmol, 1 equiv), a dipolarophile (2.5 mmol, 5 equiv) and ethyl glyoxylate trimer (102 mg, 1 mmol, 1 equiv) were dissolved in sodium dried xylene (80 ml). The flask was fitted with a condenser and a soxhlet extractor containing activated 4A molecular sieves and the reaction mixture refluxed for 18 hours. The reaction mixture was allowed to cool to room temperature and the solvent removed *in vacuo* to afford the crude material. Purification by gradient column chromatography eluting with 1 : 9 diethyl ether : light petroleum to 1 : 1 diethyl ether : light petroleum followed by

recrystallisation from diethyl ether afforded a compound as colourless cubes. The structure was assigned as that of the title compound on the basis of spectroscopic data. Yield (dependant on dipolarophile): *N*-phenylmaleimide (20 mg, 12%), maleic anhydride (31 mg, 18%), dimethyl maleate (24 mg, 14%), dimethyl fumarate (27 mg, 16%), methyl propiolate (17 mg, 10%). M.p. 108.5-109.5°C; Found C 71.3, H 5.56, N 3.97%, $C_{20}H_{19}NO_4$ requires C 71.20, H 5.68, N 4.15%; ν_{max} (KBr disc) 3066, 2990, 1740, 1700, 1447, 1207, 1099, 765, 725, 697 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.32-7.58 (10H, m, Ph), 6.44 (1H, s, 6-H), 5.03 (1H, s, 3α-H), 4.20 (2H, q, *J* 7.1 Hz, CH_2CH_3), 4.05 (1H, d, *J* 18.2 Hz, NCH_2), 3.75 (1H, d, *J* 18.2 Hz, NCH_2), 1.26 (3H, t, *J* 7.1 Hz, CH_2CH_3); n.O.e. expt: (δ, %), 6.45 **6-H**-Ph (10.3%), 5.0 **3α-H**-NCH_2 (5.5%), -Ph (3.5%), 4.05 **NCH_2**-NCH_2 (21.7%), 3.75 **NCH_2**-NCH_2 (20.8%), -3α-H (5.7%); $^m/_z$ (CI, NH_3) 338 (100%, MH^+), 309 (40%), 118 (30%), 91 (40%).

Attempted preparation of N–*phenyl-1-aza-9-carboethoxy-2,6-diphenyl-4-oxa[4.3.0^{1,6}]bicyclononan-5-one-7,8-dicarboximide,* preparation of *(2R,6R,7S,9S)-1-aza-7,9-di(carboethoxy)-2,6-diphenyl-4,8-dioxa[4.3.0^{1,6}]bicyclononan-5-one* (**4.22**), and *(2R,6R,7S,9R)-1-aza-7,9-di(carboethoxy)-2,6-diphenyl-4,8-dioxa[4.3.0^{1,6}]bicyclononan-5-one* (**4.23**).



(**4.22**)



(**4.23**)

Diphenylmorpholinone (**1.168**) (126 mg, 0.5 mmol, 1 equiv), ethyl glyoxylate trimer (102 mg, 1 mmol, 1 equiv), and *N*-phenylmaleimide (433 mg, 2.5 mmol, 5 equiv) were dissolved in sodium dried xylene (80 ml). The flask was fitted with a condenser and a soxhlet extractor containing activated 4A molecular sieves and the reaction mixture refluxed for 18 hours. The reaction mixture was allowed to cool to room temperature and the solvent removed *in vacuo* to afford the crude material. Purification by gradient column chromatography eluting

with 1 : 9 diethyl ether : light petroleum to 1 : 1 diethyl ether : light petroleum followed by recrystallisation from diethyl ether afforded two compounds as colourless solids. These were assigned the structures of the title compounds on the basis of spectroscopic data.

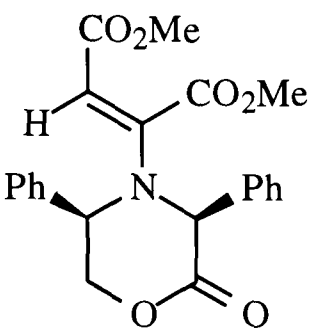
(2R,6R,7S,9S)-1-Aza-7,9-di(carboethoxy)-2,6-diphenyl-4,8-dioxa[4.3.0^{1,6}]bicyclononan-5-one (**4.22**).

Yield (37 mg, 17%). M.p. 130-133°C; Found C 65.71, H 5.75, N 2.92%, $C_{24}H_{25}NO_7$ requires C 65.60, H 5.73, N 3.19%; ν_{max} (KBr disc) 3064, 2984, 1779, 1740, 1197, 1038, 701 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.35-7.90 (10H, m, Ph), 4.84 (1H, d, *J* 5.6 Hz, 9β-H), 4.49 (1H, dd, *J* 11.6, *J'* 4.0 Hz, 2α-H), 4.34 (1H, d, *J* 5.6 Hz, 7β-H), 4.15-4.25 (5H, m, 3α-H and 2 x CH_2CH_3), 4.05 (1H, t, *J* 11.6 Hz, 3β-H), 1.24-1.34 (6H, m, 2 x CH_2CH_3); n.O.e. expt: (δ, %), 4.85 **9β-H**-7β-H (12%), -Ph (6.7%), 4.5 **2α-H**-3α-H (7.4%), 4.35 **7β-H**-9β-H (7.3%), -Ph (2.5%), 4.2 **3α-H**-3β-H (5.7%), -2α-H (1.8%), 4.05 **3β-H**-3α-H (19.7%), -Ph (3.7%); $^m/_z$ (CI, NH_3) 440 (20%, MH^+), 340 (60%), 338 (90%), 336 (100%), 104 (80%); $[\alpha]_D^{25}$ -35.4 (c 0.28, $CHCl_3$).

(2R,6R,7S,9R)-1-Aza-7,9-di(carboethoxy)-2,6-diphenyl-4,8-dioxa[4.3.0^{1,6}]bicyclononan-5-one (**4.23**).

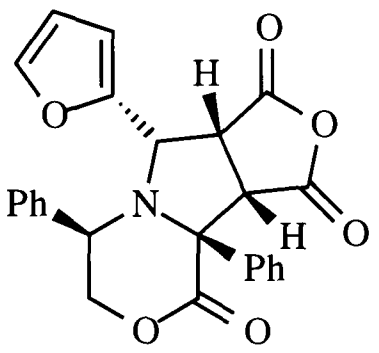
Yield (31 mg, 14%). M.p. 140-143°C; Found C 65.60, H 5.73, N 3.45%, $C_{24}H_{25}NO_7$ requires C 65.60, H 5.73, N 3.19%; ν_{max} 2986, 1771, 1738, 1725, 1197, 1184, 1038, 706 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.37-7.82 (10H, m, Ph), 4.80 (1H, d, *J* 1.9 Hz, 7β-H), 4.67 (1H, d, *J* 1.9 Hz, 9α-H), 4.65-4.68 (1H, m, 2α-H), 4.12-4.26 (3H, m, 3α-H and CH_2CH_3), 4.05 (1H, t, *J* 11.8 Hz, 3β-H), 3.97-4.05 (1H, m, CH_2CH_3), 3.76-3.83 (1H, m, CH_2CH_3), 1.27 (3H, t, *J* 7.2 Hz, CH_3), 0.94 (3H, t, *J* 7.2 Hz, CH_2CH_3); n.O.e. expt: (δ, %), 4.65 **2α-H**-Ph (7.8%), -3α-H (5.6%), -9α-H (3.8%), 4.25 **3α-H**-3β-H (11%), -2α-H (8.2%); $^m/_z$ (CI, NH_3), 440 (100%, MH^+), 395 (30%), 338 (20%), 252 (15%), 218 (15%), 104 (50%); $[\alpha]_D^{24.5}$ +2.0 (c 0.40, $CHCl_3$).

Attempted preparation of *9-carboethoxy, 9-phenyl or 9-furyl-(2*R,*6*R*)-1-aza-7,8-di(carbomethoxy)-2,6-diphenyl-4-oxa[4.3.0^{1,6}]bicyclonon-7-en-5-one,* preparation of *(3*S,*5*R*)*-N-*(*E*-dimethyl-butenedioate)-3,5-diphenyl-morpholin-2-one* (**4.29**).



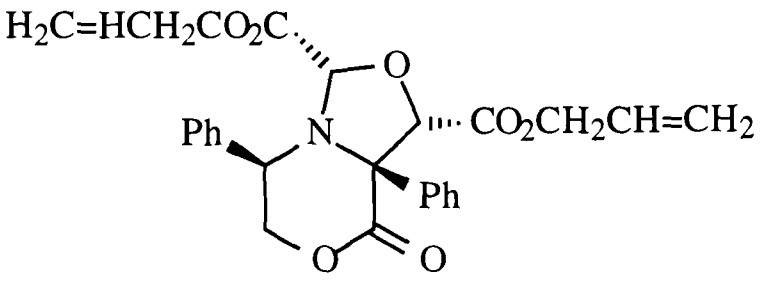
Diphenylmorpholinone (**1.168**) (100 mg, 0.4 mmol, 1 equiv), aldehyde (2 mmol, 5 equiv) and dimethyl acetylenedicarboxylate (340 mg, 2.4 mmol, 6 equiv)were dissolved in sodium dried xylene (80 ml). The flask was fitted with a condenser and a soxhlet extractor containing activated 4A molecular sieves and the reaction mixture refluxed for 18 hours. The reaction mixture was allowed to cool to room temperature and the solvent removed *in vacuo* to afford the crude material. Purification by gradient column chromatography eluting with 1 : 9 diethyl ether : light petroleum to 1 : 1 diethyl ether : light petroleum followed by recrystallisation from ethyl acetate afforded a colourless solid. The structure was assigned as that of the title compound on the basis of spectroscopic data. Yield (dependent on aldehyde): benzaldehyde (89 mg, 56%), furfuraldehyde (139 mg, 90%), ethyl glyoxylate trimer (126 mg, 80%). M.p. 169-171°C; Found C 67.05, H 5.38, N 3.24%, $C_{22}H_{21}NO_6$ requires C 66.83, H 5.35, N 3.54%; ν_{max} (KBr disc) 2950, 1769, 1739, 1702, 1580, 1166, 1044 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.26-7.63 (10H, m, Ph), 5.48 (1H, s, C=CH), 4.89 (1H, dd, *J* 11.6, *J'* 5.0 Hz, 5α-H), 4.85 (1H, s, 3α-H), 4.24 (1H, dd, *J* 12.6, *J'* 5.0 Hz, 6α-H), 4.17 (1H, t, *J* 12.1 Hz, 6β-H), 3.69 (3H, s, OMe_2), 3.58 (3H, s, OMe_1); n.O.e. expt: (δ, %), 5.50 **C=CH**-3α-H (9.8%), -Ph (6.6%), -Me_2 (1.5%), 4.90 **5α-H**-Ph (12.2%), -6α-H (8.4%), 4.82 **3α-H**-C=CH (13.2%), -Ph (4.1%), -Ph (2.8%), -Me_1 (1.6%); $^m/_z$ (CI, NH_3) 396 (100%, MH^+), 276 (20%), 122 (65%), 105 (25%); $[\alpha]_D^{25}$ +8.9 (c 0.27, $CHCl_3$).

(2R,6R,7S,8R,9S)-1-Aza-2,6-diphenyl-9-furyl-4-oxa[4.3.0^{1,6}]bicyclononan-5-one-7,8-dicarboxylic anhydride (**4.30**).



Diphenylmorpholinone (**1.168**) (253 mg, 1 mmol, 1 equiv), maleic anhydride (490 mg, 5 mmol, 5 equiv), and freshly distilled furfuraldehyde (960 mg, 10 mmol, 10 equiv), were dissolved in sodium dried xylene (80 ml). The flask was fitted with a condenser and a soxhlet extractor containing activated 4A molecular sieves and the reaction mixture refluxed for 18 hours. The reaction mixture was allowed to cool to room temperature and the solvent removed *in vacuo* to afford the crude material. Purification by gradient column chromatography eluting with 1 : 9 diethyl ether : light petroleum to 1 : 1 diethyl ether : light petroleum afforded the title compound as pale yellow needles (60 mg, 14%). M.p. 231-234°C; Found C 70.16, H 4.17, N 3.19%, $C_{25}H_{19}NO_6$ requires C 69.92, H 4.46, N 3.26%; ν_{max} (KBr disc) 3030, 2972, 1868, 1790, 1755, 1153, 1003, 947, 751, 700 cm^{-1}; δ_H (500 MHz, C_6D_6) 7.63-7.65 (2H, m, Ph), 6.99-7.11 (6H, m, Ph), 6.93 (1H, d, *J* 1.8 Hz, O-CH=CH), 6.77-6.79 (2H, m, Ph), 5.82 (1H, d, *J* 3.1 Hz, O-CH=CH-CH), 5.74 (1H, dd, *J* 3.2, *J'* 1.9 Hz, O-CH=CH), 4.52 (1H, d, *J* 10.3 Hz, 9β-H), 3.80 (1H, dd, *J* 11.8, *J'* 5.2 Hz, 2α-H), 3.57 (1H, t, *J* 11.8 Hz, 3β-H), 3.41 (1H, dd, *J* 11.8, *J'* 5.2 Hz, 3α-H), 3.07 (1H, d, *J* 10.6 Hz, 7β-H), 2.86 (1H, t, *J* 10.4 Hz, 8β-H); n.O.e. expt: (δ, %), 4.50 **9β-H**-8β-H (14.0%), -Fu (6.3%), -Ph (3.6%), -2α-H (3%), -Ph (2.4%), 3.80 **2α-H**-3α-H (6.9%), -Ph (6.8%), -9β-H (2.6%), -Fu (2.2%), 3.60 **3β-H**-3α-H (20.4%), -Ph (4.8%), -Ph (4.3%), 3.40 **3α-H**-3β-H (24.5%), -2α-H (10.7%), 3.10 **7β-H**-Ph (8.2%), -8β-H (8.1%), 2.90 **8β-H**-9β-H (13.5%), -7β-H (9%); $^m/_z$ (CI, NH_3) 447 (45%, MNH_4^+), 430 (100%, MH^+), 254 (30%), 252 (90%), 104 (50%); $[\alpha]_D^{22}$ -80 (c 0.25, $CHCl_3$).

Attempted preparation of *(2R,6S,8R,12R)-1-aza-4,10-dioxa-8,12-diphenyl[6.4.0^{1,8}.0^{2,6}]tricyclododecan-3,9-dione*, preparation of *(2R,6R,7S,9S)-1-aza-7,9-di(carboallyloxy)-2,6-diphenyl-4,8-dioxa[4.3.0^{1,6}]bicyclononan-5-one* (**4.31**).

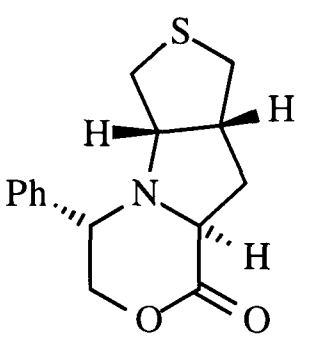


Diphenylmorpholinone (**1.168**) (253 mg, 1 mmol, 1 equiv) and allyl glyoxylate (**3.5**) (456 mg, 4 mmol, 4 equiv), were dissolved in sodium dried xylene (80 ml). The flask was fitted with a condenser and a soxhlet extractor containing activated 4A molecular sieves and the reaction mixture refluxed for 18 hours. The reaction mixture was allowed to cool to room temperature and the solvent removed *in vacuo* to afford the crude material. Purification by gradient column chromatography eluting with 1 : 9 diethyl ether : light petroleum to 1 : 1 diethyl ether : light petroleum afforded the title compound as a colourless powder (111 mg, 24%). M.p. 140-142°C; Found C 67.18, H 5.15, N 3.07%, $C_{26}H_{25}NO_7$ requires C 67.38, H 5.44, N 3.02%; ν_{max} (KBr disc) 3030, 2959, 1767, 1735, 1720, 1260, 1201, 1180, 1089, 1074, 705 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.80-7.82 (2H, m, Ph), 7.36-7.50 (8H, m, Ph), 5.83-5.90 (1H, m, C**H**=CH_2), 5.52-5.57 (1H, m, C**H**=CH_2), 5.26-5.33 (2H, m, CH=C**H**$_2$), 5.09-5.12 (2H, m, CH=C**H**$_2$), 4.84 (1H, d, *J* 1.8 Hz, 9β-H), 4.71 (1H, d, *J* 1.8 Hz, 7β-H), 4.68 (1H, dd, *J* 11.6, *J'* 4.3 Hz, 2α-H), 4.56-4.66 (2H, m, CO_2C**H**$_2$), 4.43-4.48 (1H, m, CO_2C**H**$_2$), 4.24 (1H, dd, *J* 12.0, *J'* 4.3 Hz, 3α-H), 4.20 (1H, dd, *J* 13.0, *J'* 5.7 Hz, CO_2C**H**$_2$), 4.06 (1H, t, *J* 11.8 Hz, 3β-H); n.O.e. expt: (δ, %), 4.85 **9β-H**-7β-H (5.3%), 4.70 **7β-H**-Ph (5.6%), -9β-H (3.1%), 4.25 **3α-H**-3β-H (20%), 4.05 **3β-H**-3α-H (21.8%), -Ph (7.6%), -7β-H (2.3%); $^m/_z$ (CI, NH_3) 464 (30%, MH^+), 350 (20%), 252 (40%), 104 (100%), 58 (60%); $[\alpha]_D^{22}$ -5.9 (c 2.59, $CHCl_3$).

5.6 X-RAY CRYSTAL STRUCTURE DETERMINATION DATA.

(See: **Appendix** for listings of atomic co-ordinates, bond lengths, angles and thermal parameters relating to X-Ray Crystal Structure Determinations).

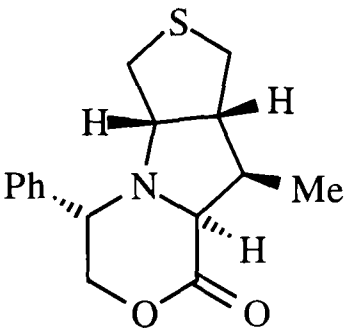
(2*S*,6*R*,8*S*,12*S*)-1-Aza-10-oxa-12-phenyl-4-thia[6.4.$0^{1,8}$.$0^{2,6}$]tricyclododecan-9-one (**3.15**).



Structure Determined by Simon Hopes.

Crystal data for (**3.15**): $C_{15}H_{17}NO_2S$, monoclinic, $P2_1$, a = 14.202(3), b = 5.613(1), c = 16.456(1) Å, V = 681.2 Å^3, Z = 2, D_c = 1.342(5) g cm^{-3}, $\lambda(CuK_\alpha)$ = 1.54180 Å, μ = 7.03 cm^{-1}, *F(000)* = 292, T = 295 K, R = 0.0285, R = 0.0285 for 2618 unique reflections, I>3σ(I). Data for crystallographic analysis were measured on an Enraf-Nonius CAD-4F diffractometer using graphite monochromated CuK_α radiation. Structural data was preprocessed by RC85 before solving by direct methods using the SHELXS-86 package. Atomic co-ordinates, bond lengths, angles and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre.

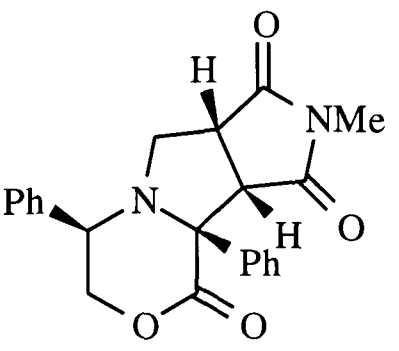
(2*S*,6*R*,7*R*,8*S*,12*S*)-1-Aza-7-methyl-10-oxa-12-phenyl-4-thia[6.4.$0^{1,8}$.$0^{2,6}$]tricyclododecan-9-one (**3.23**).



Structure Determined by Andrew McMullan.

Crystal data for (**3.23**): $C_{16}H_{19}NO_2S$, monoclinic, $P2_1$, a = 8.647(5), b = 9.684(2), c = 9.070(2) Å, β = 110.29(3)°, V = 720.93 Å^3, Z = 2, D_x = 1.333 g cm^{-3}, λ(CuK_α) = 1.54180 Å, *F(000)* = 924, T = 298(2) K, R = 0.067, R_w = 0.044 for 2150 unique reflections, I>3σ(I). Data for crystallographic analysis were measured on an Enraf-Nonius CAD-4F diffractometer using graphite monochromated CuK_α radiation. Structural data was preprocessed by RC85 before solving by direct methods using the SHELXS-86 package. Atomic co-ordinates, bond lengths, angles and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre.

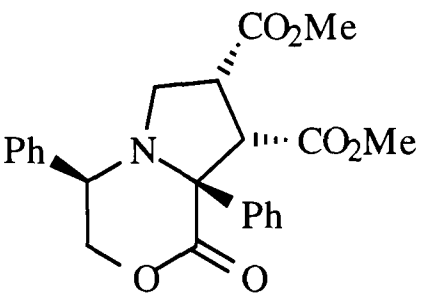
(2*R*,6*R*,7*S*,8*R*)-*N*-Methyl-1-aza-2,6-diphenyl-4-oxa[4.3.$0^{1,6}$]bicyclononan-5-one-7,8-dicarboximide (**4.11**).



Structure Determined by Giles Hamblett.

Crystal data for (**4.11**): $C_{22}H_{20}N_2O_4$, monoclinic, $P2_1/c$, a = 8.374(3), b = 25.279(2), c = 8.971(1) Å, β = 102.54(2)°, V = 1854.05 Å^3, Z = 4, D_x = 1.35 g cm^{-3}, λ(CuK_α) = 1.54180 Å, T = 293 K, R = 0.0443 for 2752 observed reflections, I>3σ(I). Data for crystallographic analysis were measured on a Enraf-Nonius CAD-4F diffractometer using graphite monochromated CuK_α radiation. Structural data was solved by direct methods using CRYSGRAPH. Atomic co-ordinates, bond lengths, angles and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre.

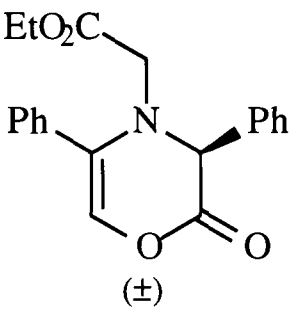
(2*R*,6*R*,7*S*,8*R*)-1-Aza-7,8-di(carbomethoxy)-2,6-diphenyl-4-oxa[4.3.$0^{1,6}$]bicyclononan-5-one (**4.15**).



Structure Determined by Giles Hamblett.

Crystal data for (**4.15**): $C_{23}H_{23}NO_6$, monoclinic, *I2/a*, *a* = 18.315(3), *b* = 11.011(7), *c* = 20.582(2) Å, β = 91.67(1)°, *V* = 4149.14 Å^3, Z = 8, D_x = 1.31 g cm^{-3}, λ(CuK_α) = 1.54180 Å, *T* = 293 K, *R* = 0.0371 for 2408 observed reflections, I>3σ(I). Data for crystallographic analysis were measured on an Enraf-Nonius CAD-4F diffractometer using graphite monochromated CuK_α radiation. Structural data was solved by direct methods using CRYSGRAPH. Atomic co-ordinates, bond lengths, angles and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre.

(3*S*)-*N*-(Carboethoxymethyl)-3,5-diphenyl-5,6-dehydromorpholin-2-one (**4.21**).



Structure Determined by Andrew McMullan.

Crystal data for (**4.21**): $C_{20}H_{19}NO_4$, monoclinic, $P2_1/b$, *a* = 9.707(1), *b* = 12.907(2), *c* = 15.044(2) Å, γ = 111.16(1)°, *V* = 1757.67 Å^3, Z = 4, D_x = 1.331(4) g cm^{-3}, λ(CuK_α) = 1.54180 Å, *F(000)* = 732, *T* = 298(2) K, *R* = 0.048 for 2830 unique reflections, I>3σ(I). Data for crystallographic analysis were measured on an Enraf-Nonius CAD-4F diffractometer using graphite monochromated CuK_α radiation. Structural data was preprocessed by RC85 before solving by direct methods using the SHELXS-86 package. Atomic co-ordinates, bond lengths, angles and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre.

CHAPTER FIVE

References

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References

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APPENDIX

Atomic Co-ordinates, Bond Lengths, Angles and Thermal Parameters for (3.15).

ATOMIC CO-ORDINATES AND ISOTROPIC TEMPERATURE FACTORS.

Atom	x/a	y/b	z/c	U(iso)
S(1)	-0.67148(3)	0.0127(2)	-0.95179(5)	0.0558
C(2)	-0.6667(1)	-0.2886(4)	-0.8804(2)	0.0502
C(3)	-0.7686(1)	-0.3564(3)	-0.8454(2)	0.0445
N(4)	-0.79560(8)	-0.2845(3)	-0.6860(1)	0.0381
C(5)	-0.7742(1)	-0.4574(3)	-0.5629(2)	0.0428
C(6)	-0.6887(1)	-0.3948(3)	-0.4638(2)	0.0386
C(7)	-0.6418(1)	-0.1789(3)	-0.4782(2)	0.0425
C(8)	-0.5636(1)	-0.1290(3)	-0.3862(2)	0.0487
C(9)	-0.5322(1)	-0.2893(4)	-0.2761(2)	0.0516
C(10)	-0.5784(1)	-0.5053(4)	-0.2598(2)	0.0512
C(11)	-0.6556(1)	-0.5567(3)	-0.3530(2)	0.0459
C(12)	-0.8603(1)	-0.4801(5)	-0.4578(2)	0.0567
O(13)	-0.94108(8)	-0.5506(3)	-0.5515(2)	0.0613
C(14)	-0.9623(1)	-0.4035(4)	-0.6704(2)	0.0534
C(15)	-0.8934(1)	-0.1988(3)	-0.6926(2)	0.0468
C(16)	-0.9002(1)	-0.0793(4)	-0.8506(3)	0.0601
C(17)	-0.8341(1)	-0.2205(4)	-0.9580(2)	0.0530
C(18)	-0.7745(1)	-0.0644(5)	-1.0645(2)	0.0615
O(19)	-1.03086(9)	-0.4432(4)	-0.7490(2)	0.0730
H(21)	-0.641(1)	-0.391(4)	-0.959(2)	0.0522
H(22)	-0.620(1)	-0.266(3)	-0.784(2)	0.0522
H(31)	-0.779(1)	-0.526(4)	-0.855(2)	0.0454
H(51)	-0.764(1)	-0.613(4)	-0.609(2)	0.0430
H(71)	-0.664(1)	-0.061(3)	-0.555(2)	0.0425
H(81)	-0.533(1)	0.023(4)	-0.400(2)	0.0492
H(91)	-0.481(1)	-0.259(4)	-0.211(2)	0.0528
H(101)	-0.557(1)	-0.632(4)	-0.184(2)	0.0531
H(111)	-0.684(1)	-0.692(4)	-0.351(2)	0.0467
H(121)	-0.873(1)	-0.309(4)	-0.410(2)	0.0590
H(122)	-0.850(1)	-0.613(4)	-0.373(2)	0.0590
H(151)	-0.905(1)	-0.084(3)	-0.606(2)	0.0473
H(161)	-0.962(1)	-0.085(4)	-0.891(2)	0.0617
H(162)	-0.875(1)	0.101(4)	-0.841(2)	0.0617
H(171)	-0.874(1)	-0.318(3)	-1.019(2)	0.0547
H(181)	-0.811(1)	0.087(4)	-1.091(2)	0.0623
H(182)	-0.751(1)	-0.166(4)	-1.158(3)	0.0623

ANISOTROPIC TEMPERATURE FACTORS.

Atom	U(11)	U(22)	U(33)	U(23)	U(13)	U(12)
S(1)	0.0495(2)	0.0615(3)	0.0585(2)	0.0017(2)	0.0004(2)	-0.0082(2)
C(2)	0.0463(8)	0.064(1)	0.0478(9)	0.0017(8)	0.0132(7)	0.0102(8)
C(3)	0.0478(8)	0.0445(9)	0.0447(8)	-0.0101(7)	0.0074(6)	-0.0012(7)
N(4)	0.0298(5)	0.0470(7)	0.0402(6)	-0.0038(5)	0.0031(4)	0.0020(5)
C(5)	0.0381(7)	0.0449(9)	0.0466(7)	-0.0006(7)	0.0036(5)	-0.0036(7)
C(6)	0.0348(6)	0.0425(8)	0.0398(7)	-0.0026(6)	0.0050(5)	0.0017(6)
C(7)	0.0400(7)	0.0406(8)	0.0477(8)	0.0012(7)	-0.0003(6)	0.0030(6)
C(8)	0.0429(8)	0.048(1)	0.057(1)	-0.0068(7)	-0.0014(7)	-0.0014(7)
C(9)	0.0456(8)	0.064(1)	0.0502(9)	-0.0097(8)	-0.0066(7)	0.0088(8)
C(10)	0.0537(9)	0.062(1)	0.0447(7)	0.0078(8)	0.0017(6)	0.0164(9)
C(11)	0.0481(8)	0.0416(9)	0.0509(8)	0.0034(7)	0.0096(7)	0.0042(6)
C(12)	0.0405(8)	0.087(1)	0.0582(9)	0.011(1)	0.0057(7)	-0.014(1)
O(13)	0.0429(6)	0.086(1)	0.0741(8)	0.0069(7)	0.0053(6)	-0.0223(6)
C(14)	0.0332(7)	0.078(1)	0.063(1)	-0.0121(9)	0.0052(7)	-0.0078(8)
C(15)	0.0309(7)	0.060(1)	0.0577(9)	-0.0076(8)	0.0036(6)	0.0032(7)
C(16)	0.0402(9)	0.078(1)	0.073(1)	0.009(1)	-0.0048(8)	0.0093(9)
C(17)	0.0485(9)	0.072(1)	0.0474(9)	-0.0058(8)	-0.0101(7)	-0.0112(8)
C(18)	0.056(1)	0.090(2)	0.0487(9)	0.0114(9)	-0.0098(8)	-0.007(1)
O(19)	0.0441(6)	0.114(1)	0.0883(9)	-0.010(1)	-0.0103(6)	-0.0200(8)

INTERATOMIC ANGLES

C(18) - S(1) - C(2)	89.1(1)	C(3) - C(2) - S(1)	105.5(1)
H(21) - C(2) - S(1)	109.7(12)	H(21) - C(2) - C(3)	110.7(11)
H(22) - C(2) - S(1)	100.0(11)	H(22) - C(2) - C(3)	118.0(10)
H(22) - C(2) - H(21)	112.0(14)	N(4) - C(3) - C(2)	111.4(1)
C(17) - C(3) - C(2)	108.9(1)	C(17) - C(3) - N(4)	106.4(1)
H(31) - C(3) - C(2)	111.6(10)	H(31) - C(3) - N(4)	108.2(11)
H(31) - C(3) - C(17)	110.2(10)	C(5) - N(4) - C(3)	115.4(1)
C(15) - N(4) - C(3)	107.8(1)	C(15) - N(4) - C(5)	115.9(1)
C(6) - C(5) - N(4)	114.2(1)	C(12) - C(5) - N(4)	108.4(1)
C(12) - C(5) - C(6)	109.4(1)	H(51) - C(5) - N(4)	109.6(11)
H(51) - C(5) - C(6)	108.2(10)	H(51) - C(5) - C(12)	106.9(10)
C(7) - C(6) - C(5)	122.4(1)	C(11) - C(6) - C(5)	119.6(1)
C(11) - C(6) - C(7)	118.0(1)	C(8) - C(7) - C(6)	120.6(2)
H(71) - C(7) - C(6)	119.6(10)	H(71) - C(7) - C(8)	119.8(10)
C(9) - C(8) - C(7)	120.8(2)	H(81) - C(8) - C(7)	118.2(10)
H(81) - C(8) - C(9)	121.0(10)	C(10) - C(9) - C(8)	119.3(2)
H(91) - C(9) - C(8)	122.7(12)	H(91) - C(9) - C(10)	118.0(12)
C(11) - C(10) - C(9)	119.9(2)	H(101) - C(10) - C(9)	123.1(11)
H(101) - C(10) - C(11)	117.0(11)	C(10) - C(11) - C(6)	121.3(2)
H(111) - C(11) - C(6)	115.8(12)	H(111) - C(11) - C(10)	122.8(12)
O(13) - C(12) - C(5)	109.4(1)	H(121) - C(12) - C(5)	106.8(11)
H(121) - C(12) - O(13)	108.9(11)	H(122) - C(12) - C(5)	111.0(11)
H(122) - C(12) - O(13)	106.8(11)	H(122) - C(12) - H(121)	113.9(16)
C(14) - O(13) - C(12)	115.0(1)	C(15) - C(14) - O(13)	114.7(1)
O(19) - C(14) - O(13)	119.1(2)	O(19) - C(14) - C(15)	126.2(2)
C(14) - C(15) - N(4)	110.9(1)	C(16) - C(15) - N(4)	103.6(1)
C(16) - C(15) - C(14)	114.2(2)	H(151) - C(15) - N(4)	110.0(10)
H(151) - C(15) - C(14)	106.7(11)	H(151) - C(15) - C(16)	111.6(11)
C(17) - C(16) - C(15)	105.6(2)	H(161) - C(16) - C(15)	111.6(12)
H(161) - C(16) - C(17)	109.4(13)	H(162) - C(16) - C(15)	109.3(11)
H(162) - C(16) - C(17)	108.7(11)	H(162) - C(16) - H(161)	111.9(17)
C(16) - C(17) - C(3)	104.6(1)	C(18) - C(17) - C(3)	108.8(1)
C(18) - C(17) - C(16)	113.8(2)	H(171) - C(17) - C(3)	114.6(12,
H(171) - C(17) - C(16)	105.6(11)	H(171) - C(17) - C(18)	109.4(12)
C(17) - C(18) - S(1)	105.7(1)	H(181) - C(18) - S(1)	109.1(11)

INTERATOMIC DISTANCES

S(1) - C(2)	1.799(2)	S(1) - C(18)	1.800(2)
C(2) - C(3)	1.527(2)	C(2) - H(21)	0.96(2)
C(2) - H(22)	1.07(2)	C(3) - N(4)	1.473(2)
C(3) - C(17)	1.537(3)	C(3) - H(31)	0.97(2)
N(4) - C(5)	1.462(2)	N(4) - C(15)	1.471(2)
C(5) - C(6)	1.517(2)	C(5) - C(12)	1.527(2)
C(5) - H(51)	0.97(2)	C(6) - C(7)	1.388(2)
C(6) - C(11)	1.392(2)	C(7) - C(8)	1.385(2)
C(7) - H(71)	0.98(2)	C(8) - C(9)	1.374(3)
C(8) - H(81)	0.96(2)	C(9) - C(10)	1.386(3)
C(9) - H(91)	0.93(2)	C(10) - C(11)	1.382(2)
C(10) - H(101)	1.01(2)	C(11) - H(111)	0.86(2)
C(12) - O(13)	1.450(2)	C(12) - H(121)	1.06(2)
C(12) - H(122)	1.05(2)	O(13) - C(14)	1.342(2)
C(14) - C(15)	1.522(3)	C(14) - O(19)	1.200(2)
C(15) - C(16)	1.510(3)	C(15) - H(151)	0.99(2)
C(16) - C(17)	1.537(3)	C(16) - H(161)	0.94(2)
C(16) - H(162)	1.08(2)	C(17) - C(18)	1.524(3)
C(17) - H(171)	0.94(2)	C(18) - H(181)	1.02(2)
C(18) - H(182)	1.04(2)		

Atomic Co-ordinates, Bond Lengths, Angles and Thermal Parameters for (3.32).

ATOMIC CO-ORDINATES AND ISOTROPIC TEMPERATURE FACTORS.

Atom	x/a	y/b	z/c	u(iso)
S(4)	0.5012(1)	0.5673(1)	0.2815(1)	0.0733
O(10)	0.6566(3)	-0.0415(3)	0.2692(3)	0.0707
O(13)	0.8998(4)	0.0488(3)	0.3871(4)	0.0892
N(1)	0.5309(3)	0.2257(3)	0.2192(3)	0.0492
C(2)	0.5635(4)	0.3034(4)	0.3669(4)	0.0545
C(3)	0.4304(5)	0.4142(5)	0.3498(5)	0.0669
C(5)	0.7111(5)	0.5300(4)	0.4056(5)	0.0683
C(6)	0.7307(4)	0.3734(4)	0.3973(4)	0.0546
C(7)	0.7866(4)	0.3285(4)	0.2621(4)	0.0555
C(8)	0.6916(4)	0.1943(3)	0.2081(4)	0.0488
C(9)	0.7629(4)	0.0644(5)	0.2968(4)	0.0608
C(11)	0.4955(4)	-0.0183(4)	0.1558(5)	0.0633
C(12)	0.4174(4)	0.1084(4)	0.1975(4)	0.0550
C(14)	0.9726(5)	0.3280(5)	0.3007(5)	0.0718
C(15)	0.2510(4)	0.1313(4)	0.0773(4)	0.0524
C(16)	0.1140(4)	0.0632(5)	0.0826(4)	0.0607
C(17)	-0.0382(5)	0.0778(6)	-0.0316(5)	0.0716
C(18)	-0.0574(5)	0.1680(4)	-0.1551(6)	0.0723
C(19)	0.0758(5)	0.2400(4)	-0.1632(5)	0.0703
C(20)	0.2301(4)	0.2217(4)	-0.0470(5)	0.0628

ANISOTROPIC TEMPERATURE FACTORS.

Atom	U(11)	U(22)	U(33)	U(23)	U(13)	U(12)
S(4)	0.0678(6)	0.0722(7)	0.0848(7)	-0.0160(7)	0.0238(5)	0.0070(6)
O(10)	0.071(2)	0.066(2)	0.073(2)	0.015(1)	0.014(1)	0.008(2)
O(13)	0.073(2)	0.089(3)	0.105(2)	0.027(2)	-0.004(2)	0.004(2)
N(1)	0.052(2)	0.056(2)	0.041(1)	-0.006(1)	0.016(1)	-0.000(1)
C(2)	0.057(2)	0.074(2)	0.045(2)	-0.014(2)	0.023(2)	-0.005(2)
C(3)	0.058(2)	0.095(3)	0.062(2)	-0.019(2)	0.026(2)	-0.006(2)
C(5)	0.065(2)	0.086(4)	0.062(2)	-0.017(2)	0.024(2)	-0.010(2)
C(6)	0.058(2)	0.070(3)	0.043(2)	-0.016(2)	0.014(2)	-0.003(2)
C(7)	0.059(2)	0.065(2)	0.048(2)	-0.000(2)	0.022(2)	-0.001(2)
C(8)	0.054(2)	0.051(2)	0.042(2)	0.004(2)	0.014(1)	0.008(2)
C(9)	0.056(2)	0.063(2)	0.060(2)	0.001(2)	0.016(2)	-0.001(3)
C(11)	0.062(2)	0.058(3)	0.066(2)	0.003(2)	0.015(2)	-0.001(2)
C(12)	0.055(2)	0.062(3)	0.050(2)	-0.000(2)	0.020(2)	-0.006(2)
C(14)	0.063(3)	0.078(3)	0.082(3)	-0.003(3)	0.031(2)	-0.001(2)
C(15)	0.054(2)	0.056(2)	0.057(2)	-0.008(2)	0.027(2)	-0.005(2)
C(16)	0.065(2)	0.059(2)	0.070(2)	-0.018(2)	0.030(2)	-0.014(2)
C(17)	0.056(2)	0.085(3)	0.092(3)	-0.024(3)	0.031(2)	-0.019(2)
C(18)	0.053(2)	0.074(3)	0.089(3)	-0.012(2)	0.010(2)	0.001(2)
C(19)	0.060(3)	0.070(3)	0.075(3)	0.006(2)	0.009(2)	-0.002(2)
C(20)	0.058(2)	0.061(3)	0.073(2)	0.007(2)	0.021(2)	-0.009(2)

INTERATOMIC ANGLES

C(3)	- S(4)	- C(5)	90.5(2)
C(9)	- O(10)	- C(11)	116.5(3)
C(2)	- N(1)	- C(8)	106.4(2)
C(2)	- N(1)	- C(12)	115.1(3)
C(8)	- N(1)	- C(12)	115.9(3)
N(1)	- C(2)	- C(3)	111.2(3)
N(1)	- C(2)	- C(6)	105.1(3)
C(3)	- C(2)	- C(6)	109.6(3)
S(4)	- C(3)	- C(2)	106.1(3)
S(4)	- C(5)	- C(6)	105.7(3)
C(2)	- C(6)	- C(5)	109.5(3)
C(2)	- C(6)	- C(7)	105.7(3)
C(5)	- C(6)	- C(7)	113.1(3)
C(6)	- C(7)	- C(8)	102.4(3)
C(6)	- C(7)	- C(14)	114.8(3)
C(8)	- C(7)	- C(14)	118.7(3)
N(1)	- C(8)	- C(7)	102.7(2)
N(1)	- C(8)	- C(9)	111.1(3)
C(7)	- C(8)	- C(9)	117.7(3)
O(10)	- C(9)	- O(13)	118.9(4)
O(10)	- C(9)	- C(8)	114.4(3)
O(13)	- C(9)	- C(8)	126.8(4)
O(10)	- C(11)	- C(12)	110.8(3)
N(1)	- C(12)	- C(11)	109.0(3)
N(1)	- C(12)	- C(15)	114.5(3)
C(11)	- C(12)	- C(15)	109.9(3)
C(12)	- C(15)	- C(16)	122.0(3)
C(12)	- C(15)	- C(20)	120.5(3)
C(16)	- C(15)	- C(20)	117.5(3)
C(15)	- C(16)	- C(17)	122.6(4)
C(16)	- C(17)	- C(18)	119.4(4)
C(17)	- C(18)	- C(19)	119.8(4)
C(18)	- C(19)	- C(20)	119.8(4)
C(15)	- C(20)	- C(19)	120.9(3)

INTERATOMIC DISTANCES

S(4)	- C(3)	1.794(5)
S(4)	- C(5)	1.810(4)
O(10)	- C(9)	1.341(5)
O(10)	- C(11)	1.434(4)
O(13)	- C(9)	1.193(4)
N(1)	- C(2)	1.476(4)
N(1)	- C(8)	1.459(4)
N(1)	- C(12)	1.469(5)
C(2)	- C(3)	1.542(6)
C(2)	- C(6)	1.533(5)
C(5)	- C(6)	1.531(5)
C(6)	- C(7)	1.528(5)
C(7)	- C(8)	1.525(5)
C(7)	- C(14)	1.523(5)
C(8)	- C(9)	1.505(5)
C(11)	- C(12)	1.510(5)
C(12)	- C(15)	1.490(5)
C(15)	- C(16)	1.371(5)
C(15)	- C(20)	1.389(5)
C(16)	- C(17)	1.371(5)
C(17)	- C(18)	1.385(7)
C(18)	- C(19)	1.370(6)
C(19)	- C(20)	1.396(5)

Atomic Co-ordinates, Bond Lengths, Angles and Thermal Parameters for (4.11).

ATOMIC CO-ORDINATES AND ISOTROPIC TEMPERATURE FACTORS.

	x	y	z	U_{eq}
O1	0.5442 (2)	0.29650 (5)	0.3892 (2)	0.0432
O2	0.4591 (2)	0.26693 (5)	0.1568 (2)	0.0474
O3	0.8165 (2)	0.23041 (5)	0.2692 (2)	0.0529
O4	1.1960 (2)	0.36004 (7)	0.3044 (3)	0.0725
N	0.7039 (2)	0.38414 (5)	0.2882 (2)	0.0337
N1	1.0310 (2)	0.28774 (6)	0.3022 (2)	0.0423
C2	0.5356 (2)	0.29964 (7)	0.2394 (2)	0.0363
C4	0.6356 (2)	0.34225 (6)	0.1790 (2)	0.0333
C6	0.7414 (2)	0.36910 (7)	0.4492 (2)	0.0345
C7	0.5915 (2)	0.34268 (7)	0.4828 (2)	0.0390
C8	0.7775 (2)	0.41705 (7)	0.5528 (2)	0.0381
C9	0.7124 (3)	0.46642 (8)	0.5087 (3)	0.0510
C10	0.7378 (3)	0.50892 (9)	0.6091 (3)	0.0580
C11	0.8278 (3)	0.50246 (9)	0.7552 (3)	0.0547
C12	0.8944 (4)	0.4540 (1)	0.7997 (3)	0.0630
C13	0.8705 (3)	0.41140 (9)	0.6996 (2)	0.0536
C14	0.8416 (2)	0.40635 (7)	0.2314 (2)	0.0396
C15	0.9169 (2)	0.36055 (7)	0.1548 (2)	0.0412
C16	0.7891 (2)	0.31602 (7)	0.1336 (2)	0.0364
C17	0.8729 (2)	0.27244 (7)	0.2404 (2)	0.0378
C20	1.0665 (3)	0.33828 (8)	0.2600 (3)	0.0488
C22	1.1473 (3)	0.25535 (9)	0.4091 (3)	0.0577
C23	0.5244 (2)	0.36776 (7)	0.0372 (2)	0.0364
C24	0.4808 (2)	0.34062 (8)	−0.1004 (2)	0.0431
C25	0.3751 (3)	0.36338 (9)	−0.2245 (2)	0.0503
C26	0.3140 (3)	0.4136 (1)	−0.2134 (3)	0.0583
C27	0.3569 (3)	0.44074 (9)	−0.0770 (3)	0.0607
C28	0.4598 (3)	0.41785 (8)	0.0486 (2)	0.0495

INTERATOMIC ANGLES

C2—O1—C7	119.1 (1)	C10—C11—C12	119.3 (2)
C4—N0—C6	116.1 (1)	C11—C12—C13	120.9 (2)
C4—N0—C14	105.4 (1)	C8—C13—C12	120.5 (2)
C6—N0—C14	115.2 (1)	N0—C14—C15	107.1 (1)
C17—N1—C20	113.2 (2)	C14—C15—C16	105.3 (1)
C17—N1—C22	123.6 (2)	C14—C15—C20	111.4 (2)
C20—N1—C22	123.0 (2)	C16—C15—C20	105.5 (1)
O1—C2—O2	119.1 (2)	C4—C16—C15	104.2 (1)
O1—C2—C4	118.9 (1)	C4—C16—C17	115.5 (1)
O2—C2—C4	121.8 (2)	C15—C16—C17	103.7 (1)
N0—C4—C2	115.7 (1)	O3—C17—N1	123.1 (2)
N0—C4—C16	104.7 (1)	O3—C17—C16	128.2 (2)
C2—C4—C16	109.5 (1)	N1—C17—C16	108.8 (1)
N0—C4—C23	109.0 (1)	O4—C20—N1	124.3 (2)
C2—C4—C23	107.8 (1)	O4—C20—C15	127.2 (2)
C16—C4—C23	110.0 (1)	N1—C20—C15	108.5 (2)
N0—C6—C7	107.6 (1)	C4—C23—C24	121.4 (2)
N0—C6—C8	111.7 (1)	C4—C23—C28	119.6 (2)
C7—C6—C8	107.2 (1)	C24—C23—C28	118.9 (2)
O1—C7—C6	112.2 (2)	C23—C24—C25	120.5 (2)
C6—C8—C9	122.1 (2)	C24—C25—C26	120.4 (2)
C6—C8—C13	119.8 (2)	C25—C26—C27	119.4 (2)
C9—C8—C13	118.0 (2)	C26—C27—C28	120.6 (2)
C8—C9—C10	121.1 (2)	C23—C28—C27	120.2 (2)
C9—C10—C11	120.2 (2)		

INTERATOMIC DISTANCES

O1—C2	1.333 (2)	C8—C9	1.385 (3)
O1—C7	1.442 (2)	C8—C13	1.385 (3)
O2—C2	1.199 (2)	C9—C10	1.388 (3)
O3—C17	1.213 (2)	C10—C11	1.373 (3)
O4—C20	1.204 (3)	C11—C12	1.368 (4)
N0—C4	1.471 (2)	C12—C13	1.389 (3)
N0—C6	1.460 (2)	C14—C15	1.549 (3)
N0—C14	1.469 (2)	C15—C16	1.536 (3)
N1—C17	1.376 (2)	C15—C20	1.505 (3)
N1—C20	1.383 (3)	C16—C17	1.528 (2)
N1—C22	1.461 (3)	C23—C24	1.390 (3)
C2—C4	1.533 (2)	C23—C28	1.389 (3)
C4—C16	1.576 (2)	C24—C25	1.388 (3)
C4—C23	1.546 (2)	C25—C26	1.381 (3)
C6—C7	1.509 (3)	C26—C27	1.381 (4)
C6—C8	1.518 (2)	C27—C28	1.388 (3)

Atomic Co-ordinates, Bond Lengths, Angles and Thermal Parameters for (4.15).

ATOMIC CO-ORDINATES AND ISOTROPIC TEMPERATURE FACTORS.

	x	y	z	U_{eq}
O2	0.0569 (1)	−0.2630 (2)	0.1079 (1)	0.0767
O4	0.1162 (1)	−0.1452 (2)	0.0415 (1)	0.0837
O16	0.07318 (9)	0.3500 (1)	0.18500 (7)	0.0628
O18	0.0365 (1)	0.3274 (1)	0.08367 (8)	0.0658
O28	0.16090 (8)	0.1318 (2)	0.08171 (7)	0.0618
O29	0.09208 (8)	0.1038 (2)	−0.00907 (6)	0.0598
N7	0.00433 (8)	0.0929 (1)	0.20520 (7)	0.0431
C1	0.0868 (4)	−0.3674 (3)	0.0750 (3)	0.0970
C3	0.0768 (1)	−0.1564 (2)	0.0858 (1)	0.0542
C5	0.0437 (1)	−0.0559 (2)	0.12428 (9)	0.0454
C6	0.0902 (1)	−0.0271 (2)	0.1852 (1)	0.0492
C8	0.1200 (1)	0.1668 (2)	0.23787 (9)	0.0476
C9	0.1428 (1)	0.1147 (2)	0.30336 (9)	0.0528
C10	0.2146 (1)	0.1222 (2)	0.3255 (1)	0.0672
C11	0.1854 (2)	0.0321 (3)	0.4260 (2)	0.0901
C12	0.2356 (2)	0.0819 (3)	0.3867 (2)	0.0812
C13	0.1141 (2)	0.0225 (4)	0.4050 (2)	0.0940
C14	0.0928 (2)	0.0638 (3)	0.3442 (1)	0.0753
C15	0.0877 (1)	0.2917 (2)	0.2472 (1)	0.0568
C17	0.0457 (1)	0.2817 (2)	0.1362 (1)	0.0509
C19	0.02327 (9)	0.1508 (2)	0.15037 (9)	0.0436
C20	−0.0593 (1)	0.1556 (2)	0.1645 (1)	0.0503
C21	−0.0851 (1)	0.1202 (2)	0.2238 (1)	0.0611
C22	−0.1597 (1)	0.1233 (3)	0.2350 (2)	0.0774
C23	−0.2080 (1)	0.1610 (3)	0.1873 (2)	0.0802
C24	−0.1831 (2)	0.1955 (4)	0.1282 (2)	0.0905
C25	−0.1093 (1)	0.1936 (3)	0.1165 (1)	0.0758
C26	0.0359 (1)	0.0681 (2)	0.09042 (9)	0.0439
C27	0.1040 (1)	0.1040 (2)	0.05516 (9)	0.0478
C30	0.1555 (2)	0.1277 (5)	−0.0477 (2)	0.0822

INTERATOMIC ANGLES

C1—O2—C3	115.8 (2)	O16—C15—C8	110.7 (2)
C15—O16—C17	117.9 (2)	O16—C17—O18	118.7 (2)
C27—O29—C30	115.6 (2)	O16—C17—C19	118.3 (2)
C6—N7—C8	114.0 (1)	O18—C17—C19	122.4 (2)
C6—N7—C19	109.5 (1)	N7—C19—C17	114.7 (1)
C8—N7—C19	116.4 (1)	N7—C19—C20	110.4 (1)
O2—C3—O4	122.6 (2)	C17—C19—C20	105.8 (1)
O2—C3—C5	110.9 (2)	N7—C19—C26	105.6 (1)
O4—C3—C5	126.5 (2)	C17—C19—C26	110.7 (1)
C3—C5—C6	111.2 (2)	C20—C19—C26	109.7 (1)
C3—C5—C26	116.7 (2)	C19—C20—C21	121.2 (2)
C6—C5—C26	103.3 (2)	C19—C20—C25	120.2 (2)
N7—C6—C5	103.9 (2)	C21—C20—C25	118.6 (2)
N7—C8—C9	111.8 (2)	C20—C21—C22	120.1 (3)
N7—C8—C15	107.2 (2)	C21—C22—C23	120.6 (3)
C9—C8—C15	109.3 (2)	C22—C23—C24	119.8 (3)
C8—C9—C10	120.4 (2)	C23—C24—C25	120.4 (3)
C8—C9—C14	121.8 (2)	C20—C25—C24	120.5 (3)
C10—C9—C14	117.8 (2)	C5—C26—C19	100.0 (1)
C9—C10—C12	121.3 (3)	C5—C26—C27	112.5 (2)
C12—C11—C13	120.1 (3)	C19—C26—C27	111.7 (2)
C10—C12—C11	119.8 (3)	O28—C27—O29	124.5 (2)
C11—C13—C14	120.3 (3)	O28—C27—C26	124.3 (2)
C9—C14—C13	120.8 (3)	O29—C27—C26	111.2 (2)

INTERATOMIC DISTANCES

O2—C1	1.449 (4)	C9—C10	1.381 (3)
O2—C3	1.314 (3)	C9—C14	1.379 (3)
O4—C3	1.186 (3)	C10—C12	1.380 (4)
O16—C15	1.450 (3)	C11—C12	1.358 (5)
O16—C17	1.341 (3)	C11—C13	1.366 (5)
O18—C17	1.199 (2)	C13—C14	1.378 (4)
O28—C27	1.202 (2)	C17—C19	1.530 (3)
O29—C27	1.334 (2)	C19—C20	1.549 (3)
O29—C30	1.451 (3)	C19—C26	1.556 (3)
N7—C6	1.467 (2)	C20—C21	1.378 (3)
N7—C8	1.454 (2)	C20—C25	1.391 (3)
N7—C19	1.482 (2)	C21—C22	1.392 (3)
C3—C5	1.498 (3)	C22—C23	1.366 (5)
C5—C6	1.528 (3)	C23—C24	1.365 (5)
C5—C26	1.538 (3)	C24—C25	1.381 (4)
C8—C9	1.512 (3)	C26—C27	1.515 (3)
C8—C15	1.511 (3)		

Atomic Co-ordinates, Bond Lengths, Angles and Thermal Parameters for (4.21).

ATOMIC CO-ORDINATES AND ISOTROPIC TEMPERATURE FACTORS.

Atom	x/a	y/b	z/c	u(iso)	
O(1)	-0.0323(1)	0.2848(1)	0.22507(7)	0.0598	
O(7)	-0.0524(2)	0.4501(1)	0.2237(1)	0.0757	
N(4)	0.1211(1)	0.33697(9)	0.06315(7)	0.0434	
C(6)	0.0145(2)	0.2089(1)	0.1795(1)	0.0534	
C(5)	0.0976(1)	0.2350(1)	0.10631(9)	0.0435	
C(3)	0.0117(2)	0.3860(1)	0.08530(9)	0.0477	
C(2)	-0.0239(2)	0.3798(1)	0.1836(1)	0.0564	
C(8)	-0.1297(2)	0.3326(1)	0.0306(1)	0.0481	
C(9)	-0.2696(2)	0.3092(1)	0.0658(1)	0.0621	
C(10)	-0.3944(2)	0.2631(2)	0.0122(2)	0.0729	
C(11)	-0.3801(2)	0.2423(2)	-0.0757(1)	0.0715	
C(12)	-0.2420(2)	0.2661(1)	-0.1114(1)	0.0672	
C(13)	-0.1179(2)	0.3104(1)	-0.0590(1)	0.0572	
C(14)	0.2728(2)	0.4111(1)	0.05152(9)	0.0479	
C(15)	0.3497(2)	0.4611(2)	0.1362(1)	0.0649	
C(20)	0.1579(1)	0.1567(1)	0.06514(9)	0.0443	
C(21)	0.1564(2)	0.1436(1)	-0.02696(9)	0.0498	
C(22)	0.2079(2)	0.0665(1)	-0.0644(1)	0.0585	
C(23)	0.2618(2)	0.0026(1)	-0.0110(1)	0.0649	
C(24)	0.2643(2)	0.0157(1)	0.0797(1)	0.0650	
C(25)	0.2131(2)	0.0921(1)	0.1181(1)	0.0552	occ.
O(160)	0.294(1)	0.4380(9)	0.2094(5)	0.0800	0.549(7)
O(170)	0.4854(3)	0.5373(3)	0.1191(2)	0.0585	0.549(7)
C(180)	0.5663(4)	0.6009(3)	0.1930(3)	0.0667	0.549(7)
C(190)	0.6310(6)	0.5346(5)	0.2486(4)	0.0910	0.549(7)
O(161)	0.2866(9)	0.4688(9)	0.2041(6)	0.0630	0.451(7)
O(171)	0.5015(3)	0.4807(5)	0.1303(2)	0.0698	0.451(7)
C(181)	0.5900(6)	0.5146(5)	0.2095(4)	0.0873	0.451(7)
C(191)	0.6085(7)	0.6308(5)	0.2344(6)	0.1004	0.451(7)

INTERATOMIC ANGLES

C(6)	- O(1)	- C(2)	118.7(1)	C(21)	- C(22)	- C(23)	120.3(1)
C(5)	- N(4)	- C(3)	113.7(1)	C(22)	- C(23)	- C(24)	119.8(1)
C(5)	- N(4)	- C(14)	117.1(1)	C(23)	- C(24)	- C(25)	120.5(1)
C(3)	- N(4)	- C(14)	117.8(1)	C(20)	- C(25)	- C(24)	120.2(1)
O(1)	- C(6)	- C(5)	123.2(1)	C(15)	- O(160)	- O(161)	79.4(18)
N(4)	- C(5)	- C(6)	119.7(1)	C(15)	- O(170)	- C(180)	117.2(2)
N(4)	- C(5)	- C(20)	118.4(1)	C(15)	- O(170)	- O(171)	76.2(3)
C(6)	- C(5)	- C(20)	121.8(1)	C(180)	- O(170)	- O(171)	96.3(4)
N(4)	- C(3)	- C(2)	112.9(1)	O(170)	- C(180)	- C(190)	111.3(5)
N(4)	- C(3)	- C(8)	110.9(1)	O(170)	- C(180)	- O(171)	28.1(1)
C(2)	- C(3)	- C(8)	110.5(1)	C(190)	- C(180)	- O(171)	83.3(4)
O(1)	- C(2)	- O(7)	119.9(2)	O(170)	- C(180)	- C(181)	83.2(5)
O(1)	- C(2)	- C(3)	115.9(1)	C(190)	- C(180)	- C(181)	28.1(3)
O(7)	- C(2)	- C(3)	124.1(2)				
C(3)	- C(8)	- C(9)	122.7(1)	O(171)	- C(180)	- C(181)	55.2(4)
C(3)	- C(8)	- C(13)	119.1(1)	O(170)	- C(180)	- C(191)	175.7(8)
C(9)	- C(8)	- C(13)	118.2(1)	C(190)	- C(180)	- C(191)	64.8(6)
C(8)	- C(9)	- C(10)	120.2(2)	O(171)	- C(180)	- C(191)	148.0(7)
C(9)	- C(10)	- C(11)	120.5(2)	C(181)	- C(180)	- C(191)	92.9(7)
C(10)	- C(11)	- C(12)	119.7(2)	C(180)	- C(190)	- C(181)	56.1(7)
C(11)	- C(12)	- C(13)	120.4(2)	C(180)	- C(190)	- C(191)	30.9(3)
C(8)	- C(13)	- C(12)	121.0(2)	C(181)	- C(190)	- C(191)	87.0(8)
N(4)	- C(14)	- C(15)	114.3(1)	C(15)	- O(161)	- O(160)	80.0(17)
C(14)	- C(15)	- O(160)	123.8(4)	C(15)	- O(171)	- O(170)	69.3(3)
C(14)	- C(15)	- O(170)	110.7(2)	C(15)	- O(171)	- C(180)	98.4(3)
O(160)	- C(15)	- O(170)	125.5(4)	O(170)	- O(171)	- C(180)	55.7(3)
C(14)	- C(15)	- O(161)	124.3(4)	C(15)	- O(171)	- C(181)	118.3(3)
O(160)	- C(15)	- O(161)	20.6(10)	O(170)	- O(171)	- C(181)	100.7(5)
O(170)	- C(15)	- O(161)	119.2(5)	C(180)	- O(171)	- C(181)	45.0(3)
C(14)	- C(15)	- O(171)	110.5(2)	C(180)	- C(181)	- C(190)	95.7(8)
O(160)	- C(15)	- O(171)	116.5(5)	C(180)	- C(181)	- O(171)	79.8(6)
O(170)	- C(15)	- O(171)	34.4(2)	C(190)	- C(181)	- O(171)	175.3(10)
O(161)	- C(15)	- O(171)	124.4(5)	C(180)	- C(181)	- C(191)	30.9(3)
C(5)	- C(20)	- C(21)	120.7(1)	C(190)	- C(181)	- C(191)	64.8(7)
C(5)	- C(20)	- C(25)	120.3(1)	O(171)	- C(181)	- C(191)	110.8(6)
C(21)	- C(20)	- C(25)	119.0(1)	C(180)	- C(191)	- C(190)	84.3(7)
C(20)	- C(21)	- C(22)	120.0(1)	C(180)	- C(191)	- C(181)	56.2(5)
				C(190)	- C(191)	- C(181)	28.1(3)

ANISOTROPIC TEMPERATURE FACTORS.

Atom	U(11)	U(22)	U(33)	U(23)	U(13)	U(12)
O(1)	0.0640(6)	0.0749(7)	0.0468(5)	-0.0007(5)	0.0125(4)	0.0235(5)
O(7)	0.0894(9)	0.0838(8)	0.0777(8)	-0.0303(7)	0.0086(7)	0.0356(7)
N(4)	0.0433(6)	0.0401(5)	0.0451(5)	0.0006(4)	0.0028(4)	0.0124(4)
C(6)	0.0554(7)	0.0559(7)	0.0473(7)	0.0053(6)	0.0047(6)	0.0161(6)
C(5)	0.0424(6)	0.0437(6)	0.0418(6)	0.0016(5)	-0.0019(5)	0.0113(5)
C(3)	0.0501(7)	0.0406(6)	0.0529(7)	-0.0034(5)	0.0035(5)	0.0149(5)
C(2)	0.0531(8)	0.0623(8)	0.0568(8)	-0.0133(7)	0.0038(6)	0.0186(6)
C(8)	0.0510(7)	0.0393(6)	0.0591(8)	0.0012(5)	0.0000(6)	0.0191(5)
C(9)	0.0560(9)	0.0638(9)	0.073(1)	-0.0012(7)	0.0051(7)	0.0264(7)
C(10)	0.0499(9)	0.079(1)	0.105(2)	0.001(1)	0.0002(9)	0.0269(8)
C(11)	0.063(1)	0.070(1)	0.093(1)	-0.0036(9)	-0.0226(9)	0.0261(8)
C(12)	0.076(1)	0.0645(9)	0.066(1)	-0.0012(8)	-0.0154(8)	0.0263(8)
C(13)	0.0606(8)	0.0559(8)	0.0564(8)	0.0016(6)	-0.0014(6)	0.0223(7)
C(14)	0.0463(7)	0.0495(7)	0.0432(7)	-0.0005(5)	0.0052(5)	0.0072(5)
C(15)	0.0527(8)	0.095(1)	0.0508(9)	-0.0166(8)	0.0047(7)	-0.0020(8)
C(20)	0.0422(6)	0.0421(6)	0.0461(7)	0.0023(5)	-0.0019(5)	0.0112(5)
C(21)	0.0527(7)	0.0505(7)	0.0469(7)	-0.0001(5)	-0.0045(5)	0.0186(6)
C(22)	0.0664(9)	0.0588(8)	0.0544(8)	-0.0103(6)	-0.0041(6)	0.0243(7)
C(23)	0.075(1)	0.0556(9)	0.078(1)	-0.0109(7)	-0.0063(8)	0.0320(8)
C(24)	0.082(1)	0.0589(9)	0.071(1)	0.0045(7)	-0.0095(8)	0.0367(8)
C(25)	0.0625(9)	0.0536(8)	0.0527(8)	0.0044(6)	-0.0064(6)	0.0219(6)
O(160)	0.085(4)	0.115(6)	0.051(2)	-0.018(2)	0.010(2)	-0.020(3)
O(170)	0.044(1)	0.067(2)	0.059(1)	0.001(1)	-0.0018(8)	0.006(1)
C(180)	0.055(2)	0.069(2)	0.073(2)	-0.007(2)	-0.015(2)	0.008(2)
C(190)	0.079(3)	0.102(4)	0.115(4)	-0.011(3)	-0.038(3)	0.036(3)
O(161)	0.052(2)	0.097(5)	0.054(3)	-0.028(3)	0.008(2)	0.010(3)
O(171)	0.052(2)	0.095(3)	0.067(2)	-0.020(2)	-0.006(1)	0.015(2)
C(181)	0.065(3)	0.124(5)	0.094(4)	-0.022(3)	-0.031(3)	0.026(3)
C(191)	0.081(4)	0.100(5)	0.119(5)	-0.024(4)	-0.021(3)	-0.001(3)

INTERATOMIC DISTANCES

O(1)	- C(6)	1.399(2)
O(1)	- C(2)	1.352(2)
O(7)	- C(2)	1.202(2)
N(4)	- C(5)	1.410(2)
N(4)	- C(3)	1.458(2)
N(4)	- C(14)	1.448(2)
C(6)	- C(5)	1.334(2)
C(5)	- C(20)	1.475(2)
C(3)	- C(2)	1.514(2)
C(3)	- C(8)	1.534(2)
C(8)	- C(9)	1.386(2)
C(8)	- C(13)	1.392(2)
C(9)	- C(10)	1.396(3)
C(10)	- C(11)	1.368(3)
C(11)	- C(12)	1.371(3)
C(12)	- C(13)	1.380(2)
C(14)	- C(15)	1.499(2)
C(15)	- O(160)	1.217(7)
C(15)	- O(170)	1.354(3)
C(15)	- O(161)	1.214(7)
C(15)	- O(171)	1.405(4)
C(20)	- C(21)	1.395(2)
C(20)	- C(25)	1.393(2)
C(21)	- C(22)	1.384(2)
C(22)	- C(23)	1.382(2)
C(23)	- C(24)	1.375(3)
C(24)	- C(25)	1.380(2)
O(160)	- O(161)	0.43(2)
O(170)	- C(180)	1.436(5)
O(170)	- O(171)	0.818(4)
C(180)	- C(190)	1.488(6)
C(180)	- O(171)	1.728(7)
C(180)	- C(181)	1.242(7)
C(180)	- C(191)	0.768(6)
C(190)	- C(181)	0.705(5)
C(190)	- C(191)	1.353(8)
O(171)	- C(181)	1.441(6)
C(181)	- C(191)	1.493(8)