Nitroacrylates:: versatile reagents in organic synthesis

MChem, Darren Orton

Nitroacrylates: Versatile Reagents in Organic Synthesis

Darren Orton, MChem.

Ph.D Thesis

University of Durham

Department of Chemistry

May 2001

Copyright

Declaration

This work was conducted in the Department of Chemistry at the University of Durham between October 1997 and September 2000. A three month CASE placement was taken in the Medicinal Chemistry Department of Pfizer UK, at the Central Research facility in Sandwich, between April 1999 and July 1999. The work has not been submitted for a degree in this, or any other university. It is my own work, unless otherwise indicated.

Acknowledgements

Thanks to my supervisors: Dr. Patrick G. Steel and Dr Mark E. Bunnage, for constant advice and guidance. Also thanks to the other members of laboratory CG1 for their help and encouragement – Phil, Ed, Bill, Anne and Ganesh.

Many thanks to: Dr Simon De-Sousa, Dr Les Oates and Dr Liz Grayson (for advice and assistance); Gordon, Malcolm and Ray (glass blowers); Jimmy and Joe (Stores); Dr Alan Kenwright, Ian McKeag and Catherine Heffernan (NMR); Dr Mike Jones and Lara Turner (MS) and Lenny Lauchlan (HPLC)

I also wish to thank EPSRC for funding and Pfizer for a CASE award.

Abbreviations

Ac	: acetyl
acac	: acetylacetonato
AIBN	: α,α-azoisobutyronitrile
AIDS	: acquired immume deficiency syndrome
Ar	: aromatic
bp	: boiling point
Bz	: benzoyl
Bn	: benzyl
Boc	: *tert*-butoxycarbonyl
br	: broad
Bu	: butyl
CDI	: 1,1'-carbonyldiimidazole
CI	: chemical ionisation
d	: doublet
dba	: dibenzylideneacetone
DCC	: *N,N'*-dicyclohexylcarbodiimide
DCM	: dichloromethane
DEAD	: diethyl azodicarboxylate
DIBALH	: diisobutylaluminium hydride
DMF	: *N,N*-dimethylformamide
DMS	: dimethyl sulfide
DMSO	: dimethylsulfoxide
EDCI	: *N*-ethyl-*N'*-(3-dimethylaminopropyl)carbodiimide hydrochloride
EI	: electron impact ionisation
Et	: ethyl
FMO	: frontier molecular orbital
GC	: gas chromatography
HIV	: human immunodeficiency virus

HMDS : 1,1,1,3,3,3-hexamethyldisilazide

HMPA : hexamethylphosphoramide

HOBt : hydroxybenzotriazole

HOMO : highest occupied molecular orbital

HPLC : high performance liquid chromatography

IR : infrared

^{i}Pr : *iso*-propyl

LDA : lithium diisopropylamide

LUMO : lowest unoccupied molecular orbital

m : multiplet

*m*CPBA : *meta*-chloroperoxybenzoic acid

Me : methyl

mp : melting point

Ms : methanesulfonyl

MS : mass spectrometry

NMR : nuclear magnetic resonance

Ph : phenyl

Py : pyridine

q : quartet

s : singlet

SEM : trimethylsilylethoxymethyl

t : triplet

TBS : *tert*-butyldimethylsilyl

Tf : trifluoromethanesulfonyl

TFA : trifluoroacetic acid

TFAA : trifluoroacetic anhydride

THF : tetrahydrofuran

THP : tetrahydropyran-2-yl

TLC : thin layer chromatography

TMS : trimethylsilyl

Z : benzyloxycarbonyl

Abstract

Nitroacrylates: Versatile Reagents in Organic Synthesis.

Darren Orton

Ph.D 2001

Nitroacrylates are stable, crystalline solids and have frequently been used in synthesis as reactive dienophiles in the Diels-Alder reaction. The regio- and diastereoselectivity of the Diels-Alder reaction is controlled by the electronic properties of the nitro group. This thesis describes work to utilise the nitro group to provide control of stereochemistry in the synthesis of natural products.

The thesis begins by discussing the synthesis of nitroacrylates using both a nitro-aldol and radical based route. An investigation into their selectivity in the Diels-Alder reaction with a diverse array of dienes is discussed. As part of this investigation a large increase in diastereoselectivity was observed for the reaction of ethyl β-nitroacrylate and 1-methoxycyclohexa-1,4-diene when Lewis acids were added. The origin of this selectivity is unknown and similar dienes show only a modest increase in selectivity on addition of $ZnCl_2$.

An application of the resultant adducts has been demonstrated in the synthesis of a simple bicyclic β-amino acid and then subsequently applied to the diastereoselective synthesis of chorismate-based β-amino acids (2*S**, 3*S**)-DHAA and the antibiotic oryzoxymycin. The key steps involve a base-mediated ring-opening reaction of the 7-oxa-bicyclo[2,2,1]hept-5-ene and a CsF mediated coupling of the lactate moiety. The progress toward the synthesis of a related anthranilate synthase inhibitor is also discussed.

Finally, in the context of a synthesis of the structurally unique diterpene Vinigrol **1** we have shown that nitroacrylates can be employed as substituted ketene equivalents in the formation of cyclic alpha-chiral ketones.

Contents

Section A: Introduction

Chapter 1: Introduction to Nitroacrylates 1

1.1 General Introduction 2

1.2 Background to Nitroacrylate Chemistry 3

1.2.1 Introduction 3

1.2.2 Literature Syntheses of Nitroacrylates 5

1.2.3 Synthetic Applications of Nitroacrylates 7

1.2.3.1 Diels-Alder and Other Cycloadditions 7

1.2.3.2 Michael Additions 11

1.3 β-Amino Acids 13

1.3.1 Introduction to β-Amino Acids 13

1.3.2 γ-Hydroxy-β-Amino acids 13

1.3.3 Synthesis of γ-Hydroxy-β-Amino Acids 16

1.3.3.1 Synthesis *via* Homologation of α-Amino Acids 17

1.3.3.2 Synthesis *via* Oxidation of Vinyl β-Amino Acids 18

1.3.3.3 Synthesis using Modified Sugar Templates 20

1.4 Ketene Equivalents 21

1.4.1 Introduction 21

1.4.2 Previous Applications of Ketene Equivalents 22

1.5 Proposed Work 27

1.5.1 Previous Work within the Group 27

1.5.2 Proposed Work 28

Section B: Results and Discussion

Chapter 2: Synthesis and Cycloadditions of Nitroacrylates 31

2.1 Introduction 31

2.2 Synthesis of Ethyl β-Nitroacrylate 31

2.3 Chiral Auxiliary Synthesis 34

2.4 Nitroacrylate Diels-Alder Reactions 36

2.4.1 Introduction 36

2.4.2 Background to Nitroacrylate Diels-Alder Reactions 37

2.4.3 Cycloaddition Reactions 38

2.4.4 Discussion of Cycloaddition Results 51

2.5 Conclusions 54

Chapter 3: β-Amino Acids 56

3.1 Introduction 56

3.2 Background to Chorismate based Natural Products 57

3.3 Results and Discussion 60

3.3.1 Synthesis of Bicyclic β-Amino Acids 60

3.3.2 Synthesis of (2*S*, 3*S*)-DHAA 65

3.3.3 Progress toward the Synthesis of Oryzoxymycin 68

3.3.4 Inhibitors of Anthranilate Synthase 75

3.3.4.1 Introduction 75

3.3.4.2 Progress toward the Synthesis of Enzyme Inhibitors 76

3.4 Conclusions and Future Work 78

Chapter 4: Vinigrol 79

4.1 Introduction 79

4.2 Introduction to Vinigrol 80

4.2.1 Isolation and Background 80

4.2.2 Previous Synthetic Approaches 80

4.3 Proposed Strategy 83

4.4 Results and Discussion 86

4.4.1 Nitroacrylates as Substituted Ketene Equivalents 86

4.4.2 Nitronate Alkylations 93

4.4.2.1 Introduction 93

4.4.2.2 Alkylation Studies 94

4.4.2.3 Michael Addition Reactions 96

4.5 Conclusions and Future Work 97

Section C: Experimental

Chapter 5: Experimental **98**

5.1 Introduction 99

5.2 Experimental Details 100

Section D: Appendix :

Lectures, Seminars and Colloquia

Lectures and Seminars from invited speakers 1997-2000 142

First Year Induction Course 149

Seminars, Colloquia and Presentations by the Author 150

Section E: References

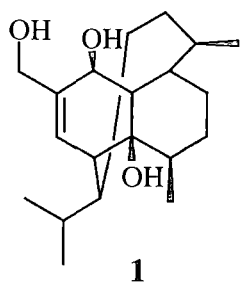
References 152

SECTION A: Introduction

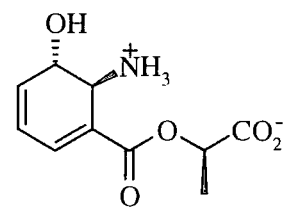
Chapter 1: Introduction to Nitroacrylates

1.1 General Introduction

Nitroacrylates have found widespread use in organic synthesis particularly in the Diels-Alder reaction. The aim of the project was to develop the established methodology with an emphasis on selectivity and the synthesis of natural products. In the context of these goals, we set out to explore the synthesis of nitroacrylates *via* a number of routes, their use in the Diels-Alder reaction to control the selectivity of the initial adduct and subsequent elaboration of the adducts into natural products, notably vinigrol **1** and oryzoxymycin **2** (Figure 1).



1



2

Figure 1

Whilst the total synthesis of these natural products represented the major goal of the project, we also sought to demonstrate the use of nitroacrylates as ketene equivalents in the synthesis of α-chiral ketones and as convenient synthons for the formation of β-amino acids.

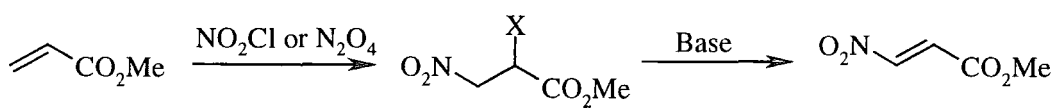
The remainder of this chapter summarises previously published work in the synthesis of nitroacrylates, their use in the synthesis of natural products and puts this area of research into context with other literature procedures in the fields of β-amino acids and ketene equivalents.

In chapter 2 the preparation of nitroacrylates and subsequently their reactivity and selectivity in the Diels-Alder reaction with a number of simple dienes are discussed. Chapter 3 details our study into the elaboration of the resultant Diels-Alder adducts into naturally occurring β-amino acids, notably in the synthesis of oryzoxymycin **2** and other chorismate-based natural products. Chapter 4 deals with the application of nitroacrylates as substituted ketene equivalents to give α-chiral ketones in the context of the synthesis of the core structure of vinigrol **1**.

1.2 Background to Nitroacrylate Chemistry

1.2.1 Introduction

β-Nitroacrylates were first reported in 1952 by Shechter *et al.*[1] as part of an investigation into the addition of nitryl chloride (NO_2Cl) or dinitrogen tetroxide to a number of unsaturated systems, including acrylates. Addition of nitryl chloride to methyl acrylate in a variety of solvents gave methyl 2-chloro-3-nitro-propionate **4** as the exclusive regioisomer (Scheme 1).



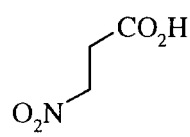
3 **4** - X = Cl, **5** - X = OH **6**

Scheme 1

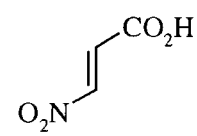
Analogously, the reaction between dinitrogen tetroxide and methyl acrylate gave intermediate **5** after hydrolysis. Having studied these reactions and analysed the by-products, Shechter *et al.* suggested that the reaction occurs *via* a radical mechanism.

Subsequently, intermediate **4** was converted into methyl 3-nitroacrylate **6** by reaction with bases such as pyridine, *N*,*N*-dimethylaniline or anhydrous sodium acetate.

In addition to interesting chemical properties, β-nitroacrylates have been shown to possess potent biological activity as the free acid. Singer *et al.*[2] have examined the biological properties of 3-nitropropionic acid **7** and 3-nitroacrylic acid **8** with succinate dehydrogenase (Figure 2). Singer *et al.* concluded that 3-nitropropionic acid **7** is recognised as a substrate by the enzyme and undergoes oxidation to 3-nitroacrylic acid **8**. In the second step, irreversible Michael addition of a thiol group from the enzyme to the nitroacrylate leads to inactivation of the enzyme.



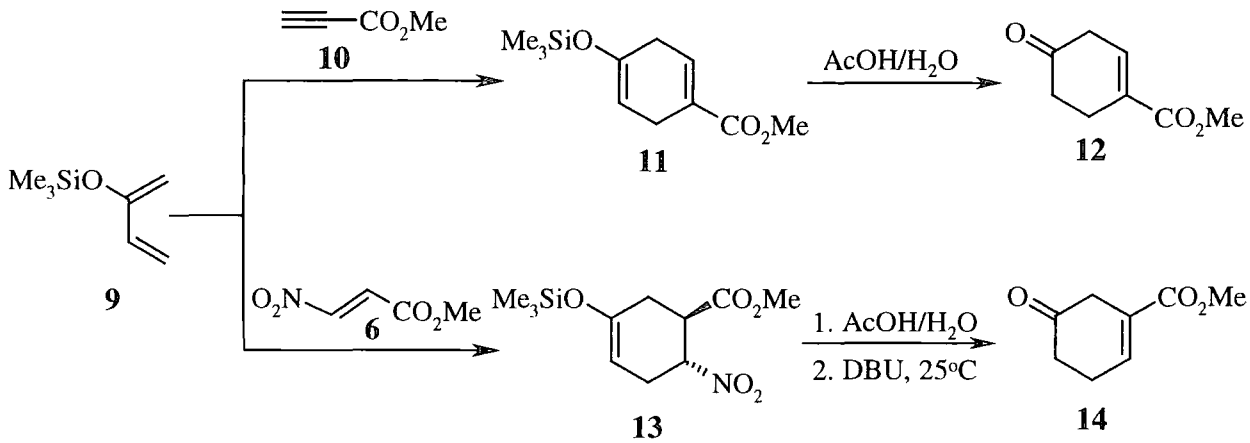
7



8

Figure 2

The combination of the electron-withdrawing effects of the nitro and ester groups in nitroacrylates produce a very electron deficient double bond and consequently a low energy LUMO, therefore, they readily undergo Diels-Alder reactions with electron rich dienes. The synthetic versatility of nitroacrylates was first demonstrated by Danishefsky[3] in their application as synthetic equivalents to alkyl propiolates. The typical regioselectivity for alkyl propiolates in the Diels-Alder reaction is demonstrated in scheme 2 for the synthesis of substituted cyclohexenones i.e. 4-substituted cyclohex-3-enone **12** from 2-substituted butadiene **9**.

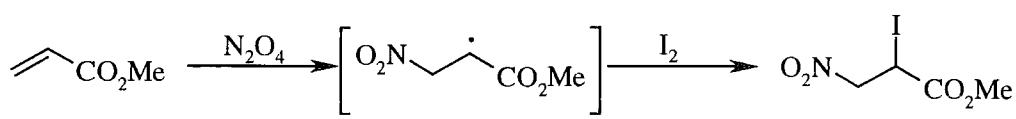


Scheme 2

Danishefsky showed that the regioselectivity shown by alkyl propiolates was completely inverted by the use of a nitroacrylate as the dienophile. The nitro group not only serves as an activating group, it also predominates over the ester in the control of regiochemistry to give initial adduct **13**. Subsequent hydrolysis of the trimethylsilyl enol-ether and facile β-elimination of nitrous acid gave the corresponding 3-substituted cyclohexenone **14**.

1.2.2 Literature Syntheses of Nitroacrylates

Following on from the pioneering work of Schechter *et al.*, Emmons and Stevens[4] endorsed the radical mechanism hypothesis by the use of excess iodine to trap the intermediate radical **15**, to give methyl 2-iodo-3-nitropropionate **16** in 75% yield (Scheme 3).

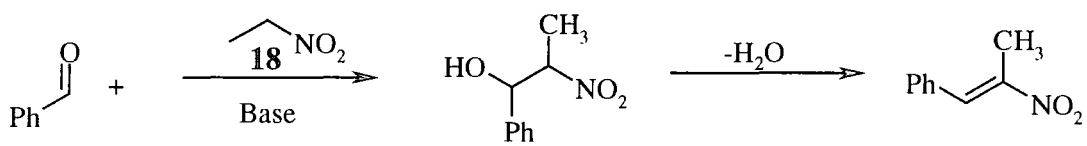


3 **15** **16**

Scheme 3

No purification of the intermediate iodo compound **16** was required and, following dehydrohalogenation with sodium acetate, methyl β-nitroacrylate **6** was obtained in good yield. This approach was later refined by Husser and McMurry[5] who showed that better yields could be obtained by using the acrylate as the reagent in excess and by rapid addition of N_2O_4. This procedure now represents the established method for the synthesis of nitroacrylates from acrylates.

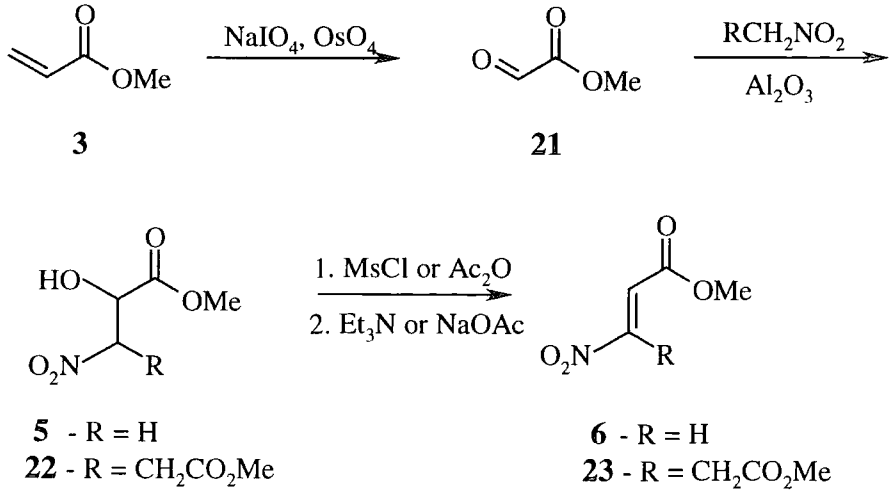
A second method for the synthesis of nitroacrylates was developed using methodology developed in the 1970's in the synthesis of various functionalised nitroalkenes using a nitro-aldol (Henry) approach. For example, Smallridge *et al.*[6] used this approach, to give styrene **20** from benzaldehyde **17** and nitroethane **18** (Scheme 4). This approach to nitroalkenes has the added advantage that if aromatic aldehydes are used, dehydration often occurs spontaneously.



17 **19** **20**

Scheme 4

This strategy was first demonstrated in the synthesis of nitroacrylate **6** by Clive *et al.*[7] using glyoxylate **21** as the electrophile (Scheme 5). Glyoxylate **21**, generated *via* osmium tetroxide dihydroxylation / periodate cleavage of acrylate **3** was subsequently treated with nitromethane in the presence of neutral alumina to give the hydroxy intermediate **5**. Dehydration was achieved *via* mesylation and *in-situ* elimination to give the required nitroacrylate **6** in 76% overall yield.



Scheme 5

Kozikowski and Wu[8] have reported the only example of a substituted β-nitroacrylate to be used in synthesis. Nitroacrylate **23** was synthesised using a substituted nitroalkane in a nitro-aldol approach (Scheme 5). In this case dehydration was effected by activation with acetic anhydride and subsequent treatment with sodium acetate.

1.2.3 Synthetic Applications of Nitroacrylates

In contrast to simple nitroalkenes, β-nitroacrylates have been used in synthesis surprisingly rarely. The remainder of this section reviews the literature where β-nitroacrylates have been utilised in the synthesis of natural products. Although not covered in this thesis, the use of α-nitroacrylates has considerable literature precedence, principally as a Michael acceptor.[9]

1.2.3.1 Diels-Alder and Other Cycloadditions

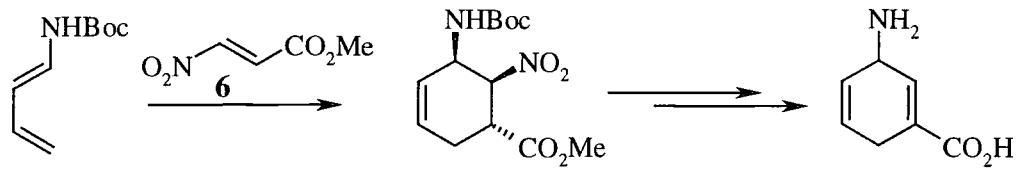
A number of groups have followed up on the initial observation that nitroacrylates can act as alkyl propiolate equivalents.[10] A representative example is the synthesis of the

γ-aminobutyrate aminotransferase (GABA-T) inhibitor isogabaculine **24** by Danishefsky and Hershenson,[11] (Figure 3).

24 **25**

Figure 3

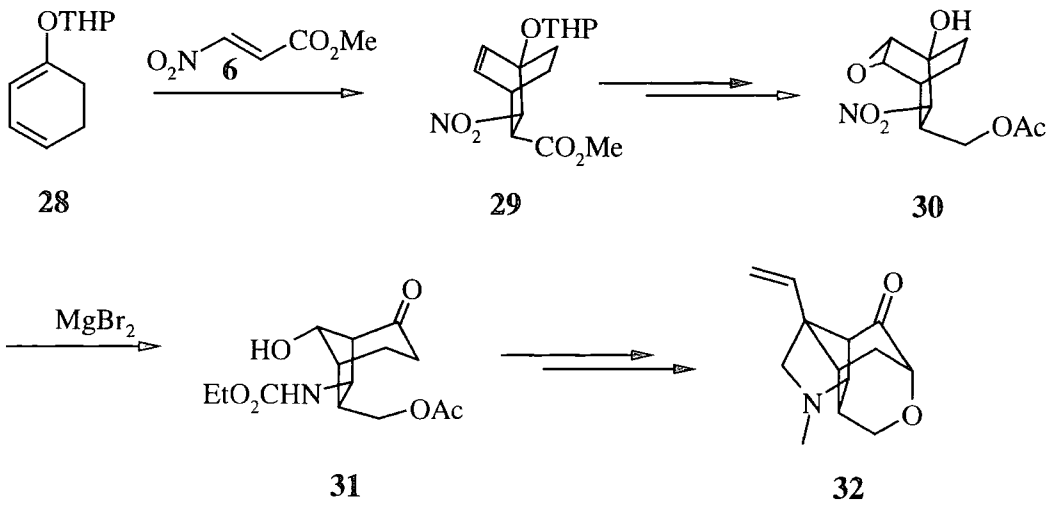
Using conventional methodology with alkyl propiolates, the Diels-Alder reaction would exclusively give access to the 1,2-regioisomer **25**. The reaction between methyl β-nitroacrylate **6** and the 1-substituted diene **26** gave intermediate **27** as a single regioisomer (Scheme 6). Subsequent elimination of nitrous acid, hydrolysis of the ester and removal of the Boc group to give isogabaculine **24** completed the synthesis.



26 **27** **24**

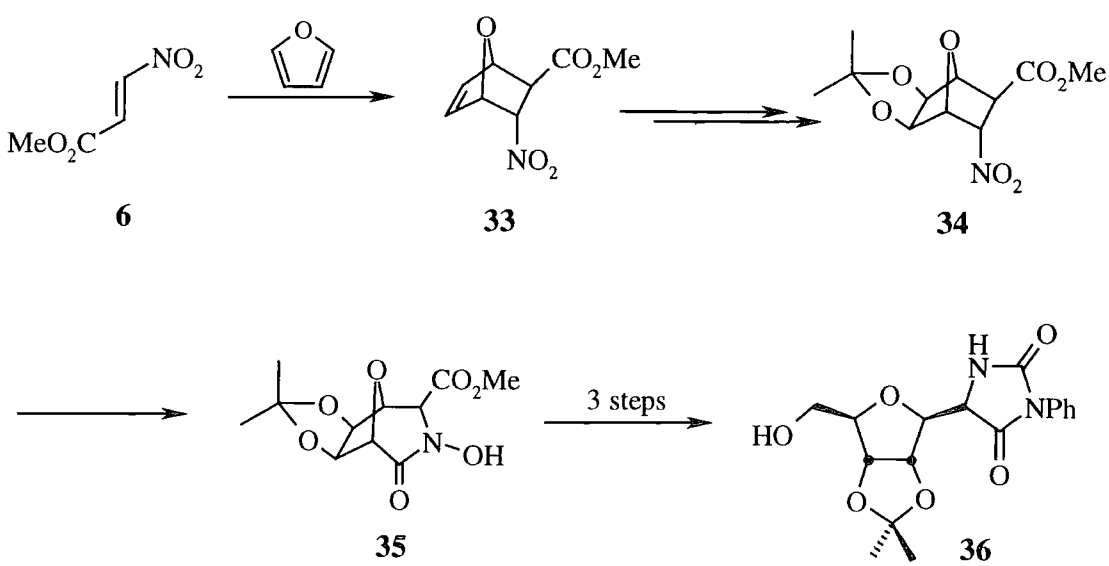
Scheme 6

In an approach to the synthesis of gelsemine, Fleming *et al.*[12] used a similar method with diene **28** and methyl β-nitroacrylate in a Diels-Alder reaction (Scheme 7). The reaction was also completely regioselective, and in this case the THP group induces stereocontrol to give **29** in 43% yield. Following a number of functional group interconversions to give alcohol **30** a Lewis acid catalysed rearrangement occurs to give alcohol **31**. Further elaboration of the structure gave a highly advanced intermediate **32** in the synthesis of the gelsemine ring structure.



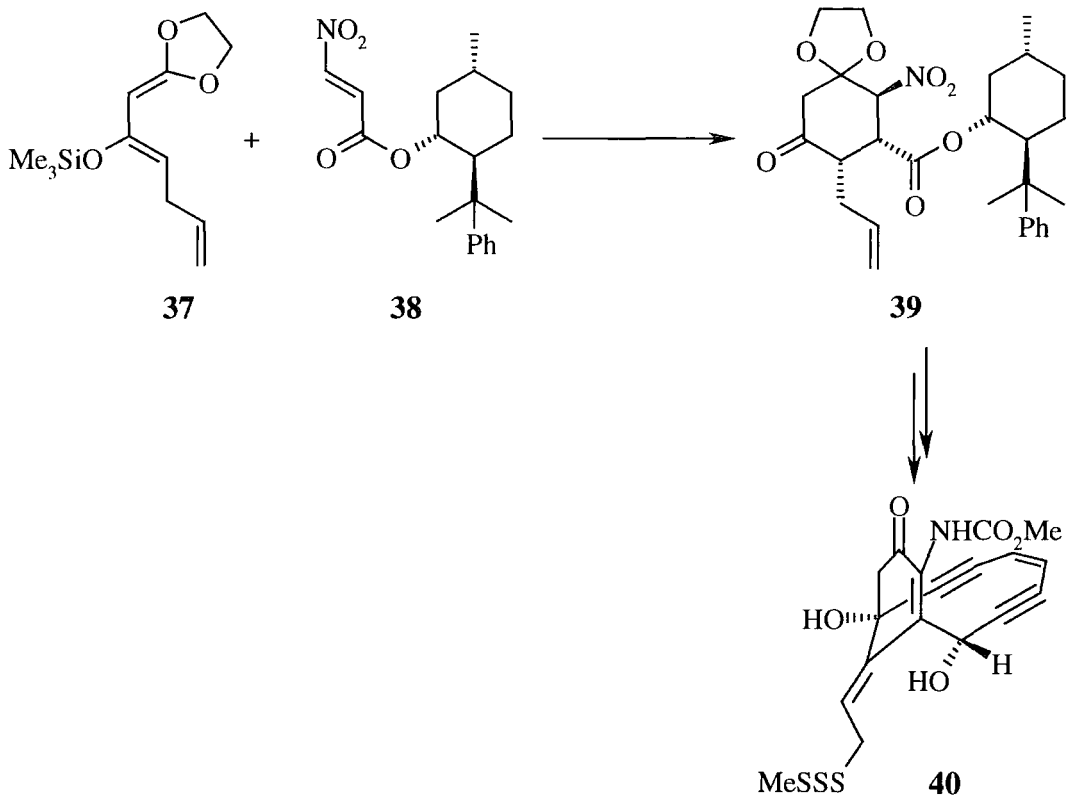
Scheme 7

Nitroacrylates have also been utilised by Sera *et al.*[13] in a Diels-Alder reaction with furan, to give the pure crystalline *endo*-adduct **33** after chromatography (Scheme 8). Following dihydroxylation and protection of the resultant diol as the acetonide **34**, photoisomerisation gave hydroxylamine **35**, which is then converted into the hydantoin C-riboside **36** in three steps.



Scheme 8

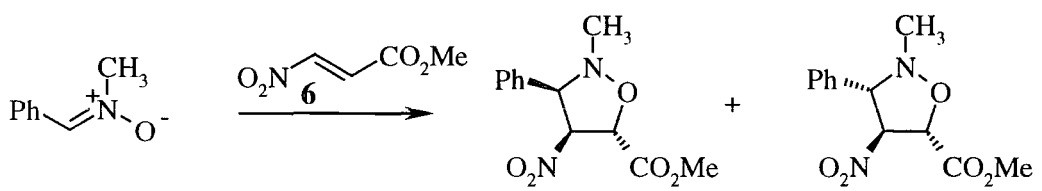
In the only previous example of a chiral nitroacrylate in a Diels-Alder reaction Clive and Selvakumar[7] describe the total synthesis of (−)-calicheamicinone **40** (Scheme 9). The synthesis uses functionalised nitroacrylate **38**, and the ketene acetal **37** to give ketone **39** as the single stereoisomer after crystallisation. The enantioselectivity was achieved using the (-)-8-phenylmenthyl ester as a chiral auxiliary on the nitroacrylate.



37 **38** **39** **40**

Scheme 9

In addition to [4+2] cycloadditions, Padwa *et al.*[14] briefly describe a number of dipolar cycloaddition reactions of nitrone **41**, including methyl β-nitroacrylate to give the *cis*-diastereoisomer **42** as the major product (Scheme 10).

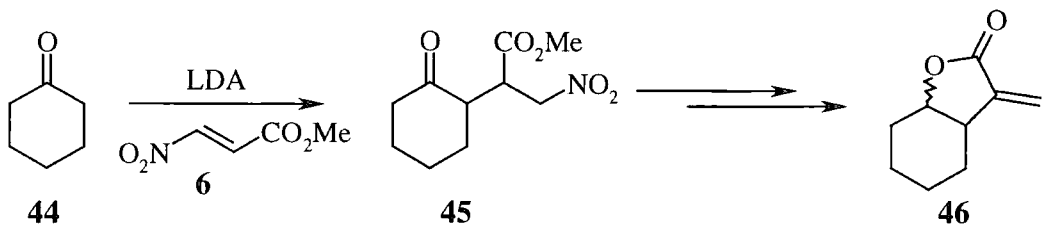


41 **42** - major **43** - minor

Scheme 10

1.2.3.2 Michael Additions

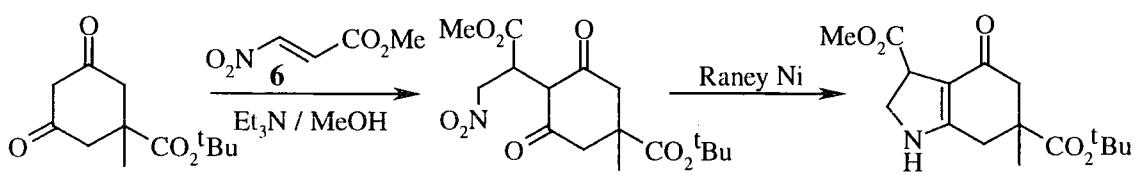
As in Diels-Alder reactions, the regioselectivity in the Michael addition of nitroacrylates is controlled by the nitro group. McMurry and Patterson[15] have used nitroacrylates in the synthesis of α-methylenebutyrolactones *via* a Michael addition (Scheme 11). The pre-formed enolate of cyclohexanone undergoes a Michael reaction to give adduct **45** as the exclusive regioisomer. Following reduction of the ketone with $NaBH_4$ and lactonisation, the nitro group was eliminated as nitrous acid to give **46** in high yield. α-Methylenebutyrolactones have been shown to be common intermediates in previous syntheses of sesquiterpenes.[16]



44 **45** **46**

Scheme 11

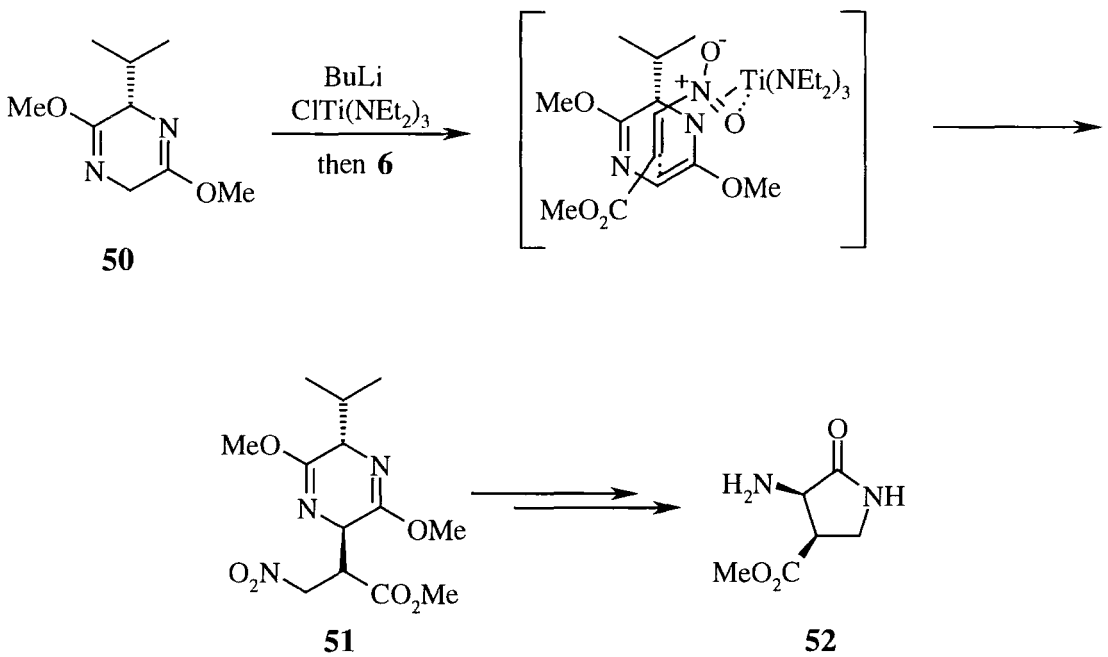
Bartlett *et al.*[17] have reported the use of diketone **47** as a precursor in the Michael reaction with nitroacrylates in the synthesis of a semi-rigid template for the hydrogen bonding array of a peptide α-helix. The initial Michael reaction was followed by catalytic reduction of the nitro group using Raney nickel (Scheme 12). The corresponding amine undergoes spontaneous cyclisation to the hexahydroindolone **49**. The methyl and *tert*-butyl esters were sequentially hydrolysed and coupled to peptides to evaluate their conformations.



47 **48** **49**

Scheme 12

In a study of the Michael addition of bislactim **50** to nitroacrylates to give Michael adducts, Schöllkopf *et al.*[18] observed a small degree of diastereoselectivity in the formation of adduct **51**. This selectivity was explained by invoking chelation of the nitro group with the titanium species in an eight-membered transition state with complete facial selectivity due to the isopropyl group (Scheme 13). Hydrolysis of the bislactim and catalytic reduction of the nitro group gave access to the α-aminolactam **52**.



50 **51** **52**

Scheme 13

1.3 β-Amino Acids

1.3.1 Introduction to β-Amino Acids

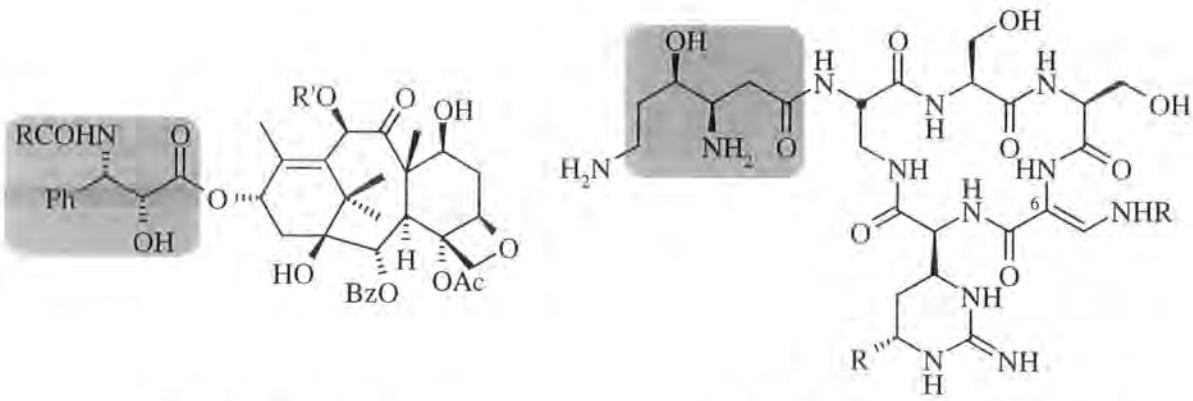
β-Amino acids are emerging as an important topic in organic chemistry and as an interesting class of compounds in medicinal chemistry. A number of comprehensive reviews of the field of β-amino acids have been published.[19] In this section no attempt will be made to repeat this detail, but the aspects of the field that relate to this thesis will be discussed. β-Amino acids are found in humans, animals, microorganisms and plants, either in the free form or as components of peptides with antibiotic, anti fungal, cytotoxic and/or anticancer activities. Peptides that contain β-amino acids are generally more stable to enzymatic hydrolysis because the enzyme is not able to recognise the amide bond as readily as in the α-amino acid case. Moreover, the ability of short β-peptide oligomers to form well-defined, remarkably stable secondary structures has enhanced the potential of these compounds as mimics of α-peptides.[20]

1.3.2 γ-Hydroxy-β-Amino Acids

β-Amino acids that incorporate an α- or γ-hydroxyl group are important structural motifs in natural products. The α-hydroxy-β-amino acids have been extensively studied in the literature largely due to the discovery of Taxol® **53**, a broad-spectrum cancer chemotherapeutic agent and subsequently its synthetic analogue, Taxotere® **54**. However, this thesis describes the use of nitroacrylates in the synthesis of oryzoxymycin, which is a naturally occurring antibiotic that incorporates a γ-hydroxy-β-amino acid core structure. This section reviews the literature concerning examples

of natural products that contain the less well studied γ-hydroxy-β-amino acid moiety, their interesting biological properties and methods used in their synthesis.

The first known examples of natural products with the γ-hydroxy-β-amino acid moiety are the tuberactinomycins A **55** and N **56**, [21] (Figure 4). These natural products form part of a class of compounds that were first marketed by both Ciba and Pfizer as tuberculostatic agents in the 1960's.



53 - R = Ph, R' = Ac
54 - R = 'BuO, R' = H

55 - R = OH (tuberactinomycin A)
56 - R = H (tuberactinomycin N)

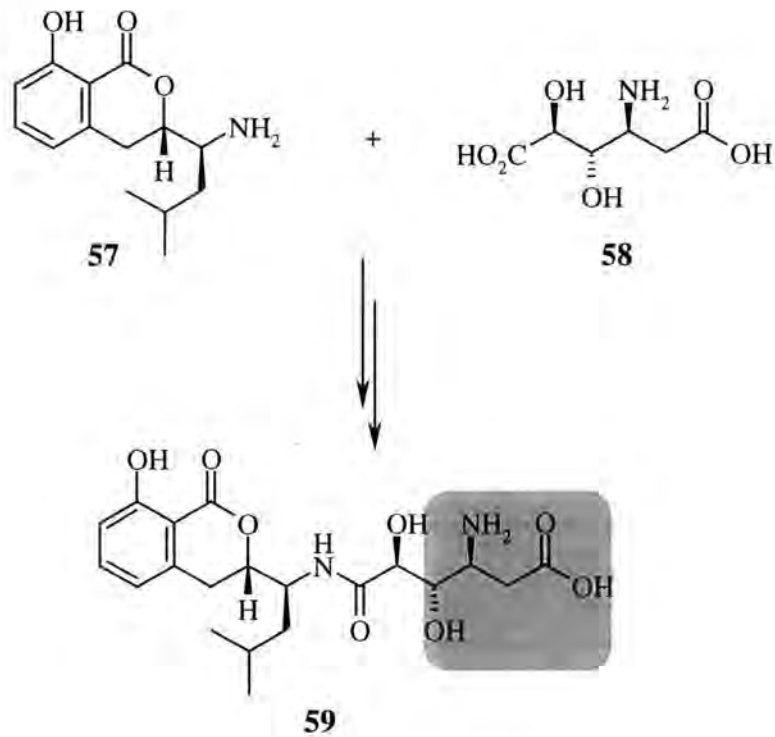
Figure 4

The tuberactinomycin family of compounds were isolated from the culture broth of *Streptomyces griseoverticillatus* var. *tuberacticus* and are cyclic homopentapeptides incorporating a γ-hydroxy-β-lysine side chain. All compounds of the class are active against gram-positive bacteria, mycobacteria and show antituberculous activity. However, in this case, subsequent investigations into the therapeutic use of modified tuberactinomycins have shown that the side chain is not required for biological activity.

The AI-77's are a small family of 3,4-dihydroisocoumarin-based natural products, which were isolated from a culture broth of *Bacillus pumilus* AI-77.[22] The biological

activity of AI-77-B **59** is of some interest, as it exhibits potent antiulcerogenicity against stress ulcers without having some of the side effects that accompany existing gastroprotective drugs.[23]

The first total synthesis of AI-77-B **59** was reported[24] in 1989 with three other total syntheses being described since. All synthetic strategies involve a similar coupling procedure between the 3,4-dihydroisocoumarin **57** with the γ-hydroxy-β-amino acid **58** (Scheme 14).

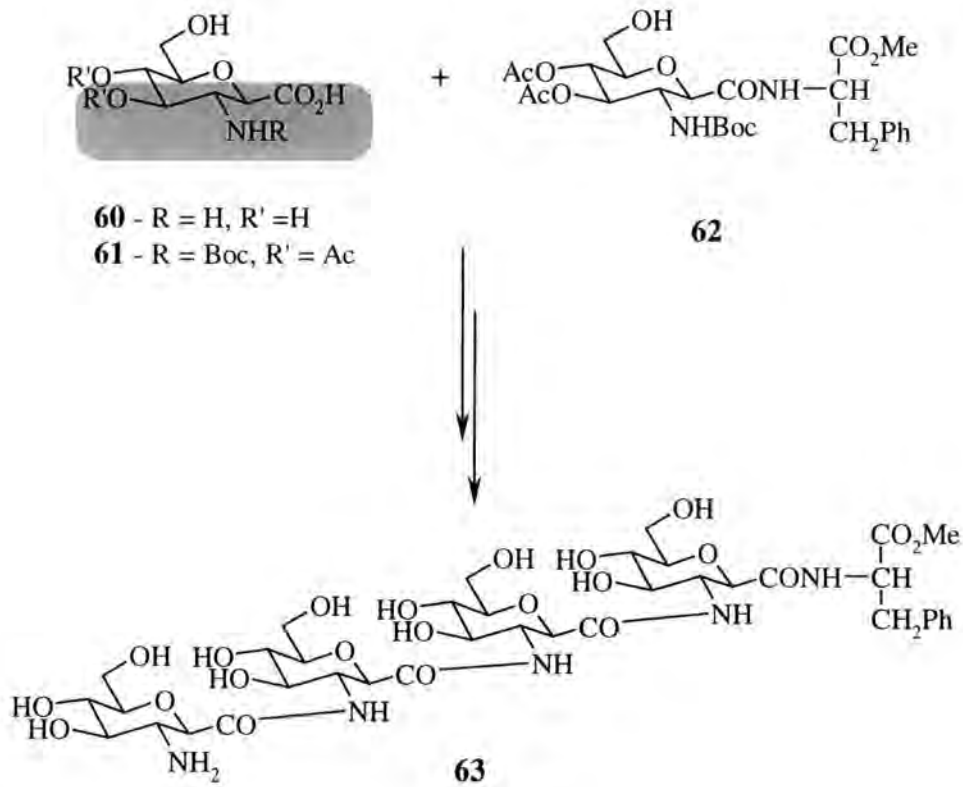


Scheme 14

The γ-hydroxy-β-amino acid moiety also forms the basis for a new class of carbohydrate mimetics called 'carbopeptoids' in which the glycosidic bonds are replaced with amido linkages. In the first detailed report of a preparation of this class of compound, Ichikawa *et al.*[25] prepared the monomer unit **60** from D-glucosamine hydrochloride. Following C-terminal linkage with L-phenylalanine methyl ester, compound **62** was also produced.

Using three cycles of the two step procedure of (i) removal of the Boc group with 2N HCl/EtOAc and (ii) coupling with a monomer unit using the BOP reagent[26] and

Hünig's base gave the protected tetramer. Subsequent *O*-deacylation (NaOMe in MeOH) gave the oligosaccharide analogue **63**.



Scheme 15

Ichikawa *et al.* have proposed that such 'carbopeptoids' would be resistant to glycosidases and may have interesting biological activities as carbohydrate or peptido mimetics. In fact the carbopeptoid **63**, after sulfation, has been found to show a strong inhibitory potency against HIV infection to CD4 cell although it is composed of only four pseudo-glucose units.

1.3.3 Synthesis of γ-Hydroxy-β-Amino Acids

In this section the limited number of methods which have been described in the literature for the preparation of the γ-hydroxy-β-amino acid moiety are summarised. The reports follow three distinct strategies:

(1) Arndt-Eistert homologation of α-amino acids.

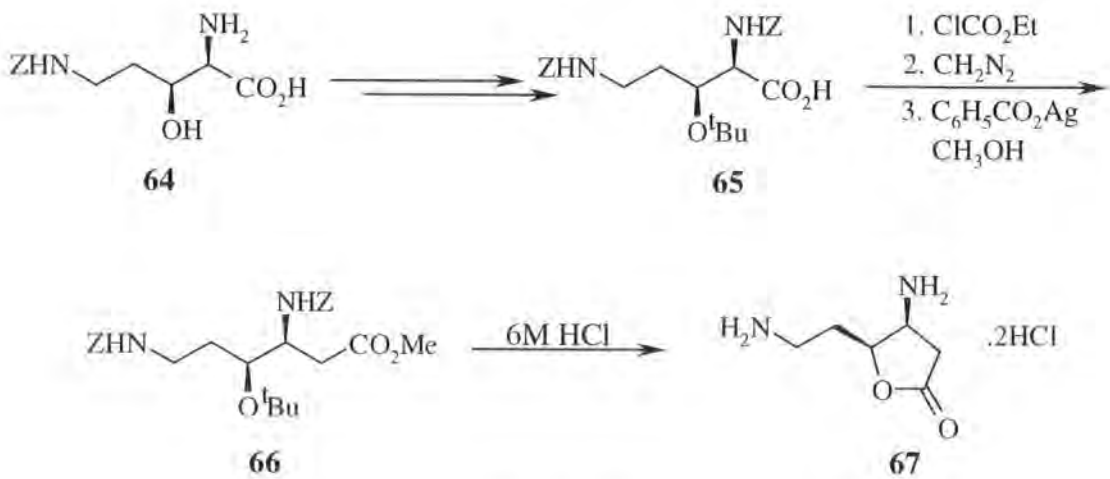
(2) Oxidation of vinyl β-amino acid derivatives.

(3) Use of modified sugar templates.

1.3.3.1 Synthesis *via* Homologation of α-Amino Acids

In the first approach to the synthesis of γ-hydroxy-β-amino acids, the β- and γ-stereochemistry is obtained from the chiral pool, in the form of α-amino acids which are generally inexpensive and readily available in enantiomerically pure forms.

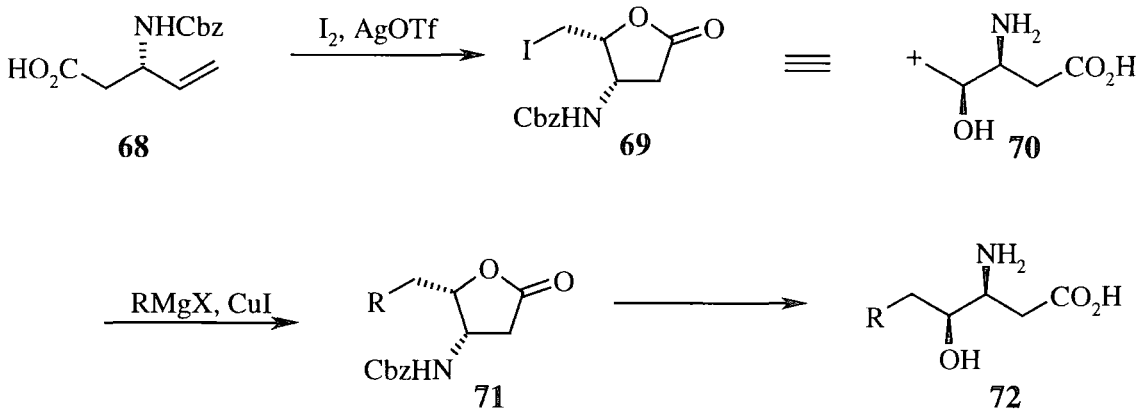
In the context of the synthesis of tuberactinomycins A and N, Shiba *et al.*[27] reported the synthesis of the γ-hydroxy-β-lysine side chain using an Arndt-Eistert reaction (Scheme 16). The serine derivative **65** was treated with ethyl chloroformate and then diazomethane to afford a diazoketone. Wolff rearrangement of the diazoketone was carried out in the presence of silver benzoate in methanol to give ester **66**. Hydrolysis of the product with 6M hydrochloric acid gave the γ-hydroxy-β-lysine side as the lactone di-hydrochloride **67** which is completely identical to the natural specimen obtained from the acid-catalysed cleavage of tuberactinomycins A and N.



Scheme 16

1.3.3.2 Synthesis *via* Oxidation of Vinyl β-Amino Acids

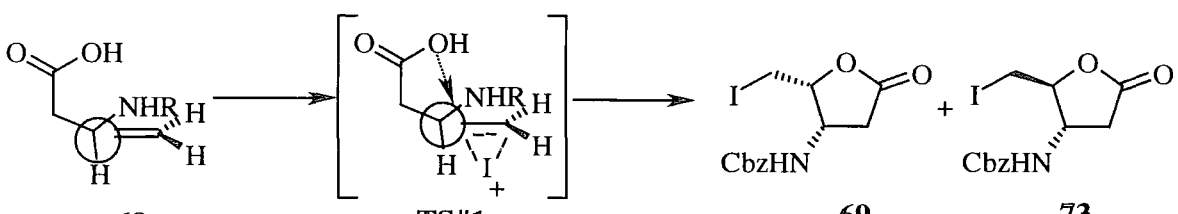
A number of related approaches to γ-hydroxy-β-amino acids have been reported using the vinyl β-amino acid template. The stereochemistry of the amino group, ultimately derived from α-amino acids, controls the stereochemistry of the oxidation reaction. One method that was reported by Zappia *et al.*[28] used an iodolactonisation strategy using 3-amino-4-pentenoic acid derivative **68** (Scheme 17).



68 **69** **70** **71** **72**

Scheme 17

From a synthetic point of view the iodolactone **69** can be considered to be equivalent to the electrophilic synthon **70**, thus nucleophilic substitution using organocuprates was investigated to obtain a number of γ-functionalised *syn*-γ-hydroxy-β-amino acids. Zappia *et al.* proposed that control of the new chiral centre is achieved due to the well-defined intramolecular transition state **TS#1** in the iodolactonisation step giving the *cis*-diastereoisomer **69** as the major product (Scheme 18).

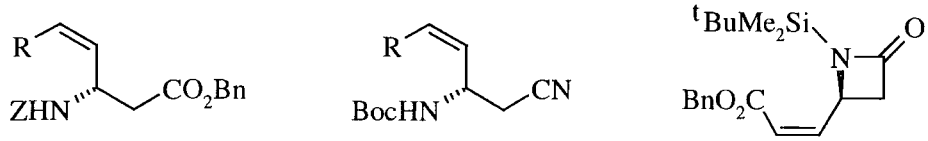


68 **TS#1** **69** **73**

Cis / trans ratio 15 : 1

Scheme 18

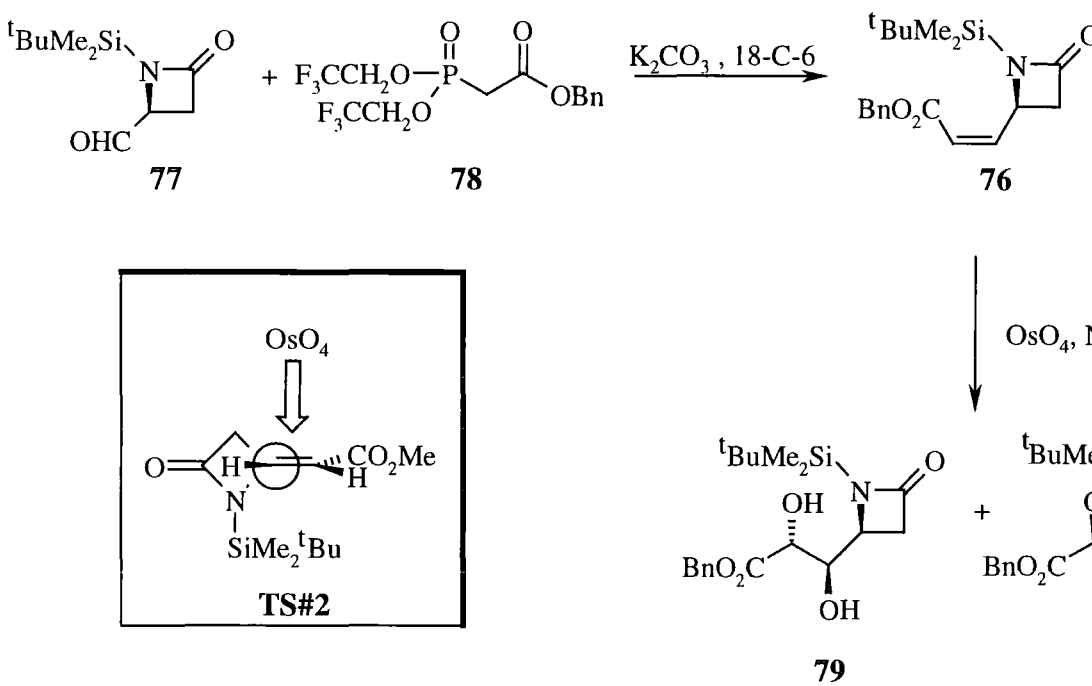
In the synthesis of the γ-hydroxy-β-amino acid fragment of AI-77-B, a number of related approaches have used protected forms of vinyl β-amino acids including **74-76** in a dihydroxylation procedure (Figure 5).



74 **75** **76**

Figure 5

The use of protected β-amino acids as templates is exemplified by Thomas *et al.*[29] using azetidinone **76** to provide simultaneous protection of the amino and carboxyl groups and to give scope for the stereoselective introduction of the vicinal diol moiety (Scheme 19). Synthesis of azetidinone **76** was achieved in 70% yield from a (*Z*)-selective Wittig reaction between 4-formylazetidinone **77** and bis(trifluoroethyl) phosphonate **78** in the presence of potassium carbonate.

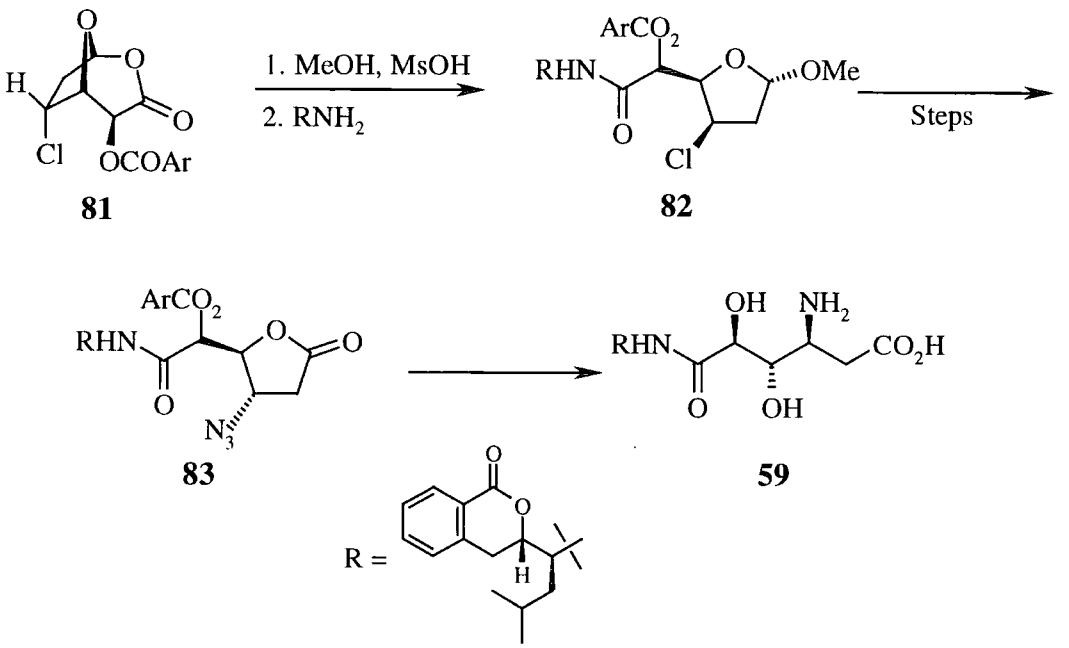


Scheme 19

The stereoselectivity of the dihydroxylation reaction using osmium tetroxide / *N*-methyl-morpholine *N*-oxide (NMO) favours the (1'*S*, 2'*S*)-diastereoisomer: **79** : **80** = 82 : 18. Thomas *et al.* proposed that this stereoselectivity is consistent with oxidation from the least hindered face of the alkene in transition state **TS#2**. Following protection of the diol and a coupling procedure, the hydroxy-β-amino acid moiety was revealed using basic hydrolysis with aqueous sodium hydroxide followed by HCl.

1.3.3.3 Synthesis using Modified Sugar Templates

A strategy for the synthesis of the γ-hydroxy-β-amino acid structure **58** was reported by Durgnat and Vogel[30] for the total synthesis of AI-77-B **59** *via* methyl furanoside **82** obtained from lactone **81** (Scheme 20). Following an S_N2 displacement reaction to introduce the azide functionality, the corresponding azido methyl furanoside was converted to lactone **83** using *m*CPBA with 0.1 eq. of $BF_3.OEt_2$ according to the method developed by Grieco.[31] Reduction of the azide functionality using tributylstannane and hydrolysis of the lactone gave AI-77-B **59**.



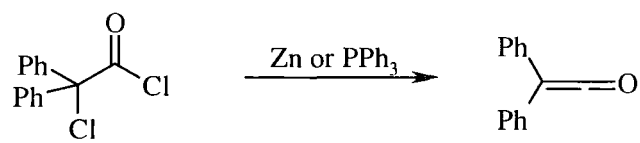
Scheme 20

1.4 Ketene Equivalents

1.4.1 Introduction

In addition to functioning as a convenient synthon in the synthesis of β-amino acid derivatives, we also anticipated that β-nitroacrylates would act as substituted ketene equivalents. This section reviews examples and applications of ketene equivalents in organic synthesis with a particular emphasis on substituted ketene equivalents.

Ketenes are usually efficiently generated '*in-situ*' using a number of methods, including pyrolysis of carboxylic acids, dehydrohalogenation of acyl halides and dehalogenation of α-halo acyl halides (Scheme 21).



84 **85**

Scheme 21

Ketenes react preferentially with dienes in an overall [2+2] manner to give cyclobutanes rather than by a [4+2] cycloaddition to give the Diels-Alder adducts. Ketenes are generally considered to undergo [2+2] cycloadditions using an allowed pathway in which a [π2s + π2a] process occurs (Figure 6).[32]

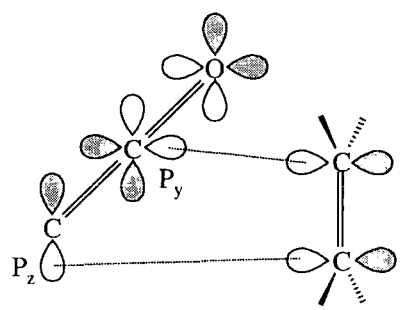
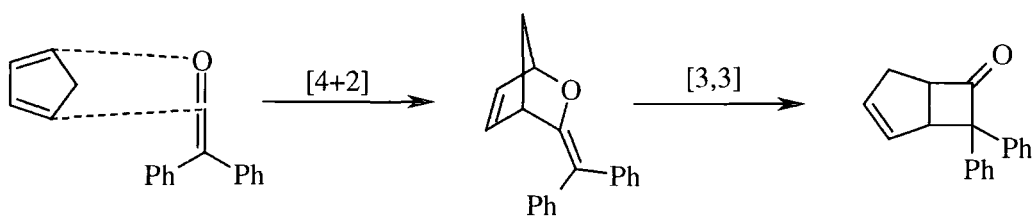


Figure 6

However, a recent study by Yamabe[33] showed that ketenes such as **85** undergo a two-step mechanism with cyclopentadiene (Scheme 22). The initial [4+2] cycloaddition was validated by spectroscopic observations of the intermediate adduct **87** at low temperature. A subsequent [3,3] sigmatropic rearrangement gave the cyclobutanone **88**.

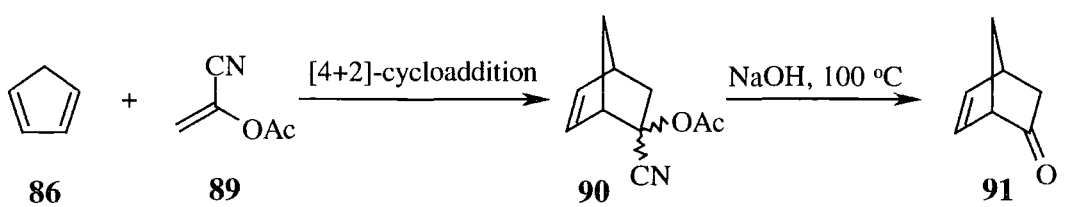


86 **85** **87** **88**

Scheme 22

1.4.2 Previous Applications of Ketene Equivalents

Since the early investigations of Staudinger[34] clearly established that ketenes form [2+2]-adducts with cyclopentadienes, rather than the coveted norbornenones, several synthetically useful ketene equivalents have been developed.[35] The first example of a ketene equivalent was reported in 1956 by Bartlett,[36] and involved a two-stage sequence in which, α-acetoxyacrylonitrile **89** undergoes an initial [4+2] cycloaddition with cyclopentadiene **86** followed by conversion into norbornenone **91** using sodium hydroxide (Scheme 23).

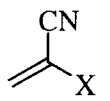


86 **89** **90** **91**

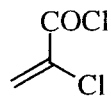
Scheme 23

Other simple ketene equivalents have been developed to use a similar two step approach including compounds **92-96**. In general, the first generation of ketene equivalents suffered from low reactivity in the Diels-Alder reaction, so only the highly reactive cyclopentadiene has been used to demonstrate their use.

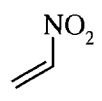
In recent years a number of groups have published reports on new chiral ketene equivalents including **97-99** (Figure 7). Some of these have embodied vinyl sulfoxides since they are reasonable dienophiles and have been shown to give high enantioselectivity.[37]



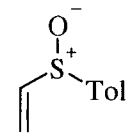
92 - X = Cl
93 - X = SCH_3



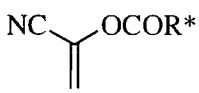
94



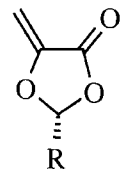
95



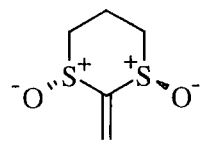
96



97



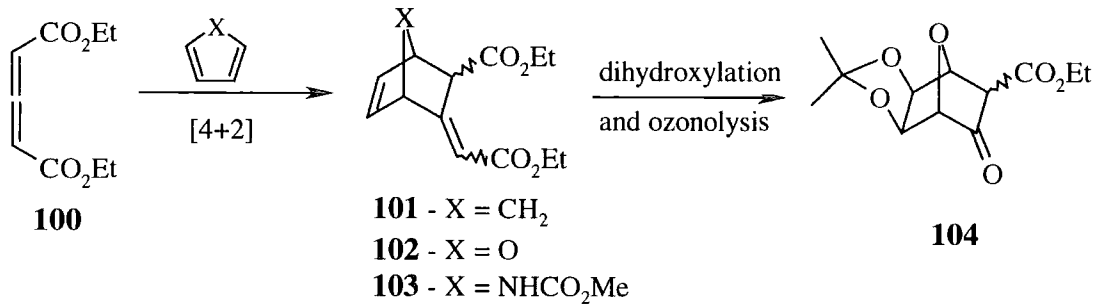
98



99

Figure 7

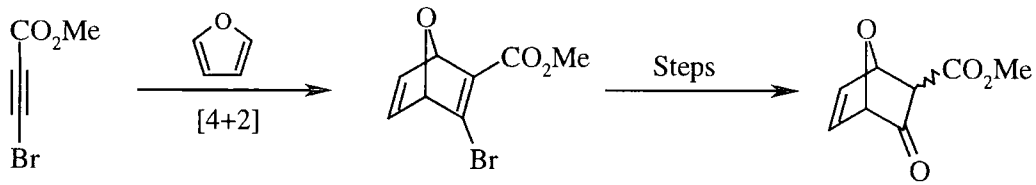
Although there are numerous examples of ketene equivalents, only a limited number of them incorporate an ester substituent and there are currently no examples of a simple alkyl substituent. One example of an ester-substituted ketene equivalent, reported by Kozikowski *et al.*[38] uses the highly reactive allene **100** (Scheme 24). The initial Diels-Alder reaction was demonstrated with a number of dienes, including cyclopentadiene and the relatively unreactive dienes furan and pyrrole, to give adducts **101**, **102** and **103** respectively. Removal of the internal alkene by dihydroxylation and protection allows subsequent ozonolysis to cleave the external alkene giving β-keto ester **104**.



100 **101** - X = CH_2
102 - X = O
103 - X = $NHCO_2Me$ **104**

Scheme 24

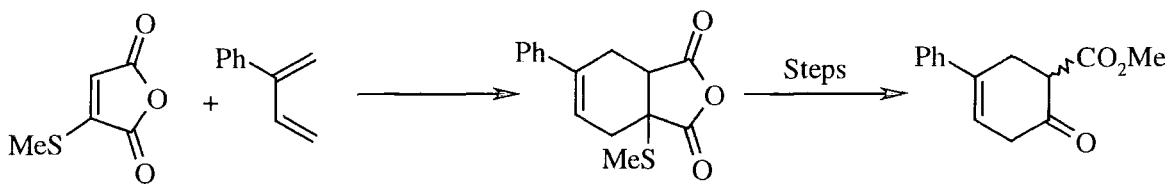
In a study directed toward substituted analogues of shikimic acid, Leroy[39] reported the use of methyl 3-bromopropiolate **105** as an ester-substituted ketene equivalent (Scheme 25). The initial [4+2]-cycloaddition gave adduct **106** in 43-60% yield and subsequent treatment with 1,2-ethanedithiol followed by Nafion–H® gave β-keto ester **107**.



105 **106** **107**

Scheme 25

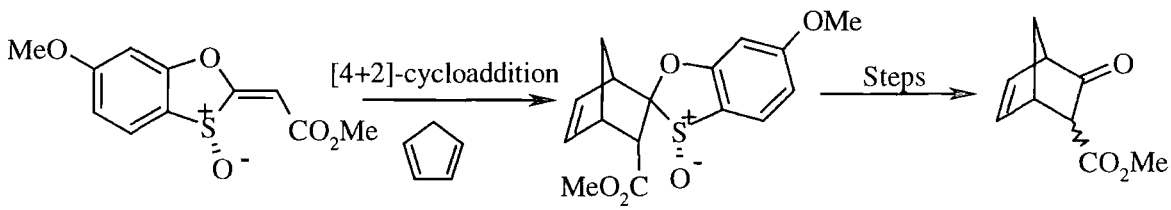
In the first of two examples of acrylate derivatives, Trost and Lunn[40] reported the use of methylthiomaleic anhydride **108** as the first regioselective ester substituted ketene equivalent (Scheme 26). Initial Diels-Alder reactions with a number of unsymmetrical dienes gave intermediate adducts, such as **110**, with high regioselectivity. The Diels-Alder reaction in other cases was also highly diastereoselective. However, subsequent oxidative decarboxylation and hydrolysis proceeds *via* a planar intermediate to give β-keto ester **111** as a mixture of enantiomers.



108 **109** **110** **111**

Scheme 26

The second example of an acrylate-based ester-substituted ketene equivalent, reported by Fallis *et al.*,[41] demonstrates the use of sulfoxide **112**. The initial Diels-Alder reaction with cyclopentadiene affords the enantiopure isomer **113** in 77% yield after a single recrystallisation (Scheme 27). Again, subsequent steps to reveal the β-keto ester **114** result in racemisation at the carbon α to the ester.



112 **113** **114**

Scheme 27

In all cases of ester-substituted ketene equivalents the stereochemistry at the α-carbon is scrambled due to the keto-enol tautomerisation (Figure 8). Any future strategy directed toward controlling stereochemistry at this chiral centre would require derivatisation of the ester group at an intermediate stage.

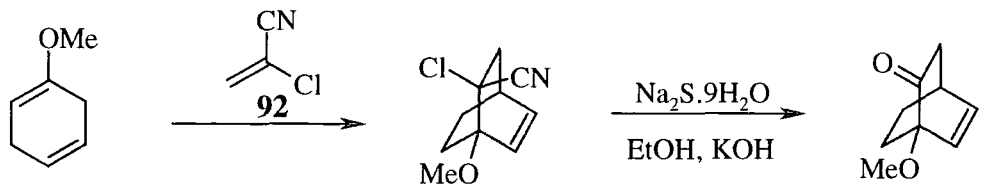
Figure 8

Additionally, in all examples of ester-substituted ketene equivalents the regio- and diastereoselectivity of the Diels-Alder reaction is controlled by the ester functionality. Therefore the development of a synthetic substituted ketene equivalent that would reverse this selectivity would prove to be synthetically useful in organic chemistry. Our investigation focused on the use nitroacrylates to enable the reversal of this selectivity as well as controlling the regio- and stereoselectivity in the initial Diels-Alder reaction to give α-chiral ketones.

1.5 Proposed Work

1.5.1 Previous Work within the Group

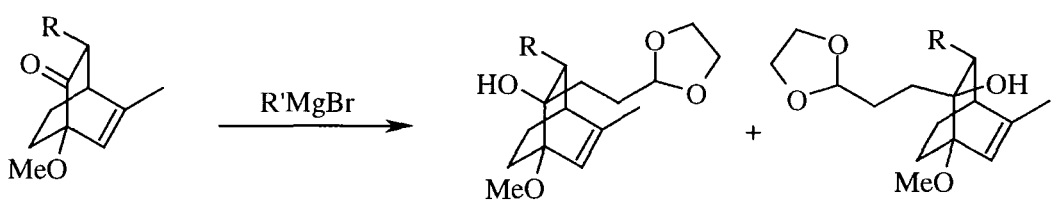
Our group became interested in using nitroacrylates following an investigation into the use of α-chloroacrylonitrile as a ketene equivalent to form the bicyclic enone **117** as part of a model study into the synthesis of vinigrol **1** (Scheme 28).



115 **116** **117**

Scheme 28

It was found that the addition of allyl magnesium bromide to enone **117** gave a 2:1 mixture of isomers **119** and **121** (Scheme 29). Previous studies concluded that only limited selectivity could be achieved with R = H and systems with R = alkyl should be studied. Analogous examples by Kim *et al.*[42] show that in the bicyclic compound **118** nucleophilic attack shows complete selectivity, favouring the formation of alcohol **120**. Attempts within the group to selectively incorporate an alkyl group into bicyclic compound **117** *via* enolate formation and alkylation resulted in inseparable mixtures.



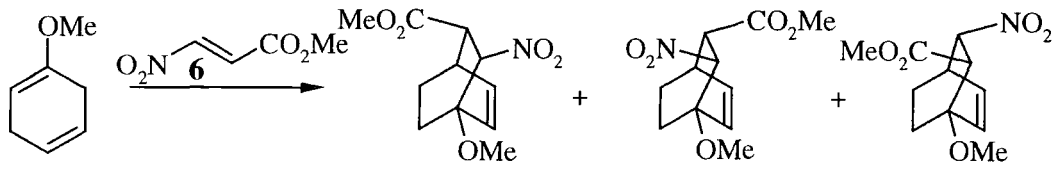
117 - R = H
118 - R = ^{n}Bu

119 - R = H
120 - R = ^{n}Bu

121 - R = H
122 - R = ^{n}Bu

Scheme 29

Work started within the group to utilise nitroacrylates as a substituted ketene equivalent with the Diels-Alder reaction of diene **115** and methyl β-nitroacrylate **6** to give adducts **123**, **124** and **125**. The use of catalytic zinc iodide in the reaction has shown that dramatic increases in selectivity can be achieved (Scheme 30).



115

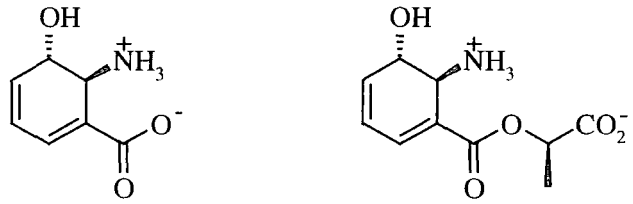
	123		**124**		**125**
PhH, 80°C	50	:	37	:	13
ZnI_2, PhH, 0°C	95	:	5	:	0

Scheme 30

1.5.2 Proposed Work

The project was mainly concerned with investigating the efficient synthesis of nitroacrylates to enable an investigation into their selectivity in the Diels-Alder reaction with a range of simple dienes. This investigation focused on determining the origins of the dramatic increase in selectivity in the Diels-Alder reaction between diene **115** and nitroacrylate **6** by the addition of zinc iodide.

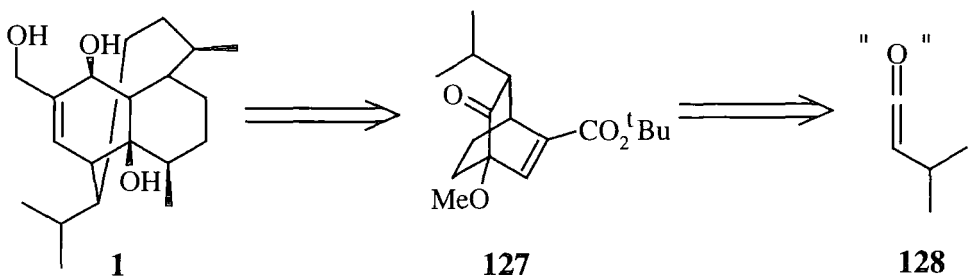
In the second phase we envisaged the use of the resultant Diels-Alder adducts, which represent versatile synthetic intermediates, to provide access to a variety of structures with control of stereochemistry, in particular, in the synthesis of β-amino acids including (2*S*, 3*S*)-dihydrohydroxyanthranilic acid (DHAA) **126** and the antibiotic oryzoxymycin **2** (Figure 9).



126 **2**

Figure 9

Additionally, we explored the use of nitroacrylates as substituted ketene equivalents in the stereoselective synthesis of α-chiral ketone **127**, which is an advanced intermediate in the synthesis of vinigrol. It is anticipated that this methodology could be extended to incorporate an ester-based chiral auxiliary to incorporate absolute asymmetric control.



1 **127** **128**

Scheme 31

SECTION B: Results & Discussion

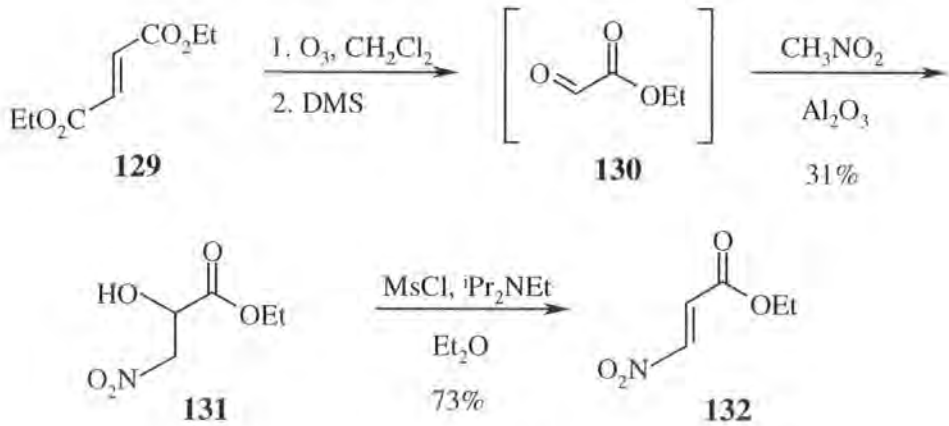
Chapter 2: Synthesis and Cycloadditions of Nitroacrylates

2.1 Introduction

The initial focus of the project was to develop an efficient synthesis of ethyl β-nitroacrylate and to extend this methodology to the synthesis of a chiral analogue with a view to an enantioselective Diels-Alder reaction. The nitroacrylates were subsequently examined in the Diels-Alder reaction with a diverse array of dienes.

2.2 Synthesis of Ethyl β-Nitroacrylate

Two routes have been described (see section 1.2.2) in the literature for the synthesis of simple nitroacrylates. The initial strategy chosen for development was based on the route reported by Clive *et al.*[7] using a nitro-aldol reaction. Initial attempts to give the requisite glyoxylate **130** *via* periodate oxidation of diethyl tartrate[43] gave poor yields, therefore an alternative procedure starting from diethyl fumarate **129** was developed (Scheme 32).



Scheme 32

Ozonolysis[44] of diethyl fumarate **129** afforded good yields of glyoxylate **130** provided the reaction was performed without methanol as a solvent. Addition of methanol

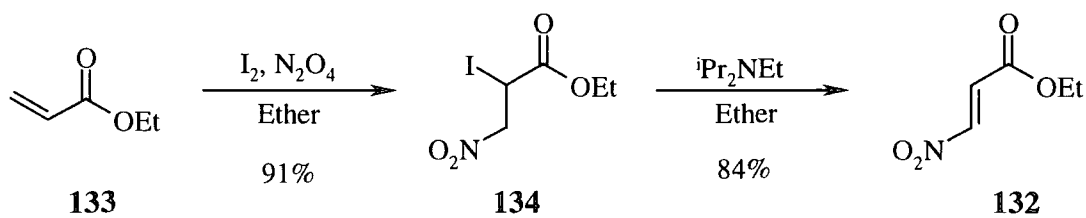
produced the dimethyl acetal, which was more susceptible to polymerisation. The reaction mixture was immediately distilled and the product was taken onto the next stage, since extensive polymerisation occurred on standing. Glyoxylate **130** was identified by the characteristic singlet at 9.40 ppm in the ^{1}H-NMR spectrum. Literature conditions for the subsequent nitroaldol reaction[45] were optimised by using nitromethane as the solvent to afford nitroalcohol **131** in 31% yield over the two stages. Additional solvents described in literature procedures slowed the reaction and gave poorer yields. Nitroalcohol **131** was characterised by the distinctive OH stretch in the infrared and was confirmed by microanalysis. The development of a suitable procedure for dehydration to yield nitroacrylate **132** was unexpectedly difficult, and appreciable effort was required before a satisfactory method was found. Literature reports[7] suggested that dehydration could be achieved (table 1, entry 1), by mesylation with MsCl and *in situ* elimination using Et_3N to give the desired nitroacrylate in good yields. In our hands this procedure led to decomposition of the starting materials possibly *via* a *retro*-Henry mechanism. Table 1 shows some of the modifications that were made to the literature procedure in order to prevent decomposition.

Table 1. Reaction conditions for the synthesis of ethyl β-nitroacrylate.

Entry	Activating group	Base	Solvent / Temp.	Result	Ref.
1	MsCl (1.2eq.)	Et_3N (2.4eq.)	CH_2Cl_2/RT	Decomp.	7
2	MsCl (1.2eq.)	Et_3N (2.4eq.)	Et_2O/0 °C	15 - 30% yield	-
3	MsCl (1.2eq.)	CH_3CO_2K	Et_2O/0 °C	Decomp.	-
4	Ac_2O (1.2eq.)	Et_3N (2.4eq.)	Et_2O/0 °C	15 – 30% yield	46
5	MsCl (1.2eq.)	Py (2.4eq.)	Et_2O/0 °C	Decomp.	-
6	DCC/$Cu^{(I)}Cl$	-	Et_2O/0 °C	21% yield	47
7	TFAA (1.0eq.)	Et_3N (2.0eq.)	CH_2Cl_2/-10 °C	28% conversion	46
8	MsCl (1.2eq.)	$^iPr_2NEt$ (2.2eq)	Et_2O/0 °C	33% conversion	-
9	MsCl (5.0eq.)	$^iPr_2NEt$ (2.2eq)	Et_2O/0 °C	73% Yield	-

The ultimate solution involved the use of the more hindered $^{i}Pr_2NEt$ in preference to Et_3N; the solvent was replaced with Et_2O to remove the $^{i}Pr_2NEt.HCl$ from solution. The reaction was carried out at 0°C and five equivalents of mesyl chloride were added to ensure complete mesylation. The modified procedure gave nitroacrylate **132** as a crystalline solid in 73% yield as exclusively the *E*-isomer as characterised by a 14 Hz (*trans*) coupling in the ^{1}H-NMR. Using this method up to 5 g of pure nitroacrylate **132** was produced and was sufficient to initiate the investigation into its selectivity in the Diels-Alder reaction. However, principally due to extensive polymerisation of the glyoxylate intermediate **130** the procedure was unsuitable for further scale-up to produce large quantities of nitroacrylate **132**.

In order to prepare larger quantities of this compound, the procedure reported by McMurry[5] was used. Following this method, treatment of ethyl acrylate with iodine and dinitrogen tetroxide gave the intermediate iodo nitro compound **134** in 91% yield (Scheme 33). In our hands attempts to achieve dehydrohalogenation of **134**, following literature procedures,[5] using sodium acetate gave extensive decomposition. Using experience gained from the dehydration of nitroalcohol **131**, the literature procedure was modified by using 1.1eq of $^{i}Pr_2NEt$ in ether at 0 °C to give nitroacrylate **132** in 84% yield.



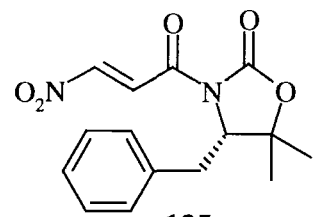
133 **134** **132**

Scheme 33

A highly modified work-up procedure was required to prevent decomposition, however, the reaction was carried out routinely on a large scale to produce >20g of nitroacrylate.

2.3 Chiral Auxiliary Synthesis

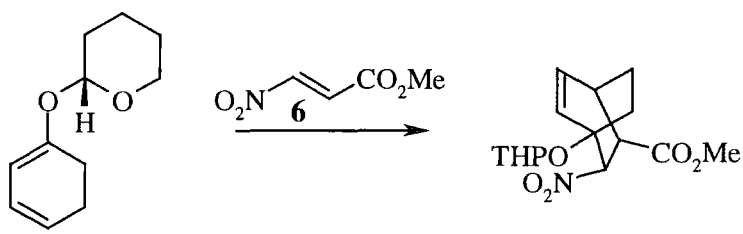
A number of different approaches reported in the literature may be used to allow the development of a stereoselective methodology for the Diels-Alder reaction of nitroacrylates. One approach and the method that was chosen to investigate, was to incorporate a chiral auxiliary into the ester functionality of the nitroacrylate. The chosen auxiliary was the oxazolidinone-based 'Superquat' developed by *Davies et al.*[48] to give dienophiles such as **135** that favour the approach of the diene from one side of the double bond only (Figure 10).



135

Figure 10

A related approach with respect to the Diels-Alder reaction with oxygenated dienes would be to use a chiral auxiliary in the diene moiety. This strategy has been used in the synthesis of gelsemine (see section 1.2.3.1) by Fleming *et al.*[12] in which the reaction between diene **28** and nitroacrylate **6** proceeds with high stereoselectivity to give adduct **29** (Scheme 34).

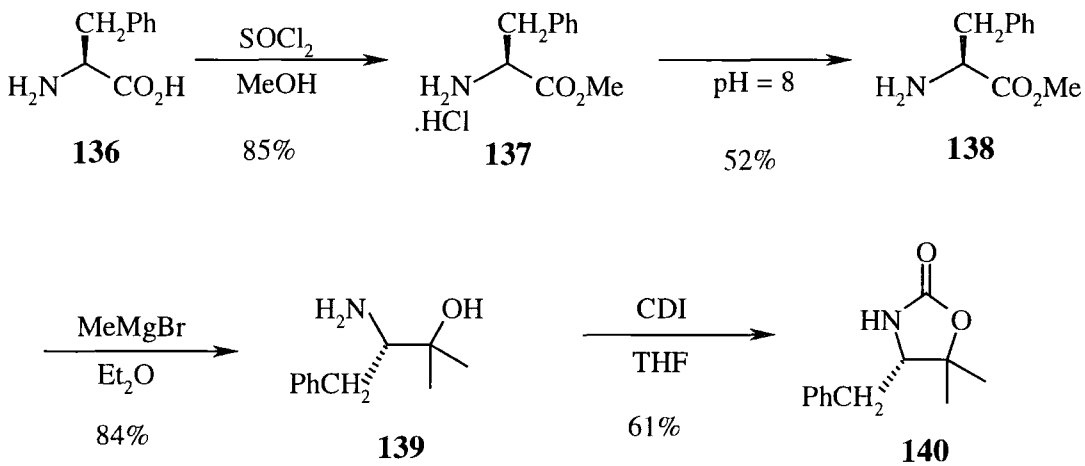


28 **29**

Scheme 34

Preparation of the Superquat auxiliary was achieved by following the literature procedure[49] starting from D-phenylalanine **136** (Scheme 35). Firstly, D-phenylalanine

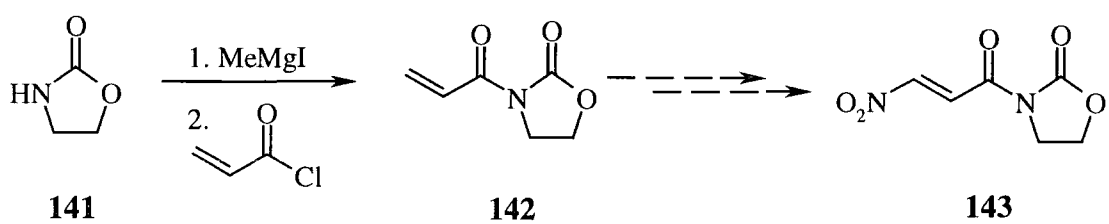
was converted into its methyl ester **137** in good yield using dry HCl in methanol. In the subsequent Grignard reaction it was important to produce the free amine **138** first using sodium bicarbonate in order to achieve good yields of amino alcohol **139**. Subsequent treatment of this intermediate with CDI according to the procedure reported by Shioiri *et al.*[50] gave the 'Superquat' auxiliary **140** in 23% overall yield from D-phenylalanine and was identical by NMR to the literature data.[48]



136 **137** **138** **139** **140**

Scheme 35

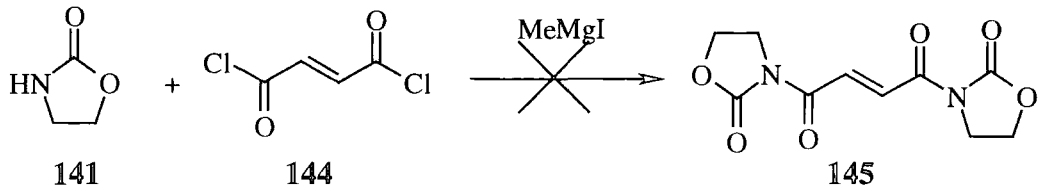
Methods for the incorporation of the 'Superquat' chiral auxiliary into the nitroacrylate functionality were investigated using commercially available oxazolidinone **141** in a model study. Using the literature conditions[51] (BuLi / THF) the coupling reaction between **141** and acryloyl chloride resulted in decomposition. The procedure was modified to use MeMgI as the base to give the desired product **142** in 41% yield (Scheme 36). The functionalised nitroacrylate **143** would then be accessible using the nitro-aldol or the radical-based chemistry developed in section 2.2.



141 **142** **143**

Scheme 36

Attempts to form the fumarate derivative **145**, analogous to diethyl fumarate **129**, by treating oxazolidinone **141** with MeMgI and trapping with 0.5 equivalents of fumaryl chloride **144** gave decomposition products (Scheme 37).



141 **144** **145**

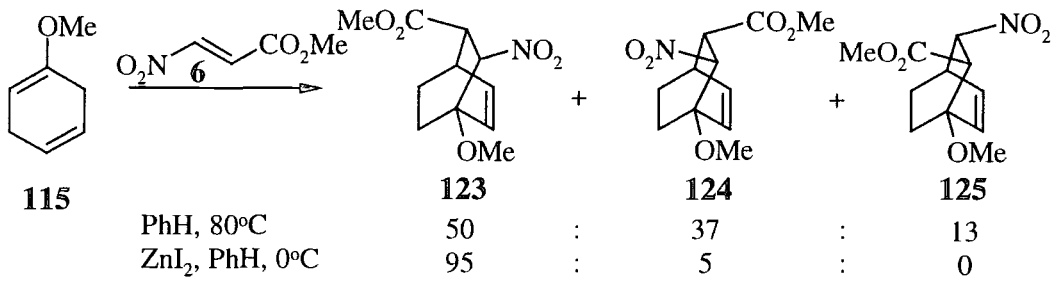
Scheme 37

It was at this stage that we became aware of a report by Clive *et al.*[7] that suggested oxazolidinone substituted nitroacrylates were not accessible using the nitro-aldol route. Accompanied by the failure to achieve the synthesis of **145** using a number of methods prompted us to curtail the investigation into incorporating a chiral auxiliary and concentrate on the use of ethyl β-nitroacrylate **132** in the Diels-Alder reaction and the synthesis of natural products.

2.4 Nitroacrylate Diels-Alder Reactions

2.4.1 Introduction

Having developed an efficient synthesis of ethyl β-nitroacrylate the project focused on investigating its reactivity and selectivity in Diels-Alder reactions. As discussed in chapter 1, previous work in the group has shown that the Diels-Alder reaction between methyl 3-nitroacrylate **6** and 1-methoxycyclohexa-1,4-diene **115** shows a dramatic increase in selectivity by adding zinc iodide (Scheme 38).

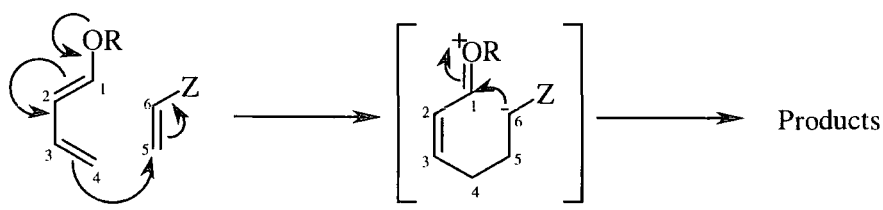


Scheme 38

This section discusses the background to the reaction and describes our investigation into the origin and scope of the increase in selectivity between thermal and Lewis acid catalysed reactions using of a number of Diels-Alder reactions between nitroacrylate **132** and a diverse array of dienes.

2.4.2 Background to Nitroacrylate Diels-Alder reactions

The Diels-Alder reaction has emerged as an effective procedure for the construction of enantiomerically enriched organic compounds. An attractive feature of the reaction resides in the possibility, in principle, of generating up to four contiguous stereocentres in one step, often with remarkable regio- and stereoselectivity. A number of publications have focused on thermal nitroacrylate Diels-Alder reactions with oxygenated dienes,[52] however, there have been no detailed investigation into the effect of Lewis acids on the reaction. In particular, our study aimed to ascertain whether the increase in selectivity is derived from zinc iodide acting as a conventional Lewis acid in a concerted process or by promoting a related tandem Michael-aldol mechanism first proposed by Woodward and Katz[53] (Scheme 39).



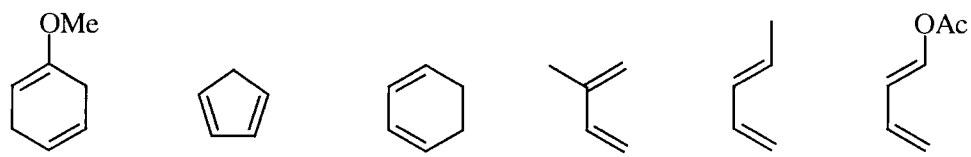
Scheme 39

In the tandem Michael-aldol reaction the formation of the C4-5 bond occurs first and the selectivity is based on a Michael addition, which as demonstrated in section 1.2.3.2 is high in the case of nitroacrylates. Subsequent formation of the C6-1 bond *via* an aldol reaction to give cyclohexenes competes with protonation to give Michael adducts as products.

2.4.3 Cycloaddition Reactions

Our initial studies explored the selectivity of nitroacrylate **132** in the Diels-Alder reaction with dienes **115, 86** and **146** - **149** with each diene being examined under thermal (reflux in benzene and 0°C in DCM) and Lewis acid catalysed conditions (Figure 11).

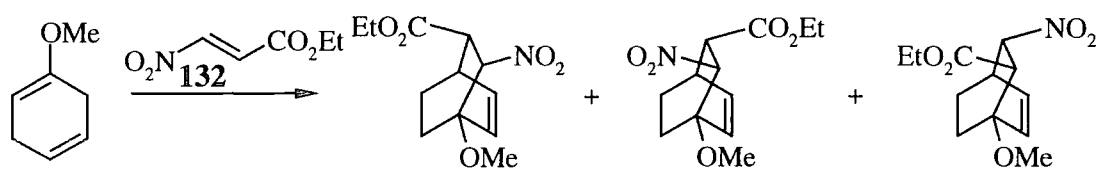
1. 1-Methoxycyclohexa-1,4-diene – **115**
2. Cyclopentadiene – **86**
3. Cyclohexadiene – **146**
4. 2-Methylbutadiene - **147**
5. 1-Methylbutadiene - **148**
6. *trans*-1-Acetoxybutadiene - **149**



115 **86** **146** **147** **148** **149**

Figure 11

Reactions with 1-Methoxycyclohexa-1,4-diene



115 **150** **151** **152**

Scheme 40

The Diels-Alder reaction of nitroacrylate **132** and diene **115** was studied under various conditions in order to find the optimal selectivity with an acceptable rate of reaction (Scheme 40). Rearrangement from the 1,4 species to the conjugated 1,3 species occurs under the reaction conditions and the thermal Diels-Alder reaction is complete within 3 hours to give a 56 : 28 : 16 mixture of isomers **150**, **151** and **152** respectively. Table 2 shows the selectivity for the Lewis acid catalysed reaction under various conditions. It was concluded from this data that the optimum conditions for Lewis acid catalysed reactions were 0 °C with 0.1eq. of $ZnCl_2$. The selectivity appears to be proportional to temperature but slow reaction rates for cycloadditions performed at –20°C were considered impractical.

Table 2. Results of the Diels-Alder reaction with diene **115**.

Conditions	No. equiv. $ZnCl_2$	Reaction time (hr)	Yield (%)	**150** : **151** : **152** ratio
Thermal/80 °C	0	3	46	56 : 28 : 16
$ZnCl_2$/20 °C	1.0	3	39	95 : 5 : 0
$ZnCl_2$/0 °C	1.0	5	35	97 : 3 : 0
$ZnCl_2$/0 °C	0.1	14	60 †	97 : 3 : 0
$ZnCl_2$/-20 °C	1.0	72	~25% rxn	-
$ZnCl_2$/-20 °C	0.1	168	~20% rxn	-
Thermal/0 °C	0	48	No reaction	-

(†) Aqueous work up.

In order to investigate if the increase in selectivity is derived from the isomerisation process the 1,4-diene was substituted with the conjugated 1,3-diene and the Diels-Alder reactions were repeated. The results in table 3 showed that the thermal reaction gave a cleaner reaction giving approximately a 2:1 mixture, which corresponds well with literature ratios for 1-oxygenated dienes.[52] The selectivity of the Lewis acid

catalysed reaction was identical to the 1,4-diene case. Therefore we concluded that the increase in selectivity is independent of the isomerisation process.

Table 3. Results of the Diels-Alder reaction with 1-Methoxycyclohexa-1,3,diene.

Conditions	No. equiv. $ZnCl_2$	Reaction time (hr)	Yield (%)	**150** : **151** : **152** ratio
Thermal/80 °C	0	3	63	65 : 31 : 4
$ZnCl_2$/0 °C	1.0	7	52 †	95 : 5 : 0
Thermal/0 °C	0	48	59	69 : 31 : 0

(†) Aqueous work up.

Microanalysis and mass spectrum (CI, MH^+=256) confirmed the correct compound. Identification of the individual isomers was achieved by a combination of ^{1}H-NMR, COSY and nOe experiments. Identification of isomer **150** was relatively straightforward since it had been acquired in 97% purity from the Lewis acid catalysed reaction. The three pieces of evidence shown in Figure 12 confirmed the structure of the major isomer **150**.

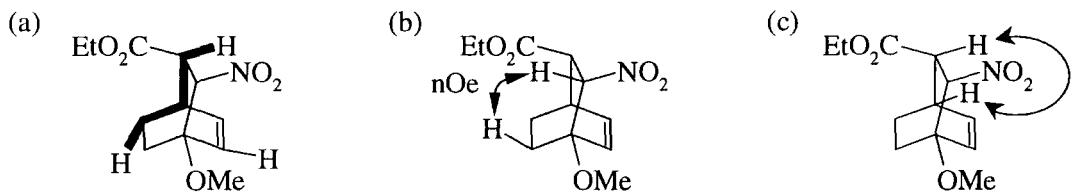
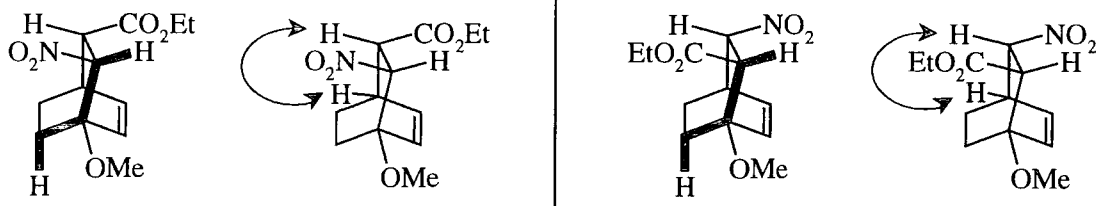


Figure 12 (a) ^{4}J=2 Hz coupling present with *exo*-ester hydrogen (b) nOe shows nitro α-hydrogen is over the alkyl bridge (c) Coupling of the ester α-hydrogen to the bridgehead proton (COSY).

Identification of the two other isomers proved more difficult because the analytical data corresponded to the mixture of all three isomers. However most of the signals were reasonably dispersed, enabling identification by COSY and ^{1}H-NMR splitting patterns. Figure 13 shows the two isomers and their distinctive ^{3}J and ^{4}J couplings.

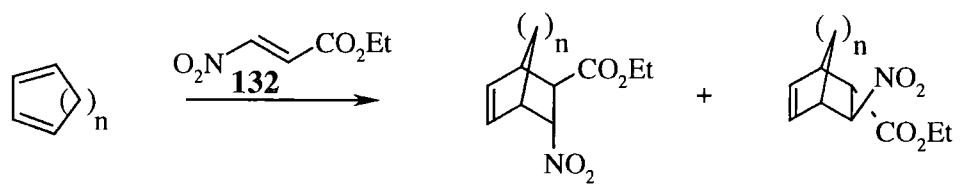


151 **152**

Figure 13

The regiochemistry of the Diels-Alder isomers **151** and **152** was determined by ^{3}J couplings of the bridgehead proton (δ=3.2 ppm). Furthermore, the C-2 and C-3 *endo*-hydrogens have splitting patterns that suggest ^{4}J coupling to the alkyl bridge (C-7 and C-8). Thus, using this evidence, adduct **151** corresponds the *exo*-product with the desired regiochemistry and adduct **152** corresponds to the *endo*-product with the undesired regiochemistry. Attempts to confirm the structure of the individual isomers by separating them by HPLC were unsuccessful.

Reactions with Cyclopentadiene and Cyclohexadiene



86 - n = 1
146 - n = 2

153 - n = 1
154 - n = 2

155 - n = 1
156 - n = 2

Scheme 41

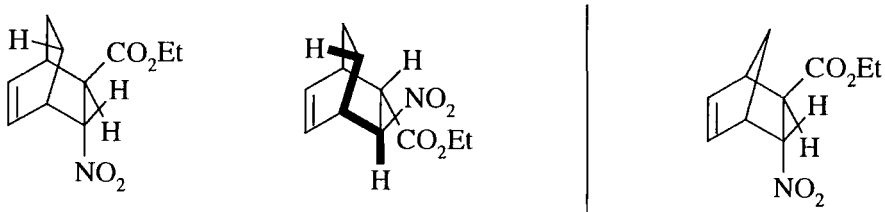
Cyclopentadiene and cyclohexadiene were included in the study due to their reactivity and the fact that they clearly demonstrate the *endo* : *exo* selectivity. Table 4 shows the details of the reactions between nitroacrylate **132** and dienes **86** and **146** (Scheme 41).

Table 4. Results of the Diels-Alder reaction with cyclopentadiene and cyclohexadiene.

Diene	Conditions	No. equiv. $ZnCl_2$	Reaction time.	Yield (%)	Endo : Exo ratio
86	Thermal/-50 °C	0	10 sec	70	88 : 12
146	Thermal/80 °C	0	4.5 hr	64	82 : 18
146	$ZnCl_2$/0 °C	1.0	144 hr	67	90 : 10
146	Thermal/0 °C	0	144 hr	84% reaction	89 : 11

The thermal Diels-Alder reaction between nitroacrylate **86** and cyclopentadiene proved to be very fast, with full conversion occurring within 10 seconds at room temperature. This fact has made it difficult to demonstrate an improvement between the thermal and Lewis acid mediated reactions. Cyclohexadiene is considerably less reactive towards **132** with a reaction time of 4.5 hr for the thermal reaction. In these cases only a small increase in selectivity was observed, which seems to be consistent with the lower reaction temperature as opposed to the addition of $ZnCl_2$.

The only distinction that could be made in order to assign the *endo*- and *exo*-isomers **154** and **156** respectively was taken from the splitting patterns of the ^{1}H-NMR in which the *endo*-hydrogens show an extra ^{4}J coupling to the alkyl bridge protons (Figure 14).



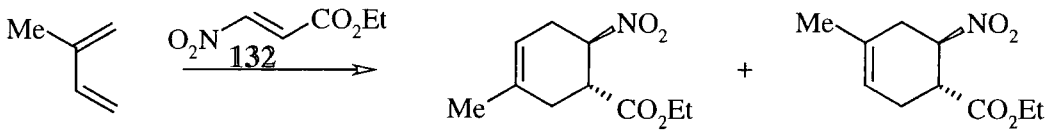
154 **156** **153**

Figure 14

Isomers **153** and **155** were identified by comparing ^{1}H-NMR details with literature values.[54] Additionally, differences between the alkene protons were observed. In the *exo*-isomer the olefinic signals were superimposed in the ^{1}H-NMR, whereas in the

endo isomer the olefinic protons appear as two distinct multiplets. We speculate that the *endo* nitro group interacts with one side of the alkene, thus polarising the double bond.

Reactions with 2-Methylbutadiene



147 **157** **158**

Scheme 42

Analysis of the reaction between nitroacrylate **132** and 2-methylbutadiene **147** allows the regioselectivity of the dienophile to be explored (Scheme 42). Table 5 shows the results for the thermal and Lewis acid catalysed Diels-Alder reactions. The thermal reaction was complete within 4 hr, demonstrating that 2-methylbutadiene is a relatively activated diene. ^{1}H-NMR analysis showed that dienophile **132** is partially regioselective in the reaction with 2-methylbutadiene.

Table 5. Results of the Diels-Alder reaction with 2-methylbutadiene.

Conditions	No. equiv. $ZnCl_2$	Reaction time (hr)	Yield (%)	Regioisomer ratio **157** : **158**
Thermal / 80 °C	0	4	61	56 : 44
$ZnCl_2$ / 0 °C	1.0	48	58	55 : 45
Thermal / 0 °C	0	48	95% reaction	59 : 41

Following satisfactory mass spectrum results (CI, M^+=213), identification of the isomers was achieved by ^{1}H-NMR and COSY (Figure 15).

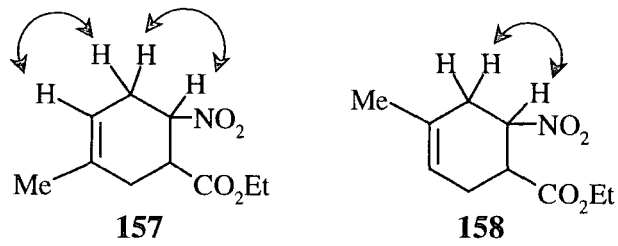
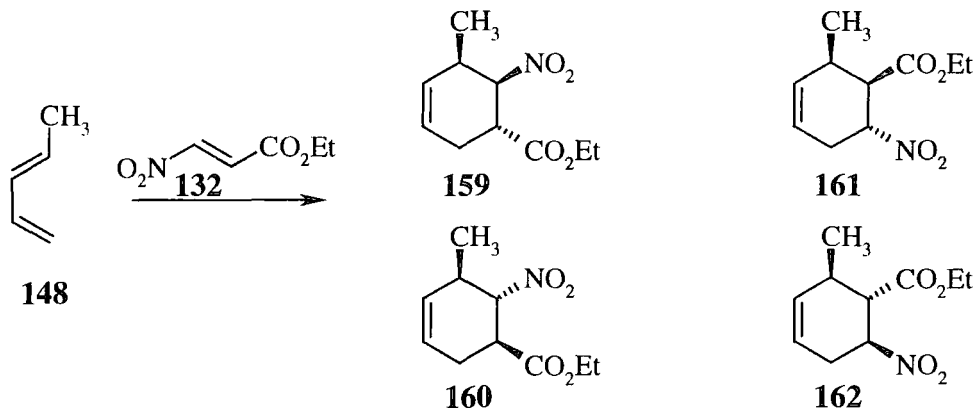


Figure 15 COSY results.

Reactions with trans-1-Methylbutadiene



Scheme 43

Analysis of the reaction of nitroacrylate **132** and *trans*-1-methylbutadiene **148** allows the exploration of the combined regio- and *endo* : *exo* selectivity of the dienophile and the results are summarised in table 6 (Scheme 43).

Table 6. Results of the Diels-Alder reaction with 1-methylbutadiene.

Conditions	No. equiv. $ZnCl_2$	Reaction time (hr)	Yield (%)	Regioisomer ratio	Endo : Exo ratio
Thermal/80 °C	0	4	61	71 : 29	55 : 45
$ZnCl_2$/0 °C	1.0	60	66	73 : 27	55 : 45
Thermal/0 °C	0	60	94% reaction	74 : 26	54 : 46

Analogous to 2-methylbutadiene, the thermal reaction for diene **148** was complete within 4 hours and no increase in selectivity was observed for the reaction with $ZnCl_2$. Assignment of individual isomers proved unexpectedly difficult because ^{1}H-NMR analysis shows a very complex mixture of isomers. Consequently, we tentatively report that the dienophile **132** was only partially regio- and *endo*-selective toward *trans*-1-methylbutadiene. The majority of peaks in the ^{1}H-NMR overlap, however, in conjunction with COSY experiments partial identification of isomers **159, 160** and **161** was possible(Figure 16).

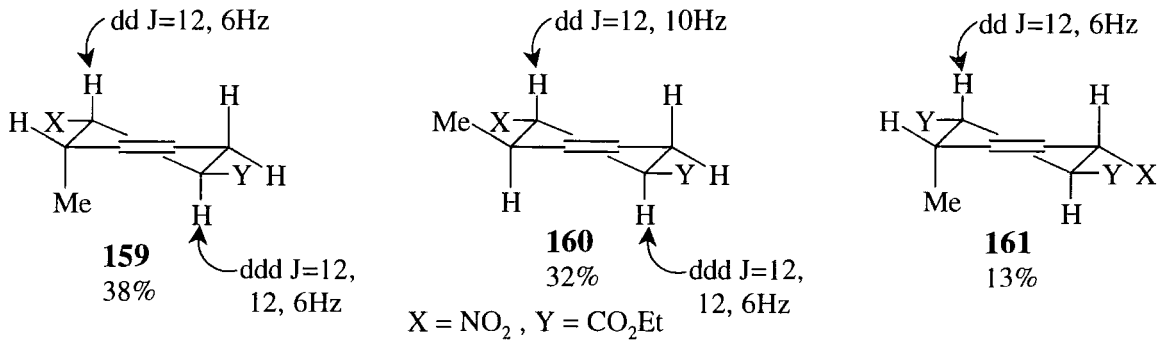
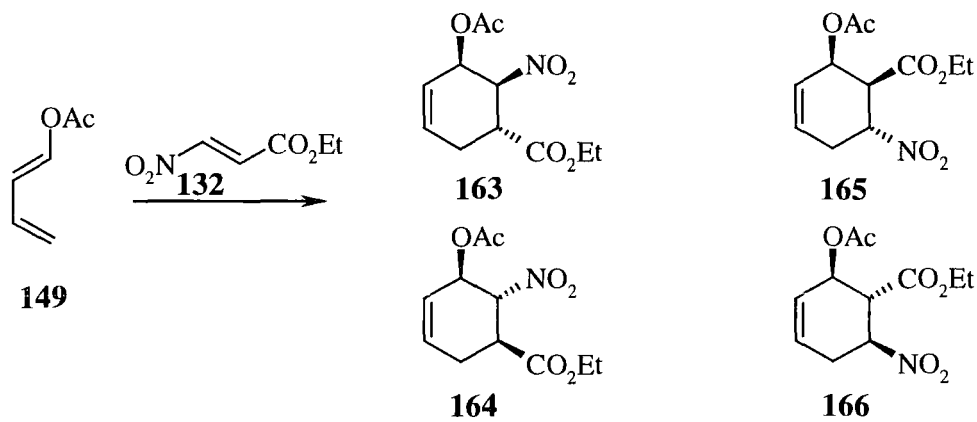


Figure 16

The ratios were obtained by using the integration of the ^{1}H-NMR and using analytical HPLC. Attempts to separate the adducts by preparative HPLC or *via* derivatisation in order to aid the assignment of configuration and isomer ratio were unsuccessful.

Reactions with trans-1-Acetoxybutadiene



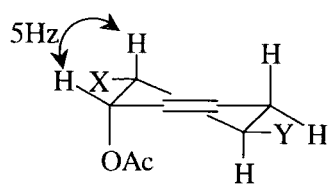
Scheme 44

With the results for the alkyl dienes **86** and **146** - **148** in hand, we decided to test the selectivity of nitroacrylate **132** with *trans*-1-acetoxybutadiene **149** (Scheme 44). Yoshimura[55] reports that the thermal reaction at 25°C and 100°C yields 57% and 21% respectively of a single diastereoisomer after recrystallisation. Table 7 shows the results obtained in the thermal and Lewis acid catalysed reactions.

Table 7 Results of the Diels-Alder reaction with *trans*-1-acetoxybutadiene.

Conditions	No. equiv. $ZnCl_2$	Reaction time (hr)	Yield (%)	**163** (%)
Thermal/80 °C	0	7	59	74
$ZnCl_2$/0 °C	1.0	144	66	84
Thermal/0 °C	0	144	40% reaction	76

The Lewis acid catalysed reaction shows a small increase in selectivity compared to the thermal reaction. Attempts to re-crystallise the crude adducts gave white needles but was unsuccessful in the separation of the major isomer. Consequently, the adducts could not be obtained in high enough purity to enable the ratios for accurate regio- and *endo*-selectivity to be determined. From comparison of the ^{1}H-NMR spectra with literature values, the major isomer was identified as adduct **163**, which corresponds to *endo* addition with the desired regioselectivity (Figure 17).



X = NO_2 , Y = CO_2Et

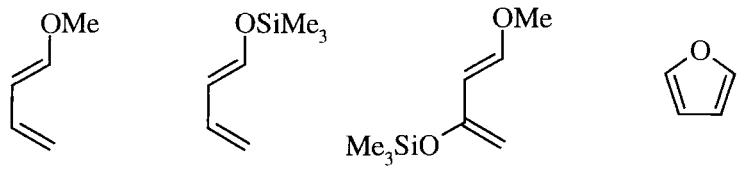
161

Figure 17

The lack of selectivity observed with simple alkyl dienes compared with the alkoxy dienes **115** and **149** suggested that the electron donating properties of the dienes are

important for selectivity. To further explore this theory we decided to investigate dienes **167** – **170** (Figure 18).

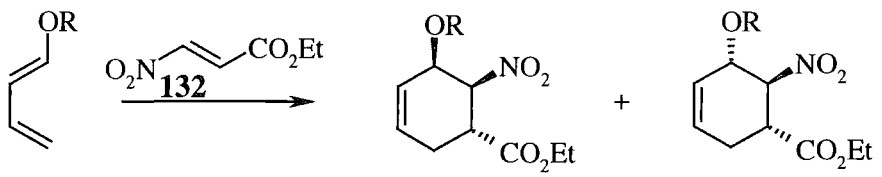
7. 1-Methoxybutadiene – **167**
8. 1-(Trimethylsiloxy)-butadiene - **168**
9. Danishefskys diene - **169**
10. Furan - **170**



167 **168** **169** **170**

Figure 18

Reactions with 1-Methoxybutadiene and 1-[(Trimethylsilyl)oxy]-butadiene



167 R=Me,
168 R=$SiMe_3$

171 R=Me,
172 R=$SiMe_3$

173 R=Me,
174 R=$SiMe_3$

Scheme 45

Both dienes **167** and **168** were chosen explicitly to mimic the reaction of 1-methoxycyclohexa-1,4-diene **115** (Scheme 45). The thermal reactions were complete within 2.5 hr with ^{1}H-NMR showing good regioselectivity and moderate *endo* : *exo* ratio (Table 8). These studies showed that the reaction is inhibited by the addition of $ZnCl_2$.

Table 8. Results of the Diels-Alder reaction with dienes **167** and **168**.

Diene	Conditions	No. equiv. $ZnCl_2$	Reaction time (hr).	Yield (%)	Regioisomer ratio	Endo : Exo ratio
167	Thermal/80 °C	80	2.5	89	88 : 12	61 : 39
168	Thermal/80 °C	80	2.5	75	96 : 4	75 : 25
167	$ZnCl_2$/0 °C	0.1	48	10% reaction	-	-
168	$ZnCl_2$/0 °C	0.1	48	40% reaction	-	-
167	$ZnCl_2$/0 °C	1.0	48	0% reaction	-	-
168	$ZnCl_2$/0 °C	1.0	48	0% reaction	-	-
168	Thermal/0 °C	0	21	80	95 : 5	72 : 28

Assignment of the individual isomers was achieved using ^{1}H-NMR following satisfactory mass spectrum results. Distinguishing between the *endo*- and *exo*-isomers was achieved by studying coupling constants between the nitro proton (~4.8ppm) and the CHOR proton (~4.3ppm) (Figure 19). The regioisomers were distinguished by the extra splitting for the nitro α-proton.

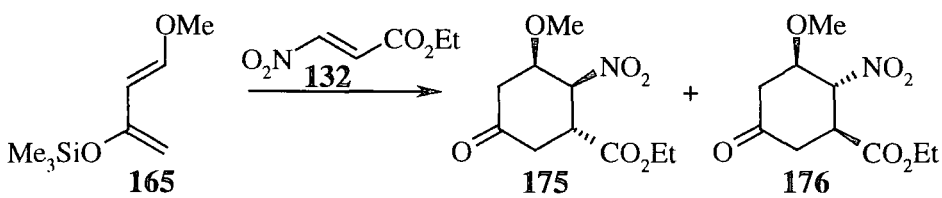
171 - R = Me
172 - R = $SiMe_3$

X = NO_2 , Y = CO_2Et

173 - R = Me
174 - R = $SiMe_3$

Figure 19.

Reactions with Danishefsky's diene



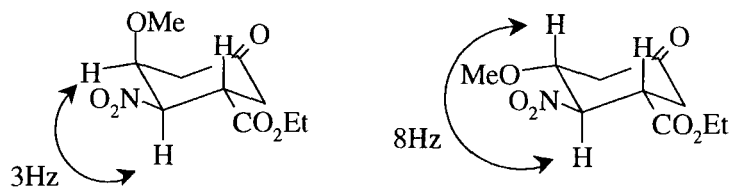
Scheme 46

Danishefsky's diene was studied in the Diels-Alder reaction with nitroacrylate **132** because it is a very reactive diene and there is literature precedence for the reaction[52] (Scheme 46). Table 9 shows the results for both thermal and Lewis acid catalysed reactions. Interestingly, although **165** is considered a reactive diene the thermal reaction takes 10 hr.

Table 9. Results of the Diels-Alder reaction with Danishefsky's diene.

Conditions	No. equiv. $ZnCl_2$	Reaction time (hr)	Yield (%)	Ratio **175 : 176**
Thermal/80 °C	0	10	53	35 : 65
$ZnCl_2$/0 °C	1.0	30	41	25 : 75

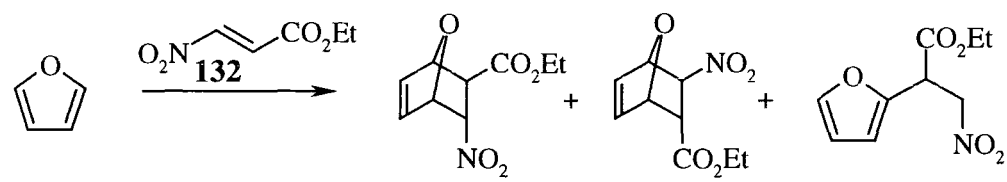
Under thermal conditions a 2 : 1 ratio was observed in favour of the *exo*-isomer. A small increase in *exo*-selectivity was noted for the Lewis acid catalysed reaction although lower yields were obtained due to the presence of significant quantities of an additional unidentified product. Adducts **175** and **176** were identified by ^{1}H-NMR splitting patterns (Figure 20).



175 - Endo **176** - Exo

Figure 20

Reactions with Furan



166 **177** **178** **179**

Scheme 47

Furan was included into the study in order to evaluate the effect that the oxygen moiety in the cyclic diene has on the Diels-Alder reaction and for direct comparison with cyclopentadiene (Scheme 47).

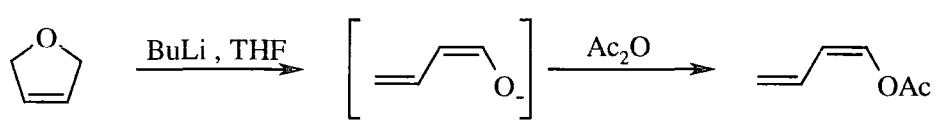
Table 10. Results of the Diels-Alder reaction with furan.

Conditions	No. equiv. $ZnCl_2$	Reaction time (hr)	Yield (%)	Ratio **177 : 178 : 179**
Thermal/25°C	0	60	98	62 : 38 : 0
$ZnCl_2$/0°C	1.0	72	70	56 : 29 : 15

The adducts were separated by chromatography and identified by comparison with literature ^{1}H-NMR values.[56] The selectivity of the Diels-Alder reaction between furan and nitroacrylate **132** is affected by the reversibility of the reaction. In $CDCl_3$, both isomers undergo the *retro*-Diels-Alder reaction to give starting materials. The minor product **179** was identified on the basis of comparison of the NMR spectra and we speculated that it is produced *via* Michael addition or decomposition of products promoted by the Lewis acid.

Reactions with cis-Acetoxybutadiene

In order to investigate the mechanism involved in the Diels-Alder reactions we prepared *cis*-1-acetoxybutadiene using a 'one-pot' procedure described by Rautenstrauch[57] (scheme 48). Treatment of 2,5-dihydrofuran **180** with ^{n}BuLi and subsequent trapping of the anion **181** with acetic anhydride gave the *cis*-diene **182** in 23% yield.



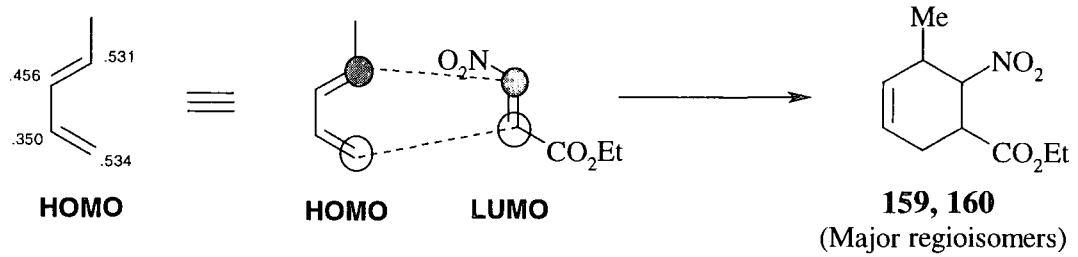
180 **181** 23% **182**

Scheme 48

Following suitable mass spectrum results (EI, M^+=112) the *cis*-relationship was characterised by a small (6 Hz) coupling across the C1-2 double bond. No reaction was observed for the *cis*-diene **182** under thermal or Lewis acid catalysed conditions.

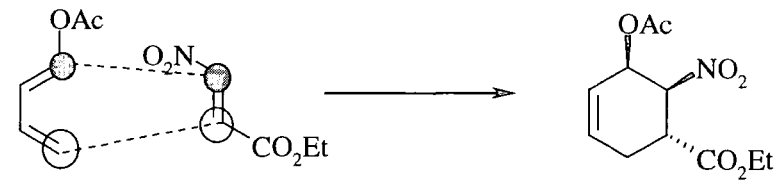
2.4.4 Discussion of Cycloaddition Results

The poor selectivity shown by the simple alkyl dienes **86** and **146** - **148** can be rationalised by FMO theory. Using 1-methylbutadiene as an example, the methyl group (+I) has only a minimal effect on the size of the coefficients of the diene.[32] The coefficients of the nitroacrylate can also be rationalised to be similar in size with the nitro group slightly dominating over the ester functionality, thus, Diels-Alder reactions of the two components gives low selectivity (Scheme 49). Additionally, there were no large increases in selectivity or rate of reaction with the addition of Lewis acids therefore we concluded that the methoxy group was important for increased selectivity.



Scheme 49

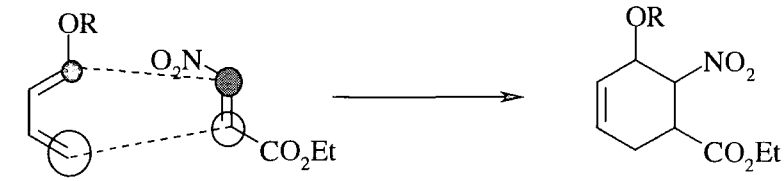
Analogously, the increase in selectivity using *trans*-1-acetoxybutadiene **149** can also be explained by FMO theory. The 1-acetoxy functionality produces a significant difference in size between the coefficients at the 1- and 4-postion of the diene thus giving greater regioselectivity (Scheme 50). The increase in *endo*-selectivity suggests that there is also a substantial secondary orbital interaction between the nitro group and the diene functionality.



163
(Major product)

Scheme 50

This explanation can be further extended to explain the excellent regioselectivity and the short reaction times shown for the thermal reaction of the alkoxy dienes **167** and **168**. The introduction of the alkoxy group has a greater effect on the size of the coefficients of the 1- and 4-position of the diene (Scheme 51).



167 - R=Me
168 - R=$SiMe_3$

171, 173 - R=Me
172, 174 - R=$SiMe_3$
(Major regioisomers)

Scheme 51

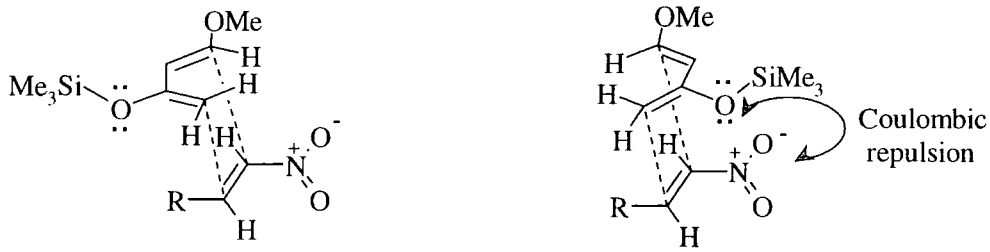
The rapid reaction rates for the thermal reaction are explained by the smaller energy difference between the HOMO of the diene and the LUMO of the dienophile.

A number of explanations have been put forward for the inhibition of the Diels-Alder reaction of dienes **167** and **168** by the addition of Lewis acids. However, subsequent repetition of the reaction suggests that the dienes undergo decomposition in the presence of Lewis acids

The Diels-Alder reaction with Danishefsky's diene shows *exo*-selectivity, which is in accordance with a study of nitroolefins in the Diels-Alder reaction with Danishefsky's diene by Node *et al.*[58] They speculate that the selectivity may be explained by a

coulombic repulsion between the nitro group and the electron rich oxygen of the OTMS group (Figure 21).

We also observed 100% regioselectivity, which is consistent with both activating groups enlarging the coefficient at the 4-position.



Exo-addition Endo-addition

Figure 21

The reaction using *cis*-1-acetoxybutadiene was important to study because the *cis*-geometry for the diene forces the equilibrium towards the *trans*-oid conformation, in which, the concerted reaction would not occur (Figure 22). The alternative non-concerted mechanism would occur in both *cis*- and *trans*-oid conformations, thus suggesting that the dienes are reacting *via* a concerted Diels-Alder reaction.

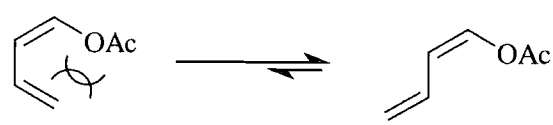
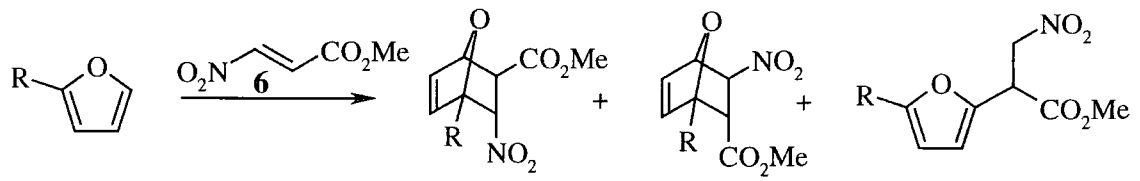


Figure 22

This mechanistic consideration is especially relevant in the case of furan where Michael addition products are isolated from the reaction. A recent publication by Itoh *et al.*[59] showed that furans **170** and **183** react with methyl β-nitroacrylate **6** to give Diels-Alder and Michael adducts (Scheme 52).



170 - R = H
183 - R = OMe

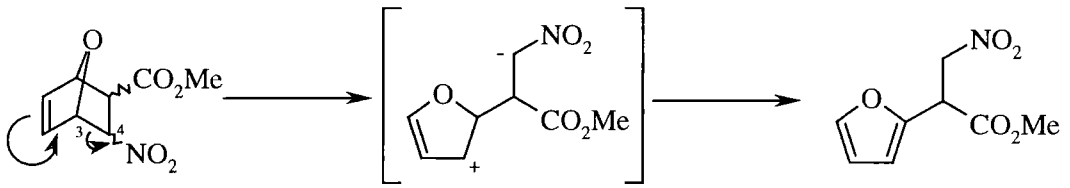
33 - R = H
184 - R = OMe

185 - R = H
186 - R = OMe

187 - R = H
188 - R = OMe

Scheme 52

In conclusion, Itoh *et al.* suggested that during normal reaction conditions, the initial Diels-Alder adduct can be converted *via* cleavage of the C3-4 bond to give Michael addition products (Scheme 53).



Scheme 53

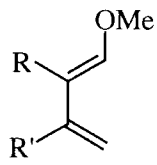
However, in our case, Michael addition products were only obtained in the Lewis acid catalysed reaction. This suggests that the product decomposition to the Michael adduct is catalysed by Lewis acids.

2.5 Conclusions

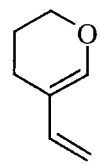
This chapter has detailed two routes to the efficient synthesis of ethyl β-nitroacrylate and subsequent Diels-Alder reactions with a diverse array of dienes. The use of alkyl-substituted dienes has shown that $ZnCl_2$ does not exert a significant effect in the sense of the classical Lewis acid influencing the coefficients of the dienophile. Small increases in selectivity were observed for the Diels-Alder reactions using *trans*-1-acetoxybutadiene and Danishefsky's diene. Surprisingly, methoxydiene **167**, which was used for its direct similarity to diene **115**, undergoes decomposition in the

reaction with $ZnCl_2$. The results of the reactions involving *cis*-1-acetoxybutadiene **182** have suggested that the mechanism is concerted and the decomposition of the furan adducts is catalysed by the addition of $ZnCl_2$.

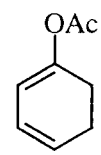
Future work could focus on alkoxy dienes such as **189** and **190** which would be more stable to the addition of Lewis acids and to investigate the selectivity of diene **191** (Figure 23).



189



190



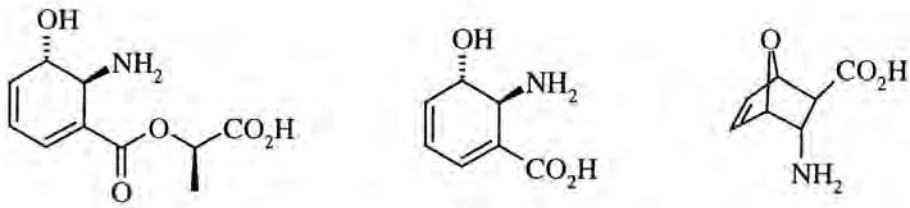
191

Figure 23

Chapter 3: β-Amino Acids

3.1 Introduction

In chapter 2 we described our investigation into the reactivity and selectivity of nitroacrylates in the Diels-Alder reaction. A second goal of the project was to demonstrate that the resultant adducts from the nitroacrylate Diels-Alder reaction can act as convenient synthons for the synthesis of β-amino acids. In this context, we envisaged the synthesis of two chorismate-based, γ-hydroxy-β-amino acid natural products, oryzoxymycin **2** and (2*S*, 3*S*)-dihydrohydroxyanthranilic acid (DHAA) **126** isolated from of *Streptomyces venezuelae,* var. *oryzoxymyceticus* and *Streptomyces aureofaciens* respectively (Figure 24).[60]



2 **126** **192**

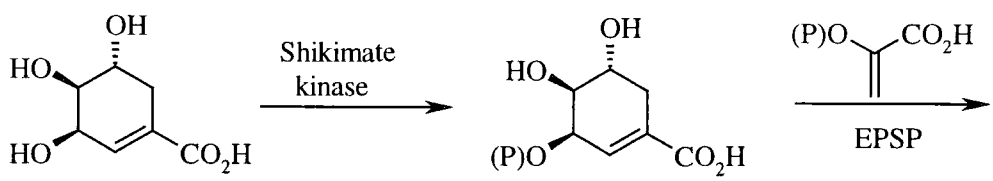
Figure 24

In addition to the total synthesis of these natural products we anticipated that the strategy employed would provide a general route to the synthesis of a diverse array of cyclic and bicyclic β-amino acids. As an example of this approach the diastereoselective synthesis of the bicyclic β-amino acid **192** was envisaged using a furan Diels-Alder approach to control the stereochemistry. Analogous structures to bicyclic β-amino acid **192** have been shown to induce β-turns into peptides[61] and act as potent herbicides.[62]

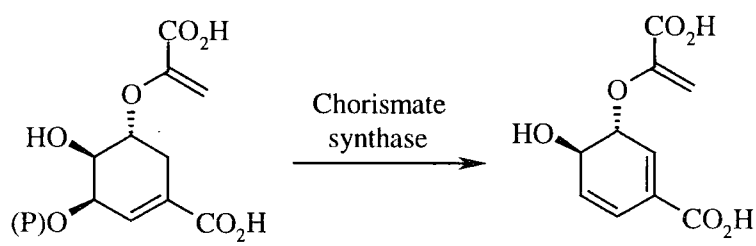
3.2 Background to Chorismate-Based Natural Products

A number of γ-hydroxy-β-amino acids are known (see section 1.3.2) and in general they exhibit antibacterial properties. In the case of oryzoxymycin the major antibacterial effect was noted against the growth of *Xanthanomous oryzae*.[60]

The exact pathway for the biosynthesis of oryzoxymycin or DHAA has not yet been reported but they are believed to be by-products of the shikimic acid pathway. Microorganisms and plants utilize the shikimic acid pathway for the biosynthesis of the aromatic amino acids phenylalanine, tyrosine and tryptophan with chorismate as a key intermediate. Under normal growth conditions, 20% of the carbon fixed by plants flows through this metabolic sequence and is therefore a target pathway for many potential herbicides and genetics-based products.[63] The steps that are common to all of the aromatic amino acids involve the transformation of shikimate **193** to chorismate **196** (Scheme 54). The conversions include selective phosphorylation at the 3-hydroxyl position, introduction of the enolpyruvyl side chain, catalysed by 5-enolpyruvylshikimate 3-phosphate (EPSP) synthase, and the formation of the diene functionality with chorismate synthase.



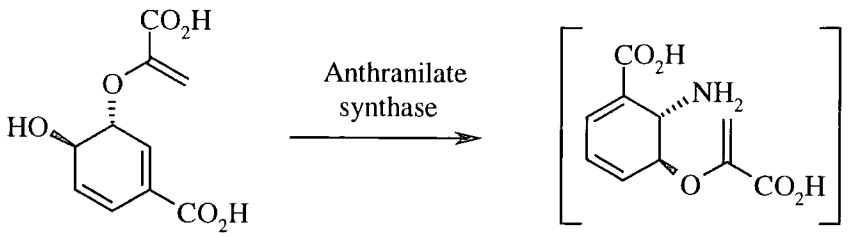
Shikimate - **193** Shikimate 3-phosphate - **194**



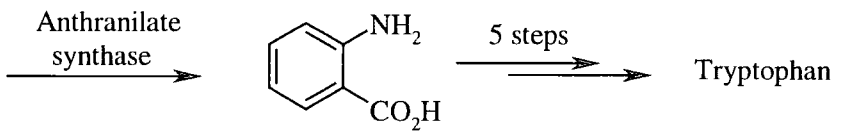
5-Enolpyruvylshikimate 3-phosphate - **195** Chorismate - **196**

Scheme 54

The first specific step in the biosynthesis of tryptophan involves a glutamine-dependent amination / aromatisation sequence using anthranilate synthase (AS) to give anthranilic acid **198**, which is subsequently converted into tryptophan in 5 steps (Scheme 55).[64]



Chorismate - **196** ADIC - **197**

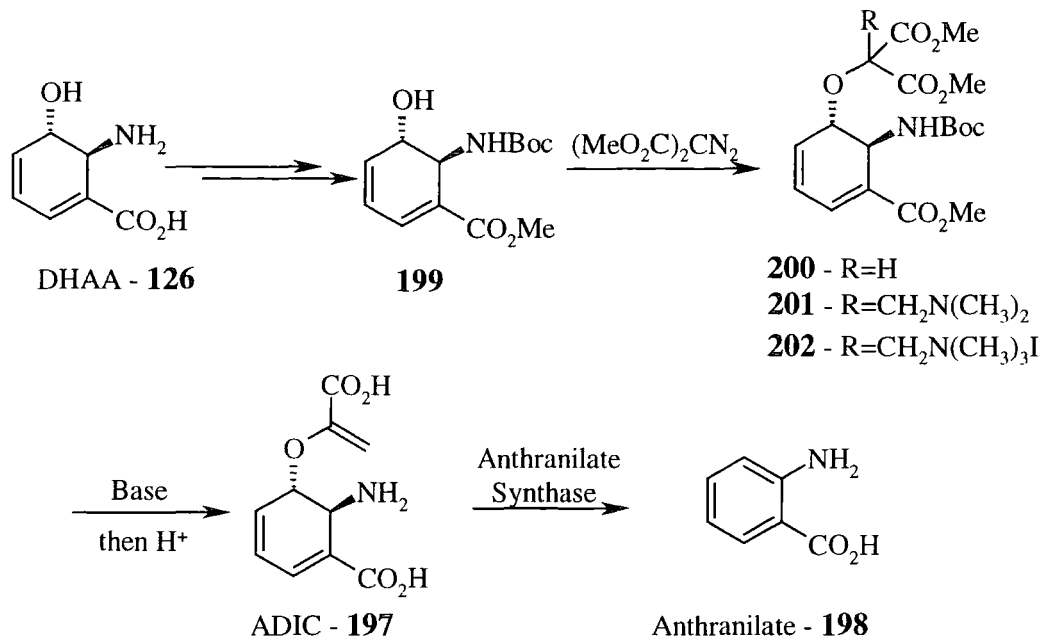


Anthranilate - **198**

Scheme 55

The proposed intermediate in the conversion is 2-amino-2-deoxyisochorismate (ADIC) **197** which is analogous to the oryzoxymycin and DHAA core structures. In the formation of this intermediate, anthranilate synthase catalyses a formal *syn*-1,5 displacement of hydroxide by glutamine. Whilst the definitive mechanism is unknown, the reaction is believed to be facilitated by chelation of the 4-hydroxyl group by magnesium at the active site of anthranilate synthase. The exact pathway by which ADIC undergoes aromatisation has also not yet been resolved, although studies by Floss *et al.*[65] suggest that an intramolecular *syn*-elimination pathway does not occur because the third methyl hydrogen in pyruvate comes from the addition of a proton from the solvent.

This reaction pathway has been shown to be credible by the synthesis of ADIC by Ganem *et al.*[66] from an isolated sample of (2*S*, 3*S*)-DHAA **126** and the observation that it is processed by anthranilate synthase to anthranilate (Scheme 56).

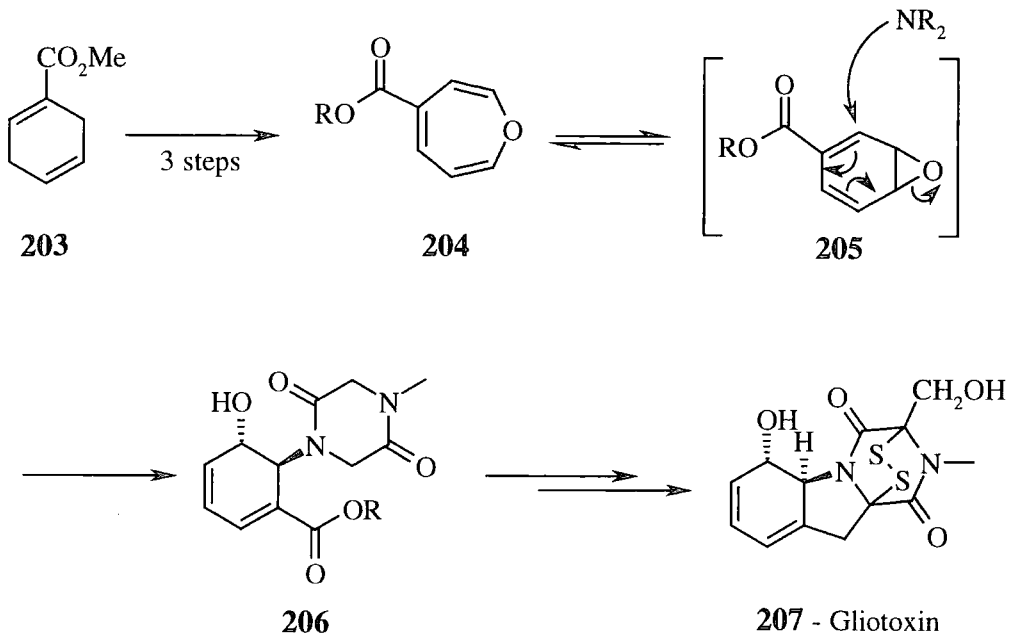


Scheme 56

In the context of this background, we speculate that DHAA and the core structure of oryzoxymycin arise from defects in the biosynthetic pathway in the EPSP synthase step. In the case of DHAA it can be envisaged that the enolpyruvyl side chain of chorismate **196** is missing and therefore when it is processed by anthranilate synthase the introduction of the nitrogen functionality gives DHAA because subsequent elimination does not occur to give anthranilate **198**. The mechanism by which oryzoxymycin acquires the lactate side chain is unknown and is open to further speculation.

Surprisingly, although considerable efforts have been made to prepare intermediates in the shikimic acid pathway and inhibitors of the individual enzymes (see section 3.3.4) there have been no reports of the synthesis of oryzoxymycin.

The synthesis of the DHAA core structure has been reported by Kishi *et al.*[67] in the synthesis of gliotoxin **207**. The synthesis describes the reaction between diene epoxide **205**, which exists in equilibrium with oxepin **204**, and an amide-based nucleophile in a *syn*-1,5-reaction that ultimately opens the epoxide to give alcohol **206** (Scheme 57).

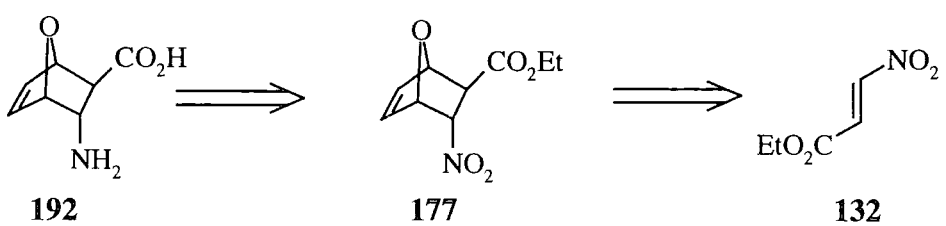


Scheme 57

3.3 Results and Discussion

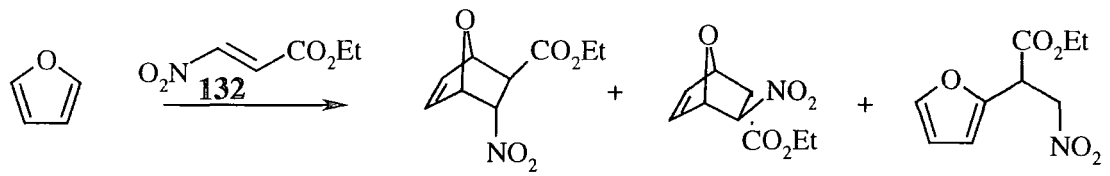
3.3.1 Synthesis of bicyclic β-amino acids

In order to demonstrate that the adducts from the nitroacrylate Diels-Alder reactions can be used in the selective synthesis of β-amino acids we have studied a method for the synthesis of bicyclic β-amino acid **192** (Scheme 58). The strategy uses the *endo*-adduct **177** formed in the Diels-Alder reaction between nitroacrylate **132** and furan (discussed further in section 2.4.3). Subsequent elaboration of the nitro and ester groups would provide access to β-amino acid **192**.



Scheme 58

The first objective in the synthesis was the scale-up of the Diels-Alder reaction between nitroacrylate **132** and furan (Scheme 59). Using thermal reaction conditions (benzene, 25°C), the reaction was repeated on a 1 g scale to give small quantities of the individual pure diastereoisomers following careful chromatography. On a larger (10 g) scale, however, repeated chromatography of the mixture was required to achieve separation due to the close R_f values of the two compounds. Attempts to purify the *endo*-isomer *via* crystallisation gave only small quantities of a slightly improved ratio of isomers.



177 **178** **179**

Scheme 59

Due to this practical problem we then set out to increase the *endo*-selectivity of the reaction in order to eliminate the ineffective chromatography. Table 11 shows a summary of the changes made to the reaction primarily in the reaction conditions in order to achieve enhanced selectivity. These results show that using chloroform as the solvent at –20 °C increases the *endo*-selectivity to approximately 4:1. In order to determine whether the increase in selectivity was due to the increased polarity of chloroform compared to benzene, the more polar acetonitrile was investigated as a solvent. The selectivity of the Diels-Alder reaction returned to 2:1 with acetonitrile, however, a 3-fold increase in the rate of reaction was observed. The slightly acidic nature of chloroform is unlikely to be the source of the increase in selectivity because repeating the reaction using nitromethane as the solvent also gave approximately a 2:1 ratio for *endo*-selectivity.

Table 11

Lewis Acid	Temp (°C)	Reaction time (hr)	Yield (%)	Ratio **177** : **178** : **179**
Thermal (Benzene)	25	60	98	63 : 37 : 0
$ZnCl_2$ (1.0eq/CH_2Cl_2)	0	72	62	56 : 29 : 15
Thermal ($CHCl_3$)	-20	120	90	78 : 22 : 0
Thermal ($CHCl_3$)	50	2	72	65 : 35 : 0
Thermal (CH_3CN)	-20	36	96	70 : 30 : 0
Thermal (CH_3NO_2)	-20	-	-	70 : 30 : 0

The addition of a number of different Lewis acids was investigated including $Zn(OTf)_2$, $Cu(OTf)_2$ and BF_3OEt_2, but no increase in selectivity and only a small increase in the rate of reaction was observed. The reaction was repeated on a 10 g scale using chloroform as the solvent at –20 °C, and following careful chromatography gave 11.4g (72%) of the pure *endo*-diastereoisomer as a white solid which could be stored for several months at –20 °C.

Identification of the compounds was achieved by comparison with the literature[56] and confirmed by 2-D NMR. The rigid 7-oxa-bicyclo[2,2,1]hept-5-ene ring structure allows the use of coupling constants to determine the relationship of the protons in the compound (Figure 25). The *endo*-isomer **177** shows 3-H to 4-H coupling, indicative of an *exo* 3-H. COSY experiments also showed no coupling for the corresponding *exo*-isomer **178** suggesting that the 3-H is *endo*.

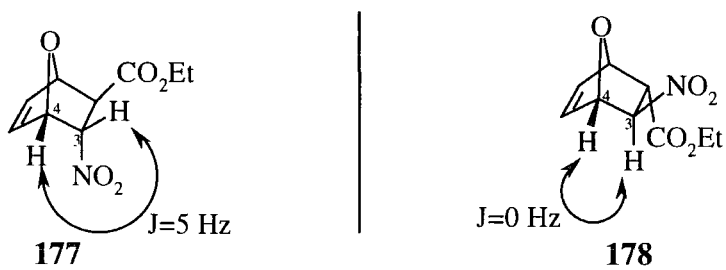
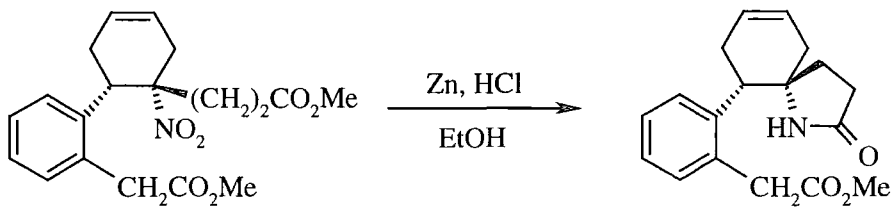


Figure 25

The two compounds also show a small 2-H to 3-H coupling constant (3 Hz) confirming the *trans*-relationship. By NMR we have also shown that both *endo*- and *exo*-isomers undergo the *retro*-Diels-Alder reaction to give nitroacrylate **132** and furan in solution at room temperature. This leads us to believe that there is a high degree of equilibration occurring in this reaction.

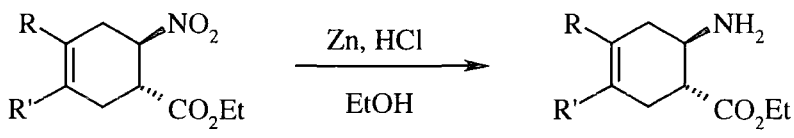
During the investigation into the furan Diels-Alder reaction the conditions for the reduction of the nitro group were evaluated using the readily available mixture of adducts **157** and **158**. There are relatively few examples in the literature where an aliphatic nitro group is reduced in the presence of an alkene. However, Bryce *et al.*[68] describe the selective reduction of the aliphatic nitro compound **208** and subsequent *in-situ* lactamisation to give **209** (Scheme 60).



208 91% **209**

Scheme 60

Using the above conditions on the model compounds **157** and **158**, the selective reduction of the nitro group was achieved, albeit in low yield (17%) (Scheme 61). The amino product was identified by the fact that the chemical shift of the C-6 proton had moved from 4.9 ppm in the nitro compound to 2.4 ppm for the amine. The transformation is also clear in the infrared spectrum with the loss of the nitro stretch at 1552cm^{-1} and the appearance of a weak NH stretch at 3377cm^{-1}.



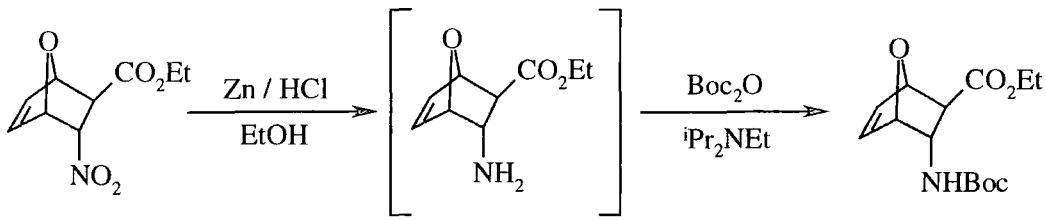
157 - R = H, R' = Me
158 - R = Me, R' = H

17%

210- R = H, R' = Me
211 - R = Me, R' = H

Scheme 61

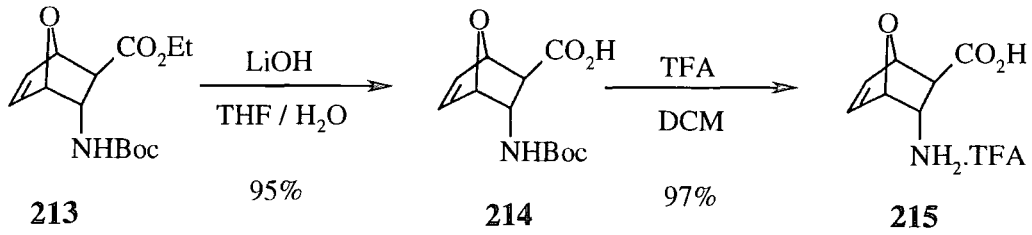
Selective reduction of the nitro group using the Bryce conditions on the furan Diels-Alder adduct **177** gave the desired amino ester **212** in low yield (28%). Although the reaction gave a clean conversion, the low yield was obtained due to problems in the isolation process. In order to circumvent this problem a 'one-pot' reduction and Boc protection procedure was developed (Scheme 62). Following the reduction step, the excess zinc was removed by filtration and the intermediate amine hydrochloride was Boc protected using Boc_2O and excess ethyl diisopropylamine.



177 **212** 83% (2 steps) **213**

Scheme 62

Using this 'one pot' procedure the desired Boc protected amino ester **213** was isolated in 83% overall yield for the two steps. The conversion is clear in the infrared with a strong carbamate stretch (1692 cm^{-1}) and by the loss of the nitro stretch (~1550 cm^{-1}). Subsequent deprotection of **213** to reveal the bicyclic β-amino acid **192** was achieved using a two-step procedure. Firstly, ester hydrolysis was achieved in excellent yield using LiOH to give the corresponding acid as a white solid characterised by the introduction of an OH stretch in the infrared, the absence of the ethyl ester signals in the ^{1}H-NMR and satisfactory microanalysis results. Removal of the Boc group was achieved by treating the acid **214** with TFA / DCM (1:4). Microanalysis confirmed that the water-soluble product was the TFA salt of the β-amino acid **215** (Scheme 63).

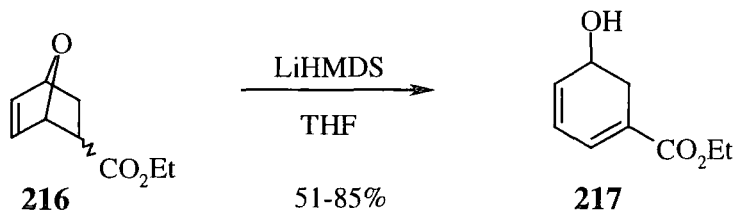


213 **214** **215**

Scheme 63

3.3.2 Synthesis of (2*S**, 3*S**)-DHAA

Having successfully developed a general route to β-amino acid **192**, the project focussed on extending the methodology to the synthesis of DHAA **126**. The chosen strategy uses a base-mediated ring-opening reaction of the bicyclic ester **213**. This method allows the *anti*-relationship of the NHBoc group and the oxygen bridge to be transferred into the *trans*-relationship of the amino and hydroxyl functionality in the product. There is considerable literature precedence for the ring opening of similar bicyclic structures, such as that demonstrated by Brion[69] using LiHMDS in the synthesis of ester **217** (Scheme 64).

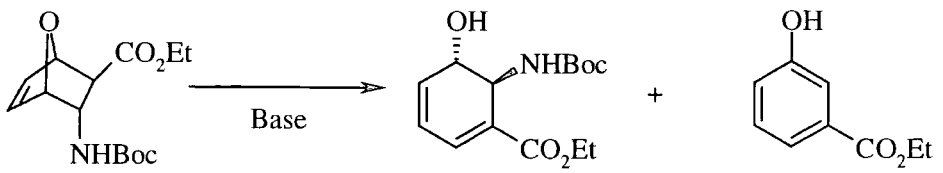


216 **217**

Scheme 64

Initial attempts to obtain hydroxy ester **218** using these literature conditions, although appearing (TLC) to give efficient consumption of starting material, afforded low levels of conversion (43%) into the desired product (Scheme 65). Assuming that the low levels of conversion were due to reversibility of the ring-opening, we initially attempted to enhance the fragmentation through the use of higher reaction temperatures and / or trapping of the intermediate alkoxide. However, higher

temperatures led only to increased amounts of phenol **219** and the use of literature methods to enable trapping of the intermediate alkoxide[70] with silylating reagents resulted in extensive decomposition.



213 **218** **219**

Scheme 65

Subsequently, a number of bases, conditions and work-up procedures were investigated in order to achieve reproducible and efficient yields (Table 12). The results show that changing to the more basic, less co-ordinating potassium salt afforded a high degree of conversion.

Table 12

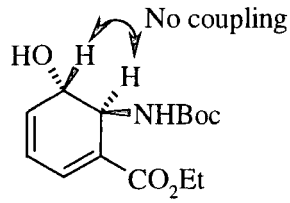
Base	Temp (°C)	Quenching conditions	Time (min)	Yields (%)		
				213	**218**	**219**
LiHMDS	0	NH_4Cl (aq)	60	25	43	13
LiHMDS / [15]-crown-5	0	NH_4Cl (aq)	60	22	44	10
LDA	0	NH_4Cl (aq)	60	35	31	18
LiTMP	-30 - RT	NH_4Cl (aq)	180	28	32	8
KHMDS	-50 to RT	NH_4Cl (aq)	30	22	41	24
KHMDS	-50 to RT	MeOH then NH_4Cl (aq)	20	0	71	4

In addition to changes made to the base, a number of changes to the procedure were required for a satisfactory work-up procedure in order to prevent aromatisation. It proved necessary to quench the resultant alkoxide rapidly by an inverse quench into a

mixture of methanol and ethyl acetate, followed by washing with saturated ammonium chloride solution. We postulate that the methanol acts as a homogeneous proton source allowing a rapid quench of the alkoxide, with the ammonium chloride acting as a buffer to neutralise the basic solution. Following this protocol hydroxy ester **218** was isolated in a reproducible 71% yield.

Interestingly, the major decomposition pathway to give aromatic products is the elimination of the NHBoc group to give phenol **219** rather than dehydration to give anthranilate products. This is consistent with McCormick's[71] earlier work on the isolation and stability of DHAA **126**.

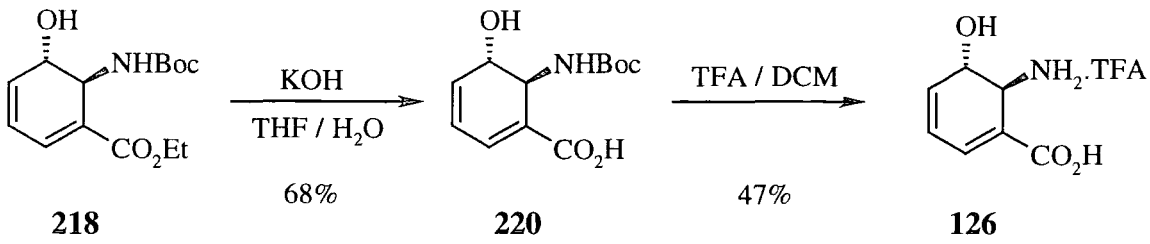
Characterisation of the alcohol was achieved by NMR with a new olefinic proton at 7.2 ppm and the distinctive OH stretch in the infrared. By 2D-NMR (COSY), no coupling was observed between the 5-*H* and 6-*H* protons, confirming their *trans*-relationship (Figure 26).



218

Figure 26

The first step in the deprotection to give DHAA **126** was the hydrolysis of the α-β-unsaturated ester functionality. Conventional literature conditions for hydrolysis (LiOH in THF / H_2O) at room temperature produced no reaction. After some experimentation, clean conversion into acid **220** was achieved by the use of 10 equivalents of KOH at 40 °C for 5 hours (Scheme 66). The diastereoselective synthesis of DHAA was completed by the use of TFA / DCM (1 : 4) to remove the Boc group. The water-soluble product was confirmed as DHAA **126** by NMR and accurate mass spectrum results.

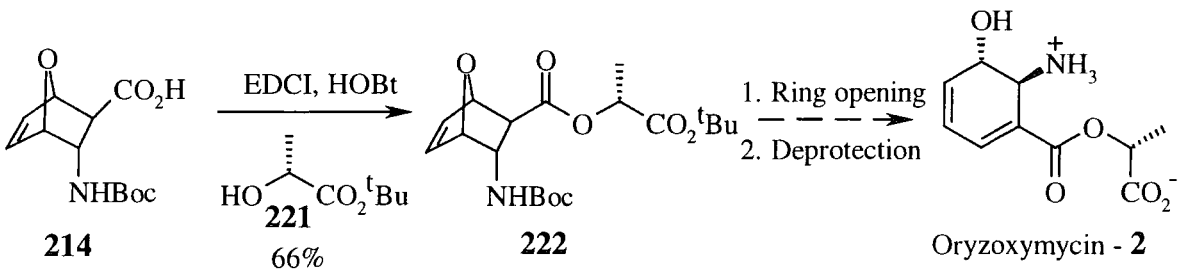


218 **220** **126**

Scheme 66

3.3.3 Progress toward the Synthesis of Oryzoxymycin

With the synthesis of DHAA complete, we set about further extending the methodology to the synthesis of the naturally occurring antibiotic oryzoxymycin **2**. Two strategies were investigated for the introduction of the lactate side chain of oryzoxymycin. Firstly, we investigated a strategy which involved coupling of the lactate side chain followed by the base-mediated ring-opening reaction (Scheme 67).

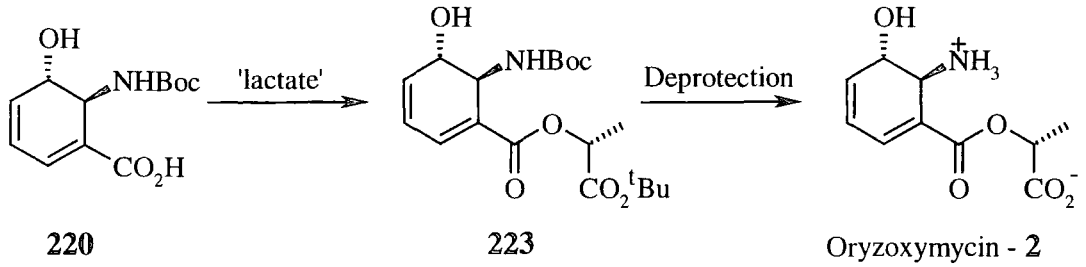


214 **222** Oryzoxymycin - **2**

Scheme 67

Introduction of the side chain was achieved with a carbodiimide coupling procedure[72] to give the *tert*-butyl ester **222** in 66% yield. Characterisation was achieved principally by NMR spectra and mass spectrum results. Unfortunately, attempts to ring open the coupled material using the literature conditions[69] or the modified procedure developed in section 3.3.2 resulted in complete decomposition of the starting material.

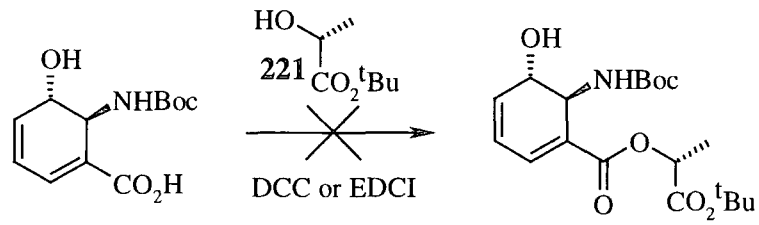
Our second strategy started from acid **220** and involved coupling with lactate **221** (or equivalent) to give the protected oryzoxymycin **223** (Scheme 68).



220 **223** Oryzoxymycin - **2**

Scheme 68

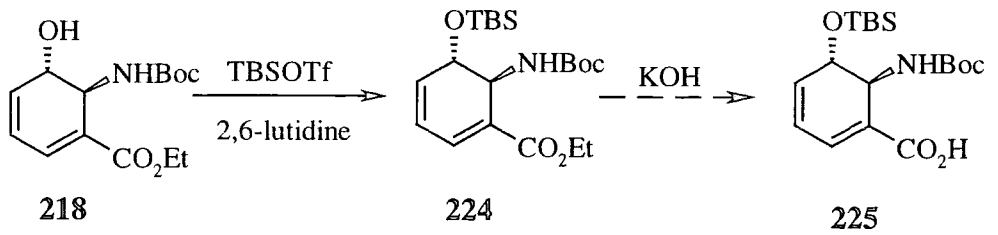
With sufficient quantities of acid **220** in hand, we attempted to couple the *tert*-butyl protected lactate ester **221** using the carbodiimide type coupling procedure described for acid **214**. This procedure and a number of related modified procedures gave poor yields (0-5%), which were insufficient for full characterisation (Scheme 69). Attempts to effect the coupling by the formation of the corresponding acid chloride followed by reaction with the *tert*-butyl protected lactate ester also proved unsuccessful.



220 **223**

Scheme 69

A number of reasons were put forward for the low yields, such as steric hindrance around the carbonyl functionality and interference by the 5-hydroxyl functionality. Protection of the 5-hydroxyl group was effected with the use of TBSOTf and 2,6-lutidine to give the crude TBS protected alcohol **224** albeit in 14% yield as a brown oil. Attempts to purify this compound by chromatography resulted in aromatic by-products. Hydrolysis of the crude ester **224** was very slow (5 days) and pure acid **225** could not be obtained (Scheme 70).

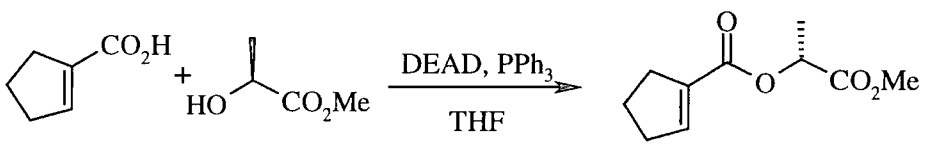


218 **224** **225**

Scheme 70

At this stage it was concluded that protection of the 5-hydroxyl gave compounds that were too unstable to handle and subsequently the synthesis of oryzoxymycin was carried out with the free hydroxyl functionality.

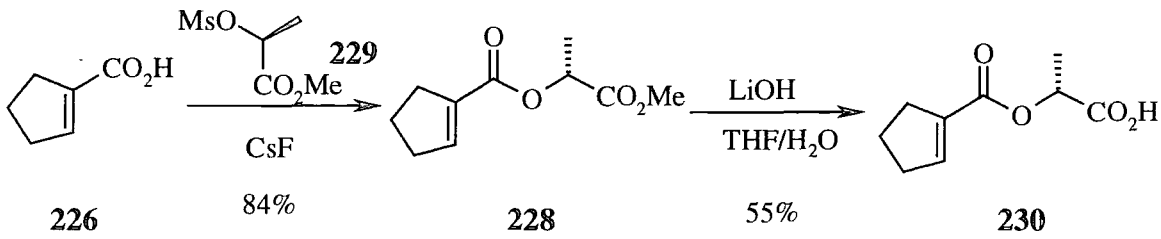
This slow hydrolysis of ester **224** demonstrated that the carbonyl group is extremely hindered. Therefore an alternative approach using the carboxylate group as the nucleophile in an S_N2 reaction was explored using cyclopent-1-enecarboxylic acid **226** as a model study. The starting acid was prepared from the commercially available methyl ester in 40% yield. Firstly, using the corresponding (*S*)-(-)-lactate ester **227** in a Mitsunobu approach gave the desired diester **228** in 26% yield (Scheme 71).



226 **227** **228**

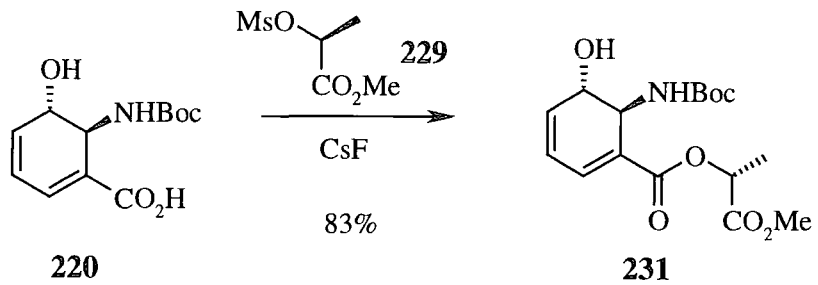
Scheme 71

Subsequently, the coupling was effected more efficiently (84%) according to the method reported by Otera *et al.*[73] by activation of the carboxyl functionality with CsF and treatment with mesylate **229**, obtained from mesylation of commercially available methyl-(*S*)-(-)-lactate **227** in quantitative yield (Scheme 72).[74] The model system was also used to assess reactivity of the two esters. Treatment of the diester **228** with LiOH gave hydrolysis of the external ester exclusively to give the desired acid **230** in 55% yield.



Scheme 72

The CsF-catalysed coupling procedure was extended to hydroxy acid **220** to give the protected oryzoxymycin **231** in 83% yield (Scheme 73). Accurate mass spectra results and NMR spectra verified the proposed structure.



Scheme 73

The compound was obtained as a mixture of diastereoisomers but unfortunately we were unable to separate them by HPLC. Figure 27 shows the analytical HPLC trace for the crude mixture of diastereoisomers.

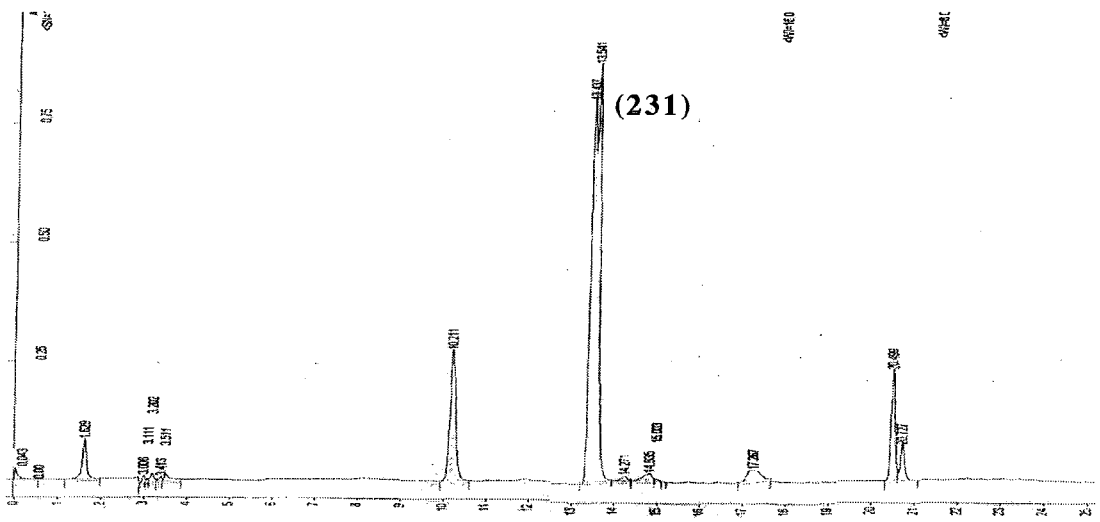
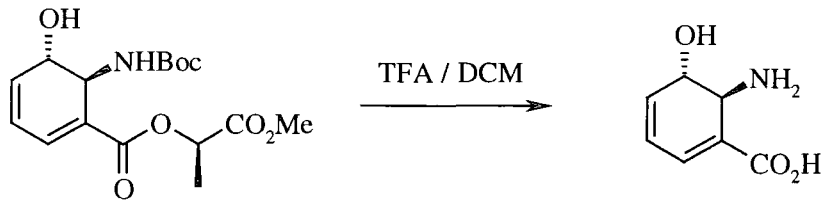


Figure 27

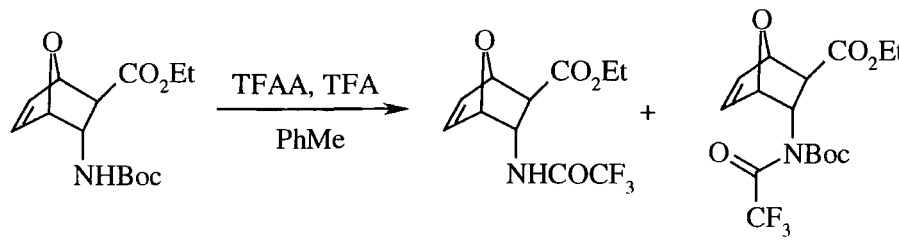
With intermediate **231** in hand we attempted to remove the Boc group under standard conditions (TFA/DCM). This procedure and other modified conditions resulted in the removal of the Boc group and, unfortunately, the acid catalysed fragmentation of the lactate side chain to give DHAA **126** (Scheme 74).



231 **126**

Scheme 74

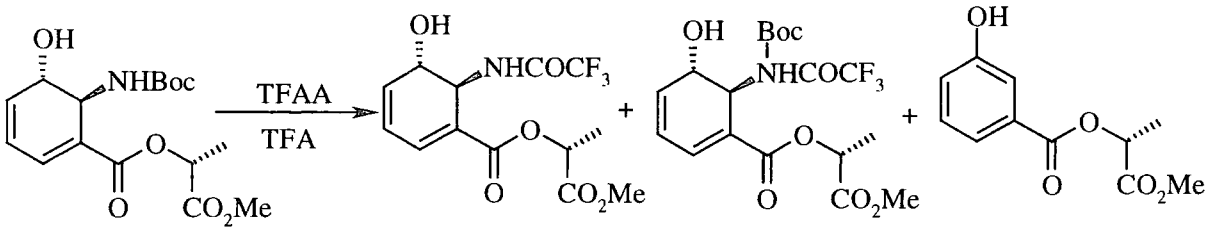
At this stage alternative strategies for removing Boc groups were explored in the context of a model study using the readily available carbamate **213**. The most effective procedure[75] entailed treatment with TFAA to trifluoroacetylate the NH and subsequent removal of the Boc group was achieved with TFA under mild conditions (Scheme 75). The reaction generated the desired trifluoroacetamide **232** in 59% yield and the intermediate **233** in 5% yield.



213 **232** **233**

Scheme 75

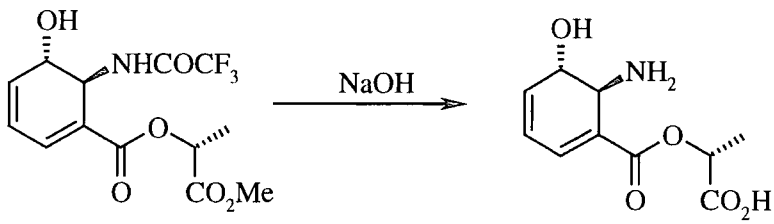
The above procedure was applied to the protected oryzoxymycin **231** resulting in a mixture of the desired compound **234**, the intermediate **235** and phenol **236** (Scheme 76).



231 **234** **235** **236**

Scheme 76

In an attempt to optimise the reaction we investigated the use of DCM, THF, Et_2O, PhMe, CH_3CN and $CHCl_3$ as solvents in a small library approach. By NMR the optimal solvent for the reaction was $CHCl_3$, and following work-up, gave trifluoroacetamide **234** in 71% with no aromatic products or fragmentation of the lactate side chain. Trifluoroacetamide **234** was unstable on standing, therefore it was treated immediately with base (NaOH) at 0°C to give oryzoxymycin (Scheme 77).



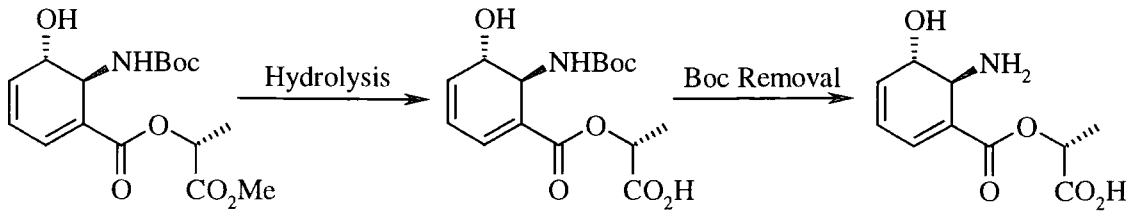
234 Oryzoxymycin - **2**

Scheme 77

Although NMR showed the clean removal of the methyl ester and mass spectrum results showed the molecular ion that corresponds to oryzoxymycin, we were unable to ascertain if a CF_3CO signal in the carbon NMR spectra corresponded to a salt or the intact trifluoroamide functionality. Infrared proved inconclusive due to the two ester carbonyl stretches masking any possible trifluoroacetamide stretch.

To circumvent this problem with the hydrolysis step of trifluoroamide **234**, our second approach to the deprotection focused on firstly hydrolysing the ester group of **231** to enable protonation and removal of salts. Subsequent treatment of the acid with

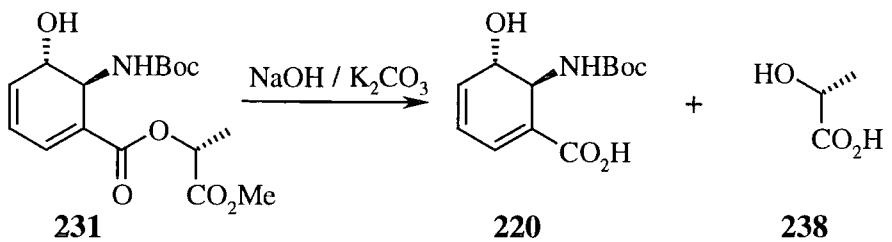
TFA or dry HCl would then give pure oryzoxymycin as the TFA or HCl salt respectively (Scheme 78).



231 **237** Oryzoxymycin - **2**

Scheme 78

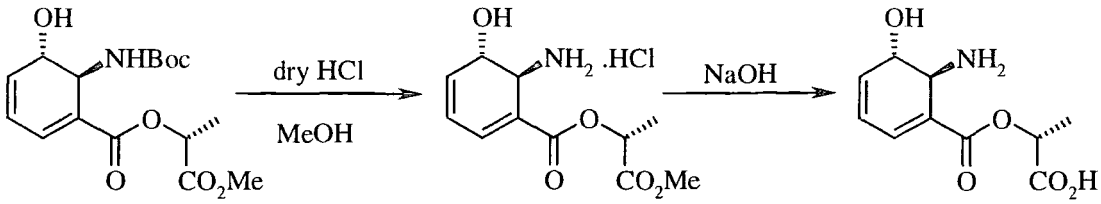
The hydrolysis of the ester functionality with NaOH resulted in unexpected hydrolysis of the internal ester to give acid **220** and lactic acid **238** (Scheme 79). Deprotection of a similar lactate-containing compound has been reported by Charlton *et al.*[76] using K_2CO_3. However, using this procedure the corresponding acid **237** was obtained in poor yield (16%) and only moderate purity.



231 **220** **238**

Scheme 79

In our third approach to the deprotection of oryzoxymycin, alternative conditions for the removal of the Boc group were investigated. After some experimentation the Boc group was removed using dry HCl in MeOH (generated from $SOCl_2$ in MeOH) (Scheme 80). In order to monitor the reaction, a solution of the carbamate **231** in CD_3OD was placed in a NMR tube and followed by proton NMR. Clean conversion into the corresponding amine hydrochloride **239** was observed within 1 hour.



Scheme 80

Treatment of HCl salt **239** with NaOD gives pure oryzoxymycin by NMR, which was identical to the compound from the hydrolysis of trifluoroamide **234**. However, the procedure also produces sodium chloride, which could not be removed using ion-exchange chromatography due to the instability of the lactate side chain. HPLC was also unable to purify or resolve the two diastereoisomers. Consequently, full analytical data could not be obtained for oryzoxymycin.

3.3.4. Inhibitors of Anthranilate Synthase

3.3.4.1 Introduction

In a study directed towards understanding the mechanism by which anthranilate synthase catalyses the *syn*-1,5-displacement reaction (discussed in section 3.2) Bartlett *et al.*[77] have detailed the synthesis of a number designed inhibitors of anthranilate synthase and other related enzymes. Compounds **240** and **241** mimic the transition state in the anthranilate synthase reaction and act as competitive inhibitors to anthranilate synthase (Figure 28).

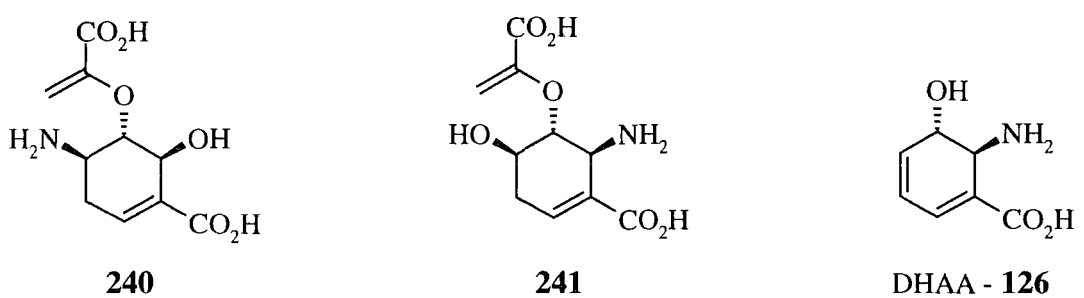
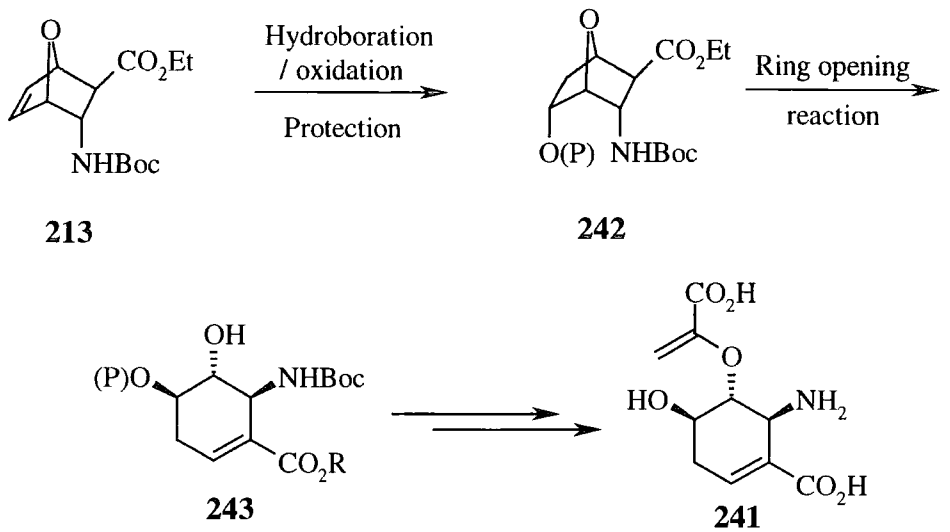


Figure 28

Both compounds **240** and **241** possess a similar structure to DHAA **126** and in a parallel approach we have extended our methodology towards the synthesis of the related oxygenated species **241**. Our initial strategy was to introduce the additional oxygen functionality at an early stage using a directed hydroboration strategy on ester **213** (Scheme 81). Following protection of the resulting alcohol, the base-mediated ring-opening reaction (developed in section 3.3.2) would give alcohol **243**. Introduction of the pyruvate group by established methods and deprotection would give access to the desired enzyme inhibitor **241**.



213 **242** **243** **241**

Scheme 81

3.3.4.2 Progress toward the Synthesis of Enzyme Inhibitors

The regio- and stereoselective introduction of the 4-hydroxyl functionality was one of the challenging steps in the synthesis. Conventional methods for hydroboration / oxidation of double bonds involve reaction on the less-hindered *exo*-face of oxa-bicyclo-[2,2,1]-heptenes (Figure 29).[38]

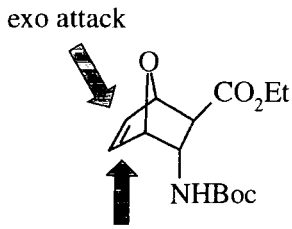
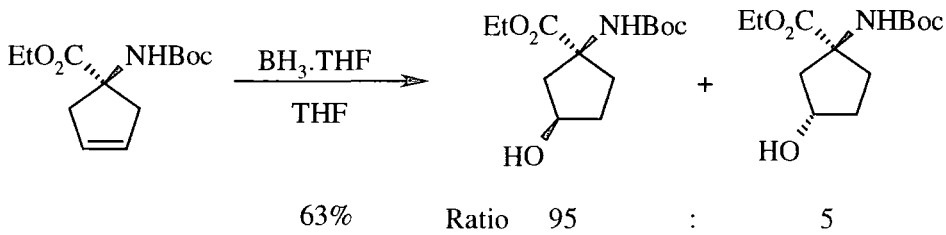


Figure 29

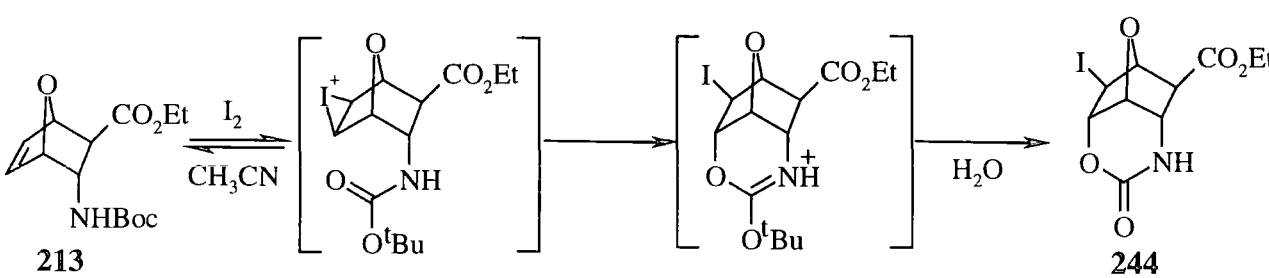
We first envisaged directed hydroboration of the *endo*-face of the molecule using the NHBoc group as the directing group according to the method described by Hodgson *et al.*[78] where hydroboration / oxidation occurs on the same face of the molecule as the NHBoc group (Scheme 82).



Scheme 82

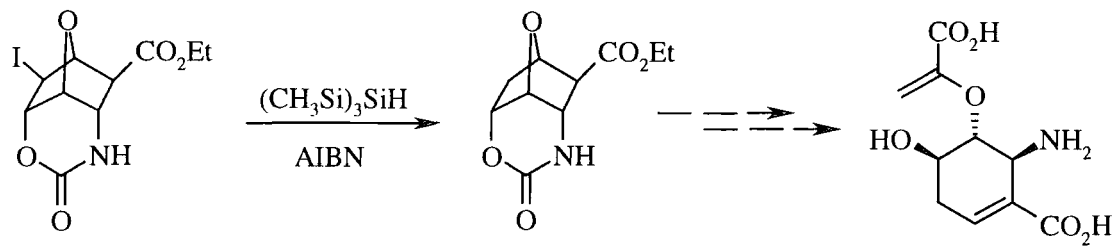
Using this procedure treatment of ester **213** with BH_3.THF gave clean conversion into an unidentified product that did not correspond to the desired alcohol.

The procedure that was ultimately successful in the selective introduction of the oxygen functionality was an iodocarbamation strategy based upon a report by Zappia *et al.*[79] Ester **213** was stirred with iodine at room temperature to give the desired cyclic carbamate **244** in 47% yield following *in-situ* hydrolysis (Scheme 83).



Scheme 83

Subsequent radical dehalogenation by treating iodo ester **244** with $^{n}Bu_3SnH$ / AIBN[80] gave clean conversion into ester **245** but we were unable to remove the tri-^{n}butyl tin salts from the crude product. Using *tris*-trimethylsilyl silane / AIBN[81] gave clean conversion into pure ester **245** in 52% yield (Scheme 84). Unfortunately, due to time constraints of the project we were unable to continue with this synthesis.

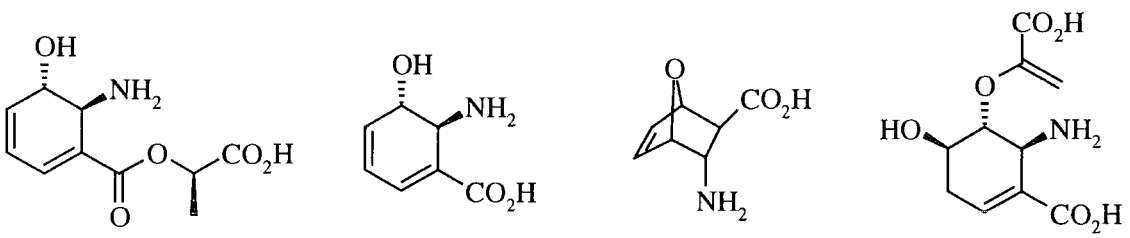


244 **245** **241**

Scheme 84

3.4 Conclusions and Future Work

This study has demonstrated that nitroacrylate Diels-Alder adducts can act as convenient precursors for β-amino acids. During this investigation we have described the synthesis of the β-amino acid **192** and extended the methodology to incorporate the diastereoselective synthesis of DHAA **126** and the naturally occurring antibiotic oryzoxymycin **2**, although further work is required to enable full characterisation. Future work would focus on continuing the synthesis of the anthranilate synthase transition state mimic **241** and to develop this methodology to the synthesis of related natural products (Figure 30).



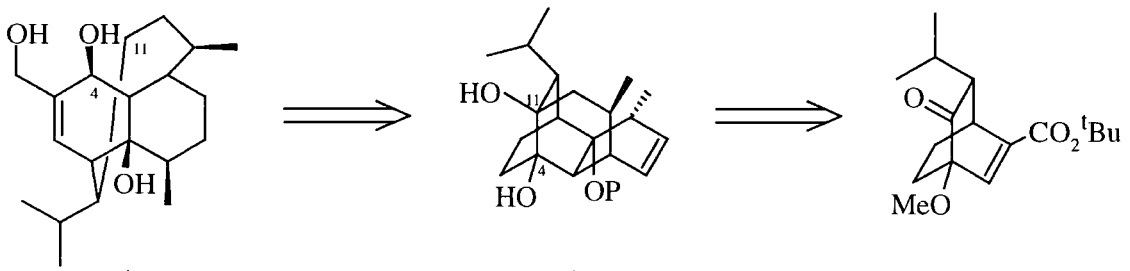
2 **126** **192** **241**

Figure 30

Chapter 4: Vinigrol

4.1 Introduction

In chapters 2 and 3 we have shown that nitroacrylates act as reactive dienophiles in the Diels-Alder reaction and the resultant adducts are convenient synthons for the synthesis of β-amino acids. This chapter describes a further demonstration of the utility of the nitroacrylate Diels-Alder adducts in a synthetic approach to the structurally unique diterpene Vinigrol **1**. The strategy behind the retrosynthesis of the diterpene relies on the formation of a bond between C-4 and C-11 to give the pentacyclic diol **246** (Scheme 85). The synthesis of diol **246** is envisaged using bicyclic ketone **127** as a key intermediate.



1 **246** **127**

Scheme 85

Whilst the total synthesis of vinigrol represents a major goal within the group, we have used the process as a vehicle to demonstrate that nitroacrylates act as substituted ketene equivalents to allow regio- and stereoselective synthesis of the bicyclic ketone **127**.

4.2 Introduction to Vinigrol

4.2.1 Isolation and Background

Vinigrol was first isolated in 1987 by Uchida *et al.*[82] from a culture of the fungal strain *Virgaria nigra.* It was extracted from the mycelium, purified by solvent extraction followed by chromatography on silica gel and then isolated as crystals ($C_{20}H_{34}O_3$, mp 108 °C). In a screen for platelet-activating factor (PAF) antagonists, vinigrol was found to decrease the arterial blood pressure of anaesthetised rats dose-dependently when administered intravenously. In addition it was found that **1** and its salts are tumour necrosis factor (TNF) antagonists and therefore it has potential for use in the treatment of hypertension, endotoxic shock inflammation, infections, cachexia and to arrest progression from AIDS-related complex to AIDS.[83]

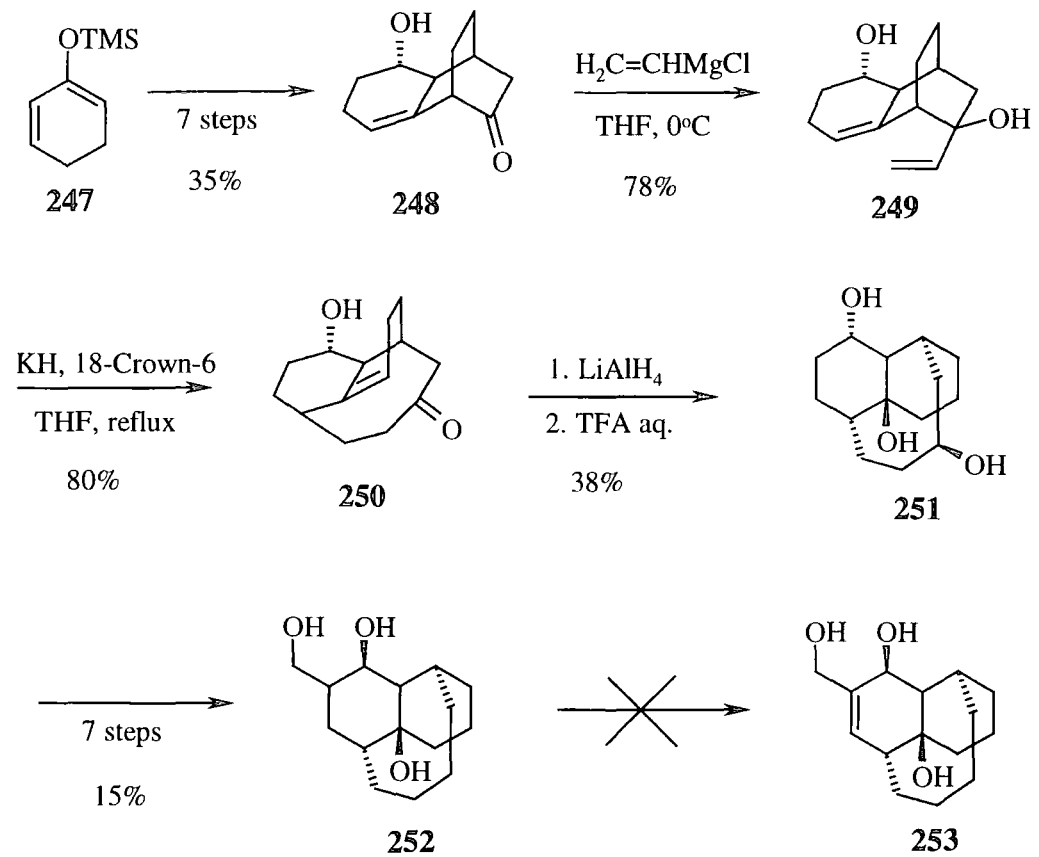
The structure and absolute stereochemistry was determined by Tada *et al.*[84] using a combination of X-ray analysis, ^{1}H-NMR spectroscopy and the NOESY spectrum of an acylated derivative. Vinigrol possesses eight chiral centres and a unique decahydro-[1,5]-butanonapthalene ring structure and combined with its interesting biological activities makes it a challenging synthetic target in organic chemistry.

4.2.2 Previous Synthetic Approaches

To date, the total synthesis of vinigrol has not been reported. Furthermore, only two groups have published synthetic routes to the tricyclic ring system. However, a number of other reports discuss methodology applicable to this novel skeleton. [85]

The only successful generation of the tricyclic skeleton is that reported by Hanna *et al.*[86] using an anionic oxy-Cope rearrangement of bicyclic allylic alcohol **249** as the key step to form the 8 membered ring (Scheme 86). Preparation of **249** involved a chelation-controlled addition of vinylmagnesium chloride to hydroxyenone **248**. Following the oxy-Cope reaction and reduction of ketone **250** with $LiAlH_4$, the

tertiary alcohol in compound **251** was introduced in 38% yield *via* regio- and stereoselective hydration of the double bond using aqueous TFA. Triol **251** corresponds to the novel decahydro-[1,5]-butanonapthalene ring structure of vinigrol **1**. The removal of the unwanted hydroxyl functionality and functionalisation of ring A to afford **252** requires a further 7 steps in 15% overall yield. Unfortunately, the synthesis of vinigrol could not be completed because it was not possible to introduce the double bond into the A ring to yield the intermediate target **253**.

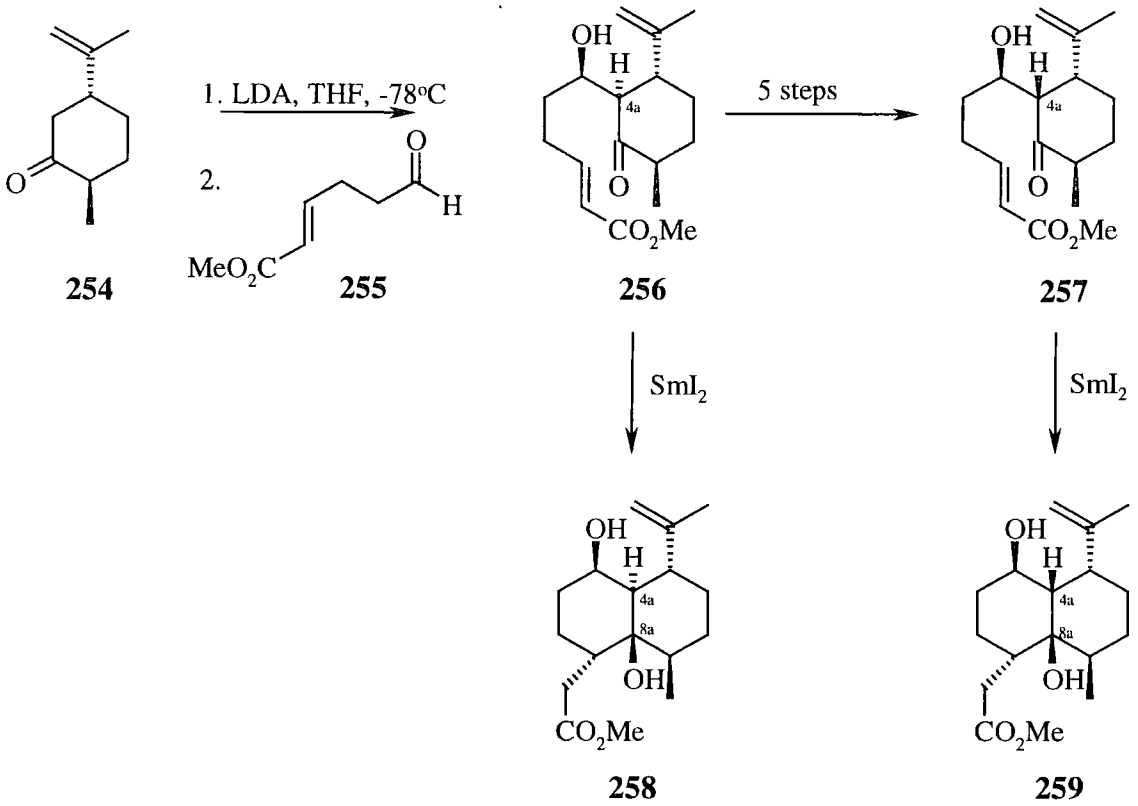


Scheme 86

In two alternative approaches, Matsuda and co-workers[87] have demonstrated the use of SmI_2 in the construction of bicyclic ring systems relevant to vinigrol. The first of these describes a very concise method for the synthesis of the cis-decalin diol **259**, which corresponds to vinigrol (Scheme 87). The synthesis begins with an *anti*-selective aldol reaction of methyl 6-oxo-2-hexanoate **255** with the Li-enolate

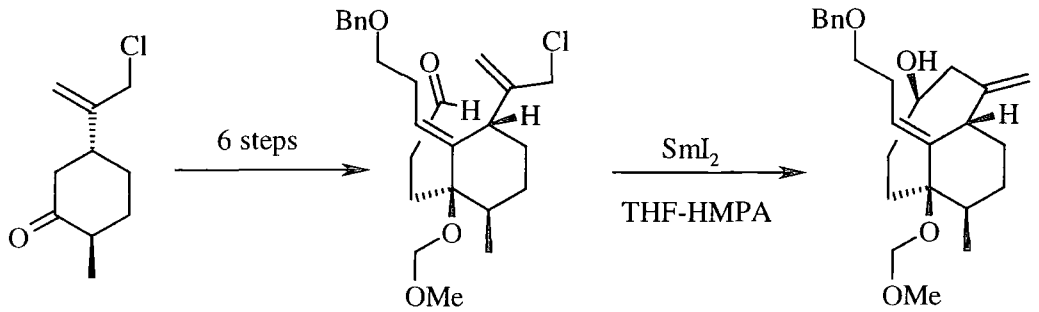
generated from (+)-dihydrocarvone **254** to provide the *anti*-β-hydroxy ketone **256** (Scheme 2). Since this intermediate possesses the wrong stereochemistry at C-4a, a 5-step procedure was required to gain access to the *syn*-β-hydroxy ketone **257**.

Interestingly, both **256** and **257** undergo the SmI_2-promoted cyclisation to give *trans*- and *cis*-decalin diols **258** and **259** respectively as the sole products with the required stereochemistry at C-8a. However, to date, the synthesis neglects the inherent difficulty in the synthesis of vinigrol, namely the formation of the 8-membered ring.



Scheme 87

In a recent paper Matsuda and co-workers[88] describe the 8-membered ring-closure reaction through the intramolecular reductive coupling of aldehyde **261** using SmI_2 which is available from chlorodihydrocarvone **260** in 6 steps (Scheme 88). The reaction occurs instantaneously at room temperature to give the cyclooctanol **262**, which is relevant to the 8-6 fused ring system of vinigrol as the only detectable product.

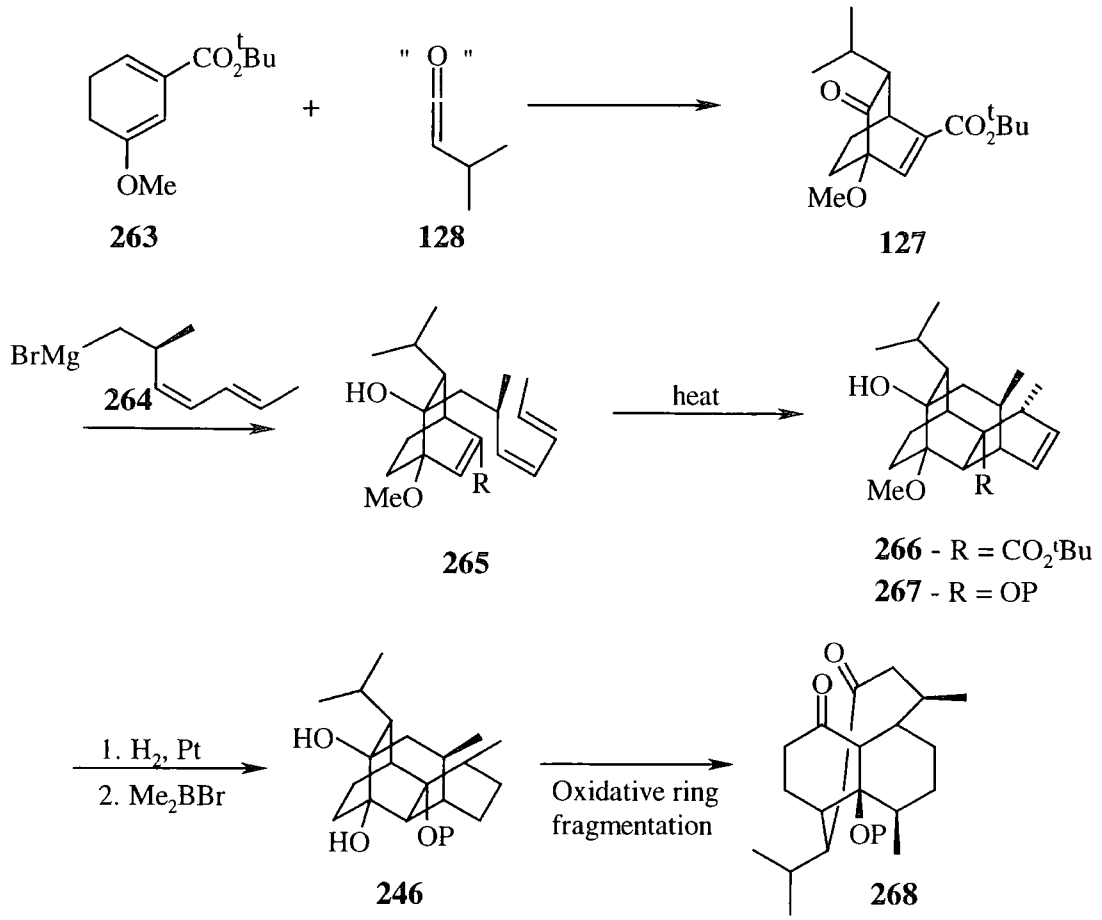


260 **261** **262**

Scheme 88

4.3 Proposed Strategy

The fundamental strategy behind our synthetic approach to vinigrol is to construct the eight-membered ring in a masked form thus avoiding the normal difficulties with the formation of medium-sized rings. The synthesis relies upon a successive Diels-Alder reaction / oxidative ring fragmentation strategy to reveal the tricyclic ring system **268** (Scheme 89). In the context of the preparation of ketone **127** we have envisaged the design of a substituted ketene equivalent thus enabling the selective incorporation of the isopropyl group into the bicyclic ring structure. Using diene **263,** accessible from the Birch reduction of *tert*-butyl 3-methoxybenzoate, and a nitroalkene-based dienophile in a Diels-Alder approach, followed by a Nef reaction, would provide access to ketone **127** with control of regio- and diastereoselectivity. With the methoxy ketone **127** in hand we anticipate that the alkyl side chain **264** (or equivalent) could be introduced by using it as a nucleophile to attack the carbonyl group.



Scheme 89

Using this methodology, the facial selectivity of the Grignard addition will be controlled by the *exo*-isopropyl group and favourable interactions of the double bond (Figure 31).

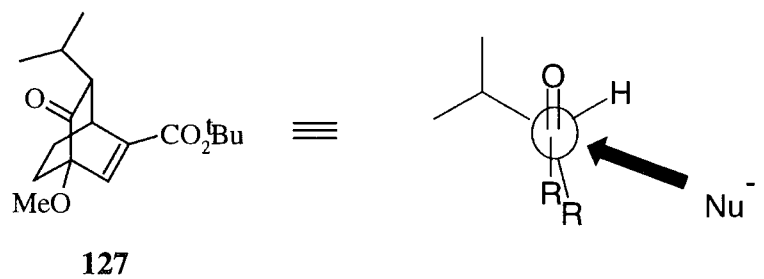
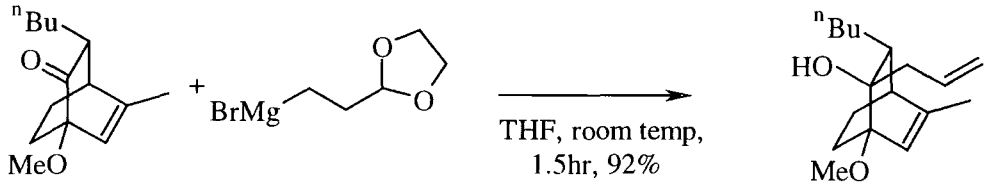


Figure 31

This approach has been demonstrated by Kim *et al.*[42] on the closely related bicyclic ketone **118**. The synthesis uses the ^{n}butyl group at the α-position to direct the

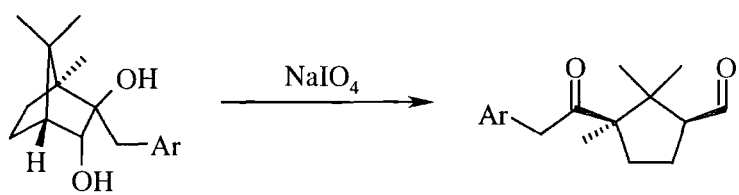
nucleophilic attack of a Grignard reagent to the *endo*-face of the molecule with 92% selectivity (Scheme 90).



118 **120**

Scheme 90

With **265** in hand we anticipate an intramolecular Diels-Alder reaction between the newly introduced *Z,E*-diene functionality and the newly formed α,β-unsaturated alkene. Subsequent Baeyer-Villiger rearrangement of the *tert*-butyl ester group (or equivalent) would yield the pentacyclic structure **267**. Reduction of the double bond and deprotection of the methyl ether would give diol **246** (Scheme 89). Using diol **246** in another key step in the synthesis in an oxidative fragmentation reaction using $NaIO_4$ or $Pb(OAc)_4$ (or equivalent) would yield the diketone **268**. In the case of diol **246**, the rigid structure places the hydroxyl groups at an angle of 60° to each other. LaBarge and Rubin[89] report a representative example of the cleavage using diol **269** (Scheme 91). This reaction clearly demonstrates that the 5-membered transition state of periodate cleavage tolerates the inherent 60° angle.

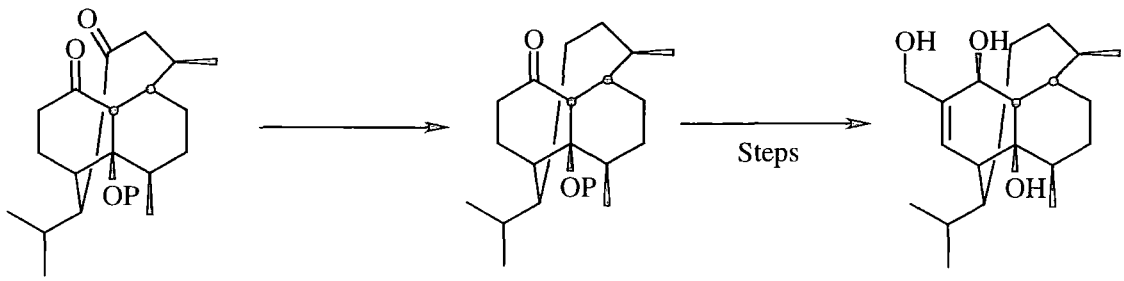


269 **270**

Scheme 91

According to molecular models the undesired ketone at C-11 is the more accessible of the two ketones, allowing the possibility of selective removal to give ketone **271**.

Introduction of the C-7 hydroxymethyl and Δ 6,7 olefin followed by selective reduction of the C-8 carbonyl from the α-face and deprotection would give access to vinigrol (Scheme 92).



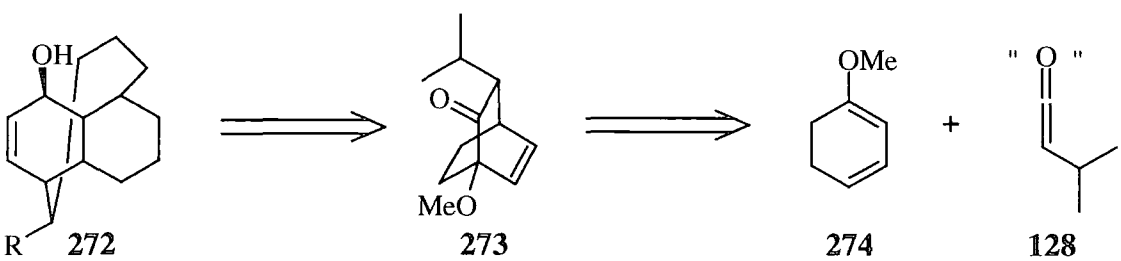
268 **271** Vinigrol - **1**

Scheme 92

4.4 Results and Discussion

4.4.1 Nitroacrylates as Substituted Ketene Equivalents

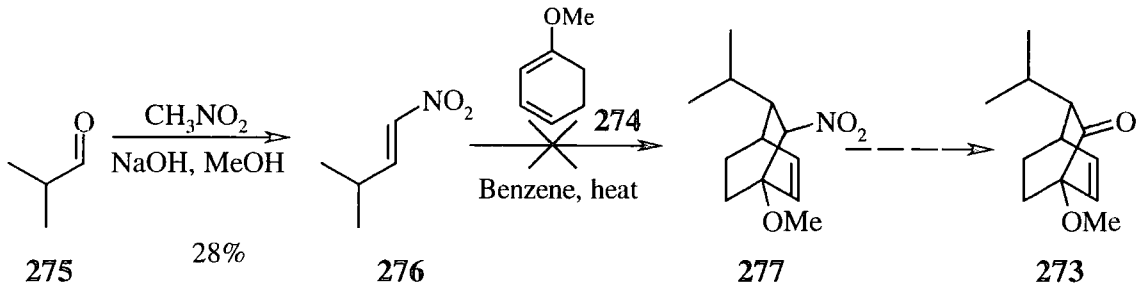
In accordance with the overall goal, to develop an approach to the total synthesis of vinigrol, the intermediate target was the synthesis of the vinigrol ring structure **272** (Scheme 93). Therefore, the initial target in the synthesis was the formation of ketone **273**, as outlined in the previous section, would result from a cycloaddition reaction of diene **274** and a functionalised ketene equivalent **128**.



272 **273** **274** **128**

Scheme 93

No procedures have been reported in the literature for an alkyl ketene equivalent (discussed in section 1.4.1) and consequently new methodology was required. Our first approach investigated the use of nitroalkene **276** as a substituted ketene equivalent because nitro groups can be converted into ketones *via* a Nef reaction. This dienophile was also chosen because a conventional *endo*-selective Diels-Alder reaction would allow direct incorporation of the isopropyl group in the *exo*-position with the desired regiochemistry. A subsequent Nef reaction would give access to ketone **273**.



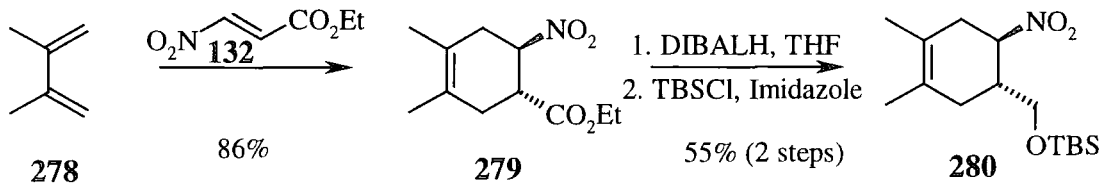
275 **276** **277** **273**

Scheme 94

Synthesis of nitroalkene **276** was achieved in moderate yield (28%) from a base-mediated dehydration between isobutyraldehyde **275** and nitromethane. The product was characterised by the large 14 Hz (*trans*) coupling between the olefinic protons and by comparison with NMR literature values[90] (Scheme 94). The Diels-Alder reaction was attempted under both thermal and Lewis acid catalysed conditions with diene **274** but unfortunately no reaction was observed and only starting materials were recovered.

In order to enhance the reactivity of the dienophile in the Diels-Alder reaction, our second approach to ketone **273** investigated the use of nitroacrylates as substituted ketene equivalents. The methodology was first tested using 2,3-dimethylbuta-1,3-diene **278** in a model study (Scheme 95) because nitroacrylates have never been reported as ketene equivalents This particular diene was chosen because an initial Diels-Alder reaction would give no regio- or diastereoisomeric products, thus

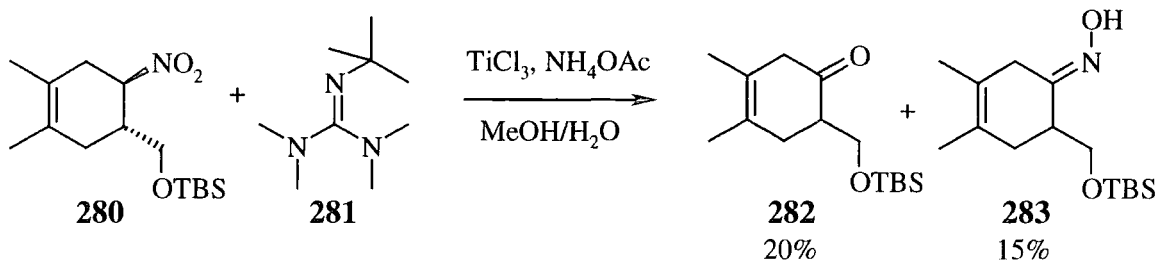
simplifying the NMR spectra. Heating a mixture of diene **278** and nitroacrylate **132** resulted in a clean 86% conversion into a single diastereoisomer by NMR which was identified by comparison with NMR literature values. Although the ester group can act as a versatile handle for the incorporation of a number of functional groups, including the isopropyl group, in this model study we chose to convert the ester into a TBS ether. Treatment with 3.5 equivalents of DIBALH gave the corresponding alcohol, which was immediately protected using TBSCl / imidazole to give the TBS ether **280**. The product was identified by the absence of the ester carbonyl stretch in the infrared and a new signal in the ^{1}H-NMR at 3.6 ppm corresponding to the new methylene group.



278 **279** **280**

Scheme 95

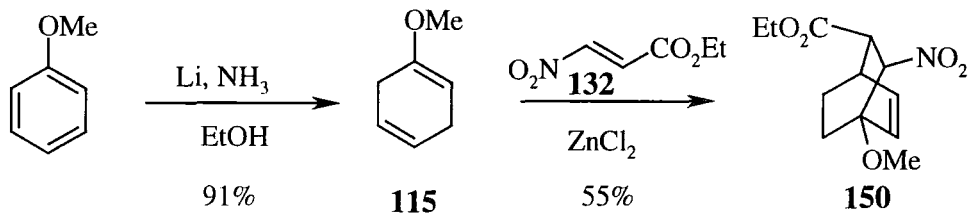
With the intermediate nitro compound **280** in hand, we commenced a study into Nef reactions. A number of groups including Hewson and MacPherson[91] have shown that related nitro groups can be efficiently converted into the corresponding ketone using $TiCl_3$, buffered by NH_4OAc. Using this procedure with **280** no reaction was observed and starting material was recovered. In a change to the literature procedure, we chose to use 2-*tert*-butyl-1,1,3,3-tetramethylguanidine as the base in a minimal amount of methanol in the formation of the initial nitronate species. Using these conditions the nitro compound **280** underwent the Nef reaction to give the desired ketone **282** in 20% yield along with the intermediate hydroxylamine **283** in 15% yield (Scheme 96). Ketone **282** was identified by the absence of the $CHNO_2$ proton in the ^{1}H-NMR and the appearance of the characteristic carbonyl peak at 211 ppm in the ^{13}C-NMR. The success of this reaction, albeit in a 20% yield, represents the first use of a nitroacrylate as a substituted ketene equivalent.



Scheme 96

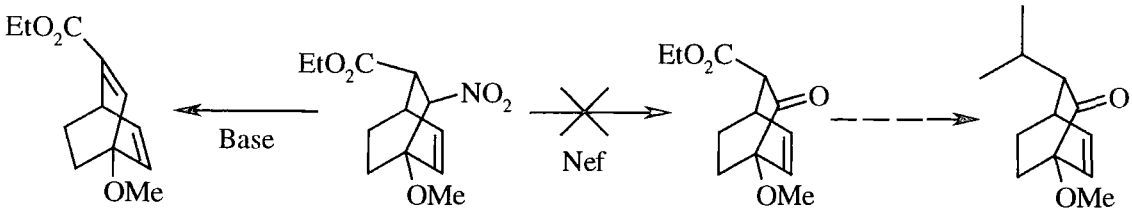
No attempt was made to optimise this particular conversion and our attention was then focused on applying this methodology to the core structure of vinigrol **1**, in particular, to the formation of ketone **273**.

The first goal was the synthesis of multi-gram quantities of the *endo*-nitro bicyclic compound **150**. Following the literature procedure for the Birch reduction of anisole by Zimmerman and Wang[92] moderate yields of diene **115** were obtained along with a significant amount of inseparable impurities (Scheme 97). In a change to the literature procedure, the reaction was allowed to stir for 3 hr as opposed to 15 min, before the addition of the proton source (EtOH) to give a 91% yield of the desired 1,4-diene with no trace of the inseparable impurities. Using the procedure developed in section 2.4.3, the Diels-Alder reaction between diene **115** and nitroacrylate **132** was performed on a 10g scale to give the desired *endo*-isomer **150** in 55% yield accompanied by a small amount (3%) of the *exo*-isomer.



Scheme 97

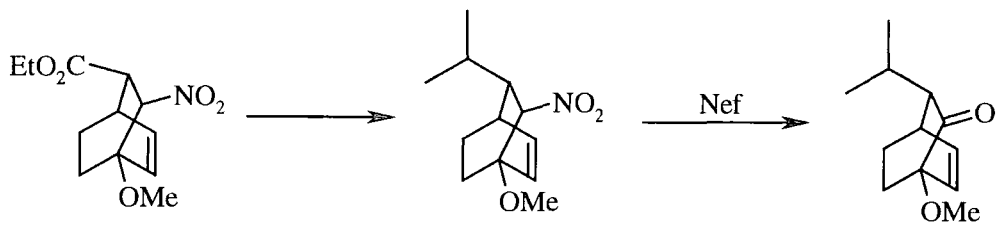
With large quantities of the bicyclic structure in hand, we explored the generation of the ketone **273**. Our initial strategy focussed on the Nef procedure described above to give the β-keto ester **285**. However this procedure and all base-mediated reactions to form the intermediate nitronate species resulted in the formation of α,β-unsaturated ester **284** (Scheme 98).



284 **150** **285** **273**

Scheme 98

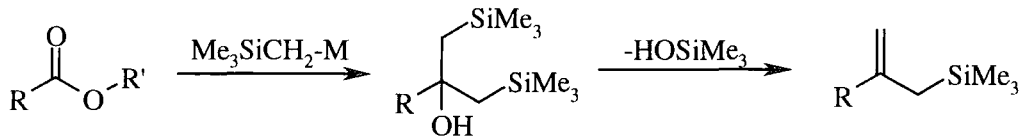
Another approach was to first convert the ester group into an isopropyl group, thus reducing the acidity of the hydrogen β to the nitro group. A subsequent Nef reaction on the nitro group would then give access to ketone **273** (Scheme 99).



150 **277** **273**

Scheme 99

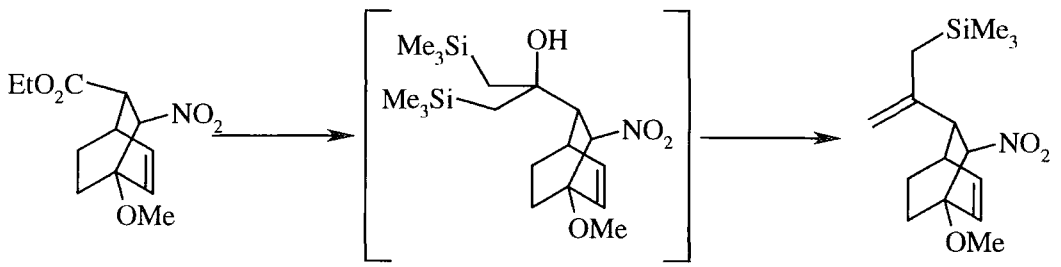
A number of literature reports[93] describe the conversion of an ester into an allylsilane by the addition of trimethylsilylmethylmagnesium chloride *via* the corresponding tertiary alcohol (Scheme 100). Subsequent treatment of this intermediate with acid promotes a Peterson olefination reaction to give the corresponding allylsilane. We envisaged the treatment of a corresponding allylsilane with strong acid followed by selective reduction of the olefin to give the desired isopropyl group.



Scheme 100

Initial attempts using to form alcohol **286** following literature procedures[93] gave extensive decomposition to the α,β-unsaturated ester **284**, presumably due to the

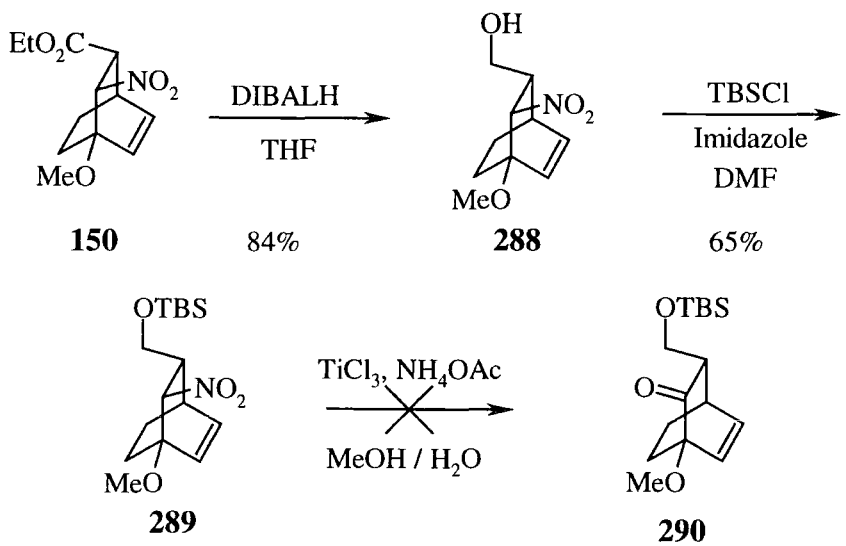
Grignard reagent acting as a base to eliminate HNO_2 (Scheme 101). Attempts to convert the Grignard reagent to the less basic organocerium equivalent[94] gave a complex mixture of products.



150 **286** **287**

Scheme 101

At this stage we chose to follow the methodology developed in the model system using the corresponding TBS ether, opposed to the ester, to reduce the possibility of the elimination of the nitro group. Ester **150** was reduced using 3.5 equivalents of DIBALH to give alcohol **288** in 84% yield (Scheme 102). Alcohol **288** was characterised by the loss of the carbonyl stretch in the infrared and a new peak in the NMR that corresponding to the new methylene at 3.8 ppm. Subsequent TBS protection of the alcohol was achieved using TBSCl / imidazole to give the TBS ether **289** in 65% yield.



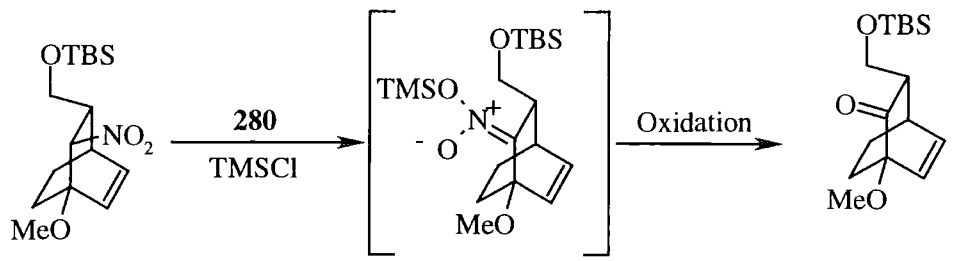
150 84% **288** 65%

289 **290**

Scheme 102

Under conditions identical to those in the model study, nitro compound **289** did not undergo the Nef reaction to ketone **290**. Alternative procedures for the Nef reaction were attempted including sodium chlorite,[95] tin (II) chloride,[96] VO(acac)[97] and ceric ammonium nitrate[98] but starting material was recovered in every case. We postulated that Nef reaction fails at the nitronate formation step due to the strain involved in the formation of an sp^2 centre at C-3 in the rigid bicyclic ring system of **150**.

Our attention then focused on the formation and trapping of the nitronate intermediate as the corresponding silyl nitronate species (Scheme 103). Silyl nitronate **291** was formed *in-situ* using a procedure based on the report by Palomo *et al.*[99] which involved treatment of nitro compound **289** with 2-*tert*-butyl-1,1,3,3-tetramethylguanidine **280** and TMSCl with a catalytic amount of potassium iodide. Following literature procedures to convert silylnitronate **291** into ketone **290** including oxidation by oxone, *m*CPBA[99] or ceric ammonium nitrate[100] gave only recovered starting materials.



289 **291** **290**

Scheme 103

In order to confirm that the silyl nitronate **291** was formed CD_3OD was added to quench the reaction and 70% deuterium incorporation was measured by ^{1}H-NMR. This result suggested that the addition of an electrophile to a pre-formed nitronate species was a possible alternative strategy toward the synthesis of vinigrol.

4.4.2 Nitronate Alkylations

4.4.2.1 Introduction

In a parallel approach, an alternative strategy was investigated for the synthesis of vinigrol **1** using a nitronate alkylation strategy. In this approach we envisaged alkylation of nitronate intermediate **292**, thus producing an sp^2 centre at C-3 which may allow an *endo*-approach of a suitable electrophile (Figure 32).

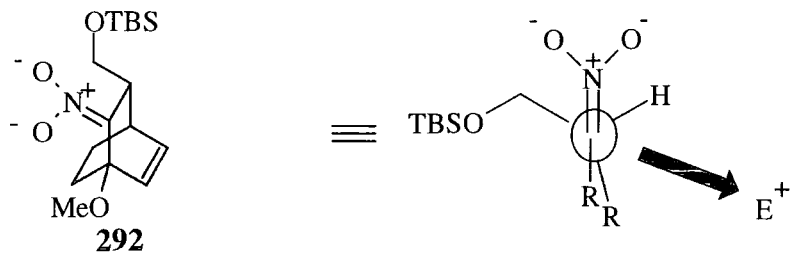
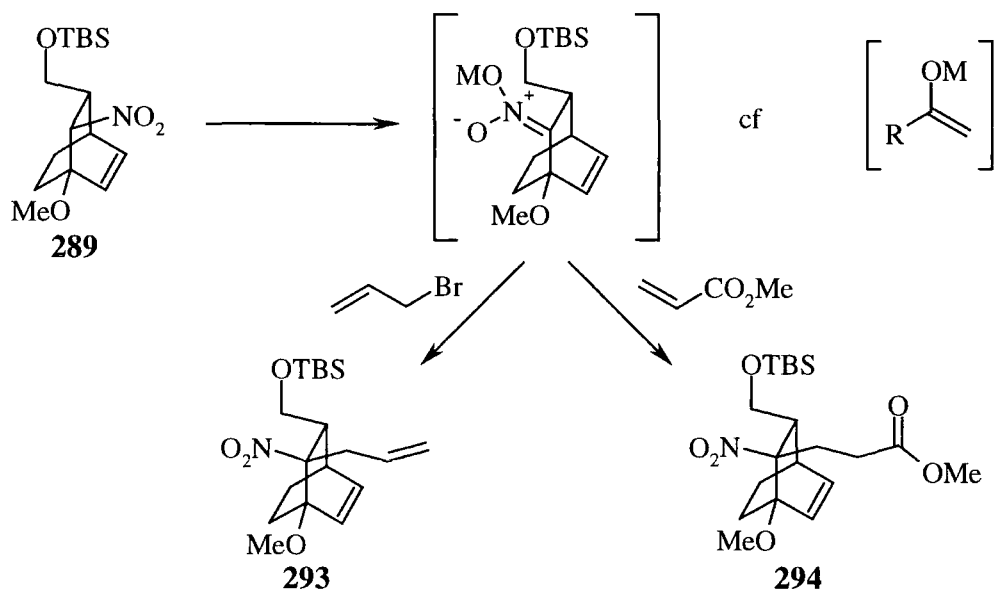


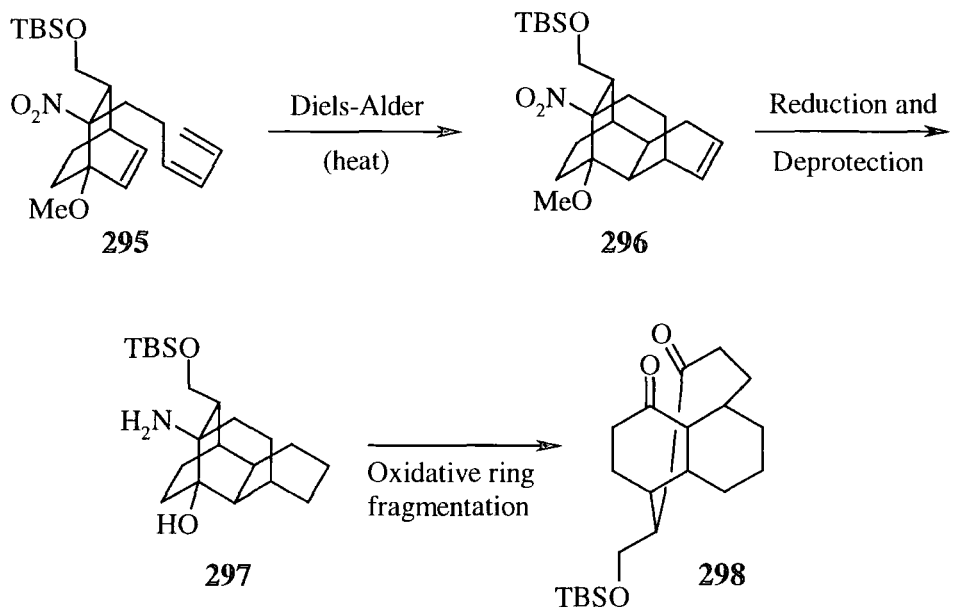
Figure 32

Using this methodology we envisaged alkylation with allyl bromide or Michael addition using various acrylates (Scheme 104). Nitronates are comparable to enolates and have been reported mostly in their reactions with aldehydes (Henry reaction). However, reports have shown nitronates reacting in Michael reactions.[68,101]



Scheme 104

To incorporate this methodology into the synthesis of vinigrol, the envisaged route would include homologation of the alkyl side chain of **293** or **294** into the relevant diene **295**. Subsequent intramolecular Diels-Alder reaction to give **296** followed by reduction of the nitro group and removal of the methyl ether would give amino alcohol **297** (Scheme 105). Oxidative cleavage would then produce diketone **298** with the vinigrol ring structure.

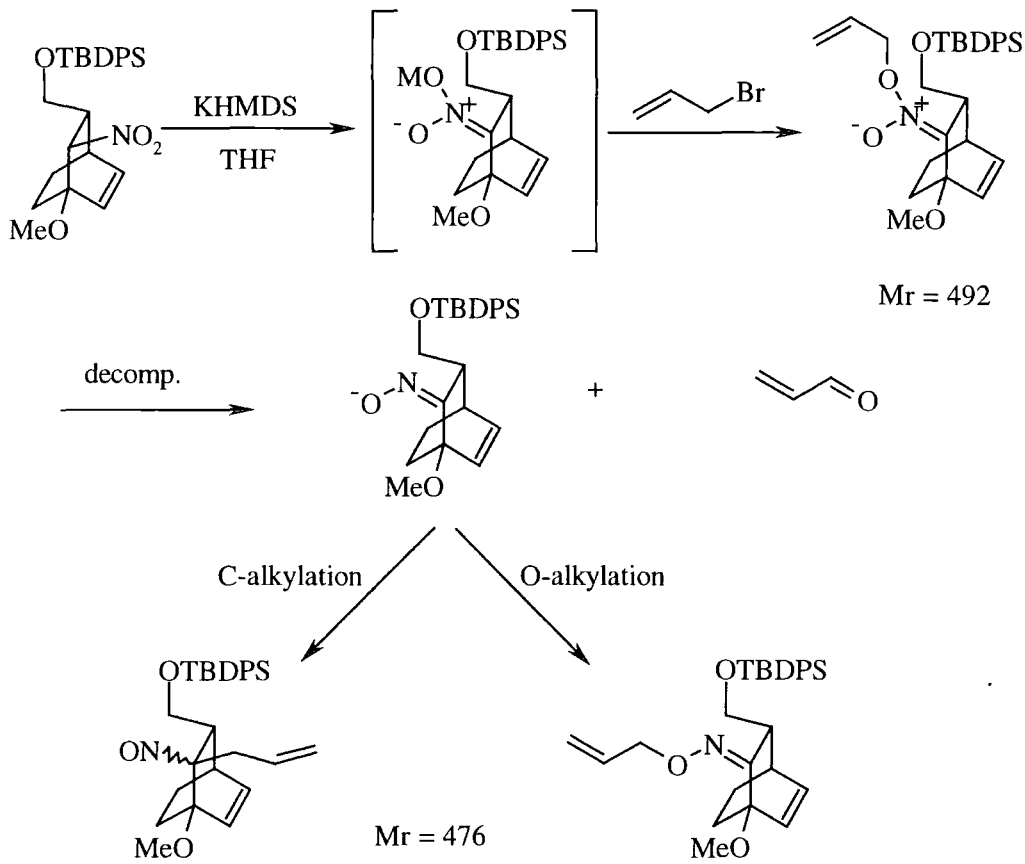


Scheme 105

4.4.2.2 Alkylation Studies

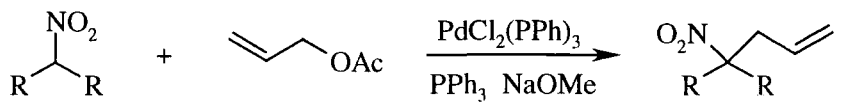
Initially, formation of the nitronate species **292** and alkylation with allyl bromide to give **293** was studied (Scheme 104). Using bases such as sodium methoxide / sodium hydride to form the intermediate nitronate, then alkylation with allyl bromide gave no reaction. Subsequent deuterium studies using CD_3OD showed that no deprotonation had occurred during the reaction. Using stronger basic conditions of KHMDS at reflux in THF for 2 hr followed by the addition of 5 equivalents of allyl bromide gave an intractable mixture of products corresponding to a mass of 476. One possible pathway for the reaction is the formation of substituted hydroxylamines resulting *via*

O-alkylation of the nitronate followed by decomposition to give acrolein and a hydroxylamine, which then undergoes further alkylation with the excess allyl bromide (Scheme 106).



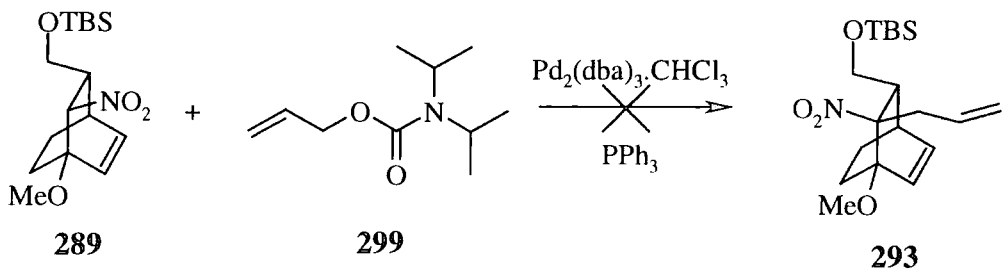
Scheme 106

The propensity of allyl bromide toward O-alkylation can be rationalised by the hard nature of the electrophile undergoing alkylation by the hard oxygen centre. A number of groups including Wade *et al.*[102] have shown how this aspect of the alkylation of nitronates can be avoided using a palladium-based alkylation strategy (Scheme 107).



Scheme 107

Using the literature conditions no reaction was observed and starting materials were recovered. Attempts to modify the procedure by using carbamate **299**, which acts as the allyl moiety for the π-allyl palladium complex and releases disopropylamide as a strong base,[103] also gave only recovered starting materials (Scheme 108).

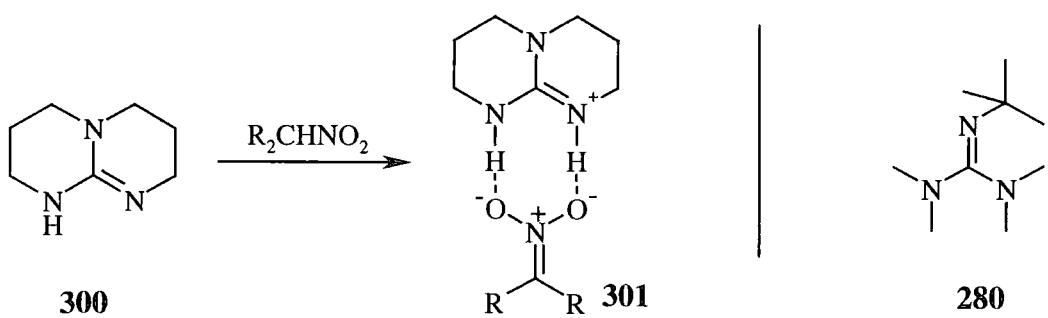


289 **299** **293**

Scheme 108

4.4.2.3 Michael Addition Reactions

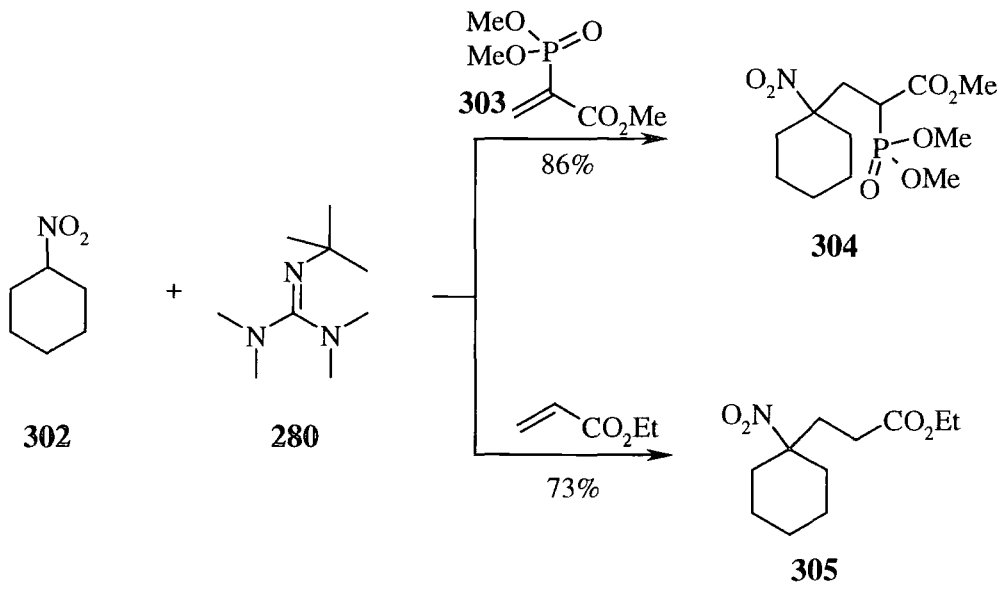
Using the Michael reaction, we anticipated that the soft nature of the electrophile could be exploited to react at the softer carbon centre. We studied the use of a number of guanidine bases in a model study with nitrocyclohexane including 2-*tert*-butyl-1,1,3,3-tetramethylguanidine **280** and the cyclic amidine **300**, which is reported[104] to be more reactive toward nitro groups due to its ability to form a hydrogen bonding complex **301** (Scheme 109).



300 **301** **280**

Scheme 109

In the model study nitrocyclohexane and 2-*tert*-butyl-1,1,3,3-tetramethylguanidine **280** were stirred at room temperature with either ethyl acrylate or acrylate **303** to give clean conversions into **305** and **304** respectively (Scheme 110).



Scheme 110

Unfortunately, due to time constraints we were unable to apply this methodology to bicyclic nitro compound **289**.

4.5 Conclusions and Future Work

In this chapter we have demonstrated the first use of nitroacrylates as substituted ketene equivalents to give cyclic ketones. This methodology was not applicable to the synthesis of bicyclic ketones relevant to the synthesis of vinigrol **1**. We speculate that this is due to the increase in strain that the introduction of a new sp^2 centre into the molecule. Attempts to use an alkylation reaction using allyl bromide gave products possibly resulting from O-alkylation. An initial model study into the use of a Michael addition strategy was successful and future work should focus on applying this methodology to the synthesis of vinigrol.

SECTION C: Experimental

Chapter 5: Experimental.

5.1 Introduction

All reactions were undertaken under an inert atmosphere of dry nitrogen or argon in pre-dried glassware. All solvents were distilled (dried) prior to use by standard procedures.

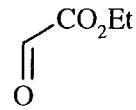
Nuclear magnetic resonance (NMR) spectra were obtained on a Varian Mercury 200 (^{1}H at 199.975 MHz, ^{13}C at 50.289 MHz), Varian Oxford Unity 300 (^{1}H at 299.908 MHz, ^{13}C at 75.412 MHz) or Varian Inova 500 (^{1}H at 499.779 MHz, ^{13}C at 125.669 MHz) spectrometers with $CDCl_3$ as the solvent (δ=7.26 for ^{1}H and 77.2 for ^{13}C) unless otherwise stated and are recorded in ppm (δ units) downfield of tetramethylsilane (δ=0). Splitting patterns are described as singlet (s), doublet (d), triplet (t), quartet (q) or multiplet (m). Coupling constants are given in Hz. All ^{13}C spectra were proton decoupled.

Infra Red (IR) spectra were recorded on a Perkin Elmer FT-IR 1720X spectrometer, in a liquid film (NaCl plates) or on the above machine fitted with a Graseby Specac Single Reflection Diamond ATR (10500 series) "Golden Gate" accessory, as specified in the text.

Low resolution mass spectra (EI, CI or ES) were recorded on a VG Analytical 7070E organic mass spectrometer, or a Micromass Autospec mass spectrometer. Gas chromatography – mass spectra (GC-MS) were recorded using a Hewlett Packard 5890 Series II gas chromatograph equipped with a 25m SE30 column connected to a VG mass lab trio 1000.

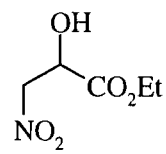
Flash chromatography was performed using Kieselgel 300-400 mesh silica, using $KMnO_4$ to develop TLC plates, when not visible by UV. Gas chromatography was recorded using a Hewlett Packard 5890 or 5890 series II gas chromatograph. Melting points were determined using GallenKamp melting point apparatus and are uncorrected.

5.2 Experimental details



Preparation of ethyl glyoxylate (130).[44]

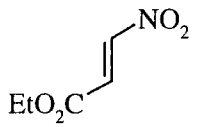
Ozone was bubbled through a solution of diethyl fumarate (40 g, 230 mmol) in CH_2Cl_2 (400 cm^3) at –78 °C for 5 hr. The solution was purged with oxygen to remove the excess ozone from solution. Dimethyl sulphide (54.1 g, 1.15mol) was added and the solution was allowed to warm to 25 °C over 14 hr. The solution was evaporated under reduced pressure and vacuum distilled (bp 54 °C at 35 mbar), [lit. 40-45 °C at 29 mbar] to yield 39.5 g of the desired glyoxylate as a colourless oil. The distilled material was found to polymerise on standing so it was used directly in the next step. δ_H (200 MHz): 1.39 (3H, t, J=7 Hz, OCH_2CH_3), 4.38 (2H, q, J=7 Hz, OCH_2CH_3), 9.40 (1H, s, CHO).



Preparation of ethyl 2-hydroxy-3-nitropropionate (131).

To a crude solution of ethyl glyoxylate **130** (39.5 g, 387 mmol) in nitromethane (70 cm^3) was added Al_2O_3 (Brockmann grade II, 60 g) and the mixture was stirred at 25 °C for 36 hr. The mixture was filtered, evaporated under reduced pressure and the residue was purified by column chromatography eluting with 30-60% EtOAc in petroleum ether to yield 19.6 g (31%) of the desired alcohol as a crystalline white solid (mp 43 °C). (Found : C, 36.84%; H, 5.59%; N, 8.34%, $C_5H_9NO_5$ requires C, 36.81%; H, 5.56%; N, 8.59%), δ_H (300 MHz): 1.34 (3H, t, J=7 Hz, OCH_2CH_3), 3.30 (1H, d, J=5 Hz, CHOH), 4.36 (2H, m, OCH_2CH_3), 4.62 (1H, dt, J=5 and 4 Hz, 2-H), 4.77 (2H, d, J=4 Hz, 3-H_2). δ_C (50.3 MHz): 14.2 (OCH_2CH_3), 63.2 (OCH_2CH_3), 67.7

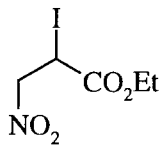
(2-*C*), 77.0 (3-*C*), 170.8 (*C*O_2Et), *m/z* (ES^+) 186 (MNa^+), υ_{max} (KBr disc) 3478 (OH), 1744 (C=O), 1562 (NO_2), 1421, 1378, 1224, 1124, 1048, 1016, 861 and 845 cm^{-1}.



Preparation of ethyl *E*-3-nitropropionate (132).[5]

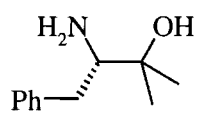
Method A : To a solution of nitroalcohol **131** (2.0 g, 12.2 mmol) in Et_2O (100 cm^3) at 0 °C was added MsCl (7.0 g, 61.2 mmol). The reaction mixture was stirred for 2 min, followed by dropwise addition of a solution of $^iPr_2NEt$ (3.5 g, 26.9 mmol) in Et_2O (5 cm^3). The reaction mixture was stirred at 0 °C for 5 min. The suspension was immediately extracted with cooled (0 °C) 1M HCl solution (50 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by chromatography eluting with 10% Et_2O in petroleum ether to yield 1.3 g (73%) of the desired nitroacrylate as a crystalline yellow solid.

Method B : To a solution of iodo ester **134** (25 g, 91.6 mmol) in Et_2O (1.2L) at 0 °C was added a solution of $^iPr_2NEt$ (13.0 g, 100 mmol) in Et_2O (40 cm^3) dropwise over 20 min. The resultant suspension was immediately passed through two separate 150 g plugs of silica and flushed with 10% Et_2O in petroleum ether (200 cm^3). The solution was evaporated under reduced pressure and the residue was purified by column chromatography eluting with 10% Et_2O in petroleum ether to yield 11.2 g (84%) of the desired nitroacrylate as a crystalline yellow solid (mp = 26 °C). δ_H (300 MHz): 1.35 (3H, t, J=7 Hz, OCH_2CH_3), 4.32 (2H, q, J=7 Hz, OCH_2CH_3), 7.09 (1H, d, J=13 Hz, 2-*H*), 7.68 (1H, d, J=13 Hz, 3-*H*), δ_C (75.4 MHz): 14.2 (OCH_2CH_3), 62.6 (OCH_2CH_3), 127.8 (2-*C*), 149.1 (3-*C*), 162.7 (*C*O_2Et), υ_{max} (neat) 1731 (C=O), 1658, 1645, 1537 (NO_2), 1468, 1447, 1256, 1302, 1172, 1096, 1033, 950, 859, 763 and 676 cm^{-1}.



Preparation of ethyl 2-iodo-3-nitropropionate (134).[5]

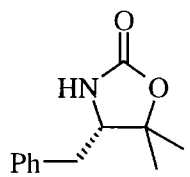
To a mixture of ethyl acrylate (41 g, 410 mmol) and iodine (31 g, 122 mmol) in Et_2O (400 cm^3) at 0 °C was added N_2O_4 (9.5 cm^3, 166 mmol). The reaction mixture was stirred at 0 °C for 1 hr and then at 25 °C for 4 hr. The resultant mixture was washed with saturated $Na_2S_2O_3$ solution (6x 300 cm^3). The combined aqueous layers were re-extracted with Et_2O (200 cm^3). The organic layers were combined, dried ($MgSO_4$) and evaporated under reduced pressure. Excess ethyl acrylate was removed under high vacuum to yield 30.3 g (91%) as a yellow oil. δ_H (300 MHz): 1.31 (3H, t, J=7 Hz, OCH_2CH_3), 4.28 (2H, m, OCH_2CH_3), 4.67 (1H, dd, J=15 and 4 Hz, 2-*H*), 4.88 (1H, dd, J=11 and 4 Hz, 3-*H*), 5.10 (1H, dd, J=15 and 11 Hz, 3-*H*), δ_C (50.3 MHz): 8.3 (2-*C*), 13.9 (OCH_2CH_3), 63.1 (OCH_2CH_3), 77.1 (CH_2NO_2), 168.8 (CO_2Et), *m/z* (CI^+) 291 (MNa^+), υ_{max} (neat) 2983, 1733 (C=O), 1560 (NO_2), 1374, 1247, 1196, 1119, 1019 and 856 cm^{-1}.



Preparation of 3-amino-2-methyl-4-phenyl-butan-2-ol (139).[48]

A solution of HCl salt **137** (1.0 g, 4.65 mmol) in water (15 cm^3) was adjusted to pH=8 by the addition of saturated $NaHCO_3$ solution. EtOAc (30 cm^3) was added and the organic layer was separated, dried ($MgSO_4$) and evaporated under reduced pressure to give 0.43 g (2.4 mmol) of the free amine. The amine was dissolved in Et_2O (50 cm^3) and added to MeMgBr (3M in Et_2O, 17.6 cm^3, 53 mmol). The reaction mixture was stirred at reflux for 1 hr and then quenched by the addition of saturated NH_4Cl solution

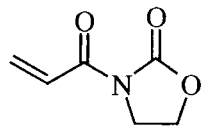
(30 cm^3). The residue was partitioned between EtOAc (50 cm^3) and water (30 cm^3). The organic layer was separated, dried ($MgSO_4$) and evaporated under reduced pressure to give 0.36 g (84%) of the desired amino alcohol as a light brown oil. δ_H (300 MHz): 1.20-1.34 (6H, m, $C(CH_3)_2$), 2.27 (1H, dd, J=13.5 and 11.5 Hz, $CHCH_2Ph$), 2.80 (1H, dd, J=11.5 and 3 Hz, $CHCH_2Ph$), 3.03 (1H, dd, J=13.5 and 3 Hz, $CHCH_2Ph$), 7.17-7.36 (5H, m, Ph), δ_C (75.4 MHz): 24.1 and 27.4 ($C(CH_3)_2$), 39.4 ($CHCH_2Ph$), 61.7 ($CHNH_2$), 71.6 ($C(CH_3)_2$), 126.6, 128.8, 129.3 and 140.0 (Ph), υ_{max} (neat) 3364 (OH), 1658, 1602, 1494, 1453, 1381, 1366, 1159, 1076, 1031, 960, 735 and 699 cm^{-1}.



Preparation of (*S*)-4-benzyl-5,5-dimethyl-oxazolidin-2-one (140).[48]

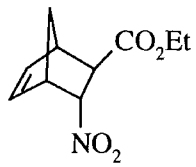
To a solution of amino alcohol **139** (0.36 g, 2.0 mmol) in THF (15 cm^3) was added CDI (0.36 g, 2.2 mmol) and the mixture was stirred at 25 °C for 8 hr. The mixture was partitioned between EtOAc (50 cm^3) and water (30 cm^3). The organic layer was separated, washed with brine, dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by chromatography eluting with 80% Et_2O in petroleum ether to give 0.25 g (61%) of the desired oxazolidinone as a crystalline white solid (mp 66 °C). (Found : C, 70.22%; H, 7.41%; N, 6.86%, $C_{12}H_{15}NO_2$ requires C, 70.22%; H, 7.37%; N, 6.82%), δ_H (300 MHz): 1.46 and 1.49 (6H, m, $C(CH_3)_2$), 2.67 (1H, dd, J=13 and 11 Hz, $CHCH_2Ph$), 2.84 (1H, dd, J=13 and 3 Hz, $CHCH_2Ph$), 3.68 (1H, dd, J=11 and 3 Hz, $CHCH_2Ph$), 4.78 (1H, br s, NH), 7.1-7.4 (5H, m, Ph), δ_C (50.3 MHz): 22.1 and 27.7 ($C(CH_3)_2$), 37.3 ($CHCH_2Ph$), 63.2 ($CHCH_2Ph$), 83.3 (CH_3CCH_3), 127.3, 129.0, 129.2 and 137.0 (Ph), 158.0 (CO_2Et), *m/z* (CI) 206 (MH^+), 223 (MNH_4^+),

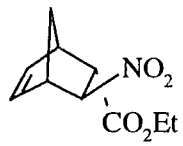
υ_{max} (Golden Gate) 3276 (NH), 1762 (C=O), 1495, 1454, 1380, 1301, 1189, 1143, 1096, 996, 883, 771 and 701 cm^{-1}.



Preparation of 3-acryloyl-oxazolidin-2-one (142).[106]

To a solution of oxazolidin-2-one (2.0 g, 23 mmol) in THF (50 cm^3) at –20 °C was added MeMgI (3.0M solution in THF, 7.7 cm^3, 23 mmol). The solution was stirred at –20 °C for 15 min followed by dropwise addition of acryloyl chloride (2.25 g, 25 mmol). The reaction mixture was stirred at –20 °C for 30 min and then at 0 °C for 15 min. The reaction was quenched by the addition of saturated NH_4Cl solution (5 cm^3). The resultant slurry was partitioned between Et_2O (100 cm^3) and saturated NH_4Cl solution (50 cm^3). The organic layer was washed with brine (20 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure to give 1.3 g (41%) of the desired acrylamide as a light yellow solid (mp 79 °C). (Found : C, 50.83%; H, 5.04%; N, 9.75%, $C_6H_7NO_3$ requires C, 51.07%; H, 5.00%; N, 9.92%), δ_H (200 MHz): 4.08 (2H, t, J=8 Hz, 5-*H*$_2$), 4.44 (2H, t, J=8 Hz, 4-*H*$_2$), 5.90 (1H, dd, J=10 and 2 Hz, 3'-*H*), 6.55 (1H, dd, J=17 and 2 Hz, 3'-*H*), 7.49 (1H, dd, J=17 and 10 Hz, 2'-*H*), δ_C (50.3 MHz): 42.8 (4-*C*), 62.3 (5-*C*), 127.2 (3'-*C*), 131.9 (2'-*C*), 153.5 (N*C*O$_2$R), 153.5 (*C*ONR$_2$), *m/z* (CI) 142 (MH^+), 159 (MNH_4^+), υ_{max} (Golden Gate) 1770 (NCO_2), 1676 (CONR), 1388, 1255, 1120, 1002, 748 and 691 cm^{-1}.





Preparation of ethyl *trans*-3-nitro-bicyclo[2.2.1]hept-5-ene-2-carboxylate (153 and 155)

To a solution of nitroacrylate **132** (0.1 g, 0.69 mmol) in CH_2Cl_2 (1 cm^3) at –50 °C was added a solution of cyclopentadiene (92 mg, 1.38 mmol) in CH_2Cl_2 (1 cm^3). The reaction mixture was stirred at –50 °C for 5 min. The resulting solution was evaporated under reduced pressure and the residue was purified by column chromatography eluting with 10% Et_2O in petroleum ether to yield 0.13 g (87%) of the title compound as a colourless oil (Endo : Exo ratio = 88 : 12).

Endo isomer (**153**): δ_H (300 MHz): 1.30 (3H, t, J=7 Hz, OCH_2CH_3), 1.50-1.80 (2H, m, 7-H_2), 3.04 and 3.23 (2H, br s, 1-*H* and 4-*H*), 3.61 (1H, m, 2-*H*), 4.21 (2H, q, J=7 Hz, OCH_2CH_3), 5.42 (1H, t, J=4 Hz, 3-*H*), 6.09 and 6.48 (2H, m, 5-*H* and 6-*H*), δ_C (75.4 MHz): 14.4 (OCH_2CH_3), 46.4, 47.5 and 47.9 (1-*C*, 4-*C* and 7-*C*), 49.2 (2-*C*), 61.8 (OCH_2CH_3), 87.8 (3-*C*), 133.7 and 139.5 (5-*C* and 6-*C*), 172.2 (CO_2Et).

Exo isomer (**155**): δ_H (300 MHz): 1.26 (3H, t, J=7 Hz, OCH_2CH_3), 1.50-1.80 (2H, m, 7-H_2), 3.34 and 3.49 (2H, br s, 1-*H* and 4-*H*), 3.70 (1H, m, 2-*H*), 4.14 (2H, q, J=7 Hz, OCH_2CH_3), 4.72 (1H, m, 3-*H*), 6.10-6.32 (2H, m, 5-*H* and 6-*H*), δ_C (75.4 MHz): 14.4 (OCH_2CH_3), 45.2, 47.2 and 50. 1 (1-*C*, 4-*C* and 7-*C*), 50.5 (2-*C*), 61.5 (OCH_2CH_3), 87.8 (3-*C*), 134.8 and 138.7 (5-*C* and 6-*C*), 171.7 (CO_2Et).

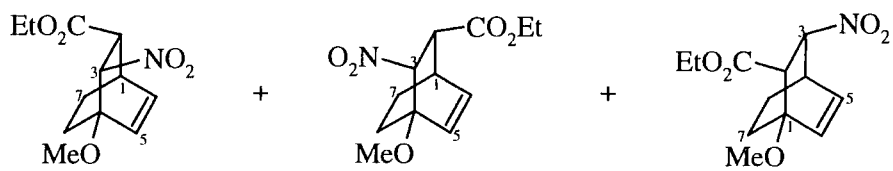
m/z (CI) 212 (MH^+) 165 ($M-HNO_2$), υ_{max} (neat) 1729 (C=O), 1542 (NO_2), 1376, 1265, 1251, 1032 and 703 cm^{-1}.

General procedures for the Diels-Alder reactions of nitroacrylate **132** with dienes **115**, **86**, **146-149** and **167-169**.

Method A : To a solution of nitroacrylate **132** (0.1 g, 0.69 mmol) in benzene (2 cm^3) was added the corresponding diene (1.38 mmol). The reaction mixture was stirred at 80 °C until GC analysis showed the reaction was complete. The resulting solution was evaporated under reduced pressure and the residue purified by chromatography eluting with 10% Et_2O in petroleum ether .

Method B : To a solution of nitroacrylate **132** (0.1 g, 0.69 mmol) in CH_2Cl_2 (2 cm^3) at 0 °C was added $ZnCl_2$ (0.1eq, 1M solution in Et_2O) followed by the corresponding diene (1.38 mmol). The reaction mixture was stirred at 0 °C until GC analysis showed the reaction was complete. The resulting solution was partitioned between CH_2Cl_2 (5 cm^3) and water (5 cm^3). The organic layer was separated, dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by chromatography eluting with 10% Et_2O in petroleum ether .

Method C : To a solution of nitroacrylate **132** (0.1 g, 0.69 mmol) in CH_2Cl_2 (2 cm^3) at 0 °C was added the corresponding diene (1.38 mmol). The reaction mixture was stirred at 0 °C until GC analysis showed the reaction was complete. The resulting solution was evaporated under reduced pressure and the residue was purified by chromatography eluting with 10% Et_2O in petroleum ether .



Reaction of 1-methoxy-cyclohexa-1,4-diene (115) with nitroacrylate (132) to give ethyl 4-methoxy-*trans*-3-nitro-bicyclo[2.2.2]oct-5-ene-2-carboxylate (150, 151 and 152)

Using *method A* the reaction mixture was stirred for 3 hr to yield 81 mg (46%, Ratio = 56 : 28 : 16). Using *method B* the reaction mixture was stirred for 14 hr to yield 0.1 g

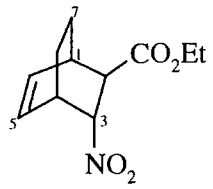
(60%, Ratio = 97 : 3 : 0). Using *method C* no reaction was observed by GC after 72 hr. The mixture of isomers was isolated as a colourless oil. (Found : C, 56.57%; H, 6.83%; N, 5.19%, $C_{12}H_{17}NO_5$ requires C, 56.46%; H, 6.71%; N, 5.49%).

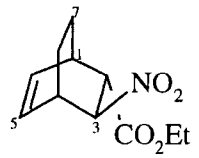
Endo isomer (**150**): δ_H (500 MHz) : 1.29 (3H, t, J=7 Hz, OCH_2CH_3), 1.35-2.04 (4H, m, 7-H_2 and 8-H_2), 3.05 (1H, m, 1-*H*), 3.15 (1H, ddd, J=5, 3 and 2 Hz, 2-*H*), 3.44 (3H, s, OCH_3), 4.21 (2H, q, J=7 Hz, OCH_2CH_3), 5.42 (1H, d, J=5 Hz, 3-*H*), 6.16 (1H, d, ^{3}J=8.5 Hz, 5-*H*), 6.45 (1H, dd, J=8.5 and 7 Hz, 6-*H*), δ_C (126 MHz) : 14.4 (OCH_2CH_3), 21.4 (7-*C*), 26.0 (8-*C*), 32.4 (1-*C*), 50.3 (2-*C*), 51.3 (OCH_3), 62.0 (OCH_2CH_3), 79.0 (4-*C*), 87.0 (3-*C*), 132.3 and 132.5 (5-*C* and 6-*C*), 171.1 (CO_2Et).

Exo isomer (**151**): δ_H (500 MHz): 1.25 (3H, t, J=7 Hz, OCH_2CH_3), 1.35-2.07 (4H, m, 7-H_2 and 8-H_2), 3.13 (1H, m, 1-*H*), 3.41 (1H, dd, J=5 and 3 Hz, 2-*H*), 3.50 (3H, s, OCH_3), 4.15 (2H, q, J=7 Hz, OCH_2CH_3), 5.14 (1H, dd, J=5 and 2 Hz, 3-*H*), 6.29 (1H, dd, J=8.5 and 6 Hz, 6-*H*), 6.36 (1H, d, J=8.5 Hz, 5-*H*), δ_C (126 MHz): 14.4 (OCH_2CH_3), 23.9 and 24.0 (7-*C* and 8-*C*), 31.9 (1-*C*), 48.6 (2-*C*), 51.8 (OCH_3), 62.0 (OCH_2CH_3), 79.7 (4-*C*), 86.4 (3-*C*), 131.6 and 133.5 (5-*C* and 6-*C*), 171.4 (CO_2Et).

Regioisomer (**152**): δ_H (500 MHz): 1.32 (3H, t, J=7 Hz, OCH_2CH_3), 1.35-2.08 (4H, m, 7-H_2 and 8-H_2), 3.39 (1H, m, 4-*H*), 3.46 (1H, dd, J=4 and 2 Hz, 2-*H*), 3.50 (3H, s, OCH_3), 4.21 (2H, q, J=7 Hz, OCH_2CH_3), 5.00 (1H, ddd, J=4, 3 and 0.5 Hz, 3-*H*), 6.18 (1H, ddd, J=8.5, 6 and 0.5 Hz, 6-*H*), 6.53 (1H, d, J=8.5 Hz, 5-*H*), δ_C (126 MHz): 14.4 (OCH_2CH_3), 21.8 (7-*C*), 25.2 (8-*C*), 33.8 (4-*C*), 49.1 (2-*C*), 51.8 (OCH_3), 62.0 (OCH_2CH_3), 79.4 (1-*C*), 86.9 (3-*C*), 129.6 and 135.1 (5-*C* and 6-*C*), 171.1 (CO_2Et).

m/z (CI) 256 (MH^+), υ_{max} (neat) 1731 (C=O), 1555 (NO_2), 1464, 1375, 1277, 1200 and 1037 cm^{-1}.





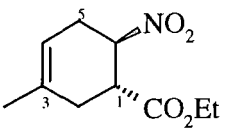
Reaction of cyclohexa-1,3-diene (146) with nitroacrylate (132) to give ethyl *trans*-3-nitro-bicyclo[2.2.2]oct-5-ene-2-carboxylate (154 and 156).

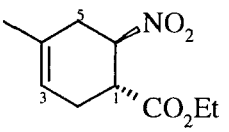
Using *method A* the reaction mixture was stirred for 4.5 hr to yield 99 mg (64%, Endo : Exo ratio = 82 : 18). Using *method B* the reaction mixture was stirred for 144 hr to yield 103 mg (67%, Endo : Exo ratio = 90 : 10). Using *method C* GC showed 84% reaction after 144 hr (Endo : Exo ratio = 89 : 11). The mixture of isomers was isolated as a colourless oil.

Endo isomer (**154**): δ_H (300 MHz): 1.30 (3H, t, J=7 Hz, OCH_2CH_3), 1.30-1.70 (4H, m, 7-H_2 and 8-H_2), 3.10 (1H, m, 1-*H*), 3.24 (1H, m, 4-*H*), 3.47 (1H, m, 2-*H*), 4.23 (2H, q, J=7 Hz, OCH_2CH_3), 5.09 (1H, dd, J=4 and 3 Hz, 3-*H*), 6.14 (1H, t, J=7 Hz, 6-*H*), 6.43 (1H, t, J=7 Hz, 5-*H*), δ_C (75.4 MHz): 14.4 (OCH_2CH_3), 19.9 (7-*C*), 22.2 (8-*C*), 32.8 (4-*C*), 34.3 (1-*C*), 48.0 (2-*C*), 61.7 (OCH_2CH_3), 85.6 (3-*C*), 130.4 (6-*C*), 135.2 (5-*C*), 171.9 (CO_2Et).

Exo isomer (**156**): δ_H (300 MHz): 1.30 (3H, t, J=7 Hz, OCH_2CH_3), 1.30-1.70 (4H, m, 7-H_2 and 8-H_2), 3.18 (1H, m, 1-*H*), 3.38 (1H, m, 4-*H*), 3.50 (1H, m, 2-*H*), 4.23 (2H, q, J=7 Hz, OCH_2CH_3), 4.85 (1H, ddd, J=4, 3 and 3 Hz, 3-*H*), 6.25 (2H, m, 5-*H* and 6-*H*), δ_C (75.4 MHz): 14.4 (OCH_2CH_3), 18.8 (7-*C*), 24.1 (8-*C*), 32.4 (4-*C*), 35.3 (1-*C*), 46.6 (2-*C*), 61.6 (OCH_2CH_3), 86.5 (3-*C*), 131.4 (6-*C*), 134.6 (5-*C*), 171.9 (CO_2Et).

m/z (CI) 226 (MH^+), 179 (M-HNO_2), υ_{max} (neat) 1731 (C=O), 1547 (NO_2), 1465, 1379 1281, 1195 and 1032 cm^{-1}.





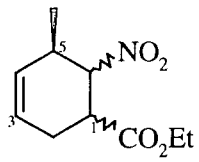
Reaction of 2-methylbutadiene (147) with nitroacrylate (132) to give ethyl 3-methyl-*trans*-6-nitrocyclohex-3-enecarboxylate (157) and ethyl 4-methyl-*trans*-6-nitrocyclohex-3-enecarboxylate (158).

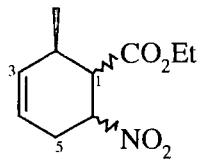
Using *method A* the reaction mixture was stirred for 4 hr to yield 90 mg (61%, regioisomer ratio = 56 : 44). Using *method B* the reaction mixture was stirred for 48 hr to yield 85 mg (58%, regioisomer ratio = 55 : 45). Using *method C,* GC showed 95% reaction after 48 hr (regioisomer ratio = 59 : 41). The mixture of isomers was isolated as a colourless oil.

Major isomer (**157**): δ_H (500 MHz): 1.26 (3H, t, J=7 Hz, OCH_2CH_3), 1.70 (3H, br s, CH_3), 2.20-2.85 (4H, m, 2-H_2 and 5-H_2), 3.29 (1H, ddd, J=11, 11 and 6.5 Hz, 1-*H*), 4.18 (1H, q, J=7 Hz, OCH_2CH_3), 4.86 (1H, ddd, J=11, 11 and 6 Hz, 6-*H*), 5.36 (1H, m, 4-*H*), δ_C (126 MHz): 14.2 (OCH_2CH_3), 22.7 (CH_3), 30.6 and 32.5 (2-*C* and 5-*C*), 43.2 (1-*C*), 61.5 (OCH_2CH_3), 82.3 (6-*C*), 117.2 (3-*C*), 132.9 (4-*C*), 172.3 (CO_2Et).

Minor isomer (**158**): δ_H (500 MHz): 1.25 (3H, t, J=7 Hz, OCH_2CH_3), 1.72 (3H, s, CH_3), 2.20-2.85 (4H, m, 2-H_2 and 5-H_2), 3.19 (1H, ddd, J=11, 11 and 6.5 Hz, 1-*H*), 4.17 (1H, q, J=7 Hz, OCH_2CH_3), 4.92 (1H, ddd, J=11, 11 and 6 Hz, 6-*H*), 5.41 (1H, m, 3-*H*), δ_C (126 MHz): 14.2 (OCH_2CH_3), 22.7 (CH_3), 27.9 and 34.9 (2-*C* and 5-*C*), 42.6 (1-*C*), 61.5 (OCH_2CH_3), 82.6 (6-*C*), 119.2 (3-*C*), 130.9 (4-*C*), 172.3 (CO_2Et).

m/z (EI) 214 (MH^+), 167 ($M-HNO_2$), υ_{max} (neat) 1735 (C=O), 1555 (NO_2), 1446, 1379, 1309, 1228, 1186 and 1032 cm^{-1}.

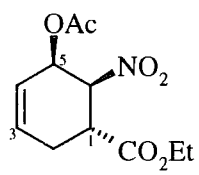




Reaction of *trans*-1-methylbuta-1,3-diene (148) with nitroacrylate (132) to give ethyl 5-methyl-*trans*-6-nitrocyclohex-3-enecarboxylate (159 and 160) and ethyl 2-methyl-*trans*-6-nitrocyclohex-3-enecarboxylate (161 and 162).

Using *method A* the reaction mixture was stirred for 4 hr to yield 90 mg (61%, Ratio = 38 : 33 : 17 : 12). Using *method B* the reaction mixture was stirred for 60 hr to yield 97 mg (66%, Ratio = 39 : 34 : 16 : 11). Using *method C* GC showed 94% reaction after 60 hr and 100% after 72 hr (Ratio = 40 : 34 : 14 : 12) . The mixture of isomers was isolated as a colourless oil.

All 4 isomers (**159-162**): δ_H (500 MHz): 0.94-1.17 (3H, m, C*H*$_3$), 1.22-1.28 (3H, m, OCH$_2$C*H*$_3$), 2.15-3.10 (3H, m, C*H*CH$_3$ and C*H*$_2$), 3.28 (1H, m, 1-*H*), 4.07-4.15 (2H, m, OC*H*$_2$CH$_3$), 4.50-5.00 (1H, m, 6-*H*), 5.4-5.7 (2H, m, 3-*H* and 4-*H*), δ_C (75.4 MHz): 14.2 (OCH$_2$*C*H$_3$), 15.9-19.7 (*C*H$_3$), 28.5-31.7 (*C*H$_2$), 32.4-36.3 (*C*HCH$_3$), 38.3-50.9 (1-*C*), 61.4 (O*C*H$_2$CH$_3$) 83.2-90.0 (6-*C*), 121.4-132.3 (3-*C* and 4-*C*), 172.0-173.0 (*C*O$_2$Et), *m/z* (EI) 214 (MH$^+$), 167 (M-HNO$_2$), υ_{max} (neat) 1735 (C=O), 1553 (NO$_2$), 1444, 1379, 1294, 1262, 1245, 1186 and 1019 cm^{-1}.

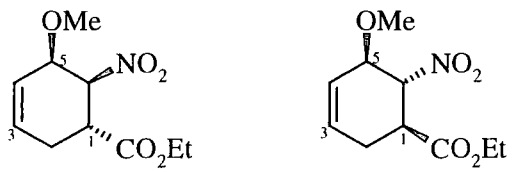


Reaction of *trans*-1-acetoxybutadiene (149) with nitroacrylate (132) to give ethyl 5-acetoxy-*trans*-6-nitro-cyclohex-3-enecarboxylate (163).[55]

Using *method A* the reaction mixture was stirred for 7 hr to yield 105 mg (59% - ratio **163** = 74%). Using *method B* the reaction mixture was stirred for 144 hr to yield 117

mg (66% - ratio **163** = 84%). Using *method C* the reaction mixture was stirred for 144 hr to give 40% reaction (ratio **163** = 76%).

Major isomer (**163**): δ_H (500 MHz): 1.28 (3H, t, J=7 Hz, OCH_2CH_3), 2.01 (3H, s, OAc), 2.24-2.81 (2H, m, *H*$_2$), 3.47 (1H, ddd, J=12, 12 and 6 Hz, 1-*H*), 4.22 (2H, m, OCH_2CH_3), 4.95 (1H, dd, J=12 and 5 Hz, 6-*H*), 5.80 (1H, m, 5-*H*), 6.02 (2H, m, 3-*H* and 4-*H*), δ_C (75.4 MHz): 14.3 (OCH_2CH_3), 20.9 ($OCOCH_3$), 29.2 (2-*C*), 38.2 (1-*C*), 61.8 (OCH_2CH_3), 66.0 (5-*C*), 83.5 (6-*C*), 122.8 and 131.4 (3-*C* and 4-*C*), 169.6 ($OCOCH_3$), 172.6 (CO_2Et), *m/z* (CI) 275 (MNH_4^+), υ_{max} (neat) 1745 (C=O), 1557 (NO_2), 1438, 1374, 1331, 1305, 1229, 1189, 1120, 1093, 1026, 949, 911, 861 and 702 cm^{-1}.



Reaction of 1-methoxybutadiene (167) with nitroacrylate (132) to give ethyl 5-methoxy-*trans*-6-nitro-cyclohex-3-enecarboxylate (171 and 173).

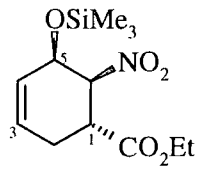
Using *method A* the reaction mixture was stirred for 2.5 hr to yield 140 mg (89%, Endo : Exo ratio = 61 : 39). Using *method B* the reaction mixture was stirred for 48 hr GC showed 10% reaction. The mixture of isomers was isolated as a white solid.

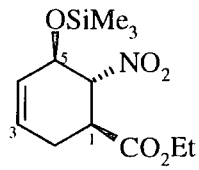
Endo isomer (**171**): δ_H (300 MHz): 1.27 (3H, t, J=7 Hz, OCH_2CH_3), 2.11-2.80 (2H, m, 2-*H*$_2$), 3.35 (3H, s, OCH_3), 3.38 (1H, m, 1-*H*), 4.20 (2H, m, OCH_2CH_3), 4.37 (1H, m, 5-*H*), 4.82 (1H, dd, J=12 and 5 Hz, 6-*H*), 5.7-6.1 (2H, m, 3-*H* and 4-*H*), δ_C (75.4 MHz): 14.2 (OCH_2CH_3), 29.3 (2-*C*), 37.7 (1-*C*), 57.7 (OCH_3), 61.5 (OCH_2CH_3), 72.7 (5-*C*), 84.9 (6-*C*), 123.5 and 130.1 (3-*C* and 4-*C*), 173.1 (CO_2Et).

Exo isomer (**173**): δ_H (300 MHz): 1.24 (3H, t, J=7 Hz, OCH_2CH_3), 2.10-2.88 (2H, m, 2-*H*$_2$), 3.28 (1H, m, 1-*H*), 3.39 (3H, s, OCH_3), 4.20 (2H, m, OCH_2CH_3), 4.43 (1H, m, 5-*H*), 4.83 (1H, dd, J=12 and 9 Hz, 6-*H*), 5.72-6.18 (2H, m, 3-*H* and 4-*H*), δ_C (75.4

MHz): 14.0 (OCH_2CH_3), 28.3 (2-*C*), 42.8 (1-*C*), 56.3 (OCH_3), 61.8 (OCH_2CH_3), 78.3 (5-*C*), 86.4 (6-*C*), 125.4 and 127.2 (3-*C* and 4-*C*), 170.7 (CO_2Et).

m/z (CI) 247 (MNH_4^+), 200 (M-HNO_2), υ_{max} (neat) 1713 (C=O), 1549 (NO_2), 1384, 1305, 1190, 1088, 1035 and 859 cm^{-1}.





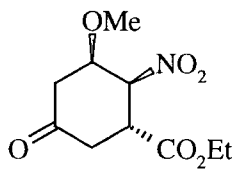
Reaction of 1-[(trimethylsilyl)oxy]butadiene (168) with nitroacrylate (132) to give ethyl *trans*-6-nitro-5-trimethylsiloxycyclohex-3-enecarboxylate (172 and 174).

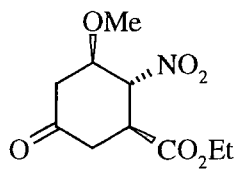
Using *method A* the reaction mixture was stirred for 2.5 hr to yield 150 mg (75%, Endo : Exo ratio = 75 : 25). Using *method B* the reaction mixture was stirred for 48 hr GC showed 40% reaction. Using *method C* the reaction mixture was stirred for 21 hr to yield 160 mg (80%, Endo : Exo ratio = 72 : 28). The mixture of isomers was isolated as a colourless oil. (Found : C, 50.02%; H, 7.38%; N, 5.05%, $C_{12}H_{21}NO_2Si$ requires C, 50.15%; H, 7.37%; N, 4.87%)

Endo isomer (**172**): δ_H (300 MHz): 0.08 (9H, s, TMS), 1.27 (3H, t, J=7 Hz, OCH_2CH_3), 2.00-2.80 (2H, m, 2-H_2), 3.49 (1H, m, 1-*H*), 4.17 (2H, m, OCH_2CH_3), 4.74 (2H, m, 5-*H* and 6-*H*), 5.40-6.00 (2H, m, 3-*H* and 4-*H*), δ_C (75.4 MHz): 0.1 (TMS), 14.2 (OCH_2CH_3), 29.3 (2-*C*), 37.4 (1-*C*), 61.4 (OCH_2CH_3), 65.3 (5-*C*), 86.3 (6-*C*), 126.7 and 128.3 (3-*C* and 4-*C*), 173.3 (CO_2Et).

Exo isomer (**174**): δ_H (300 MHz): 0.11 (9H, s, TMS), 1.23 (3H, t, J=7 Hz, OCH_2CH_3), 2.00-2.80 (2H, m, 2-H_2), 3.36 (1H, m, 1-*H*), 4.17 (2H, m, OCH_2CH_3), 4.74 (2H, m, 5-*H* and 6-*H*), 5.40-6.00 (2H, m, 3-*H* and 4-*H*), δ_C (75.4 MHz): -0.1 (TMS), 14.1 (OCH_2CH_3), 28.3 (2-*C*), 42.8 (1-*C*), 61.8 (OCH_2CH_3), 71.1 (5-*C*), 89.5 (6-*C*), 125.8 and 129.3 (3-*C* and 4-*C*), 170.8 (CO_2Et).

m/z (CI) 305 (MNH_4^+), 288 (MH^+), 241 (M-HNO_2), υ_{max} (neat) 1733 (C=O), 1555 (NO_2), 1380, 1297, 1252, 1183, 1087, 954, 894, 844 and 750 cm^{-1}.





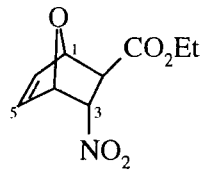
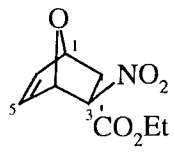
Reaction of Danishefsky's diene (169) with nitroacrylate (132) to give ethyl 3-methoxy-*trans*-2-nitro-5-oxo-cyclohexanecarboxylate (175 and 176)

Using *method A* the reaction mixture was stirred for 10 hr to yield 90 mg (53%, *endo : exo* ratio = 35 : 65) as a crystalline white solid. Using *method B* the reaction mixture was stirred for 30 hr to yield 69 mg (41%, ratio of isomers = 25 : 75) as a mixture with an unknown compound.

Exo isomer (**175**): δ_H (300 MHz): 1.26 (3H, t, J=7 Hz, OCH_2CH_3), 2.3-3.06 (4H, m, 4-H_2, 6-H_2), 3.38 (3H, s, OCH_3), 3.45 (1H, ddd, J=12, 10 and 6 Hz, 1-*H*), 4.06 (1H, ddd, J=10, 7.5 and 4.5 Hz, 5-*H*), 4.20 (2H, q, J=7 Hz, OCH_2CH_3), 5.07 (1H, dd, J=10 and 7.5 Hz, 6-*H*),δ_C (75.4 MHz): 14.1 (OCH_2CH_3), 39.8 and 42.0 (4-*C* and 6-*C*), 43.6 (1-*C*), 57.8 (OCH_3), 62.6 (OCH_2CH_3), 78.1 (5-*C*), 87.0 (6-*C*), 169.6 (CO_2Et), 202.3 (R*C*OR).

Endo isomer (**176**): δ_H (300MHz): 1.28 (3H, t, J=7 Hz, OCH_2CH_3), 2.34-3.03 (4H, m, 4-H_2 and 6-H_2), 3.31 (3H, s, OCH_3), 3.82 (1H, ddd, J=13.5, 11 and 5.5 Hz, 1-*H*), 4.21 (2H, q, J=7 Hz, OCH_2CH_3), 4.56 (1H, m, 5-*H*), 5.11 (1H, dd, J=11 and 3 Hz, 2-*H*), δ_C (75.4 MHz): 14.2 (OCH_2CH_3), 40.3 and 40.6 (4-*C* and 6-*C*), 42.4 (1-*C*), 57.7 (OCH_3), 62.1 (OCH_2CH_3), 77.4 (5-*C*), 84.7 (2-*C*), 171.6 (CO_2Et), 202.7 (R*C*OR).

υ_{max} (neat) 3342, 1736 (C=O), 1560 (NO_2), 1390, 1298, 1270, 1194, 1101, 1028, 1012, 888 and 770 cm^{-1}.

Reaction of furan with nitroacrylate (170) to give ethyl *trans*-3-nitro-7-oxa-bicyclo[2,2,1]hept-5-ene-2-carboxylate (177 and 178).[56]

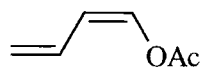
Method A : To a solution of nitroacrylate **132** (0.1 g, 0.69 mmol) in benzene (2 cm^3) was added furan (0.23 g, 3.44 mmol) and the reaction mixture was stirred at 25 °C for 60 hr. The resulting solution was evaporated under reduced pressure. The residue was purified by chromatography eluting with 5-10% Et_2O in petroleum ether to give the *endo* isomer **177** - 90 mg (61%) and the *exo* isomer **178** - 55 mg (37%).

Method B : To a solution of nitroacrylate **132** (0.3 g, 2.07 mmol) in CH_2Cl_2 (5 cm^3) at 0 °C was added $ZnCl_2$ (1M solution in Et_2O, 0.21 cm^3, 0.21 mmol) followed by furan (0.7 g, 10.3 mmol). The reaction mixture was stirred at 0 °C for 72 hr. The resulting solution was washed with water, dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by chromatography eluting with 5-10% Et_2O in petroleum ether to give the *endo* isomer **177** - 170 mg (39%), the *exo* isomer **178** - 90 mg (20%) and compound **179** (11%).

Endo isomer (**177**): White solid (mp 56 °C), δ_H (300 MHz): 1.33 (3H, t, J=7 Hz, OCH_2CH_3), 3.23 (1H, d, J=3 Hz, 2-*H*), 4.27 (2H, q, J=7 Hz, OCH_2CH_3), 5.34 (1H, s, 1-*H*), 5.47 (1H, d, J=5 Hz, 4-*H*), 5.54 (1H, dd, J=5 and 3 Hz, 3-*H*), 6.39 (1H, dd, J=6 and 2 Hz, 5-*H*), 6.73 (1H, dd, J=6 and 2 Hz, 6-*H*), δ_C (75.4 MHz): 14.4 (OCH_2CH_3), 49.2 (2-*C*), 62.4 (OCH_2CH_3), 79.3 (4-*C*), 83.5 (1-*C*) 84.5 (3-*C*), 133.9 and 139.1 (5-*C* and 6-*C*), 169.9 (CO_2Et), *m/z* (CI) 231 (MNH_4^+), υ_{max} (neat) 1717 (C=O), 1589 (NO_2), 1224, 1185, 1017, 905, 874 and 655 cm^{-1}.

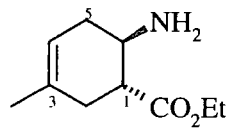
Exo isomer (**178**): Pale yellow solid (mp 35 °C), δ_H (300 MHz): 1.28 (3H, t, J=7 Hz, OCH_2CH_3), 3.96 (1H, m, 2-*H*), 4.17 (2H, q, J=7 Hz, OCH_2CH_3), 4.84 (1H, m, 1-*H*), 5.34 (1H, m, 3-*H*), 5.51 (1H, m, 4-*H*), 6.54 (2H, m, 5-*H* and 6-*H*), δ_C (75.4 MHz): 14.3 (OCH_2CH_3), 49.9 (2-*C*), 61.9 (OCH_2CH_3), 79.3 (4-*C*), 84.2 (1-*C*), 86.8 (3-*C*),

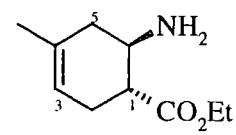
134.5 (6-*C*), 138.5 (5-*C*), 168.9 (*C*O_2Et), *m/z* (CI) 231 (MNH_4^+), υ_{max} (neat) 1735 (C=O), 1544 (NO_2), 1376, 1269, 1246, 1222, 1197, 1020, 903, 875, 816, 787 and 718 cm^{-1}.



Preparation of *cis*-1-acetoxybutadiene (182).[57]

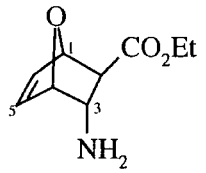
To a solution of 2,5-dihydrofuran (2.0 g, 29 mmol) in THF (60 cm^3) at –65 °C was added ^{n}BuLi (2.5M in hexanes, 12.8 cm^3, 32 mmol) with vigorous stirring. The resulting mixture was stirred at –25 °C for 2 hr and then cooled to –65 °C. Acetic anhydride (26.6 g, 261 mmol) was added and the solution was stirred at –25 °C for 2 hr. The reaction mixture was poured into a cooled (5 °C) mixture of pentane (150 cm^3), saturated $NaHCO_3$ (400 cm^3) and solid $NaHCO_3$ (5 g). The mixture was stirred for 45 min at 5 °C and the pentane layer was removed. The aqueous layer was further extracted with pentane (2x 50 cm^3). The pentane layers were combined, washed with brine, dried ($MgSO_4$) and evaporated under reduced pressure. The residue was distilled to yield 0.73 g (23%) of the desired diene as a colourless oil (bp 54-56 °C at 40 mbar). δ_H (300 MHz): 2.18 (3H, s, OAc), 5.11 (1H, d, J=10 Hz, 4-*H*), 5.25 (1H, d, J=17 Hz, 4-*H*), 5.51 (1H, dd, J=10 and 6 Hz, 2-*H*), 6.70 (1H, dt, J=17 and 10 Hz, 3-*H*), 7.06 (1H, d, J=6 Hz, 1-*H*), δ_C (50.3 MHz): 20.8 (OAc), 113.5 (4-*C*), 117.8 (2-*C*), 129.0 (3-*C*), 134.3 (1-*C*), 167.6 (OAc), *m/z* (EI) 112 (M^+), υ_{max} (neat) 1763 (C=O), 1655, 1429, 1372, 1209, 1166, 1047, 997, 908, 789 and 674 cm^{-1}.





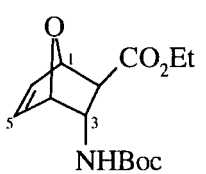
Preparation of ethyl *trans*-6-amino-3-methylcyclohex-3-enecarboxylate (210) and ethyl *trans*-6-amino-4-methylcyclohex-3-enecarboxylate (211).

To a solution of nitro esters **157** and **158** (0.2 g, 0.94 mmol) in EtOH (20 cm^3) was added concentrated HCl solution (3.1 cm^3) followed by powdered zinc (3.5 g) and the mixture was stirred at reflux for 16 hr. The reaction mixture was filtered to remove excess zinc and the solids washed with water (30 cm^3) and CH_2Cl_2 (30 cm^3). The resultant filtrate was adjusted to pH=8 by the addition of saturated $NaHCO_3$ solution. The CH_2Cl_2 layer was separated, filtered, dried ($MgSO_4$), and evaporated under reduced pressure. The residue was purified by column chromatography eluting with 7% MeOH in CH_2Cl_2 to yield 30mg (17%) of the desired amines as a colourless gum. Isomers **108** and **109**: δ_H (200 MHz): 1.26 (3H, t, J=7 Hz, OCH_2CH_3), 1.65 (5H, br s, NH_2 and CH_3), 1.7-2.3 (4H, m, 2-H_2 and 5-H_2), 2.37 (1H, ddd, J=10, 10 and 6 Hz, 6-*H*), 3.17 (1H, ddd, J=10, 10 and 6 Hz, 1-*H*), 4.16 (2H, q, J=7 Hz, OCH_2CH_3), 5.31 (1H, br s, alkene). Major isomer (**210**): δ_C 14.5 (OCH_2CH_3), 23.3 (CH_3), 28.9 (2-*C*), 33.5 (5-*C*), 48.5 (6-*C*), 48.8 (1-*C*), 60.6 (OCH_2CH_3), 118.9 and 132.3 (3-*C* and 4-*C*), 175.3 (CO_2Et). Minor isomer (**211**): δ_C 14.5 (OCH_2CH_3), 23.1 (CH_3), 34.4 (5-*C*), 39.1 (2-*C*), 48.9 (6-*C*), 49.4 (1-*C*), 60.6 (OCH_2CH_3), 119.5 and 132.7 (3-*C* and 4-*C*), 175.5 (CO_2Et). m/z (EI) 183 (M^+). υ_{max} (neat) 3377, 1729, 1444, 1377, 1300, 1258, 1177, 1035, 861 and 786 cm^{-1}.



Preparation of ethyl 3-*endo*-amino-7-oxa-bicyclo[2.2.1]hept-5-ene-2-*exo*-carboxylate (212).

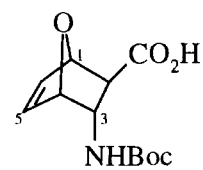
To a solution of nitro ester **177** (0.17 g, 0.79 mmol) in EtOH (20 cm^3) was added concentrated HCl solution (3.1 cm^3) followed by powdered zinc (3.5 g) and the mixture was stirred at reflux for 16 hr. The reaction mixture was filtered to remove excess zinc and the solids washed with water (30 cm^3) and CH_2Cl_2 (30 cm^3). The resultant biphasic filtrate was taken to pH=8 by the addition of saturated $NaHCO_3$ solution. The CH_2Cl_2 layer was separated, dried ($MgSO_4$), and evaporated under reduced pressure. The residue was purified by column chromatography eluting with 10% MeOH in CH_2Cl_2 to yield 40 mg (28%) as a colourless gum. δ_H (300 MHz): 1.29 (3H, t, J=7 Hz, OCH_2CH_3), 2.44 (1H, d, J=6 Hz, 2-*H*), 4.03 (3H, m, NH_2 and 3-*H*), 4.20 (2H, q, J=7 Hz, OCH_2CH_3), 5.15 (2H, br s, 1-*H* and 4-*H*), 6.63-6.71 (2H, m, 5-*H* and 6-*H*), δ_C (50.3 MHz): 14.3 (OCH_2CH_3), 52.3 (2-*C*), 54.2 (3-*C*), 61.8 (OCH_2CH_3), 79.8 and 82.9 (1-*C* and 4-*C*), 134.0 and 138.9 (5-*C* and 6-*C*), 172.4 (CO_2Et), υ_{max} (neat) 3246, 3148, 2979, 1716 (C=O), 1588, 1370, 1318, 1224, 1184, 1016, 905, 874 and 655 cm^{-1}.



Preparation of ethyl 3-*endo*-*tert*-butoxycarbonylamino-7-oxa-bicyclo[2,2,1]hept-5-ene-2-*exo*-carboxylate (213).

To a solution of nitro ester **177** (5.0 g, 23.5 mmol) in EtOH (500 cm^3) was added concentrated HCl solution (40 cm^3, 400 mmol) followed by portionwise addition of

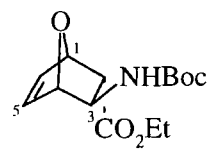
zinc powder (38 g, 590 mmol). The reaction mixture was stirred at 25 °C for 12 hr. The reaction mixture was filtered to remove the excess zinc. To the resulting solution was added $^{i}Pr_2NEt$ (52 g, 400 mmol) and di-*tert*-butyl dicarbonate (10.2 g, 47.0 mmol). The reaction mixture was stirred at 25 °C for 20 hr. The reaction mixture was evaporated under reduced pressure to around 100 cm^3 and the residue was partitioned between EtOAc (500 cm^3), saturated $NaHCO_3$ (300 cm^3) and water (300 cm^3). The organic layer was separated, dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by column chromatography eluting with 30% Et_2O in petroleum ether to give 5.5 g (83%) of the desired carbamate as a white solid (mp 90 °C). (Found : C, 59.32%; H, 7.35%; N, 5.04%, $C_{14}H_{21}NO_5$ requires C, 59.35%; H, 7.47%; N, 4.94%), δ_H (500 MHz): 1.29 (3H, t, J=7 Hz, OCH_2CH_3), 1.44, (9H, s, Boc), 2.05 (1H, d, J=4 Hz, 2-*H*), 4.21 (2H, q, J=7 Hz, OCH_2CH_3), 4.30 (1H , br s, N*H*Boc), 4.56 (1H, br s, 3-*H*), 5.06 (1H, br s, 4-*H*), 5.13 (1H, s, 1-*H*), 6.47 (1H, d, J=6 Hz, 5-*H*), 6.61 (1H, d, J=6 Hz, 6-*H*), δ_C (125.7 MHz): 14.4 (OCH_2CH_3), 28.5 (Boc), 52.6, (2-*C*), 53.3 (3-*C*), 61.5 (OCH_2CH_3), 79.2 (4-*C*), 80.2 (Boc), 82.3 (1-*C*), 134.7 (5-*C*), 138.0 (6-*C*), 155.2 (NCO_2), 172.0 (CO_2Et), *m/z* (ES^+) 284 (MH^+), υ_{max} (Golden Gate) 3336, 2979, 1731 (CO_2Et), 1692 (NCO_2), 1523, 1367, 1315, 1250, 1173, 1050, 1012, 911, 874 and 731 cm^{-1}.



Preparation of 3-*endo-tert*-butoxycarbonylamino-7-oxa-bicyclo[2,2,1]hept-5-ene-2-*exo*-carboxylic acid (214).

To a solution of ester **213** (0.7 g, 2.47 mmol) in THF (10 cm^3) was added LiOH (0.3 g, 12 mmol) in H_2O (2 cm^3). The solution was stirred vigorously at 25 °C for 4 hr. The reaction mixture was diluted with water (10 cm^3) and the resulting solution was extracted with Et_2O (20 cm^3). The aqueous layer was adjusted to pH=1 with 6M HCl

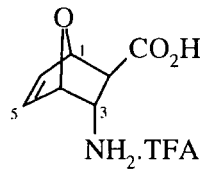
and extracted with EtOAc (3x 30 cm^3). The organic layers were combined, dried ($MgSO_4$) and evaporated under reduced pressure to give 0.59 g (95%) of the desired acid as a white solid (mp 138 °C). (Found : C, 56.59%; H, 6.78%; N, 5.39%, $C_{12}H_{17}NO_5$ requires C, 56.46%; H, 6.71%; N, 5.49%), δ_H (400 MHz): 1.37 (9H, s, Boc), 2.24 (1H, d, J=3 Hz, 2-*H*), 4.07 (1H, d, J=5 Hz, 3-*H*), 4.92 (1H, d, J=3 Hz, 4-*H*), 4.99 (1H, s, 1-*H*), 6.35 (1H, d, J=6 Hz, 5-*H*), 6.56 (1H, d, J=6 Hz, 6-*H*), 6.86 (1H, d, J=5 Hz, N*H*Boc), 12.42 (1H, br s, CO_2H), δ_C (100.6 MHz): 28.2 (Boc), 49.6 (2-*C*), 52.6 (3-*C*), 78.0 (4-*C*), 78.5 (Boc), 81.6 (1-*C*), 134.2 (5-*C*), 137.0 (6-*C*), 155.4 (NCO_2), 173.4 (CO_2H), *m/z* (ES^+) 256 (MH^+), 278 (MNa^+), υ_{max} (neat) 3210 (OH), 1712 (C=O), 1526, 1396, 1369, 1251, 1167, 1039, 906, 863 and 737 cm^{-1}.



Preparation of ethyl 3-*exo*-*tert*-butoxycarbonylamino-7-oxa-bicyclo[2,2,1]hept-5-ene-2-*endo*-carboxylate.

To a solution of the nitro ester **178** (2.0 g, 9.4 mmol) in EtOH (400 cm^3) was added concentrated HCl (15 cm^3, 165 mmol) followed by portionwise addition of zinc powder (20 g, 310 mmol). The reaction mixture was stirred at 25 °C for 12 hr. The reaction mixture was filtered and $^iPr_2NEt$ (21.3 g, 165 mmol) and di-*tert*-butyl dicarbonate (4.0 g, 18.8 mmol) was added. The reaction mixture was stirred at 25 °C for 24 hr. The reaction mixture was evaporated under reduced pressure to around 100 cm^3 and the residue was partitioned between EtOAc (500 cm^3), saturated $NaHCO_3$ (300 cm^3) and water (300 cm^3). The organic layer was separated, dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by column chromatography eluting with 30% Et_2O in petroleum ether to give 2.02 g (76%) of the desired carbamate as a white solid (mp 51 °C). δ_H (300 MHz): 1.23 (3H, t, J=7 Hz, OCH_2CH_3), 1.44, (9H, s, Boc), 2.69 (1H, m, 2-*H*), 4.06 (1H, br s, N*H*Boc), 4.10 (2H,

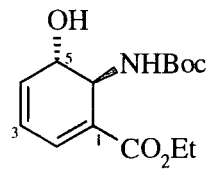
q, J=7 Hz, OCH_2CH_3), 4.78 (1H, br s, 1-*H*), 4.89 (1H, br s, 4-*H*), 5.14 (1H, m, 3-*H*), 6.36-6.45 (2H, m, 5*H* and 6-*H*), δ_C (75.4 MHz): 14.4 (OCH_2CH_3), 28.6 (Boc), 52.6, (2-*C*), 54.6 (3-*C*), 61.2 (OCH_2CH_3), 78.8 (4-*C*), 80.0 (Boc), 85.5 (1-*C*), 135.5 and 135.7 (5-*C* and 6-*C*), 155.5 (NCO_2), 170.5 (CO_2Et), *m/z* (ES^+) 284 (MH^+), 306 (MNa^+), υ_{max} (Golden Gate) 2977 (NH), 1709 (C=O), 1510, 1366, 1160, 1012, 883, 856 and 695cm^{-1}.



Preparation of the TFA salt of 3-*endo*-amino-7-oxa-bicyclo[2,2,1]hept-5-ene-2-*exo*-carboxylic acid (215).

To a solution of acid **214** (0.1 g, 0.39 mmol) in DCM (4 cm^3) was added TFA (1 cm^3, 13.1 mmol). The solution was stirred at 25 °C for 2 hr. The reaction mixture was evaporated under reduced pressure. The resultant colourless oil was triturated using Et_2O (3 cm^3) to give 59 mg (97%) of the desired amino acid as a white solid.

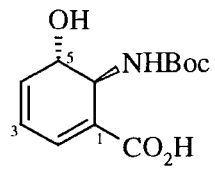
(Found : C, 40.41%; H, 3.83%; N, 4.92%, $C_9H_{10}NO_5F_3$ requires C, 40.16%; H, 3.74%; N, 5.20%), δ_H (D_2O - 300 MHz): 2.60 (1H, d, J=3 Hz, 2-*H*), 4.10 (1H, m, 3-*H*), 5.27 (1H, d, J=4 Hz, 4-*H*), 5.34 (1H, s, 1-*H*), 6.55 (1H, d, J=6 Hz, 5-*H*), 6.83 (1H, d, J=6 Hz, 6-*H*), δ_C (75.4 MHz): 53.5 (2-*C*), 56.6 (3-*C*), 83.2 (4-*C*), 88.1 (1-*C*), 137.3 (5-*C*), 145.2 (6-*C*), 179.6 (CO_2H), *m/z* (ES^+) 156 (MH^+), 173 (MNH_4^+), υ_{max} (neat) 1655 (C=O), 1181, 1136, 1021, 903, 821, 798 and 719 cm^{-1}.



Preparation of ethyl (5*S*, 6*S* / 5*R*, 6*R*)-6-*tert*-butoxycabonylamino-*trans*-5-hydroxy-cyclohexa-1,3-dienecarboxylate (218).

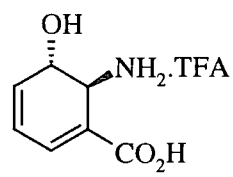
To a solution of KHMDS (1.05 g, 5.28 mmol) in THF (20 cm^3) at –50 °C was added dropwise a solution of ester **213** (0.5 g, 1.76 mmol) in THF (5 cm^3). The solution was stirred at –50 → 25 °C for 20 min. The reaction mixture was added to a stirring mixture of EtOAc (90 cm^3) and MeOH (10 cm^3). The resulting solution was washed with saturated NH_4Cl solution. The organic layer was separated, dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by column chromatography eluting with 35-60% EtOAc in petroleum ether to give 356 mg (71%) of the desired alcohol as a white solid (mp 94 °C). δ_H (300 MHz): 1.29 (3H, t, J=7 Hz, OCH_2CH_3), 1.43 (9H, s, Boc), 4.21 (2H, m, OCH_2CH_3), 4.35 (1H, s, 5-*H*), 4.69 (1H, s, N*H*), 4.78 (1H, m, 6-*H*), 6.26 (2H, m, 3-*H* and 4-*H*), 7.17 (1H, m, 2-*H*), δ_C (126 MHz): 14.4 (OCH_2CH_3), 28.6 (Boc), 50.2 (6-*C*), 61.1 (OCH_2CH_3), 67.8 (5-*C*), 80.2 (Boc), 124.7 (3-*C*), 127.4 (1-*C*), 132.8 (2-*C*), 133.8 (4-*C*), 155.6 (NCO_2), 166.1 (CO_2Et), *m/z* (ES^+) 284 (MH^+), 306 (MNa^+), υ_{max} (neat) 3400 (OH), 2979 (NH), 2931 (NH), 1716 (CO_2Et), 1700 (NCO_2), 1584, 1514, 1392, 1366, 1245, 1169, 1079, 1017, 915 and 737cm^{-1}.

The major by-product in the reaction was ethyl 2-hydroxybenzoate **(219)**[107] isolated as a light yellow solid. δ_H (300 MHz): 1.38 (3H, t, J=7 Hz, OCH_2CH_3), 4.37 (2H, q, OCH_2CH_3), 7.08-7.63 (4H, m, Ph), δ_C (50.3 MHz): 14.5.(OCH_2CH_3), 61.6 (OCH_2CH_3), 116.6, 120.5, 121.9, 129.8, 131.7 and 156.2 (Ph), 167.3 (CO_2Et), *m/z* (ES^+) 167 (MH^+), 189 (MNa^+), υ_{max} (Golden Gate) 3294 (OH), 2980, 1743 (C=O), 1678, 1366, 1233, 1137 and 753cm^{-1}.



Preparation of (5*S*, 6*S* / 5*R*, 6*R*)-6-*tert*-butoxycabonylamino-*trans*-5-hydroxy-cyclohexa-1,3-dienecarboxylic acid (220).[66]

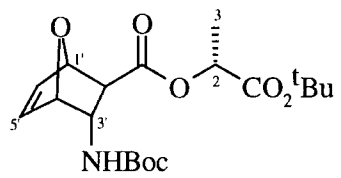
To a solution of **218** (1.1 g, 3.89 mmol) in THF (20 cm^3) was added KOH (2.2 g, 38.9 mmol) in H_2O (5 cm^3). The solution was stirred at 40 °C for 6 hr. The reaction mixture was diluted with water (30 cm^3) and washed with Et_2O (20 cm^3). The aqueous layer was adjusted to pH=1 with 6M HCl and extracted with EtOAc (3x 40 cm^3). The organic layers were combined, dried ($MgSO_4$) and evaporated under reduced pressure to give 0.67 g (68%) of the desired acid as a light yellow solid (mp 167 °C). (Found : C 56.28%; H 6.77%; N 5.38%, $C_{12}H_{17}NO_5$ requires C 56.46%; H 6.71%; N 5.49%), δ_H (DMSO^{d6} - 200 MHz): 1.36 (9H, s, Boc), 3.90 (1H, s, 5-*H*), 4.43 (1H, d, J=7 Hz, 6-*H*), 5.07 (1H, m, O*H*), 6.17 (2H, m, 3-*H* and 4-*H*), 6.58 (1H, d, J=7 Hz, N*H*), 6.99 (1H, m, 2-*H*), δ_C (DMSO - 75.4 MHz): 28.3 (Boc), 49.1 (6-*C*), 66.2 (5-*C*), 77.7 (Boc), 123.9, 126.9, 133.1 and 133.3 (alkene), 155.1 (NCO_2), 167.4 (CO_2H), *m/z* (ES^+) 256 (MH^+), 278 (MNa^+), υ_{max} (Golden Gate) 3295 (OH), 2979 (NH), 1682 (C=O), 1504, 1366, 1240, 1158, 1004, 854 and 736, cm^{-1}.



Preparation of the TFA salt of DHAA (126).[71]

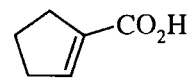
To a solution of acid **220** (25 mg, 0.1 mmol) in DCM (4 cm^3) was added TFA (0.5 cm^3, 6.6 mmol). The solution was stirred at 0 °C for 1 hr. The reaction mixture was evaporated under reduced pressure. The resultant colourless oil was triturated using Et_2O (3 cm^3) to give 12 mg (47%) of the desired amino acid as a light brown gum.

HRMS *m/z* (ES^+) calc for MH^+ =156.0661 measured=156.0660, δ_H (D_2O - 300 MHz): 4.25 (1H, d, J=6 Hz, 6-*H*), 4.44 (1H, t, J=6 Hz, 5-*H*), 6.18-6.35 (2H, m, 3-*H* and 4-*H*), 7.00 (1H, d, J=5 Hz, 2-*H*), δ_C (D_2O - 75.4 MHz): 51.7 (6-*C*), 65.8 (5-*C*), 125.6, 130.2, 130.6 and 132.5 (alkene), *m/z* (ES^+) 156 (MH^+), υ_{max} (Golden Gate) 3295 (OH), 2979 (NH_2), 1682 (C=O), 1504, 1366, 1240, 1158, 1004, 854 and 736, cm^{-1}.



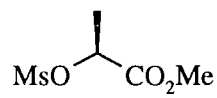
Preparation of *tert*-butyl (2*R*)-2-[3'-*endo*-*tert*-butoxycarbonylamino-7'-oxa-bicyclo[2,2,1]hept-5'-ene-2'-*exo*-carbonyloxy]-propionate (222).

To a solution of acid **214** (0.40 g, 1.57 mmol), *tert*-butyl lactate **221** (0.28 g, 2.04 mmol), HOBt (0.28 g, 2.04 mmol) and EDCI (0.39 g, 2.04 mmol) in DCE (5 cm^3) was added Et_3N (0.21 g, 2.04 mmol). The solution was stirred at 25 °C for 5 hr. The reaction mixture was partitioned between EtOAc (20 cm^3) and water (20 cm^3). The organic layers were combined, dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by column chromatography eluting with 25% EtOAc in petroleum ether to give 0.39 g (66%) of the title compound as a colourless oil. δ_H (500 MHz): 1.42 and 1.45 (18H, m, 2x Boc), 1.48 (3H, m, 3-H_3), 2.14 (1H, s, 2'-*H*), 4.36 (1H , m, N*H*), 4.58 (1H, br s, 3'-*H*), 5.01-5.28 (3H, m, 2-*H*, 1'-*H* and 4'-*H*), 6.48 (1H, d, J=6 Hz, 5'-*H*), 6.63 (1H, m, 6'-*H*), δ_C (126 MHz): 17.1 (3-*C*), 28.1 and 28.5 (2x Boc), 52.2 (2'-*C*), 52.6 (3'-*C*), 69.8 (2-*C*), 79.3 (4'-*C*), 80.0 and 82.1 (2x Boc), 82.4 (1'-*C*), 134.6 (5'-*C*), 138.2 (6'-*C*), 155.0 (NCO_2), 169.4 and 171.5 (CO_2Et), *m/z* (CI) 401 (MNH_4^+), υ_{max} (neat) 2977, 1730 (C=O), 1519, 1367, 1252, 1163, 1099, 972 and 905cm^{-1}.



Preparation of cyclopent-1-enecarboxylic acid (226).[108]

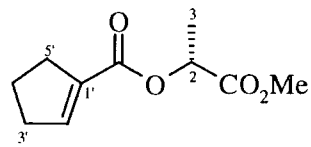
To a solution of ethyl cyclopent-1-enecarboxylate (10.0 g, 79.0 mmol) in THF (100 cm^3) was added LiOH (9.5 g, 400 mmol) in H_2O (25 cm^3). The solution was stirred vigorously at 25 °C for 72 hr. The reaction mixture was diluted with water (50 cm^3) and the resulting solution was extracted with Et_2O (80 cm^3). The aqueous layer was adjusted to pH=1 with 6M HCl and extracted with EtOAc (3x 200 cm^3). The organic layers were combined, dried ($MgSO_4$) and evaporated under reduced pressure to give 3.5 g (40%) of the desired acid as a white solid (mp 119 °C), (Found : C, 64.02%; H, 7.218%; N, 0%, $C_6H_8O_2$ requires C, 64.27%; H, 7.19%; N, 0%), δ_H (300 MHz): 1.98 (2H, m, 4-H_2), 2.54 (4H, m, 3-H_2 and 5-H_2), 6.94 (1H, m, 2-*H*), 12.00 (1H, br s, CO_2H), δ_C (75.4 MHz): 23.3, 31.1 and 33.8 (3-*C*, 4-*C* and 5-*C*), 136.3 (1-*C*), 147.1 (2-*C*), 171.2 (*C*=O), *m/z* (ES^+) 113 (MH^+), 135 (MNa^+), υ_{max} (Golden Gate) 2968 (OH), 1662 (C=O), 1620, 1427, 1288, 1233, 1091, 914, 731 and 545cm^{-1}.



Preparation of methyl (2*S*)-2-methanesulfonyloxy propionic acid (229).[109]

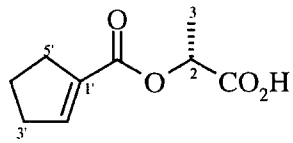
To a solution of methyl-(*S*)-(-)-lactate **227** (10.4 g, 100 mmol) in CH_2Cl_2 (100 cm^3) was added Et_3N (13.3 g, 132 mmol). To this solution was added MsCl (9.0 g, 110 mmol) dropwise over 10 min and the solution was stirred for 30 min at 0 °C. The reaction mixture was partioned between CH_2Cl_2 (3x 50 cm^3) and 1M HCl (50 cm^3). The organic layers were combined and evaporated under reduced pressure to give 19.1 g (quant.) of the desired ester as a yellow oil. δ_H (300 MHz): 1.62 (3H, d, J=7 Hz, $CHCH_3$), 3.15 (3H, s, SO_2CH_3), 3.80 (3H, s, OCH_3), 5.14 (1H, q, J=7 Hz,

C*H*CH_3), δ_C (75.4 MHz): 18.6 ($CH\mathit{C}H_3$), 39.3 ($SO_2\mathit{C}H_3$), 53.1 ($O\mathit{C}H_3$), 74.4 ($\mathit{C}HCH_3$), 170.2 ($\mathit{C}O_2CH_3$), υ_{max} (neat) 3026, 1757 (C=O), 1452, 1360, 1222, 1178, 1089, 1033, 975, 945, 854, 817 and 739 cm^{-1}.



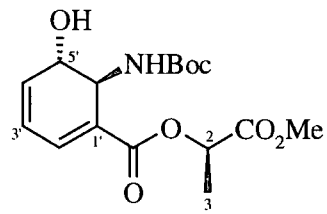
Preparation of methyl (2*R*)-2-[cyclopent-1'-enecarbonyloxy]-propionate (228).

CsF (0.81 g, 5.34 mmol) was dried under vacuum at 150 °C for 5 hr. DMF (5 cm^3) was added and the suspension was stirred at 25 °C for 30 min. To this suspension was added acid **226** (0.30 g, 2.67 mmol) and the resulting suspension was stirred at 25 °C for 30 min. Mesylate **229** (0.97 g, 5.34 mmol) was added and the reaction mixture was stirred at 50 °C for 24 hr. The resulting suspension was partitioned between EtOAc (3x 150 cm^3) and water (100 cm^3). The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by column chromatography eluting with 15% EtOAc in petroleum ether to yield 0.44 g (84%) as a colourless oil. (Found : C 60.50%, H 7.18%; N 0%, $C_{10}H_{14}O_4$ requires C 60.59%; H 7.12%; N 0%), δ_H (300 MHz): 1.52 (3H, d, J=7 Hz, 3-H_3), 1.98 (2H, m, 4'-H_2), 2.46-2.65 (4H, m, 3'-H_2 and 5'-H_2), 3.75 (3H, s, O$\mathit{C}H_3$), 5.14 (1H, q, J=7 Hz, 2-*H*), 6.89 (1H, m, 2'-*H*), δ_C (75.4 MHz): 17.3 (3-*C*), 23.3, 31.5 and 33.8 (3'-*C*, 4'-*C*, and 5'-*C*), 52.5 ($O\mathit{C}H_3$), 68.5 (2-*C*), 135.9 (1'-*C*), 145.6 (2'-*C*), 164.7 ($\mathit{C}O_2Me$), 171.8 ($\mathit{C}O_2R$), *m/z* (ES^+) 199 (MH^+), 221 (MNa^+), υ_{max} (neat) 1754 (C=O), 1720 (C=O), 1628, 1451, 1437, 1368, 1277, 1214, 1133, 1102, 1045, 977 and 742 cm^{-1}.



Preparation of (2*R*)-2-[cyclopent-1'-enecarbonyloxy]-propionic acid (230).

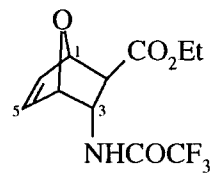
To a solution of ester **228** (0.1 g, 0.51 mmol) in THF (2 cm^3) was added LiOH (17 mg, 0.71 mmol) in H_2O (0.5 cm^3). The solution was stirred vigourously at 25 °C for 1 hr. The reaction mixture was partitioned between EtOAc (4x 25 cm^3) and water (20 cm^3). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to yield 51 mg (55%) of the desired acid as a white solid (mp 88 °C). δ_H (300 MHz): 1.57 (3H, d, J=7 Hz, 3-H_3), 1.97 (2H, m, 4'-H_2), 2.43-2.65 (4H, m, 3'-H_2 and 5'-H_2), 5.17 (1H, q, J=7 Hz, 2-*H*), 6.90 (1H, m, 2'-*H*), δ_C (75.4 MHz): 17.1 (3-*C*), 23.8, 31.0 and 34.2 (3'-*C*, 4'-*C*, and 5'-*C*), 68.4 (2-*C*), 136.4 (1'-*C*), 145.8 (2'-*C*), 170.6 (CO_2H), 171.3 (CO_2R), *m/z* (ES^+) 185 (MH^+), 207 (MNa^+).



Preparation of methyl (2*R*, 5'*S*, 6'*S* / 2*R*, 5'*R*, 6'*R*)-2-[-6'-*tert*-butoxycarbonyl amino-*trans*-5'-hydroxy-cyclohexa-1,3-diene-1'-carboxyloxy]-propionate (231).

CsF (0.24 g, 1.57 mmol) was dried under vacuum at 150 °C for 5 hr. DMF (5 cm^3) was added and the suspension was stirred at 25 °C for 30 min. To this suspension was added acid **220** (0.20 g, 0.78 mmol) and the resulting suspension was stirred at 25 °C for 30 min. Mesylate **229** (0.29 g, 1.57 mmol) was added and the reaction mixture was stirred at 50 °C for 24 hr. The resulting suspension was partitioned between EtOAc (3x 100 cm^3) and water (60 cm^3). The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated under reduced pressure. The residue was

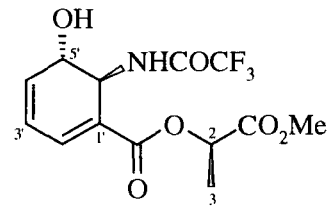
purified by column chromatography eluting with 40% EtOAc in petroleum ether to yield 0.22 g (83%) as a white solid (hygroscopic). HRMS *m/z* (ES^+) calc for MH^+ =342.1553 measured=342.1554, δ_H (500 MHz): 1.36 (9H, s, Boc), 1.46 (3H, m, 3-*H*$_3$), 3.68 (3H, s, OC*H*$_3$), 4.27 (1H, s, 5'-*H*), 4.42-4.63 (1H, m, N*H*), 4.69 (1H, m, 6'-*H*), 5.12 (1H, m, 2-*H*), 6.23 (2H, m, 3'-*H* and 4'-*H*), 7.18 (1H, m, 2'-*H*), δ_C (126 MHz): 17.1 (3-*C*), 28.4 (Boc), 50.0 (6'-*C*), 52.5 (O*C*H$_3$), 67.7 (5'-*C*), 68.9 (2-*C*), 80.0 (Boc), 124.4 (3'-*C*), 126.4 (1'-*C*), 133.5 (2'-*C*), 134.9 (4'-*C*), 155.6 (N*C*O$_2$), 165.3 and 171.3 (*C*O$_2$R), υ_{max} (neat) 3373 (OH), 2978 (NH), 1759 (CO_2Me), 1716 (CO_2R), 1696 (NCO_2), 1519, 1454, 1099, 1011, 915 and 735cm^{-1}.



Preparation of ethyl 3-*endo*-(trifluoroacetylamino)-7-oxa-bicyclo[2,2,1]hept-5-ene-2-*exo*-carboxylate (232).

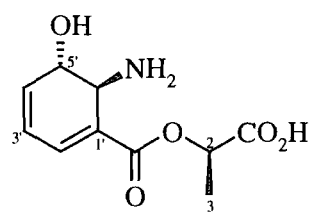
To a solution of ester **213** (0.2 g, 0.71 mmol) in dry toluene (5 cm^3) at 0 °C was added TFAA (0.45 g, 2.12 mmol). The reaction mixture was stirred for 3 min and the resultant solution was added TFA (0.16 g, 1.4 mmol). The solution was stirred at 0 °C for 1 hr. The solution was evaporated under reduced pressure and the residue was purified by column chromatography eluting with 30% Et_2O in cyclohexane to give 105 mg, (59%) of the desired trifluoroacetamide as a yellow oil. δ_H (300 MHz): 1.31 (3H, t, J=7 Hz, OCH$_2$C*H*$_3$), 2.22 (1H, d, J=3 Hz, 2-*H*), 4.24 (2H, q, J=7 Hz, OC*H*$_2$CH$_3$), 4.86 (1H, br s, 3-*H*) 5.22 and 5.25 (2H, m, 1-*H* and 4-*H*), 5.90 (1H, br s, N*H*COCF$_3$), 6.48 (1H, dd, J=6 and 2 Hz, 5-*H*), 6.73 (1H, dd, J=6 and 2 Hz, 6-*H*), δ_C (50.3 MHz): 4.3 (OCH$_2$*C*H$_3$), 51.2 and 52.5 (2-*C* and 3-*C*), 61.9 (O*C*H$_2$CH$_3$), 78.7 (4-*C*), 82.4 (1-*C*), 115.7 (q, J=300 Hz, *C*F$_3$), 134.0 (5-*C*), 138.6 (6-*C*), 157.4 (q, J=38 Hz, *C*OCF$_3$), 171.2 (*C*O$_2$Et), ^{19}F-NMR (188.2 MHz): δ -76.35 (CF$_3$), *m/z* (ES^+) 280

(MH^+), 302 (MNa^+), υ_{max} (neat) 3304, 1722 (CO_2Et), 1702 ($COCF_3$), 1549, 1151, 1016, 877, 718, 584 and 519 cm^{-1}.



Preparation of methyl (2*R*, 5'*S*, 6'*S* / 2*R*, 5'*R*, 6'*R*)-2-[6'-trifluoroacetylamino-*trans*-5'-hydroxy-cyclohexa-1,3-diene-1'-carboxyloxy]-propionate (234).

To a solution of hydroxy ester **231** (0.1 g, 0.29 mmol) in dry chloroform (2 cm^3) was added TFAA (0.18 g, 0.88 mmol). The reaction mixture was stirred for 3 min and to the resultant solution was added TFA (67 mg, 0.58 mmol). The solution was stirred at 25 °C for 1 hr. The solution was concentrated *in vacuo* and the residue was purified by column chromatography eluting with 10-60% EtOAc in petroleum ether to give 70 mg (71%) as a yellow oil. δ_H (200 MHz): 1.55 (3H, m, 3-*H*$_3$), 3.77 (3H, s, OC*H*$_3$), 5.26 (2H, m, 5'-*H* and 2-*H*), 5.49 (1H, m, 6'-*H*), 6.50 (2H, m, 3'-*H* and 4'-*H*), 7.44 (1H, m, 2'-*H*),), *m/z* (ES^+) 360 (MNa^+).

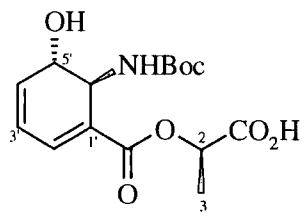


Preparation of oryzoxymycin (2).[60]

Method A : To a solution of trifluoroacetamide **234** (10 mg, 0.03 mmol) in MeOH (1 cm^3) was added water (0.5 cm^3) followed by NaOH (5 mg, 0.21 mmol). The solution was stirred at 25 °C for 1 hr. The solution was adjusted to pH=5 and passed through an oasis® cartridge eluting with 0-50% MeOH in water. The solution was

freeze-dried to give 40 mg of a white solid. δ_H (NaOD in D_2O - 300 MHz): 1.25 (3H, d, J=7 Hz, 3-*H*$_3$), 3.69 (1H, m, 6'-*H*), 4.04 (1H, q, J=7 Hz, 2-*H*), 4.07 (1H, m, 5'-*H*), 6.04 (2H, m, 3'-*H* and 4'-*H*), 7.59 (1H, m, 2'-*H*), δ_C (NaOD in D_2O – 75.4 MHz): 20.4 (3-*C*), 51.2 (6'-*C*), 65.5 (5'-*C*), 68.2 (2-*C*), 125.8, 126.0, 130.9 and 134.6 (alkenes), 171.9 and 181.9 (*C*O_2R), *m/z* (CI) 228 (MH^+).

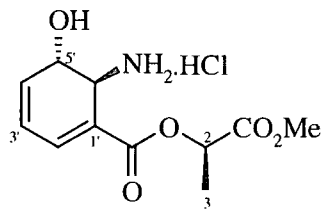
Method B : To a solution of HCl salt **239** (25 mg, 0.1 mmol) in D_2O (1 cm^3) was added NaOD (40%, 0.1 cm^3). The solution was stirred at 25 °C for 15 min. The reaction mixture was adjusted to pH=5 and freeze-dried under reduced pressure to give 34 mg of a white solid. δ_H (CD_3OD - 300 MHz): 1.26 (3H, d, J=7 Hz, 3-*H*$_3$), 3.99 (1H, q, J=7 Hz, 2-*H*), 4.05 (1H, d, J=9 Hz, 5'-*H*), 4.43 (1H, d, J=9 Hz, 6'-*H*), 6.08 (2H, m, 3'-*H* and 4'-*H*), 6.90 (1H, m, 2'-*H*).



Preparation of (2*R*, 5'*S*, 6'*S* / 2*R*, 5'*R*, 6'*R*)-2-[6'-*tert*-butoxycarbonylamino-*trans*-5'-hydroxy-cyclohexa-1,3-diene-1'-carboxyloxy]-propionic acid (237).

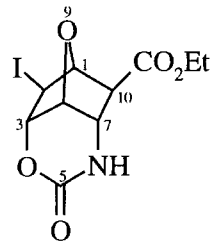
To a solution of ester **231** (25 mg, 0.07 mmol) in MeOH (4 cm^3) was added water (2 cm^3) followed by K_2CO_3 (20 mg, 0.154 mmol). The solution was stirred vigourously at 25 °C for 20 hr. The reaction mixture was partitioned between EtOAc (20 cm^3) and 0.1M HCl (20 cm^3). The organic layers were combined, dried ($MgSO_4$) and evaporated under reduced pressure. The residue was separated by HPLC to give 5 mg (16%) of the desired acid as a brown gum (~90% purity by ^{1}H-NMR). δ_H (CD_3OD - 300 MHz): 1.42 (9H, s, Boc), 1.45 (3H, m, 3-*H*$_3$), 4.16 (1H, s, 5'-*H*), 4.65 (1H, m, 6'-*H*), 4.97 (1H, m, 2-*H*), 6.24 (2H, m, 3'-*H* and 4'-*H*), 7.23 (1H, m, 2'-*H*), δ_C (126 MHz): 18.3 (3-*C*), 28.8 (Boc), 67.9 (6'-*C*), 72.9 (5'-*C*), 68.9 (2-*C*), 80.2 (Boc), 125.8

(3'-*C*), 127.8 (1'-*C*), 133.6 (2'-*C*), 134.7 (4'-*C*), 158.0 (NCO_2), 167.4 and 178.4 (CO_2R), *m/z* (ES^-) 326 (MH^-), 254 (M-lactate)



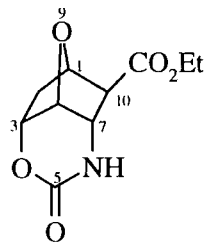
Preparation of the HCl salt of methyl (2*R*, 5'*S*, 6'*S* / 2*R*, 5'*R*, 6'*R*)-2-[6'-amino-*trans*-5'-hydroxy-cyclohexa-1,3-diene-1'-carboxyloxy]-propionate (239).

To a solution of the hydroxy ester **231** (50 mg, 0.15 mmol) in CD_3OD (1 cm^3) was added a premixed solution of $SOCl_2$ (43 µl, 0.59 mmol) in MeOH (1 cm^3). The solution was stirred at 25 °C for 1 hr. The solution was evaporated under reduced pressure to give 37 mg (89%) of the desired amine as the HCl salt as a colourless gum. δ_H (CD_3OD - 200 MHz): 1.51 (3H, m, 3-H_3), 3.75 (3H, s, OCH_3), 4.28-4.42 (2H, m, 5'-*H* and 6'-*H*), 5.23 (1H, m, 2-*H*), 6.43 (2H, m, 3'-*H* and 4'-*H*), 7.47 (1H, m, 2'-*H*), δ_C (50.3 MHz): 17.2 (3-*C*), 52.2 (6'-*C*), 53.0 (OCH_3), 65.2 (5'-*C*), 70.8 (2-*C*), 123.1, 125.0, 135.2 and 138.5 (alkenes), 166.0 and 172.9 (CO_2R), *m/z* (ES^+) 242 (MH^+), 264 (MNa^+), υ_{max} (neat) 3327 (OH), 2955 (NH), 1706 (C=O), 1583, 1451, 1400, 1269, 1226, 1099, 1047, 975 and 743 cm^{-1}.



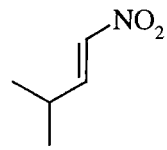
Preparation of ethyl 2-iodo-5-oxa-4,9-dioxa-6-aza-tricyclo[5,2,1,$0^{3,8}$]decane-10-carboxylate (244).

To a solution of ester **213** (0.5 g, 1.76 mmol) in CH_3CN (15 cm^3) was added I_2 (1.35 g, 5.3 mmol) and the solution was stirred at 25 °C for 16 hr. The reaction mixture was partitioned between EtOAc (4x 100 cm^3) and saturated $Na_2S_2O_3$ solution (100 cm^3). The organic layers were combined, washed with brine, dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by column chromatography eluting with 60% EtOAc in petroleum ether to give 290 mg (47%) of the desired carbamate as a white solid (mp 159 °C). (Found : C 33.99%; H 3.43%; N 3.92%, $C_{10}H_{12}NO_5I$ requires C 34.01%; H 3.43%; N 3.97%), δ_H (500 MHz): 1.30 (3H, t, J=7 Hz, OCH_2CH_3), 2.77 (1H, d, J=3 Hz, 10-*H*), 4.04 (1H, d, J=3 Hz, 2-*H*), 4.21 (2H, q, J=7 Hz, OCH_2CH_3), 4.39 (1H, m, 7-*H*), 4.57 (1H, t, J=5 Hz, 8-*H*), 4.96 (1H, s, 1-*H*), 5.19 (1H, m, 3-*H*), 6.41 (1H, d, J=5 Hz, N*H*), δ_C (126 MHz): 14.4 (OCH_2CH_3), 23.4 (2-*C*), 52.6 (7-*C*), 57.3 (10-*C*), 62.5 (OCH_2CH_3), 69.5 (8-*C*), 87.3 (3-*C*), 87.5 (1-*C*), 149.6 (NCO_2), 169.2 (CO_2Et), *m/z* (ES^+) 354 (MH^+), 376 (MNa^+), υ_{max} (Golden Gate) 1715 (CO_2Et), 1670 (NCO_2), 1209, 1126, 1003, 851, 753 and 420cm^{-1}.



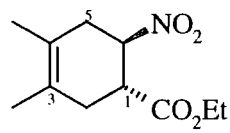
Preparation of ethyl 5-oxa-4,9-dioxa-6-aza-tricyclo[5,2,1,$0^{3,8}$]decane-10-carboxylate (245).

To a suspension of **244** (0.30 g, 0.85 mmol) in benzene (10 cm^3) was added $(Me_3Si)_3SiH$ (0.32 g, 1.27 mmol) and AIBN (10mg). The solution was stirred at 60 °C for 30 hr. The reaction mixture was partitioned between EtOAc (4x 50 cm^3) and water (60 cm^3). The organic layers were combined, washed with brine, dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by column chromatography eluting with 50-100% EtOAc in petroleum ether to give 100 mg (52%) of the desired carbamate as a white solid (mp 156 °C). (Found : C 53.12%; H 5.97%; N 6.03%, $C_{10}H_{13}NO_5$ requires C 52.86%; H 5.77%; N 6.16%), δ_H (500 MHz): 1.28 (3H, J=7 Hz, OCH_2CH_3), 1.75 (1H, dd, J=14 and 3 Hz, 2-*H-endo*), 2.52 (1H, m, 2-*H-exo*), 2.67 (1H, d, J=2 Hz, 10-*H*), 4.19 (2H, q, J=7 Hz, OCH_2CH_3), 4.37 (1H, m, 7-*H*), 4.53 (1H, t, J=5 Hz, 8-*H*), 4.85 (2H, m, 1-*H* and 3-*H*), 6.59 (1H, s, N*H*), δ_C (126 MHz): 14.4 (OCH_2CH_3), 37.92 (2-*C*), 53.7 (7-*C*), 57.8 (10-*C*), 61.9 (OCH_2CH_3), 68.2 (8-*C*), 75.9 and 79.5 (1-*C* and 3-*C*), 150.8 (NCO_2), 170.8 (CO_2Et), *m/z* (ES^+) 228 (MH^+), 250 (MNa^+), υ_{max} (Golden gate) 3286 (NH), 1715 (C=O), 1665, 1191, 123, 1095, 1015, 803, 760 and 705 cm^{-1}.



Preparation of *E*-3-methyl-1-nitro-but-1-ene (276).[90]

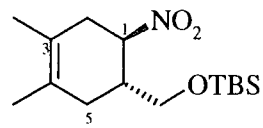
To a solution of nitromethane (4.24 g, 69.4 mmol) and isobutyraldehyde (5.0 g, 69.4 mmol) in MeOH (20 cm^3) at 0 °C was added NaOH (3.3 g, 83.3 mmol). The reaction mixture was stirred at 25 °C for 6 hr. The reaction mixture was partitioned between Et_2O (4x 80 cm^3) and water (100 cm^3). The organic layers were combined, washed with water (20 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by column chromatography eluting with 10% Et_2O in petroleum ether to give 2.2 g (28%) of the desired nitroalkene as a colourless oil. δ_H (300 MHz): 1.14 (6H, d, J=7 Hz, $CH(CH_3)_2$), 2.58 (1H, m, $CH(CH_3)_2$), 6.94 (1H, d, J=14 Hz, 1-*H*), 7.25 (1H, dd, J=14 and 7 Hz, 2-*H*), δ_C (50.3 MHz): 21.1 ($CH(CH_3)_2$), 28.5 ($CH(CH_3)_2$), 138.3 and 148.7 (1-*C* and 2-*C*), *m/z* (EI) 115 (M^+), υ_{max} (neat) 1645, 1529 (NO_2), 1467, 1351, 970, 843 and 741 cm^{-1}.



Preparation of ethyl 3,4-dimethyl-6-nitro-cyclohex-3-enecarboxylate (279).

To a solution of nitroacrylate **132** (1.0 g, 6.9 mmol) in benzene (15 cm^3) at 25 °C was added 2,3-dimethylbuta-1,3-diene **278** (2.8 g, 34.5 mmol). The reaction mixture was stirred at 50 °C for 16 hr. The resulting solution was evaporated under reduced pressure and the residue was purified by column chromatography eluting with 5% Et_2O in petroleum ether to yield 1.35 g (86%) of the desired ester as a yellow oil. δ_H (300 MHz): 1.24 (3H, t, J=7 Hz, OCH_2CH_3), 1.64 (6H, s, 2x CH_3), 2.05-2.65 (4H, m, 2-H_2 and 5-H_2), 3.21 (1H, ddd, J=12, 12 and 6 Hz, 1-*H*), 4.16 (2H, q, J=7 Hz,

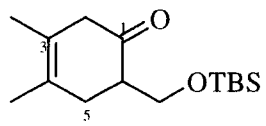
OCH_2CH_3), 4.85 (1H, ddd, J=12, 12 and 6 Hz, 6-*H*), δ_C (75.4 MHz): 14.3 (OCH_2CH_3), 18.5 and 18.8 (2x CH_3), 34.0 and 36.4 (2-*C* and 5-*C*), 43.4 (1-*C*), 61.5 (OCH_2CH_3), 82.8 (6-*C*), 122.6 and 124.5 (3-*C* and 4-*C*), 172.5 (CO_2Et), υ_{max} (neat) 2920, 1735 (C=O), 1555 (NO_2), 1444, 1382, 1310, 1232, 1187 and 1031 cm^{-1}.



Preparation of *trans*-4-[(*tert*-butyldimethylsiloxy)methyl]-1,2-dimethyl-5-nitro-cyclohexene (280).

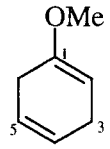
To a solution of the nitro ester **279** (0.5 g, 2.2 mmol) in THF (50 cm^3) at –78 °C was added DIBALH (1M in THF, 7.71 cm^3, 7.71 mmol) dropwise over 5 min. The solution was stirred at –78 → 25 °C for 4 hr. To the reaction mixture was added MeOH (1 cm^3) and the resultant slurry was diluted with EtOAc (200 cm^3) and water (200 cm^3). The mixture was filtered with celite and the organic layer was separated. The aqueous layer was re-extracted with EtOAc (250 cm^3). The organic layers were combined, washed with brine, dried ($MgSO_4$) and evaporated under reduced pressure. The residue was dissolved in DMF (2 cm^3) and was added TBSCl (0.50 g, 3.3 mmol) and imidazole (0.37 g, 5.5 mmol) and the solution was stirred at 25 °C for 2 hr. The reaction mixture was partitioned between EtOAc (2x 40 cm^3) and water (40 cm^3). The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by column chromatography eluting with 5% Et_2O in petroleum ether to yield 0.36 g (55%) as a colourless oil. (Found : C 60.19%; H 9.99%; N 4.44%, $C_{15}H_{29}NO_3Si$ requires C 60.16%; H 9.76%; N 4.68%), δ_H (300 MHz): 0.02 (6H, s, TBS), 0.88 (9H, s, TBS), 1.63 (6H, s, 2x CH_3), 2.03-2.89 (5H, m, 3-H_2, 4-*H* and 6-H_2), 3.54 (2H, m, CH_2OTBS), 4.71 (1H, ddd, J=10, 10 and 6 Hz, 5-*H*), δ_C (75.4 MHz): -5.5 (TBS), 18.5 (TBS), 18.8 and 18.9 (2x CH_3), 26.0 (TBS), 33.3, 36.4 and 39.7 (3-*C*, 4-*C* and 6-*C*), 63.1 (CH_2OTBS), 84.4 (5-*C*), 121.7

and 125.4 (1-*C* and 2-*C*), *m/z* (CI) 300 (MH^+), 317 (MNH_4^+), υ_{max} (neat) 2928, 2857, 1549 (NO_2), 1471, 1387, 1255, 1087, 839 and 777 cm^{-1}.



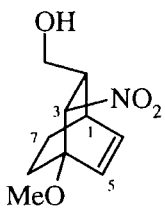
Preparation of 6-[(*tert*-Butyldimethylsiloxy)methyl]-3,4-dimethyl-cyclohex-3-enone (282).

To a solution of nitro ether **280** (105 mg, 0.35 mmol) and 2-*tert*-butyl-1,1,3,3-tetramethylguanidine (90 mg, 0.53 mmol) in methanol (1 cm^3) was added a suspension of ammonium acetate (0.54 g, 7.02 mmol) and $TiCl_3$ (1M in CH_2Cl_2/THF, 1.75 cm^3, 1.75 mmol) in water (20 cm^3). The resultant dark suspension was stirred at 25 °C for 12 hr. The reaction mixture was partitioned between Et_2O (4x 20 cm^3) and saturated $NaHCO_3$ solution (30 cm^3). The organic layers were washed with water (20 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by column chromatography eluting with 2-20% Et_2O in petroleum ether to give 28 mg (20%) of the desired ketone as a colourless oil. δ_H (300 MHz): 0.04 (6H, s, TBS), 0.87 (9H, s, TBS), 1.64 and 1.71 (2x CH_3), 2.11-3.07 (5H, m, 2-H_2, 5-H_2 and 6-*H*), 3.65 (1H, dd, J=10 and 8 Hz, CH_2OTBS), 3.94 (1H, dd, J=10 and 5 Hz, CH_2OTBS), δ_C (50.3 MHz): -5.2 (TBS), 18.5 and 18.9 (2x CH_3), 26.1 (TBS), 35.7, 46.2 and 50.6 (2-*C*, 5-*C* and 6-*C*), 62.5 (CH_2OTBS), 123.3 and 126.1 (3-*C* and 4-*C*), 211.4 (*C*=O), *m/z* (ES^+) 291 (MNa^+), υ_{max} (neat) 2954, 2928, 2857, 1717 (C=O), 1255, 1100, 837 and 777 cm^{-1}.



Preparation of 1-methoxycyclohexa-1,4-diene (115).[92]

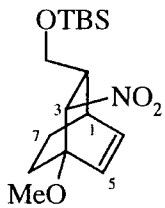
To a solution of anisole (100 g, 930 mmol) in Et_2O (300 cm^3) at –78 °C was added liquid ammonia (1.3L) followed by the portionwise addition of lithium metal (25 g) over 20 min with stirring. The blue solution was stirred for 3 hr and EtOH (300 cm^3) was added. The reaction mixture was allowed to stir at –78 °C for a further 3 hr. The reaction was quenched by the addition of $NH_4Cl_{(S)}$ (50 g) and the solution was allowed to warm to 25 °C over 12 hr. The colourless solution was partitioned between Et_2O (3x 600 cm^3) and water (800 cm^3). The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated under reduced pressure. The crude product was vacuum distilled to yield 93.1 g (91%) of the desired diene as a colourless oil (bp 50 °C at 40 mbar). δ_H (300 MHz): 2.61-2.97 (4H, m, 3-H_2 and 6-H_2), 3.55 (3H, s, OCH_3), 4.63 (1H, s, 2-*H*), 5.69 (2H, br s, 4-*H* and 5-*H*), δ_C (50.3 MHz): 26.4 and 28.6 (3-*C* and 6-*C*), 53.7 (OCH_3), 90.7, 123.2, 124.6 and 152.9 (1-*C*, 2-*C*, 4-*C* and 5-*C*), *m/z* (EI) 110 (M^+), υ_{max} (neat) 1735, 1553, 1444, 1379, 1294, 1262, 1245, 1186 and 1019 cm^{-1}.



Preparation of *trans*-2-hydroxymethyl-3-nitro-4-methoxybicyclo[2.2.2]oct-5-ene (288)

To a solution of nitro ester **150** (0.3 g, 1.18 mmol) in THF (25 cm^3) at –78 °C was added DIBALH (1M in THF, 4.13cm^3, 4.13 mmol) dropwise over 5 min. The solution

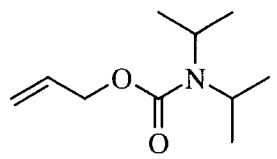
was stirred at –78 → 25 °C for 4 hr. To the reaction mixture was added MeOH (1 cm^3) and the resultant slurry was diluted with EtOAc (400 cm^3) and water (400 cm^3). The mixture was filtered with celite and the organic layer was separated. The aqueous layer was further extracted with EtOAc (2x 250 cm^3). The organic layers were combined, washed with brine, dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by column chromatography eluting with 30-60% EtOAc in petroleum ether to give 210 mg (84%) of the desired alcohol as a white solid (mp 47 °C). (Found : C 56.47%, H 7.14%; N 6.39%, $C_{10}H_{15}NO_4$ requires C 56.33%; H 7.09%; N 6.57%), δ_H (500 MHz): 1.20-1.85 (5H, m, 7-H_2, 8-H_2 and O*H*), 2.35 (1H, m, 2-*H*), 2.65 (1H, m, 1-*H*), 3.40 (3H, s, OCH_3), 3.72 (2H, m, CH_2OH), 4.63 (1H, d, J=5 Hz, 3-*H*), 6.19 (1H, d, J=9 Hz, 5-*H*), 6.48 (1H, dd, J=9 and 7 Hz, 6-*H*), δ_C (126 MHz): 20.1 and 26.8 (7-*C* and 8-*C*), 31.0 (1-*C*), 48.3 (2-*C*), 51.4 (OCH_3), 64.0 (CH_2OH) , 79.2 (4-*C*), 90.5 (3-*C*), 131.2 (5-*C*), 134.2 (6-*C*), *m/z* (CI) 231 (MNH_4^+), υ_{max} (Golden Gate) 3294 (OH), 2938, 1552 (NO_2), 1367, 1117, 1061, 1030, 1001 and 698cm^{-1}.



Preparation of *trans*-2-[(*tert*-Butyldimethylsiloxy)methyl]-3-nitro-4-methoxybicyclo [2.2.2]oct-5-ene (289).

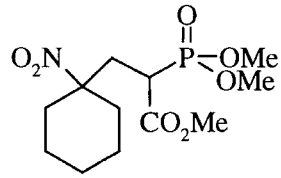
To a solution of alcohol **288** (0.5 g, 2.35 mmol) in DMF (5 cm^3) was added TBSCl (0.42 g, 2.82 mmol) and imidazole (0.40 g, 5.87 mmol) and the resulting solution was stirred at 25 °C for 2 hr. The reaction mixture was partitioned between EtOAc (2x 80 cm^3) and water (60 cm^3). The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by column chromatography eluting with 10% EtOAc in petroleum ether to yield 0.5 g (65%) as a white solid (mp 49 °C). (Found : C 58.87%, H 8.96%; N 4.20%,

$C_{16}H_{29}NO_4Si$ requires C 58.68%; H 8.93%; N 4.28%), δ_H (500 MHz): 0.05 (6H, s, TBS), 0.87 (9H, s, TBS), 1.20-1.85 (4H, 7-H_2 and 8-H_2), 2.33 (1H, m, 2-*H*), 2.60 (1H, m, 1-*H*), 3.40 (3H, s, OCH_3), 3.66 (2H, m, CH_2OTBS), 4.64 (1H, d, J=5 Hz, 3-*H*), 6.17 (1H, d, J=9 Hz, 5-*H*), 6.48 (1H, dd, J=9 and 7 Hz, 6-*H*), δ_C (126 MHz): -5.3 (TBS), 18.4 (TBS), 20.2 and 26.8 (7-*C* and 8-*C*), 26.0 (TBS), 31.5 (1-*C*), 48.2 (2-*C*), 51.3 (O*C*H_3), 64.0 (*C*H_2OTBS), 79.2 (4-*C*), 90.1 (3-*C*), 131.1 (5-*C*), 134.4 (6-*C*), *m/z* (CI) 328 (MH^+), 345 (MNH_4^+), υ_{max} (Golden Gate) 2928, 1739, 1549 (NO_2), 1469, 1364, 1248, 1081, 833, 774 and 694 cm^{-1}.



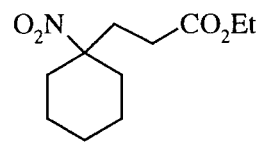
Preparation of Diisopropyl carbamic acid allyl ester (299).[110]

To a solution of diisopropylamine (25.3 g, 250 mmol) in THF (100 cm^3) was added Et_3N (25 g, 250 mmol. The solution was cooled to 0 °C and allylchloroformate (20 g, 167 mmol) was added with stirring. The reaction mixture was stirred at 25 °C for 1 hr. The reaction mixture was filtered, concentrated and diluted with Et_2O. The mixture was again filtered, concentrated and the residue was vacuum distilled (89 °C at 20 mbar), [lit. 83 °C at 13 mbar] to yield 8.3 g (27%) of the desired carbamate as a colourless oil. δ_H (300 MHz): 1.19 (12H, d, J=7 Hz, CH(CH_3)$_2$), 3.90 (2H, br s, C*H*(CH$_3$)$_2$), 4.57 (2H, d, OCH_2), 5.13-5.33 (2H, m, CH_2=CH), 4.93 (1H, m, CH$_2$=C*H*), δ_C (75.4 MHz): 21.1 (CH(*C*H$_3$)$_2$, 45.9 (*C*H(CH$_3$)$_2$, 65.5 (OCH$_2$), 117.1 and 133.7 (*C*H$_2$=*C*H), 155.5 (N*C*O$_2$), *m/z* (CI) 186 (MNH_4^+), υ_{max} (neat) 2970, 1693 (C=O), 1440, 1368, 1310, 1218, 1134, 1053 and 771cm^{-1}.



Preparation of trimethyl 3-(1-nitro-cyclohexyl)-2-phosphonopropionate (304).

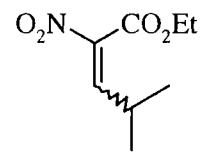
To a solution of nitrocyclohexane **302** (0.2 g, 1.55 mmol) and 2-*tert*-butyl-1,1,3,3-tetramethylguanidine (0.4 g, 2.33 mmol) in CH_3CN (5 cm^3) was added trimethyl 2-phosphonoacrylate (60 mg, 3.10 mmol). The solution was stirred at 25 °C for 24 hr. The reaction mixture was partitioned between EtOAc (2x 50 cm^3) and water (40 cm^3). The organic layer was separated, dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by column chromatography eluting with 10% Et_2O in petroleum ether to give 0.43 g (86%) of the desired adduct as a pale yellow oil. δ_H (300 MHz): 1.20-3.10 (13H, m, CH_2 and CH), 3.75 (9H, m, 3x OCH_3), δ_C (75.4 MHz): 22.3, 24.7, 33.4, 37.1 and 39.6 (CH_2), 90.6 (CNO_2), 169.0 (CO_2Me), *m/z* (CI) 324 (MH^+), 341 (MNH_4^+).



Preparation of ethyl 3-(1-nitro-cyclohexyl)-propionate (305).

To a solution of nitrocyclohexane **302** (0.2 g, 1.55 mmol) and 2-*tert*-butyl-1,1,3,3-tetramethylguanidine (0.4 g, 2.33 mmol) in CH_3CN (5 cm^3) was added ethyl acrylate (0.34 cm^3, 3.10 mmol). The solution was stirred at 25 °C for 24 hr. The reaction mixture was partitioned between EtOAc (2x 50 cm^3) and water (40 cm^3). The organic layer was separated, dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by column chromatography eluting with 10% Et_2O in petroleum ether to give 0.26 g (73%) of the desired ester as a colourless oil. δ_H (300 MHz):

1.21 (3H, t, J=7 Hz, OCH_2CH_3), 1.22-2.45 (14H, m, 7x CH_2), 4.08 (2H, q, J=7 Hz, OCH_2CH_3), δ_C (75.4 MHz): 14.3 (OCH_2CH_3), 22.4, 24.8, 28.5, 34.0 and 35.1 (CH_2), 60.9 (OCH_2CH_3), 90.7 (CNO_2), 172.3 (CO_2Et), *m/z* (CI) 247 (MNH_4^+), υ_{max} (neat) 2940, 2868, 1736 (C=O), 1536 (NO_2), 1450, 1379, 1346, 1303, 1179, 1021 and 843 cm^{-1}.



Preparation of ethyl 4-methyl-2-nitro-pent-2-enoate .

To a solution of nitroacetate (5.0 g, 38 mmol) and isobutyraldehyde (5.4 g, 75 mmol) in toluene (20 cm^3) was added piperidine (135 mg, 1.90 mmol) and benzoic acid (139 mg, 1.14 mmol). The solution was stirred at reflux in a Dean-Stark apparatus for 2 hr. The reaction mixture was dissolved in EtOAc (50 cm^3) and washed with 1M HCl (30 cm^3), saturated $NaHCO_3$ solution (30 cm^3) and brine (20 cm^3). The organic layers were dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by column chromatography eluting with 10% Et_2O in petroleum ether to give 1.0 g (15%) of the desired α-nitroacrylate as a colourless oil. Isomer ratio=2.3:1.

Major isomer δ_H (300 MHz): 1.13 (6H, d, J=7 Hz, 2x CH_3), 1.33 (3H, t, J=7 Hz, OCH_2CH_3), 2.62 (1H, m, 4-*H*), 4.31 (2H, q, J=7 Hz, OCH_2CH_3), 6.65 (1H, d, J=12 Hz 3-*H*), δ_C (75.4 MHz): 14.2 (OCH_2CH_3), 21.7 (CH_3), 28.5 (4-*C*), 63.0 (OCH_2CH_3), 142.8 (2-*C*) 145.5 (3-*C*), 159.0 (CO_2Et).

Minor isomer δ_H (300 MHz): 1.13 (6H, d, J=7 Hz, 2x CH_3), 1.34 (3H, t, J=7 Hz, OCH_2CH_3), 2.86 (1H, m, 4-*H*), 4.35 (2H, q, J=7 Hz, OCH_2CH_3), 7.03 (1H, d, J=12 Hz 3-*H*), δ_C (75.4 MHz): 14.1 (OCH_2CH_3), 21.8 (CH_3), 28.1 (4-*C*), 62.8 (OCH_2CH_3), 143.3 (2-*C*) 148.6 (3-*C*), 160.1 (CO_2Et).

m/z (ES^+) 210 (MNa^+), υ_{max} (neat) 2972, 1736 (C=O), 1537 (NO_2), 1376, 1258, 1155, 1055 and 874 cm^{-1}.

SECTION D: Appendix

Lectures, Seminars and Colloquia

Appendix

Lectures and Seminars from invited speakers 1997–2000

1997

October 8 Professor E Atkins, Department of Physics, University of Bristol
Advances in the control of architecture for polyamides: from nylons to genetically engineered silks to monodisperse oligoamides

October 15 Dr. R M Ormerod, Department of Chemistry, Keele University*
Studying catalysts in action

October 21 Professor A F Johnson, IRC, Leeds*
Reactive processing of polymers: science and technology

October 22 Professor R J Puddephatt, University of Western Ontario*
Organoplatinum chemistry and catalysis

October 23 Professor M R Bryce, University of Durham, Inaugural Lecture.
New Tetrathiafulvalene Derivatives in Molecular, Supramolecular and Macromolecular Chemistry: controlling the electronic properties of organic solids

October 28 Professor A P de Silva, The Queen's University, Belfast
Luminescent signalling systems"

October 29 Professor R Peacock, University of Glasgow*
Probing chirality with circular dichroism

November 5 Dr. M Hii, Oxford University*
Studies of the Heck reaction

November 11 Professor V Gibson, Imperial College, London*
Metallocene polymerisation

November 12 Dr. J Frey, Department of Chemistry, Southampton University
Spectroscopy of liquid interfaces: from bio-organic chemistry to atmospheric chemistry

November 19 Dr. G Morris, Department of Chemistry, Manchester Univ.*
Pulsed field gradient NMR techniques: Good news for the Lazy and DOSY

November 20 Dr. L Spiccia, Monash University, Melbourne, Australia
Polynuclear metal complexes

November 25 Dr. R Withnall, University of Greenwich
Illuminated molecules and manuscripts

November 26 Professor R W Richards, University of Durham, Inaugural Lecture
A random walk in polymer science

December 2 Dr. C J Ludman, University of Durham*
Explosions

December 3 Professor A P Davis, Department. of Chemistry, Trinity College Dublin*
Steroid-based frameworks for supramolecular chemistry

December 10 Sir G Higginson, former Professor of Engineering in Durham and retired Vice-Chancellor of Southampton Univ.
1981 and all that.

December 10 Professor M Page, University of Huddersfield*
The mechanism and inhibition of beta-lactamases

1998

January 14 Professor D Andrews, University of East Anglia
Energy transfer and optical harmonics in molecular systems

January 20 Professor J Brooke, University of Lancaster
What's in a formula? Some chemical controversies of the 19th century

January 27 Professor R Jordan, Dept. of Chemistry, Univ. of Iowa, USA.
Cationic transition metal and main group metal alkyl complexes in olefin polymerisation

January 28 Dr. S Rannard, Courtaulds Coatings (Coventry)
The synthesis of dendrimers using highly selective chemical reactions

February 3 Dr. J Beacham, ICI Technology
The chemical industry in the 21st century

February 4 Professor P Fowler, Department of Chemistry, Exeter University
Classical and non-classical fullerenes

February 17 Dr. S Topham, ICI Chemicals and Polymers
Perception of environmental risk; The River Tees, two different rivers

February 18 Professor G Hancock, Oxford University*
Surprises in the photochemistry of tropospheric ozone

February 24 Professor R Ramage, University of Edinburgh*
The synthesis and folding of proteins

February 25 Dr. C Jones, Swansea University
Low coordination arsenic and antimony chemistry

March 4 Professor T C B McLeish, IRC of Polymer Science Technology, Leeds University
The polymer physics of pyjama bottoms (or the novel rheological characterisation of long branching in entangled macromolecules)

March 11 Professor M J Cook, Dept of Chemistry, UEA
How to make phthalocyanine films and what to do with them.

March 17 Professor V Rotello, University of Massachusetts, Amherst
The interplay of recognition & redox processes – from flavoenzymes to devices

March 18 Dr. J Evans, Oxford University
Materials which contract on heating (from shrinking ceramics to bullet proof vests)

October 7 Dr. S Rimmer, Ctr Polymer, University of Lancaster
New Polymer Colloids

October 21 Professor P Unwin, Department of Chemistry, Warwick University
Dynamic Electrochemistry: Small is Beautiful

October 23 Professor J C Scaiano, Department of Chemistry, University of Ottawa, Canada
In Search of Hypervalent Free Radicals

October 26 Dr. W Peirs, University of Calgary, Alberta, Canada
Reactions of the Highly Electrophilic Boranes $HB(C_6F_5)_2$ and $B(C_6F_5)_3$ with Zirconium and Tantalum Based Metallocenes

October 27 Professor A Unsworth, University of Durham*
What's a joint like this doing in a nice girl like you?

October 28 Professor J P S Badyal, University of Durham
Tailoring Solid Surfaces, Inaugural Lecture

November 4 Dr. N Kaltscoyannis, Department of Chemistry, UCL, London
Computational Adventures in d & f Element Chemistry

November 3 Dr. C J Ludman, Chemistry Department, University of Durham*
Bonfire night Lecture

November 10 Dr. J S O Evans, Chemistry Department, University of Durham
Shrinking Materials

November 11 Dr. M Wills, Department of Chemistry, University of Warwick*
New Methodology for the Asymmetric Transfer Hydrogen of Ketones

November 12 Professor S Loeb, University of Windsor, Ontario, Canada
From Macrocycles to Metallo-Supramolecular Chemistry

November 17 Dr. J McFarlane*
Nothing but Sex and Sudden Death!

November 18 Dr. R Cameron, Department of Materials Science & Metallurgy, Cambridge University
Biodegradable Polymers

November 24 Dr. B G Davis, Department of Chemistry, University of Durham*
Sugars and Enzymes

December 1 Professor N Billingham, University of Sussex
Plastics in the Environment - Boon or Bane

December 2 Dr. M Jaspers, Department of Chemistry, University of Aberdeen*
Bioactive Compounds Isolated from Marine Inverterates and Cyanobacteria

December 9 Dr. M Smith Department. of Chemistry, Warwick University
Multinuclear solid-state magnetic resonance studies of nanocrystalline oxides and glasses

1999

January 19 Dr. J Mann, University of Reading*
The Elusive Magic Bullet and Attempts to find it?

January 20 Dr. A Jones, Department of Chemistry, University of Edinburgh
Luminescence of Large Molecules: from Conducting Polymers to Coral Reefs

January 27 Professor K Wade, Department of Chemistry, University of Durham*
Foresight or Hindsight? Some Borane Lessons and Loose Ends

February 3 Dr. C Schofield, University of Oxford*
Studies on the Stereoelectronics of Enzyme Catalysis

February 9 Professor D J Cole-Hamilton, St. Andrews University
Chemistry and the Future of life on Earth

February 10 Dr. C Bain, University of Oxford
Surfactant Adsorption and Marangoni Flow at Expanding Liquid Surfaces

February 17 Dr. B Horrocks, Department of Chemistry, Newcastle University
Microelectrode techniques for the Study of Enzymes and Nucleic Acids at Interfaces

February 23	Dr. C Viney, Heriot-Watt* *Spiders, Slugs And Mutant Bugs*
February 24	Dr. A-K Duhme, University of York *Bioinorganic Aspects of Molybdenum Transport in Nitrogen-Fixing Bacteria*
March 3	Professor B Gilbert, Department of Chemistry, University of York *Biomolecular Damage by Free Radicals: New Insights through ESR Spectroscopy*
March 9	Dr. Michael Warhurst, Chemical Policy issues, Friends of the Earth *Is the Chemical Industry Sustainable?*
March 10	Dr. A Harrison, Department of Chemistry, The University of Edinburgh *Designing Model MagneticMaterials*
March 17	Dr. J Robertson, University of Oxford* *Recent Developments in the Synthesis of Heterocyclic Natural Products*
May 11	Dr. John Sodeau, University of East Anglia *Ozone Holes and Ozone Hills*
May 12	Dr. Duncan Bruce, Exeter University *The Synthesis and Characterisation of Liquid-Crystalline Transition Metal Complexes*
October 12	Dr. S. Beckett (Nestle) *Chocolate for the next Millennium*
October 13	Professor G. Fleet, University of Oxford* *Sugar Lactone and Amino Acids*
October 19	Professor K. Gloe, TU Dresden, Germany *Tailor Made Molecules for the Selective binding of Metal Ions*
October 20	Professor S. Lincoln, University of Adelaide *Aspects of Complexation and Supramolecular Chemistry*
October 25	Professor S. Collins, University of Waterloo, Canada *Methacrylate Polymerization Using Zirconium Enolate Initiators: Polymerization Mechanisms and Control of Polymer Tacticity*
October 26	Dr. D. Hughes (Astra Zeneca) *Perspectives in Agrochemistry*
October 27	Dr. C. Braddock, Imperial College *Novel catalysts for Atom Economic Transformations*
November 3	Professor D.W. Smith, University of Waikato, NZ *The Strengths of C-C and C-H Bonds in Organic and Organometallic Molecules: Empirical, Semi-empirical and Ab Initio Calculations*

November 10 Dr. I. Samuel, Department of Physics, University of Durham
Improving Organic Light Emitting Diodes by Molecular, Optical and Device Design

November 16 Professor A. Holmes
Conjugated Polymers for the Market Place

November 17 Dr. J. Rourke, University of Warwick*
C-H Activation Induced by Water

November 18 Dr. G. Siligardi, Kings College London
The Use of Circular Dichrosim to Detect and Characterise Biomolecular Interactions in Solution.

November 23 Professor B. Caddy
Trace evidence - a challenge for the forensic scientist

November 24 Professor T. Jones, Imperial College
Atomic and Molecular Control of Inorganic and Organic Semiconductor Thin Films

November 30 Rev. R. Lancaster
Principles and Practice

December 8 Professor D. Crout, Department of Chemistry, University of Warwick*
More than Simply Sweet: Carbohydrates in Medicine and Biology

2000

January 12 Professor D. Haddleton, Department of Chemistry, University of Warwick
Atom Transfer Polymerisation - What's all the Hype About?

January 19 Dr. P.R. Fielden, UMIST
Miniaturised Chemical Analysis (Lab-on-a-Chip): Functional or Merely Fashionable?

January 25 Professor B. Meijer
From Supramolecular Architecture Towards Functional Materials

January 26 Professor S. Flisch, University of Edinburgh
The challenges involved in protein glycosylation - synthesis of glycan chains and selective attachment to proteins

February 2 Chick Wilson, Head of Crytallography, ISIS, Rutherford Appleton Lab
Protons in motion? Neutron diffraction studies of hydrogen atoms in organic crystal structures.

February 9 Dr. S. Moratti, University of Cambridge
Shape and Stereoselectivity in Polymer

February 15 Professor D. Phillips
A Little Light Relief

February 16 Professor Kocienski, University of Glasgow*
Asymmetric Synthesis Using Planar Chiral TT-Allyl Cationic Complexes

February 23 Dr. N. Clarke, UMIST
The Flow of Polymer Blends

February 22 Professor G. Stuart
Brewing - Evolution from a Craft into a Technology

March 1 Professor D. Tildsley, Unilever (Head of Research)
Computer Simulation of Interfaces: Fact and Friction

March 7 Prof. Motherwell, Unviersity College, London*
Curiosity and Simplicity - Essential Ingredients for the Discovery of New Reactions

March 8 Professor J. Courtieu, Universite de Paris-Sud, Orsay
Chiral Recognition through NMR in Liquid Crystal Solvents: an Order Affair

March 9 Dr. Antony Fairbanks, Dyson-Perrins Laboratory, Oxford
Selectivity in Glycoside Formation"

March 20 Professor S Marder, Professor of Chemistry and Optical Sciences, University of Arizona
Design of Molecules for Two-Photon Absorption and their Application to 3D Polymerization and Imaging

March 21 Professor E. Rizzardo, CSIRO Mol. Sci. Victoria, Australia
Designed Polymers by Free Radical Addition-Fragmentation Processes

May 5 Professor R. Hochstrasser, University Pennsylvania, USA
Ultrafast Molecular and Protein Dynamics seen through their Vibrations

* *Those attended by the author.*

First Year Induction Course

This course consists of a series of one-hour lectures on services available in the department.

Safety Matters	Mr. D. Hunter
Electrical Appliances	Mr. B.T. Barker
Library Facilities	Mrs. M. Hird
Mass Spectrometry	Dr. M. Jones
NMR Spectroscopy	Dr. A.M. Kenwright
Glass-Blowing Techniques	Mr. R. Hart, & Mr. G. Haswell

Two courses, each of 8 hours tuition were attended.

Synthetic Organometallic Chemistry	Prof. D. Parker
Practical Nuclear Magnetic Resonance	Dr. A.M. Kenwright

One course of 28 hours tuition was also attended.

The Molecular Basis of Disease	Dr. K. Elborough (Biology Department)

Seminars, Colloquia, Presentations and Publications

December	1997	Modern Aspects of Stereochemistry, Sheffield
April	1998	1998 RSC National Congress, Durham
June	1998	Graduate Colloquia, Durham
December	1998	Modern Aspects of Stereochemistry, Sheffield
March	1999	Novel Organic Chemistry, 10th SCI Symposium, Glasgow
July	1999	Graduate Colloquia, Durham
September	1999	10th Medicinal Chemistry Symposium, Cambridge, UK
December	1999	Modern Aspects of Stereochemistry, Sheffield
July	2000	Graduate Colloquia, Durham‡
August	2000	220th National Meeting of the ACS, Washington DC†

† Poster presentation by author

‡ Oral presentation by author

SECTION E: References

References

1. (a) H. Shechter, F. Conrad, A. L. Daulton and R. B. Kaplan, *J. Am. Chem. Soc.*, 1952, **74**, 3052; (b) H. Shechter and F. Conrad, *J. Am. Chem. Soc.*, 1953, **75**, 5610.

2. (a) C. J. Coles, D. E. Edmondson and T. P. Singer, *J. Biol. Chem.*, 1979, **254**, 5161; (b) R. L. Baxter, A. B. Hanley, H. W-S. Chan, S. L. Greenwood, E. M. Abbot, I. J. McFarlane and K. Milne, *J. Chem. Soc., Perkin Trans. I*, 1992, 2495; (c) P. Shaw, *Biochemistry*, 1967, **6**, 2253.

3. S. Danishefsky, M. P. Prisbylla and S. Hiner, *J. Am. Chem. Soc.*, 1978, **100**, 2918. See also M. Petrzilka and J. I. Grayson, *Synthesis*, 1981, 753.

4. T. E. Stevens and W. D. Emmons, *J. Am. Chem. Soc.*, 1958, **80**, 338.

5. J. E. McMurry and J. H. Musser, *Org. Synth.*, 1977, **56**, 65.

6. (a) A. F. McAnda, K. D. Roberts, A. J. Smallridge, A. Ten and M. A. Trewhella, *J. Chem. Soc., Perkin Trans. I*, 1998, 501; (b) R. Ballini, R. Castagnani and M. Petrini, *J. Org. Chem.*, 1992, **57**, 2160; (c) J. Melton and J. E. McMurry, *J. Org. Chem.*, 1975, **40**, 2138; (d) A. G. M. Barrett and G. G. Graboski, *Chem. Rev.*, 1986, **86**, 751.

7. (a) D. L. J. Clive and N. Selvakumar, *Chem. Commun.*, 1996, 2543; (b) D. L. J. Clive, Y. Bo, Y. Tao, S. Daigneault, Y-J. Wu and G. Meignan, *J. Am. Chem. Soc.*, 1996, **118**, 4904; (c) D. L. J. Clive, Y. Bo, Y. Tao, S. Daigneault, Y-J. Wu and G. Meignan, *J. Am. Chem. Soc.*, 1998, **120**, 10332; (d) D. L. J. Clive, Y Bo, N. Selvakumar, R. McDonald and B. D. Santarsiero, *Tetrahedron*, 1999, **55**, 3277.

8. A. P. Kozikowski and J-P. Wu, *Synlett*, 1991, 465.

9. (a) R. S. Fornicola, E. Oblinger and J. Montgomery, *J. Org. Chem.*, 1998, **63**, 3528; (b) D. C. Horwell, P. D. Nichols, G. S. Ratcliffe and E. Roberts, *J. Org. Chem.*, 1994, **59**, 4418; (c) J. E. Baldwin, S. B. Haber, C. Hoskins and L. I. Kruse, *J. Org. Chem.*, 1977, **42**, 1239.

10. For a good example see S. P. Tanis and Y. M. Abdallah, *Synth. Commun.*, 1986, **16**, 251.

11. S. Danishefsky, and F. M. Hershenson, *J. Org. Chem.*, 1979, **44**, 1180.

12. C. Clarke, I. Fleming, J. M. D. Fortunak, P. T. Gallagher, M. C. Honan, A. Mann, C. O. Nübling, P. R. Raithby and J. J. Wolff, *Tetrahedron,* 1988, **44**, 3931.

13. A. Sera, K. Itoh and H. Yamaguchi, *Tetrahedron Lett.*, 1990, **31**, 6547.

14. A. Padwa, L. Fisera, K. F. Koehler, A. Rodriguez and G. S. K. Wong, *J. Org. Chem.*, 1984, **49**, 276.

15. J. W. Patterson and J. E. McMurry, *Chem. Commun.*, 1971, 488.

16. K. Naya, M. Hayashi, I. Tagagi, S. Nakamura and M. Kobayashi, *Bull. Chem. Soc. Jpn.*, 1972, **45**, 3673.

17. R. E. Austin, R. A. Maplestone, A. M. Sefler, K. Liu, W. N. Hruzewicz, C. W. Liu, H. S. Cho, D. E. Wemmer and P.A. Bartlett, *J. Am. Chem. Soc.*, 1997, **119**, 6461.

18. K. Busch, U. M. Groth, W. Kuhnle and U. Schollköpf, *Tetrahedron*, 1992, **48**, 5607.

19. For comprehensive reviews see (a) D. C. Cole, *Tetrahedron,* 1994, **50**, 9517; (b) *Enantioselective Synthesis of β-Amino Acids*, ed. E Juaristi, Wiley-VCH, New York, 1997; (c) P. Murer, B. Rheiner, E. Juaristi and D. Seebach, *Heterocycles*, 1994, **39**, 319; (d) S. Abele and D. Seebach, *Eur. J. Org. Chem.*, 2000, 1; (e) G. Cardillo and C. Tomasini, *Chem. Soc. Rev.*, 1996, 117.

20. For example see (a) D. Seebach and J. L. Matthews, *Chem. Commun.*, 1997, 2015; (b) S. Krauthäuser, L. A. Christianson, D. R. Powell and S. H. Gellman, *J. Am. Chem. Soc.*, 1997, **119**, 11719; (c) D. H. Appella, J. J. Barchi Jr., S. R. Durell and S. H. Gellman, *J. Am. Chem. Soc.*, 1999, **121**, 2309.

21. (a) T. Ando, K. Matsuura, R. Izumi, T. Noda, T. Take, A. Nagata and J. Abe, *J. Antibiot.,* 1971, **24**, 680; (b) T. Wakamiya, T. Shiba and T. Kaneko, *Bull. Chem. Soc. Jpn.*, 1972, **45**, 3668; (c) T. Wakamiya, T. Teshima, I. Kubota, T. Shiba and T. Kaneko, *Bull. Chem. Soc. Jpn.*, 1974, **47**, 2292.

22. (a) Y. Shimojima, H. Hayashi, T. Ooka and M. Shibukawa, *Tetrahedron Lett.*, 1982, **23**, 5435; (b) Y. Shimojima, H. Hayashi, T. Ooka and M. Shibukawa, *Tetrahedron*, 1984, **40**, 2519.

23. Y. Shimojima, T. Shirai, T. Baba and H. Hayashi, *J. Med. Chem.*, 1985, **28**, 3.

24. (a) Y. Hamada, A. Kawai, Y. Kohno, O. Hara and T. Shiori, *J. Am. Chem. Soc.*, 1989, **111**, 1524; (b) Y. Hamada, O. Hara, A. Kawai, Y. Kohno and T. Shiori, *Tetrahedron*, 1991, **47**, 8635.

25. Y. Suhara, J. E. K. Hildreth and Y. Ichikawa, *Tetrahedron Lett.*, 1996, **37**, 1575. See also K. C. Nicolaou, H. Flörke, M. G. Egan, T. Barth and V. A. Estevez, *Tetrahedron Lett.*, 1995, **36**, 1775.

26. (a) B. Castro, J. R. Dormoy, G. Evin and C. Selve, *Tetrahedron*, 1975, **31**, 1219 (b) S. T. Anisfeld and P. Lansbury Jnr, *J. Org. Chem.*, 1990, **55**, 5560.

27. T. Teshima, T. Ando and T. Shiba, *Bull. Chem. Soc. Jpn.*, 1980, **53**, 1191.

28. G. D. Monache, D. Misiti, P. Salvatore and G. Zappia, *Tetrahedron Asymmetry,* 2000, **11**, 1137.

29. S. D. Broady, J. E. Rexhausen and E. J. Thomas, *J. Chem. Soc., Perkin Trans. I*, 1999, 1083. See also R. A. Ward and G. Procter, *Tetrahedron*, 1995, **51**, 12301.

30. J-M. Durgnat and P. Vogel, *Helv. Chim. Acta*, 1993, **76**, 222.

31. P. A. Grieco, T. Ogari and Y. Yokoyama, *Tetrahedron Lett.*, 1978, **17**, 419.

32. (a) P. V. Alston and R. M. Ottenbrite, *J. Org. Chem.*, 1975, **40**, 1111 (b) I. Fleming, In *'Frontier Orbitals and Organic Chemical Reactions'*, Wiley, London, 1996.

33. S. Yamabe and D. Tatsuo, *J. Am. Chem. Soc.*, 1996, **118**, 6518.

34. H. Staudinger and E. Suter, *Chem. Ber.*, 1920, **53B**, 1092.

35. For comprehensive reviews see (a) V. K. Aggarwal, A. Ali, M. P. Coogan, *Tetrahedron,* 1999, **55**, 293; (b) S. Ranganthan, D. Ranganthan and A. K. Mehrotra, *Synthesis*, 1977, 289.

36. P. D. Bartlett and B. E. Tate, *J. Am. Chem. Soc.*, 1956, **78**, 2473.

37. (a) V. K. Aggarwal, Z. Gültekin, R. S. Grainger, H. Adams and P. L. Spargo, *J. Chem. Soc., Perkin Trans. I*, 1998, 2771; (b) W. R. Roush and B. B. Brown, *J. Org. Chem.*, 1992, **57**, 3380.

38. A. P. Kozikowski, W. C. Floyd and P. Kuniak, *J. Chem. Soc., Chem. Commun.*, 1977, 582.

39. J. Leroy, *Tetrahedron Lett.*, 1992, **33**, 2969. See also T. G. Back and D. Wehrli, *Synlett*, 1995, 1123.

40. B. M. Trost and G. Lunn, *J. Am. Chem. Soc.*, 1977, **99**, 7079.

41. J. Martynow, M. Dimitroff and A. G. Fallis, *Tetrahedron Lett.*, 1993, **34**, 8201.

42. D. Kim, P. J. Shim, J. Lee, C. W. Park, S. W. Hong and S. Kim, *J. Org. Chem.*, 2000, **65**, 4864. See also S. A. Monti and Y-L. Yang, *J. Org. Chem.*, 1979, **44**, 897.

43. J. K. Whitesell, C-L. Liu, C. M. Buchanan, H-H. Chen and M. A. Minton, *J. Org. Chem.*, 1986, **51**, 551.

44. M. E. Jung, K. Shishido and L. H. Davis, *J. Org. Chem.*, 1982, **47**, 891.

45. (a) G. Rosini, R. Ballini, M. Petrini and P. Sorrenti, *Synthesis*, 1985, 515; (b) G. Rosini, R. Ballini and P. Sorrenti, *Synthesis*, 1983, 1014.

46. S. E. Denmark, Y-C. Moon, C. J. Cramer, M. S. Dappen and C. B. W. Senanayake, *Tetrahedron*, 1990, **46**, 7373.

47. P. Knochel and D. Seebach, *Synthesis*, 1982, 1017.

48. S. G. Davies and H. J. Sanganese, *Tetrahedron Asymmetry*, 1995, **6**, 671.

49. G. Desimoni, G. Dusi, G. Faita, P. Quadrelli and P. Righetti, *Tetrahedron*, 1995, **51**, 4131.

50. M. Masui and T. Shiori, *Tetrahedron*, 1995, **51**, 8363.

51. D. A. Evans, K. T. Chapman and J. Bisaha, *J. Am. Chem. Soc.*, 1988, **110**, 1239.

52. R. J. Stoodley and W-H. Yuen, *Chem. Commun.*, 1997, 1371.

53. R. B. Woodward and T. J. Katz, *Tetrahedron*, 1959, **5**, 70. See also (a) M. Koerner and B. Rickborn, *J. Org. Chem.*, 1990, **55**, 2662; (b) O. Riant and H. Kagan, *Tetrahedron,* 1994, **50**, 4543.

54. J. P. Michael and N. F. Blom, *J. Chem. Soc., Perkin Trans. 1*, 1989, 623.

55. C. Shin, M. Yamara, E. Inui, Y. Ishida and J. Yoshimura, *Bull. Chem. Soc. Jpn.*, 1978, **51**, 2618.

56. G. Just, A. Martel, K. Grozinger and M. Ramjeesingh, *Can. J. Chem.*, 1975, **53**, 131.

57. V. Rautenstrauch, *Helv. Chim. Acta*, 1972, **55**, 594.

58. M. Node, K. Nishide, H. Imazato, R. Kurosaki, T. Inoue and T. Ikariya, *Chem. Commun.*, 1996, 2559.

59. K. Itoh, K. Kitoh and A. Sera, *Heterocycles*, 1999, **51**, 243. See also M. M. Campbell, A. D. Kaye and M. Sainsbury, *Tetrahedron,* 1982, **38**, 2783.

60. (a) T. Hashimoto, S. Takahashi, H. Naganawa, T. Takita, K. Maeda and H. Umezawa, *J. Antibiot.*, 1972, **25**, 350; (b) T. Hashimoto, S. Kondo, H. Naganawa, T. Takita, K. Maeda and H. Umezawa, *J. Antibiot.,* 1974, **27**, 86; (c) T. Hashimoto, S. Kondo, T. Takita, M. Hamada, T. Takeuchi, Y. Okami, *J. Antibiot.,* 1968, **21**, 653.

61. D. E. Hibbs, M. B. Hursthouse, I. G. Jones, W. Jones, K. M. A. Malik and M. North, *J. Org. Chem.*, 1998, **63**, 1496.

62. (a) C. W. Laidley, W. G. Dauben, Z. R. Guo, J. Y. L. Lam and J. E. Casida, *Bioorg. Med. Chem.*, 1999, **7**, 2937; (b) J. P. Thiery, I. Blazsek, S. Legras, S. Marion, M. Reynes, A. Anjo, R. Adam and J. L. Misset, *Hepatology*, 1999, **29**, 1406; (c) D. L. Siehl, M. V. Subramanian, E. W. Walters, J. H. Blanding, T. Niderman and C. Weinmann, *Weed Science*, 1997, **45**, 628.

63. K. M. Herrmann, *Plant Cell*, 1995, **7**, 907.

64. (a) R. M. Romero, M. F. Roberts and J. D. Phillipson, *Phytochemistry*, 1995, **39**, 263; (b) C. T. Walsh, M. D. Erion, A. E. Walts, J. J. Delany III and G. A. Berchtold, *Biochemistry*, 1987, **26**, 4734.

65. Y. Asano, J. J. Lee, T. L. Shieh, F. Spreafico, C. Kowal and H. G. Floss, *J. Am. Chem. Soc.*, 1985, **107**, 4314.

66. C-Y. P. Teng and B. Ganem, *J. Am. Chem. Soc.*, 1984, **106**, 2463. See also (a) P. P. Policastro, K. G. Au, C. T. Walsh and G. A. Berchtold, *J. Am. Chem. Soc.*, 1984, **106**, 2443; (b) K. M. Mattia and B. Ganem, *J. Org. Chem.*, 1994, **59**, 720.

67. T. Fukuyama, S-I. Nakatsuka and Y. Kishi, *Tetrahedron,* 1981, **37**, 2045. See also (a) R. M. DeMarinis, C. N. Filer, S. M. Waraszkiewicz and G. A. Berchhold, *J. Am. Chem. Soc.*, 1974, **96**, 1192; (b) J. D. Richardson, T. C. Bruice, S. M. Waraszkiewicz and G. A. Berchhold, *J. Org. Chem.*, 1974, **39**, 2088.

68. J. M. Gardiner and M. R. Bryce, *J. Org. Chem.* 1990, **55**, 1261.

69. F. Brion, *Tetrahedron Lett.,* 1982, **23**, 5299. See also (a) M. M. Campbell, A. D. Kaye, M. Sainsbury and R. Yavarzadeh, *Tetrahedron Lett.,* 1984, **25**, 1629 and 2461; (b) M. M. Campbell, A. D. Kaye, M. Sainsbury and R. Yavarzadeh, *Tetrahedron Lett.,* 1984, **25**, 2461; (c) D. Rajapaksa, B. A. Keay and R. Rodrigo, *Can. J. Chem.*, 1984, **62**, 826; (d) E. Couché, R. Deschatrettes, K. Poumellec, M. Bortolussi, G. Mandville and R. Bloch, *Synlett*, 1999, 87.

70. T. D. Krizan and J. C. Martin, *J. Am. Chem. Soc.*, 1983, **105**, 6155.

71. J. R. D. McCormick, J. Reichenthal, U. Hirsch and N. O. Sjolander, *J. Am. Chem. Soc.*, 1962, **84**, 3711.

72. S. Nozaki and I. Muramatsu, , *Bull. Chem. Soc. Jpn.*, 1982, **55**, 2165.

73. J. Otera, K. Nakazawa, K. Sekoguchi and A. Orita, *Tetrahedron*, 1997, **53**, 13633.

74. R. G. Shea , J. N. Fitzner, J. E. Fankhauser, A. Spaltenstein, P. A. Carpino, R. M. Peevey, D. V. Pratt, B. J. Tenge and P. B. Hopkins, *J. Org. Chem.*, 1986, **51**, 5243.

75. (a) M. Rodriguez and M. Goodman, *J. Med. Chem.*, 1984, **27**, 1668; (b) S. Hanessian and R. Schaum, *Tetrahedron Lett.*, 1997, **38**, 163; (c) J. Fischer, C. Kilpert, U. Klein and W. Steglich, *Tetrahedron*, 1986, **42**, 2063; (d) R. F. W.

Jackson, A. B. Rettie, A. Wood and M. J. Withes, *J. Chem. Soc., Perkin Trans. I*, 1994, 1719.

76. J-P. Pete, *Tetrahedron Lett.*, 1992, **33**, 6073.

77. M. C. Kozlowski, N. J. Tom, C. T. Seto, A. M. Sefler and P. A. Bartlett, *J. Am. Chem. Soc.*, 1995, **117**, 2128.

78. D. M. Hodgson, A. J. Thompson, S. Wadman and C. J. Keats, *Tetrahedron*, 1999, **55**, 10815.

79. M. C. Di Giovanni, D. Misiti and G. Zappia, *Tetrahedron,* 1993, **49**, 11321. See also S. G, Davies, G. D. Smyth and A. M. Chippindale, *J. Chem. Soc., Perkin Trans. I*, 1999, 3089.

80. Y. Hanazawa, M. Suzuki, Y. Kobayashi and T. Taguchi, *J. Org. Chem.*, 1991, **56**, 1718.

81. C. Chatgilialoglu, *Acc. Chem. Res.*, 1992, **25**, 188. See also C. Chatgilialoglu, *J. Org. Chem.*, 1988, **53**, 3641.

82. T. Ando, Y. Tsurumi, N. Ohato, I. Uchida, K. Yoshida and M. Okuhara, *J. Antibiot.*, 1988, **41**, 25.

83. D. B. Norris, P. Depledge and A. Jackson, *Chem. Abstr.*, 1991, **115**, 64776*h*.

84. I. Uchida, T. Ando, N. Fukami, K. Yoshida, M. Hashimoto, T. Tada, S. Koda and Y. Morimoto, *J. Org. Chem.*, 1987, **52**, 5292.

85. (a) G. Mehta and K. S. Reddy, *Synlett*, 1996, 625; (b) C-S. Chu, T-H. Lee and C-C. Liao, *Synlett*, 1994, 635.

86. (a) J. F. Devaux, I. Hanna, J-Y. Lalemand, *J. Org. Chem.*, 1993, **58**, 2349; (b) J. F. Devaux, I. Hanna, J-Y. Lalemand, *J. Org. Chem.*, 1997, **62**, 5062.

87. M. Kito, T. Sakai, N. Haruta, H. Shirahama and F. Matsuda, *Synlett*, 1996, 1057.

88. (a) F. Matsuda, M. Kito, T. Sakai, N. Okada, M. Miyashita and H. Shirahama, *Tetrahedron,* 1999, **55**, 14369; (b) M. Kito, T. Sakai, H. Shirahama, M. Miyashita and F. Matsuda, *Synlett*, 1997, 219.

89. M. B. Rubin and R. G. LaBarge, *J. Org. Chem.*, 1966, **31**, 3283. See also Y-L. Zhong and T. K. M. Shing, *J. Org. Chem.*, 1997, **62**, 2622.

90. D. Lucet, S. Sabelle, O. Kostelitz, T. Le and C. Mioskowski, Eur. *J. Org. Chem.*, 1999, 2583.

91. A. T. Hewson and D. T. MacPherson, *J. Chem. Soc., Perkin Trans. I*, 1985, 2625. See also X-J. Hao, M. Node and K. Fuji, *J. Chem. Soc., Perkin Trans. I*, 1992, 1505.

92. H. E. Zimmermann and P. A. Wang, *J. Am. Chem. Soc.*, 1993, **115**, 2205.

93. M. B. Anderson and P. L. Fuchs, *Synth. Commun.*, 1987, **17**, 621.

94. (a) B. A. Narayanan and W. H. Bunnelle, *Tetrahedron Lett.*, 1987, **28**, 6261; (b) T. Imamoto, *Pure & Appl. Chem.*, 1990, **62**, 747; (c) T. V. Lee, J. A. Channon, C. Cregg, J. R. Porter, F. S. Roden and H. T-L. Yeoh, *Tetrahedron*, 1989, **45**, 5877; (d) T. V. Lee, J. R. Porter and F. S. Roden, *Tetrahedron Lett.*, 1988, **29**, 5009.

95. R. Ballini and M. Petrini, *Tetrahedron Lett.*, 1989, **30**, 5329.

96. N. B. Das, J. C. Sarma, R. P. Sharma and M. Bordolio, *Tetrahedron Lett.*, 1993, **34**, 869.

97. P. A. Bartlett, F. R. Green III and T. R. Webb, *Tetrahedron Lett.*, 1977, 331.

98. F. Balzano, C. Malanga and R. Menicalgli, *Synth. Commun.*, 1997, **27**, 1509.

99. J. M. Aizpurua, M. Oiarbide and C. Palomo, *Tetrahedron Lett.*, 1987, **28**, 5361. See also (a) E. W. Colvin, A. K. Beck, B. Bastani, D. Seebach, Y. Kai and J. D. Dunitz, *Helv. Chim. Acta*, 1980, **63**, 697; (b) G. A. Olah, B. G. B. Gupta, S. C. Narang and R. Malhotra, *J. Org. Chem.*, 1979, **44**, 4272.

100. G. A. Olah and B. G. B. Gupta, *Synthesis*, 1980, 44.

101. (a) K. Klager, *J. Org. Chem.* 1955, **20**, 650; (b) N. Ono, A. Kamimura, H. Miyake, I. Hamamoto and A. Kaji, *J. Org. Chem.* 1985, **50**, 3692.

102. P. A. Wade, S. D. Morrow and S. A. Hardinger, *J. Org. Chem.*, 1982, **47**, 365. See also (a) P. Aleksandrowicz, H. Piotrowska and W. Sas, *Tetrahedron,*

1982, **38**, 1321; (b) P. Aleksandrowicz, H. Piotrowska and W. Sas, *Monatshefte für Chemie,* 1982, **113**, 1221.

103. J. P. Ganet and D. Ferroud, *Tetrahedron Lett.*, 1984, **25**, 3579.

104. (a) P. H. Boyle, M. A. Convery, A. P. Davis, G. D. Hosken and B. A. Murray, *J. Chem. Soc., Chem. Commun.*, 1992, 239; (b) A. P. Davis and K. J. Dempsey, *Tetrahedron Asymmetry,* 1995, **6**, 2829.

105. N. Kolocouris, G. B. Foscolos, A. Kolocouris, P. Marakos, N. Pouli, G. Fytas, S. Ikeda and E. De Clercq, *J. Med. Chem.*, 1994, **37**, 2896.

106. G-J. Ho and D. J. Mathre, *J. Org. Chem.*, 1995, **60**, 2271.

107. M. V. Perkins, W. Kitching, R. A. I. Drew, C. J. Moore and W. A. Konig, *J. Chem. Soc., Perkin Trans. 1*, 1990, **4**, 1111.

108. J. Palaty, and F. S. Abbott, *J. Med. Chem.*, 1995, **38,** 3398.

109. Y. Tanabe, H. Yamamoto, M. Murakami, K. Yanagi, Y. Kubota, *J. Chem. Soc. Perkin Trans. 1*, 1995, 935.

110. D. Hoppe, R. Hanko, A. Broenneke, *Angew. Chem.*, 1980, **92**, 637.