Stereoselective routes to cyclic β-amino acid derivatives

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STEREOSELECTIVE ROUTES TO CYCLIC β-AMINO ACID DERIVATIVES

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DECLARATION

The work discussed in this thesis was conducted in the Department of Chemistry at the University of Durham between October 2000 and July 2003. It is the work of the author and results generated in collaboration with other people are indicated. The work has not been submitted for a degree at this or any other university.

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This thesis is dedicated to the memories of my late grandparents (Gopolang and Masesane Tema) who brought me up and taught me very valuable lessons that kept me going when things were tough during my studies.

I also wish to thank the University of Botswana for funding.

ABBREVIATIONS

Ac	: Acetyl
acac	: Acetylacetonate
ACHC	: 2-Aminocyclohexane-1-carboxylic acid
AIBN	: 2,2'-Azoisobutyronitrile
ACPC	: 2-Aminocyclopentane-1-carboxylic acid
APC	: 3-Aminopyrrolidine-4-carboxylic acid
APiC	: 4-Aminopiperidine-3-carboxylic acid
Bn	: Benzyl
Boc	: tert-Butyloxycarbonyl
bp	: Boiling point
br	: Broad
^{n}Bu	: Butyl
^{t}Bu	: tert-Butyl
Bz	: Benzoyl
cat.	: Catalytic
CI	: Chemical ionisation
d	: Doublet
DBU	: 1,8-Diazobicyclo[2.2.2]octane
DCC	: N,N-Dicyclohexylcarbodiimide
DEAD	: Diethyl azodicarboxylate
DHAA	: 5,6-Dihydroanthranilic acid
DMF	: N,N-Dimethylformamide
DMSO	: Dimethyl sulphoxide
DIPEA	: N,N-Diisopropyl-N-ethylamine
EDCI	: N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide hydrochloride
EI	: Electron impact ionisation
ES	: Electron spray
Et	: Ethyl
GC	: Gas chromatography
HATU	: O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
HPLC	: High performance liquid chromatography

IR	: Infra red
KHMDS	: Potassium 1,1,1,3,3,3-hexamethyldisilazide
LiHMDS	: Lithium 1,1,1,3,3,3-hexamethyldisilazide
m	: Multiplet
*m*CPBA	: *meta*-Chloroperbenzoic acid
Me	: Methyl
Ms	: Methanesulphonyl
MS	: Mass spectrometry
NMM	: 4-Methylmorpholine
NMO	: N-Methylmorpholine-N-oxide
NMR	: Nuclear magnetic resonance
Pd/C	: Palladium on activated carbon
PLE	: Pig liver esterase
^{i}Pr	: *iso*-Propyl
PTAB	: Phenyltrimethylammonium tribromide
PyBOP	: benzotriazol-1-yl-oxy-trispyrrolidino phosphonium hexaflourophosphate
q	: Quartet
s	: Singlet
t	: Triplet
TBAF	: Tetrabutylammonium flouride
TBHP	: tert-Butyl hydroperoxide
TBS	: tert-Butyldimethylsilyl
TEA	: Triethylamine
TFA	: Triflouroacetic acid
THF	: Tetrahydrofuran
TLC	: Thin layer chromatography
TMEDA	: N,N,N',N'-tetramethyl-1,2-ethylenediamine
TMS	: Trimethylsilyl
Ts	: *p*-Toluenesulphonyl

ABSTRACT

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PhD-August 2003

The literature structure of the natural product oryzoxymycin and an array of 3-mono-, 3,4-di- and 3,4,5-tri-hydroxylated derivatives of 2-aminocyclohexane-1-carboxylic acid (ACHC) were stereoselectively prepared from oxanorbornene adducts derived from the Diels Alder reaction of ethyl (E)-3-nitroacrylate and furan. The central reaction for these syntheses was the base mediated β-elimination of the oxygen bridge of the oxanorbornene adducts or their derivatives.

The asymmetric synthesis of the literature structure of oryzoxymycin involved chiral HPLC or enzyme catalysed kinetic resolution of the *endo*-carbamate oxanorbornene adduct. KHMDS promoted β-elimination of the oxygen bridge of the optical pure adduct afforded a 5,6-dihydro-5-hydroxyanthranilate which was converted to oryzoxymycin through CsF mediated coupling to a lactate and deprotection.

Alternatively, the double bonds of the dihydrohydroxyanthranilates were stereoselectively reduced to give the 3-hydroxylated ACHC derivatives. The di- and trihydroxylated ACHC derivatives were prepared from the oxanorbornene adducts through selective oxidation sequences that took advantage of substrate stereocontrolled processes. The oxidation reactions which feature in the synthesis of the polyhydroxylated ACHC derivatives were epoxidation and OsO_4 catalysed dihydroxylation.

The structures of intermediates and final products were characterised by NMR, IR and MS. The X-ray-structures of the crystalline compounds were also recorded.

CONTENTS

CHAPTER ONE

GENERAL INTRODUCTION

1.1 INTRODUCTION

The central theme of this thesis is the description of asymmetric routes employed in the synthesis of the natural product oryzoxymycin **4** and an array of hydroxylated cyclohexane based β-amino acid derivatives of type **5** based on the Diels-Alder reaction of ethyl (*E*)-3-nitroacrylate **1** and furan as summarized in Figure 1.1.

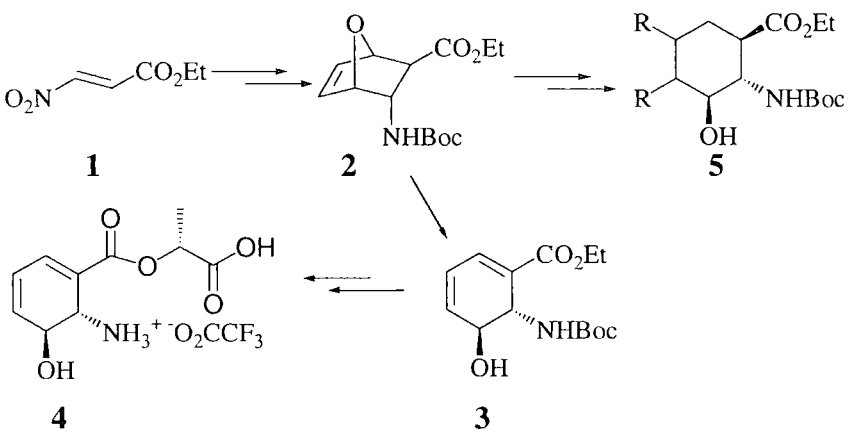


Figure 1.1: Overview of the project

Numerous methodologies for the synthesis of cyclic β-amino acid derivatives have emerged over the last ten years and these are reviewed in Chapter 1 together with the uses of 3-nitroacrylates in Diels-Alder reactions. Subsequent Chapters are devoted to the discussion of the work directed towards oryzoxymycin chemistry and 7-oxanorbornene routes to cyclic β-amino acid derivatives of type **5**. Chapter 5 documents the reaction procedures employed in the study together with spectroscopic and analytical data.

1.2 USES OF 3-NITROACRYLATES IN DIELS-ALDER REACTIONS

3-Nitroacrylates are potent dienophiles, and they generally require low reaction temperatures for the Diels-Alder reaction to occur. Several examples reported in literature have shown that the nitro group is also very effective at controlling the regiochemistry of the reaction with unsymmetrical dienes.[1,2]

Danishefsky and co-workers have studied the Diels-Alder reaction of nitroacrylate **6** with various heteroatom-substituted dienes.[3] Cycloaddition of *trans*-1-trimethylsilyloxy-1,3-butadiene **7** to **6** gave the corresponding adduct **8** in good yield with high regioselectivity, Figure 1.2. Subsequent treatment of **8** with DBU gave the dihydrobenzene derivative **9** in 71 % yield. This sequence of reactions was used as an alternative method for the Diels-Alder reaction of methyl propiolate with **7**. The advantage of using methyl β-nitroacrylate lies in the ability of the nitro function to control the regiochemistry.

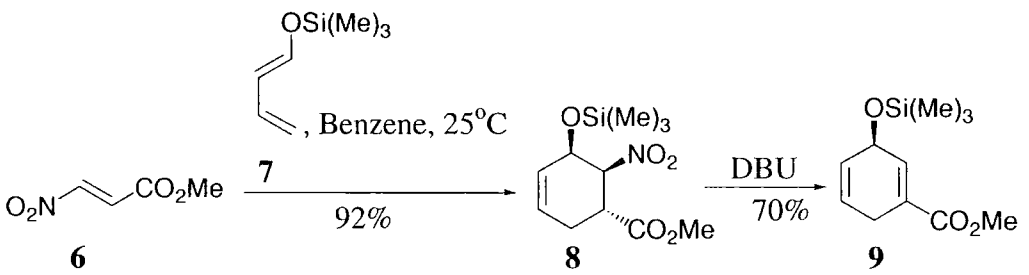


Figure 1.2: Danishefsky's synthesis of **9**

Similarly, the Diels-Alder reaction of nitroacrylate **6** with amino substituted dienes has been applied to the synthesis of isogabaculine **13**.[4] To this end, the reaction of *t*-butyl 1,3-butadiene-1-carbamate **10** with **6** gave the adduct **11** in good yield, Figure 1.3. Treatment of **11** with DBU gave the dihydrobenzene derivative **12**, which upon hydrolysis afforded isogabaculine **13** in moderate yield.[4]

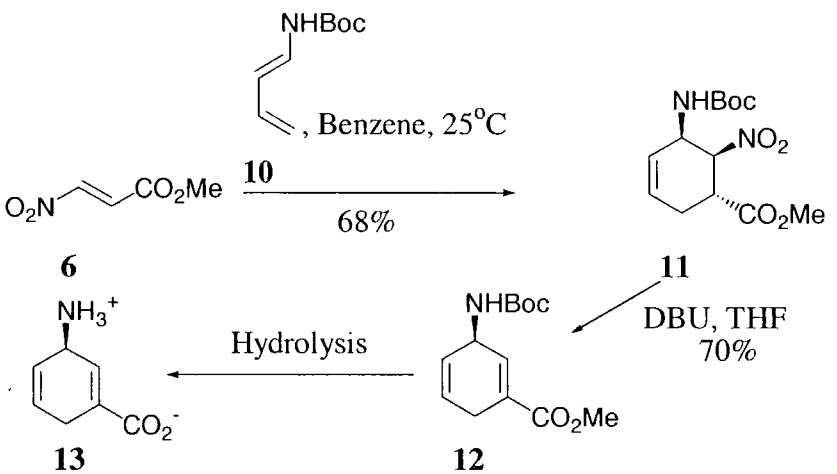


Figure 1.3: Synthesis of isogabaculine **13**

Corey's reaction of 2-trimethylsilyloxy-1,3-butadiene **14** with nitroacrylate **6** at room temperature gave adduct **15** as the only isomer in quantitative yield.[5] Treatment of **15** with aqueous acetic acid afforded *trans*-4-nitro-3-carbomethoxycyclohexanone **16** in 72% yield. Reaction of **16** with DBU in THF afforded the cyclohexenone **17** in good yield,[5] Figure 1.4.

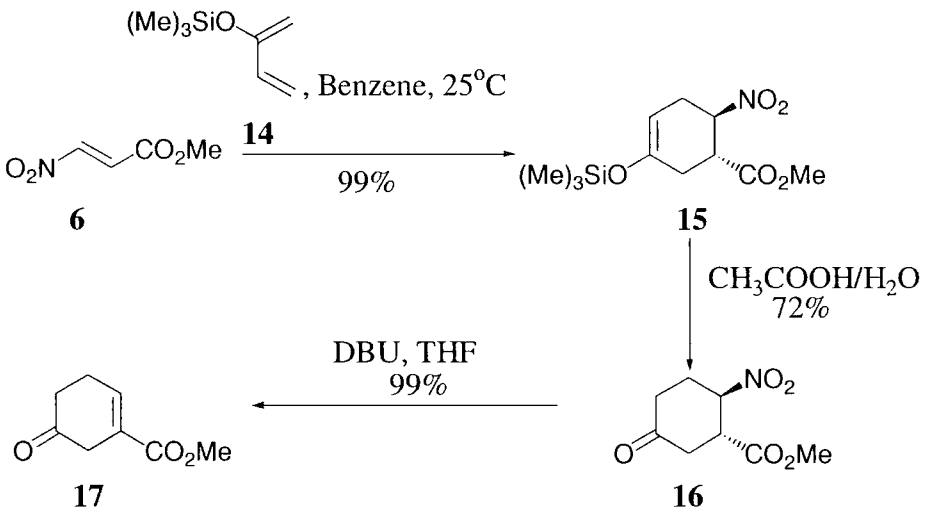


Figure 1.4: Corey's synthesis of **17**

Further studies by Corey involved the Diels-Alder reaction of nitroacrylate **6** with the hindered 1,1-dimethoxy-3-trimethylsilyloxy-1,3-butadiene **18** and this afforded cyclohexenone **19**.[5] DBU mediated elimination of nitrous acid from **19**, then gave the resorcinol derivative **20** in excellent yield, Figure 1.5.

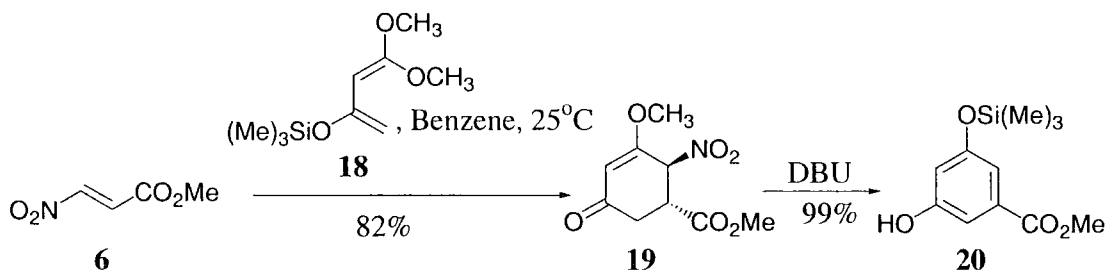


Figure 1.5: Synthesis of the resorcinol derivative **20**

Starting with the Diels-Alder reaction of nitroacrylate **6** and furan, Just and coworkers have reported the synthesis of 3,4-isopropylidene-2,5-anhydroallose **27** in 14% overall yield.[6] The Diels-Alder reaction at room temperature gave a 3:1

mixture of adducts **22** and **21** respectively, Figure 1.6. This mixture was dihydroxylated with OsO_4 and then treated with acetone in the presence of *p*-toluenesulfonic acid to give acetonides **23** and **24**. Subsequent DBU mediated elimination of nitrous acid gave **25**. Ozonolysis of **25** and subsequent reduction with $NaBH_4$ gave the triol **26**, which was converted into 3,4-isopropylidene-2,5-anhydroallose **27**.[6]

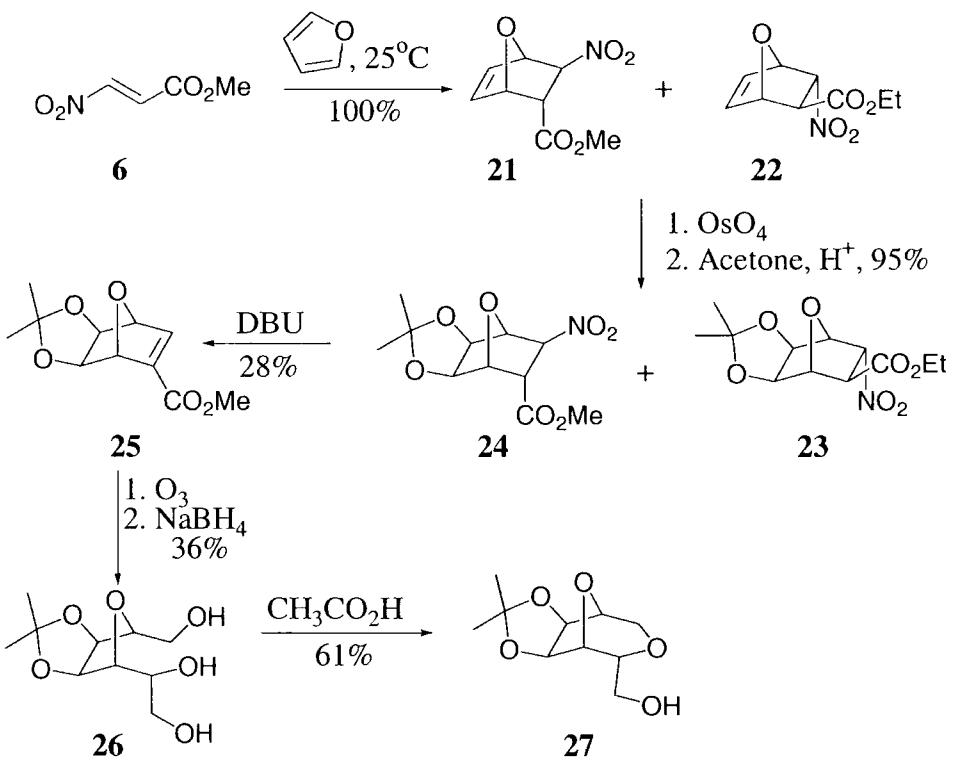


Figure 1.6: Synthesis of 3,4-isopropylidene-2,5-anhydroallose **27**

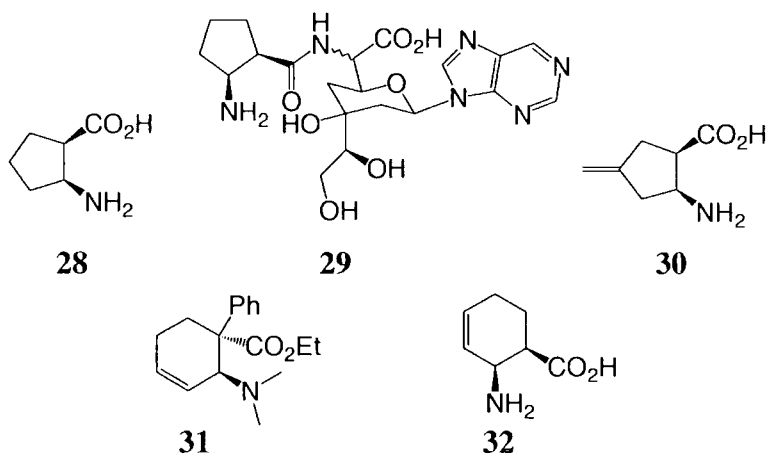
1.3 SUMMARY OF APPLICATIONS OF 3-NITROACRYLATES

It is evident from the examples discussed above that the sequence of the Diels-Alder reaction of 3-nitroacrylates and elimination of nitrous acid has been used as an alternative method for the Diels-Alder reaction of methyl propiolates. The advantages of using 3-nitroacrylates is their greater reactivity as dienophiles and ability of the nitro group to control the regiochemistry. Even though it is conceivable that the reduction of the nitro group would give entry to β-amino acid intermediates, to the best of our knowledge this chemistry has not been explored.

1.4 SYNTHESIS OF CYCLIC β-AMINO ACIDS-A LITERATURE REVIEW

1.4.1 INTRODUCTION

The last few years have seen a surge of interest in cyclic β-amino acids and this has been accompanied by a proliferation of novel procedures for their synthesis.[7] This class of compounds have received so much attention due to their biological activity and lately because of the properties of their oligopeptides. There are a few naturally occurring cyclic β-amino acids with various biological properties, hence the interest in synthesis of derivatives. (*1R*, *2S*)-2-Aminocyclopentanecarboxylic acid (cispentacin) **28** is found, for example, in the antibiotic amipurimycin **29** and has also been isolated in the free form from strains of *Streptomyces* and *Bacillus*. [8-11] A synthetic derivative of cispentacin with a 3-*exo*-cyclic double bond (compound **30**) has been shown to have a favourable activity-tolerability profile against yeast cells and has been selected for clinical studies as a novel antifungal agent for the oral treatment of yeast infections.[12] In contrast, tilidine **31**, a cyclohexenyl synthetic β-amino acid derivative is an opioid analgesic used to control moderate to severe pain.[11] Another synthetic cyclic β-amino acid **32** showed a less favourable toxicogical profile but higher activity against the yeast *Candida albicans*.[12]



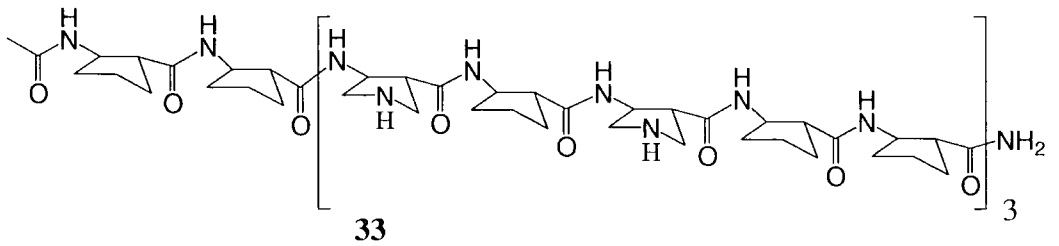
28 **29** **30**

31 **32**

Figure 1.7: Biologically active cyclic β-amino acid derivatives

In recent years interest in cyclic β-amino acids has resulted from the pioneering work of Gellman[13-17] and Seebach[18,19] who have found that oligomeric structures derived from β-amino acids adopted defined secondary structures analogous to those observed

in proteins. Gellman has gone further and shown that β-17 oligomer **33** has significant activity against four species of bacteria including vancomycin resistant *Enterococcus faecium* and methicillin resistant *staphylococcus aureus*.[20]



33

Figure 1.8: Gellman's β-17 oligomer **33**

Given the significance of cyclic β-amino acids, it is not surprising that the development of synthetic routes to these compounds has become an important challenge for organic chemists. Numerous methodologies for the synthesis of β-amino acids have emerged and in this review these will be summarised under five broad approaches, namely; reductive amination, Curtius rearrangement, Michael addition, cycloaddition approaches and miscellaneous strategies.

1.4.2 REDUCTIVE AMINATION

Cyclic β-amino acids have been prepared by the reduction of enamines prepared easily from the corresponding cyclic β-ketoesters. The reductive amination studies of Xu and co-workers culminated in the preparation of the enantiopure ethyl *cis*-2-amino-1-cyclohexanecarboxylate **36**, Figure 1.9.[21] To this end, β-ketoester **34** was allowed to react with with (*S*)-α-methylbenzylamine in the presence of acetic acid, and the resulting enamine **35** was reduced in *situ* with $NaBH_4$. The highest diastereoselectivity was achieved when the reaction was run in isobutyric acid with $NaBH_4$ as the reducing agent.[21] The diastereomeric purity of **36** was enriched through recrystallization as its HBr salt.

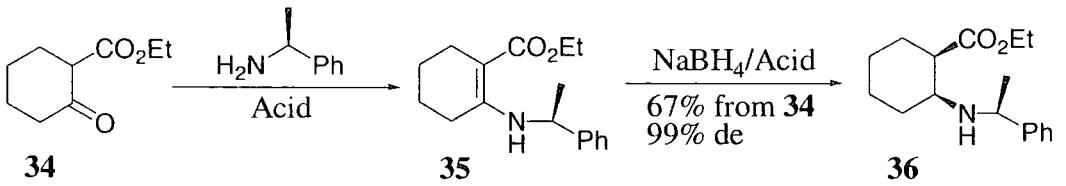


Figure 1.9: Xu's synthesis of **36**

Inspired by Xu's work, Gellman and coworkers have intensively exploited the reductive amination methodology in the synthesis of 3-aminopyrrolidine-4-carboxylic acid (APC) **39** and 2-aminocyclopentanecarboxylic acid (ACPC) **44** using optically pure (*R*)-α-methylbenzylamine as a chiral auxiliary.[22,23] For the synthesis of **44**, the reduction of the enamine with sodium in THF/^{i}PrOH afforded the amino alcohol **42** and after the removal of the auxiliary and protection of the resulting amino group, oxidation of the primary alcohol provided **44**, Figure 1.11.[22] This route was found to suffer from low yields in the enamine reduction step and to overcome this difficulty, $NaBH_3CN$ was used instead as the hydride donor in the synthesis of **39**, Figure 1.10.[23]

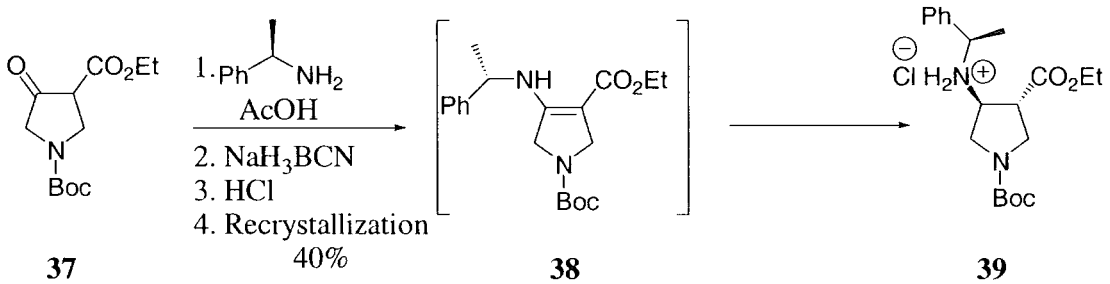


Figure 1.10: Gellman's synthesis of APC **39**

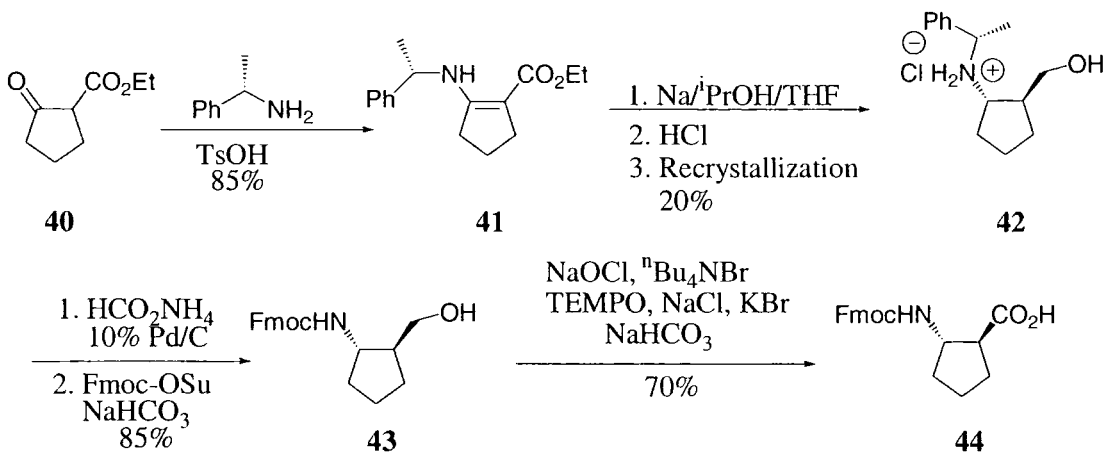


Figure 1.11: Gellman's synthesis of ACPC **44**

In his most recently published work, Gellman has extended his reductive amination protocol to the synthesis of *trans*-4-aminopiperidine-3-carboxylic acid (APiC) **47**.[24] Starting with commercially available β-oxo ester **45**, a short, practical and scalable synthesis of APiC was achieved. Thus, hydrogenolytic removal of the benzyl group of **45** and reaction with di-*tert*-butyl dicarbonate provided the Boc-protected β-oxo ester, which was allowed to react with (*R*)-(+)-α-methylbenzylamine in refluxing benzene in the presence of a catalytic amount of *p*-toluenesulphonic acid to afford enamine **46** in 71% yield, Figure 1.12. Reduction of the enamine with $NaBH_4$ gave a 4:1 ratio of the two *cis* diastereomers of the expected β-amino ester. This mixture was then treated with sodium ethoxide in ethanol, causing epimerisation to the *trans*-β-aminoester **47**. Through a two-stage crystallization protocol, a single *trans* diastereomer was isolated in 16% yield from enamine **46** and its absolute configuration was established by crystallographic analysis.[24]

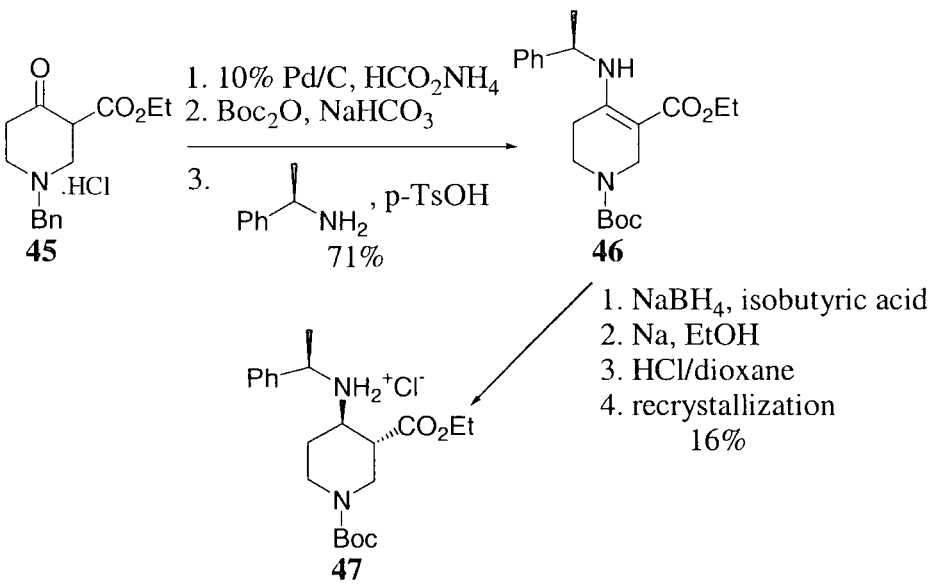


Figure 1.12: Gellman's synthesis of **47**

1.4.3 CURTIS REARRANGEMENT AND HOFMANN DEGRADATION

Cyclic 1,2-dicarboxylates are ideal precursors for the synthesis of cyclic β-amino acids by conversion of one of the carboxy groups into an amine by Curtis or Hofman rearrangements. The Curtis protocol, which involves alkyl migration to an electron-deficient nitrogen is one of the most popular procedure employed by chemists in the synthesis of cyclic β-amino acids.

Kobayashi and co-workers have investigated the Curtis methodology in the preparation of β-amino acid **50** from cyclic diester **48**.[25] Kobayashi's strategy was adopted by Gellman and co-workers in the synthesis of **51**.[26] To this end, the PLE-catalysed hydrolysis of the *meso* diester **48** furnished the monoester **49** quantitatively and with excellent enantioselectivity (>96 %). The monoester **49** was then converted to the β-amino ester **51** by the Curtis protocol followed by reduction of the double bond,[25,26] Figure 1.13. Optically pure monoesters of type **48** could also be accessed by cinchona alkaloid mediated enantioselective desymmetrization of *meso*-anhydrides.[27] It is worth noting that **51** could be converted to its *trans* isomer by base mediated epimerisation.[26]

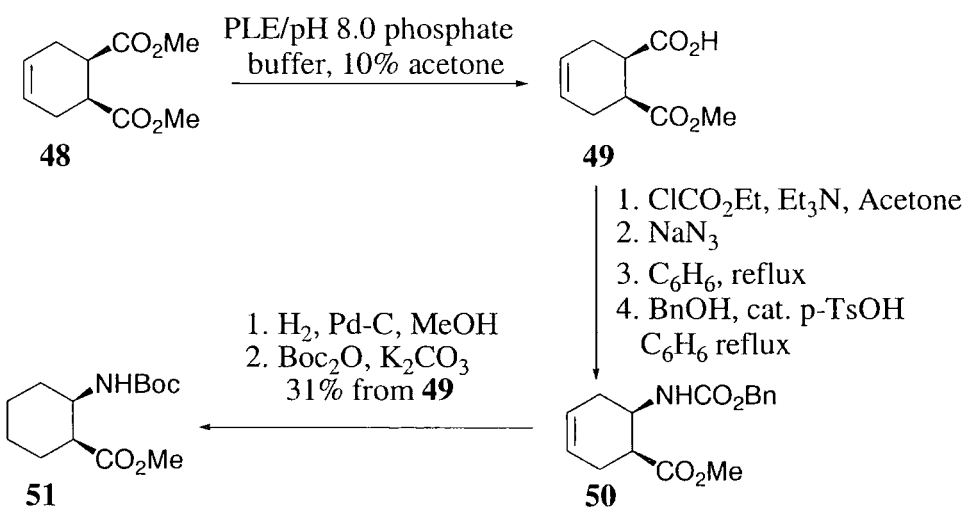


Figure 1.13: Kobayashi-Gellman's synthesis of **51**

Kobayashi and co-workers then went further and prepared a monohydroxyl derivative **53** of β-amino acid **52**.[28] To this end, hydrolysis of ester **52** and iodolactonization under two-phase conditions gave an iodolactone which upon base-mediated

dehydrohalogenation and methanolysis furnished the allylic alcohol **53**. Starting with **53**, Gellman and co-workers prepared β-amino acid **55** with an extra amino group in place of the hydroxyl group.[26] The key steps included the S_N2 reaction of an activated hydroxyl derivative of **53** with an azide, reduction and protection, Figure 1.14.

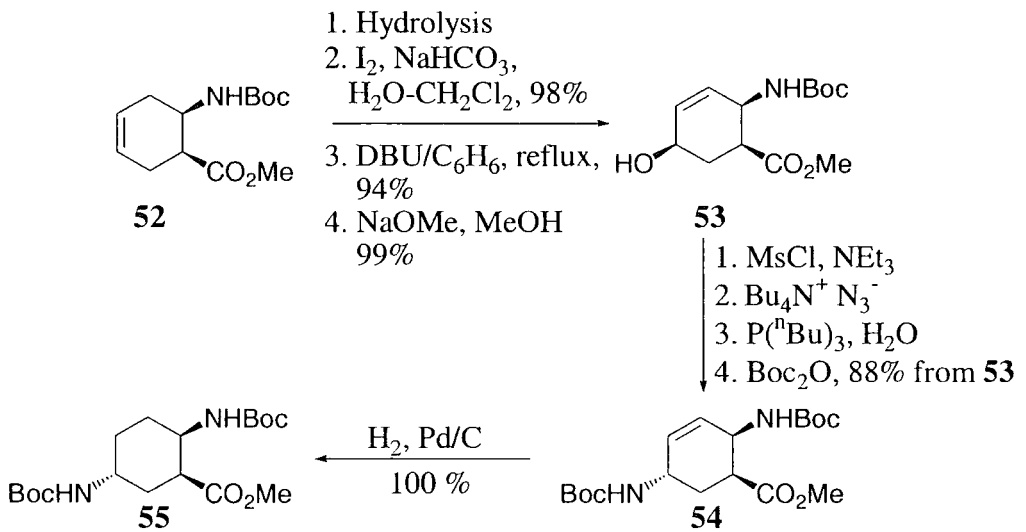


Figure 1.14: Kobayashi-Gellman's synthesis of **55**

In their approach to the hydroxylated *trans*-aminocyclohexane β-amino acid **59**, Wipf and Wang began with adduct **57** available from the titanium catalysed asymmetric Diels-Alder reaction of butadiene and asymmetric fumarate **56**.[29] The Curtis rearrangement proceeded with retention of stereochemistry to give unsaturated β-amino acid **58**, Figure 1.15. In three steps, namely hydrolysis, epoxidation and methanolysis, **58** was elaborated to the polyhydroxyl β-amino acid derivative **59**.

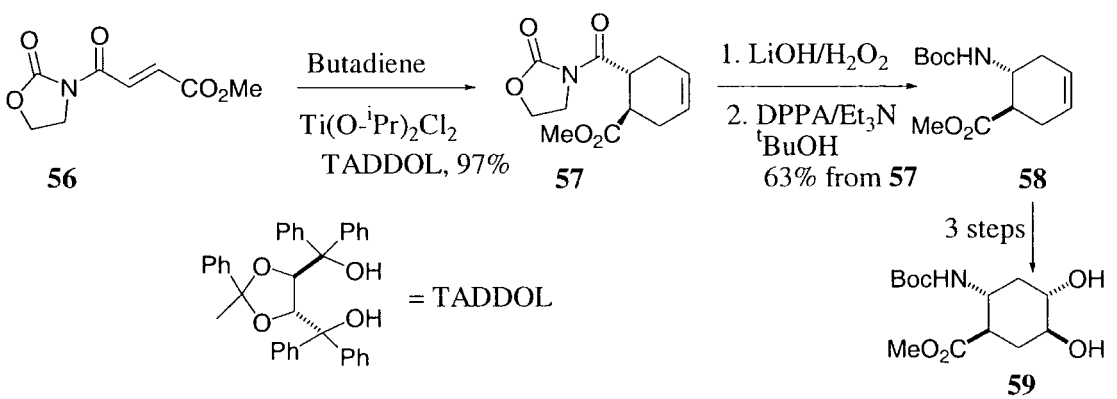


Figure 1.15: Wipf and Wang's synthesis of **59**

Recently, Couche and co-workers have developed a method for the synthesis of monohydroxylated cyclohexyl β-amino acid derivative **64** as outlined in Figure 1.16.[30] Starting from bicyclic hemiester **60** obtained by enzymatic hydrolysis of the corresponding *meso* diester, the polyfunctionalised cyclohexane **64** was prepared with high stereoselectivity. The synthetic strategy involved a Curtis reaction followed by *retro*-Michael ring opening reaction and reduction to give **64** in good yield.[30]

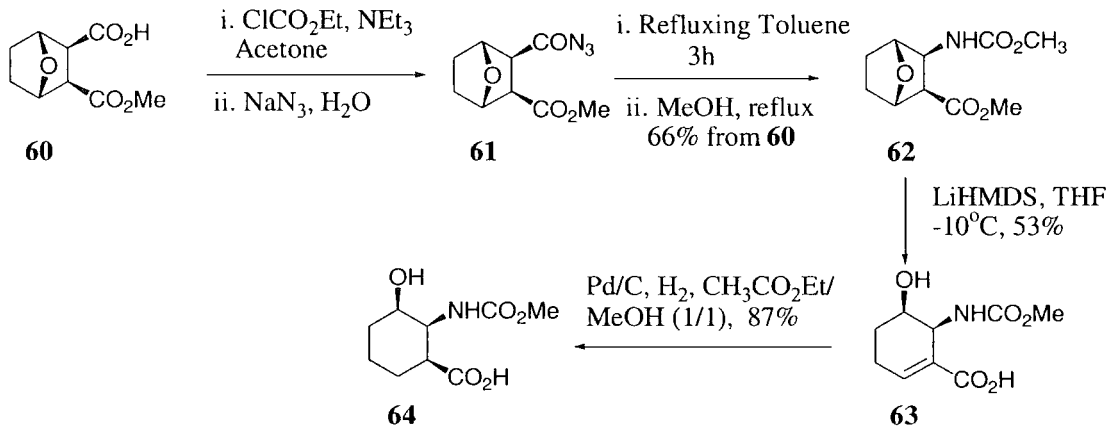


Figure 1.16: Couché's synthesis of **64**

The Curtis rearrangement protocol was also employed by Mangelinckx and De Kimpe in the synthesis of the strained α-substituted cyclopropyl β-amino acid derivatives **67**. Starting from the corresponding 1-aryl and 1-alkylcyclopropane-1,2-dicarboxylates **65**, selective monosaponification and subsequent Curtis reaction led to cyclopropyl β-amino acids derivatives of type **67** in moderate yields, Figure 1.17.[31] It is worthwhile to note that the regioselective monosaponification is controlled by steric effects, hence the bigger the α-substituent R, the better was the regioselectivity.[31]

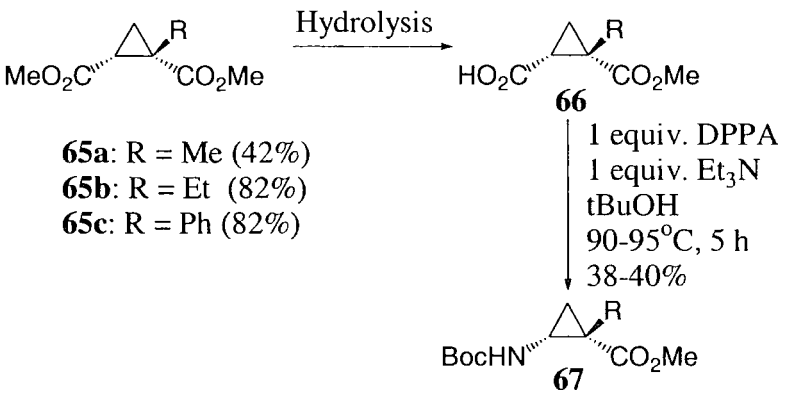


Figure 1.17: Mangelinckx and De Kimpe's synthesis of **67**

Berkessel has utilised a Hofmann degradation approach in the synthesis of **71** as illustrated in Figure 1.18.[32] The diacid precussor **68** was readily obtained in enantiomerically pure form by crystallization of the commercially available racemate with the auxiliary (*R*)-1-phenylethylamine. The advantage of this route is that all three steps from the diacid **68** to the amino acid **71** could be carried out in a one-pot procedure. First, the diacid **68** was heated to reflux in acetyl chloride and then concentrated. The residue was taken up in dichloromethane and conversion into the amide **70** was effected within minutes by pumping gaseous ammonia through the solution. Subsequent treatment of amide **70** with the oxidant phenyliodine (III) *bis*(trifluoroacetate) (PIFA) led to the Hofmann degradation product **71** in good yields, Figure 1.18.

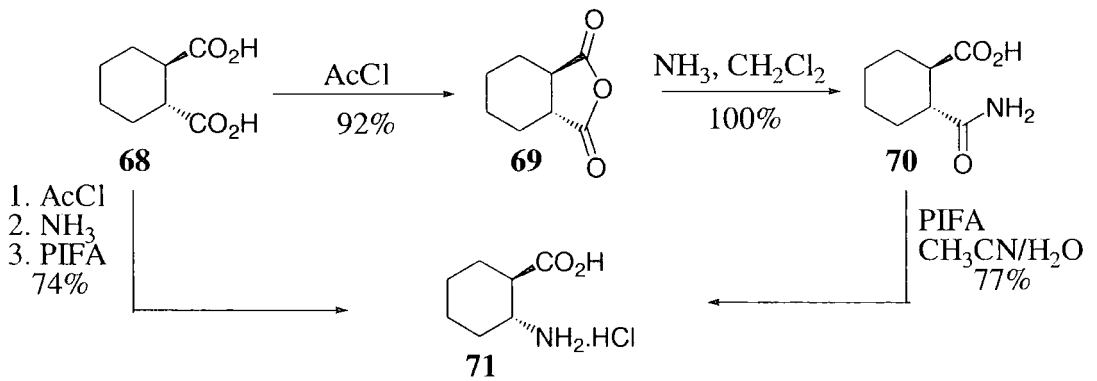


Figure 1.18: Berkessel's synthesis of **71**

1.4.4 MICHAEL ADDITION

Conjugate addition of chiral amine nucleophiles to cyclic α,β-unsaturated carboxylic acid derivatives represents one of the most attractive methods for the stereoselective synthesis of cyclic β-amino acids. Therefore, it is not surprising that asymmetric synthesis of cyclic β-amino acids *via* conjugate addition of chiral metallated amines has attracted the interest of several research groups.

Davies and co-workers have studied the stereoselective conjugate addition of homochiral lithium (α-methylbenzyl)benzylamide to *tert*-butyl 1-cyclopentene-1-carboxylate and 1-cyclohexene-1-carboxylate.[33] These studies culminated in the synthesis of *cis*-2-aminocyclopentane-1-carboxylic acid and *cis*-2-aminocyclohexane-

1-carboxylic acid derivatives with over 98 % diastereomeric selectivity, Figure 1.19. This methodology also provided the *trans* isomers since the *cis*-products **72** and **74** were isomerised to their C-1 epimers **73** and **75** respectively in good yield and excellent d.e.[33]

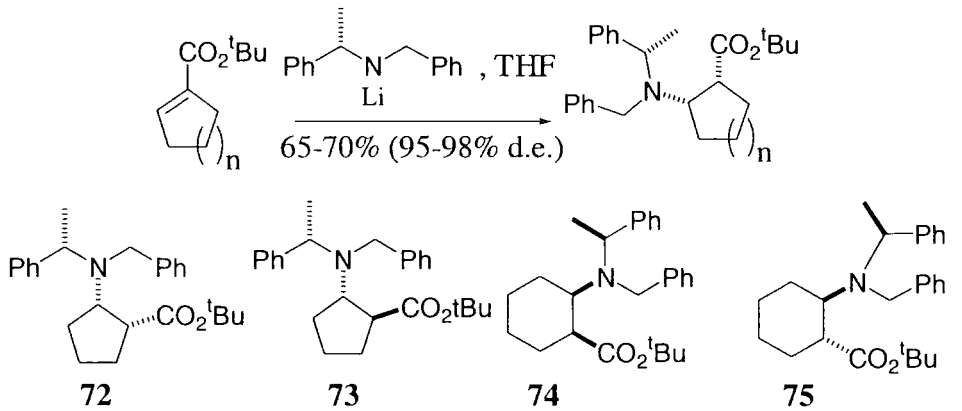


Figure 1.19: Davies's conjugate addition studies.

In a similar manner, Enders and co-workers have developed a highly enantioselective protocol for the conjugate addition of lithiated (*S*)-(-)-2-methoxymethyl-1-trimethylsilylamino-pyrrolidine (TMS-SAMP) to ω-halo-substituted α,β-unsaturated enoates followed by subsequent ring closure of the intermediate ester enolate to give *trans*-2-aminocycloalkanecarboxylic acid derivatives of type **79**, Figure 1.20.[34] This method therefore provides a direct entry to the *trans*-isomers while the Davies method is *cis* selective.

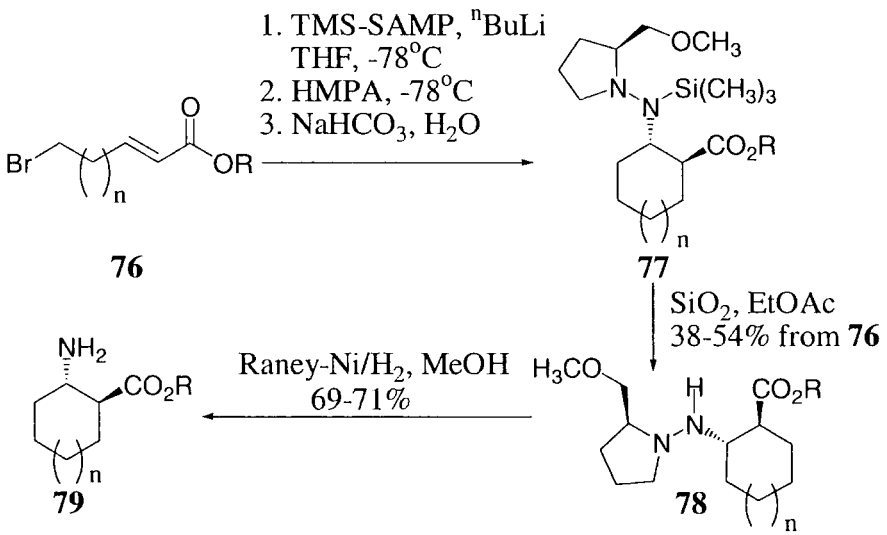
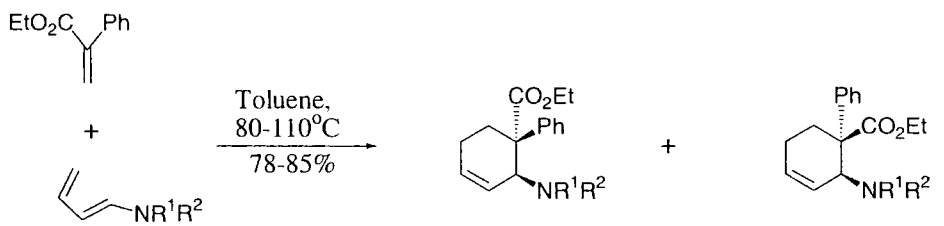


Figure 1.20: Enders synthesis of cyclic β-amino acids of type **79**

1.4.5 CYCLOADDITION APPROACHES

The [4 + 2] cycloaddition (Diels-Alder reaction) remains one of the most frequently employed synthetic methods for the construction of six-membered ring systems. The high regio- and stereoselectivity typically displayed by this reaction and the ease of execution have contributed towards its popularity. Therefore, it is not suprising that the reaction of 1-aminodiene and acrylate derivatives has been explored by a large number of chemists as a route to cyclohexyl β-amino acid derivatives.

Overman and co-workers have employed the Diels-Alder approach utilizing carbamate **80c** as the diene in the synthesis of analgesic tilidine **81a**, Figure 1.21.[35] The cycloaddition of diene **80c** with ethyl atropate was stereospecific and afforded a single crystalline cycloadduct **81c** in 84% yield. Cleavage of the amino protecting group in **81c** and subsequent methylation yielded tilidine **81a** in 64% overall yield starting from **80c**. Use of benzyl *trans*-1,3-butadiene-1-carbamate gave adducts **81b** and **82b** in yields of 71 and 20% respectively. In contrast, the cycloaddition of *trans*-1-(dimethylamino)-1,3-butadiene **80a** with ethyl atropate occurred in the opposite stereochemical sense to afford tilidine as the minor stereoisomer in a 3:1 mixture with isomer **82a**.[35]



80a: $R^1 = R^2 = Me$
80b: $R^1 = H$; $R^2 = CO_2CH_2Ph$
80c: $R^1 = H$; $R^2 = CO_2CH_2CCl_3$

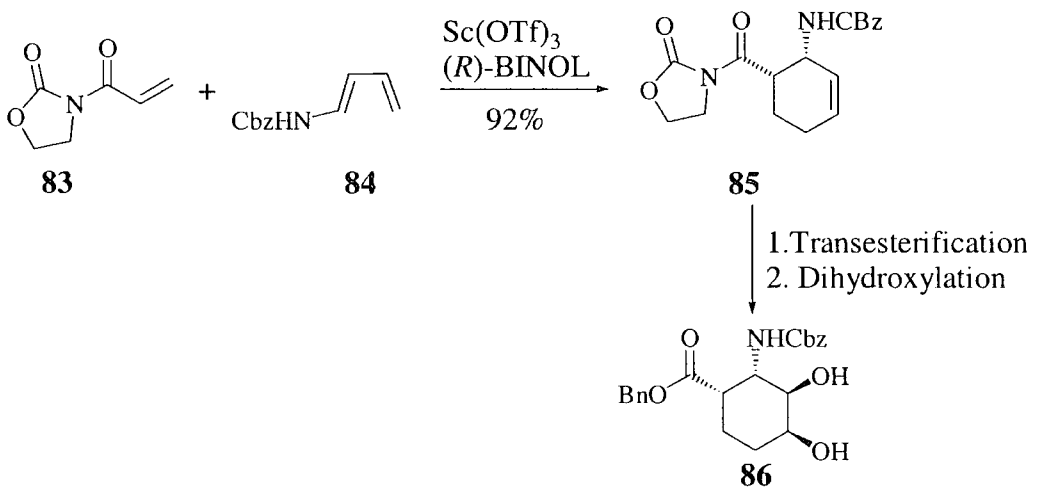
81a: $R^1 = R^2 = Me$
81b: $R^1 = H$; $R^2 = CO_2CH_2Ph$
81c: $R^1 = H$; $R^2 = CO_2CH_2CCl_3$

82a: $R^1 = R^2 = Me$
82b: $R^1 = H$; $R^2 = CO_2CH_2Ph$

Figure 1.21: Overman's synthesis of tilidine derivatives **82** and their isomers.

In a related study, the dihydroxylated *trans*-aminocyclohexane β-amino acid **86** was recently prepared in three steps by Wipf and Wang from the asymmetric Diels-Alder reaction of oxazolidinone **83** and aminodiene **84**.[29] In the presence of Kobayashi's chiral scandium catalyst the *endo* product **85** was isolated in 92% yield and 90% ee,

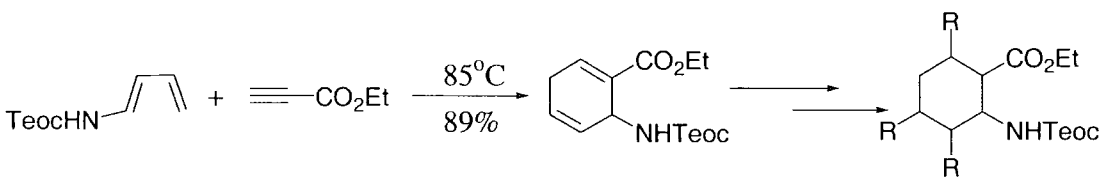
Figure 1.22. After saponification of **85** and benzyl ester formation, dihydroxylation proceeded smoothly to give diol **86** in 74% yield from aminodiene **84**.[29]



83 **84** **85** **86**

Figure 1.22: Wipf and Wang's synthesis of **86**

In their approach to a potential inhibitor of the chorismate-utilizing enzymes, Kozlowski and co-workers featured the Diels-Alder reaction of aminodiene **87** and ethyl propiolate **88** to give unsaturated intermediate **89**, Figure 1.23.[36] Compound **89** is a potentially versatile intermediate to an array of cyclohexyl β-amino acid derivatives of type **90** through reduction oxidation of the double bonds.



87 **88** **89** **90**

Figure 1.23: Potential of Kozlowski's Diels-Alder reaction of **89** and **90**.

Aitken and co-workers have described a short synthesis of *cis*-2-amino-1-cyclobutanecarboxylic acids **94** on the basis of the photochemical [2 + 2] cycloaddition reaction between ethylene and uracil **91**, Figure 1.24.[37] To this end, irradiation of a solution of uracil **91** under an ethylene atmosphere afforded the expected cyclobutane adduct **92** in 75% isolated yield. Hydrolysis of the heterocyclic moiety and the resulting urea function gave cyclobutane β-amino amino acid **94** in 52% overall yield.[37] This short synthesis from readily available starting materials

illustrates a useful strategy which could be developed further to give ring substituted cyclobutane β-amino acids through use of other uracils and/or olefins.

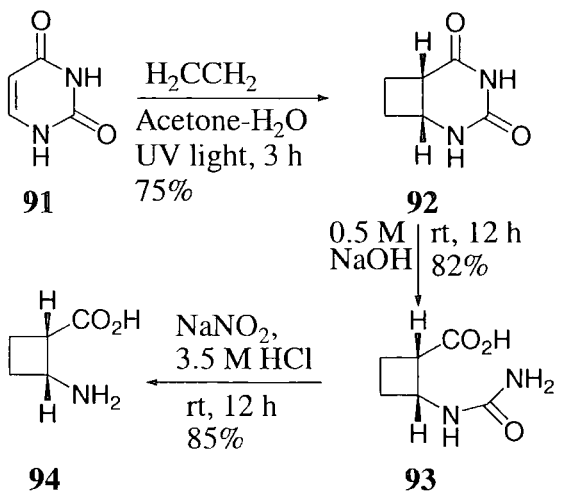


Figure 1.24: Aitken's synthesis of **94**

1.4.6 MISCELLANEOUS STRATEGIES

The obvious route to ACHC **96** involves the reduction of anthranilic acid **95**, Figure 1.25. Indeed, when a solution of anthranilic acid in *iso*-amyl alcohol was treated with sodium, amino acid **96** was isolated.[32] However, the method has been reported to be tedious and low yielding necessitating the need for more effective methods.

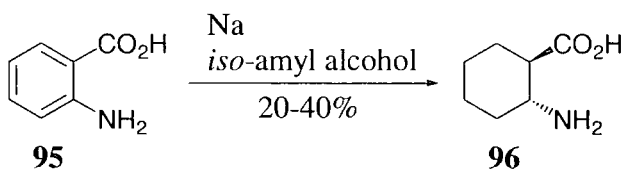


Figure 1.25: Reduction of anthranilic acid **96**

Among the variety of synthetic methods for cyclic β-amino acids classified as miscellaneous, the most interesting and having the greatest potential for general application is the ring closing metathesis approach recently reported by Abell and Gardiner.[38] This methodology was used to prepare the unsubstituted *trans* cyclic β-amino acid derivative **100** from the precursor **97** which is readily available from allylation reactions, Figure 1.26. Treatment of **97** with Grubbs ruthenium catalyst **98** afforded **99** as a single diastereoisomer in 96% yield. Hydrogenation in the presence

of 10% Pd/C followed by re-protection with benzyl chloroformate gave the *trans* ACHC derivative **100** in good yield.[38]

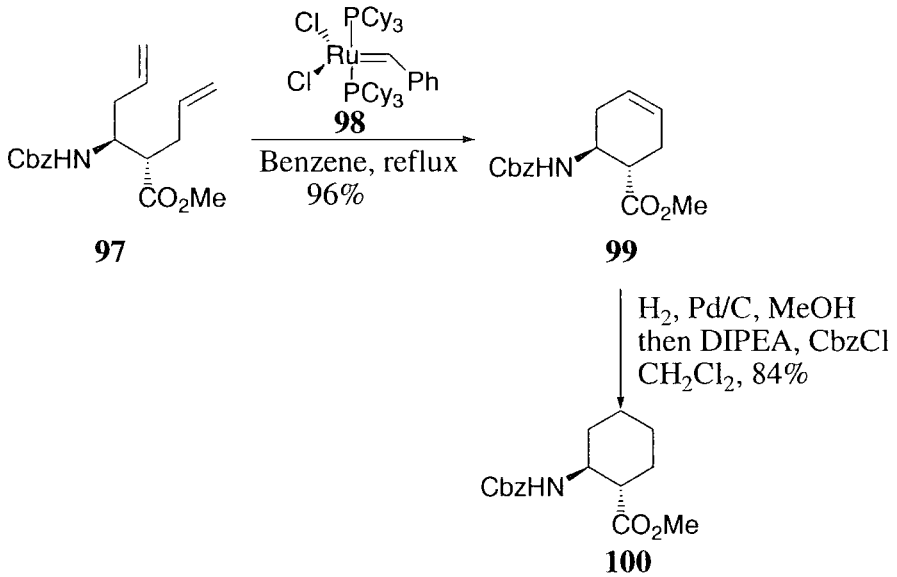


Figure 1.26: Abell and Gardiner's synthesis of ACHC derivative **100**

Another interesting protocol for the synthesis of cyclic β-amino acids by Miyata and co-workers involved sulfanyl radical addition–cyclization of oxime ethers connected with alkenes.[39] In this method the sulfanyl radical attacks the terminal alkenyl group in the substrate **101** to give the cyclic species **104**, Figure 1.27. The reaction proceeds *via* the aminyl radical **103** which is a product of 5-*exo*-*trig* cyclization of **102**. Subsequent reduction of the oxime function and conversion of the phenylsulfanylmethyl group into a carboxyl group gives the desired cyclic amino acids of type **105** including (-)-cispentacin and 4-amino-3-pyrrolidinecarboxylic acid.[39] This approach has the potential to provide routes to both carbocyclic and heterocyclic cyclic β-amino acids.

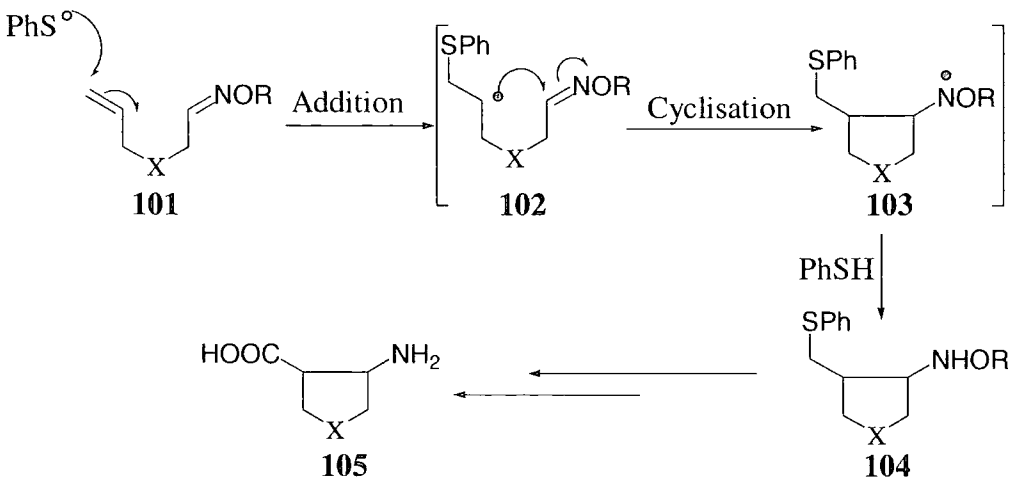


Figure 1.27: Miyata's synthesis of cyclic β-amino acid derivatives of type **105**

Fülöp and co-workers have reported the synthesis of the cispentacin benzologue 1-aminoindane-2-carboxylic acid **110** starting from an intact ring structure.[40] Addition of chlorosulphonyl isocyanate (CSI) to indene **106** followed by ring opening and isomerization gave both *cis*- and *trans*-1-aminoindane-2-carboxylic acids **108** and **110**, Figure 1.28.

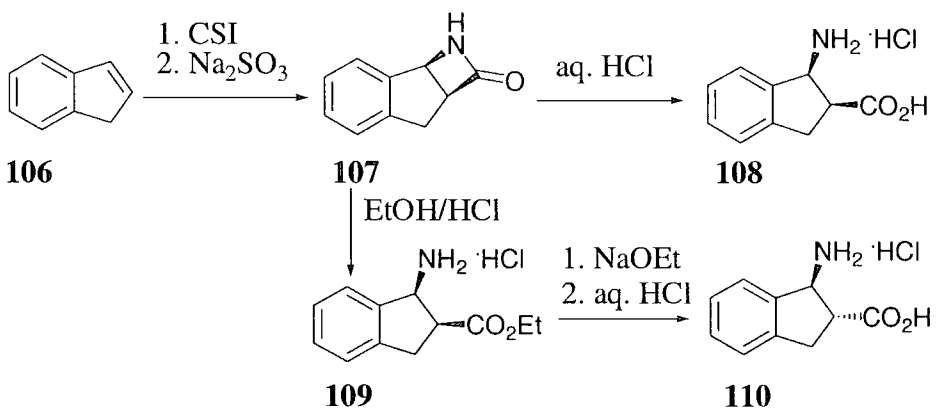
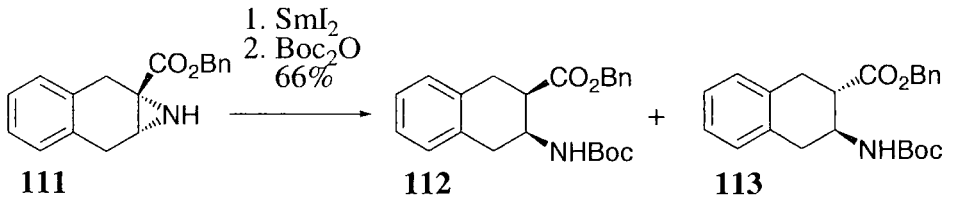


Figure 1.28: Fülöp's synthesis of **108** and **110**

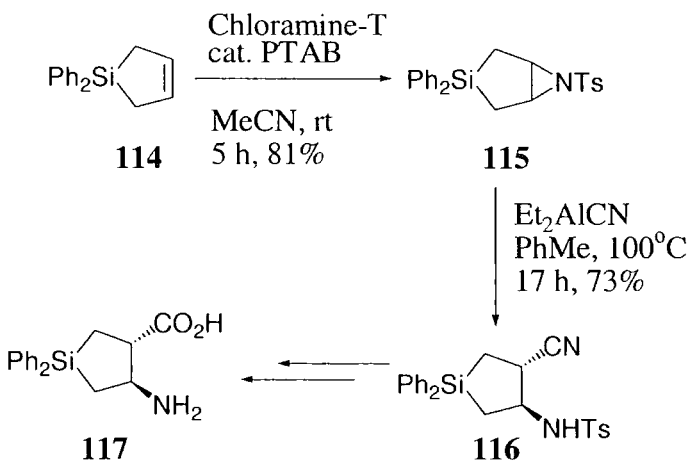
In contrast to Fülöp's method, a SmI_2-promoted aziridine ring opening protocol was described by Kawahata and Goodman in the synthesis of β-amino acids **112** and **113**.[41] To this end, treatment of aziridine **111** with with SmI_2 and subsequent protection of the resulting amine gave a 1:1 mixture of the two β-amino acids **112** and **113** (Figure 1.29), separated by column chromatography.



111 112 113

Figure 1.29: Kawahata and Goodman Aziridine ring opening reaction

Also starting from a pre-formed ring, Matthews and co-workers have prepared novel cyclic sila-substituted β-amino acids through nucleophilic ring opening of an intermediate aziridine with an umpolung synthon for the carboxylate anion.[42] This route involved the Sharpless aziridination[43] of the silacyclopent-3-ene **114** followed by ring opening to give the cyano compound **116**, Figure 1.30. Amine deprotection and nitrile hydrolysis afforded the target β-amino acid **117**.



114 **115** **116** **117**

Figure 1.30: Matthews' synthesis of **117**

1.4.7 SUMMARY OF SYNTHETIC METHODS REVIEW

Considerable progress has been made in the synthesis of cyclic β-amino acid derivatives. Many strategies are now available for the preparation of these β-amino acids and each of the strategies discussed has its own advantages and limitations. Rapid progress is therefore expected in the synthesis of substituted and optically active derivatives of cyclic β-amino acids in the next decade.

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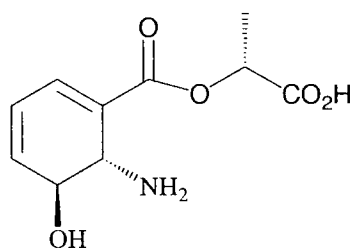
CHAPTER TWO

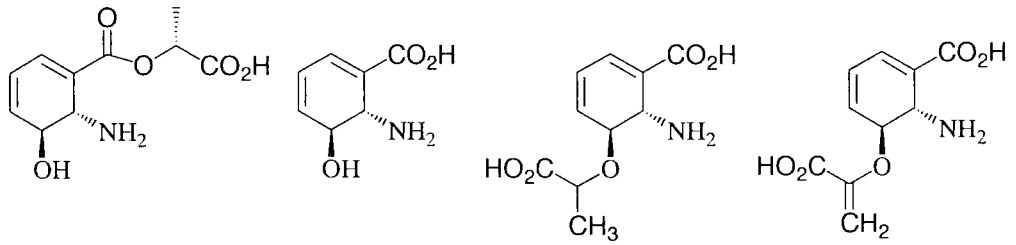
STEREOSELECTIVE SYNTHESIS OF THE STRUCTURE OF ORYZOXYMYCIN



4

2.1 INTRODUCTION

In 1968, Hashimoto and co-workers reported the isolation of a novel anthranilate, oryzoxymycin **4** from a soil sample of *Streptomyces venezuelae*, var. *oryzoxymyceticus* and this compound was shown to exhibit moderate activity against *Xanthomonas oryzae*.[44] On the basis of spectroscopic and degradation studies, the structure of oryzoxymycin was elucidated as a composite of (*R*)-lactic acid and (*5S*, *6S*)-dihydrohydroxyanthranilic acid **118** (DHAA), a compound previously isolated from *Streptomyces aureofaciens*.[45,46] The absolute stereochemistry of oryzoxymycin was also established through degradation reactions and subsequent comparison with known substances.[47] Oryzoxymycin is structurally interesting in that the position of the lactate moiety differs from the common C-5 enoylpyruvate substitution of related structures **119** and **120** (Figure 2.1) which are intermediates in the biosynthesis of anthranilates.[48-50] The proof of the structure of oryzoxymycin therefore presents a special synthetic challenge.



4 **118** **119** **120**

Figure 2.1: Structure of Oryzoxymycin **4** and related structures

2.2 RETROSYNTHETIC ANALYSIS FOR ORYZOXYMYCIN

Our general strategy for the synthesis of oryzoxymycin is based on the retrosynthetic analysis shown in Figure 2.2. Disconnection at the ester bond furnished the lactic acid unit and dihydroanthranilic acid **118** as key building blocks. Dihydroanthranilic acid **118** could be generated from the base induced fragmentation of the bicyclic amino ester **2** which in turn could be derived from a Diels-Alder reaction between β-nitroacrylate **1** and furan. From this retrosynthetic analysis, a plan for a stepwise and stereocontrolled total synthesis of oryzoxymycin was evolved.

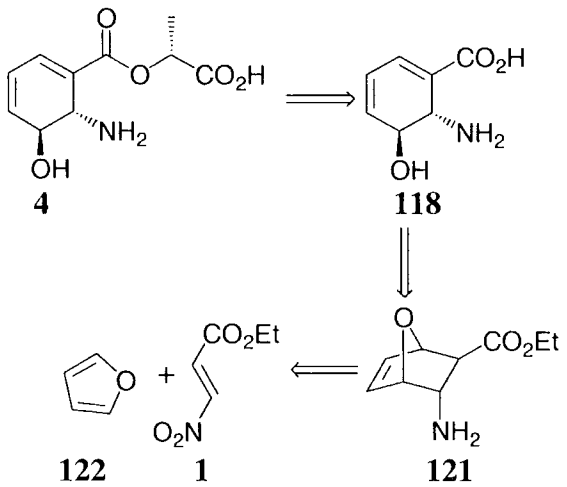


Figure 2.2 : Retrosynthetic analysis for oryzoxymycin **4**

2.3 PREVIOUS WORK ON ORYZOXYMYCIN IN OUR GROUP

Prior to this work, a PhD student in our group did some preliminary work on the synthesis of oryzoxymycin based on the retrosynthetic analysis shown in Figure 2.2.[51] To this end, nitroacrylate **1**, prepared through a modification of the McMurry method[52], reacted with furan in $CHCl_3$ at room temperature to give a mixture of oxanorbornenyl adducts favouring the required *endo*-nitro isomer **123**. Enhanced selectivity was obtained by running the reaction at –20 °C to give a separable 4:1 mixture of the two isomers in over 90% yield. Subsequent selective conversion into the protected aminoester **2** was achieved in a single pot by reduction with Zn/HCl followed by addition of a large excess of $^{i}Pr_2NEt$ and $(Boc)_2O$. KHMDS induced fragmentation of **2** allowed the isolation of cyclohexadiene **3** in a reproducible 71% yield together with variable amounts of ethyl 3-hydroxybenzoate.

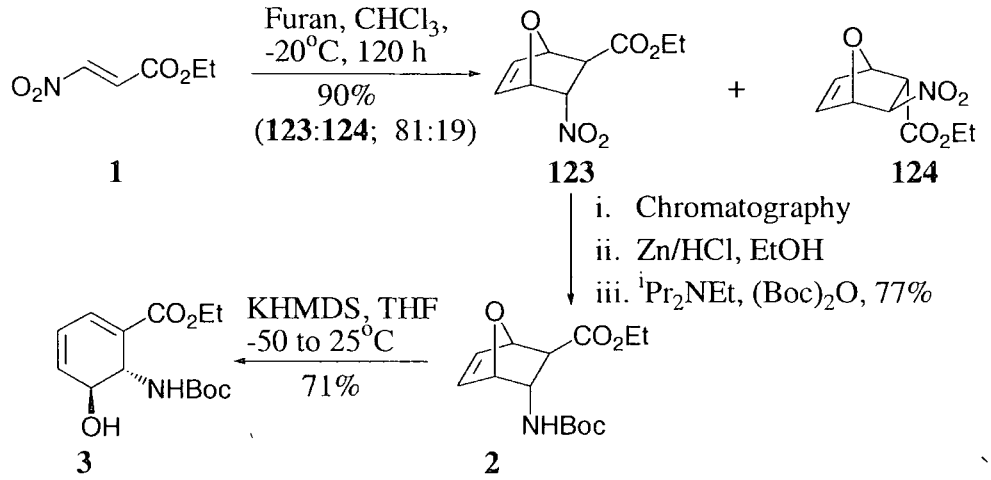


Figure 2.3: Synthesis of diene **3**

Although the transformation summarised in Figure 2.3 secured the correct relative stereochemical relationship of the hydroxyl and amine groups in the cyclohexadienyl moiety of oryzoxymycin, all the chiral intermediates described thus far were racemic. It was apparent, however, that the racemic material could be resolved after the introduction of the chiral lactate side chain of oryzoxymycin. To this end, anthranilate ester **3** was hydrolysed with KOH and the resultant acid treated with CsF and mesylate **126** in DMF to give the desired lactate coupled product **127** as a mixture of two diastereoisomers, which, unfortunately proved impossible to separate. It is instructive to draw attention to the fact that attempts to couple the Boc-protected dihydroanthranilic acid **125** to lactic acid methyl ester in the presence of DCC or EDCI proved unsuccessful.[51]

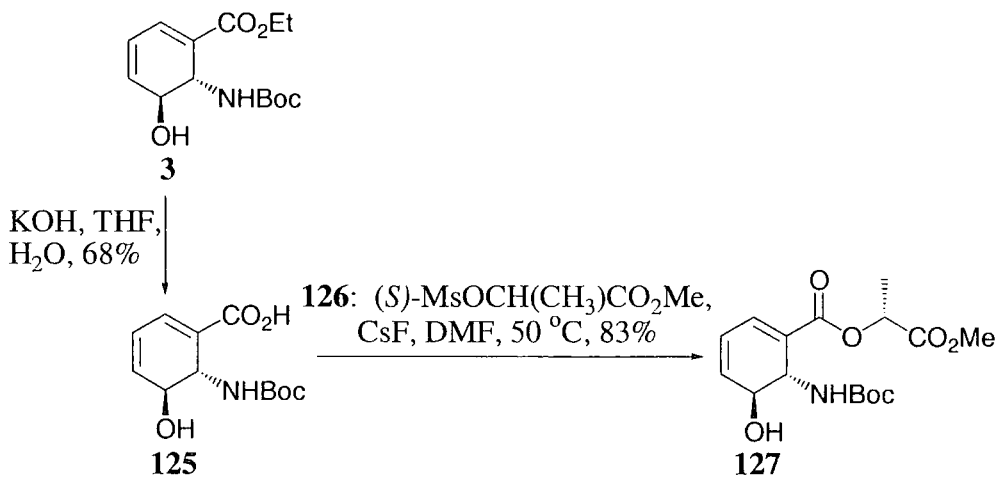


Figure 2.4: Racemic synthesis of oryzoxymycin

2.4 SYNTHETIC CHALLENGES

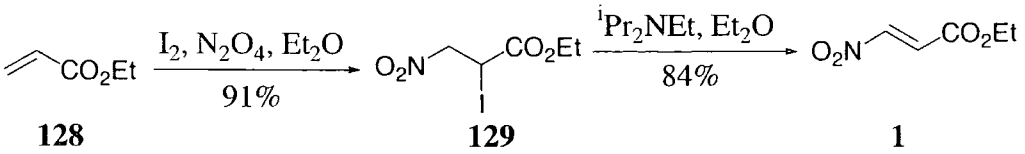
Asymmetric synthesis was among the tasks remaining in the preparation of oryzoxymycin and the bicyclic adduct **2** presented a very convenient opportunity to carry out resolution at that stage of the synthesis. Indeed, there are numerous literature examples of resolution of bicyclic adducts similar to **2** by enzyme mediated kinetic resolution or chiral HPLC.[53,54] Another challenge was to select a protecting group for the lactic acid which could be removed selectively.

Building on the work already done in our laboratory, efforts towards addressing the listed challenges will be discussed in subsequent sections of this chapter.

2.5 SYNTHESIS OF ETHYL (E)-3-NITROACRYLATE 1

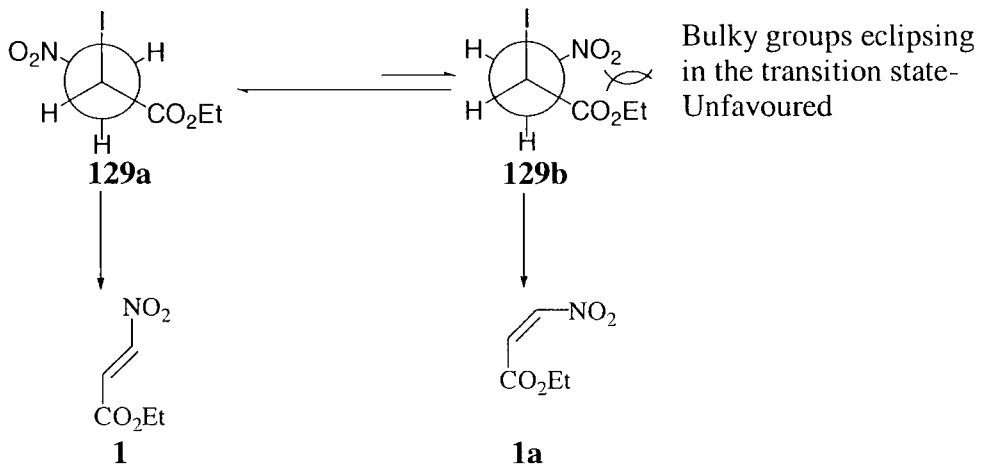
The general strategy for the synthesis of oryzoxymycin (see retrosynthetic analysis in Figure 2.2) identified nitroacrylate **1** as a major intermediate from which the bicyclic adduct **2** could be generated. Consequently, the first experiment to be undertaken was the synthesis of **1** on the basis of precedent in our laboratory.[51] It was also known from the work of McMurry that **1** could be prepared in two steps from acrylates.[52] Thus, treatment of ethyl acrylate **128** with iodine and N_2O_4 gave iodonitro ester **129** in quantitative yield (93%), Figure 2.5. Elimination of HI with Hunig's base in ether afforded exclusively the title compound in 73% yield. The selectivity for the *Z*-isomer can be explained by considering the relative stability of conformations **129a** and **129b** that are suitable for *anti*-elimination, Figure 2.6. Thus, on the basis of the conformations of **17**, it was anticipated that the *Z*-isomer ought to be the major product. With this sequence of reactions, nitroacrylate **1** could be generated in 10-20 g batches and contrary to reports that highlights the instability of nitroalkenes,[55] ethyl (E)-β-nitroacrylate **1** was found to be stable for months when stored in a refrigerator.

The NMR (^1H, ^{13}C) spectra of both compounds **1** and **129** were consistent with the proposed structures and comparable to those reported in literature.[52] The ^1H NMR spectrum of compound **1** showed the presence of two vinylic hydrogens with a characteristic *trans*-coupling (J = 13.6 Hz) assigned to H-2 and 3.



128 **129** **1**

Figure 2.5: Synthesis of nitroacrylate **1**



129a **129b**

1 **1a**

Figure 2.6: Conformations leading to the (E)- and (Z)-isomers

2.6 REACTION OF NITROACRYLATE 1 AND FURAN

The preparation of nitroacrylate **1** set the stage for the crucial cycloaddition reaction with furan as the diene. The ability of furan to undergo [4+2]-cycloadditions with various π-bonds is well established[56,57] and has attracted the attention of many research groups as it allows for the construction of valuable synthetic intermediates. The initial cycloaddition affords a substituted 7-oxabicyclo[2.2.1]hept-5-ene (7-oxanorbornene) that can be manipulated with impressive selectivity to give interesting target molecules. In the event, execution of the Diels Alder reaction of **1** and furan proceeded smoothly and delivered the target molecule efficiently and stereospecifically. Thus, subjection of nitroacrylate **1** to cycloaddition reaction with furan in CH_2Cl_2 at -20°C for five days afforded an 80:20 mixture of adducts **123** and **124** respectively in 90% yield, Figure 2.3. When the temperature of the reaction was increased to room temperature, considerable acceleration of the reaction was observed but was accompanied by a significant reduction in diastereoselectivity (2:1 mixture of **123** and **124** respectively). The two isomers were easily separated by column chromatography.

Having achieved the expedient synthesis of bicyclic intermediate **123**, we were in a position to address the reduction of the nitro group to an amine. To this end, treatment of **123** with concentrated hydrochloric acid and zinc powder afforded the bicyclic β-amino ester **121**. Subsequent addition of a large excess of $^{i}Pr_2NEt$ and Boc_2O gave protected aminoester **2** in 77% yield over the two steps.

The ^{1}H and ^{13}C spectra of **2** exhibited all the features consistent with the bicyclic structure including the singlet at δ 1.30 assigned to the Boc protons and two doublets at δ 6.46 and 6.59 with coupling constant J = 5.7 assigned to the vinylic protons. The proposed structure of **2** was finally confirmed by X-ray crystallography (see X-ray structure in Appendix 1)

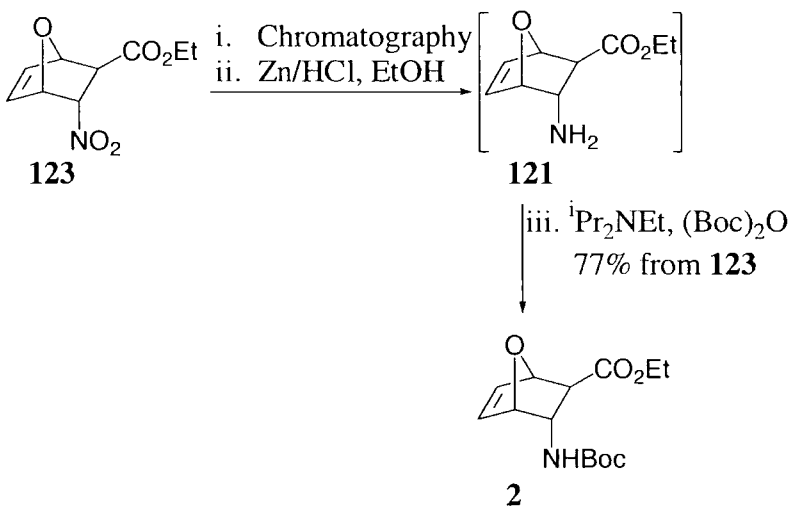


Figure 2.7: Reduction of the nitro group of adduct **123**

2.7 RESOLUTION OF THE OXANORBORNENE ADDUCT 2

2.7.1 ENZYME-CATALYSED KINETIC RESOLUTION

Enzymes, as biocatalysts, have captured an important place in organic synthesis. Arguably, esterases, such as pig liver esterase (PLE), have proved to be the most widely successful enzymes in asymmetric synthesis.[53] Esterases are cheap, stable, do not require a coenzyme and tolerate a wide range of substrates and chemical conditions. It appeared of interest therefore to examine the use of these enzymes for the resolution of the oxanorbornene adduct **2**.

To set the stage for the kinetic resolution of the oxanorbornene adduct **2**, screening reactions were first examined with PLE in various solvents (i.e. CH_3OH, CH_3CN, $(C_2H_5)_2O$ and CH_2Cl_2). Among the solvents studied, diethyl ether proved suitable for the PLE enantioselective hydrolysis of substrate **2**. Thus, treatment of a solution of **2** in diethyl ether and pH 7.8 phosphate buffer with PLE at room temperature afforded acid **(-)-130** and ester **(+)-2**, Figure 2.8. The reactions were stopped at 50% conversion and the products were purified by column chromatography. The success of this resolution hinged on the ability of the enzymes to react preferentially with the (-)-ester.

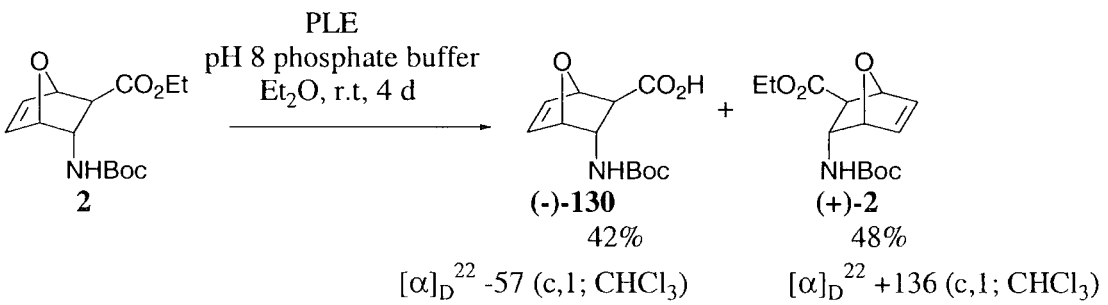
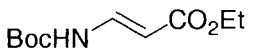


Figure 2.8: PLE mediated kinetic resolution of **2**

2.7.2 CHIRAL HIGH-PERFOMANCE LIQUID CHROMATOGRAPHY RESOLUTION

High performance liquid chromatography (HPLC) on chiral stationary phase has become a reliable method for the separation and determination of optically active isomers. Direct chiral separation using cyclodextrin-based and macrocyclic antibiotic-based HPLC columns continue to be common and enantioseparation on many novel chiral stationary phases has also been reported.[54] Successful HPLC methods for the resolution of cyclic β-amino acids include chiral crown ether stationary phases[58] and glycopeptide antibiotic teicoplanin stationary phases.[59] On the basis of these literature observations, and to complement the enzyme mediated resolution, we turned our attention to an investigation of the enantiomer separation of bicyclic β-amino ester **2** using preparative chiral HPLC method. To this end, subjection of **2** to a Chiralpak AD HPLC column eluting with a 95:5 mixture of hexane and ethanol gave both enantiomers of **2** together with the *retro*-Diels Alder product **131** (see Appendix 2 for

the chromatogram). The chiral HPLC separation was done in collaboration with Mr Steve Jackson at GlaxoSmithKline.

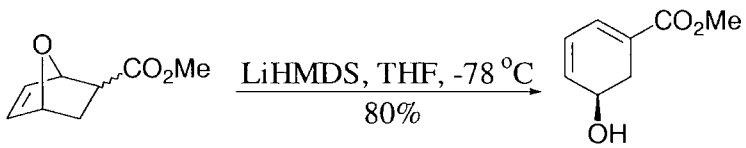


131

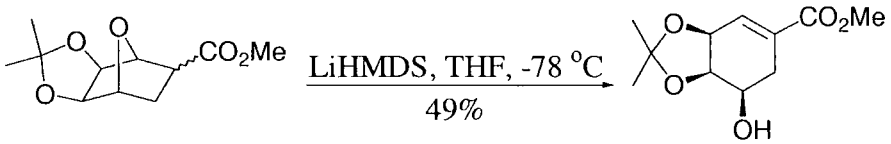
Figure 2.9: *Retro* Diels-Alder product **131**

2.8 SYNTHESIS OF THE STRUCTURE (-)-ORYZOXYMYCIN

In the event that the oxygen bridge of oxanorbornene systems could be eliminated, optically pure **(+)-2** could serve as a potential precussor to the cyclohexadiene moiety of oryzoxymycin. Indeed, LiHMDS induced fragmentations of oxanorbornane systems were first reported by Brion.[60] Further work by Campbell and co-workers demonstrated that the LiHMDS induced fragmentation can also be effected on oxanorbornene **132** and the substituted oxanorbornane adduct **134** to give cyclohexadiene **133** and cyclohexene **135** respectively, Figure 2.10.[61-65] On the basis of these important precedents, it was presumed that adduct **(+)-2** could be fragmented using LiHMDS or related bases.



132 **133**

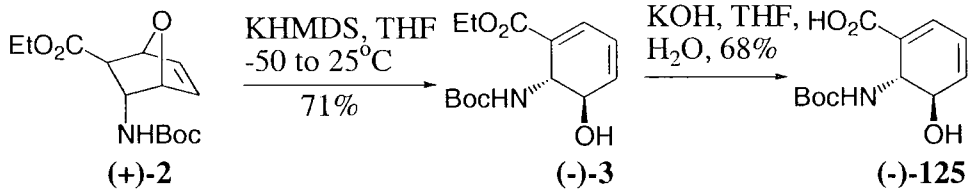


134 **135**

Figure 2.10: Campbell's fragmentation of bicyclic adducts **132** and **134**

Using a protocol previously established in our laboratory,[51] the oxygen bridge of adduct **(+)-2** was eliminated using KHMDS, which was found to be more effective that LiHMDS. In the event, treatment of **(+)-2** with KHMDS in THF afforded substituted diene **(-)-3**, ($[\alpha]_D^{22}$ –269) in acceptable yields together with ethyl 3-hydroxybenzoate as a by-product, Figure 2.11. The ^{1}H NMR of **(-)-3** showed

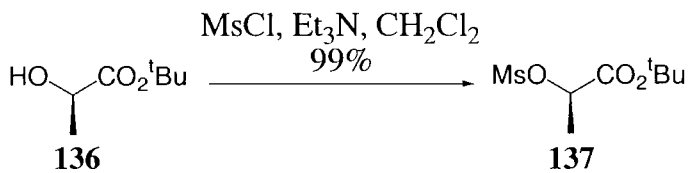
characteristic resonances at δ 6.26 integrating for two protons and a doublet at δ 7.17 with coupling constant J = 4.8 Hz assigned to H-3, H-4 and H-1 respectively. It is instructive to note that the product from this easily executed fragmentation reaction already has much in common with the targeted cyclic intermediate **118**. To set the stage for the crucial esterification reaction, ester **(-)-3** had to be hydrolysed. To this end, treatment of **(-)-3** with excess KOH in THF and water afforded acid **(-)-125** ($[\alpha]_D^{22}$ –332) in 68% yield.



(+)-2 **(-)-3** **(-)-125**

Figure 2.11: Synthesis of acid **(-)-125**

In a parallel sequence of reactions, the hydroxyl group of *t*-butyl lactate was activated to make it amenable to the esterification step. Thus, treatment of a solution of commercially available lactate **136** in CH_2Cl_2 with triethylamine followed by cooling (0°C) and addition of MsCl afforded mesylate **137**, $[\alpha]_D^{20.5}$ +49 in 99% yield.



136 **137**

Figure 2.12: Synthesis of mesylate **137**

Having achieved the expedient synthesis of intermediates **(-)-125** and **137**, attention was then focused on formation of the ester bond between the two substances by a procedure developed in our laboratory in the preliminary studies towards oryzoxymycin.[51] Consequently, treatment of acid **(-)-125** with CsF and mesylate **137** in DMF gave the desired lactate coupled product **138** as a single isomer, $[\alpha]_D^{22}$; -171 (c; 1, $CHCl_3$), Figure 2.13. It is instructive to discuss the mechanistic profile of the CsF mediated coupling reaction. Otera and co-workers suggested that the reaction proceeds on the surface of solid CsF, since fluoride anions could not be detected during the course of the reaction.[66] Hydrogen bonding between CsF and an active

hydrogen of the nucleophile (the acid hydrogen in this case) was thought to be responsible for the smooth reaction.

Both the 1D and 2D NMR spectra of **138** displayed all the features consistent with the proposed structure. Most noticeable was the HMBC correlations between the cyclohexadienylcarboxylate carbonyl carbon and the lactate H-2 which confirmed the point of attachment of the lactate unit, Figure 2.14.

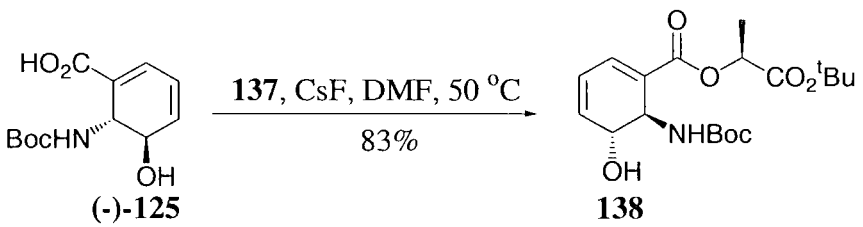


Figure 2.13: Coupling of the lactate **137** to **(-)-125**

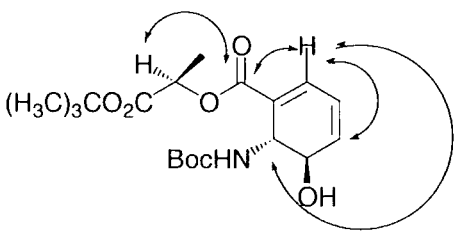


Figure 2.14: Selected HMBC correlations of **138**

As indicated in Section 2.4, the selection of the *t*-butyl protecting group for the lactic acid was not arbitrary; it was reasoned that since it is acid labile, its removal would be coupled to that of the Boc group. Indeed, exposure of **138** to TFA in CH_2Cl_2 achieved complete deprotection to afford (-)-oryzoxymycin salt **139** in good yield, $[\alpha]_D^{21}$ –199 (c; 1, H_2O). Unlike the literature natural product, **139** showed appreciable stability when stored at 0°C or in solution of water at room temperature. However, when kept at room temperature in a dry state, **139** gradually decomposed, but, unlike the literature compound, no dimeric product was detected.[45] One characteristic of the synthetic (-)oryzoxymycin comparable to that of the literature compound was its solubility in methanol and water, but insolubility in most organic solvents.

High resolution mass spectrometry established the molecular formula $C_{10}H_{11}NO_4$ for structure **139**. The IR spectrum featured a hydroxyl band at 3413 cm^{-1}, a broad acid

band at 3550-2800 cm^{-1} and bands at 1726 and 1679 cm^{-1} due to the carbonyls of the ester and the acid. The ^1H NMR spectrum exhibited a doublet integrating for three protons at δ_H 1.57 with coupling constant $J_{2,3}$ 7.2 Hz and this was assigned to lactate methyl hydrogens. A multiplet at δ_H 4.44 integrating for two hydrogens was assigned to H-5' and H-6', whilst a quartet at δ_H 5.17 with coupling constant $J_{2,3}$ 7.2 Hz was assigned to H-2. A multiplet at δ_H 6.49 integrating for two hydrogens was assigned to H-3' and H-4' while a doublet at δ_H 7.57 with coupling constant J = 5.5 Hz was assigned to H-2 of the cyclohexadiene moiety. The ^{13}C NMR spectrum was also consistent with the proposed structure with the two carbonyls resonances at δ_C 166.2 and 176.3.

138 **139**

Figure 2.15: Deprotection of both the Boc and *t*-butyl groups

The processes described thus far have culminated in the first synthesis of the enantiomer of the structure of the reported in literature as oryzoxymycin. Unfortunately, as the results show, the optical rotation values of the two compounds were inconsistent (**139** $[\alpha]_D^{21}$ –199 (c; 1, H_2O); Literature oryzoxymycin $[\alpha]_D^{21}$ +349 (c;1, H_2O)).[47] Significant differences were also observed in the infrared spectrum both in the carbonyl region and the characteristic fingerprint region, Figures 2.16 and 2.17.

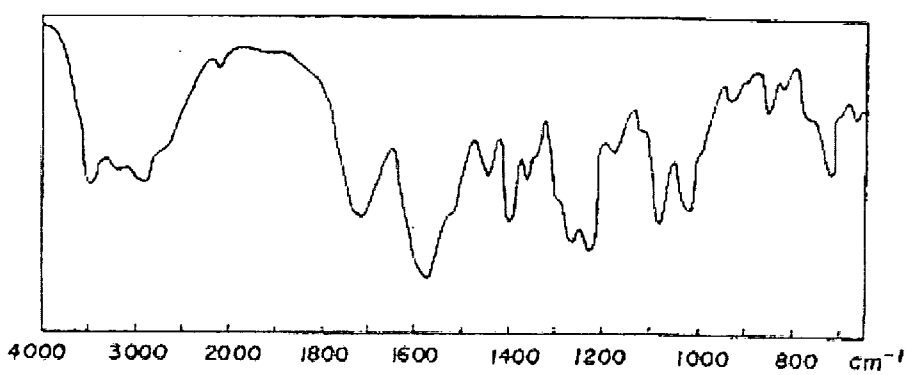


Figure 2.16: Literature IR spectrum of oryzoxymycin[44]

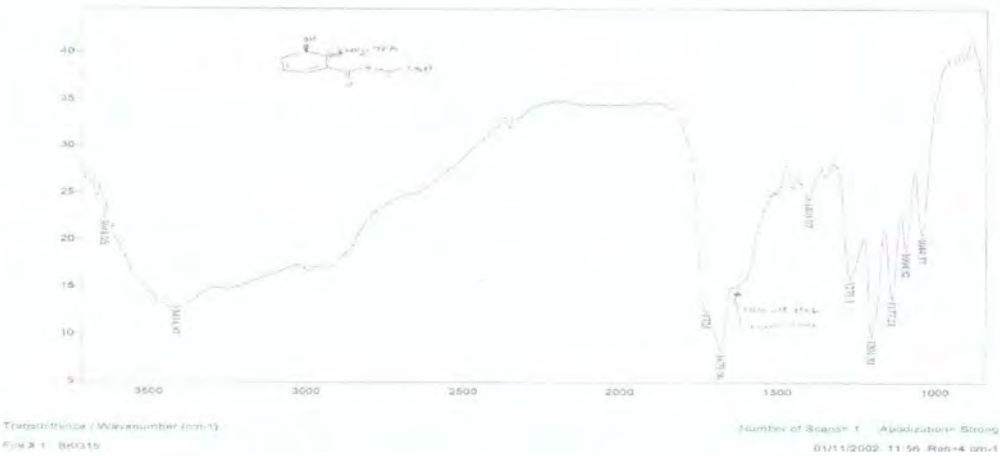
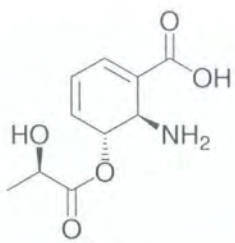


Figure 2.17: IR spectrum of oryzoxymycin

On the basis of these results, the assumption at this stage was that the correct structure for oryzoxymycin was the isomeric C-5 lactate ester **140**, Figure 2.18. It is instructive to draw attention to the fact that related structures have this pattern of substitution.[48-50] Another possibility considered was a diastereomeric structure isomeric at C-2 of the lactate side chain.

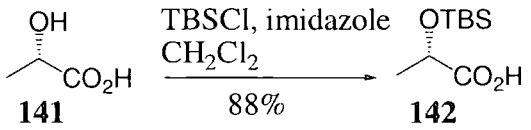


140

Figure 2.18: Possible structure of oryzoxymycin

To test the assumption stated above, a study towards the synthesis of **140** was undertaken. During the planning stages of this synthesis, the task of achieving the coupling of the lactate unit to the cyclic moiety was not regarded as being too difficult. After all, *in situ* activations of the carboxylic groups with coupling reagents like EDCI followed by reaction with nucleophiles are routinely carried out in organic synthesis.[67,68] Below we report preliminary results towards synthesis of **140**.

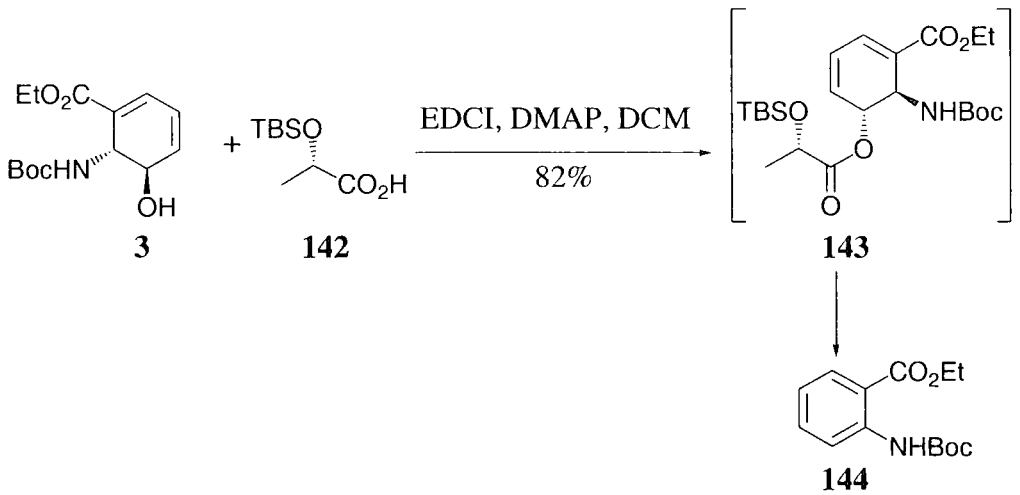
To set the stage for the crucial coupling reaction, the hydroxyl-function of (*S*)-lactic acid **141** had to be protected. To this end, addition of TBSCl and imidazole to a stirred solution of acid **141** afford the OH-TBS protected lactic acid **142** in good yield, Figure 2.19. The choice of the HF labile TBS protecting group was based on the assumption that its removal could be coupled to that of the Boc group.



141 **142**

Figure 2.19: Protection of the (S)-lactic acid **142**

Unfortunately, when ester **3** was treated with lactic acid **142** in the presence of EDCI and DMAP at 25 °C, all that was isolated was the fully protected anthranilic acid derivative **144** in 82 % yield, Figure 2.20. Repeating the reaction at low temperature (0 °C) did not change the outcome. This results suggested that intermediate **143** was itself an unstable substance under the reaction conditions, hence the aromatisation to **144**. Repeating the reaction with acid **125** instead of ester **3** led to isolation of N-Boc protected anthranilic acid.



3 **142** **143** **144**

Figure 2.20: EDCI Coupling of the lactate **142** to **3**

The disappointing results forced us to look at other ways of activating the carboxylic acid of the lactic acid **142**. One of the widely used methods for the activation of carboxylic groups is conversion into acid chlorides using thionyl chloride.[69, 70] In the context of the synthesis of intermediate **143**, acid **142** was treated with thionyl

chloride in THF and after 12 h **3** was added to the reaction mixture. Unfortunately, the only detectable product was again the protected anthranilic acid derivative **144**. The instability of the coupled product **143** was attributed to steric interaction between the bulky Boc group and the lactate side chain. Indeed, when the less sterically encumbered isobutyric acid **145** was used instead of lactic acid **142** ester **146** was isolated in 90% yield, Figure 2.21.

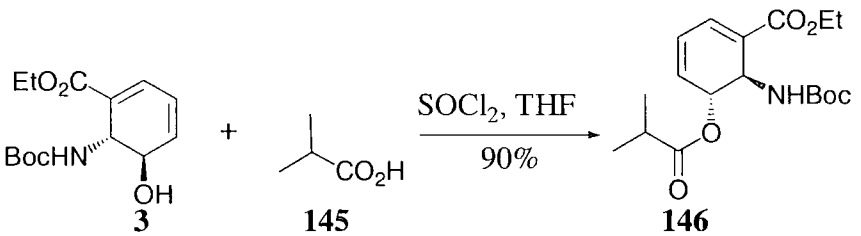
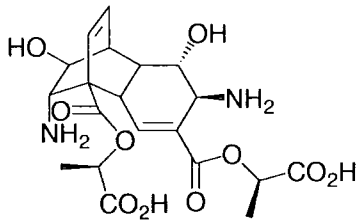


Figure 2.21: Synthesis of **146**

At this point, we suspended the attempts towards synthesis of **140** and with the appropriate intermediates and strategy in hand, we set out to synthesise the (+)-diastereoisomer of the literature structure of oryzoxymycin. The results of this work will be discussed in the subsequent section.

2.9 SYNTHESIS OF (+)-DIASTEREOISOMER OF ORYZOXYMYCIN

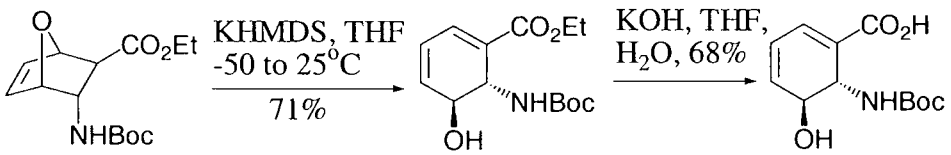
The readiness of oryzoxymycin to dimerize into **147** was reported by Hashimoto and co-workers.[45] On the other hand, the synthesised (-)-oryzomycin salt **139** showed appreciable stability at low temperature and in solution but still decomposed when kept at room temperature as a solid. In the search for a more stable structure of oryzoxymycin, we considered the synthesis of its (+)-analog, isomeric at C-2 of the lactic acid. Below, we therefore report the synthesis of (+)-diastereoisomer of oryzoxymycin that took advantage of the versatile methodologies developed during the synthesis of (-)-oryzoxymycin.



147

Figure 2.22: Diels-Alder Dimer of oryzoxymycin

Through our previously established synthetic pathway, oxanorbornene system **(-)-2** could be fragmented in the presence of a base to give a cyclohexadiene system. In the event, treatment of the bicyclic adduct **(-)-2** with KHMDS in THF afforded diene **(+)-3**, $[\alpha]_D^{22}$ +266 (c; 1, $CHCl_3$) in 71% yield. Hydrolysis of the ester of **(+)-3** with KOH in THF/H_2O gave acid **(+)-125**, $[\alpha]_D^{22}$ +348 (c; 1, $CHCl_3$) in 68% yield, Figure 2.23.



(-)-2 **(+)-3** **(+)-125**

Figure 2.23: Synthesis of the acid **(+)-125**

With the required building blocks in hand, attention was then turned to the convergent union of lactate **137** and intermediate **(+)-125** on the basis of the procedure established in the synthesis of (-)-oryzoxymycin. To this end, treatment of acid **(+)-125** with lactate **137** in the presence of CsF in DMF at elevated temperature (50°C) gave the protected (+)-isomer of oryzoxymycin **148** $[\alpha]_D$ +181 (c; 1, $CHCl_3$) in excellent yield. The point of attachment for the lactate, as in the previous case, was confirmed by HMBC correlation experiments. Final deprotection of both the Boc and *t*-butyl groups was effected by treatment with TFA in CH_2Cl_2 to give the (+)-isomer salt of oryzoxymycin **149** $[\alpha]_D$ +165 (c; 1, H_2O), Figure 2.24. Unfortunately, this salt also decomposed when left in a solid state at room temperature.

Oryzoxymycin isomer **149** was confirmed as the product of the sequence of reactions described above by elemental analysis which established the molecular formula $C_{10}H_{13}NO_5.C_2HO_2F_3$. The IR spectrum featured two bands at 1703 and 1677 cm^{-1} due to the two carbonyls, whilst a broad band at 3350-2800 cm^{-1} was characteristic of the

acid group. The ^{1}H and ^{13}C spectra displayed all the features consistent with the proposed structure.

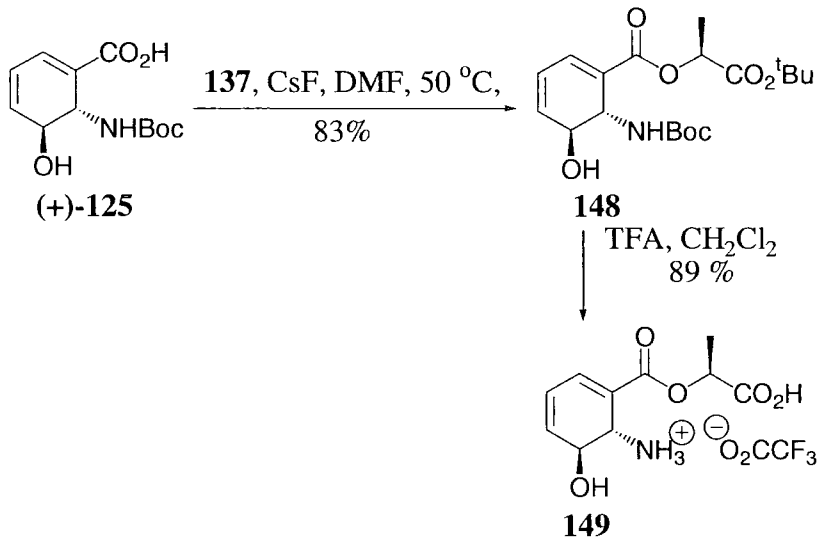


Figure 2.24: Synthesis of (+)-diastereomer of oryzoxymycin **149**

It is appropriate, at this juncture, to note that the synthesis of both compounds **139** and **149** did not achieve our aim of proving the reported structure of oryzoxymycin. While the literature oryzoxymycin was characterised as an HCl salt, **139** and **149** were characterised as TFA salts. Whether this discrepancy could be responsible for the differences observed between the optical rotations of the synthesised compounds and the literature oryzoxymycin is not obvious. It is worth noting that addition of a few drops of 5 M HCl to a water solution of either **139** or **149** did not significantly change the observed rotation.

Among the tasks remaining in this synthesis was ascertaining the absolute stereochemistry of the cyclohexadiene moiety of oryzoxymycin. It was known from the work of McCormick and coworkers that (+)-*trans*-2,3-dihydro-3-hydroxyanthranilic acid (DHAA) can be hydrogenated in the presence of Palladium to give 2-amino-3-hydroxycyclohexane-1-carboxylic acid $[\alpha]_D^{21}$ –35 (c;1, H_2O).[71] The reduction was repeated by Hashimoto to prove the absolute stereochemistry of oryzoxymycin.[47] Thus, on the basis of these precedents, acid **(+)-125** was reduced by treatment with Pd/C in ethanol under a hydrogen atmosphere and subsequently treated with TFA to remove the Boc and give substituted cyclohexane **151** $[\alpha]_D^{21}$ –32 (c;1,

H_2O) in excellent yield. Alternatively, **125** was treated with TFA to give **152** $[\alpha]_D^{21}$ + 339 (c;1, H_2O) and subsequent reduction gave **151** in 93 % from **125**. On the basis of the consistency of the results with literature data, the absolute structure of **149** must be (*2S*)-[(*5S*, *6S*)-6-amino-5-hydroxy-1,3-cyclohexadiene-1-carbonyloxy]-propionic acid TFA salt.

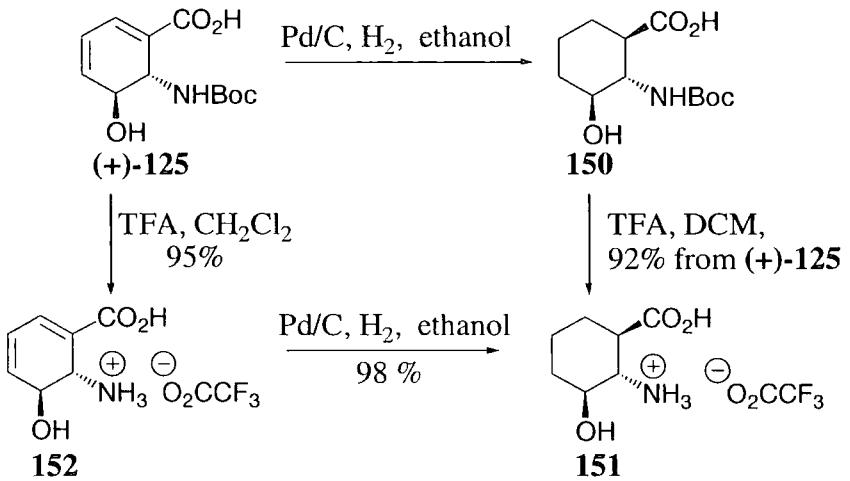


Figure 2.25: Reduction and deprotection of **(+)-125**

2.10 SUMMARY

The reaction processes described in this chapter have culminated in the synthesis of the enantiomer and the (+)-diastereoisomer of the literature structure of oryzoxymycin. This is the first reported synthesis of the structure described by Hashimoto as oryzoxymycin.[72] Memorable highlights of this route include the demonstration of the Diels-Alder reaction of nitroacrylates and furan as an efficient method for the construction of highly functionalised cyclohexyl rings, the utility of enzymes in kinetic resolution and the use of CsF in the formation of ester bonds in the presence of a free hydroxyl group. This achievement bodes well for the future application of this chemistry to the total synthesis of other related structures of biological or structural interest.

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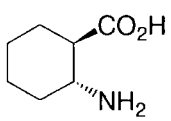
CHAPTER THREE

SYNTHESIS OF THE 3,4,5-TRIHYDROXYL DERIVATIVES OF ACHC

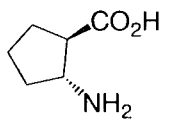
3.1 INTRODUCTION

During the course of the synthesis of the structure of oryzoxymycin discussed in Chapter 2, it was recognised that cyclohexadiene **125** could be functionalised in a controlled and selective fashion taking advantage of substrate stereo-controlled processes to give derivatives of 2-aminocyclohexane-1-carboxylic acid (ACHC). In this chapter, the synthesis of an array of 3,4,5-trihydroxyl derivatives of ACHC, which took advantage of the above observations will be discussed.

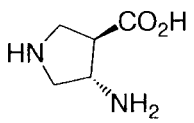
Trans-2-aminocyclohexane-1-carboxylic acid (*trans*-ACHC) **96** is a member of a new class of compounds called cyclic β-amino acids. Along side 2-aminocyclopentanecarboxylic acid (ACPC) **153** and 4-aminopyrrolidinecarboxylic acid (APC) **154**, ACHC **96** represent an interesting structure that has been the target of a number of syntheses.[11,73] As discussed in Chapter 1, most of the published syntheses of *trans*-ACHC and its derivatives are based on the following reactions; reduction of anthranilic acid,[32] Curtis rearrangement,[26] reductive amination[23] and Diels Alder reaction of amino dienes and acrylates.[29]



ACHC **96**



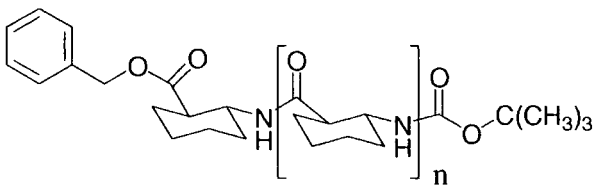
ACPC **153**



APC **154**

Figure 3.1: *Trans*-ACHC **96** and related structures

Much of the interest in ACHC **96** and related compounds is a consequence of the ability of their oligomers to form well-defined secondary structures analogous to those of natural peptides.[15] In this respect, Gellman and co-workers have recently examined the tetramer **155** and the hexamer **156** (Figure 3.2) of optically active *trans*-ACHC, using crystallography and 2D NMR and these revealed perfect 14-helical conformations.[13] Oligomers of ACHC and other cyclic β-amino acids therefore have a particular appeal for extending our understanding of protein structure and stabilization.



Tetramer **155**, n = 3 and hexamer **156**, n = 5

Figure 3.2: Gellman's tetramer **155** and hexamer **156**

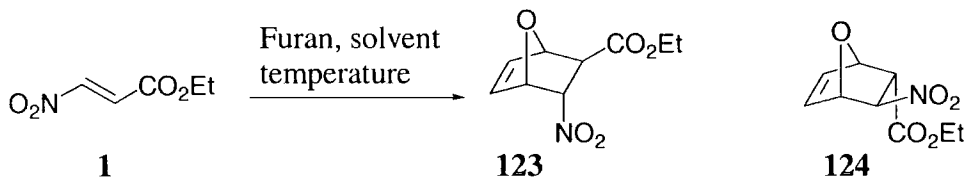
Recently, increasing work has been devoted to the synthesis of cyclic β-amino acids with extra functionalities appended at specific positions around the rings. A few examples of these substituted cyclic β-amino acids were discussed in Chapter 1. Subsequent studies will undoubtedly be focused on the effects of the functionalities on the stability of the oligomers derived from the substituted cyclic β-amino acids.

In view of the importance of β-peptides, there is a need for the synthesis of their building blocks, β-amino amino acids. In particular, water-soluble hydroxylated or aminated derivatives of ACHC have attractive properties and a high intrinsic propensity for helical folding.[14,17,26] Consequently, we report in this chapter the synthesis of an array of 3,4,5-trihydroxy derivatives of ACHC that took advantage of the Diels-Alder reaction of (E)-3-nitroacrylate and furan described in Chapter 1 for synthesis of the structure of oryzoxymycin.

3.2 PREPARATION OF THE OXANORBORNENE INTERMEDIATES

In Chapter 1, the *endo*-nitro adduct was accessible as the major product through a reaction of nitroacrylate **1** and furan in $CHCl_3$ at –20 °C. Realising that the *exo*-nitro adduct was as important in the synthesis of DHAA derivatives, a study of the effects of temperature and solvents on the Diels Alder reaction was conducted in the hope of shifting selectivity towards the *exo*-nitro adduct. Thus, repeating the reaction of nitroacrylate **1** and furan at 25 °C and 40 °C gave a 2:1 mixture of adducts **123** and **124** respectively. When the reaction was carried out in other solvents such as CH_3CN, MeOH, $(CF_3)_2CHOH$ and toluene at both 25 °C and elevated temperatures, the 2:1 ratio was maintained, Figure 3.3. These observations can be attributed to the preferred *endo*-nitro transition state geometry. Just and co-workers have reported the preference for the *exo*-nitro adduct when the reaction of methyl 3-nitroacrylate and furan was

carried out without a solvent.[6] However, in our case, this reaction afforded a 3:1 mixture in favour of the *endo*-nitro adduct **123**.



1 **123** **124**

Solvent	Temperature (°C)	Yield of 123(%)/124 (%)	
$CHCl_3$	-20	72	18
$CHCl_3$	25	60	30
$CHCl_3$	40	60	30
CH_3CN	25	60	30
Toluene	25	60	30
Toluene	80	60	30
MeOH	25	60	30
$(CF_3)CHOH$	25	60	30
Furan	25	68	22

Figure **3.3**: Solvents and temperature effects on the Diels Alder reaction

The Diels Alder adducts were separable by column chromatography and subsequent reduction of the nitro group for each adduct as described in Chapter 1 afforded oxanorbornene intermediates **3** and **158**, Figure 3.4. It was assumed at planning stages that it should be possible to functionalise the double bonds of intermediates **3** and **158** in a controlled and selective fashion by taking advantage of the rigid shape of the substrates. The functionalised adducts could then be elaborated to cyclohexyl derivatives by base mediated elimination of the oxygen bridge. A complementary route would be the reversal of the functionalisation and fragmentation sequence of reactions, Figure 3.4.

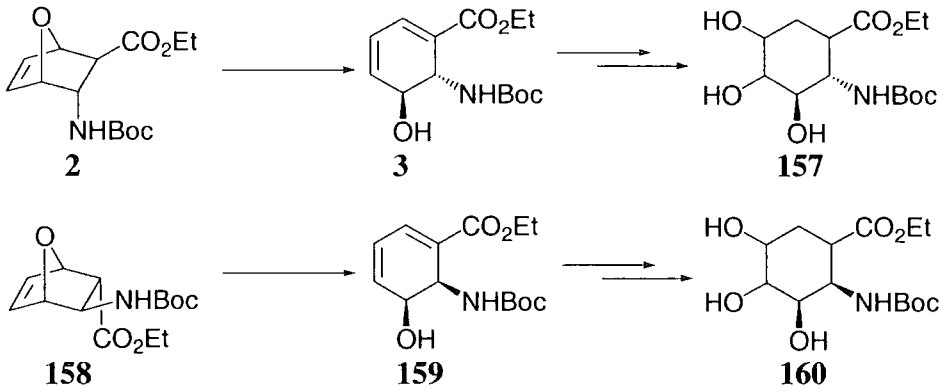


Figure 3.4: General strategy for elaboration of adducts **2** and **158** into β-amino acids of type **157** and **160**

In the first section of this chapter, results on the use of OsO_4 mediated dihydroxylation for the elaboration of bicyclic adducts **2** and **158** to 3,4,5-trihydroxy derivatives of *trans*-ACHC will be discussed. Subsequent sections will then document our work towards trihydroxy derivatives of ACHC using epoxidation reactions.

3.3 *CIS* DIHYDROXYLATION

3.3.1 INTRODUCTION

Osmium tetraoxide (OsO_4) is the most reliable reagent available for the *cis* dihydroxylation of alkenes to give the corresponding *cis*-diols. Although stoichiometric osmylation has been reported in the literature,[74] it is more usual, for reasons of cost and safety, to use osmium tetraoxide catalytically in the presence of inexpensive co-oxidants. Inorganic cooxidants such as sodium or potassium chlorate and hydrogen peroxide were the first to be used, but have the disadvantage that appreciable over-oxidation can occur to give keto or acid products.[75] Amine N-oxides and organic peroxides on the other hand have been found to be very effective as co-oxidants in the dihydroxylation reactions.[74,75] Minato and co-workers have also described the use of $K_2Fe(CN)_6$ in the presence of K_2CO_3 for the osmium catalysed dihydroxylation of alkenes.[76]

Figure 3.5 presents a succinct summary of the catalytic cycles in the osmium-catalysed dihydroxylation of alkenes using NMO as the co-oxidant. Through the work

of Sharpless and co-workers, two catalytic cycles were deduced.[77] Under homogeneous conditions the co-oxidant has constant access to all the catalytic intermediates, therefore the turnover for the dihydroxylation is locked into the second cycle. Kwong found that that this second catalytic cycle was virtually eliminated by performing the reaction under biphasic conditions.[78] Under these conditions, osmylation takes place in the organic layer and the resulting osmium (VI) monoglycolate ester **163** undergoes hydrolysis releasing the diol to the organic layer and the Os (VI) to aqueous layer where it is oxidised back to Os (VIII). Entry of the osmium glycolate into the second cycle is therefore prevented.

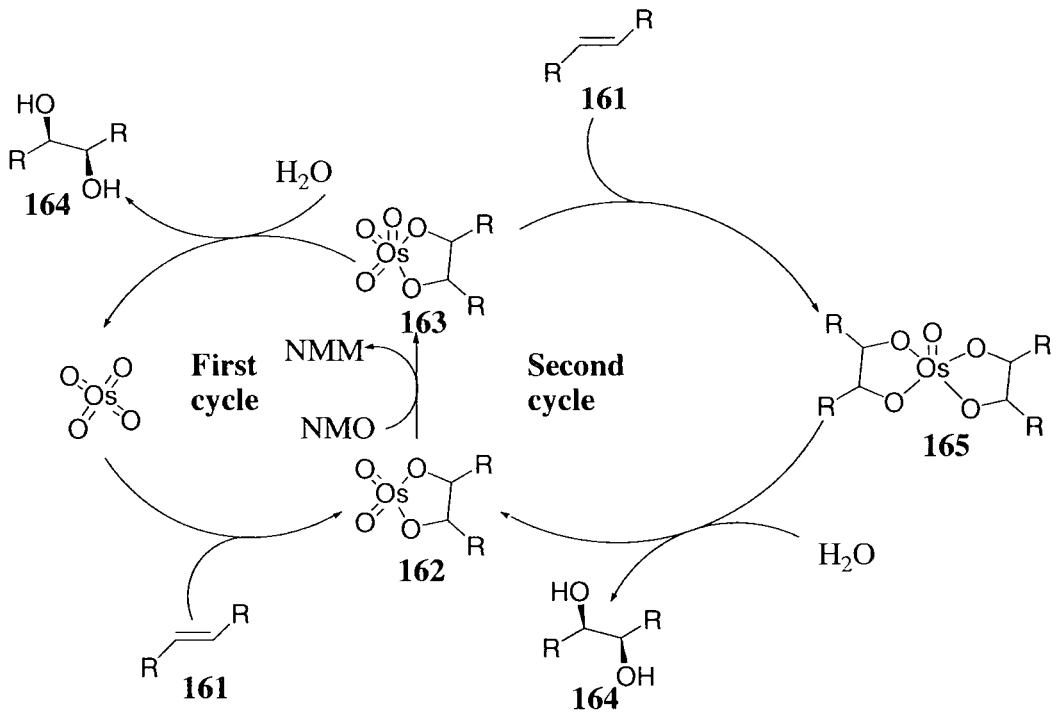


Figure 3.5: The two catalytic cycles for osmium catalysed dihydroxylation[78]

3.3.2 SYNTHESIS OF THE *ANTI-ANTI-ANTI-SYN* ACHC DERIVATIVE 168

On the basis of the exceptional scope and reliability of the osmium catalysed dihydroxylation reaction, we decided to feature this reaction in the synthesis of polyhydroxylated derivatives of ACHC using oxanorbornene systems **2** and **158** as starting materials. Thus, on the basis of the precedence set in Chapter 2, adduct **2** was treated with KHMDS in THF to give cyclohexadiene **3** in 71% yield. Treatment of **3** with catalytic OsO_4 in the presence of $Me_3NO.H_2O$ as the co-oxidant afforded the

substituted cyclohexene **166** as a single diastereoisomer, which was then characterised as its triacetoxy derivative **167**, Figure 3.6.

It is instructive to address the interesting stereochemical outcome of the above dihydroxylation reaction. The delivery of the diol on the same face as the carbamate and on the face opposite to the allylic hydroxyl group in the osmium catalysed dihydroxylation of **3** was certainly not suprising. Dihydroxylation of alkenes that contain chiral centres can lead to high levels of stereoselectivity. Indeed, Kishi has reported that the OsO_4 mediated oxidation of cyclic allylic alcohols led to formation of a *syn-anti* triol with high levels of stereoselectivity.[79, 80] Furthermore, the ability of cyclic homoallylic carbamates to give high levels of *syn* selectivity in the osmium mediated dihydroxylation reactions is well documented.[81] Cyclohexadiene **3** has these two chemical processes acting in cooperation, hence the high level of stereoselectivity.

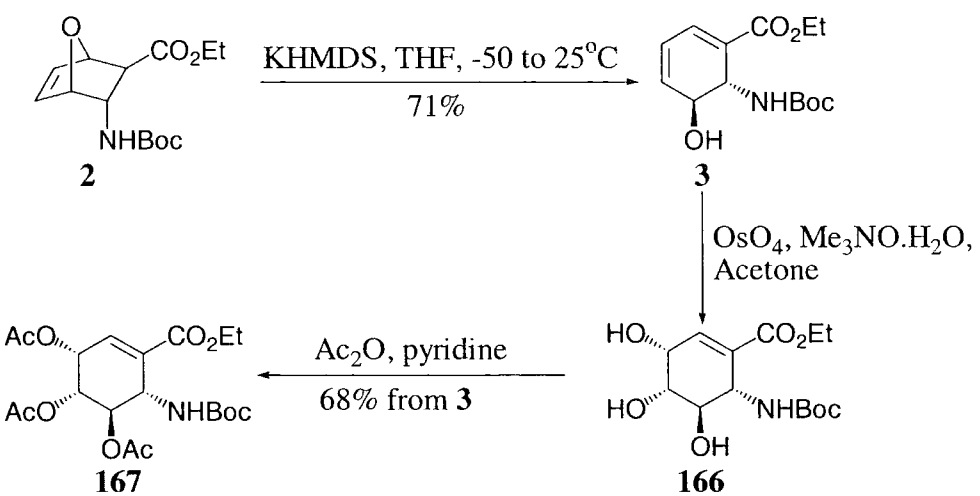


Figure 3.6: Synthesis of cyclohexene **167**

To complete the synthesis, it was necessary to reduce the double bond in a selective fashion. It was anticipated that substrate-stereocontrolled processes could secure the vicinal stereochemical relations in the reduction step. Gratifyingly, when a solution of **167** in ethanol was treated with a catalytic amount of Pd/C under a hydrogen atmosphere, ACHC derivative **168** was the only detectable product, Figure 3.7. It is noteworthy that the addition of the hydride during the reduction took place on the more hindered diastereo-face of the alkene probably due to the coordination of the

palladium to the carbamate. It was known from the work of McCormick and co-workers on similar systems that the hydride adds preferentially on the same face as the amino group.[71] Thus, on the basis of this precedent, the selective formation of **168** was not suprising. The same stereoselective reduction was observed when **166** was used as the substrate to give **169**, Figure 3.7. Triol **169** was then acetylated under the standard conditions to give **168.**

High-resolution mass spectrometry established the molecular formula $C_{20}H_{31}NO_{10}$ for ACHC derivative **168**. The ^{1}H and ^{13}C NMR featured all the peaks consistent with the cyclohexane structure. The relative stereochemistry was confirmed by across the ring NOESY correlation between H-1 and and H-3 and that between H-2 and H-4, Figure 3.8.

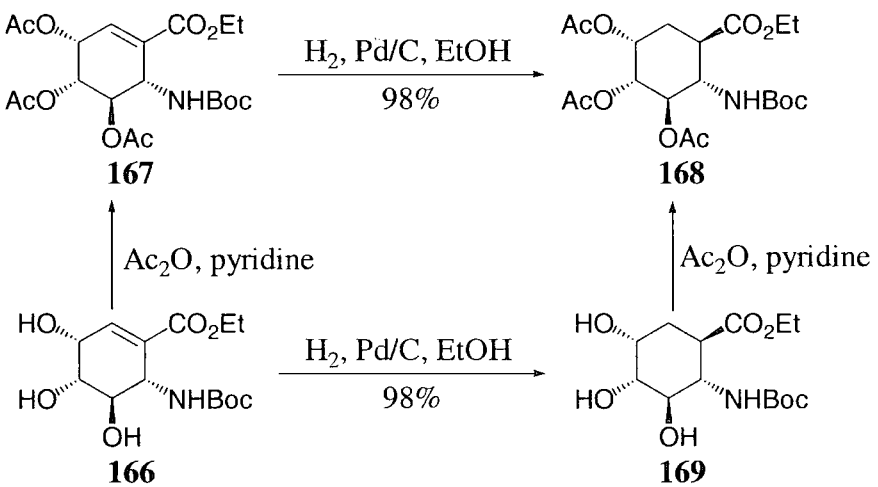


Figure 3.7: synthesis of *anti-anti-anti-syn* triacetoxy ACHC derivative **168**

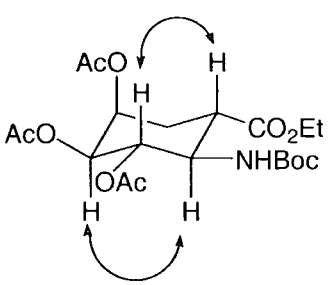


Figure 3.8: Selected NOESY interactions for **168**

3.3.3 SYNTHESIS OF THE *ANTI-ANTI-SYN-SYN* ACHC DERIVATIVE 178

Having achieved the stereoselective synthesis of the *anti-anti-anti-syn* triacetoxy ACHC derivative **168**, attention was turned on setting the stereochemistry of the C-4 and 5 *syn*-hydroxyl groups on the same face as the allylic hydroxyl group and *anti* to the homoallylic carbamate. Donohoe and co-workers have carried out extensive studies on the directed dihydroxylation of cyclic allylic alcohols and have found that the OsO_4/TMEDA oxidant delivered the *syn-syn* isomer through hydrogen-bonding mediated processes, Figure 3.9.[82] This reaction proceed through a five membered chelate of TMEDA with OsO_4 thereby increasing the electron density on the oxo ligands and making them better hydrogen bond acceptors.

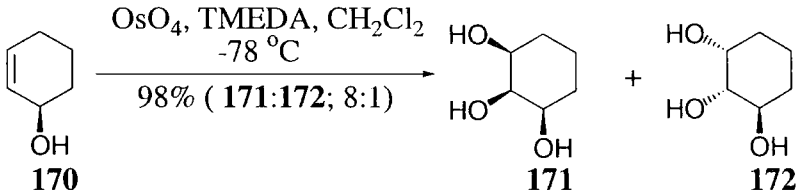


Figure 3.9: Donohoe's OsO_4/TMEDA dihydroxylation of **170**

In the context of intermediate **3**, hydrogen bonding could either be between the chelate and the allylic alcohol or the chelate and the homoallylic carbamate. In the event, treatment of a solution of cyclohexadiene **3** in CH_2Cl_2 or acetone with one molar equivalent of OsO_4 in the presence of TMEDA afforded trihydroxylcyclohexene **166** as the only detectable product, Figure 3.10. The dihydroxylation still occurred preferentially on the same diastereoface as under the previous conditions without TMEDA.

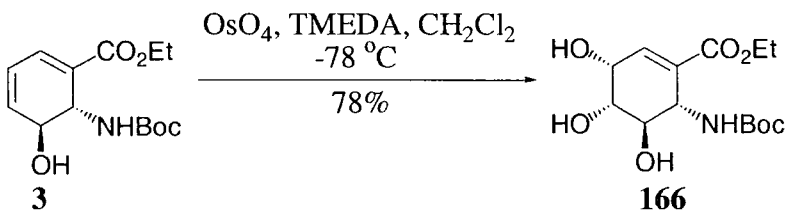
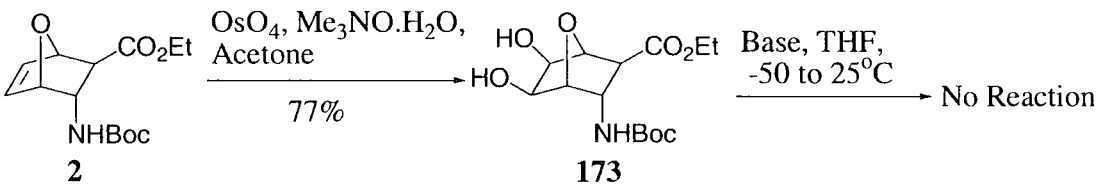


Figure 3.10: OsO_4/TMEDA mediated dihydroxylation of **166**

Next, we examined the Prevost reaction[62] as a route to dihydroxylation of **3** on the upper diastereoface. It is instructive to preface this reaction with a few remarks. The

Prevost reaction involves heating the alkene with iodine and a silver salt (usually the benzoate or acetate). In this reaction, iodine reacts with the π bond on the less sterically hindered face to afford a transient iodonium ion, which is then intercepted by the nucleophilic silver carboxylate to give a *trans*-iodo-ester. The iodo-ester is then hydrolysed to give the *cis*-diol on the more hindered face. In the case at hand, treatment of cyclohexadiene **3** with iodine and silver acetate in acetic acid and water gave a synthetically useless mixture of products including diiodo isomers. The above observation can be attributed to non facio-discrimination of the iodination reaction and the opening of the iodonium ring by an iodide ion.

The disappointing results forced us to modify our synthetic strategy towards functionalising bicyclic adduct **2** before the elimination of the oxygen bridge. Employing a known procedure,[64] **2** was dihydroxylated from the *exo*-face by treatment with catalytic OsO_4 in the presence of $Me_3NO.H_2O$ to give diol **173**. With diol **173** in hand, attention was turned towards elimination of its oxygen bridge. Andrio and co-workers have reported a LiHMDS mediated fragmentation of a comparable oxanorbornane system with unprotected hydroxyl groups.[83] Unfortunately, all attempts at the use of either KHMDS or LiHMDS in variable equivalences to eliminate the oxygen bridge of **173** failed to give any of the anticipated cyclohexenyl products.



Base: LiHMDS or KHMDS

Figure 3.11: Synthesis of **173** and attempts towards its fragmentation

The failure of the fragmentation reactions of diol **173** was certainly not suprising. The addition of the base must have led to the deprotonation of the hydroxyl groups, placing more negative charge on the substrate and making the formation of the enolate, which leads to β-elimination of the oxygen bridge very difficult. Diol **173** therefore had to be converted into a form amenable to the fragmentation step. To this end, a solution of **173** in acetone was treated with 2,2-dimethoxypropane in the

presence of p-TsOH to give acetonide **174** in 61% yield, Figure 3.12. Although fragmentation of related acetonide systems has been reported,[65] acetonide **174** was inert to both LiHMDS and KHMDS. It seemed reasonable to conclude that the cyclic acetonide moiety increased the rigidity of **174** and therefore made the elimination of the oxygen bridge less likely.

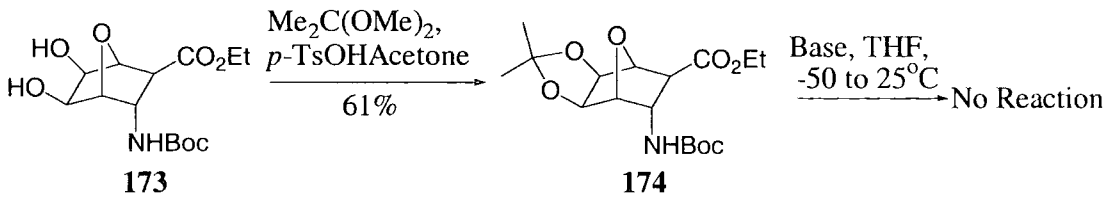


Figure 3.12: Synthesis of **174** and attempts towards its fragmentation

At this point, a persilylated derivative of **173** was considered as a possible less rigid substrate for the base mediated fragmentation reaction. To prepare this derivative, a solution of **173** in CH_2Cl_2 was treated with TBSCl in the presence of imidazole to give **175** in excellent yield. Initial attempts to fragment **175** using KHMDS were futile. Gratifyingly, LiHMDS gave the desired substituted cyclohexene **176** albeit accompanied by the unexpected loss of the Boc protecting group, Figure 3.13. It is not clear to what the discrepancy between KHMDS and LiHMDS should be attributed. The ^1H NMR spectrum of **176** exhibited all the features consistent with the proposed structure including a characteristic doublet at δ 6.87 with coupling constant J = 3.2 Hz assigned to H-2.

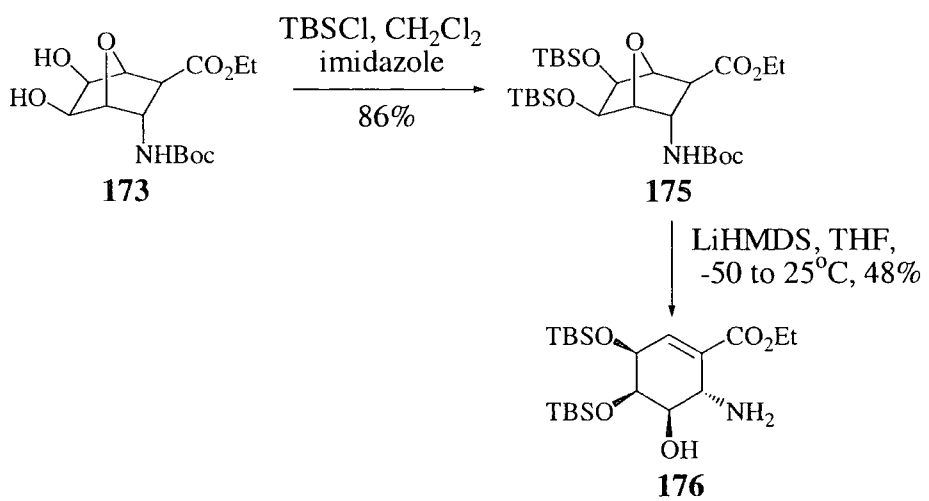


Figure 3.13: Persilylation of **173** and fragmentation of *bis* TBS ether **175**

In spite of the moderate yields for the fragmentation reaction, **176** was elaborated to *anti-anti-syn-syn* triacetoxy derivative of ACHC through the sequence of reactions shown in Figure 3.14. Thus, TBAF mediated desilylation of **176** and subsequent peracetylation afforded **177** in 52% over the two steps. Reduction of the double bond by treatment of a solution of **177** in EtOH with a catalytic amount of 10% Pd/C under a hydrogen atmosphere proved to be *facio*-selective and afforded the *anti-anti-syn-syn* isomer **178** as the only product. The hydrogen was delivered to the double bond on the same face as that occupied by the carbamate and opposite to the C-3 acetoxy group.

The ^{1}H and ^{13}C spectra of **178** displayed all the features consistent with the proposed structure. The relative stereochemistry around the ring was suggested by the NOESY interactions shown in Figure 3.15.

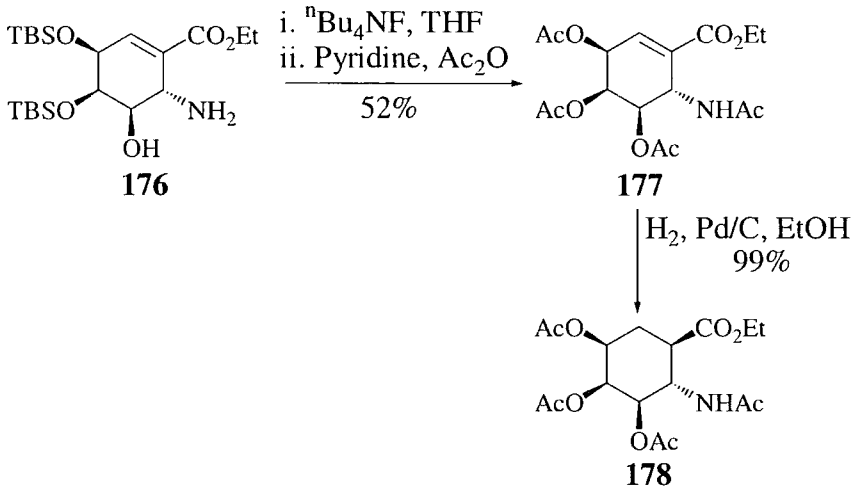


Figure 3.14: synthesis of *anti-anti-syn-syn* triacetoxy ACHC derivative **178**

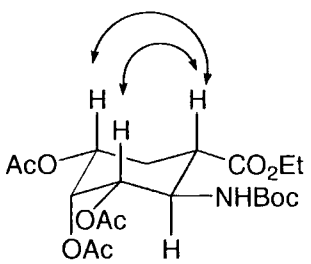


Figure 3.15: Selected NOESY interactions of **178**

3.3.4 SYNTHESIS OF THE *SYN-SYN-SYN-SYN* ACHC DERIVATIVE 182

The cis dihydroxylation chemistry discussed thus far employed the *endo* carbamate adduct **2** as the starting material and therefore gave the 2,3-*anti* geometry in the subsequent ACHC derivatives. It therefore appeared attractive to apply the *cis* dihydroxylation protocols on the *exo* carbamate adduct **158** as a route to ACHC derivatives with a 2,3-*syn* relationship. Thus, subjection of adduct **158** to the action of KHMDS in THF afforded cyclohexadiene **159** in 71% yield. Attempts to procure **159** from **3** through a Mitsunobu reaction[84] were thwarted by aromatisation which gave the N-Boc protected ethyl anthranilate. Having obtained **158**, OsO_4 mediated dihydroxylation and peracylation afforded cyclohexenyl **179** as the only isomer, Figure 3.16. It is evident from this reaction that the ability of the homo-allylic carbamate to direct delivery of the diol on the upper face overrides the *anti* preference of the allylic alcohol.

Another route to the cyclohexenyl intermediate **179** involved the sequence of reactions shown in Figure 3.16. Thus, dihydroxylation of bicyclic adduct **158** and subsequent protection of the resulting diol gave **180**. LiHMDS mediated fragmentation afforded intermediate **181** and contrary to **176** without the loss of the Boc group. Desilylation and acetylation under standard conditions gave the desired intermediate **179** in acceptable yield.

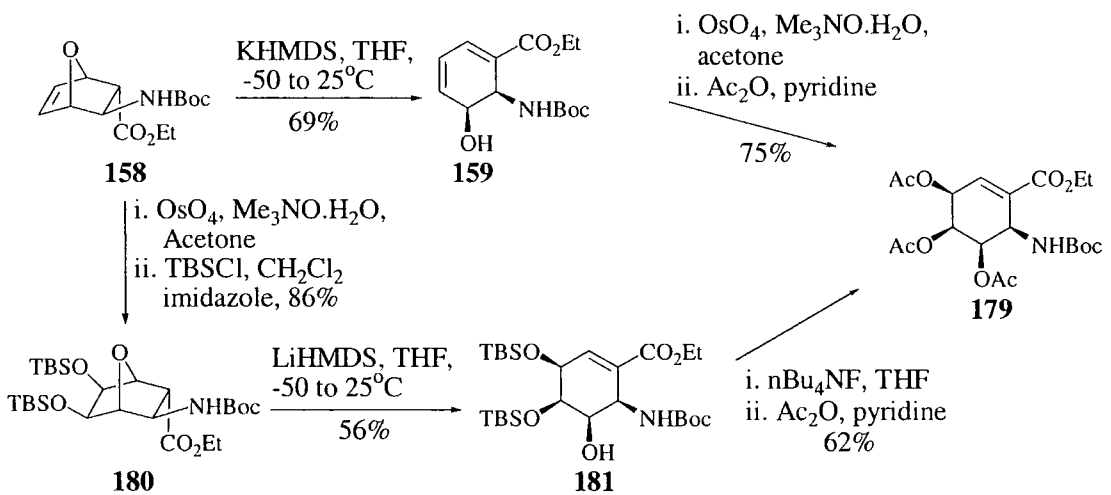
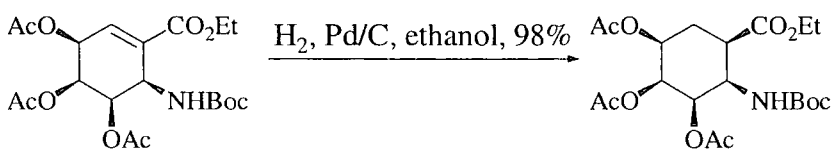


Figure 3.16: Two routes to cyclohexenyl intermediate **179**

The preparation of intermediate **179** set the stage for the reduction of the π bond to afford the triacetoxy derivative of ACHC. Considering the chiral environment around the π bond and results from the previous reduction reactions, it seemed reasonable to expect that the reducing agent would discriminate between the two diastereotopic faces of the ring. However, predicting from which side of the molecule the reduction would occur was difficult. In the event, treatment of a solution of **179** in ethanol with a catalytic amount of 10% w/w Pd/C under a hydrogen atmosphere gave the *syn-syn-syn-syn* ACHC derivative **182**, Figure 3.17. The hydrogen was delivered to the double bond from the less hindered face of the molecule and in contrast to related systems discussed in the preceding sections, the carbamate did not direct the hydrogenation.

The ^{1}H and ^{13}C spectra of **182** were consistent with the proposed structure. The relative stereochemistry was confirmed by NOESY correlations shown in Figure 3.18.



179 **182**

Figure 3.17: Synthesis of the *syn-syn-syn-syn* ACHC derivative **182**

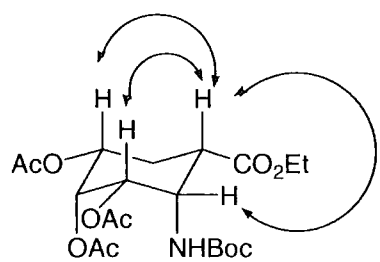


Figure 3.18: Selected NOESY interactions of **182**

In summary, OsO_4 catalysed dihydroxylation was found to be an effective method for the stereoselective synthesis of cyclohexyl β-amino acids **168**, **178** and **182** from bicyclic adducts **2** and **158**.

3.4 EPOXIDATION AS A ROUTE TO *TRANS* DIHYDROXYLATION

3.4.1 SYNTHESIS OF THE ALL *ANTI* ACHC DERIVATIVE 188

The dihydroxylation processes described thus far have culminated in the synthesis of derivatives of ACHC with a 4,5-*syn*-dihydroxyl relationship. To introduce stereochemical diversity in this synthetic approach, it appeared reasonable to explore routes towards the corresponding *anti* diols. Our strategy towards these intermediates with a 4,5-*anti* relationship identified epoxidation as a central reaction. Thus, treatment of a solution of cyclohexadiene **3** in CH_2Cl_2 with *m*CPBA and $NaHCO_3$ resulted in a highly selective oxidation of the remote π bond to give a separable 9:1 mixture of epoxides **183** and **184** respectively, Figure 3.19. Preliminary acetylation of the hydroxyl group enhanced the selectivity and allowed the isolation of epoxide **186** as the only isomer, Figure 3.20.

There have been sporadic reports on the stereoselective epoxidation of 4-aminocycloalkenes. For example, highly stereoselective amide-directed epoxidation of 4-aminocyclopentenes has been reported by Barrett and co-workers.[85] On the other hand, the peracid epoxidation of cyclic olefins with allylic directing hydroxyl groups is well documented.[86] In the context of the results of the epoxidation of **3**, the stereochemistry of the peroxide attack and the configuration of the resulting epoxide was directed by the homoallylic carbamate.

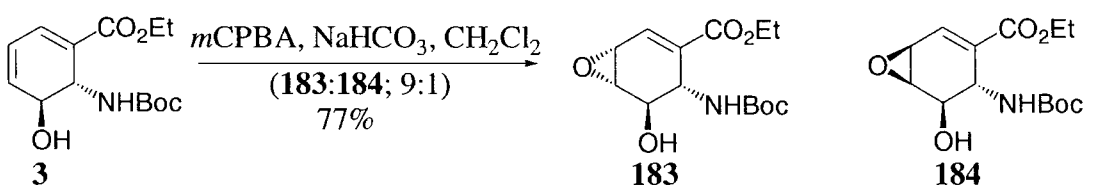


Figure 3.19: Epoxidation of **3**

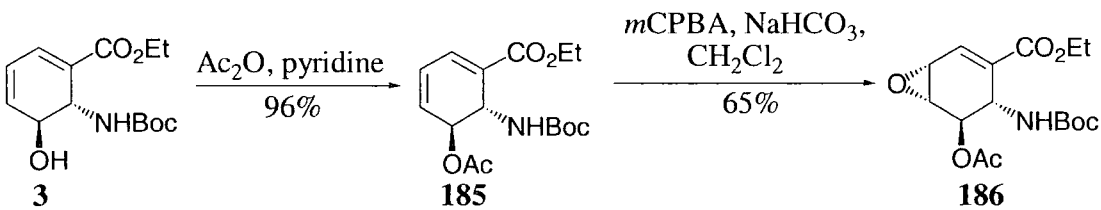


Figure 3.20: Synthesis and epoxidation of **185**

With intermediate **186** in hand, attention was turned towards the opening of the epoxide ring. To this end, treatment of epoxide **186** with aqueous perchloric acid led to a single *trans* diol isomer, albeit accompanied by loss of the Boc group, Figure 3.21. Characterisation of the fully acetylated derivative **187** suggested that nucleophilic attack had occurred at the allylic position. This was subsequently confirmed by ring opening of the epoxide with $ZnCl_2$ in the presence of acetic acid to give the crystalline chlorohydrin **189**, Figure 3.22. The structure of **189** was confirmed by X-ray crystallographic analysis (see Appendix 3). Finally, the reduction of the π bond under the conditions described previously afforded the all *anti* isomer **188** in excellent yield.

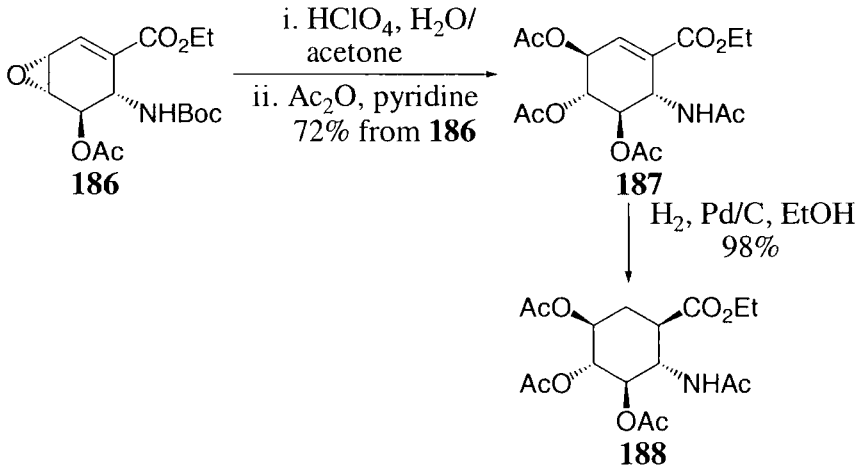


Figure 3.21: Synthesis of the all *anti* isomer **188**

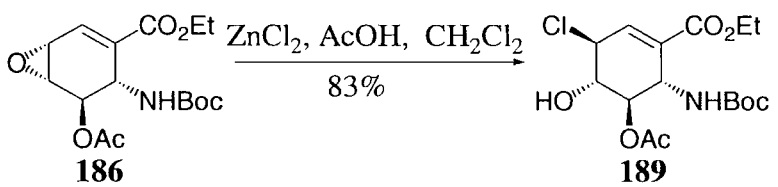


Figure 3.22: Opening of epoxide **186** with acetic acid in the presence of $ZnCl_2$

The structural assigment of the all *anti* isomer **188** was based on 1D and 2D NMR experiments. The observation of 10.0 Hz H_aH_b coupling constants in the ^1H NMR spectrum of **188** for the ring protons (H-1, H-2, H-3, H-4 and H-5) was indicative of H_aH_b *anti* diaxial relationships and supported the indicated stereochemistry. This was

subsequently confirmed by NOESY interactions between H-1 and H-3, H-1 and H-5 and also H-2 and H-4, Figure 3.23.

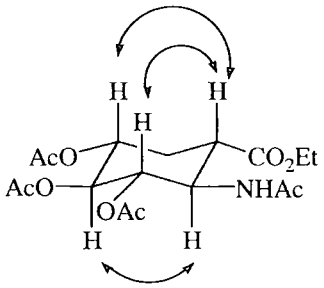


Figure 3.23: Selected NOESY interactions for the all *anti* isomer **188**

3.4.2 SYNTHESIS OF THE *ANTI-ANTI-SYN-ANTI* ACHC DERIVATIVE 195

The initial strategy to procure the alternative epoxide involved selective *exo* face epoxidation of the oxanorbornene system **2** and subsequent β-elimination of the oxygen bridge. To this end, a solution of adduct **2** in CH_2Cl_2 was treated with *m*CPBA and $NaHCO_3$ to give a 61% yield of epoxide **190**, Figure 2.24. Unfortunately, epoxide **190** decomposed under the basic conditions required for the β-elimination of the oxygen bridge.

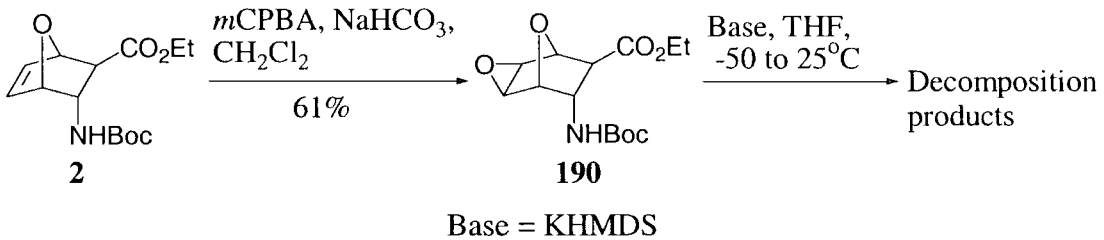
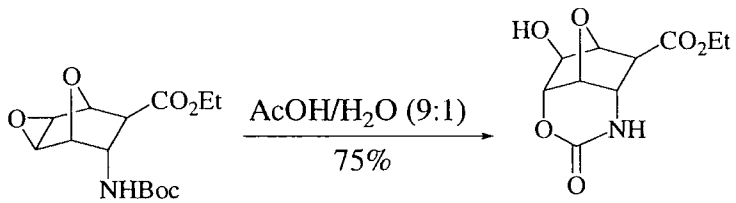


Figure 3.24: Synthesis of epoxide **190**

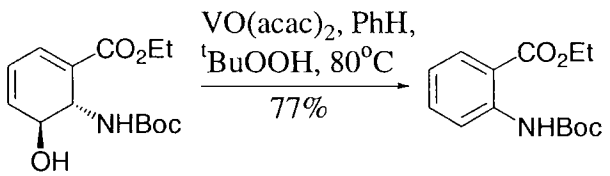
In the event that a regioselective opening of the epoxide ring could be achieved, adduct **190** could serve as a precursor to the *anti-anti-syn-anti* ACHC derivative. Unfortunately, when epoxide **190** was subjected to the action of a mixture of acetic acid and water, cyclic carbamate **191**, which was inert to the action of sodium ethoxide, was isolated in 75 % yield, Figure 3.25. Attempts to eliminate the oxygen bridge of this system with a large excess of KHMDS were also futile.



190 **191**

Figure 3.25: Opening of epoxide **190**

The disappointing results forced us to modify our synthetic strategy and methods which could override the dominant directing effect of the carbamate group of cyclohexadiene **3** were considered. It was known from the work of Sharpless and co-workers that the vanadium-based epoxidation of allylic alcohols with *t*-butyl hydroperoxide (TBHP) had a more *syn*-directive effect than *m*CPBA.[87, 88] Thus, on the basis of these precedents, a solution of cyclohexadiene **3** and catalytic $VO(acac)_2$ in refluxing benzene was treated with TBHP and the reaction was monitored by TLC. Unfortunately, the protected anthranilate **144** was the only product isolated from this reaction, Figure 3.26. The readiness of cyclohexadienes related to **3** to aromatise has been documented,[36] therefore isolation of **144** as the sole product was not suprising. Repeating the reaction at low temperature did not change the results.



3 **144**

Figure 3.26: Reaction of **3** with ^tBuOOH in the presence of $VO(acac)_2$

Next, a range of polar solvents were surveyed for the epoxidation of **3** on the assumption that they may disrupt the directing effect of the carbamate group. Gratifyingly, when a solution of the cyclohexadiene **3**, *m*CPBA and $NaHCO_3$ in CH_3CN was stirred at room temperature for 16 h, a separable 2:1 mixture of isomers favouring the desired *syn* epoxyalcohol **184** was isolated in excellent yield, Figure 3.27. However, when the reaction was carried out in other solvents, such as DMF, THF, MeOH, IPA or CF_3CH_2OH instead of CH_3CN, a 1:1 mixture of the epoxides was isolated. It was known from the work of Shu and Shi on epoxidation in CH_3CN that the actual oxidant was peroxyimidate **193**, formed by nucleophilic attack on the

solvent by *m*CPBA,[89] Figure 3.28. The modified steric and electronic properties of the oxidant were most likely responsible for the observed reversed stereoselectivity.

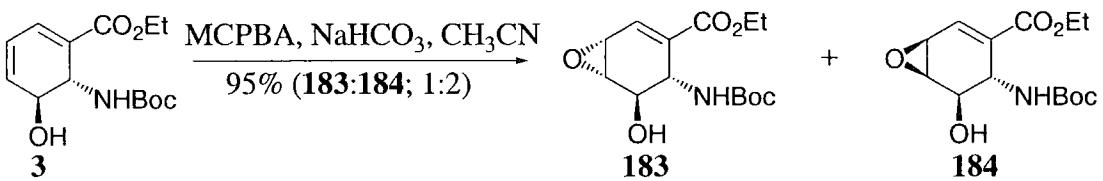


Figure 3.27: Epoxidation of cyclohexadiene **3** in CH_3CN

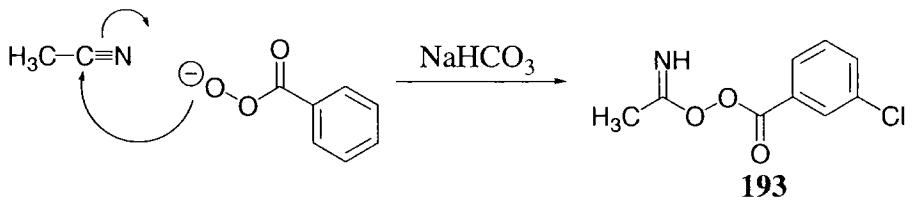


Figure 3.28: Possible route to peroxyimidate **193**

Among the tasks remaining was the opening of the epoxide ring of **184** and reduction of the π bond to give hopefully the *anti-anti-syn-anti* derivative of ACHC. Thus, acid-catalysed opening of the epoxide ring in **184** was regioselective and after acetylation, **194** was isolated as the only detectable product in 69 % yield, Figure 3.29. Reduction of the double bond under the previously described protocol afforded the *anti-anti-syn-anti* ACHC derivative **195** in excellent yield.

The analytical and NMR data of **195** were consistent with the proposed structure. The relative configurations of the cyclohexane substituents were suggested by the observation of NOESY effects between H-1 and H-3, and also H-3 and H-4, Figure 3.30.

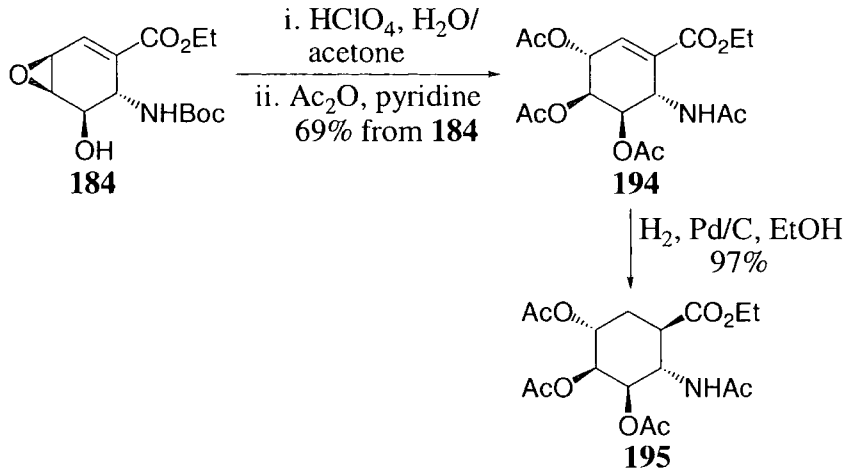


Figure 3.29: Synthesis of the *anti-anti-syn-anti* ACHC derivative **195**

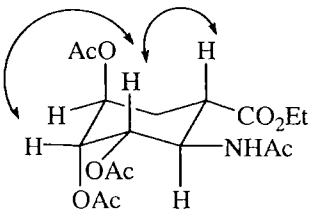


Figure 3.30: Selected NOESY interactions for **195**

3.4.3 SYNTHESIS OF THE *ANTI-SYN-SYN-ANTI* ACHC DERIVATIVE 198

It was considered interesting to compare the *facio* selectivity of the epoxidation of cyclohexadiene **3** to that of **159**. With both the carbamate and hydroxyl groups on the same face in cyclohexadiene **159** and therefore operating in cooperation, it was presumed that epoxidation would occur preferentially on the upper face. Thus, subjection of a solution of **159** in CH_2Cl_2 to the action of *m*CPBA in the presence of $NaHCO_3$ at room temperature resulted in the formation of only isomer **196** in 70% yield, Figure 3.31. Unlike **3**, alternative solvents such as CH_3CN, DMF, MeOH and H_2O/acetone or prior acetylation of the hydroxyl group did not affect the *facio* selectivity of the epoxidation of **159**. Attempts to protect the hydroxyl group with the bigger TBS group led to aromatisation giving the ethyl anthranilate **144**. Cyclohexadiene **159** was itself a rather unstable substance. Under acidic conditions, **159** undergoes aromatisation to give again the ethyl anthranilate **144**.

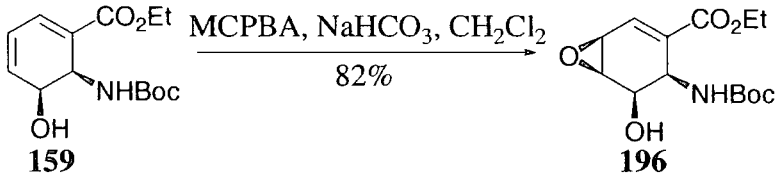


Figure 3.31: Epoxidation of cyclohexadiene **159**

As with the previous related systems, acid-catalysed opening of the epoxide ring in **196** was regioselective and after acetylation gave cyclohexene **197** in good yield, Figure 3.32. Subsequent reduction of the double bond gave the *anti-syn-syn-anti* ACHC derivative **198**. The hydrogen was delivered on the same face as that occupied by the carbamate and opposite to the 3-acetoxy group.

Initial relative stereochemical assignments of **198** were based on the observed NOESY interactions as shown in Figure 3.33. The structure of **198** was subsequently confirmed by X-ray crystallographic analysis (see Appendix 4).

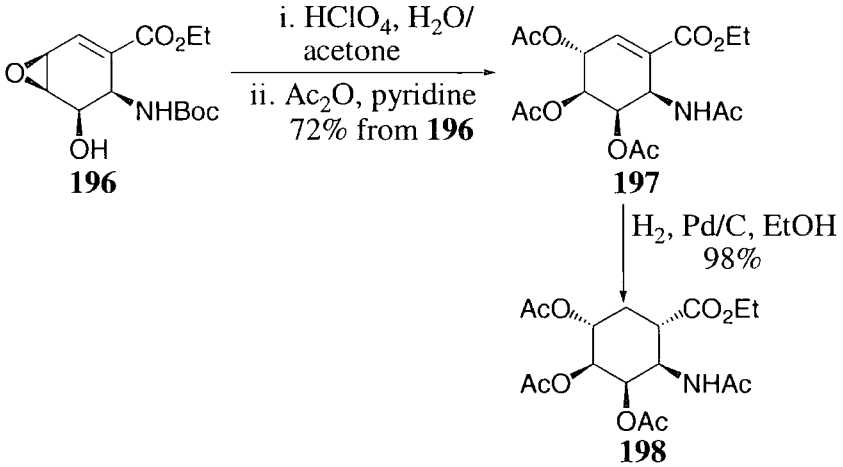


Figure 3.32: Synthesis of the *anti-syn-syn-anti* ACHC derivative **198**

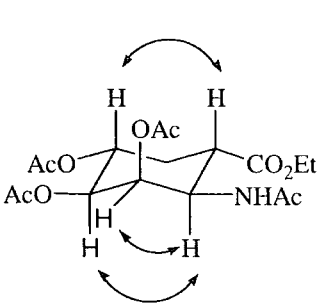


Figure 3.33: Selected NOESY interactions for **198**

In conclusion, epoxidation has proved to be an effective reaction in the synthesis of trihydroxyxlated β-amino acid derivatives **188**, **195** and **198** from the Diels-Alder adducts of (E)-3-nitroacrylate **1** and furan.

3.4 SUMMARY

The stereoselective syntheses of six 3,4,5-trihydroxyl derivatives of ACHC described in this chapter are distinguished by the use of substrate-stereocontrolled processes to secure stereochemical relationships around the cyclohexane rings. The enforced reliance of the syntheses on simple classic reactions at ambient conditions is another positive attribute of the strategy worth mentioning. The key reactions employed in the syntheses are Diels Alder reaction, OsO_4 mediated *cis*-dihydroxylation and epoxidation as a route to *trans*-dihydroxylation. Through these reactions, novel trihydroxylated ACHC derivatives were prepared and reported for the first time.[90] This strategy has potential for future application in the synthesis of aminocarbasugars and aminoshikimic acid derivatives.

3.5 REFERENCES

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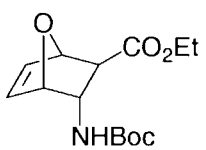
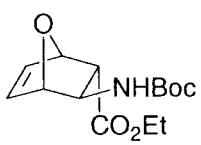
CHAPTER FOUR

FURTHER CHEMISTRY OF ADDUCTS 2 AND 158



2

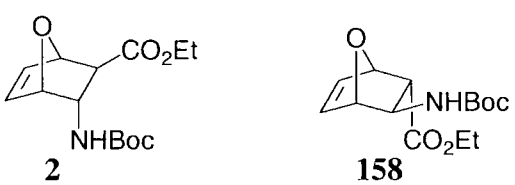


158

4.1 INTRODUCTION

The synthesis of trihydroxyl ACHC derivatives featuring the base mediated β-elimination of the oxygen bridges of oxanorbornene adducts **1** and **158** as one of the main reactions was discussed in Chapter 3. During these studies, interesting observations suggested that the oxanorbornene strategy possessed potential as a stereoselective approach to mono and dihydroxylated cyclohexyl β-amino acid derivatives. It was also realised that employing a transition metal-catalysed ring–opening reaction for the fragmentation of the oxabicyclic compounds would add structural diversity to our oxanorbornene route to cyclohexyl β-amino acid derivatives.

The results of the synthesis of mono and dihydroxylated β-amino acids will be discussed in the first section of this chapter. Subsequent sections will document results of the reaction of adduct **2** with catalytic amount of palladium complexes in the presence of zinc and organic acids.



2 **158**

Figure 4.1: Oxanorbornene adducts **2** and **158**

4.2 SYNTHESIS OF THE 3-HYDROXYL DERIVATIVES OF ACHC

4.2.1 INTRODUCTION

The β-elimination of the oxygen bridges of adducts **2** and **158** to give cyclohexadienes **3** and **159** respectively and subsequent reduction of the double bonds of these cyclohexadienes would furnish 3-hydroxyl ACHC derivatives of type **199** and **200**. The oxanorbornene adducts were derived from the reaction of ethyl (E)-3-nitroacrylate **1** and furan, Figure 4.2. On the basis of precedence delineated in Chapter 3, it was anticipated that substrate stereo-controlled processes would control the

reduction of the $\Delta^{1,2}$ double bond and therefore set the stereochemistry of C-1 in the ACHC derivatives **199** and **200**.

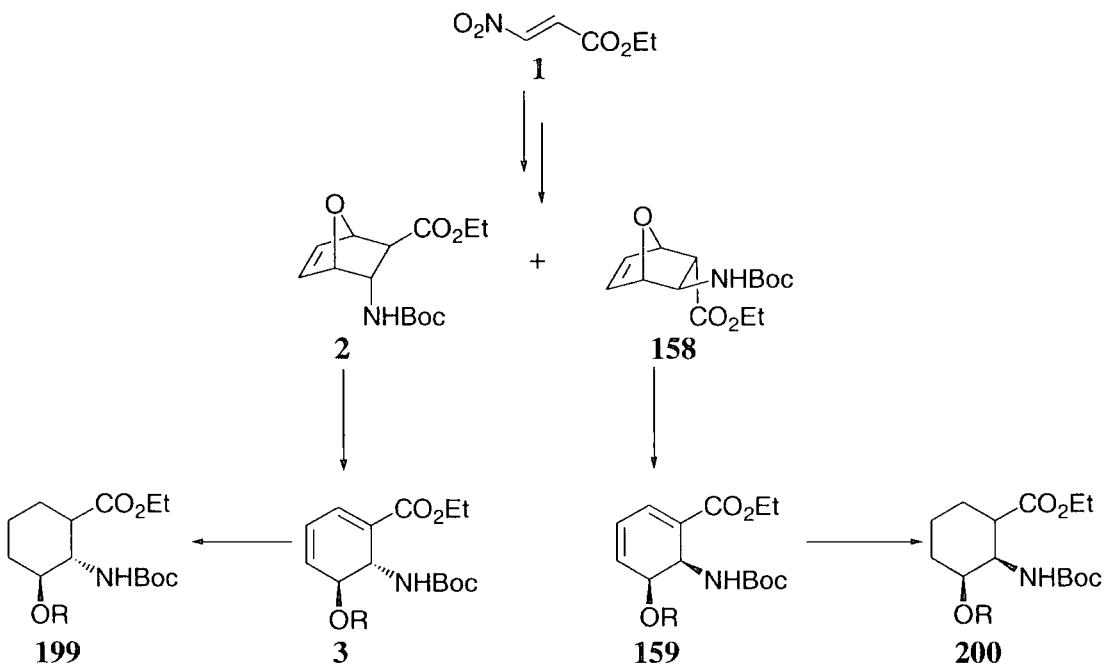


Figure 4.2: Plan for the synthesis of 3-hydroxyl ACHC derivatives **199** and **200**

4.2.2 SYNTHESIS OF THE *ANTI-ANTI* 3-ACETOXY ACHC DERIVATIVE 203

As discussed in Chapters 2 and 3, base mediated β-elimination of the oxygen bridge of adduct **2** to give cyclohexadiene **3** (R = H) was accompanied by variable amounts of ethyl-3-hydroxybenzoate. It seemed reasonable to infer that the reduction of the double bond of adduct **2** prior to β-elimination of the oxygen bridge would eliminate the by-product. In the event, treatment of a solution of adduct **2** in ethanol with Pd/C under a hydrogen atmosphere afforded **201** in 98% yield. Subsequent β-elimination of the oxygen bridge of **201** with KHMDS in THF and acetylation of the crude product gave substituted cyclohexene **202** in 68% over the two steps, Figure 4.3.

The ^{1}H HMR spectrum of **202** showed all the peaks consistent with the proposed structure including a singlet at δ 2.01 assigned to the acetyl group and the multiplet at δ 7.14 assigned to H-2. To complete the synthesis, the π bond of **202** was reduced

under the standard conditions to give the *anti-anti* ACHC derivative **203** in 97% yield. The relative stereochemistry was assigned on the basis of NOESY correlations, Figure 4.4.

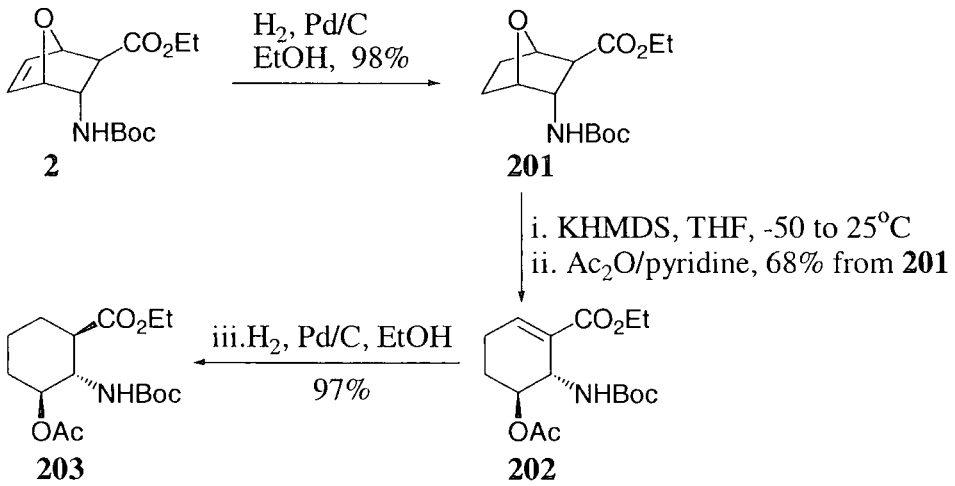


Figure 4.3: Synthesis of the *anti-anti* ACHC derivative **203**

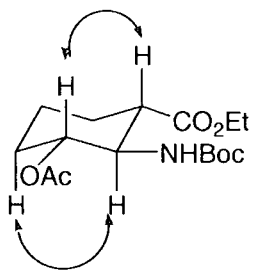


Figure 4.4: Selected NOESY interactions for **203**

The importance of cyclohexyl β-amino acid derivatives as building blocks for β-peptides was discussed in Chapter 3. ACHC derivative **203** was considered as the simplest member of the oxanorbornene derived ACHC derivatives. Model studies were therefore conducted on its suitability in peptide synthesis. As a prelude to involvement of **203** in the synthesis of peptides, the reactivity of its amine functionality with benzoic acid was investigated. First, **203** had to be converted to a form amenable to the crucial coupling step. To this end, a solution of **203** in CH_2Cl_2 was treated with TFA to give **204** in quantitative yield. Subsequently, a solution of **204** and benzoic acid in CH_2Cl_2 was treated with PyBop in the presence of triethylamine (TEA) to give **205** in 84 % yield. The structure of the coupled product was confirmed by elemental analysis, mass spectrometry and NMR spectroscopy.

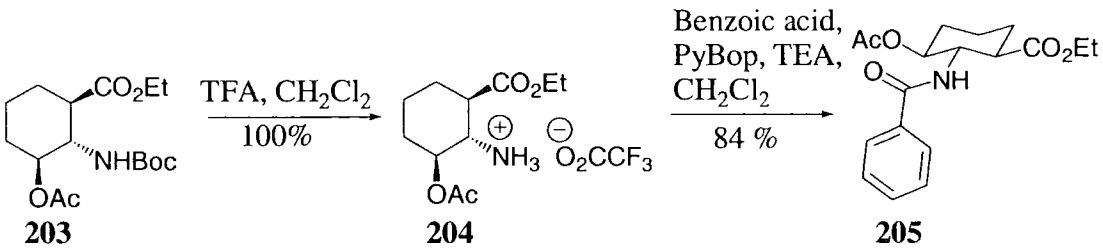


Figure 4.5: Synthesis of **205**

To study the reactivity of the acid group of **203** with amines, it was decided to take advantage of the chemistry already discussed in Chapter 1. Consequently, adduct **2** was subjected to the action of KHMDS to give a cyclohexadienyl intermediate which was hydrolysed to afford the acid **125**, Figure 4.6. Subsequent acetylation and reduction of the π bonds gave the *anti-anti*-3-acetoxy ACHC derivative **206** in 75% yield from **125**.

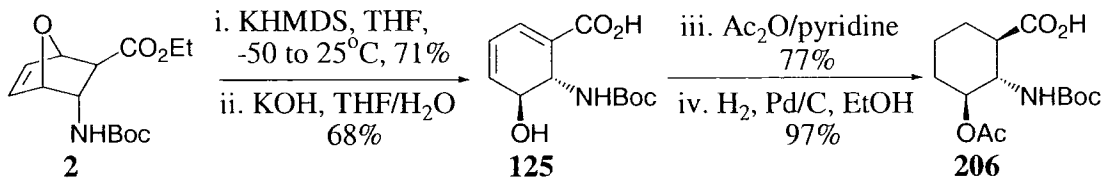
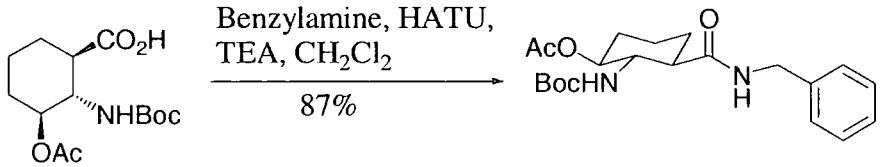


Figure 4.6: Synthesis of the *anti-anti* ACHC derivative **206**

With β-amino acid **206** in hand, attention was turned to its reaction with amines in the presence of coupling reagents. To this end, a solution of **206**, benzylamine and triethylamine (TEA) in CH_2Cl_2 was treated with PyBop to give the coupled product (detected by GC-MS), which proved impossible to purify. Fortunately, when the coupling reagent HATU was used instead of PyBop, the coupled product **207** was isolated as a white solid in 83% yield. The overall process involved initial *in situ* activation of the carboxylic group of **206** by HATU followed by subsequent reaction with benzyl amine to give the amide **207**, Figure 4.7. One characteristic of amide **207** worth mentioning is that it was found to be sparingly soluble in most organic solvents.

The ^{1}H NMR spectrum of **207** displayed all the features consistent with the coupled product including a multiplet at δ 2.45 assigned to the H-1 proton and two doublets at

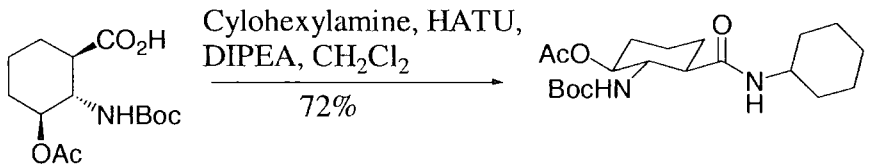
δ 4.25 and 4.47 with coupling constant J = 14.8 Hz assigned to the two *prochiral* benzylic protons.



206 **207**

Figure 4.7: Synthesis of the coupled product **207**

For a more relevant model study, acid **206** was coupled to cyclohexylamine in the presence of HATU under the conditions described above to give the coupled product **208** in 72 %. Surprisingly, **208** was found to be insoluble in most organic solvents and its NMR spectra were measured in DMSO.



206 **208**

Figure 4.8: Synthesis of couple product **208**

The processes described thus far have culminated in the synthesis of *anti-anti* ACHC derivative **203** and ascertained its suitability as a building block in peptide synthesis. The insolubility of amides **207** and **208** in most organic solvents was somewhat suprising.

4.2.3 SYNTHESIS OF THE *SYN-SYN* 3-ACETOXY ACHC DERIVATIVE 210

The synthesis of the *anti-anti* ACHC derivative **203** discussed in the preceding section employed the *endo* carbamate adduct **2** as the starting material. To increase the stereochemical diversity of our strategy, it seemed logical to involve the *exo* carbamate adduct **158** as a starting material. To this end, the oxanorbornene adduct **158** was opened as described in Chapter 2 and subsequent acetylation gave cyclohexadiene **209** in good yield, Figure 4.9. Catalytic hydrogenation of the double bonds was performed in the presence of catalytic amount of 10 % Pd/C under a

hydrogen atmosphere at room temperature to give the *syn-syn* ACHC derivative **210**. It was assumed that hydrogen added to the double bond from the least hindered side of the molecule. The *syn-syn* configuration was supported by NOESY correlations shown in Figure 4.10 and comparison with literature data of related structures.[30]

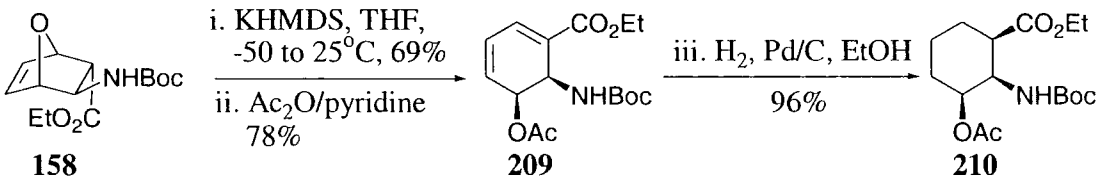


Figure 4.9: Synthesis of the syn-syn ACHC derivative **210**

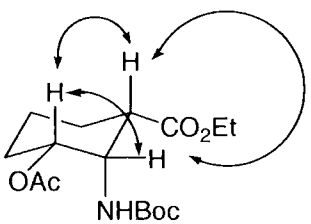


Figure 4.10: Selected NOESY correlations for **210**

4.3 SYNTHESIS OF THE 3,4-DIHYDROXYL ACHC DERIVATIVES

4.3.1 INTRODUCTION

Through a previously established synthetic pathway (Chapter 3), epoxides **183**, **184** and **196** could be selectively prepared in good yields using oxanorbornene adducts **2** and **158** as starting materials. Provided that a regioselective reductive ring opening could be achieved, these epoxides could serve as precursors to dihydroxyl ACHC derivatives. It was known from the work of Danishefsky and co-workers that treatment of vinylic epoxides with Pd/C under a hydrogen atmosphere led to homoallylic alcohols.[91] In the course of the synthesis of baccatin III and taxol, Danishefsky and co-workers showed that treatment of a solution of epoxide **211** in ethanol with Pd/C under a hydrogen atmosphere at low temperature selectively opened the epoxide ring without reducing the double bond to give **212** in excellent yield, Figure 4.12. The palladium catalysed epoxide opening reaction involves oxidative addition of hydrogen to palladium, coordination of the palladium to the double bond of the substrate and subsequent opening of the epoxide through

formation of the palladium π-allyl cation complex **214**. The product is then released from the palladium through β-hydrogen elimination, Figure 4.12.

On the basis of this precedent, it was decided to feature the reductive epoxide ring opening reaction as one of the strategies in the synthesis of 3,4-dihydroxyl ACHC derivatives using epoxides **183**, **184** and **196**. Alternative strategies included the use of the hydroxyl group of the cyclohexadiene systems to direct oxygenation of the $\Delta^{3,4}$ double bond and hydroboration of the oxanorbornene adducts prior to β-elimination of the oxygen bridge.

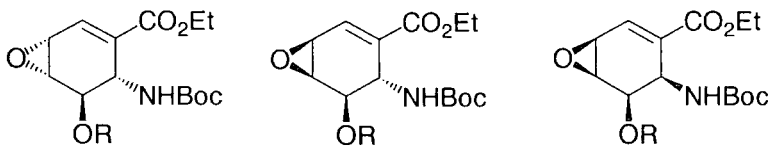


Figure 4.11: Epoxides **183**, **184** and **196**

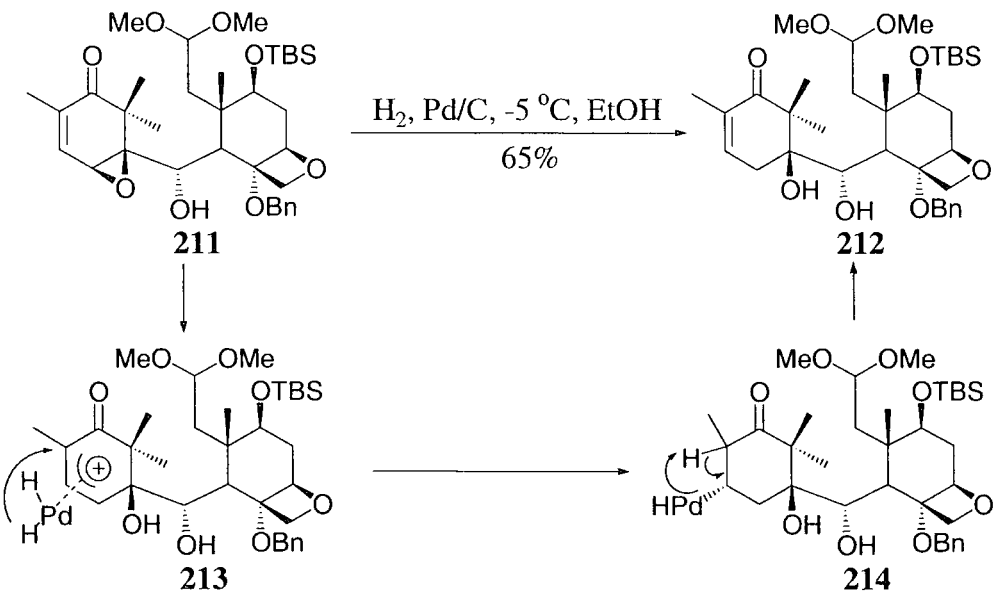
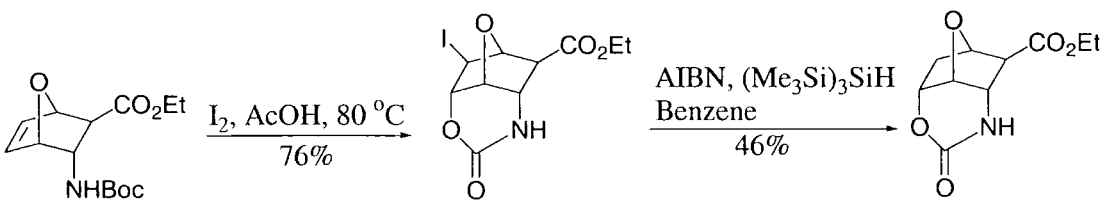


Figure 4.12: Danishefsky's opening of the epoxide ring of **211**

4.3.2 SYNTHESIS OF THE *ANTI-ANTI-ANTI* ACHC DERIVATIVE 217

Initial attempts towards the *anti-anti-anti* 3,4-dihydroxyl ACHC derivative involved setting the relative stereochemistry of the functionalities on the bicyclic adduct **2** prior

to the elimination of the oxygen bridge. To this end, a solution of adduct **2** in acetonitrile was treated with iodine to give the tricyclic iodocarbamate **215** in moderate yield. The yield was improved by performing the reaction in acetic acid. In this reaction, the iodine engages the double bond in adduct **2** from its less hindered convex face and elicits an intramolecular attack by the proximal carbamate. A radical abstraction of the iodine was then conducted with 2,2'-azobisisobutyronitrile (AIBN) as the radical initiator to give tricyclic carbamate **216** in 46% yield. *Tris*-(trimethylsilyl)silane served as the chain transfer reagent. With the *anti-anti-anti* stereochemistry around the six membered ring set, attention was turned towards hydrolysis of the cyclic carbamate and β-elimination of the oxygen bridge. As matters transpired, attempts to use **216** as an intermediate in the synthesis of the *anti-anti-anti* ACHC derivative were thwarted by the resistance of the cyclic carbamate to the action of sodium ethoxide. Attempts to eliminate the oxygen bridge of the tricyclic carbamate **216** were also futile, probably due to the extra rigidity conferred by the carbamate ring.



2 **215** **216**

Figure 4.13: Synthesis of tricyclic carbamate **216**

The disappointing results forced us to modify our synthetic strategy and consider epoxide **183** as an intermediate in the synthesis of the *anti-anti-anti* ACHC derivative. Epoxide **183** was prepared in good overall yield from oxanorbornene adduct **2** by β-elimination of the oxygen bridge, acetylation and *m*CPBA epoxidation, Figure 4.14. When a solution of epoxide **183** in ethanol was treated with 10 % Pd/C under a hydrogen atmosphere followed by acetylation, the *anti-anti-anti* 3,4-diacetoxy ACHC derivative **217** was isolated in 88 % yield over the two steps.

The structure of the ACHC derivative **217** was determined by IR, MS, ^{1}H and ^{13}C NMR. The stereochemical elucidation was based on the analysis of the ^{1}H NMR spectrum and NOESY interactions. The ^{1}H NMR spectrum exhibited a doublet at δ

4.88 with coupling constant J = 9.5 Hz assigned to H-3. The observation of the 9.5 Hz H_aH_b coupling constant in the ^1H NMR spectrum of **217** was consistent with *anti* diaxial relationships between H-3 and both H-2 and H-4 and this supports the indicated stereochemistry. The relative stereochemistry was supported by NOESY interactions shown in Figure 4.15.

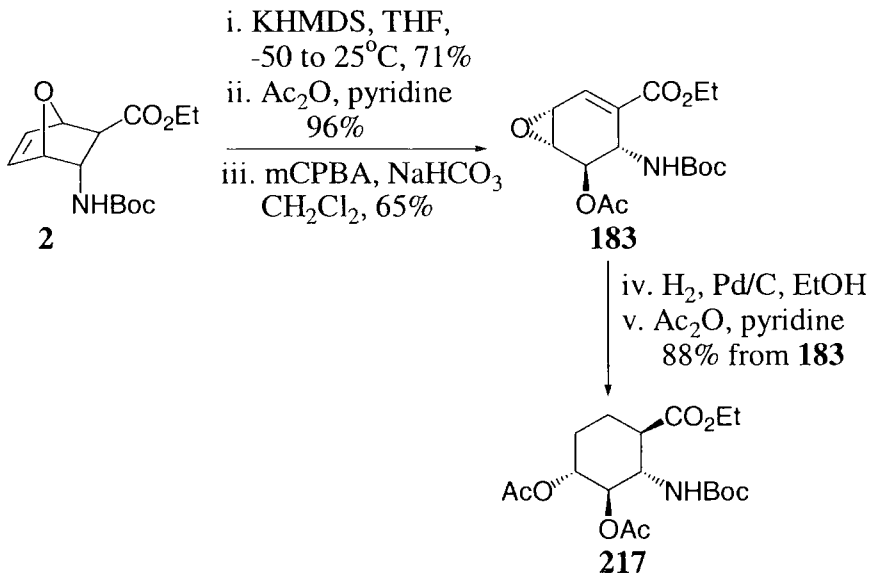


Figure 4.14: Synthesis of the *anti-anti-anti* ACHC derivative **217**

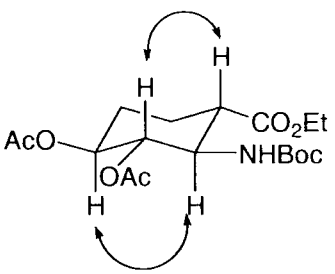


Figure 4.15: Selected NOESY interactions for **217**

4.3.3 SYNTHESIS OF THE *ANTI-ANTI-SYN* ACHC DERIVATIVE 218

With the favourable results on the synthesis of the *anti-anti-anti* ACHC derivative **217** in hand, we moved on to apply the epoxide route developed in the preparation of the *anti-anti-syn* ACHC **218** from epoxide **184**. The conditions for the procurement of epoxide **184** were delineated in Chapter 3. Consequently, treatment of a solution of the cyclohexadiene system derived from adduct **2** in acetonitrile with *m*CPBA and $NaHCO_3$ gave a 2:1 mixture of isomers favouring the desired *syn* epoxyalcohol **184**.

Subjection of epoxide **184** to the action of Pd/C under a hydrogen atmosphere followed by acetylation afforded the *trans-trans-syn* ACHC derivative **218** in good yield. It is worth noting that hydrogen added to the enoate double bond exclusively on the lower face of the molecule and it seemed reasonable to assume that the carbamate was involved in directing this process.

The ^{1}H NMR spectrum of **218** displayed all the features consistent with the proposed structure including the doublet of doublets at δ 4.86 with coupling constants J = 11.5 and 2.5 Hz assigned to H-3. The big coupling constant (J = 11.5 Hz) was indicative of an *anti* diaxial relationship between H-3 and H-2 while the smaller one (J = 2.5 Hz) was consistent with a *syn* equatorial-axial relationship between H-3 and H-4. The stereochemical relationships of **218** were also supported by the NOESY interactions shown in Figure 4.17.

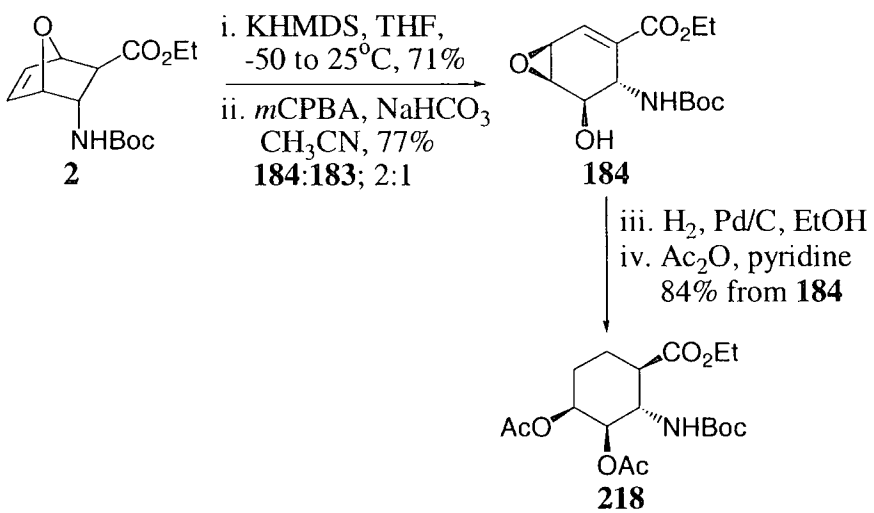


Figure 4.16: Synthesis of the *anti-anti-syn* ACHC derivative **218**

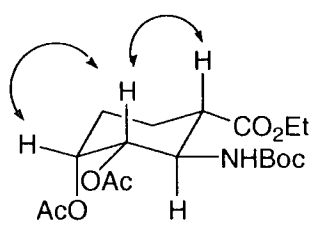


Figure 4.17: Selected NOESY interactions for **218**

An alternative route to the *anti-anti-syn* ACHC derivative **218** involved the subjection of oxanorbornene adduct **2** to the hydroboration/oxidation reaction. Hydroboration

was expected to occur on the *exo* face of adduct **2** but predicting the regiochemistry of the reaction was difficult. In the event, a solution of adduct **2** in THF with 9-BBN was stirred for 24 h and then 3 M NaOH and H_2O_2 were added to the reaction mixture to afford a 1:1 mixture of the two hydroxyl adducts **219** and **220** in 65 % yield, Figure 4.18. Unfortunately, these adducts proved impossible to separate. The lack of regioselectivity in the hydroboration reaction also made pursuing this strategy less attractive.

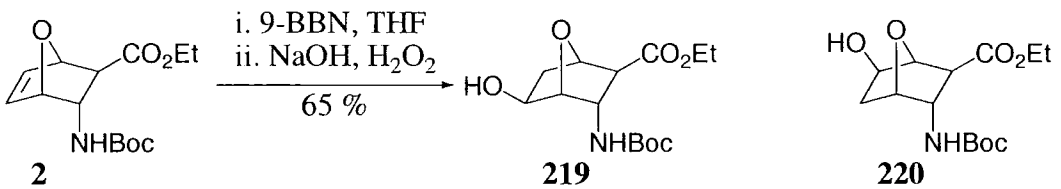


Figure 4.18: Hydroboration oxidation of **2**

Another alternative method considered for the *anti-anti-syn* ACHC derivative **218** was to use the allylic hydroxyl group to direct the substitution of the $\Delta^{3,4}$ double bond. It was thought that diethyl phosphate **221** or ethyl formate **222** might react with iodine in a manner similar to those observed for substrates studied by Bartlet and Jernstedt,[92] Figure 4.20. The reaction involves the addition of iodine to the double bond eliciting an intramolecular attack by the phosphoryl oxygen to furnish cyclic phosphate **225** which would be amenable to further transformation.

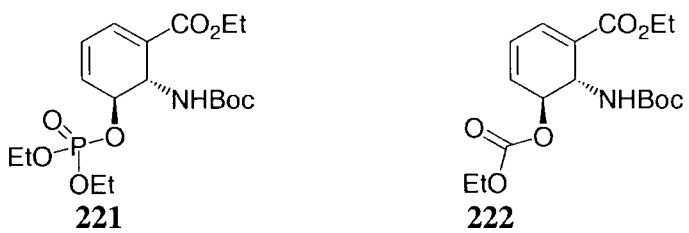


Figure 4.19: Phosphate **221** and ethylformate **222**

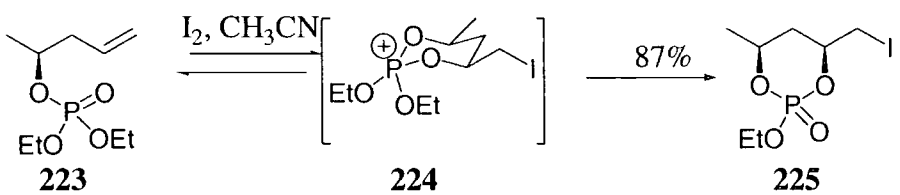
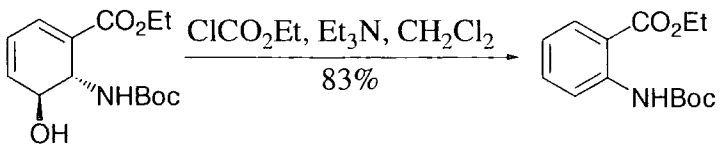


Figure 4.20: Bartlett's synthesis of **225**

However, attempts to append the diethyl phosphoryl group to the hydroxyl group of cyclohexadiene **3** in the presence of K_2CO_3 or triethylamine as the base were unsuccessful. Using chloroethylformate led to aromatisation in under 1 h and the completely protected anthranilic acid **144** was isolated in 83%. Attempts to perform the reaction at low temperatures also led to **144**.



3 **144**

Figure 4.21: Reaction of **3** with chloroethylformate

4.3.4 SYNTHESIS OF THE *SYN-SYN-SYN* ACHC DERIVATIVE 226

The synthesis of dihydroxyl ACHC derivatives discussed thus far employed *endo* carbamate **2** as the starting material and therefore gave the 2,3-*anti* geometry in the ACHC derivatives. The β-elimination of the oxygen bridge of the *exo* carbamate adduct **158** and subsequent elaboration into dihydroxyl ACHC derivatives would secure a 2,3-*syn* configuration. Through a previously established synthetic pathway (Chapter 3), epoxide **196** was prepared in three steps from adduct **158**, Figure 4.22. With epoxide **196** in hand, the palladium catalysed opening of the epoxy ring and subsequent reduction of the double bond proceeded smoothly and gave the *syn-syn-syn* ACHC derivative **226** as the only product. A stereochemical issue of great importance presented itself here. In the reduction of the enoate double bond, the addition of the hydrogen took place on the opposite side of the molecule to which the carbamate was located. This observation suggested that placing the 3-hydroxyl group on the same face as the carbamate completely reversed the directing ability of the latter.

Both the ^1H and ^{13}C spectra of **226** displayed all the features consistent with the proposed structure. The relative stereochemical relationships around the ring were based on the NOESY interactions shown in Figure 4.23.

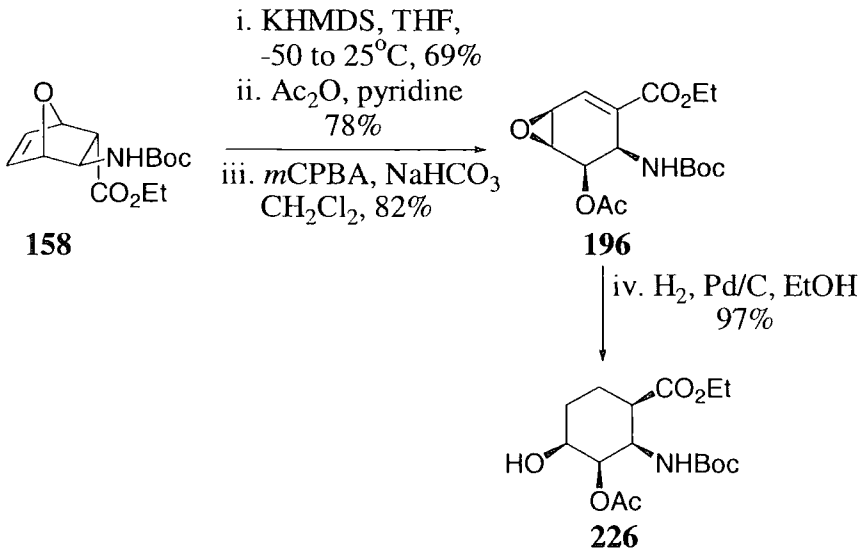


Figure 4.22: Synthesis of the syn-syn-syn ACHC derivative **226**

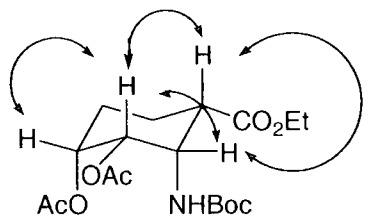


Figure 4.23: Selected NOESY interactions for **226**

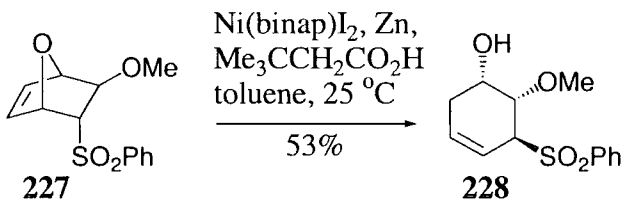
4.3.5 SUMMARY

The stereoselective syntheses described in the preceding sections revealed the power of oxanorbornene adducts derived from the Diels Alder reaction of ethyl (E)-3-nitroacrylate and furan in the preparation of oxygenated ACHC derivatives. The most interesting feature of the strategy is its reliance on basic reagents to carry out non-trivial structural transformations. Whilst the chemistry described above was conducted on a racemic series, it is pertinent to note that the oxanorbornene adduct **2** is amenable to an efficient enzyme mediated kinetic resolution and chiral HPLC resolution.[72]

4.4 REACTION OF ADDUCT 2 WITH CATALYTIC AMOUNT OF PALLADIUM IN THE PRESENCE OF ZINC AND ORGANIC ACIDS

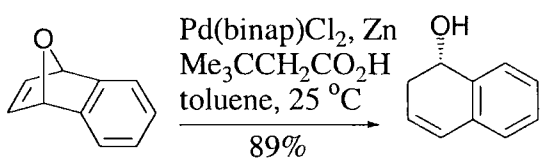
4.4.1 INTRODUCTION

The reductive ring opening of oxanorbornene systems catalysed by Ni (II) and Pd (II) complexes in the presence of organic acids and zinc powder was recently reported by Cheng and co-workers, Figures 4.24 and 4.25.[93] Prior to Cheng's report, Lautens reported a rhodium-catalysed ring opening reaction in the presence of an organic acid in which the carboxylate group added to the olefin as a nucleophile.[94-96] In Cheng's case, the carboxylic acid was the hydrogen source. The key steps for Cheng's reductive ring opening reaction are shown in Figure 4.26. The reaction is initiated by the reduction of Pd (II) to Pd (0) by the zinc powder. Oxidative addition of the organic acid to Pd (0) led to the generation of the Pd (II) hydride species.[97] Coordination of the double bond of adduct **229** to the Palladium and subsequent insertion of the double bond to the Pd-hydride bond led to the formation of intermediate **232**. β-Elimination of the oxygen bridge of adduct **232** followed by protonation afforded the product **230** and the Pd (II) species which was reduced to Pd (0) by the zinc.



227 **228**

Figure 4.24: Cheng's Ni (II) reductive ring opening of **227**



229 **230**

Figure 4.25: Cheng's Pd (II) reductive ring opening of **229**

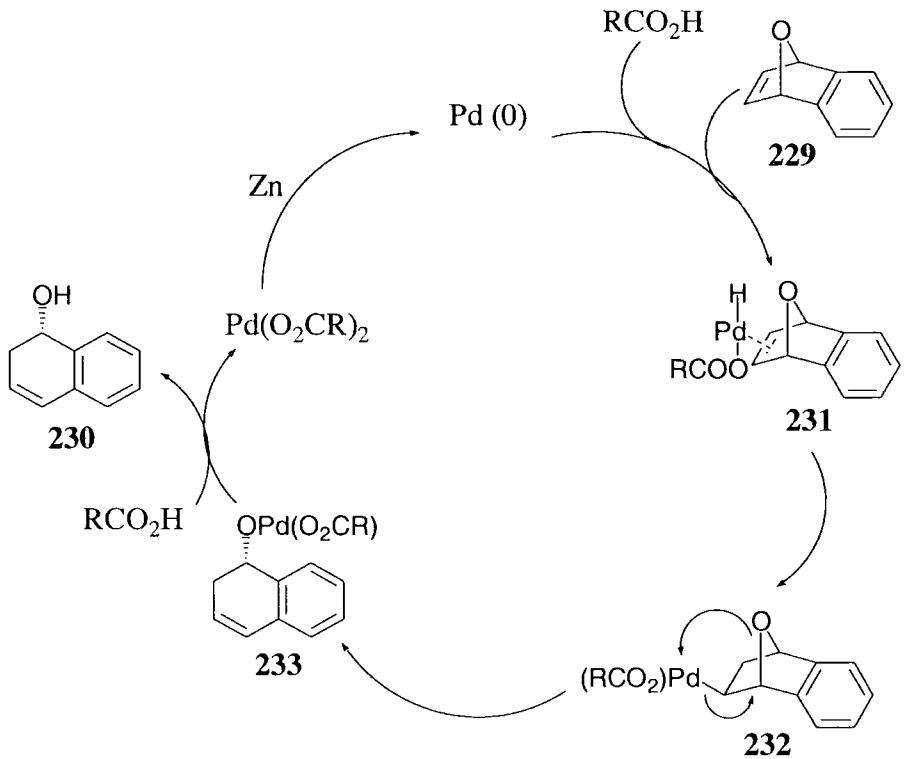
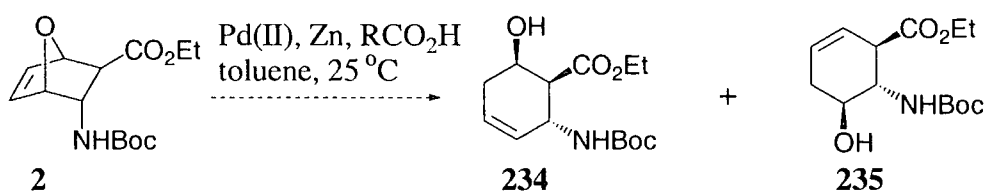


Figure 4.26: Catalytic cyclic for Cheng's Pd catalysed reductive ring opening of **229**

4.4.2 REACTION OF OXARBORNENE ADDUCT 1 WITH PALLADIUM

On the basis of the precedent discussed above, it was considered reasonable to apply the reductive ring opening conditions to the oxarnorbornene adduct **2** as an alternative to the base mediated fragmentation discussed in Chapters 2 and 3. The advantage of this approach over the base mediated fragmentation is that all the stereochemical relationships set by the Diels-Alder reaction would be preserved. In the event that the reductive ring opening reaction is successful, adduct **2** would furnish either cyclohexene **234** or **235** (Figure 4.27) which could then be elaborated to ACHC derivatives by functionalising the double bond.



2 **234** **235**

Figure 4.27: Potential cyclohexene systems from **2**

Initial attempts to reductively open **2** using $(Ph_3P)_2NiCl_2$ or $(CH_3CN)_2PdCl_2$ in toluene were unsuccessful. Suspecting that solubility was responsible for the failure of the reaction, it was decided to use a more polar solvent. When acetonitrile was used as the solvent, the nickel complex still showed no activity on the oxanorbornene adduct **2**. However, in the presence of benzoic acid, zinc metal and palladium chloride, the double bond of **2** was reduced when acetonitrile was used as the solvent and **201** was isolated in 94% yield, Figure 4.28. On the basis of the catalytic cycle for the Pd catalysed reductive ring opening reaction shown in Figure 4.26, the interesting reduction was not suprising. Instead of β-elimination of the oxygen bridge in intermediate **236**, protonation occurred and gave oxanornornane system **201**, Figure 4.28. Control experiments indicated that no reaction occurred in the absence of zinc powder, benzoic acid or palladium catalyst.

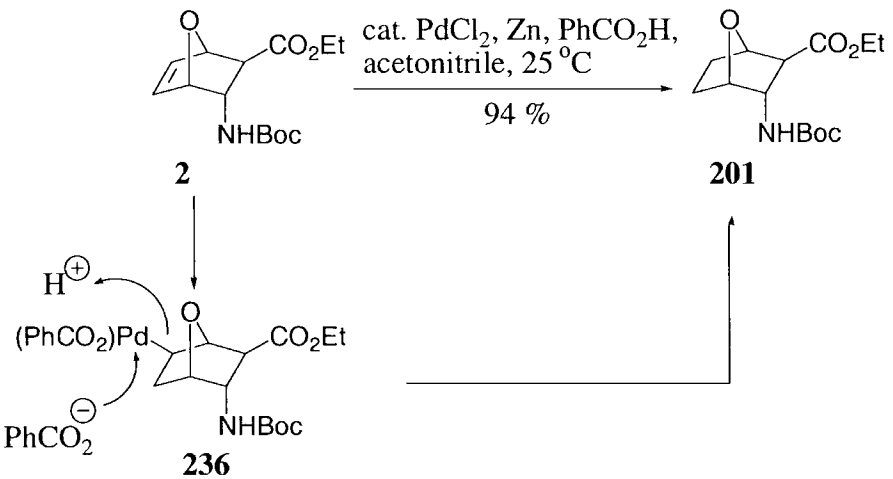
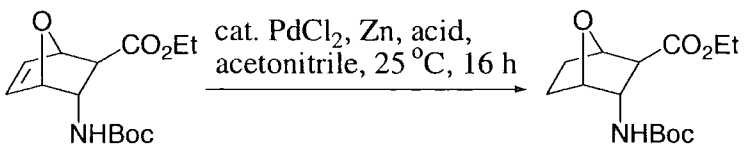


Figure 4.28: Transfer hydrogenation of **2**

On the basis of the results so far, it seemed $PdCl_2$ was an effective catalyst for transfer hydrogenation using benzoic acid as the hydride source and zinc as the reducing agent. To test if the hydride source had any effect on the reaction, several organic acids were tested in the transfer hydrogenation protocol and all afforded adduct **201** in excellent yields, Figure 4.29. The type of the organic acid did not affect the yield or the duration of the reaction. No reaction was observed when the reaction was performed in the presence of either methanol, benzyl alcohol or phenol. Alcohols were therefore not appropriate hydride sources for the $PdCl_2$ catalysed transfer hydrogenation protocol.



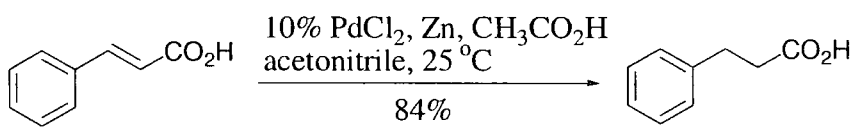
2 **201**

Entry	Organic acid	yield
1	HCO_2H	96
2	CH_3CO_2H	94
3	$CH_3CO_2NH_4$	97
4	$PhCO_2H$	93

Figure 4.29: Effect of various acids on the yields of the transfer hydrogenation of **2**

The palladium catalysed transfer hydrogenation can be extended to other substrates. To this end, cinnamic acid **237** was successively reduced to 3-phenylpropanoic acid **238** in 84 % yield using CH_3CO_2H as the hydride source, Figure 4.30. It is instructive to note that cinnamic acid was not reduced in the absence of another organic acid. Cinnamic acid could not therefore act as a hydride source to reduce itself under these reaction conditions.

The ^1H NMR spectrum of **238** showed the characteristic triplets at δ 2.61 and 2.89 with coupling constant J = 8.4 Hz assigned to H-3 and H-2 protons respectively. MS and IR data were also consistent with the proposed structure.

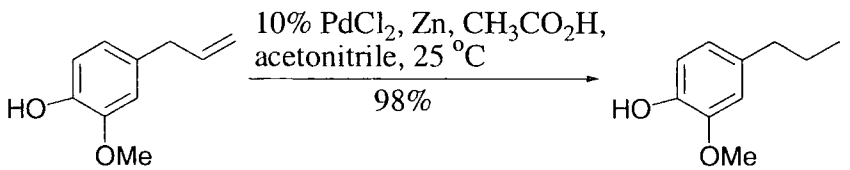


237 **238**

Figure 4.30: Reduction of cinnamic acid **237**

In a similar way to cinnamic acid, eugenol **239** was reduced to give **240** in 98% yield, Figure 4.31. The discrepancy in yields of the reduction of cinnamic acid and eugenol can be attributed to the different purification steps. While hydroeugenol **240** was purified by washing with 2 M HCl, flash chromatography was necessary for the purification of **238**.

The ^{1}H NMR spectrum of **240** displayed all the features consistent with the proposed structure including a triplet at δ 0.95 with coupling constant J = 7.6 Hz assigned to H-3', a multiplet at δ 1.63 assigned to H-2' and another triplet at δ 2.53 with coupling constant J = 7.6 Hz assigned to H-1'.

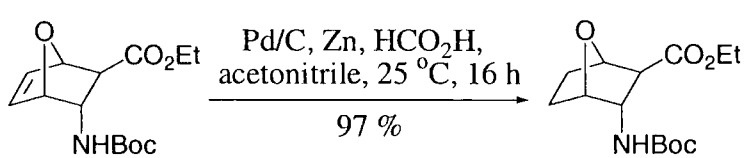


239 **240**

Figure 4.31: Reduction of eugenol **239**

The results discussed above suggested that the transfer hydrogenation protocol can be used for substrates with electron deficient double bonds comparable to cinnamic acid and terminal un-activated double bonds exemplified by eugenol. It is also reasonable to conclude that aromatic systems are inert to the transfer hydrogenation conditions.

It was conceivable that Pd/C could be used as the catalyst instead of the more expensive palladium chloride. Treatment of a solution of adduct **2** with a catalytic amount of Pd/C, zinc powder and formic acid afforded adduct **201** in 97% yield. Control reactions indicated that no reaction occurred in the absence of the Pd/C catalyst or formic acid. However, when the reaction was performed using a quantitative amount of Pd/C, the reduction preceded smoothly in the absence of zinc powder. Interestingly, when either benzoic acid or acetic acid was used as the hydride source in the Pd/C catalysed transfer hydrogenation, no reaction was observed.



2 **201**

Figure 4.32: Pd/C catalysed transfer hydrogenation in the presence of formic acid

4.4.3 SUMMARY

On the basis of the processes described in the above section, $PdCl_2$ has proved to be an effective catalyst for transfer hydrogenation with organic acids as hydride sources and zinc as the reducing agent. Pd/C is only effective as a transfer hydrogenation catalyst when formic acid is used as the hydride source. The reaction conditions discussed above should be suitable for the reduction of a wide variety of organic substrates. The procedure also offers an economical, safe and convenient alternative to available procedures. Future work in this area will include using chiral ligands to test the asymmetric version of the catalytic reaction.

4.5 REFERENCES

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CHAPTER 5
EXPERIMENTAL PROCEDURES

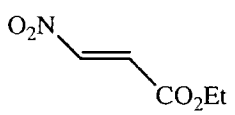
5.1 GENERAL EXPERIMENTAL CONDITIONS

All reactions were carried out in clean oven-dried glassware (110°C) under a Nitrogen or Argon atmosphere. Solvents were purified and dried by standard methods prior to use. Cited reaction temperatures refer to the external bath temperatures. The phrase 'removed under reduced pressure' refers to solvent removal with a Büchi rotary-evaporator using a laboratory vacuum pump and a bath temperature of 30°C.

IR spectra were scanned on a Perkin Elmer 1720X FT Infra-red spectrophotometer. Melting points were measured using a Gallenkamp melting point apparatus and are uncorrected. All reactions were followed by TLC on 60 F_{254} silica gel sheets with visualization effected by UV illumination and/or $KMnO_4$ solution followed by heating or iodine vapour. Silica gel 60, 40-63u was used for flash chromatography.

All Nuclear Magnetic Resonance spectra (^1H and ^{13}C) were recorded on Varian Oxford (300 MHz or 400 MHz or 500 MHz) spectrometers. Chemical shifts are reported in ppm (δ) relative to tetramethylsilane. ^1H NMR data are reported as follows: chemical shift (number of protons, multiplicity, coupling constant, proton identity) and ^{13}C as: chemical shift (carbon identity). The ^1H NMR spectra were fully assigned by the use of COSY experiments while those for ^{13}C were assigned by HETCOR experiments. NOESY was employed to determine the relative stereochemistry where applicable.

5.2 EXPERIMENTAL PROCEDUCES

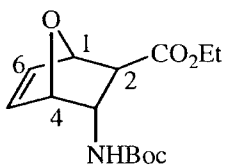


1

Ethyl (*E*)-3-nitropropenoate 1:

A solution of DIPEA (5.8 g, 45mmol) in diethyl ether (10 cm^3) was added dropwise to a vigorously stirred and cooled (0 °C) solution of compound **129** (10.0 g, 37 mmol) in diethyl ether (200 cm^3) and the mixture was stirred for 15 minutes. The resulting suspension was filtered through a plug of silica. The silica was flushed with 10 % diethyl ether in petroleum ether and the solvent was removed under reduced pressure

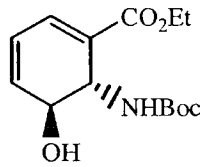
to give an orange solid. The orange solid was passed through a short column of silica gel using petroleum ether/diethyl ether (9:1) as the eluent to afford title compound **1** (4.00 g, 73 %) as a yellow solid; m.p 36-38 °C. ν_{max} (KBr disk): 3415, 1736, 1638, 1542 cm^{-1}; δ_H (200 MHz, $CDCl_3$): 1.35 (3H, *t*, J = 7.0 Hz, $OCH_2\underline{C}H_3$), 4.32 (2H, *q*, J = 7.0 Hz, $OC\underline{H}_2CH_3$), 7.09 (1H, *d*, J = 13.6 Hz, H-2), 7.68 (1H, *d*, J = 13.6, H-3). δ_C (75 MHz, $CDCl_3$): 13.9 ($OCH_2\underline{C}H_3$), 62.4 ($O\underline{C}H_2CH_3$), 127.6 (C-2), 148.9 (C-3), 162.6 (C-1); MS (EI): *m/z* 145 (M^+), 100 (100%).



2

Ethyl *endo*-3-*tert*-butoxycarbonylamino-7-oxabicyclo[2,2,1]hept-5-ene-*exo*-2-carboxylate 2:

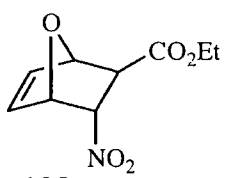
Concentrated HCl (28 cm^3) was added to a solution of Diels-Alder adduct **123** (3.5 g, 18 mmol) in EtOH (200 cm^3) at room temperature and this was followed by portionwise addition of zinc powder (26.6 g, 407 mmol). The mixture was stirred at room temperature for 12 hours and then filtered. The filtrate was treated with $^iPr_2Net$ (36.4 g, 282 mmol) and di-*tert*-butyldicarbonate (7.0 g, 32mmol). The mixture was stirred at 25 °C for 20 hours. The solvent was removed at reduced pressure to about 10 cm^3. The reduced solution was partitioned between ethyl acetate (50 cm^3), sat. $NaHCO_3$ (30 cm^3) and water (30 cm^3). The organic layer was separated, dried ($MgSO_4$) and removal of the solvent under reduced pressure gave a white solid which was purified by flash chromatography using petroleum ether/Et_2O (7:3) as the eluent to give the title compound **2** (406 mg, 89%) as a white solid, mp 88-90°C; υ_{max} (KBr disk): 3353, 2982, 1737,1700 cm^{-1}; δ_H (500 MHz, $CDCl_3$): 1.27 (3H, *t*, J = 7.2 Hz, $OCH_2\underline{C}H_3$), 1.30 (9H, *s*, $OC(CH_3)_3$), 2.05 (1H, *d*, J = 3.0 Hz, H-2), 4.20 (2H, *q*, J = 7.2 Hz, $OC\underline{H}_2CH_3$), 4.32 (1H, br, NH), 4.52 (1H, br, H-3), 5.08 (1H, br, H-4), 5.11 (1H, *s*, H-1), 6.46 (1H, *d*, J = 5.7 Hz, H-5), 6.59 (1H, *d*, J = 5.7 Hz, H-6); δ_C (125 MHz, $CDCl_3$): 14.5 ($OCH_2\underline{C}H_3$), 28.7 ($OC(\underline{C}H_3)_3$), 52.6 (C-2), 53.6 (C-3), 61.6 ($O\underline{C}H_2CH_3$), 75.0 (C-4), 79.3 ($O\underline{C}(CH_3)_3$), 82.4 (C-1), 134.7 (C-5), 138.0 (C-6), 157.4 (NCO_2), 172 ($\underline{C}O_2C_2H_5$); *m/z* (EI): 283 (M^+), 57 (100%).



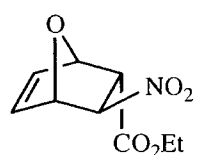
3

Ethyl *trans*-6-tert-butoxycarbonylamino-5-hydroxy-1,3-cyclohexadiene-1 -carboxylate 3:

To a solution of KHMDS (530 mg, 2.64 mmol) in THF (10 cm^3) at –50 °C was added a solution of adduct **2** (250 mg, 0.88 mmol) in THF (2.5 cm^3). The solution was then warmed up to room temperature (20 minutes) and quenched with a mixture of ethyl acetate and ethanol (50 cm^3, 19:1). The mixture was washed with sat. NH_4Cl (25 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure. The resulting residue was purified by flash chromatography eluting with petroleum ether/ethyl acetate mixture (3:2) to give cyclohexadiene **3** (359 mg, 72%) as a pale yellow gum. ν_{max} (KBr disk): 2979, 2931, 1716, 1700 1584 cm^{-1}; δ_H (500 MHz, $CDCl_3$): 1.28 (3H, *t*, J = 7.0 Hz, $OCH_2\underline{CH_3}$), 1.42 (9H, *s*, $OC(CH_3)_3$), 4.20 (2H, *q*, J = 7.0 Hz, $O\underline{CH_2}CH_3$), 4.36 (1H, *s*, H-5), 4.48 (1H, br, NH), 4.76(1H, *m*, H-6), 6.26 (2H, *m*, H-3 and 4), 7.17 (1H, *d*, J = 4.8 Hz, H-2); δ_C (125 MHz, $CDCl_3$): 14.1 ($OCH_2\underline{C}H_3$), 28.3 ($OC(CH_3)_3$), 50.0 (C-6), 60.8 (OCH_2CH_3), 67.7(C-5), 80.0 ($OC(CH_3)_3$), 124.5 (C-3), 132.6 (C-2), 133.5 (C-4), 155.4 (NCO_2), 165.9 ($CO_2C_2H_5$); MS m/z (CI): 284 (M^+ + 1); Anal. calcd. For $C_{14}H_{21}NO_5$: C, 59.35; H, 7.47; N, 4.94. Found: C, 59.20; H, 7.53; N, 4.80. The major by-product of the reaction was ethyl 2-hydroxybenzoate identified by comparison with authentic sample.



123



124

Diels-Alder Reaction:

Furan (5.4 cm^3, 74mmol) was added to a solution of α,β-unsaturated ester **1** (5.38g, 37mmol) in chloroform (20 cm^3) at –20°C. The reaction was stirred at -20°C for five days. Removal of the solvent under reduced pressure afforded a mixture of the *endo*-nitro isomer and the *exo*-nitro isomer (4:1) as a yellow oil. The oil was subjected to flash column chromatography using petroleum ether/diethyl ether (7:3) as the eluting

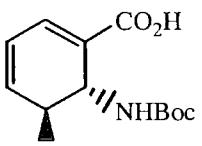
solvent to afford the *Endo*-nitro adduct **123** as a white solid (68%) and *Exo*-nitro isomer **124** as yellow oil (17%).

Ethyl *endo*-3-nitro-7-oxa-bicyclo[2,2,1] hepta-5-ene-*exo*-2-carboxylate 123:

mp 54-56°C; υ_{max} (KBr disk): 2982, 1722, 1587 cm^{-1}; δ_H (300 MHz, $CDCl_3$): 1.32 (3H, t, J = 7.2 Hz, $OCH_2C\underline{H}_3$), 3.23 (1H, d, J = 3.0 Hz, H-2), 4.27 (2H, q, J = 7.2, $OC\underline{H}_2CH_3$), 5.34 (1H, s, H-1), 5.48 (1H, d, J = 5.0 Hz, H-3), 5.54 (1H, dd, J = 5.0 and 4.0 Hz, H-4), 6.39 (1H, dd, J = 5.8 and 1.6 Hz, H-5), 6.73 (1H, dd, J = 5.8 and 1.6 Hz, H-6). δ_C (75 MHz, $CDCl_3$): 14.4 ($OCH_2\underline{C}H_3$), 49.2 (C-2), 62.4 ($O\underline{C}H_2CH_3$), 79.3 (C-4), 83.5 (C-1), 84.5 (C-3), 133.9 and 139.1 (C-5 and C-6), 169.9 ($\underline{C}O_2C_2H_5$).

Ethyl *exo*-3-nitro-7-oxa-bicyclo[2,2,1] hepta-5-ene-*endo*-2-carboxylate 124:

υ_{max} (Liq. Film): 2990, 1733, 1549 cm^{-1}; δ_H (300 MHz, $CDCl_3$): 1.28 (3H, t, J = 7.2 Hz, $OCH_2C\underline{H}_3$), 3.94 (1H, t, J = 3.8 and 2.8 Hz, H-2), 4.16 (2H, J = 7.2 Hz, $OC\underline{H}_2CH_3$), 4.82 (1H, d, J = 2.8 Hz, H-1), 5.32 (1H, d, J = 3.8 Hz, H-3), 5.50 (1H, bs, H-4), 6.54 (2H, m, H-5 and H-6). δ_C (75 MHz, $CDCl_3$): 14.3 ($OCH_2\underline{C}H_3$), 49.9 (C-2), 61.9 ($O\underline{C}H_2CH_3$), 79.3 (C-4), 84.2 (C-1), 134.5 (C-6), 138.5 (C-5), 168.9 ($\underline{C}O_2C_2H_5$);

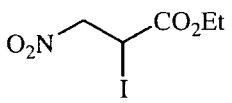


125

***Trans*-6-*tert*-Butoxycarbonylamino-5-hydroxycyclohexa-1,3-diene-1-carboxylic acid 125**:

To a solution of ester **3** (300 mg, 1.06 mmol) in THF (10 cm^3) was added KOH (595 mg, 10.60 mmol) in H_2O (2 cm^3). The mixture was stirred at 40°C for six hours, then diluted with water (20 cm^3) and extracted with ethyl acetate (20 cm^3). The aqueous solution was adjusted to pH 1 with 5M HCl and further extracted with ethyl acetate (3 x 30 cm^3). The organic layers were mixed, dried ($MgSO_4$) and concentrated under reduced pressure to give **125** as a white powder (200 mg, 74%); m.p. 165-167°C; ν_{max} (KBr disk); 3361 (*br*), 2922, 1689, 1650 cm^{-1}; δ_H (500 MHz, (CD_3OD): 1.47 (9H, *s*, ($OC(CH_3)_3$), 4.19 (1H, *d*, J = 3.5 Hz, H-5), 4.75 (1H, *d*, J = 6.5 Hz, H-6), 5.72 (1H, *d*, J = 6.5 Hz, NH), 6.28 (2H, *m*, H-3 and 4), 7.15 (1H, *d*, J = 5.0 Hz, H-2). δ_C (125 MHz, CD_3OD): 28.4 ($OC(\underline{C}H_3)_3$), 50.2 (C-6), 67.7 (C-5), 78.8 ($O\underline{C}(CH_3)_3$), 124.9 (C-

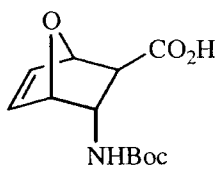
3), 128.0 (C-1), 134.5 (C-4), 156 (NCO_2), 167.4 (CO_2H); MS *m/z* (CI): 256 (MH^+), 217 (100%).



129

Ethyl 2-iodo-3-nitropropaniate 129:

N_2O_4 (9.5 cm^3, 271 mmol) was added to a stirred and cooled (0°C) mixture of ethyl acrylate **128** (44.5 cm^3, 410 mmol) and iodine (31 g, 122 mmol) in diethyl ether (400 cm^3). The reaction mixture was stirred for 1 hour at 0°C and then at room temperature for 4 hours. The resulting dark solution was washed with saturated $Na_2S_2O_3$ solution (5 x 200 cm^3). The aqueous layer was extracted with diethyl ether (200 cm^3) and the organic layers were combined and dried over magnesium sulphate. The solvent was removed under reduced pressure and excess ethyl acrylate was distilled off under *vacuo* at room temperature to give the title compound **129** (31.1 g, 93 %) as a yellow oil; υ_{max} (Liq. film): 2984, 1731, 1560 cm^{-1}; δ_H (250 MHz, $CDCl_3$): 1.31 (3H, *t*, J = 7.0 Hz, $OCH_2\underline{CH_3}$), 4.27 (2H, *m*, $OC\underline{H_2}CH_3$), 4.67 (1H, *dd*, J = 14.8 and 4.3 Hz, H-3), 4.88 (1H, *dd*, J = 10.8 and 4.3 Hz H-3), 5.09 (1H, *dd*, J = 15.0 and 11.0 Hz, H-2); δ_C (50 MHz, $CDCl_3$): 8.5 (C-2), 14.1 ($OCH_2\underline{C}H_3$), 63.4 ($O\underline{C}H_2CH_3$), 77.4 (C-3), 169.6 (C-1); MS (EI): *m/z* 273 (M^+), 227 (100%).

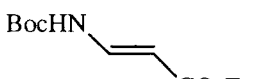


130

***Endo*-3-*tert*-butoxycarbonylamino-7-oxabicyclo[2,2,1]hepta-5-ene-*exo*-2-carboxylic acid 130**;

To a solution of racemic **2** (500 mg, 1.77 mmol) in diethyl ether (2.0 cm^3) was added pH 8 phosphate buffer (50 cm^3). Porcine Liver Esterase (100 mg) was then added and the mixture was stirred at room temperature for 5 days. Ethyl acetate (30 cm^3) was then added to the reaction mixture and the layers were separated. The aqueous layer was further extracted with ethyl acetate (2 x 20 cm^3) and the organic layers were mixed, dried ($MgSO_4$) and concentrated under reduced pressure. The residue was subjected to flash chromatography eluting with petroleum ether/ ethyl acetate (1:1) to

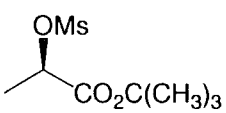
give the ester (+)-**2**, $[\alpha]_D^{22}$ +136 (245 mg, 49%) and acid **130** (218 mg, 48 mg); m.p. 136-138°C; $[\alpha]_D^{22}$ –58 (c,1; $CHCl_3$); ν_{max} (KBr disk): 3210 (br), 1712, 1526 cm^{-1}; δ_H (500 MHz, $CDCl_3$): 1.44 (9H, s, $OC(CH_3)_3$), 2.23 (1H, *d*, J = 3.2 Hz, H-2), 4.28 (1H, *d*, J = 4.8 Hz, H-3), 4.61 (1H, br, NH), 5.05 (1H, *d*, J = 2.9 Hz, H-4), 5.39 (1H, *s*, H-1), 6.47 (1H, *d*, J = 4.5 Hz, H-5), 6.67 (1H, *d*, J = 4.5 Hz, H-6), 7.94 (1H, br, CO_2H); δ_C (125 MHz, $CDCl_3$): 28.3 ($OC(\underline{C}H_3)_3$), 53.6 (C-2), 54.1 (C-3), 78.6 (C-4), 79.2 ($O\underline{C}(CH_3)_3$), 82.0 (C-1), 133.4 (C-5), 139.1 (C-6), 157.4 (NCO_2), 173.9 (CO_2H); *m/z* (ES^+): 256 (MH^+, 100%), 278 (MNa^+), 34%); Anal. cald for $C_{12}H_{17}NO_5$: C, 56.46; H, 6.71; N, 5.49. Found: C, 56.50; H, 6.74; N, 5.43.



131

Ethyl (E)-3-*tert*-butoxycarbonylaminoacrylate 131:

Racemic oxanorbornene adduct **2** was subjected to Prep. HPLC, column 2" x 20 cm chiralpak AD eluting with Hexane/ethanol (85:15) to give **(+)-2**; $[\alpha]_D^{20.8}$ +143, **(-)-2**; $[\alpha]_D^{20.8}$ –140 and Light yellow solid **131** as a by-product; m.p. 92-94°C; ν_{max} (KBr disk): 3298, 2979, 1750, 1691, 1636, 1516 cm^{-1}; δ_H (500 MHz, $CDCl_3$): 1.25 (3H, *t*, J = 7.20 Hz, $OCH_2C\underline{H}_3$), 1.47 (9H, *s*, $OC(CH_3)_3$), 4.15 (2H, *q*, J = 7.20 Hz, $OC\underline{H}_2CH_3$), 5.30 (1H, *d*, J = 13.8 Hz, H-2), 7.12 (1H, br, NH), 7.78 (1H, *dd*, J = 13.8 and 12.9 Hz, H-3); δ_C (125 MHz, $CDCl_3$): 14.6 ($OCH_2\underline{C}H_3$), 28.5 ($OC(\underline{C}H_3)_3$), 60.2 ($O\underline{C}H_2CH_3$), 82.5 ($O\underline{C}(CH_3)_3$), 99.0 (C-2), 140.1 (C-3), 152.0 (NCO_2), 167.8 (CO_2); MS *m/z* (CI): 233 ($MNH4^+$, 88%), 216 (MH^+, 100%); Anal. calcd. For $C_{10}H_{17}NO_7$: C, 55.80; H, 7.96; N, 6.51. Found: C, 56.27; H, 8.11; N, 6.14.

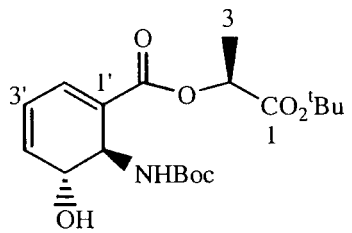


137

***t*-Butyl (2R)-(+)-2-methanesulphonyloxypropionate 137**:

To a solution of *t*-butyl lactate **136** (400 mg, 2.74 mmol) in CH_2Cl_2 (10 cm^3) was added triethylamine (496 µl, 3.56 mmol). This solution was cooled (0 °C) and to it was added MsCl (233 µl). The mixture was stirred at 0°C for 45 minutes and then partitioned between CH_2Cl_2 (20 cm^3) and 1 M HCl (10 cm^3). The aqueous layer was washed with CH_2Cl_2 (2 x 5 cm^3). The organic extracts were combined, dried ($MgSO_4$)

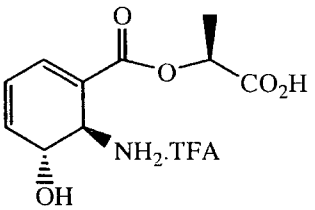
and concentrated under reduced pressure to give mesylate **137** as a white solid (770 mg, 99%); mp 41-42°C; $[\alpha]_D^{20.5}$ +49 (c; 1.02 in $CHCl_3$); ν_{max} (KBr disk): 2984, 1742, 1459,1360 cm^{-1}; δ_H (500 MHz, $CDCl_3$): 1.49 (9H, *s* $OC(CH_3)_3$), 1.57 (3H, *d*, J = 6.9, H-3), 3.14 (3H, *s*, SCH_3), 5.00 (1H, *q*, J = 6.9 Hz, H-2); δ_C (125 MHz, $CDCl_3$); 18.8 (C-2), 28.2 ($OC(\underline{C}H_3)_3$), 39.4 (SCH_3), 75.0 (C-2), 83.6 ($O\underline{C}(CH_3)_3$), 168.7 (CO_2); MS m/z (CI (NH_3)): 242 (MH+, 100%), 186 (25%), 102 (22%); Anal. cald. For $C_8H_{16}O_5S$: C, 42.84; H, 7.19. Found: C, 42.87; H, 7.23.



138

***Tert*-Butyl (-)-2-[*trans*-6'-*tert*-butoxycarbonylamino-5'-hydroxycyclohexa-1',3'-diene-1'-carboxyloxy]propionate 138**:

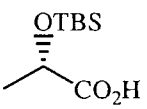
CsF (240 mg, 1.57 mmol) was dried under vacuum at 150°C for 5 hours. A suspension of the dried CsF in DMF (5 cm^3) was stirred at 25 °C for 30 minutes. To this suspension was added acid **(-)-125** (200 mg, 0.78 mg) and the mixture was stirred at 25°C for 30 minutes. Mesylate **137** was then added and the reaction mixture was stirred at 50°C. After 24 hours the reaction mixture was partitioned between ethyl acetate (3 x 50 cm^3) and water (50 cm^3). The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure to give a yellow oil. This was subjected to column chromatography eluting with petrol/ethyl acetate (6:4) to give **138** as a white gum (204 mg, 68%); $[\alpha]_D^{21.6}$ –171 (c 1, $CHCl_3$); δ_H (500 MHz, $CDCl_3$): 1.43 and 1.46 (18H, *s*, 2 x $OC(CH_3)_3$), 1.51 (3H, *d*, J = 6.9 Hz, H-3), 2.90 (1H, br, OH), 4.55 (1H, br, H-5'), 4.76 (1H, *m*, H-6') 5.06 1H, *q*, J = 6.9 Hz, H-2), 6.30 (2H, *m*, H-3' and 4'), 7.22 (1H, *d*, J = 5.5 Hz, H-2'); δ_C (125 MHz, $CDCl_3$): 17.1 (C-3), 28.2 and 28.4 2 x $OC(\underline{C}H_3)_3$), 51.2 (C-6'), 68.9 (C-5'), 69.4 (C-2), 80.2 and 80.4 (2 x $O\underline{C}(CH_3)_3$), 125.3 (C-3'), 125.3 (C-1'), 133.5 (C-4'), 152.1 (NCO_2), 169.4 and 170.1 (2 x CO_2); MS m/z (ES^+): 406 $(MNa)^+$.



139

(-)-2-[*trans*-6'-amino-5'-hydroxy-1',3'-cyclohexadiene-1'-carboxyloxy]propanoic acid 139:

To a solution of ester **138** (140 mg, 0.37 mg) in dichloromethane (5 cm^3) was added trifluoroacetic acid (112 µl, 1.46 mmol). This mixture was then stirred until all the starting material was consumed (TLC ca. 12 h). The solvent was removed under reduced pressure to give a brown gum which was dissolved in water (20 cm^3) and washed with ethyl acetate (20 cm^3). The aqueous phase was concentrated under reduced pressure to give **139** as a yellow gum (75 mg, 89%); $[\alpha]_D^{20.8}$ –199 (c, 1; H_2O); HRMS (ES^+): Calcd. For $C_{10}H_{11}NO_5$: M^+ - H_2O, 209.0688. Found: 209.0690; ν_{max} (KBr disk): 3413, 3550-2800 (br), 1726, 1679, 1580 1271 cm^{-1}; δ_H (500 MHz, D_2O): 1.57 (3H, *d*, J = 7.2 Hz, H-3), 4.42 (1H, *m*, H-6'), 4.45 (1H, *d*, J = 1.2 Hz, H-5'), 5.16 (1H, *q*, J = 7.2 Hz, H-2), 6.49 (2H, *m*, H-3' and H-4'), 7.57 (1H, *d*, J = 1.5 Hz, H-2'); δ_C (125 MHz, D_2O): 16.4 (C-3), 48.4 (C-6'), 63.9 (C-5'), 71.2 (C-2), 121.2 (C-1'), 125.3 (3'), 132.5 (C-4'), 138.8 (C-2'), 166.2 (CO_2), 176.3 (C-1), MS m/z (CI): 228 (MH^+).

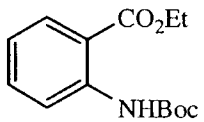


142

(S)-2-*Tert*-Butylsilyloxypropanoic acid 142:

To a stirring solution of (S)-lactic acid **141** (500 mg, 5.56 mmol) in CH_2Cl_2 was added imidazole (760 mg, 11.10 mmol) and TBSCl (1.26 g, 8.33 mmol). The reaction mixture was stirred at room temperature for 24 h and then 1 M HCl (100 cm^3) and ethyl acetate (100 cm^3) were added. The organic layer was removed. The aqueous phase was washed with ethyl acetate (2 x 50 cm^3) and the organic fractions were combined and concentrated. The residue was subjected to column chromatography eluting with petroleum ether/ethyl acetate (6:4) to give **142** as a yellow oil (996 mg, 88%); ν_{max} (thin film): 3430, 2941, 1731, 1463 cm^{-1}; δ_H (400 MHz, $CDCl_3$): 0.10 (3H, *s*, CH_3Si), 0.14 (3H, *s*, CH_3Si), 0.91 (9H, *s*, $(CH_3)_3CSi$), 1.45 (3H, *d*, J = 6.8 Hz, H-3),

4.36 (1H, *q*, J = 6.8 Hz, H-2); δ_C (100 MHz, $CDCl_3$): 0.5 ($(CH_3)_2Si$), 1.62 ($(CH_3)_3\underline{C}Si$), 26.3 (C-3), 30.9 ($(\underline{C}H_3)_3CSi$), 73.8 (C-2), 180.9 (C-1); *m/z* (CI): 205 (MH^+, 75 %), 159 (100 %).



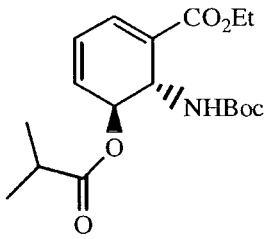
144

Ethyl N-*tert*-butoxycarbonylanthranilate 144:

To a solution of **142** (240 mg, 1.18 mmol), EDCI (150 mg, 1.18 mmol) and DMAP (140 mg, 1.18 mg) in CH_2Cl_2 (10 cm^3) was added cyclohexadiene **3** (220 mg, 0.78 mmol) and the reaction mixture was stirred at room temperature and monitored by thin layer chromatography. After 6 h **144** was isolated as a yellow gum (169 mg, 82 %); ν_{max} (thin film): 3255, 2975, 1728, 1693, 1598 cm^3, δ_H (400 MHz, $CDCl_3$) 1.40 (3H, *t*, J = 7.2 Hz, $OCH_2C\underline{H}_3$), 1.52 (9H, *s*, $OC(CH_3)_3$), 4.36 (2H, *q*, J = 7.2 Hz, $OC\underline{H}_2CH_3$), 6.98 (1H, *dt*, J = 7.2 and 1.2 Hz, H-5), 7.49 (1H, *dt*, J = 7.2 and 2.0 Hz, H-4), 8.01 (1H, *ddd*, J = 7.2, 2.0 and 0.4 Hz, H-3), 8.44 (1H, *dd*, J = 7.2 and 1.2 Hz, H-6), 10.34 (1H, br, NH); δ_C (100 MHz, $CDCl_3$): 14.4 ($OCH_2\underline{C}H_3$), 28.5 ($OC(\underline{C}H_3)_3$), 61.4 ($O\underline{C}H_2CH_3$), 80.7 ($O\underline{C}(CH_3)_3$), 114.7 (C-2), 118.9 (C-6), 121.3 (C-5), 131.1 (C-3), 134.6 (C-4), 142.5 (C-1), 153.1 (NCO_2), 168.3 (CO_2); *m/z* (ES^+): 288 (MNa^+, 100%).

Mitsunobu reaction:

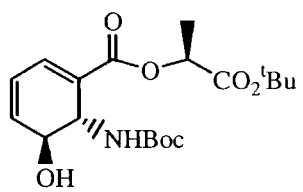
A solution of cyclohexadiene **3** (730 mg, 2.58 mg) and Ph_3P (810 mg, 3.10 mmol) in THF (10 cm^3) was added dropwise to a solution of 95% DIPAD (0.54 cm^3, 3.10 mmol) and benzoic acid (390 mg, 3.10 mmol) in THF (10 cm^3) at room temperature. After stirring for 12 h, the reaction mixture was neutralised with $NaHCO_3$ solution and extracted with ethyl acetate (3 x 50 cm^3). The combined organic layers were washed with H_2O (10 cm^3), dried $MgSO_4$) and concentrated under reduced pressure. The residue was subjected to flash chromatography eluting with petroleum ether/ ethyl acetate (7:3) to give **144** (320 mg, 47%) and an unidentified mixture



146

Ethyl *trans*-6-*tert*-butoxycarbonylamino-5-*iso*-butoxyloxy-1,3-cyclohexadiene-1-carboxylate 146:

A solution of **142** (540 mg, 2.65 mmol) and thionyl chloride (0.19 cm^3, 2.65 mmol) in (THF 10 cm^3) was stirred at room temperature for 8 h and then cyclohexadiene **3** (250 mg, 0.88 mmol) and triethylamine (0.61 cm^3, 4.4 mmol) was added. The reaction mixture was stirred for 3 h and then poured into a conical flask with 1M HCl (20 cm^3). This was extracted with ethyl acetate (3 x 20 cm^3), dried ($MgSO_4$) and concentrated. The residue was subjected to column chromatography eluting with petroleum ether/ ethyl acetate (4:1) to give **146** as pale yellow gum (280 mg, 90%); ν_{max} (KBr disk): 3353, 2978, 1717, 1701, 1513 cm^{-1}; δ_H (400 MHz, $CDCl_3$): 1.09 (6H, *m*, $(C\underline{H}_3)_2CH$), 1.29 (3H, *t*, J = 7.2 Hz, $OCH_2C\underline{H}_3$), 1.41 (9H, *s*, $OC(CH_3)_3$), 2.46 (1H, *m*, $(CH_3)_2C\underline{H}$), 4.23 (2H, *q*, J= 7.2 Hz, $OC\underline{H}_2CH_3$), 4.37 (1H, *d*, J = 7.6 Hz, NH), 4.82 (1H, *d*, J = 7.6 Hz, H-6), 5.22 (1H, br, H-5), 6.32 (2H, *m*, H-3 and 4), 7.16 (1H, *m*, H-2); δ_C (100 MHz, $CDCl_3$): 14.4 ($OCH_2\underline{C}H_3$), 19.1 ($(\underline{C}H_3)_2CH$), 28.5 ($OC(\underline{C}H_3)_3$), 33.9 ($(CH_3)_2\underline{C}H$), 46.5 (C-6), 61.2 ($O\underline{C}H_2CH_3$), 68.8 (C-5), 80.2 ($O\underline{C}(CH_3)_3$), 126.7 (C-4), 128.2 (C-1), 129.2 (C-3), 133.3 (C-2), 154.9 (NCO_2), 166.8 (CO_2Et), 176 ($(CH_3)_2CH\underline{C}O_2$); *m/z* ($ES^+$): 376 ($MNa^+$).

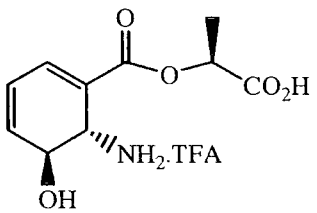


148

***Tert*-Butyl (+)-2-[*trans* -6'-*tert* -butoxycarbornylamino-5'-hydroxycyclohexa-1',3'-diene-1'-carboxyloxy]propionate 148**:

Using acid **(+)-125** (200 mg, 0.78 mmol) in the coupling procedure described for **138** gave **148** as a yellow gum (205 mg, 68%); $[\alpha]_D^{21.6}$ +181 (c, 1; $CHCl_3$); δ_H (500 MHz, $CDCl_3$): 1.43 and 1.46 (18H, *s*, 2 x $OC(CH_3)_3$), 1.49 (3H, *d*, J = 6.9 Hz, H-3), 2.78 (1H, br, OH), 4.40 (1H, br, NH), 4.52 (1H, br, H-5'), 4.78 (1H, *m*, H-6'), 5.04 (1H, *q*,

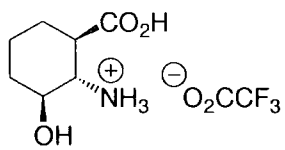
J = 6.9 Hz, H-2), 6.27 (2H, *m*, H-3' and 4'), 7.24 (1H, *d*, J = 5.5 Hz, H-2'); δ_C (125 MHz, $CDCl_3$): 17.2 (C-3), 28.2 and 28.6 (2 x $OC(\underline{C}H_3)_3$), 50.6 (C-6'), 68.4 (C-5'), 69.7 (C-2), 80.2 and 82.3 (2 x $O\underline{C}(CH_3)_3$), 124.6 (C-3'), 125.2 (C-1), 133.5 (C-4'), 134.5 (C-2'), 152 (NCO_2), 170.0 and 170.1 (CO_2); *m/z* (ES^+): 406 $(MNa)^+$.



149

(+)-2-[*trans*-6'-amino-5'-hydroxy-1',3'-cyclohexadiene-1'-carboxyloxy]propanoic acid 149:

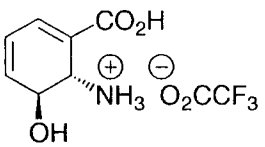
Deprotection of **148** (140 mg, 0.37 mmol) using the procedure described for **139** afforded **149** as a white solid (74 mg, 89%); m.p. 106-108°C, $[\alpha]_D^{21.3}$ +165 (c, 1; $CHCl_3$) ν_{max} (KBr): 3425 (br), 2927, 1703, 1677, 1589 cm^{-1}; δ_H (500 MHz, D_2O): 1.55 (3H, *d*, J = 7.0 Hz, H-3), 4.39 (1H, *d*, J = H-6'), 4.43 (1H, *dd*, J = 3.0 and 1.5 Hz, H-5'), 5.18 (1H, *q*, J = 7.0 Hz, H-2), 6.47 (2H, *m*, H-3' and 4'), 7.55 (1H, *d*, J = 5.5 Hz, H-2'); δ_C (125 MHz, D_2O): 16.2 (C-3), 48.5 (C-6'), 63.9 (C-5'), 70.5 (C-2), 121.0 (C-1'), 125.3 (C-3'), 132.8 (C-4), 139.1 (C-2'), 166.1 (CO_2H), 175.3 (C-1); *m/z* (CI): 228 (MH^+, 100%), 210 (96%), 138 (42%); Anal. Calcd. For $C_{10}H_{13}NO_5.C_2HO_2F_3$: C,46.61; H, 4.96; N, 4.53; F, 25.87. Found: C, 46.60, H, 5.34; N, 4.64.



151

(-)-*Anti-anti*-2-amino-3-hydroxycyclohexane-1-carboxylic acid TFA salt 151:

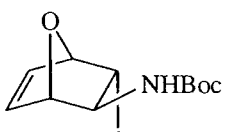
A solution of **152** (100 mg, 0.39 mmol) in CH_3CH_2OH was treated with catalytic amount of Pd/C and the solution was stirred for 48 h to give **151** as a colourless gum in 98% yield. $[\alpha]_D^{21}$ - 32 (c, 1; H_2O); δ_H (500 MHz, D_2O): 1.40 (2H, *m*, H-6), 1.81 (2H, *m*, H-5), 2.05 (2H, *m*, H-4), 2.58 (1H, *m*, J = 8.0 and 4.0 Hz, H-1), 3.18 (1H, *t*, J = 8.0 Hz, H-2), 3.58 (1H, *m*, H-3); δ_C (125 MHz, D_2O): 22.5 (C-6), 28.2 (C-5), 32.7 (C-4), 45.6 (C-1), 56.7 (C-2), 70.1 (C-3), 176.4 (CO_2); *m/z* (CI): 160 (MH^+, 10 %), 116 (100 %).



152

(+)-*Trans*-2,3-dihydro-2-amino-3-hydroxyanthranilic acid TFA salt 152:

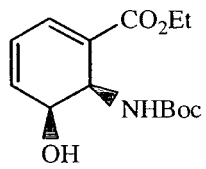
To a solution of **(+)-125** (500 mg, 1.77 mg) in CH_2Cl_2 (20 cm^3) was added TFA (1.40 cm^3, 14.12 mmol). The solution was stirred at room temperature for 4 h to give **152** (273 mg, 100%) as a white solid; m.p. 137-139 °C; . $[\alpha]_D^{21}$ + 339 (c, 1; H_2O); δ_H (500 MHz, D_2O): 4.35 (1H, *d*, J = 3.0 Hz, H-6), 4.43 (1H, *t*, J = 3.0 Hz, H-5), 6.44 (2H, *m*, H-3 and 4), 7.44 (1H, *d*, J = 5.5 Hz, H-2); δ_C (125 MHz, D_2O): 48.8 (C-6), 64.1 (C-5), 122.1 (C-1), 125.4 (C-3), 132.1 (C-2), 138.0 (C-4), 168.5 (CO2), *m/z* (CI): 156 (MH^+, 16 %), 138 (100%).



158

Ethyl *exo*-3-*tert*-butoxycarbonylamino-7-oxabicyclo[2.2.1]hept-5-ene-*endo*-2-carboxylate 158:

Employing the reduction and protection procedure described for the synthesis of **2**, **124** (5.00 g, 23.5 mmol) was elaborated to give **158** as a white solid (5.5 g, 83%) mp 50-52 °C, υ_{max} (KBr disk): 3291, 2978, 1738, 1703 cm^{-1}; δ_H (500 MHz, $CDCl_3$): 1.24 (3H, *t*, J = 7.2 Hz, $OCH_2C\underline{H}_3$), 1.45 (9H, *s*, $OC(C\underline{H}_3)_3$), 2.69 (1H, *t*, J = 4.8 and 3.2 Hz, H-2), 4.02 (1H, *br*, H-3), 4.12 (2H, *q*, J = 7.2 Hz, $OC\underline{H}_2CH_3$), 4.78 (1H, *s*, H-4), 4.82 (1H, *br*, NH), 5.12 (1H, *d*, J = 4.8 Hz, H-1), 6.37 (1H, *dd*, J = 5.2 and 1.6 Hz, H-5), 6.46 (1H, *dd*, J = 5.2 and 1.6 Hz, H-6); δ_C (125 MHz, $CDCl_3$): 14.0 ($OCH_2\underline{C}H_3$), 28.2 ($OC(\underline{C}H_3)_3$), 52.1 (C-2), 54.3 (C-3), 60.8 ($O\underline{C}H_2CH_3$), 78.4 (C-1), 79.6 (C-3), 85.1 (C-4), 135.2 (C-6), 135.4 (C-5), 155.3 (NCO_2), 170.2 ($\underline{C}OC_2H_5$); *m/z* (EI): 283(M^+), 57(100%).



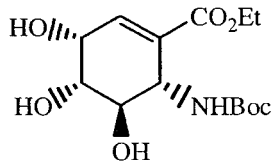
159

Ethyl *syn*-6-*tert*-butoxycarbonylamino-5-hydroxy-1,3-cyclohexadiene-1 -carboxylate 159:

Employing the KHMDS mediated β-elimination procedure described for the synthesis of **3**, **158** (500 mg, 1.76 mmol) was used instead of **2** to give **159** as a yellow gum; (340 g, 68%) ν_{max} (KBr disk): 3389 (br), 2982, 1689, 1523 cm^{-1}; δ_H (500 MHz, $CDCl_3$): 1.28 (3H, *t*, J = 7.0 Hz, $OCH_2C\underline{H}_3$), 1.42 (9H, *s*, $OC(CH_3)_3$), 3.48 (1H, br, OH), 4.22 (2H, *q*, J = 7.0 Hz, $OC\underline{H}_2CH_3$), 4.64 (1H, *t*, J = 7.5 Hz, H-5), 4.67 (1H, br, NH), 4.77 (1H, *d*, J = 7.5 Hz, H-6), 6.05 (1H, *t*, J = 5.5 Hz, H-3), 6.11 (1H, *d*, J = 7.5 Hz, H-4), 7.10 (1H, *d*, J = 5.5 Hz, H-2); δ_C (125 MHz, $CDCl_3$): 14.4 ($OCH_2\underline{C}H_3$), 28.5 ($OC(\underline{C}H_3)_3$), 46.9 (C-6), 61.6 ($O\underline{C}H_2CH_3$), 71.4 (C-5), 81.6 ($O\underline{C}(CH_3)_3$), 122.2 (C-3), 127.9 (C-1), 135.2 (C-2), 138.8 (C-4), 157.5 (NCO_2), 166.1 (CO_2); *m/z* (CI): 284 (MH^+, 13%), 182 (100%).

General procedure for hydroxylation

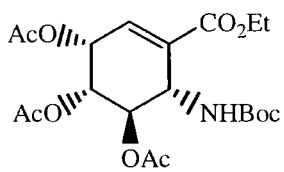
To a solution of substrate (1.0 equivalent) in acetone (15 cm^3) was added $Me_3NO.H_2O$ (1.1 equivalent) and 4 wt % OsO_4 in water (0.01 equivalent). The resulting mixture was stirred and monitored by TLC until all the starting material was consumed (12 hours). The solvent was then removed under reduced pressure and the residue was dissolved in ethyl acetate (10 cm^3). The acetate solution was washed with saturated $NaHSO_3$ (5 cm^3) and the aqueous phase was extracted with ethyl acetate (5 cm^3 x 3). The organic layers were combined, dried over $MgSO_4$ and the solvent was removed under reduced pressure to give the crude diol.



166

Ethyl *syn-anti-anti*-6-*tert*-butoxycarbonylamino-3,4,5-trihydroxycyclohex-1-ene-1-carboxylate 166:

Using the general procedure for OsO_4 dihydroxylation, $Me_3NO.H_2O$ (93 mg, 0.84 mmol), 4% wt. OsO_4 in water (50 μl) and diene **3** (120 mg, 0.42 mmol) gave a crude product which was subjected to column chromatography eluting with petroleum ether/ethyl acetate (7:3) to give **166** as a colourless oil (104 mg, 78%); ν_{max} (thin film): 3424, 2980, 1710,1513 cm^{-1}; δ_H (400MHz, $CDCl_3$): 1.26 (3H, *t*, J = 6.8 Hz, $OCH_2C\underline{H}_3$), 1.40 (9H, *s*, $OC(CH_3)_3$), 3.83 (1H, br, H-4), 4.05 (1H, br, H-5), 4.18 (2H, *q*, J = 6.8 Hz, $OC\underline{H}_2CH_3$), 4.35 (1H, *m*, H-6), 4.45 (1H, br, H-3), 5.61 (1H, br, NH), 6.82 (1H, *s*, H-2); δ_C (100 MHz, $CDCl_3$): 14.3 ($OCH_2\underline{C}H_3$), 28.6 ($OC(\underline{C}H_3)_3$), 51.5 (C-6), 61.3 ($O\underline{C}H_2CH_3$), 66.0 (C-3), 70.5 (C-4), 71.7 (C-5), 80.2 ($O\underline{C}(CH_3)_3$), 131.7 (C-1), 132.2 (C-2), 156.3 (NCO_2), 166.3 (CO_2Et); *m/z* (CI): 318 (MH^+, 49%), 182 (100%).

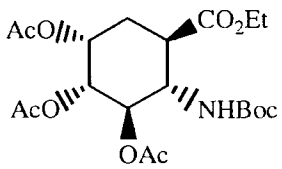


167

Ethyl *syn-anti-anti*-3,4,5-triacetoxy-6-*tert*-butoxycarbonylamino-cyclohex-1-ene-1-carboxylate 167:

166 (100mg, 0.30 mmol) was dissolved in pyridine (2.5 cm^3, 31.0 mmol) and acetic anhydride (2.5 cm^3, 26.5 mmol) and stirred at room temperature for 16 h. Water (20 cm^3) was then added and the mixture was stirred for further 3 h. The mixture was extracted with ethyl acetate (3 x 20 cm^3). The combined organic extracts were washed with 2M HCl (30 cm^3), sat. $NaHCO_3$ (30 cm^3) and water (30 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with petroleum ether/ethyl acetate (7:2) to give tri-acetate **167** as a thick yellow oil (127 mg, 68%). δ_H (500 MHz, $CDCl_3$): 1.28 (3H, *t*, J = 7.2 Hz, $OCH_2C\underline{H}_3$), 1.42 (9H, *s*, $OC(CH_3)_3$), 2.07 (9H, *s*, 3 x CH_3CO), 4.23 (2H, *q*, J = 7.2 Hz, $OC\underline{H}_2CH_3$), 4.42 (1H, br, NH), 4.70 (1H, br, H-6), 5.26 (1H, br, H-5), 5.32

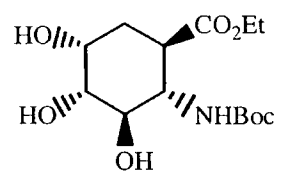
(1H, *dd*, J = 6.6 and 4.2 Hz, H-4), 5.67 (1H, *t*, J = 3.6 Hz , H-3), 6.76 (1H, br, H-2); δ_C (125 MHz, $CDCl_3$): 14.0 ($OCH_2\underline{C}H_3$), 20.5 and 20.7 (3 x $\underline{C}H_3CO$), 28.2 ($OC(\underline{C}H_3)_3$), 48.3 (C-6), 61.4 ($O\underline{C}H_2CH_3$), 65.6 (C-3), 66.1 (C-4), 70.2 (C-5), 79.9 ($O\underline{C}(CH_3)_3$), 133.0 (C-1), 134.3 (C-2), 154.4 (NCO_2), 164.6 ($\underline{C}O_2C_2H_5$), 169.1, 169.3 and 169.8 (3 x $CH_3\underline{C}O$); *m/z* (CI): 444 (MH^+); Anal. calcd. For $C_{20}H_{29}NO_{10}$: C, 54.42; H, 6.59; N, 3.16. Found: C, 54.23; H, 6.52; N, 3.18.



168

Ethyl *anti-anti-anti-syn*-3,4,5-triacetoxy-2-*tert*-butoxycarbonylaminocyclo hexanecarboxylate 168:

Using the general acetylation procedure, triol **169** (400 mg, 1.41 mmol) in pyridine (5 cm^3) and acetic anhydride (5 cm^3) afforded triacetate **168** as a pale yellow gum (502 mg, 90%); δ_H (500 MHz, $CDCl_3$): 1.29 (3H, *t*, J = 7.0 Hz, $OCH_2C\underline{H}_3$), 1.40 (9H, *s*, $OC(CH_3)_3$), 1.74 and 1.96 (2H, *m*, 6-HH), 2.93 (1H, *dd*, J = 8.5 and 4.4 Hz, H-1), 3.94 (1H, br, H-5), 4.11 (2H, *q*, J = 7.0 Hz, $OC\underline{H}_2CH_3$), 4.22 (1H, br, H-4), 4.53 (1H, br, H-3), 4.59 (1H, br, H-2), 5.64 (1H, br, NH); δ_C (125 MHz, $CDCl_3$): 14.4 ($OCH_2\underline{C}H_3$), 21.0 (3 x $\underline{C}H_3CO$), 24.9 (C-6), 28.4 ($OC(\underline{C}H_3)_3$), 41.8 (C-1), 48.5 (C-5), 54.1 (C-2), 61.5 ($O\underline{C}H_2CH_3$), 77.0 (C-4), 79.8 (H-3), 81.2 ($O\underline{C}(CH_3)_3$), 155.0 (NCO_2), 169.8 (CO_2), 171.1, 172.8 and 173.2 (3 x $CH_3\underline{C}O$); *m/z* (CI): 463 (MNH_4^+, 3%), 446 (MH^+, 5%), 346 (100%), 232 (93%). HRMS (ES+): $C_{17}H_{25}NO_9Na$ requires M^+ 468.1846 Found: 468.1849. **168** was also prepared from **167** by Pd/C catalysed hydrogenation.

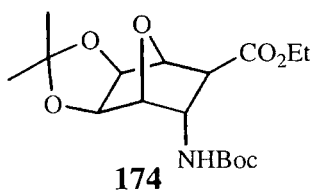


169

Ethyl *anti-anti-anti-syn*-2-*tert*-butoxycarbonylamino-3,4,5-trihydroxycyclo hexanecarboxylate 169:

To a solution of ester **166** (500 mg, 1.57 mmol) in ethanol (20 cm^3) was added 10% Pd/C (100 mg) and the suspension was stirred under hydrogen for 48 h. The suspension was then filtered and the filtrate was concentrated under reduced pressure

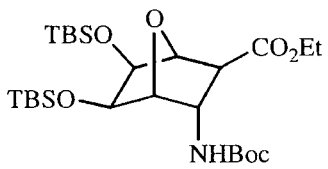
to give **169** as a white solid (490 mg 98%); m.p. 36-38°C; ν_{max} (KBr disk): 3420 (br), 2979, 1722, 1515 cm^{-1}; δ_H (500 MHz, $(CD_3)_2CO$): 1.21 (3H, t, J = 7.0 Hz, $OCH_2C\underline{H}_3$), 1.37 (9H, *s*, $OC(CH_3)_3$), 1.64 and 1.96 (2H, m, 6-HH), 2.50 (1H, *dt*, *J* = 12.0 and 3.5 Hz, H-1), 2.90 (1H, br, H-5), 3.31(1H, *t*, *J* = 3.6 Hz, H-3), 3.46 (1H, br, H-4), 3.58 (1H, *m*, H-2), 4.05 (2H, *q*, *J* = 7.0 Hz, $OC\underline{H}_2CH_3$), 5.98 (1H, br, NH); δ_C (125 MHz, $(CD_3)_2CO$): 13.9 ($OCH_2\underline{C}H_3$), 25.3 (C-6), 28.0 ($OC(\underline{C}H_3)_3$), 42.9 (C-5), 48.3 (C-1), 55.9 (C-2), 60.2 ($O\underline{C}H_2CH_3$), 75.2 (C-4), 77.5 (H-3), 81.2 ($O\underline{C}(CH_3)_3$), 155.3 (NCO_2), 173.1 (CO_2); MS *m/z* (CI): 320 (MH^+, 62%), 264 (100%); Anal. calcd for $C_{14}H_{25}NO_7$: C, 52.65; H, 7.89; N, 4.39. Found: C, 52.48; H,7.75; N, 4.25.



174

Ethyl *endo*-3-*tert*-butoxycarbonylamino-5,6-O,O-isopropylidine-5,6-dihydroxy-7-oxabicyclo[2,2,1]heptane-*exo*-2-carboxylate 174:

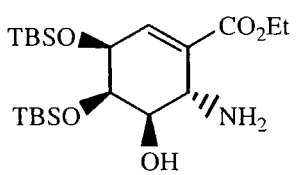
Diol **173** (500 mg, 1.58 mmol) was dissolved in acetone and to this solution was added dimethoxypropane (221 mg, 2.51 mmol) and p-TsOH (15 mg, 0.08 mmol). The mixture was stirred and monitored by TLC. The solvent was removed under reduced pressure and the residue was dissolved in ethyl acetate (15 cm^3). The solution was then washed with saturated $NaHCO_3$ (5 cm^3) and the aqueous layer was extracted with ethyl acetate (10 cm^3 x 3). The combined organic layers were washed with brine (10 cm^3), dried over $MgSO_4$ and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography eluting with a $(CH_3CH_2)_2O$/petroleum ether mixture (7:3) to give the title compound **174** (390 mg, 61%) as a white solid, mp 118-120°C; υ_{max} (KBr disk): 3269, 2983, 1741, 1683, 1667,1546 cm^{-1}; δ_H (500 MHz, $CDCl_3$): 1.23 (3H, *t*, J = 7.2 Hz, $OCH_2C\underline{H}_3$), 1.39 (6H, *s*, $C(CH_3)_2$), 1.42 (9H, *s*, $OC(CH_3)_3$), 2.13 (1H, *d*, J = 5.4 Hz, H-2), 4.15 (3H, *m*, $OC\underline{H}_2CH_3$ and H-3), 4.32 (1H, *d*, J = 5.4 Hz, H-5), 4.43 (1H, br, H-6), 4.56 (1H, *s*, H-1), 4.72 (1H, br, H-4), 4.97 (1H, br, NH); δ_C (125 MHz, $CDCl_3$): 14.3 ($OCH_2\underline{C}H_3$), 26.0 ($C(\underline{C}H_3)_2$), 28.5 ($OC(\underline{C}H_3)_3$), 49.8 (C-2), 53.2 (C-3), 61.7 ($O\underline{C}H_2CH_3$), 78.4 (C-4), 80.8 (C-6), 81.9 (C-5), 82.6 (C-1), 111.8 ($(CH_3)_2\underline{C}O_2$), 155.5 (NCO_2), 171.5 ($\underline{C}O_2C_2H_5$); *m/z* (EI): 357 (M^+), 57 (100%); Anal. Calcd for $C_{17}H_{18}NO_7$: C, 57.13; H, 7.61; N, 3.92. Found: C, 57.05; H, 7.66; N, 3.81.



175

Ethyl *endo*-3-*tert*-butoxycarbonylamino-5,6-O,O-bis(tert-butyldimethylsilyl)-5, 6-dihydroxy-7-oxabicyclo[2,2,1]heptane-*exo*-2-carboxylate 175:

To a solution of diol **173** (500 mg, 1.58 mmol) in anhydrous DMF (20 cm^3) were added DMAP (583 mg, 4.78 mmol) and TBSCl (600 mg, 4.00 mmol). The mixture was then stirred over night, quenched with sat. NH_4Cl solution (10 cm^3), and extracted with ethyl acetate (10 cm^3 x 3). The combined organic extracts were washed with water (10 cm^3), dried ($MgSO_4$) and concentrated to leave a residue, which was purified by flash chromatography eluting with petroleum ether/$(CH_3CH_2)_2O$ (7:3) to give disilyl ether **175** as a white solid (860 mg, 86%), mp 150-152°C; υ_{max} (KBr disk): 3372, 2959, 1737, 1699, 1677, 1520 cm^{-1}; δ_H (500 MHz, $CDCl_3$): 0.09, 0.12 (12H, *s*, 2 x $Si(CH_3])_2$), 0.91 (18H, *s*, 2 x $SiC(CH_3)_3$), 1.26 (3H, *t*, J = 7.0 Hz, $OCH_2C\underline{H}_3$), 1.44 (9H, *s*, $OC(CH_3)_3$), 2.08 (1H, *d*, J = 4.6 Hz, H-2), 3.92 (1H, *d*, J = 5.3 Hz, H-6), 4.09 (1H, br, H-3), 4.18 (1H, *q*, J = 7.0 Hz, $OC\underline{H}_2CH_3$), 4.25 (1H, br, H-5), 3.47 (1H, *s*, H-1), 4.52 (1H, br, H-4), 4.63 (1H, br, NH); δ_C (125 MHz, $CDCl_3$): -4.9, -5.0 (2 x $Si(CH_3)_2$), 14.1 ($OCH_2\underline{C}H_3$), 18.5, 18.6 (2 x $Si\underline{C}(CH_3)_3$), 26.0 ($SiC(\underline{C}H_3)_3$), 28.3 ($OC(\underline{C}H_3)_3$), 49.8 (C-2), 53.2 (C-3), 61.4 ($O\underline{C}H_2CH_3$), 71.6 (C-5), 77.3 (C-6), 80.3 (C-4), 80.4 ($O\underline{C}(CH_3)_3$), 85.4 (C-1), 155.4 (NCO_2), 171.1 ($CO_2C_2H_5$); *m/z* (EI): 547(M^+), 376 (100 %); Anal. calcd. for $C_{26}H_{51}NO_7Si_2$: C, 57.21; H, 9.42; N, 2.57. Found: C, 57.14; H, 9.38; N, 2.59.

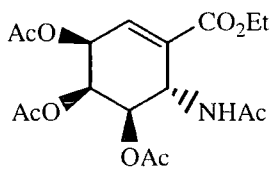


176

Ethyl *syn-syn-anti*-6-amino-3,4-*bis*-(*tert*-butyldimethylsilyloxy)-5-hydroxycyclo hex-1-ene-1-carboxylate 176:

To a solution of LiHMDS (231 mg, 1.38 mmol) in THF (20 cm^3) at –50°C was added a solution of oxanorbornene **175** (250 mg, 0.46 mmol) in THF (5 cm^3). The solution was stirred at 25°C for 2 hours. The reaction mixture was then quenched with ethyl

acetate/ethanol (9:1) and stirred for 5 minutes. Saturated NH_4Cl solution was added to the reaction mixture and the resulting two layers were separated. The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure to give the crude product. Flash chromatography eluting with ethyl acetate/petroleum ether (3:2) afforded **176** as a light yellow oil (98 mg, 48%); ν_{max} (KBr disk): 3410, 2985, 1734, 1538 cm^{-1}; δ_H (400 MHz, $CDCl_3$): 0.14 (12H, *s*, 2 x $Si(CH_3)_3$), 0.90 (9H, *s*, $SiC(CH_3)_3$), 0.91 (9H, *s*, $SiC(CH_3)_3$), 1.33 (3H, *t*, J = 7.2Hz, $OCH_2C\underline{H}_3$), 3.25 (1H, br, OH), 4.02 (1H, *dd*, J = 5.6 and 5.0 Hz, H-5), 4.08 (1H, *dd*, J = 7.4 and 5.6 Hz, H-6), 4.13 (1H, *t*, J = 2.4 Hz, H-4), 4.26 (2H, *q*, J = 7.2 Hz, $OC\underline{H}_2CH_3$), 4.41 (1H, *dd*, J = 3.2 and 2.4 Hz, H-3), 4.68 (2H, br, NH_2), 6.87 (1H, d, J = 3.2 Hz, H-2); δ_C (100 MHz, $CDCl_3$): 0.1 ($Si(CH_3)_2$), 18.8 ($OCH_2\underline{C}H_3$), 23.0 ($Si\underline{C}(CH_3)_3$), 30.6 ($SiC(\underline{C}H_3)_3$), 55.8 (C-6), 66.3 ($O\underline{C}H_2CH_3$), 73.8 (C-3), 76.4 (C-4), 77.4 (C-5), 118.7 (C-1), 132.1 (C-2), 170.2 (CO_2). *m/z* (CI): 446 (MH^+, 8%), 297 (100%).

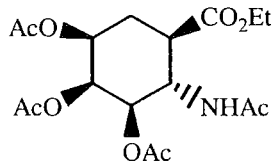


177

Ethyl *syn-syn-anti*-3,4,5-triacetoxy-6-N-acetylaminocyclohex-1-ene-1-carboxylate 177:

Tetra-n-butylammonium fluoride (0.5 cm^3 of 1M solution in THF, 0.5 mmol) was added to a stirred solution of disilyl ether **176** (90 mg, 0.20 mmol) in THF (2.5 cm^3). After 16 hours, the mixture was concentrated under reduced pressure to afford yellow oil. The oil was dissolved in pyridine (1.5 cm^3, 18.6 mmol) and acetic anhydride (1.5 cm^3, 15.9 mmol) and the solution was stirred for 20 hours. Water (5 cm^3) and ethyl acetate (10 cm^3) were added to the reaction mixture and the resulting layers were separated. The aqueous layer was extracted with ethyl acetate (2 x 10 cm^3). The organic extracts were combined, washed with 2M HCl (10 cm^3), saturated $NaHCO_3$ (10 cm^3), water (10cm^3), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with petroleum ether/ethyl acetate (7:3) to give tri-acetate **177** as a yellow gum (41 mg, 52%). ν_{max} (KBr disk): 3343, 2977, 1711, 1639, 1521 cm^{-1}; δ_H (500 MHz, $CDCl_3$): 1.27 (3H, *t*, J = 7.2 Hz, $OCH_2C\underline{H}_3$), 1.97 (3H, *s*, CH_3CO), 2.03 (3H, *s*, CH_3CO), 2.06 (3H, *s*, CH_3CO), 2.15 (3H, *s*, CH_3CO), 4.25 (2H, *q*, J = 7.2 Hz, $OC\underline{H}_2CH_3$), 5.13 (1H, *dd*, J = 5.5 and 2.0

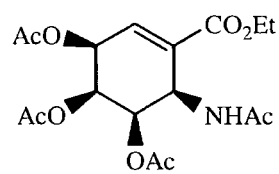
Hz, H-5), 5.44 (1H, br H-6), 5.62 (1H, br, H-4), 5.65 (2H, *m*, H-3 and NH), 6.79 (1H, br, H-2); δ_C (125 MHz, $CDCl_3$): 14.3 ($OCH_2\underline{C}H_3$), 20.7 ($\underline{C}H_3CO$), 20.8 ($\underline{C}H_3CO$), 21.2 ($\underline{C}H_3CO$), 23.5 ($\underline{C}H_3CO$), 43.6 (C-6), 61.8 ($O\underline{C}H_2CH_3$), 66.4 (C-5), 67.8 (C-3), 68.8 (C-4), 132.0 (C-1), 136 (C-2), 164.3, 169.2, 169.6, 169.8 (carbonyls); *m/z* (CI): 386 (MH^+, 100%).



178

Ethyl *anti-anti-syn-syn*-3,4,5-triacetoxy-2-N-acetylaminocyclohexane-1-carboxylate 178:

To a solution of cyclohexene **177** (100 mg, 0.26 mmol) in ethanol (10 cm^3) was added 10% Pd/C (20 mg) and the suspension was stirred under hydrogen for 24 h. The suspension was then filtered and the filtrate was concentrated under reduced pressure to give **178** as a colourless gum (98 mg, 99%); ν_{max} (KBr disk): 3408, 2982, 1741, 1668, 1538 cm^{-1}; δ_H (400 MHz, $CDCl_3$): 1.23 (3H, *s*, J = 7.2 Hz, $OCH_2C\underline{H}_3$), 1.97 (3H, *s*, CH_3CO), 2.00 (3H, *s*, CH_3CO), 2.01 (3H, *s*, CH_3CO), 2.10 (2H, *m*, HH-6), 2.19 (3H, *s*, CH_3CO), 2.75 (1H, *dd*, J = 10.2 and 9.2 Hz, H-1), 4.12 (2H, *q*, J = 7.2 Hz, $OC\underline{H}_2CH_3$), 4.91 (1H, *m*, H-3), 4.92 (1H, *m*, H-2), 4.96 (1H, *m*, H-4), 5.54 (1H, *m*, H-5), 6.24 (1H, br, NH); δ_C (100 MHz, $CDCl_3$): 14.2 ($OCH_2\underline{C}H_3$), 20.9 ($\underline{C}H_3CO$), 21.0 ($\underline{C}H_3CO$), 21.2 (2 x $\underline{C}H_3CO$), 23.7 (C-6), 38.5 (C-1), 47.2 (C-2), 61.7 ($O\underline{C}H_2CH_3$), 68.0 (C-4), 68.6 (C-3), 70.6 (C-5), 169.1, 169.6, 169.8, 170.0, 170.9 (carbonyls); *m/z* (CI): 388 (MH^+, 100%). HRMS (ES^+): $C_{17}H_{25}NO_9Na$ requires M^+ 410.1427. Found: 410.1388.

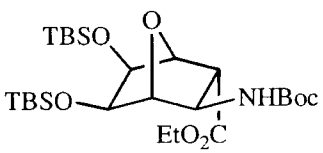


179

Ethyl *syn-syn-syn*-3,4,5-triacetoxy-6-N-acetylaminocyclohex-1-ene-1-carboxylate 179:

Using the same procedure as that employed for the preparation of compound **166**, diene **159** (120 mg, 0.23 mmol) in acetone (10 cm^3), $Me_3NO.H_2O$ (52 mg, 0.47

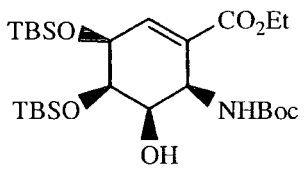
mmol), 4% wt OsO_4 in water (50 μl), pyridine (2.5 cm^3, 31.0 mmol), and acetic anhydride (2.5 cm^3, 26.5 mmol) gave a crude product. The crude product was purified by flash chromatography eluting with petroleum ether/ethyl acetate (7:3) to afford compound **179** (110 mg, 75%) as a white gum; ν_{max} (KBr disk): 3463, 2980, 1755, 1721, 1507 cm^{-1}; δ_H (500 MHz, $CDCl_3$): 1.28 (3H, *t*, J = 7.0 Hz, $OCH_2\underline{C}H_3$), 1.44 (9H, *s*, $OC(CH_3)_3$), 2.04 (3H, *s*, CH_3CO), 2.06 (3H, *s*, CH_3CO), 2,14 (3H, *s*, CH_3CO), 4.26 (2H, *q*, J = 7.0 Hz, $OC\underline{H}_2CH_3$), 4.85 (1H, br, NH), 5.07 (2H, *m*, H-4 and 6), 5.61 (2H, *m*, H-3 and 5), 6.75 (1H, br, C-2); δ_C (125 MHz, $CDCl_3$): 14.3 ($OCH_2\underline{C}H_3$), 20.8 (2 x $\underline{C}H_3CO$), 21.1 ($\underline{C}H_3CO$), 28.5 ($OC(\underline{C}H_3)_3$), 45.1 (C-6), 61.7 ($O\underline{C}H_2CH_3$), 66.8 (C-4), 67.9 (C-3), 68.7 (C-5), 79.7 ($O\underline{C}(CH_3)_3$), 132.2 (C-1), 136.1 (C-2), 155.2 (NCO_2), 164.5 (CO_2), 169.6, 169.7, 169.9 (3 x $CH_3\underline{C}O$); *m/z* (ES^+): 466 (MNa^+).



180

Ethyl *exo*-3-*tert*-butoxycarbonylamino-5,6-O,O-bis(tert-butyldimethylsilyl)-5, 6-dihydroxy-7-oxobicyclo[2,2,1]heptane-*endo*-2-carboxylate 180:

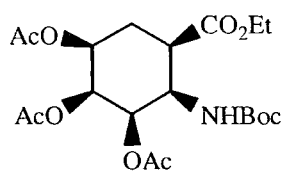
By employing the general procedure for dihydroxylation, adduct **158** (500 mg, 1.77 mmol) afforded a diol which was treated with imidazole (324 mg, 4.78 mmol) and TBSCl (600 mg, 4.00 mmol). The mixture was then stirred over night, quenched with 2M HCl (10 cm^3), and extracted with ethyl acetate (10 cm^3 x 3). The combined organic extracts were washed with water (10 cm^3), dried ($MgSO_4$) and concentrated to leave a residue, which was purified by flash chromatography eluting with petroleum ether/$(CH_3CH_2)_2O$ (7:3) to give disilyl ether **180** as a white solid (860 mg, 86%), mp 108-110°C; υ_{max} (KBr disk): 3368, 2951, 1730, 1698, 1672, 1528 cm^{-1}; δ_H (500 MHz, $CDCl_3$): 0.11, 0.12 (12H, *s*, 2 x $Si(CH_3])_2$), 0.91 (18H, *s*, 2 x $SiC(CH_3)_3$), 1.28 (3H, *t*, J = 7.0 Hz, $OCH_2C\underline{H}_3$), 1.42 (9H, *s*, $OC(CH_3)_3$), 2.63 (1H, *d*, J = 4.6 Hz, H-2), 3.95 (1H, *d*, J = 5.3 Hz, H-6), 3.97 (1H, *s*, H-1), 4.09 (1H, *q*, J = 7.0 Hz, $OC\underline{H}_2CH_3$), 4.22 (1H, br, H-5), 4.48 (1H, dd, J = 6.5 and 1.5 Hz, H-3), 4.52 (1H, br, H-4), 4.78 (1H, br, NH); δ_C (125 MHz, $CDCl_3$): -4.9, -5.0 (2 x $Si(CH_3)_2$), 14.1 ($OCH_2\underline{C}H_3$), 18.5, 18.6 (2 x $Si\underline{C}(CH_3)_3$), 26.0($SiC(\underline{C}H_3)_3$), 28.3 ($OC(\underline{C}H_3)_3$), 49.8 (C-2), 53.2 (C-3), 61.4 ($O\underline{C}H_2CH_3$), 71.6 (C-5), 77.3 (C-6), 80.3 (C-4), 80.4 ($O\underline{C}(CH_3)_3$), 85.4 (C-1), 155.4 (NCO_2), 171.1 ($CO_2C_2H_5$); *m/z* (EI): 547(M^+), 376 (100 %).



181

Ethyl *syn-syn-syn*-6-*tert*-butoxycarbonylamino-3,4-*bis*(*tert*-butyldimethyl silyloxy)-5-hydroxycyclohex-1-ene-1-carboxylate 181:

To a solution of LiHMDS (231 mg, 1.38 mmol) in THF (20 cm^3) at –50°C was added a solution of oxanorbornene **180** (250 mg, 0.46 mmol) in THF (5 cm^3). The solution was stirred at 25°C for 2 hours. The reaction mixture was then quenched with ethyl acetate/ethanol (9:1) and stirred for 5 minutes. Saturated NH_4Cl solution was added to the reaction mixture and the resulting two layers were separated. The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure to give the crude product. Flash chromatography eluting with ethyl acetate /petroleum ether (3:2) afforded **181** as a pale yellow oil (129 mg, 56%); ν_{max} (KBr disk): 3412, 2987, 1732, 1688, 1534 cm^{-1}; δ_H (400 MHz, $CDCl_3$): 0.12 (12H, *s*, 2 x $Si(CH_3)_3$), 0.92 (9H, *s*, $SiC(CH_3)_3$), 0.93 (9H, *s*, $SiC(CH_3)_3$), 1.28 (3H, *t*, J = 7.2Hz, $OCH_2C\underline{H}_3$), 1.43 (9H, *s*, $OC(CH_3)_3$), 3.70 (1H, br, OH), 4.05 (1H, *m*, H-5), 4.08 (1H, *m*, H-6), 4.13 (1H, *t*, J = 2.4 Hz, H-4), 4.26 (2H, *q*, J = 7.2 Hz, $OC\underline{H}_2CH_3$), 4.52 (1H, *dd*, J = 3.2 and 2.4 Hz, H-3), 4.84 (2H, br, NH_2), 6.72 (1H, d, J = 3.2 Hz, H-2); δ_C (100 MHz, $CDCl_3$): 0.1 ($Si(CH_3)_2$), 18.8 ($OCH_2\underline{C}H_3$), 23.0 ($Si\underline{C}(CH_3)_3$), 30.6 ($SiC(\underline{C}H_3)_3$), 55.8 (C-6), 66.3 ($O\underline{C}H_2CH_3$), 73.8 (C-3), 76.4 (C-4), 77.4 (C-5), 118.7 (C-1), 132.1 (C-2), 170.2 (CO_2). *m/z* (ES^+): 568 (MNa^+).

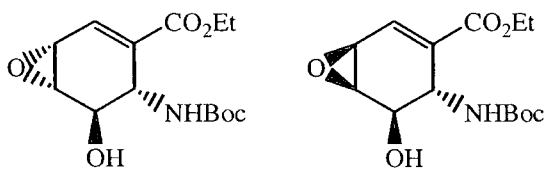


182

Ethyl *syn-syn-syn-syn*-3,4,5-triacetoxy-2-*tert*-butoxycarbonylamino-cyclo hexanecarboxylate 182:

To a solution of cyclohexene **179** (100 mg, 0.26 mmol) in ethanol (10 cm^3) was added 10% Pd/C (20 mg) and the suspension was stirred under hydrogen for 24 h. The suspension was then filtered and the filtrate was concentrated under reduced pressure to give **182** as a yellow oil (98 mg, 98%); ν_{max} (thin film): 3455, 2979, 1747, 1513 cm^{-1}

[1]; δ_H (500 MHz, $CDCl_3$): 1.22 (3H, *t*, J = 7.5 Hz, $OCH_2C\underline{H}_3$), 1.41 (9H, *s*, $OC(CH_3)_3$), 2.00 (3H, *s*, CH_3CO), 2.01 (6H, *s*, 2 x CH_3CO), 2.06 (2H, *m*, HH-6), 2.16 (3H, *s*, CH_3CO), 2.73 (1H, *m*, H-1), 4.22 (2H, *q*, J = 7.5 Hz, $OC\underline{H}_2CH_3$), 4.63 (1H, *m*, H-2), 4.87 (2H, *m*, H-4 and 5), 5.16 (1H, *d*, J = 11.0 Hz, NH), 5.53 (1H, *s*, H-3); δ_C (125 MHz, $CDCl_3$): 14.2 ($OCH_2\underline{C}H_3$), 20.8 ($\underline{C}H_3CO$), 21.0 (2 x $\underline{C}H_3CO$), 22.8 (C-6), 28.5 ($OC(\underline{C}H_3)_3$), 41.8 (C-1), 48.7 (C-2), 61.5 ($O\underline{C}H_2CH_3$), 68.6 (C-4), 68.7 (C-5), 70.5 (C-3), 79.7 ($O\underline{C}(CH_3)_3$), 155.8 (NCO_2), 169.4, 169.7, 170.1, 170.8 (carbonyls); *m/z* (ES^+): 468 (MNa^+).



183 **184**

Epoxidation of diene 3:

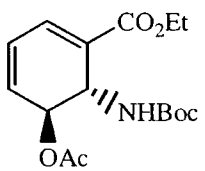
To a solution of diene **3** (1.00 g, 3.53 mmol) in CH_2Cl_2 (20 cm^3) was added mCPBA (1.23 g, 7.06 mmol) and $NaHCO_3$ (890 mg, 10.6 mmol). The mixture was stirred at room temperature for 36 hr. The mixture was then partitioned between concentrated $NaHCO_3$ solution (25 cm^3) and ethyl acetate (25 cm^3) and the layers were separated. The aqueous layer was extracted with ethyl acetate (2 x 25 cm^3) and the organic extractions were mixed, dried ($MgSO_4$) and concentrated under reduced pressure to give the crude product of 9:1 mixture of epoxides **183** as a colourless oil (721 mg, 68%) and **184** as a white gum (90 mg, 9%). The two isomers were separated by flash chromatography eluting with petroleum ether/ethyl acetate (7:4).

Ethyl *anti-anti*-6-*tert*-butoxycarbonylamino-3,4-epoxy-5-hydroxycyclohex-1-ene-1-carboxylate 183:

ν_{max} (thin film): 3439 (br), 2979, 1718, 1499 cm^{-1}; δ_H (500 MHz, $CDCl_3$): 1.27 (3H, *t*, J = 7.0 Hz, $OCH_2C\underline{H}_3$), 1.40 (9H, *s*, $OC(CH_3)_3$), 3.54 (1H, *t*, J = 4.0 Hz, H-3), 3.74 (1H, br, H-4), 4.24 (2H, *q*, J = 7.0 Hz, $OC\underline{H}_2CH_3$), 4.41 (1H, br, H-5), 4.73 (1H, *d*, J = 10.0 Hz, NH), 4.87 (1H, *d*, J = 10.0 Hz, H-6), 7.32 (1H, *d*, J = 4.0 Hz, H-2); δ_C (125 MHz, $CDCl_3$): 14.3 ($OCH_2\underline{C}H_3$), 28.6 ($OC(\underline{C}H_3)_3$), 46.4 (C-3), 49.3 (C-6), 58.1 (C-4), 61.4 ($O\underline{C}H_2CH_3$), 67.0 (C-5), 80.2 ($O\underline{C}(CH_3)_3$), 133.0 (C-1), 137.3 (C-2), 155.3 (NCO_2), 165 (CO_2); *m/z* (CI): 300 (MH^+, 25%), 261 (100%).

Ethyl *syn-anti*-6-*tert*-butoxycarbonylamino-3,4-epoxy-5-hydroxycyclohex-1-ene-1-carboxylate 184:

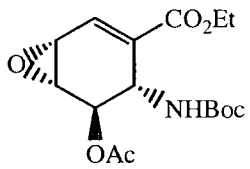
ν_{max} (thin film): 3435 (br), 2972, 1725, 1492 cm^{-1}; δ_H (500 MHz, $CDCl_3$): 1.28 (3H, *t*, J = 7.0 Hz, $OCH_2C\underline{H}_3$), 1.41 (9H, *s*, $OC(CH_3)_3$), 3.50 (1H, *t*, J = 4.0 Hz, H-3), 3.70 (1H, *dd*, J = 4.0 and 1.5 Hz, H-4), 4.18 (4H, *m*, $OC\underline{H}_2CH_3$, H-5, and H-6), 5.49 (1H, br, NH), 6.92 (1H, *d*, J = 4.0 Hz, H-2); δ_C (125 MHz, $CDCl_3$): 14.3 ($OCH_2\underline{C}H_3$), 28.5 ($OC(\underline{C}H_3)_3$), 48.3 (C-3), 52.5 (C-6), 55.6 (C-4), 61.5 ($O\underline{C}H_2CH_3$), 71.6 (C-5), 80.6 ($O\underline{C}(CH_3)_3$), 130.1 (C-1), 133.4 (C-2), 156.7 (NCO_2), 165.5 (CO_2); *m/z* (CI): 300 (MH^+, 20%), 166 (100%).



185

Ethyl *anti*-5-acetoxy-6-*tert*-butoxycarbonylamino-1,3-cyclohexadiene-1-carboxylate 185:

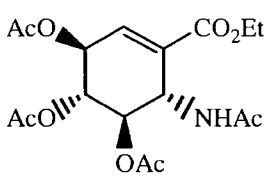
To a solution of cyclohexadiene **3** (500 mg, 1.77 mmol) in anhydrous pyridine (5 cm^3, 64.5 mmol) was added acetic anhydride (5 cm^3, 53.0 mmol). The reaction mixture was then stirred at room temperature for 20 hours. 2M HCl (20 cm^3) and ethyl acetate (20 cm^3) were added and the resulting layers were separated. The aqueous layer was extracted with ethyl acetate (2 x 20 cm^3) and the organic layers were combined, dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by flash chromatography eluting with petroleum ether/ethyl acetate (4:1) to give acetate **185** as a white solid (550 mg, 96%), mp 42-44°C; υ_{max} (KBr disk): 3285, 2983, 1737, 1717, 1679, 1648, 1527 cm^{-1}; δ_H (500 MHz, $CDCl_3$): 1.30 (3H, t, J = 7.0 Hz, $OCH_2C\underline{H}_3$), 1.42 (9H, s, $OC(CH_3)_3$), 2.00 (3H, s, CH_3CO), 4.28 (2H, q, J = 7.0 Hz, $OC\underline{H}_2CH_3$), 4.37 (1H, br, NH), 4.46 (1H, br, H-6), 5.25 (1H, br, H-5), 6.34 (2H, br, H-3 and 4), 7.17(IH, br, H-2); δ_C (125 MHz, $CDCl_3$): 14.1 ($OCH_2\underline{C}H_3$), 20.8 ($\underline{C}H_3CO$), 28.2 ($OC(\underline{C}H_3)_3$), 46.2 (C-6), 61.0 ($O\underline{C}H_2CH_3$), 68.8 (C-5), 80.0 ($O\underline{C}(CH_3)_3$), 126.6 and 127.8 (C-3 and 4) 128.7 (C-2), 133.1 (C-1), 154.6 (NCO_2), 165.5 ($CH_3\underline{C}O$), 169.8 ($\underline{C}O_2C_2H_5$); *m/z* (CI): 326 (MH^+, 100%) Anal. calcd. For $C_{16}H_{23}NO_6$: C, 59.06; H, 7.13; N, 4.31. found: C, 58.79; H, 7.11; N, 4.30.



186

Ethyl *anti-anti*-5-acetoxy-6-*tert*-butoxycarbonylamino-3,4-epoxy-5-acetoxycyclohex-1-ene-1-carboxylate 186:

To a solution of diene **185** (200 mg, 0.59 mmol) in CH_2Cl_2 (10 cm^3) was added mCPBA (310 mg, 1.77 mmol) and $NaHCO_3$ (300 mg, 3.52 mmol). The mixture was stirred at room temperature for 36 hours. The mixture was then partitioned between concentrated $NaHCO_3$ solution (25 cm^3) and ethyl acetate and the layers were separated. The aqueous layer was extracted with ethyl acetate (2 x 25 cm^3) and the organic extractions were combined, dried ($MgSO_4$) and concentrated under reduced pressure to give the crude product. Flash chromatography eluting with petroleum ether/ethyl acetate (7:3) gave epoxide **186** as a colourless oil (136 mg, 65%); ν_{max} (thin film): 3442, 2979, 1653, 1494 cm^{-1}; δ_H (400 MHz, $CDCl_3$): 1.25 (3H, *t*, J = 7.2 Hz, $OCH_2C\underline{H}_3$), 1.38 (9H, *s*, $OC(CH_3)_3$), 2.00 (3H, *s*, CH_3CO), 3.50 (1H, *dd*, J = 7.5 and 3.9 Hz, H-3), 3.79 (1H, *br*, H-4), 4.19 (2H, *q*, J = 7.2 Hz, $OC\underline{H}_2CH_3$), 4.16 (1H, *d*, J = 9.9 Hz, NH), 4.87 (1H, *d*, J = 9.9 Hz, H-6), 5.32 (1H, *br*, H-5), 7.28 (1H, *br*, H-2); δ_C (100 MHz, $CDCl_3$): 14.3 ($OCH_2\underline{C}H_3$), 21.0 ($\underline{C}H_3CO$), 28.5 ($OC(\underline{C}H_3)_3$), 46.3 (C-3), 46.8 (C-6), 55.6 (C-4), 61.5 ($O\underline{C}H_2CH_3$), 68.7 (C-5), 80.0 ($O\underline{C}(CH_3)_3$), 133.4 (C-1), 136.6 (C-2), 154.4 (NCO_2), 164.8 ($\underline{C}O_2C_2H_5$), 169.9 ($CH_3\underline{C}O$); *m/z* (CI): 342 (MH^+), 303 (100%); Anal. Calcd. For $C_{16}H_{23}NO_7$: C, 56.30; H, 6.79; N, 4.10. Found: C, 56.27; H, 6.85; N, 4.11.

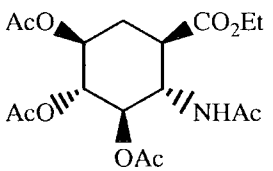


187

Ethyl *anti-anti-anti*-3,4,5-triacetoxy-2-N-acetylaminocyclohex-1-ene-1-carboxylate 187:

A solution of epoxide **186** (270 mg, 0.79 mmol) in H_2O/Acetone (1:1) was treated with $HClO_4$ (5 µl, 0.08 mmol). The solution was stirred at room temperature for 24 h and the solvent was removed under reduced pressure. The residue was stirred in pyridine (5 cm^3) and acetic anhydride (5 cm^3) for 24 h and then partitioned between

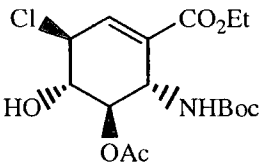
2M HCl (20 cm^3) and ethyl acetate (20 cm^3). The organic layer was washed with saturated $NaHCO_3$ (20 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure. The resulting residue was columned using petroleum ether/ ethyl acetate (7:3) as the eluting solvent to give **187** as a pale yellow gum (226 mg, 74%); ν_{max} (KBr disk): 3387, 2935, 1752, 1663, 1537 cm^{-3}; δ_H (500 MHz, $CDCl_3$): 1.27 (3H, *t*, J = 7.0 Hz, $OCH_2\underline{C}H_3$), 1.93 (3H, *s*, CH_3CO), 2.05 (3H, *s*, CH_3CO), 2.06 (3H, *s*, CH_3CO), 2.08 (3H, *s*, CH_3CO), 4.21 (2H, *q*, J = 7.0 Hz, $OC\underline{H}_2CH_3$), 5.01 (1H, *m*, H-6), 5.32 (2H, *m*, H-4 and H-5), 5.58 (1H, br, NH), 6.72 (1H, *d*, J = 4.5 Hz, H-2); δ_C (125 MHz, $CDCl_3$): 14.3 ($OCH_2\underline{C}H_3$), 20.9, 21.0 and 23.4 (4 x $\underline{C}H_3CO$), 49.7 (C-6), 61.7 ($O\underline{C}H_2CH_3$), 69.7 (C-3), 70.4 and 71.3 (C-4 and C-5), 132.0 (C-1), 135.0 (C-2), 164.6 (CO_2), 169.6, 169.7, 170.1 and 170.4 (4 x $CH_3\underline{C}O$); *m/z* (CI): 386 (MH^+), 208 (100%).



188

Ethyl *anti-anti-anti-anti*-3,4,5-triacetoxy-2-N-acetylaminocyclohexane-1-carboxylate 188:

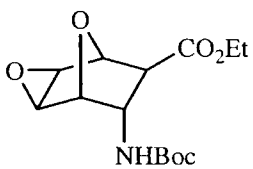
To a solution of ester **187** (100 mg, 0.26 mmol) in ethanol (10 cm^3) was added 10% Pd/C (20 mg) and the suspension was stirred under hydrogen for 24 h. The suspension was then filtered and the filtrate was concentrated under reduced pressure to give **188** as a white gum (98 mg, 98%); ν_{max} (KBr disk): 3247, 2947, 1741, 1660, 1565 cm^{-1}; δ_H (500 MHz, $CDCl_3$): 1.23 (3H, *t*, J = 7.0 Hz, $OCH_2\underline{C}H_3$), 1.88 (1H, *m*, H-6), 1.90 (3H, *s*, CH_3CON), 2.01 (3H, *s*, CH_3CO), 2,03 (3H, *s*, 2 x CH_3CO), 2.28 (1H, *t*, J = 13.0 Hz, H-6), 2.57 (1H, *dt*, J = 13.0 and 3.5 Hz, H-1), 4.12 (2H, *q*, J = 7.0 Hz, $OC\underline{H}_2CH_3$), 4.33 (1H, *q*, J = 10.0 Hz, H-2), 4.88 (1H, *m*, H-5), 4.96 (1H, *t*, J = 10.0 Hz, H-3), 5.21 (1H, *t*, J = 10.0 Hz, H-4), 5.49 (1H, *d*, J = 10.0 Hz, NH); δ_C (125 MHz, $CDCl_3$): 14.3 ($OCH_2\underline{C}H_3$), 20.9 and 21.1 (3 x $\underline{C}H_3CO$), 23.4 ($\underline{C}H_3CON$), 30.3 (C-6), 44.4 (C-1), 52.5 (C-2), 61.8 ($O\underline{C}H_2CH_3$), 70.6 (C-5), 72.9 (C-4), 73.2 (C-3), 169.8, 170.4, 170.8 and 171.3 (carbonyls); *m/z* (CI): 388 (MH^+, 100%); HRMS (ES^+): $C_{17}H_{25}NO_9Na$ requires M^+, 410.1427. Found: 410.1467.



189

Ethyl *anti-anti-anti*-5-acetoxy-6-*tert*-butoxycarbonylamino-3-chloro-4-hydroxy-1-cyclohexene-1-carboxylate 189:

To solution of epoxide **186** (240 mg, 0.75mmol) in dichloromethane was added acetic acid (120 µl, 2.10 mmol) and $ZnCl_2$ (102mg, 0.75mmol). The mixture was stirred at room temperature until all the starting material was consumed (TLC ca. 12 h). The solvent was remove under reduced pressure and the residue was subjected to column chromatography eluting with petroleum ether/ethyl acetate (7:3) to give **189** as a white solid (200 mg, 83%); m.p 158-160°C; ν_{max} (KBr disk): 3447 (br), 2979, 1765, 1703, 1652, 1536 cm^{-1}; δ_H (500 MHz, $CDCl_3$): 1.30 (3H, *t*, J = 7.0 Hz, $OCH_2C\underline{H}_3$), 1.42 (9H, *s*, $OC(CH_3)_3$), 2.10 (3H, *s*, CH_3CO), 2.86 (1H, br, OH), 4.12 (1H, *m*, H-4), 4.24 (2H, *q*, J = 7.0 Hz, $OC\underline{H}_2CH_3$), 4.61 (2H, *m*, H-3 and 6), 4.80 (1H, br, NH), 5.16 (1H, br, H-5), 6.81 (1H, *s*, H-2); δ_C (125 MHz, $CDCl_3$): 14.3 ($OCH_2\underline{C}H_3$), 21.1 ($\underline{C}H_3CO$), 28.5 ($OC(\underline{C}H_3)_3$), 50.3 (C-3), 57.3 (C-6), 61.7 ($O\underline{C}H_2CH_3$), 72.8 (C-4), 73.7 (C-5), 80.9 ($O\underline{C}(CH_3)_3$), 131.7 (C-1), 136.5 (C-2), 155.2 (NCO_2), 165.0 (CO_2), 170.9 ($CH_3\underline{C}O$); *m/z* (ES^+): 400 (MNa^+).

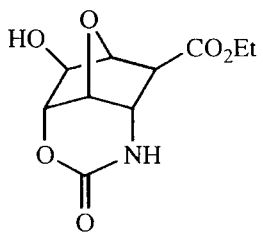


190

Ethyl *endo*-3-*tert*-butoxycarbonylamino-5,6-epoxy-7-oxabicyclo[2,2,1]hexane-2-carboxylate 190:

To a stirred solution of the bicyclic alkene **2** (500 mg, 1.77 mmol) in CH_2Cl_2(10 cm^3) was added solid $NaHCO_3$(300 mg, 3.54 mmol) and *m*CPBA (305 mg, 1.77 mmol). After 28 hours the reaction was quenched with 20% aqueous solution of Na_2SO_3 (5 cm^3) and the resulting layers were separated. The aqueous layer was extracted with CH_2Cl_2 (10 cm^3 x 2) and the combined organic extracts were washed with H_2O, dried ($MgSO_4$) and evaporated under reduced pressure. The resulting residue was purified by flash chromatography eluting with $(CH_3CH_2)_2O$/petroleum ether (7:3) to give

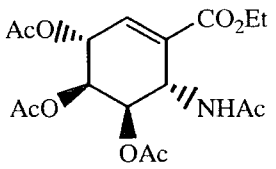
epoxide **190** as a white solid (322 mg, 61%), mp 34-36°C; υ_{max} (KBr disk): 3378, 2979, 1717, 1521 cm^{-1}; δ_H (500MHz, $CDCl_3$): 1.28 (3H, t, J = 7.0 Hz, $OCH_2C\underline{H}_3$), 1.44 (9H, s, $OC(CH_3)_3$), 2.25 (1H, d, J = 4.5, H-2), 3.47 (1H, d, J = 3.5, H-6), 3.59 (1H, d, J = 3.5, H-5), 4.21 (2H, q, J = 7.0 Hz, $OC\underline{H}_2CH_3$), 4.42 (1H, m, H-3), 4.74 (3H, br, C-1, C-4, NH). δ_C (125 MHz, $CDCl_3$): 14.4 ($OCH_2\underline{C}H_3$), 28.5 ($OC(\underline{C}H_3)_3$), 48.4 (C-5), 49.5 (C-6), 52.4 (C-2), 57.8 (C-3), 61.9 ($O\underline{C}H_2CH_3$), 75.0, 77.0 (C-1, C-4), 81.0 ($O\underline{C}(CH_3)_3$), 155.4 ($N\underline{C}O_2$), 170.8 ($CO_2C_2H_5$); *m/z* (EI): 299 (M^+), 57 (100%); Anal. Calcd. for $C_{14}H_{21}NO_6$: C, 56.18; H, 7.07; N, 4.68. Found: C, 56.17; H, 7.21; N, 4.47.



191

Ethyl 2-hydroxy-5-oxo-4,9-dioxa-6-azatricyclo[3,3,1,$1^{1,8}$]decane-10-carboxylate 191:

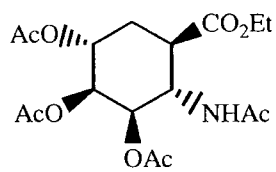
A solution of epoxide **190** (200 mg, 1.01 mmol) in $AcOH/H_2O$ (9:1, 10 cm^3) was stirred at room temperature for 30 minutes. The reaction was quenched with sat. $NaHCO_3$ (10 cm^3). The resulting solution was extracted with ethyl acetate (10 cm^3 x 3). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure to afford the crude product. Purification of the crude product by flash chromatography eluting with ethyl acetate/hexane (7:3) gave **191** (120 mg, 75%) as a white solid, mp 37-39°C; υ_{max} (KBr disk): 3448 (br), 2979, 1733, 1681, 1463 cm^{-1}; δ_H (400 MHz, $CDCl_3$): 1.29 (3H, t, J = 7.2 Hz, $OCH_2C\underline{H}_3$), 2.59 (1H, d, J = 2.4 Hz, H-10), 3.83 (1H, d, J = 1.2 Hz, H-2), 4.21 (2H, q, J = 7.2 Hz, $OC\underline{H}_2CH_3$), 4.32 (1H, m, H-7), 4.54 (1H, t, J = 1.2 and 1.5 Hz, H-8), 4.61 (2H, m, H-1 and 3), 5.98 (1H, br, NH); δ_C (100 MHz, $CDCl_3$): 14.1 ($OCH_2\underline{C}H_3$), 53.1 (C-7), 54.3 (C-10), 61.9 ($O\underline{C}H_2CH_3$), 67.2 (C-8), 75.6 (C-2), 79.1 (C-2), 85.1 and 85.5 (C-1 and 3), 150.1 (C-5), 170.1 ($CO_2C_2H_5$); *m/z* (EI): 243 (M^+), 98 (100%); Anal. Calcd. For $C_{10}H_{13}NO_6$: C, 49.38; H, 5.39; N, 5.76. Found: C, 49.22; H, 5.15; N, 5.84.



194

Ethyl *anti-syn-anti*-3,4,5-triacetoxy-6-N-acetylaminocyclohex-1-ene-1-carboxylate 194:

A solution of epoxide **184** (270 mg, 0.79 mmol) in H_2O/Acetone (1:1) was treated with $HClO_4$ (5 µl, 0.08 mmol). The solution was stirred at room temperature for 24 h and the solvent was removed under reduced pressure. The residue was stirred in pyridine (5 cm^3) and acetic anhydride (5 cm^3) for 24 h and then partitioned between 2M HCl (20 cm^3) and ethyl acetate (20 cm^3). The organic layer was washed with saturated $NaHCO_3$ (20 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure. The resulting residue was columned using petroleum ether/ ethyl acetate (7:3) as the eluting solvent to give **194** as a pale yellow gum (226 mg, 74%); ν_{max} (KBr disk): 3379, 2996, 1744, 1663, 1543 cm^{-1}; δ_H (500 MHz, $CDCl_3$): 1.26 (3H, *t*, J = 7.0 Hz, $OCH_2\underline{CH_3}$), 1.97 (3H, *s*, CH_3CO), 2.01 (3H, *s*, CH_3CO), 2.06 (3H, *s*, CH_3CO), 2.08 (3H, *s*, CH_3CO), 4.27 (2H, *q*, J = 7.0 Hz, $O\underline{CH_2}CH_3$), 4.97 (1H, *dd*, J = 8.5 and 3.5 Hz, H-6), 5.28 (1H, *dd*, J = 8.5 and 2.5 Hz, H-4), 5.39 (1H, *dd*, J = 8.5 and 3.5 Hz, H-5), 5.57 (1H, *dd*, J = 8.5 and 2.5 Hz, H-3), 5.85 (1H, *d*, J = 8.5 Hz, NH), 6.87 (1H, *d*, J = 2.5 Hz, H-2); δ_C (125 MHz, $CDCl_3$): 14.3 ($OCH_2\underline{CH_3}$), 21.0 ($\underline{CH_3}CO$), 21.1 (2 x $\underline{CH_3}CO$), 23.3 ($\underline{CH_3}CO$), 47.7 (C-6), 61.8 ($O\underline{CH_2}CH_3$), 68.9 (C-4), 69.0 (C-3), 70.4 (C-5), 130.5 (C-1), 138.0 (C-2), 164.6, 169.6, 169.7 and 170.5 (carbonyls); *m/z* (CI): 386 (MH^+, 100%).

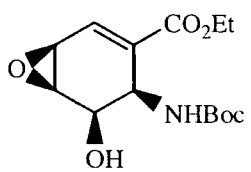


195

Ethyl *anti-anti-syn-anti*-3,4,5-triacetoxy-2-N-acetylaminocyclohexane-1-carboxylate 195:

To a solution of cyclohexene **194** (100 mg, 0.26 mmol) in ethanol (10 cm^3) was added 10% Pd/C (20 mg) and the suspension was stirred under hydrogen for 48 h. The suspension was then filtered and the filtrate was concentrated under reduced pressure to give **195** as a colourless gum (98 mg, 99%); ν_{max} (KBr disk): 3379, 2981, 1743,

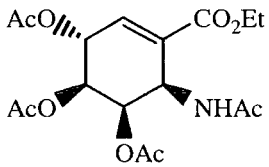
1549 cm^{-1}; δ_H (500 MHz, $CDCl_3$):1.24 (3H, t, J = 7.0 Hz, $OCH_2C\underline{H}_3$), 1.90 (3H, *s*, CH_3CO), 2.00 (3H, *s*, CH_3CO), 2.03 (1H, *m*, H-6), 2.10 (3H, *s*, CH_3CO), 2.16 (3H, *s*, CH_3CO), 2.17 (1H, *m*, H-6), 2.71 (1H, *dt*, J = 11.5 and 4.0 Hz, H-1), 4.14 (2H, *q*, J = 7.0 Hz, $OC\underline{H}_2CH_3$), 4.52 (1H, *q*, J = 11.5 Hz, H-2), 5.04 (1H, *m*, H-5), 5.14 (1H, *dd*, J = 11.5 and 3.0 Hz, H-3), 5.25 (1H, *t*, J = 3.0 Hz, H-4), 5.50 (1H, *d*, J = 11.5 Hz, NH); δ_C (125 MHz, $CDCl_3$): 14.4 ($OCH_2\underline{C}H_3$), 21.0 ($\underline{C}H_3CO$), 21.3 ($\underline{C}H_3CO$), 23.5 ($\underline{C}H_3CO$), 27.8 (C-6), 43.8 (C-1), 49.4 (C-2), 61.6 ($O\underline{C}H_2CH_3$), 68.6 (C-5), 68.8 (C-4), 70.3 (C-3), 169.4, 169.8, 170.0, 171.3 and 171.8 (carbonyls); *m/z* (CI): 388 (MH^+, 100%); HRMS (ES^+): Found M^+, 410.1417. $C_{17}H_{25}NO_9$ requires 410.1427.



196

Ethyl *syn-syn*-6-*tert*-butoxycarbonylamino-3,4-epoxy-5-hydroxycyclohex-1-ene-1-carboxylate

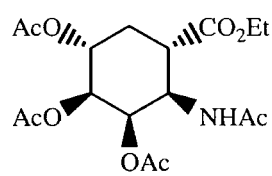
To a solution of diene **159** (1.00 g, 3.53 mmol) in CH_2Cl_2 (20 cm^3) was added *m*CPBA (1.23 g, 7.06 mmol) and $NaHCO_3$ (890 mg, 10.6 mmol). The mixture was stirred at room temperature for 36 hr. The mixture was then partitioned between concentrated $NaHCO_3$ solution (25 cm^3) and ethyl acetate (25 cm^3) and the layers were separated. The aqueous layer was extracted with ethyl acetate (2 x 25 cm^3) and the organic extractions were mixed, dried ($MgSO_4$) and concentrated under reduced pressure to give the crude product **196** as a white gum (865 mg, 82%); ν_{max} (KBr disk): 3437, 2979, 1720, 1498 cm^{-1}; δ_H (500 MHz, $CDCl_3$): 1.27 (3H, *t*, J = 7.5 Hz, $OCH_2C\underline{H}_3$), 1.41 (9H, *s*, $OC(CH_3)_3$), 3.24 (1H, *br*, OH), 3.53 (1H, *dd*, J = 4.5 and 4.0 Hz, H-3), 3.67 (1H, *m*, H-4), 4.21 (3H, *m*, $OC\underline{H}_2CH_3$ and H-5), 4.80 (1H, *d*, J = 8.5 Hz, NH), 4.98 (1H, *dd*, J = 8.5 and 4.5 Hz, H-6), 7.16 (1H, *d*, J = 4.0 Hz, H-2); δ_C (125 MHz, $CDCl_3$): 14.3 ($OCH_2\underline{C}H_3$), 28.5 ($OC(\underline{C}H_3)_3$), 47.8 (C-6), 48.3 (C-2), 59.0 (C-4), 61.6 ($O\underline{C}H_2CH_3$), 68.4 (C-5), 80.2 ($O\underline{C}(CH_3)_3$), 135.6 (C-1), 136.8 (C-2), 156.9 (NCO_2), 164.7 (CO_2); *m/z* (ES^+): 322 (MNa^+, 100%).



197

Ethyl *anti-syn-syn*-3,4,5-triacetoxy-2-N-acetylaminocyclohex-1-ene-1-carboxylate 197:

A solution of epoxide **196** (270 mg, 0.79 mmol) in H_2O/Acetone (1:1) was treated with $HClO_4$ (5 µl, 0.08 mmol). The solution was stirred at room temperature for 24 h and the solvent was removed under reduced pressure. The residue was stirred in pyridine (5 cm^3) and acetic anhydride (5 cm^3) for 24 h and then partitioned between 2M HCl (20 cm^3) and ethyl acetate (20 cm^3). The organic layer was washed with saturated $NaHCO_3$ (20 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure. The resulting residue was columned using petroleum ether/ ethyl acetate (7:3) as the eluting solvent to give **197** as a pale yellow gum (218 mg, 72%); ν_{max} (KBr disk):3377, 2989, 1745, 1675, 1535 cm^{-1}; δ_H (500 MHz, $CDCl_3$): 1.26 (3H, *t*, J = 7.0 Hz, $OCH_2C\underline{H}_3$), 1.96 (3H, *s*, CH_3CON), 2.08 (3H, *s*, CH_3CO), 2.09 (3H, *s*, CH_3CO), 2.10 (3H, *s*, CH_3CO), 4.23 (2H, *q*, J = 7.0 Hz, $OC\underline{H}_2CH_3$), 5.22 (1H, *dd*, J = 5.5 and 2.0 Hz, H-4), 5.46 (2H, *m*, H-5 and 6), 5.58 (2H, *m*, H-3 and NH), 6.82 (1H, *d*, J = 2.5 Hz, H-2); δ_C (125 MHz, $CDCl_3$): 14.3 ($OCH_2\underline{C}H_3$), 21.0 ($\underline{C}H_3CO$) 21.1 (2 x $\underline{C}H_3CO$), 23.4 ($\underline{C}H_3CON$), 44.8 (C-6), 61.8 ($O\underline{C}H_2CH_3$), 68.0 (C-3), 68.4 (C-5), 70.6 (C-4), 133.2 (C-1), 135.0 (C-2), 164.9 ($CH_3\underline{C}ON$), 169.1, 169.3, 169.9, 170.0 (carbonyls); *m/z* (ES^+): 408 (MNa^+, 100%).

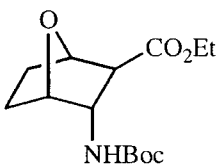


198

Ethyl *anti-syn-syn-anti*-3,4,5-triacetoxy-2-N-acetylaminocyclohexane-1-carboxylate 198:

To a solution of cyclohexene **197** (100 mg, 0.26 mmol) in ethanol (10 cm^3) was added 10% Pd/C (20 mg) and the suspension was stirred under hydrogen for 24 h. The suspension was then filtered and the filtrate was concentrated under reduced pressure to give **198** as a white solid (98 mg, 98 %); m.p. 196-198°C; ν_{max} (KBr disk): 3271, 2986, 1747, 1651, 1556 cm^{-1}; δ_H (500 MHz, $CDCl_3$): 1.23 (3H, *t*, J = 7.0 Hz,

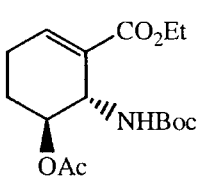
$OCH_2C\underline{H}_3$), 1.79 (2H, *m*, H-6), 1.91 (3H, *s*, CH_3CO), 1.97 (3H, *s*, CH_3CON), 2.03 (3H, *s*, CH_3CO), 2.16 (3H, *s*, CH_3CO), 2.77 (1H, *m*, H-1), 4.12 (2H, *q*, J = 7.0 Hz, $OC\underline{H}_2CH_3$), 4.50 (1H, *m*, H-2), 5.05 (2H, *m*, H-4 and 5), 5.50 (1H, br, H-3), 5.56 (1H, *d*, J = 8.0 Hz, NH); δ_C (125 MHz, $CDCl_3$): 14.3 ($OCH_2\underline{C}H_3$), 20.8 ($\underline{C}H_3CO$), 21.2 ($\underline{C}H_3CO$), 21.2 ($\underline{C}H_3CO$), 23.3 ($\underline{C}H_3CON$), 30.0 (C-6), 42.7 (C-1), 49.6 (C-2), 61.7 ($O\underline{C}H_2CH_3$), 68.5 (C-5), 71.5 (C-3), 71.8 (C-4), 169.3, 169.9, 170.0, 170.7, 171.4 (carbonyls); *m/z* (ES^+): 410 (MNa^+).



201

Ethyl *endo*-3-*tert*-butoxycarbonylamino-7-oxabicyclo[2,2,1]heptane-*exo*-2-carboxylate 201:

Bicyclic alkene **2** (400 mg, 1.40 mmol) was stirred with 10% Pd/C (80 mg) in ethanol (15 cm^3) under hydrogen over night. After the reaction, Pd/C was filtered off and the filtrate was concentrated under reduced pressure to give the saturated adduct **201** (390 mg, 98%) as a white solid, mp 92-94°C; υ_{max} (KBr disk): 3346 (br), 2992, 1739, 1709, 1523 cm^{-1}; δ_H (500 MHz, $CDCl_3$): 1.26 (3H, t, J = 7.2 Hz, $OCH_2C\underline{H}_3$), 1.43 (9H, s, $OC(C\underline{H}_3)_3$), 1.84 (4H, m, H-5 and 6), 2.14 (1H, d, J = 5.0 Hz, H-2), 4.17 (2H, q, J = 7.2 Hz, $OC\underline{H}_2CH_3$), 4.22 (1H, br, H-3), 4.72 (2H, br, H-1 and 4), 5.40 (1H, br, NH); δ_C (125 MHz, $CDCl_3$): 14.1 ($OCH_2\underline{C}H_3$), 30.0 (C-5 and 6), 28.3 ($OC(\underline{C}H_3)_3$), 55.0 (C-2), 56.2 (C-3), 61.1 ($O\underline{C}H_2CH_3$), 78.3 and 79.6 (C-1 and 4), 80.1 ($O\underline{C}(CH_3)_3$), 155.2 (NCO_2), 172.0 ($CO_2C_2H_5$); *m/z* (EI): 285 (M^+), 57 (100%); Anal. calcd. for $C_{14}H_{23}NO_5$: C, 58.93; H, 8.12; N, 4.91. Found: C, 58.23; H, 8.07; N, 4.74.

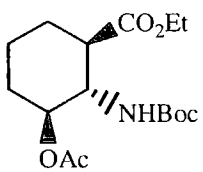


202

Ethyl *trans*-5-acetoxy-6-*tert*-butoxycarbonylaminocyclohex-1-ene-1-carboxylate 202:

To a solution of KHMDS (530 mg, 2.64 mmol) in THF (10 cm^3) at –50 °C was added a solution of adduct **201** (250 mg, 0.88 mmol) in THF (2.5 cm^3). The solution was

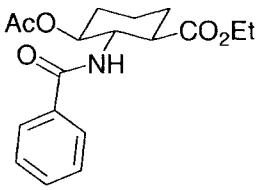
then warmed up to room temperature (20 minutes) and quenched with a mixture of ethyl acetate and ethanol (50 cm^3, 19:1). The mixture was washed with sat. NH_4Cl (25 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure. The resulting residue was purified by flash chromatography eluting with petroleum ether/ethyl acetate mixture (3:2) to give cyclohexene **202** as a pale yellow gum (359 mg, 68%). ν_{max} (KBr disk): 3361, 2969, 1713, 1652, 1515 cm^{-1}; δ_H (500 MHz, $CDCl_3$): 1.28 (3H, *t*, J = 7.0 Hz, $OCH_2C\underline{H}_3$), 1.44 (9H, *s*, $OC(CH_3)_3$), 1.71 (2H, *m*, H-4), 2.03 (3H, *s*, CH_3CO), 2.25 (2H, *m*, H-3), 4.20 (2H, *q*, J = 7.0 Hz, $OC\underline{H}_2CH_3$), 4.40 (1H, br, NH), 4.49 (1H, br, H-6), 5.08 (1H, br, H-5), 7.19 (1H, *dd*, J = 4.2 and 2.3 Hz, H-2); δ_C (125 MHz, $CDCl_3$): 14.1 ($OCH_2\underline{C}H_3$), 20.7 (C-4), 21.1 (C-3), 21.3 ($\underline{C}H_3CO$), 28.3 ($OC(\underline{C}H_3)_3$), 47.0 (C-6), 60.7 ($O\underline{C}H_2CH_3$), 70.5 (C-5); 79.7 ($O\underline{C}(CH_3)_3$), 128.1 (C-1), 143.0 (C-2), 154.5 (NCO_2), 165.9 ($CH_3\underline{C}O$), 170.0 (CO_2); *m/z* (CI): 328 (MH^+, 100%).



203

Ethyl *anti-anti*-3-acetoxy-2-*tert*-butoxycarbonylaminocyclohexanecarboxylate 203:

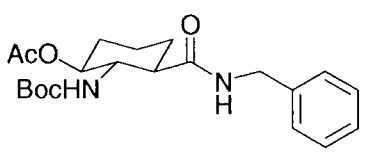
To solution of cyclohexene **202** (500 mg, 1.77 mmol) in ethanol (20 cm^3) was added 10% Pd/C (100 mg) and the solution was stirred under hydrogen for 48 h. The reaction mixture was then filtered and the filtrate was concentrated under reduced pressure to give ACHC derivative **203** as a colourless oil (498 mg, 99%); ν_{max} (liq. film): 3367 (br), 2938, 1727, 1688, 1535 cm^{-1}; δ_H (500MHz, $CDCl_3$): 1.23 (3H, *t*, J = 7.5 Hz, $OCH_2C\underline{H}_3$), 1.40 (9H, *s*, $OC(CH_3)_3$), 1.52 and 1.77 (2H, *m*, HH-5), 1.54 and 1.87 (2H, *m*, HH-6), 1.55 and 2.05 (2H, *m*, HH-4), 2.08 (3H, *s*, CH_3CO), 2.36 (1H, *dt*, J = 12.3 and 3.9 Hz, H-1), 3.22 (1H, br, OH), 3.42 (1H, br, H-3), 3.49 (1H, br, H-2), 4.12 (2H, *q*, J = 7.5 Hz, $OC\underline{H}_2CH_3$), 4.81 (1H, br, NH); δ_C (125 MHz, $CDCl_3$): 14.4 ($OCH_2\underline{C}H_3$), 23.1 (C-6), 28.5 ($OC(\underline{C}H_3)_3$), 28.8 (C-5), 33.9 (C-4), 48.6 (C-1), 58.3 (C-2), 60.9 ($O\underline{C}H_2CH_3$), 74.1 (C-3), 80.2 ($O\underline{C}(CH_3)_3$), 157.0 (NCO_2), 173.4 ($\underline{C}O_2Et$); *m/z* (CI): 330 (MH^+, 53%), 232 (100%).



205

Ethyl *anti-anti*-3-acetoxy-2-N-benzoylaminocyclohexane-1-carboxylate 205:

To a solution of **202** (200 mg, 0.61 mmol) in CH_2Cl_2 (10 cm^3) was added TFA (0.1 cm^3, 1.31 mmol) and the mixture was stirred at 25 °C for 5 h. The solvent was then removed under pressure and the residue was suspended in CH_2Cl_2, treated with triethylamine (1.0 cm^3, 7.22 mmol), benzoic acid (100 mg, 0.73 mmol) and PyBop (455 mg, 0.875 mmol) and the mixture was stirred for 16 h. The reaction mixture was then washed with 1 M HCl (20 cm^3) and the solvent was removed under pressure. The residue was recrystalized from $CHCl_3$ to give **205** as colourless crystals (171 mg, 84 %); m.p. 176-178°C; ν_{max} (KBr disk): 3268, 2943, 1731, 1645, 1558 cm^{-1}; δ_H (500 MHz, $CDCl_3$): 1.11 (3H, *t*, J = 7.0 Hz, $OCH_2C\underline{H}_3$), 1.40 (1H, *m*, H-5), 1.63 (1H, *m*, H-4), 1.70 (1H, *m*, H-6), 1.86 (1H, *m*, H-5), 1.93 (1H, *m*, H-6), 1.95 (3H, *s*, CH_3CO), 2.01 (1H, *m*, H-4), 2.48 (1H, *dt*, J = 11.5 and 3.0 Hz, H-1), 4.07 (2H, *q*, J = 7.0 Hz, $OC\underline{H}_2CH_3$), 4.40 (1H, *m*, H-2), 4.87 (1H, *dt*, J = 11.5 and 4.5 Hz, H-3), 6.20 (1H, *d*, J = 9.5 Hz, NH), 7.38 (2H, *t*, J = 7.5 Hz, H-3' and 5'), 7.45 (1H, *t*, J = 7.5 Hz, H-4'), 7.67 (2H, *d*, J = 7.5 Hz, H-2' and 6'); δ_C (125 MHz, $CDCl_3$): 14.3 ($OCH_2\underline{C}H_3$), 21.3 ($\underline{C}H_3CO$), 23.1 (C-5), 28.3 (C-6), 31.0 (C-4), 49.6 (C-1), 54.5 (C-2), 61.3 ($O\underline{C}H_2CH_3$), 74.1 (C-3), 127.1 (C-2' and 6'), 128.8 (C-3'and 5'), 131.7 (C-4'), 134.8 (C-1'), 167.0 (CO_2), 171.9 ($CH_3\underline{C}O$), 172.7 (PhCON); *m/z* (ES^+): 356 (MNa^+, 100%); Anal. calcd. For $C_{18}H_{25}NO_5$: C, 64.85; H, 6.95; N, 4.20. Found: C, 64.88; H, 6.96; N, 4.21.

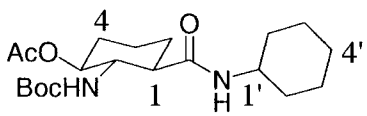


207

N-Benzyl-[*anti-anti*-3-acetoxy-2-*tert*-butoxycarbonylamino-cyclohexane-1-carboxyl]amide 207:

A solution of **206** (250 mg, 1.09 mmol), benzylamine (0.14 cm3, 1.31 mmol), and triethylamine in CH_2Cl_2 (10 cm^3) was treated with HATU (501 mg, 1.31 mmol) and the reaction was stirred for 16 h. 1 M HCl (20 cm^3) was added to the reaction mixture

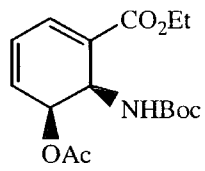
and the layers were separated. The organic layer was then dried ($MgSO_4$), concentrated under reduced pressure and recrystalisation from ethyl acetate afforded **207** as a white solid (360 mg, 87%); m.p. 182-184 °C; ν_{max} (KBr disk): 3450, 2933, 1734, 1689,1644 cm^{-1}; δ_H (500 MHz, CD_3OD): 1.39 (9H, *s*, $OC(CH_3)_3$), 1.45 (2H, *m*, HH-4), 1.57 (2H, *m*, HH-5), 1.83 (2H, *m*, HH-6), 2.00 (3H, *s*, CH_3CO), 2.45 (1H, *dt*, J = 11.6 and 3.2 Hz, H-1), 3.74 (1H, *t*, J = 11.6 Hz, H-2), 4.25 (1H, *d*, J = 14.8 Hz, NCH_2Ph), 4.47 (1H, *d*, J = 14.8 Hz, NCH_2Ph), 4.75 (1H, *m*, H-3), 7.28 (5H, *m*, aromatic protons); δ_C (100 MHz, CD_3OD): 19.9 ($\underline{C}H_3CO$), 22.8 (C-5), 27.6 ($OC(\underline{C}H_3)_3$), 29.1 (C-6), 30.8 (C-4), 42.9 ($N\underline{C}H_2Ph$), 49.4 (C-1), 54.6 (C-2), 74.9 (C-3), 78.7 ($O\underline{C}(CH_3)_3$), 126.9, 127.3, 128.4, 138.7 (Ph carbons), 156.5 (NCO_2), 174.1 (NCO), 174.4 ($CH_3\underline{C}O$); *m/z* (ES^+): 413 (MNa^+)



208

N-Cyclohexyl-[*anti-anti*-3-acetoxy-2-*tert*-butoxycarbonylamino-cyclohexanecarboxyl]amide 208:

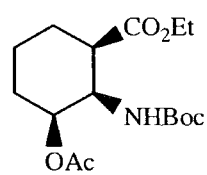
Employing the same procedure as that described for the synthesis of **207**, **206** (250 mg, 1.09 mmol) afforded **208** as a white solid (292 mg, 72%); m.p. 260-262 °C; ν_{max} (KBr disk): 3311, 2933, 1738, 1693, 1645, 1547 cm^{-1}; δ_H (400 MHz, DMSO): 1.12 (1H, *m*, H-4'), 1.23 (4H, *m*, HH-3' and 5'), 1.35 (9H, *s*, $OC(CH_3)_3$), 1.41 (2H, *m*, HH-5), 1.63 (4H, *m*, HH-2' and 6'), 1.84 (4H, *m*, HH-4 and 6), 2.01 (3H, *s*, CH_3CO), 2.53 (1H, *dd*, J = 9.0 and 10.2 Hz, H-1), 3.48 (2H, *m*, H-1' and H-2), 4.57 (1H, *m*, H-3); δ_C (100 MHz, DMSO): 21.4 (C-3'), 23.2 (C-6), 23.6 (C-4'), 24.8 (C-5'), 25.9 (C-5), 28.8 ($OC(\underline{C}H_3)_3$), 31.2 (C-2'), 31.5 (C-6'), 32.8 (C-4), 38.9 (C-1), 46.4 (C-2), 48.3 (C-1'), 76.0 (C-3), 79.3 ($O\underline{C}(CH_3)_3$), 152.3 (NCO_2), 166.3 (NCO), 170.5 ($CH_3\underline{C}O$); *m/z* (ES^+): 405 (MNa^+).



209

Ethyl *syn*-5-acetoxy-6-*tert*-butoxycarbonylamino-1,3-cyclohexadiene-1-carboxylate 209:

To a solution of cyclohexadiene **159** (500 mg, 1.77 mmol) in CH_2Cl_2 anhydrous pyridine (0.5 cm^3, 6.45 mmol) was added acetic anhydride (0.5 cm^3, 5.30 mmol). The reaction mixture was then stirred at room temperature for 20 hours. The solvent was removed under reduced pressure and the crude product was purified by flash chromatography eluting with petroleum ether/ethyl acetate (4:1) to give acetate **209** as a yellow solid (449 mg, 78%); m.p. 76-78°C; ν_{max} (KBr disk): 3330, 2984, 1710,1522 cm^{-1}; δ_H (500 MHz, $CDCl_3$): 1.27 (3H, *t*, J = 7.0 Hz, $OCH_2\underline{CH_3}$), 1.41 (9H, *s*, $OC(CH_3)_3$), 2.09 (3H, *s*, CH_3CO), 4.25 (2H, *q*, J = 7.0 Hz, $OC\underline{H_2}CH_3$), 4.56 (1H, *d*, J = 10.0 Hz, NH), 5.00 (1H, *dd*, J = 10.0 and 7.5 Hz, H-6), 5.66 (1H, *d*, J = 7.5 Hz, H-5), 6.00 (1H, *d*, J = 9.5 Hz, H-4), 6.16 (1H, *dd*, J = 9.5 and 5.5 Hz, H-3), 7.12 (1H, *d*, J = 5.5 Hz, H-2), δ_C (125 MHz, $CDCl_3$): 14.3 ($OCH_2\underline{C}H_3$), 21.2 ($\underline{C}H_3CO$), 28.5 ($OC(\underline{C}H_3)_3$), 43.7 (C-6), 61.2 ($O\underline{C}H_2CH_3$), 71.6 (C-5), 79.7 ($O\underline{C}(CH_3)_3$), 124.0 (C-3), 128.6 (C-1), 134.0 (C-2), 134.3 (C-4), 155.2 (NCO_2), 165.8 (CO_2), 170.5 ($CH_3\underline{C}O$); *m/z* (CI): 326 (MH^+, 100%).

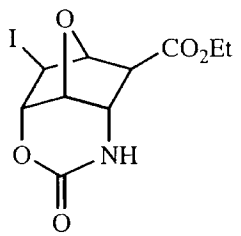


210

Ethyl *syn-syn*-3-acetoxy-2-*tert*-butoxycarbonylaminocyclohexanecarboxylate 210:

To solution of cyclohexene **209** (250 mg, 0.77 mmol) in ethanol (20 cm^3) was added 10% Pd/C (100 mg) and the solution was stirred under hydrogen for 48 h. The reaction mixture was then filtered and the filtrate was concentrated under reduced pressure to give ACHC derivative **210** as a white solid (243 mg, 96%); m.p. 53-55 °C; ν_{max} (KBr disk): 3373, 2982, 1744, 1715, 1524 cm^{-1}; δ_H (500 MHz, $CDCl_3$): 1.23 (3H, *t*, J = 7.0 Hz, $OCH_2\underline{CH_3}$), 1.40 (9H, *s*, $OC(CH_3)_3$), 1.56 (2H, *m* HH-5), 1.72 (2H, *m*, HH-4), 1.81 (2H, *m*, HH-6), 1.99 (3H, *s*, CH_3CO), 2.62 (1H, *dd*, J = 10.5 and 5.5 Hz, H-1), 4.16 (2H, *q*, J = 7.0 Hz, $OC\underline{H_2}CH_3$), 4.47 (1H, *m*, H-2), 4.83 (1H, *m*, H-3), 4.98

(1H, *br*, NH); δ_C (125 MHz, $CDCl_3$): 14.3 ($OCH_2\underline{C}H_3$), 21.2 (C-6), 21.3 ($\underline{C}H_3CO$), 22.9 (C-4), 26.5 (C-5), 28.5 ($OC(\underline{C}H_3)_3$), 43.9 (C-1), 49.8 (C-2), 60.9 ($O\underline{C}H_2CH_3$), 72.4 (C-3), 79.6 ($O\underline{C}(CH_3)_3$), 155.6 (NCO_2), 170.5 and 172.7 (carbonyls); *m/z* (ES^+): 352 (MNa^+, 100%).



215

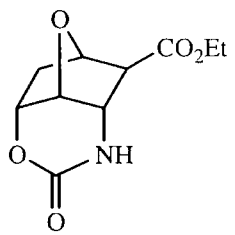
Ethyl *exo*-2-iodo-5-oxo-4,9-dioxa-6-azatricyclo[3,3,1,$1^{1,8}$]decane-*exo*-10-carboxylate 215:

To a solution of bicyclic adduct **2** (500 mg, 1.77 mmol) in acetonitrile (15 cm^3) was added iodine (1.35 g, 5.31 mmol). The reaction was stirred at room temperature and monitored by TLC (16 hours). The reaction was quenched with ethyl acetate (100 cm^3) and then washed with sat. NaS_2O_4 (100 cm^3) The resulting two layers were separated and the aqueous layer was extracted with ethyl acetate (50 cm^3 x 2). The organic layers were combined, dried ($MgSO_4$) and concentrated under reduced pressure. The resulting residue was purified by flash chromatography eluting with Et_2O/petroleum ether (6:4) to give the tricyclic iodocarbamide **215** (298 mg, 48%) as a white solid, mp 164-166°C; υ_{max} (KBr disk): 3448, 2979, 1733 cm^{-1}; δ_H (400 MHz, $CDCl_3$): 1.29 (3H, t, J = 7.2 Hz, $OCH_2C\underline{H}_3$), 2.59 (1H, d, J = 2.4 Hz, H-10), 3.83 (1H, d, J = 1.2 Hz, H-2), 4.21 (2H, q, J = 7.2 Hz, $OC\underline{H}_2CH_3$), 4.32 (1H, m, H-7), 4.54 (1H, t, J = 5.1, H-8), 4.61 (2H, m, H-1 and H-3), 5.98 (1H, d, J = 5.2Hz, NH); δ_C (100 MHz, $CDCl_3$): 14.1 ($OCH_2\underline{C}H_3$), 53.1 (C-7), 54.3 (C-10), 61.9 ($O\underline{C}H_2CH_3$), 67.2 (C-8), 75.6 (C-2), 79.1 (C-2), 85.1, 85.5 (C-1 and C-3), 150.1 (C-5), 170.1 ($CO_2C_2H_5$); *m/z* (EI): 353 (M^+), 194 (100%); Anal. calcd for $C_{10}H_{12}NO_5I$: C, 34.01; H, 3.43; N, 3.97. Found: C, 34.19; H, 3.50; N, 3.81.

Prevost Reaction:

A mixture of AcOAg (620 mg, 3.6 mmol) and iodine (450 mg, 1,77mmol) in glacial acetic acid(10 cm^3) was stirred at room temperature until all the iodine was consumed. At this point, the bicyclic alkene **2** (500 mg, 1.77 mmol) in CH_3COOH (5 cm^3) was

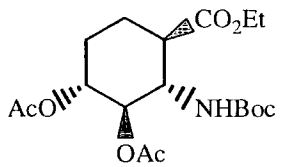
added. The reaction mixture was heated at 60°C for 30 minutes before a mixture of CH_3COOH/H_2O (50:1, 5 cm^3) was added. The reaction mixture was then heated at 80°C for 5 hours. The reaction was quenched with sat. $NaHCO_3$ (15 cm^3) and the yellow precipitate of AgI was filtered off. The filtrate was extracted with AcOEt (10 cm^3 x 3), dried ($MgSO_4$) and concentrated under reduced pressure. The resulting residue was purified by flash chromatography eluting with $(CH_3CH_2)_2O$/Petroleum ether (6:4) to give tricyclic carbamide **215** as a white solid (470 mg, 76%).



216

Ethyl 5-oxo-4,9-dioxa-6-azatricyclo3,3,1,$1^{1,8}$]decane-*exo*-10-carboxylate 216:

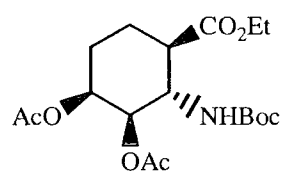
To a solution of the tricyclic iodocarbamide **215** (500 mg, 1.42 mmol) in benzene was added $(Me_3Si)_3SiH$ (525 mg, 2.12 mmol) and AIBN (20 mg, 0.014mmol) at 60°C. The reaction mixture was stirred and monitored by TLC (48 hours) and then quenched with water (50 cm^3). The solution was then extracted with ethyl acetate (50 cm^3 x 3). The organic layers were combined, dried ($MgSO_4$) and concentrated under reduced pressure. The resulting residue was purified by flash chromatography eluting with ethyl acetate/petroleum ether (7:1) to give tricyclic carbamide **216** (150 mg, 46%) as a white solid; mp 156-158°C; δ_H (500 MHz, $CDCl_3$): 1.29 (3H, t, J = 7.5 Hz, $OCH_2C\underline{H}_3$), 1.74 (1H, dd, J = 14.1 and 3.4 Hz, H-2), 2.53 (1H, m, H-2), 2.68 (1H, d, J = 2.5 Hz, H-10), 4.21 (2H, q, J = 7.5 Hz, $OC\underline{H}_2CH_3$), 4.38 (1H, m, H-7), 4.54 (1H, t, J = 4.5 Hz, H-8), 4.87 (2H, m, H-1 and 3), 6.30 (1H, br, NH); δ_C (125 MHz, $CDCl_3$): 14.1 ($OCH_2\underline{C}H_3$), 37.6 (C-2), 53.5 (C-7), 57.6 (C-10), 61.7 ($O\underline{C}H_2CH_3$), 68.0 (C-8), 75.7 and 79.2 (C-1 and 3), 150.5 (NCO_2), 170.6 ($CO_2C_2H_5$); *m/z* (EI): 227 (M^+), 115 (100%); Anal. calcd. For $C_{10}H_{13}NO_5$: C, 52.86; H, 5.77; N, 6.16. Found: C, 52.66; H, 5.84; N, 6.05.



217

Ethyl *anti-anti-anti*-3,4-diacetoxy-2-*tert*-butylcarbonylaminocyclohexane-1-carboxylate 217:

To a solution of epoxide **186** (100 mg, 0.29 mmol) in ethanol (10 cm^3) was added 10% Pd/C (20 mg) and the suspension was stirred under hydrogen for 48 h. The suspension was then filtered and the filtrate was concentrated under reduced pressure. The residue was dissolved in pyridine (2.5 cm^3) and treated with Ac_2O (2.5 cm^3). After stirring for 24 h, 1 M HCl (10 cm^3) was added and the layers were separated. The organic layer was dried ($MgSO_4$), concentrated under pressure and subjected to column chromatography eluting with petroleum ether/ethyl acetate (7:3) to give **217** as a colourless gum (98 mg, 99%); ν_{max} (KBr disk): 3319, 2979, 1732, 1692, 1543 cm^{-1}; δ_H (500 MHz, $CDCl_3$): 1.23 (3H, *t*, J = 7.0 Hz, $OCH_2C\underline{H}_3$), 1.37 (9H, *s*, $OC(CH_3)_3$), 1.70 (1H, *m*, H-6), 1.94 (1H, *m*, H-6), 2.00 (3H, *s*, CH_3CO), 2.02 (3H, *s*, CH_3CO), 2.14 (2H, *m*, HH-5), 2.47 (1H, *dt*, J = 9.0 and 3.0 Hz, H-1), 3.88 (1H, *m*, H-2), 4.13 (2H, *q*, J = 7.0 Hz, $OC\underline{H}_2CH_3$), 4.88 (1H, *d*, J = 9.5 Hz, H-3), 4.98 (1H, *m*, H-4); δ_C (125 MHz, $CDCl_3$): 14.3 ($OCH_2\underline{C}H_3$), 20.9 and 21.2 (2 x $\underline{C}H_3CO$), 24.9 (C-6), 28.4 ($OC(\underline{C}H_3)_3$), 28.8 (C-5), 48.5 (C-1), 54.1 (C-2), 61.3 ($O\underline{C}H_2CH_3$), 72.6 (C-3), 75.0 (C-4), 79.9 ($O\underline{C}(CH_3)_3$), 155.0 (NCO_2), 170.3, 171.0, 172.2 (CO_2 and 2 x $CH_3\underline{C}O$); *m/z* (CI): 405 (MNH_4^+, 71%), 388 (MH^+, 36%), 349 (100%).

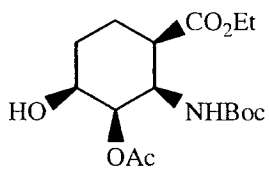


218

Ethyl *anti-anti-syn*-3,4-diacetoxy-2-*tert*-butylcarbonylaminocyclohexane-1-carboxylate 218:

To a solution of epoxide **184** (100 mg, 0.33 mmol) in ethanol (10 cm^3) was added Pd/C (20 mg) under a hydrogen atmosphere and the mixture was stirred for 48 h. The solvent was then removed under reduced pressure and the residue was dissolved in pyridine (2.5 cm^3) and treated with Ac_2O (2.5 cm^3). After stirring for 24 h, 2 M HCl (10 cm^3) was added to the reaction mixture and the layers were separated. The organic

layer was dried ($MgSO_4$), concentrated under reduced pressure and subjected to column chromatography eluting with petroleum ether/ethyl acetate (7:3) to give **218** as a white gum (107 mg, 84%); ν_{max} (KBr disk): 3385, 2975, 1737, 1525 cm^{-1}; δ_H (500 MHz, $CDCl_3$): 1.25 (3H, *t*, J = 7.2 Hz, $OCH_2C\underline{H}_3$), 1.39 (9H, *s*, $OC(CH_3)_3$), 1.64 (1H, *m*, H-5), 1.81 (1H, *m*, H-6), 1.95 (2H, *m*, H-5 and 6), 2.01 (3H, *s*, CH_3CO), 2.13 (3H, *s*, CH_3CO), 2.51 (1H, *t*, J = 11.5 Hz, H-1), 4.16 (3H, *m*, $OC\underline{H}_2CH_3$ and H-2), 4.45 (1H, *d*, J = 9.5 Hz, NH), 4.86 (1H, *dd*, J = 11.5 and 2.5 Hz, H-3), 5.32 (1H, br, H-4); δ_C (125 MHz, $CDCl_3$) 14.4 (OCH_2CH_3), 21.0 (CH_3CO), 21.5 (CH_3CO), 23.1 (C-6), 27.8 (C-5), 28.5 ($OC(\underline{C}H_3)_3$), 48.8 (C-1), 50.7 (C-2), 61.2 ($O\underline{C}H_2CH_3$), 69.4 (C-4), 73.3 (C-3), 79.7 ($O\underline{C}(CH_3)_3$), 155.1 (NCO_2), 170.6, 171.O, 172.8 (carbonyls); *m/z* (CI): 388 (MH^+, 100%).



226

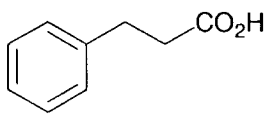
Ethyl *syn-syn-syn*-3-acetoxy-2-*tert*-butylcarbonylamino-4-hydroxycyclohexane-1-carboxylate 226:

To a solution of epoxide **196** (R = Ac) (100 mg, 0.29 mmol) in ethanol (10 cm^3) was added 10% Pd/C (20 mg) and the suspension was stirred under hydrogen for 48 h. The suspension was then filtered and the filtrate was concentrated under reduced pressure to give **226** as a colourless gum (97 mg, 97%) ν_{max} (KBr disk): 3438, 3374, 2975, 1729, 1699, 1513 cm^{-1}; δ_H (500 MHz, $CDCl_3$): 1.23 (3H, *t*, J = 7.0 Hz, $OCH_2C\underline{H}_3$), 1.40 (9H, *s*, $OC(CH_3)_3$), 1.57 (1H, *m*, H-5), 1.63 (1H, *m*, H-6), 2.02 (2H, *m*, H-5 and 6), 2.07 (3H, *s*, CH_3CO), 2.60 (1H, *m*, J = 11.5 and 3.5 Hz, H-1), 4.07 (2H, *m*, H-4 and OH), 4.13 (2H, *q*, J = 7.0 Hz, $OC\underline{H}_2CH_3$), 4.52 (1H, br, H-2), 4.85 (1H, *m*, H-3), 5.72 (1H, br, NH); δ_C (125 MHz, $CDCl_3$): 14.3 ($OCH_2\underline{C}H_3$), 17.4 (C-6), 21.2 ($\underline{C}H_3CO$), 28.5 ($OC(\underline{C}H_3)_3$), 28.9 (C-5), 44.4 (C-1), 50.0 (C-2), 61.0 ($O\underline{C}H_2CH_3$), 68.9 (C-4), 72.6 (C-3), 79.4 ($O\underline{C}(CH_3)_3$), 155.9 (NCO_2), 170.2 (CO_2), 172.3 ($CH_3\underline{C}O$); *m/z* (ES^+): 368 (MNa^+).

General procedure for $PdCl_2$ catalysed transfer hydrogenation

To a solution of substrate (1.0 equivalent) was added an organic acid (3.0 equivalent), $PdCl_2$ (0.1 equivalent) and zinc (3.0 equivalent). The reaction mixture was stirred for

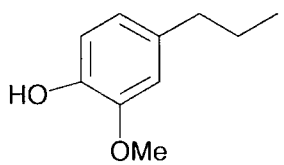
16 h and then filtered. The filtrate was concentrated under reduced pressure to give the product.



238

3-phenylpropanoic acid 238:

Using the general procedure for $PdCl_2$ catalysed transfer hydrogenation, cinnamic acid (250 mg, 1.69 mmol) was reduced in the presence of acetic acid (0.29 cm^3, 5.07 mmol) to give **238** as a white solid (213 mg, 84%); ν_{max} (KBr): 3029-2290 (br), 1697, 1415 cm^{-1}; δ_H (400 MHz, $CDCl_3$): 2.61 (2H, *t*, J = 8.4, HH-3), 2.89 (2H, *t*, J = 8.4 Hz, H-2), 7.15 (5H, *m*, PhH); δ_C (100 MHz, $CDCl_3$): 30.8 (C-3), 35.9 (C-2), 126 (C-4), 128.5 (C-2 and 6), 128.8 (C-3 and 5), 140.4 (C-1), 179.6 (CO_2H); *m/z* (ES^-): 150 (M^-)



240

2-methoxy-4-propylphenol:

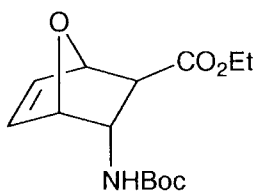
Using the general procedure for $PdCl_2$ catalysed transfer hydrogenation, eugenol (430 mg, 2.82 mmol) was reduced in the presence of acetic acid (0.48 cm^3, 8.46 mmol) to give **240** as a yellow oil (459 mg, 98%); ν_{max} (KBr disk): 3450, 2959, 1607, 1516 cm^{-1}; δ_H (400 MHz, $CDCl_3$): 0.95 (3H, *t*, J = 7.6 Hz, $C\underline{H}_3CH_2CH_2$), 1.63 (3H, *m*, $CH_3C\underline{H}_2CH_2$), 2.53 (2H, *t*, J = 7.6 Hz, $CH_3CH_2C\underline{H}_2$), 3.87 (3H, *s*, OCH_3), 5.55 (1H, *s*, OH), 6.70 (2H, *m*, H-3 and H-6), 6.85 (1H, *d*, J = 7.2 Hz, H-5); δ_C (100 MHz, $CDCl_3$): 14.1 ($\underline{C}H_3CH_2CH_2$), 25.1 ($CH_3\underline{C}H_2CH_2$), 38.0 ($CH_3CH_2\underline{C}H_2$), 56.1 (OCH_3), 111.3 (C-3), 114.3 (C-5), 121.2 (C-6), 134.9 (C-4), 143.7 (C-2), 146.5 (C-1); *m/z* (EI^+): 166 (M^+, 43 %), 137 (100 %).

CHAPTER SIX

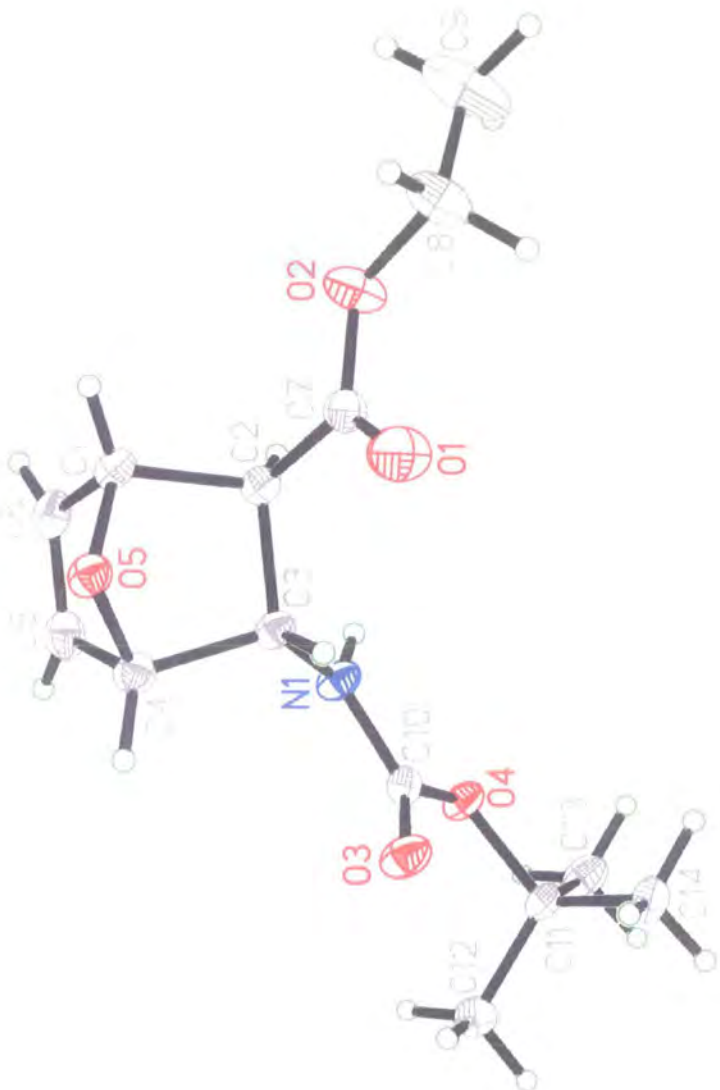
APPENDICES

6.1 APPENDIX 1

X-RAY DATA FOR OXANORBORNENE ADDUCT 2



2



X-ray structure of oxanorbornene adduct **2**

Table 1. Crystal data and structure refinement for 03RMD019.

Identification code	03rmd019	
Empirical formula	$C_{14} H_{21} N O_5$	
Formula weight	283.32	
Temperature	120(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/n	
Unit cell dimensions	a = 8.5458(2) Å	α= 90°.
	b = 11.2435(2) Å	β= 96.1040(10)°.
	c = 15.3706(3) Å	γ = 90°.
Volume	1468.51(5) $Å^3$	
Z	4	
Density (calculated)	1.281 Mg/m^3	
Absorption coefficient	0.097 mm^{-1}	
F(000)	608	
Crystal size	0.32 x 0.24 x 0.18 mm^3	
Theta range for data collection	2.25 to 27.49°.	
Index ranges	-11<=h<=10, -14<=k<=14, -19<=l<=19	
Reflections collected	14755	
Independent reflections	3367 [R(int) = 0.0272]	
Completeness to theta = 27.49°	99.9 %	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3367 / 0 / 265	
Goodness-of-fit on F^2	1.056	
Final R indices [I>2sigma(I)]	R1 = 0.0402, wR2 = 0.1050	
R indices (all data)	R1 = 0.0439, wR2 = 0.1072	
Largest diff. peak and hole	0.410 and -0.284 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for 03RMD019. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
N(1)	-803(1)	3909(1)	2016(1)	21(1)
O(1)	-442(1)	3119(1)	4483(1)	37(1)
C(8)	-2167(2)	4290(2)	5543(1)	40(1)
C(13)	1968(2)	6500(1)	539(1)	31(1)
O(2)	-2695(1)	4077(1)	4616(1)	33(1)
C(12)	2674(2)	4385(1)	267(1)	31(1)
O(4)	805(1)	4990(1)	1296(1)	21(1)
C(5)	-3415(2)	2088(1)	1652(1)	25(1)
O(5)	-2399(1)	1275(1)	2969(1)	20(1)
C(7)	-1699(1)	3481(1)	4168(1)	22(1)
O(3)	1638(1)	3190(1)	1863(1)	26(1)
C(11)	2308(1)	5287(1)	952(1)	21(1)
C(14)	3611(2)	5396(1)	1700(1)	27(1)
C(2)	-2389(1)	3318(1)	3226(1)	19(1)
C(1)	-3507(1)	2206(1)	3117(1)	20(1)
C(6)	-4431(1)	2323(1)	2224(1)	24(1)
C(10)	650(1)	3964(1)	1736(1)	19(1)
C(4)	-1871(1)	1806(1)	2191(1)	21(1)
C(3)	-1147(1)	2973(1)	2613(1)	18(1)
C(9)	-3176(3)	5220(2)	5854(1)	61(1)

Table 3. Bond lengths [Å] and angles [°] for 03RMD019.

N(1)-C(10)	1.3572(14)	C(1)-O(5)-C(4)	95.61(8)
N(1)-C(3)	1.4479(14)	O(1)-C(7)-O(2)	123.73(11)
O(1)-C(7)	1.2013(15)	O(1)-C(7)-C(2)	125.81(11)
C(8)-C(9)	1.467(2)	O(2)-C(7)-C(2)	110.46(10)
C(8)-O(2)	1.4677(16)	O(4)-C(11)-C(12)	110.39(9)
C(13)-C(11)	1.5197(17)	O(4)-C(11)-C(14)	110.03(9)
O(2)-C(7)	1.3312(15)	C(12)-C(11)-C(14)	112.98(11)
C(12)-C(11)	1.5177(17)	O(4)-C(11)-C(13)	102.55(9)
O(4)-C(10)	1.3505(13)	C(12)-C(11)-C(13)	110.77(11)
O(4)-C(11)	1.4788(12)	C(14)-C(11)-C(13)	109.62(11)
C(5)-C(6)	1.3270(18)	C(7)-C(2)-C(3)	113.00(9)
C(5)-C(4)	1.5161(17)	C(7)-C(2)-C(1)	111.61(9)
O(5)-C(1)	1.4454(13)	C(3)-C(2)-C(1)	100.60(9)
O(5)-C(4)	1.4503(13)	O(5)-C(1)-C(6)	102.00(9)
C(7)-C(2)	1.5154(16)	O(5)-C(1)-C(2)	101.10(8)
O(3)-C(10)	1.2143(14)	C(6)-C(1)-C(2)	106.26(9)
C(11)-C(14)	1.5179(17)	C(5)-C(6)-C(1)	105.59(10)
C(2)-C(3)	1.5427(15)	O(3)-C(10)-O(4)	126.10(10)
C(2)-C(1)	1.5722(15)	O(3)-C(10)-N(1)	124.11(10)
C(1)-C(6)	1.5138(16)	O(4)-C(10)-N(1)	109.79(9)
C(4)-C(3)	1.5614(16)	O(5)-C(4)-C(5)	101.99(9)
		O(5)-C(4)-C(3)	98.54(8)
C(10)-N(1)-C(3)	119.17(10)	C(5)-C(4)-C(3)	109.57(9)
C(9)-C(8)-O(2)	107.58(14)	N(1)-C(3)-C(2)	113.79(9)
C(7)-O(2)-C(8)	115.90(11)	N(1)-C(3)-C(4)	116.49(9)
C(10)-O(4)-C(11)	120.49(9)	C(2)-C(3)-C(4)	101.36(8)
C(6)-C(5)-C(4)	105.75(10)		

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for 03RMD019. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
N(1)	18(1)	18(1)	27(1)	6(1)	6(1)	2(1)
O(1)	27(1)	54(1)	27(1)	-3(1)	-3(1)	7(1)
C(8)	53(1)	42(1)	24(1)	-7(1)	2(1)	6(1)
C(13)	26(1)	31(1)	38(1)	11(1)	9(1)	-4(1)
O(2)	37(1)	37(1)	23(1)	-5(1)	4(1)	12(1)
C(12)	30(1)	36(1)	29(1)	-9(1)	12(1)	-8(1)
O(4)	17(1)	20(1)	26(1)	5(1)	7(1)	-1(1)
C(5)	27(1)	24(1)	22(1)	2(1)	-2(1)	-4(1)
O(5)	21(1)	17(1)	24(1)	4(1)	5(1)	0(1)
C(7)	24(1)	19(1)	24(1)	0(1)	5(1)	-2(1)
O(3)	21(1)	23(1)	37(1)	5(1)	9(1)	4(1)
C(11)	17(1)	24(1)	24(1)	0(1)	7(1)	-5(1)
C(14)	22(1)	28(1)	31(1)	-2(1)	1(1)	-6(1)
C(2)	18(1)	17(1)	21(1)	2(1)	3(1)	1(1)
C(1)	16(1)	20(1)	24(1)	3(1)	4(1)	0(1)
C(6)	20(1)	23(1)	29(1)	3(1)	-2(1)	-2(1)
C(10)	19(1)	18(1)	20(1)	-1(1)	3(1)	-2(1)
C(4)	23(1)	19(1)	22(1)	2(1)	6(1)	0(1)
C(3)	17(1)	17(1)	21(1)	3(1)	4(1)	1(1)
C(9)	98(2)	53(1)	31(1)	-10(1)	5(1)	27(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for 03RMD019.

	x	y	z	U(eq)
H(8B)	-990(30)	4550(20)	5597(15)	80(7)
H(8A)	-2280(20)	3548(19)	5832(13)	54(5)
H(13C)	1090(20)	6466(16)	82(12)	43(5)
H(13B)	1710(20)	7091(16)	995(12)	43(5)
H(13A)	2930(20)	6782(15)	299(11)	38(4)
H(12C)	1770(20)	4279(16)	-179(12)	45(5)
H(12B)	2920(20)	3616(18)	526(12)	46(5)
H(12A)	3580(20)	4660(16)	-21(11)	40(4)
H(5)	-3562(19)	2124(15)	1037(11)	36(4)
H(14C)	3850(20)	4651(17)	1990(11)	42(5)
H(14B)	4520(20)	5679(15)	1467(10)	34(4)
H(14A)	3326(19)	5997(15)	2143(11)	33(4)
H(2)	-2983(17)	4028(13)	3036(9)	21(3)
H(1)	-4070(16)	2039(12)	3610(9)	18(3)
H(6)	-5510(20)	2581(14)	2117(10)	31(4)
H(4)	-1114(18)	1290(14)	1945(10)	26(4)
H(3)	-177(16)	2761(12)	2970(9)	16(3)
H(9C)	-2800(20)	5420(19)	6460(14)	59(6)
H(9B)	-4220(40)	4910(30)	5810(20)	101(10)
H(9A)	-3260(30)	5910(30)	5470(20)	100(9)
H(1N)	-1370(19)	4543(15)	1987(10)	29(4)

Table 6. Torsion angles [°] for 03RMD019.

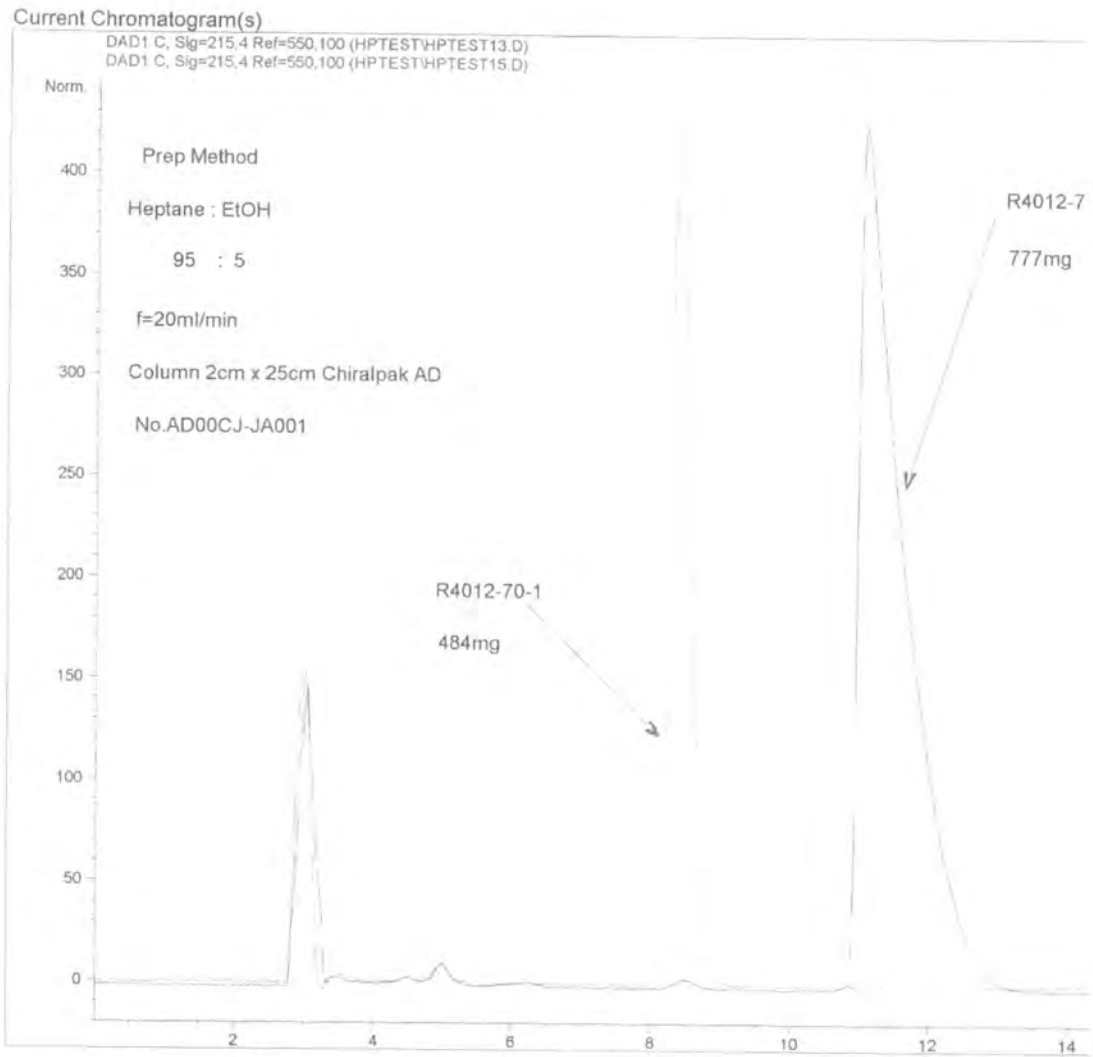
C(9)-C(8)-O(2)-C(7)	164.31(16)
C(8)-O(2)-C(7)-O(1)	0.45(19)
C(8)-O(2)-C(7)-C(2)	179.74(11)

C(10)-O(4)-C(11)-C(12)	63.40(13)
C(10)-O(4)-C(11)-C(14)	-61.97(13)
C(10)-O(4)-C(11)-C(13)	-178.55(10)
O(1)-C(7)-C(2)-C(3)	-17.54(17)
O(2)-C(7)-C(2)-C(3)	163.18(10)
O(1)-C(7)-C(2)-C(1)	94.99(14)
O(2)-C(7)-C(2)-C(1)	-84.28(11)
C(4)-O(5)-C(1)-C(6)	50.10(9)
C(4)-O(5)-C(1)-C(2)	-59.38(9)
C(7)-C(2)-C(1)-O(5)	-88.23(10)
C(3)-C(2)-C(1)-O(5)	31.90(10)
C(7)-C(2)-C(1)-C(6)	165.64(9)
C(3)-C(2)-C(1)-C(6)	-74.24(10)
C(4)-C(5)-C(6)-C(1)	0.89(13)
O(5)-C(1)-C(6)-C(5)	-33.03(12)
C(2)-C(1)-C(6)-C(5)	72.46(12)
C(11)-O(4)-C(10)-O(3)	-3.00(17)
C(11)-O(4)-C(10)-N(1)	177.65(9)
C(3)-N(1)-C(10)-O(3)	9.81(17)
C(3)-N(1)-C(10)-O(4)	-170.82(9)
C(1)-O(5)-C(4)-C(5)	-49.49(10)
C(1)-O(5)-C(4)-C(3)	62.74(9)
C(6)-C(5)-C(4)-O(5)	31.36(12)
C(6)-C(5)-C(4)-C(3)	-72.33(12)
C(10)-N(1)-C(3)-C(2)	150.80(10)
C(10)-N(1)-C(3)-C(4)	-91.80(13)
C(7)-C(2)-C(3)-N(1)	-109.15(11)
C(1)-C(2)-C(3)-N(1)	131.74(10)
C(7)-C(2)-C(3)-C(4)	125.00(10)
C(1)-C(2)-C(3)-C(4)	5.88(10)
O(5)-C(4)-C(3)-N(1)	-165.77(9)
C(5)-C(4)-C(3)-N(1)	-59.73(12)
O(5)-C(4)-C(3)-C(2)	-41.72(10)
C(5)-C(4)-C(3)-C(2)	64.32(11)

Symmetry transformations used to generate equivalent atoms:

6.2 APPENDIX 2

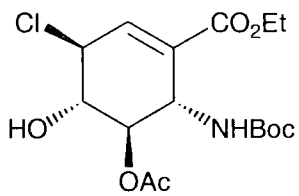
CHIRAL HPLC CHROMATOGRAM



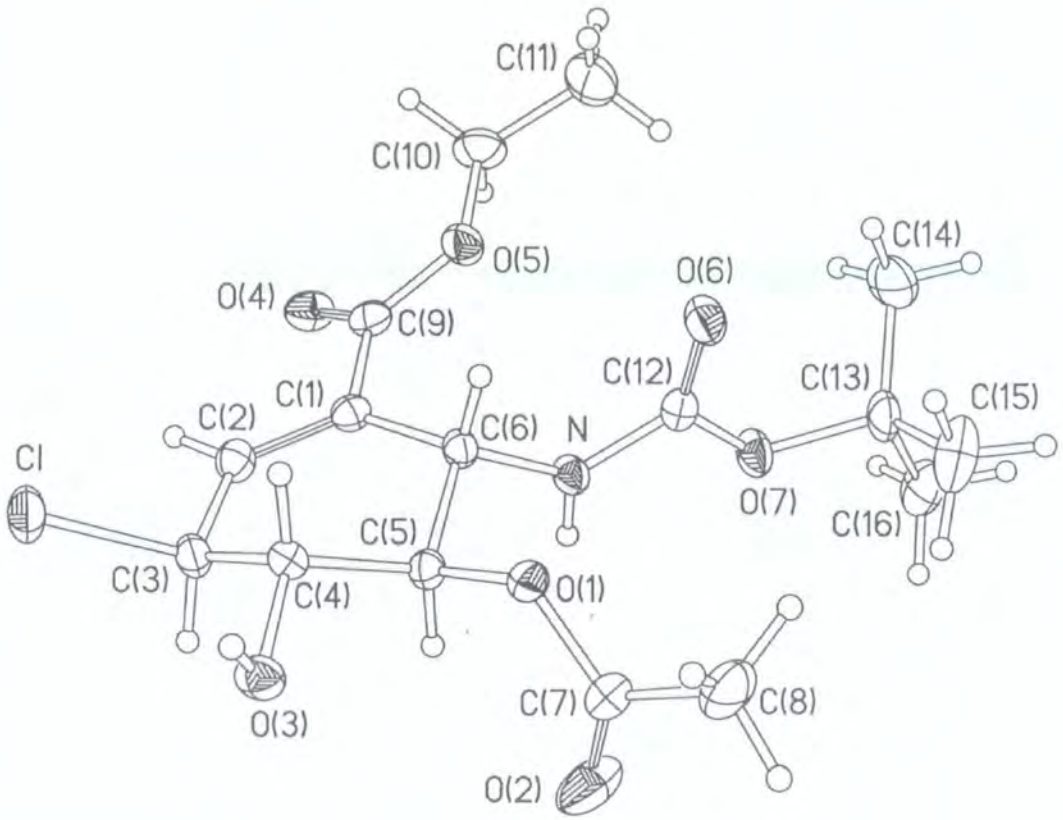
Chiral HPLC chromatogram

6.3 APPENDIX 3

X-RAY DATA FOR CHLOROHYDRIN 189



189



X-ray structure of chlorohydrin **189**

Table 1. Crystal data and structure refinement for 02srv008.

Identification code	Alltraustr101	
Empirical formula	C16 H24 Cl N O7	
Formula weight	377.81	
Temperature	120(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P2_1/c$ (No. 14)	
Unit cell dimensions	a = 9.927(1) Å	α= 90°
	b = 8.811(1) Å	β= 96.14(1)°
	c = 22.579(3) Å	γ = 90°
Volume	1963.6(4) Å^3	
Z	4	
Density (calculated)	1.278 g/cm^3	
Absorption coefficient	0.229 mm^{-1}	
F(000)	800	
Crystal size	0.38 × 0.11 × 0.09 mm^3	
θ range for data collection	1.81 to 29.00°.	
Index ranges	$-13 \leq h \leq 11, -12 \leq k \leq 12, -29 \leq l \leq 30$	
Reflections collected	17291	
Independent reflections	5173 [R(int) = 0.0408]	
Reflections with I>2σ(I)	3731	
Completeness to θ = 29.00°	99.3 %	
Absorption correction	Integration	
Max. and min. transmission	0.9843 and 0.9380	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	5173 / 0 / 322	
Largest final shift/e.s.d. ratio	0.001	
Goodness-of-fit on F^2	1.024	
Final R indices [I>2σ(I)]	R1 = 0.0372, wR2 = 0.0784	
R indices (all data)	R1 = 0.0642, wR2 = 0.0895	
Largest diff. peak and hole	0.317 and -0.232 e.Å^{-3}	

Table 2. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($Å^2 \times 10^4$) for 02srv008. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
Cl	2589.0(4)	4612.1(5)	3163.1(2)	280(1)
O(1)	4429(1)	6939(1)	5178.2(4)	190(2)
O(2)	3477(1)	9237(1)	5280.8(6)	412(3)
O(3)	4113(1)	7215(1)	3940.9(5)	224(2)
O(4)	-129(1)	2345(1)	4815.3(5)	266(2)
O(5)	1604(1)	2345(1)	5543.7(5)	239(2)
O(6)	3678(1)	4358(1)	6391.8(5)	255(2)
O(7)	1918(1)	5778(1)	6661.0(4)	248(2)
N	2169(1)	5553(1)	5708.3(5)	187(2)
C(1)	1689(1)	4122(2)	4776.4(6)	179(3)
C(2)	1453(2)	4338(2)	4188.9(6)	200(3)
C(3)	2223(2)	5463(2)	3857.0(6)	202(3)
C(4)	3545(2)	5956(2)	4212.4(6)	176(3)
C(5)	3215(1)	6390(2)	4836.1(6)	170(3)
C(6)	2724(2)	5025(2)	5173.9(6)	169(3)
C(7)	4410(2)	8387(2)	5392.0(7)	245(3)
C(8)	5689(2)	8714(2)	5784.6(10)	389(4)
C(9)	942(2)	2859(2)	5041.2(7)	200(3)
C(10)	1008(2)	1025(2)	5813.9(8)	313(4)
C(11)	1883(3)	685(2)	6384.5(9)	454(5)
C(12)	2684(2)	5157(2)	6264.2(6)	194(3)
C(13)	2393(2)	5771(2)	7304.1(6)	269(3)
C(14)	2467(3)	4157(2)	7541.9(9)	415(5)
C(15)	3728(2)	6618(3)	7407.7(9)	440(5)
C(16)	1264(2)	6635(2)	7562.8(8)	351(4)

Table 3. Selected bond lengths [Å] and angles [°] for 02srv008.

Cl-C(3)	1.8084(15)	C(1)-C(2)	1.336(2)
O(1)-C(7)	1.3649(17)	C(1)-C(9)	1.497(2)
O(1)-C(5)	1.4439(17)	C(1)-C(6)	1.515(2)
O(2)-C(7)	1.1967(19)	C(2)-C(3)	1.500(2)
O(3)-C(4)	1.4139(17)	C(3)-C(4)	1.527(2)
O(4)-C(9)	1.2157(18)	C(4)-C(5)	1.5281(19)
O(5)-C(9)	1.3284(18)	C(5)-C(6)	1.5315(19)
O(5)-C(10)	1.4672(18)	C(7)-C(8)	1.497(2)
O(6)-C(12)	1.2212(18)	C(10)-C(11)	1.505(3)
O(7)-C(12)	1.3515(17)	C(13)-C(15)	1.517(3)
O(7)-C(13)	1.4780(18)	C(13)-C(14)	1.519(3)
N-C(12)	1.3496(18)	C(13)-C(16)	1.523(2)
N-C(6)	1.4552(18)		
C(7)-O(1)-C(5)	117.39(11)	N-C(6)-C(5)	109.31(11)
C(9)-O(5)-C(10)	116.15(12)	C(1)-C(6)-C(5)	110.43(11)
C(12)-O(7)-C(13)	120.42(12)	O(2)-C(7)-O(1)	123.41(14)
C(12)-N-C(6)	123.32(12)	O(2)-C(7)-C(8)	126.30(15)
C(2)-C(1)-C(9)	117.43(13)	O(1)-C(7)-C(8)	110.28(14)
C(2)-C(1)-C(6)	123.30(13)	O(4)-C(9)-O(5)	124.19(13)
C(9)-C(1)-C(6)	119.17(12)	O(4)-C(9)-C(1)	123.88(14)
C(1)-C(2)-C(3)	123.08(13)	O(5)-C(9)-C(1)	111.91(12)
C(2)-C(3)-C(4)	112.37(12)	O(5)-C(10)-C(11)	107.00(15)
C(2)-C(3)-Cl	108.63(10)	O(6)-C(12)-N	125.77(14)
C(4)-C(3)-Cl	109.40(10)	O(6)-C(12)-O(7)	125.10(13)
O(3)-C(4)-C(3)	110.87(12)	N-C(12)-O(7)	109.13(12)
O(3)-C(4)-C(5)	109.76(11)	O(7)-C(13)-C(15)	109.33(14)
C(3)-C(4)-C(5)	107.37(12)	O(7)-C(13)-C(14)	110.47(13)
O(1)-C(5)-C(4)	109.14(11)	C(15)-C(13)-C(14)	113.43(17)
O(1)-C(5)-C(6)	106.77(11)	O(7)-C(13)-C(16)	101.77(13)
C(4)-C(5)-C(6)	111.93(11)	C(15)-C(13)-C(16)	111.23(15)
N-C(6)-C(1)	111.49(12)	C(14)-C(13)-C(16)	109.99(15)

Table 4. Anisotropic displacement parameters ($Å^2 \times 10^4$) for 02srv008. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2}U_{11} + ... + 2 h k a^* b^* U_{12}]$

	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
Cl	349(2)	336(2)	156(2)	-41(2)	29(1)	-23(2)
O(1)	207(5)	164(5)	192(5)	-11(4)	-13(4)	-7(4)
O(2)	343(7)	263(6)	605(9)	-158(6)	-63(6)	65(5)
O(3)	253(6)	204(5)	225(5)	37(4)	76(5)	0(5)
O(4)	209(5)	210(5)	370(6)	20(5)	-12(5)	-21(4)
O(5)	293(6)	205(5)	216(5)	41(4)	9(4)	-44(4)
O(6)	247(6)	319(6)	194(5)	-4(4)	-2(4)	61(5)
O(7)	270(6)	329(6)	148(5)	-16(4)	36(4)	54(5)
N	195(6)	216(6)	151(6)	3(5)	25(5)	44(5)
C(1)	164(7)	166(6)	207(7)	-8(5)	23(5)	18(5)
C(2)	175(7)	223(7)	196(7)	-22(6)	-8(6)	-1(6)
C(3)	231(7)	230(7)	144(6)	3(6)	13(5)	33(6)
C(4)	199(7)	166(6)	163(7)	17(5)	15(5)	8(6)
C(5)	171(7)	175(6)	160(6)	-9(5)	1(5)	4(6)
C(6)	180(7)	190(7)	139(6)	0(5)	20(5)	17(5)
C(7)	289(8)	193(7)	249(8)	-38(6)	14(6)	-10(6)
C(8)	422(11)	267(9)	439(11)	-99(8)	-133(9)	-39(8)
C(9)	203(7)	164(7)	239(7)	-8(5)	51(6)	27(6)
C(10)	387(10)	206(8)	356(9)	72(7)	79(8)	-31(7)
C(11)	737(17)	321(10)	298(10)	100(8)	25(10)	-57(10)
C(12)	201(7)	210(7)	172(7)	-22(5)	27(6)	-26(6)
C(13)	337(9)	333(9)	135(7)	-45(6)	15(6)	1(7)
C(14)	616(14)	423(11)	216(9)	55(8)	92(9)	104(10)
C(15)	370(11)	624(14)	327(10)	-209(10)	38(8)	-76(10)
C(16)	424(11)	401(10)	244(9)	-89(8)	109(8)	-6(9)

Table 5. Hydrogen coordinates ($\times 10^3$) and isotropic displacement parameters ($Å^2 \times 10^3$) for 02srv008.

	x	y	z	U(iso)
H(03)	481(2)	690(2)	383.2(9)	38(6)
H(1N)	151(2)	617(2)	567.1(8)	32(5)
H(2)	83(2)	376(2)	395.5(7)	24(4)
H(3)	167(2)	634(2)	375.1(7)	17(4)
H(4)	416(2)	510(2)	424.3(6)	11(4)
H(5)	254(2)	718(2)	481.4(6)	11(4)
H(6)	347(2)	438(2)	529.6(7)	14(4)
H(81)	573(2)	976(2)	589.2(9)	43(6)
H(82)	645(3)	852(3)	557.2(11)	65(8)
H(83)	575(3)	804(3)	614.6(12)	80(8)
H(101)	99(2)	20(2)	552.3(8)	31(5)
H(102)	7(2)	132(2)	585.6(8)	36(5)
H(111)	286(3)	48(3)	631.3(12)	81(9)
H(112)	149(2)	-19(3)	655.0(10)	52(6)
H(113)	185(2)	149(3)	666.0(11)	65(7)
H(141)	155(2)	364(3)	741.9(10)	56(7)
H(142)	258(2)	417(3)	796.2(12)	69(7)
H(143)	323(2)	361(3)	739.9(10)	53(6)
H(151)	444(2)	604(2)	726.8(9)	45(6)
H(152)	398(2)	680(3)	782.5(11)	62(7)
H(153)	364(2)	766(3)	721.1(11)	72(8)
H(161)	121(2)	769(3)	741.6(9)	46(6)
H(162)	148(2)	671(2)	800.4(9)	43(5)
H(163)	41(2)	611(3)	748.2(10)	52(6)

Table 6. Torsion angles [°] for 02srv008.

C(9)-C(1)-C(2)-C(3)	-174.18(13)	O(1)-C(5)-C(6)-N	72.10(14)
C(6)-C(1)-C(2)-C(3)	2.2(2)	C(4)-C(5)-C(6)-N	-168.54(11)
C(1)-C(2)-C(3)-C(4)	17.6(2)	O(1)-C(5)-C(6)-C(1)	-164.90(11)
C(1)-C(2)-C(3)-Cl	138.74(13)	C(4)-C(5)-C(6)-C(1)	-45.54(16)
C(2)-C(3)-C(4)-O(3)	-168.84(12)	C(5)-O(1)-C(7)-O(2)	-4.5(2)
Cl-C(3)-C(4)-O(3)	70.41(13)	C(5)-O(1)-C(7)-C(8)	174.33(14)
C(2)-C(3)-C(4)-C(5)	-48.95(15)	C(10)-O(5)-C(9)-O(4)	3.2(2)
Cl-C(3)-C(4)-C(5)	-169.69(9)	C(10)-O(5)-C(9)-C(1)	-175.35(13)
C(7)-O(1)-C(5)-C(4)	120.16(13)	C(2)-C(1)-C(9)-O(4)	-24.0(2)
C(7)-O(1)-C(5)-C(6)	-118.68(13)	C(6)-C(1)-C(9)-O(4)	159.46(14)
O(3)-C(4)-C(5)-O(1)	-56.49(14)	C(2)-C(1)-C(9)-O(5)	154.46(13)
C(3)-C(4)-C(5)-O(1)	-177.09(11)	C(6)-C(1)-C(9)-O(5)	-22.03(17)
O(3)-C(4)-C(5)-C(6)	-174.46(12)	C(9)-O(5)-C(10)-C(11)	-177.70(15)
C(3)-C(4)-C(5)-C(6)	64.95(15)	C(6)-N-C(12)-O(6)	2.0(2)
C(12)-N-C(6)-C(1)	119.19(15)	C(6)-N-C(12)-O(7)	-177.58(12)
C(12)-N-C(6)-C(5)	-118.44(14)	C(13)-O(7)-C(12)-O(6)	12.0(2)
C(2)-C(1)-C(6)-N	133.47(14)	C(13)-O(7)-C(12)-N	-168.48(12)
C(9)-C(1)-C(6)-N	-50.25(17)	C(12)-O(7)-C(13)-C(15)	59.71(19)
C(2)-C(1)-C(6)-C(5)	11.75(19)	C(12)-O(7)-C(13)-C(14)	-65.80(19)
C(9)-C(1)-C(6)-C(5)	-171.97(12)	C(12)-O(7)-C(13)-C(16)	177.43(14)

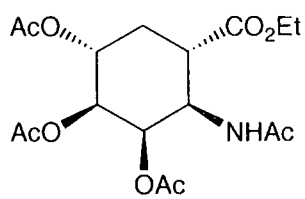
Table 7. Hydrogen bonds for 02srv008 [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
O(3)-H(03)...O(6)#1	0.81(2)	1.97(2)	2.765(2)	166(2)
N-H(1N)...O(4)#2	0.85(2)	2.11(2)	2.902(2)	154(2)

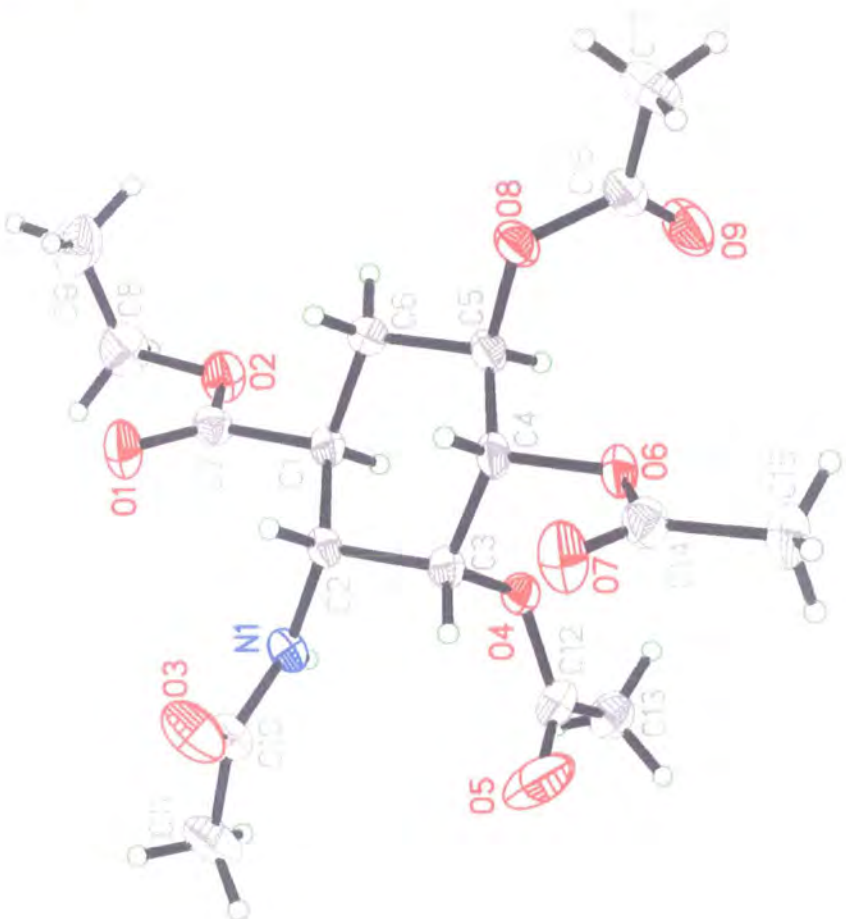
Symmetry transformations used to generate equivalent atoms: #1 -x+1,-y+1,-z+1 #2 -x,-y+1,-z+1

6.4 APPENDIX 4

X-RAY DATA FOR ACHC DERIVATIVE 198



198



X-ray structure of ACHC derivative **198**

Table 1. Crystal data and structure refinement for 03rmd015.

Identification code	2,3-cistriol	
Empirical formula	$C_{17} H_{25} N O_9$	
Formula weight	387.38	
Temperature	120(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	Pbca	
Unit cell dimensions	a = 19.3864(7) Å	α= 90°.
	b = 9.4800(4) Å	β= 90°.
	c = 21.6482(8) Å	γ = 90°.
Volume	3978.6(3) $Å^3$	
Z	8	
Density (calculated)	1.293 Mg/m^3	
Absorption coefficient	0.105 mm^{-1}	
F(000)	1648	
Crystal size	0.44 x 0.36 x 0.24 mm^3	
Theta range for data collection	1.88 to 27.50°.	
Index ranges	-25<=h<=25, -12<=k<=12, -28<=l<=28	
Reflections collected	41625	
Independent reflections	4566 [R(int) = 0.0820]	
Completeness to theta = 27.50°	100.0 %	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4566 / 0 / 344	
Goodness-of-fit on F^2	1.070	
Final R indices [I>2sigma(I)]	R1 = 0.0498, wR2 = 0.1116	
R indices (all data)	R1 = 0.0752, wR2 = 0.1267	
Largest diff. peak and hole	0.553 and -0.260 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for 03rmd015. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(4)	546(1)	4088(1)	1121(1)	25(1)
O(1)	1594(1)	3920(2)	3234(1)	36(1)
O(6)	1270(1)	2016(1)	466(1)	27(1)
O(8)	2612(1)	2522(2)	922(1)	30(1)
O(2)	2001(1)	5946(2)	2831(1)	34(1)
N(1)	307(1)	3784(2)	2398(1)	22(1)
O(7)	864(1)	-153(2)	687(1)	41(1)
C(2)	929(1)	3232(2)	2111(1)	21(1)
O(9)	2660(1)	3909(2)	74(1)	44(1)
O(3)	-42(1)	1660(2)	2740(1)	43(1)
C(1)	1516(1)	4310(2)	2133(1)	22(1)
C(3)	769(1)	2820(2)	1439(1)	22(1)
C(4)	1411(1)	2258(2)	1115(1)	24(1)
C(5)	2014(1)	3270(2)	1151(1)	25(1)
C(10)	-153(1)	2930(2)	2671(1)	27(1)
C(7)	1694(1)	4686(2)	2798(1)	25(1)
C(6)	2164(1)	3691(2)	1819(1)	25(1)
O(5)	-542(1)	3251(2)	1059(1)	59(1)
C(12)	-134(1)	4186(2)	978(1)	33(1)
C(14)	996(1)	747(2)	313(1)	30(1)
C(16)	2863(1)	2903(2)	358(1)	30(1)
C(15)	873(1)	649(3)	-371(1)	39(1)
C(11)	-815(1)	3613(3)	2881(1)	40(1)
C(9)	2916(2)	5793(3)	3611(1)	49(1)
C(8)	2228(1)	6394(3)	3449(1)	41(1)
C(13)	-303(1)	5626(3)	741(1)	39(1)
C(17)	3400(1)	1881(3)	155(1)	41(1)

Table 3. Bond lengths [Å] and angles [°] for 03rmd015.

O(4)-C(12)	1.359(2)	N(1)-C(2)-C(1)	111.30(14)
O(4)-C(3)	1.451(2)	N(1)-C(2)-C(3)	109.21(14)
O(1)-C(7)	1.208(2)	C(1)-C(2)-C(3)	110.43(14)
O(6)-C(14)	1.356(2)	C(7)-C(1)-C(2)	110.76(14)
O(6)-C(4)	1.449(2)	C(7)-C(1)-C(6)	108.70(14)
O(8)-C(16)	1.363(2)	C(2)-C(1)-C(6)	109.71(15)
O(8)-C(5)	1.447(2)	O(4)-C(3)-C(4)	108.32(14)
O(2)-C(7)	1.337(2)	O(4)-C(3)-C(2)	107.34(14)
O(2)-C(8)	1.472(2)	C(4)-C(3)-C(2)	111.10(14)
N(1)-C(10)	1.341(2)	O(6)-C(4)-C(5)	107.20(14)
N(1)-C(2)	1.453(2)	O(6)-C(4)-C(3)	110.36(14)
O(7)-C(14)	1.204(2)	C(5)-C(4)-C(3)	112.62(15)
C(2)-C(1)	1.531(2)	O(8)-C(5)-C(4)	106.88(15)
C(2)-C(3)	1.538(2)	O(8)-C(5)-C(6)	107.48(14)
O(9)-C(16)	1.201(2)	C(4)-C(5)-C(6)	111.22(15)
O(3)-C(10)	1.232(2)	O(3)-C(10)-N(1)	121.83(18)
C(1)-C(7)	1.521(2)	O(3)-C(10)-C(11)	122.11(18)
C(1)-C(6)	1.544(2)	N(1)-C(10)-C(11)	116.06(18)
C(3)-C(4)	1.524(2)	O(1)-C(7)-O(2)	124.53(17)
C(4)-C(5)	1.515(3)	O(1)-C(7)-C(1)	124.27(17)
C(5)-C(6)	1.528(2)	O(2)-C(7)-C(1)	111.15(15)
C(10)-C(11)	1.508(3)	C(5)-C(6)-C(1)	111.16(15)
O(5)-C(12)	1.200(3)	O(5)-C(12)-O(4)	123.73(19)
C(12)-C(13)	1.494(3)	O(5)-C(12)-C(13)	125.5(2)
C(14)-C(15)	1.501(3)	O(4)-C(12)-C(13)	110.71(18)
C(16)-C(17)	1.488(3)	O(7)-C(14)-O(6)	123.19(17)
C(9)-C(8)	1.491(4)	O(7)-C(14)-C(15)	125.7(2)
		O(6)-C(14)-C(15)	111.05(17)
C(12)-O(4)-C(3)	117.00(15)	O(9)-C(16)-O(8)	123.49(18)
C(14)-O(6)-C(4)	116.83(14)	O(9)-C(16)-C(17)	126.53(19)
C(16)-O(8)-C(5)	117.65(14)	O(8)-C(16)-C(17)	109.97(18)
C(7)-O(2)-C(8)	116.10(16)	O(2)-C(8)-C(9)	111.82(19)
C(10)-N(1)-C(2)	121.49(16)		

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for 03rmd015. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ...\ + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(4)	24(1)	29(1)	21(1)	3(1)	0(1)	5(1)
O(1)	51(1)	38(1)	20(1)	1(1)	-1(1)	-10(1)
O(6)	36(1)	31(1)	16(1)	-2(1)	1(1)	3(1)
O(8)	29(1)	36(1)	25(1)	4(1)	8(1)	9(1)
O(2)	42(1)	32(1)	29(1)	-3(1)	-2(1)	-8(1)
N(1)	27(1)	17(1)	21(1)	0(1)	6(1)	1(1)
O(7)	60(1)	37(1)	28(1)	0(1)	2(1)	-8(1)
C(2)	25(1)	20(1)	18(1)	0(1)	2(1)	2(1)
O(9)	48(1)	49(1)	35(1)	14(1)	15(1)	10(1)
O(3)	54(1)	23(1)	51(1)	1(1)	20(1)	-7(1)
C(1)	25(1)	22(1)	20(1)	2(1)	1(1)	0(1)
C(3)	25(1)	20(1)	20(1)	0(1)	1(1)	1(1)
C(4)	30(1)	27(1)	14(1)	-1(1)	1(1)	6(1)
C(5)	26(1)	28(1)	20(1)	3(1)	4(1)	6(1)
C(10)	34(1)	23(1)	25(1)	-5(1)	7(1)	-7(1)
C(7)	25(1)	26(1)	24(1)	-3(1)	1(1)	0(1)
C(6)	23(1)	31(1)	23(1)	0(1)	0(1)	1(1)
O(5)	42(1)	59(1)	77(1)	18(1)	-30(1)	-14(1)
C(12)	31(1)	42(1)	27(1)	3(1)	-9(1)	1(1)
C(14)	32(1)	33(1)	25(1)	-5(1)	2(1)	5(1)
C(16)	30(1)	35(1)	26(1)	1(1)	8(1)	-2(1)
C(15)	52(1)	42(1)	23(1)	-5(1)	-3(1)	3(1)
C(11)	40(1)	34(1)	45(1)	-7(1)	20(1)	-6(1)
C(9)	58(2)	49(2)	40(1)	-4(1)	-12(1)	-9(1)
C(8)	48(1)	39(1)	35(1)	-14(1)	-1(1)	-12(1)
C(13)	33(1)	49(1)	34(1)	7(1)	-5(1)	10(1)
C(17)	40(1)	40(1)	44(1)	1(1)	20(1)	4(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for 03rmd015.

	x	y	z	U(eq)
H(3)	410(10)	2150(20)	1414(9)	20(5)
H(5)	1925(9)	4070(20)	917(9)	17(4)
H(2)	1076(9)	2370(20)	2321(8)	16(4)
H(1)	1378(9)	5160(20)	1913(9)	20(5)
H(4)	1536(10)	1370(20)	1308(9)	24(5)
H(1N)	209(10)	4640(20)	2364(9)	24(5)
H(6B)	2294(10)	2850(20)	2039(10)	26(5)
H(6A)	2546(11)	4360(20)	1829(9)	26(5)
H(8B)	2227(12)	7400(30)	3399(11)	47(7)
H(11B)	-848(14)	4590(30)	2802(13)	63(9)
H(11C)	-1203(18)	3100(40)	2720(16)	81(10)
H(15C)	1252(15)	1050(30)	-591(13)	58(8)
H(15B)	821(14)	-340(30)	-482(14)	61(8)
H(17C)	3177(14)	1040(30)	29(12)	50(7)
H(8A)	1849(15)	6140(30)	3728(13)	58(8)
H(17B)	3644(14)	2250(30)	-174(14)	58(8)
H(15A)	436(15)	1150(30)	-465(13)	58(8)
H(17A)	3691(17)	1620(30)	466(16)	72(10)
H(9C)	2907(14)	4750(40)	3640(13)	64(8)
H(9B)	3271(15)	6050(30)	3291(14)	61(8)
H(11A)	-864(18)	3320(40)	3272(18)	86(11)
H(9A)	3094(16)	6190(30)	4016(15)	70(9)
H(13C)	-700(15)	5570(30)	481(14)	61(8)
H(13B)	69(14)	6040(30)	504(13)	54(7)
H(13A)	-382(15)	6210(30)	1084(15)	68(9)

Table 6. Torsion angles [°] for 03rmd015.

C(10)-N(1)-C(2)-C(1)	-150.78(16)
C(10)-N(1)-C(2)-C(3)	87.03(19)
N(1)-C(2)-C(1)-C(7)	60.51(19)
C(3)-C(2)-C(1)-C(7)	-178.02(14)
N(1)-C(2)-C(1)-C(6)	-179.48(14)
C(3)-C(2)-C(1)-C(6)	-58.01(18)
C(12)-O(4)-C(3)-C(4)	132.31(16)
C(12)-O(4)-C(3)-C(2)	-107.65(17)
N(1)-C(2)-C(3)-O(4)	60.76(17)
C(1)-C(2)-C(3)-O(4)	-61.94(17)
N(1)-C(2)-C(3)-C(4)	179.02(15)
C(1)-C(2)-C(3)-C(4)	56.31(19)
C(14)-O(6)-C(4)-C(5)	150.68(15)
C(14)-O(6)-C(4)-C(3)	-86.34(18)
O(4)-C(3)-C(4)-O(6)	-56.26(18)
C(2)-C(3)-C(4)-O(6)	-173.93(14)
O(4)-C(3)-C(4)-C(5)	63.49(18)
C(2)-C(3)-C(4)-C(5)	-54.18(19)
C(16)-O(8)-C(5)-C(4)	108.03(17)
C(16)-O(8)-C(5)-C(6)	-132.49(17)
O(6)-C(4)-C(5)-O(8)	-67.79(17)
C(3)-C(4)-C(5)-O(8)	170.65(13)
O(6)-C(4)-C(5)-C(6)	175.18(14)
C(3)-C(4)-C(5)-C(6)	53.6(2)
C(2)-N(1)-C(10)-O(3)	6.4(3)
C(2)-N(1)-C(10)-C(11)	-172.71(18)
C(8)-O(2)-C(7)-O(1)	0.3(3)
C(8)-O(2)-C(7)-C(1)	-177.13(16)
C(2)-C(1)-C(7)-O(1)	25.8(2)
C(6)-C(1)-C(7)-O(1)	-94.8(2)
C(2)-C(1)-C(7)-O(2)	-156.75(15)
C(6)-C(1)-C(7)-O(2)	82.64(18)
O(8)-C(5)-C(6)-C(1)	-171.98(15)
C(4)-C(5)-C(6)-C(1)	-55.3(2)

C(7)-C(1)-C(6)-C(5)	179.06(16)
C(2)-C(1)-C(6)-C(5)	57.8(2)
C(3)-O(4)-C(12)-O(5)	-5.6(3)
C(3)-O(4)-C(12)-C(13)	171.42(16)
C(4)-O(6)-C(14)-O(7)	0.7(3)
C(4)-O(6)-C(14)-C(15)	179.49(16)
C(5)-O(8)-C(16)-O(9)	7.8(3)
C(5)-O(8)-C(16)-C(17)	-170.96(18)
C(7)-O(2)-C(8)-C(9)	83.4(2)

Symmetry transformations used to generate equivalent atoms: