Total Synthesis of (+)-Belactosin A

A thesis submitted by James Nicholas Scutt in partial fulfilment of the requirements for the degree of Doctor of Philosophy

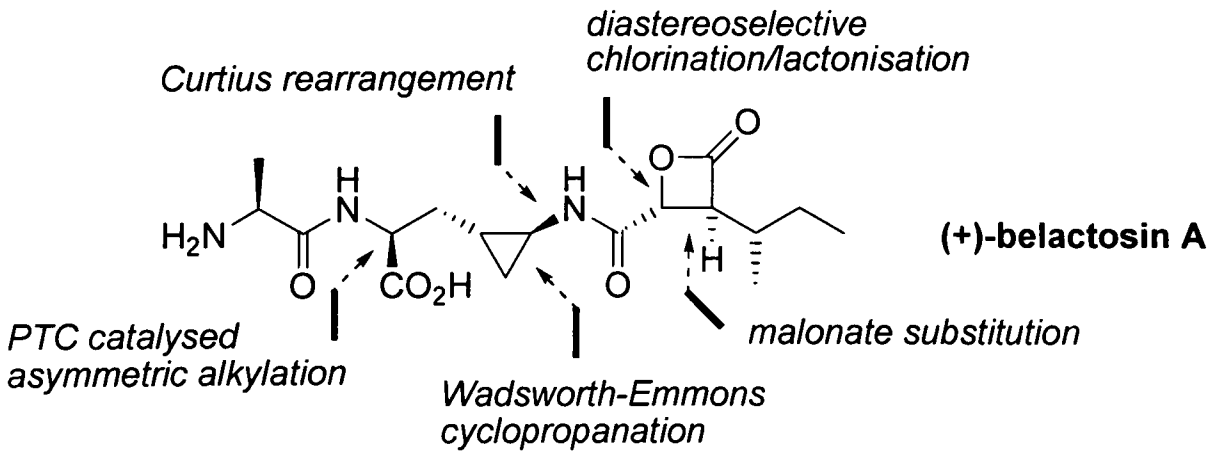
Heilbron Laboratory
Department of Chemistry
Imperial College London
London SW7 2AY

January 2005

Contents

Abstract

(+)-Belactosin A is a novel peptide, first isolated in Japan in 1997, that has recently been shown to be a potent proteasome inhibitor. It contains a novel aminocyclopropyl alanine amino acid core, and a novel carboxamido β-lactone. Chapter 1 presents the isolation, structure and biological properties of (+)-belactosin A, then proceeds to review all relevant synthetic work prior to the start of our research programme, and also work published since we began investigations into this area. Chapter 2 begins with our synthetic plan aimed towards the total synthesis of (+)-belactosin A and analogues, then discusses execution of this strategy. All four stereosiomers of the central amino acid were successfully synthesised using an unusual epoxide cyclopropanation, and an organocatalytic amino acid synthesis as the two key steps. Efforts were also made to synthesise the β-lactone moiety using organocatalysis, but this was eventually accessed by a one-pot diastereoselective chlorination/lactonisation strategy. Finally, the first total synthesis of (+)-belactosin A was achieved using a new amino acid coupling procedure. Chapter 3 summarises the findings discussed in Chapter 2, and Chapter 4 gives full experimental details and spectroscopic and physical data for all new compounds prepared.



Acknowledgements

I would like to thank Prof. Alan Armstrong for giving me the opportunity to work in his research group, and for his encouragement, patience and support over the past three years. I would also like to acknowledge the financial support given by both Prof. Alan Armstrong and the EPSRC.

Thanks must also go to all the members of the Armstrong group who have contributed to the excellent time I have had during my studies, and with whom I have had the pleasure of sharing a lab over the past three years. From my first year, to final year, I would like to thank Nick C, Huw, Nick D, Rich, Chris, Tim, Dick, Jenna, Fred, Ian, Graham, Nat, Tom, Nicky, Steve, Nigel, Jamie, Lizzie, Rich, Dave and Hans. Special thanks also go to Dave, Steve, Jamie and Lizzie for careful proof-reading of this thesis, and very helpful suggestions.

I would also like to acknowledge the technical support I have received, in particular Mr. Pete Haycock from the Imperial College NMR support service, and all staff from the Imperial College Mass Spectrometry Service.

Finally, I would like to thank my parents for their continued support throughout many years as a student.

Abbreviations

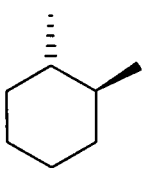
^{1}H	Proton
^{13}C	Carbon-13
Å	Angstrom(s)
Ac	Acetyl
aq.	Aqueous
Ar	Aryl substituent
BEMP	2-*tert*-Butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine
Boc	tert-Butoxycarbonyl
t-Bu	*tert*-Butyl
Bn	Benzyl
br	Broad
cat	Catalyst/Catalytic
CBz	Benzyl carbamate
CI	Chemical ionisation
d	Doublet
DCC	*N,N'*-Dicyclohexylcarbodiimide
dd	Doublet of doublets (etc.)
DMAP	4-(*N*-dimethylamino)pyridine
DMF	*N,N'*-Dimethylformamide
DMSO	Dimethyl sulfoxide
d.e.	Diastereomeric excess
DPPA	Diphenyl phosphoryl azide
d.r.	Diastereoisomeric ratio
dt	Doublet of triplets
EDCI	1-[3-(Dimethylamino)propyl]-3-ethylcarbodiimide methiodide
e.e.	Enantiomeric excess
Eq	Equivalent(s)
Et	Ethyl
FAB	Fast Atom Bombardment

g	Gram(s)
GC	Gas chromatography
h	Hour(s)
HOAt	1-Hydroxy-7-azabenzotriazole
HOBt	1-Hydroxybenzotriazole
HOSA	Hydroxylamine-*O*-sulfonic acid
Hunig's base	*N*,*N*-Diisopropylethylamine
Hz	Hertz
IR	Infrared
J	Coupling constant (in Hz)
L	Ligand
LiHMDS	Lithium hexamethyldisilazide
LiTMP	Lithium 2,2,6,6-tetramethylpiperidide
LDA	Lithium di-*iso*-propylamide
m	Multiplet
M	Molar
Me	Methyl
mg	Milligram(s)
MHz	Megahertz
min	Minute(s)
ml	Millilitre(s)
mmol	Millimole(s)
m.p.	Melting point
MS	Molecular sieves
m/z	Mass/charge ratio (in mass spectrometry)
NaHMDS	Sodium hexamethyldisilazide
NMR	Nuclear magnetic resonance
Nu	Nucleophile
petrol	Petroleum ether (b.p. 40-60°C)
Ph	Phenyl
ppm	Part(s) per million
Proton sponge	*N*,*N*,*N*′,*N*′-Tetramethyl-1,8-naphthalenediamine
q	Quartet

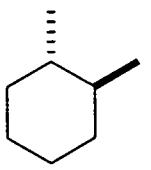
r.t.	Room temperature
s	Singlet
sat.	Saturated
t	Triplet
TBAB	Tetrabutylammonium bromide
TBAI	Tetrabutylammonium iodide
TEMPO	2,2,6,6-Tetramethyl-1-piperidinyloxyl radical
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin layer chromatography
Ts	*p*-Toluenesulfonyl

Stereochemical notation

Throughout this thesis, the pictorial representation of stereochemistry is consistent with the conventions proposed by Maehr.* Thus, solid/broken wedges represent absolute configuration, in which case, greater narrowing of the wedges indicates distance from the viewer. In contrast, structures drawn with solid/broken lines represent racemates.



single enantiomer



racemate

* Maehr, J. *J. Chem. Ed.* **1985**, *62*, 114.

CHAPTER 1

Introduction

Chapter 1: Introduction

1.1 Isolation and structure of (+)-belactosin A

The natural product (+)-belactosin A (UCK14A$_1$) (+)-**1** (Figure 1) was first reported in the patent literature in 1997 by scientists at Kyowa Hakko Kogyo Co. Ltd..[1] It is a novel *Streptomyces* metabolite isolated using a yeast-based assay from the culture broth of KY11780. In addition, belactosin B **2** and belactosin C **3** (Figure 2) were also isolated in smaller quantities.[2]

The structure and relative stereochemistry of (+)-belactosin A was elucidated after MS and NMR investigations, and reported in the Japanese literature in 1999.[3] Spectral analysis showed that (+)-**1** possessed a unique central amino acid - 3-(2-aminocyclopropyl)-alanine (AcpAla) - and a unique carboxamido β-lactone. The absolute stereochemistry was assigned as shown for (+)-**1**, revealing an L-alanine component, a (2*S*, 1′*R*, 2′*S*)-AcpAla component **4** and a (2*R*, 3*S*, 1′*S*)-β-lactone component **5** (Figure 1).

(+)-belactosin A (+)-**1**

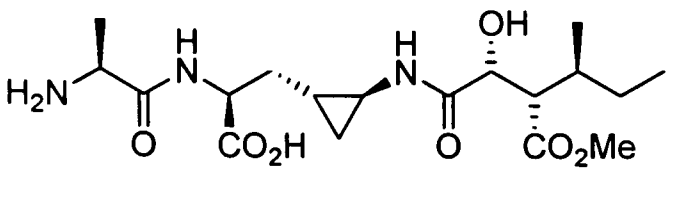
L-alanine

(2*S*, 1′*R*, 2′*S*)-AcpAla **4**

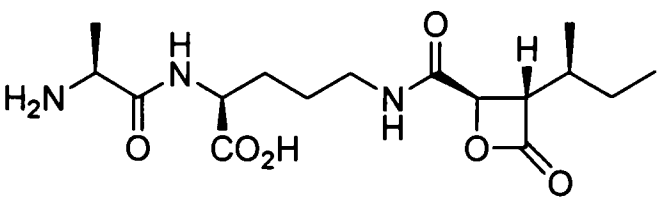
(2*R*, 3*S*, 1′*S*)-**5**

Figure 1

Belactosin B **2** contains a β-hydroxy methyl ester which is thought to be the result of methanol-induced ring opening of (+)-**1** during isolation,[2] whereas (-)-belactosin C **3** contains an ornithine, rather than AcpAla central fragment (Figure 2).



belactosin B **2**



(-)-belactosin C **3**

Figure 2

1.2 Proteasome inhibition

The 26S proteasome is a large, multiprotein enzyme complex present in the cytoplasm and nucleus of all eukaryotic cells.[4] It consists of a 20S catalytic core, capped at either end by 19S regulatory subunits (Figure 3).[4] Evidence suggests that the 26S proteasome plays a critical role in the regulation of cell-cycle growth and survival, through both the degradation of short-lived regulatory proteins that govern cellular functions, and also the degradation of damaged or obsolete cellular proteins.[4] Blockade of proteasome function halts cell division, and since malignant cells are particularly sensitive to the loss of proteasome activity,[4] proteasome inhibition has therefore become a logical target for therapeutic intervention. Proteasome inhibitors can be subdivided into five classes: peptide aldehydes, peptide vinyl sulfones, peptide boronates, peptide epoxy ketones and β-lactones.[5] The exact mechanism of action of each type of proteasome inhibitor is complex and still under investigation, but in all cases it is thought that there is a crucial interaction between the electrophilic site on the inhibitor and the threonine residue in the active site of the proteasome.[5]

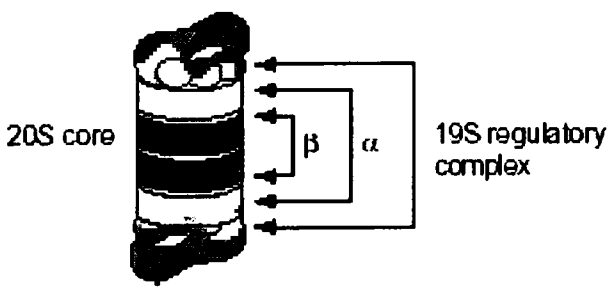


Figure 3: The 20S Proteasome[4]

1.2.1 Biological activity of (+)-belactosin A

It has been shown that (+)-belactosin A (+)-**1** induces the arrest of human cancer cells at the G2/M phase of the cell-cycle, through a highly selective and irreversible inhibition of the 20S proteasome (chymotrypsin-like activity).[6] In contrast, belactosin

B **2** has been shown to be inactive, which is consistent with a β-lactone-threonine interaction (Table 1). Activity profiles revealed that (+)-**1** exhibited a higher potency for proteasome inhibition *in vitro* (IC_{50} = 0.21 μM) than for growth-inhibition of HeLa S3 cells (IC_{50} = 51 μM), which therefore suggested that a more cell-permeable (+)-belactosin A analogue may be more active.[6] On this basis a series of more lipophilic derivatives were synthesised, and from initial SAR studies the benzyl-ester derivative KF33955 **1**-*benzyl ester* was identified as being most potent (Figure 4).

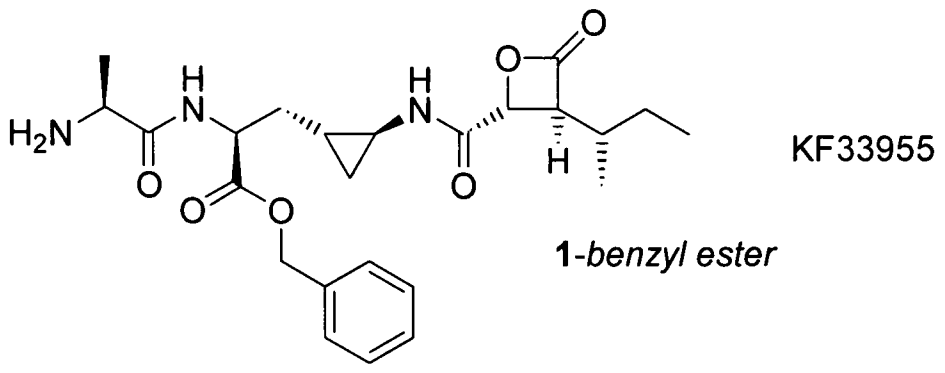
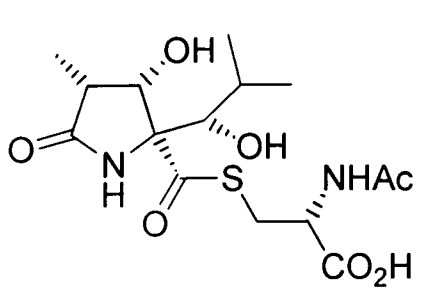


Figure 4

KF33955 exhibits a 100-fold greater growth-inhibitory activity against HeLa S3 cells (IC_{50} = 0.46 μM) than (+)-**1** (Table 1), and is also competitive, if not superior to more established proteasome inhibitors such as lactacystin and MG-132 **7** (Figure 5, Table 1).[6] *In vivo* activity has also been claimed for KF33955 (10 mg/Kg/day): T/C of 49 % in BALB/c-nu/nu mice implanted with WiDr tumour cells.[7]



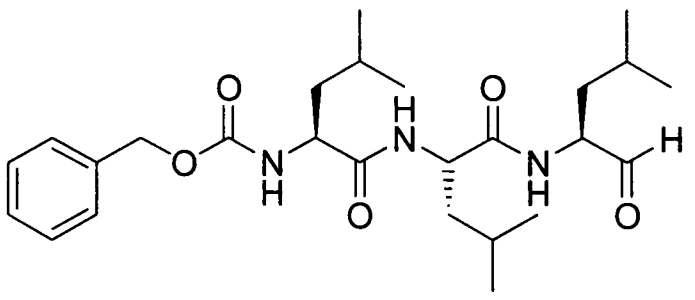


Figure 5

Compound	IC_{50} (μM)	
	Proteasome inhibition	Growth inhibition
Belactosin A	0.21	51
Belactosin B	>10	>300
Belactosin C	0.21	200
KF33955	**0.048**	**0.46**
Lactacystin	0.28	*not tested*
MG-132	0.021	*not tested*

Table 1[6]

(+)-Belactosin A **1** is therefore a useful lead compound for the treatment of disease whose etiology is dependant on the unregulated ubuiquitin-proteasome pathway.[6] In future, workers at Kyowa Hakko Kogyo Co. Ltd. plan to analyse the precise binding site and molecular action of KF33955 **1**-*benzyl ester* through the use of radio/biotin-labelled belactosins.[6]

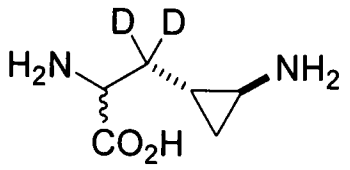
1.3 Review of previous synthetic work

Clearly, the interesting structure and impressive biological activity of (+)-**1** make it both a challenging and desirable target for synthetic studies. However, we were surprised to find only two relevant synthetic approaches at the time we embarked upon our research programme. The first of these was a synthesis of the central AcpAla fragment by de Meijere,[8] and the second was the synthesis of an isomeric β-lactone, included in an SAR patent filed by Kyowa Hakko Kogyo Co. Ltd..[7]

1.3.1 De Meijere's synthesis of (2*S*/*R*, 1′*R**, 2′*S**)-AcpAla

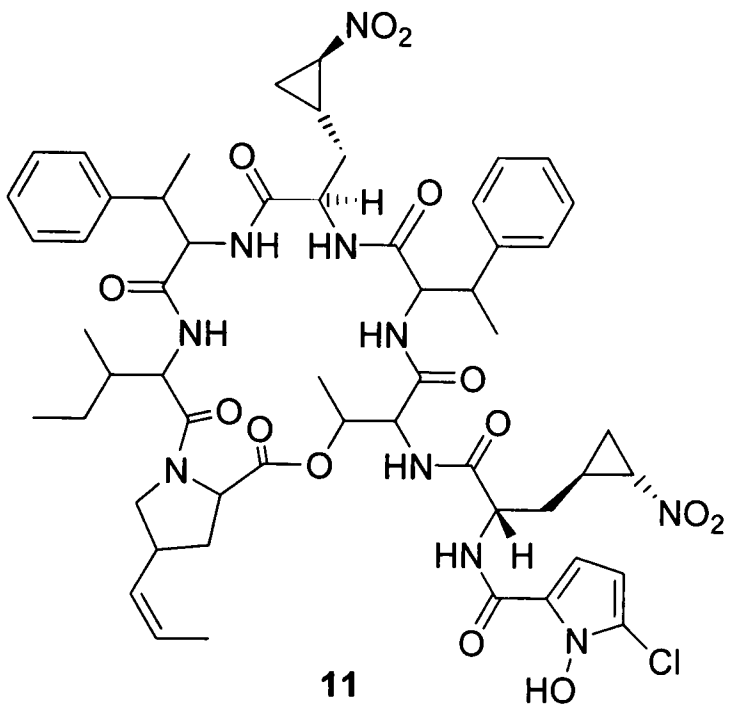
In 2000 de Meijere attempted synthesis of the central AcpAla amino acid core of (+)-**1**, and was successful in accessing deuterium-labelled (2*S*/*R*, 1′*R**, 2′*S**)-AcpAla **8** as a mixture of four stereoisomers (Figure 6).[8] Inspiration for this synthesis was taken

from his long established work on the nitro-analogue 3-(2-nitrocyclopropyl)-alanine) (NcpAla) **9** and **10**, found in the peptidolactone hormaomycin **11** (Figure 6).[9,10]



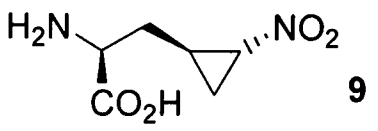
8

(2*S*/*R*, 1'*R**, 2'*S**)-3,3-D_2-AcpAla



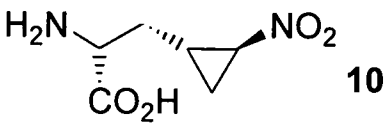
11

hormaomycin



9

(2*S*, 1'*R*, 2'*R*)-NcpAla

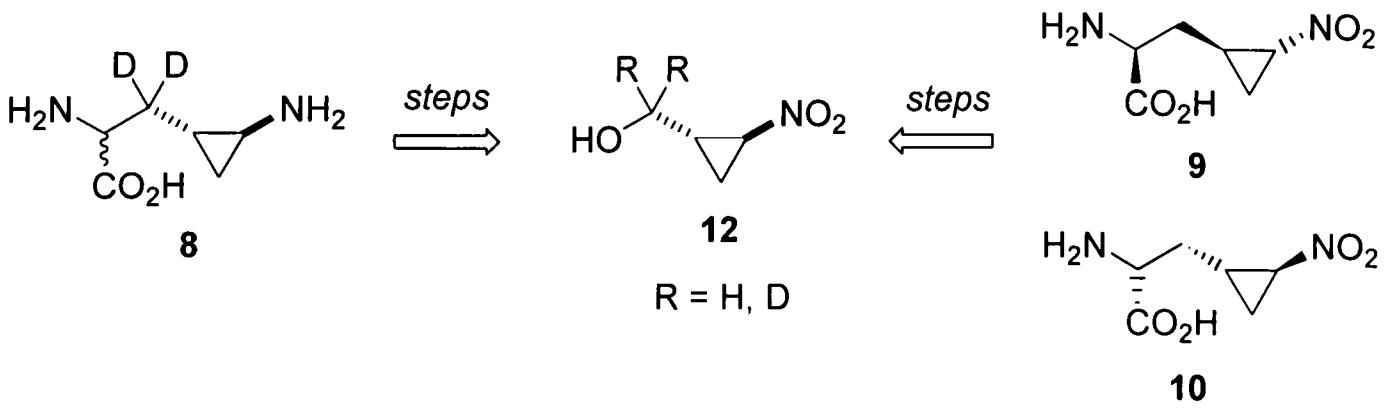


10

(2*R*, 1'*S*, 2'*R*)-NcpAla

Figure 6

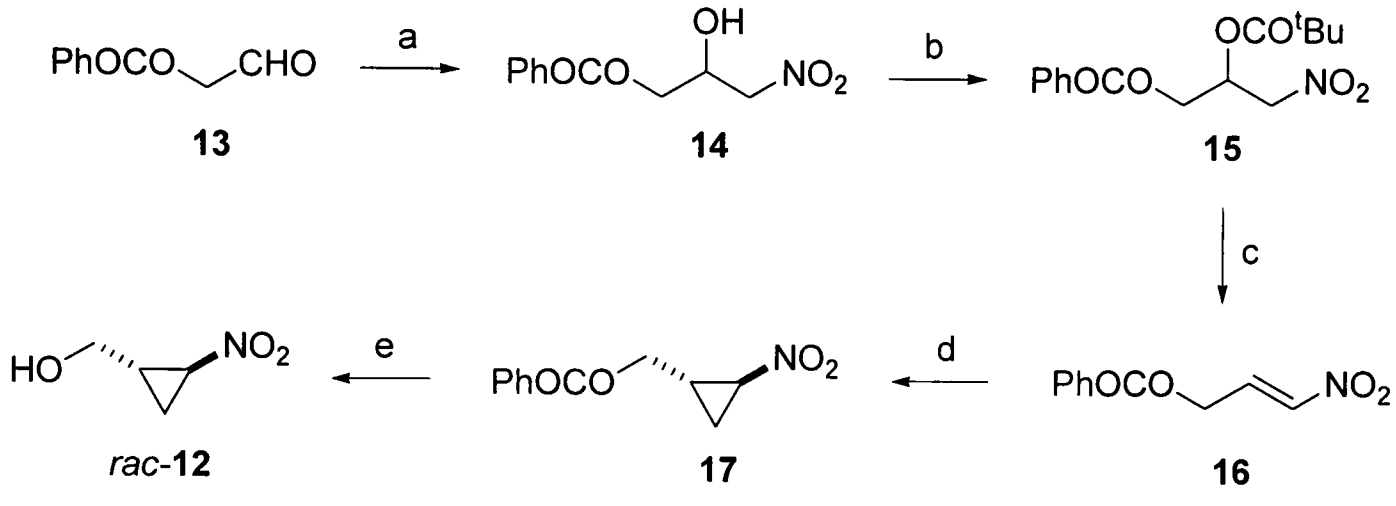
The key intermediate in de Meijere's synthesis of both (2*S*/*R*, 1'*R**, 2'*S**)-3,3-D_2-AcpAla **8** and **9**/**10** was *trans*-nitrocyclopropyl methanol **12** (Scheme 1), and since 1993 he has reported four unique routes to this compound. Two of these routes provide access to racemic material, whilst two produce non-racemic products. The various approaches to the synthesis of nitrocyclopropyl methanol **12** shall be discussed first.



8 → (*steps*) → **12** (R = H, D) ← (*steps*) ← **9** / **10**

Scheme 1

The first of these approaches used a sulfoxonium ylide mediated addition/ring-closure sequence to cyclopropanate nitroalkene **16** (Scheme 2).[10] This five-step route started with a nitro-aldol addition of nitromethane to aldehyde **13**, acylation of alcohol **14** with pivaloyl chloride, then subsequent treatment with sodium acetate to effect elimination. Cyclopropanation using Corey's dimethylsulfoxonium methylide reagent then generated the required *trans*-nitro cyclopropane **17**, but in low yield of 13%. Final hydrolysis then furnished the target *rac*-**12** (Scheme 2).

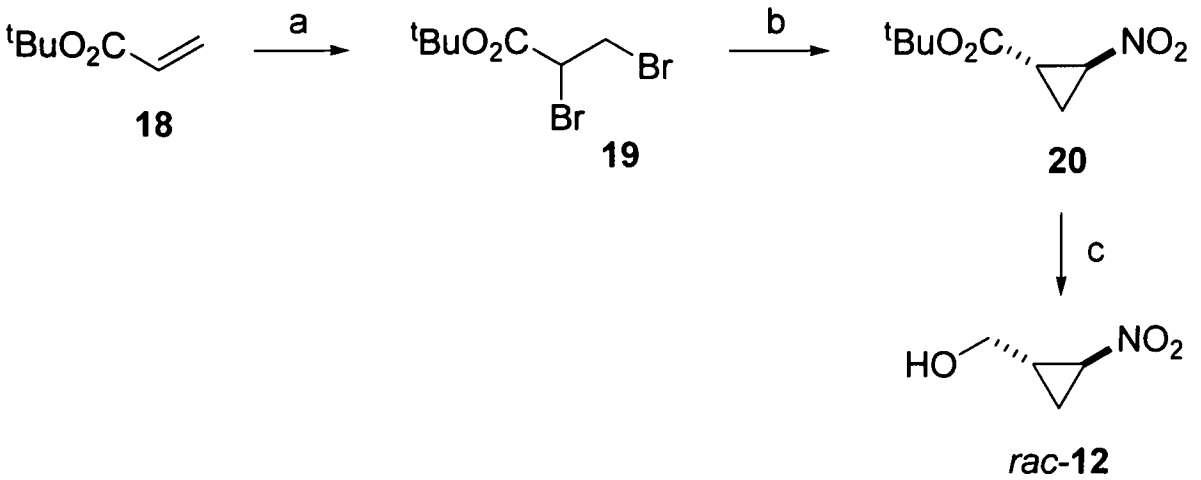


13 **14** **15** **16** **17** ***rac*-12**

Scheme 2

Reagents and conditions: (a) $MeNO_2$, NaOMe, 94 % (b) ^tBuCOCl, 97 % (c) NaOAc, 86% (d) $Me_2SO{=}CH_2$, 13% (e) NaOH, 61%.

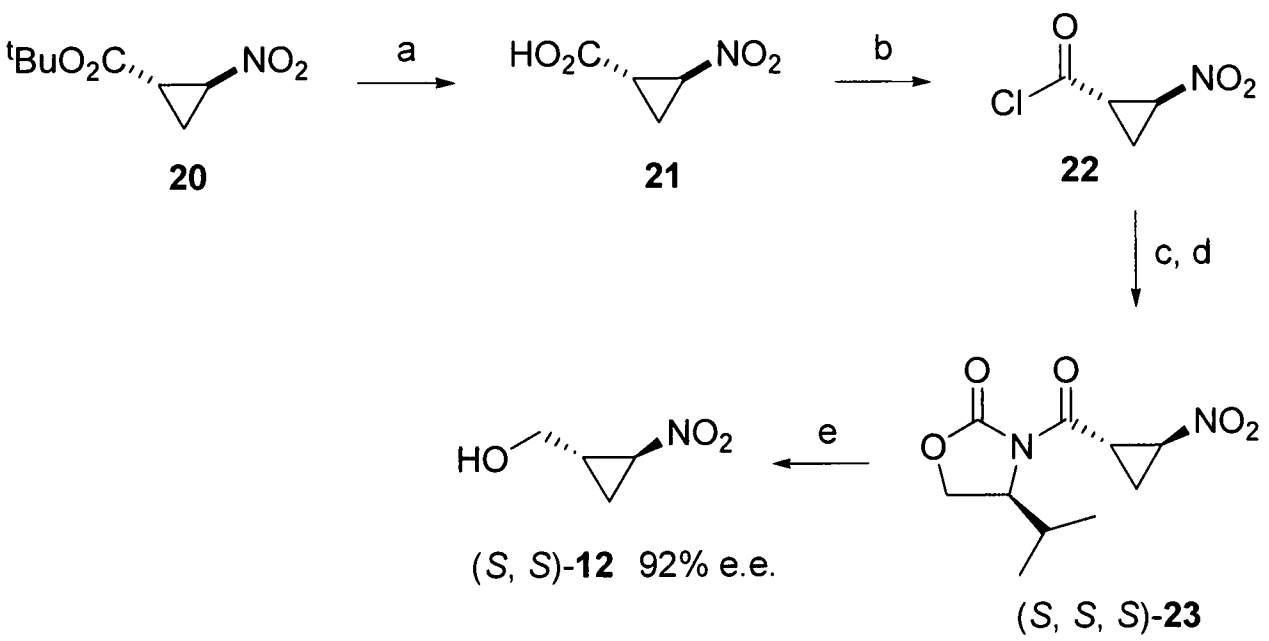
De Meijere's second approach to *rac*-**12** relied on a more direct three-step sequence based on the double substitution of the 1,2-dibromo ester **19** by nitromethane (Scheme 3).[10] This route was first published in 1993, but was significantly improved in 2003 by subtle changes to the experimental procedure.[11] Treatment of *tert*-butyl acrylate **18** with bromine forms the 1,2-dibromo propionate **19**, which upon treatment with $MeNO_2/K_2CO_3$ then undergoes a double substitution reaction to establish the *trans*-nitro cyclopropane **20** in 59% yield. A final addition of lithium aluminium hydride to *trans*-nitrocyclopropane **20** then successfully reduced the *tert*-butyl ester to reveal the target alcohol *rac*-**12** (Scheme 3).



Scheme 3

Reagents and conditions: (a) Br_2, 81% (b) $MeNO_2$, K_2CO_3, 59 % (c) $LiAlH_4$, 98 %

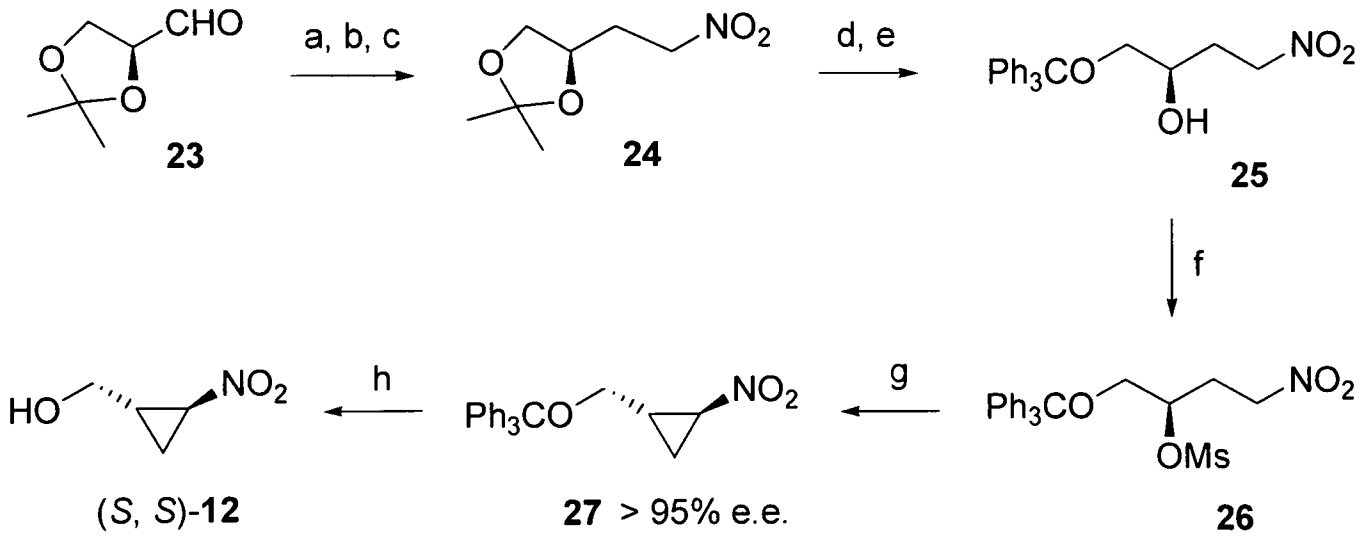
The first of the asymmetric routes was separation-based,[8] and intercepts nitro-cyclopropane **20** (*vide supra*). Hydrolysis of *tert*-butyl ester **20** and activation as the acid chloride **22** allowed coupling with lithiated (*S*)-4-isopropyl-1,3-oxazolidin-2-one to give a mixture of diastereoisomers, which were then separated by recrystallisation to afford the more crystalline oxazolidinone (*S*, *S*, *S*)-**23** in 21% yield (one step, five recrystallisations). Reductive cleavage of the auxiliary then furnished (*S*, *S*)-nitrocyclopropyl methanol **12** in 92% e.e. (Scheme 4).



Scheme 4

Reagents and conditions: (a) TFA, CH_2Cl_2, 84 % (b) $SOCl_2$, 97% (c) BuLi, (S)-4-isopropyl-1,3-isoxazolidin-2-one (d) 5 x crystallisations hexane/$CHCl_3$, 21 % (2 steps) (e) $LiAlH_4$, 87 %.

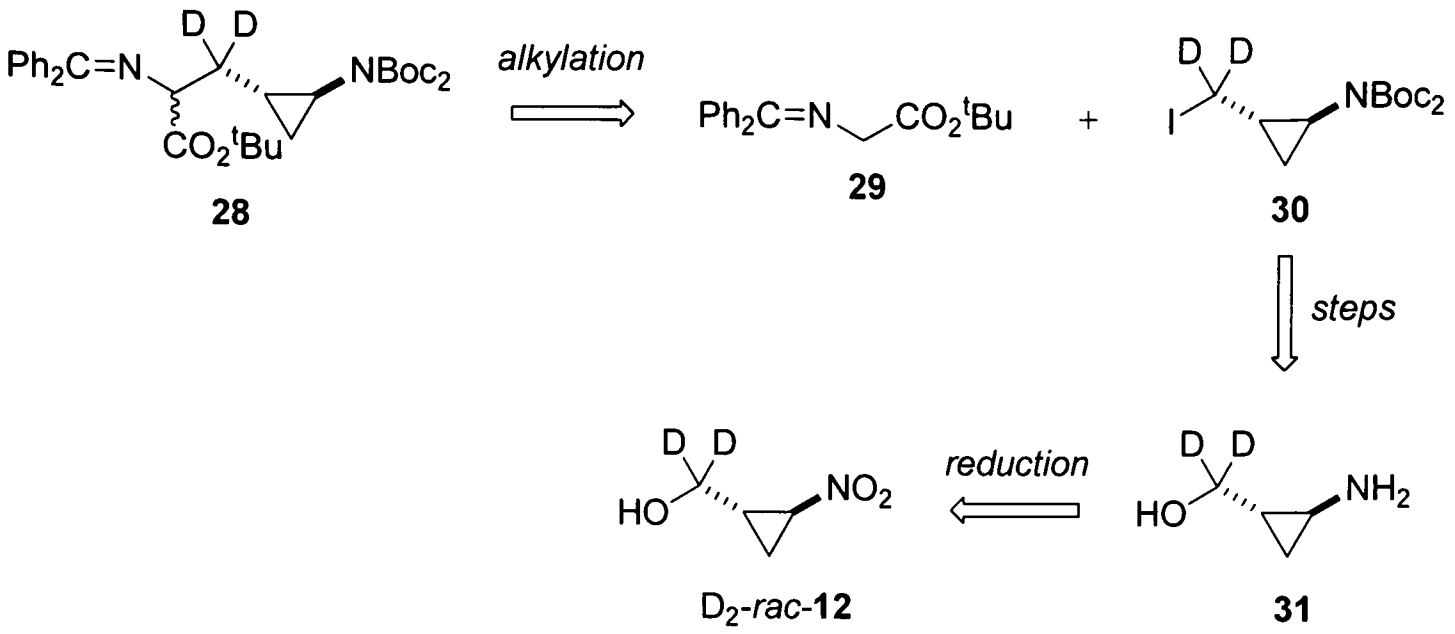
The second asymmetric route to (*S*, *S*)-**12** is a lengthy eight-step procedure relying on the cyclisation of an enantiomerically pure γ-nitro mesylate **26** (Scheme 5).[10] This approach utilised glyceraldehyde acetonide as the source of chirality, allowing synthesis of both nitrocyclopropane enantiomers from either enantiomer of the starting material. Nitromethane addition to aldehyde **23** was followed by acetylation then conjugate reduction to afford nitroalkane **24**. The acetonide was removed with tosic acid to reveal the diol, followed by subsequent trityl-protection of the primary alcohol to afford **25**, and mesylation of the remaining secondary hydroxyl group to afford **26**. This γ-nitro mesylate **26** was then heated with Na_2CO_3 in $PhCH_3$ to effect a *trans*-selective 3-*exo*-tet ring closure, affording cyclopropane **27** (> 95% e.e.), followed by subsequent deprotection under acidic conditions to reveal the target nitrocyclopropane (*S*, *S*)-**12** (Scheme 5).



Scheme 5

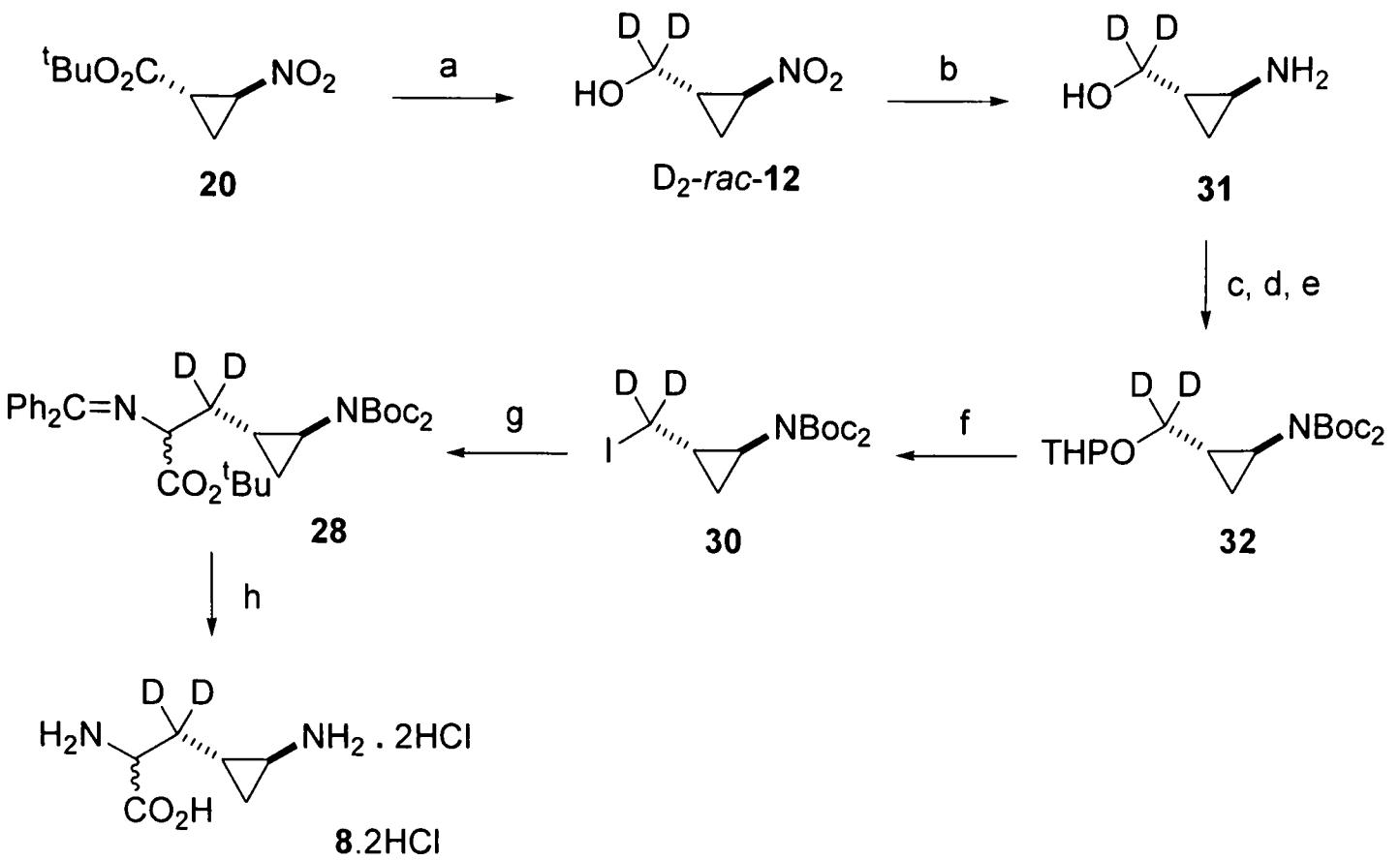
Reagents and conditions: (a) $MeNO_2$, KF (b) Ac_2O, DMAP (c) $NaBH_4$, 71 % (3 steps) (d) TsOH, 80 % (e) Ph_3CCl, 87 % (f) MsCl, NEt_3, 91 % (g) Na_2CO_3, $PhCH_3$, 57 % (h) TsOH, 87 %.

As previously stated, de Meijere used D_2-*rac*-**12** as the starting point for his synthesis of dideutero-AcpAla **28**.[8] The key transformations in this approach involved the chemoselective nitro-reduction of D_2-*rac*-**12**, and glycine enolate alkylation of α-iodo cyclopropylamine **30** (Scheme 6).



Scheme 6

This work was carried out in the racemic series, using D_2-*rac*-**12**, synthesised *via* the more concise *tert*-butyl acrylate route (see previous Scheme 3/Scheme 4). The first step was reduction of ester **20** using $LiAlD_4$, in 83% yield, then chemoselective reduction of the nitro group in quantitative yield to furnish cyclopropylamine **31**. After a series of protections (Boc-protection of amine, THP-protection of alcohol and second amine Boc-protection), the THP group was removed, allowing synthesis of iodide **30** in a one-pot reaction using I_2/dppe. The low yield of iodide **30** (34%) was reportedly due to the instability of the product. Glycine alkylation using BuLi/THF afforded **28** in 82% yield, but as an inseparable mixture of C2-diastereoisomers with little stereoselection (precise d.r. not reported). The final step involved global deprotection of all acid-labile protecting groups to furnish amino acid **8**.2HCl (Scheme 7).



Scheme 7

Reagents and conditions: (a) $LiAlD_4$, 83 % (b) H_2, Pd/C, 100 % (c) Boc_2O, MeOH, 71 % (d) DHP, PPTS, CH_2Cl_2, 97% (e) Boc_2O, DMAP, MeCN, 90% (f) I_2, dppe, CH_2Cl_2, 34 % (g) **29**, BuLi, 82 % (h) 1M HCl, 93 %.

In conclusion, although de Meijere had established a rapid three-step sequence to *rac*-**12** (47 % overall yield), synthesis of enantiomerically pure (*S*, *S*)-**12** required eight steps (22 % overall yield) using the chiral pool approach, and seven steps (7 % overall yield) *via* the separation approach. In addition, final glycine alkylation of cyclopropyl iodide **30** was achieved without useful levels of stereoselection, and separation of the diastereoisomers was not achieved.

1.3.2 Synthesis of a related (isomeric) β-lactone

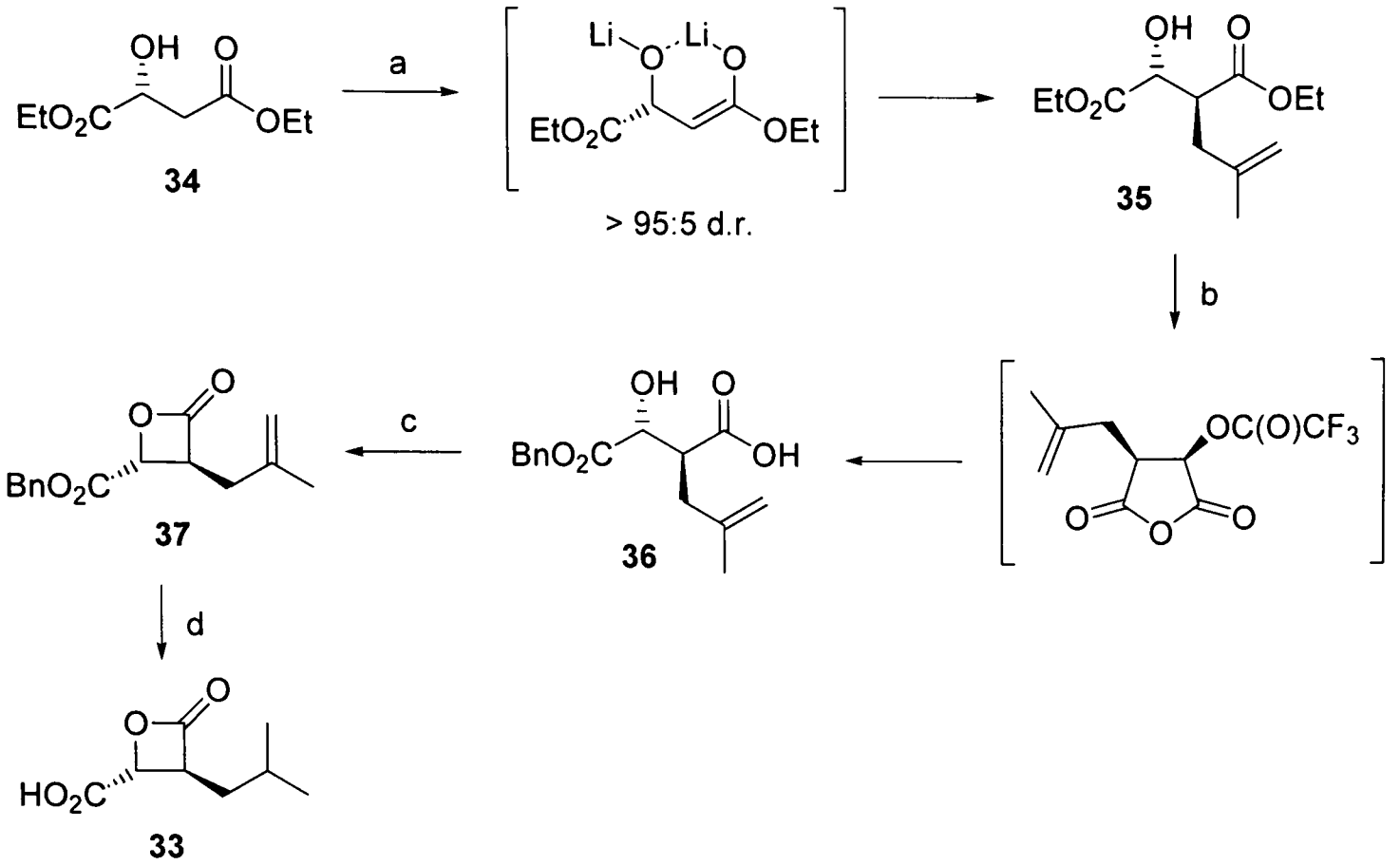
In contrast to the central AcpAla amino acid, the β-lactone moiety had not yet succumbed to synthesis. However, related work is found in an SAR patent filed by Kyowa Hakko Kogyo Co. Ltd. in 2000,[7] describing the synthesis and evaluation of around 50 derivatives of the natural product (based on different groups at the amine/carboxylate positions). Most derivatives were based upon degradation products, but due to its sensitivity, this was not a viable approach to obtain the basic

β-lactone fragment. Chemical synthesis of **5** was complicated by the exocyclic stereocentre, so workers switched the target to the much simpler isobutyl isomer **33** (Scheme 8).

5 **33**

Scheme 8

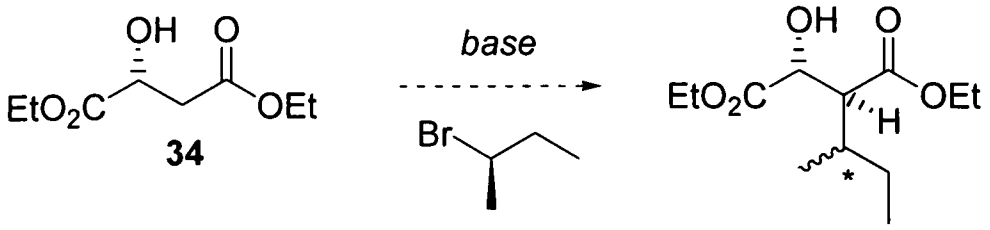
The synthetic sequence to **33** relies on the cyclisation of an activated β-hydroxy carboxylic acid precursor, and begins with a diastereoselective alkylation of (*R*)-(+)-malate **34** using 3-bromo-2-methylpropene, to furnish the allyl-derivative **35** in 81 % yield (presumably >95 % d.r.). Hydrolysis of **35** followed by treatment with trifluoroacetic acid/benzyl alcohol according to the methodology of Guérin,[12] then effected a mono-esterification through cyclisation to the anhydride and regioselective ring-opening. Acid activation of **36** using bis(2-oxo-3-oxazolidinyl)phosphinic chloride then induced cyclisation to **37** in 44 % yield, which was followed by hydrogenation/hydrogenolysis to give β-lactone acid **33** in 94% yield (Scheme 9).



Scheme 9

Reagents and conditions: (a) 3-bromo-2-methylpropene, 2 eq. LiHMDS, 81 % (>95% d.e.) (b) 1,4-dioxane, aq. KOH; TFAA; BnOH, NEt_3, DMAP, 100 % (c) bis(2-oxo-3-oxazolidinyl)phosphinic chloride, NEt_3, 44% (d) H_2, Pd/C, EtOH, 94%.

Although this is a concise four-step sequence to enantiomerically pure β-lactone **33** (34% overall yield), it is doubtful this methodology could be extended to access natural (2*R*, 3*S*, 1′*S*)-β-lactone **5**. This is because alkylation of **34** with 2*R*-bromo-butane (for example), is likely to give poor results because of competing S_N2/S_N1 and elimination pathways (Scheme 10).



Scheme 10

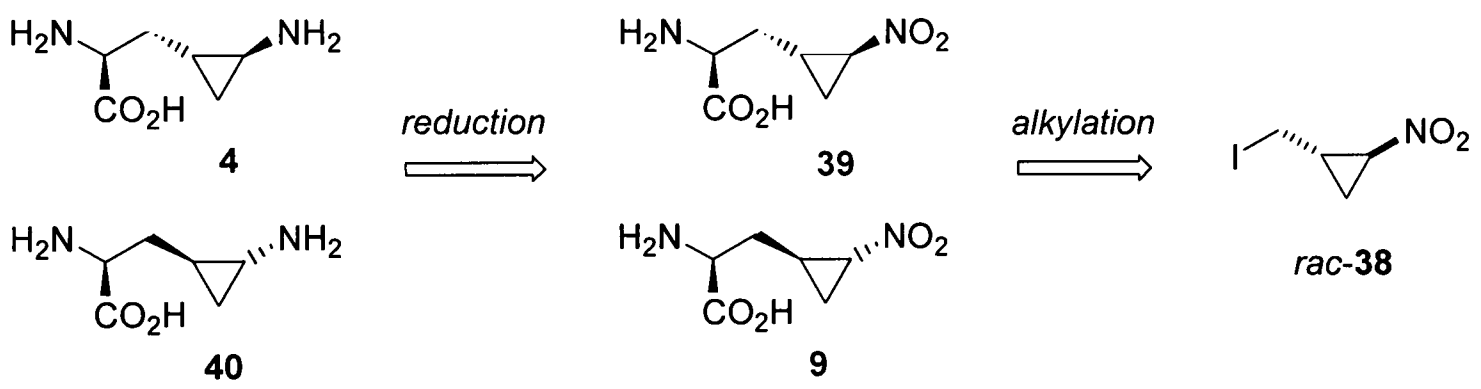
1.4 Recent synthetic work

Since we began our total synthesis project there has been increasing interest in (+)-belactosin A (+)-**1**, particularly from groups synthesising compounds closely related

to the central amino acid AcpAla.[13,14] After we published our enantioselective route to both (2*R*, 1′*S*, 2′*R*)-AcpAla and (2*S*, 1′*S*, 2′*R*)-AcpAla (*vide infra*),[15] both de Meijere[16] and Vederas[17] then reported their asymmetric routes to this amino acid. Similarly, after we published the first total synthesis of (+)-belactosin A,[18] de Meijere then successfully completed his synthesis.[19] These approaches will be briefly discussed *vide infra.*

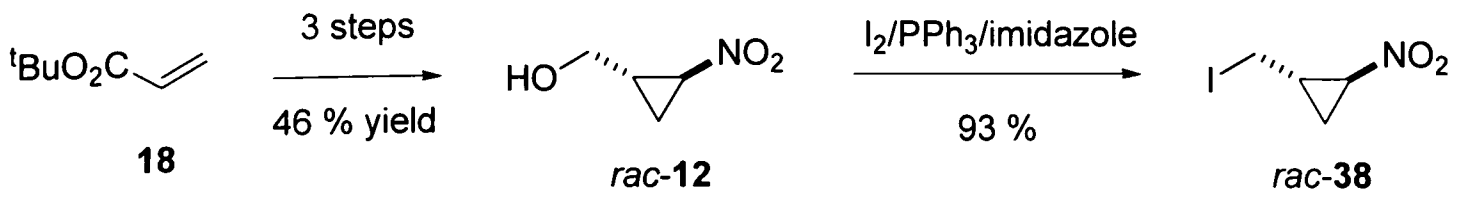
1.4.1 De Meijere's synthesis of AcpAla (all isomers)

This route is similar to earlier work in the de Meijere group, but avoids the need to synthesise enantiomerically pure nitrocyclopropyl methanol (*S*, *S*)-**12**. Instead, alkylation of *rac*-**38** using a chiral glycine template then allows access to **9**/**39** through separation of the diastereomers (after deprotection).[16] In addition, reduction of the nitro group was left to the final step in the synthetic sequence (Scheme 11).

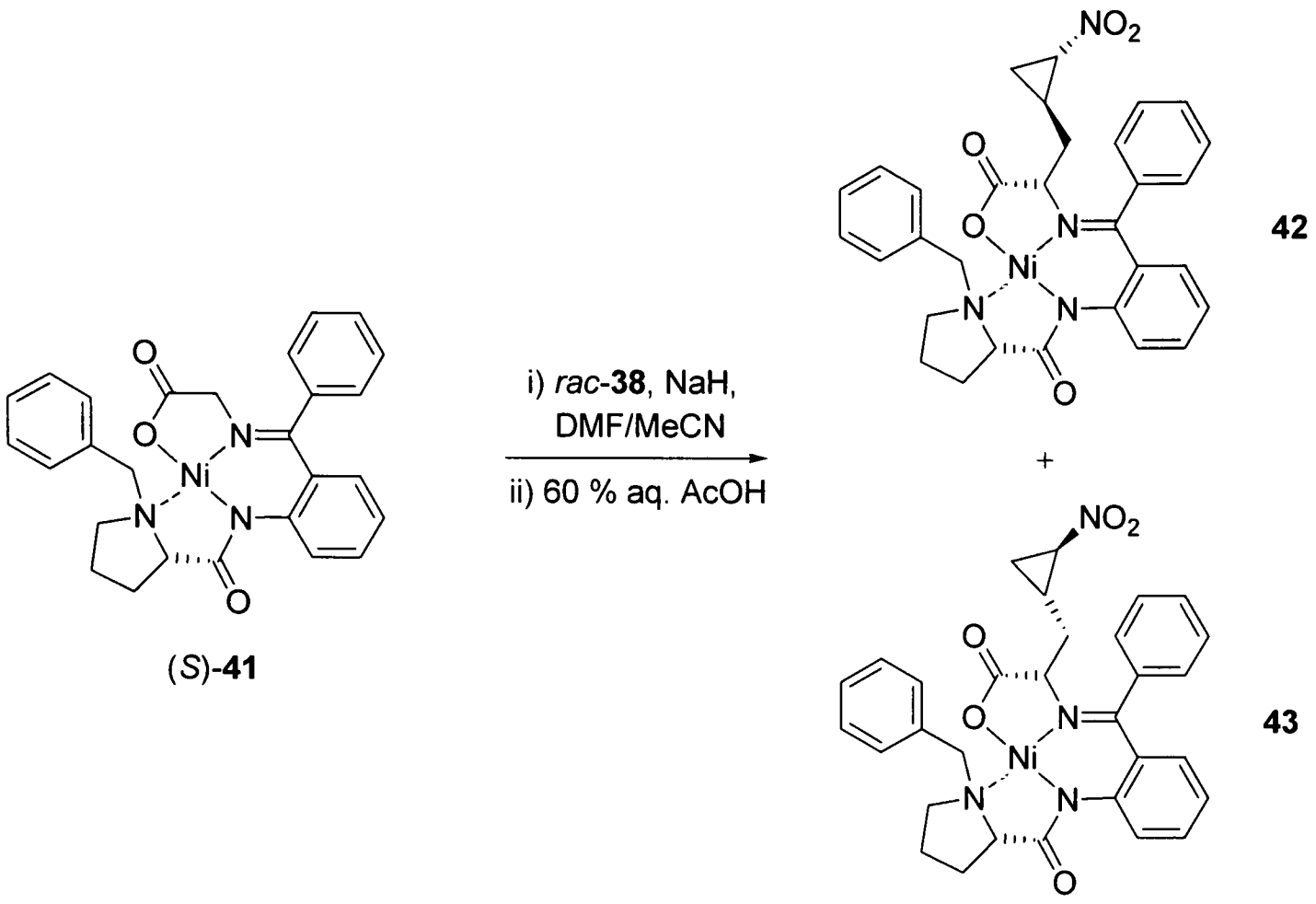


Scheme 11

Nitrocyclopropyl iodide *rac*-**38** was synthesised from the known alcohol *rac*-**12** in high yield using standard iodination chemistry (Scheme 12). This iodide was then alkylated with a stoichiometric amount of *S*-proline-based nickel-glycine complex (*S*)-**41**, generating a mixture of two C2-isomers **42** and **43** as the major components. Only "trace" (unquantified) amounts of the undesired diastereoisomers were observed (Scheme 13).



Scheme 12



Scheme 13

The precipitate formed from this reaction was found to be enriched in **42** (86:14 **42/43** ratio), whereas the reaction liquor was enriched in **43** (25:75 **42/43** ratio). After further manipulations/recrystallisations and deprotection of the auxiliary (6 M HCl; DOWEX) the desired free amino acids **39** and **9** were isolated in modest overall yields (Figure 7). The same sequence of alkylation, separation and deprotection was also used to synthesise isomers **44** and **10**, using nickel-complex (*R*)-**41** (Figure 7).

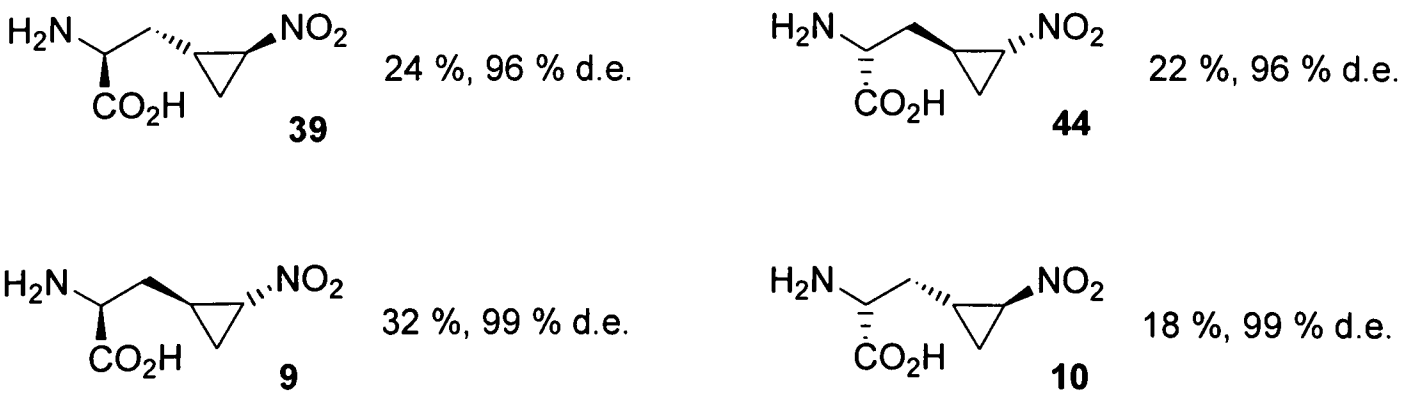
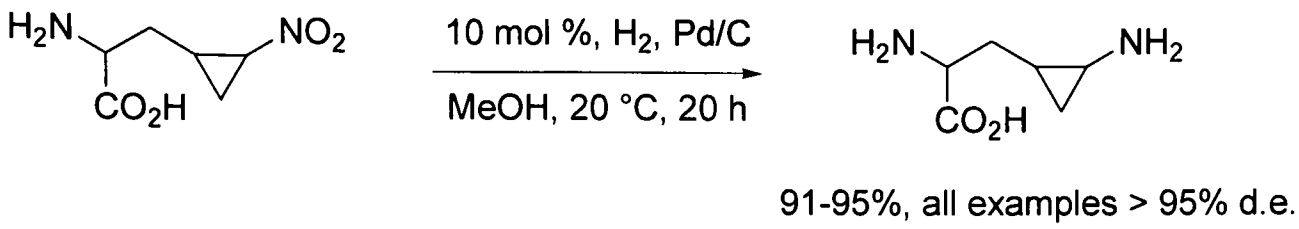


Figure 7

The key hydrogenation of these compounds was then achieved under standard conditions, with all four *trans*-AcpAla stereoisomers being synthesised in high yield

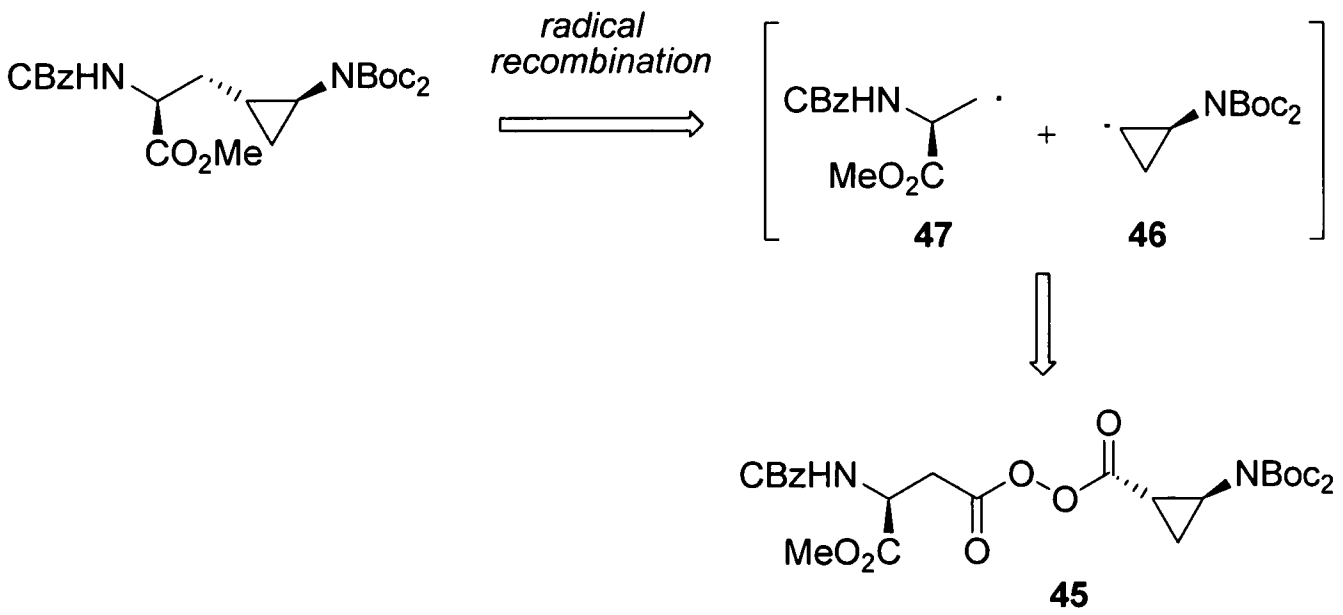
without epimerisation (Scheme 14). In contrast, previous attempts to hydrogenate the corresponding HCl-salts had resulted in substantial cyclopropane ring-opening.[8]



Scheme 14

1.4.2 Vederas' synthesis of (2*S*, 1'*R*, 2'*S*)-AcpAla

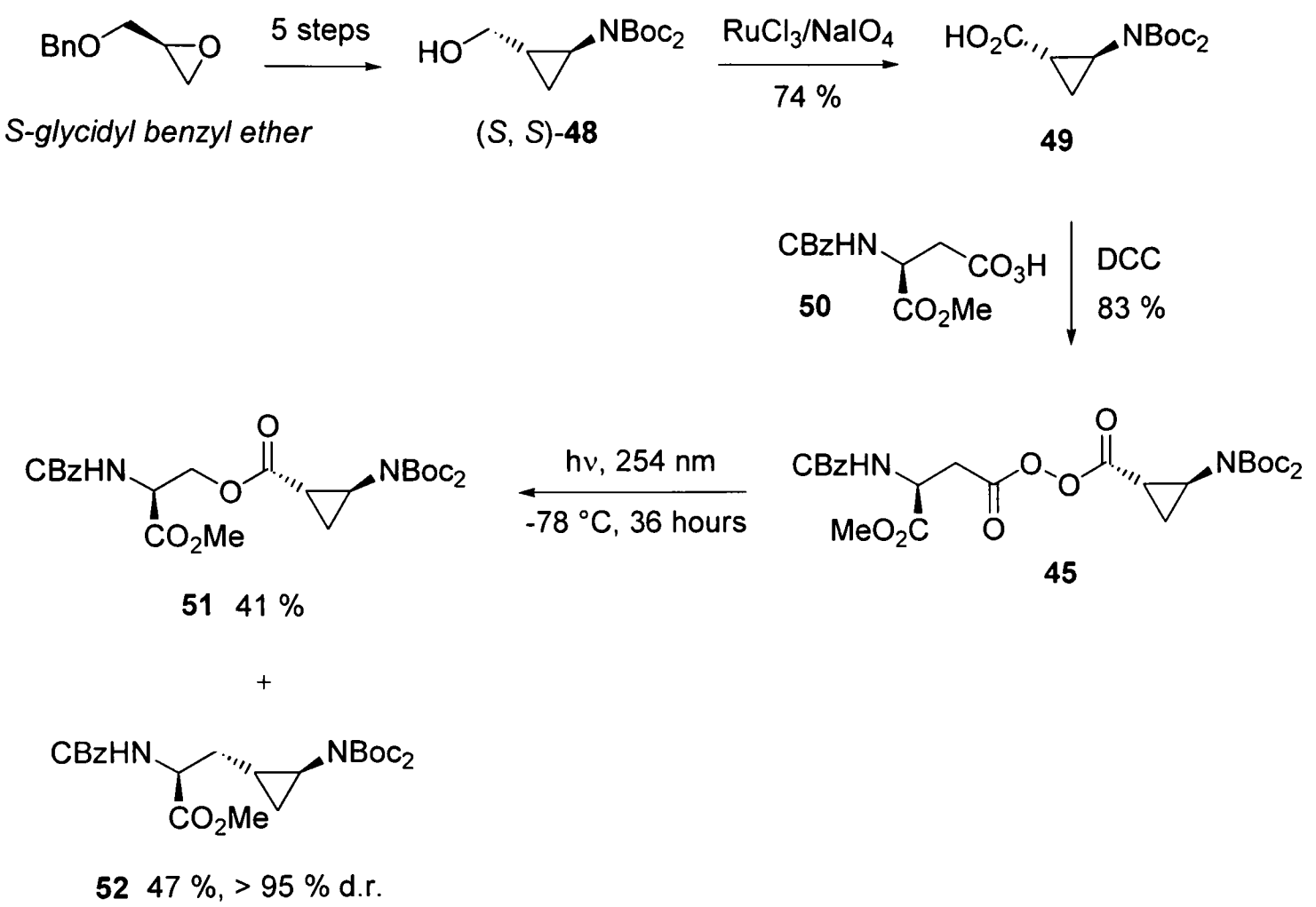
The synthesis by Vederas is noteworthy since it is markedly different to all other published work in the area. The key transformation relied on the coupling of cyclopropyl and alanine radicals, obtained *via* the photolysis of an unsymmetrical diacyl peroxide (Scheme 15).[17] Under the conditions of the reaction, the fully assembled alanine radical **47** recombined with the cyclopropyl radical **46** with overall retention of configuration.



Scheme 15

Vederas utilised our published procedure to synthesise enantiomerically pure aminocyclopropyl methanol (*S*, *S*)-**48**,[15] then oxidised this to the acid **49** using $RuCl_3/NaIO_4$ in 74 % yield (Scheme 16). Coupling of acid **49** with L-aspartic acid peracid **50** using standard DCC conditions furnished the key peroxide **45** in 83 %

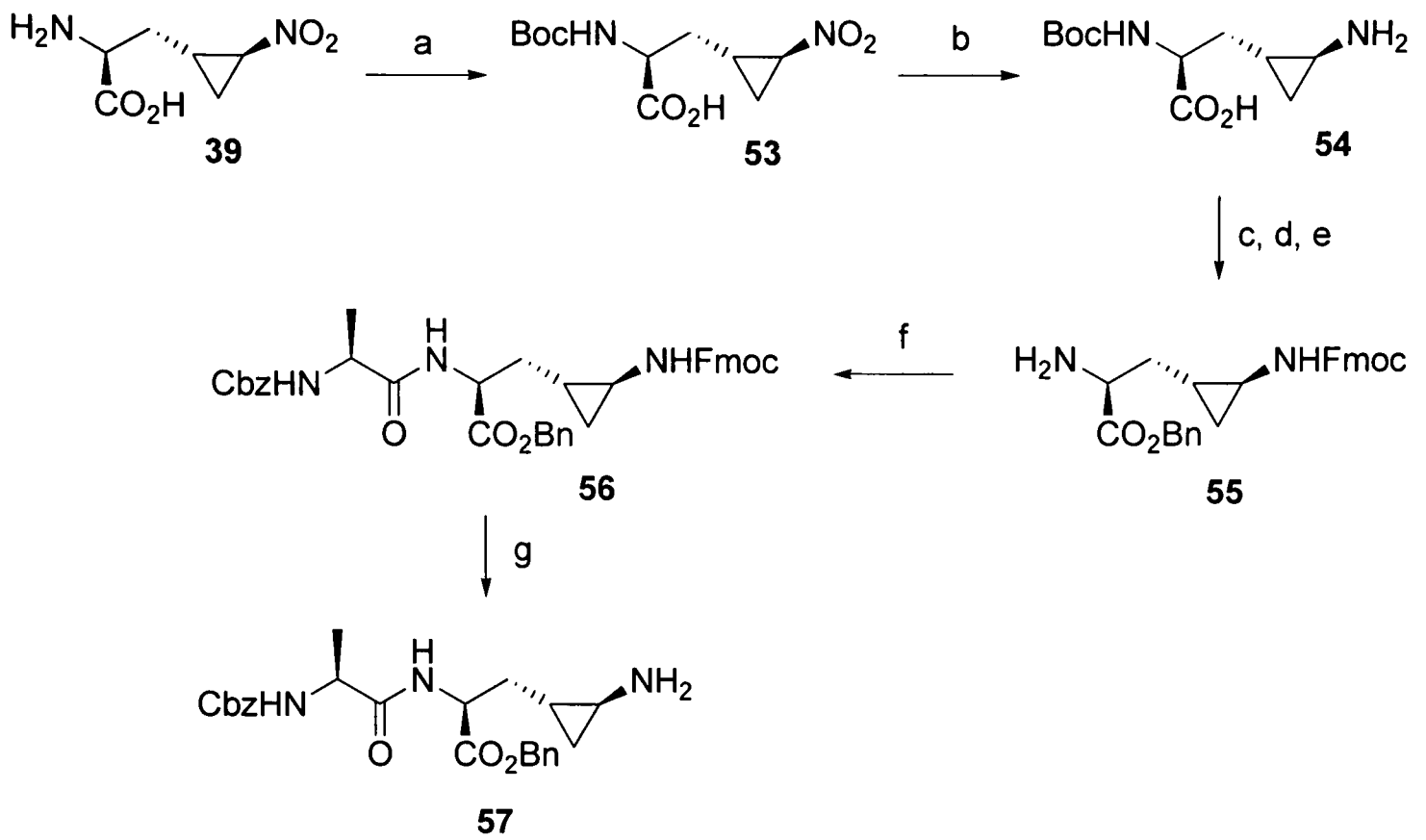
yield. Photolysis of neat **45** at -78 °C for 36 hours then produced a mixture of ester **51** in 41 %, and the desired (2*S*, 1'*R*, 2'*S*)-AcpAla **52** in 47 % yield and > 95 % d.e. (Scheme 16). The formation of **51** indicates that fragmentation of **45** to cyclopropyl radical **46** is less favoured than fragmentation to alanine radical **47**.



Scheme 16

1.4.3 De Meijere's total synthesis of (+)-belactosin A

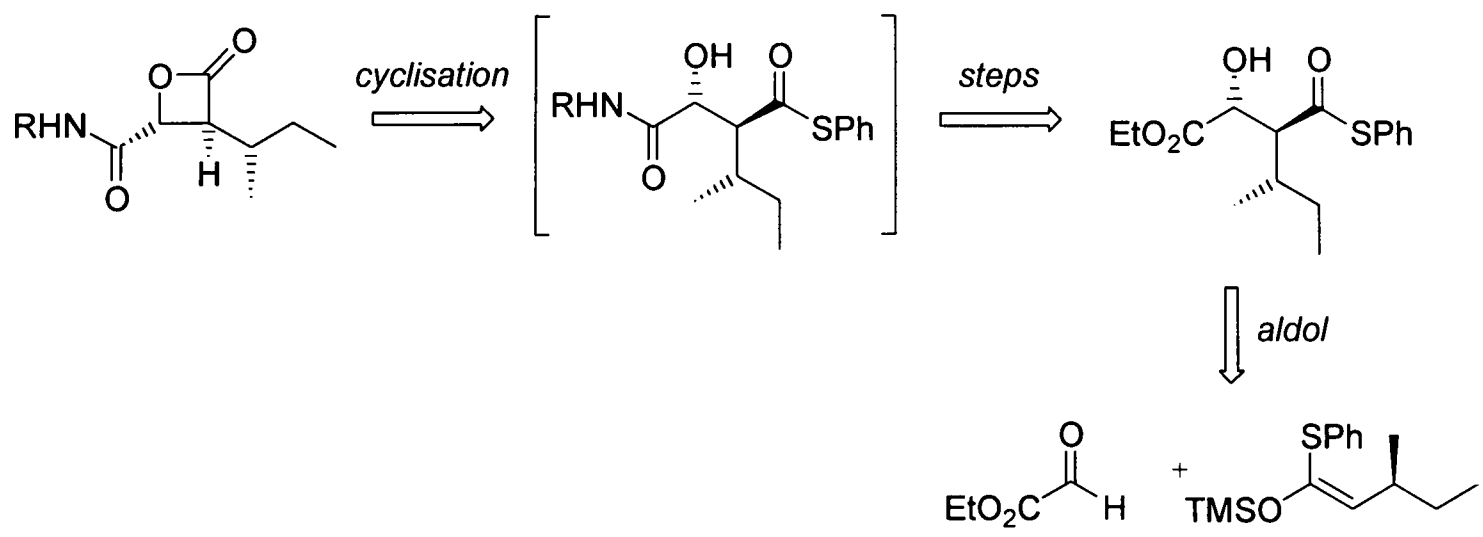
Having recently developed a new separation-based route to (2*S*, 1'*R*, 2'*S*)-AcpAla **4** (see section 1.4.1), de Meijere then attempted the total synthesis of (+)-**1**.[19] Initial attempts to orthogonally protect **4** were low yielding, so **39** was at first Boc-protected (98% yield) to distinguish between the two amines. Standard hydrogenation conditions resulted in cyclopropane cleavage, but under reducing metal conditions (Zn/AcOH) the target amine **54** was furnished in high yield. Following Fmoc-protection of the amine, benzyl-protection of the acid and subsequent Boc-deprotection, amine **54** was then coupled to CBz-Ala-OH using EDCI and HOAt. Finally, the Fmoc group was removed using diethylamine to reveal the *N*-Ala-AcpAla framework **57** (Scheme 17).



Scheme 17

Reagents and conditions: (a) Boc_2O/Na_2CO_3, 6M aq. HOH/dioxane, 98% (b) Zn/AcOH (c) Fmoc-OSu/Na_2CO_3, 75% (2 steps) (d) CBzCl/DMAP, Hunig's base, 81% (e) TFA/$^{i}Pr_3SiH$ (f) CBz-Ala-OH/EDCI/HOAt, 94% (2 steps) (g) Et_2NH.

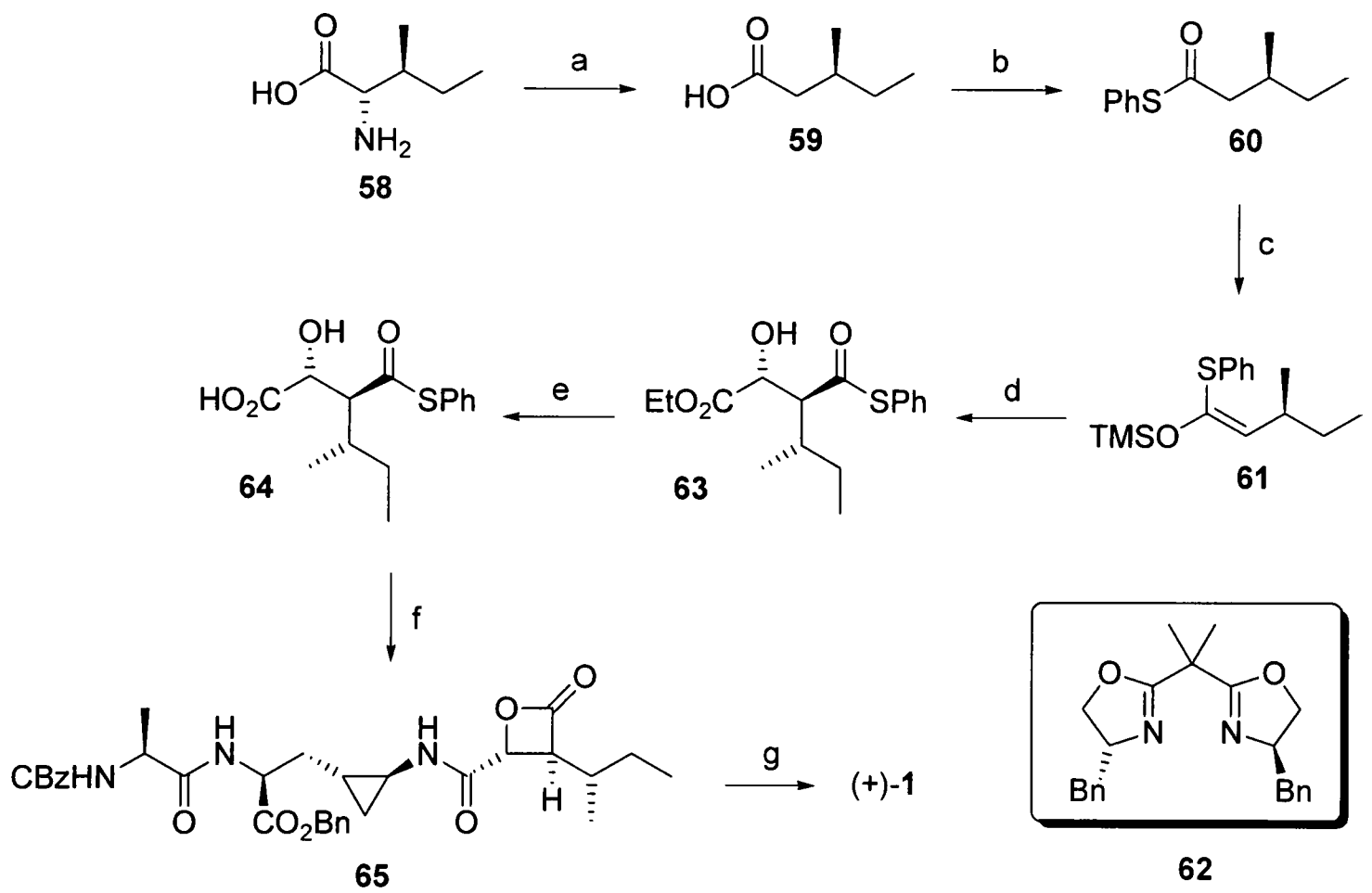
The β-lactone moiety was constructed by cyclisation of an enantiomerically pure β-hydroxy thio ester, which was itself derived from an anti-selective aldol reaction (Scheme 18).



Scheme 18

The sequence began by hydrodeamination of L-isoleucine **58** (using aq. NaOH/HOSA)[20] to give acid **59** in 84 % yield, followed by conversion over two steps

to the (Z)-silyl thio ketene acetal **61**. Using a $Sn(OTf)_2$/bisoxazoline **62** catalytic system developed by Evans,[21] **61** was then reacted with ethyl glyoxylate to afford the malic acid derivative **63** in 99 % yield (> 40:1 d.r.). At this stage a chemoselective ethyl ester hydrolysis was required, and after much experimentation, this was achieved in 74 % yield using 10 % aq. HCl/dioxane under strict temperature control (60 °C ± 3 °C). Acid **64** was then coupled to amine **57** (using EDCI/HOAt), which also fortuitously mediated β-lactonisation under the reaction conditions to furnish peptide **65**. Finally, hydrogenolysis in acetic acid afforded (+)-belactosin A (+)-**1** in 52 % yield over 2 steps (Scheme 19).



Scheme 19

Reagents and conditions: (a) HOSA/aq. NaOH, 83 % (b) PhSH/DCC/DMAP, 97% (c) LiTMP/TMSCl, 92% (d) EtO_2CCHO/cat. $Sn(OTf)_2$/**62**, 99 % (e) aq. HCl/dioxane, 74 % (f) **57**/EDCI/HOAt/TMP (g) H_2/Pd/C, AcOH, 52 % (2 steps).

De Meijere's recent work reports the synthesis of orthogonally protected (2*S*, 1′*R*, 2′*S*)-AcpAla **54** in eight steps but very low overall 7% yield. The weakest point in this synthesis was the low-yielding separation-based alkylation, using a stoichiometric amount of chiral (non racemic) glycine template. In contrast, Vederas' synthesis of protected (2*S*, 1′*R*, 2′*S*)-AcpAla **52** utilised an impressive radical recombination

approach to construct the required framework (in 47% yield), but relied on our methodology to synthesise (*S*, *S*)-**48**. De Meijere's synthesis of the right-hand side of (+)-**1** was reasonably efficient, but followed a similar approach to that used by workers at Kyowa Hakko Kogyo Co. Ltd.. In both cases, the β-lactone moiety was formed by cyclisation of a malic acid derivative, with de Meijere constructing this key precursor by a modern catalytic anti-selective aldol reaction. After hydrolysis of the ethyl ester, attempted amino acid coupling also resulted in an unexpected but highly efficient β-lactonisation under the reaction conditions, which therefore avoided a potentially problematic (independent) cyclisation step.

CHAPTER 2

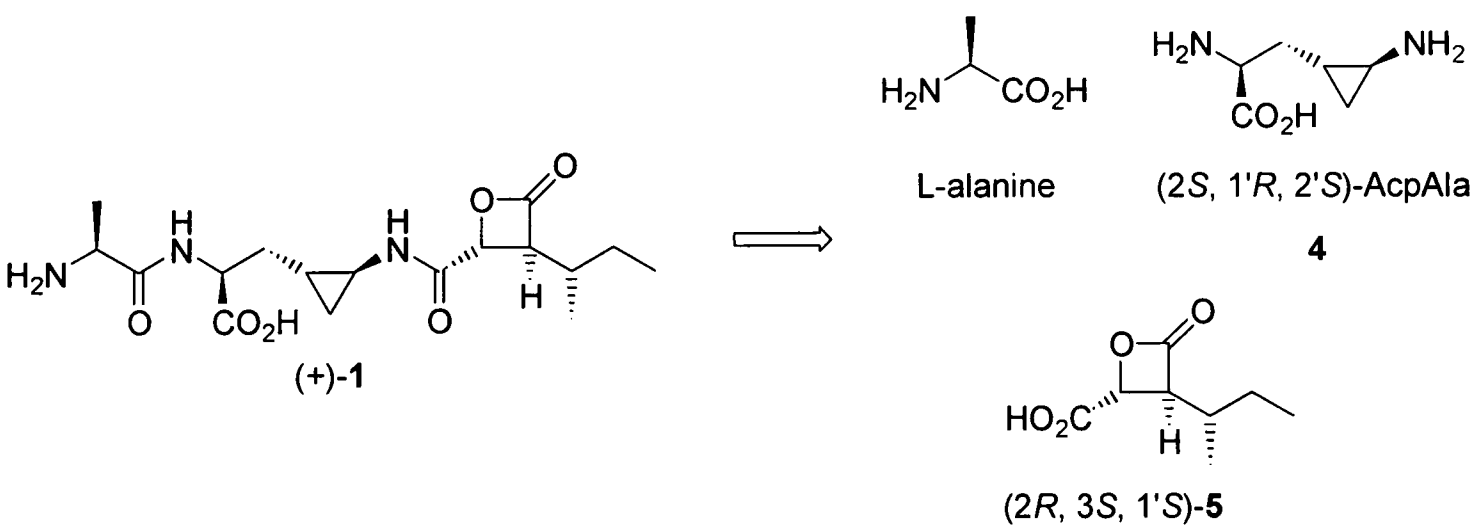
Results and discussion

Chapter 2: Results and discussion

2.1 Project aims

The principal aim of this research project was the total synthesis of (+)-belactosin A (+)-**1**. Isolation of (+)-**1** from nature is very inefficient, so a viable synthetic route to this important anti-cancer lead would greatly aid future SAR studies and investigations into its precise mode of action. From discussions in section 1.3, it is clear that previous work towards the synthesis of (+)-**1** was not well advanced. The central AcpAla amino acid had only been synthesised as a mixture of isomers, whilst synthesis of the natural β-lactone moiety had not yet been attempted.

Total synthesis of (+)-**1** is simplified through amide-disconnection, revealing L-alanine, (2*S*, 1′*R*, 2′*S*)-AcpAla **4** and (2*R*, 3*S*, 1′*S*)-β-lactone **5** (Scheme 20). We aimed to achieve a succinct and stereocontrolled synthesis of both **4** and **5**, either by the application and extension of modern catalytic methodology, or by further developing underexploited chemistry. Of the functionality present in (+)-belactosin A, we envisaged that the cyclopropylamine, β-lactone and AcpAla amino acid stereocentre would provide the greatest scope for synthetic investigation.



Scheme 20

Additionally, we aimed to devise a flexible synthetic sequence which would also allow access to isomeric (+)-belactosin A analogues, based upon the four stereoisomers of *trans*-AcpAla and the two stereoisomers of the *trans*-β-lactone (each featuring a 1′S exocyclic stereocentre). Combination of these components with L-

alanine would then lead to eight potentially valuable analogues for biological evaluation (Figure 8).

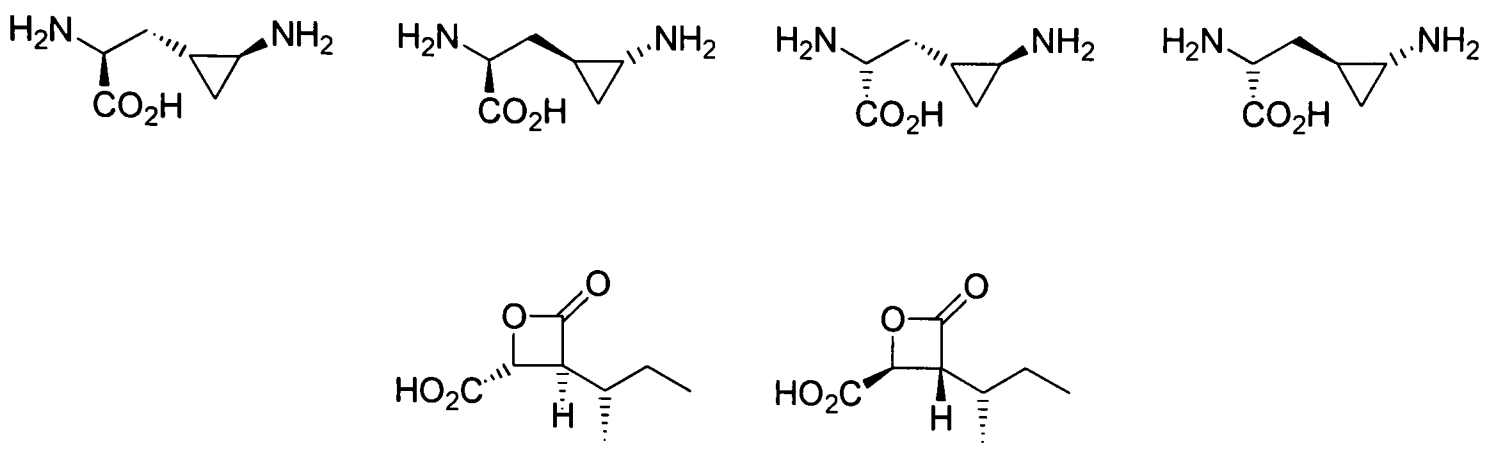
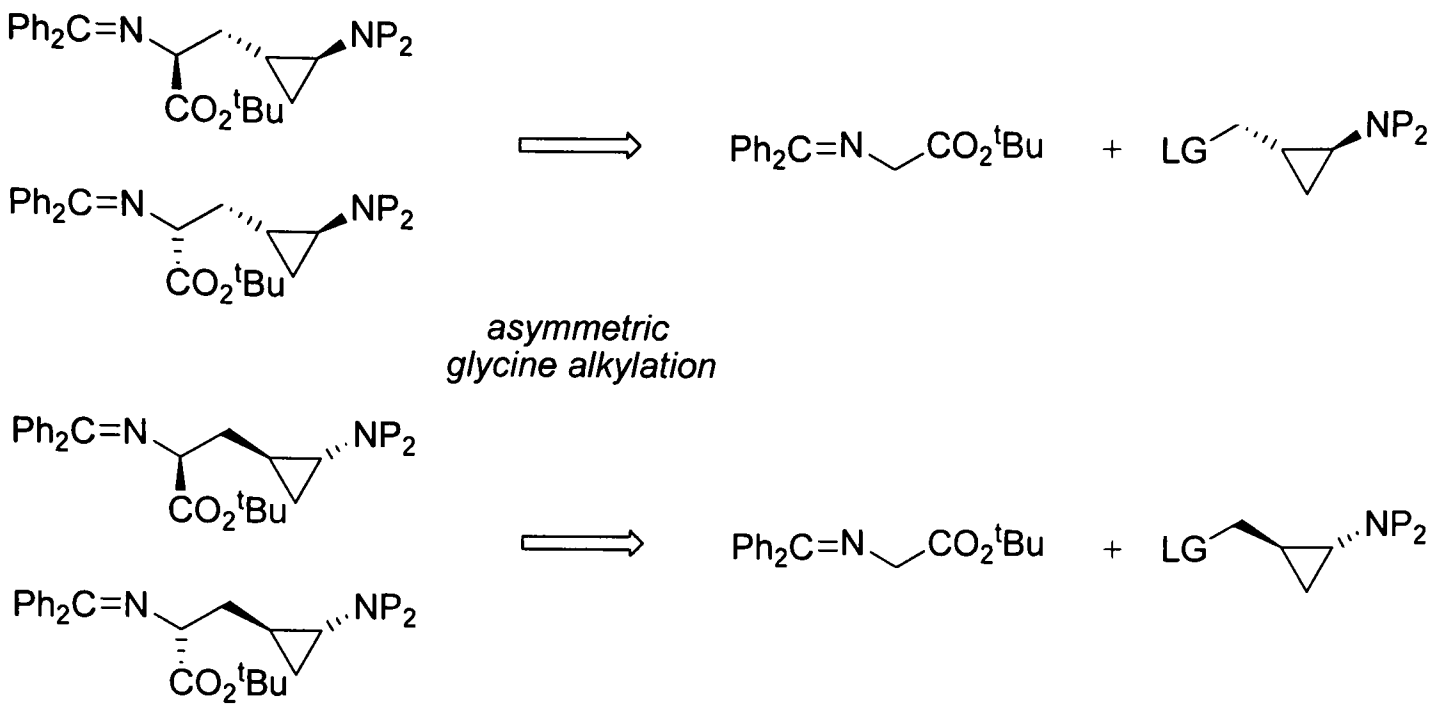


Figure 8

The ensuing chapters describe our ultimately successful synthesis of all four *trans*-AcpAla stereoisomers,[15,18] the synthesis of the natural β-lactone stereoisomer,[18] and the completion of the first total synthesis of (+)-belactosin A.[18]

2.1.1 Synthesis of *trans*-AcpAla isomers - overview of synthetic strategy

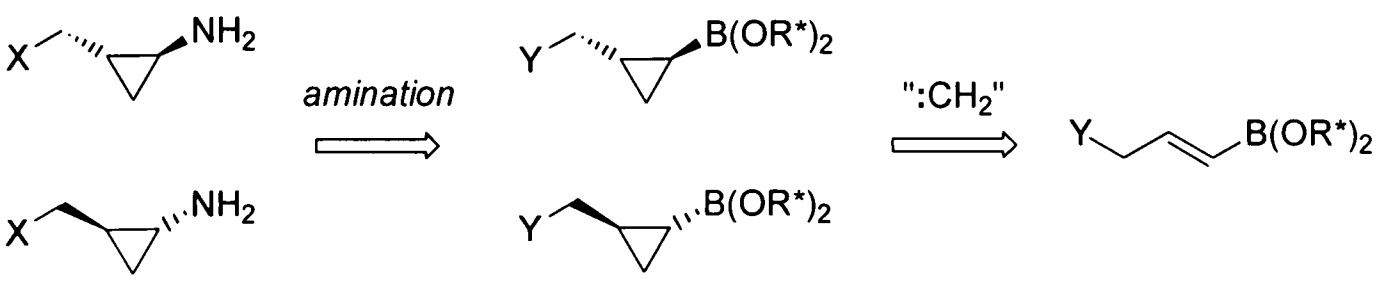
The first major challenge in the total synthesis of (+)-**1** (and analogues) was the synthesis of all four stereoisomers of *trans*-AcpAla. The key features of this central fragment are the cyclopropylamine and amino acid functionality. In order to make our synthesis as modular and rapid as possible, we planned to construct the amino acid stereocentre directly using glycine alkylation. Although this basic strategy was also used by de Meijere (in his non-selective synthesis of (2*S*/*R*, 1′*R**, 2′*S**)-AcpAla **8**),[8] we aimed to fully exploit this approach by using stereoselective phase-transfer glycine-alkylations.[22] This strategy therefore permits a rapid (divergent) synthesis of each C2-epimeric pair from a common α-activated cyclopropylamine (Scheme 21).



Scheme 21

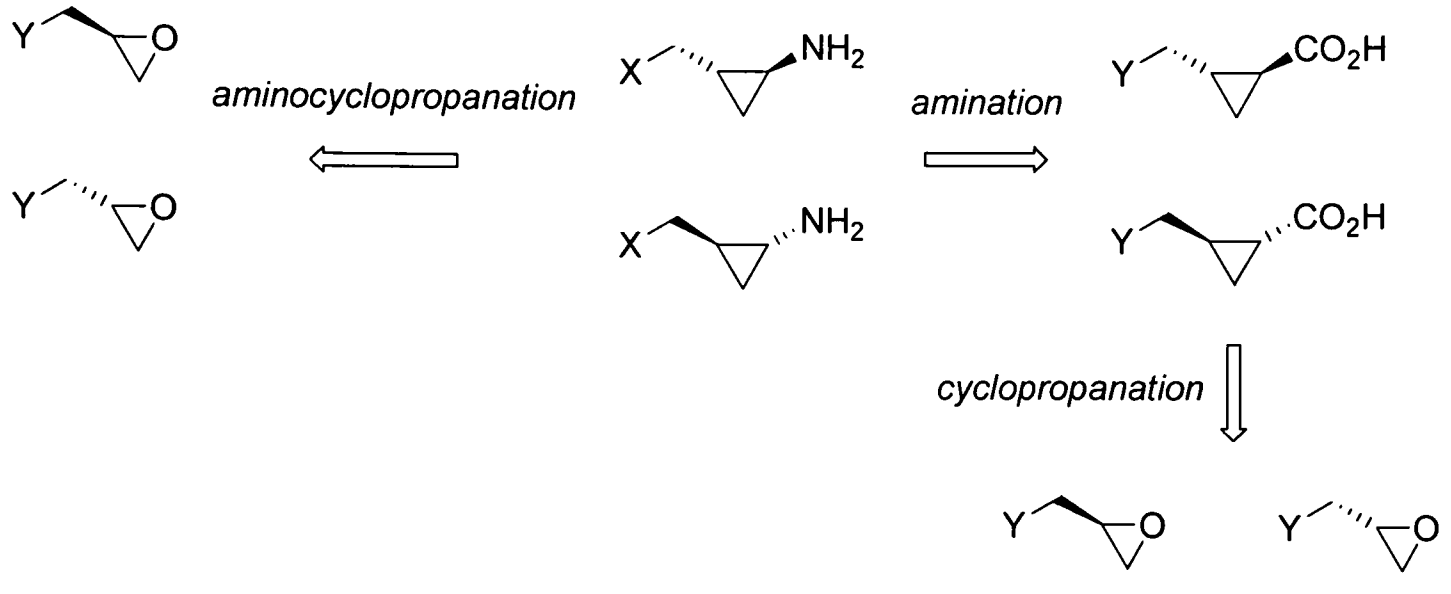
We viewed this to be a excellent approach, not only because it allowed rapid access to all stereoisomers, but also as an important test of the glycine-alkylation methodology. Asymmetric phase transfer glycine alkylation has become a powerful method of catalytic amino acid synthesis over recent years,[23] but to date the majority of this work has involved relatively simple electrophiles such as benzyl halides. We believed this application would be the most challenging example to date,[22(b)] and furthermore would build upon our group's interest in the synthetic application of organocatalysis.

Synthesis of the aminocyclopropyl moiety is conceptually more difficult, since no general and direct method of asymmetric aminocyclopropanation presently exists. Accordingly, we planned to use amine-transfer methodology, and initially aimed to investigate two independent approaches, with only the most successful ultimately being pursued. The more speculative of these two approaches relied on the novel amination of cyclopropyl boronic esters, which themselves would be accessed by the stereoselective cyclopropanation of enantiopure vinyl boronic esters (Scheme 22).



Scheme 22

The second approach relied on an unusual epoxide cyclopropanation. In this case we aimed to convert epoxides directly to cyclopropylamines, or alternatively access cyclopropyl esters which could later be aminated by acyl nitrene rearrangement. Direct aminocyclopropanation of epoxides has been reported only once previously,[24] whereas conversion of epoxides to cyclopropyl esters has attracted slightly more attention, but important stereochemical issues were still to be addressed (Scheme 23).



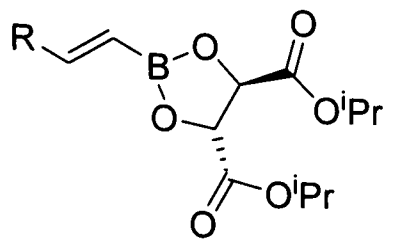
Scheme 23

2.2 Boronic ester route

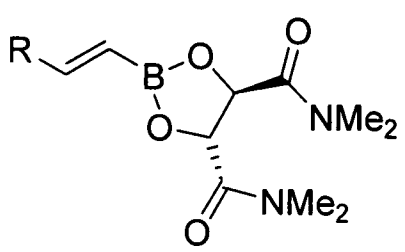
2.2.1 Introduction

Chiral (non-racemic) vinyl boronic esters have been used to direct stereoselective cyclopropanations for many years.[25,26,27] This process benefits from a stereospecific cyclopropanation, meaning that the geometry of the cyclopropane is dependant only on the *E*/*Z* geometry of the starting olefin. In addition, the residual boronic ester functionality can then be exploited by further synthetic manipulation, such as oxidation to cyclopropanols[28] and various metal-mediated cross-couplings.[29]

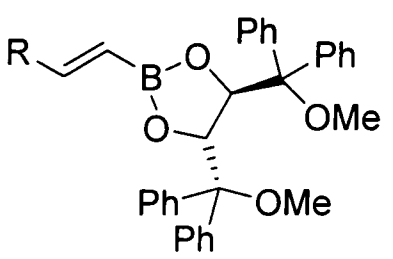
Tartrate-based vinyl boronic esters (such as **66**, **67** and **68**) reliably induce stereoselective cyclopropanations, with scaffold **68** becoming most popular in recent years due to its enhanced stability to chromatographic purification (Figure 9, Scheme 24).[27]



66

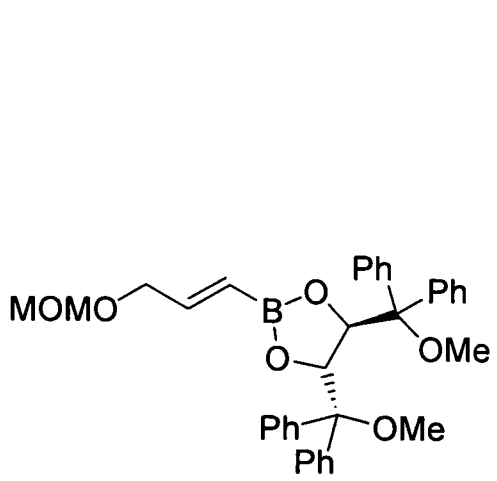


67

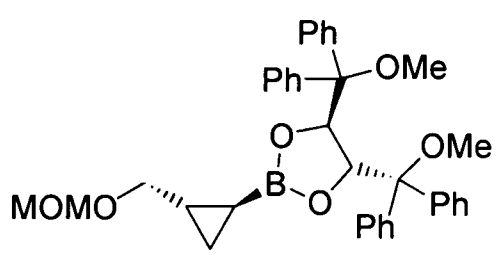


68

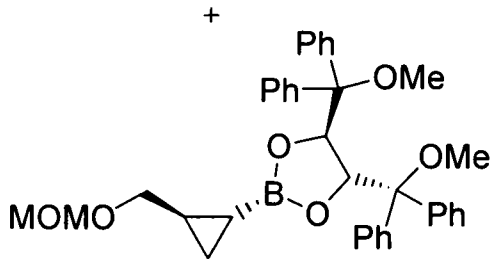
Figure 9



69



70



71

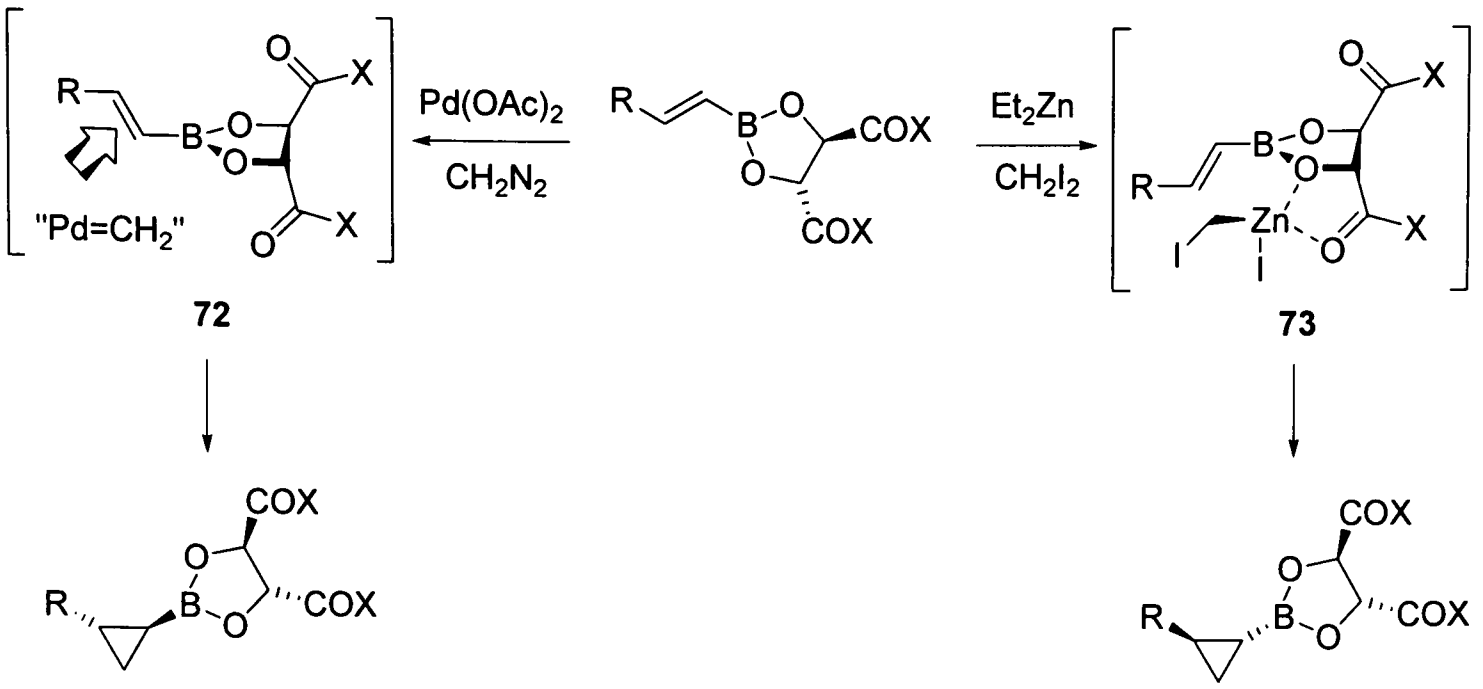
CH_2N_2, 5 mol % $Pd(OAc)_2$

ether, 0 °C

98 %, 86:14 (**70/71**)

Scheme 24

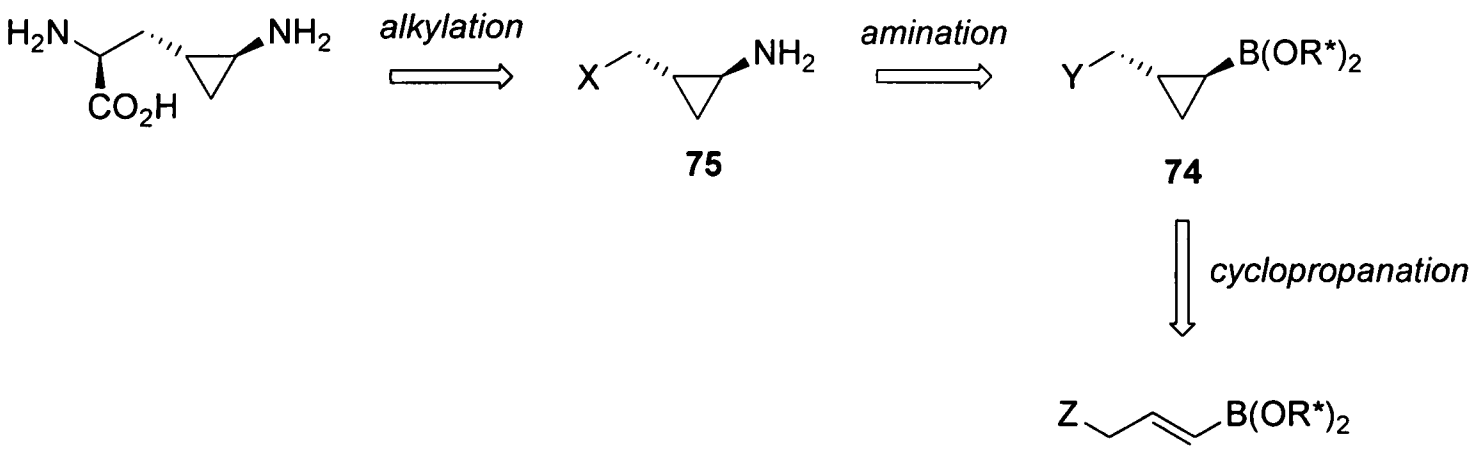
The sense of stereoinduction is determined by the conditions used. Under diazomethane conditions ($CH_2N_2/Pd(OAc)_2$)[26] cyclopropanation occurs from the less hindered prochiral face, whereas under Simmons-Smith conditions ($ZnEt_2/CH_2I_2$)[25] precomplexation leads to a directed methylene transfer from the opposite face (Scheme 25).



Scheme 25

2.2.2 Synthesis of cyclopropyl boronic esters

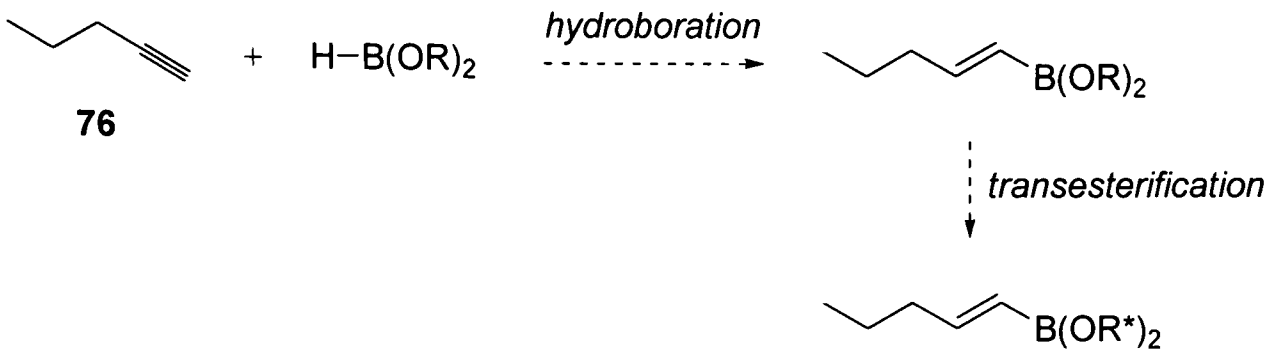
We aimed to extend the scope of this methodology by combining the cyclopropanation step with a novel amine-transfer reaction, which then potentially would provide access to either cyclopropylamine enantiomer in a concise sequence. Thus, key electrophile **75** would be obtained *via* amination of cyclopropyl boronic ester **74**, which itself would be obtained by diastereoselective cyclopropanation of a vinyl boronic ester (Scheme 26).



Scheme 26

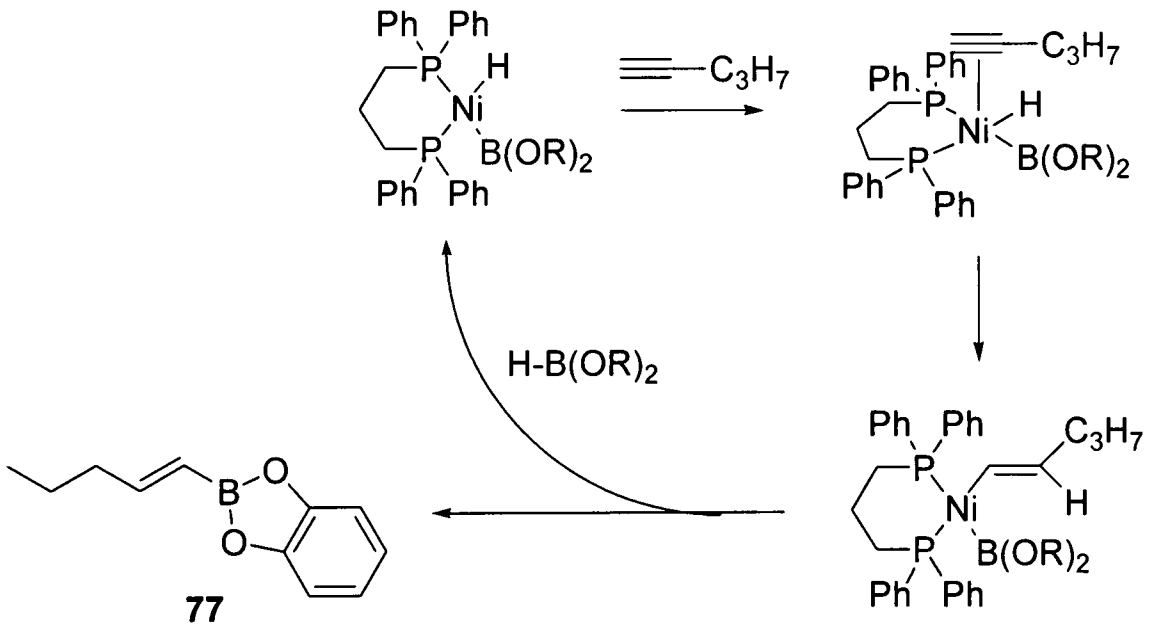
We planned to synthesise *trans*-vinyl boronic esters through the hydroboration of alkynes, and began this work using 1-pentyne **76** as our simple model substrate. It had previously been demonstrated that direct alkyne hydroboration using chiral

dioxaborolanes was usually low-yielding,[26] so we began investigating a route based upon the subsequent exchange of an achiral diol for a chiral one (Scheme 27).



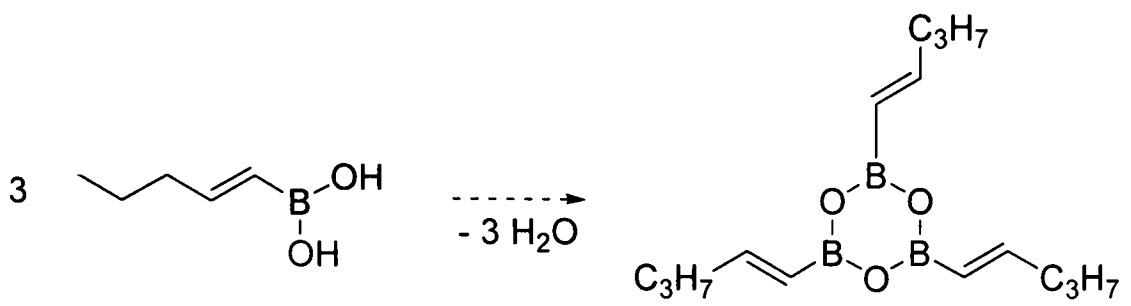
Scheme 27

Of the various hydroborating agents tested, catecholborane was found to be the most efficient, which in combination with Ni(II)-catalysis (1 mol % $NiCl_2$(dppp), r.t.)[30,31] resulted in a high-yielding and rapid reaction. This hydroboration was also shown to be completely regioselective, and presumably proceeds by oxidative addition of catecholborane to Ni(0), coordination of the alkyne, migratory insertion, followed by a reductive elimination (Scheme 28).[30]



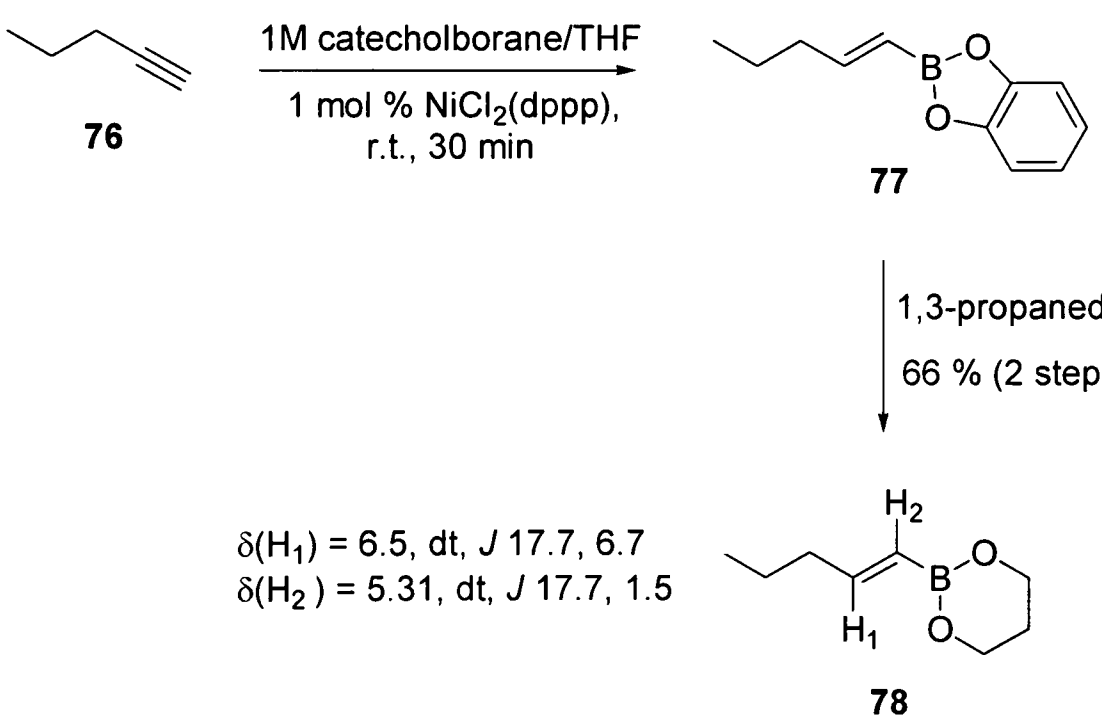
Scheme 28

The catecholboronic ester **77** was too sensitive to be isolated, and so was hydrolysed *in situ* to the corresponding boronic acid by the addition of distilled water. Unfortunately, this acid was also found to be difficult to purify (presumably because of partial boroxine formation upon drying,[32] Scheme 29) so we began investigating a *direct* transesterification to avoid the problematic hydroysis step.



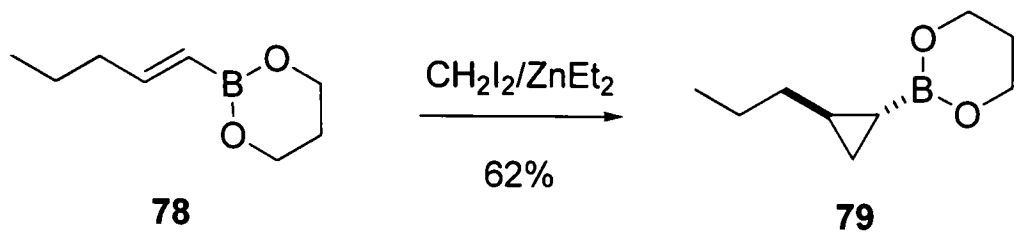
Scheme 29

To simplify the optimisation process, we first attempted transesterification using (achiral) 1,3-propanediol, and after some experimentation complete conversion was achieved by adding 1.1 eq. 1,3-propanediol to a solution of **77** in acetonitrile. After extraction of the lipophilic product into petrol, and subsequent distillation, vinyl boronic ester **78** was isolated in 66 % yield over 2 steps (Scheme 30). As expected, **78** displayed a large $J_{H1\text{-}H2}$ coupling of 17.7Hz in the 250MHz ^{1}H NMR, which is typical of a *trans*-vinyl boronic ester.[26]



Scheme 30

The cyclopropanation of **78** was performed using the Simmons-Smith ($CH_2I_2/ZnEt_2$) protocol.[25] The product of this reaction was observed to be much more stable to chromatography, with the desired cyclopropyl boronic ester **79** being isolated in 62 % yield after purification (Scheme 31).

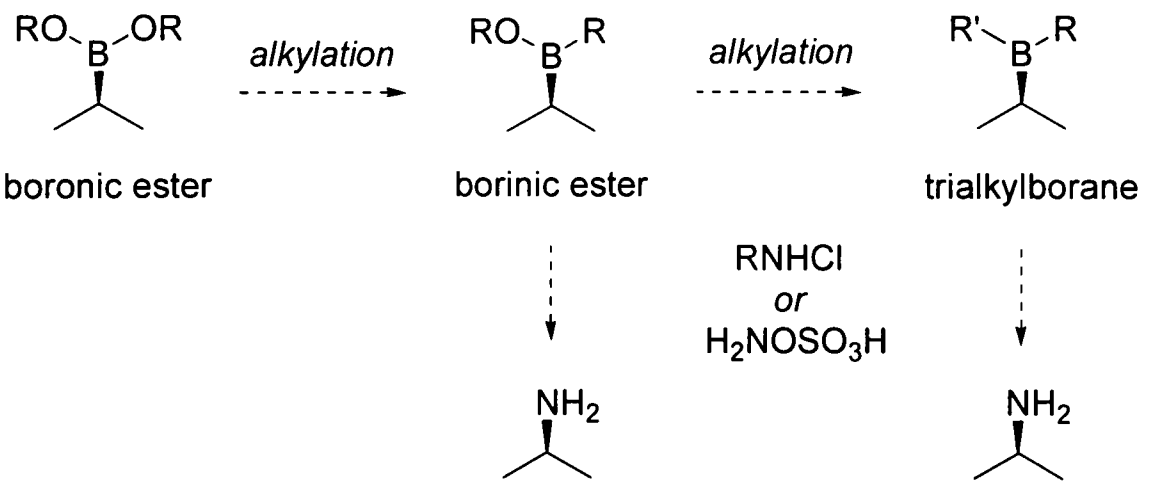


Scheme 31

2.2.3 Amination of cyclopropyl boronic esters

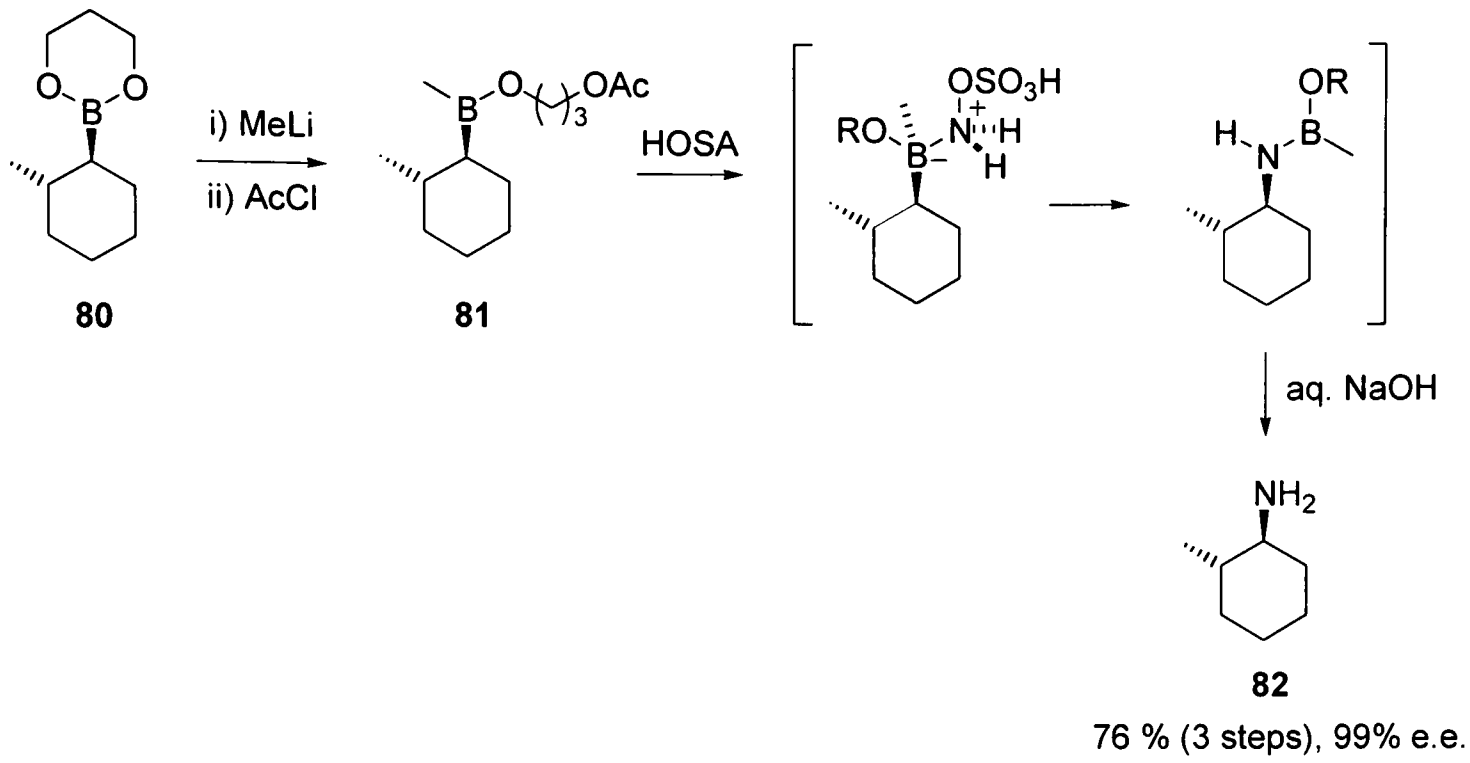
With the target cyclopropane in hand, we began investigating the proceeding amine-transfer reaction. To the best of our knowledge no previous examples of cyclopropyl boronic ester amination exist in the literature.

The first general method we attempted follows pioneering work by Brown, and represents a stereospecific amination analogous to the more familiar alkylborane oxidation. To promote initial nucleophilic attack, boronic esters must first be converted to the more electrophilic borinic esters/trialkylboranes, which upon subsequent treatment with primary chloroamines or HOSA[33] then undergo amine-transfer with retention of configuration (Scheme 32).



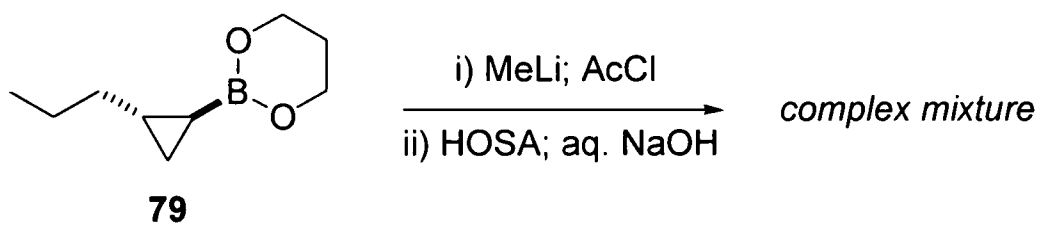
Scheme 32

For example, Brown reports conversion of enantiopure boronic ester **80** to amine **82** by this alkylation/amination procedure. Treatment of **80** with MeLi then acetyl chloride generates borinic ester **81**, which then undergoes a stereospecific rearrangement to amine **82** in 76% yield (99% e.e.) upon addition of HOSA and aq. NaOH (Scheme 33).



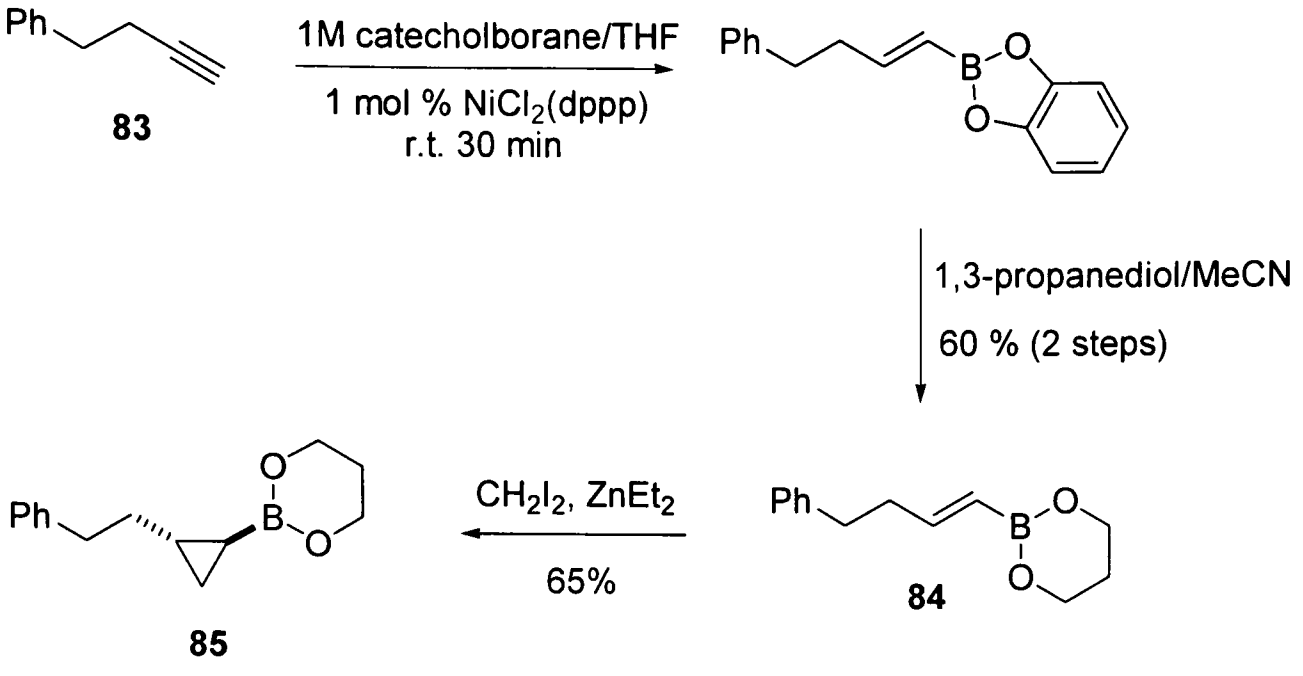
Scheme 33

We attempted amination of **79** using the conditions described above, but in our case analysis of the crude product revealed a complex mixture of products, from which the desired product could not be identified (Scheme 34).



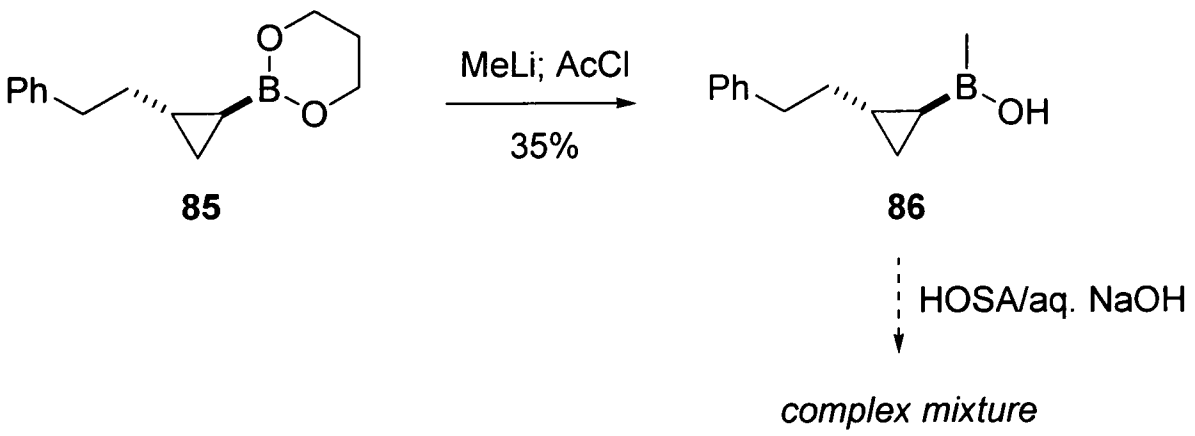
Scheme 34

An additional problem in this work was visualisation of the compounds by TLC, so as a result we switched to UV-active 4-phenyl-1-butyne **83** as our test substrate. The hydroboration/transesterification step was repeated in an overall yield of 60 % (2 steps), and the cyclopropanation proceeded in similar 65 % yield (Scheme 35).



Scheme 35

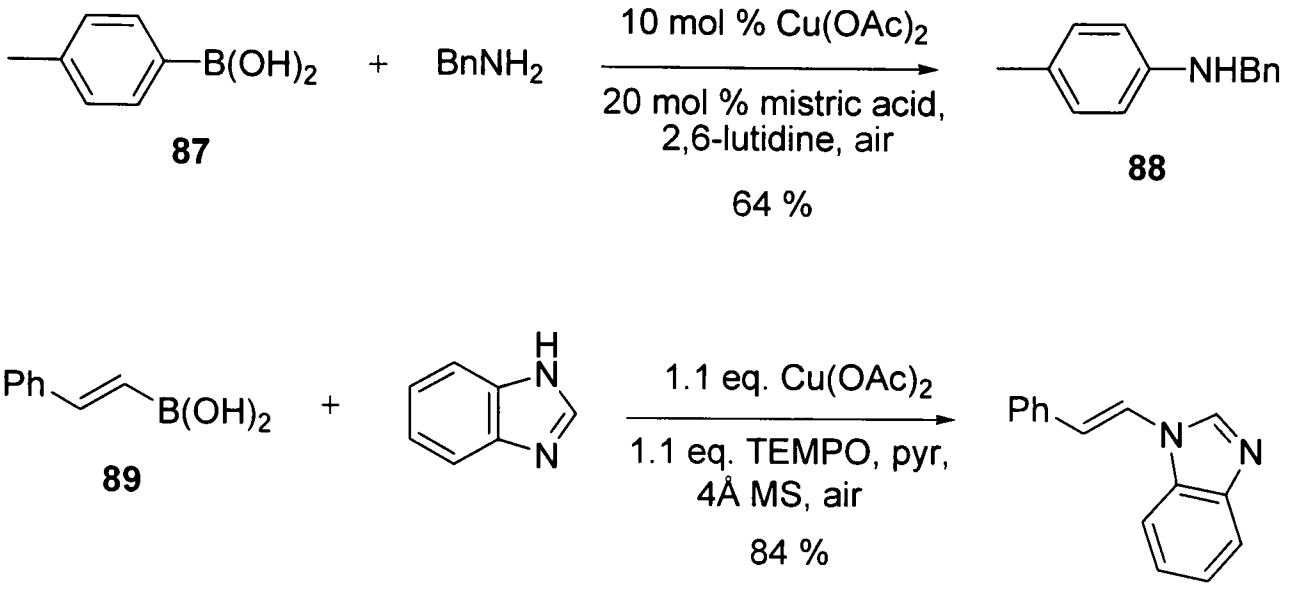
The same amination conditions were applied to **85** however, but the desired product was again not observed. Since we were uncertain at which stage this sequence failed, we first attempted to isolate the borinic ester. To this end we treated **85** with MeLi followed by AcCl, and after chromatography isolated material consistent with borinic acid **86** (Scheme 36). This suggested that the desired alkylation with MeLi proceeded in only moderate yield, with the pendant propane-diol undergoing hydrolysis on purification. Finally, the correct oxidation state of **86** prompted us to attempt amination of this species directly (aq. NaOH/HOSA), but again only a complex mixture of products was obtained.



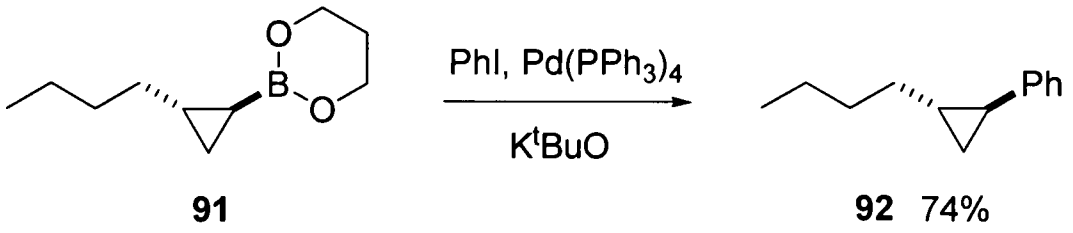
Scheme 36

As an alternative, a copper-catalysed boronic acid-amine coupling was also attempted. It had previously been demonstrated by Buchwald[34] and Lam[35] that both aryl and vinyl boronic acids are suitable substrates for this reaction (for example, Scheme 37), so on the basis of similar electronics we postulated that a cyclopropyl version may be

possible. Indeed, there are many examples of metal-mediated cross-couplings where aryl and vinyl boronic esters have been successfully replaced by cyclopropyl boronic esters, such as the Suzuki coupling of **91** with phenyl iodide reported by Marsden (Scheme 38).[29]

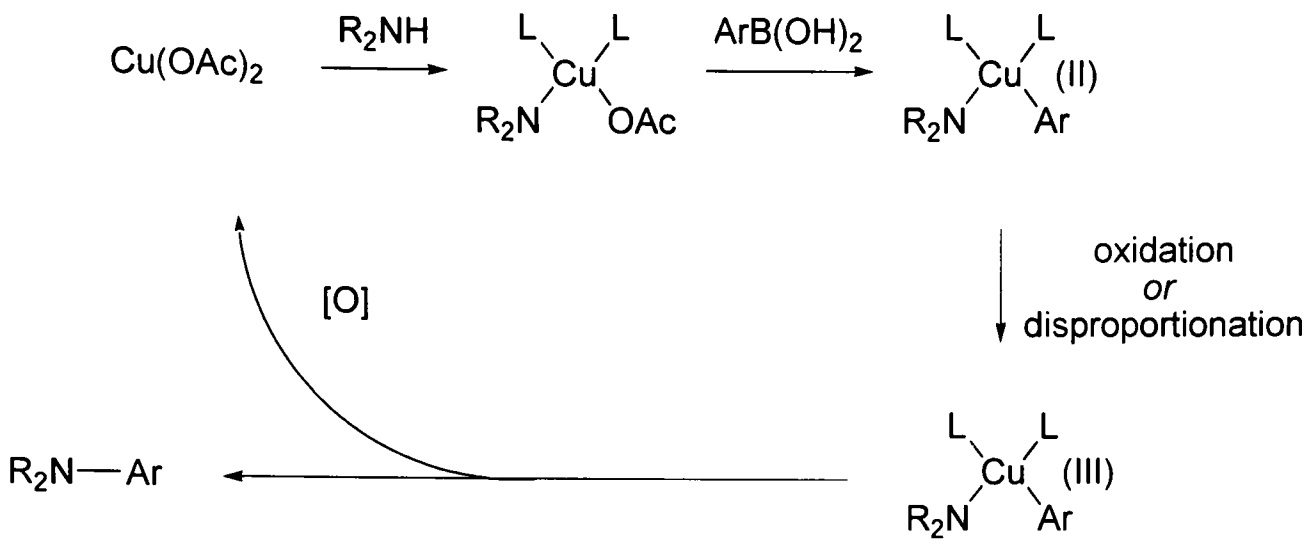


Scheme 37



Scheme 38

The mechanism of this amine-boronic acid cross-coupling is complex and not well understood. However, it is proposed that initial amine substitution is followed by transmetallation of the boronic acid/ester, oxidation (or possibly disproportionation) of Cu(II) to Cu(III), then reductive elimination.[36] To complete the catalytic cycle, Cu(I) must then be reoxidised to Cu(II) (Scheme 39).



Scheme 39

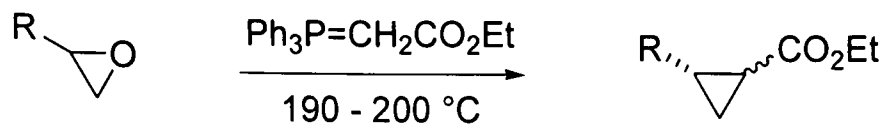
We briefly investigated this reaction, using conditions reported by Lam for his successful cross-couplings of vinyl boronic acids. Unfortunately both benzylamine and the more acidic *tert*-butylcarbamate failed to aminate either the cyclopropyl boronic ester **85** (or its corresponding acid) under the reported conditions.

Although these two approaches were not exhaustively investigated, we were simultaneously investigating the alternative strategy of epoxide cyclopropanation, which was showing much greater promise. Accordingly, we decided not to pursue the boronic ester amination sequence any further, and concentrate our efforts solely on the epoxide route which will be presented in the next section.

2.3 Epoxide cyclopropanation route

2.3.1 Introduction

The direct conversion of epoxides to cyclopropanes has been known for over 45 years. In 1959, Denney and Boskin reported that conventional phosphoranes reacted with terminal epoxides when heated neat at 190-200 °C in a sealed tube.[37] Styrene oxide was shown to give 21% of the corresponding *trans*-cyclopropyl ethyl ester **93**, whilst 1,2-epoxyoctane gave 26% of the cyclopropyl ethyl ester **94** (Scheme 40).

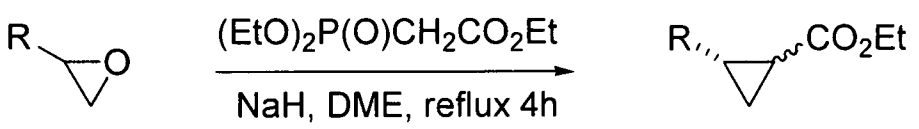


93 R = Ph, 21 % > 95 % d.e *trans*

94 R = C_6H_{13}, 26 % d.r. not reported

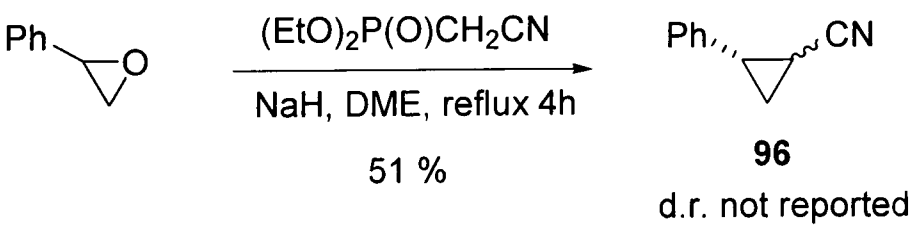
Scheme 40

Further progress was made in 1961 when Wadsworth and Emmons described the use of phosphonate carbanions for the same reaction,[38] again reporting the reaction to be *trans*-selective for styrene oxide (42% yield **93**). The greater reactivity of phosphonate anions permitted much milder conditions (heating as a 1 M solution), which possibly accounts for the significantly improved yields. In addition to the use of triethylphosphonoacetate, the reaction was also shown to be successful using diethylcyanomethyl phosphonate, which yielded **96** in 51% yield (Scheme 41).



93 R = Ph, 42 % > 95 % d.e. *trans*

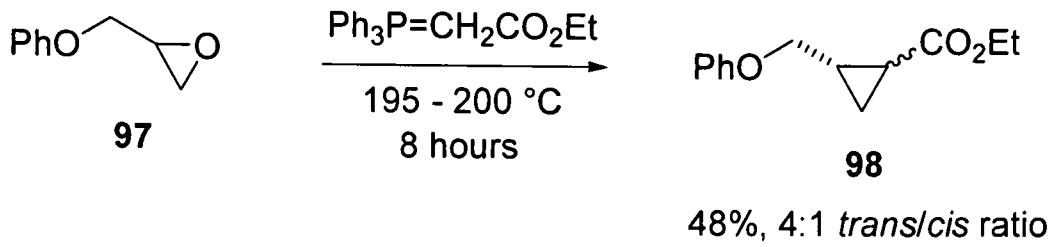
95 R = C_3H_2, 21 % d.r. not reported



Scheme 41

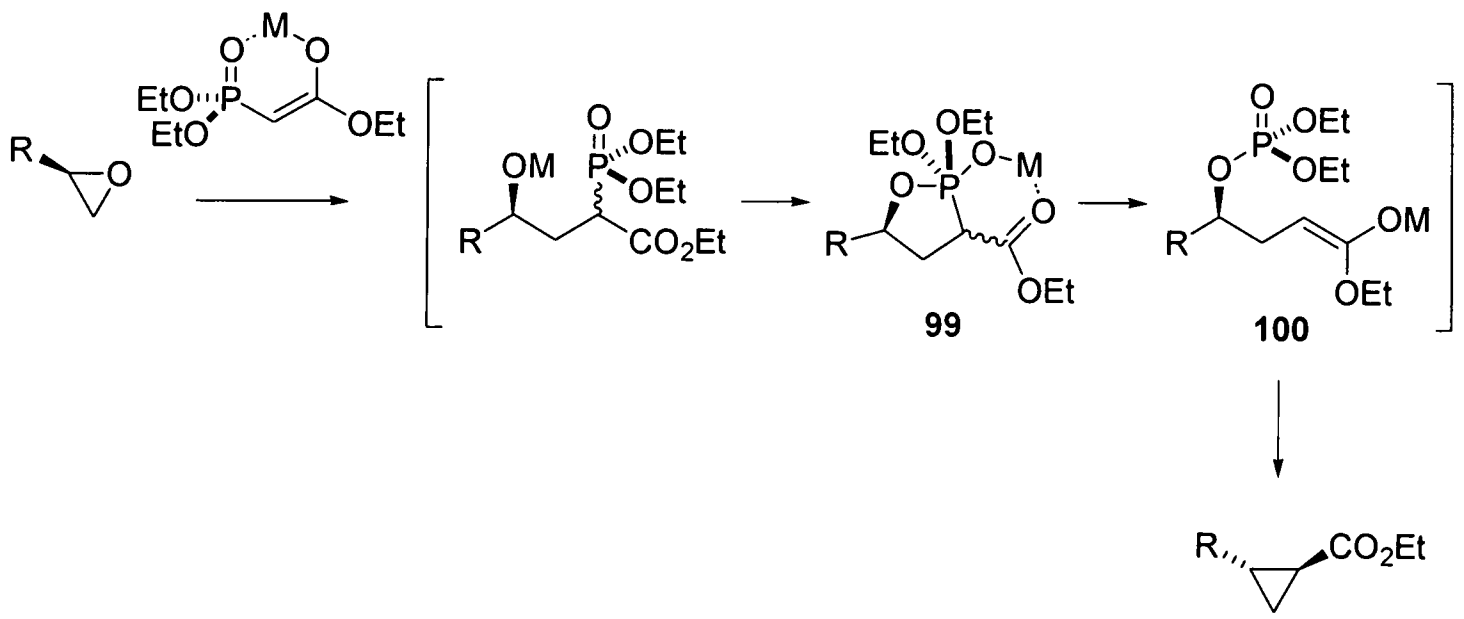
Since these original reports, this cyclopropanation reaction has received very little attention (approximately just 15 applications).[39] Of these examples, many are limited to using ethylene oxide as the epoxide, and cyclopropanes are prepared in only low-to-modest yields (20-50%). For reactions involving aryl epoxides there is good precedent for *trans*-selectivity, but for alkyl-epoxides the situation is less clear. One exception is the Wittig cyclopropanation of alkyl-based epoxide **97**, which was shown to furnish **98** as a 4:1 *trans*/*cis* mixture of products (Scheme 42).[40] All other studies

fail to discuss the level of stereoselection. In addition, alkyl-based epoxides generally give lower cyclopropane conversions than aryl epoxides, presumably because the final ring closure is not accelerated by a benzylic leaving-group.



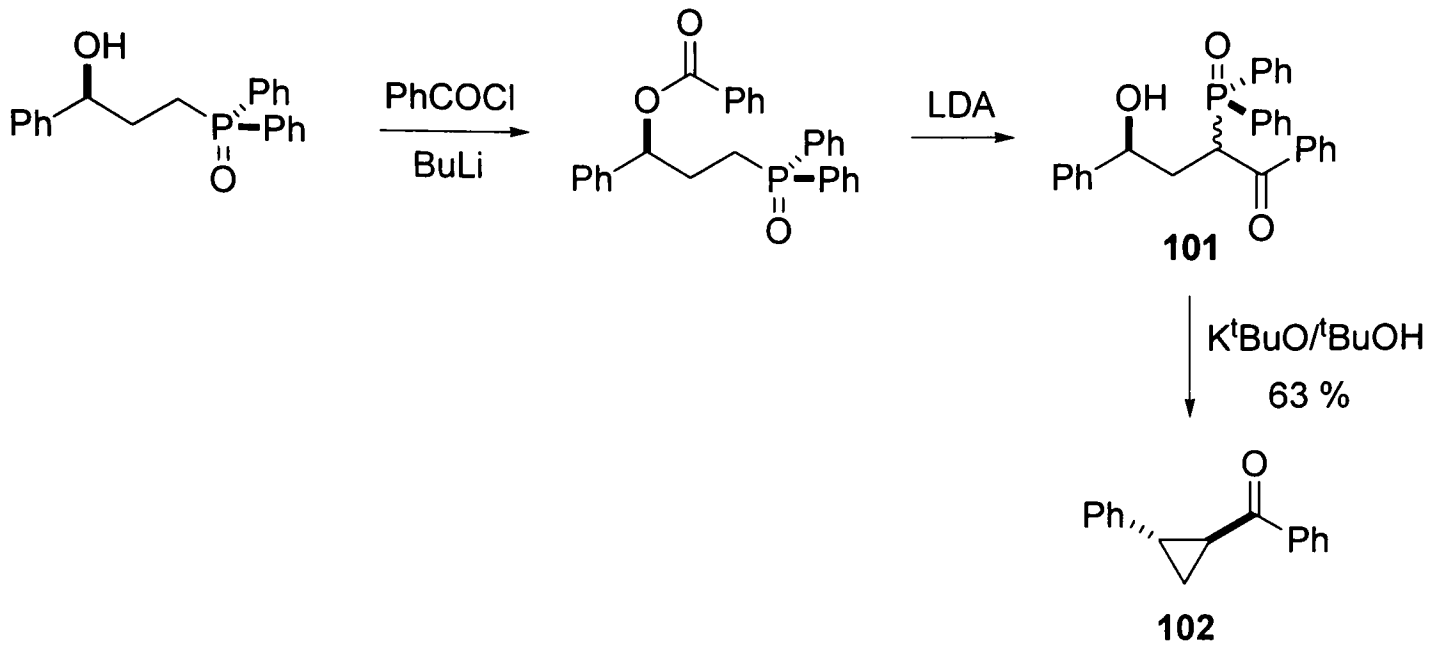
Scheme 42

To date there have been no investigations into the mechanism of the Wadsworth-Emmons cyclopropanation. However, the original proposal[37,38] suggests attack of the phosphonate anion at the less hindered end of the epoxide, then ring closure to form the 5-coordinate phosphorus cycle **99**. With an adjacent electron-withdrawing group, **99** then collapses to a phosphate and stabilised anion (intermediate **100**), which finally undergoes a 3-*exo*-tet cyclisation (Scheme 43). There are two key issues to consider with this mechanism - stereoselectivity and stereospecificity.



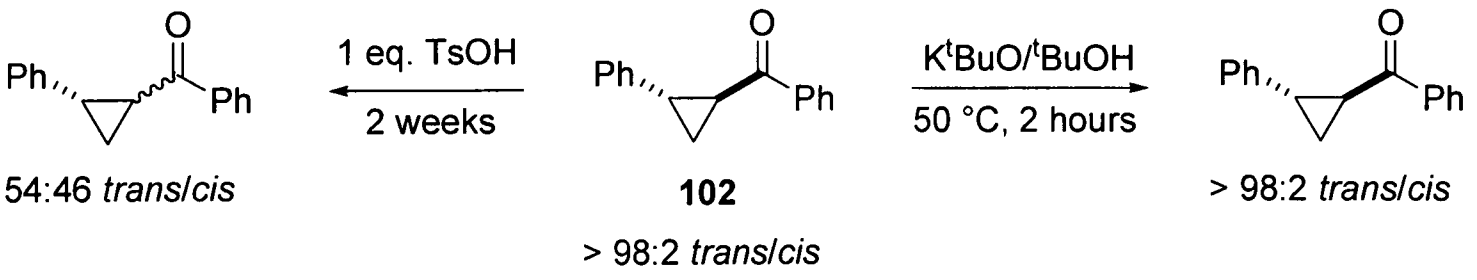
Scheme 43

It was initially suggested that the observed *trans*-stereoselection (for aryl examples) results from product equilibration under the reaction conditions,[38] but more recent work by Warren suggests otherwise.[41] During his investigations into a conceptually similar but multi-step cyclopropanation reaction, *trans*-selectivity was again observed. In this case the key cyclisation of **101** to **102** occurred at room temperature in the presence of an excess of K^tBuO (Scheme 44).



Scheme 44

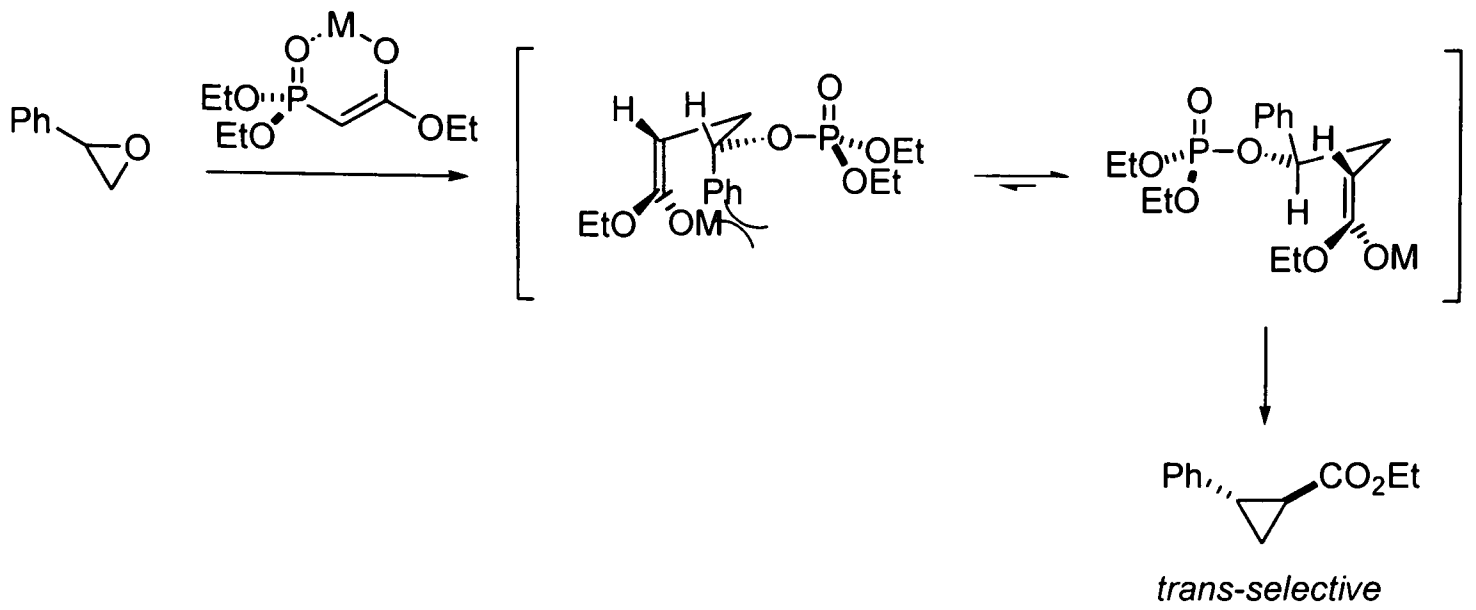
In order to probe the origin of this selectivity, a sample of diastereomerically pure cyclopropane **102** was exposed to potential equilibration conditions. After stirring **102** for two weeks with 1 equivalent of tosic acid, almost complete epimerisation was observed (**102** recovered in 54:46 *trans*/*cis* ratio), suggesting little energy difference between *trans* and *cis*-stereoisomers. By contrast, a similar sample of **102** was left unchanged after stirring for six hours at 50 °C with ten equivalents of K^{t}BuO (Scheme 45). This was taken as evidence that the cyclisation was kinetically controlled, as under the reaction conditions no epimerisation was observed.



Scheme 45

As a result, it is also likely that the Wadsworth-Emmons cyclopropanation proceeds under kinetic control. As such, the observed selectivity is then explained by a lower-energy transition state leading to the *trans*-product (in comparison to that leading to the *cis*-product), presumably because this arrangement avoids repulsive 'syn-pentane'-type interactions (Scheme 46). Furthermore, these interactions are also likely to be less severe in the c*is*/*trans* products (since a metal enolate is more bulky than an

ethyl ester), which then may explain the lack of stereoselectivity under equilibration conditions.



Scheme 46

The second key issue is that of stereospecificity. If one cyclopropanates an enantiomerically pure epoxide does this necessarily lead to an enantiomerically pure cyclopropane? The mechanism originally proposed by Wadsworth and Emmons does suggest that the reaction proceeds *via* an S_N2-like inversion at the epoxide stereocentre, but at the start of this project there were only inconclusive optical rotation measurements to suggest that this was the case.[42,43,44] Critically, the *extent* of this chirality transfer was unknown.

2.3.2 Stereoselectivity and stereospecificity

The central (2*S*, 1'*R*, 2'*S*)-AcpAla amino acid **4** of (+)-belactosin A contains a *trans*-cyclopropylamine moiety as its key feature (Figure 10). The Wittig cyclopropanation had previously demonstrated poor diastereoselectivity, so we began our work by re-examining the Wadsworth-Emmons cyclopropanation.

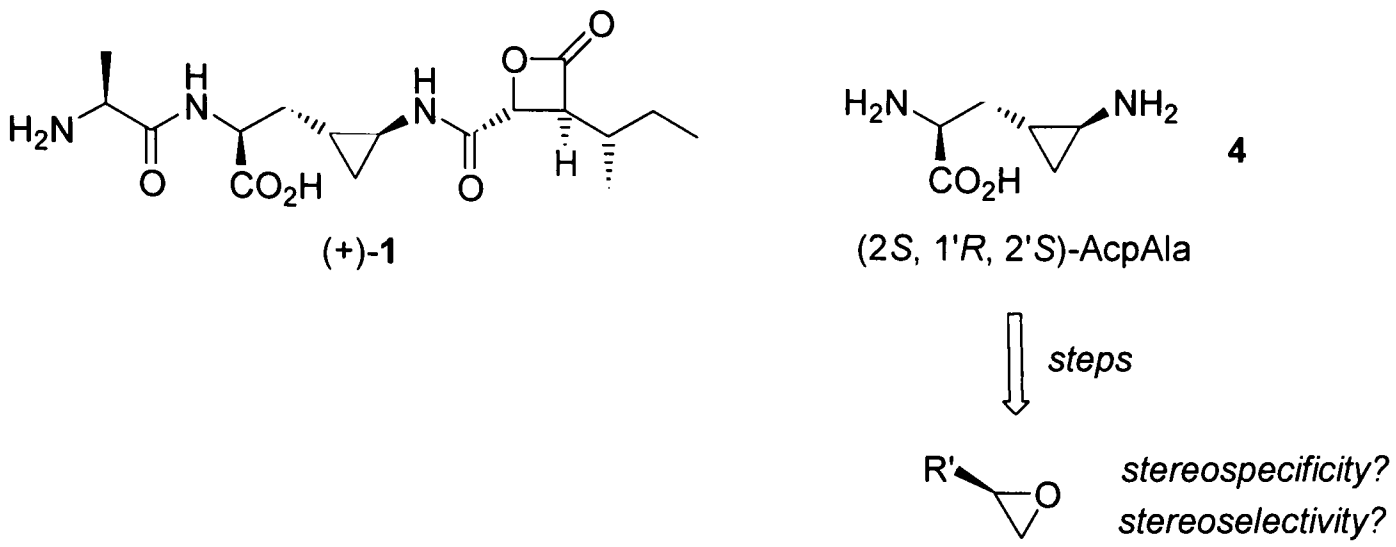
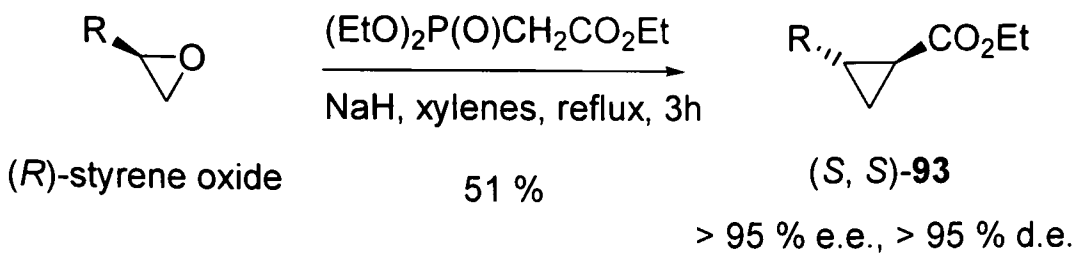


Figure 10

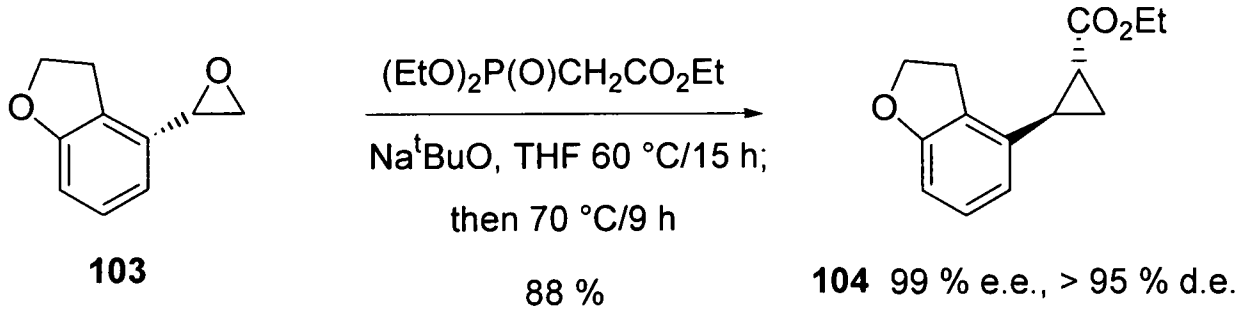
Investigations commenced by repeating the cyclopropanation of styrene oxide using both triethylphosphonoacetate and diethylcyanomethyl phosphonate, originally described by Wadsworth and Emmons. We applied NaH/xylenes (reflux) conditions more recently reported by Meul in the patent literature,[39(i)] and confirmed synthesis of *trans*-cyclopropyl ethyl ester **93**, and also nitrile cyclopropane **96** as its *trans*-isomer (Scheme 47). Under these newer conditions, both **93** (51% yield) and **96** (64% yield) were synthesised in slightly higher yields than previously reported by Wadsworth and Emmons.

Additionally, the stereospecificity of the reaction was investigated through the cyclopropanation of *R*-styrene oxide. After chiral HPLC analysis, we were delighted to see that cyclopropane **93** was formed as a single enantiomer ((*S*, *S*)-**93**, >95 % e.e., by comparison with racemic material) with an optical rotation confirming S_N2-like inversion at the internal stereocentre (Scheme 47).[15] We believe this represents the first confirmation that the Wadsworth-Emmons cyclopropanation is fully stereospecific, and confirms to us the potential of this reaction in complex total synthesis.



Scheme 47

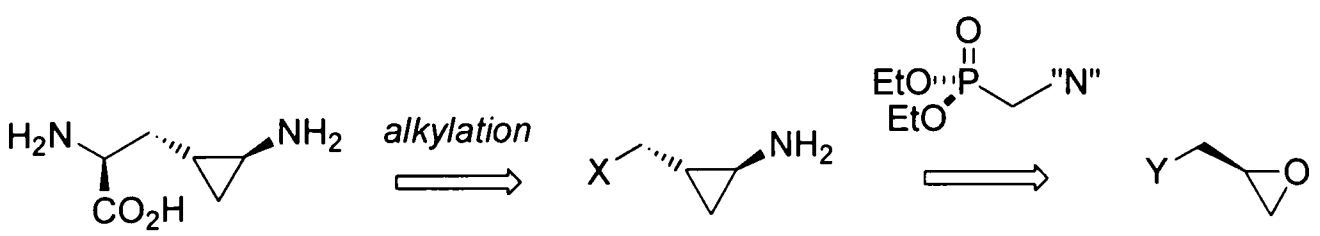
After this work was completed, workers at Bristol-Myers Squibb reported a similar cyclopropanation of aryl epoxide **103**,[45] again confirming clean stereochemical inversion. In this case, extensive optimisation revealed the most efficient cyclopropanation was achieved by heating **103** with Na^{t}BuO in THF at 60 °C for 15 hours, then at 70 °C for a further 9 hours, affording **104** in 88% yield (Scheme 48).



Scheme 48

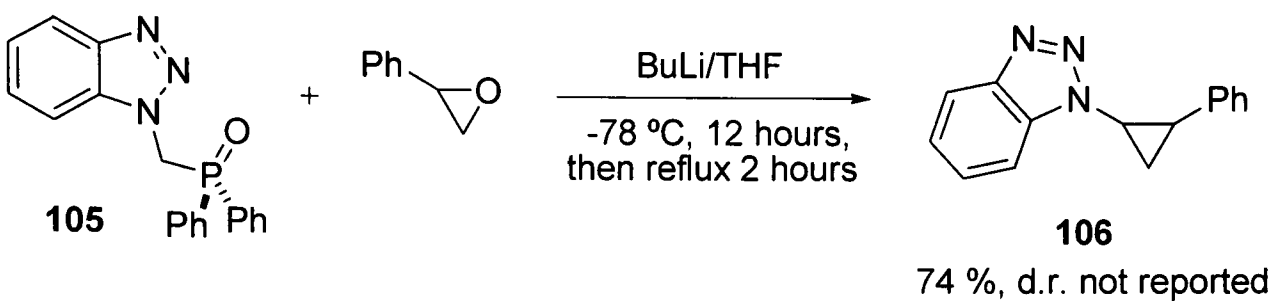
2.3.3 Wadsworth-Emmons aminocyclopropanation

Encouraged by this result, we began investigating nitrogen-stabilised phosphonates, with the ambitious aim of performing a direct enantiospecific and diastereoselective aminocyclopropanation (Scheme 49).



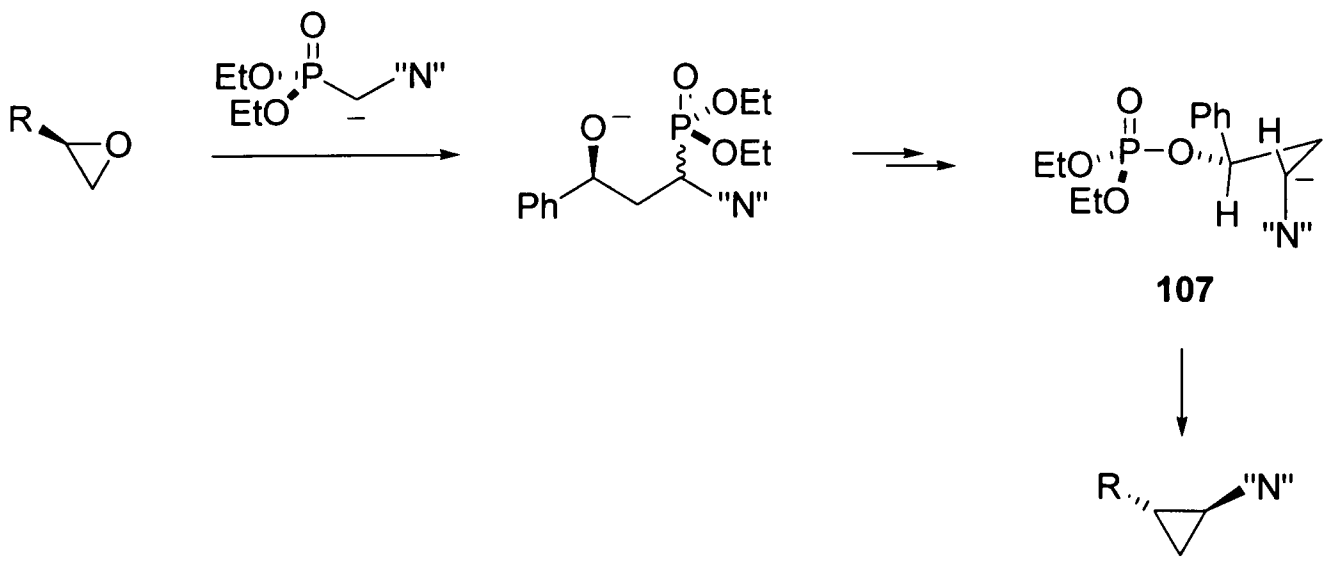
Scheme 49

As stated earlier, direct aminocyclopropanation had only been achieved once previously. A report by Katritzky described the cyclopropanation of styrene oxide using benzotriazole phosphine oxide **105** (Scheme 50),[24] but since cyclopropane **106** cannot be 'deprotected', an alternative reagent must be developed.



Scheme 50

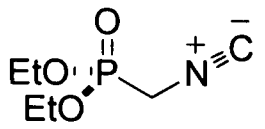
Most other epoxide cyclopropanations in the literature have been performed using ester-stabilised phosphonates, but alternative examples have included ketone,[39(g)] nitrile and enamine-substituted phosphonates.[39(b)] We noted that attempts to use diethyl benzylphosphonate had failed[38] (despite the anion being more nucleophilic), which suggests that a strongly electron-withdrawing group is crucial for success. The requirement of an anion-stabilising group is also consistent with the Wadsworth-Emmons olefination, and is explained by the need to stabilise negative charge after phosphonate transfer (intermediate **107**, Scheme 51). Indeed, Katritzky had also previously demonstrated that benzotriazole can stabilise an α-carbanion.[46]



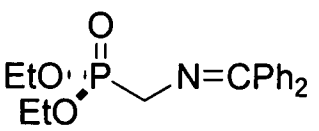
Scheme 51

Of the various carbanion-stabilising nitrogen-based groups available, we chose to investigate phosphonates bearing isonitrile, benzophenone imine and nitro

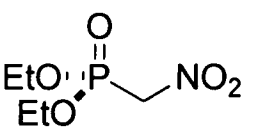
substituents (Figure 11). Only the isonitrile phosphonate **108** had previously been shown to ring open epoxides (requiring Lewis-acid $BF_3.OEt_2$-activation),[47] but in this case subsequent phosphonate transfer had not been reported, possibly because of low-temperature quenching of the reaction. Phosphonate **109** has been shown to react with activated halides under biphasic conditions,[48] and also to successfully olefinate a range of ketones (to form azadienes).[49] Nitro-phosphonate **110** has also been used as an olefination reagent, but in this case there are conflicting reports with regard to its level of reactivity.[50,51]



108



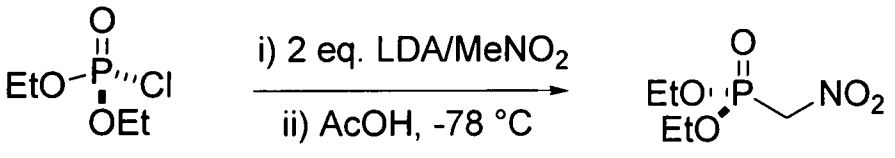
109



110

Figure 11

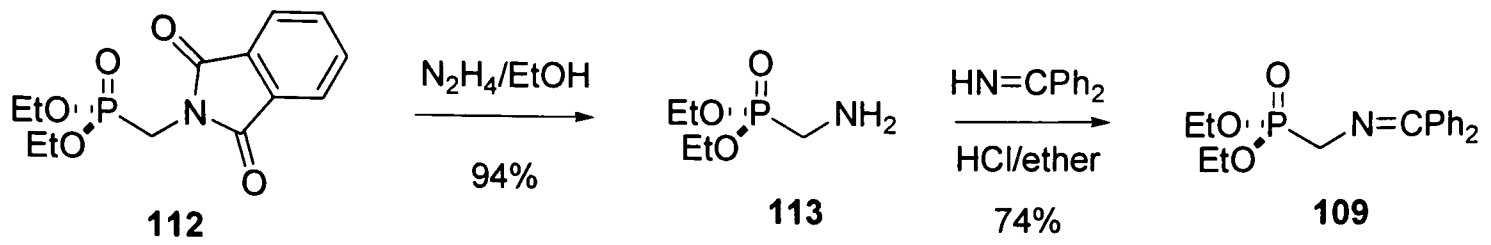
Of the desired reagents, only the isonitrile phosphonate **108** was commercially available, so our first task was to synthesise **109** and **110**. The nitro-phosphonate **110** was accessed by phosphorylation of nitromethane using chlorophosphate **111**, following a general procedure by Kandil.[52] Two equivalents of base were required to prevent reprotonation of the anion by the product, and following a low temperature acidic quench, phosphonate **110** was successfully isolated in 52 % yield (Scheme 52).



111 52% **110**

Scheme 52

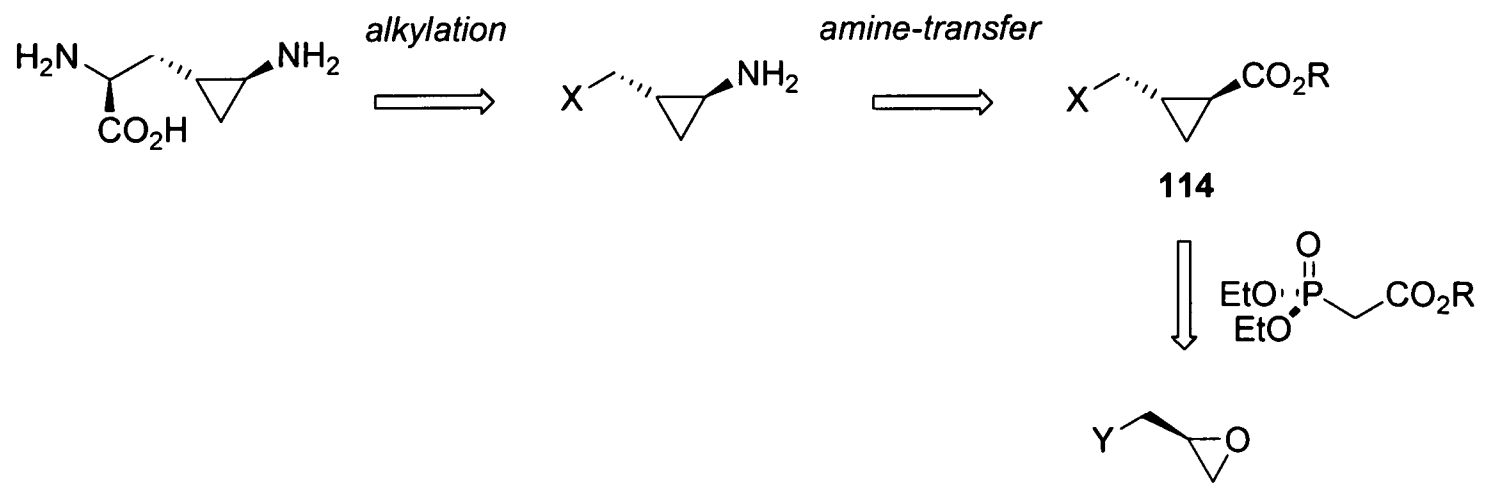
Next, benzophenone imine phosphonate **109** was synthesised using a high-yielding two-step literature procedure. Phthalimido phosphonate **112** was first deprotected with hydrazine to reveal amine **113**,[49] then condensed with benzophenone imine using anhydrous HCl to afford **109** in 74% yield (Scheme 53).[48]



Scheme 53

With phosphonates **108, 109** and **110** in hand we next attempted the epoxide cyclopropanation, using styrene oxide as a model substrate. However, attempted cyclopropanation using all phosphonates failed under standard conditions (NaH/xylenes, heat). In addition, no improvements were observed using a range of different solvents (xylenes, THF, DMF), bases (NaH, BuLi, KHMDS, K_2CO_3/R_4NX, $^iPr_2NEt/LiCl$) and Lewis acids ($BF_3.OEt_2$, $LiClO_4$, $Sc(OTf)_3$, TMSCl, $AlEt_2Cl$). We attribute this failure to the decomposition of **108** and **109** under the reaction conditions, and the unreactivity of phosphonate **110** (which was recovered unchanged).

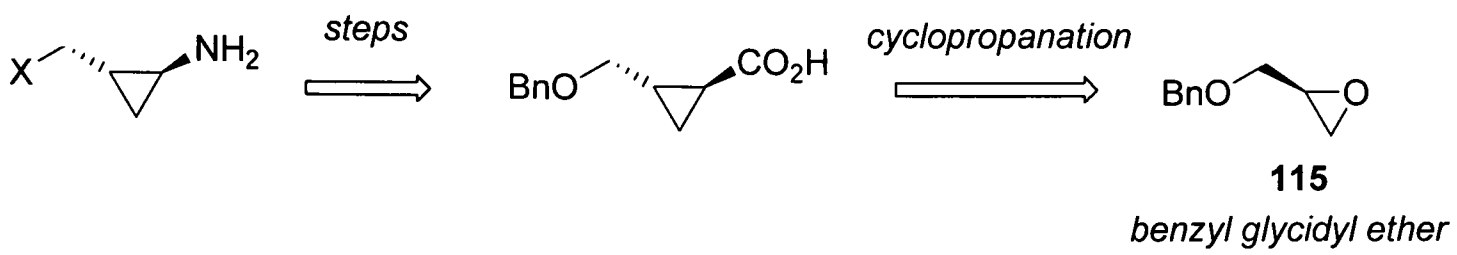
In light of these results, we returned to the standard Wadsworth-Emmons cyclopropanation. As a synthetic re-evaluation, we now aimed to combine this reaction with a subsequent amine-transfer from ester **114** (Scheme 54). We had confidence in this approach since cyclopropyl acyl nitrene rearrangements were well documented in the literature, therefore an optimisation of the cyclopropanation was initiated first.



Scheme 54

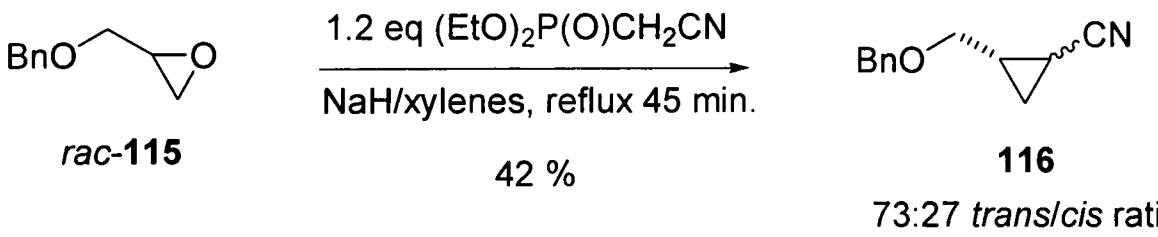
2.3.4 Optimisation of Wadsworth-Emmons cyclopropanation

We began optimisation of the cyclopropanation reaction using an epoxide with α-oxygen functionality, so as to later permit conversion to a cyclopropyl methylhalide (required for eventual glycine alkylation). Consideration of the anticipated protecting group manipulations led us to select benzyl glycidyl ether **115** as our starting epoxide (Scheme 55).



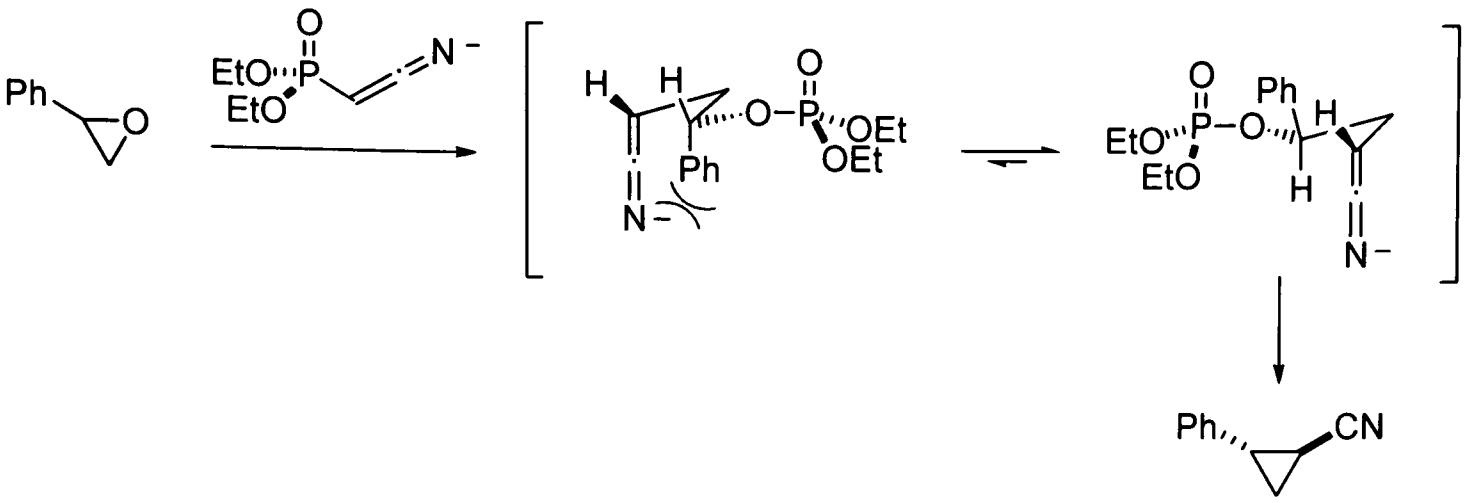
Scheme 55

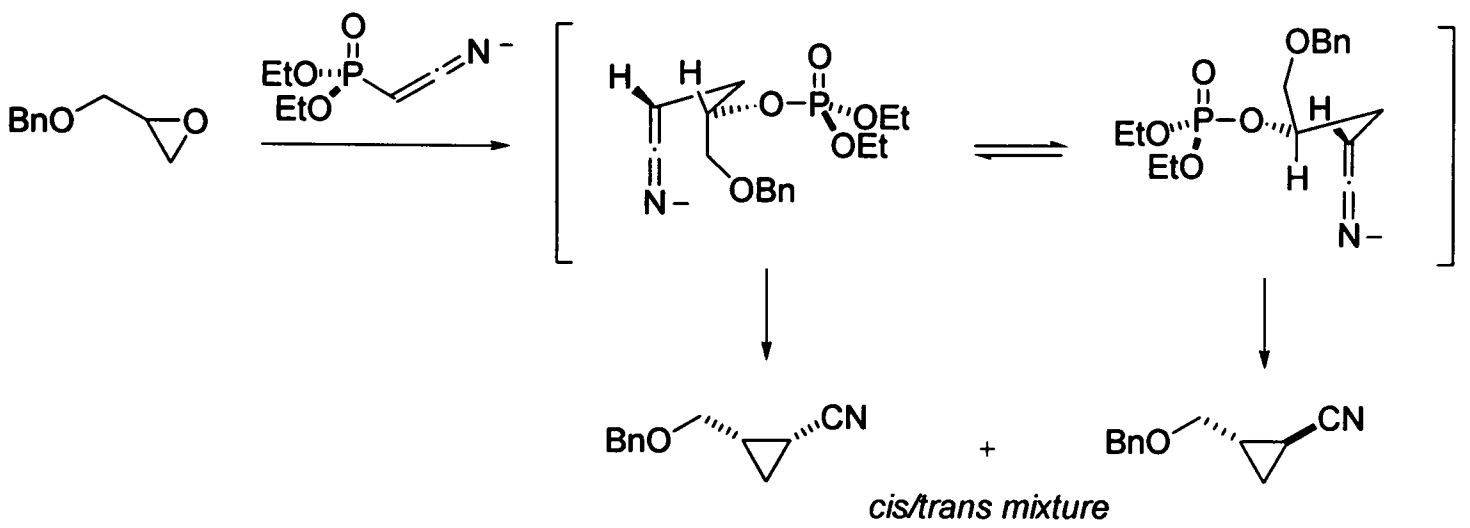
Previous work had demonstrated that alkyl-based epoxides are more challenging substrates for this reaction than aryl-substituted epoxides, so on this basis we began investigations using the more efficient diethylcyanomethyl phosphonate. Accordingly, we reacted *rac*-**115** with 1.2 equivalents of phosphonate under standard conditions (NaH/xylenes, reflux), and successfully isolated cyclopropane **116** in 42 % yield, but disappointingly as a 73:23 *trans/cis* mixture (Scheme 56).



Scheme 56

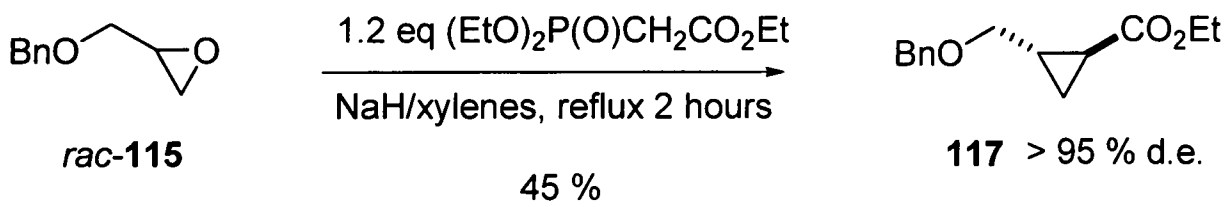
In comparison to the previous styrene-oxide example (see previous Scheme 47), we postulate that the lower selectivity of this reaction was due to reduced 'syn-pentane' interactions in the transition-state leading to the *cis*-product, rather than a switch to product equilibration. This is presumably because *A-value*(CH_2OBn)<<*A-value* (Ph) (Scheme 57). Since our main criterion was a *trans*-selective cyclopropanation, this nitrile-cyclopropanation was therefore not pursued any further.





Scheme 57

In contrast, when we reacted *rac*-**115** with 1.2 equivalents of triethylphosphonoacetate (NaH/xylenes, reflux), we were delighted to see formation of the desired cyclopropane **117** in 45 % yield as a single diastereoisomer (Scheme 58)



Scheme 58

Use of ^{1}H NMR coupling constants to unambiguously assign the stereochemistry of **117** was difficult, but *trans*-stereochemistry was confirmed on the basis of nOe measurements. The key enhancements were those of H_3 and H_6. H_3 displayed

enhancements to H_5 and H_1/H_2 only, whereas H_6 showed enhancements to H_4 and H_1/H_2 only (Figure 12, Table 2).

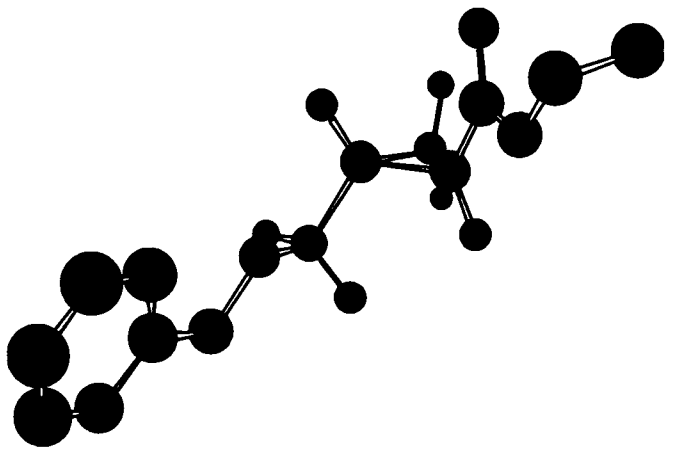
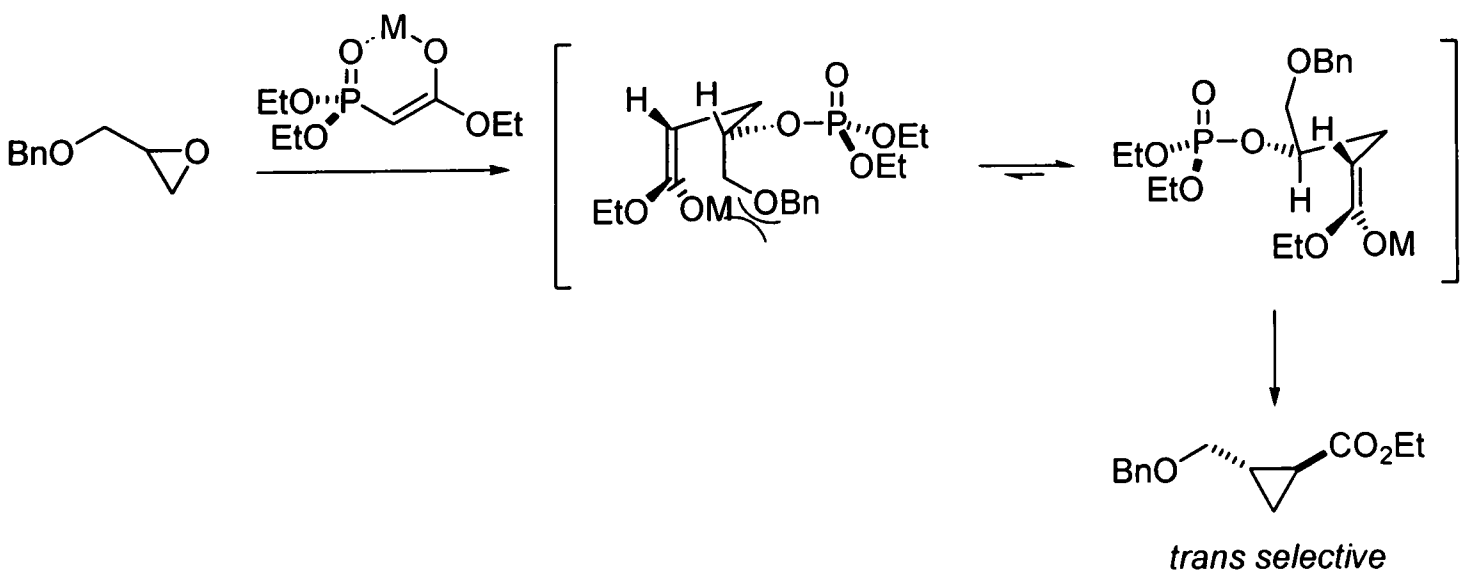


Figure 12: MM2 minimised conformation of **117** (Chem3D)

Irradiated proton	nOe / %				
	H_1	H_2	H_1/H_2	H_4	H_5
H_3	2.65	-	-	-	2.50
H_6	-	-	1.90	3.21	-

Table 2

In this case we believe that the greater steric bulk of the ethyl ester enolate (compared to nitrile anion) preferentially raises the energy of the transition state leading to the *cis*-product, which then explains the observed *trans*-stereoselection by following the reaction path of lowest activation energy (Scheme 59).



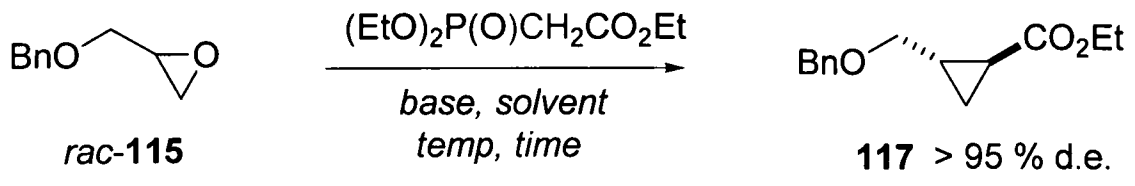
Scheme 59

An equally important issue to address was the level of chirality transfer, and this was investigated by repeating the reaction using (*S*)-**115**. Here, we were again delighted to see that cyclopropane **117** was formed as a single enantiomer, as determined by use of a chiral shift reagent (> 95 % e.e., by comparison with racemic material using 35 mol % $Eu(hfc)_3$) (Figure 13). Assuming the same inversion mechanism as demonstrated earlier for the cyclopropanation of (*R*)-styrene oxide, we assigned the product cyclopropane as the (*S*, *S*)-**117** enantiomer.

(*S*, *S*)-**117** > 95% e.e., >95 % d.e.

Figure 13

Encouraged by this success, we next began efforts to optimise this process. Solvents were screened with a diverse range of dielectric constants, and a selection of the most popular strong bases were tested (including NaH, K^{t}BuO, KHMDS, LHMDS and BuLi). We found that sodium hydride and potassium *tert*-butoxide were the most effective bases, and that two equivalents of phosphonate were required to achieve full conversion of the epoxide. Since all previous examples of epoxide cyclopropanation required significant heating, we therefore conducted most of our reactions at the reflux temperature of the solvent, and a selection of these results are shown below (Scheme 60, Table 3).



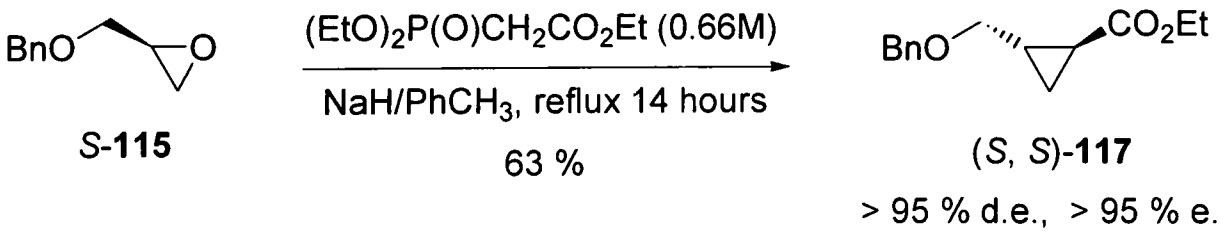
Scheme 60

Entry	Base	Solvent	Temp/ °C	Time/ h	Yield **117**/ %
1	K^{t}BuO	DMF	70	14	27 (31)*
2	K^{t}BuO	DME	82	14	32
3	K^{t}BuO	THF	65	14	55
4	K^{t}BuO	THF	65	24	25
5	K^{t}BuO	$PhCH_3$	110	14	28
6	K^{t}BuO	Hexane	68	14	30
7	Na^{t}BuO	DME	70	14	45
8	NaH	DMF	70	14	20 (29)*
9	NaH	DME	82	14	56
10	NaH	THF	65	14	49
11	**NaH**	**$PhCH_3$**	**110**	**14**	**63**
12	NaH	$PhCH_3$	110	24	54
13	NaH	Hexane	68	14	32

*Yield with respect to recovered starting material. All reactions conducted with triethylphosphonoacetate concentration of 0.66M.

Table 3

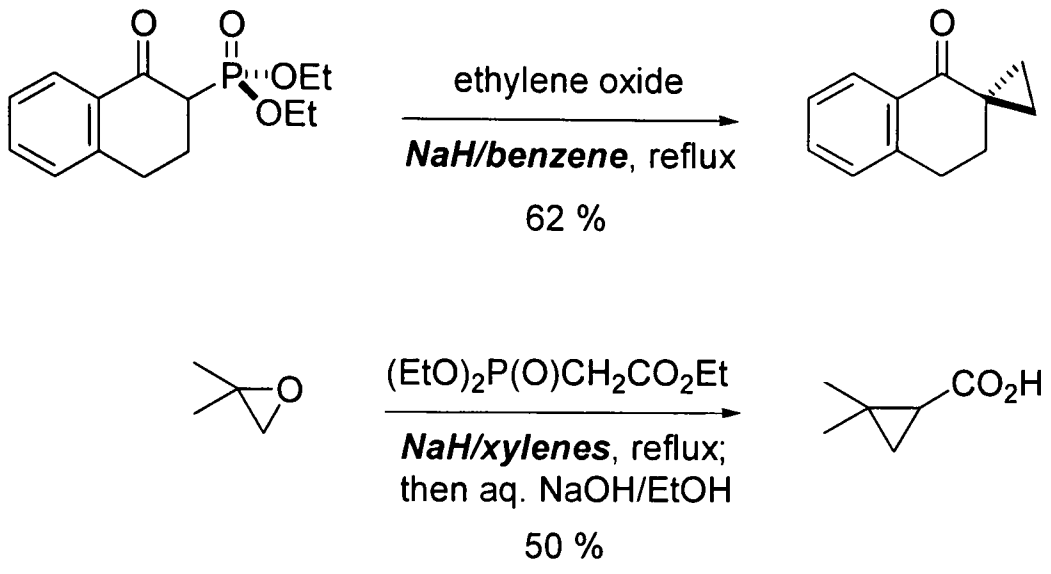
The highest yield of **117** obtained was 63 % (entry 11), achieved using NaH/$PhCH_3$ at reflux for 14 hours (Scheme 61). Entry 7 corresponds to conditions developed by workers at Bristol-Myers Squibb,[45] but unfortunately this resulted in a much lower cyclopropanation yield.



Scheme 61

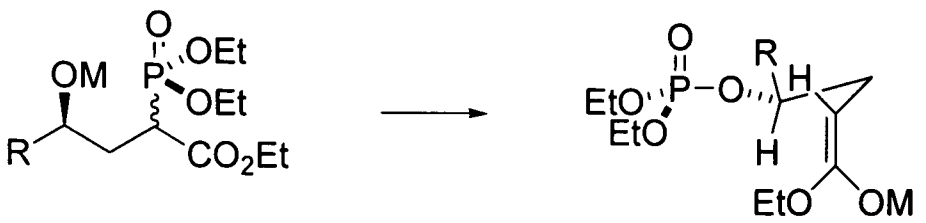
These results (and others not displayed) demonstrated that sodium hydride was generally a more effective base than potassium *tert*-butoxide. Furthermore, when using sodium hydride we also found that higher-boiling non-polar solvents consistently gave better results. This trend is also in agreement with optimised

conditions used by both Meul[39(i)] and Weimer[39(g)] for other Wadsworth-Emmons cyclopropanations (for example, Scheme 62).



Scheme 62

The reason for higher yields in non-polar solvents is as yet unexplained, but may in part be due to the general principle of non-polar solvents accelerating bimolecular reactions (in such cases as this where one species is charged and the other is neutral). In these cases the starting materials are preferentially destabilised, since they have higher charge density than the transition-state structure, and as such the activation energy is reduced and reaction rate is increased. Additionally, an explanation based on pKa solvent-dependence is also plausible. We believe that the crucial phosphonate-transfer process only proceeds because the new P-O bond compensates for producing a less stable anion (Scheme 63). In different solvents this energy balance is also affected by differing alkoxide **119** *vs* ester enolate **100** stability. In polar solvents, the pKa_H of alkoxide **119** is significantly lower than that of ester enolate **100**, since the alkoxide has higher charge density so can be more efficiently solvated. In non-polar solvents neither is stabilised preferentially, and both anions have a more similar pKa_H. Although extensive pKa tables are not available for all solvents, this effect is reflected by acidity trends in H_2O compared to DMSO (in addition to hydrogen-bonding effects). This reasoning therefore implies that phosphonate transfer is more facile in non-polar solvents than polar solvents.



119 **100**

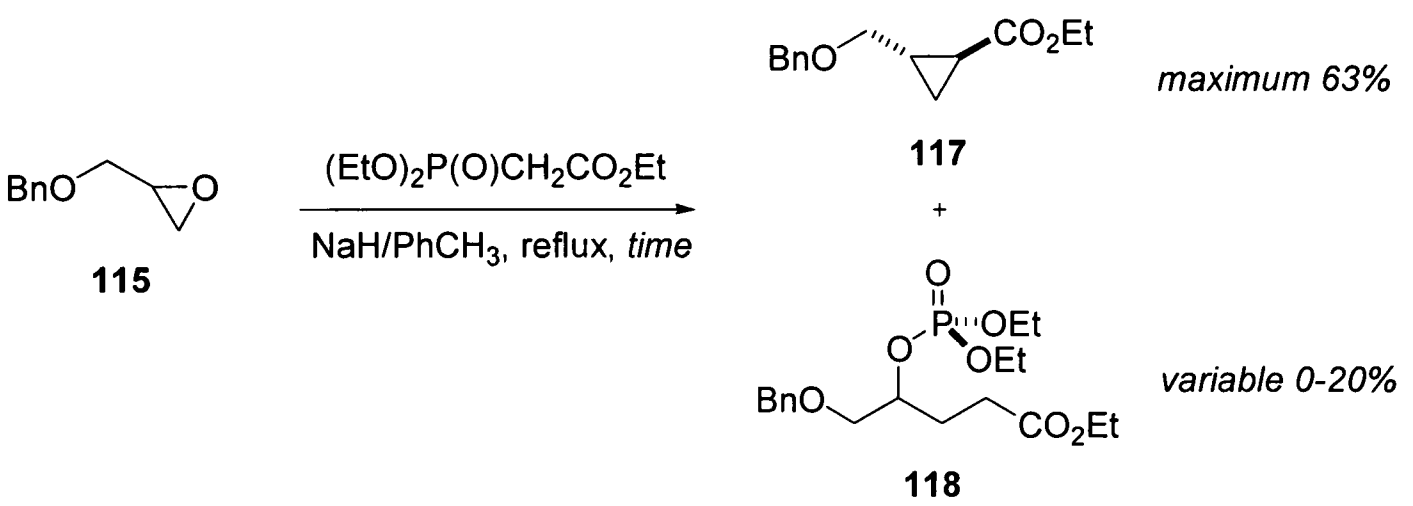
pKa(ROH) - *approx*. 16 (H_2O) pKa(RCH_2CO_2Et) - *approx*. 30 (H_2O)

pKa(ROH) - *approx*. 30 (DMSO) pKa(RCH_2CO_2Et) - *approx*. 30 (DMSO)

Scheme 63

2.3.5 Increasing reactivity

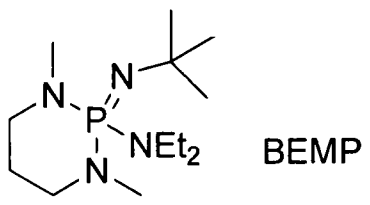
Further examination of the reaction between triethylphosphonoacetate and *rac*-**115** (under optimised NaH/$PHCH_3$, reflux conditions) identified phosphate **118** as being a significant side-product, isolated in variable 0 – 20% yields (Scheme 64).



Scheme 64

Since phosphate **118** corresponded to the final intermediate in the proposed reaction cascade, we envisaged that further heating under the reaction conditions would likely promote full conversion to cyclopropane **117**. However, by comparing entry 11/Table 3 (14 hour reflux, 63 % yield of **117**, 78:22 **117/118** ratio) and entry 12 (24 hour reflux, 54 % yield of **117**, 100:0 **117/118** ratio), this prolonged heating can be seen to have a detrimental effect on the isolated yield of **117**, suggesting that phosphate decomposition and/or cyclopropane decomposition[45] was occurring. In an attempt to minimise this decomposition, we therefore attempted cyclopropanation of *rac*-**115** at

room temperature (using triethylphosphonoaceate/NaH in toluene), but under these conditions no cyclopropanation was observed even over an extended period of time. This is also consistent with findings from workers at Bristol-Myers Squibb, who reported that the cyclopropanation of **103** (using triethylphosphonoacetate) was only successful at temperatures above 50 °C. In order to promote a lower temperature cyclopropanation we next attempted to either increase epoxide reactivity, or alternatively increase phosphonate anion nucleophilicity. Accordingly, we tested a range of Lewis acids (e.g. $BF_3.OEt_2$, Et_2AlCl, $Ti(O^iPr)_3$, $LiClO_4$, $Sc(OTf)_3$), but in all cases the introduction of these additives either led to a retarded reaction, or a complex mixture of products. The alternative strategy of increasing phosphonate anion nucleophilicity was then investigated, and to this end we attempted to promote the cyclopropanation of **115** using crown ethers, and the use of Schwesinger bases (such as BEMP **120** (Figure 14), but in both cases cyclopropanation efficiency was not improved. Additionally we also attempted the reaction under both Masamune-Roush conditions ($^iPr_2NEt$/LiCl, MeCN reflux)[53] and phase transfer conditions (solid $KOH/PhCH_3$ and aq. $KOH/PhCH_3$), but we found both of these to completely suppress cyclopropanation.



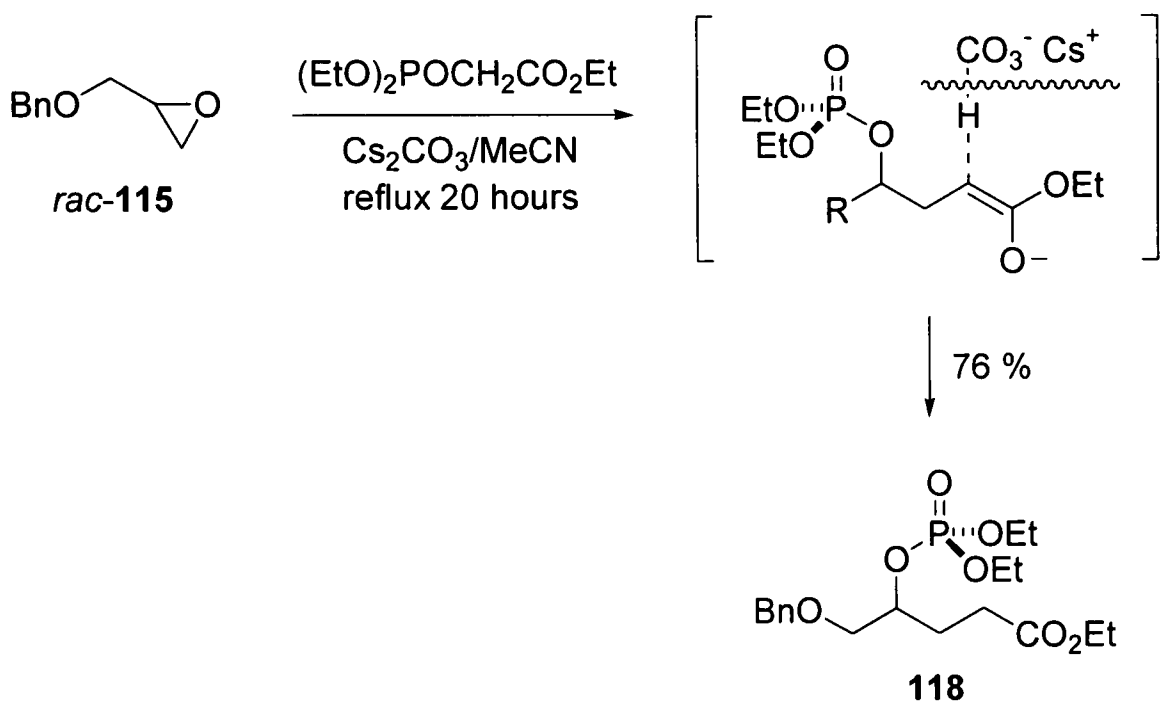
BEMP

120

Figure 14

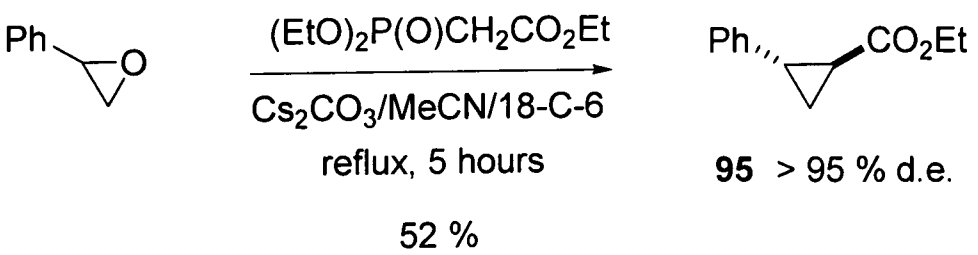
However, more success was achieved using a solid Cs_2CO_3-promoted reaction developed by Delmas for the olefination of aldehydes.[54] We were attracted to this procedure because cesium anions are known to be highly reactive (the "cesium effect"), which we hoped would therefore promote epoxide ring-opening and subsequent phosphonate transfer/cyclisation. Indeed, the authors had already provided IR data which explained the increased reactivity of cesium-based phosphonate anions as being the result of significant C-M bond character.[54] We applied these conditions to the cyclisation of **115**, and again found that non-polar solvents induced highest reactivity, but to overcome viscosity problems acetonitrile was chosen as the reaction solvent. Unfortunately, the product of this reaction was not the desired cyclopropane

117, but the acyclic phosphate **118**, produced in 76 % yield (Scheme 65). The exclusive formation of **118** can be explained by rapid reprotonation of the enolate by $CsHCO_3$, and in this case since **118** is significantly less acidic than $CsHCO_3$ little subsequent deprotonation (and cyclisation) then occurs. Only under more forcing conditions (*rac*-**115** in Cs_2CO_3/DMF at 90 °C for 24 hours) was this equilibrium driven towards ester deprotonation (and hence formation of cyclopropane **117**), through the irreversible extrusion of phosphate anion. In this case however, the product was formed only in low yield and as an intractable *cis*/*trans* mixture.



Scheme 65

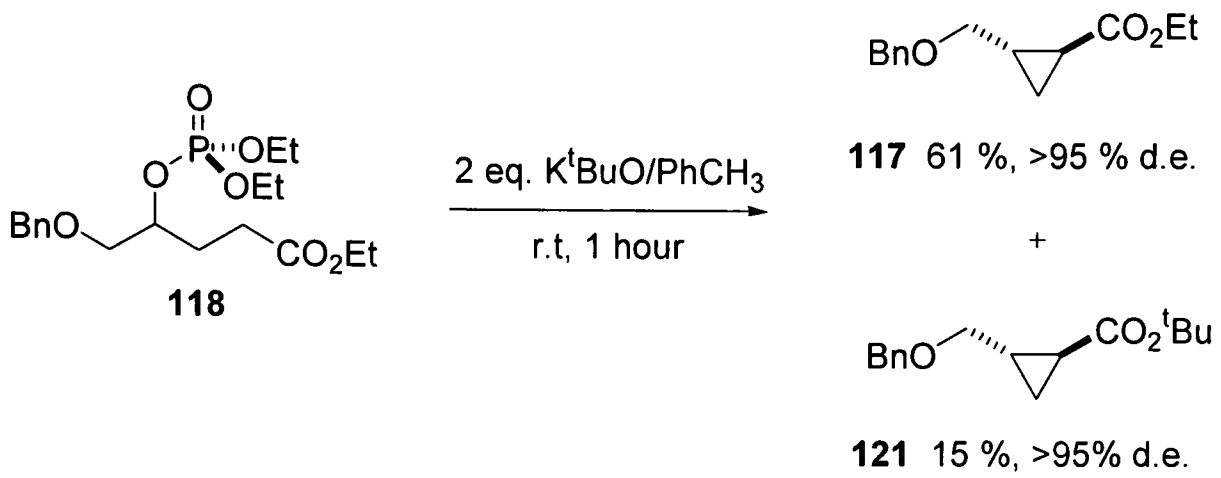
In contrast, we did find that this Cs_2CO_3-promoted procedure was effective for the direct cyclopropanation of styrene oxide (Scheme 66), which is likely explained by a more rapid 3-*exo*-tet cyclisation involving a benzylic phosphate.



Scheme 66

We briefly investigated the cyclisation of phosphate **118**, and eventually achieved this using potassium *tert*-butoxide in non-polar solvents. Use of more polar solvents (such

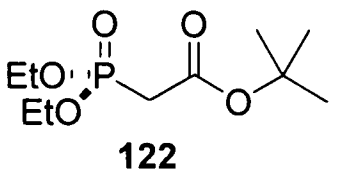
as THF or MeCN) resulted in a complex mixture of products, but when using 2 eq. K^{t}BuO/PhCH$_3$ at room temperature we obtained **117** in 61 % yield (> 95 % d.r.), in addition to 15 % of the transesterified *tert*-butyl ester **121** (Scheme 67).



Scheme 67

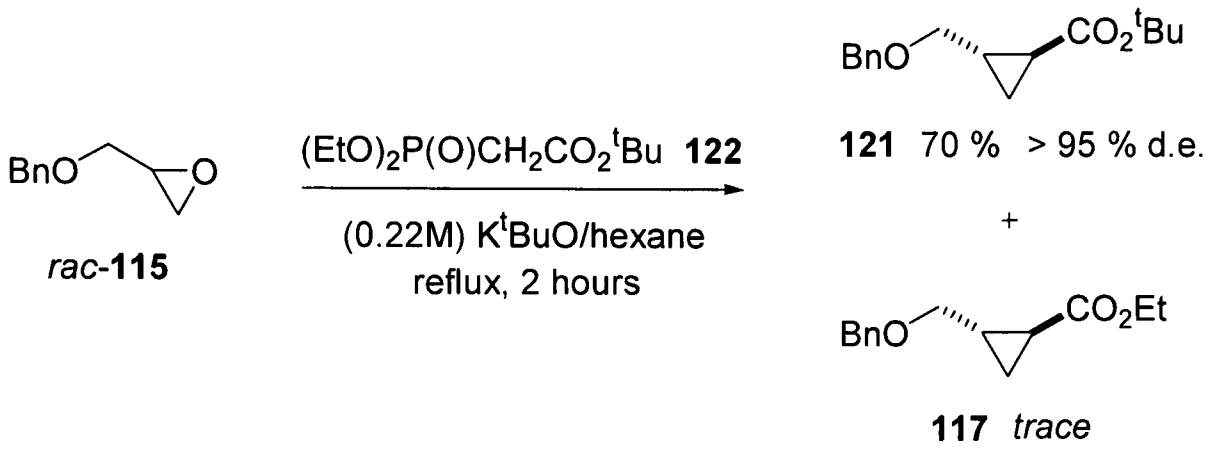
2.3.6 Room temperature Wadsworth-Emmons cyclopropanation

Since previous efforts to conduct a lower temperature cyclopropanation had failed, we alternatively attempted to reduce the decomposition/polymerisation of phosphate **118**/cyclopropane **117** through the introduction of a bulky *tert*-butyl ester group. Accordingly, we began investigations into the cyclopropanation of *rac*-**115** using *tert*-butyl ester phosphonate **122** (Figure 15), and to our great surprise this resulted in a much quicker cyclopropanation in comparison to that induced by triethylphosphonoacetate. Epoxide **115** was consumed in less than 2 hours (using NaH/**122**/PhCH$_3$ at reflux), compared to 14 hours previously using triethylphosphonoacetate under the same conditions. The initial yield of *tert*-butyl ester cyclopropane **121** was only 41 % (in addition to cyclopropyl ethyl ester **117** in 16 % yield), but subsequent optimisation improved the yield of **121** to 70 % (> 95 % d.e.), using K^{t}BuO/hexane at higher dilution (Scheme 68). The presence of cyclopropyl ethyl ester **117** is presumably due to nucleophilic substitution at phosphorus releasing free ethoxide into solution.



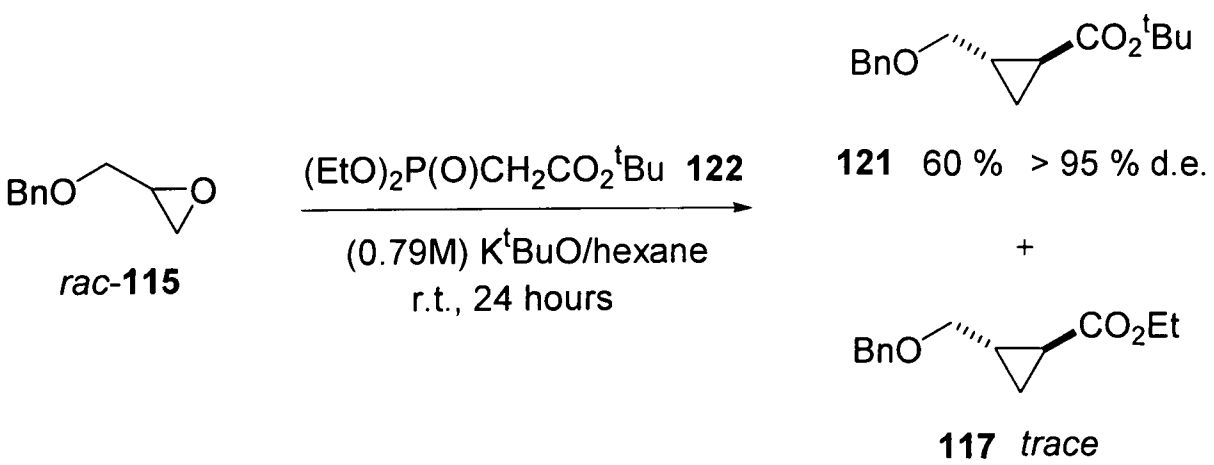
122

Figure 15



Scheme 68

As a consequence of this significant rate increase we then reinvestigated the possibility of conducting a room temperature cyclopropanation of *rac*-**115**. All previous efforts to achieve this transformation using triethylphosphonoacetate had failed, but to our delight reaction of *rac*-**115** with **112** (under K^{t}BuO/hexane conditions) at high concentration yielded cyclopropane **121** in 60 % yield and > 95% d.e. after just 24 hours (Scheme 69). This was the first example of an ambient temperature epoxide cyclopropanation, and therefore constitutes an important advance in the methodology.



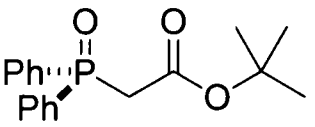
Scheme 69

It is plausible that the increased reactivity of **122** is due to the excellent solubility of its anion in hexane, since in contrast, deprotonated triethylphosphonoacetate was observed to form a viscous paste which only became soluble upon heating.

Accordingly, the concentration of (free) deprotonated **122** is likely to be far higher than that of (free) triethylphosphonoacetate anion under the same conditions, which is then reflected in the relative rates of cyclopropanation. Furthermore, this change in solubility is likely explained by the introduction of a more lipophilic *tert*-butyl ester group.

2.3.7 Horner cyclopropanation

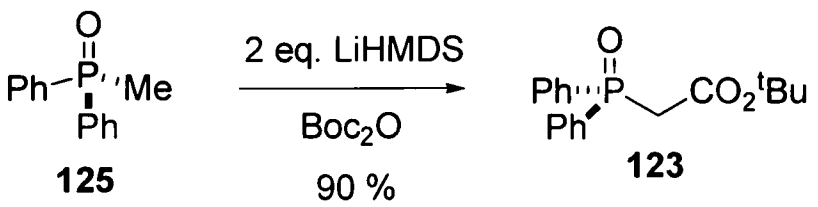
Our final effort to increase cyclopropanation efficiency involved the synthesis and application of phosphine oxide **123** (Figure 16). Building on previous results, we planned to increase reagent lipophilicity by combining the *tert*-butyl ester moiety with two additional phenyl groups. We hoped this modification would also reduce nucleophilic attack at phosphorus (since phosphine oxides are known to be less electrophilic then phosphonates), and by the change in substituents, this also prevents release of ethoxide into solution, which had previously 'consumed' some product by transesterification.



123

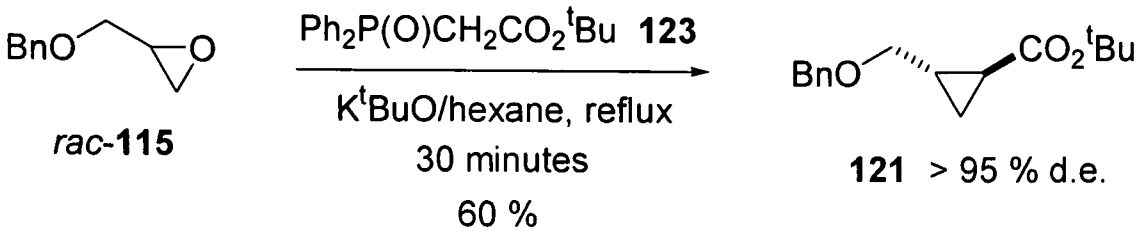
Figure 16

The target reagent **123** was synthesised in high 90 % yield by acylation of methyldiphenyl phosphine oxide **125**, using Boc-anhydride.[55] As in the previous synthesis of nitro phosphonate **110** (see previous Scheme 52), two equivalents of base (LiHMDS) were required to prevent quenching of the anion by the product (Scheme 70).



Scheme 70

Unfortunately however, although this compound was found to be an even more reactive cyclopropanating agent than **122** under the same K^{t}BuO/hexane (reflux) conditions (reaction complete in 30 minutes), reaction efficiency was not improved (Scheme 71). Furthermore, **123** also mediated a lower-yielding room-temperature cyclopropanation of *rac*-**115** than phosphonate **122**.



Scheme 71

2.3.8 Asymmetric Wadsworth-Emmons cyclopropanation

The success of an ambient-temperature cyclopropanation prompted us to attempt an asymmetric Wadsworth-Emmons cyclopropanation *via* kinetic resolution. Indeed, the equivalent olefination of racemic carbonyl compounds (under kinetic resolution control) using a variety of phosphorus-based reagents has been known for many years.[56] Of these reagents, (-)-8-phenyl-menthyl phosphonate **125** has achieved notable success. Furthermore, since **124/125** are likely to be even more lipophilic than *tert*-butyl phosphonate **122** (Figure 17), this suggests that these chiral phosphonates may also be successful in room temperature cyclopropanations.

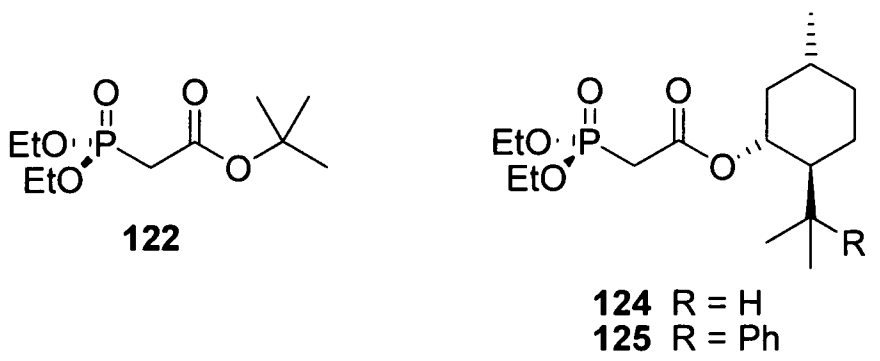
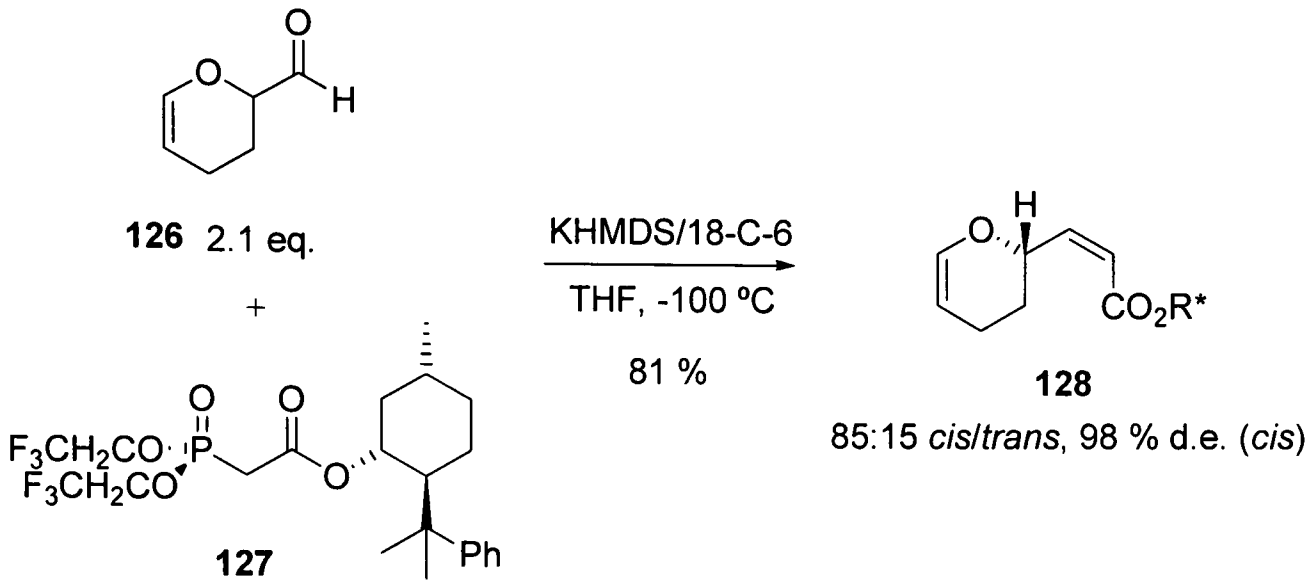


Figure 17

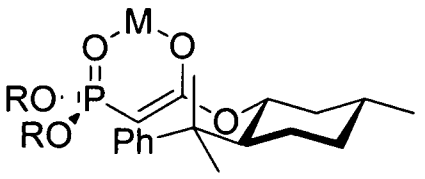
Rein was the first to achieve the kinetic resolution of racemic aldehydes, selecting phosphonates known to be either *Z* or *E*-selective to furnish *Z*/*E* enoates with opposite

α-stereochemistry. For example, the kinetic resolution of racemic aldehyde **126** with phosphonate **127** affords enoate **128** in high diastereoselectivity (Scheme 72).[57]



Scheme 72

This reaction is believed to proceed by an initial irreversible nucleophilic attack, so the observed product simply reflects the lowest-energy open transition-state assembly. Key to this observed selectivity is the defined structure of phosphonate **127**, which exists in only its *Z*-isomeric conformer that effectively shields one prochiral face (structure **129**, Figure 18).[58] In combination with a *cis*-selective olefination (since **127** is a Still-phosphonate)[59] and a Felkin-Anh addition, this then explains the observed diastereoselectivity and formation of enoate **128**.

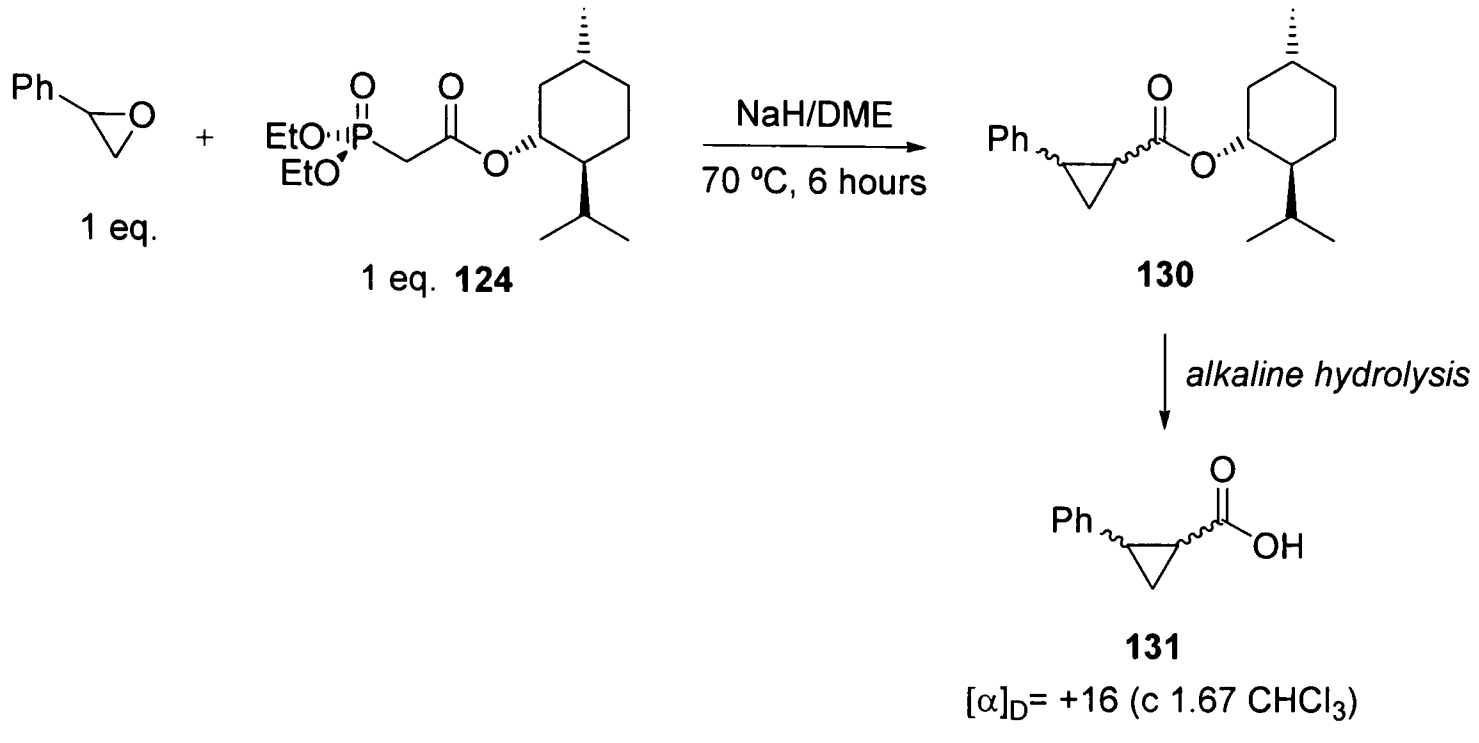


129

Figure 18

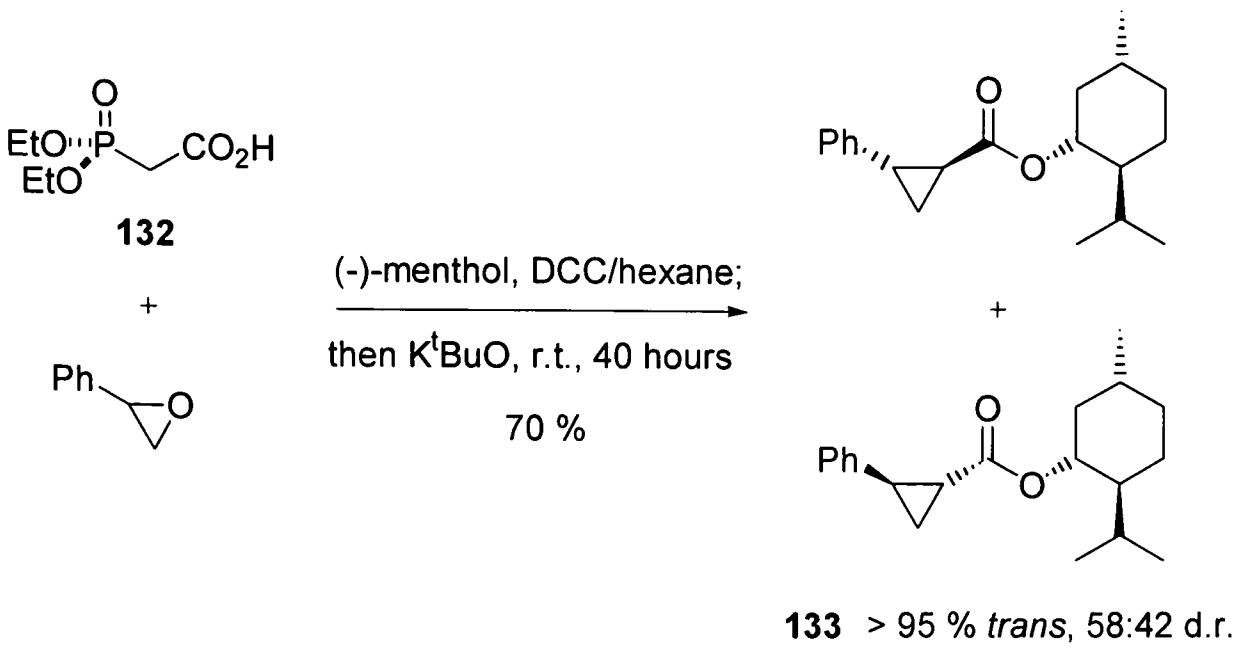
We believe the epoxide cyclopropanation also proceeds by initial irreversible ring-opening, meaning that the lowest-energy *R*-epoxide/phosphonate *vs* *S*-epoxide/phosphonate transition-state will direct the kinetic resolution. Indeed, we later discovered that Tömösközi had already attempted this reaction in 1966,[42] but for unknown reasons used a 1:1 ratio of phosphonate **124** and *rac*-styrene oxide. The product menthyl cyclopropane **130** (yield not reported) was subsequently hydrolysed

to the acid **131**, but not surprisingly this displayed only a small optical rotation (Scheme 73).



Scheme 73

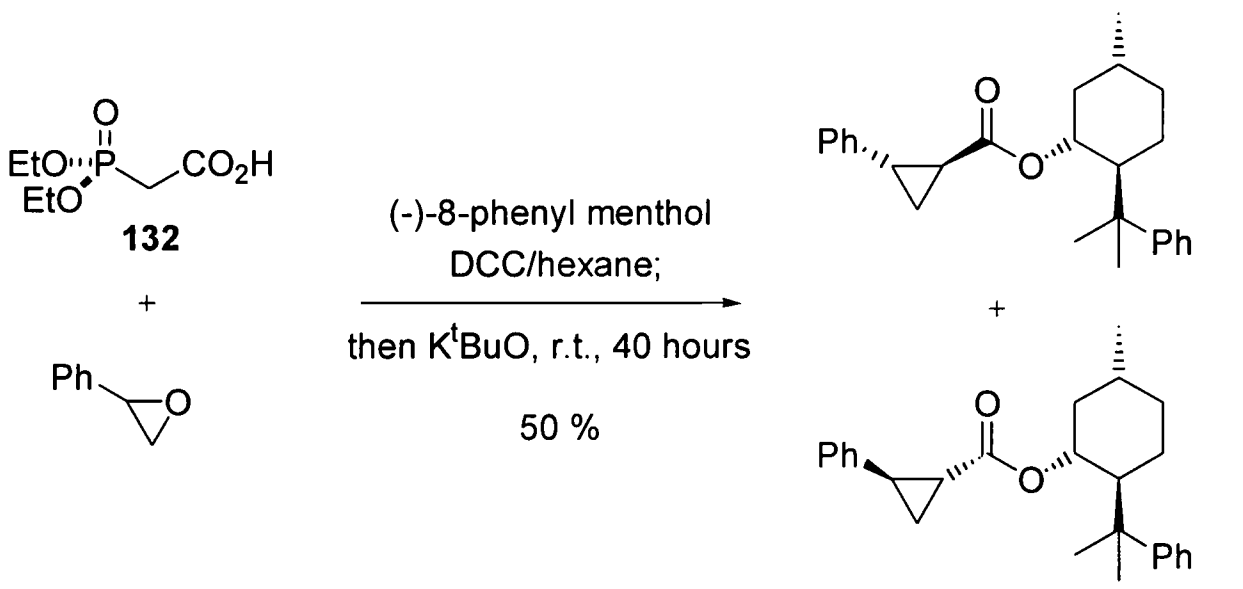
In contrast, we hoped that by conducting this reaction at a lower temperature, and using a two-fold excess of epoxide we may promote a successful kinetic resolution. We began this work by synthesising (-)-menthyl phosphonate **124**, in near quantitative yield, by dehydration of **132** to its ketene (using DCC/CH_2Cl_2),[60] then trapping with (-)-menthol. This procedure was equally successful in hexane, which then permitted a one-pot esterification/cyclopropanation reaction from commercially available reagents. Using 1 eq. chiral phosphonate **124** (assuming 100 % conversion in the esterification step) and 2 eq. *rac*-styrene oxide (under K^tBuO/hexane conditions) we achieved synthesis of **133** in 70 % yield after 40 hours at room temperature (Scheme 74). Unfortunately however, menthyl cyclopropane **133** was produced with little stereoinduction (> 95 % *trans*, approximately 58:42 d.r. by slow-pulse ^{13}C NMR).



133 > 95 % *trans*, 58:42 d.r.

Scheme 74

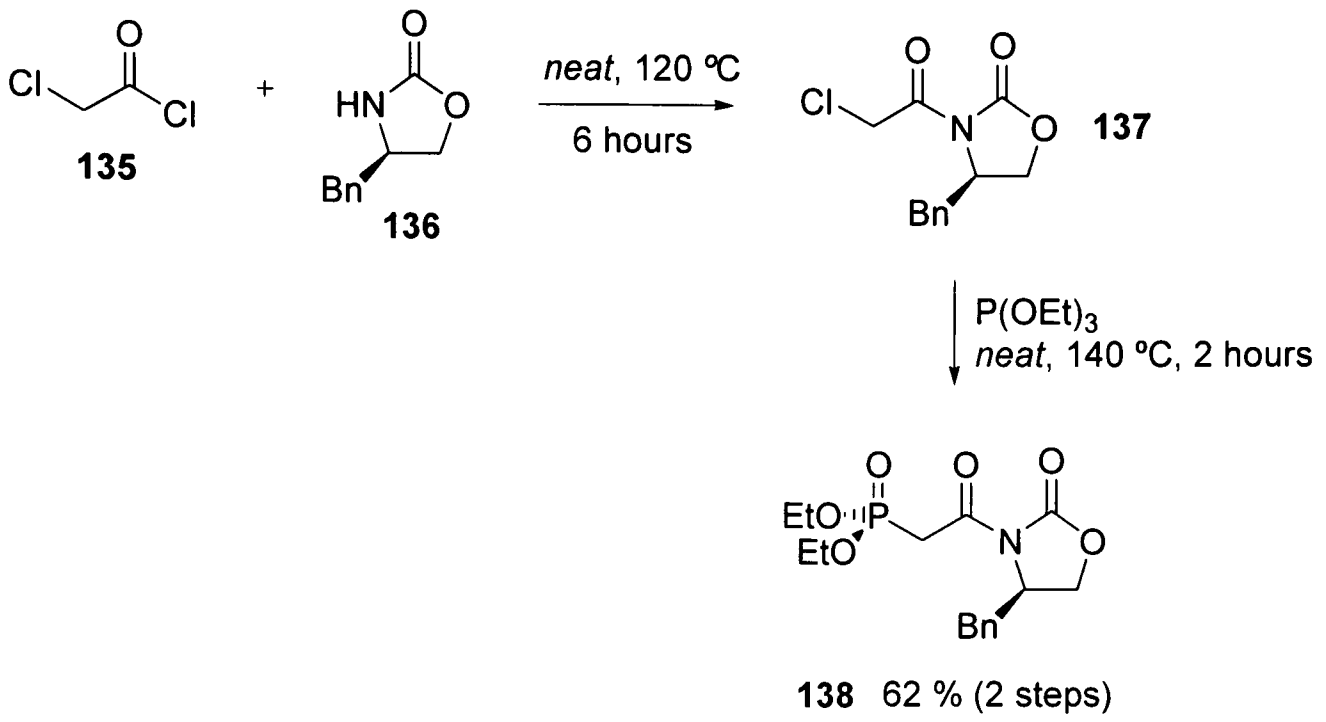
On this basis we switched to (-)-8-phenyl menthyl phosphonate **125**, which is usually much more selective.[56] However, under the same conditions we failed to achieve any improvements in selectivity, and a slight reduction in the cyclopropanation yield (Scheme 75).



134 > 95 % *trans*, 51:49 d.r.

Scheme 75

As an alternative, we synthesised oxazolidinone-based phosphonate **138** by a method adapted from work by Jacobsen.[61] Chloroacetyl chloride **135** was aminated with (*R*)-4-benzyl-2-oxazolidinone **136** (neat 120 °C/6 hours), then treated with triethylphosphite to generate the target phosphonate **138** in 62 % yield (2 steps) (Scheme 76).



Scheme 76

Unfortunately, phosphonate **138** failed to cyclopropanate styrene oxide at room temperature, and gave a complex mixture of products at elevated temperatures.

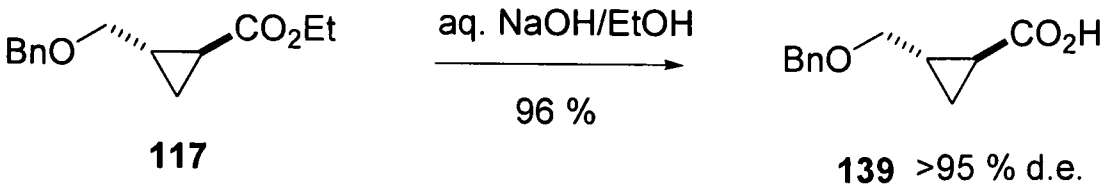
In conclusion, the lack of selectivity when using menthol-based phosphonates **124** and **125** indicates that (under the reaction conditions) the (*R*)-styrene oxide/phosphonate transition-state is similar in energy to the alternative (*S*)-styrene oxide/phosphonate transition-state assembly. This is potentially explained by epoxide ring-opening requiring the phosphonate anion to approach relatively far from existing α-asymmetry. Alternatively, the initial epoxide ring-opening may be reversible, in which case the lack of selectivity would be explained by comparable product stability.

2.4 Conversion of cyclopropyl ester to aminocyclopropyl electrophile

2.4.1 Deprotection of cyclopropyl ester

In the previous section we developed procedures to access both cyclopropyl ethyl ester **117** in 63% yield, and cyclopropyl *tert*-butyl ester **121** in 70% yield. We considered both these compounds to be excellent starting points for the total synthesis of (+)-**1**, depending upon the efficiency of each ester deprotection. Warren had earlier demonstrated that similar cyclopropanes were stable to base (see previous Scheme

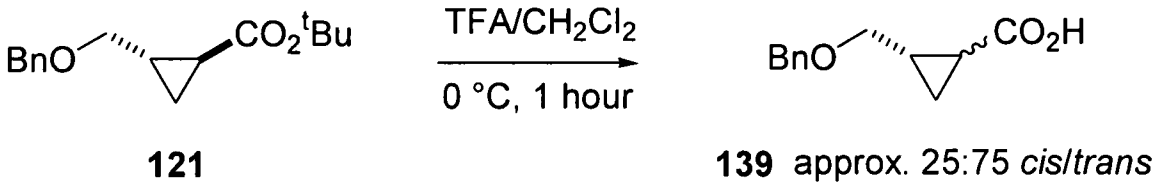
44),[41] so we were reasonably confident that aq. NaOH/EtOH induced hydrolysis would be successful. As expected, submitting **117** to these conditions successfully led to the desired acid **139** in 96 % yield without epimerisation (Scheme 77).



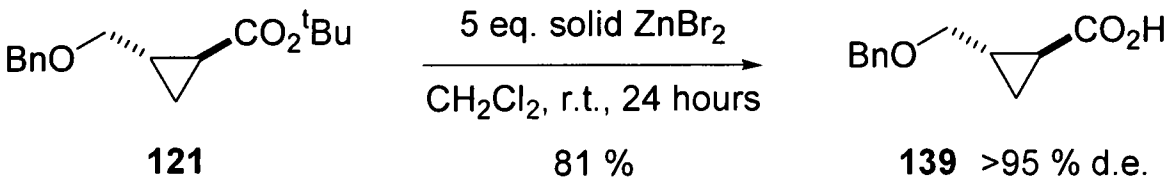
117 **139** >95 % d.e.

Scheme 77

By contrast, **121** was rapidly epimerised upon treatment with TFA/CH_2Cl_2, affording the corresponding acid **139** in approximate 25:75 *cis/trans* ratio (Scheme 78). Since Warren had also shown protic acid to cause epimerisation in other α-acyl cyclopropanes (see previous Scheme 44),[41] we then began investigating a Lewis-acid promoted deprotection. As a result, we attempted deprotection using a solid $ZnBr_2/CH_2Cl_2$ system, recently reported by Lubell[62] to be selective for *tert*-butyl ester deprotection in the presence of other acid-labile functionality. After stirring **121** for 24 hours at room temperature with five equivalents solid $ZnBr_2$, we were delighted to see formation of the desired acid **139** in 81% yield without epimerisation (Scheme 78).



121 **139** approx. 25:75 *cis/trans*



121 81 % **139** >95 % d.e.

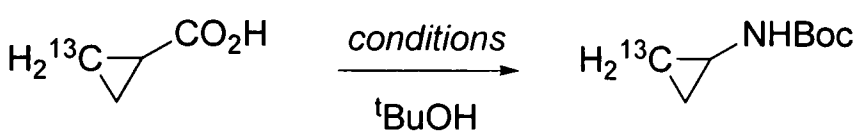
Scheme 78

The overall two-step cyclopropanation/hydrolysis yields are similar for both of these processes, but we decided to continue the total synthesis of (+)-**1** using the cyclopropyl ethyl ester **117** route (with subsequent aq. NaOH hydrolysis), since we considered this procedure to be more applicable to scaleup.

2.4.2 Curtius rearrangement

With *trans*-cyclopropyl acid **139** in hand we required a stereospecific amination to generate the desired *trans*-cyclopropylamine. This transformation is typically achieved using acyl nitrene methodology, since it is known that rearrangement to the isocyanate intermediate proceeds with retention of stereochemistry. Accordingly, our starting point was to investigate the direct Curtius rearrangement of acid **139**.

Since cyclopropyl-based Curtius rearrangements often proceed in only moderate yields, we therefore began by researching the efficiency of each modification. Our primary reference was a methodological study by Kuttab.[63] Here, ^{13}C-labelled cyclopropyl acid **140** was subjected to various rearrangement conditions to generate the corresponding isocyanate which was subsequently (or *in situ*) trapped with *tert*-butanol to form the Boc-protected cyclopropylamine **141** directly (Scheme 79, Table 4).



140 **141**

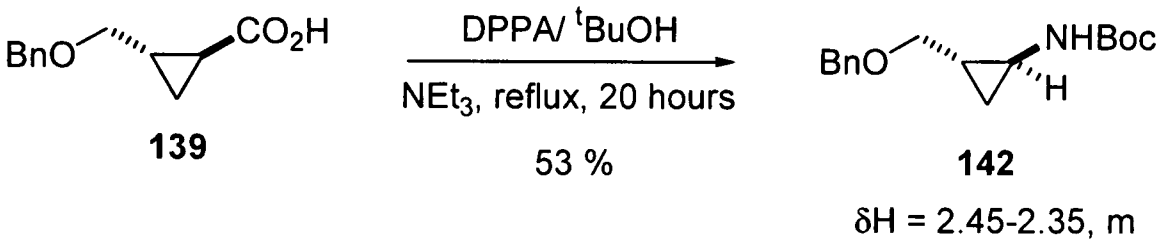
Scheme 79

Entry	Conditions	Yield **141**/%
1	**DPPA/NEt_3/^{t}BuOH, reflux 5 hours.**	**73**
2	DPPA/NEt_3/^{t}BuOH/CuCl, reflux 3 hours.	5
3	**DPPA/NEt_3/^{t}BuOH/$PhCH_3$, reflux 6 hours.**	**81**
4	i) DPPA/NEt_3/$PhCH_3$. ii) ^{t}BuOH, reflux 5 hours.	47
5	i) $ClCO_2Et$/NEt_3/H_2O/acetone 0 °C. ii) NaN_3. iii) ^{t}BuOH, reflux 5 hours.	22
6	i) $SOCl_2$ reflux 1 hour. ii) NaN_3/H_2O/acetone 0 °C. iii) ^{t}BuOH reflux 8 hours	7

Table 4[63]

This work demonstrated that the highest yields of **141** were achieved using diphenylphosphoryl azide (DPPA) in combination with *tert*-butanol (entries 1 and 3). This is a modification introduced by Yamada,[64] and employs DPPA as both an activating agent and subsequent (non-explosive) azide-transfer reagent. The use of CuCl-catalysis, as well as performing a two-step reaction resulted in a dramatic decrease in yield. Other methods (entries 5, 6) provided poorer conversions, which in this case may be due to low boiling point intermediates.

On this basis, we submitted cyclopropyl acid **139** to DPPA/NEt_3/^{t}BuOH conditions, and were delighted to see formation of the Boc-protected cyclopropylamine **142** in 53 % yield as a single diastereoisomer (Scheme 80). The cyclopropyl C<u>H</u>N proton appeared at 2.35-2.45ppm in the 250MHz ^{1}H NMR.



139 **142**

δH = 2.45-2.35, m

Scheme 80

Using nOe analysis **142** was identified as the *trans*-stereoisomer, confirming the stereospecific rearrangement from acid **139**. H_3 showed enhancements to H_2/H_5 only, whereas H_6 showed enhancements to H_1/H_4 only (Figure 19, Table 5).

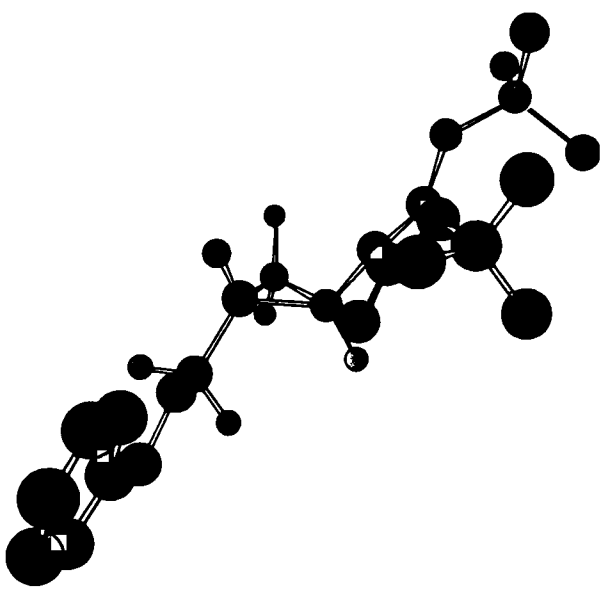
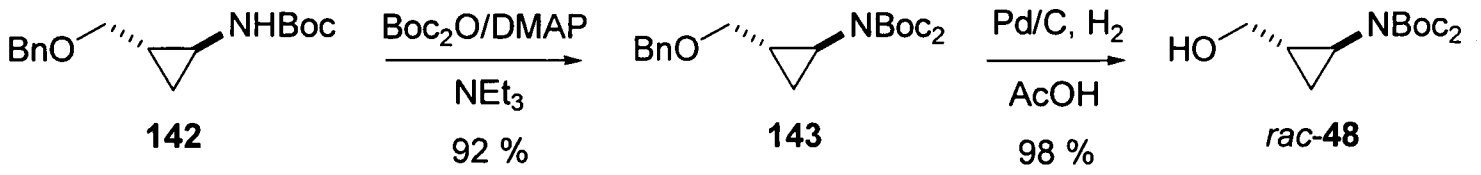


Figure 19 : MM2 minimised conformation of **142** (Chem3D)

Irradiated proton	nOe / %				
	H_1	H_2	H_1/H_2	H_4	H_5
H_3	-	3.83	-	-	4.90
H_6	4.30	-	-	4.70	-

Table 5

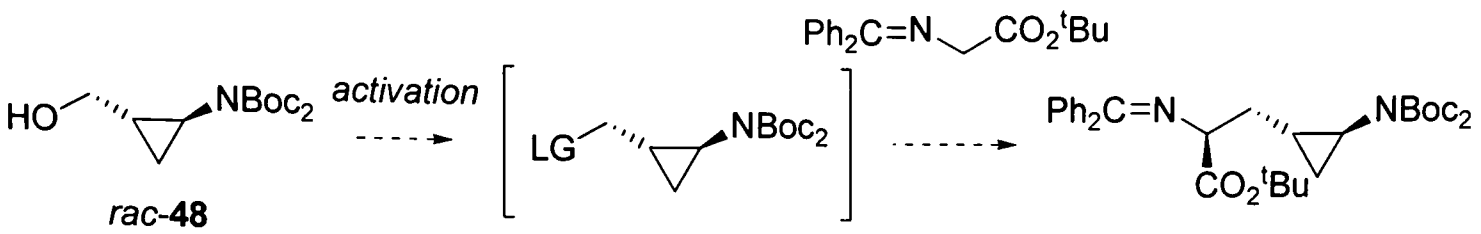
Carbamate **142** was then subsequently converted to the bis-Boc-amine **143** (under standard Boc_2O/DMAP/NEt_3 conditions), then deprotected by AcOH-catalysed hydrogenolysis (H_2, Pd/C in THF) to afford the target aminocyclopropyl methanol *rac*-**48** (Scheme 81). Previous attempts to deprotect **143** in methanol also resulted in substantial Boc-deprotection, but in THF the high yield of *rac*-**48** indicates no such Boc-deprotection or competing cyclopropane reduction.



Scheme 81

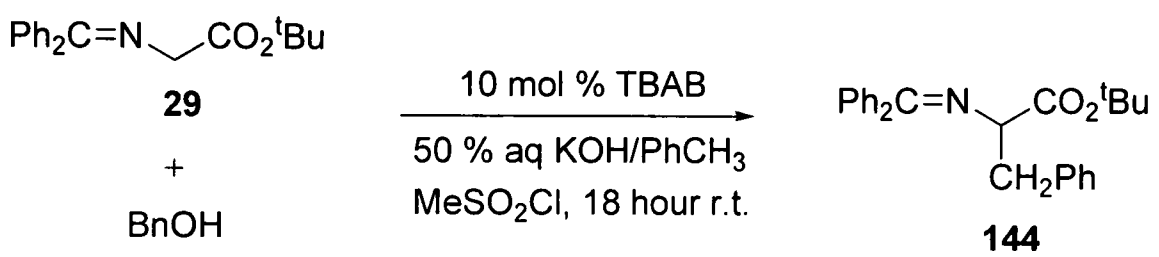
2.4.3 Phase-transfer mesylation

Our next task was to activate *rac*-**48** to allow glycine alkylation. Previous work by de Meijere (section 1.3.1) utilised an α-iodo aminocyclopropyl electrophile in his non-selective alkylation reaction, but reported synthesis of iodide **30** in only low 34% yield due to its "instability". We approached this problem as a challenge to develop a one-pot reaction, involving both electrophile activation then glycine alkylation. This would therefore avoid the problem of isolating the iodide, and may become a useful general procedure when dealing with sensitive electrophiles (Scheme 82).



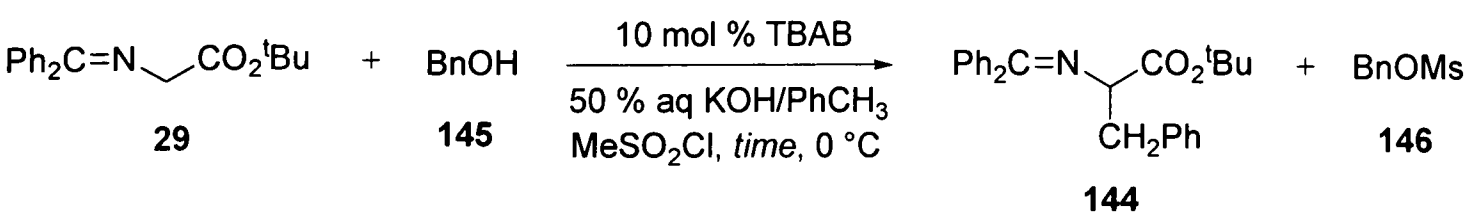
Scheme 82

To make activation of *rac*-**48** compatible with the anticipated phase-transfer glycine alkylation step, we required activation under phase transfer conditions. We discovered that Lygo had also considered this idea, using an *in situ* sulfonylation to achieve the desired alcohol activation.[65] Mesylates were found to be more reactive to glycine alkylation than tosylates, but this alkylation was still only achieved in low levels (Scheme 83).



Scheme 83

We hoped to improve this reaction, and started by first re-examining the efficiency of the mesylation step. Following a procedure developed by Szeja,[66] we reacted benzyl alcohol with 1.5 equivalents of mesyl chloride under 50 % aq. KOH/CH_2Cl_2 ($BnEt_3NCl$ catalysis) conditions, and confirmed rapid and complete mesylation after 15 minutes at –5 °C. Using this methodology we then attempted subsequent glycine alkylation in a one-pot reaction, and monitored the progress of this reaction by 250MHz ^1H NMR analysis (Scheme 84, Table 6).



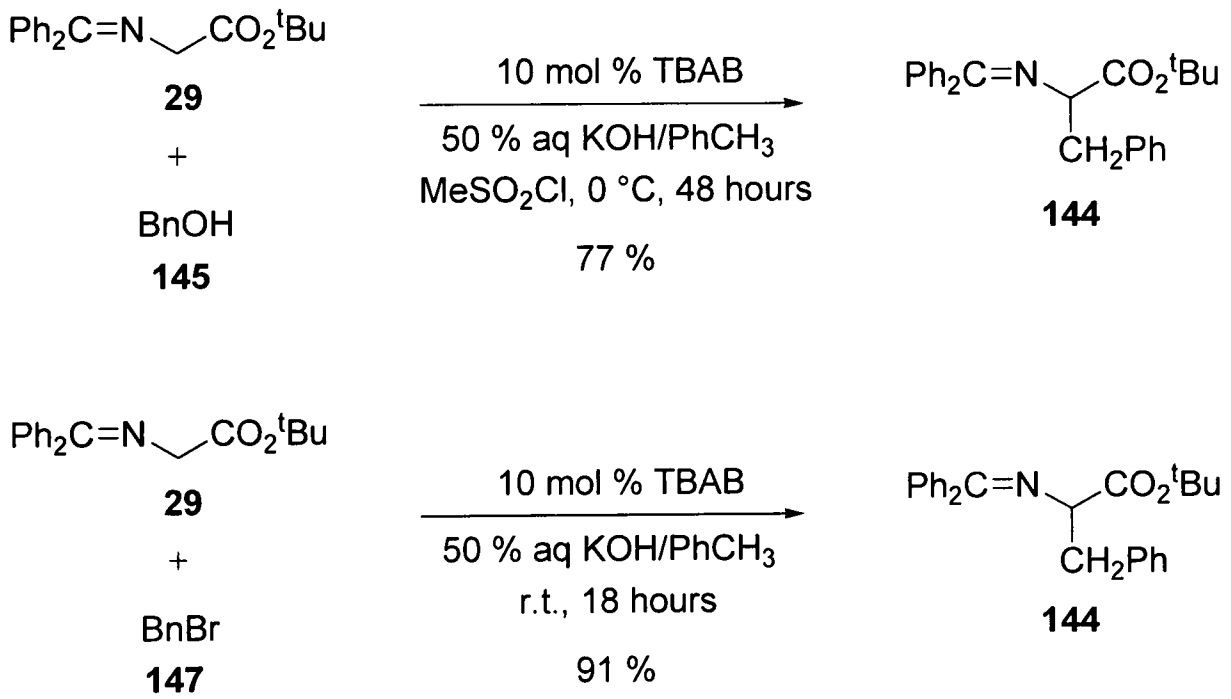
Scheme 84

Time/h	^{1}H NMR ratio*			
	29	**145**	**144**	**146**
18	25	12	48	13
48	4	18	78	0

*Approximate ratio from 250MHz ^{1}H NMR of crude reaction mixture

Table 6

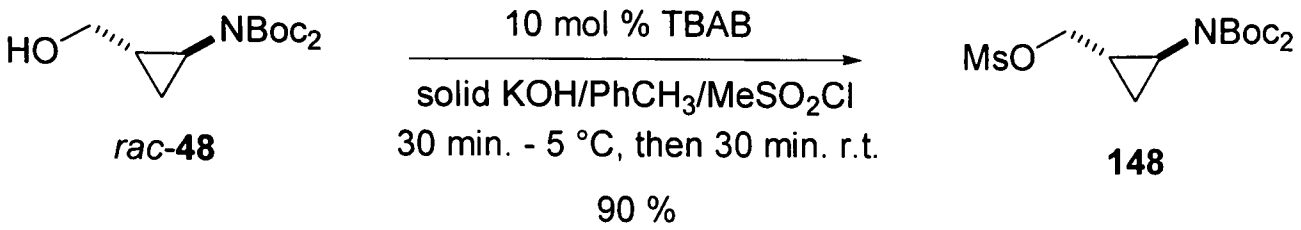
After 18 hours at 0 °C, ^{1}H NMR analysis revealed glycinate **144** was present in 48%, which increased to 78% after complete consumption of the benzyl mesylate **146** (48 hours, 0 °C). A subsequent repetition of this procedure then furnished **144** in 77 % isolated yield, meaning that this approach was now competitive with using benzyl bromide as the electrophile (Scheme 85).



Scheme 85

Following these promising results, we attempted mesylation of cyclopropyl alcohol *rac*-**48**, but found this to be much more problematic. Under the previous liquid-liquid phase-transfer conditions we achieved less than 50 % conversion, even using a three equivalent excess of mesyl chloride. This result promped us to examine solid-liquid phase transfer conditions, since a reduced water content in the organic phase usually means hydrolysis is reduced and anions are more reactive.[67,68] Using solid KOH in $PhCH_3$ (TBAB catalysis) and 1.5 equivalents of mesyl chloride, we were delighted to

achieve 80 % mesylation (^{1}H NMR yield) after just 30 minutes at –5 °C, or 90 % isolated yield of **148** using two equivalents mesyl chloride (Scheme 86).

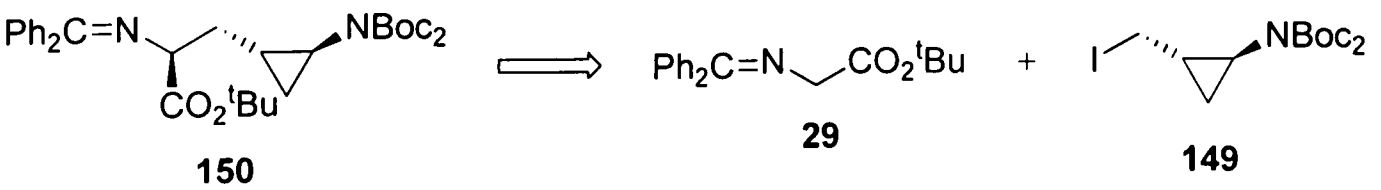


Scheme 86

Having developed a high-yielding mesylation procedure under phase-transfer conditions, we next attempted exploratory glycine alkylation. Unfortunately, under a range of conditions mesylate **148** was found to be unreactive, either in a one-pot reaction from alcohol *rac*-**48**, or in a separate alkylation step from **148**. Furthermore, addition of catalytic amounts of NaI and TBAI also failed to induce alkylation, presumably since the iodide was not formed under the reaction conditions. This result demonstrated that cyclopropyl mesylate **148** was much less reactive than benzyl mesylate, suggesting a better leaving group was required to achieve successful alkylation, and on this basis we returned to the idea of using a cyclopropyl iodide electrophile.

2.4.4 Synthesis of aminocyclopropyl iodide

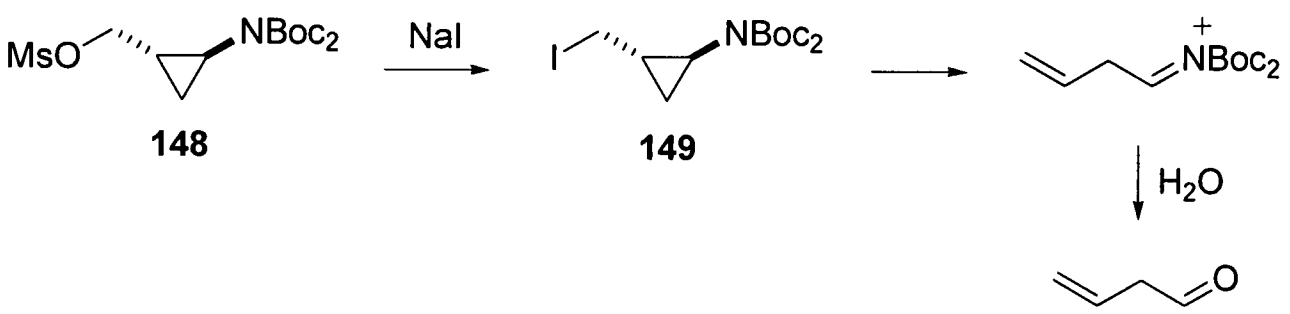
De Meijere had already demonstrated the intrinsic compatability of glycine **29** with (dideutero)cyclopropyl iodide **30** as part of his non-selective synthesis of (2*S*/*R*, 1′*R**, 2′*S**)-AcpAla **8**, albeit under BuLi/THF conditions (section 1.3.1, Scheme 7).[8] Furthermore, since iodides are also known to be the most reactive electrophiles for phase-transfer glycine alkylation, we considered that iodide **149** would provide our greatest chance of success (Scheme 87).



Scheme 87

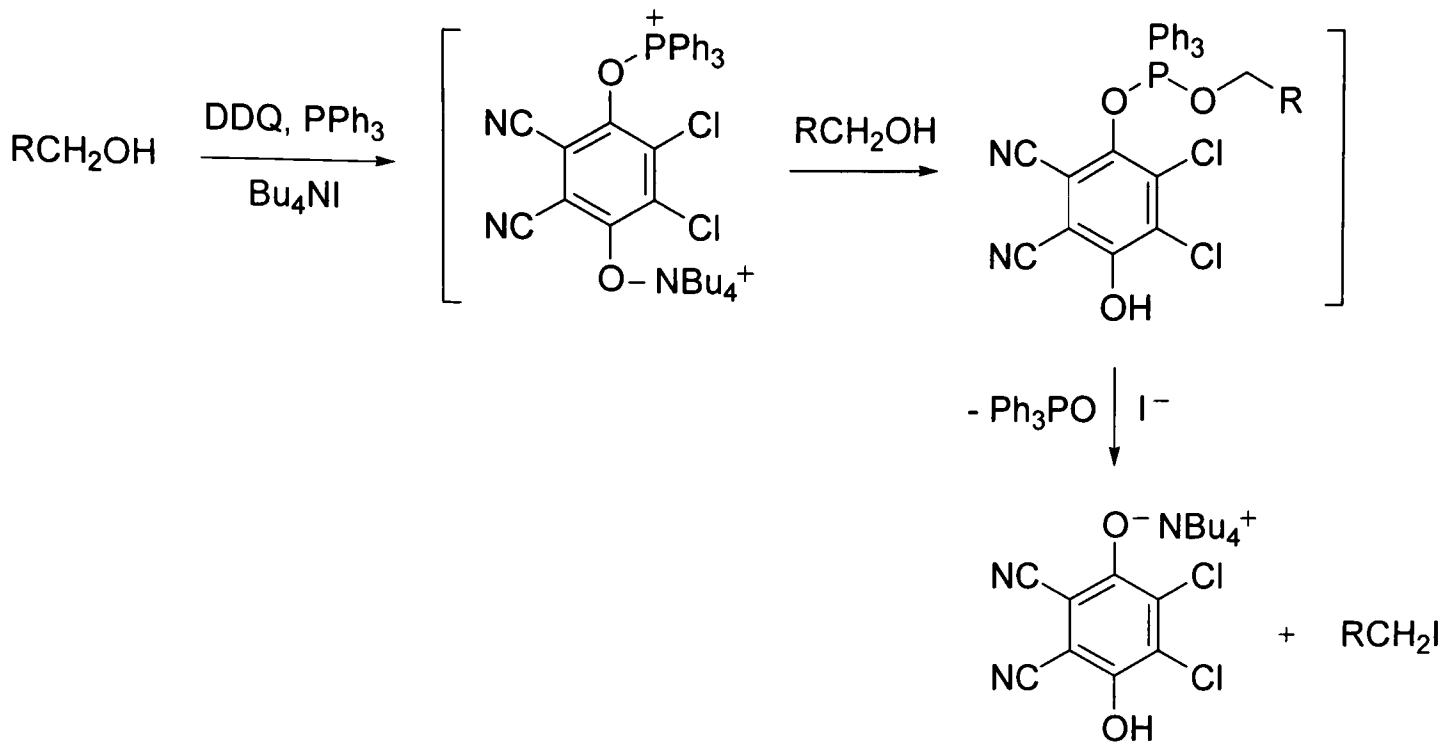
The problem with this strategy lies with the synthesis of iodide **149**, due to its "limited stability".[8] From this general statement it is unclear whether **149** is unstable under the reaction conditions, unstable to purification, or unstable upon storage. We planned to investigate alternative iodination procedures to de Meijere, aiming to synthesise **149** in both high yield and high purity.

Our initial suspicion was that the 'electrophilic' iodination conditions (I_2/dppe) used by de Meijere may have been incompatible with the cyclopropylamine, so we favoured synthesis using an iodide source. We began this work by attempting the Finkelstein-type iodination of mesylate **148** using 5 eq. NaI in acetone (dark), but found this reaction to be prohibitively slow. However, attempted acceleration by heating was also unsuccessful, as this resulted in rapid and complete decomposition. The ^{1}H NMR of the crude product clearly showed aldehyde and olefin signals, which presumably arise from iodination, ring cleavage, then hydroysis (Scheme 88)



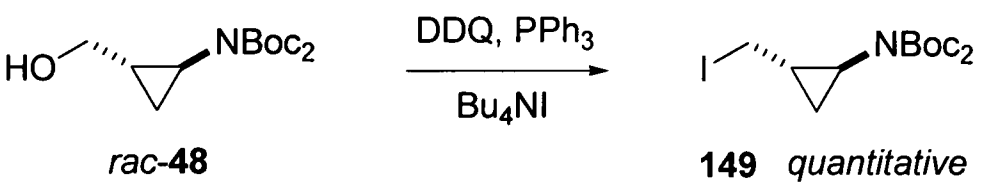
Scheme 88

After some experimentation we did achieve complete conversion, using 10 eq. NaI/acetone (dark) for 40 hours. However, the crude product showed significant side-products, and after flash column chromatography iodide **149** was isolated in only 25% yield. Because we suspected this low yield was due to the harsh conditions required for synthesis (ten-fold excess of reagents, prolonged reaction times), we therefore began searching for a milder alternative. With this in mind we became attracted to a recent communication by Iranpoor,[69] who reported a novel and high-yielding iodination procedure compatible with other sensitive functionalities. This reaction relies on the DDQ-activation of triphenylphosphine, in combination with a tetraalkyl ammonium source of iodide. The proposed mechanism involves initial aromatisation of DDQ by PPh_3, attack of the alcohol on the phosphonium salt, then displacement by iodide (Bu_4NI) in the standard fashion (Scheme 89).



Scheme 89

On application of these conditions to our cyclopropyl alcohol *rac*-**48**, we were delighted to see complete and instantaneous conversion to iodide **149**. By-products were removed by chromatography (following the literature procedure) to afford the iodide **149** in an isolated yield of 60 %. This was more than twice the yield achieved using the NaI-procedure, but we suspected further improvements could be made by avoiding the chromatographic work-up. After some experimentation, we then successfully managed to remove by-products through trituration, providing iodide **149** in essentially quantitative yield and of sufficient purity to continue the synthetic sequence (Scheme 90). Iodide **149** was observed to partially decompose upon storage, but if used immediately this could be avoided.

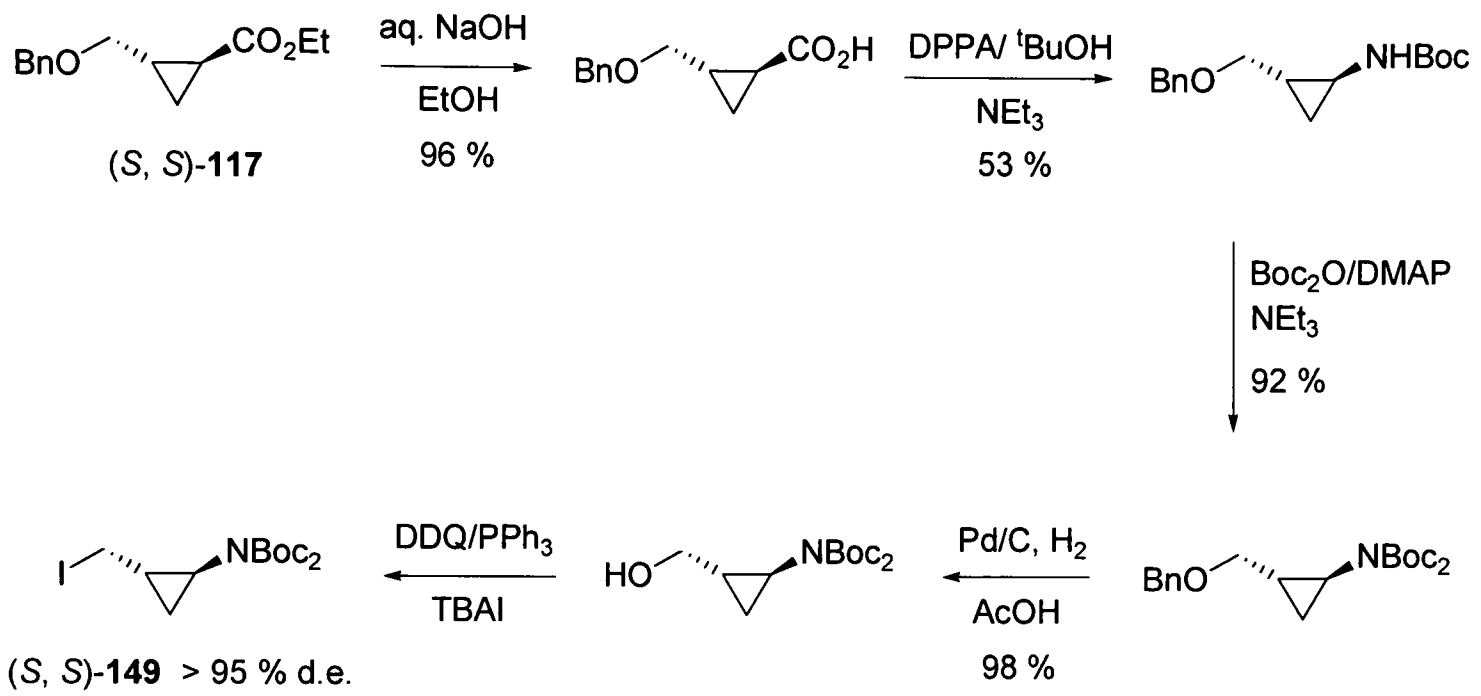


rac-**48** **149** *quantitative*

Scheme 90

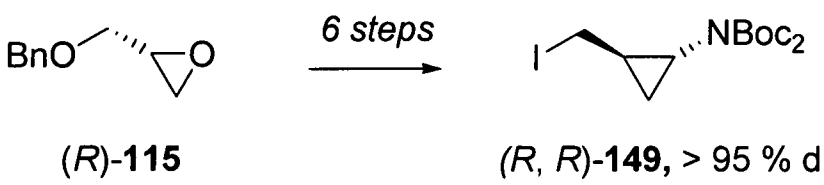
2.4.5 Further work towards total synthesis and synthetic analogues

With an efficient synthesis of racemic iodide *rac*-**149** developed, the sequence was repeated using cyclopropane (*S*, *S*)-**117** to allow continuation of the total synthesis (Scheme 91). All steps were repeated in similar yield and diastereoselectivity.



Scheme 91

In addition, in order to synthesise all four stereoisomers of the central *trans*-AcpAla amino acid we also required the enantiomeric iodide (*R*, *R*)-**149**, and this was synthesised in six steps from *R*-glycidol benzyl ether (*R*)-**115** (all steps in similar yield and selectivity) (Scheme 92).



Scheme 92

Since a concise and high-yielding synthesis of both cyclopropyl iodides (*S*, *S*)-**149** and (*R*, *R*)-**149** had now been achieved, we next focussed our attention to introducing the amino acid moiety by asymmetric alkylation.

2.5 Organocatalytic amino acid synthesis

2.5.1 Introduction

"Organocatalysis is the acceleration of chemical reactions with a substoichiometric amount of an organic compound that does not contain a metal atom",[70] and is currently of great interest since these reactions often proceed with exceptional levels of efficiency and selectivity.[70] One of the most useful and well-developed areas of organocatalysis is asymmetric phase transfer catalysis, which has shown greatest success in alkylation, conjugate addition and epoxidation reactions. In these cases, high selectivity is often achieved because (usually) only the more lipophilic nucleophile-catalyst complex can enter the electrophile-containing organic phase.[71] The catalyst is usually based on a chiral quaternary ammonium salt, and the reaction can be performed under both liquid-liquid and solid-liquid phase transfer conditions.

In its simplest form, there are three steps involved in catalytic phase transfer reactions (Figure 20).[71]

i) Deprotonation of the nucleophile HY by the base. This generally occurs at the interface between the two phases.

ii) Ion-exchange of the nucleophile anion MY with the cation of the chiral quaternary ammonium salt (QX), to form a lipophilic cation-anion pair QY.

iii) Extraction of complex QY into the organic phase, and reaction with the electrophile. The product remains in the organic phase and the catalyst is regenerated.

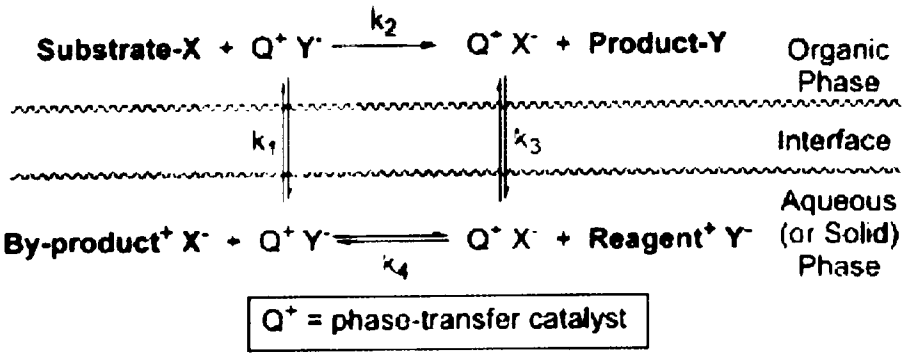
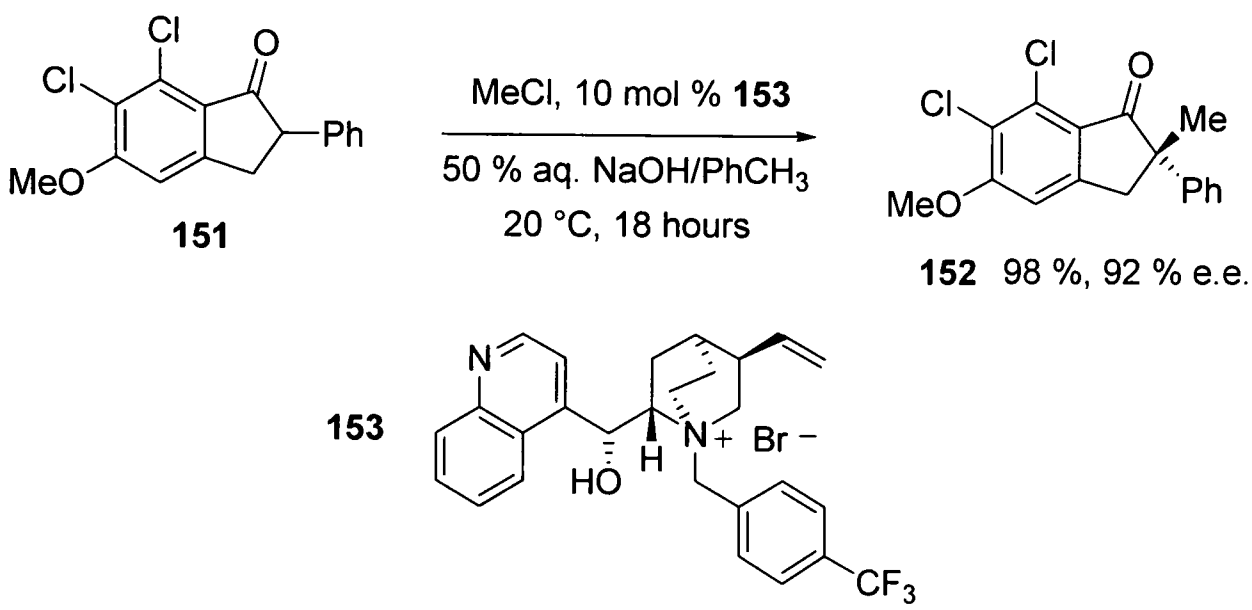


Figure 20[22(c)]

Asymmetric phase-transfer catalysis was first used to synthesise chiral (non racemic) amino acids by O'Donnell in 1989.[72] Inspiration for this methodology was taken from workers at Merck, who reported the enantioselective alkylation of phenylindanone **151** with MeCl under chiral phase transfer conditions (Scheme 93).[73] This impressive reaction was achieved only after detailed investigations, with cinchona alkaloid salt **153** ultimately being found to be the most effective phase-transfer catalyst.



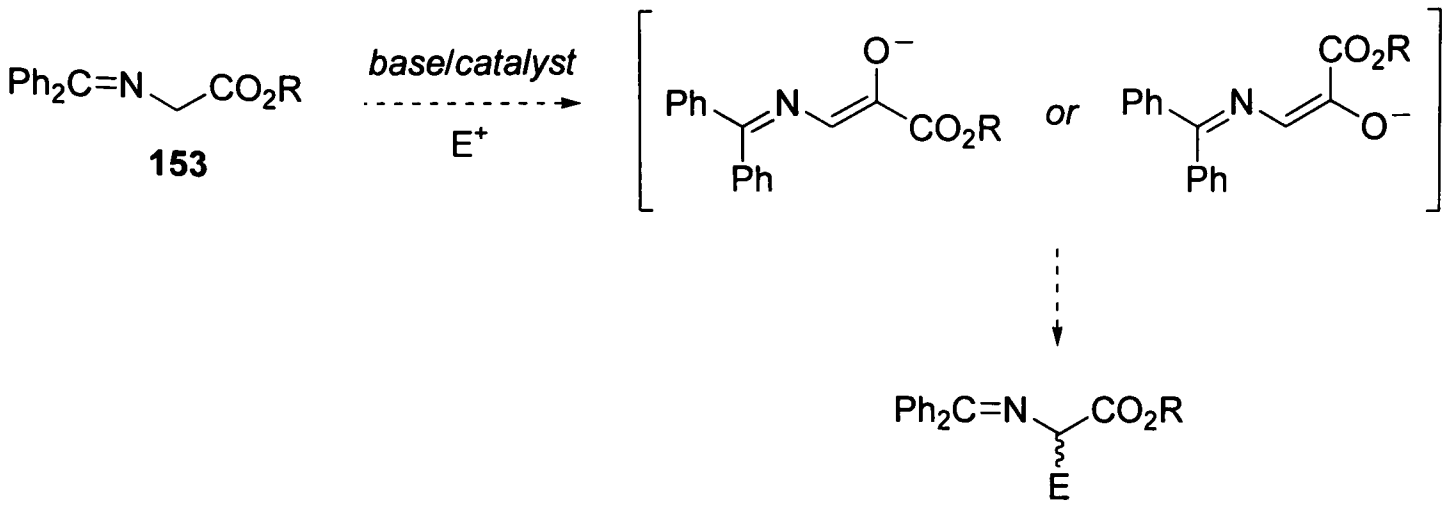
151

152 98 %, 92 % e.e.

153

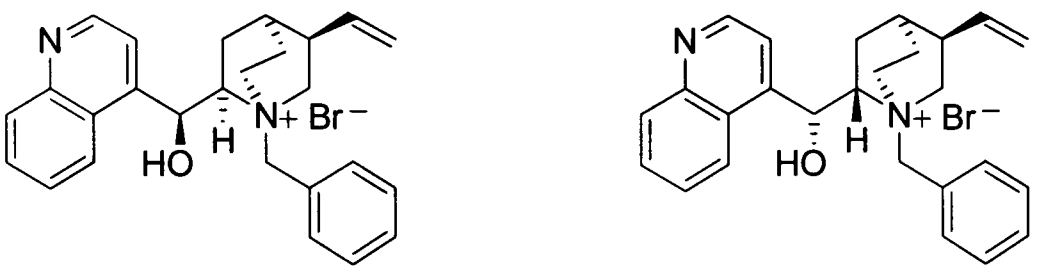
Scheme 93

O'Donnell recognised the similarity of indanone **151** to the Schiff base glycine esters **153** he had introduced earlier,[22(b)] so on that basis attempted the enantioselective alkylation of **153** under similar conditions (Scheme 94). This was very ambitious since in this case the situation is more complex - enolate **153** can exist in either *E* or *Z*-isomeric forms,[74] and the monoalkylated product is also susceptible to a second deprotonation,[74] leading to either racemisation or dialkylation (Scheme 94)



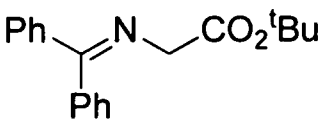
Scheme 94

However, after extensive optimisation it was found that a combination of *tert*-butyl glycine imine **29** and the *N*-benzyl cinchona salts **154/155** (Figure 21) did successfully induce stereoselective alkylations,[72] thereby allowing entry to a range of non-natural amino acids.



cinchonidine-based catalyst **154**

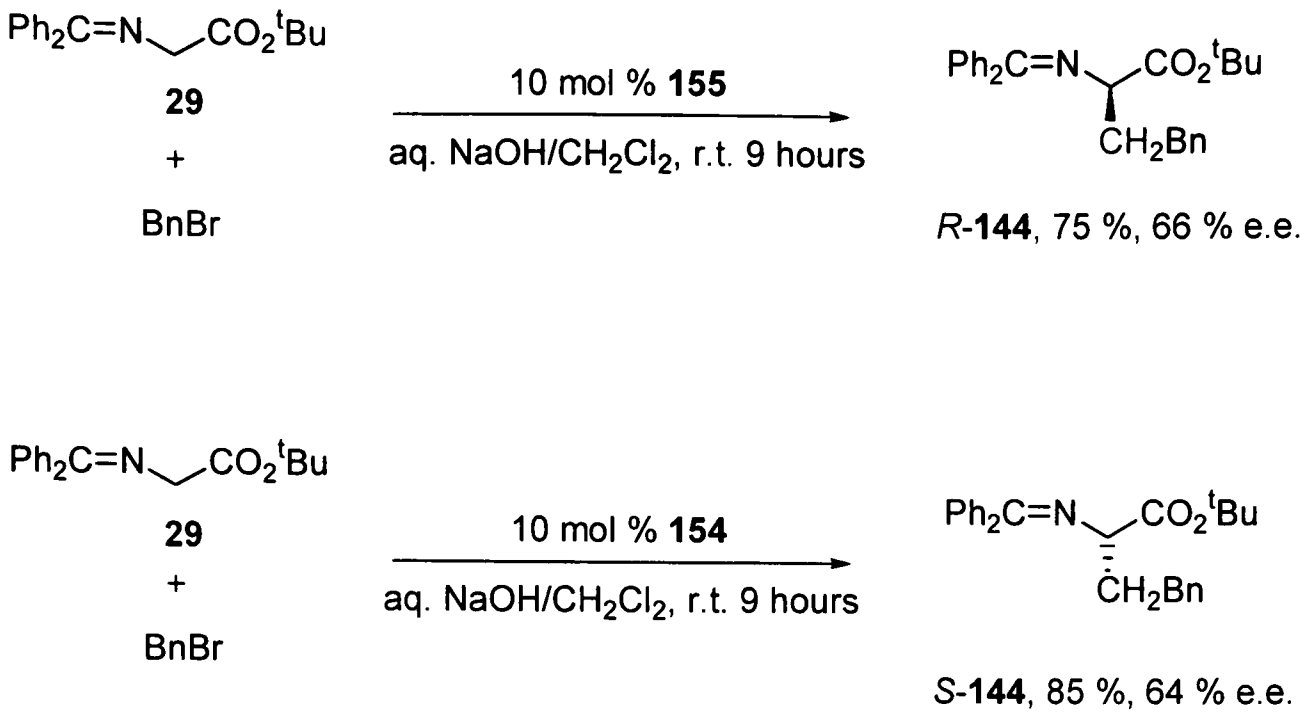
cinchonine-based catalyst **155**



tert-butyl Schiff base **29**

Figure 21

For example, reaction of **29** with benzyl bromide under aq. KOH/CH_2Cl_2 conditions (10 mol % **155**) furnished glycinate *R*-**144** in 75 % yield and 66 % e.e., whilst the opposite enantiomer of the product, *S*-**144** (85 %, 64 % e.e.), was also conveniently synthesised using the psuedoenantiomeric catalyst **154** (Scheme 95).



Scheme 95

This was a remarkable result, which has since been explained by two key features. The first of these is that the complexed glycine enolate exists only as its *E*-isomer,[75] and the second is that the glycine starting material **153**-ethyl ester (pKa = 18.7) is considerably more acidic than the alkylated product (pKa = 22.8)[76]. This is the direct consequence of increased $A_{1,3}$ strain after alkylation, meaning that under the reaction conditions only the starting glycine **153** can be deprotonated (Figure 22).

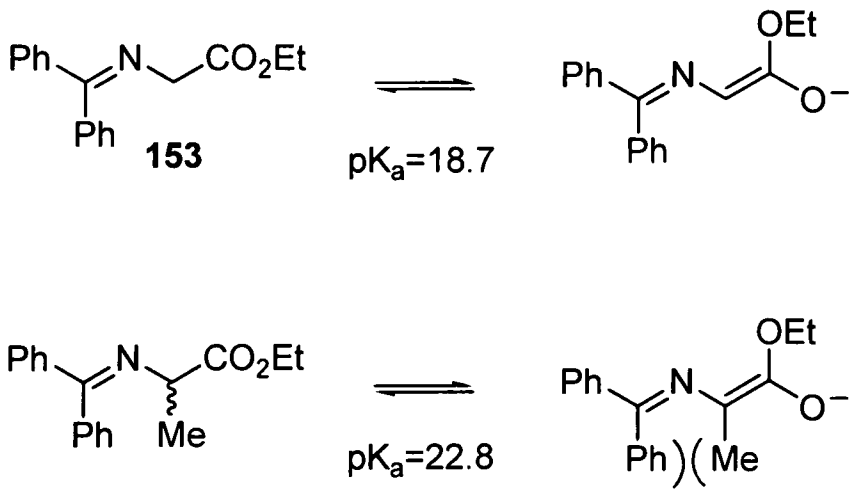
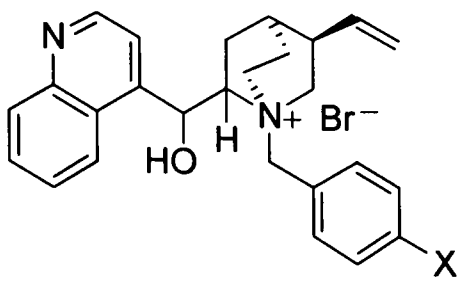


Figure 22

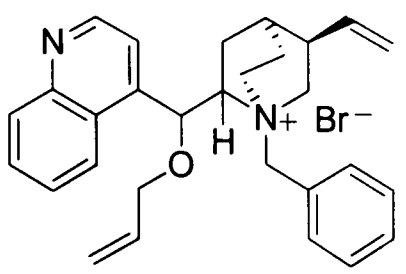
Since this pioneering work, there has been continued interest in catalyst evolution. From these 1st-Generation Catalysts (**154** and **155**), further improvements were made by O'Donnell in 1994 who introduced *O*-alkylation (2nd-Generation Catalysts),[77] then later in 1997 by Lygo[78] and Corey[75] who independently developed 3rd-Generation Catalysts by introducing the *N*-9-anthracenylmethyl group (Figure 23).

1st-Generation
Merck/O'Donnell



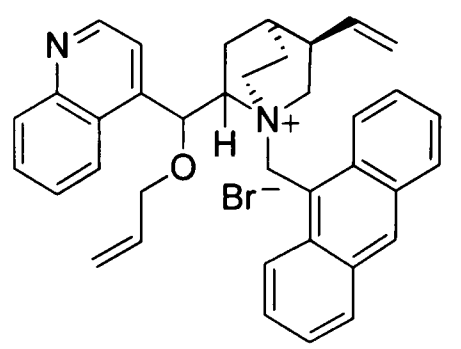
154 8*S*, 9*R* (cinchonidinium)
155 8*R*, 9*S* (cinchonium)

2nd-Generation
O'Donnell



8*S*, 9*R* (cinchonidinium)
8*R*, 9*S* (cinchonium)

3rd-Generation
Lygo/Corey

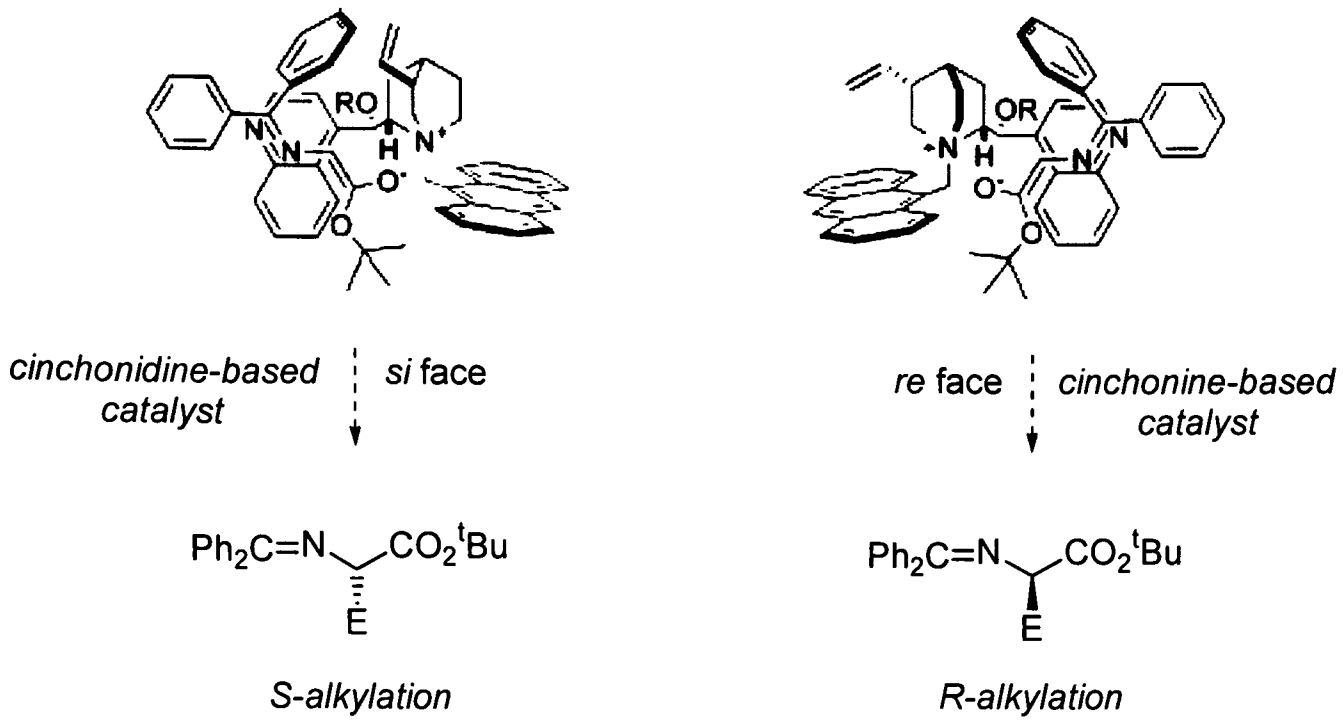


156 8*S*, 9*R* (cinchonidinium)
157 8*R*, 9*S* (cinchonium)

Figure 23

Using these 3rd-Generation Catalysts **156** and **157**, glycine alkylations have been achieved with exceptional selectivities.[75,78] In addition, Corey has developed solid-liquid phase transfer conditions (solid $CsOH.H_2O/CH_2Cl_2$, -78 °C to -60 °C) which are generally more selective than traditional room temperature liquid-liquid conditions employed by O'Donnell and Lygo (aq. $KOH/PhCH_3$, rt). This is because the use of a solid base permits lower temperature reactions, and reduces the water content in the organic phase.

Molecular modelling and crystal structure data suggest the reaction proceeds *via* an early transition state "with the major reaction channel being through the most stable geometry of the tight ion pair"[75] of cation **156/157** and enolate **29**. The stereochemical induction is thought to arise because each enolate-catalyst complex presents the opposite prochiral face of the glycine enolate to the electrophile. For the cinchonidine-based catalyst, only the *si* face of the enolate carbon is accessible to the incoming electrophile, so *S*-alkylation is observed. For the cinchonine-based catalyst, only the *re* face of the enolate carbon is accessible to the incoming electrophile, so *R*-alkylation is observed (Scheme 96).[22(c)]



Scheme 96[22(c)]

In recent years most work in this area has continued to concentrate on catalyst design, with notable contributions from the groups of Jew and Park,[79] Najera,[80] Maruoka[81] and Shibasaki.[82] Of these, the C_2-symmetric spiro ammonium salts (such as **158**, Figure 24) developed in the Maruoka group have been most impressive, catalysing asymmetric glycine alkylation even at very low-loadings (0.2-1.0 mol %). Despite this however, the 3rd-Generation cinchona-based catalysts **156** and **157** still remain highly popular as they provide excellent selectivities and are available in short synthetic sequences.

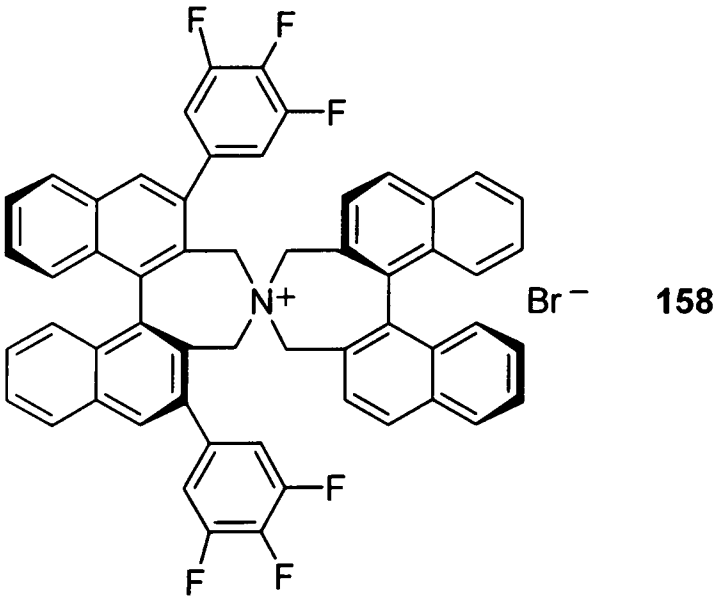
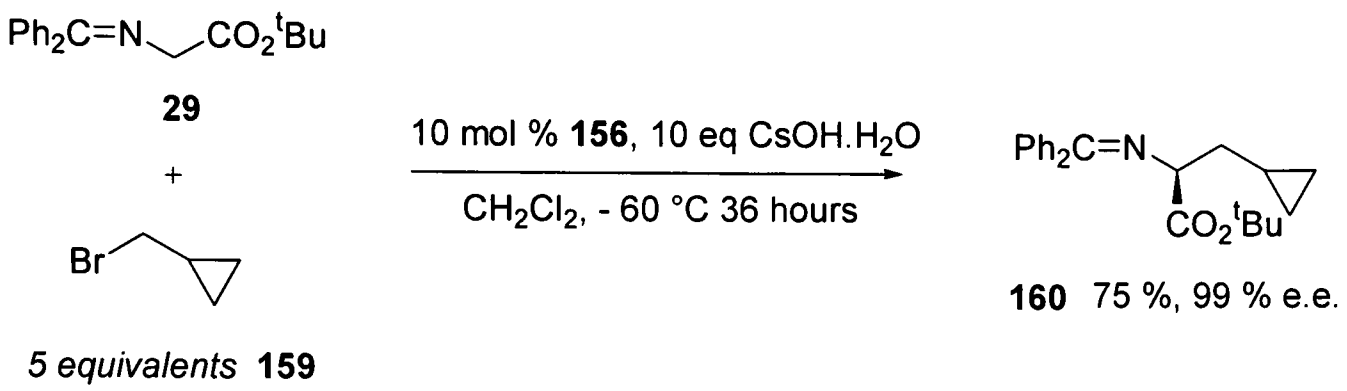


Figure 24

At the time we began our investigations, most examples of asymmetric phase transfer glycine alkylations involved relatively simple (activated) electrophiles such as

primary iodides, benzyl or allyl iodides/bromides and α-halo carbonyl species. Of these literature examples, the most relevant was the glycine alkylation of (unsubstituted) α-bromo cyclopropane **159**, reported by Corey (Scheme 97).[75] Although this reaction proceeded with excellent selectivity, a large excess of halide **159** was required to achieve good conversions.

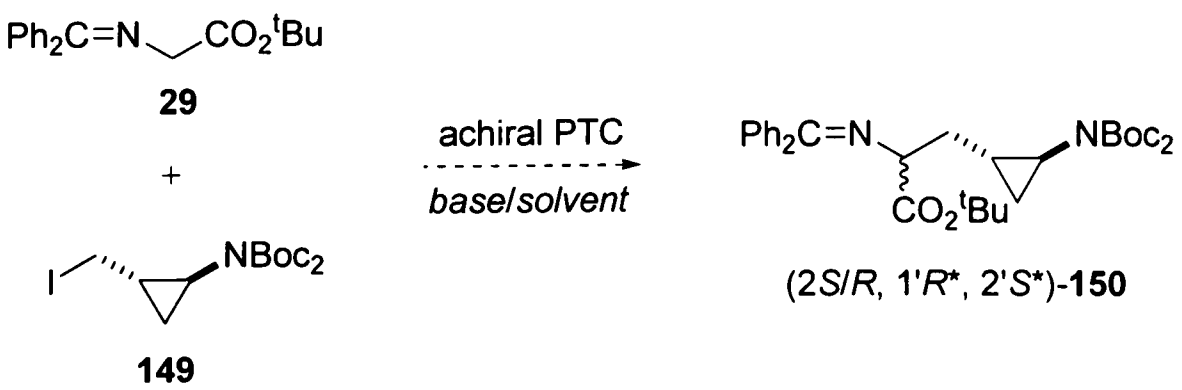


Scheme 97

In our case, iodide **149** would be the limiting reagent, so significant optimisation was required. As stated earlier, we believed our goal of synthesising all four stereoisomers of the central *trans*-AcpAla amino acid would be the most challenging application of this methodology to date, and interested readers are directed towards a recent review by O'Donnell[22(b)] which contains all significant synthetic applications.

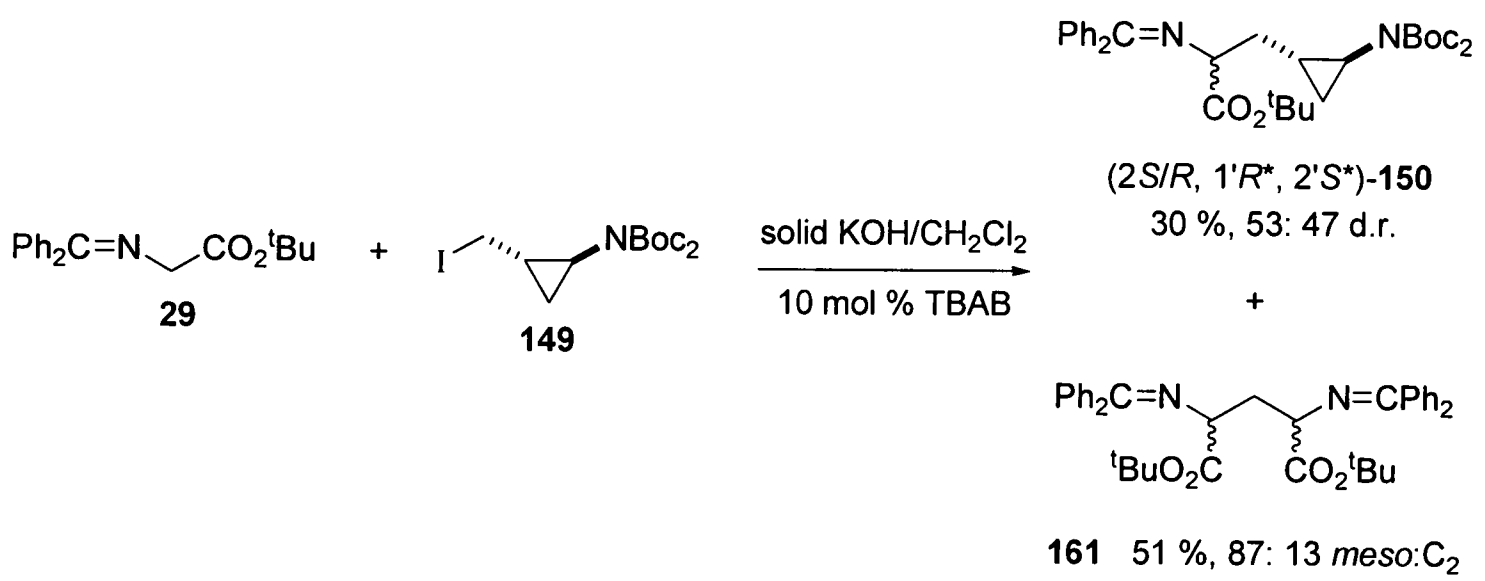
2.5.2 Non-selective glycine alkylation

De Meijere had previously demonstrated little 1,3-diastereomeric induction (precise d.r. not reported) for his cyclopropyl iodide glycine alkylation (section 1.3.1, Scheme 7). However, we wanted to confirm this under phase-transfer conditions, and also optimise the glycine alkylation before employing chiral catalysts (Scheme 98).



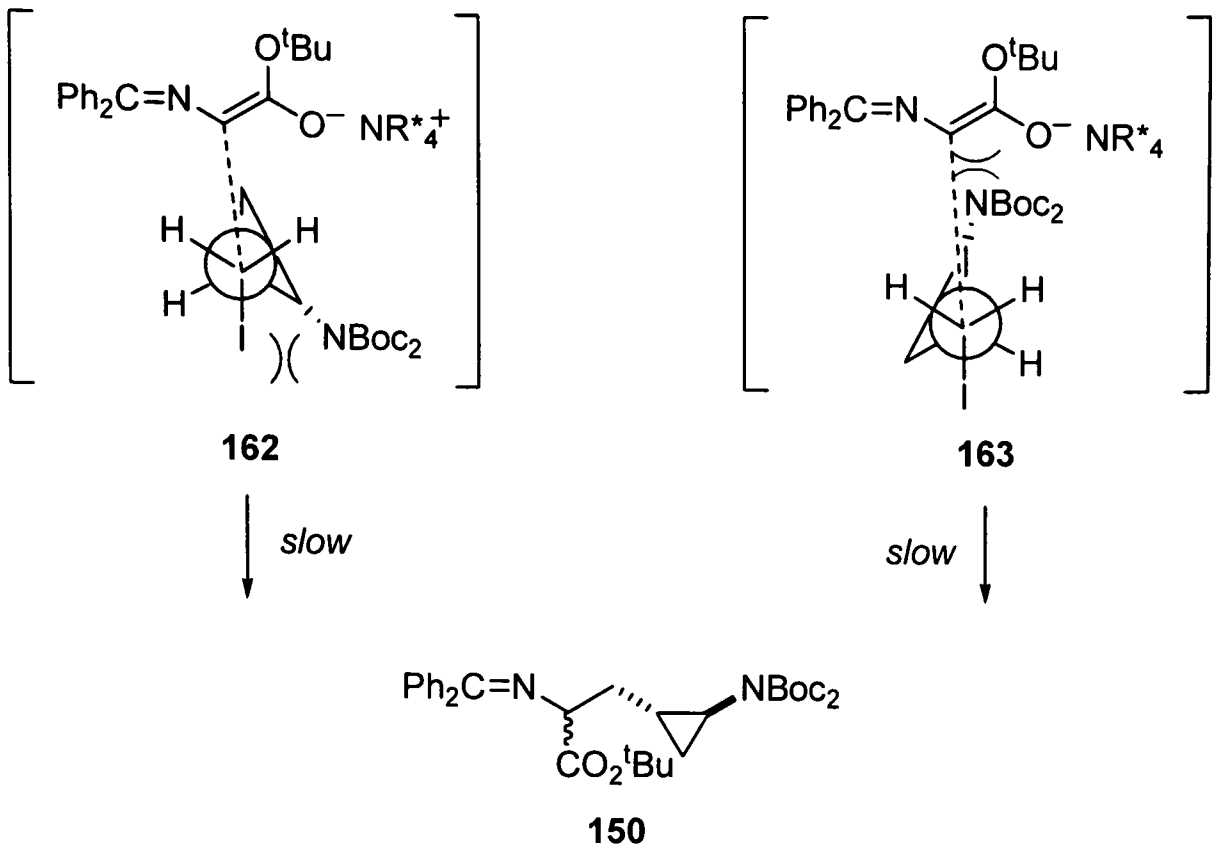
Scheme 98

We began investigating this glycine alkylation using TBAB as the catalyst, under conventional liquid-liquid (aq. KOH/solvent) phase-transfer conditions. However, this procedure failed to achieve any alkylation, even after stirring for 2 days at room temperature, so we switched to solid-liquid phase-transfer catalysis as this is known to offer higher reaction rates.[68] Pleasingly, through use of solid KOH/CH_2Cl_2 (TBAB catalysis) we obtained the desired AcpAla product **150** in 30 % yield (2 steps from the alcohol) as a 53:47 ratio of C2-stereoisomers (Scheme 99). Interestingly, the major product of this reaction was the 1,3-diamino acid derivative **161**, which formally arises from the double alkylation of dichloromethane. While this type of side-product has been observed in other phase-transfer catalysed alkylations of active methylene compounds,[83] to the best of our knowledge it has not been reported previously in alkylations of **29**, and serves as a warning of the potential reactivity of CH_2Cl_2 when relatively unreactive electrophiles are employed.



Scheme 99

A plausible explanation for the low reactivity of **149** is based on steric arguments. In order to achieve S_N2 acceleration by cyclopropyl $\sigma^*_{C\text{-}C}/\sigma^*_{C\text{-}I}$ mixing, two transition-state arrangements are likely. The first of these transition states (**162**) is destabilised by the repulsive I-$NBoc_2$ interactions, and the second transition state (**163**) is destabilised by approach of the glycine **29** enolate close to the $NBoc_2$ moiety (Scheme 100). Although the $NBoc_2$ group is three carbon atoms away from the reacting centre, it occupies a large volume of 3-dimensional space, and as such these interactions are likely to be significant. Accordingly, both reaction pathways are consistent with the observed slow reaction rate.



Scheme 100

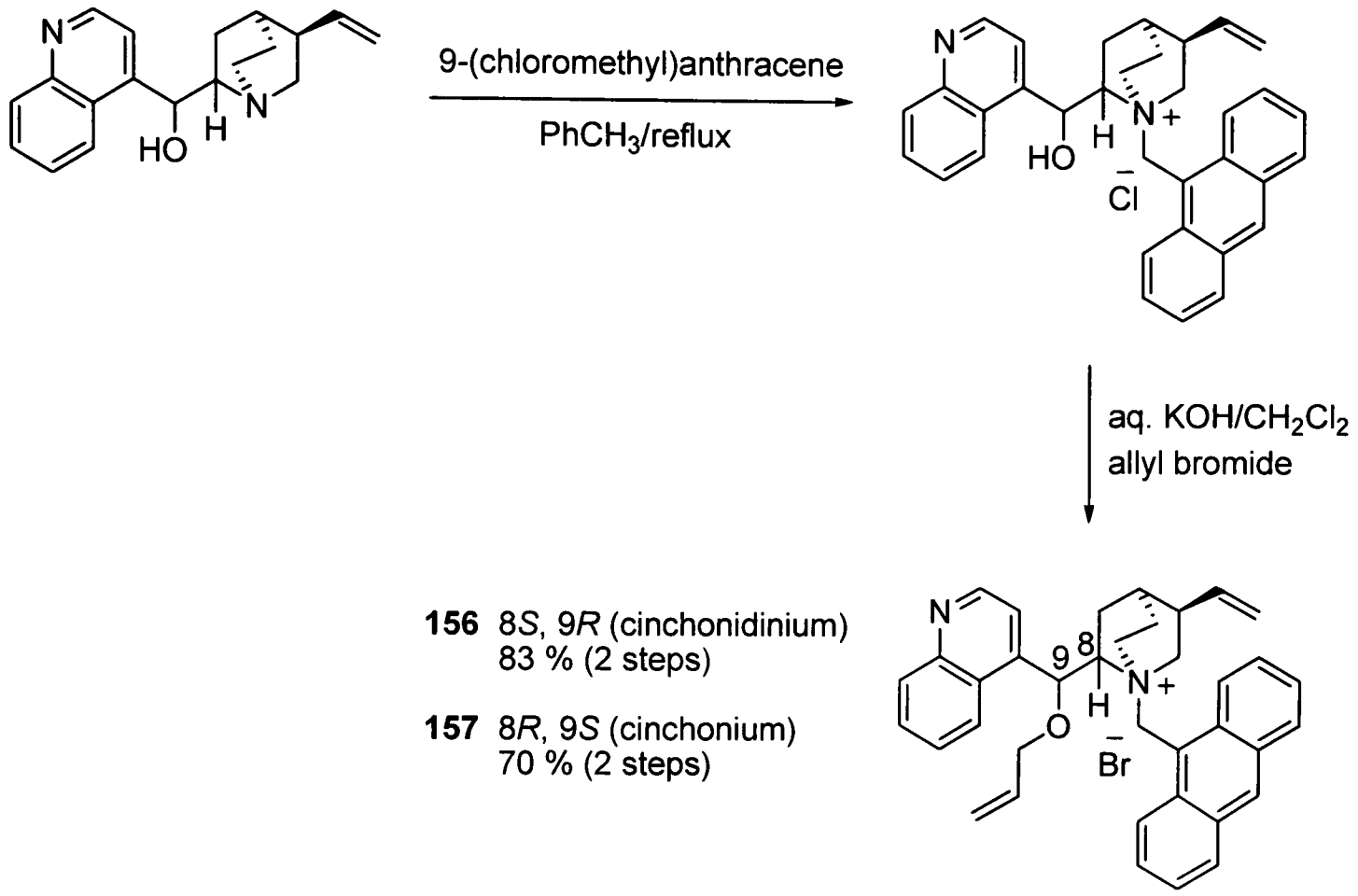
By switching to toluene as the reaction solvent, the pathway to the side-product **161** was removed, and **150** was generated in 55 % (2 steps from the alcohol) as a 44:56 d.r. mixture of C2-isomers (Scheme 101).

Scheme 101

2.5.3 Asymmetric glycine alkylation

Having established successful conditions for the glycine alkylation of **149** in the racemic series, we progressed to using both enantiomerically pure iodides (*S*, *S*)-**149** and (*R*, *R*)-**149**. The requirement of solid-liquid phase transfer conditions meant that we needed to apply Corey's conditions,[75] with a switch from dichloromethane to

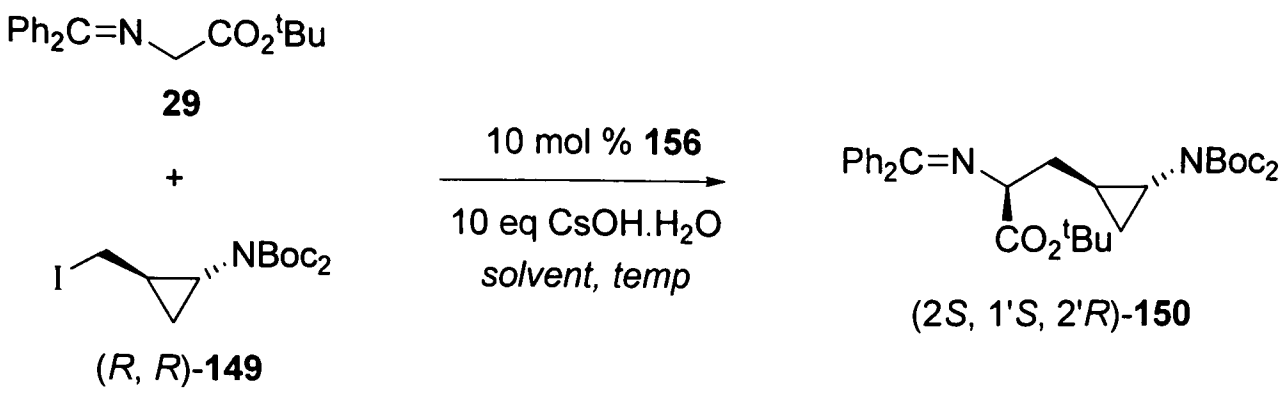
toluene as the solvent being required in order to avoid the CH_2Cl_2-alkylation pathway. The first task was to synthesise both pseudoenantiomers of the 3rd-Generation Catalyst, which following the literature procedure[75] proceeded in high overall yield for both catalysts **156** and **157** (Scheme 102).



Scheme 102

Since we had previously observed a lack of intrinsic 1,3-stereoinduction for the alkylation of *rac*-**149** using achiral catalysis, we were hopeful that all four glycine alkylations of (*S*, *S*)-**149** and (*R*, *R*)-**149** (using chiral catalysis) would proceed a similarly high level of stereoselection. We began optimisations using the less-valuable iodide (*R*, *R*)-**149** (not required for total synthesis), obtained directly from the iodination of alcohol (*R*, *R*)-**144**. In combination with the cinchonidinium-based catalyst **156**, this should induce 2*S*-alkylation and therefore provide the (2*S*, 1′*S*, 2′*R*)-AcpAla stereoisomer.

However, extensive optimisation was required to accomplish efficient substitution with this demanding electrophile **149**, and these results are shown below (Scheme 103, Table 7).



Scheme 103

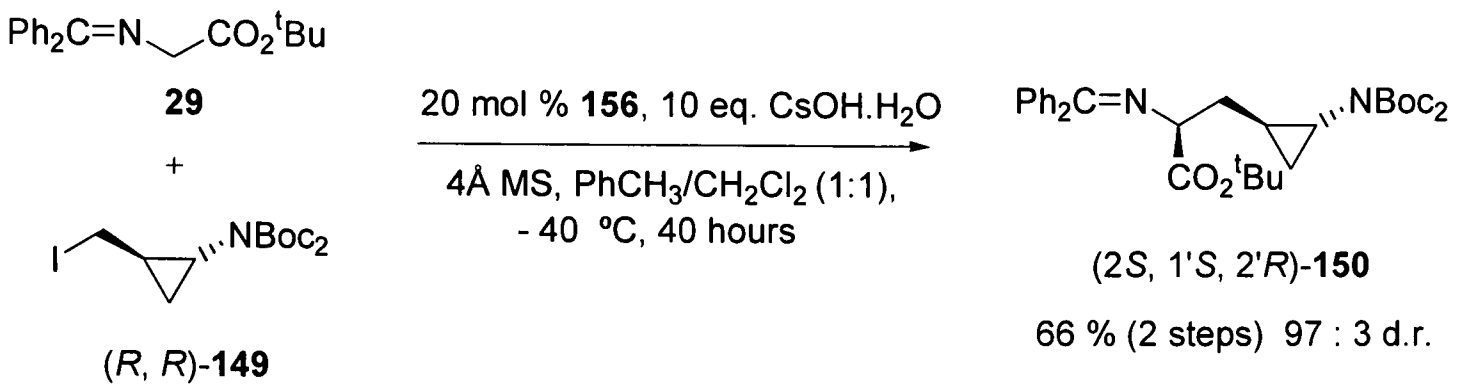
Entry[a]	Temp/°C	[**149**]/M	Equiv. **29**	Time	d.e.[d]	Yield/%[e]
1[b]	-20	0.09	1.0	3d	29	27
2	-20	0.09	1.0	3d	38	40
3	-40	0.07	2.0	7d	>95	28
4	-40	0.33	2.0	6d	>95	50
5[c]	**-40**	**0.22**	**2.0**	**40h**	**94**	**66**

[a]10 mol% **156** (with respect to **29**), $PhCH_3$, 4Å molecular sieves. [b]Molecular sieves omitted. [c]1:1 $PhCH_3/CH_2Cl_2$ solvent. [d]Estimated by integration of the 500MHz ^1H NMR spectrum. [e]Yield from **144**.

Table 7

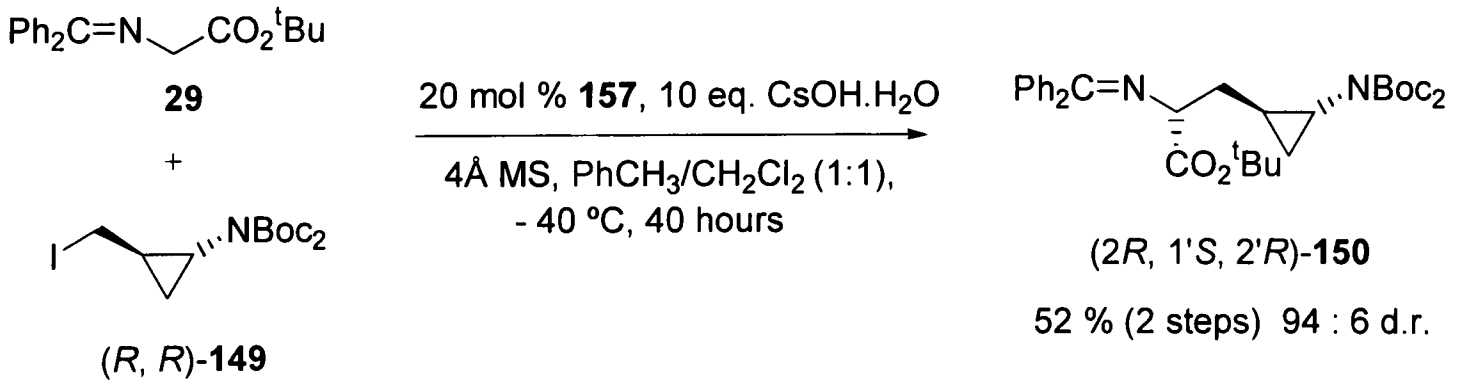
No reaction was observed using 10 mol % **156** and 10 eq. solid $CsOH.H_2O$ at -78 °C in toluene over many days, so we began optimisation at a significantly higher temperature. At -20 °C alkylation of (*R*, *R*)-**149** was achieved with only 29 % d.e. (entry 1). However, through the use of 4Å molecular sieves this was improved to 38% d.e. (entry 2), which has previously been attributed to a closer contact cation-anion pair being generated in the absence of water.[84] Further lowering of the temperature to -40 °C then led to a dramatic increase in selectivity (>95% d.e., entry 3), but in our case the reaction was prohibitively slow with only approximately 53 % conversion after 7 days. We believe that this dramatic change in selectivity was the result of a change in mechanism, not simply due to a decrease in temperature. The most likely explanation is that at lower temperatures only the catalyst-enolate complex is soluble-enough to enter the solution and become alkylated, whilst at higher temperatures the metal-enolate pair may also enter solution. We next made efforts to increase the reaction rate by increasing the concentration, but this was only moderately successful, increasing conversion to approximately 70 % after 6 days (entry 4). We reasoned that

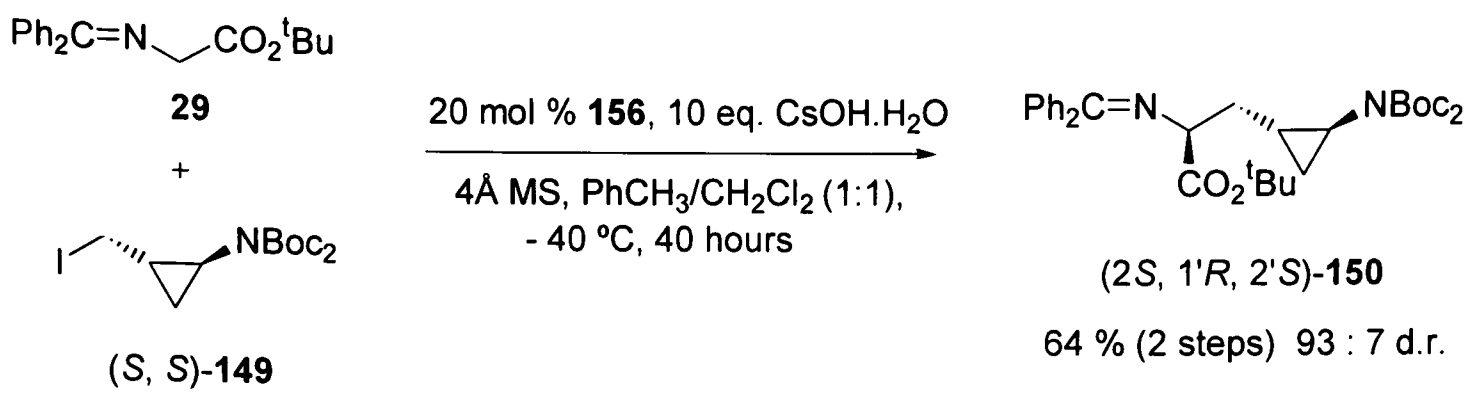
the reduced reaction rate was due to the limited solubility of catalyst **156** in the toluene solvent, and as a result we decided to use a mixed toluene/CH_2Cl_2 (1:1) solvent system in the hope of improving catalyst solubility. In addition, a high iodide concentration was utilised to minimise any CH_2Cl_2 *bis*-alkylation. Using these conditions we were delighted to see that iodide alkylation was complete in 40 hours at -40 °C, to give protected AcpAla (2*S*, 1′*S*, 2′*R*)-**150** in 66% yield and 97:3 d.r. (entry 5 and Scheme 104).



Scheme 104

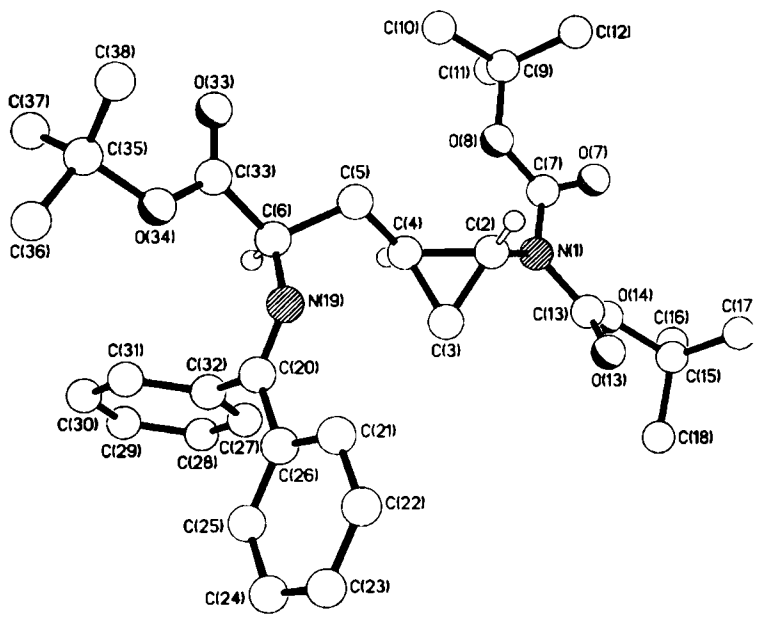
With the optimised reaction conditions developed, we then proceeded to alkylate (*R*, *R*)-**149** with the alternative pseudoenantiomeric catalyst **157**, and also alkylate iodide (*S*, *S*)-**149** using both catalysts **156** and **157**. All alkylations proceeded with similarly high stereoselectivity, demonstrating complete catalyst-control (Scheme 105). This, therefore, achieved our goal of synthesising all four stereoisomers of the central AcpAla amino acid.





Scheme 105

In addition, we also successfully recrystallised (2*S*, 1′*R*, 2′*S*)-**150** (required for the total synthesis), and its enantiomer (2*R*, 1′*S*, 2′*R*)-**150**, to diastereomeric purity. This then allowed us to confirm that glycine alkylation had proceeded with the expected sense of stereoinduction by crystallographic analysis of (2*R*, 1′*S*, 2′*R*)-**150**. As expected, *R*-stereoinduction was obtained using cinchonium catalyst **157** (Figure 25).



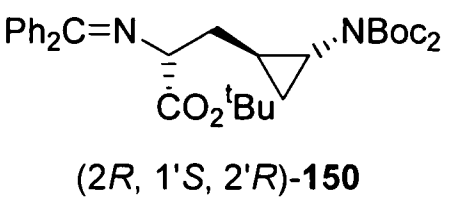
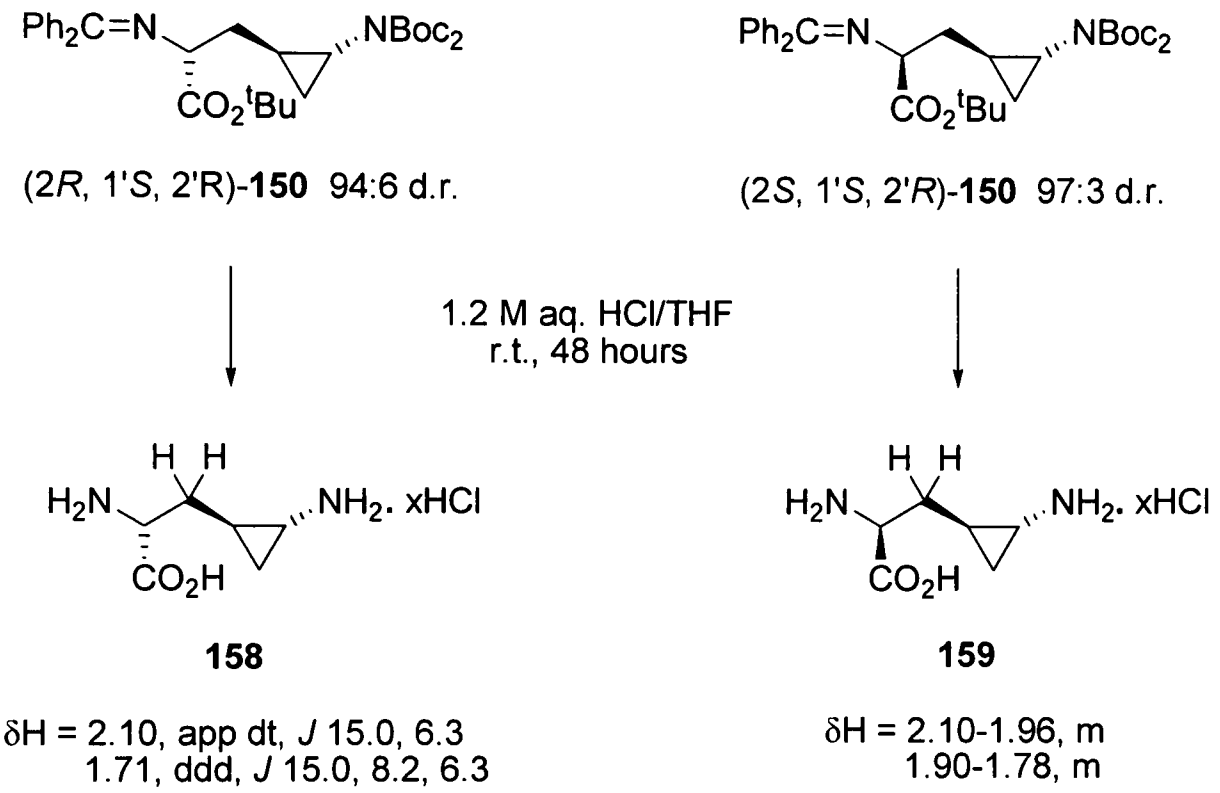


Figure 25: X-ray structure of (2*R*, 1′*S*, 2′*R*)-**150**

Before continuing with the total synthesis, we took the opportunity to check that the relative stereochemistry of the natural AcpAla fragment had been correctly assigned. This was carried out by comparing the ^{1}H NMR of the natural AcpAla fragment (obtained by degradation),[7] with both synthetic diastereomers that we had synthesised. Determination of the absolute configuration was not possible, since the optical rotation of natural AcpAla had not been provided. Natural AcpAla was characterised as its fully deprotected HCl-salt, so our first task was global hydrolysis of (2*R*, 1′*S*, 2′*R*)-**150** and (2*S*, 1′*S*, 2′*R*)-**150** using aq. HCl in THF (Scheme 106).



Scheme 106

The most diagnostic protons appeared to be those of the methylene bridge (Scheme 106), and pleasingly the ^{1}H NMR spectrum of **158** was in very good agreement with that of the genuine sample,[7] confirming the reported relative stereochemistry (Figure 26).

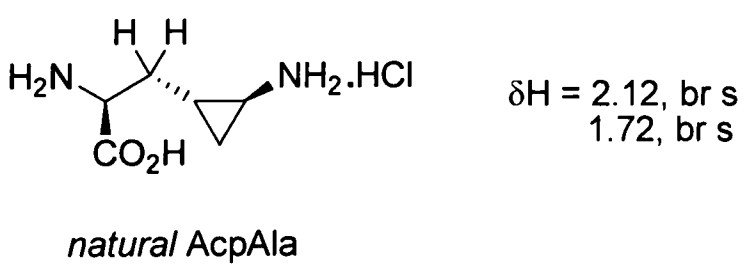
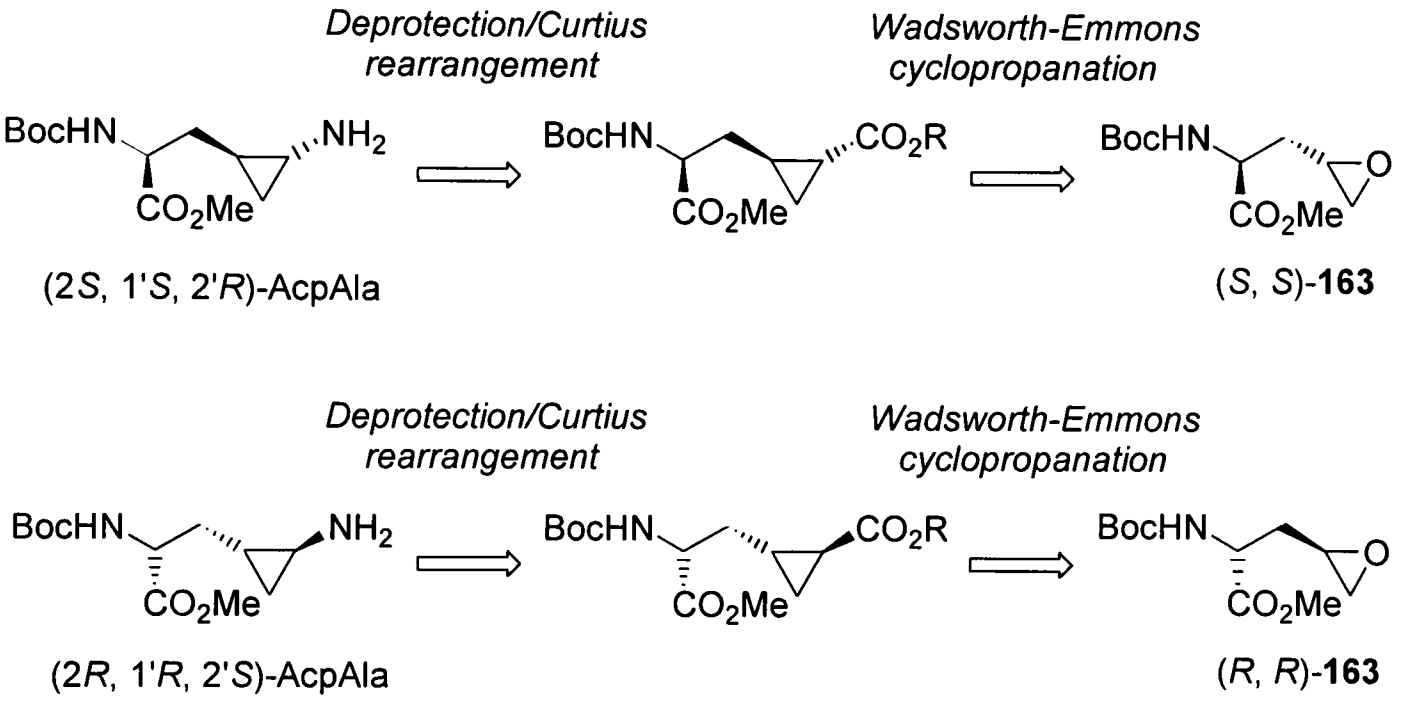


Figure 26

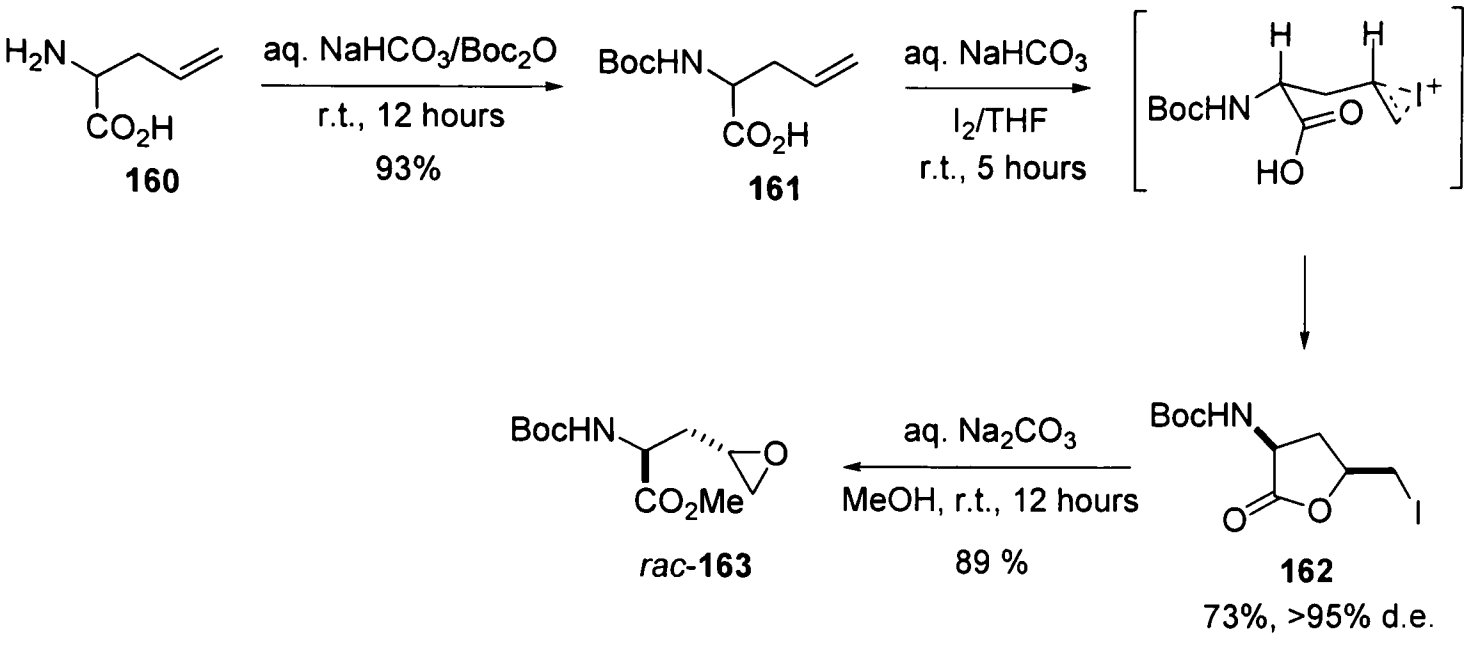
2.6 Alternative route to (2*S*, 1′*S*, 2′*R*)-AcpAla and (2*R*, 1′*R*, 2′*S*)-AcpAla

Before continuing with the total synthesis of (+)-**1**, we also aimed to evaluate an alternative synthesis of the non-natural enantiomeric pair (2*S*, 1′*S*, 2′*R*)-AcpAla and (2*R*, 1′*R*, 2′*S*)-AcpAla, *via* a fully diastereoselective approach. In this instance we were primarily interested in testing the cyclopropanation methodology on a more demanding substrate, rather than improving our established route to all four AcpAla isomers. This new approach was conceptually similar, but differed by the late-stage Wadsworth-Emmons cyclopropanation/Curtius rearrangement of a fully assembled epoxy amino acid template (Scheme 107).



Scheme 107

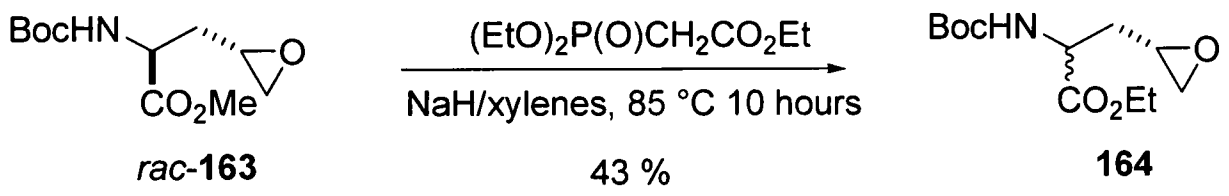
Chemistry has been developed by Guillerm[85] which allows synthesis of both enantiomers of epoxy amino acid *rac*-**163** from either *S*-allyl glycine or *R*-allyl glycine, using a diastereoselective iodolactonisation as the key step. We began this work by initial Boc-protection of (±)-allyl glycine **160** under standard conditions (furnishing **161** in high 93 % yield), then iodolactonisation upon treatment with aq. $NaHCO_3$ and I_2 to afford the *cis*-iodolactone **162** in 73 % yield and > 95% d.e.. Iodolactone **162** was then subsequently ring-opened using aq. Na_2CO_3/MeOH, affording epoxide *rac*-**163** in 89 % yield (Scheme 108).



160 **161** ***rac*-163** **162**

Scheme 108

Epoxide *rac*-**163** was subjected to a range of cyclopropanation conditions, varying the base, solvent and temperature, but disappointingly all combinations failed to induce the desired transformation. From the complex mixture products we were only able to identify material consistent with the transesterified ethyl ester epoxide **164** (43 % yield, mixture of C2-epimers) (Scheme 109). Similar results were also obtained using diethylcyanomethyl phosphonate.

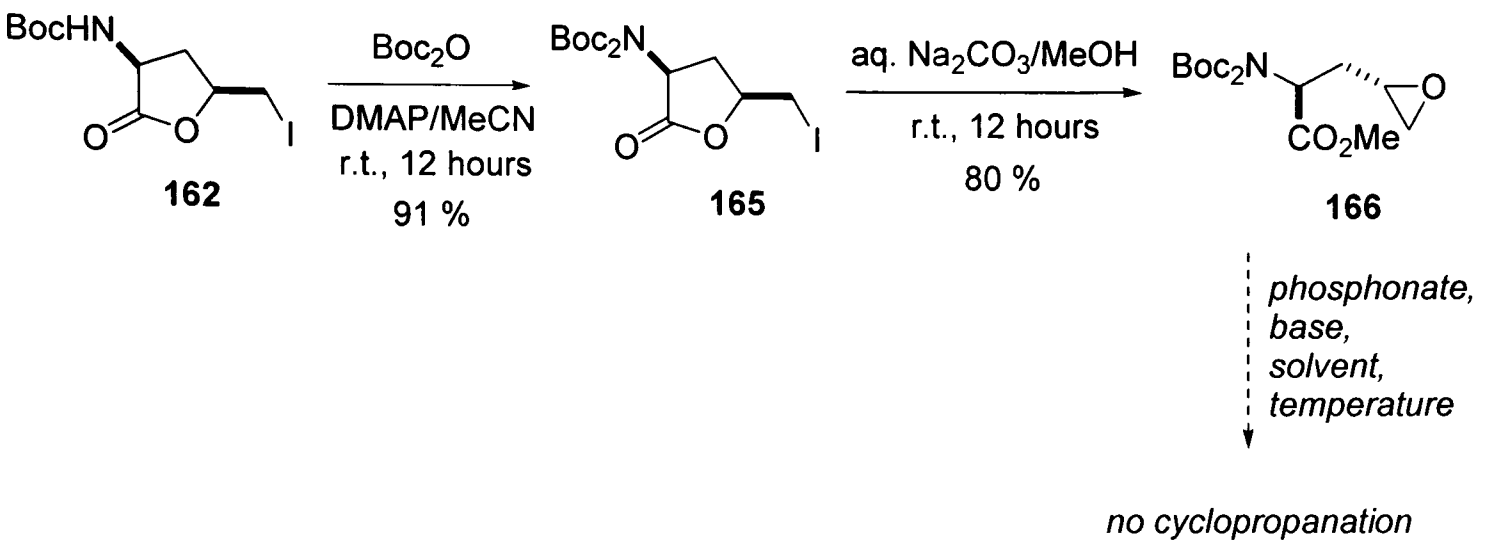


***rac*-163** **164**

Scheme 109

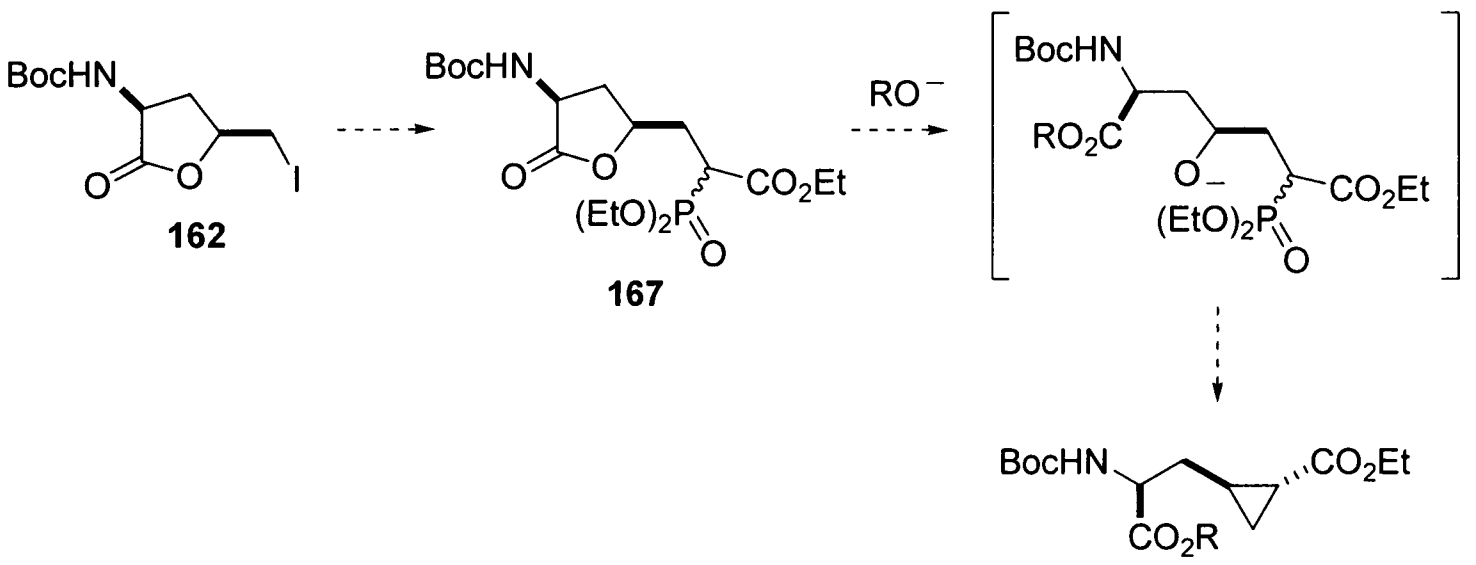
These results indicate that *rac*-**163**, not surprisingly, is a more problematic substrate. The major reaction path is evidently phosphonate polymerisation, leading to free ethoxide which then attacks the ester and scrambles the amino acid stereocentre. To minimise this self-condensation, we experimented with the slow addition of phosphonate anion to a refluxing solution of *rac*-**163**, but no improvements were evident. Additionally we attempted using the Cs_2CO_3/MeCN (reflux) conditions we had developed earlier (section 2.3.5), but in this case we obtained mainly decomposition. Since it was plausible that this failure was caused by the acidic NHBoc group of *rac*-**163**, a second Boc-protection/ring opening sequence was

performed to afford **166** (Scheme 110), but again no cyclopropanation was observed under a range of cyclopropanation conditions.



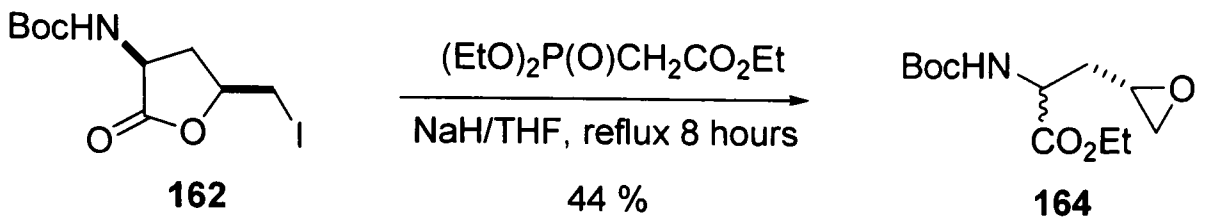
Scheme 110

Examination of the reaction sequence suggested more success may be achieved if triethylphosphonoacetate was alkylated with iodide **162**, rather than attempting to ring-open epoxide *rac*-**163**. This was considered to be a more facile nucleophilic substitution, which when followed by subsequent ring-opening of lactone **167**, should intercept the key cyclopropanation intermediate (Scheme 111).



Scheme 111

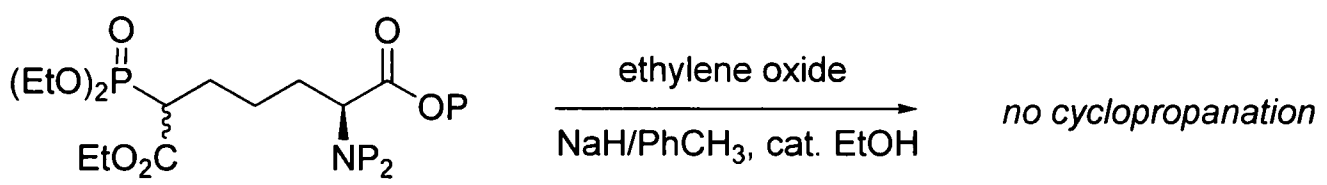
Unfortunately however, all attempts to alkylate iodide **162** with triethylphosphonoacetate failed under a range of conditions (NaH/xylenes/reflux, NaH/DMF/60 °C, NaH/THF/15-C-5/reflux). Again, the only new product identified was consistent with epoxide **164** as a mixture of C2-isomers (Scheme 112). Furthermore, attempted alkylation of bis-protected **165** was similarly unsuccessful.



162 **164**

Scheme 112

After this work was completed, a similar result from workers at Bristol-Myers Squibb came to our attention.[39(h)] Here the authors report an unsuccessful attempt to cyclopropanate the "fully protected" phosphonate amino acid **168** with ethylene oxide (Scheme 113). This failure was attributed to the "incompatibility of the strongly basic cyclopropanating conditions and the acidic α-ester functionality",[39(h)] and to achieve the desired reaction, it was necessary to first reduce **168** to the corresponding protected amino alcohol.



168

Scheme 113

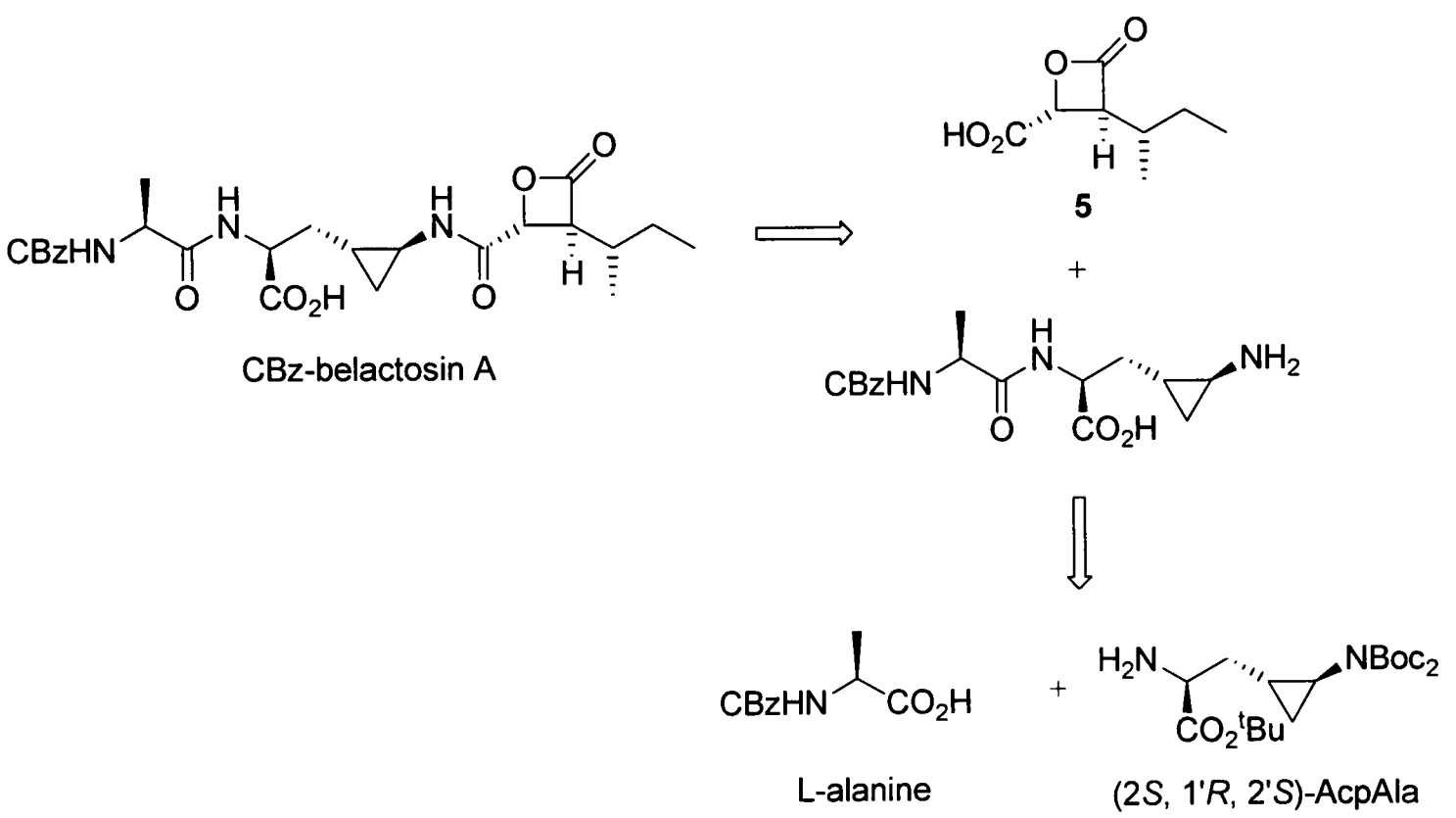
In conclusion, **163** and **162** may be poor substrates for the cyclopropanation reaction due to their α-acidity. It is plausible that partial reprotonation of the phosphonate anion by the substrate generates neutral phosphonate, which is then a superior substrate for polymerisation. In our case, we may also have achieved success by reducing the amino acid moiety, but through the addition of extra steps this route becomes much less attractive. As a result we pursued this work no further, and returned to the total synthesis of (+)-**1**.

2.7 Coupling of (2*S*, 1′*R*, 2′*S*)-AcpAla to L-alanine

We continued with the total synthesis by considering in which order to perform the amide couplings. It had been suggested that belactosin B **2** was derived from (+)-

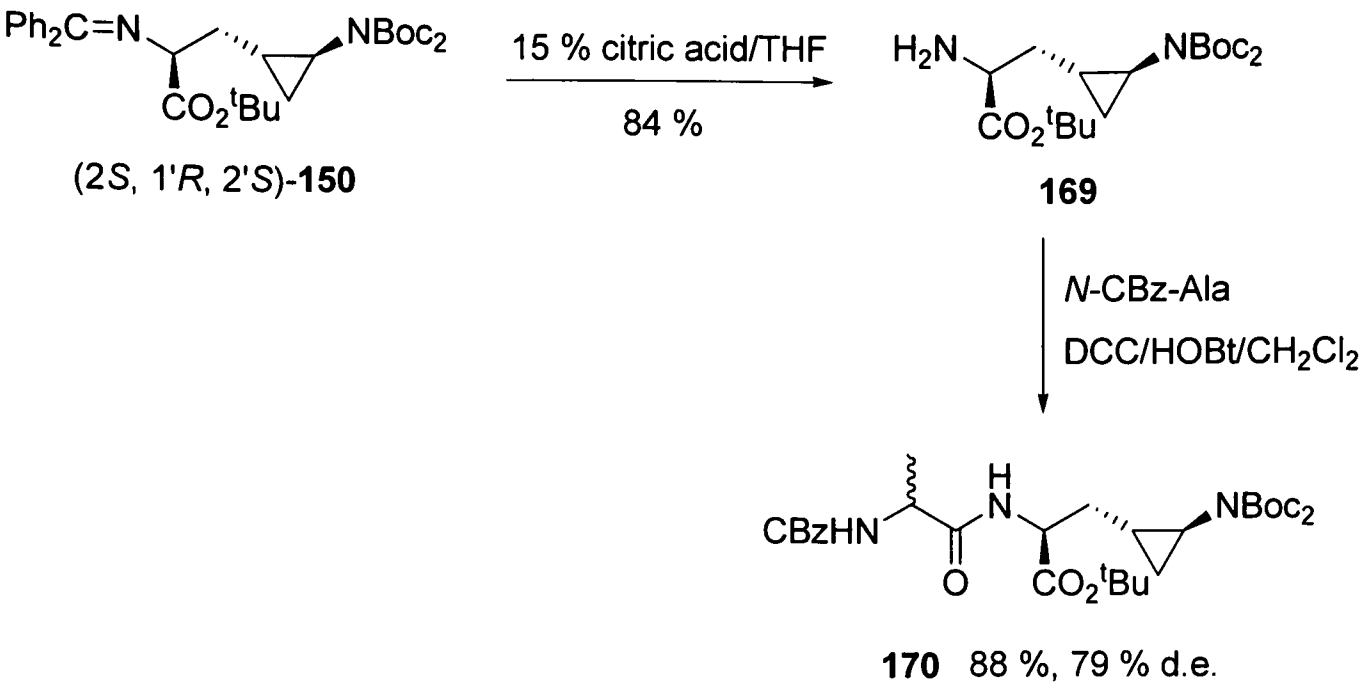
belactosin A (+)-**1** *via* methanol-induced β-lactone ring-opening,[2] and that the biological activity of (+)-**1** is primarily due to its β-lactone moiety.[6] Taken together, this implies that the β-lactone is sensitive, so ideally should be coupled at a late stage. We therefore first made efforts to complete the left-hand-side of (+)-belactosin A by coupling (deprotected) (2*S*, 1′*R*, 2′*S*)-**150** to a suitably protected L-alanine component.

N-Boc-Ala would have been our favoured coupling partner, since the Boc-protecting group is known to suppress epimerisation,[86] but in order to achieve orthogonal protection (with respect to the bis Boc-protected cyclopropylamine **150**), we chose *N*-CBz-Ala as our alanine residue (Scheme 114).



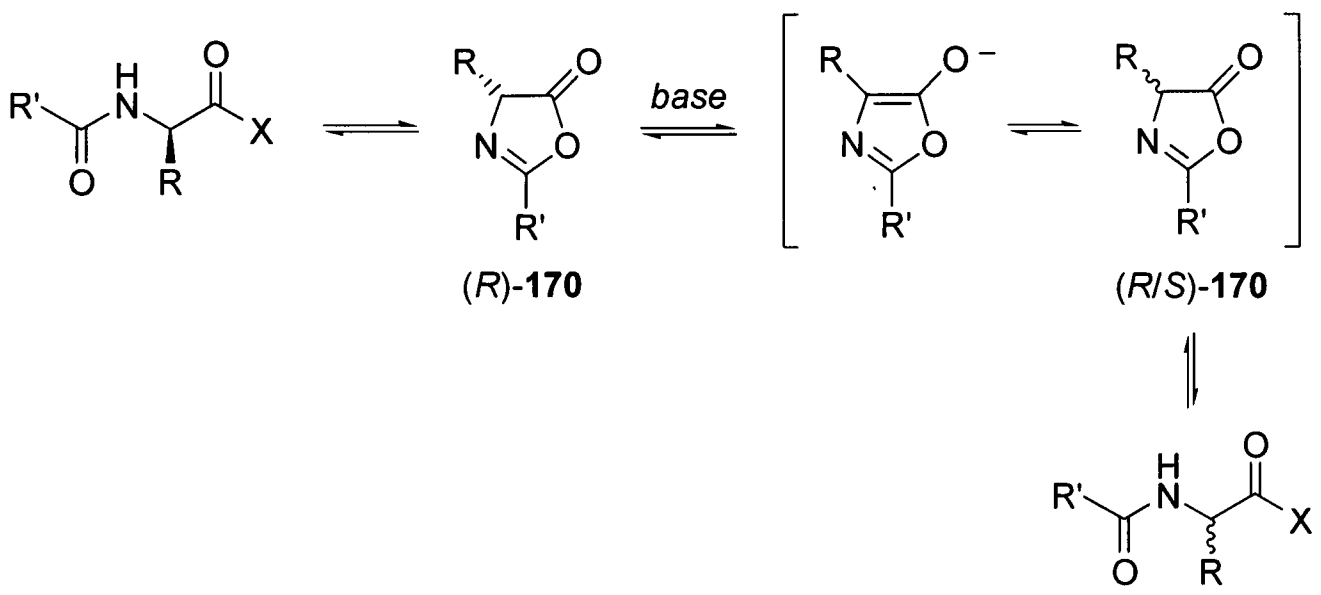
Scheme 114

Initial chemoselective hydrolysis of (2*S*, 1′*R*, 2′*S*)-**150** using 15 % aq. citric acid removed the benzophenone imine moiety, furnishing amine **169** in 84 % yield. Submitting **169** and *N*-CBz-Ala to standard DCC/HOBt/CH_2Cl_2 coupling conditions then led to the desired peptide **170** in 88 % yield. However, disappointingly **170** was isolated with partial epimerisation at the alanine stereocentre (79 % d.e.) (Scheme 115).



Scheme 115

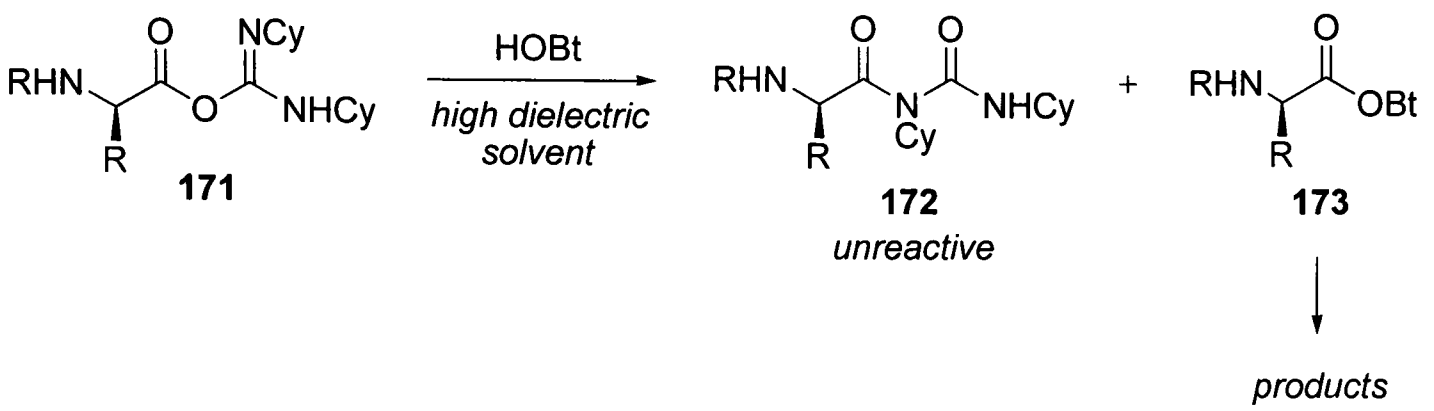
This type of epimerisation (or racemisation) is a common problem encountered in amino acid coupling reactions, and for *N*-acylated activated acids primarily results from intramolecular cyclisation through oxygen to form oxazolones such as **170**. These species are highly acidic (due to the potential to become aromatic), and as such suffer from facile deprotonation at the α-stereocentre, with resultant loss of chirality (Scheme 116).[87]



Scheme 116

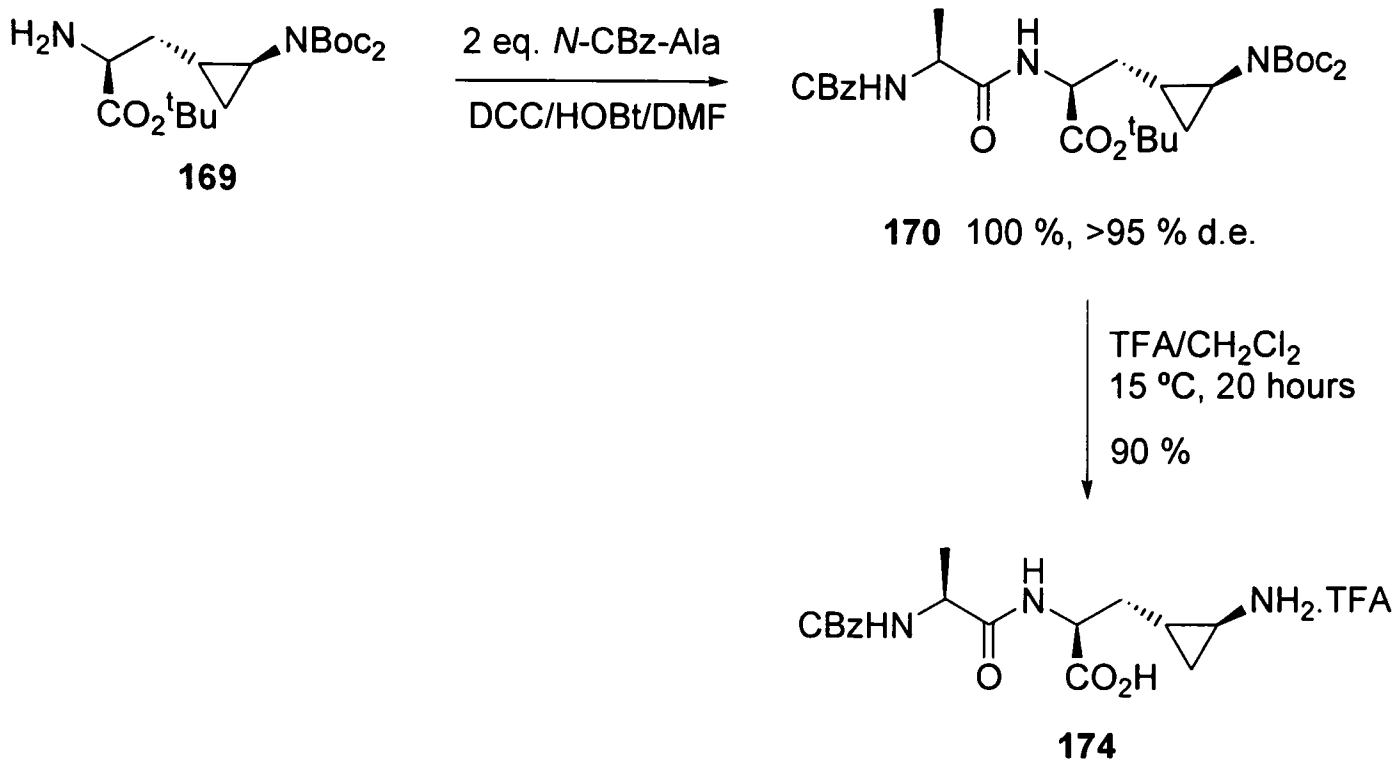
This mechamism of epimerisation is particularly problematic when using carbodiimide coupling agents such as DCC, since these reagents form highly reactive *O*-acylisourea intermediates. As a result, additives such as HOBt have been introduced in order to convert these compounds to less-reactive and less-epimerisable OBt-esters.[87] It is plausible, therefore, that our loss of chirality was due to the slow

conversion of *O*-acylisourea **171** to OBt-ester **173** (Scheme 117), so as a result we began investigating a change in solvent, as we had observed that HOBt failed to dissolve in dichloromethane. On switching to DMF, in which HOBt was fully soluble, we were delighted to see complete suppression of epimerisation, but the overall yield of peptide **170** was reduced to only 47%. This reduction in coupling yield often accompanies changing to a solvent of higher dielectric constant, and is explained by partial rearrangement of *O*-acylisourea **171** to the unreactive urea **172** (Scheme 117).[87]



Scheme 117

As a result, we employed two equivalents of the inexpensive and commercial *N*-CBz-alanine, which then furnished peptide **170** in quantitative yield without epimerisation. Subsequent global deprotection of all acid-labile protecting groups using TFA in CH_2Cl_2 (15 °C for 20 hours) also proceeded without epimerisation, and gave coupling partner **174** in 90 % yield (Scheme 118).

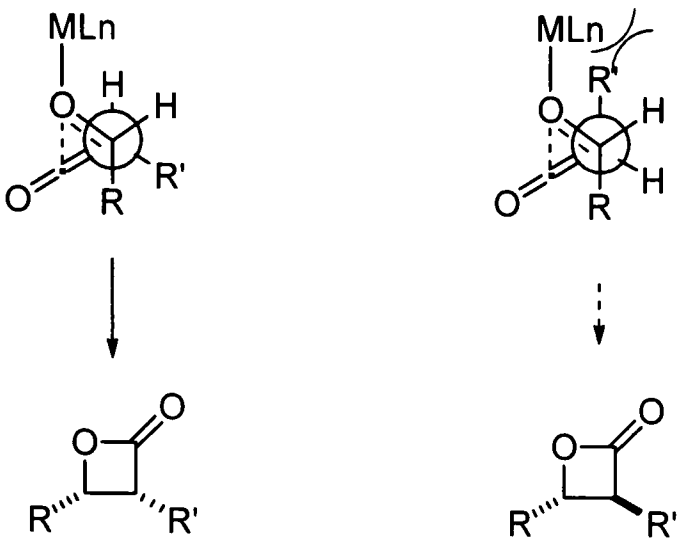


Scheme 118

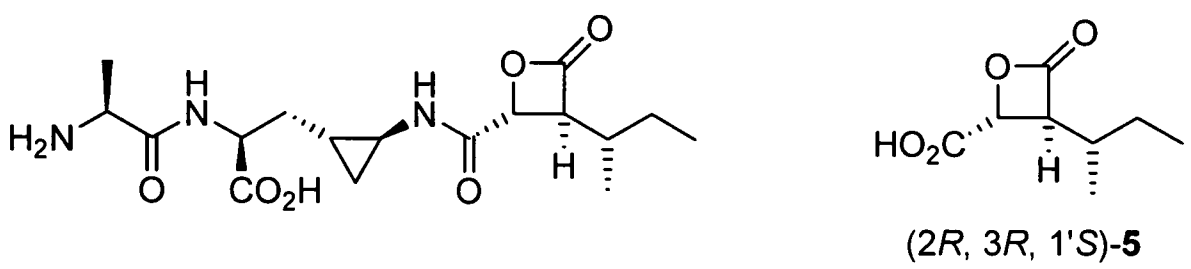
Having completed the left-hand-side of (+)-belactosin A (+)-**1** we then addressed the synthesis of the β-lactone coupling moiety.

2.8 Synthesis of β-lactone – overview of synthetic strategy

The second major challenge in the total synthesis of (+)-**1** (and analogues), was the synthesis of both *trans*-β-lactone stereoisomers. There are numerous methods available to synthesise chiral (non racemic) β-lactones,[88] but most of these involve chiral synthons or diastereoselective approaches. By contrast there are very few catalytic, asymmetric routes to β-lactones,[89] and we saw this as an opportunity to further develop this area. The most useful and direct catalytic asymmetric routes to β-lactones involve the formal 'cycloaddition' of a ketene with an aldehyde. This reaction can be further divided into genuine Lewis-acid catalysed [2+2] cycloadditions, and also 'net' [2+2] cycloadditions *via* an amine catalysed aldol-lactonisation sequence. To the best of our knowledge, all examples of Lewis-acid promoted [2+2] cycloadditions are *cis*-selective,[88,90,91] (to avoid catalyst/R interactions,[92] Scheme 119) and since total synthesis of (+)-belactosin A (+)-**1** would require synthesis of *trans*-β-lactone **5** (Figure 27), we began investigating the alternative amine-catalysed approach.



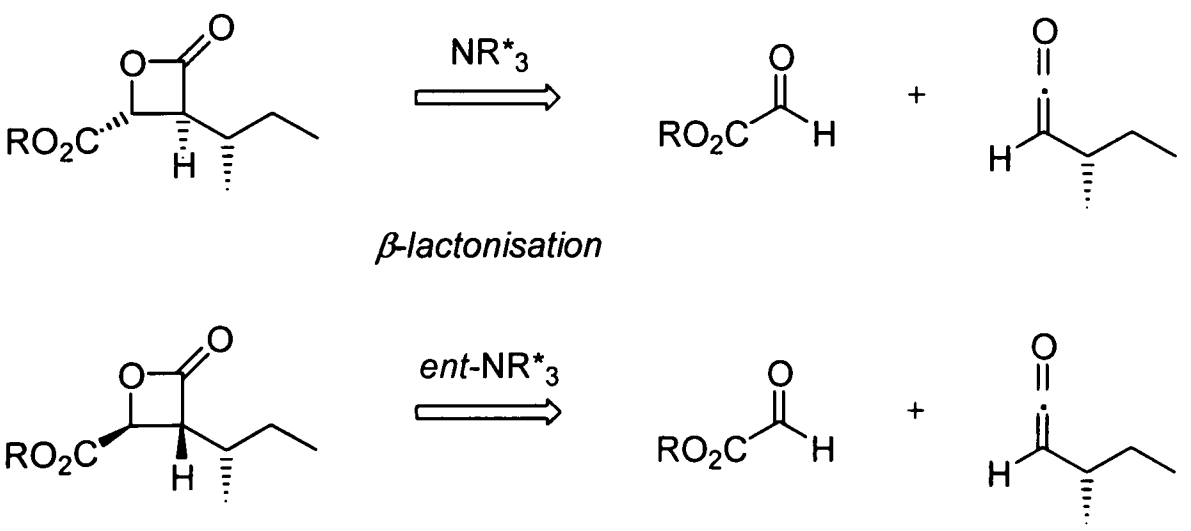
Scheme 119



(2*R*, 3*R*, 1'*S*)-**5**

Figure 27

This reaction typically involves the β-lactonisation of ketene with chloral,[93] to afford mono-substituted products, but we hoped to extend this methodology by using glyoxylates as the electron-deficient aldehyde partner, and access *trans*-β-lactones (Scheme 120). In theory, both *trans*-stereoisomers could then be accessed through use of enantiomeric amine catalysts.

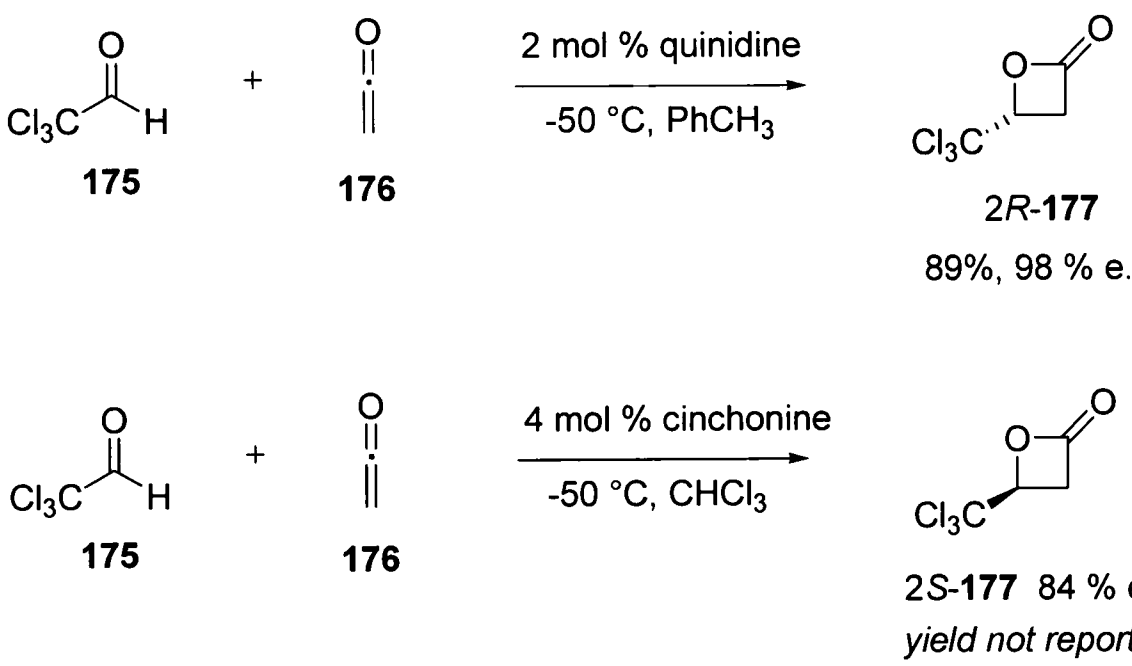


Scheme 120

2.8.1 Organocatalytic β-lactonisation

2.8.2 Introduction

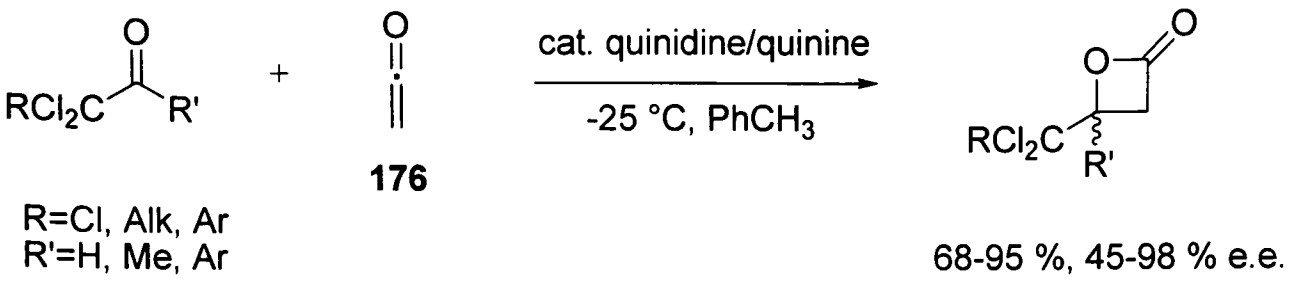
This organocatalytic β-lactonisation was first developed by Wynberg in 1982,[93] and represents one of the first catalytic enantioselective reactions. He reported that the 'cycloaddition' of chloral and ketene could be catalysed by a range of chiral amines, and identified cinchona alkaloids as leading to β-lactones with the highest enantioenrichment. Impressive enantioselectivities were achieved using low loadings of the catalyst, and both enantiomers of the product were available from either quinidine or cinchonine/quinine. Quinidine was found to induce 2*R*-stereochemistry (2*R*-**177**)†, whilst cinchonine and quinine both efficiently induced 2*S*-stereochemistry (2*S*-**177**) (Scheme 121).[94]



Scheme 121

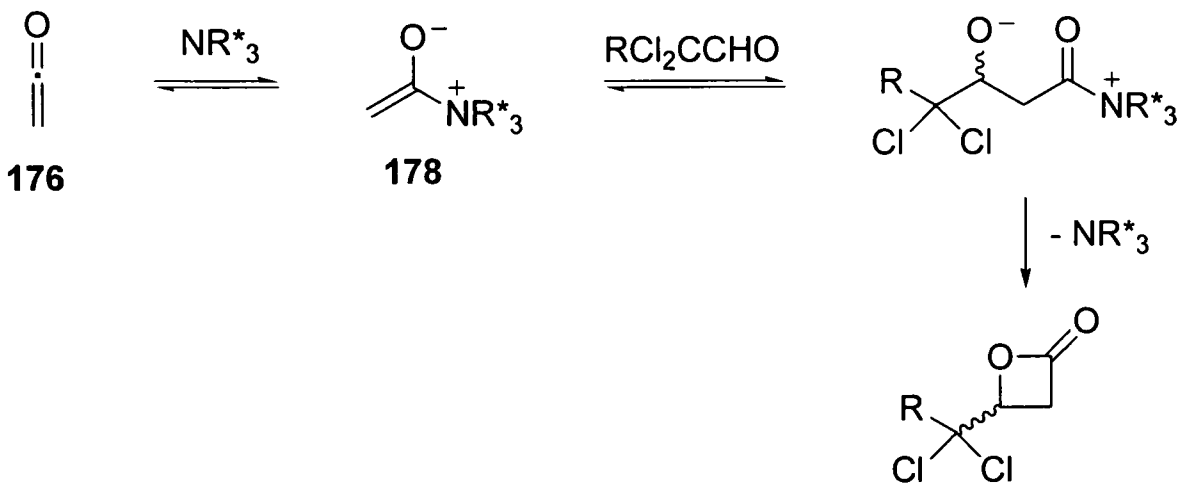
However, subsequent substrate-scope investigations revealed severe limitations to this reaction, with only very reactive carbonyl compounds such as poly α-chlorinated aldehydes (less commonly ketones) being effective in this transformation.[94] Monochlorinated aldehydes failed to react, and electron-poor trichloroacetophenones only reacted under more forcing conditions (Scheme 122).

† This non-systematic numbering is used throughout this discussion for ease of comparison between different β-lactones.



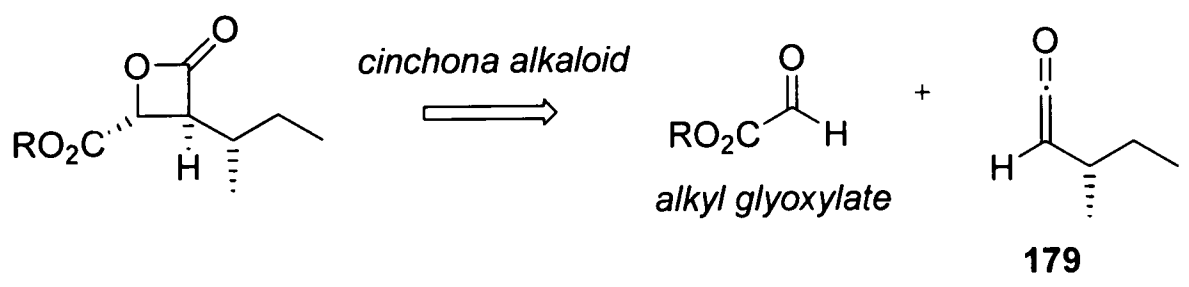
Scheme 122

The proposed mechanism of this reaction involves attack of the tertiary amine on the ketene to generate a zwitterionic enolate, aldol addition (*via* an open transition state), then lactonisation with concomitant release of the catalyst (Scheme 123).[95] Only highly activated, electron-poor aldehydes are suitable for this reaction for two reasons. Firstly, the enolate **178** is of relatively low-energy since it is an overall neutral species, and secondly the aldehyde is not activated by a Lewis-acid.



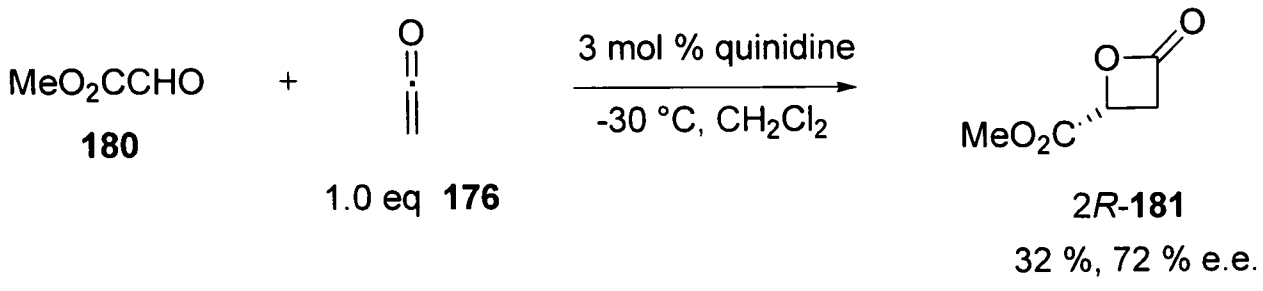
Scheme 123

Disconnection of our target β-lactone by retro [2+2] reveals a glyoxylate and an α-substituted ketene **179** (Scheme 124). Since glyoxylates are also highly activated (same oxidation level as chloral) we hoped that this would also be a suitable substrate for this type of 'cycloaddition'.



Scheme 124

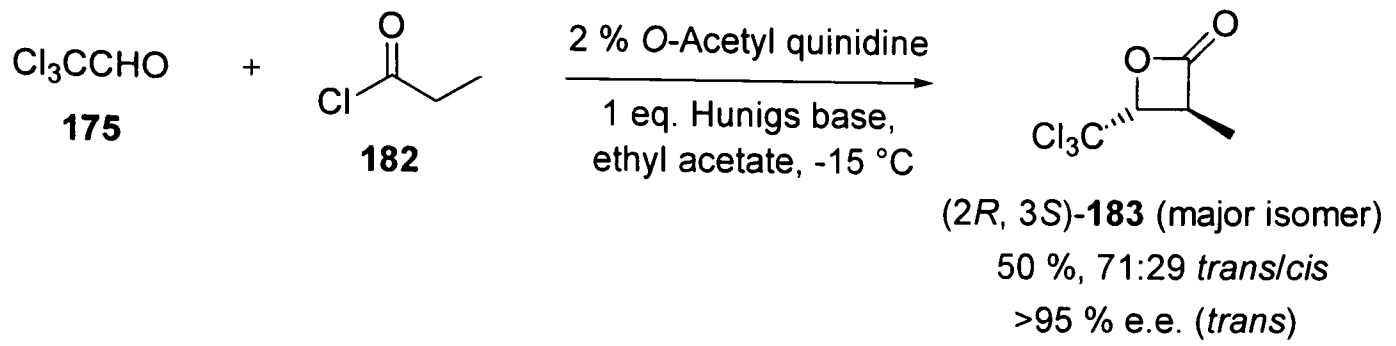
Indeed, after a thorough literature search we did find one application of this idea by Guérin,[96] in which the product β-lactones were used to make chiral polymers. This communication describes the reaction of methyl glyoxylate with gaseous ketene in the presence of either catalytic quinidine or quinine (Scheme 125). However, this approach was only moderately successful, with a large excess of ketene being required to achieve good conversions, and much lower selectivities being achieved using catalytic quinine, even at higher loadings. The absolute C2-configurations of the products were reported to be the same as for the chloral-based examples, but from the data provided it is not clear how this was determined.



Scheme 125

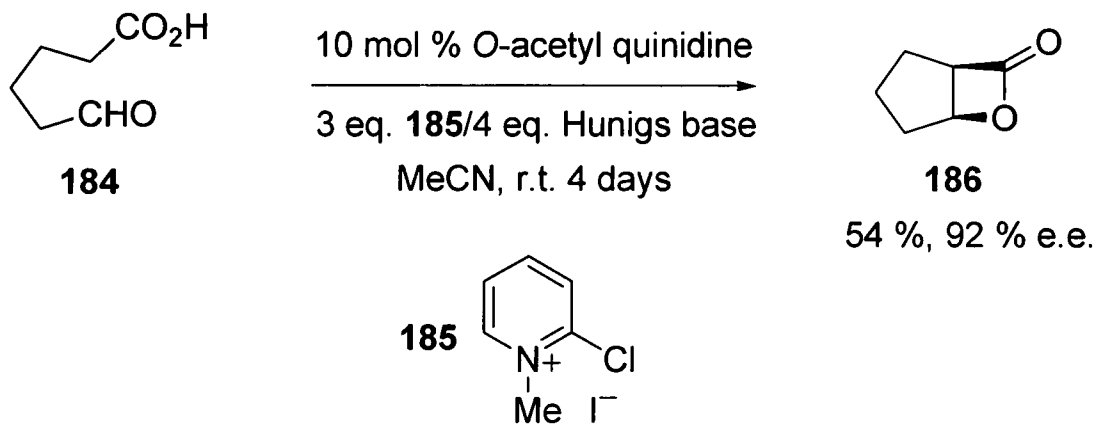
The second key issue for our speculative β-lactonisation was that of *trans/cis* selectivity, since at the time we started our work only one (non-bicyclic) 1,2-disubstituted β-lactone had been synthesised using this organocatalytic approach. A patent filed in 1993 described the 'cycloaddition' of chloral with methyl ketene, leading to β-lactone **183** in respectable *trans*-selectivity (71:29 *anti/syn* ratio) (Scheme 126).[97] These authors were also the first to introduce *in situ* ketene generation (for this type of organocatalytic β-lactonisation), which is very useful when diverting from the more stable silyl ketenes. This was achieved by the dehydrochlorination of acid chlorides, using a stiochiometric amount of non-nucleophilic base in combination with a catalytic amount of chiral amine. The catalyst

used was *O*-acetyl quinidine, and optimisation studies revealed that Hunig's base was the most effective base. Use of triethylamine as the base was found to induce lower enantioselectivities, probably due to competitive organocatalysis.



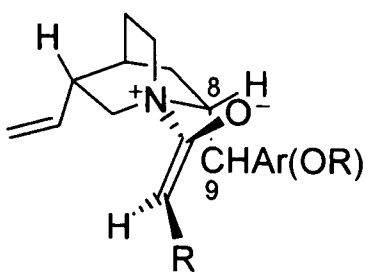
Scheme 126

More recently, Romo has developed conditions for the successful β-lactonisation of unactivated aldehydes.[98] This was achieved by switching to intramolecular cyclisation, in which ketenes were generated directly from carboxylic acids using Mukaiyama's reagent **185** (rather than from the acid chloride). This reaction also yields disubstituted products, but in this case, the constraints of the bicyclic system restrict products to *cis*-β-lactones (for example **186**, Scheme 127).

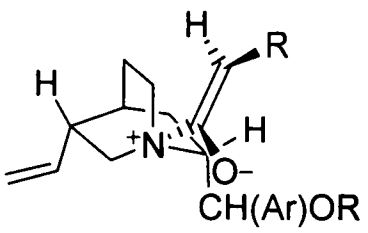


Scheme 127

A model has been proposed by both Calter[99] and Romo[98] to account for the observed C3-stereoinduction. Assuming a *Z*-enolate geometry, enforced by approach of the cinchona alkaloid opposite to the ketene substitutent, the enolate itself can be orientated either towards open space, rotomer **187**, or towards the ethylene bridge of the quinuclidine core, rotomer **188** (shown for quinidine, Figure 28).[99]



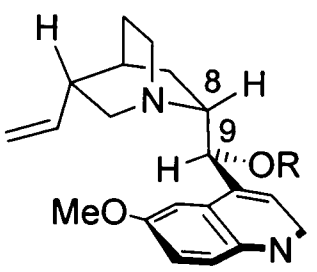
187



188

Figure 28

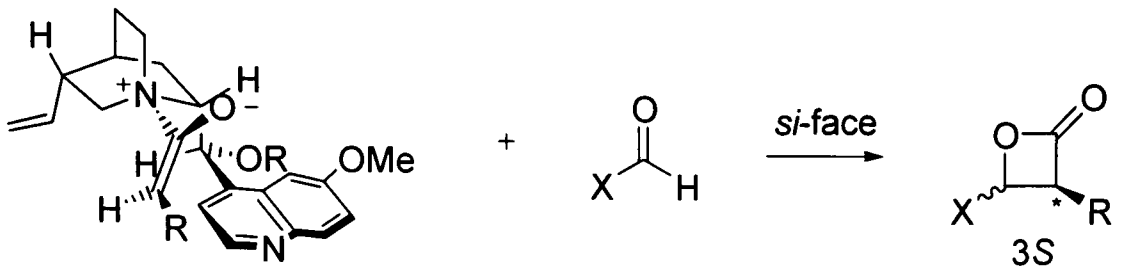
Rotomer **187** is thought to be favoured on the basis of steric repulsion, which therefore means the C8-substituent imparts a stereodirecting effect to approaching electrophiles. Both Wynberg[100] and Romo[101] have investigated the precise orientation of the C9-substituents in solution (using both molecular modelling and H_8-H_9 nOe enhancements) and have concluded that the *app-closed*[101] conformation **189** is the lowest-energy arrangement (shown for quinidine, Figure 29). However, since it is likely that *N*-acylation/enolate formation induces a significant conformational change, the ground-state catalyst-ketene complex structure is still not known, and there continues to be some debate in this area.[102] Nevertheless, Romo proposes an *app-open*[98] reactive complex conformation that does appear to efficiently shield the correct face of the enolate by the quinoline ring (Scheme 128). Using quinidine as the catalyst, only the *si*-face of the enolate **190** is accessible to the incoming aldehyde, inducing 3*S*-stereochemistry, whilst when using quinine as the catalyst, only the *re*-face of the enolate **191** is accessible to the aldehyde, inducing 3*R*-stereochemistry (Scheme 128). More recently, Letka has drawn similar conclusions using molecular modelling (Monte Carlo calculations, Macromodel, AMBER force field) to investigate the lowest-energy conformation of a benzoquinine-phenyl ketene complex. Indeed, his calculations for this complex reveal that the lowest energy minimum in which the *si*-face of the enolate was exposed was almost 7kcal/mol higher in energy.[103]



189

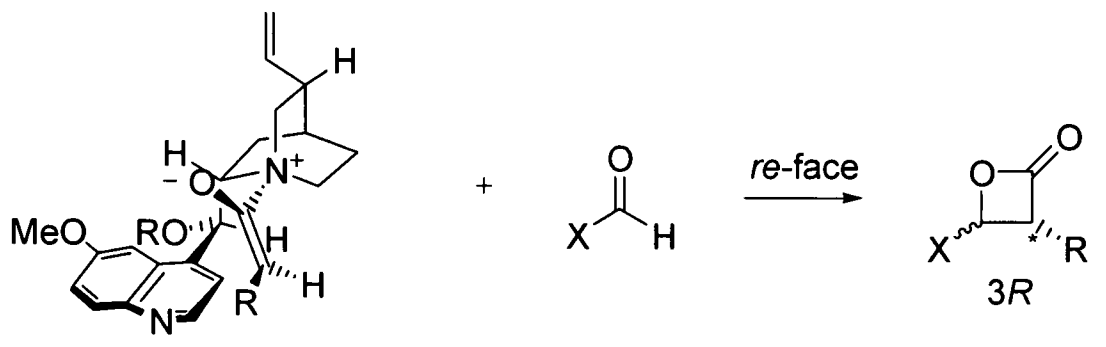
app-closed conformation

Figure 29



190

'app-open' quinidine-ketene complex

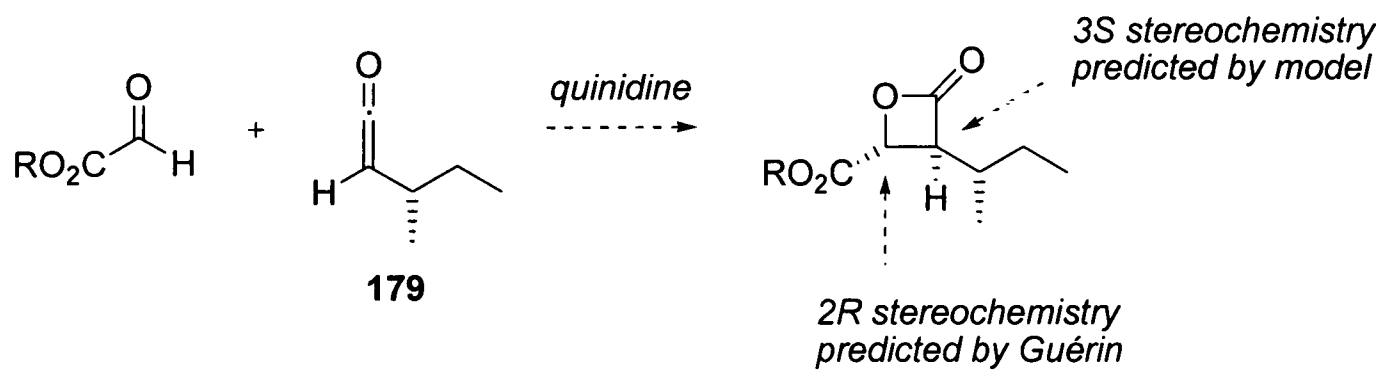


191

'app-open' quinine-ketene complex

Scheme 128

However, because only a single synthesis of a (non-bicyclic) 1,2-disubstituted β-lactone exists, at present there is no model for C2-stereoinduction. Despite this, we were reasonably confident in achieving *trans*-selectivity on the precedent of chloral-based *trans*-β-lactone (2*R*, 3*S*)-**183** (see previous Scheme 126).[97] In addition, both the previous model (for C3-induction) and previous work by Guérin (for C2-induction – implied by the synthesis of 2*R*-**181** and 2*S*-**181**)[96] also suggest that quinidine should generate the required (2*R*, 3*S*)-β-lactone (Scheme 129).



Scheme 129

2.8.3 Glyoxylate-based organocatalytic β-lactonisation

We hoped to apply cinchona-alkaloid catalysis to the synthesis of natural β-lactone **5**, and began exploratory work with β-lactone ethyl ester **192** as the target (Figure 30), since this allowed us to start from commercially available ethyl glyoxylate. Additionally, we aimed to use triethylamine as both the base and organocatalyst in order to simplify the initial optimisation process.

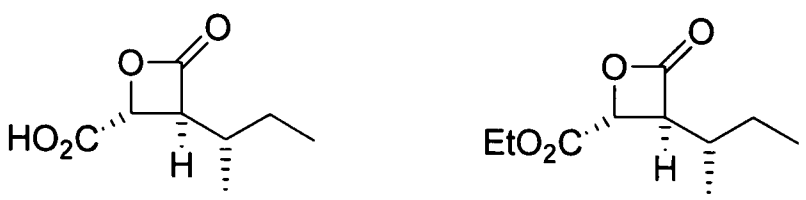
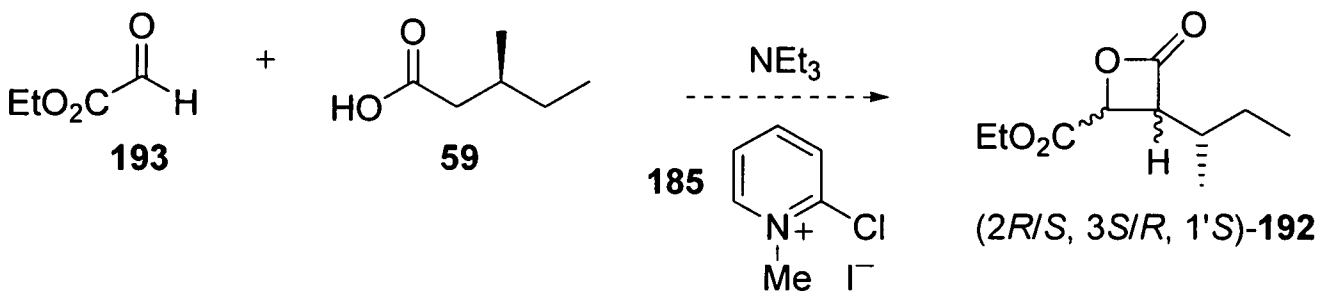


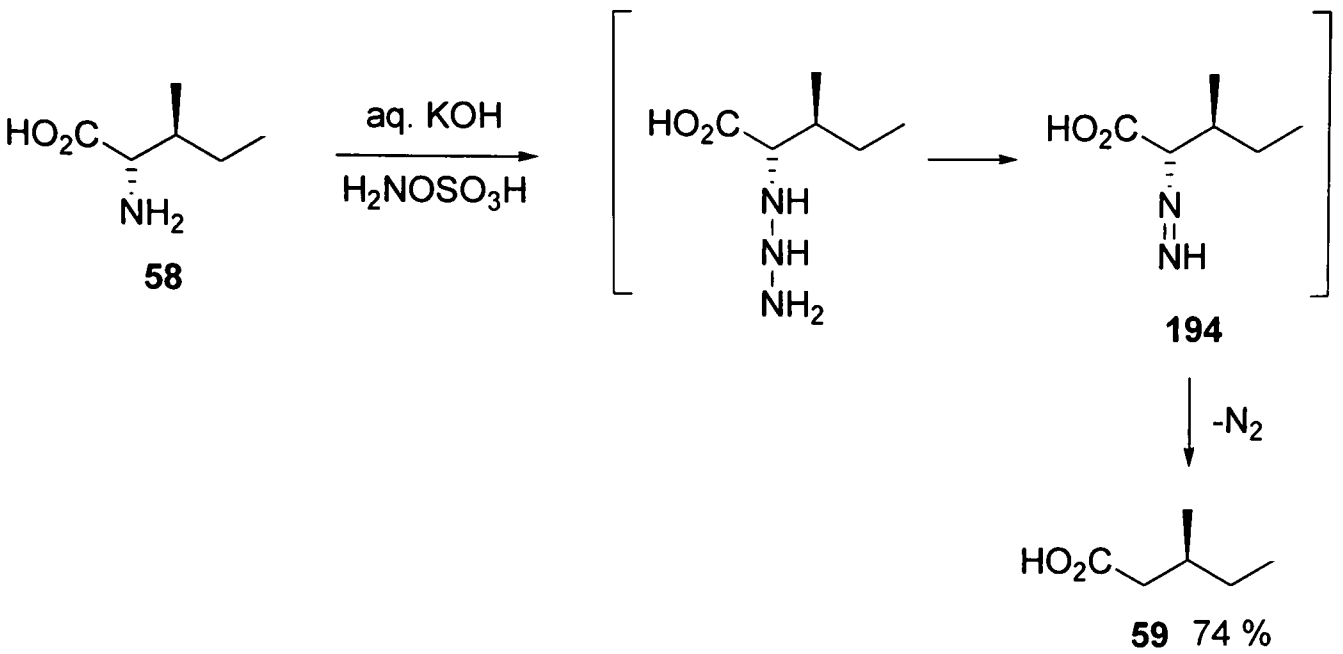
Figure 30

We were interested in using either acid chlorides or carboxylic acids as the ketene precursor, but started work investigating the Mukaiyama salt activation of carboxylic acid **59**, as this permitted a more concise overall sequence (Scheme 130).



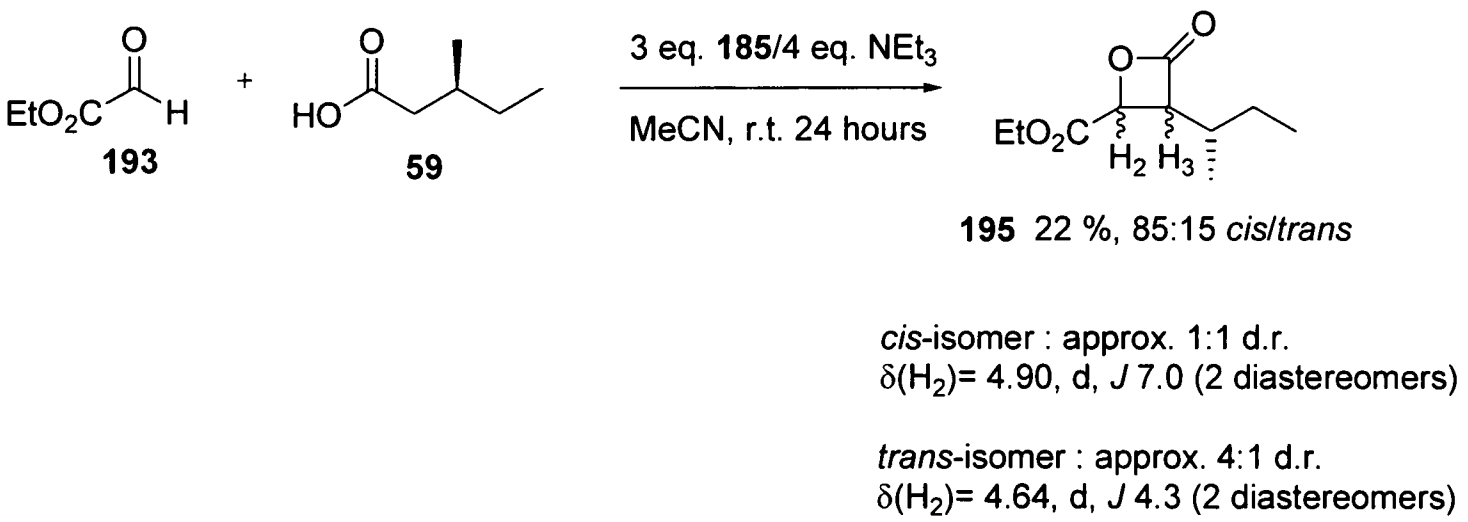
Scheme 130

The required carboxylic acid **59** was synthesised from L-isoleucine **58** under aq. KOH/HOSA conditions[20] in a simple and high-yielding transformation (Scheme 131). Usually amino acids are hydrodeaminated in a two-step halogenation/reduction sequence, but we found this relatively unknown direct reduction to be highly efficient. The reaction is general for most amines, and we believe that it likely proceeds *via* a double amination then elimination to intercept the Wolff-Kishner intermediate **194** (Scheme 131).



Scheme 131

With acid **59** in hand, we subsequently investigated the β-lactonisation using Romo's procedure,[98] and were delighted to see formation of the desired compound **195**, albeit in a low 22 % yield (85:15 *cis/trans*) (Scheme 132). As expected, the 'low-grade' (methyl *vs* ethyl) exocyclic stereocentre provided little stereoinduction, with the product being obtained as a mixture of two *cis*-isomers (approximately 1:1 d.r.), and two *trans*-isomers (approximately 4:1 d.r.). These *cis/trans* stereoisomers were distinguished by characteristic ^{1}H NMR data: for *cis*-β-lactones $J_{H2\text{-}H3}$ is typically 6.5 Hz, and for *trans*-β-lactones, $J_{H2\text{-}H3}$ is typically 4-4.5 Hz.[104,105]

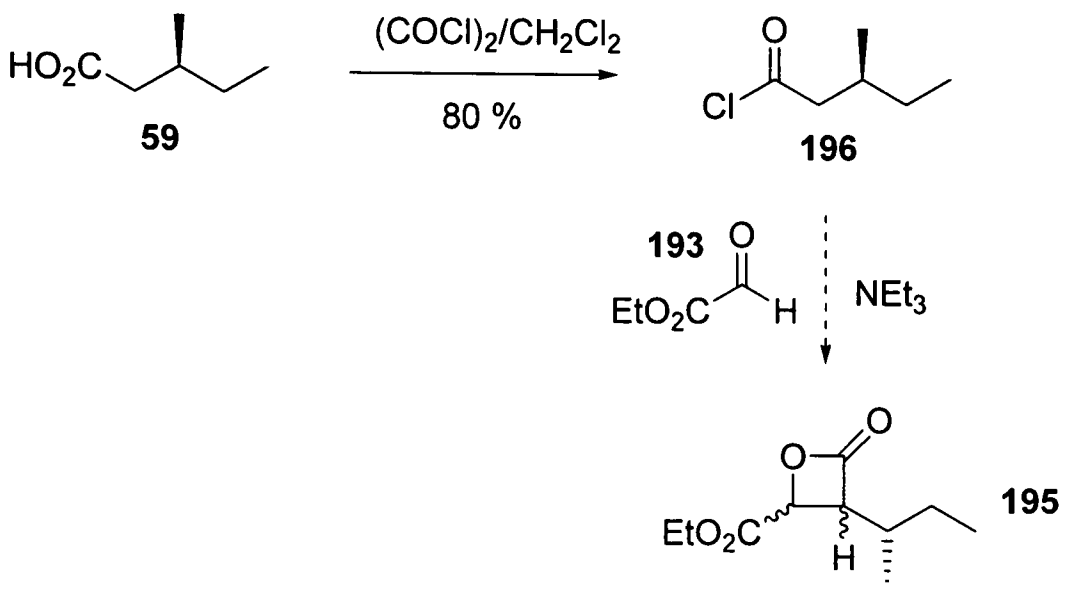


Scheme 132

Although we were disappointed with the observed *cis*-stereoselection, we continued with optimisation in the hope that on switching to cinchona alkaloid catalysis an improvement in the relative stereochemistry may also occur. However, after further

experimentation using Mukaiyama salt activation we achieved no further yield enhancement, so we turned our attention to the acid chloride version.

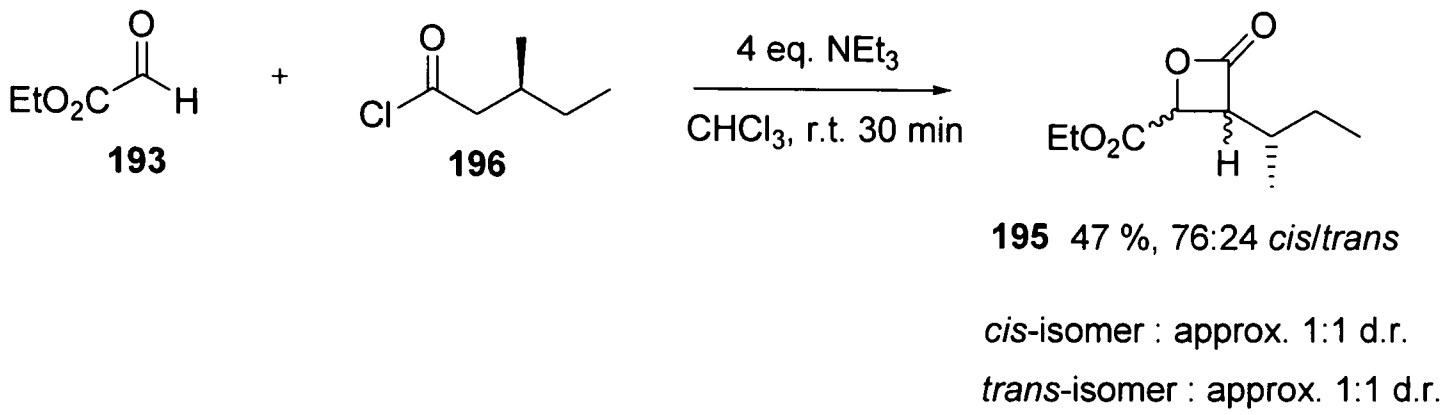
The desired acid chloride **196** was obtained directly from carboxylic acid **59** using standard oxalyl chloride chemistry, and then reacted with ethyl glyoxylate and triethylamine under a range of conditions (Scheme 133).



Scheme 133

Initial investigations into this reaction were disappointing. Chloroform was identified as the best solvent, but the reaction was very low-yielding, and highly dependant upon the order of reagent addition. Ketene dimer appeared to be the major product when either adding glyoxylate **193** to a **196**/NEt_3 mixture, or alternatively adding acid chloride **196** to a **193**/NEt_3 mixture. The first result simply reflected an alternative dimerisation pathway in the absence of aldehyde, but the second appeared to suggest that the ketene was a more reactive electrophile than glyoxylate **193**. We felt this was unlikely, and after a series of ^1H NMR experiments discovered that glyoxylate **193** was being consumed by NEt_3-mediated polymerisation (loss of CHO singlet at 9.3 ppm, and appearance of a CH acetal multiplet at 5.5-5.7 ppm). Indeed, very similar conditions (cat. NEt_3/CH_2Cl_2) have been used by Bunel to polymerise methyl glyoxylate, in which case the polymerisation was then made irreversible by end-termination using isocyanates.[106] By analogy, it is plausible that a similar ketene-mediated end-termination may be occurring in our β-lactonisation reaction, meaning only sub-stoichiometric amounts of glyoxylate may be available for the reaction, which may in part explain the low observed yields of **195**.

In order to minimise these problems, and direct the reaction towards β-lactonisation, we explored the inverse direct addition of NEt_3 to a **193/196** mixture. To our delight this resulted in a significant improvement, and we isolated the desired β-lactone **195** in 47 % yield and 76:24 *cis/trans* ratio, again, as two sets of *cis* and *trans* isomers (Scheme 134).



Scheme 134

Following this success, we then attempted an asymmetric version of this reaction by switching from triethylamine to a Hunig's base/cinchona alkaloid combination, and began work using a quinidine-based catalyst as precedent suggested that this would lead to the desired (2*R*, 3*S*)-**195** stereochemistry. In addition, to prevent ketene consumption (by catalyst *O*-acylation)[99] we chose commercially available hydroquinidine 4-chlorobenzoate **197** (Figure 31).

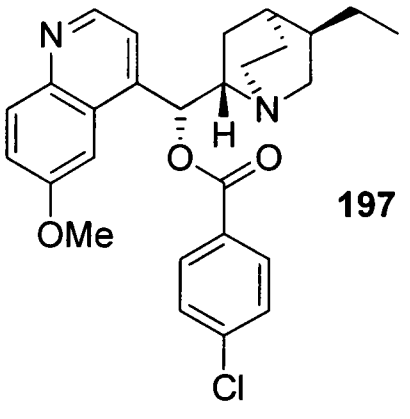
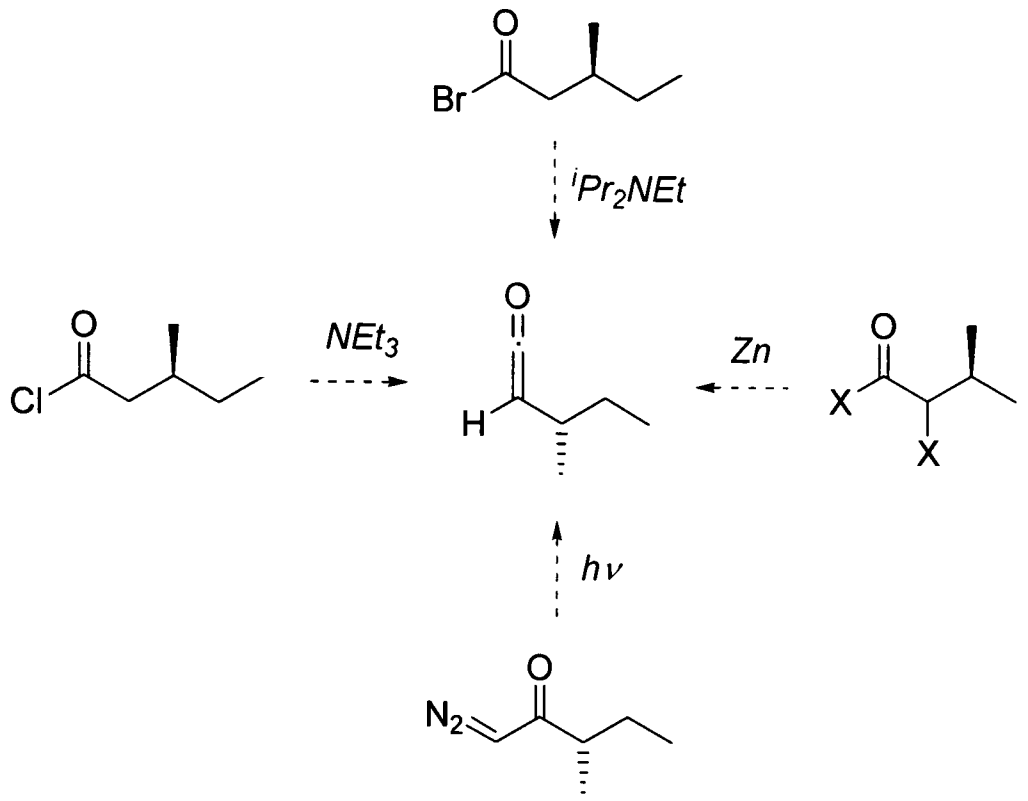


Figure 31

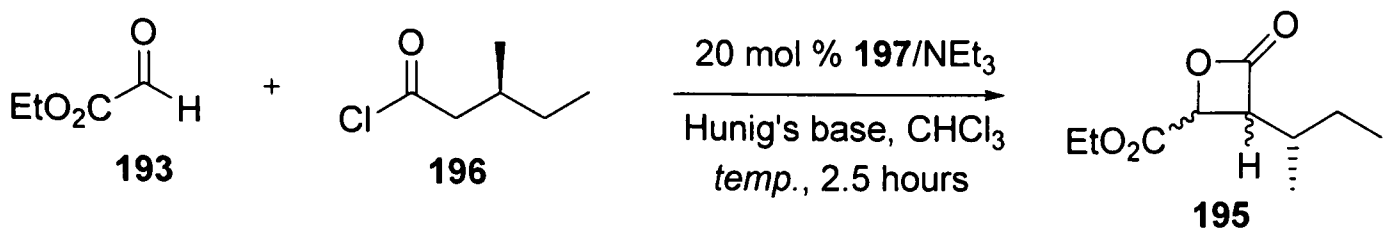
In our hands however, this Hunig's base/**197** combination only generated trace amounts of β-lactone **195**, with subsequent ^{1}H NMR investigations indicating that this was because Hunig's base failed to efficiently deprotonate acid chloride **196** - possibly due to increased steric hindrance. Ketene formation *via* dehydrochlorination

is known to be sensitive to sterics,[107] and in these instances alternative ketene precursors such as acid bromides,[90] α-halo acid halides[107] and diazoketones[103] have been favoured (Scheme 135).



Scheme 135

However, because we considered the acid chloride approach to be more general (due to the commercial availability of acid chlorides), we persevered with the dehydrochlorination approach, testing a variety of other non-nucleophilic bases such as proton sponge, BEMP, NaH/15-C-5 and Na_2CO_3. Unfortunately however, all attempts failed to induce β-lactonisation, so we returned to using triethylamine-mediated deprotonation. The difficulty in this strategy was to prevent triethylamine acting as the organocatalyst, but after some experimentation we did achieve significant selectivities at –50 °C, despite **195** being isolated in only trace amounts due to increased glyoxylate polymerisation. This polymerisation was further reduced by another improvement to the procedure, this time involving the slow addition of a **193/196** mixture to NEt_3/**197**, providing β-lactone **195** in significantly higher yields. The results of subsequent optimisation under these general conditions are shown below (Scheme 136, Table 8).



Scheme 136

Entry	Eq. NEt_3	Eq. Hunig's base	Temp/°C	Yield **195** (*cis*/*trans*)	d.r. *cis*-**195**
1	1	-	-50	20 (90:10)	91:9*
2	2	-	-50	42 (83:17)	84:16*
3	2	-	-78	trace	-
4	2	-	-25	48 (81:19)	76:24*
5	**0.2**	**2**	**-25**	**42 (82:18)**	**> 95:5**
6	0.1	2	0	35 (70:30)	> 95:5

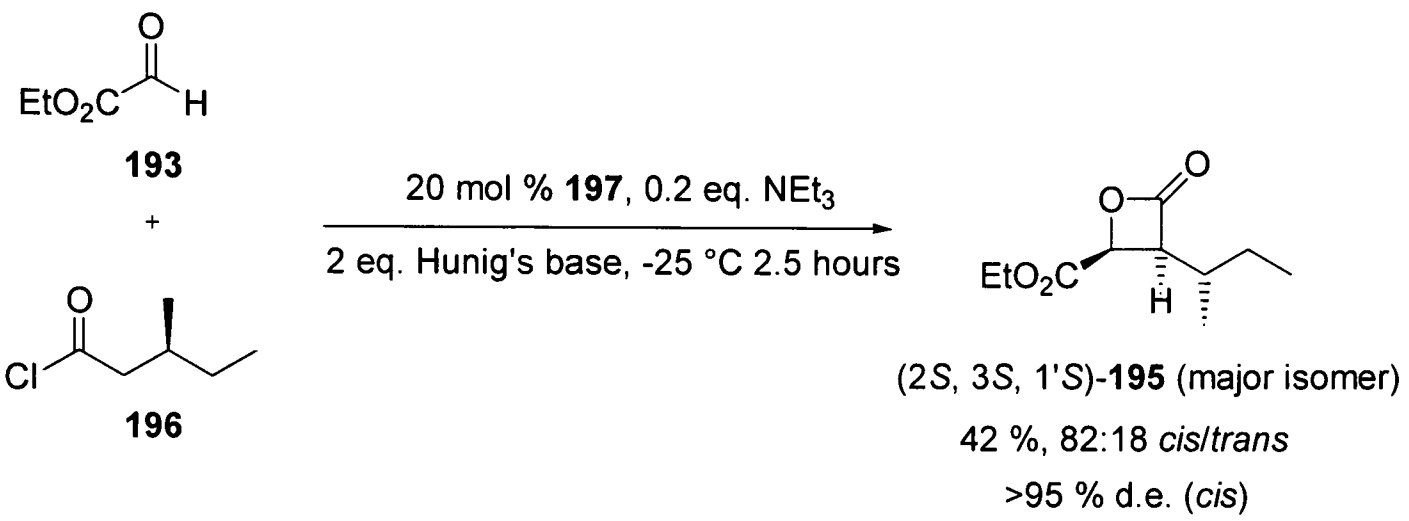
* Approximate ratio from slow-pulse ^{13}C NMR

Table 8

With 20 mol % of catalyst **197** and 1 eq. NEt_3 at –50 °C, β-lactone **195** was produced in high *cis*-selectivity (90:10 *cis*/*trans*) and high diastereoselectivity (91:9 d.r. *cis*-isomer), but only in low 20 % yield (entry 1). This yield was increased to 42 % by using 2 eq. NEt_3, but in this case both the *cis*/*trans* ratio and diastereoselectivity were eroded, presumably because of increased triethylamine organocatalysis (entry 2). Temperature investigations revealed very little reaction at -78 °C, but slightly improved yields and similar *cis*/*trans* ratio at –25 °C (entry 4). In this case however, the diastereoselectivity of the *cis*-product was reduced (presumably because triethylamine is a better nucleophile at higher temperatures), so to maintain deprotonation, but reduce competitive organocatalysis, we switched to a 20 mol % **197**/0.2 eq. NEt_3/2 eq. Hunig's base mixture - hoping that the excess Hunig's base would recycle the catalytic triethylamine. To our delight, this dual catalytic procedure resulted in a 42 % yield of **195** (82:18 *cis*/*trans* ratio) with excellent diastereoselectivity (> 95 % d.e. *cis*-isomer) (entry 5).

Since previous work on C2 and C3 stereoinduction had suggested this reaction would be *trans*-selective, it was initially difficult to assign the absolute stereochemistry of

the β-lactone product **195**. However, since all examples of C3-induction (for quinidine/quinine catalysed β-lactonisation, β-lactamisation, and related processes) are to the best of our knowledge correctly predicted by the *app-open* model, we are reasonably confident in assigning the product β-lactone as the (2*S*, 3*S*, 1′*S*)-**195** stereoisomer (Scheme 137). This then implies that the absolute configuration of 2*R*-**181** and 2*S*-**181** (see previous Scheme 125) reported by Guérin may be incorrect, which is presumably because they were assigned on the precedent of 2*R*-**177** and 2*S*-**177** stereoinduction.



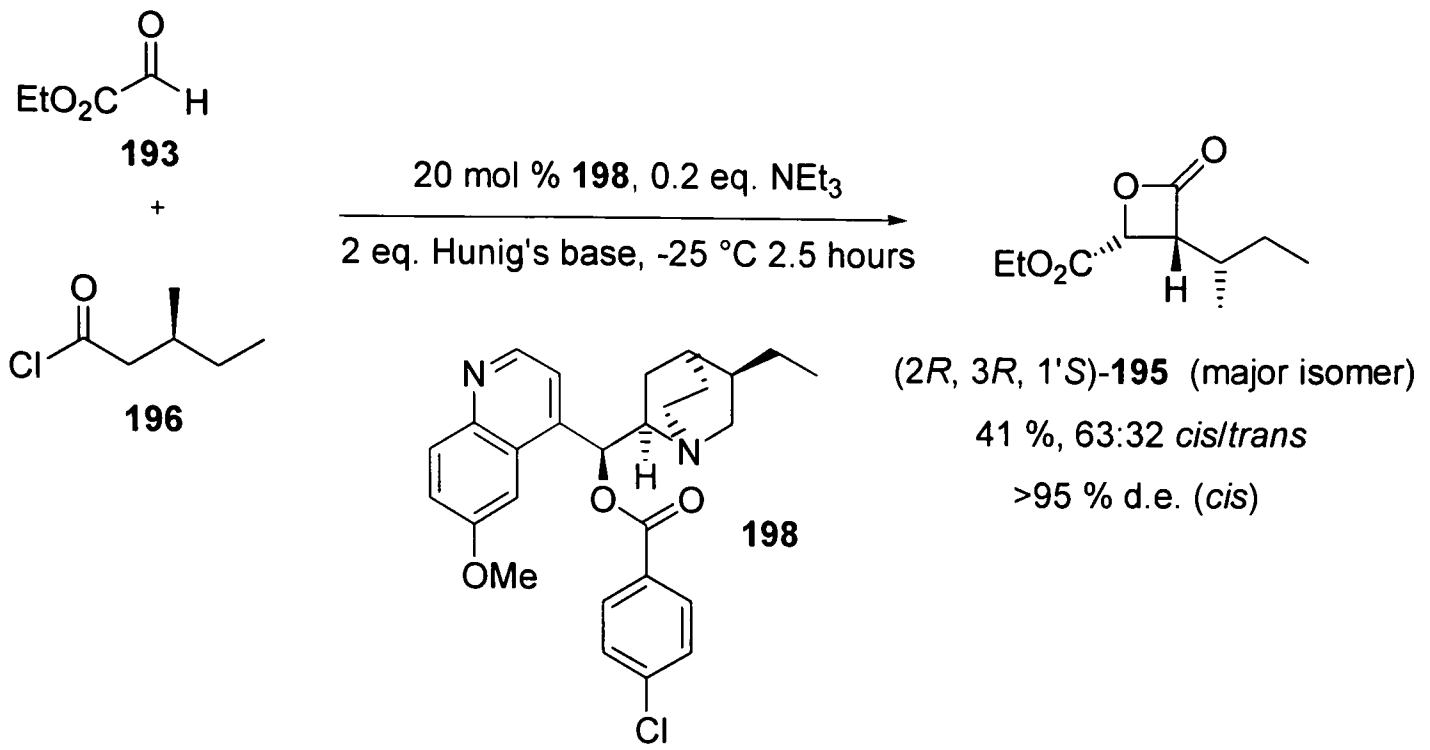
(2*S*, 3*S*, 1'*S*)-**195** (major isomer)

42 %, 82:18 *cis/trans*

>95 % d.e. (*cis*)

Scheme 137

The alternative diastereoisomer (2*R*, 3*R*, 1′*S*)-**195** was then also successfully synthesised using the psuedoenantiomeric catalyst **198** in a similar 41 % yield (63:32 *cis/trans*) and high diastereoselectivity (> 95% d.e. *cis*-isomer) (Scheme 138), demonstrating complete catalyst control for the reaction. Additionally, we were also able to isolate both *cis*-isomers (2*S*, 3*S*, 1′*S*)-**195** and (2*R*, 3*R*, 1′*S*)-**195** as single diastereoisomers by flash column chromatography.



Scheme 138

Since we had established that this organocatalytic β-lactonisation was consistently *cis*-selective, it was no longer a valid strategy for the synthesis of natural β-lactone **5**. Despite this, we believe this methodology has great potential for synthesising the two *cis*-β-lactones **199** and **200**, which themselves would be of use in SAR studies (Figure 32). This would simply involve using either benzyl or *tert*-butyl glyoxylate, so that deprotection could then be executed without ring-opening. In addition, it is likely that using two equivalents of ketene precursor would significantly improve yields, as has previously been shown for related studies.[108,109]

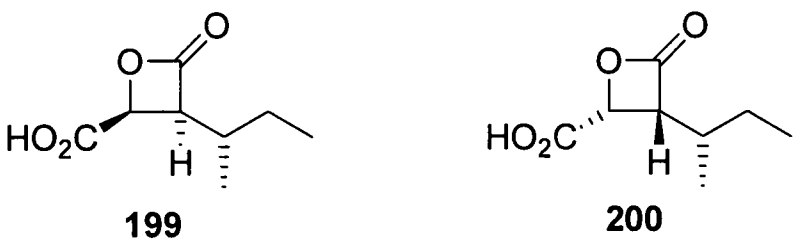
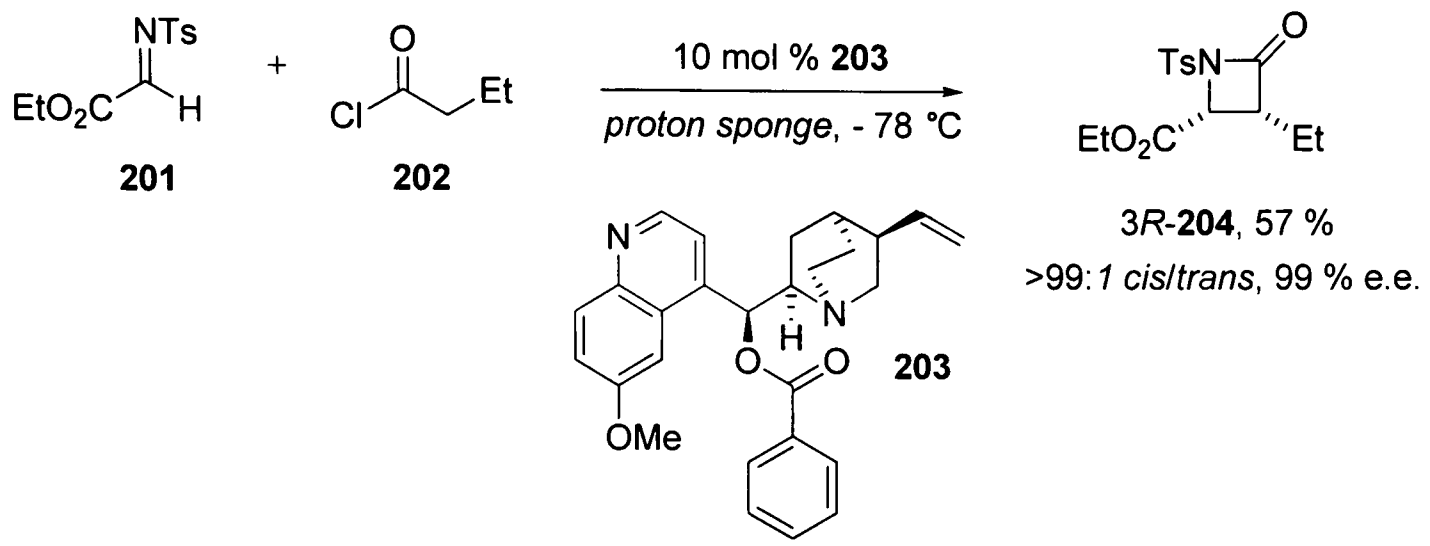


Figure 32

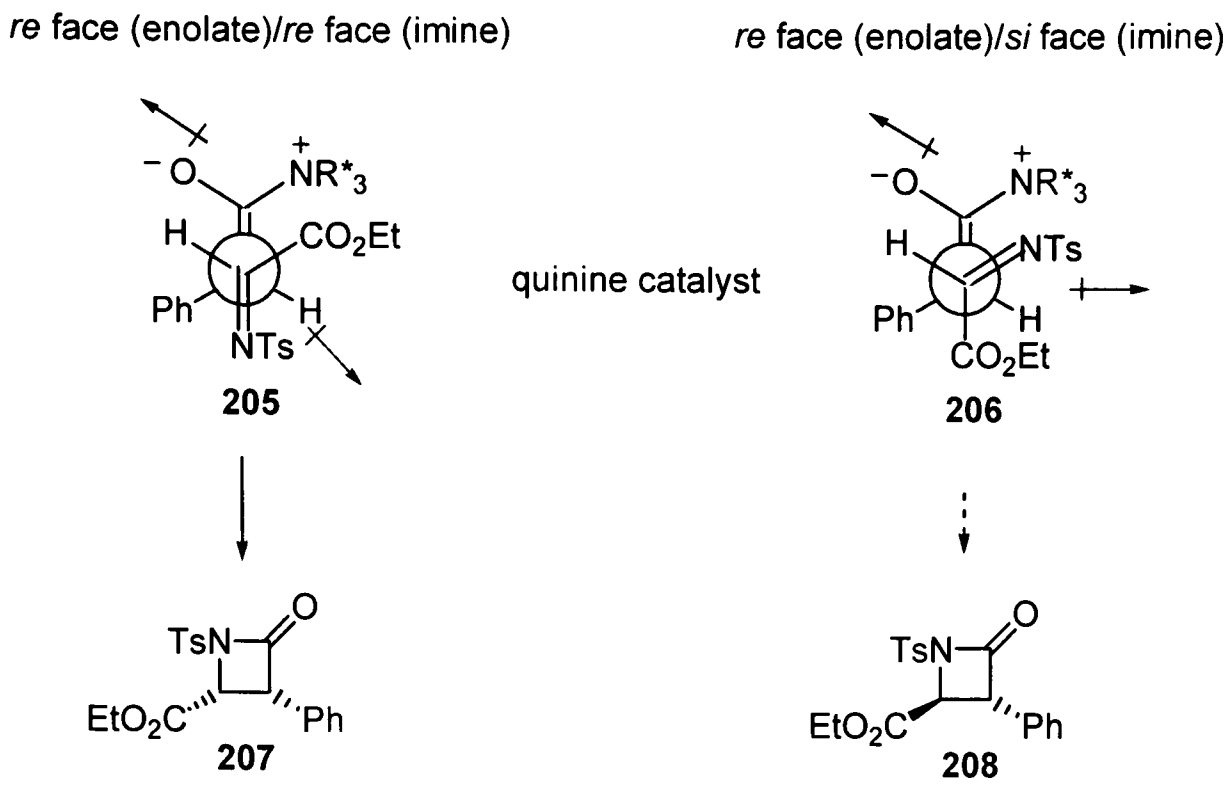
Evidence for the contrasting *cis*-selectivity of this glyoxylate-based β-lactonisation, in comparison to the *trans*-selectivity of chloral-based β-lactonisation, is provided by the closely related organocatalytic β-lactamisation. This reaction was first developed by Lectka,[110] and involves the 'cycloaddition' of glyoxylate imine **201** with various ketenes formed *in situ*. For examples leading to 1,2-disubstituted products, it has been shown that β-lactams are furnished in both excellent *cis*-selectivity and

enantioselectivity. Again, quinidine catalysis leads to 3*S*-stereochemistry, whilst quinine catalysis leads to 3*R*-stereochemistry (Scheme 139).



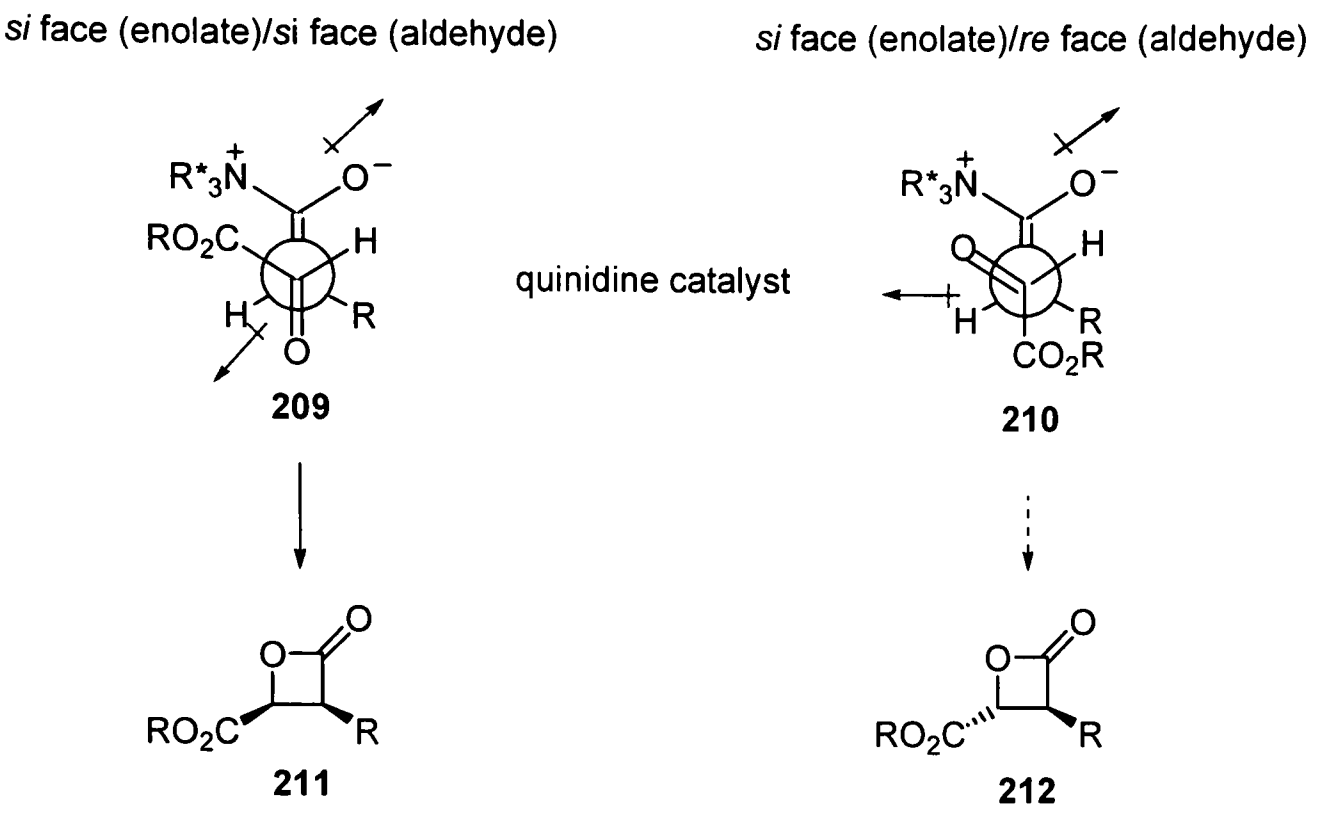
Scheme 139

In addition to modelling the ground-state conformation of the phenyl ketene-benzoyl quinine complex, Lectka has also modelled the open transition-state of this complex with imine **201** (using Macromodel, AMBER force field, docked at a 2.2 Å transition state distance), to investigate the *cis*/*trans* diastereoselectivity.[103] The lowest energy assembly leading to the *cis*-product **207** was found to be **205**, whilst the lowest-energy assembly leading to the *trans*-product **208** was found to be **206** (Scheme 140). In addition, arrangement **205**, was found to be "several kilocalories"[103] lower in energy, which is consistent with the observed *cis*-product **207**. As expected, the benzoyl quinine catalyst presents the *re*-face of the complex to the incoming electrophile inducing 3*R* stereochemistry.



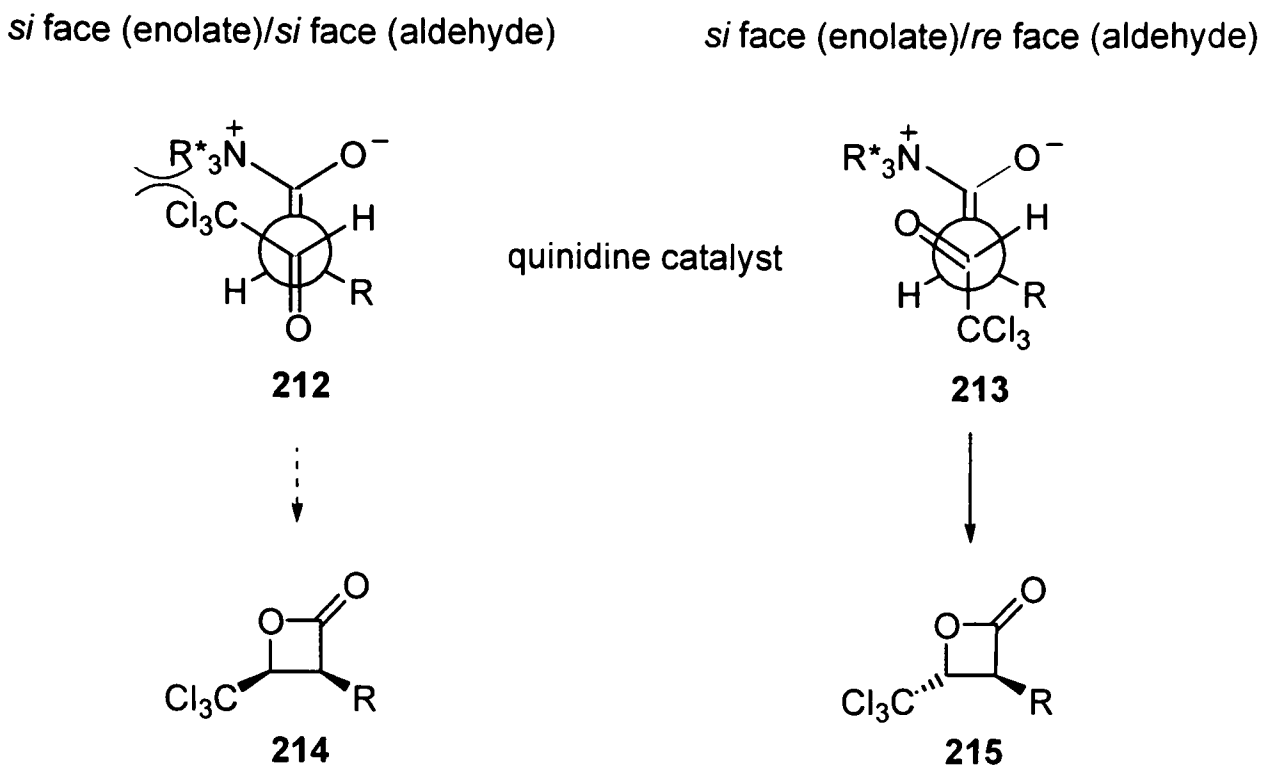
Scheme 140

Lectka provides no explanation for why **205** and **206** are the lowest-energy arrangements (leading to *cis*-β-lactone **207** and *trans*-β-lactone **208** respectively), but within the constraints of a staggered conformation, arrangement **205** appears to achieve the best dipole-dipole repulsion for *re-re* interaction, whilst arrangement **206** similarly appears to achieve the best dipole-dipole repulsion for *re-si* interaction. Furthermore, on a qualitative level, it appears that dipole-repulsions are more efficiently achieved in **205**, which does lead to the observed *cis*-product **207**. Since our glyoxylate-based β-lactonisation is also *cis*-selective, it is plausible that the corresponding assembly **209** is lower in energy than **210** for the same reasons (Scheme 141). Because quinidine was used for our optimisation process (see previous Scheme 136, Table 8), arrangement **209** depicts *si-si* interation, and **210** depicts *si-re* interaction.



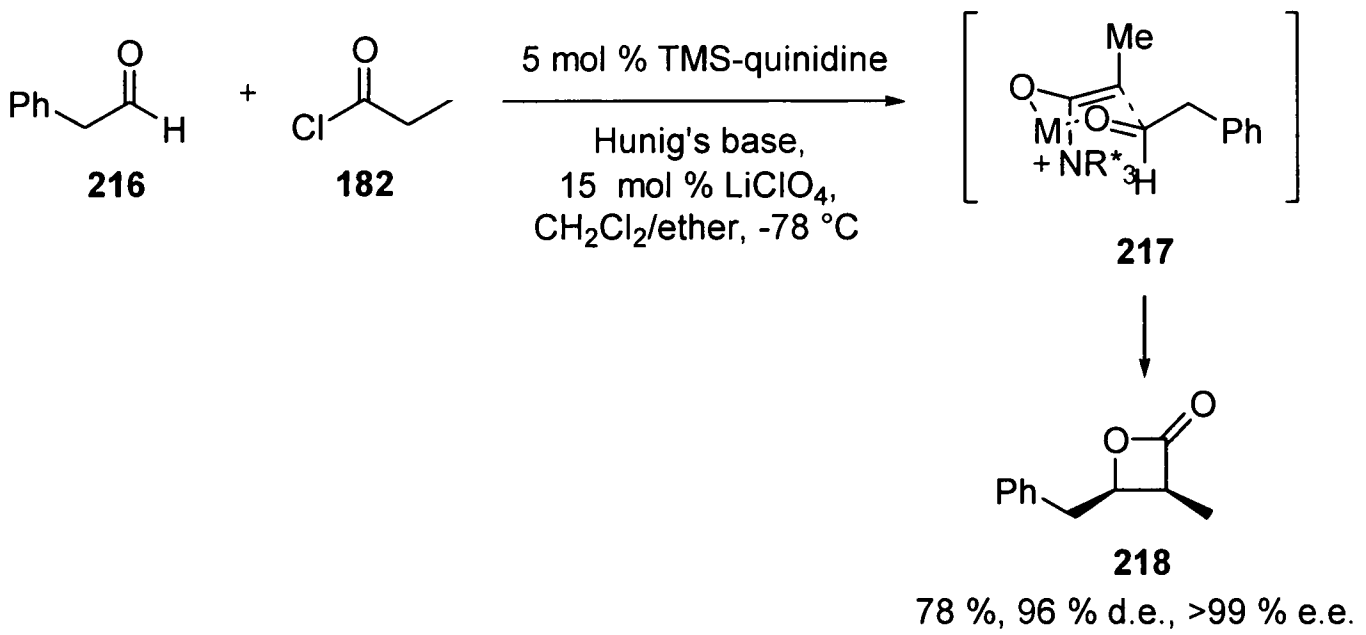
Scheme 141

In contrast, although similar electronic arguments can be applied to the chloral-based β-lactonisation, arrangement **212** may be destabilised because of increased steric repulsion between the bulky CCl_3 and NR_3 moieties (Scheme 142). As a result, arrangement **213** may then become lower in energy than **212**, which explains the observed *trans*-product **215**. This model also provides the first rationale for the C2-stereoinduction observed in mono-substituted β-lactones 2*R*-**177** and 2*S*-**177** based on chloral (see previous Scheme 121).



Scheme 142

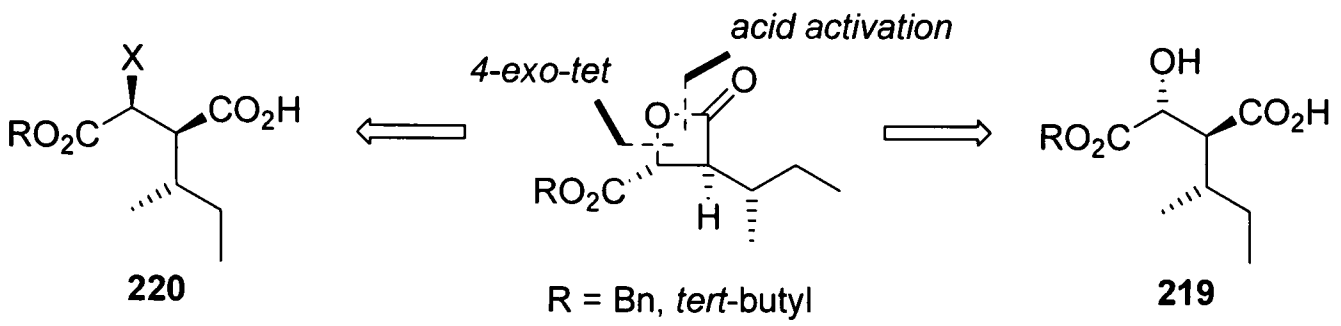
Very recently, Nelson has reported that catalytic lithium perchlorate promotes the β-lactonisation of a diverse range of unactivated aldehydes.[109] In this case however, it is postulated that the Lewis-acid mediates a closed transition state, which leads to 1,2-disubstituted *cis*-β-lactones (for example **218**) by placing the aldehyde alkyl group in a pseudoequatorial position (intermediate **217**, Scheme 143).



Scheme 143

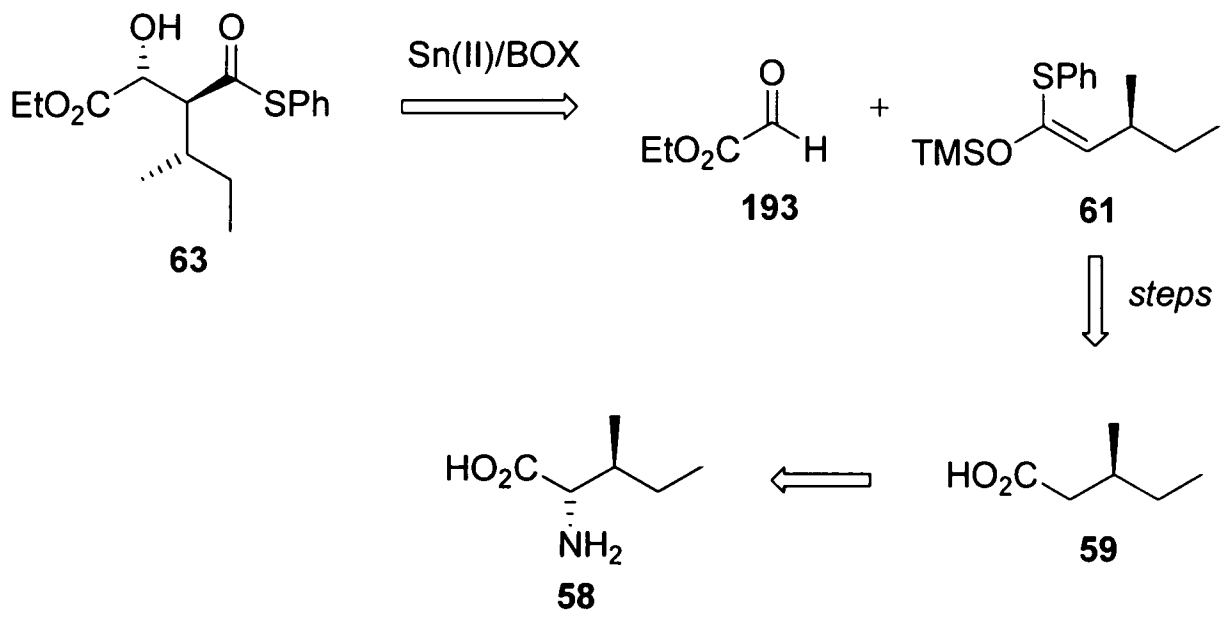
2.9 Diastereoselective synthesis of β-lactone

Having established that the organocatalytic β-lactonisation was not suitable for synthesising **5** (without additional ring-opening/inversion chemistry), we planned a more conventional approach based on the cyclisation of a chiral synthon. Accordingly, we aimed to synthesise β-lactone **5** by the cyclisation of a benzyl or *tert*-butyl protected succinate derivative. This type of cyclisation is possible through either carboxylic acid activation (*via* succinate **219**), or 4-*exo*-tet ring closure of a carboxylate, with inversion of the β-carbon stereocentre (*via* succinate **220**, Scheme 144).



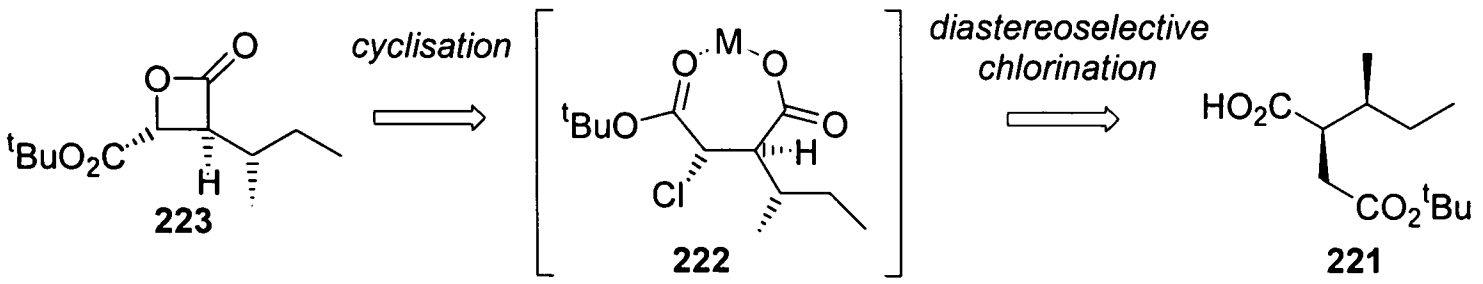
Scheme 144

The more conventional acid activation lends itself to an anti-selective aldol reaction, using an alkyl glyoxylate and an enolate derived from acid **59**. A successful application of this approach was later reported by de Meijere (section 1.4.3),[19] reacting silyl thioketene acetal **61** with ethyl glyoxylate **193** under Sn(II)/bisoxazoline catalytic conditions developed by Evans (Scheme 145).[21]



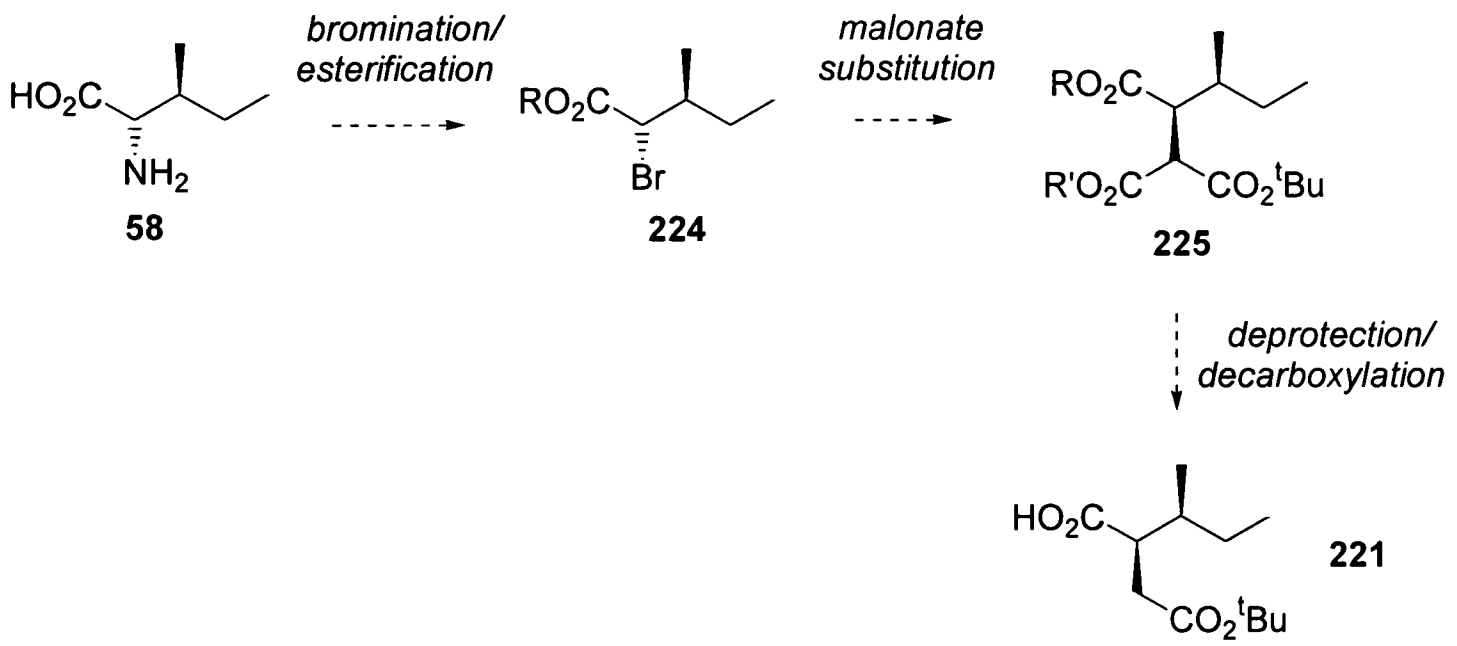
Scheme 145

In contrast, we proposed a fully diastereoselective synthesis of **223** from L-isoleucine **58**, utilising a diastereoselective chlorination of an α-substituted succinate **221**, and a 4-*exo*-tet cyclisation of the resulting β-chloro carboxylic acid **222** as the key steps (Scheme 146).



Scheme 146

We considered this to be a more elegant route to construct the β-lactone moiety **223**, since the original α-stereocentre of **58** is retained throughout the sequence. We envisaged synthesis of **221** *via* bromination of L-isoleucine (with retention of stereochemistry), esterification, malonate substitution (with inversion of stereochemistry) then a final double-deprotection/decarboxylation sequence to furnish **221** (Scheme 147).



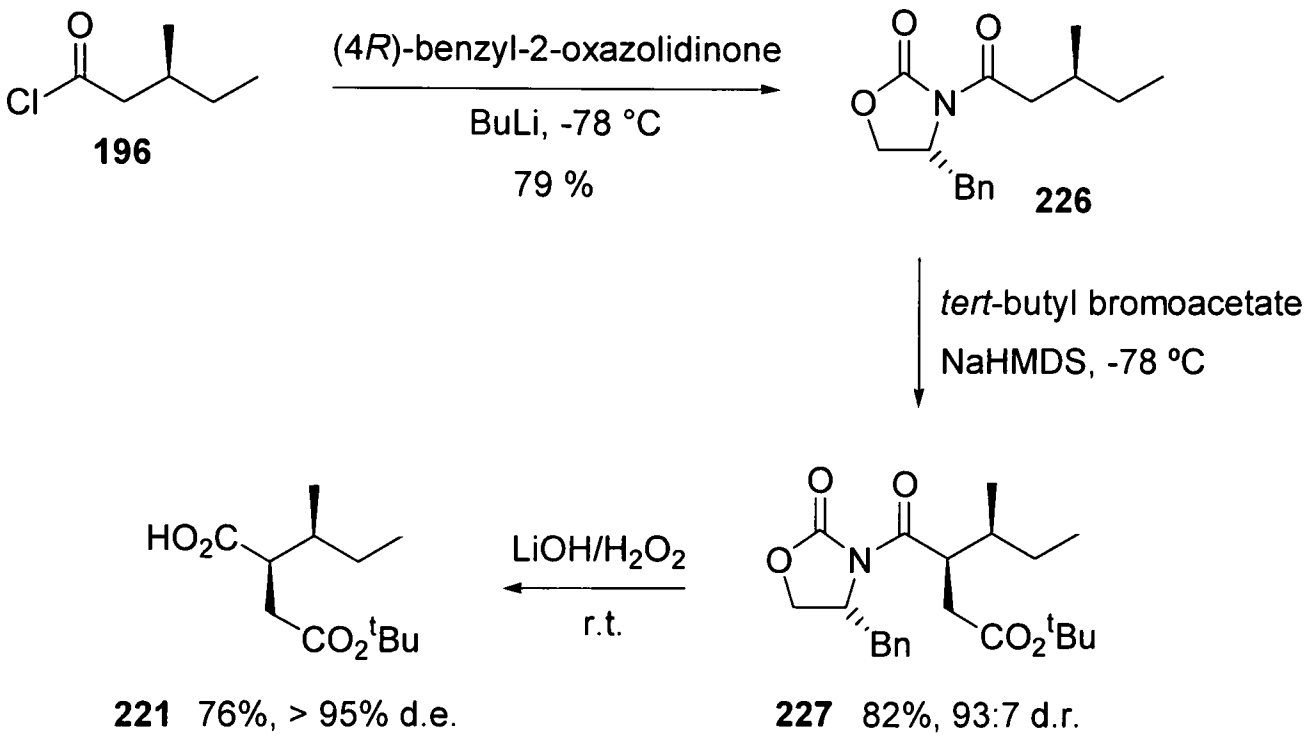
Scheme 147

However, before spending time developing and optimising the potentially difficult malonate substitution step (requiring total inversion of stereochemistry), we first planned to check the validity of the late-stage chlorination/lactonisation, so a more reliable approach to succinate **221** was initially undertaken.

2.9.1 Synthesis of β-lactone *via* Evans alkylation

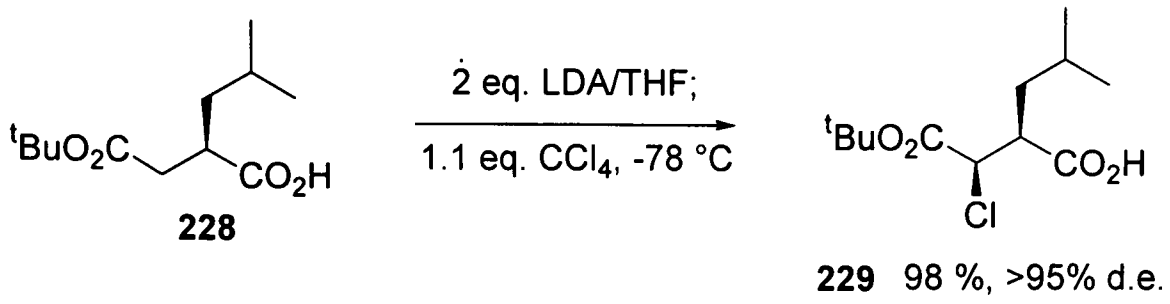
Perhaps the most obvious synthesis of succinate **221** utilises conventional Evans alkylation chemistry, and this was the basis of our alternative route.

This simple two-step procedure began by first coupling chloride **196** to (4*R*)-benzyl-2-oxazolidinone under standard conditions, then alkylation of **226** using *tert*-butyl bromoacetate to give **227** in 82 % yield and high diastereoselectivity (93:7 d.r.).[111] Recrystallisation and hydrolysis using $LiOH/H_2O_2$ then gave the requisite acid **221** in 76 % yield and >95 % d.e. (Scheme 148).



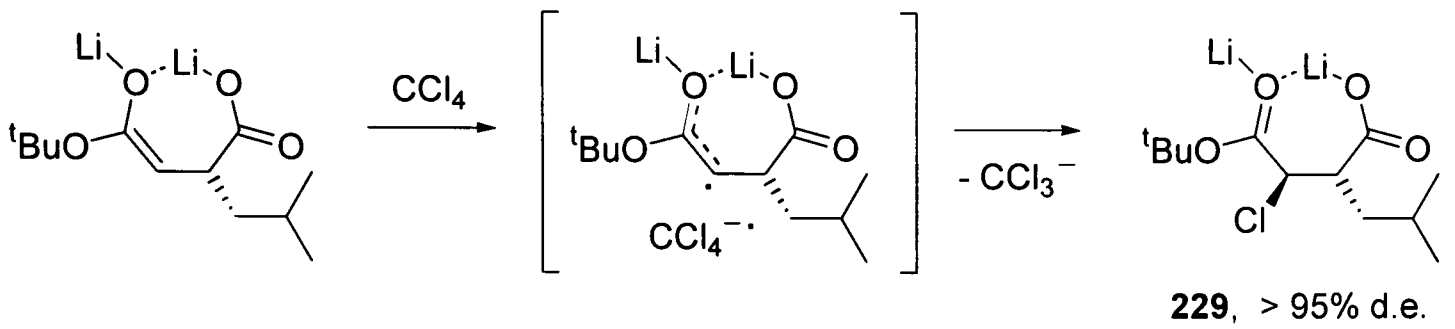
Scheme 148

Key precedent for the chlorination-lactonisation sequence came from workers at AstraZeneca, who conducted a similar reaction on the isomeric succinate **228**.[112] In this example, **228** was first treated with 2 eq. LDA/1.1 eq. CCl_4 to afford the *syn* chloride **229** in 98 % yield (presumably > 95 % d.r.) (Scheme 149). The chlorination of enolates using carbon tetrachloride was first reported by Arnold in 1978,[113] and is thought to proceed *via* a radical anion-radical pair mechanism.[114] By analogy to related work by Crimmin,[115] the stereoinduction presumably arises because the dianion adopts a cyclic (chelated) transition-state, which then directs the electrophile to the less-hindered face (Scheme 150). In addition, the exceptional stereoselectivity observed (**229** furnished in >95% d.e.) is most likely due to the steric bulk of CCl_4.



228 **229** 98 %, >95% d.e.

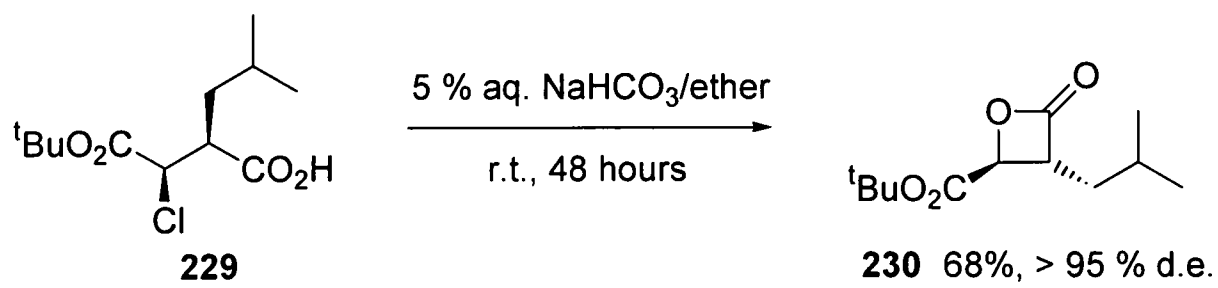
Scheme 149



229, > 95% d.e.

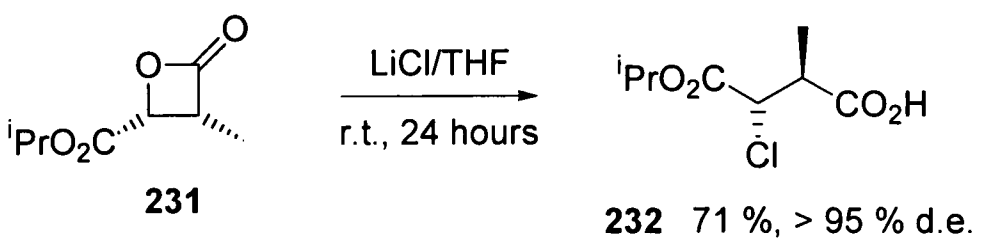
Scheme 150

These workers then cyclised chloride **229** under biphasic conditions, using 5 % aq. $NaHCO_3$ in ether, to give *trans*-β-lactone **230** in 68 % yield (unpurified, presumably > 95 % d.r.) (Scheme 151).[112] It is interesting to note that no cyclisation was observed under the original chlorination conditions, which is also consistent with work by Miller demonstrating S_N2 ring-opening of **231** at the β-stereocentre, using LiCl in THF (Scheme 152).[116]



229 **230** 68%, > 95 % d.e.

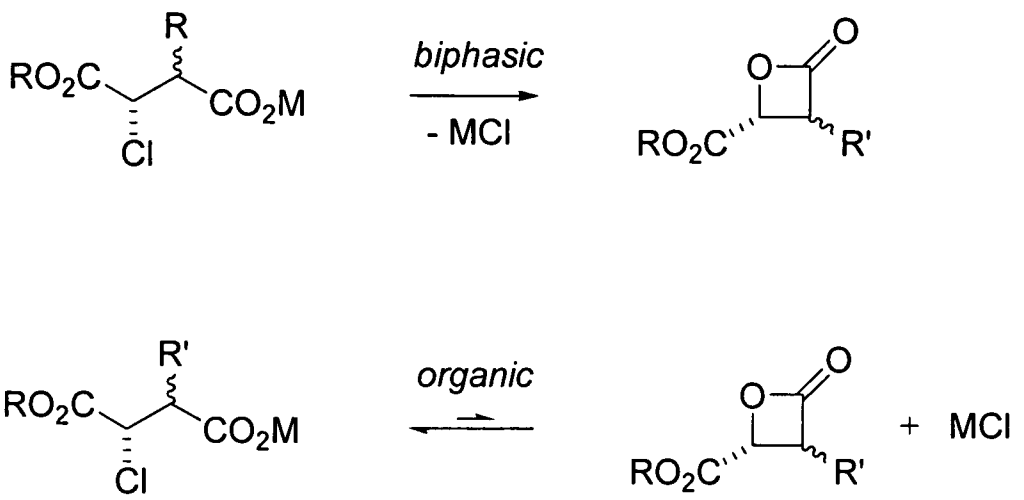
Scheme 151



231 **232** 71 %, > 95 % d.e.

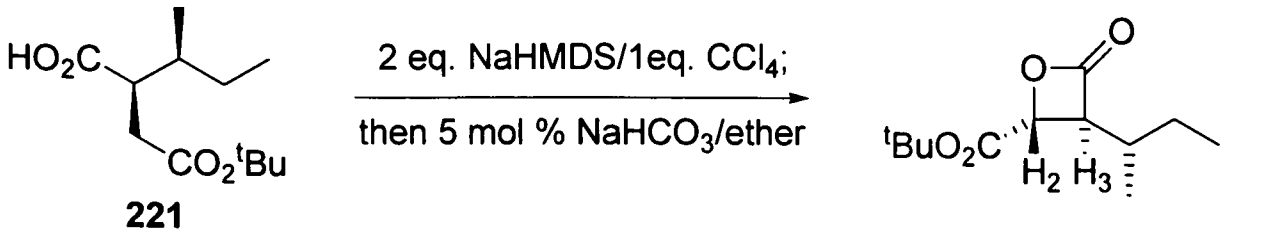
Scheme 152

Taken together, this suggests that biphasic conditions simply bias the equilibrium towards β-lactone **230** by separating the (aqueous-soluble) metal chloride from the organic soluble β-lactone. Over an extended time period all metal chloride becomes removed from the organic phase, so by Le Chatelier's principle chloride **229** then becomes fully converted. Furthermore, the success of the modified Wynberg β-lactonisation (which generates NR_3.HCl *in situ*) may indicate that a metal-chloride source is also required to achieve ring-opening, by preferential coordination of the carboxylate *vs* the β-lactone carbonyl group (Scheme 153).



Scheme 153

We hoped to combine these two reactions to produce a one-pot chlorination-lactonisation, and to this end began work work by treating succinate **221** with 2 eq. NaHMDS followed by 1 eq. CCl_4. To our delight we observed a highly diastereoselective chlorination (by ^{1}H NMR analysis of the crude product), so accordingly this material was then cyclised under the literature biphasic conditions to afford β-lactone **223** as a single diastereoisomer. After further work we managed to successfully combine both steps, to achieve a direct conversion of **221**, yielding **223** in 55 % (>95 % d.e., 2 steps) (Scheme 154). The *trans*-stereochemistry of β-lactone **223** was evident in the ^{1}H NMR, with **223** displaying a typical $J_{H2\text{-}H3}$ coupling constant of 4.3Hz. In addition, all stereochemistry was then confirmed by X-ray crystallography (Figure 33).



221

Scheme 154

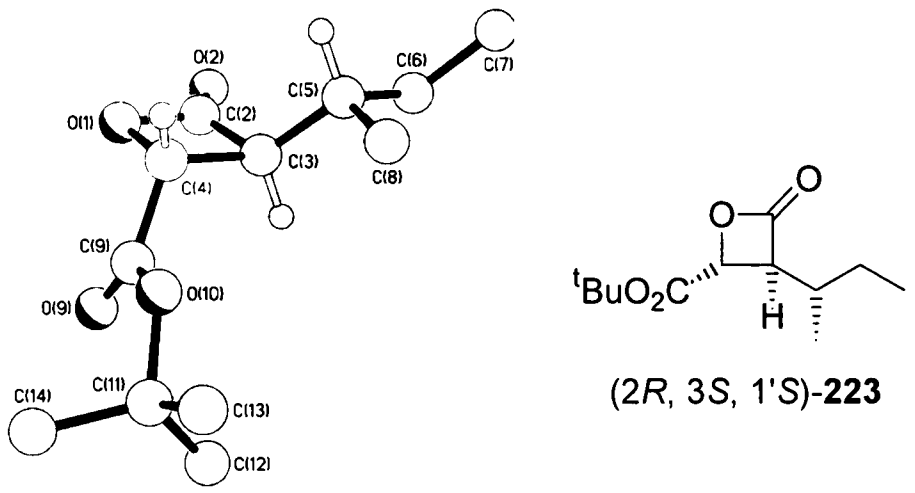
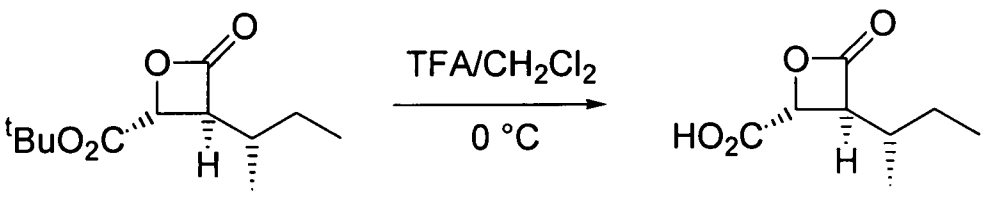


Figure 33: X-ray structure of **223**

Final deprotection of the *tert*-butyl ester was then achieved using TFA/CH_2Cl_2 at 0 °C so as to avoid epimerisation, affording acid **5** in 90 % yield (Scheme 155).

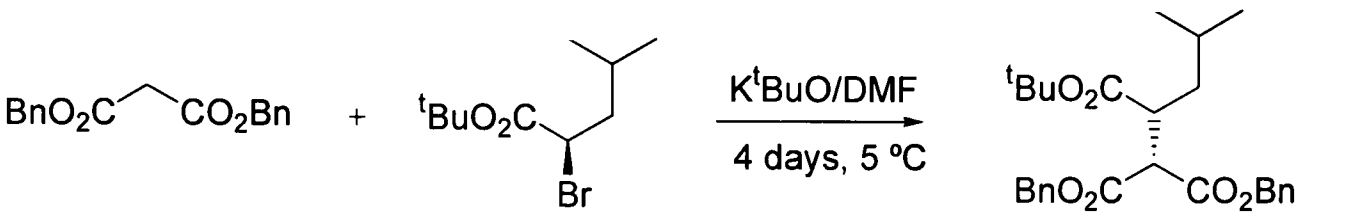


Scheme 155

2.9.2 Synthesis of succinate *via* malonate substitution

Having established a successful chlorination/lactonisation sequence we returned to the synthesis of succinate **221** by the malonate substitution route. However, after a thorough literature search we were surprised to find only two examples of such malonate substitutions with clean inversion of C2-stereochemistry. The first of these was by workers at British Bio-Technology Ltd.,[117,118] who reported synthesis of **234**

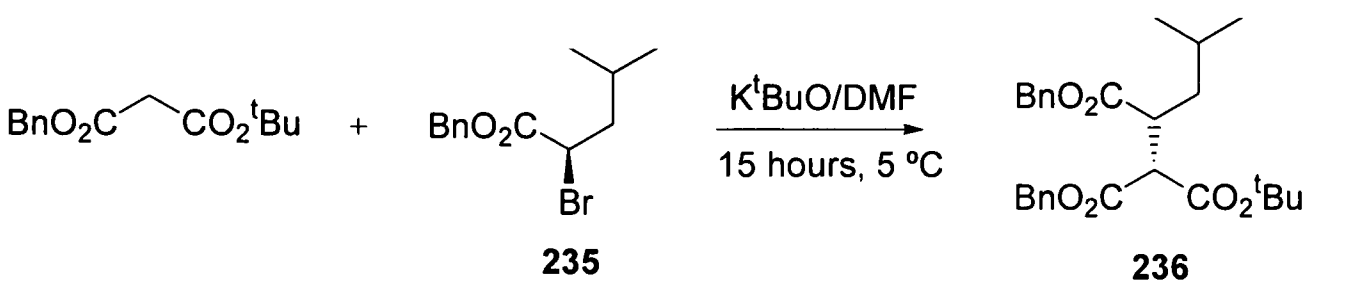
via the S_N2 substitution of α-bromo *tert*-butyl ester **233** with dibenzylmalonate, using K^{t}BuO in DMF (presumably >95 % d.e. at C2) (Scheme 156). The second example is very similar, but in this case it was discovered that by switching from *tert*-butyl to benzyl-protection, reaction times were reduced from 4 days to 15 hours (under identical conditions).[119] This result indicates that the reaction is very sensitive to steric crowding at the reaction centre (Scheme 157).



233 **234**

50%, > 95% d.e. at C2

Scheme 156

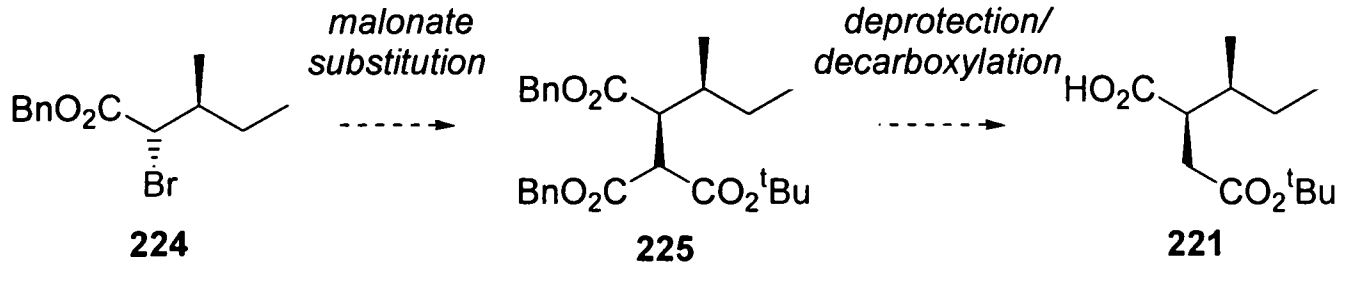


235 **236**

89 %, > 95% d.e. at C2

Scheme 157

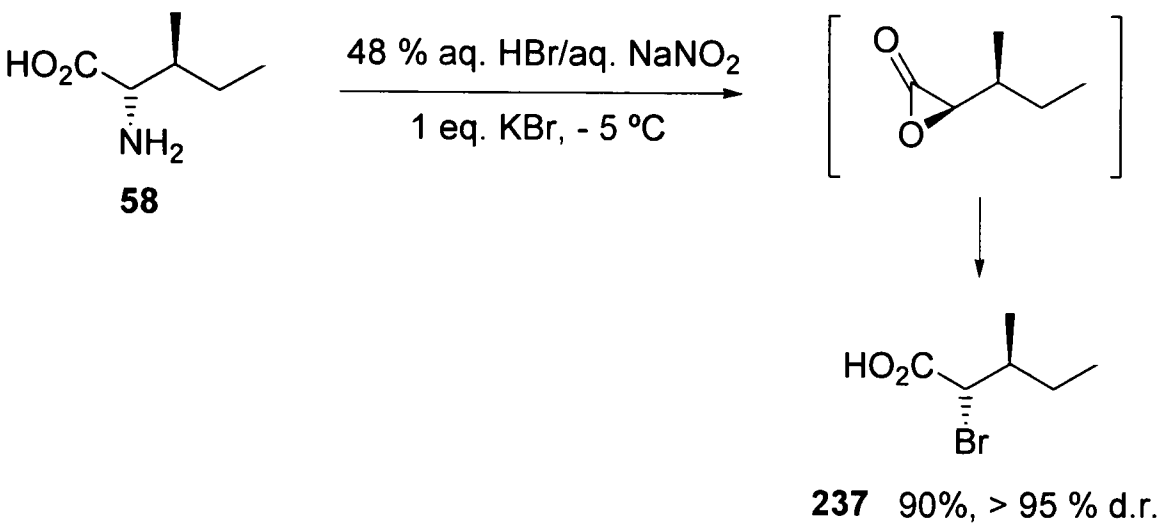
We planned a similar malonate substitution using α-bromo benzyl ester **224** to exploit similar rate-enhancement. Use of benzyl *tert*-butyl malonate **235** then permited potentially rapid access to succinate **221**, after simple hydrogenolysis/decarboxylation steps (Scheme 158).



224 **225** **221**

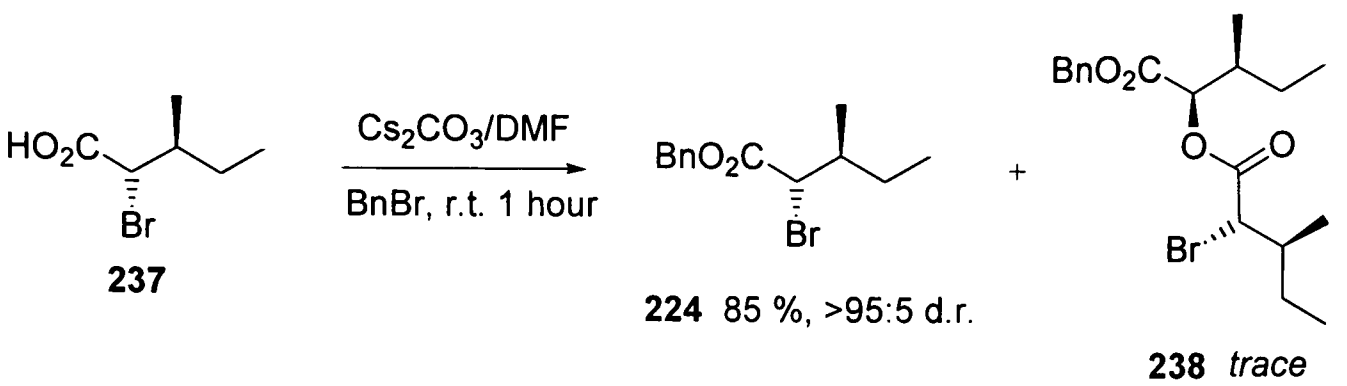
Scheme 158

The first step in this sequence involved synthesis of α-bromo acid **237** from L-isoleucine **58** under standard diazotisation conditions. The reaction is known to proceed by a double inversion mechanism, so that C2-stereochemistry is retained. Test reactions revealed the addition of potassium bromide was crucial for obtaining high yields, and after recrystallisation, **237** was obtained in 90 % and >95 % d.e. (Scheme 159).



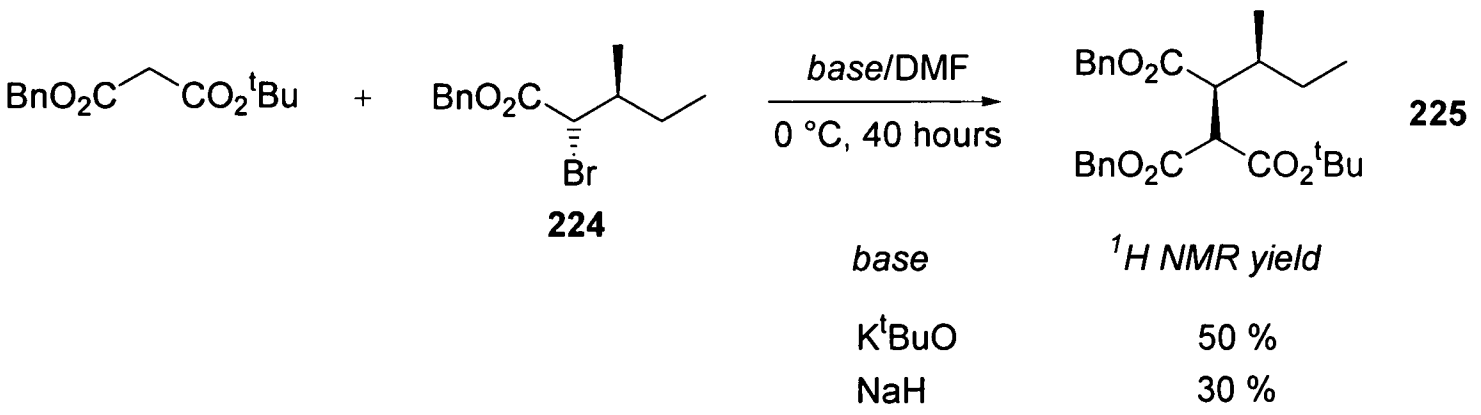
Scheme 159

We next required benzyl protection of acid **237**, and first attempted this under acid-catalysed transesterification conditions ($BnOH/PhCH_3$/cat. TsOH – azeotropic reflux), but found this to cause substantial C2-epimerisation. As an alternative, we considered alkylation of **237** with benzyl bromide, but this approach is also complicated by the acidic α-stereocentre. Accordingly, we planned to use mild alkylation conditions (Cs_2CO_3/DMF, r.t.) developed by Jung[120] which have been shown to be compatibile with epimerisable compounds. Under these conditions, we were delighted to achieve benzyl-protection of **237** without epimerisation, in addition to synthesis of material consistent with 'dimer' **238**. This 'dimerisation' no doubt reflects the enhanced reactivity of cesium carboxylates, but could be minimised through the slow inverse addition of acid **237** to a benzyl bromide/Cs_2CO_3 slurry, affording ester **224** in 85 % yield (> 95 % d.e.) (Scheme 160).



Scheme 160

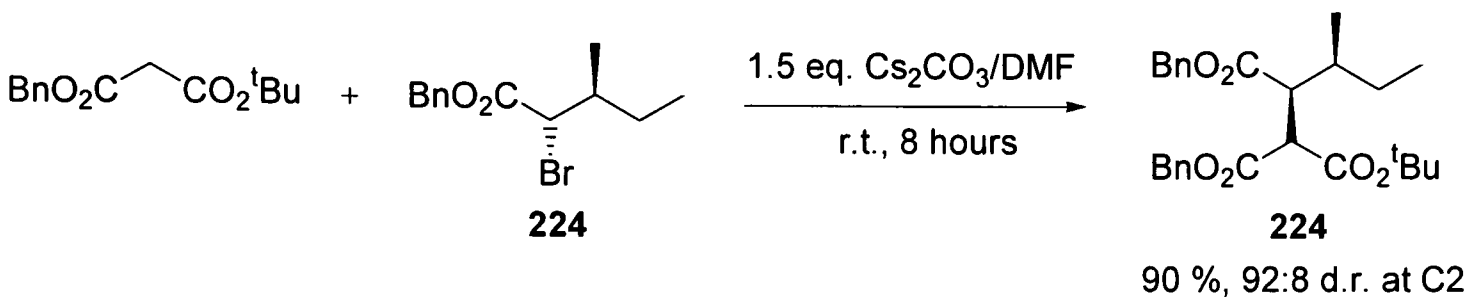
We began investigating the malonate substitution by applying the same conditions reported previously (see previous Scheme 156),[117] but in our case we observed a much slower reaction. This is presumably because of increased steric hindrance, as the reaction centre is now adjacent to a secondary carbon stereocentre. Using 1.0 eq. K^{t}BuO/DMF **225** was synthesised in only 50 % (^{1}H NMR yield) after 40 hours at 0 °C, whereas even poorer conversions were obtained using 1.0 eq. NaH/DMF (30 % ^{1}H NMR yield after 40 hours at 0 °C) (Scheme 161). In addition, the rate of alkylation appeared to rapidly decrease over time, meaning that significant conversions were never achieved even after 7 days. It was plausible that this rate decrease was due to competitive deprotonation of the product by the reactant, so we attempted to increase the amount of malonate anion using both an excess of benzyl *tert*-butyl malonate (but later found separation to be difficult), and also an excess of K^{t}BuO, but this resulted in complete epimerisation of **225**.



Scheme 161

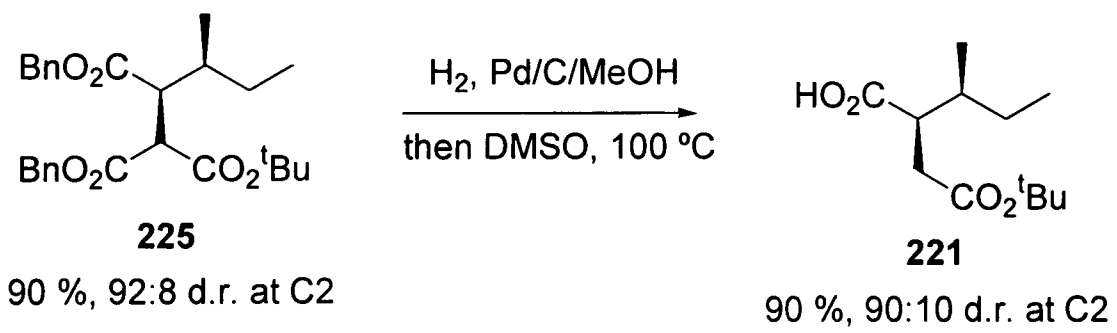
Since we had already demonstrated that cesium carbonate was effective at deprotonating triethylphosphonoacetate (of similar acidity to the malonate, section 2.3.5), and compatible with the α-stereocentre of **224**, we planned a Cs_2CO_3-promoted malonate substitution. To our delight, treatment of an equimolar ratio of

224/malonate with 1.5 eq. Cs_2CO_3/DMF resulted in complete alkylation after just eight hours at room temperature, affording malonate **225** in 90 % yield and 92:8 C2-ratio (Scheme 162). We also experimented with lower temperatures and a one-pot reaction (from acid **58**), but both of these modifications extended the reaction time and consequently increased epimerisation.



Scheme 162

Our next step was the double-hydrogenolysis/decarboxylation reaction sequence. Hydrogenolysis occurred smoothly using H_2, Pd/C in MeOH, but under these conditions no decarboxylation was observed. We next attempted decarboxylation under a range of conditions (including amine[119] and Cu(I)-catalysis[121]), but all efforts were unsuccessful either due to substantial α-epimerisation or low conversions. We eventually achieved clean decarboxylation by heating the diacid as a solution in DMSO (100 °C, 1 hour), furnishing succinate **221** in 90 % yield (2 steps) and 90:10 C2-ratio (Scheme 163). Intercepting **221** now completes our diastereoselective route to β-lactone **223** in five steps from L-isoleucine.

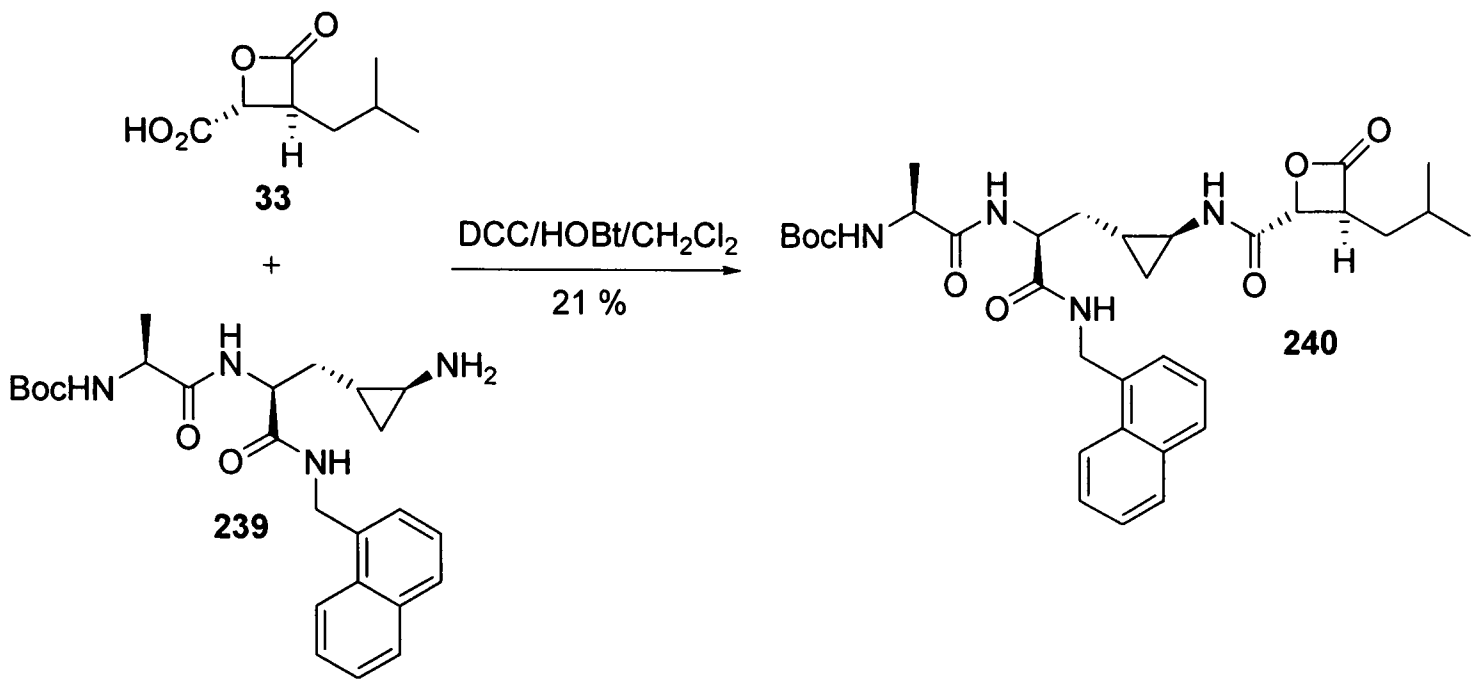


Scheme 163

2.10 Final coupling – synthesis of *N*-CBz-belactosin A

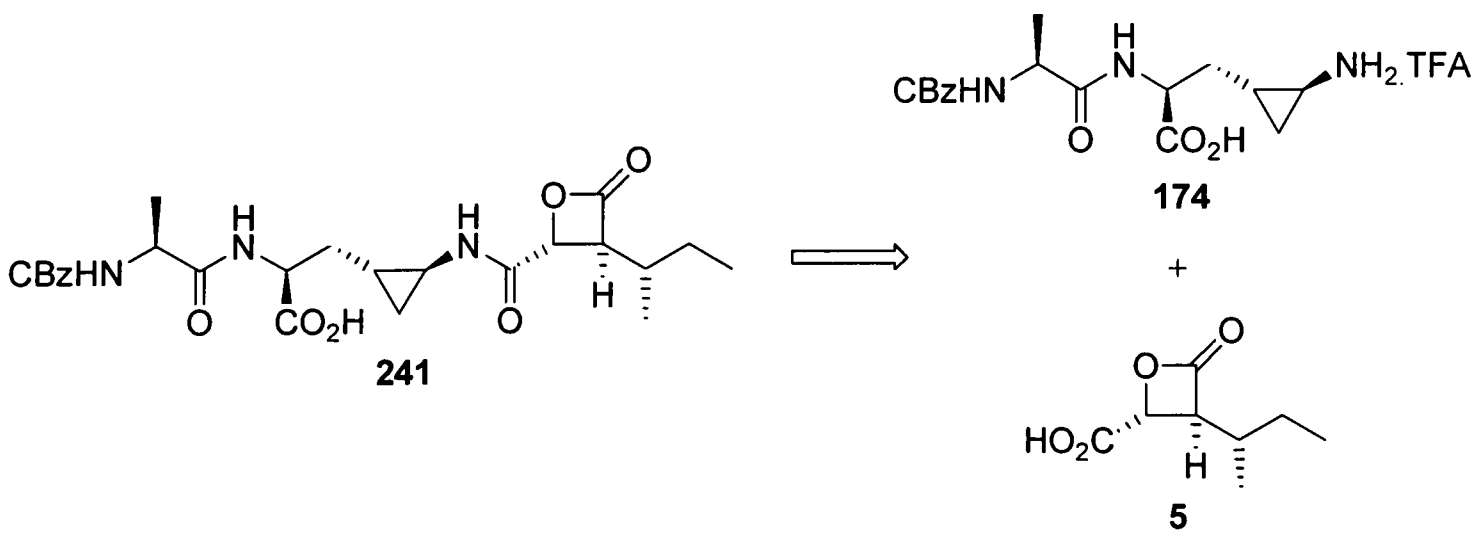
With both fragments **174** and **5** in hand, we were in a position to attempt the crucial amino acid coupling to assemble the framework of the natural product. A similar

coupling was reported in the SAR patent filed by Kyowa Hakko Kogyo Co. Ltd.,[7] but here derivative **240** was only isolated in 21 % yield, which no doubt reflects the difficulty of this coupling (Scheme 164).



Scheme 164

Further complexity exists with our anticipated coupling of **174** and **5**, since the *N*-Ala-AcpAla component **174** possesses both amine and acid functionality (Scheme 165). Throughout this project we have endeavoured to follow the most concise route to targets, so in this case we decided against additional protection/deprotection steps, meaning a selective peptide coupling was required.

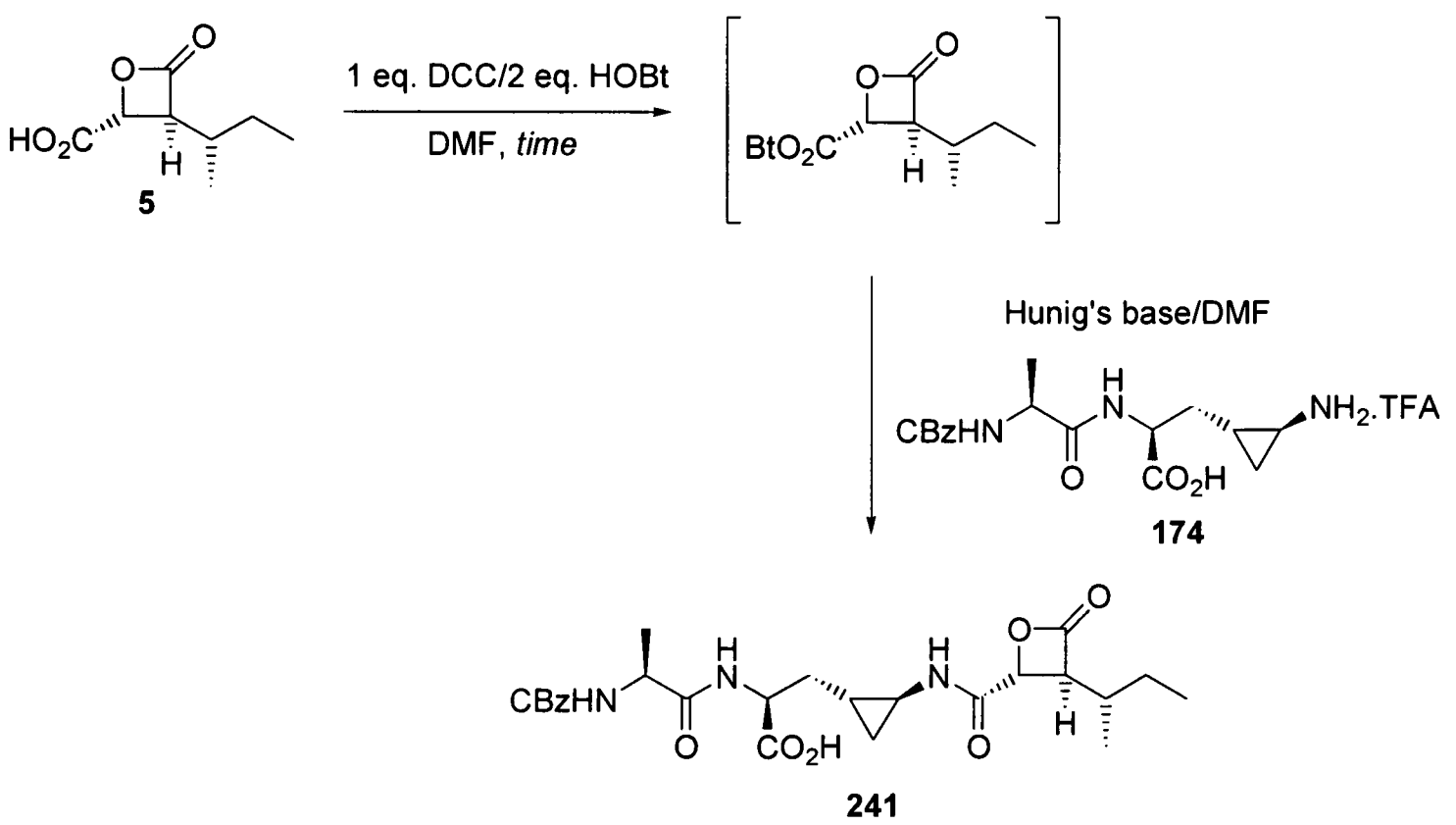


Scheme 165

Selective peptide couplings rely on the greater nucleophilicity of amine *vs* acid residues, such that upon addition to an activated partner usually only amide formation

occurs. This is generally achieved by preforming mixed anhydrides. However, we found it difficult to achieve significant activation of **5** using either isobutyl chloroformate,[122] or using Boc_2O/DMAP/pyridine conditions developed by Datta.[123]

An alternative was to attempt selective carbodiimide-activation,[124] again using DMF as the reaction solvent to minimise epimerisation. After a series of trial reactions we attempted the preactivation of **5** using 1 eq. DCC and 2 eq. HOBt over a range of time periods, followed by addition of this solution to a second mixture of **174** and Hunig's base in DMF. Products were purified directly by flash column chromatography, to avoid loss of material associated with an aqueous workup, and the results of this work are shown below (Scheme 166, Table 9).

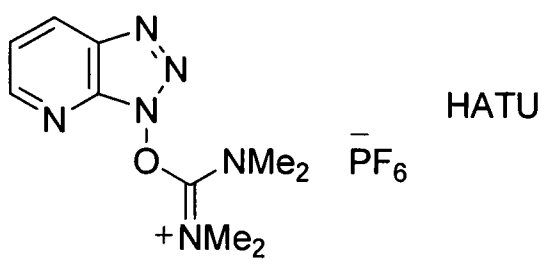


Scheme 166

Entry	Activation time	Yield/% **241**
1	2h	0
2	30 min	25
3	5 min	33

Table 9

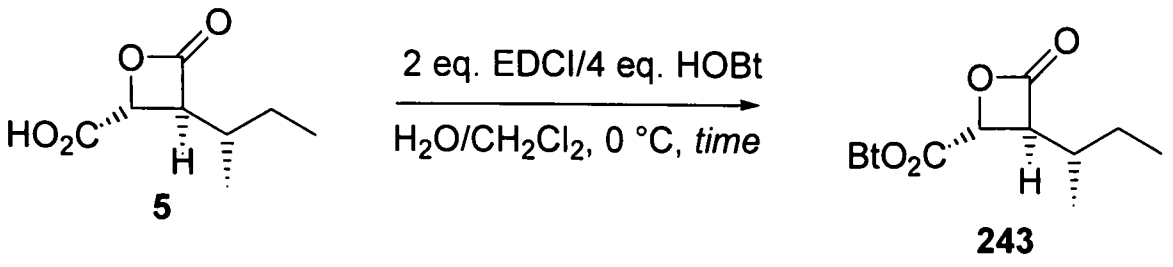
From this table it is evident that the highest yield was achieved after only 5 minutes of activation time, giving *N*-CBz-belactosin A **241** in 33 % yield as a single diastereomer after purification (entry 3). Reduced yields were obtained following longer activation times, probably because side-reactions such as acyl-transfer generated unreactive amides.[87] Although this yield was an improvement to the simpler patent coupling, we were not satisfied with the conversion. From analysis of the crude ^{1}H NMR, the low yield of **241** appeared to be due to incomplete activation of acid **5**, but in this case use of excess DCC was not possible since any unreacted activating agent was likely to consume coupling partner **174**. To promote activation, we initially tested newer coupling reagents such the aminium salt HATU **242** (reportedly one of the most reactive agents),[87] but in our hands the coupling conversion was not improved (Figure 34).



242

Figure 34

An alternative idea came from work originally by Nozaki,[125] then later developed by Grabowski and co-workers at Merck.[126] Here, EDCI-promoted amino acid couplings performed under biphasic H_2O/CH_2Cl_2 (0 °C) conditions were shown to proceed with reduced racemisation, probably because hydrogen-bonding interactions at the interphase boundary inhibited intramolecular proton transfer.[126] We were attracted to this procedure not only due to epimerisation suppression, but also because the conditions appeared to provide the opportunity to achieve high levels of OBt-activation. We aimed to use an excess of both (water-soluble) EDCI and (water-soluble) HOBt to promote activation of **5**, then transfer only the organic phase to a second solution of **174**/Hunig's base. In theory, only the activated OBt-ester **243** would be organic-soluble, so excess coupling reagents/additives would remain in the aqueous phase. We began this work by investigating the optimum activation time, and the results of these investigations are shown below (Scheme 167. Table 10).



Scheme 167

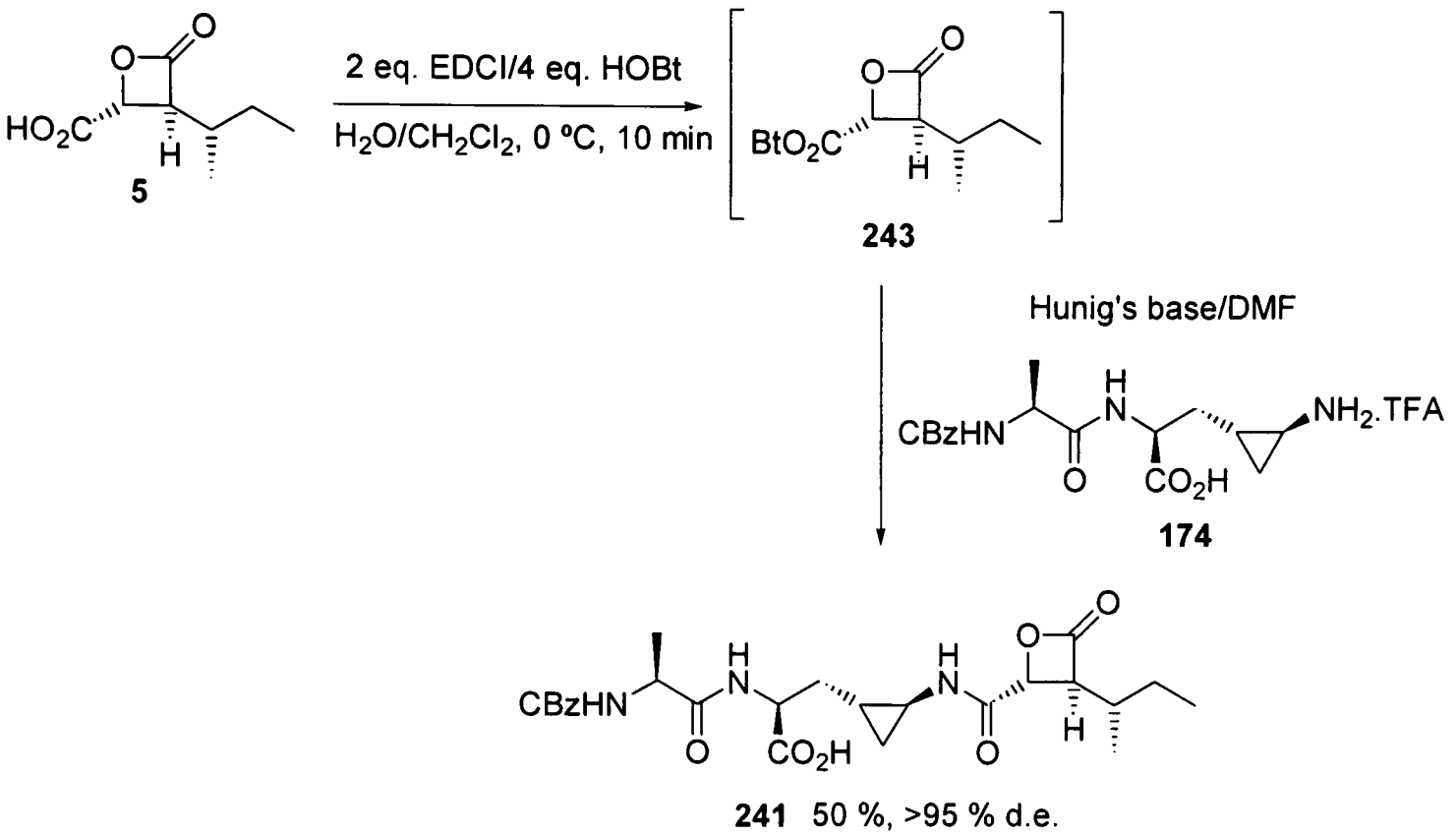
Entry	Time	% **5***	% **243***
1	3h	86	0
2	1h	31	24
3	30min	27	38
4	15min	21	45
5	**10min**	**8**	**65**
6	7min	19	49

*^{1}H NMR yield of **5** and **243** components in the organic phase

Table 10

Entries 1-5 suggest that shorter reaction times result in greater activation. We explain this by initial rapid activation of **5**, with subsequent hydrolysis of the product after complete consumption of EDCI. In addition, entries 5 and 6 reveal that maximum activation requires rapid stirring for 10 minutes at 0 °C.

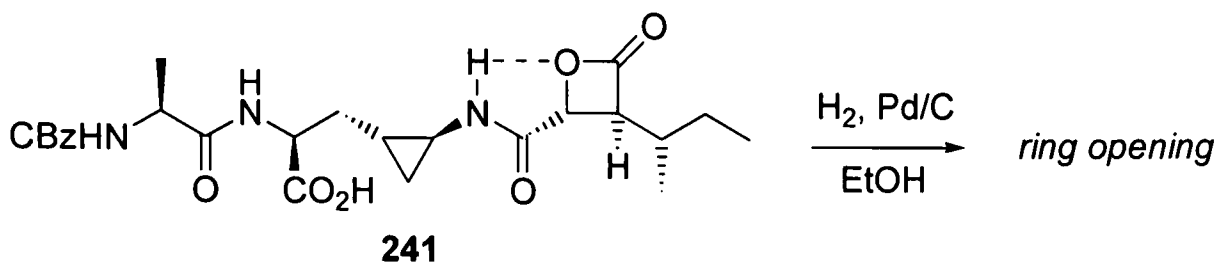
Using this optimised procedure, we then performed the coupling of **5** and **174**, and were delighted to see that the overall yield of **241** was substantially increased to 50 % as a single diastereomer after purification. We believe that this method of activation may also be of use to other challenging examples of selective amino acid couplings.



Scheme 168

2.11 Deprotection of CBz – first total synthesis of (+)-belactosin A

CBz-deprotection is typically achieved by hydrogenolysis, using an alcohol solvent to maximise hydrogen absorption and therefore increase reaction rates. We were aware that de Meijere had reported partial cyclopropane reduction during the hydrogenation of *N*-Boc-NcpAla **53** (section 1.4.3),[19] but in our case we hoped that steric hindrance may prevent this. The second issue to consider was that of β-lactone ring-opening, but again literature precedent suggested this should not be a problem since benzyl-protected β-lactone **37** was successfully hydrogenated under H_2, Pd/C in EtOH conditions (section 1.3.2).[7] On this basis we subjected *N*-CBz-belactosin A **241** to H_2, Pd/C/EtOH conditions, and after 20 hours at room temperature found all reactant to be consumed. Unfortunately, ^{1}H NMR analysis revealed a complex mixture of products which did appear to include significant ring-opening. This result was surprising, but is possibly explained by hydrogen-bond activation of the β-lactone, only possible after coupling to cyclopropylamine **174** (Scheme 169).

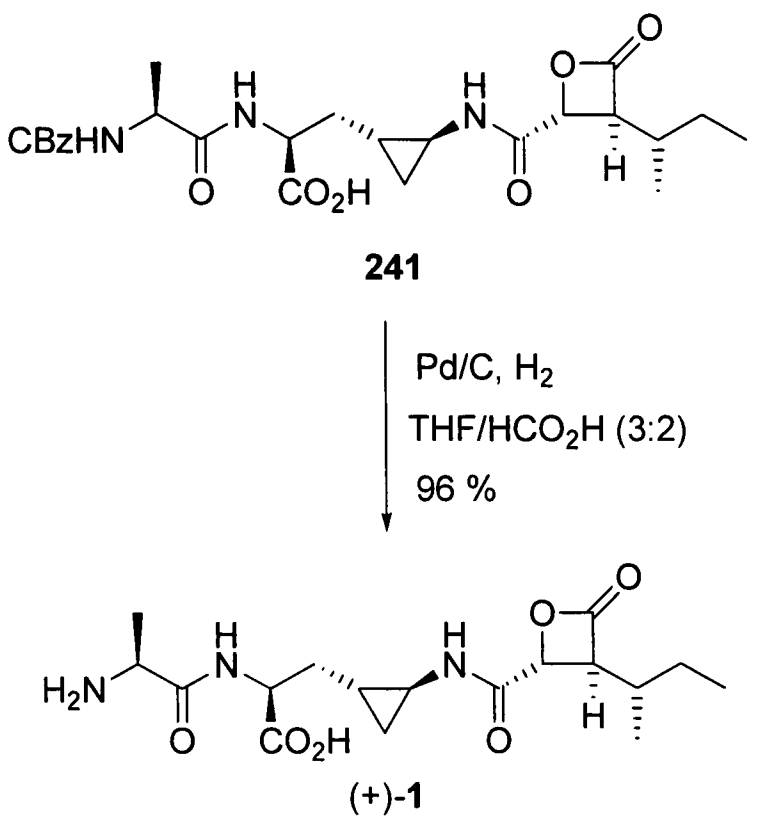


241

Scheme 169

As a result, we attempted the same reaction in non-nucleophilic solvents (THF and ethyl acetate) but in both cases no hydrogenolysis was observed. In contrast, deprotection was achieved using Pearlman's catalyst (in THF), but this was also accompanied by substantial decomposition. After further experimentation, successful deprotection was achieved by hydrogenolysis using H_2, Pd/C in THF under TFA activation. This however gave the corresponding TFA salt of belactosin A (+)-**1**, and although this material could be taken to its isoelectric pH (as determined by ^{1}H NMR spectroscopy using 5% $NaHCO_3/D_2O$), subsequent purification to remove sodium trifluoroacetate proved troublesome. Further consideration suggested that the free amino acid could be generated directly if we used a volatile acid catalyst with a higher pKa than that of the carboxylate group in (+)-**1**, and to our delight, the first total synthesis of (+)-belactosin A was achieved using H_2 and Pd/C in a THF/HCO_2H (3:2 ratio) mixed solvent, affording (+)-**1** in 96% yield (Scheme 170).

The synthetic sample (m.p. 186-187□C, $[\alpha]_D^{21}$ +4.8 (*c* 0.84, H_2O) (lit. m.p 184-185□C, $[\alpha]_D^{27}$ +4.8 (*c* 0.37, H_2O)[1]) displayed satisfactory HRMS data, and its TLC R_f value (0.5, butanol:acetic acid:water (71:14:15 v/v/v)), ^{1}H NMR (Figure 35) and ^{13}C NMR spectra were identical to those reported for the natural product (Figure 36).[1]


CBzHN
H
N
O
CO2H
H
N
O
O
O
H
241
Pd/C, H2
THF/HCO2H (3:2)
96 %
H2N
H
N
O
CO2H
H
N
O
O
O
H
(+)-1

Scheme 170

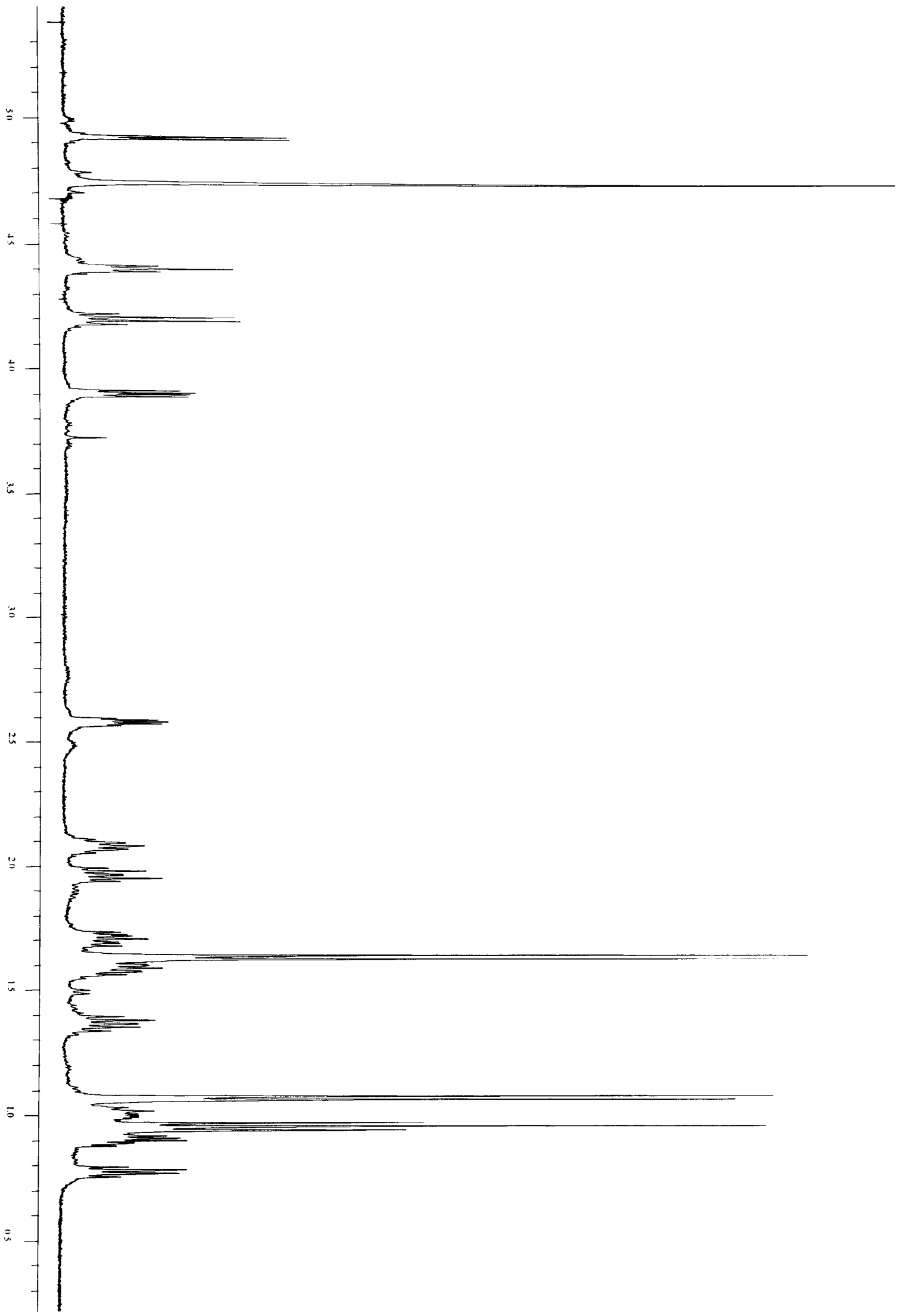


Figure 35: 500 MHz (D_2O) ^1H NMR of synthetic (+)-belactosin A

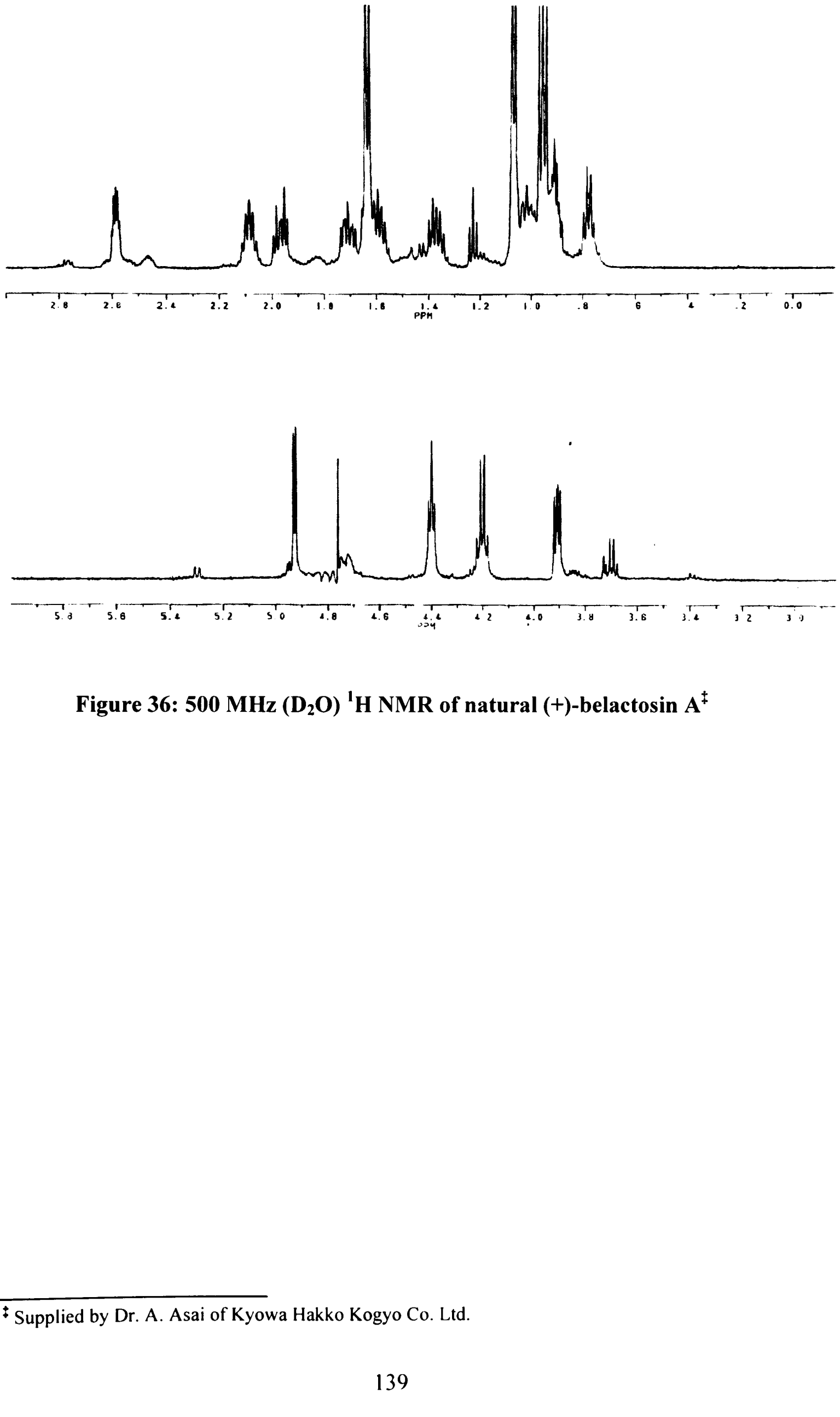


Figure 36: 500 MHz (D_2O) ^1H NMR of natural (+)-belactosin A‡

‡ Supplied by Dr. A. Asai of Kyowa Hakko Kogyo Co. Ltd.

CHAPTER 3

Conclusion

Chapter 3: Conclusion

3.1 Synopsis of results

This thesis presents the first total synthesis of the important proteasome inhibitor (+)-belactosin A (+)-**1**. The synthesis of (+)-**1** required substantial reaction development and optimisation for many of the key steps, and provides the target in a concise and elegant fashion. The key features of the synthesis are shown below (Figure 37).

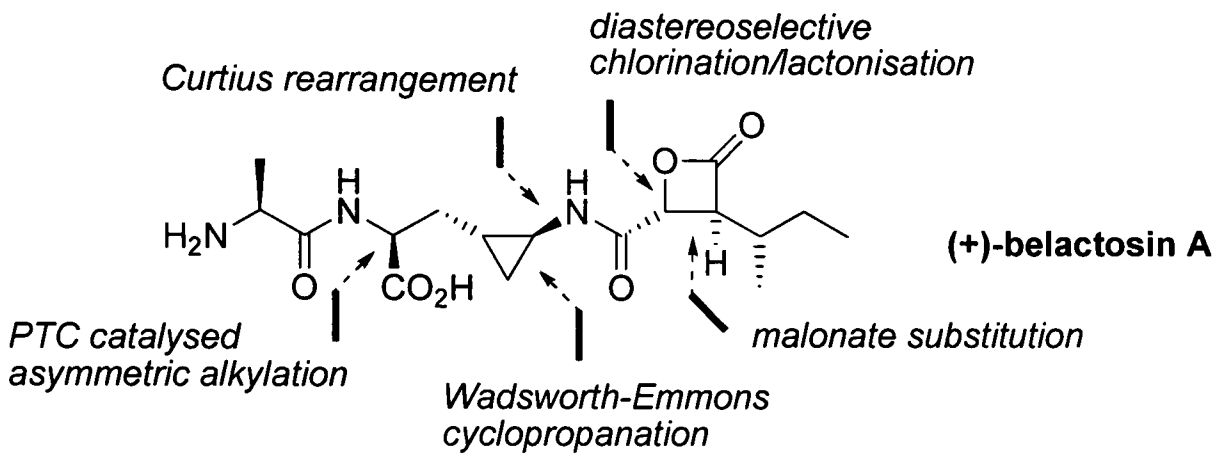
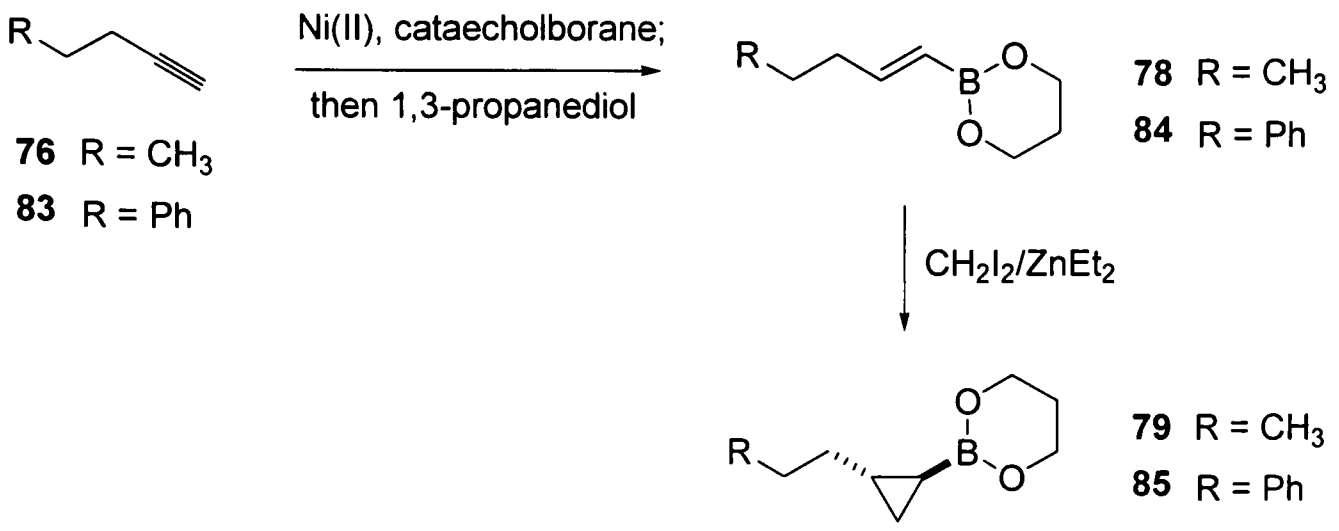


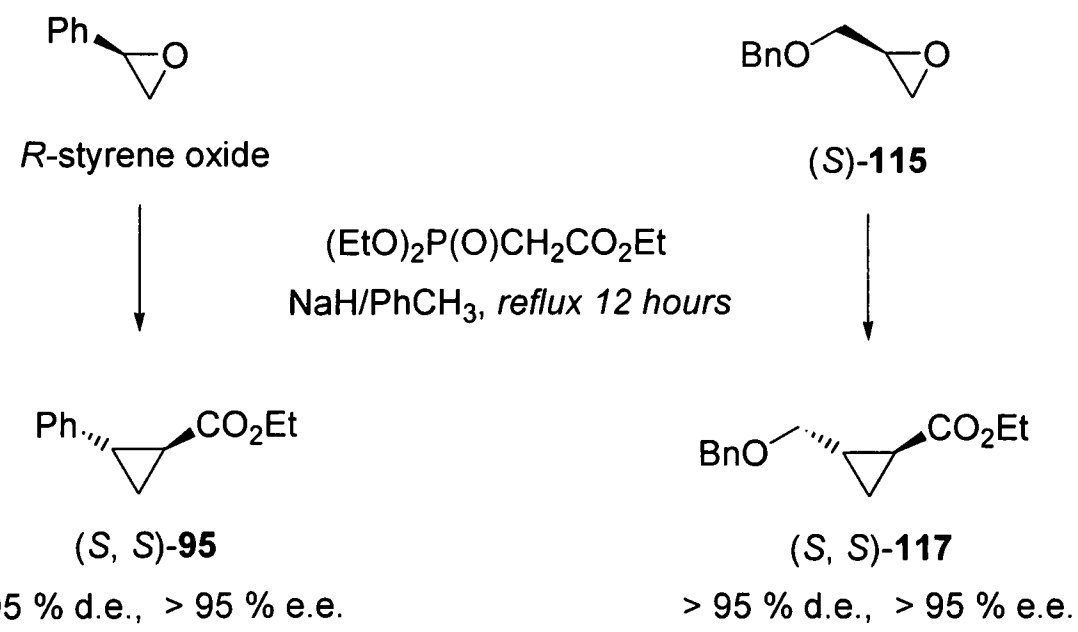
Figure 37

Section 2.2 described our efforts towards the amination of cyclopropyl boronic esters. En route to this attempted amination, two model cyclopropanes **79** and **85** were synthesised from their corresponding alkynes **76** and **83**, using a Ni(II)-catalysed hydroboration/transesterification reaction then a Simmons-Smith cyclopropanation (Scheme 171). We attempted amination of both **79** and **85** under two sets of conditions, but unfortunately both were unsuccessful.



Scheme 171

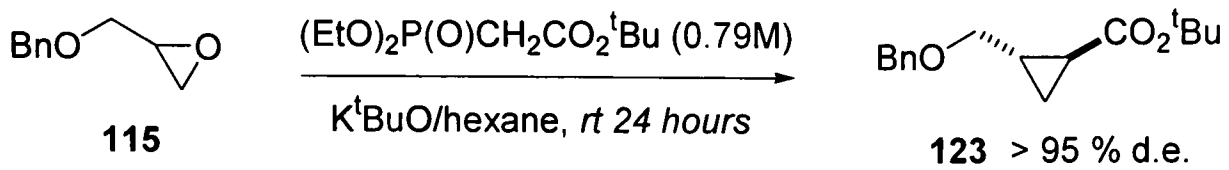
The alternative strategy of epoxide cyclopropanation was discussed in section 2.3. We established for the first time that the Wadsworth-Emmons cyclopropanation (using triethylphophonoacetate) was stereospecific for both styrene oxide and benzyl glycidyl ether, and that to convert alkyl-based epoxides to *trans*-cyclopropanes an ester-stabilised phosphonate must be used (Scheme 172). Substantial optimisation was required to achieve respectable cyclopropane yields, during which side-products where identified that appeared to confirm the proposed mechanism.



Scheme 172

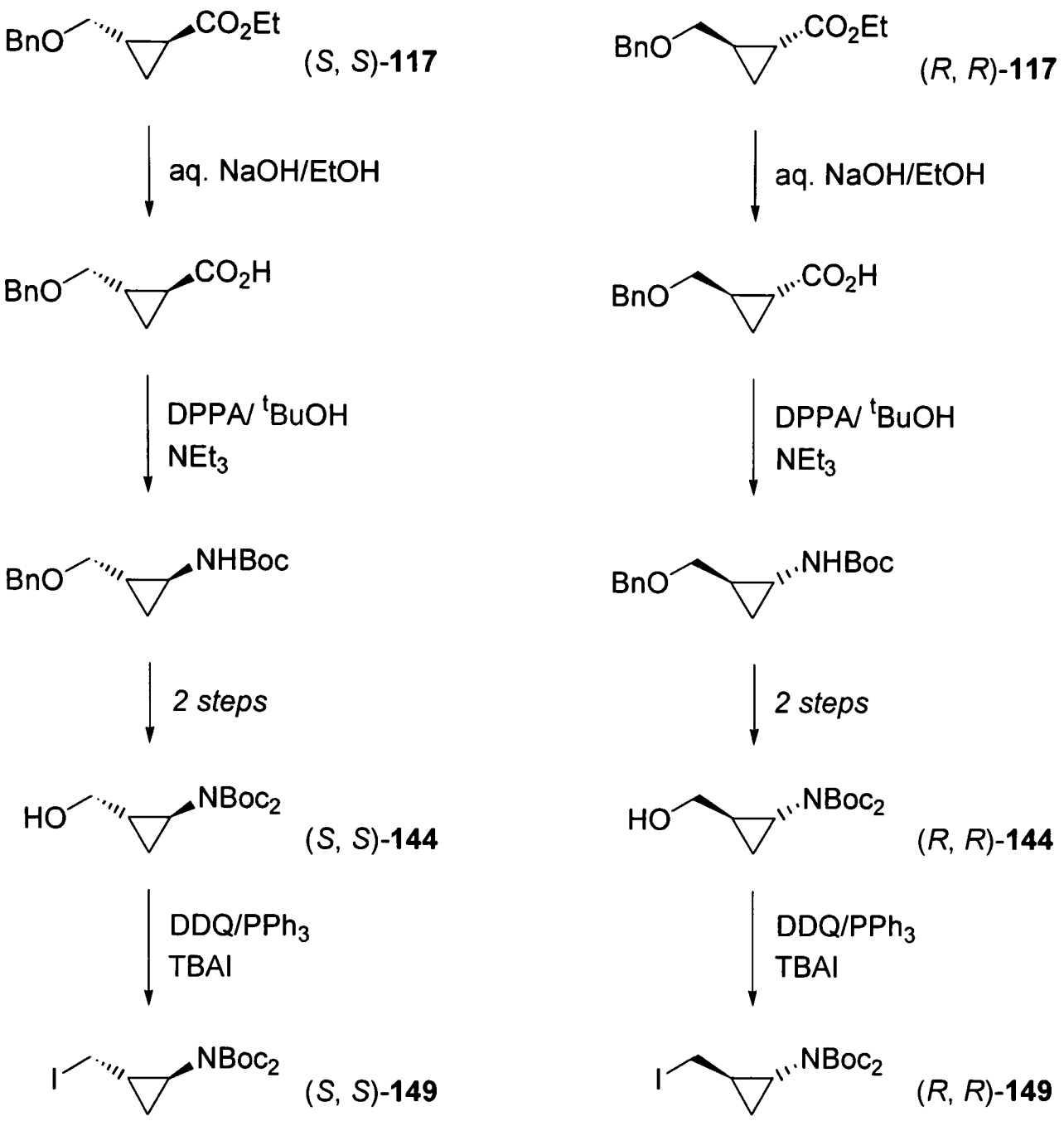
Additionally, we discovered that the more lipophilic *tert*-butyl phosphonate **122** was a much more active cyclopropanating agent than triethylphosphonoacetate, and furthermore, this then led to the first room temperature epoxide cyclopropanation (Scheme 173). We also made efforts to carry out both a direct aminocyclopropanation

and asymmetric Wadsworth-Emmons cyclopropanation (*via* kinetic resolution), but both of these attempts were ultimately unsuccessful.



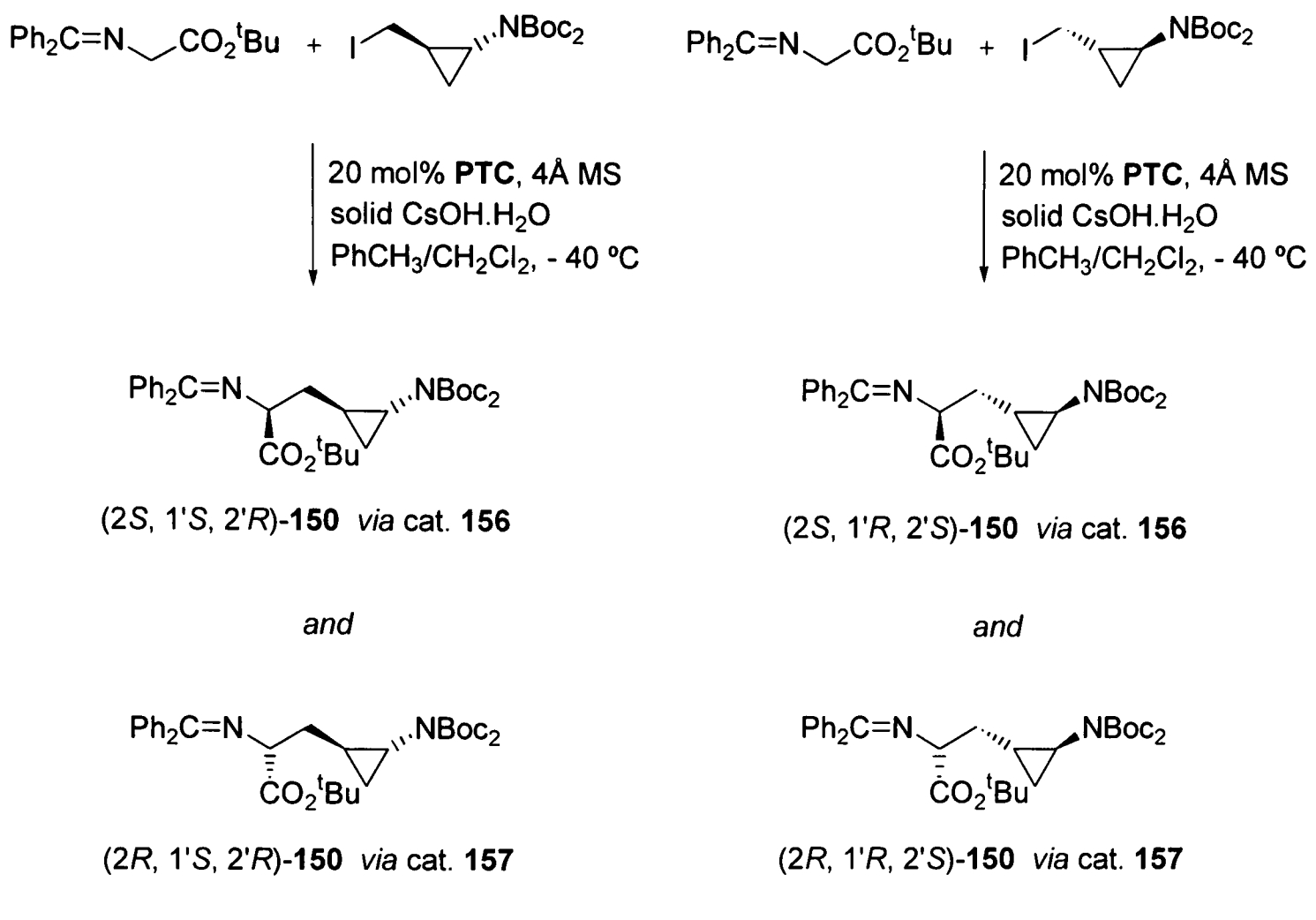
Scheme 173

Section 2.4 summarised the chemistry used to transform cyclopropyl ethyl ester **117** into the key aminocyclopropyl electrophile. Cyclopropane **117** was deprotected (without epimerisation) under standard basic conditions, and the resulting acid was then aminated by Curtius rearrangement. Following amine-protection and benzyl ether deprotection, we briefly attempted a one-pot mesylation/glycine-alkylation of alcohol **144**, but despite achieving excellent levels of mesylation the resulting cyclopropyl mesylate was observed to be inert to glycine substitution. Finally, cyclopropyl iodide **149** was successfully synthesised using a new and mild iodination prodedure (Scheme 174).



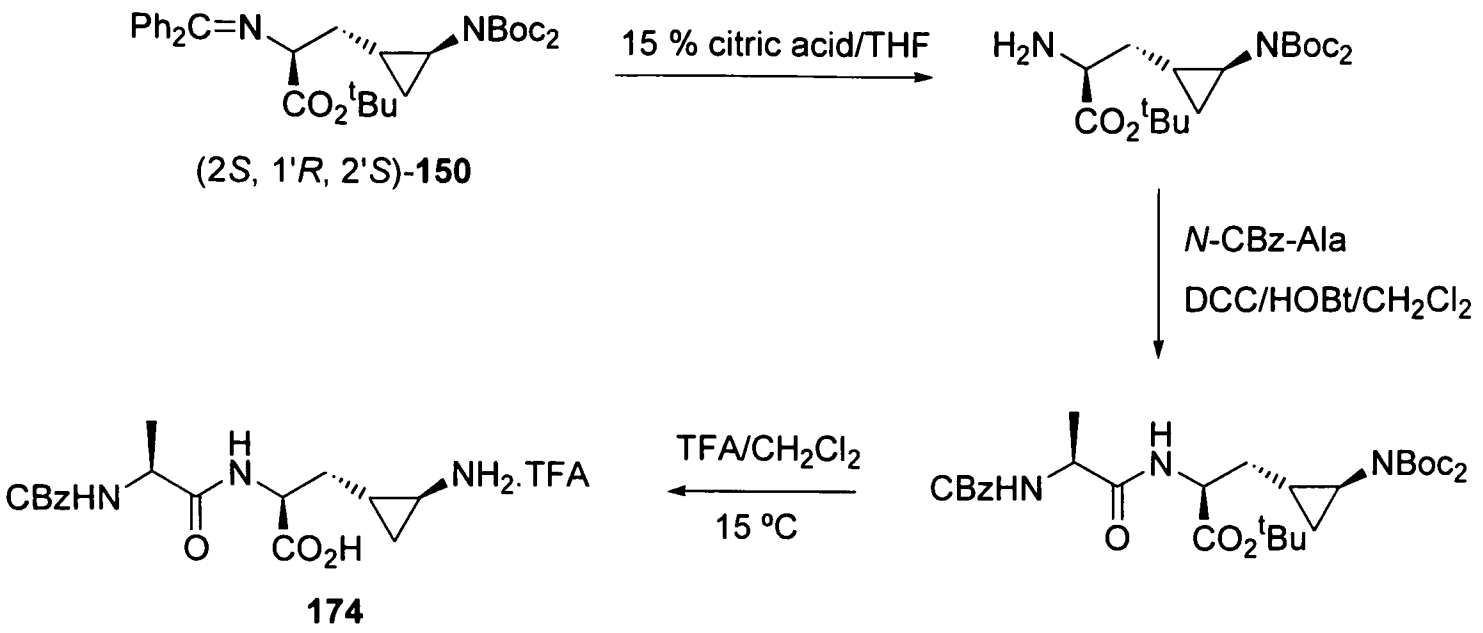
Scheme 174

Section 2.5 describes the optimisation required to achieve the stereoselective glycine alkylation of both iodide enantiomers (*S*, *S*)-**149** and (*R*, *R*)-**149**, using both phase-transfer catalysts **156** and **157**, to successfully generate all four *trans*-AcpAla stereoisomers in excellent diastereoselectivity (Scheme 175). We believe that this work constitutes an impressive application of this reaction.



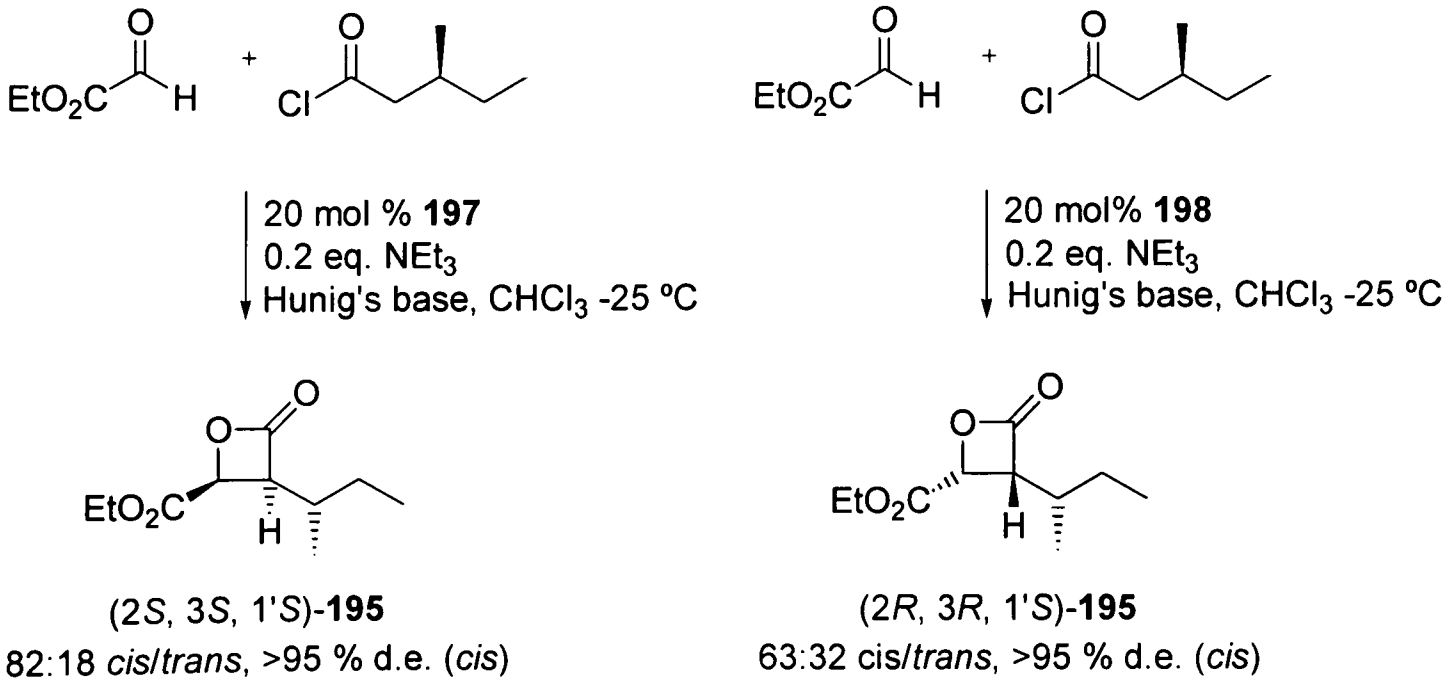
Scheme 175

An alternative synthesis of (2*S*, 1'*S*, 2'*R*)-**150** and (2*R*, 1'*R*, 2'*S*)-**150**, *via* a direct cyclopropanation of their corresponding epoxy amino acid, was also briefly investigated (section 2.6), but the Wadsworth-Emmons cyclopropanation of these much more demanding substrates failed. We then continued with the total synthesis of (+)-**1** by deprotection of the natural AcpAla isomer (2*S*, 1'*R*, 2'*S*)-**150**, followed by coupling with *N*-CBz-Ala using DCC/HOBt in DMF to avoid epimerisation. Cleavage of all acid-labile protecting groups was then achieved under acidic conditions to afford **174** (section 2.7) (Scheme 176).



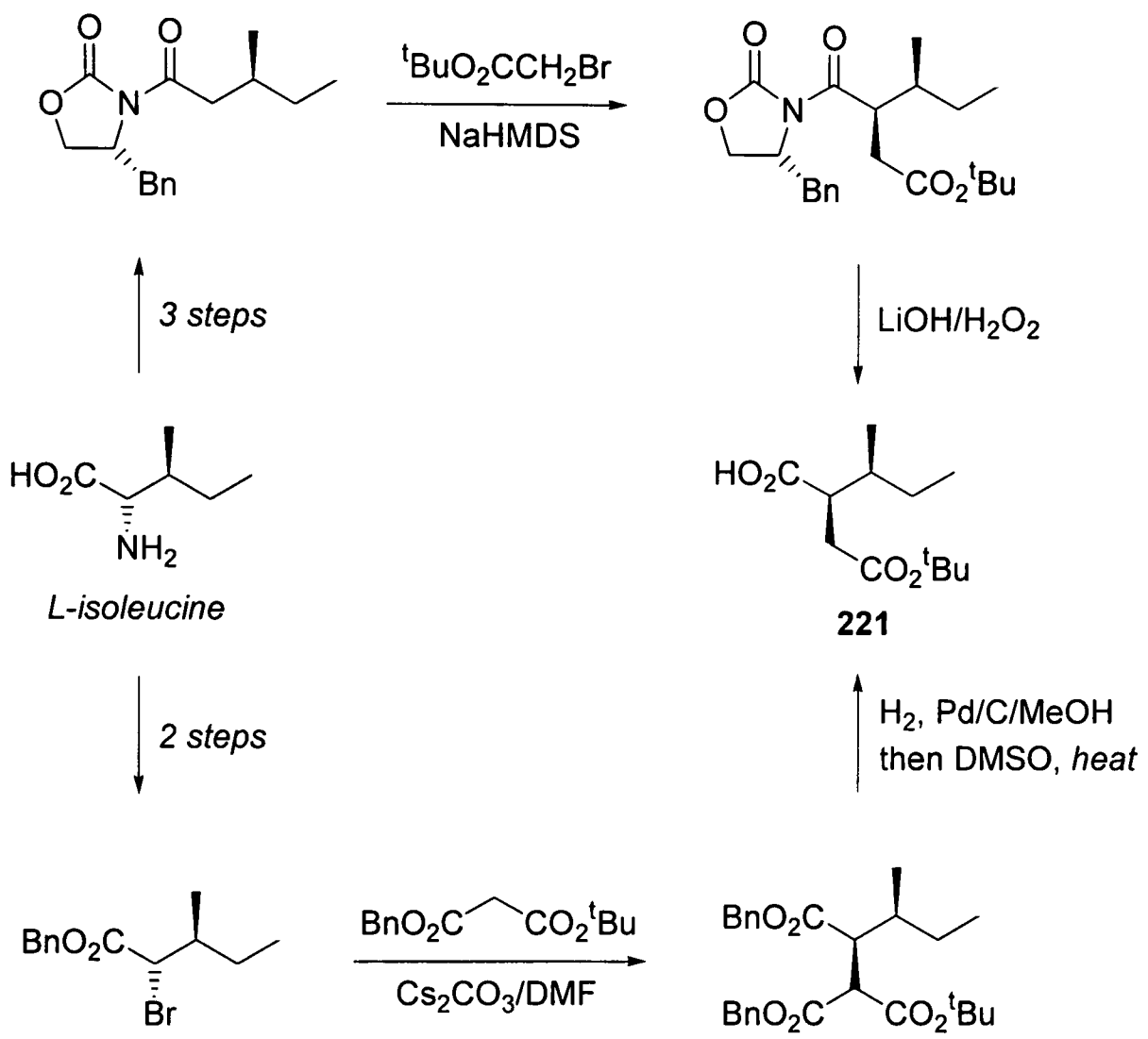
Scheme 176

Section 2.8 desribed our efforts to develop a modified Wynberg β-lactonisation reaction, using ethyl glyoxyate as the activated aldehyde partner. Substantial reaction development was required to synthesise the desired β-lactone using triethylamine catalysis, then even further optimisation to achieve asymmetric β-lactonisation using cinchona-alkaloid catalysis. In contrast to what has previously been shown for chloral-based β-lactonisation, this reaction was shown to be consistently *cis*-selective, and hence was not appropriate for synthesising the β-lactone moiety of (+)-**1**. Nevertheless, we did demonstrate complete catalyst control in synthesis of (2*S*, 3*S*, 1′*S*)-**195** and (2*R*, 3*R*, 1′*S*)-**195** (Scheme 177).



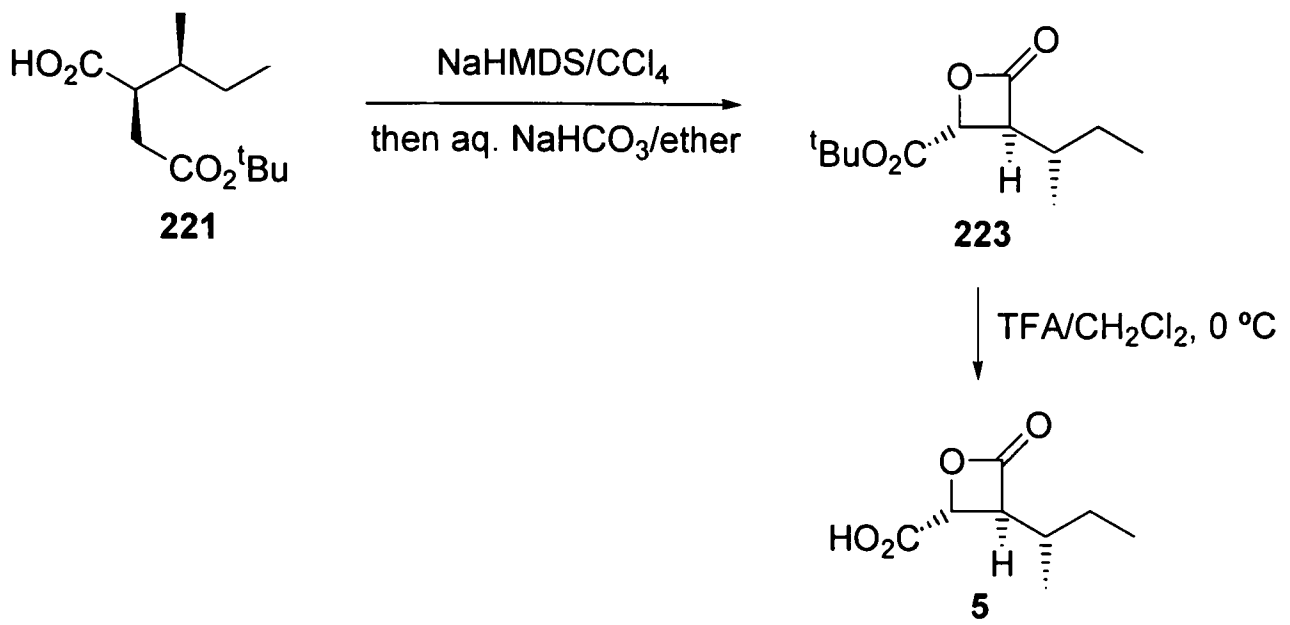
Scheme 177

The natural *trans*-β-lactone was eventually synthesised through the cyclisation of an enantiopure synthon (Section 2.9). The succinate precursor **221** was synthesised *via* both a conventional route based on Evans alkylation chemistry, then by a more impressive, fully diastereoselective route from L-isoleucine - using a malonate S_N2 substitution as the key step (Scheme 178).



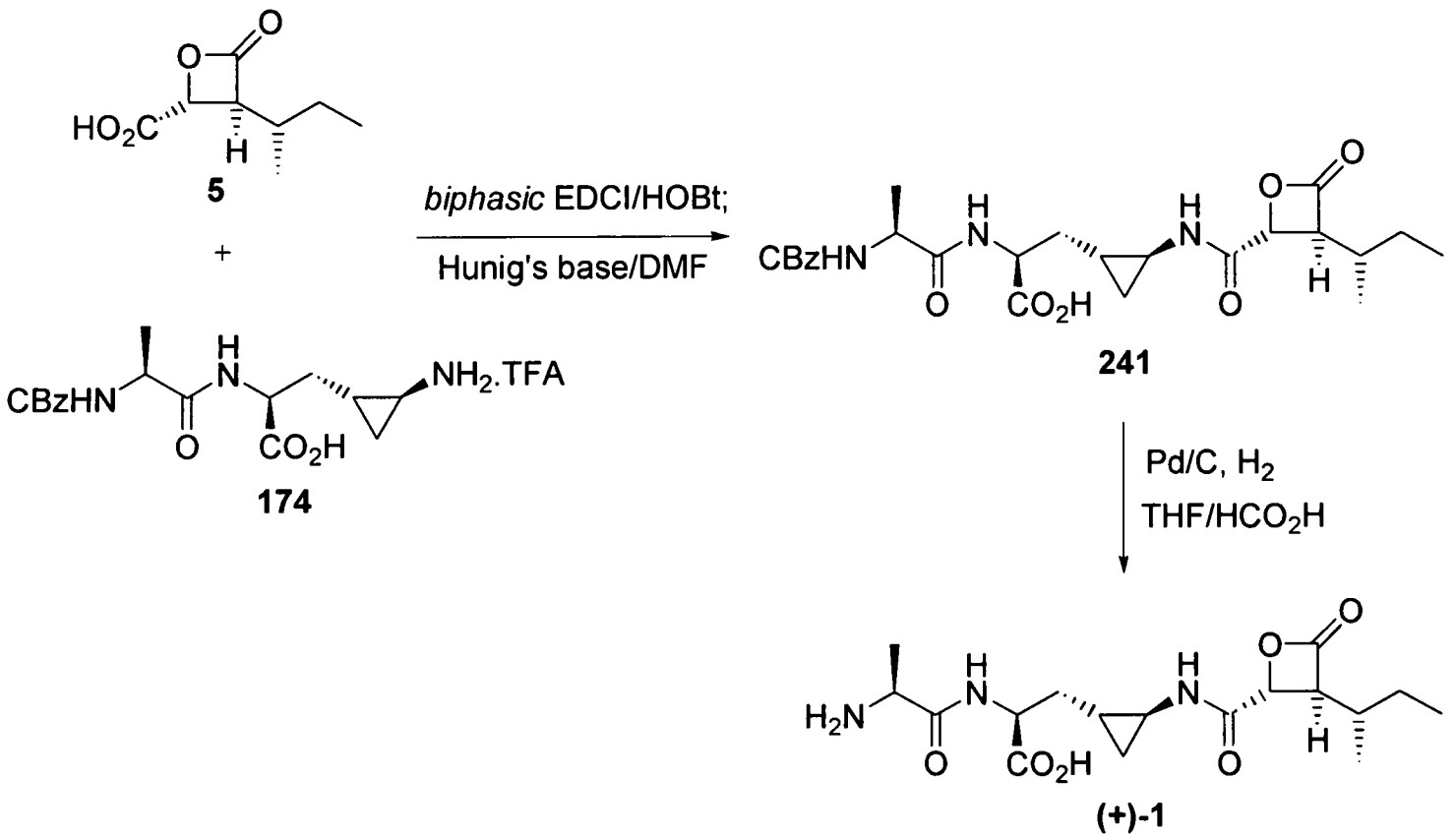
Scheme 178

Succinate **121** was then successfully chlorinated in high diastereoselectivity and cyclised under biphasic conditions, to afford (natural configuration) β-lactone **223** (Scheme 179). Although it was our aim to also synthesise the alternative *trans*-β-lactone stereoisomer, this was not achieved due to time constraints. However, synthesis of non-natural *trans*-β-lactone would presumably be successful following the Evans alkylation route using the alternative (2*S*)-benzyl-2-oxazolidinone auxilliary. Finally, TFA-mediated deprotection of **223** then yielded β-lactone carboxylic acid **5** (Scheme 179).



Scheme 179

Section 2.10 described our work towards the selective coupling of cyclopropylamine **174** and β-lactone **5**. In order to avoid additional protection/deprotection steps we successfully developed a new amino acid coupling procedure, which furnished peptide **241** in high yield. Section 2.11 relates to the final hydrogenolysis of CBz-belactosin A **241**, which was eventually achieved using formic acid-activation, to complete the first total synthesis of (+)-belactosin A (+)-**1** (Scheme 180).



Scheme 180

CHAPTER 4

Experimental

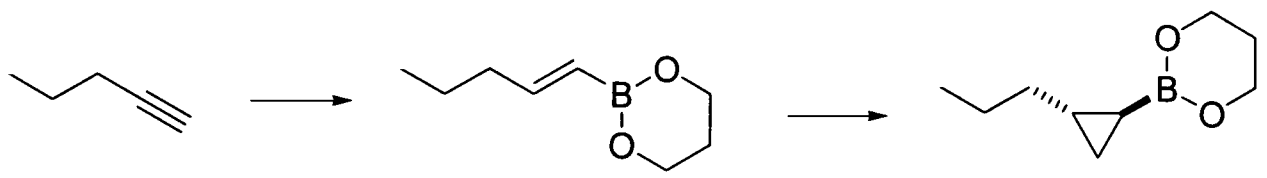
Chapter 4: Experimental

4.1 General procedures

All reactions were carried out under a positive pressure of N_2 unless otherwise stated. Solvents were freshly distilled before use from sodium/benzophenone (diethyl ether, THF) or CaH_2 (dichloromethane). Liquid reagents were distilled prior to use, while commercial solids were used as supplied. Solutions of butyllithium were titrated against diphenylacetic acid before use. NMR analyses were performed on Bruker 250, 400 or 500 MHz instruments in *d*-chloroform (unless otherwise stated); chemical shifts are quoted in ppm relative to TMS (as referenced to chloroform), with coupling constants quoted in Hz. Infrared analyses (in cm^{-1}) were recorded on an Agilent 5190D chromatograph and a Mattson Satellite FTIR spectrometer respectively. Optical rotations were measured on an Optical Activity Autopolarimeter. Mass spectrometry was carried out by CI using ammonia (unless otherwise stated).

4.2 Compound syntheses

2-((1*S, 2*S**)-2-Propylcyclopropyl)-1,3,2-dioxaborinane (79)**

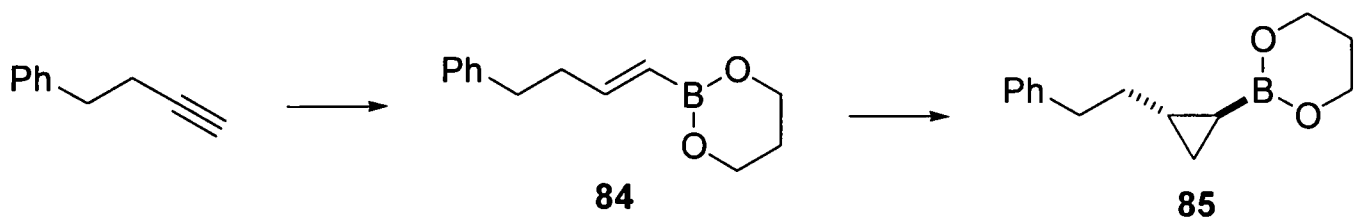


78 **79**

To a solution of catecholborane (20.35 ml, 20.35 mmol, 1 M solution in THF) at room temperature was added 1-pentyne **76** (2.00 ml, 20.35 mmol) dropwise over 5 minutes. To this mixture was then added 1,3-bis[(diphenylphosphino)propane]nickel dichloride (0.22 g, 0.41 mmol) in one portion, followed by stirring at room temperature (water bath) for 30 minutes, then addition of 1,3-propanediol (1.62 ml, 22.39 mmol). After stirring for 45 minutes solvents were removed *in vacuo*, and the crude product was then redissolved acetonitrile (20 ml) and extracted with petrol (10 x 20 ml). Petrol fractions were combined, followed by removal of solvents *in vacuo* then Kugelrohr distillation to afford vinyl boronic ester **78** (2.51 g, 66 %), as a colourless oil.

To a solution of diiodomethane (2.35 ml, 15.28 mmol) in CH_2Cl_2 (25 ml) was added diethylzinc (7.64 ml, 7.64 mmol, 1 M solution in hexanes) dropwise at 0 °C. After 10 minutes vinylboronic ester **78** (1.04 g, 5.53 mmol) was added as a solution in CH_2Cl_2 (6 ml), followed by stirring for 5 minutes at 0 °C then overnight at room temperature. Solvents were removed *in vacuo* and the crude product was purified by flash column chromatography (4 petrol : 1 ether eluant, 2 % triethylamine base-wash) to afford the *title compound* **79** (0.53 g, 62 %) as a colourless oil; ν_{max}/cm^{-1}(film) 3066, 2995, 2956, 2893, 1483, 1419, 1337, 1276, 1226, 1191; δ_H (250 MHz, $CDCl_3$) 3.94-3.90 (4H, m, OCH_2), 1.93-1.84 (2H, m, CH_2), 1.43-1.10 (4H, m, CH_2), 0.95-0.75 (4H, m, CH_3, RC*H*(cyclopropyl)), 0.54 (1H, ddd, *J*7.6, 6.0, 3.0, C*H*$_2$(cyclopropyl)), 0.26 (1H, ddd, *J*9.2, 5.0, 3.0, C*H*$_2$(cyclopropyl)), -0.60 (1H, app dt, *J*9.2, 6.0, CHB); δ_C (62 MHz, $CDCl_3$) 61.6, (CH_2), 37.5 (CH_2), 27.4 (CH_2), 22.8 (CH_2), 17.5 (CH), 13.9 (CH_3), 10.9 (CH_2), one CB missing; *m/z* (CI, NH_3) 186 $[M + NH_4]^+$, Found : $[M + NH_4]^+$, 186.1668. $C_9H_{21}BNO_2$ requires : 186.1665.

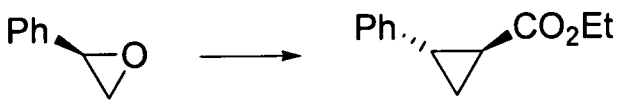
2-((1*S**, 2*S**)-2-Phenethylcyclopropyl)-1,3,2-dioxaborinane (85)



To a solution of catecholborane (6.00 ml, 6.00 mmol, 1 M solution in THF) at room temperature was added 4-phenyl-1-butyne **83** (0.42 ml, 6.00 mmol) dropwise over 5 minutes. To this mixture was then added 1,3-bis[(diphenylphosphino)propane]nickel dichloride (65 mg, 0.06 mmol) in one portion followed by stirring at room temperature (water bath) for 30 minutes, then addition of 1,3-propanediol (0.87 ml, 12.00 mmol). After stirring for 45 minutes solvents were removed *in vacuo*, and the crude product was then redissolved acetonitrile (20 ml) and extracted with petrol (10 x 20ml). Petrol fractions were combined, followed by removal of solvents *in vacuo* then Kugelrohr distillation to afford vinyl boronic ester **84** (0.78 g, 60 %), as a colourless oil.

To a solution of diiodomethane (2.20 ml, 14.34 mmol) in CH_2Cl_2 (23 ml) was added diethylzinc (7.16 ml, 7.16 mmol, 1 M solution in hexanes) dropwise at 0 °C. After 10 minutes vinylboronic ester **84** (1.03 g, 4.77 mmol) was added as a solution in CH_2Cl_2 (5 ml), followed by stirring for 5 minutes at 0 °C then overnight at room temperature. Solvents were removed *in vacuo* and the crude product was purified by flash column chromatography (4 petrol : 1 ether eluant, 2 % triethylamine base-wash) to afford the *title compound* **85** (0.71 g, 65 %) as a colourless oil; ν_{max}/cm^{-1}(film) 3062, 3025, 2938, 1603, 1482, 1419, 1347, 1276, 1227, 1101, 739, 699; δ_H (250 MHz, $CDCl_3$) 7.33-7.20 (5H, m, Ar), 4.05-3.90 (4H, m, OCH_2), 2.75 (2H, app t, *J*7.9, CH_2), 1.96-1.71 (2H, m, CH_2), 1.71-1.43 (2H, m, CH_2), 1.00-0.87 (1H, m, RC*H*(cyclopropyl)), 0.65 (1H, ddd, *J*7.6, 5.4, 3.1, C*H*$_2$(cyclopropyl)), 0.26 (1H, ddd, *J*9.2, 6.1, 3.1, C*H*$_2$(cyclopropyl)), -0.60 (1H, app dt, *J*9.2, 5.4, CHB); δ_C (62 MHz, $CDCl_3$) 142.7 (C), 128.5 (CH), 128.2 (CH), 125.6 (CH), 61.6 (CH_2), 37.5 (CH_2), 35.9 (CH_2), 27.5 (CH_2), 22.8 (CH_2), 17.7 (CH), 13.9 (CH_3), 11.1 (CH_2), one CB missing; *m/z* (CI, NH_3) 248 $[M + NH_4]^+$, Found : $[M + NH_4]^+$, 248.1828. $C_{14}H_{23}BNO_2$ requires : 248.1822.

(1*S*, 2*S*)-Ethyl 2-phenylcyclopropanecarboxylate ((*S*, *S*)-93)[127,128]



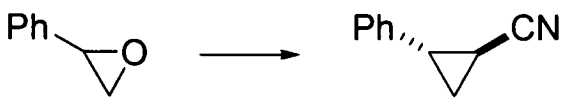
(*S*, *S*)-**93**

To a suspension of sodium hydride (30 mg, 0.75 mmol, 60% in mineral oil) in xylenes (5 ml) was added triethylphosphonoacetate (0.12 ml, 0.62 mmol) dropwise at room temperature. After stirring for 15 minutes *R*-styrene oxide (68 µl, 0.59 mmol) was added dropwise. This mixture was then heated at reflux for 3 hours, followed by cooling to room temperature and removal of solvents *in vacuo*. The crude material was purified *via* flash column chromatography (3 petrol : 1 ether eluant, 2 % triethylamine base-wash), to yield the *title compound* (*S*, *S*)-**93** (61 mg, 51 % yield) as a colourless oil; $[\alpha]^{22}_D$ +240 (*c* 1.05, $CHCl_3$), > 95% e.e. (95.5 : 0.05 hexane : isopropanol, 2ml/min, OD column); δ_H (250 MHz, $CDCl_3$) 7.33-7.07 (5H, m, Ar*H*),

4.17 (2H, q, *J*7.0, CH_3CH_2O), 2.52 (1H, ddd, *J*9.2, 6.4, 4.3, ArC*H*), 1.90 (1H, ddd, *J*8.2, 5.2, 4.3, C*H*CO_2Et), 1.60 (1H, ddd, *J*9.2, 5.2, 4.6, CH_2(cyclopropyl)), 1.28-1.22 (4H, m, CH_2(cyclopropyl), OCH_2CH_3).

Characterisation data correspond to literature values.[127,128]

(1*S**, 2*S**)-2-Phenylcyclopropanecarbonitrile (96)[129]

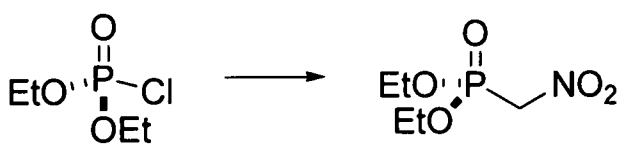


96

To a suspension of sodium hydride (30 mg, 0.75 mmol, 60 % in mineral oil) in xylenes (5 ml) was added diethylcyanomethylphosphonate (0.10 ml, 0.62 mmol) dropwise at room temperature. After stirring for 15 minutes styrene oxide (68 µl, 0.59 mmol) was added dropwise. This mixture was then heated at reflux for 45 minutes, followed by cooling to room temperature and removal of solvents *in vacuo*. The crude material was purified *via* flash column chromatography (3 petrol : 1 ether eluant, 2% triethylamine base-wash), to yield the *title compound* **96** (57 mg, 64 %); δ_H (250 MHz, $CDCl_3$) 7.36-7.09 (5H, m, ArH), 2.64 (1H, ddd, *J*8.9, 6.4, 4.9, C*H*Ph), 1.66-1.42 (3H, m, CH_2(cyclopropyl), C*H*CN).

Characterisation data correspond to literature values.[129]

Diethyl(nitromethyl)phosphonate (110)[130]

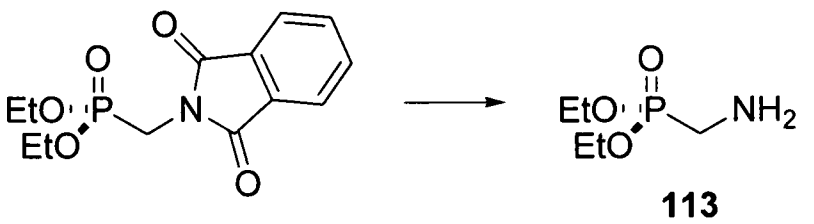


110

To a solution of diisopropylamine (3.10 ml, 22.00 mmol) in THF (100 ml) at 0 °C was added butyllithium (8.80 ml, 22.00 mmol, 2.5 M in hexanes) dropwise. After stirring for 20 minutes the mixture was cooled to –78 °C, followed by the addition of nitromethane (59.4 µl, 11.00 mmol) in THF (100 ml) dropwise over 1 hour. This

solution was stirred for a further hour after which a solution of diethyl chlorophosphonate **111** (1.59 ml, 11.00 mmol) in THF (15 ml) was added dropwise over 30 minutes. The resulting mixture was stirred for 3 hours at –78 °C then overnight at –30 °C. Subsequent cooling to –78 °C was followed by addition of a solution of glacial acetic acid (2.50 ml, 44.00 mmol) in THF (20 ml) over 30 minutes, then warming to room temperature and quenching with water (150 ml). The crude product was purified by sequential extractions into ethyl acetate (3 x 50 ml) and saturated potassium carbonate, followed by acidification of the aqueous layer (glacial AcOH to pH 7, concentrated HCl to pH 2), then final extraction with ethylacetate (2 x 50 ml). After drying over magnesium sulfate solvents were removed *in vacuo* to afford the *title compound* **110** (1.13 g, 52%) as a colourless oil; δ_H (250 MHz, $CDCl_3$) 4.94 (2H, d, *J*15.6, CH_2NO_2), 4.27 (4H, dq, *J*8.5, 7.3, CH_2O), 1.39 (6H, t, *J*7.3, CH_3). Characterisation data correspond to literature values.[130]

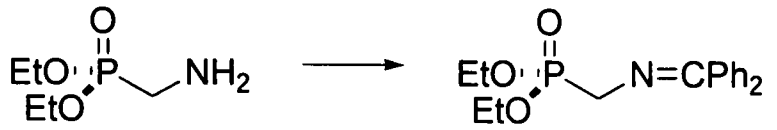
Diethyl(aminomethyl)phosphonate (113)[49]



113

To a solution of diethyl(phthalimidomethyl)phosphonate **112** (2.50 g, 8.41 mmol) in absolute ethanol (35 ml) was added hydrazine hydrate (0.45 ml, 9.25 mmol) dropwise over 5 mins. The mixture was stirred at room temperature overnight, then heated at reflux for 4 hours. After cooling to room temperature and removal of solvents *in vacuo* (bath temp < 30°C) toluene (30 ml) was added to cause precipitation of the side-product. After washing with toluene all organic extracts were combined and concentrated *in vacuo* to afford the *title compound* **113** (1.30 g, 94%) as a colourless oil; δ_H (250 MHz, $CDCl_3$) 4.21-4.08 (4H, m, OCH_2), 3.01 (2H, d, *J*10.4, CH_2NH_2), 1.50 (2H, br s, NH_2), 1.34 (6H, t, *J*7.0, CH_3).
Characterisation data correspond to literature values.[49]

Diethyl *N*-(diphenylmethylene)aminomethyl phosphonate (109)[48]

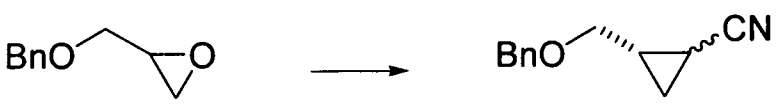


109

To a solution of benzophenone imine (1.31 ml, 7.90 mmol) in CH_2Cl_2 (20 ml) was added hydrogen chloride (7.79 ml, 7.79 mmol, 1M solution in ether) dropwise at 0 °C. After stirring for 5 minutes diethyl(aminomethyl)phosphonate **113** (1.30 g, 7.79 mmol) was added as a solution in CH_2Cl_2 (20 ml) at 0 °C, followed by stirring at room temperature for 2 hours. Solvents were then removed *in vacuo* followed by dilution with diethylether (30 ml) and washing with distilled water (2 x 20 ml). Organic extracts were combined, dried over magnesium sulphate then concentrated *in vacuo* to give a clear oil which was precipitated with hexane to furnish the *title compound* **109** (1.90 g, 74%) as a white crystalline solid (m.p. 59-60 °C); δ_H (250 MHz, $CDCl_3$) 7.64-7.19 (10H, m, Ar*H*), 4.18 (4H, m, OCH_2), 3.93 (2H, d, *J*17.7, CH_2N), 1.33 (6H, t, *J*7.0, CH_3).

Characterisation data correspond to literature values.[48]

2-(Benzyloxymethyl)cyclopropanecarbonitrile (116)[131]



116

To a suspension of sodium hydride (34 mg, 0.85 mmol, 60 % in mineral oil) in xylenes (6 ml) was added diethyl(cyanomethyl)phosphonate (1.13 ml, 0.79 mmol) dropwise over 5 mins. After stirring at room temperature for 10 minutes benzylglycidyl ether *rac*-**115** (0.10 ml, 0.66 mmol) was added dropwise, followed by heating at reflux for 45 minutes. The solution was allowed to cool to room temperature, diluted with ethyl acetate (100 ml) and washed with saturated aqueous ammonium chloride (50 ml) then concentrated *in vacuo*. The crude material was purified *via* flash column chromatography (2 petrol : 1 ether eluant), to yield the *title*

compound **116** as a mixture of isomers (47 mg, 42 %, 73:27 *trans*/*cis*) both as colourless oils.

^{1}H NMR for *trans*-**116**: δ_H (250 MHz, $CDCl_3$) 7.42-7.25 (1H, m, Ar*H*), 4.54 (2H, s, PhCH_2O), 3.52 (1H, dd, *J*12.0, 5.0, BnOCH_2), 3.39 (1H, dd, *J*12.0, 6.0, BnOCH_2), 1.82-1.71 (1H, m, RC*H*(cylopropyl)), 1.34 (1H, app dt, *J*8.5, 5.0, C*H*CN), 1.23 (1H, app dt, *J*8.9, 5.0, CH_2(cyclopropyl)), 1.08-1.00 (1H, m, CH_2(cyclopropyl)).

^{1}H NMR for *cis*-**116**: δ_H (250 MHz, $CDCl_3$) 7.40-7.26 (5H, m, Ar*H*), 4.59 (2H, s, PhCH_2O), 3.75 (1H, dd, *J*12.0, 5.0, BnOCH_2), 3.53 (1H, dd, *J*12.0, 8.0, BnOCH_2), 1.68-1.52 (2H, m, RC*H*(cyclopropyl), C*H*CN), 1.27-1.18 (1H, m, CH_2(cyclopropyl)), 1.01-0.94 (1H, m, CH_2(cyclopropyl)).

Characterisation data correspond to literature values.[131]

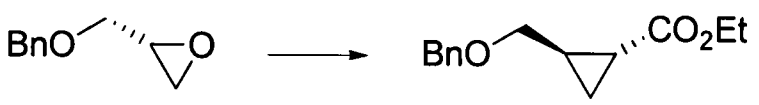
(1*S*, 2*S*)-Ethyl 2-(benzyloxymethyl)cyclopropanecarboxylate ((*S*, *S*)-117)

(*S*, *S*)-**117**

To a suspension of sodium hydride (3.08 g, 76.74 mmol, 60 % in mineral oil) in toluene (110 ml) was added triethylphosphonoacetate (15.00 ml, 73.08 mmol) dropwise over 30 mins. After stirring at room temperature for 10 minutes *S*-benzyl glycidyl ether (*S*)-**115** (5.60 ml, 36.54 mmol) was added dropwise, followed by heating at reflux for 14 hours. The solution was cooled to room temperature, diluted with ethylacetate (300 ml), then washed with saturated aqueous ammonium chloride (2 x 150 ml). After drying over magnesium sulfate and concentration *in vacuo*, the crude material was purified *via* flash column chromatography (4 petrol : 1 ether eluant), to yield the *title compound* (*S*, *S*)-**117** (5.39 g, 63 %) as a colourless oil; $[\alpha]^{22}_D$ +77 (*c* 0.42, $CHCl_3$), > 95% e.e. (35 mol % Eu(hfc)$_3$); ν_{max}/cm^{-1}(film) 2982, 2860, 1724, 1643, 1454, 1368, 1321, 1203, 1181, 1093, 738, 698; δ_H (250 MHz, $CDCl_3$) 7.38-7.26 (5H, m, Ar*H*), 4.52 (2H, s, PhCH_2O), 4.12 (2H, q, *J*7.1, OCH_2CH$_3$), 3.45 (1H, dd, *J*10.4, 6.1, BnOCH_2), 3.36 (1H, dd, *J*10.4, 6.4, BnOCH_2), 1.81-1.68 (1H, m, H_3), 1.60-1.53 (1H, m, H_6), 1.29-1.18 (4H, m, OCH$_2$CH_3, H_5), 0.86 (1H, ddd, *J*10.4, 6.3, 4.3, H_4); δ_C (62 MHz, $CDCl_3$) 173.8 (C), 138.1 (C), 128.4 (CH), 127.7 (CH), 72.7

(CH_2), 71.5 (CH_2), 60.5 (CH_2), 21.6 (CH), 18.5 (CH), 14.2 (CH_3), 12.9 (CH_2), one aromatic missing; m/z (CI, NH_3) 235 $[M+H]^+$, found : $[M+H]^+$, 235.1325. $C_{14}H_{19}O_3$ requires : 235.1334.

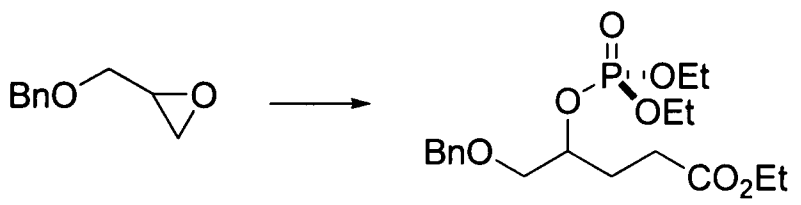
(1*R*, 2*R*)-Ethyl 2-(benzyloxymethyl)cyclopropanecarboxylate ((*R*, *R*)-117)



(*R*, *R*)-**117**

Cyclopropane (*R*, *R*)-**117** ($[\alpha]^{22}_D$ -77 (*c* 0.44, $CHCl_3$)) was synthesised using the general procedure described for (*S*, *S*)-**117**, in similar yield. ^{1}H NMR data correspond to compound (*S*, *S*)-**117**.

Ethyl 5-(benzyloxy)-4-(diethoxyphosphoryloxy)pentanoate (118)

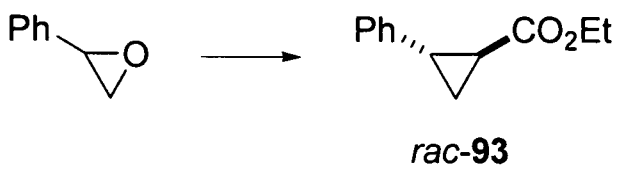


118

To a suspension of cesium carbonate (1.71 g, 5.25 mmol) in dry acetonitrile (4 ml) was added triethylphosphonoacetate (0.52 ml, 2.62 mmol) and benzyl glycidyl ether *rac*-**115** (0.20 ml, 1.31 mmol) dropwise. This mixture was then heated at reflux for 20 hours, followed by cooling to room temperature and filtration through a short pad of celite (washing with ethyl acetate, 2 x 100 ml). Solvents were then removed *in vacuo*, and the residue was purified directly by flash column chromatography (ether eluant) to afford the *title compound* **118** (0.39 g, 76 %) as a colourless oil; ν_{max}/cm^{-1}(film) 3031, 2986, 2934, 1727, 1642, 1454, 1370, 1259, 1180, 1011, 741; δ_H (400 MHz, $CDCl_3$) 7.28-7.19 (5H, m, Ar*H*), 4.53-4.45 (3H, m, PhCH_2O, OCH_2CHOP), 4.09-3.97 (6H, m, OCH_2CH_3), 3.56 (1H, dd, *J* 10.4, 5.3, OCH_2CHOP), 3.52 (1H, dd, *J* 10.4,

4.9, OCH_2CHOP), 2.40 (2H, t, *J* 7.5, CH_2CO$_2$Et), 2.04-1.88 (2H, m, CH_2CH$_2$CO$_2$Et), 1.27-1.16 (9H, m, OCH$_2$CH_3); δ_C (100 MHz, $CDCl_3$) 173.0 (C), 137.8 (C), 128.3 (CH), 128.1 (CH), 127.6 (CH), 76.4 (CH, d, $J_{C\text{-}P}$ 6.0), 73.2 (CH_2), 71.6 (CH_2, d, $J_{C\text{-}P}$ 2.6), 63.7 (CH_2, d, $J_{C\text{-}P}$ 5.0), 63.7 (CH_2, d, $J_{C\text{-}P}$ 4.0), 60.4 (CH_2), 29.6 (CH_2), 27.5 (CH_2, d, $J_{C\text{-}P}$ 5.0), 16.5 (CH_3, d, $J_{C\text{-}P}$ 6.0), 16.0 (CH_3, d, $J_{C\text{-}P}$ 6.0), 14.1 (CH_3); m/z (CI, NH_3) 389 $[M+H]^+$, found : $[M+H]^+$, 389.1726. $C_{18}H_{30}O_7P$ requires : 389.1729.

(1*S**, 2*S**)-Ethyl 2-phenylcyclopropanecarboxylate (*rac*-93)

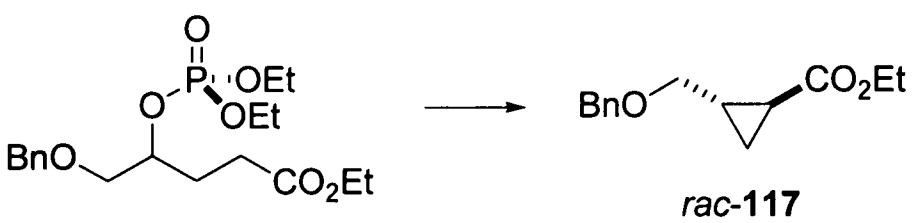


rac-**93**

To a suspension of cesium carbonate (2.14 g, 6.56 mmol) and 18-crown-6 (35 mg, 0.13 mmol) in dry toluene (1 ml) was added triethylphosphonoacetate (0.39 ml, 2.00 mmol) then styrene oxide (0.15 ml, 1.31 mmol). This mixture was then heated at 100 °C (bath temp) for 5 hours, followed by cooling to room temperature and filtration through a short pad of celite (washing with CH_2Cl_2, 2 x 100 ml). The crude residue was then purified directly by flash column chromatography (3 petrol : 1 ether eluant) to afford the *title compound rac*-**93** (0.13 g, 52 %) as a colourless oil.

^{1}H NMR data correspond to compound (*S*, *S*)-**93**.

(1*S**, 2*S**)-Ethyl 2-(benzyloxymethyl)cyclopropanecarboxylate (*rac*-117)

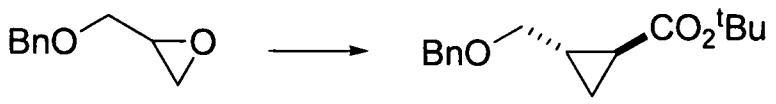


rac-**117**

To a solution of phosphate **118** (0.10 g, 0.26 mmol) in dry toluene (2 ml) was added potassium *tert*-butoxide (58 mg, 0.52 mmol) in one portion, followed by stirring at room temperature for 1 hour. The mixture was then diluted with ether (100 ml), and

washed with saturated ammonium chloride (100 ml). Organics were combined, dried over magnesium sulphate and concentrated *in vacuo*. The crude product was then purified by flash column chromatography (4 petrol : 1 ether eluant) to afford the *title compound rac*-**117** (37 mg, 61 %) and *rac*-**121** (10 mg, 15 %) both as clear oils.
^{1}H NMR data correspond to compounds **117** and **121**.

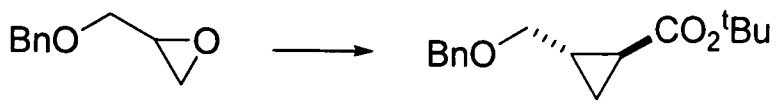
(1*S, 2*S**)-*tert*-Butyl 2-(benzyloxymethyl)cyclopropanecarboxylate (*rac*-121)**



rac-**121**

To a suspension of potassium *tert*-butoxide (0.11 g, 0.96 mmol) in hexane (4 ml) was added *tert*-butyl diethylphosphonoacetate (0.20 ml, 0.87 mmol) with stirring at room temperature for 5 minutes. To this solution was then added benzyl glycidyl ether *rac*-**115** (0.67 ml, 0.44 mmol) and the mixture was then heated at reflux for 2 hours. Most of the solvent was blown down under a nitrogen stream then purified by flash column chromatography (2 petrol : 1 ether eluant) to afford the *title compound rac*-**121** (0.08 g, 70 %) as a colourless oil; ν_{max}/cm^{-1}(film) 2978, 2859, 1721, 1454, 1392, 1367, 1325, 1212,1153, 1091, 847, 738; δ_H (250 MHz, $CDCl_3$) 7.36-7.26 (5H, m, Ar*H*), 4.53 (2H, s, PhCH_2O), 3.43 (1H, dd, *J*10.4, 6.3, BnOCH_2), 3.38 (1H, dd, *J*10.4, 6.3, BnOCH_2), 1.71-1.65 (1H, m, H_3), 1.50-1.43 (10H, m, H_6, $CO_2{}^tBu$), 1.16-1.12 (1H, m, H_5), 0.86 (1H, ddd, *J*8.6, 6.3, 4.5, H_4); δ_C (62 MHz, $CDCl_3$) 172.9 (C), 138.2 (C), 128.4 (CH), 127.6 (CH), 80.3 (C), 72.5 (CH_2), 71.6 (CH_2), 28.1 (CH_3), 21.0 (CH), 19.5 (CH), 12.7 (CH_2), one aromatic missing; m/z (CI, NH_3) 280 $[M+NH4]^+$, found : $[M+H]^+$, 280.1906. $C_{16}H_{26}NO_3$ requires : 280.1912.

(1*S**, 2*S**)-*tert*-Butyl 2-(benzyloxymethyl)cyclopropanecarboxylate (*rac*-121)

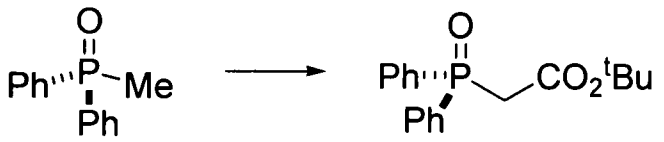


rac-**121**

To a suspension of potassium *tert*-butoxide (0.12 g, 1.05 mmol) in hexane (1 ml) was added *tert*-butyl diethylphosphonoacetate (0.19 ml, 0.78 mmol) with stirring at room temperature for 5 minutes. To this solution was then added benzyl glycidyl ether *rac*-**115** (0.10 ml, 0.66 mmol) and the mixture was stirred at room temperature for 24 hours. Most of the solvent was blown down under a nitrogen stream then purified by flash column chromatography (2 petrol : 1 ether eluant) to afford the *title compound* *rac*-**121** (0.10 g, 60 %) as a colourless oil.

^{1}H NMR data correspond to compound *rac*-**121**.

tert-Butyl 2-(diphenylphosphoryl)acetate (123)

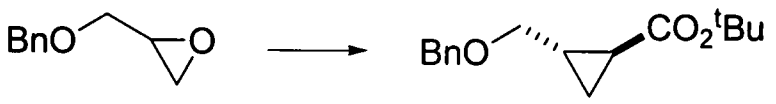


123

To a solution of methyldiphenylphosphine oxide **125** (2.50 g, 11.56 mmol), and di-*tert*-butyl dicarbonate (3.03 g, 13.87 mmol) in dry THF (2 ml) at –78 °C was added LiHMDS (28.90 ml, 28. 90 mmol, 1M solution in hexanes) dropwise over 30 minutes. After stirring for 15 mins the solution was allowed to warm to room temperature, diluted with ether (150 ml) and washed with saturated aq. ammonium chloride (150 ml). Organic extracts were combined, dried over magnesium sulfate, and solvents removed *in vacuo*. Then crude solid was then recrystallised from ether/hexane to afford the *title compound* **123** (3.29 g, 90 %) as a white crystalline solid (m.p. 93-94 °C); ν_{max}/cm^{-1}(film) 1721, 1651, 1438, 1368, 1286, 1194, 1163, 1122, 720, 694; δ_H (400 MHz, $CDCl_3$) 7.83-7.78 (5H, m, ArH), 7.57-7.47 (5H, m, ArH), 3.42 (2H, d, *J* 15.0, CH_2), 1.21 (9H, s, Boc); δ_C (100 MHz, $CDCl_3$) 165.1 (C), 132.1 (C, d, J_{C-P}

103.0), 132.1 (C, d, $J_{C\text{-}P}$ 2.3), 131.2 (CH, d, $J_{C\text{-}P}$ 9.7), 128.5 (CH, d, $J_{C\text{-}P}$ 12.1), 82.2 (C), 40.3 (CH_2, d, $J_{C\text{-}P}$ 61.0), 27.6 (CH_3); m/z (CI, NH_3) 317 $[M+H]^+$, found : $[M+H]^+$, 317.1321. $C_{18}H_{22}O_3P$ requires : 317.1307.

(1*S, 2*S**)-*tert*-Butyl 2-(benzyloxymethyl)cyclopropanecarboxylate (121)**

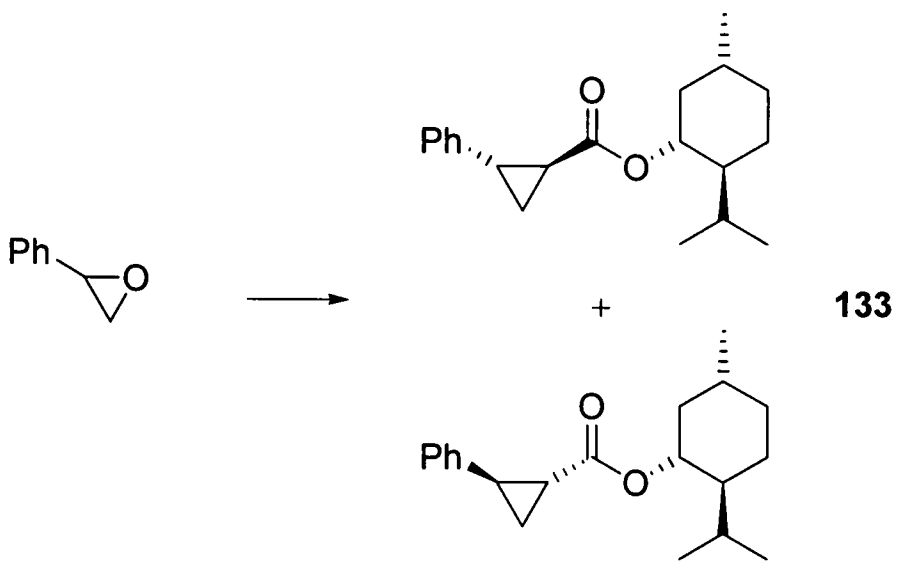


rac-**121**

To a solution of *tert*-butyl 2-(diphenylphosphoryl)acetate **123** (0.83 g, 2.62 mmol) in dry toluene (4 ml) was added sodium hydride (0.11 g, 2.75 mmol, 60 % in mineral oil). After stirring at room temperature for 10 minutes gas evolution had ceased and benzyl glycidyl ether *rac*-**115** (0.10 ml, 0.66 mmol) was added dropwise. After heating at reflux for 30 minutes the mixture was cooled to room temperature, diluted with ether (100 ml) then washed with saturated aqueous ammonium chloride (150 ml). Organic extracts were combined, dried over magnesium sulfate, and solvents removed *in vacuo*. The crude product was then purified by flash column chromatography (4 petrol : 1 ether eluant) to afford the *title compound rac*-**121** (0.19 g, 55 %) as a clear oil.

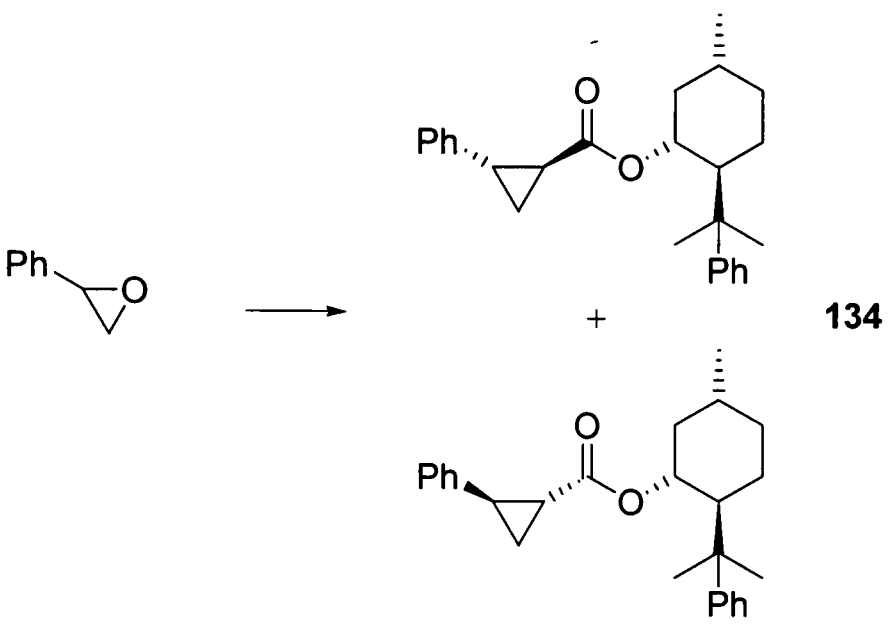
^{1}H NMR data correspond to compound **121**.

(1*S*, 2*S*)-((1*R*, 2*S*, 5*R*)-2-Isopropyl-5-methylcyclohexyl) 2-phenylcyclopropanecarboxylate and (1*R*, 2*R*)-((1*R*, 2*S*, 5*R*)-2-Isopropyl-5-methylcyclohexyl) 2-phenylcyclopropanecarboxylate (133)



To a mixture of diethylphosphonoacetic acid **132** (0.13 g, 0.66 mmol) and (-)-menthol (0.10 g, 0.66 mmol) in hexane (2 ml), was added DCC (0.14 g, 0.66 mmol) with stirring at room temperature for 15 minutes. To this suspension was then added potassium *tert*-butoxide (81 mg, 0.72 mmol) in one portion followed by further stirring for 5 minutes, then addition of styrene oxide (0.15 ml, 1.31 mmol). This mixture was then stirred at room temperature for 40 hours, followed by removal of solvents *in vacuo* and direct purification by flash column chromatography (9 petrol : 1 ether eluant, 5 % triethylamine base-wash) to afford the *title compound* **133** (70 mg, 70 %, 58:42 d.r.) as a clear oil; ν_{max}/cm^{-1}(film) 3030, 2955, 2927, 1721, 1457, 1405, 1337, 1320, 1264, 1188, 1176, 754; δ_H (400 MHz, $CDCl_3$) 7.31-7.10 (5H, m, Ar*H*), 4.75-4.69 (1H, m, CO_2CH), 2.55-2.48 (1H, m, PhC*H*), 2.03-0.77 (21H, m, menthylC*H*, CH_2, $CHCO_2R$); δ_C (100 MHz, $CDCl_3$) 172.9 (C, isomer A), 172.9 (C, isomer B), 140.3 (C, isomer A), 140.3 (C, isomer B), 128.5 (CH, isomer A), 128.4 (C, isomer B), 126.4 (CH), 126.2 (CH), 126.1 (CH), 74.4 (CH, isomer A), 74.4 (CH, isomer B), 47.1 (CH), 41.0 (CH_2), 34.3 (CH_2), 31.4 (CH), 26.3 (CH, isomer A), 26.2 (CH, isomer B), 26.0 (CH, isomer A), 26.0 (CH, isomer B), 24.4 (CH, isomer A), 24.4 (CH, isomer B), 23.5 (CH_2, isomer A), 23.4 (CH_2, isomer B), 22.0 (CH_3), 20.8 (CH_3), 17.1 (CH, isomer A), 17.1 (CH, isomer B), 16.4 (CH_2, isomer A), 16.4 (CH_2, isomer B), seven missing; m/z (CI, NH_3) 318 $[M+NH_4]^+$, found : $[M+NH_4]^+$, 318.2425. $C_{20}H_{32}NO_2$ requires : 318.2433.

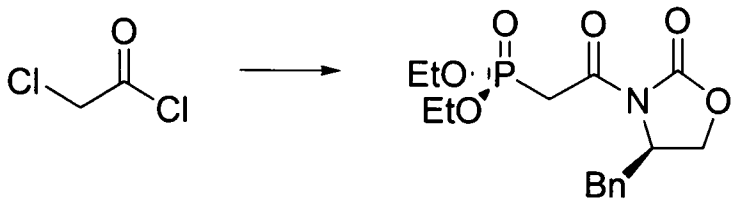
(1*S*, 2*S*)-((1*R*, 2*S*, 5*R*)-5-Methyl-2-(2-phenylpropan-2-yl)cyclohexyl) 2-phenylcyclopropanecarboxylate and (1*R*, 2*R*)-((1*R*, 2*S*, 5*R*)-5-Methyl-2-(2-phenylpropan-2-yl)cyclohexyl) 2-phenylcyclopropanecarboxylate (134)



To diethylphosphonoacetic acid **132** (42 mg, 0.22 mmol) was added a solution of (-)-8-phenyl menthol (0.05 g, 0.22 mmol) in hexane (0.5 ml). To this solution was then added DCC (47 mg, 0.23 mmol) and the mixture was stirred at room temperature for 30 minutes. To this suspension was then added potassium *tert*-butoxide (29 mg, 0.26 mmol) in one portion followed by further stirring for 5 minutes, then addition of styrene oxide (0.05 ml, 0.26 mmol). This mixture was then stirred at room temperature for 40 hours, followed by removal of solvents *in vacuo* and direct purification by flash column chromatography (9 petrol : 1 ether eluant, 5 % triethylamine base-wash) to afford the *title compound* **134** (20 mg, 50 %, 51:49 d.r.) as a clear oil; ν_{max}/cm^{-1}(film) 3029, 2954, 2923, 1716, 1496, 1457, 1406, 1324, 1189, 909, 755, 698; δ_H (400 MHz, $CDCl_3$) 7.39-6.80 (10H, m, Ar*H*), 4.84-4.78 (1H, m, CO_2CH), 2.40-2.28 (1H, m, PhC*H*), 2.07-0.86 (23H, m, menthylC*H*, CH_2, C*H*CO_2R); δ_C (100 MHz, $CDCl_3$) 172.7 (C, isomer A), 172.6 (C, isomer B), 151.6 (C), 140.3 (C), 128.3 (CH), 127.9 (CH), 127.8 (CH), 126.3 (CH), 126.0 (CH), 125.9 (CH), 125.2 (CH), 124.9 (CH), 125.4 (CH), 74.7 (CH, isomer A), 50.7 (CH_3, isomer A), 50.6 (CH_3, isomer B), 41.8 (CH_2, isomer A), 41.7 (CH_2, isomer B), 39.7 (C, isomer A), 39.5 (C, isomer B), 34.6 (CH_2, isomer A), 34.5 (CH_2, isomer B), 31.3 (CH), 28.2 (CH_3), 27.7 (CH_3), 26.6 (CH_2), 26.5 (CH_2), 25.9 (CH), 25.8 (CH), 25.3 (CH_3), 24.6 (CH_3), 24.4 (CH), 24.2 (CH), 21.8 (CH_3), 17.4 (CH_2), 17.0 (CH), eight missing; m/z

(CI, NH_3) 394 $[M+NH_4]^+$, found : $[M+NH_4]^+$, 394.2745. $C_{26}H_{36}NO_2$ requires : 394.2746.

(*R*)-Diethyl 2-(4-benzyl-2-oxooxazolidin-3-yl)-2-oxoethylphosphonate (138)[132]

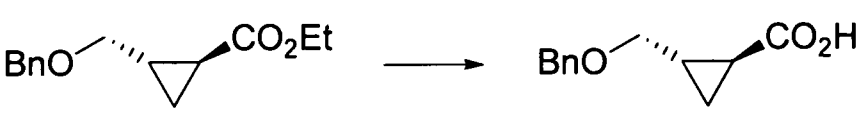


138

To chloroacetyl chloride **135** (1.80 ml, 22.57 mmol) was added *R*-4-benzyl-2-oxazolidinone **136** (2.00 g, 11.29 mmol), followed by heating at 120 °C for 6 hours. After cooling to room temperature, hexane (10 ml) was added, followed by rapid stirring and decanting (x 4) to remove excess starting materials. Further volatiles were removed by azeotroping with toluene (5 ml), then at high vacuum. To this crude mixture was then added triethylphosphite (7.83 ml, 45.16 mmol) followed by further heating at 140 °C for 2 hours. After cooling to room temperature excess reagents were removed as described above, followed by flash column chromatography (ethyl acetate eluant) to afford the *title compound* **138** (2.50 g, 62 %).

Characterisation data for **138** ($[\alpha]^{22}_D$ -43 (*c* 4.0, $CHCl_3$)) correspond to literature values for *ent*-**138**.[132]

(1*S*, 2*S*)-2-(Benzyloxymethyl)cyclopropanecarboxylic acid ((*S*, *S*)-139)



(*S*, *S*)-**139**

To a solution of cyclopropane (*S*, *S*)-**117** (4.73 g, 20.22 mmol) in ethanol (150 ml), was added 0.5 M sodium hydroxide solution (80 ml, 40.00 mmol) over 5 mins. The mixture was then stirred at room temperature overnight, diluted with water (300 ml), acidified to pH 4 (concentrated HCl) then extracted with ethyl acetate (3 x 200 ml).

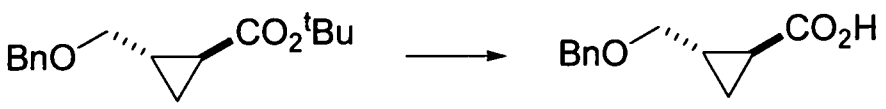
Organic extracts were combined, dried over magnesium sulfate then concentrated *in vacuo* to afford the *title compound* (*S*, *S*)-**139** (4.03 g, 96 %) as a colourless oil; $[\alpha]^{28}_{D}$ +81 (*c* 0.60, $CHCl_3$); ν_{max}/cm^{-1}(film) 3429, 3031, 2928, 2864, 1693, 1454, 1229, 1085, 739, 699; δ_H (250 MHz, $CDCl_3$) 7.37-7.26 (5H, m, Ar*H*), 4.53 (2H, s, PhCH_2O), 3.48 (1H, dd, *J*10.4, 6.1, BnOCH_2), 3.36 (1H, dd, *J*10.4, 6.7, BnOCH_2), 1.87-1.75 (m, 1H, H_3), 1.61-1.54 (1H, m, H_6), 1.29 (1H, app q, *J*4.3, H_5), 0.95 (1H, ddd, *J*10.8, 6.5, 4.3, H_4); δ_C (62 MHz, $CDCl_3$) 180.1 (C), 138.0 (C), 128.4 (CH), 127.7 (CH), 72.7 (CH_2), 71.2 (CH_2), 22.5 (CH), 18.4 (CH), 13.7 (CH_2), one aromatic missing; m/z (CI, NH_3) 224 $[M+NH_4]^+$, found : $[M+NH_4]^+$, 224.1280. $C_{12}H_{18}NO_3$ requires : 224.1270.

(1*R*, 2*R*)-2-(Benzyloxymethyl)cyclopropanecarboxylic acid ((*R*, *R*)-139)

(*R*, *R*)-**139**

Cyclopropane (*R*, *R*)-**139** ($[\alpha]^{22}_{D}$ -103 (*c* 0.51, $CHCl_3$)) was synthesised using the general procedure described for (*S*, *S*)-**139**, in similar yield. ^{1}H NMR data correspond to compound (*S*, *S*)-**139**.

(1*S, 2*S**)-2-(Benzyloxymethyl)cyclopropanecarboxylic acid (*rac*-139)**

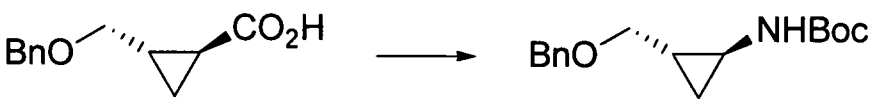


rac-**139**

To a solution of *rac*-**121** (65 mg, 0.25 mmol) in CH_2Cl_2 (2.5 ml) was added zinc dibromide (0.28 g, 1.25 mmol) in one portion. This suspension was then stirred rapidly at room temperature for 24 hours. Ether (100 ml) was added and the product was extracted into saturated sodium bicarbonate solution (150 ml), which was then

carefully acidified to ~ pH 4 (concentrated HCl) and finally extracted into CH_2Cl_2 (2 x 150 ml). Solvents were dried over magnesium sulfate then removed *in vacuo* to afford the *title compound rac*-**139** (41 mg, 81 %) as a colourless oil.
^{1}H NMR data correspond to compound (*S*, *S*)-**139**.

tert-Butyl (1*S*, 2*S*)-2-(benzyloxymethyl)cyclopropylcarbamate ((*S*, *S*)-142)



(*S*, *S*)-**142**

To a solution of cyclopropyl acid (*S*, *S*)-**139** (3.62 g, 17.55 mmol) in *tert*-butanol (200 ml) was added triethylamine (3.18 ml, 22.82 mmol) then diphenylphosphoryl azide (4.55 ml, 21.07 mmol) dropwise. The mixture was heated at reflux for 20 hours, cooled to room temperature and diluted with ethyl acetate (300 ml). Organics were washed with water (2 x 100 ml), dried over magnesium sulfate and finally concentrated *in vacuo*. The crude product was purified *via* flash column chromatography (1 petrol : 1 ether eluant) to afford the *title compound* (*S*, *S*)-**142** (2.58 g, 53 %) as a colourless oil; $[\alpha]^{22}_D$ +39 (*c* 0.10, $CHCl_3$); ν_{max}/cm^{-1}(film) 3334, 2977, 1706, 1513, 1366, 1252, 1169, 1099, 739, 698; δ_H (250 MHz, $CDCl_3$) 7.37-7.26 (5H, m, Ar*H*), 4.72 (1H, br s, N*H*Boc), 4.52 (2H, s, PhCH_2O), 3.46 (1H, dd, *J*10.2, 6.6, BnOCH_2), 3.29 (1H, dd, *J*10.2, 6.8, BnOCH_2), 2.45-2.35 (1H, m, H_6), 1.43 (9H, s, Boc), 1.29-1.16 (1H, m, H_3), 0.79-0.67 (m, 2H, H_4, H_5); δ_C (62 MHz, $CDCl_3$) 156.4 (C), 138.3 (C), 128.4 (CH), 127.7 (CH), 127.6 (CH), 79.4 (C), 72.7 (CH_2), 71.8 (CH_2), 28.4 (CH_3), 28.1 (CH), 20.1 (CH), 12.1 (CH_2); m/z (CI, NH_3) 278 $[M+H]^+$, found : $[M+H]^+$, 278.1759. $C_{16}H_{24}NO_3$ requires : 278.1756.

tert-Butyl (1*R*, 2*R*)-2-(benzyloxymethyl)cyclopropylcarbamate (*R*, *R*)-142

(*R*, *R*)-**142**

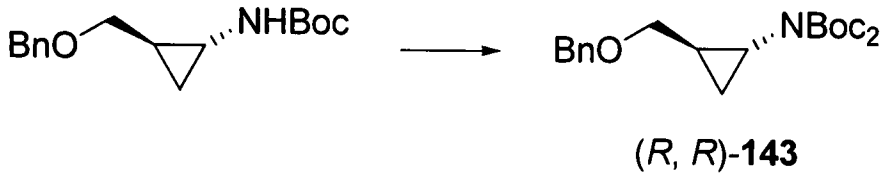
Cyclopropane (*R*, *R*)-**142** ($[\alpha]^{22}_{D}$ -30 (*c* 0.40, $CHCl_3$)) was synthesised using the general procedure described for (*S*, *S*)-**142**, in similar yield. ^{1}H NMR data correspond to compound (*S*, *S*)-**142**.

(1*S*, 2*S*)-*O*-(Benzyl)-*N*-(bis-Boc)-aminocyclopropyl methanol ((*S*, *S*)-143)

(*S*, *S*)-**143**

To a solution of cyclopropylamine (*S*, *S*)-**142** (2.16 g, 7.77 mmol) in acetonitrile (100 ml) was added di-*tert*-butyl dicarbonate (5.09 g, 23.32 mmol) as a solution in acetonitrile (25 ml), then DMAP (0.29 g, 2.33 mmol) in one portion. The mixture was then stirred at room temperature for 48 hours, followed by removal of solvents *in vacuo*, drying over magnesium sulfate, and purification *via* flash column chromotography (2 petrol : 1 ether eluant) to afford the *title compound* (*S*, *S*)-**143** (2.69 g, 92%) as a white solid (m.p. 88-89 °C); $[\alpha]^{28}_{D}$ +44 (*c* 1.50, $CHCl_3$); ν_{max}/cm^{-1}(film) 3064, 2979, 1787, 1743, 1712, 1367, 1285, 1253, 1164, 1116, 855, 739, 698; δ_H (250 MHz, $CDCl_3$) 7.33-7.23 (5H, m, Ar*H*), 4.51 (2H, s, PhCH_2O), 3.82 (1H, dd, *J*10.1, 4.6, BnOCH_2), 3.12 (1H, dd, *J*10.1, 7.8, BnOCH_2), 2.49-2.43 (1H, m, H_6), 1.48 (18H, s, Boc_2), 1.40-1.27 (1H, m, H_3), 0.98 (1H, app q, *J*6.6, H_4), 0.90-0.83 (1H, m, H_5); δ_C (62 MHz, $CDCl_3$) 152.9 (C), 138.3 (C), 128.4 (CH), 127.7 (CH), 127.7 (CH), 82.2 (C), 72.7 (CH_2), 71.0 (CH_2), 32.12 (CH), 28.05 (CH_3), 22.5 (CH), 14.8 (CH_2); m/z (CI, NH_3) 378 $[M+H]^+$, found : $[M+H]^+$, 378.2291. $C_{21}H_{32}NO_5$ requires : 378.2280.

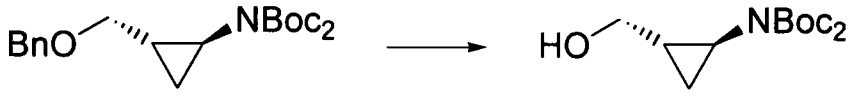
(2*R*, 2*R*)-*O*-(Benzyl)-*N*-(bis-Boc)-aminocyclopropyl methanol ((*R*, *R*)-143)



(*R*, *R*)-**143**

Cyclopropane (*R*, *R*)-**143** ($[\alpha]^{22}_{D}$ -44 (*c* 0.37, $CHCl_3$)) was synthesised using the general procedure described for (*S*, *S*)-**143**, in similar yield. ^{1}H NMR data correspond to compound (*S*, *S*)-**143**.

(1*S*, 2*S*)-*N*-(bis-Boc)-aminocyclopropyl methanol ((*S*, *S*)-48)

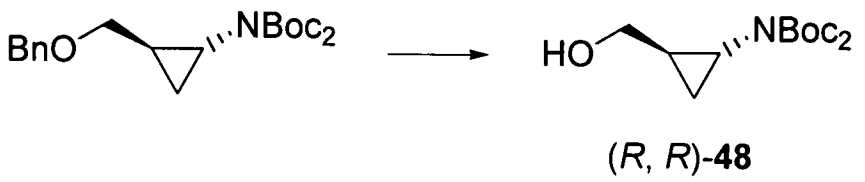


(*S*, *S*)-**48**

To a mixture of bis-protected amine (*S*, *S*)-**143** (0.50 g, 1.32 mmol), and 10 % palladium on carbon (75 mg) was added THF (3 ml) and the mixture was thoroughly purged with H_2 until the solvent volume was approximately 2 ml. Glacial acetic acid (0.05 ml) was then added and the mixture stirred at room temperature for 3 days. The suspension was diluted with ethyl acetate (100 ml), neutralised with solid potassium carbonate (approximately 5 g), then passed through a short pad of celite and further washed with ethyl acetate (2 x 50 ml). Solvents were removed *in vacuo* and the crude product was purified by flash column chromatography (2 ether : 1 petrol eluant) to yield the *title compound* (*S*, *S*)-**48** (0.44 g, 98 %) as a colourless oil; $[\alpha]^{28}_{D}$ +4.37 (*c* 1.37, $CHCl_3$); ν_{max}/cm^{-1}(film) 3487, 2980, 1741, 1710, 1368, 1285, 1163, 1118, 1035, 853, 782; δ_H (250 MHz, $CDCl_3$) 3.87 (1H, dd, *J*10.8, 5.0, BnOCH_2), 3.10 (1H, dd, *J*10.8, 9.6, BnOCH_2), 3.05 (1H, br s, OH), 2.44 (1H, ddd, *J*6.1, 5.8, 3.3, H_6), 1.49 (18H, s, Boc_2), 1.22-1.35 (1H, m, H_3), 0.89-0.94 (2H, m, H_4, H_5); δ_C (62 MHz, $CDCl_3$) 153.4 (C), 83.0 (C), 65.0 (CH_2), 32.7 (CH), 28.0 (CH_3), 24.8 (CH), 13.6

(CH_2); m/z (CI, NH_3) 288 $[M+H]^+$, found : $[M+H]^+$, 288.1817. $C_{14}H_{26}NO_5$ requires : 288.1811.

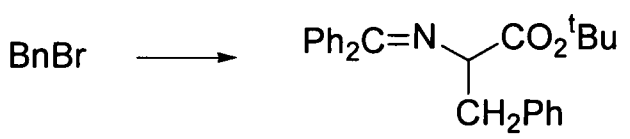
(1*R*, 2*R*)-*N*-(bis-Boc)-aminocyclopropyl methanol ((*R*, *R*)-48)



(*R*, *R*)-**48**

Cyclopropane (*R*, *R*)-**48** ($[\alpha]^{22}_D$ –3.0 (*c* 1.99, $CHCl_3$)) was synthesised using the general procedure described for (*S*, *S*)-**48**, in similar yield. ^1H NMR data correspond to compound (*S*, *S*)-**48**.

***tert*-Butyl *N*-(diphenylmethylene)glycinate (*rac*-144)[65]**

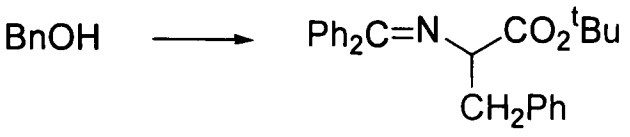


rac-**144**

To a solution of *N*-(diphenylmethylene)glycine *tert*-butyl ester **29** (0.14 g, 0.46 mmol) and TBAB (14 mg, 0.04 mmol) in toluene (3.8 ml) was added benzyl bromide (50 µl, 0.42 mmol), then 50 % aq KOH solution (1 ml, 20 eq). This biphasic mixture was stirred rapidly at room temperature for 18 hours, followed by dilution with CH_2Cl_2 (150 ml) and washing with distilled water (100 ml). Organic extracts were combined, dried over magnesium sulfate, then concentrated *in vacuo* to afford the *title compound* *rac*-**144** (0.15 g, 91 %) as a colourless oil.

Characterisation data correspond to literature values.[65]

tert-Butyl *N*-(diphenylmethylene)glycinate (*rac*-144)[65]

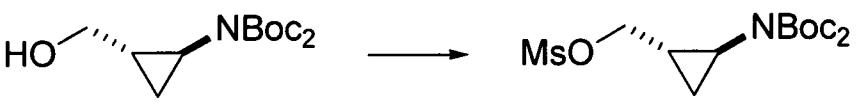


rac-**144**

To a solution of *N*-(diphenylmethylene)glycine *tert*-butyl ester **29** (0.16 g, 0.53 mmol) and TBAB (16 mg, 0.05 mmol) in toluene (2 ml) was added a solution of 50 % aq KOH (1 ml, 20 eq). This biphasic mixture was then cooled to 0 °C and a solution of mesyl chloride (56 µl, 0.73 mmol) in toluene (2 ml) was added dropwise over 30 minutes followed by rapid stirring for 48 hours. After warming to room temperature CH_2Cl_2 (150 ml) was added and the organic layer was washed with distilled water (100 ml). Organic extracts were combined, dried over magnesium sulfate, then concentrated *in vacuo*. This crude residue was then purified by flash column chromatography (4 petrol : 1 ether eluant) to afford the *title compound rac*-**144** (0.14 g, 77 %) as a colourless oil.

Characterisation data correspond to literature values.[65]

Mesylate *rac*-148

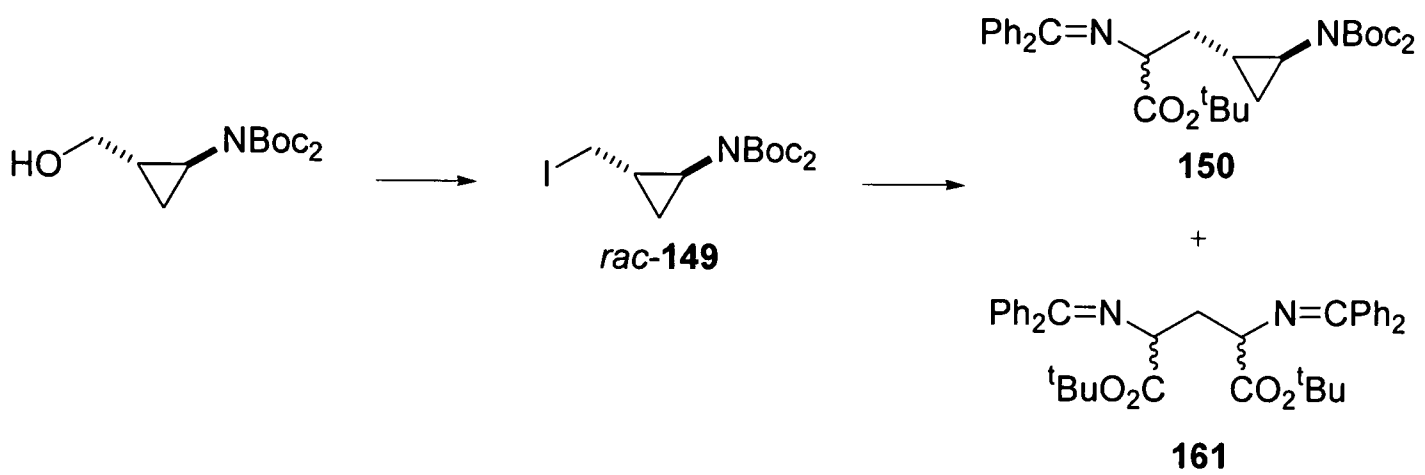


rac-**148**

To a solution of *rac*-**48** (0.12 g, 0.43 mmol) and TBAB (28 mg, 0.09 mmol) in dry toluene (3 ml) at –5 °C was added powdered KOH (0.48 g, 8.60 mmol) followed by rapid stirring. A solution of mesyl chloride (67 µl, 0.86 mmol) in toluene (3 ml) was then added dropwise over 30 minutes, followed by warming to room temperature and stirring for an additional 30 minutes. The crude mixture was then passed through a short pad of celite (washing with CH_2Cl_2, 2 x 100 ml) followed by concentration *in vacuo* and purification by flash column chromatography (1 petrol : 1 ether eluant) to afford the *title compound rac*-**148** (0.14 g, 90 %) as a colourless oil; δ_H (250 MHz,

$CDCl_3$) 4.52 (1H, dd, *J*10.8, 5.5, BnOCH_2), 3.91 (1H, dd, *J*10.8, 8.6, BnOCH_2), 3.04 (3H, s, $MeSO_2$), 2.60-2.54 (1H, m, H_6), 1.54-1.43 (19H, m, Boc_2O, H_3), 1.14-0.97 (2H, m, H_4, H_5).

(2*S/R*, 1'*S, 2'*R**)-(*N*-(bis-Boc)-*N*-(diphenylmethylene)-3-(2-aminocyclopropyl)) alanine *tert*-butyl ester (150) and (2*R/S*, 4*R/S*)-bis(*N*-Diphenylmethylene)amino-pentanedioic acid di-*tert*-butyl ester (161)**



rac-**149**

150

+

161

To a solution of 2,3-dichloro-5,6-dicyano-p-benzoquinone (79 mg, 0.35 mmol) in chloroform (4.5 ml), was added triphenylphosphine (91 mg, 0.35 mmol) followed by stirring at room temperature for 10 minutes. Tetrabutylammonium iodide (0.13 g, 0.35 mmol), was then added in one portion and the slurry stirred for a further 5 minutes. To this mixture was added a solution of alcohol *rac*-**48** (50 mg, 0.17 mmol) in chloroform (2.0 ml) followed by additional stirring for 10 mins. Petrol (100 ml) was then added with vigorous stirring for 5 mins, and the resulting mixture was passed through a short pad of celite and further washed with petrol (2 x 100 ml). Solvents were removed *in vacuo*, followed by final addition of petrol (5 x 5ml) and removal of triphenylphosphine oxide by filtration. Subsequent concentration of the filtrate *in vacuo* then afforded *rac*-**149** in high purity.

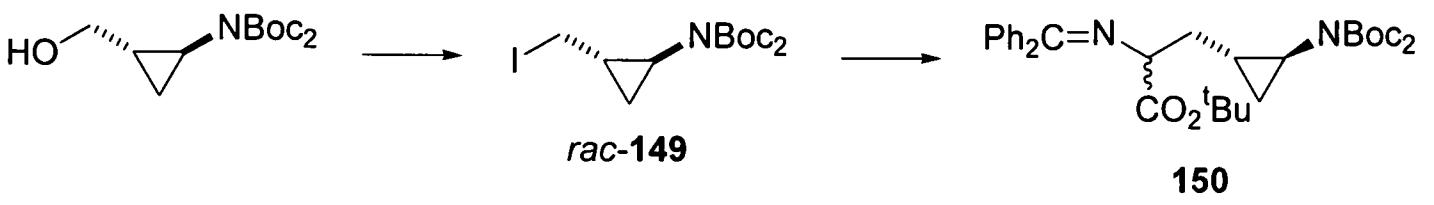
To a suspension of powdered KOH (0.10 g, 0.17 mmol) and TBAB (6 mg, 0.02 mmol) in dichloromethane (1 ml) at 0 °C was added *N*-(diphenylmethylene)glycine *tert*-butyl ester (0.10 g, 0.34 mmol) in one portion. A solution of *rac*-**149** (0.17 mmol, assuming 100 % conversion from alcohol) in CH_2Cl_2 (1.5 ml) was then added dropwise and the mixture was stirred at 0 °C for 30 minutes then at room temperature overnight. The suspension was filtered through a short pad of celite (washing with

CH_2Cl_2, 2 x 100 ml), concentrated *in vacuo*, then purified by flash column chromatography (3 petrol : 1 ether eluant) to afford a mixture of **150** (30 mg, 30%, 53:47 d.r.) and **161** (53 mg, 51%, 87:13 *meso*:C_2) both as clear oils.

Data for **150**: see (2*S*, 1'*S*, 2'*R*)-**150**/(2*R*, 1'*R*, 2'*S*)-**150** and (2*R*, 1'*S*, 2'*R*)-**150**/(2*S*, 1'*R*, 2'*S*)-**150**.

Data for **161**: ν_{max}/cm^{-1}(film) 2921, 2853, 1734, 1622, 1460, 1376, 1151, 695; δ_H (250 MHz, $CDCl_3$) 7.83-6.74 (20H, m, Ar*H*), 4.18 (2H, t, *J*7.2, $Ph_2C{=}NCH$ minor), 4.06 (2H, t, *J*6.4, $Ph_2C{=}NCH$ major), 2.89 (app dt, *J*6.4, 13.7, CH_2 major), 2.66 (t, *J*7.2, CH_2 minor), 2.23-2.17 (m, CH_2 major), 1.37 (18H, Boc, minor), 1.35 (18H, Boc, major); δ_C (62 MHz, $CDCl_3$) 170.7 (C), 170.3 (C), 139.7 (C), 136.4 (C), 130.1 (CH), 128.9 (CH), 128.3 (CH), 127.9 (CH), 127.8 (CH), 127.6 (CH), 80.9 (C), 63.5 (CH), 62.4 (CH), 37.5 (CH_2), 28.0 (CH_3); m/z (CI, NH_3) 603 $[M+H]^+$, found : $[M+H]^+$, 603.3229. $C_{39}H_{43}N_2O_4$ requires : 603.3223.

(2*S/R*, 1'*S, 2'*R**)-(*N*-(bis-Boc)-*N*-(diphenylmethylene)-3-(2-aminocyclopropyl)) alanine *tert*-butyl ester (150)**

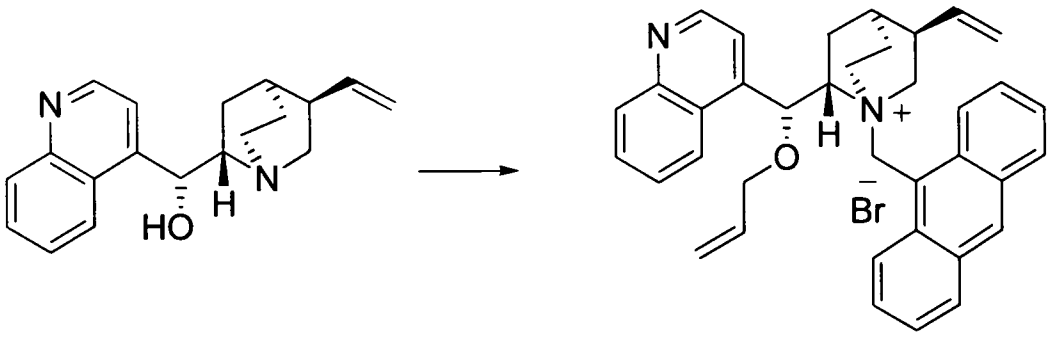


To a solution of 2,3-dichloro-5,6-dicyano-p-benzoquinone (0.23 g, 1.08 mmol) in chloroform (14 ml), was added triphenylphosphine (0.29 g, 1.11 mmol) followed by stirring at room temperature for 10 minutes. Tetrabutylammonium iodide (0.38 g, 1.11 mmol), was then added in one portion and the slurry stirred for a further 5 minutes. To this mixture was added a solution of alcohol *rac*-**48** (0.16 g, 0.54 mmol) in chloroform (6.0 ml) followed by additional stirring for 10 mins. Petrol (150 ml) was then added with vigorous stirring for 5 mins, and the resulting mixture was passed through a short pad of celite and further washed with petrol (2 x 100 ml). Solvents were removed *in vacuo*, followed by final addition of petrol (5 x 5ml) and removal of triphenylphosphine oxide by filtration. Subsequent concentration of the filtrate *in vacuo* then afforded *rac*-**149** in high purity.

To a suspension of powdered KOH (0.45 g, 8.12 mmol) and TBAB (17 mg, 0.05 mmol) in toluene (3 ml) at 0 °C was added *N*-(diphenylmethylene)glycine *tert*-butyl ester (0.12 g, 0.54 mmol) in one portion. A solution of *rac*-**149** (0.54 mmol, assuming 100 % conversion from alcohol) in toluene (3 ml) was then added dropwise and the mixture was stirred at 0 °C for 30 minutes then at room temperature for 2 hours. The suspension was then filtered through a short pad of celite (washing with CH_2Cl_2, 2 x 100 ml), concentrated *in vacuo*, then purified by flash column chromatography (3 petrol : 1 ether eluant) to afford the *title compound* **150** (0.17 g, 55 %, 44:56 d.r.) as a clear oil.

Data for **150**: see (2*S*, 1'*S*, 2'*R*)-**150**/(2*R*, 1'*R*, 2'*S*)-**150** and (2*R*, 1'*S*, 2'*R*)-**150**/(2*S*, 1'*R*, 2'*S*)-**150**.

O (9)-Allyl-*N*-9-anthracenylmethylcinchonidinium bromide (156)[75]



156

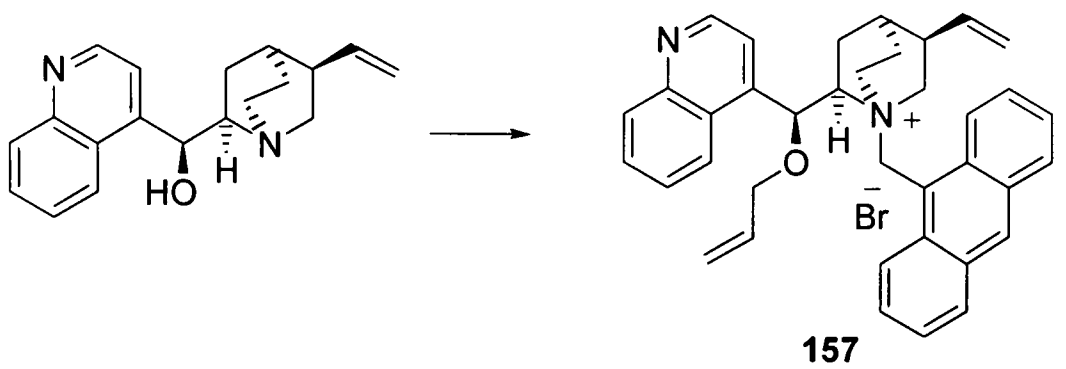
To a suspension of cinchonidine (2.00 g, 6.79 mmol) in toluene (20 ml) was added 9-(chloromethyl)anthracene (1.61 g, 7.10 mmol), and the mixture was heated at reflux for 2 hours. After cooling to room temperature solvents were removed *in vacuo*, followed by recrystallisation (CH_2Cl_2/ether) to afford *N*-9-anthracenylmethylcinchonidinium chloride as a light yellow solid (3.38g, 96%).

To a suspension of *N*-9-anthracenylmethylcinchonidinium chloride (3.38 g, 6.49 mmol), in CH_2Cl_2 (27 ml), was added allyl bromide (1.71 ml, 19.79 mmol), then 50% aqueous potassium hydroxide (3.60 ml). The mixture was stirred vigorously at room temperature for 4 hours, followed by dilution with water (100 ml), washing with CH_2Cl_2 (2 x 50 ml), then drying over sodium sulphate and concentration *in vacuo*. The crude product was recrystallised first from methanol/CH_2Cl_2, then from CH_2Cl_2/ether to afford the *title compound* **56** (3.36 g, 86%) as a light yellow solid; δ_H

(400 MHz, CD_3OD) 9.02 (1H, d, *J*4.6), 8.89 (1H, s), 8.76 (1H, d, *J*9.0), 8.57 (1H, m), 8.44 (1H, d, *J*9.0), 8.25-8.19 (3H, m), 7.95-7.92 (3H, m), 7.79-7.77 (2H, m), 7.65-7.61 (2H, m), 6.95 (1H, bs), 6.42-6.37 (2H, m), 5.88 (1H, d, *J*13.9), 5.60-5.64 (2H, m), 5.54 (1H, dd, *J*10.5, 1.2), 5.00 (1H, d, *J*13.5), 4.96 (1H, d, *J*6.9), 4.56-4.39 (m, 4H), 3.79 (1H, d, *J*11.0), 3.24 (1H, app. t, *J*12.2), 2.901H, dt, *J*10.8, 5.9), 2.48 (2H, m), 2.17 (1H, m), 1.96 (1H, d, *J*2.9).

Characterisation data correspond to literature values.[75]

O (9)-Allyl-*N*-9-anthracenylmethylcinchonium bromide (157)[133]



157

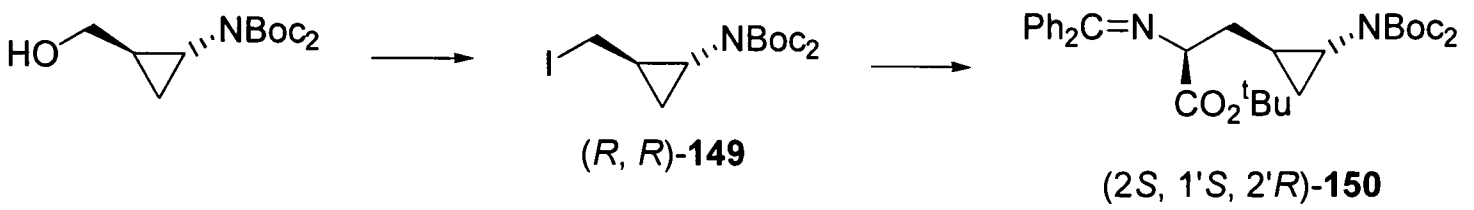
To a suspension of cinchonine (2.00 g, 6.79 mmol) in toluene (20 ml) was added 9-(chloromethyl)anthracene (1.61 g, 7.10 mmol), and the mixture was heated at reflux for 2 hours. After cooling to room temperature solvents were removed *in vacuo*, followed by recrystallisation (CH_2Cl_2/ether) to afford *N*-9-anthracenylmethylcinchonium chloride as a light yellow solid (3.28 g, 93 %).

To a suspension of *N*-9-anthracenylmethylcinchonium chloride (2.88 g, 5.52 mmol), in CH_2Cl_2 (24 ml), was added allyl bromide (1.46 ml, 16.82 mmol), then 50% aqueous potassium hydroxide (2.88 ml). The mixture was stirred vigorously at room temperature for 4 hours, followed by dilution with water (100 ml), washing with CH_2Cl_2 (2 x 50 ml), then drying over sodium sulphate and concentration *in vacuo*. The crude product was first purified by flash column chromatography (9 CH_2Cl_2 : 1 MeOH eluant), then recrystallised from ethanol/ether to afford the *title compound* **157** (3.34 g, 75 %) as a light yellow solid; δ_H (400 MHz, CD_3OD) 9.02 (1H, d, *J*4.6), 8.94 (1H, d, *J*9.0), 8.80 (1H, s), 8.68 (1H, m), 8.29 (1H, d, *J*8.9), 8.20-8.16 (3H, m), 7.93-7.90 (3H, m), 7.83-7.79 (1H, m), 7.70-7.66 (1H, m), 7.62-7.58 (2H, m), 6.88 (1H, bs), 6.45-6.36 (1H, m), 6.05 (2H, s), 5.98-5.89 (m, 1H), 5.71 (1H, d, *J*17.3), 5.61 (1H, d,

*J*10.5), 5.18 (1H, d, *J*10.4), 5.04 (1H, d, *J*17.2), 4.55-4.33 (4H, m), 4.24 (1H, t, *J*11.5), 3.14 (1H, t, *J*11.0), 2.82-2.75 (1H, m), 2.54 (1H, t, *J*11.8), 2.25 (1H, d, *J*7.7), 1.82 (1H, br s), 1.62 (1H, m), 1.18 (1H, m).

Characterisation data correspond to literature values.[133]

(2*S*, 1'*S*, 2'*R*)-(*N*-(bis-Boc)-*N*-(diphenylmethylene)-3-(2-aminocyclopropyl)) alanine *tert*-butyl ester ((2*S*, 1'*S*, 2'*R*)-150)



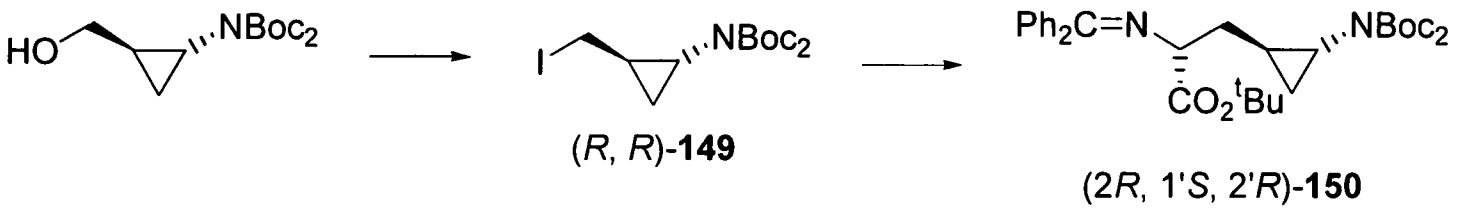
(*R*, *R*)-**149** (2*S*, 1'*S*, 2'*R*)-**150**

To a solution of 2,3-dichloro-5,6-dicyano-p-benzoquinone (79 mg, 0.35 mmol) in chloroform (4.5 ml), was added triphenylphosphine (91 mg, 0.35 mmol) followed by stirring at room temperature for 10 minutes. Tetrabutylammonium iodide (0.13 g, 0.35 mmol), was then added in one portion and the slurry stirred for a further 5 minutes. To this mixture was added a solution of alcohol (*R*, *R*)-**48** (50 mg, 0.17 mmol) in chloroform (2.0 ml) followed by additional stirring for 10 mins. Petrol (100 ml) was then added with vigorous stirring for 5 mins, and the resulting mixture was passed through a short pad of celite and further washed with petrol (2 x 100 ml). Solvents were removed *in vacuo*, followed by final addition of petrol (5 x 5ml) and removal of triphenylphosphine oxide by filtration. Subsequent concentration of the filtrate *in vacuo* then afforded (*R*, *R*)-**149** in high purity.

To a mixture of powdered $CsOH.H_2O$ (0.29 g, 1.74 mmol), *N*-(diphenylmethylene)glycine *tert*-butyl ester **29** (0.10 g, 0.35 mmol), *O*(9)-allyl-*N*-(9-anthracenylmethyl)-cinchonidinium bromide **156** (21 mg, 0.04 mmol) and activated 4Å molecular sieves (0.35 g) at –40 °C was added a solution of crude iodide (*R*, *R*)-**149** (0.17 mmol assuming 100 % conversion from alcohol) as a solution in toluene/CH_2Cl_2 (1:1, 0.8 ml). The resultant slurry was then stirred rapidly at –40 °C for 40 hours. The mixture was then diluted with further dichloromethane (10 ml) and quickly passed through a short pad of celite, followed by further washing with dichloromethane (3 x 50 ml). Solvents were then removed *in vacuo* and the crude

product was purified *via* flash column chromotography (4 petrol : 1 ether eluant, 5 % triethylamine base-wash), to afford the *title compound* (2*S*, 1'*S*, 2'*R*)-**150** (65 mg, 66 % from alcohol, 97 : 3 d.r.) as a colourless oil; $[\alpha]^{22}_{D}$ –52 (*c* 0.12, $CHCl_3$); ν_{max}/cm^{-1}(film) 3059, 2978, 1787, 1733, 1368, 1286, 1160, 1159, 1160, 698; δ_H (500 MHz, d^8-tol) 7.83-7.81 (2H, m, Ar*H*), 7.15-6.98 (8H, m, Ar*H*), 4.21 (1H, dd, *J*8.6, 4.8, $Ph_2C{=}NCH$), 2.61 (1H, ddd, *J*13.8, 8.6, 4.5, $Ph_2C{=}NCHCH_2$), 2.32-2.39 (1H, m,$CH(NBoc_2)$), 1.55 (1H, ddd, *J*13.8, 10.0, 4.8, $Ph_2C{=}NCHCH_2$), 1.40 (18H, s, Boc_2), 1.33 (9H, s, $CO_2{}^tBu$), 1.17-1.11 (1H, m, RC*H*(cyclopropyl)), 0.71-0.67 (1H, m, CH_2(cyclopropyl)), 0.50 (1H, app q, *J*6.6, CH_2(cyclopropyl)); δ_C (125 MHz, $CDCl_3$) 171.0 (C), 170.1 (C), 152.8 (C), 139.5 (C), 136.6 (C), 130.1 (CH), 130.0 (CH), 128.7 (CH), 128.4 (CH), 128.3 (CH), 128.2 (CH), 128.0 (CH), 127.9 (CH), 82.1 (C), 80.9 (C), 65.5 (CH), 35.9 (CH_2), 34.6 (CH), 28.1 (CH_3), 28.0 (CH_3), 20.4 (CH), 16.3 (CH_2); m/z (CI, NH_3) 565 $[M+H]^+$, found : $[M+H]^+$, 565.3296. $C_{33}H_{45}N_2O_6$ requires : 565.3278.

(2*R*, 1'*S*, 2'*R*)-(*N*-(bis-Boc)-*N*-(diphenylmethylene)-3-(2-aminocyclopropyl)alanine *tert*-butyl ester ((2*R*, 1'*S*, 2'*R*)-150)



(*R*, *R*)-**149**

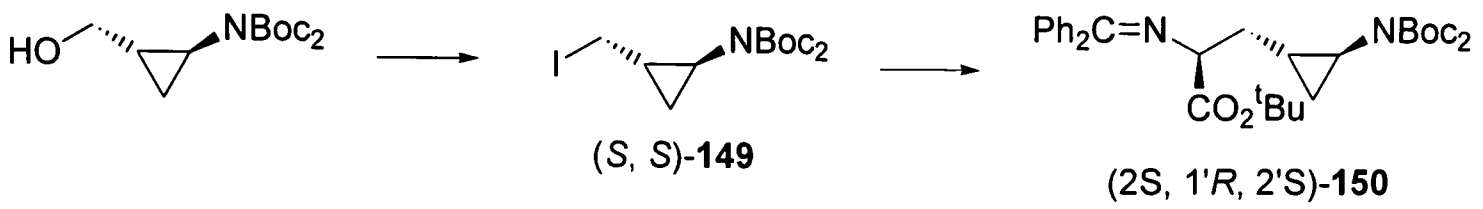
(2*R*, 1'*S*, 2'*R*)-**150**

To a solution of 2,3-dichloro-5,6-dicyano-p-benzoquinone (79 mg, 0.35 mmol) in chloroform (4.5 ml), was added triphenylphosphine (91 mg, 0.35 mmol) followed by stirring at room temperature for 10 minutes. Tetrabutylammonium iodide (0.13 g, 0.35 mmol), was then added in one portion and the slurry stirred for a further 5 minutes. To this mixture was added a solution of alcohol (*R*, *R*)-**48** (50 mg, 0.17 mmol) in chloroform (2.0 ml) followed by additional stirring for 10 mins. Petrol (100 ml) was then added with vigorous stirring for 5 mins, and the resulting mixture was passed through a short pad of celite and further washed with petrol (2 x 100 ml). Solvents were removed *in vacuo*, followed by final addition of petrol (5 x 5ml) and

removal of triphenylphosphine oxide by filtration. Subsequent concentration of the filtrate *in vacuo* then afforded (*R*, *R*)-**149** in high purity.

To a mixture of powdered $CsOH.H_2O$ (0.29 g, 1.74 mmol), *N*-(diphenylmethylene)glycine *tert*-butyl ester **29** (0.10 g, 0.35 mmol), *O*(9)-allyl-*N*-(9-anthracenylmethyl)-cinchonium bromide **157** (21 mg, 0.04 mmol) and activated 4Å molecular sieves (0.35 g) at –40 °C was added a solution of crude iodide (*R*, *R*)-**149** (0.17 mmol, assuming 100 % conversion from alcohol) as a solution in toluene/CH_2Cl_2 (1:1, 0.8 ml). The resultant slurry was then stirred rapidly at –40 °C for 40 hours. The mixture was then diluted with further dichloromethane (10 ml) and quickly passed through a short pad of celite, followed by further washing with dichloromethane (3 x 50 ml). Solvents were then removed *in vacuo* and the crude product was purified *via* flash column chromotography (4 petrol : 1 ether eluant, 5 % triethylamine base-wash), to afford the *title compound* (2*R*, 1'*S*, 2'*R*)-**150** (51 mg, 52 % from alcohol, 94 : 6 d.r.) which was then recrystallised from ether/hexane to yield colourless needles (m.p. 127-128 °C, > 95 % d.r.); $[\alpha]^{22}_D$ +21 (*c* 0.39, $CHCl_3$); ν_{max}/cm^{-1}(film) 3059, 2978, 1787, 1735, 1368, 1285, 1258, 1160, 1116, 801, 783, 698; δ_H (500 MHz, d^8-tol) 7.82-7.80 (2H, m, Ar*H*), 7.16-6.98 (8H, m, Ar*H*), 4.28 (1H, app t, *J*6.3, $Ph_2C{=}NCH$), 2.73-2.69 (1H, m, $Ph_2C{=}NCHCH_2$), 2.41-2.39 (1H, m, C*H*$NBoc_2$), 1.47-1.28 (29H, m, $Ph_2C{=}NCHCH_2$, Boc_2, $CO_2{}^tBu$, RC*H*(cyclopropyl)), 0.85-0.81 (1H, m, CH_2(cyclopropyl)), 0.74 (1H, app q, *J*6.5, CH_2(cyclopropyl)); δ_C (125 MHz, $CDCl_3$) 171.0 (C), 169.7 (C), 153.0 (C), 139.6 (C), 136.7 (C), 132.4 (CH), 130.1 (CH), 130.0 (CH), 128.8 (CH), 128.5 (CH), 128.3 (CH), 128.0 (CH), 127.8 (CH), 82.1 (C), 80.9 (C), 65.0 (CH), 36.2 (CH_2), 33.8 (CH), 28.1 (CH_3), 28.0 (CH_3), 20.4 (CH), 16.7 (CH_2); m/z (CI, NH_3) 565 $[M+H]^+$, found : $[M+H]^+$, 565.3304. $C_{33}H_{45}N_2O_6$ requires : 565.3278.

(2*S*, 1'*R*, 2'*S*)-(*N*-(bis-Boc)-*N*-(diphenylmethylene)-3-(2-aminocyclopropyl)) alanine *tert*-butyl ester ((2*S*, 1'*R*, 2'*S*)-150)



(*S*, *S*)-**149**

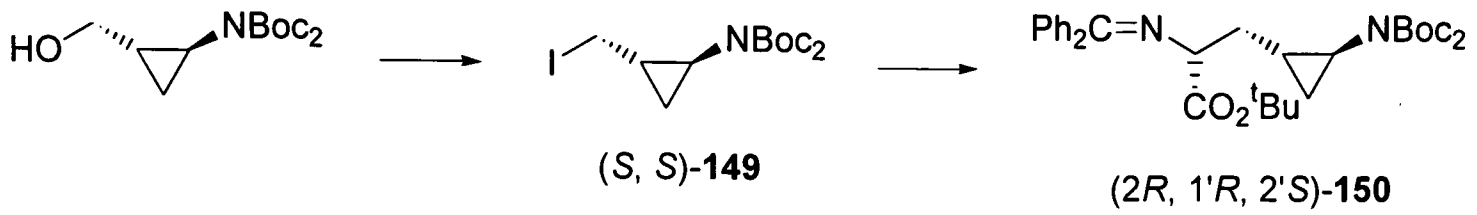
(2S, 1'*R*, 2'S)-**150**

To a solution of 2,3-dichloro-5,6-dicyano-p-benzoquinone (0.47 g, 2.12 mmol) in chloroform (25 ml), was added triphenylphosphine (0.55 g, 2.12 mmol) followed by stirring at room temperature for 10 minutes. Tetrabutylammonium iodide (0.79 g, 2.12 mmol), was then added in one portion and the slurry stirred for a further 5 minutes. To this mixture was added a solution of alcohol (*S*, *S*)-**48** (0.30 g, 1.03 mmol) in chloroform (10 ml) followed by additional stirring for 10 mins. Petrol (150 ml) was then added with vigorous stirring for 5 mins, and the resulting mixture was passed through a short pad of celite and further washed with petrol (2 x 100 ml). Solvents were removed *in vacuo*, followed by final addition of petrol (5 x 5ml) and removal of triphenylphosphine oxide by filtration. Subsequent concentration of the filtrate *in vacuo* then afforded (*S*, *S*)-**149** in high purity.

To a mixture of powdered $CsOH.H_2O$ (1.73 g, 10.30 mmol), *N*-(diphenylmethylene)glycine *tert*-butyl ester **29** (0.61 g, 2.06 mmol), *O*(9)-allyl-*N*-(9-anthracenylmethyl)-cinchonidinium bromide **156** (0.125 g, 0.21 mmol) and activated 4Å molecular sieves (2.0 g) at –40 °C was added a solution of crude iodide (*S*, *S*)-**149** (1.03 mmol, assuming 100 % conversion from alcohol) as a solution in toluene/CH_2Cl_2 (1:1, 4.75 ml). The resultant slurry was then stirred rapidly at –40 °C for 40 hours. The mixture was then diluted with further dichloromethane (30 ml) and quickly passed through a short pad of celite, followed by further washing with dichloromethane (2 x 150 ml). Solvents were then removed *in vacuo* and the crude product was purified *via* flash chromotography (4 petrol : 1 ether eluant, 5 % triethylamine base-wash), to afford the *title compound* (2*S*, 1'*R*, 2'*S*)-**150** (0.37 g, 64 % from alcohol, 93 : 7 d.r.) which was then recrystallised from ether/hexane to yield colourless needles (m.p. 127-128 °C, > 95 % d.r.).

^1H NMR data for (2*S*, 1'*R*, 2'*S*)-**150** ($[\alpha]^{27}_D$ -24 (*c* 1.32, $CHCl_3$)) correspond to compound (2*R*, 1'*S*, 2'*R*)-**150**.

(2*R*, 1'*R*, 2'*S*)-(*N*-(bis-Boc)-*N*-(diphenylmethylene)-3-(2-aminocyclopropyl)) alanine *tert*-butyl ester ((2*R*, 1'*R*, 2'*S*)-150)



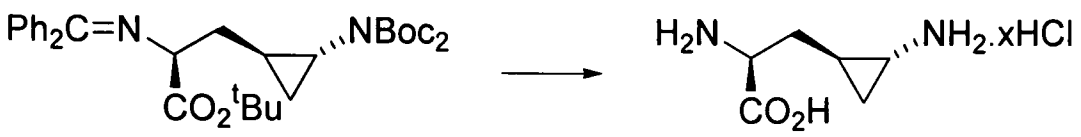
(*S*, *S*)-**149** (2*R*, 1'*R*, 2'*S*)-**150**

To a solution of 2,3-dichloro-5,6-dicyano-p-benzoquinone (0.16 g, 0.72 mmol) in chloroform (9 ml), was added triphenylphosphine (0.19 g, 0.72 mmol) followed by stirring at room temperature for 10 minutes. Tetrabutylammonium iodide (0.27 g, 0.72 mmol), was then added in one portion and the slurry stirred for a further 5 minutes. To this mixture was added a solution of alcohol (*S*, *S*)-**48** (0.10 g, 0.35 mmol) in chloroform (4.0 ml) followed by additional stirring for 10 mins. Petrol (150 ml) was then added with vigorous stirring for 5 mins, and the resulting mixture was passed through a short pad of celite and further washed with petrol (2 x 100 ml). Solvents were removed *in vacuo*, followed by final addition of petrol (5 x 5ml) and removal of triphenylphosphine oxide by filtration. Subsequent concentration of the filtrate *in vacuo* then afforded (*S*, *S*)-**149** in high purity.

To a mixture of powdered $CsOH.H_2O$ (0.58 g, 3.48 mmol), *N*-(diphenylmethylene)glycine *tert*-butyl ester **29** (0.21 g, 0.70 mmol), *O*(9)-allyl-*N*-(9-anthracenylmethyl)-cinchonium bromide **157** (42 mg, 0.07 mmol) and activated 4Å molecular sieves (0.7 g) at –40 °C was added a solution of crude iodide (*S*, *S*)-**149** (0.35 mmol assuming 100 % conversion from alcohol) as a solution in toluene/CH_2Cl_2 (1:1, 1.60 ml). The resultant slurry was then stirred rapidly at –40 °C for 40 hours. The mixture was then diluted with further dichloromethane (20 ml) and quickly passed through a short pad of celite, followed by further washing with dichloromethane (2 x 100 ml). Solvents were then removed *in vacuo* and the crude product was purified *via* flash column chromotography (4 petrol : 1 ether eluant, 5 % triethylamine base-wash), to afford the *title compound* (2*R*, 1'*R*, 2'*S*)-**150** (0.12 g, 60 % from alcohol, 92 : 8 d.r.) as a colourless oil.

^{1}H NMR data for (2*R*, 1'*R*, 2'*S*)-**150** ($[\alpha]^{22}_D$ +58 (*c* 0.12, $CHCl_3$)) correspond to compound (2*S*, 1'*S*, 2'*R*)-**150**.

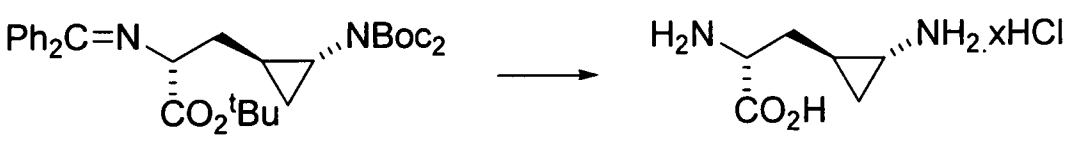
(2*S*, 1'*S*, 2'*R*)-Aminocyclopropyl alanine.xHCl (158)



158

To a solution of amino acid (2*S*, 1'*S*, 2'*R*)-**150** (65 mg, 0.11 mmol) in THF (1 ml), was added 1.2 M HCl (2.60 ml), followed by stirring at room temperature for 48 hours. The mixture was dilluted with distilled water (50 ml), washed with ether (2 x 25 ml), then aqueous fractions were concentrated *in vacuo* and freeze-dried to afford the *title compound* **158** (22 mg), as a glassy solid; $[\alpha]^{22}_{D}$ -10 (*c* 0.41, MeOH); ν_{max}/cm^{-1}(film) 3403, 2992, 2927, 1737, 1603, 1504; δ_H (250 MHz, D_2O) 4.04 (1H, app t, *J*6.3, H_2NCH), 2.58-2.52 (1H, m, $CHNH_2$), 2.10-1.96 (1H, m, H_2NCHCH_2), 1.90-1.78 (1H, m, H_2NCHCH_2), 1.37-1.22 (1H, m, RC*H*(cyclopropyl)), 1.05 (1H, ddd, *J*9.5, 7.0, 4.3, CH_2(cyclopropyl)), 0.84 (1H, app q, *J*7.0, CH_2(cyclopropyl)); δ_C (125 MHz, $CDCl_3$) 175.0 (C), 55.7 (CH), 34.4 (CH_2), 30.7 (CH), 15.6 (CH), 12.7 (CH_2); m/z (CI, NH_3) 145 $[M\text{-}xHCl+H]^+$, found : $[M\text{-}xHCl+H]^+$, 145.0977. $C_6H_{13}N_2O_2$ requires : 145.0981.

(2*R*, 1'*S*, 2'*R*)-Aminocyclopropyl alanine.xHCl (159)

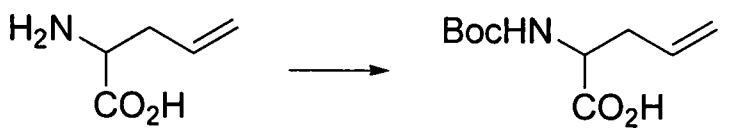


159

To a solution of amino acid (2*R*, 1'*S*, 2'*R*)-**150** (51 mg, 0.09 mmol) in THF (1ml), was added 1.2 M HCl (2.60 ml), followed by stirring at room temperature for 48 hours. The mixture was dilluted with distilled water (50 ml),washed ether (2 x 25 ml), then aqueous fractions were concentrated *in vacuo* and then freeze-dried to afford the *title compound* **159** (17 mg), as a glassy solid; $[\alpha]^{22}_{D}$ -8 (*c* 0.30, MeOH); ν_{max}/cm^{-1}(film) 3427, 3012, 2934, 1735, 1621, 1509; δ_H (250 MHz, D_2O) 4.00 (1H, app t, *J*6.3, H_2NCH), 2.56-2.50 (1H, m, $CHNH_2$), 2.10 (1H, app dt, *J*15.0, 6.3, H_2NCHCH_2), 1.71

(1H, ddd, *J*15.0, 8.2, 6.3, H_2NCHCH_2), 1.37-1.22 (1H, m, RC*H*(cyclopropyl)), 1.04 (1H, ddd, *J*9.8, 6.9, 4.1, CH_2(cyclopropyl)), 0.82 (1H, app q, *J*6.9, CH_2(cyclopropyl)); δ_C (125 MHz, $CDCl_3$) 175.4 (C), 55.1 (CH), 34.5 (CH_2), 30.7 (CH), 15.8 (CH), 12.6 (CH_2); m/z (CI, NH_3) 145 $[M\text{-}xHCl+H]^+$, found : $[M\text{-}xHCl+H]^+$, 145.0977. $C_6H_{13}N_2O_2$ requires : 145.0978.

2-*tert*-Butoxycarbonylamino-pent-4-enoic acid (161)[134]

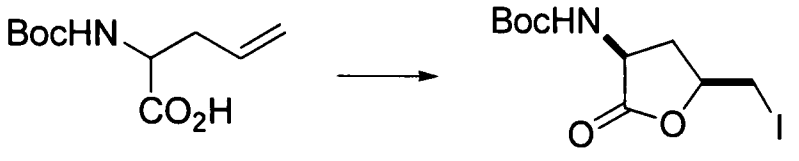


161

To a mixture of (±) allylglycine (1.50 g, 13.93 mmol), sodium hydrogen carbonate (3.28 g, 39.09 mmol), and di-*tert*-butyl dicarbonate (5.12 g, 23.45 mmol) was added THF (50 ml) then distilled water (50 ml). The mixture was stirred overnight at room temperature followed by washing with ether (50 ml) and acidification of the aqueous layer to approximately pH 4 (aqueous citric acid). The aqueous layer was extracted with ethyl acetate (2 x 40 ml), followed by drying over magnesium sulfate and removal of solvents *in vacuo* to furnish a crude solid. Recrystallisation from ether/pentane afforded the *title compound* **161** (2.61 g, 93%) as a white crystalline solid (m.p. 109-111°C); δ_H (250 MHz, $CDCl_3$) 5.83-5.66 (1H, m, C*H*=CH_2), 5.21-5.15 (2H, m, CH=CH_2), 5.01 (1H, d, *J*7.6, NHBoc), 4.39 (1H, m, BocHNC*H*), 2.65-2.50 (2H, m, CH_2), 1.45 (9H, s, Boc).

Characterisation data correspond to literature values.[134]

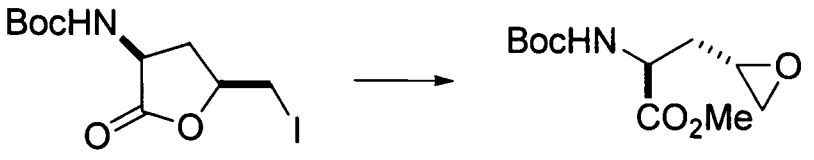
tert-Butyl (3*S, 5*S**)-5-(iodomethyl)-2-oxo-tetrahydrofuran-3-ylcarbamate (162)**[85]



162

To a mixture of amino acid **161** (1.13 g, 5.24 mmol) and sodium hydrogen carbonate (4.74 g, 56.38 mmol) was added THF (20 ml) then distilled water (55 ml). This suspension was cooled to 0 °C followed by the dropwise addition of a solution of iodine (3.99 g, 15.72 mmol) in THF (30 ml) over 30 mins with subsequent stirring at this temperature for 5 hours. Saturated aqueous sodium sulfite (150 ml) was added, followed by extraction with dichloromethane (3 x 50 ml) and washing with saturated sodium bicarbonate (2 x 30 ml). After drying over magnesium sulfate and concentration *in vacuo* the crude solid was recrystallised from ethylacetate/pentane to afford the *title compound* **162** (1.45 g, 81%) as a white crystalline solid (m.p. 126-128°C); ν_{max}/cm^{-1}(film) 2978, 2926, 1781, 1707, 1528, 1367, 1291, 1162; δ_H (250 MHz, $CDCl_3$) 5.18 (1H, s, NHBoc), 4.51-4.39 (2H, m, BocHNC*H*, OC*H*CH_2I), 3.44 (1H, dd, *J*10.4, 4.9, CH_2I), 3.31 (1H, dd, *J*10.4, 7.9, CH_2I), 3.03-2.93 (1H, m, CH_2), 1.94-1.80 (1H, m, CH_2), 1.44 (9H, s, Boc); δ_C (62 MHz, $CDCl_3$) 174.0 (C), 155.3 (C), 80.7 (C), 76.0 (CH), 51.8 (CH), 37.0 (CH_2), 28.3 (CH_3), 5.6 (CH_2); m/z (CI, NH_3) 359 $[M + NH_4]^+$, found : $[M + NH_4]^+$, 359.0481. $C_{10}H_{20}N_2O_4I$ requires : 359.0468. Characterisation data correspond to literature values.[85]

(*S)-Methyl 2-(*tert*-butoxycarbonyl)amino-3-((*S**)-oxiran-2-yl)propanoate (163)**[85]

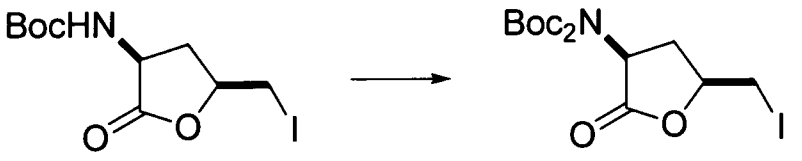


163

To a mixture of iodolactone **162** (1.00 g, 2.93 mmol) and sodium carbonate (0.93 g, 8.79 mmol) was added methanol (15 ml), followed by stirring at room temperature overnight. This mixture was then diluted with ethyl acetate (2 x 40 ml) and washed with saturated ammonium chloride (2 x 25 ml). Organic fractions were combined, dried over magnesium sulfate, then concentrated *in vacuo* to yield a crude solid. Recrystallisation from ether/pentane afforded the *title compound* **163** (0.64 g, 89%) as a white crystalline solid (m.p. 77-79 °C); δ_H (250 MHz, $CDCl_3$) 5.30 (1H, m, NHBoc), 4.43 (1H, m, BocHNC*H*), 3.73 (3H, s, OCH_3), 2.97 (1H, m, C*H*(O)CH_2), 2.73 (1H, dd, *J*5.0, 4.2, (O)CH_2), 2.48 (1H, dd, *J*5.0, 3.1, (O)CH_2), 2.01 (1H, ddd, *J*14.1, 6.9, 3.4, CH_2), 1.92 (1H, ddd, *J*14.1, 7.3, 5.0, CH_2), 1.44 (9H, s, Boc).

Characterisation data correspond to literature values.[85]

di-*tert*-Butyl (3*S, 5*S**)-5-(iodomethyl)-2-oxo-tetrahydrofuran-3-ylcarbamate (165)**

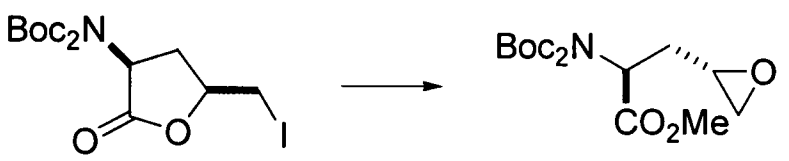


165

To a mixture of iodolactone **162** (0.50 g, 1.47 mmol) and DMAP (36 mg, 0.29 mmol) in acetonitrile (6 ml), was added di-*tert*-butyl dicarbonate (0.64 g, 2.93 mmol) dropwise as solution in acetonitrile (3 ml). The mixture was stirred at room temperature overnight, followed by dilution with dichloromethane (100 ml), washing with saturated sodium hydrogen carbonate (2 x 30 ml) then drying over magnesium sulfate. Solvents were removed *in vacuo* to afford a crude solid, which was

recrystallised from ether/pentane to afford the *title compound* **165** (0.59 g, 91 %) as a white crystalline solid (m.p. 86-88 °C); ν_{max}/cm^{-1}(film) 2980, 2935, 1789, 1735, 1698, 1383, 1368, 1298, 1238, 1168, 1134; δ_H (250 MHz, $CDCl_3$) 5.18 (1H, dd, *J*9.5, 1.2, Boc_2NCH), 4.63-4.51 (1H, m, $OCHCH_2I$), 3.50 (1H, dd, *J*9.8, 5.5, CH_2I), 3.26 (1H, dd, *J*9.8, 9.2, CH_2I), 2.82 (1H, ddd, *J*12.4, 9.5, 6.4, CH_2), 2.17 (1H, ddd, *J*12.4, 10.7, 9.5, CH_2), 1.50 (18H, s, Boc); δ_C (62 MHz, $CDCl_3$) 172.5 (C), 151.5 (C), 84.2 (C), 76.2 (CH), 55.7 (CH), 33.6 (CH_2), 28.0 (CH_3), 5.1 (CH_2); m/z (CI, NH_3) 459 $[M+NH_4]^+$, found : $[M+NH_4]^+$, 459.0997. $C_{15}H_{28}N_2O_6I$ requires : 459.0992.

(*S)-Methyl 2-(di-*tert*-butoxycarbonyl)amino-3-((*S**)-oxiran-2-yl)propanoate (166)**



166

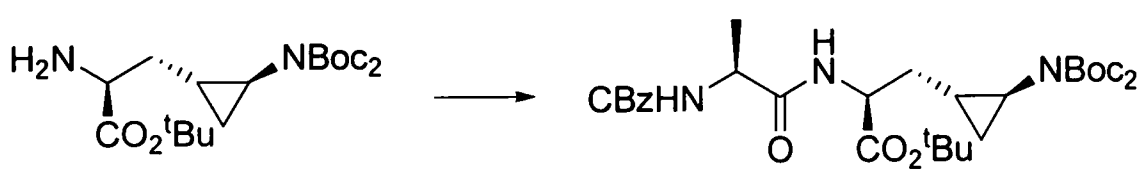
To a mixture of iodolactone **165** (0.20 g, 0.45 mmol) and sodium carbonate (0.14 g, 1.35 mmol) was added methanol (4 ml), and the mixture was then stirred at room temperature overnight. The suspension was diluted with ethyl acetate (2 x 15 ml) and washed with saturated ammonium chloride (25 ml). Organic fractions were combined and dried over magnesium sulfate, followed by concentration *in vacuo* and purification by flash column chromatography (ether eluant) to afford the *title compound* **166** (0.12 g, 80%) as a colourless oil; ν_{max}/cm^{-1}(film) 2984, 1789, 1745, 1700, 1369, 1146, 1121; δ_H (250 MHz, $CDCl_3$) 5.07 (1H, dd, *J*4.6, 10.1, Boc_2NCH), 3.70 (3H, s, OCH_3), 3.00-2.92 (1H, m, $CH(O)CH_2$), 2.77-2.73 (1H, m, OCH_2), 2.46 (1H, dd, *J* 5.2, 2.7, OCH_2), 2.34 (1H, ddd, *J*14.6, 6.4, 4.6, CH_2), 2.06 (1H, ddd, *J*14.6, 10.1, 5.8, CH_2), 1.47 (18H, s, Boc); δ_C (62 MHz, $CDCl_3$) 170.6 (C), 151.8 (C), 83.4 (C), 56.0, 52.3, 49.2 (CH_2), 47.2 (CH), 33.5 (CH_2), 27.9 (CH_3); m/z (CI, NH_3) 346 $[M+H]^+$, found : $[M+H]^+$, 346.1866. $C_{16}H_{28}NO_7$ requires : 346.1866.

(*S*)-2-Amino-3-((1*S*, 2*S*)-2-di-(*tert*-butoxycarbonyl)amino-cyclopropyl)-propionic acid *tert*-butyl ester (169)

169

To a solution of (2*S*, 1′*R*, 2′*S*)-**150** (0.29 g, 0.52 mmol), in THF (5.5 ml), was added 15 % aqueous citric acid (2.70 ml) dropwise at room temperature. The mixture was then stirred rapidly for 1.5 hours, followed by dilution with ethyl acetate (100 ml), washing with saturated sodium bicarbonate (100 ml), then further extraction with ethyl acetate (100 ml). Organic fractions were combined and dried over magnesium sulfate, followed by removal of solvents *in vacuo*. The crude mixture was then purified by flash column chromatography (ethyl acetate eluant), to afford the *title compound* **169** (0.17 g, 84 %) as a clear oil; $[\alpha]^{23}_{D}$ 26.8 (*c* 1.34, $CHCl_3$); ν_{max}/cm^{-1}(film) 3403, 2979, 2933, 1785, 1733, 1367, 1282, 1254, 1159, 1118, 852, 752; δ_H (250 MHz, $CDCl_3$) 3.54 (1H, dd, *J* 7.3, 5.2, $H_2NCH(CO_2{}^tBu)$), 2.41-2.35 (1H, m, $CHNBoc_2$), 1.92-1.80 (2H, m, NH_2, H_2NCHCH_2), 1.47-1.28 (29H, m, Boc_2, $CO_2{}^tBu$, $(CO_2{}^tBu)CHCH_2$), 1.13-1.00 (1H, m, RCH(cyclopropyl)), 0.85-0.81 (2H, m, CH_2(cyclopropyl)); δ_C (100 MHz, $CDCl_3$) 174.5 (C), 153.2 (C), 82.3 (C), 80.9 (C), 54.6 (CH), 37.6 (CH_2), 33.9 (CH), 28.0 (CH_3), 19.4 (CH), 16.7 (CH_2); m/z (CI, NH_3) 401 $[M+H]^+$, found : $[M+H]^+$, 401.2654. $C_{20}H_{37}N_2O_6$ requires : 401.2652.

N-CBz-L-Alanine-(*S*)-2-Amino-3-((1*S*, 2*S*)-2-di-(*tert*-butoxycarbonyl)amino-cyclopropyl)-propionic acid *tert*-butyl ester (170)

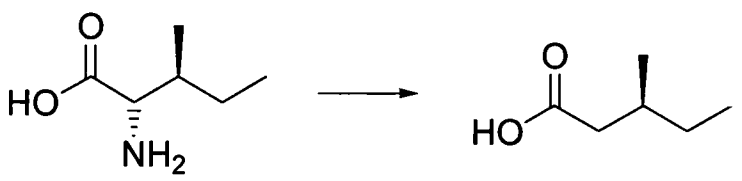


170

To a mixture of DCC (33 mg, 0.16 mmol) and HOBt (43 mg, 0.32 mmol) in DMF (1 ml), was added a solution of amine **169** (32 mg, 0.08 mmol) and *N*-CBz-Ala (36 mg,

0.16 mmol) in DMF (1.5 ml). The mixture was then stirred at room temperature for 1 hour. DMF was removed at high vacuum (warm water bath), followed by addition of ether (3 ml) and filtration. The filtrate was concentrated and purified by flash column chromatography (2 ether : 1 petrol eluant) to afford the *title compound* **170** (50 mg, 100 %) as a white foam; $[\alpha]^{20}_{D}$ 6.0 (*c* 2.0, $CHCl_3$); ν_{max}/cm^{-1}(film) 3314, 2980, 2933, 1726, 1674, 1368, 1274, 1257, 1160, 1121, 738; δ_H (250 MHz, $CDCl_3$) 8.75 (1H, d, *J* 9.5, N*H*CH($CO_2{}^tBu$)), 7.36-7.28 (5H, m, Ar), 5.73 (1H, d, *J* 7.3, CBzN*H*), 5.10 (2H, s, $PhCH_2$), 4.77-4.70 (1H, m, NHC*H*($CO_2{}^tBu$)), 4.35 (1H, app quintet, *J* 7.3, CBzNHC*H*(Me)), 2.48-2.40 (2H, m, C*H*$NBoc_2$, NHCH($CO_2{}^tBu$)CH_2), 1.50-1.40 (30H, m, Boc_2, $CO_2{}^tBu$, Me), 1.18-1.05 (1H, m, NHCH($CO_2{}^tBu$)CH_2), 0.98-0.84 (1H, m, RC*H*(cyclopropyl)), 0.80-0.72 (1H, m, CH_2(cyclopropyl)), 0.66 (1H, app q, CH_2(cyclopropyl)); δ_C (100 MHz, $CDCl_3$) 171.9 (C), 170.3 (C), 155.6 (C), 153.8 (C), 136.5 (C), 128.5 (CH), 128.0 (CH), 128.0 (CH), 83.2 (C), 81.7 (C), 66.6 (CH_2), 51.5 (CH), 50.2 (CH), 35.1 (CH), 34.4 (CH_2), 28.0 (CH_3), 19.8 (CH), 16.7 (CH_2), 13.7 (CH_3); m/z (CI, NH_3) 606 $[M+H]^+$, found : $[M+H]^+$, 606.3381. $C_{31}H_{48}N_3O_9$ requires : 606.3391.

(*S*)-3-Methyl pentanoic acid (59)[135]



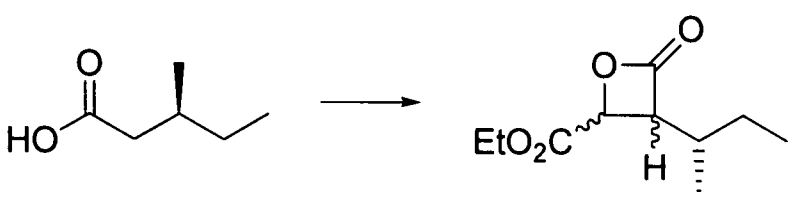
59

To a mixture of potassium hydroxide (17.10 g, 0.31 mol), and L-isoleucine **58** (4.00 g, 30.49 mmol) was added distilled water (120 ml) with stirring. After 10 minutes the solution was cooled with an ice-bath, and hydroxylamine-*O*-sulfonic acid (16.96 g, 0.15 mol) was added slowly over 30 minutes. The mixture was then allowed to warm to room temperature and stir overnight, followed by acidification to approximately pH 2 (concentrated H_2SO_4) and extraction with diethyl ether (2 x 200 ml). After drying over magnesium sulfate, the solvent was blown down under a nitrogen stream, and the crude product distilled (b.p. 196 °C), to afford the *title compound* **59** (2.62 g, 74 %) as a clear oil; $[\alpha]^{20}_{D}$ +7.9 (*c* 2.8, $CHCl_3$), δ_H (250 MHz, $CDCl_3$) 11.60 (1H, br s, CO_2H),

2.36 (1H, dd, *J* 15.0, 6.1, HO_2CCH_2), 2.14 (1H, dd, *J* 15.0, 7.9, HO_2CCH_2), 2.00-1.80 (1H, m, $CH(CH_3)Et$), 1.48-1.16 (2H, m, $CH(CH_3)CH_2CH_3$), 0.96 (3H, d, *J* 6.7, $C(CH_3)H$), 0.89 (3H, app t, *J* 7.3, $CH(CH_3)CH_2CH_3$).

Characterisation data correspond to literature values.[135]

(2*S/R*, 3*S/R*)-Ethyl 3-((*S*)-*sec*-butyl)-4-oxooxetane-2-carboxylate (195)

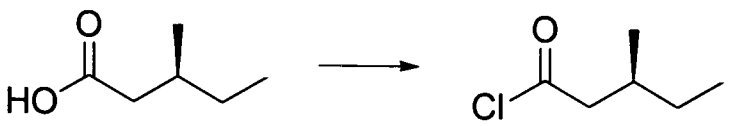


195

To a slurry of Mukaiyama's reagent (0.62 g, 2.41 mmol) in acetonitrile (10 ml) was added triethylamine (0.45 ml, 3.21 mmol) followed by stirring at room temperature for 5 minutes. To this mixture was added solutions of ethyl glyoxylate (0.25 ml, 1.20 mmol, 50 % solution in toluene) in acetonitrile (3 ml) and acid **159** (0.10 ml, 0.802 mmol) in acetonitrile (3.5 ml) simultaneously over 8 hours, then this mixture was stirred for a further 15 hours. The solution was diluted with ether (100 ml) then washed with water (100 ml) and dried over magnesium sulfate. Solvents were removed *in vacuo*, and the crude mixture was then purified by flash column chromatography (2 petrol : ether eluant) to afford the *title compound* **195** (35.4 mg, 22 %) as a complex mixture of four isomers (85:15 *cis/trans* ratio, *cis*-isomer approximately 1:1 d.r., *trans*-isomer approximately 4:1 d.r).

Data for *cis*-**195**: see (2*S*, 3*S*, 1′S)-**195** and (2*R*, 3*R*, 1′S)-**195**. Distinct signals of *trans*-**195** were also identified: δ_H (250 MHz, $CDCl_3$) 4.64 (1H, d, *J* 4.3, EtO_2CCH major and minor isomers), 3.67 (1H, dd, *J* 7.6, 4.3, EtO_2CCHCH major isomer), 3.59 (1H, dd, *J* 8.9, 4.3, EtO_2CCHCH minor isomer).

(*S*)-3-Methyl pentanoic acid chloride (196)[136]

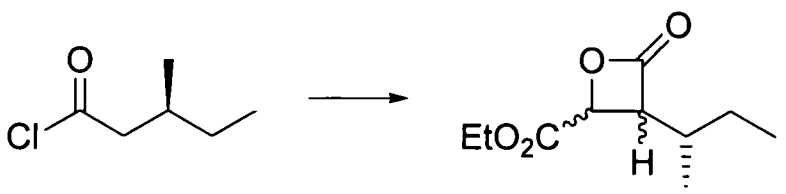


196

To a solution of acid **159** (2.60 g, 22.38 mmol), in dichloromethane (15 ml) at 0□C was added a solution of oxalyl chloride (6.83 ml, 78.34 mmol) in dichloromethane (15 ml) dropwise over 20 min, and the solution was then stirred for 1 hour. Most of the solvent was blown-down under a nitrogen stream, and the crude mixture distilled (b.p. 140-141□C), to yield the *title compound* **196** (2.41 g, 80 %) as a clear oil; $[\alpha]^{20}_{D}$ +6.5 (*c* 1.8, $CHCl_3$); δ_H (250 MHz, $CDCl_3$) 2.89 (1H, dd, *J* 16.2, 5.8, ClO_2CCH_2), 2.67 (1H, dd, *J* 16.2, 7.9, ClO_2CCH_2), 2.10-1.91 (1H, m, $CH(CH_3)Et$), 1.49-1.18 (2H, m, $CH(CH_3)CH_2CH_3$), 0.98 (3H, d, *J* 6.7, $C(CH_3)H$), 0.91 (3H, app t, *J* 7.3, $CH(CH_3)CH_2CH_3$).

Characterisation data correspond to literature values.[136]

(2*S/R*, 3*S/R*)-Ethyl 3-((*S*)-*sec*-butyl)-4-oxooxetane-2-carboxylate (195)

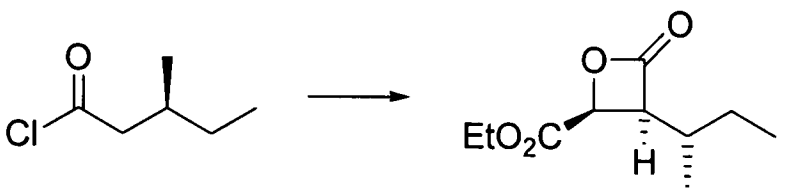


195

To a mixture of acid chloride **196** (0.05 ml, 0.36 mmol) and ethyl glyoxylate (0.16 ml, 0.77 mmol, 50 % in toluene) in chloroform (0.5 ml), was added triethylamine (0.20 ml, 1.45 mmol) rapidly, and the mixture was stirred at room temperature for a further 30 minutes. Most of the solvent was blown down under a nitrogen stream and the crude product was purified by flash column chromatography (2 petrol : ether eluant) to afford the *title compound* **195** (27.0 mg, 47 %) as a complex mixture of four isomers (79:21 *cis/trans* mixture, *cis*-isomer approximately 1:1 d.r., *trans*-isomer approximately 1:1 d.r.).

Data for *cis*-**195** : see (2*S*, 3*S*, 1′S)-**195** and (2*R*, 3*R*, 1′S)-**195**. Distinct signals of *trans*-**195** were also identified: δ_H (250 MHz, $CDCl_3$) 4.64 (1H, d, *J* 4.3, EtO_2CCH isomer A and B), 3.67 (1H, dd, *J* 7.6, 4.3, EtO_2CCHCH isomer A), 3.59 (1H, dd, *J* 8.9, 4.3, EtO_2CCHCH isomer B).

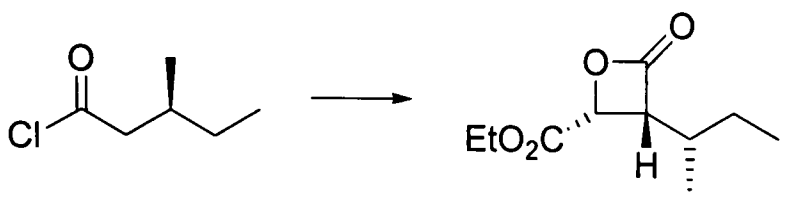
(2*S*, 3*S*)-Ethyl 3-((*S*)-*sec*-butyl)-4-oxooxetane-2-carboxylate ((2*S*, 3*S*, 1′*S*)-150)



(2*S*, 3*S*, 1′*S*)-**195**

To a cooled solution of hydroquinidine 4-chlorobenzoate **197** (68 mg, 0.15 mmol), triethylamine (20 μl, 0.15 mmol) and hunig's base (0.25 ml, 0.73 mmol) in chloroform (1 ml) at –25 °C, was added a mixture of acid chloride **196** (0.10 ml, 0.73 mmol) and ethyl glyoxylate (0.33 ml, 1.45 mmol, 50 % in toluene) as a solution in chloroform (1 ml) dropwise over 30 minutes. This mixture was then stirred at this temperature for 2.5 hours. After warming to room temperature most of the solvents were blown down under a nitrogen stream and the crude mixture was purified directly by flash column chromatography (2 petrol : 1 ether eluant) to afford a 82:18 *cis*/*trans* mixture (61 mg, 42 %), or the *title compound* (2*S*, 3*S*, 1′S)-**195** (50 mg, 34 %, >95 : 5 d.r.); $[\alpha]^{24}_D$ –4.0 (*c* 1.0, $CHCl_3$); ν_{max}/cm^{-1}(film) 2965, 1841, 1753, 1644, 1465, 1379, 1259, 1206, 1031, 800; δ_H (400 MHz, $CDCl_3$) 4.90 (1H, d, *J* 7.0, EtO_2CCH), 4.37-4.25 (2H, m, $CH_3CH_2O_2C$), 3.76 (1H, dd, *J* 10.9, 7.0, EtO_2CCHCH), 2.00-1.79 (2H, m, $CH(CH_3)Et$, CH_2CH_3), 1.33 (3H, t, *J*7.1, $CH_3CH_2O_2C$), 1.29-1.19 (1H, m, CH_2CH_3), 0.92-0.85 (6H, m, $CH(CH_3)Et$, CH_2CH_3); δ_C (100 MHz, $CDCl_3$) 168.7 (C) 167.7 (C), 70.2 (CH), 62.0 (CH_2), 61.7 (CH), 32.0 (CH), 26.3 (CH_2), 17.0 (CH_3), 14.0 (CH_3), 11.3 (CH_3); m/z (CI, NH_3) 218 $[M+NH_4]^+$, found : $[M+NH_4]^+$, 218.1394 $C_{10}H_{20}NO_4$ requires : 218.1392.

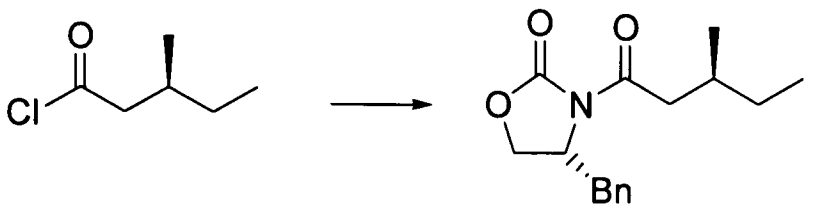
(2*R* ,3*R*)-Ethyl 3-((*S*)-*sec*-butyl)-4-oxooxetane-2-carboxylate ((2*R*, 3*R*, 1′*S*)-195)



(2*R*, 3*R*, 1′*S*)-**195**

To a cooled solution of hydroquinine 4-chlorobenzoate **198** (68 mg, 0.15 mmol), triethylamine (20 µl, 0.15 mmol) and hunig's base (0.25 ml, 0.73 mmol) in chloroform (1 ml) at –25 °C, was added a mixture of acid chloride **196** (0.10 ml, 0.73 mmol) and ethyl glyoxylate (0.33 ml, 1.45 mmol, 50 % in toluene) as a solution in chloroform (1 ml) dropwise over 30 minutes. This mixture was then stirred at this temperature for 2.5 hours. After warming to room temperature most of the solvents were blown down under a nitrogen stream and the crude mixture was purified directly by flash column chromatography (2 petrol : 1 ether eluant) to afford a 63:32 *cis/trans* mixture (60 mg, 41 %), or the *title compound* (2*R*, 3*R*, 1′*S*)-**195** (41 mg, 28 %, >95 : 5 d.r.); $[\alpha]^{24}_{D}$ –11.1 (*c* 1.1, $CHCl_3$); ν_{max}/cm^{-1}(film) 2966, 1842, 1754, 1466, 1379, 1207, 1107, 1034, 932, 851; δ_H (400 MHz, $CDCl_3$) 4.90 (1H, d, *J* 7.0, EtO_2CCH), 4.33-4.25 (2H, m, $CH_3CH_2O_2C$), 3.77 (1H, dd, *J* 10.1, 7.0, EtO_2CCHCH), 2.00-1.88 (1H, m, $CH(CH_3)Et$), 1.49-1.38 (1H, m, CH_2CH_3), 1.33 (3H, t, *J*7.2, $CH_3CH_2O_2C$), 1.14-1.05 (4H, m, CH_2CH_3, $CH(CH_3)Et$), 0.86 (3H, m, CH_2CH_3); δ_C (100 MHz, $CDCl_3$) 168.8 (C) 167.7 (C), 70.3 (CH), 62.1 (CH2), 61.3 (CH), 32.0 (CH), 27.8 (CH_2), 16.1 (CH3), 14.1 (CH_3), 10.5 (CH_3); m/z (CI, NH_3) 218 $[M+NH_4]^+$, found : $[M+NH_4]^+$, 218.1394 $C_{10}H_{20}NO_4$ requires : 218.1392.

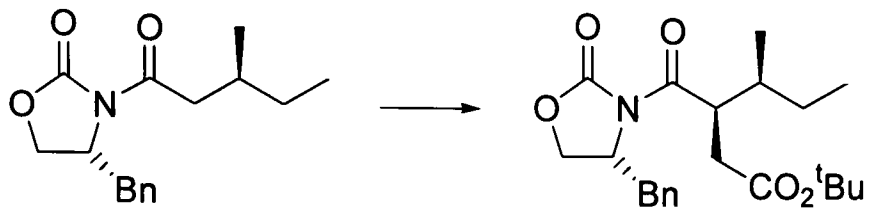
(*R*)-4-Benzyl-3-((*S*)-3-methylpentanoyl)oxazolidin-2-one (226)



226

To a cooled solution of (4*R*)-benzyl-2-oxazolidinone (3.97 g, 23.39 mmol) in THF (60 ml) at –78 °C, was added butyllithium (9.85 ml, 24.63 mmol, 2.50 M solution in hexanes) dropwise. After stirring for 30 minutes acid chloride **196** (2.93 ml, 21.27 mmol) was added dropwise and the solution was further stirred for 30 minutes at –78 °C, then allowed to warm to room temperature and stirred for an additional 2 hours. Solvents were removed *in vacuo*, dichloromethane (200 ml) was added, and the organic solution was washed with saturated ammonium chloride (150 ml). The solution was dried over magnesium sulfate, concentrated *in vacuo*, and purified by flash column chromatography (2 petrol : 1 ether eluant), to afford the *title compound* **226** (4.87 g, 79 %) as a white solid (m.p. 41-42 °C); $[\alpha]^{20}_{D}$ –46.9 (*c* 1.6, $CHCl_3$); ν_{max}/cm^{-1}(film) 3060, 2964, 1782, 1699, 1454, 1386, 1352, 1266, 1208, 736; δ_H (250 MHz, $CDCl_3$) 7.36-7.18 (5H, m, ArH), 4.72-4.62 (1H, m, N*H*Bn), 4.21-4.10 (2H, m, CH_2Ph), 3.29 (1H, dd, *J* 13.3, 3.1, OCH_2), 2.94-2.76 (2H, m, C(O)CH_2), 2.75 (1H, dd, *J* 13.3, 9.6, OCH_2), 2.07-1.93 (1H, m, C*H*(CH_3)), 1.52-1.16 (2H, m, C$H_2$$CH_3$), 0.98 (3H, d, *J* 6.7, CH(CH_3)), 0.91 (3H, app t, *J* 7.3, CH_2CH_3); δ_C (62 MHz, $CDCl_3$) 172.9 (C), 153.4 (C), 135.4 (C), 128.9 (CH), 128.4 (CH), 127.3 (CH), 66.1 (CH_2), 55.2 (CH), 42.1 (CH_2), 37.9 (CH_2), 31.2 (CH), 29.3 (CH_2), 19.2 (CH_3), 11.4 (CH_3); m/z (CI, NH_3) 276 $[M+H]^+$, found : $[M+H]^+$, 276.1600. $C_{16}H_{22}NO_3$ requires : 276.1600.

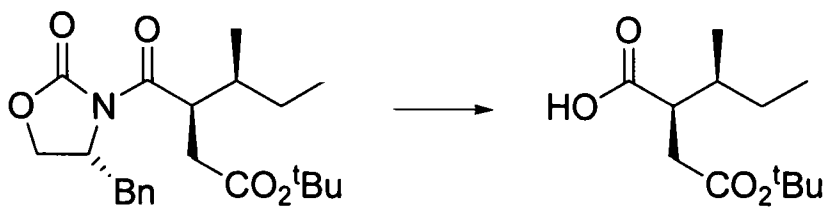
(3*R*, 4*S*)-*tert*-Butyl 3-((*R*)-4-benzyl-2-oxooxazolidine-3-carbonyl)-4-methylhexanoate (227)



227

To a cooled solution of oxazolidinone **226** (2.00 g, 7.26 mmol) in THF (6 ml) at –78 ℃ was added NaHMDS (8.41 ml, 8.00 mmol, 0.95 M solution in THF), dropwise. After stirring at this temperature for 1 hour, *tert*-butyl bromoacetate (3.52 ml, 21.79 mmol) was added dropwise, and the mixture was stirred overnight at –78 ℃. After warming to room temperature, dichloromethane (200 ml) was added and the solution was washed with saturated ammonium chloride (2 x 50 ml). After drying over magnesium sulfate, and removal of solvents *in vacuo*, the crude product was recrystallised from petrol/ether to afford the *title compound* **227** (2.31 g, 82 %, > 95 % d.e.) as a white solid (m.p. 107-108 °C); $[\alpha]^{20}_{D}$ –62.7 (*c* 1.4, $CHCl_3$); ν_{max}/cm^{-1}(film) 3031, 2977, 1779, 1694, 1392, 1351, 1245, 1155, 701; δ_H (250 MHz, $CDCl_3$) 7.38-7.23 (5H, m, ArH), 4.69-4.60 (1H, m, N*H*Bn), 4.23-4.14 (3H, m, 2 x CH_2Ph, CH_2CO$_2$^{t}Bu), 3.33 (1H, dd, *J* 13.4, 3.1, OCH_2), 2.89-2.70 (2H, m, OCH_2, C(O)CH), 2.36 (1H, dd, *J* 16.8, 3.4, $CH_2CO_2{}^tBu$), 1.85-1.67 (2H, m, C*H*(CH_3), CH_2CH_3), 1.42 (9H, s, $CO_2{}^tBu$), 1.30-1.20 (1H, m, CH_2CH_3), 0.93 (3H, app t, *J* 7.3, CH_2CH_3), 0.85 (3H, d, *J* 6.7, CH(CH_3)); δ_C (125 MHz, $CDCl_3$) 175.5 (C), 172.0 (C), 152.9 (C), 135.8 (C), 128.5 (CH), 128.9 (CH), 127.2 (CH), 80.6 (C), 65.7 (CH2), 55.7 (CH), 43.4 (CH), 37.4 (CH_2), 35.6 (CH), 32.2 (CH_2), 28.0 (CH_3), 27.9 (CH_2), 14.7 (CH_3), 11.9 (CH_3); m/z (CI, NH_3) 407 $[M+H]^+$, found : $[M+H]^+$, 407.2539. $C_{22}H_{35}N_2O_5$ requires : 407.2546.

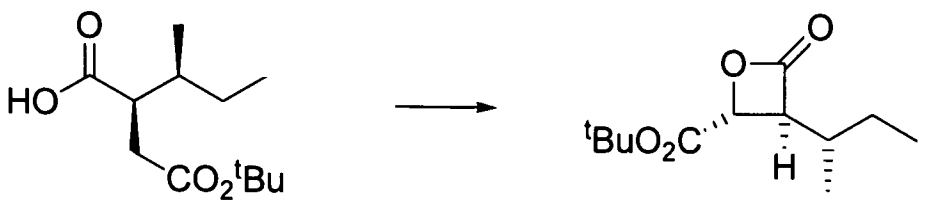
(2*R*, 3*S*)-2-(2-*tert*-Butoxy-2-oxoethyl)-3-methylpentanoic acid (221)



221

To a cooled solution of oxazolidinone **227** (1.50 g, 3.86 mmol), in THF (50 ml) at 0 ℃, was added aqueous hydrogen peroxide (1.95 ml, 15.46 mmol, 27% w/w) dropwise, then lithium hydroxide (0.32 g, 7.73 mmol) as a solution in H_2O (20 ml). The solution was then slowly allowed to warm to room temperature and stirred overnight. The mixture was diluted with saturated sodium sulfite (40 ml), washed with saturated sodium bicarbonate (40 ml), and the auxillary was removed by extraction with dichloromethane (3 x 50 ml), to afford (4*R*)-benzyl-2-oxazolidinone (0.52 g, 76 % recovered) after recrystallisation. The aqueous layer was then acidified to pH 1.5 (concentrated HCl), extracted with ethyl acetate (2 x 100 ml), then dried over magnesium sulphate to yield the *title compound* **221** (0.82 g, 92 %) as a clear oil; $[\alpha]^{22}_D$ –23.3 (*c* 0.86, $CHCl_3$); ν_{max}/cm^{-1}(film) 3440, 2971, 1731, 1706, 1458, 1368, 1251, 1156, 945, 842; δ_H (250 MHz, $CDCl_3$) 2.85 (1H, ddd, *J* 11.0, 4.6, 3.9, HO_2CCH), 2.58 (1H, dd, *J* 16.6, 11.0, $CH_2CO_2{}^tBu$), 2.26 (1H, dd, *J* 16.6, 3.9, $CH_2CO_2{}^tBu$), 1.90-1.77 (1H, m, $CH(CH_3)$), 1.47-1.14 (11H, m, CH_2CH_3, $CO_2{}^tBu$), 0.91 (3H, app t, *J* 7.3, CH_2CH_3), 0.87 (3H, d, *J* 7.0, $CH(CH_3)$); δ_C (62 MHz, $CDCl_3$) 181.2 (C), 171.8 (C), 80.9 (C), 45.6 (CH), 36.2 (CH), 32.6 (CH_2), 28.0 (CH_3), 27.2 (CH_2), 15.7 (CH_3), 11.8 (CH_3); m/z (CI, NH_3) 248 $[M+NH_4]^+$, found : $[M+NH_4]^+$, 248.1857. $C_{12}H_{26}NO_4$ requires : 248.1862.

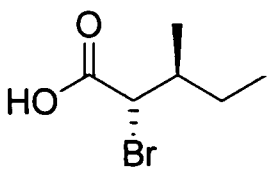
(2*R*, 3*S*)-*tert*-Butyl 3-((*S*)-sec-butyl)-4-oxooxetane-2-carboxylate (223)



223

To a cooled solution of succinate **221** (0.69 g, 2.71 mmol), in THF (20 ml) at –78 °C, was added LiHMDS (6.54 ml, 6.54 mmol, 1.00 M solution in hexanes), dropwise. After stirring at –78 °C for 45 minutes carbon tetrachloride (0.32 ml, 3.27 mmol) was added dropwise. The mixture was then stirred at –78 °C for 30 minutes, followed by warming to room temperature and stirring for a further 10 minutes. Most of the solvent was removed *in vacuo* followed by the addition of ether (20 ml) then 5 % aqueous sodium bicarbonate (20 ml) with subsequent rapid stirring for 20 hours. The mixture was diluted with ether (150 ml), washed with saturated sodium bicarbonate (2 x 50 ml), then dried over magnesium sulfate and concentrated *in vacuo*. The crude material was purified by flash column chromatography (3 petrol : 1 ether eluant), to afford the *title compound* **223** (0.38 g, 55 %, > 95 % d.e.) as a white solid, which was recrystallised (ether/petrol) to afford the product as white needles (m.p. 44-45 °C); $[\alpha]^{20}_{D}$ –8.2 (*c* 0.73, $CHCl_3$); ν_{max}/cm^{-1}(film) 2966, 2934, 2879, 1839, 1752, 1703, 1460, 1370, 1238, 1157, 1105, 1010, 930; δ_H (250 MHz, $CDCl_3$) 4.53 (1H, d, *J* 4.3, $^tBuO_2CCH$), 3.58 (1H, dd, *J* 7.8, 4.3, $^tBuO_2CCHCH$), 2.05-1.88 (1H, m, $CH(CH_3)Et$), 1.68-1.51 (1H, m, CH_2CH_3), 1.48 (9H, s, $CO_2{}^tBu$), 1.39-1.21 (1H, m, CH_2CH_3), 1.01 (3H, d, *J* 6.7, $CH(CH_3)Et$), 0.91 (3H, app t, *J* 7.6, CH_2CH_3); δ_C (125 MHz, $CDCl_3$) 169.1 (C), 167.5 (C), 83.5 (C), 69.5 (CH), 62.4 (CH), 33.5 (CH_2), 27.9 (CH_3), 26.8 (CH_2), 16.3 (CH_3), 11.0 (CH_3); m/z (CI, NH_3) 246 $[M+NH_4]^+$, found : $[M+NH_4]^+$, 246.1696. $C_{12}H_{24}NO_4$ requires : 246.1705.

(2*S*, 3*S*)-2-Bromo-3-methyl-pentanoic acid (237)[137]

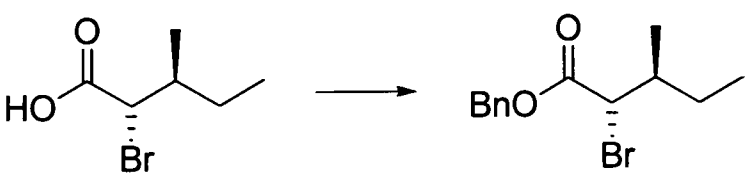


237

To a mixture of L-isoleucine **58** (4.00 g, 30.50 mmol) and potassium bromide (3.63 g, 30.50 mmol) was added 48% aqueous hydrogen bromide (30 ml), then distilled water (20 ml). This mixture was then stirred at room temperature for 10 minutes, followed by cooling to – 5 °C and slow addition of sodium nitrite (4.21 g, 61.01 mmol) over 15 minutes. After stirring at this temperature overnight, distilled water (30 ml) and saturated sodium sulfite (100 ml) were added, followed by extraction with dichloromethane (2 x 100 ml). Organic extracts were then dried over magnesium sulfate, and concentrated *in vacuo*. The crude product was then recrystallised from petrol (40-60), to yield the *title compound* **237** (5.35 g, 90 %, >95% d.e.) as a crystalline solid (m.p. 39 °C). $[\alpha]^{22}_{D}$ –4.8 (*c* 1.5, MeOH); δ_H (250 MHz, $CDCl_3$) 11.29 (1H, br s, CO_2H), 4.10 (1H, d, *J* 7.9, C*H*Br), 2.10-1.94 (1H, m, C*H*(CH_3)Et), 1.81-1.65 (1H, m, CH_2CH_3), 1.40-1.15 (1H, m, CH_2CH_3), 1.03 (3H, d, *J* 6.7, CH(CH_3)Et), 0.90 (3H, app t, *J* 7.5, CH_2CH_3).

Characterisation data correspond to literature values.[137]

(2*S*, 3*S*)-Benzyl 2-bromo-3-methylpentanoate (224)

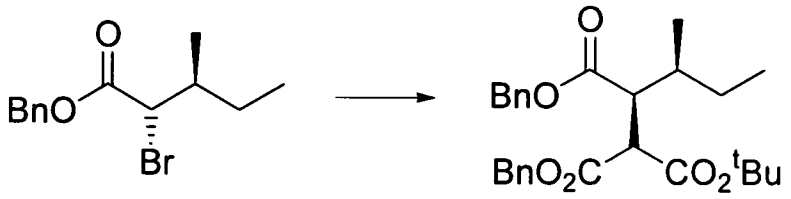


223

To a suspension of cesium carbonate (5.64 g, 17.30 mmol) and benzyl bromide (2.06 ml, 17.30 mmol) in DMF (30 ml) was added a solution of **237** (2.25 g, 11.53 mmol) in DMF (5 ml) dropwise over 20 minutes. After stirring at room temperature for 30 minutes the mixture was carefully acidified to pH 3 (1 M HCl), and the crude product was extracted with petrol/ethyl acetate (3:1, 300ml). This solution was subsequently

washed with distilled water (3 x 150 ml), dried over magnesium sulfate, then concentrated *in vacuo*. The crude product was purified by flash column chromatography (20 petrol : 1 ether eluant), to afford the *title compound* **224** (2.80 g, 85 %, >95:5 d.r.) as a clear oil; $[\alpha]^{22}_{D}$ –17.5 (*c* 0.8, $CHCl_3$); ν_{max}/cm^{-1}(film) 3067, 3034, 2966, 1744, 1497, 1455, 1381, 1266, 1143, 995, 750, 696; δ_H (400 MHz, $CDCl_3$) 7.39-7.33 (5H, m, ArH), 5.21 (2H, s, $PhCH_2$), 4.15 (1H, d, *J* 8.4, CHBr), 2.10-2.00 (1H, m, C*H*(CH_3)Et), 1.77-1.67 (1H, m, CH_2CH_3), 1.35-1.24 (1H, m, CH_2CH_3), 0.98 (3H, d, *J* 7.1, CH(CH_3)Et), 0.89 (3H, app t, *J* 7.5, CH_2CH_3); δ_C (125 MHz, $CDCl_3$) 169.3 (C), 135.2 (C), 128.6 (CH), 128.5 (CH), 128.3 (CH), 67.5 (CH_2), 53.0 (CH), 38.3 (CH), 26.2 (CH_2), 16.2 (CH_3), 10.5 (CH_3); m/z (CI, NH_3) 302 (Br^{79}), 304 (Br^{81}) $[M+NH_4]^+$, found: $[M+NH_4]^+$, 302.0758 (^{79}Br), 304.0743 (^{81}Br). $C_{13}H_{21}NO_2Br$ requires : 302.0756 (^{79}Br), 304.0735 (^{81}Br).

(2*S*, 3*S*)-1,2-Dibenzyl 1-*tert*-butyl 3-methylpentane-1,1,2-tricarboxylate (225)

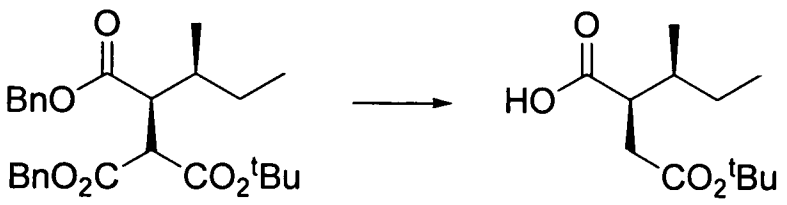


225

To a mixture of benzyl ester **224** (0.22 g, 0.88 mmol), and cesium carbonate (0.42 g, 1.32 mmol), was added benzyl *tert*-butyl malonate (0.25 g, 0.88 mmol) as a solution in DMF (8 ml). This mixture was stirred rapidly at room temperature for 8 h, acidified to pH 3 (1 M HCl aq), then extracted with petrol/ethyl acetate (3:1, 200 ml). After washing with distilled water (2 x 100 ml) organic extracts were combined, dried over magnesium sulfate and concentrated *in vacuo*. The crude product was then purified by flash column chromatography (5 petrol : 1 ether eluant), to afford the *title compound* **224** as an inseparable mixture of two major C3-isomers (0.36 g, 90 %, approximate 1:1 C3-ratio, 92:8 C2 ratio) as clear oils; ν_{max}/cm^{-1}(film) 3034, 2968, 1731, 1498, 1455, 1369, 1259, 1152, 1002, 752, 697; δ_H (500 MHz, $CDCl_3$) 7.38-7.30 (10H, m, ArH), 5.24-5.00 (4H, m, $PhCH_2O$), 3.89 (0.5H, d, *J* 10.8, $BnO_2CCHCO_2{}^tBu$ isomer A), 3.87 (0.5H, d, *J*, 11.2, $BnO_2CCHCO_2{}^tBu$ isomer B), 3.21 (0.5H, dd, *J* 10.8, 3.3,

C*H*CH(CH_3)Et isomer A), 3.19 (0.5H, dd, *J* 11.2, 3.3, C*H*CH(CH_3)Et isomer B), 1.68-1.62 (1H, m, C*H*(CH_3)Et), 1.59-1.45 (2H, m, CH_2CH_3), 1.36 (4.5H, s, $CO_2{}^tBu$ isomer A), 1.33 (4.5H, s, $CO_2{}^tBu$ isomer B), 1.04 (1.5H, d, *J* 7.1, CH(CH_3) isomer A), 0.97 (1.5H, d, *J* 6.7, CH(CH_3) isomer B), 0.87 (1.5H, app t, *J* 7.1, CH_2CH_3 isomer A), 0.79 (1.5H, app t, *J* 7.3, CH_2CH_3 isomer B); δ_C (125 MHz, $CDCl_3$) 172.2 (C, isomer A), 172.19 (C, isomer B), 168.4 (C, isomer A), 168.3 (C, isomer B), 167.0 (C, isomer A), 166.9 (C, isomer B), 135.7 (C), 135.3 (C), 135.2 (C), 128.4 (CH), 128.4 (CH), 128.3 (CH), 128.2 (CH), 128.0 (CH), 128.0 (CH), 82.2 (C, isomer A), 82.2 (C, isomer B), 66.95 (CH, isomer A), 66.31 (CH, isomer B), 53.43 (CH, isomer A), 53.20 (CH, isomer B), 49.8 (CH), 35.3 (CH_3), 27.6 (CH_3), 25.0 (C, isomer A), 24.8 (C, isomer B), 17.7 (CH_3, isomer A), 17.4 (CH_3, isomer B), 12.2 (CH_3, isomer A), 12.1 (CH_3, isomer B), four missing; m/z (CI, NH_3) 472 $[M+NH_4]^+$, found : $[M+NH_4]^+$, 472.2711. $C_{27}H_{38}NO_6$ requires : 472.2699.

(2*R*, 3*S*)-2-(2-*tert*-Butoxy-2-oxoethyl)-3-methylpentanoic acid (221)

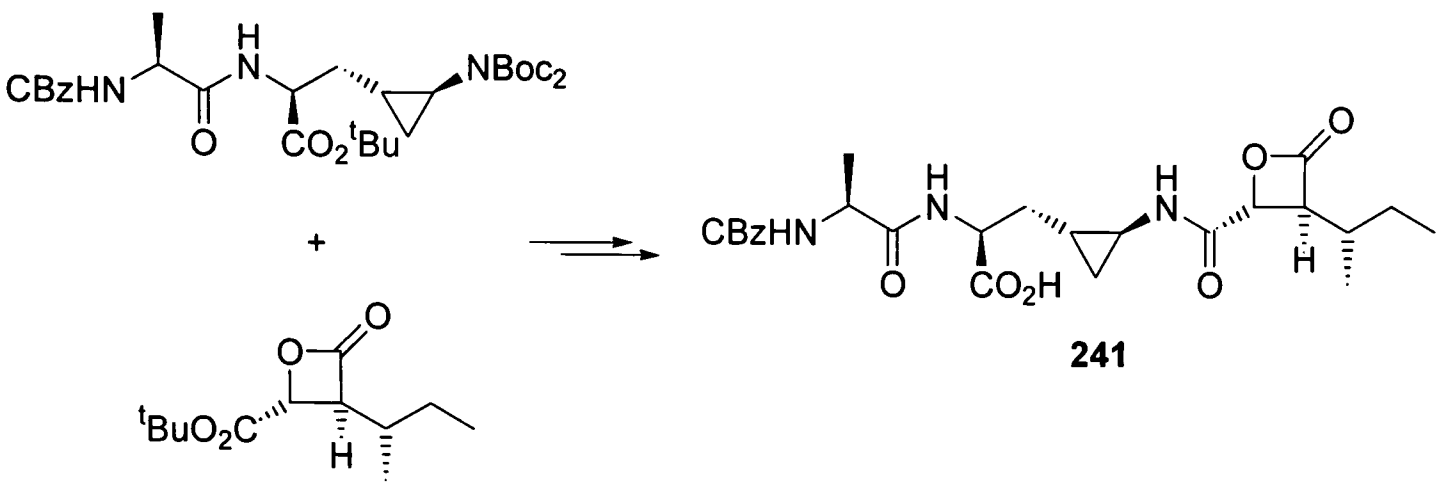


221

To a mixture of **225** (0.22 g, 0.47 mmol) and 10 % palladium on carbon (0.11 g) was added dry methanol (4 ml). The mixture was then thoroughly purged with hydrogen (4 x balloon volume), placed under a hydrogen atmosphere then stirred at room temperature for 1 hour. After filtration solvents were removed *in vacuo*, followed by the addition of dry DMSO (2.5 ml) and heating at 100 °C for 1 hour. Saturated sodium bicarbonate (30 ml) was then added, and the aqueous phase was washed with CH_2Cl_2 (50 ml). After acidification to pH 3 (1 M HCl), the product was then extracted with CH_2Cl_2 (2 x 100 ml). Organic extracts were then combined, dried over magnesium sulfate, and then concentrated *in vacuo* to afford the *title compound* **221** (98 mg, 90 %, 90:10 d.r) as a colourless oil.

^{1}H NMR data correspond to compound **221**.

N-CBz-Belactosin A (241)



241

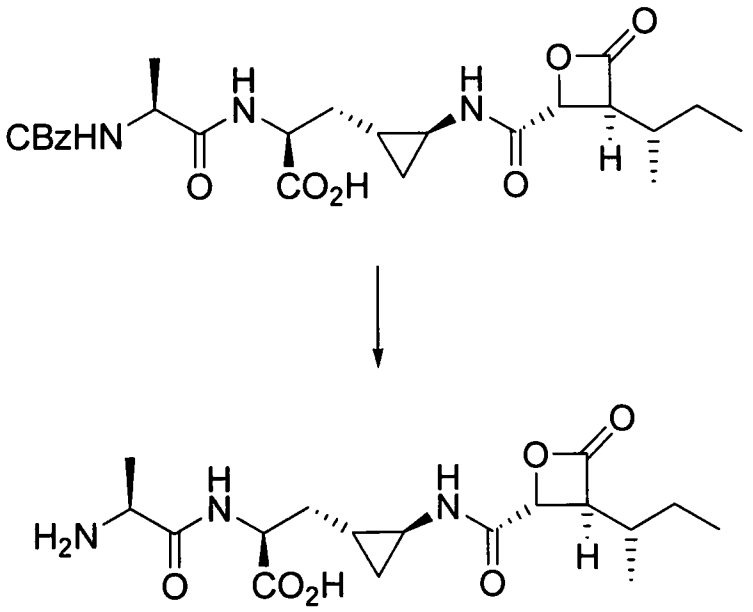
To a stirred solution of amino acid **170** (0.20 g, 0.33 mmol) in dichloromethane (3.70 ml) at 0 °C was added TFA (3.70 ml) dropwise, and the mixture was placed in a fridge (approx 15 °C) for 20 h. Solvents were removed *in vacuo*, and the mixture was diluted with distilled water (25 ml), and washed with ether (25 ml). Aqueous fractions were concentrated *in vacuo*, and the residue was then freeze dried to afford trifluoroacetate **174** (0.14 g, 90 %) as a glassy solid.

To a solution of **223** (0.14 g, 0.59 mmol) in dichloromethane (4 ml) at 0 °C, was added TFA dropwise (4 ml). The mixture was then stirred at this temperature for 15 hours, after which solvents were removed *in vacuo*, and the residue azeotroped from toluene/MeOH (2:1, 4 ml). After further concentration the mixture was then purified by column chromatography (9 $CHCl_3$: 1 MeOH : 0.1 AcOH eluant), to afford β-lactone carboxylic acid **5** (0.92 g, 90 %) as a clear oil.

To a cooled solution of β-lactone carboxylic acid **5** (36 mg, 0.21 mmol) in CH_2Cl_2 (2.30 ml) at 0 ℃ was added distilled water (2.30 ml), then HOBt (0.11 g, 0.84 mmol) and EDCI (81 mg, 0.42 mmol). This biphasic mixture was then stirred rapidly at 0 ℃ for 10 minutes, followed by direct transfer of the organic phase to a cooled solution (0 ℃) of trifluoroacetate **174** (65 mg, 0.14 mmol) and Hunig's base (73 µl, 0.42 mmol) in DMF (1 ml) (previously stirred for 10 min). This mixture was then stirred at this temperature for a further hour, followed by removal of all solvents at high vacuum. The crude material was directly purified by flash column chromatography (9.5 $CHCl_3$: 0.5 MeOH : 0.1 AcOH eluant), then recrystallised from ethyl acetate/pentane to afford *N*-CBz belactosin A **241** (35 mg, 50 %) as a white foam; $[\alpha]^{23}_D$ –8.7 (*c* 0.69, $CHCl_3$); ν_{max}/cm^{-1}(film) 3416, 2964, 1837, 1717, 1662, 1525, 1454, 1260, 1097, 909,

733; δ_H (400 MHz, d_6-acetone) 9.03 (1H, d, *J* 9.1, N*H*CH(CO_2H)), 8.02 (1H, s, (cyclopropyl)CHN*H*), 7.38-7.27 (5H, m, Ar), 6.41 (1H, d, *J* 7.7, CBzN*H*), 5.06 (2H, s, $PhCH_2$), 4.81 (1H, d, *J* 4.4, NHC(O)C*H*), 4.78-4.74 (1H, m, NHC*H*(CO_2H)), 4.43-4.36 (1H, m, CBzNHC*H*(Me)), 3.70 (1H, dd, *J* 8.0, 4.4, NHC(O)CHC*H*), 2.64-2.62 (1H, m, (cyclopropyl)C*H*NH), 2.36 (1H, app dt, *J* 14.6, 2.9, NHCH(CO_2H)CH_2), 1.98-1.92 (1H, m, C*H*(CH_3)Et), 1.70-1.60 (1H, m, CH_2CH_3), 1.39 (3H, d, *J* 7.0, CBzNHCH(CH_3)), 1.32-1.18 (2H, m, NHCH(CO_2H)CH_2, CH_2CH_3), 1.03 (3H d, *J* 6.6, CH(CH_3)Et), 0.96-0.81 (5H, m, CH_2CH_3, RC*H*(cyclopropyl), CH_2(cyclopropyl)), 0.61-0.56 (1H, m, CH_2(cyclopropyl)); δ_C (100 MHz, $CDCl_3$) 174.3 (C), 173.8 (C), 171.1 (C), 168.7 (C), 155.9 (C), 136.2 (C), 128.5 (CH), 128.1 (CH), 127.9 (CH), 70.2 (CH), 66.7 (CH_2), 62.9 (CH), 51.5 (CH), 50.4 (CH), 33.8 (CH), 33.4 (CH_2), 29.5 (CH), 26.7 (CH_2), 19.1 (CH_3), 16.8 (CH), 16.3 (CH_3), 11.0 (CH_3), 10.2 (CH_2); m/z (FAB, +ve) 504 $[M+H]^+$, found : $[M+H]^+$, 504.2345. $C_{25}H_{34}N_3O_8$ requires : 504.2346.

Belactosin A ((+)-1)[1]



(+)-**1**

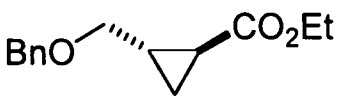
To a mixture of *N*-CBz-belactosin A **241** (24 mg, 0.05 mmol) and palladium on carbon (24 mg), was added THF (1ml) and the mixture was thoroughly purged with H_2 until the solvent volume was approximately 0.30 ml. To this suspension was added formic acid (0.20 ml), and the mixture was stirred at room temperature for 2.5 hours under a balloon pressure of H_2. The suspension was then filtered (washing with CH_2Cl_2, 2 x 2 ml) and concentrated *in vacuo*. Distilled water was added (2 x 1 ml),

and the dissolved filtrate was again filtered and concentrated at high vacuum. The residue was finally azeotroped with toluene/MeOH (2:1, 3 ml), to afford pure belactosin A (+)-**1** (17 mg, 96 %) as a white solid (m.p. 186-187 °C); $[\alpha]^{21}_{D}$ +4.8 (*c* 0.84, H_2O); ν_{max}/cm^{-1}(film) 3252, 3074, 2964, 1832, 1674, 1598, 1397, 1205, 1139, 911, 801, 723; δ_H (500 MHz, D_2O) 4.92 (1H, d, *J* 4.5, NHC(O)C*H*), 4.40 (1H, app t, *J* 5.7, NHC*H*(CO_2H)), 4.20 (1H, q, *J* 7.1, H_2NCH(Me)), 3.90 (1H, dd, *J* 7.4, 4.5, NHC(O)CHC*H*), 2.58 (1H, app dt, *J* 7.4, 3.7, (cyclopropyl)C*H*NH), 2.11-2.05 (1H, m, C*H*(CH_3)Et), 1.96 (1H, app dt, *J* 14.4, 6.0, NHCH(CO_2H)CH_2), 1.70 (1H, ddd, J 14.4, 8.4, 5.6, NHCH(CO_2H)CH_2), 1.63 (3H, d, *J* 7.1, H_2NCH(CH_3)), 1.62-1.55 (1H, m, CH_2CH_3), 1.41-1.32 (1H, m, CH_2CH_3), 1.06 (3H, d, *J* 6.7, CH(CH_3)Et), 1.02-0.87 (5H, m, RC*H*(cyclopropyl), CH_2CH_3, CH_2(cyclopropyl)), 0.77 (1H, app dt, *J* 7.4, 6.0, CH_2(cyclopropyl)); δ_C (125 MHz, D_2O) 178.5, 173.5, 172.7, 170.8, 71.7, 62.7, 55.7, 50.0, 34.5, 33.6, 29.2, 27.0, 17.3, 16.7, 16.2, 12.0, 11.1; m/z (FAB, +ve) 370 $[M+H]^+$, found : $[M+H]^+$, 370.1981. $C_{17}H_{28}N_3O_6$ requires : 370.1978.

Characterisation data correspond to literature values.[1]

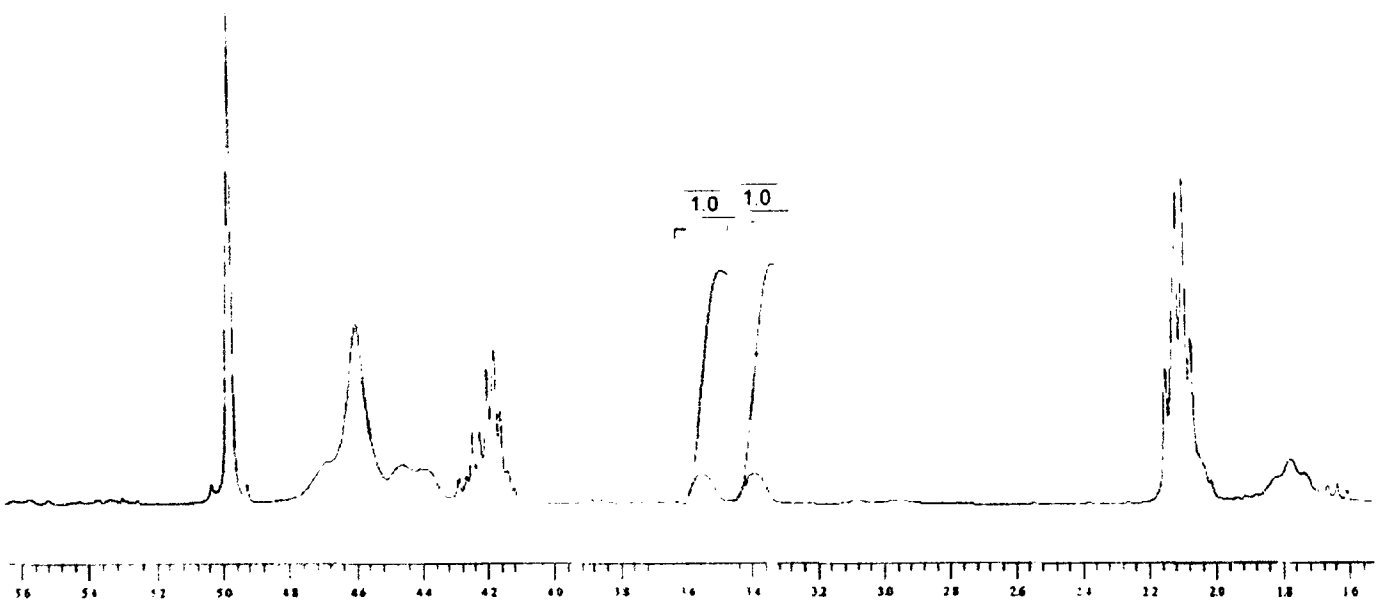
Appendix 1: Chiral shift experiment

(1*S**, 2*S**)-Ethyl 2-(benzyloxymethyl)cyclopropanecarboxylate



+ 35 mol% $Eu(hfc)_3$

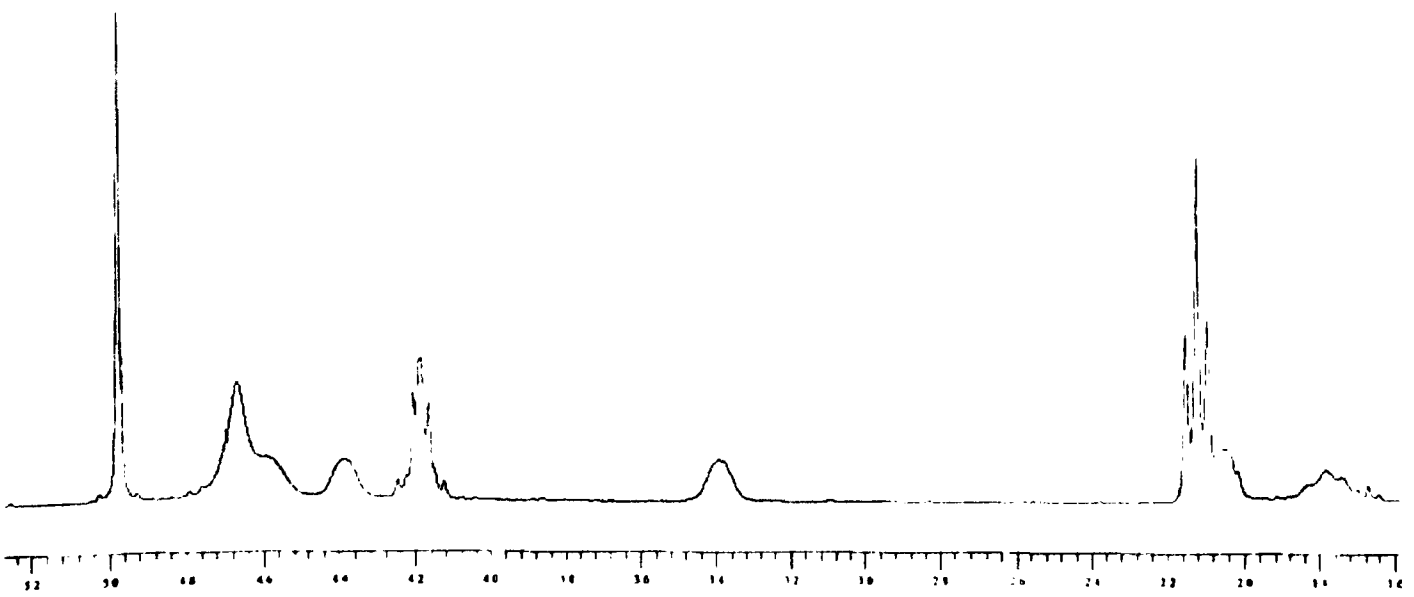
rac-**117**



(1*S*, 2*S*)-Ethyl 2-(benzyloxymethyl)cyclopropanecarboxylate

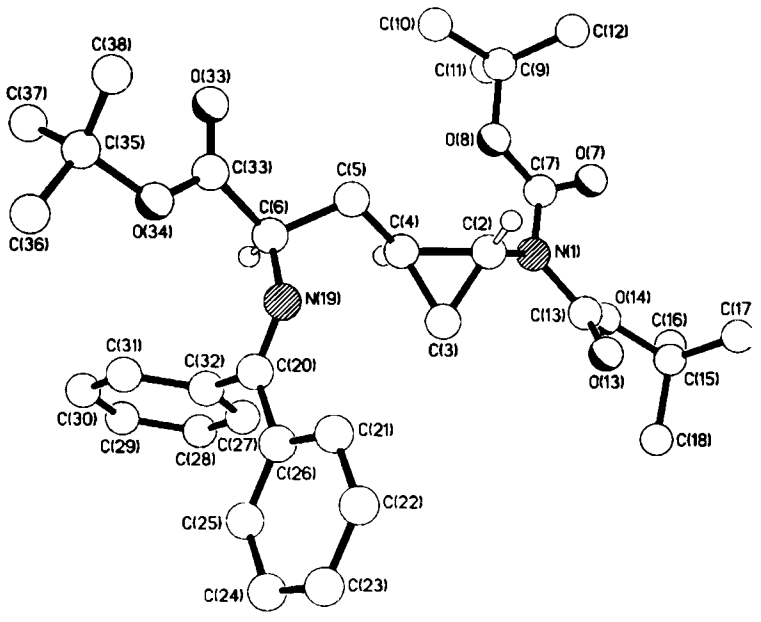
+ 35 mol% $Eu(hfc)_3$

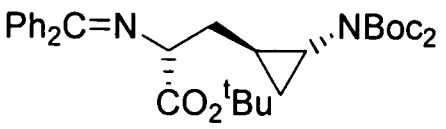
(*S*, *S*)-**117**



Appendix 2: X-ray crystallographic data

((2*R*, 1'*S*, 2'*R*)-150) (2*R*, 1'*S*, 2'*R*)-(*N*-(bis-boc)-*N*-(diphenylmethylene)-3-(2-aminocyclopropyl)) alanine *tert*-butyl ester





(2*R*, 1'*S*, 2'*R*)-**150**

Crystal data and structure refinement for (2*R*, 1'*S*, 2'*R*)-150)

Identification code	AA0303	
Empirical formula	C33 H44 N2 O6	
Formula weight	564.70	
Temperature	293(2) K	
Diffractometer, wavelength	Bruker P4, 1.54178 Å	
Crystal system, space group	Monoclinic, P2(1)	
Unit cell dimensions	a = 11.8756(11) Å	alpha = 90°
	b = 7.0112(5) Å	beta = 104.975(5)°
	c = 20.7657(10) Å	gamma = 90°
Volume, Z	1670.3(2) $Å^3$, 2	
Density (calculated)	1.123 Mg/m^3	
Absorption coefficient	0.619 mm^{-1}	
F(000)	608	
Crystal colour / morphology	Colourless needles	
Crystal size	0.80 x 0.17 x 0.13 mm^3	

Theta range for data collection	2.20 to 65.98°
Index ranges	0<=h<=14, -8<=k<=0, -24<=l<=23
Reflns collected / unique	3325 / 3164 [R(int) = 0.0341]
Reflns observed [F>4sigma(F)]	2838
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3164 / 644 / 422
Goodness-of-fit on F^2	1.064
Final R indices [F>4sigma(F)]	R1 = 0.0510, wR2 = 0.1403
	R1+ = 0.0510, wR2+ = 0.1403
	R1- = 0.0510, wR2- = 0.1402
R indices (all data)	R1 = 0.0572, wR2 = 0.1456
Absolute structure parameter	x+ = 1.1(9), x- = 0.0(9)
	Chirality indeterminate, assigned based on known centres at C(2) & C(4)
Extinction coefficient	0.022(2)
Largest diff. peak, hole	0.193, -0.167 $eÅ^{-3}$
Mean and maximum shift/error	0.000 and 0.000

Bond lengths [Å] and angles [deg] for XX

N(1)-C(7)	1.401(5)
N(1)-C(13)	1.417(4)
N(1)-C(2)	1.447(5)
C(2)-C(3)	1.497(5)
C(2)-C(4)	1.504(5)
C(3)-C(4)	1.501(5)
C(4)-C(5)	1.507(5)
C(5)-C(6)	1.537(5)
C(6)-N(19)	1.458(5)
C(6)-C(33)	1.515(5)
C(7)-O(8')	1.212(19)
C(7)-O(7')	1.229(14)
C(7)-O(7)	1.234(7)
C(7)-O(8)	1.310(6)
O(8)-C(9)	1.470(7)
C(9)-C(12)	1.468(7)
C(9)-C(10)	1.505(9)
C(9)-C(11)	1.532(10)
O(8')-C(9')	1.49(2)
C(9')-C(10')	1.495(16)
C(9')-C(12')	1.500(16)
C(9')-C(11')	1.503(16)
C(13)-O(13')	1.15(2)
C(13)-O(13)	1.213(6)
C(13)-O(14)	1.303(6)
C(13)-O(14')	1.310(17)
O(14)-C(15)	1.483(5)
C(15)-C(17)	1.474(7)
C(15)-C(16)	1.499(8)
C(15)-C(18)	1.544(7)
O(14')-C(15')	1.49(2)
C(15')-C(18')	1.499(16)
C(15')-C(17')	1.501(16)

C(15')-C(16')	1.504(17)
N(19)-C(20)	1.282(4)
C(20)-C(32)	1.496(4)
C(20)-C(26)	1.501(4)
C(21)-C(22)	1.3900
C(21)-C(26)	1.3900
C(22)-C(23)	1.3900
C(23)-C(24)	1.3900
C(24)-C(25)	1.3900
C(25)-C(26)	1.3900
C(27)-C(28)	1.3900
C(27)-C(32)	1.3900
C(28)-C(29)	1.3900
C(29)-C(30)	1.3900
C(30)-C(31)	1.3900
C(31)-C(32)	1.3900
C(33)-O(33)	1.199(5)
C(33)-O(33')	1.228(19)
C(33)-O(34)	1.320(6)
C(33)-O(34')	1.34(5)
O(34)-C(35)	1.478(5)
C(35)-C(38)	1.500(7)
C(35)-C(37)	1.506(6)
C(35)-C(36)	1.519(7)
O(34')-C(35')	1.48(2)
C(35')-C(37')	1.502(17)
C(35')-C(36')	1.502(17)
C(35')-C(38')	1.503(17)

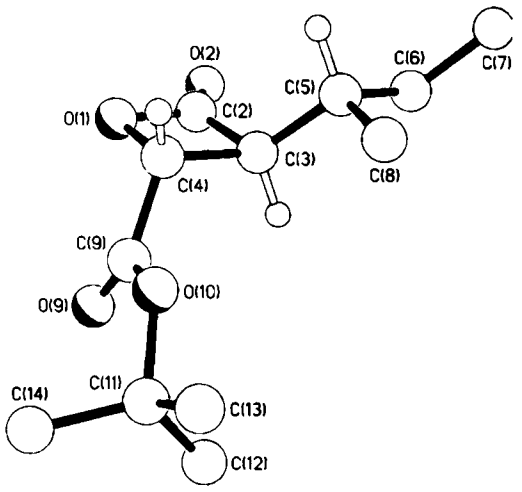
C(7)-N(1)-C(13)	120.3(3)
C(7)-N(1)-C(2)	119.4(3)
C(13)-N(1)-C(2)	117.1(3)
N(1)-C(2)-C(3)	119.6(4)
N(1)-C(2)-C(4)	119.4(4)

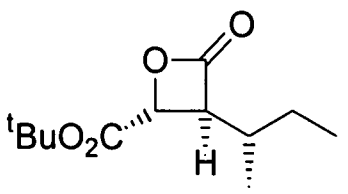
C(3)-C(2)-C(4)	60.0(3)
C(2)-C(3)-C(4)	60.2(2)
C(3)-C(4)-C(2)	59.8(2)
C(3)-C(4)-C(5)	121.1(4)
C(2)-C(4)-C(5)	119.1(3)
C(4)-C(5)-C(6)	112.6(3)
N(19)-C(6)-C(33)	111.6(3)
N(19)-C(6)-C(5)	107.7(3)
C(33)-C(6)-C(5)	110.3(3)
O(8')-C(7)-O(7')	126.7(12)
O(8')-C(7)-O(7)	114.6(10)
O(7')-C(7)-O(7)	56.1(8)
O(8')-C(7)-O(8)	25.0(8)
O(7')-C(7)-O(8)	109.3(9)
O(7)-C(7)-O(8)	123.2(5)
O(8')-C(7)-N(1)	108.6(9)
O(7')-C(7)-N(1)	118.4(9)
O(7)-C(7)-N(1)	124.2(4)
O(8)-C(7)-N(1)	111.0(4)
C(7)-O(8)-C(9)	122.5(5)
C(12)-C(9)-O(8)	112.0(6)
C(12)-C(9)-C(10)	112.5(6)
O(8)-C(9)-C(10)	102.1(5)
C(12)-C(9)-C(11)	111.1(8)
O(8)-C(9)-C(11)	109.2(6)
C(10)-C(9)-C(11)	109.6(7)
C(7)-O(8')-C(9')	119.9(16)
O(8')-C(9')-C(10')	94.9(19)
O(8')-C(9')-C(12')	107.9(19)
C(10')-C(9')-C(12')	112.7(15)
O(8')-C(9')-C(11')	115(2)
C(10')-C(9')-C(11')	113.2(15)
C(12')-C(9')-C(11')	112.3(14)
O(13')-C(13)-O(13)	30.5(9)

O(13')-C(13)-O(14)	114.4(11)
O(13)-C(13)-O(14)	125.8(4)
O(13')-C(13)-O(14')	129.6(13)
O(13)-C(13)-O(14')	123.4(8)
O(14)-C(13)-O(14')	29.0(9)
O(13')-C(13)-N(1)	122.4(11)
O(13)-C(13)-N(1)	121.7(4)
O(14)-C(13)-N(1)	112.4(4)
O(14')-C(13)-N(1)	107.6(7)
C(13)-O(14)-C(15)	120.9(4)
C(17)-C(15)-O(14)	111.9(5)
C(17)-C(15)-C(16)	113.7(6)
O(14)-C(15)-C(16)	101.7(4)
C(17)-C(15)-C(18)	110.5(5)
O(14)-C(15)-C(18)	108.6(4)
C(16)-C(15)-C(18)	110.0(6)
C(13)-O(14')-C(15')	116.2(14)
O(14')-C(15')-C(18')	116.4(19)
O(14')-C(15')-C(17')	106.0(18)
C(18')-C(15')-C(17')	114.3(14)
O(14')-C(15')-C(16')	95.4(16)
C(18')-C(15')-C(16')	113.0(15)
C(17')-C(15')-C(16')	110.0(14)
C(20)-N(19)-C(6)	120.3(3)
N(19)-C(20)-C(32)	125.3(3)
N(19)-C(20)-C(26)	117.3(3)
C(32)-C(20)-C(26)	117.3(2)
C(22)-C(21)-C(26)	120.0
C(23)-C(22)-C(21)	120.0
C(24)-C(23)-C(22)	120.0
C(23)-C(24)-C(25)	120.0
C(26)-C(25)-C(24)	120.0
C(25)-C(26)-C(21)	120.0
C(25)-C(26)-C(20)	120.42(18)

C(21)-C(26)-C(20)	119.58(18)
C(28)-C(27)-C(32)	120.0
C(27)-C(28)-C(29)	120.0
C(30)-C(29)-C(28)	120.0
C(31)-C(30)-C(29)	120.0
C(30)-C(31)-C(32)	120.0
C(31)-C(32)-C(27)	120.0
C(31)-C(32)-C(20)	119.6(2)
C(27)-C(32)-C(20)	120.4(2)
O(33)-C(33)-O(33')	39(4)
O(33)-C(33)-O(34)	124.4(4)
O(33')-C(33)-O(34)	116(3)
O(33)-C(33)-O(34')	125(3)
O(33')-C(33)-O(34')	121(4)
O(34)-C(33)-O(34')	6(5)
O(33)-C(33)-C(6)	123.2(4)
O(33')-C(33)-C(6)	113(3)
O(34)-C(33)-C(6)	112.3(3)
O(34')-C(33)-C(6)	112(2)
C(33)-O(34)-C(35)	122.7(4)
O(34)-C(35)-C(38)	110.8(5)
O(34)-C(35)-C(37)	109.2(5)
C(38)-C(35)-C(37)	113.3(5)
O(34)-C(35)-C(36)	101.8(4)
C(38)-C(35)-C(36)	110.6(5)
C(37)-C(35)-C(36)	110.7(4)
C(33)-O(34')-C(35')	120(4)
O(34')-C(35')-C(37')	109(3)
O(34')-C(35')-C(36')	102(3)
C(37')-C(35')-C(36')	111.6(16)
O(34')-C(35')-C(38')	110(3)
C(37')-C(35')-C(38')	111.9(16)
C(36')-C(35')-C(38')	111.6(16)

((2*R*, 3*S*, 1′*S*)-223) (2*R*, 3*S*)-*tert*-butyl 3-((*S*)-sec-butyl)-4-oxooxetane-2-carboxylate





(2*R*, 3*S*, 1′*S*)-**223**

Crystal data and structure refinement for (2*R*, 3*S*, 1′*S*)-223

Identification code	AA0305	
Empirical formula	C12 H20 O4	
Formula weight	228.28	
Temperature	293(2) K	
Diffractometer, wavelength	Bruker P4, 1.54178 Å	
Crystal system, space group	Orthorhombic, P2(1)2(1)2(1)	
Unit cell dimensions	a = 6.0476(7) Å	alpha = 90°
	b = 11.4445(7) Å	beta = 90°
	c = 19.263(3) Å	gamma = 90°
Volume, Z	1333.2(3) $Å^3$, 4	
Density (calculated)	1.137 Mg/m^3	
Absorption coefficient	0.692 mm^{-1}	
F(000)	496	
Crystal colour / morphology	Colourless needles	
Crystal size	1.00 x 0.33 x 0.10 mm^3	
Theta range for data collection	4.59 to 64.99°	
Index ranges	0<=h<=7, 0<=k<=13, -22<=l<=0	
Reflns collected / unique	1342 / 1342 [R(int) = 0.0000]	
Reflns observed [F>4sigma(F)]	1091	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F^2	

Data / restraints / parameters	1342 / 0 / 146
Goodness-of-fit on F^2	1.059
Final R indices [F>4sigma(F)]	R1 = 0.0509, wR2 = 0.1389
	R1+ = 0.0509, wR2+ = 0.1389
	R1- = 0.0511, wR2- = 0.1395
R indices (all data)	R1 = 0.0617, wR2 = 0.1479
Absolute structure parameter	x+ = 0.0(6), x- = ******
Extinction coefficient	0.033(3)
Largest diff. peak, hole	0.144, -0.124 $eÅ^{-3}$
Mean and maximum shift/error	0.000 and 0.000

Bond lengths [Å] and angles [deg] for XX

O(1)-C(2)	1.343(6)
O(1)-C(4)	1.461(4)
C(2)-O(2)	1.189(6)
C(2)-C(3)	1.513(5)
C(3)-C(5)	1.518(5)
C(3)-C(4)	1.538(5)
C(4)-C(9)	1.522(5)
C(5)-C(8)	1.527(5)
C(5)-C(6)	1.532(6)
C(6)-C(7)	1.515(6)
C(9)-O(9)	1.187(4)
C(9)-O(10)	1.328(4)
O(10)-C(11)	1.484(4)
C(11)-C(12)	1.498(6)
C(11)-C(14)	1.511(6)
C(11)-C(13)	1.518(5)

C(2)-O(1)-C(4)	91.6(3)
O(2)-C(2)-O(1)	126.8(4)
O(2)-C(2)-C(3)	137.5(5)
O(1)-C(2)-C(3)	95.8(3)
C(2)-C(3)-C(5)	119.3(3)
C(2)-C(3)-C(4)	82.5(3)
C(5)-C(3)-C(4)	120.0(3)
O(1)-C(4)-C(9)	111.3(3)
O(1)-C(4)-C(3)	90.0(3)
C(9)-C(4)-C(3)	114.1(3)
C(3)-C(5)-C(8)	109.2(3)
C(3)-C(5)-C(6)	109.1(3)
C(8)-C(5)-C(6)	112.8(3)
C(7)-C(6)-C(5)	114.2(4)
O(9)-C(9)-O(10)	127.6(4)
O(9)-C(9)-C(4)	123.5(3)

O(10)-C(9)-C(4)	108.8(3)
C(9)-O(10)-C(11)	121.9(3)
O(10)-C(11)-C(12)	109.7(3)
O(10)-C(11)-C(14)	108.6(3)
C(12)-C(11)-C(14)	113.0(4)
O(10)-C(11)-C(13)	103.0(3)
C(12)-C(11)-C(13)	110.7(4)
C(14)-C(11)-C(13)	111.4(4)

References

[1] Mizukami, T.; Asai, A.; Yamashita, Y.; Katahira, R.; Hasegawa, A.; Ochiai, K.; Akinaga, S. Eur. Patent 768317, 1997; *Chem. Abstr.* **1997**, *126*, 338840.

[2] Asai, A.; Hasegawa, A.; Ochiai, K.; Yamashita Y.; Mizukami, T. *J. Antibiot.*, **2000**, *53*, 81.

[3] Hasegawa, A.; Asai, A.; Katahira, R.; Yoshida, A.; Saita, Y.; Ikeda, S.-I. *Tennen Yuki Kagobutsu Toronkai Koen Yoshishu* **1999**, *41*, 385.

[4] Adams, J. *Trends Mol. Med.* **2002**, *8*, 49.

[5] Beil, M.; Waschołowski, V.; Giannis, A.; *Angew. Chem. Int. Ed. Eng.* **2004**, *43*, 6414.

[6] Asai, A.; Tsujita, T.; Sharma, S. V.; Yamashita, Y.; Akinaga, S.; Funakoshi, M.; Kobayashi, H.; Mizukami, T. *Biochem. Pharm.* **2004**, *67*, 227.

[7] Asai, A.; Mizukami, T.; Yamashita, Y.; Akinaga, S.; Ikeda, S.; Kanda, Y. Eur. Patent 1166781, 2000; *Chem. Abstr.* **2000**, *133*, 120677.

[8] Brandl, M.; Kozhushkov, S. I.; Loscha, K.; Kokoreva, O. V.; Yufit, D. S.; Howard, J. A. K.; de Meijere, A. *Synlett* **2000**, 1741.

[9] Zindel, J.; Zeeck, A.; König, W.A.; de Meijere, A. *Tetrahedron Lett.* **1993**, *34*, 1917.

[10] Zindel, A.; de Meijere, A. *J. Org. Chem.* **1995**, *60*, 2968.

[11] Larionov, O. V; Savel'eva, T. F; Kochetkov, K. A; Ikonnokov, N. S; Kozhushkov, S. I; Yufit, D. S; Howard, J. A. K; Khrustalev, V. N; Belokon, Y. N; de Meijere, A. *Eur. J. Org. Chem.* **2003**, 869.

[12] Cammas, S.; Renard, I.; Boutault, K.; Guérin, P. *Tetrahedron: Asymmetry* **1993**, *4*, 1925.

[13] Diez, D.; Garcia, P.; Marcos, I. S.; Garrido, N. M.; Basabe, P.; Broughton, H. B.; Urones, J. G. *Org Lett.* **2003**, *5*, 3687.

[14] Pietruszka, J.; Witt, A.; Frey, W. *Eur. J. Org. Chem.* **2003**, 3219.

[15] Armstrong A.; Scutt, J. N. *Org Lett.* **2003**, *5*, 2331.

[16] Larionov, O. V.; Kozhushkov, S. I.; Brandl M.; de Meijere, A. *Mendeleev Commun.* **2003**, 199.

[17] Jain, R. P.; Vederas, J. C. *Org Lett.* **2003**, *5*, 4669.

[18] Armstrong, A.; Scutt, J. N. *Chem. Commun.* **2004**, 510.

[19] Larionov, O. V.; de Meijere, A. *Org Lett.* **2004**, *6*, 2153.

[20] Doldouras, G. A.; Kollonitsch, J. *J. Am. Chem. Soc.* **1978**, *1*, 341.

[21] Evans, D. A.; MacMillan, D. W. C.; Campos, K.R. *J. Am. Chem. Soc.* **1997**, *119*, 10859.

[22] For reviews in this area, see: (a) Maruoka, K.; Ooi, T. *Chem. Rev.* **2003**, *103*, 3013. (b) O'Donnell, M. J. *Acc. Chem. Res.* **2004**, *37*, 506. (C) Lygo, B.; Andrews, B. I. *Acc. Chem. Res.* **2004**, *37*, 518.

[23] For a recent review on catalytic approaches to amino acids, see: Ma, J. A. *Angew. Chem. Int. Ed. Engl.* **2003**, *42*, 4290.

[24] Katritzky, A. R.; Wu, H.; Xie, L.; Jiang, J. *J. Heterocyclic Chem.* **1995**, *32*, 595.

[25] Imai, T.; Mineta, H.; Nishida, S. *J. Org. Chem.* **1990**, *55*, 4986.

[26] Fontani, P.; Carboni, B.; Vaultier, M.; Carrie, R. *Tetrahedron Lett.* **1989**, *30*, 4815.

[27] Pietruszka, J.; Witt, A. *J. Chem. Soc., Perkin Trans. 1* **2000**, 4293.

[28] Luithle, J. E. A.; Pietruszka, J. *Eur. J. Org. Chem.* **2000**, 2557.

[29] Hildebrand, J. P.; Marsden, S. P. *Synlett* **1996**, 893.

[30] Gridnev, I. D.; Miyaura, N.; Suzuki, A. *Organometallics* **1993**, *12*, 589.

[31] Zaidlewicz, M.; J. Meller, *Main Group Met. Chem.* **2000**, *23*, 765.

[32] Alkyl boronic acids are known to be difficult to isolate: Charette, A. B.; Lebel, H. *Org. Synth.* Vol. 76, 86

[33] Brown, H. C.; Heydkamp, W. R.; Baeuer, E.; Murphy, W. S. *J. Am . Chem. Soc.* **1964**, *86*, 3565.

[34] Buchwald, S. L.; Antilla, J. C. *Org Lett.* **2001**, *3*, 2077.

[35] Lam, P. Y. S.; Vincent, G.; Clark, C. G.; Deudon, S.; Jadhav, P. K. *Tetrahedron Lett.* **2001**, *42*, 3415.

[36] Lam, P. Y. S.; Clark, C. G.; Saubern, S.; Adams, J.; Averill, K. M.; Chan, D. M. T.; Combs, A. *Synlett* **2000**, 674.

[37] Denney, D. B.; Boskin, M. J. *J. Am. Chem. Soc.* **1959**, *81*, 6330.

[38] Wadsworth, W. S.; Emmons, W. D. *J. Am. Chem. Soc.* **1961**, *83*, 1733.

[39] (a) Tomoskozi, I. *Tetrahedron* **1966**, *22*, 179. (b) Portnoy, N. A.; Yong, K. S.; Aguiar, A. M. *Tetrahedron Lett.* **1971**, 2559. (c) Fitzsimmons, B. J.; Fraser-Reid, B. *Tetrahedron* **1984**, *40*, 1279. (d) Clive, D. L. J.; Daigneault, S. *J. Chem. Soc., Chem. Commun.* **1989**, 332. (e) Petter, R. C. *Tetrahedron Lett.* **1989**, *30*, 399. (f) Petter, R. C.; Banerjee, S; Englard, S. *J. Org. Chem.* **1990**, *55*, 3088. (g) Jacks, T. E.; Nibbe, H; Wiemer, D. F. *J. Org. Chem.* **1993**, *58*, 4584. (h) Robl, J. A.; Sieber-McMaster, E.;

Sulsky, R. *Tetrahedron Lett.* **1996**, *37*, 8985. (i) Meul, T.; Kampfen, U. US. Pat. 5149869, 1992; *Chem. Abstr.* **1992**, *118*, 38500. (j) Padmavathi, V.; Sharmila, K; Reddy, A. S.; Reddy, D. B. *Ind. J. Chem. B.* **2001**, *40*, 11.

[40] Tripathi, R. C.; Gupta, R. C.; Singh, R.; Saxena, A. K.; Anand, N. *Ind. J. Chem. B.* **1985**, *24*, 853.

[41] Nelson, A.; Warren, S. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3425.

[42] Tömösközi, I. *Tetrahedron* **1963**, *19*, 1969.

[43] Tömösközi, I. *Tetrahedron* **1966**, *22*, 179.

[44] Izydore, R. A.; Ghirardelli, R. D. *J. Org. Chem.* **1973**, *38*, 1790.

[45] Singh, A. K; Rao, M. N; Simpson, J. H; Li, W; Thornton, J. E; Kuehner, D. E; Kacsur, D. J. *Org. Proc. Res. Dev.* **2002**, *6*, 618.

[46] Katritzky, A. R.; Yang, Z.; Lam, J. N. *J. Org. Chem.* **1991**, *56*, 6917.

[47] Groth, U.; Lehmann, L.; Richter, L.; Schöllkopf, U. *Liebigs Ann Chem.* **1993**, 427.

[48] Genet, J. P.; Uziel, J.; Touzin, A. M.; Juge, S. *Synthesis* **1990**, 41.

[49] Davidsen, S.; Phillips, G.; and Martin, S. *Org. Synth.* 1987, **65**, 119.

[50] Franklin, A. S. *Synlett* **2000**, 1154.

[51] Fujii, M. *Chem. Lett.* **1992**, 933.

[52] Kandil, A. A.; Porter, T. M.; Slessor, K. N. *Synthesis*, **1987**, 411.

[53] Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfeld, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.* **1984**, *25*, 2183.

[54] Mouloungui, Z.; Delmas, M.; Gaset, A. *J. Org. Chem.* **1989**, *54*, 3936.

[55] Johnson, C. R.; Imamoto, T. *J. Org. Chem.* **1987**, *52*, 2170.

[56] For reviews in this area, see: (a) Rein, T.; Reiser, O. *Acta Chem. Scand.* **1996**, *50*, 369. (b) Rein, T.; Pedersen, T. M. *Synthesis* **2002**, 579.

[57] Rein, T.; Kann, N.; Kreuder, R.; Gangloff, B.; Reiser, O. *Angew Chem. Int. Ed. Engl.* **1994**, 33, 556.

[58] Gais, H-J., Schmiedl, G.; Ossenkamp, R. K. L. *Liebigs Ann Recl.* **1997**, 2419.

[59] Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405.

[60] Nahmany, M.; Melman, A. *Org. Lett.* **2001**, *3*, 3733.

[61] Goodman, S. N.; Jacobsen, E. N. *Adv. Synth. Catal.* **2002**, *344*, 953.

[62] Kaul, R.; Brouillette, Y.; Sajjadi, Z.; Hansford, K. A.; Lubell, W. D. *J. Org. Chem.* **2004**, *69*, 6131.

[63] Kuttab, S.; Mabic, S. *J. Label. Compd. Radiopharm.* **2002**, *45*, 813.

[64] Shioiri, T.; Ninomiya, K.; Yamada, S-i. *J. Am. Chem. Soc.* **1971**, *94*, 6203.

[65] Lygo, B.; Crosby, J.; Lowdon, T. R.; Peterson, J. A.; Wainwright, P. G. *Tetrahedron* **2001**, *57*, 2403.

[66] Szeja, W. *Synthesis* **1979**, 822.

[67] Ooi, T.; Takeuchi, M.; Kameda, M.; Maruoka, K. *J. Am. Chem. Soc.* **2000**, *122*, 5228.

[68] Yadav, G. D.; Jadhav, Y. B. *Org. Proc. Res. Dev.* **2003**, *7*, 588.

[69] Iranpoor, N.; Firouzabadi, H.; Aghapour, Gh.; Vaez zadeh A. R. *Tetrahedron* **2002**, *58*, 8689.

[70] For a recent review on organocatalysis, see: Dalko, P. I.; Moisan, L. *Angew. Chem. Int. Ed. Engl.* **2004**, *43*, 5138.

[71] Ojima, I. *Catalytic Asymmetric Synthesis*; Wiley-VCH: New York, 2000, p. 728.

[72] O'Donnell, M. J.; Bennett, W. D.; Wu, S. *J. Am. Chem. Soc.* **1989**, *111*, 2353-2355.

[73] Dolling, U-F.; Davis, P.; Grabowski, E. J. J. *J. Am .Chem. Soc.* **1984**, *106*, 446.

[74] Ojima, I. *Catalytic Asymmetric Synthesis*; Wiley-VCH: New York, 2000, p. 736.

[75] Corey, E. J; Xu, F; Noe, M. C. *J. Am. Chem. Soc.* **1997**, *119*, 12414.

[76] O'Donnell, M. J.; Bennett, W. D.; Bruder, W. A.; Jacobsen, W. N.; Knuth, K.; LeClef, B.; Polt, R. L.; Bordwell, F. G.; Mrozack, S. R.; Cripe, T. A. *J. Am. Chem. Soc.* **1988**, *110*, 8520.

[77] O'Donnell M. J.; Wu, S.; Esikova, I.; Mi, A. US. Pat. 5554753, 1996; *Chem. Abstr.* **1996**. *123*, 9924.

[78] Lygo, B; Wainwright, P.G. *Tetrahedron Lett.* **1997**, *38*, 8595.

[79] Jew, S-s.; Jeong, B-S.; Yoo, M-S.; Huh, H.; Park, H.-g. *Chem. Commun.* **2001**, 1244.

[80] Chinchilla, R.; Mazón, P.; Nájera, C. *Tetrahedron: Asymmetry* **2002**, *13*, 927.

[81] Ooi, T.; Kameda, M.; Maruoka, K. *J. Am. Chem. Soc.* **2003**, *125*, 5139.

[82] Shibuguchi, T.; Fakuta, Y.; Akachi, Y.; Sekine, A.; Ohshima, T.; Shibasaki, M. *Tetrahedron Lett.* **2002**, 9539.

[83] Dalgaard, L.; Jensen, L.; Lawesson, S.-O. *Tetrahedron* **1974**, *30*, 93.

[84] Chen, G; Deng, Y; Gong, L; Mi, A; Cui, X; Jiang, Y; Choi, M. C. K; Chan, A. S. C. *Tetrahedron: Asymmetry* **2001**, 12, 1567-1571.

[85] Guillerm, D.; Lavrador, K.; Guillerm, G. *Synth. Commun.* **1995**, *25*, 877.

[86] Bodanszky, M. *Principles of Peptide Synthesis*; Springer-Verlag: Berlin, 1984; pp 158-172.

[87] Marder, O.; Albericio, F. *Chemistry Today* **2003**, *21*, 35.

[88] For reviews in this area, see: (a) Pommier, A.; Pons, J-M. *Synthesis* **1993**, *5*, 441. (b) Yang, H. W.; Romo, D. *Tetrahedron* **1999**, *55*, 6403.

[89] Schneider, C. *Angew. Chem. Int. Ed. Engl.* **2002**, *41*, 744.

[90] Nelson, S. G.; Wan, Z. *Org. Lett.* **2000,** *2*, 1883.

[91] Evans, D. A.; Janey, J. M. *Org. Lett.* **2000,** *3*, 2125.

[92] Lecea, B.; Arrieta, A.; Lopez, X.; Ugalde, F.; Cossio, F. P. *J. Am. Chem. Soc.* **1995**, *117*, 12314.

[93] Wynberg, H.; Starling, E. M. J. *J. Am. Chem. Soc.* **1982**, *104*, 166.

[94] Corrected sense of stereoinduction: Wynberg, H.; Starling, E. M. J. *J. Org. Chem.* **1985**, *50*, 1977.

[95] Wynberg, H. *Topics in Stereochemistry* **1986**, *16*, 87-130.

[96] Ramiandrasoa, P.; Guérin, P.; Girault, J. P.; Bascou, P.; Hammouda, A.; Cammas, S.; Vert, M. *Polymer Bulletin* **1993**, *30*, 501.

[97] Jackson, B. Swiss Patent. CH681302A5, 1993; *Chem. Abstr.* **1993**, *119*, 95313.

[98] Cortez, G. S.; Tennyson, R. L.; Romo, D. *J. Am. Chem. Soc.* **2001**, *123*, 7945.

[99] Calter, M. A. *J. Org. Chem.* **1996**, *61*, 8006.

[100] Dijkstra, G. D. H.; Kellogg, R. M.; Wynberg, H. *J. Org. Chem.* **1990**, *55*, 6121.

[101] Cortez, G. S.; Oh, S. H.; Romo, D. *Synthesis* **2001**, 1731.

[102] Orr, R. K.; Calter, M. A. *Tetrahedron* **2003**, *59*, 3545.

[103] Taggi, A. E.; Hafez, A. M.; Wack, H.; Young, B.; Ferraris, D.; Lectka, T. *J. Am. Chem. Soc.* **2002**, *124*, 6626.

[104] Mulzer, J.; Pointner, A.; Chucholowski, A.; Brüntrup, G. *J. Chem. Soc., Chem. Commun.* **1979**, 52.

[105] Mulzer, J.; Zippel, M.; Brüntrup, G.; Segner, J.; Finke, J. *Liebigs Ann. Chem.* **1980**, 1108.

[106] Brachais, C. H.; Huguet, J.; Bunel, C. *Polymer* 1997, *38*, 4959.

[107] Brady, W. T.; Smith, L. *J. Org. Chem.* **1971**, *36*, 1637.

[108] Taggi, A. E.; Wack, H.; Hafez, A. M.; France, S.; Lectka, T. *Org. Lett.* **2002**, *4*, 627.

[109] Zhu, C.; Shen, X.; Nelson, S. *J. Am. Chem. Soc.* **2004**, *126*, 5352.

[110] Taggi, A. E.; Hafez, A. M.; Wack, H.; Young, B.; Drury, W. J.; Lectka, T. *J. Am. Chem. Soc.* **2000**, *122*, 7831.

[111] Evans, D. A.; Wu, L. D.; Wiener, J. J. M.; Johnson, J. S.; Ripin, D. H. B.; Tedrow, J. S. *J. Org. Chem.* **1999**, *64*, 6411.

[112] Barlaam, B.; Bird, T. G.; der Brempt, C. L.-v.; Campbell, D.; Foster, S. J.; Maciewicz, R. *J. Med. Chem.* **1999**, *42*, 4890.

[113] Arnold, R. T.; Kulenovic, S. T. *J. Org. Chem.* **1978**, *43*, 3687.

[114] Meyers, C. Y.; Kolb, V. M. *J. Org. Chem.* **1987**, *43*, 1985.

[115] Beckett, R. P.; Crimmin, M. J.; Davis M. H.; Spavold, Z. *Synlett* **1993**, 137.

[116] Bajwa, J. S.; Miller, M. J. *J. Org. Chem.* **1983**, *48*, 1114.

[117] Campion, C.; Davidson, A. H.; Dickens, J. P.; Crimmin, M. J. US Patent US5240958, 1993; *Chem. Abstr.* **1993**, *113*, 212677.

[118] Hirayama, R.; Yamamoto, M.; Tsukida, T.; Matsuo, K.; Obata, Y.; Sakamoto, F.; Ikeda, S. *Bioorg. Med. Chem.* **1997**, *5*, 765.

[119] Fujisawa, T.; Igeta, K.; Odake, S.; Morita, Y.; Yasuda, J.; Morikawa, T. *Bioorg. Med. Chem.* **2001**, *10*, 2569.

[120] Parrish, J. P.; Dueno, E. E.; Kim, S-I.; Jung, K. W. *Synth. Commun.* **2000**, *30*, 2687.

[121] Toussaint, O.; Capdevielle, P.; Maumy, M. *Tetrahedron* **1984**, *40*, 3229.

[122] Wei, H-X.; Truitt, C. L.; Paré, P. W. *Tetrahedron Lett.* **2003**, *44*, 831.

[123]Mohapatra, D. K.; Datta, A. *J. Org. Chem.* **1999**, *64*, 6879.

[124] Argyrou, A.; Sun, G.; Palfey, B. A.; Blanchard, J. S. *Biochemistry* **2003**, *42*, 2218.

[125] Nozaki, S.; Kimura, A.; Muramatsu, I. *Chem. Lett.* **1997**, 1057.

[126]Ho, G.-J.; Emerson, K. M.; Mathre, D. J.; Shuman, R. F.; Grabowski, E. J. J. *J. Org. Chem.* **1995**, *60*, 3569.

[127] Evans, D. A.; Woerpel, K. A.; Hinman, M. M.; Faul, M. M. *J. Am. Chem. Soc.* **1991**, *113*, 726.

[128] Barrett, A. G. M.; Braddock, D. C.; Lenoir, I.; Tone, H. *J. Org. Chem.*, **2001**, *66*, 8260.

[129] Johnson, C.; Rogers, P. *J. Org. Chem.* **1973**, *38*, 1793.

[130] Clare, B. W.; Ferro, V.; Skelton, B. W.; Stick, R. V.; White, A. H. *Aust. J. Chem.* **1993**, *46*, 805.

[131] Langer, P.; Freifeld, I. *Org. Lett.* **2001**, *3*, 3903.

[132] Davies, N. G. M. PhD thesis, University of London, 2002.

[133] Viswanathan, R.; Prabhakaran, E. N.; Plotkin, M. A.; Johnston, J. N. *J. Am. Chem. Soc.* **2003**, *125*, 163.

[134] Biagini, S. C. G.; Gibson, S. E.; Keen, S. P. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2485.

[135] Aronica, L. A.; Terreni, S.; Caporusso, A. M.; Salvadori, P. *Eur. J. Org. Chem.* **2001**, *22*, 4321.

[136] Mori, K.; Kamada, A.; Kido, M.; *Liebigs Ann.Chem.* **1991**, *8*, 775.

[137] Roeder, M.; Spiegelstein, O.; Schurig, V.; Bialer, M.; Yagen, B. *Tetrahedron Asymm.* **1999**, *10*, 841.