University of Southampton

Novel Radical Based Routes to Pyrrolidine trans-Lactams

By Anawat Ajavakom

Doctor of Philosophy

Faculty of Science

Department of Chemistry

September 2003

University of Southampton

Abstract

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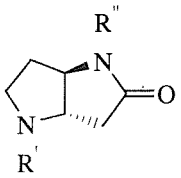
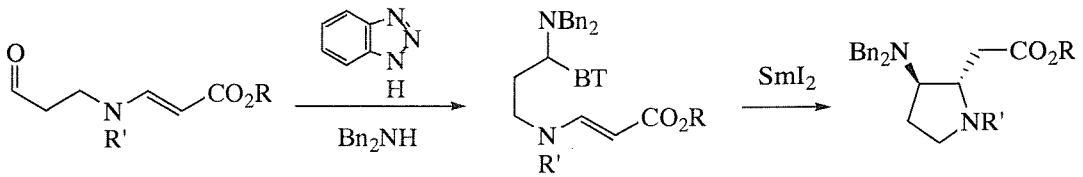
This thesis is concerned with the development of novel routes to the pyrrolidine *trans*-lactams **246**, which proved to be HNE inhibitors, based on a radical cyclisation mediated by either samarium diiodide or tributyltin hydride.



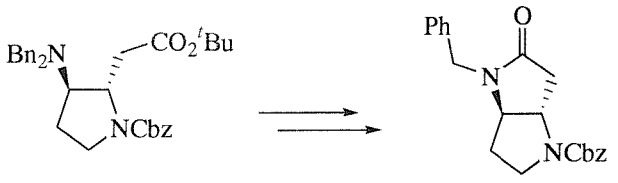
Pyrrolidine *trans*-lactams **246**

Chapter 2 describes the synthesis of precursors **214** and the radical cyclisation of α-aza radicals derived from *N*-(benzotriazolylalkyl) alkenylamines **264** mediated by samarium diiodide to access the *trans*-2,3-disubstituted pyrrolidines **267**.



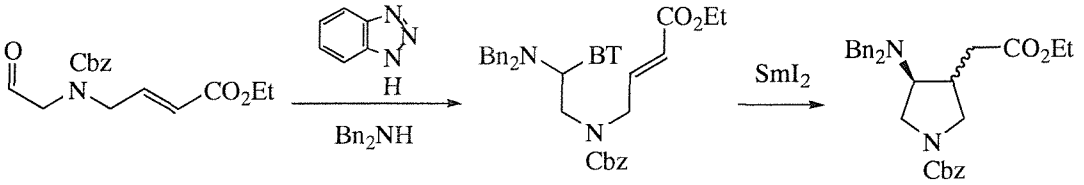
214 **264** **267**

After these results, the development of the synthetic route of pyrrolidine *trans*-lactam was described. The cyclisation of the pyrrolidine derivative **245** successfully gave pyrrolidine *trans*-lactam **253**.



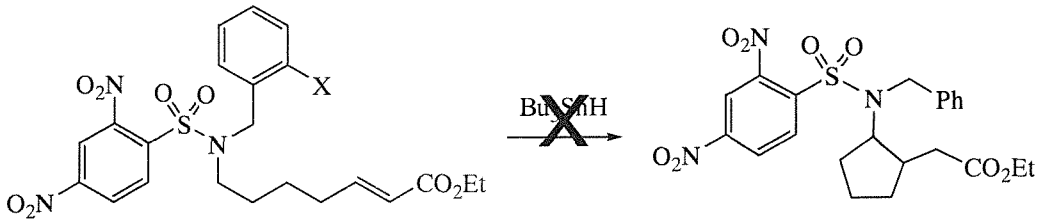
245 253

It also details the samarium diiodide promoted radical cyclisation of benzotriazole adduct **298** derived from aldehyde **297** to obtain the 3,4-disubstituted pyrrolidine **299**.



297 298 299

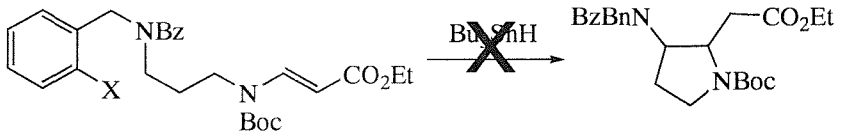
Chapter 3 presents the other strategy to make an α-aza radical, using radical translocation. Efforts were focused on the synthesis of 2,4-dinitrophenyl sulfonamide precursors **325** and **333** and their cyclisations, which failed to give cyclopentyl derivative **321**.



325; X = I
333; X = Br

321

The synthesis of *o*-halobenzyl benzamides **355** and **356** is described later. However, their cyclisations failed to give the desired pyrrolidine product **354**.



355; X = Br
356; X = I

354

Contents

Preface

The research described in this thesis was carried out under the supervision of Prof. Jeremy Kilburn at the University of Southampton between October 1999 and January 2003. No part of this thesis has been previously submitted at this or any other University

Acknowledgements

It has been a privilege to be able to carry out the research under the supervision of Prof. Jeremy Kilburn. Without his encouraging, supportive, and useful advice, I could not have come this far.

Special thanks to Dr. Roderick Bates and Prof. John Miller for leading me here, University of Southampton.

I am indebted to GlaxoSmithKline for providing the financial support of the project and specially Dr Ian Baldwin for his help throughout the research, and his assistance and availability during my time in Stevenage. I also would like to thank Tim, John, and Susanna for all their help and the good time when I was there.

I must thank Joan Street and Neil Wells for all the help with NMR experiments, John Langley and Julie Herniman for the mass spectroscopy analysis.

I also would like to thank all the past and present members of the Kilburn empire. Faye and Alex for being helpful, Jon and Lee for being friendly, Pla, Sarah, and Suvi for everything. Especially Sarah for helping me with proof reading. Nittaya, Sandra, Andrea, Max, and Richard for being good friends. Many thanks to Rob, Marco, and Wendy (from 5th flr.), Boon-ek and everybody in Bradley group.

Thank you very very much to Pam, for being kind, understanding, and supportive at all times and in all conditions over the last year.

Finally, I would like to thank my parents in Thai.

"ผมขอใช้โอกาสนี้กราบขอบพระคุณ คุณพ่อและคุณแม่ที่รักและเคารพที่สุดของผม ที่คอยเป็นห่วงเป็นใยและอุดหนุนค้ำจุนผมตลอดมา ถึงแม้ 18 ปีที่ผ่านมาผมจะอยู่ห่างบ้านไกลเมือง คุณพ่อและคุณแม่ก็คอยเอาใจช่วยและพร้อมที่จะช่วยเหลือผมเสมอมา ถึงแม้เมื่อเทียบกับบุญคุณอันใหญ่หลวงดั่งมหาสมุทรของคุณพ่อและคุณแม่แล้ว มันคงเป็นเพียงการตอบแทนบุญคุณที่น้อยนิดดั่งเม็ดทราย แต่อย่างน้อยการนำเอาปริญญาเอกกลับไปเมืองไทยครั้งนี้ คงจะทำให้คุณพ่อและคุณแม่ภูมิใจและดีใจบ้างไม่มากก็น้อย"

Abbreviations

Ac	acetyl
Am.	American
aq.	aqueous
Ar	aryl
Biochem.	Biochemistry
Bn	benzyl
Boc	*tert*-butoxy carbonyl
bp.	boiling point
br s	broad singlet
BTH	benzotriazole
Bu	butyl
^{n}BuLi	*normal*-butyllithium
^{t}Bu	*tert*-butyl
Bz	benzoyl
Can.	Canadian
cat.	catalytic amount
Chem.	Chemistry
CI	chemical ionization
Cbz	benzyloxy carbonyl
CbzCl	benzyl chloroformate
Clin.	Clinical
Commun.	Communication
Comput.	Computational
d	doublet
DBA	dibenzylamine
DCC	1,3-dicyclohexylcarbodiimide
DCM	dichloromethane
DCU	1,3-dicyclohexylurea
DEPT	distortionless enhancement by polarization transfer
DIC	1,3-diisopropylcarbodiimide

dil.	diluted
DIPEA	diisopropyl ethyl amine
DIU	1,3-diisopropylurea
DMAP	4-(dimethylamino)pyridine
DMF	dimethylformaldehyde
DMSO	dimethyl sulfoxide
EI	electron ionisation
eq	equivalent
ES	electrospray
Et	ethyl
EtO	ethoxy
EtOAc	ethyl acetate
EWG	electron withdrawing group
HMPA	hexamethylphosphoramide
HNE	Human Neutrophil Elastase
HRMS	high resolution mass spectroscopy
hv	light
Hz	hertz
IR	infrared
J	coupling constant
J.	journal
Jpn.	Japan
L	ligand
LDA	lithium diisopropylamine
Lett.	Letters
liq.	liquid
lit.	literature
m	multiplet
M	metal
maj	major
Me	methyl
Med.	Medicinal
MeO	methoxy

ms	molecular sieves
MS	mass spectroscopy
min	minor
mp.	melting point
MHz	megahertz
n	*normal*
NMR	nuclear magnetic resonance
NOE	nuclear overhauser effect
o-	*ortho*
Org.	Organic
p-	*para*
petrol	petroleum ether, bp. 40-60 °C
PG	protecting group
Ph	phenyl
ppm	part per million
p-TsOH	*para*-toluenesulfonic acid
py	pyridine
q	quartet
Res.	Research
Respir.	Respiratory
Rev.	Reviews
R_f	retention factor
rt.	room temperature
s	singlet
sat.	saturated
Sci.	Science
Soc.	Society
sol.	solution
Syn.	Synthesis
t	*tertiary*
t	triplet
TEA	triethylamine
tert-	*tertiary*

Tf	trifluoromethanesulfonyl
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
Ts	tosyl
TS	transition state

Chapter 1 Introduction

1.1) Pharmaceutical background

1.1.1) Biological background

As part of the host response to injury, inflammatory cells release potent proteolytic enzymes into the extracellular environment. These enzymes can also degrade the structural elements of lung tissue, disrupt cells and stimulate further inflammation.[1] This results in irreversible airway damage and impaired lung function,[2] and therefore, activity of these proteases must be regulated. Proteases are inhibited by antiproteases and a balance between them is required for normal lung function. An imbalance between pulmonary proteases and antiproteases can result in pathological changes in lung structure and chronic lung diseases, such as emphysema, chronic bronchitis and asthma.[3] In addition, in chronic diseases there is an influx of inflammatory cells and these may release large amount of lung proteases that damage lung tissue.[4,5]

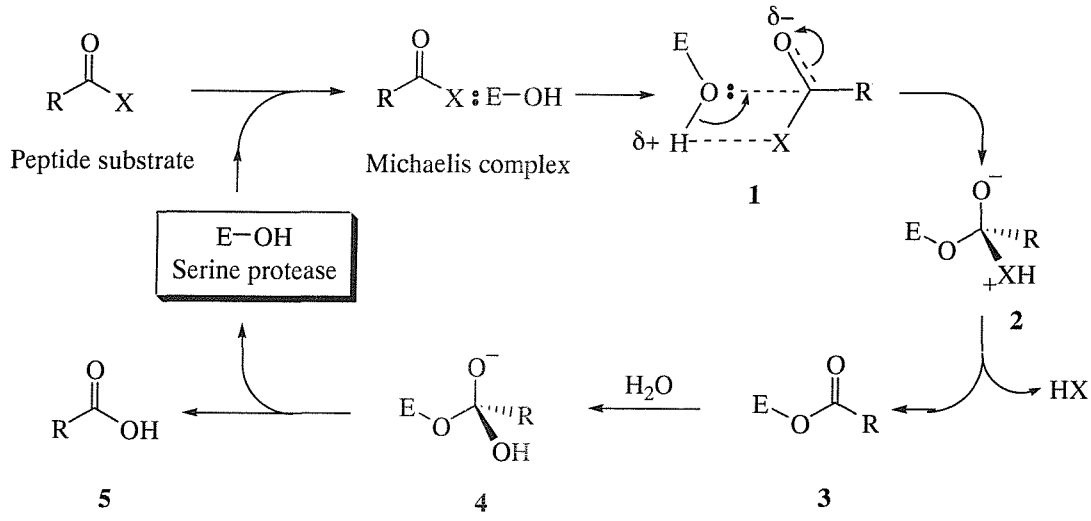
Lung proteases

The classification of lung proteases is based on their catalytic mechanisms and they are classified as serine, cysteine, aspartic or metalloproteases. In general, the majority of proteases known and characterized belong to the serine protease family.

Serine proteases[6]

Serine proteases are a group of well-studied endopeptidases, which have a similar action and mechanism and have a catalytic active serine residue in their active centers. The serine protease reaction mechanism was demonstrated schematically by Kraut.[6] Their crystallographic and NMR studies indicated that the peptide bonds within a

polypeptide substrate were hydrolysed by serine protease (**Scheme 1**). Serine protease catalysis involves formation of ester **3** between the hydroxy group of the reactive serine and the carbonyl group of the peptide substrate *via* a Michaelis complex and a non-covalent enzyme-substrate complex **1**, a tetrahedral intermediate **2** and a release of the first peptide. Covalent acyl-enzyme intermediate **3** is hydrolysed in the deacylation stage of the reaction *via* a tetrahedral intermediate transition state (TS) **4**, restoring the free hydroxy group of the serine and releasing the second cleavage peptide **5**.



Scheme 1

The serine proteases of the lung are derived from the neutrophil azurophilic granule and include human neutrophil elastase (HNE),[7] cathepsin G and proteinease-3.

Human neutrophil elastase (HNE)

HNE is the most potent protease released by the neutrophil. Its primary amino acid sequence has been completely determined.[7] Four isozymes of HNE are known and range in molecular weight from 24-30 kDa. HNE is released to respond to inflammatory stimuli and has a major role in protein digestion following phagocytosis. Moreover, HNE degrades the extracellular matrix and cells to allow neutrophil migration through the tissue and it also creates a destructive environment for the removal of pathogens.

1.1.2) Inhibitors of serine proteases

Protease inhibitors

Protease inhibitors represent the third largest group of functional proteins in mammals by weight after albumin and the immunoglobulins.[8] These inhibitors play a key role in the regulation of the proteolytic processes mentioned above. Although endogenous inhibitors are nearly always proteins, small non-proteinaceous inhibitors directed against host proteases are produced in some microorganisms.[9]

Serine protease inhibitors

In a now classic review article Laskowski and Kato grouped the serine protease inhibitors into 17 distinct superfamilies on the basis of sequence homology,[9] structural similarity and mechanisms of inhibition. The X-ray crystal structure of at least one representative is known for 12 of these families.

Standard mechanism inhibitors

Typical protease inhibitors are relatively small proteins of between 29 and 190 amino acid residues, with an exposed reactive site-binding loop of a characteristic conformation, which reacts with its cognate serine protease. Protein inhibitor-serine protease interaction has been studied in detail, particularly for the soybean-trypsin inhibitor.[9] The interaction involves 1:1 association between the inhibitor and the protease. The standard mechanism can be represented as in **scheme 2**.[10]

$$E + I \rightleftharpoons EI \rightleftharpoons E + I^*$$

Scheme 2

E is the protease, and I is the inhibitor. Inhibition resembles hydrolysis of normal substrates except that the complex EI is rapidly formed and is much more stable than the Michaelis enzyme-substrate complex. The reactive site peptide bond is hydrolysed to yield free enzyme E and cleaved modified inhibitor I*. However the apparent rate of association of I* with E is generally several orders of magnitude slower than the

corresponding rate for I, resulting in extremely low hydrolysis of the bond. Furthermore, hydrolysis does not proceed to completion, due to an equilibrium established between I with I*.

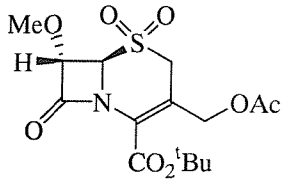
The serine protease inhibitor[11] (serpin) superfamily are much larger (350 amino residues) than the small protein inhibitor of serine proteases outlined above, and show deviations from the standard mechanism of inhibition with respect to complex stability and reversibility of inhibition. Although serpins seem to interact with their target proteases like the canonical inhibitors *via* an exposed binding loop, the resulting complexes are extremely stable. Ultimately the complexes dissociate to reveal cleaved serpin that is no longer inhibitory.

1.1.3) Inhibitors of HNE

HNE can degrade the major structural components of the lung and its main target is elastin, which is the key molecule responsible for elastic recoil and architectural support.[12] The regeneration of elastin is inefficient and most of the elastin synthesized is aberrant. The destruction of lung elastin can cause the loss of elastic recoil, radial tension and destruction of alveolar walls. This decreases the surface area available for gaseous diffusion and can result in obstructive lung disease. Excessive elastase release has also been implicated in respiratory diseases.[13] Uncontrolled HNE activity is implicated in the pathogenesis of obstructive lung diseases. Evidence for this includes experiments in animals, where the synthetic neutrophil elastase induced the degradation of lung tissue.[14] In addition, uncontrolled HNE activity may be the result of a relative antiprotease deficiency, which causes a protease-antiprotease imbalance and results in tissue destruction and lung disease. Hence the activity of HNE must be controlled.

In recent years, many HNE inhibitors have been reported. The clinical candidate low molecular weight HNE inhibitors are elastase inhibitors, which have been developed as potential drugs for treating emphysema, which is known to arise either by genetic or environmental factors, such as oxidants that are present in cigarette smoke. Experimental evidence for this hypothesis in animals suggest that synthetic and natural elastase

inhibitors could be used to replace the lost elastase inhibitory factors in the lung and thereby prevent or retard the progression of this disease.[15, 16]



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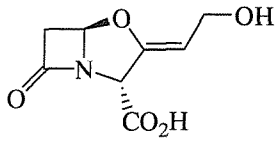

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Figure 1

Not only a variety of heterocyclic lactones, but also the derivatives of β–lactam esters, such as β–lactam **6** (**Figure 1**), were found to be efficient inhibitors of HNE.[17] These compounds were discovered as a result of early observations that the benzyl ester of β- lactamase, clavulanic acid **7**, weakly inhibited HNE.[18] Compound **8**, synthesized by chemists at Merck[19], also proved to be a potent elastase inhibitor **(Figure 2)**.

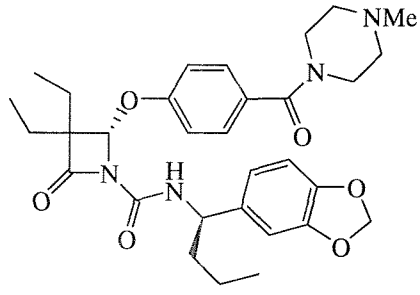

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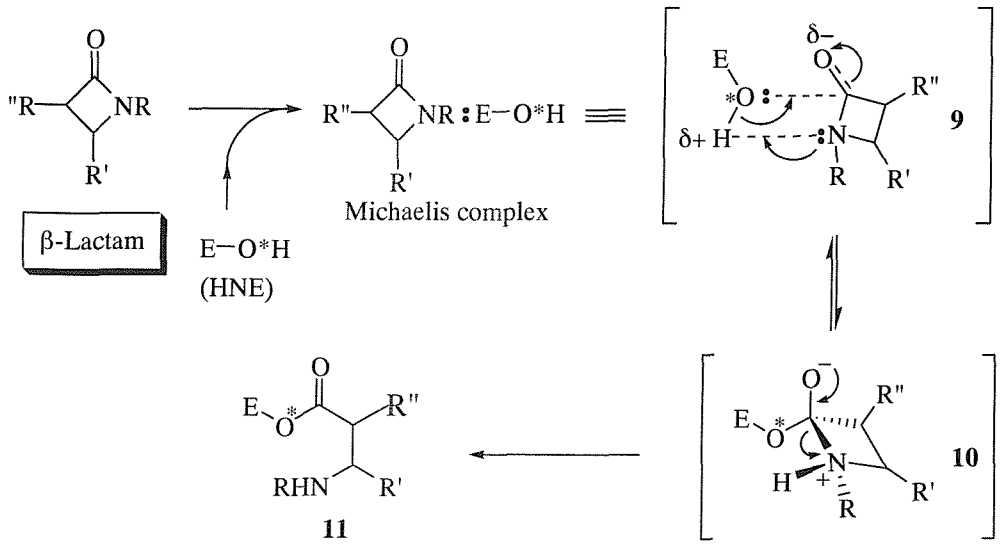
Figure 2

β-Lactam derivatives proved that they have potential in inhibition of HNE. The mechanism of inhibition of β-lactam derivatives can also be illustrated schematically in the same way as the serine protease case (**Scheme 3**). The HNE is symbolized by E-OH, with –OH representing the reactive serine side chain. The first intermediate is the Michaelis complex, which is in the form of non-covalent HNE-β-lactam complex **9**. This is followed by an intermediate tetrahedral adduct **10** in which a covalent bond is formed between the β-lactam carbonyl carbon atom and the reactive HNE oxygen atom (O*). A

proton is shown as partially transferred from O* to the β-lactam nitrogen atom. When the transfer is completed, the tetrahedral intermediate breaks down to liberate the β-amino ester **11**. β-Lactam derivatives are good HNE inhibitors because they have a highly strained four-membered ring, which can be easily cleaved by HNE and they also form a very stable acyl-enzyme adducts **11**.



Scheme 3

Some years ago, pyrrolidine *trans*-lactones and pyrrolidine *trans*-lactams were identified as potent inhibitors of HNE. Chemists at GlaxoSmithKline (GSK) have recently developed new templates **12** [20]and **13** [21] **(Figure 3)**, which possess inhibitory activity against serine protease such as trypsin, chymotrypsin, cathepsin G, and thrombin. The discovery that these templates were also effective inhibitors of HNE, led to the study of these compounds as potential therapeutic agents for respiratory disease.

12 **13**

Figure 3

In chronic bronchitis, HNE is also thought to play a pivotal role in causing recurrent productive cough and lung infection. In order to develop a therapy for chronic bronchitis, the hydrochloride salt of pyrrolidine *trans*-lactam **14**[22] was synthesized by Cooke and colleagues from GSK (**Figure 4**).

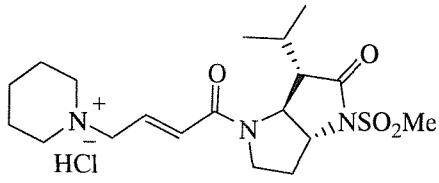


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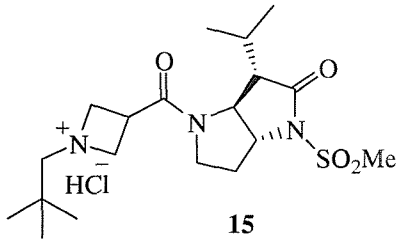
Figure 4

Three further derivatives of pyrrolidine *trans*-lactams **15**, **16** and **17**, have been reported which proved to have more activity in inhibiting HNE in human whole blood and comparable pharmacokinetic properties (**Figure 5**).[23]



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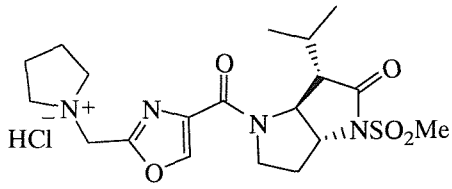

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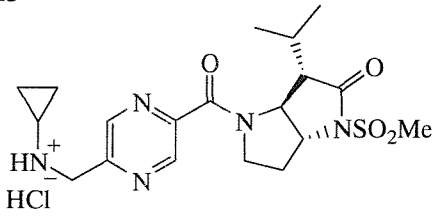

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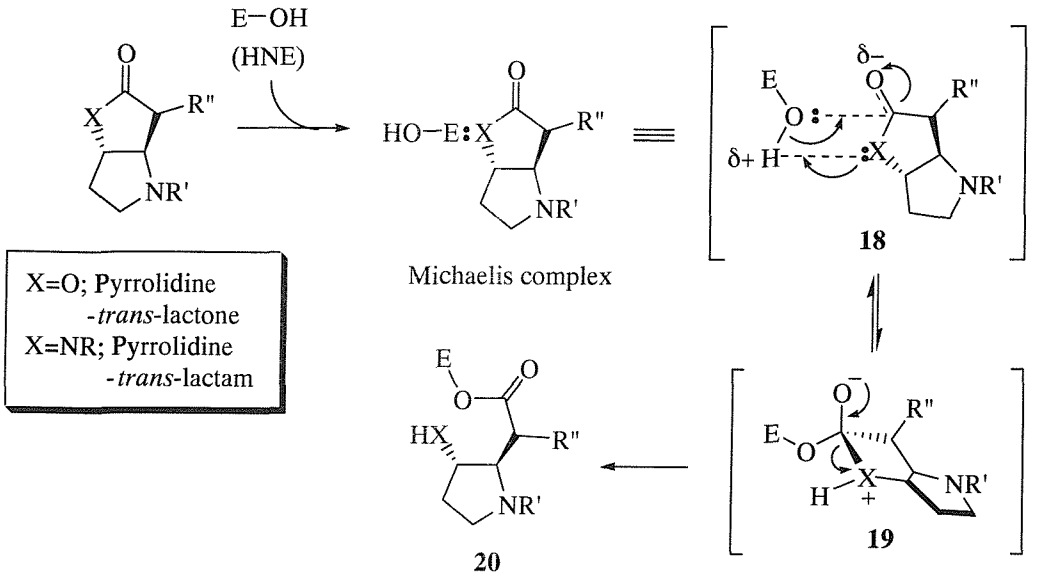
Figure 5

As in the case of β-lactam inhibitors, pyrrolidine *trans*-lactone **12**, and pyrrolidine *trans*-lactam **13** and **14** also have highly strained skeletons based on the 5,5-*trans*-fused ring system.

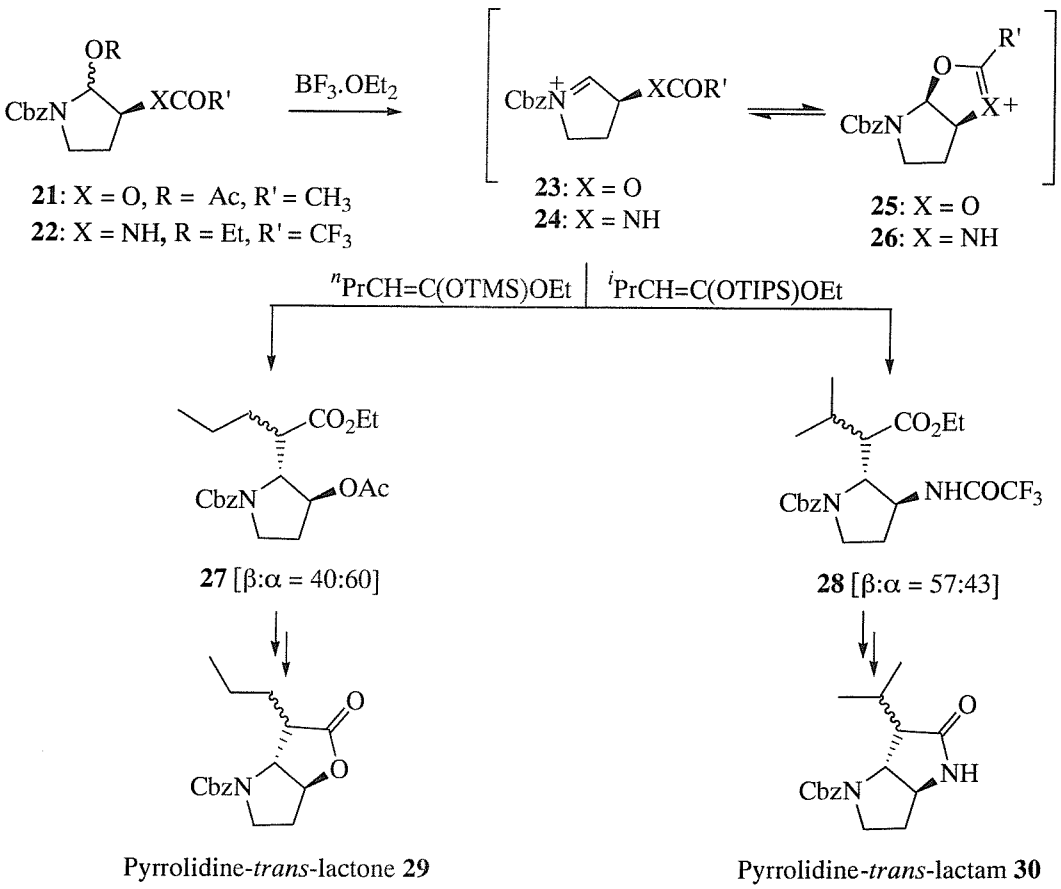


Scheme 4

Again the inhibitory mechanism of pyrrolidine *trans*-lactones and lactams (**Scheme 4**) is similar to that for β-lactam derivatives (**Scheme 3**). Michaelis complex is formed from the enzyme (HNE) and HNE inhibitor either lactone or lactam. The tetrahedral intermediate **19** is formed from non-covalent intermediate **18**, as the proton transfer from HNE oxygen to heteroatom X proceeds. The cleavage of the C-X bond releases the strain of the bicyclic system **19** and leads to formation of the very stable pyrrolidine ester **20**.

1.1.4) Synthesis of pyrrolidine-*trans*-lactones and pyrrolidine-*trans*-lactams

Chemists at GSK developed several synthetic routes to pyrrolidine-trans-lactones and lactams. The most critical step of the synthesis is control of the stereochemistry of a disubstituted pyrrolidine system to give the *trans*-diastereomer. In early synthesis, acyl-iminium chemistry was used to control the stereoselectivity of the pyrrolidine rings (**Scheme 5**).[24,25]

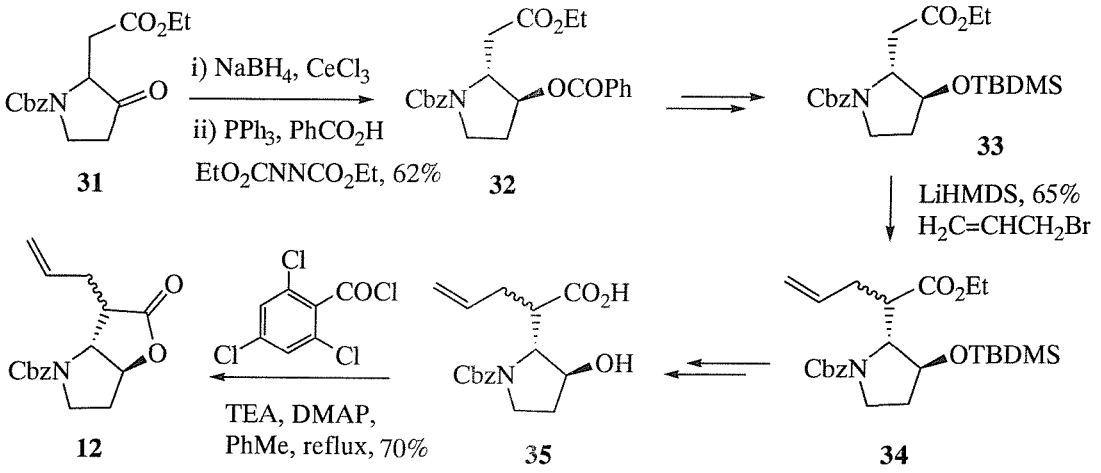


Scheme 5

Treatments of **21** and **22** with $BF_3{\cdot}OEt_2$ forms the cationic intermediates **23** and **24** and **25** and **26**, which preferentially allow nucleophilic attack from the less hindered *exo* face. After being reacted with silyl ketene acetals, pyrrolidine derivatives **27** and **28** were produced but with poor stereoselectivity. These were subsequently converted into the pyrrolidine *trans*-lactone **29** and pyrrolidine *trans*-lactam **30**. However, β-stereo-selectivity was not good enough.

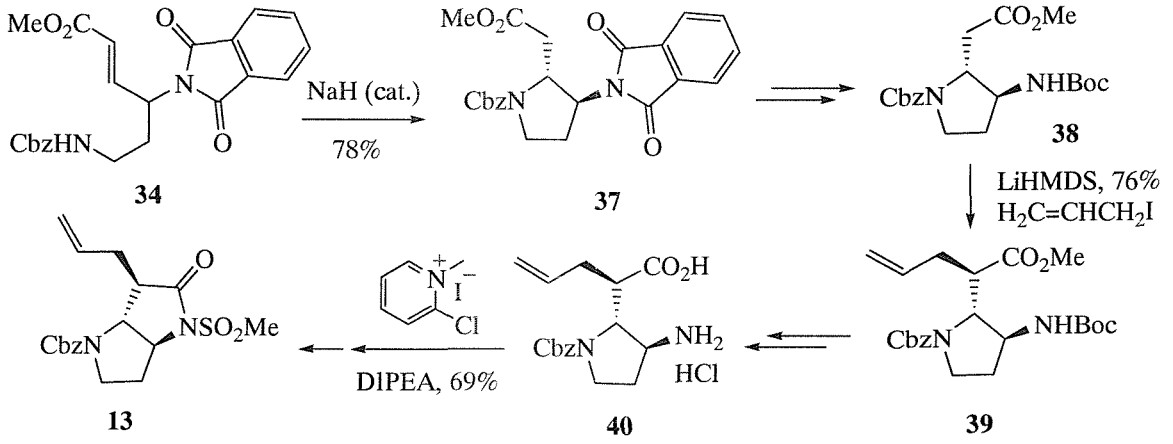
A reduction-alkylation protocol was considered (**Scheme 6**).[26] Initially the reduction of the known keto-ester **31** with $NaBH_4$ gave a 5:1 ratio of *cis*-cyclised lactone to *trans*-hydroxyester. $CeCl_3$ was used to prevent over-reduction, and a rapid work-up avoided extensive cyclisation of the intermediate to give the *cis*-lactone. Treatment with benzoic acid under Mitsunobu conditions gave the *trans*-benzoate **32** in a moderate yield. Reprotected **33** was alkylated to give the corresponding compound **34** with a substituent adjacent to the ester

in 65% yield. Again the 1:1 ratio of β/α stereoselectivity in this alkylation step was unsatisfactory. After deprotection, precursor **35** was cyclised to give pyrrolidine *trans*-lactone **12** in 70% yield **(Scheme 6)**.



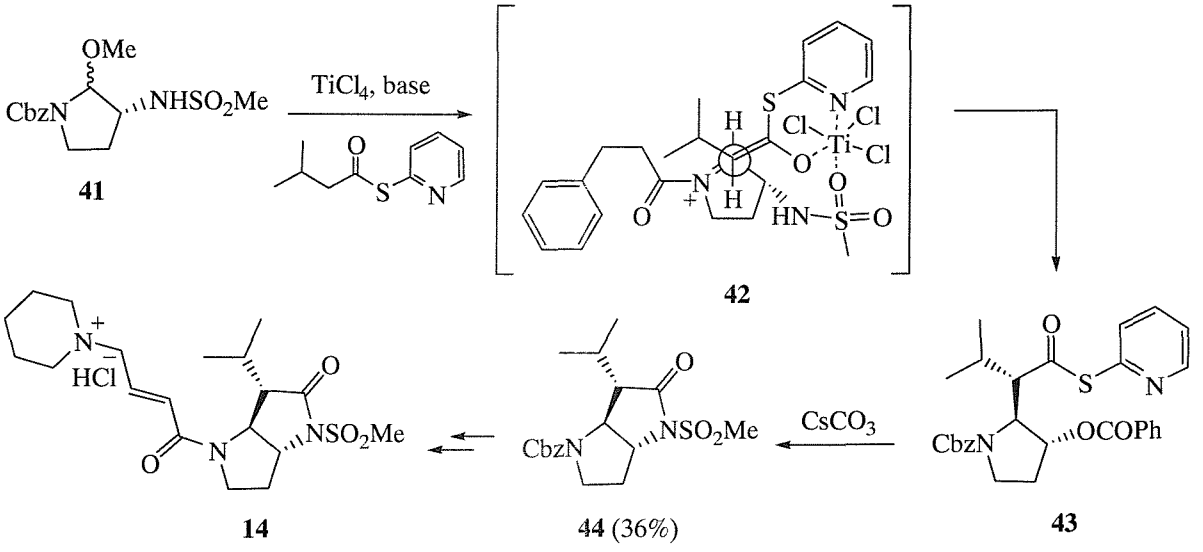
Scheme 6

The synthesis of pyrrolidine *trans*-lactam **13** started from the 5-*exo*-trig cyclisation of the carbamate precursor **36** mediated by the catalytic amount of NaH, which gave the 2,3-*trans*-disubstituted pyrrolidine **37** in 78% yield **(Scheme 7)**.[21] Reprotected **38** was alkylated to give the corresponding compound **39** in 76% with more than 10:1 ratio of β/α isomers. Lactamization of deprotected **40** was achieved with 2-chloro-1-methylpyridinium iodide and DIPEA, followed by the protection of the free amide gave the corresponding pyrrolidine *trans*-lactam **13** in a good yield.



Scheme 7

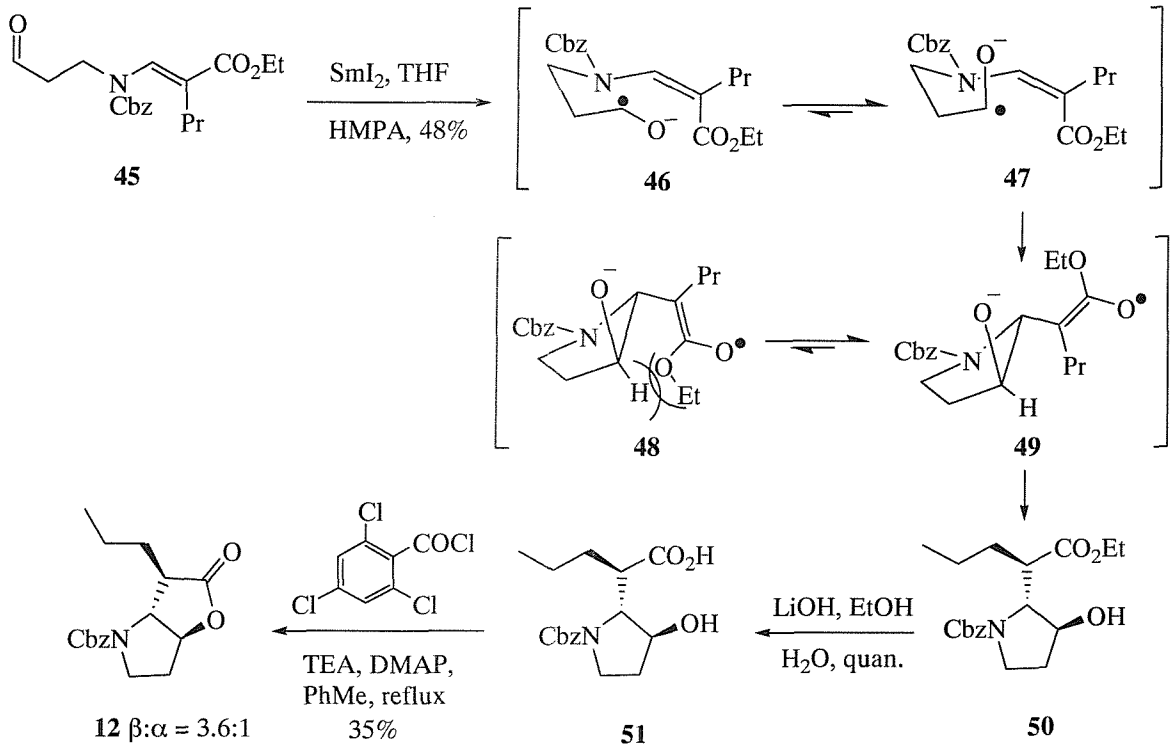
Another strategy for the synthesis of the bicyclic *trans*-system was the cyclisation *via* a titanium enolate of a thiopyridyl ester (**Scheme 8**).[27] This pyrrolidine *trans*-lactam **14** was previously synthesized by the acyl-iminium strategy, however the cyclisation yield and the enantioselectivity were not satisfactory.[22] Treatment of the titanium enolate with compound **41** led to a mixture of the major β-diastereomer **43** and minor α-diastereomer in a ratio of 12:1. The coordination between titanium and sulfonamide may increase the selectivity of the β-product. Cesium carbonate was used as a reagent for the cyclisation of β-diastereomer **43** to give the pyrrolidine *trans*-lactam **44** in 36% yield for the two steps. Finally **44** was deprotected under transfer hydrogenation conditions, followed by acylation with the corresponding carboxylic acid to obtain hydrochloride salt **14 (Scheme 8)**.



Scheme 8

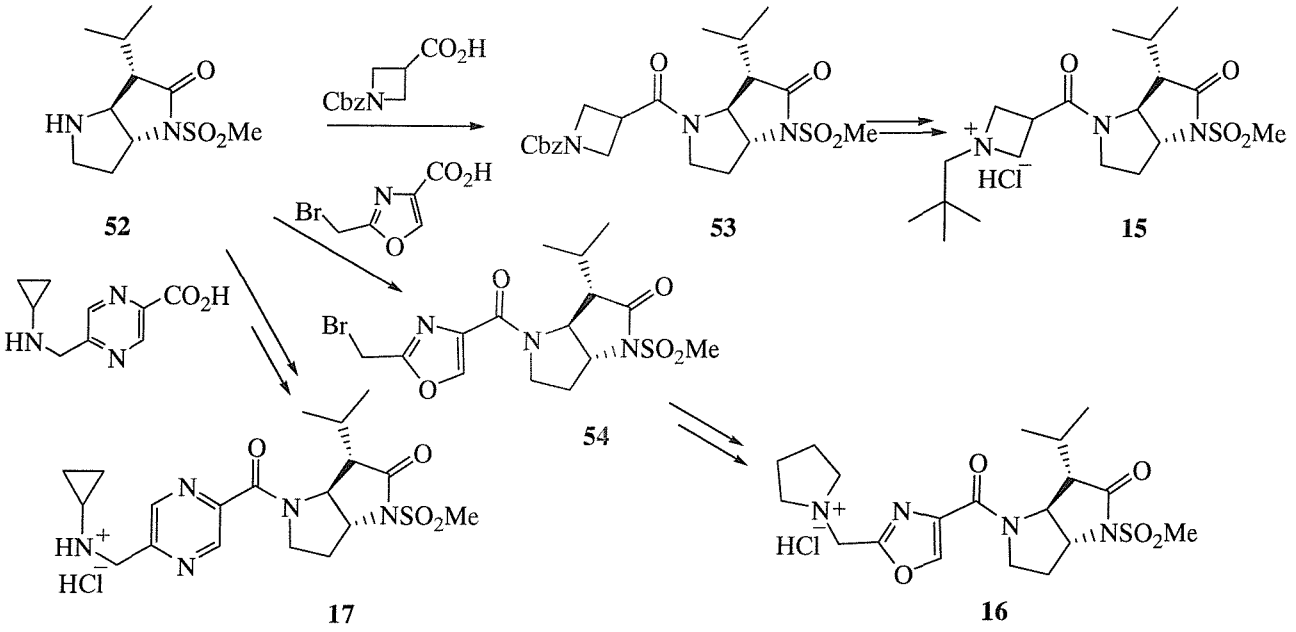
A stereoselective synthesis was also achieved using an intramolecular 5-*exo*-trig cyclisation mediated by SmI_2 (**Scheme 9**).[28] Aldehyde precursor **45** was cyclised *via* radical intermediates **47** and **49** to give the β-*trans*-pyrrolidine derivative **50** in a moderate yield of 48%. The outcome *trans*-stereochemistry could be explained by the preference of the radical TS **47** rather than the TS **46**, which would have the electronic repulsion between the developing methylene radical centre and the negatively charged oxygen atom. In the next step, the preference for the formation of β-product from TS **49** (rather than TS **48**) may be described in terms of minimising the steric clash between the ethyl

ester moiety and the hydrogen atom on O$^-$-carbon. As a consequence, the cyclisation gave the β-diastereomer **50** as a major product. Hydrolysis of **50** using LiOH in ethanol, quantitatively gave a corresponding carboxylic acid **51**, which was cyclised to give the pyrrolidine *trans*-lactone **12** in 35% yield (**Scheme 9**).



Scheme 9

Pyrrolidine *trans*-lactams **15**, **16** and **17** were synthesized from the same lactam precursor **52**, which can be easily made by deprotecting Cbz group of pyrrolidine *trans*-lactam **44** (**Scheme 10**).[23]



Scheme 10

1.2) Chemical background

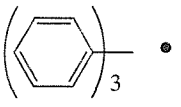
The purpose of this project was to discover novel routes to the pyrrolidine-*trans*-lactam based on a radical cyclisation approach and which would allow the efficient preparation of novel analogues. The proposed project would involve an investigation of methods for generating the required radical precursor, and a study of the stereochemical outcome of such radical cyclisations.

1.2.1) Radical chemistry

The past forty years have witnessed an unparalleled development of new synthetic methods in the field of organic chemistry. Many of these novel methodologies involve the same basic ionic processes, which were involved in the early development of the mechanistic picture of organic chemistry. Within the last three decades however a new approach to bond formation has emerged, namely the use of homolytic or radical reactions. It is already evident that these processes, well known in the polymer industry, have a great role to play in the organic synthesis of complex molecules.

I) Basic principles of radicals

Radical chemistry dates back to 1900 when Gomberg investigated the formation and reactions of the triphenyl methyl radical **55** (**Figure 6**).[29] The pace of development was rather slow over the next couple of decades and radicals were rarely used in synthesis. However, deeper insights into the formation, structure, and reactions of radicals have been continually gained by many researchers. The results of these early investigations have led to the rapid development in recent years in the use of radical cyclisation for the formation of aliphatic C-C bonds and in the synthesis of target molecules.



55

Figure 6

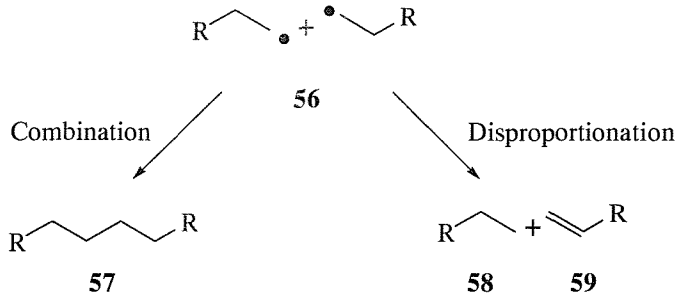
Radicals are species with at least one unpaired electron, which react easily amongst themselves in bond forming reactions. In the liquid phase, most of these reactions occur with diffusion-controlled rates. This high reactivity can also be a disadvantage as radicals may recombine randomly resulting in undesired reactions. An important and very attractive feature of the radical reactions is their high degree of functional group tolerance. Radicals are usually stable under protic conditions so alcohols or even water may, in principle, be used in radical chemistry, and protic functional groups do not need protection.

Once formed, radicals may react in addition or substitution reactions as they can have an electrophilic or nucleophilic character depending on the substituents attached to the radical center. Two types of radical interactions are distinguishable: reactions between radicals and reactions between a radical species and a non- radical compound.

II) Reaction between radicals

Reactions between radicals are in most cases very fast, which could theoretically make direct radical-radical combination the most synthetically useful reaction. However, direct radical- radical reactions have several disadvantages[30]: difficulty in controlling the reaction in order to give high selectivity; the reaction with non-radicals is likely; and the reaction needs at least one equivalent of radical initiator.

There are two types of radical-radical reaction: combination and disproportionation (**Scheme 11**). In the former case, the reaction combines two radicals **56** together and forms a dimer **57**. On the other hand, disproportionation proceeds with hydrogen atom abstraction leading to two fragment molecules, a saturated one **58** and an unsaturated one **59**.



Scheme 11

III) Reaction between radicals and non-radicals

The second method for the synthesis of the products using radical chemistry employs reactions between radicals and non- radicals. It has many advantages[30]:

- The selectivity may be influenced by varying the substituents.
- The concentration of the radicals is easily controlled.
- The reaction proceeds with non-stoichiometric amount of the initiator.

Free-radical mechanisms are the best way to explain the radical-nonradical reactions, since they divide the chain reactions into three simple steps (**Figure 7**).[31] The first step is the formation of free radicals, which is the initiation step. It normally occurs

by the homolytic cleavage of a bond, in which each fragment retains one electron. The second step involves the generation of a new radical. This type of step is called propagation, since the new radical can react with another molecule producing another radical. The propagation steps eventually stop when two radicals meet each other, and this step is called termination (**Figure 7**).

Initiation

$$A + B \longrightarrow A^{\bullet} + {}^{\bullet}B$$

Propagation

$$A^{\bullet} + B \longrightarrow A\text{–}B^{\bullet}$$

$$A^{\bullet} + HB \longrightarrow AH + {}^{\bullet}B$$

$$RAB^{\bullet} \longrightarrow RA + {}^{\bullet}B$$

$${}^{\bullet}A\text{–}B \longrightarrow A\text{–}B^{\bullet}$$

$$A^{\bullet} + RB \longrightarrow RA + {}^{\bullet}B$$

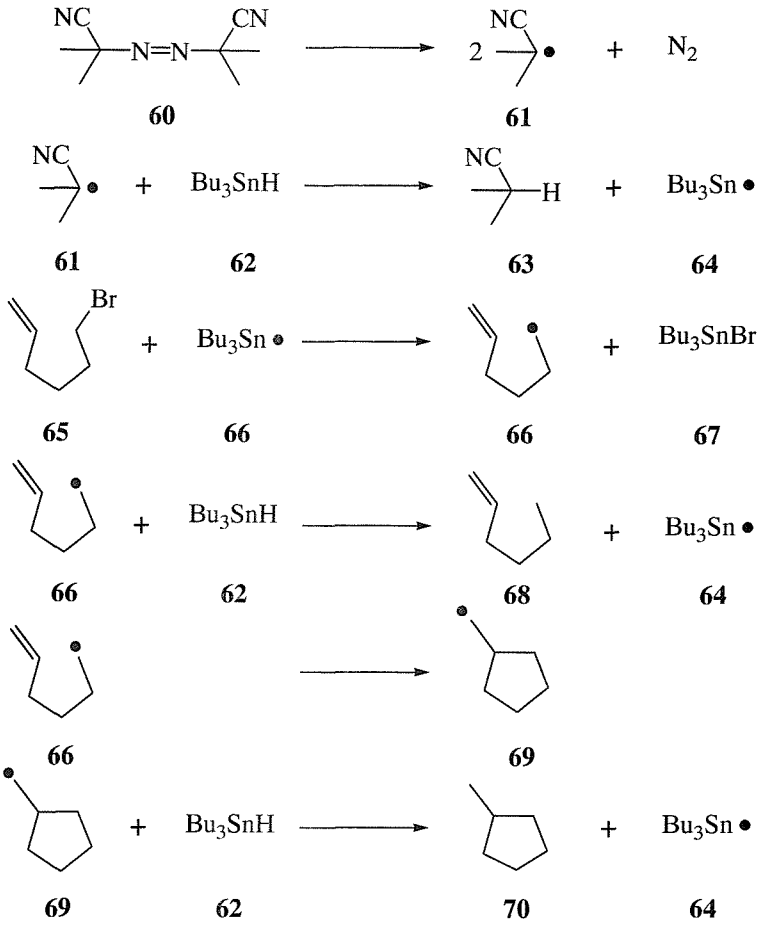
Termination

$$A^{\bullet} + {}^{\bullet}B \longrightarrow A\text{–}B$$

Figure 7

Example of radical reactions

The scope of radical reactions in organic synthesis is very wide.[30, 32] One example is the tributyltin hydride (Bu_3SnH) **62** method for the radical cyclisation of 6-bromo-1-hexene **65** reported by Wallis (**Scheme 12**).[33] In the initiation step, 2,2'-azo-bis-isobutyronitrile (AIBN) **60** is utilised together with Bu_3SnH **62** to trigger the radical sequence. Generated tributyltin radical **64** reacts with bromide **65** to give hexenyl radical **66** and tributyltin bromide **67**, which undergo either direct reduction to give a 1-hexene **68** or intramolecular 5-*exo*-trig cyclisation to give methyl cyclopentane **70** *via* a cyclopentyl methyl radical **69**. Each step produces tributyltin radical **64**, which is eventually quenched.

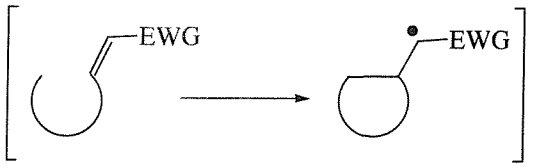


Scheme 12

1.2.2) Intramolecular radical cyclisation

Formation of carbon-carbon bonds by intramolecular additions (cyclisations) of carbon radicals onto alkenes are important reactions in organic synthesis (**Scheme 13**). The rate of cyclisation largely depends on the substituents on the radical species and on the alkene bond. In general, electron-donating groups on the radical species and electron-withdrawing groups on the alkene accelerate the cyclisation.

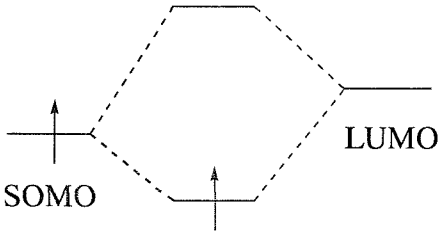
Radical cyclisation



Intramolecular Michael-type radical addition

Scheme 13

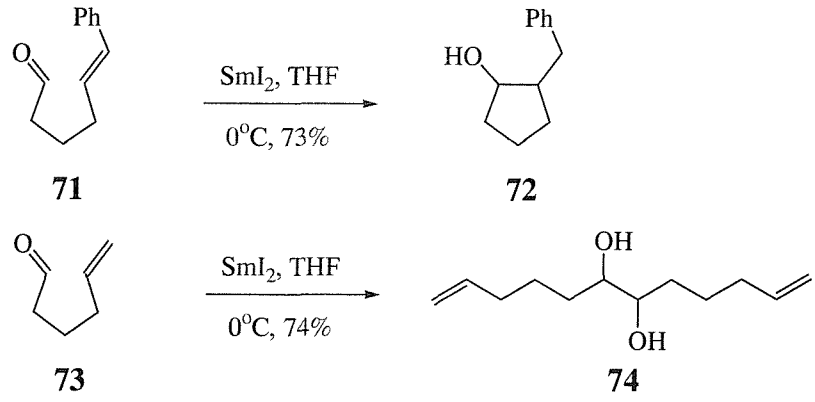
Frontier molecular orbital (FMO) theory offers a good explanation of the substituent effects. In the case of intramolecular Michael-type radical addition, the singly occupied molecular orbital (SOMO) of the radical interacts with the lowest unoccupied molecular orbital (LUMO) or the highest occupied molecular orbital (HOMO) of the alkene bond (**Scheme 14**).[34] Nucleophilic radicals undergo Michael-type free radical conjugate addition to alkenes (or alkynes) attached to an electron-withdrawing group (EWG) (**Scheme 13**). The addition rate of nucleophilic radicals is increased because the EWG at the alkene lowers the LUMO energy, reduces the SOMO-LUMO gap, and also stabilizes the product radical.



FMO interaction of nucleophilic
radical with an electron-poor alkene

Scheme 14

Enholm and Trivellas demonstrated this with a nice example of how an electron-withdrawing group on the alkene can affect a cyclisation.[35] When compound **71**, which possesses a phenyl group as an electron-deficient olefin, was reacted with SmI_2 under the condition described (**Scheme 15**), the desired 2-substituted cyclopentyl alcohol **72** could be isolated. However, when the same reaction condition was applied to **73**, which has no EWG at the terminus on the alkene bond, only the pinacol coupled product **74** was obtained in 74% yield rather than the reductively cyclised product.



Scheme 15

I) Regioselectivity

Baldwin[36] established a set of useful rules for ring closure in 1976. Three rules predict the relative facility of ring forming reactions:

I) Tetrahedral Systems
   a) 3 to 7-*exo*-tet are all favoured.
   b) 3 to 7-*endo*-tet are all disfavoured.

II) Trigonal Systems
   a) 3 to 7-*exo*-trig are all favoured.
   b) 3 to 5-*endo*-trig are disfavoured; 6 to 7-*endo*-trig are favoured.

III) Digonal Systems
   a) 3 to 4-*exo*-dig are disfavoured; 5 to 7-*exo*-dig are favoured.
   b) 3 to 7-*endo*-dig are all favoured.

For the closures to a carbon atom, the favoured paths to the transition states can be explained by the fact that subtended angle between the three interacting atoms is maintained during the reaction pathway, becoming the angle between these atoms in the product (**Figure 8**). Thus the favoured ring closures are those in which the length and the nature of the linking chain enables the terminal atoms to achieve the required trajectories to form the final ring bond. The disfavoured cases in fact require severe distortion of bond angles and distances to achieve such trajectories.

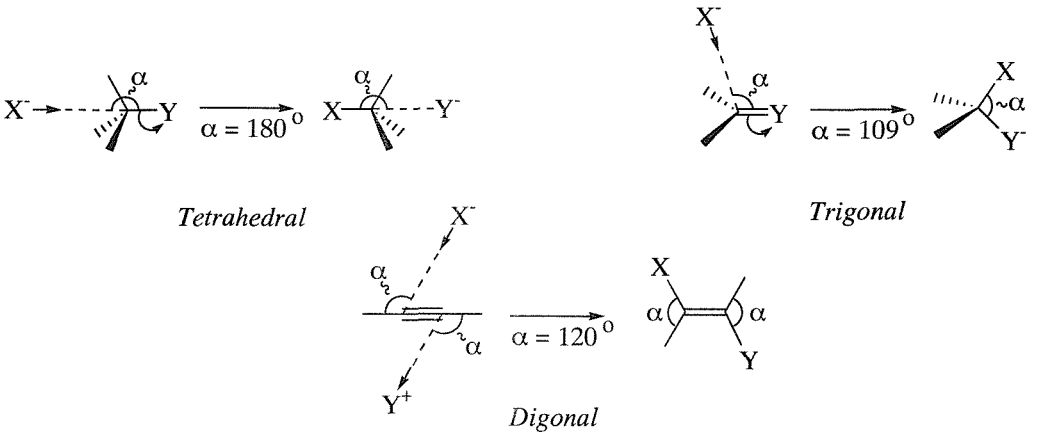
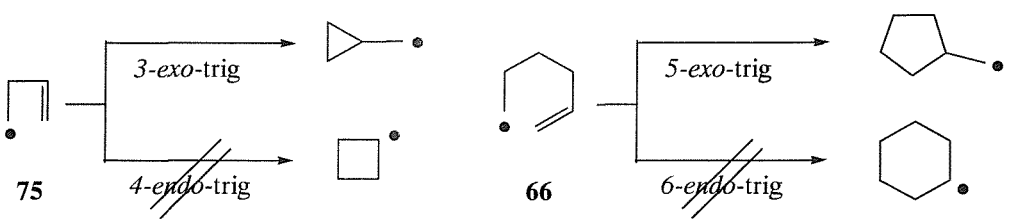


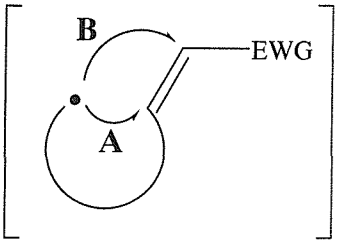
Figure 8

Although this treatment has been discussed for nucleophilic closures (X- in **Figure 8**), it also applies to homolytic and cationic processes. Thus radical **75** closes only by the 3-*exo*-trig not the 4-*endo*-trig mode. Similarly, radical **66** yields preferentially the cyclopentyl methyl radical by 5-*exo*-trig closure rather than the 6-*endo*-trig pathway (**Scheme 16**). In both cases the thermodynamically less stable product is formed.[37]

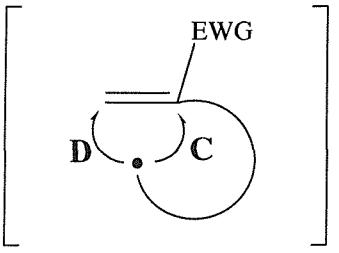


Scheme 16

In the series of intramolecular free radical Michael additions, the position of the EWG attached to the radical acceptor has significant influence on the regioselectivity. Apart from the dependence of ring size, pathway **A** is a preferred route if the EWG is at the terminus of the carbon-carbon double bond (**Scheme 17**), whereas pathway **D** is favorable if the EWG is in the inner position.



Pathway **A**: *exo*, Michael addition
Pathway **B**: *endo*, anti-Michael addition

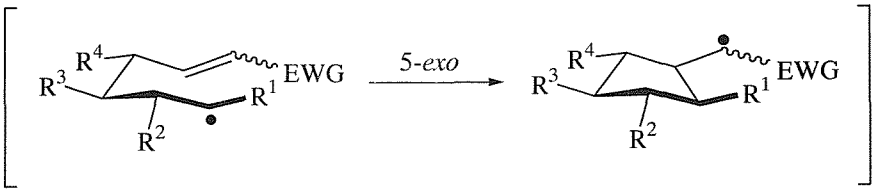


Pathway **C**: *exo*, anti-Michael addition
Pathway **D**: *endo*, Michael addition

Scheme 17

II) Stereoselectivity

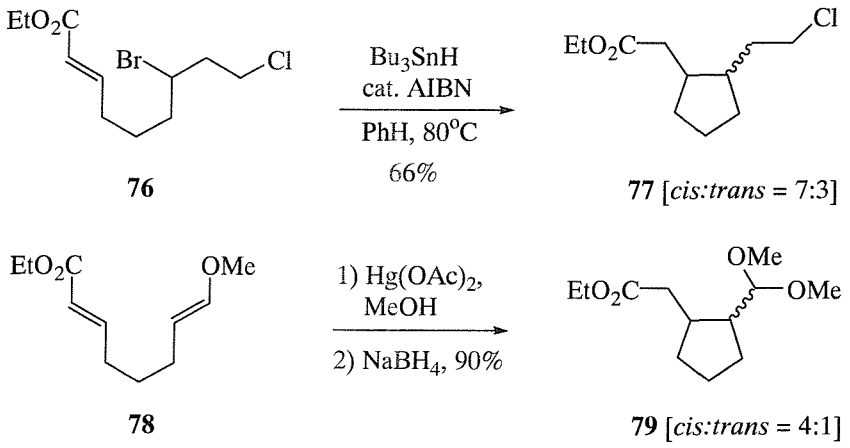
The Beckwith-Houk chair-like transition state model serves as the basis for predictions and rationalizations of stereoselectivity in 5-*exo* hexenyl radical cyclisations (**Scheme 18**).[38,39]



Scheme 18

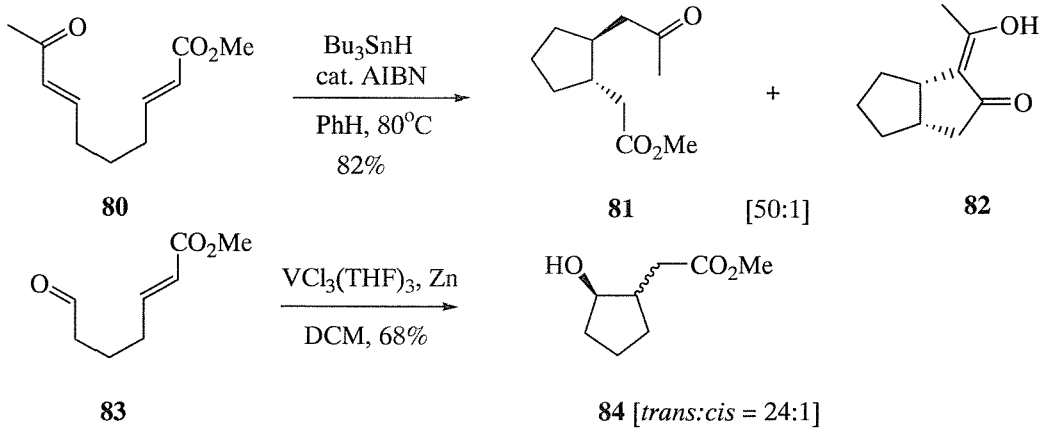
As predicted by the Beckwith-Houk model, the R^1 substituent at the 1-position of hexenyl radicals affords *cis*-1,2-disubstitued cyclopentanes as the major diastereomer. Results from reactions promoted by tin hydride[40] and mercury (II) acetate[41] are consistent with the predictions (**Scheme 19**), and gave cyclopentyl products **77** (*cis* : *trans* = 7:3)

and **79** (*cis* to *trans* = 4:1) in 66% and 90% yields, from the unsaturated precursors **76** and **78**.



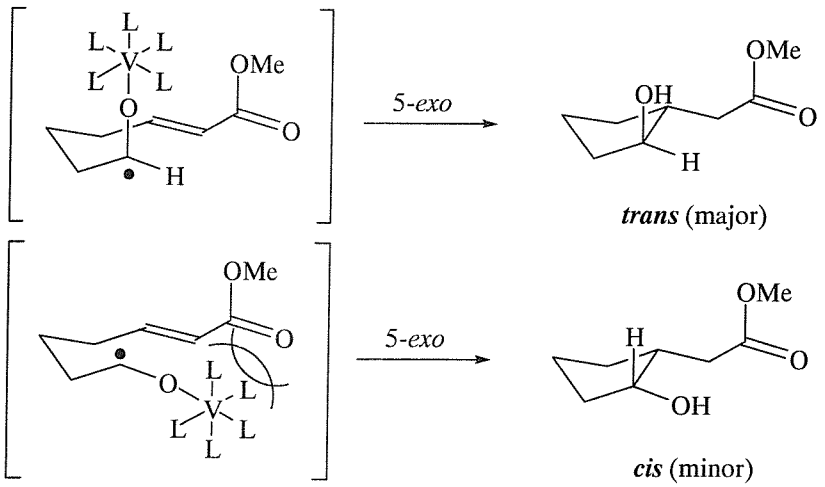
Scheme 19

A high percentage of *trans*-1,2- disubstituted cyclopentanes has been observed by Enholm[42] and Torii[43] in the studies of the cyclisations of *o*-stannyl ketyls and *o*-vanadyl ketyls (**Scheme 20**). The cyclisation with Bu_3SnH of precursor **80** provided **81** and **82** in 82% yield and the other cyclisation with a vanadyl reagent of ketone **83** gave **84** in 68% yield.



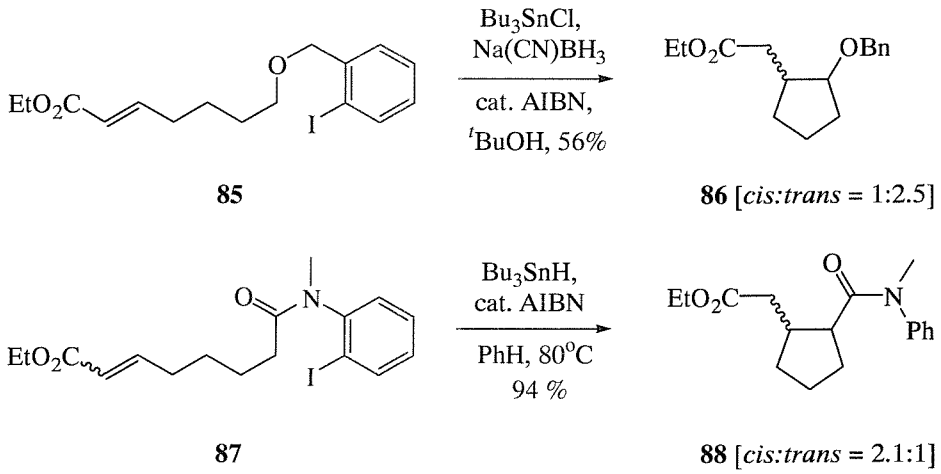
Scheme 20

In the latter case, it is suggested that the bulky organometallic group disfavours a *cis* arrangement in the chair-like TS (**Scheme 21**).



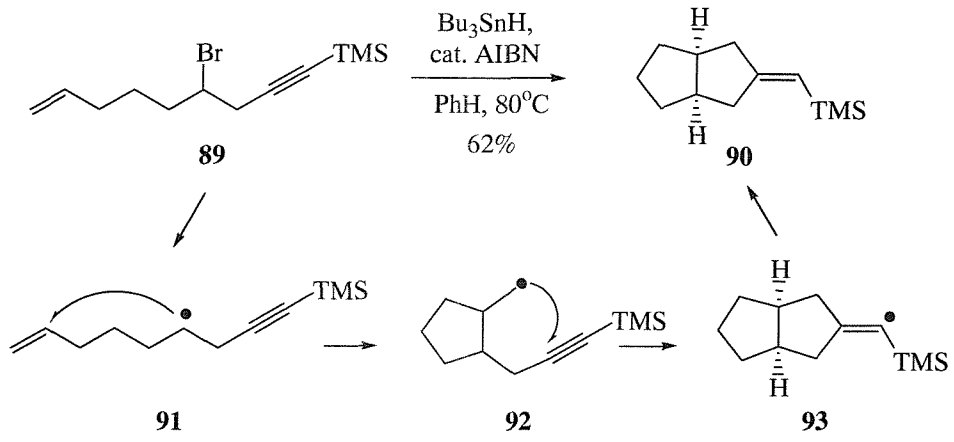
Scheme 21

Carbonyl groups and heteroatoms such as oxygen or nitrogen stabilize adjacent carbon-centered radicals. Curran and Snieckus employed these functional groups in the design of reactions that rely on this 1,5-hydrogen atom transfer to initiate the cyclisations (**Scheme 22**).[44,45] From iodide precursor **85** the radical cyclisation leads to cyclic compound **86** in 56% as a mixture of diastereomers (*cis* 1: *trans* 2.5). However, using iodide precursor **87** the cyclisation resulted in a 94% yield of cyclic compound **88** and with a different ratio of diastereomers (*trans* 1: *cis* 2.1).



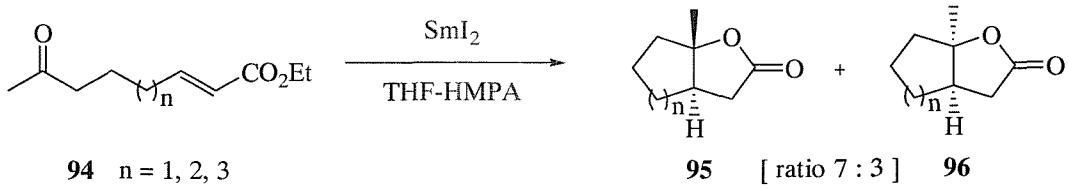
Scheme 22

Another important example from Kilburn uses tandem radical cyclisation (**Scheme 23**).[46] Treatment of bromide precursor **89** under Bu_3SnH standard condition stereoselectively produced *cis* fused bicyclic product **90** in 62% yield. Its pathway also illustrated in the **scheme 23**, proceeds by the first radical intermediate **91** cyclising onto the terminal alkene bond. The five-membered ring radical **92** undergoes another 5-*exo* cyclisation with an alkyne moiety to produce **93**, which is quenched to give the final product **90**.



Scheme 23

The last example of the application of intramolecular cyclisation is shown by the work undertaken by Fukusawa and Sakai in the synthesis of bicyclic γ-lactones **95** and **96 (Scheme 24)**.[47]



Scheme 24

Treatment of several *trans*-unsaturated keto- or aldo-esters **94** with SmI_2 in THF or THF-HMPA (10:1) afforded bicyclic lactones **95** and **96** in moderate to good yields (30-92 %). Reactions of these substrates with SmI_2 were examined under a variety of conditions. Carrying out the reaction at reflux conditions or/and changing the amount of SmI_2 from 2 eq. to 4 eq. gave more satisfactory results. The 7:3 ratio of a mixture of

trans- to *cis*-isomers was almost independent of the reaction conditions. Therefore these bicyclic lactones **95** and **96** were inferred to be the kinetic products of the reaction.

1.2.3) Use of samarium (II) iodide in radical cyclisation

Samarium was first discovered by L. de Boisbaudran in 1879. However it took nearly a century for samarium to establish itself as one of the most useful elements in the Lanthanide series. Since the early 1980s, samarium (II) iodide (SmI_2) has been increasingly recognized as a reducing agent capable of meeting the intensifying demands of synthetic organic chemistry. Kagan and co-workers[48,49,50,51] developed a convenient synthesis of SmI_2 and outlined its general reactivity with common organic functional groups. Because of this SmI_2 has become of general interest and importance to synthetic organic chemists.

Because SmI_2 is a one-electron reducing agent, the transformations carried out with it are single-electron transfer processes with mechanisms similar to those established with other one-electron reducing systems. There are several attractive features of SmI_2 that render its use advantageous over many other similar reducing agents. The first is that samarium ions are excellent Lewis acids. Thus in reactions with polarized functional groups, complexation with either Sm(II) and Sm(III) can greatly facilitate electron transfer by lowering the energy of the lowest unoccupied orbital of the substrate. Also, although they are considered rather powerful reducing agents, Sm(II) species are reasonably stable in alcohols, in water, and, apparently, even in acidic and basic aqueous solutions. Consequently, for reaction processes that generate reactive intermediates requiring immediate quenching upon generation, the use of SmI_2 in the presence of protic solvent additives provides a means to produce these species and protonate them before they can react *via* unproductive pathways.

SmI_2 is a powerful one-electron reducing agent that can be prepared in moderate concentration (0.1M) in THF by one of several different reactions from samarium metal (**Scheme 25**).[52,53]

$$Sm + CH_2I_2 \xrightarrow[\text{rt, 1 hr}]{\text{THF}} SmI_2 + 0.5\ H_2C{=}CH_2$$

$$Sm + I_2 \xrightarrow[\text{heat, 24 hr}]{\text{THF}} SmI_2$$

$$Sm + 2\ NaI \xrightarrow[\text{MeCN}]{2\ Me_3SiCl} SmI_2 + Me_3Si\text{-}SiMe_3 + 2\ NaCl$$

Scheme 25

However the route developed by Kagan and co-workers[48] in late 1980s, has become the most convenient pathway of making SmI_2. Samarium reacts easily under mild condition (one hour at room temperature) with 1,2-diiodoethane in THF to give SmI_2 (**Scheme 26**).[54]

$$Sm + IH_2C{=}CH_2I \xrightarrow[\text{rt, 1 hr}]{\text{THF}} SmI_2 + H_2C{=}CH_2$$

Scheme 26

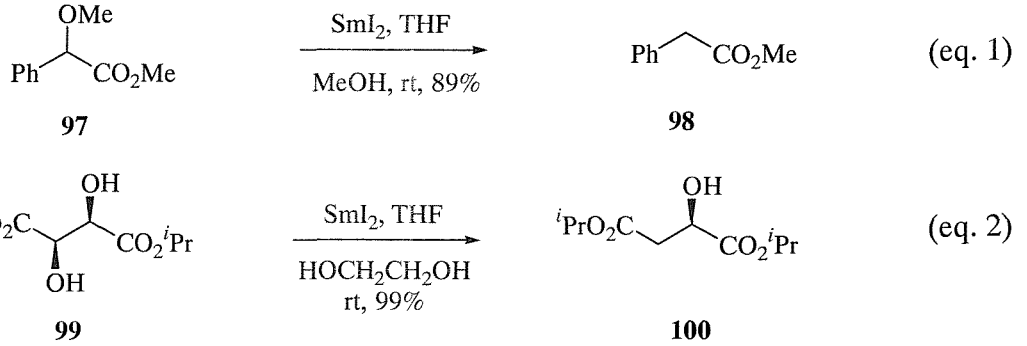
It is very easy to follow the formation of SmI_2, as the colour of SmI_2 solutions are deeply coloured i.e. it is blue in THF, purple in hexamethylphosphoramide (HMPA)-THF and Sm^{3+} salts are light yellow or orange. Inanaga has suggested the intense deep purple coloring of a solution of SmI_2 in THF-HMPA might be due to solvated electrons.[55] Barbier reactions with SmI_2 may be greatly accelerated by the presence of HMPA. Electron-donating ligands increase the reduction potential of low valent metals, so SmI_2 ligated to HMPA is a more powerful reductant rather than SmI_2 alone.

The usual reagent for many radical cyclisations is tributyltin hydride, however the reagent is very toxic and problems can occur on purification of tin residues. Thus SmI_2 can be a good replacement for tributyltin hydride. Use of SmI_2 can be split into four main

groups: I) Functional group reductions, II) Intermolecular additions, III) Intramolecular additions, and IV) Fragmentation reactions.

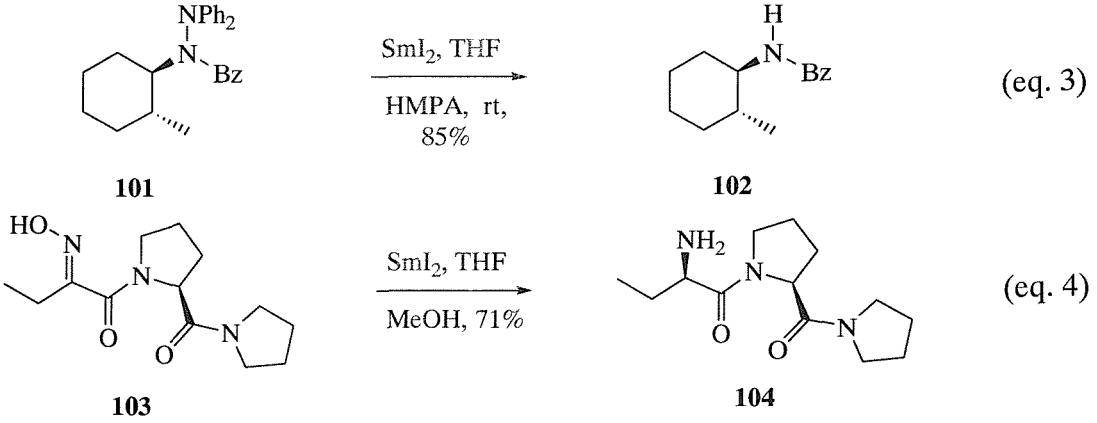
I) Functional group reductions

SmI_2 can reduce a wide range of functional groups e.g. α-alkoxy esters[56], alcohols[56], hydrazines[57], and hydroxylamines[58]. The first example introduced by Kusuda and his colleagues (eq. 1).[56] The reduction of methoxy derivative **97** proceeded smoothly to give saturated ester **98**. The same paper also showed the one-step conversion of tartrate **99** to Maleate **100** (eq. 2)[56] (**Scheme27**).



Scheme 27

Cyclic hydrazine **101** was converted into amide **102** by the exposure of SmI_2 in the presence of HMPA in a good yield (eq. 3).[57] Keck and his co-workers have used SmI_2 to cleave reductively the N-O bond of hydroxylamine **103** into amine **104** (eq. 4)[58] (**Scheme 28**).

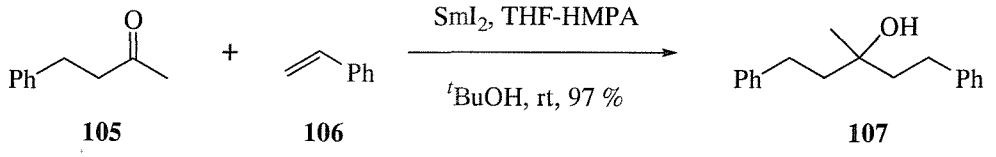


Scheme 28

II) Intermolecular additions

i) Reductive couplings of carbonyls with alkenes or ketones

Anion radicals generated by treatment of ketones such as **105** with SmI_2 attack olefins such as **106** affording the corresponding addition products **107** (**Scheme 29**).[59] Merit of this reaction is that it can be easily monitored by the colour change from purple to yellow.



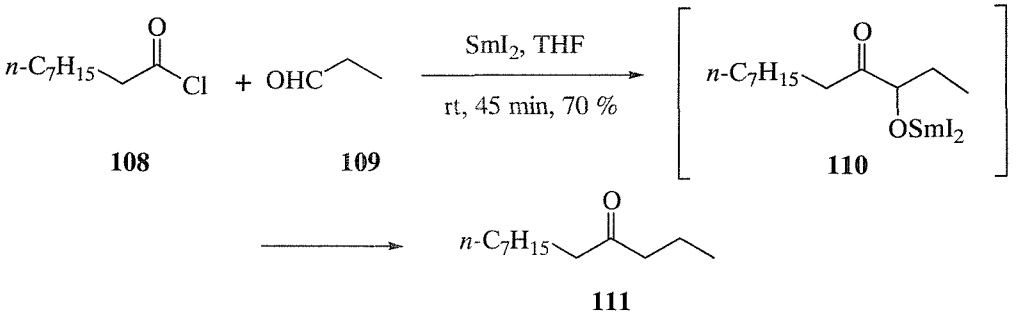
105 **106** **107**

Scheme 29

ii) Reductive couplings of halides with carbonyls or alkenes

Unlike some reagents that are only capable of initiating radical cascades, SmI_2 has demonstrated a tremendous potential to sustain domino processes that begin with anionic reactions as well. This special character gives SmI_2 its reputation for being an unparalleled reagent for conducting sequential reactions under reductive coupling conditions.

One example of reductive couplings of halides with carbonyls or alkenes reported by Kagan and colleagues, is the addition of acyl chloride **108** to carbonyl substrate **109** (**Scheme 30**).[60] The acyloin intermediate **110** was reductively cleaved *in situ* to provide a one-pot synthesis of the corresponding carbonyl compound **111**.

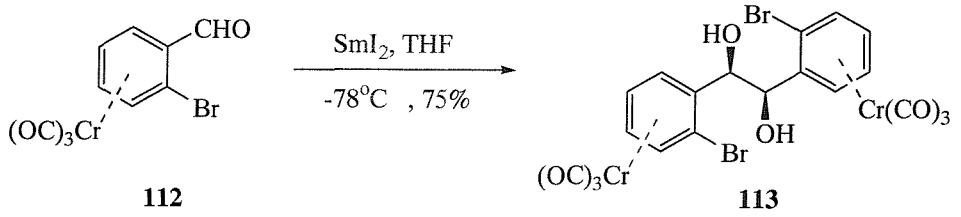


108 **109** **110** **111**

Scheme 30

iii) Pinacol coupling reactions

This coupling reaction would be traditionally carried out with active metals such as sodium, magnesium, or aluminum, but it can also be accomplished with SmI_2. Uemura and co-workers have discovered that the coupling of the planar chiral organometallic aldehyde **112** leads to *threo*-diol **113** in high yield, and as a single diastereomer **(Scheme 31)**.[61]

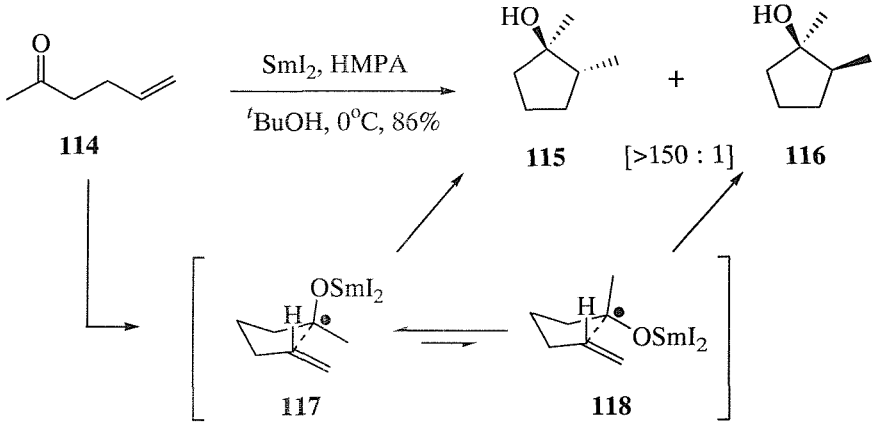


112 **113**

Scheme 31

III) Intramolecular additions

Molander and his colleagues have reported that ketone **114** cyclises in the presence of *tert*-butanol and HMPA, leading to cyclopentane compounds **115** and **116 (Scheme 32)**.[62] Treatment of ketone **114** with SmI_2 at 0°C could provide alcohols **115** and **116** in 86% yield with a >150:1 diastereoselectivity in favour of *trans*-cyclopentane **115**. The cyclisation proceeds *via* a chair-like TS similar to 5-hexenyl radical and there are two possible conformations **117** and **118**, which can be formed. However, electronic repulsion between the π-system and the oxygen lone pair is thought to favour **117** forming exclusively the *trans*-cyclopentane **115**.

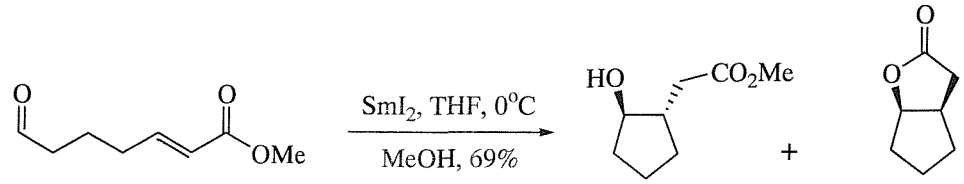


114 **115** [>150 : 1] **116**

117 **118**

Scheme 32

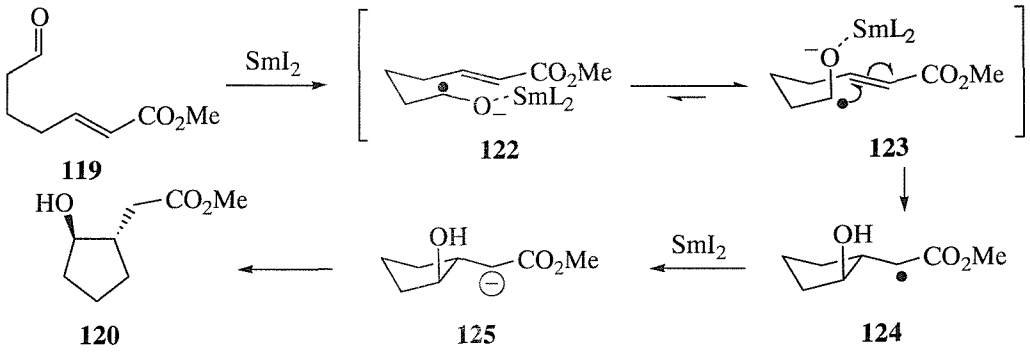
Another simple intramolecular radical cyclisation of the aldehyde **119** using SmI_2 gives *trans*-cyclopentyl alcohol **120** as the major product (**Scheme 33**).[35] An annulated γ-lactone **121**, which derived from *cis*-cyclopentyl alcohol, was obtained as a minor product in 17% yield.



119 **120** [*trans*/*cis* = 3.1:1] **121**

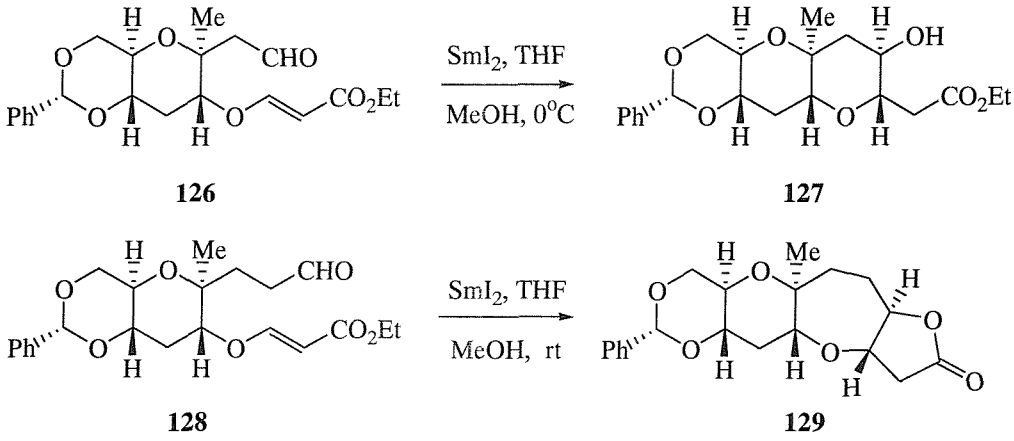
Scheme 33

The stereochemical outcome of this cyclisation can be rationalised using a chair-like TS model (**Scheme 34**). Initially samarium co-ordinates with oxygen to give a ketyl radical. This radical intermediate prefers to adopt conformation **123** with an axial oxy-samarium substituent, in order to avoid a steric or electronic interaction with the alkene substituent. Next, the radical intermediate **123** undergoes 5-*exo*-trig cyclisation to give radical **124**, which is further reduced to an anion and quenched to give the final cyclised product **120** with the *trans*-disubstituted pentyl isomer **120** as the major isomer.



Scheme 34

Goh Matsuo and colleagues reported an extremely facile and efficient strategy for the highly stereoselective synthesis of *trans*-fused 6,6- and 6,7-membered ether ring systems having an angular methyl group, based on SmI_2-induced reductive intramolecular cyclisation (**Scheme 35**).[63]

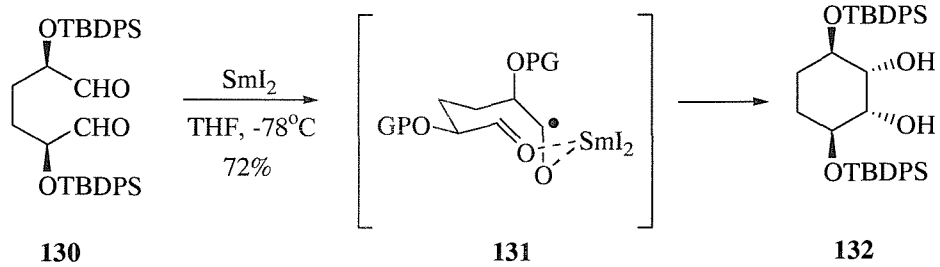


126 **127**

128 **129**

Scheme 35

Upon treatment with 2.2 equivalents of SmI_2 in the presence of MeOH in THF at 0°C, 6,6-membered ether ring **127** was stereoselectively synthesized from the precursor **126**. *Trans*-fused 6,7-membered ether ring **129** could be gained from precursor **128** by treating with the same amount of SmI_2 and MeOH at room temperature. Again the electronic repulsion between oxygen lone pair and double bond could explain why *trans*-products are favoured.

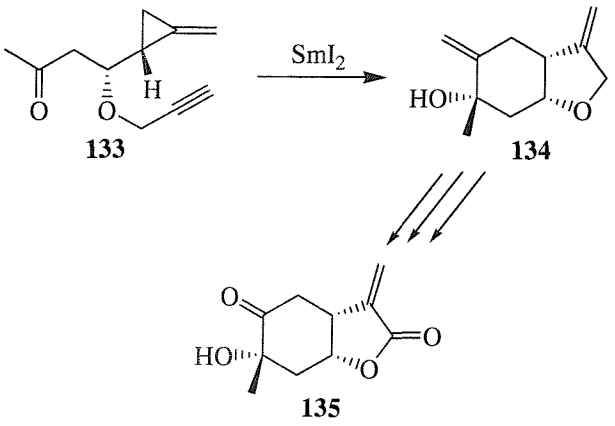


130 **131** **132**

Scheme 36

SmI_2 has also been employed in a stereocontrolled pinacol cyclisation (**Scheme 36**).[64] The origin of stereocontrol in this case is thought to be the formation of a nine-membered cyclic ketyl radical **131**. As a result, the cyclisation of **130** produced *cis*-diolcyclohexane derivative **132**. This chelation transition state

may be formed in order to avoid the steric hindrance with two bulky –OTBDPS groups, which exist in the substrate molecule.



133 **134** **135**

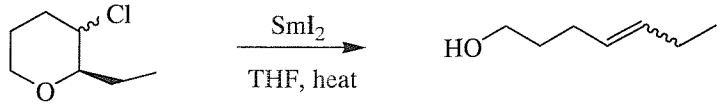
Paeonilactone B

Scheme 37

Another example of radical cyclisation using SmI_2 is the work of Boffey and Kilburn.[65] They used a cascade radical reaction to synthesize paeonilactone B **135 (Scheme 37)**. Ketone **133** was reduced by SmI_2 to give a ketyl radical, which underwent a 5-*exo* cyclisation onto the radical trap of the alkene producing bicyclic **134**. Paeonilactone B **135** could be obtained in good yields.

IV) Fragmentation reactions

An easy example of these fragmentation reactions (or reductive eliminations) is the cleavage of cyclic-β-halo tetrahydropyran **136** with SmI_2 providing mixtures of *E* and *Z* olefin product **137** in good yield **(Scheme 38)**.[66] This diastereomeric halide precursor **136** undergoes elimination reaction by initial formation of the organosamarium followed by rapid β-elimination.



136 **137**

Scheme 38

1.2.3) Intramolecular addition of neutral C-centered α-aza radical

Intramolecular cyclisations have been reviewed in the previous section (**1.2.3**). However, in terms of making pyrrolidine derivatives, it is also necessary to introduce the intramolecular addition of neutral C-centered α-aza radical to C-C double bonds. α-Aza radicals have attracted the interest of synthetic organic chemists for the synthesis of a wide range of biological important nitrogen-containing products, which are also the structural subunits common to numerous alkaloid families, amino acids, and peptides. Investigation of strategies based on iminium **138**, and amino-substituted carbanions **139**[67] were thoroughly carried out (**Figure 9**). Recent progress in the use of free radicals in organic synthesis has stimulated several research groups to investigate amino-substituted radicals **140** as reactive intermediates for the formation of new C-C bonds.

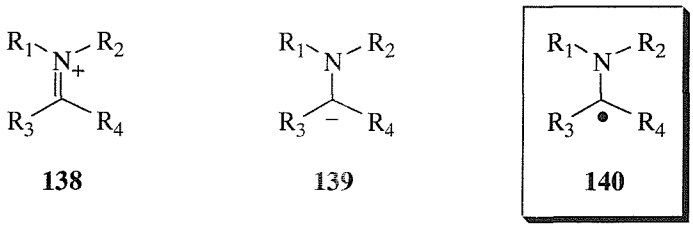
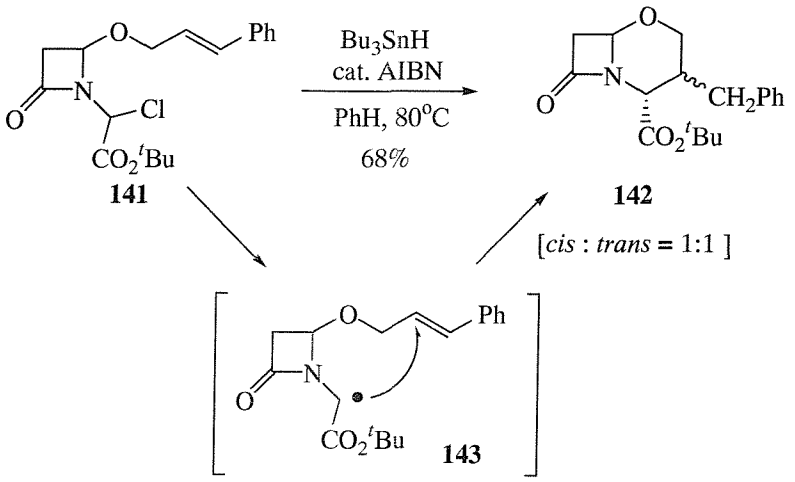


Figure 9

α-Aza radical **140** is highly stabilized, due to the interaction between the nitrogen lone pair and the radical center.[68,69] Increasing the substitution at the nitrogen atom enhances the stability of such radicals. α-Aza radicals are electron-rich transient species, thus they are strongly nucleophilic and react with electron-deficient alkenes or alkynes. Intramolecular additions to unactivated alkenes are possible with acylated, sulfonylated, or protonated derivatives. 1-Amino-substituted radicals are not used much, which may be attributed mainly to the difficulty of their generation.

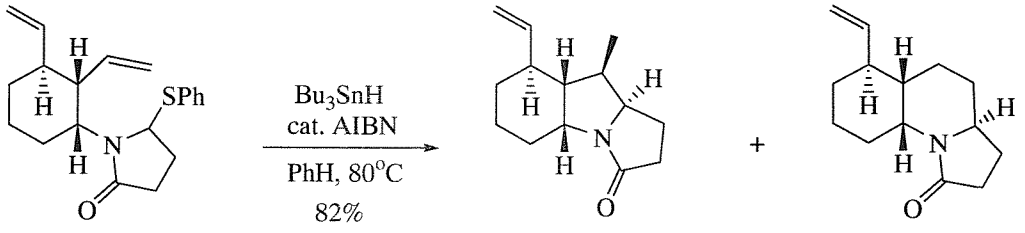
Herein several strategies to generate reactive α-aza radical intermediates will be described and are exemplified with intramolecular radical cyclisations. Bachi and Hoornaert have reported the synthesis of fused bicyclic β-lactams, using an α-aza radical (**Scheme 39**).[70] Formation of the α-aza radical intermediate **143** from chloro-compound **141** was initiated using Bu_3SnH and AIBN. Radical **143** underwent 6-*exo*-cyclisation to

afford [4.2.0] bicyclic system **142** in ca. 1:1 diastereomeric ratio. The 7-*endo*-mode could occur when there was no phenyl group at the terminal double bond.



Scheme 39

An α-aza radical was generated from a thiophenol derivative using Bu_3SnH and AIBN. Hart and Tsai have described an approach to the synthesis of indolizidines and pyrrolizidines *via* this α-aza radical cyclisation (**Scheme 40**).[71] Treatment of thiophenoxyl substrate **144** with Bu_3SnH gave no reduced product but *exo*-cyclisation product **145** and *endo*-cyclisation product **146** in 51% and 31% yields. Both cyclisations proceeded with high stereoselectivity and no other diastereomers of tricyclic derivatives **145** and **146** were observed.

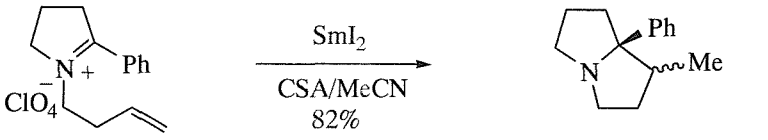


144 **145** [ratio = 5:3] **146**

Scheme 40

Substrate **147** was prepared from corresponding γ-lactam and phenylmagnesium bromide followed by work-up with aq. perchloric acid.[72] Treatment of this iminium salt **147** with SmI_2 and at least 1 equivalent of camphorsulfonic acid (CSA) in anhydrous acetonitrile afforded the cyclised products **148** in 82% yield with traces of the reduced

product (**Scheme 41**). The ratio of the cyclised diastereomers α-Me to β-Me was 10:1. However, in a similar cyclisation of the piperidine derivative 1:1 mixture was produced in a yield of 60% with 10% of reduced product. According to the results, the reaction of the pyrrolidine substrate was significantly more efficient and stereoselective than the corresponding process with the piperidine substrate.

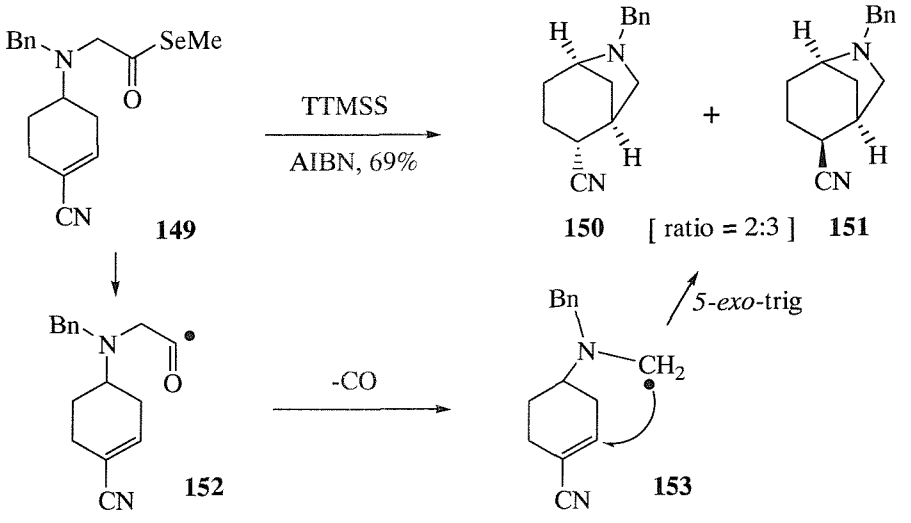


147 **148**

[α-Me : β-Me = 10:1]

Scheme 41

Another method to produce an α-aza radical is the decarbonylation from α-amino selenoester and has been reported by Quirante.[73] They succeeded in constructing the 6-azabicyclic[3.2.1]octane skeleton. This skeleton is pharmacologically interesting due to many bioactive compounds containing it in their structures. This report is also one of the examples[74,75,76] of the use of tris(trimethylsilyly)silane (TTMSS) as a free radical mediator due to its similar properties to tributyltin hydride. Treatment of selenoester **149** with TTMSS/AIBN gave the derivatives **150** and **151** in 2:3 ratio and 69% combined yield (**Scheme 42**).

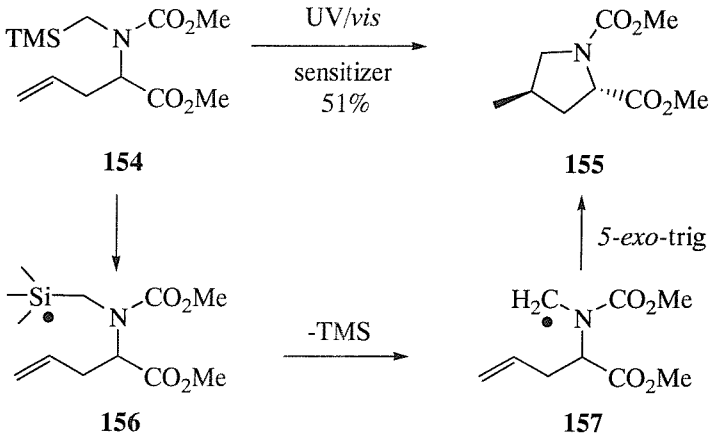


149 **150** [ratio = 2:3] **151**

152 **153**

Scheme 42

Initially acyl radical **152** is generated followed by the decarbonylative step to give α-aza radical **153**. This then undergoes 5-*exo*-trig cyclisation affording **150** and **151**. A remarkable point is that acyl radical **152** only undergoes the decarbonylation instead of the addition to the unsaturated bond or being trapped by hydrogen atom to give the corresponding aldehyde. This particular pathway was considered to be favoured since the stability of α-aza radical is greatly enhanced as a result of the interaction of the nitrogen lone pairs with the radical centre.



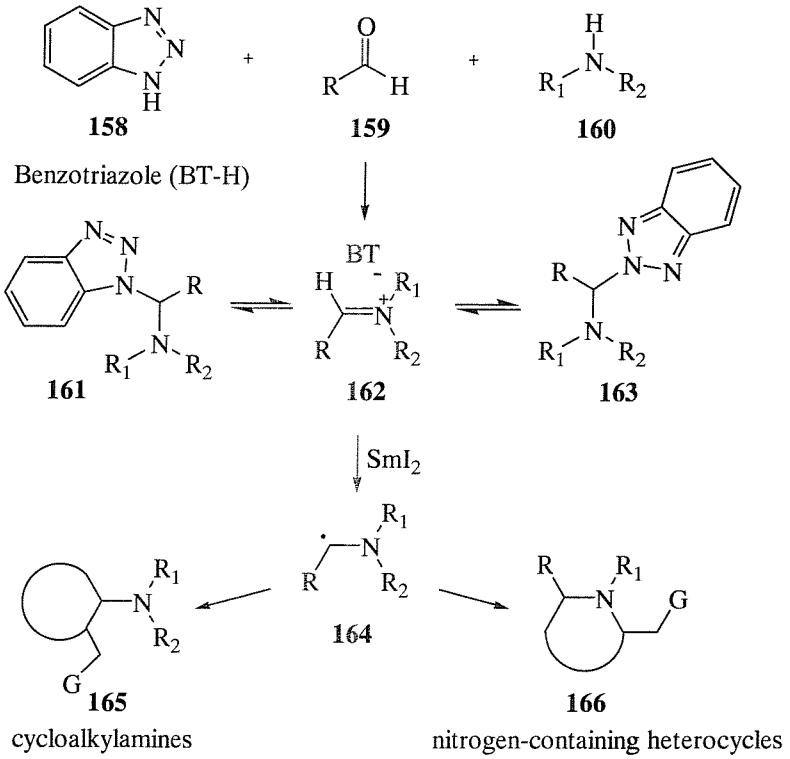
Scheme 43

The last example uses photoinduced electron transfer (PET). PET, which is single electron transfer, can generate an α-aza radical under non-oxidative, nontoxic, and mild conditions. Jonas used UV/*vis* light as the irradiator of α-silylmethylamino derivative **154** in the presence of a sensitizer into an α-silylmethylamino radical **156** (**Scheme 43**).[77] After fragmentation by loss of the trimethylsilyl group, radical cyclisation of the resulting α-aza radical **157** derived from starting materials **154** led to a *trans*-pyyrolidine **155** in 51% yield.

I) α-Aza radicals using benzotriazole stabilised iminium

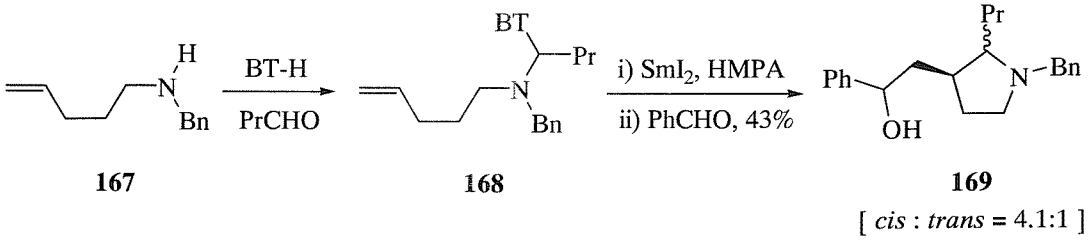
Aurrecoechea has reported the cyclisation of α-aza radicals **164** derived from *N*-(benzotriazolylalkyl) alkenylamines **161** and **163** and iminium salts **162**, generated in *situ* from aldehydes **159** by treatment with benzotriazole **158** and a secondary amine **160** (**Scheme 44**).[78] By analogy to the preparation of ketyl radicals from aldehydes, they used SmI_2 to give α-aza radicals **164**. This α-aza

radical **164** constitutes a very simple entry into either cycloalkylamines **165** or nitrogen-containing heterocycles **166**.



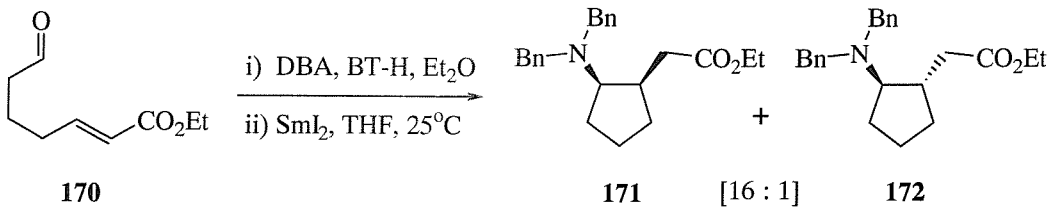
Scheme 44

Katritzky, Aurrecoechea, and co-workers have also applied this method to cascade radical cyclisations (**Scheme 45**).[79] A strongly nucleophilic α-aza radical reacts promptly with electron-deficient double bonds, followed by further reduction to a carbanion, which can finally be trapped with an electrophile. *N*-(α-Aminobutyl)benzotriazole **168**, prepared by the reaction between secondary amine **167**, butyraldehyde, and benzotriazole, was treated with SmI_2 and quenched with benzaldehyde to give 43% of the corresponding pyyrolidine derivative **169** as a mixture of *cis* and *trans* (4.1 to 1) diastereomers (**Scheme 45**).



Scheme 45

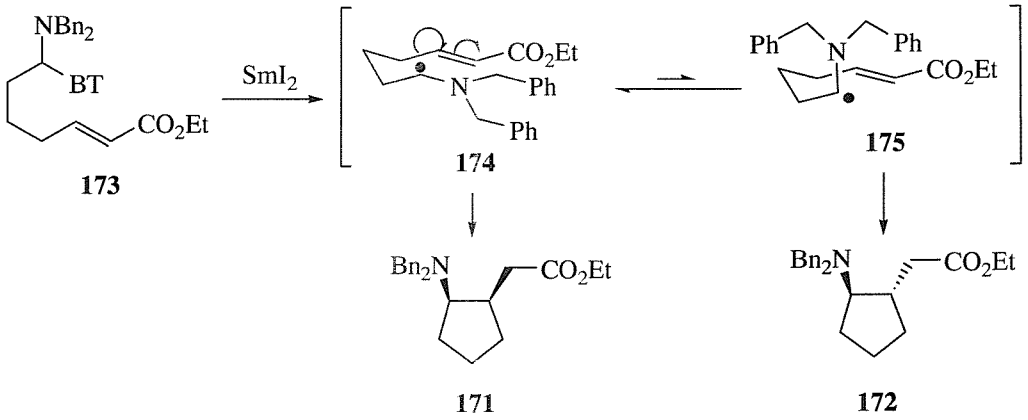
Aurrecoechea has also described cyclisation of the benzotriazole adducts derived from aldehyde **170**, which gave the amino cyclopentane **171** and **172** with the *cis*-isomer as the major product (**Scheme 46**).[76]



170 **171** [16 : 1] **172**

Scheme 46

With the cyclisation of aldehyde **119** (p. 30), stereoelectronic repulsion between the samarium-bound alkoxide and the alkene leads to the *trans*-cyclopentyl alcohol **120** as the major product. In the case of radical **174** (**Scheme 47**), stereoelectronic repulsion between the amine residue and alkene is not as significant as that between oxygen anion and alkene described in **scheme 33** and **34**, whereas placing the bulky dibenzyl amino group in an axial orientation, as in **175**, is presumably disfavoured for steric reasons (1,3-steric clash between hydrogen atom and dibenzyl amine group). The cyclisation of the benzotriazole adduct **173** leads preferentially to the *cis*-cyclopentyl amine **171**.

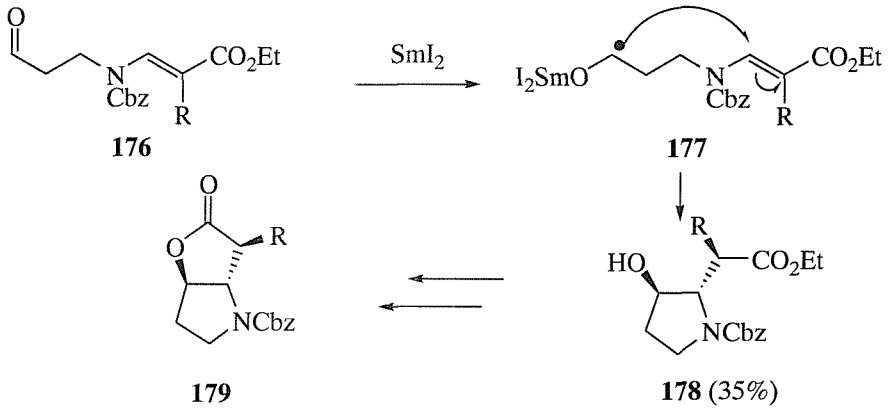


173 **174** **175** **171** **172**

Scheme 46

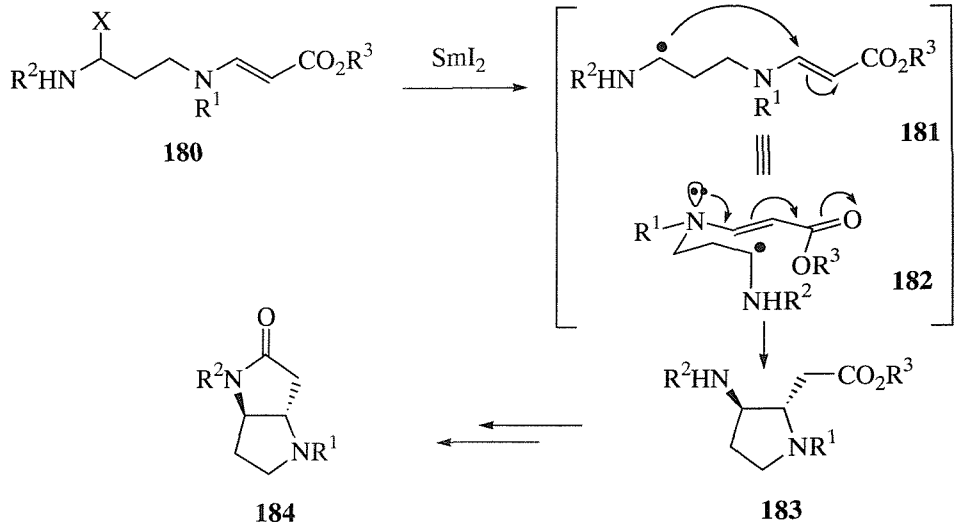
1) Basic idea of the benzotriazole strategy

A novel route to pyrrolidine *trans*-lactones has been developed by chemists at GSK[80], relying on a stereoselective radical cyclisation, using SmI_2 to generate the ketyl radical **177** from aldehyde **176 (Scheme 48)**. The cyclisation produces both the desired *trans*-lactone **179**, and the required stereochemistry at the third chiral center (α to the lactone carbonyl).



Scheme 48

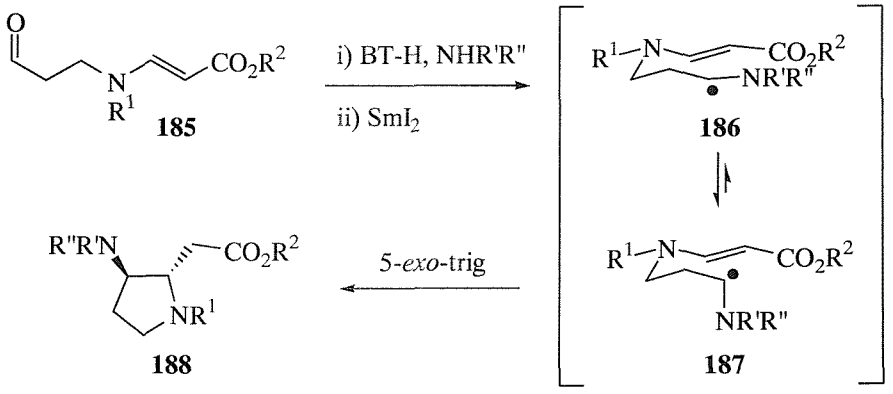
This proposal concerns the investigation of analogous routes to pyrrolidine *trans*-lactams **184**, based on the radical cyclisation of α-aza radicals **181 (Scheme 48)**. The project will also involve a study of the stereochemical outcome of such cyclisations.



Scheme 49

However, the system we are going to approach is not so different from the substrate of the cyclisation in **scheme 46**, which gave *cis*-cyclopentyl derivative as the major product. The influence of nitrogen atom in ring and its protecting group were not known at the outset of this project. The conjugation of the nitrogen lone pair with the alkene (i.e. the enamine) might affect the conformation of the cyclisation precursor (as shown as an intermediate **182**), and would alter the polarisation of the alkene (**Scheme 49**). And therefore might affect the electronic repulsion between the alkene and the aza-radical species thus promoting formation of the *trans*-product **183**.

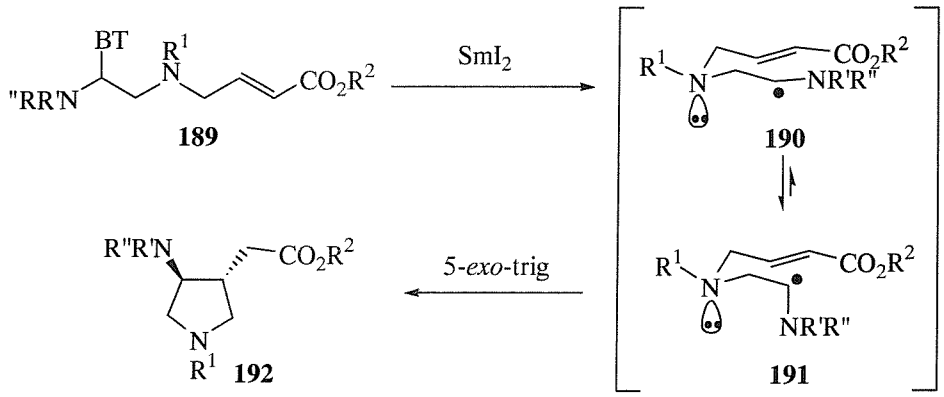
If the Aurrecoechea method[76] is used with aldehyde **185**, it may also be possible to influence the stereochemical outcome with the steric bulk of substituents of the radical acceptor portion. Thus, the amine portion NR'R" can adopt an axial orientation in the chair-like[81] TS **187 (Scheme 50)**, tolerating 1,3-diaxial interactions in preference to the steric clash with large group R^2 which would result from the amine NR'R" in an equatorial orientation as in **186.**



Scheme 50

We also planned to investigate cyclisation of precursor **189**, which has the nitrogen atom in a different position with respect to the system shown in **scheme 50**, again using the Aurrecoechea method (**Scheme 51**).[76] Here a considerable factor is that the lone pair on the enamine nitrogen should have a less significant 1,3-steric clash with the dibenzylamine group than a hydrogen atom on a methylene. As a consequence, the radical intermediate would prefer TS **191** rather

than TS **190**; therefore the 5-*exo*-trig cyclisation might give the final product as a *trans*-diastereomer **192**.



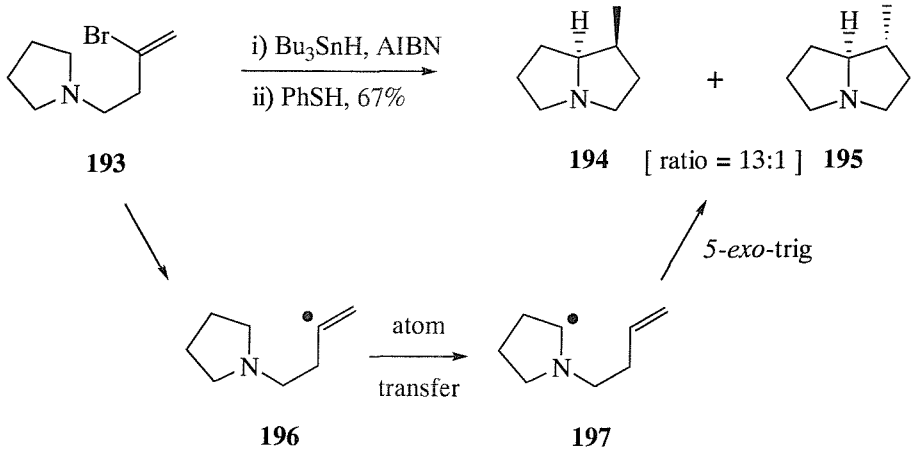
Scheme 51

An attractive extension to this methodology would be to use chiral amines as the amine component in the iminium formation, which may then allow control of absolute stereochemistry.

II) α-Aza radicals by radical translocation

The other strategy to make an α-aza radical, using radical translocation (1,5-hydrogen atom abstraction), was also to be investigated. Generation of a reactive radical species by radical translocation is well reported and has been used widely for generating α-aza radicals.[82,83]

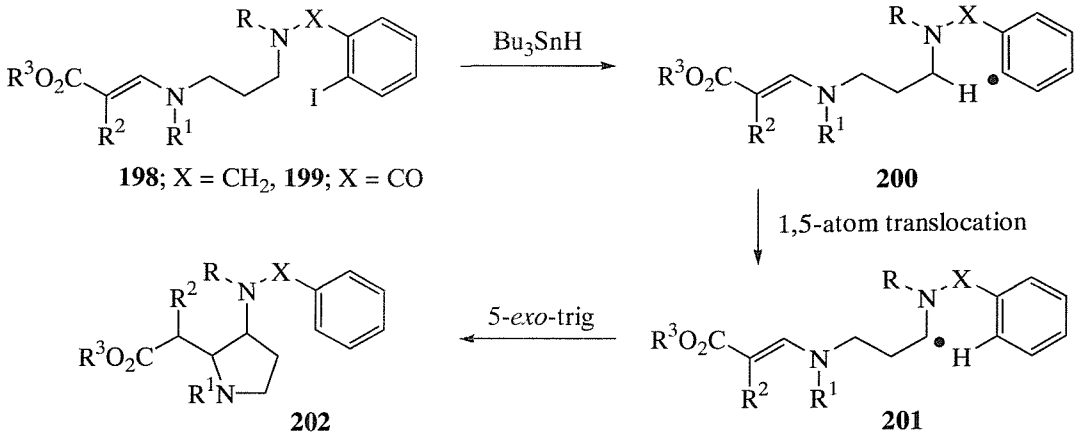
One application of this 1,5-atom translocation was reported by Pillai group.[84] Heliotridane **194** and Psedoheliotridane **195** were synthesized by 5-*exo*-trig cyclisation of α-aza radical **197**, which could be generated by this 1,5-hydrogen atom transfer of vinyl radical **196 (Scheme 52)**. Refluxing of bromide precursor **193** in benzene along with the addition of Bu_3SnH and AIBN followed by the addition of excess thiophenol gave a mixture of hydrobromide salts of **193** and **194** in 67% total yield and in an extremely diastereoselective 13:1 ratio.



Scheme 52

Basic idea of the radical translocation strategy

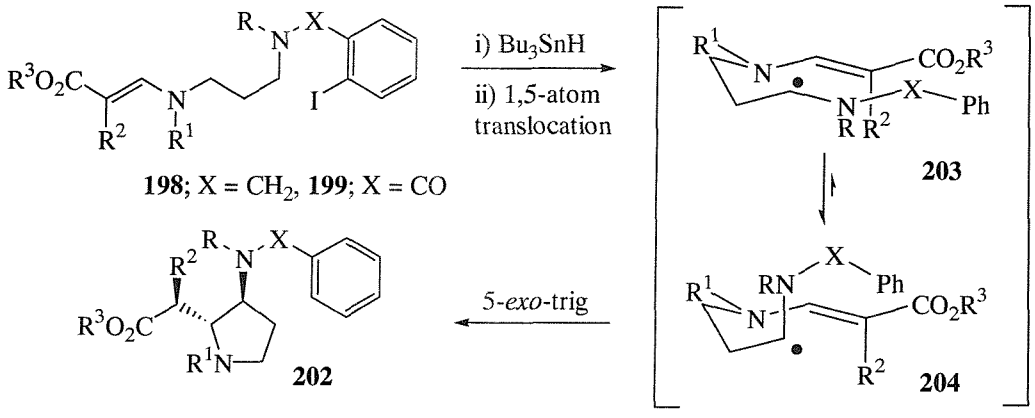
This methodology can be readily adapted for the synthesis of pyrrolidine *trans*-lactams, using, for example *o*-iodobenzylamine **198** or *o*-iodobenzamide **199** as the radical precursor (**Scheme 53**). After formation of radical **200** using Bu_3SnH, 1,5-atom translocation would lead to an α-aza radical intermediate **201**. This intermediate **201** would undergo 5-*exo*-trig cyclisation to make cyclised product **202**.



Scheme 53

Once again, stereochemistry should be influenced by steric bulk of R^2 and R^3 disfavouring the *cis* product. Intermediate **204**, with the NRXPh group in the

axial orientation, could be more favoured than intermediate **203**, due to the steric clash which may occur when NRXPh group is in an equatorial orientation (**Scheme 54**). An advantage of this approach is that a range of propane diamines can be used, allowing introduction of further functionality around the pyrrolidine ring, and potentially influencing the stereochemical control.

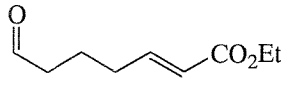


Scheme 54

Chapter 2 Cyclisations via Benzotriazole Precursors

2.1) Initial studies

The aim of these initial studies was to investigate the SmI_2-promoted radical cyclisations using the benzotriazole strategy with some simple substrates. In order to do so, simple aldehyde substrate **205** was chosen as an initial target (**Figure 10**). With its electron-deficient double bond and aldehyde moiety, ethyl heptenoate is an ideal skeleton for the simplest 5-*exo*-trig radical cyclisation promoted by SmI_2.[35]



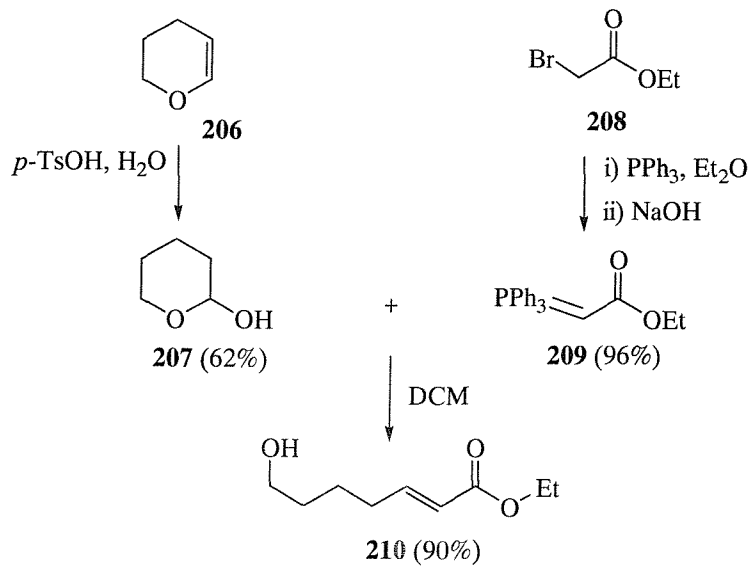
205

Figure 10

2.1.1) Synthesis of substrate 205

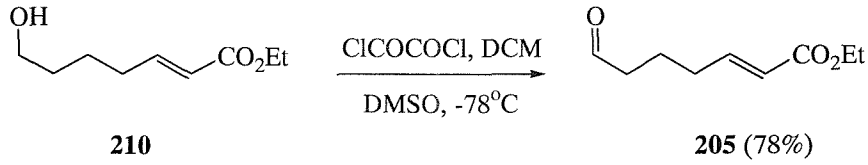
Dihydropyran **206** was treated with *p*-toluenesulfonic acid (*p*-TsOH) to give lactol **207** in a moderate yield (**Scheme 55**). Distillation under reduced pressure[85] gave lactol **207** as clear, colourless, and viscous oil. Ethyl bromoacetate **208** was reacted with triphenylphosphine in Et_2O followed by addition of NaOH to give the Wittig reagent **209**

in an excellent 96% yield.[86] Lactol **207** was converted into alcohol **210** by reacting with the Wittig reagent **209** in a very good yield of 90%.[87]



Scheme 55

Swern oxidation[88] was used to oxidise the alcohol **210** to the aldehyde substrate **205 (Scheme 56)**.[89] The overall yield of 41% (from dihydropyran **206**) was good enough to allow the synthesis of precursor **205** on a gram scale.



Scheme 56

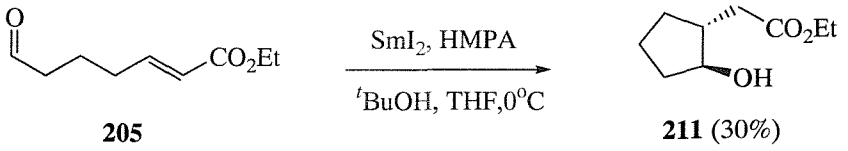
2.1.2) Simple cyclisation of aldehyde precursor 205

SmI_2-promoted radical cyclisations were investigated using two methods; normal addition and reverse addition.

1) Normal addition[90] proceeds by adding the substrate solution into the SmI_2 and proton source solution *via* syringe pump or syringe cylinder.
2) Reverse addition[90] consists of adding the SmI_2 and proton source solution into the substrate solution *via* cannula.

Furthermore, Aurrecoechea carried out his cyclisations in the absence of HMPA, which are known to enhance the reducing potential of SmI_2 and to have considerable influence on the stereochemical outcome of ensuing reactions.[91] Our cyclisations of aldehydes will thus be investigated as a route to pyrrolidine *trans*-lactams, using SmI_2, with and without additives such as HMPA or MeOH, and with chiral amines.

In order to get used to the radical cyclisation with SmI_2, a simple intramolecular radical cyclisation was attempted by the normal addition method of SmI_2 with the aldehyde substrate **205**. The target molecule, cyclopentyl alcohol **211**, was obtained in 30% yield as a mixture of diastereomers (*cis* 1: *trans* 3) (**Scheme 57**). According to the literature[35], a cyclisation of the very similar system, methyl ester **119**, gave the desired product **120** and **121** in a yield of 69% with a 1:3.1 *cis : trans*-ratio (**Scheme 33**).

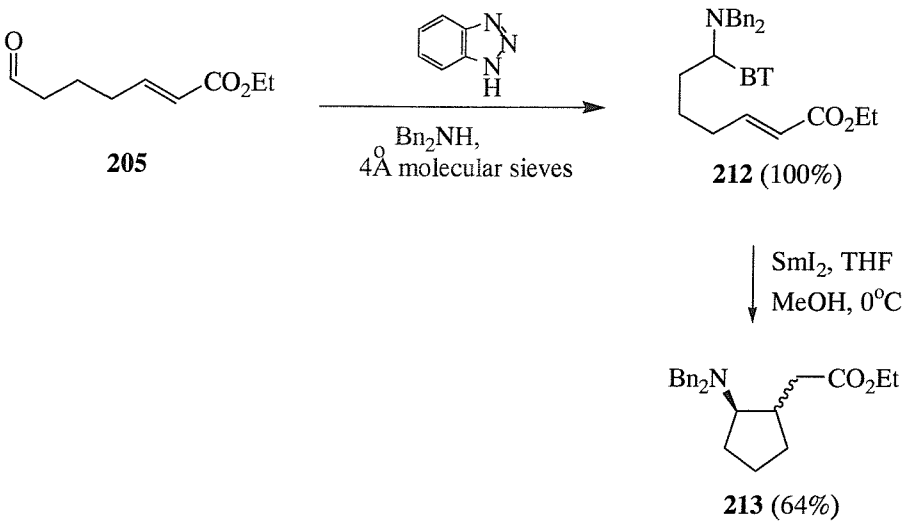


205 **211** (30%)

Scheme 57

2.1.3) Cyclisation *via* benzotriazole adduct

In order to prepare the benzotriazole adduct precursor **212**, the Aurreocoechea method[92] was utilized. Treating aldehyde **205** with benzotriazole and dibenzyl amine in the presence of the activated 4Å molecular sieves overnight, provided benzotriazole adduct **212** quantitatively (**Scheme 58**).



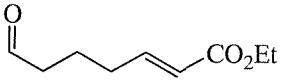
Scheme 58

This type of precursor is quite sensitive to silica gel, so NMR was used to confirm that the reaction was complete instead of the TLC, and purification using column chromatography was not possible. Benzotriazole adduct precursor **212** was treated with SmI_2 in the presence of MeOH in THF by the normal addition at 0°C to give the cyclopentyl amine **213** in a good yield of 64 % and a 1:16 ratio of diastereomers (**Scheme 58**).

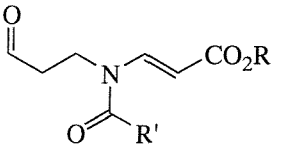
The stereoselectivity of this reaction (*cis* 16 to *trans* 1)[93] showed a striking contrast to the simple SmI_2 promoted cyclisation of aldehyde **205** (*cis* 1 to *trans* 3.1). According to Aurrecoechea[78], this diastereoselectivity is obtained using a reverse addition of SmI_2, where SmI_2 is added to the substrate solution. Normal addition of substrate to SmI_2 gave a lower stereoselectivity (*cis* 4.3 to *trans* 1) but he also found that still retained the preference for the *cis*-isomer.

2.2) Cyclisations *via* benzotriazole precursors of propyl amino propenoate system

Having completed the cyclisations of the simple aldehyde substrate **205** (**Figure 11**) for the initial studies, a further investigation was then undertaken with the enamide system **214**, to produce the desired pyrrolidine *trans*-lactams.



205

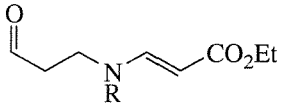


214

Figure 11

2.2.1) Synthesis of ethyl ester aldehyde substrates 215 and 216

Two aldehyde substrates **215** and **216** were chosen as they both have the same ethyl ester moiety as aldehyde **205** (**Figure 12**). Aldehyde **215** has carbobenzyloxy group as an *N*-protecting group, while aldehyde **216** has *tert*-butoxycarbonyl group instead.



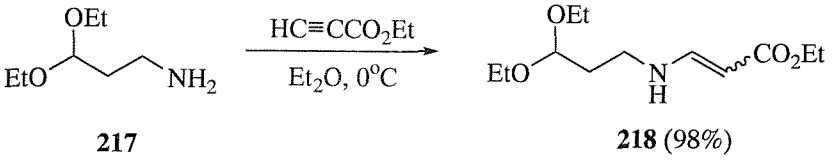
215; R = Cbz
216; R = Boc

Figure 12

I) Synthesis of Cbz-ethyl ester aldehyde substrate 215

Reaction of 1-amino-3, 3-diethoxyl propane **217** with ethyl propiolate at 0°C provided amine **218** in quantitative yield (**Scheme 59**).[94] The experiments described in the literature were carried out at room temperature, so several attempts were tried at room temperature, but none of the desired product **218** was formed under these conditions. In addition, the enamine **217** was obtained as a mixture of 5:4 *cis-trans* isomers (**Scheme 59**). Interestingly, this ratio changed within several hours leading to a predominance of

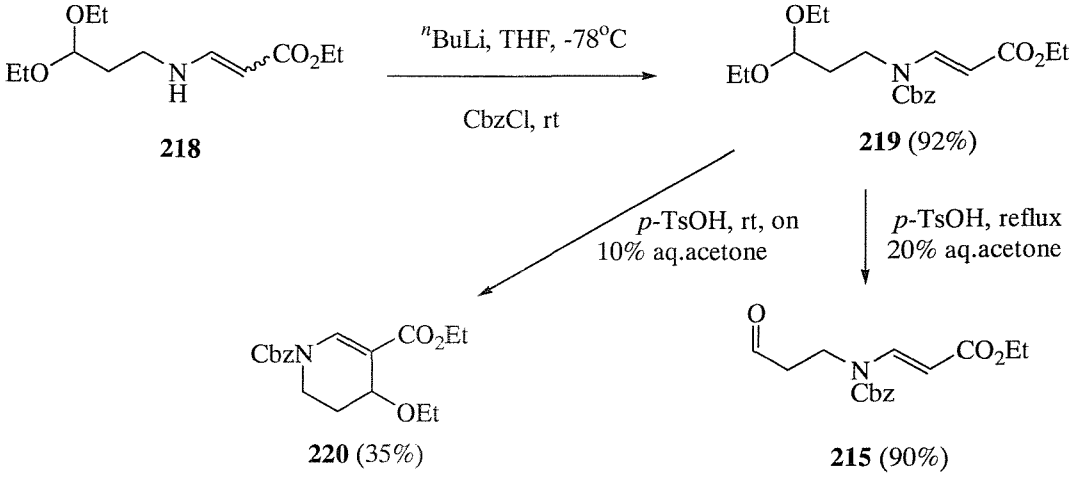
cis-isomer. The driving force for this is presumably due to the formation of an intramolecular hydrogen bond between N*H* and C*O*. However, after the insertion of the *N*-protecting group, *cis*-isomer would be ultimately converted into the desired *trans*-product.



217 **218** (98%)

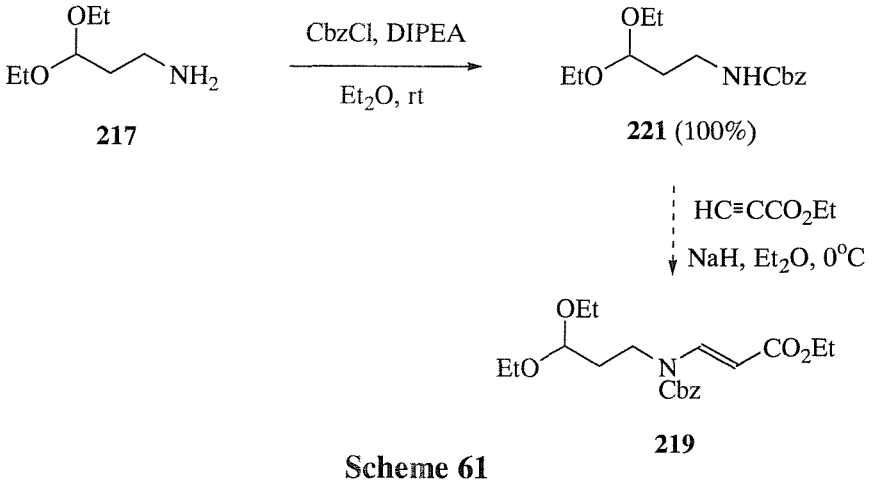
Scheme 59

Again following the literature procedure[94], enamine **218** was treated with *n*-butyl lithium at –78°C followed by the addition of benzyl chloroformate (CbzCl) to give compound **219** in excellent yield. Initial attempts to deprotect the acetal were carried out using 10% aq. acetone, but this procedure instead gave heterocycle **220 (Scheme 60)**. The intramolecular cyclisation probably occurs due to the relatively low amount of water used in the reaction. Instead *p*-TsOH was used to deprotect acetal **219** by refluxing in 20% aq. acetone solution for 3 hours, giving aldehyde **215** in 90% yield. This reaction could also be carried out at room temperature for 2-3 days to give the aldehyde precursors in a range of moderate yields. The overall yield from 1,1'-diethoxy-amino propane was 80%, and high enough to allow the aldehyde precursors to be produced on a gram scale.



Scheme 60

Another strategy to synthesise enamine **219** was attempted. As an alternative approach, we tried to protect the amine **217** before carrying out the coupling reaction with ethyl propiolate (**Scheme 61**). According to these plans, protected amino diethoxy propane **221** was obtained in an excellent yield from the reaction between amine **217** and CbzCl with DIPEA under mild conditions. However, the reaction with ethyl propiolate using NaH at 0°C in Et_2O did not give the desired enamide **219** but only decomposition products at the baseline, and some remaining starting materials.

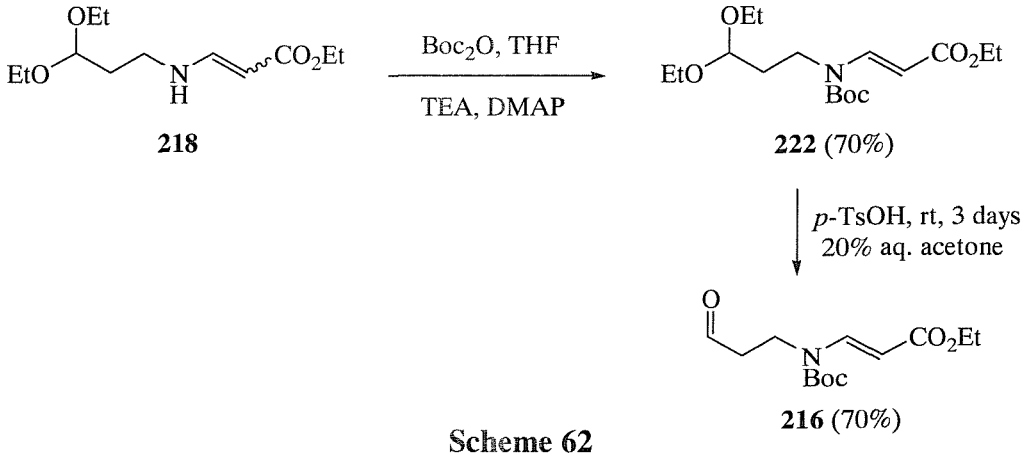


217 **221** (100%) **219**

Scheme 61

I) Synthesis of Boc-ethyl ester aldehyde substrate 216

Synthesis of this *tert*-butoxycarbonyl protected aldehyde precursor **216**, from amine **218** was accomplished in two steps (**Scheme 62**). Firstly the secondary amine **218** was treated with Boc_2O in the presence of 1.5 eq of TEA and a catalytic amount of DMAP to give Boc-enamide **222** in 70% yield. Acetal **222** was deprotected with *p*-TsOH in 20% aq. acetone to give aldehyde precursor **216** in 70% yield.

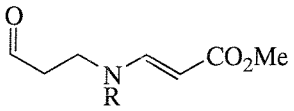


218 **222** (70%) **216** (70%)

Scheme 62

2.2.2) Synthesis of methyl ester aldehyde substrates 223 and 224

Methyl ester aldehyde substrates **223** and **224** were selected to be the next targets in order to investigate the effect of the size of alkyl ester in the cyclisation (**Figure 13**). Again the Boc- and Cbz-groups were chosen to be the protecting groups of the precursors.

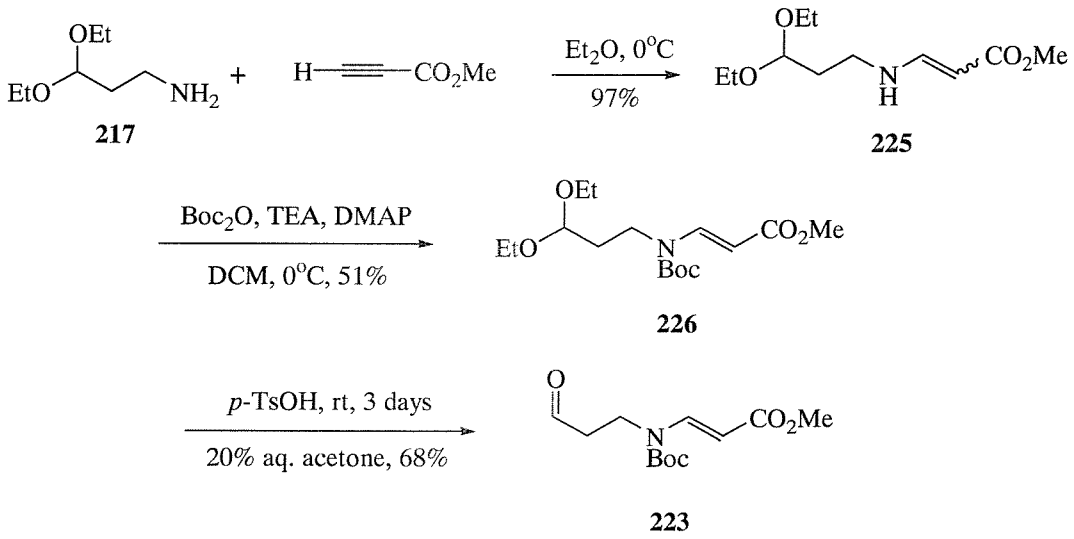


223; R = Boc
224; R = Cbz

Figure 13

I) Synthesis of Boc-methyl ester aldehyde substrate 223

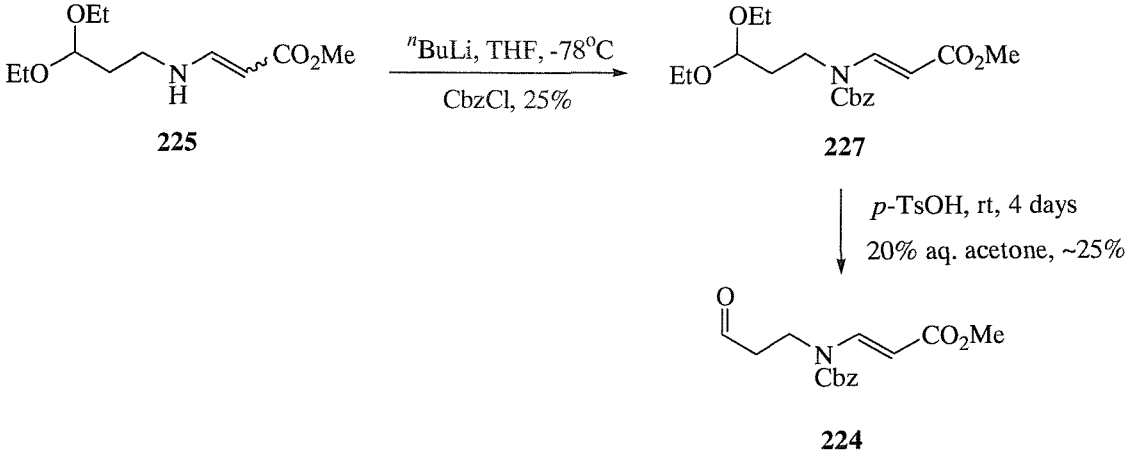
An analogous synthetic route for the ethyl ester aldehyde **215** and **216** was used to make methyl ester aldehyde **223** (**Scheme 63**). Methyl propiolate was reacted with amine **217** to produce enamine **225** as a 1:1.4 mixture of *cis*- and *trans*-isomers in a nearly quantitative yield. Enamide **226** was obtained in a moderate yield of 51% by treating amine **225** with Boc_2O in the presence of triethyl amine and DMAP at 0°C. The reaction of acetal **226** with *p*-TsOH in 20% aq. acetone gave aldehyde precursor **223** in 68% yield.



Scheme 63

II) Synthesis of Cbz-methyl ester aldehyde substrate 224

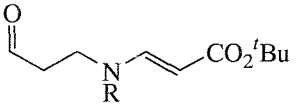
To investigate the effect of the *N*-protecting group in the radical cyclisation reactions, a Cbz-group was also used to protect secondary enamine **225** (**Scheme 64**). ^{n}BuLi was used to deprotonate amine **225** before reaction with benzyl chloroformate to give **227** in 25% yield. The reaction using ^{n}BuLi, gave many products, which were difficult to purify causing the poor yield. Acetal **227** was treated with *p*-TsOH in 20% aq. acetone to give aldehyde **224** in a poor yield. Several methods to improve the yields of these two steps were attempted, but ~25% of impure product was the best yield obtained. The cyclisation of this aldehyde precursor **224** was abandoned, because it was not worth trying with substrate, which had a lot of impurities in it.



Scheme 64

2.2.3) Synthesis of *tert*-butyl ester aldehyde substrates 228 and 229

To complete the investigation on how the size of alkyl ester group effects the cyclisation, the bulky *tertiary* butyl group was chosen (**Figure 14**).

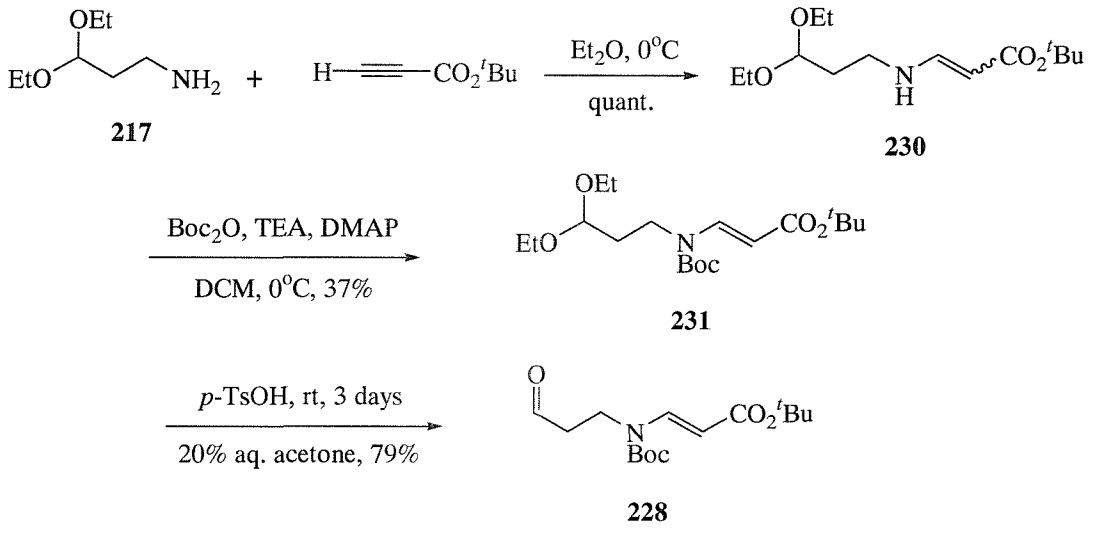


228; R = Boc
229; R = Cbz

Figure 14

I) Synthesis of Boc-*tert*-butyl ester aldehyde substrate 228

The synthesis of **228** starts with a coupling between amino propane **217** and acetylene to afford quantitatively a secondary amine **230** as a 1:2.7 mixture of *cis*- and *trans*-isomers (**Scheme 65**). Obviously, *trans*-isomer was predominantly formed, because of the bulky ^{t}Bu-ester group, which decreased the formation of an intramolecular hydrogen bond between N*H* and *CO*. The Boc protection of amine **230** by treating with Boc_2O in the presence of base gave compound **231** in a yield of 37%. The relatively low yield may be due to the bulky *tert*-butyl ester group preventing the reaction with Boc_2O. Treatment of this Boc-amine **231** with *p*-TsOH gave the aldehyde precursor **228** in moderate yield of 79% (**Scheme 65**).

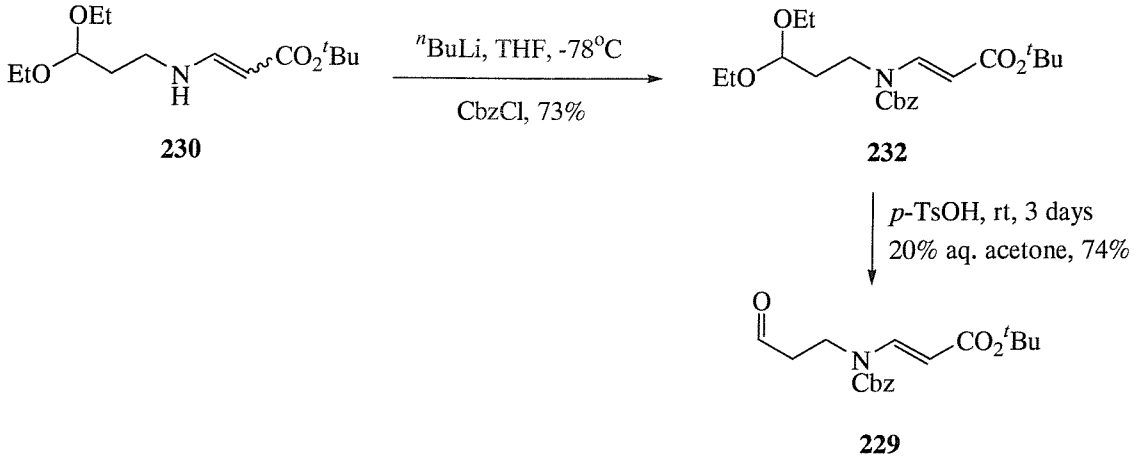


Scheme 65

II) Synthesis of Boc-*tert*-butyl ester aldehyde substrate 229

Aldehyde **229** was also synthesized in the same way as other Cbz-protected cyclisation precursors (**Scheme 66**). ^{n}BuLi was used to deprotonate amine **230** at –78°C. This was followed by treatment of the yellow solution with CbzCl at the same temperature to obtain protected amine **232** in 73% yield. Then acetal **232** was converted

into aldehyde **229** in 74% yield by stirring *p*-TsOH in 20% aq. acetone at room temperature for 3 days.



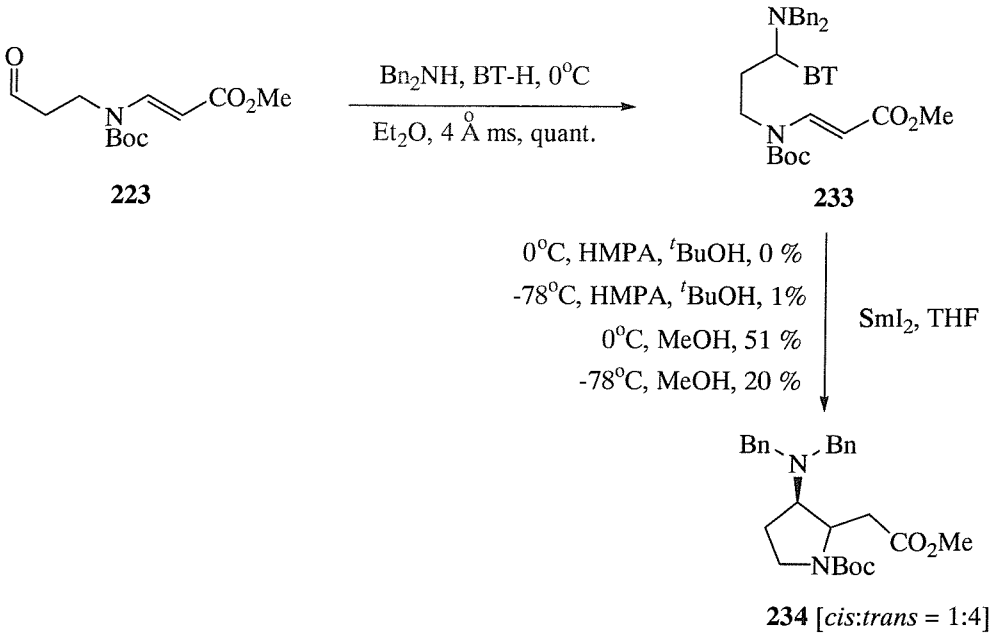
230 **232** **229**

Scheme 66

2.3) Cyclisation of enamidyl aldehyde 214 *via* the benzotriazole adducts

2.3.1) Cyclisation of methyl ester precursor 223

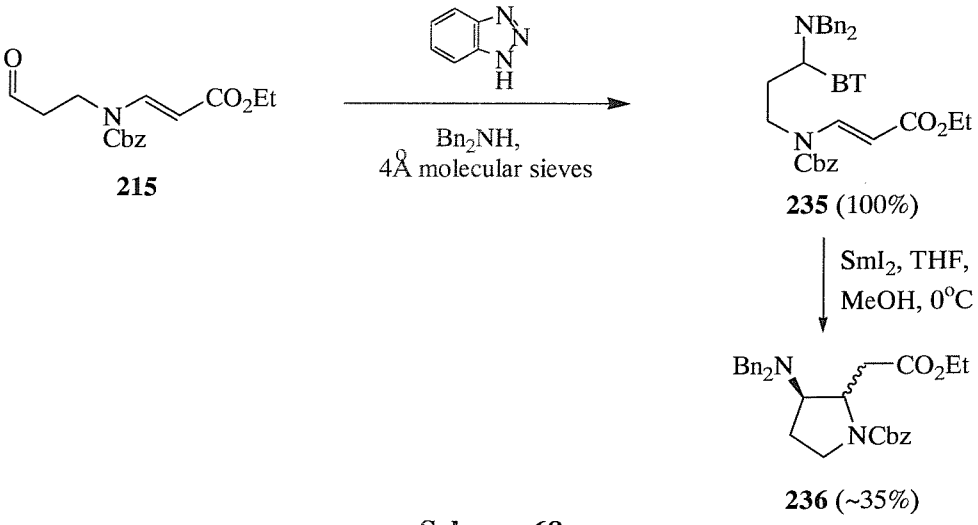
The cyclisation of this aldehyde precursor **223** was successfully carried out to afford the Boc-Me pyrrolidine derivative (**Scheme 67**). Benzotriazole adduct **233** was made quantitatively from aldehyde **223**. In order to find the best condition, the cyclisations of adduct **233** were attempted with the reverse addition of SmI_2 solution in the presence of proton sources either HMPA-^{t}BuOH or MeOH at the different temperature 0°C or –78°C. Pyrrolidine derivative **234** was produced in best yield of 51% at 0°C using MeOH. At –78°C the cyclisation gave the cyclised product **234** in 20% yield. However, almost no desired product **234** was found in the cyclisation with HMPA-^{t}BuOH. The ratio of the *cis*- and *trans*-diastereomers **234** was 1:4, which represented the best stereoselectivity of all our cyclisations.



Scheme 67

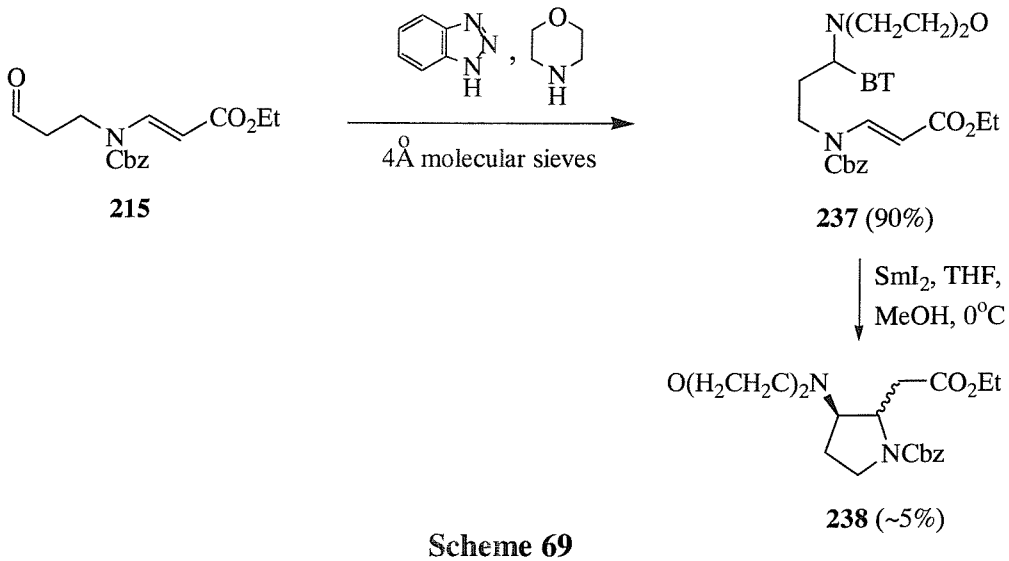
2.3.2) Cyclisation of ethyl ester precursor 215 and 216 with MeOH

The benzotriazole adduct precursor **235** was synthesized from aldehyde **215** and dibenzyl amine by the same method[92], as previously described. The precursor **215** was treated with SmI_2, using the same conditions as with methyl ester **223**, to give the impure pyrrolidine derivative **236** in ~35 % yield (as a mixture of diastereomers) (**Scheme 68**). The purification of impure pyrrolidine derivative **236** was extremely difficult. Column chromatography in varying solvent systems and HPLC (both acetonitrile system and EtOAc-hexane system) were tried, but no satisfactory purification was discovered.



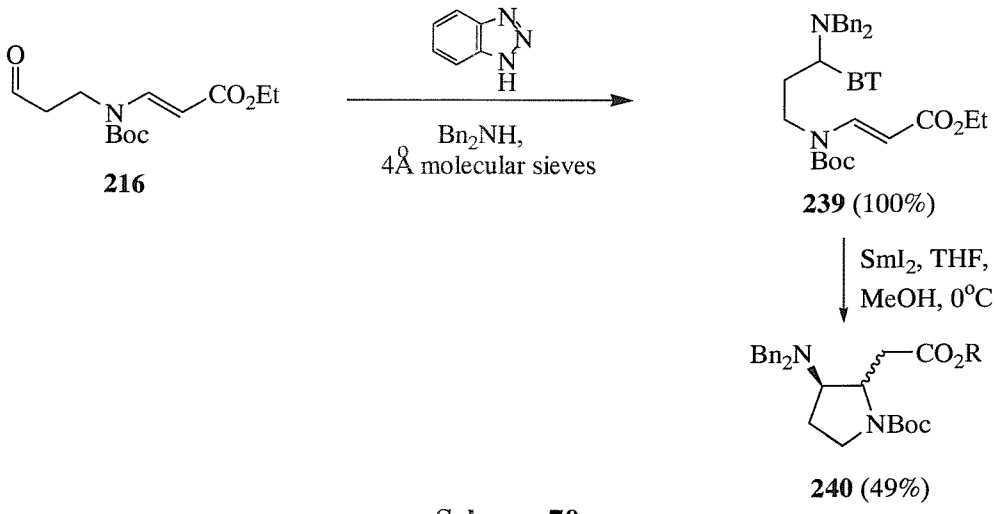
Scheme 68

While having a problem with the purification of pyrrolidine derivative **236** another cyclisation with the benzotriazole adduct **237** was accomplished. The benzotriazole adduct precursor **237** was synthesized from aldehyde **215** and morpholine using the same method[92], as previously described. The benzotriazole adduct precursor **237** was treated with SmI_2, under the same conditions, to give again the impure pyrrolidine derivative **238** in ~5% yield (**Scheme 69**).



Scheme 69

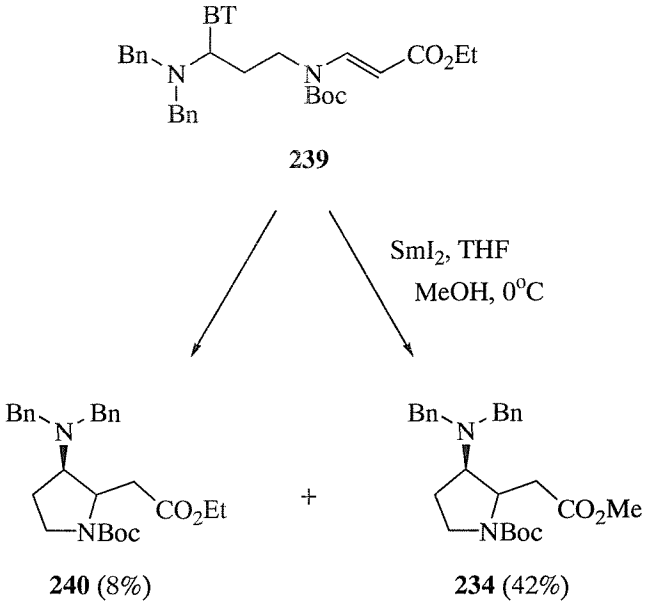
However, this pyrrolidine **238** was formed in too small a quantity to get the detailed information from proton NMR, although MS and TLC results confirmed its formation. This poor result led us to concentrate on the dibenzyl amine group for the synthesis of the series of radical precursors.



Scheme 70

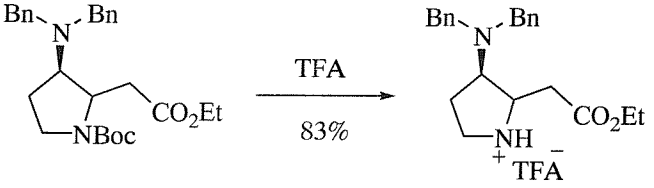
Due to problems with purification of the impure cyclic compound **236**, the carbobenzyloxy protecting group onto the nitrogen atom was changed into *tert*-butoxycarbonyl group in the hope that the isomers of the cyclised compound could be separated more easily and to determine the effect of the steric bulk of the *N*-protecting group on the stereoselectivity. Treatment of aldehyde **216** with benzotriazole and dibenzyl amine in the presence of activated 4Å molecular sieves overnight, provided benzotriazole adduct **239** in a quantitative yield (**Scheme 70**). Benzotriazole adduct precursor **216** was treated with SmI_2 in the presence of MeOH in THF at 0°C to give the cyclised derivative **240** in a moderate yield of ~49%. This cyclisation was carried out by the reverse addition method of SmI_2.

The crude oil from the reaction with SmI_2, which could not be purified by column chromatography, was purified again with HPLC (EtOAc-hexane system as a solvent) to give compound **240** as a mixture of diastereomers as the minor product and methyl ester **234** as a diastereomeric mixture as the major product (**Scheme 71**). Clearly MeOH, which was added in order to increase the reactivity of SmI_2, had undergone an exchange to give the methyl ester **234**.



Scheme 71

In order to determine the stereochemistry of this pyrrolidine system, we tried to make a crystalline derivative of the ethyl ester **240**. Treating compound **240** with TFA gave deprotected TFA salt **241** in 83% yield (**Scheme 72**). However the recrystallisation using ether failed to give a crystalline product.

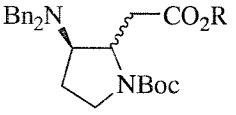


240 **241**

Scheme 72

2.3.3) Cyclisation of ethyl ester precursors 215 and 216 with EtOH

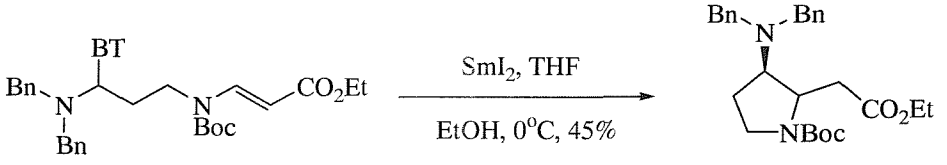
In initial work we studied the cyclisation of ethyl ester **239** in the presence of MeOH, leading to a mixture of methyl and ethyl ester products **234** and **240** (**Figure 15**). In order to prevent this exchange of the alkyl ester group, we studied the cyclisation using the appropriate alcohol to match the ester of the cyclisation precursor.



234; R = Me
240; R = Et

Figure 15

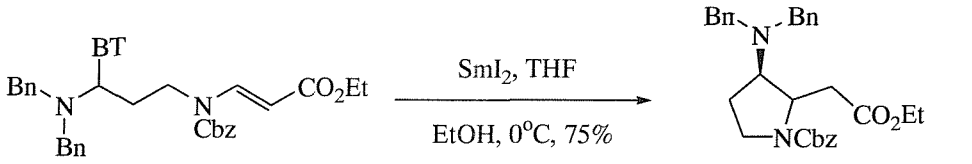
EtOH was used in the reverse addition cyclisation with benzotriazole adduct **239**, instead of MeOH, to afford Boc-Et pyrrolidine derivative **240** in a moderate yield of 45% and as a 1:3 ratio of *cis*- and *trans*-diastereomers (**Scheme 73**).



239 **240** [*cis*:*trans* = 1:3]

Scheme 73

The reverse addition was also used to cyclise the benzotriazole adduct **235** giving Cbz-Et pyrrolidine derivative **236** in a yield of 75% and as a 1:2.9 mixture of *cis*- and *trans*-diastereomers (**Scheme 74**). The yields of both cyclisations with EtOH were not as good as other cyclisations, which more commonly used MeOH and ^{t}BuOH as their proton sources, however the exchange of the alkyl ester was successfully prevented.

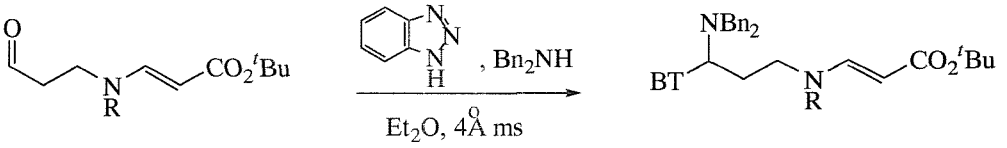


235 **236** [*cis*:*trans* = 1:2.9]

Scheme 74

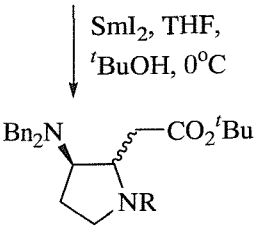
2.3.4) Cyclisation of *tert*-butyl ester precursors 228 and 229

The cyclisations of **228** and **229** (**Scheme 75**) *via* benzotriazole adducts **242** and **243**, which were synthesized from the same Aurrecoechea method[92] in nearly quantitative yields, were achieved by the reverse addition of SmI_2 at 0°C with ^{t}BuOH (**Scheme 75**). The pyrrolidine derivatives **244** and **245** were both obtained in moderate yields (**244**; 51% and **245**; 50%). The ratio of their *cis*- and *trans*-diastereomers were 1:2.6 for the Boc-protected derivative **244** and 1:1.9 for the Cbz-protected derivative **245**.



228 : R = Boc
229 : R = Cbz

242 : R = Boc ; 94%
243 : R = Cbz ; 95%

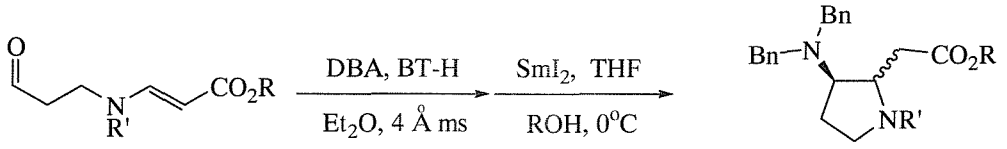


244 : R = Boc ; 51% [*cis*:*trans* = 1:2.6]
245 : R = Cbz ; 50% [*cis*:*trans* = 1:1.9]

Scheme 75

2.4) Summary of cyclisation results

Aldehyde precursors were converted into pyrrolidine derivatives in two steps (**Scheme 76**). In the first step, aldehydes were treated with benzotriazole and dibenzylamine to obtain corresponding benzotriazole adducts quantitatively. The cyclisations of the benzotriazole adducts were achieved by the reverse addition of SmI_2 at 0°C with corresponding alcohol. The corresponding alcohols were used to prevent the exchange of the ester, which has been observed once when Boc-Et aldehyde **216** was cyclised with MeOH. The pyrrolidine derivatives were obtained in moderate yields and moderate stereoselectivity (**Scheme 76**). Pleasingly the desired *trans*-isomer was the major product in each cyclisation. (Proof of stereochemistry and discussion concerning the origins of the selectivity appear later in this chapter.)



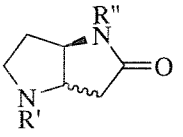
223 : R = Me, R' = Boc
216 : R = Et, R' = Boc
215 : R = Et, R' = Cbz
228 : R = ^{t}Bu, R' = Boc
229 : R = ^{t}Bu, R' = Cbz

234 : R = Me, R' = Boc; 51%, *cis/trans* = 1:4.0
240 : R = Et, R' = Boc; 45%, *cis/trans* = 1:3.0
236 : R = Et, R' = Cbz; 75%, *cis/trans* = 1:2.9
244 : R = ^{t}Bu, R' = Boc; 51%, *cis/trans* = 1:2.6
245 : R = ^{t}Bu, R' = Cbz; 50%, *cis/trans* = 1:1.9

Scheme 76

2.5) Synthesis of pyrrolidine *trans*-lactam derivatives

The key radical cyclisations were accomplished and were found to be diastereoselective. However, the true target compound of the project is pyrrolidine *trans*-lactam derivative **246** (**Figure 26**). In order to complete the project, the synthetic route of this 5,5-bicyclic system had to be developed.

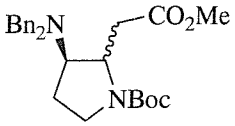


246

Figure 16

2.5.1) Initial attempt to make the pyrrolidine *trans*-lactam

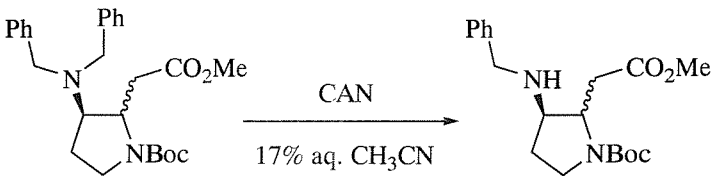
To accomplish the synthesis of pyrrolidine *trans*-lactam, Boc-Me pyrrolidine derivative **234** was chosen (**Figure 17**). Boc-Me pyrrolidine diastereomers were successfully separated by preparatory HPLC at GSK.



234

Figure 17

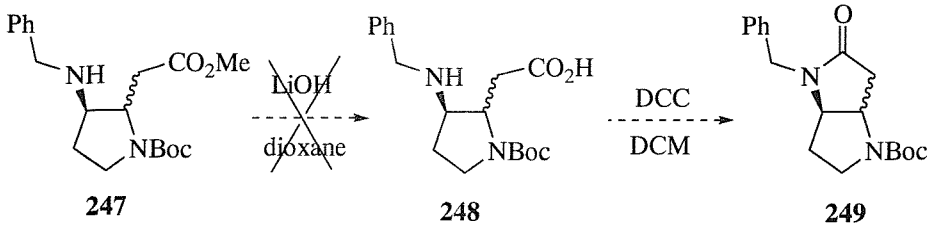
The strategy required monodebenzylation, followed by conversion of the methyl ester into a carboxylic acid, which could then undergo cyclisation (**Scheme 77**). Following the procedure of Davies[95], Boc-Me pyrrolidine derivative **234** was selectively debenzylated to give monobenzylamine derivative **247**, using cerium ammonium nitrate (CAN) in 17% aq. acetonitrile solution in an excellent yield of 94%.



234 **247** (94%)

Scheme 77

Unfortunately the hydrolysis of the methyl ester **247** using LiOH in dioxane failed to give carboxylic acid **248** (**Scheme 78**). The conversion of the methyl ester into the carboxylic acid should go without any problems to give the desired product, but isolation of the zwitterionic product could not be achieved. Several attempts failed to obtain product **248**, and purification by column chromatography did not give the product **248**. Instead a direct cyclisation, using DCC was attempted without any purification. The reaction did not give the cyclised product **249** or even starting material **248**. It might be because direct reaction from the crude product, with impurities such as LiOH and water, was not appropriate for the cyclisation.

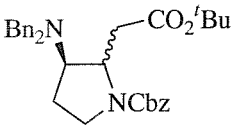


247 248 249

Scheme 78

2.5.2) Synthesis of the pyrrolidine lactam from Cbz-^{t}Bu pyrrolidine 245

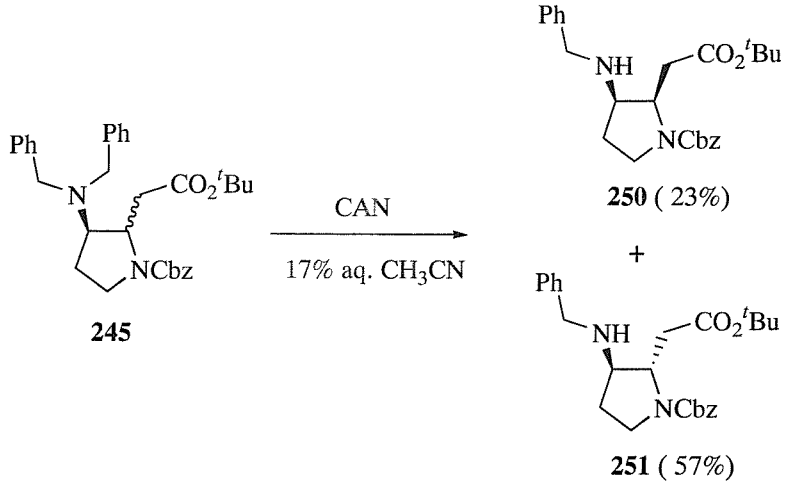
Another approach to solve the polarity problem was to use the reaction without any aqueous solvent or aqueous work-up. In this method, the *tert*-butyl ester group from Cbz-^{t}Bu **245** was deprotected with TFA, so that aqueous solvent or aqueous work-up was avoided (**Figure 18**).



245

Figure 18

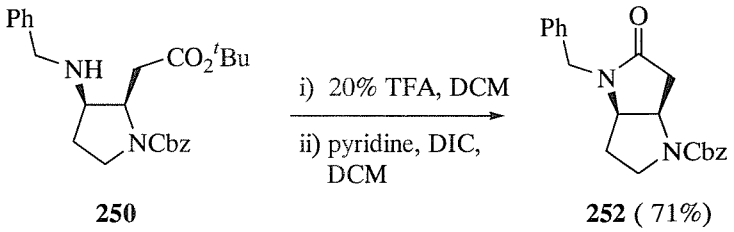
The strategy starts from the monodebenzylation of pyrrolidine derivative **245** following the literature method[95] (**Scheme 79**). The monodebenzylation with CAN in 17% aq. acetonitrile gave the secondary benzylamine 87% yield. This reaction not only gave an excellent yield, but also provided two diastereomers **250** (23%) and **251** (57%), which were separable by column chromatography.



Scheme 79

I) Synthesis of the pyrrolidine *cis*-lactam from Cbz-^{t}Bu pyrrolidine 250

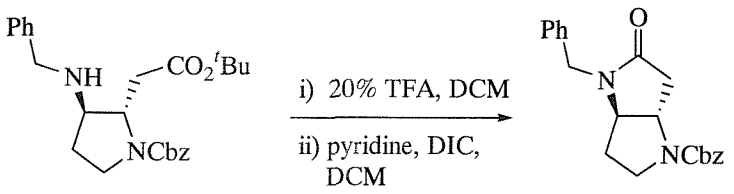
Monobenzylamine **250** was treated with TFA in DCM for 1 hour, before being evaporated. The crude oil was neutralized by DIPEA, followed by the addition of DIC to give pyrrolidine *cis*-lactam **252** in 71% yield (**Scheme 80**). It was necessary to get rid of DIU, which was formed in the coupling reaction, by first filtration followed by column chromatography.



Scheme 80

II) Synthesis of the pyrrolidine *trans*-lactam from Cbz-^{t}Bu pyrrolidine 251

Pyrrolidine *trans*-lactam **253** was prepared by the same method used for the synthesis of *cis*-derivative **252** (**Scheme 81**). After the treatment of *tert*-butyl ester **251** with TFA, the crude oil was neutralized with DIPEA and reacted with DIC to give the pyrrolidine *trans*-lactam **253** in a good yield of 79%.

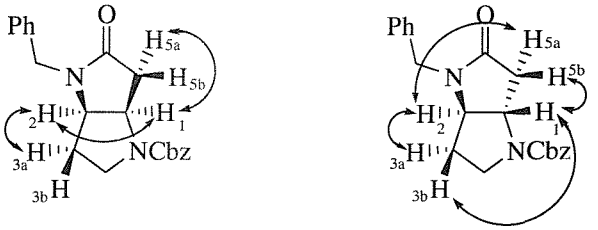


251 **253** (79%)

Scheme 81

III) Confirmation of the stereochemistry of lactams

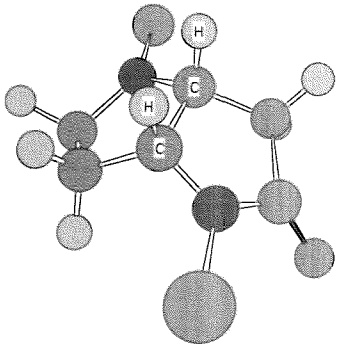
In order to confirm the stereochemistry, both *cis*- and *trans*-pyrrolidine lactams **252** and **253** were characterized using IR spectroscopy and NOE experiments. As already mentioned, *trans*-lactam **253** is more strained than *cis*-lactam **252**. Thus infrared spectrum of *trans*-lactam **253** shows a carbonyl stretching frequency of 1698 cm^{-1}, the *cis*-lactam **252** has a carbonyl stretch at 1686 cm^{-1}. This is consistent with previous results reported by colleagues at GSK[28] and Smith.[96]

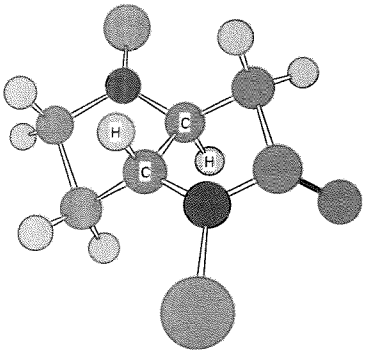


252 **253**

Figure 19

NOE experiments were instead used to confirm the configurations of pyrrolidine lactams **252** and **253** (**Figure 19**). The results that NOE (7.91%) was observed between H1 and H2 in *cis*-lactam **252** but not in *trans*-lactam **253**, showed the strong evidence for a difference in ring fusion system.[28,94] In additional, NOEs of H1-H5a (0.54%), H1-H3a (2.04%), and H2-H3a (2.23%) were observed in lactam **252** confirming its *cis*-stereochemistry, while NOEs of H1-H3b (2.23%), H1-H5b (0.76%) and H2-H3a (1.90%), H2-H5a (2.57%), which being observed in lactam **253**, confirmed the *trans*-stereochemistry.





252

H-C-C-H = 1.95°

253

H-C-C-H = 176.23°

Figure 20

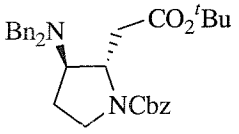
The coupling constants, especially the diagnostic-coupling constant between H1 and H2 in both lactams, which can be predicted by Macromodel[97], could also provide the evidence for assignment of the *cis-trans* stereochemistry. According to the ^{1}H-NMR data, *cis*-lactam has a coupling constant of 10 Hz, while *trans*-lactam has one of 12 Hz. Considering the models, which were calculated as the most stable conformations of both lactams, the dihedral angles of H1-C-C-H2 of *cis*- and *trans*- lactams **252** and **253** are 1.95° and 176.23° (**Figure 20**). The vicinal coupling constant between H1 and H2 in each system can be estimated using Karplus-Conroy equation.[98] However, the results were not convincing, since both of dihedral angles are close to 0° and 180°, which could possibly give the same range of coupling constants.

2.5.3) Conclusion

The attempt to lactamize Boc-Me pyrrolidine **234** failed to give pyrrolidine *trans*-lactam. Eventually pyrrolidine *trans*-lactam **253** was successfully synthesized from Cbz-^{t}Bu pyrrolidine **245**.

2.6) Stereochemical assignment of pyrrolidine derivatives

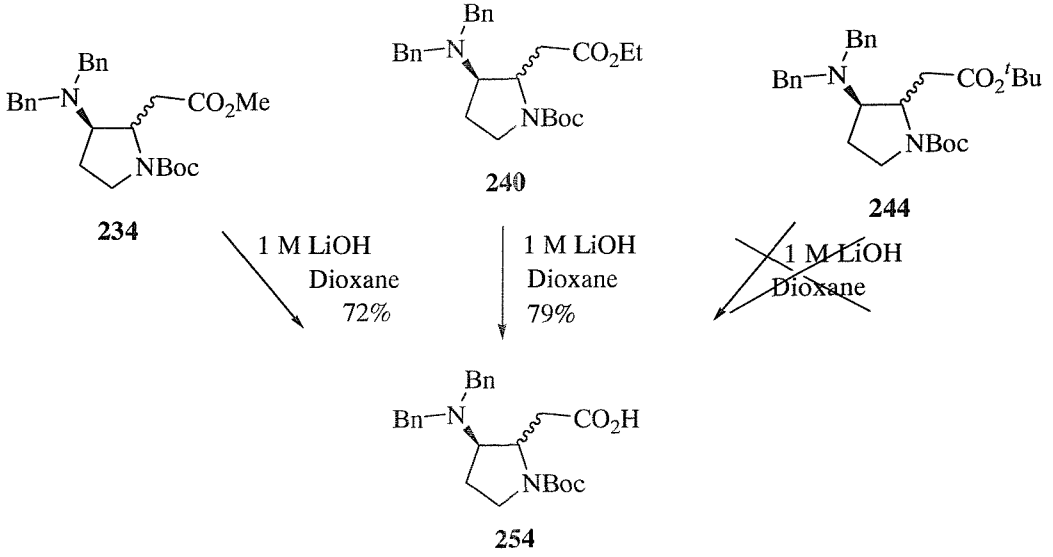
Having established that the major diastereomer of pyrrolidine **245** was the *trans*-isomer (by conversion to the *trans*-lactam) (**Figure 21**), correlation of the stereochemistry of the other pyrrolidines was carried out.



245

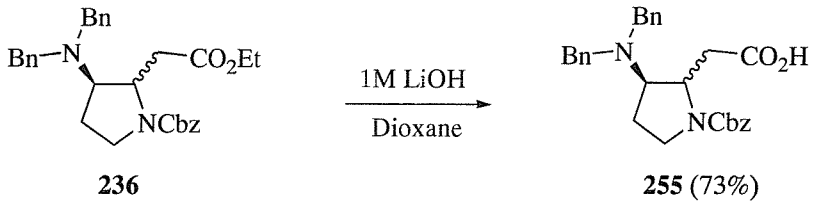
Figure 21

In the Boc pyrrolidine series, the method was to hydrolyze the alkyl esters into carboxylic acids, so that the same derivative could be obtained. Then the ratio of all mixtures could be easily compared with Boc-Me derivative **234**. Boc-Me **234** and Boc-Et **240** were treated with LiOH in dioxane[99]. LiOH was chosen to hydrolyze the Boc-Me **234** and Boc-Et **240** (**Scheme 82**). According to the ^{13}C-NMR, both hydrolysis gave the same carboxylic acid derivative **254** as the major isomer in good yields. As expected, treating Boc-^{t}Bu **244** with LiOH failed to give **254**.



Scheme 82

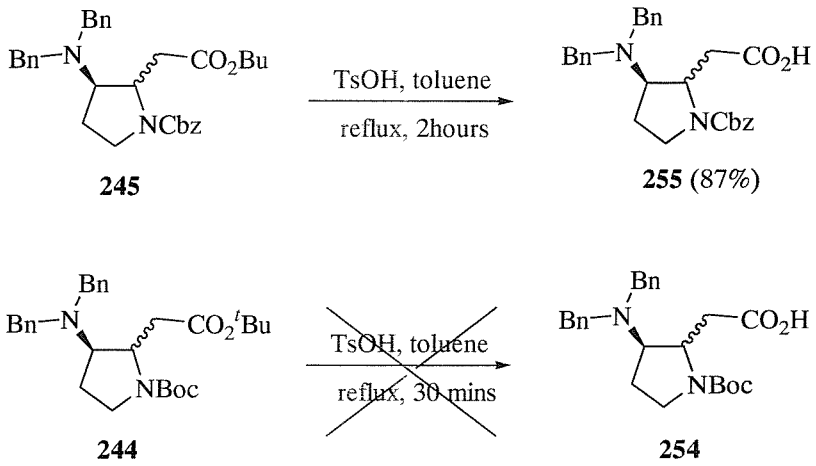
LiOH was also used to hydrolyze Cbz-Et **236** (**Scheme 83**). The reaction gave the corresponding carboxylic acid **255** in 73% yield.



236 **255** (73%)

Scheme 83

p-TsOH was used for the hydrolysis of Boc-^{t}Bu **244** and Cbz-^{t}Bu **245** (**Scheme 84**). For Cbz-^{t}Bu **245**, 2 hours reflux with *p*-TsOH[100,101] in toluene gave the Cbz carboxylic acid **255** in 87% yield. Again according to ^{13}C-NMR, the major diastereoisomer of two Cbz-carboxylic acids were shown to be identical. However, the treatment of Boc-^{t}Bu **244** with *p*-TsOH not only hydrolyzed the *tert*-butyl ester but also deprotected the Boc group (**Scheme 84**).



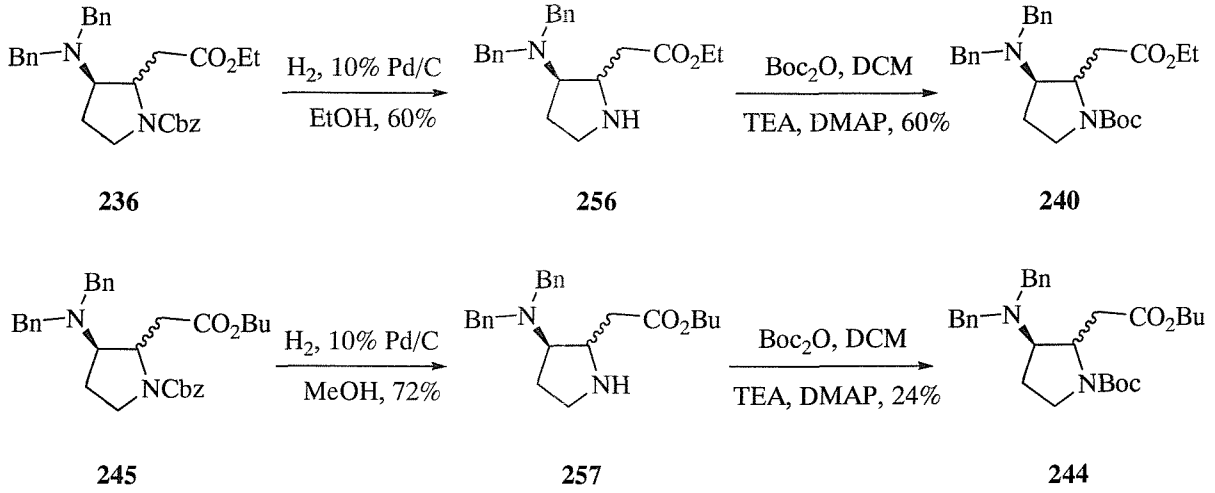
245 **255** (87%)

244 **254**

Scheme 84

In order to relate the Cbz-pyrrolidines with the Boc-protected pyrrolidines, the removal of the Cbz-group from **236** and **245** was successfully achieved by hydrogenation using Pd/C as a catalyst, the secondary amines **256** and **257** were gained in 60% yield for ethyl ester **236** and 72% yield for ^{t}Bu ester **245**. These two amines **256** and **257** were protected again with Boc group by reacting with Boc_2O in the presence of TEA and DMAP to convert both of them into Boc-Et **240** and Boc-^{t}Bu **244** in 60% and 24% yield

(**Scheme 85**). From the ^{13}C-NMR results, the major isomer was confirmed again to be identical with that from the original Boc-Et **240** and Boc-^{t}Bu **244**.

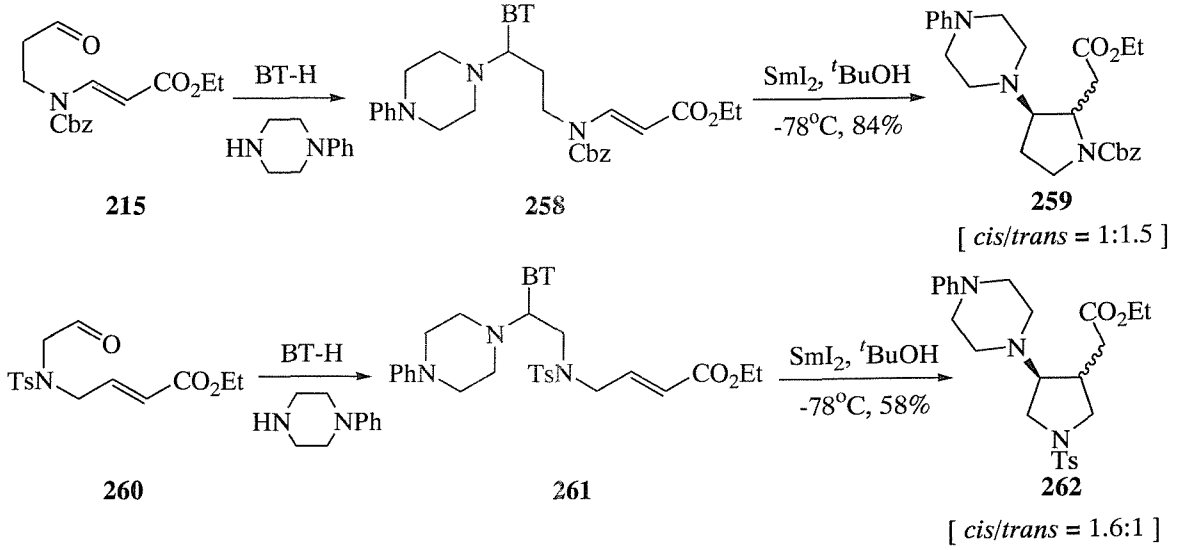


Scheme 85

Eventually correlation of the stereochemistry of other pyrrolidines to Cbz-^{t}Bu derivative **245** was successfully completed.

2.7) Further proof of stereochemistry

During the course of our studies, Aurrecoechea[102] reported the results of a closely related study. The SmI_2-promoted cyclisation of neutral α-aminoalkyl radicals generated from benzotriazole adducts were reported (**Scheme 86**). The corresponding



Scheme 85

benzotriazole adducts **258** or **261** were synthesised from aldehydes **215** or **260** and a variety of secondary amines such as 1-phenylpiperazine using the same Aurrecoechea method. Treatment of **258** and **261** with SmI_2 gave corresponding α-aza radicals, which underwent 5-*exo*-trig cyclisation to give 3-amino pyrrolidines **259** and **262**.

Though the way they made benzotriazole adducts was nearly the same as ours, THF was used as solvent instead of Et_2O, which we used. Their cyclisations were carried out at –78°C by normal addition with ^{t}BuOH (2.0 eq) as a proton source, whereas our cyclisations were achieved at 0°C by reverse addition in the presence of corresponding alcohol (2.3 eq). Although the yield varies from moderate to good yields, the stereoselectivity itself was poor. According to this paper[102], an upfield shift was observed in the ^{13}C-NMR spectrum for the ring methine carbon (*C*H-N) of the *cis*-diastereomer[103,104] relative to the *trans*-diastereomer.

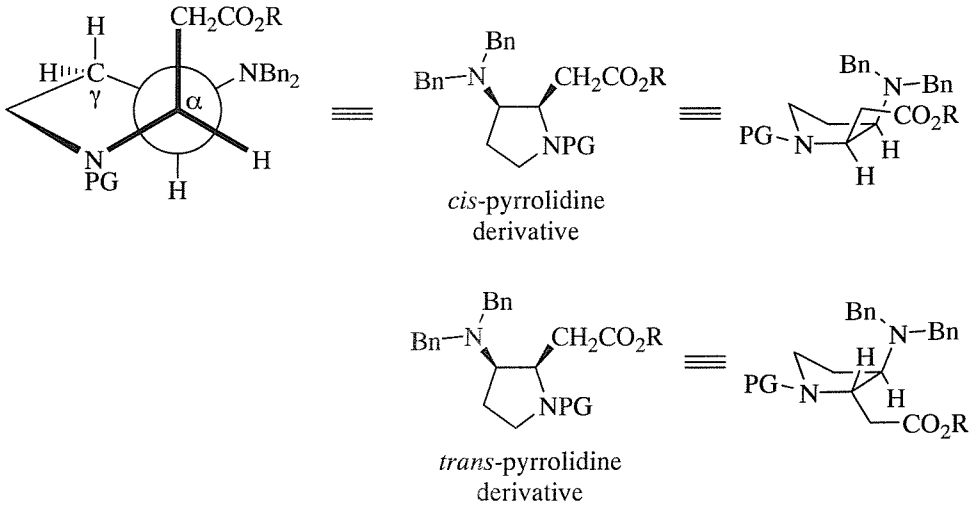


Figure 22

As our system was so similar to theirs, a similar analysis was therefore applied to the pyrrolidines. The occurrence of eclipsing interactions between an α-ring methine carbon and a γ-ring methylene carbon in the *cis*-diastereomers is called a 'γ-gauche effect'.[105] As the Newman projection of our rigid system, *cis*-isomer, the van der Waals radii of CH_2CO_2R and of the hydrogen atom on the γ-C overlap, as a result, the σ-bonding electrons are moved from H towards the γ-C atom (**Figure 22**).

Table 1; Selected ^{1}H- and ^{13}C-NMR resonances of pyrrolidine derivatives

Pyrrolidine	C*H*-N [a]	γ-C [a]	α-*C*H-N [a]	Pyrrolidine	C*H*-N [a]	γ-C [a]	α-*C*H-N [a]
cis-**236** [b]	4.48	23.6	64.1	*trans*-**236** [b]	4.17	24.0	65.3
cis-**245** [b]	4.49	24.3	64.5	*trans*-**245** [b]	4.11	27.3	65.0
cis-**234** [c]	4.56	23.4	63.9	*trans*-**234** [c]	4.15	27.5	65.1
cis-**240** [b]	4.39	23.6	64.2	*trans*-**240** [b]	4.08	24.2	65.3
cis-**244** [b]	4.70	24.3	64.0	*trans*-**244** [b]	4.00	27.4	65.2

[a] Determined on the individual isomers from DEPT experiments, and C-H correlation results.
[b] Samples dissolved in $_{d6}$-DMSO.
[c] Samples dissolved in $CDCl_3$, and taken at 50°C.

Hence, α-CH is shielded by γ-C, which now has higher electron density, causing a ^{13}C chemical upfield shift[104] ranging from 0.5-1.2 ppm (**Table 1**). Also γ-C is simultaneously shifted upfield from 0.4-4.1 ppm by the γ-gauche effect of α-CH (**Table 1**). This γ-gauche effect indeed was the key in leading to the assignment of the stereochemistry of the pyrrolidine products. The corresponding downfield shifts observed for C*H*-N in the ^{1}H-NMR spectra of the *cis*-isomers when compared to the same resonance in the *trans*-ones, also support this explanation (**Table 1**).

Table 2; The ratios of the mixture of pyrrolidine diastereomers

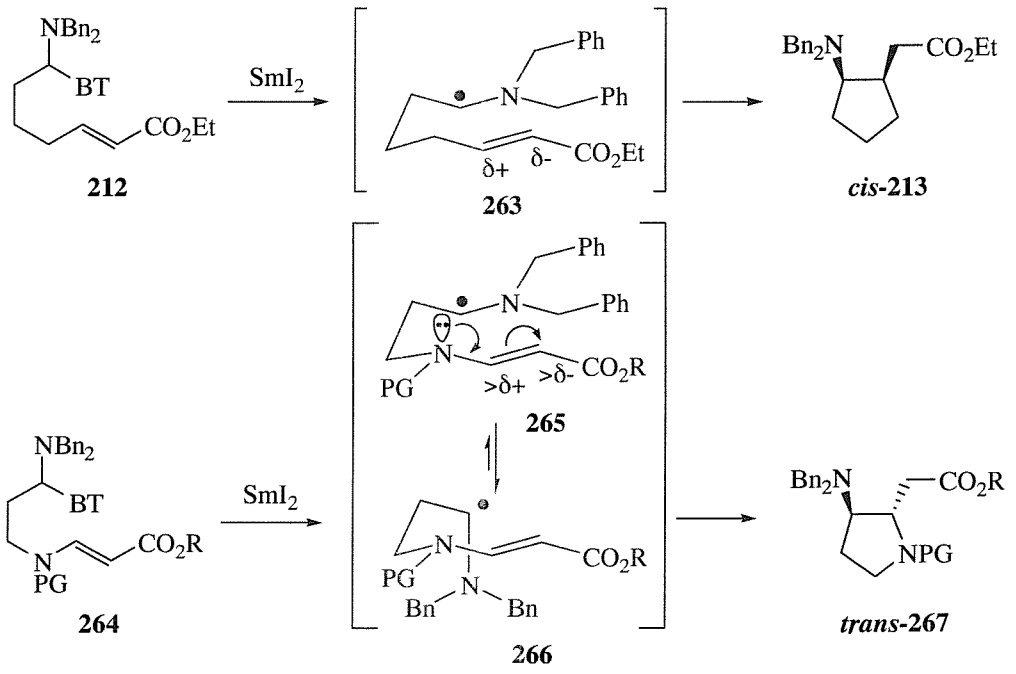
	Me- (yield), [ratio] *cis : trans*	Et- (yield), [ratio] *cis : trans*	^{t}Bu- (yield), [ratio] *cis : trans*
Cbz-	-	**236** (75%), [1: 2.9]	**245** (50%), [1: 1.9]
Boc-	**234** (51%), [1: 4]	**240** (45%), [1: 3]	**244** (51%), [1: 2.6]

Hence the stereochemistry of our system was confirmed by the NMR results. The results indicate that our reactions have better *trans*-stereoselectivity than those of Suero and Aurrecoechea[102] In terms of the comparison of ratios of the mixture of diastereomers,

the best diastereoselectivity can be observed for the case of Boc-Me pyrrolidine derivative **234**, which gives four times as much *trans*-isomer than the *cis*-isomer (**Table 2**). For the Cbz-^{t}Bu pyrrolidine derivative **245**, the ratio of the mixture showed the lowest selectivity to be *cis* 1 to *trans* 1.9. Interestingly, as the *N*-protecting group and the alkyl ester group get bigger, lower diastereoselectivity is obtained.

2.7.1) Discussions

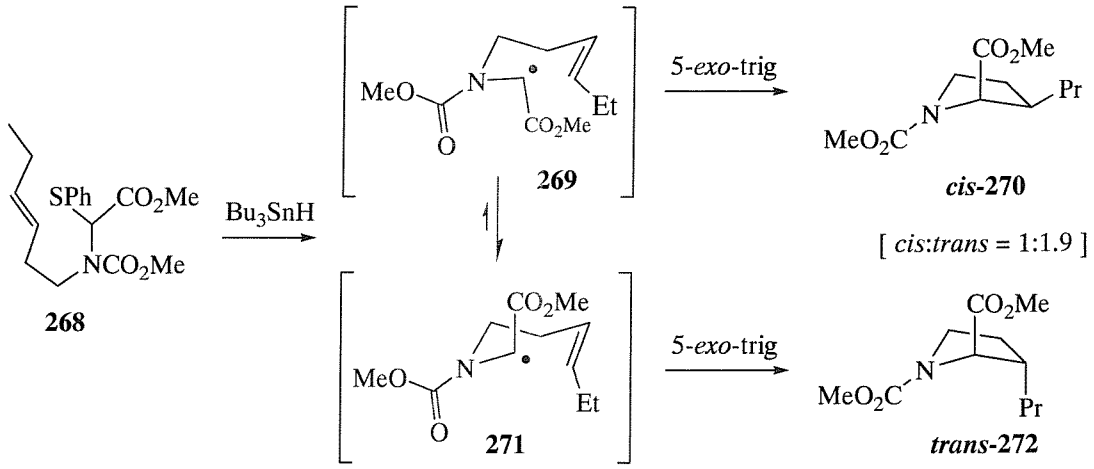
As the chair-like TS **263** prefers to have a bulky dibenzyl amine group in an equatorial position, the *cis*-preference can be explained in the former cyclisation (**Scheme 87**). However, the cyclisation of precursor **264** having one nitrogen atom adjacent to the double bond, gave the *trans*-isomer **267** as a major product. In this system greater electronic repulsion of π system caused by the contribution from nitrogen lone pair, forces the equatorial positioned dibenzylamine group in TS **265** into an axial position, which is more stable, and favoured TS **266** to give mainly a *trans*-disubstituted pyrrolidine **267**.



Scheme 87

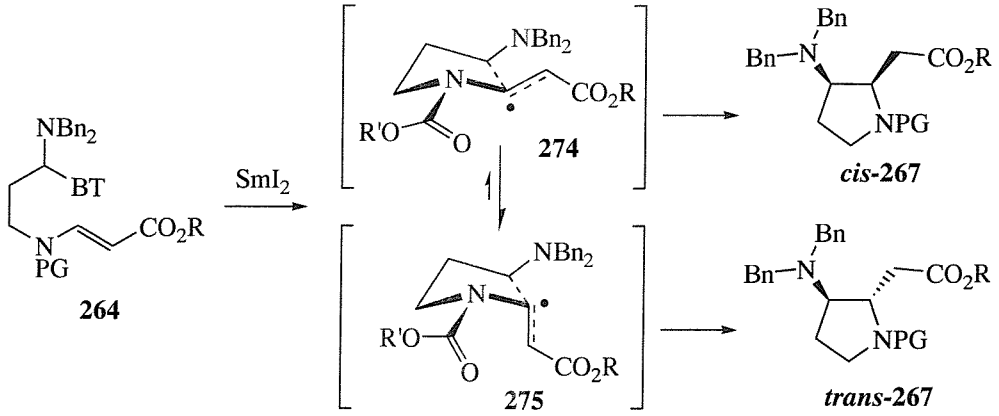
Speckamp[106,107] observed the *trans*-preference in pyrrolidine formation from the cyclisation of thiophenyl ester precursor **268** with Bu_3SnH and AIBN (**Scheme 88**). This result accommodates the Beckwith rules regarding 5-*exo*-trig cyclisation with the key

difference that the pseudo-allylic-1,3-strain forced the ester group into less hindered axial position. Radical intermediate **269**, which would cyclise to give the *cis*-isomer **270**, is obviously counterbalanced by the pseudo-allylic-1,3-strain that develops between the ester group and the *N*-carbonyl function. As a result, the more favorable radical intermediate **271** led to *trans*-isomer **272** in 1.9:1 ratio to *cis*-isomer **270**.



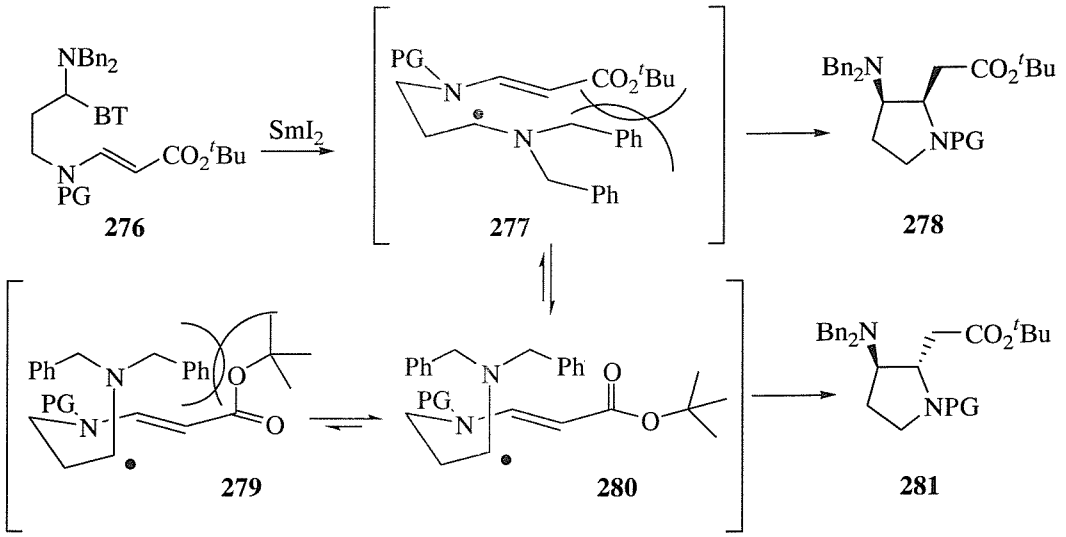
Scheme 88

Considering Speckamp's results, our diastereoselectivity could be alternatively explained by the pseudo-allylic-1,3-strain theory (**Scheme 89**). After the treatment with SmI_2, α-aza radical would attack double bond giving two alternative boat-like intermediates **274** and **275**, which have the psuedo-allylic conformations shown. In TS **274**, pseudo-allylic-1,3-strain occurrs between the ester unit and the *N*-carbonyl function. This in fact leads to a slight preference for the *trans*-isomer **267** through the alternative boat-like TS **275**, whereby such an interaction would be avoided.



Scheme 89

Lower stereoselectivity was observed with larger alkyl esters, a conceivable explanation could be obtained when we reconsidered the TS of the cyclisation (**Scheme 90**). Initially, the insertion of bigger alkyl ester group was expected to enhance the *trans*-preference of the cyclisation, by avoiding the steric clash between dibenzylamine group and the alkyl ester moiety in TS **277**. However, the TS leading to *trans*-cyclised product **281** could be considered as an equilibrium between the *cis*- and *trans*- forms, **279** and **280**, of the conjugated π system. According to the literature[108], the *trans*-form **279** is calculated to be more stable configuration than the *cis*-form. This in fact means that TS **279** may reduce some of the diastereoselectivity, due to the steric clash between dibenzylamine group and *tert*-butoxide group. However this force is not as crucial as TS **277**, so the cyclisation gives less *trans*-cyclised pyrrolidine **281** but still retains the *trans*-preference.

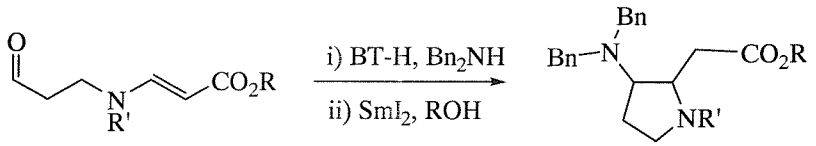


Scheme 90

2.8) Cyclisation *via* benzotriazole precursor of ethyl amino butenoate system

2.8.1) The reason for using the ethylamino butenoate system

In the previous section, the synthesis and results of the cyclisation of aldehyde precursors **214** have been discussed (**Scheme 91**). The cyclisation showed good diastereoselectivity but only moderate yields. In order to improve the diastereoselectivity of the cyclisation, we considered the position of the groups on the 5 membered ring and their interactions.



214 **267**

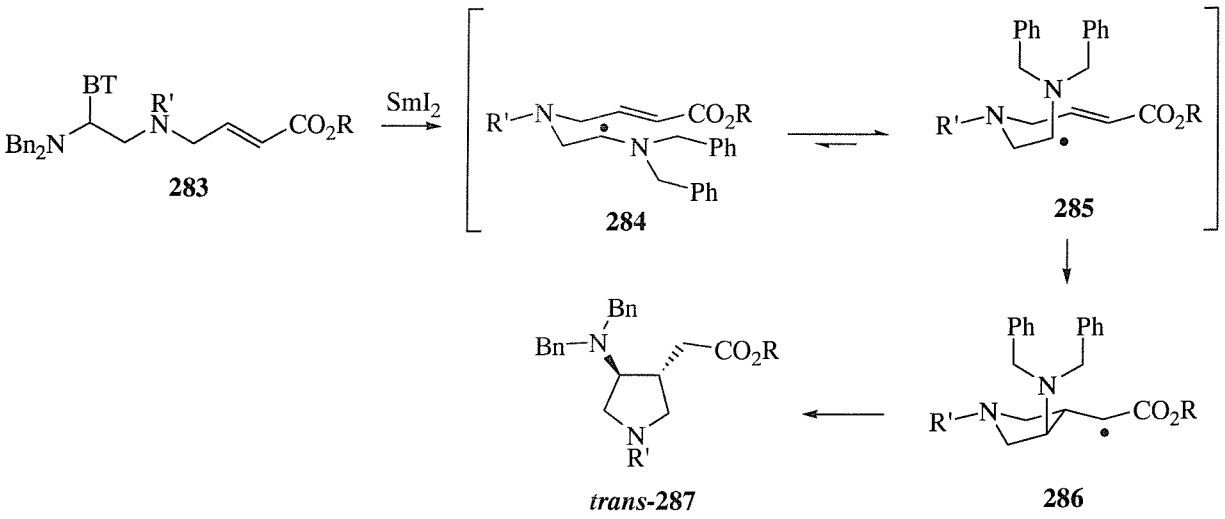
Scheme 91

In the chair-like TS **282** (**Scheme 92**), there is 1,3-steric hindrance between the bulky dibenzyl amine and the axial hydrogen atom, which could possibly reduce the *trans*-preference of the cyclisation and give less of the cyclised *trans*-1,2-disubstituted pyrrolidine product **267**.

282 ***trans*-267**

Scheme 92

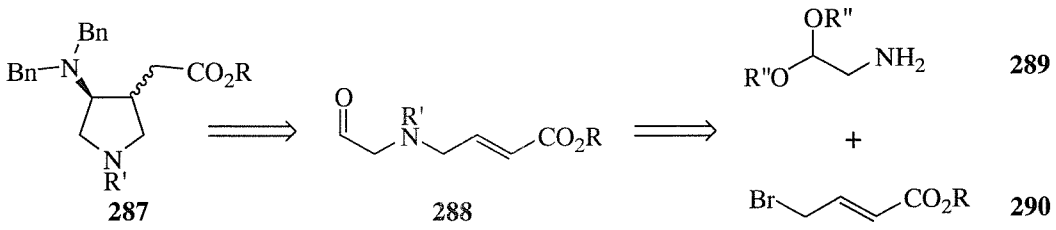
However switching to precursor **283**, *trans*-2,3-disubstituted pyrrolidine **287** would be produced *via* radical intermediates **284**, **285** and **286** (**Scheme 93**). This cyclisation route is advantageous since the 1,3-diaxial interaction in chair-like intermediate **285** is now with a nitrogen lone pair of electrons, rather than the C-H in intermediate **282** (**Scheme 92**).



Scheme 93

2.8.2) Retrosynthesis

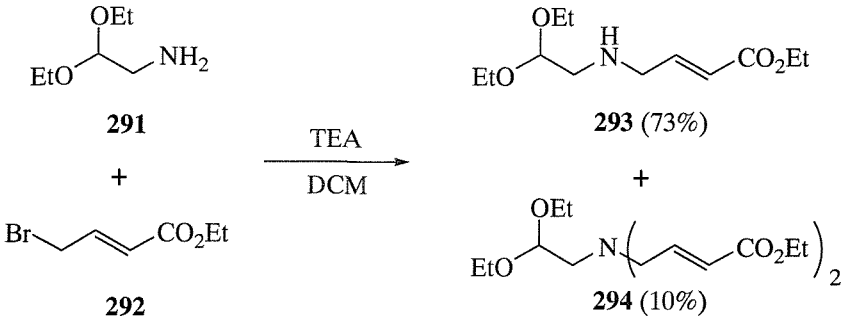
From the benzotriazole strategy, the required substrate for the cyclisation would be aldehyde precursor **288**, which could be synthesized by the simple coupling between amine **289** and bromo-alkyl acrylate **290** (**Scheme 94**).



Scheme 94

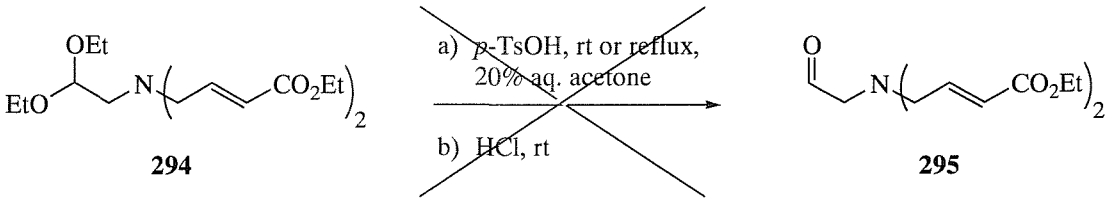
2.8.3) Synthesis of ethylamino butenoate system

For the initial coupling reaction, 2,2'-diethoxy-1-aminoethane **291** and ethyl-3-bromo-crotonate **292** were selected as the starting materials (**Scheme 95**). The reaction gave the desired secondary amine **293**, but the tertiary amine **294** was also produced as a by-product.



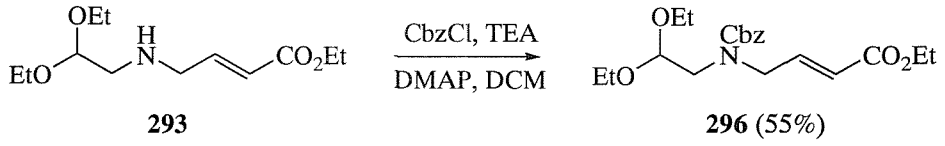
Scheme 95

To reduce the amount of **294** formed, the temperature and the concentration of the starting materials had to be strictly controlled. The best method was to add dropwise the diluted solution of ethyl-3-bromo-crotonate **292** into the concentrated solution of the amine starting materials at 0°C, and it raised the yield of desired product **293** up to 73% **(Scheme 95)**.



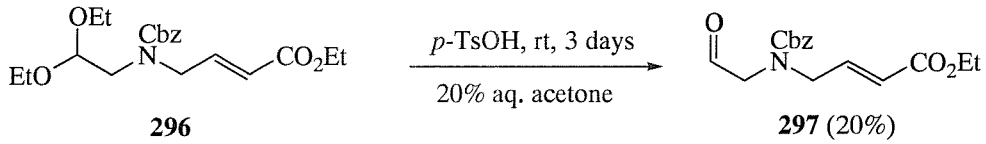
Scheme 96

Even though compound **294** was not the desired product, it may be useful for making an aldehyde **295**, which then would be used as the precursor of a radical cyclisation **(Scheme 96)**. However, treating acetal **294** with *p*-TsOH in 20% aq. acetone at room temperature, in the normal way did not give the desired aldehyde **295**. Reflux for 2 hours with *p*-TsOH in the same solvent did not provide the desired product **295** either. Using HCl instead also failed to give the desired product **295**, therefore this idea of making aldehyde **295** was abandoned.



Scheme 97

Protection of amine **293** was carried out by treatment with CbzCl in the presence of TEA and DMAP in DCM. The protecting reaction successfully provided the desired product **296** in a moderate yield of 55% (**Scheme 97**).



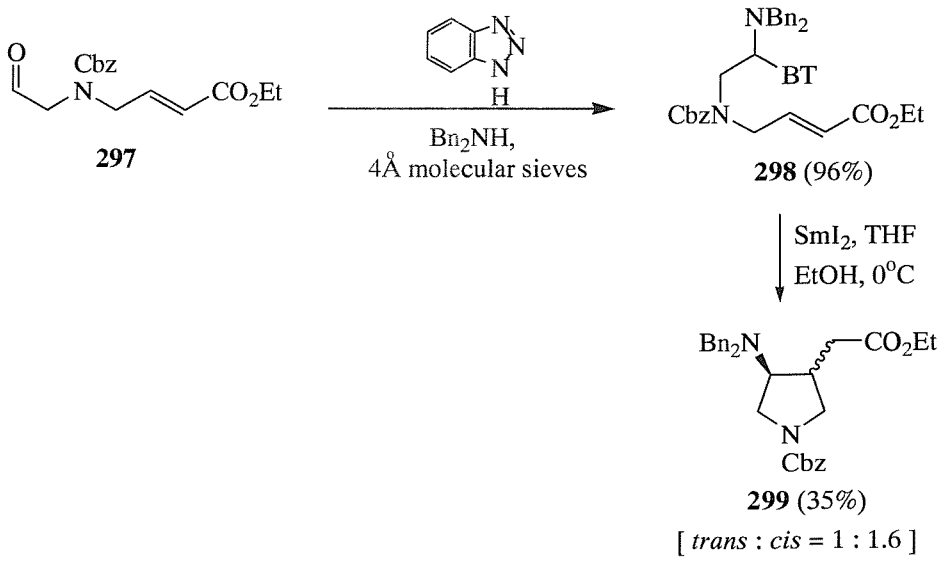
296 **297** (20%)

Scheme 98

Treatment of acetal **296** with *p*-TsOH in 20% aq. acetone at room temperature for 3 days gave aldehyde **297** in a relatively poor yield of 20% (**Scheme 98**).

2.8.4) Cyclisation of aldehyde substrate 297

The Aurrecoechea procedure was again used to make a benzotriazole adduct from aldehyde **297** (**Scheme 99**). Benzotriazole adduct **298** was obtained in 96% yield when aldehyde **297** was treated with benzotriazole and dibenzyl amine in ether at 0°C in the presence of 4 Å molecular sieves. SmI_2 was used to promote the radical cyclisation of this precursor **298** in THF at 0°C with EtOH as a proton source. The reaction provided the desired pyrrolidine derivative **299** as a mixture of diastereomers (*trans : cis* = 1 : 1.6) in a yield of 35%.



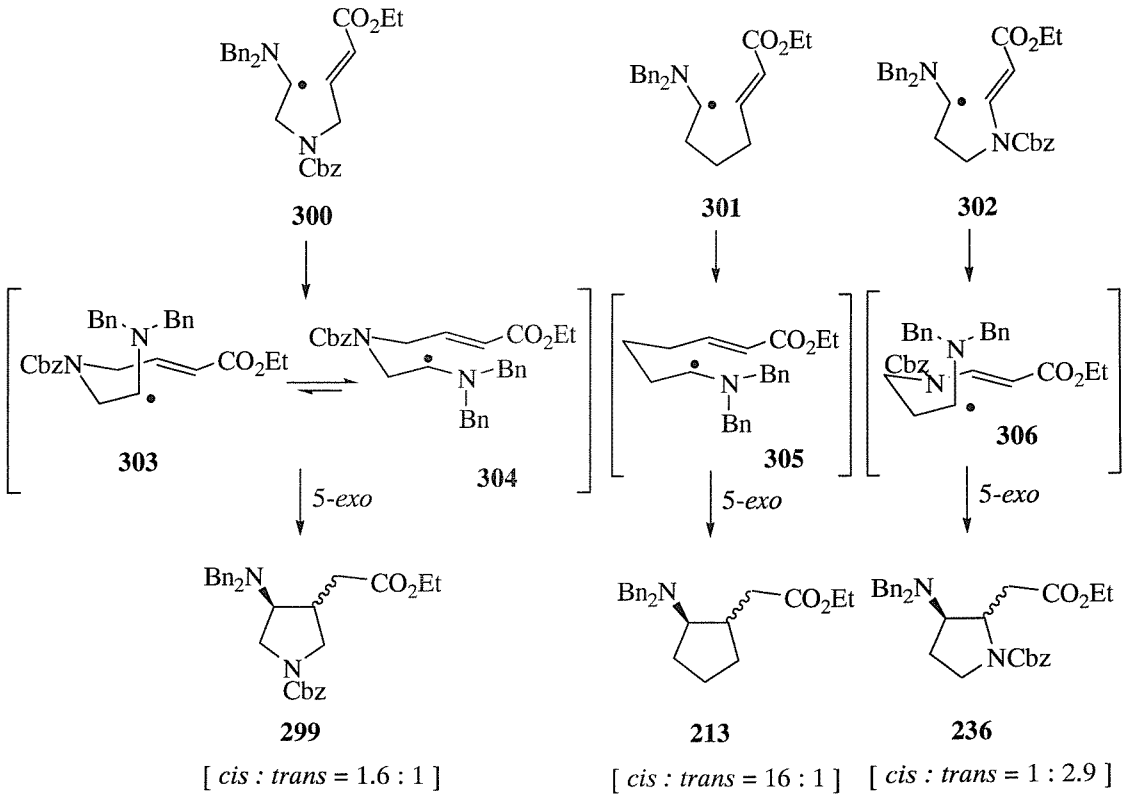
297 **298** (96%)

299 (35%)

[*trans* : *cis* = 1 : 1.6]

Scheme 99

The diastereoselectivity (*trans:cis* = 1:1.6) was disappointing but appears to confirm our hypothesis that the *trans*-selectivity obtained for cyclisations of the radical **302** described earlier is a consequence of the electronic repulsion contributed by the enamine nitrogen lone pair towards double bond, which forced the dibenzyl amine group into an axial position (**Scheme 100**). Without this electronic contribution, the cyclisation of radical **301** exclusively gave *cis*-isomer **213** as a major product as the substituent is in an equatorial position in a chair-like conformation **305**. In the case of system **300**, although it still remains a *cis* preference from the similar cyclisation of **301**, but having one nitrogen atom in the position, where no 1,3-steric hindrance could be formed with dibenzylamine group, decreased the trend of the *cis* preference cyclisation. This result was consistent with the Aurecoechea's results.[102]



Scheme 100

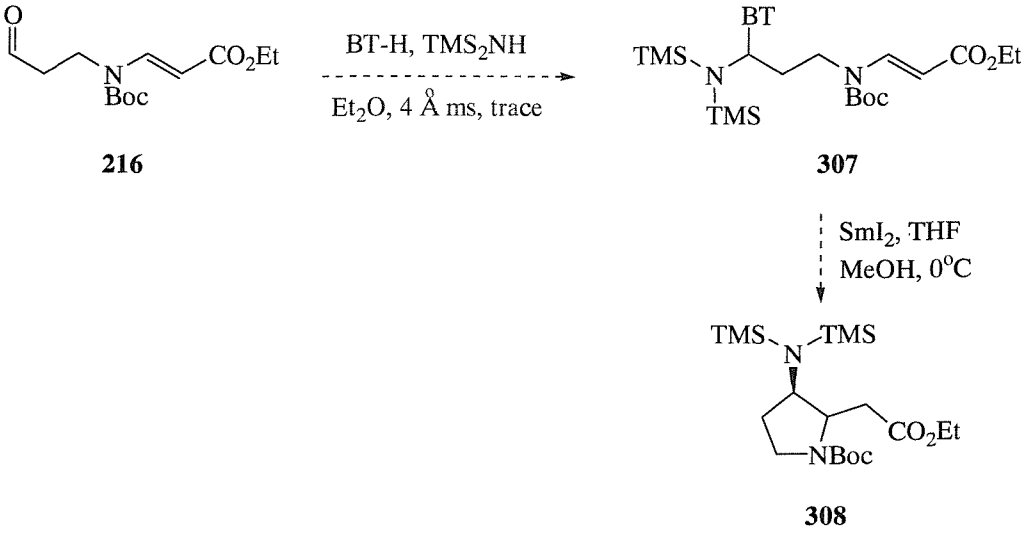
2.8.5) Conclusion

The synthetic route to aldehyde precursor **297** was developed. *trans*-2,3-Disubstituted pyrrolidine product **299** was successfully synthesized by the SmI_2 promoted cyclisation. The reaction (*trans:cis* = 1:1.6) was not as diastereoselective as we expected.

2.9) Other attempts

2.9.1) Using TMS_2NH instead of Bn_2NH to make the corresponding benzotriazole adduct

Aldehyde precursor **216** was also reacted with hexamethyldisilazane and benzotriazole under the same conditions previously described in the dibenzylamine case. It was hoped that this benzotriazole adduct **307** might give a cyclised product **308** which could be easily deprotected to give the free amine product (**Scheme 101**). However, the desired benzotriazole compound **307** could not be formed satisfactorily.

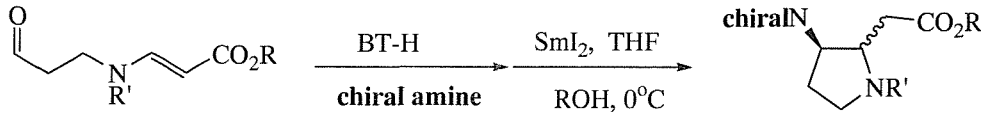


216 **307** **308**

Scheme 101

2.9.2) Synthesis of chiral benzotriazole adduct by using chiral amine

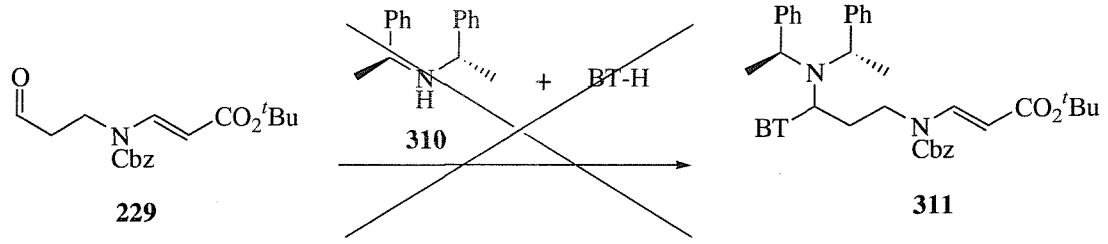
As we could understand the selectivity of the cyclisation, we thought that use of a chiral amine to make a chiral benzotriazole adduct was worth attempting. Reacting the chiral amine with an aldehyde substrate **214** and benzotriazole may give better stereoselectivity and hopefully would give enantioselectivity from the radical cyclisation (**Scheme 102**).



214 **309**

Scheme 102

Unfortunately it was again not possible to form the benzotriazole adduct **311** using chiral amine **310** and aldehyde **229**, even when carrying out the reaction at reflux in benzene (**Scheme 103**). The reason was presumably due to the steric hindrance.



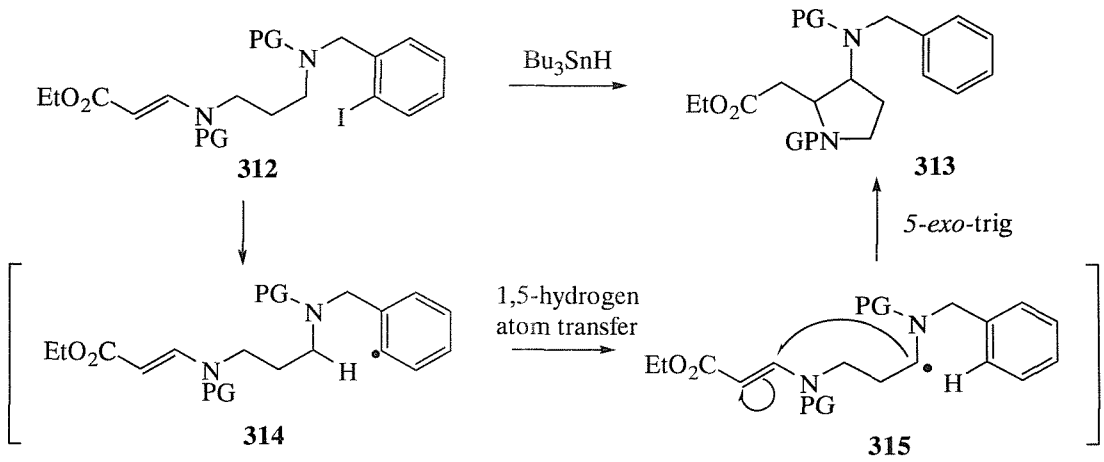
229 **310** **311**

Scheme 103

Chapter 3 Cyclisations via 1,5-Hydrogen Atom Transfer

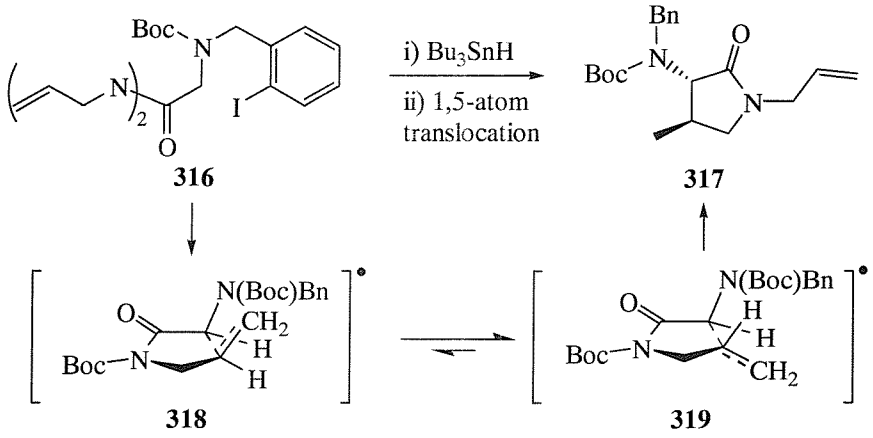
Radical translocation strategy

An alternative approach to the desired pyrrolidines is to use radical translocation (1,5-hydrogen atom abstraction) to generate the appropriate α-amino radical species, which can achieve the 5-*exo*-trig cyclisation.[83] By using tributyltin hydride (Bu_3SnH), halobenzyl amine **312** could be converted into 1,2-disubstituted cyclopentene **313** *via* radical intermediates **314** and **315** (**Scheme 104**). Once the radical intermediate **314** is formed, 1,5-atom transfer gives radical **315**, which then undergoes 5-*exo*-trig cyclisation to form desired cyclic product **313**.



Scheme 104

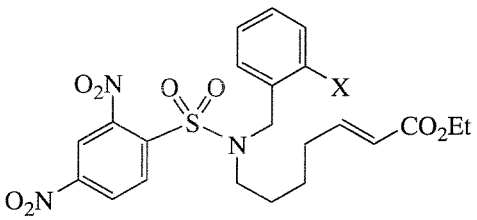
Rancourt and colleagues reported the applications of this idea to γ-lactam formation *via* a 1,5-hydrogen atom transfer process (**Scheme 105**).[109] Unsaturated amide **316** was treated with Bu_3SnH and 1,1'-azobis(cyclohexane carbonitrile) (ACCN) at 80°C to give γ-lactam **317** (*trans/cis* = 7/1) in 60% yield. The *trans*-3,4-disubstituted γ-lactam **317** was formed as the major product of the reaction, as rationalized by the TS **318** and **319 (Scheme 105)**.



Scheme 105

3.1) 1,5-Hydrogen atom transfer of 2,4-dinitrophenyl sulfonamide system

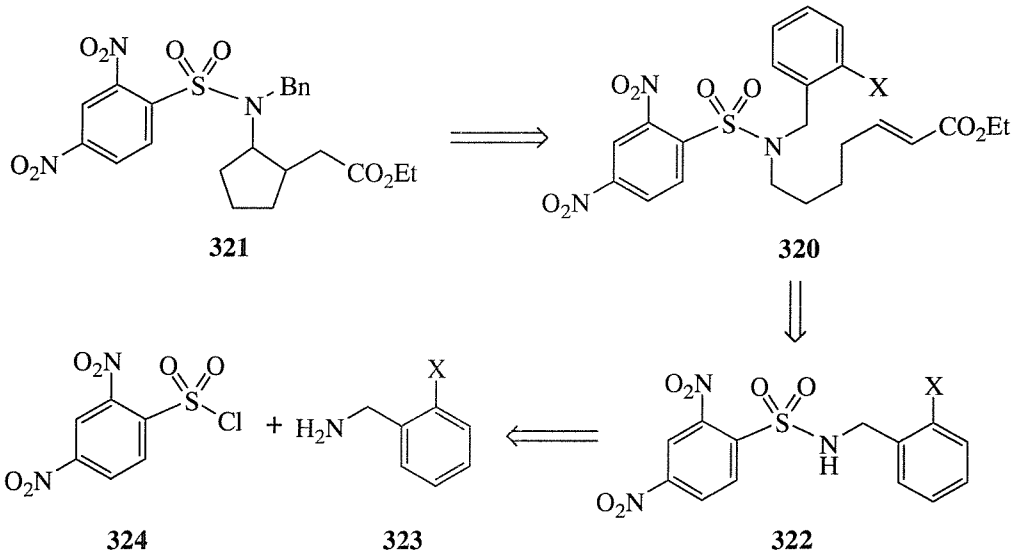
Initially 2,4-dinitrophenyl sulfonamide **320** was chosen as a substrate to check the feasibility of a radical translocation cyclisation (**Figure 23**). Aryl sulfonamides are stable protecting groups for amines[110], and they have the added bonus of being highly crystalline. It can also be easily removed by simple basic hydrolysis.[111,112]



320

Figure 23

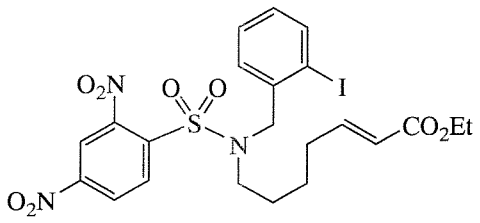
Sulfonamide **320** was to be prepared from the Mitsunobu coupling of amine **322** with the corresponding alkyl heptenoate alcohol. Sulfonamide **322** should be available from the simple reaction between halo-benzyl amine **323** and commercially available 2,4-dinitrophenyl sulfonide chloride (DNPSCl) **324** (**Scheme 106**).



Scheme 106

3.1.1) Synthesis of the cyclisation iodide precursor 325

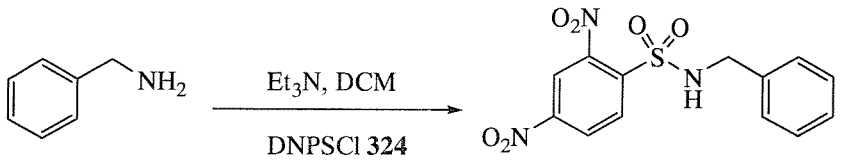
Our first target precursor was aryl sulfonamide **325** (**Figure 24**). Aryl iodide was chosen, as it is a good radical precursor.



325

Figure 24

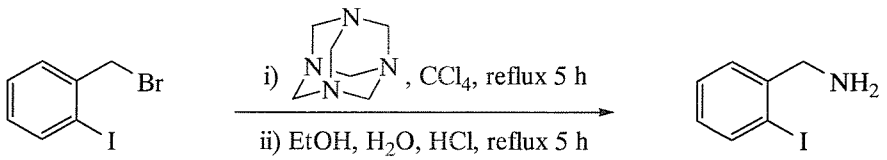
Initially benzyl amine **326** was used instead of *o*-iodo-benzyl amine in the coupling reaction with DNPSCl **324** in the presence of base, to ensure that the reaction worked. As a result the corresponding benzyl sulfonamide **327** was produced in a good yield (**Scheme 107**).



326 **327** (65%)

Scheme 107

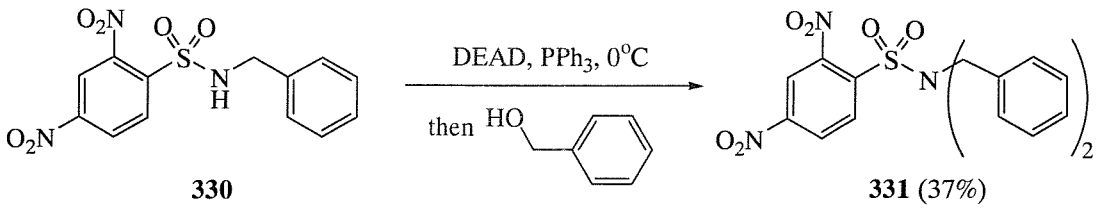
Since the reaction was successful with benzylamine, the next step was to carry out this reaction with *o*-iodobenzyl amine **329**. In order to synthesise this precursor **329**, *o*-iodobenzyl bromide **328** was used to make the appropriate amine **329** (**Scheme 108**). The reaction was carried out following the method of Bowman.[113] First refluxing *o*-iodobenzyl bromide **328** with hexamethylene tetramine in carbon tetrachloride overnight gave amine adducts as a precipitate. The amine salt was refluxed overnight again in a mixture of ethanol, water and hydrochloric acid to obtain *o*-iodobenzyl amine **329** in an overall excellent yield of 82%.



328 **329** (82%)

Scheme 108

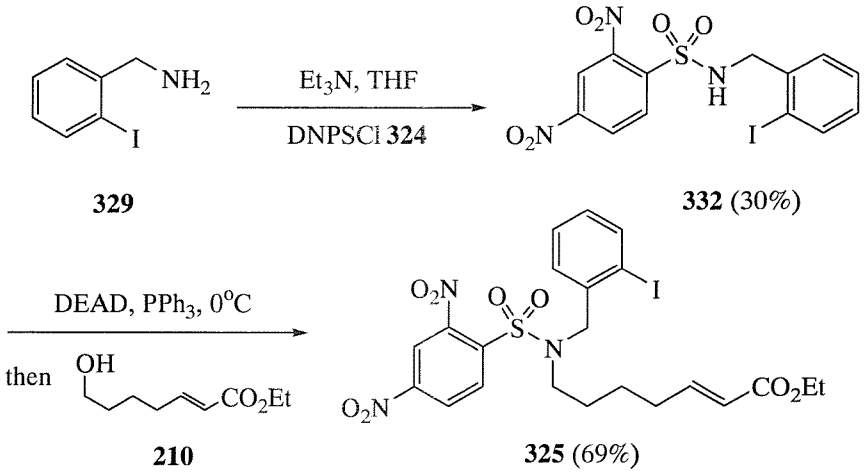
As a test reaction for the Mitsunobu coupling, benzyl sulfonamide **330** was used instead of the corresponding iodobenzyl sulfonamide with benzyl alcohol. As a result, the corresponding dibenzyl sulfonamide **331** was produced in quantitative yield (**Scheme 109**).



330 **331** (37%)

Scheme 109

Reaction of DNPSCl **324** with *o*-iodo-benzyl amine **329** in the presence of the 1.5 equivalents of triethylamine gave the corresponding sulfonamide **332** as a yellow powder but in only 30% yield (**Scheme 110**). The Mitsunobu reaction[114] was used to achieve the alkylation of compound **332** with alcohol **210**, affording sulfonamide **325**. Again there was a problem in separation of the alkylated sulfonamide **325** from the starting materials **332** using column chromatography. To solve this problem, the reaction time was prolonged and the reaction was carried out at high concentration to give **325** in 69% yield.



329 **332** (30%)

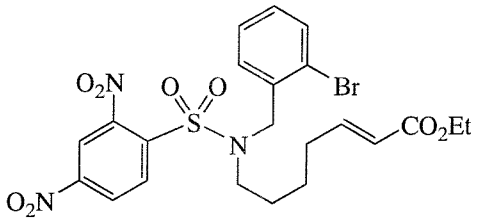
210 **325** (69%)

Scheme 110

3.1.2) Synthesis of the cyclisation bromide precursor 333

Although iodide precursor **325** was successfully synthesized, the yield of sulfonamide **332** was poor and far from satisfactory. In terms of improving the overall yield, a smaller halogen atom was chosen instead of iodide. Bromide was an alternative

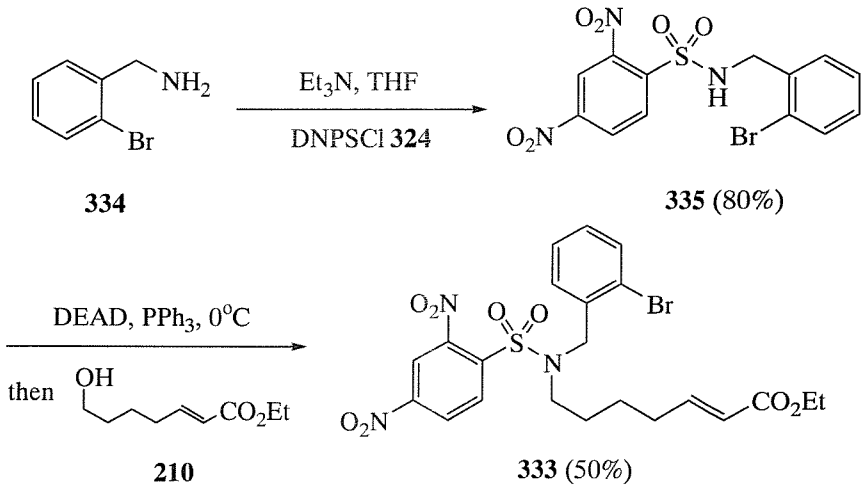
choice for our new target precursor **333**, and bromide is also a well-known halogen precursor in radical reactions promoted by Bu_3SnH (**Figure 25**).



333

Figure 25

As an analogue to the synthesis of the iodide precursor **325,** *o*-bromobenzyl derivative **333** was synthesized (**Scheme 111**). The yield of the coupling between *o*-bromo-benzyl amine **334** and DNPSCl **324** was improved from 30% to 60~80%, and the Mitsunobu reaction was improved in terms of the ease of the purification.

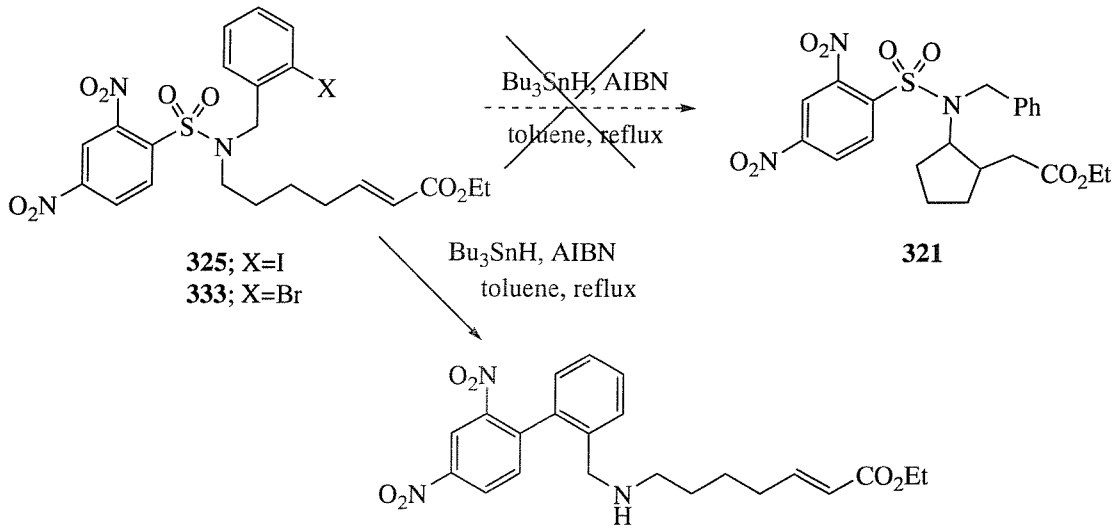


Scheme 111

3.1.3) Cyclisation *via* radical translocation of precursors 325 and 333

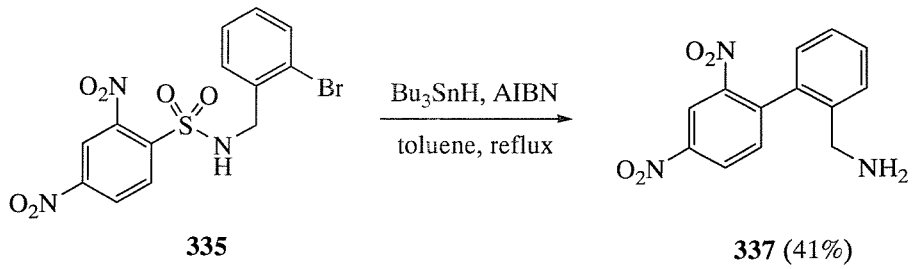
Radical translocation was attempted in order to achieve the 5-*exo*-trig cyclisation of iodo- and bromo-precursors **325** and **333** (**Scheme 112**). Refluxing **325** and **333** in

toluene with Bu_3SnH and catalytic amount of AIBN, did not give the desired cyclopentyl derivative **321**. However both reactions provided an unexpected product **336** in 27-32% yield.



Scheme 112

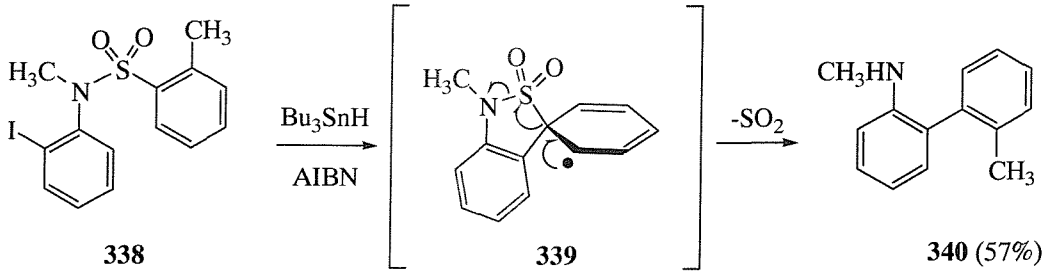
^{1}H-NMR of **336** revealed that the heptenoate side chain was intact (**Scheme 112**). The dinitrophenyl sulfonyl portion has changed, according to ^{1}H-NMR, but retains the 1,2,4-trisubstitution pattern. In order to rationalise this radical reaction, an analogous reaction was carried out by reacting bromide **335** under identical conditions giving product **337**, which is analogous to **336** from the previous reaction (**Scheme 113**).



Scheme 113

Motherwell and his colleagues demonstrated the intramolecular free radical *ipso* substitution of sulfonyl aromatic derivative **338** (**Scheme 114**).[115] This represents a novel

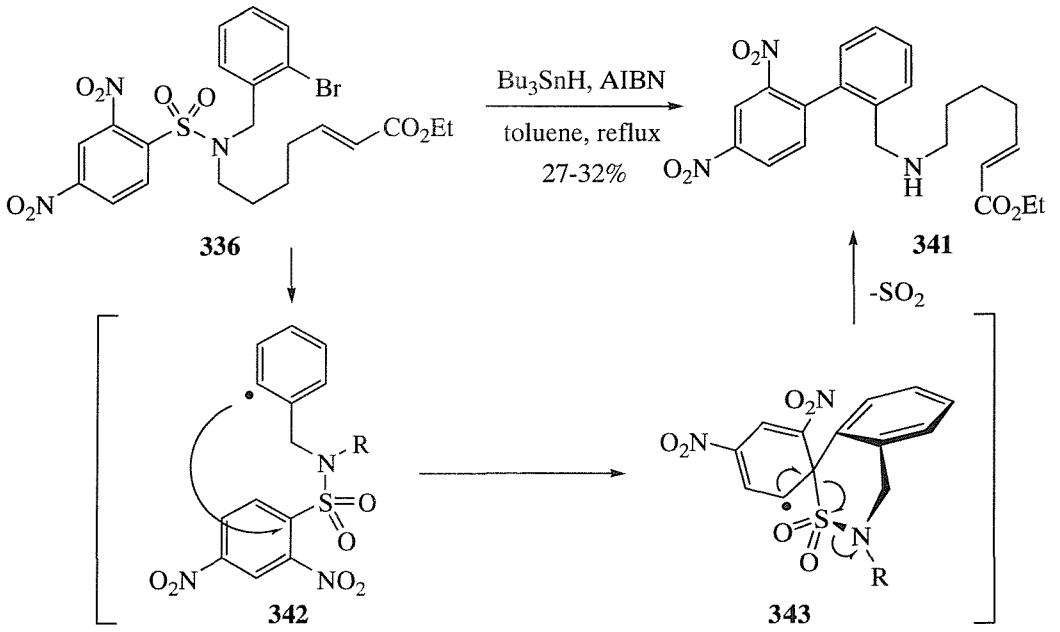
approach for biaryl coupling. Treatment of aryl sulfonamide **338** with Bu_3SnH and AIBN initiated the aryl radical, which cyclised to the spiro-intermediate **339**. This radical intermediate **339** then loses sulfur dioxide, to regain the aromatisation and efficiently give the biaryl product **340**.



338 **339** **340** (57%)

Scheme 114

By rationalising our unexpected results with that of Motherwell along with strong supports from NMR and MS data we came to the conclusion that precursors **325** and **333** would not achieve radical cyclisations as expected. The side reaction with dinitrobenzene sulfonyl groups produced biaryl derivative **341** instead *via* radical TS **342** and **343** (**Scheme 115**). The radical attacks the carbon adjacent to the sulfur atom to give the spiro intermediate **343**, which then loses sulfur dioxide to produce the secondary amine **341**.



336 **341** **342** **343**

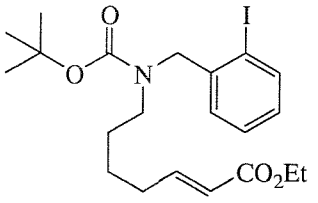
Scheme 115

3.1.4) Conclusion

Bromo- and iodo-benzyl dinitro sulfonamide precursors **325** and **333** were synthesized. However, the 2,4-dinitrophenyl sulfonamide system gave us unexpected biaryl products *via* the intramolecular free radical *ipso* substitution. Due to these problems with the dinitro-benzene sulfonamide group, it was necessary to change the protecting group in order to make the radical cyclisation possible.

3.2) 1,5-Hydrogen atom transfer of halide benzamide system

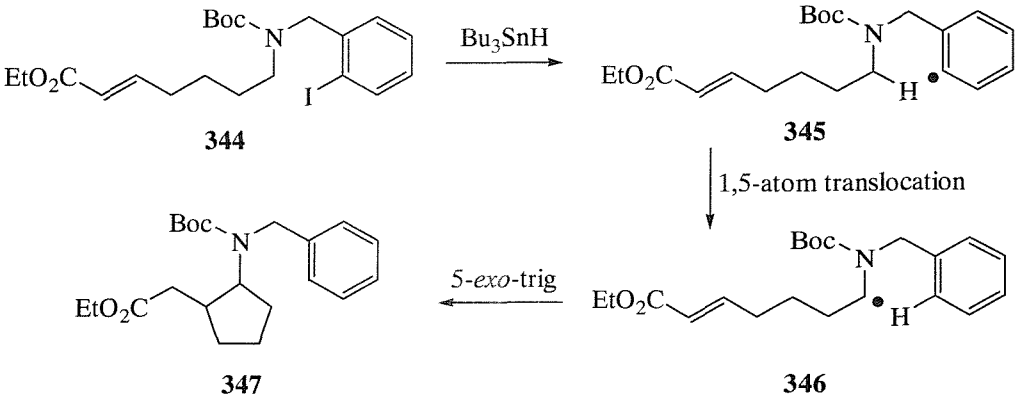
We focused on target **344** with a *tert*-butoxycarbonyl protecting group (**Figure 26**).



344

Figure 26

To achieve the intramolecular radical cyclisation, treatment of precursor **344** with Bu_3SnH should generate the radical species **345** (**Scheme 116**). Following this, 1,5-hydrogen atom transfer should occur to produce radical intermediate **346**, which will undergo the radical cyclisation and give the desired cyclopentyl product **347**.

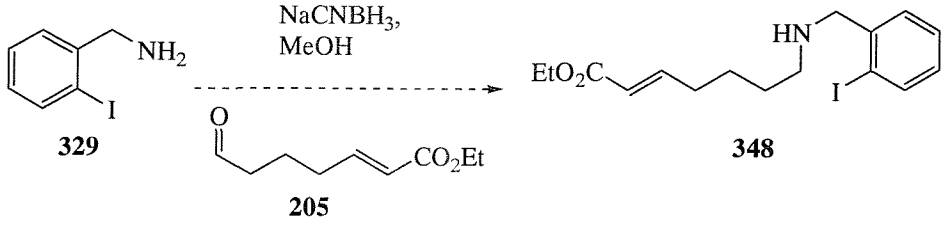


344 **345** **347** **346**

Scheme 116

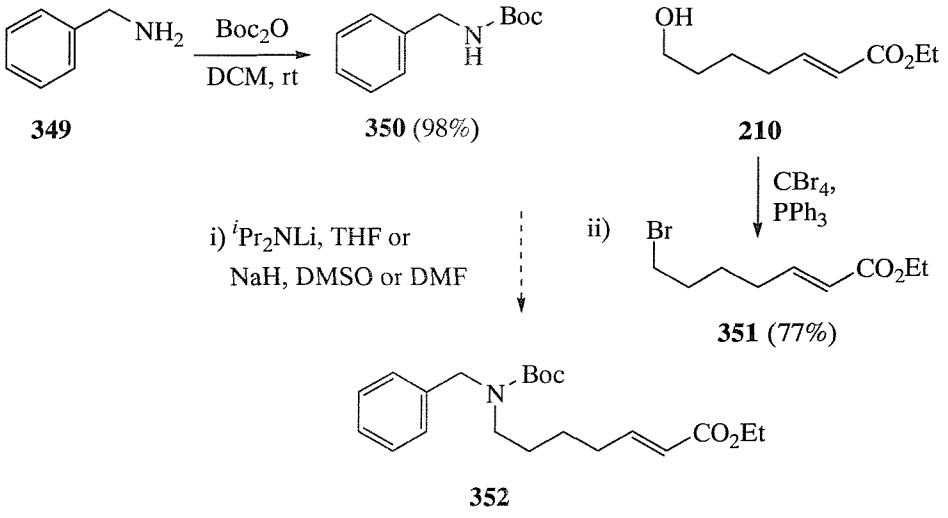
3.2.1) Synthesis of substrate 344

The approach towards compound **344** was the reductive amination[116], to introduce an alkyl group into **329** (**Scheme 117**). Following the literature procedure[116], precursor **329** was stirred at room temperature for three days with aldehyde **205** and sodium cyanoborohydride in order to give amine **348**. However no target compound **348** was produced and only starting material **329** was recovered.



Scheme 117

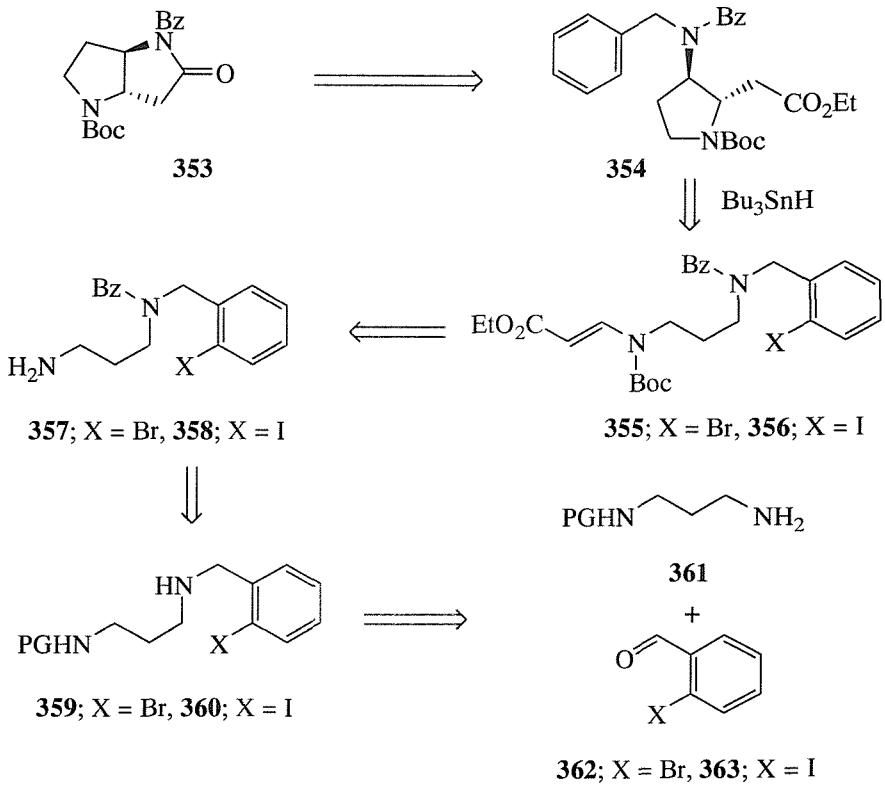
An alternative approach to the amine precursor **344** was attempted (**Scheme 118**). To confirm that the reaction works, benzylamine **349** was used instead of corresponding *o*-halobenzylamine. Firstly treatment of benzylamine **349** with Boc_2O and TEA gave excellent yield of secondary carbamate **350**. Treating alcohol **210** with carbon tetrabromide and triphenylphosphine gave bromide **351** in a good yield of 77%.[117,118] However the alkylation of this secondary carbamate **350** with bromide **351** using NaH in either DMSO or DMF or LDA in THF as base, gave only starting materials back.



Scheme 118

3.3) Alternative 1,5-atom transfer strategy

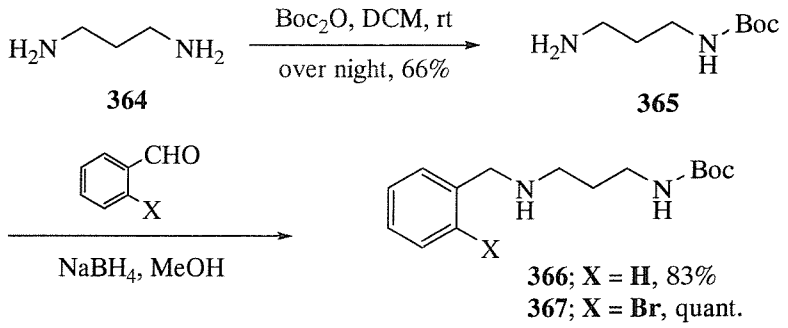
Since our efforts failed to give the desired target precursor **344**, an alternative approach to pyrrolidine *trans*-lactams **353** was chosen (**Scheme 119**). *trans*-Pyrrolidine **354**, which is the precursor for **353**, was to be derived from halide precursors **355** and **356**. These halo-benzyl carbamates **355** and **356** may possibly be synthesized from urethanes **357** and **358**, which can be made from 1,3-*N,N'*-disubstituted propyl amines **359** and **360**. The starting materials for the reductive amination to gain precursors **359** and **360** are protected diamino propane **361** and the corresponding halo-benzaldehyde **362** and **363**.



Scheme 119

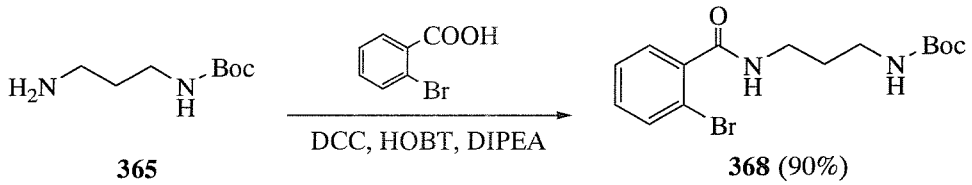
3.3.1) Synthesis of bromide substrate 355

Synthesis of substrates **355** began with the reaction of diaminopropane **364** and Boc_2O to give a protected amine **365** in quantitative yield (**Scheme 120**). Reductive amination[119] was attempted to insert a benzyl group onto the other primary amine of **365** by treating the mixture of compound **365** and benzaldehyde or *o*-bromo-benzaldehyde **362** with $NaBH_4$. For both X = H and X = Br, the reactions worked well to give **366** in 83% yield, and **367** in quantitative yield. $NaCNBH_3$ was initially used followed by Borsch's procedure [116], but the reaction failed to afford the desired compounds.



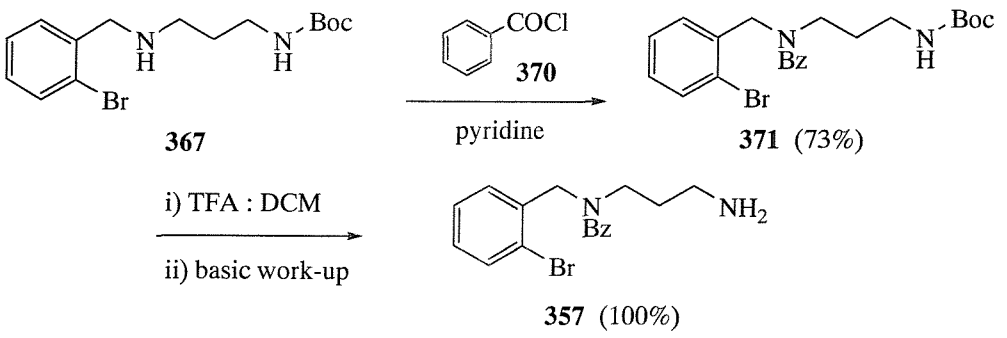
Scheme 120

An alternative procedure involved coupling between amine **365** and *o*-bromobenzoic acid to give product **368** in an excellent yield. The product **368** was difficult to isolate from DCU, so it was decided to stay with the reductive amination (**Scheme 121**).



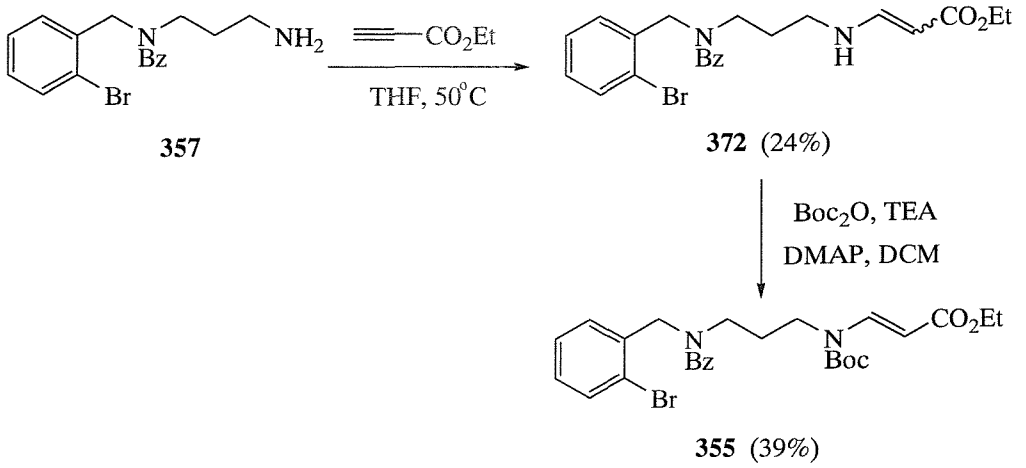
Scheme 121

o-Bromo-benzylamine **371** was obtained 73% yield from the coupling of **367** with benzoyl chloride **370**, which is easily prepared by refluxing benzoic acid in thionyl chloride overnight[120], in the presence of TEA and catalytic amount of DMAP. Treatment of **371** with TFA gave the TFA salt quantitatively. Basic work-up gave the free primary amine **357** ready for the next coupling reaction (**Scheme 122**).



Scheme 122

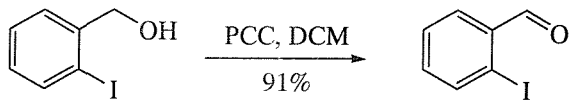
The coupling between amine **357** and ethyl propiolate was first attempted using the same conditions as secondary amine **218**, however only starting materials were obtained. Another attempt followed the procedure of Nohara[121] In this reaction both starting materials were stirred in DMF at 90°C, but it simply gave decomposition of starting materials. The reaction seemed to work at 50°C determined from the TLC, but again after removal of DMF, the desired compound **372** was found to have decomposed. Finally the coupling worked to give **372** (1:1 mixture of *E*:*Z*) in 24% yield after changing the solvent from DMF to THF again at 50°C. Reaction of amine **372** with Boc_2O to afford a protected precursor **355** in 39% yield (**Scheme 123**).



Scheme 123

3.3.2) Synthesis of iodide substrate 356

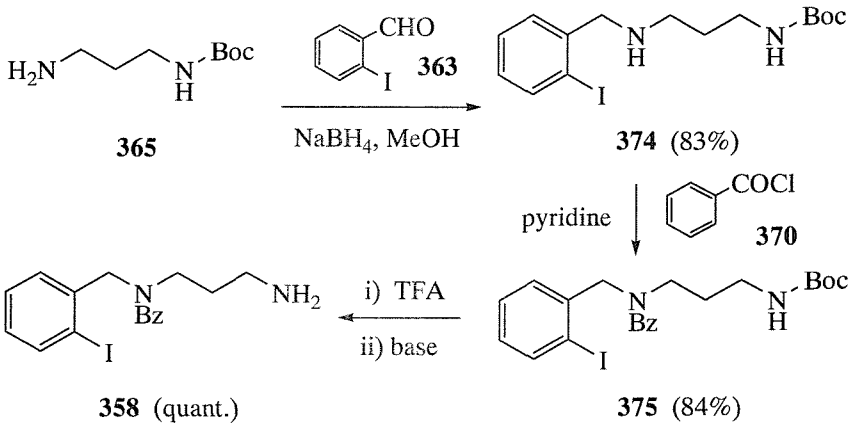
In order to make an iodide precursor **356** (analogous to bromide **355**), *o*-iodo-benzyl alcohol **373** was stirred with PCC overnight to give aldehyde **363** in 91% (**Scheme 124**), using the well developed method of Larock.[122]



373 **363**

Scheme 124

Following the same synthetic route as for bromide **355**, reductive amination of monoBoc-propylamine **365** with *o*-iodo-benzaldehyde **363** using $NaBH_4$ in MeOH gave **374** in an excellent yield of 83%. The benzoylation of **374** with benzoyl chloride **370** in the presence of TEA and DMAP gave **375** in 84% yield. Deprotection of **375** with TFA and the basic work-up gave primary amine **358** quantitatively (**Scheme 125**).

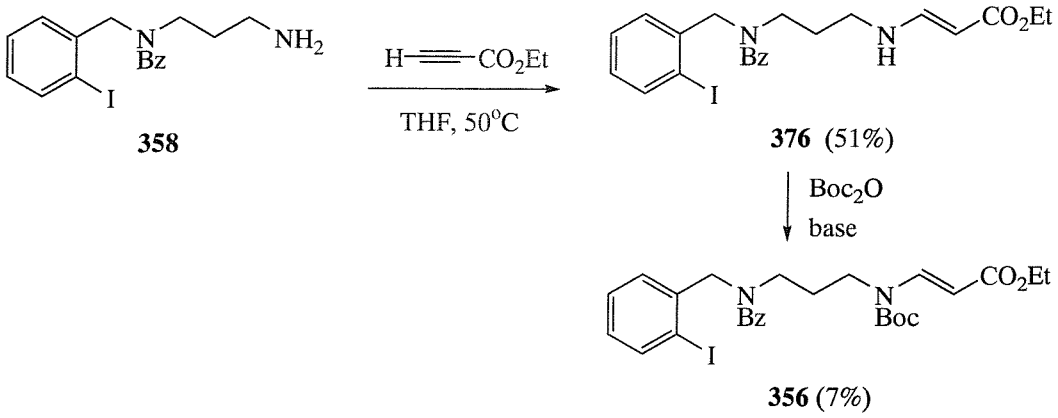


365 **374** (83%)

358 (quant.) **375** (84%)

Scheme 125

Coupling at 50°C in THF between **358** and ethyl propiolate to give enamine **376** (mixture of ca. 1:1 *E*:*Z*-isomers) in 51% yield in a small scale, gave only 10% yield when scaled up. Protecting **376** with Boc group gave an iodide precursor **356** in a low yield of 7% (**Scheme 126**).



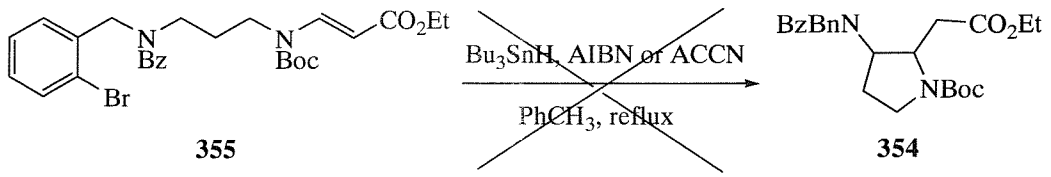
Scheme 126

3.3.3) Cyclisation of bromo- and iodo- substrates 355 and 356

Now that the synthetic routes to both the bromide and iodide precursors **355** and **356** had been developed (**Scheme 120 - 126**), the cyclisation of these precursors was attempted using two procedures described by Curran[123]: either refluxing the substrate together with Bu_3SnH and AIBN in toluene for 8 hours or slow (8 hour) addition of Bu_3SnH and AIBN to the substrate in refluxing toluene using a syringe pump.

I) Cyclisation of bromide substrate 355

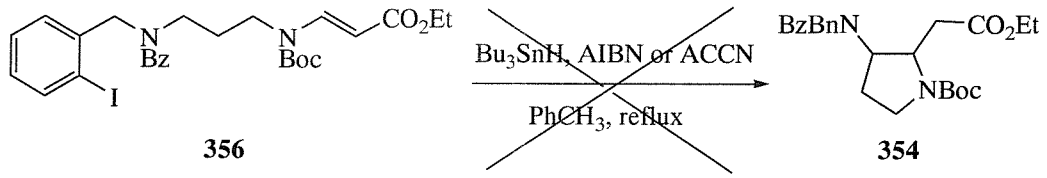
The cyclisation of substrate **355** with Bu_3SnH was attempted many times. Use of both AIBN and ACCN as radical initiators, did not give the cyclised products **354** but only the starting materials. Even a cyclisation with SmI_2 was investigated, but again failed to give the desired products **354**. Unfortunately all attempts seemed to result with nothing but starting material **355** (**Scheme 127**).



Scheme 127

II) Cyclisation of iodide substrate 356

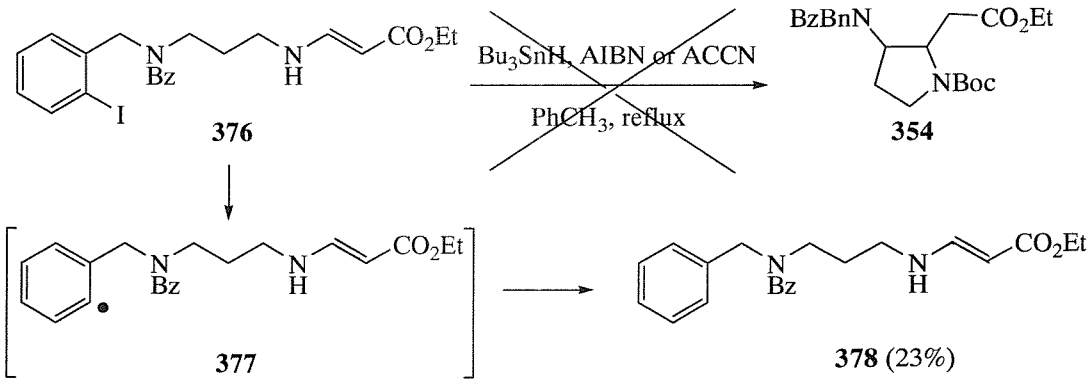
As the cyclisation of bromide substrate **355** struggled to give the cyclised product, and with the fact that in general only starting materials were recovered, we came to the conclusion that the bromide substrate **355** was not the best precursor to produce an aryl radical. The iodide compound **356** was our alternative choice for the cyclisation substrate. As $Bu_3Sn\bullet$ abstracts $I\bullet$ more easily than $Br\bullet$, the cyclisation of iodide **356** should be easier than with bromide **355**.



356 **354**

Scheme 128

However, treating iodide precursor **356** with Bu_3SnH and AIBN or ACCN using syringe-pump methods could not provide the desired product **354**. Recovery of only starting material again showed no signs of the generated aryl radical intermediate **(Scheme 128)**.



376 **354**

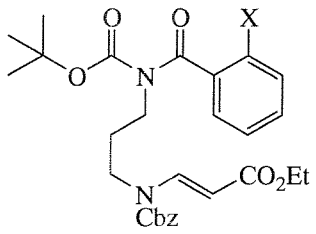
377 **378** (23%)

Scheme 129

The cyclisation with the unprotected iodide compound **376** was also investigated under the standard procedure. No signs of the cyclised product **354** were found, but deiodated compound **378** was recovered in 23% yield from the cyclisation **(Scheme 129)**. This data shows that the aryl radical intermediate **377** was generated, but it did not proceed with the 1,5-hydrogen atom translocation.

3.3.4) Alternative attempt

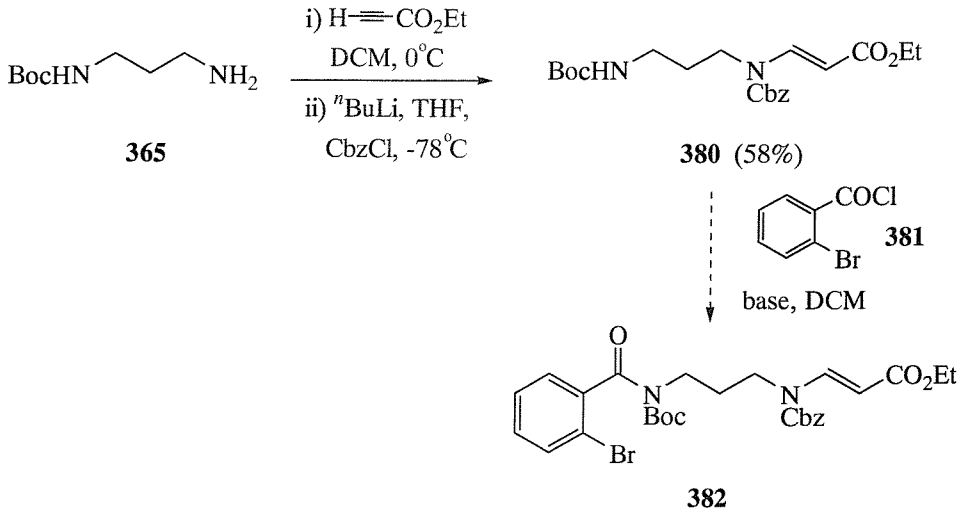
The synthesis of another alternative cyclisation precursor **379** was simultaneously attempted (**Figure 27**).



379

Figure 27

In order to avoid the low-yield-problem in the coupling reaction terminal alkyne (both bromide **355** and iodide **356** cases), the coupling reaction between mono-Boc protected diamino propane **365** and ethyl propiolate was carried out first in DCM at 0°C (**Scheme 130**). The crude oil from the coupling was directly treated with ^{n}BuLi in THF at –78°C and then with CbzCl to give enamide **380** in 58% yield. The next step was supposed to insert *o*-bromo-benzoyl group into **380**. Treatment of **380** with *o*-bromo-benzoyl chloride **381**, which easily synthesized by refluxing the corresponding *o*-bromo-benzoic acid in thionyl chloride, might give precursor **382**. However this strategy was abandoned, as the cyclisation of such systems (**355** and **356**) was not successful.



Scheme 130

3.3.5) Conclusion

The bromide and iodide precursors **355** and **356** were synthesized. However the cyclisations of these two substrates were not successful. The cyclisation of unprotected enamine **376** was also attempted, but only dehalogenated compound **378** was produced.

Chapter 4 Experimental Section

4.1) General Experimental

Solvents and reagents were purified according to the procedures outlined in Perin and Amarego, "Purification of Laboratory Chemicals", when required.[124]

All reactions requiring anhydrous conditions were conducted in flame dried glassware under a static, inert atmosphere unless otherwise stated. Where degassed solvents were used, a stream of Ar has been passed through them immediately prior to use.

Flash column chromatography was performed according to the procedure described by Still[125], using Sorbsil C60, 40-60 mesh silica gel (SiO_2).

Solvents were all commercial grade and used without further purification unless otherwise stated. THF was distilled from benzophenone ketal. Et_2O and toluene were distilled from sodium. DCM was distilled from CaH_2 and petroleum ether was distilled and the fraction boiling between 40°C and 60°C was used throughout.

4.2) Instrumental

Infrared spectra were recorded on a Bio-Rad Golden Gate ATR FT-IR spectrometer.

^{1}H-NMR spectra were all obtained at 300 MHz on a Bruker AC 300 and a Pfizer ASP 300 spectrometer, and at 400 MHz on a Bruker DPX400 spectrometer. Peak positions are quoted in ppm relative to the residual chloroform signal (δ = 7.27 ppm) or DMSO signal (δ = 2.40 ppm), using the following abbreviations: singlet (s), doublet (b), triplet (t), quartet (q), multiplet (m), broad singlet (br s), and broad multiplet (br m).

^{13}C-NMR spectra were all obtained at 75 MHz on a Bruker AC 300 and a Pfizer ASP 300 spectrometer, and at 100 MHz on a Bruker DPX400 spectrometer. The multiplicities of the signals are indicated in parentheses, using the following abbreviations: quaternary carbon (C), primary carbon (CH), secondary carbon (CH_2), and tertiary carbon (CH_3), and in some cases were elucidated using the distortionless

enhancement by phase transfer (DEPT) spectral editing technique with second pulse at 135°.

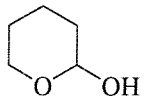
COSY, ^{13}C-^{1}H correlation, and NOE experiments were performed on a Bruker DPX 400 spectrometer.

Mass spectroscopy data was obtained on a ThermoQuest Trace MS gas chromatography mass spectrometer configured for open access operation.

Compounds were named using the program ACD/Name version 2.51 from Advanced Chemistry Development Inc. or naming program from ChemDraw version 5.0.

4.3) Experimental for *Chapter 2*

Tetrahydro-2-pyranol (207):



207

Following a method by Woods.[85]

Dihydropyran (20.0 g, 0.24 mol) was stirred at room temperature with *p*-TsOH (4.6 g, 0.1 eq) in 10% aq. THF (560 mL). The reaction mixture was poured into Et_2O (200 mL) and brine (200 mL). The aqueous layer was extracted by Et_2O (3x50 mL) and combined organic layers were washed with water (50 mL) and dried ($MgSO_4$). After the removal of solvent *in vacuo*, the crude product was distilled to give tetrahydro-2-pyranol **207** (15.0 g, 62%) as a colourless liquid.

b.p: 52-60°C/ 5 mmHg (lit.[85] 62-66°C/ 9-10 mmHg).

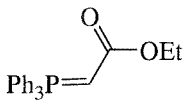
IR: ν_{max} (film)/cm^{-1} 3362 (br, OH), 2938 (s, CH_2), 2854 (CH), 1076 (s, COC).

δ_H (300 MHz, $CDCl_3$): 4.82 (1H, m, O*H*), 4.45 (1H, m, OC*H*OH), 4.05 (1H, m, CH_AH_BO), 3.55 (1H, m, CH_AH_BO), 1.90-1.75 (2H, m, CH_2CHOH), 1.60-1.40 (4H, m, CH_2CH_2).

δ_C (75.5 MHz, $CDCl_3$): 94.5 (CH), 63.9 (CH_2), 32.0 (CH_2), 25.3 (CH_2), 20.4 (CH_2).

Spectroscopically identical to that reported by Woods.[85]

Phosphono ethylacetate (209):



209

Based on a method published by Hanack.[86]

Ethyl bromoacetate **208** (44 g, 0.27 mol) was added into a round bottom flask, containing PPh_3 (70 g, 0.27 mol)/ 600 mL of Et_2O in it. The reaction mixture was stirred at room temperature for 18 hours. The white precipitate was filtered off after 4 hours, and

again after18 hours. Combined white precipitate was treated with 2M NaOH solution (500 mL) for 48 hours at room temperature. The reaction mixture was extracted with CH_2Cl_2 (5x120 mL). The combined organic extracts were washed with water (3x120 mL) and dried ($MgSO_4$). The solvent was removed *in vacuo* to give phosphono ethylacetate **209** (90 g, 96%) as colourless crystals.

m.p: 126-127°C (lit.[86] 128°C).

IR: ν_{max} (film)/cm^{-1} 2978 (CH_3), 2943 (CH_2), 2895 (CH), 1604 (s, CO), 1483 (PAr), 754 (PC).

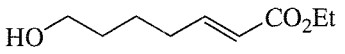
δ_H (300 MHz, $CDCl_3$): 7.75-7.45 (15H, m, Ar*H*), 3.50 (2H, q, *J* 7, CH_2CH_3), 1.95 (1H, s, *CH*CO), 1.21 (3H, t, *J* 7, CH_2CH_3).

δ_C (75.5 MHz, $CDCl_3$): 166.9 (C), 149.1 (C), 121.7 (CH), 121.7 (CH), 121.7 (CH), 62.6 (CH_2), 32.2 (CH), 14.4 (CH_3).

EI^+MS: *m/z* 349 ($[M + H]^+$, 100%).

The data was found to be consistent with that reported by Hanack.[86]

Ethyl (*E*)-7-hydroxy-2-heptenoate (210):



210

Using a method published by Tsai.[126]

Dihydro-2-pyranol **207** (10 g, 98 mmol) was stirred with ylide **209** (68 g, 196 mmol) together in DCM (400 mL) at room temperature for 66 hours. After the removal of solvent *in vacuo*, Et_2O (100 mL) was added to the resulting gum to initiate precipitation of Ph_3PO, which was removed by filtration. The crude product was purified by flash column chromatography (SiO_2) eluting with petroleum ether / Et_2O (1:1v/v). Alcohol **210** (14 g, 90%) was obtained as a colourless oil.

TLC: R_f = 0.13 (petroleum ether / EtOAc (3:1 v/v)).

IR: ν_{max} (film)/cm^{-1} 3427 (br, OH), 2979 (CH_3), 2940 (CH_2), 2875 (CH), 1716 (s, CO), 1653 (C=C).

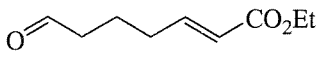
δ_H (300 MHz, $CDCl_3$): 6.95 (1H, dt, *J* 16, 7, C*H*=CHCO), 5.82 (1H, dt, *J* 16, 1, CH=C*H*CO), 4.18 (2H, q, *J* 7, CH_2CH_3), 3.64 (2H, t, *J* 6, CH_2OH), 2.23 (2H, dq, *J* 1, 7, CH_2CH=), 1.60-1.50 (4H, m, CH_2CH_2), 1.27 (3H, t, *J* 7, CH_2CH_3).

δ_C (75.5 MHz, $CDCl_3$): 166.9 (C), 149.1 (CH), 121.7 (CH), 62.6 (CH_2), 60.4 (CH_2), 32.2 (CH_2), 32.0 (CH_2), 25.2 (CH_2), 14.4 (CH_3).

CIMS: *m/z* 190 ($[M + NH_4^+]^+$, 5%), 173 ($[M + H]^+$, 90%), 127 ($[M - OEt^-]^+$, 100%).

Spectroscopic data were consistent with those reported by Tsai.[126]

Ethyl (*E*)-7-oxo-2-heptenoate (205):



205

Following the modified method of Swern oxidation by Bachi.[87,127]

Oxalyl chloride (1.38 mL, 15.8 mmol) in DCM (50 mL) was cooled to -78°C. DMSO (2.05 mL, 31.5 mmol) in DCM (20 mL) was added dropwise to reaction mixture at the temperature between -50°C and -60°C. After 2 minutes, alcohol **210** (2.00 g, 12.8 mmol) in DCM (10 mL) was added over 15 minutes keeping the temperature under -50°C and stirred for a further 15 minutes. TEA (8.76 mL, 63.0 mmol) was added (again temperature below -50°C) and the reaction mixture were allowed to warm to room temperature overnight. Water (100 mL) was added to the reaction mixture, washed with DCM (3x50 mL) and combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by column chromatography (SiO_2) eluting with EtOAc / petroleum ether (1:8 v/v) to give **205** (1.53 g, 78%) as a colorless oil.

TLC: R_f = 0.30 (petroleum ether / Et_2O (4:1 v/v)).

IR: ν_{max} (film)/cm^{-1} 2980 (CH_3), 2943 (CH_2), 2875 (CH), 2711 (w, CHO), 1716 (s, CO), 1653 (C=C).

δ_H (300 MHz, $CDCl_3$): 9.75 (1H, s, C*H*O), 6.89 (1H, dt, *J* 16, 7, C*H*=CHCO), 5.80 (1H, dt, *J* 16, 2, CH=C*H*CO), 4.13 (2H, q, *J* 7, CH_2CH_3), 2.47 (2H, dt, *J* 1, 7, CH_2CHO), 2.22 (2H, qd, *J* 7, 1, CH_2CH=), 1.77 (4H, quintet, *J* 7, 7, CH_2CH_2), 1.30 (3H, t, *J* 7, CH_2CH_3).

δ_C (75.5 MHz, $CDCl_3$): 201.8 (C), 166.6 (C), 147.7 (CH), 122.4 (CH), 60.4 (CH_2), 43.1 (CH_2), 31.4 (CH_2), 20.4 (CH_2), 14.4 (CH_3).

CIMS: *m/z* 188 ($[M + NH_4^+]^+$, 10%), 171 ($[M + H]^+$, 100%).

The data were found to be consistent with that reported by Weinges.[128]

General method for the synthesis of SmI_2 solution:

Following a modified version of methods by Molander[129] and Curran[130].

Excess I_2 was removed from ICH_2CH_2I by extraction with DCM and $Na_2S_2O_3$. Combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. THF was added to Samarium metal (2.5 equivalent relative to aldehyde or benzotriazole adduct precursor) in a previously thoroughly dried flask and stirred at room temperature under a flow of Ar, then purified ICH_2CH_2I (5 eq) was added. When the solution turned blue, it was allowed to stir for 90-120 minutes. Proton source such as MeOH, EtOH, or ^{t}BuOH (2.5 eq) was added and the solution turned deep dark green or purple.

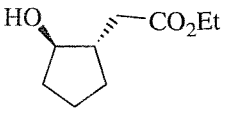
Normal addition[90]:

The precursor in THF was added dropwise into the solution of SmI_2 in THF at 0°C *via* syringe pump over 90 minutes if using HMPA or 30-60 minutes if using corresponding alcohol.

Reverse addition[90]:

The solution of SmI_2 in THF was added dropwise into the solution of precursor in THF over 30 minutes *via* cannular at 0°C.

(1S, 2R)-1- Ethoxy carbonyl-2-hydroxy-cyclopenatne (211) (Normal addition):



211

SmI_2 was prepared in *situ* from samarium metal (391 mg, 2.6 mmol) and ICH_2CH_2I (366 mg, 1.3 mmol) in THF (20 mL). After 90 minutes, HMPA (1.13 mL, 6.5

mmol) was added and the solution turned purple. Aldehyde precursor **205** (100 mg, 0.65 mmol), ^{t}BuOH (95 mg, 1.3 mmol) in THF (10 mL) was added over 90 minutes at 0°C. The reaction mixture was allowed to warm to room temperature overnight. The crude was washed by aq. citric acid (1g in 20 mL of water) and extracted with 50% EtOAc-hexane (3x25 mL). The combined organic extracts were washed with brine (70 mL), water (2x50 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude oil was purified by column chromatography (SiO_2) eluting with EtOAc / petroleum ether (2:3 v/v). The product **211** (30 mg, 30%) was obtained as a colourless oil.

TLC: R_f = 0.67 (petroleum ether / EtOAc (3:1 v/v)).

IR: ν_{max} (film)/cm^{-1} 3412 (br, OH), 2950 (CH_2), 2870 (CH), 1719 (s, CO), 1438 (cyclopentane).

δ_H (300 MHz, $CDCl_3$): 4.14 (2H, q, *J* 7, C*H*$_2$CH$_3$), 3.85 (1H, q, *J* 6, C*H*OH), 3.00 (1H, br s, O*H*), 2.32 (2H, m, C*H*$_2$CO$_2$Et), 2.05-1.80 (3H, m), 1.72-1.50 (3H, m), 1.24 (1H, m), 1.21 (3H, t, *J* 7, CH$_2$C*H*$_3$).

δ_C (75.5 MHz, $CDCl_3$): 174.3 (C), 80.0 (CH), 60.7 (CH_2), 44.6 (CH_2), 38.6 (CH), 34.4 (CH_2), 30.8 (CH_2), 22.0 (CH_2), 14.3 (CH_3).

CIMS: *m/z* 173 ([M + H]$^+$, 40%), 155 ([M – OH$^-$]$^+$, 100%).

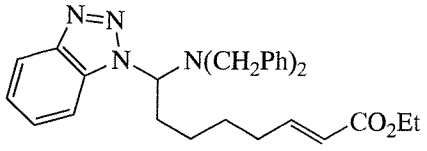
Spectroscopic data were found to be consistent with that reported by Pandey.[89]

General method for the synthesis of benzotriazole adducts:

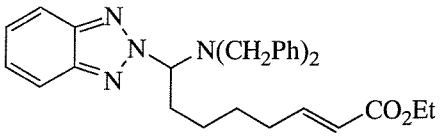
Following a modified version of method by Aurrecoechea.[78]

Dibenzyl amine (DBA) (1 eq) was added to aldehyde precursor (1eq) in dry Et_2O at 0°C in the presence of activated 4Å molecular sieves (by activating in microwave about 2-3 minutes immediately prior to use). After 5-15 minutes, benzotriazole (BTH) (1 eq) in Et_2O was added slowly into the reaction mixture at 0°C.

Ethyl (*E*)-7-(1,2,3-benzotriazolyl)-7-(dibenzylamino)-2-heptenoate (212A and B):



212A



212B

Benzotriazole adduct **212** was prepared *in situ* from DBA (102 mg, 0.52 mmol), aldehyde **205** (88 mg, 0.52 mmol), and BTH (62 mg, 1 eq) in Et_2O (20 mL). The reaction mixture was stirred for 15 minutes before being allowed to warm to room temperature and stirred overnight. The mixture was diluted with DCM (20 mL) and filtered through a celite filter aid. The solvent was removed *in vacuo*, to give crude benzotriazole adduct **212** (240 mg, 99%) as a yellow oil, and as a 1:1 mixture of 1-sustituetd isomer **A** : 2-sustituetd isomer **B**.

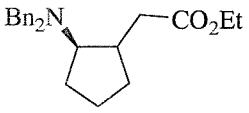
IR: ν_{max} (film)/cm^{-1} 3019 (ArH), 2933 (CH_2), 2854 (CH), 1719 (s, CO), 1651 (C=C).

δ_H (300 MHz, $CDCl_3$): 8.00 (0.5H, d, *J* 10, Ar*H*-4_A), 7.88-7.80 (1H, m, Ar*H*-$4,7_B$), 7.40-7.20 (12H, m, Ar*H*), 7.02 (0.5H, d, *J* 10, Ar*H*-7_A), 6.73 (1H, dt, *J* 16, 7, C*H*=CHCO), 5.57 (1H, dd, *J* 16, 7, CH=C*H*CO), 5.51 (0.39H, t, *J* 7, NCH_AN), 5.42 (0.61H, t, *J* 7, NCH_BN), 4.25 (2H, m, N(C$H_X$$H_Y$Ph)$_2$), 4.15 (2H, q, *J* 8, C$H_2$$CH_3$), 3.28 (2H, d, *J* 16, N(C$H_X$$H_{YA}$Ph)$_2$), 3.20 (2H, d, *J* 16, N(C$H_X$$H_{YB}$Ph)$_2$), 2.50-2.30 (2H, m, NCHCH_2), 2.10-1.90 (2H, m, CH_2CH=C), 1.60-1.40 (2H, m, CH_2C$H_2$$CH_2$), 1.20 (3H, t, *J* 8, CH_2CH_3).

CIMS: *m/z* 469 ([M + H]$^+$, 10%), 198 ([N(CH_2Ph)$_2$]$^+$, 100%).

The data were found to be consistent with that reported by Aurrecoechea.[78]

2-Dibenzylamino-1-ethoxycarbonyl methyl-cyclopentane (213) (Normal addition):



213

SmI_2 was prepared *in situ* from samarium metal (392 mg, 5 eq) and ICH_2CH_2I (410 mg, 2.6 eq) in dry THF (15 mL). After 2 hours, MeOH (0.06 ml, 2.6 eq) was added slowly to the SmI_2 solution at room temperature. Benzotriazole adduct **212** (200 mg, 0.43

mmol) in THF (5 mL) was added dropwise over 15 minutes maintaining the reaction temperature below 0°C. The reaction mixture was stirred for a further 90 minutes and then allowed to warm to room temperature overnight. The reaction mixture was treated with sat. aq. K_2CO_3 (30 mL), followed by washing with water (20 mL) and extracted with EtOAc (4x50 mL). The combined organic extracts were washed with water (20mL), brine (20mL) and dried ($MgSO_4$). The solvent was removed under reduced pressure to afford a yellow oil, which was purified by flash column chromatography (SiO_2) eluting with petroleum ether / EtOAc (7:1 → 5:1 v/v). Two fractions [R_f = 0.65 (DCM / EtOAc (3:1 v/v)) (90 mg, 60%) and R_f = 0.43 (DCM / EtOAc (3:1 v/v)) (6 mg, 4%)], corresponding to the two diastereomers of **213**, were collected. The product **213** (96 mg, 64%) was obtained as a colourless oil.

IR: ν_{max} (film)/cm^{-1} 3027 (Ar), 2938 (CH_2), 2867 (CH), 1730 (s, CO), 1452 (cyclopentane).

δ_H (300 MHz, $CDCl_3$): 7.43-7.23 (10H, m, ArH), 4.14 (2H, q, *J* 7, CH_2CH_3), 3.85 (1H, d, *J* 14, $CH_{Atrans}H_BPh$), 3.57 (2H, AB q, *J* 14, $CH_{2cis}Ph$), 3.41 (1H, d, *J* 14, $CH_AH_{Btrans}Ph$), 3.09 (1H, m, $CHNBn_2$), 2.90 (1H, dd, *J* 16, 4, $CH_AH_BCO_2Et$), 3.09 (1H, m, $CHCH_2CO_2Et$), 2.22 (1H, dd, *J* 16, 11, $CH_AH_BCO_2Et$), 1.88-1.50 (6H, m, $CH_2CH_2CH_2$), 1.30 (3H, t, *J* 7, CH_2CH_3).

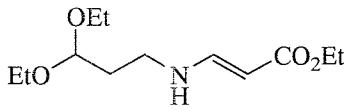
δ_C (75.5 MHz, $CDCl_3$): 174.1 (C_{cis}), 170.1(C_{trans}), 139.5 (C), 128.7 (CH), 128.1 (CH), 126.6 (CH), 65.5 (CH), 60.3 (CH_{2trans}), 60.1 (CH_{2cis}), 56.1 (CH_{2cis}), 54.6 (CH_{2trans}), 38.4 (CH), 33.7 (CH_2), 29.9 (CH_{2trans}), 29.4 (CH_{2cis}), 27.4 (CH_2), 21.3 (CH_{2cis}), 21.0 (CH_{2trans}), 14.2 (CH_{3cis}) 14.1 (CH_{3trans}).

ES^+MS: *m/z* 352 ($[M + H]^+$, 100%).

HRMS: *m/z* 352.2277 (calcd for $C_{23}H_{30}NO_2$, 352.2282).

The data were found to be consistent with that reported by Aurrecoechea.[78]

Ethyl-3-[(3,3-diethoxypropyl) amino]-2-propenoate (218):



218

Using a modified version of method by Macdonald.[80]

Ethyl propiolate (500 mg, 3.4 mmol) was added dropwise into 1-amino-3, 3-diethoxy propane **217** (330 mg, 1 eq) in Et_2O (10 mL) at 0°C. After 4 hours, the reaction was allowed to warm to room temperature, and then stirred for a further 16 hours. The solvent was removed *in vacuo* to give enamine **218** (826 mg, 100%) as a colourless oil and as a 4:5 mixture of *E* and *Z* isomers.

TLC: R_f = 0.45 (EtOAc / DCM (1:4 v/v)).

IR: ν_{max} (film)/cm^{-1} 3471 (br, NH), 2978 (CH_3), 2938 (CH_2), 1727 (s, CO), 1625 (s, C=C), 1130 (s, COC).

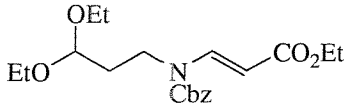
δ_H (300 MHz, $CDCl_3$): 7.81 (0.56H, br, (*Z*)-N*H*), 7.45 (0.44H, dd, *J* 13, 8, (*E*)-NC*H*=CH), 6.57 (0.56H, dd, *J* 13, 8, (*Z*)-NC*H*=CH), 5.17 (0.44H, br, (*E*)-N*H*), 4.67 (0.56H, d, *J* 13, (*Z*)- NCH=C*H*), 4.52 (1H, t, *J* 6, C*H*$(OEt)_2$), 4.40 (0.44H, d, *J* 8, (*E*)-NCH=C*H*), 4.08 (0.88H, q, *J* 7, (*E*)-$CO_2CH_2CH_3$), 4.06 (1.12H, q, *J* 7, (*Z*)-$CO_2CH_2CH_3$), 3.67-3.56 (2H, m, OCH_2CH_3), 3.52-3.41 (2H, m, OCH_2CH_3), 3.20 (1.12H, q, *J* 7, (*Z*)-CH_2CH_2NH), 3.09 (0.88H, q, *J* 7, (*E*)-CH_2CH_2NH), 1.88-1.75 (2H, dq, *J* 6, 7, $CH_2CH(OEt)_2$), 1.25-1.14 (9H, m, $CO_2CH_2CH_3$ and CH_2CH_3).

δ_C (75.5 MHz, $CDCl_3$): 170.9 (C_Z) and 169.8 (C_E), 152.3 (CH_E) and 149.2 (CH_Z), 102.1 (CH_E) and 100.8 (CH_Z), 85.4 (CH_Z) and 81.9 (CH_E), 62.1 (CH_{2E}) and 61.7 (CH_{2Z}), 59.0 (CH_{2E}) and 58.7 (CH_{2Z}), 44.8 (CH_2), 35.2 (CH_2), 15.4 (CH_3), 14.70 and 14.68 (CH_{3E+Z}).

ClMS: *m/z* 244 ($[M + H]^+$, 5%).

The data were found to be consistent with that reported by Macdonald.[80]

Ethyl (*E*)-3-[(benzyl carbonyl)(3,3-diethoxy propyl) amino]-2-propenoate (219):



219

Based on a method by Macdonald.[80]

The enamine **218** (300 mg, 1.22 mmol) was dissolved in THF (10 mL) under argon and cooled to -78°C. ^{n}BuLi (0.49 mL, 1 eq) was added dropwise over 10 minutes to give a yellow-green solution. After 30 minutes, CbzCl (0.17 mL, 1 eq) in 5 mL of THF was added dropwise over 15 minutes, and the cooling bath was removed immediately. The reaction mixture was allowed to warm to room temperature overnight. The solvent was removed *in vacuo*. The crude oil was purified by column chromatography (SiO_2) eluting with EtOAc / DCM (1:8 v/v) to give an enamide **219** (426 mg, 92%) as a colourless oil.

TLC: R_f = 0.72 (petroleum ether / Et_2O (3:2 v/v)).

IR: ν_{max} (film)/cm^{-1} 2978 (CH_3), 2928 (CH_2), 1725 (s, CO), 1702 (s, CO), 1626 (s, C=C), 1128 (s, COC).

δ_H (300 MHz, $CDCl_3$): 8.22 (1H, d, *J* 14, NC*H*=CH), 7.43-7.33 (5H, m, Ar*H*), 5.32 (1H, d, *J* 14, NCH=C*H*), 5.26 (2H, s, CH_2Ph), 4.50 (1H, t, *J* 6, C*H*$(OEt)_2$), 4.19 (2H, q, *J* 7, CH_2CH_3), 3.65 (4H, m, OCH_2CH_3), 3.45 (2H, m, NCH_2 CH_2), 1.88 (2H, dt, *J* 6, 6, NCH_2CH_2), 1.22-1.15 (9H, t, *J* 7, OCH_2CH_3 and $CO_2CH_2CH_3$).

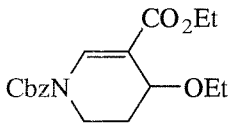
δ_C (75.5 MHz, $CDCl_3$): 167.8 (C), 142.1 (CH), 135.4 (C), 128.8 (CH), 128.7 (CH), 128.5 (CH), 100.9 (C), 98.6 (CH), 81.9 (CH), 69.0 (CH_2), 61.7 (CH_2), 60.5 (CH_2), 40.9 (CH_2), 31.2 (CH_2), 15.4 (CH_3), 14.5 (CH_3).

ES$^+$MS: *m/z* 425.29 ([M + 2Na]$^+$, 10%), 402.27 ([M + Na]$^+$, 15%), 380.30 ([M + H]$^+$, 5%).

HRMS: *m/z* 402.1876 (calcd for $C_{20}H_{29}NO_6Na$, 402.1983).

The data were found to be consistent with that reported by Macdonald.[78]

1-Benzyl 3-ethyl 4-ethoxy-1,4,5,6-tetrahydro-1,3-pyridine dicarboxylate (220):



220

Acetal **219** (200 mg, 0.53 mmol) was stirred with *p*-TsOH (150 mg, 0.69 mmol) in 10% aq. acetone (100 mL) overnight. The solvent was removed *in vacuo*, and the

residue was redissolved in Et_2O (50 mL) and washed with $NaHCO_3$ (50 mL). The aqueous layer was extracted by Et_2O (3x30 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude oil was purified by flash column chromatography (SiO_2) eluting with petroleum ether / EtOAc (1:1 v/v) to give **220** (60 mg, 35%) as a colourless oil.

TLC: R_f = 0.55 (petroleum ether / EtOAc (1:1 v/v)).

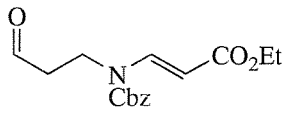
IR: ν_{max} (film)/cm^{-1} 2974 (CH_3), 2928 (CH_2), 1727 (s, CO), 1698 (s, CO), 1628 (s, C=C), 1190 (s, COC).

δ_H (300 MHz, $CDCl_3$): 8.14 (1H, br s, C*H*=CCO_2Et), 7.50-7.30 (5H, m, Ar*H*), 5.18 (2H, s, PhCH_2), 4.27 (1H, s, C*H*OEt), 4.14 (2H, q, *J* 7, CH_2CH_3), 4.00 (1H, br m, NCH_AH_B), 3.53 (2H, q, *J* 7, CH_2CH_3), 3.30 (1H, br m, NCH_AH_B), 2.03 (1H, br m, $NCH_2CH_AH_B$), 1.46 (1H, m, $NCH_2CH_AH_B$), 1.23 (3H, t, *J* 7, CH_2CH_3), 1.12 (3H, t, *J* 7, CH_2CH_3).

δ_C (75.5 MHz, $CDCl_3$): 167.1 (C), 137.7 (CH), 135.5 (C), 128.8 (CH), 128.7 (C), 128.4 (CH), 68.7 (CH_2), 65.9 (CH), 64.4 (CH_2), 60.3 (CH_2), 37.8 (CH_2), 26.0 (CH_2), 15.8 (CH_3), 15.8 (CH), 14.5 (CH_3).

ES^+MS: *m/z* 342 ($[M + Na]^+$, 20%).

Ethyl (*E*)-3-[(benzyloxy carbonyl)(3-oxo-propyl) amino]-2-propenoate (215):



215

Following a method published by Macdonald.[78]

Acetal **219** (2.02 g, 6.8 mmol) was refluxed with *p*-TsOH (2.02 g, 6.8 mmol) in 20% aq. acetone (180 mL) for 3 hours. The reaction mixture was diluted with Et_2O (200 mL) and washed with aq. $NaHCO_3$ (50 mL). The aqueous layer was extracted with Et_2O (3x20 mL). The combined organic extracts were dried ($MgSO_4$), and the solvent was removed *in vacuo*. The crude oil was purified by column chromatography (SiO_2) eluting with petroleum ether / EtOAc (8:1 → 3:1 v/v) to give aldehyde **215** (115 mg, 90%) as a colourless oil.

TLC: R_f = 0.47 (petroleum ether / EtOAc (2:1 v/v)).

IR: ν_{max} (film)/cm^{-1} 2933 (CH_2), 2652 (w, CHO), 1722 (s, CO), 1695 (s, CO), 1625 (s, C=C), 1190 (s, COC).

δ_H (300 MHz, $CDCl_3$): 9.77 (1H, s, CHO), 8.20 (1H, d, *J* 15, NC*H*=CH), 7.40-7.30 (5H, m, Ar*H*), 5.28 (2H, s, CH_2Ph), 5.23 (1H, d, *J* 15, NCH=C*H*), 4.22 (2H, q, *J* 7, CH_2CH_3), 3.93 (2H, t, *J* 7, NHCH_2CH_2), 2.77 (2H, t, *J* 7, CH_2CH_2NH), 1.29 (3H, t, *J* 7, CH_2CH_3).

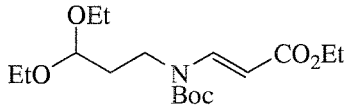
δ_C (75.5 MHz, $CDCl_3$): 199.4 (C), 171.1 (C), 167.3 (C), 153.2 (C), 141.5 (CH), 135.1 (CH), 128.8 (CH), 128.5 (CH), 98.6 (CH), 69.1 (CH_2), 60.2 (CH_2), 41.1 (CH_2), 38.3 (CH_2), 14.4 (CH_3).

ES$^+$MS: *m/z* 306 ([M + H]$^+$, 50%), 276 ([M – Et$^-$]$^+$, 100%).

HRMS: *m/z* 306.1329 (calcd for $C_{16}H_{20}NO_5$, 306.1341).

The data were found to be consistent with that reported by Macdonald.[78]

Ethyl (*E*)-3-[(*tert*-butoxy carbonyl)(3,3-diethoxy propyl) amino]-2-propenoate (222):



222

Enamine **218** (9.1 g, 37.0 mmol), TEA (7.7 mL, 1.5 eq), and DMAP (0.9 g, 0.2 eq) were dissolved in DCM (450 mL). Boc_2O (8.1 g, 1 eq) in 20 mL of DCM was added dropwise to the reaction mixture at 0°C. The reaction mixture was allowed to warm to room temperature overnight. The reaction was quenched with dil. aq. HCl (2x100 mL), followed by washing with water (2x50 mL). Aqueous layer was extracted with DCM (4x20 mL). The combined organic extracts were dried ($MgSO_4$). The solvent was removed *in vacuo*. After purification by column chromatography (SiO_2) eluting with EtOAc / petroleum ether (1:5 → 1:3 (v/v)), protected enamine **222** (9.0 g, 70%) was obtained as a colourless oil.

TLC: R_f = 0.45 (petroleum ether / EtOAc (3:1 v/v)).

IR: ν_{max} (film)/cm^{-1} 2977 (CH_3), 2935 (CH_2), 1724 (s, CO), 1701 (s, CO), 1623 (s, C=C), 1132 (s, COC).

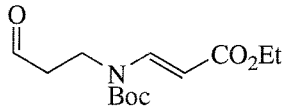
δ_H (300 MHz, $CDCl_3$): 7.90 (1H, d, *J* 14, NC*H*=CH), 4.99 (1H, d, *J* 14, NCH=C*H*), 4.28 (1H, t, *J* 6, *CH*$(OEt)_2$), 3.92 (2H, q, *J* 7, $CO_2CH_2CH_3$), 3.39 (4H, m, OCH_2CH_3), 3.20 (2H, m, $NHCH_2$ CH_2), 1.60 (2H, dt, *J* 6, 7, $NHCH_2CH_2$), 1.26 (9H, s, $C(CH_3)_3$), 1.01 (3H, t, *J* 7, $CO_2CH_2CH_3$), 0.95 (6H, t, *J* 7, OCH_2CH_3).

δ_C (75.5 MHz, $CDCl_3$): 167.1 (C), 151.3 (C), 141.9 (CH), 100.2 (CH), 96.5 (CH), 82.2 (C), 60.9 (CH_2), 59.1 (CH_2), 39.8 (CH_2), 30.6 (CH_2), 27.4 (CH_3), 14.7 (CH_3), 13.8 (CH_3).

ES^+MS: *m/z* 346 $([M + H]^+$, 20%), 300 $([M - OEt^-]^+$, 60%), $([M - Boc]^+$, 100%).

HRMS: *m/z* 368.2052 (calcd for $C_{17}H_{31}NO_6Na$, 368.2049).

Ethyl (*E*)-3-[(*tert*-butoxycarbonyl)(3-oxo propyl) amino}-2-propenoate (216):



216

Using a method described by Macdonald.[78]

Acetal **222** (100 mg, 0.29 mmol) was stirred with *p*-TsOH (72 mg, 1.3 eq) in 20% aq. acetone (30 mL) at room temperature for 3 days. The reaction mixture was diluted with Et_2O (20 mL) and washed with aq. $NaHCO_3$ (10 mL). The aqueous layer was washed with water (10 mL), extracted with Et_2O (2x15 mL). The combined organic extracts were dried ($MgSO_4$), and the solvent was removed *in vacuo*. The crude oil was purified by column chromatography (SiO_2) eluting with petroleum ether / EtOAc (5:1 → 3:1 v/v) to give aldehyde **216** (70 mg, 70%) as a colourless oil.

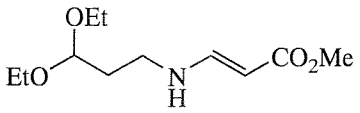
TLC: R_f = 0.21 (petroleum ether / EtOAc (3:1 v/v)).

IR: ν_{max} (film)/cm^{-1} 2979 (CH_3), 2935 (CH_2), 2670 (w, CHO), 1722 (s, CO), 1702 (s, CO), 1623 (s, C=C), 1140 (s, COC).

δ_H (300 MHz, $CDCl_3$): 9.79 (1H, s, CHO), 8.16 (1H, d, *J* 15, NC*H*=CH), 5.13 (1H, d, *J* 15, NCH=C*H*), 4.17 (2H, q, *J* 7, CH_2CH_3), 3.88 (2H, t, *J* 7, $NHCH_2CH_2$), 2.72 (2H, t, *J* 7, CH_2CH_2NH), 1.54 (9H, s, $C(CH_3)_3$), 1.29 (3H, t, *J* 7, CH_2CH_3).

δ_C (75.5 MHz, $CDCl_3$): 199.7 (CHO), 167.7 (C), 151.9 (C), 142.1 (CH), 97.4 (CH), 83.9 (C), 60.2 (CH_2), 41.3 (CH_2), 38.0 (CH_2), 28.2 (CH_3), 14.2 (CH_3).

Methyl-3-[(3,3-diethoxy propyl) amino]-2-propenoate (225):



225

Using a modified version of method by Macdonald.[78]

Methyl propiolate (285 mg, 3.4 mmol) was added dropwise to 1-amino-3,3-diethoxy propane **217** (500 mg, 1 eq) in Et_2O (20 mL) at 0°C. The reaction mixture was stirred at 0°C for 5 hours, before being allowed to warm to room temperature overnight. The solvent was removed *in vacuo* to give enamine **225** (753 mg, 97%) as a bright yellow oil and as a 1:1.4 mixture of *Z* and *E* isomers.

TLC: R_f = 0.30 (petroleum ether / Et_2O (1:3 v/v)).

IR: ν_{max} (film)/cm^{-1} 3334 (br, NH), 2975 (CH_3), 2932 (CH_2), 2878 (CH), 1671 (s, CO), 1611 (s, C=C), 1148 (s, COC).

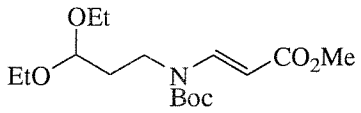
δ_H (300 MHz, $CDCl_3$): 7.80 (0.4H, br s, (*Z*)-NH), 7.68 (0.6H, dd, *J* 8, 13, (*E*)-NHC*H*=CH), 6.58 (0.4H, dd, *J* 8, 13, (*Z*)-NHC*H*=CH), 5.15 (0.6H, br s, (*E*)-NH), 4.67 (0.6H, d, *J* 13, (*E*)-CH=C*H* CO_2Me), 4.54 (1H, t, *J* 5, C*H*$(OEt)_2$), 4.43 (0.4H, d, *J* 8, (*Z*)-CH=C*H*CO_2Me), 3.70-3.60 (2H, m, $OCH_AH_BCH_3$), 3.62 (1.8H, s, (*E*)-CO_2CH_3), 3.60 (1.2H, s, (*Z*)-CO_2CH_3), 3.52-3.42 (2H, m, $OCH_AH_BCH_3$), 3.24 (0.8H, q, *J* 7, (*Z*)-CH_2CH_2NH), 3.11 (1.2H, q, *J* 6, (*E*)-CH_2CH_2NH), 1.91-1.77 (2H, m, $CHCH_2CH_2$), 1.18 (6H, t, *J* 7, OCH_2CH_3).

δ_C (75.5 MHz, $CDCl_3$): 171.2 (C_Z) and 170.2 (C_E), 152.4 (CH_E) and 149.3 (CH_Z), 102.1 (CH_E) and 101.9 (CH_Z), 85.0 (CH_Z) and 81.5 (CH_E), 62.1 (CH_{2E}) and 61.7 (CH_{2Z}), 50.6 (CH_{3E}) and 50.3 (CH_{3Z}), 44.8 (CH_2), 35.2 (CH_2), 15.4 (CH_3).

CIMS: *m/z* 232 ($[M + H]^+$, 8%), 186 ($[M - OEt^-]^+$, 100%).

HRMS: *m/z* 254.1360 (calcd for $C_{11}H_{21}NO_4Na$, 254.1363).

Methyl (*E*)-3-[(*tert*-butoxy carbonyl)(3,3-diethoxy propyl) amino]-2-propenoate (226):



226

Enamine **225** (230 mg, 1 mmol), TEA (151 mg, 1.5 eq), and DMAP (24.4 mg, 0.2 eq) were dissolved in DCM (20 mL). Boc_2O (218 mg, 1 eq) was added dropwise to the reaction mixture at 0°C. The reaction mixture was stirred further at room temperature overnight. The reaction was quenched with dil. aq. HCl (20 mL) followed by washing with water (2x20 mL). The aqueous layer was extracted with DCM (3x10 mL), and the combined organic layers were dried ($MgSO_4$). After removal of solvent *in vacuo*, the crude oil was purified by column chromatography eluting with EtOAc / petroleum ether (1:7 → 1:3 v/v) to give carbamate **226** (170 mg, 51%) as a colourless oil.

TLC: R_f = 0.57 (petroleum ether / diethyl ether (1:3 v/v)).

IR: ν_{max} (film)/cm^{-1} 2977 (CH_3), 2932 (CH_2), 2879 (CH), 1719 (s, CO), 1700 (s, CO), 1624 (s, C=C), 1132 (s, COC).

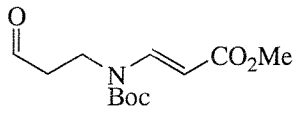
δ_H (300 MHz, $CDCl_3$): 8.13 (1H, d, *J* 14, NC*H*=CH), 5.18 (1H, d, *J* 14, NCH=C*H*), 4.45 (1H, t, *J* = 5, C*H*$(OEt)_2$), 3.67 (3H, s, CO_2CH_3), 3.63-3.52 (2H, m, CH_2CH_2NH), 3.42 (4H, q, *J* 7, OCH_2CH_3), 1.81 (2H, m, $CHCH_2CH_2$), 1.47 (9H, s, CH_3), 1.15 (3H, t, *J* 7, OCH_2CH_3), 1.14 (3H, t, *J* 7, OCH_2CH_3).

δ_C (75.5 MHz, $CDCl_3$): 168.4 (C), 152.0 (C), 142.8 (CH), 100.8 (CH), 96.7 (CH), 83.1 (C), 61.6 (CH_2), 51.3 (CH_3), 40.4 (CH_2), 31.2 (CH_2), 28.1 (CH_3), 15.3 (CH_3)

ES^+MS: *m/z* 354 ($[M + Na]^+$, 100%).

HRMS: *m/z* 354.1888 (calcd for $C_{16}H_{29}NO_6$ Na, 354.1887).

Methyl (*E*)-3-[(*tert*-butoxy carbonyl)(3-oxo propyl) amino]-2-propenoate (223):



223

Using a method described by Macdonald.[78]

Acetal **226** (1 g, 3.02 mmol) and *p*-TsOH (750 mg, 1.3 eq) were stirred together in 20% aq. acetone (300 mL) for 3 days. The mixture was diluted with Et_2O (200 mL), and quenched with sat. aq. $NaHCO_3$ (100 mL). The aqueous layer was extracted with Et_2O (3x100 mL), and the combined organic layers were dried ($MgSO_4$). The solvent was removed *in vacuo*. The crude oil was purified by column chromatography eluting with EtOAc / petroleum ether (1:10 → 1:5 v/v) to give aldehyde **223** (530 mg, 68%) as a colourless oil.

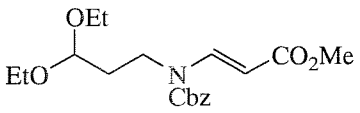
TLC: R_f = 0.27 (EtOAc / petroleum ether (3:7 v/v)).

IR: ν_{max} (film)/cm^{-1} 2978 (CH_3), 2953 (CH_2), 2750 (w, CHO), 1714 (s, CO), 1708 (s, CO), 1623 (s, C=C), 1140 (s, COC).

δ_H (300 MHz, $CDCl_3$): 9.78 (1H, s, CHO), 8.13 (1H, d, *J* 14, NC*H*=CH), 5.13 (1H, d, *J* 14, NCH=C*H*), 3.86 (2H, t, *J* 7, CH_2CH_2N), 3.71 (3H, s, CO_2CH_3), 2.72 (2H, t, *J* 7, CH_2CH_2N), 1.51 (9H, s, $(CH_3)_3C$).

δ_C (75.5 MHz, $CDCl_3$): 199.6 (CH), 168.1 (C), 151.8 (C), 142.3 (CH), 97.0 (CH), 83.9 (C), 51.5 (CH_3), 41.2 (CH_2), 38.0 (CH_2), 28.1 (CH_3).

Methyl (*E*)-3-[(benzyloxy carbonyl)(3,3-diethoxy propyl) amino]-2-propenoate (227):



227

Based on a method by Macdonald.[78]

2.05 M of ^{n}BuLi in hexane (0.61 mL, 1 eq) was added dropwise to a solution of methyl ester **225** (300 mg, 1.3 mmol) in THF (10 mL) at -78°C. After 30 minutes, CbzCl (220 mg, 1 eq) in THF (5 mL) was added slowly over 20 minutes at -78°C, and then the reaction was allowed to warm to room temperature overnight. The reaction was quenched with aq. sol. NH_4Cl (10 mL), washed with water (10 mL). The aqueous layer was extracted with EtOAc (3x10 mL), and the combined organic layers were dried ($MgSO_4$) and the solvent was removed *in vacuo*. The crude was purified by column chromatography eluting with EtOAc / petroleum ether (1:10 → 1:8 v/v) to give carbamate **227** (100 mg, 25%) as a colourless oil.

TLC: R_f = 0.47 (EtOAc / petroleum ether (3:7 v/v)).

IR: ν_{max} (film)/cm^{-1} 3067 (Ar), 3034 (Ar), 2975 (CH_3), 2930 (CH_2), 2883 (CH), 1731 (s, CO), 1715 (s, CO), 1627 (s, C=C), 1137 (s, COC).

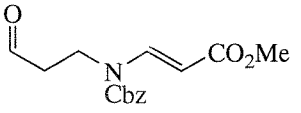
δ_H (300 MHz, $CDCl_3$): 8.23 (1H, d, *J* 14, NC*H*=CH), 7.38 (5H, m, ArH), 5.32 (1H, d, *J* 14, NCH=C*H*), 5.28 (2H, s, CH_2Ph), 4.00 (1H, t, *J* 6, C*H*$(OEt)_2$), 3.73 (3H, s, CO_2CH_3), 3.72-3.57 (4H, m, OCH_2CH_3), 3.46 (2H, m, CH_2CH_2N), 1.91 (2H, q, *J* 6, CH_2CH_2N), 1.20 (6H, t, *J* 7, OCH_2CH_3).

δ_C (75.5 MHz, $CDCl_3$): 168.2 (C), 142.3 (CH), 135.3 (C), 128.83 (CH), 128.76 (CH), 128.5 (CH), 127.1 (C), 100.8 (CH), 98.2 (CH), 69.0 (CH_2), 61.7 (CH_2), 51.5 (CH_3), 40.9 (CH_2), 31.2 (CH_2), 15.4 (CH_3).

ES$^+$MS: *m/z* 753 ([2M + Na]$^+$, 100%), 388 ([M + Na]$^+$, 50%), 320 ([M - OEt$^-$]$^+$, 40%).

HRMS: *m/z* 388.1730 (calcd for $C_{19}H_{27}NO_6$ Na, 388.1731).

Methyl (*E*)-3-[(benzyloxy carbonyl)(3-oxo propyl) amino]-2-propenoate (224):



224

Using a method described by Macdonald.[78]

Acetal **227** (100 mg, 0.27 mmol) and *p*-TsOH (63 mg, 1.2 eq) were stirred together in 20% aq. acetone (25 mL) for 4 days. The mixture was diluted with Et_2O (20 mL), and quenched with sat. aq. $NaHCO_3$ (20 mL). Aqueous layer was extracted with

Et_2O (2x15 mL). Combined organic layers were dried ($MgSO_4$), and the solvent was removed *in vacuo*. The crude oil was purified by column chromatography eluting with EtOAc / petroleum ether (1:9 → 1:5 v/v) to give aldehyde **224** (20 mg, 25%) as a colourless oil.

TLC: R_f = 0.27 (EtOAc / petroleum ether (3:7 v/v)).

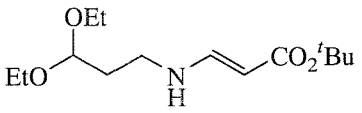
IR: ν_{max} (film)/cm^{-1} 3094 (Ar), 3033 (Ar), 2952 (CH_2), 2852 (w, CHO), 2733 (w, CHO), 1712 (s, CO), 1625 (s, C=C), 1155 (s, COC).

δ_H (300 MHz, $CDCl_3$): 9.79 (1H, s, CHO), 8.20 (1H, d, *J* 15, NC*H*=CH), 7.40 (5H, m, ArH), 5.27 (2H, s, CH_2Ph), 5.23 (1H, d, *J* 15, NCH=C*H*), 3.94 (2H, t, *J* 6, CH_2CH_2N), 3.74 (3H, s, CO_2CH_3), 2.77 (2H, t, *J* 6, CH_2CH_2N).

δ_C (75.5 MHz, $CDCl_3$): 199.2 (CH), 167.7 (C), 142.5 (CH), 134.9 (C), 128.8 (CH), 128.7 (CH), 128.5 (CH), 127.1 (C), 98.2 (CH), 69.2 (CH), 51.5 (CH_3), 41.0 (CH_2), 38.2 (CH_2).

CIMS: *m/z* 292 ($[M + H]^+$, 10%), 248 ($[M - OEt^-]^+$, 27%).

***tert*-Butyl-3-[(3,3-diethoxy propyl) amino]-2-propenoate (230):**



230

Using a modified version of method by Macdonald.[78]

tert-Butyl propiolate (1.26 g, 10 mmol) in Et_2O (5 mL) was added dropwise to 1-amino-3,3-diethoxy propane **217** (1.47 g, 1 eq) in Et_2O (60 mL) at 0°C. The reaction mixture was stirred at 0°C for 4 hours, before being allowed to warm to room temperature overnight. The solvent was removed *in vacuo* to give enamine **230** (2.68 g, 98%) as a colourless oil, and as a 1:2.7 mixture of *Z* and *E* isomers.

TLC: R_f = 0.45 (cyclohexane / Et_2O (1:2 v/v)).

IR: ν_{max} (film)/cm^{-1} 3335 (br, NH), 2974 (CH_3), 2930 (CH_2), 2877 (CH), 1662 (s, CO), 1612 (s, C=C), 1120 (s, COC).

δ_H (300 MHz, $CDCl_3$): 7.78 (0.3H, br s, (*Z*)-NH), 7.40 (0.7H, dd, *J* 8, 13, (*E*)-NHC*H*=CH), 6.53 (0.3H, dd, *J* 8, 13, (*Z*)-NHC*H*=CH), 4.94 (0.7H, br s, (*E*)-NH), 4.65

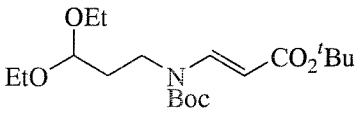
(0.7H, d, *J* 13, (*E*)-CH=C*H*CO_2Me), 4.55 (1H, t, *J* 5, C*H*$(OEt)_2$), 4.37 (0.3H, d, *J* 8, (*Z*)-CH=C*H*CO_2Me), 3.65 (2H, dq, *J* 9, 7, $OCH_AH_BCH_3$), 3.49 (2H, dq, *J* 9, 7, $OCH_AH_BCH_3$), 3.23 (0.6H, q, *J* 7, (*Z*)-CH_2CH_2NH), 3.11 (1.4H, q, *J* 6, (*E*)-CH_2CH_2NH), 1.90-1.81 (2H, m, $CHCH_2CH_2$), 1.46 (9H, s, $C(CH_3)_3$), 1.21 (6H, t, *J* 7, OCH_2CH_3).

δ_C (75.5 MHz, $CDCl_3$): 171.0 (C_Z) and 169.0 (C_E), 151.9 (CH_E) and 148.5 (CH_Z), 102.0 (CH_E) and 100.7 (CH_Z), 87.3 (CH_Z) and 83.5 (CH_E), 78.2 (C), 61.9 (CH_{2E}) and 61.4 (CH_{2Z}), 45.0 (CH_2), 35.1 (CH_2), 28.5 (CH_3), 15.3 (CH_3).

CIMS: *m/z* 274 ($[M + H]^+$, 80%).

HRMS: *m/z* 296.1829 (calcd for $C_{14}H_{27}NO_4Na$, 296.1832).

tert-Butyl (*E*)-3-[(_tert_-butoxy carbonyl)(3,3-diethoxy propyl)amino]-2-propenoate (231):



231

Enamine **230** (713 mg, 2.61 mmol), TEA (397 mg, 1.5 eq), and DMAP (64 mg, 0.2 eq) were dissolved in DCM (55 mL). Boc_2O (570 mg, 1 eq) in DCM (10 mL) was added dropwise to the reaction mixture at 0°C. The reaction mixture was stirred further at room temperature overnight. The reaction was quenched with dil. aq. HCl (50 mL) followed by washing with water (2x50 mL). The aqueous layer was extracted with DCM (3x50 mL), and the combined organic layers were dried ($MgSO_4$). After removal of solvent *in vacuo*, the crude oil was purified by biotage column chromatography eluting with EtOAc / cyclohexane (1:9 → 1:5 v/v) to give carbamate **231** (362 mg, 37%) as a colourless oil.

TLC: R_f = 0.52 (cyclohexane / Et_2O (1:2 v/v)).

IR: ν_{max} (film)/cm^{-1} 2976 (CH_3), 2932 (CH_2), 2874 (CH), 1724 (s, CO), 1702 (s, CO), 1623 (s, C=C), 1124 (s, COC).

δ_H (300 MHz, $CDCl_3$): 8.09 (1H, d, *J* 14, NC*H*=CH), 5.16 (1H, d, *J* 14, NCH=C*H*), 4.48 (1H, t, *J* = 6, C*H*$(OEt)_2$), 3.65 (2H, dq, *J* 9, 7, $OCH_AH_BCH_3$), 3.60 (2H, t, *J* 7,

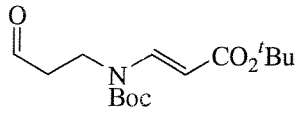
CH_2CH_2NH), 3.50 (2H, dq, *J* 9, 7, $OCH_AH_BCH_3$), 1.87 (2H, dt, *J* 6, 7, $CHCH_2CH_2$), 1.53 (9H, s, $C(CH_3)_3$), 1.47 (9H, s, $C(CH_3)_3$), 1.22 (6H, t, *J* 7, OCH_2CH_3).

δ_C (75.5 MHz, $CDCl_3$): 168.0 (C), 147.2 (C), 142.1 (CH), 100.8 (CH), 99.0 (CH), 83.3 (C), 79.8 (C), 61.5 (CH_2), 40.3 (CH_2), 31.2 (CH_2), 28.0 (CH_3), 27.4 (CH_3), 15.3 (CH_3)

ES^+MS: *m/z* 396 ($[M + Na]^+$, 100%).

HRMS: *m/z* 396.2344 (calcd for $C_{19}H_{35}NO_6Na$, 396.2356).

tert-Butyl (*E*)-3-[(_tert_-butoxy carbonyl)(3-oxo propyl)amino]-2-propenoate (228):



228

Using a method described by Macdonald.[78]

Acetal **231** (1.0 g, 2.68 mmol) and *p*-TsOH (750 mg, 1.3 eq) were stirred together in 20% aq. acetone (244 mL) for 3 days. The mixture was diluted with Et_2O (150 mL), and quenched with sat. aq. $NaHCO_3$ (100 mL). The aqueous layer was extracted with Et_2O (3x100 mL), and the combined organic layers were dried ($MgSO_4$). The solvent was removed *in vacuo*. The crude oil was purified by column chromatography eluting with EtOAc / cyclohexane (1:9 → 1:6 v/v) to give an aldehyde **228** (630 mg, 79%) as a colourless oil.

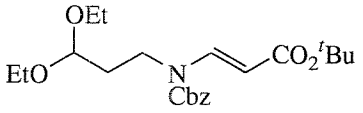
TLC: R_f = 0.37 (cyclohexane / Et_2O (1:2 v/v)).

IR: ν_{max} (film)/cm^{-1} 2976 (CH_3), 2933 (CH_2), 2829 (w, CHO), 2729 (w, CHO), 1719 (s, CO), 1701 (s, CO), 1622 (s, C=C), 1124 (s, COC).

δ_H (300 MHz, $CDCl_3$): 9.76 (1H, s, CHO), 8.02 (1H, d, *J* 14, NC*H*=CH), 5.02 (1H, d, *J* 14, CH=C*H*CO_2Bu), 3.83 (2H, t, *J* 7, CH_2CH_2NH), 2.70 (2H, t, *J* 7, $CHOCH_2CH_2$), 1.47 (9H, s, $(CH_3)_3C$), 1.44 (9H, s, $(CH_3)_3C$).

δ_C (75.5 MHz, $CDCl_3$): 199.6 (CH), 166.9 (C), 151.8 (C), 141.2 (CH), 99.0 (CH), 83.5 (C), 80.0 (C), 41.1 (CH_2), 37.8 (CH_2), 28.2 (CH_3), 28.0 (CH_3).

***tert*-Butyl (*E*)-3-[(benzyloxy carbonyl)(3,3-diethoxy propyl)amino]-2-propenoate (232):**



232

Based on a method by Macdonald.[78]

1.6 M of ^{n}BuLi in hexane (22.9 mL, 1 eq) was added dropwise to a solution of *tert*-butyl ester **230** (10.0 g, 36.58 mmol) in THF (180 mL) at -78°C. After 1 hour, CbzCl (6.24 g, 1 eq) in THF (20 mL) was added slowly over 35 minutes at -78°C, and then the reaction was allowed to warm to room temperature overnight. The reaction was quenched with aq. sol. NH_4Cl (50 mL), washed with water (50 mL). The aqueous layer was extracted with EtOAc (3x50 mL), and combined organic layers were dried ($MgSO_4$) and the solvent was removed *in vacuo*. The crude was purified by column chromatography eluting with EtOAc / cyclohexane (1:9 → 1:7 v/v) to give carbamate **232** (10.9 mg, 73%) as a colourless oil.

TLC: R_f = 0.62 (cyclohexane / Et_2O (1:2 v/v)).

IR: ν_{max} (film)/cm^{-1} 3073 (Ar), 3035 (Ar), 2974 (CH_3), 2931 (CH_2), 2879 (CH), 1728 (s, CO), 1701 (s, CO), 1624 (s, C=C), 1128 (s, COC).

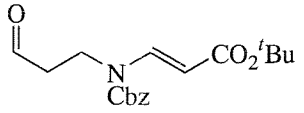
δ_H (300 MHz, $CDCl_3$): 8.12 (1H, d, *J* 14, NC*H*=CH), 7.35 (5H, m, ArH), 5.26 (1H, d, *J* 14, CH=C*H*$CO_2{}^t$Bu), 5.23 (2H, s, CH_2Ph), 4.43 (1H, t, *J* 6, C*H*$(OEt)_2$), 3.70-3.58 (4H, m, $OCH_AH_BCH_3$ and CH_2CH_2N), 3.46 (2H, m, $OCH_AH_BCH_3$), 1.89 (2H, dt, *J* 6, 7, $CHCH_2CH_2$), 1.48 (9H, s, $(CH_3)_3C$), 1.19 (6H, t, *J* 7, OCH_2CH_3).

δ_C (75.5 MHz, $CDCl_3$): 167.1 (C), 153.5 (C), 141.3 (CH), 135.4 (C), 128.8 (CH), 128.7 (CH), 128.4 (CH), 100.9 (CH), 100.4 (CH), 80.0 (C), 68.9 (CH_2), 61.7 (CH_2), 40.8 (CH_2), 31.3 (CH_2), 28.4 (CH_3), 15.4 (CH_3).

ES$^+$MS: *m/z* 364 ([M - OEt$^-$]$^+$, 40%), 430 ([M + Na]$^+$, 60%), 837 ([2M + Na]$^+$, 100%).

HRMS: *m/z* 430.2195 (calcd for $C_{22}H_{33}NO_6Na$, 430.2200).

***tert*-Butyl (*E*)-3-[(benzyloxy carbonyl)(3-oxo propyl)amino]-2-propenoate (229):**



229

Using a method described by Macdonald.[78]

Acetal **232** (2.3 g, 5.52 mmol) and *p*-TsOH (1.4 g, 1.3 eq) were stirred together in 20% aq. acetone (150 mL) for 3 days. The mixture was diluted with Et_2O (100 mL), and quenched with sat. aq. $NaHCO_3$ (200 mL). Aqueous layer was extracted with Et_2O (4x50 mL). Combined organic layers were dried ($MgSO_4$). The solvent was removed *in vacuo*. The crude oil was purified by column chromatography eluting with EtOAc / petroleum ether / TEA (1:9:0.05 → 1:7:0.05 v/v) to give an aldehyde **229** (1.4 g, 74%) as a colourless oil.

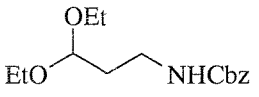
TLC: R_f = 0.32 (cyclohexane / Et_2O (1:2 v/v)).

IR: ν_{max} (film)/cm^{-1} 3075 (Ar), 3037 (Ar), 2974 (CH_3), 2974 (CH_2), 2731 (w, CHO), 1720 (s, CO), 1697 (s, CO), 1623 (s, C=C), 1138 (COC).

δ_H (300 MHz, $CDCl_3$): 9.75 (1H, s, CHO), 8.09 (1H, d, *J* 14, NC*H*=CH), 7.35 (5H, m, ArH), 5.22 (2H, s, CH_2Ph), 5.12 (1H, d, *J* 14, CH=C*H*$CO_2{}^t$Bu), 3.90 (2H, t, *J* 7, CH_2CH_2N), 2.73 (2H, t, *J* 6, $CHOCH_2CH_2$) 1.46 (9H, s, $C(CH_3)_3$).

δ_C (75.5 MHz, $CDCl_3$): 210.7 (CH), 173.9 (C), 166.8 (C), 154.2 (CH), 136.0 (C), 128.72 (CH), 128.68 (CH), 128.4 (CH), 114.5 (CH), 80.3 (C), 69.1 (CH_2), 38.2 (CH_2), 28.2 (CH_3) 27.2 (CH_2).

1-[(Benzyl carbonyl) amino]-3,3-diethoxy propane (221):



221

Following a method by Macdonald.[78]

CbzCl (0.97 ml, 6.8 mmol) was added dropwise into 1-amino-3, 3-diethoxy propane **217** (1.0 g, 6.8 mmol), DIPEA (1.48 ml, 1.2 eq.) / DCM (20 mL) solution at

room temperature. The reaction mixture was left stirring for 30 minutes. After removing the solvent *in vacuo*, the crude amide **221** (2.0 g, 100%) was obtained as a colourless oil.

TLC: R_f = 0.32 (petroleum ether / Et_2O (1:1 v/v)).

IR: ν_{max} (film)/cm^{-1} 3377 (br, NH), 3056 (Ar), 3028 (Ar), 2972 (CH_3), 2938 (CH_2), 2874 (CH), 1703 (s, CO), 1129 (s, COC).

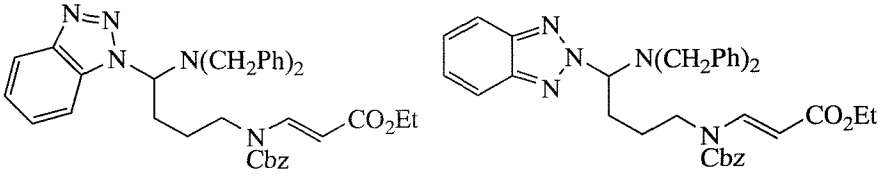
δ_H (300 MHz, $CDCl_3$): 7.40-7.25 (5H, m, Ar*H*), 5.30 (1H, br s, N*H*), 5.16 (2H, s, CH_2Ph), 4.55 (1H, t, *J* 6, *CH* $(OEt)_2$), 3.65 (2H, dq, *J* 10, 7, $CH_AH_BCH_3$), 3.50 (2H, dq, *J* 10, 7, $CH_AH_BCH_3$), 3.30 (2H, q, *J* 6, $NHCH_2CH_2$), 1.86 (2H, q, *J* 6, $NHCH_2CH_2$), 1.22 (6H, t, *J* 7, CH_2CH_3).

δ_C (75.5 MHz, $CDCl_3$): 156.5 (C), 136.9 (C), 128.6 (CH), 128.163 (CH), 128.161 (CH), 102.1 (CH), 66.6 (CH_2), 61.9 (CH_2), 37.3 (CH_2), 33.5 (CH_2), 15.5 (CH_3).

CIMS: *m/z* 281 ($[M + H]^+$, 27%), 207 ($[M - OEt^- - Et^-]^+$, 100%).

Spectroscopically identified to that reported by Macdonald.[78]

Ethyl (*E*)-3-{[3-(1,2,3-benzotriazolyl)-3-(dibenzylamino)-propyl](benzyloxy carbonyl) amino}-2-propenoate (235A and B):



235A **235B**

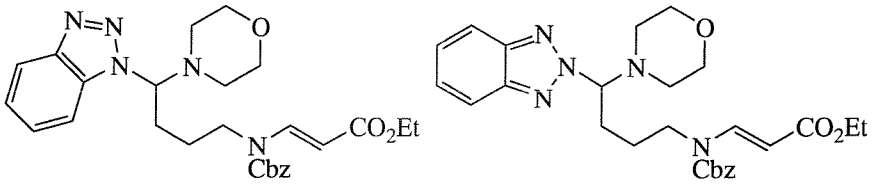
Benzotriazole adduct **235** was prepared *in situ* from DBA (102 mg, 0.52mmol), aldehyde **215** (159 mg, 0.52 mmol), and BTH (62 mg, 0.52 mmol) in Et_2O (18 mL). The reaction mixture was stirred further 15 minutes before being allowed to warm to room temperature and stirred overnight. The mixture was diluted with DCM (30 mL) and filtered through a celite filter aid. The solvent was removed *in vacuo*, to give crude benzotriazole adduct **235** (200 mg, 100%) as a yellow oil, and as a 1:1 mixture of regioisomers **A** and **B**.

IR: ν_{max} (film)/cm^{-1} 3062 (Ar), 3035 (Ar), 2976 (CH_3), 2931 (CH_2), 2896 (CH), 1729 (s, CO), 1707 (s, CO), 1627 (s, C=C), 1154 (s, COC).

δ_H (300 MHz, $CDCl_3$): 8.08 (1H, d, *J* 14, NC*H*=CH), 8.03 (0.5H, m, Ar*H-4*$_A$), 7.88 (1H, m, Ar*H-4,7*$_B$), 7.40-7.10 (17.5H, m, Ar*H*), 5.59 (0.5H, t, *J* 7, NCH_AN), 5.52 (0.5H, t, *J* 7, NCH_BN), 5.10-4.95 (3H, m, NCH=C*H* and CO_2CH_2Ph), 4.07 (2H, q, *J* 8, CH_2CH_3), 4.05-3.95 (2H, m, N(CH_XH_YPh)$_2$), 3.85-3.75 (1H, m, $CH_2CH_{2A}N$), 3.40-3.10 (3H, m, N(CH_XH_YPh)$_2$ and $CH_2CH_{2B}N$), 2.80-2.60 (2H, m, NCHCH_2), 1.20 (3H, t, *J* 8, CH_2CH_3).

ES$^+$MS: *m/z* 485 ([M – BT$^-$]$^+$, 20%), 198 ([N(CH_2Ph)$_2^-$]$^+$, 100%).

Ethyl (*E*)-3-{[3-(1,2,3-benzotriazolyl)-3-(morpholino)-propyl](benzyloxy carbonyl) amino}-2-propenoate (237A and B):



237A **237B**

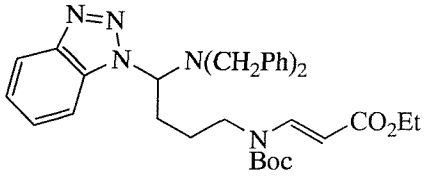
Benzotriazole adduct **237** was prepared *in situ* from morpholine (46.3 mg, 0.52 mmol), aldehyde **215** (159 mg, 0.52 mmol), and BTH (62 mg, 0.52 mmol) in Et_2O (18 mL). The reaction mixture was stirred further 20 minutes before being allowed to warm to room temperature and stirred overnight. The mixture was diluted with DCM (20 mL) and filtered through a celite filter aid. The solvent was removed *in vacuo*, to give crude benzotriazole adduct **237** (240 mg, 90%) as a yellow oil, and as a 1:1 mixture of regioisomers **A** and **B**.

IR: ν_{max} (film)/cm^{-1} 2958 (CH_3), 2854 (CH), 1728 (s, CO), 1701 (s, CO), 1626 (s, C=C), 1147 (s, COC).

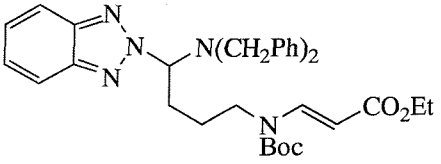
δ_H (300 MHz, $CDCl_3$): 8.19 (1H, d, *J* 14, NC*H*=CH), 8.02 (0.5H, d, *J* 8, Ar*H-4*$_A$), 7.85-7.82 (1H, m, Ar*H-4,7*$_B$), 7.48-7.25 (7.5H, m, Ar*H*), 5.51 (0.5H, t, *J* 7, NCH_AN), 5.43 (0.5H, t, *J* 7, NCH_BN), 5.33 (0.5H, d, *J* 14, NCH=CH_A), 5.28 (0.5H, d, *J* 14, NCH=CH_B), 5.20-5.08 (2H, m, CO_2CH_2Ph), 4.12 (1H, q, *J* 7, $CH_{2A}CH_3$), 4.11 (1H, q, *J* 7, $CH_{2B}CH_3$), 3.95-3.77 (1H, m, $CH_2CH_{2A}N$), 3.70-3.50 (5H, m, O(CH_2CH_2)$_2$N and $CH_2CH_{2B}N$), 2.90-2.36 (6H, m, O(CH_2CH_2)$_2$N and CH_2CH_2N), 1.22 (1.5H, t, *J* 7, CH_2CH_{3A}), 1.21 (1.5H, t, *J* 7, CH_2CH_{3B}).

ES$^+$MS: *m/z* 487 ([M + H]$^+$, 10%), 487 ([M - BT$^-$]$^+$, 100%).

Ethyl (*E*)-3-{[3-(1,2,3-benzotriazolyl)-3-(dibenzylamino)-propyl](*tert*-butoxy carbonyl) amino}-2-propenoate (239A and B):



239A



239B

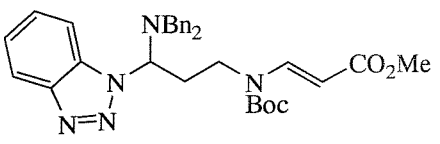
Benzotriazole adduct **239** was prepared *in situ* from DBA (109 mg, 0.55 mmol) in Et_2O (1 mL), aldehyde **216** (150 mg, 0.55 mmol), and BTH (66 mg, 0.55 mmol) in Et_2O (20 mL). The reaction mixture was stirred further 15 minutes before being allowed to warm to room temperature and stirred overnight. The mixture was diluted with DCM (100 mL) and filtered through a celite filter aid. The solvent was removed *in vacuo*, to give crude benzotriazole adduct **239** (330 mg, 100%) as a yellow oil, and as a 1:1 mixture of regioisomers **A** and **B**.

IR: ν_{max} (film)/cm^{-1} 2979 (CH_3), 2935 (CH_2), 1722 (s, CO), 1702 (s, CO), 1623 (s, C=C), 1140 (s, COC).

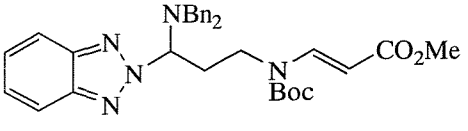
δ_H (300 MHz, $CDCl_3$): 8.05 (1H, d, *J* 14, NC*H*=CH), 8.02 (0.5H, d, *J* 8, Ar*H*-4_A), 7.88 (1H, m, Ar*H*-$4,7_B$), 7.40-7.10 (12.5H, m, Ar*H*), 5.60 (0.5H, t, *J* 7, NCH_BN), 5.52 (0.5H, t, *J* 7, NCH_AN), 4.98 (0.5H, d, *J* 14, NCH=CH_A), 4.95 (0.5H, d, *J* 14, NCH=CH_B), 4.05-3.95 (4H, m, CH_2CH$_3$ and N(CH_XH$_Y$Ph)$_2$), 3.80-3.70 (1H, m, CH$_2$CH_{2A}N), 3.35-3.22 (1H, m, CH$_2$CH_{2B}N), 3.25 (1H, d, *J* 14, N(CH$_X$$H_{YA}$Ph)$_2$), 3.17 (1H, d, *J* 14, N(H$_X$$H_{YB}$Ph)$_2$), 2.80-2.60 (2H, m, C$H_2CH_2$N), 1.32 (4.5H, s, C(C$H_3$)$_3$), 1.29 (4.5H, s, C(CH_3)$_3$), 1.20 (3H, t, *J* 8, CH$_2$CH_3).

ES$^+$MS: *m/z* 570 ([M + H]$^+$, 10%), 450 ([M – BT$^-$]$^+$, 20%), 198 ([N(CH$_2$Ph)$_2^-$]$^+$, 100%).

Methyl (*E*)-3-{[3-(1,2,3-benzotriazolyl)-3-(dibenzylamino) propyl](*tert*-butoxy carbonyl) amino}-2-propenoate (233A and B):



233A



233B

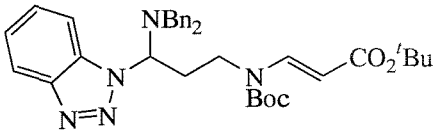
Benzotriazole adduct **233** was prepared *in situ* from DBA (394.6 mg, 2 mmol), aldehyde **223** (515 mg, 2 mmol), and BTH (238.3 mg, 2 mmol) in Et_2O (120 mL). The reaction mixture was stirred further 2 hours before being allowed to warm to room temperature and stirred overnight. The mixture was diluted with DCM (100 mL) and filtered through a celite filter aid. The solvent was removed *in vacuo*, to give crude benzotriazole adduct **233** (1.2 g, 100%) as a yellow oil, and as a 1:1.2 mixture of regioisomers **A** and **B**.

IR: ν_{max} (film)/cm^{-1} 3070 (Ar), 3038 (Ar), 2977 (CH_3), 2952 (CH_2), 1720 (s, CO), 1704 (s, CO), 1625 (s, C=C), 1137 (s, COC).

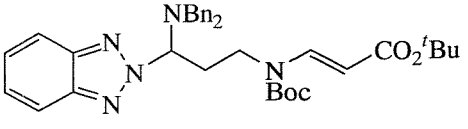
δ_H (300 MHz, $CDCl_3$): 8.15 (1H, m, NC*H*=CH), 8.12 (0.55H, dd, *J* 4, 7, Ar*H*-4_A), 7.94 (0.9H, dd, *J* 4, 7, Ar*H*-$4,7_B$), 7.47-7.16 (12.55H, m, Ar*H*), 5.68 (0.45H, t, *J* 7, NCH_AN), 5.61 (0.55H, t, *J* 7, NCH_BN), 5.08 (0.45H, d, *J* 15, NCH=CH_B), 5.06 (0.55H, d, *J* 15, NCH=CH_A), 4.16 (0.9H, d, *J* 14, NC($H_{XB}H_YPh)_2$), 4.14 (1.1H, d, *J* 14, N(C$H_{XA}H_YPh)_2$), 3.71 (3H, s, CO_2CH_3), 3.37 (1.1H, d, *J* 14, NC($H_XH_{YA}Ph)_2$), 3.28 (0.9H, d, *J* 14, N($CH_XH_{YB}Ph)_2$), 2.86-2.62 (2H, m, NCH_2CH_2), 1.53-1.43 (2H, m, NCH_2CH_2), 1.43 (4.05H, s, C($CH_{3B})_3$), 1.40 (4.95H, s, C($CH_{3A})_3$).

ES^+MS: *m/z* 578 ($[M + H]^+$, 1%), 437 ($[M - BT^-]^+$, 20%), 198 ($[N(CH_2Ph)_2^-]^+$, 100%).

***tert*-Butyl (*E*)-3-{[3-(1,2,3-benzotriazolyl)-3-(dibenzylamino) propyl](*tert*-butoxy carbonyl) amino}-2-propenoate (242A and B):**



242A



242B

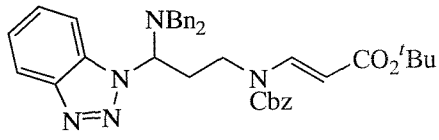
Benzotriazole adduct **242** was prepared *in situ* from DBA (132 mg, 0.67 mmol), aldehyde **228** (200 mg, 0.67 mmol), and BTH (80 mg, 0.67 mmol) in Et_2O (30 mL). The reaction mixture was stirred further 2 hours before being allowed to warm to room temperature and stirred overnight. The mixture was diluted with DCM (20 mL) and filtered through a celite filter aid. The solvent was removed *in vacuo*, to give crude benzotriazole adduct **242** (393 mg, 94%) as a yellow oil, and as a 1:1 mixture of regioisomers **A** and **B**.

IR: ν_{max} (film)/cm^{-1} 3061(Ar), 3030 (Ar), 2975 (CH_3), 2931 (CH_2), 1722 (s, CO), 1704 (s, CO), 1622 (s, C=C), 1127 (s, COC).

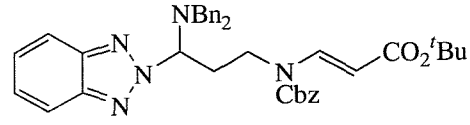
δ_H (300 MHz, $CDCl_3$): 8.11 (0.5H, d, *J* 8, Ar*H*-4$_A$), 7.98 (0.5H, d, *J* 14, NC*H*$_A$=CH), 7.94 (0.5H, d, *J* 14, NC*H*$_B$=CH), 7.88 (0.5H, dd, *J* 3, 6, Ar*H*-4$_B$), 7.76 (0.5H, dd, *J* 3, 6, Ar*H*-7$_B$), 7.50-7.14 (12H, m, Ar*H*), 7.07 (0.5H, d, *J* 8, Ar*H*-7$_A$), 5.59 (0.5H, t, *J* 7, NC*H*$_A$N), 5.53 (0.5H, t, *J* 7, NC*H*$_B$N), 4.92 (0.5H, d, *J* 14, NCH=C*H*$_A$), 4.86 (0.5H, d, *J* 14, NCH=C*H*$_B$), 4.06 (1H, d, *J* 14, NC*H*$_{XA}$H$_Y$Ph), 4.03 (1H, d, *J* 14, NC*H*$_{XB}$H$_Y$Ph), 3.76-3.66 (1H, m, $CH_2CH_{2A}N$), 3.26 (1H, d, *J* 14, NCH$_X$*H*$_{YB}$Ph), 3.17 (1H, d, *J* 14, NCH$_X$*H*$_{YA}$Ph), 3.08-2.98 (1H, m, $CH_2CH_{2B}N$), 2.73 (1H, q, *J* 7, NCHC*H*$_{2A}$), 2.70-2.52 (1H, m, NCHC*H*$_{2B}$), 1.37 (9H, s, C(C*H*$_3$)$_3$), 1.32 (4.5H, s, C(C*H*$_{3A}$)$_3$), 1.29 (4.5H, s, C(C*H*$_{3B}$)$_3$).

ES$^+$MS: *m/z* 598 ([M + H]$^+$, 3%), 479 ([M- BT$^-$]$^+$, 100%), 198 ([N(CH$_2$Ph)$_2^-$]$^+$, 80%).

tert-Butyl (*E*)-3-{[3-(1,2,3-benzotriazolyl)-3-(dibenzylamino) propyl](benzyloxy carbonyl) amino}-2-propenoate (243A and B):



243A



243B

Benzotriazole adduct **243** was prepared *in situ* from DBA (318 mg, 1.61 mmol), aldehyde **229** (538 mg, 1.61 mmol), and BTH (192 mg, 1.61 mmol) in Et_2O (100 mL). The reaction mixture was stirred further 2 hours before being allowed to warm to room temperature and stirred overnight. The mixture was diluted with DCM (100 mL) and filtered through a celite filter aid. The solvent was removed *in vacuo*, to give crude benzotriazole adduct **243** (964 mg, 95%) as a yellow oil, and as a 1:1 mixture of regioisomers **A** and **B**.

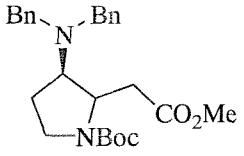
IR: ν_{max} (film)/cm^{-1} 3063 (Ar), 3030 (Ar), 2975 (CH_3), 2931 (CH_2), 2852 (CH), 1728 (s, CO), 1702 (s, CO), 1625 (s, C=C), 1133 (s, COC).

δ_H (300 MHz, $CDCl_3$): 8.11 (0.5H, d, *J* 7, Ar*H*-4$_A$), 8.10 (0.5H, d, *J* 15, NC*H*$_A$=CH), 8.08 (0.5H, d, *J* 15, NC*H*$_B$=CH), 7.88 (0.5H, dd, *J* 3, 7, Ar*H*-4$_B$), 7.76 (0.5H, dd, *J* 3, 7, Ar*H*-7$_B$), 7.50-7.27 (12H, m, Ar*H*), 7.19 (0.5H, d, *J* 7, Ar*H*-7$_A$), 5.69 (0.5H, t, *J* 7, NC*H*$_A$N), 5.63 (0.5H, t, *J* 7, NC*H*$_B$N), 5.16 (1H, s, $OCH_{2A}Ar$), 5.10(1H, s, $OCH_{2B}Ar$), 5.07 (0.5H,

d, *J* 15, NCH=CH_A), 5.00 (0.5H, d, *J* 15, NCH=CH_B), 4.15 (1H, d, *J* 14, NCH_{XA}H$_Y$Ph), 4.05 (1H, d, *J* 15, NCH_{XB}H$_Y$Ph), 3.92 (1H, q, *J* 7, CH$_2$CH_{2A}N), 3.54-3.38 (1H, m, CH$_2$CH_{2B}N), 3.34 (1H, d, *J* 15, NCH$_X$$H_{YB}$Ph), 3.26 (1H, d, *J* 14, NCH$_X$$H_{YA}$Ph), 2.93-2.67 (2H, m, NCHCH_2), 1.45 (9H, s, C(CH_3)$_3$).

ES$^+$MS: *m/z* 513 ([M$^+$- BT$^-$]$^+$, 80%), 198 ([N(CH$_2$Ph)$_2^-$]$^+$, 100%).

tert-Butyl (3*R*)-3-(dibenzylamino)-2-(methoxy carbonyl methyl) pyrrolidine-1-carboxylate (234) (Reverse addition):



234

SmI_2 was prepared from samarium metal (676 mg, 5 eq) and ICH_2CH_2I (583 mg, 2.3 eq) in THF (30 mL). After 2 hours, MeOH (0.52 mL, 2.3 eq) was added into the solution at room temperature. The SmI_2 solution was added dropwise over 30 minutes *via* cannular at 0°C into the THF solution (10 mL) of benzotriazole adduct precursor **233** (500 mg, 0.9 mmol). The reaction mixture was stirred at 0°C for a further 90 minutes before being allowed to warm to room temperature for 3 hours. The reaction was quenched with sat. aq. K_2CO_3 (30 mL) followed by washing with water (30 mL). The mixture was extracted with EtOAc (4x30 mL). The combined organic extracts were washed with brine (20 mL), water (20 mL) and dried ($MgSO_4$). The solvent was removed *in vacuo*. The crude oil was purified by column chromatography (SiO_2) eluting with EtOAc / petroleum ether / TEA (0:1:0.05 → 1:7:0.05 v/v). Pyrrolidine **234** (200 mg, 51%) was obtained as a colourless oil, and as a mixture of diastereomers (1:4). The mixture was isolated and purified by prep HPLC at Glaxo to give **234 *cis*** as a minor product, and **234 *trans*** as a major product.

TLC: R_f = 0.40 (petroleum ether / EtOAc (3:1 v/v)).

IR: ν_{max} (film)/cm^{-1} 2977 (CH_3), 1738 (s, CO), 1688 (s, CO).

234 *cis*: δ_H (300 MHz, $CDCl_3$, 50°C): 7.33-7.13 (10H, m, Ar*H*), 4.56 (1H, q, *J* 6, C*H*CH$_2$CO$_2$Me), 3.84 (2H, d, *J* 14, (PhCH_AH$_B$)$_2$N), 3.65 (3H, s, CO$_2$CH_3), 3.54 (2H, d, *J*

14, ($PhCH_AH_B)_2N$), 3.41-3.15 (3H, m, CH_2NBoc and $CHNBn_2$), 3.15-2.93 (1H, br m, $CH_AH_BCO_2Me$), 2.39 (1H, dd, *J* 6, 15, $CH_AH_BCO_2Me$), 1.95-1.81 (1H, m, $CHCH_AH_BCH_2$), 1.74-1.43 (1H, m, $CHCH_AH_BCH_2$), 1.43 (9H, s, $C(CH_3)_3$).

δ_C (75.5 MHz, $CDCl_3$, 50°C): 172.9 (C), 154.2 (C), 139.0 (C), 128.6 (CH), 128.3 (CH), 127.0 (CH), 79.3 (C), 65.0 (CH), 63.9 (CH), 56.3 (CH_3), 51.6 (CH_2), 44.0 (CH_2), 35.0 (CH_2), 28.4 (CH_3), 23.4 (CH_2).

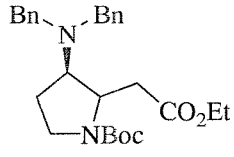
234 ***trans***: δ_H (300 MHz, $CDCl_3$, 50°C): 7.35-7.15 (10H, m, Ar*H*), 4.15 (1H, br m, $CHCH_2CO_2Me$), 3.71 (2H, d, *J* 14, $(PhCH_AH_B)_2N$), 3.70-3.55 (1H, br m, CH_AH_BNBoc), 3.56 (3H, s, CO_2CH_3), 3.51 (2H, d, *J* 14, $(PhCH_AH_B)_2N$), 3.33 (1H, dt, 6, 7, $CHNBn_2$), 3.23 (1H, dt, *J* 11, 7, CH_AH_BNBoc), 2.67-2.42 (2H, m, CH_2CO_2Me), 1.95 (2H, q, *J* 7, $NCHCH_2CH_2$), 1.43 (9H, s, $(CH_3)_3C$).

δ_C (75.5 MHz, $CDCl_3$, 50°C): 171.9 (C), 154.2 (C), 139.6 (C), 128.6 (CH), 128.2 (CH), 127.0 (CH), 79.9 (C), 65.1 (CH), 56.3 (CH), 54.8 (CH_2), 51.4 (CH_3), 45.4 (CH_2), 38.0 (CH_2), 28.5 (CH_3), 27.5 (CH_2).

ES^+MS: *m/z* 439 ($[M + H]^+$, 100%).

HRMS: *m/z* 439.2613 (calcd for $C_{26}H_{35}N_2O_4$, 439.2597).

***tert*-Butyl (3*R*)-3-(dibenzylamino)-2-(ethoxy carbonyl methyl) pyrrolidine-1-carboxylate (240):**



240

<u>From cyclisation of benzotriazole adduct **239** (Reverse addition)</u>:

SmI_2 was prepared by stirring samarium metal (659 mg, 5 eq) and ICH_2CH_2I (569 mg, 2.3 eq) in THF (20 mL). After 100 minutes, EtOH (0.1 mL, 2.3 eq) was added into the solution at room temperature. The SmI_2 solution was added dropwise over 30 minutes *via* cannular at 0°C into the THF solution (13 mL) of benzotriazole adduct precursor **239** (500 mg, 0.88 mmol). The reaction mixture was stirred at 0°C for a further 2 hours before being allowed to warm to room temperature for 1 hour. The reaction was quenched with

sat. aq. K_2CO_3 (30 mL) followed by washing with water (30 mL). The mixture was extracted with EtOAc (4x30 mL). The combined organic extracts were washed with brine (20 mL), water (30 mL) and dried ($MgSO_4$). The solvent was removed *in vacuo*. The crude oil was purified by column chromatography (SiO_2) eluting with EtOAc / petroleum ether / TEA (0:1:0.05 → 1:7:0.05 v/v). Pyrrolidine **240** (180 mg, 45%) was obtained as a colourless oil, and as a mixture of diastereomers (*cis* : *trans* = 1:3).

TLC: R_f = 0.44 (petroleum ether / EtOAc (3:1 v/v)).

IR: ν_{max} (film)/cm^{-1} 3028 (ArH), 2976 (CH_3), 2935 (CH_2), 2889 (CH), 1731 (s, CO), 1686 (s, CO).

δ_H (400 MHz, $_{d6}$-DMSO, 80°C): 7.32-7.17 (10H, m, ArH), 4.39 (0.25H, apparent q, *J* 6, $CH_{cis}CH_2CO_2Et$), 4.08 (0.75H, dt, *J* 7, 5, $CH_{trans}CH_2CO_2Et$), 4.04 (0.5H, q, *J* 7, $CH_{2cis}CH_3$), 3.98 (1.5H, q, *J* 7, $CH_{2trans}CH_3$), 3.77 (0.5H, d, *J* 14, $(PhCH_{Acis}H_B)_2N$), 3.65 (1.5H, d, *J* 14, $(PhCH_{Atrans}H_B)_2N$), 3.60 (0.5H, d, *J* 15, $(PhCH_AH_{Bcis})_2N$), 3.56 (1.5H, d, *J* 14, $(PhCH_AH_{Btrans})_2N$), 3.50 (0.75H, dt, *J* 11, 7, $CH_{Atrans}H_BNBoc$), 3.29 (0.75H, apparent q, $CH_{trans}NBn_2$), 3.26-3.15 (0.75H, m, $CH_{cis}NBn_2$ anb $CH_{2cis}NBoc$), 3.15 (0.75H, dt, *J* 11, 8, $CH_AH_{Btrans}NBoc$), 2.95 (0.25H, dd, *J* 5, 15, $CH_{Acis}H_BCO_2Et$), 2.55-2.43 (1.5H, m, $CH_{2trans}CO_2Et$), 2.33 (0.25H, dd, *J* 6, 15, $CH_AH_{Bcis}CO_2Et$), 1.96 (1.5H, q, *J* 7, $NCHCH_{2trans}CH_2$), 1.95-1.87 (0.25H, m, $NCHCH_{Acis}H_BCH_2$), 1.70-1.56 (0.25H, m, $NCHCH_AH_{Btrans}CH_2$), 1.38 (9H, s, $C(CH_3)_3$), 1.18 (0.75H, t, *J* 7, $CO_2CH_2CH_{3cis}$), 1.13 (2.25H, t, *J* 7, $CO_2CH_2CH_{3trans}$).

δ_C (100 MHz, $_{d6}$-DMSO): 172.1 and 170.8 (C), 153.5 (C), 140.1 (C), 128.7 (CH), 128.6 (CH), 127.3 (CH), 79.0 (C), 65.3 and 64.2 (CH), 60.3 and 60.2 (CH_2), 56.6 and 56.2 (CH), 55.3 and 54.4 (CH_2), 45.6 and 45.3 (CH_2), 38.1 and 37.3 (CH_2), 28.5 (CH_3), 24.2 and 23.6 (CH_2), 14.4 (CH_3).

ES^+MS: *m/z* 453 $([M + H]^+$, 100%).

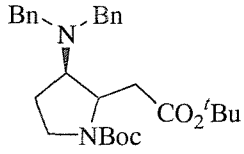
HRMS: *m/z* 453.2747 (calcd for $C_{27}H_{37}N_2O_4$, 453.2753).

From protection of free pyrrolidine **256**:

Pyrrolidine **256** (16 mg, 0.045 mmol) was dissolved in DCM (2 mL). TEA (9.5 μL, 1.5 eq) was added into the solution at room temperature, after 15 minutes, DMAP (1.6 mg, 0.3 eq) was added. After 15 minutes, Boc_2O (10 mg, 1 eq) in DCM (0.5 mL)

was added slowly into the reaction mixture at 0°C. The reaction mixture was allowed to warm to room temperature overnight. The reaction was quenched with dil. aq. HCl (5 mL) followed by washing with water (2 mL). Aqueous layer was extracted with DCM (3x2 mL). The combined organic extracts were dried ($MgSO_4$). The solvent was removed *in vacuo*. The crude oil was purified by column chromatography (SiO_2) eluting with EtOAc / petroleum ether / TEA (1:7:0.05 → 1:5:0.05 v/v) to give pyrrolidine **240** (12 mg, 60%) as a colourless oil.

tert-Butyl (3*R*)-3-(dibenzylamino)-2-(_tert_-butoxy carbonyl methyl) pyrrolidine-1-carboxylate (244):



244

From cyclisation of benzotriazole adduct **242** (Reverse addition):

SmI_2 was prepared by stirring samarium metal (475 mg, 5 eq) and ICH_2CH_2I (410 mg, 2.3 eq) in THF (12 mL). After 90 minutes, ^tBuOH (139 μL, 2.3 eq) was added into the solution at room temperature. The SmI_2 solution was added dropwise over 30 minutes *via* cannular at 0°C into the THF solution (10 mL) of benzotriazole adduct precursor **242** (378 mg, 0.63 mmol). The reaction mixture was stirred at 0°C for a further 90 minutes before being allowed to warm to room temperature overnight. The reaction was quenched with sat. aq. K_2CO_3 (20 mL) followed by washing with water (20 mL). The mixture was extracted with EtOAc (4x20 mL). The combined organic extracts were washed with brine (20 mL), water (20 mL) and dried ($MgSO_4$). The solvent was removed *in vacuo*. The crude oil was purified by column chromatography (SiO_2) eluting with EtOAc / petroleum ether / TEA (1:9:0.05 → 1:7:0.05 v/v). Pyrrolidine **244** (160 mg, 51%) was obtained as a colourless oil, and as a mixture of diastereomers (*cis* : *trans* = 1:2.6).

TLC: R_f = 0.52 (EtOAc / petroleum ether (1:3 v/v)).

IR: ν_{max} (film)/cm^{-1} 3027 (ArH), 2974 (CH_3), 2931 (CH_2), 2887 (CH), 1726 (s, CO), 1691 (s, CO).

δ_H (400 MHz, $_{d6}$-DMSO, 80°C): 7.30-7.14 (10H, m, ArH), 4.70 (0.28H, apparent q, *J* 6, C*H*$_{cis}$CH$_2$CO$_2$^{t}Bu), 4.00 (0.72H, apparent q, *J* 6, C*H*$_{trans}$CH$_2$CO$_2$^{t}Bu), 3.75 (0.56H, d, *J* 14, (PhC*H*$_{Acis}$H$_B$)$_2$N), 3.65 (1.44H, d, *J* 14, (PhC*H*$_{Atrans}$H$_B$)$_2$N), 3.58 (0.56H, d, *J* 14, (PhCH$_A$*H*$_{Bcis}$)$_2$N), 3.54 (1.44H, d, *J* 14, (PhCH$_A$*H*$_{Btrans}$)$_2$N), 3.70 (0.72H, dt, *J* 10, 7, C*H*$_{Atrans}$H$_B$NBoc), 3.32 (0.72H, apparent q, *J* 5, C*H*$_{trans}$NBn$_2$), 3.26-3.14 (0.84H, m, C*H*$_{cis}$NBn$_2$ and C*H*$_{2cis}$NBoc), 3.13 (0.72H, dt, *J* 11, 7, CH$_A$*H*$_{Btrans}$NBoc), 2.91 (0.28H, dd, *J* 5, 16, C*H*$_{Acis}$H$_B$CO$_2$^{t}Bu), 2.49-2.40 (1.44H, m, C*H*$_{2trans}$CO$_2$^{t}Bu), 2.24 (0.28H, dd, *J* 5, 15, CH$_A$*H*$_{Bcis}$CO$_2$ ^{t}Bu), 1.94 (1.44H, q, *J* 7, NCHC*H*$_{2trans}$CH$_2$), 1.92-1.84 (0.28H, m, NCHC*H*$_{Acis}$H$_B$CH$_2$), 1.67-1.54 (0.28H, m, NCHCH$_A$*H*$_{Btrans}$CH$_2$), 1.39 (2.52H, s, C(CH$_{3cis}$)$_3$), 1.38 (2.52H, s, C(CH$_{3cis}$)$_3$), 1.37 (6.48H, s, C(CH$_{3trans}$)$_3$), 1.32 (6.48H, s, C(CH$_{3trans}$)$_3$).

δ_C (100 MHz, $_{d6}$-DMSO): 170.0 and 169.3 (C), 158.0 (C), 140.2 (C), 128.6 (CH), 128.4 (CH), 127.0 (CH), 80.1 (C), 78.8 (C), 65.2 and 65.0 (CH), 57.0 and 56.1 (CH), 56.1 and 54.8 (CH$_2$), 45.4 and 44.1 (CH$_2$), 38.8 and 36.0 (CH$_2$), 28.6 and 28.5 (CH$_3$), 28.22 and 28.16 (CH$_3$), 27.4 and 24.3 (CH$_2$).

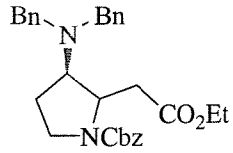
EI: *m/z* 241 (1/2[M + 2H]$^+$, 3%), 481 ([M + H]$^+$, 100%).

HRMS: *m/z* 481.3069 (calcd for $C_{29}H_{40}N_2O_4$, 481.3061).

From protection of free pyrrolidine **257**:

Pyrrolidine **257** (20 mg, 0.053 mmol) was dissolved in DCM (2 mL). TEA (11 μL, 1.5 eq) was added into the solution at room temperature, after 15 minutes, DMAP (2.0 mg, 0.3 eq) was added. After 15 minutes, Boc$_2$O (12 mg, 1 eq) in DCM (0.5 mL) was added slowly into the reaction mixture at 0°C. The reaction mixture was allowed to warm to room temperature overnight. The reaction was quenched with dil. aq. HCl (2 mL) followed by washing with water (2 mL). Aqueous layer was extracted with DCM (3x10 mL). Combined organic extracts were dried (MgSO$_4$). The solvent was removed *in vacuo*. The crude oil was purified by column chromatography (SiO$_2$) eluting with EtOAc / petroleum ether / TEA (0:1:0.05 → 1:6:0.05 v/v) to give pyrrolidine **244** (6 mg, 24%) as a colourless oil

Benzyl (3*R*)-3-(dibenzylamino)-2-(ethoxy carbonyl methyl) pyrrolidine-1-carboxylate (236) (Reverse addition):



236

SmI_2 was prepared by stirring samarium metal (1.34 g, 5 eq) and ICH_2CH_2I (1.15 g, 2.3 eq) in THF (15 mL). After 90 minutes, EtOH (240 μL, 2.3 eq) was added into the solution at room temperature. The SmI_2 solution was added dropwise *via* cannular at 0°C into the THF solution (15 mL) of benzotriazole adduct precursor **235** (1.08 g, 1.78 mmol). The reaction mixture was stirred at 0°C for a further 90 minutes before being allowed to warm to room temperature overnight. The reaction was quenched with sat. aq. K_2CO_3 (30 mL) followed by washing with water (20 mL). The mixture was extracted with EtOAc (4x20 mL). The combined organic extracts were washed with brine (20 mL), water (20 mL) and dried ($MgSO_4$). The solvent was removed *in vacuo*. The crude oil was purified by column chromatography (SiO_2) eluting with EtOAc / petroleum ether / TEA (0:1:0.05 → 1:7:0.05 v/v). Pyrrolidine **236** (650 mg, 75%) was obtained as a colourless oil, and as a mixture of diastereomers (*cis* : *trans* = 1:2.9).

TLC: R_f = 0.45 (EtOAc / petroleum ether (1:3 v/v)).

IR: ν_{max} (film)/cm^{-1} 3028 (ArH), 2977 (CH_3), 2940 (CH_2), 2893 (CH), 1730 (s, CO), 1697 (s, CO).

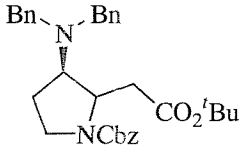
δ_H (400 MHz, $_{d6}$-DMSO, 80°C): 7.38-7.17 (15H, m, ArH), 5.16 (2H, s, CO_2CH_2Ph), 4.48 (0.26H, apparent q, *J* 5, $CH_{cis}CH_2CO_2Et$), 4.17 (0.74H, apparent q, *J* 5, $CH_{trans}CH_2CO_2Et$), 4.01-3.90 (2H, m, CH_2CH_3), 3.77 (0.52H, d, *J* 15, $(PhCH_{Acis}H_B)_2N$), 3.67 (1.48H, d, *J* 14, $(PhCH_{Atrans}H_B)_2N$), 3.67-3.56 (0.74H, m, $CH_{Atrans}H_BNCbz$), 3.62 (0.52H, d, *J* 15, $(PhCH_AH_{Bcis})_2N$), 3.56 (1.48H, d, *J* 14, $(PhCH_AH_{Btrans})_2N$), 3.40-3.19 (2.26H, m, $CH_{cis}NBn_2$, $CH_{trans}NBn_2$ and $CH_{2cis}NCbz$), 2.97 (0.26H, dd, *J* 5, 15, $CH_{Acis}H_BCO_2Et$), 2.56-2.46 (1.48H, m, $CH_{2trans}CO_2Et$), 2.39 (0.26H, dd, *J* 6, 15, $CH_AH_{Bcis}CO_2Et$), 2.00 (1.48H, q, *J* 7, $NCHCH_{2trans}CH_2$), 2.00-1.91 (0.26H, m, $NCHCH_{Acis}H_BCH_2$), 1.76-1.63 (0.26H, m, $NCHCH_AH_{Btrans}CH_2$), 1.14 (0.78H, t, *J* 7, $CO_2CH_2CH_{3cis}$), 1.12 (2.22H, t, *J* 7, $CO_2CH_2CH_{3trans}$).

δ_C (100 MHz, $_{d6}$-DMSO): 172.0 and 170.8 (C), 154.0 (C), 140.0 (C), 137.5 (C), 129.9 (CH), 128.7 (CH), 128.6 (CH), 128.1 (CH), 127.7 (CH), 127.3 (CH), 66.2 (CH_2), 65.3 and 64.1 (CH), 60.4 and 60.3 (CH_2), 57.1 and 56.7 (CH), 56.2 and 54.4 (CH_2), 45.9 and 45.5 (CH_2), 38.3 and 37.0 (CH_2), 24.0 and 23.6 (CH_2), 14.4 (CH_3).

ES^+MS: *m/z* 487 ($[M + H]^+$, 100%), 509 ($[M + Na]^+$, 40%), 995 ($[2M + Na]^+$, 25%).

HRMS: *m/z* 487.2591 (calcd for $C_{30}H_{35}N_2O_4$, 487.2597).

Benzyl (3*R*)-3-(dibenzylamino)-2-(*tert*-butoxy carbonyl methyl) pyrrolidine - 1-carboxylate (245) (Reverse addition):



245

SmI_2 was prepared by stirring samarium metal (1.90 g, 5 eq) and ICH_2CH_2I (1.64 g, 2.3 eq) in THF (40 mL). After 90 minutes, ^{t}BuOH (550 μL, 2.3 eq) was added into the solution at room temperature. The SmI_2 solution was added dropwise *via* cannular at 0°C into the THF solution (50 mL) of benzotriazole adduct precursor **243** (1.60 g, 2.53 mmol). The reaction mixture was stirred at 0°C for a further 2 hours before being allowed to warm to room temperature overnight. The reaction was quenched with sat. aq. K_2CO_3 (50 mL) followed by washing with water (50 mL). The mixture was extracted with EtOAc (4x40 mL). The combined organic extracts were washed with brine (50 mL), water (40 mL) and dried ($MgSO_4$). The solvent was removed *in vacuo*. The crude oil was purified by column chromatography (SiO_2) eluting with EtOAc / petroleum ether / TEA (1:9:0.05 → 1:7:0.05 v/v). Pyrrolidine **245** (650 mg, 50%) was obtained as a colourless oil, and as a mixture of diastereomers (*cis* : *trans* = 1:2).

TLC: R_f = 0.60 (petroleum ether / EtOAc (3:1 v/v)).

IR: ν_{max} (film)/cm^{-1} 3028 (ArH), 2974 (CH_3), 2935 (CH_2), 2888 (CH), 1724 (s, CO), 1701 (s, CO).

δ_H (400 MHz, $_{d6}$-DMSO, 80°C): 7.37-7.19 (15H, m, ArH), 5.14-5.03 (2H, m, CO_2CH_2Ph), 4.49 (0.33H, apparent q, *J* 6, $CH_{cis}CH_2CO_2{}^tBu$), 4.11 (0.67H, dt, *J* 4, 7,

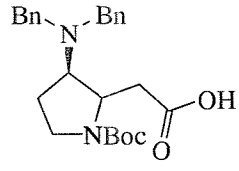
$CH_{trans}CH_2CO_2{}^tBu$), 3.82 (0.67H, d, *J* 15, $(PhCH_{Acis}H_B)_2N$), 3.73 (1.33H, d, *J* 14, $(PhCH_{Atrans}H_B)_2N$), 3.67 (0.67H, d, *J* 15, $(PhCH_AH_{Bcis})_2N$), 3.62 (1.33H, d, *J* 14, $(PhCH_AH_{Btrans})_2N$), 3.64-3.57 (0.67H, m, $CH_{Atrans}H_BNCbz$), 3.42 (0.67H, apparent q, $CH_{trans}NBn_2$), 3.39-3.24 (1.67H, m, $CH_{cis}NBn_2$, $CH_{2cis}NCbz$ and $CH_AH_{Btrans}NCbz$), 2.98 (0.33H, dd, *J* 5, 15, $CH_{Acis}H_BCO_2{}^tBu$), 2.54 (0.67H, dd, *J* 7, 15, $CH_{Atrans}H_BCO_2{}^tBu$), 2.47 (0.67H, dd, *J* 4, 15, $CH_AH_{Btrans}CO_2{}^tBu$), 2.21 (0.33H, dd, *J* 6, 15, $CH_AH_{Bcis}CO_2{}^tBu$), 2.04 (1.33H, q, *J* 7, $NCHCH_{2trans}CH_2$), 2.01-1.94 (0.33H, m, $NCHCH_{Acis}H_BCH_2$), 1.77-1.66 (0.33H, m, $NCHCH_AH_{Btrans}CH_2$), 1.38 (3H, s, $C(CH_3)_3$), 1.35 (6H, s, $C(CH_3)_3$).

δ_C (100 MHz, $_{d6}$-DMSO): 171.0 (C), 154.0 (C), 140.0 (C), 139.3 (C), 128.8 (CH), 128.6 (CH), 128.4 (CH), 127.9 (CH), 127.6 (CH), 127.1 (CH), 80.0 (C), 66.2 (CH_2), 65.0 and 64.5 (CH), 57.1 and 56.5 (CH), 56.0 and 54.8 (CH_2), 45.6 and 44.2 (CH_2), 38.8 and 35.9 (CH_2), 28.1 (CH_3), 27.3 and 24.3 (CH_2).

ES^+MS: *m/z* 515 ($[M + H]^+$, 100`%).

HRMS: *m/z* 515.2901 (calcd for $C_{32}H_{38}N_2O_4$, 515.2905).

2-[(3*R*)-1-(*tert*-Butoxy carbonyl)-3-(dibenzylamino) tetrahydro-1*H*-2-pyrrolyl] acetic acid (254):



254

From pyrrolidine **234**:

Pyrrolidine **234** (50 mg, 0.11 mmol) was dissolved in dioxane (3.7 mL). LiOH (1.3 mL of a 1M solution in water) was added at room temperature, and the reaction was stirred overnight. The solvent was removed *in vacuo* and, the residue was dissolved in water (2 mL). The aqueous solution was acidified with dil. aq. HCl (10 mL), and extracted with DCM (3x10 mL). The combined organic extracts were dried ($MgSO_4$). The solvent was removed *in vacuo*. The crude oil was purified by column chromatography (SiO_2) eluting with DCM / EtOAc / MeOH (1:0:0 → 10:5:1 v/v) to give pyrrolidine **254** (35 mg, 72%) as a colourless oil. (*cis* : *trans* = 1 : 4)

From pyrrolidine **240**:

Pyrrolidine **240** (35 mg, 0.08 mmol) was dissolved in dioxane (2.4 mL). LiOH (1.3 mL of a 1M solution in water) was added at room temperature, and the reaction was stirred overnight. The solvent was removed *in vacuo* and, the residue was dissolved in water (2 mL). The aqueous solution was acidified with dil. aq. HCl (20 mL), and extracted with DCM (3x15 mL). The combined organic extracts were dried ($MgSO_4$). The solvent was removed *in vacuo*. The crude oil was purified by column chromatography (SiO_2) eluting with DCM / EtOAc / MeOH (1:0:0 → 10:5:1 v/v) to give pyrrolidine **254** (26 mg, 79%) as a colourless oil. (*cis* : *trans* = 1 : 5)

TLC: R_f = 0.21 (DCM / EtOAc / MeOH (8:2:0.1 v/v)).

IR: ν_{max} (film)/cm^{-1} 3500-2500 (br, OH), 3064 (Ar), 3028 (Ar), 2976 (CH_3), 2924 (CH_2), 2889 (CH), 1729 (s, CO), 1690 (s, CO), 1164 (s, COC).

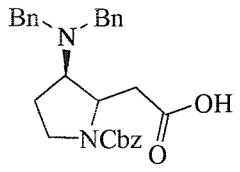
δ_H (400 MHz, $_{d6}$-DMSO, 80°C): 7.38-7.14 (10H, m, ArH), 4.40 (0.2H, apparent q, *J* 5, $CH_{cis}CH_2CO_2H$), 4.17 (0.8H, dt, *J* 8, 4, $CH_{trans}CH_2CO_2H$), 3.78 (0.4H, d, *J* 14, $(PhCH_{Acis}H_B)_2N$), 3.63 (1.6H, d, *J* 14, $(PhCH_{Atrans}H_B)_2N$), 3.57 (1.6H, d, *J* 15, $(PhCH_AH_{Bcis})_2N$), 3.55 (0.4H, d, *J* 14, $(PhCH_AH_{Btrans})_2N$), 3.52-3.41 (0.8H, m, $CH_{Atrans}H_BNCbz$), 3.26 (0.8H, dt, *J* 4, 6, $CH_{trans}NBn_2$), 3.24-3.10 (1.4H, m, $CH_{cis}NBn_2$ and $CH_{2cis}NCbz$), 2.96 (0.2H, dd, *J* 4, 15, $CH_{Acis}H_BCO_2H$), 2.46 (0.8H, dd, *J* 4, 15, $CH_{Atrans}H_BCO_2H$), 2.36 (0.8H, dd, *J* 7, 15, $CH_AH_{Btrans}CO_2H$), 2.39 (0.2H, dd, *J* 7, 15, $CH_AH_{Bcis}CO_2H$), 1.99-1.92 (1.6H, m, $NCHCH_{2trans}CH_2$), 1.95-1.85 (0.2H, m, $NCHCH_{Acis}H_BCH_2$), 1.67-1.56 (0.2H, m, $NCHCH_AH_{Btrans}CH_2$), 1.37 (7.2H, s, $C(CH_{3trans})_3$), 1.36 (1.8H, s, $C(CH_{3cis})_3$).

δ_C (100 MHz, $_{d6}$-DMSO, 80°C): 172.4 (C), 153.9 (C), 140.2 (C), 128.7 (CH), 128.5 (CH), 127.2 (CH), 79.3 (C), 66.0 and 65.0 (CH), 58.0 and 57.0 (CH), 56.2 and 54.8 (CH_2), 45.3 and 44.0 (CH_2), 38.2 and 35.1 (CH_2), 28.5 (CH_3), 27.6 and 24.8 (CH_2).

ES^+MS: *m/z* 425 ($[M + H]^+$, 30%), 447 ($[M + Na]^+$, 10%).

HRMS: *m/z* 425.2438 (calcd for $C_{25}H_{33}N_2O_4$, 425.2435).

2-[(3*R*)-1-(*tert*-Benzyloxy carbonyl)-3-(dibenzylamino) tetrahydro-1*H*-2-pyrrolyl] acetic acid (255):



255

From pyrrolidine **236**:

Pyrrolidine **236** (30 mg, 0.062 mmol) was dissolved in dioxane (1.5 mL). LiOH (0.6 mL of a 1M solution in water) was added at room temperature, and the reaction was stirred overnight. The solvent was removed *in vacuo* and, the residue was dissolved in water (2 mL). The aqueous solution was acidified with dil. aq. HCl (2 mL), and extracted with DCM (4x10 mL). The combined organic extracts were dried ($MgSO_4$). The solvent was removed *in vacuo*. The crude oil was purified by column chromatography (SiO_2) eluting with DCM / EtOAc / MeOH (1:0:0 → 10:2:0.1 v/v) to give pyrrolidine **255** (20 mg, 73%) as a colourless oil. (*cis* : *trans* = 1 : 5)

From pyrrolidine **245**:

Using a method described by Honkanen.[131]

Pyrrolidine **245** (30 mg, 0.058 mmol) was dissolved in dry toluene (6 mL), and *p*-TsOH (14 mg, 1.3 eq) was added. The solution was boiled under reflux overnight. The solvent was removed *in vacuo*. The crude oil was purified by column chromatography (SiO_2) eluting with DCM / EtOAc / MeOH (1:0:0 → 8:2:0.1 v/v) to give pyrrolidine **255** (23 mg, 87%) as a colourless oil. (*cis* : *trans* = 1 : 4)

TLC: R_f = 0.24 (DCM / EtOAc / MeOH (8:2:0.1 v/v)).

IR: ν_{max} (film)/cm^{-1} 3500-2500 (br OH), 3029 (ArH), 2924 (CH_2), 2853 (CH), 1701 (s, CO).

δ_H (400 MHz, $_{d6}$-DMSO, 80°C): 7.40-7.20 (15H, m, ArH), 5.07 (2H, s, CH_2Ar), 4.54 (0.2H, apparent q, $CH_{cis}CH_2CO_2H$), 4.21 (0.8H, dt, *J* 8, 4, $CH_{trans}CH_2CO_2H$), 3.81 (0.4H, d, *J* 15, $(PhCH_{Acis}H_B)_2N$), 3.67 (1.6H, d, *J* 15, $(PhCH_{Atrans}H_B)_2N$), 3.60 (1.6H, d, *J* 15,

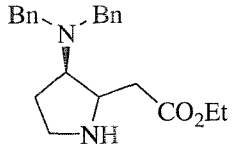
(PhCH$_A$*H*$_{Btrans}$)$_2$N), 3.60-3.50 (1.2H, m, C*H*$_{Atrans}$H$_B$NCbz and (PhCH$_A$*H*$_{Bcis}$)$_2$N), 3.40-3.22 (2.2H, m, C*H*NBn$_2$, C*H*$_{2cis}$NCbz and CH$_A$*H*$_{Btrans}$NCbz), 3.00 (0.2H, dd, *J* 4, 16, C*H*$_{Acis}$H$_B$CO$_2$H), 2.52-2.42 (1.6H, m, C*H*$_{2trans}$CO$_2$H), 2.34 (0.2H, dd, *J* 6, 16, CH$_A$*H*$_{Bcis}$CO$_2$H), 2.05-2.00 (1.6H, m, NCHC*H*$_{2trans}$CH$_2$), 1.95 (0.2H, m, NCHC*H*$_{Acis}$H$_B$CH$_2$), 1.65 (0.2H, m, NCHCH$_A$*H*$_{Bcis}$CH$_2$).

δ_C (75.5 MHz, $CDCl_3$): 206.5 (C), 175.1 (C), 138.3 (C), 136.5 (C), 128.81 (CH), 128.80 (CH), 128.44 (CH), 128.40 (CH), 128.0 (CH), 127.3 (CH), 67.0 (CH_2), 65.7 and 64.7 (CH), 56.3 and 55.6 (CH), 54.8 (CH_2), 45.6 and 44.3 (CH_2), 38.9 and 38.2 (CH_2), 29.7 and 23.3 (CH_2).

ES$^+$MS: *m/z* 459 ([M + H]$^+$, 100%).

HRMS: *m/z* 459.2276 (calcd for $C_{28}H_{31}N_2O_4$, 459.2278).

Ethyl 2-[(3*R*)-3-(dibenzylamino)tetrahydro-1*H*-2-pyrrolyl]acetate (256):



256

Using a modified version of method described by Mirrington.[132]

Pyrrolidine **236** (30 mg, 0.062 mmol) and 10% Pd/C (7.6 mg, 0.1 eq) were stirred in EtOH (2 mL) at room temperature for 15 minutes. The mixture was stirred in the flask filled with H_2 gas at room temperature overnight. The whole mixture was filtered through celite, and the solvent was removed *in vacuo*. The crude oil was purified by column chromatography eluting with EtOAc / DCM / MeOH (0:1:0 → 1:5:0.01 v/v) to give **256** (13 mg, 60%) as a colourless oil. (*cis* : *trans* = 1 : 4)

TLC: R_f = 0.35 (DCM / EtOAc / MeOH (7:2:1 v/v)).

IR: ν_{max} (film)/cm^{-1} 3361 (NH), 3060 (Ar), 3023 (Ar), 2929 (CH_3), 2867 (CH), 1731 (s, CO), 1698 (s, CO).

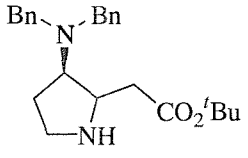
δ_H (300 MHz, $CDCl_3$): 7.40-7.20 (10H, m, ArH), 4.09 (2H, q, *J* 7, $CO_2CH_2CH_3$), 3.82 (1.6H, d, *J* 14, (PhC*H*$_{Atrans}$H$_B$)$_2$N), 3.79 (0.4 H, d, *J* 14, (PhC*H*$_{Acis}$H$_B$)$_2$N), 3.53 (0.4H, d, *J*

14, (PhCH$_A$*H*$_{Bcis}$)$_2$N), 3.49 (0.8H, dt, *J* 3, 9, C*H*$_{trans}$CH$_2$CO$_2$Et), 3.42 (1.6H, d, *J* 14, (PhCH$_A$*H*$_{Btrans}$)$_2$N), 3.16-3.04 (3.2H, m, C*H*$_{cis}$CH$_2$CO$_2$Et, C*H*$_2$NH and C*H*NBn$_2$), 2.91 (0.2H, dd, *J* 4, 17, C*H*$_{Acis}$H$_B$CO$_2$Et), 2.79 (0.8H, dd, *J* 3, 17, C*H*$_{Atrans}$H$_B$CO$_2$Et), 2.61 (0.2H, dd, *J* 10, 17, CH$_A$*H*$_{Bcis}$CO$_2$ ^{t}Bu), 2.32 (0.8H, dd, *J* 9, 17, CH$_A$*H*$_{Btrans}$CO$_2$Et), 2.00-1.80 (2H, m, NCHC*H*$_2$CH$_2$), 1.23 (3H, s, CO$_2$CH$_2$C*H*$_3$).

δ_C (75.5 MHz, $CDCl_3$): 172.6 (C), 139.6 (C), 128.8 (CH), 128.5 (CH), 127.2 (CH), 64.1 (CH), 60.8 (CH_2), 56.2 (CH), 55.2 (CH_2), 44.7 (CH_2), 37.7 (CH_2), 22.3 (CH_2), 14.3 (CH_3).

ES$^+$MS: *m/z* 353 ([M+ H]$^+$, 100%), 375 ([M+ Na]$^+$, 10%), 705 ([2M+ H]$^+$, 5%).
HRMS: *m/z* 353.2216 (calcd for $C_{22}H_{29}N_2O_2$, 353.2224).

tert-Butyl-2-[(3*R*)-3-(dibenzylamino) tetrahydro-1*H*-2-pyrrolyl] acetate (257):



257

Using a method described by Mirrington.[130]

Pyrrolidine **245** (60 mg, 0.117 mmol) was dissolved in MeOH (3.6 mL). 10% Pd/C (14.4 mg, 0.1 eq) was added into the solution. The mixture was stirred in the flask filled with H_2 gas at room temperature overnight. The mixture was filtered through celite, and the solvent was removed *in vacuo*. The crude oil was purified by column chromatography (SiO_2) eluting with DCM / EtOAc / MeOH (1:0:0 → 11:5:0.1 v/v) to give pyrrolidine **257** (32 mg, 72%) as a colourless oil. (*cis* : *trans* = 1 : 4.3)

TLC: R_f = 0.45 (DCM / EtOAc / MeOH (7:2:1 v/v)).

IR: ν_{max} (film)/cm^{-1} 3343 (br NH), 3028 (ArH), 2975 (CH_3), 2929 (CH_2), 2802 (CH), 1724 (s, CO).

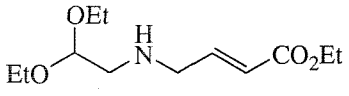
δ_H (400 MHz, $CDCl_3$): 7.30-7.10 (10H, m, ArH), 3.75 (1.62H, d, *J* 14, (PhC*H*$_{Atrans}$H$_B$)$_2$N), 3.73 (0.38 H, d, *J* 15, (PhC*H*$_{Acis}$H$_B$)$_2$N), 3.43 (0.38H, d, *J* 15, (PhCH$_A$*H*$_{Bcis}$)$_2$N), 3.35 (1.62H, d, *J* 14, (PhCH$_A$*H*$_{Btrans}$)$_2$N), 3.29 (0.81H, dt, *J* 3, 9, C*H*$_{trans}$CH$_2$CO$_2$ ^{t}Bu), 3.04 (0.19H, dt, *J* 4, 10, C*H*$_{cis}$CH$_2$CO$_2$ ^{t}Bu), 2.96 (2H, t, *J* 7,

CH_2NH), 2.92 (0.81H, apparent q, *J* 9, $CH_{trans}NBn_2$), 2.84 (0.19H, apparent q, *J* 10, $CH_{cis}NBn_2$), 2.70 (0.19H, dd, *J* 4, 17, $CH_{Acis}H_BCO_2\ ^tBu$), 2.61 (0.81H, dd, *J* 3, 17, $CH_{Atrans}H_BCO_2\ ^tBu$), 2.38 (0.19H, dd, *J* 10, 17, $CH_AH_{Bcis}CO_2\ ^tBu$), 2.04 (0.81H, dd, *J* 9, 17, $CH_AH_{Btrans}CO_2{}^tBu$), 1.98-1.68 (2H, m, $NCHCH_2CH_2$), 1.38 (1.71H, s, $CO_2{}^tBu_{cis}$), 1.35 (7.29H, s, $CO_2\ ^tBu_{trans}$).

δ_C (75.5 MHz, $CDCl_3$): 172.2 (C), 139.6 (C), 128.6 (CH), 128.3 (CH), 127.0 (CH), 81.1 (C), 63.8 (CH_2), 56.4 (CH), 55.1 (CH_2), 44.7 (CH_2), 38.6 (CH), 28.1 (CH_3), 22.3 (CH_2).

ES^+MS: *m/z* 381 ($[M + H]^+$, 100%).

Ethyl (*E*)-4-[(2,2-diethoxy ethyl) amino]-2-butenoate (293):



293

2,2-diethoxyethylamine **291** (1.33 g, 0.01 mol) was dissolved in DCM (5 mL). Ethyl 4-bromocrotonate **292** (1.93 g, 1 eq) in DCM (25 mL) was added dropwise into the amine solution at 0°C. The reaction was allowed to warm to room temperature after 1 hour, and then stirred overnight. The solvent was evaporated under reduced pressure. The crude oil was purified by column chromatography (SiO_2) eluting with EtOAc / petroleum ether (1:10 → 1:6 v/v) to give amine **293** (1.80 g, 73%) as a colorless oil.

TLC: R_f = 0.10 (EtOAc/ petroleum ether (1:3 v/v)).

IR: ν_{max} (film)/cm^{-1} 3350 (br, NH), 2975 (CH_3), 2931 (CH_2), 2879 (CH), 1663 (s, CO), 1641 (s, C=C), 1056 (COC).

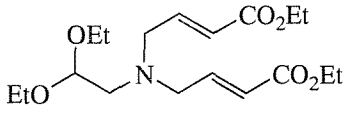
δ_H (300 MHz, $CDCl_3$): 6.96 (1H, dt, *J* 16, 6, CH_2CH=CH), 5.98 (1H, dt, *J* 16, 2, CH_2CH=C*H* CO_2Et), 4.58 (1H, t, *J* 6, $CH_2CH(OEt)_2$), 4.18 (2H, q, *J* 7, $CO_2CH_2CH_3$), 3.76-3.63 (2H, m, $OCH_AH_BCH_3$), 3.60-3.48 (2H, m, $OCH_AH_BCH_3$), 3.43 (1H, dd, *J* 2, 6, $NHCH_2CH$=CH), 2.73 (2H, d, *J* 6, $NHCH_2CH(OEt)_2$), 1.25 (6H, t, *J* 7, OCH_2CH_3), 1.21 (3H, t, *J* 7, $CO_2CH_2CH_3$).

δ_C (75.5 MHz, $CDCl_3$): 171.3 (C), 146.5 (CH), 121.9 (CH), 102.2 (CH), 62.8 (CH_2), 60.5 (CH_2), 51.8 (CH_2), 50.3 (CH_2), 15.5 (CH_3), 14.3 (CH_3).

EI$^+$MS: *m/z* 246 ([M + H]$^+$, 65%), 491 ([2M + H]$^+$, 40%).

HRMS: *m/z* 246.1695 (calcd for $C_{12}H_{14}NO_4$, 246.1700).

Ethyl (*E*)-4-[(2,2-diethoxy ethyl)(3-ethoxy carbonyl allyl) amino]-2-butenoate (294):



294

2,2-diethoxyethylamine **291** (1.33 g, 0.01 mol) was dissolved in DCM (20 mL). Ethyl 4-bromocrotonate **292** (1.93 g, 1 eq) in DCM (10 mL) was added into the amine solution at 0°C. The reaction was allowed to warm to room temperature after 1 hour, and then stirred at room temperature overnight. The solvent was evaporated under reduced pressure to give the crude tertiary amine **294** (1.25 g, 51%) as a yellow oil.

TLC: R_f = 0.39 (petroleum ether / EtOAc (3:1 v/v)).

IR: ν_{max} (film)/cm^{-1} 2978 (CH_3), 2938 (CH_2), 2891 (CH), 1720 (s, CO), 1662 (C=C), 1058 (COC).

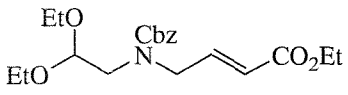
δ_H (300 MHz, $CDCl_3$): 6.89 (2H, dt, *J* 16, 6, CH_2CH=CH), 5.93 (2H, dt, *J* 16, 2, CH_2CH=C*H* CO_2Et), 4.49 (1H, t, *J* 6, $CH_2CH(OEt)_2$), 4.18 (2H, q, *J* 7, $CO_2CH_2CH_3$), 3.72-3.60 (2H, m, $OCH_AH_BCH_3$), 3.57-3.43 (2H, m, $OCH_AH_BCH_3$), 3.31 (4H, dd, *J* 1, 6, NCH_2CH=CH), 2.62 (2H, d, *J* 6, $NHCH_2CH(OEt)_2$), 1.28 (6H, t, *J* 7, OCH_2CH_3), 1.21 (6H, t, *J* 7, $CO_2CH_2CH_3$).

δ_C (75.5 MHz, $CDCl_3$): 166.4 (C), 145.8 (CH), 123.1 (CH), 100.8 (CH), 63.3 (CH_2), 60.7 (CH_2), 56.8 (CH_2), 56.0(CH_2), 15.5 (CH_3), 14.4 (CH_3).

EI$^+$MS: *m/z* 359 ([M + H]$^+$, 5%), 396 ([M + K]$^+$, 100%), 753 ([2M + K]$^+$, 20%).

HRMS: *m/z* 358.2229 (calcd for $C_{18}H_{32}NO_6$, 358.2224).

Ethyl (*E*)-4-[(benzyloxy carbonyl)(2,2-diethoxy ethyl) amino]-2-butenoate (296):



42

DMAP (165 mg, 0.3 eq) and TEA (590 mg, 1.3 eq) were added into a solution of the starting secondary amine **293** (1.10 g, 4.49 mmol) in DCM (50 mL). CbzCl (766 mg, 1 eq) in DCM (10 mL) was added dropwise into the reaction mixture at 0°C, and then the reaction was allowed to warm to room temperature overnight. The reaction was quenched with dil. aq. HCl (20 mL), washed with water (20 mL). The aqueous layer was extracted with EtOAc (3x15 mL), and the combined organic layers were dried ($MgSO_4$) and the solvent was removed *in vacuo*. The crude oil was purified by column chromatography eluting with EtOAc / petroleum ether (0:1 → 1:7 v/v) to give carbamate **296** (810 mg, 48%) as a colourless oil.

TLC: R_f = 0.33 (EtOAc / petroleum ether (1:3 v/v)).

IR: ν_{max} (film)/cm^{-1} 3095 (Ar), 3037 (Ar), 2976 (CH_3), 2938 (CH_2), 2897 (CH), 1729(s, CO), 1706 (s, CO), 1625 (C=C), 1055 (COC).

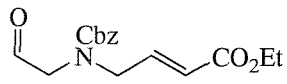
δ_H (300 MHz, $CDCl_3$): 7.45-7.30 (5H, m, Ar*H*), 6.87 (0.5H, dt, *J* 15, 5, CH_2CH_A=CH), 6.86 (0.5H, dt, *J* 15, 5, CH_2CH_B=CH), 5.86 (0.5H, d, *J* 15, CH=$CH_A CO_2Et$), 5.81 (0.5H, d, *J* 15, CH=$CH_B CO_2Et$), 5.17 (1H, s, $CO_2CH_A Ph$), 5.14 (1H, s, $CO_2CH_B Ph$), 4.63 (0.5H, t, *J* 5, $CH_2CH_A(OEt)_2$), 4.51 (0.5H, t, *J* 5, $CH_2CH_B(OEt)_2$), 4.19 (2H, q, *J* 7, $CO_2CH_2CH_3$), 4.20-4.13 (2H, m, $NHCH_2CH$=CH), 3.80-3.38 (4H, m, OCH_2CH_3), 3.35 (1H, d, *J* 5, $NCH_{2A}CH(OEt)_2$), 3.31 (1H, d, *J* 5, $NCH_{2B}CH(OEt)_2$), 1.29 (3H, t, *J* 7, $CO_2CH_2CH_3$), 1.20 (3H, t, *J* 7, OCH_2CH_{3A}), 1.15 (3H, t, *J* 7, OCH_2CH_{3B}).

δ_C (75.5 MHz, $CDCl_3$): 166.2 (C), 156.2 and 156.0 (C), 143.9 and 143.6 (CH), 136.5 (C), 128.7 and 128.6 (CH), 128.4 (CH), 128.2 and 128.0 (CH), 122.2 and 122.0 (CH), 102.1 and 101.8 (CH), 67.7 and 67.6 (CH_2), 63.7 and 63.5 (CH_2), 60.6 (CH_2), 50.8 (CH_2), 50.1 and 49.6 (CH_2), 15.5 and 15.4 (CH_3), 14.4 (CH_3).

ES^+MS: *m/z* 402 ($[M + Na]^+$, 100%), 781 ($[2M + Na]^+$, 50%).

HRMS: *m/z* 402.1885 (calcd for $C_{20}H_{29}NO_6Na$, 402.1887).

Ethyl (*E*)-4-[(benzyloxy carbonyl)(2-oxo ethyl) amino]-2-butenoate (297):



297

Following the procedure of Macdonald.[78]

Acetal **296** (500 mg, 1.32 mmol) and *p*-TsOH (330 mg, 1.4 eq) were stirred together in 20% aq. acetone (50 mL) for 3 days. The reaction was refluxed for 2 hours. The reaction mixture was quenched with sat. aq. $NaHCO_3$ (20 mL), and washed with water (20 mL). Aqueous layer was extracted with Et_2O (3x30 mL). Combined organic layers were dried ($MgSO_4$). The solvent was removed *in vacuo*. The crude oil was purified by column chromatography eluting with EtOAc / petroleum ether (1:10 → 1:5 v/v) to give aldehyde **297** (100 mg, 25%) as a colourless oil and as a 1:1 mixture of rotamers.

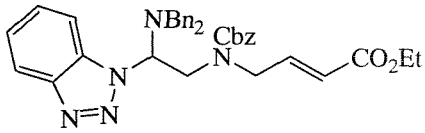
TLC: R_f = 0.40 (DCM / EtOAc / MeOH (8:2:0.1 v/v)).

IR: ν_{max} (film)/cm^{-1} 3066 (Ar), 3036 (Ar), 2976 (CH_3), 2938 (CH_2), 2897 (CH), 2749 (w, CHO), 1704 (s, CO).

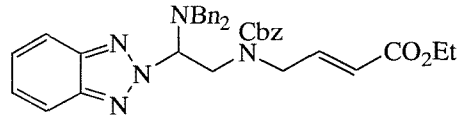
δ_H (300 MHz, $CDCl_3$): 9.62 (0.5H, s, CHO), 9.57 (0.5H, s, CHO), 7.42-7.25 (5H, m, Ar*H*), 6.86 (0.5H, dt, *J* 15, 5, CH_2CH_A=CH), 6.81 (0.5H, dt, *J* 15, 5, CH_2CH_B=CH), 5.92 (0.5H, d, *J* 15, CH=$CH_A CO_2Et$), 5.87 (0.5H, d, *J* 15, CH=$CH_B CO_2Et$), 5.18 (1H, s, $CO_2CH_{2A}Ph$), 5.15 (1H, s, $CO_2CH_{2B}Ph$), 4.20 (2H, q, *J* 7, $CO_2CH_2CH_3$), 4.18-4.01 (4H, m, NCH_2CH=CH and NCH_2CHO), 1.30 (3H, t, *J* 7, $CO_2CH_2CH_3$).

δ_C (75.5 MHz, $CDCl_3$): 197.12 and 197.05 (CH), 165.6 (C), 156.1 and 155.6 (C), 142.2 and 142.1 (CH), 135.9 (C), 128.6 (CH), 128.3 (CH), 128.0 (CH), 123.4 and 123.0 (CH), 68.1 (CH_2), 60.6 (CH_2), 57.2 and 56.7 (CH_2), 49.4 and 49.1 (CH_2), 14.2 (CH_3).

Ethyl (*E*)-3-{[3-(1,2,3-benzotriazolyl)-3-(dibenzylamino) ethyl](benzyloxy carbonyl) amino}-2-butenoate (298A and B):



298A



298B

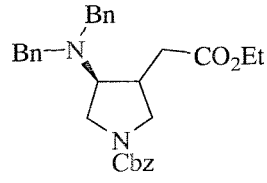
Benzotriazole adduct **298** was prepared *in situ* from DBA (47.3 mg, 0.26 mmol), aldehyde **297** (80 mg, 0.26 mmol), and BTH (28.6 mg, 1 eq) in Et_2O (10 mL). The reaction mixture was stirred further an hour before being allowed to warm to room temperature and stirred overnight. The whole mixture was diluted with DCM (10 mL) and filtered through a celite filter aid. The solvent was removed *in vacuo*, to give crude benzotriazole adduct **298** (150 mg, 96%) as a colourless oil, and as a 1:1.5 mixture of regioisomer **A** and **B**. (Both of them have two rotamers at the amide bond.)

IR: ν_{max} (film)/cm^{-1} 3087 (Ar), 3064 (Ar), 3033 (Ar), 2975 (CH_3), 2908 (CH_2), 2849 (CH), 1727(s, CO), 1703 (s, CO), 1625 (C=C).

δ_H (300 MHz, $CDCl_3$): 8.13-8.05 (0.4H, m, Ar*H*-4$_A$), 7.99-7.93 (0.6H, m, Ar*H*-4$_B$), 7.91-7.84 (0.6H, m, Ar*H*-7$_B$), 7.50-7.11 (17H, m, Ar*H*), 7.05-7.00 (0.4H, m, Ar*H*-7$_A$), 6.72-6.53 (1H, m, CH_2CH=CH), 5.91 (0.6H, t, *J* 7, NCH_BN), 5.80 (0.4H, t, *J* 7, NCH_AN), 5.68 (0.6H, d, *J* 15, CH=CH_BCO$_2$Et), 5.59 (0.4H, d, *J* 15, CH=CH_ACO$_2$Et), 5.09-4.88 (2H, m, CO_2CH_2Ph), 4.52-3.91 (2H, m, NCH_2CH=CH), 4.26 (1.2H, d, *J* 15, NC$H_{XB}H_Y$Ph), 4.22 (0.8H, d, *J* 15, NC$H_{XA}H_Y$Ph), 4.16 (2H, q, *J* 7, CH_2CH_3), 3.73-3.25 (2H, m, CHCH_2N), 3.46 (0.8H, d, *J* 15, NCH$_X$H$_{YA}$Ph), 3.34 (1.2H, d, *J* 15, NCH$_X$H$_{YB}$Ph), 1.25 (3H, t, *J* 7, CH_2CH_3).

ES$^+$MS: *m/z* 485 ([M - BT$^-$]$^+$, 40%), 198 ([NH(CH$_2$Ph)$_2$]$^+$, 100%).

Benzyl (3*R*)-3-(dibenzylamino)-4-(ethoxy carbonyl methyl) pyrrolidine-1-carboxylate (299) (Reverse addition):



299

SmI_2 was prepared from samarium metal (179 mg, 5 eq) and ICH_2CH_2I (154 mg, 2.3 eq) in THF (5 mL). After 90 minutes, EtOH (31.4 μL, 2.3 eq) was added into the solution at room temperature. The SmI_2 solution was added dropwise *via* cannular at 0°C into the THF solution (5 mL) of benzotriazole adduct precursor **298** (150 mg, 0.24 mmol). The reaction mixture was stirred at 0°C for an hour before being allowed to warm

to room temperature overnight. The reaction was quenched with sat. aq. K_2CO_3 (10 mL) followed by washing with water (10 mL). The mixture was extracted with EtOAc (3x10 mL). The combined organic extracts were washed with brine (10 mL), water (10 mL) and dried ($MgSO_4$). The solvent was removed *in vacuo*. The crude oil was purified by column chromatography (SiO_2) eluting with EtOAc / petroleum ether / TEA (1:10:0.05 → 1:7:0 v/v). Pyrrolidine **299** (40 mg, 35%) was obtained as a colourless oil, and as a mixture of diastereomers (*trans* : *cis* = 1:1.6).

TLC: R_f = 0.40 (petroleum ether / EtOAc (2:1 v/v)).

IR: ν_{max} (film)/cm^{-1} 3029 (ArH), 2975 (CH_3), 2942 (CH_2), 2890 (CH), 1730 (s, CO), 1703 (s, CO).

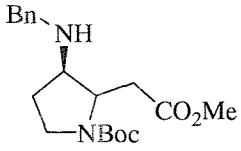
δ_H (300 MHz, $CDCl_3$): 7.35-7.10 (15H, m, Ar*H*), 5.03 (2H, s, CO_2CH_2Ph), 4.03 (H, q, *J* 7, $CO_2CH_2CH_3$), 3.85-3.69 (3H, m, $(PhCH_AH_B)_2N$ and $CH_AH_BCHCH_2CO_2Et$), 3.56-3.42 (1H, m, $CH_AH_BCHNBn_2$), 3.44-3.28 (2H, m, $(PhCH_AH_B)_2N$), 3.38-3.22 (1.36H, m, $CH_AH_BCHNBn_2$ and $CH_{trans}NBn_2$,), 3.02-2.89 (0.64H, m, $CH_{cis}NBn_2$), 2.85-2.72 (1.72H, m, $CH_AH_{Btrans}CO_2Et$, $CH_{trans}CH_2CO_2Et$ and $CH_AH_BCHCH_2CO_2Et$), 2.75-2.65 (0.64H, m, $CH_{Acis}H_BCO_2Et$), 2.65-2.52 (0.64H, m, $CH_{cis}CH_2CO_2Et$), 2.34-2.22 (0.36H, m, $CH_{Atrans}H_BCO_2Et$), 2.01-1.86 (0.64H, m, $CH_AH_{Bcis}CO_2Et$), 1.16 (H, t, *J* 7, $CO_2CH_2CH_3$).

δ_C (75.5 MHz, $CDCl_3$): 172.7 and 172.6 (C_{trans}), 172.3 and 172.1 (C_{cis}), 162.8 and 154.8 (C), 139.2 (C), 138.3 and 136.8 (C), 128.8 and 128.7 (CH), 128.5 (CH), 128.44 and 128.39 (CH), 128.1 and 127.9 (CH), 127.7 (CH), 127.2 (CH), 66.8 (CH_2), 62.9 and 62.2 (CH_{trans}), 62.0 and 61.0 (CH_{cis}), 60.6 (CH_2), 54.7 (CH_2), 49.9 and 49.6 (CH_2), 47.2 and 47.1 (CH_{2trans}), 42.8(CH_{2cis}), 37.6 and 36.7 (CH_{trans}), 36.6 and 35.9 (CH_{cis}), 36.3 and 36.0 (CH_{2cis}), 32.4 and 32.2(CH_{2cis}), 14.2 (CH_3).

ES$^+$MS: *m/z* 487 ($[M + H]^+$, 100%), 509 ($[M + Na]^+$, 40%), 995 ($[2M + Na]^+$, 25%).

HRMS: *m/z* 487.2591 (calcd for $C_{30}H_{35}N_2O_4$, 487.2597).

***tert*-Butyl (3*R*)-3-(benzylamino)-2-(methoxy carbonyl methyl) pyrrolidine -1-carboxylate (247):**



247

Following the procedure of Bull.[94]

Compound **234** (50 mg, 0.11 mmol) was dissolved in 17% aq. CH_3CN (3 mL). CAN (165 mg, 2.1 eq) was added portionwise at room temperature. The reaction was stirred at room temperature overnight. The reaction was quenched by the addition of sat. aq. $NaHCO_3$ (5 mL) and stirred vigorously for 10 minutes before extracting with Et_2O (3x5 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude oil was purified by column chromatography (SiO_2) eluting with EtOAc / petroleum ether (1:5 → 1:3 v/v) to give pyrrolidine **247** (38 mg, 94%) as a colourless oil, and as a mixture of diastereomers (*cis : trans* = 1:5.5).

TLC: R_f = 0.13 (DCM / EtOAc / petroleum ether (8:2:0.5 v/v)).

IR: ν_{max} (film)/cm^{-1} 3339 (br, NH), 3028 (ArH), 2974 (CH_3), 2928 (CH_2), 2888 (CH), 1735 (s, CO), 1690 (s, CO).

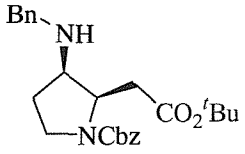
δ_H (400 MHz, $_{d6}$-DMSO, 80°C): 7.20-7.00 (5H, m, ArH), 4.07 (0.15H, m, $CH_{trans}CH_2CO_2CH_3$), 3.75 (0.85H, ddd, *J* 2, 5, 9, $CH_{cis}CH_2CO_2CH_3$), 3.62 (0.30H, s, $PhCH_{2trans}N$), 3.59 (1.70H, s, $PhCH_{2cis}N$), 3.49-3.45 (0.15H, m, $CH_{trans}NHBn$), 3.44 (3H, s, CO_2CH_3), 3.36-3.24 (1H, m, $CH_{Acis}H_BNBoc$ and $CH_{Atrans}H_BNBoc$), 3.14-3.06 (0.85H, m, $CH_AH_{Bcis}NBoc$), 3.00-2.90 (1H, m, $CH_{cis}NHBn$ and $CH_AH_{Btrans}NBoc$), 2.54 (0.15H, dd, *J* 8, 18, $CH_{Atrans}H_BCO_2CH_3$), 2.49 (0.85H, dd, *J* 5, 15, $CH_{Acis}H_BCO_2CH_3$), 2.25 (0.85H, dd, *J* 9, 15, $CH_AH_{Bcis}CO_2CH_3$), 2.26-2.20 (0.15H, m, $CH_AH_{Btrans}CO_2CH_3$), 1.89-1.77 (1H, m, $NCHCH_{Acis}H_BCH_2$ and $NCHCH_{Atrans}H_BCH_2$), 1.67 (0.15H, m, $NCHCH_AH_{Btrans}CH_2$), 1.58 (0.85H, m, $NCHCH_AH_{Bcis}CH_2$), 1.28 (1.35H, s, $C(CH_3)_{3trans}$), 1.27 (7.65H, s, $C(CH_3)_{3cis}$).

δ_C (100 MHz, $_{d6}$-DMSO, 80°C): 171.3 (C), 154.0 (C), 141.3 (C), 128.3 (CH), 128.1 (CH), 126.7 (CH), 78.8 (C), 62.0 (CH_2), 60.1 (CH), 51.4 (CH), 51.0 (CH_3), 45.0 (CH_2), 43.0 (CH_2), 38.5 (CH_2), 28.6 (CH_3).

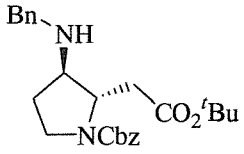
ES^+MS: *m/z* 349 ($[M + H]^+$, 100%), 697.0 ($[2M + H]^+$, 25%).

HRMS: *m/z* 371.1935 (calcd for $C_{19}H_{28}N_2O_4$, 371.1941).

Benzyl (3*R*)-3-(benzylamino)-2-(*tert*-butoxy carbonyl methyl) pyrrolidine-1-carboxylate (250 and 251):



250



251

Following the procedure of Bull.[94]

Dibenzylamine **245** (300 mg, 0.9 mmol) was dissolved in 17% aq. CH_3CN (6 mL). CAN (672 mg, 2.1 eq) was added portionwise into the starting material solution at room temperature. The reaction was stirred at room temperature for 3 days. The reaction was quenched with sat aq. $NaHCO_3$ (20 mL) and stirred vigorously for 15 minutes, before being extracted with Et_2O (3x20 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2) eluting with EtOAc / petroleum ether (1:10 → 1:7 v/v) to give *cis*-monobenzyl amine **250** (50 mg, 20%) and *trans*-monobenzyl amine **251** (150 mg, 61%) both as a colourless oil. Starting material (30 mg, 10%) was also recovered from the column.

<u>*cis*-Monobenzyl amine **250**</u>

TLC: R_f = 0.23 (petroleum ether / EtOAc (3:1 v/v)).

IR: ν_{max} (film)/cm^{-1} 3290 (br, NH), 3061 (Ar), 3031 (Ar), 2976 (CH_3), 2926 (CH_2), 2852 (CH), 1732 (s, CO), 1700 (s, CO).

δ_H (400 MHz, $_{d6}$-DMSO, 80°C): 7.40-7.20 (5H, m, ArH), 5.08 (2H, s, CO_2CH_2Ph), 4.26 (1H, m, $CHCH_2CO_2{}^tBu$), 3.73 (2H, s, $PhCH_2N$), 3.40-3.25 (3H, m, CHNHBn and CH_2NCbz), 2.64 (1H, dd, *J* 8, 15, $CH_AH_BCO_2{}^tBu$), 2.35 (1H, dd, *J* 5, 15, $CH_AH_BCO_2{}^tBu$), 2.08-1.97 (1H, m, $CHCH_AH_BCH_2$), 1.75-1.64 (1H, m, $CHCH_AH_BCH_2$), 1.37 (9H, s, $CO_2{}^tBu$).

δ_C (75.5 MHz, $CDCl_3$): 170.5 (C), 154.7 (C), 139.8 (C), 136.9 (C), 128.4 (CH), 128.2 (CH), 128.1 (CH), 127.8 (CH), 127.5 (CH), 127.0 (CH), 80.8 (C), 66.7 (CH_2), 62.3 (CH), 60.0 (CH), 51.5 (CH_2), 44.9 (CH_2), 39.4 (CH_2), 28.9 (CH_2), 27.1 (CH_3).

ES^+MS: *m/z* 425 ($[M + H]^+$, 100%), 447 ($[M+ Na]^+$, 75%), 463 ($[M + K]^+$, 80%).

HRMS: *m/z* 425.2431 (calcd for $C_{25}H_{33}N_2O_4$, 425.2435).

trans-Monobenzyl amine **251**

TLC: R_f = 0.12 (petroleum ether / EtOAc (3:1 v/v)).

IR: ν_{max} (film)/cm^{-1} 3323 (br, NH), 3060 (Ar), 3030 (Ar), 2975 (CH_3), 2936 (CH_2), 2884 (CH), 1717 (s, CO), 1699 (s, CO).

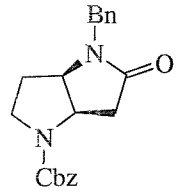
δ_H (400 MHz, $_{d6}$-DMSO, 80°C): 7.40-7.20 (5H, m, ArH), 5.10 (2H, s, CO_2CH_2Ph), 3.97 (1H, m, $CHCH_2CO_2{}^tBu$), 3.75 (2H, s, $PhCH_2N$), 3.54 (1H, dt, *J* 9, 10, CH_AH_BNCbz), 3.40-3.25 (1H, m, CH_AH_BNCbz), 3.13-3.12 (1H, m, *CH*NHBn), 2.57 (1H, dd, *J* 4, 15, $CH_AH_BCO_2{}^tBu$), 2.33 (1H, dd, *J* 9, 15, $CH_AH_BCO_2{}^tBu$), 2.08-1.97 (1H, m, $CHCH_AH_BCH_2$), 1.82-1.74 (1H, m, $CHCH_AH_BCH_2$), 1.39 (9H, s, $CO_2{}^tBu$).

δ_C (75.5 MHz, $CDCl_3$): 170.4 (C), 154.8 (C), 140.1 (C), 136.9 (C), 128.40 (CH), 128.38 (CH), 128.1 (CH), 127.8 (CH), 127.5 (CH), 127.0 (CH), 80.7 (C), 66.6(CH_2), 61.4 (CH), 60.6 (CH), 51.6 (CH_2), 44.6 (CH_2), 38.3 (CH_2), 29.6 (CH_2), 28.1 (CH_3).

ES^+MS: *m/z* 425 ($[M + H]^+$, 100%), 447 ($[M + Na]^+$, 12%), 849 ($[2M + Na]^+$, 10%).

HRMS: *m/z* 425.2435 (calcd for $C_{25}H_{33}N_2O_4$, 425.2435).

(3aR, 6aR)-4-Benzyl-5-oxo-hexahydro-pyrrolo [3,2-*b*] pyrrolidine-1-carboxylic acid benzyl ester (252):



252

TFA (0.4 mL) was added slowly into the *cis*-monobenzyl amine **250** (50 mg, 0.12 mmol) / DCM (2.0 mL) solution at room temperature. The reaction mixture was stirred at room temperature overnight. The solvent was removed *in vacuo*. The residue was dissolved in DCM (8 mL). To this DCM solution DIPEA (46 mg, 3 eq) was added slowly. After 30 minutes, DIC (15.5 mg, 1.3 eq) was added dropwise, and the reaction was stirred at room temperature overnight. The reaction was quenched with sat. aq. $NaHCO_3$ (10 mL), and washed with water (10 mL). Aqueous layer was extracted with

DCM (3x10 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude oil was purified by column chromatography (SiO_2) eluting with EtOAc / DCM (0:1 → 1:10 v/v) to give a pyrrolidine *cis*-lactam **252** (30 mg, 71%) as a colourless oil.

TLC: R_f = 0.25 (DCM / EtOAc / MeOH (8:2:0.1 v/v)).

IR: ν_{max} (film)/cm^{-1} 3062 (Ar), 3033 (Ar), 2953 (CH_3), 2925 (CH_2), 2885 (CH), 1686 (s CO).

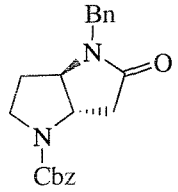
δ_H (300 MHz, $CDCl_3$): 7.42-7.20 (10H, m, ArH), 5.20-5.08 (2H, AB pattern, CO_2CH_2Ph), 4.87 (1H, dd, *J* 11, 15, NCH_AH_BPh), 4.41-4.29 (1H, dd, *J* 10, 15, CH_AH_BNCbz), 4.16 (1H, dd, *J* 6, 15, NCH_AH_BPh), 4.13-4.06 (1H, m, CH_AH_BNCbz), 3.77-3.62 (1H, quintet, *J* 10, $CHCHNCbz$), 3.24 (1H, ddt, *J* 6, 10, 11, $CHCHNCbz$), 2.80-2.58 (2H, m, CH_2CONBn), 2.12-2.00 (1H, dt, *J* 6, 14, $CHCH_AH_BCH_2$), 1.87-1.73 (1H, ddt, *J* 6, 11, 14, $CHCH_AH_BCH_2$).

δ_C (75.5 MHz, $CDCl_3$): 173.8 (C), 173.2 (C), 136.3 (C), 136.1 (C), 128.82 (CH), 128.80 (CH), 128.6 (CH), 128.04 (CH), 128.02 (CH), 128.00 (CH), 67.2 and 67.0 (CH_2), 62.4 and 61.4 (CH), 54.8 and 54.1 (CH), 44.6 and 44.5 (CH_2), 44.3 and 43.9 (CH_2), 38.7 and 37.7 (CH_2), 28.1 and 27.8 (CH_2).

ES^+MS: *m/z* 351 ($[M + H]^+$, 40%), 373 ($[M + Na]^+$, 100%), 701 ($[2M + H]^+$, 40%), 723 ($[2M + Na]^+$, 50%).

HRMS: *m/z* 373.1520 (calcd for $C_{21}H_{22}N_2O_3Na$, 373.1523).

(3aR, 6aS)-4-Benzyl-5-oxo-hexahydro-pyrrolo [3,2-*b*] pyrrolidine-1-carboxylic acid benzyl ester (253):



253

TFA (0.4 mL) was added into the *trans*-monobenzyl amine **251** (70 mg, 0.17 mmol) / DCM (2.0 mL) solution at room temperature. The reaction mixture was stirred at room temperature overnight. The solvent was removed *in vacuo*. The residue was

dissolved in DCM (12 mL). To this DCM solution DIPEA (69.8 mg, 3 eq) was added slowly. After 30 minutes, DIC (24 mg, 1.3 eq) was added dropwise, and the reaction was stirred at room temperature overnight. The reaction was quenched with sat. aq. $NaHCO_3$ (12 mL), and washed with water (12 mL). Aqueous layer was extracted with DCM (3x15 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude oil was purified by column chromatography (SiO_2) eluting with EtOAc / DCM / MeOH (0:1:0 → 2:8:0.1 v/v) to give a pyrrolidine *trans*-lactam **253** (50 mg, 79%) as a colourless oil.

TLC: R_f = 0.48 (DCM / EtOAc / MeOH (8:2:0.1 v/v)).

IR: ν_{max} (film)/cm^{-1} 3062 (Ar), 3032 (Ar), 2958 (CH_3), 2925 (CH_2), 2855 (CH), 1698 (s CO).

δ_H (300 MHz, $CDCl_3$): 7.45-7.20 (10H, m, ArH), 5.10 (2H, AB pattern, CO_2CH_2Ph), 4.51 (2H, AB pattern, NCH_2Ph), 3.82-3.71 (1H, t, *J* 10, CH_AH_BNCbz), 3.59 (1H, dt, *J* 7, 11, CH_AH_BNCbz), 3.33 (1H, ddd, *J* 6, 10, 12, CHCHNCbz), 3.13 (1H, ddd, *J* 5, 10, 12, CHCHNCbz), 2.93-2.80 (1H, br m, CH_AH_BCONBn), 2.47 (1H, br m, CH_AH_BCONBn), 1.92 (1H, dt, *J* 5, 10, $CHCH_AH_BCH_2$), 1.61 (1H, quintet, *J* 10, $CHCH_AH_BCH_2$).

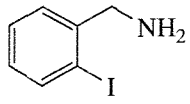
δ_C (75.5 MHz, $CDCl_3$): 176.7 (C), 155.3 (C), 136.5 (C), 136.3 (C), 128.7 (CH), 128.6 (CH), 128.4 (CH), 128.2 (CH), 128.0 (CH), 127.8 (CH), 67.1 (CH_2), 63.8 (CH), 61.8 (CH), 49.2 (CH_2), 46.0 (CH_2), 39.4 (CH_2), 29.7 (CH_2).

ES^+MS: *m/z* 351 ($[M + H]^+$, 100%), 373 ($[M + Na]^+$, 80%).

HRMS: *m/z* 351.1701 (calcd for $C_{21}H_{23}N_2O_3$, 351.1703).

4.4) Experiment for *Chapter 3*

o-Iodobenzyl amine (328):



328

Based on a modified method by Bowman.[111]

o-Iodobenzyl bromide **327** (3.4 g, 11.45 mmol) in carbon tetrachloride (10 mL) was added dropwise to a solution of hexamethylenetetramine (1.7 g, 1.1 eq) in carbon tetrachloride (45 mL) and heated under reflux overnight. The hexamethylenetetramine adduct (4.73 g, 94%) was obtained after the filtration, and this salt was refluxed for overnight in EtOH (20 mL), water (4 mL) and conc. HCl (10 mL). Evaporation to dryness *in vacuo* gave a semi-crystalline residue, which was basified to pH 14 with 10% aq. NaOH and extracted by ether (3x30 mL). The organic layers were extracted with dil. aq. HCl (100 mL). The aqueous layer was basified to pH 14 with 10% aq. NaOH and extracted with Et_2O (5x20 mL). The combined organic layers were washed with water (20 mL), dried ($MgSO_4$). The solvent was evaporated to dryness to yield *o*-Iodobenzyl amine **328** (2.2 g, 82%) as a yellow oil.

TLC: R_f = 0.79 (DCM/ EtOAc (3:1 v/v)).

IR: ν_{max} (film)/cm^{-1} 3401 (NH_2), 3029 (Ar), 2901 (CH_2), 2820 (CH), 1009 (C-N).

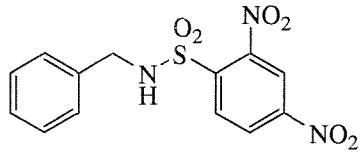
δ_H (300 MHz, $CDCl_3$): 7.78 (1H, d, *J* 7, Ar*H*), 7.40-7.30 (2H, m, Ar*H*), 6.90-6.85 (1H, m, Ar*H*), 3.82 (2H, s, CH_2NH_2), 1.57 (2H, s, CH_2NH_2).

δ_C (75.5 MHz, $CDCl_3$): 144.9 (C), 139.4 (CH), 128.7 (CH), 128.6 (CH), 128.5 (CH), 98.9 (C), 51.3 (CH_2).

CIMS: *m/z* 234 ($[M + H]^+$, 15%), 108 ($[M - I]^+$, 100%).

Data were spectroscopically found to be consistent with that reported by Bowman.[111]

***N*1-(2-Benzyl)-2,4-dinitro-1-benzenesulfonamide (326):**



326

Following a modified method by Fukuyama.[133]

Benzyl amine (66.7 mg, 0.62 mmol) and TEA (0.09 ml, 1.5 eq) were dissolved in DCM (15 ml). DNBSCl (165.3 mg, 1 eq) in DCM (5 mL) was added slowly to the reaction at 0°C. The reaction mixture was stirred further 15 minutes before being allowed to warm to room temperature overnight. The reaction was quenched with dil. aq. HCl (20 mL), followed by washing with water (20 ml). The organic extract was dried ($MgSO_4$) and the solvent was evaporated *in vacuo*. The crude oil was purified by column chromatography (SiO_2) eluting with petroleum ether / EtOAc (4:1 v/v) to give sulfonamide **326** (120 mg, 65%) as a yellow solid.

TLC: R_f = 0.26 (petroleum ether/ EtOAc (3:1 v/v)).

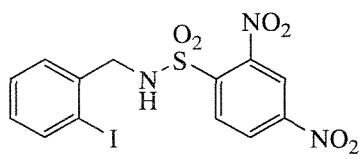
IR: ν_{max} (film)/cm^{-1} 3378 (s, NH), 3107 (Ar), 3086 (Ar), 2361 (CH), 1535 (s, NO_2), 1348 (s, SO_2), 1162 (s, SO_2).

δ_H (300 MHz, $CDCl_3$): 8.60 (1H, d, *J* 2, Ar*H*), 8.34 (1H, dd, *J* 2, 9, Ar*H*), 8.06 (1H, d, *J* 8, Ar*H*), 7.29-7.20 (4H, m, Ar*H*), 5.97 (1H, t, *J* 7, N*H*), 4.42 (2H, d, *J* 7, CH_2NH).

EI$^+$MS: *m/z* 336 ($[M + H]^+$, 5%), 288 ($[M - NO_2^-]^+$, 10%), 231 ($[M - BnNH^-]^+$, 35%).

Spectroscopic data were found to be consistent with that reported by Fukuyama.[131]

***N*1-(2-Iodobenzyl)-2,4-dinitro-1-benzenesulfonamide (332):**



332

Following a modified method by Fukuyama.[131]

o-Iodobenzyl amine **331** (144.5 mg, 0.62 mmol) and TEA (0.09 ml, 1.5 eq) were dissolved in DCM (15 ml). DNBSCl (165.3 mg, 1 eq) in DCM (5 mL) was added slowly to the reaction at 0°C. The reaction mixture was stirred further 15 minutes before being allowed to warm to room temperature overnight. The reaction was quenched with dil. aq. HCl (20 mL), followed by washing with water (20 ml). The organic extract was dried ($MgSO_4$) and the solvent was evaporated *in vacuo*. The crude oil was purified by column chromatography (SiO_2) eluting with petroleum ether / EtOAc (7:1 → 4:1 v/v) to give sulfonamide **332** (80 mg, 30%) as a yellow solid.

TLC: R_f = 0.38 (petroleum ether/ EtOAc (3:1 v/v)).

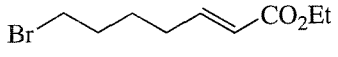
IR: ν_{max} (film)/cm^{-1} 3359 (s, NH), 3116 (Ar), 1537 (s, NO_2), 1341 (s, SO_2), 1166 (s, SO_2).

δ_H (300 MHz, $CDCl_3$): 8.65 (1H, d, *J* 2, Ar*H*), 8.34 (1H, dd, *J* 2, 9, Ar*H*), 8.03 (1H, d, *J* 9, Ar*H*), 7.68 (1H, d, *J* 8, Ar*H*), 7.41 (1H, dd, *J* 1, 8, Ar*H*), 7.30 (1H, t, *J* 7, Ar*H*), 6.96 (1H, dt, *J* 1, 7, Ar*H*), 6.30 (1H, t, *J* 7, N*H*), 4.48 (2H, d, *J* 7, CH_2NH).

δ_C (100 MHz, $CDCl_3$): 139.7 (C), 139.6 (C), 137.7 (C), 132.2 (CH), 132.1 (CH), 130.9 (C), 130.2 (CH), 130.1 (CH), 128.5 (CH), 126.7 (CH), 120.6 (CH), 98.9 (C), 52.5 (CH_2).

EI^+MS: *m/z* 463 ($[M + H]^+$, 16%).

Ethyl (*E*)-7-bromo-2-heptenoate (351):



351

Using a method published by Smith.[115]

Carbon tetrabromide (263 mg, 0.80 mmol) was added to alcohol **210** (124 mg, 0.72 mmol) in DCM (10 mL) at 0°C. PPh_3 (416 mg, 1.58 mmol) in DCM (10 mL) was added dropwise and the reaction mixture was stirred for 1.5 hours at 0°C. Et_2O (100 mL) was added and precipitating Ph_3PO was removed by filtration through celite. After the removal of solvent *in vacuo*, the crude yellow oil was purified by column

chromatography eluting with petroleum ether / EtOAc (5:1 v/v) to give bromide **351** (104 mg, 77%) as a colourless oil.

TLC: R_f = 0.62 (petroleum ether / EtOAc (3:1 v/v)).

IR: ν_{max} (film)/cm^{-1} 2987 (CH_3), 2939 (CH_2), 2864 (CH), 1714 (s, CO), 1654 (C=C).

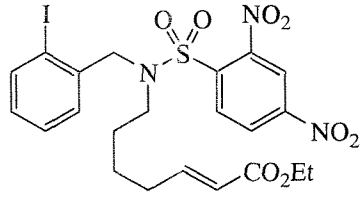
δ_H (300 MHz, $CDCl_3$): 6.93 (1H, dt, *J* 15, 7, C*H*=CHCO$_2$Et), 5.82 (1H, dt, *J* 15, 1, CH=C*H*CO$_2$Et), 4.19 (2H, q, *J* 7, C*H*$_2$CH$_3$), 3.42 (2H, t, *J* 7, C*H*$_2$Br), 2.25 (2H, dq, *J* 1, 7, C*H*$_2$CH=CH), 1.90 (2H, m, C*H*$_2$CH$_2$Br), 1.58 (2H, m, CH$_2$C*H*$_2$CH$_2$), 1.22 (3H, t, *J* 7, CH$_2$C*H*$_3$).

δ_C (75.5 MHz, $CDCl_3$): 166.7 (C), 148.3 (CH), 122.0 (CH), 60.4 (CH_2), 32.4 (CH_2), 32.2 (CH_2), 31.3 (CH_2), 26.7 (CH_2), 14.4 (CH_3).

CIMS: *m/z* 235 ([^{79}BrM + H]$^+$, 10%), 237 ([^{81}BrM + H]$^+$, 12%).

Spectroscopic data were found to be consistent with that reported by Hanessian.[40]

Ethyl (*E*)-7-[(2-iodobenzyl)(2,4-dinitrophenyl sulfonyl)amino]-2-heptenoate (324):



324

Using a modified Mitsunobu reaction developed by Burgess.[134]

DEAD (0.2 mL, 1.1 mmol) was added over 5 minutes to an ice-cold mixture of alcohol **210** (240 mg, 1.1 mmol), Ph_3P (340 mg, 1.3 eq), and sulfonamide **332** (500 mg, 1.1 mmol) in THF (7 mL). The reaction mixture was stirred for 4 days afterwhich the THF was removed *in vacuo*. The resultant residue was purified by flash column chromatography (SiO_2) eluting with EtOAc / petroleum ether (1:7 → 1:4 v/v) affording an ethyl ester **324** as a yellow powder (473 mg, 69%).

TLC: R_f = 0.20 (petroleum ether/ EtOAc (3:1 v/v)).

IR: ν_{max} (film)/cm^{-1} 3100 (Ar), 2987 (CH_3), 2936 (CH_2), 1709 (s, CO), 1536 (s, NO_2), 1346 (s, SO_2), 1161 (s, SO_2).

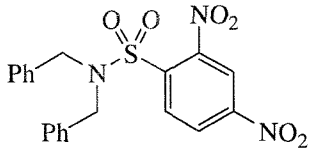
δ_H (300 MHz, $CDCl_3$): 8.47 (1H, d, *J* 2, Ar*H*), 8.32 (1H, dd, *J* 2, 9, Ar*H*), 8.01 (1H, d, *J* 8, Ar*H*), 7.64 (1H, dd, *J* 1, 8, Ar*H*), 7.40-7.22 (2H, m, Ar*H*), 6.91 (1H, dt, *J* 2, 7, Ar*H*), 6.79 (1H, dt, *J* 15, 7, CH_2CH=$CHCO_2Et$), 5.70 (1H, dt, *J* 15, 1, CH_2CH=$CHCO_2Et$), 4.60 (2H, s, CH_2Ar), 4.15 (2H, q, *J* 7, $CO_2CH_2CH_3$), 3.37 (2H, t, *J* 7, NCH_2CH_2), 2.10 (2H, dt, *J* 1, 7, CH_2CH_2CH), 1.52-1.31 (4H, m, $NCH_2CH_2CH_2$ and $CH_2CH_2CH_2CH$), 1.27 (2H, t, *J* 7, $CO_2CH_2CH_3$).

δ_C (75.5 MHz, $CDCl_3$): 166.6 (C), 149.7 (C), 148.1 (CH), 139.7(CH), 139.1 (C), 137.4 (C), 132.4 (C), 130.0 (CH), 129.5 (CH), 129.4 (CH), 128.9 (CH), 126.3 (CH), 122.0 (CH), 119.9 (CH), 98.9 (C), 60.4 (CH_2), 56.3 (CH_2), 48.7 (CH_2), 31.5 (CH_2), 27.6 (CH_2), 24.9 (CH_2), 14.4 (CH_3).

CIMS: *m/z* 635 ($[M + NH_4^+]^+$, 8%), 481 ([M – heptenoate moiety + $NH_4^+]^+$, 100%).

HRMS: *m/z* 640.0238 (calcd for $C_{22}H_{24}IN_3O_8SNa$, 640.0221).

N1,N1-Dibenzyl-2,4-dinitro-1-benzenesulfonamide (330):



330

From Mitsunobu reaction:

Using a modified Mitsunobu reaction developed by Burgess.[132]

DEAD (0.03 mL, 0.17 mmol) was added over 2 minutes to an ice-cold mixture of benzylalcohol (20 mg, 0.17 mmol), Ph_3P (53 mg, 1.2 eq), and sulfonamide **329** (60 mg, 0.17 mmol) in THF (1 mL). The reaction mixture was stirred for 4 days afterwhich the THF was removed *in vacuo*. The resultant residue was purified by flash chromatography (SiO_2) eluting with EtOAc / petroleum ether = 1:7 → 1:4 (v/v) to give sulfonamide **330** (25 mg, 37%) as a cream solid.

TLC: R_f = 0.31 (petroleum ether/ EtOAc (3:1 v/v)).

IR: ν_{max} (film)/cm^{-1} [1] 3094 (Ar), 2917 (CH_2), 1537 (s, NO_2), 1347 (s, SO_2), 1162 (s, SO_2).

δ_H (300 MHz, $CDCl_3$): 8.49 (1H, d, *J* 2, Ar*H*), 8.26 (1H, dd, *J* 2, 9, Ar*H*), 7.95 (1H, d, *J* 9, Ar*H*), 7.30-7.24 (6H, m, Ar*H*), 7.18-7.12 (4H, m, Ar*H*), 4.42 (4H, s, NCH_2Ph).

δ_C (75.5 MHz, $CDCl_3$) 149.8 (C), 148.1 (C), 140.2 (C), 135.1 (C), 133.1 (CH), 129.2 (CH), 128.8 (CH), 128.6 (CH), 126.2 (CH), 120.0 (CH), 51.9 (CH_2).

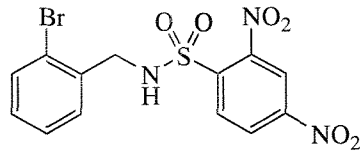
ES^+MS: *m/z* 450 ($[M + H]^+$, 52%), 877 ($[2M + Na]^+$, 100%).

HRMS: *m/z* 877.1568 (calcd for $C_{40}H_{34}N_3O_{12}S_2Na$, 877.1573).

From reaction with K_2CO_3:

Benzylbromide (30 mg, 0.17 mmol) in DMF (0.3 mL) was added into the DMF (0.7 mL) solution of sulfonamide **329** (60 mg, 1 eq) and K_2CO_3 (84 mg, 3 eq). The reaction mixture was stirred further 2 days. The reaction was quenched with dil. aq. HCl (5 mL), followed by washing with water (10 ml). Aqueous layer was extracted with EtOAc (2x20 mL). The combined organic extracts were dried ($MgSO_4$) and the solvent was evaporated *in vacuo*. The crude yellow solid was purified by column chromatography (SiO_2) eluting with EtOAc / petroleum ether (1:6 → 1:3 v/v) to give sulfonamide **330** (80 mg, 100%) as a cream solid.

N1-(2-bromobenzyl)-2,4-dinitro-1-benzenesulfonamide (335):



335

Following a modified method by Fukuyama.[131]

o-Bromobenzyl amine **334** (150 mg, 0.81 mmol) and TEA (0.17 ml, 1.5 eq) was dissolved in THF (20 ml). DNBSCl (215 mg, 1 eq) in THF (10 mL) was added slowly to the reaction at 0°C. The reaction mixture was stirred further 15 minutes before being allowed to warm to room temperature overnight. The reaction was quenched with dil. aq. HCl (20 mL), followed by washing with water (15 ml). Aqueous layer was extracted with EtOAc (3x10 mL). The combined organic extracts were dried ($MgSO_4$) and the solvent was evaporated *in vacuo*. The crude yellow solid was purified by column

chromatography (SiO_2) eluting with petroleum ether / EtOAc (7:1 → 4:1 v/v) to give sulfonamide **335** (290 mg, 80%) as a yellow solid.

TLC: R_f = 0.38 (petroleum ether/ EtOAc (3:1 v/v)).

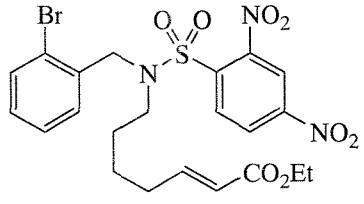
IR: ν_{max} (film)/cm^{-1} 3337 (s, NH), 3116 (Ar), 2923 (CH_2), 1537 (s, NO_2), 1347 (s, SO_2), 1171 (s, SO_2).

δ_H (300 MHz, $CDCl_3$): 8.63 (1H, d, *J* 2, Ar*H*), 8.31 (1H, dd, *J* 2, 8, Ar*H*), 8.00 (1H, d, *J* 8, Ar*H*), 7.68 (1H, d, *J* 8, Ar*H*), 7.38 (1H, dd, *J* 1, 8, Ar*H*), 7.25 (1H, dt, *J* 1, 8, Ar*H*), 7.11 (1H, dt, *J* 1, 8, Ar*H*), 6.32 (1H, t, *J* 7, N*H*), 4.50 (2H, d, *J* 7, CH_2NH).

δ_C (75.5 MHz, $CDCl_3$): 174.5 (C), 139.8 (C), 134.9 (C), 133.1 (C), 132.4 (CH), 131.6 (CH), 130.3 (CH), 127.8 (CH), 126.9 (CH), 126.9 (CH), 123.8 (C), 120.8 (CH), 48.6 (CH_2).

EI^+MS: *m/z* 415 ($[^{79}BrM + H]^+$, 10%), 417 ($[^{81}BrM + H]^+$, 11%).

Ethyl (*E*)-7-[(2-bromobenzyl)[(2,4-dinitrophenyl sulfonyl)amino]-2-heptenoate(333):



333

Using a modified Mitsunobu reaction developed by Burgess.[132]

DEAD (1.05 g, 6.0 mmol) was added over 5 minutes to an ice-cold mixture of alcohol **210** (1.03 g, 6.0 mmol), Ph_3P (2.05 g, 1.3 eq) and sulfonamide **335** (2.5 g, 6.0 mmol) in THF (40 mL). The reaction mixture was stirred for 4 days afterwhich the THF was removed *in vacuo*. The resultant residue was purified by flash column chromatography (SiO_2) eluting with EtOAc / petroleum ether (1:7 → 1:4 v/v) to give sulfonamide **333** (1.72 g, 50%) as a yellow powder.

TLC: R_f = 0.23 (petroleum ether/ EtOAc (3:1 v/v)).

IR: ν_{max} (film)/cm^{-1} 3100 (Ar), 2980 (CH_3), 2936 (CH_2), 1710 (s, CO), 1536 (s, NO_2), 1346 (s, SO_2), 1162 (s, SO_2).

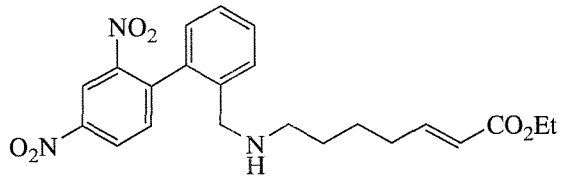
δ_H (300 MHz, $CDCl_3$): 8.49 (1H, d, *J* 2, Ar*H*), 8.41 (1H, dd, *J* 2, 9, Ar*H*), 8.12 (1H, d, *J* 9, Ar*H*), 7.51 (1H, dd, *J* 1, 8, Ar*H*), 7.42 (1H, dd, *J* 1, 7, Ar*H*), 7.29 (1H, dt, *J* 1, 7, Ar*H*), 7.16 (1H, dt, *J* 1, 8, Ar*H*), 6.82 (1H, dt, *J* 15, 7, C*H*=CHCO$_2$Et), 5.72 (1H, dt, *J* 15, 1, CH=C*H*CO$_2$Et), 4.68 (2H, s, CH_2Ar), 4.18 (2H, q, *J* 7, CH_2CH$_3$), 3.38 (2H, t, *J* 7, NCH_2CH$_2$CH$_2$), 2.13 (1H, dq, *J* 1, 7, CH_2CH=CH), 1.56-1.34 (4H, t, *J* 7, NCH$_2$CH_2CH_2), 4.18 (3H, t, *J* 7, CH$_2$CH_3).

δ_C (75.5 MHz, $CDCl_3$): 166.4 (C), 149.5 (C), 147.8 (CH), 139.0 (C), 134.2(C), 133.0 (CH), 132.5 (CH), 130.0 (CH), 129.7 (CH), 127.9 (CH), 127.6 (C), 126.0 (CH), 123.6 (C), 121.8 (CH), 119.7 (CH), 60.2 (CH_2), 51.3 (CH_2), 48.6 (CH_2), 31.3 (CH_2), 27.4 (CH_2), 24.8(CH_2), 14.2 (CH_3).

EI$^+$MS: *m/z* 569 ([^{79}BrM + H]$^+$, 10%), 571 ([^{81}BrM + H]$^+$, 11%).

HRMS: *m/z* 569.0373 (calcd for $C_{22}H_{24}{}^{79}BrN_3O_8SNa$, 569.0359).

Ethyl (*E*)-7-[(2',4'-dinitrobiphenyl-2-yl methyl)amino]-2-heptenoate (336):



336

From iodide precursor:

The solution of Bu_3SnH (51 mg, 2 eq) and AIBN (30 mg, 2 eq) in THF (4 mL) was added 5 hours to a solution of iodobenzyl sulfonamide **324** (50 mg, 0.09 mmol) in toluene (5 mL) at 100°C. The reaction was refluxed overnight. The solvent was removed *in vacuo*. The residue was dissolved in CH_3CN (30 mL). The solution was washed with petroleum ether (20 mL). CH_3CN layer was dried ($MgSO_4$) and the solvent was removed *in vacuo*. The crude was purified by column chromatography eluting with petroleum ether / EtOAc (7:1 → 3:1v/v) to give starting materials **33** (10 mg, 20%) back and biaryl amine **336** (5 mg, 27%) as a yellow oil.

From bromide precursor:

The solution of Bu_3SnH (297 mg, 2 eq) and AIBN (180 mg, 2 eq) in THF (10 mL) was added 5 hours to a solution of bromobenzyl sulfonamide **333** (300 mg, 0.51 mmol) in toluene (20 mL) at 100°C. The reaction was refluxed overnight. The solvent was removed *in vacuo*. The residue was dissolved in CH_3CN (30 mL). The solution was washed with petroleum ether (20 mL). CH_3CN layer was dried ($MgSO_4$) and the solvent was removed *in vacuo*. The crude was purified by column chromatography eluting with petroleum ether / EtOAc (7:1 → 3:1v/v) to get 30 mg of starting materials back, and 170 mg of mixture of by-products. The residue was then purified again by column chromatography eluting with petroleum ether / EtOAc (10:1 → 3:1v/v) to give biaryl amine **336** (70 mg, 32%) as a yellow oil.

TLC: R_f = 0.1 (petroleum ether / EtOAc (3:1 v/v)).

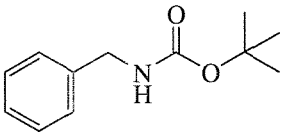
IR: ν_{max} (film)/cm^{-1} 3459 (NH), 3103 (Ar), 2926 (CH_2), 2855 (CH), 1714 (s, CO), 1653 (C=C), 1549 (s, NO_2).

δ_H (300 MHz, $CDCl_3$): 7.95 (1H, d, *J* 8, ArH), 7.72 (1H, br s, ArH), 7.65 (1H, br d, *J* 7, ArH), 7.49 (1H, d, *J* 8, ArH), 7.36 (1H, dd, *J* 1, 7, ArH), 7.24 (1H, dt, *J* 1, 7, ArH), 7.11 (1H, dt, *J* 1, 7, ArH), 6.84 (1H, dt, *J* 7, 16, CH_2CH=CH), 5.75 (1H, d, *J* 16, CH_2 CH=C*H*), 4.66 (2H, d, *J* 1, CH_2Ar), 4.17 (2H, q, *J* 7, $CO_2CH_2CH_3$), 3.36 (2H, m, NCH_2CH_2), 2.11 (2H, q, *J* 7, CH_2CH_2CH), 1.56-1.32 (4H, m, CH_2CH_2), 1.26 (3H, t, *J* 7, $CO_2CH_2CH_3$).

δ_C (100 MHz, $CDCl_3$): 166.3 (C), 148.5 (CH), 133.4 (CH), 133.3 (C), 132.0 (CH), 131.9 (CH), 130.5 (C), 130.3 (CH), 129.9 (CH), 128.5 (C), 128.3 (CH), 128.2 (CH), 128.0 (C), 122.3 (CH), 121.2 (CH), 60.6 (CH_2), 51.5 (CH_2), 48.7 (CH_2), 31.9 (CH_2), 27.4 (CH_2), 27.2 (CH_2), 14.7 (CH_3).

ES^+MS: *m/z* 450 ($[M + Na]^+$, 100%).

***tert*-Butyl *N*-benzyl carbamate (350):**



350

Following the method published by Kanazawa.[135]

Boc_2O (2.18 g, 10 mmol) was added dropwise into benzylamine **349** (1.07 g, 10 mmol) and TEA (1.4 ml, 1.1 eq.) / DCM (100 mL) solution at 0°C. The reaction mixture was left stirring overnight. The reaction was quenched with dil. aq. HCl (50 mL), followed by washing with water (50 ml). The aqueous layers were extracted with DCM (3x20 mL). Combined organic extracts were dried ($MgSO_4$). After removing the solvent *in vacuo*, the crude colourless oil **350** (2.02 g, 98%) was obtained.

TLC: R_f = 0.82 (MeOH / DCM (1:3 v/v)).

m.p. 53-55°C (lit.[134] 55.5-56.5°C).

IR: ν_{max} (film)/cm^{-1} 3339 (NH), 3304 (amide), 3065 (Ar), 2980 (CH_3), 2929 (CH_2), 2869 (CH), 1676 (s, CO).

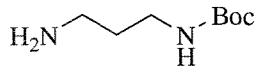
δ_H (300 MHz, $CDCl_3$): 7.40-7.25 (5H, m, Ar*H*), 4.91 (1H, br s, N*H*), 4.32 (2H, br, CH_2Ph), 1.48 (9H, s, CH_3).

δ_C (75.5 MHz, $CDCl_3$): 155.9 (C), 138.9 (C), 128.6 (CH), 127.4 (CH), 127.3 (CH), 79.4 (C), 44.6 (CH_2), 28.4 (CH_3).

ES^+MS: *m/z* 143 (1/2($[M + 2K]^+$), 100%), 249 ($[M + MeCN + H]^+$, 10%).

Spectroscopically identified to that reported by Muller.[134]

tert-Butyl _N_-(3-amino propyl)carbamate (365):



365

Based on a method published by Muller.[134]

Boc_2O (9.0 g, 41 mmol) / DCM (800 mL) was added dropwise by a dropping funnel, over a period of 12 hours under vigorous stirring into 1,3-diaminopropane **364** (16.0 g, 216 mmol) / Et_2O (80 mL). The stirring was continued overnight. The reaction was then washed with a 2M solution of Na_2CO_3 (2x200 mL), and water (2x200 ml). Aqueous layer was extracted with DCM (3x100 mL). Combined organic extracts were dried ($MgSO_4$) and the solvent was evaporated *in vacuo* to afford protected amine **365** (7.2 g, 100%) as a colourless oil.

TLC: R_f = 0.82 (MeOH/ DCM (1:3 v/v)).

IR: ν_{max} (film)/cm^{-1} 3332 (NH), 2976 (CH_3), 2931 (CH_2), 2869 (CH), 1691 (s, CO).

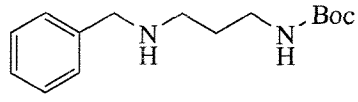
δ_H (300 MHz, $CDCl_3$): 5.02 (1H, m, N*H*), 3.12 (2H, dt, *J* 8, CH_2CH_2NH), 2.71 (2H, t, *J* 8, $NH_2CH_2CH_2$), 1.53 (2H, tt, *J* 8, $CH_2CH_2CH_2$), 1.40 (2H, br, NH_2), 1.45 (9H, s, $C(CH_3)_3$).

δ_C (75.5 MHz, $CDCl_3$): 156.3 (C), 79.1 (C), 39.7 (CH_2), 38.5 (CH_2), 35.5 (CH_2), 28.5 (CH_3).

EI^+MS: *m/z* 175 ($[M + H]^+$, 100%).

Spectroscopic data were found to be consistent with that reported by Muller.[136]

***tert*-Butyl *N*-(3-benzylamino propyl)carbamate (366);**



366

Following the method published by Mori.[117]

A mixture of amine **365** (174 mg, 1 mmol) and benzaldehyde (106 mg, 1 eq) were stirred at room temperature for 40 minutes. The reaction mixture was dried by high vacuum pump to remove water. The residue was dissolved in MeOH (3 mL). To this methanolic solution $NaBH_4$ (37.8 mg, 1 eq) was added at 0°C, and the whole mixture was stirred at room temperature overnight. After the MeOH was removed *in vacuo*, the residue was extracted with Et_2O (10 mL). The ether layer was washed with water and dried ($MgSO_4$). The solvent was evaporated to give the carbamate **366** (220 mg, 83%) as a pale yellow oil.

TLC: R_f = 0.23 (EtOAc / DCM (1:1 v/v)).

IR: ν_{max} (film)/cm^{-1} 3332 (NH), 3030 (Ar), 2974 (CH_3), 2930 (CH_2), 2863 (CH), 1689 (s, CO).

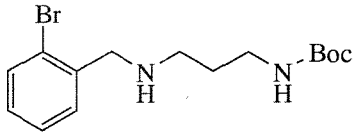
δ_H (300 MHz, $CDCl_3$): 7.22 (5H, m, ArH), 5.58 (1H, br s, NH), 3.70 (2H, s, CH_2Ph), 3.14 (2H, q, *J* 6, CH_2CH_2NHBoc), 2.62 (2H, t, *J* 6, $BnNHCH_2CH_2$), 2.25 (1H, br s, NH), 1.60 (2H, quintet, *J* 6, $CH_2CH_2CH_2$), 1.42 (9H, s, $C(CH_3)_3$).

δ_C (75.5 MHz, $CDCl_3$): 155.9 (C), 139.8 (C), 128.0 (CH), 127.8 (CH), 126.6 (CH), 78.4 (C), 53.6 (CH_2), 46.8 (CH_2), 38.8 (CH_2), 29.3 (CH_2), 28.1 (CH_3).

ES^+MS: *m/z* 265 ($[M + H]^+$, 100%), 529 ($[2M + H]^+$, 7%).

HRMS: *m/z* 265.1909 (calcd for $C_{15}H_{25}N_2O_2$, 265.1910).

tert-Butyl _N_-[3-(2-bromobenzyl amino) propyl]carbamate (367):



367

Following the method described by Mori.[117]

A mixture of amine **365** (4.46 g, 25.6 mmol) and *o*-bromo benzaldehyde (4.74 g, 1 eq) were stirred at room temperature for 1 hour. The reaction mixture was dried by high vacuum pump to get rid of generated water. The residue was dissolved in MeOH (3 mL). To this methanolic solution $NaBH_4$ (970 mg, 1 eq) was added with ice cooling, and the whole mixture was stirred at room temperature overnight. After the MeOH was removed *in vacuo*, the residue was extracted with Et_2O (100 mL). The organic layer was washed with water (50 mL) and dried ($MgSO_4$). The solvent was evaporated to give carbamate **367** (8.77 g, 100%) as a pale yellow oil.

TLC: R_f = 0.06 (EtOAc / DCM / MeOH (78:20:2 v/v/v)).

IR: ν_{max} (film)/cm^{-1} 3330 (NH), 3060(Ar), 2974 (CH_3), 2930 (CH_2), 2863 (CH), 1688 (s, CO).

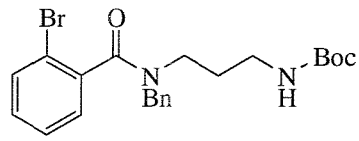
δ_H (300 MHz, $CDCl_3$): 7.49 (1H, d, *J* 8, ArH), 7.33 (1H, dd, *J* 1, 8, ArH), 7.23 (1H, t, *J* 8, ArH), 7.07 (1H, dt, *J* 1, 8, ArH), 5.35 (1H, br s, NH), 3.79 (2H, s, CH_2Ph), 3.15 (2H, q, *J* 7, CH_2CH_2NHBoc), 2.63 (2H, t, *J* 7, $ArCH_2NHCH_2CH_2$), 2.15 (1H, br s, NH), 1.63 (2H, quintet, *J* 7, $CH_2CH_2CH_2$), 1.40 (9H, s, $C(CH_3)_3$).

δ_C (75.5 MHz, $CDCl_3$): 155.9 (C), 138.7 (C), 132.5 (CH), 130.0 (CH), 128.4 (CH), 127.2 (CH), 123.7 (C), 78.6 (C), 53.4 (CH_2), 46.7 (CH_2), 39.0 (CH_2), 29.5 (CH_2), 28.2 (CH_3).

ES^+TOF MS: *m/z* 343 ($[^{79}BrM + H]^+$, 100%), 345 ($[^{81}BrM + H]^+$, 98%).

HRMS: *m/z* 343.1013 (calcd for $C_{15}H_{24}N_2O_2Br$, 343.1016).

***tert*-Butyl *N*-[3-(2-bromobenzoyl amino)propyl]carbamate (368):**



368

o-Bromobenzoic acid (201 mg, 1 eq), HOBT (163 mg, 1 eq) and DIPEA (129.3 mg, 0.17 mL, 1 eq) were added to a solution of amine **365** (174 mg, 1 mmol) in DCM (8 mL) at room temperature. After 5 minutes stirring, DCC (247.6 mg, 1.2 eq) in DCM (2 mL) was added slowly to the reaction mixture at room temperature and the solution was stirred for a further 22 hours. The mixture was washed with dil. aq. HCl (20 mL), and then with sat. aq. $NaHCO_3$ (20 mL). Aqueous layer was extracted with DCM (3x20 mL). Combined organic layers were dried ($MgSO_4$). The solvent was removed *in vacuo*. The crude residue was purified by column chromatography eluting with EtOAc / petroleum ether / MeOH (1:10:0 → 1:3:1 v/v) to give amide **368** (320 mg, 90%) as a white solid, contaminated with DCU.

TLC: R_f = 0.49 (EtOAc / DCM (1:1 v/v)).

IR: ν_{max} (film)/cm^{-1} 3355 (NH), 3311 (NH), 3065 (Ar), 2930 (CH_3), 2850 (CH_2), 1675 (s, CO), 1636 (s, CO).

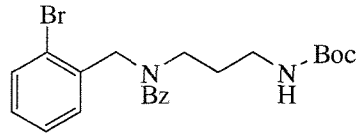
δ_H (300 MHz, CD_3OD): 7.63 (1H, d, *J* 8, ArH), 7.43-7.30 (3H, m, ArH), 3.39 (2H, t, *J* 7, CH_2NHBoc), 3.17 (2H, t, *J* 7, ArCONHCH_2), 1.77 (2H, quintet, *J* 7, $CH_2CH_2CH_2$), 1.44 (9H, s, $C(CH_3)_3$).

δ_C (75.5 MHz, CD_3OD): 171.0 (C), 158.5 (C), 140.0 (C), 134.1 (CH), 132.1 (CH), 129.7 (CH), 128.6 (CH), 120.3 (C), 79.9 (C), 38.8 (CH_2), 38.2 (CH_2), 30.5 (CH_2), 28.7 (CH_3).

ES^+MS: *m/z* 379 ($[^{79}BrM + Na]^+$, 100%), 381 ($[^{81}BrM + Na]^+$, 99%).

HRMS: *m/z* 379.0602 (calcd for $C_{15}H_{21}N_2O_3BrNa$, 379.0633).

***tert*-Butyl-*N*-[3-(benzoyl-2-bromobenzyl amino)propyl]carbamate (371):**



371

Carbamate **369** (3.0 g, 8.74 mmol), pyridine (760 mg, 1.3 mmol), and DMAP (189 mg, 1.3 mmol) were dissolved in DCM (120 mL). After 10 minutes, benzoyl chloride (1.23 g, 1 eq) in DCM (10 mL) was added slowly into the starting materials solution at 0°C, and then the reaction was allowed to warm to room temperature and stirred overnight. The reaction was quenched with aq. sol. $NaHCO_3$ (100 mL), washed with water (100 mL). The aqueous layer was extracted with DCM (3x40 mL), and the combined organic layers were dried ($MgSO_4$) and the solvent was removed *in vacuo*. The crude was purified by column chromatography eluting with EtOAc / DCM (1:9 → 1:6 v/v) to give carbamate **371** (2.86 g, 73%) as a colourless oil.

TLC: R_f = 0.60 (MeOH / EtOAc / DCM (1:3:16 v/v)).

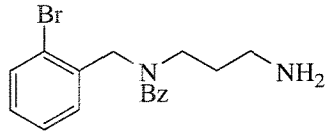
IR: ν_{max} (film)/cm^{-1} 3343 (NH), 3058 (Ar), 2973 (CH_3), 2928 (CH_2), 2877 (CH), 1707 (s, CO), 1628 (s, CO).

δ_H (250 MHz, DMSO, 120 °C): 7.62 (1H, dd, *J* 1, 8, ArH), 7.43 (7H, m, ArH), 7.25 (1H, dt, *J* 2, 8, ArH), 6.13 (1H, br m, NH), 4.67 (2H, s, CH_2Ph), 3.33 (2H, t, *J* 7, CH_2CH_2NH), 2.92 (2H, t, *J* 7, CH_2CH_2NH), 1.72 (2H, quintet, *J* 7, $CHCH_2CH_2$), 1.37 (9H, s, $C(CH_3)_3$).

δ_C (75.5 MHz, $CDCl_3$): 171.2 (C), 156.1 (C), 135.9 (C), 133.4 (CH), 130.0 (CH), 129.3 (CH), 128.70 (CH), 128.68 (CH), 128.0 (CH), 126.61 (CH), 126.59 (C), 123.4 (C), 79.2 (C), 52.9 (CH_2), 42.3 (CH_2), 37.7 (CH_2), 28.6 (CH_3), 27.6 (CH_2).

ES^+MS: *m/z* 447 ($[^{79}BrM + H]^+$, 18%), 449 ($[^{81}BrM + H]^+$, 19%), 469 ($[^{79}BrM + Na]^+$, 23%), 471 ($[^{81}BrM + Na]^+$, 25%).

***N*1-(3-aminopropyl)-*N*1-(2-bromobenzyl)benzamide (357):**



357

Amide **371** (66 mg, 0.15 mmol) was dissolved in DCM (1 mL). TFA (1 mL) was added slowly into the reaction. After an hour, sat. aq. $NaHCO_3$ (3 mL) was dropped slowly to quenched the reaction. Organic layer was separated and dried ($MgSO_4$). The solvent was removed *in vacuo* to give the primary amine **357** (53 mg, 100%) as a colourless oil.

TLC: R_f = 0.11 (MeOH / EtOAc / DCM (1:50:50 v/v)).

IR: ν_{max} (film)/cm^{-1} 3070 (Ar), 3032 (Ar), 1728 and 1703 (s dimer, CO_2H), 1625 (amide), 1128 (s, CF_3).

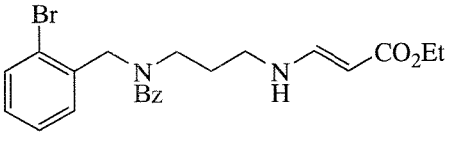
δ_H (250 MHz, DMSO, 140 °C): 7.60 (1H, dd, *J* 1, 8, ArH), 7.48-7.33 (7H, m, ArH), 7.24 (1H, dt, *J* 2, 8, ArH), 4.66 (2H, s, CH_2Ph), 3.45 (2H, t, *J* 7, CH_2CH_2NH), 2.82 (2H, t, *J* 7, CH_2CH_2NH), 1.91 (2H, quintet, *J* 7, $CHCH_2CH_2$).

δ_C (75.5 MHz, $CDCl_3$): 174.1 (C), 135.0 (C), 134.8 (C), 133.5 (CH), 130.6 (CH), 129.7 (CH), 128.8 (CH), 128.3 (CH), 128.2 (CH), 126.8 (CH), 123.2 (C), 53.3 (CH_2), 41.7 (CH_2), 36.9 (CH_2), 25.3 (CH_2).

ES^+MS: *m/z* 347 ($[^{79}BrM + H]^+$, 100%), 349 ($[^{81}BrM + H]^+$, 98%).

HRMS: *m/z* 347.0728 (calcd for $C_{17}H_{20}N_2OBr$, 347.0759).

Ethyl-3-{[3-(benzoyl-2-bromobenzyl amino)propyl]amino}-2-propenoate (372):



372

Benzamide **357** (518 mg, 1.49 mmol), and TEA (192 mg, 1.3 eq) were dissolved in THF (80 mL). Ethyl propiolate (146 mg, 1 eq) in THF (10 mL) was added dropwise into the starting materials solution at 0°C. The reaction was stirred at 50°C overnight. The reaction was quenched with dil. aq. HCl (20 mL), and washed with water (20 mL). The aqueous layer was extracted with EtOAc (3x20 mL). Combined organic layers were dried ($MgSO_4$) and the solvent was removed *in vacuo*. The crude oil was purified by column

chromatography eluting with EtOAc / DCM (1:3 → 1:1 v/v) to give enamine **372** (160 mg, 24%) as a colourless oil, and a 1:2 mixture of *cis*- and *trans*-isomers.

TLC: R_f = 0.60 (MeOH / EtOAc / DCM (1:10:40 v/v)).

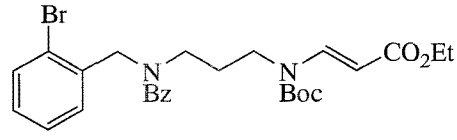
IR: ν_{max} (film)/cm^{-1} 3315 (NH), 3059 (Ar), 2976 (CH_3), 2933 (CH_2), 2875 (CH), 1664 (br s, CO), 1600 (s, C=C).

δ_H (300 MHz, DMSO, 80 °C): 7.60 (1H, dd, *J* 1, 8, ArH), 7.46-7.35 (7H, m, ArH), 7.29 (1H, m, NC*H*=CH), 7.24 (1H, dt, *J* 2, 8, ArH), 6.67 (0.33H, br m, NH*cis*), 6.58 (0.67H, br s, NH*trans*), 4.65 (2H, s, CH_2Ph), 4.50 (0.67H, d, *J* 13, CH=C$H_{trans}CO_2Et$), 4.48 (0.33H, d, *J* 13, CH=C$H_{cis}CO_2Et$), 4.02 (0.66H, q, *J* 7, C$H_{2cis}CH_3$), 4.01 (1.34H, q, *J* 7, C$H_{2trans}CH_3$), 3.36 (2H, t, *J* 7, NBzCH_2CH_2), 3.20 (0.66H, q, *J* 7, $CH_2CH_{2cis}NH$), 2.91 (1.34H, q, *J* 7, $CH_2CH_{2trans}NH$), 1.81-1.70 (2H, m, $CH_2CH_2CH_2$), 1.182 (0.99H, t, *J* 7, CH_2CH_{3cis}), 1.177 (2.01H, t, *J* 7, CH_2CH_{3trans}).

δ_C (75.5 MHz, DMSO, 80 °C): 171.5 (C), 168.7 (C), 149.9 (C), 142.4 (CH), 136.9 (C), 136.6 (CH), 133.1 (CH), 129.7 (CH), 129.5 (CH), 129.1 (C), 128.6 (CH), 128.3 (CH), 126.7 (CH), 122.8 (C), 93.7 (CH), 84.2 (CH_2), 58.0 (CH_2), 45.6 (CH_2), 41.5 (CH_2), 27.4 (CH_2), 14.9 (CH_3).

ES^+MS: *m/z* 445 ($[^{79}BrM + H]^+$, 13%), 447 ($[^{81}BrM + H]^+$, 15%).

Ethyl (*E*)-3-{[3-(benzoyl-2-bromobenzyl amino)propyl](*tert*-butoxy carbonyl)amino}-2-propenoate (355):



355

Enamine **372** (160 mg, 0.36 mmol), TEA (55 mg, 1.5 eq), and DMAP (13 mg, 0.3 eq) were dissolved in DCM (7 mL). Boc_2O (78.4 mg, 1 eq) in DCM (3 mL) was added slowly into the reaction mixture at 0°C, and then the reaction was allowed to warm to room temperature and stirred overnight. The reaction was quenched with dil. aq. HCl (10 mL), and washed with water (10 mL). The aqueous layer was extracted with EtOAc (3x10 mL). Combined organic layers were dried ($MgSO_4$) and the solvent was removed

in vacuo. The crude oil was purified by column chromatography eluting with EtOAc / DCM (1:5 → 1:3 v/v) to give a precursor **355** (76 mg, 39%) as a colourless oil.

TLC: R_f = 0.70 (MeOH / EtOAc / DCM (1:10:40 v/v)).

IR: ν_{max} (film)/cm^{-1} 3061 (Ar), 2978 (CH_3), 2933 (CH_2), 1720 (s, CO), 1702 (s, CO), 1630 (s, C=C).

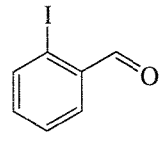
δ_H (300 MHz, $CDCl_3$): 8.17 (0.5H, br d, *J* 14, NCH_A=CH), 8.03 (0.5H, br d, *J* 14, NCH_B=CH), 7.60-7.50 (1H, br m, ArH), 7.48-7.25 (5H, m, ArH), 7.17 (1H, dt, *J* 1, 8, ArH), 5.16 (0.5H, br d, *J* 14, CH=C$H_A$$CO_2$Et), 4.95 (0.5H, br d, *J* 14, CH=C$H_B$$CO_2$Et), 4.89 (1H, br s, CH_{2A}Ph), 4.57 (1H, br s, CH_{2B}Ph), 4.20 (2H, q, *J* 7, $CO_2CH_2CH_3$), 3.68-3.56 (1H, br m, BzNC$H_{2A}$$CH_2$), 3.56-3.40 (1H, br m, CH_2CH_{2A}NBoc), 3.40-3.24 (1H, br m, BzNC$H_{2B}$$CH_2$), 3.24-3.08 (1H, br m, CH_2CH_{2B}NBoc), 1.99-1.83 (1H, br m, $CH_2CH_{2A}CH_2$), 1.99-1.83 (1H, br m, $CH_2CH_{2B}CH_2$), 1.49 (4.5 H, br s, $C(CH_{3A})_3$), 1.41 (4.5 H, br s, $C(CH_{3B})_3$), 1.30 (3H, t, *J* 7, $CO_2CH_2CH_3$).

δ_C (75.5 MHz, $CDCl_3$): 174.1 (C), 167.9 (C), 151.8 (C), 142.4 (CH), 136.8 (C), 133.2 (C), 129.9 (CH), 129.4 (CH), 129.3 (CH), 128.7 (CH), 128.10 (CH), 128.06 (CH), 126.67 (CH), 126.65 (C), 97.3 (CH), 83.4 (C), 60.1 (CH_2), 53.2 (CH_2), 47.7 (CH_2), 43.0 (CH_2), 28.1 (CH_3), 25.0 (CH_2), 14.6 (CH_3).

ES^+MS: *m/z* 545 ($[^{79}BrM + H]^+$, 35%), 547 ($[^{81}BrM + H]^+$, 34%).

HRMS: *m/z* 567.1462 (calcd for $C_{27}H_{33}N_2O_5BrNa$, 567.1465).

o-Iodobenzaldehyde (363):



363

Following the method published by Larock.[120]

o-Iodobenzyl alcohol **373** (1.0 g, 1 mmol) and PCC (g, 3 eq) were vigorously stirred in 20 mL of DCM at room temperature overnight. The reaction mixture was filtered through celite, washed with dil. aq. HCl (3x20 mL), and dried over $MgSO_4$. The organic phase was removed *in vacuo* to yield brown oil. EtOAc was added to the oil, and

the solution was filtered through silica gel to give benzaldehyde **363** (897 mg, 91%) as a light brown oil.

TLC: R_f = 0.77 (EtOAc / DCM (1:3 v/v)).

IR: ν_{max} (film)/cm^{-1} 2851 (CHO), 2742 (CHO), 1690 (s, CHO).

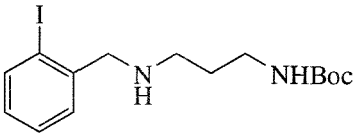
δ_H (300 MHz, CD_3OD): 10.07 (1H, s, CHO), 7.95 (1H, d, *J* 8, ArH), 7.88 (1H, d, *J* 7, ArH), 7.47 (1H, t, *J* 7, ArH), 7.29 (1H, t, *J* 8, ArH).

δ_C (75.5 MHz, CD_3OD): 195.8 (CH), 140.6 (CH), 135.5 (CH), 135.1 (C), 130.3 (CH), 128.7 (CH), 100.8 (C).

CIMS: *m/z* 545 ([M + H]$^+$, 40%).

Spectroscopic data were found to be consistent with that reported by Muller.[134]

***tert*-Butyl-*N*-[3-(2-iodobenzyl amino)propyl]carbamate (374):**



374

Following the method published by Mori.[117]

A mixture of amine **365** (3.24 g, 18.6 mmol) and *o*-iodobenzaldehyde **363** (4.31 g, 1 eq) were stirred at room temperature in THF (10 mL). The reaction was evaporated *in vacuo*. The residue was dissolved in MeOH (80 mL). To this methanolic solution, $NaBH_4$ (704 mg, 1 eq) was added portionwise at 0°C, and the whole mixture was stirred at room temperature overnight. After MeOH was removed *in vacuo*, the residue was dissolved in Et_2O (30 mL). The organic portion was washed with water (30 mL) and dried ($MgSO_4$). The crude was purified by column chromatography eluting with DCM / EtOAc / MeOH (1:0:0 → 8:2:0.1 v/v) to give carbamate **374** (6.0 g, 83%) as a colourless oil.

TLC: R_f = 0.23 (DCM / EtOAc / MeOH (8:2:0.1 v/v)).

IR: ν_{max} (film)/cm^{-1} 3336 (br, NH), 3051 (Ar), 2974 (CH_3), 2929 (CH_2), 1689 (s, CO).

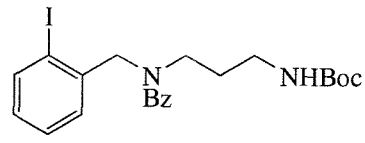
δ_H (300 MHz, $CDCl_3$): 7.80 (1H, dd, *J* 1, 8, ArH), 7.40-7.29 (2H, m, ArH), 6.29 (1H, dt, *J* 2, 8, ArH), 3.78 (2H, s, CH_2Ar), 3.22 (2H, q, *J* 6, CH_2NHCH_2Ar), 2.70 (2H, t, *J* 6, CH_2NHBoc), 1.68 (2H, quintet, *J* 6, $CH_2CH_2CH_2$), 1.43 (9H, s, $C(CH_3)_3$).

δ_C (75.5 MHz, $CDCl_3$): 171.3 (C), 156.2 (C), 142.2 (C), 129.8 (CH), 129.0 (CH), 128.4 (CH), 98.5 (CH), 79.1 (C), 58.4 (CH_2), 47.3 (CH_2), 39.5 (CH_2), 29.9 (CH_3), 28.6 (CH_2).

ES^+MS: *m/z* 391 ($[M + H]^+$, 100%).

HRMS: *m/z* 391.0881 (calcd for $C_{15}H_{24}N_2O_2I$, 391.0877).

tert-Butyl-_N_-[3-(benzoyl-2-iodobenzyl amino)propyl]carbamate (375):



375

TEA (155.6 mg, 1.2 eq) was added into the DCM (20 mL) solution of carbamate **374** (500 mg, 1.28 mmol). After 5 minutes, DMAP (31 mg, 0.2 eq) was added to the reaction mixture. The reaction was cooled to 0°C, and benzoyl chloride (180 mg, 1 eq) in DCM (5 mL) was added dropwise to the solution. The reaction mixture was allowed to warm to room temperature and stirred overnight. The reaction was quenched with dil. aq. HCl (10 mL), washed with water (10 mL). The aqueous layer was extracted with DCM (3x15 mL). Combined organic layers were dried ($MgSO_4$), and the solvent was removed *in vacuo*. The crude was purified by column chromatography eluting with EtOAc / DCM (1:10 → 1:7 v/v) to give carbamate **375** (529 mg, 84%) as a colourless oil.

TLC: R_f = 0.59 (DCM / EtOAc / MeOH (8:2:0.1 v/v)).

IR: ν_{max} (film)/cm^{-1} 3338 (br, NH), 3057 (Ar), 2975 (CH_3), 2930 (CH_2), 1695 (s, CO), 1625 (s, CO).

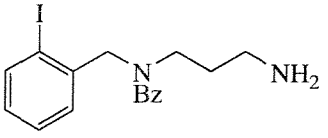
δ_H (300 MHz, $_{d6}$-DMSO, 80 °C): 7.87 (1H, dd, *J* 1, 8, ArH), 7.48-7.40 (6H, m, ArH), 7.30 (1H, dd, *J* 2, 8, ArH), 7.06 (1H, ddt, *J* 0.5, 2, 8, ArH), 6.29 (1H, br, NH), 4.58 (1H, s, CH_2Ar), 3.31 (2H, t, *J* 7, $NBzCH_2CH_2$), 2.89 (2H, apparent q, *J* 7, CH_2CH_2NH), 1.90 (2H, quantet, *J* 7, $CH_2CH_2CH_2$), 1.36 (9H, s, $C(CH_3)_3$).

δ_C (75.5 MHz, $CDCl_3$): 174.2 (C), 156.2 (C), 140.0 (CH), 138.6 (C), 135.8 (C), 130.1 (CH), 129.5 (CH), 128.9 (CH), 128.7 (CH), 127.5 (CH), 126.6 (CH), 98.2 (C), 79.2 (C), 57.8 (CH_2), 42.3 (CH_2), 37.6 (CH_2), 28.6 (CH_3), 27.6 (CH_2).

ES^+MS: *m/z* 495 ($[M + H]^+$, 100%), 989 ($[2M + H]^+$, 48%), 1011 ($[2M + Na]^+$, 52%).

HRMS: *m/z* 517.0950 (calcd for $C_{22}H_{27}N_2O_3INa$, 517.0959).

_N_1-(3-aminopropyl)-_N_1-(2-iodobenzyl)benzamide (358):



358

Carbamate **375** (97 mg, 0.2 mmol) was dissolved in DCM (5 mL). TFA (1 mL) was added slowly at room temperature. The reaction mixture was stirred for 5 hours. The mixed solvent was removed *in vacuo* to give a TFA salt of **358** (116 mg, 100%) as a colourless oil.

TLC: R_f = 0.08 (DCM / EtOAc / MeOH (8:2:0.1 v/v)).

IR: ν_{max} (film)/cm^{-1} 3452 (br, NH), 3063 (Ar), 2953 (CH_3), 2901 (CH_2), 1777 (CO_2H), 1675 (CO), 1620 (NH_3^+), 1162 (s, CF_3).

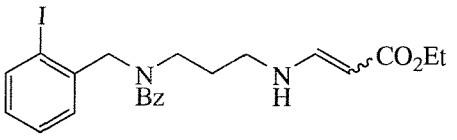
δ_H (300 MHz, $CDCl_3$): 7.87 (1H, dd, *J* 1, 8, ArH), 7.80 (2H, br s, NH_2), 7.50-7.30 (6H, m, ArH), 7.23 (1H, dd, *J* 1, 7, ArH), 7.08 (1H, m, dt, *J* 1, 8, ArH), 4.53 (2H, s, NCH_2Ar), 3.63 (2H, br m, CH_2NH_2), 3.08 (2H, br m, CH_2CH_2NBz), 1.85 (2H, br m, $CH_2CH_2CH_2$).

δ_C (75.5 MHz, $CDCl_3$): 174.2 (C), 140.4 (CH), 137.1 (C), 133.5 (C), 131.4 (CH), 130.3 (CH), 129.2 (CH), 129.0 (CH), 128.0 (CH), 126.8 (CH), 98.4 (C), 58.5 (CH_2), 41.7 (CH_2), 37.3 (CH_2), 25.2 (CH_2).

ES^+MS: *m/z* 395 ($[M + H]^+$, 100%).

HRMS: *m/z* 395.0617 (calcd for $C_{17}H_{20}N_2OI$, 395.0615).

Ethyl-3-{[3-(benzoyl-2-iodobenzyl amino)propyl]amino}-2-propenoate (376):



376

Benzamide **358** (60 mg, 0.12 mmol), and TEA (1 mL, excess) were dissolved in THF (3 mL). Ethyl propiolate (12 mg, 1 eq) in THF (2 mL) was added dropwise at 0°C. The reaction was stirred at 50°C overnight. The solvent was removed *in vacuo*. The crude oil was purified by column chromatography eluting with DCM / EtOAc / MeOH (1:0:0 → 5:1:0.1 v/v) to give enamine **376** (30 mg, 51%) as a colourless oil, and as a 1:1 mixture of *cis*- and *trans*-isomers.

TLC: R_f = 0.60 (DCM / EtOAc / MeOH (8:2:0.1 v/v)).

IR: ν_{max} (film)/cm^{-1} 3340 (br, NH), 3057 (Ar), 2927 (CH), 1664 (CO), 1624 (s, C=C).

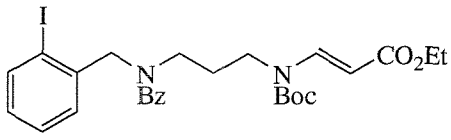
δ_H (300 MHz, $CDCl_3$): 7.83 (1H, d, *J* 7, ArH), 7.70-7.17 (8H, m, NC*H*=CH and ArH), 7.02 (1H, t, *J* 7, ArH), 6.03 (1H, d, *J* 15, CH=C*H*CO_2Et), 4.60 (1H, br s, CH_{2A}Ph), 4.26 (1H, br s, CH_{2B}Ph), 4.20 (2H, q, *J* 7, $CO_2CH_2CH_3$), 3.63-3.47 (1H, br m, BzNC$H_{2A}CH_2$), 3.47-3.31 (1H, br m, CH_2CH_{2A}NH), 3.31-3.13 (1H, br m, BzNC$H_{2B}CH_2$), 3.13-2.98 (1H, br m, CH_2CH_{2B}NH), 1.94-1.84 (1H, br m, $CH_2CH_{2A}CH_2$), 1.84-1.73 (1H, br m, $CH_2CH_{2B}CH_2$), 1.29 (3H, t, *J* 7, $CO_2CH_2CH_3$).

δ_C (75.5 MHz, $CDCl_3$): 169.2 (C), 157.3 (C), 143.8 (C), 140.1 (CH), 136.9 (C), 130.1 (CH), 129.7 (CH), 129.00 (CH), 128.97 (CH), 128.7 (CH), 127.9 (CH), 126.7 (CH), 108.0 (C), 95.4 (CH), 60.0 (CH_2), 59.8 (CH_2), 42.5 (CH_2), 26.2 (CH_2), 23.7 (CH_2), 14.7 (CH_3).

ES$^+$MS: *m/z* 493 ([M + H]$^+$, 100%).

HRMS: *m/z* 493.0988 (calcd for $C_{22}H_{25}N_2O_3I$, 493.0982).

Ethyl (*E*)-3-{[3-(benzoyl-2-iodobenzyl amino)propyl](*tert*-butoxy carbonyl)amino}-2-propenoate (356):



356

Enamine **376** (123 mg, 0.25 mmol), TEA (38 mg, 1.5 eq), and DMAP (9 mg, 0.3 eq) were dissolved in DCM (5 mL). Boc_2O (54.5 mg, 1 eq) in DCM (2 mL) was added slowly into the reaction mixture at 0°C, and then the reaction was allowed to warm to room temperature and stirred overnight. The reaction was quenched with dil. aq. HCl (5 mL), and washed with water (5 mL). The aqueous layer was extracted with DCM (3x10 mL). Combined organic layers were dried ($MgSO_4$), and the solvent was removed *in vacuo*. The crude oil was purified by column chromatography eluting with EtOAc / DCM (1:10 → 1:9 v/v) to give a precursor **356** (84 mg, 23%) as a colourless oil.

TLC: R_f = 0.70 (MeOH / EtOAc / DCM (1:10:40 v/v)).

IR: ν_{max} (film)/cm^{-1} 3245 (br, NH), 3071 (Ar), 3027 (Ar), 2956 (CH_3), 2902 (CH_2), 1737 (s, CO), 1720 (s, CO), 1656 (CO), 1591 (s, C=C).

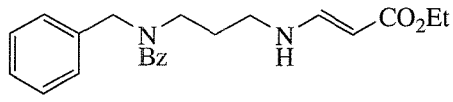
δ_H (300 MHz, $CDCl_3$): 8.18 (0.5H, br d, *J* 14, NCH_A=CH), 8.03 (0.5H, br d, *J* 14, NCH_B=CH), 7.91-7.81 (1H, br m, ArH), 7.51-7.20 (5H, m, ArH), 7.06-6.97 (1H, m, ArH), 5.18 (0.5H, br d, *J* 14, CH=C$H_A$$CO_2$Et), 4.96 (0.5H, br d, *J* 14, CH=C$H_B$$CO_2$Et), 4.84 (1H, br s, CH_{2A}Ph), 4.51 (1H, br s, CH_{2B}Ph), 4.21 (2H, q, *J* 7, $CO_2CH_2CH_3$), 3.70-3.56 (1H, br m, BzNC$H_{2A}$$CH_2$), 3.56-3.40 (1H, br m, CH_2CH_{2A}NH), 3.40-3.24 (1H, br m, BzNC$H_{2B}$$CH_2$), 3.24-3.08 (1H, br m, CH_2CH_{2B}NBoc), 1.99-1.83 (1H, br m, $CH_2CH_{2A}CH_2$), 1.99-1.83 (1H, br m, $CH_2CH_{2B}CH_2$), 1.50 (4.5 H, br s, $C(CH_{3A})_3$), 1.42 (4.5 H, br s, $C(CH_{3B})_3$), 1.27 (3H, t, *J* 7, $CO_2CH_2CH_3$).

δ_C (75.5 MHz, $CDCl_3$): 172.5 (C), 167.9 (C), 152.0 (C), 142.4 (CH), 136.2 (C), 133.38 (CH), 133.36 (C), 129.9 (CH), 129.4 (CH), 128.74 (CH), 128.1 (CH), 126.69 (CH), 126.65 (CH), 123.2 (C), 97.3 (CH), 83.4 (C), 60.1 (CH_2), 53.2 (CH_2), 47.7 (CH_2), 43.0 (CH_2), 28.1 (CH_3), 26.0 (CH_2), 14.5 (CH_3).

ES^+MS: *m/z* 593 ($[M + H]^+$, 50%), 615 ($[M + Na]^+$, 100%), 1206 ($[2M + Na]^+$, 90%).

HRMS: *m/z* 615.1313 (calcd for $C_{27}H_{33}N_2O_5INa$, 615.1326).

Ethyl-3-{[3-(benzoyl benzylamino)propyl](*tert*-butoxy carbonyl)amino}-2-propenoate (378):



378

Iodobenzyl benzamide **376** (300 mg, 0.67 mmol) was dissolved in toluene (50 mL). Bu_3SnH (392 mg, 2eq) and AIBN (45 mg, 0.2 eq) were added into the starting material solution. The reaction was stirred at 80°C for 5 hours. AIBN (20 mg, 0.15eq) was added to the reaction mixture. The reaction was stirred at 80°C for further 16 hours. The reaction was quenched with 2M of aq. KF solution (30 mL), and the whole mixture was stirred vigorously overnight. Aqueous layer was extracted with toluene (2x20 mL). Combined organic layers were evaporated *in vacuo*. The crude oil was purified twice by column chromatography eluting with EtOAc / petroleum ether (1:10 → 1:7 v/v) and again with EtOAc / petroleum ether (1:10 → 1:9 v/v) to give a benzyl benzamide **378** (84 mg, 23%) as a colourless oil.

TLC: R_f = 0.29 (petroleum ether / EtOAc (3:1 v/v)).

IR: ν_{max} (film)/cm^{-1} 3287 (br, NH), 3060 (Ar), 3027 (Ar), 2970 (CH_3), 2927 (CH_2), 2855 (CH), 1732 (s, CO), 1702 (s, CO), 1671 (CO), 1625 (s, C=C).

δ_H (300 MHz, $CDCl_3$): 7.45-7.12 (10H, m, ArH), 6.04 (1H, d, *J* 15, NC*H*=CH), 4.86-4.60 (1H, br m, CH=C*H*CO_2Et), 4.53 (2H, br s, CH_2Ph), 4.26 (2H, q, *J* 7, $CO_2CH_2CH_3$), 3.62-2.95 (4H, br m, BnNCH_2CH_2 and CH_2CH_2NH), 1.90-1.60 (2H, br m, $CH_2CH_2CH_2$), 1.36 (3H, t, *J* 7, $CO_2CH_2CH_3$).

δ_C (75.5 MHz, $CDCl_3$): 171.7 and 171.6 ($C_{cis+trans}$), 166.7 (C), 148.9 (CH), 136.0 (C), 129.7 (C), 128.9 (CH), 128.7 (CH), 128.6 (CH), 127.8 (CH), 126.9 (CH), 126.6 (CH), 106.3 and 106.0 ($CH_{cis+trans}$), 60.0 and 59.9 ($CH_{2cis+trans}$), 52.9 (CH_2), 40.7 (CH_2), 37.0 (CH_2), 29.7 (CH_2), 14.3 and 14.1 ($CH_{3cis+trans}$).

Ethyl-3-{[3-(benzoyl-2-bromobenzyl amino)propyl](*tert*-butoxy carbonyl)amino}-2-propenoate (380):

380

Ethyl propiolate (1.13 g, 11.5 mmol) / DCM (25 mL) was added slowly into the amine **365** (2 g, 1 eq) / DCM (50 mL) solution at 0°C. The reaction was stirred at room temperature overnight. The solvent was removed *in vacuo* to give an enamine (2.7 g, 85%) as a crude oil. Enamine (160 mg, 0.36 mmol) was dissolved in THF (20 mL). ^{n}BuLi (100 mg, 1.4 eq) in THF (2 mL) was added dropwise into the reaction mixture at -78°C. After 30 minutes, the solution turned yellow, and CbzCl (189.4 mg, 1 eq) / THF (3 mL) was added dropwise again at -78°C. The reaction was stirred at -78°C for an hour, before being allowed to warm to room temperature overnight. The reaction was quenched with sat. aq. NH_4Cl (10 mL), and washed with water (10 mL). The aqueous layer was extracted with EtOAc (3x15 mL). Combined organic layers were dried ($MgSO_4$) and the solvent was removed *in vacuo*. The crude oil was purified by column chromatography eluting with EtOAc / DCM (1:10 → 1:7 v/v) to gain enamide **380** (260 mg, 58% or 49% from two steps) as a colourless oil.

TLC: R_f = 0.36 (petroleum ether / EtOAc (3:1 v/v)).

IR: ν_{max} (film)/cm^{-1} 3236 (br, NH), 3070 (Ar), 3015 (Ar), 2969 (CH_3), 2954 (CH_2), 2904 (CH), 1738 (s, CO), 1655 (s, CO), 1590 (s, C=C).

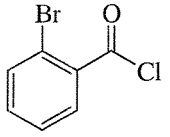
δ_H (300 MHz, $CDCl_3$): 8.20 (1H, d, *J* 14, NC*H*=CH), 7.40-7.30 (5H, m, ArH), 5.26 (2H, s, CH_2Ph), 5.22 (1H, d, *J* 14, CH=C*H*CO_2Et), 4.12 (2H, q, *J* 7, C*H*$_2$$CH_3$), 3.65 (2H, t, *J* 7, CH_2C*H*$_2$NCbz), 3.13-3.02 (2H, m, BocNHC*H*$_2$$CH_2$), 1.74 (2H, quintet, *J* 7, CH_2C*H*$_2$$CH_2$), 1.43 (9H, s, C($CH_3$)$_3$), 1.25 (3H, t, *J* 7, CH_2C*H*$_3$).

δ_C (75.5 MHz, $CDCl_3$): 167.6 (C), 156.2 (C), 153.8 (C), 141.8 (CH), 135.2 (C), 128.9 (CH), 128.8 (CH), 128.5 (CH), 98.7 (CH), 79.5 (C), 69.2 (CH_2), 60.3 (CH_2), 41.1 (CH_2), 37.6 (CH_2), 28.5 (CH_3), 27.2 (CH_2), 14.5 (CH_3).

ES$^+$MS: *m/z* 429 ([M + Na]$^+$, 45%), 835 ([2M + Na]$^+$, 100%).

HRMS: *m/z* 429.1998 (calcd for $C_{21}H_{30}N_2O_6Na$, 429.1996).

2-Bromobenzene-1-carbonyl chloride (381):



381

o-Bromobenzoic acid (1 g, 5 mmol) was refluxed with thionyl chloride (10 mL) overnight under argon. Thionyl chloride was removed *in vacuo*. The crude yellow oil was identified by ^{1}H and ^{13}C-NMR to be chloride **381** (1.2 g, 100%).

TLC: R_f = 0.3 (EtOAc / petroleum ether (1:19 v/v)).

IR: ν_{max} (film)/cm^{-1} 3070 (Ar), 1779 (s, CO).

δ_H (300 MHz, $CDCl_3$): 8.09 (1H, dd, *J* 2, 7, ArH), 7.72 (1H, dd, *J* 1, 7, ArH), 7.52-7.43 (2H, m, ArH).

δ_C (75.5 MHz, $CDCl_3$): 165.8 (C), 134.8 (CH), 134.6 (C), 134.4 (CH), 133.3 (CH), 127.6 (CH), 121.5 (C).

EI^+MS: *m/z* 219 ($[M + H]^+$, 4%), 183 ($[M - Cl^-]^+$, 100%), 155 ($[M - COCl^-]^+$, 40%).

Spectroscopic data were found to be consistent with that reported by Ranson.[137]

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