Abstract: Novel Oxidatively Activated Safety Catch Linkers

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Solid phase organic synthesis is a powerful technique to facilitate rapid synthesis and easy purification of organic compounds. The advancement of linkers and cleavage strategies is of paramount importance for the success of this approach. This thesis is concerned with the development of a robust safety catch linker system aimed to allow a broad range of commonly used reagents to be employed in a synthetic sequence carried out on a solid support.

Chapter 1 outlines the principles of solid phase organic synthesis, the terminology associated with this approach and the advantages and disadvantages compared to conventional solution phase methods. Common attachment and release strategies for various functional groups are described and the safety catch principle is introduced.

Chapter 2 discusses the design features of the linker system. Proof of principle is demonstrated for the attachment and release strategies with a simple solution phase model system.

Chapter 3 describes the adaptation of the linker system to the solid phase. Key transformations are modelled with solution phase experiments and subsequently applied to solid phase. The loading determination of the solid phase system is also described.

Chapter 4 reports an assessment of the reactivity of the linker system in the coupling transformation of aliphatic alcohols and amines. The chemoselectivity and efficiency of the CAN debenzylation/cyclorelease protocol is also evaluated.

Chapter 5 demonstrates the utility of the linker system with the optimisation of a simple synthetic sequence in solution followed by adaptation to the solid phase. The synthesis of a pilot library of aryl alcohols utilizing a Suzuki coupling on solid support is described. The attachment and release of amines is also demonstrated with solid phase examples.

Chapter 6 examines the potential of the linker system as an analytical tool to assess the outcome of stereoselective transformations. A chiral auxiliary is attached to the solid phase by aid of the safety catch linker and released into solution. A solution phase model system is developed to aid preliminary investigations in solution prior to adaptation to the solid phase.

Acknowledgements

First, I thank my supervisor Professor S.G. Davies for allowing me to work within his laboratory and for his advice and encouragement throughout the project. It has been a great pleasure to follow his directions out of complicated situations created during the course of my work.

Secondly, I thank my day-to-day supervisors Dr. Andrew D. Smith and Dr. Andrew W. Mulvaney for sharing their expertise in chemistry, advice and encouragement.

I am also greatly indebted to those who have assisted me with their constructive criticism, meaning proof-reading, during the cross-country writing of this text, those include Dr. Andrew Smith, Dr. Angela Russell, Dr. Christopher Garner and Jim Thomson for his help with the experimental section. Big thanks to all of you.

The departmental technical staff, who made this work possible get special thanks: Dr. Tim Claridge, Dr. Barbara O'Dell and Tina Jackson of the NMR lab, Dr. Neil Oldham, Robin Procter and Dr. Joanna Kirkpatrick for assistance with the mass spectra and bringing the equipment back to life after countless messy samples run by yours truly and Anne Douglas of the ICL for the elemental analysis. Additionally, Levi Dash and other members of the staff at Stores for supplying the tools of the trade, thanks to you.

Also, thanks to the many members of the SGD group, past and present, who have made my adventures in the UK an enjoyable experience, inside the lab and outside: particularly (in random order) Mulv and Angie for advice, friendship and countless curry sessions, the Scousers for my favourite nickname (the Codfather), Anne Tennant-Eyles gets thanks for all her help, Hippy and Vickers for all the lighters I've "borrowed", Marcus for late night chemistry sessions, Keiji and Yutaka for trying to teach me Japanese, Smith for calming me down, Cat for her Elvis "similar voices" comparison, Pete for trying to pronounce my name correctly (yet unsuccessfully), Jon Withey, Min, Becky, Miles, Shyam, Scott, Jim and all the others I've enjoyed a pint or "two" with, which leaves only Nadeam to thank.

My college advisor at Wolfson, Dr. Christina Redfield, has been of invaluable assistance during the course of this work and for her help and advice I am grateful.

I thank my parents Skarphedinn and Sigridur for their support, financial and mental, throughout my education and career. Elin, Dagur and Eva thank you for your love, support and patience.

Abbreviations

ACE-Cl	α-Chloroethyl chloroformate
APCI	Atmospheric pressure chemical ionisation
Ar	Aryl
aq.	Aqueous
9-BBN	9-Borabicyclo[3.3.1]nonane
Bn	Benzyl
b.p.	Boiling point
br	Broad
Bu	Butyl
n-BuLi	*n*-Butyllithium
CAN	Cerium(IV) ammonium nitrate, $Ce(NO_3)_6(NH_4)_2$
Cbz	Benzyloxycarbonyl
cy	Cyclohexyl
d	Doublet
dba	Dibenzylideneacetone
DCC	*N,N'*-dicyclohexylcarbodiimide
DCE	Dichloroethane
DCM	Dichloromethane
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
d.e.	Diastereomeric excess
DHP	Dihydropyranyl
DIAD	Diisopropyl azodicarboxylate
DIC	*N,N'*-Diisopropylcarbodiimide
DIPEA	Diisopropylethylamine
DMF	*N,N*-Dimethylformamide
DMS	Dimethylsulfide
DMSO	Dimethylsulfoxide
DPPF	Bis(diphenylphosphino)ferrocene
D^{t}BAD	Di-*tert*-butylazodicarboxylate
EDCI	*N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride
e.e.	Enantiomeric excess
ESI	Electrospray ionisation
Et	Ethyl
eq.	Equivalents
FG	Functional group
FMOC	Fluorenylmethoxycarbonyl
FTIR	Fourier-transform infra red
gem	Geminal
h	Hours
HAL	Hyper acid labile
HBTU	*O*-Benzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium hexafluorophosphate
n-Hex	*n*-Hexyl
HOBt	1-Hydroxybenzotriazole
HPLC	High performance liquid chromatography
LHMDS	Lithium hexamethyldisilylazide
J	Coupling constant
LDA	Lithium diisopropylamide
Me	Methyl
min	Minutes
m.p.	Melting point
m/z	Mass/charge
NMR	Nuclear magnetic resonance
OAc	Acetate
PEG	Polyethylene glycol
PG	Protecting group
Ph	Phenyl
PMB	*para*-Methoxybenzyl
i-Pr	*iso*-Propyl
R	Alkyl
r.t.	Room temperature
s	Singlet
SASRIN	Super acid sensitive resin
SCL	Safety catch linker
SPOS	Solid phase organic synthesis
t	Triplet
TBAF	Tetrabutylammonium fluoride
TBDMS	*tert*-Butyl dimethylsilyl
TBTU	*O*-Benzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium tetrafluoroborate
TESH	Triethylsilane
TFA	Trifluoroacetic acid
THP	Tetrahydropyranyl
THF	Tetrahydrofuran
t.l.c.	Thin layer chromatography
TMOF	Trimethyl orthoformate
Ts	Tosyl
q	Quartet

Contents

Abstract i
Acknowledgements ii
Abbreviations iii
Contents iv

1 Introduction 1
1.1 Introduction to Solid Phase Organic Synthesis 1
1.1.1 SPOS terminology 1
1.1.2 Schematic protocol for Solid Phase Organic Synthesis 2
1.2 Development of SPOS 3
1.2.1 Merrifield's peptide synthesis 3
1.2.2 Small molecule synthesis: Benzodiazepines 5
1.3 Advantages and disadvantages of SPOS 6
1.4 Resins, linkers and cleavage strategies in solid phase synthesis 8
1.4.1 Electrophilically cleaved linkers 9
1.4.2 Other cleavage strategies 9
1.4.3 Manipulating linker lability 10
1.5 Attachment and release of amines and alcohols 11
1.6 Safety catch linkers 14
1.6.1 Kenner's safety catch principle 14
1.6.2 Safety catch linkers for the release of amines and alcohols 15
1.7 Aim of the project 18
1.7.1 Limitations of current technologies 18
1.7.2 Design of a novel oxidatively activated safety catch linker 18
2 Linker design and synthesis 22
2.1 Linker design 22
2.1.1 Linker design features 23
2.1.2 Activation strategy 24
2.2 Linker synthesis 27
2.2.1 Retrosynthetic analysis 27
2.2.2 Synthesis of key intermediate **68** 28
2.3 Development of a model system 28
2.3.1 Design of model 28
2.3.2 Synthesis 29
2.3.3 Debenzylation/cyclorelease protocol 29
2.4 Transformations on model system 30
2.4.1 Ester formation 30
2.4.2 Suzuki coupling and debenzylation/cyclorelease 31
2.5 Conclusions 32
3 Adaptation to solid phase 34
3.1 Introduction 34
3.1.1 Solution phase model compounds 34
3.2 Solution phase model reactions 36
3.2.1 Synthesis of model compound **95** 36
3.2.2 Synthesis of key intermediate **88** 37
3.2.3 Ester synthesis 38
3.2.4 Attempted hydroboration oxidation 39
3.2.5 Suzuki-Miyaura cross coupling 40
3.2.6 Hydrolysis experiments 42
3.2.7 Making of model compounds and debenzylation/cyclorelease in solution 43
3.3 Solid phase synthesis 45
3.3.1 Monitoring reactions on solid phase 45
3.3.2 Synthesis of polymer supported carboxylic acid **90** 47
3.3.3 Attachment, debenzylation/cyclorelease protocol 48
3.3.4 Synthesis of resin precursor and loading determination 50
3.4 Conclusions 52
4 Model studies in solution 54
4.1 Introduction 54
4.1.1 Identification of alternative spacers 54
4.1.2 Preparation of model compounds 55

4.2 Methods for amide and ester formation 56
4.3 Aliphatic alcohols, solution phase studies 58
4.3.1 Attachment of alcohols/ester formation 58
4.3.2 Debenzylation/cyclorelease 60
4.4 Coupling of amines to model systems 61
4.4.1 Coupling of primary and secondary amines 61
4.4.2 Coupling of cyclic amines 64
4.5 Investigations into premature cyclization 67
4.6 Debenzylation/cyclorelease protocol of model amides 69
4.6.1 Release of primary amines 69
4.6.2 Release of secondary amines 72
4.6.3 Release of heterocycles 73
4.7 Conclusions 76
5 Solid phase studies 78
5.1 Introduction 78
5.2 Attachment,derivatisation and release of alcohols 79
5.2.1 Solution phase model studies 79
5.2.2 Solid phase model studies 80
5.2.3 Parallel synthesis of a demonstrative library 82
5.3 Attachment and debenzylation/cyclorelease of amines on solid phase 84
5.3.1 Introduction 84
5.3.2 Attachment of primary amines 84
5.3.3 Attachment of secondary amines 85
5.3.4 Primary amine release, debenzylation/cyclorelease protocol 87
5.3.5 Secondary amine release, debenzylation/cyclorelease protocol 87
5.4 Amine derivatisation 89
5.4.1 Introduction 89
5.4.2 Attempted *N*-alkylation 89
5.4.3 Derivatisation of piperazine derivatives 90
5.4.4 Derivatisation of benzyl amide 91
5.5 Conclusions 92
6 Chiral auxiliary studies 94
6.1 Introduction 94
6.2 Oxazolidinone based chiral auxiliaries on polymer 95
6.2.1 Polymer supported Evans auxiliaries 95
6.2.2 Polymer supported SuperQuat auxiliaries 97
6.2.3 Linkers as analytical tools 99
6.3 Results and discussion 100
6.3.1 Synthesis and elaboration of polymer bound chiral auxiliary **270** 100
6.3.2 Synthesis of solution phase model system **273** 103
6.3.3 Attempted selective cleavage of acyl fragment 105
6.4 Conclusions 106
7 Experimental 108
7.1 General Experimental 108
7.2 General Experimental Procedures 110
7.3 Experimental for Chapter II 112
7.4 Experimental for Chapter III 119
7.5 Experimental for Chapter IV 138
7.6 Experimental for Chapter V 174
7.7 Experimental for Chapter VI 197

Appendix A .....

1 Chapter I: Introduction

1.1 Introduction to Solid Phase Organic Synthesis

Solid phase organic synthesis (SPOS) has become an important synthetic strategy within the chemistry community. SPOS involves reactions being performed on substrates attached to insoluble supports. Parallel synthesis of large collections of structurally similar small molecules and natural product analogues, termed libraries or arrays, on polymeric support for high throughput screening in pharmacological assays increases throughput immensely. This is due to increased efficiency, the ease of automation of SPOS and the ability to drive reactions to completion with excess reagents that are easily filtered from the insoluble support, making purification of intermediates unnecessary. The major limitations of SPOS are the lack of optimised reactions available compared to the solution phase counterpart, problems with loading of the substrate and release of the product from the polymeric support in addition to difficulties in reaction monitoring. These problems remain a challenge for organic chemists to solve. This introduction will briefly describe the historical development of reactions adapted to solid phase synthesis and the advantages and disadvantages in comparison with conventional solution phase syntheses. Attachment and release strategies of different functional groups from insoluble supports will be briefly discussed along with terminology associated with these methods.

1.1.1 SPOS terminology

The *resin* is a polymeric backbone, inert to the chemistry undertaken on the substrate. The substrate is attached to this backbone using a *linker* which takes the form of a bifunctional molecule capable of both attachment to the polymeric backbone and reversible attachment *via* a functional group of the substrate molecule. Linkers can be pre-synthesised in solution and grafted on a functionalised resin either directly or *via* the functional group of a spacer. The

functionality of the linker molecule to which the substrate is attached can be referred to as the *anchoring group*, and the linker construct may be considered as both an immobilisation mechanism and a protecting group for the substrate while attached to the resin. The use of a *spacer* is optional but offers some advantages. A spacer is generally a hydrocarbon chain located between the resin and the linker to reduce steric interactions between the polymeric backbone and the reactive site. Spacers can also be used to alter the swelling properties of the resin by fine tuning of the hydrophobic/hydrophilic character and therefore allow some control of the range of solvents able to swell the resin (Figure 1.1).[1]

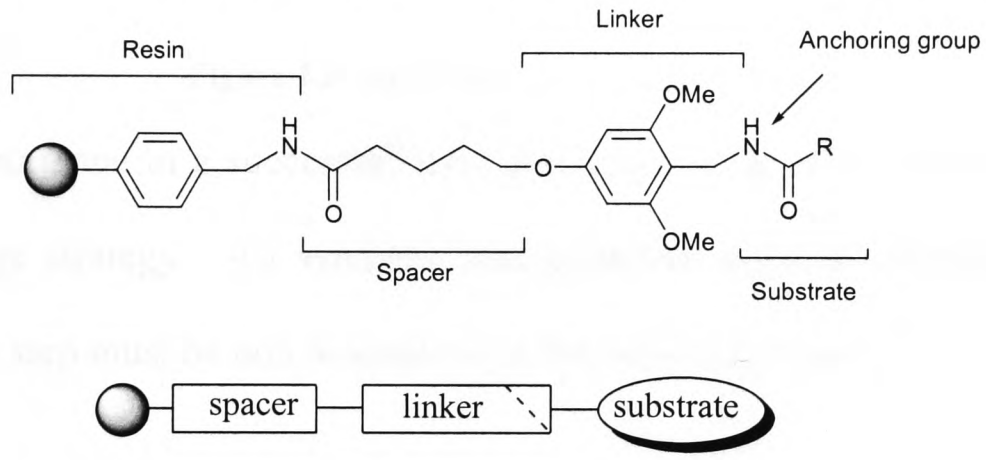


Figure 1.1: Schematic representation of a resin, spacer and linker

1.1.2 Schematic protocol for solid phase synthesis

A characteristic scheme for solid phase organic synthesis consists of the attachment of a substrate to the anchoring group of a linker prior to synthetic manipulations. The substrate can be preloaded to the linker in solution before grafting or directly loaded on a resin bound linker after the grafting has taken place.[2] After the desired synthetic manipulations have taken place a cleavage step is undertaken to afford the product in solution. Linkers can either regenerate the original functional group upon cleavage (A) or the cleavage step can allow conversion to different functional group(s) (B) as a means of introducing structural diversity to the products (Figure 1.2).[3]

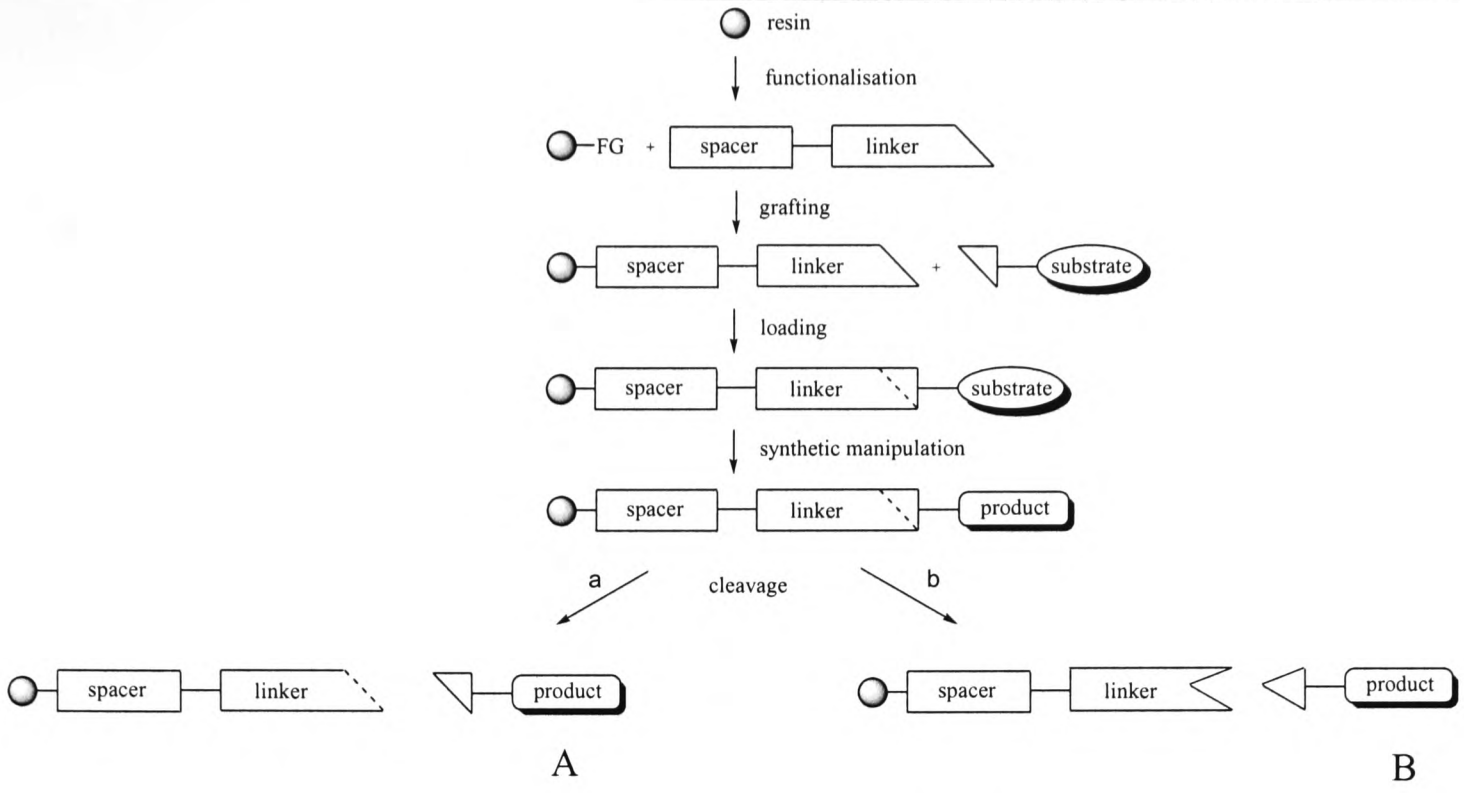


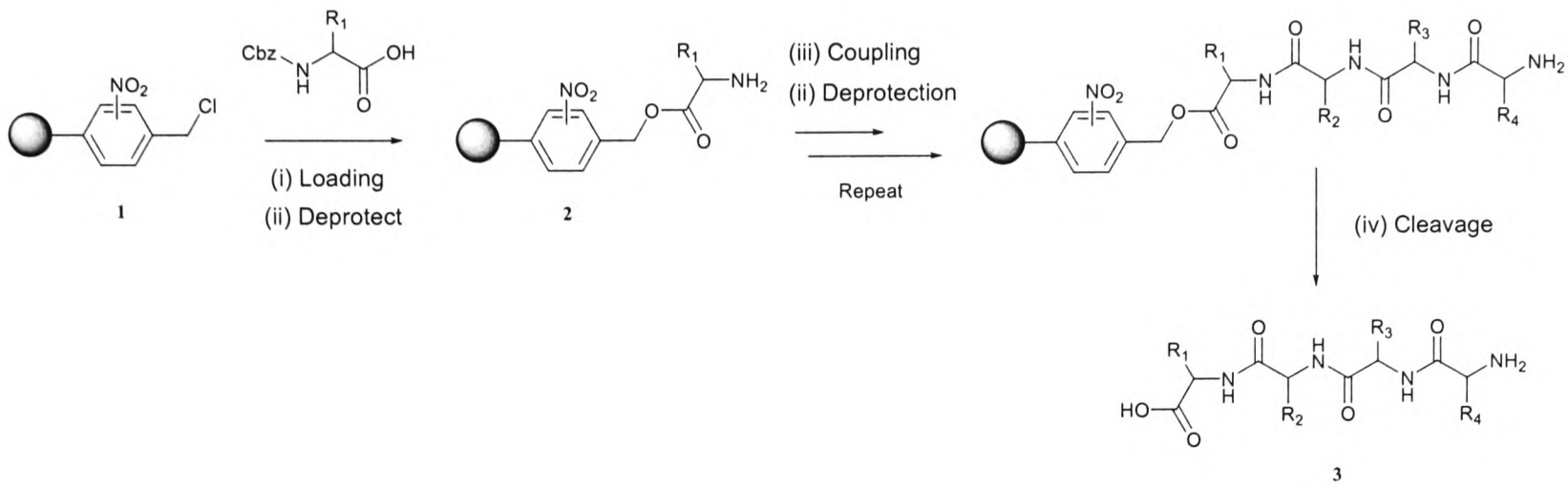
Figure 1.2: Solid phase synthesis flowchart

Of paramount importance in a successful solid phase synthesis is the choice of solid support, linker and cleavage strategy. All synthetic manipulations must be orthogonal to the linker, while the cleavage step must be non deleterious to the released product.

1.2 Development of SPOS

1.2.1 Merrifield's peptide synthesis

SPOS is based on R.B. Merrifield's pioneering work in 1963[4] in peptide synthesis. Merrifield utilized chloromethylated polystyrene derivatives crosslinked with 2 % divinylbenzene as the insoluble support. The first step of the peptide synthetic sequence involved the attachment of an *N*-benzyloxycarbonyl protected amino acid through its *C*-terminus to the resin **1** and subsequent *N*-deprotection with 30 % HBr in acetic acid furnishes the immobilised amino acid **2** (Scheme 1.1).



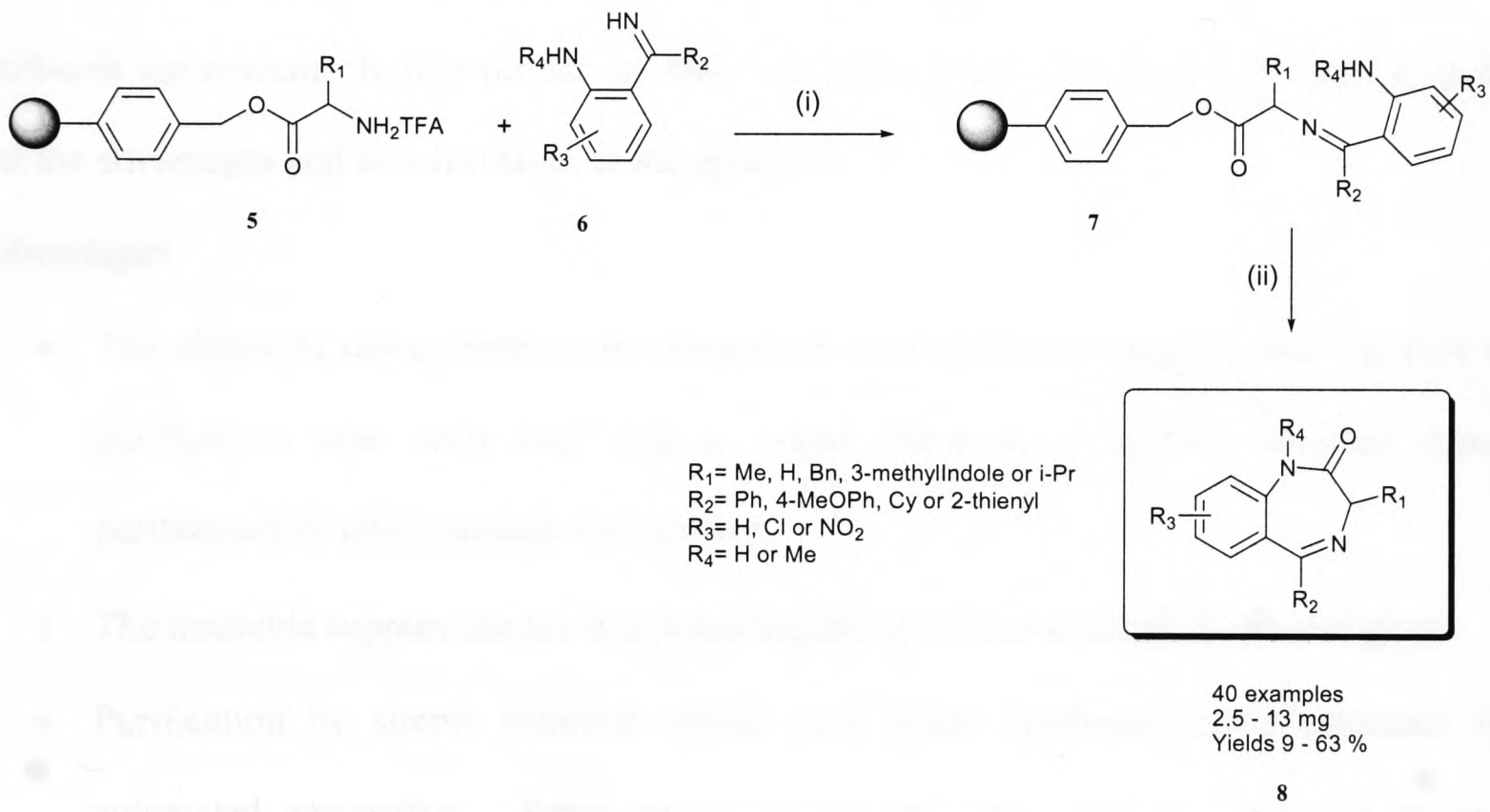
Scheme 1.1: *Reagents and conditions:* (i) NEt_3, EtOAc, Δ 48 h; (ii) 30 % HBr, AcOH, r.t. 5 h; (iii) DCC, DMF, r.t. 18 h; (iv) $NaOH_{(aq)}$, EtOH.

The use of *o,m*-nitro-chloromethylated polystyrene resin **1** allows selective deprotection of the *N*-benzyloxycarbonyl group with minimal loss of peptide from the resin by increasing the stability of the anchoring ester bond towards acid catalysed cleavage. The resin thus acts as a *C*-terminus protecting group through the synthetic sequence as well as rendering the growing peptide chain insoluble. Subsequent peptide bond formation utilizing *N,N'*-dicyclohexylcarbodiimide in DMF as the coupling agent, followed by *N*-deprotection and repetition gave tetrapeptides **3** which were cleaved from the resin by saponification with NaOH in EtOH. To further demonstrate the feasibility of the technology Merrifield and coworkers synthesized the 124 residue protein bovine ribonuclease A with automated methods in 3 % overall yield.[5] Solid supports have also been utilized for other linear oligomers such as oligosaccharides[6] and oligonucleotides.[7] The ability to rapidly synthesise peptides, small proteins and other biopolymers has made solid phase synthesis a powerful tool to facilitate the study of biological systems.

It was proposed[8] at an early stage that Merrifield's approach would have potential advantages for organic chemistry with applications other than to linear oligopolymers. Solid phase organic synthesis has since become a highly active area of research particularly used in the past decade as a strategy to rapidly synthesise drug candidates with automated methods for high throughput screening in biological assays.

1.2.2 Small molecule synthesis: Benzodiazepines

Pioneering work by Bunin and Ellman[9] in 1992 described the synthesis of an array of ten 1,4-benzodiazepine-2-one derivatives on a solid support demonstrated the potential of SPOS technology for the synthesis of small druglike molecules. A similar approach was independently described by DeWitt[10] *et al.* who reported the parallel synthesis of a 40 member array of 1,4-benzodiazepine-2-one analogs. The synthesis consisted of loading 5 different amino acids on Merrifield's resin **4** to give **5** followed by transimination with 8 benzophenone imines **6** to furnish 40 immobilised imines **7**. Subsequent cleavage with TFA generated a 40 member array of the desired compounds **8**, with isolated yields ranging from 9 - 63 % based on the loading of the commercially available resins (Scheme 1.2).



Scheme 1.2: *Reagents and conditions:* (i) DCE, heat; (ii) TFA, heat.

The cleavage strategy merits attention since only resin sites possessing the required nucleophilic functional group will be cleaved *via* the cyclative cleavage process. Any unreacted starting material or intermediate will therefore remain on polymer and will not contaminate the final product when cleaved into solution. This principle has been extensively used in solid phase synthesis[11] since very high levels of purity can be achieved with this method.

Subsequent SPOS protocols have enabled pharmaceutical researchers to access a vast number of different structural scaffolds of pharmaceutical relevance and have been used to make libraries of compounds for screening in biological assays with automated methods.[12] Solid phase protocols are widely used to analogue different regions of lead molecules to establish structure activity relationships in screening programs aimed at lead optimisation[13] and to generate libraries of structurally complex molecules for screening for interesting biological properties.[14]

1.3 Advantages and disadvantages of SPOS

In comparison to traditional solution phase synthesis a number of advantages of solid phase protocols are evident. Before further discussion of solid phase techniques it is useful to point out the advantages and disadvantages of the approach:

Advantages

- The ability to drive reactions to completion with excess of reagents, and the ease of purification after each step with a simple filtration of soluble reagents makes purification of intermediates unnecessary.
- The insoluble support can act as a protecting group for the attached functional group.
- Purification by simple filtration makes solid phase synthesis highly amenable for automated approaches. Resin beads can be split into spatially separated reaction compartments allowing multiple reactions to be carried out, with washing steps carried out in parallel in the same reaction vessel using split and mix methods.[15] These advantages can lead to significant reduction in time and cost per synthesised compound if used in a proficient manner.
- In a low loading polymer, complete spatial separation of reactive sites may be assumed. This suppresses intermolecular reactions of the attached molecules and promotes

intramolecular reactions. This effect of high dilution, or the hyperentropic effect,[16] can be beneficial in intramolecular cyclization-release protocols.

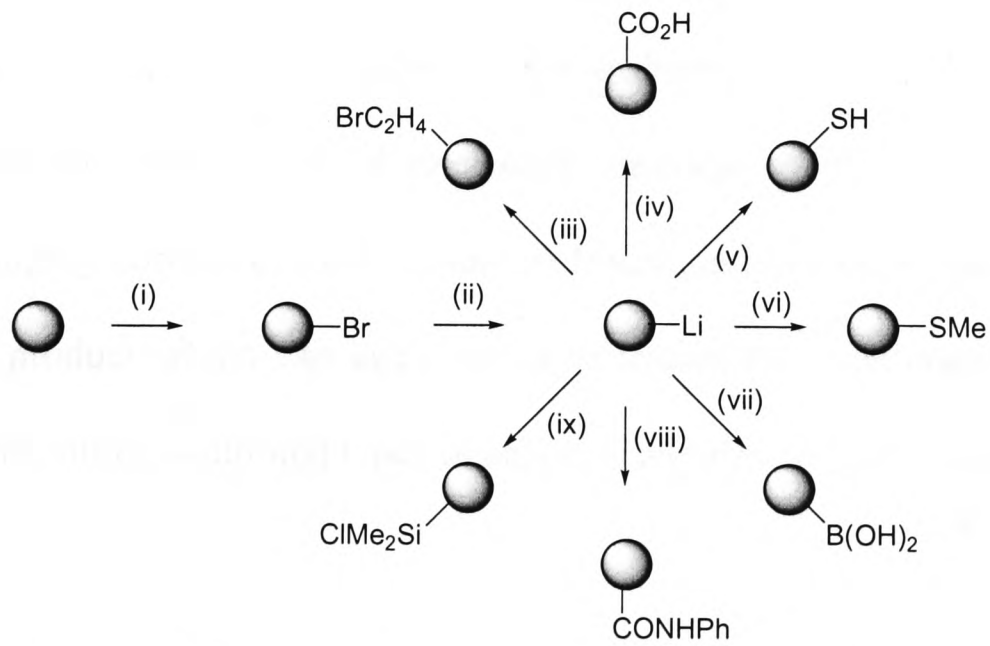
Disadvantages

- Reliable high yielding chemical transformations that have been adapted to the solid phase remain relatively few compared to the solution phase counterpart.[17]
- As in conventional solution phase protecting group chemistry the attachment of the substrate and release of product from the polymer support requires two additional steps in the reaction sequence.
- Reaction monitoring on solid phase is problematic since many common solution phase techniques become unavailable. NMR techniques on solid phase[18] still have to reach the maturity to become comparable to the sophistication of the solution phase counterpart. Colorimetric monitoring has been used to some extent[19] as well as combustion analysis.[20] FTIR and monitoring of the mass balance currently remain the methods of choice for monitoring reactions on solid phase.

Furthermore the chemistry undertaken on polymer and the cleavage strategy must be orthogonal to both the anchoring group and to the product released into solution upon cleavage, which can greatly restrict the chemistry available in the planning of a synthetic sequence. For example, acidic conditions cannot be used with acid labile anchoring groups since premature cleavage into solution could occur. Similarly, acid sensitive functionalities cannot be synthesised utilizing such anchoring groups without appropriate protection since the cleavage conditions would be deleterious to the product. To meet these conflicting requirements numerous attachment-release or linking strategies have been developed.[1-3,17,21] Thus, if a successful solid phase synthesis is to be undertaken the choice of solid support and attachment-cleavage strategy are both crucial.

1.4 Resins, linkers and cleavage strategies in solid phase synthesis

An enormous range of different product classes have been synthesised and released from insoluble supports since the inception of the approach. This has been achieved with a wide range of different polymeric supports, anchoring groups, linkers and combinations thereof. Polystyrene crosslinked with divinylbenzene (1 - 5 %) is still the predominant resin used for SPOS, although to allow the use of more polar solvents other resins have been developed, such as polystyrene/polyethylene glycol copolymers (PEG resins).[22] Since Merrifield's approach to use the benzyl ester linkage to immobilise an amino acid a wide range of functionalised resins have been developed for other molecules/species. Following the work of Farrall and Fréchet[23] who described a bromination/lithiation protocol of crosslinked polystyrene to access functionalised resins a large number of such resins are now commercially available[24] and readily employed in SPOS (Scheme 1.3). As opposed to conventional SPOS, polymer supported reagents, catalysts and scavengers have found widespread use in multi-step organic syntheses.[25]



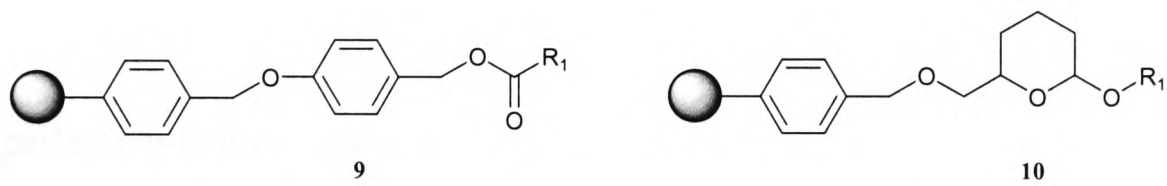
Scheme 1.3: *Reagents and conditions:* (i) Br_2, $FeCl_3$; (ii) n-BuLi, hexane, toluene or benzene, 60°C, 3 h; (iii) $BrCH_2CH_2Br$, benzene, 150 min.; (iv) CO_2, THF; (v) S_8, THF, 1 h then $LiAlH_4$; (vi) Me_2S_2, THF; (vii) $B(OMe)_3$, THF, r.t., 20 h, aq. HCl, dioxane, 60°C, 1.5 h; (viii) PhNCO, benzene; (ix) $SiCl_2Me_2$, benzene, r.t. 45 min.

A great number of linkers and cleavage strategies have been developed to tailor attachment and release strategies to different product classes and chemical functionalities. Categorization of linkers is not trivial[3] since the cleavage strategy used can either regenerate the original attached functional group or a different functional group on the linker molecule, while some linkers can

release different functionalities under various conditions. To provide an overview of linkers developed to date the most important and widely used cleavage strategies are discussed.

1.4.1 Electrophilically cleaved linkers

Electrophilically cleaved linkers are the most common, with proton sources generally used to facilitate cleavage of a wide range of functionalities including amides, amines, alcohols, thiols and sulfonamides.[2] An important member of this class is the *p*-hydroxymethylphenol linker **9** introduced by Wang.[26] Carboxylic acids are cleaved from the Wang linker with 50 % TFA in DCM. Linkers based on the chemistry of the acetal group also belong to this class of linkers of which the THP linker **10** introduced by Ellman[27] is the most commonly used (Figure 1.3).



9

Wang linker
Cleavage: 50% TFA/DCM
Released: carboxylic acid

10

THP linker
Cleavage: TFA/H_2O (95/5)
Released: alcohol

Figure 1.3: Acid cleavable linkers

One disadvantage of acid cleavable resins is the inability to use acidic conditions in any synthetic manipulations due to risk of premature cleavage of the product from the resin. Secondly TFA is highly corrosive, incompatible with automation and can be difficult to remove from the cleaved product which can again result in instability upon compound storage. To overcome these difficulties additional types of supports and linkers have been developed.

1.4.2 Other cleavage strategies

Nucleophilically cleaved linking strategies have also found a widespread use. For example, oxygen nucleophiles can be used to cleave benzyl ester linkages to release carboxylic acids with saponification[4] or as esters through transesterification.[28] The reverse approach can be used to cleave alcohols from carboxylic acid based linkages with a range of nucleophiles. Another variation uses halogen nucleophiles, which have been used to cleave alcohols from silyl based

linker such as **11**.[29] Photocleavable linkers constitute another sub-class of which the *o*-nitrobenzyl linker[30] **12** is the most widely used (Figure 1.4).

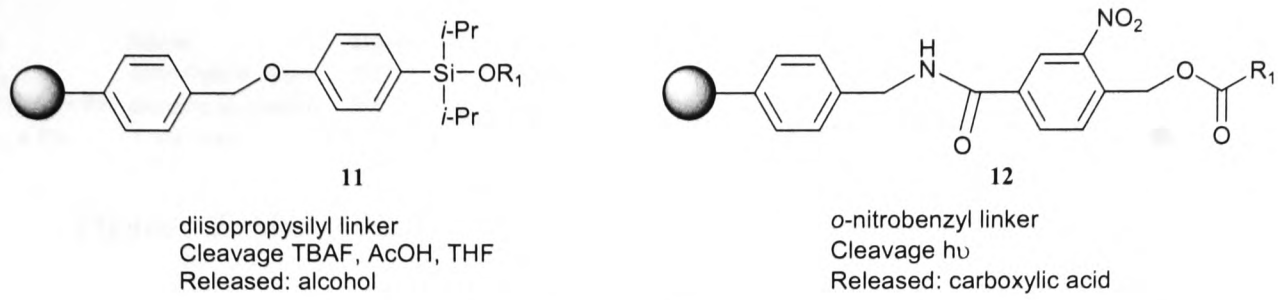
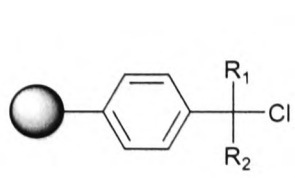


Figure 1.4: Nucleophilically cleaved linker **11** and photocleavable linker **12**.

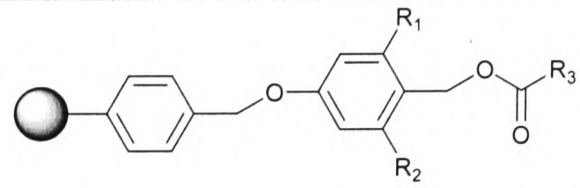
Among other cleavage strategies are metal assisted cleavage procedures such as palladium catalysed allyl transfer,[31] reductive cleavage using catalytic hydrogenation[32] to cleave peptides from Merrifield's resin, and oxidative cleavage of an alkoxybenzyl group from the Wang linker using DDQ[33] to release alcohols into solution.

1.4.3 Manipulating linker lability

Most linkers and cleavage strategies have directly evolved from solution phase protecting group chemistry of which the benzylic moiety is the most important. A wide range of acid cleavable linkers were developed for peptide synthesis of which many have been useful in the synthesis of small drug-like molecules on solid supports. Merrifield's approach to manipulate the acid lability of chloromethylated polystyrene *via* nitration was followed by a range of functionalised resins, linkers and alternative *N*-protection strategies to allow orthogonal deprotection on acid labile resins. Introduction of phenyl groups on the benzylic carbon of Merrifield's resin **4** stabilises the cation intermediate facilitating cleavage under acidic conditions. The benzhydryl[34] **13** and trityl[35] **14** resins are examples of this strategy, these and related resins have been used to great effect to release a variety of functionalities. Another related and widely used strategy to manipulate cleavage conditions is to use aromatic substitution to alter the stability of the resulting cation upon cleavage. Examples of this strategy are the SASRIN[26] **15** and HAL[36] **16** linkers where the introduction of methoxy substituents on the Wang linker **9** is used to fine tune the cleavage conditions (Figure 1.5).



	R	Name	Cond.	Cleaved
4	R_1, R_2 = H	Merrifield's resin	HF	RCOOH
13	R_1 = H, R_2 = Ph	Benzhydryl resin	HF	$RCONH_2$
14	R_1, R_2 = Ph	Trityl resin	1 % TFA/AcOH	RCOOH



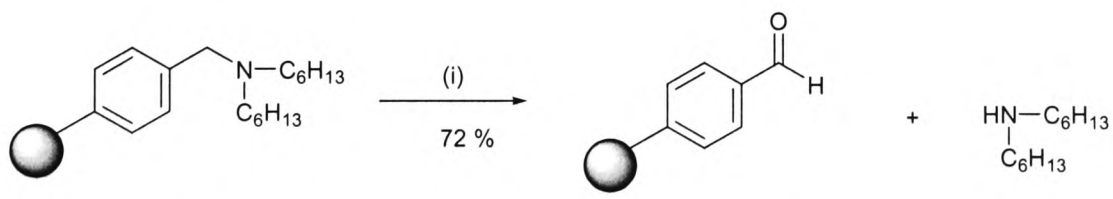
	R	Name	Cond.
9	R_1, R_2 = H	Wang linker	50 % TFA
15	R_1 = H, R_2 = OMe	Sasrin linker	1 % TFA
16	R_1, R_2 = OMe	HAL linker	0.1 % TFA

Figure 1.5: Manipulation of cleavage conditions of acid labile resins and linkers

1.5 Attachment and release of amines and alcohols

Acid labile resins derived from the benzylic moiety originally developed for peptide synthesis have been used to attach and release amines from polymeric supports using harsher cleavage conditions than for amides and carboxylic acids.[37] The direct release of amines from Merrifield's resin under acidic conditions has not been reported. Amines are readily attached to such resins *via* reductive amination[38] or nucleophilic displacement.[39]

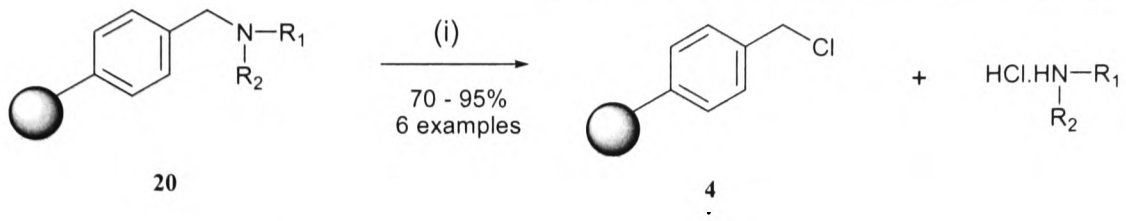
To release amines from Merrifield's resin two alternative methods have been introduced in the literature that merit discussion. Previous work from this laboratory has shown that treatment of Merrifield's resin bound secondary amine **17** with CAN oxidatively cleaved the amine from polymer affording a recyclable benzaldehyde-type resin **18** and dihexyl amine **19** in solution (Scheme 1.4).[38]



17 18 19

Scheme 1.4: *Reagents and conditions:* (i) CAN (5 eq.), MeCN:H_2O (5:1), r.t.

In an alternative strategy developed by Leysen *et al.*[39] resin bound amines **20** were treated with α-chloroethyl chloroformate, followed by reflux in MeOH, to release the amine hydrochloride salts and regenerate Merrifield's resin **4** (Scheme 1.5).



Scheme 1.5: *Reagents and conditions:* (i) α-chloroethyl chloroformate, DCE then MeOH, Δ.

A widely used method to release amines from solid supports utilises a carbamate anchoring group to hydroxymethylated polystyrene **21**, as introduced initially by Letsinger *et al.*[40] Since cleavage of the carbamate linkage requires vigorous conditions such as hydrogen bromide in acetic acid it was later modified by Marsh *et al.*[41] The activated carbamate linkage of **22** can be readily cleaved with neat TFA (Figure 1.6). However, benzyl carbamates are also known to be labile towards other reaction conditions such as nucleophiles, organometallic reagents and reducing agents.[42] For example, the carbamate linkage can also be reductively cleaved with $LiAlH_4$ to release *N*-methyl tertiary amines as an alternative to acidic cleavage.[43]

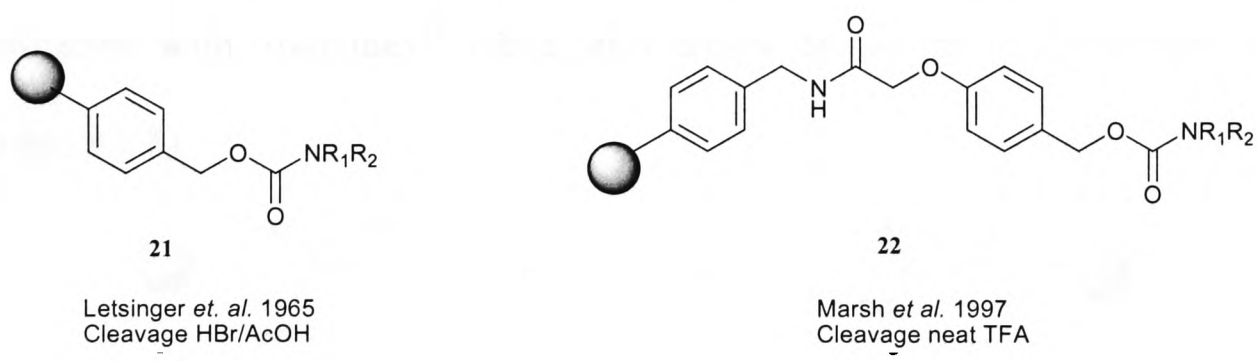


Figure 1.6: Carbamate based cleavage strategies for amines

Other linkage strategies that release amines include cleavage under nucleophilic conditions based on nucleophilic displacement of silyl groups from linker **23** to release the amines into solution,[44] and a carbamate-based linker **24** that may be cleaved by palladium-catalysed allyl transfer (Figure 1.7).[45] Further strategies include a formamidine based linkage,[46] the ADCC (4-acetyl-3,5-dioxo-1-methylcyclohexane carboxylic acid) linker developed by Bannwarth *et al.*,[47] sulfonamide based linkage,[48] oxidative cleavage of a DDQ labile *p*-methoxybenzyl based linker,[49] and hydrazine[50] and triazine[51] based strategies.

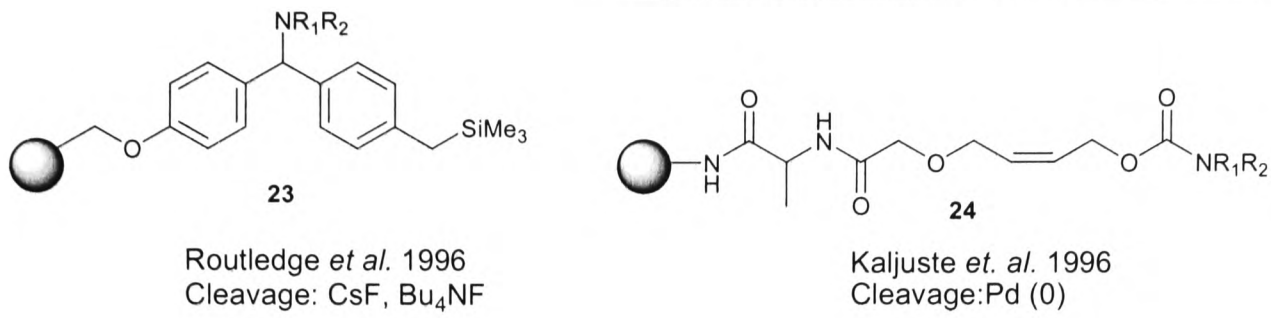


Figure 1.7: Cleavage strategies for amines

Alcohols have been immobilized on a broad variety of functionalised resins and linkers,[52] most commonly as benzylic ethers **25**,[53] acetals **26**,[27] esters **27**[54] or silyl ethers **28**.[29] Benzylic ether resins **25** are derived from solid phase peptide synthesis and can be used for immobilisation of alcohols either *via* nucleophilic displacement of resin bounds halides[55] or under Mitsunobu[56] conditions for aryl alcohols. Release from these benzylic ether resins **25** can be facilitated *via* mild acid conditions while forcing acid conditions are required for cleavage of acetal linkers **26**.[27] Alcohols are released from esters **27** by saponification with alkali metal hydroxides[57] or transesterification with alkoxides[58] while silyl ethers **28** are most commonly cleaved with TBAF[29] (Figure 1.8).

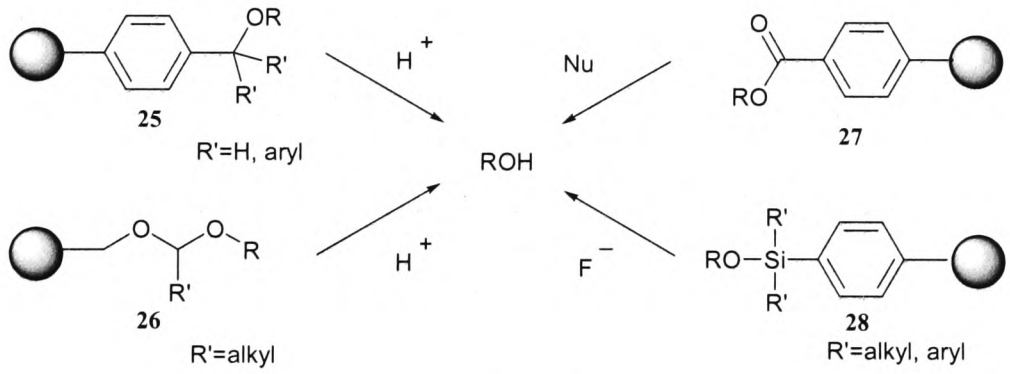


Figure 1.8: Cleavage strategies for alcohols

Other strategies include cleavage of ethers by β–elimination with base[59] and reductive cleavage of esters[60] and amides[61] to yield alcohols. Because of the wide range of compounds that may be synthesised on solid phase[17] and the number of different reactions that are required for these syntheses it is impossible to design a "universal linker" that is stable towards all possible combinations of reactions undertaken. There is therefore great interest in the development of linkers that are stable towards a wide variety of conditions, yet are readily cleaved under mild conditions. One approach to achieve these goals is the development of chemically robust safety catch linkers.

1.6 Safety catch linkers

1.6.1 Kenner's safety catch principle

The safety catch principle was introduced by Kenner *et al.*[62] in 1971. The principle describes an unreactive linker that is stable to the chemistry undertaken in a synthetic sequence. At the end of the synthetic sequence the linker is converted by a simple and yet mild chemical transformation into a reactive species ready to undergo a cleavage step. The cleavage step can either occur intramolecularly or with a species in solution. Kenner's initial approach consisted of sulfonamide linker **29** which is resistant to cleavage under basic conditions due to the low pK_a (2.5) of the amide hydrogen and the stability of the resulting anion **30**. *N*-alkylation with diazomethane affords linker **31** which is activated towards nucleophilic displacement, allowing multidirectional cleavage under mild conditions with amines and alkoxides to afford the corresponding products into solution (Figure 1.9).

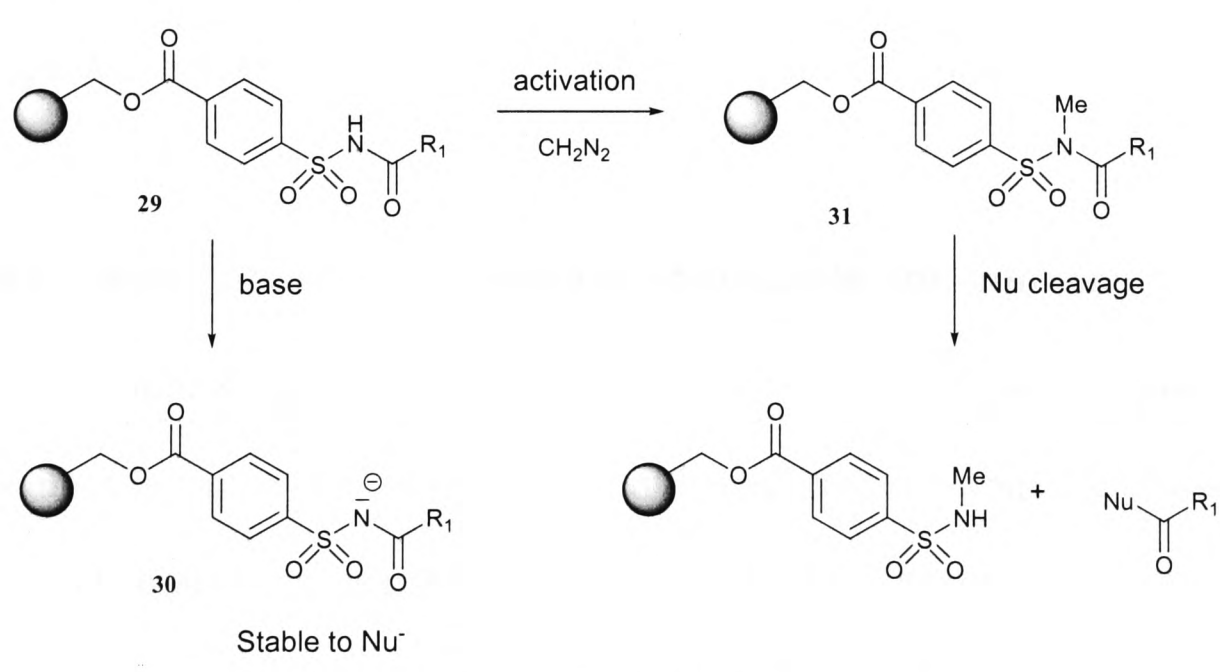
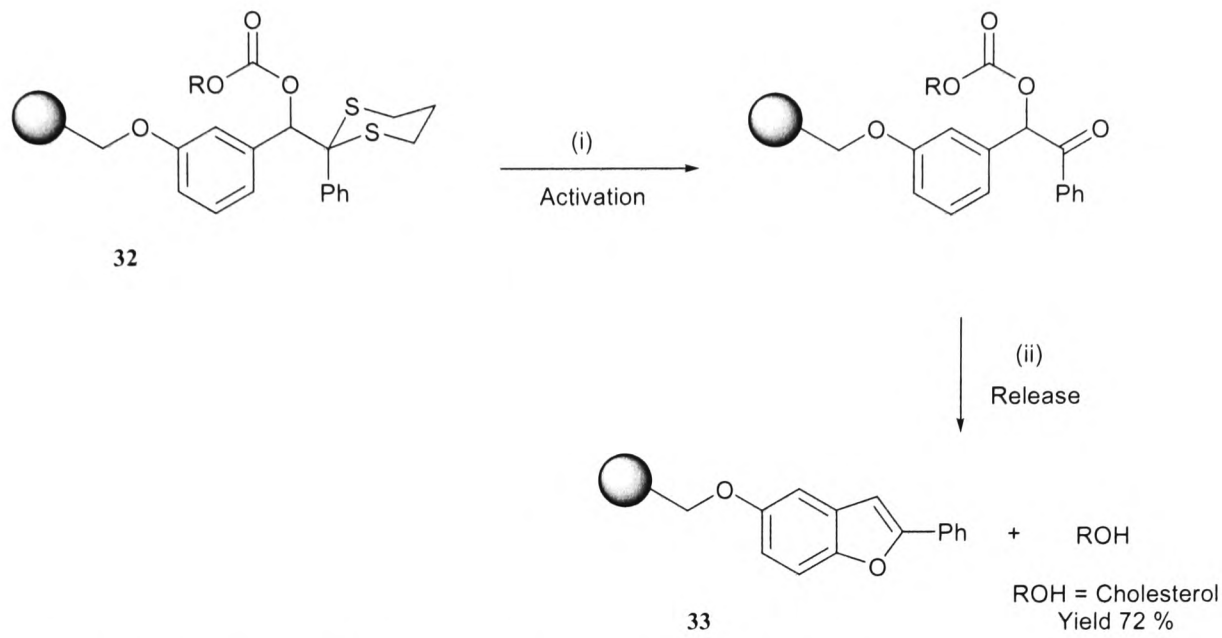


Figure 1.9: Kenners safety catch sulfonamide linker

Numerous safety catch linkers have since been developed to release a broad variety of functional groups into solution. Sophisticated activation/release strategies have been developed which are orthogonal to sensitive functional groups in the released products. These include the photocleavable linker **32** developed by Balasubramanian *et al.*[63] As a cleavage strategy the safety catch linker utilizes a thioacetal deprotection followed by a photochemically induced

cyclization to form a resin bound benzofuran **33** with concomitant release of the product (Scheme 1.6).

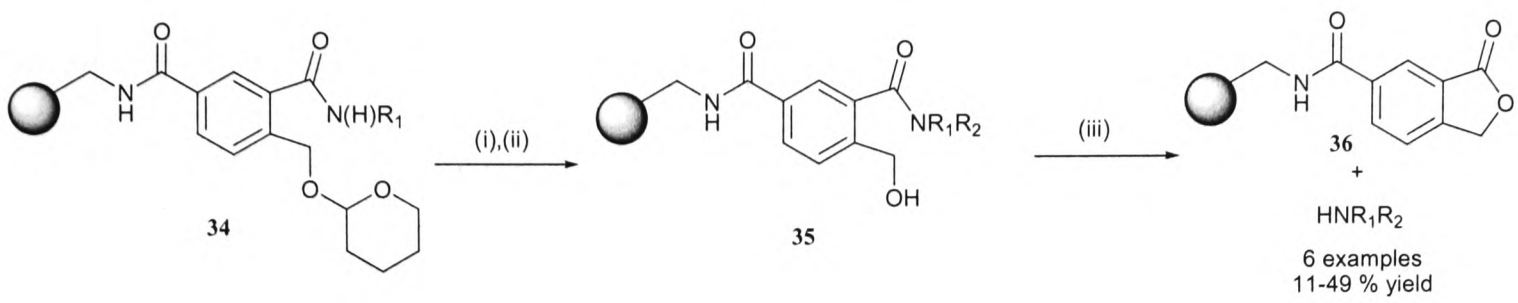


Scheme 1.6: *Reagents and conditions:* (i) $Hg(ClO_4)_2$, THF:H_2O (10:1), 20°C; (ii) hν (350 nm), 28°C 3 h.

Despite rapid developments in the design of safety catch linkers,[64] relatively few have been developed for the anchoring and release of amines and alcohols allowing the use of a broad variety of reaction conditions such as organometallics, strong bases such as BuLi and LHMDS and/or strong acidic conditions.

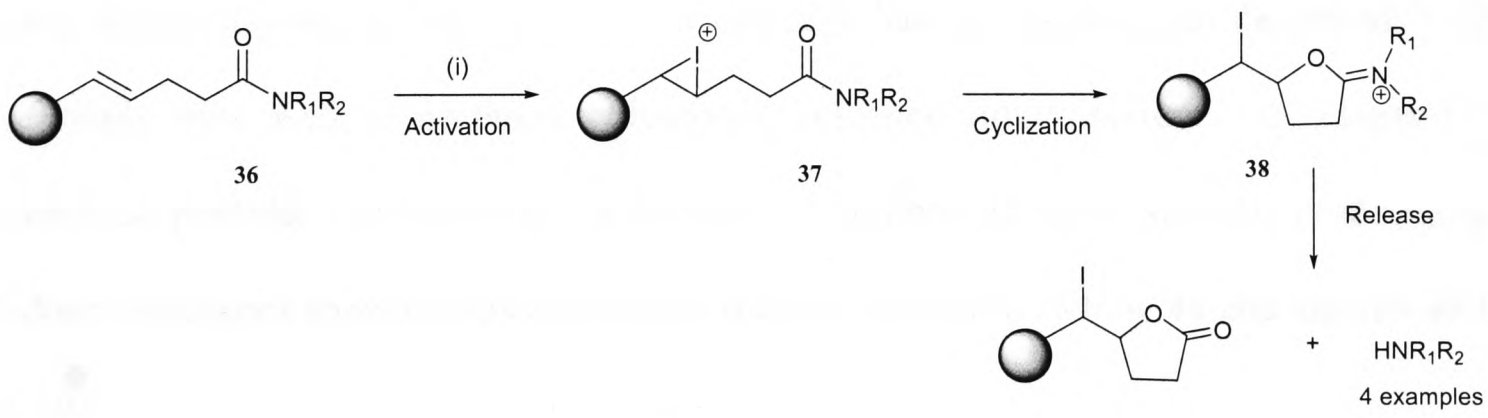
1.6.2 Safety catch linkers for the release of alcohols and amines

The cyclorelease strategy developed by Bannwarth *et al.*[65] for the solid phase synthesis of secondary amines is particularly noteworthy. In the reported synthesis the release of product from the resin relied upon a base promoted cyclisation process, however the synthetic sequence also employed basic reaction conditions and premature release of primary amines was circumvented by an acid labile safety catch. Hence after alkylation of **34** the safety catch was activated by treatment with TFA to afford **35** from which secondary amine was released under basic conditions (Scheme 1.7).



Scheme 1.7: *Reagents and conditions* (i) KO^{t}Bu, THF then R_2Br; (ii) TFA, THF, H_2O; (iii) NaOH, Et_2O.

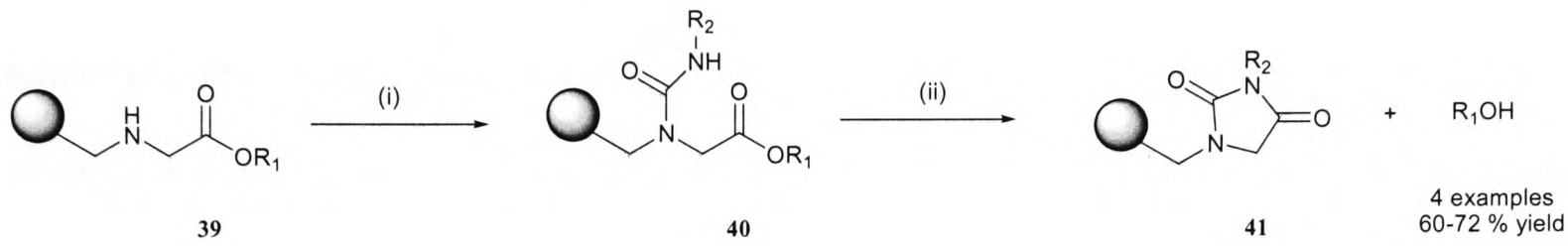
Using this strategy, the THP deprotection, followed by base-induced cyclorelease, will not tolerate acid or base sensitive functionalities in the product without prior protection and subsequent postcleavage deprotection. To overcome this limitation, other protection strategies may be used for the hydroxyl functionality, allowing tailoring of the release strategy to be orthogonal to the synthetic sequence undertaken and the released product. A similar amine releasing linker utilizes activation by addition of iodine to **36** to form an iodonium species **37**. Concomitant iodocyclisation and hydrolysis of resin bound **38** promotes release of the amine into solution.[66] The linker system is based on 5-polystyrenyl-4-pentenoic acid, which is easily synthesised on polystyrene bound benzaldehyde *via* a Wittig olefination protocol (Scheme 1.8).



Scheme 1.8: *Reagents and conditions:* (i) 0.1 M I_2 in THF:H_2O (4:1), r.t. 2 h.

This linker system is stable toward both acid and base and other mild reagents widely used in organic synthesis, but is not compatable with strong bases due to possible complications arising from enolisation by deprotonation of the acidic protons α to the carbonyl group. The presence of the double bond as a safety catch also limits the linker system to chemistry orthogonal to the alkene functionality.

A similar concept utilises natural α-amino acids[67] as linkers for alcohols and amines employing similar activation by a simple chemical transformation followed by cyclorelease. For example, a glycine-ester based linker **39** described by Raghavan and coworkers[68] uses a cyclorelease strategy induced by reaction with phenylisocyanate. The resulting urea derivative **40** subsequently undergoes base mediated cyclorelease of the target alcohol *via* formation of the resin bound hydantoin **41** (Scheme 1.9).

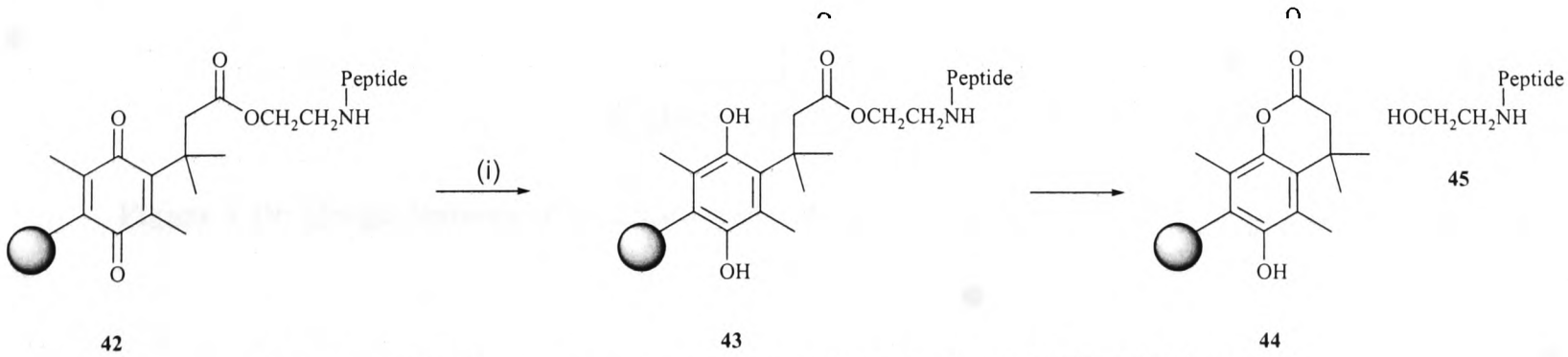


39 **40** **41**

Scheme 1.9: *Reagents and conditions:* (i) R_2NCO, MePh:DMF (1:1), r.t. 8 h; (ii) *i*-Pr_2NH, r.t. 1 h.

Although this process has the advantage of using mild cleavage conditions, the amine functionality of **39** needs suitable protection to prevent reactions with electrophiles, giving rise to undesired side reactions.

A drug delivery system based on lactonisation to release amine based prodrugs into solution *in vivo* after activation by an enzyme ester cleavage has previously been described.[69] The same principle was used to design a reductively activated linker system[70] to release *C*-terminal modified peptides into solution. Reduction of quinone **42** with $Na_2S_2O_4$ produces quinol **43** which undergoes spontaneous cyclisation-release furnishing lactone **44** and alcohol **45** (Scheme 1.10).



42 **43** **44** **45**

Scheme 1.10: *Reagents and conditions:* (i) $Na_2S_2O_4$, H_2O:THF (5:8), r.t. 2 h.

1.7 Aim of the project

1.7.1 Limitations of current technologies

It is clear from the limitations described above that a safety catch linker system for both amines and alcohols robust enough to tolerate a broad variety of reaction conditions has yet to be developed. Such a system would allow the use of strong bases such as BuLi and LHMDS, strong nucleophiles such as Grignard reagents and strong reducing and/or oxidative conditions. Relatively few safety catch linker systems exist that allow a multistep organic synthesis utilizing a broad range of commonly used reagents. To overcome some of these limitiations, this thesis is concerned with model studies directed toward the preparation of a novel safety catch linker system.

1.7.2 Design of a novel oxidatively activated safety catch linker

This thesis is concerned with the design and synthesis of a novel safety catch linker for the attachment and release of amines and alcohols from solid phase. The linker system is derived from 2,2-dimethyl-4-aminobutanoic acid (Figure 1.10).

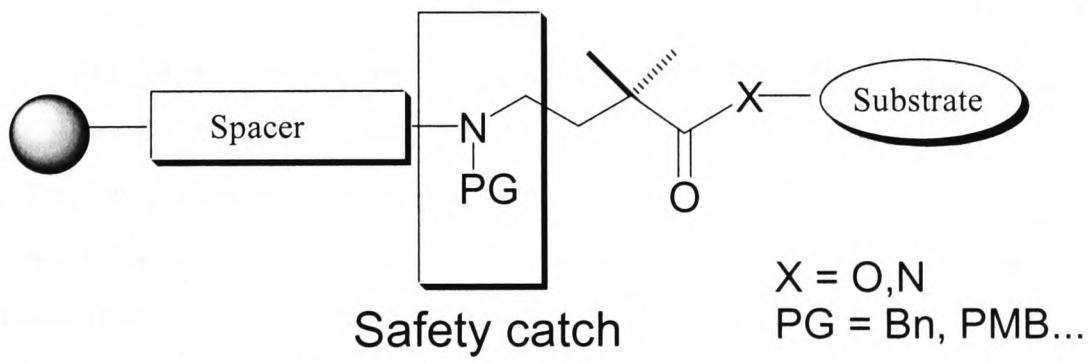


Figure 1.10: Design features of the 2,2,-dimethyl-4-aminobutanoic acid safety catch linker system

References

[1] R. Warrass, "Solid Phase Anchors in Organic Chemistry", in *Combinatorial Chemistry, Synthesis, Analysis, Screening*, ed. G. Jung, Wiley-VCH, Chichester, 1999.

[2] F. Guillier, D. Orain, M. Bradley, *Chem. Rev.*, 2000, **100**, 2091.

[3] A. C. Comely, S. E. Gibson, *Angew. Chem. Int. Ed.*, 2001, **40**, 1012.

[4] R. B. Merrifield, *J. Am. Chem. Soc.*, 1963, **85**, 2149.

[5] B. Gutte, R.B. Merrifield, *J. Biol. Chem.*, 1971, **246**, 1922; R.B. Merrifield, *Solid Phase Synthesis*, Nobel lecture, 1984 (http://nobelprize.org/chemistry/laureates/1984/merrifield-lecture.pdf).

[6] S.J. Danishefsky, K.F. McClure, J.T. Randolph, R.B. Ruggeri, *Science*, 1993, **260**, 1307; O.J. Plante, E.R. Palmacci, P.H. Seeberger, *Science*, 2001, **291**, 1523 and L.A Marcaurelle, P.H. Seeberger, *Curr. Opin. Chem. Biol.*, 2002, **6**, 289.

[7] R.L. Letsinger, V. Mahadevan, *J. Am. Chem. Soc.*, 1965, **87**, 3526; S.P.A. Fodor, J.L. Read, M.C. Pirrung, L. Stryer, A.T. Lu, D. Solas, *Science*, 1991, **251**, 767.

[8] C.C. Leznoff, *Accts. Chem. Res.*, 1978, **11**, 327.

[9] B.A. Bunin, J.A. Ellman, *J. Am. Chem. Soc.*, 1992, **114**, 10997.

[10] S.H. DeWitt, J.S. Kiely, C.J. Stankovic, M.C. Schroeder, D.M.R. Cody, M.R. Pavia, *Proc. Natl. Acad. Sci. U.S.A.*, 1993, **90**, 6909.

[11] D. Obrecht, J.M. Villalgordo, *Solid Supported Combinatorial and Parallel Synthesis of Small-Molecular-Weight Compound Libraries*, 1st . edn. Elsevier Science Ltd., Oxford, 1998, p. 96.

[12] For recent advances see: R.E. Dolle, *J. Comb. Chem.*, 2004, **7**, 623.

[13] K.C. Nicolau, R.M. Evans, A.J. Roecker, R. Hughes, M. Downes, J.A. Pfefferkorn, *Org. Biomol. Chem.*, 2003, **1**, 908-920.

[14] M.D. Burke, S.L. Schreiber, *Angew. Chem.*, 2003, **43**, 46.

[15] R.A., Houghten, *Proc. Natl. Acad. Sci., U.S.A.*, 1985, **82**, 5131 and A. Furka, F. Sebestyen, M. Asgedom; G. Dibo, *Abstr. 14th Int. Congr. Biochem. Prague, Checkoslovakia*, 1998, **5**, 47 and A. Furka, F. Sebestyen, M. Asgedom, D. Gibo, *Int. J. Pept. Protein Res.*, 1991, **37**, 487.

[16] J.I. Crowley, H. Rapoport, *Acc. Chem. Res.*, 1976, **9**, 135.

[17] F.Z. Dörwald, *Organic Synthesis on Solid Phase*, Wiley-VCH, Chichester, 2002.

[18] S.K. Sarkar, R.S. Garigipati, J.L. Adams, P.A. Keifer, *J. Am. Chem. Soc.*, 1996, **118**, 2305.

[19] F. Gaggini, A. Porcheddu, G. Reginato, M. Rodriquez, M. Taddei, *J. Comb. Chem.*, 2004, **6**, 805.

[20] B. Yan, C.F. Jewell, S. W. Myers, *Tetrahedron*, 1988, **54**, 11755.

[21] J. Wills, S. Balasubramanian, *Curr. Opin. Chem. Biol.*, 2003, **7**, 346; K. Gordon, S. Balasubramanian, *J. Chem. Technol. Biotechnol.*, 1999, **74**, 835; I.W. James, *Tetrahedron*, 1999, **55**, 4855.

[22] E. Bayer, *Angew. Chem., Int. Ed. Engl.*, 1991, **30**, 113.

[23] M.J. Farrall, J.M. Frechet, *J. Org. Chem.*, 1976, **41**, 3877.

[24] Novabiochem 2004/5 Catalog.

[25] S.V. Ley, I.R. Baxendale, R.N. Bream, P.S. Jackson, A.G. Leach, D.B. Longbottom, M. Nesi, J.S. Scott, R.I. Storer, S.J. Taylor, *J. Chem. Soc., Perkin Trans. 1*, **2000**, 3815.

[26] S.S. Wang, *J. Am. Chem. Soc*, 1973, **95**, 1328.

[27] L.A. Thompson, J.A. Ellman, *Tetrahedron Lett.*, 1994, **35**, 9333.

[28] L.F. Tietze, T. Hippe, A. Steinmetz, *Synlett*, 1996, 1043.

[29] M. Reggelin, V. Brenig, R. Welcker, *Tetrahedron Lett.*, 1998, **39**, 4801.

[30] D.H. Rich, S.K. Gurwara, *J. Am. Chem. Soc.*, 1975, **97**, 1575.

[31] H. Kunz, B. Dombo, *Angew. Chem., Int. Ed. Engl.*, 1988, **27**, 711.

[32] J.M. Schlatter, R.H. Mazur, *Tetrahedron Lett.*, 1977, **18**, 2851.

[33] T.L. Deegan, O.W. Gooding, S. Baudart, J.A. Porco, *Tetrahedron Lett.*, 1997, **38**, 4973.

[34] P.G. Pietta, G.R. Marshall, *Chem. Commun.*, 1970, 650.

[35] J.M.J Fréchet, K.E. Hague, *Tetrahedron Lett.*, 1975, **16**, 3055.

[36] F. Albericio, G. Barany, *Tetrahedron Lett.*, 1991, **32**, 1015.

[37] M.F. Gordeev, D.V. Patel, E.M. Gordon, *J. Org. Chem.*, 1996, **61**, 924-928; A.V. Purandare, M.A. Poss, *Tetrahedron Lett.*, 1998, **39**, 935; I.A. Nash, B.W. Bycroft, W.C. Chan, *Tetrahedron Lett.*, 1996, **37**, 2625; K.H. Bleicher, J.R. Wareing, *Tetrahedron Lett.*, 1998, **39**, 4587; P. Forns, S. Sevilla, M. Erra, A. Ortega, J. Fernandez, N. de la Figuera, D. Fernandez-Forner, F. Albericio, *Tetrahedron Lett.*, 2003, **44**, 6907.

[38] S.G. Davies, S.D. Bull, A.W. Mulvaney, R.S. Prasad, A.D. Smith, *Chem. Comm.*, 2000, **5**, 337; S.G. Davies, S.D. Bull, G. Fenton, A.W. Mulvaney, R.S. Prasad, A.D. Smith, *J. Chem. Soc. Perkin Trans. 1*, 2000, **22**, 3765.

[39] P. Conti, D. Demont, J. Cals, H.C.J. Ottenheijm, D. Leysen, *Tetrahedron Lett.*, 1997, **38**, 2915.

[40] R.L. Letsinger, M.J. Kornet, V. Mahadevan, D.M. Jerina, *J. Am. Chem. Soc.*,1965, **86**, 5163.

[41] I.R. Marsh, H. Smith, M. Bradley, *Mol. Diversity*, 1997, **2**, 165.

[42] T.W. Green, P.G.M. Wuts, *Protective Groups in Organic Chemistry*, 3rd edn., John Wiley, Chichester, 1999.

[43] C.Y. Ho, M.J. Kukla, *Tetrahedron Lett.*, 1997, **38**, 2799.

[44] A. Routledge, T. Stock, S.L. Flitsch, N.J. Turner, *Tetrahedron Lett.*, 1997, **38**, 8287.

[45] K. Kaljuste, A. Unden, *Tetrahedron Lett.*, 1996, **37**, 3031.

[46] P.S. Furth, M.S. Reitman, A.F. Cook, *Tetrahedron Lett.*, 1997, **38**, 5403.

[47] W. Bannwarth, J. Huebscher, R. Barner, *Bioorg. Med. Chem. Lett.*, 1996, **6**, 1525.

[48] C. Kay, P. Murray, L. Sandow, A.B. Holmes, *Tetrahedron Lett.*, 1997, **38**, 6941; M.S. Congreve, C. Kay, J.J. Scicinski, S.V. Ley, G. Williams, P.J. Murray, S.C. McKeown, S.P. Watson, *Tetrahedron Lett.*, 2003, **44**, 4153.

[49] S. Kobayashi, Y. Aoki, *Tetrahedron Lett.*, 1998, **39**, 7345.

[50] J.H. Kirchhoff, S. Brase, D. Enders, *Tetrahedron Lett.*, 2001, **3**, 71.

[51] S. Brase, J. Köbberling, D. Enders, R. Lazny, M. Wang, *Tetrahedron Lett.*, 1999, **40**, 2105.

[52] For a review see N-H Nam, S. Sardari, K. Parang, *J. Comb. Chem.*, 2003, **5**, 479.

[53] R.S. Garigipati, *Tetrahedron Lett.*, 1997, **38**, 6807.

[54] C. Gennari, S. Ceccarelli, U. Piarulli, K. Aboutayab, M. Donghi, I. Paterson, *Tetrahedron*, 1998, **54**, 14999.

[55] W.R. Li, Y.S. Lin, N.M. Hsu, *J. Comb. Chem.*, 2001, **3**, 634.

[56] Y.H. Wang, S.R. Wilson, *Tetrahedron Lett.*, 1997, **38**, 4021.

[57] C.C. Leznoff, D.M. Dixit, *Can. J. Chem.*, 1977, **55**, 3351.

[58] M.J. Kurth, L.A. Randall, K. Takenouchi, *J. Org. Chem.*, 1996, **61**, 8755.

[59] Y. Wang, H. Zhang, W. Voelter, *Chem. Lett.* 1995, 273.

[60] L.F. Tietze, T. Hippe, A. Steinmetz, *Chem. Commun.*, 1998, 793.

[61] P.C. Hutchison, T.D. Heightman, D.J. Procter, *Org. Lett.*, 2002, **4**, 4583.

[62] G.W. Kenner; J.R. McDermott, R.C. Sheppard, *J. Chem. Soc., Chem. Comm.*, 1971, 636.

[63] A. Routledge, C. Abell, S. Balasubramanian, *Tetrehedron Lett.*, 1997, **38**, 1227.

[64] For reviews see: A.J. Wills, S. Balasubramanian, *Curr. Op. Chem. Biol.*, 2002, **102**, 2607; W.S. Wade, F. Yang, T.J. Sowin, *J. Comb. Chem.*, 2000, **2**, 266; K. Gordon, S. Balasubramanian, *J. Chem. Technol. Biotechnol.*, 1999, **74**, 835; M. Pátek, M. Lebl, *Biopolymers*, 1998, **47**, 353.

[65] H. Glatz, W. Bannwarth, *Tetrahedron Lett.*, 2003, **44**, 149.

[66] M. Guo, L. Varady, *Tetrahedron Lett.*, 2002, **56**, 5611.

[67] G. Subra, M. Amblard, J. Martinez, *Tetrahedron Lett.*, 2002, **43**, 9221; J.C. Kappel, G. Barany, *J. Comb. Chem.*, 2005, **7**, 78.

[68] S. Raghavan, A. Rajender, *Chem. Comm.*, 2002, **15**, 1572.

[69] R.B. Greenwald, Y.H. Choe, C.D. Conover, K. Shum, D. Wu, M. Royzen, *J. Med. Chem.*, 2000, **43**, 475.

[70] A. Zheng, D. Shan, B. Wang, *J. Org. Chem.*, 1999, **64**, 156.

2 Chapter II: Linker Design and Synthesis

2.1 Linker design

This chapter describes preliminary studies towards the development and synthesis of a novel safety catch linker derived from 2,2-dimethyl-4-(*N*-benzylamino)butanoic acid for the attachment and release of amines and alcohols from solid support. The linker is attached to the solid support of choice through a spacer attached to a tertiary amine functionality designed to act as a safety catch device during the elaboration of the substrate prior to activation by *N*-deprotection. This design feature requires a bespoke protecting group that is orthogonal to the synthetic transformations undertaken. In this way a deprotection/activation strategy which is non-deleterious to the released product can be chosen (Figure 2.1).

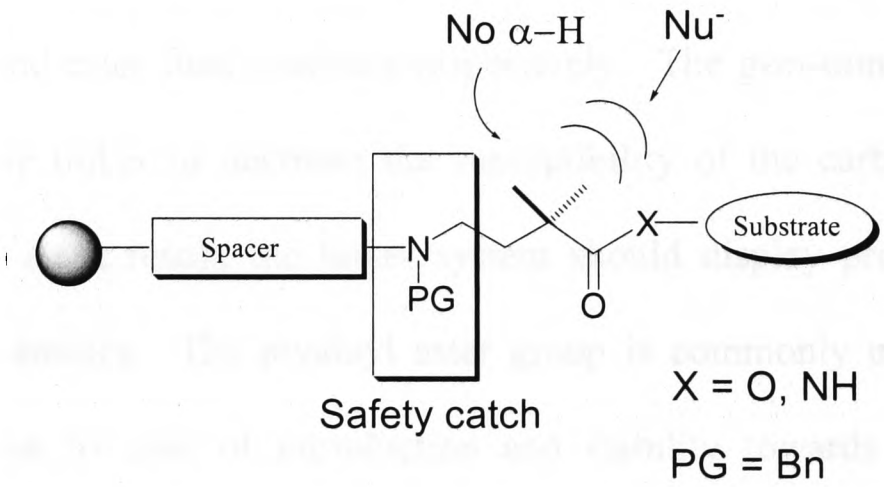


Figure 2.1: Design features of the safety catch linker system

The spacer is designed to minimise steric interactions between the reactive site and the polymeric backbone, and allows manipulation of the hydrophobic/hydrophilic character of the resin. The design of the safety catch linker system incorporates key design features employing chemistry developed and used within the Davies' group. As a model study, *N*-benzyl protection of the *N* atom was chosen with oxidative chemoselective mono *N*-debenzylation utilizing CAN chosen as an activation strategy (Figure 2.2).[1]

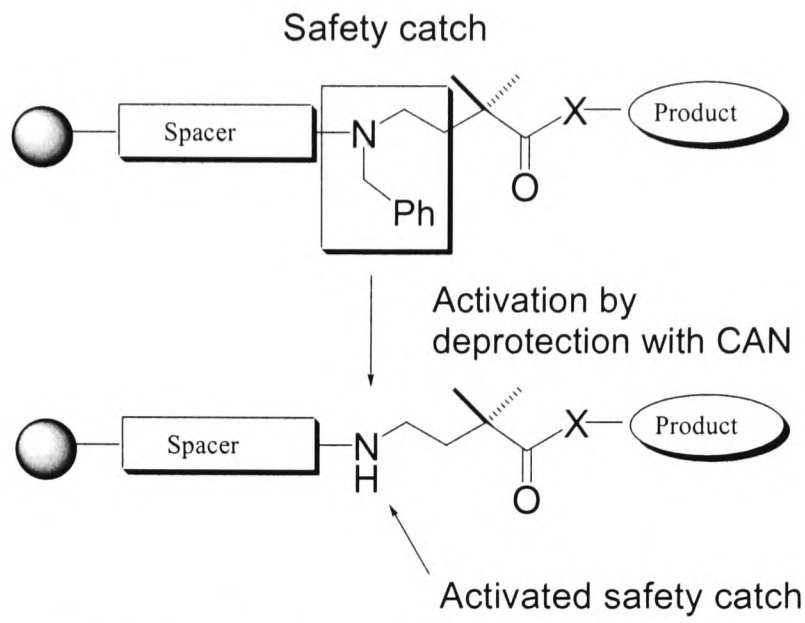


Figure 2.2: Deprotection and activation of the safety catch

2.1.1 Linker design features

The linker system should allow anchoring of both amines and alcohols to the polymeric support as amides and ester functionalities respectively. The *gem*-dimethyl substituents are incorporated into the linker to decrease the susceptibility of the carbonyl functionality to nucleophilic attack. As a result, the linker system should display properties analogous to pivaloyl esters and amides. The pivaloyl ester group is commonly used for protection of primary alcohols due to ease of introduction and stability towards a range of reaction conditions[2] whereas deprotection requires harsh basic[3] or reductive conditions.[4] Due to steric hindrance, pivaloyl chloride can be used to selectively protect primary alcohols in the presence of secondary alcohols.[4] Mixed pivaloyl anhydrides of peptides are also used for activation and to direct nucleophilic attack in peptide couplings.[5]

Furthermore, the *gem*-dimethyl substituents render the carbonyl group non-enolizable, allowing the use of strong bases during a reaction sequence on the resin bound substrate.

In addition, after activation of the safety catch device by *N*-debenzylation, the presence of a secondary amine should allow a spontaneous cyclization with concomitant release of the product into solution, a related example is discussed *vide supra*. The *gem*-dimethyl substituents should promote this concomitant cyclization as described by Thorpe and Ingold

in 1915.[6] The introduction of two alkyl substituents should increase both the rate and the equilibrium constant for the cyclisation reaction, as it has been shown by Allinger and Zalkow that this phenomenon has a thermodynamic basis, termed the *gem*-dimethyl effect.[7] The loss of entropy upon cyclisation of a disubstituted open chain is reduced relative to an unsubstituted species due to fewer rotational degrees of freedom in the substituted open chain species, resulting in the desired cyclization (Figure 2.3).

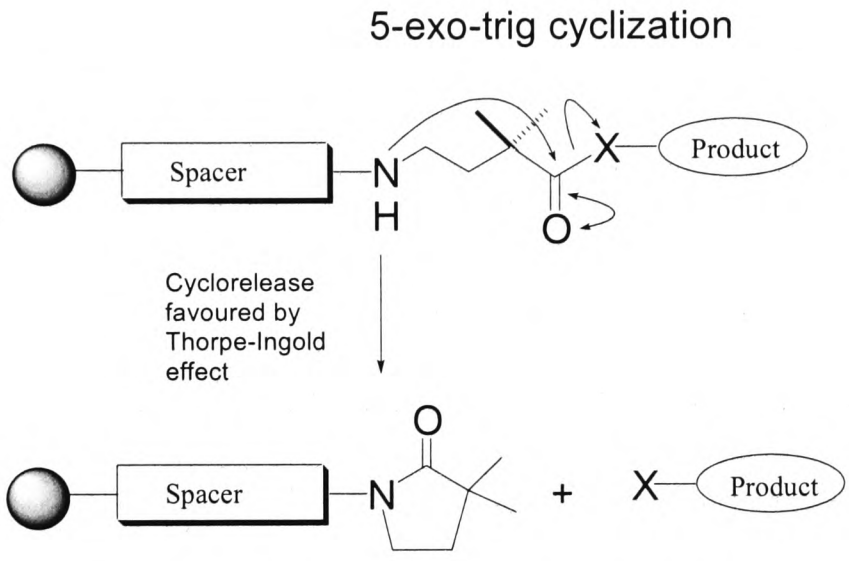


Figure 2.3: Cyclorelease of product into solution

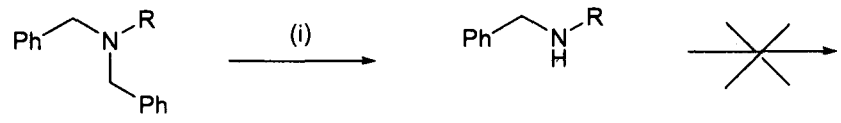
The predicted 5-exo-trig cyclization and subsequent formation of a 5-membered lactam on the resin should release the product into solution. The product should be easily isolated by simply washing the resin bound γ-lactam.

2.1.2 Activation strategy

As a means to protect and activate the safety catch device before the cyclization release protocol the *N*-benzyl functionality was chosen as a model study. The *N*-benzyl moiety is a widely used *N*-protection strategy in solution phase organic synthesis due to its robustness and relative ease of introduction either *via* reductive amination[1] or nucleophilic displacement.[8] A broad variety of deprotection strategies have been investigated with catalytic hydrogenolysis being the most widely used. Furthermore debenzylation has been successfully adapted to solid phase.[1,9]

Davies *et al.*[1] have previously reported that treatment of *N*-benzyl tertiary amines **46** - **52** with aqueous CAN results in oxidative mono *N*-debenzylation in a chemoselective fashion to

afford the corresponding secondary amines **53** - **57**. This methodology has been extended for the synthesis and release of secondary amines from solid support, as discussed *vide supra*. This debenzylation protocol has been shown to work for a range of *N*-benzyl tertiary amines in yields ranging from 54 - 90 %, although the *N*-methyl and *N*-ethyl tertiary dibenzylamines **51** and **52** do not afford the secondary amines **58** and **59** upon treatment with CAN (Scheme 2.1).

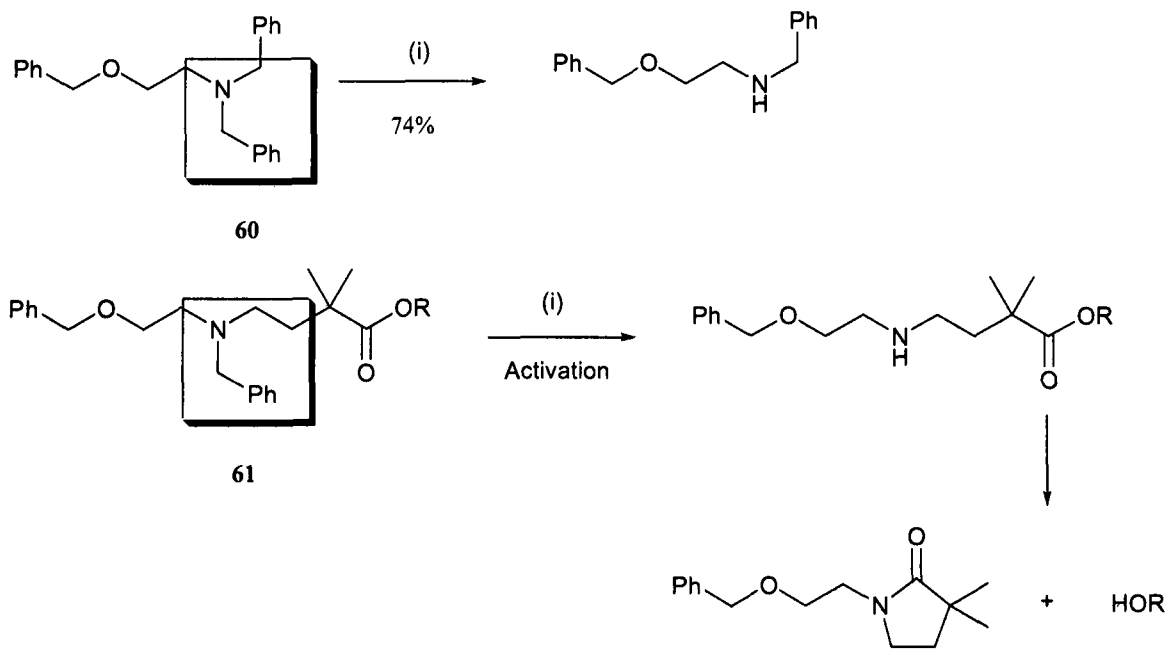


46 - 52 **53 - 59**

	R	Yield (%)
53	Bn	90
54	*n*-Pr	69
55	*n*-Bu	72
56	*n*-Hex	54
57	*t*-Bu	68
58	Me	-
59	Et	-

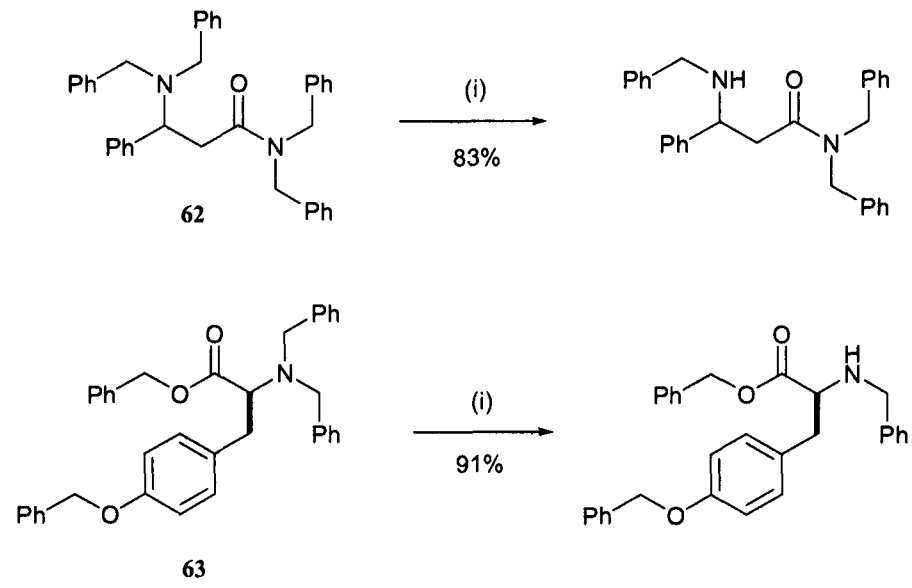
Scheme 2.1: *Reagents and conditions:* (i) CAN (2.1 eq.), MeCN:H_2O (5:1), r.t.

In the proposed linker, activation of the safety catch device by *N*-deprotection of a tertiary amine to a secondary amine has been chosen, with the chemoselective monodeprotection of *N*-benzyl tertiary amines with CAN proposed to be used in this reaction. Scheme 2.2 depicts the debenzylation of secondary amine **60** previously reported in the literature[1] in comparison with the *N*-debenzylation of a possible model compound **61** where the benzyl group acts as the safety catch followed by cyclorelease of the product into solution.



Scheme 2.2: *Reagents and conditions:* (i) CAN (2.1 eq.), MeCN:H_2O (5:1), r.t.

The scope and limitiations of this chemoselective monodebenzylation with CAN are well documented.[1,10] It has been shown previously that the *N*-benzyl amide functionality of **62** and benzyl ether of **63** are inert towards debenzylation by CAN and therefore the deprotection activation protocol should not affect such functionalities on the resin bound substrate. Also, as a result of this selectivity the CAN mediated *N*-benzyl deprotection/activation should not affect the linker system bound to Merrifield's resin *via* the benzylic ether linkage (Scheme 2.3).



Scheme 2.3: *Reagents and conditions:* (i) CAN (2.1 eq.), MeCN:H_2O (5:1), r.t.

Furthermore, it has been demonstrated that CAN debenzylation conditions leave cyclic benzylamines intact since treatment of *N*-benzylpiperidine **64**, *N*-benzyl proline ethyl ester **65** and *N*-benzylpiperidine-4-one **66** with CAN in aqueous THF returned starting materials only (Figure 2.4).

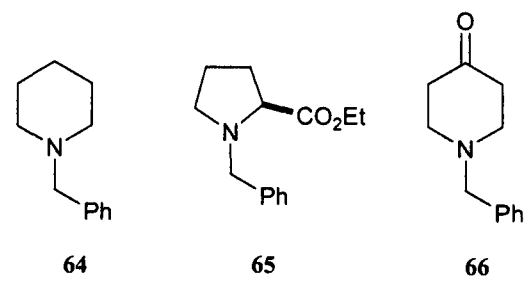


Figure 2.4: Some examples of benzylamines not deprotected by aqueous CAN

2.2 Linker synthesis

2.2.1 Retrosynthetic analysis

A viable and synthetically useful linker system should be easily synthesised in few steps in good overall yield, starting from inexpensive commercially available materials. Ideally, each step in the synthesis should be easily scaled-up without creating complications with purification. A large scale synthesis of the linker system in solution should allow easy access to a model system for optimisation and analysis in the solution phase prior to adaptation to the solid phase. Also, it should be easily attached to a broad variety of different commercially available resins allowing the use of a polymeric support of choice.

To achieve these goals a generic retrosynthetic analysis of the proposed safety catch linker system **67** was undertaken and 3,3-dimethyl-5-hydroxydihydrofuran-2-one **68** was immediately identified as a feasible key intermediate. **68** may be readily synthesised in two steps from commercially available materials according to a literature procedure.[11] The spacer and safety catch construct **69** should be readily available from a simple bifunctional alkyl chain *via* reductive amination, by routes **a** or **b**, before attachment to a functionalised resin **70** (Figure 2.5).

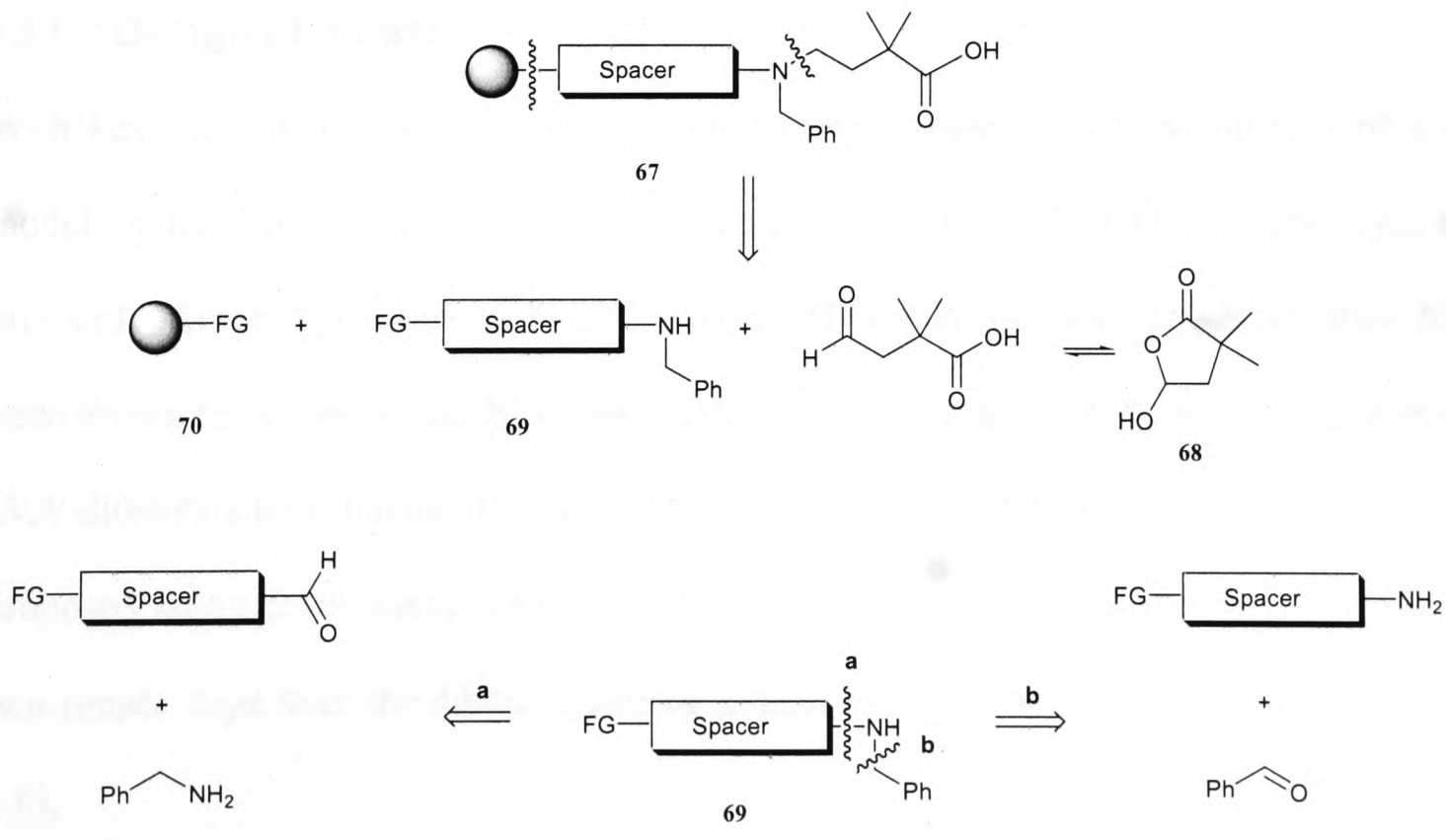
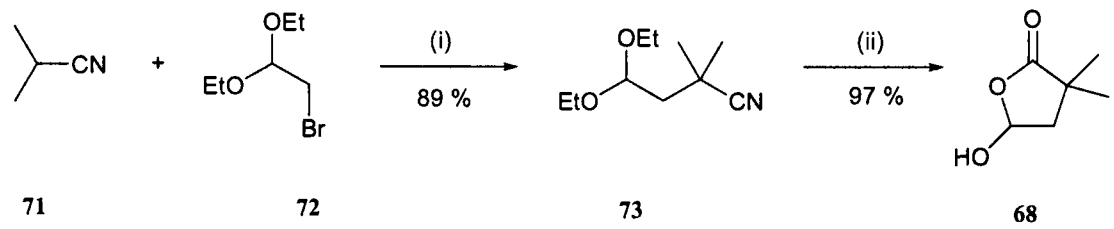


Figure 2.5: Generic retrosynthetic analysis of the safety catch linker system

2.2.2 Synthesis of the key intermediate 68

Dihydrofuranone **68** was prepared in two steps, sequential treatment of *iso*-butyronitrile **71** with LDA then bromoacetal **72** followed by reflux for 16 hours afforded nitrile **73** in 89 % yield on a 53 g scale.[12] Acid hydrolysis of the nitrile **73** was readily achieved *via* a modified literature procedure,[11] affording the desired dihydrofuranone key intermediate **68** consistently in good to excellent yield (63 - 97 %). ^{1}H NMR spectroscopy of the crude product revealed clean conversion and **68** was used in subsequent procedures without further purification (Scheme 2.4).



71 72 73 68

Scheme 2.4: *Reagents and conditions:* (i) LDA, THF, Δ 16 h; (ii) HCl:AcOH:H_2O (20:10:5), Δ 16 h.

This two step procedure fulfills the criteria for a viable linker system providing access to multigram quantities of key intermediate **68**.

2.3 Development of a model system

2.3.1 Design of model

With key intermediate **68** in hand, attention turned towards the development of a simple model system to demonstrate proof of principle for the debenzylation and cyclorelease protocol. Since *N*,*N*-dibenzyl-*N*-methylamine **51** and *N*,*N*-dibenzyl-*N*-ethylamine **52** have been shown to be inert towards *N*-monodebenzylation (Section 2.1.2), methyl 2,2-dimethyl-4-(*N*,*N*-dibenzylamino)butanoate **74** was chosen as the simplest functional analog of the proposed safety catch linker system **75**. This model system **74** is predicted to be accessible in two simple steps from the dihydrofuranone key intermediate **68** and dibenzylamine **53** (Figure 2.6).

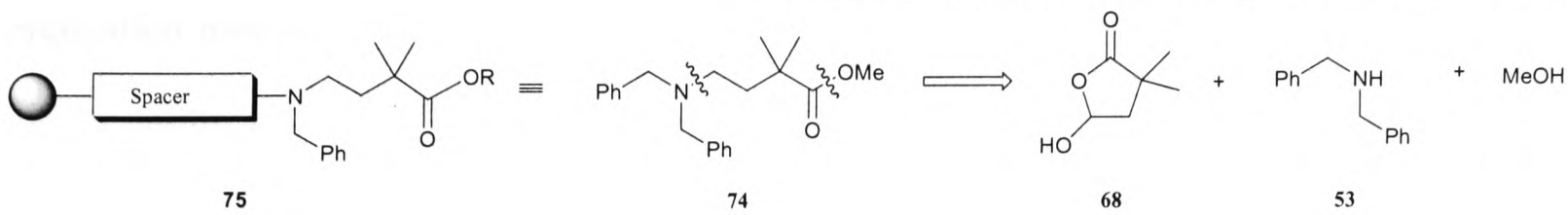
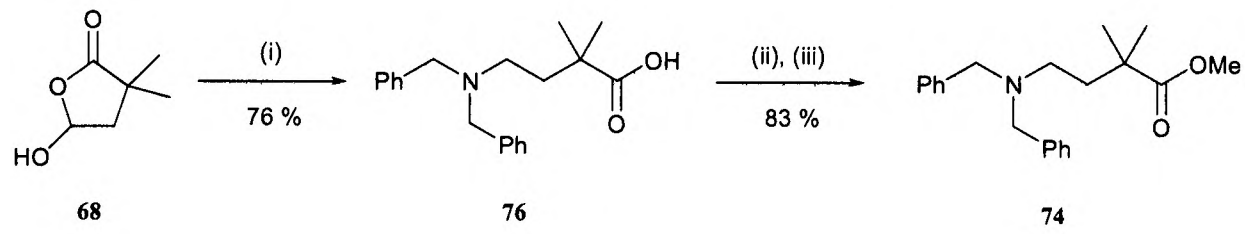


Figure 2.6: Retrosynthetic analysis of model system

2.3.2 Synthesis

Initial efforts toward the synthesis of model substrate **74** focussed on the reductive amination of **68** with dibenzylamine **53**. Treatment of **68** with dibenzylamine **53** in a MeOH:TMOF mixture and subsequent reduction with $NaBH_4$ at 0°C afforded the desired carboxylic acid **76** in 76 % isolated yield. ^{1}H NMR analysis of the crude product revealed clean conversion to **76** and no further purification was necessary before subsequent steps. The methyl ester **74** was conveniently prepared as the hydrochloride salt with HCl in MeOH, with the free amine **74** generated upon treatment with aqueous NaOH in 83 % yield (Scheme 2.5).

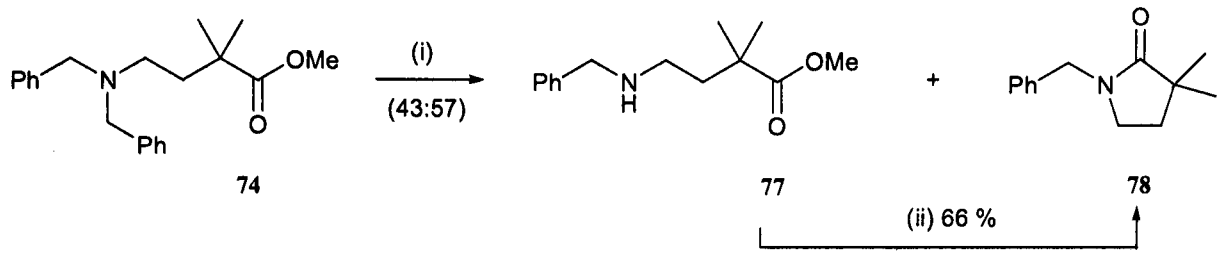


Scheme 2.5: *Reagents and conditions:* (i) Bn_2NH **53**, MeOH:TMOF then $NaBH_4$, 0°C; (ii) HCl:MeOH, Δ 2 h; (iii) $NaOH_{(aq)}$.

2.3.3 Debenzylation/cyclorelease protocol

With the model system **74** prepared subsequent studies attempted to demonstrate the cyclization and release protocol. Thus, methyl ester **74** was treated according to a literature procedure previously shown to be optimal for the cleavage of secondary amines from Merrifield's resin.[1] Treatment of **74** with excess CAN (5 eq.) in MeCN:H_2O (5:1) for 16 hours resulted in complete consumption of the starting material and mono *N*-debenzylation, affording a 43:57 mixture of the cyclization precursor **77** and the known[13] lactam **78**. The

cyclization reaction was driven to completion by refluxing in MeOH for 16 hours to afford the lactam **78** in 66 % yield (Scheme 2.6).



Scheme 2.6: *Reagents and conditions:* (i) 5 eq. CAN, MeCN:H_2O (5:1), r.t. 16 h; (ii) MeOH, Δ 16 h.

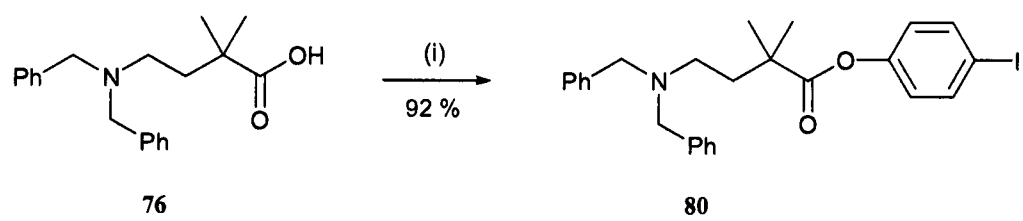
Having demonstrated the proof of principle for the methyl 2,2-dimethyl-4-(*N*,*N*-dibenzylamino)butanoate **74** model system, the demonstration of a simple attachment, transformation and release protocol for an analogous model system in the solution phase, was attempted.

2.4 Transformations on model system

Halogenated phenolate esters were chosen as a model study for this protocol as the products can be used for a range of transformations of which the Suzuki coupling is the most widely used and has been adapted to the solid phase by a variety of groups.[14]

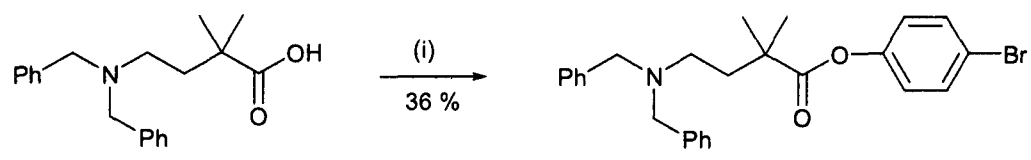
2.4.1 Ester formation

There are a broad variety of methods available for coupling alcohols and amines to carboxylic acids to form esters and amides respectively. As a starting point, standard peptide coupling methods[15] were employed, with the use of DIC, HOBt and DIPEA[16], *p*-iodophenol **79** and carboxylic acid **76** afforded the desired *p*-iodophenyl ester **80** as a white crystalline solid in 92 % yield after chromatography (Scheme 2.7).



Scheme 2.7: *Reagents and conditions:* (i) *p*-iodophenol **79**, DIC, HOBt, DIPEA, DMF, r.t. 63 h.

With this encouraging result delineated, a method to minimize workup for scaling purposes was sought. Ideally the product should either be pure after aqueous workup or following recrystallization from the crude reaction mixture. Attempted synthesis of the analogous *p*-bromophenyl ester **81** on a 2 g scale using same conditions afforded the product contaminated with the diisopropyl urea byproduct. Purification by recrystallisation failed, affording mixtures of product **81** and the urea byproduct. This problem has been previously addressed by the use of EDCI[17] the urea byproduct of which is soluble in acidic aqueous media. Treatment of **76** with EDCI and *p*-bromophenol **82** in DMF for 72 hours afforded a approximately 20:80 mixture of starting material **76** and product **81** respectively. The product **81** was recrystallized from the crude reaction mixture in 36 % yield (Scheme 2.8).

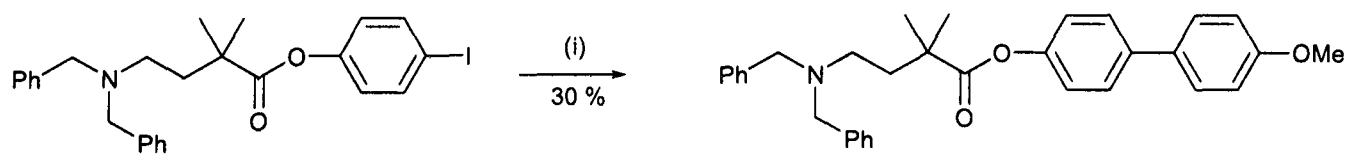


76 **81**

Scheme 2.8: *Reagents and conditions:* (i) *p*-bromophenol **82**, EDCI, HOBt, DIPEA, DMF, r.t. 16 h.

2.4.2 Suzuki coupling and debenzylation/cyclorelease

To exemplify a simple transformation on the model system a modified literature procedure[18] was used to couple *p*-methoxyphenylboronic acid **83** to the previously synthesised *p*-iodophenyl ester **80** *via* a Suzuki coupling. This transformation is ideal as a starting point since it has been extensively studied and is known to tolerate a broad variety of different functionalities.[14] An initial attempt resulted in incomplete conversion to the product, giving **84** in only 30 % isolated yield after chromatography (Scheme 2.9).

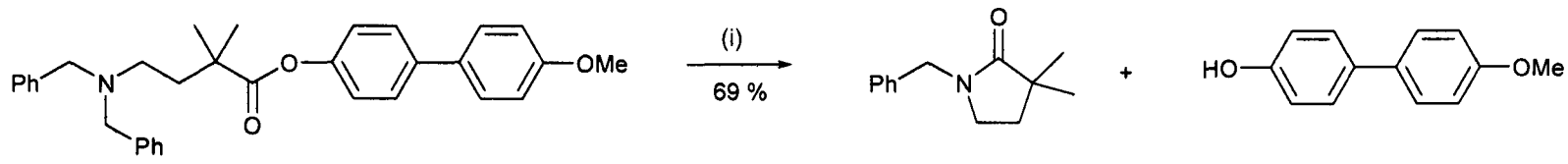


80 **84**

Scheme 2.9: *Reagents and conditions:* (i) *p*-methoxyphenylboronic acid **83**, Pd_2dba_3, K_2CO_3, DMF, r.t. 20 h.

With only small amounts of **84** in hand debenzylation was attempted by portionwise addition of CAN and subsequent monitoring of the reaction by t.l.c. After 20 hours of stirring with 2.1

eq. of CAN the starting material **84** was still present in the reaction mixture but after the addition of a total of 4.1 equivalents of CAN and 40 hours stirring, no starting material was detected (Scheme 2.10).



84 **78** **85**

Scheme 2.10: *Reagents and conditions:* (i) 4.1 eq. CAN, MeCN:H_2O (5:1), r.t. 40 h.

^{1}H NMR spectroscopic analysis of the crude reaction product revealed complete consumption of the starting material and an approximately 50:50 mixture of the expected products **78** and **85**[19] in 69 % combined yield confirming the success of the debenzylation/cyclorelease protocol.

2.5 Conclusions

The debenzylation/cyclorelease protocol for the described safety catch linker system has been demonstrated with solution phase experiments using a simple analogue of the system. However, this model system is unsuitable for a general study since it is not transferable to the solid phase due to selectivity problems upon debenzylation/activation. First attempts to couple aryl alcohols to the linker system were successful but scaling attempts were met with difficulty. The following chapter describes the development of a more general model system that adequately mimics the solid phase system in order to address these problems.

References

[1] S.D. Bull, S.G. Davies, G. Fenton, A. Mulvaney, R.S. Prasad, A.D. Smith, *J. Chem. Soc., Perkin Trans. 1.*, 2000, 3765; S.D. Bull, S.G. Davies, G. Fenton, A.W. Mulvaney, R.S. Prasad, A.D. Smith, *Chem. Commun.*, 2000, 337.

[2] See page 713 for reactivity chart: T.H. Greene, P.G.M. Wutz, *Protective Groups in Organic Synthesis*, 3rd edn., John Wiley, Chichester, 1999.

[3] P.G. Gassman, W.N. Schenk, *J. Org. Chem.*, 1977, **42**, 918.

[4] For example, see: D. Boschelli, T. Takemasa, Y. Nishitani, S. Masamune, *Tetrahedron Lett.*, 1985, **26**, 5239.

[5] C. Nájera, T. Abellán, J.M. Sansano, *Eur. J. Org. Chem.*, 2000, 2809.

[6] R.M. Beesley, C.K. Ingold, J.F. Thorpe, *J. Chem. Soc.*, 1915, **107**, 1080.

[7] N.L. Allinger, V. Zalkow, *J. Org. Chem.*, 1960, **25**, 701.

[8] T.H. Greene, P.G.M. Wutz, *Protective Groups in Organic Synthesis*, 3rd edn., John Wiley, Chichester, 1999.

[9] P. Conti, D. Demont, J. Cals, H.C.J. Ottenheijm, D. Leysen, *Tetrahedron Lett.*, 1997, **38**, 2915.

[10] B. Hungerhoff, S.S. Samanta, J. Roels, P. Metz, *Synlett*, 2000, 77.

[11] H. Abbayes, *Bull. Soc. Chim. Fr.*, 1970, **10**, 3667.

[12] H. Mizuno, K. Domon, K. Tanino, I. Kuwajima, *J. Org. Chem.*, 1999, **64**, 2648.

[13] T. Naito, H. Tanada, Y. Suzuki, H. Saito, T. Kiguchi, I. Ninomiya, *Heterocycles*, 1993, **36**, 2345.

[14] S. Bräse, J.H. Kirchhoff, J. Köbberling, *Tetrahedron*, 2003, **59**, 885.

[15] J.C. Sheehan, G.P. Hess, *J. Am. Chem. Soc.*, 1955, **77**, 1067.

[16] Y.M. Angell, C.G. Echeverria, D.H. Rich, *Tetrahedron Lett.*, 1994, **35**, 5981.

[17] J.C. Sheehan, P.A. Cruickshank, G.L. Boshart, *J. Org. Chem.*, 1961, **26**, 2525.

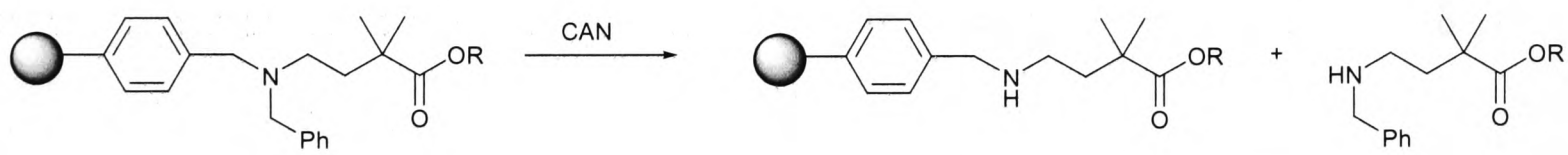
[18] J.W. Guiles, S.G. Johnson, W.V. Murray, *J. Org. Chem.*, 1996, **61**, 5169.

[19] R.J. Edsall, H.A. Harris, E.S. Manas, R.E. Mewshaw, *Bioorg. Med. Chem.*, 2003, **11**, 3457.

3 Chapter III: Adaptation to solid phase

3.1 Introduction

Chapter 2 demonstrated the debenzylation/cyclorelease protocol for a simple model system. Further efforts were directed towards the development of a more general solution phase model system that would mimic the key transformations on solid phase. The dibenzylamine model system **74** described previously incorporates a benzylic carbon representing the spacer and an aromatic ring representing the polystyrene terminus. This system, if adapted to the solid phase to give **86**, would not allow selective deprotection/activation of the safety catch since the polymer supported benzyl amine functionality is readily cleaved with CAN (Chapter 2, Section 2.1.2) and would therefore detach the linker construct **87** from the polymer (Figure 3.1).



86, R = Me

87, R = Me

Figure 3.1: CAN cleavage of model system **86** on solid phase

Ideally, a more general approach would allow control over the carbon chain length incorporated in the spacer. The spacer should have a readily derivatized functional group allowing attachment to a commercially available functionalized resin of choice.

3.1.1 Solution phase model compounds

Two approaches were envisaged from a reexamination of the generic retrosynthetic analysis of the safety catch linker system (Chapter 2, Section 2.2.1). Both approaches (Figure 3.2, **a** and **b**) were anticipated to be accessible from a common intermediate, carboxylic acid **88**, readily synthesised from commercially available materials and the key intermediate dihydrofuranone **68**. These approaches, allowing access to safety catch linker systems **89** and **90** with 4 carbon atoms incorporated in the spacer chain were anticipated to be feasible starting points towards a robust solid phase system. The known spacer-safety catch intermediate *N*-benzyl-3-butenyl

amine **91** is available *via* nucleophilic displacement of bromoalkene **92** with benzylamine **93**.[1] Subsequent reductive amination of dihydrofuranone **68** with **91** should afford the desired carboxylic acid **88**. The alkyl and aryl esters of **88** could then be subjected to hydroboration-oxidation protocols and the resulting alcohol used in a nucleophilic displacement reaction to attach the linker to Merrifield's resin **4** to furnish **89** (route **a**). Alternatively, hydroboration of carboxylic acid **88** (or esters) followed by a palladium-catalysed Suzuki-Miyaura cross-coupling could be used to attach the linker system to commercially available bromopolystyrene **94** to furnish **90** (route **b**).

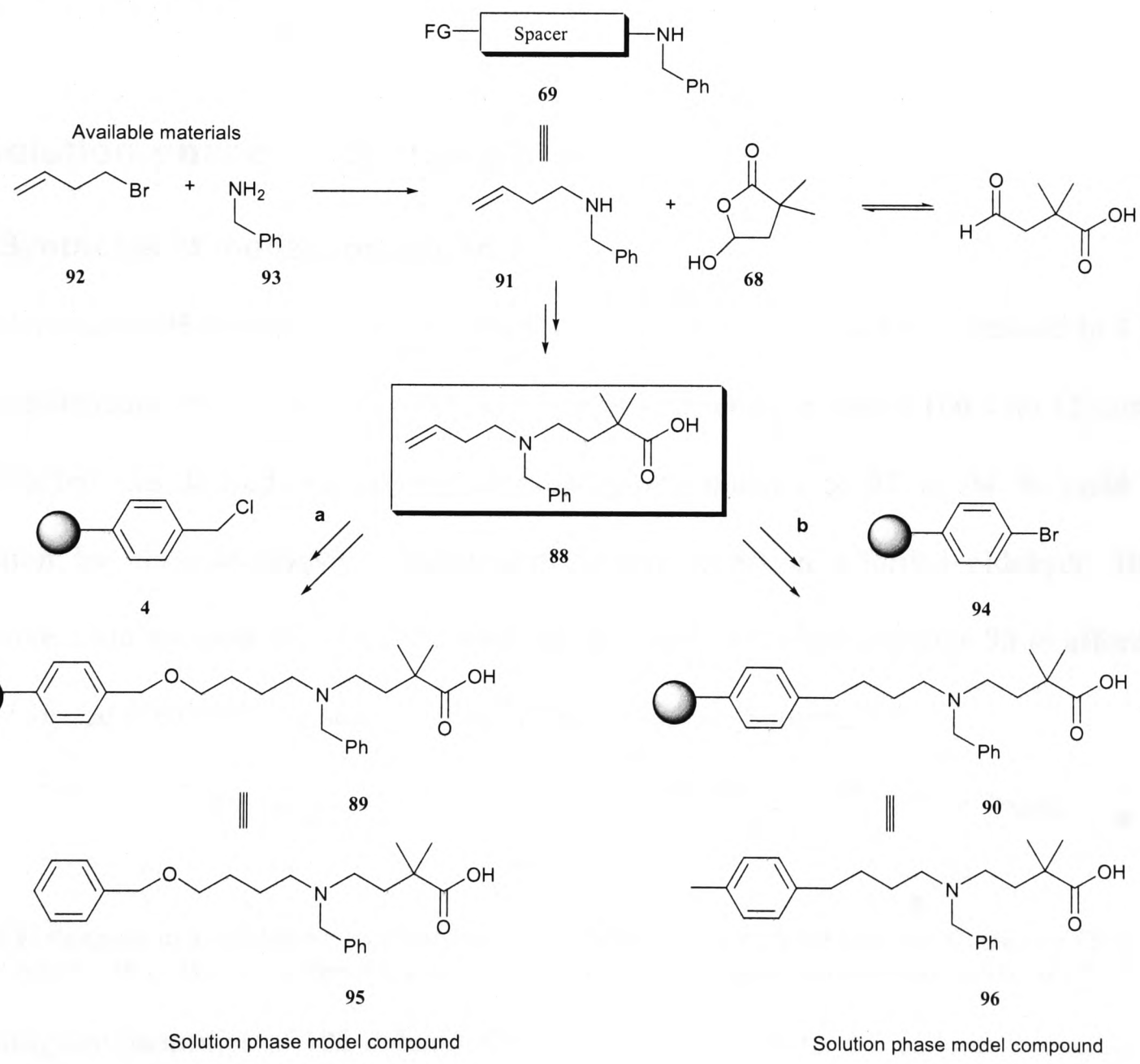


Figure 3.2: Approaches towards solid phase safety catch linker systems

Initial studies focussed on the preparation of solution phase model systems **95** and **96** in order to mimic the key transformations before adaption to solid phase. Oxidation of *O*-benzyl monoprotected 1,4-butanediol **97** followed by sequential reductive aminations with benzylamine **93** and dihydrofuranone **68** was identified as a feasible approach toward model

compound **95**. The alternative model compound **96** should be readily accessible from a Suzuki-Miyaura cross coupling of key intermediate **88** with 4-bromotoluene **98** (Figure 3.3).

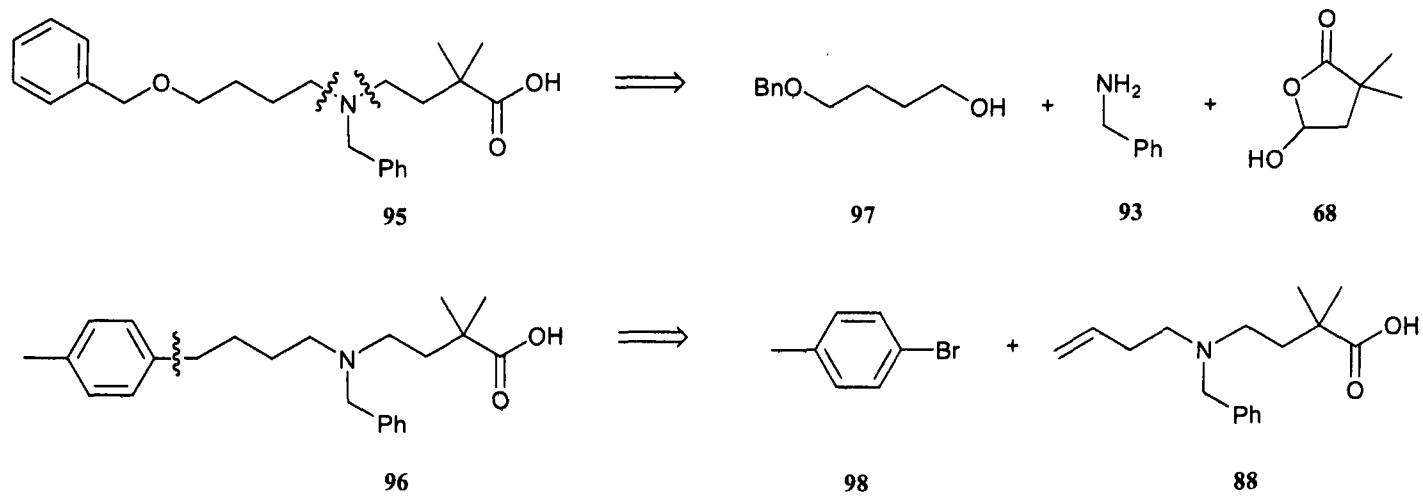
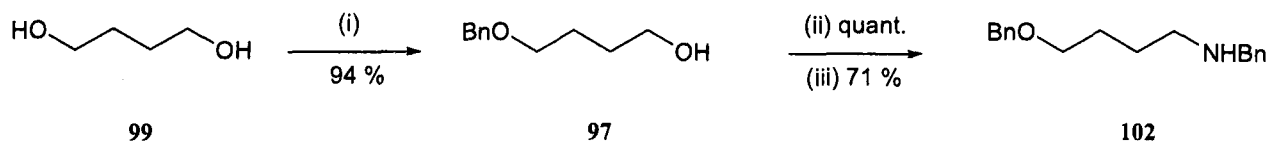


Figure 3.3: Approaches towards solution phase model compounds **95** and **96**.

3.2 Solution-phase model reactions

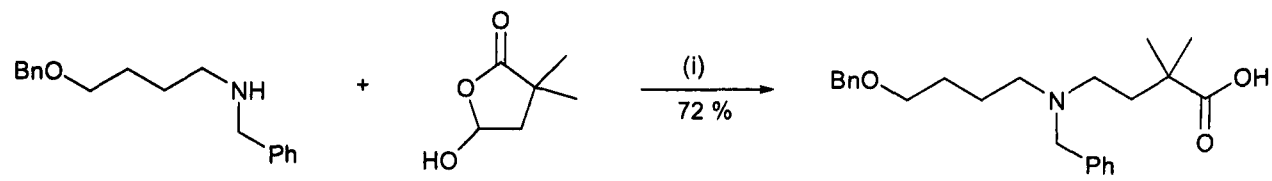
3.2.1 Synthesis of model compound 95

The model system **95** incorporating the *O*-benzyl ether functionality was synthesised in 4 steps from 1,4-butenediol **99**. Treatment of **99** with NaOH and benzyl bromide **100** with 15-crown-5 ether afforded the desired monoprotected 4-benzyloxy butan-1-ol **97** in 94 % yield after purification by chromatography. Subsequent Swern oxidation afforded aldehyde **101** in quantitative yield and was followed by reductive amination with benzylamine **93** to afford **102** in 71 % isolated yield on a 9 g scale for the two-step process (Scheme 3.1).



Scheme 3.1: *Reagents and conditions:* (i) BnBr **100** (5 eq.), NaOH (6 eq.), 15-crown-5, 10°C, then r.t. 16 h; (ii) $(COCl)_2$, DMSO, -78°C, DCM, 1 h then Et_3N 15 min.; (iii) $BnNH_2$ **93**, TMOF, MeOH then $NaBH_4$, 0°C.

With multigram quantities of **102** in hand, the optimal conditions for the reductive amination of dihydrofuranone **68** could be identified. A comparison study was carried out with $NaBH_4$ and $NaHB(OAc)_3$[2] as reducing agents. $NaBH_4$ was found to be unsuitable for this transformation, however the reaction was found to progress smoothly utilizing $NaHB(OAc)_3$ as the reducing agent affording the desired model compound **95** in 72 % isolated yield (Scheme 3.2).



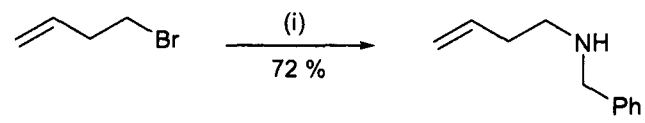
102 68 95

Scheme 3.2: *Reagents and conditions:* (i) MeOH, TMOF (1.6 eq.) then $NaHB(OAc)_3$, 0°C.

Attempts to scale up this process met with limited success. Synthesis of **95** on a 6 g scale afforded the crude product contaminated with unknown impurities and column chromatography yielded only 34 % of the product **95** of sufficient purity for further synthesis.

3.2.2 Synthesis of key intermediate 88

With the solution phase model compound **95** in hand, efforts were directed towards synthesis of key intermediate **88** and subsequent adaptation of the safety catch linker system to the solid phase. The spacer-safety catch construct *N*-benzyl-but-3-enyl-amine **91** was readily prepared *via* a modified literature procedure.[1] Treatment of commercially available bromide **92** with excess benzylamine **93** (5 eq.) with gentle heating to 70°C gave complete conversion to the desired product **91** with no overalkylation observed. Purification by fractional distillation afforded the amine **91** in acceptable yield (72 %) on a convenient 10 g scale (Scheme 3.3).

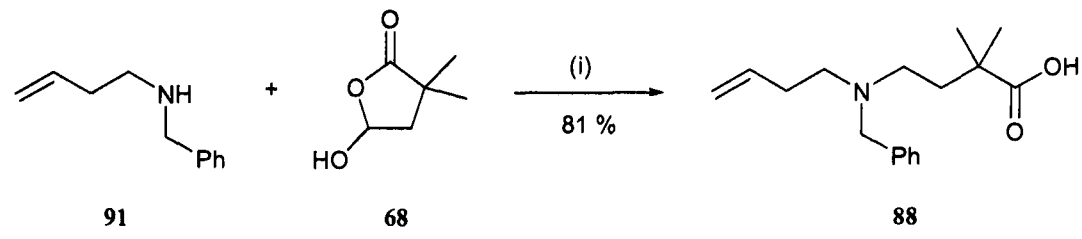


92 91

Scheme 3.3: *Reagents and conditions:* (i) $BnNH_2$ **93**, (5 eq.), 70°C 16 h.

The optimal conditions for the reductive amination of dihydrofuranone **68** with amine **91** could then be sought. An initial test reaction was carried out utilising MeOH, TMOF and $NaBH_4$ as the reducing agent. The iminium formation was allowed to progress overnight at room temperature, the reaction mixture was cooled to 0°C and the reducing agent added portionwise. After stirring for 2 hours at room temperature and reflux for 1 hour simple aqueous workup afforded **88** in 64 % yield, no impurities were detected in the ^1H NMR spectrum of the crude reaction mixture. This reaction under the described conditions was readily suitable for scale-up

and afforded the desired carboxylic acid **88** in multigram quantities in 81 % isolated yield (Scheme 3.4).



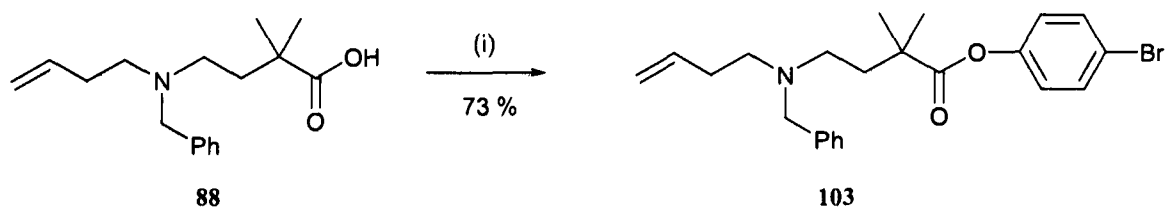
91 **68** **88**

Scheme 3.4: *Reagents and conditions:* (i) MeOH, TMOF (1.6 eq.), 16 h then $NaBH_4$, 0°C.

With the key intermediate carboxylic acid **88** prepared, functionalisation of the double bond was investigated (Figure 3.2, a and b). Before hydroboration-oxidation of the double bond of **88** to afford an alcohol functionality on the spacer, protection of the carboxylic acid as an ester was undertaken due to possible chemoselectivity problems upon attachment to Merrifield's resin *via* nucleophilic displacement.

3.2.3 Ester synthesis

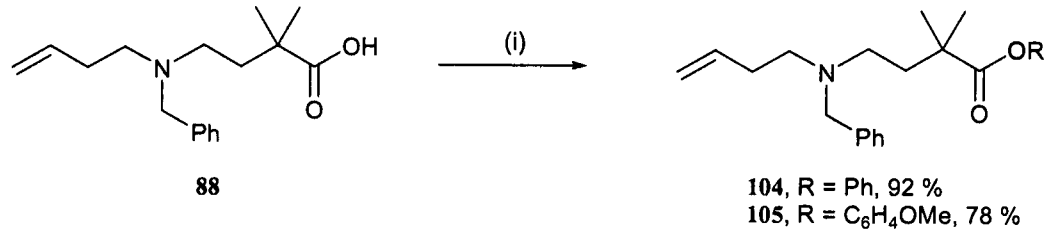
An unsuccessful attempt to make the *p*-bromophenyl ester of dibenzylamine derived model carboxylic acid **76** in good yield (Chapter 2, Section 2.4.1) prompted an investigation of the coupling of this substrate to the analogous carboxylic acid **88**. In an attempt to drive the reaction to completion **88** was treated with 3 equivalents of *p*-bromophenol **82** and an excess of EDCI (2 eq.) and HOBt (2 eq.) with DIPEA in DCM. Simple aqueous workup with afforded a mixture of DIPEA, urea byproduct, and the product **103** as assessed by ^{1}H NMR spectroscopy. Further washing with 10 % aqueous HCl and finally NaOH afforded the desired product **103** in 73 % yield, the *p*-bromophenyl ester **103** was pure according to t.l.c. analysis and ^{1}H NMR investigation (Scheme 3.5).



88 **103**

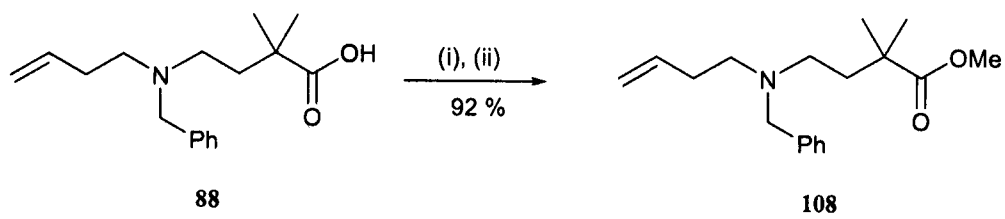
Scheme 3.5: *Reagents and conditions:* (i) *p*-bromophenol **82** (3 eq.), EDCI (2 eq.), HOBt (2 eq.), DIPEA (4 eq.), DCM, 16 h.

Having identified the optimal conditions and workup for this transformation, phenyl ester **104** and *p*-methoxyphenyl ester **105** were prepared. The *p*-methoxyphenyl ester **105** was selected as it was predicted that the resonance from the *p*-methoxy group would aid with ^{1}H NMR analysis of the crude reaction mixtures in attempted model reactions. Treatment of **88** under the optimised conditions with either phenol **106** or *p*-methoxyphenol **107** afforded the desired products, phenyl ester **104** in 92 % isolated yield and the analogous *p*-methoxyphenyl ester **105** in 78 % isolated yield. These transformations were suitable for scale-up and afforded the desired products on a convenient 3 - 4 g scale (Scheme 3.6).



Scheme 3.6: *Reagents and conditions:* (i) phenol **106** or *p*-methoxyphenol **107** (3 eq.), EDCI (2 eq.), HOBt (2 eq.), DIPEA (4 eq.), DCM, 16 h.

Furthermore, the methyl ester of carboxylic acid **88** could also be accessed on a multigram scale. Treatment of **88** under refluxing conditions in MeOH presaturated with gaseous hydrochloric acid, and subsequent basic aqueous workup afforded the desired methyl ester **108** in 92 % yield without the need for purification (Scheme 3.7).



Scheme 3.7: *Reagents and conditions:* (i) HCl:MeOH, Δ 2 h; (ii) 2 M NaOH.

Having identified the optimal conditions for the ester coupling, further model studies aimed to identify a feasible derivatization and grafting process transferrable to solid phase.

3.2.4 Attempted hydroboration oxidation

Functionalisation of the spacer *via* a hydroboration-oxidation protocol in order to graft the safety catch linker to Merrifield's resin **4** *via* nucleophilic displacement was next investigated (Figure 3.4).

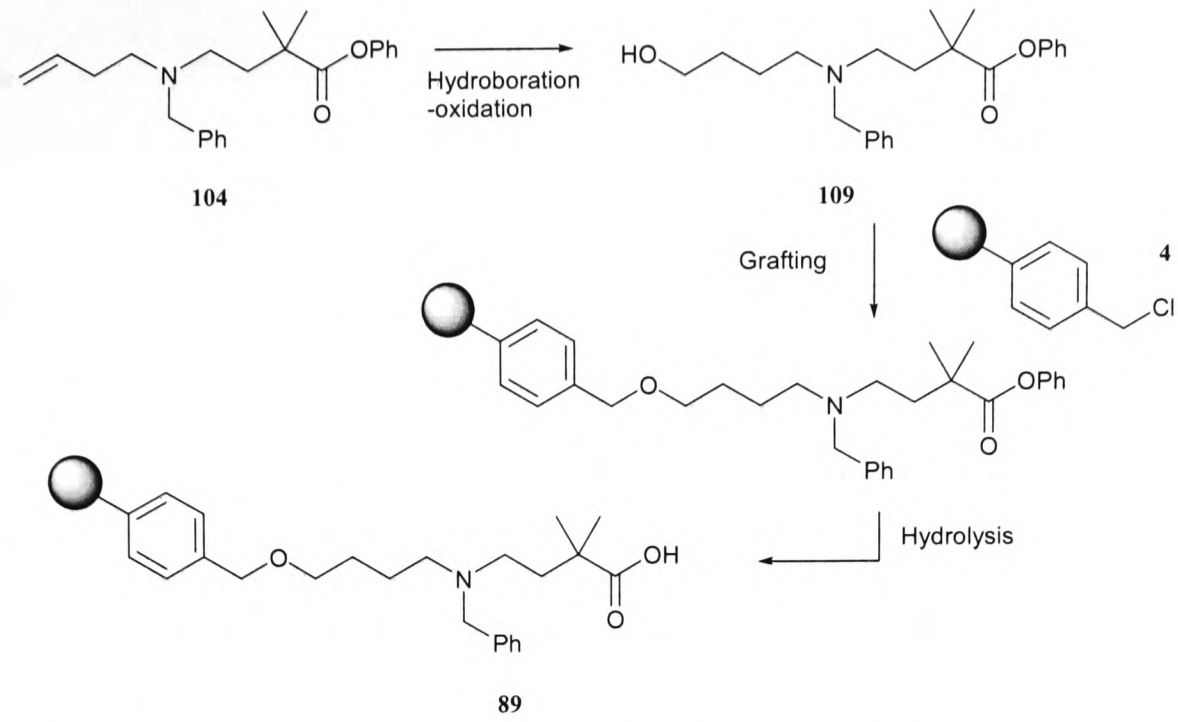
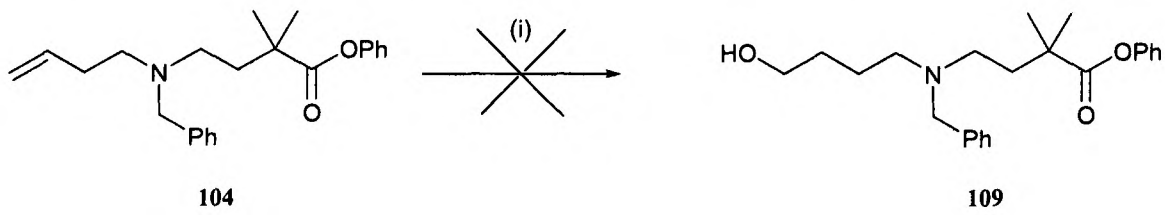


Figure 3.4: Planned approach to a polymer bound safety catch linker **89** (Figure 3.2, route a)

Initial attempts at hydroboration of the double bond of the phenyl ester **104** followed a modified literature procedure.[3] Treatment of **104** with 9-BBN followed by oxidation utilizing H_2O_2/NaOH resulted in a complex mixture of products by ^1H NMR spectroscopic and t.l.c. analysis of the crude reaction product. Attempts to adjust the reaction conditions using both 9-BBN and BH_3 for the hydroboration failed to give the desired product **109** sufficiently pure for full characterization after purification by chromatography (Scheme 3.8).

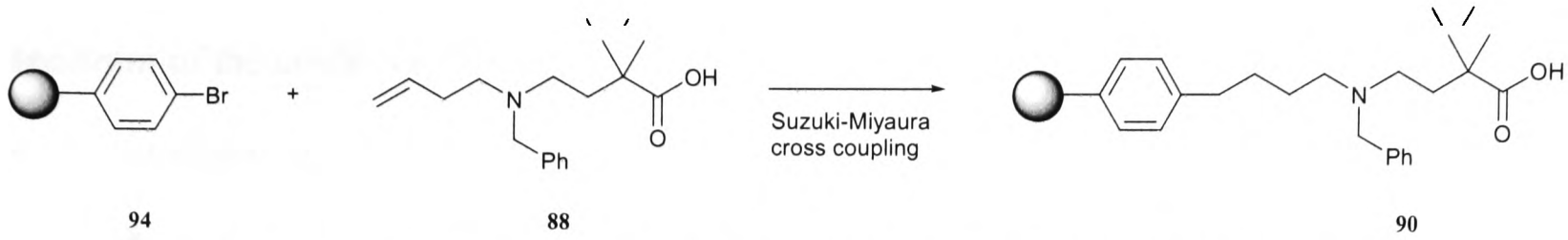


Scheme 3.8: *Reagents and conditions:* (i) 9-BBN or BH_3-THF, THF then H_2O_2, NaOH.

Due to the problems encountered with this transformation this route was abandoned and focus was directed towards an alternative approach (Figure 3.2, route b).

3.2.5 Suzuki-Miyaura cross coupling

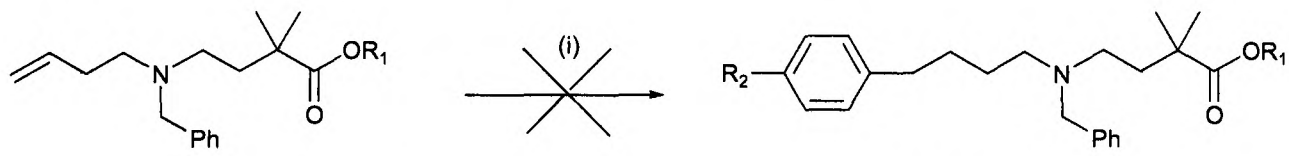
Attention was therefore turned towards solution phase model studies designed to mimic a Suzuki-Miyaura cross-coupling[4] with bromopolystyrene. Bromotoluene **98** and 4-bromoanisole **110** were identified as suitable substrates to mimic the polystyrene terminus in solution phase studies (Figure 3.5).



94 88 90

Figure 3.5: Planned approach to a polymer bound safety catch linker **90** (Figure 3.2, route b).

The most straightforward route towards the desired solution phase model compound **96** was anticipated to be the direct attachment of **88** to 4-bromotoluene **98**. A literature procedure[5] was employed to prepare the $Pd(OAc)_2$/DPPF catalyst. Treatment of **88** with 9-BBN to generate the resulting alkylborane was followed by treatment with the pre-prepared catalyst solution, 4-bromotoluene and base (K_2CO_3). Gentle heating to 60°C overnight afforded a complex mixture of products according to analysis of the ^1H NMR spectrum of the crude reaction product. Repeated attempts to achieve this transformation and separate the product **96** from the complex mixture gave no success. Similarly, repeated attempts to use the *p*-methoxyphenyl ester **105** and methyl ester **108** as substrates in this transformation to couple with 4-bromotoluene **98** or 4-bromoanisole **110** yielded complex mixtures. In each case ^1H NMR spectroscopic analysis indicated complete consumption of the starting material, consistent with complete conversion in the hydroboration step to afford the desired alkylborane intermediate. Further purification attempts did not yield the desired products **111 - 113** of sufficient purity for characterization (Scheme 3.9).



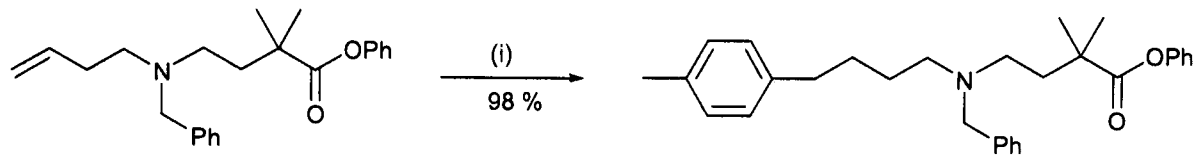
88, R_1 = H
105, R_1 = *p*-$MeOC_6H_4$
108, R_1 = Me

96, R_1 = H, R_2 = Me
111, R_1 = *p*-$MeOC_6H_4$, R_2 = Me
112, R_1 = Me, R_2 = Me
113, R_1 = Me, R_2 = OMe

Scheme 3.9: *Reagents and conditions:* (i) 4-MeC_6H_4Br **98** or 4-$MeOC_6H_4Br$ **110**, 9-BBN in THF then alkylborane, DPPF, $Pd(OAc)_2$, K_2CO_3, DMF, 60°C 16 h.

After numerous attempts and adjustments of the reaction conditions, some success was achieved with phenyl ester **104**, utilizing 9 % catalyst loading. Additionally, peroxide was used in the workup to oxidise possible alkylborane residues. Under these conditions a small scale experiment afforded the product in clean conversion according to analysis of the ^1H NMR

spectrum of the crude reaction product. Separation of the product from Pd residues and excess 4-bromotoluene by chromatography afforded the desired compound **114** in 74 % yield, pure according to ^{1}H NMR and combustion analysis (Scheme 3.10).



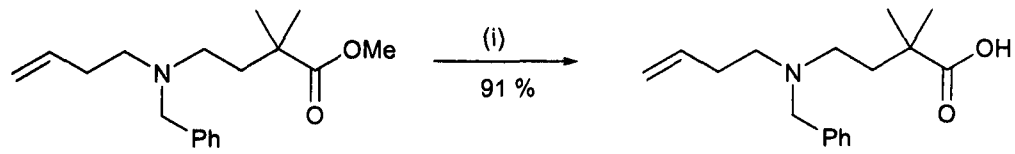
104 114

Scheme 3.10: *Reagents and conditions:* (i) 9-BBN in THF then 4-bromotoluene **98**, DPPF, $Pd(OAc)_2$, K_2CO_3, DMF, 60°C 16 h.

Attempts to scale up this process were similarly successful, with the optimal yield for the reaction on a 1 g scale synthesis affording **114** in 98 % yield. Disappointingly, attempts to apply identical conditions to the coupling of the free carboxylic acid **88** with 4-bromotoluene **98** were unsuccessful.

3.2.6 Hydrolysis experiments

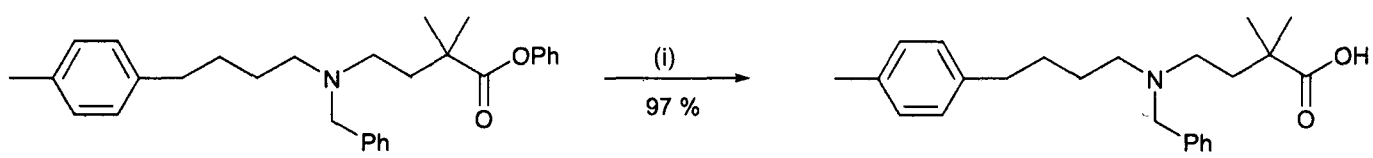
Due to the necessity of protecting the carboxylic acid functionality prior to attachment to the model substrate **98**, attention was turned towards the hydrolysis of the ester bond to obtain the desired carboxylic acid **96**. Pivaloyl esters are known to be mildly susceptible towards hydrolysis under basic conditions[6] and the esters of carboxylic acids **88** and **96** were expected to show similar reactivity. It was envisaged that **114** could serve as a starting material in solution phase model experiments designed to mimic the polymer supported carboxylic acid **90**. In an initial model experiment the methyl ester **108** was subjected to basic hydrolytic conditions with 5 equivalents of LiOH in MeOH:H_2O (5:1) solvent and the reaction monitored by t.l.c. No reaction was detected after 1 hour of stirring at room temperature suggesting that the *gem*-dimethyl substituents suppress the hydrolysis of the ester bond as expected in the design features of the safety catch linker system. The reaction mixture was therefore refluxed for 4 hours, at which point no starting material was detected by t.l.c. and the known carboxylic acid **88** was subsequently extracted with DCM after neutralization and isolated in 91 % yield (Scheme 3.11).



108 88

Scheme 3.11: *Reagents and conditions:* (i) 5 eq. LiOH, MeOH:H_2O (3:1), Δ 4 h.

With this result in hand an analogous reaction was carried out with the Suzuki-Miyura cross coupling product, phenyl ester **114**. Treatment of **114** with LiOH (5 eq.) in THF:H_2O at room temperature for 16 hours gave a 33:67 mixture of starting material **114** and product **96** respectively, indicating mild susceptibility to hydrolytic conditions. To ensure reaction completion in an acceptable timeframe the mixture was refluxed with 10 eq. of LiOH for 6 hours with purification by column chromatography resulting in 97 % isolated yield of the desired acid **96** (Scheme 3.12).



114 96

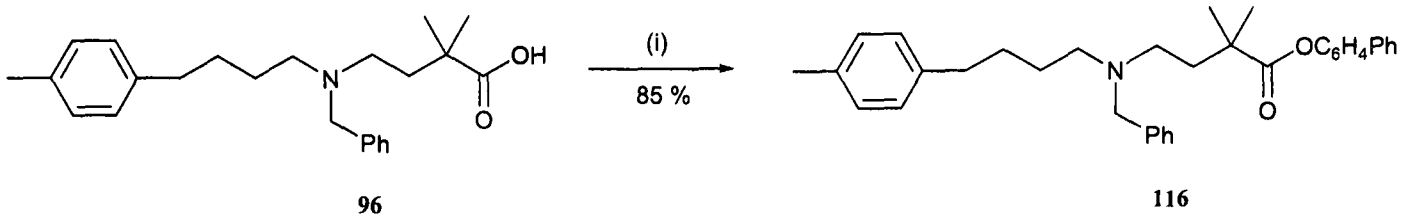
Scheme 3.12: *Reagents and conditions:* (i) 10 eq. LiOH, THF:H_2O (5:1), Δ 4 h.

Thus, the desired model compound, carboxylic acid **96** has been synthesised and isolated utilizing a Suzuki-Miyaura cross coupling protocol followed by hydrolysis. This protocol is anticipated to be amenable to solid phase. Further studies were directed toward delineating the optimal conditions for the cyclorelease strategy to be applicable to solid phase.

3.2.7 Making of model compounds and debenzylation/cyclorelease in solution

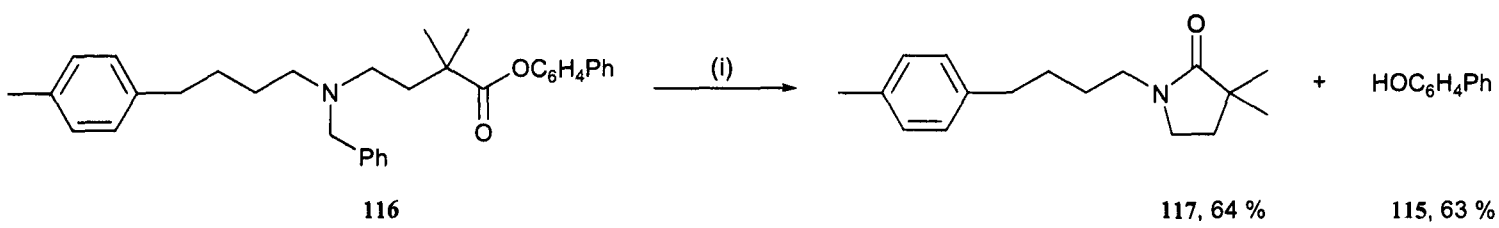
For the demonstration of the cyclization-release protocol, 4-phenylphenol **115**, a white crystalline solid at room temperature, was attached to the model carboxylic acid **96**. This substrate should be easily isolated from the CAN mediated debenzylation/cyclorelease of the derived ester **116**. Beneficially, the biaryl group could also serve as a protecting group for the carboxylic acid in the Suzuki-Miyaura cross coupling reactions. Upon solid phase the efficiency of the grafting reaction and hence the polymer loading could also be determined from the quantity of **115** isolated from hydrolysis to afford the polymer supported carboxylic

acid **90**. Thus, treatment of **96** with 3 equivalents of 4-phenylphenol **115** with EDCI and 2 equivalents of HOBt in DCM for 16 hours afforded the desired biaryl ester **116** in 85 % isolated yield after chromatography (Scheme 3.13).



Scheme 3.13: *Reagents and conditions:* (i) 4-phenylphenol **115** (3 eq.), EDCI (2 eq.), HOBt (2 eq.), DIPEA (4 eq.), DCM.

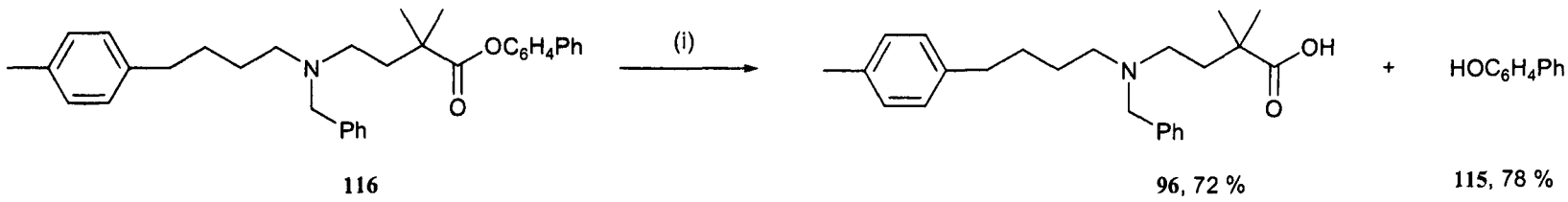
With the biaryl ester **116** in hand the optimal conditions for the debenzylation/cyclorelease protocol in solution were sought. A series of small scale test reactions were carried out to *N*-debenzylate the model substrate **116** utilizing MeCN:H_2O (5:1) as the solvent system and variable numbers of equivalents of CAN. Treatment of **116** with 2.1, 3.1 and 4.2 equivalents of CAN for 2 hours, gave disappointing results. Analysis of the ^1H NMR spectra of the crude reaction mixtures indicated incomplete conversions and that complex mixtures had been formed. However, changing the solvent to THF:H_2O (8:1) afforded the expected *N*-debenzylation products lactam **117** and 4-phenylphenol **115**, although incomplete conversions were observed utilizing 2.1, 3.1 and 4.2 equivalents of CAN for 2 hours. The optimal conditions for this transformation in THF:H_2O (8:1) were exposure of **116** to 5.0 equivalents of CAN for 16 hours, yielding the desired lactam **117** and 4-phenylphenol **115**. Subsequent scale-up procedures met with partial success, affording lactam **117** and 4-phenylphenol **115** in a disappointing 64 and 63 % yield respectively on 1 g scale (Scheme 3.14).



Scheme 3.14: *Reagents and conditions:* (i) CAN (5.0 eq.), THF:H_2O (8:1), 16 h.

To simulate the hydrolysis step of **116** on solid phase the isolated yield for this transformation was determined in solution phase. Treatment of **116** with LiOH (10 eq.) in THF:H_2O (8:1) under reflux for 6 hours gave complete conversion to products **96** and **115**. Subsequent

separation by chromatography gave **96** and **115** in 72 % and 78 % yield respectively (Scheme 3.15).



Scheme 3.15: *Reagents and conditions:* 10 eq. LiOH, THF:H_2O (5:1), Δ 6 h.

Having successfully demonstrated and optimised these reactions with a solution phase model system, further efforts were directed towards adaptation of the safety catch linker system to the solid phase. Before the analogous solid phase reactions are reported common methods to determine reaction progress and loading on polymeric supports will be discussed briefly.

3.3 Solid phase synthesis

3.3.1 Monitoring reactions on solid phase

Traditional NMR and mass spectrometry methods cannot be used to monitor reaction progress on solid phase. FTIR analysis is the method of choice for most researchers to monitor the presence or absence of functional groups on the resin, however this method can only be used qualitatively. The most readily available method is the preparation of KBr discs containing a small amount (~ 10 mg) of ground resin which is suitable for monitoring solid phase reactions when large amounts of resins are used but obviously affects the yield with smaller amounts.

The yields of solid-supported reactions or loading of polymers may be calculated based on the returned mass of the dry polymer product. However this method is unreliable, firstly due to possible significant loss of polymer during handling caused by static interactions with glassware. Secondly, the complete conversion of the reaction undertaken has to be assumed since the conversion cannot be quantitatively determined by other methods. Solvents and impurities can become trapped within the polymeric matrix and therefore the dry mass of the polymer can be misleading. However, the mass gain or loss of the polymer during a reaction

can be of help in determining the success or failure of a reaction when used in conjunction with FTIR analysis of the beads.

A range of methods to qualitatively and quantitatively determine the loading of polymeric bound species have been developed to monitor reaction progress. Among the most widely used examples of colorimetric assays involve the use of ninhydrin and bromophenol blue[7] to quantify the loading of amines on polymeric supports. The most straightforward method to determine polymer loadings is the quantification of released protecting groups from the polymeric support. The fluorenylmethoxycarbonyl (FMOC) has been used to detect amines and alcohols by quantifying the piperidine-dibenzylfulvene adduct by its absorbance (301 nm) upon release from polymeric support.[7] The same approach can be used with any molecule selectively removed from the polymer, however it relies on the assumption that complete conversion is achieved.

To calculate the maximum theoretical loading of a polymeric product the following equation can be used:

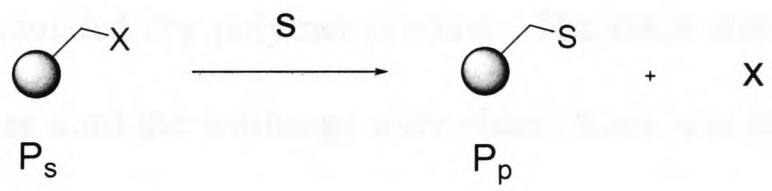


Figure 3.6: Reaction on polymeric material; P_s - polymer supported substrate; P_p - polymer supported product

Definition of variables:

L_s = Loading of starting polymer (mol/g)

L_p = Loading of product polymer (mol/g)

MW_X = Relative molecular mass of X (g/mol)

MW_S = Relative molecular mass of S (g/mol)

For 1 g of P_S with loading L_S

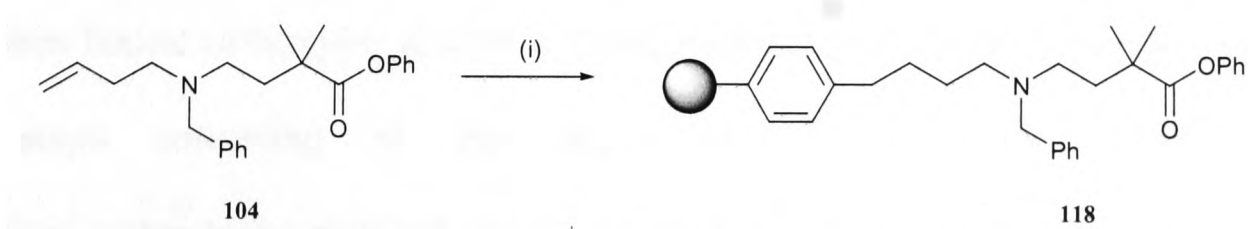
Max. theoretical loading:

$$L_P = \frac{L_S}{1 + L_S(MW_S - MW_X)} \qquad \textbf{Equation 3.1}$$

With the maximum theoretical loading from Equation 3.1 the expected mass of the polymer product can be calculated and compared to the isolated dry mass.

3.3.2 Synthesis of polymer supported carboxylic acid 90

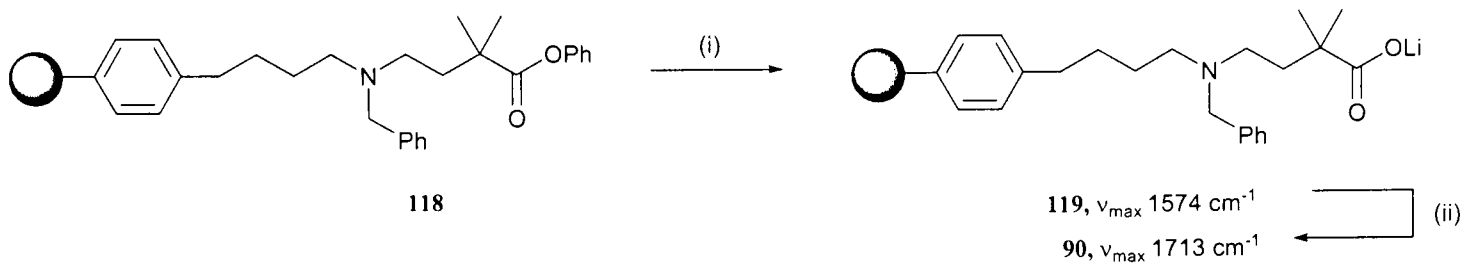
Having successfully demonstrated key transformations with a solution phase model system further efforts were aimed at the successful adaptation of these transformations on a polymeric support. Repetition of the Suzuki-Miyaura cross coupling of 4-bromotoluene **98** with phenyl ester **104** in solution was identified as a feasible starting point in solid phase studies (Section 3.2.5, Scheme 3.10). The transformation was carried out under analogous conditions replacing 4-bromotoluene with bromopolystyrene **94**. Thus, **104** was treated with 9-BBN at 0°C and allowed to stir at room temperature for 4 hours. The hydroboration mixture (2 eq.) was reacted with prewashed bromopolystyrene resin **94** (1.00 g, L_s 3.22 mmol/g, 3.22 mmol) with 9 % $Pd(OAc)_2$/DPPF catalyst loading. The maximum theoretical loading of the product polymer **118** is L_p 1.71 mmol/g (Equation 3.1) and therefore the mass gain of the polymer should correspond to 1.88 g of isolated dry polymer product. The resin was thoroughly washed with organic solvents and water until the washings were clear. Care was taken to wash out the high boiling DMF with nonvolatile solvents (THF and DCM) and the last washing was done with DCM in order to swell the resin. The observed dry mass of **118** was 1.90 g which is consistent with the calculated theoretical loading and an indication of the success of the reaction. Upon drying to a constant mass *in vacuo* IR investigation revealed a stretch in the carbonyl region characteristic of an ester (ν_{max}/cm^{-1} 1748)[8] and analogous to the solution phase model system **114** (ν_{max}/cm^{-1} 1751) (Scheme 3.16).



104 118

Scheme 3.16: *Reagents and conditions:* (i) 9-BBN in THF then bromopolystyrene **94**, DPPF, $Pd(OAc)_2$, K_2CO_3, DMF, 60°C 16 h.

The phenyl ester **118** was subsequently hydrolysed under analogous conditions to those previously described for the solution phase model system (Section 3.2.6, Scheme 3.12). Treatment of **118** with 10 equivalents of LiOH in THF:H_2O (8:1) under reflux for 4 hours, followed by repeated washings of the resin with organic solvents afforded the resin bound lithium carboxylate **119** as confirmed by IR investigation of the resin (ν_{max}/cm^{-1} 1574) (Scheme 3.17).



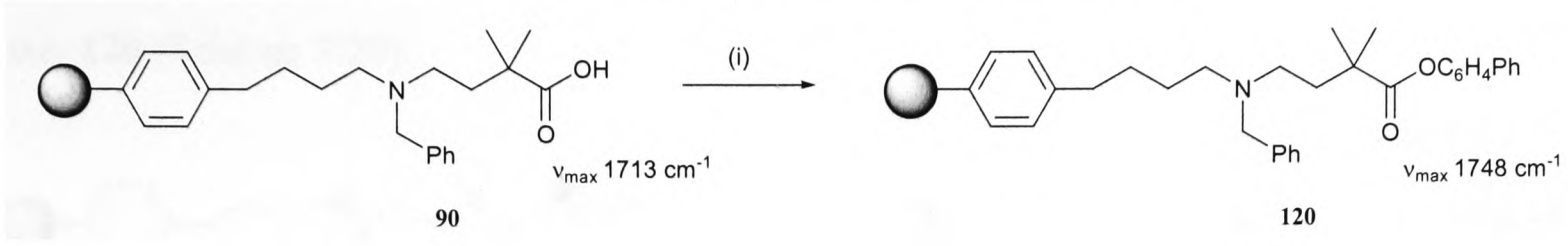
Scheme 3.17: *Reagents and conditions:* (i) 10 eq. LiOH, THF:H_2O (5:1), Δ 4 h; (ii) 10 % HCl, then H_2O (pH 7).

The resin was further washed with DMF and aqueous 10 % HCl to protonate the carboxylate salt **119**. Subsequent adjustment of the pH to neutral and further washings with organic solvents afforded the resin bound carboxylic acid **90** as indicated by the IR stretch characteristic of a carboxylic acid (ν_{max}/cm^{-1} 1713),[8] corresponding to the solution phase analogue **96** (ν_{max}/cm^{-1} 1710). However, in this case, the observed mass (879 mg) was somewhat higher after drying to a constant mass *in vacuo* than that expected from the calculated maximum theoretical loading (778 mg). While this indicates that unknown impurities or solvent could be trapped within the polymer, no trace of the ester functionality was visible in the resulting IR spectrum. Complete conversion was therefore assumed and the resin was carried forward to the next step.

3.3.3 Attachment, debenzylation/cyclorelease protocol

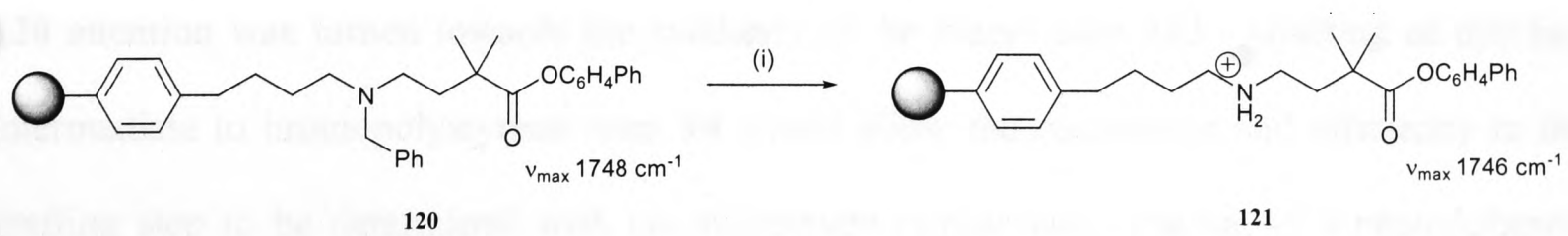
With the resin bound carboxylic acid **90** in hand, attention was turned to performing a sequence of two steps consisting of the attachment of a substrate followed by the debenzylation/cyclorelease protocol, analogous to the sequence previously carried out with the solution phase model system **96**. 4-phenylphenol **115** was used as a substrate in this sequence as in the solution phase model studies. Treatment of **90** with excess alcohol (6.5 eq.) to ensure

complete conversion of the reaction with DIC/HOBt activation afforded the desired polymer bound biaryl ester **120** according to investigation of the IR spectrum of the resulting resin. The observed IR stretch in the carbonyl region (ν_{max}/cm^{-1} 1748)[8] was consistent with that observed in the solution phase model system **116** (ν_{max}/cm^{-1} 1750) (Scheme 3.18).



Scheme 3.18: *Reagents and conditions:* (i) 4-Phenylphenol **115** (6.5 eq.), DIC (4 eq.), HOBt (4 eq.), DIPEA (8 eq.), DCM 16 h.

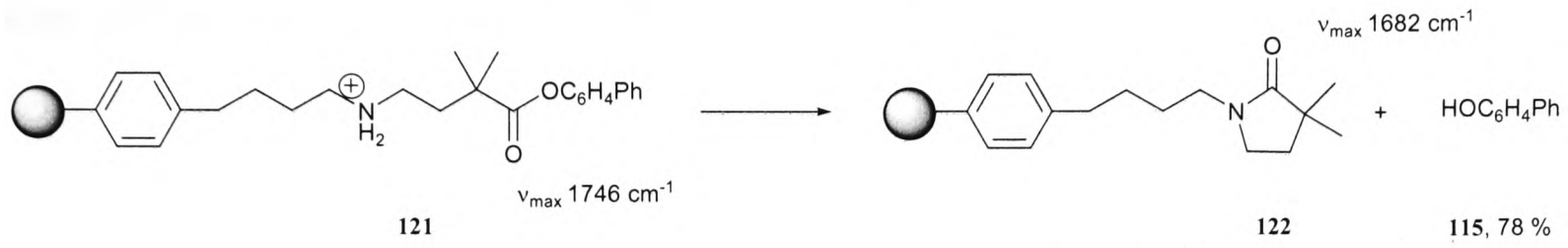
Attention was next turned towards the debenzylation/cyclorelease protocol successfully achieved with the solution phase system (Section 3.2.7, Scheme 3.14). Early attempts to achieve this transformation by treatment of phenyl ester **120** with CAN resulted in disappointing results since quenching with aqueous sodium bicarbonate solution afforded a sticky resin that proved difficult to manipulate in subsequent washings with organic solvents. Thus, an alternative procedure was employed. **120** was treated with 5 equivalents of CAN in THF:H_2O (8:1) solvent and stirred overnight. After washing with organic solvent and water to dissolve the inorganic residues the resulting yellow resin was dried *in vacuo* to a constant mass and subjected to IR investigation before treatment with base. The IR investigation of the resulting polymer product **121** revealed an intact ester bond (ν_{max}/cm^{-1} 1746) indicating that the cyclization does not occur before treatment with base (Scheme 3.19).



Scheme 3.19: *Reagents and conditions:* (i) CAN (5.0 eq.), THF:H_2O (8:1), 16 h.

An attempt was made to expose the resin to NEt_3 but due to poor swelling of the resin no cyclization was detected by IR investigation. However, upon treatment with a mixture of DCM:NEt_3 (5:1) the resin swelled and the desired product 4-phenylphenol **115** was subsequently detected by t.l.c. IR investigation of the resulting resin indicated a complete

conversion of the polymer bound biaryl ester **121** (ν_{max}/cm^{-1} 1746) to polymer bound lactam **122** (ν_{max}/cm^{-1} 1682).[8] The bulk of the organic solvent and NEt_3 was evaporated *in vacuo* and the resulting residue afforded the desired 4-phenylphenol **115** after aqueous workup. A yield of 78 % of 4-phenylphenol was calculated, based on the maximum theoretical loading of the biaryl ester **120** (Scheme 3.20).

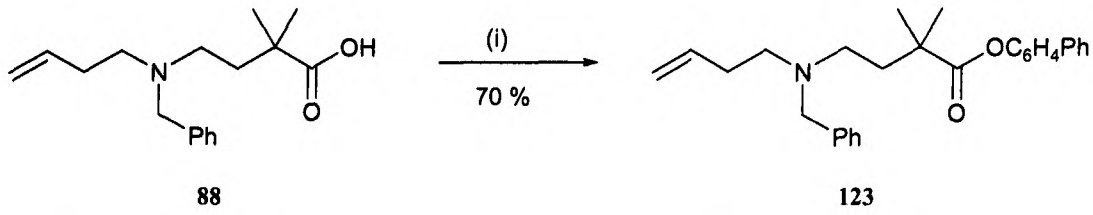


Scheme 3.20: *Reagents and conditions:* (i) DCM:NEt_3 (5:1), 30 min.

This property of the linker system is consistent with the secondary amine functionality of **121** being trapped as an unreactive quaternary ammonium species. This property is highly beneficial and allows complete control over the release of the product into solution. In addition, this allows the inorganic residues from the CAN reaction to be washed out of the polymeric matrix before release of the product into solution, preventing undesired side reactions with the released product. No impurities were detected in a HPLC trace of the resulting 4-phenylphenol or by an investigation of the ^1H NMR spectra of the product.

3.3.4 Synthesis of resin precursor and loading determination

Having successfully demonstrated these key transformations with the solid phase linker system **120** attention was turned towards the synthesis of the biaryl ester **123**. Grafting of this key intermediate to bromopolystyrene resin **94** would allow the conversion and efficiency in the grafting step to be determined with the subsequent release and isolation of 4-phenylphenol. Thus, treatment of **88** with 3 equivalents of 4-phenylphenol **115** with EDCI/HOBt activation in DCM for 16 hours afforded **123** in 70 % yield. The reaction was subsequently scaled up to afford the desired product from recrystallisation on a convenient 12 g scale (Scheme 3.21).

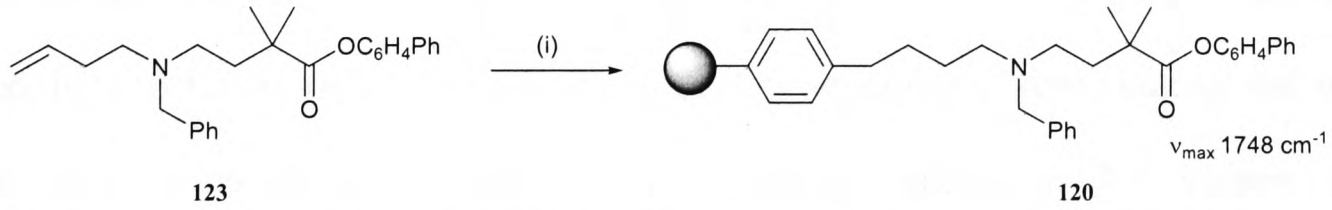


88 123

Scheme 3.21: *Reagents and conditions:* (i) 4-phenylphenol **115** (3 eq.), EDCI (1.5 eq.), HOBt (2 eq.), DIPEA (4 eq.), DCM.

With this route the synthesis of resin precursor **123** was achieved on a multigram scale in 5 steps without recourse to purification by chromatography.

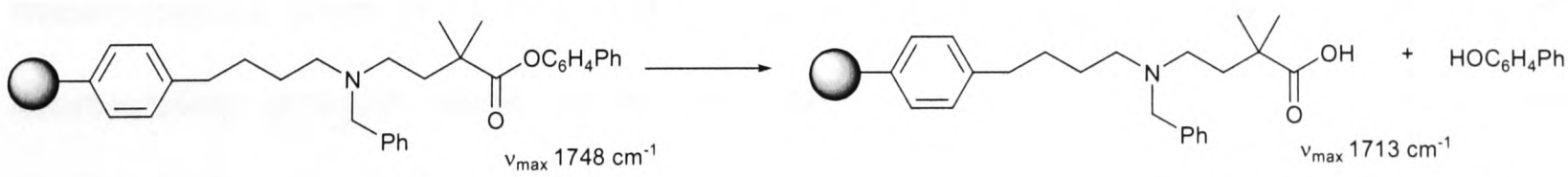
With the resin precursor **123** prepared, attachment to bromopolystyrene resin was attempted *via* Suzuki-Miyaura cross coupling. Treatment of **123** with 9-BBN and subsequent exposure to prewashed bromopolystyrene **94** (3.00 g, L_s 3.22 mmol/g, 9.66 mmol) in the presence of 9 % $Pd(OAc)_2$/DPPF catalyst and K_2CO_3 in DMF for 16 hours afforded the resin **120** with identical spectroscopic properties to those previously observed (Scheme 3.18). The recovered mass of the resin (6.50 g) was in accordance with the mass expected (6.38 g) according to the maximum theoretical loading (1.52 mmol/g) (Scheme 3.22).



123 120

Scheme 3.22: *Reagents and conditions:* (i) 9-BBN in THF then bromopolystyrene **94**, DPPF, $Pd(OAc)_2$, K_2CO_3, DMF, 60°C 16 h.

To determine the polymer loading, the ester **120** (6.50 g, 9.66 mmol) was saponified and 4-phenylphenol **115** isolated after aqueous workup. Treatment of **120** with 10 equivalents LiOH with THF:H_2O (8:1) under refluxing conditions for 4 hours afforded the desired 4-phenylphenol **115** pure, as assessed by investigation of the ^1H NMR spectra. The isolated amount of **115** (1.65 g, 9.69 mmol) indicated that complete conversion had been achieved in the grafting of the linker system on bromopolystyrene resin **94** (Scheme 3.23).



120 90 115

Scheme 3.23: *Reagents and conditions:* (i) 10 eq. LiOH, THF:H_2O (5:1), Δ 4 h.

The resin was dried to a constant mass and the loading calculated from the constant mass (5.60 g) of the resin **90** and number of moles of 4-phenylphenol **115** isolated (determined loading, 1.73 mmol/g).

3.4 Conclusions

Two approaches, accessible *via* a common intermediate carboxylic acid **88**, to graft the safety catch linker system on a polymeric support have been evaluated. Attempts to develop a route allowing the linker system to be grafted to Merrifield's resin *via* an alcohol were met with limited success. However, the described linker system has successfully been adapted to the solid phase utilizing a Suzuki-Miyaura cross coupling to graft the safety catch linker on to bromopolystyrene resin. A solution phase model system designed to mimic the key transformations prior to adaptation to the solid phase has been developed, however this model system is not anticipated to be amenable to large scale synthesis. The grafting of the linker was simulated in a solution phase experiment with 4-bromotoluene representing the resin. A substrate was successfully loaded on the solution phase model system and the debenzylation/cyclorelease protocol demonstrated.

The key transformations were subsequently repeated with a solid phase system and the cyclization product isolated and the purity determined. The loading of the resin was determined with detachment of a protecting group from the solid phase system and subsequent isolation. Before chemistry can be carried out on the solid phase system the attachment and release of other functional groups, aliphatic alcohols and amines, has to be demonstrated with a readily accessible solution phase model system. The reactivity profile of the ester and amide coupling transformations needs to be evaluated and the efficiency and chemoselectivity of the CAN debenzylation protocol needs to be assessed. The following chapter describes these investigations.

References

[1] K.M.J. Brands, A.A.P. Mekel, U.K. Pandit, *Tetrahedron*, 1991, **47**, 2005.

[2] A.F. Abdel-Magid, C.A. Maryanoff, K.G. Carson, *Tetrahedron Letters*, 1990, **31**, 5595; A.F. Abdel-Magid, K.G. Carson, B.D. Harris, C.A Maryanoff, R.D. Shah, *J. Org. Chem.*, 1996, **61**, 3849.

[3] A. Mulvaney, S.G. Davies, Oxford Diversity traceless linker, unpublished results.

[4] N. Miyaura, T. Ishiyama, H. Sasaki, M. Ishikawa, M. Satoh, A. Suzuki, *J. Am. Chem. Soc.*, 1989, **111**, 314.

[5] M. Palucki, D.L. Hughes, N. Yasuda, C. Yang, P.J. Reider, *Tetrahedron Lett.*, 2001, **42**, 6811.

[6] T.H. Greene, P.G.M. Wutz, *Protective Groups in Organic Synthesis*, 3rd edn., John Wiley, Chichester, 1999.

[7] B.A. Bunin, *The Combinatorial Index*, Academic Press, London, 1998.

[8] For selected IR data for polymer-supported compounds see Appendix I.

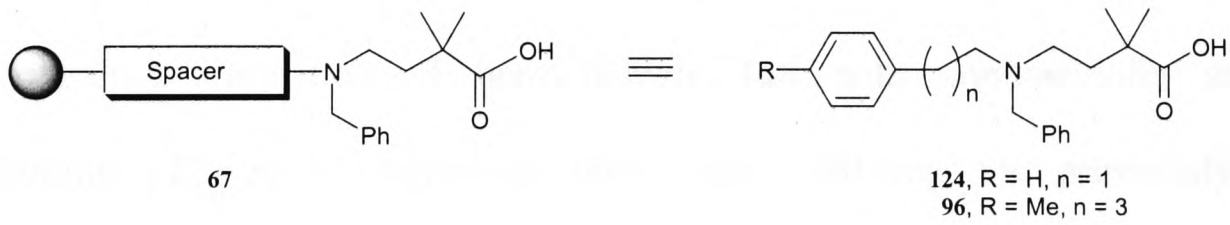
4 Chapter IV: Model studies in solution

4.1 Introduction

The previous chapter described the debenzylation/cyclorelease protocol for the release of aryl alcohols. This chapter is concerned with assessing the reactivity in the coupling transformation for aliphatic alcohols and amines respectively along with the chemoselectivity and efficiency of the CAN debenzylation/activation protocol.

4.1.1 Identification of alternative spacers

Two alternative model systems were envisaged to mimic the safety catch linker system **67** in solution. The systems used the carboxylic acids **124** and **96** that incorporate differing alkyl chain lengths (spacers) between the *N*-benzyl functionality and the aromatic ring representing the polystyrene terminus. Changing the length of the spacer in this manner should not affect the solution phase studies undertaken (Figure 4.1).



67

124, R = H, n = 1
96, R = Me, n = 3

Figure 4.1: Model systems **124** and **96** for solution phase studies

The carboxylic acid **124** with a two carbon spacer incorporated was anticipated to be accessible *via* reductive amination of dihydrofuranone **68** with *N*-benzyl phenylethylamine **125** (Figure 4.2, route **a**). This approach should be readily adapted to solid phase since *N*-ethylpolystyrenyl amine is commercially available, however the spacer length would be limited to commercially available polystyrenyl alkylamines. In addition an alternative approach would be needed to determine the efficiency of the linker grafting on the insoluble support.

Carboxylic acid incorporating a butenyl spacer **96** was previously isolated from the hydrolysis of the phenyl ester **114** (Scheme 3.12, Section 3.26) and should be accessible in two steps from the resin precursor **123** and 4-bromotoluene **98** utilizing the Suzuki-Miyaura cross coupling

protocol followed by hydrolysis (Figure 4.2, route **b**). However, this route is not anticipated to be amenable to the preparation of large quantities of material since 7 steps are required for this system from commercially available materials.

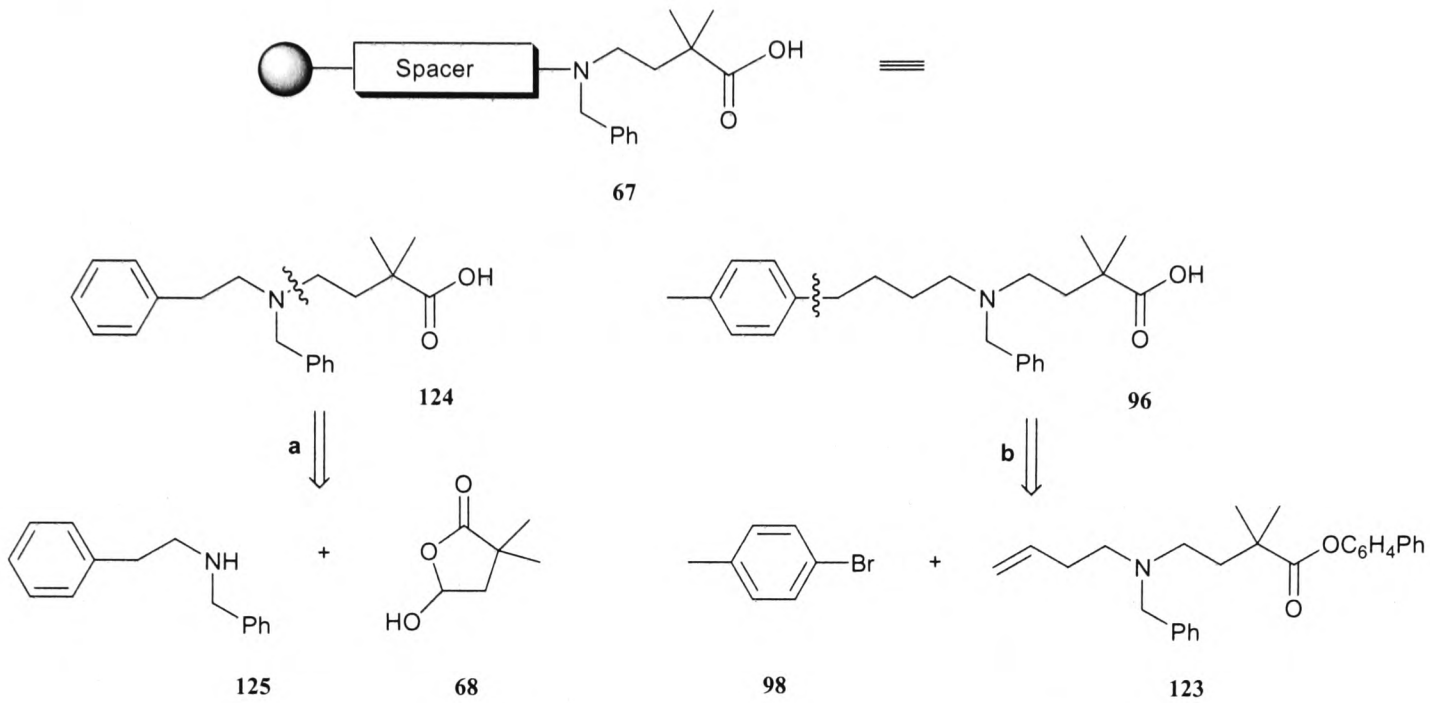
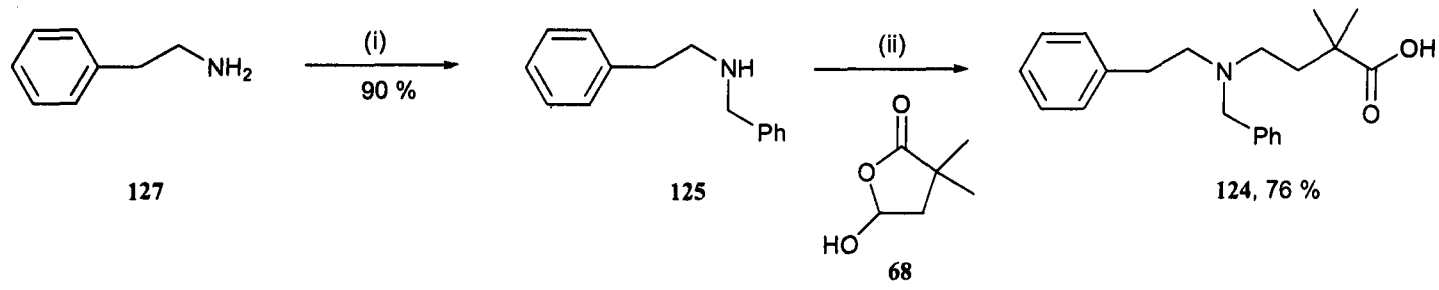


Figure 4.2: Suggested routes towards model systems **124** and **96**.

4.1.2 Preparation of model compounds

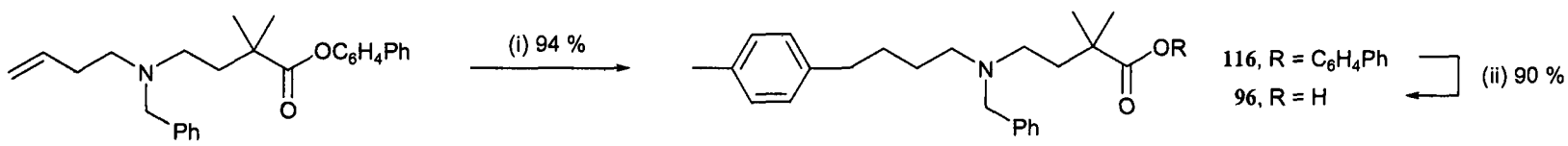
The spacer-safety catch construct **125** of model compound **124** was readily synthesised in 90 % yield *via* reductive amination of benzaldehyde **126** with commercially available *N*-phenylethylamine **127** on a convenient 60 g scale utilising the previously optimised TMOF/$NaBH_4$ protocol (*vide supra*). The reductive amination of dihydrofuranone **68** with amine **125** progressed smoothly under conditions similar to those used previously for the analogous dibenzylamine model compound **76** (Scheme 2.5, Section 2.3.2) to afford **124** in 76 % yield. The purity was assessed to be >98 % by analysis of the ^{1}H NMR spectra of the crude product. Thus, **124** was readily accessible in 68 % overall yield from **127** without recourse to column chromatography (Scheme 4.1).



127 125 68 124, 76 %

Scheme 4.1: *Reagents and conditions:* (i) PhCHO **126**, MeOH, TMOF, then $NaBH_4$, 0°C, 1 h then r.t. 16 h; (ii) MeOH, TMOF, 2 h r.t. then $NaBH_4$, 0°C 1 h then r.t. 16 h.

With **124** prepared, the known biaryl carboxylic ester **116** was readily synthesised from **123** *via* Suzuki-Miyaura cross coupling with 4-bromotoluene **98** in 94 % yield after chromatography. Reflux under hydrolytic conditions afforded the desired carboxylic acid **96** in 90 % yield. Both transformations were highly reliable and repeatedly afforded the desired compounds on an acceptable scale (2 - 3 g). Optimal results for this two step transformation were achieved *via* direct hydrolysis of the Suzuki-Miyaura coupling reaction mixture giving carboxylic acid **96** in 84 - 90 % yield for the two step transformation after column chromatography (Scheme 4.2).



123

Scheme 4.2: *Reagents and conditions:* (i) 9-BBN in THF then 4-bromotoluene **98**, DPPF, $Pd(OAc)_2$, K_2CO_3, DMF, 60°C, 16 h; (ii) LiOH (10 eq.), THF:H_2O (8:1), Δ 16 h.

With multigram quantities of the model carboxylic acids **124** and **96** in hand an investigation of the reactivity of the ester and amide coupling transformation with alcohols and amines respectively could take place to mimic their immobilization on the solid phase.

Before further discussion of these key transformations the most widely used methods of activating carboxylic acids towards amide and ester formation will be discussed.

4.2 Methods for amide and ester formation

Perhaps the most widely used method to activate carboxylic acids towards amide or ester bond formation is *via* acid chlorides.[1] As well as thionyl chloride and oxalyl chloride, a wide range of alternative coupling methods have been developed and most have emerged from the peptide synthesis field.[2] Carbodiimides[3] {typically *N,N'*-diisopropylcarbodiimide (DIC) **128** or *N,N'*-

dicyclohexylcarbodiimide (DCC) **129**} have found widespread use but their use is complicated by competing side reactions.[4] Activation of acid **130** by carbodiimides generates a highly active *O*-acylisourea **131** which can rearrange to the corresponding *N*-acylurea **132**. This intramolecular rearrangement can greatly affect the yield and creates purification problems if precautions are not taken. However, it can be suppressed by addition of excess nucleophile that will react with the *O*-acylisourea **131** before the rearrangement can take place. This is usually achieved by addition of a suitable reagent which forms an active ester **133** that is still reactive in aminolysis or transesterification to give **134**. HOBt[5] **135** is the most widely used reagent for this purpose and is easily removed by a simple aqueous workup after use. One disadvantage of the carbodiimide method is the separation of the dialkylurea byproduct **136** from the crude reaction mixture. This byproduct is soluble in most organic solvents and chromatography is therefore necessary when the reagents are employed in solution (Figure 4.3).

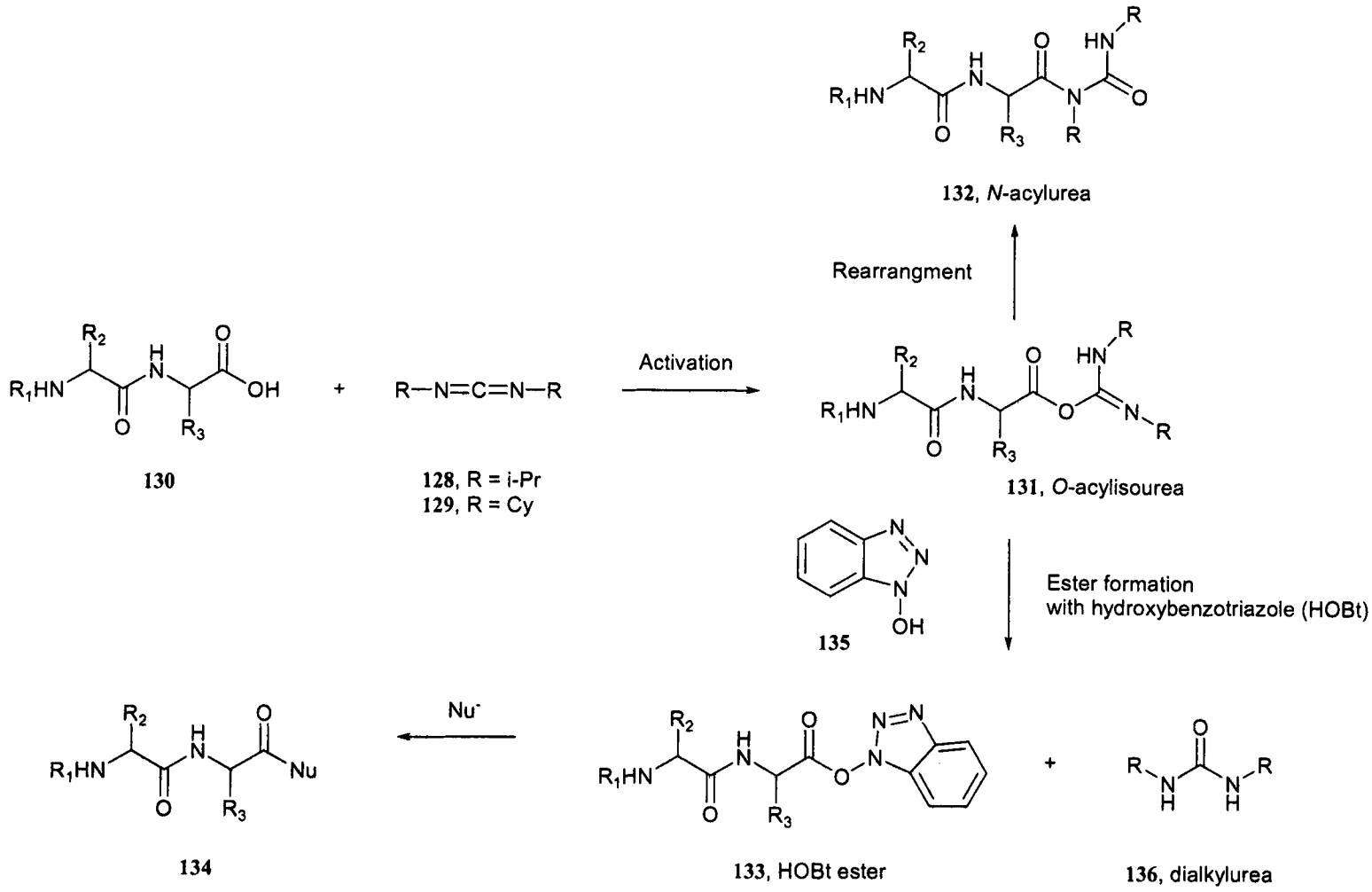


Figure 4.3: Rearrangment of O-acyisolurea to N-acylurea and HOBt activation

This problem has been circumvented by the development of an alternative reagent based on the same principle. EDCI[6] {*N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride **137**} is an alternative to DIC **128** and DCC **129** which generates a water soluble urea, rendering

chromatography unnecessary. Another class of similar reagents that use the same activation principle are uronium based,[7] of which TBTU[8] **138** and HBTU[9] **139** are representatives. These reagents generate highly active *O*-acylisouronium intermediate **140** which cannot undergo intramolecular rearrangement. They contain a built in equivalent of HOBt **135** that acts as a leaving group upon formation of the intermediate **140** with subsequent formation of activated esters (Figure 4.4).

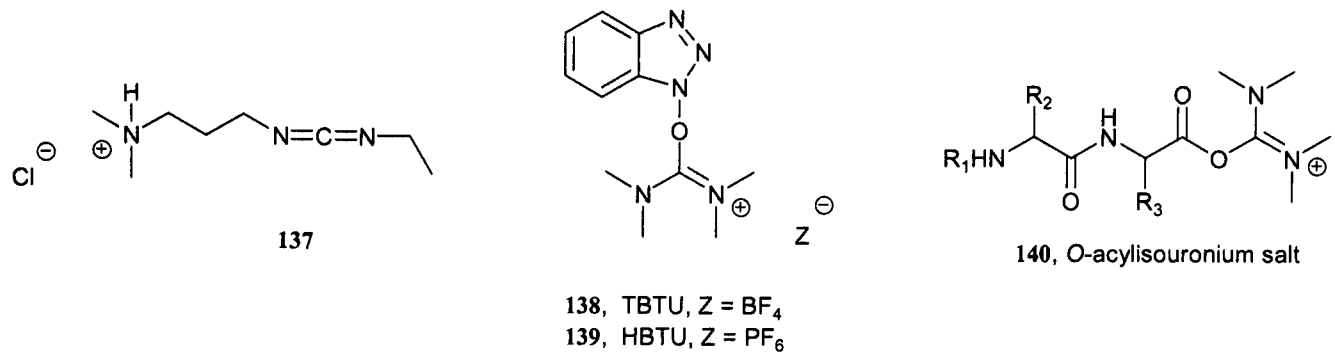


Figure 4.4: Alternative coupling reagents, EDCI **137** and uronium based reagents **138** and **139**.

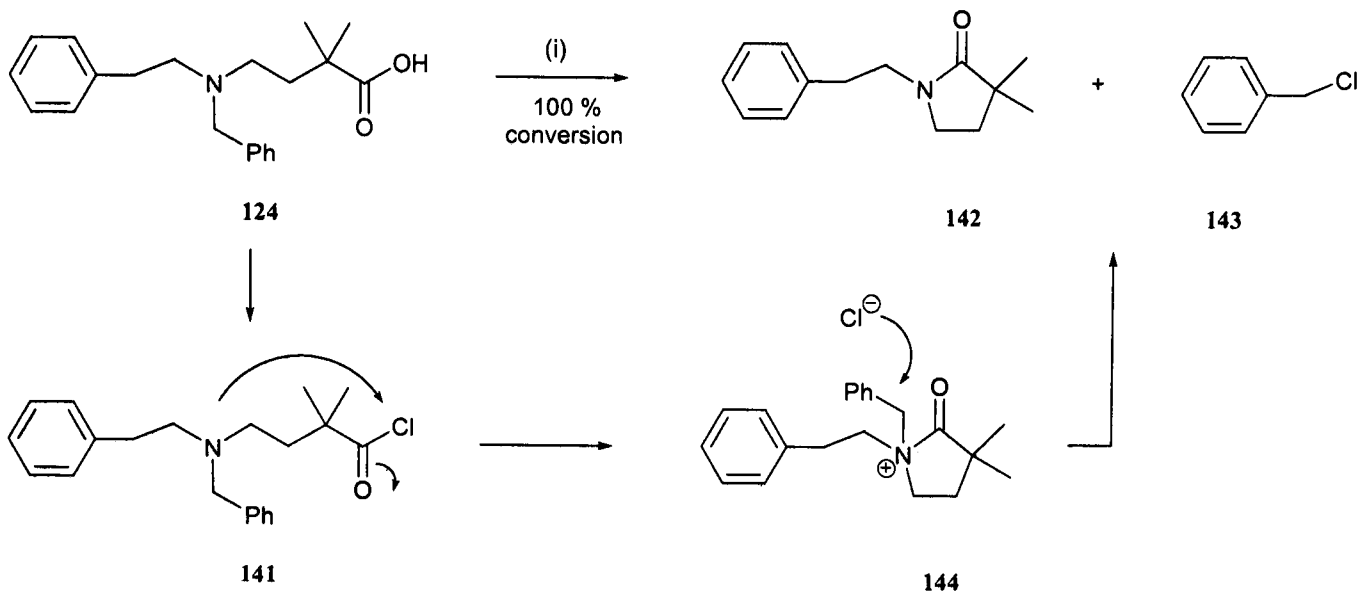
These reagents give superior results compared to the carbodiimides both with respect to racemisation and yields when sterically hindered carboxylic acids, alcohols or amines are employed and have found widespread use as coupling reagents.[1] However, these reagents give urea byproducts which are highly soluble in organic solvents and a purification step is therefore required when employed in solution.

4.3 Aliphatic alcohols, solution phase studies

4.3.1 Attachment of alcohols / ester formation

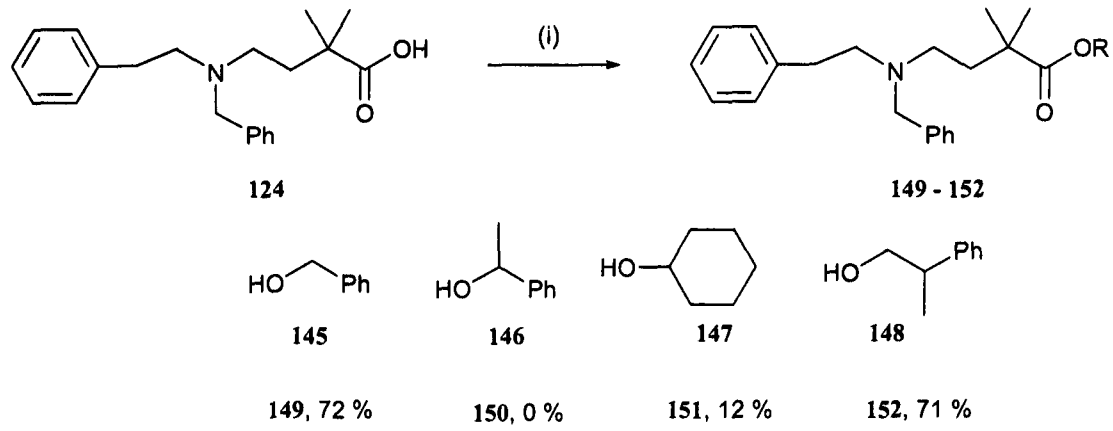
As an initial approach to a route for the synthesis of ester and amide derivatives of **124** and **96** suitable for scale-up, derivatisation of **124** to the corresponding acid chloride **141** was evaluated. However, upon treatment of **124** with thionyl chloride in DCM the lactam **142** was detected in the reaction mixture and analysis of the ^{1}H NMR spectra of the crude reaction mixture indicated a mixture of the lactam **142** and benzyl chloride **143** had been formed. This product distribution is consistent with initial activation of the carboxylic acid by acid chloride formation followed by intramolecular nucleophilic attack of the tertiary amine to afford the

activated lactam **144**. In this undesired side reaction, nucleophilic attack of the released chloride ion then affords the lactam **142** and benzyl chloride **143**. Due to this side reaction this approach was abandoned (Scheme 4.3).



Scheme 4.3: *Reagents and conditions:* (i) $SOCl_2$, DCM, r.t. 16 h.

As an alternative activation strategy, the use of EDCI **137** and HOBt **135** was investigated. To study the reactivity of the model system **124** in these ester coupling transformations, a range of primary and secondary aliphatic alcohols with differing substitution in the α and β positions were chosen. Thus, **124** was treated with the alcohols **145** - **148** utilizing EDCI/HOBt activation, employing conditions previously found to be optimal for aryl ester formation (Section 3.2.3). Treatment of **124** with benzyl alcohol **145** afforded the ester **149** in 72 % yield after chromatography. Moreover, upon treatment of **124** under the same conditions in the presence of the secondary alcohol 1-phenylethyl alcohol **146** no formation of ester **150** was detected. Under the same conditions, treatment with cyclohexyl alcohol **147** resulted in slow formation of the product ester **151**, giving only 12 % isolated yield after 16 hours reaction time. However, the β substituted primary alcohol **148** afforded the product **152** in 71 % yield (Scheme 4.4).

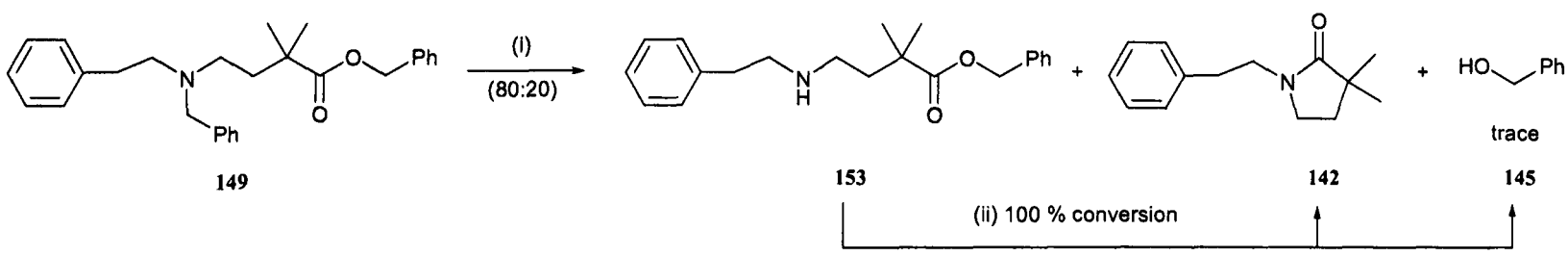


Scheme 4.4: *Reagents and conditions:* (i) alcohol **145 - 148** (3 eq.), EDCI, HOBt, DIPEA, DCM, 16 h.

These observations are in accordance with the expected pivaloyl like properties of the safety catch linker system and indicate that 1° alcohols, but not 2° alcohols, readily couple under these conditions. This may however be used to achieve immobilisation and selective protection of a primary alcohol in the presence of hindered nucleophiles in the same transformation.

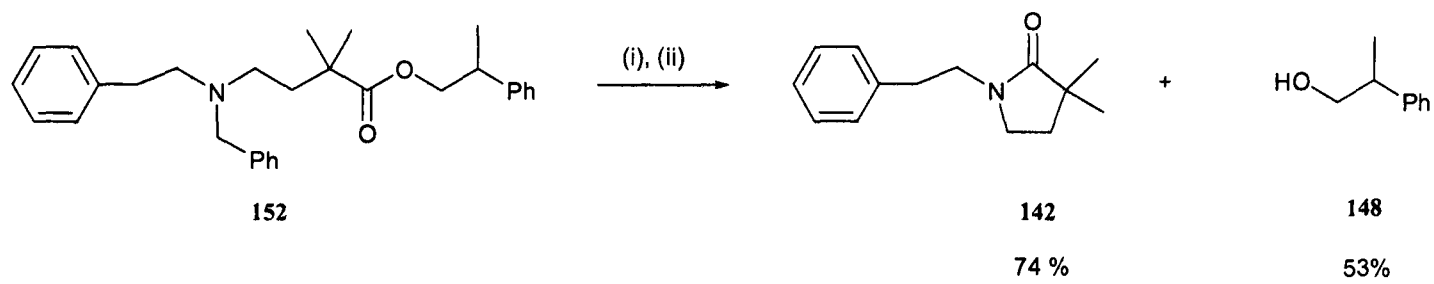
4.3.2 Debenzylation/cyclorelease

The chemoselectivity of the CAN *N*-debenzylation was further investigated by chemoselective *N*-debenzylation of the *O*-benzyl ester **149**.[10] Thus, *O*-benzyl ester **149** was treated with 5 eq. of CAN in THF:H_2O for 16 hours. Investigation of the ^1H NMR spectrum of the resulting crude reaction mixture revealed a 80:20 mixture of the debenzylated product **153**, lactam **142** and a trace of benzyl alcohol **145** confirming that chemoselective *N*-debenzylation had taken place and indicating that some spontaneous cyclisation had taken place. No trace was found of the alternative *O*-debenzylation product **124** or starting material **149** in this investigation. Isolation of the unstable intermediate **153** was not attempted but the cyclization was driven to completion by refluxing in toluene for 6 hours, giving complete conversion to the desired lactam **142** (Scheme 4.5).



Scheme 4.5: *Reagents and conditions:* (i) CAN (5 eq.), THF:H_2O (8:1), r.t. 16 h; (ii) MePh, Δ 6 h.

To further demonstrate the debenzylation/cyclorelease protocol, ester **152** was subjected to the same protocol as previously described. Treatment of **152** with CAN for 16 hours and subsequent reflux in toluene for 16 hours resulted in complete conversion to the desired products. Separation by chromatography gave the lactam **142** and alcohol **148** in 53 % and 74 % isolated yields respectively over the two step process (Scheme 4.6).



152 **142** **148**

74 % 53%

Scheme 4.6: *Reagents and conditions:* (i) CAN (5 eq.), THF:H_2O (8:1), r.t. 16 h; (ii) MePh, Δ 16 h.

These investigations have established a reactivity profile for a range of aliphatic alcohols in the ester coupling transformation with carboxylic acid **124**. The expected chemoselectivity of the CAN *N*-debenzylation protocol in the presence of the *O*-benzyl functionality of **149** has also been confirmed and the debenzylation/cyclorelease protocol has been demonstrated with good isolated yields of the expected products **142** and **148**.

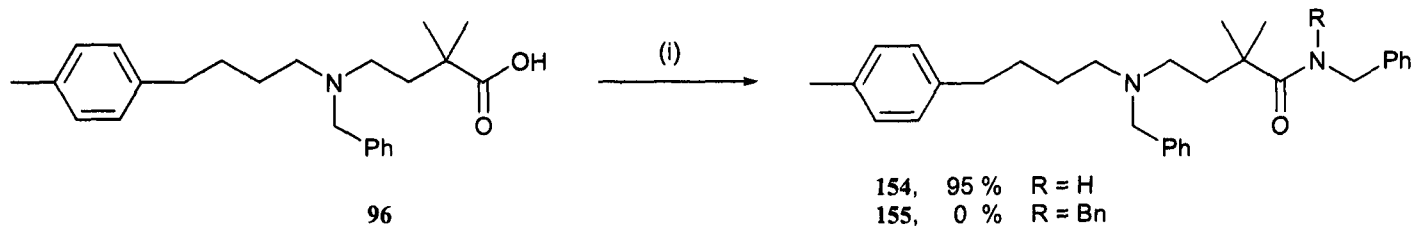
4.4 Coupling of amines to model systems

Having examined the coupling and release of a range of aliphatic alcohols, further investigations focussed on an analogous investigation of primary and secondary amines. As a starting point in this investigation *N*-benzylamine **93** and *N,N*-dibenzylamine **53** were chosen as a suitable candidates for amide formation from carboxylic acid **96**. Furthermore the CAN *N*-debenzylation protocol should be chemoselective towards the *N*-tertiary amine functionality of amides **154** and **155** in accordance with previous observations (Scheme 2.3, Section 2.1.2).[11]

4.4.1 Coupling of primary and secondary amines

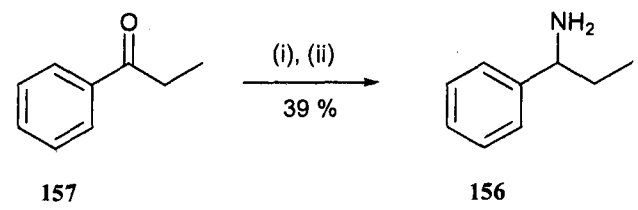
Treatment of **96** with EDCI/HOBt in the presence of *N*-benzylamine **93** in DCM afforded the desired amide **154** in 95 % yield after chromatography. However, analogous treatment of **96** in

the presence of *N,N*-dibenzylamine **53** afforded no amide **155**, only returning a mixture of starting materials (Scheme 4.7).



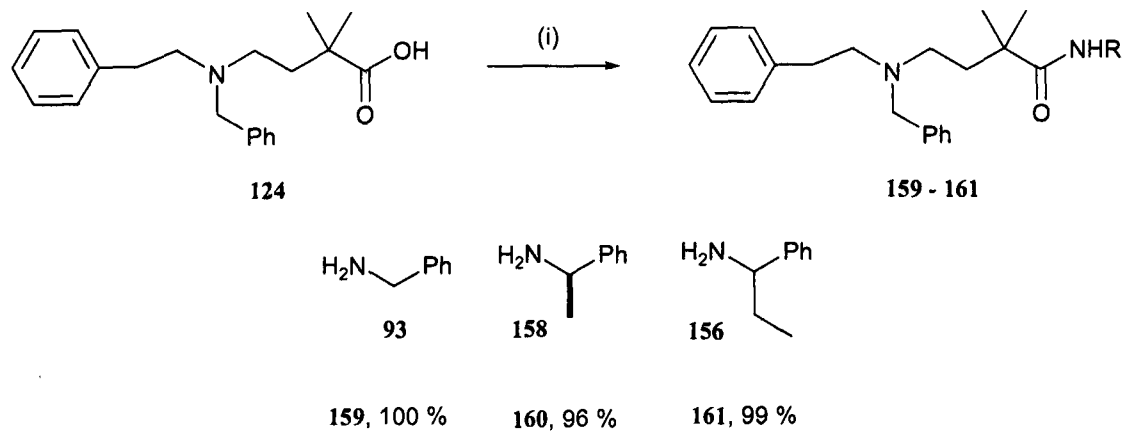
Scheme 4.7: *Reagents and conditions:* (i) *N*-benzylamine **93** (3 eq.), *N,N*-dibenzylamine **53** (3 eq.), EDCI (2 eq.), HOBt (2 eq.), DIPEA (4 eq.), DCM.

The reactivity of α-substituted primary benzylamines in the amide coupling reaction with carboxylic acid **124** was next studied in order to construct a reactivity profile. Amine **156** was therefore prepared in a two-step process[12] from propiophenone **157** in 39 % overall yield (Scheme 4.8).



Scheme 4.8: *Reagents and conditions:* (i) $HCONH_2$, HCOOH, 180°C 8 h; (ii) $HCl_{conc.}$, Δ 1 h.

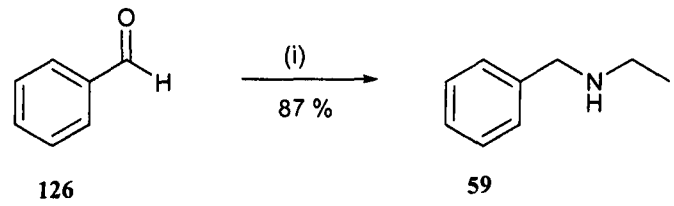
Treatment of **124** with amines **93**, **158** and **156** in the presence of EDCI/HOBt in DCM afforded the desired amides **159** - **161** in excellent yield (96 - 100 %) after 16 hours indicating that α-substitution has no deleterious effect on the conversion in this transformation (Scheme 4.9).



Scheme 4.9: *Reagents and conditions:* (i) amine **93**, **158** or **156**, EDCI, HOBt, DIPEA, DCM, r.t. 16 h.

To study the reactivity profile of secondary amines a range of differentially substituted *N*-alkyl benzylamines were subjected to an analogous study with the model system **124**. *N*-benzyl-*N*-methylamine **58** and *N,N*-dibenzylamine **53** are commercially available, (*S*)-*N*-methyl-*N*-α-

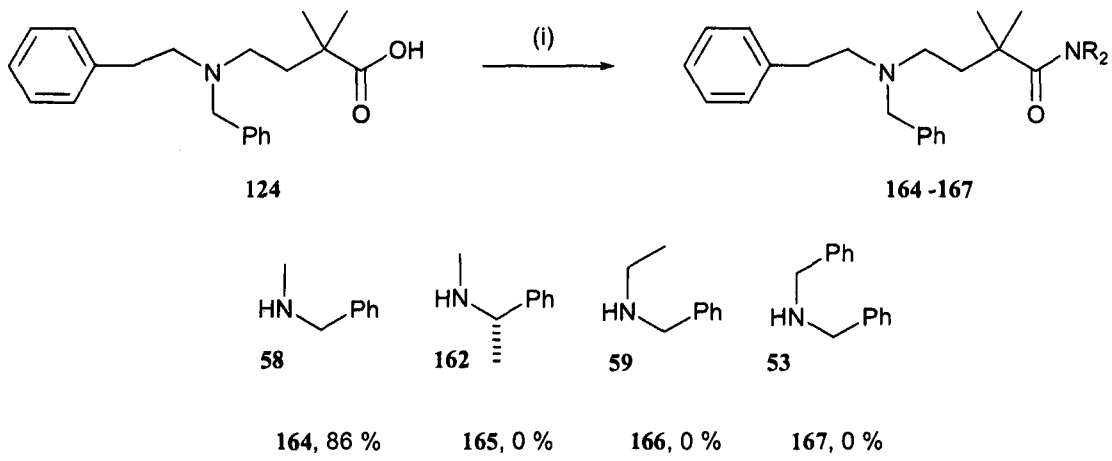
methylbenzylamine **162** was available within the laboratory[13] and *N*-benzyl-*N*-ethylamine **59** was prepared *via* reductive amination of ethylamine **163** with benzaldehyde **126** in 87 % yield (Scheme 4.10).



126 59

Scheme 4.10: *Reagents and conditions:* (i) MeOH, TMOF, NEt_3, HCl.H_2NEt **163**.HCl, r.t. 4 h then $NaBH_4$ 0°C.

A range of procedures were carried out to identify the optimal conditions for this reaction. Both EDCI **137** and TBTU **138** were evaluated as activating species in DCM, however, these attempts were unsuccessful and yielded either starting materials or complex mixtures in all cases. Treatment of **124** with EDCI/HOBt in the presence of 4 equivalents *N*-benzyl-*N*-methylamine **58** in DMF afforded a mixture of the product **164** and starting material **124** in 86 % and 8 % yields respectively after 16 hours. Attempts to use these optimal conditions to couple amines **162, 59** and **53** to the model system **124** did not yield the amide derivatives **165** - **167**. However these simple experiments give a clear view of the reactivity profile of non-cyclic secondary amines in this reaction (Scheme 4.11).



124 164 -167

58 162 59 53

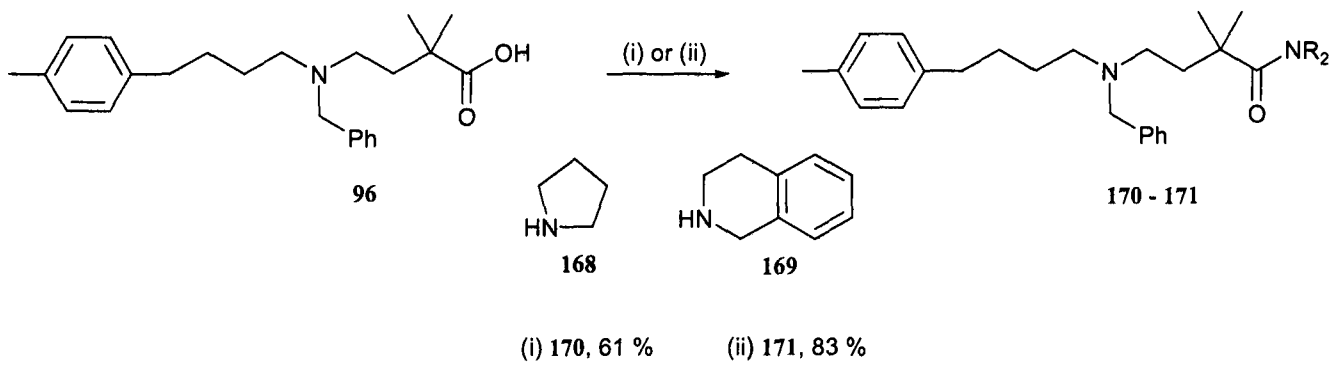
164, 86 % 165, 0 % 166, 0 % 167, 0 %

Scheme 4.11: *Reagents and conditions:* (i) amine **58, 161, 59** and **53** (4 eq.), EDCI (1.5 eq.), HOBt (2 eq.), DIPEA (4 eq.), DMF, r.t. 16 h.

With these results in hand attention was next focussed on more nucleophilic cyclic amines to further gain understanding of this transformation.

4.4.2 Coupling of cyclic amines

To study the reactivity of cyclic amines in this transformation a range of cyclic scaffolds were subjected to the coupling conditions previously described. Initial investigations focussed on the 5 and 6 membered scaffolds with pyrrolidine **168** and 1,2,3,4-tetrahydro-isoquinoline **169** used in the amide coupling with model system **96**. Treatment of **96** under the previously optimized conditions using EDCI/HOBt and 2 eq. of pyrrolidine **168** afforded the desired product **170** in a moderate 61 % yield after column chromatography. The coupling of model system **96** with 1,2,3,4-tetrahydro-isoquinoline **169** was achieved using a large excess of amine (10 eq.) to afford the desired amide **171** in acceptable 83 % yield after column chromatography. These amide couplings indicate that this transformation is readily achievable using a large excess of nucleophile. Further investigations aimed to identify optimal conditions suitable for a range of cyclic secondary amines (Scheme 4.12).

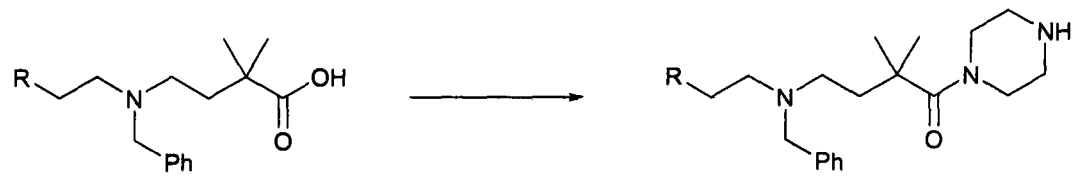


Scheme 4.12: *Reagents and conditions:* (i) pyrrolidine **168** (2 eq.), EDCI (1.5 eq.), HOBt (1.5 eq.), DIPEA (2 eq.), DCM; (ii) 1,2,3,4-tetrahydro-isoquinoline **169** (10 eq.), EDCI (2 eq.), HOBt (2 eq.), DIPEA (4 eq.), DCM.

Investigations to couple six membered nitrogen containing heterocycles used substituted piperazines as substrates.[14] The piperazine scaffold is a privileged substructure,[15] and such systems exhibit a range of pharmacological properties. Preparation of differentially derivatized piperazines is not readily achieved in solution without prior monoprotection, whereas the strategy described herein should allow access to such monoprotected and differentially protected piperazines. EDCI **137** and TBTU **138** were evaluated as activating agents in this investigation in attempts to identify the optimal conditions for this transformation.

Treatment of model system **96** with 4 equivalents of piperazine **172** using TBTU **138** for activation in DCM for 16 hours afforded the desired amide **173** in 99 % yield. Attempts to

repeat and scale-up the successful transformation with the piperazine substrate to the *N*-phenylethamine model system **124** were undertaken. The application of the previous conditions using DCM were unsuccessful, however using DMF afforded **174** in 86 % crude yield. However, scale up of this reaction was problematic and afforded a mixture of starting material **124** and product **174**, resulting in a disappointing 30 % yield after purification by chromatography (Scheme 4.13).

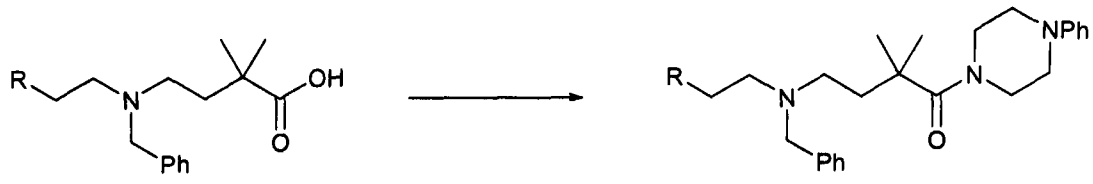


Scheme 4.13: *Reagents and conditions:* (i) piperazine **172** (4 eq.), TBTU (1.5 eq.), HOBt (2 eq.), DIPEA (4 eq.), DCM; (ii) piperazine (4 eq.), EDCI (1.5 eq.), HOBt (2 eq.), DIPEA (4 eq.), DMF.

Attention next turned to attempts to couple *N*-phenyl piperazine **175** to the model system **96**. Treatment of model system **96** with 3 equivalents of *N*-phenyl piperazine **175** in the presence of TBTU **138** for activation afforded the desired amide **176** in 84 % yield after chromatography.

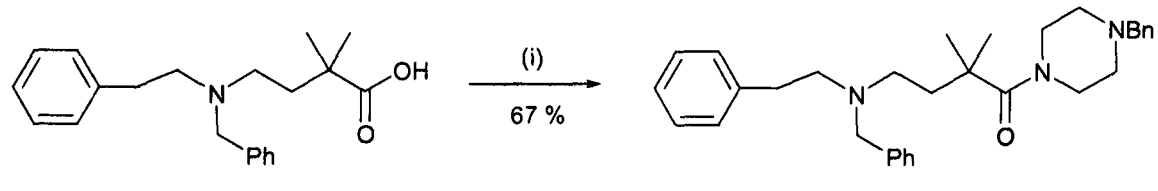
In a detailed analysis of ^{1}H NMR spectra obtained from isolated column fractions of the products from this reaction, lactam **117** was identified as a side product indicating competing cyclization in an intramolecular cyclization of the intermediate *O*-acylisouronium species (Figure 4.4, Section 4.2). To suppress this side reaction efforts were made to drive the reaction to completion using an excess of HOBt and amine **175**. These attempts were unsuccessful with chromatography affording amide **176** and starting material **96** in 77 % and 19 % isolated yield respectively.

These observations are consistent with a competing hydrolysis of the intermediate HOBt ester, presumably from water originating from the HOBt hydrate used in these experiments. However, it was found that multigram quantities of compound **177** may be accessed by treatment with *N*-phenyl piperazine **175** (4 equivalents) and EDCI/HOBt, affording the desired amide **177** in 74 % isolated yield after chromatography (Scheme 4.14).



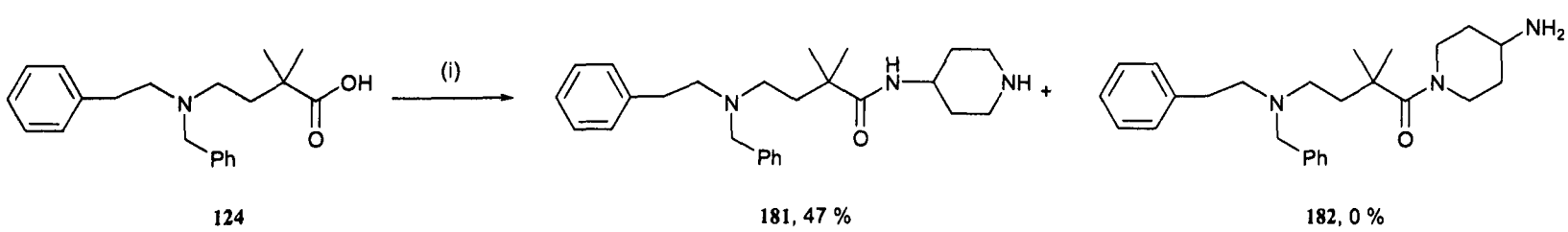
Scheme 4.14: *Reagents and conditions:* (i) *N*-phenyl piperazine **175** (3 eq.), TBTU (1.5 eq.), DIPEA (3 eq.), DCM; (ii) *N*-phenyl piperazine **175** (4 eq.), TBTU (1.5 eq.), HOBt (2 eq.), DIPEA (3 eq.), DCM; (iii) *N*-phenyl piperazine (4 eq.), EDCI (1.5 eq.), HOBt (2 eq.), DIPEA (4 eq.), DCM.

To investigate the chemoselectivity of the CAN *N*-debenzylation protocol towards non-cyclic *N*-benzyl tertiary amines in the presence of cyclic *N*-benzyl tertiary amines (Figure 2.4, Section 2.1.2) the analogous *N*-benzyl piperazine substrate **178** was also prepared. Treatment of acid **124** with 4 equivalents of *N*-benzyl piperazine **179** in the presence of EDCI/HOBt afforded amide **178** in 67 % isolated yield after chromatography (Scheme 4.15).



Scheme 4.15: *Reagents and conditions:* (i) *N*-benzyl piperazine **179** (4 eq.), EDCI (1.5 eq.), HOBt (2 eq.), DIPEA (4 eq.), DCM.

Due to the difficulty of coupling secondary amines to the model systems **96** and **124** an investigation of the selectivity of amide coupling with respect to secondary and primary amines was undertaken. 4-Amino piperidine **180** was identified as a suitable candidate to act as a model in order to investigate the regioselectivity of amide formation. Thus, acid **124** was treated with 2 equivalents of 4-amino piperidine **180** with EDCI/HOBt activation to afford **181** in 47 % yield after chromatography. The alternative product **182** was not detected in the crude reaction mixture or following purification (Scheme 4.16).



Scheme 4.16: *Reagents and conditions:* (i) 4-amino piperidine **180** (2 eq.), EDCI (1.5 eq.), HOBt (2 eq.), DIPEA (4 eq.), DMF.

This experiment indicates that primary amines may be selectively protected in the presence of secondary amines due to the low reactivity of the latter functionality.

4.5 Investigations into premature cyclization

The lactam formation due to activation of carboxylic acids **124** (Scheme 4.3) and **96** (Scheme 4.14) was deemed worthy of further investigation. Thus, the stability of the *O*-acylurea intermediate **183** was asessed, this species needs to be generated in the absence of any external nucleophile, TBTU **138** would not be suitable for this activation since the reagent has a built in equivalent of the HOBt reagent **135** that would generate the HOBt ester **184** upon nucleophilic attack. To assess the properties of this intermediate the model carboxylic acid **124** must be treated with EDCI **137** with no nucleophiles present (Figure 4.5).

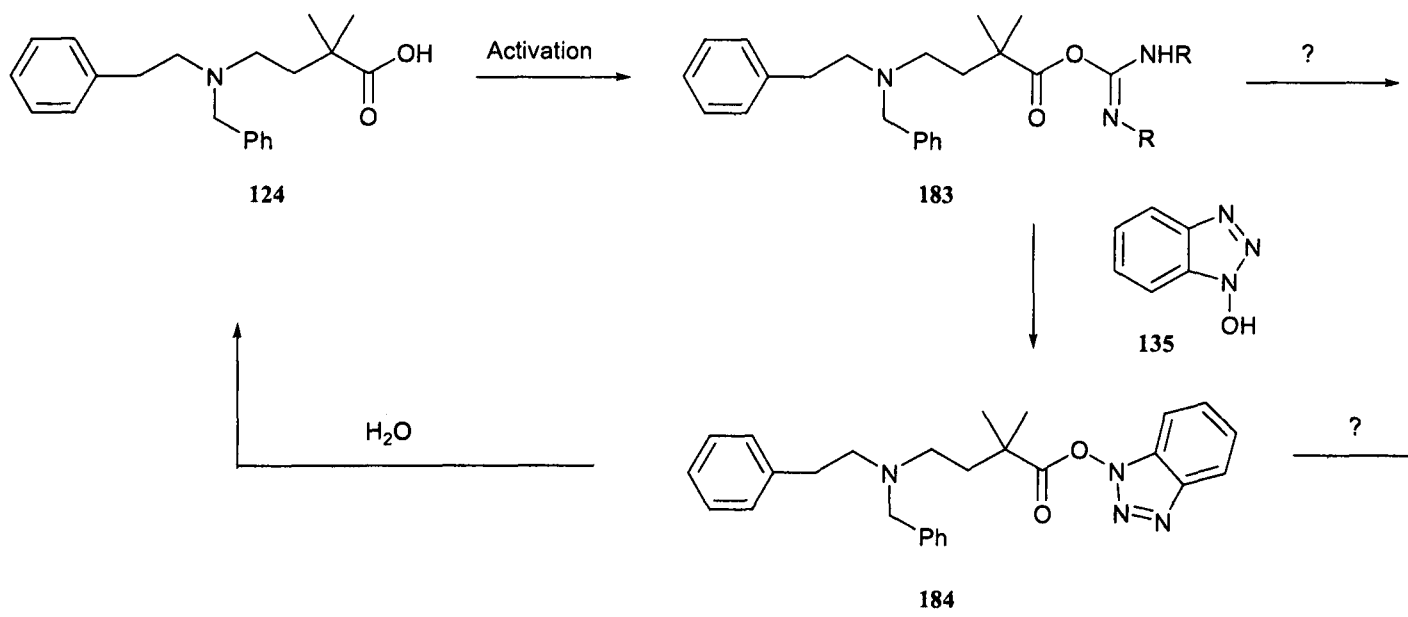
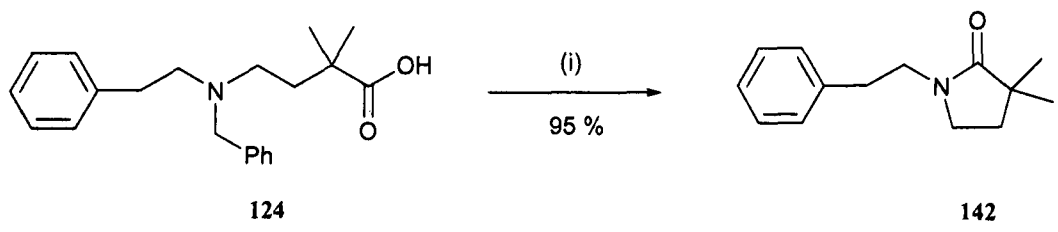


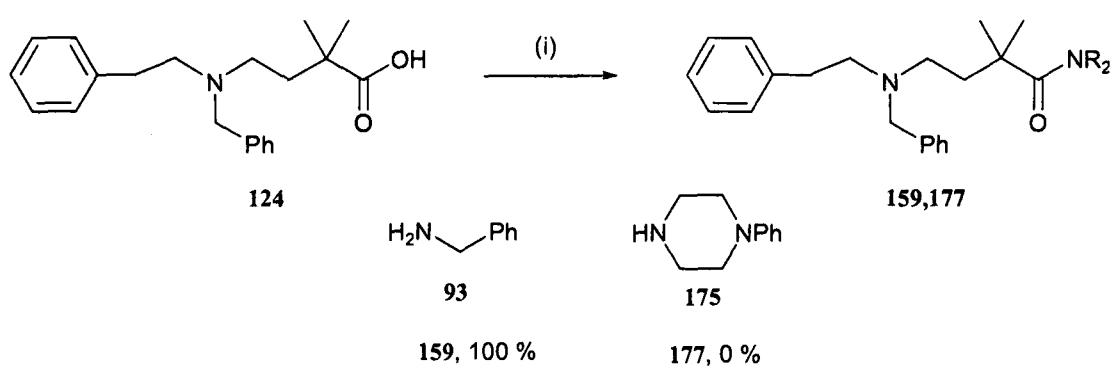
Figure 4.5: Intermediates in ester and amide coupling reaction

Thus, the carboxylic acid **124** was treated with EDCI to generate in complete conversion the known cyclization product lactam **142** after 2 hours reaction time. Lactam **142** was subsequently isolated in 95 % yield. Furthermore, no impurities were detected by analysis of the ^{1}H NMR spectra of the crude reaction product (Scheme 4.17).



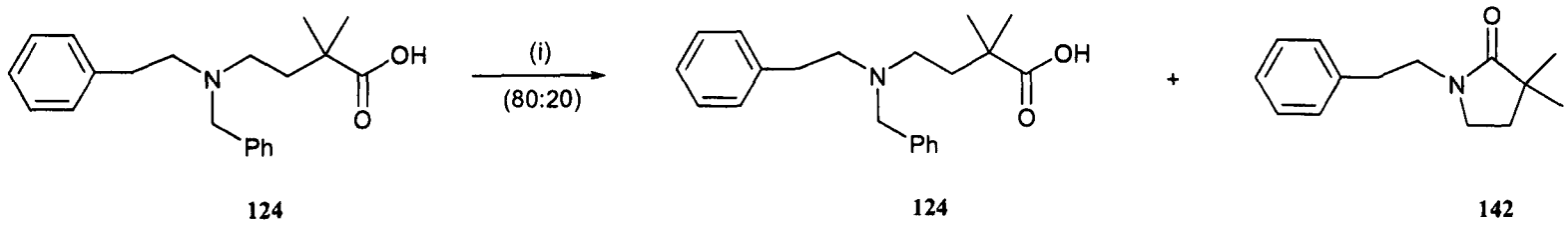
Scheme 4.17: *Reagents and conditions:* (i) EDCI **137**, DCM, r.t. 2 h.

Further investigations focused on the effect of competing external nucleophiles to suppress this unwanted side reaction. Thus, two transformations previously carried out successfully (Scheme 4.9 and 4.14) with EDCI/HOBt activation were repeated in the absence of HOBt **135**. Treatment of carboxylic acid **124** with EDCI, benzylamine **93** and DIPEA afforded the desired amide **159** in quantitative yield as before, but attempted coupling of *N*-phenyl piperazine **175** with 4 equivalents of amine afforded a complex mixture as revealed by investigation of the ^{1}H NMR spectrum of the crude reaction product. No trace was detected of the coupling product, amide **177**. These simple experiments confirm the usefulness of the HOBt ester activation in coupling with hindered and hence less reactive nucleophiles (Scheme 4.18).



Scheme 4.18: *Reagents and conditions:* (i) benzylamine **93** (2 eq.), EDCI (1.5 eq.), DIPEA (4 eq.), DCM, 16 h; (i) *N*-phenyl piperazine **175** (4 eq.), EDCI (1.5 eq.), DIPEA (4 eq.), DCM, 16 h.

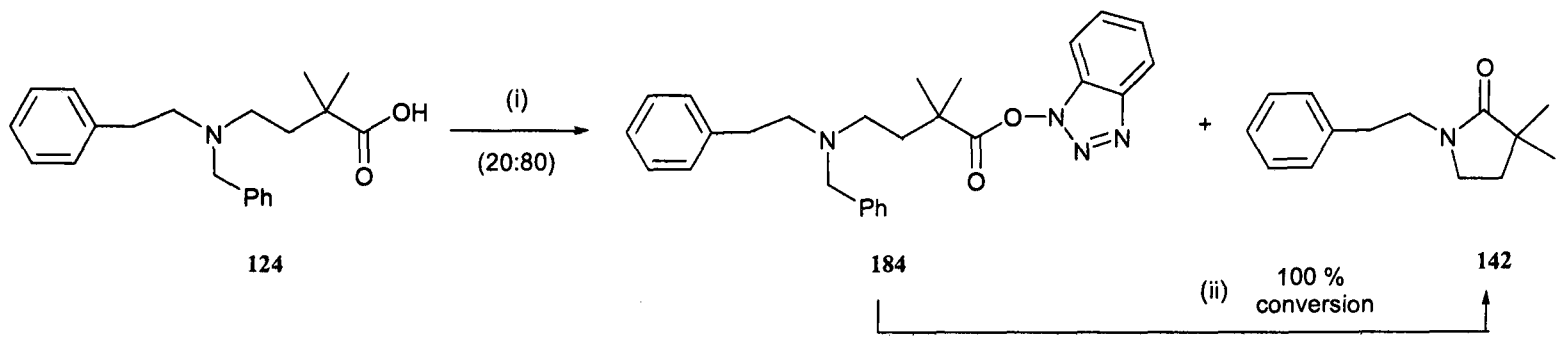
Having demonstrated that the activated *O*-acylisourea species **183** cyclizes spontaneously to the lactam **142** (Scheme 4.17) when exposed to EDCI **137** in the absence of a nucleophile, further investigations were directed at the stability and fate of the intermediate HOBt ester **184**. To this end, the HOBt ester was generated in the absence of other nucleophiles. Treatment of carboxylic acid **124** with EDCI **137** and HOBt **135** monohydrate afforded a (80:20) mixture of starting material **124** and lactam **142** after 6 days (Scheme 4.19).



Scheme 4.19: *Reagents and conditions:* (i) EDCI **137**, HOBt **135**, DCM, 16 h.

To suppress the assumed hydrolysis of the ester intermediate **184** the HOBt monohydrate was stirred over molecular sieves in DCM before addition of other reagents. This afforded a 80:20

mixture of lactam **142** and the assumed HOBt ester **184** after 6 days. No starting material **124** was observed in the crude reaction mixture in this case. The reaction mixture was stored *in vacuo* and the progress monitored by analysis of the ^{1}H NMR spectra of aliquots from the sample. After a further 6 days a mixture of approx. 90:10 lactam **142**:ester **184** was observed. After a further 8 days complete conversion to the lactam **142** was observed (Scheme 4.20).



Scheme 4.20: *Reagents and conditions:* (i) EDCI **137** (1.5), HOBt **135** (2 eq.), DCM, sieves, 6 days; (ii) *vacuo*, r.t. 14 days.

These experiments gave useful information on the stability of the activated intermediates formed from acid **124**. While exclusion of water from the reaction mixture results in 100 % conversion to the lactam **142**, this should not be a problem when these transformations are carried out on solid phase since large excesses of nucleophile can be used without complicating the purification protocol. Additionally, recovered starting material attached to polymer can easily be resubmitted to the same conditions to drive the reaction to completion if starting material is detected after the initial reaction. Understanding of the reactivity of these key intermediates should make adaptation of the coupling reaction to solid phase more straightforward.

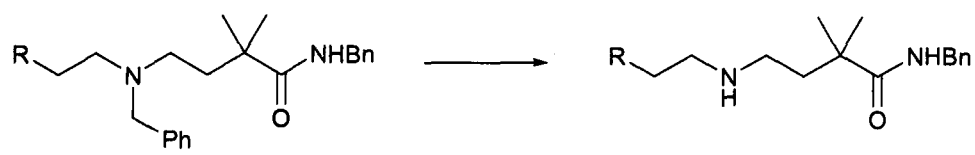
4.6 Debenzylation/cyclorelease protocol of model amides

4.6.1 Release of primary amines

Having prepared a range of amides from model systems **96** and **124**, further investigations were directed towards their susceptibility towards the debenzylation/cyclorelease protocol. To demonstrate this strategy for release of a simple primary amine and to investigate the

chemoselectivity of the CAN debenzylation protocol benzyl amide **159** was used as a model substrate.

A range of attempts to chemoselectively mono-*N*-debenzylate **159** with CAN were carried out using different concentrations, solvents and workup procedures with the isolated yields of the desired product ranging from 56 - 80 %. Treatment of **159** with 5 eq. of CAN with THF:H_2O (8:1) as solvent for 16 hours afforded 80 % of the desired mono-*N*-debenzylated product **185** and was found to be the optimal procedure as in the case of aryl and aliphatic alcohols as discussed previously. Investigation of the ^1H NMR spectrum of the crude reaction product confirmed selective mono-*N*-debenzylation of the tertiary amine functionality of **159** since the *N*-benzyl amide functionality was intact. This result is in accordance with the previously observed selectivity of this reaction as discussed in Section 2.1.2. As an alternative to the CAN strategy, an alternative debenzylation protocol developed by Leysen *et al.*[16] (Scheme 1.5, Section 1.5) utilizing α-chloroethyl chloroformate (ACE-Cl) was also assessed. Treatment of amide **154** with 4 equivalents of ACE-Cl under reflux in DCE for 16 hours followed by reflux in MeOH for 2 hours afforded the debenzylated product **186** in 59 % isolated yield after chromatography. This alternative debenzylation strategy may be used to deprotect the safety catch linker in the presence of products sensitive towards oxidation, thus allowing the choice of a deprotection strategy orthogonally tailored to be non-deleterious to the product to be released from the polymer (Scheme 4.21).



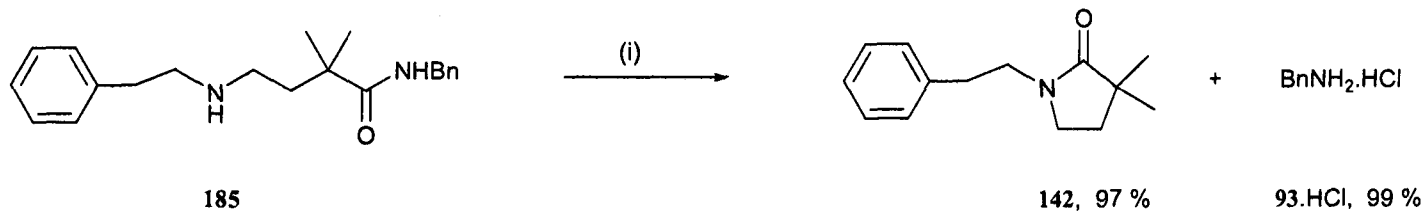
159, R = Ph
154, R = $MeC_6H_4CH_2CH_2$

(i) **185**, R =Ph, 80 %,
(ii) **186**, R = $MeC_6H_4CH_2CH_2$, 59%

Scheme 4.21: *Reagents and conditions:* (i) CAN (5 eq.), THF:H_2O (8:1), r.t. 16 h; (ii) ACE-Cl (4 eq.), DCE, Δ 16 h then MeOH, Δ 2 h.

Debenzylated amide **185** was found to be stable at room temperature with conditions subsequently sought to promote its cyclization. The amide **185** was therefore dissolved in toluene and heated at reflux, with t.l.c. monitoring of the reaction mixture indicating total

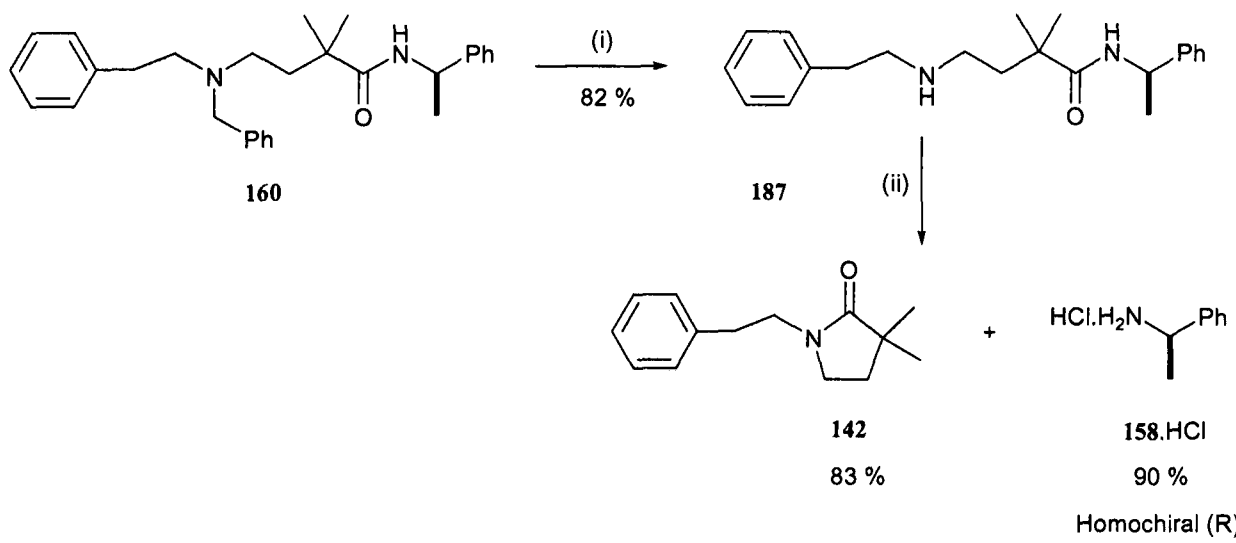
consumption of the starting material after 16 hours. Treatment of the crude reaction mixture with aqueous HCl and DCM followed by aqueous workup afforded the amine salt **93**.HCl in excellent yield (99 %). Following this work-up procedure the lactam **142** was retained in the organic layer and subsequently isolated in 97 % yield (Scheme 4.22).



185 **142**, 97 % **93**.HCl, 99 %

Scheme 4.22: *Reagents and conditions:* (i) MePh, Δ 16 h; (ii) 10 % HCl_{aq}.

Having identified optimal conditions for this transformation, an investigation to confirm if the absolute configuration of the attached (*R*)-α-methylbenzylamine **158** to the model system **124** would be conserved in the debenzylation/cyclorelease protocol was carried out. Thus, amide **160** was subjected to CAN debenzylation affording debenzylated secondary amine **187** in 82 % isolated yield after chromatography. The product **187** was heated at reflux in toluene for 16 hours. The released amine **158**.HCl and lactam **142** were isolated in 90 % and 83 % yield respectively (Scheme 4.23).



160 **187** **142** 83 % **158**.HCl 90 % Homochiral (R)

Scheme 4.23: *Reagents and conditions:* (i) CAN (5 eq.), THF:H_2O (8:1), r.t. 16 h; (ii) MePh, Δ 16 h.

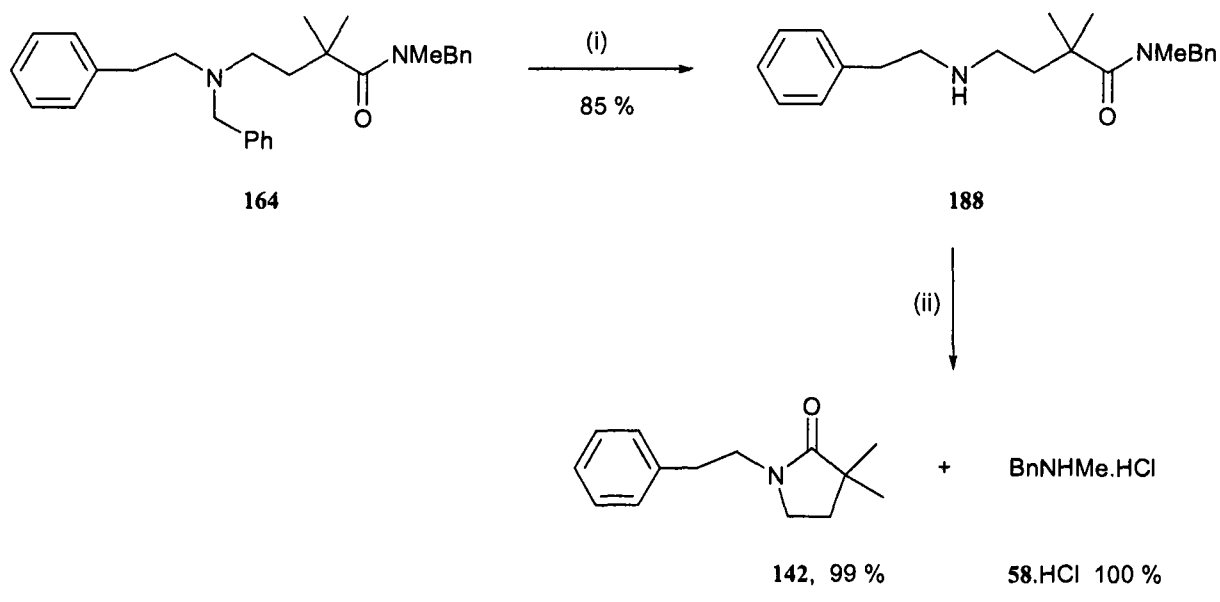
The specific rotation of the isolated amine sample **158**.HCl {$[\alpha]_D^{22}$ +2.6 (c=1.0, H_2O)}, was found to be identical to an authentic sample and consistent with the literature value {lit.[17] $[\alpha]_D^{22}$ +2.3 (c=2.9, H_2O)}. To further confirm the absolute configuration and e.e. of the sample an aliquot of the amine salt was converted to its free amine **158** and subjected to a ^1H NMR

investigation with (*S*)-*O*-acetylmandelic acid as a chiral shift reagent. The sample was found to consist of the *R* enantiomer in >95 % e.e. when compared with authentic samples of the (*R*)-**158** and (*S*)-**158** enantiomers.

Having identified the optimal conditions for the transformations described above and demonstrated the debenzylation/cyclorelease protocol for primary amines, attention was turned towards the repetition of this process with more complex systems.

4.6.2 Release of secondary amines

The chemoselective *N*-debenzylation of the tertiary amine functionality of **164** in the presence of a tertiary amide functionality was next investigated. Treatment of **164** with 5 equivalents of CAN resulted in chemoselective mono-*N*-debenzylation of the tertiary amine resulting in an 85 % isolated yield of mono-*N*-debenzylated product **188** after chromatography. Cyclization of **188** was subsequently promoted by heating in toluene, with gentle heating at 60 - 70°C overnight affording the amine salt **58**.HCl in quantitative yield. The amine salt isolated was indistinguishable from an authentic sample as assessed by analysis of the ^{1}H NMR spectrum. The other cyclization product, lactam **142** was isolated in 99 % yield (Scheme 4.24).

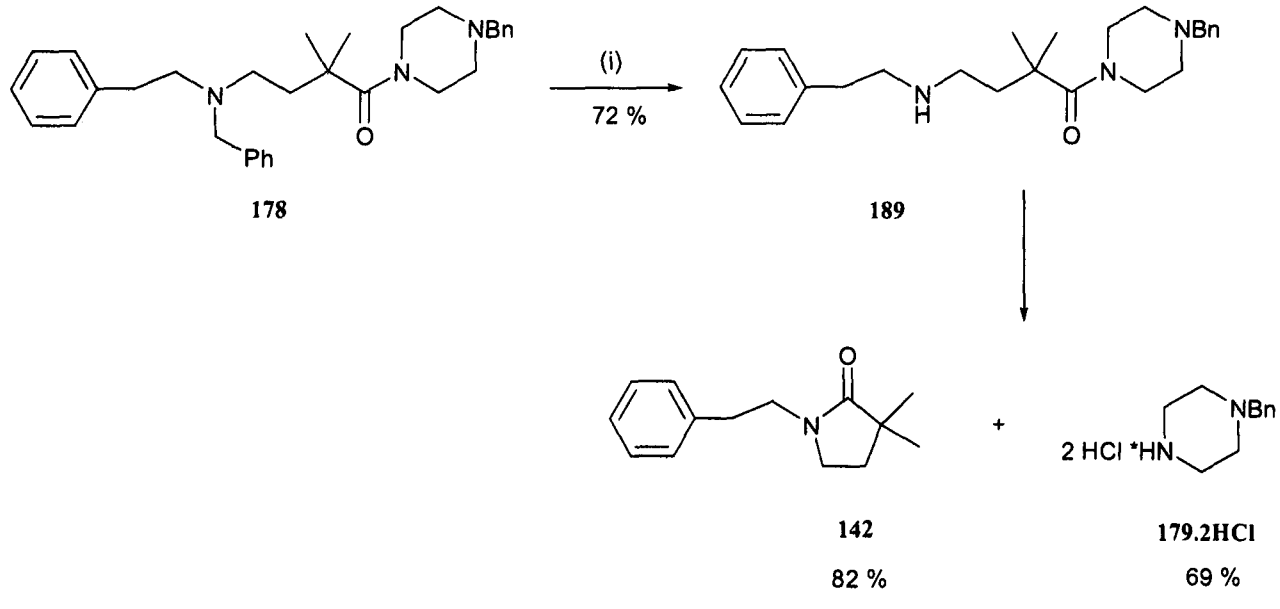


Scheme 4.24: *Reagents and conditions:* (i) CAN (5 eq.), THF:H_2O (8:1), r.t. 16 h; (ii) MePh, 70°C 16 h.

Having demonstrated the debenzylation/cyclorelease protocol for these simple derivatives of non-cyclic amines, attention was directed towards the derivatives of nitrogen containing heterocycles.

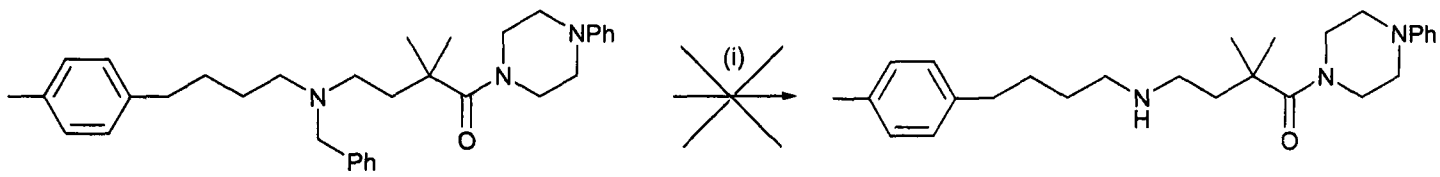
4.6.3 Release of heterocycles

To further assess the chemoselectivity of the CAN debenzylation protocol model compound **178** was subjected to CAN debenzylation. Treatment of **178** with 5 equivalents of CAN in THF:H_2O (8:1) for 16 hours afforded the debenzylated secondary amine derivative **189**, with analysis of the ^1H NMR spectrum of the crude reaction mixture revealing a total consumption of the starting material and a chemoselective *N*-debenzylation of the tertiary amine functionality. The cyclic *N*-benzyl functionality remained intact in this transformation as confirmed by the absence of the alternative debenzylation product piperazine derivative **174** isolated previously. The secondary amine **189** was found to cyclise on standing and due to the instability of the product, purification by chromatography was not readily achieved and only a small sample of the pure product was obtained, therefore the characterization data had to be obtained from the crude reaction mixture. Thus, a small sample was filtered through a plug of silica and refluxed in toluene to afford the cyclization products **142** and **179**.2HCl. The aqueous workup described previously gave amine hydrochloride **179**.2HCl and lactam **142** in 69 % and 82 % yields respectively. An authentic sample of the amine hydrochloride salt was prepared and was found to have identical spectroscopic properties as the reaction product (Scheme 4.25).



Scheme 4.25: *Reagents and conditions:* (i) CAN (5 eq.), THF:H_2O (8:1), r.t. 16 h; (ii) MePh, Δ 16 h.

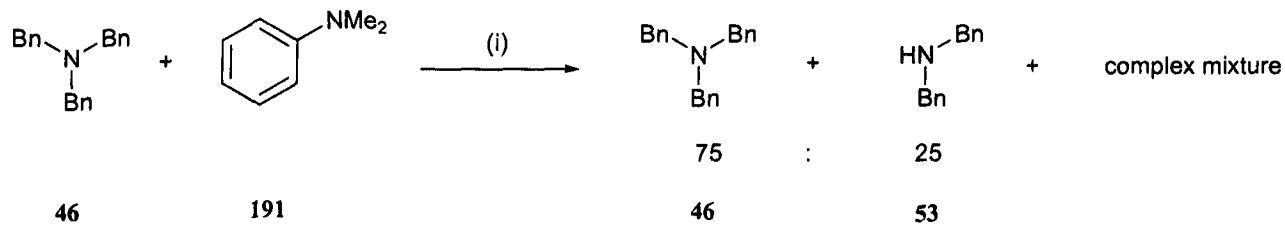
To develop a debenzylation/cyclorelease protocol for differentially derivatized piperazines a study was carried out with the *N*-phenyl piperazine derived amide **176** as a model substrate. Treatment of **176** with CAN afforded a complex mixture of products and no sign of benzaldehyde was detected by analysis of the ^{1}H NMR spectrum of the resulting crude reaction product, indicating that debenzylation to give **190** had not been successful (Scheme 4.26).



176 **190**

Scheme 4.26: *Reagents and conditions:* (i) CAN (5 eq.), THF:H_2O (8:1), r.t., 4 h.

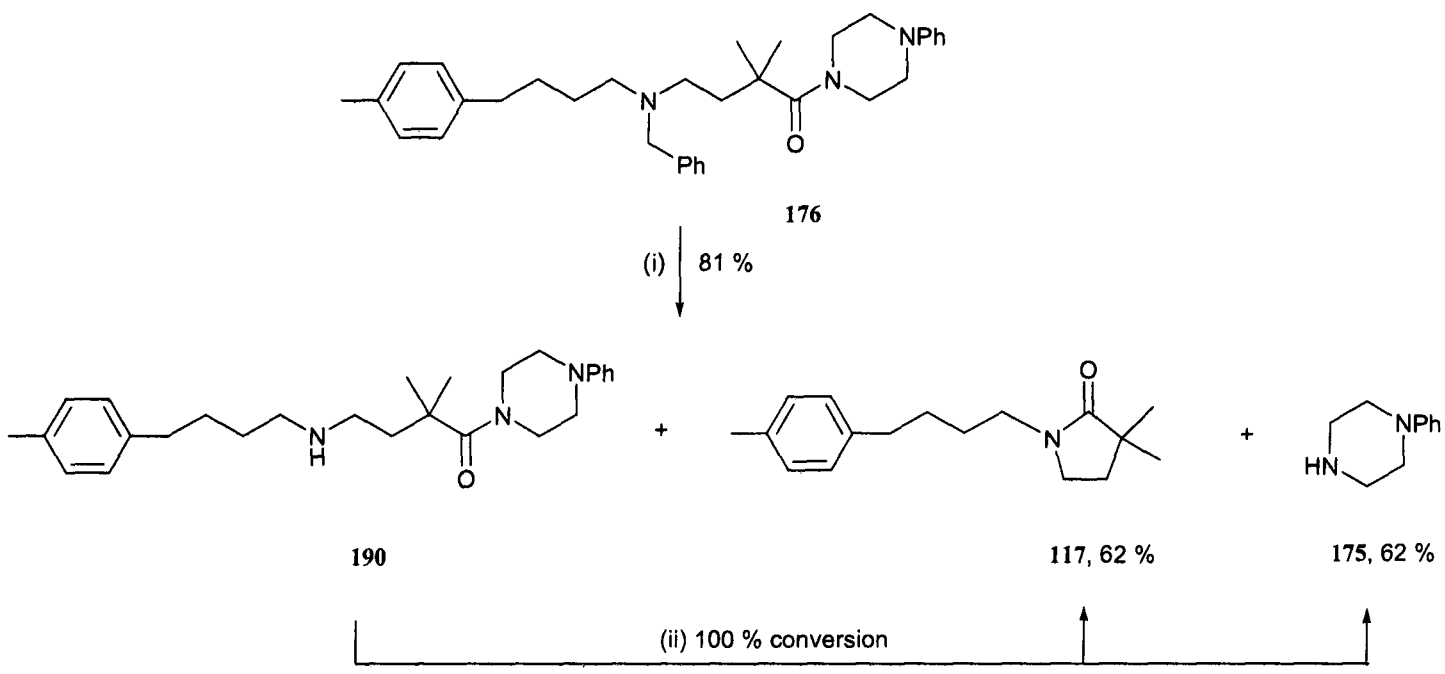
A further model reaction was undertaken to assess whether the anilinic nitrogen interferes with the desired mono-*N*-debenzylation. For this purpose, *N,N*-dimethylaniline **191** was subjected to the CAN debenzylation conditions in the presence of 1 equivalent of tribenzylamine **46**. Tribenzylamine **46** is known to undergo *N*-monodebenzylation under similar conditions (Scheme 2.1, Section 2.1.2). Treatment of **46** with 5 equivalents of CAN in the presence of *N,N*-dimethylaniline **191** afforded a 75:25 mixture of tribenzylamine **46** and dibenzylamine **53** respectively. However, *N,N*-dimethylaniline **191** was totally consumed in this model experiment and gave a complex mixture of unidentified products according to analysis of the ^{1}H NMR spectrum of the crude reaction mixture (Scheme 4.27).



Scheme 4.27: *Reagents and conditions:* (i) CAN (5 eq.), THF:H_2O (8:1), r.t. 16 h.

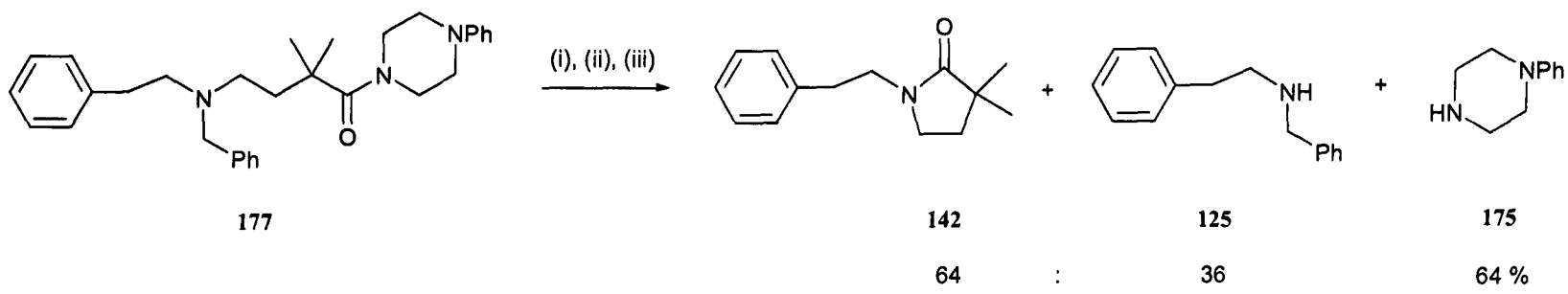
Attention next turned to assess whether amide **176** and the analogous substrate **177** would undergo chemoselective mono-*N*-debenzylation with the ACE-Cl protocol previously described. Treatment of **176** with ACE-Cl in refluxing DCE for 16 hours and subsequent reflux in MeOH afforded 80 % combined yield of a 88:12:12 mixture of the debenzylated product **190**, the desired lactam **117** and *N*-phenyl piperazine **175** respectively, indicating that

spontaneous cyclization takes place in the reaction. The mixture was subsequently refluxed in DCM to drive the cyclization to completion. To isolate the desired amine an aliquot of the fully cyclized mixture was partitioned between 10 % aqueous HCl to extract the released amine **175** and DCM. The lactam **117** was isolated from the mixture in 62 % yield and the amine salt was neutralized and repeatedly extracted into DCM to afford **175** in 62 % yield (Scheme 4.28).



Scheme 4.28: *Reagents and conditions:* (i) ACE-Cl (4 eq.), DCE, Δ 16 h then MeOH, Δ 2h. (ii) DCM, Δ 16 h.

The attempted ACE-Cl *N*-monodebenzylation of *N*-phenylethylamine derived substrate **177** was met with limited success. The *N*-phenyl piperazine derivative **177** was subjected to the conditions used earlier for the analogous model compound **176** and the reaction progress monitored by ^{1}H NMR analysis. To ensure complete conversion the starting material **177** was refluxed with 4 equivalents of ACE-Cl for 24 hours and with MeOH for another 24 hours. ^{1}H NMR spectroscopic analysis of the crude reaction product revealed the presence of the lactam **142** and an undesired component, *N*-benzyl-*N*-2-phenylethylamine **125**. To further identify the undesired component the cyclization was driven to completion and the desired *N*-phenyl piperazine **175** isolated from the resulting mixture with aqueous workup in 64 % yield. Evaporation of the organic solvent afforded a 64:36 mixture of the lactam **142** and previously prepared secondary amine **125** as its hydrochloride salt. The hydrochloride salt **125**.HCl was prepared independently to confirm the identity of the undesired component (Scheme 4.29).



177 142 : 125 175

64 : 36 64 %

Scheme 4.29: *Reagents and conditions:* (i) ACE-Cl (4 eq.), DCE, Δ 24 h; (ii) MeOH, Δ 24 h; (iii) MePh, Δ 16 h.

Despite inconsistent results ACE-Cl remains the debenzylation strategy of choice in the case of amines sensitive towards oxidative conditions.

4.7 Conclusions

Two solution phase model systems with alternative length of the spacer have been developed. The reactivity profile of the ester and amide coupling with a range of amines and alcohols has been evaluated and undesired side reactions identified. A simple attachment/release sequence has been demonstrated for alcohols and amines, utilizing two alternative debenzylation strategies. A study of the chemoselectivity of the CAN debenzylation has been undertaken and selectivities observed in previous investigations confirmed. The following chapter describes the development of an attachment, derivatisation and release sequence and subsequent synthesis of a small demonstrative pilot library.

References

[1] J. Jones, *Amino Acid and Peptide Synthesis*, Oxford University Press, 2000, p. 27.

[2] F.Z. Dörwald, *Organic Synthesis on Solid Phase*, Wiley-VCH, Chichester, 2002, p. 324 - 368.

[3] J.C. Sheehan, G.P. Hess, *J. Am. Chem. Soc.*, 1955, **77**, 1067

[4] G. Barany, R.B. Merrifield, "Solid Phase Peptide Synthesis" in *The Peptides Vol. 2, Analysis, Synthesis, Biology Vol. 2*, ed. E. Gross, J. Meienhofer, Academic Press, London 1980.

[5] W. König, R. Geiger, *Chem. Ber.*, 1970, **103**, 788.

[6] J.C. Sheehan, P.A. Cruickshank, G.L. Boshart, *J. Org. Chem.*, 1961, **26**, 2525.

[7] R. Knorr, A. Trzeciak, W. Bannwarth, D. Gillessen, *Tetrahedron Lett.*, 1989, **30**, 1927.

[8] For example see: K.H. Bleicher, J.R. Wareing, *Tetrahedron Lett.*, 1998, **39**, 4591.

[9] For example see: E.E. Baird, P.B. Dervan, *J. Am. Chem. Soc.*, 1996, **118**, 6141.

[10] R. Shyam Prasad, D.Phil. thesis, University of Oxford, 2002

[11] S.D. Bull, S.G. Davies, G. Fenton, A. Mulvaney, R.S. Prasad, A.D. Smith, *J. Chem. Soc., Perkin Trans. 1.*, 2000, 3765; S.D. Bull, S.G. Davies, G. Fenton, A.W. Mulvaney, R.S. Prasad, A.D. Smith, *Chem. Commun.*, 2000, 337.

[12] B. Ho, A.M. Crider, J.P. Stables, *Eur. J. Med. Chem.*, 2001, **36**, 265.

[13] Kindly supplied by Mr. Jim Thomson.

[14] J.M. Salvino, B. Gerard, H.F. Ye, B. Sauvagnat, R.E. Dolle, *J. Comb. Chem.*, 2003, **5**, 260.

[15] D.A. Horton, G.T. Bourne, M.L. Smythe, *Chem. Rev.*, 2003, **103**, 893.

[16] P. Conti, D. Demont, J. Cals, H.C.J. Ottenheijm, D. Leysen, *Tetrahedron Lett.*, 1997, **38**, 2915.

[17] B. Krzyzanowska, W.J. Stec, *Synthesis*, 1982, **4**, 270.

5 Chapter V: Solid phase studies

5.1 Introduction

Having successfully demonstrated the debenzylation/cyclorelease protocol for alcohols and amines in solution, further investigations were aimed at the development of a simple and reliable couple/derivatize/cleave protocol for application in the solid phase synthesis of a small library of compounds utilizing the safety catch linker. The sequence should fulfill the following three criteria before adaptation to solid phase:

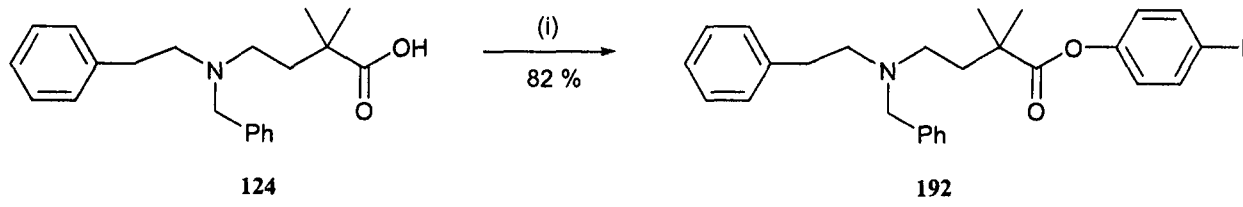
- The substrate needs to be easily coupled to the polymer in high yield with complete conversion for easy access of multigram quantities of the product.
- The chemical transformations used in the derivatisation need to be highly reliable and proceed to complete conversion.
- The derived product attached should be tolerant towards the debenzylation strategy used to activate the linker system and easily isolated in good yield.

Transfer of such a reaction sequence to the solid phase although proven to be successful in solution is not straightforward. Before assessing the generality of reactions on solid phase, a model reaction needs to be driven to completion, as incomplete reaction conversion in any derivatisation step would lead to cleavage of mixtures from the polymer. Monitoring of reaction conversion is best achieved by cleavage of the intermediate from the polymeric support since the only alternatives involve monitoring by mass balance and/or by FTIR, neither of which methods are quantitative or accurate. In this chapter attempted derivatisations of solution phase model compounds are discussed and subsequent transfer to the solid phase.

5.2 Attachment,derivatization and release of alcohols

5.2.1 Solution phase model studies

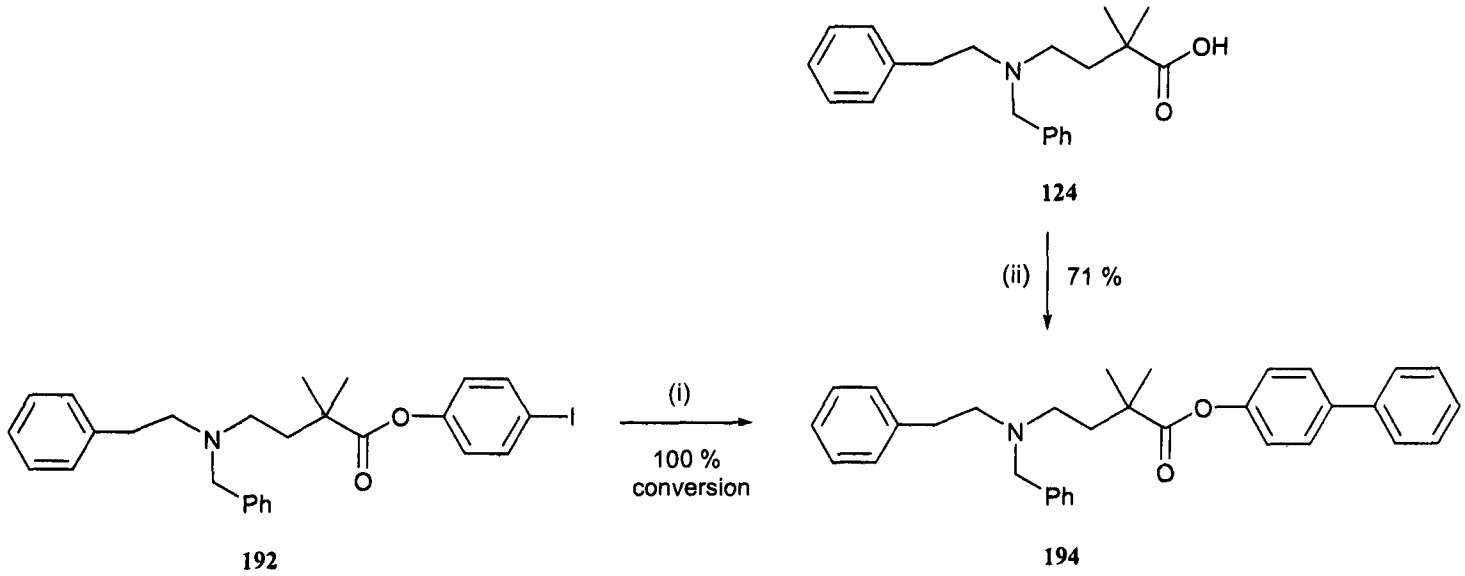
Initial studies towards synthesis on the solid phase focussed on substrates attached *via* an ester linkage, with the Suzuki coupling of *p*-iodophenol chosen as a representative reaction (Scheme 2.9, Section 2.4.2). Studies then commenced by reexamining an analogous model system **124**, aimed at the optimization of this process before adaptation to the solid phase. Hence, the analogous *p*-iodophenyl ester was prepared by treatment of **124** with excess *p*-iodophenol **79** to afford the product **192** on 2 g scale in 82 % isolated yield after chromatography (Scheme 5.1).



124 **192**

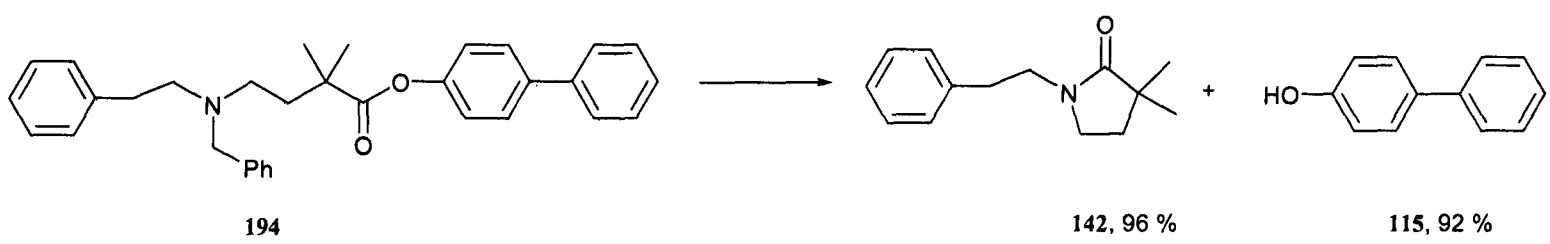
Scheme 5.1: *Reagents and conditions:* (i) *p*-iodophenol **79**, EDCI, HOBt, DIPEA, DCM r.t. 16 h.

The optimal conditions for the Suzuki coupling of *p*-iodophenyl ester **192** with phenylboronic acid **193** as a model substrate were then sought. Treatment of **192** with phenylboronic acid **193** and portionwise addition (20 %) of the palladium catalyst ($Pd_2(dba)_3$) gave the desired biaryl ester product **194** with complete conversion. Isolation of the product was hampered by contamination from the palladium ligand, dibenzylideneacetone. The two components were inseparable by chromatography and no pure product was isolated from the transformation. To confirm the identity of the product, an authentic sample of the product ester **194** was conveniently prepared by treatment of carboxylic acid **124** with excess 4-phenylphenol **115** under standard coupling conditions and isolated in 71 % yield after chromatography (Scheme 5.2).



Scheme 5.2: *Reagents and conditions:* (i) phenylboronic acid **193** (2 eq.), $Pd_2(dba)_3$ (0.2 eq.), K_2CO_3 (2.5 eq.), DMF, r.t. 24 h; (ii) 4-phenylphenol **115**, EDCI, HOBt, DIPEA, DCM r.t. 16 h.

To complete the synthetic sequence in solution, **194** was subjected to CAN debenzylation. Treatment of **194** with 5 equivalents of CAN for 16 hours in THF:H_2O (8:1) afforded a 50:50 mixture of the lactam **142** and 4-phenylphenol **115** giving **142** and **115** in 96 % and 92 % yield respectively after chromatography (Scheme 5.3).



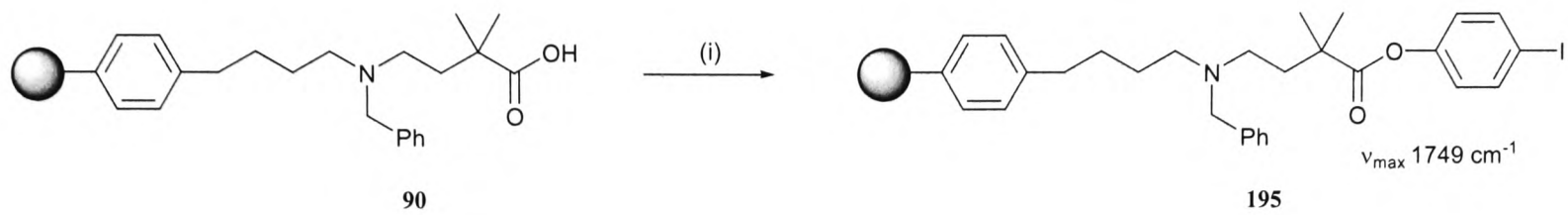
Scheme 5.3: *Reagents and conditions:* (i) CAN (5 eq.), THF:H_2O (8:1), r.t. 16 h.

Having successfully identified the optimal conditions for this Suzuki coupling and cyclorelease in solution attention was focussed on the solid phase and subsequent synthesis of a demonstrative library.

5.2.2 Solid phase model studies

In order to transfer this protocol to a solid phase system the polymer bound Suzuki substrate *p*-iodophenyl ester **195** was prepared. Carboxylic acid **90** was activated with DIC/HOBt and treated with a large excess of *p*-iodophenol **79** (10 eq.) to ensure complete conversion to afford the desired *p*-iodophenyl ester resin **195**. IR investigation of the carbonyl region of the product resin indicated complete consumption of the starting material with the observed IR stretch (ν_{max}/cm^{-1} 1749) analogous to the observed value from the solution phase counterpart **194**

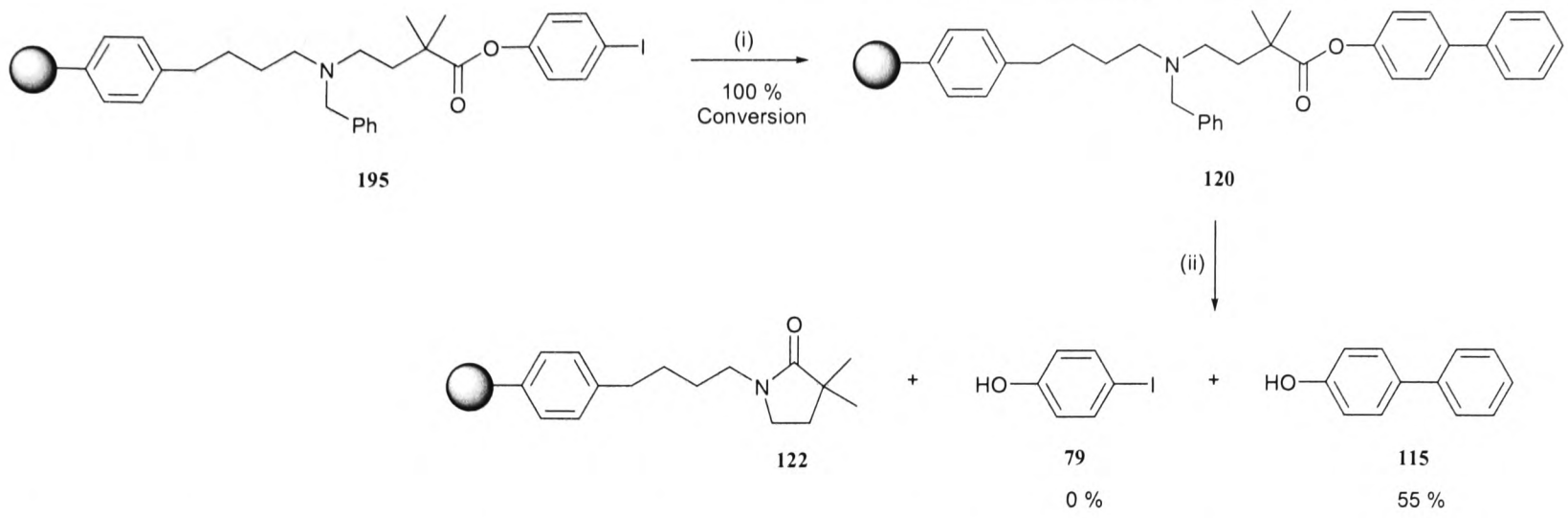
(ν_{max}/cm^{-1} 1752). The dry mass of the resin recovered from this transformation was also consistent with the expected mass calculated for a maximum theoretical loading of the product **195** and the loading determination of the polymer supported carboxylic acid **90** (1.73 mmol/g, Scheme 3.23, Section 3.3.4) (Scheme 5.4).



90 **195**

Scheme 5.4: *Reagents and conditions:* (i) *p*-iodophenol **79** (10 eq.), DIC (3 eq.), HOBt (4 eq.), DIPEA (8 eq.), DCM, r.t. 16 h.

With multigram quantities of resin **195** prepared, attention turned towards the Suzuki coupling of the resin bound substrate. Thus, *p*-iodophenyl ester resin **195** was subjected to Pd mediated coupling with phenylboronic acid **193** utilizing excess reagents at room temperature. Neither IR investigation or mass balance could be used to obtain information on the conversion to the known biaryl resin **120** (Scheme 3.22, Section 3.3.4) due to the similar properties of the substrate **195** and product **120**. The product resin was therefore debenzylated with CAN and the cyclization facilitated with stirring in a NEt_3:DCM mixture (Scheme 3.20, Section 3.3.3). Analysis of the cleavage product mixture revealed incomplete conversion of the *p*-iodophenol **79** to the corresponding 4-phenylphenol **115**, indicating slower reaction rate at room temperature on the polymer supported system **195** than the analogous solution phase counterpart **192**. However, complete conversion was observed in the Suzuki transformation upon heating of the reaction at 70°C and portionwise addition of the catalyst over 48 hours. Debenzylation of **120** with 5 eq. of CAN and subsequent cyclization afforded the Suzuki product 4-phenylphenol **115** in 55 % yield. No starting material, *p*-iodophenol **79** was detected in the isolated product, however, IR investigation of the residual resin revealed a trace of ester (ν_{max}/cm^{-1} 1749) along with the expected polymer supported lactam **122** (ν_{max}/cm^{-1} 1682) indicating incomplete conversion in the debenzylation and/or cyclization (Scheme 5.5).



Scheme 5.5: *Reagents and conditions:* (i) phenylboronic acid **193** (5 eq.), $Pd_2(dba)_3$ (0.2 eq.), K_2CO_3 (5 eq.), DMF, 70°C, 48 h; (ii) CAN (5 eq.), THF:H_2O (8:1), r.t. 16 h.

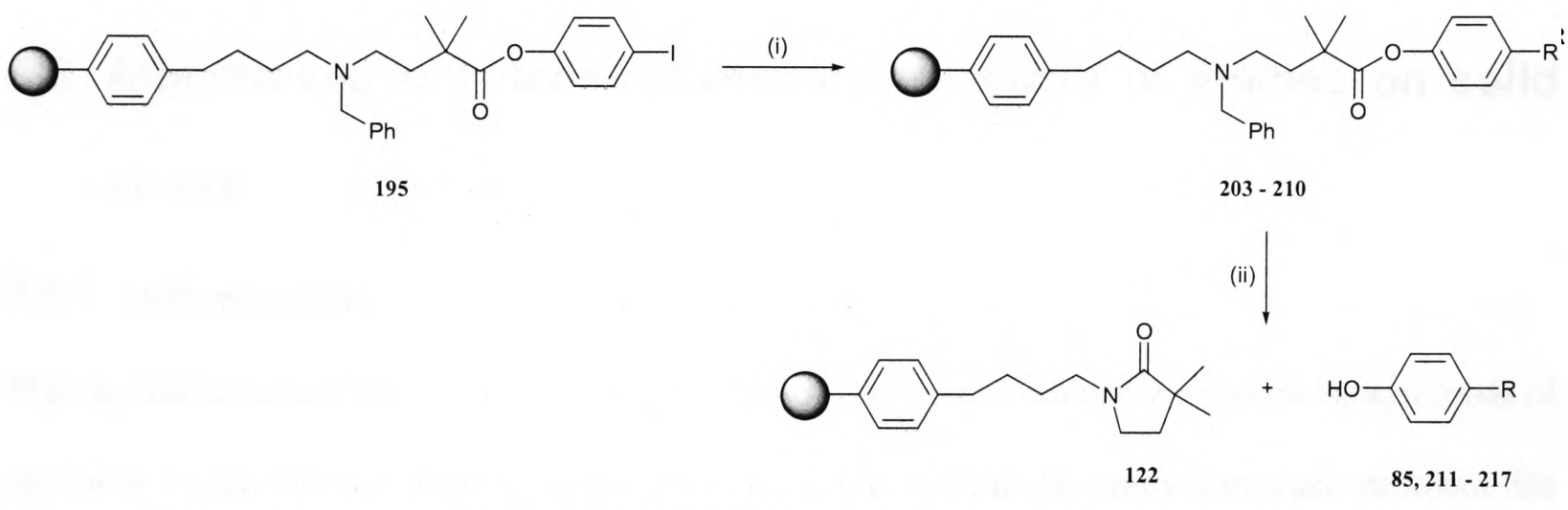
Following this successful transformation, attention then turned to the preparation of a small library of Suzuki coupling products to assess the generality of these transformations on solid phase.

5.2.3 Parallel synthesis of a demonstrative library

A set of boronic acids **83, 196 - 202** and *p*-iodophenyl ester resin **195** were subjected to the optimised reaction conditions for the Suzuki coupling of the chosen model substrates described previously. The substrate resin **195** was split into eight portions and parallel synthesis of polymer supported Suzuki products **203 - 210** was undertaken using a Carousel reaction station. The chosen set consisted of a diverse range of boronic acids (Scheme 5.6, Table 5.1) of which products were anticipated to be tolerant towards oxidative debenzylation with CAN and subsequent cyclorelease from the safety catch linker.

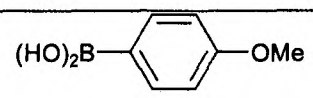
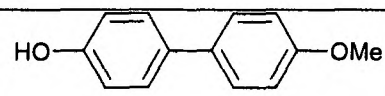
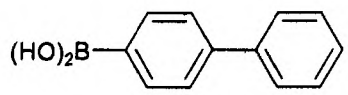
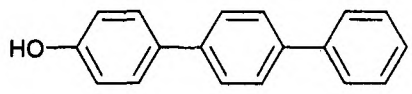
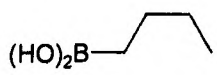
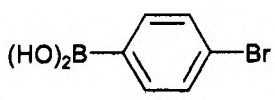
Table 5.1 summarises the results of the library synthesis. The yields of the synthesised library components **85** and **211 - 217** ranged from 0 - 79 % and HPLC purities, detected at 254 nm, ranged from 59 - 92 % after purification. ^{1}H NMR analysis of the product **214** from entry #5 after cleavage revealed an approximately 20:80 mixture of *p*-iodophenol **79** and the desired product **214** respectively in the cleavage mixture. This result presumably reflects the slower reaction rate due to steric hindrance in the boronic acid substrate **199**. The products in entries #1, 2 and 5 have been evaluated as ligands for the β-estrogen receptor in an analogous library

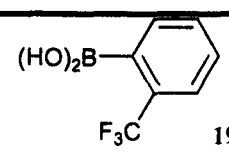
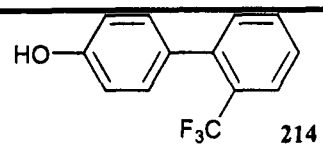
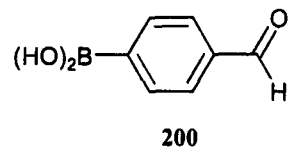
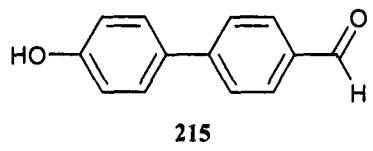
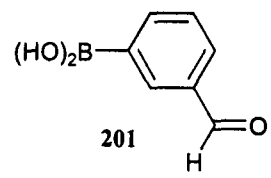
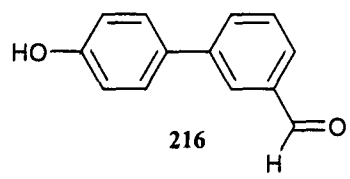
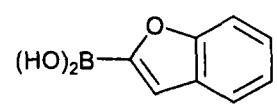
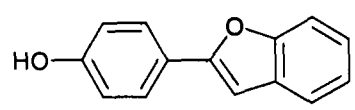
synthesis of 4-hydroxy biphenyls.[1] Disappointingly, no products were detected from entries #3 and 4 with the cleavage reaction yielding only a mixture of starting material **79** and unidentified impurities. The formyl biphenyls **215**[2] and **216** were isolated in good yields and high purity by ^{1}H NMR analysis and HPLC (purity 90 - 91 %). Synthesis of benzofuran derivative **217**[3] (entry #8) yielded an approximately 86:14 mixture of product and *p*-iodophenol **79** according to ^{1}H NMR spectroscopic analysis. In all cases, investigations of the IR spectra of the resulting resins revealed the presence of an ester functionality indicating incomplete conversion to the polymer supported lactam **122** either due to incomplete debenzylation or cyclization (Scheme 5.6, Table 5.1).



Scheme 5.6: *Reagents and conditions:* (i) $(HO)_2BR$ **85, 196 - 203** (5 eq.), $Pd_2(dba)_3$ (0.2 eq.), K_2CO_3 (5 eq.), DMF, 70°C, 48 h; (ii) CAN (5 eq.), THF:H_2O (8:1), r.t. 16 h.

Table 5.1: Results from library synthesis

#	Substrate	Product	Yield (%)	HPLC (%)	MW	LRMS (M-H)
1	 **83**	 **85**	43	89	200	199
2	 **196**	 **211**	51	92	246	245
3	 **197**	**212** not detected				
4	 **198**	**213** not detected				

5	 199	 214	74	59	238	237
6	 200	 215	79	90	198	197
7	 201	 216	74	91	198	197
8	 202	 217	61	86	210	209

5.3 Attachment and debenzylation/cyclorelease of amines on solid phase

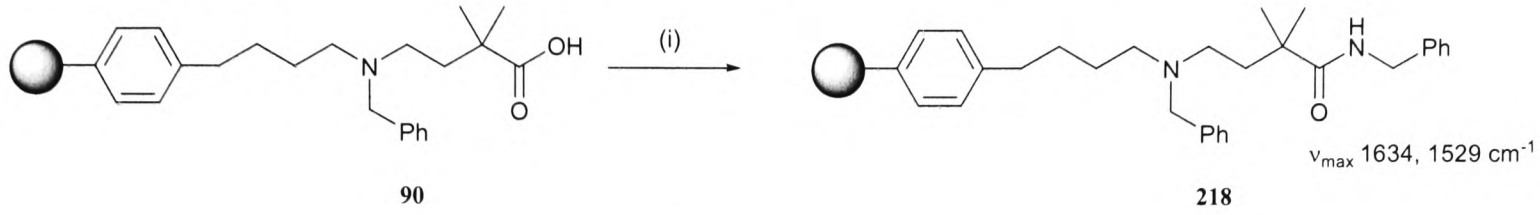
5.3.1 Introduction

Having demonstrated the successful application of the linker system for solid phase synthesis of alcohols focus turned towards demonstration of the debenzylation/cyclorelease protocol for amines on solid phase. Prior to investigations towards derivatisation and subsequent library syntheses, key transformations in this area need to be adapted to the solid phase and demonstrated with model experiments. Initial studies were aimed at the amide coupling reaction of both secondary and primary amines to the polymer supported carboxylic acid **90**.

5.3.2 Attachment of primary amines

As a starting point in this investigation attachment of benzylamine **93** to polymer supported carboxylic acid **90** was identified as a suitable transformation. Thus, carboxylic acid **90** was activated with DIC/HOBt in DCM and treated with excess benzylamine **93** (6 equivalents) to ensure complete conversion to afford the polymer supported *N*-benzylamide **218** after 16 hours. The mass recovered was in accordance with the calculated maximum theoretical loading and IR investigations revealed the characteristic frequencies for an amide bond in the carbonyl region

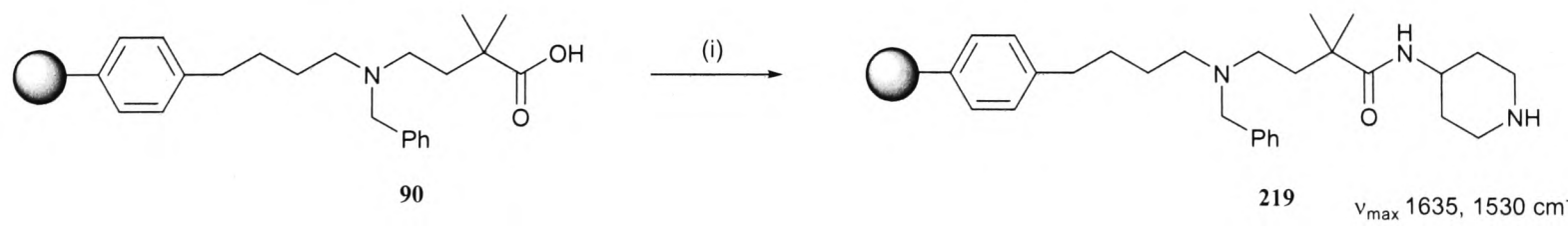
(ν_{max}/cm^{-1} 1634, 1529) similar to the solution phase analog **154** (ν_{max}/cm^{-1} 1643, 1529). No trace of the starting carboxylic acid resin **90** was detected in the IR investigation, further confirming complete conversion to the desired product **218** (Scheme 5.6).



90 218

Scheme 5.6: *Reagents and conditions:* (i) benzylamine **93** (6 eq.), DIC (3 eq.), HOBt (3 eq.), DIPEA (6 eq.), DCM, 16 h.

The attachment of the primary amino group of the bifunctional 4-amino piperidine **180** was also investigated. The mass recovered from this transformation was somewhat higher than the mass calculated from the maximum theoretical loading, indicating unwanted impurities may have been trapped within the polymer matrix. No starting carboxylic acid **90** with C=O stretch (ν_{max}/cm^{-1} 1713) was detected in the IR spectrum of the product resin **219**. The presence of a strong N-H stretch (ν_{max}/cm^{-1} 3432) indicated that the substrate is bound to the resin *via* the primary amine functionality as an amide (ν_{max}/cm^{-1} 1635, 1530) and the selective primary amine coupling over secondary had been achieved, consistent with the selectivity observed in the analogous solution phase study (Scheme 5.7).



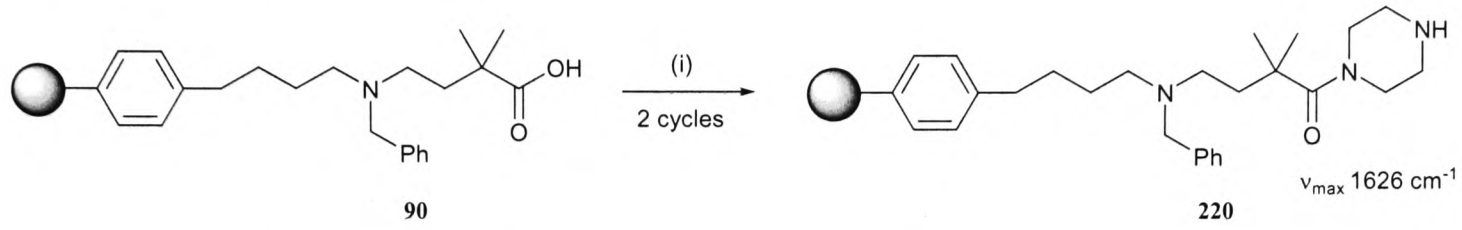
90 219

Scheme 5.7: *Reagents and conditions:* (i) 4-amino piperidine **180** (6 eq.), EDCI (4 eq.), HOBt (4 eq.), DIPEA (6 eq.), DCM, 16 h.

5.3.3 Attachment of secondary amines

Initial efforts to couple secondary amines to the polymer supported carboxylic acid **90** utilized piperazine **172** and *N*-phenyl piperazine **175**. Treatment of **90** with 8 equivalents of piperazine **172** employing only TBTU for activation resulted in a mixture of the starting carboxylic acid **90** (ν_{max}/cm^{-1} 1713), lactam **122** (ν_{max}/cm^{-1} 1682) and piperazine derived amide **220** (ν_{max}/cm^{-1} 1626) judging from analysis of the IR spectrum of the product resin. Thus, to suppress the

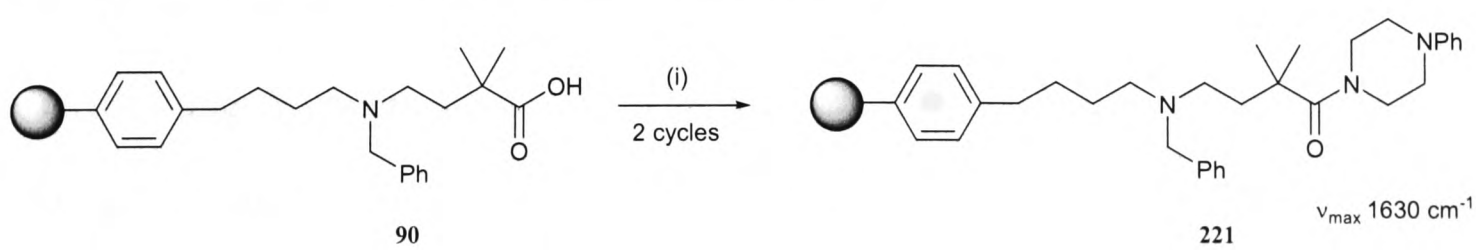
undesireable cyclization the transformation was performed with excess of HOBt (4.0 eq.) and 10 equivalents of amine **172**, employing TBTU for activation. IR investigation of the resulting resin indicated the presence of the product amide **220** and starting material **90**. The resin was subsequently resubjected to the same conditions to afford the desired product **220**, with the mass recovered from the overall process in accord with the calculated maximum theoretical loading (Scheme 5.8).



90 220

Scheme 5.8: *Reagents and conditions:* (i) piperazine **172** (10 eq.), TBTU (2 eq.), HOBt (4 eq.), DIPEA (10 eq.), DCM, 16 h.

The coupling of *N*-phenyl piperazine **175** to carboxylic acid **90** in an analogous transformation using 10 equivalents of amine employing TBTU/HOBt (2 equivalents of each reagent) for activation resulted in significant cyclization to the lactam **122**, although the cyclization could be suppressed by excess HOBt and amine **175**. Treatment of carboxylic acid **90** with 25 equivalents of *N*-phenyl piperazine **175** and 4 equivalents of HOBt employing TBTU activation afforded the desired amide **221** (ν_{max}/cm^{-1} 1630) without cyclization to the polymer supported lactam **122**, as assessed by analysis of the IR spectrum of the resulting resin. However, a trace of the starting material **90** was detected and the resin was subsequently resubjected to the same conditions to drive the reaction to completion. The mass recovery was in accordance with the mass calculated from the maximum theoretical loading and no trace of starting material **90** could be detected in the final product **221** (Scheme 5.9).

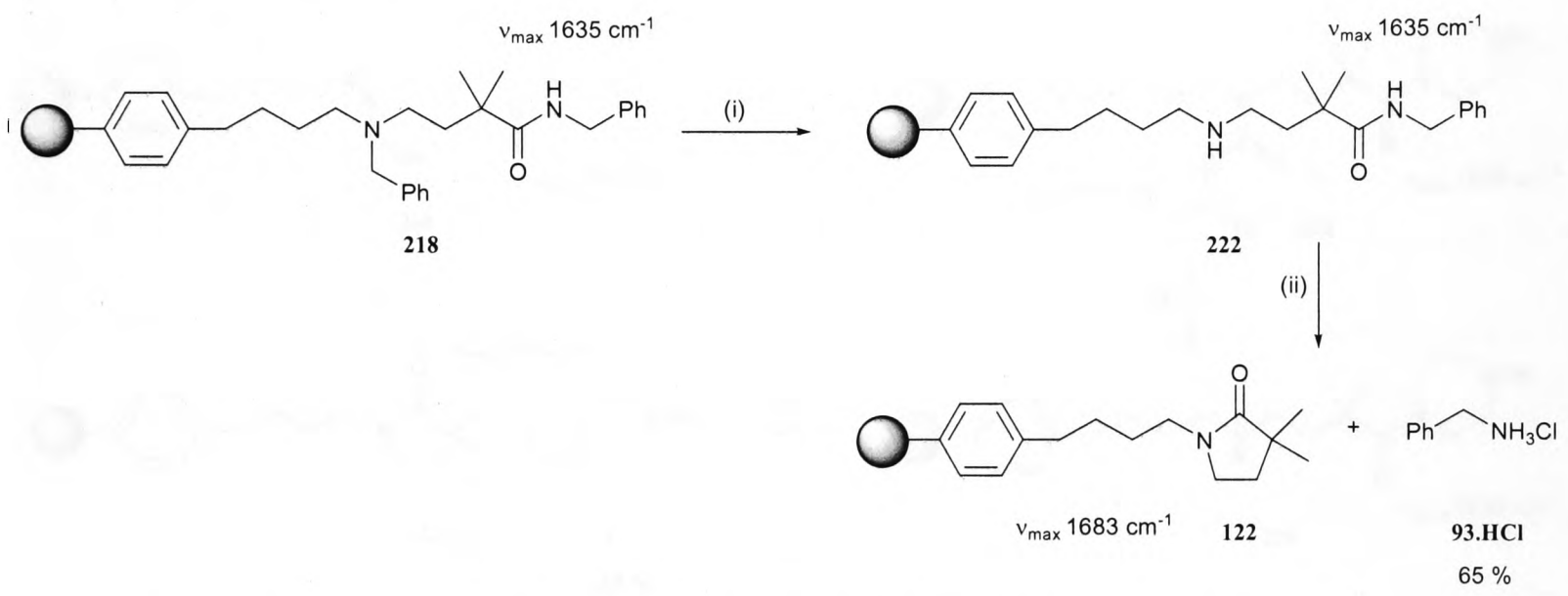


90 221

Scheme 5.9: *Reagents and conditions:* (i) *N*-phenyl piperazine **175** (25 eq.), DIC (4 eq.), HOBt (4 eq.), DIPEA (25 eq.), DCM, 16 h.

5.3.4 Primary amine release, debenzylation/cyclorelease protocol

To demonstrate the debenzylation/cyclorelease protocol **218** was treated with CAN to afford amide **222** (ν_{max}/cm^{-1} 1635, 1529) which was subsequently heated in toluene for 48 hours to promote the cyclization. This treatment resulted in complete conversion to the lactam **122** (ν_{max}/cm^{-1} 1683) judging by IR analysis of the resulting resin. No trace of amide **218** or **222** was detected (ν_{max}/cm^{-1} 1635) after the cyclization indicating complete conversion in both the debenzylation and cyclization steps. The released amine was converted to its hydrochloride salt **93.HCl** and isolated in 65 % yield based on the theoretical loading of **218** and the loading determination of carboxylic acid **90** (Scheme 5.10).



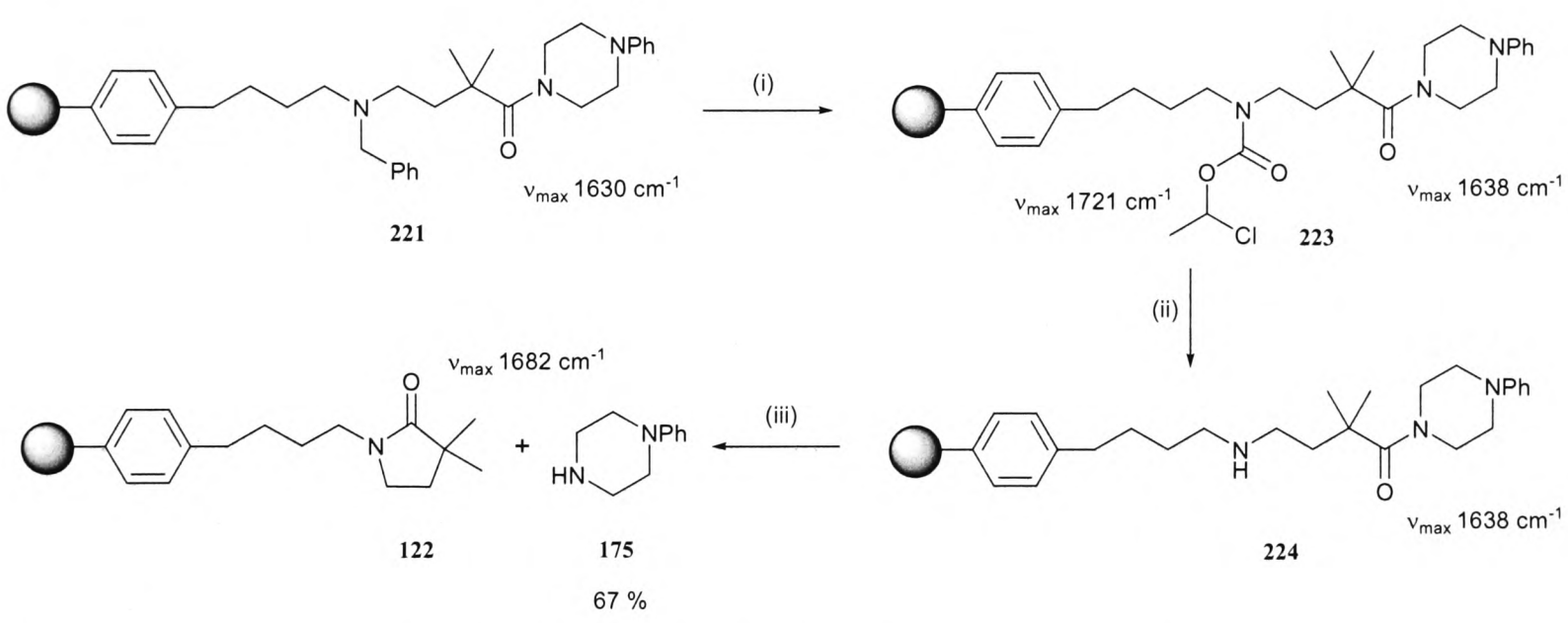
Scheme 5.10: *Reagents and conditions:* (i) CAN (5 eq.), THF:H_2O (8:1), r.t. 16 h; (ii) Δ 48 h.

These successful coupling and release transformations for the release of primary amine **93.HCl** confirm the utility of adopting solution phase model studies prior to adaptation to solid phase.

5.3.5 Secondary amine release, debenzylation/cyclorelease protocol

To demonstrate the debenzylation/cyclorelease protocol for a resin bound secondary amine the more challenging *N*-phenyl piperazine **175** was chosen for study. The sensitivity of this substrate to oxidative debenzylation precludes the use of CAN, so the ACE-Cl debenzylation protocol[4] described previously (Scheme 4.29, Section 4.6.3) was explored as a route to release 175 from the safety catch linker. Thus, the resin **221** was treated with 4 eq. of ACE-Cl in DCE at reflux. The IR spectrum of the resulting resin revealed a strong signal in the carbonyl region

(ν_{max}/cm^{-1} 1721) consistent with carbamate **223** which was refluxed in MeOH for 3 hours. The IR spectrum of this resin showed only a trace of the carbamate absorption and the intact amide bond (ν_{max}/cm^{-1} 1638) of **224**. Subsequent reflux in toluene for 16 hours liberated the amine **175** into solution in 67 % yield. Disappointingly, the resulting product was contaminated with an unidentified component consisting of 20 -30 % of the released sample as assessed from the ^1H NMR spectrum. IR investigation of the residual resin revealed the presence of amide and incomplete conversion to lactam **122** (ν_{max}/cm^{-1} 1682), although further reflux in toluene did not yield any more amine into solution indicating an incomplete debenzylation step (Scheme 5.11).



Scheme 5.11: *Reagents and conditions:* (i) ACE-Cl (4 eq.), DCE, Δ 16 h; (ii) MeOH, Δ, 16 h; (iii) toluene, Δ 16 h.

This transformation demonstrates the debenzylation/cyclorelease protocol to afford secondary amines attached to the safety catch linker into solution. ACE-Cl debenzylation has been found to be problematic due to incomplete conversions and impure product upon release, however this transformation can be used in the case of products sensitive towards oxidation as in the case of *N*-phenyl piperazine **175**.

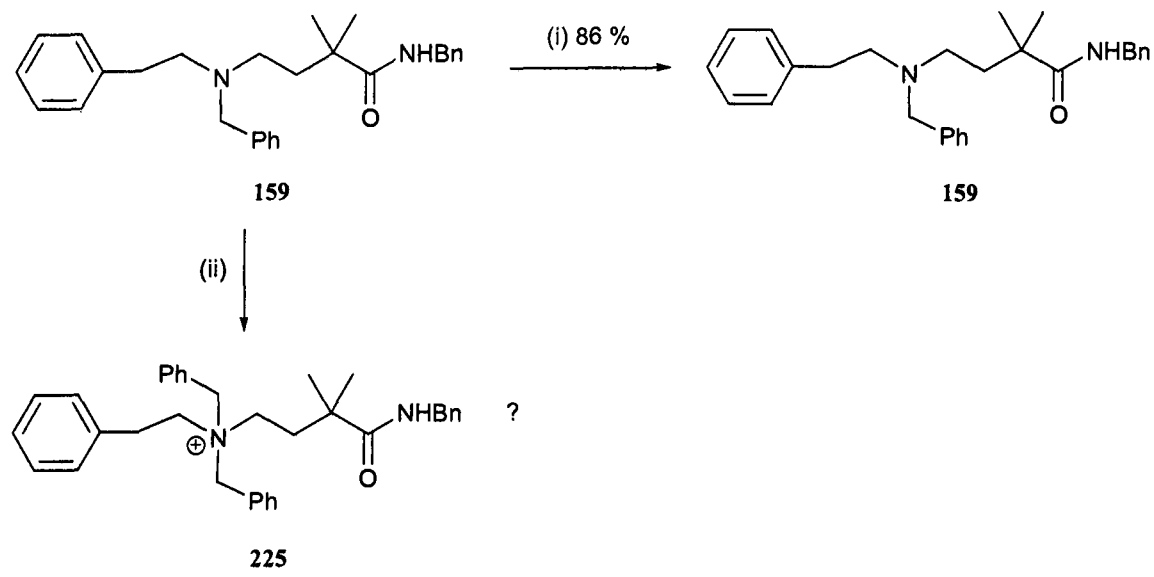
5.4 Amine derivatisation

5.4.1 Introduction

Having successfully demonstrated the attachment and release of amines from the safety catch linker, preliminary studies were undertaken in solution aimed at identifying a simple derivatisation protocol readily adaptable to the solid phase. Such a protocol could subsequently be employed to demonstrate a simple library synthesis and allow yields and purities to be determined for a range of products upon release into solution.

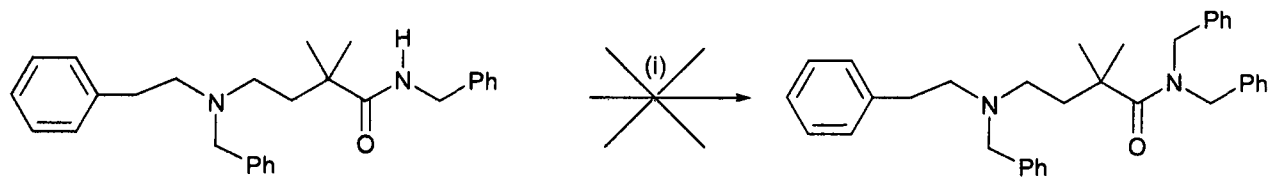
5.4.2 Attempted *N*-alkylation

N-alkylation of the *N*-benzyl amide **159** as a possible route to secondary amines on the safety catch linker was examined. Initial studied investigated the stability of the model system towards strong bases. Deprotonation of **159** with *n*-BuLi at -78˚C followed by warming to room temperature and quench with water afforded 86 % of returned starting material, confirming the stability of the amide model system. Furthermore, amide **159** was treated with 3 equivalents of benzyl bromide **100** to assess the reactivity in possible quaternization of the tertiary nitrogen to give **225**. The presence of the starting material was monitored and was fully consumed in 6 days. Slow conversion of the starting material to the assumed quaternized species **225** should be beneficial when *N*-alkylation is attempted on the amide nitrogen of **159** or other nitrogen containing substrates attached to the safety catch linker (Scheme 5.12).



Scheme 5.12: *Reagents and conditions:* (i) *n*-BuLi, THF, -78˚C then r.t., H_2O; (ii) BnBr **100** (3 eq.), THF, 6 days, r.t.

Attempts to deprotonate and selectively *N*-alkylate the amide nitrogen with a range of bases (NaH, KOtBu or BuLi) and benzyl bromide **100**, did not afford the tertiary amide species **167**, resulting in no reaction after 3 hours and presumably the formation of the quaternary ammonium species **225** on prolonged reaction time. No evidence was found of *N*-alkylation of the amide nitrogen. This result is not particularly surprising, since steric hindrance from the *gem*-dimethyl substituents should make this transformation difficult. Beneficially, due to the unreactive nature of the amide and tertiary nitrogen species, *N*-deprotonation of a substrate attached to the safety catch linker system followed by quench with an alkyl halide should result in a selective alkylation on the substrate according to the results described above (Scheme 5.13).

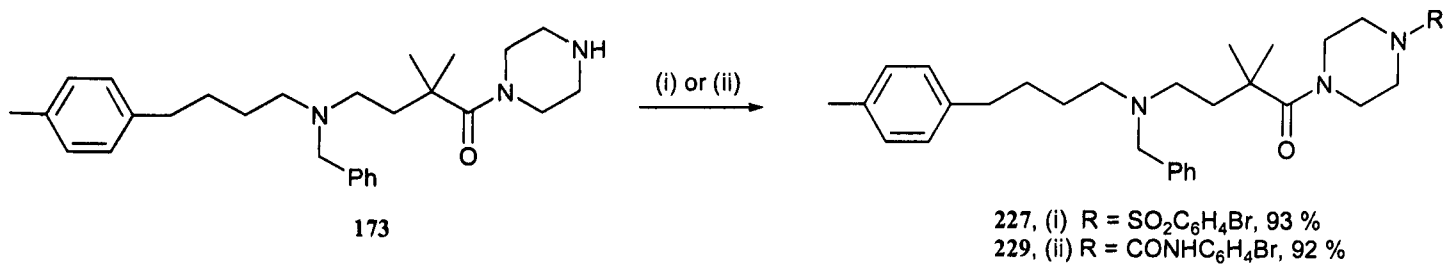


159 **167**

Scheme 5.13: *Reagents and conditions:* (i) *n*-BuLi, THF, -78°C, 30 min., then BnBr **100** (3 eq.), 6 days, r.t.

5.4.3 Derivatisation of piperazine derivatives

Early investigations to identify a suitable derivatisation sequence to employ in a solid phase synthesis of amines were aimed at differentially functionalised piperazine derivatives which are known to be pharmacologically privileged substructures.[5] Thus, treatment of **173** with *p*-bromophenylsulfonyl chloride **226** in DCM for 2 hours afforded the desired product **227** in 93 % isolated yield after chromatography. Similarly, treatment of **173** with *p*-bromophenyl isocyanate **228** in DCM for 2 hours afforded the desired product **229** in excellent yield (92 %) after chromatography (Scheme 5.14).



173

Scheme 5.14: *Reagents and conditions:*. (i) *p*-bromophenylsulfonyl chloride **226** (1.1 eq.), DCM, r.t. 2 h; (ii) *p*-bromophenyl isocyanate **228** (1.1 eq.), DCM, r.t. 2 h.

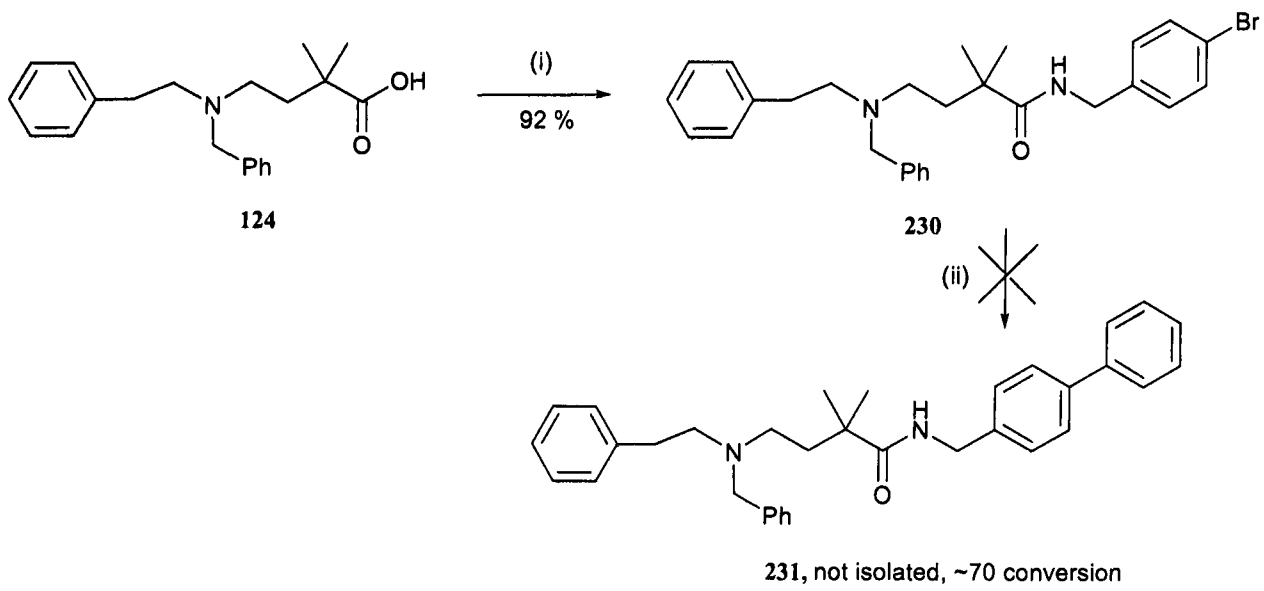
Prior to further derivatisation, a preliminary investigation was carried out into the debenzylation of **227** and **229** with ACE-Cl. However, treatment with ACE-Cl in DCE at reflux gave inconsistent results, giving only complex mixtures of unidentified products (Scheme 4.29, Section 4.6.3). Furthermore, attempts to reductively aminate benzaldehyde **126** with the piperazine derivative **174** were found to be problematic and did not yield the desired compound **178** (Scheme 5.15).

174 178

Scheme 5.15: *Reagents and conditions:* (i) PhCHO **126**, MeOH, TMOF, 16 h then $NaBH_4$, 0°C, 1 h then r.t. 16 h.

5.4.4 Derivatisation of benzyl amide

Finally, as an alternative to the derivatives described above, the bromobenzylamide **230** was identified as a suitable candidate for the optimization of a simple Suzuki transformation. Treatment of **124** with *p*-bromobenzylamine employing EDCI and HOBt in DCM for activation afforded the desired amide **230** in 92 % yield after chromatography (Scheme 5.16).



Scheme 5.16: *Reagents and conditions:* (i) *p*-bromobenzylamine hydrochloride, EDCI, HOBt, DIPEA, DCM, r.t. 16 h; (ii) phenylboronic acid **193**, $Pd(OAc)_2$, $P(Ph)_3$, K_2CO_3, DMF 80°C, 16 h.

Initial attempts to use a Suzuki protocol with $Pd(OAc)_2$, $P(Ph)_3$, and K_2CO_3 as base in DMF with gentle heating (70 - 80°C) to couple phenylboronic acid **193** with **230** met with limited success. Monitoring of the conversion by ^1H NMR spectroscopy of the crude reaction mixture indicated that ~70 % conversion had been achieved. However, attempted purification of the product **231** with column chromatography failed due to solubility of palladium residues in the solvent system used ($MeOH/CHCl_3$). Further attempts were carried out to drive the reaction to completion but the conversion was found to be inconsistent. Due to these problems none of the desired product was isolated and this approach was abandoned.

5.5 Conclusions

To demonstrate the utility of the safety catch linker a simple synthetic protocol was optimized in solution with a model system prior to adaptation to solid phase. Subsequently, the protocol was repeated on polymer and followed by a demonstrative library synthesis of derivatised phenols to determine the yields and purities of the released products. Furthermore, the debenzylation/cyclorelease protocol was demonstrated for amines on solid phase prior to attempts to develop an analogous synthetic sequence to model a library synthesis of amines in solution. Disappointingly these attempts were met with limited success due to problems with conversion and purification.

The library synthesis described above confirms the success of the approach. The solution phase model system developed could subsequently be used to optimize more challenging synthetic sequences prior to solid phase library syntheses to fully utilize the robustness of the linker system.

References

[1] R.J. Edsall, H.A. Harris, E.S. Manas, R.E. Mewshaw, *Bioorg. Med. Chem.*, 2003, **11**, 3457.

[2] M. Lourak, R. Vanderesse, Y. Fort, P. Caubere, *J. Org. Chem.*, 1989, **54**, 4844.

[3] R. Dupont, P. Cotelle, *Tetrahedron*, 2001, **57**, 5585.

[4] P. Conti, D. Demont, J. Cals, H.C.J. Ottenheijm, D. Leysen, *Tetrahedron Lett.*, 1997, **38**, 2915.

[5] D.A. Horton, G.T. Bourne, M.L. Smythe, *Chem. Rev.*, 2003, **103**, 893.

6 Chapter VI: Chiral auxiliary studies

6.1 Introduction

Chiral auxiliaries represent an attractive methodology for the asymmetric synthesis of chiral building blocks and have proven to be a powerful tool to obtain high and predictable stereoselectivities for a broad range of substrates and functional groups.[1] In this approach the prochiral substrate is attached to a chiral molecule (auxiliary) which is used to induce stereoselectivity in a chiral transformation, giving rise to one or more stereogenic centres on the substrate. The major diastereomeric product can then be purified to homogeneity and detached from the auxiliary. Fundamental to this approach is the necessity for attachment and detachment of the auxiliary and the separation the chiral product from the auxiliary after synthesis.

The major advantages of solid phase organic synthesis are the ability to drive reactions to completion with excess reagents and the ease of purification after each step, with only a simple filtration nescessary prior to release and isolation of the product. A chiral auxiliary immobilised on solid phase[2] would combine the advantages of both these approaches, allowing the stereoselective preparations of chiral substances followed by detachment of the product and easy recovery/recycling of the polymer bound auxiliary. Such an approach obviates the necessity for chromatography to separate the chiral product from the auxiliary after synthesis (Figure 6.1).

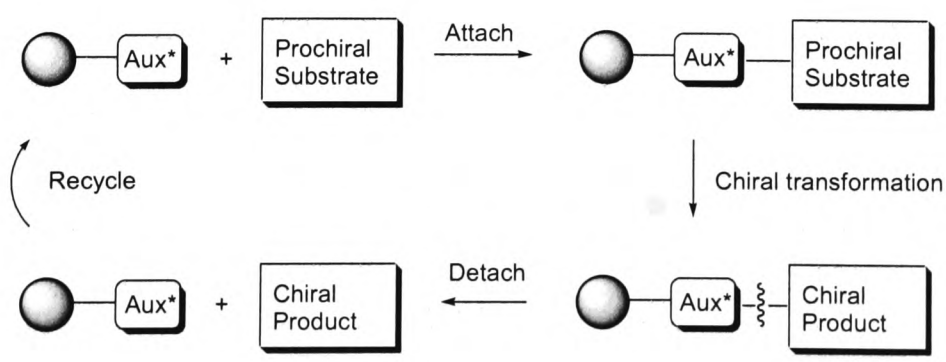


Figure 6.1: Polymer supported chiral auxiliary

A high degree of stereocontrol in polymer supported reactions is imperative. Optimisation of stereoselective transformations on polymeric supports is necessary prior to the general

applicability of this approach. However, in general this is hampered by the difficulty of reaction monitoring on solid phase[3] due the insensitivity of the analytical methods available. A readily cleavable linker incorporated in the polymeric support would allow an analytical fragment[4] to be cleaved, allowing ^{1}H NMR spectroscopy to be employed to analyse the reaction outcome on the auxiliary (Figure 6.2).

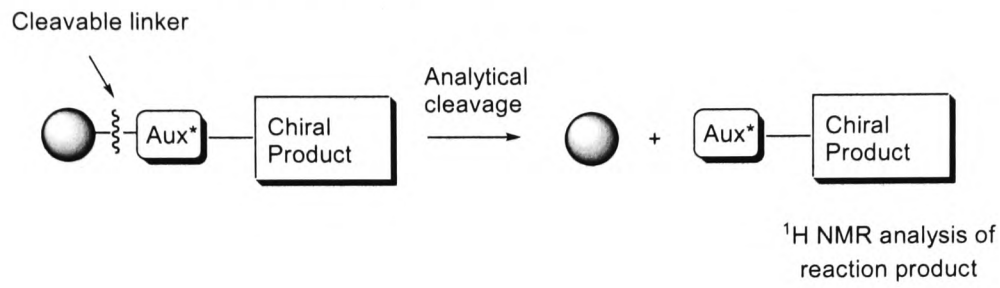


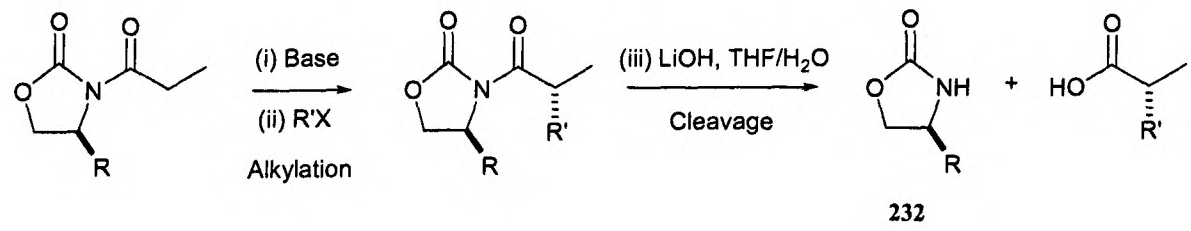
Figure 6.2: Cleavage of analytical fragment from polymer

This chapter describes a preliminary study into the potential of the safety catch linker as an analytical tool for such transformations on an oxazolidin-2-one derived chiral auxiliary.

6.2 Oxazolidinone based chiral auxiliaries on polymer

6.2.1 Polymer supported Evans auxiliaries

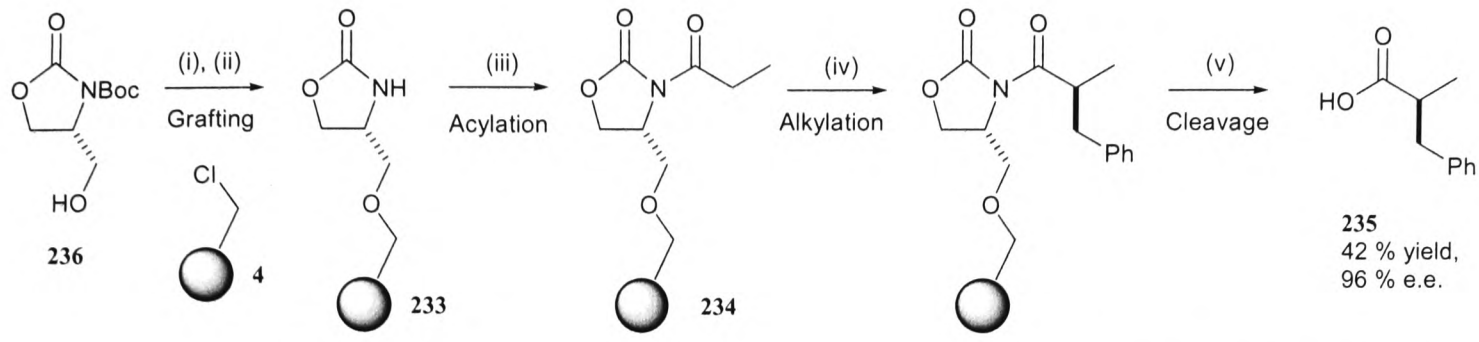
Oxazolidin-2-one based chiral auxiliaries **232**, initially developed by Evans, have found widespread use in solution phase asymmetric synthesis due to their efficiency in a broad range of stereoselective manipulations[5] and accessibility from readily available α-amino acids in a two step high yielding process (Scheme 6.1).[6]



Scheme 6.1: α-alkylation using Evans auxiliary **232**

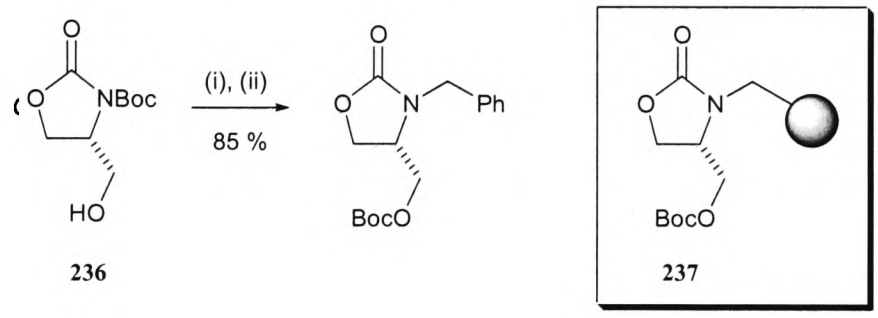
Much effort has been made to immobilise oxazolidine-2-one based chiral auxiliaries on polymer supports.[2,7] Allin and Shuttleworth[8] reported asymmetric transformations on polymer supported L-Serine derived **233** grafted on Merrifield's resin **4** through the alcohol functionality. The report claimed a stereoselective α-alkylation of **234** with benzyl bromide

100, which was subsequently cleaved to afford 2-benzylpropanoic acid **235** in 42 % yield and 96 % e.e. upon cleavage from the polymer supported auxiliary (Scheme 6.2).



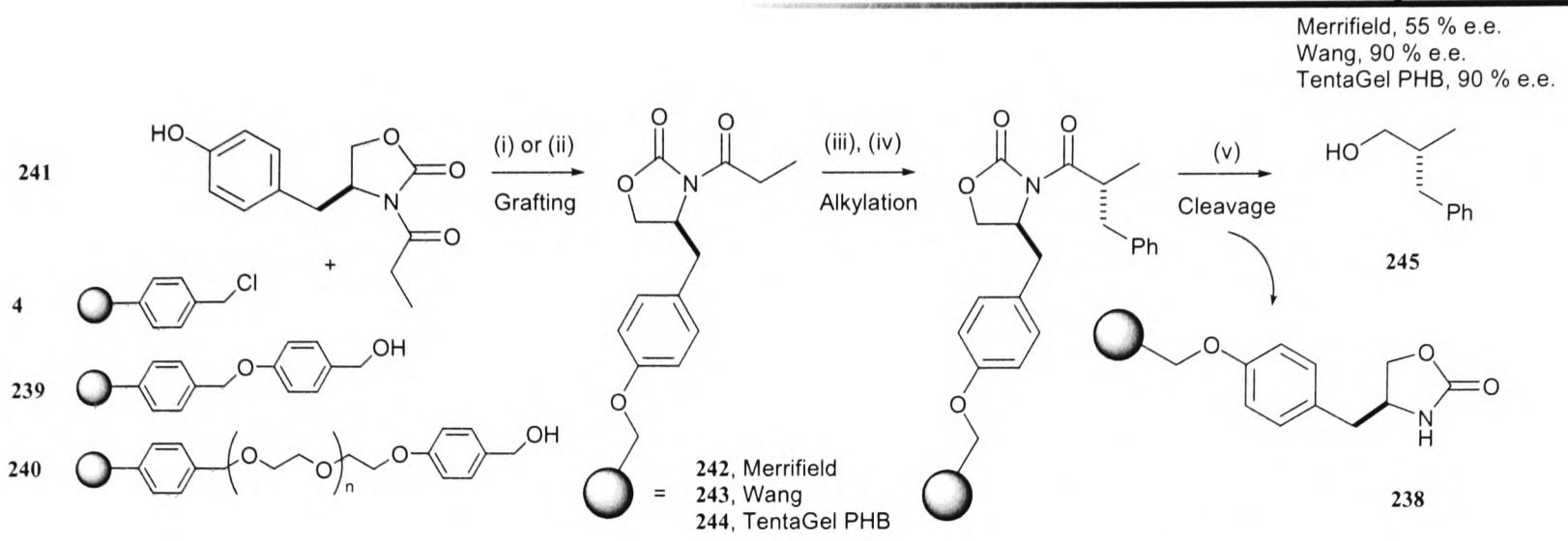
Scheme 6.2: *Reagents and conditions:* (i) 1.5 eq. KH, 18-crown-6, DMF; (ii) HCl, DCM; (iii) $(PrO)_2CO$, Et_3N, DMAP, THF; (iv) 2 eq. LDA, 0°C, 2 eq. BnBr **100** then NH_4Cl; (v) LiOH, THF:H_2O.

These findings have been questioned by Davies *et al.*,[9] who reexamined the grafting process of **236** with a solution phase model experiment and concluded that the most likely outcome of the grafting process was the formation of *N*-bound auxiliary **237**. This finding underlines the importance of careful examination of each transformation with a solution phase model system prior to adaptation to solid phase. In light of these findings, the origin of the reported e.e. of the Allin investigations remains unexplained (Scheme 6.3).



Scheme 6.3: *Reagents and conditions:* (i) KH, 18-crown-6, DMF; (ii) BnCl, DMF.

More success has been achieved with the analogous tyrosine based oxazolidinone **238**, first used by Burgess *et al.*[3] who carried out a comparative study of three different supports **4**, **239** and **240** with different resin/spacer/linker combinations. In each case the *N*-acylated auxiliary **241** was grafted to the solid support *via* nucleophilic displacement or Mitsunobu coupling. The supported auxiliaries **242** - **244** were deprotonated with LDA and the resulting enolates alkylated with benzyl bromide **100**. Reductive cleavage with $LiBH_4$ afforded alcohol **245** with e.e.'s ranging from 55 - 90 % (Scheme 6.4).



Scheme 6.4: *Reagents and conditions:* (i) **4**, nucleophilic displacement; (ii) **239** and **240**, Mitsunobu coupling; (iii) LDA; (iv) BnBr **100**; (v) $LiBH_4$.

The Wang linker **239** was found to be the optimal support, indicating that the choice of support plays an important role for successful stereoselective transformations. Burgess noted in his report that these reactions were difficult to carry out and optimisation work was hampered by difficulties in monitoring the reactions. Since this initial report, the tyrosine based Evans' auxiliary **238** has been used for a range of stereoselective transformations on solid phase including aldol reactions,[10,11] conjugate addition,[11] Diels-Alder cycloaddition[12] and 1,3-dipolar cycloadditions.[13]

6.2.2 Polymer supported SuperQuat auxiliaries

A limitation of Evans auxiliaries that would prevent the recylability of such species immobilized on polymer is the significant amount of endocyclic cleavage[14] observed upon exposure of **246** to hydrolytic conditions. This problem has been addressed by Davies *et al.*[15] by *gem*-dimethyl substitution in the 5-position, which is designed to block the Burgi-Dunitz[16] trajectory of nucleophilic attack at the endocyclic carbonyl of **247**. These alternative auxiliaries of which **248 - 250** are representatives and named "SuperQuats", are cleaved predominantly in the exocyclic position. Furthermore, this *gem*-dimethyl substitution enhances the stereodirecting capability of the auxiliaries[17] making them attractive for adaptation to solid phase asymmetric synthesis (Figure 6.3).

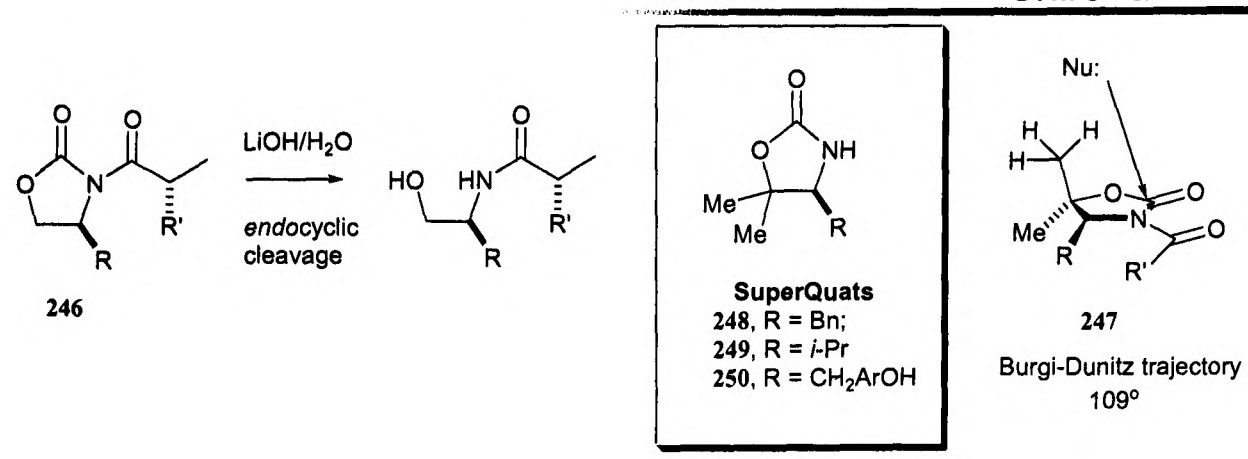
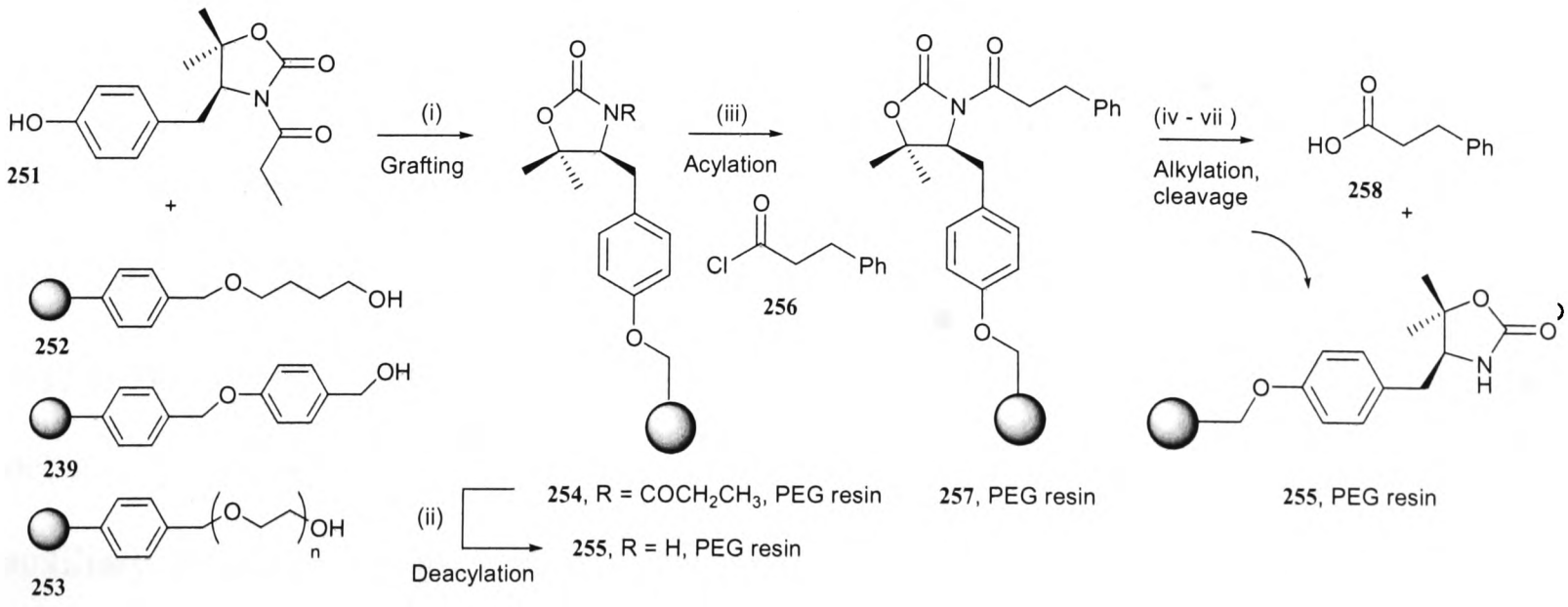


Figure 6.3: Endocyclic cleavage of Evans auxiliary **246** and SuperQuat chiral auxiliaries **248- 250**

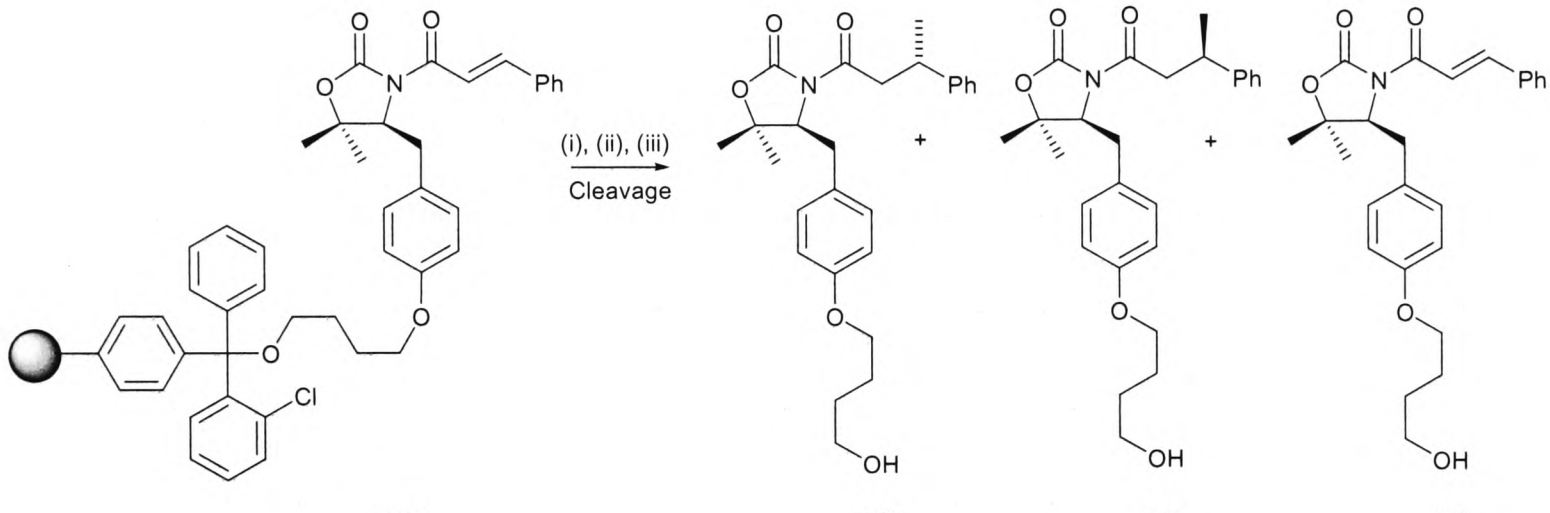
Davies and Mortimer[7] have carried out preliminary investigations to assess the feasibility of adapting tyrosine based SuperQuat auxiliary **250** to the solid phase. In these studies, immobilisation of *N*-acylated auxiliary **251** was examined with a range of supports. The Mitsunobu couplings of *N*-propionyl SuperQuat **251** to Merrifield's resin substituted with polystyrenyl-4-hydroxybutyl ether linker **252** and Wang linker **239** met with limited success. Grafting onto PEG resin **253** afforded a resin **254** with FTIR bands in the carbonyl region identical to those observed in an analogous solution phase model compound (ν_{max}/cm^{-1} 1778 and 1704). The resin **254** was readily de-acylated to give **255** as observed by disappearance of both FTIR bands being replaced by a single band (ν_{max}/cm^{-1} 1752), however, attempts to re-acylate with hydrocinnamoyl chloride **256**, and stereoselectively alkylate **257** with benzyl bromide **100** gave hydrocinnamic acid **258** only after release with LiOH in THF:H_2O. Furthermore, due to low loading the PEG supported SuperQuat **254** was found to be of limited utility (Scheme 6.5).



Scheme 6.5: *Reagents and conditions:* (i) DtBAD, PPh_3, DCM; (ii) LiOH, THF:H_2O, 12h.; (iii) BuLi, THF,then **256**; (iv) LHMDS; (v) BnBr **100**; (vi) NH_4Cl, (vii) LiOH, THF:H_2O.

6.2.3 Linkers as analytical tools

To address these problems and gain insight into the product identities after each step, Davies and Mortimer synthesised[7] an alternative chlorotrityl supported SuperQuat **259** which allowed an analytical cleavage[4] of the auxiliary with TFA. Conjugate addition to **259** followed by acidic cleavage afforded a mixture addition products **260** and **261** with negligible diastereoselectivity (<5 % d.e.) and *N*-cinnamyl-*O*-4-hydroxybutyl SuperQuat **262** in a ratio of 2.4:2.4:1 as assessed by ^{1}H NMR spectroscopic analysis of the cleaved mixture (Scheme 6.6).



259 260 261 262

Scheme 6.6: *Reagents and conditions:* (i) MeMgBr, CuBr.DMS, THF; (ii) NH_4Cl; (ii) 5 % TFA, 5 % TESH, DCM.

This disappointing result, coupled with the acid lability of the chlorotrityl support, that precludes the use of acidic chemistry, led to a reinvestigation into linker design in order to assess the outcome of stereoselective transformations. Given that the conversion of the Suzuki reaction on the solid support was optimised by monitoring through the CAN debenzylation/cyclorelease protocol (Scheme 5.4, Section 5.2.2), the possible utility of the safety catch linker in conjunction with polymer supported (*S*)-tyrosine SuperQuat **263** was investigated. The (*S*)-tyrosine SuperQuat auxiliary **250** was attached to the polymer supported safety catch linker with a simple prochiral substrate and the debenzylation/cyclorelease protocol was examined. Successful cleavage of the intact auxiliary, prochiral substrate and/or chiral product will allow the outcome of stereoselective transformations undertaken on polymer to be assessed in solution (Figure 6.4).

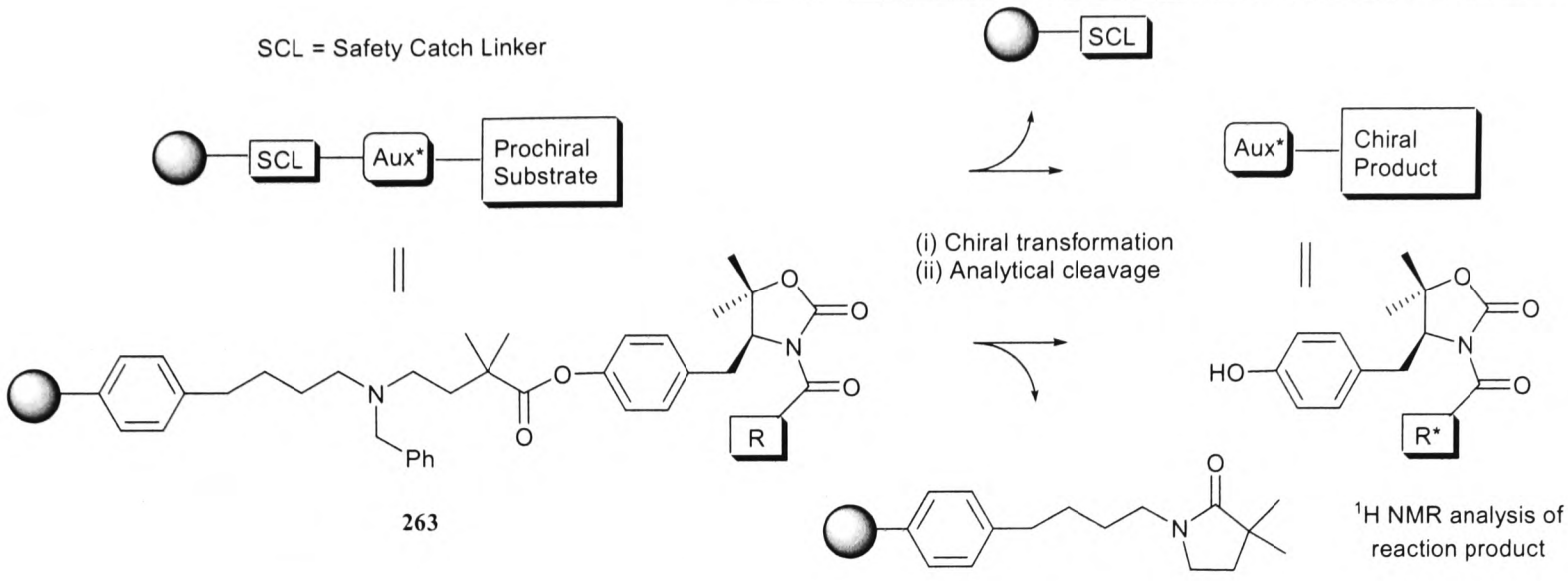


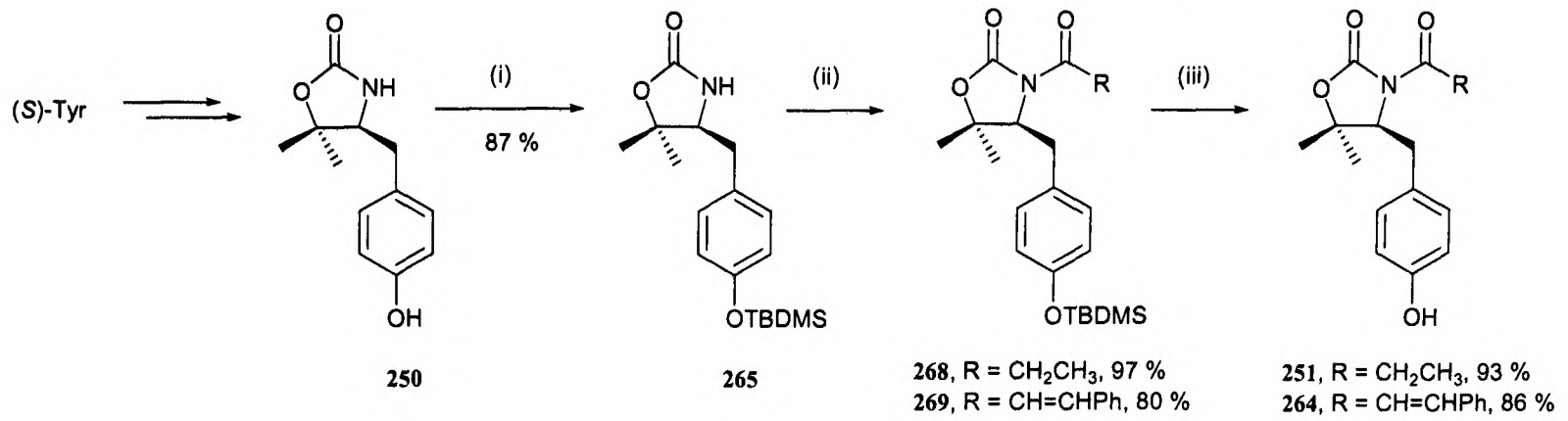
Figure 6.4: Determination of reaction outcome upon release from polymer

Furthermore, a readily accessible solution phase model system has to be available for preliminary studies in solution prior to adaptation and optimisation of stereoselective transformations on a solid support by aid of the safety catch linker system. The following work describes the development of such a model system. Once the optimal conditions have been identified the solid supported safety catch linker could be replaced by a simple alkyl spacer and the optimal reaction sequence reproduced and subsequently automated.

6.3 Results and Discussion

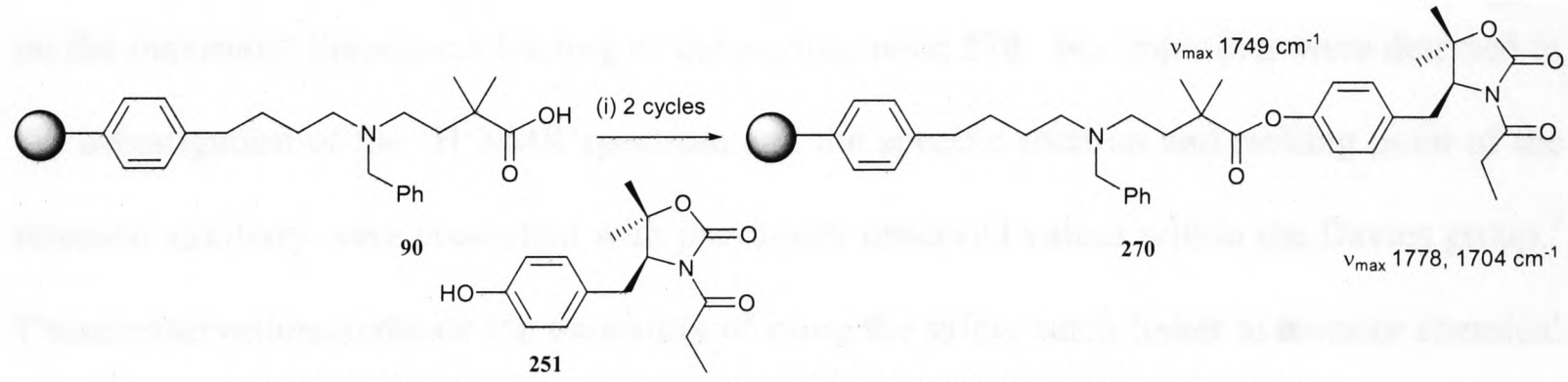
6.3.1 Synthesis and elaboration of polymer bound chiral auxiliary 270

For this investigation and for the development of a readily accessible solution phase model system, two alternative auxiliaries were envisaged, (*S*)-*N*-propionyl SuperQuat **251** and (*S*)-*N*-*trans*-cinnamoyl SuperQuat **264**. **251** and **264** were prepared *via* a selective *O*-silylation protection strategy. Thus, *O*-silylation of **250**[18] was readily achieved with TBDMSCl in DCM to afford the silylated intermediate **265** in 87 % yield after recrystallisation. Deprotonation with BuLi in THF followed by acylation with propionyl chloride **266** or *trans*-cinnamoyl chloride **267** progressed smoothly to afford the *O*-TBDMS protected **268** and **269** in 97 % and 80 % yields respectively. Finally, deprotection with TBAF in THF afforded the desired acylated SuperQuats **251** and **264** in 93 % and 86 % yields respectively after chromatography (Scheme 6.7).[19]



Scheme 6.7: *Reagents and conditions:* (i) TBDMSCl, imidazole, DCM, 24 h; (ii) BuLi, -76°C, THF, RCOCl **266** or **267** then NH_4Cl; (iii) TBAF, THF, 3 h.

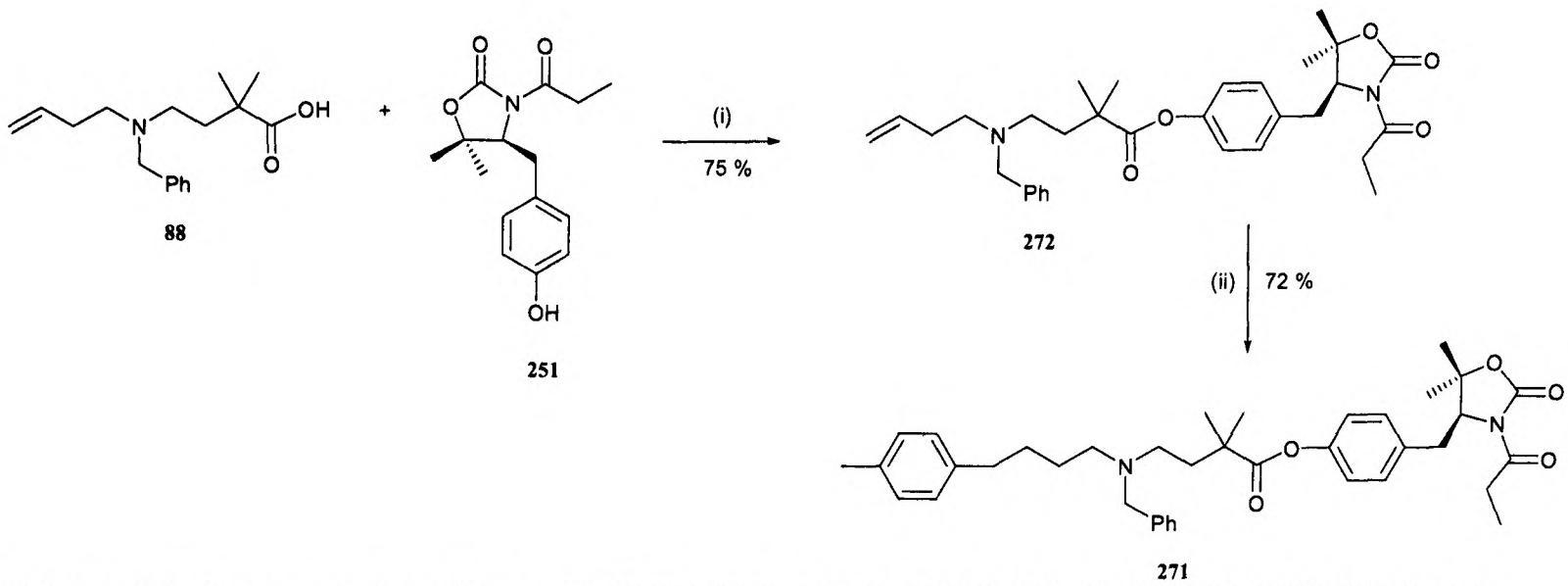
(*S*)-*N*-propionyl SuperQuat **251** was then readily attached to the solid supported carboxylic acid **90** using standard protocols. The resin **90** was treated twice with 4 equivalents of (*S*)-*N*-propionyl SuperQuat **251** to ensure reaction completion, and the excess auxiliary was recovered from the reaction mixture for recycling. The recovered dry mass was in accordance with the calculated maximum theoretical loading and investigation of the FTIR spectrum revealed three bands clearly visible in the carbonyl region (ν_{max}/cm^{-1} 1778 (endocyclic), 1749 (ester) and 1704 (exocyclic)) (Scheme 6.8).



Scheme 6.8: *Reagents and conditions:* (i) EDCI, HOBt, DIPEA, DCM, 20 h.

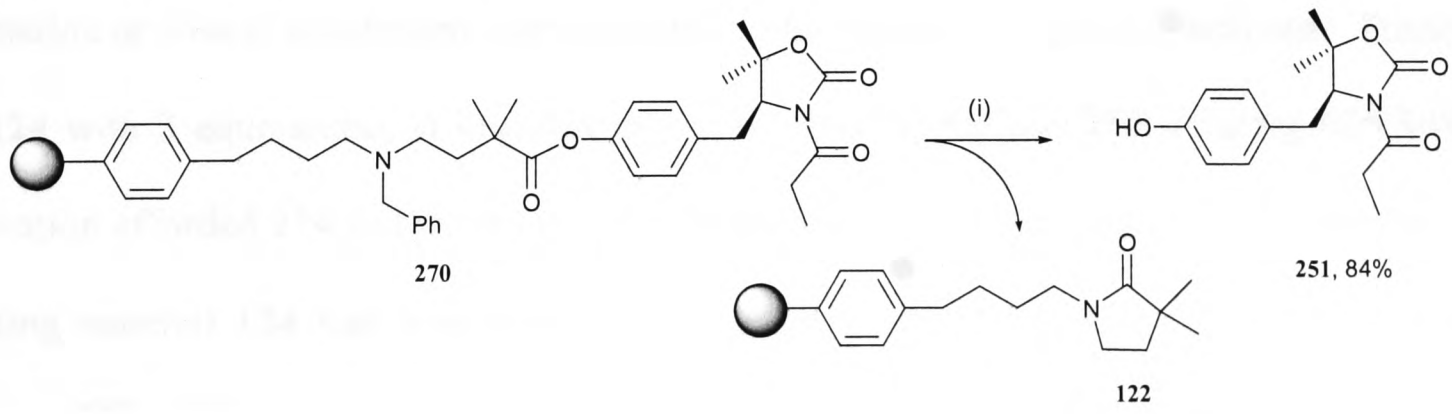
To verify the structural identity of the polymer bound species **270** from the IR bands observed, the analogous solution phase compound **271** was prepared in two steps from carboxylic acid **88**. Treatment of **88** with 2 equivalents of (*S*)-*N*-propionyl SuperQuat **251** under standard coupling conditions afforded the desired ester **272** analytically pure in 75 % yield after chromatography. The ester **272** was readily coupled with 4-bromotoluene **98** utilizing Suzuki-Miyaura cross coupling conditions. Hydroboration of **272** with 9-BBN at 0°C and subsequent treatment with 4-bromotoluene **98** and $Pd(OAc)_2$/DPPF afforded the solution phase model compound **271** analytically pure in 72 % yield after chromatography.

The IR bands detected in the carbonyl region from **271** were consistent with the solid phase species **270** (ν_{max}/cm^{-1} 1778 (endocyclic), 1750 (ester), 1702 (exocyclic) (Scheme 6.9).



Scheme 6.9: *Reagents and conditions:* (i) EDCI, HOBt, DIPEA, DCM, 42 h; (ii) 9-BBN, THF, 0°C then 4-bromotoluene **98**, $Pd(OAc)_2$, DPPF, DMF, 60°C 16 h.

The proposed debenzylation/cyclorelease was then examined, the polymer bound auxiliary **270** was treated with 5 equivalents of CAN and subsequently washed with THF and water to remove the inorganic residues. The cyclization was then promoted by treatment with a DCM:NEt_3 mixture to afford the *N*-propionyl SuperQuat **251** in solution in 84 % yield based on the maximum theoretical loading of the starting resin **270**. No impurities were detected in the investigation of the ^1H NMR spectrum and the specific rotation and melting point of the released auxiliary were consistent with previously observed values within the Davies group.[7] These observations indicate the feasibility of using the safety catch linker to monitor chemical transformations on the *N*-acyl fragment of the chiral auxiliary since it can be recovered intact from the polymer (Scheme 6.10).



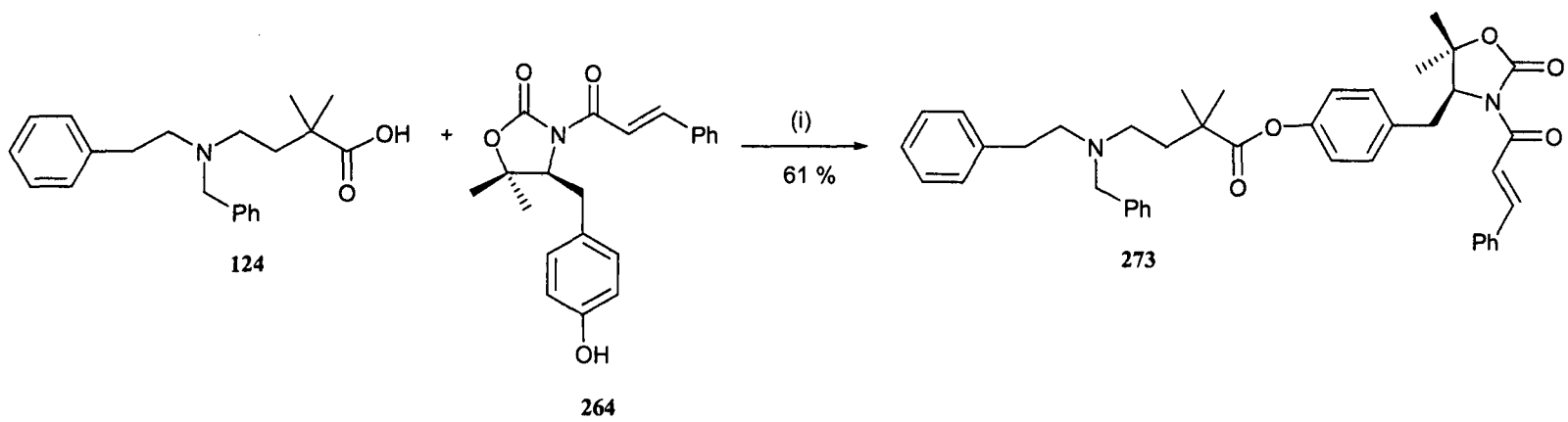
Scheme 6.10: *Reagents and conditions:* (i) CAN (5 eq.), THF:H_2O (8:1), 5 h.

Having demonstrated the debenzylation/cyclorelease to recover the intact chiral auxiliary and substrate **251** further efforts were aimed at the development of a readily accessible model

system to enable the study of asymmetric transformations in solution prior to adaptation to solid phase.

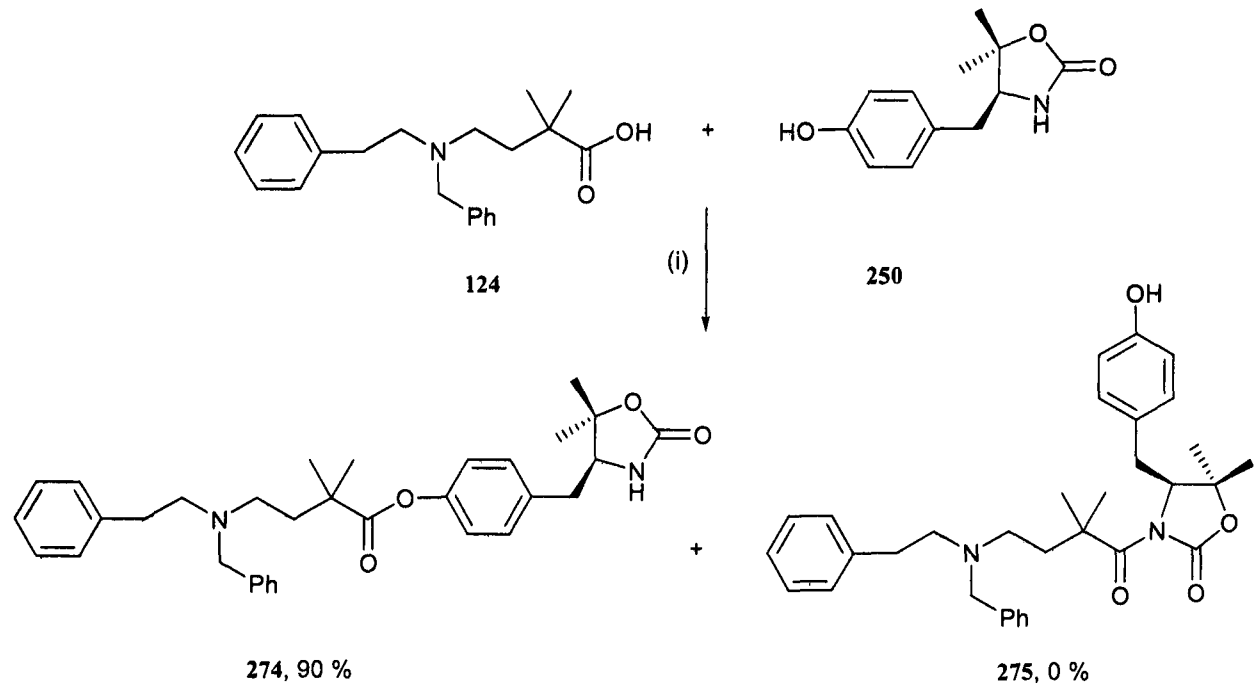
6.3.2 Synthesis of solution phase model system 273

Ideally the solution phase model system should be accessible without the use of protecting groups and should be easily scaleable. With the differentially protected (*S*)-*N*-cinnamoyl SuperQuat **264** in hand the corresponding model compound **273** was conveniently prepared from carboxylic acid **124** utilising standard coupling protocols. Treatment of **124** with 4 equivalents of (*S*)-*N*-cinnamoyl SuperQuat **264** afforded the desired ester **273** in 61 % yield after separation from the residual chiral auxiliary *via* column chromatography which could subsequently be recycled (Scheme 6.11).



Scheme 6.11: *Reagents and conditions:* (i) EDCI, HOBt, DIPEA, DCM, 16 h.

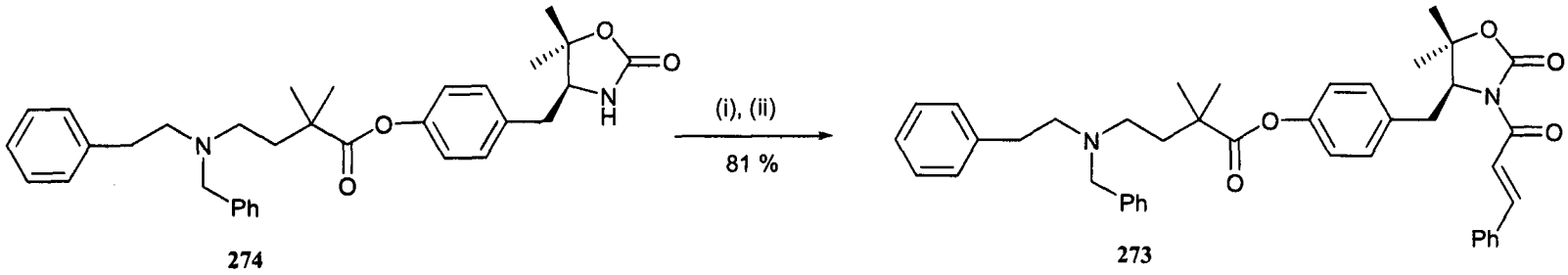
Earlier work within the Davies group has shown that regioselective protection of (*S*)-tyrosine SuperQuat **250** is non-trivial, requiring *O*-silyl protection to affect selective *N*-acylation.[7] Therefore, the regioselectivity of the carboxylic acid **124** towards **250** with respect to ester formation or *N*-acyl attachment was examined under standard coupling conditions. Treatment of **124** with 3 equivalents of unprotected (*S*)-tyrosine SuperQuat **250** utilizing EDCI/HOBt activation afforded **274** as the sole reaction product in 90 % yield after chromatography. The starting material **124** was also isolated (9 %) and no trace was detected of the alternative product **275**. This successful transformation, if applicable to the solid supported carboxylic acid **90** would negate the use of protecting groups (Scheme 6.7, Section 6.3.1) and simplifies access to the model system **273** in solution (Scheme 6.12).



Scheme 6.12: EDCI, HOBt, DIPEA, DCM, 16 h.

Having demonstrated this key transformation, attention was turned towards identification of the optimal conditions for *N*-acylation of **274** to gain alternative access to the desired solution phase model system **273** obviating the need for protecting group chemistry.

In this investigation deprotonation with *n*-BuLi and acylation with *trans*-cinnamoyl chloride **267** was chosen as a suitable model. Thus, starting from a literature procedure,[7] solution of **274** in THF was charged with 1.3 eq. *n*-BuLi at 0°C followed by addition of 1.1 eq. of *trans*-cinnamoyl chloride followed by stirring for 3 hours. Investigation of the ^{1}H NMR spectra of the resulting crude product revealed an incomplete reaction conversion (~65 %), problems were met with purification of the desired product **273**, resulting in a disappointing 44 % yield and recovery of 19 % of the starting material after chromatography. However, treatment of **274** with LHMDS at -78°C and subsequent addition of *trans*-cinnamoyl chloride **267** afforded the desired product **272** in 81 % yield after chromatography, on a 1 g scale (Scheme 6.13).



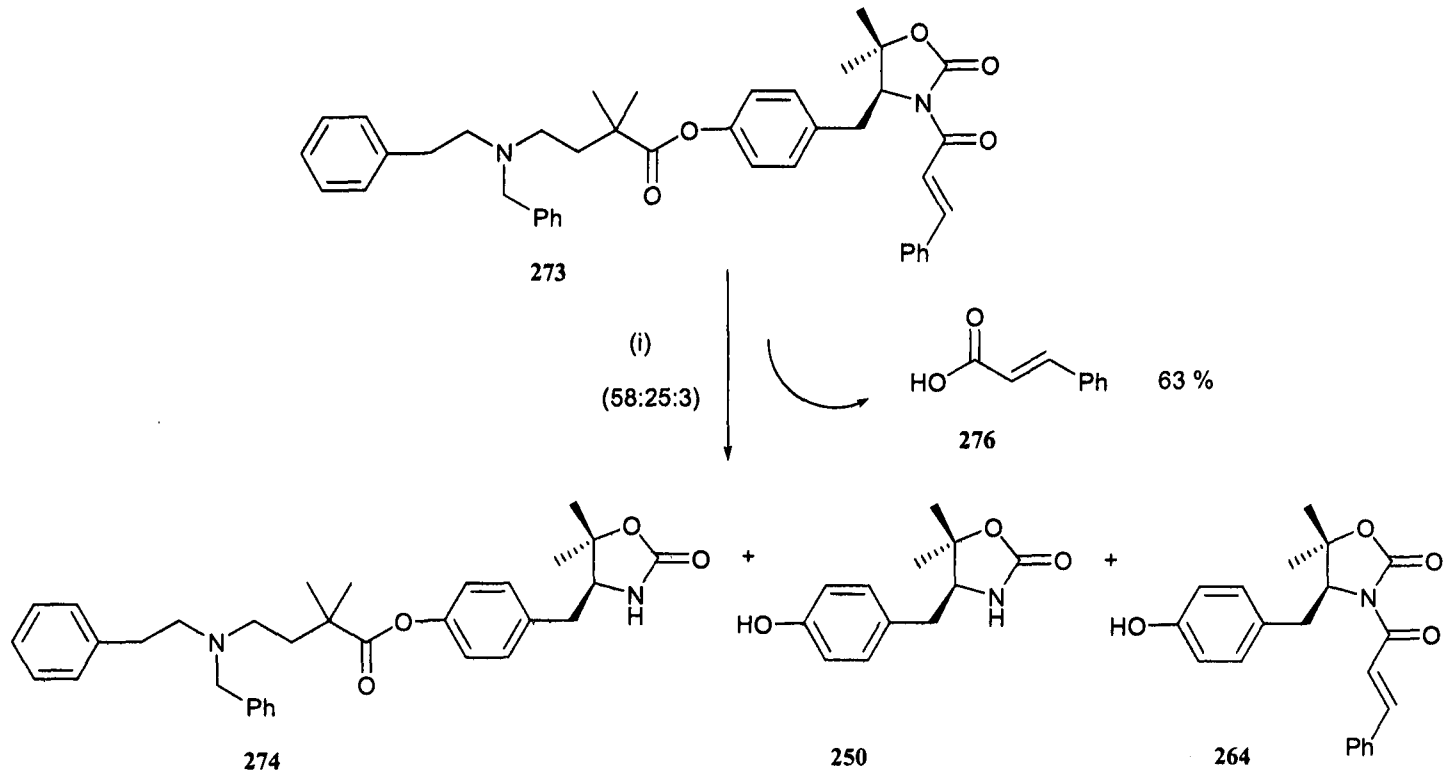
Scheme 6.13: *Reagents and conditions:* (i) LHMDS (1.1 eq.), -78°C THF, 30 min.; (ii) *trans*-cinnamoyl chloride **267** (1.3 eq.) 3 h then NH_4Cl.

No evidence of any undesired side reactions was observed in these reactions, demonstrating the robustness of the model system towards strong base. Thus, a solution phase system

incorporating chiral auxiliary **250** attached to the safety catch linker designed to model the solid phase counterpart, has been prepared. **273** is available from (*S*)-tyrosine SuperQuat **250** and carboxylic acid **124** in two high yielding steps without recourse to protecting group chemistry, allowing easy access to multigram quantities of material.

6.3.3 Attempted selective cleavage of acyl fragment

Finally, the competitive hydrolysis of the *N*-acyl fragment within **273** with respect to ester hydrolysis of the anchoring group was examined. The released carboxylic acid **276** should be readily extracted from the product mixture, however cleavage of the ester bond connecting the linker and auxiliary would complicate recycling of the polymer upon solid phase. Cleavage of this *N*-acyl fragment to afford a chiral product into solution on a polymer supported auxiliary after a stereoselective transformation would allow the e.e. to be analysed by derivatisation and compared to the result obtained from the analytical fragment released by CAN debenzylation. Thus, treatment of **273** with 2 equivalents of LiOH in THF:H_2O (3:1) for 7 hours at 0°C afforded the desired *trans*-cinnamic acid **276** in 63 % isolated yield after base extraction and acidification (pH 1). Analysis of the ^{1}H NMR spectrum of the resulting residue revealed a 13:58:25:3 mixture of starting material **273** and the cleavage products: **274**, **250** and **264** respectively. This result demonstrates that the rate of hydrolysis of the ester bond of **273** is comparatively slower than the competing hydrolysis releasing the *N*-acyl fragment of the auxiliary. This property is presumably due to steric hindrance originating from the *gem*-dimethyl substituents on the linker system (Scheme 6.14).



Scheme 6.14: *Reagents and conditions:* (i) LiOH (2 eq.), THF:H_2O (3:1), 0°C 7 h.

6.4 Conclusions

A series of model experiments indicate that the developed safety catch linker can be used as a monitoring and optimization device for asymmetric transformations on solid phase. The *N*-propionyl SuperQuat chiral auxiliary **251** was attached to the safety catch linker and the CAN debenzylation/cyclorelease protocol employed to release the intact auxiliary into solution. Prior to further work with this system, asymmetric transformations to be adapted to the polymer by aid of the safety catch linker need to be modelled in solution. For this purpose, a readily scaleable route was devised to gain access to multigram quantities of a solution phase analog of the system.

References

[1] G. Procter, *Asymmetric Synthesis*, Oxford University Press, Oxford, 1996.

[2] For a recent review see: C.W.Y. Chung, P.H. Toy, *Tetrahedron: Asymmetry*, 2004, **15**, 387.

[3] K. Burgess, D. Lim, *Chem. Commun.*, 1997, 785.

[4] M.S. Congreve, S.V. Ley, J.J. Scicinski, *Chem. Eur. J.*, 2002, **8**, 1769.

[5] D.A. Evans, M.D. Ennis, D.J. Mathre, *J. Am. Chem. Soc.*, 1982, **104**, 1737; C.H. Heathcock, *Aldrichimica Acta*, 1990, **23**, 99; P. Pollock, J. Dambacher, R. Anness, M. Bergdahl, *Tetrahedron Lett.*, 2002, **43**, 3693; D.A. Evans, K. Chapman, J. Bisaha, *J. Am. Chem. Soc.*, 1988, **110**, 1238.

[6] D.A. Evans, *Aldrichimica Acta*, 1982, **15**, 23.

[7] D.A.B. Mortimer, D.Phil Thesis, University of Oxford, 2002.

[8] S.M. Allin, S.J. Shuttleworth, *Tetrahedron Lett.*, 1996, **37**, 8023; S.M. Allin, C.A. Johnson, A. Timm, *Tetrahedron Lett.*, 2005, **46**, 2495.

[9] S.P. Bew, S.D. Bull, S.G. Davies, *Tetrahedron Lett.*, 2000, **41**, 7577.

[10] A.V. Purandare, S. Natarajan, *Tetrahedron Lett.*, 1997, **38**, 8777.

[11] C.W. Phoon, C. Abell, *Tetrahedron Lett.*, 1998, **39**, 2655.

[12] J.D. Winkler, W. McCoull, *Tetrahedron Lett.*, 1998, **39**, 4935.

[13] G. Faita, A. Paio, P. Quadrelli, F. Rancati, P. Seneci, *Tetrahedron Lett.*, 2000, **41**, 1265.

[14] D.A. Evans, T.C. Britton, J.A. Ellman, *Tetrahedron Lett.*, 1987, **28**, 6141.

[15] S.G. Davies, H.J. Sanganee, *Tetrahedron: Asymmetry*, 1995, **6**, 671; S.D. Bull, S.G. Davies, S. Jones, M.E.C. Polywka, R.S. Prasad, H.J. Sanganee, *Synlett*, 1998, 519.

[16] H.B. Burgi, J.D. Dunitz, *Structure Correlation*, VCH: Veinheim, 1996, p. 269.

[17] S.D. Bull, S.G. Davies, M.S. Key, R.L. Nicholson, E.D. Savory, *Chem. Commun.*, 2000, 1721.

[18] Available in three steps *via* modified literature procedure from commercially available (*S*)-tyrosine; S.D. Bull, S.G Davies, S. Jones, H. Sanganee, *J. Chem. Soc., Perkin Trans. I*, 1999, **21**, 387; for detailed experimental protocols see ref. 7.

[19] **251** was synthesised by Dr. D.A.B. Mortimer, see. ref. 7, p. 97.

7 Chapter VII: Experimental

7.1 General Experimental

General (Solution) All reactions not involving aqueous reagents were carried out under argon or nitrogen in flame-dried apparatus which were allowed to cool *in vacuo* employing standard vacuum line techniques. Reactions described as being performed at –78°C or –20°C were cooled by means of an acetone/dry ice bath, and those at 0°C by an ice/water bath.

General (Polymer supported) All reactions not involving aqueous reagents were carried out under argon or nitrogen in flame-dried apparatus which were allowed to cool *in vacuo* employing standard vacuum line techniques. Reactions were carried out using either standard glassware or in a Carousel® 12 Place Reaction Station supplied by Radleys Discovery Technologies. Bromopolystyrene was supplied by Argonout Technologies and used as supplied. Loading refers to maximum theoretical loading unless otherwise indicated.

Solvents THF, ether and DCM were dried by passage through a column of Aluminium Oxide (activated, basic, Brockmann 1, standard grade). Water was distilled. All other solvents were used as supplied (Analytical or HPLC grade) without prior purification. Ether refers to diethyl ether. Petrol refers to 40 - 60°C petroleum ether.

Reagents *n*-Butyllithium (*n*-BuLi) was used as a solution in hexanes and was titrated against diphenylacetic acid prior to use. All organometallic reagents were used as supplied.

Chromatography Column chromatography was performed using silica gel (Kieselgel 60). t.l.c. was performed on Merck plates, aluminium coated with silica gel 60 F_{254}. Plates were visualized either by UV light (254 nm), iodine and 10 % ethanolic solution of phosphomolybdic acid hydrate. HPLC was carried out on a Gilson instrument comprising of Gilson 306 pumps, Gilson 811C dynamic mixer, Gilson 806 manomeric module with automated injection on a Gilson 215 Liquid handler, configured with a Gilson 819 valve actuator. Separations were

performed on a Hypersil® Elite C18 column (5μm particle size, 150x4.6mm). All experiments were performed under gradient elution with deionised H_2O (containing 0.1% TFA) and CH_3CN. Detection was at λ 254 nm with a Gilson 170 Diode Array Detector with equipment control and data collection managed by Gilson Unipoint LC software version 3.01.

Infra-red spectroscopy Infra-red spectra were recorded as thin film (film) or as KBr discs (KBr) using a Perkin-Elmer Paragon 1000 FT spectrometer and a Bruker Tensor 27 FT-IR. Selected peaks are reported in cm^{-1}.

NMR spectroscopy ^1H NMR spectra were recorded on Bruker DPX-200 (^1H 200 MHz and ^{13}C 50 MHz), Bruker DPX-400 (^1H 400 MHz and ^{13}C 100 MHz) or Bruker AM-500 (^1H 500 MHz and ^{13}C 125 MHz) spectrometers. Chemical shifts (δ_H) are reported in parts per million (ppm) and are referenced to the residual solvent peak. Coupling constants (*J*) are measured in Hertz and are calculated using a first order approximation, quoted values are averaged. Carbon chemical shifts (δ_C) are quoted in ppm and are referenced using residual solvent signals. Proton and Carbon assignment was performed with the aid of COSY to establish the ^1H-^1H coupling and APT, HMQC and HMBC to establish the ^1H-^{13}C coupling. Both ^1H and ^{13}C performed on the AM-500 were obtained by Dr Barbara O'Dell of the Chemistry Research Laboratory.

Mass Spectroscopy Low resolution mass spectra (*m/z*) were recorded on either a VG Masslab 20-250 instrument (ESI), or Platform Micromass instrument (CI, NH_3). Major peaks are listed with intensities quoted as percentages of the base peak. Accurate mass measurements were recorded on a GCMS machine or a VG Autospec instrument (conducted by Mr. R. Procter and Dr. J. Kirkpatrick).

Polarimetry Optical rotations were recorded on a Perkin-Elmer 241 polarimeter, using a path length of 10cm with concentrations (*c*) given in g/100 mL solvent and temperature as recorded. Specific rotations are quoted in units of $10^{-1}degcm^2g^{-1}$.

Elemental Analysis Elemental analyses were obtained by Mrs A. Douglas of the Inorganic Chemistry Analytical Department using an Elementar Vario EL combustion elemental analyser.

Melting Points Melting points were recorded on a Gallenkamp hot stage apparatus and are uncorrected.

7.2 General Experimental Procedures

Representative Procedure 1 for CAN oxidation in solution: CAN (5.0 eq.) was added to a stirred solution of the requisite tertiary amine (1.0 eq.) in THF/H_2O (8/1) or MeCN/H_2O (5/1) and stirred for 16 hours at room temperature. The reaction was quenched with either a 2 M aqueous solution of NaOH or saturated aqueous bicarbonate solution ($NaHCO_3$) and extracted into ether or DCM. The organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo* and the resulting crude product purified as described.

Representative Procedure 2 for carbodiimide coupling reactions in solution: To a solution of the requisite carboxylic acid in DCM or DMF was added DIPEA, nucleophile (amine or alcohol), HOBt and coupling reagent (EDCI, TBTU or DIC). The reaction mixture was stirred at room temperature for 16 hours. The resulting solution was partitioned with 10 % aqueous HCl and then 2 M aqueous NaOH. The organic layer was dried (Na_2SO_4), concentrated *in vacuo* before purification as described.

Representative Procedure 3 for carbodiimide coupling reactions on polymer support: To a suspension of the requisite carboxylic acid in DCM was added DIPEA, nucleophile (amine or alcohol), HOBt and coupling reagent (EDCI, TBTU or DIC). The reaction mixture was stirred

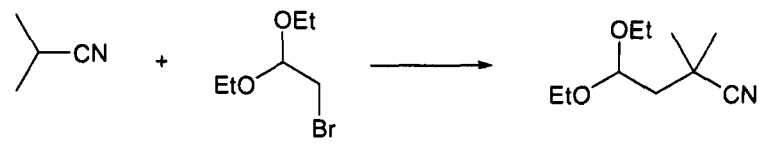
at room temperature for 16 hours. The resin was transferred to a funnel, washed repeatedly with DMF, MeOH and DCM then dried to a constant mass *in vacuo*.

Representative Procedure 4 for Suzuki couplings on polymer support: To a stirred suspension of the polymer supported *p*-iodophenyl ester (1.0 eq.) in DMF, boronic acid (4.0 eq.) and K_2CO_3 (5.0 eq.) was added Pd_2dba_3 (0.20 eq.) portionwise over 36 hours at 70 °C. The resin was washed repeatedly with DMF, water, THF and DCM and then dried to a constant mass *in vacuo*.

Representative Procedure 5 for CAN oxidation on polymer support: CAN (5.0 eq.) was added to a stirred suspension of the requisite resin (1.0 eq.) in THF:H_2O (8:1). After stirring for 16 hours the resin was transferred to a funnel and washed repeatedly with THF, water, THF and DCM. The resin was then treated with DCM:NEt_3 (5:1) and the filtrate was concentrated *in vacuo*. The resulting residue was filtered through a plug of silica (EtOAc eluent) and the solvent was removed *in vacuo*. The resin was dried *in vacuo* to a constant mass.

7.3 Experimental for Chapter II

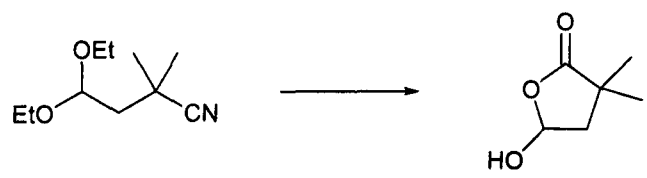
Preparation of 2,2-dimethyl-4,4-diethoxy butyronitrile 73[1]



71 72 73

A solution of *n*-BuLi (1.6 M, 200 mL, 0.320 mol, 1.0 eq.) was added dropwise *via* cannula to a stirred solution of diisopropylamine (45.2 mL 0.320 mol, 1.0 eq.) in THF (400 mL) at –78°C. To the resulting solution of LDA was added *iso*-butyronitrile **71** (28.6 mL, 0.320 mol, 1.0 eq.) in THF (300 mL) at –78°C. After stirring for 1 hour the reaction mixture was warmed to –20°C and bromoacetaldehyde diethyl acetal **72** (48.0 mL, 0.320 mol, 1.0 eq.) was added dropwise *via* cannula. After the addition was complete the reaction mixture was allowed to warm slowly to room temperature and then refluxed overnight. The solvent was evaporated *in vacuo* and the resulting residue partitioned between ether (200 mL) and water (200 mL). The organic layer was washed with 10 % aqueous HCl (200 mL) and then water (200 mL). The resulting organic solution was dried ($MgSO_4$) and concentrated *in vacuo* to afford the title compound **73** as a colourless oil (52.7 g, 89 %); δ_H (400 MHz, $CDCl_3$) 1.19 (6 H, t, *J* 7.1, 2×CH_2CH_3), 1.36 (6 H, s, CMe_2), 1.81 (2 H, d, *J* 5.5, C(3)H_2), 3.51 (2 H, m, dq, *J* 9.3, 7.1, CH_2CH_3), 3.64 (2 H, dq, *J* 9.3, 7.1, CH_2CH_3), 4.69 (1 H, t, *J* 5.5, C(4)*H*).

Preparation of 3,3-dimethyl-5-hydroxydihydrofuran-2-one 68[2]

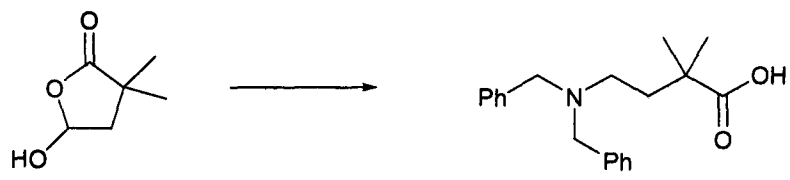


73 68

73 (29.8 g, 0.161 mol) was refluxed overnight in a mixture of concentrated HCl, acetic acid and water (100:50:25 mL). The reaction mixture was cooled to room temperature and extracted with DCM (200 mL, 2×). The aqueous layer was saturated with NaCl and re-extracted with

DCM (200 mL, 2×). The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo* to afford **68** as an oily residue (20.2 g, 97 %). The oily residue was subsequently used for further synthesis without purification. Subsequently, an analytical sample was prepared *via* recrystallisation from EtOAc:petrol (1:1, 3 mL/g) at –20°C to afford **68** as a crystalline yellow solid; m.p. 57 - 58 °C (lit.[2] 54 - 55°C); δ_H (250 MHz, $CDCl_3$) 1.26 (3 H, s, *Me*), 1.37 (3 H, s, *Me*), 2.04 (1 H, dd, *J* 13.5, 3.4, C(4)H_aH_b) 2.30 (1 H, dd, *J* 13.5, 5.8, C(4) H_aH_b), 4.70 (1 H, br s, O*H*), 5.87 (1 H, dd, *J* 5.8, 3.4, C(5)*H*).

Preparation of 2,2-dimethyl-4-(*N*,*N*-dibenzylamino)butanoic acid 76



68 **76**

A solution of dibenzylamine **53** (1.48 mL, 7.69 mmol, 1.0 eq.), TMOF (1.35 mL, 12.3 mmol, 1.6 eq.) and **68** (1.00 g, 7.69 mmol, 1.0 eq.) in MeOH (250 mL) was stirred at room temperature overnight. After cooling to 0°C, $NaBH_4$ (291 mg, 7.69 mmol, 1.0 eq.) was cautiously added portionwise and the reaction mixture stirred for 2 hours at room temperature and 1 hour at reflux. Solvents were removed *in vacuo* and the crude reaction mixture partitioned between water (30 mL) and DCM (30 mL). The aqueous layer was extracted with DCM (30 mL, 2×). The aqueous layer was adjusted to pH 7 with 10 % aqueous HCl and the product extracted with DCM (30 mL, 3×). The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo* to afford **76** as a yellow oil (1.81 g, 76 %); ν_{max} (film)/cm^{-1} 3062, 2871 (C-H), 2528 (O-H), 1714 (C=O); δ_H (400 MHz, $CDCl_3$) 0.91 (6 H, s, CMe_2), 1.77 (2 H, t, *J* 5.7, C(3)H_2), 2.74 (2 H, t, *J* 5.7, C(4)H_2), 3.71 (4 H, s, N(CH_2Ph)$_2$), 7.3 - 7.4 (10 H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 26.4 (CMe_2), 34.3 (*C*(3)H_2), 42.1 (*C*(2)), 48.4 (*C*(4)H_2), 57.9 (N(*C*H_2Ph)$_2$), 128.4 (Ph_{para}), 128.7, 130.2 ($Ph_{ortho,meta}$), 134.5 (Ph_{ipso}), 180.1 (*C*O); *m/z* (APCI$^+$) 312 (MH^+, 100 %); HRMS $C_{20}H_{25}NO_2$ (MH^+) requires 312.1964; found 312.1967.

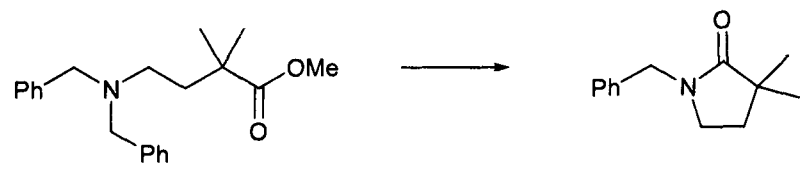
Preparation of methyl 2,2-dimethyl-4-(*N*,*N*-dibenzylamino)butanoate 74



76 74

To MeOH (25 mL) was added $SOCl_2$ (2 mL, excess), then **76** (500 mg, 1.61 mmol) and the resulting solution refluxed for 2 hours. The solvent was removed *in vacuo* and the resulting residue partitioned between 2 M NaOH (10 mL) and DCM (25 mL). The aqueous layer was extracted with DCM (25 mL). The combined organic layers were dried (Na_2SO_4), concentrated *in vacuo* and passed through silica (MeOH:$CHCl_3$, 1:9) to afford **74** as a yellow oil (433 mg, 83 %); ν_{max} (film)/cm^{-1} 3028, 2950 (C-H), 1731 (C=O); δ_H (400 MHz, $CDCl_3$) 1.10 (6 H, s, CMe_2), 1.79 - 1.83 (2 H, m, C(3)H_2), 2.37 - 2.41 (2 H, m, C(4)H_2), 3.52 (3 H, s, O*Me*), 3.57 (4 H, s, 2×NCH_2Ph), 7.23 - 7.37 (10 H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 25.3 (CMe_2), 37.4 (*C*(3)H_2), 41.2 (*C*(2)), 49.1 (*C*(4)H_2), 51.6 (O*Me*), 58.1 (N(*C*H_2Ph)$_2$), 126.8 (Ph_{para}), 128.1, 128.7 ($Ph_{ortho,meta}$), 134.0 (Ph_{ipso}), 178.1 (*C*O); *m/z* (ESI^+) 326 (MH^+, 100 %); HRMS $C_{21}H_{27}NO_2$ (MH^+) requires 326.2120; found 326.2118.

Preparation of *N*-benzyl-3,3-dimethyl-pyrrolidin-2-one 78[3]

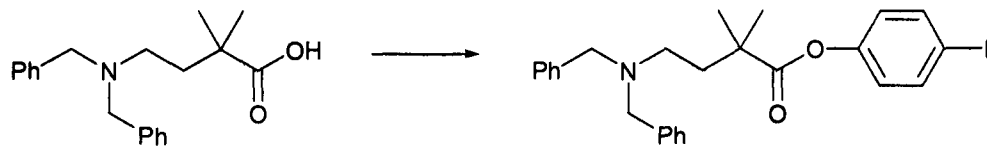


74 78

Following Representative Procedure **1**, CAN (588 mg, 1.07 mmol, 5.0 eq.) was added to a stirred solution of **74** (70 mg, 0.215 mmol, 1.0 eq.) in MeCN:H_2O (5:1, 3 mL). Saturated aqueous $NaHCO_3$ solution (6 mL) was added after 16 hours and the solution was extracted with ether (20 mL, 2×). The combined organic layers were dried ($MgSO_4$), concentrated *in vacuo* and the product distribution was studied by 400 MHz ^{1}H NMR. The resulting residue was refluxed in MeOH (5 mL) for 16 hours and the solvent was removed *in vacuo* before being

filtered through a plug of silica (MeOH:$CHCl_3$, 1:9) to afford the desired compound **78** as a yellow oil (29 mg, 66 %); δ_H (400 MHz, $CDCl_3$) 1.18 (6 H, s, C*Me*$_2$), 1.83 (2 H, t, *J* 6.9, C(4)*H*$_2$), 3.13 (2 H, t, *J* 6.9, C(5)*H*$_2$), 4.44 (2 H, s, NC*H*$_2$Ph), 7.21 - 7.34 (5 H, m, *Ph*).

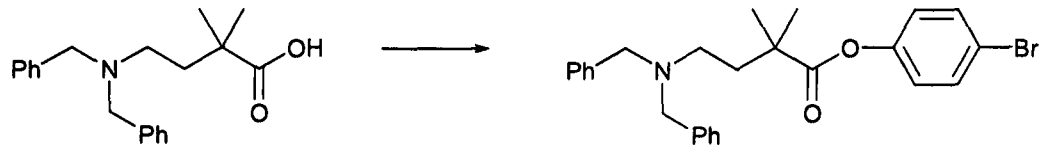
Preparation of 4'-iodophenyl 2,2-dimethyl-4-(*N*,*N*-dibenzylamino)butanoate 80



76 **80**

Following Representative Procedure **2**, to a stirred solution of **76** (135 mg, 0.433 mmol, 1.0 eq.), *p*-iodophenol **79** (95 mg, 0.433 mmol, 1.0 eq.), HOBt (70 mg, 0.520 mmol, 1.2 eq.) and DIPEA (152 μL, 0.867 mmol, 2.0 eq.) in DMF (3 mL) was added DIC (82 μL, 0.520 mmol, 1.2 eq.). The resulting solution was stirred for 60 hours and partitioned between water (30 mL) and DCM (20 mL). The aqueous layer was extracted with DCM (20 mL). The combined organic layers were washed with water (60 mL, 4×), dried (Na_2SO_4) and concentrated *in vacuo*. Further purification by column chromatography on silica gel (MeOH:$CHCl_3$, 1:99 – 1:9, stepwise elution) afforded the desired compound **80** as a white crystalline solid (205 mg, 92 %); m.p. 92 - 93°C; ν_{max} (KBr)/cm^{-1} 2990, 2931, 2790 (C-H), 1747 (C=O); δ_H (400 MHz, $CDCl_3$) 1.26 (6 H, s, C*Me*$_2$), 1.93 - 1.98 (2 H, m, C(3)*H*$_2$), 2.50 - 2.54 (2 H, m, C(4)*H*$_2$), 3.62 (4 H, s, N(C*H*$_2$Ph)$_2$), 6.47 - 6.51 (2 H, m, *Ar*), 7.23 - 7.40 (10 H, m, *Ph*), 7.58 - 7.62 (2 H, m, *Ar*); δ_C (100 MHz, $CDCl_3$) 25.4 (C*Me*$_2$), 37.5 (*C*(3)H$_2$), 41.6 (*C*(2)), 49.2 (*C*(4)H$_2$), 58.3 (2×NCH$_2$Ph), 89.6 (Ph$_{para}$), 123.8 (Ph$_{ortho,meta}$), 126.9 (Ph$_{para}$), 128.2, 128.7, 138.3 (Ph$_{ortho,meta}$), 139.5, 150.6 (Ph$_{ipso}$), 175.8 (*C*O); *m/z* (APCI$^+$) 514 (MH$^+$, 100 %); HRMS $C_{26}H_{29}NO_2I$ (MH$^+$) requires 514.1243; found 514.1256.

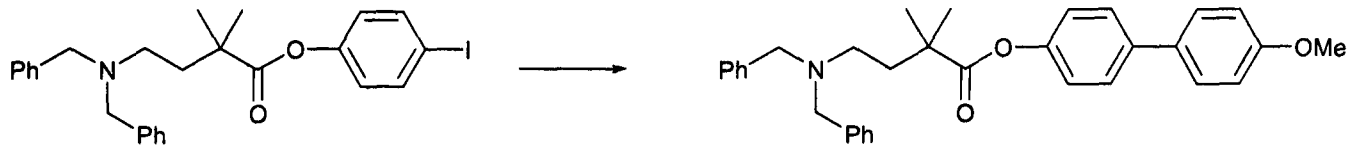
Preparation of 4'-bromophenyl 2,2-dimethyl-4-(*N*,*N*-dibenzylamino)butanoate 81



76 **81**

Following Representative Procedure **2**, to a stirred solution of **76** (300 mg, 0.963 mmol, 1.0 eq.), *p*-bromophenol **82** (167 mg, 0.963 mmol, 1.0 eq.), HOBt (156 mg, 1.16 mmol, 1.2 eq.) and DIPEA (337 μL, 1.93 mmol, 2.0 eq.) in DMF (8 mL) was added EDCI (222 mg, 1.16 mmol, 1.2 eq.). The resulting solution was stirred for 60 hours and partitioned between water (50 mL) and DCM (30 mL). The aqueous layer was extracted with DCM (30 mL). The combined organic layers were washed with water (100 mL, 4×), dried (Na_2SO_4) and concentrated *in vacuo*. Crystallisation from ether:petrol (8:2) at 20°C afforded the desired compound **81** as a white crystalline solid (163 mg, 36 %); m.p. 96 - 97°C; ν_{max} (KBr)/cm^{-1} 3026, 2944, 2799 (C-H), 1752 (C=O); δ_H (400 MHz, $CDCl_3$) 1.28 (6 H, s, CMe_2), 1.95 - 1.99 (2 H, m, C(3)H_2), 2.51 - 2.55 (2 H, m, C(4)H_2), 3.63 (4 H, s, N(CH_2Ph)$_2$), 6.59 - 6.63 (2 H, m, *Ar*), 7.24 - 7.43 (12 H, m, 2×*Ar*, 10×*Ph*); δ_C (100 MHz, $CDCl_3$) 25.4 (CMe_2), 37.5 (*C*(3)H_2), 41.6 (*C*(2)), 49.2 (*C*(4)H_2), 58.3 (N(*C*H_2Ph)$_2$), 118.6 (Ph_{para}), 123.4 ($Ph_{ortho,meta}$), 126.9 (Ph_{para}), 128.2, 128.7, 132.3 ($Ph_{ortho,meta}$), 139.5, 149.8 (Ph_{ipso}), 175.9 (*C*O); *m/z* (APCI$^+$) 466 (MH^+, 100 %); HRMS $C_{26}H_{29}NO_2Br$ (MH^+) requires 466.1382; found 466.1362.

Preparation of (4''-methoxy-4'-biphenyl) 2,2-dimethyl-4-(*N*,*N*-dibenzylamino) butanoate 84



80 84

A solution of **80** (76 mg, 0.148 mmol, 1.0 eq.), Pd_2dba_3 (9 mg, 0.00890 mmol, 0.060 eq.), K_2CO_3 (51 mg, 0.370 mmol, 2.5 eq.) and *p*-methoxyphenylboronic acid **83** (30 mg, 0.198 mmol, 1.34 eq.) in DMF (5 mL) was stirred at room temperature for 20 hours. The reaction mixture was partitioned between water (60 mL) and DCM (20 mL). The aqueous layer was extracted with DCM (20 mL). The combined organic layers were washed with water (60 mL, 2×), dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (ether:petrol, 1:9) afforded the desired compound **84** as white crystalline solid (22 mg, 30 %); m.p. 102 - 104°C; ν_{max} (KBr)/cm^{-1} 3026, 2923, 2836, 2798 (C-H), 1751 (C=O); δ_H (400 MHz, $CDCl_3$) 1.29 (6 H, s, C*Me*$_2$), 1.98 - 2.02 (2 H, m, C(3)*H*$_2$), 2.55 - 2.59 (2 H, m, C(4)*H*$_2$), 3.64 (4 H, s, N(C*H*$_2$Ph)$_2$), 3.87 (3 H, s, O*Me*), 6.81 - 6.83 (2 H, m, *Ar*), 6.99 - 7.02 (2 H, m, *Ar*), 7.24 - 7.52 (14 H, m, 4×*Ar*, 10×*Ph*); δ_C (100 MHz, $CDCl_3$) 25.9 (C*Me*$_2$), 38.0 (*C*(3)H$_2$), 42.0 (*C*(2)), 49.8 (*C*(4)H$_2$), 55.8 (O*Me*), 58.8 (N(*C*H$_2$Ph)$_2$), 114.7, 122.2 (Ph$_{ortho,meta}$), 127.3 (Ph$_{para}$), 128.0, 128.6, 128.7, 129.2 (Ph$_{ortho,meta}$), 133.5, 138.8, 140.1, 150.3, 159.6 (Ph$_{ipso,para}$), 176.7 (*C*O); *m/z* (APCI$^+$) 494 (MH$^+$, 100 %); HRMS $C_{33}H_{36}NO_3$ (MH$^+$) requires 494.2695; found 494.2678.

Alternative preparation of *N*-benzyl-3,3-dimethyl pyrrolidin-2-one 78 and preparation of 4'-methoxy biphenyl-4-ol 85

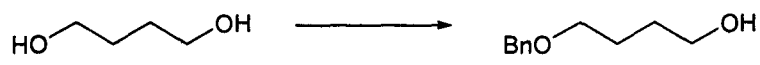


84 78 85

Following Representative Procedure **1**, CAN (73 mg, 0.133 mmol, 4.1 eq.) was added portionwise to a stirred solution of **84** (16 mg, 0.0324 mmol, 1.0 eq.) in MeCN:H_2O (8:1) (0.5 mL). The mixture was quenched with saturated aqueous $NaHCO_3$ solution (1 mL) and extracted with DCM (5 mL, 3×) after 40 hours. The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo* to afford crude (9 mg). ^1H NMR investigation of the crude product revealed a c.a. 50:50 mixture of the desired lactam **78** with identical spectroscopic properties to those previously described and 4'-methoxy-biphenyl-4-ol **85** with identical spectroscopic properties to those described *vide infra*.

7.4 Experimental for Chapter III

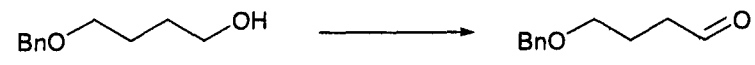
Preparation of 4-benzyloxy butan-1-ol 97[4]



99 97

To a stirred solution of **99** (18.0 g, 200 mmol, 2.0 eq.) and 15-crown-5 ether (0.60 mL, 0.030 mmol) in THF (200 mL) at 10°C was added finely ground NaOH (24.0 g, 600 mmol, 6.0 eq.) and benzylbromide (11.9 mL, 100 mmol, 1.0 eq.). The reaction mixture was stirred overnight at room temperature, diluted with ether (200 mL) and the organic layer washed with brine (200 mL, 2×). The organic layer was dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography on silica gel (EtOAc:petrol, 1:9 - 1:1, stepwise elution) afforded the desired compound **97** as a colourless oil (17.0 g, 94 %); δ_H (200 MHz, $CDCl_3$) 1.63 - 1.75 (4 H, m, C(2)H_2 and C(3)H_2) 2.60 (1 H, br s, O*H*), 3.52 (2 H, t, *J* 5.9, C(4)H_2), 3.64 (2 H, m, C(1)H_2), 4.53 (2 H, s, OCH_2Ph), 7.27 - 7.37 (5 H, m, *Ph*).

Preparation of 4-benzyloxybutanal 101[5]

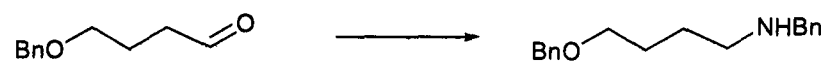


97 101

A solution of oxalyl chloride (7.51 mL, 86.1 mmol, 1.8 eq.) and DMSO (11.2 mL, 158 mmol, 3.3 eq.) was stirred at –78°C in DCM (100 mL) for 10 min. **97** (8.62 g, 47.8 mmol, 1.0 eq.) was then added as a solution in DCM (75 mL) and the resultant solution stirred for 1 hour at –78°C. Triethylamine (19.8 g, 196 mmol, 4.1 eq.) was then added and stirring continued for 15 min. The resulting mixture was concentrated *in vacuo*. The residue was then partitioned between saturated aqueous $NaHCO_3$ solution (200 mL) and ether (200 mL). The aqueous layer was extracted with ether (200 mL). The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo* to afford the desired compound **101** as a yellow liquid (8.52 g, quant.); δ_H (200 MHz, $CDCl_3$) 1.96 (2 H, quintuplet, *J* 6.4 C(3)H_2), 2.56 (2 H, td, *J* 7.1, 1.5, C(2)H_2),

3.52 (2 H, t, *J* 6.0, C(4)H_2), 4.50 (2 H, s, OCH_2Ph), 7.25 - 7.40 (5 H, m, *Ph*), 9.79 (1 H, t, *J* 1.5, C*H*O).

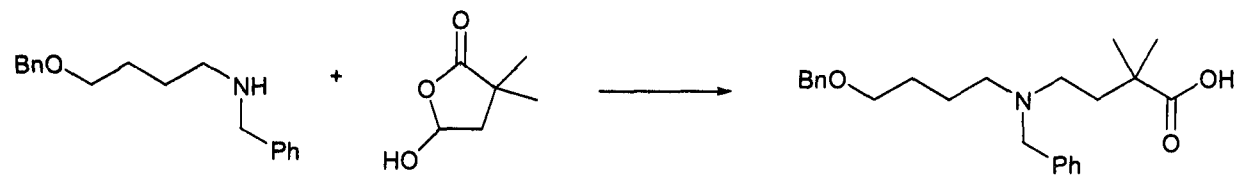
Preparation of 1-benzyloxy-4-(*N*-benzylamino) butane 102



101 **102**

A solution of **101** (8.52 g, 47.8 mmol, 2.0 eq.) and benzylamine **93** (5.22 mL, 47.8 mmol, 1.0 eq.) in TMOF (750 mL) was stirred at room temperature for 2 hours. MeOH (250 mL) was added to the reaction mixture followed by portionwise addition of $NaBH_4$ (2.35 g, 62.2 mmol, 1.3 eq.) at 0°C. The reaction mixture was stirred overnight at room temperature, concentrated *in vacuo* and partitioned between water (300 mL) and DCM (300 mL). The aqueous layer was extracted with DCM (300 mL). The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. Purification of the residue by column chromatography (EtOAc:petrol, 1:9 - 4:6, stepwise elution) gave the desired compound **102** as a colourless oil (9.10 g, 71 %); ν_{max} (film)/cm^{-1} 3307 (N-H), 3028, 2934, 2857 (C-H); δ_H (400 MHz, $CDCl_3$) 1.47 (1 H, br s, N*H*), 1,59 - 1.74 (4 H, m, C(2)H_2 and C(3)H_2), 2.68 (2 H, app. t, *J* 7.0, C(1)H_2), 3.52 (2 H, t, *J* 6.1, C(4)H_2), 3.81 (2 H, s, NCH_2Ph), 4.52 (2 H, s, OCH_2Ph), 7.25 - 7.39 (10 H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 26.9 (*C*(2)H_2), 27.6 (*C*(3)H_2), 49.2 (*C*(4)H_2), 54.0 (N*C*H_2Ph), 70.3 (*C*(1)H_2), 72.9 (O*C*H_2Ph), 126.9 (2×Ph_{para}), 127.4, 127.6, 128.1, 128.4 ($Ph_{ortho,meta}$), 138.6, 140.6 (Ph_{ipso}); *m/z* (APCI$^+$) 270 (MH^+, 100 %); HRMS $C_{18}H_{23}NO$ (MH^+) requires 270.1858; found 270.1857.

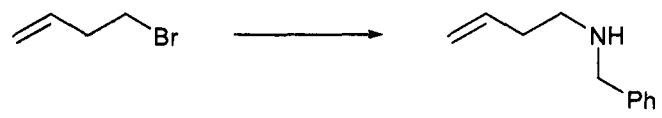
Preparation of 2,2-dimethyl-4-[*N*-benzyl-*N*-(4'-benzyloxybutyl)amino]butanoic acid 95



102 68 95

A solution of **102** (100 mg, 0.371 mmol, 1.0 eq.), **68** (48 mg, 0.371 mmol, 1.0 eq.) and TMOF (65.0 µl, 0.594 mmol, 1.6 eq.) was stirred in MeOH at room temperature for 2 hours. The solution was cooled to 0°C and $NaHB(OAc)_3$ (94 mg, 0.445 mmol, 1.2 eq.) was added portionwise. The resulting mixture was stirred at room temperature overnight and the solvent removed *in vacuo*. The residue was partitioned between water (20 mL, pH adjusted to neutral with 10 % aqueous HCl) and DCM (20 mL). The aqueous layer was extracted with DCM (20 mL). The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography on silica gel ($MeOH:CHCl_3$, 1:99 - 1:9, stepwise elution) gave the desired compound **95** as a colourless viscous oil (102 mg, 72 %); ν_{max} (film)/cm^{-1} 3061, 3029, 2945, 2858 (C-H), 2500 (O-H), 1716 (C=O); δ_H (400 MHz, $CDCl_3$) 1.07 (6 H, s, CMe_2), 1.52 - 1.66 (2 H, m, C(3)H_2), 1.70 - 1.79 (4 H, m, C(2')H_2 and C(3')H_2), 2.61 - 2.68 (2 H, m, C(4)H_2), 2.75 (2 H, t, *J* 5.7, C(1')H_2), 3.45 (2 H, t, *J* 6.1, C(4')H_2), 3.77 (2 H, s, NCH_2Ph), 4.46 (2 H, s, OCH_2Ph), 7.25 - 7.39 (10 H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 21.6 (CMe_2), 26.9, 27.3 (*C*(2')H_2 and *C*(3')H_2), 34.4 (*C*(3)H_2), 42.5 (*C*(2)), 49.2 (*C*(1')H_2), 52.4 (*C*(4)H_2), 57.3 (N*C*H_2Ph), 69.5 (*C*(4')H_2), 73.0 (O*C*H_2Ph), 127.7 (2×Ph_{para}), 128.4, 128.6, 128.8, 130.3 ($Ph_{ortho,meta}$), 133.7, 138.3 (Ph_{ipso}), 180.4 (*C*O); *m/z* ($APCI^+$) 384 (MH^+, 100 %); HRMS $C_{24}H_{33}NO_3$ (MH^+) requires 384.2539; found 384.2523.

Preparation of *N*-benzyl-*N*-(but-3-enyl)amine 91[6]



92 91

A mixture of **92** (10.0 mL, 98.5 mmol, 1.0 eq.), benzylamine **93** (53.8 mL, 493 mmol, 5.0 eq.) and K_2CO_3 (15.3 g, 110 mmol, 1.12 eq.) was stirred at 70°C overnight. The reaction mixture was allowed to cool to room temperature, diluted with Et_2O (100 mL) and washed with water (100 mL, 2×). The solvent was removed *in vacuo* and reduced pressure fractional distillation afforded the desired compound **91** as colourless liquid (11.4 g, 72 %); b.p. 100 - 120, 15 mm Hg (lit.[6] 100 - 120°C, 13 mm Hg); δ_H (400 MHz, $CDCl_3$) 1.24 (1 H, br s, N*H*), 2.31 (2 H, m, C(2)H_2), 2.73 (2 H, t, *J* 6.8, C(1)H_2), 3.82 (2 H, s, NCH_2Ph), 5.05 - 5.15 (2 H, m, C(4)H_2), 5.18 (1 H, ddt, *J* 17.2, 10.4, 7.0, C(3)*H*), 7.24 - 7.40 (5 H, m, *Ph*).

Preparation of 2,2-dimethyl-4-[*N*-benzyl-*N*-(but-3'-enyl)amino]butanoic acid 88

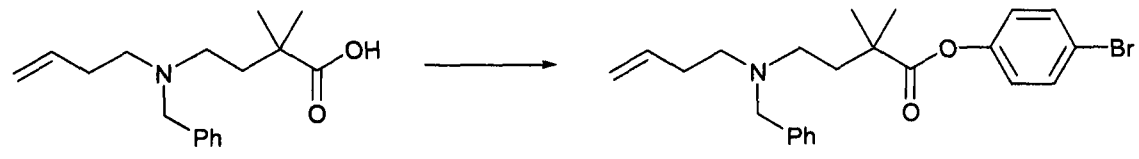


91 68 88

A solution of **91** (10.9 g, 67.6 mmol, 1.0 eq.), **68** (8.80 g, 67.6 mmol, 1.0 eq.) and TMOF (11.8 mL, 108 mmol, 1.6 eq.) in MeOH (1.0 L) was stirred overnight at room temperature. The reaction mixture was cooled to 0°C and $NaBH_4$ (3.07 g, 81.1 mmol, 1.2 eq.) added portionwise. Stirring was continued for 1 hour at 0°C, 2 hours at room temperature and then refluxed for 1 hour. Solvents were removed *in vacuo*, the resulting residue treated with water (250 mL) and the pH was adjusted to neutral with 10 % aqueous HCl. The aqueous layer was extracted with DCM (200 mL, 3×) and the combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography on silica gel (MeOH:$CHCl_3$, 1:99 - 1:9, stepwise elution) afforded **88** as a yellow viscous oil (15.0 g, 81 %); ν_{max} (film)/cm^{-1} 3070,

2969, 2801 (C-H), 2521 (O-H), 1710 (C=O); δ_H (400 MHz, $CDCl_3$) 1.05 (6 H, s, C*Me*$_2$), 1.71 - 1.74 (2 H, m, C(3)*H*$_2$), 2.37 - 2.43 (2 H, m, C(2')*H*$_2$), 2.66 - 2.70 (2 H, m, C(1')*H*$_2$), 2.75 - 2.78 (2 H, m, C(4)*H*$_2$), 3.79 (2 H, s, NC*H*$_2$Ph), 5.02 - 5.10 (2 H, m, C(4')*H*$_2$), 5.70 (1 H, ddt, *J* 17.4, 10.2, 6.8, C(3')*H*), 7.29 - 7.38 (5 H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 26.7 (C*Me*$_2$), 29.2 (*C*(2')H_2), 34.4 (*C*(3)H_2), 42.4 (*C*(2)), 49.1 (*C*(4)H_2), 51.9 (*C*(1')H_2), 57.5 (N*C*H_2Ph), 117.2 (*C*(4')H_2), 128.4 (Ph_{para}), 128.8, 130.2 ($Ph_{ortho,meta}$), 133.8 (Ph_{ipso}), 134.4 (*C*(3')H), 180.3 (*C*O); *m/z* (APCI$^+$) 276 (MH^+, 100 %); HRMS $C_{17}H_{25}NO$ (MH^+) requires 276.1964; found 276.1962.

Preparation of 4''-bromophenyl 2,2-dimethyl-4-[*N*-benzyl-*N*-(but-3'-enyl)amino] butanoate 103

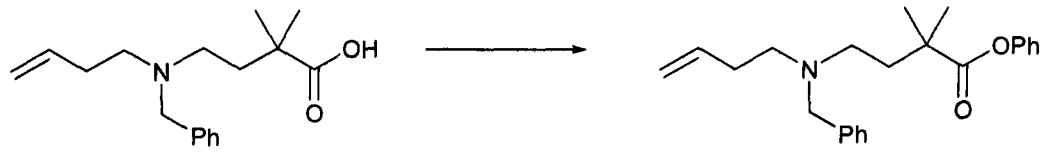


88 **103**

Following Representative Procedure **2**, to a stirred solution of **88** (157 mg, 0.570 mmol, 1.0 eq.), *p*-bromophenol **82** (296 mg, 1.71 mmol, 3.0 eq.), HOBt (154 mg, 1.14 mmol, 2.0 eq.) and DIPEA (0.399 mL, 2.28 mmol, 4.0 eq.) in DCM (10 mL) was added EDCI (219 mg, 1.14 mmol, 2.0 eq.). The resulting solution was stirred for 16 hours and partitioned between water (20 mL) and DCM (20 mL). The aqueous layer was extracted with DCM (20 mL). The combined organic layers were washed with 10 % aqueous HCl (20 mL, 2×) then 2 M NaOH (20 mL). The solution was dried (Na_2SO_4) and concentrated *in vacuo* to afford the desired compound **103** as a colourless oil (178 mg, 73 %); ν_{max} (film)/cm^{-1} 3063, 3027, 2974 (C-H), 1753 (C=O); δ_H (400 MHz, $CDCl_3$) 1.30 (6 H, s, C*Me*$_2$), 1.87 - 1.91 (2 H, m, C(3)*H*$_2$), 2.24 - 2.31 (2 H, m, C(2')*H*$_2$), 2.50 - 2.60 (4 H, m, C(4)*H*$_2$ and C(1')*H*$_2$) , 3.62 (2 H, s, NC*H*$_2$Ph), 4.99 - 5.01 (2 H, m, C(4')), 5.81 (1 H, ddt, *J* 17.0, 9.8, 6.9, C(3')*H*), 6.75 - 6.79 (2 H, m, *Ar*), 7.25 - 7.35 (5 H, m, *Ph*), 7.43 - 7.47 (2 H, m, *Ar*); δ_C (100 MHz, $CDCl_3$) 25.4 (C*Me*$_2$), 31.5 (*C*(2')H_2), 37.4 (*C*(3)H_2), 41.6 (*C*(2)), 49.3 (*C*(4)H_2), 53.2 (*C*(1')H_2), 58.5 (N*C*H_2Ph), 115.5 (*C*(4')H_2),

118.6 ($Ph_{ipso,para}$), 123.3 ($Ph_{ortho,meta}$), 126.8 (Ph_{para}), 128.2, 128.6, 132.3 ($Ph_{ortho,meta}$), 136.9 (*C*(3')H), 139.6, 149.9 ($Ph_{ipso,para}$), 175.9 (*C*O); *m/z* (ESI^+) 430 (MH^+, 100 %); HRMS $C_{23}H_{29}NO_2Br$ (MH^+) requires 430.1382; found 430.1382.

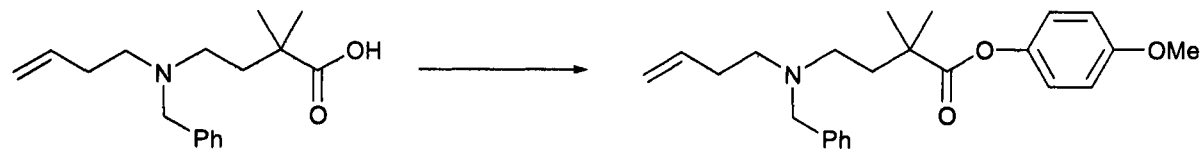
Preparation of phenyl 2,2-dimethyl-4-[*N*-benzyl-*N*-(but-3'-enyl)amino]butanoate 104



88 **104**

Following Representative Procedure **2**, to a stirred solution of **88** (2.00 g, 7.26 mmol, 1.0 eq.), phenol **106** (2.05 g, 21.8 mmol, 3.0 eq.), HOBt (1.96 g, 14.5 mmol, 2.0 eq.) and DIPEA (5.08 mL, 29.0 mmol, 4.0 eq.) in DCM (120 mL) was added EDCI (2.78 g, 14.5 mmol, 2.0 eq.). The resulting solution was stirred for 16 hours and partitioned between water (200 mL) and DCM (200 mL). The aqueous layer was washed with DCM (200 mL). The combined organic layers were washed with 10 % aqueous HCl (400 mL, 2×) then 2 M NaOH (400 mL). The resulting organic solution was dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography on silica gel (EtOAc:petrol, 1:99 - 1:9, stepwise elution) afforded the desired compound **104** as a colourless oil (2.35 g, 92 %); ν_{max} (film)/cm^{-1} 3064, 3028, 2975 (C-H), 1750 (C=O); δ_H (400 MHz, $CDCl_3$) 1.33 (6 H, s, C*Me*$_2$), 1.90 - 1.94 (2 H, m, C(3)*H*$_2$), 2.26 - 2.32 (2 H, m, C(2')*H*$_2$), 2.56 - 2.62 (4 H, m, C(4)*H*$_2$ and C(1')*H*$_2$), 3.65 (2 H, s, NC*H*$_2$Ph), 4.99 - 5.09 (2 H, m, C(4')), 5.83 (1 H, ddt, *J* 17.2, 10.4, 6.7, C(3')*H*$_2$), 6.92 - 6.95 (2 H, m, *Ph*), 7.21-7.38 (8 H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 25.4 (C*Me*$_2$), 31.6 (*C*(2')H_2), 37.4 (*C*(3)H_2), 41.5 (*C*(2)), 49.4 (*C*(4)H_2), 53.3 (*C*(1')H_2), 58.5 (N*C*H_2Ph), 115.5 (*C*(4')H_2), 121.5 (Ph_{ortho}), 125.6, 126.8 (Ph_{para}), 128.2, 128.8, 129.3 ($Ph_{ortho,meta}$), 136.9 (*C*(3')H), 139.7, 150.9 (Ph_{ipso}), 176.2 (*C*O); *m/z* ($APCI^+$) 352 (MH^+, 100 %); HRMS $C_{23}H_{30}NO_2$ (MH^+) requires 352.2277; found 352.2284.

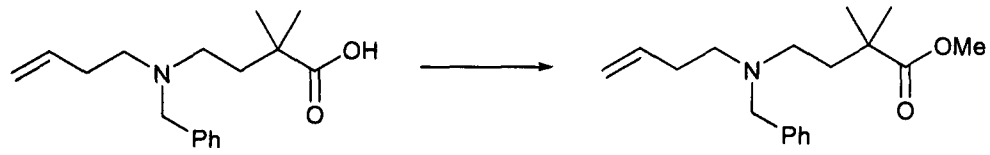
Preparation of 4''-methoxyphenyl 2,2-dimethyl-4-[*N*-benzyl-*N*-(but-3'-enyl)amino] butanoate 105



88 **105**

Following Representative Procedure **2**, to a stirred solution of **88** (1.00 g, 3.63 mmol, 1.0 eq.), *p*-methoxyphenol **107** (1.35 g, 10.9 mmol, 3.0 eq.), HOBt (981 mg, 7.26 mmol, 2.0 eq.) and DIPEA (2.54 mL, 14.5 mmol, 4.0 eq.) in DCM (60 mL) was added EDCI (1.39 g, 7.26 mmol, 2.0 eq.). The resulting solution was stirred for 16 hours then partitioned between water (200 mL) and DCM (200 mL). The aqueous layer was extracted with DCM (200 mL). The combined organic layers were washed with 10 % aqueous HCl (200 mL, 2×) then 2 M NaOH (200 mL). The resulting organic solution was dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography on silica gel (EtOAc:petrol, 2:8) afforded the desired compound **105** as a colourless oil (1.08 g, 78 %); $C_{24}H_{31}NO_3$ requires C 75.56 %, H 8.19 %, N 3.67 %; found C 75.20 %, H 8.18 %, N 3.98 %; ν_{max} (film)/cm^{-1} 3063, 3027, 2948, (C-H), 1749 (C=O); δ_H (400 MHz, $CDCl_3$) 1.29 (6 H, s, C*Me*$_2$), 1.88 - 1.92 (2 H, m, C(3)*H*$_2$), 2.25 - 2.31 (2 H, m, C(2')*H*$_2$), 2.54 - 2.61 (4 H, m, C(4)*H*$_2$ and C(1')*H*$_2$), 3.64 (2 H, s, NC*H*$_2$Ph), 3.81 (3 H, s, O*Me*), 4.98 - 5.08 (2 H, m, C(4')*H*$_2$), 5.82 (1 H, ddt, *J* 17.2, 10.4, 6.8, C(3')*H*), 6.82 - 6.89 (4 H, m, *Ar*), 7.23 - 7.37 (5 H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 25.4 (C*Me*$_2$), 31.6 (*C*(2')H_2), 37.4 (*C*(3)H_2), 41.5 (*C*(2)), 49.4, 53.2 (*C*(4)H_2 and *C*(1')H_2), 55.6 (O*Me*), 58.5 (N*C*H_2Ph), 114.4 ($Ph_{ortho,meta}$), 115.4 (*C*(4')H_2), 122.2 ($Ph_{ortho,meta}$), 126.8 (Ph_{para}), 128.2, 128.8 ($Ph_{ortho,meta}$), 136.9 (*C*(3')H), 139.7, 144.4, 157.1 ($Ph_{ipso,para}$), 176.5 (*C*O); *m/z* (APCI$^+$) 381 (MH^+, 100 %); HRMS $C_{24}H_{32}NO_3$ (MH^+) requires 382.2382; found 382.2387.

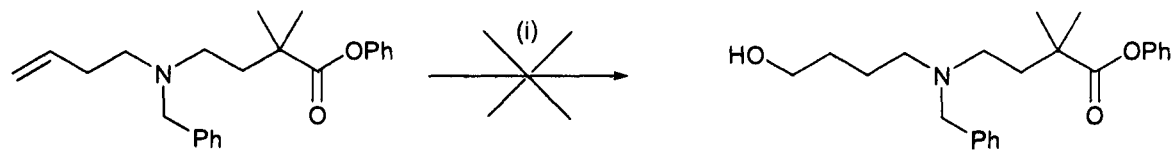
Preparation of methyl 2,2-dimethyl-4-[*N*-benzyl-*N*-(but-3'-enyl)amino]butanoate 108



88 **108**

Gaseous HCl was bubbled through a solution of **88** in MeOH (1.13 g, 4.11 mmol). The resultant solution was refluxed for 2 hours. The solvent was then removed *in vacuo* and the residue partitioned between 2 M NaOH (50 mL) and DCM (50 mL). The aqueous layer was extracted with DCM (50 mL, 2×). The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo* to afford the desired compound **108** as a yellow liquid (1.09 g, 92 %). An analytical sample was subsequently prepared *via* reduced pressure fractional distillation; b.p. 158°C, 10 mm Hg; $C_{18}H_{27}NO_2$ requires C 74.70 %, H 9.40 %, N 4.84 %; found C 74.21 %, H 9.35 %, N 4.92 %; ν_{max} (film)/cm^{-1} 3064, 2975, 2945, 2803 (C-H), 1732 (C=O); δ_H (400 MHz, $CDCl_3$) 1.14 (6 H, s, C*Me*$_2$), 1.74 - 1.78 (2 H, m, C(3)*H*$_2$), 2.22 - 2.27 (2 H, m, C(2')*H*$_2$), 2.41 - 2.45 (2 H, m, C(4)*H*$_2$), 2.51 - 2.55 (2 H, m, C(1')*H*$_2$), 3.58 (2 H, s, NC*H*$_2$Ph), 3.60 (3 H, s, O*Me*), 4.97 - 5.07 (2 H, m, C(4')*H*$_2$), 5.79 (1 H, ddt, *J* 17.0, 10.2, 6.7, C(3')*H*), 7.22 - 7.35 (5 H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 25.3 (C*Me*$_2$), 31.4 (*C*(2')H_2), 37.1 (*C*(3)H_2), 41.2 (*C*(2)), 49.3 (*C*(4)H_2), 51.6 (O*Me*), 53.0 (*C*(1')H_2), 58.3 (N*C*H_2Ph), 115.5 (*C*(4')H_2), 126.8 (Ph_{para}), 128.1, 128.9 ($Ph_{ortho,meta}$), 136.8 (Ph_{ipso}), 139.5 (*C*(3')H), 178.1 (*C*O); *m/z* (APCI$^+$) 290 (MH^+, 100 %); HRMS $C_{18}H_{28}NO_2$ (MH^+) requires 290.2120; found 290.2121.

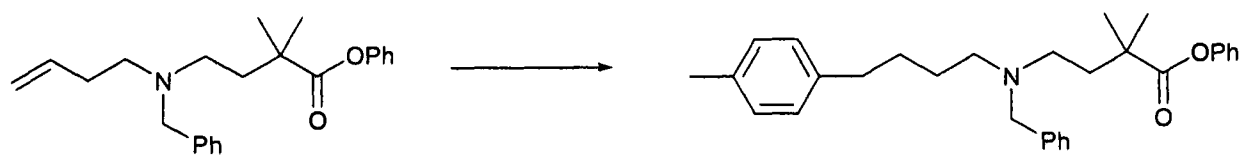
Attempted preparation of phenyl 2,2-dimethyl-4-{*N*-benzyl-*N*-[4'-hydroxybutan-1'-yl] amino}butanoate 109



104 109

A solution of BH_3-THF complex (1.71 mL, 1.71 mmol, 3.0 eq.) was added dropwise to a stirred solution of **104** (200 mg, 0.569 mmol, 1.0 eq.) in THF (4 mL) at 0°C. After 3 hours, H_2O (0.133 mL, excess) was added maintaining a temperature of 0°C. After a further 1.5 hours, aqueous 2 M NaOH solution (0.853 mL, 0.853 mL, 3.0 eq.) was added followed by 35 % aqueous hydrogen peroxide solution (61.0 μL, 0.626 mmol, 1.1 eq.). The mixture was then heated at 50°C for 1 hour then allowed to cool to room temperature. The resulting solution was partitioned between water (20 mL) and DCM (20 mL). The aqueous layer was extracted with DCM (20 mL). The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. Analysis of the 400 MHz ^1H NMR spectrum of the reaction product (201 mg) indicated a complete conversion to the desired product **109**. However, attempted purification by chromatography on silica gel failed to afford the reaction product of sufficient purity for full characterization; δ_H (400 MHz, $CDCl_3$) 1.32 (6 H, s, CMe_2), 1.60 - 1.75 (4 H, m, C(2')H_2 and C(3')H_2), 1.85 - 1.96 (2 H, m, C(3)H_2), 2.55 - 2.65 (4 H, m, C(4)H_2 and C(1')H_2), 3.61 (2 H, t, *J* 5.1, C(4')H_2), 3.89 (2 H, s, NCH_2Ph), 6.92 - 6.93 (2 H, m, *Ph*), 7.20 - 7.48 (8 H, m, *Ph*).

Preparation of phenyl 2,2-dimethyl-4-{*N*-benzyl-*N*-[4'-(*p*-tolyl)butyl]amino}butanoate 114

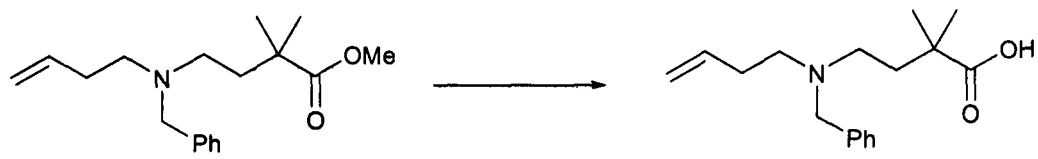


104 114

A solution of 9-BBN (6.26 mL, 3.13 mmol, 0.5 M in THF, 1.1 eq.) was added dropwise to a stirred solution of **104** (1.00 g, 2.84 mmol, 1.0 eq.) in THF (3 mL) at 0°C. Stirring was

continued for 1 hour at 0°C and 4 hours at room temperature. 4-Bromotoluene **98** (584 mg, 3.41 mmol, 1.2 eq.) was added to the hydroboration mixture as a solution in DMF (1.5 mL) and K_2CO_3 (783 mg, 5.70 mmol, 2.0 eq.). The catalyst was prepared separately by the following procedure: DPPF (173 mg, 0.313 mmol, 0.11 eq.) was dissolved in DMF (4 mL). $Pd(OAc)_2$ (57 mg, 0.256 mmol, 0.090 eq.) was then added and the solution degassed before heating at 60°C for 30 min. The catalyst was added to the reaction mixture *via* cannula and the combined mixture heated at 60°C overnight under nitrogen. The reaction mixture was allowed to cool to room temperature, diluted with petrol (10 mL) and quenched with hydrogen peroxide (1 mL, 35 % solution in water). After stirring for further 2 hours the reaction mixture was partitioned between water (40 mL) and DCM (40 mL). The aqueous layer was extracted with DCM (40 mL). The combined organic layers were washed with water (100 mL, 4×), dried (Na_2SO_4) and concentrated *in vacuo*. Purification by chromatography on silica gel, (EtOAc:petrol, 2:8) afforded the desired compound **114** as a colourless oil (1.24 g, 98 %); $C_{30}H_{37}NO_2$ requires C 81.22 %, H 8.41 %, N 3.16 %; found C 81.02 %, H 8.74 %, N 3.33 %; ν_{max} (film)/cm^{-1} 3026, 2933, 2859 (C-H), 1751 (C=O); δ_H (400 MHz, $CDCl_3$) 1.32 (6 H, s, C*Me*$_2$), 1.54 - 1.60 (2 H, m, C(3')*H*$_2$), 1.60 - 1.67 (2 H, m, C(2')*H*$_2$), 1.90 - 1.94 (2 H, m, C(3)*H*$_2$), 2.35 (3 H, s, *Me*Ar), 2.50 - 2.59 (6 H, m, C(4)*H*$_2$, C(1')*H*$_2$ and C(4')*H*$_2$), 3.62 (2 H, s, NC*H*$_2$Ph), 6.94 - 6.97 (2 H, m, *Ar*), 7.07 - 7.13 (4 H, m, 2×*Ar*, 2×*Ph*), 7.22 - 7.40 (8 H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 21.0 (*Me*Ar), 25.4 (*C*(3')H$_2$), 25.7 (C*Me*$_2$), 29.3 (*C*(2')H$_2$), 35.3 (*C*(4')H$_2$), 37.5 (*C*(3)H$_2$), 41.6 (*C*(2)), 49.6 (*C*(4)H$_2$), 53.6 (*C*(1')H$_2$), 58.7 (NCH$_2$Ph), 121.5 (Ph$_{ortho}$), 125.6, 126.7 (Ph$_{para}$), 128.2, 128.3, 128.8, 128.9, 129.3 (Ph$_{ortho,meta}$), 135.0, 139.5, 139.9, 151.0 (Ph$_{ipso,para}$), 176.2 (*C*O); *m/z* (APCI$^+$) 444 (MH$^+$, 100 %); HRMS $C_{30}H_{38}NO_2$ (MH$^+$) requires 444.2903; found 444.2903.

Alternative preparation of 2,2-dimethyl-4-[*N*-benzyl-*N*-(but-3'-enyl)amino] butanoic acid 88



108 88

A solution of **108** (200 mg, 0.691 mmol, 1.0 eq.) and $LiOH.H_2O$ (144 mg, 3.46 mmol, 5.0 eq.) in $THF:H_2O$ (8:1) was stirred vigorously at reflux for 4 hours. The resulting solution was adjusted to neutral pH with 10 % aqueous HCl and extracted with DCM (10 mL, 3×). The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo* to afford the desired compound **88** (174 mg, 91 %) with identical spectroscopic properties to those previously described.

Preparation of 2,2-dimethyl-4-{*N*-benzyl-*N*-[4'-(*p*-tolyl)butyl]amino}butanoic acid 96

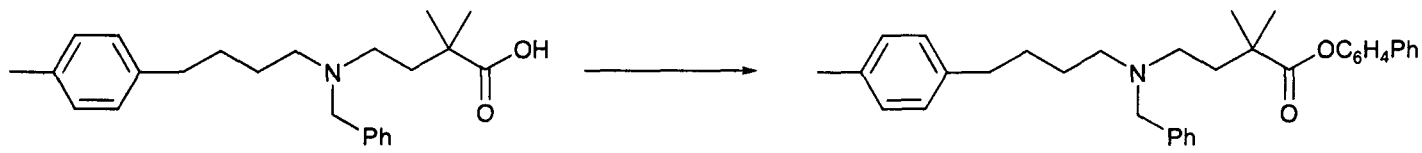


114 96

A solution of **114** (747 mg, 1.68 mmol, 1.0 eq.) and $LiOH.H_2O$ (706 mg, 16.8 mmol, 10.0 eq.) in $THF:H_2O$ (8:1) was stirred vigorously at reflux for 6 hours. The organic solvent was removed *in vacuo* and the resulting solution partitioned between water (200 mL) and DCM (200 mL). The pH was adjusted to neutral with 10 % aqueous HCl and the organic layer collected. The aqueous layer was extracted with DCM (200 mL). The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo* before purification by column chromatography on silica gel ($MeOH:CHCl_3$, $CHCl_3$ - 4:96, stepwise elution) to afford the desired compound **96** as a colourless oil (602 mg, 97 %); ν_{max} (film)/cm^{-1} 3024, 2930, 2861 (C-H)), 2522 (O-H), 1710 (C=O); δ_H (400 MHz, $CDCl_3$) 1.07 (6 H, s, CMe_2), 1.55 - 1.61 (2 H, m, C(3')H_2), 1.65 - 1.73 (4H, m, C(2')H_2 and C(3)H_2), 2.31 (3 H, s, *Me*Ar), 2.55 - 2.63 (4 H, m, C(1')H_2 and C(4')H_2),

2.74 - 2.77 (2 H, m, C(4)H_2), 3.76 (2 H, s, NCH_2Ph), 7.02 - 7.04 (2 H, m, *Ar*), 7.08 - 7.10 (2 H, m, *Ar*), 7.34 - 7.37 (5 H, m, *Ph*), 10 - 12 (1 H, br s, COO*H*); δ_C (100 MHz, $CDCl_3$) 21.0 (*Me*Ar), 23.9 (*C*(3')H_2), 26.9 (C*Me*$_2$), 29.0 (*C*(2')H_2), 34.3 (*C*(4')H_2), 34.9 (*C*(3)H_2), 42.6 (*C*(2)), 49.2 (*C*(4)H_2), 52.4 (*C*(1')H_2), 57.3 (N*C*H_2Ph), 128.2 (Ph_{para}), 128.6, 128.9, 129.1, 130.3 ($Ph_{ortho,meta}$), 133.3, 135.4, 138.0 ($Ph_{ipso,para}$), 180.3 (*C*O); *m/z* (APCI$^+$) 368 (MH^+, 100 %); HRMS $C_{24}H_{34}NO_2$ (MH^+) requires 368.2590; found 368.2589.

Preparation of 4''-biphenyl 2,2-dimethyl-4-{*N*-benzyl-*N*-[4'-(*p*-tolyl)butyl]amino} butanoate 116

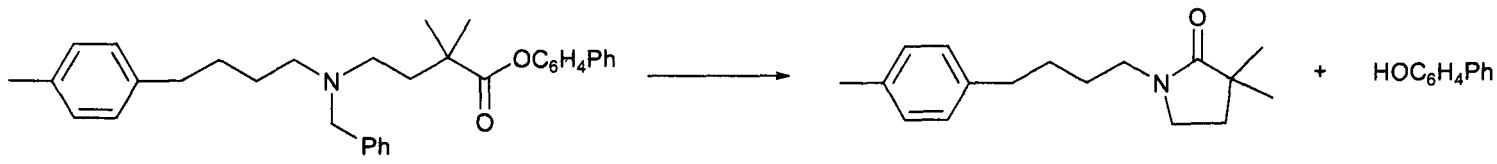


96 116

Following Representative Procedure **2**, to a stirred solution of **96** (528 mg, 1.44 mmol, 1.0 eq.), 4-phenylphenol **115** (734 mg, 4.31 mmol, 3.0 eq.), HOBt (389 mg, 2.87 mmol, 2.0 eq.) and DIPEA (1.00 mL, 5.75 mmol, 4.0 eq.) in DCM (30 mL) was added EDCI (551 mg, 2.87 mmol, 2.0 eq.). The resulting solution was stirred at room temperature for 24 hours and partitioned between water (30 mL) and DCM (30 mL). The aqueous layer was extracted with DCM (30 mL). The combined organic layers were washed with 10 % aqueous HCl (50 mL) and 2 M aqueous NaOH solution (30 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography on silica gel (EtOAc:petrol, 1:9) afforded the title compound **116** as a colourless oil (636 mg, 85 %); $C_{36}H_{41}NO_2$ requires C 83.20 %, H 7.95 %, N 2.70 %; found C 82.85 %, H 8.18 %, N 2.88 %; ν_{max} (film)/cm^{-1} 3028, 2932, 2857 (C-H), 1750 (C=O); δ_H (400 MHz, $CDCl_3$) 1.31 (6 H, s, C*Me*$_2$), 1.52 - 1.64 (4 H, m, C(2')H_2 and C(3')H_2), 1.88 - 2.01 (2 H, m, C(3)H_2), 2.31 (3 H, s, *Me*Ar), 2.45 - 2.57 (6 H, m, C(1')H_2, C(4)H_2 and C(4')H_2), 3.59 (2 H, s, NCH_2Ph), 6.97 - 7.09 (6 H, m, *Ar*), 7.24-7.58 (12 H, m, 2×*Ar*, 10×*Ph*); δ_C (100 MHz, $CDCl_3$) 21.0 (*Me*Ar), 25.4 (C*Me*$_2$), 26.7 (*C*(3')H_2), 29.3 (*C*(2')H_2), 35.3 (*C*(4')H_2), 37.5 (*C*(3)H_2), 41.6

(C(2)), 49.6 (C(4)H_2), 53.6 (C(1')H_2), 58.7 (NCH_2Ph), 121.8 (Ph_{ortho}), 126.8, 127.1 (Ph_{para}), 127.3, 128.1, 128.2, 128.3, 128.8, 128.8, 129.0 ($Ph_{ortho,meta}$), 135.0, 138.8, 139.5, 139.9, 140.5, 150.4 ($Ph_{ipso,para}$), 176.3 (CO); *m/z* (ESI$^+$) 520 (MH^+, 100 %); HRMS $C_{36}H_{42}NO_2$ (MH^+) requires 520.3216; found 520.3212.

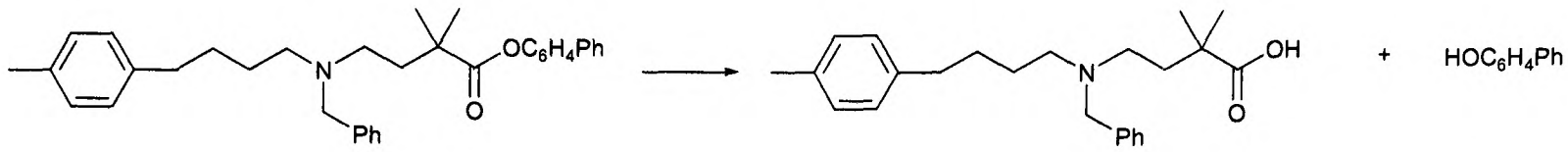
Preparation of *N*-[4'-(*p*-tolyl)butyl]-3,3-dimethyl-pyrrolidin-2-one 117 and 4-phenylphenol 115[7]



116 117 115

Following Representative Procedure **1**, CAN (5.27 g, 9.63 mmol, 5.0 eq.) was added to a stirred solution of **116** (1.00 g, 1.93 mmol, 1.0 eq.) in THF:H_2O (8:1, 100 mL). Saturated aqueous $NaHCO_3$ solution (50 mL) was added after 16 hours and the solution was extracted with ether (200 mL, 3×). Combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography on silica gel (EtOAc:petrol, 2:8 - 3:7, stepwise elution) afforded the desired compound **117** as a colourless oil (317 mg, 64 %); ν_{max} (film)/cm^{-1} 2958, 2926, 2863 (C-H), 1686 (C=O); δ_H (400 MHz, $CDCl_3$) 1.14 (6 H, s, CMe_2), 1.51 - 1.61 (4 H, m, C(2')H_2 and C(3')H_2), 1.83 (2 H, t, *J* 6.7, C(4)H_2), 2.31 (3 H, s, *Me*Ar), 2.60 (2 H, t, *J* 7.2, C(4')H_2), 3.21 (2 H, t, *J* 6.7, C(5)H_2), 3.28 (2 H, t, *J* 6.8, C(1')H_2), 7.05 - 7.10 (4 H, m, *Ar*); δ_C (100 MHz, $CDCl_3$) 21.0 (*Me*Ar), 24.6 (CMe_2), 26.6, 28.5 (C(2')H_2) and (C(3')H_2), 34.1, 34.9 (C(4)H_2 and C(4')H_2), 40.6 (C(3)), 42.3 (C(1')H_2), 43.5 (C(5)H_2), 128.3, 129.0 ($Ph_{ortho,meta}$), 135.1, 139.0 ($Ph_{ipso,para}$), 179.4 (CO), m/z (APCI$^+$) 260 (MH^+, 100 %); HRMS $C_{17}H_{26}NO$ (MH^+) requires 260.2014; found 260.2013. The desired 4-phenylphenol **115** was isolated as slightly yellow solid (206 mg, 63 %). A sample was recrystallysed from DCM (–20°C) for further analysis to afford white needles (136 mg, 42 %); m.p. 158 - 160°C (lit.[7] 164 - 166°C); δ_H (400 MHz, $CDCl_3$) 4.89 (1 H, b s, O*H*), 6.89 - 6.96 (2 H, m, *Ar*), 7.27 - 7.58 (7 H, m, *Ar*).

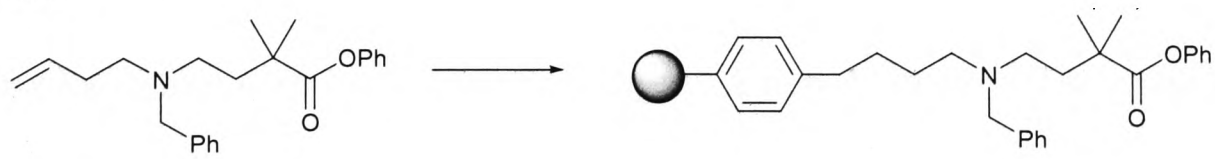
Alternative preparation of 2,2-dimethyl-4-{*N*-benzyl-*N*-[4'-(*p*-tolyl)butyl]amino}butanoic acid 96 and 4-phenylphenol 115



116 96 115

A solution of **116** (2.00 g, 3.85 mmol, 1.0 eq.) and $LiOH.H_2O$ (1.60 g, 38.5 mmol, 10.0 eq.) in $THF:H_2O$ (8:1) was stirred vigorously at reflux for 6 hours. The organic solvent was removed *in vacuo* and the resulting solution partitioned between water (200 mL) and DCM (400 mL), the pH was adjusted to neutral with 10 % aqueous HCl. The aqueous layer was extracted with DCM (400 mL). The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography on silica gel ($MeOH:CHCl_3$, 2:98) afforded 4-phenylphenol **115** as white powder (512 mg, 78 %) with identical spectroscopic properties to those previously described. **96** was also isolated as a colourless oil (1.02 g, 72 %) with identical spectroscopic properties to those previously described.

Preparation of phenyl 2,2-dimethyl 4-{*N*-benzyl-*N*-[4'-(*p*-polystyrenyl)butyl]amino} butanoate 118

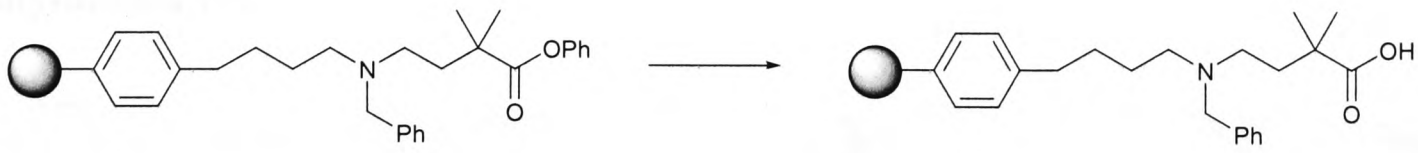


104 118

A solution of 9-BBN (14.2 mL, 7.08 mmol, 0.5 M in THF, 2.2 eq.) was added dropwise to a stirred solution of **104** (2.26 g, 6.44 mmol, 2.0 eq.) in THF (10 mL) at 0°C. Stirring was continued for 1 hour at 0°C and 4 hours at room temperature. Bromopolystyrene resin **94** (1.00 g, 3.22 mmol, Argonout Technologies, 3.22 mmol/g, 106 μm, 1.0 eq.) was washed repeatedly with DMF, THF and DCM and dried *in vacuo* for 3 hours. The catalyst was prepared separately by the following procedure: DPPF (196 mg, 0.354 mmol, 0.11 eq.) was dissolved in

DMF (9 mL), $Pd(OAc)_2$ (65 mg, 0.29 mmol, 0.090 eq.) was then added and the solution degassed before heating at 60°C for 30 min. The hydroboration mixture was concentrated under reduced pressure to 5 mL and transferred to the flask containing the prewashed bromopolystyrene resin *via* cannula followed by K_2CO_3 (1.11 g, 8.05 mmol, 2.5 eq.). The catalyst was transferred to the resin suspension *via* cannula and the resulting mixture heated under nitrogen at 60°C for 18 hours. The resin was transferred to a funnel in DMF and washed with DMF, water, 0.2 M HCl and 2 M aqueous NaOH solution. The resin was further sequentially washed with water, DMF, MeOH, THF, DCM, ether, THF and DCM. The resin was transferred to a round bottom flask, dried *in vacuo* to a constant mass to afford **118** as dark brown powder (1.90 g); ν_{max} (KBr)/cm^{-1} 3024, 2921, 2854 (C-H), 1748 (C=O); loading 1.71 mmol/g.

Preparation of 2,2-dimethyl 4-{*N*-benzyl-*N*-[4'-(*p*-polystyrenyl)butyl]amino} butanoic acid 90



118 90

A suspension of the phenyl ester resin **118** (1.00 g, ~1.71 mmol, 1.0 eq.) in THF:H_2O (8:1) (36 mL) was stirred at reflux with $LiOH.H_2O$ (721 mg, 17.1 mmol, 10 eq.). The resulting resin was washed repeatedly with DMF, water and THF. The resin was dried *in vacuo* to a constant mass (997 mg) to yield the lithium carboxylate salt **119** of the desired carboxylic acid; ν_{max} (KBr)/cm^{-1} 2928 (C-H), 1574 (C=O). The resin (897 mg, ~1.54 mmol) was further washed repeatedly with THF, DMF and 10 % aqueous HCL, the pH was adjusted to neutral with aqueous 2 M aqueous NaOH solution and the resin repeatedly washed with DMF, water and THF. The resin was dried *in vacuo* to a constant mass to afford **90** as dark brown powder (879 mg); ν_{max} (KBr)/cm^{-1} 2923 (C-H), 2566, (O-H), 1713 (C=O); loading 1.98 mmol/g.

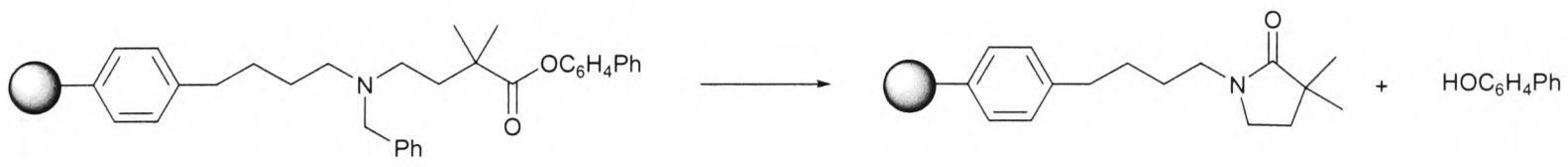
Preparation of 4''-biphenyl 2,2-dimethyl-4-{*N*-benzyl-*N*-[4'- (*p*-polystyrenyl)butyl]amino} butanoate 120



90 120

To a stirred suspension of **90** (879 mg, ~1.54 mmol, 1.0 eq.), 4-phenylphenol **115** (1.72 g, 10.1 mmol, 6.5 eq.), HOBt (839 mg, 6.2 mmol, 4.0 eq.) and DIPEA (2.17 mL, 12.4 mmol, 8.0 eq.) in DCM (10 mL) was added DIC (0.97 mL, 6.2 mmol, 4.0 eq.). After 16 hours the resin was transferred to a funnel and washed repeatedly with DMF, MeOH and DCM. The resin was dried *in vacuo* to a constant mass to afford **120** as dark brown powder (950 mg); ν_{max} (KBr)/ cm^{-1} 3024, 2922, 2853 (C-H), 1748 (C=O), loading 1.52 mmol/g.

Preparation of *N*-[4'-(*p*-polystyrenyl)butyl]-3,3-dimethyl pyrrolidin-2-one 122 and 4-phenylphenol 115



120 122 115

CAN (1.25 g, 2.28 mmol, 5.0 eq.) was added to a stirred suspension of **120** (300 mg, ~0.456 mmol, 1.0 eq.) in THF:H_2O (8:1) (3 mL). After 4 hours reaction time the resin was transferred to a funnel and washed repeatedly with DCM, THF and water. The resin was dried *in vacuo* to a constant mass to afford the debenzylated product **121** as a pale yellow powder (315 mg); ν_{max} (KBr)/cm^{-1} 3020, 2921, 2854 (C-H), 1746 (C=O). Subsequently the resin (271 mg, ~0.392 mmol) was stirred in a mixture of DCM:NEt_3 (5:1) (5 mL) for one hour and washed repeatedly with DCM (20 ml, 3×). The combined organic layers were repeatedly washed with 10 % aqueous HCl (50 ml, 3×). The organic layer was concentrated *in vacuo* to afford the desired 4-phenylphenol **115** with identical spectroscopic properties to those previously described (52 mg,

78 %); HPLC (MeCN/H_2O, 254 nm) >99 %. The resin was dried *in vacuo* to a constant mass to afford **122** as a pale brown powder (209 mg); ν_{max} (KBr)/cm^{-1} 3024, 2924, 2859 (C-H), 1682 (C=O).

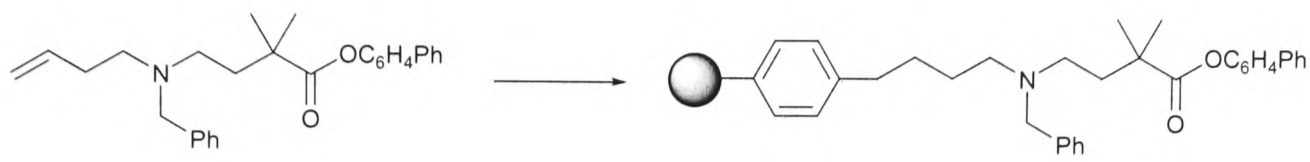
Preparation of 4''-biphenyl 2,2-dimethyl-4-[*N*-benzyl-*N*-(but-3'-enyl)amino]butanoate 123



88 **123**

Following Representative Procedure **2**, to a stirred solution of **88** (200 mg, 0.726 mmol, 1.0 eq.), 4-phenylphenol **115** (371 mg, 2.18 mmol, 3.0 eq.), HOBt (196 mg, 1.45 mmol, 2.0 eq.) and DIPEA (0.508 mL, 2.90 mmol, 4.0 eq.) in DCM (15 mL) was added EDCI (209 mg, 1.09 mmol, 1.5 eq.). The resulting solution was stirred for 16 hours and washed with 10 % aqueous HCl (10 mL) and 2 M NaOH (10 mL). The solution was dried (Na_2SO_4), and concentrated *in vacuo* to afford the desired product **123** as a white waxy solid (218 mg, 70 %). An analytical sample was prepared *via* recrystallization from petrol:DCM (9:1) at –20°C to afford the desired compound **123** as white needles; m.p. 71 - 73°C; $C_{29}H_{33}NO_2$ requires C 81.46 %, H 7.78 %, N 3.28 %; found C 81.47 %, H 7.95 %, N 3.48 %; ν_{max} (KBr)/cm^{-1} 3063, 2948, 2835 (C-H), 1745 (C=O); δ_H (400 MHz, $CDCl_3$) 1.36 (6 H, s, C*Me*$_2$), 1.93 - 1.97 (2 H, m, C(3)*H*$_2$), 2.28 - 2.34 (2 H, m, C(2')*H*$_2$), 2.59 - 2.64 (4 H, m, C(1')*H*$_2$ and C(4)*H*$_2$), 3.67 (2 H, s, NC*H*$_2$Ph), 5.00 - 5.11 (2 H, m, C(4')*H*$_2$), 5.84 (1 H, ddt, *J* 17.2, 10.2, 6.8, C(3')*H*), 7.00 - 7.03 (2 H, m, *Ar*), 7.26 - 7.61 (12 H, m, 2×*Ar,* 10×*Ph*); δ_C (100 MHz, $CDCl_3$) 25.4 (C*Me*$_2$), 31.6 (*C*(2')H_2), 37.4 (*C*(3)H_2), 41.6 (*C*(2)), 49.5 (*C*(4)H_2), 53.3 (*C*(1')H_2), 58.5 (N*C*H_2Ph), 115.5 (*C*(4')H_2), 121.8 (Ph_{ortho}), 126.8, 127.1 (Ph_{para}), 127.3, 128.1, 128.2, 128.8, 128.8 ($Ph_{ortho,meta}$), 136.9 (*C*(3')H), 138.7, 139.7, 140.5, 150.4 ($Ph_{ipso,para}$), 176.3 (*C*O); *m/z* (ESI^+) 428 (MH^+, 100 %); HRMS $C_{29}H_{34}NO_2$ (MH^+) requires 428.2590; found 428.2588.

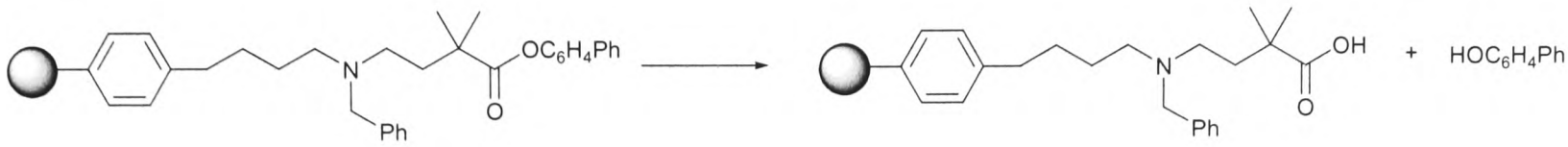
Alternative preparation of 4''-biphenyl 2,2-dimethyl-4-{*N*-benzyl-*N*-[4'-(*p*-polystyrenyl) butyl]amino}butanoate 120



123 120

A solution of 9-BBN (42.5 mL, 21.3 mmol, 0.5 M in THF, 2.2 eq.) was added dropwise to a stirred solution of **123** (8.28 g, 19.3 mmol, 2.0 eq.) in THF (25 mL) at 0°C. Stirring was continued for 1 hour at 0°C and 4 hours at room temperature. Bromopolystyrene resin (3.00 g, 9.66 mmol, Argonout Technologies, 3.22 mmol/g, 106 μm, 1.0 eq.) was washed repeatedly with DMF, THF and DCM and dried *in vacuo* for 3 hours. The catalyst was prepared separately by the following procedure: DPPF (589 mg, 1.06 mmol, 0.11 eq.) was dissolved in DMF (20 mL), $Pd(OAc)_2$ (195 mg, 0.869 mmol, 0.090 eq.) was then added and the solution degassed before heating at 60°C for 30 min. The hydroboration mixture was concentrated under reduced pressure to 5 mL and transferred to the flask containing the prewashed bromopolystyrene resin *via* cannula followed by K_2CO_3 (3.34 g, 24.2 mmol, 2.5 eq.). The catalyst was transferred to the resin suspension *via* cannula and the resulting mixture heated under nitrogen at 60°C for 18 hours. The resin was transferred to a funnel in DMF and washed with DMF, water, 0.2 M aqueous HCl, NEt_3, DMF, MeOH, THF, DCM, ether, THF and DCM. The resin was transferred to a round bottom flask, dried *in vacuo* to a constant mass (6.50 g) to afford **120** with identical spectroscopic properties to those previously described; loading 1.52 mmol/g.

Preparation and loading determination of 2,2-dimethyl 4-{*N*-benzyl-*N*-[4'-(*p*-polystyrenyl) butyl]amino}butanoic acid 90

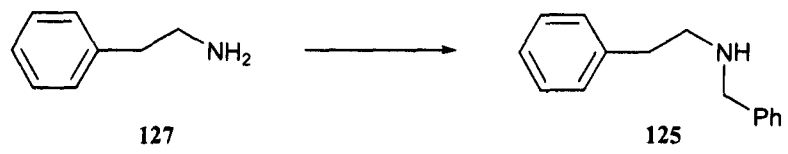


120 90 115

The resin **120** (6.50 g, 9.66 mmol, 1.0 eq.), as a suspension in THF:H_2O (8:1) (100 mL), was stirred at reflux with LiOH.H_2O (4.05 g, 17.1 mmol, 10.0 eq.). The resulting resin was washed repeatedly with water and THF. The washings were collected and the THF removed *in vacuo*. The water layer was acidified with 10 % aqueous HCl and repeatedly extracted with DCM (3×). Evaporation of the solvent *in vacuo* afforded 4-phenylphenol **115** (1.65 g, 9.69 mmol) with identical spectroscopic properties to those previously described. The resin was further washed repeatedly with THF, DMF and 10 % aqueous HCL, the pH was then adjusted to neutral with aqueous 2 M NaOH solution and again repeatedly washed with DMF, water and THF. The resin was dried *in vacuo* to a constant mass to afford **90** a dark brown powder (5.60 g) with identical spectroscopic properties to those previously described; determined loading 1.73 mmol/g.

7.5 Experimental for Chapter IV

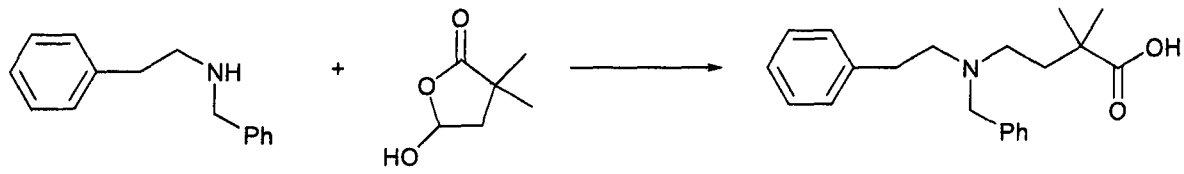
Preparation of *N*-benzyl-*N*-2-phenylethylamine 125[8]



127 125

A solution of **127** (42.2 mL, 336 mmol, 1.0 eq.), benzaldehyde **126** (34.2 mL, 336 mmol, 1.0 eq.) and TMOF (58.8 mL, 538 mmol, 1.6 eq.) in MeOH (1.2 L) was stirred for 1 hour at room temperature. The reaction mixture was cooled to 0°C and $NaBH_4$ (15.3 g, 403 mmol, 1.2 eq.) added portionwise. Stirring was continued for 1 hour at 0°C and then at room temperature for 16 hours. Solvents were removed *in vacuo*, the resulting residue partitioned between water (600 mL) and EtOAc (600 mL). The aqueous layer was extracted with EtOAc (600 mL). Combined organic layers were washed with brine (1.0 L), dried (Na_2SO_4) and concentrated *in vacuo* to afford the desired compound **125** as a colourless oil (63.6 g, 90 %); δ_H (400 MHz, $CDCl_3$) 1.39 (1 H, br s, N*H*), 2.84 - 2.96 (4 H, m, NCH_2CH_2Ph), 3.83 (2 H, s, NCH_2Ph), 7.12 - 7.43 (10 H, m, *Ph*).

Preparation of 2,2-dimethyl-4-[*N*-benzyl-*N*-(2'-phenylethyl)amino]butanoic acid 124

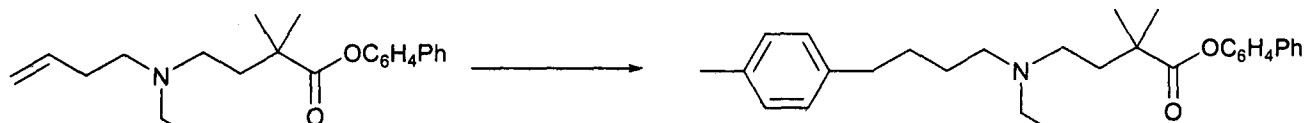


125 68 124

A solution of **125** (11.7 g, 55.4 mmol, 1.0 eq.), **68** (7.93 g, 60.9 mmol, 1.1 eq.) and TMOF (9.69 mL, 88.6 mmol, 1.6 eq.) in MeOH (1.2 L) was stirred for 2 hours at room temperature. The reaction mixture was cooled to 0°C and $NaBH_4$ (2.51 g, 66.4 mmol, 1.2 eq.) added portionwise, stirring was continued for 1 hour at 0°C and overnight at room temperature. The solvent was removed *in vacuo* and partitioned between water (400 mL) and DCM (300 mL), the pH of the water layer was adjusted to neutral with 10 % aqueous HCl. The aqueous layer was then extracted with DCM (300 mL, 3×). The combined organic layers were dried (Na_2SO_4) and

concentrated *in vacuo* to afford the desired compound **124** as brown viscous oil (13.7 g, 76 %); ν_{max} (film)/cm^{-1} 2520 (O-H), 3062, 3027, 2961, 2868 (C-H), 1712 (C=O); δ_H (400 MHz, $CDCl_3$) 1.10 (6 H, s, C*Me*$_2$), 1.77 (2 H, t, *J* 5.9, C(3)*H*$_2$), 2.81 - 2.96 (6 H, m, C(4)*H*$_2$, C(1')*H*$_2$ and C(2')*H*$_2$), 3.85 (2 H, s, NC*H*$_2$Ph), 7.12 - 7.42 (10 H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 26.7 (C*Me*$_2$), 31.5 (*C*(2')H$_2$), 34.6 (*C*(3)H$_2$), 42.3 (*C*(2)), 49.3 (*C*(4)H$_2$), 54.3 (*C*(1')H$_2$), 57.7 (NCH$_2$Ph), 126.6, 128.4 (Ph$_{para}$), 128.6, 128.6, 128.8, 130.18 (Ph$_{ortho,meta}$), 134.1, 138.4 (Ph$_{ipso}$), 180.4 (*C*O); *m/z* (ESI$^+$) 326 (MH$^+$, 100 %); HRMS $C_{21}H_{28}NO_2$ (MH$^+$) requires 326.2120; found 326.2106.

Alternative preparation of 4''-biphenyl 2,2-dimethyl-4-{*N*-benzyl-*N*-[4'-(*p*-tolyl)butyl] amino}butanoate 116

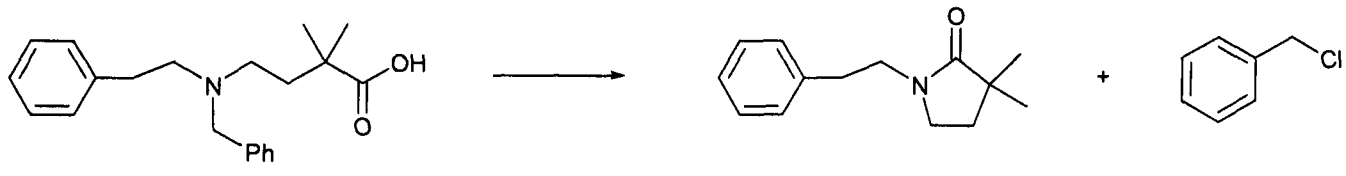


123 116

A solution of 9-BBN (10.3 mL, 5.15 mmol, 0.5 M in THF, 1.1 eq.) was added dropwise to a stirred solution of **123** (2.00 g, 4.68 mmol, 1.0 eq.) in THF (6 mL) at 0°C. Stirring was continued for 1 hour at 0°C and 4 hours at room temperature. 4-Bromotoluene **98** (960 mg, 5.61 mmol, 1.2 eq.) was added to the hydroboration mixture as a solution in DMF (3 mL) and K_2CO_3 (1.29 g, 9.34 mmol, 2.0 eq.). The catalyst was prepared separately by the following procedure: DPPF (285 mg, 0.514 mmol, 0.11 eq.) was dissolved in DMF (8 mL), $Pd(OAc)_2$ (94 mg, 0.421 mmol, 0.090 eq.) was then added and the solution degassed before heating at 60°C for 30 min. The catalyst was added to the reaction mixture *via* cannula and the combined mixture heated at 60°C overnight under nitrogen. The reaction mixture was allowed to cool to room temperature, diluted with petrol (20 mL) and quenched with hydrogen peroxide (2 mL, 35 % solution in water). After stirring for further 2 hours the reaction mixture was partitioned between water (80 mL) and DCM (80 mL). The aqueous layer was extracted with DCM (80

mL). The combined organic layers were washed with water (200 mL, 4×), dried (Na_2SO_4) and the solvent removed *in vacuo*. Purification by chromatography on silica gel, (EtOAc:petrol, 2:8) afforded the desired compound **116** as a colourless oil (2.28 g, 94 %) with identical spectroscopic properties to those previously reported.

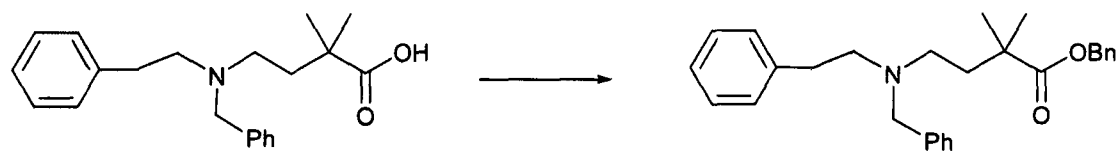
Attempted preparation of 2,2-dimethyl-4-[*N*-benzyl-*N*-(2'-phenylethyl)amino]butanoyl chloride 141, preparation of *N*-(2'-phenylethyl) 3,3-dimethyl-pyrrolidin-2-one 142 and benzyl chloride 143[9]



124 142 143

To a stirred solution of **124** (232 mg, 0.714 mmol, 1.0 eq.) in DCM (2 mL) was added excess $SOCl_2$. After 16 hours of stirring at room temperature under nitrogen the solution was partitioned between water (15 mL) and DCM (15 mL). The aqueous layer was extracted with DCM (15 mL). The combined organic layers were dried (Na_2SO_4) and the solvent removed *in vacuo* to afford an approximately 38:62 mixture (204 mg) of the lactam **142** with spectroscopic properties identical to those described *vide infra* and benzyl chloride **143**.

Preparation of benzyl 2,2-dimethyl-4-[*N*-benzyl-*N*-(2'-phenylethyl)amino]butanoate 149

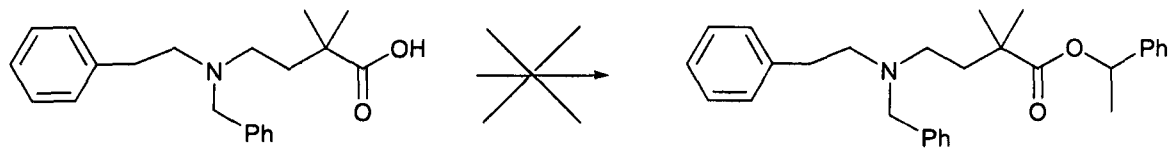


124 149

Following Representative Procedure **2**, to a stirred solution of **124** (250 mg, 0.769 mmol, 1.0 eq.), benzyl alcohol **145** (0.239 mL, 2.31 mmol, 3.0 eq.), HOBt (208 mg, 1.54 mmol, 2.0 eq.) and DIPEA (0.538 mL, 3.08 mmol, 4.0 eq.) in DCM (20 mL) was added EDCI (221 mg, 1.15 mmol, 1.5 eq.). The resulting solution was stirred for 16 hours, diluted with DCM (20 mL), washed with 10 % aqueous HCl (40 mL) and 2 M aqueous NaOH solution (40 mL). The

resultant solution was dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography on silica gel (EtOAc:petrol, 1:9) afforded the desired compound **149** as a yellow viscous oil (229 mg, 72 %); ν_{max} (film)/cm^{-1} 3028, 2946, 2806 (C-H), 1728 (C=O); δ_H (400 MHz, $CDCl_3$) 1.21 (6 H, s, C*Me*$_2$), 1.78 - 1.82 (2 H, m, C(3)*H*$_2$), 2.47 - 2.51 (2 H, m, C(4)*H*$_2$), 2.65 - 2.76 (4 H, m, C(1')*H*$_2$ and C(2')*H*$_2$), 3.61 (2 H, s, NC*H*$_2$Ph), 5.09 (2 H, s, OC*H*$_2$Ph), 7.12 - 7.39 (15 H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 25.4 (C*Me*$_2$), 33.4 (*C*(2')H$_2$), 37.4 (*C*(3)H$_2$), 41.3 (*C*(2)), 49.5 (*C*(4)H$_2$), 55.4 (*C*(1')H$_2$), 58.4 (NCH$_2$Ph), 66.1 (OCH$_2$Ph), 125.8, 126.8, 128.0 (Ph$_{para}$), 128.1, 128.1, 128.2, 128.5, 128.7, 128.8 (Ph$_{ortho,meta}$), 136.3, 139.6, 140.6 (Ph$_{ipso}$), 177.5 (*C*O); *m/z* (ESI$^+$) 416 (MH$^+$, 100 %); HRMS $C_{28}H_{34}NO_2$ (MH$^+$) requires 416.2590; found 416.2589.

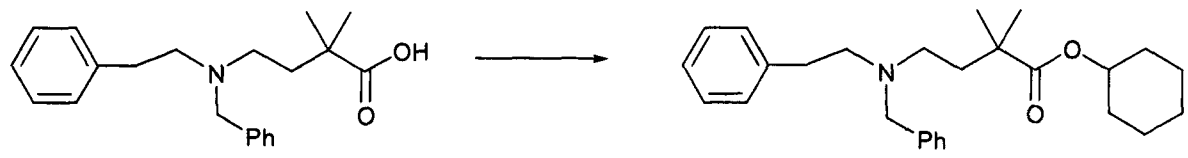
Attempted preparation of (α-methybenzyl-1''-yl) 2,2-dimethyl-4-[*N*-benzyl-*N*-(2'-phenylethyl)amino]butanoate 150



124 **150**

Following Representative Procedure **2**, to a stirred solution of **124** (250 mg, 0.769 mmol, 1.0 eq.), α-methylbenzyl alcohol **146** (0.278 mL, 2.31 mmol, 3.0 eq.), HOBt (208 mg, 1.54 mmol, 2.0 eq.) and DIPEA (0.403 mL, 2.31 mmol, 3.0 eq.) in DCM (20 mL) was added EDCI (221 mg, 1.15 mmol, 1.5 eq.). The resulting solution was stirred for 16 hours, diluted with DCM (20 mL), washed with 10 % aqueous HCl (40 mL) and 2 M aqueous NaOH solution (40 mL). The resultant solution was dried (Na_2SO_4) and concentrated *in vacuo*. ^{1}H NMR spectroscopic analysis of the crude reaction product (346 mg) revealed that none of the desired product **150** had been formed.

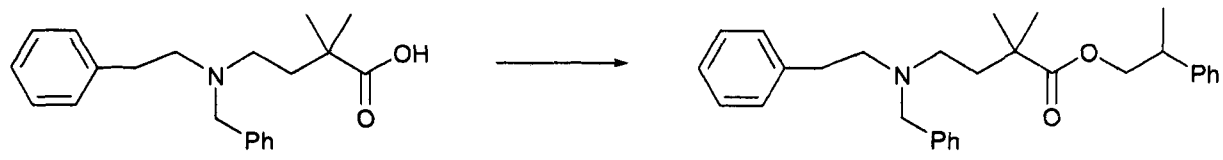
Preparation of cyclohexyl 2,2-dimethyl-4-[*N*-benzyl-*N*-(2'-phenylethyl)amino] butanoate 151



124 151

Following Representative Procedure **2**, to a stirred solution of **124** (250 mg, 0.769 mmol, 1.0 eq.), cyclohexanol **147** (0.244 mL, 2.31 mmol, 3.0 eq.), HOBt (208 mg, 1.54 mmol, 2.0 eq.) and DIPEA (0.538 mL, 3.08 mmol, 4.0 eq.) in DCM (20 mL) was added EDCI (221 mg, 1.15 mmol, 1.5 eq.). The resulting solution was stirred for 16 hours then washed with 10 % aqueous HCl (30 mL) and 2 M aqueous NaOH solution (30 mL). The resultant solution was dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography on silica gel (EtOAc:petrol, 1:9 - 2:8, stepwise elution) afforded the desired compound **151** as a colourless oil (39 mg, 12 %); ν_{max} (film)/cm^{-1} 3027, 2935, 2859, (C-H), 1722 (C=O); δ_H (400 MHz, $CDCl_3$) 1.16 (6 H, s, C*Me*$_2$), 1.31 - 1.57 (6 H, m, C(3'')*H*$_2$, C(4'')*H*$_2$ and C(5'')*H*$_2$), 1.64 - 1.82 (6 H, m, C(2'')*H*$_2$, C(6'')*H*$_2$ and C(3)*H*$_2$), 2.49 - 2.53 (2 H, m, C(4)*H*$_2$), 2.69 - 2.80 (4 H, m, C(1')*H*$_2$ and C(2')*H*$_2$), 3.66 (2 H, s, NC*H*$_2$Ph), 4.70 - 4.75 (1 H, m, C(1'')), 7.15 - 7.45 (10 H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 23.6, 25.4 (*C*(3'')H$_2$, *C*(4'')H$_2$ and *C*(5'')H$_2$), 25.5 (C*Me*$_2$), 31.4 (*C*(2'')H$_2$ and *C*(6'')H$_2$), 33.5 (*C*(2')H$_2$), 37.2 (*C*(3)H$_2$), 41.2 (*C*(2)), 49.6 (*C*(4)H$_2$), 55.5 (*C*(1')H$_2$), 58.5 (NC*H*$_2$Ph), 72.1 (*C*(1'')H), 125.8, 126.8 (Ph$_{para}$), 128.1, 128.2, 128.7, 128.8 (Ph$_{ortho,meta}$), 139.5, 140.6 (Ph$_{ipso}$), 177.0 (*C*O); *m/z* (ESI^+) 408 (MH^+, 100 %); HRMS $C_{27}H_{38}NO_2$ (MH^+) requires 408.2903; found 408.2895.

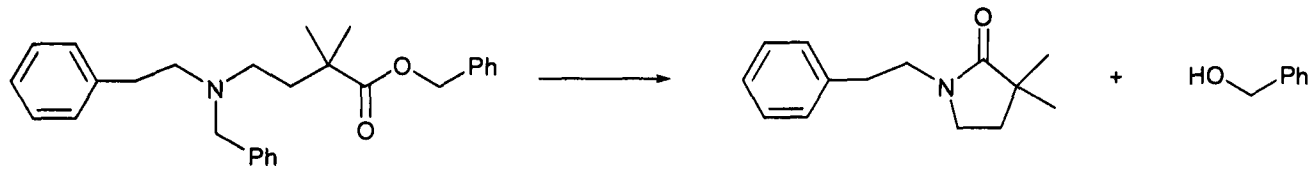
Preparation of 2''-phenylprop-1''-yl 2,2-dimethyl-4-[*N*-benzyl-*N*-(2'-phenylethyl)amino] butanoate 152



124 152

Following Representative Procedure **2**, to a stirred solution of **124** (544 mg, 1.67 mmol, 1.0 eq.), 2-phenylpropan-1-ol **148** (0.701 mL, 5.02 mmol, 3.0 eq.), HOBt (452 mg, 3.35 mmol, 2.0 eq.) and DIPEA (0.878 mL, 5.02 mmol, 3.0 eq.) in DCM (20 mL) was added EDCI (481 mg, 2.51 mmol, 1.5 eq). The resulting solution was stirred for 16 hours and washed with 10 % aqueous HCl (30 mL) and 2 M aqueous NaOH solution (30 mL). The solution was dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography on silica gel (EtOAc:petrol, 1:9) afforded the desired compound **152** as a colourless oil (525 mg, 71 %); ν_{max} (film)/cm^{-1} 3027, 2967, 2807 (C-H), 1726 (C=O); δ_H (400 MHz, $CDCl_3$) 1.12 (6 H, s, C*Me*$_2$), 1.31 (3 H, d, *J* 7.0, C(3'')*H*$_3$), 1.71 - 1.75 (2 H, m, C(3)*H*$_2$), 2.44 - 2.48 (2 H, m, C(4)*H*$_2$), 2.64 - 2.79 (4 H, m, C(1')*H*$_2$ and C(2')*H*$_2$), 3.04 - 3.13 (1 H, m, C(2'')*H*), 3.62 (2 H, s, NC*H*$_2$Ph), 4.06 - 4.22 (2 H, m, C(1'')*H*$_2$), 7.16 - 7.47 (15 H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 18.1 (*C*(3'')H$_3$), 25.3 (C*Me*$_2$), 33.5 (*C*(2')H$_2$), 37.2 (*C*(3)H$_2$), 39.0 (*C*(2'')H), 41.3 (*C*(2)), 49.5 (*C*(4)H$_2$), 55.4 (*C*(1')H$_2$), 58.4 (N*C*H$_2$Ph), 69.2 (*C*(1'')H$_2$), 125.9, 126.6, 126.8 (Ph$_{para}$), 127.3, 128.2, 128.3, 128.4, 128.8 (Ph$_{ortho,meta}$), 139.5, 140.6, 143.2 (Ph$_{ipso}$), 177.5 (CO); *m/z* (ESI$^+$) 444 (MH$^+$, 100 %); HRMS $C_{30}H_{38}NO_2$ (MH$^+$) requires 444.2903; found 444.2905.

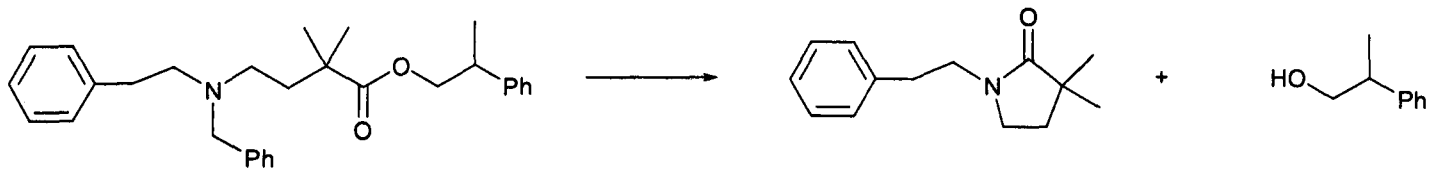
Preparation of *N*-(2'-phenylethyl) 3,3-dimethyl-pyrrolidin-2-one 142 and benzyl alcohol 145[10]



149 142 145

Following Representative Procedure **1**, CAN (198 mg, 0.361 mmol, 5.0 eq.) was added to a stirred solution of **149** (30 mg, 0.0723 mmol, 1.0 eq.) in THF:H_2O (8:1) (2 mL). After 16 hours the mixture was partitioned with 2 M aqueous NaOH solution (10 mL) and ether (10 mL). The aqueous layer was extracted with ether (10 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford a 80:20 mixture of the desired debenzylated product **153**; δ_H (400 MHz, $CDCl_3$) 1.21 (6 H, s, C*Me*$_2$), 1.76 - 1.81 (2 H, m, C(3)*H*$_2$), 2.61 - 2.65 (2 H, m, C(4)*H*$_2$), 2.80 - 2.89 (4 H, m, C(1')*H*$_2$ and C(2')*H*$_2$), 4.71 (3 H, s, OC*H*$_2$Ph), 7.00 - 7.50 (10 H, m, *Ph*); lactam **142** with identical spectroscopic properties to those described *vide infra* and a trace of benzyl alcohol **145**. The mixture was refluxed in toluene for 6 hours, the solvent was removed *in vacuo* to afford lactam **142** and a trace of benzyl alcohol **145** (21 mg).

Preparation of *N*-(2'-phenylethyl) 3,3-dimethyl-pyrrolidin-2-one 142 and 2-phenylpropan-1-ol 148[11]



152 142 148

Following Representative Procedure **1**, CAN (494 mg, 0.903 mmol, 5.0 eq.) was added to a stirred solution of **152** (80 mg, 0.181 mmol, 1.0 eq.) in THF:H_2O (8:1) (6 mL). After 3 hours the mixture was partitioned with 2 M aqueous NaOH solution (5 mL) and ether (20 mL). The

aqueous layer was extracted with ether (20 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The crude residue was refluxed in toluene for 16 hours. The solvent was removed and separation by column chromatography on silica gel (EtOAc:petrol, 1:9 - 4:6, stepwise elution) afforded 2-phenylpropan-1-ol **148** (13 mg, 53 %) as a colourless oil; δ_H (200 MHz, $CDCl_3$) 1.30 (3 H, d, *J* 6.9, CH_3CHPh), 2.93 - 3.01 (1 H, m, CH_3CHPh), 3.72 (2 H, d, *J* 6.8, CH_2OH), 7.20 - 7.40 (5 H, m, *Ph*). **142** was also isolated as a colourless oil (29 mg, 74 %); ν_{max} (film)/cm^{-1} 2961, 2928, 2866 (C-H), 1685 (C=O); δ_H (400 MHz, $CDCl_3$) 1.08 (6 H, s, CMe_2), 1.77 (2 H, t, *J* 6.8, C(4)H_2), 2.85 (2 H, t, *J* 7.4, C(2')H_2), 3.12 (2 H, t, *J* 6.8, C(5)H_2), 3.54 (2 H, t, *J* 7.4, C(1')H_2), 7.20 - 7.32 (5 H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 24.5 (CMe_2), 33.7 (C(2')H_2), 34.2 (C(4)H_2), 40.5 (C(3)), 43.9, 44.1 (C(1')H_2 and C(5)H_2), 126.4 (Ph_{para}), 128.4, 128.7 ($Ph_{ortho,meta}$), 138.8 (Ph_{ipso}), 179.4 (CO); *m/z* (ESI^+) 218 (MH^+, 100 %); HRMS $C_{14}H_{20}NO$ (MH^+) requires 218.1545; found 218.1548.

Preparation of benzyl 2,2-dimethyl-4-{*N*-benzyl-*N*-[4'-(*p*-tolyl)butyl]amino} butanamide 154

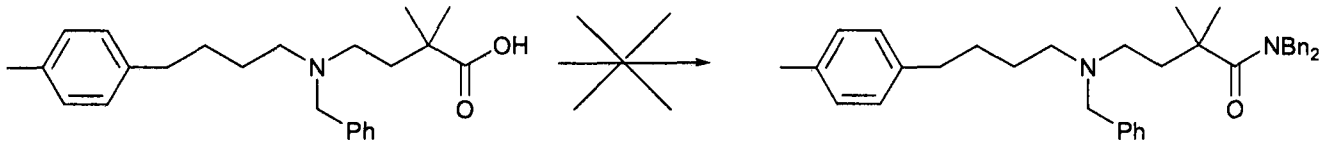


96 154

Following Representative Procedure **2**, to a stirred solution of **96** (252 mg, 0.686 mmol, 1.0 eq.), benzylamine **93** (0.225 mL, 2.06 mmol, 3.0 eq.), HOBt (185 mg, 1.37 mmol, 2.0 eq.) and DIPEA (0.480 mL, 2.74 mmol, 4.0 eq.) in DCM (15 mL) was added EDCI (263 mg, 1.37 mmol, 2.0 eq.). The resulting solution was stirred for 16 hours and washed with water (30 mL), 10 % aqueous HCl (30 mL, 2×) and 2 M aqueous NaOH solution (30 mL). The organic layer was dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography on silica gel (MeOH:$CHCl_3$, 1:99 - 4:96, stepwise elution) afforded the desired compound **154** as a colourless oil (296 mg, 95 %); ν_{max} (film)/cm^{-1} 3345 (N-H), 3027, 2930, 286 (C-H), 1641, 1516

(C=O); δ_H (400 MHz, $CDCl_3$) 1.17 (6 H, s, C*Me*$_2$), 1.47 - 1.49 (2 H, m, C(2')*H*$_2$), 1.52 - 1.58 (2 H, m, C(3')*H*$_2$), 1.74 (2 H, t, *J* 7.4, C(3)*H*$_2$), 2.34 (3 H, s, *Me*Ar), 2.39 (2 H, t, *J* 7.4, C(1')*H*$_2$), 2.45 (2 H, t, *J* 7.2, C(4)*H*$_2$), 2.53 (2 H, t, *J* 7.4, C(4')*H*$_2$), 3.51 (2 H, s, NC*H*$_2$Ph), 4.38 (2 H, d, *J* 5.4, NHC*H*$_2$Ph), 6.90 (1 H, t, *J* 5.4, N*H*), 7.04 - 7.12 (4 H, m, *Ar*), 7.23 - 7.36 (10 H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 21.0 (*Me*Ar), 26.1 (C*Me*$_2$), 26.2 (*C*(3')H$_2$), 29.3 (*C*(2')H$_2$), 35.2 (*C*(4')H$_2$), 37.5 (*C*(3)H$_2$), 41.6 (*C*(2)), 43.5 (NH*C*H$_2$Ph), 49.6 (*C*(4)H$_2$), 53.5 (*C*(1')H$_2$), 58.4 (NCH$_2$Ph), 126.9, 127.3 (Ph$_{para}$), 127.8, 128.2, 128.3, 128.6, 129.0, 129.0 (Ph$_{ortho,meta}$), 135.1, 138.9, 139.2, 139.4 (Ph$_{ipso,para}$), 177.4 (*C*O); *m/z* (ESI$^+$) 457 (MH$^+$, 100 %); HRMS $C_{31}H_{41}N_2O$ (MH$^+$) requires 457.3219; found 457.3214.

Attempted preparation of *N,N*-dibenzyl 2,2-dimethyl-4-{*N'*-benzyl-*N'*-[4'-(*p*-tolyl)butyl] amino}butanamide 155



96 155

Following Representative Procedure **2**, to a stirred solution of **96** (546 mg, 1.49 mmol, 1.0 eq.), dibenzylamine (0.857 mL, 4.46 mmol, 3.0 eq.), HOBt (402 mg, 2.97 mmol, 2.0 eq.) and DIPEA (1.04 mL, 5.94 mmol, 4.0 eq.) in DCM (30 mL) was added EDCI (570 mg, 2.97 mmol, 2.0 eq.). The resulting solution was stirred for 16 hours and washed with water (30 mL), 10 % aqueous HCl (30 mL, 2×) and 2 M aqueous NaOH solution (30 mL). The organic layer was dried (Na_2SO_4) and concentrated *in vacuo*. ^{1}H NMR spectroscopic analysis of the crude reaction product (1.18 g) revealed that none of the desired product **155** had been formed.

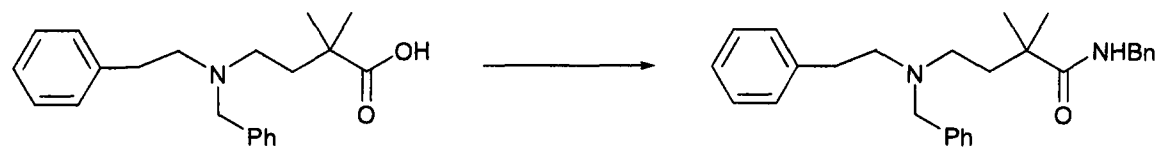
Preparation of 1-phenylpropylamine 156[12]



157 156

A mixture of propiophenone **157** (13.4 g, 100 mmol, 1.0 eq.) and formamide (18.5 g, 400 mmol, 4.0 eq.) was refluxed at 180°C with portionwise addition of formic acid (17 mL, 440 mmol, 4.4 eq.) over 8 hours. The solution was allowed to cool to r.t. then extracted with toluene (50 mL, 3×), the combined organic extracts were dried ($MgSO_4$), concentrated *in vacuo* to yield an oily residue which was subsequently refluxed in concentrated HCl (20 mL) for 1 hour. The resulting mixture was allowed to cool to room temperature and then extracted with toluene. The separated aqueous layer was basified to pH 11 (2 M aqueous NaOH solution) and extracted with EtOAc (75 mL, 3×). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo to afford the desired compound **156** as a colourless oil (5.30 g, 39 %) which was used without further purification; δ_H (200 MHz, $CDCl_3$) 0.87 (3 H, t, *J* 7.4 CH_2CH_3), 1.79 - 1.89 (2 H, m, CH_2CH_3), 3.90 (1 H, t, *J* 7.1, $CHCH_2CH_3$), 4.74 (2H, br s, NH_2), 7.18 - 7.36 (5 H, m, *Ph*).

Preparation of benzyl 2,2-dimethyl-4-[*N*-benzyl-*N*-(2'-phenylethyl)amino]butanamide 159



124 159

Following Representative Procedure **2**, to a stirred solution of **124** (3.20 g, 9.83 mmol, 1.0 eq.), benzylamine **93** (3.22 mL, 29.5 mmol, 3.0 eq.), HOBt (2.66 g, 19.7 mmol, 2.0 eq.) and DIPEA (6.88 mL, 39.3 mmol, 4.0 eq.) in DCM (100 mL) was added EDCI (2.45 g, 12.8 mmol, 1.3 eq.). The resulting solution was stirred for 16 hours then washed with 10 % aqueous HCl (150 mL) and 2 M aqueous NaOH solution (150 mL), then dried (Na_2SO_4) and concentrated *in vacuo*.

Purification by column chromatography on silica gel (MeOH:$CHCl_3$, 2:98) afforded the desired compound **159** as a yellow viscous oil (4.08 g, 100 %); ν_{max} (film)/cm^{-1} 3351 (N-H), 3027, 2957 (C-H), 1643, 1529 (C=O); δ_H (400 MHz, $CDCl_3$) 1.20 (6 H, s, CMe_2), 1.76 (2 H, t, *J* 7.4, C(3)H_2), 2.55 (2 H, t, *J* 7.4, C(4)H_2), 2.65 - 2.76 (4 H, m, C(1')H_2 and C(2')H_2), 3.63 (2 H, s, NCH_2Ph), 4.40 (2 H, d, *J* 5.4, NHCH_2Ph), 6.65 (1 H, t, *J* 5.4, N*H*CH_2Ph), 7.12 - 7.47 (15 H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 26.1 (CMe_2), 33.1 (*C*(2')H_2), 37.6 (*C*(3)H_2), 41.5 (*C*(2)), 43.5 (NH*C*H_2Ph), 49.6 (*C*(4)H_2), 55.4 (*C*(1')H_2), 58.4 (N*C*H_2Ph), 125.9, 126.9, 127.4 (Ph_{para}), 127.8, 128.2, 128.3, 128.7, 128.7, 129.0 ($Ph_{ortho,meta}$), 138.8, 139.1, 140.4 (Ph_{ipso}), 177.3 (*C*O); *m/z* (ESI^+) 415 (MH^+, 100 %); HRMS $C_{35}H_{35}N_2O$ (MH^+) requires 415.2749; found 415.2754.

Preparation of (*R*)-(α-methylbenzyl) 2,2-dimethyl-4-[*N*-benzyl-*N*-(2'-phenylethyl)amino] butanamide 160

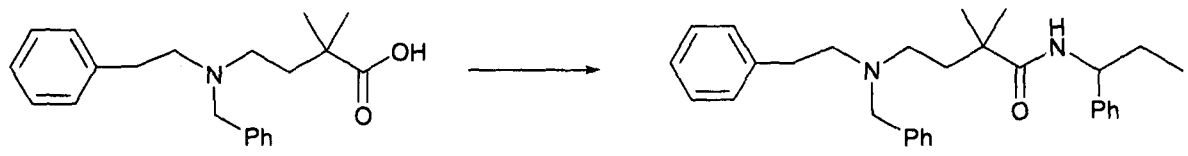


124 160

Following Representative Procedure **2**, to a stirred solution of **124** (793 mg, 2.44 mmol, 1.0 eq.), (*R*)-α-methylbenzylamine **158** (1.26 mL, 9.76 mmol, 4.0 eq.), HOBt (659 mg, 4.88 mmol, 2.0 eq.) and DIPEA (1.71 mL, 9.76 mmol, 4.0 eq.) in DCM (30 mL) was added EDCI (702 mg, 3.66 mmol, 1.5 eq.). The resulting solution was stirred for 16 hours, diluted with DCM (30 mL), washed with 10 % aqueous HCl (60 mL) and 2 M aqueous NaOH solution (60 mL). The solution was then dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography on silica gel (MeOH:$CHCl_3$, 2:98) afforded the desired compound **160** as a yellow viscous oil (1.00 g, 96 %); $[\alpha]_D^{25}$ +38.8 (c= 1.0, $CHCl_3$); ν_{max} (film)/cm^{-1} 3339 (N-H), 3061, 3027, 2929 (C-H), 1634, 1530 (C=O); δ_H (400 MHz, $CDCl_3$) 1.16 (6 H, s, CMe_2), 1.46 (3 H, d, *J* 7.0, C(α)*Me*), 1.74 (2H, t, *J* 7.8, C(3)H_2), 2.51 (2 H, t, *J* 7.8, C(4)H_2),), 2.65 - 2.75 (4 H, m, C(1')H_2 and C(2')H_2), 3.62 (2 H, s, NCH_2Ph), 5.13 (1 H, m, C(α)*H*), 6.08 (1 H, d, *J* 7.6,

CON*H*), 7.13 - 7.39 (15 H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 21.5 (C(α)*Me*), 25.7, 25.9 (C*Me*$_2$), 33.2 (*C*(2')H_2), 37.9 (*C*(3)), 41.2(*C*(2)), 48.5 (*C*(α)Me), 49.5 (*C*(4)H_2), 55.5 (*C*(1')H_2), 58.5 (NC*H*$_2$Ph), 125.8, 126.2, 126.8 (Ph_{para}), 127.3, 128.2, 128.2, 128.6, 128.8, 128.8 ($Ph_{ortho,meta}$), 139.4, 140.6, 143.4 (Ph_{ipso}), 176.3 (*C*O); *m/z* (ESI^+) 429 (MH^+, 100 %); HRMS $C_{29}H_{37}N_2O$ (MH^+) requires 429.2096; found 429.2094.

Preparation of 1''-phenyl prop-1''-yl 2,2-dimethyl-4-[*N*-benzyl-*N*-(2'-phenylethyl)amino] butanamide 161



124 161

Following Representative Procedure **2**, to a stirred solution of **124** (259 mg, 0.797 mmol, 1.0 eq.), 1-phenylpropylamine **156** (430 mg, 3.19 mmol, 4.0 eq.), HOBt (215 mg, 1.59 mmol, 2.0 eq.) and DIPEA (0.557 mL, 3.19 mmol, 4.0 eq.) in DCM (20 mL) was added EDCI (229 mg, 1.19 mmol, 1.5 eq.). The resulting solution was stirred for 16 hours then diluted with DCM (20 mL) before being washed with 10 % aqueous HCl (40 mL) and 2 M aqueous NaOH solution (40 mL). The resultant solution was dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography on silica gel (MeOH:$CHCl_3$, 2:98) afforded the desired compound **161** as a yellow viscous oil (350 mg, 99 %); ν_{max} (film)/cm^{-1} 3350 (N-H), 3027, 2964 (C-H), 1641, 1495 (C=O); δ_H (400 MHz, $CDCl_3$) 0.89 (3 H, t, *J* 7.5, C(3'')*H*$_3$), 1.16 (6 H, s, C*Me*$_2$), 1.69 - 1.84 (4 H, m, C(3)*H*$_2$ and C(2'')*H*$_2$), 2.44 - 2.55 (2 H, m, C(4)*H*$_2$), 2.63 - 2.73 (4 H, m, C(1')*H*$_2$ and C(2')*H*$_2$), 3.62 (2 H, s, NC*H*$_2$Ph), 4.87 (1 H, app. q, *J* 7.5, C(1'')*H*), 6.03 (1 H, d, *J* 8.0, N*H*), 7.11 - 7.40 (15 H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 10.8 (*C*(3'')H_3), 25.8 (C*Me*$_2$), 28.9 (*C*(1'')H), 33.0 (*C*(2')H_2), 37.8 (*C*(3)H_2), 41.2 (*C*(2)), 49.5 (*C*(4)H_2), 54.7 (*C*(2'')H_2), 55.3 (*C*(1')H_2), 58.2 (N*C*H_2Ph), 125.9, 126.6, 127.3 (Ph_{para}), 128.2, 128.3, 128.5, 128.6, 128.8, 128.9

($Ph_{ortho,meta}$), 138.9, 140.4, 142.4 (Ph_{ipso}), 176.5 (*C*O); *m/z* (ESI^+) 443 (MH^+, 100 %); HRMS $C_{30}H_{39}N_2O$ (MH^+) requires 443.3062; found 443.3061.

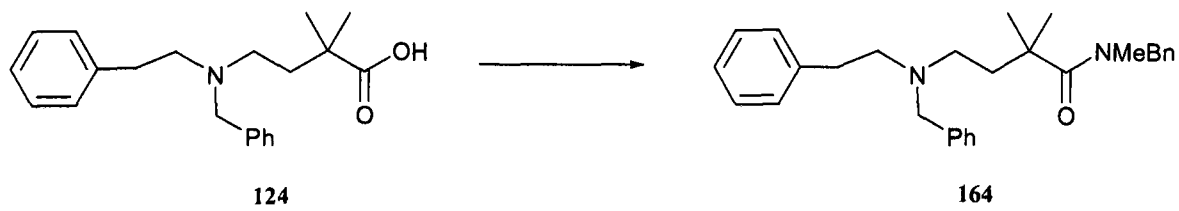
Preparation of *N*-benzyl-*N*-ethylamine 59[13]



126 **163**.HCl **59**

A solution of benzaldehyde **126** (5.98 mL, 58.8 mmol, 1.0 eq.), TMOF (8.60 mL, 78.6 mmol, 1.3 eq.), NEt_3 (10.0 mL, 73.3 mmol, 1.2 eq.) and ethylamine hydrochloride **163**.HCl (5.30 g, 64.7 mmol, 1.1 eq.) in MeOH (120 mL) was stirred at room temperature for 4 hours. After cooling to 0°C, $NaBH_4$ (3.20 g, 84.6 mmol, 1.4 eq.) was cautiously added portionwise and the reaction mixture stirred for 2 hours at 0°C and 16 hours at room temperature. Solvents were removed *in vacuo* and the crude reaction mixture partitioned between water (100 mL) and EtOAc (100 mL). The aqueous layer was extracted with EtOAc (100 mL). The combined organic layers were washed with 2 M aqueous NaOH solution (100 mL), dried ($MgSO_4$) and concentrated *in vacuo* to afford **59** as a colourless oil (6.86 g, 87 %); δ_H (200 MHz, $CDCl_3$) 1.15 (3 H, t, *J* 7.1, CH_2CH_3), 1.23 (1 H, br s, N*H*), 2.70 (2 H, q, *J* 7.1, CH_2CH_3), 3.81 (2 H, s, NCH_2Ph), 7.22 - 7.39 (5 H, m *Ph*).

Preparation of *N*-benzyl-*N*-methyl 2,2-dimethyl-4-[*N*'-benzyl-*N*'-(2'-phenylethyl)amino] butanamide 164

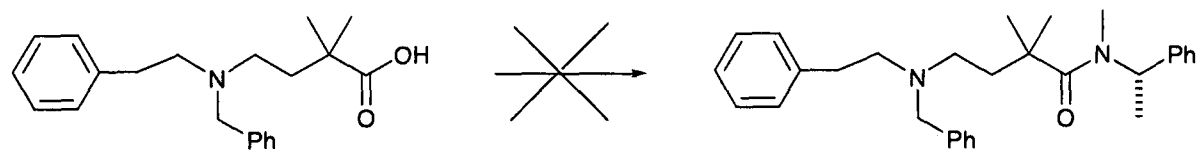


124 **164**

Following Representative Procedure **2**, to a stirred solution of **124** (228 mg, 0.701 mmol, 1.0 eq.), *N*-benzyl-*N*-methylamine **58** (0.364 mL, 2.81 mmol, 4.0 eq.), HOBt (190 mg, 1.40 mmol, 2.0 eq.) and DIPEA (0.491 mL, 2.81 mmol, 4.0 eq.) in DMF (10 mL) was added EDCI (202

mg, 1.05 mmol, 1.5 eq.). The resulting solution was stirred for 16 hours and partitioned between DCM (35 mL) and 10 % aqueous HCl (50 mL), the organic layer was washed with 2 M aqueous NaOH solution (50 mL) and then water (50 mL). The solution was dried (Na_2SO_4) and concentrated *in vacuo* to afford the desired compound **164** as a yellow viscous oil (260 mg, 86 %); ν_{max} (film)/cm^{-1} 3027, 2931, 2806 (C-H), 1627 (C=O); δ_H (400 MHz, $CDCl_3$) 1.29 (6 H, s, C*Me*$_2$), 1.76 - 1.86 (2 H, m, C(3)*H*$_2$), 2.52 - 2.57 (2 H, m, C(4)*H*$_2$), 2.68 - 2.85 (4 H, m, C(1')*H*$_2$ and C(2')*H*$_2$), 2.87 (3 H, s, N*Me*CH$_2$Ph), 3.64 (2 H, s, N'C*H*$_2$Ph), 4.51 (2 H, s, NMeC*H*$_2$Ph), 7.12 - 7.41 (15 H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 27.7 (C*Me*$_2$), 34.0 (*C*(2')H$_2$), 36.1 (N*Me*CH$_2$Ph), 38.8 (*C*(3)H$_2$), 42.2 (*C*(2)), 50.0 (*C*(4)H$_2$), 53.5 (NMe*C*H$_2$Ph), 56.3 (*C*(1')H$_2$), 59.1 (N'*C*H$_2$Ph), 126.3, 126.7, 127.3 (Ph$_{para}$), 127.7, 128.0, 128.6, 129.0, 129.2, 129.3 (Ph$_{ortho,meta}$), 138.0, 140.1 141.0 (Ph$_{ipso}$), 176.9 (*C*O); *m/z* (ESI$^+$) 429 (MH$^+$, 100 %); HRMS $C_{29}H_{37}N_2O$ (MH$^+$) requires 429.2906; found 429.2920. The starting material **124** was also isolated (18 mg, 8 %).

Attempted preparation of (*S*)-[*N*-methyl-*N*-(α-methylbenzyl)] 2,2-dimethyl-4-[*N*'-benzyl-*N*'-(2'-phenylethyl)amino]butanamide 165

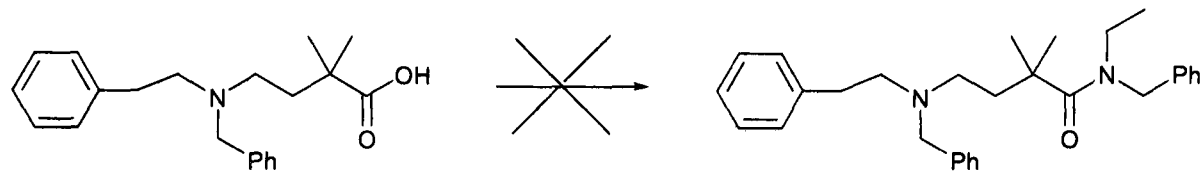


124 165

Following Representative Procedure **2**, to a stirred solution of **124** (50 mg, 0.154 mmol, 1.0 eq.), (*S*)-*N*-methyl-*N*-α-methylbenzylamine **162** (83 mg, 0.615 mmol, 4.0 eq.), HOBt (42 mg, 0.308 mmol, 2.0 eq.) and DIPEA (0.108 mL, 0.615 mmol, 4.0 eq.) in DMF (2 mL) was added EDCI (44 mg, 0.231 mmol, 1.5 eq.). The resulting solution was stirred for 16 hours and partitioned between DCM (5 mL) and 10 % aqueous HCl (5 mL). The organic layer was washed with 2 M aqueous NaOH solution (5 mL) and then water. The organic layer was dried

(Na_2SO_4) and concentrated *in vacuo*. ^{1}H NMR spectroscopic analysis of the crude reaction product (44 mg) revealed that none of the desired amide **165** had been formed.

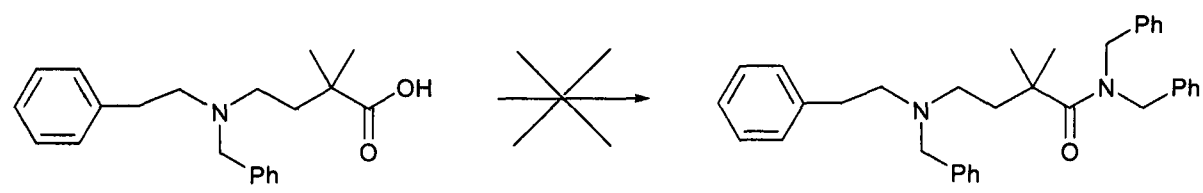
Attempted preparation of *N*-benzyl-*N*-ethyl 2,2-dimethyl-4-[*N*'-benzyl-*N*'-(2'-phenylethyl) amino]butanamide 166



124 166

Following Representative Procedure **2**, to a stirred solution of **124** (97 mg, 0.298 mmol, 1.0 eq.), *N*-benzyl-*N*-ethylamine **59** (160 mg, 1.19 mmol, 4.0 eq.), HOBt (81 mg, 0.597 mmol, 2.0 eq.) and DIPEA (0.208 mL, 1.19 mmol, 4.0 eq.) in DMF (5 mL) was added EDCI (86 mg, 0.448 mmol, 1.5 eq.). The resulting solution was stirred for 16 hours and partitioned between DCM (10 mL) and 10 % aqueous HCl (10 mL). The organic layer was washed with 2 M aqueous NaOH solution (10 mL) and then water (10 mL). The organic layer was dried (Na_2SO_4) and concentrated *in vacuo*. ^{1}H NMR spectroscopic analysis of the crude reaction product (115 mg) revealed that none of the desired amide **166** had been formed.

Attempted preparation of *N,N*-dibenzyl 2,2-dimethyl-4-[*N*'-benzyl-*N*'-(2'-phenylethyl) amino]butanamide 167

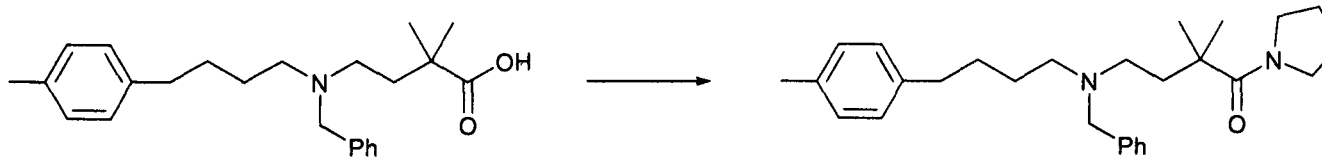


124 167

Following Representative Procedure **2**, to a stirred solution of **124** (215 mg, 0.662 mmol, 1.0 eq.), dibenzylamine **53** (0.508 mL, 2.64 mmol, 4.0 eq.), HOBt (179 mg, 1.32 mmol, 2.0 eq.) and DIPEA (0.463 mL, 2.64 mmol, 4.0 eq.) in DMF (10 mL) was added EDCI (190 mg, 0.992 mmol, 1.5 eq.). The resulting solution was stirred for 16 hours and partitioned between DCM

(10 mL) and 10 % aqueous HCl (20 mL). The organic layer was washed with 2 M aqueous NaOH solution (20 mL). The organic layer was dried (Na_2SO_4) and concentrated *in vacuo*. ^1H NMR spectroscopic analysis of the crude reaction product (482 mg) revealed that none of the desired amide **167** had been formed.

Preparation of pyrrolidin-1''-yl 2,2-dimethyl-4-{*N*-benzyl-*N*-[4'-(*p*-tolyl)butyl]amino} butanamide 170

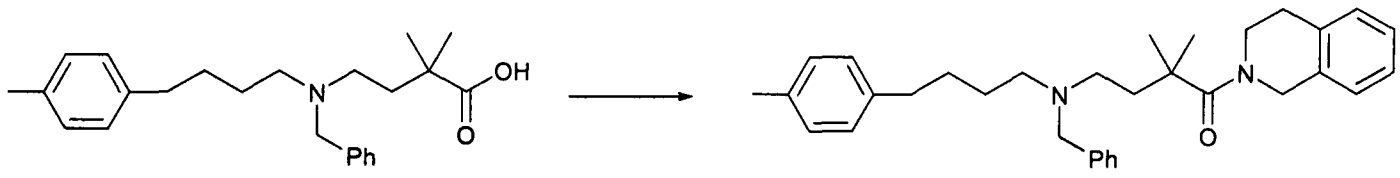


96 **170**

Following Representative Procedure **2**, to a stirred solution of **96** (300 mg, 0.816 mmol, 1.0 eq.), pyrrolidine **168** (0.136 mL, 1.63 mmol, 2.0 eq.), HOBt (165 mg, 1.22 mmol, 1.5 eq.) and DIPEA (0.285 mL, 1.63 mmol, 2.0 eq.) in DCM (20 mL) was added EDCI (235 mg, 1.22 mmol, 1.5 eq.). The resulting solution was stirred for 16 hours and partitioned between water (20 mL) and DCM (20 mL). The aqueous layer was extracted with DCM (20 mL). The combined organic layer was washed with 10 % aqueous HCl (50 mL) and 2 M aqueous NaOH solution (50 mL). The solution was dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography on silica gel (MeOH:$CHCl_3$, 2:98 - 1:9, stepwise elution) afforded the desired compound **170** as a pale yellow solid (209 mg, 61 %); m.p. 54 - 56°C; $C_{28}H_{40}N_2O$ requires C 79.95 %, H 9.59 %, N 6.66 %; found C 79.75 %, H 9.67 %, N 6.77 %; ν_{max} (film)/cm^{-1} 2974, 2928, 2854 (C-H), 1614 (C=O); δ_H (400 MHz, $CDCl_3$) 1.20 (6 H, s, C*Me*$_2$), 1.49 - 1.52 (2 H, m, C(2')*H*$_2$), 1.58 - 1.65 (2 H, m, C(3')*H*$_2$), 1.65 - 1.85 (6 H, m, C(3)*H*$_2$, C(3'')*H*$_2$ and C(4'')*H*$_2$), 2.32 - 2.36 (5 H, m, C(4)*H*$_2$ and *Me*Ar), 2.45 (2 H, t, *J* 7.2, C(1')*H*$_2$), 2.55 (2 H, t, *J* 7.6, C(4')*H*$_2$), 3.39 (4 H, t, *J* 6.8, C(2'')*H*$_2$ and C(5'')*H*$_2$), 3.52 (2 H, s, NC*H*$_2$Ph), 7.05 - 7.25 (4 H, m, *Ar*), 7.22 - 7.30 (5 H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 21.0 (*Me*Ar), 22.8 (*C*(3'')H$_2$ and *C*(4'')H$_2$) 26.4 (C*Me*$_2$), 26.8 (*C*(3')H$_2$), 29.3 (*C*(2')H$_2$), 35.3 (*C*(4')H$_2$), 37.3

(C(3)H_2), 41.7 (C(2)), 47.1 (C(2'')H_2 and C(5'')H_2), 49.5 (C(4)H_2), 53.9 (C(1')H_2), 58.9 (NCH_2Ph), 126.7 (Ph_{para}), 128.1, 128.3, 128.8, 128.9 ($Ph_{ortho,meta}$), 135.0, 139.5, 140.1 ($Ph_{ipso,para}$), 175.2 (CO); *m/z* (ESI$^+$) 421 (MH^+, 100 %); HRMS $C_{28}H_{41}N_2O$ (MH^+) requires 421.3219; found 421.3210.

Preparation of 1'',2'',3'',4''-tetrahydroisoquinol-2''-yl 2,2-dimethyl-4-{*N*-benzyl-*N*-[4'-(*p*-tolyl)butyl]amino}butanamide 171

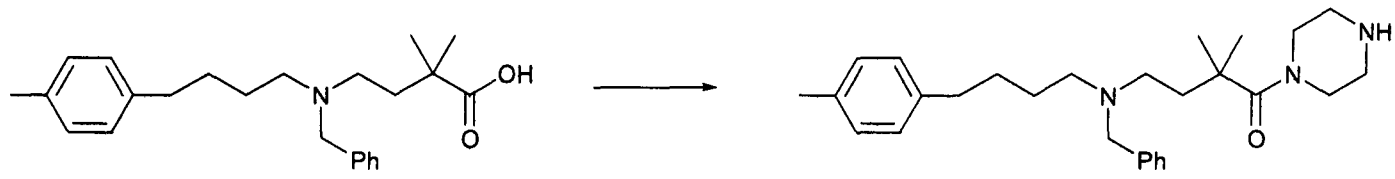


96 171

Following Representative Procedure **2**, to a stirred solution of **96** (1.00 g, 2.72 mmol, 1.0 eq.), 1,2,3,4-tetrahydro-isoquinoline **169** (3.45 mL, 27.2 mmol, 10.0 eq.), HOBt (735 mg, 5.44 mmol, 2.0 eq.) and DIPEA (1.90 mL, 10.9 mmol, 4.0 eq.) in DCM (60 mL) was added EDCI (1.04 g, 5.44 mmol, 2.0 eq.). The resulting solution was stirred for 48 hours and partitioned between water (100 mL) and DCM (120 mL), the organic layer was washed with 10 % aqueous HCl (100 mL, 2×) and 2 M NaOH (100 mL). The organic solution was then dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography on silica gel (MeOH:$CHCl_3$, $CHCl_3$ - 1:9, stepwise elution) afforded the desired compound **171** as a yellow oil (1.09 g, 83 %); ν_{max} (film)/cm^{-1} 3024, 2930, 2856 (C-H), 1674, 1634 (C=O); δ_H (400 MHz, $CDCl_3$) 1.27 (6 H, s, CMe_2), 1.40 - 1.48 (2 H, m, C(2')H_2), 1.50 - 1.60 (2 H, m, C(3')H_2), 1.80 - 1.84 (2 H, m, C(3)H_2), 2.32 (3 H, s, *Me*Ar), 2.34 - 2.39 (4 H, m, C(1')H_2 and C(4)H_2), 2.51 (2 H, t, *J* 7.6, C(4')H_2), 2.82 (2 H, t, *J* 5.9, C(4'')H_2), 3.47 (2 H, s, NCH_2Ph), 3.72 (2 H, t, *J* 5.9, C(3'')H_2), 4.65 (2 H, s, C(1'')H_2), 7.03 - 7.31 (13 H, m, 8×*Ar*, 5×*Ph*); δ_C (100 MHz, $CDCl_3$) 21.0 (*Me*Ar), 26.7 (CMe_2), 27.2 (C(3')H_2), 28.9 (C(2')H_2), 29.3 (C(4'')H_2), 35.3 (C(4')H_2), 38.4 (C(3)H_2), 41.7 (C(2)), 43.0 (C(3'')H_2) 47.3 (C(1'')H_2), 49.7 (C(4)H_2), 53.8 (C(1')H_2), 58.7 (NCH_2Ph), 125.8 (Ph_{para}), 126.3, 126.6, 126.7, 128.1, 128.3, 128.7, 128.8, 128.9 ($Ph_{ortho,meta}$),

133.4, 134.4, 135.0, 139.5, 140.0 ($Ph_{ipso,para}$), 175.4 (*C*O); *m/z* (ESI^+) 483 (MH^+, 100 %); HRMS $C_{33}H_{43}N_2O$ (MH^+) requires 483.3375; found 483.3360.

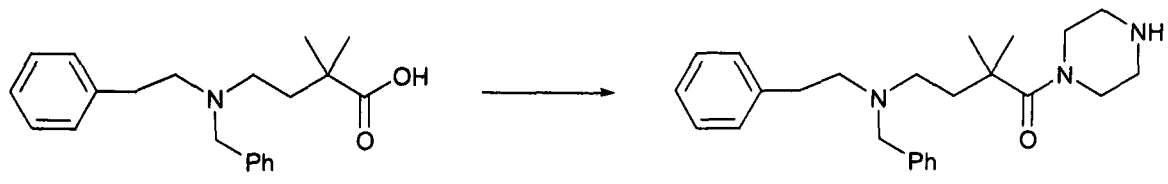
Preparation of piperazin-1''-yl 2,2-dimethyl-4-{*N*-benzyl-*N*-[4'-(*p*-tolyl)butyl]amino} butanamide 173



96 173

Following Representative Procedure **2**, to a stirred solution of **96** (500 mg, 1.36 mmol, 1.0 eq.), piperazine **172** (469 mg, 5.44 mmol, 4.0 eq.) and DIPEA (0.952 mL, 5.44 mmol, 4.0 eq.) in DCM (10 mL) was added TBTU (655 mg, 2.04 mmol, 1.5 eq.). The resulting solution was stirred for 16 hours and partitioned between water (100 mL) and DCM (100 mL). The aqueous layer was extracted with DCM (100 mL). The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography on silica gel (MeOH:$CHCl_3$, $CHCl_3$ - 4:6, stepwise elution) afforded the desired compound **173** as a colourless viscous oil (584 mg, 99 %); ν_{max} (film)/cm^{-1} 2934, 2858 (C-H), 1623 (C=O); δ_H (400 MHz, $CDCl_3$) 1.22 (6 H, s, C*Me*$_2$), 1.49 - 1.55 (2 H, m, C(2')*H*$_2$), 1.56 - 1.63 (2 H, m, C(3')*H*$_2$), 1.72 - 1.77 (2 H, m, C(3)*H*$_2$), 1.98 (1 H, br s, N*H*), 2.32 (3 H, s, *Me*Ar), 2.37 - 2.41 (2 H, m, C(4)*H*$_2$), 2.46 (2 H, t, *J* 7.0, C(1')*H*$_2$), 2.55 (2 H, t, *J* 7.0, C(4')*H*$_2$), 2.70 (4 H, t, *J* 5.0, C(3'')*H*$_2$ and C(5'')*H*$_2$), 3.47 (4 H, t, *J* 5.0, C(2'')*H*$_2$ and C(6'')*H*$_2$), 3.53 (2 H, s, NC*H*$_2$Ph), 7.04 - 7.10 (4 H, m, *Ar*), 7.23 - 7.32 (5 H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 21.0 (*Me*Ar), 26.7 (*C*(3')H$_2$), 27.3 (C*Me*$_2$), 29.3 (*C*(2')H$_2$), 35.3 (*C*(4')H$_2$), 38.3 (*C*(3)H$_2$), 41.5 (*C*(2)), 46.1 (*C*(2'')H$_2$ and *C*(6'')H$_2$), 49.7 (*C*(4)H$_2$), 50.5 (*C*(3'')H$_2$ and *C*(5'')H$_2$), 53.9 (*C*(1')H$_2$), 58.9 (NC*H*$_2$Ph), 126.7 (Ph_{para}), 128.1, 128.2, 128.4, 128.9 ($Ph_{ortho,meta}$), 135.0, 139.5, 139.9 ($Ph_{ipso,para}$), 175.0 (*C*O); *m/z* (ESI^+) 436 (MH^+, 100 %); HRMS $C_{28}H_{42}N_3O$ (MH^+) requires 436.3328; found 436.3328.

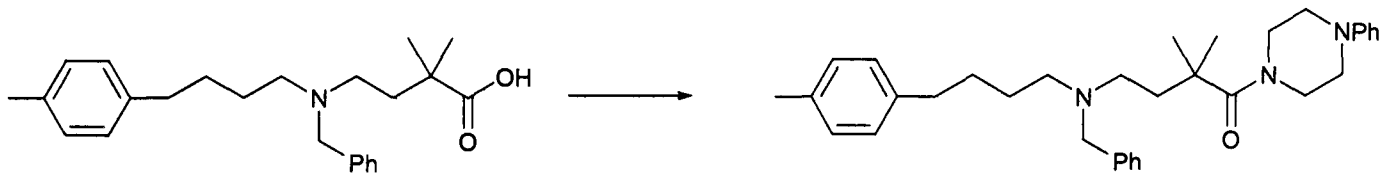
Preparation of piperazin-1''-yl 2,2-dimethyl-4-[*N*-benzyl-*N*-(2'-phenylethyl)amino] butanamide 174



124 174

Following Representative Procedure **2**, to a stirred solution of **124** (2.30 g, 7.08 mmol, 1.0 eq.), piperazine **172** (2.44 g, 28.3 mmol, 4.0 eq.), HOBt (1.91 g, 14.2 mmol, 2.0 eq.) and DIPEA (4.95 mL, 28.3 mmol, 4.0 eq.) in DMF (100 mL) was added EDCI (2.03 g, 10.6 mmol, 1.5 eq.). The resulting solution was stirred for 16 hours, diluted with DCM (300 mL) and washed with water (300 mL), 2 M aqueous NaOH solution (300 mL) and brine (300 mL). The solution was then dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography afforded the desired compound **174** as a yellow viscous oil (841 mg, 30 %); ν_{max} (film)/cm^{-1} 3025, 2943, 2816 (C-H), 1622 (C=O); δ_H (400 MHz, $CDCl_3$) 1.23 (6 H, s, CMe_2), 1.73 - 1.77 (2 H, m, C(3)H_2), 2.20 (1 H, br s, N*H*), 2.46 - 2.51 (2 H, m, C(4)H_2), 2.69 - 2.81 (8 H, m, C(1')H_2, C(2')H_2, C(3'')H_2 and C(5'')H_2), 3.48 - 3.50 (4 H, m, C(2'')H_2 and C(6'')H_2), 3.63 (2 H, s, NCH_2Ph), 7.14 - 7.36 (10 H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 27.2 (CMe_2), 33.6 (*C*(2')H_2), 38.4 (*C*(3)H_2), 41.5 (*C*(2)), 46.1 (*C*(2'')H_2, *C*(3'')H_2, *C*(5'')H_2 and *C*(6'')H_2), 49.6 (*C*(4)H_2), 55.9 (*C*(1')H_2), 58.8 (N*C*H_2Ph), 125.9, 126.8 (Ph_{para}), 128.2, 128.3, 128.8, 128.9 ($Ph_{ortho,meta}$), 139.7, 140.6 (Ph_{ipso}), 175.0 (*C*O); *m/z* (ESI^+) 394 (MH^+, 100 %); HRMS $C_{25}H_{36}N_3O$ (MH^+) requires 394.2858; found 394.2866.

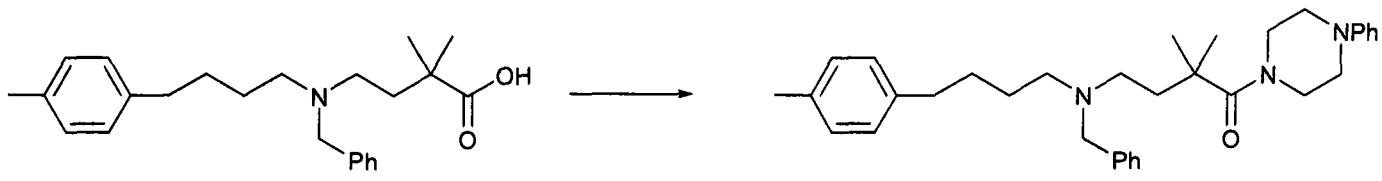
Preparation of (4''-phenyl)piperazin-1''-yl 2,2-dimethyl-4-{*N*-benzyl-*N*-[4'-(*p*-tolyl)butyl] amino}butanamide 176



96 **176**

To a stirred solution of **96** (72 mg, 0.196 mmol, 1.0 eq.), *N*-phenyl piperazine **175** (90 μL, 0.588 mmol, 3.0 eq.) and DIPEA (0.103 mL, 0.587 mmol, 3.0 eq.) in DCM (1 mL) was added TBTU (94 mg, 2.04 mmol, 1.5 eq.). The resulting solution was stirred for 16 hours and partitioned between water (10 mL) and DCM (10 mL). The aqueous layer was extracted with DCM (10 mL). The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography on silica gel (MeOH:$CHCl_3$, 1:99 - 1:9, stepwise elution) afforded a fraction (69 mg) consisting of lactam **117** and unidentified impurities. The desired compound **176** was also isolated as a colourless viscous oil (84 mg, 84 %); $C_{34}H_{45}N_3O$ requires C 79.80 %, H 8.86 %, N 8.21 %; found C 79.67 %, H 8.68 %, N 8.44 %; ν_{max} (film)/cm^{-1} 3024, 2933, 2855 (C-H), 1630, 1600 (C=O); δ_H (400 MHz, $CDCl_3$) 1.27 (6 H, s, C*Me*$_2$), 1.49 - 1.56 (2 H, m, C(2')*H*$_2$), 1.59 - 1.66 (2 H, m, C(3')*H*$_2$), 1.78 - 1.86 (2 H, m, C(3)*H*$_2$), 2.34 (3 H, s, *Me*Ar), 2.40 - 2.44 (2 H, m, C(4)*H*$_2$), 2.48 (2 H, t, *J* 7.0, C(1')*H*$_2$), 2.56 (2 H, t, *J* 7.6, C(4')*H*$_2$), 3.07 (4 H, t, *J* 5.1, C(3'')*H*$_2$ and C(5'')*H*$_2$), 3.54 (2 H, s, NC*H*$_2$Ph), 3.69 (4 H, t, *J* 5.1, C(2'')*H*$_2$ and C(6'')*H*$_2$), 6.90 - 7.35 (14 H, m, 4×*Ar*, 10×*Ph*); δ_C (100 MHz, $CDCl_3$) 21.0 (*Me*Ar), 26.8 (*C*(3')H$_2$), 27.3 (C*Me*$_2$), 29.3 (*C*(2')H$_2$), 35.3 (*C*(4')H$_2$), 38.5 (*C*(3)H$_2$), 41.6 (*C*(2)), 44.8 (*C*(2'')H$_2$ and *C*(6'')H$_2$), 49.3, 49.7 (*C*(4)H$_2$), *C*(3'')H$_2$ and *C*(5'')H$_2$), 54.0 (*C*(1')H$_2$), 58.9 (NC*H*$_2$Ph), 116.3 (Ph$_{ortho}$), 120.3 , 125.8 (Ph$_{para}$), 126.9, 128.2, 128.3, 128.8, 129.2 (Ph$_{ortho,meta}$), 135.0, 139.5, 140.0, 150.9 (Ph$_{ipso,para}$), 175.1 (*C*O); *m/z* (ESI^+) 512 (MH^+, 100 %); HRMS $C_{34}H_{46}N_3O$ (MH^+) requires 512.3641; found 512.3636.

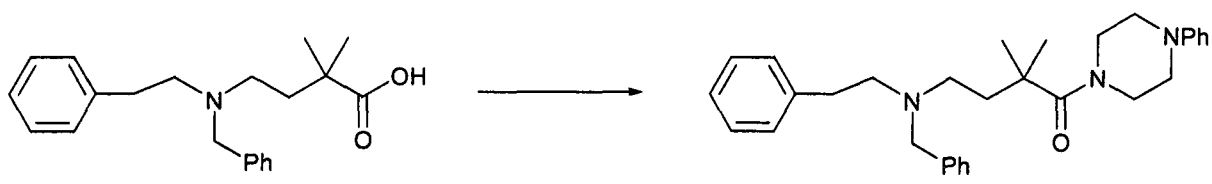
Alternative preparation of (4''-phenyl)piperazin-1''-yl 2,2-dimethyl-4-{*N*-benzyl-*N*-[4'-(*p*-tolyl)butyl]amino}butanamide 176



96 176

Following Representative Procedure **2**, to a stirred solution of **96** (500 mg, 1.36 mmol, 1.0 eq.), *N*-phenyl piperazine **175** (0.831 mL, 5.44 mmol, 4.0 eq.), HOBt (368 mg, 2.72 mmol, 2.0 eq.) and DIPEA (0.952 mL, 5.44 mmol, 4.0 eq.) in DCM (15 mL) was added TBTU (655 mg, 2.04 mmol, 1.5 eq.). The resulting solution was stirred for 16 hours and partitioned between water (100 mL) and DCM (100 mL). The aqueous layer was extracted with DCM (100 mL). The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography on silica gel (MeOH:$CHCl_3$, $CHCl_3$ - 1:9, stepwise elution) afforded the desired compound **176** as a colourless viscous oil (539 mg, 77 %) with identical spectroscopic properties to those previously described. The starting material **96** was also isolated (96 mg, 19 %).

Preparation of (4''-phenyl)piperazin-1''-yl 2,2-dimethyl-4-[*N*-benzyl-*N*-(2'-phenylethyl) amino]butanamide 177

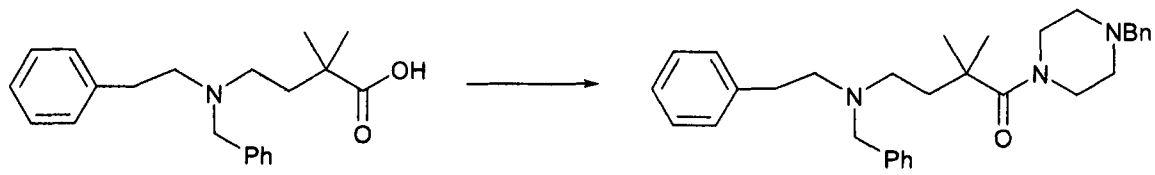


124 177

Following Representative Procedure **2**, to a stirred solution of **124** (2.00 g, 6.15 mmol, 1.0 eq.), *N*-phenyl piperazine **175** (3.76 mL, 24.6 mmol, 4.0 eq.), HOBt (1.66 g, 12.3 mmol, 2.0 eq.) and DIPEA (4.30 mL, 24.6 mmol, 4.0 eq.) in DCM (100 mL) was added EDCI (1.77 g, 9.23 mmol, 1.5 eq.). The resulting solution was stirred for 16 hours, diluted with DCM (100 mL), then

washed with 10 % aqueous HCl (100 mL, 2×) and 2 M aqueous NaOH solution (100 mL). The solution was dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography on silica gel (MeOH:$CHCl_3$, 2:98) afforded the desired compound **177** as a yellow viscous oil (2.13 g, 74 %); ν_{max} (film)/cm^{-1} 3025, 2947, 2820 (C-H), 1630, 1600 (C=O); δ_H (400 MHz, $CDCl_3$) 1.26 (6 H, s, C*Me*$_2$), 1.78 - 1.80 (2 H, m, C(3)*H*$_2$), 2.48 - 2.52 (2 H, m, C(4)*H*$_2$), 2.71 - 2.81 (4 H, m, C(1')*H*$_2$ and C(2')*H*$_2$), 3.04 - 3.07 (4 H, m, C(3'')*H*$_2$ and C(5'')*H*$_2$), 3.61 (2 H, s, NC*H*$_2$Ph), 3.64 - 3.69 (4 H, m, C(2'')*H*$_2$ and C(6'')*H*$_2$), 6.89 - 6.94 (2 H, m, *Ph*), 7.13 - 7.34 (13 H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 27.1 (C*Me*$_2$), 33.5 (*C*(2')H$_2$), 38.3 (*C*(3)H$_2$), 41.5 (*C*(2)), 44.7 (*C*(2'')H$_2$ and *C*(6'')H$_2$), 49.2 (*C*(3'')*H*$_2$ and *C*(5'')*H*$_2$), 49.5 (*C*(4)H$_2$), 55.8 (*C*(1')H$_2$), 58.7 (N*C*H$_2$Ph), 116.2 (Ph$_{ortho}$), 120.2, 125.8 (3×Ph$_{para}$), 126.9, 128.1, 128.2, 128.6, 129.1 (Ph$_{ortho,meta}$), 139.5, 140.4, 150.8 (Ph$_{ipso}$), 175.0 (*C*O); *m/z* (ESI^+) 470 (MH^+, 100 %); HRMS $C_{31}H_{40}N_3O$ (MH^+) requires 470.3171; found 470.3167.

Preparation of 4''-benzyl-piperazin-1''-yl 2,2-dimethyl-4-[*N*-benzyl-*N*-(2'-phenylethyl) amino]butanamide 178

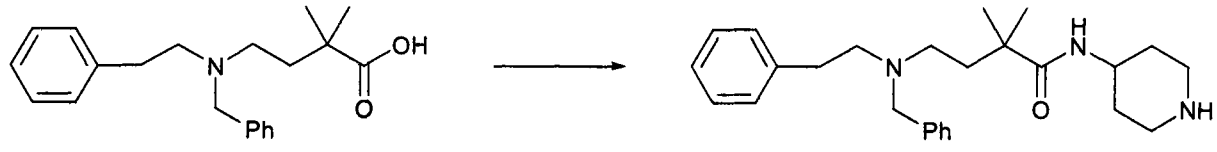


124 178

Following Representative Procedure **2**, to a stirred solution of **124** (500 mg, 1.54 mmol, 1.0 eq.), *N*-benzyl piperazine **179** (1.07 mL, 6.15 mmol, 4.0 eq.), HOBt (416 mg, 3.08 mmol, 2.0 eq.) and DIPEA (1.08 mL, 6.15 mmol, 4.0 eq.) in DCM (20 mL) was added EDCI (442 mg, 2.31 mmol, 1.5 eq.). The resulting solution was stirred for 16 hours, washed with 10 % aqueous HCl (20 mL) and 2 M aqueous NaOH solution (20 mL). The solution was then dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography on silica gel (MeOH:$CHCl_3$, 2:98) afforded the desired compound **178** as a yellow viscous oil (502 mg, 67 %); ν_{max} (film)/cm^{-1} 3061, 3026, 2933, 2807 (C-H), 1629 (C=O); δ_H (500 MHz, $CDCl_3$) 1.24 (6

H, s, CMe_2), 1.76 - 1.79 (2 H, m, C(3)H_2), 2.35 - 2.37 (4 H, m, C(3'')H_2 and C(5'')H_2), 2.51 - 2.54 (2 H, m, C(4)H_2), 2.74 - 2.80 (4 H, m, C(1')H_2 and C(2')H_2), 3.48 (2 H, s, N'CH_2Ph), 3.36 - 3.58 (4 H, m, C(2'')H_2 and C(6'')H_2), 3.66 (2 H, s, NCH_2Ph), 7.16 - 7.37 (15 H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 27.1 (CMe_2), 33.6 (C(2')H_2), 38.3 (C(3)H_2), 41.4 (C(2)), 44.8 (C(2'')H_2 and C(6'')H_2), 49.7 (C(4)H_2), 53.0 (C(3'')H_2 and C(5'')H_2), 55.8 (C(1')H_2), 58.7 (NCH_2Ph), 62.7 (N'CH_2Ph), 125.8, 126.8, 127.1 (Ph_{para}), 128.1, 128.2, 128.2, 128.6, 128.7, 128.9 ($Ph_{ortho,meta}$), 137.7, 139.7, 140.5 (Ph_{ipso}), 174.9 (*C*O); *m/z* (ESI$^+$) 484 (MH^+, 100 %); HRMS $C_{32}H_{42}N_3O$ (MH^+) requires 484.3328; found 484.3332.

Preparation of piperidin-4''-yl 2,2-dimethyl-4-[*N*-benzyl-*N*-(2'-phenylethyl)amino] butanamide 181

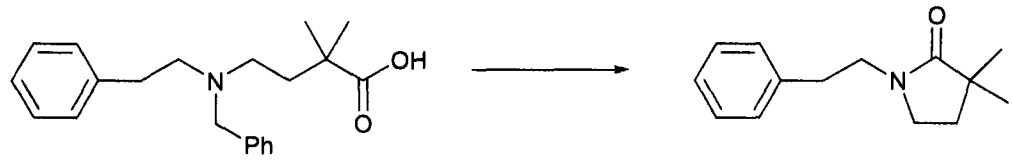


124 181

Following Representative Procedure **2**, to a stirred solution of **124** (200 mg, 0.615 mmol, 1.0 eq.), 4-amino piperidine **180** (0.129 mL, 1.23 mmol, 2.0 eq.), HOBt (166 mg, 1.23 mmol, 2.0 eq.) and DIPEA (0.430 mL, 2.46 mmol, 4.0 eq.) in DCM (10 mL) was added EDCI (177 mg, mmol, 1.5 eq.). The resultant solution was stirred for 16 hours, then it was washed with water (10 mL) and 2 M aqueous NaOH solution (10 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography on silica gel (MeOH:$CHCl_3$, 1:9 - MeOH, stepwise elution) afforded the desired compound **181** as a colourless oil (119 mg, 47 %); ν_{max} (film)/cm^{-1} 3345 (N-H), 3027, 2946, 2810 (C-H), 1644 (C=O); δ_H (400 MHz, $CDCl_3$) 1.12 (6 H, s, CMe_2), 1.24 (2 H, qd, *J* 12.0, 4.0, C(3'')H_A and C(5'')H_A), 1.68 - 1.72 (2 H, m, C(3)H_2), 1.81 - 1.84 (2 H, m, C(3'')H_B and C(5'')H_B), 2.46 - 2.50 (2 H, m, C(4)H_2), 2.63 - 2.78 (6 H, m, C(1')H_2, C(2')H_2, C(2'')H_A and C(6'')H_A), 3.00 - 3.07 (3 H, m, N*H*, C(2'')H_B and C(6'')H_B), 3.64 (2 H, s, NCH_2Ph), 3.78 - 3.85 (1 H, m, C(4'')*H*), 5.71 (1 H, d, *J* 7.9, CON*H*), 7.13 - 7.29 (10 H, m,

Ph); δ_C (100 MHz, $CDCl_3$) 25.8 (C*Me*$_2$), 33.0, 33.4 (*C*(2')H_2, *C*(3'')H_2 and *C*(5'')H_2), 37.8 (*C*(3)H_2), 41.1 (*C*(2)), 45.2 (*C*(2'')H_2 and *C*(6'')H_2), 46.5 (*C*(4'')H, 49.4 (*C*(4)H_2), 55.5 (*C*(1')H_2), 58.4 (NCH_2Ph), 125.9, 126.8 (Ph_{para}), 128.1, 128.3, 128.7, 128.8 ($Ph_{ortho,meta}$), 139.4, 140.5 (Ph_{ipso}), 176.4 (*C*O); *m/z* (ESI$^+$) 408 (MH^+, 100 %); HRMS $C_{26}H_{38}N_3O$ (MH^+) requires 408.3015; found 408.3013.

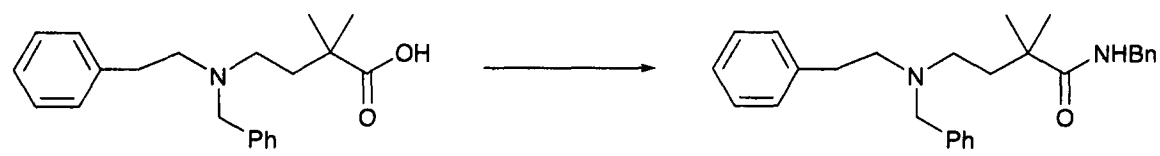
Stability assessment of 124, preparation of *N*-(2'-phenylethyl) 3,3-dimethyl-pyrrolidin-2-one 142



124 142

A solution of **124** (600 mg, 1.85 mmol, 1.0 eq) and EDCI (389 mg, 2.03 mmol, 1.1 eq.) in DCM (20 mL) was stirred at room temperature for 16 hours. The organic solvent was washed with 10 % aqueous HCl (15 mL) and 2 M aqueous NaOH solution (15 mL) to afford **142** as a yellow oil (380 mg, 95 %) with identical spectroscopic properties to those previously reported.

Alternative preparation of benzyl 2,2-dimethyl-4-[*N*-benzyl-*N*-(2'-phenylethyl)amino] butanamide 124

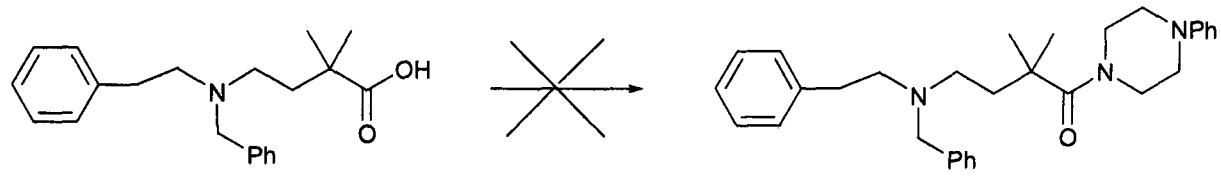


124 159

To a stirred solution of **124** (211 mg, 0.649 mmol, 1.0 eq.), benzylamine **93** (0.142 mL, 1.30 mmol, 2.0 eq.) and DIPEA (0.454 mL, 2.60 mmol, 4.0 eq.) in DCM (10 mL) was added EDCI (187 mg, 0.974 mmol, 1.5 eq.). The resulting solution was stirred for 16 hours and partitioned between DCM (10 mL) and 10 % aqueous HCl (20 mL). The organic layer was then washed with and 2 M aqueous NaOH solution (20 mL), dried (Na_2SO_4) and concentrated *in vacuo* to

afford the desired compound **159** as a yellow viscous oil (268 g, 100 %) with identical spectroscopic properties to those described previously.

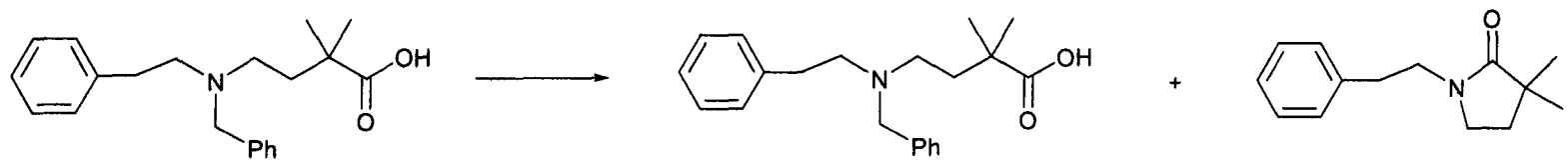
Attempted preparation of (4''-phenyl)piperazin-1''-yl 2,2-dimethyl-4-[*N*-benzyl-*N*-(2'-phenylethyl)amino]butanamide 177



124 177

To a stirred solution of **124** (219 mg, 0.674 mmol, 1.0 eq.), *N*-phenyl piperazine **175** (0.412 mL, 2.70 mmol, 4.0 eq.) and DIPEA (0.471 mL, 2.70 mmol, 4.0 eq.) in DCM (10 mL) was added EDCI (194 mg, 1.01 mmol, 1.5 eq.). The resulting solution was stirred for 16 hours and partitioned between DCM (10 mL) and 10 % aqueous HCl (20 mL). The organic layer was then washed with 2 M aqueous NaOH solution (20 mL), dried (Na_2SO_4) and concentrated *in vacuo*. ^{1}H NMR spectroscopic analysis of the crude reaction product (152 mg) revealed that none of the desired amide **177** had been formed.

Stability assessment of 124, preparation of *N*-(2'-phenylethyl) 3,3-dimethyl-pyrrolidin-2-one 142

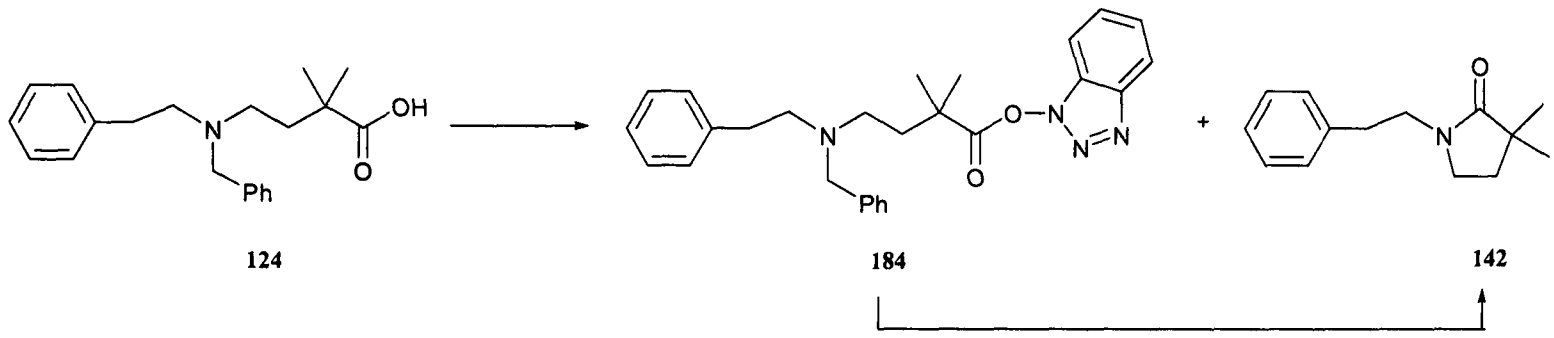


124 124 142

To a stirred solution of **124** (231 mg, 0.710 mmol, 1.0 eq.), HOBt (192 mg, 1.42 mmol, 2.0 eq.) in DCM (10 mL), was added EDCI (177 mg, 0.924 mmol, 1.3 eq.). The resulting solution was stirred at room temperature for 6 days and washed with 10 % aqueous HCl (10 mL) and then water (10 mL), the pH was adjusted to neutral with 2 M aqueous NaOH solution. The organic layer was dried (Na_2SO_4) and concentrated *in vacuo*. The resulting residue (210 mg) was

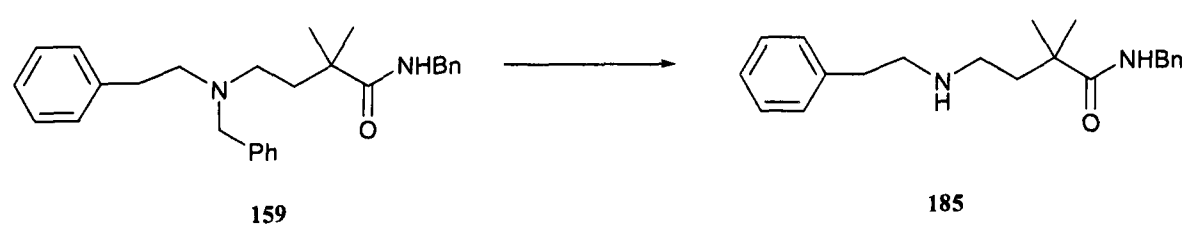
subjected to ^{1}H NMR spectroscopic analysis to reveal an approximately 80:20 mixture of starting material **124** and lactam **142** respectively.

Stability assessment of 124, preparation of *N*-(2'-phenylethyl) 3,3-dimethyl-pyrrolidin-2-one 142



To a stirred solution of **124** (100 mg, 0.308 mmol, 1.0 eq.), HOBt (83 mg, 0.615 mmol, 2.0 eq.) in DCM (10 mL) over molecular sieves, was added EDCI (77 mg, 0.400 mmol, 1.3 eq.). The resulting solution was stirred at room temperature for 16 hours and washed with 10 % aqueous HCl (15 mL) and 2 M aqueous NaOH solution (15 mL). The organic layer was dried (Na_2SO_4) and concentrated *in vacuo*. The resulting residue (104 mg) was dried *in vacuo* and the reaction progress monitored by ^{1}H NMR spectroscopy. ^{1}H NMR data for intermediate **184**, δ_H (200 MHz, $CDCl_3$) 1.45 (6 H, s, C*Me*$_2$), 1.74 - 1.80 (2 H, m, C(3)*H*$_2$), 2.68 - 2.81 (2 H, m, C(4)H$_2$), 2.81 - 2.89 (4 H, m, C(1')H$_2$ and C(2')H$_2$), 3.75 (2 H, s, NC*H*$_2$Ph), 7.17 - 7.42 (14 H, m, 4×*Ar*, 10×*Ph*).

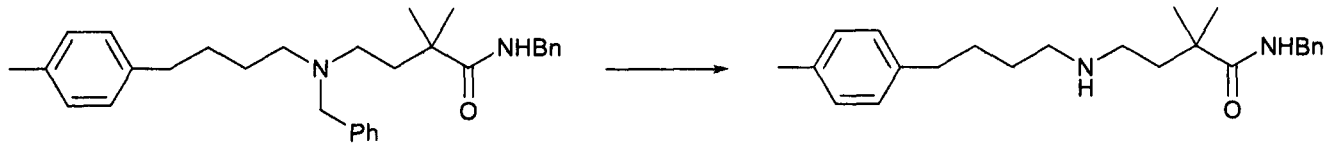
Preparation of benzyl 2,2-dimethyl-4-[*N*-(2'-phenylethyl)amino]butanamide 185



Following Representative Procedure **1**, CAN (6.15 g, 11.2 mmol, 5.0 eq.) was added to a stirred solution of **159** (929 mg, 2.24 mmol, 1.0 eq.) in THF:H_2O (8:1) (90 mL). After 16 hours the mixture was partitioned between 2 M aqueous NaOH solution (100 mL) and ether (200 mL).

The aqueous layer was extracted with ether (200 mL). Combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography on silica gel (MeOH:$CHCl_3$, 2:98 - 3:7, stepwise elution) afforded the desired compound **185** as a colourless oil (579 mg, 80 %); ν_{max} (film)/cm^{-1} 3339 (N-H), 3028, 2929 (C-H), 1641, 1532 (C=O); δ_H (400 MHz, $CDCl_3$) 1.20 (6 H, s, CMe_2), 1.72 (2 H, t, *J* 7.4, C(3)H_2), 2.21 (1 H, br s, N*H*), 2.62 (2 H, t, *J* 7.4, C(4)H_2), 2.69 - 2.82 (4 H, m, C(1')H_2 and C(2')H_2), 4.40 (2 H, d, *J* 5.6, NHCH_2Ph), 6.97 (1 H, t, *J* 5.6, N*H*CH_2Ph), 6.97 - 7.34 (10 H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 26.2 (CMe_2), 36.0 (*C*(2')H_2), 40.3 (*C*(2)), 41.5 (*C*(3)H_2), 43.6 (NH*C*H_2Ph), 45.6 (*C*(4)H_2), 50.9 (*C*(1')H_2), 126.2, 127.3 (Ph_{para}), 127.7, 128.5, 128.6, 128.7 ($Ph_{ortho,meta}$), 138.7, 139.6 (Ph_{ipso}), 177.5 (*C*O); *m/z* (ESI^+) 325 (MH^+, 100 %); HRMS $C_{21}H_{29}N_2O$ (MH^+) requires 325.2280; found 325.2278.

Preparation of benzyl 2,2-dimethyl-4-{*N*-[4'-(*p*-tolyl)butyl]amino}butanamide 186

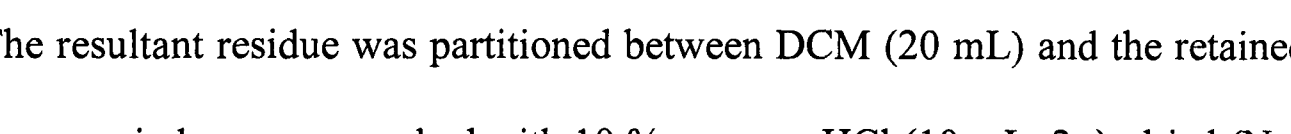


154 186

A solution of **154** (250 mg, 0.547 mmol, 1.0 eq.) and α-chloroethyl chloroformate (0.236 mL, 2.19 mmol, 4.0 eq.) in was refluxed for 16 hours in dichloroethane (10 mL). The solvent was removed *in vacuo* and the resulting residue refluxed in MeOH (10 mL) for 2 hours. The solvent was removed *in vacuo* and the resulting crude mixture partitioned between water (10 mL) and DCM (10 mL). The organic layer was washed with 2 M aqueous NaOH solution (10 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography on silica gel (MeOH:$CHCl_3$, 1:99 - MeOH, stepwise elution) afforded the desired compound **186** as a yellow oil (119 mg, 59 %); ν_{max} (film)/cm^{-1} 3323 (N-H), 3027, 2928, 2858 (C-H), 1643, 1531 (C=O); δ_H (400 MHz, $CDCl_3$) 1.21 (6 H, s, CMe_2), 1.47 - 1.62 (4 H, m, C(2')H_2 and C(3')H_2), 1.80 (2 H, t, *J* 7.1, C(3)H_2), 2.32 (3 H, s, *Me*Ar), 2.53 - 2.61 (4 H, m, C(1')H_2 and C(4')H_2), 2.67 (2 H, t, *J* 7.1, C(4)H_2), 4.12 (1 H, br s, N*H*), 4.40 (1 H, d, *J* 5.5, NHCH_2Ph), 7.04 - 7.10 (4

H, m, *Ar*), 7.18 (1 H, t, *J* 5.5, N*H*CH_2Ph), 7.23 - 7.33 (5 H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 21.0 (*Me*Ar), 26.2 (C*Me*$_2$), 28.6, 29.1 (*C*(2')H_2) and (*C*(3')H_2), 35.2 (*C*(4')H_2), 39.4 (*C*(3)H_2), 41.5 (*C*(2)), 43.6 (NH*C*H_2Ph), 45.5 (*C*(4)H_2), 49.2 (*C*(1')H_2), 127.3 (Ph_{para}), 127.7, 128.2, 128.6, 129.0 ($Ph_{ortho,meta}$), 135.2, 138.8, 139.0 ($Ph_{ipso,para}$), 177.4 (*C*O); *m/z* (ESI$^+$) 367 (MH^+, 100 %); HRMS $C_{24}H_{35}N_2O$ (MH^+) requires 367.2749; found 367.2743.

Preparation of *N*-(2'-phenylethyl) 3,3-dimethyl-pyrrolidin-2-one 142 and benzylamine hydrochloride 93.HCl[14]



185 **142** **93.HCl**

185 (210 mg, 0.648 mmol, 1.0 eq.) was refluxed in toluene (20 mL) for 16 hours. The organic layer was washed with 10 % aqueous HCl (10 mL). The organic layer was concentrated *in vacuo*. The resultant residue was partitioned between DCM (20 mL) and the retained aqueous layer. The organic layer was washed with 10 % aqueous HCl (10 mL, 2×), dried (Na_2SO_4) and concentrated *in vacuo* to afford **142** (136 mg, 97 %) with identical spectroscopic properties to those previously described. The combined aqueous layers co-evaporated with MeOH *in vacuo* to a constant mass to afford benzylamine hydrocloride **93.HCl** as a white crystalline solid (92 mg, 99 %); m.p. 258 - 260°C (lit.[14] 262 - 263°C); δ_H (200 MHz, CD_3OD) 4.16 (2 H, s, NCH_2Ph), 7.45 - 7.52 (5 H, m, *Ph*).

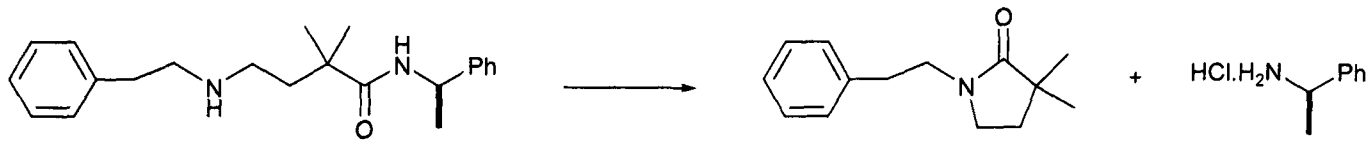
Preparation of (*R*)-(α-methylbenzyl) 2,2-dimethyl-4-[*N*-(2'-phenylethyl)amino] butanamide 187



160 187

Following Representative Procedure **1**, CAN (2.44 g, 4.46 mmol, 5.0 eq.) was added to a stirred solution of **160** (382 mg, 0.891 mmol, 1.0 eq.) in THF:H_2O (8:1) (20 mL). After 16 hours the mixture was partitioned with 2 M aqueous NaOH solution (40 mL) and ether (40 mL). The aqueous layer was extracted with ether (40 mL). Combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography on silica gel (MeOH:$CHCl_3$, 1:9 - 4:6, stepwise elution) afforded the desired compound **187** as a yellow viscous oil (247 mg, 82 %); $[\alpha]_D^{25}$ +51.8 (c = 1.0, $CHCl_3$); ν_{max} (film)/cm^{-1} 3342 (N-H), 2968 (C-H), 1639, 1527 (C=O); δ_H (500 MHz, $CDCl_3$) 1.19 (6 H, s, C*Me*$_2$), 1.49 (3 H, d, *J* 7.0, C(α)*Me*), 1.81 (2 H, t, *J* 7.3, C(3)*H*$_2$), 2.72 (2 H, t, *J* 7.3, C(4)*H*$_2$), 2.84 - 2.92 (4 H, m, C(1')*H*$_2$ and C(2')*H*$_2$), 3.00 - 3.50 (1 H, br s, N*H*), 5.07 (1 H, m, C(α)*H*), 6.64 (1 H, d, *J* 7.0 Hz, CON*H*), 7.13 - 7.39 (10 H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 21.7 (C(α)*Me*), 26.0, 26.1 (C*Me*$_2$), 36.0 (*C*(2')H_2), 40.5 (*C*(2)), 41.3 (*C*(3)H_2), 45.6 (*C*(4)H_2), 48.6 (*C*(α)Me), 51.0 (*C*(1')H_2), 126.1, 126.2 (Ph_{para}), 127.2, 128.4, 128.5, 128.6 ($Ph_{ortho,meta}$), 139.7, 143.6 (Ph_{ipso}), 176.5 (*C*O); *m/z* (ESI$^+$) 339 (MH^+, 100 %); HRMS $C_{22}H_{31}N_2O$ (MH^+) requires 339.2436; found 339.2438.

Preparation of *N*-(2'-phenylethyl) 3,3-dimethyl-pyrrolidin-2-one 142 and (*R*)-α-methylbenzylamine hydrochloride 158.HCl[15]



187 142 158.HCl

187 (207 mg, 0.612 mmol, 1.0 eq.) was refluxed in toluene (15 mL) for 24 hours. The organic layer was washed with 10 % aqueous HCl (20 mL). The organic layer was concentrated *in vacuo*. The resultant residue was partitioned between DCM (20 mL) and the retained aqueous layer. The organic layer was washed with 10 % aqueous HCl (20 mL, 2×), dried (Na_2SO_4) and concentrated *in vacuo* to afford **142** (111 mg, 83 %) with identical spectroscopic properties to those previously described. The combined aqueous layers were co-evaporated with MeOH *in vacuo* to a constant mass to afford (*R*)-α-methylbenzylamine hydrochloride **158.HCl** as a white crystalline solid (87 mg, 90 %); m.p. 165 - 167°C (lit.[15] 169 - 170°C); $[\alpha]_D^{22}$ +2.6 (c=1.0, H_2O) (lit.[15] $[\alpha]_D^{22}$ +2.3 (c=2.9, H_2O)); δ_H (200 MHz, CD_3OD) 1.68 (3 H, d, *J* 6.9, C(α)*Me*), 4.50 (1 H, q, *J* 6.9, C(α)*H*), 7.43 - 7.52 (5 H, m, *Ph*). An analytical sample of the amine hydrochloride salt was treated with 2 M aqueous NaOH solution. The free amine was extracted from this solution with DCM. The organic layer was dried and concentrated *in vacuo* to furnish **158**. ^1H NMR analysis of a 1:1 mixture of (*S*)-*O*-acetylmandelic acid and the amine **158**, and comparison with authentic samples, confirmed the e.e. to be greater than 95 %.[16]

Preparation of *N*-benzyl-*N*-methyl 2,2-dimethyl-4-[*N*'-(2'-phenethyl)amino] butanamide 188



164 188

Following Representative Procedure **1**, CAN (2.86 g, 5.21 mmol, 5.0 eq.) was added to a stirred solution of **164** (447 mg, 1.04 mmol, 1.0 eq.) in THF:H_2O (8:1) (40 mL). After 16 hours the mixture was partitioned between 2 M aqueous NaOH solution (40 mL) and ether (80 mL). The aqueous layer was extracted with ether (80 mL). Combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography on silica gel (MeOH:$CHCl_3$, 2:98 - 1:9, stepwise elution) afforded the desired compound **188** as a yellow oil (299 mg, 85 %); ν_{max} (film)/cm^{-1} 3305 (N-H), 3062, 3027, 2931 (C-H), 1622 (C=O); δ_H (400 MHz, $CDCl_3$) 1.31 (6 H, s, C*Me*$_2$), 1.89 (2 H, t, *J* 7.6, C(3)*H*$_2$), 2.77 (2 H, t, *J* 7.6, C(4)*H*$_2$), 2.86 - 2.98 (6 H, m, C(1')*H*$_2$, C(2')*H*$_2$ and N*Me*CH_2Ph), 4.39 (1 H, br s, N'*H*), 4.58 (2 H, s, NMeC*H*$_2$Ph), 7.14 - 7.34 (10 H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 26.6 (C*Me*$_2$), 35.1 (*C*(2')H_2), 36.2 (N*Me*CH_2Ph), 40.5 (*C*(2)), 41.9 (*C*(3)H_2), 45.6 (*C*(4)H_2), 50.5 (*C*(1')H_2), 53.3 (NMe*C*H_2Ph), 126.4, 127.3 (Ph_{para}), 128.3, 128.6, 128.6, 128.7 ($Ph_{ortho,meta}$), 137.2, 138.8 (Ph_{ipso}), 176.6 (*C*O); *m/z* (ESI^+) 338 (MH^+, 100 %); HRMS $C_{29}H_{37}N_2O$ (MH^+) requires 429.2906; found 429.2920.

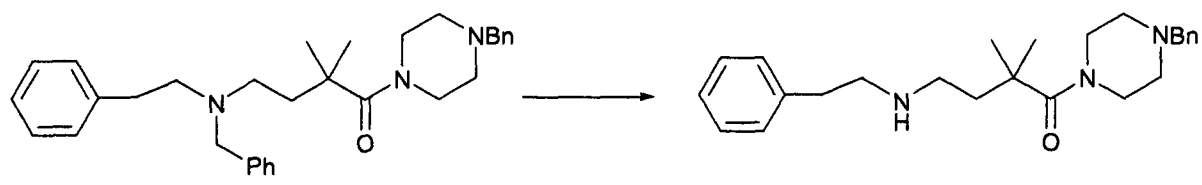
Preparation of *N*-(2'-phenylethyl) 3,3-dimethyl-pyrrolidin-2-one 142 and *N*-benzyl-*N*-methylamine hydrochloride 58.HCl[17]



188 142 58.HCl

188 (202 mg, 0.598 mmol, 1.0 eq.) was refluxed in toluene (20 mL) for 16 hours. The organic layer was washed with 10 % aqueous HCl (10 mL). The organic layer was concentrated *in vacuo*. The resultant residue was partitioned between DCM (20 mL) and the retained aqueous layer. The organic layer was washed with 10 % aqueous HCl (10 mL, 2×), dried (Na_2SO_4) and concentrated *in vacuo* to afford **142** (128 mg, 99 %) with identical spectroscopic properties to those previously described. The combined aqueous layers were co-evaporated with MeOH *in vacuo* to a constant mass to afford *N*-benzyl-*N*-methylamine hydrochloride **58.HCl** as a white crystalline solid (95 mg, 100 %); m.p. 168 - 170°C (lit.[17] 178°C); δ_H (400 MHz, $CDCl_3$) 2.47 (3 H, s, *Me*), 4.01 (2 H, s, NCH_2Ph), 7.24 - 7.52 (5 H, m, *Ph*), 9.50 - 10.5 (2 H, br s, NH_2).

Preparation of 4''-benzyl-piperazin-1''-yl 2,2-dimethyl-4-[*N*-(2'-phenylethyl)amino] butanamide 189

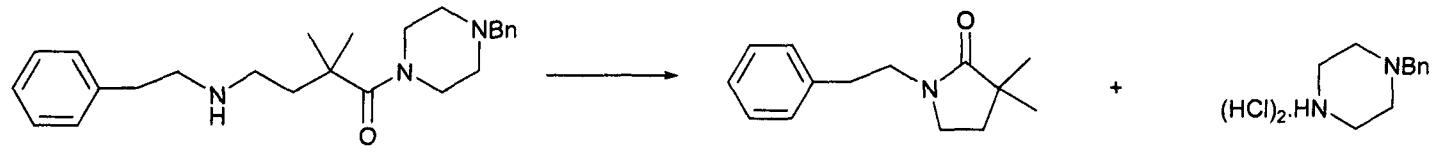


178 189

Following Representative Procedure **1**, CAN (850 mg, 1.55 mmol, 5.0 eq.) was added to a stirred solution of **178** (150 mg, 0.310 mmol, 1.0 eq.) in THF:H_2O (8:1) (10 mL). After 3 hours the mixture was partitioned with 2 M aqueous NaOH solution (20 mL) and ether (20 mL). The aqueous layer was extracted with ether (20 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Filtration through silica gel afforded the desired

compound **189** as a colourless oil (88 mg, 72 %); ν_{max} (film)/cm^{-1} 3474 (N-H), 3027, 2934 (C-H), 1626 (C=O); δ_H (400 MHz, $CDCl_3$) 1.26 (6 H, s, C*Me*$_2$), 1.84 (2 H, t, *J* 7.7, C(3)*H*$_2$), 2.39 - 2.41 (4 H, m, C(3'')*H*$_2$ and C(5'')*H*$_2$), 2.75 (2 H, m, *J* 7.7, C(4)*H*$_2$), 2.89 - 2.99 (4 H, m, C(1')*H*$_2$ and C(2')*H*$_2$), 3.49 (2 H, s, NC*H*$_2$Ph), 3.57 - 3.64 (4 H, m, C(2'')*H*$_2$ and C(6'')*H*$_2$), 4.20 - 4.40 (1 H, br s, N*H*) 7.16 - 7.37 (10 H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 26.6 (C*Me*$_2$), 34.9 (*C*(2')H$_2$), 40.3 (*C*(2)), 41.6 (*C*(3)H$_2$), 43.9, 45.4 (*C*(4)H$_2$, *C*(2'')H$_2$ and *C*(6'')H$_2$), 50.3 (*C*(1')H$_2$), 53.1 (*C*(3'')H$_2$ and *C*(5'')H$_2$), 62.8 (NCH$_2$Ph), 126.4, 172.2 (Ph$_{para}$), 128.2, 128.4, 128.6, 129.1 (Ph$_{ortho,meta}$), 137.5, 138.7 (Ph$_{ipso}$), 175.0 (*C*O), ; *m/z* (ESI$^+$) 394 (MH$^+$, 100 %); HRMS $C_{25}H_{36}N_3O$ (MH$^+$) requires 394.2858; found 394.2858.

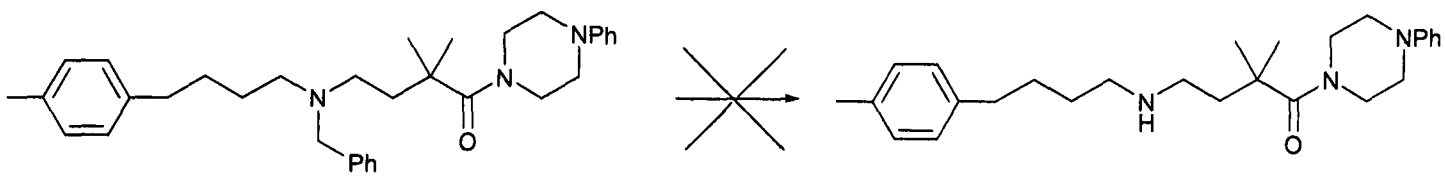
Preparation of *N*-(2'-phenylethyl) 3,3-dimethyl-pyrrolidin-2-one 142 and *N*-benzylpiperazine hydrochloride 179.2HCl



189 142 179.2HCl

189 (53 mg, 0.135 mmol, 1.0 eq.) was refluxed in toluene (5 mL) for 16 hours. The organic layer was washed with 10 % aqueous HCl (5 mL). The organic layer was concentrated *in vacuo*. The resultant residue was partitioned between DCM (5 mL) and the retained aqueous layer. The organic layer was washed with 10 % aqueous HCl (5 mL, 2×), dried (Na_2SO_4) and concentrated *in vacuo* to afford **142** (24 mg, 82 %) with identical spectroscopic properties to those previously described. The combined aqueous layers were co-evaporated with MeOH *in vacuo* to a constant mass to afford the *N*-benzylpiperazine **179.2HCl** as a white waxy solid (23 mg, 69 %); δ_H (200 MHz, CD_3OD) 3.64 (8 H, s, 4×C*H*$_2$), 4.53 (2 H, s, C*H*$_2$Ph), 7.54 - 7.69 (5 H, m, *Ph*).

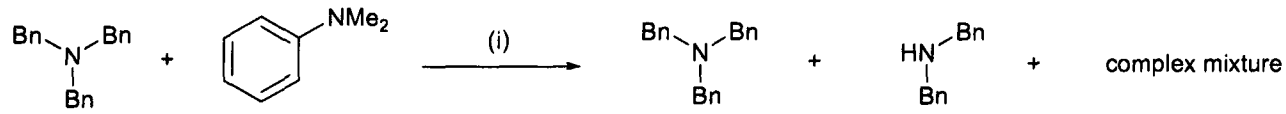
Attempted CAN debenzylation of (4''-phenyl)piperazin-1''-yl 2,2-dimethyl-4-{*N*-benzyl-*N*-[4'-(*p*-tolyl)butyl]amino}butanamide 176



176 190

Following Representative Procedure **1**, CAN (268 mg, 0.488 mmol, 5.0 eq.) was added to a stirred solution of **176** (50 mg, 0.0977 mmol, 1.0 eq.) in THF:H_2O (8:1) (1 mL). After 16 hours the mixture was partitioned with 2 M aqueous NaOH solution (5 mL) and ether (5 mL). The aqueous layer was extracted with ether (5 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. ^{1}H NMR spectroscopic analysis of the crude reaction mixture (11 mg) indicated that a complex mixture had been formed.

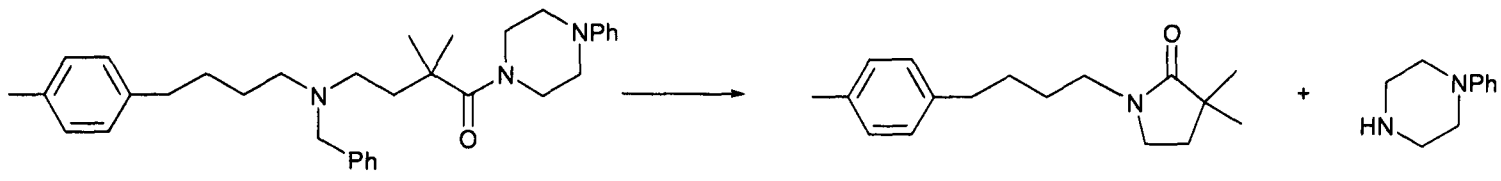
Attempted preparation of dibenzylamine 53[18]



46 191 46 53

Following Representative Procedure **1**, CAN (4.52 g, 8.25 mmol, 5.0 eq.) was added to a stirred solution of *N*,*N*-dimethylaniline **191** (200 mg, 1.65 mmol, 1.0 eq.) and tribenzylamine **46** (474 mg, 1.65 mmol, 1.0 eq.) in THF:H_2O (8:1) (20 mL). After 16 hours the mixture was partitioned with 2 M aqueous NaOH solution (20 mL) and ether (20 mL). The aqueous layer was extracted with ether (40 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo* to afford a 75:25 mixture (448 mg) of tribenzylamine **46** and dibenzylamine **53**.

Preparation of *N*-[4'-(*p*-tolyl)butyl]-3,3-dimethyl-pyrrolidin-2-one 176 and *N*-phenyl piperazine 175[19]

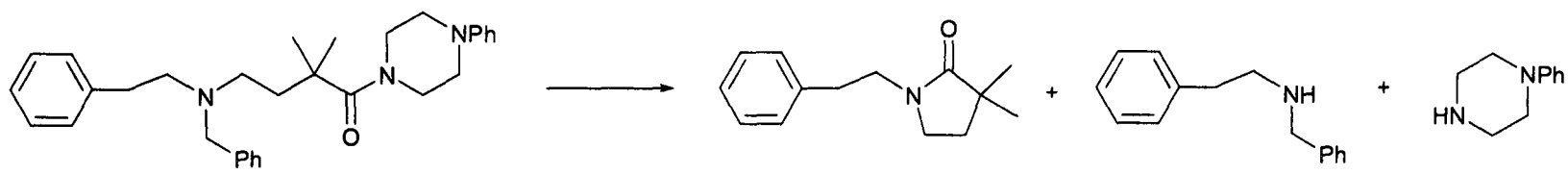


176 117 175

A solution of **176** (230 mg, 0.449 mmol, 1.0 eq.) and α-chloroethyl chloroformate (0.193 mL, 1.80 mmol, 4.0 eq.) in was refluxed for 16 hours in dichloroethane (10 mL). The solvent was removed *in vacuo* and the resulting residue refluxed in MeOH (10 mL) for 2 hours. The solvent was removed *in vacuo* and the resulting crude mixture partitioned between water (20 mL) and DCM (20 mL). The organic layer was washed with 2 M aqueous NaOH solution (20 mL), dried (Na_2SO_4) and concentrated *in vacuo* to afford the crude product (153 mg, 81 %). 400 MHz ^{1}H NMR spectroscopic analysis revealed an approximately 88:12:12 mixture of the desired debenzylated product **190**, δ_H (400 MHz, $CDCl_3$) 1.33 (6 H, s, C*Me*$_2$), 1.60 - 1.68 (4 H, m, C(2')*H*$_2$ and C(3')*H*$_2$), 1.91 - 1.95 (2 H, m, (C(3)*H*$_2$), 2.31 (3 H, s, *Me*Ar), 2.56 - 2.62 (2 H, m, C(4')*H*$_2$), 2.71 - 2.78 (4 H, m, C(4)*H*$_2$ and C(1')*H*$_2$), 3.16 (4 H, t, *J* 5.0, C(3'')*H*$_2$ and C(5'')*H*$_2$), 3.80 (4 H, t, *J* 5.0, C(2'')*H*$_2$ and C(6'')*H*$_2$), 4.50 - 5.50 (1 H, br s, N*H*), 6.89 - 6.94 (3 H, m, *Ar*), 7.04 - 7.10 (4 H, m, *Ph*), 7.26 - 7.31 (2 H, m, 1×*Ar*, 1×*Ph*); lactam **142** and *N*-phenyl piperazine **175** respectively. The crude product mixture was dissolved in DCM and heated at reflux for 16 hours to afford an approximately 50:50 mixture of lactam **142** and *N*-phenyl piperazine **175**. A sample aliquot (21 mg) containing the mixture was partitioned between 1 M aqueous HCl (2 mL) and DCM (3 mL). The aqueous layer was extracted with DCM (3 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford the lactam **142** (8 mg, 62 %) as a colourless oil with identical spectroscopic properties to those previously described. The aqueous phase was basified with 2 M aqueous NaOH solution and extracted with DCM (5 mL, 2×). The combined organic layers were concentrated *in vacuo* to

afford *N*-phenyl piperazine **175** as a colourless liquid (5 mg, 62 %); δ_H (400 MHz, $CDCl_3$) 2.15 (1 H, br s, N*H*), 3.01 - 3.17 (8 H, m, 4×CH_2), 6.81 - 7.30 (5 H, m, *Ph*).

Attempted preparation of *N*-(2'-phenylethyl) 3,3-dimethyl-pyrrolidin-2-one 142 and *N*-phenyl piperazine 175

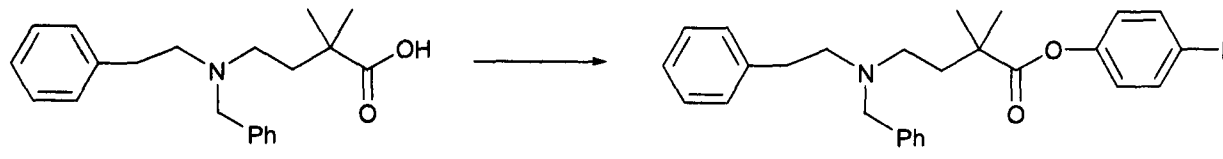


177 142 125 175

A solution of **177** (290 mg, mmol, 1.0 eq.) and α-chloroethyl chloroformate (0.267 mL, 2.47 mmol, 4.0 eq.) in was refluxed for 24 hours in dichloroethane (20 mL). The solvent was removed *in vacuo* and the resulting residue refluxed in MeOH (20 mL) for 24 hours. The solvent was removed *in vacuo* and the resulting crude residue partitioned between 2 M aqueous NaOH solution (2 mL) and DCM (10 mL). The aqueous layer was extracted with DCM (2×10 mL). The combined organic layers were washed with 2 M aqueous NaOH solution (2 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The resulting crude residue was refluxed in toluene for 16 hours to afford an approximately 36:64:64 mixture (198 mg) of *N*-benzyl-*N*-2-phenylethylamine **125**, the desired lactam **142** and *N*-phenyl piperazine **175** respectively. The mixture was partitioned between 10 % aqueous HCl (5 mL) and DCM (10 mL). The aqueous layer was extracted with DCM (10 mL). The combined organic layers were dried (Na_2SO_4), the solvent was removed *in vacuo* to afford a 36:64 mixture (131 mg) of **125.HCl** and the desired lactam **142**. An authentic sample of **125.HCl** was prepared by evaporation of 10 % aqueous HCl solution from the parent amine *N*-benzyl-*N*-2-phenylethylamine **125**; δ_H (200 MHz, $CDCl_3$) 2.91 - 3.15 (4 H, m, 2×CH_2), 3.98 (2 H, s, NCH_2Ph), 7.21 - 7.54 (5 H, m, *Ph*). The aqueous phase was basified with 2 M aqueous NaOH solution and extracted with DCM (10 mL, 2×) to afford *N*-phenyl piperazine **175** (64 mg, 64 %) with identical spectroscopic properties to those described previously.

7.6 Experimental for Chapter V

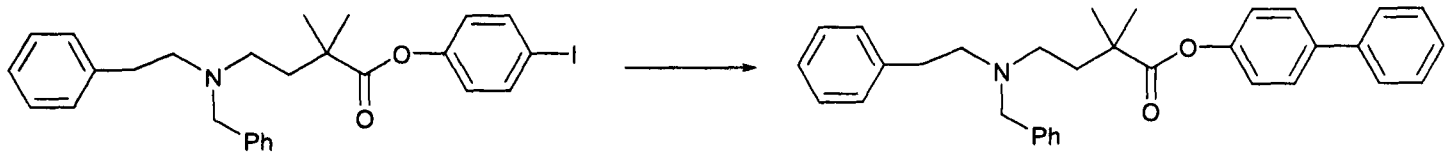
Preparation of 4''-iodophenyl 2,2-dimethyl-4-[*N*-benzyl-*N*-(2'-phenylethyl)amino] butanoate 192



124 192

Following Representative Procedure **2**, to a stirred solution of **124** (1.50 g, 4.61 mmol, 1.0 eq.), *p*-iodophenol **79** (5.08 g, 23.1 mmol, 5.0 eq.), HOBt (1.25 g, 9.23 mmol, 2.0 eq.) and DIPEA (2.42 mL, 13.8 mmol, 3.0 eq.) in DCM (60 mL) was added EDCI (1.33 g, 6.92 mmol, 1.5 eq.). The resulting solution was stirred for 16 hours then washed with 10 % aqueous HCl (60 mL) and 2 M aqueous NaOH solution (60 mL). The organic layer was dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography on silica gel (MeOH:$CHCl_3$, 2:98) afforded the desired compound **192** as a colourless oil (1.99 g, 82 %); ν_{max} (film)/cm^{-1} 3062, 3026, 2969 (C-H), 1752 (C=O); δ_H (400 MHz, $CDCl_3$) 1.31 (6 H, s, C*Me*$_2$), 1.88 - 1.92 (2 H, m, C(3)*H*$_2$), 2.58 - 2.62 (2 H, m, C(4)*H*$_2$), 2.75 - 2.84 (4 H, m, C(1')*H*$_2$ and C(2')*H*$_2$), 3.66 (2 H, s, NC*H*$_2$Ph), 6.65 - 6.68 (2 H, m, *Ar*), 7.16 - 7.57 (10 H, m, *Ph*), 7.70 - 7.72 (2 H, m, *Ar*); δ_C (100 MHz, $CDCl_3$) 25.4 (C*Me*$_2$), 33.5 (*C*(2')H$_2$), 37.3 (*C*(3)H$_2$), 41.6 (*C*(2)), 49.4 (*C*(4)H$_2$), 55.6 (*C*(1')H$_2$), 58.5 (N*C*H$_2$Ph), 89.5 (Ph$_{para}$), 123.8 (Ph$_{ortho,meta}$), 125.9, 126.9 (Ph$_{para}$), 128.3, 128.3, 128.8, 128.8, 138.4 (Ph$_{ortho,meta}$), 139.4, 140.5, 150.8 (Ph$_{ipso}$), 175.9 (*C*O); *m/z* (ESI$^+$) 528 (MH$^+$, 100 %); HRMS $C_{27}H_{31}NO_2$ (MH$^+$) requires 528.1400; found 528.1403.

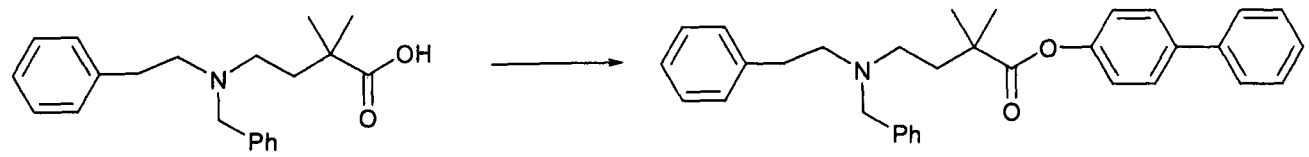
Preparation of 4''-biphenyl 2,2-dimethyl-4-[*N*-benzyl-*N*-(2'-phenylethyl)amino] butanoate 194



192 194

To a stirred solution of **192** (393 mg, 0.746 mmol, 1.0 eq.), K_2CO_3 (257 mg, 1.86 mmol, 2.5 eq.) and phenylboronic acid (182 mg, 1.49 mmol, 2.0 eq.) in DMF (20 mL) was added portionwise over 20 hours Pd_2dba_3 (136 mg, 0.149 mmol, 0.20 eq.). After 24 hours the solvent was removed *in vacuo* and the resulting residue partitioned between water (40 mL) and DCM (80 mL). The aqueous layer was extracted with DCM (80 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo* to afford a yellow oil (247 mg). Attempted purification by column chromatography (EtOAc:petrol, 1:9 - 2:8) afforded a mixture, inseparable by column chromatography, of **194** with identical spectroscopic properties to those described *vide infra* and dibenzylideneacetone[20] as revealed by 400 MHz ^{1}H NMR spectroscopic analysis.

Alternative preparation of 4''-biphenyl 2,2-dimethyl-4-[*N*-benzyl-*N*-(2'-phenylethyl) amino]butanoate 194

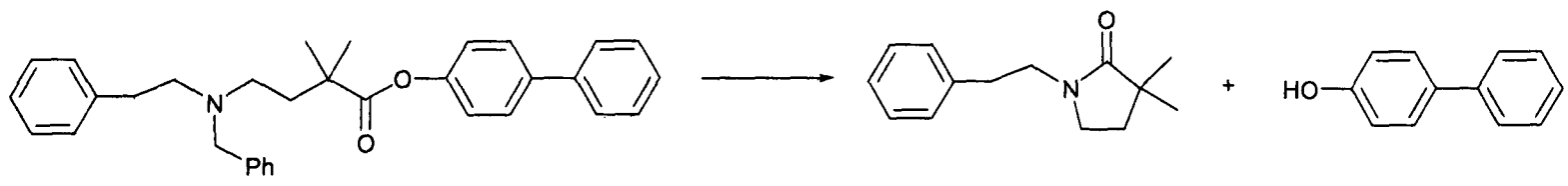


124 194

Following Representative Procedure **2**, to a stirred solution of **124** (326 mg, 1.00 mmol, 1.0 eq.), 4-phenylphenol **115** (683 mg, 4.00 mmol, 4.0 eq.), HOBt (271 mg, 2.00 mmol, 2.0 eq.) and DIPEA (0.702 mL, 4.00 mmol, 4.0 eq.) in DCM (25 mL) was added EDCI (481 mg, 2.50 mmol, 2.5 eq.) portionwise over 24 hours. The resulting solution was washed with 10 % aqueous HCl (25 mL) and 2 M aqueous NaOH solution (25 mL). The solution was dried

(Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography on silica gel (EtOAc:petrol, 1:9 - 2:8, stepwise elution) afforded the desired compound **194** as a white waxy solid (341 mg, 71 %); ν_{max} (film)/cm^{-1} 3028, 2935 (C-H), 1748 (C=O); δ_H (400 MHz, $CDCl_3$) 1.37 (6 H, s, C*Me*$_2$), 1.95 -1.99 (2 H, m, (C(3)*H*$_2$), 2.67 - 2.71 (2 H, m, (*C*(4)H_2), 2.79 - 2.88 (4 H, m, C(1')*H*$_2$ and C(2')*H*$_2$), 3.75 (2 H, s, NC*H*$_2$Ph), 7.03 - 7.05 (2 H, m, *Ar*), 7.21 - 7.62 (17 H, m, 2×*Ar*, 15×*Ph*); δ_C (100 MHz, $CDCl_3$) 25.4 (C*Me*$_2$), 33.3 (*C*(2')H_2), 37.2 (*C*(3)H_2), 41.5 (*C*(2)), 49.4 (*C*(4)H_2), 55.5 (*C*(1')H_2), 58.4 (NCH_2Ph), 121.7 ($Ph_{ortho,meta}$), 125.4, 125.9, 126.9 (Ph_{para}), 127.1, 127.2, 128.0, 128.2, 128.2, 128.7, 128.8 ($Ph_{ortho,meta}$), 138.7, 139.3, 140.3, 140.4, 150.2 ($Ph_{ipso,para}$), 176.2 (*C*O); *m/z* (ESI^+) 478 (MH^+, 100 %); HRMS $C_{33}H_{36}NO_2$ requires (MH^+) 478.2746; found 478.2740.

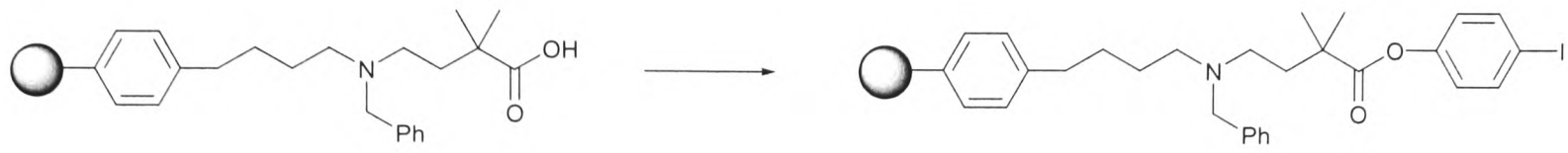
Preparation of *N*-(2'-phenylethyl) 3,3-dimethyl-pyrrolidin-2-one 142 and 4-phenylphenol 115



194 142 115

CAN (419 mg, 0.765 mmol, 5.0 eq.) was added to a stirred solution of **194** (73 mg, 0.153 mmol, 1.0 eq.) in THF:H_2O (8:1) (4 mL). The mixture was dryloaded on neutral aluminium oxide (Al_2O_3) after 16 hours. Filtration through a small plug of aluminum oxide (neutral) using EtOAc as the eluting solvent afforded a c.a. 50:50 mixture of the desired reaction products. Separation by column chromatography on silica gel (EtOAc:petrol, 2:98 - 8:2, stepwise elution) afforded the desired lactam **142** as a colourless oil (32 mg, 96 %) with identical spectroscopic properties to those previously described. The 4-phenylphenol **115** was also isolated as a white crystalline solid (24 mg, 92 %) with identical spectroscopic properties to those previously described

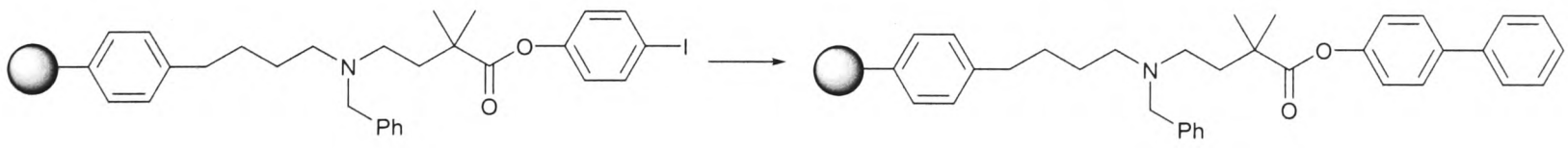
Preparation of 4''-iodophenyl 2,2-dimethyl 4-{*N*-benzyl-*N*-[4'-(*p*-polystyrenyl)butyl] amino}butanoate 195



90 195

Following Representative Procedure **3**, to a stirred suspension of **90** (2.23 g, 3.86 mmol, 1.0 eq.), *p*-iodophenol **79** (8.50 g, 38.6 mmol, 10.0 eq.), HOBt (1.57 g, 11.6 mmol, 3.0 eq.) and DIPEA (5.38 mL, 30.9 mmol, 8.0 eq.) in DCM (40 mL) was added DIC (1.81 mL, 11.6 mmol, 3.0 eq.). After 16 hours the resin was transferred to a funnel and washed repeatedly with DCM and THF. The resin was dried *in vacuo* to a constant mass to afford **195** as pale brown powder (2.73 g); ν_{max} (KBr)/cm^{-1} 3024, 2925, 2854 (C-H), 1749 (C=O); loading 1.41 mmol/g.

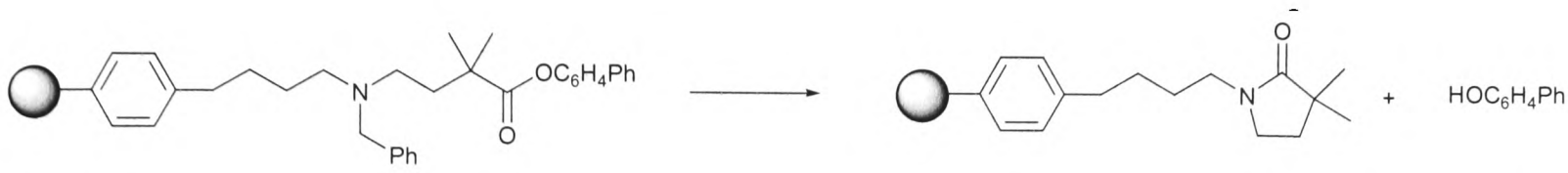
Alternative preparation of 4''-biphenyl 2,2-dimethyl-4-{*N*-benzyl-*N*-[4'-(*p*-polystyrenyl) butyl]amino}butanoate 120



195 120

Following Representative Procedure **4**, to a stirred suspension of **195** (100 mg, 0.141 mmol, 1.0 eq.), K_2CO_3 (97 mg, 0.705 mmol, 5.0 eq.) and phenylboronic acid **193** (69 mg, 0.564 mmol, 4.0 eq.) at 70°C in DMF (3 mL) was added portionwise over 36 hours, Pd_2dba_3 (26 mg, 0.0282 mmol, 0.20 eq.). The resin was repeatedly washed with DMF, water, THF and DCM. The resin was dried *in vacuo* to a constant mass to afford **120** (94 mg) with identical spectroscopic properties to those previously described; loading 1.52 mmol/g.

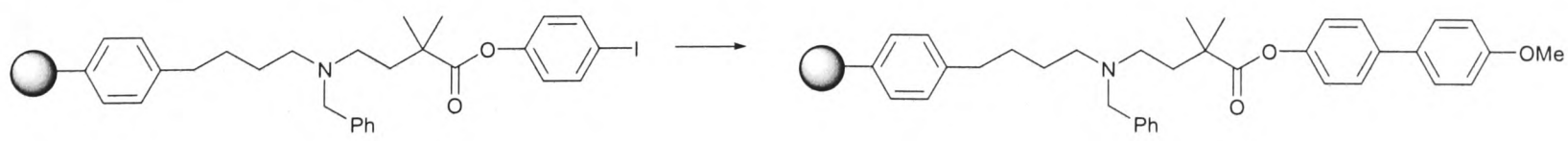
Preparation of *N*-[4'-(*p*-polystyrenyl)butyl]-3,3-dimethyl-pyrrolidin-2-one 122 and 4-phenylphenol 115



120 122 115

CAN (378 mg, 0.690 mmol, 5.0 eq.) was added to a stirred suspension of **120** (92 mg, 0.138 mmol, 1.0 eq.) in THF:H_2O (8:1) (1 mL). After stirring for 16 hours the resin was transferred to a funnel and washed repeatedly with THF, water and DCM. The resin was then treated with DCM:NEt_3 (5:1) (6 mL) and the filtrate was concentrated *in vacuo*. The resulting residue was partitioned between DCM (10 mL) and 10 % aqueous HCl (10 mL). The organic layer was washed with 10 % aqueous HCl (10 mL, 3×). The combined organic layers were removed *in vacuo* to afford 4-phenylphenol **115** (13 mg, 55 %) with identical spectroscopic properties to those previously described. The resin was dried *in vacuo* to a constant mass to afford **122** as a pale brown powder (66 mg) with identical spectroscopic properties to those previously described.

Preparation of 4'''-methoxy-biphenyl-4''-yl 2,2–dimethyl-4-{*N*-benzyl-*N*-[4'-(*p*-polystyrenyl)butyl]amino}butanoate 203



195 203

Following Representative Procedure **4**, to a stirred suspension of **195** (300 mg, 0.423 mmol, 1.0 eq.), K_2CO_3 (291 mg, 2.12 mmol, 5.0 eq.) and 4-methoxyphenylboronic acid **83** (257 mg, 1.69 mmol, 4.0 eq.) at 70°C in DMF (9 mL) was added portionwise over 36 hours Pd_2dba_3, (77 mg, 0.0846 mmol, 0.20 eq.). The resin was repeatedly washed with DMF, water, THF and DCM.

The resin was dried *in vacuo* to a constant mass to afford **203** as dark brown powder (282 mg); ν_{max} (KBr)/cm^{-1} 2927 (C-H), 1748 (C=O); loading 1.45 mmol/g.

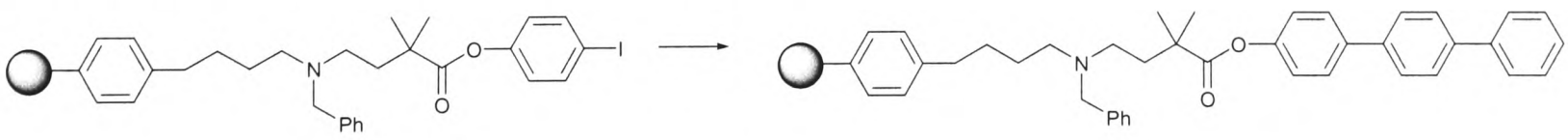
Preparation of *N*-[4'-(*p*-polystyrenyl)butyl]-3,3-dimethyl-pyrrolidin-2-one 122 and 4'-methoxy biphenyl-4-ol 85[21]



203 122 85

Following Representative Procedure **5**, CAN (1.14 g, 2.07 mmol, 5.0 eq.) was added to a stirred suspension of **203** (276 mg, 0.414 mmol, 1.0 eq.) in THF:H_2O (8:1) (3 mL) to furnish **85** as an orange solid (36 mg, 43 %); m.p. 162 - 164°C (lit.[21] 168 - 171°C); HPLC (MeCN/H_2O, 254 nm) 89 %; δ_H (400 MHz, DMSO-d_6) 3.76 (3 H, s, O*Me*), 6.82 (2 H, d, *J* 8.8, *Ar*), 6.96 (2 H, d, *J* 8.9, *Ar*), 7.41 (2 H, d, *J* 8.8, *Ar*), 7.48 (2 H, *J* 8.9, *Ar*), 9.47 (1 H, s, O*H*). The resin was dried *in vacuo* to a constant mass (253 mg) to afford **122** with identical spectroscopic properties to those previously described.

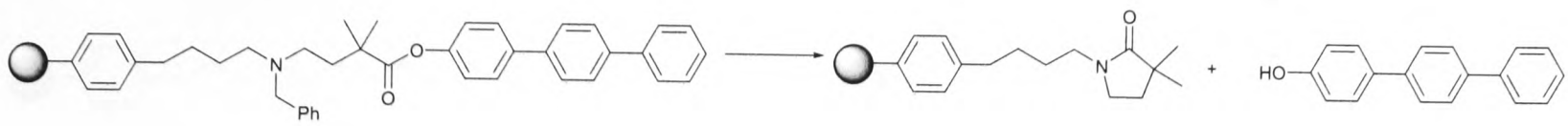
Preparation of [1'',1''':4''',1'''']-terphen-4''-yl 2,2-dimethyl-4-{*N*-benzyl-*N*-[4'-(*p*-polystyrenyl)butyl]amino}butanoate 204



195 204

Following Representative Procedure **4**, to a stirred suspension of **195** (300 mg, 0.423 mmol, 1.0 eq.), K_2CO_3 (291 mg, 2.12 mmol, 5.0 eq.) and 4-biphenylboronic acid **196** (335 mg, 1.69 mmol, 4.0 eq.) at 70°C in DMF (9 mL) was added portionwise over 36 hours Pd_2dba_3 (77 mg, 0.0846 mmol, 0.2 eq.). The resin was repeatedly washed with DMF, water, THF and DCM. The resin was dried *in vacuo* to a constant mass to afford **204** as dark brown powder (319 mg); ν_{max} (KBr)/cm^{-1} 2925 (C-H), 1748 (C=O); loading 1.36 mmol/g.

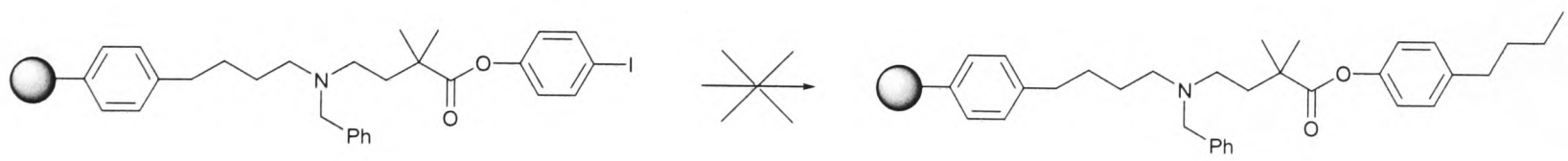
Preparation of *N*-[4'-(*p*-polystyrenyl)butyl]-3,3-dimethyl-pyrrolidin-2-one 122 and [1,1':4',1'']-terphenyl-4-ol 211[21]



204 122 211

Following Representative Procedure **5**, CAN (483 mg, 0.882 mmol, 5.0 eq.) was added to a stirred suspension of **204** (133 mg, 0.176 mmol, 1.0 eq.) in THF:H_2O (8:1) (1 mL) to furnish **211** as a pale yellow solid (22 mg, 51 %); m.p. 250 - 253°C (lit.[21] 268 - 271°C); HPLC (MeCN/H_2O, 254 nm) 92 %; δ_H (400 MHz, DMSO-d_6) 6.87 (2 H, d, *J* 8.8, Ar), 7.34 - 7.40 (1 H, m, *Ar*), 7.47 (2 H, t, *J* 7.5, *Ar*), 7.55 (2 H, d, *J* 8.5, *Ar*), 7.65 - 7.72 (4 H, m, *Ar*), 9.60 (1 H, s, O*H*). The resin was dried *in vacuo* to a constant mass (253 mg) to afford **122**.

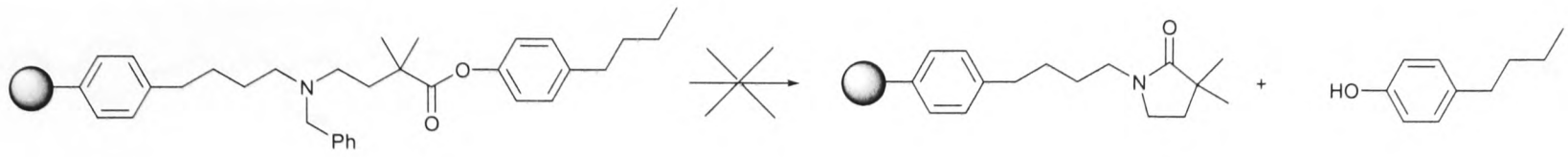
Attempted preparation of 4''-butylphenyl 2,2–dimethyl-4-{*N*-benzyl-*N*-[4'-(*p*-polystyrenyl)butyl]amino}butanoate 205



195 205

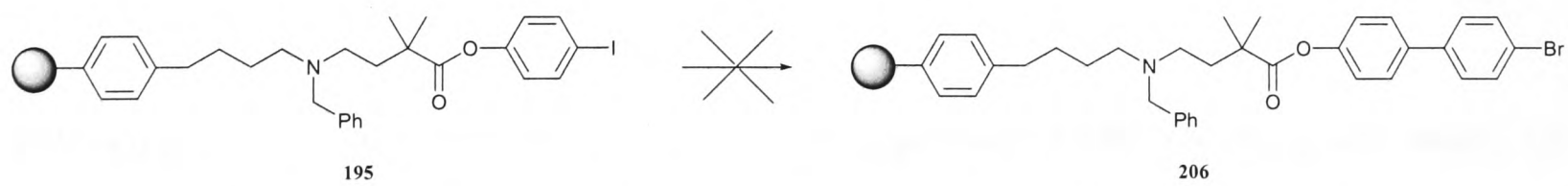
Following Representative Procedure **4**, to a stirred suspension of **195** (300 mg, 0.423 mmol, 1.0 eq.), K_2CO_3 (291 mg, 2.12 mmol, 5.0 eq.) and butylboronic acid **197** (172 mg, 1.69 mmol, 4.0 eq.) at 70° in DMF (9 mL) was added portionwise over 36 hours Pd_2dba_3 (77 mg, 0.0846 mmol, 0.20 eq.). The resin was repeatedly washed with DMF, water, THF and DCM. The resin was dried *in vacuo* to a constant mass to afford returned starting material **195** as dark brown powder (286 mg); ν_{max} (KBr)/cm^{-1} 3025, 2925 (C-H), 1751 (C=O).

Attempted preparation of *N*-[4'-(*p*-polystyrenyl)butyl]-3,3-dimethyl-pyrrolidin-2-one 122 and 4-butylphenol 212



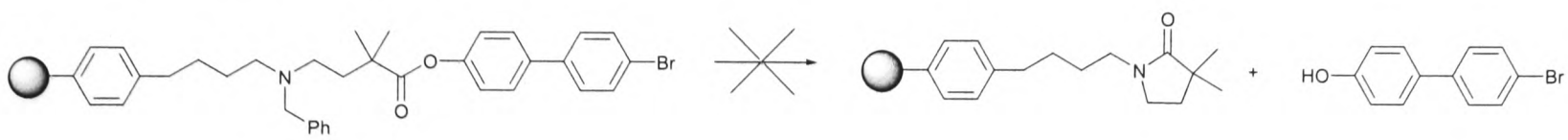
Following Representative Procedure **5**, CAN (1.04 g, 1.89 mmol, 5.0 eq.) was added to a stirred suspension of the product from the previous experiment which was assumed to be **205** (256 mg, 0.379 mmol, 1.0 eq.) in THF:H_2O (8:1) (1 mL) to furnish a yellow oily residue consisting of *p*-iodophenol **79**[22] contaminated with unidentified impurities; δ_H (200 MHz, $CDCl_3$) 4.76 (1 H, br s, O*H*), 6.60 - 6.67 (2 H, m, *Ar*), 7.48 - 7.57 (2 H, m, *Ar*). The resin was dried *in vacuo* to a constant mass (211 mg) to afford **122**.

Attempted preparation 4'''-bromo-biphenyl-4''-yl 2,2–dimethyl-4-{*N*-benzyl-*N*-[4'-(*p*-polystyrenyl)butyl]amino}butanoate 206



Following Representative Procedure **4**, to a stirred suspension of **195** (300 mg, 0.423 mmol, 1.0 eq.), K_2CO_3 (291 mg, 2.12 mmol, 5 eq.) and 4-bromophenylboronic acid **198** (338 mg, 1.69 mmol, 4.0 eq.) at 70°C in DMF (9 mL) was added portionwise over 36 hours Pd_2dba_3 (77 mg, 0.0846 mmol, 0.20 eq.). The resin was repeatedly washed with DMF, water, THF and DCM. The resin was dried *in vacuo* to a constant mass to afford returned starting material **195** as a red powder (297 mg); ν_{max} (KBr)/cm^{-1} 2925 (C-H), 1749 (C=O).

Attempted preparation of *N*-[4'-(*p*-polystyrenyl)butyl]-3,3-dimethyl-pyrrolidin-2-one 122 and 4'-bromo-biphenyl-4-ol 213



206 122 213

Following Representative Procedure **5**, CAN (1.10 g, 4.73 mmol, 5.0 eq.) was added to a stirred suspension of the product from the previous experiment which was assumed to be **206** (281 mg, 0.400 mmol, 1.0 eq.) in THF:H_2O (8:1) (3 mL) to furnish a red oily residue consisting mainly of *p*-iodophenol **79** with identical spectroscopic properties to those previously described. The resin was dried *in vacuo* to a constant mass (238 mg) to afford **122**.

Preparation of 2'''-trifluoromethyl-biphen-4''-yl 2,2–dimethyl-4-{*N*-benzyl-*N*-[4'-(*p*-polystyrenyl)butyl]amino}butanoate 207



195 207

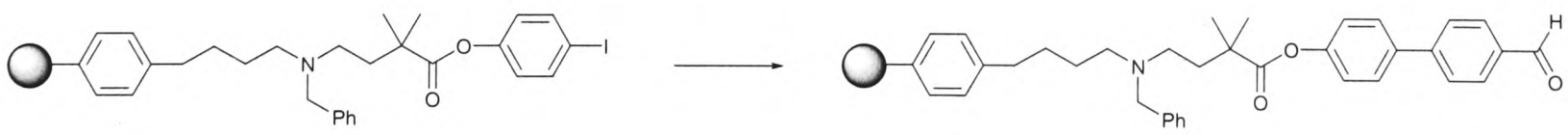
Following Representative Procedure **4**, to a stirred suspension of **195** (300 mg, 0.423 mmol, 1.0 eq.), K_2CO_3 (291 mg, 2.12 mmol, 5.0 eq.) and 2-(trifluoromethyl)phenylboronic acid **199** (321 mg, 1.69 mmol, 4.0 eq.) at 70°C in DMF (9 mL) was added portionwise over 36 hours Pd_2dba_3 (77 mg, 0.0846 mmol, 0.20 eq.). The resin was repeatedly washed with DMF, water, THF and DCM. The resin was dried to a constant mass *in vacuo* to afford **207** as dark brown powder (289 mg); ν_{max} (KBr)/cm^{-1} 3025, 2925 (C-H), 1750 (C=O); loading 1.37 mmol/g.

Preparation of *N*-[4'-(*p*-polystyrenyl)butyl]-3,3-dimethyl-pyrrolidin-2-one 122 and 2'-trifluoromethyl biphenyl-4-ol 214[21]



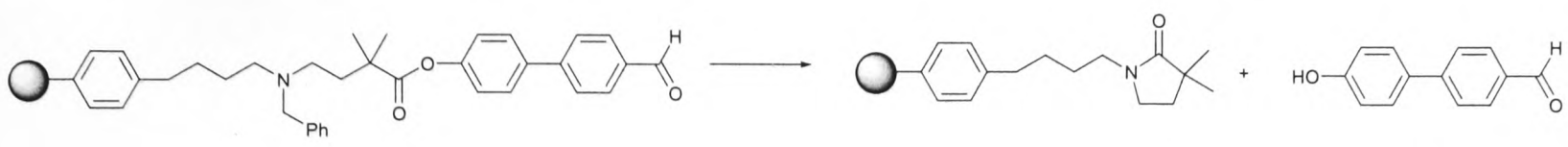
Following Representative Procedure **5**, CAN (1.10 g, 2.00 mmol, 5.0 eq.) was added to a stirred suspension of **207** (273 mg, 0.400 mmol, 1.0 eq.) in THF:H_2O (8:1) (3 mL) to furnish a 86:13 mixture of product **214** (70 mg, 74 %); HPLC (MeCN/H_2O, 254 nm) 59 %; δ_H (400 MHz, $CDCl_3$) 6.83 (2 H, d, *J* 8.6, *Ar*), 7.13 (2 H, d, *J* 8.0, *Ar*), 7.38 (2 H, d, *J* 7.0, *Ar*), 7.53 - 7.61 (1 H, m, *Ar*), 7.66 - 7.70 (1 H, m, *Ar*), 7.73 - 7.83 (1 H, m, *Ar*), 9.63 (1 H, s, O*H*) and *p*-iodophenol **79** respectively. The resin was dried *in vacuo* to a constant mass (209 mg) to afford **122**.

Preparation of 4'''-formyl-biphen-4''-yl 2,2–dimethyl-4-{*N*-benzyl-*N*-[4'-(*p*-polystyrenyl)butyl]amino}butanoate 208



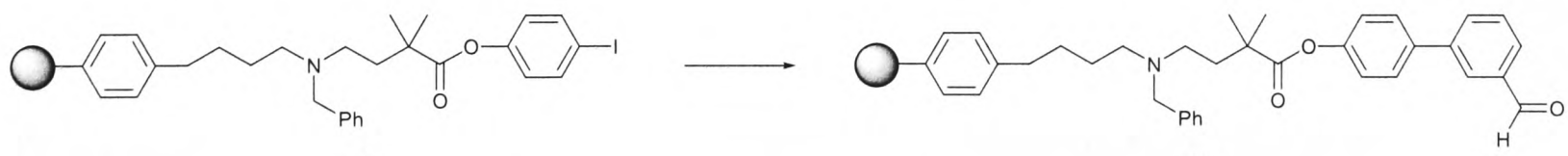
Following Representative Procedure **4**, to a stirred suspension of **195** (300 mg, 0.423 mmol, 1.0 eq.), K_2CO_3 (291 mg, 2.12 mmol, 5.0 eq.) and 4-formylphenylboronic acid **200** (253 mg, 1.69 mmol, 4.0 eq.) at 70°C in DMF (9 mL) was added portionwise over 36 hours Pd_2dba_3 (77 mg, 0.0846 mmol, 0.20 eq.). The resin was repeatedly washed with DMF, water, THF and DCM. The resin was dried *in vacuo* to a constant mass to afford **208** as dark brown powder (292 mg); ν_{max} (KBr)/cm^{-1} 2925 (C-H), 1749 (C=O, ester), 1700 (C=O, aldehyde); loading 1.45 mmol/g.

Preparation of *N*-[4'-(*p*-polystyrenyl)butyl]-3,3-dimethyl-pyrrolidin-2-one 122 and 4'-formyl-biphenyl-4-ol 215[23]



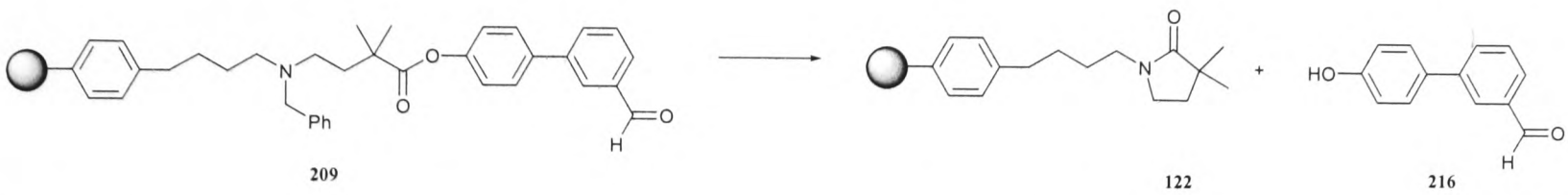
Following Representative Procedure **5**, CAN (1.09 g, 1.99 mmol, 5.0 eq.) was added to a stirred suspension of **208** (275 mg, 0.398 mmol, 1.0 eq.) in THF:H_2O (8:1) (3 mL) to furnish **215** as a yellow solid (62 mg, 79 %); m.p. 158 - 161°C (lit.[23] 176 - 178°C); HPLC (MeCN/H_2O, 254 nm) 90 %; δ_H (200 MHz, $CDCl_3$) 5.0 - 5.4 (1 H, br s, O*H*), 6.96 (2 H, d, *J* 8.7, *Ar*), 7.56 (2 H, d, *J* 8.6, *Ar*), 7.72 (2 H, d, *J* 8.2, *Ar*), 7.94 (2 H, d, *J* 8.5, *Ar*), 10.0 (1 H, s, CHO). The resin was dried *in vacuo* to a constant mass (219 mg) to afford **122**.

Preparation of 3'''-formyl-biphen-4''-yl 2,2–dimethyl-4-{*N*-benzyl-*N*-[4'-(*p*-polystyrenyl) butyl]amino}butanoate 209



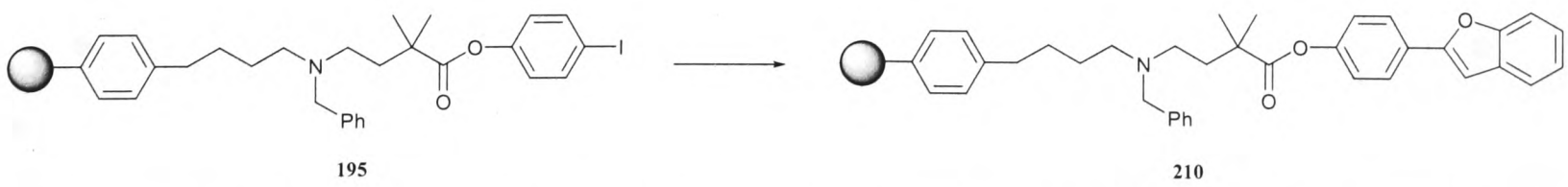
Following Representative Procedure **4**, to a stirred suspension of **195** (300 mg, 0.423 mmol, 1.0 eq.), K_2CO_3 (291 mg, 2.12 mmol, 5.0 eq.) and 3-formylphenylboronic acid **201** (253 mg, 1.69 mmol, 4.0 eq.) at 70°C in DMF (9 mL) was added portionwise over 36 hours Pd_2dba_3 (77 mg, 0.0846 mmol, 0.20 eq.). The resin was repeatedly washed with DMF, water, THF and DCM. The resin was dried *in vacuo* to a constant mass to afford **209** as dark brown powder (290 mg); ν_{max} (KBr)/cm^{-1} 2925 (C-H), 1749 (C=O, ester), 1698 (C=O, aldehyde); loading 1.45 mmol/g.

Preparation *N*-[4'-(*p*-polystyrenyl)butyl]-3,3-dimethyl-pyrrolidin-2-one 122 and 3'-formyl-biphenyl-4-ol 216



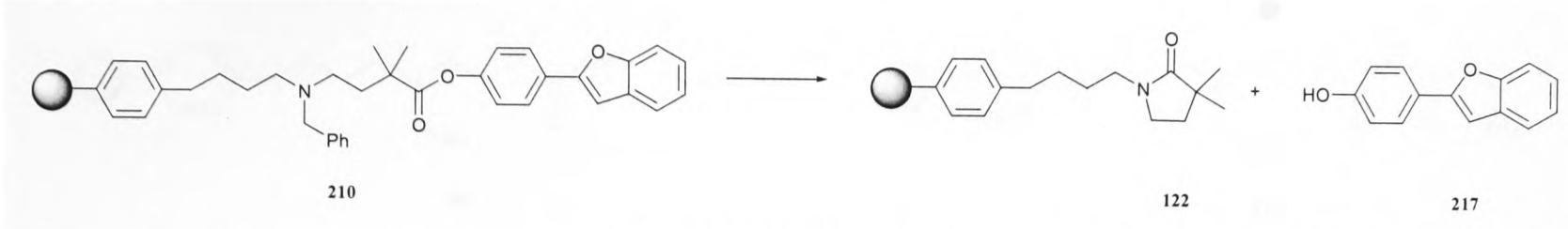
Following Representative Procedure **5**, CAN (1.05 g, 1.91 mmol, 5.0 eq.) was added to a stirred suspension of **209** (262 mg, 0.382 mmol, 1.0 eq.) in THF:H_2O (8:1) (3 mL) to furnish **216** as a yellow solid (56 mg, 74 %); m.p. 130 - 133°C; ν_{max} (KBr)/cm^{-1} 3400 (O-H), 1682 (C=O); HPLC (MeCN/H_2O, 254 nm) 91 %; δ_H (400 MHz, DMSO-d_6) 6.89 (2 H, d, *J* 8.7, *Ar*), 7.58 (2 H, d, *J* 8.8, *Ar*), 7.63 (1 H, t, *J* 7.5, *Ar*), 7.79 - 7.81 (1 H, m, *Ar*), 7.91 - 7.94 (1 H, m, *Ar*), 8.10 - 8.11 (1 H, m, *Ar*), 9.7 (1 H, O*H*), 10.1 (1 H, C*H*O); δ_C (100 MHz, $CDCl_3$) 116.8, 127.8, 128.1, 128.8, 130.4, 130.6, 137.6, 141.87, 158.5 (12×*Ar*), 194.2 (CHO); *m/z* (ESI^-) 197 [$(M-H)^-$, 100 %]; HRMS $C_{13}H_9O$ [$(M-H)^-$] requires 197.0603; found 197.0610. The resin was dried *in vacuo* to a constant mass (214 mg) to afford **122**.

Preparation of 4''-(1'''-benzofuran-2'''-yl)phenyl 2,2–dimethyl-4-{*N*-benzyl-*N*-[4'-(*p*-polystyrenyl)butyl]amino}butanoate 210



Following Representative Procedure **4**, to a stirred suspension of **195** (300 mg, 0.423 mmol, 1.0 eq.), K_2CO_3 (291 mg, 2.12 mmol, 5.0 eq.) and benzofuran-2-yl boronic acid **202** (274 mg, 1.69 mmol, 4.0 eq.) at 70°C in DMF (9 mL) was added portionwise over 36 hours Pd_2dba_3 (77 mg, 0.0846 mmol, 0.20 eq.). The resin was repeatedly washed with DMF, water, THF and DCM. The resin was dried *in vacuo* to a constant mass to afford **210** as dark brown powder (312 mg); ν_{max} (KBr)/cm^{-1} 2925 (C-H), 1749 (C=O); loading 1.43 mmol/g.

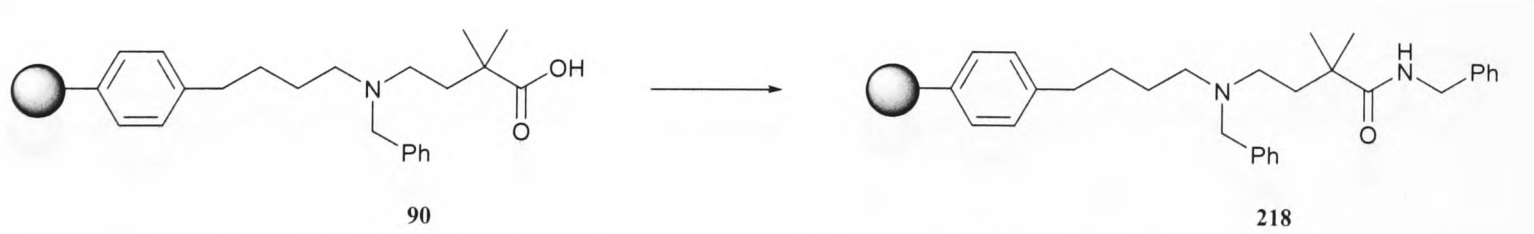
Preparation of *N*-[4'-(*p*-polystyrenyl)butyl]-3,3-dimethyl-pyrrolidin-2-one 122 and 4-(1'-benzofuran-2'-yl)phenol 217[24]



210 122 217

Following Representative Procedure **5**, CAN (1.03 g, 1.88 mmol, 5.0 eq.) was added to a stirred suspension of **210** (277 mg, 0.376 mmol, 1.0 eq.) in THF:H_2O (8:1) (3 mL) to furnish an approximately 86:14 mixture of the product **217** (49 mg, 61 %); HPLC (MeCN/H_2O, 254 nm) 86 %; δ_H (400 MHz, MeOD) 6.87 - 6.91 (2 H, m, *Ar*), 6.96 (1 H, s, C=C*H*), 7.17 - 7.25 (2 H, m, *Ar*), 7.46 - 7.48 (1 H, m, *Ar*), 7.54 - 7.57 (1 H, m, *Ar*), 7.72 - 7.76 (2 H, m, *Ar*) and *p*-iodophenol **79** respectively. The resin was dried *in vacuo* to a constant mass (260 mg) to afford **122**.

Preparation of benzyl 2,2-dimethyl-4-{*N*-benzyl-*N*-[4'-(*p*-polystyrenyl)butyl]amino} butanamide 218



90 218

Following Representative Procedure **3**, to a stirred suspension of **90** (500 mg, 0.865 mmol, 1.0 eq.), benzylamine **93** (0.566 mL, 5.19 mmol, 6.0 eq.), HOBt (351 mg, 2.56 mmol, 3.0 eq.) and DIPEA (0.904 mL, 5.19 mmol, 6.0 eq.) in DCM (10 mL) was added DIC (0.406 ml, 2.56 mmol, 3.0 eq.). After 16 hours the resin was transferred to a funnel and washed repeatedly with DMF, MeOH and DCM. The resin was dried *in vacuo* to a constant mass to afford **218** as pale brown powder (518 mg); ν_{max} (KBr)/cm^{-1} 3368 (N-H), 2928, 2845 (C-H), 1634, 1529 (C=O); loading 1.68 mmol/g.

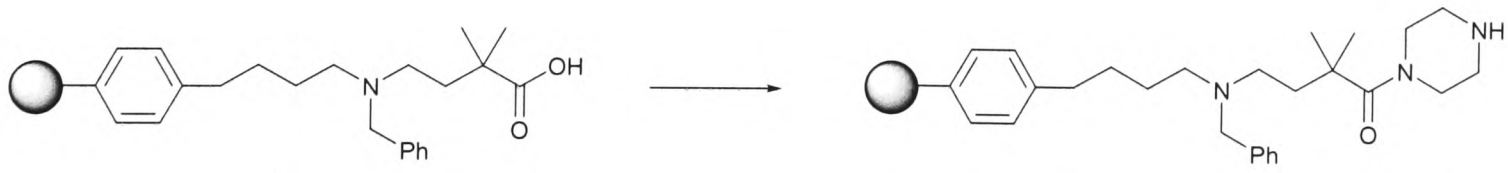
Preparation of piperidin-4''-yl 2,2-dimethyl-4-{*N*-benzyl-*N*-[4'-(*p*-polystyrenyl)butyl] amino}butanamide 219



90 219

Following Representative Procedure **3**, to a stirred suspension of **90** (300 mg, 0.519 mmol, 1.0 eq.), 4-amino-piperidine (0.327 mL, 3.11 mmol, 6.0 eq.), HOBt (281 mg, 2.08 mmol, 4.0 eq.) and DIPEA (0.544 mL, 3.11 mmol, 6.0 eq.) in DCM (10 mL) was added EDCI (398 mg, 2.07 mmol, 4.0 eq.). After 16 hours the resin was transferred to a funnel and washed repeatedly with DMF, MeOH and DCM. The resin was dried *in vacuo* to a constant mass to afford **219** as pale brown powder (329 mg); ν_{max} (KBr)/cm^{-1} 3432 (N-H), 3023, 2927, 2851 (C-H) 1635, 1530 (C=O); loading 1.70 mmol/g.

Preparation of piperazine-1''-yl 2,2-dimethyl-4-{*N*-benzyl-*N*-[4'-(*p*-polystyrenyl)butyl] amino}butanamide 220

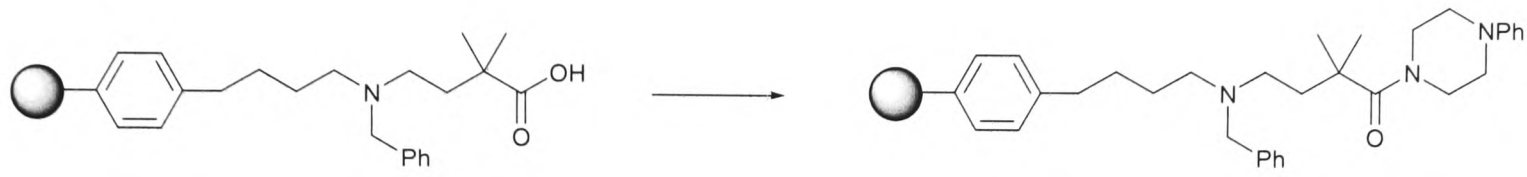


90 220

Following Representative Procedure **3**, to a stirred suspension of **90** (288 mg, 0.498 mmol, 1.0 eq.), piperazine **172** (429 mg, 4.98 mmol, 10.0 eq.), HOBt (135 mg, 0.996 mmol, 2.0 eq.) and DIPEA (0.871 mL, 4.98 mmol, 10.0 eq.) in DCM (10 mL) was added TBTU (320 mg, 0.996 mmol, 2.0 eq.). After 16 hours the resin was transferred to a funnel and washed repeatedly with DMF, MeOH and DCM. The resin was dried *in vacuo* to a constant mass to yield a mixture of product and returned starting material. The mixture was subjected to the same reaction and

work-up protocol to afford the product **220** as a dark brown powder (287 mg); ν_{max} (KBr)/cm^{-1} 3019, 2923, 2848 (C-H), 1626 (C=O); loading 1.74 mmol/g.

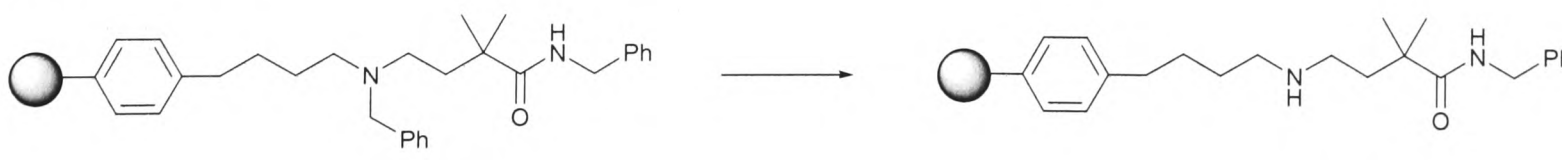
Preparation of (4''-phenyl)piperazin-1''-yl 2,2-dimethyl-4-{*N*-benzyl-*N*-[4'-(*p*-polystyrenyl)butyl]amino}butanamide 221



90 221

Following Representative Procedure **3**, to a stirred suspension of **90** (300 mg, 0.519 mmol, 1.0 eq.), from the previous step, *N*-phenyl piperazine **175** (1.95 mL, 13.0 mmol, 25.0 eq.), HOBt (280 mg, 2.08 mmol, 4.0 eq.) and DIPEA (2.27 mL, 13.0 mmol, 25.0 eq.) in DCM (10 mL) was added DIC (0.162 mL, 1.04 mmol, 2.0 eq.). After 16 hours the resin was transferred to a funnel and washed repeatedly with DMF, MeOH and DCM. The resin was dried *in vacuo* to a constant mass to yield a mixture of product and returned starting material. The mixture was subjected to the same reaction and work-up protocol to afford the product **221** as a pale brown powder (351 mg); ν_{max} (KBr)/cm^{-1} 3024, 2925, 2855 (C-H), 1630 (C=O); loading 1.54 mmol/g.

Preparation of benzyl 2,2-dimethyl-4-{*N*-(4'-(*p*-polystyrenyl)butyl]amino} butanamide 222

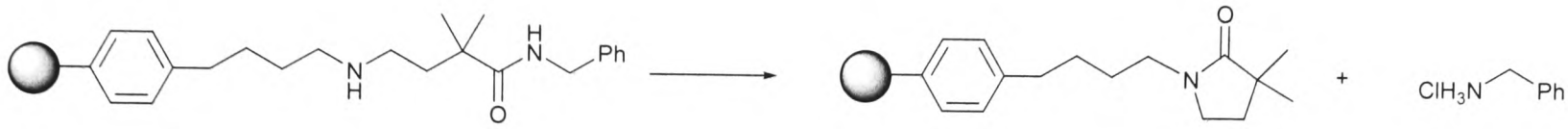


218 222

CAN (1.63 g, 2.96 mmol, 5.0 eq.) was added to a stirred suspension of **218** (355 mg, 0.593 mmol, 1.0 eq.) in THF:H_2O (8:1) (13 mL). After 16 hours the resin was transferred to a funnel and washed repeatedly with DMF, 2 M aqueous NaOH solution, water, MeOH and DCM. The resin was dried to a constant mass *in vacuo* to afford **222** as a pale brown powder (304

mg); ν_{max} (KBr)/cm^{-1} 3371 (N-H), 2951, 2921, 2845 (C-H), 1635, 1529 (C=O); loading 1.98 mmol/g.

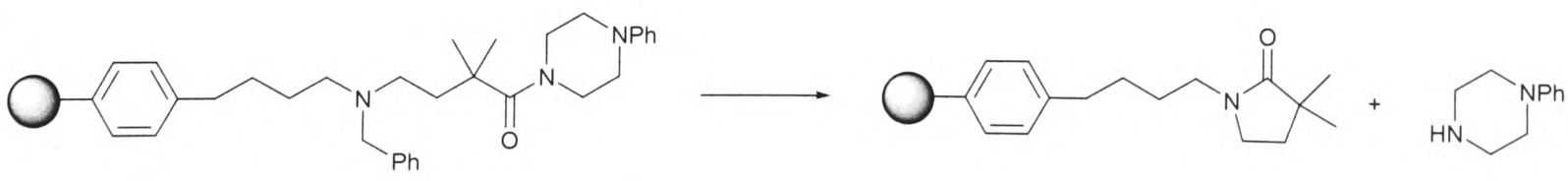
Preparation of *N*-[4'-(*p*-polystyrenyl)butyl]-3,3-dimethyl-pyrrolidin-2-one 122 and benzylamine hydrochloride 93.HCl



222 122 93.HCl

The resin **222** (300 mg, 0.585 mmol) was stirred as a suspension in toluene (10 mL) and refluxed for 48 hours. The resin was transferred to a funnel and washed repeatedly with toluene. To the combined organic washings was added 10 % aqueous HCl. The solvents were removed *in vacuo* and the residue co-evaporated with MeOH to afford benzylamine hydrochloride **93.HCl** as a white crystalline solid (55 mg, 65 %) with identical spectroscopic properties to those previously described. The resin was washed repeatedly with MeOH, THF and DCM. The resin was dried *in vacuo* to a constant mass to afford **122** as a dark brown powder (243 mg) with identical spectroscopic properties to those previously described.

Preparation of *N*-[4'-(*p*-polystyrenyl)butyl]-3,3-dimethyl-pyrrolidin-2-one 122 and *N*-phenyl piperazine 175

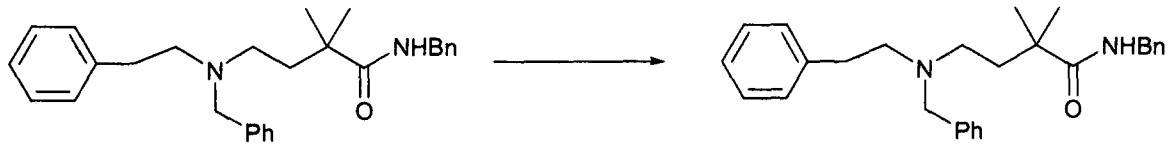


221 122 175

A stirred suspension of **221** (200 mg, 0.296 mmol, 1.0 eq.) and α-chloroethyl chloroformate (0.124 mL, 1.18 mmol, 4.0 eq.) was refluxed for 16 hours in DCE (6 mL). The resin was washed with DCM and dried *in vacuo* to a constant mass to yield **223** as pale brown powder (193 mg); ν_{max} (KBr)/cm^{-1} 2927 (C-H), 1721 (C=O, carbamate), 1638 (C=O, amide). The resin

(187 mg, 0.287 mmol) was refluxed in MeOH (5 mL) for 3 hours, transferred to a funnel and washed repeatedly with MeOH, DCM:NEt_3 (10:1) and DCM. The resin was dried *in vacuo* to a constant mass to afford **224** (160 mg); ν_{max} (KBr)/cm^{-1} 2924(C-H), 1629 (C=O, amide). The resin (143 mg, 0.257 mmol) was further refluxed in toluene (4 mL) for 16 hours, transferred to a funnel and washed repeatedly with DCM. The combined organic solvents were removed *in vacuo* to afford *N*-phenyl piperazine **175** as a colourless oil (28 mg, 67 %) with identical spectroscopic properties to those previously described. The resin was dried *in vacuo* to a constant mass to afford **122** as dark brown powder (119 mg) with identical spectroscopic properties to those previously described.

Stability assessment of benzyl 2,2-dimethyl-4-[*N*-benzyl-*N*-(2'-phenylethyl)amino] butanamide 159 with BuLi



159 **159**

A solution of **159** (200 mg, 0.483 mmol, 1.0 eq.) in THF (10 mL) was cooled to –78°C and BuLi (0.362 mL, 1.6 M in THF, 0.580 mmol, 1.2 eq.) was added dropwise. The resulting solution was then allowed to warm to room temperature over 2 hours. The solution was partitioned between water (20 mL) and DCM (20 mL). The organic layer was concentrated *in vacuo* to afford starting material **159** (171 mg, 86 %).

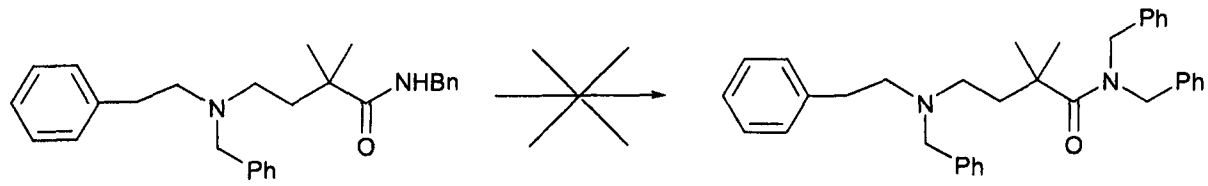
Stability assessment of benzyl 2,2-dimethyl-4-[*N*-benzyl-*N*-(2'-phenylethyl)amino] butanamide 159 with benzyl bromide 100[25]



159 225

To a solution of **159** (200 mg, 0.483 mmol, 1.0 eq.) in THF (10 mL) was added benzyl bromide **100** (0.172 mL, 1.93 mmol, 3.0 eq.). The resulting solution was stirred at room temperature for 6 days and then partitioned between water (20 mL) and DCM (20 mL). The organic layer was dried (Na_2SO_4) and concentrated *in vacuo* to afford a mixture of the assumed quaternary ammonium salt **225** (152 mg); δ_H (400 MHz, $CDCl_3$) 1.22 (6 H, s, C*Me*$_2$), 2.12 - 2.17 (2 H, m, C*H*$_2$), 2.90 - 2.94 (2 H, m, C*H*$_2$), 3.43 - 3.63 (4 H, m, 2×C*H*$_2$), 5.53 (2 H, d, *J* 3.0, CONHC*H*$_2$Ph), 4.88 (2 H, d , *J* 6.0, NC*H*$_2$Ph), 4.98 (2 H, d, *J* 6.0, NCH$_2$Ph) , 7.12 - 7.67 (20 H, m, *Ph*); ESI^+ (M^+, 100) 505; contaminated with benzyl bromide **100** and other unidentified impurities.

Attempted *N*-alkylation of benzyl 2,2-dimethyl-4-[*N*-benzyl-*N*-(2'-phenylethyl)amino] butanamide 159 with BnBr

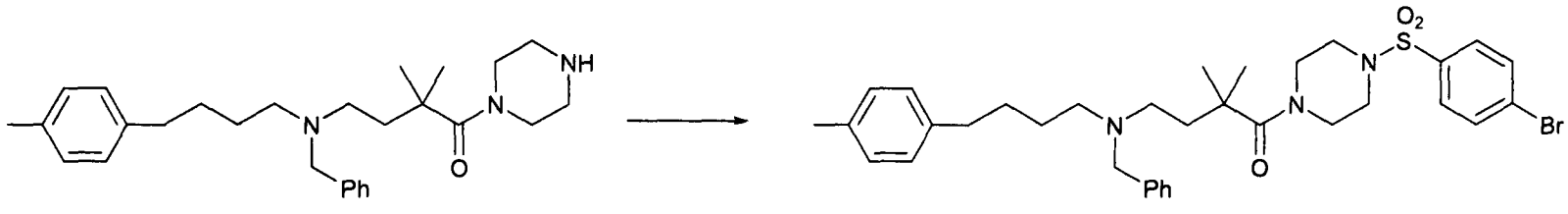


159 167

A solution of **159** (300 mg, 0.724 mmol, 1.0 eq.) in THF (10 mL) was cooled to –78°C and BuLi (0.498 mL, 1.6 M in THF, 0.870 mmol, 1.2 eq.) was added dropwise. The resulting solution was stirred at –78°C for 30 min before addition of benzyl bromide **100** (0.258 mL, 2.17 mmol, 3.0 eq.). The solution was then allowed to warm to room temperature, stirred for 6 days and monitored. The solution was quenched with aqueous NH_4Cl solution (2 mL) and partitioned between water (20 mL) and DCM (20 mL). The organic layer was concentrated *in*

vacuo. 400MHz ^{1}H NMR analysis of the resulting mixture (664 mg) revealed the presence of the assumed quarternary ammonium salt **225**, with identical properties as previously described, contaminated with benzyl bromide **100** and other unidentified impurities.

Preparation of {[4''-(4'''-bromophenyl)sulfonyl] piperazin-1''-yl} 2,2-dimethyl-4-{*N*-benzyl-*N*-[4'-(*p*-tolyl)butyl]amino}butanamide 227

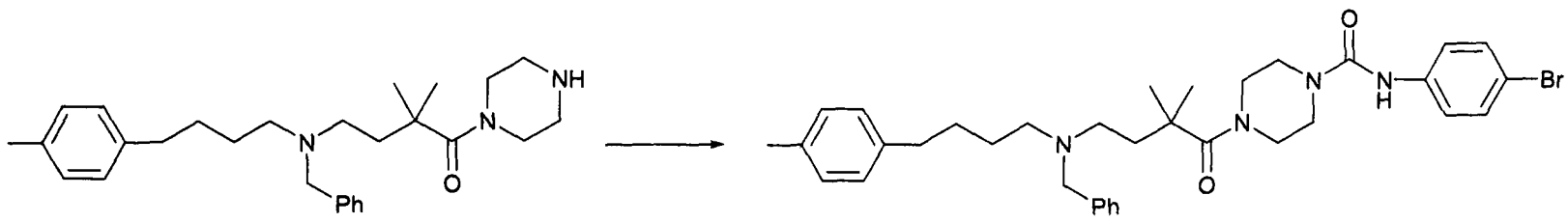


173 227

To a solution of **173** (185 mg, 0.425 mmol, 1.0 eq.) in DCM (5 mL) was added 4-bromophenylsulphonyl chloride **226** (119 mg, 0.467 mmol, 1.1 eq.). The resulting solution was stirred at room temperature for 16 hours and partitioned between water (10 mL) and DCM (10 mL). The aqueous layer was extracted with DCM (10 mL). Combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography on silica gel (MeOH:$CHCl_3$, $CHCl_3$ - 6:94, stepwise elution) afforded the desired compound **227** as a colourless waxy solid (259 mg, 93 %); $C_{34}H_{44}N_3O_3SBr$ requires C 62.37 %, H 6.77 %, N 6.42 %; found C 62.08 %, H 6.85 %, N 6.35 %; ν_{max} (film)/cm^{-1} 2976, 2927 (C-H), 1619 (C=O), 1353 (SO_2), 1168 (SO_2); δ_H (400 MHz, $CDCl_3$) 1.15 (6 H, s, C*Me*$_2$), 1.42 - 1.47 (2 H, m, C(2')*H*$_2$), 1.54 - 1.60 (2 H, m, C(3')*H*$_2$), 1.65 - 1.69 (2 H, m, C(3)*H*$_2$), 2.25 - 2.29 (2 H, m, C(4)*H*$_2$), 2.33 (3 H, s, *Me*Ar), 2.37 (2 H, t, *J* 7.2, C(1')*H*$_2$), 2.54 (2 H, t, *J* 7.6, C(4')*H*$_2$), 2.93 (2 H, t, *J* 4.9, C(3'')*H*$_2$ and C(5'')*H*$_2$), 3.45 (2 H, s, NC*H*$_2$Ph), 3.54 (2 H, t, *J* 4.9, C(2'')*H*$_2$ and C(6'')*H*$_2$), 7.04 - 7.11 (4 H, m, *Ar*), 7.25 - 7.33 (5 H, m, *Ph*), 7.57 - 7.66 (4 H, m, *Ar*); δ_C (100 MHz, $CDCl_3$) 21.0 (*Me*Ar), 26.5 (*C*(3')H$_2$), 27.1 (C*Me*$_2$), 29.2 (*C*(2')H$_2$), 35.3 (*C*(4')H$_2$), 38.5 (*C*(3)H$_2$), 41.6 (*C*(2)), 44.1 (C(2'')*H*$_2$ and C(6'')*H*$_2$), 45.8 (C(3'')*H*$_2$ and C(5'')*H*$_2$), 49.5 (*C*(4)H$_2$), 53.9 (*C*(1')H$_2$), 58.8 (NCH$_2$Ph), 126.9 (Ph$_{para}$), 128.2, 128.3, 128.8, 129.0, 129.1,

132.5 ($Ph_{ortho,meta}$), 134.6, 135.1, 139.4, 139.8, 142.0 ($Ph_{ipso,para}$), 175.3 (*C*O); *m/z* (ESI^+) 654 (MH^+, 100 %); HRMS $C_{34}H_{45}N_3O_3SBr$ (MH^+) requires 654.2365; found 654.2372.

Preparation of [4''-(4'''-bromophenyl)carboxamide piperazin-1''-yl] 2,2-dimethyl-4-{*N*-benzyl-*N*-[4'-(*p*-tolyl)butyl]amino}butanamide 229

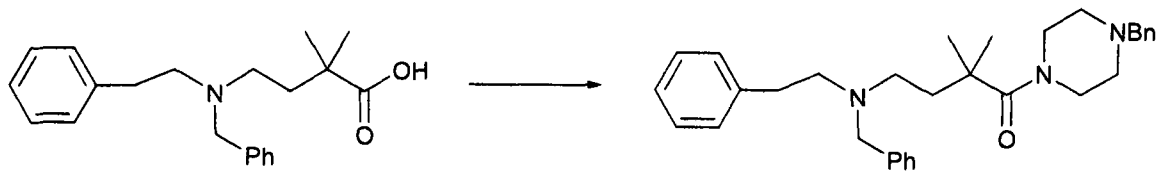


173 229

To a solution of **173** (100 mg, 0.230 mmol, 1.0 eq.) in DCM (3 mL) was added *p*-bromophenyl isocyanate (50 mg, 0.252 mmol, 1.1 eq.). The resulting solution was stirred at room temperature for 2 hours and partitioned between water (10 mL) and DCM (10 mL). The aqueous layer was extracted with DCM (10 mL). The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography on silica gel (MeOH:$CHCl_3$, $CHCl_3$ - 8:92, stepwise elution) afforded the desired compound **229** as a white solid (134 mg, 92 %); m.p. 133 - 135°C; ν_{max} (KBr)/cm^{-1} 2927, 2854 (C-H), 1669, 1636, 1613, 1590 (C=O); δ_H (400 MHz, $CDCl_3$) 1.23 (6 H, s, C*Me*$_2$), 1.51 - 1.56 (2 H, m, C(2')*H*$_2$), 1.56 - 1.65 (2 H, m, C(3')*H*$_2$), 1.71 - 1.75 (2 H, m, C(3)*H*$_2$), 2.32 (3 H, s, *Me*Ar), 2.32 - 2.36 (2 H, m, C(4)*H*$_2$), 2.47 (2 H, t, *J* 7.0, C(1')*H*$_2$), 2.57 (2 H, t, *J* 7.4, C(4')*H*$_2$), 3.25 - 3.28 (4 H, m, C(3'')*H*$_2$ and C(5'')*H*$_2$), 3.49 - 3.51 (6 H, m, NC*H*$_2$Ph and C(2'')*H*$_2$ and C(6'')*H*$_2$), 6.59 (1 H, s, N*H*), 7.05 - 7.11 (4 H, m, *Ar*), 7.17 - 7.21 (1 H, m, *Ar*), 7.26 - 7.31 (5 H, m, *Ph*), 7.40 - 7.43 (3 H, m, *Ar*); δ_C (100 MHz, $CDCl_3$) 21.0 (*Me*Ar), 26.7 (*C*(3')H$_2$), 27.2 (C*Me*$_2$), 29.3 (*C*(2')H$_2$), 35.3 (*C*(4')H$_2$), 38.5 (*C*(3)H$_2$), 41.7 (*C*(2)), 43.7 (*C*(3'')H$_2$ and *C*(5'')H$_2$), 44.4 (*C*(2'')H$_2$ and *C*(6'')H$_2$), 49.6 (*C*(4)H$_2$), 54.1 (*C*(1')H$_2$), 59.0 (NC*H*$_2$Ph), 115.8 (Ph_{ipso}), 121.6 (Ph_{ortho}), 126.8 (Ph_{para}), 128.1, 128.3, 128.9, 129.0, 131.8 ($Ph_{ortho,meta}$), 135.1, 138.0, 139.4, 140.0 ($Ph_{ipso,para}$),

154.5 (N*C*ON), 175.3 (*C*(1)O); *m/z* (ESI$^+$) 633 (MH^+, 100 %); HRMS $C_{35}H_{46}N_4O_2Br$ (MH^+) requires 633.2804; found 633.2807.

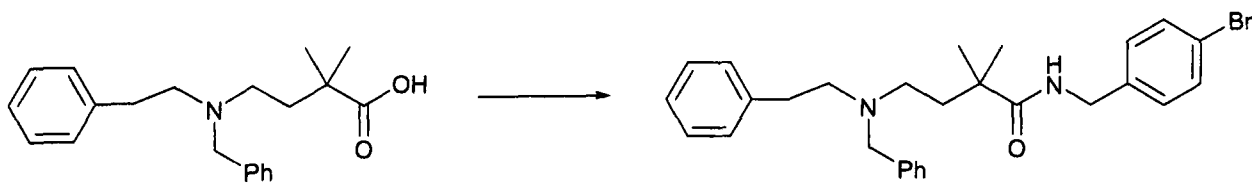
Attempted preparation of 4''-benzyl-piperazin-1''-yl 2,2-dimethyl-4-[*N*-benzyl-*N*-(2'-phenylethyl)amino]butanamide 178 *via* reductive amination



174 178

A solution of **174** (67mg, 0.170 mmol, 1.0 eq.), benzaldehyde **126** (21 μL, 0.204 mmol, 1.2 eq.) and TMOF (30 μL, 0.273 mmol, 1.6 eq.) in MeOH (5 mL) was stirred for 16 hours at room temperature. The reaction mixture was cooled to 0°C and $NaBH_4$ (10 mg, 0.273 mmol, 1.6 eq.) added portionwise. Stirring was continued for 1 hour at 0°C and then at room temperature for 16 hours. Solvents were removed *in vacuo* and the resulting residue was partitioned between water (10 mL) and DCM (10 mL). The aqueous layer was extracted with DCM (10 mL). Combined organic layers were concentrated *in vacuo*. ^{1}H NMR spectroscopic analysis of the resulting reaction product (60 mg) indicated that a complex mixture of unidentified products had been formed.

Preparation of 4'' -bromobenzyl 2,2-dimethyl-4-[*N*-benzyl-*N*-(2'-phenylethyl)amino] butanamide 230

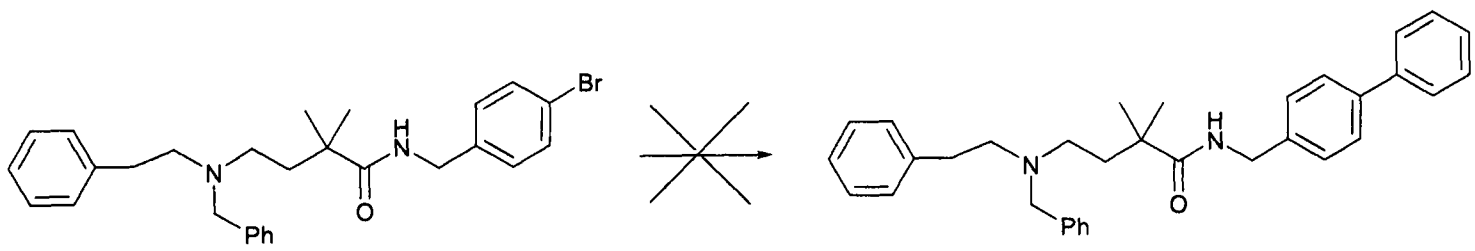


124 230

Following Representative Procedure **2**, to a stirred solution of **124** (512 mg, 1.58 mmol, 1.0 eq.), *p*-bromobenzylamine hydrochloride (701 mg, 3.15 mmol, 2.0 eq.), HOBt (425 mg, 3.15 mmol, 2.0 eq.) and DIPEA (1.38 mL, 7.88 mmol, 5.0 eq.) in DCM (15 mL) was added EDCI

(453 mg, 2.36 mmol, 1.5 eq.). The resultant solution was stirred for 16 hours and washed with 10 % aqueous HCl (20 mL) and 2 M aqueous NaOH solution (20 mL). The resultant solution was dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography on silica gel (MeOH:$CHCl_3$, 1:9) afforded the desired compound **230** as a yellow oil (715 mg, 92 %); ν_{max} (film)/cm^{-1} 3349 (N-H), 3026, 2958, 2807 (C-H), 1644 (C=O); δ_H (400 MHz, $CDCl_3$) 1.17 (6 H, s, C*Me*$_2$), 1.75 (2 H, t, *J* 7.2, C(3)*H*$_2$), 2.54 (2 H, t, *J* 7.2, C(4)*H*$_2$), 2.66 - 2.73 (4 H, m, C(1')*H*$_2$ and C(2')*H*$_2$), 3.62 (2 H, s, NC*H*$_2$Ph), 4.31 (2 H, d, *J* 5.4, NHC*H*$_2$Ar), 6.91 (1 H, t, *J* 5.4, N*H*CH$_2$Ar), 7.09 - 7.43 (14 H, m, 4×*Ar*, 10×*Ph*); δ_C (100 MHz, $CDCl_3$) 26.1 (C*Me*$_2$), 33.0 (*C*(2')H$_2$), 37.4 (*C*(3)H$_2$), 41.6 (*C*(2)), 42.8 (NCH$_2$Ar), 49.6 (*C*(4)H$_2$), 55.3 (*C*(1')H$_2$), 58.3 (N'*C*H$_2$Ph), 121.1, 126.0, 127.0 (Ph$_{ipso,para}$), 128.2, 128.3, 128.7, 129.0, 129.4, 131.7 (Ph$_{ortho,meta}$), 138.0, 138.9, 140.2 (Ph$_{ipso,para}$), 177.5 (*C*O); *m/z* (ESI$^+$) 493 (MH$^+$, 100 %); HRMS $C_{28}H_{34}N_2OBr$ (MH$^+$) requires 493.1855; found 493.1861.

Attempted Suzuki coupling of 4'' -bromobenzyl 2,2-dimethyl-4-[*N*-benzyl-*N*-(2'-phenylethyl)amino]butanamide 230 with phenylboronic acid 193



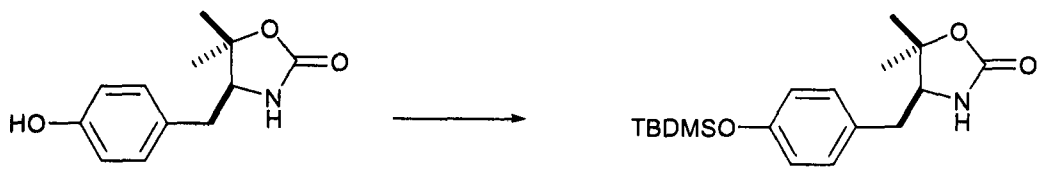
230 **231**

A solution of **230** (100 mg, 0.202 mmol, 1.0 eq.), K_2CO_3 (84 mg, 0.608 mmol, 3.0 eq.) and phenylboronic acid **193** (25 mg, 0.202 mmol, 1.0 eq.), $Pd(OAc)_2$ (4 mg, 0.016 mmol, 0.080 eq.) and $P(Ph)_3$ (9 mg, 0.032 mmol, 0.16 eq.) in DMF (2 mL) was stirred at 80°C for 16 hours. The reaction mixture was partitioned between water (20 mL) and DCM (20 mL). The organic layer was washed with water (20 mL, 2×). The solvent was removed *in vacuo* to afford a brown oil (88 mg). 400 MHz ^{1}H NMR spectroscopic analysis revealed a mixture (approx. 30:70) of starting material **230** and the assumed product **231** respectively as assessed by integration of

resonances from the benzylic amide protons.[26] Attempted separation by chromatography ($CHCl_3$:MeOH, 98:2) was unsuccessful.

7.7 Experimental for Chapter VI

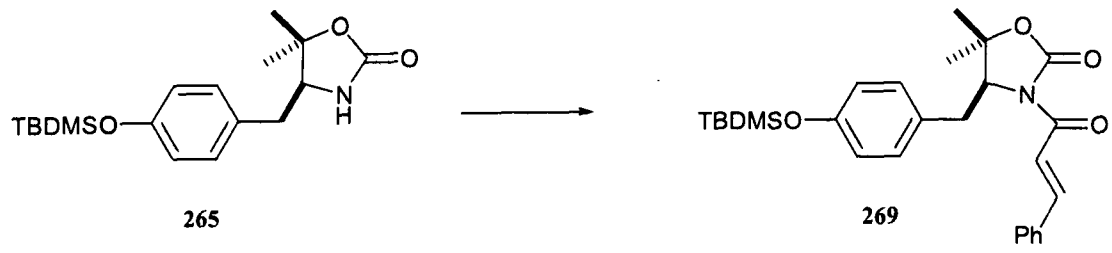
Preparation of (*S*)-4-(4'-*tert*-butyldimethylsilyloxybenzyl)-5,5-dimethyloxazolidin-2-one 265[27]



250 265

To a stirred solution of **250** (6.10 g, 27.6 mmol, 1.0 eq.) in DCM (200 mL) was added TBDMSCl (6.23 g, 41.4 mmol, 1.5 eq.) and imidazole (2.82 g, 41.4 mmol, 1.5 eq.). The reaction mixture was stirred for 24 hours to form a white slurry. The product was filtered through Celite and washed with DCM (100 mL, 3×), the filtrate was concentrated *in vacuo* to afford a white solid. The crude reaction product was recrystallised from hexanes to afford **265** as white needles from 4 crops (8.08 g, 87 %), material from 1st crop was used for analysis; m.p. 96 - 97°C (lit.[27] 95 - 96°C); $[\alpha]_D^{24}$ –66.0 (c=1.0, MeOH) (lit.[27] $[\alpha]_D^{25}$ –68.5 (c=0.98, MeOH)); δ_H (200 MHz, $CDCl_3$) 0.20 (6 H, s, Si(CH_3)$_2$), 0.99 (9 H, s, SiC(CH_3)$_3$), 1.45 (3 H, s, C(5)*Me*), 1.49 (3 H, s, C(5)*Me*), 2.59 (1 H, dd, *J* 13.4, 10.6, C(4)HCH_aH$_b$), 2.78 (1 H, dd, *J* 13.4. 3.8, C(4)HCH$_a$$H_b$), 3.64 (1 H, dd, *J* 10.6, 3.8, C(4)*H*), 4.73 (1 H, br s, N*H*), 6.79 - 7.06 (4 H, m, *Ar*).

Preparation of (*S,E*)-3-(3''-phenylacryloyl)-4-(4'-*tert*-butyldimethylsilyloxybenzyl)-5,5-dimethyloxazolidin-2-one 269

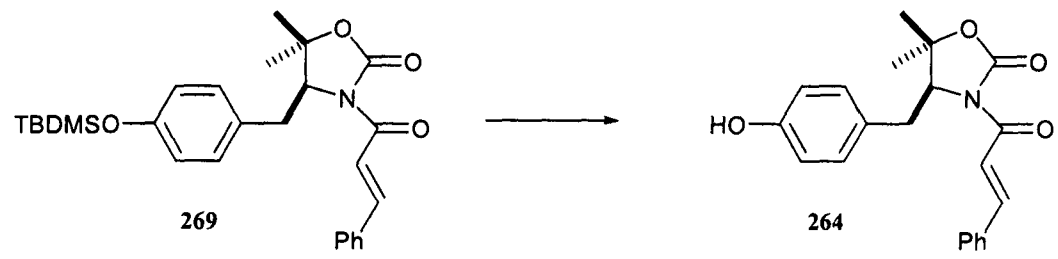


265 269

A solution of **265** (500 mg, 1.49 mmol, 1.0 eq.) in THF (12 mL) was cooled to –78°C and *n*-BuLi (1.02 mL, 1.6 M in THF, 1.64 mmol, 1.1 eq.) was added dropwise over 2 min. The resulting solution was stirred for at –78°C for 30 min before addition of *trans*-cinnamoyl chloride **267** (323 mg, 1.94 mmol, 1.3 eq.). The solution was then allowed to warm to room

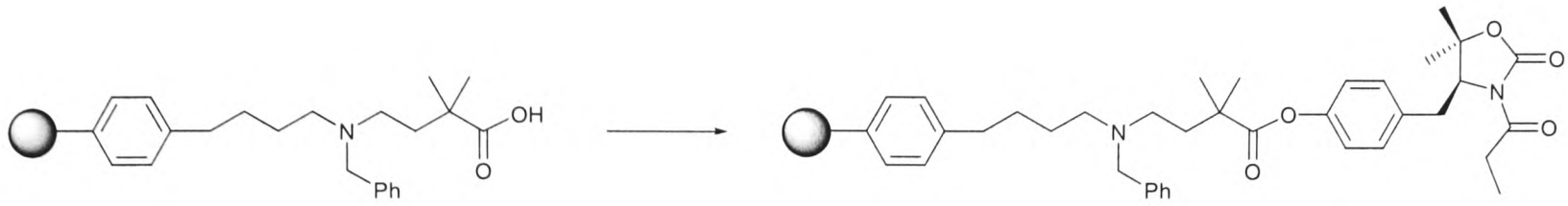
temperature and quenched with saturated aqueous NH_4Cl (4 mL) after 3 hours. The resulting solution was partitioned between water (10 mL) and EtOAc (10 mL). The aqueous layer was extracted with EtOAc (10 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Further purification by column chromatography on silica gel (EtOAc:petrol, 2:98 - 6:94, stepwise elution) afforded the desired compound **269** as a colourless oil (553 mg, 80 %); $C_{27}H_{35}NO_4Si$ requires C 69.64 %, H 7.58 %, N 3.01 %; found C 69.39 %, H 7.65 %, N 3.04 %; $[\alpha]_D^{20}$ –68.3 (c=1.0, $CHCl_3$); ν_{max} (film)/cm^{-1} 2930 (C-H), 1776 (C=O, endocyclic), 1679 (C=O, exocyclic), 1621 (C=C); δ_H (400 MHz, $CDCl_3$) 0.19 (6 H, s, $Si(CH_3)_2$), 0.99 (9 H, s, $SiC(CH_3)_3$), 1.39 (3 H, s, C(5)*Me*), 1.41 (3H, s, C(5)*Me*), 2.87 (1 H, dd, *J* 14.2, 9.7, C(4)HCH_aH_b), 3.20 (1 H, dd, *J* 14.2, 3.6, C(4)HCH_aH_b), 4.57 (1 H, dd, *J* 9.7, 3.6, C(4)*H*), 6.78 - 6.80 (2 H, m, *Ar*), 7.16 - 7.18 (2 H, m, *Ph*), 7.40 - 7.41 (3 H, m, *Ph*), 7.62 - 7.64 (2 H, m, *Ar*), 7.83 and 7.93 (2 H, ABq, J_{AB} 15.7, C(2'')*H* and C(3'')*H*); δ_C (100 MHz, $CDCl_3$) - 4.4 ($Si(CH_3)_2$), 18.2 ($SiC(CH_3)_3$), 22.3 (C(5)*Me*), 25.7 ($SiC(CH_3)_3$), 28.6 C(5)*Me*), 34.5 (C(4)CH_2), 63.9 (*C*(4)H), 82.2 (*C*(5)), 117.5 (*C*(2'')H), 120.3 ($Ph_{ortho,meta}$), 128.6 (Ph_{para}), 128.8 ($Ph_{ortho,meta}$), 129.6 ($Ph_{ipso,para}$), 130.0, 130.6 ($Ph_{ortho,meta}$), 134.6 ($Ph_{ipso,para}$), 146.0 (*C*(3'')H), 152.8 (*C*(2)O), 154.4 ($Ph_{ipso,para}$), 165.4 (*C*(1'')O); *m/z* (ESI^+) 466 (MH^+, 100 %); HRMS $C_{27}H_{36}NO_4Si$ (MH^+) requires 466.2414; found 466.2415.

Preparation of (*S*,*E*)-3-(3''-phenylacryloyl)-4-(4'-hydroxybenzyl)-5,5-dimethyloxazolidin-2-one 264



To a stirred solution of **269** (286 mg, 0.614 mmol, 1.0 eq.) in THF (25 mL) was added TBAF (1.0 M in THF, 0.614 mL, 0.614 mmol, 1.0 eq.). The resulting yellow solution was quenched with saturated aqueous NH_4Cl (4 mL) after 3 hours then partitioned between water (25 mL) and EtOAc (25 mL). The aqueous layer was extracted with EtOAc (25 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography afforded the desired compound **264** as a white solid (185 mg, 86 %); m.p. 130 - 132°C; $[\alpha]_D^{25}$ –86.0 (c=1.0, $CHCl_3$); ν_{max} (film)/cm^{-1} 3396 (O-H), 1772 (C=O, endocyclic), 1677 (C=O, exocyclic), 1616 (C=C); δ_H (400 MHz, $CDCl_3$) 1.39 (3 H, s, C(5)*Me*), 1.42 (3 H, s, C(5)*Me*), 2.88 (1 H, dd, *J* 14.5, 9.5, C(4)HCH_aH_b), 3.15 (1 H, dd, *J* 14.5, 3.5, C(4)HCH_aH_b), 4.57 (1 H, dd, *J* 9.5, 3.5, C(4)*H*), 6.19 (1 H, br s, O*H*), 6.78 - 6.80 (2 H, m, *Ar*), 7.14 - 7.16 (2 H, m, *Ar*), 7.37 - 7.41 (3 H, m, *Ph*), 7.61 - 7.63 (2 H, m, *Ph*), 7.83 and 7.93 (2 H, ABq, J_{AB} 15.7, C(2'')*H* and C(3'')*H*); δ_C (100 MHz, $CDCl_3$) 22.3 (C(5)*Me*), 28.6 (C(5)*Me*), 34.4 (C(4)CH_2), 64.0 (*C*(4)H), 82.6 (*C*(5)), 115.7 ($Ph_{ortho,meta}$), 117.2 (*C*(2'')H), 128.5 ($Ph_{ipso,para}$), 128.7, 128.9, 130.2, 130.8 ($Ph_{ortho,meta,para}$), 134.5 ($Ph_{ipso,para}$), 146.5 (*C*(3'')H), 153.0 (*C*(2)O), 154.8 ($Ph_{ipso,para}$), 165.8 (*C*(1'')O); *m/z* (ESI$^-$) 350 [$(M-H)^-$, 100 %]; HRMS $C_{21}H_{22}NO_4$ (MH^+) requires 352.1549; found 352.1548.

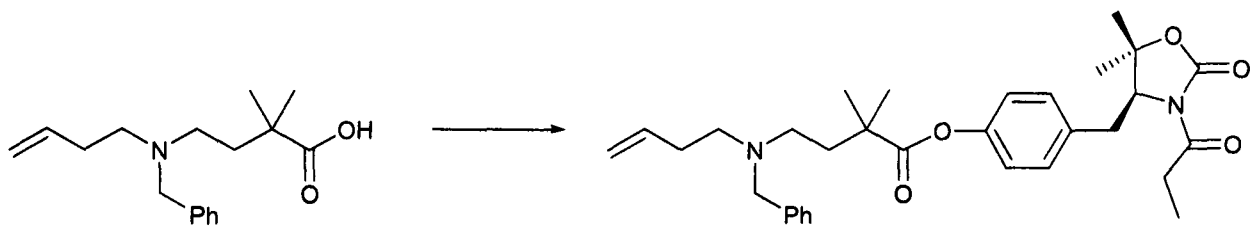
Preparation of (*S*)-[4''-(2'''-oxo-3'''-propanoyl-5''',5'''-dimethyl-oxazolidin-4'''-yl)-methyl phenyl] 2,2-dimethyl-4-{*N*-benzyl-*N*-[4'-(*p*-polystyrenyl)butyl]amino} butanoate 270



90 270

To a stirred suspension of **90** (500 mg, 0.865 mmol, 1.0 eq.), (*S*)-*N*-propionyl SuperQuat **251** (959 mg, 3.46 mmol, 4.0 eq.), HOBt (467 mg, 3.46 mmol, 4.0 eq.) and DIPEA (0.603 mL, 6.92 mmol, 4.0 eq.) in DCM (10 mL) was added EDCI (1.82 mL, 2.60 mmol, 3.0 eq.). After 20 hours the resin was transferred to a funnel and washed repeatedly with DCM and MeOH. The washings were collected and the solvent removed *in vacuo*, the resulting residue was partitioned between DCM (50 mL) and 10 % aqueous HCl (50 mL). The organic layer was washed with 10 % aqueous HCl (50 mL). The organic layer was dried (Na_2SO_4) and the solvent removed *in vacuo* to afford recovered (*S*)-**251** (780 mg). The resin was further washed repeatedly with DMF, THF and DCM and subjected to the same reaction protocol and work-up. The resin was dried *in vacuo* to a constant mass to afford **270** as pale brown powder (659 mg). ν_{max} (film)/ cm^{-1} 3025, 2926, 2853 (C-H), 1778 (C=O, endocyclic), 1749 (C=O, ester), 1701 (C=O, exocyclic); loading 1.31 mmol/g.

Preparation of (*S*,*E*)-[4'''-(2'''-oxo-3'''-propanoyl-5''',5'''-dimethyl-oxazolidin-4'''-yl)-methyl phenyl] 2,2-dimethyl-4-[*N*-benzyl-*N*-(but-3'-enyl)amino]butanoate 272

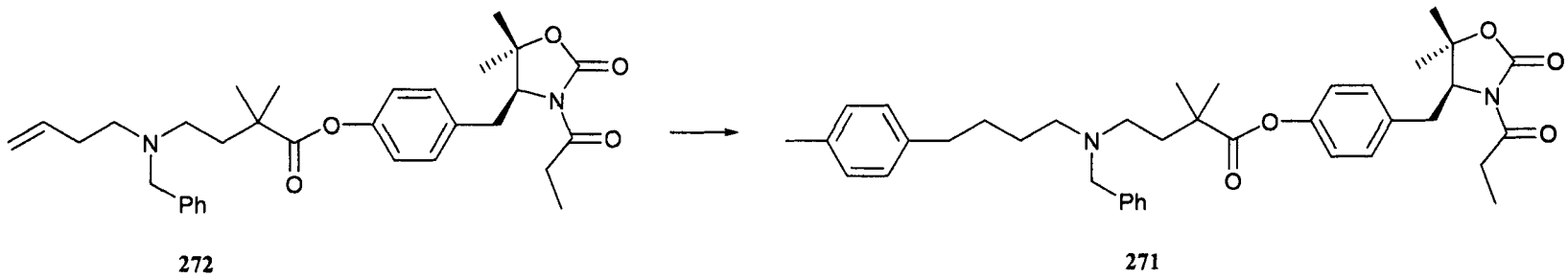


88 272

Following Representative Procedure **2**, to a stirred solution of **88** (300 mg, 1.09 mmol, 1.0 eq.), (*S*)-*N*-propionyl SuperQuat **251** (604 mg, 2.18 mmol, 2.0 eq.), HOBt (177 mg, 1.31 mmol, 1.2 eq.) and DIPEA (0.381 mL, 2.18 mmol, 2.0 eq.) in DCM (4 mL) was added DIC (0.205 mL, 1.31 mmol, 1.2 eq.). The resulting solution was stirred for 42 hours and partitioned between water (20 mL) and DCM (20 mL). The aqueous layer was extracted with DCM (20 mL). The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography on silica gel (EtOAc:petrol, 5:95 - 3:7, stepwise elution) afforded the desired compound **272** as a colourless viscous oil (437 mg, 75 %); $C_{32}H_{42}N_2O_5$ requires C 71.88 %, H 7.92 %, N 5.24 %; found C 71.89 %, H 8.17 %, N 5.38 %; $[\alpha]_D^{26}$ –21.7 (c=1.0, $CHCl_3$); ν_{max} (film)/cm^{-1} 3029, 2977, 2940 (C-H), 1778 (C=O, endocyclic), 1750 (C=O, ester), 1702 (C=O, exocyclic); δ_H (400 MHz, $CDCl_3$) 1.17 (3 H, t, *J* 7.3, CH_2CH_3), 1.30 (6 H, s, C(2)Me_2), 1.37 (3 H, s, C(5''')*Me*), 1.38 (3 H, s, C(5''')*Me*), 1.87 - 1.91 (2 H, m, (C(3)H_2)), 2.23 - 2.28 (2 H, m, C(2')H_2), 2,53 - 2.59 (4 H, m, C(4)H_2 and C(1')H_2), 2.88 (1 H, dd, *J* 14.3, 9.8, C(4''')HCH_aH$_b$), 2.95 (2 H, q, *J* 7.3, CH_2CH$_3$), 3.13 (1 H, dd, *J* 14.3, 3.5, C(4''')HCH$_a$$H_b$), 3.62 (2 H, s, NC$H_2$Ph), 4.47 (1 H, dd, *J* 9.8, 3.5, C(4''')*H*), 4.97 - 5.06 (2 H, m, C(4')H_2), 5.80 (1 H, ddt, *J* 17.0, 10.2, 6.7, C(3')*H*), 6.85 - 6.88 (2 H, m, *Ar*), 7.21 - 7.35 (7 H, m, 2×*Ar*, 5×*Ph*); δ_C (100 MHz, $CDCl_3$) 8.4 (CH_2CH_3), 22.3 (C(5''')*Me*), 25.4 (C(2)Me_2), 28.6 (C(5''')*Me*), 29.3 (CH_2CH_3), 31.5 (*C*(2')H$_2$), 34.4 (C(4''')HCH$_2$), 37.3 (*C*(3)H$_2$), 41.5 (*C*(2)), 49.4 (*C*(4)H$_2$), 53.2 (*C*(1')H$_2$), 58.4 (NCH$_2$Ph), 63.6 (*C*(4''')H), 82.1 (*C*(5''')), 115.5 (*C*(4')H$_2$), 121.7 (Ph$_{ortho,meta}$),

126.8 (Ph_{para}), 128.1, 128.8, 129.9 ($Ph_{ortho,meta}$), 134.3 ($Ph_{ipso,para}$), 136.9 (*C*(3')H), 139.6, 149.7 ($Ph_{ipso,para}$), 152.6 (*C*(2''')O), 174.3 (N*C*O), 176.2 (*C*(1)O); *m/z* (APCI$^+$) 535 (MH^+, 100 %); HRMS $C_{32}H_{43}N_2O_5$ (MH^+) requires 535.3172; found 535.3169.

Preparation of (*S*)-[4''-(2'''-oxo-3'''-propanoyl-5''',5'''-dimethyl-oxazolidin-4'''-yl)-methyl phenyl] 2,2-dimethyl-4-{*N*-benzyl-*N*-[4'-(*p*-tolyl)butyl]amino}butanoate 271

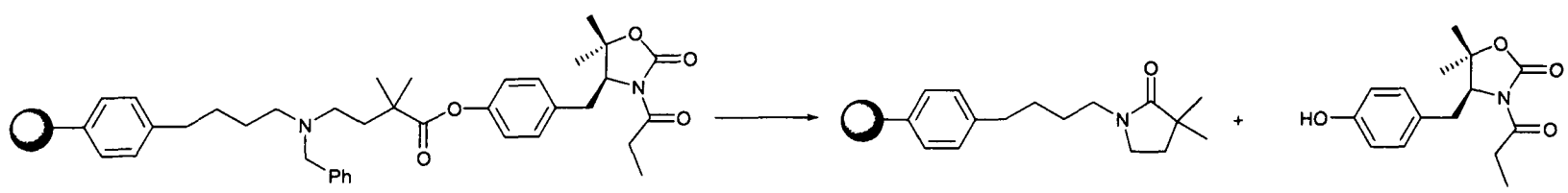


272 271

A solution of 9-BBN (0.677 mL, 0.338 mmol, 0.5 M in THF, 1.1 eq.) was added dropwise to a stirred solution of **272** (181 mg, 0.338 mmol, 1.1 eq.) in THF (1 mL) at 0°C. Stirring was continued for 1 hour at 0°C and 4 hours at room temperature. 4-Bromotoluene **98** (53 mg, 0.307 mmol, 1.0 eq.) was added to the hydroboration mixture as a solution in DMF (1 mL) and K_2CO_3 (85 mg, 0.615 mmol, 2.0 eq.). The catalyst was prepared separately by the following procedure: DPPF (9 mg, 0.0166 mmol, 0.054 eq.) was dissolved in DMF (1 mL), $Pd(OAc)_2$ (3 mg, 0.0138 mmol, 0.045 eq.) was then added and the solution degassed before heating at 60°C for 30 min. The catalyst was added to the reaction mixture *via* cannula and the combined mixture heated at 60°C overnight under nitrogen. The reaction mixture was allowed to cool to room temperature, diluted with petrol (2 mL) and quenched with hydrogen peroxide (0.11 mL, 35 % solution in water). After stirring for further 2 hours the reaction mixture was partitioned between water (20 mL) and DCM (20 mL). The aqueous layer was extracted with DCM (20 mL). The combined organic layers were washed with water (45 mL, 4×), dried (Na_2SO_4) and concentrated *in vacuo*. Purification by chromatography on silica gel, (EtOAc:petrol, petrol - 3:7, stepwise elution) afforded the desired compound **271** as a colourless viscous oil (139 mg, 72 %); $C_{39}H_{50}N_2O_5$ requires C 74.73 %, H 8.04 %, N 4.47 %; found C 74.53 %, H 8.19 %, N 4.78; $[\alpha]_D^{25}$ –17.4 (c=1.0, $CHCl_3$); ν_{max} (film)/cm^{-1} 2937, 2861, 2807 (C-H), 1778 (C=O,

endocyclic), 1748 (C=O, ester), 1704 (C=O, exocyclic); δ_H (400 MHz, $CDCl_3$) 1.18 (3 H, t, *J* 7.4, CH_2CH_3), 1.29 (6 H, s, C(2)Me_2), 1.37 (3 H, s, C(5''')*Me*), 1.38 (3 H, s, C(5''')*Me*), 1.51 - 1.57 (2 H, m, C(3')H_2), 1.57 - 1.64 (2 H, m, C(2')H_2), 1.86 - 1.90 (2 H, m, C(3)H_2), 2.33 (3 H, s, *Me*Ar), 2.47 - 2.56 (6 H, m, C(4)H_2, C(1')H_2 and C(4')H_2), 2.89 (1 H, dd, *J* 14.4, 9.6, C(4''')HCH_aH$_b$), 2.97 (2 H, q, *J* 7.4, CH_2CH$_3$), 3.14 (1 H, dd, *J* 14.4, 3.6, C(4''')HCH$_a$$H_b$), 3.59 (2 H, s, NC$H_2$Ph), 4.47 (1 H, dd, *J* 9.6, 3.6, C(4''')*H*), 6.86 - 6.89 (2 H, m, *Ar*), 7.04 - 7.10 (4 H, m, *Ar*), 7.24 - 7.34 (7 H, m, 2×*Ar*, 5×*Ph*); δ_C (100 MHz, $CDCl_3$) 8.4 (CH_2CH_3), 21.0 (*Me*Ar), 22.3 (C(5''')*Me*), 25.4 (C(2)Me_2), 26.6 (*C*(3')H$_2$), 28.6 (C(5''')*Me*), 29.3 (*C*H$_2$CH$_3$), 29.4 (*C*(2')H$_2$), 34.7 (C(4''')*C*H$_2$), 35.3 (*C*(4')H$_2$), 37.4 (*C*(3)H$_2$), 41.5 (*C*(2)), 49.5 (*C*(4)H$_2$), 53.5 (*C*(1')H$_2$), 58.6 (N*C*H$_2$Ph), 63.6 (*C*(4''')H), 82.1 (*C*(5''')), 121.7 (Ph$_{ortho,meta}$), 126.7 (Ph$_{para}$), 128.1, 128.3, 128.8, 128.9, 129.9 (Ph$_{ortho,meta}$), 134.3, 135.0, 139.5, 139.8, 149.7 (Ph$_{ipso,para}$), 152.6 (*C*(2''')O), 174.3 (N*C*O), 176.2 (*C*(1)O); *m/z* (APCI$^+$) 627 (MH$^+$, 100 %); HRMS $C_{39}H_{51}N_2O_5$ (MH$^+$) requires 627.3798; found 627.3795.

Preparation of *N*-[4'-(*p*-polystyrenyl)butyl]-3,3-dimethyl pyrrolidin-2-one 122 and (*S*)-3-propionyl-4-(4'-hydroxybenzyl)-5,5-dimethyloxazolidin-2-one 251[28]

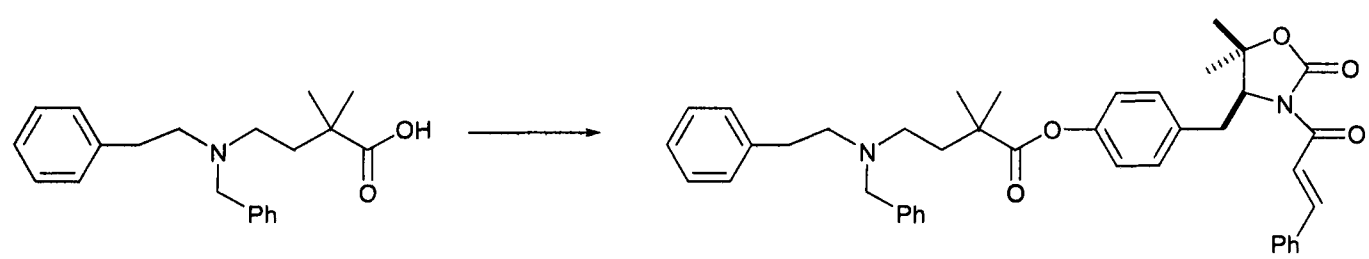


270 122 251

CAN (538 mg, 0.983 mmol, 5.0 eq.) was added to a stirred suspension of **270** (150 mg, 0.197 mmol, 1.0 eq.) in THF:H_2O (8:1) (2 mL). After stirring for 5 hours the resin was transferred to a funnel and washed repeatedly with THF, water, THF and DCM. The resin was then treated with DCM:NEt_3 (5:1) (12 mL) and the filtrate was concentrated *in vacuo*. The resulting residue was partitioned between DCM (10 mL) and 10 % aqueous HCl (5 mL). The organic layer was washed with 10 % aqueous HCl (5 mL), water (5 mL), dried (Na_2SO_4) and concentrated *in vacuo* to afford **251** (46 mg, 84 %); m.p. 119 - 121°C (lit.[28] 125 - 127°C); $[\alpha]_D^{25}$ –45.0 (c=1.0,

$CHCl_3$); (lit.[28] $[\alpha]_D^{25}$ –43.2 (c=1.0, $CHCl_3$); δ_H (200 MHz, $CDCl_3$) 1.15 (3 H, t, *J* 7.4, CH_2CH_3), 1.37 (3 H, s, C(5)*Me*), 1.39 (3 H, s, C(5)*Me*), 2.83 (1 H, dd, *J* 14.6, 9.4, C(4)HCH_aH_b), 2.93 (2 H, q, *J* 7.4, CH_2CH_3), 3.04 (1 H, dd, *J* 14.6, 4.2, C(4)HCH_aH_b), 4.44 (1 H, dd, *J* 9.4, 4.2, C(4)*H*), 5.3 - 5.7 (1 H, br s, O*H*), 6.76 - 6.80 (2 H, m, *Ar*), 7.10 - 7.14 (2 H, m, *Ar*). The resin was dried to a constant mass *in vacuo* (90 mg) to afford **122** with identical spectroscopic properties to those previously described.

Preparation of (*S*,*E*)-{4''-[2'''-oxo-3'''-(3''''-phenylacryloyl) -5''',5'''-dimethyl-oxazolidin-4'''-yl]-methyl phenyl} 2,2-dimethyl-4-[*N*-benzyl-*N*-(2'-phenylethyl)amino] butanoate 273

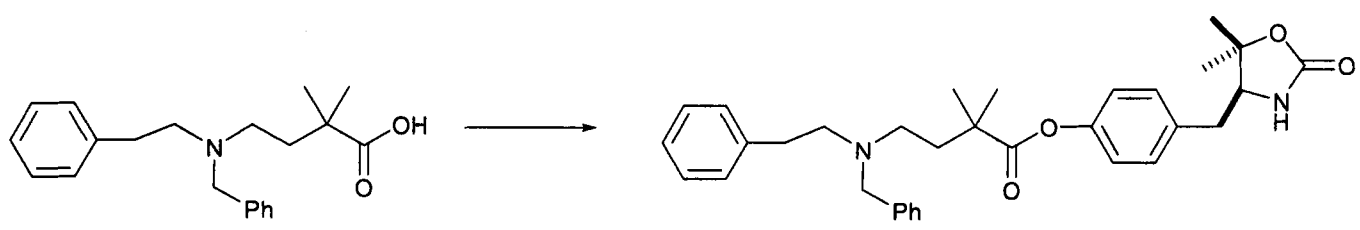


124 **273**

Following Representative Procedure **2**, to a stirred solution of **124** (37 mg, 0.114 mmol, 1.0 eq.), (*S*)-*N*-*trans*-cinnamoyl SuperQuat **264** (159 mg, 0.456 mmol, 4.0 eq.), HOBt (31 mg, 0.228 mmol, 2.0 eq.) and DIPEA (79 μL, 0.455 mmol, 4.0 eq.) in DCM (5 mL) was added EDCI (33 mg, 0.171 mmol, 1.5 eq.). The resulting solution was stirred for 16 hours and washed with 10 % aqueous HCl (5 mL) and water (5 mL). The organic layer was dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography on silica gel (EtOAc:petrol, 1:9 - 4:6, stepwise elution) afforded the desired compound **273** as a colourless viscous oil (46 mg, 61 %); $[\alpha]_D^{25}$ –42.8 (c=1.0, $CHCl_3$); ν_{max} (film)/cm^{-1} 3061, 3027, 2973 (C-H), 1770 (C=O, endocyclic), 1750 (C=O, ester), 1678 (C=O, exocyclic), 1620 (C=C); δ_H (400 MHz, $CDCl_3$) 1.32 (6 H, s, C(2)Me_2), 1.40 (3 H, s, C(5''')*Me*), 1.42 (3 H, s, C(5''')*Me*), 1.90 - 1.94 (2 H, m, C(3)H_2), 2.61 - 2.65 (2 H, m, C(4)H_2), 2.75 - 2.83 (4 H, m, C(1')H_2 and C(2')H_2), 2.94 (1 H, dd, *J* 14.7, 9.7, C(4''')HCH_aH_b), 3.27 (1 H, dd, *J* 14.7, 3.4, C(4''')HCH_aH_b), 3.71 (2 H, s, NCH_2Ph), 4.78 (1 H, dd, *J* 9.7, 3.4, C(4''')*H*), 6.90 - 7.16 (4 H, m, *Ar*), 7.19 - 7.67 (15 H,

m, *Ph*), 7.88 and 7.97 (2 H, ABq, J_{AB} 15.6, C(2'''')*H* and C(3'''')*H*); δ_C (100 MHz, $CDCl_3$) 22.4 (C(5''')*Me*), 25.4 (C(2)Me_2), 28.6 (C(5''')*Me*), 33.5 (*C*(2')H_2), 34.7 (C(4''')HCH_2), 37.4 (*C*(3)H_2), 41.5 (*C*(2)), 49.5 (*C*(4)H_2), 55.6 (*C*(1')H_2), 58.6 (NCH_2Ph), 64.0 (*C*(4''')H), 82.2 (*C*(5''')), 117.3 (*C*(2'''')H), 121.8 ($Ph_{ortho,meta}$), 125.9, 126.9, 128.2 (Ph_{para}), 128.3, 128.7, 128.8, 128.8, 128.9, 130.0, 130.7 ($Ph_{ortho,meta}$), 134.4, 134.6, 139.5, 140.5 ($Ph_{ipso,para}$), 146.3 (*C*(3'''')H), 149.7 ($Ph_{ipso,para}$), 152.6 (*C*(2''')O), 165.5 (*C*(1'''')O), 176.2 (*C*(1)O); *m/z* (ESI^+) 659 (MH^+, 100 %); HRMS $C_{42}H_{47}N_2O_5$ (MH^+) requires 659.3485; found 659.3484.

Preparation of (*S*)-[4''-(2'''-oxo-5''',5'''-dimethyl-oxazolidin-4'''-yl)-methyl phenyl] 2,2-dimethyl-4-[*N*-benzyl-*N*-(2'-phenylethyl)amino]butanoate 274

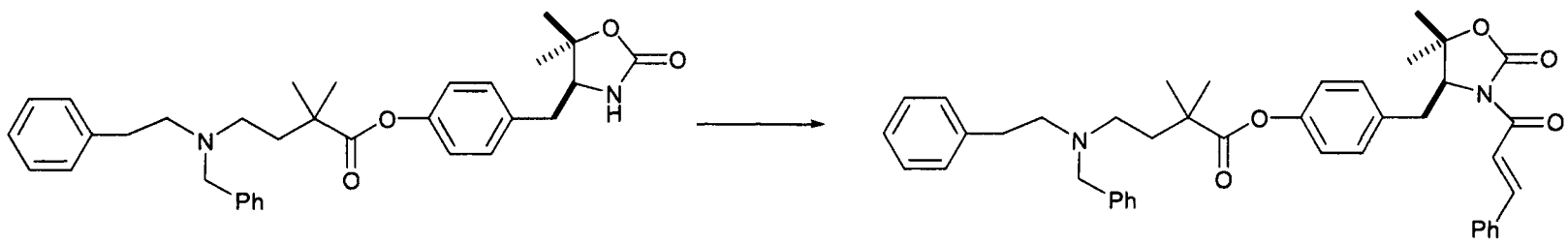


124 274

Following Representative Procedure **2**, to a stirred solution of **124** (1.00 g, 3.08 mmol, 1.0 eq.), (*S*)-tyrosine SuperQuat **250** (2.04 g, 9.23 mmol, 3.0 eq.), HOBt (832 mg, 6.15 mmol, 2.0 eq.) and DIPEA (2.15 mL, 12.3 mmol, 4.0 eq.) in DCM (60 mL) was added EDCI (1.18 g, 6.15 mmol, 2.0 eq.) portionwise over 24 hours. The resulting solution was washed with 10 % aqueous HCl (60 mL) and 2 M aqueous NaOH solution (60 mL). The organic layer was dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography on silica gel (EtOAc:petrol, 4:96) afforded the desired compound **274** as a yellow viscous oil (1.46 g, 90 %); $[\alpha]_D^{25}$ –45.3 (c=1.0, $CHCl_3$); ν_{max} (film)/cm^{-1} 3273 (N-H), 3062, 3028, 2976 (C-H), 1748 (2×C=O); δ_H (400 MHz, $CDCl_3$) 1.31 (6 H, s, C(2)Me_2), 1.46 (3 H, s, C(5''')*Me*), 1.48 (3 H, s, C(5''')*Me*), 1.89 - 1.93 (2 H, m, C(3)H_2), 2.60 - 2.64 (2 H, m, C(4)H_2), 2.68 (1 H, dd, *J* 12.8, 10.8, C(4''')HC$H_a$$H_b$), 2.72 - 2.85 (5 H, m, C(1')H_2, C(2')H_2, C(4''')HC$H_a$$H_b$), 3.67 (1 H, dd, *J* 10.8, 4.0, C(4''')*H*), 3.70 (2 H, s, NCH_2Ph), 5.03 (1 H, br s, N*H*), 6.90 - 7.15 (4 H, m, *Ar*), 7.20

- 7.40 (10 H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 22.0 (C(5''')*Me*), 25.4 (C(2)*Me*$_2$), 27.6 (C(5''')*Me*), 33.5 (*C*(2')H$_2$), 36.5 (C(4''')H*C*H$_2$), 37.3 (*C*(3)H$_2$), 41.5 (*C*(2)), 49.5 (*C*(4)H$_2$), 55.6 (*C*(1')H$_2$), 58.6 (NC*H*$_2$Ph), 63.0 (*C*(4''')H), 83.1 (*C*(5''')), 122.2 (Ph$_{ortho,meta}$), 125.9, 126.9 (Ph$_{para}$), 128.2, 128.3, 128.5, 128.8, 129.8 (Ph$_{ortho,meta}$), 134.2, 139.5, 140.5, 150.0 (Ph$_{ipso,para}$), 157.8 (*C*(2''')O), 176.2 (*C*(1)O); *m/z* (ESI$^+$) 529 (MH$^+$, 40 %), 528 (M$^+$, 100); HRMS $C_{33}H_{41}N_2O_4$ (MH$^+$) requires 529.3066; found 529.3080. The starting material **124** was also isolated as a colourless oil (90 mg, 9 %).

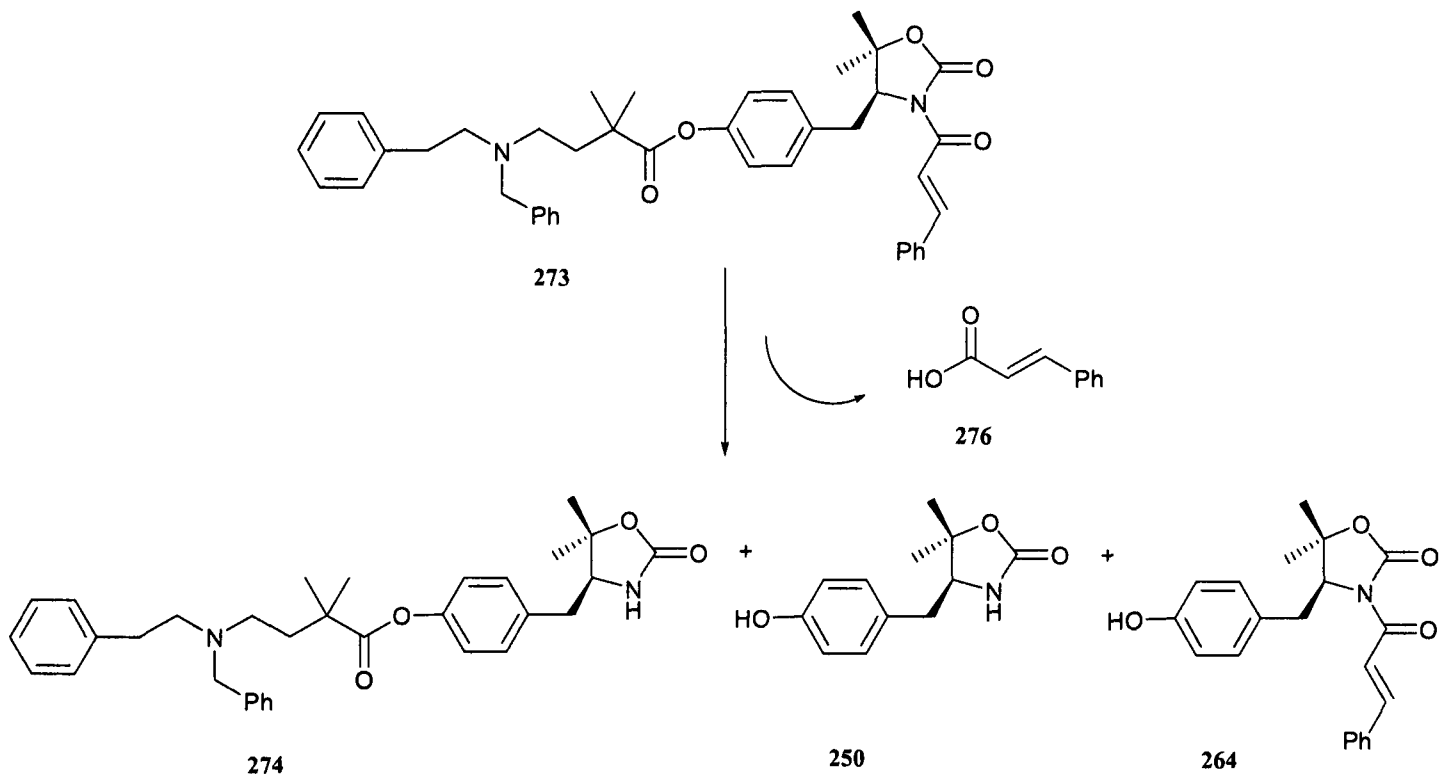
Preparation of (*S,E*)-{4''-[2'''-oxo-3'''-(3''''-phenylacryloyl) -5''',5'''-dimethyl-oxazolidin-4'''-yl]-methyl phenyl} 2,2-dimethyl-4-[*N*-benzyl-*N*-(2'-phenylethyl)amino] butanoate 273



274 273

A solution of **274** (801 mg, 1.52 mmol, 1.0 eq.) in THF (25 mL) was cooled to –78°C and LHMDS (1.67 mL, 1.0 M in THF, 1.67 mmol, 1.1 eq.) was added dropwise over 2 min. The resulting solution was stirred for –78°C for 30 min before addition of *trans*-cinnamoyl chloride **267** (328 mg, 1.97 mmol, 1.3 eq.). The solution was then allowed to warm to room temperature and quenched with saturated aqueous NH_4Cl (3 mL) after 3 hours. The resulting solution was partitioned between water (30 mL), and EtOAc (60 mL). The pH was adjusted (>7) with 2 M aqueous NaOH solution. The aqueous layer was extracted with EtOAc (60 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography on silica gel (EtOAc:petrol, 1:9 - 4:6, stepwise elution) afforded the desired compound **273** as a colourless oil (809 mg, 81 %) with identical spectroscopic properties to those previously described.

Alternative preparation of (*S*)-[4''-(2'''-oxo-5''',5'''-dimethyl-oxazolidin-4'''-yl)-methyl phenyl] 2,2-dimethyl-4-[*N*-benzyl-*N*-(2'-phenylethyl)amino]butanoate 274 and preparation of *trans*-cinnamic acid 276[29]



To a solution of **273** (56 mg, 0.0851 mmol, 1.0 eq.) in THF:H_2O (3:1) (2 mL), was added LiOH.H_2O (7 mg, 0.170 mmol, 2.0 eq.). The resulting mixture was stirred for 7 hours, saturated aqueous $NaHCO_3$ was then added (5 mL) and the aqueous layer was extracted with EtOAc (10 mL, 2×). The combined aqueous layers were dried ($MgSO_4$) and the solvent removed *in vacuo* to afford the crude reaction product (40 mg). 400 MHz ^{1}H NMR spectroscopic analysis of the crude reaction mixture indicated a 13:58:25:3 ratio of starting material **273**: deacylated species **274**: (*S*)-tyrosine SuperQuat **250**: (*S,E*)-*N*-*trans*-cinnamoyl SuperQuat **264** respectively. The aqueous layer was acidified (pH 1) and extracted with EtOAc (10 mL, 2×), dried and the solvent removed *in vacuo* to afford *trans*-cinnamic acid **276** as a white solid (8 mg, 63 %); m.p. 122 - 124°C (lit.[29] 133 - 134°C); δ_H (200 MHz, $CDCl_3$) 6.48 (1 H, d, *J* 16, C*H*=CHPh), 7.30 - 7.50 (3 H, m, *Ph*), 7.50 - 7.70 (2 H, m, *Ph*), 7.82 (1 H, d, *J* 16, C*H*=CHPh).

References

[1] H. Mizuno, K. Domon, K. Masuya, K. Tanino, I. Kuwajima, *J. Org. Chem.*, 1999, **64**, 2648.

[2] J. Micklefield, M.M. Block, A.R. Battersby, *Tetrahedron*, 1992, **48**, 7519.

[3] T. Naito, H. Tanada, Y. Suzuki, H. Saito, T. Kiguchi, I. Ninomiya, *Heterocycles*, 1993, **36**, 2345.

[4] M. Bessoddes, C. Boukarim, *Synlett*, 1996, 1119.

[5] J. Mulzer, U, Kaselow, K.D. Graske, H. Kühne, A. Sieg, H.J. Martin, *Org. Biomol. Chem.*, 2003, **1**, 4166.

[6] K.M.J. Brands, A.A.P. Mekel, U.K. Pandit, *Tetrahedron*, 1991, **47**, 2005.

[7] www.sigmaaldrich.com, 42,462-5 (Aldrich).

[8] R.N. Salvatore, A.S. Nagle, K.W. Jung, *J. Org. Chem.*, 2002, **67**, 674.

[9] www.sigmaaldrich.com, 18,555-8 (Aldrich)

[10] www.sigmaaldrich.com, 40,283-4 (Aldrich)

[11] www.sigmaaldrich.com, 17,981-7 (Aldrich)

[12] B. Miriyala, S. Bhattacharyya, J.S. Williamson, *Tetrahedron*, 2004, **60**, 1463.

[13] O. Phanstiel, Q.X. Wang, D.H. Powell, M.P. Ospina, B.A. Leeson, *J. Org. Chem.*, 1999, **64**, 803.

[14] www.sigmaaldrich.com, 21,425-6 (Aldrich)

[15] B. Krzyzanowska, W.J. Stec, *Synthesis*, 1982, **4**, 270.

[16] Racemic sample; δ_H (400 MHz, $CDCl_3$) 1.19 (3 H, d, *J* 6.9, C(α)*Me*, (*S*)-**158**), 1.23 (3 H, d, *J* 6.9, C(α)*Me*, (*R*)-**158**).

[17] W.R. Meindl, E.V. Angerer, H. Schonenberger, G. Rückdeschel, *J. Med. Chem.*, 1984, **27**, 1111.

[18] www.sigmaaldrich.com, tribenzylamine 12,892-9, dibenzylamine D3,410-8 (Aldrich).

[19] www.sigmaaldrich.com, P3,000-4 (Aldrich).

[20] www.sigmaaldrich.com, 24,642-5 (Aldrich)

[21] R.J. Edsall, H.A. Harris, E.S. Manas, R.E. Mewshaw, *Bioorg. Med. Chem.*, 2003, **11**, 3457.

[22] www.sigmaaldrich.com, I-1,020-1 (Aldrich).

[23] M. Lourak, R. Vanderesse, Y. Fort, P. Caubere, *J. Org. Chem.*, 1989, **54**, 4844.

[24] R. Dupont, P. Cotelle, *Tetrahedron*, 2001, **57**, 5585.

[25] www.sigmaaldrich.com, B1,790-5 (Aldrich).

[26] Assumed product **231**: δ_H (400 MHz, $CDCl_3$) 4.47 (2 H, d, *J* 4.9, NCH_2Ar).

[27] D.A.B. Mortimer, D.Phil. Thesis, University of Oxford, 2002, p. 194.

[28] D.A.B. Mortimer, D.Phil. Thesis, University of Oxford, 2002, p. 196.

[29] www.sigmaaldrich.com, C8,085-7 (Aldrich)

Appendix I: IR Data for Selected Polymer-Supported Compounds

