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EXPLORING THE POTENTIAL OF A NEW LINKER SYSTEM CLEAVED USING SAMARIUM(II) IODIDE

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"Behind every great scientist,
lie a heap of failed experiments"

Abstract

Exploring the potential of a new linker system cleaved using SmI_2

The well known reduction of α-heterosubstituted carbonyl compounds using SmI_2 has been employed in the design for a new linker for phase tag assisted synthesis. Building on work previously reported by the group, the research over the past 3 years has concentrated on increasing the synthetic utility of these new linker systems. The work culminated in what we believe to be the first instance of asymmetry being introduced in the final step of a phase tag assisted synthesis.

To illustrate further the potential of the linker system, studies into the synthesis of azepinones, a common structural motif found in many natural products, drugs and their pre-cursors, has been undertaken. Whilst a number of solution phase routes have been developed and optimised, their adaptation to a phase tag synthesis has proved difficult. Nevertheless, the foundations for a feasible route to such targets have been laid.

A sequential cleavage-asymmetric protonation strategy has also been developed that allows enantiomerically enriched compounds to be prepared from a phase tag assisted synthesis using our linker design. Chirality is introduced in the final step of the phase tag assisted synthesis via the enantioselective protonation of a samarium(III) enolate formed upon release of substrates from the phase tag. Our studies have resulted in many curious observations regarding the reactivity and behaviour of samarium(III) enolates.

Contents

Preface

The research described in this thesis was carried out under the supervision of Dr. David J. Procter in laboratories at the Universities of Glasgow and Manchester between October 2002 and September 2005.

Acknowledgements

Firstly, I would like to say a big thanks to Dr. David Procter for his help, support and constant enthusiasm and encouragement throughout the duration of my Ph.D.

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General thanks must go to the technical staff at both the University of Glasgow, particularly Ewan M^{c}Pherson, and at the University of Manchester where Gareth was invaluable in NMR, both for work and a wee chat now and again.

Of a less specific nature, thanks must go out to Procter group members past and present as well as latterly future! Too numerous to mention these days, they have been a constant source of entertainment and a joy to work with over the last three years. Particular thanks go to Jean-Claude for being a great flatmate and the rest of the crew who moved down to Manchester alongside me and managed to convince me it wasn't that bad! Thanks must also go out to all my pals outside chemistry for helping me appreciate the grander picture, and making sure I climb enough mountains to satisfy my cravings.

Finally, a big thanks to my parents and family for always being there when I needed advice on life and a wee bit of guidance, as well as introducing a level of stability to a sometimes hectic life.

Abbreviations

Å	Ångstrom
Ac	acetyl
AIBN	2,2'-azobis(2-methylpropionitrile)
Allyl	2-propenyl
aq.	aqueous
Ar	aryl
Boc	*tert*-butoxy carbonyl
Bn	benzyl
tBu	*tert*-butyl
nBu	*n*-butyl
Bz	benzoyl
Cbz	carboxybenzyl
CI	chemical ionisation
COSY	correlated spectroscopy
DEPT	distortionless enhancement through polarisation transfer
DIPEA	diisopropylethylamine
DMA	*N*,*N*-dimethylacetamide
DMAE	*N*,*N*-dimethylaminoethanol
DMAP	4-dimethylaminopyridine
DME	dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMPU	1,3-dimethyl-3,4,5-tetrahydro-2(1*H*)-pyrimidinone
DMSO	dimethyl sulfoxide
CPA	chiral protonating agent
dr	diastereomeric ratio
E	entgegen
ee	enantiomeric excess
EI	electron impact
equiv.	equivalents

er	enantiomeric ratio
Et	ethyl
FBS	fluorous biphasic systems
FLLE	fluorous liquid-liquid extraction
FSPE	fluorous solid phase extraction
g	gram
GC	gas chromatography
h	hour
HASC	heteroatom substituted carbonyl
HFIP	hexafluoroisopropanol
HMPA	hexamethylphosphoramide
HMQC	heteronuclear multiple quantum coherence
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
Hz	Hertz
IR	infra red
LDA	lithium diisopropylamide
LiHMDS	lithium hexamethyldisilazide
M	molarity
*m*CPBA	*meta*-chloroperoxybenzoic acid
Me	methyl
mg	milligram
min	minute
ml	millilitre
MMT	mono-*para*-methoxytrityl
mmol	millimole
mp	melting point
MPM	*para*-methoxyphenylmethyl
MS	molecular sieves
Mts	2-mesitylenesulfonyl
NaHMDS	sodium hexamethyldisilazide

NBS	*N*-bromosuccinimide
NMR	nuclear magnetic resonance
PEG	polyethylene glycol
PFMC	perfluoromethylcyclohexane
Ph	phenyl
PMB	*para*-methoxybenzyl
PPTS	pyridinium *para*-toluenesulfonate
^{i}Pr	*iso*-propyl
pyr.	pyridine
RCM	ring closing metathesis
RT	room temperature
TBAF	tetrabutylammonium fluoride
TBAI	tetrabutylammonium iodide
TBDMS	*tert*-butyldimethylsilyl
TBDPS	*tert*-butyldiphenylsilyl
TBS	see TBDMS
TFA	trifluoroacetic acid
THF	tetrahydrofuran
THP	tetrahydropyran
TIPDS	tetraisopropyldisiloxane-1,3-diyl
TLC	thin layer chromatography
TMEDA	tetramethylethylenediamine
tol.	toluene
Tris	2,4,6-triisopropylbenzenesulfonyl
Ts	*para*-toluenesulfonyl
Z	zusammen

Chapter 1: The formation of samarium(III) enolates and their applications in organic synthesis

1.1 Introduction

Samarium(II) iodide (SmI_2) is a single electron transfer reagent. Its use in organic synthesis was first described by Kagan in 1977,[1] who carried out a thorough investigation of the basic organic transformations that could be performed using the reagent.[2] Following its introduction it has been used extensively in organic synthesis.

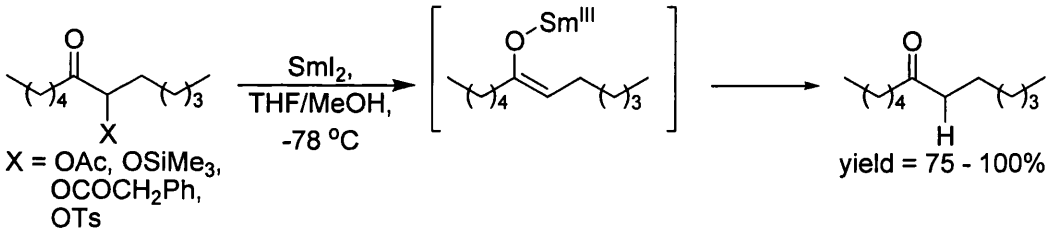
Due to the reagent's inclination to revert to the more stable samarium(III) oxidation state, it operates as a single electron donor. It is this property which enables it to mediate both radical and anionic processes or a mixture of both. The reagent has been used for a wide range of synthetic organic transformations such as functional group interconversions, Reformatsky reactions, Barbier-type reactions, aldol-type reactions, radical cyclisations, pinacolic coupling reactions, ketyl-olefin coupling reactions and conjugate additions.[3-6]

Part of the reagent's popularity arises through its ability to carry out transformations in a highly chemoselective manner and reactions with SmI_2 often also proceed with a high degree of stereoselectivity. Added to this, the reactivity, chemoselectivity, and stereoselectivity can be modified through the use of catalysts, co-solvents, or additives, thus increasing the scope of this already versatile reagent.[7-10]

The mechanisms of many SmI_2 reactions are believed to go via samarium(III) enolates, and this has proved to be an important factor in many of the reactions mentioned above. This chapter will give a summary of samarium-mediated reactions in which the key step involves a samarium(III) enolate intermediate.

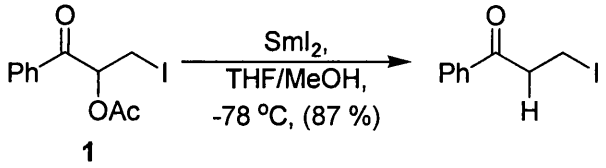
1.2 Reduction of α-heteroatom substituted carbonyl compounds

The reduction of α-heteroatom substituted carbonyl compounds is recognised as an important organic transformation and has previously been the subject of intense research. In 1986, Molander carried out the first detailed studies into the reduction of α-heteroatom substituted ketones with SmI_2.[11] At that time, the common reagents for the reduction were zinc metal and chromous ions. However, these reagents often required the use of acidic media and extended reaction times.[12-18] Alternative methods for the transformation included dissolving metal reductions[13, 19, 20] or the use of phosphorous or silica based reagents.[21-27] Initially, Molander investigated a range of α-oxygenated ketones which were reduced with SmI_2 to give the parent ketones in good yields (scheme 1.1).



Scheme 1.1

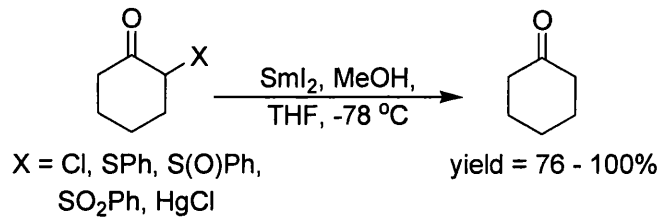
In order to explore the chemoselectivity of the reaction, Molander reduced α-acetoxy ketone **1** in the presence of a primary iodide in the β-position. Chemoselective reduction of the α-acetoxy group was observed in the presence of the iodide (scheme 1.2).



Scheme 1.2

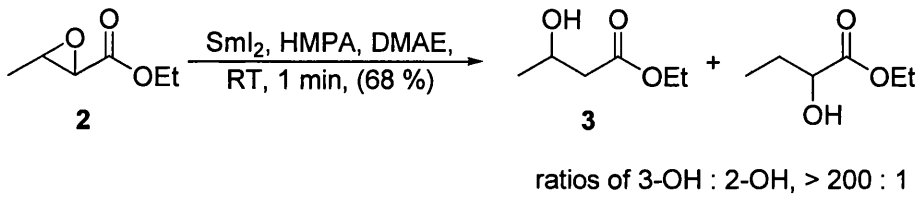
Molander also performed the reduction of an α-acetoxy ketone in the presence of cyclohexanone. No cyclohexanol was detected upon work up indicating that the reaction had taken place in the presence of an unfunctionalised ketone group.

Other analogous substrates that also underwent mild reduction were α-halosubstituted cyclohexanones and α-thiosubstituted cyclohexanones. Once again, good yields were observed in all cases (scheme 1.3).



Scheme 1.3

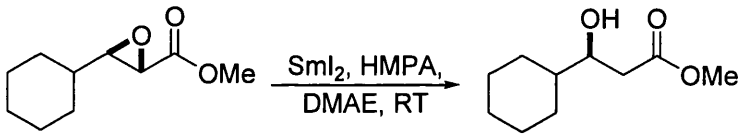
In 1987, following Molander's success in the reduction of α-heteroatom substituted ketones, Inanaga and co-workers decided to investigate the opening of α,β-epoxy esters.[28] In optimising conditions, Inanaga based his initial research on the reduction of ethyl 2,3-epoxybutyrate **2** to give ethyl 3-hydroxybutyrate **3**. The addition of hexamethylphosphoramide (HMPA) was found to highly accelerate the rate of the reaction and the yield was increased greatly upon the addition of propanol as a proton source. The presence of a strong chelating agent such as tetramethylethylenediamine (TMEDA) or *N,N*-dimethylaminoethanol (DMAE) was crucial in attaining a high level of regioselectivity. The optimum conditions were found to be 2.5 equivalents of SmI_2, 5 equivalents of HMPA and 2 equivalents of DMAE which led to ethyl 3-hydroxybutyrate **3** in 68 % yield with a negligible amount of ethyl 2-hydroxy butyrate being formed (scheme 1.4).



Scheme 1.4

Inanaga surmises that DMAE, when used as an additive, plays an important role in the reaction. It not only acts as a proton source, but also as an efficient chelating agent which removes the Lewis acidic samarium(III) species from the reaction mixture.[28] Removal of the samarium(III) species prevents it from ring-opening the epoxide in a non-regioselective manner, therefore reducing the formation of the 2-hydroxy ester. The optimised conditions were then applied to a number of other α,β-epoxy esters and good yields and selectivities were obtained.

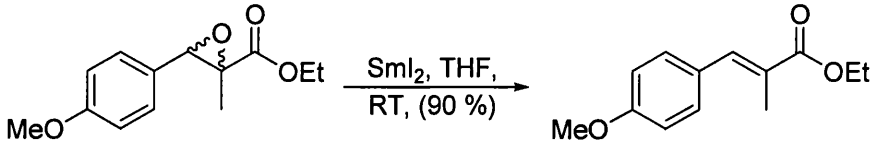
Inanaga converted optically pure α,β-epoxy ester **4** to β-hydroxy ester **5** with complete retention of configuration at the β-carbon (scheme 1.5). When combined with the Sharpless asymmetric epoxidation, this is an efficient route to optically active β-hydroxy esters.



4 **5** > 99 % ee

Scheme 1.5

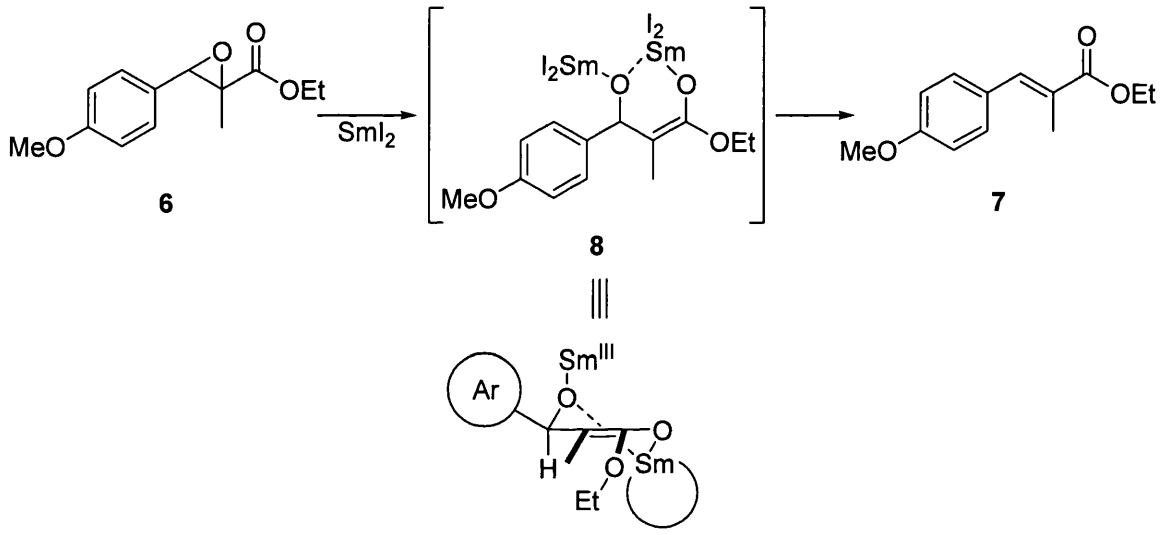
In 2002, Concellón *et al.* described a similar reaction to Inanagas', however, in this case, reduction of α,β-epoxy esters led to the formation of (*E*)-α,β-unsaturated esters with total or high diastereoselectivity.[29] Using 4 equivalents of SmI_2, Concellón was able to reduce α,β-epoxy esters such as **6** bearing a wide range of different alkyl and aryl groups to give di-, tri- or tetra-substituted (*E*)-alkenes such as **7** (scheme 1.6).



6 **7** > 98 de

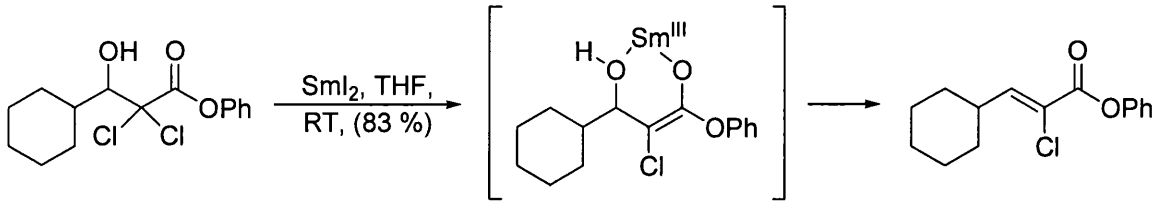
Scheme 1.6

The mechanism proposed by Concellón for the formation of the alkene goes via a 6-membered ring transition state. The SmI_2-promoted reduction of the α-carbon-oxygen bond, results in formation of a samarium(III) enolate intermediate. A 6-membered chelate intermediate **8** is now formed due to coordination of the oxophilic samarium(III) centre with the second oxygen from the epoxide. Diastereoselectivity can be explained simply through the minimisation of steric interactions. The bulkier R-group, in this case *p*-methoxyphenyl sits in an equatorial position to avoid steric clashes with the samarium coordination sphere (scheme 1.7).



Scheme 1.7

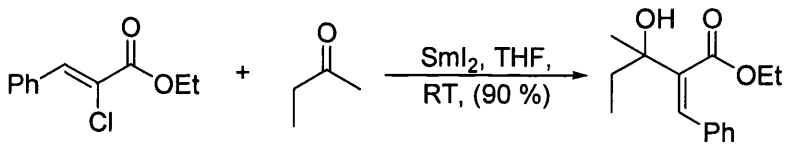
In 2004, Concellón used the reduction of α-chlorosubstituted carbonyls to construct (*Z*)-α-chloro-α,β-unsaturated esters which are important building blocks in organic synthesis.[30] Following two single electron transfers, a samarium(III) enolate **9** is formed which then undergoes β-elimination. The stereochemistry of the double bond in the product can be explained through chelation in enolate **9** giving rise to *Z*-alkene **10** (scheme 1.8).



9 **10**

Scheme 1.8

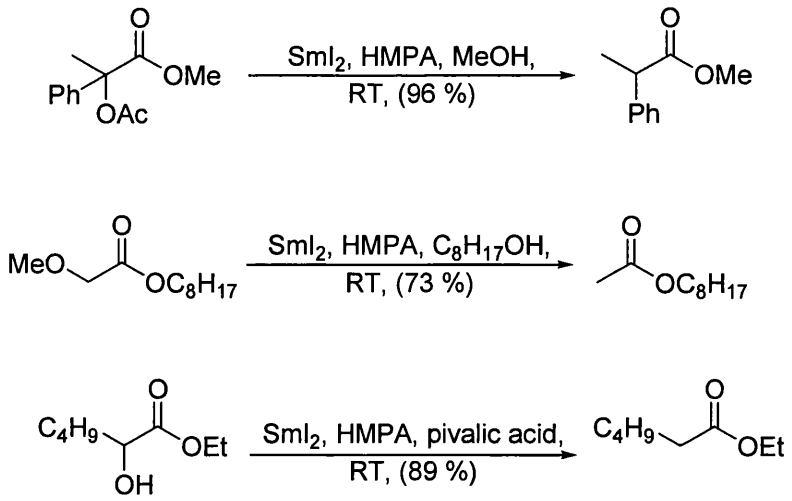
The following year, Concellón reported the reaction of (*Z*)-α-chloro-α,β-unsaturated esters with ketones or aldehydes to provide an alternative route to Baylis-Hillman adducts.[31] In scheme 1.9, reaction of the unsaturated ethyl ester **11** with butanone led to β-hydroxy ester **12** in good yield, with none of the *E*-isomer being observed.



11 **12**

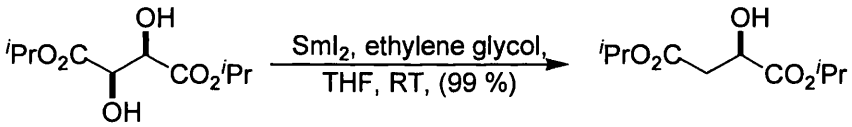
Scheme 1.9

In 1989, Inanaga and co-workers investigated the reduction of a range of α-oxygenated esters.[32] Deoxygenation of both α-acetoxy and α-methoxy esters proceeded well at room temperature using HMPA to increase the reducing potential of SmI_2. Direct reduction of α-hydroxy esters was unsuccessfully attempted. Inanaga found that a much more acidic proton source in pivalic acid was required for the reduction to occur (scheme 1.10).



Scheme 1.10

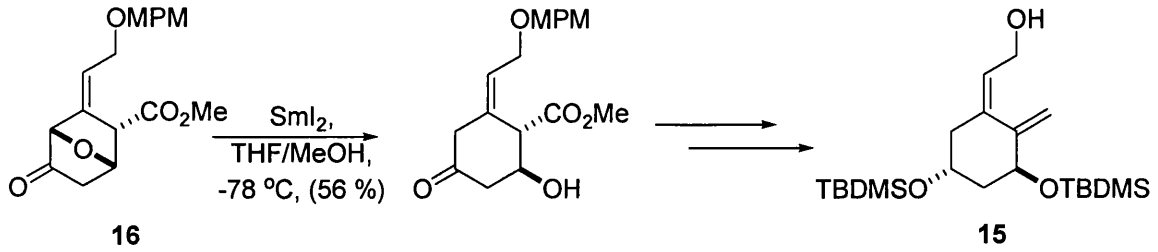
The dehydroxylation conditions were applied to the direct conversion of the naturally occurring (*R*,*R*)-tartrates to the unnatural (*R*)-malates. The best result was given by the reduction of (*R*,*R*)-diisopropyl tartrate **13** to give (*R*)-diisopropyl malate **14** using ethylene glycol as the additive (scheme 1.11).



13 **14**

Scheme 1.11

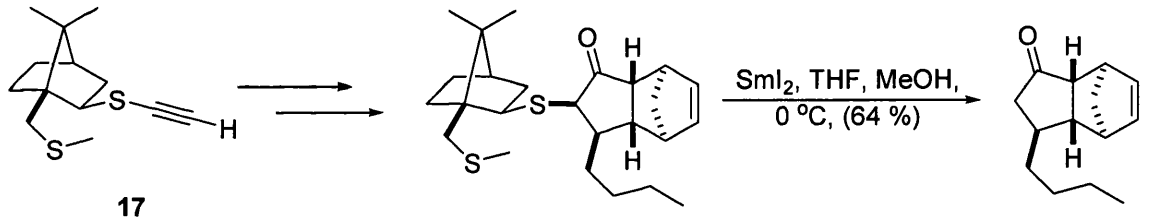
De Clercq *et al.* have utilised the SmI_2 reduction of α-heteroatom substituted carbonyl compounds in a novel synthesis of an A-ring precursor to 1α-hydroxyvitamin D **15**.[33] SmI_2 is used to reduce ketone **16** bearing a bridging oxygen atom at the α-position, thus opening the ether bridge (scheme 1.12).



16 15

Scheme 1.12

The reduction of an α-sulfanyl ketone has also been used in the final step of an asymmetric Pauson-Khand reaction to remove a chirality-controlling, chelating group.[34] Alkyne **17**, which was prepared from (1*S*)-camphor-(10)-thiol, underwent an asymmetric Pauson-Khand reaction with norbornadiene and was then alkylated to give **18**. Treatment of this compound with SmI_2 allowed the chiral α-sulfanyl group to be removed to give tricycle **19** (scheme 1.13).



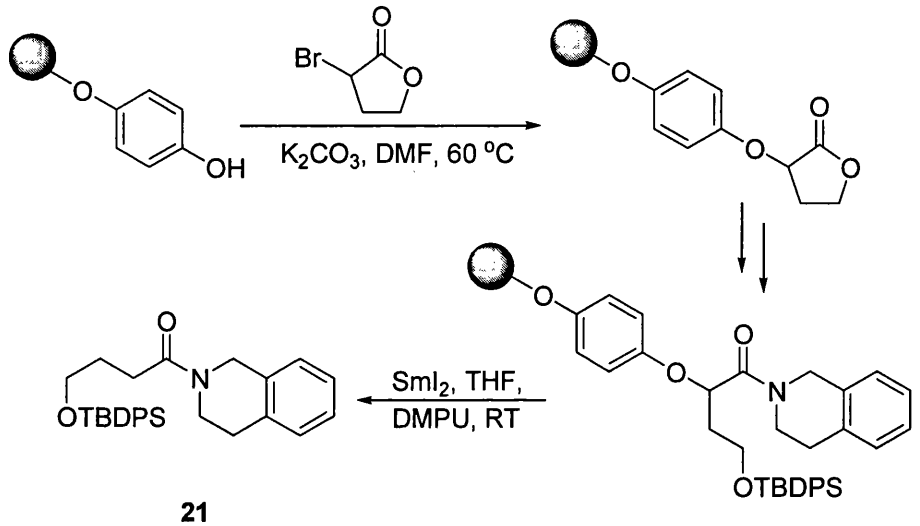
17 **18** **19** 98 : 2 dr

Scheme 1.13

Procter and co-workers have applied this organic transformation in a linker system for phase-tag assisted synthesis. Either an oxygen or sulfur heteroatom at the α-position of a carbonyl compound has been used as a linking atom to bind substrates to a phase-tag. Treatment of substrates immobilised in this way with SmI_2 cleaves the phase-tag in a traceless manner to release products.

In 2002, Procter reported the solid phase synthesis of amides and ketones in high purity.[35, 36] α-Bromo-γ-butyrolactone was immobilized using a phenol resin developed within the group. It could then be modified to give resin bound α-aryloxy amides, such as **20**, and

ketones. Treatment of these with SmI_2 gave the free carbonyl compounds, such as amide **21**, in good yields and purity (scheme 1.14).

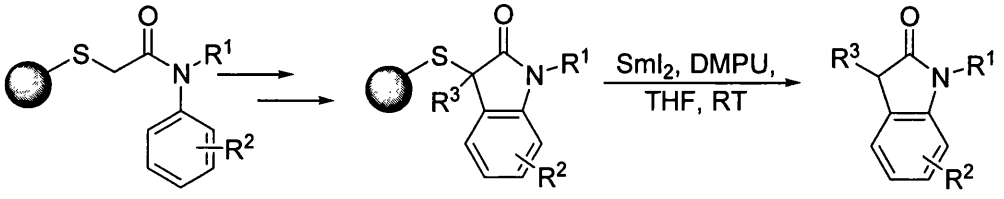


21
31 % yield, over 4 steps
88 % HPLC purity

20

Scheme 1.14

Procter has also used the linker in conjunction with the first Pummerer cyclisations on solid phase to construct oxindoles.[37] α-Sulfanyl *N*-aryl acetamides are attached to the polymer backbone via a sulfur linking atom. Activation of the sulfur link allows the substrate to undergo Pummerer cyclisation to give immobilized oxindoles **22**, which can be cleaved tracelessly from the support using SmI_2 (scheme 1.15).



22

Scheme 1.15

Products were obtained in good yields after four steps on resin to create a small library of functionalized oxindoles, a selection of which is shown below (figure 1.1).

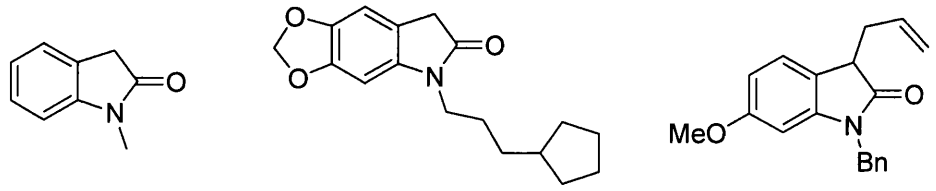
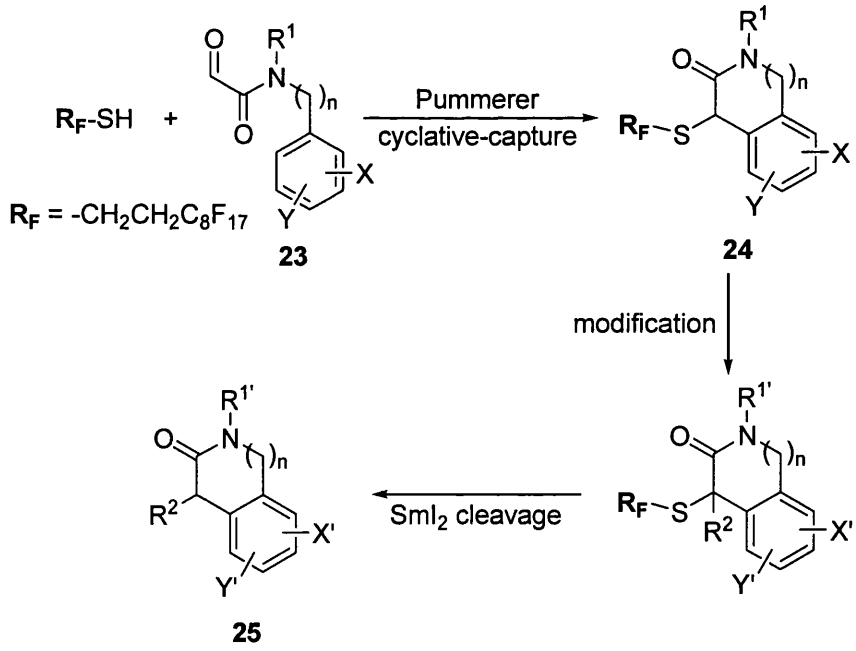


Figure 1.1

The methodology has been extended further still with the replacement of the polymer tag with a fluorous tag.[38] A new Pummerer process was also developed which allowed the fluorous tag to be introduced whilst simultaneously constructing the heterocyclic ring system. A fluorous thiol was used in a cyclative capture process with glyoxamide substrates **23**. The resultant tagged heterocycles **24** could then be further modified and purified easily using fluorous solid-phase extraction (FSPE) before cleavage with SmI_2 released the heterocycles **25** from the phase tag (scheme 1.16).



Scheme 1.16

The methodology was used to prepare a small library of nitrogen heterocycles, including oxindoles, tetrahydroisoquinolinones and tetrahydrobenzazepinones. Selected examples of products obtained from the fluorous-phase synthesis are shown below (figure 1.2).

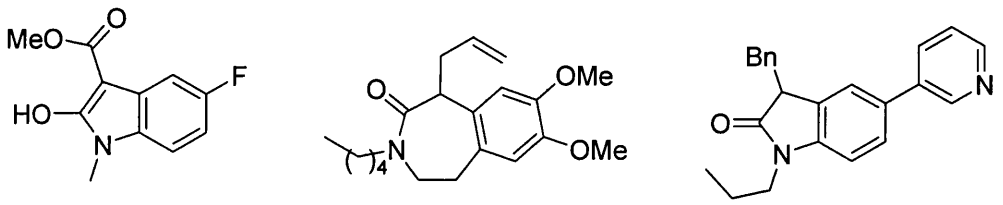
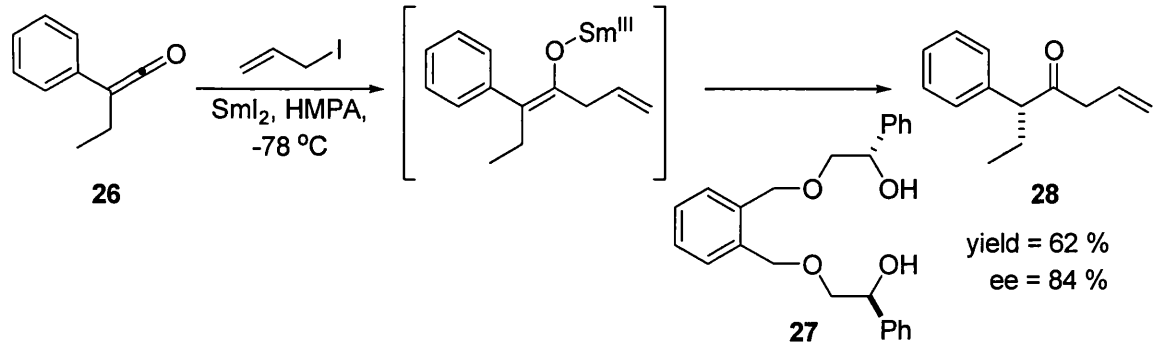


Figure 1.2

1.3 Enantioselective protonation of samarium(III) enolates

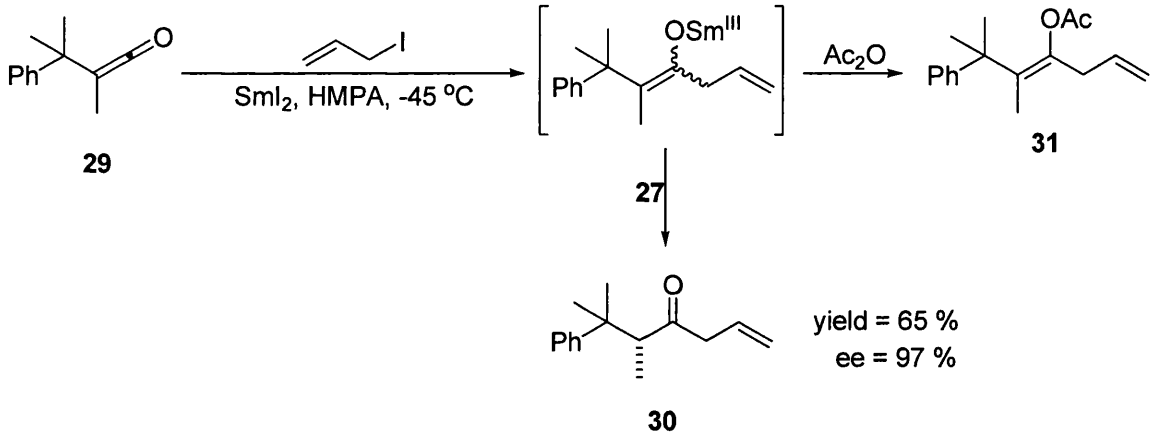
In 1988, Fehr and Galinda reported the asymmetric synthesis of (*R*)-(+) and (*S*)-(-)-damascone using a Grignard addition to a ketene followed by the asymmetric protonation of the resulting lithium enolate.[39] Takeuchi applied this principle to the asymmetric protonation of samarium(III) enolates formed from ketenes.[40] Initially he screened a number of chiral protonating agents for use in the samarium-mediated allylation of phenylethyl ketene **26**. *o*-Xylene derived proton source **27** gave the enantiomerically enriched ketone **28** in 84 % ee (scheme 1.17).



Scheme 1.17

Takeuchi *et al.* investigated various alkylating agents and their reactions with a range of unsymmetrical ketenes with the best result being observed for the conversion of ketene **29**

into ketone **30** in 97 % ee.[41] The enantiomeric excesses were not high in every case however and Takeuchi speculated that this was due to the nature of the enolate double bond. In order to investigate further, the enolate was trapped as the enol acetate **31**, and its double bond geometry determined by ^{1}H NMR and 2D ^{1}H NOESY. It was apparent that the *E*/*Z* selectivity increases with the increasing difference in bulkiness of the two substituents of the ketene, with a corresponding rise in the enantiomeric excess of the ketone from the reaction also observed (scheme 1.18).

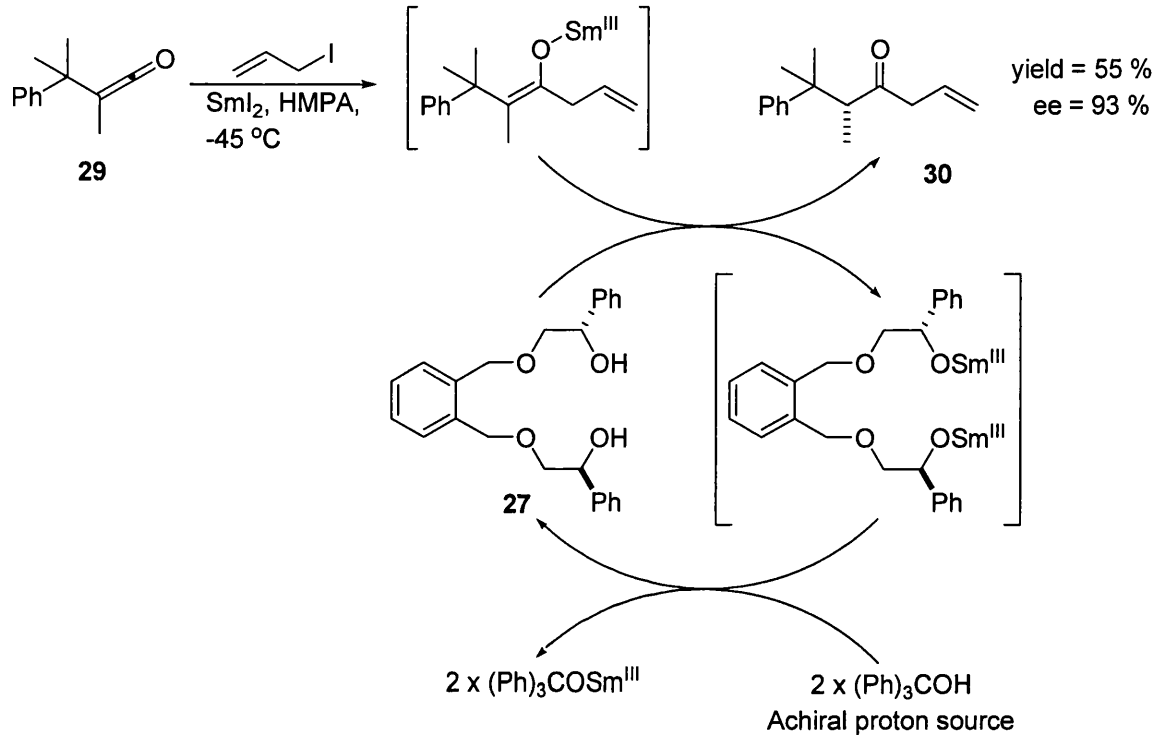


Scheme 1.18

Yanagisawa and Yamamoto reported the *catalytic* enantioselective protonation of lithium enolates[42] so it was logical for Takeuchi to look into the *catalytic* enantioselective protonation of samarium(III) enolates.[43] Using the best example from his previous work, Takeuchi applied it in a catalytic system where an achiral proton source protonates and thus regenerates the chiral proton source **27**.

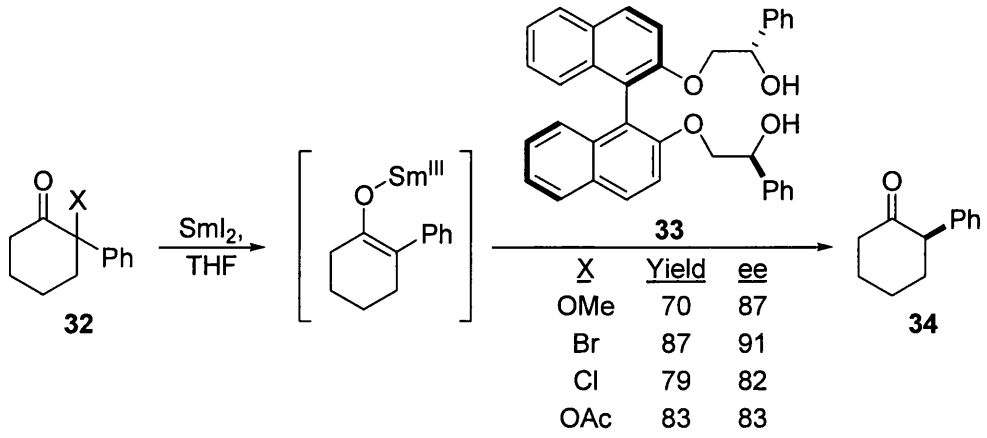
As before, the SmI_2-mediated reaction of ketene **29** with allyl iodide affords a samarium(III) enolate intermediate. Previously, Takeuchi had used a stoichiometric amount of proton source **27** to enantioselectively protonate the enolate leading to enantiomerically enriched ketone **30**.[40] In this case however, a catalytic amount of **27** was used in combination with trityl alcohol (scheme 1.19). The trityl alcohol re-protonated the conjugate base of the proton source returning it to its original state, whilst itself having a sufficiently low protonating ability so as not to achirally protonate the samarium(III)

enolate.[43] This led to a highly selective *catalytic* process yielding enantioselectivities up to 93 %, which is only 4 % lower than the analogous stoichiometric reaction.[41]



Scheme 1.19

In 1997, Takeuchi's attention turned to Molander's original work on the reduction of α-heteroatom substituted carbonyl compounds and began to investigate the feasibility of forming the requisite samarium(III) enolates using this process.[44] Takeuchi looked at the reduction of α-heterosubstituted cyclohexanone **32** bearing an α-phenyl substituent. A number of ketones were screened with BINOL derived chiral proton source **33** leading to ketone **34** in all cases. The yields were all reasonably high and the enatioselectivity ranged between 82 % and 91 % enantioselectivity (scheme 1.20).



X	Yield	ee
OMe	70	87
Br	87	91
Cl	79	82
OAc	83	83

Scheme 1.20

Subsequent work gave rise to a series of tetradentate chiral protonating agents used to protonate the enolate formed upon reduction of a number of different α-heterosubstituted ketones, and which often gave good enantioselectivities (figure 1.3).[44-46]

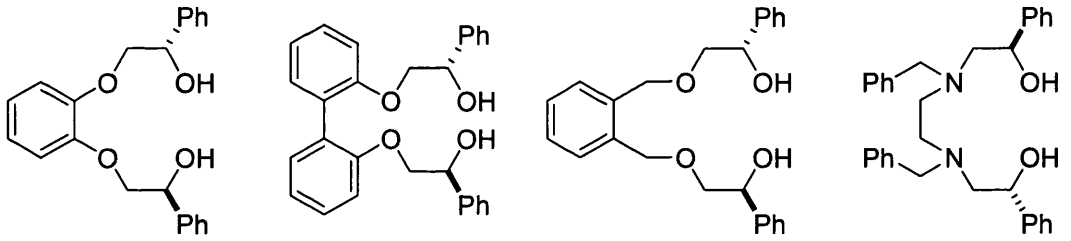
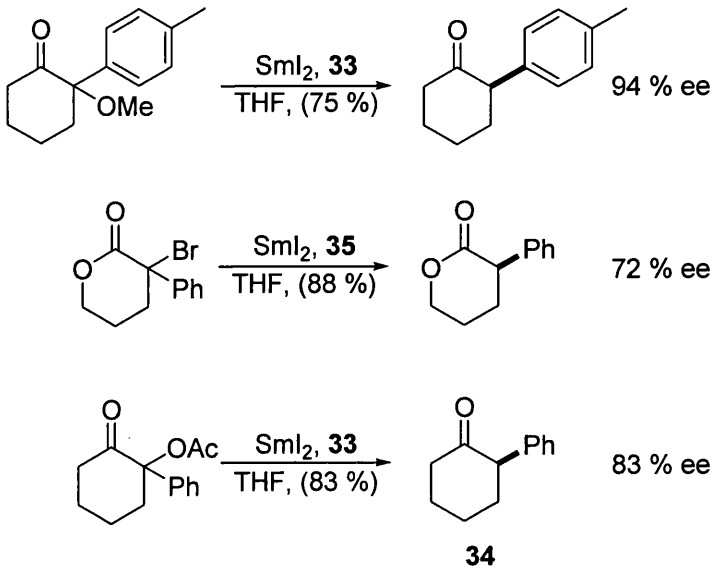


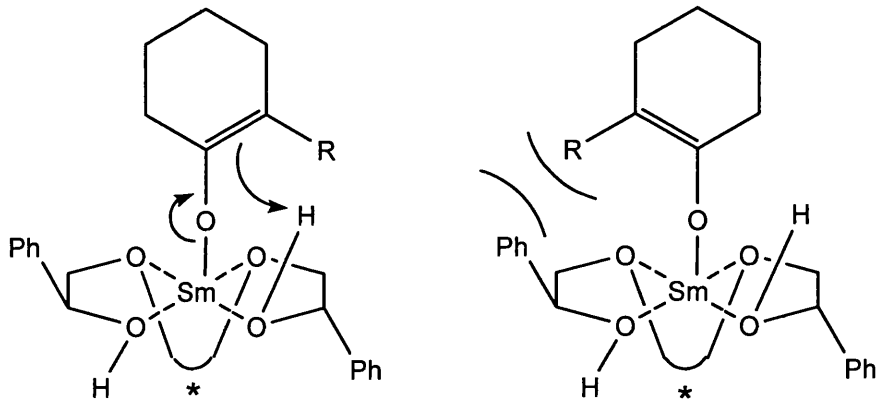
Figure 1.3

Takeuchi reduced a number of α-methoxy, α-acetoxy and α-halo cyclohexanones bearing different α-alkyl and aryl groups. In addition to this, SmI_2 was used to reduce α-halo lactones and some acyclic substrates. Illustrated below is a selection of SmI_2 reductions-asymmetric protonations performed by Takeuchi *et al.* (scheme 1.21).



Scheme 1.21

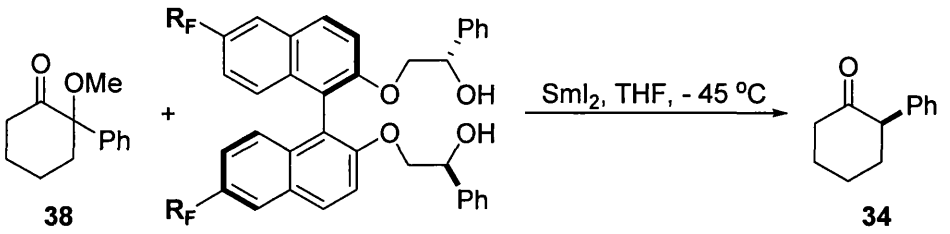
Takeuchi has proposed a transition state model to explain the enantioselectivities obtained from the reaction (figure 1.4). In transition state $\mathbf{T^1}$ **- 36**, the substituent at the α-position of the enolate is far from the phenyl ring at the left hand side of the model and therefore has no steric interaction with it. As a result, protonation from the OH of the chiral proton source takes place from the *si* face giving the product of (*R*)-configuration. Conversely in transition model $\mathbf{T^2}$ **- 36**, steric interactions between the substituent on the enolate, and the phenyl ring on the left of the model on the proton source gives rise to a higher energy conformation and protonation via this path is less favourable.



T_1 - 36 **T_2 - 36**

Figure 1.4

Takeuchi and Curran synthesised fluorous chiral BINOL derivative **37** and used it in the catalytic enantioselective protonation of the samarium(III) enolate derived from **38** (scheme 1.22).[47] As a consequence of using fluorous solid phase extraction (FSPE), the proton source could be easily recovered from the reaction mixture and used for subsequent runs, with little loss in yield and enantioselectivity.

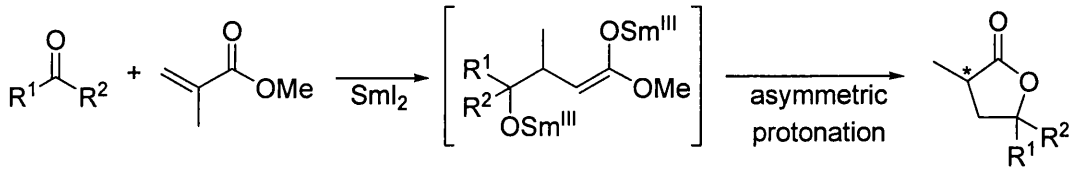


Run	Yield %	ee %	Config.	Recovered **37** %
1	82	81	*R* (+)	98
2	81	85	*R* (+)	97
3	78	86	*R* (+)	98
4	74	89	*R* (+)	99
5	73	87	*R* (+)	99

Scheme 1.22

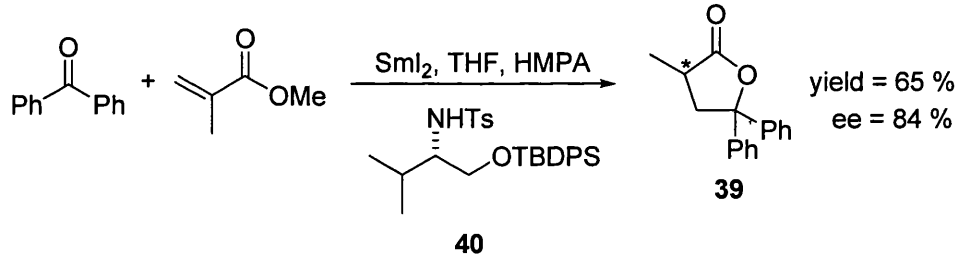
Apart from the work of Takeuchi and co-workers, there are few examples of the enantioselective protonation of samarium(III) enolates. The recent work done by Lin and co-workers on the reductive coupling of ketones with methyl methacrylate also involves the interception of a samarium(III) enolate with a chiral proton source (scheme 1.23).[48] Fukuzawa looked into the role of the proton donor in this reaction in 1988, and through deuterium labelling experiments determined that a proton was introduced into the α-carbon of the lactone.[49, 50]

Lin looked into the possibility that enantioselective protonation of the samarium(III) enolate intermediate would allow the controlled construction of α-carbon stereocentres during the formation of γ-butyrolactones.



Scheme 1.23

Lin looked at chiral alcohols, amides and amino alcohols amongst others as potential proton donors. Whilst the initial results did not give particularly high ee's, they did show the potential of asymmetric protonation in this reaction. Chiral sulfonamides were the most promising proton sources, and Lin chose to look into these further. After screening a number of sulfonamide derivatives, both with and without HMPA as an additive, he obtained lactone **39** in 84 % ee using **40** (scheme 1.24).



Scheme 1.24

Lin followed up this work by replacing the methyl ester group of the methacrylate with carbohydrate derived auxiliaries bearing amide substituents (figure 1.5). These groups acted both as chiral auxiliaries and as chiral proton sources in a new method for the asymmetric synthesis of optically active α,γ-substituted γ-butyrolactones.[51]

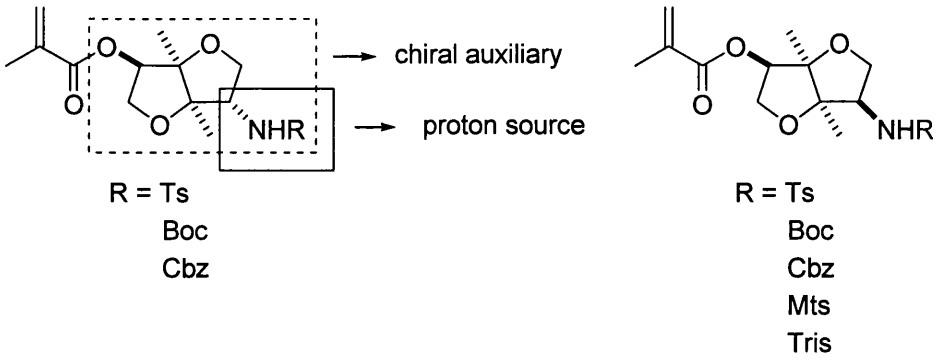
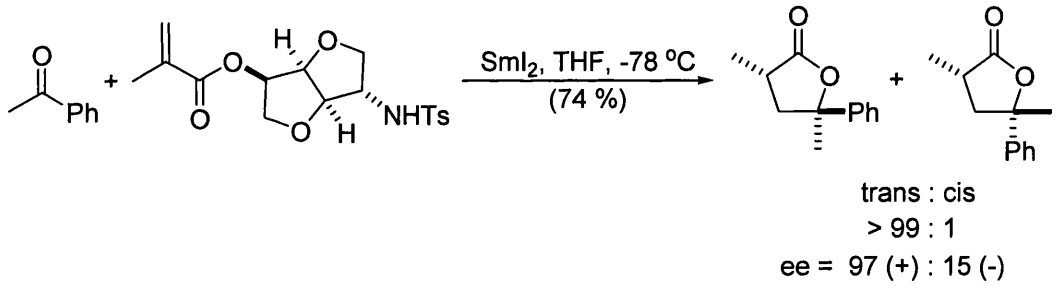


Figure 1.5

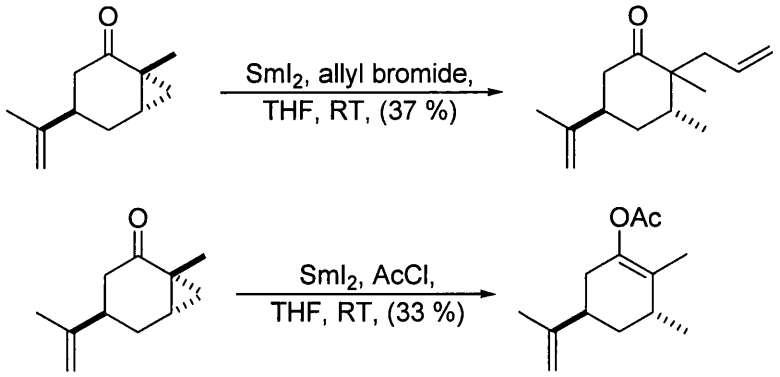
Lin investigated the reductive coupling between a number of ketones and chiral acrylates, with varying results. Firstly, the diastereomeric ratio obtained from the reaction varied greatly from 50:50 mixtures of both trans and cis isomers to greater than 99:1 in favour of the trans isomer as shown in scheme 1.25. The enantiomeric excesses of the two isomers also varied greatly with those of the trans isomers being generally high, while the cis isomers were formed with lower selectivities.



Scheme 1.25

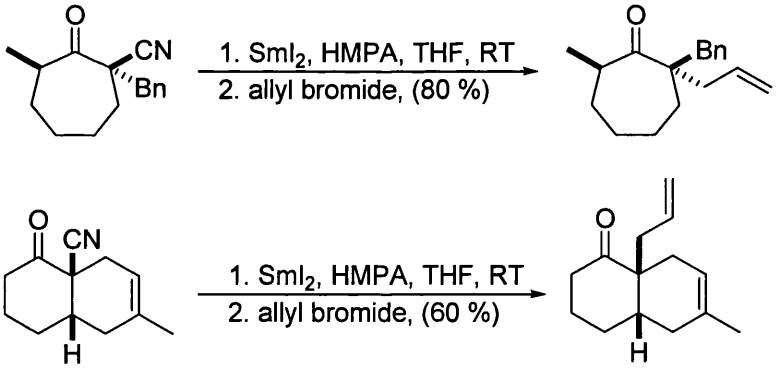
1.4 Cleavage of C-C bonds α to carbonyl groups

SmI_2 can be used to break α-carbon-carbon bonds as well as α-heteroatom-carbon bonds in carbonyl compounds. In 1991, Motherwell *et al.* used the reagent to open α,β-cyclopropane rings.[52] In trapping the enolate formed, he isolated a variety of synthetically useful intermediates (scheme 1.26).



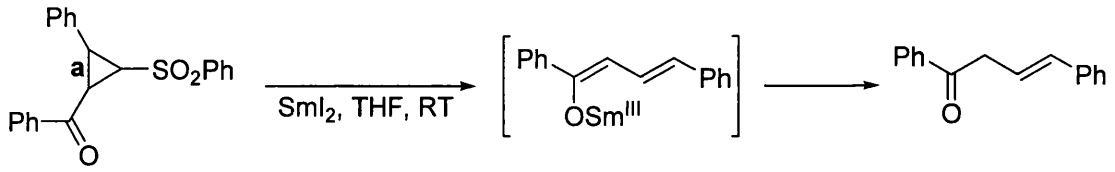
Scheme 1.26

The reduction of α-cyano compounds has been performed by treatment of such compounds with lithium naphthalide.[53] Liu and co-workers have shown SmI_2 to also be a useful reagent for this transformation.[54] Subsequent quenching of the enolate with allyl bromide led, in most cases, to a single diastereoisomer in yields of 60-80 %. The reaction allows regioselective α,α'-alkylation of ketones with retention of stereochemistry at the α' position (scheme 1.27).



Scheme 1.27

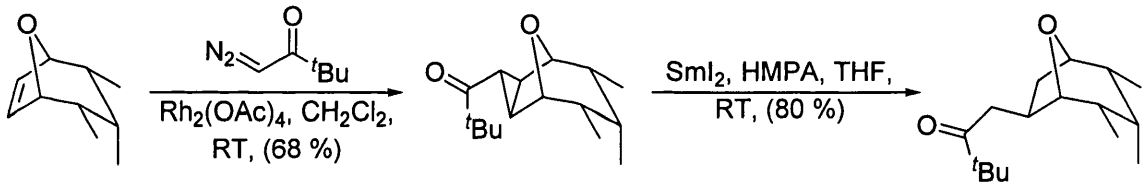
In 1999, Reutrakul *et al.* reported the regioselective cleavage of phenylsulfonyl cyclopropyl ketones using SmI_2 to give β,γ-unsaturated ketones.[55] Treatment of **41** with SmI_2 regioselectively cleaves bond **a** of the cyclopropane ring to give a β-phenylsulfonyl radical which undergoes β-elimination to form extended samarium(III) enolate **42**. The main driving force for the reaction is the stability of the radical intermediate as well as the formation of the conjugated enolate intermediate (scheme 1.28).



41 **42**

Scheme 1.28

In 2005, Chiu and co-workers reported the cyclopropanation of an oxabicyclic template **43** using either rhodium or copper catalysts.[56] The strain in the cyclopropane ring, and its propensity for ring opening, make this type of molecule a useful synthetic intermediate. Unsuccessful opening of the cyclopropane ring was attempted with $^{n}Bu_3SnH$/AIBN, however the transformation was achieved using SmI_2 to give **44**. This allowed for desymmetrisation of **45** with no concomitant opening of the ether bridge (scheme 1.29).

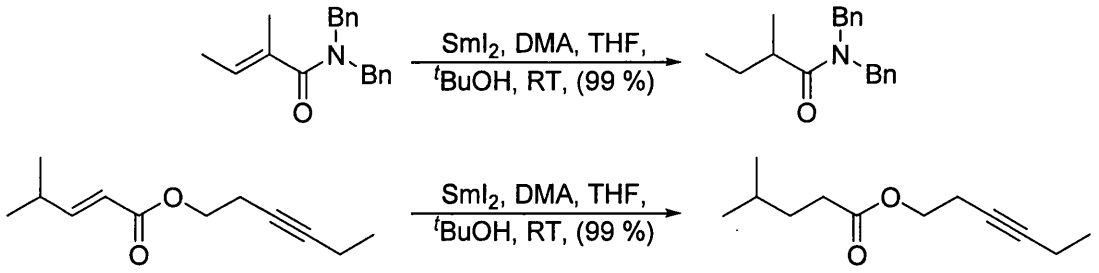


43 **45** **44**

Scheme 1.29

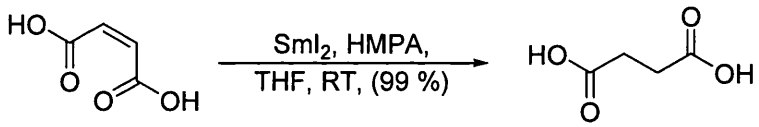
1.5 Reduction of α,β-unsaturated carbonyl compounds

In 1991, Inanaga *et al.* reported the conjugate reduction of α,β-unsaturated esters and amides using SmI_2.[57] Although this transformation had already been documented through the use of a number of varied reagents,[58-62] Inanaga's SmI_2-DMA-proton source system was a milder method for the reduction (scheme 1.30). Reduction with CD_3OD as the proton source showed deuterium incorporation on both α and β-carbons indicating a likely enolate intermediate.



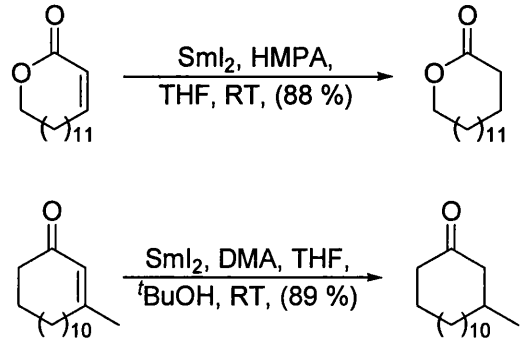
Scheme 1.30

A year later, Alper and co-workers extended the applicability of the reduction to include α,β-unsaturated acids and anhydrides.[63] Whereas Inanaga did not see any beneficial effects from using HMPA as an additive, Alper found it to be an excellent promoter for the reaction (scheme 1.31).



Scheme 1.31

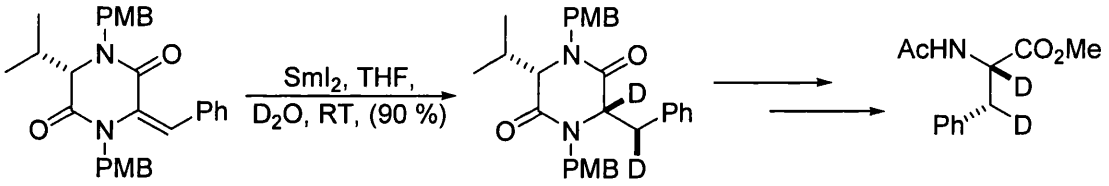
Fukuzumi and Otera extended the study further still in 1997 by performing the reduction on a number of unsaturated carbonyl compounds including α,β-unsaturated cyclic ketones and lactones.[64] Ring size obviously plays an important role in this reaction as both cyclohexenone and α,β-unsaturated valerolactone failed to undergo reduction with essentially quantitative recovery of starting material being obtained. Larger, macrocyclic ketones and lactones, however, underwent reduction in good yields (scheme 1.32).



Scheme 1.32

To summarise, Inanaga *et al.* showed that a number of α,β-unsaturated amides and esters could be rapidly and selectively reduced in the presence of alkenes, alkynes and protected amides.[57] Alper and co-workers then extended this reaction to acids[63] whilst Fukuzumi and Otera looked at cyclic systems.[64] The extensive functional group tolerance in the reaction once again shows the chemoselective nature of the reagent.

More recently, Davies *et al* have performed a diastereoselective SmI_2 and D_2O promoted conjugate reduction to gain access to isotopically labelled α-amino acids.[65, 66] Reduction of diketopiperazine derived **46** gave a samarium(III) enolate intermediate which was then diastereoselectively deuterated to give **47**. Further synthetic steps yielded protected α-amino acid **48** (scheme 1.33).

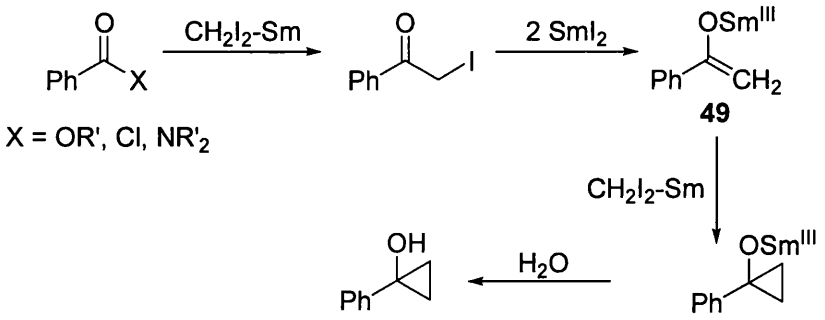


46 **47** **48**

Scheme 1.33

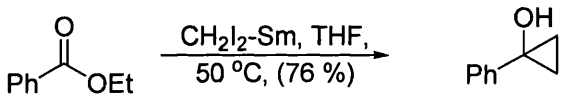
1.6 Cyclisation reactions involving samarium(III) enolates

Imamoto and co-workers reported the one-pot synthesis of cyclopropanols from esters using SmI_2.[67] He envisaged that cyclopropanols could be synthesised from carboxylic acid derivatives via a tandem one-carbon homologation route involving samarium(III) enolate **49** (scheme 1.34).



Scheme 1.34

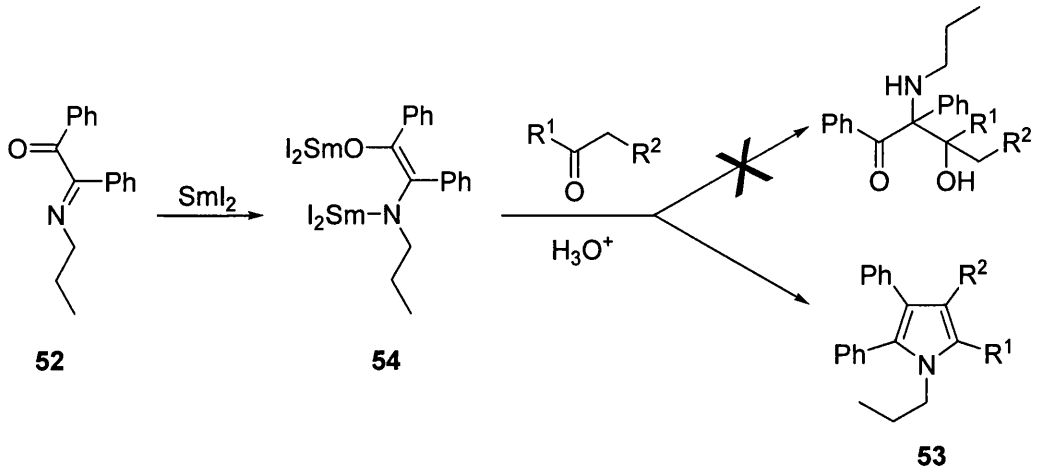
Imamoto's best result was with ethyl benzoate **50**, from which he obtained 1-phenyl cyclopropanol **51** in 76 % yield (scheme 1.35). Other lanthanide metals were tried, though none were as successful as samarium.



50 **51**

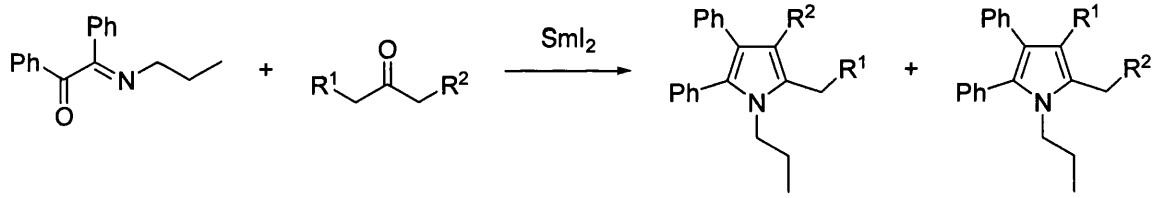
Scheme 1.35

In 2001, Namy *et al.* were investigating the SmI_2-promoted reactions of a diphenyl α-iminoketone **52**.[68] Initially hoping to prepare hydroxyaminoketones, **52** was treated with SmI_2 followed by quenching with a ketone. However, this unexpectedly led to pyrroles **53** in good yields (scheme 1.36). Namy suggests that the initial step in the reaction mechanism involves a two-electron transfer from two equivalents of SmI_2 to give samarium(III) enolate intermediate **54**.



Scheme 1.36

Namy synthesised pyrroles from ketones bearing a single methylene unit as well as from ketones bearing two non-equivalent methylene units and found that, in the latter case, a mixture of products was generally formed as illustrated in scheme 1.37.



Scheme 1.37

Figure 1.6 shows a number of varied pyrrole derivatives synthesised using Namy's method. He also attempted an analogous reaction aiming to assemble furan derivatives, but early results were not encouraging.

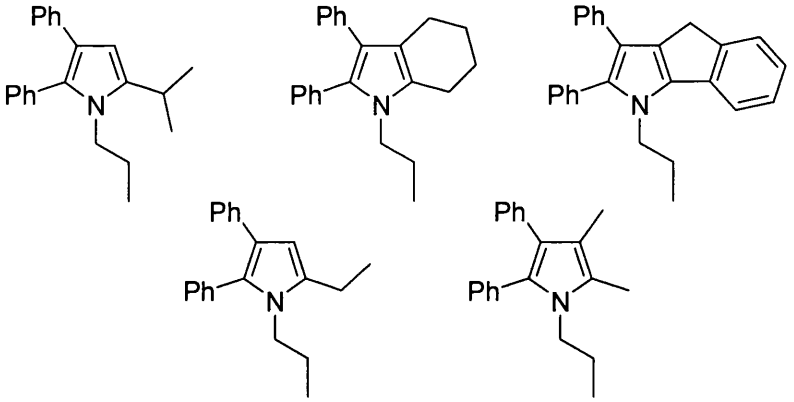
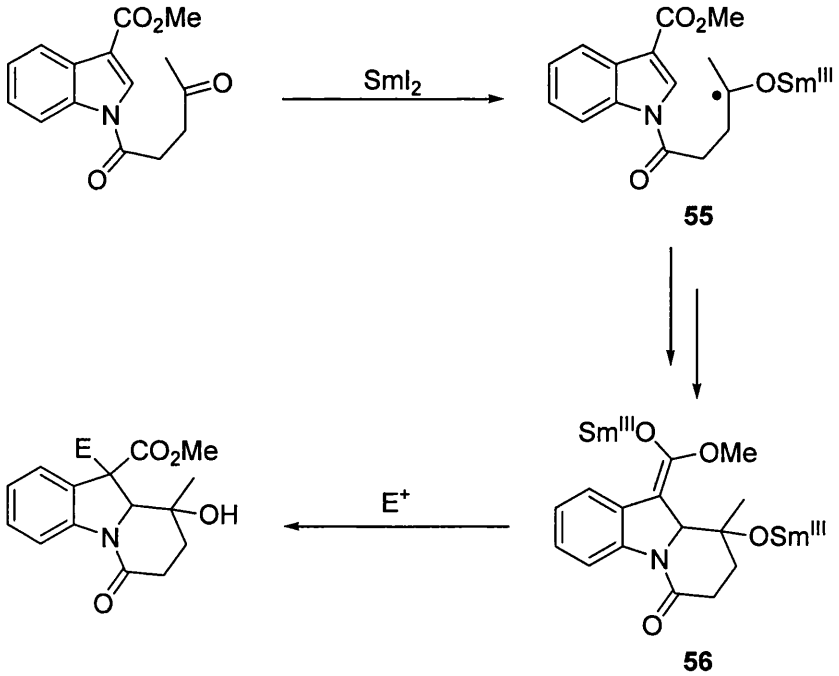


Figure 1.6

The indole unit is a core structure of many natural products and pharmaceutically important compounds. In 2003, Reissig and co-workers published a novel stereoselective synthesis of highly functionalised benzannulated pyrrolizidines and indolizidines through the SmI_2-induced cyclisations of indole derivatives.[69] The cyclisation occurs through a samarium ketyl radical **55**. After cyclisation, a second one-electron transfer occurs to form the samarium(III) enolate **56** which is subsequently quenched during work up by a proton (scheme 1.38).



Scheme 1.38

Reissig introduced yet further functionality through quenching the enolate with an electrophile other than a proton to create an efficient one-pot tandem reaction. These cascade reactions selectively generate three continuous stereogenic centres including a difficult to construct quaternary centre at the 3-position of the indole moiety, a structural motif found in many indole alkaloids. Figure 1.7 contains some of the diverse *N*-heterocycles prepared by Reissig.

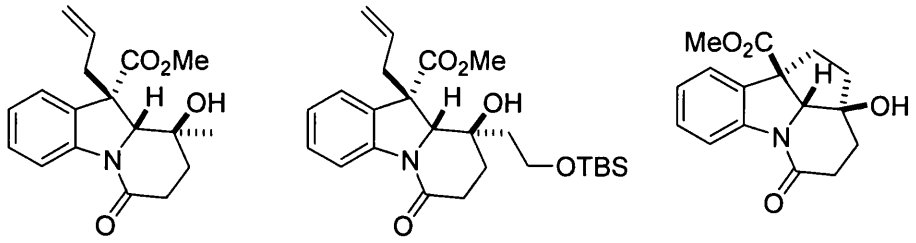
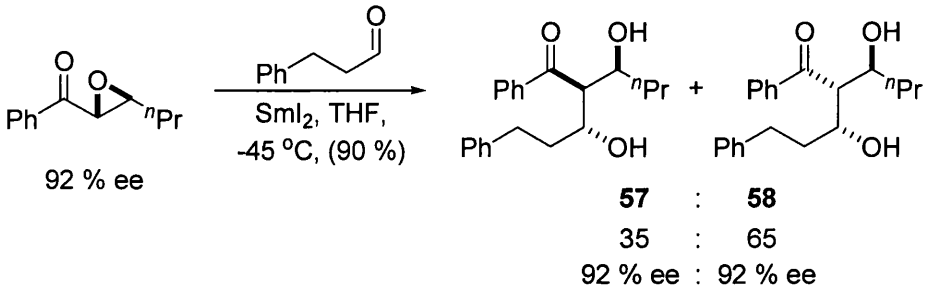


Figure 1.7

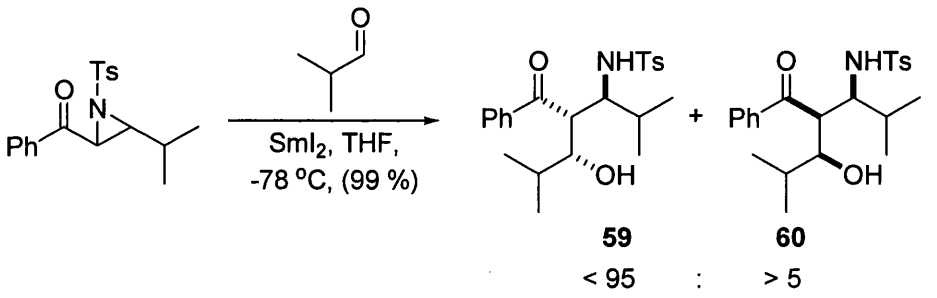
1.7 Samarium(II) iodide-mediated aldol reactions

The aldol reaction has long been recognised as one of the synthetic organic chemist's most versatile tools for the formation of carbon-carbon bonds. In recent years, Mukaiyama *et al.* have investigated various aspects of this reaction. In 2000, they developed a new method for the synthesis of unsymmetrical bis-aldols via a SmI_2-mediated reaction between aldehydes and aryl or alkyl oxiranyl ketones, an example of which is outlined in scheme 1.39.[70] Only the *anti,anti* **57** and *syn,syn* **58** bis aldols were observed and it is important to note that the optical purity of the starting material is preserved in the reaction. The mechanism proceeds through an enolate intermediate which then attacks the carbonyl of the aldehyde.



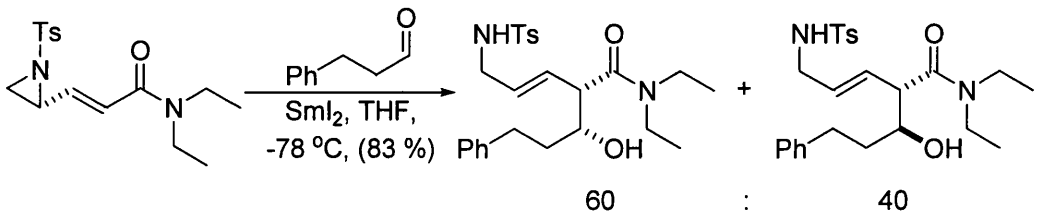
Scheme 1.39

Substituted β-amino acids, particularly β'-hydroxy derivatives, have attracted considerable attention in recent years as unnatural amino acid building blocks. In 2004, Mukaiyama looked into the synthesis of β-amino-β'-hydroxy ketones via a similar method to that illustrated above. In this case, it was a SmI_2-mediated aldol reaction between aldehydes and aryl or alkyl aziridinyl ketones.[71] Once again the reaction proposed proceeds through a samarium(III) enolate intermediate. The reaction which gave the best results afforded *anti,syn*-amino ketone **59** in high diastereoselectivity with a minor amount of *syn,anti*-amino ketone **60** being formed (scheme 1.40).



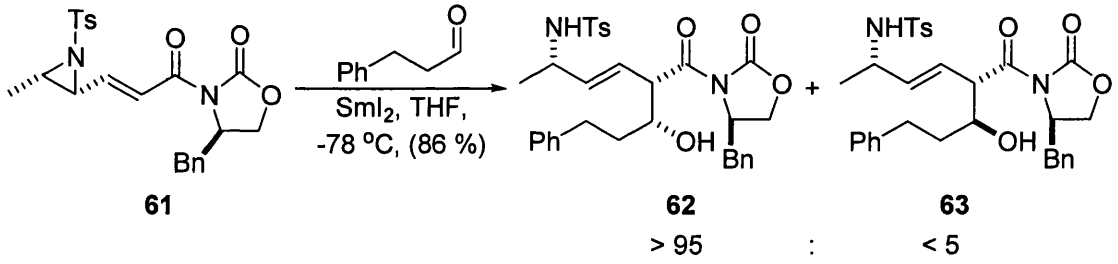
Scheme 1.40

Mukaiyama followed up this work by looking at the construction of δ-amino-β'-hydroxy-β,γ-unsaturated carbonyls using the SmI_2-mediated aldol reaction between aldehydes and γ,δ-aziridinyl-α,β-unsaturated carbonyls.[72] Firstly he investigated the reactions of esters which led to reasonable *syn/anti* selectivity, in yields of 86 % and above. Mukaiyama then turned his attention to reactions of the corresponding amides and found that the reaction was also successful, obtaining similar yields and selectivities (scheme 1.41).



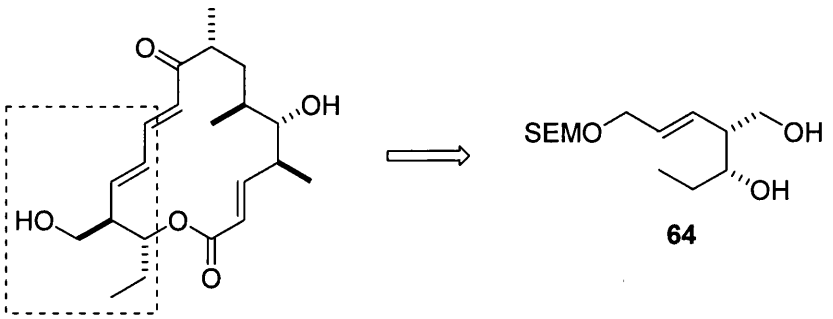
Scheme 1.41

Whilst investigating the potential of the reaction with unsaturated amides, Mukaiyama developed an asymmetric aldol reaction by incorporating an oxazolidinone chiral auxiliary in the unsaturated aziridine. Using oxazolidinone **61**, the reaction proceeded well in good yield with high *syn* diastereoselectivity to give **62** and **63** (scheme 1.42). Simple removal of the auxiliary using sodium methoxide in methanol released the unsaturated methyl ester.



Scheme 1.42

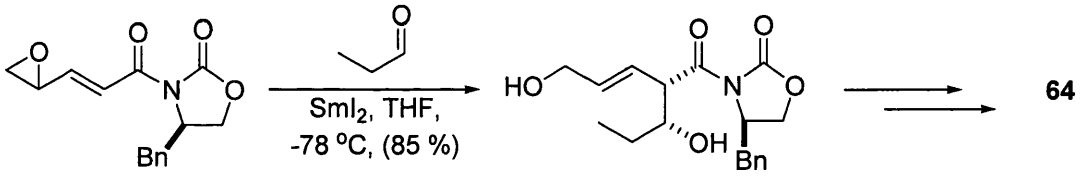
It is interesting to note that in the first two cases, Mukaiyama exploited the well known reduction of α-heteroatom substituted carbonyls in order to form the enolate which subsequently facilitates the aldol reaction. In the latter two cases, he employed the reduction of a carbon-heteroatom bond in the γ-position of an α,β-unsaturated carbonyl compound. In 2005, Mukaiyama proposed an enantioselective synthesis of the C11-C17 segment **64** of Mycinolide IV **65** using his novel method (scheme 1.43).[73]



Mycinolide IV **65**

Scheme 1.43

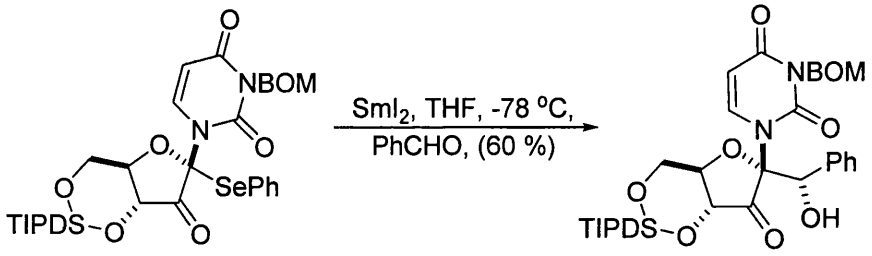
Starting from unsaturated γ,δ-epoxide **66** bearing the chiral oxazolidinone auxiliary, and its reaction with propanal, Mukaiyama was able to obtain the *syn* product as the major diastereoisomer **67**. The reaction went in good yield with the minor diastereoisomer being easily removed using chromatography. Protection of the primary alcohol followed by reductive cleavage of the auxiliary gave the segment C11-C17 **64** (scheme 1.44).



66 **67**

Scheme 1.44

Branched-chain sugar nucleosides are biologically important targets in medicinal chemistry and a number of different methods for their preparation have been reported. In 2002, Shuto and Matsuda reported a highly stereoselective SmI_2-promoted aldol reaction to construct 1'α-branched uridine derivatives.[74] The reaction once again initially begins with the reduction of an α-heteroatom substituted carbonyl to form an enolate. This is then quenched with benzaldehyde to give **68** (scheme 1.45).

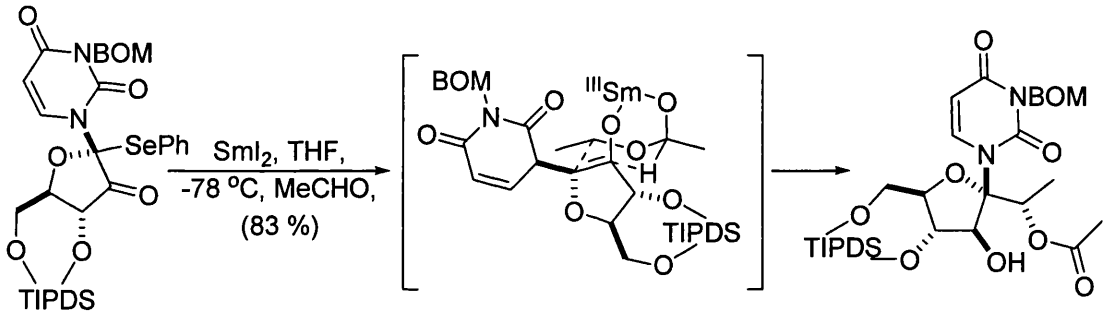


68

TIPDS = tetraisopropyldisiloxane-1,3-diyl

Scheme 1.45

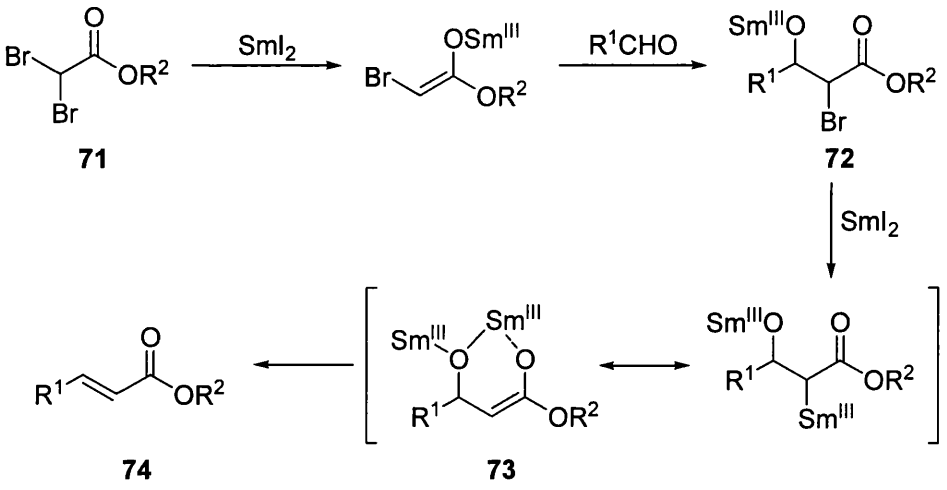
In some cases the aldol product underwent a further Tischenko reaction to afford the corresponding *anti*-1,3-diol monoesters through a chelation-controlled pathway. This SmI_2-promoted tandem aldol-Tischenko reaction of 2'-keto nucleoside **69** gives the 1'-branched nucleoside **70**. These "arabino-type" nucleosides are biologically important as a number of them have shown potent antitumor and/or antiviral effects (scheme 1.46).



69 **70**

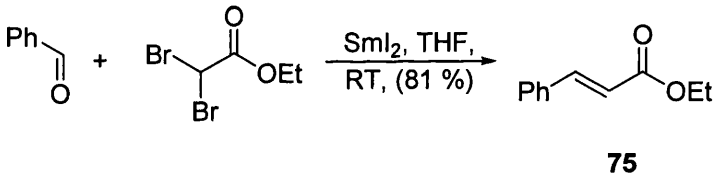
Scheme 1.46

Recently, Concellón and co-workers have reported a stereoselective method for the formation of (*E*)-α,β-unsaturated esters via a sequential aldol reaction followed by a subsequent elimination reaction.[75] Dibromoacetate **71** reacts with a number of different aldehydes to form samarium alkoxide **72** which undergoes two single-electron transfers to give samarium(III) enolate intermediate **73**. Collapse of the enolate and β-elimination affords the (*E*)-α,β-unsaturated esters **74** (scheme 1.47).



Scheme 1.47

Concellón attempted the transformation using various aldehydes all with ethyl or methyl dibromoacetate. The best result came from the reaction of ethyl dibromoacetate with benzaldehyde which proceeded in good yield to give solely the (*E*)-α,β-unsaturated ester **75** (scheme 1.48).

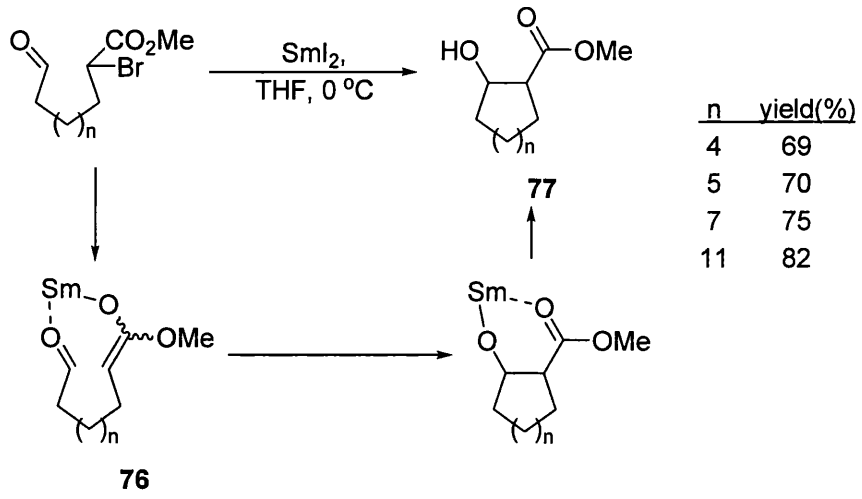


Scheme 1.48

1.8 Reformatsky-type reactions

Kagan *et al* documented the use of samarium for modified Reformatsky reactions in their seminal paper in 1980,[2] and in the mid 1980's Inanaga reported the construction of medium and large ring lactones through a SmI_2-mediated intramolecular Reformatsky reaction.[76] In 1991, Inanaga then developed a general synthesis for both medium and large-sized carbocycles by means of the Reformatsky reaction.[77] The mechanism goes through samarium(III) enolate intermediate **76** following two single-electron transfers from samarium to the carbonyl (scheme 1.49). The final coupling step, believed to be aided by

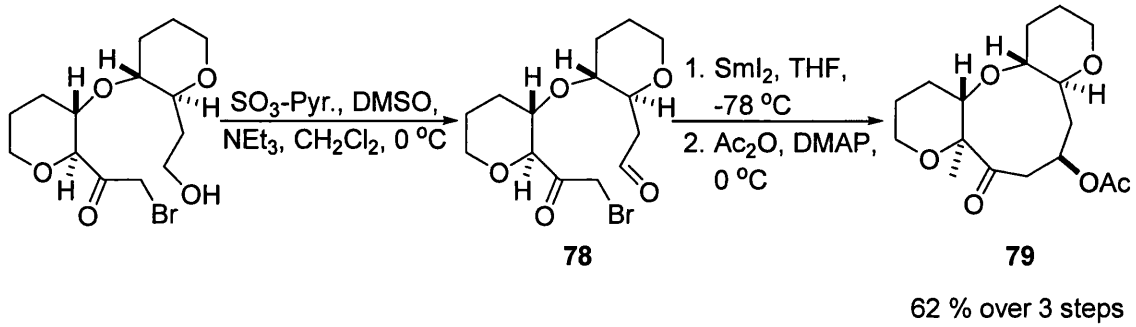
the large ionic radius, flexible co-ordination and high oxophilicity of samarium, gives carbocycle **77** after work up.



n	yield(%)
4	69
5	70
7	75
11	82

Scheme 1.49

The SmI_2-mediated Reformatsky reaction has since been used as a key ring forming step in the synthesis of a number of natural products and their precursors. In 1997, Tachibana and co-workers reported its use in the formation of the fused oxonene ring F of ciguatoxin.[78] Structure **78**, bearing a number of ether linkages as well as aldehyde and α-bromoketone moieties, undergoes the intramolecular SmI_2-promoted Reformatsky reaction to give **79**. The yield is given for three steps, namely an oxidation, Reformatsky cyclisation followed by acetylation of the secondary alcohol (scheme 1.50).

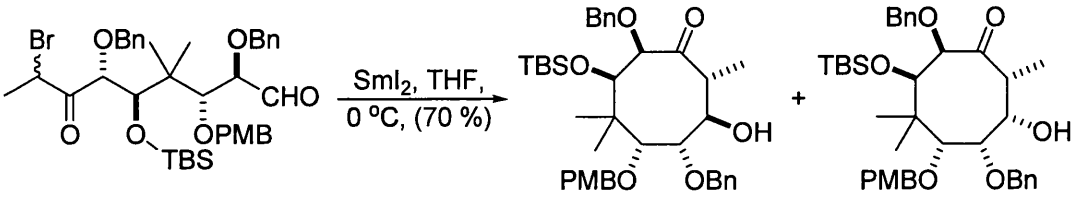


78 **79**

62 % over 3 steps

Scheme 1.50

In the late 1990's, Mukaiyama *et al.* used this transformation in the stereocontrolled synthesis of the B ring in Taxol.[79, 80] α-Bromoketo aldehyde **80** was treated with SmI_2 and the cyclisation proceeded efficiently to give the eight-membered B ring in high yield with good stereoselectivity as a mixture of aldol products at the β-carbon (scheme 1.51).

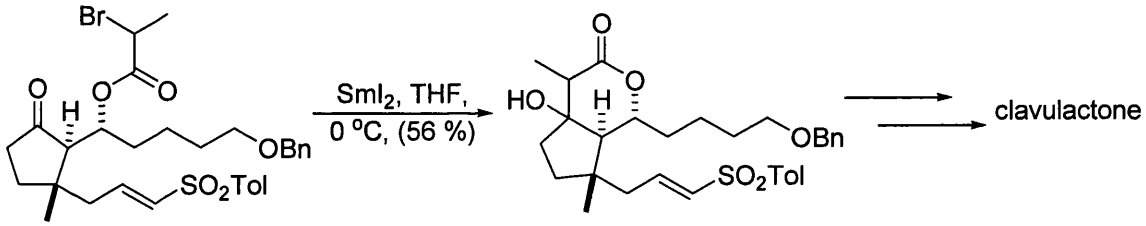


80

17 : 83

Scheme 1.51

More recently, Xu and co-workers have utilised this reaction to form a six-membered ring during model studies on the total synthesis of clavulactone.[81] Treatment of bromopropionate **81** with SmI_2 gave cyclised product **82** in modest yield (scheme 1.52). Xu found that SmI_2, was superior to other reagents such as aluminium and activated zinc.

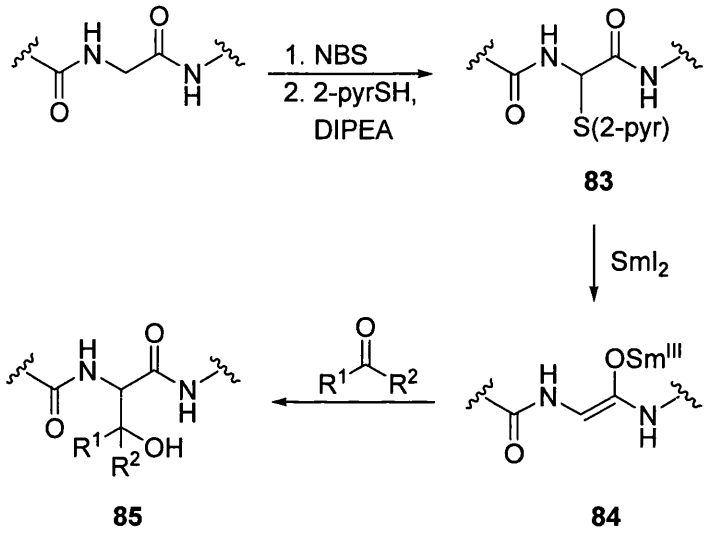


81 **82**

Scheme 1.52

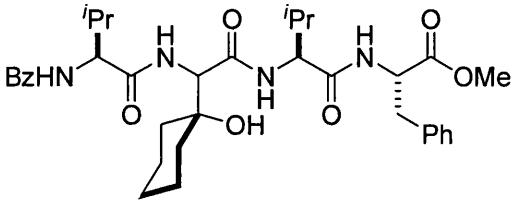
In 2000, Skrydstrup *et al.* presented a mild and simple method for the selective introduction of carbinol side chains onto glycine residues in peptides and showed its potential as a route for the preparation of peptide libraries.[82] A series of polypeptides were prepared according to a modified Reformatsky-type reaction (scheme 1.53), where treatment of a peptide backbone with *N*-bromosuccinimide followed by sulfide formation yielded α-sulfanyl amides **83**. These were then reduced at room temperature using SmI_2, to give a

samarium(III) enolate intermediate **84**. The enolate was then quenched with different aldehydes and ketones to give functionalised peptides **85**.

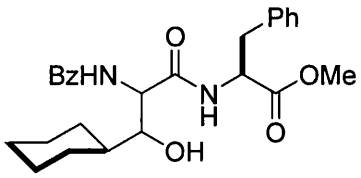


Scheme 1.53

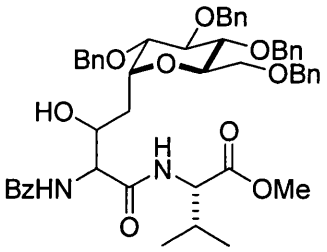
The low basicity of alkyl lanthanide species as well as the strong complexing abilities of lanthanide(III) ions to oxygen led Skrydstrup to use SmI_2 as the reducing agent. The use of strong bases to deprotonate a glycine residue could have led to competitive deprotonation of the amide protons and the method would have depended upon the stability of the intermediate enolate species and its ability to avoid protonation either inter- or intramolecularly. This is another demonstration of the mild and chemoselective nature of SmI_2. A selection of peptides prepared via this methodology is illustrated below (figure 1.8).



54 %, 1.2 : 1



60 %, 4 diast.

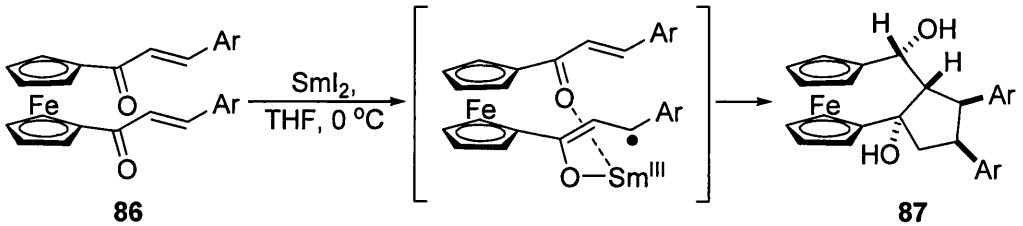


46 %, 4 diast.

Figure 1.8

1.9 Samarium(II) iodide-mediated coupling reactions

Fang and co-workers have reported the SmI_2-mediated reductive cyclisations of 1,1'-dicinnamoylferrocenes to give the corresponding [3]-ferrocenophane diol.[83] The reaction utilises SmI_2 to effect the intramolecular coupling, aldol reaction and reduction in a one-pot operation. The reaction pathway arises through a samarium chelated transition state having both *s-cis* and (*Z*)-enolate character. In the best example, **86** undergoes the transformation with SmI_2 to give diol **87** in good yield and with good selectivity (scheme 1.54).



86

Ar = -C_6H_4OMe

87

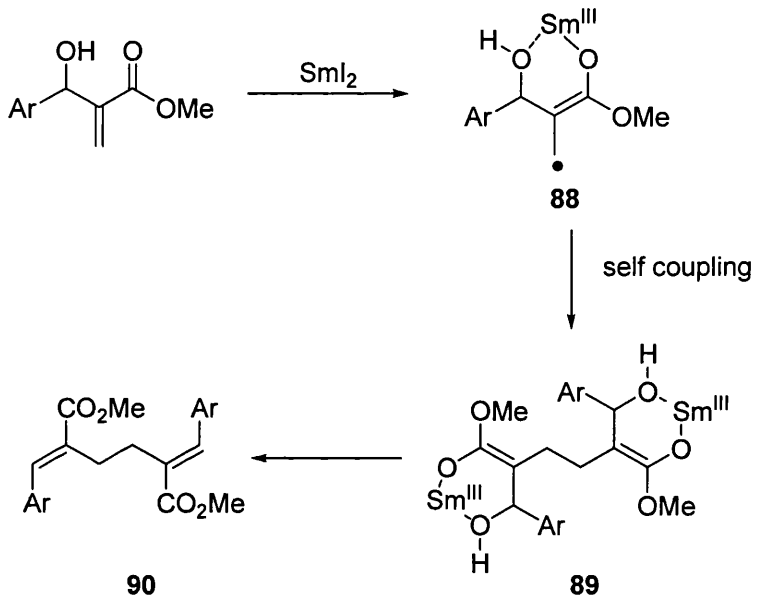
major isomer

97 % yield

ratio of isomers (86 : 14)

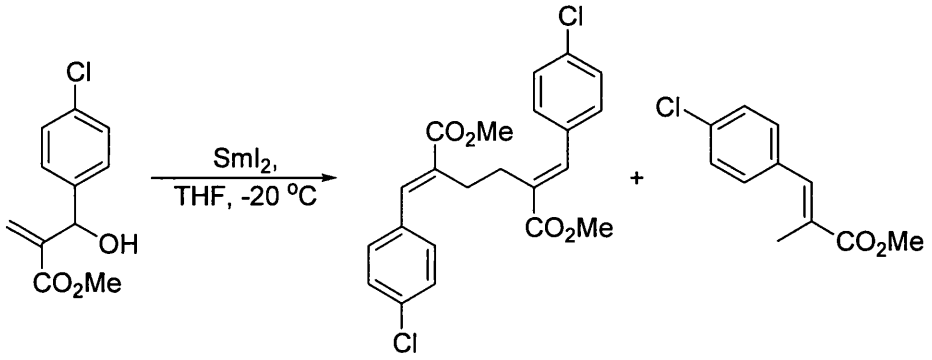
Scheme 1.54

Recently, Zhang and co-workers have documented a facile synthesis of trisubstituted alkenes via a SmI_2-mediated coupling of two identical Baylis-Hillman substrates.[84] The reaction proceeds initially through a single electron transfer to furnish a samarium(III) enolate intermediate **88** which then undergoes a radical coupling of one samarium species to another to give **89**. This collapses to form diene **90** (scheme 1.55).



Scheme 1.55

The reaction is highly temperature dependant however. An example of the transformation is outlined in scheme 1.56, which proceeded at - 20 °C to give aromatic diene **91** in 92 % yield, with 7 % of the trisubstituted alkene **92**. When the reaction was attempted under reflux conditions though, only 11 % of the desired diene was observed with 83 % of the trisubstituted alkene being isolated. In all cases, total (*E*)-selectivity was observed.

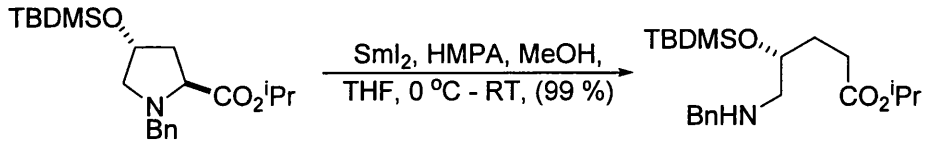


Temp.	**91** (%)	**92**(%)
-20 °C	92	7
reflux	11	83

Scheme 1.56

1.10 Reductive deamination

In 1999, Honda *et al.* published their work on the reduction of α-amino carbonyl compounds using SmI_2.[85] The initial work was done on the reduction of acyclic α-amino substituted esters. The results for the reaction were positive and Honda found that he was able to reduce primary, secondary and tertiary amines using SmI_2 with HMPA and in the presence of a proton source. He then turned his attention to cyclic systems, and in particular the reductive deamination of proline derivatives. Proline derived isopropyl ester **93** was reduced in the presence of HMPA and methanol to give acyclic ester **94** in good yield (scheme 1.57)

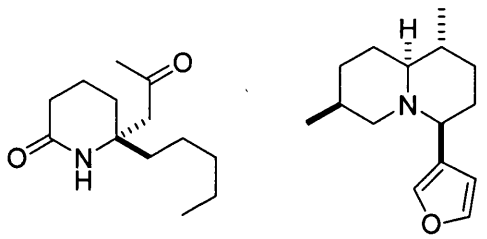


93 **94**

Scheme 1.57

Honda has applied his reductive deamination in the synthesis of a number of naturally occurring alkaloids. Illustrated in figure 1.9 are two examples. He has reported a concise enantioselective synthesis of (-)-adalinine **95**, a coccinellied alkaloid, citing a regioselective

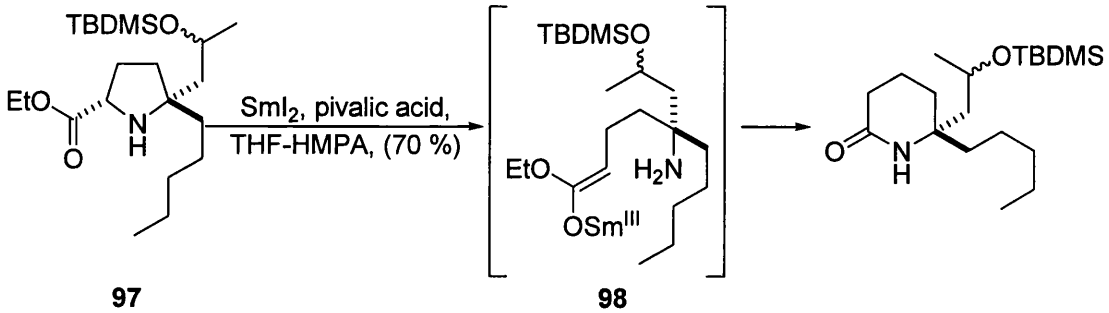
samarium-mediated carbon-nitrogen bond cleavage as well as a stereoselective Michael addition as key steps.[86] (-)-Deoxynupharidine **96** has been shown to exhibited an immunosuppressive effect as well as a central paralysis effect and weak anti-metastic activity.[87] Once again, a reductive carbon-nitrogen bond cleavage is one of the key steps in Honda's synthesis of this target.



95 **96**

Figure 1.9

As stated above, one of the key steps in the synthesis of both these natural products is a regioselective samarium-mediated carbon-nitrogen bond cleavage. Honda has utilised the reduction of α-heterosubstituted carbonyls, in this case the reduction of an α-amino ester, to gain access to the δ-lactam motif. Treatment of **97** with SmI_2 in the presence of pivalic acid leads to samarium(III) enolate intermediate **98** (scheme 1.58). **98** then undergoes cyclative ring closure to yield the protected precursor to (-)-adalinine **95**.[86]



97 **98**

Scheme 1.58

1.11 Conclusions

Throughout the course of this introduction, the formation of samarium(III) enolates and their synthetic utility has been outlined. There is a vast amount in the literature concerning samarium(III) enolates and their reactivity, and the aim of this introduction was to provide an overview of the area. The next two chapters will be concerned with work undertaken over the last three years, firstly towards a samarium-mediated cleavage strategy for phase-tag assisted synthesis, and then the development of an asymmetric approach where asymmetry is introduced in the cleavage step through enantioselective protonation of a samarium(III) enolate.

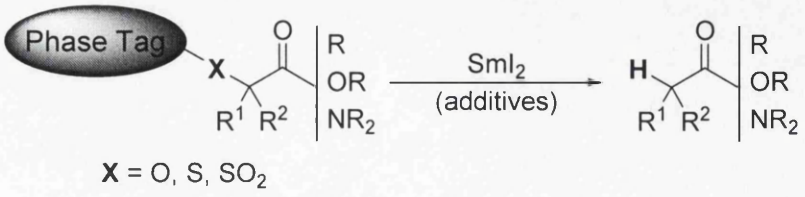
Chapter 2: New applications of a linker system cleaved using samarium(II) iodide

2.1 Linker systems

Phase tags have been used to assist the synthesis of molecules for over fifty years; firstly in peptide synthesis[88, 89], then for small molecule synthesis[90] and finally in nucleotide and oligosaccharide synthesis.[91] Since its introduction, a large number of transformations have been performed on substrates bound to resin with varying results.[92] Critical to the success of any phase-tag assisted synthesis is the linker design.

The linker can be described as a structural motif which temporarily joins the support, be it polymeric, fluorous, etc., and the substrate under manipulation. The two main requirements for a good linker are that ideally it should allow facile attachment and cleavage, and secondly it should not be adversely affected by any chemistry used to modify or extend the attached compound.

One of the drawbacks of some early linkers was that, having undergone the final cleavage step, there remained an undesirable indication of the site of attachment. On occasion an additional step was necessary in order to remove the unwanted functional group. As a result, many later linkers are termed 'traceless', the best definition of this being when an aromatic or aliphatic proton is introduced at the point of cleavage.[93] My studies have been concerned with the development of traceless linkers utilising an ether or sulfur link at the position α-to a carbonyl group which are cleaved using SmI_2 (scheme 2.1).

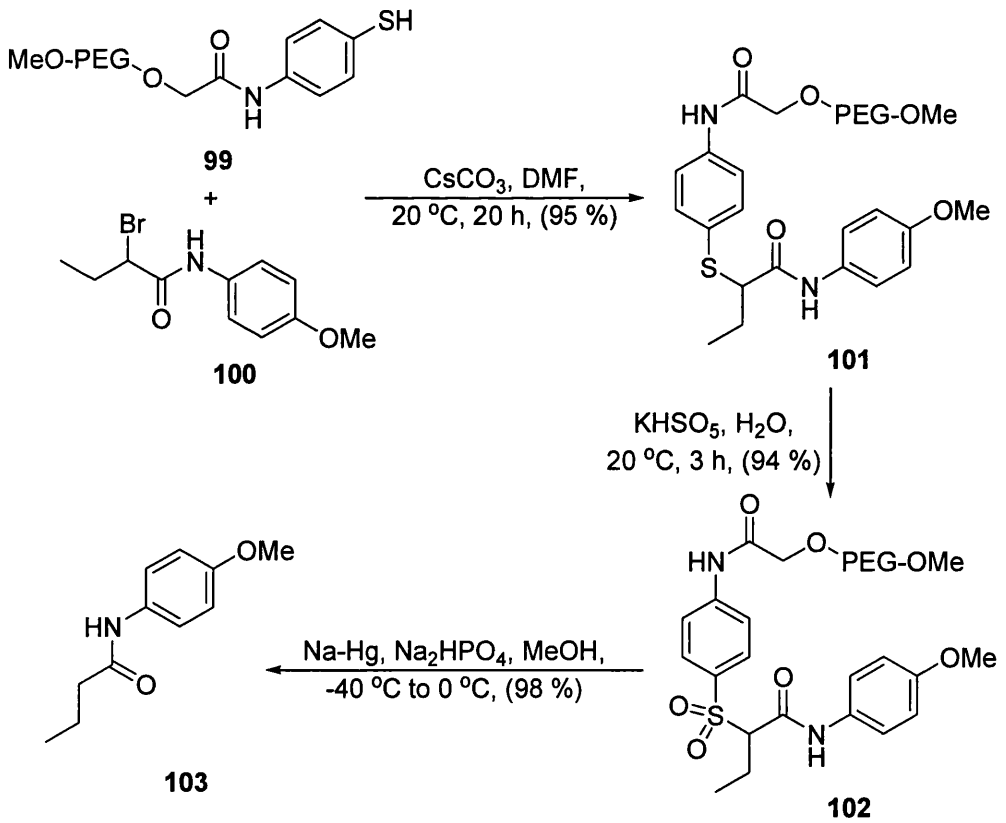


Scheme 2.1

In recent years within the group, a new linker strategy has been developed that has been applied in both solid phase[35-37] and fluorous phase[38] organic synthesis where the link to the phase tag is cleaved using SmI_2. We refer to this new class of linkers as α-Hetero-Atom Substituted Carbonyl (HASC) linkers and their cleavage is based on the well known reduction of α-heteroatom substituted carbonyl compounds using SmI_2.

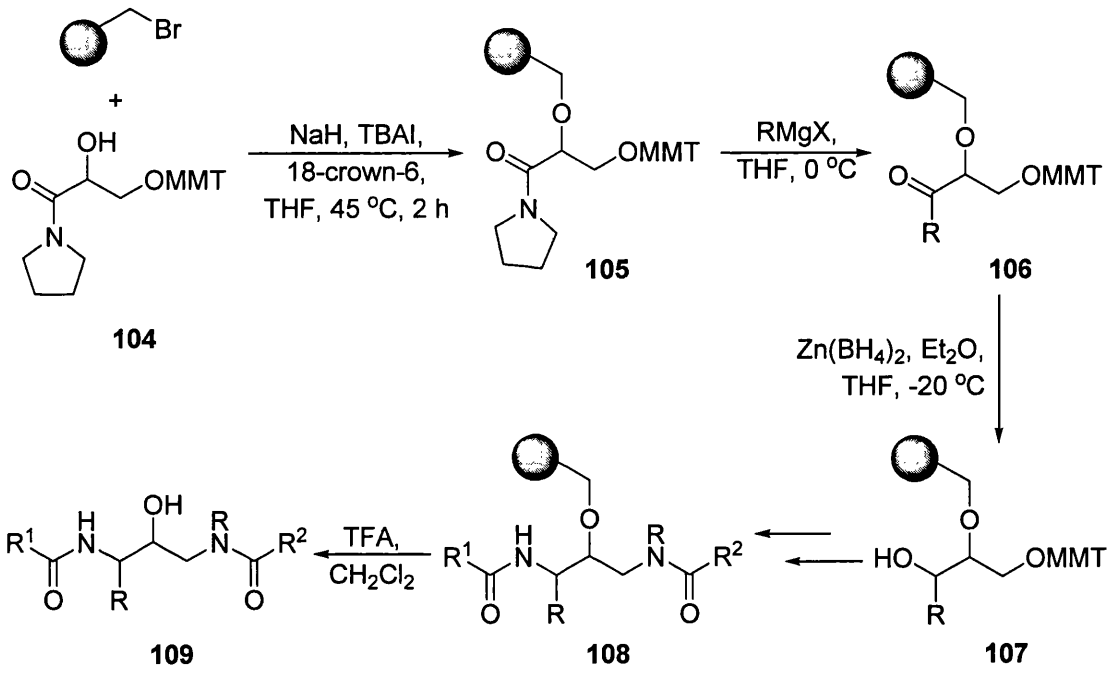
2.2 Related linker systems

In 1997, Janda and co-workers reported the cleavage of an amide from a PEG-based thiol resin linked through a sulfur heteroatom (scheme 2.2).[94] Reaction of thiol resin **99** with bromide **100** gave sulfide **101**. Oxidation to sulfone **102**, followed by reductive cleavage using a sodium amalgam gave **103**. Janda reported only one such reductive cleavage and unfortunately did not perform further modification on the supported amide before cleavage. In addition, the use of a sodium-mercury amalgam is far from ideal.



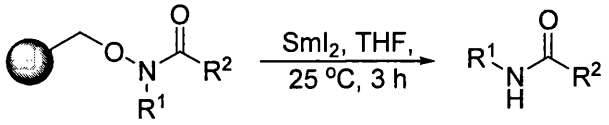
Scheme 2.2

In 1998, Ellman *et al.* reported the immobilisation of amides and ketones via an α-ether linkage.[95] He immobilised α-hydroxy amide **104** using bromo-Wang resin to give supported amide **105** (scheme 2.3). Subsequent Grignard addition to the carbonyl yielded **106**, which was then reduced to give secondary alcohol **107**. Further steps on resin were performed to modify the substrate further to afford **108**. Finally, simple cleavage of **109** from resin was executed using trifluoroacetic acid (TFA). Ellman used his methodology to produce a range of aspartyl protease inhibitors.



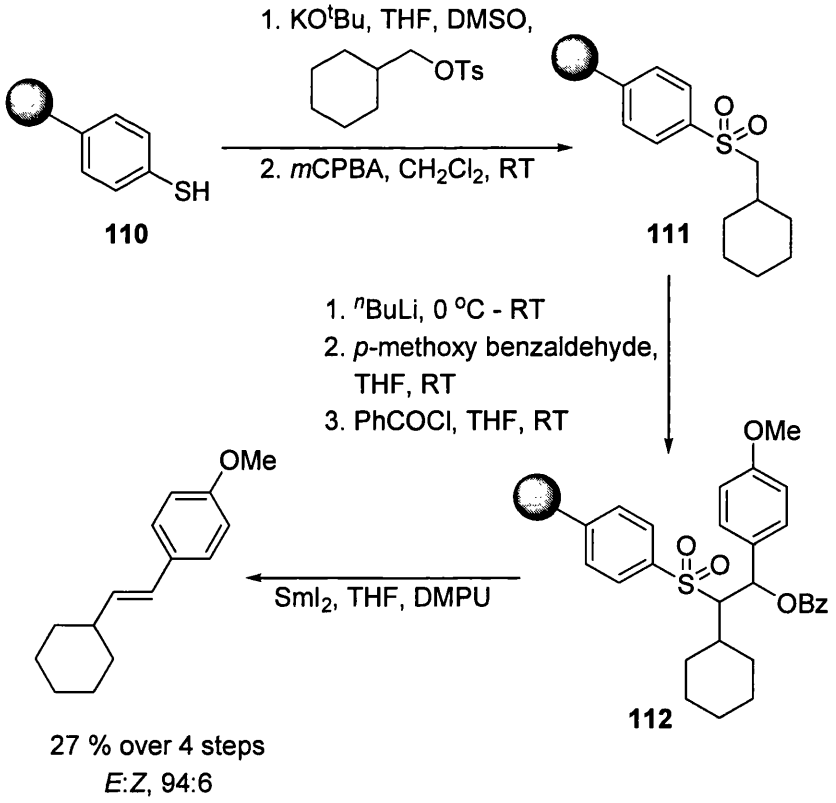
Scheme 2.3

Whilst SmI_2 had not previously been used for the cleavage of substrates from resin bound through a heteroatom α-to a carbonyl group,[35-37] the reagent has been used to selectively cleave N-O bonds to release products from a polymer backbone. In 2000, Abell and co-workers performed the reduction whilst developing a new oxime based linker for the synthesis of amides and ureas (scheme 2.4).[96]



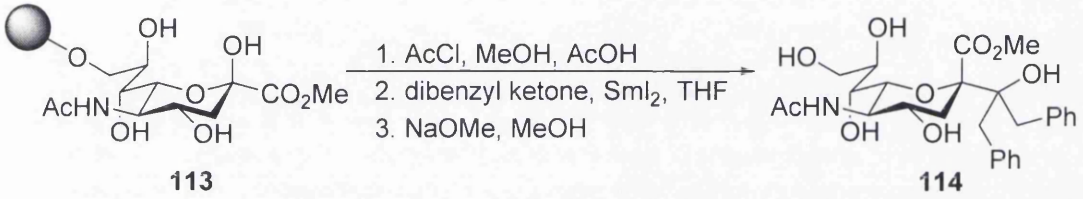
Scheme 2.4

Then, in 2003, De Clerq *et al.* reported the polymer-supported formation of carbon-carbon bonds via application of the classical Julia-Lythgoe olefination reaction.[97] Reductive elimination of β-benzoyloxysulfones using SmI_2, leads to the preferential formation of *trans* alkenes in as high as 94:6 selectivity. Thiophenol resin **110** was deprotonated and the resulting thiolate treated with a primary tosylate (scheme 2.5). Oxidation with *meta*-chloroperoxybenzoic acid (*m*CPBA) led to sulfone **111**. Following deprotonation of **111**, the α-sulfonyl carbanion reacts with benzaldehyde to give **112**. The final cleavage step uses SmI_2 as a replacement for the more traditional sodium amalgam.



Scheme 2.5

More recently in 2004, Linhardt and co-workers used the reagent in a solid phase synthesis. Instead of using SmI_2 as a cleavage reagent, Linhardt used it to mediate *C*-glycosylation on a solid support.[98] Treatment of methyl ester **113** with acetyl chloride in methanol and acetic acid yielded the neuraminic acid chloride donor. *C*-glycosylation was then carried out using SmI_2 and dibenzyl ketone before cleavage under basic conditions afforded α-*C*-glycoside **114** in 61 % yield over 5 steps (scheme 2.6).

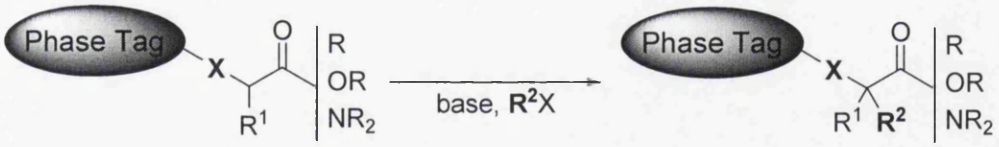


113 **114**

Scheme 2.6

2.3 Studies on an ether-based linker system

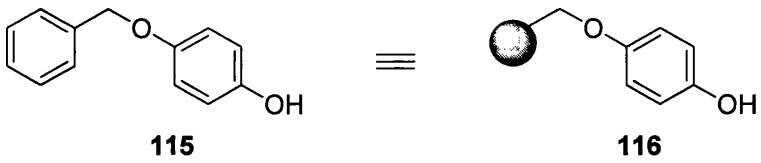
My initial goal was to develop conditions for efficient enolate alkylations at the point of attachment to the solid support using our linker system (scheme 2.7). Such an approach would allow the introduction of additional diversity and permit access to a wider range of products using the linker system.



X = O, S, SO_2

Scheme 2.7

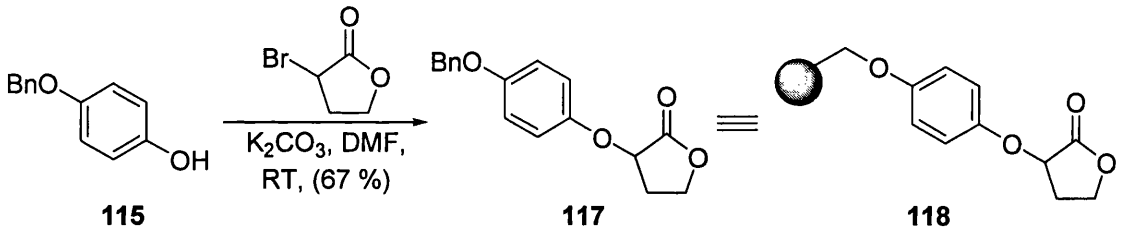
In order to evaluate the feasibility of any solid phase route, preliminary solution phase model studies are generally carried out. In our case, these involved developing the potential of one of the solid phase linker designs previously developed within the group.[35, 36] 4-Benzyloxyphenol **115** was used as an approximate model for phenol resin **116** (figure 2.1).



115 **116**

Figure 2.1

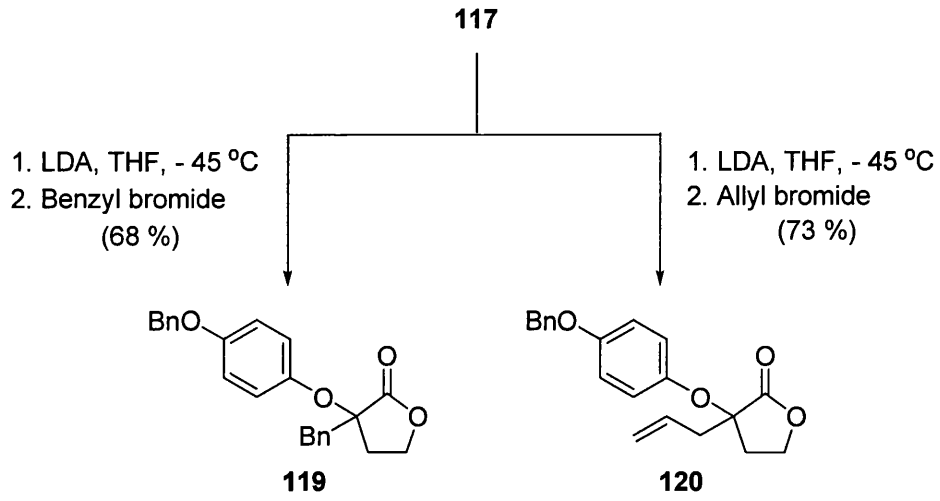
In order to begin the solution model studies we first reacted **115** with α-bromo-γ-butyrolactone in the presence of potassium carbonate. This led to the formation of **117**, our solution model for lactone **118**, immobilised through an oxygen version of our linker design (scheme 2.8).



115 **117** **118**

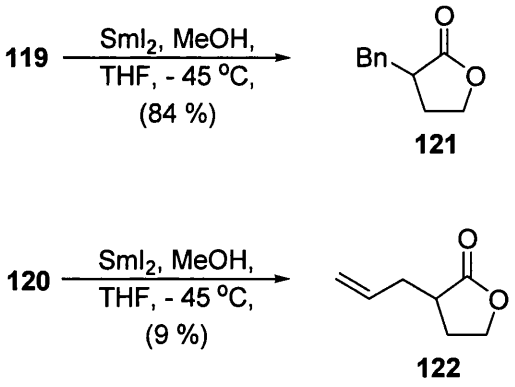
Scheme 2.8

We then began our investigation of enolate generation and alkylation. We were able to alkylate **117** using lithium diisopropylamide (LDA) at - 45 °C and either benzyl or allyl bromide to give alkylated lactones **119** and **120** in reasonable yields (scheme 2.9). Using these substrates, the feasibility of the key SmI_2 reduction could be assessed for the 'cleavage' of modified lactones.



Scheme 2.9

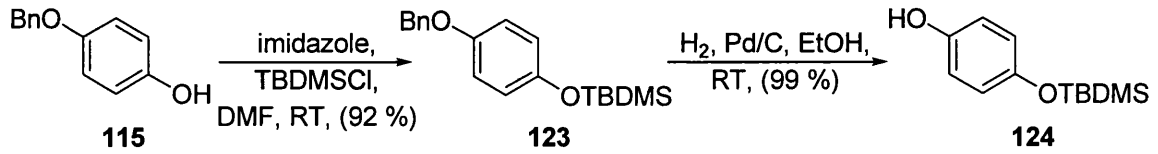
In the case of benzylated lactone **119**, it was possible to reduce off, or 'cleave', the aryloxy group using SmI_2 in THF with methanol as a co-solvent to give **121** in 84 % yield (scheme 2.10). However in the case of allylated lactone **120**, we were unable to isolate much of the desired lactone **122**. However, a quantitative yield of benzyloxyphenol was recovered which implied that the reduction proceeded well. It was assumed that **122** was lost during work up due to volatility.



Scheme 2.10

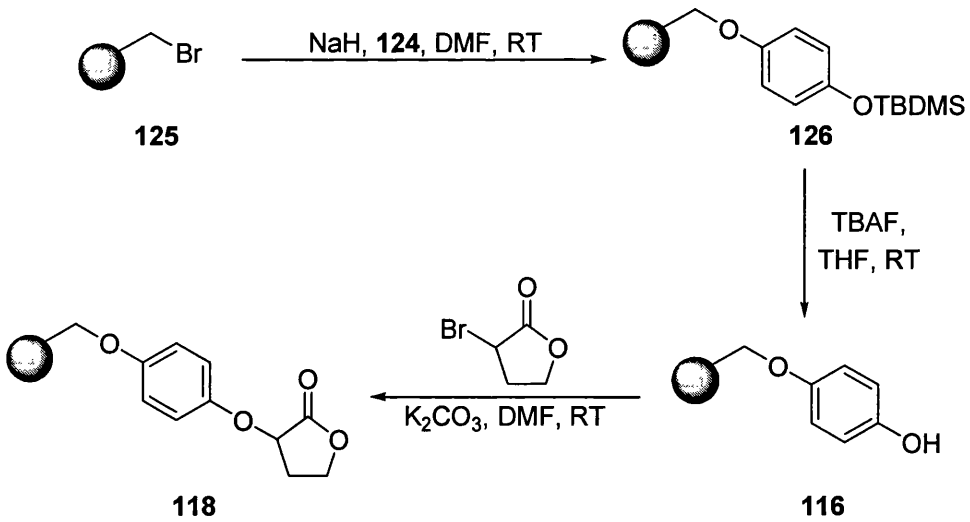
A route to prepare simple alkylated lactones, using our linker, therefore appeared feasible. The next step was to transfer the solution studies onto solid phase.

In order to apply this route on solid phase, phenol resin **116** was prepared using a route previously developed within the group.[35, 36] Benzyloxyphenol **115** was treated first with imidazole and TBDMSCl to protect the free phenol giving **123** in good yield. This was followed by selective deprotection of the benzyl group to give **124** (scheme 2.11).



Scheme 2.11

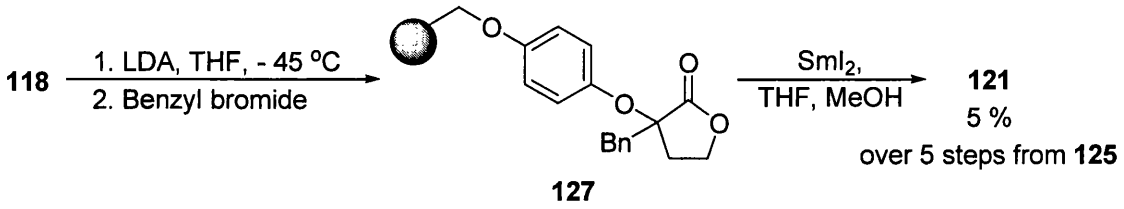
The next step in the process involved the immobilisation of **124** using commercially available bromo-Wang resin **125**. Treatment of **124** with sodium hydride in the presence of **125** afforded protected resin **126**. Simple deprotection using TBAF gave the immobilised phenol **116**. Immobilisation of α-bromo-γ-butyrolactone was achieved by stirring with phenol resin **116** and potassium carbonate. Lactone **118**, immobilised using our linker system, displayed a characteristic carbonyl IR stretch at 1788 cm^{-1} (scheme 2.12).



Scheme 2.12

We were now in a position to attempt the potentially difficult deprotonation and alkylation of the immobilised lactone using LDA and suitable carbon electrophiles. The first attempts

at alkylation to give the benzylated lactone **127** were assessed by subsequent cleavage with SmI_2 in exactly the same manner as in the solution studies (scheme 2.13). This method provided us with only a trace amount of the desired lactone **121** in less than 5 % overall yield for the five step sequence. Despite the fact that our initial studies proved disappointing, we believed our problem lay chiefly in not knowing whether it was the alkylation or cleavage step that was not proceeding efficiently.



Scheme 2.13

In solution, the alkylation conditions had to be optimised carefully. It was therefore expected that completing this step on resin would also be difficult. To optimise the reaction, an effective way to monitor the alkylation step was required. It was decided to take advantage of the Wang-based support and its ability to be cleaved at a point remote from the lactone through the use of TFA (figure 2.2). This would allow us to assess whether or not alkylation was occurring, and if so, to what extent, thus determining whether the problem with the overall sequence was arising through the alkylation or cleavage step.

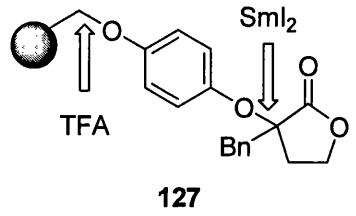
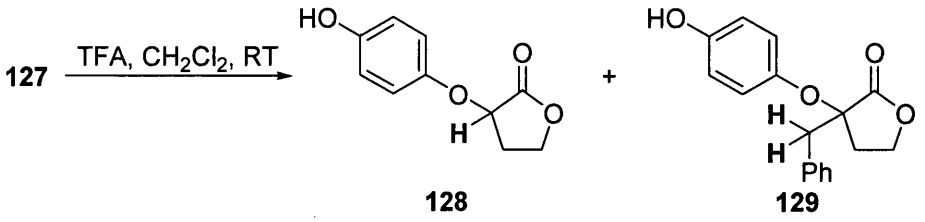


Figure 2.2

Cleavage of the linker using TFA would also circumvent any problems associated with the volatility of the cleavage product. The TFA cleavage also involved a simple work up procedure. The resin could be cleaved, filtered, and washed using dichloromethane before

concentration. The crude ^1H NMR spectrum allowed us to then assess the extent of alkylation by simply comparing the ratio of protons from the unalkylated lactone **128** and the alkylated lactone **129** (scheme 2.14).



128 **129**

Scheme 2.14

Entry	Temp. (°C)	T_1 (h)	T_2 (h)	eq. LDA	**128 : 129**
1	- 45 °C to - 20 °C	0.5	1.5	3	4 : 1
2	- 45 °C to - 20 °C	0.5	1.5	8	3 : 1
3	- 45 °C to - 20 °C	1.0	4.5	3	5 : 1
4	- 45 °C to - 20 °C	1.0	4.5	8	> 33 : 1

T_1 : Time for enolate formation

T_2 : Time allowed for stirring with benzyl bromide

Table 2.1

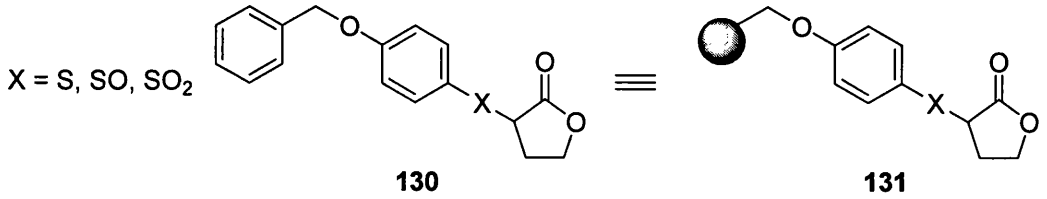
From table 2.1 it can be seen that the alkylation was proceeding, although even in the best case (table 2.1, entry 2), the reaction only went about 25 %. It can be deduced from the table that allowing a longer period for the formation of the enolate (T_1) does not have a desirable effect on the reaction. Similarly, using eight equivalents of LDA did not improve the reaction; indeed over a prolonged period of stirring with benzyl bromide it would appear to have had an adverse effect. It should also be noted that following TFA cleavage from the resin, the IR spectrum of the recovered resin showed no carbonyl stretches which indicated that all immobilised lactone, both alkylated and unalkylated was being cleaved from the resin.

Another major problem encountered with this reaction and its transferral onto solid phase was the difficulty involved in the addition of a pre-swollen polymer to a solution of LDA under an inert atmosphere. It was therefore assumed that the alkylation, rather than the cleavage, was problematic.

To summarise, a solid phase route to simple lactones has been developed using our linker system. Solid phase alkylation and cleavage of benzylated lactone **121** was achieved following a successful solution phase model study. Whilst the yield of **121** (5 % from a five step sequence) was disappointing, we had made progress and this led us to next explore an analogous linker system that would make the alkylation step more straightforward.

2.4 Studies on a sulfone-based linker system

Other members of the group have had success using sulfur as the heteroatom link α-to a carbonyl group.[37] The advantages of using a sulfide linker lie in the ability to adjust the oxidation state of the linking sulfur atom. The different sulfide oxidation states allow different types of process to be carried out. For example, in the case of the oxygen linker, a strong base such as LDA was required to form the lithium enolate that was subsequently quenched with the alkyl bromide. It was felt that the higher oxidation states of the linking sulfur atom would allow alkylation to be carried out using milder bases under more solid-phase-compatible conditions. The next logical step for us was to construct compounds of generic structure **130** as mimics of the corresponding immobilised lactones **131** (figure 2.3).

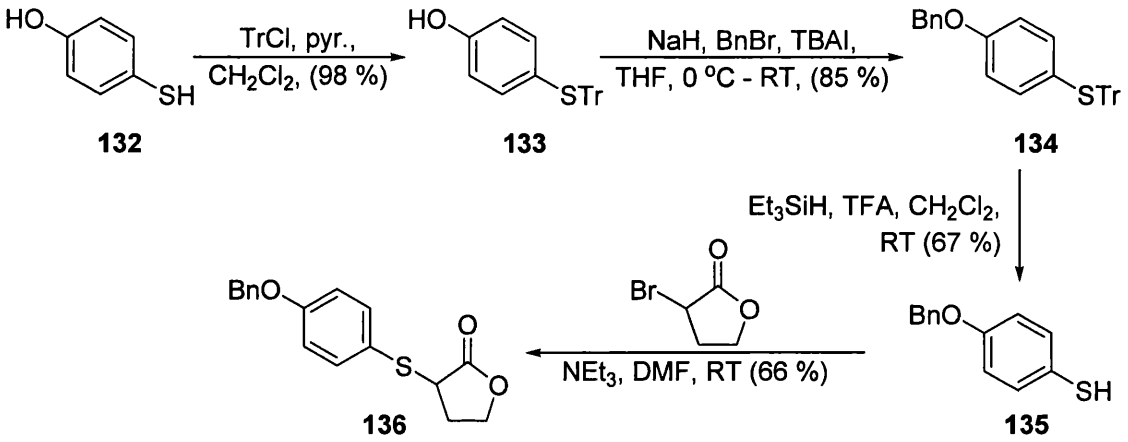


130 **131**

Figure 2.3

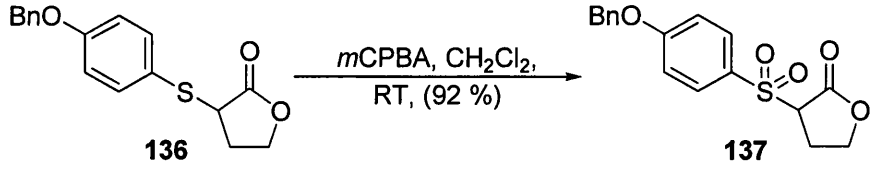
The proton at the α-position in the sulfoxide and sulfone is more acidic. Deprotonation at the α-position can therefore be achieved more easily with a weaker base and should not require the use of harsher, more basic conditions.

Once again, our studies began with a solution phase model system. Using the procedure of Routledge *et al*,[99] commercially available 4-mercaptophenol **132** was protected using trityl chloride and pyridine to give **133** in good yield (scheme 2.15). The free phenol was then protected as a benzyl ether using sodium hydride and benzyl bromide to give **134**. Removal of the trityl group with TFA afforded thiol **135**. Finally, treatment of **135** with triethylamine and α-bromo-γ-butyrolactone led to **136**, the solution model for a lactone immobilised through a sulfur version of our linker.



Scheme 2.15

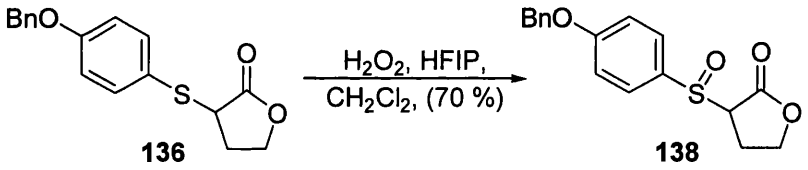
Oxidation of sulfide **136** using *m*CPBA led to sulfone **137** in an excellent 92 % yield (scheme 2.16).



Scheme 2.16

We also examined the transformation of sulfide **136** to the corresponding sulfoxide. Many of the existing methods for this transformation require careful control of the stoichiometry of the oxidant to prevent over-oxidation to sulfone **137**. This is extremely difficult to achieve on resin. In addition to this, the oxidation must also take place in a solvent that is compatible with polymers. Many conventional methods for sulfoxidation, such as the use of $NaIO_4$, require polar solvents such as methanol. As such solvents cause the resin to shrink and contract, this would result in a slow, inefficient reaction.

We accomplished the transformation using the conditions originally developed by Bégué *et al*, namely H_2O_2/HFIP (scheme 2.17).[100] Selective oxidation of **136** to sulfoxide **138** was thus achieved using solid phase compatible conditions without over-oxidation to the sulfone.

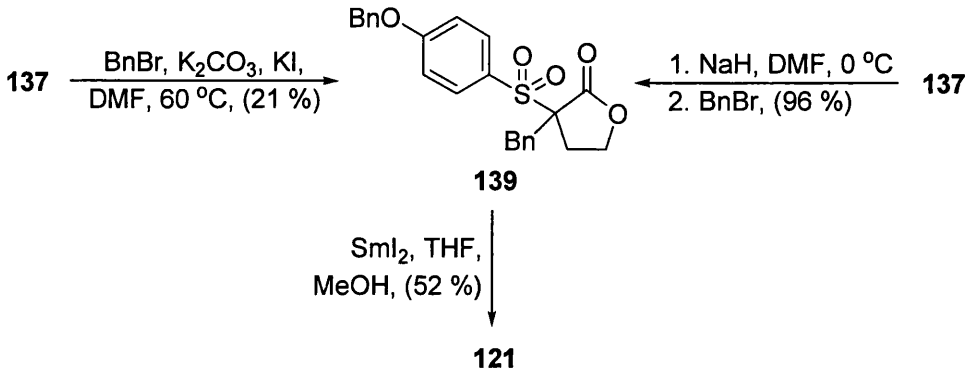


Scheme 2.17

The rate of the oxidation of sulfur by H_2O_2 is rapid and depends on the nucleophilicity of the sulfur atom. Over oxidation can be prevented through the use of hexfluoroisopropanol (HFIP) as co-solvent. It has been proposed that HFIP has two roles to play in the reaction mechanism. Firstly, it is thought to accelerate the sulfoxidation step by forming a hydrogen bond to the H_2O_2, thus activating the hydroxyl leaving group. Following this initial oxidation, HFIP then prevents over-oxidation to the sulfone by forming a strong hydrogen bond to the oxygen of the sulfoxide, thus decreasing the nucleophilicity of the sulfur atom and preventing it from reacting further with the H_2O_2.[100]

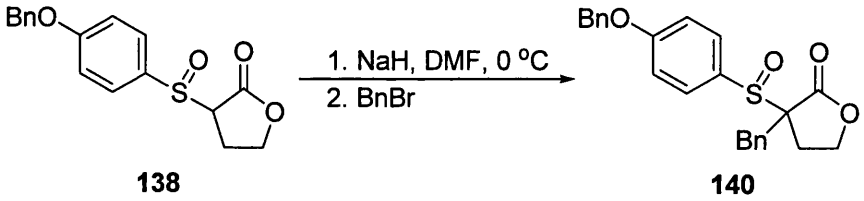
Initially, alkylation of **137** was carried out using potassium carbonate as the base and benzyl bromide (scheme 2.18). However, despite heating the reaction to 60 °C, we never obtained more than 21 % yield of benzylated lactone **139** with no starting material **137** recovered. When we switched to using sodium hydride as the base, the yield improved

greatly to 96 %.[101] Whilst the yield itself was good, we had concerns that the use of sodium hydride would not be ideal for use on solid phase with a sulfone linker. Subsequent 'cleavage' of **139** with SmI_2 proceeded well with the 'cleavage' product **121** being formed in a reasonable, unoptimised yield.



Scheme 2.18

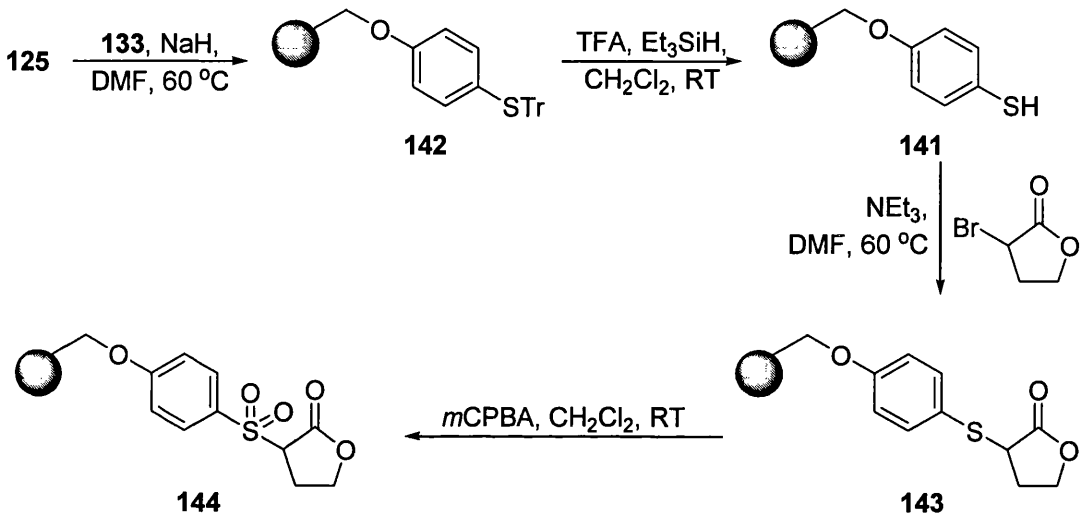
Alkylation of sulfoxide **138** using sodium hydride led to desired sulfoxide **140** by crude ^1H NMR analysis, though the reaction was never clean (scheme 2.19). Due to the diastereomeric nature of both starting material and desired product, isolation of **140** proved problematic and was never achieved.



Scheme 2.19

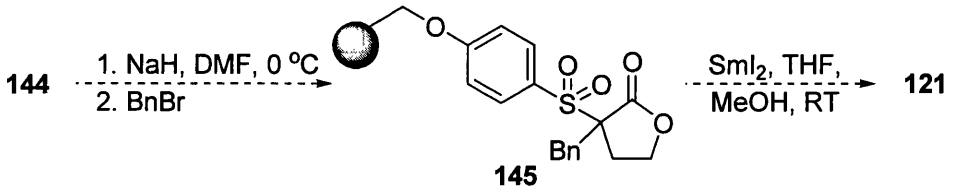
Thiol resin **141**, previously described by Routledge, was prepared from bromo-Wang resin **125** and **133** in two steps (scheme 2.20).[99] Treatment of **133** with sodium hydride and heating in DMF with bromo-Wang resin gave trityl-protected thiol resin **142**. Deprotection was achieved using TFA and triethyl silane to remove the trityl group and give thiol **141** which showed an S-H band in the IR spectrum at 2599 cm^{-1}. The use of triethyl silane with TFA is reported as acting as a carbocation scavenger in the acidic deblocking of protecting

groups in peptide synthesis and is performing a similar role in this transformation.[102] **141** was then reacted with triethylamine and α-bromo-γ-butyrolactone to give immobilised lactone **143**. The success of the immobilisation step was monitored by IR – the product showing a strong carbonyl stretch at 1787 cm^{-1}. Finally, oxidation of **143** to sulfone **144** was achieved using *m*CPBA.



Scheme 2.20

The final two steps in the solid phase synthesis were the alkylation and subsequent cleavage reaction (scheme 2.21). Despite attempting these two steps numerous times, using different conditions, we were never able to isolate any of desired lactone **121** from resin **145**.



Scheme 2.21

In the case of the sulfur linker, we believe the problem may be less to do with the chemistry used to modify the substrate and more to do with the nature of the linker itself. In order to remove the trityl protecting group, Routledge reports the use of a strong acid such as

TFA.[99] As mentioned in the previous section, TFA was used to cleave the Wang resin at a point remote from the substrate (chapter 2.3). It seems possible that we were removing at least some of linking unit from the support during the deprotection step.

2.5 Application of the HASC linker system in a synthesis of azepinones

Azepinones are a common motif found in a number of natural products, drugs and their precursors. Illustrated in figure 2.4 are three such structures. Azepinone **146** has been targeted and synthesised as a potential treatment for inflammatory diseases,[103] whilst in structure **147** the azepinone motif is being used as a conformational constraint in the design of κ-opioid receptor agonists.[104] Another example is Bengamide E **148**, a naturally occurring azepinone isolated from a marine sponge from the genus *Japus*.[105] This class of azepinone has shown a useful array of biological activity, and **148** has shown particular activity towards a human breast carcinoma cell line as well as significant anti-proliferative effects. In order to evaluate our linker system further, we decided to undertake the solid phase synthesis of a small library of functionalised azepinones using our technology.

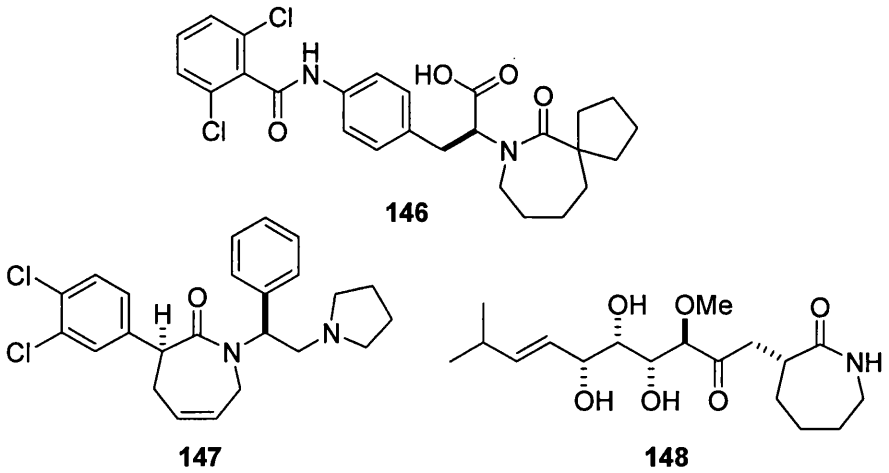
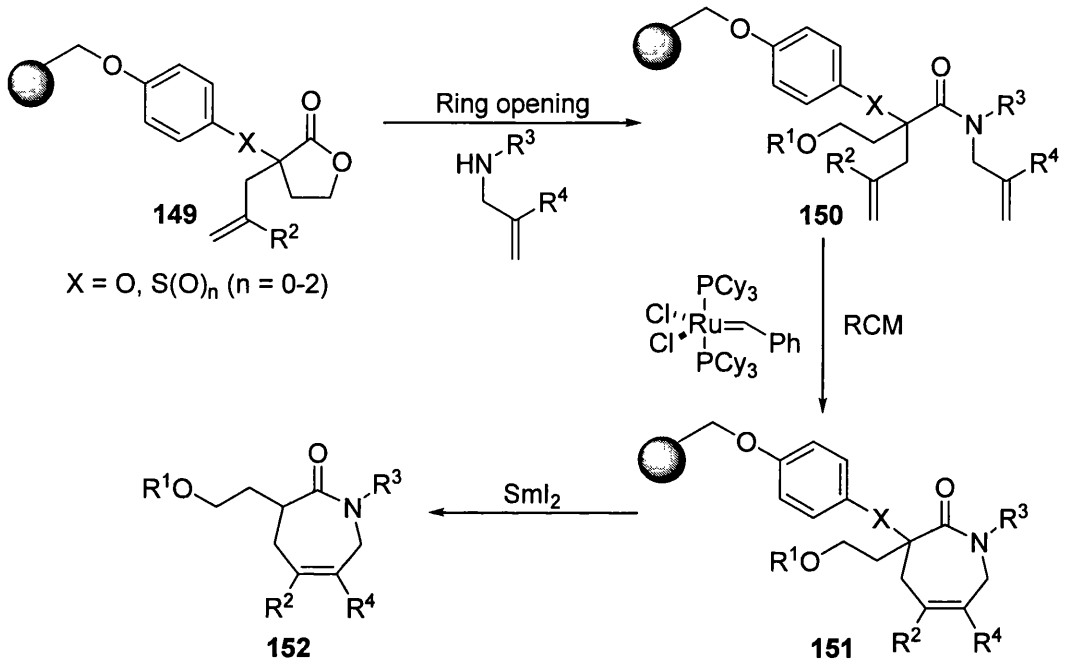


Figure 2.4

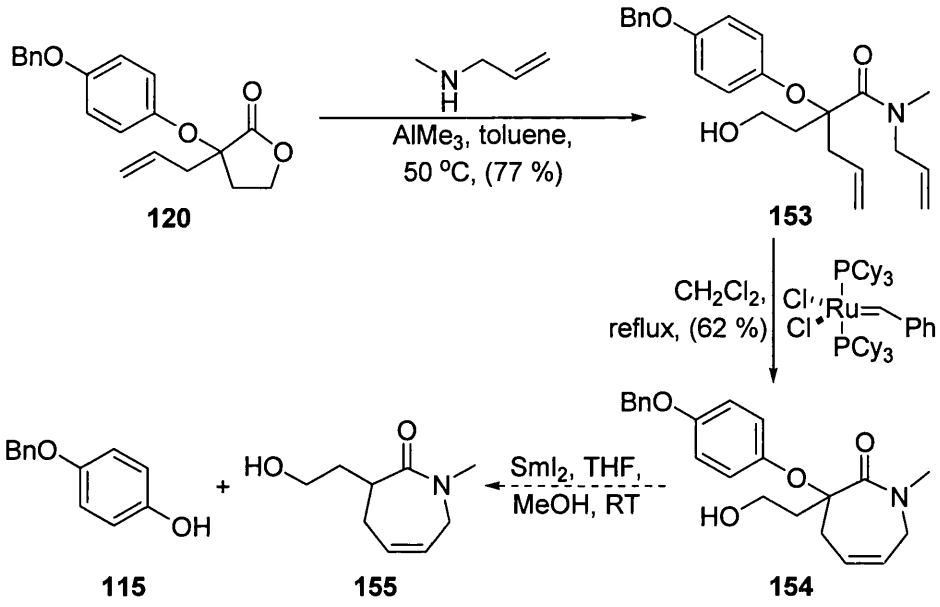
Our projected route to azepinones began with the opening of an allylated lactone **149** with an allyl amine to give **150**, the amide precursor for ring closing metathesis (RCM). RCM

on this substrate would yield lactam **151** which could then be treated with SmI_2, thus releasing the modified azepinone **152** from the polymer backbone (scheme 2.22).



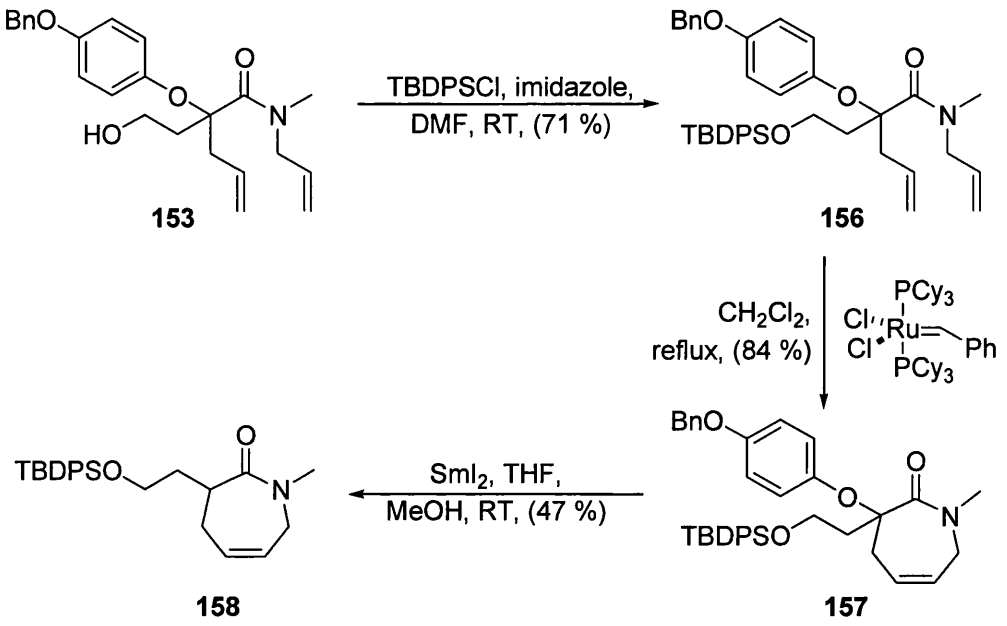
Scheme 2.22

Once again, our studies began by looking at a solution phase model system. Initially a route to a simple lactam starting from five-membered lactone **120** bearing an α-ether link was explored. The first step was ring opening of allylated lactone **120** (scheme 2.23). **120** was treated with trimethyl aluminium and *N*-methylallylamine in hot toluene to give **153** in good yield. Diallyl amide **153** underwent RCM readily with Grubbs' first generation catalyst in reasonable yield to afford lactam **154**. The final step in the sequence was once again a cleavage step using SmI_2. 'Cleavage' of lactam **154** appeared to proceed well according to TLC, however, upon work up none of desired product **155** was apparent in the crude ^1H NMR spectrum, despite there being an almost quantitative amount of **115**.



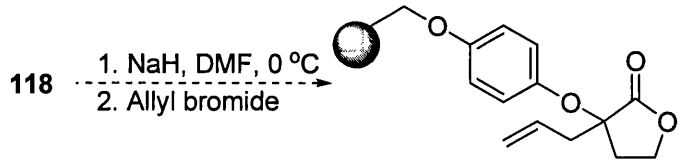
Scheme 2.23

This, we postulated, was a problem arising from **155** being lost during the aqueous work up. In order to circumvent this problem the synthetic route was amended slightly by having an additional step to protect the primary hydroxyl as a silyl ether (scheme 2.24). Diallyl amide **153** bearing the primary hydroxyl group was protected using TBDPSCl and imidazole in 71 % yield to give protected amide **156**. This then underwent RCM using Grubbs' first generation catalyst to give lactam **157**. The final reductive step using SmI_2 and methanol as a co-solvent proceeded to give **158** in moderate yield, though this step was not optimised.



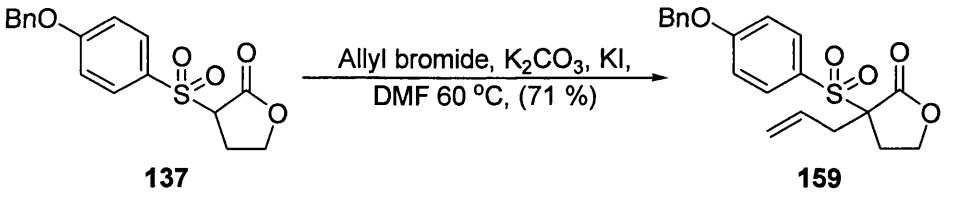
Scheme 2.24

Confident that a viable route to azepinones had been developed, the proposed route was then transferred to solid phase (scheme 2.25). As discussed in section 2.3, difficulties were immediately encountered in the alkylation of immobilised lactone **118**.



Scheme 2.25

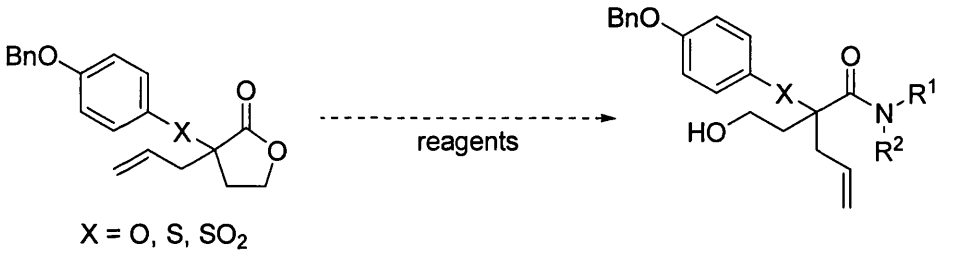
Our attention turned once again to the use of an analogous sulfur linker. It was felt that this might lead to a more facile method for allylation with the linking sulfur atom in the sulfone oxidation state. Whilst this did not occur satisfactorily with benzyl bromide as the electrophile (chapter 2.4), it was found that alkylation of sulfone **137** using allyl bromide and potassium carbonate was possible in good yield to give allylated lactone **159** (scheme 2.26). We had therefore developed a way to successfully allylate our model system using milder conditions than those needed with the ether linker, which should be transferable to a solid phase synthesis.



137 **159**

Scheme 2.26

The next step in our route involved the opening of the lactone ring using trimethyl aluminium and *N*-methylallylamine (scheme 2.27).



X = O, S, SO_2

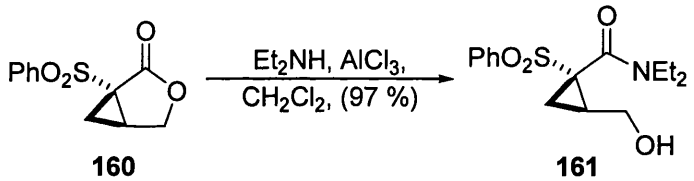
Scheme 2.27

En	Reaction conditions	Linke	Outcome
'	*N*-methylallylamine, $AlMe_3$, tol., 50 °'	O	Desired product, **153**, 77%
2	*N*-methylallylamine, $AlMe_3$, tol., 50 °'	SO_2	Starting material, **159**
3	morpholine, $AlMe_3$, tol., 50 °C	SO_2	Starting material, **159**
4	*N*-methylallylamine, $AlCl_3$, CH_2Cl_2, R	SO_2	Cleavage of Bn, **162**, 69 %
5	*N*-methylallylamine, tol., reflux	SO_2	Starting material, **159**
6	*N*-methylallylamine, CH_2Cl_2, reflux	SO_2	Unknown product
7	*N*-methylallylamine, LiHMDS, THF, F	SO_2	Starting material, **159**
8	*N*-methylallylamine, NaHMDS, THF, I	SO_2	Poor mass balance of cruc
9	morpholine, LiHMDS, THF, RT	SO_2	Poor mass balance of cruc
1	*N*-methylallylamine, $AlMe_3$, tol., 50 °'	S	Starting material, **163**

Table 2.2

Unfortunately, all attempts to open up the lactone ring of sulfone **159** with amines met with failure (table 2.2). It was postulated that the nature of the amine may have an effect on the reaction and in order to simplify things in the ^{1}H NMR spectrum of products and by-products, we opted for a symmetrical amine and employed morpholine (table 2.2, entry 3). However, once again no reaction occurred.

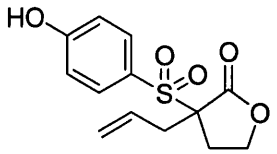
A search of the literature led us to attempt the reaction using trichloroaluminium as opposed to trimethyl aluminium. Shuto and co-workers had reported the opening of a lactone ring in a system extremely similar to ours. Butyrolactone **160** bearing a sulfone group at a quaternary centre α-to the carbonyl was opened using trichloroaluminium to afford amide **161** in excellent yield (scheme 2.28).[106, 107]



160 **161**
97 % yield
98 % ee

Scheme 2.28

This time complete consumption of starting material was observed and phenol **162** was isolated in which the benzyl group had been removed (table 2.2, entry 4, and figure 2.5). The deprotection of benzyl ethers using a similar method has previously been reported.[108]



162

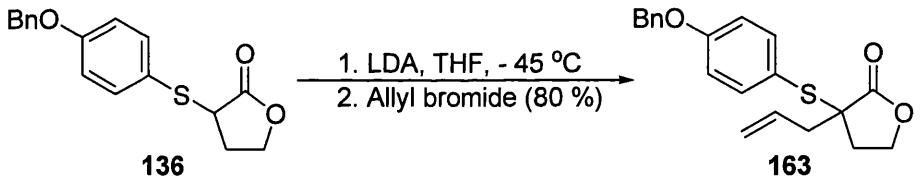
Figure 2.5

We heated starting material **159** at reflux with the amine. With toluene (table 2.2, entry 5), this gave unreacted starting material. However when the same reaction was tried in

refluxing dichloromethane (table 2.2, entry 6), the formation of an unknown product was observed.

Our attention then turned to the use of lithium or sodium hexamethyldisilazide and *N*-methylallylamine in order to generate a reactive lithium or sodium amide (table 2.2, entries 7 - 9). However none of the desired product was obtained and complete decomposition of the starting material was observed.

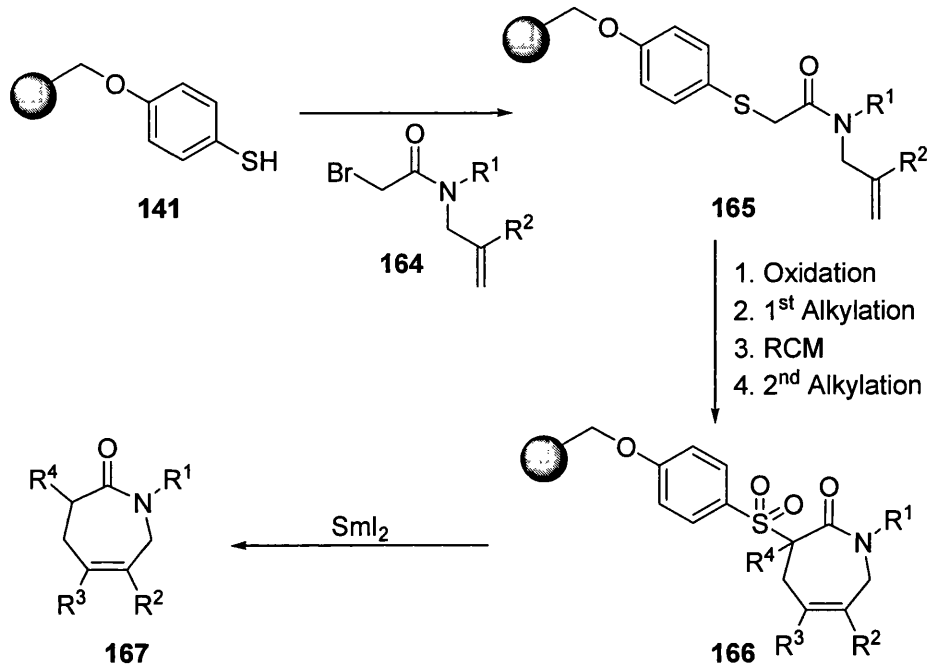
Our final attempt involved the ring opening of the lactone using our original conditions though this time on the corresponding sulfide substrate. It was believed that the sulfide substrate would have less of a tendency to sequester trimethyl aluminium (table 2.2, entry 10). Alkylation of the sulfide was carried out via the conversion of **136**, using the LDA conditions optimised for analogous ether lactone **120**, into **163** in 80 % yield (scheme 2.29). However, this substrate once again led to the formation of an unknown compound and unreacted starting material.



136 **163**

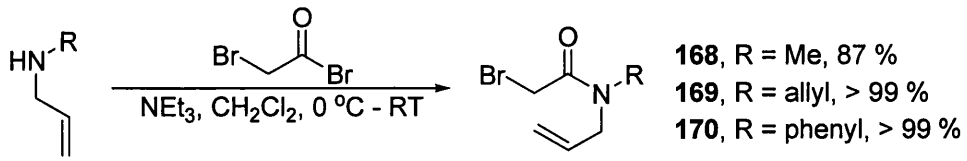
Scheme 2.29

We decided to abandon this route at this stage and looked at developing an alternative route to the lactam motif which would be amenable to transfer onto solid phase. It was proposed to by-pass the problematic ring opening step by attaching amides such as **164** onto resin **141** in the initial immobilisation step to give **165** (scheme 2.30). Oxidation of the linking sulfur atom in **165** to the sulfone oxidation state followed by allylation using potassium carbonate would lead us to the precursor for RCM as before. Formation of the lactam ring followed by a second alkylation would then lead to functionalised lactam **166**. A final cleavage using the mild conditions afforded by SmI_2, should allow us access to a range of functionalised azepinones **167**.



Scheme 2.30

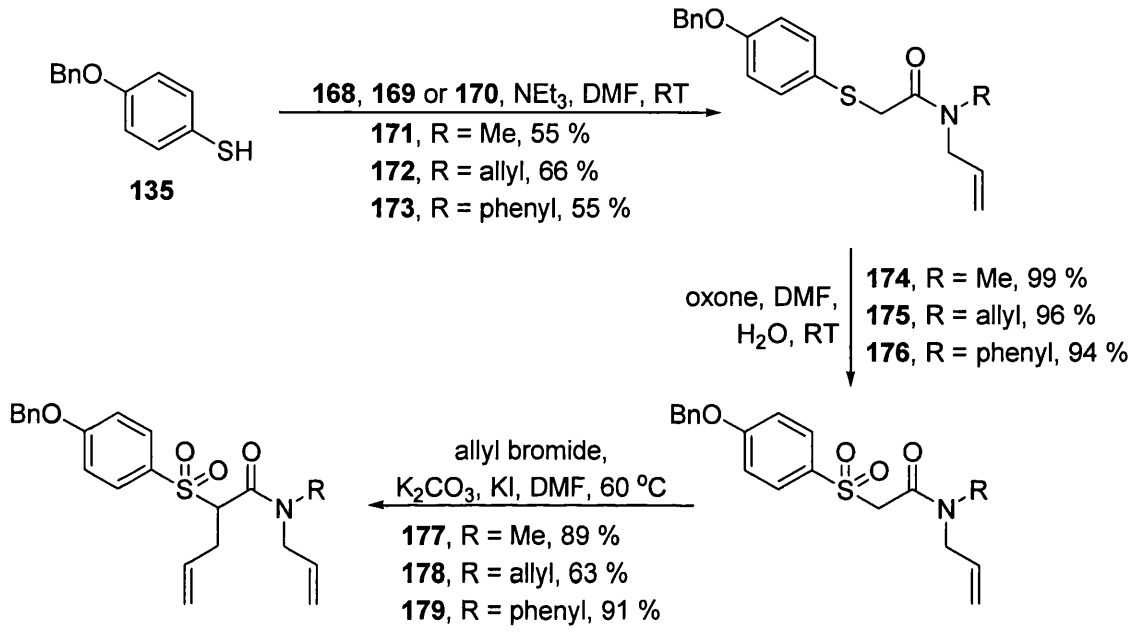
We chose to work with three amines for our solution phase studies. Firstly, reaction of *N*-methylallylamine with α-bromoacetyl bromide led to α-bromoamide **168** in 87 % yield (scheme 2.31). The same reaction was also completed using *N*-diallylamine and *N*-allylaniline, both of which led to their respective α-bromoamides **169** and **170** in near quantitative yields.



Scheme 2.31

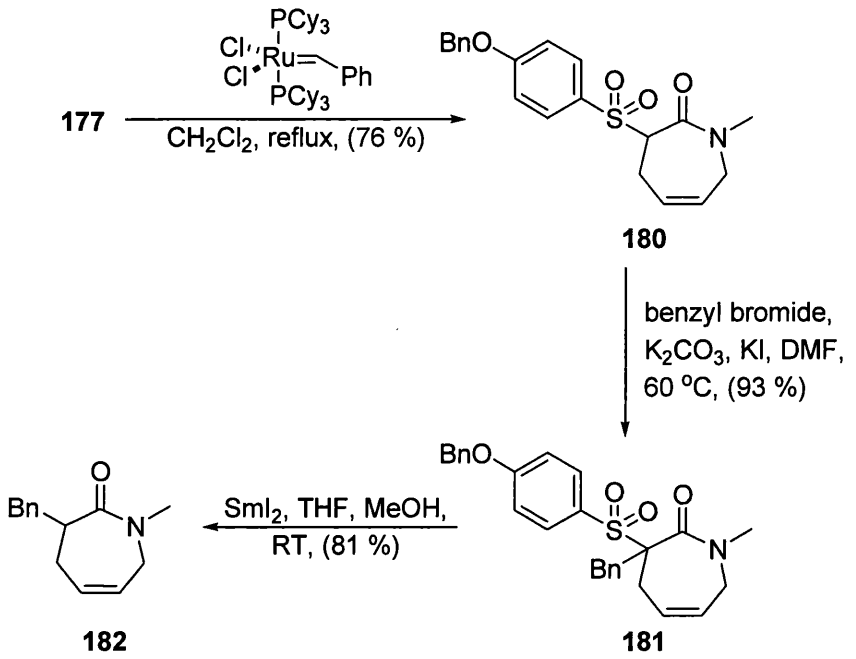
Treatment of thiol **135** with α-bromoamides **168, 169** and **170,** under basic conditions, afforded the corresponding allyl amides **171, 172** and **173** in moderate yields (scheme 2.32). The next step was oxidation of the sulfide to the sulfone which was initially attempted using *m*CPBA. This led to sulfones **174, 175** and **176** in yields of 53 – 70 %. A later attempt at the same transformation, this time using oxone gave sulfones **174, 175** and

176 in much improved yields of 94 % and above. Finally, efficient alkylation at the α-position to give diallyl amides **177**, **178** and **179** using allyl bromide and potassium carbonate was accomplished. It was believed these conditions would be transferable to solid phase.



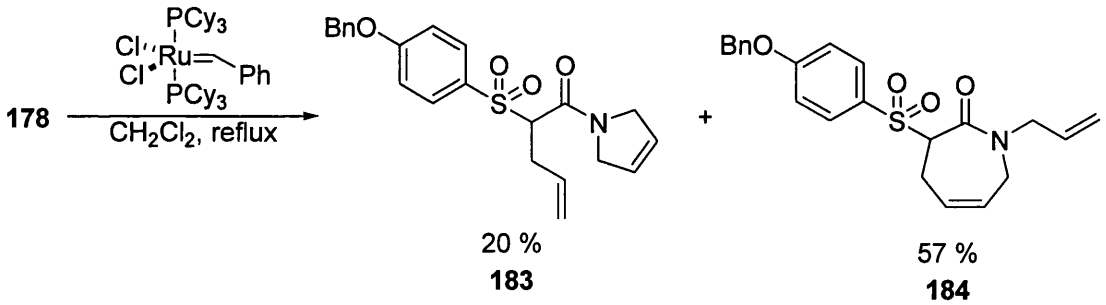
Scheme 2.32

In the case of *N*-methylallylamine-derived substrate **177**, RCM was completed using Grubbs' first generation catalyst, to give lactam **180** in reasonable yield (scheme 2.33). At this stage the second alkylation step was attempted, and pleasingly, it went in excellent yield with the use of potassium carbonate and benzyl bromide as the electrophile to give benzylated lactam **181**. The final cleavage step using SmI_2 was successful and gave desired lactam **182** in 81 % yield. Additives such as DMPU and HMPA are often added to SmI_2 reactions to increase the reduction potential of the reagent. The use of additives was necessary with the ether linker system but it is interesting to note that in the case of the sulfone the 'cleavage' worked well without the need for an additive.



Scheme 2.33

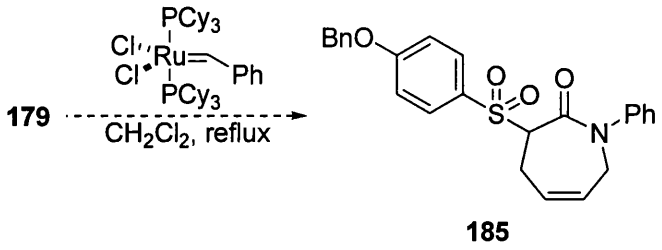
Our main reason for attempting the sequence with diallyl amine was to see which product would result from RCM on **178** (scheme 2.34). As expected a mixture of both the five (**183**) and seven (**184**) -membered rings was obtained, in an approximately 3:1 ratio in favour of the seven-membered ring. It is possible these may be kinetic and thermodynamic products although there was insufficient time to pursue this.



Scheme 2.34

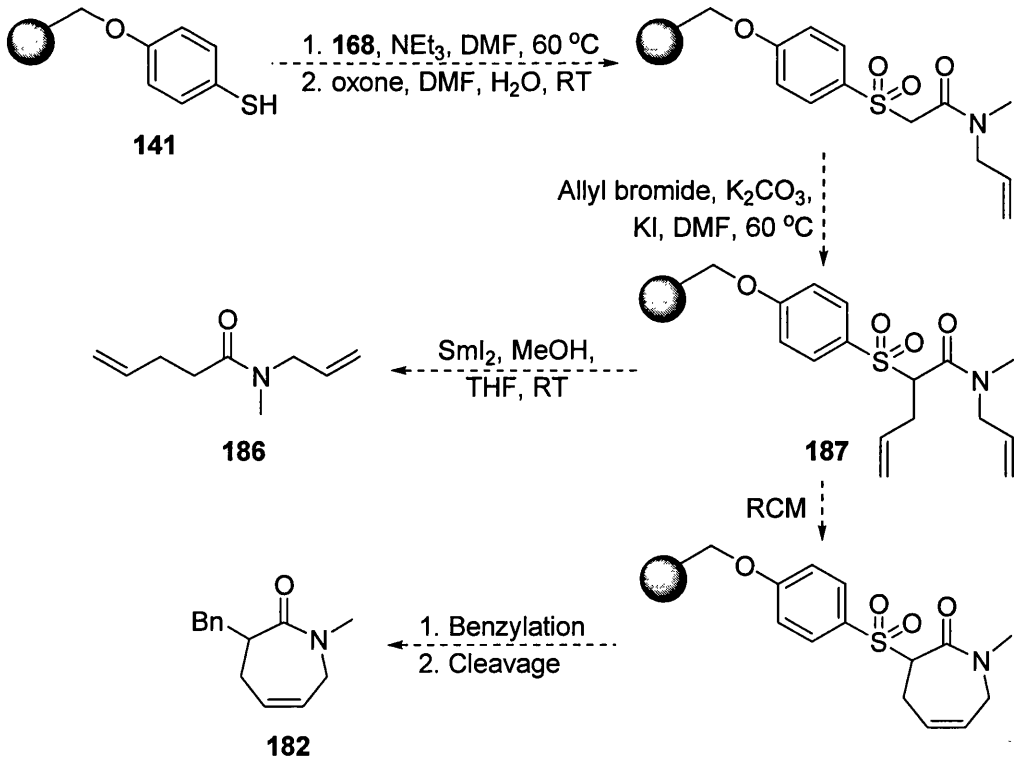
We were now at a stage to attempt RCM on substrate **179** (scheme 2.35). However, despite the presence of some of the expected product **185** present in the crude ^{1}H NMR spectrum, it was a messy reaction and none of the desired product was ever isolated. We believe this is

due to **179** existing largely as the wrong rotamer normally, and even heating it in refluxing dichloromethane does not allow it to interconvert readily to the appropriate rotamer.



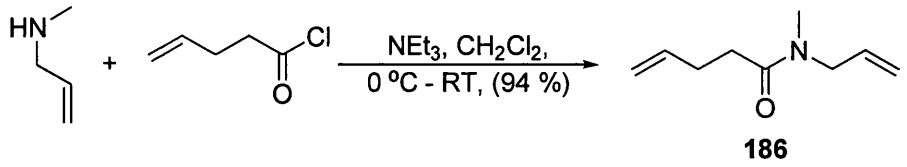
Scheme 2.35

Solid phase studies were then undertaken. Initially, the synthesis of azepinone **182** was attempted (scheme 2.36). However, although the IR spectra of intermediates in the sequence often looked satisfactory, no trace of product was obtained from the final cleavage step. Intermediate **186**, obtained after the first alkylation step, was then cleaved from resin **187**.



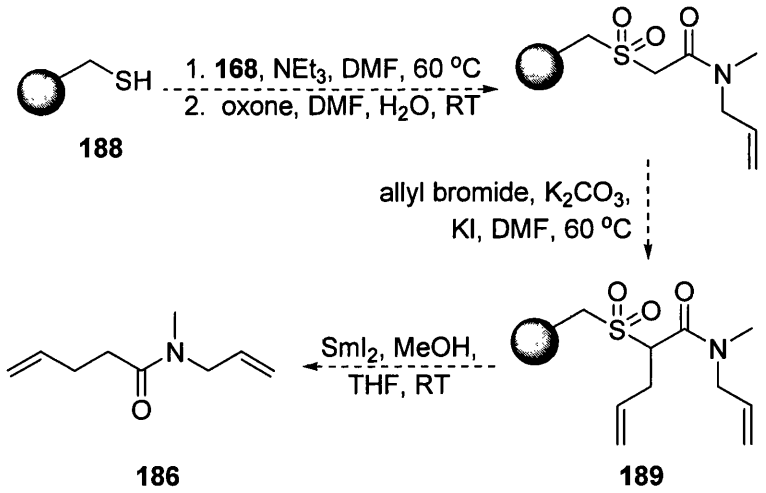
Scheme 2.36

At this stage, amide **186** would be the expected product following cleavage from the resin. An authentic example of **186** was independently prepared to help monitor the cleavage reaction by TLC (scheme 2.37). Amide **186** however was not detected upon the attempted cleavage of **186** from **187**. Suspicions once again turned to the nature of the thiol resin and in particular to the difficulties in deprotecting the trityl-protected thiol resin.



Scheme 2.37

In order to overcome this, the sequence was also followed using benzyl thiol resin **188** (scheme 2.38).[109] Sadly, no trace of the desired product **186** was found following the attempted cleavage from immobilised **189**.



Scheme 2.38

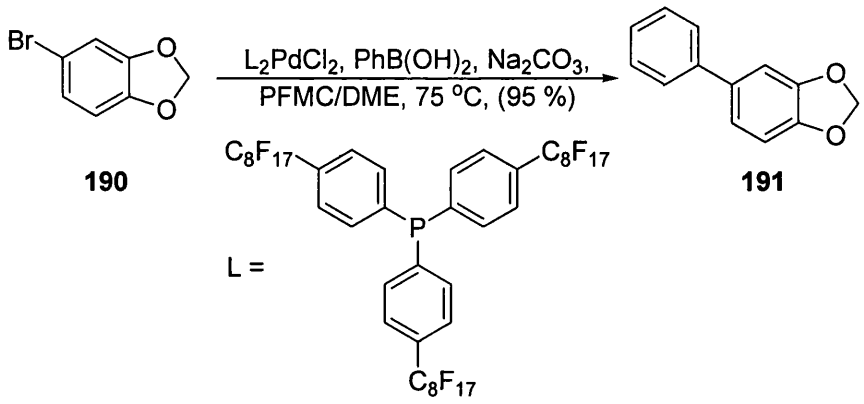
Following the attempted application of both ether and thiol linker sequences on solid phase, and the lack of a successful outcome, we turned our attention to the use of a soluble phase tag in place of an insoluble polymer tag. We chose to look at the use of a fluorous phase tag.

2.6 Fluorous-phase synthesis

Whilst polymer supported chemistry has advanced greatly over the last fifty years, limitations on reaction scope and scale have limited further development. As a result, solution phase methods have once again become more popular, particularly fluorous-tagged synthesis.[110-112] Initially pioneered by Curran in the mid 1990's,[113] fluorous phase synthesis has quickly become a useful tool for organic synthesis. One of its main advantages lies in the ease with which fluorinated components from a reaction can be separated from non-fluorinated organic molecules or reagents. Additionally, reactions can be monitored by more traditional methods such as TLC and ^{1}H NMR spectroscopy making development and optimisation of a given route much quicker than its solid phase equivalent. It also enables the characterisation of intermediates by ^{1}H and ^{13}C NMR spectroscopy.

There are a number of ways in which fluorous phase synthesis can be employed. The first is in fluorous biphasic systems (FBS), where the immiscibility of fluorous solvents with conventional organic solvents is exploited. As an example, a fluorous catalyst may be present in the fluorous phase; whilst the substrate to be modified will be in the organic phase. Both fluorous and non-fluorous layers are allowed to combine upon heating to create a homogenous mixture thus allowing catalyst and substrate to come together. Separate layers are regained upon cooling allowing for easy separation and extraction. This affords the modified substrate in high purity from the organic phase whilst the catalyst can be isolated from the fluorous phase and then reused.

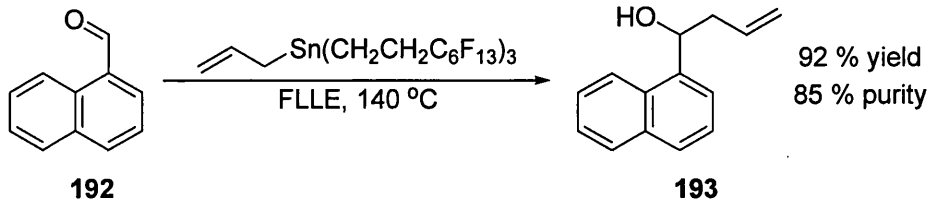
An example of such a system, reported by Bannwarth *et al*, is outlined below (scheme 2.39).[114] A fluorous bis-triphenylphosphine palladium complex was constructed and engaged for use in the palladium-catalysed Suzuki cross-coupling of aryl bromide **190** and phenyl boronic acid to yield biaryl **191**. The reaction medium was a mixture of perfluoromethylcyclohexane (PFMC) and dimethoxyethane (DME), and the catalyst was recovered and reused up to six times without significant deterioration in the yield of the reaction.



Scheme 2.39

As a continuation, the separation of fluorous and non-fluorous molecules was carried out using a technique called fluorous-liquid, liquid extraction (FLLE). Fluorous alkenes, ethers and amines are generally immiscible in organic solvents. Fluorous reagents are soluble in fluorous solvents due to favourable fluorine-fluorine interactions. This property of fluorous solvents can be employed for the extraction of fluorous reaction components from an organic phase into a fluorous phase.

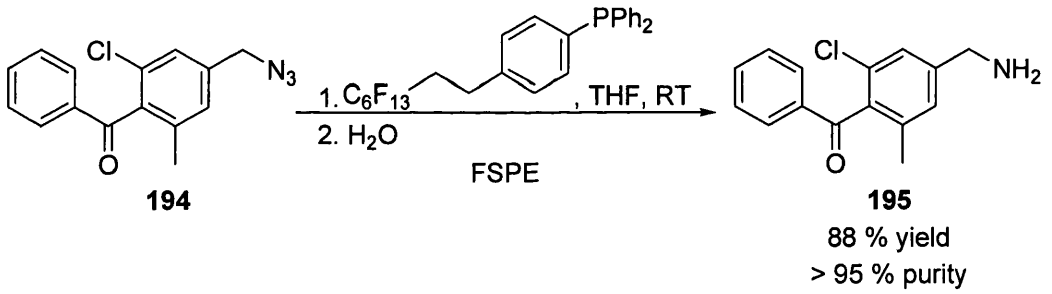
This system has been used to good effect by Curran and co-workers in the purification of allyl alcohols.[115] Aldehyde **192** was heated with a fluorous allylstannane reagent to give alcohol **193** (scheme 2.40). However, various tin by-products were also created during the reaction and FLLE was used to purify the product. Following the reaction, the crude mixture was partitioned between acetonitrile and perfluoroalkanes (FC-72), with the product being extracted into the acetonitrile layer and later isolated in high purity.



Scheme 2.40

More recently, attention has switched to the use of a technique which allows separation of fluorous-tagged compounds from non-fluorous ones using fluorous reverse phase silica gel. It is known as fluorous solid phase extraction (FSPE) and involves loading a crude mixture onto a fluorous silica column. Elution with a fluorophobic solvent, commonly 80 % methanol/water, removes the non-fluorinated compounds from the mixture. Fluorous-tagged compounds remain on the column due to the strong fluorine-fluorine interactions with the fluorous silica and can later be removed using a fluorophilic solvent such as (100 %) methanol.

Illustrated below is the use of fluorous phosphine in the Staudinger reaction on azide **194** (scheme 2.41).[116] Normally, the triphenylphosphine oxide generated as a by-product in this reaction is difficult to remove. Here it can be removed simply through FSPE to allow isolation of amine **195** in high purity.

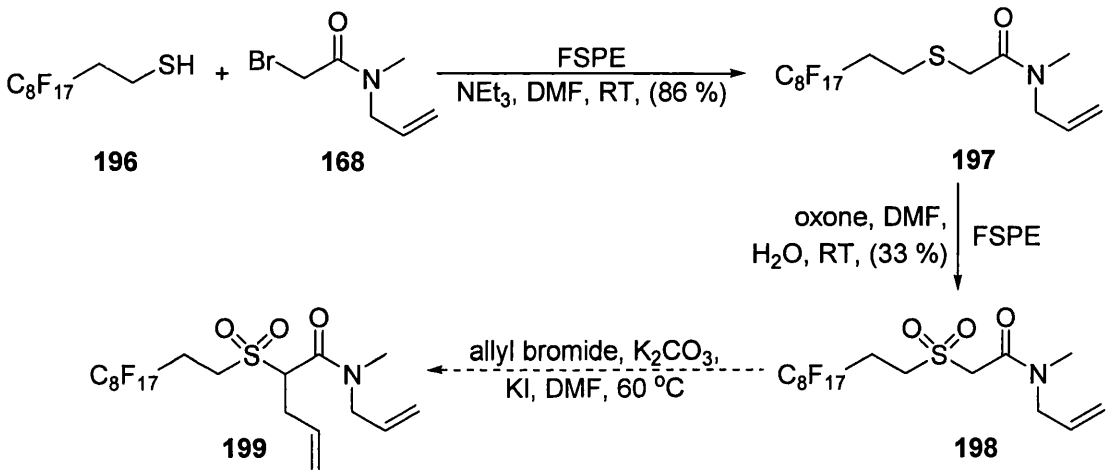


Scheme 2.41

2.7 Application of the linker system in a fluorous-phase synthesis of azepinones

Various fluorous thiols with different length perfluoroalkyl chains are commercially available. These fluorous thiols consist of a perfluoroalkyl chain and a thiol functional group separated by a saturated two carbon spacer unit. The spacer unit ensures nucleophilicity at the sulfur is maintained by minimising the strong electron withdrawing effect of the perfluoroalkyl chain.

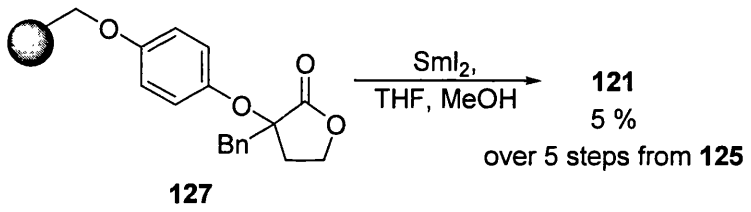
Our studies began with the immobilisation of α-bromoamide **168** using perfluorodecyl thiol **196** to give **197** in good yield (scheme 2.42). Oxidation of the sulfide with oxone led to formation of sulfone **198**. However, problems were encountered isolating **198** using FSPE and the low yield of **198** following oxidation reflects this. Alkylation was attempted to construct diallyl amide **199** using allyl bromide and potassium carbonate. Whilst some **199** was detected in the crude ^{1}H NMR spectrum, it was the minor product. This coupled with time constraints and the problems experienced in the extraction of fluorous-tagged compounds, led us to discontinue work into our fluorous linker system.



Scheme 2.42

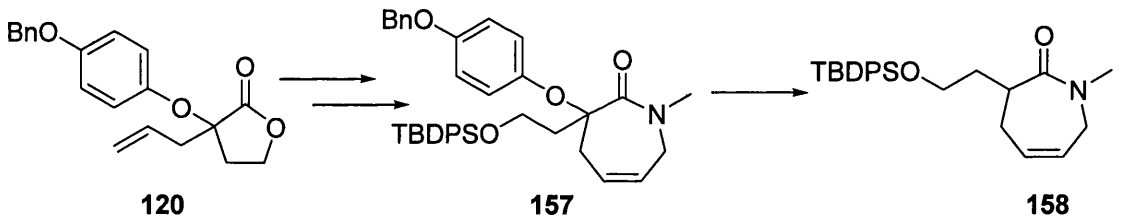
2.8 Conclusions

In chapter 2 studies into the feasibility of phase-tag assisted routes to heterocycles using our linker system have been discussed. Initially, studies were made into the alkylation of various lactones and the reduction of the products using SmI_2. A simple lactone substrate was successfully cleaved from an ether linkage to a polymer tag using the reagent, though low overall yields were obtained (scheme 2.45).



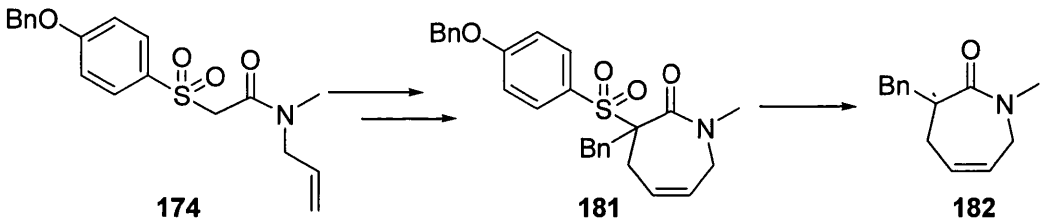
Scheme 2.45

A route toward simple azepinones that went via a key ring opening step as well as a crucial RCM step has been devised and carried out in solution phase studies into an ether-based link to a phase tag (scheme 2.46).



Scheme 2.46

In addition to this, after initial problems finding a route to azepinones whilst investigating the feasibility of a sulfone linker, we devised a route beginning from α-bromoamides that also utilised a key RCM step (scheme 2.47). Cleavage of the lactam from the resin model proceeded in an excellent 81 % yield, without the need for additives to increase the reduction potential of the reagent.



174 **181** **182**

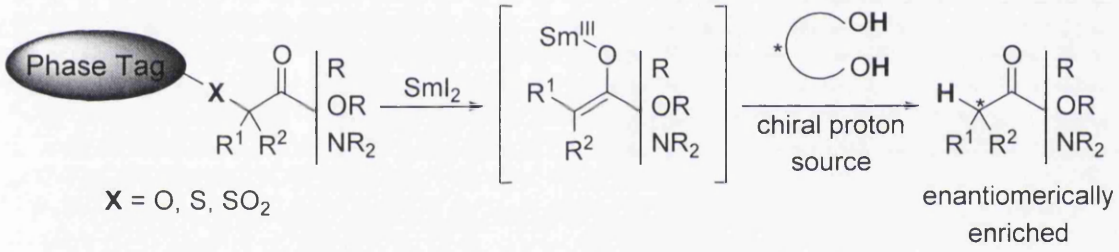
Scheme 2.47

In summary, although my studies have failed to result in a solid or fluorous phase synthesis of azepinones using our linker system, several important observations have been made that highlight the strengths and weaknesses of the linker system. A future ring closing metathesis, solid phase route to functionalised azepinones based on my successful solution phase studies should be possible, but further optimisation is clearly needed.

Chapter 3: Developing a cleavage-enantioselective protonation strategy

3.1 Introduction

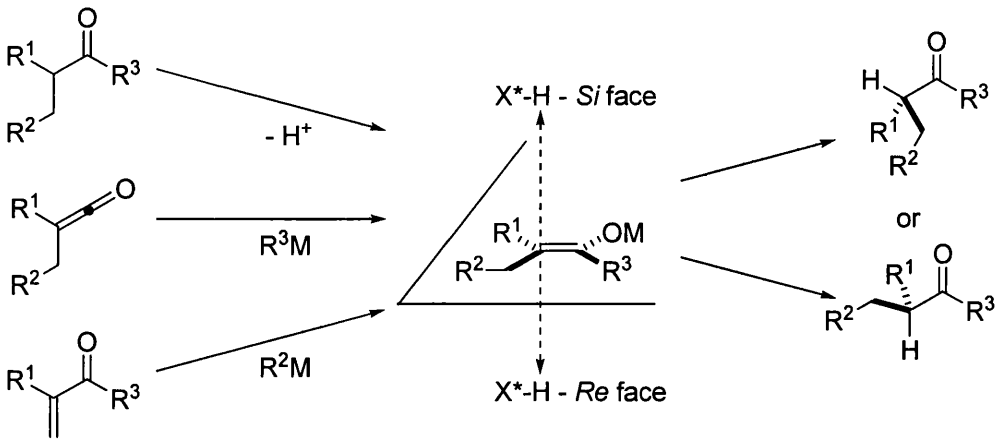
One of the goals of my PhD project was the development of a new strategy for the phase tag assisted synthesis of enantiomerically enriched carbonyl compounds using our linker system. It was proposed that cleavage of the linker in the presence of a chiral protonating agent (CPA) would allow asymmetry to be introduced in the final step of a phase-tag assisted synthesis. This would release non-racemic products from the phase tag via the asymmetric protonation of the samarium(III) enolate formed upon cleavage of the substrate from the phase tag (scheme 3.1).



Scheme 3.1

3.2 Enantioselective protonation of samarium(III) enolates

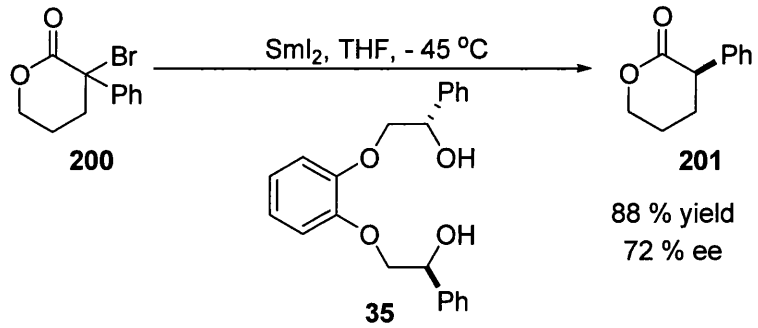
First introduced in 1976 as a means of deracemisation, the concept of enantioselective protonation of a prostereogenic centre is, in principle, a simple one.[117] Since a prochiral enol derivative has two enantiotopic faces, the proton transfer from a chiral, non-racemic proton source to the enol derivative will be kinetically favoured from either the top or bottom face, thus constructing enantiomerically enriched carbonyl compounds (scheme 3.2).



Scheme 3.2

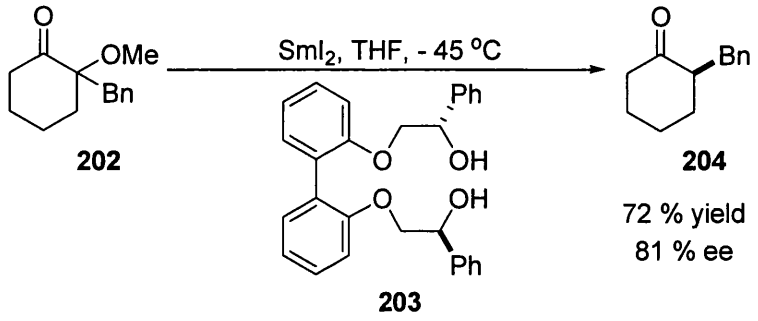
With the increased knowledge of enolate structure and reactivity, and new methods for their regio- and stereoselective formation, enantioselective protonation has become a more viable option for the production of enantiomerically enriched compounds.[118-120] An additional advantage is that, upon normal aqueous work up of the reaction, reprotonation of the CPA occurs. This renders the CPA both recoverable and reusable.

During the last three years, we have been involved only in the generation of samarium(III) enolates and their enantioselective protonation. Our work has been inspired by the work of Takeuchi *et al.* which was covered in more detail in section 1.3.[46] We were first attracted to the proton sources constructed by Takeuchi in his work on the reduction of α-hetero-substituted lactones. In the example shown, α-brominated lactone **200** is reduced in the presence of CPA **35** to give lactone **201** in good yield and in 72 % ee (scheme 3.3).



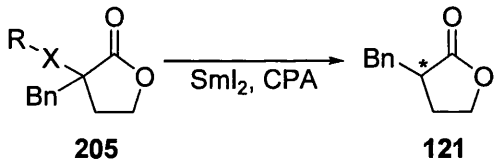
Scheme 3.3

Another example from Takeuchi's work that bears a similarity to our proposed linker system is the reduction of α-methoxy cyclohexanone **202** in the presence of CPA **203** to give α-benzylated cyclohexanone **204** once again in good yield and this time in 81 % ee (scheme 3.4).



Scheme 3.4

We chose to adopt lactones of generic structure **205** as the model system for the development of a cleavage-asymmetric protonation sequence (scheme 3.5). Because of the similarity of the model system to Takeuchi's substrates, we decided to begin our studies using proton sources used in his work in addition to other chiral proton sources.



Scheme 3.5

3.3 Preparation of chiral protonating agents

A number of different CPA's were used during our studies into the development of a sequential cleavage-enantioselective protonation strategy. As mentioned above, we focused initially on the use of CPA's developed by Takeuchi and co-workers,[40, 41, 43, 44, 46, 121] although we also examined the use of related CPA's reported by Pedrosa *et al*[122, 123] in addition to some commercially available chiral alcohols (figure 3.1).

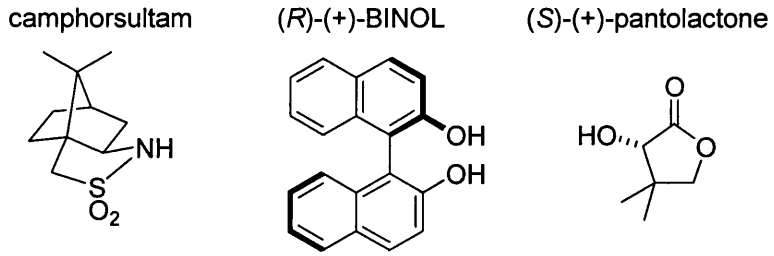


Figure 3.1

Takeuchi and co-workers have prepared a number of C_2-symmetrical diol-based proton sources and we chose to synthesise the enantiomers of those that looked the most promising for our system, diols **35** and **203** (figure 3.2).

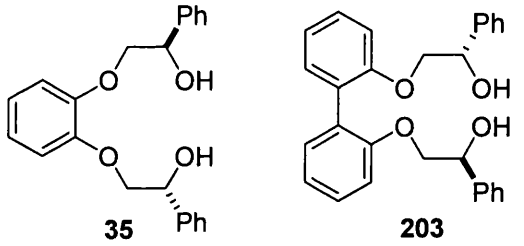
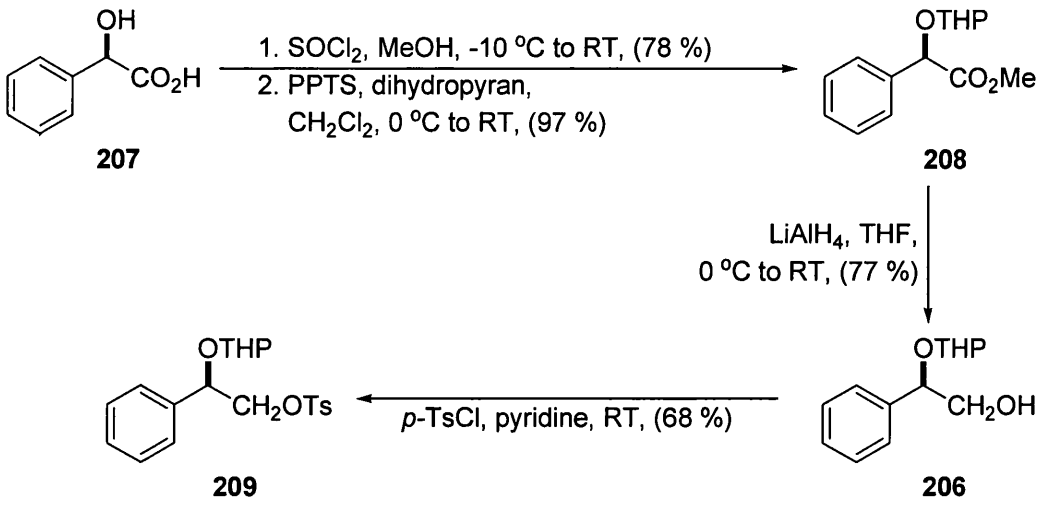


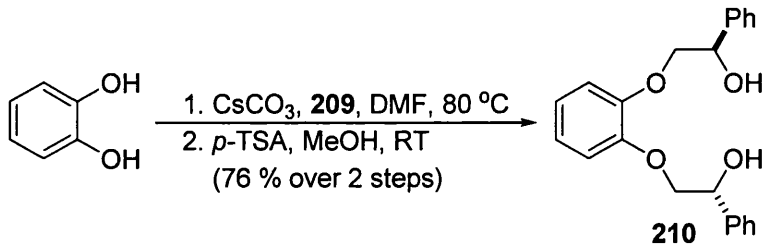
Figure 3.2

Takeuchis' synthesis followed Stephenson's method as far as alcohol **206**.[124] The route to **206** began with the conversion of *R*-(-)-mandelic acid **207** into *R*-(-)-methyl mandelate, which was achieved in 78 % yield using thionyl chloride and methanol (scheme 3.6). The next step was to protect the secondary alcohol as a tetrahydropyranyl (THP) group, which is stable to basic conditions but which could later be deprotected easily under acidic conditions. This step afforded THP ether **208** in excellent yield. The methyl ester was then reduced using lithium aluminium hydride, to give **206** in 77 % yield. Primary alcohol **206** was then converted into tosylate **209** using tosyl chloride and pyridine in 68 % yield.



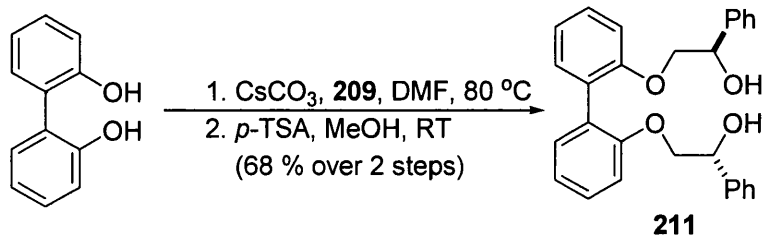
Scheme 3.6

Our first two attempts to construct **210** failed to give yields close to the 78 % reported by Takeuchi. However, by leaving the reaction to stir for longer than reported in the literature, we were able to complete the synthesis of CPA **210** by first coupling tosylate **209** with catechol to give the THP-protected chiral ligand. Deprotection under acidic conditions then gave **210** in 76 % yield over two steps (scheme 3.7).



Scheme 3.7

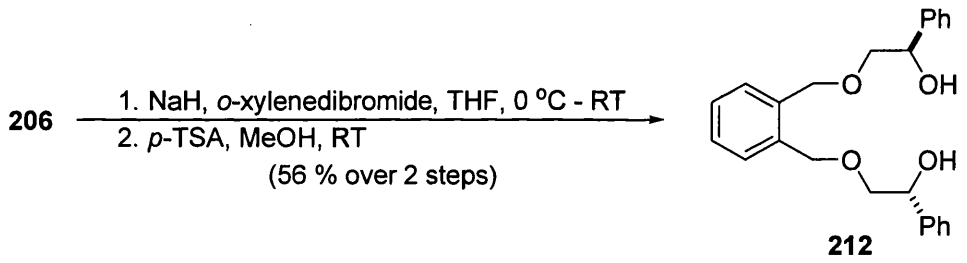
Tosylate **209** could also be used to prepare biaryl CPA **211**. Coupling **209** with 2,2'-biphenol, followed by deprotection of the secondary alcohols led to CPA **211** in 68 % yield over two steps, marginally higher than that reported by Takeuchi (scheme 3.8).



211

Scheme 3.8

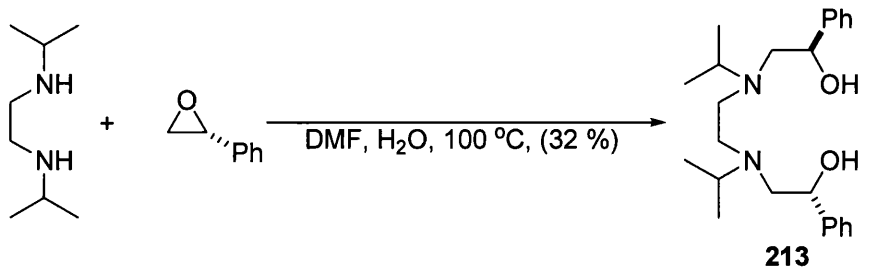
Proton source **212** was synthesised from *o*-xylenedibromide using a slightly different approach. Deprotonation of **206** using sodium hydride, followed by nucleophilic substitution of bromine in *o*-xylenedibromide, led to the formation of the protected diol. As before, deprotection was carried out under acidic conditions to give CPA **212** in 56 % yield over two steps (scheme 3.9)



212

Scheme 3.9

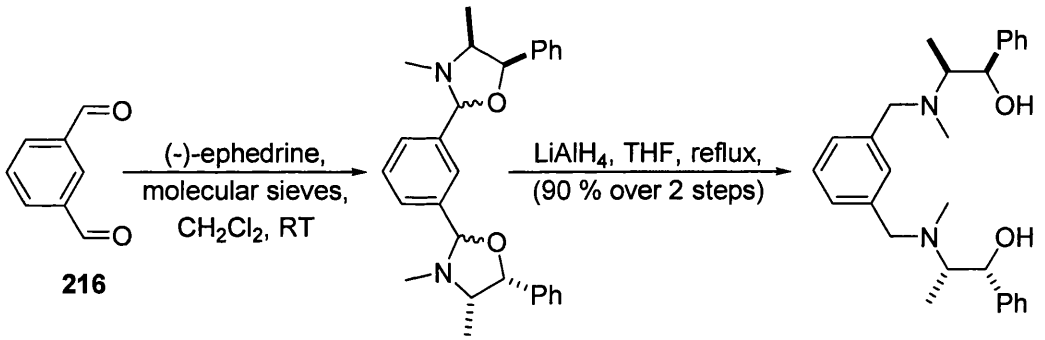
We also prepared Takeuchi's protonating agent **213** from the ring opening of (*R*)-styrene oxide with *N,N*-diisopropylethylenediamine by heating in dimethylformamide and water at 100 °C (scheme 3.10). In our hands, this reaction gave lower yields than the 52 % yield reported by Takeuchi,[46] despite following the reported protocol exactly. Repeated attempts at optimisation failed to increase the yield beyond 32 %.



213

Scheme 3.10

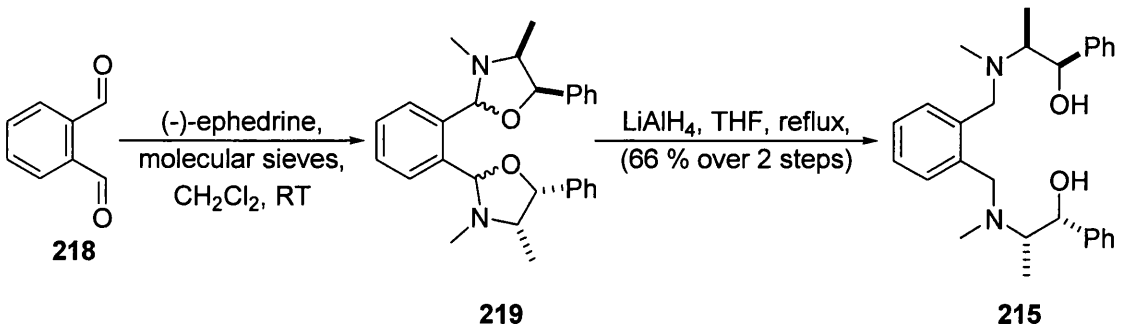
We also followed the work of Pedrosa and co-workers for the preparation of enantiopure C_2-symmetrical ephedrine-derived alcohols **214** and **215**.[122] Pedrosa originally used the ligands for the enantioselective ethylation of aldehydes using diethyl zinc, however we saw the alcohols as potential CPA's.[123] Synthesis of **214** began with the condensation of isophthaldialdehyde **216** and (-)-ephedrine to afford *meta bis*-oxazolidine **216** (scheme 3.11). Reduction using lithium aluminium hydride led to the final aminoalcohol ligand **214** in 90 % yield over two steps, which reflected the good yields reported by Pedrosa.



216 217 214

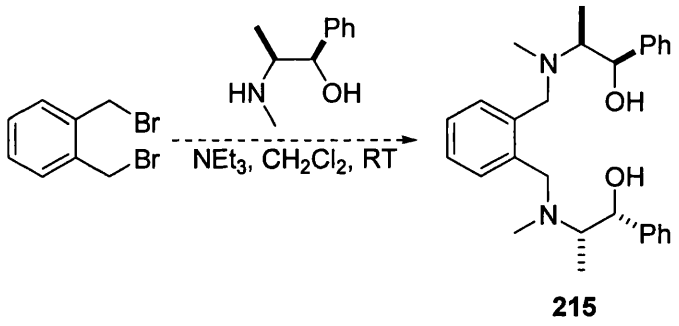
Scheme 3.11

Chiral proton source **215** was prepared in the same manner with the initial step being the condensation of phthaldialdehyde **218** with (-)-ephedrine to give *ortho bis*-oxazolidine **219** (scheme 3.12). The opening of the oxazolidine rings was once again achieved using lithium aluminium hydride to reach aminoalcohol **215** in reasonable yield.



Scheme 3.12

We had originally tried to construct CPA **215** via a more direct route. However the reaction of *o*-xylenedibromide and (-)-ephedrine in the presence of triethylamine failed to yield any of the desired product (scheme 3.13). The reaction was also attempted at elevated temperatures but with the same outcome.



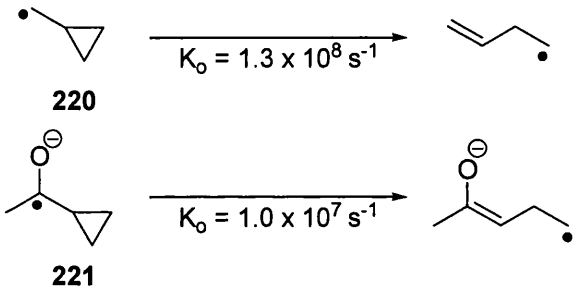
Scheme 3.13

3.4 Initial studies into the enantioselective protonation of samarium(III) enolates

Work in the group has previously investigated the mechanism of reduction of α-oxygenated carbonyl compounds with SmI_2.[36] The work was concerned with the nature of the reactive species formed during the process.

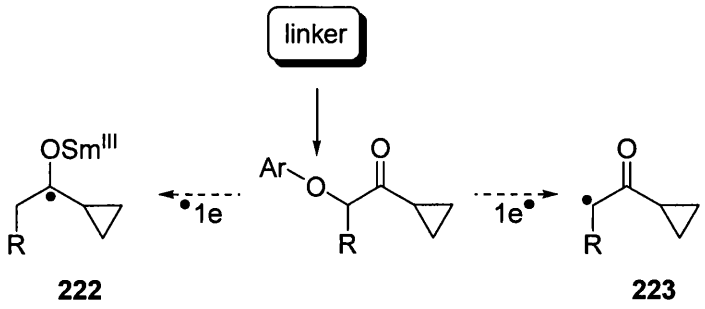
In order to investigate the mechanism by which reduction initially occurs, a cyclopropyl group was used as a mechanistic probe. The rate of fragmentation of cyclopropylmethyl

radical **220** is approximately 1.3×10^8 s^{-1} and as the ring opens rapidly it is sometimes used as a radical clock (scheme 3.14).[125] Tanko and co-workers have subsequently reported the rate of opening of cyclopropyl radical anion **221** as greater than 1.0×10^7 s^{-1} and therefore not much different to the rate of ring opening of the neutral radical **220**. Radical anions of this type should therefore also be useful radical clocks.[126] If a substrate, upon being treated with a single electron transfer reagent such as SmI_2, were to go via either radicals **220** or **221**, then opening of the cyclopropyl ring would be expected. Absence of any ring-opened product would indicate a different mechanistic pathway via an alternative radical.



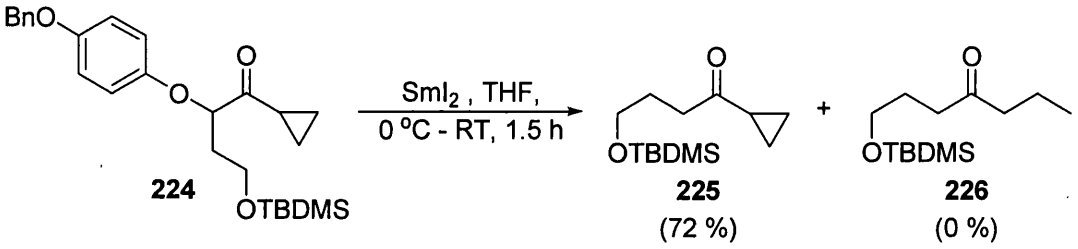
Scheme 3.14

If the mechanism for the SmI_2-induced reduction of the α-aryloxy group in our linker system proceeds via the generation of cyclopropylmethyl radical anion **222**, then fragmentation of the cyclopropyl ring would be expected to occur (scheme 3.15). However, if none of the ring opened product is obtained, it suggests the mechanism must proceed via direct reduction of the C-O bond at the α-position to give a radical such as **223**.



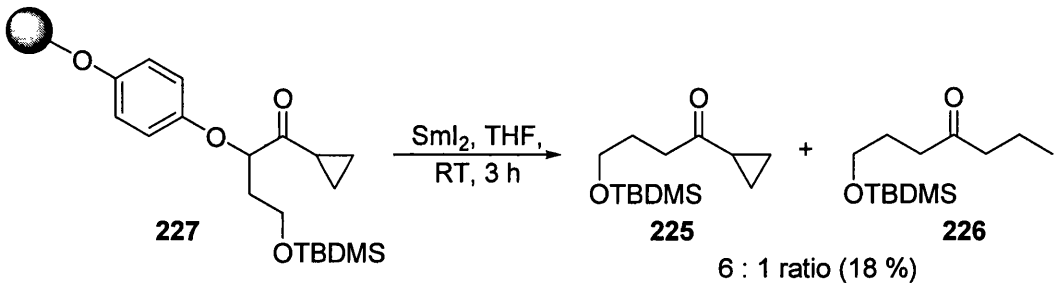
Scheme 3.15

Work done earlier in the group concerned the use of α-aryloxy substituted cyclopropyl ketone **224** as a mechanistic probe (scheme 3.17). Careful titration of **224** with SmI_2 led to the formation of cyclopropyl ketone **225** in 72 % yield (scheme 3.16). Interestingly, no trace of ring-opened product **226** was observed in the reaction. This suggested that the reaction was going directly through carbon-oxygen bond cleavage and not via the radical anion.



Scheme 3.16

Ketone **227** is the immobilised version of solution model **224**. Treatment of **227** with SmI_2 led to the cleavage of ketones **225** and **226** from the polymer backbone in an isolated yield of 18 % after 5 steps on resin and in a 6 : 1 ratio in favour of cyclopropyl ketone **225** (scheme 3.17). This shows that fragmentation of cyclopropylketones does occur but in this case it is a result of over reduction of **225** by SmI_2.



Scheme 3.17

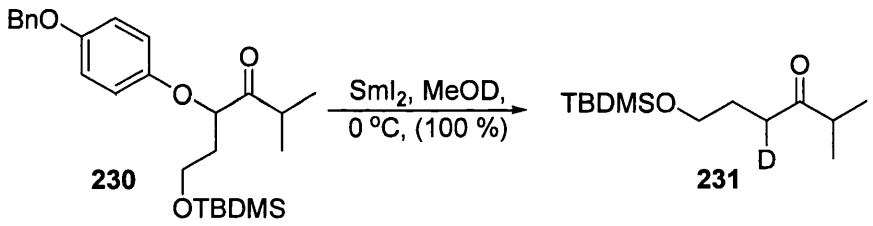
In the next sequence of mechanistic studies, the nature of the reactive intermediate formed following cleavage was investigated. The reduction of a solution model substrate was carried out under various conditions, the aim being to ascertain whether it was radical

intermediate **228**, or enolate **229** that was the reactive species quenched at the end of the reaction (figure 3.3).

228 **229**

Figure 3.3

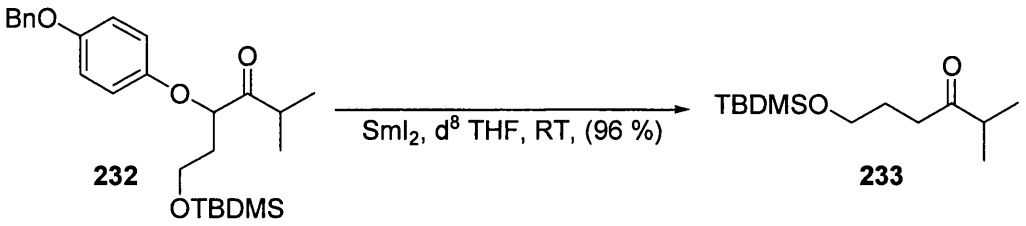
To begin, the reduction of ketone **230** was carried out in the presence of deuterated methanol (MeOD). Complete deuterium incorporation α to the carbonyl group in the product **231** was observed (scheme 3.18). Whilst this implies the presence of an enolate intermediate, it is not inconceivable that the inclusion of MeOD could lead to an alteration in the mechanistic course of the reaction.[7]



230 **231**

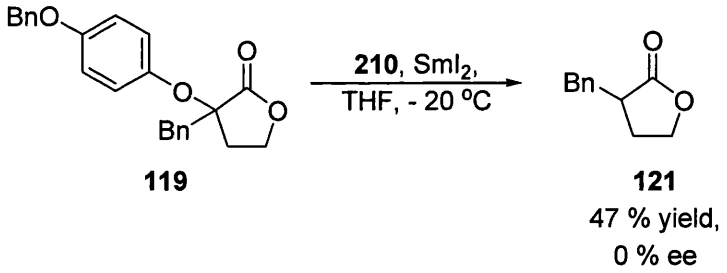
Scheme 3.18

There is literature precedent for hydrogen atom abstraction from solvent when using THF in some SmI_2 reactions.[127] This is a radical process and might occur if reactive intermediate **228** was being formed. In order to assess the extent, if any, of hydrogen atom abstraction, the reduction of isopropyl ketone **232** was carried out in d_8 THF (scheme 3.19). Deuterium incorporation would have indicated that product formation occurs via quenching of an α-radical intermediate. No deuterium incorporation was observed in **233**, indicating once more the presence of an enolate as the reactive species.



Scheme 3.19

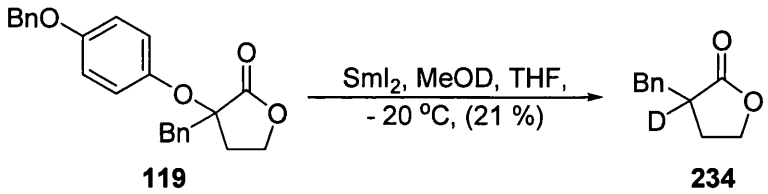
My studies into cleavage of our linker and asymmetric protonation of the resulting samarium(III) enolate began by treatment of lactone **119**, which had been prepared as in section 2.3, with SmI_2 and chiral proton source **210** (scheme 3.20). The early results were surprising and GC analysis indicated 0 % ee each time the reaction was attempted, despite altering the number of equivalents of both SmI_2 and **210**. In addition, the reaction was attempted at a number of different temperatures down as low as - 78 °C, with no effect on the enantioselectivity of the reduction. Also, as the temperature of the reaction was decreased, conversion decreased, leaving unreacted **119** which hindered purification.



Scheme 3.20

Although we had not expected high enantioselectivities with CPA **210**, we felt that the isolation of racemic **121** was significant. We felt there must be a mechanistic reason for the complete lack of selectivity observed. One possibility was that of achiral protonation during the reaction or during aqueous work up. As previous experiments in the group suggested that hydrogen atom abstraction from THF was not occurring, we concentrated on the possibility of achiral protonation of the enolate during work up. We devised some simple labelling experiments in order to verify at which stage the enolate was being protonated.

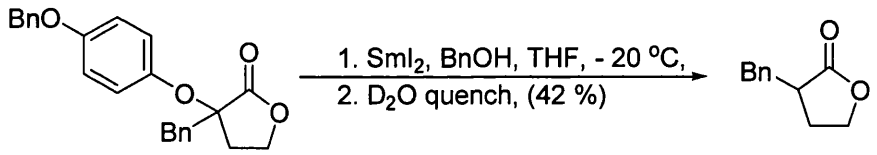
As in scheme 3.18, our initial foray into labelling was to determine whether we would witness deuterium incorporation upon reduction of **119** in the presence of MeOD (scheme 3.21). Thankfully, we observed deuterium incorporation in lactone **234** at the α-position indicating that an enolate was indeed being protonated during the reaction and not during the subsequent aqueous work up.



119 **234**

Scheme 3.21

We also carried out the reduction using benzyl alcohol as the proton source and this time used a D_2O quench (scheme 3.22). No deuterium incorporation was observed and once again we felt confident that protonation was occurring during the reaction rather than on work up. Benzyl alcohol was used as it was more similar in size and pk_a to chiral proton source **210**.



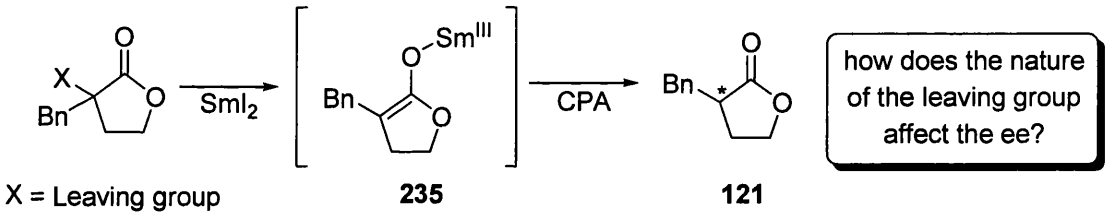
119 **121**

Scheme 3.22

We were now relatively happy that the reaction was proceeding via the expected samarium(III) enolate. But why were we obtaining racemic **121** from the 'cleavage' reactions in the presence of CPA **210**? In order to confront this problem we chose to assess the effect of the leaving group on the enantioselectivity of the reaction.

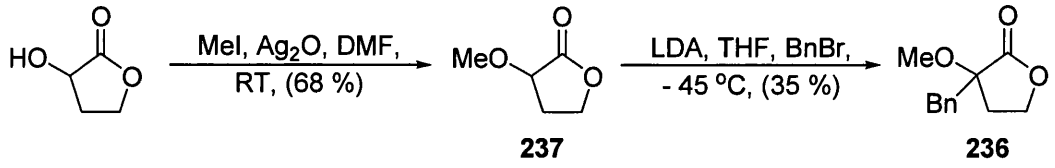
3.5 Investigating the effect of the leaving group on enantioselectivity in asymmetric protonations

In order to assess the effect of the leaving group on the enantioselectivity of the asymmetric protonation reaction, we chose to investigate the behaviour of a single enolate **235**, generated from a range of substrates. Treatment of a variety of substituted butyrolactone substrates with SmI_2, would all generate **235** allowing us a means for direct comparison of the effect of the leaving group and maybe provide us with some mechanistic insights into the reaction (scheme 3.23). Initially, we concentrated on other α-oxygenated systems, before moving on to the reduction of sulfides and sulfones.



Scheme 3.23

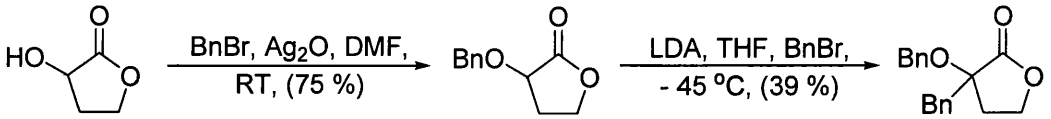
Preparation of α-methoxy substrate **236** began by methylation of α-hydroxy-γ-butyrolactone using silver oxide and methyl iodide to give **237** in 68 % yield (scheme 3.24). Benzylation of **237** using LDA and benzyl bromide then gave **236** in an unoptimised 35 % yield.



Scheme 3.24

In the same manner, the analogous α-benzyloxy substrate was also prepared. After initially benzylating α-hydroxy-γ-butyrolactone using silver oxide and benzyl bromide in 75 %

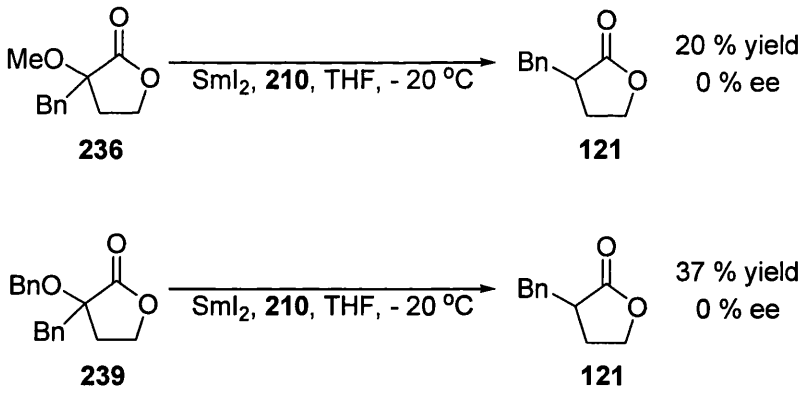
yield, α-benzyloxy-γ-butyrolactone **238** was alkylated on carbon using the conditions favoured above to give **239** in an unoptimised 39 % yield (scheme 3.25).



238 **239**

Scheme 3.25

α-Oxygenated compounds **236** and **239** were then reduced using SmI_2 in the presence of C_2-symmetric diol **210**. We once again obtained a racemic mixture of lactone **121** from both substrates in poor yields (scheme 3.26). It is perhaps not surprising that alkoxy groups should be poorer leaving groups than aryloxy substituents and thus give lower yields in the reduction.

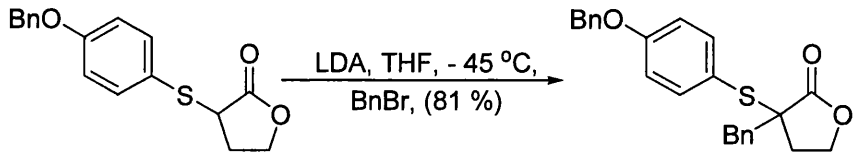


236 **121**

239 **121**

Scheme 3.26

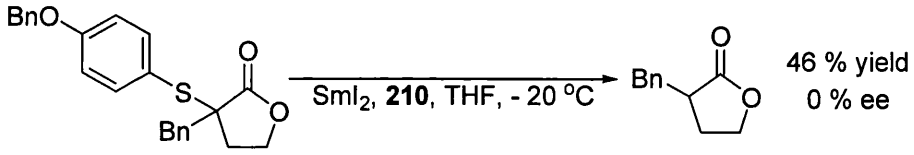
The next logical step was to investigate the effect of the linking heteroatom by exchanging oxygen for sulfide and sulfone moieties. To begin with, we chose to look at the proposed linker model and assemble the analogous sulfide and sulfone substrates. α-Arylsulfanyl-γ-butyrolactone **136** was obtained according to the route described in chapter 2.4 (scheme 2.15). Benzylation of **136** was achieved using LDA and benzyl bromide to give **240** in 81 % yield (scheme 3.27).



136 **240**

Scheme 3.27

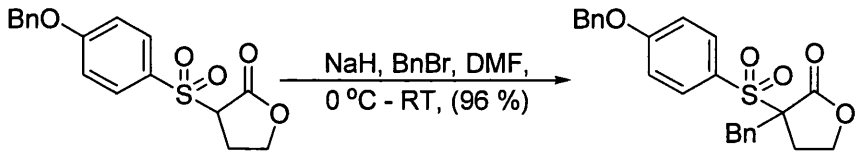
Reduction of sulfide **240** gave α-benzyl-γ-butyrolactone **121** in 46 % yield (scheme 3.28). Once again, however, chiral GC analysis indicated 0 % ee for lactone **121** obtained from the reduction of **240**.



240 **121**

Scheme 3.28

Oxidation and benzylation were carried out according to the protocol described in chapter 2.4 (scheme 2.18) to afford **139** in 96 % yield (scheme 3.29).

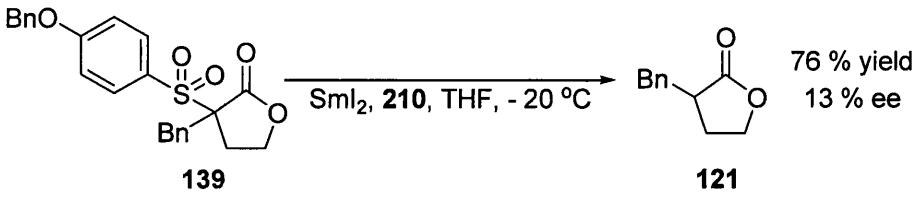


137 **139**

Scheme 3.29

This time, upon reduction of sulfone **139** with SmI_2, we obtained lactone **121** in 76 % yield. This was the highest yield obtained in any reduction to date (scheme 3.30). More importantly however, was the fact that we obtained **121** in 13 % ee. This was a low, but reproducible enantiomeric excess, indicating that asymmetric protonation of the samarium(III) enolate was occurring at last. Why should the reduction of **121** give 13 % ee

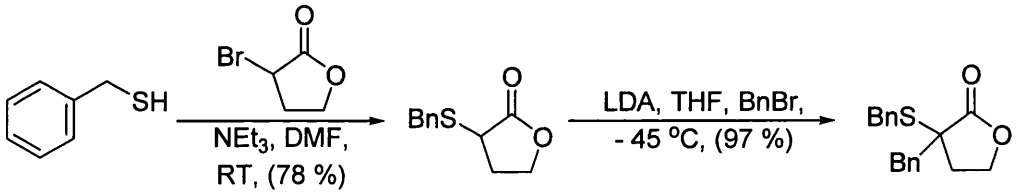
with CPA **210**, while the reduction of the corresponding ether and sulfide lactones **119** and **240**, give racemic products with the same CPA?



139 **121**

Scheme 3.30

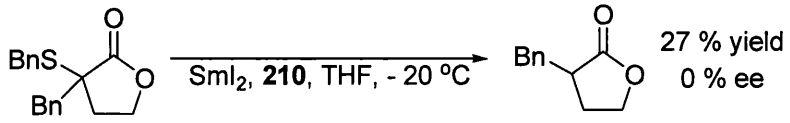
Based on a Merrifield thiol resin used previously within the group to good effect,[37] we next opted to construct a benzyl sulfide and sulfone in order to ascertain whether a similar trend was observed with other sulfide and sulfone substrates. Synthesis of benzyl sulfide **241** began with the reaction of benzylmercaptan **242** with α-bromo-γ-butyrolactone to give **243** in reasonable yield (scheme 3.31). Benzylation of **243** using LDA and benzyl bromide yielded reduction substrate **241** in 97 % yield.



242 **243** **241**

Scheme 3.31

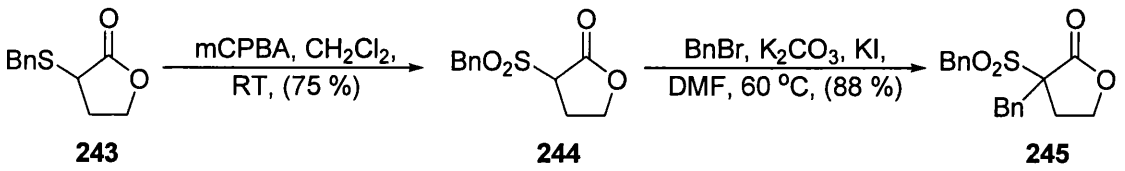
Based on our observations for the reduction of **240**, we expected the reduction of α-benzylsulfanyl lactone **241** to give benzylated lactone **121** in 0 % ee, and indeed this was found to be the case (scheme 3.32).



241 **121**

Scheme 3.32

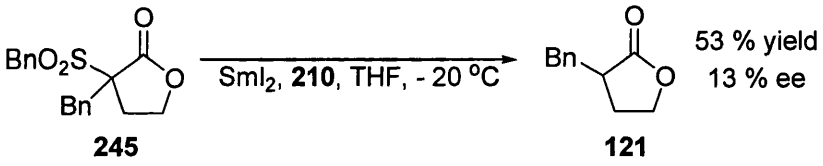
Construction of the analogous benzylated sulfone began by oxidation of **243** with *m*CPBA to give **244** in 75% yield (scheme 3.33). Alkylation of **244** was possible using potassium carbonate and benzyl bromide to give benzylated sulfone **245** in 88 % yield.



243 **244** **245**

Scheme 3.33

Reduction of the sulfone proceeded in reasonable yield to give lactone **121** in 13 % ee (scheme 3.34). This was an important result as it clarified our observation that altering the leaving group does indeed appear to have an effect on the enantioselectivity of the reduction-asymmetric protonation sequence.



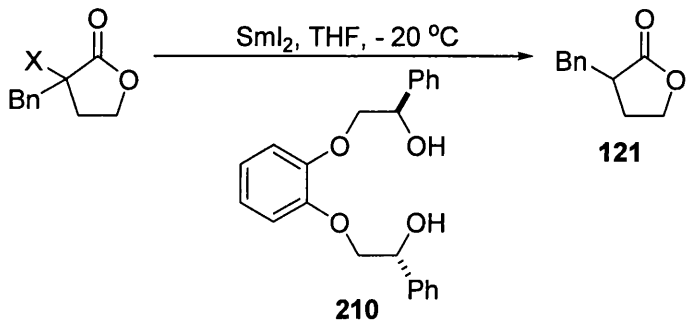
245 **121**

Scheme 3.34

All the experiments carried out in this section were completed under identical conditions using the same CPA **210** (table 3.1). This allowed for direct comparison between substrates as to the effect of the leaving group on the enantioselectivity of the reaction. The conditions were chosen as a balance between enantioselectivity and isolated yield. Whilst an increase in selectivity may have been observed at lower temperatures, reduction of all substrates was not feasible below - 20 °C, and this would have prevented direct comparisons from being made. In addition, we felt that in order to measure accurate enantioselectivities of the products, we required the reduction to yield at least 5 mg of **121**.

The results are summarised in table 3.1. It is apparent from entries 1 – 4 and 6 (table 3.1) that for sulfides and ethers, we do not observe any enantioselectivity. However, it is also

clear from entries 5 and 7 (table 3.1) that when the leaving group is a sulfone, be it aryl or alkyl, then we do obtain **121** with a small, but reproducible, enantiomeric excess.

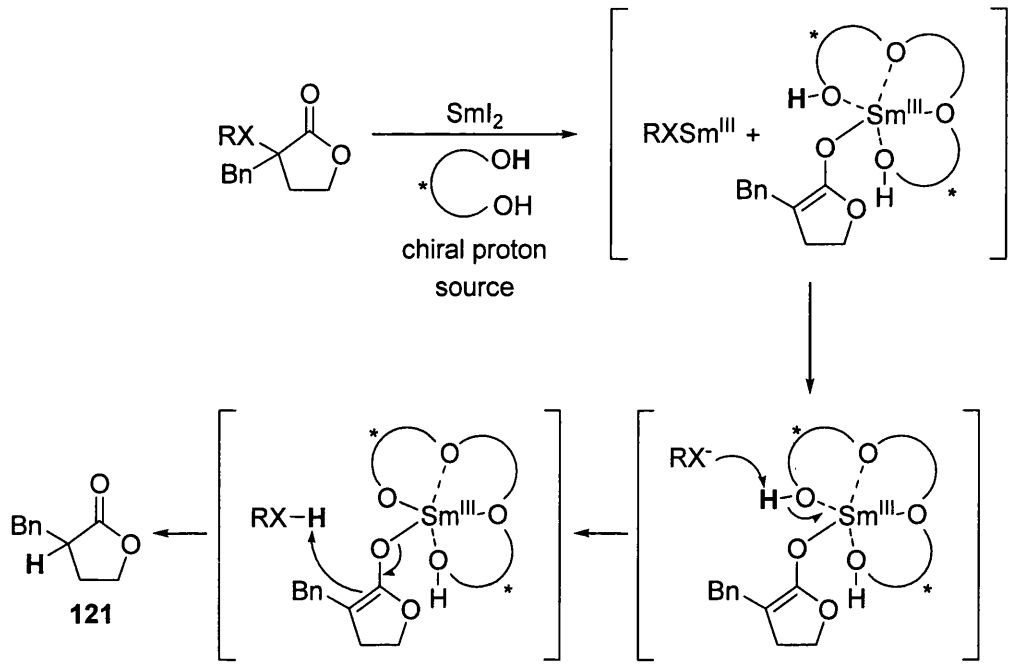


entry	Leaving group X	% yield	% ee
1	ArO- (**119**)	47	0
2	MeO- (**236**)	20	0
3	BnO- (**239**)	37	0
4	ArS- (**240**)	46	0
5	$ArS(O)_2$- (**139**)	76	13 (–)
6	BnS- (**241**)	27	0
7	$BnS(O)_2$- (**245**)	53	13 (–)

Ar = *p*BnO-C_6H_4-

Table 3.1

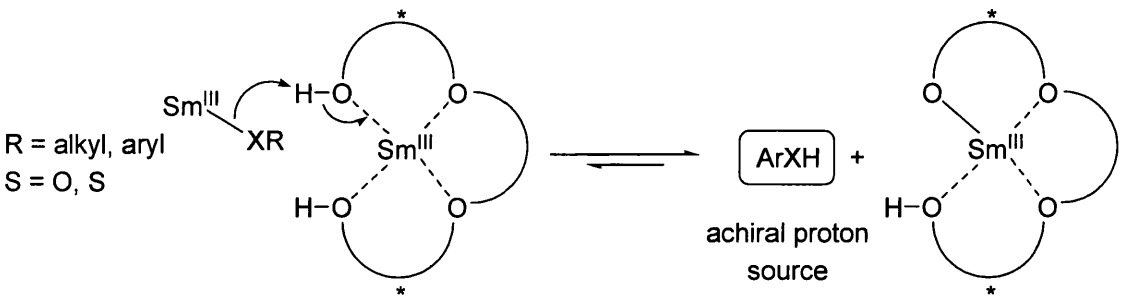
The explanation we propose for the discrepancies observed, concerns the nature of the leaving group, and its ability to interfere with the samarium(III) enolate. One possibility is that the expelled group acts as a ligand for the samarium of the enolate and thus modifies the reactivity and the asymmetry of protonation. As the expelled group is already co-ordinated to a second samarium(III) ion, modification of the samarium(III) enolate is perhaps unlikely. We believe a more likely explanation is that rather than acting as a proton donor toward the enolate, the proton source was, in some cases, donating its proton to the leaving group expelled following the reduction (scheme 3.35).



Scheme 3.35

This would result in the generation of a competing achiral proton source in the reaction mixture, thus leading to a racemic lactone product. This would account for the dramatic 'switching on or off' of the asymmetric induction. In the case of a samarium(III) phenoxide or a samarium(III) thiophenoxide expelled group this would lead to an alcohol or thiol proton source respectively.

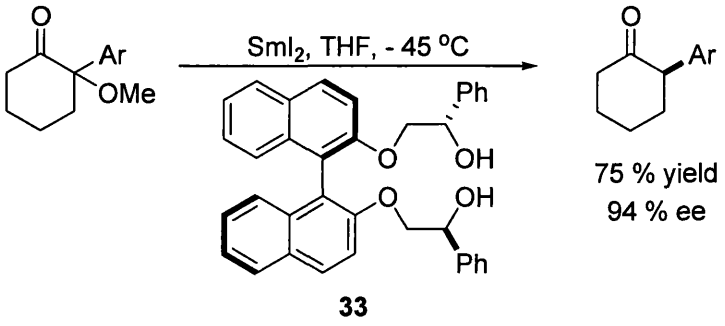
Why would samarium(III) alkoxides or thiolates be able to deprotonate the CPA? We believe multidentate chelation of the chiral proton source to the samarium(III) ion lowers the pk_a of the protons on the CPA by increasing the $\delta(+)$ on the hydroxyl protons and stabilising the conjugate base once the proton is lost (scheme 3.36). Also, as samarium is by nature very oxophilic, an additional driving force would be the formation a strong samarium-oxygen bond between the CPA and the samarium of the enolate.



Scheme 3.36

We believe there is a fine balance of pk_a's in the system. Alkoxides and thiolates lead to achiral proton sources while samarium(III) sulfinates, generated by reduction of sulfones, are insufficiently basic. This is one possible explanation for the observation of asymmetric induction with the use of sulfones.

It was clear that the leaving group was having an effect on the enantioselectivity of our sequence. Takeuchi and co-workers have reported very little effect of the leaving group on the enantioselectivity of the reaction.[46] Indeed, in section 1.3 (scheme 1.20), examples are shown where four cyclohexanone substrates bearing four different α-substituents underwent reduction-asymmetric protonation to give the ketone products with enantioselectivities between 82 and 91 %, a variation of only 9 % ee! In addition, in scheme 3.24 we outlined an example with a methoxy leaving group which gave rise to racemic product. Takeuchi and co-workers however have reported the reduction of cyclic ketones bearing α-methoxy substituents to give products with up to 94 % ee (scheme 3.37).

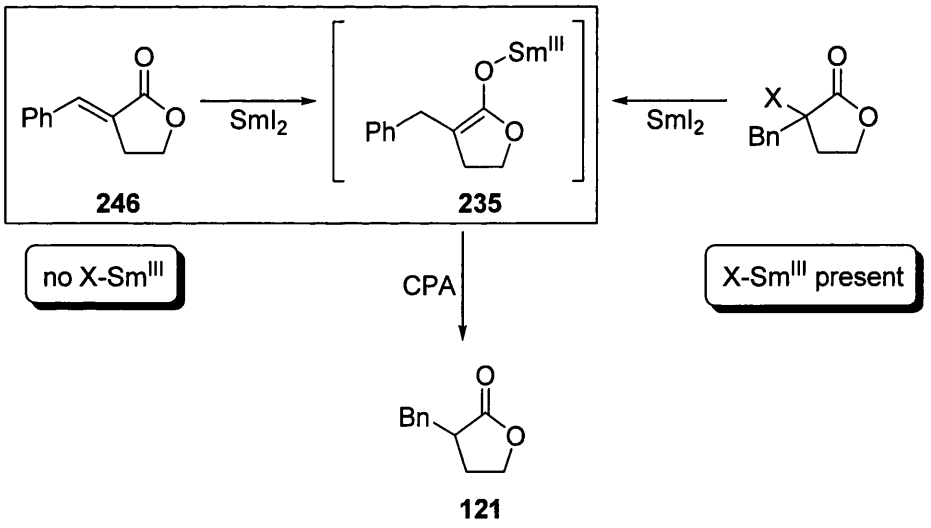


33

Scheme 3.37

To summarise, the reductions of a range of α-heterosubstituted lactones, giving rise to a common enolate intermediate, give different results in the presence of chiral proton source **210**. We originally thought that there should be no difference in the asymmetric induction obtained for each substrate as the proton source protonates the same enolate in each case. The only difference in the reactions summarised in table 3.1 is the nature of the expelled group. We therefore felt confident in stating that, at least for our system, the leaving group has an effect on the enantioselectivity of the reaction.

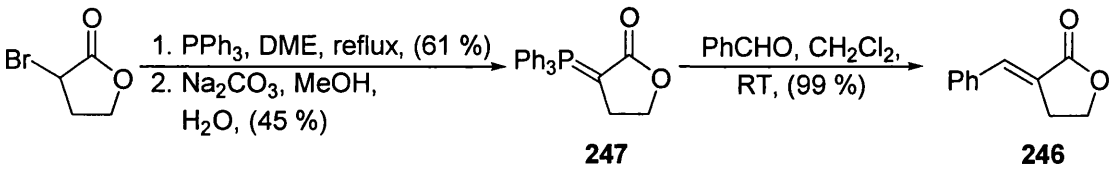
We chose to further investigate the effect of the leaving group. In order to do this, we chose to generate samarium(III) enolate **235** via an alternative method. Our proposal was that generation of **235** in the absence of an expelled group might aid us in understanding the influence of the leaving group on the enantioselectivities of the reaction. We aimed to generate enolate **235** by conjugate reduction of α,β-unsaturated lactone **246** using SmI_2 as opposed to the reduction of an α-heterosubstituted butyrolactone (scheme 3.38). Protonating agents in the reaction mixture would thus react with enolate **235** with no outside influence from a leaving group.



Scheme 3.38

Wittig reagent **247** was prepared from α-bromo-γ-butyrolactone in two steps via the phosponium salt to obtain phosphorane **247** (scheme 3.39). This was converted to α,β-

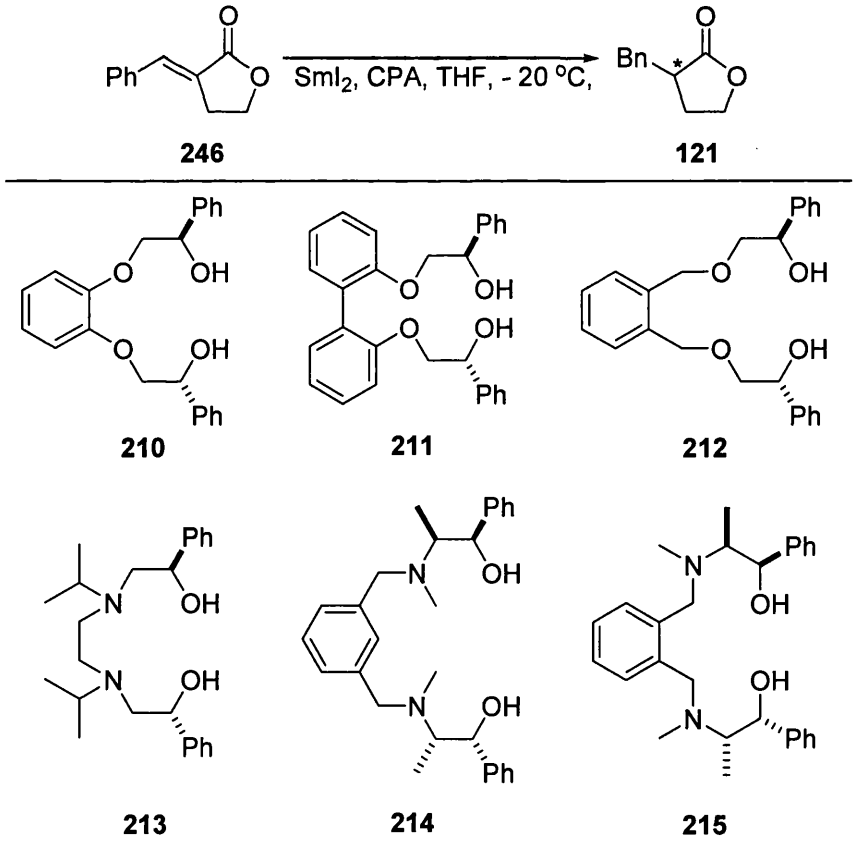
unsaturated lactone **246** via a Wittig reaction of **247** with benzaldehyde.[128] This afforded unsaturated lactone **246** in excellent yield.



247 **246**

Scheme 3.39

The general scheme for the conjugate reduction of α,β-unsaturated lactone **246** is outlined in scheme 3.40. The CPA's used for the reduction were a mixture of tetradentate ligands bearing both oxygen and nitrogen co-ordinating atoms. Proton sources **210**, **211**, **212** and **213** were those taken from Takeuchi's work,[46] whilst **214** and **215** were taken from the work of Pedrosa *et al.*[122]



Scheme 3.40

The results obtained from the conjugate reduction-asymmetric protonation of α,β-unsaturated lactone **246** are illustrated in table 3.2. All the reactions were carried out at least twice to ensure that the results were reproducible and an average of the two similar results was calculated for the table. Reasonable yields were obtained throughout with the isolated yield recorded in the table. It is important to add that in all cases no trace of starting material was apparent in the crude ^{1}H NMR spectrum. We believe some product was lost as a result of the small scale upon which our reactions were carried out. Our best result came from the reduction of **246** in the presence of xylene-derived proton source **212** that gave lactone **121** with an ee of 41 % (table 3.2, entry 3).

Crucially, we obtained non-racemic **121** from the conjugate reduction-asymmetric protonation of **246** in all the reactions with selectivities ranging from 4 – 41 % ee. Evidently, there was some selective interaction between enolate **235** and the CPA. This emphasized the mechanistic significance of obtaining racemic products using ether and thioether-based substrates. This clearly suggests that the samarium(III) alkoxides or thiolates generated from the reduction of α-oxygenated and α-sulfanyl substrates were decreasing the enantioselectivity of the process, regardless of the mechanism by which that occurs.

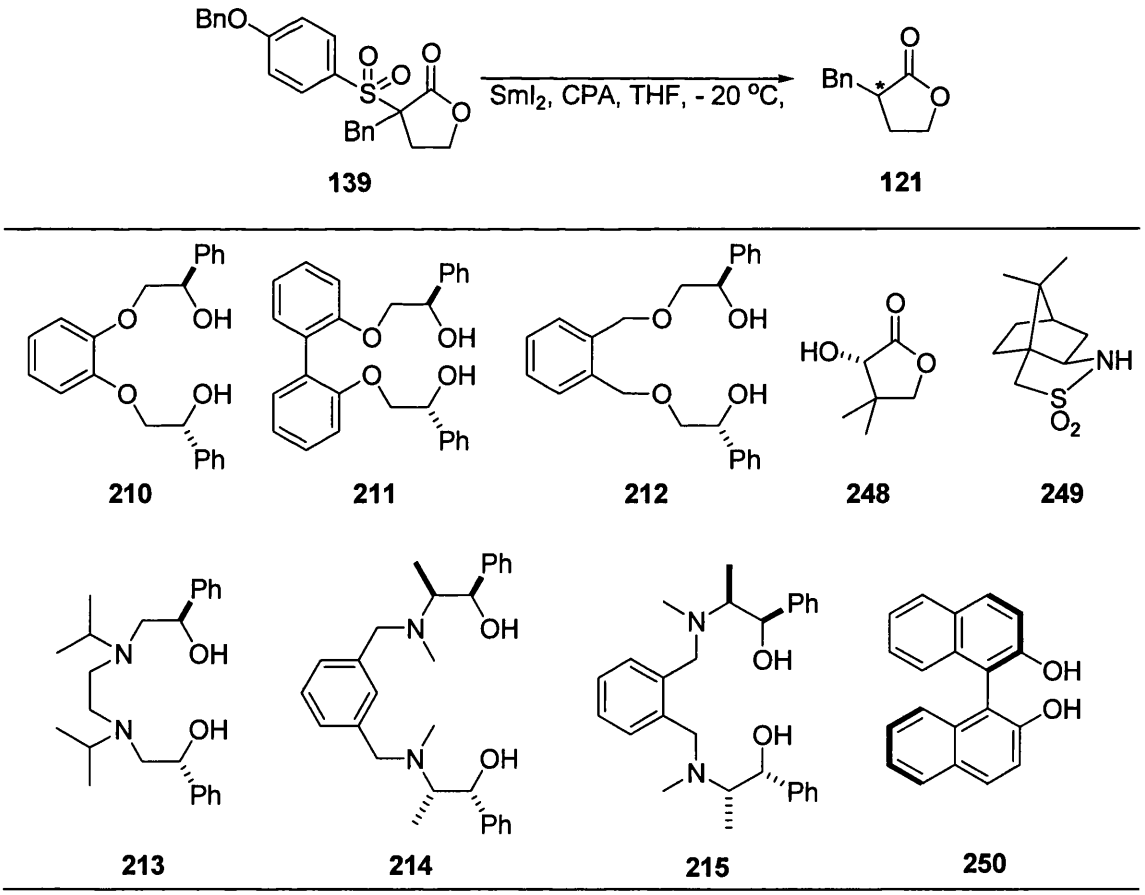
entry	CPA	Isolated yield of **121** (%)	ee of **121** (%)
1	**210**	81	13 (–)
2	**211**	47	10 (–)
3	**212**	55	41 (–)
4	**213**	43	7 (–)
5	**214**	69	4 (–)
6	**215**	62	6 (–)

Table 3.2

We were heartened by these results as we had obtained the same enantioselectivities for the reduction of α-heterosubstituted sulfones in the presence of proton source **210** (table 3.1,

entries 5 and 7) as we did for the conjugate reduction of α,β-unsaturated lactone **246** in the presence of the same proton source (table 3.2, entry 1). We therefore expected to be able to apply our best proton source from the conjugate reduction studies to the reduction of α-heterosubstituted sulfone **139** and obtain 41 % ee! Consequently, we set out to screen the same set of proton sources in the reduction of sulfone **139** as well as trying the reaction in the presence of commercially available proton sources **248**, **249** and **250**.

The general conditions for the series of experiments are shown below. α-Heterosubstituted sulfone **139** was reduced in the presence of a range of CPA's at - 20 °C (scheme 3.41). The conditions for the reduction are identical to those used for the reduction of α-heterosubstituted lactones in table 3.1 and α,β-unsaturated lactone **246** in table 3.2 (scheme 3.40).



Scheme 3.41

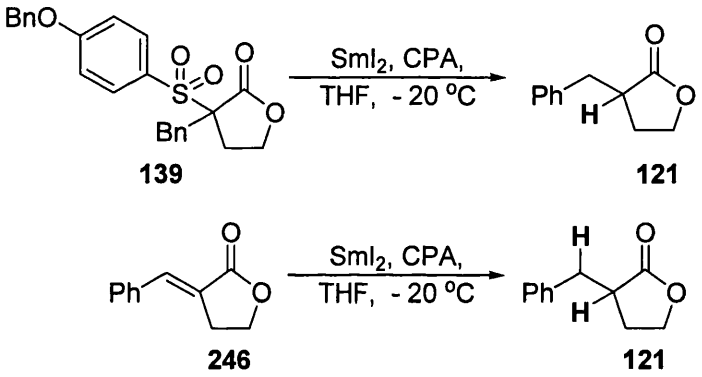
The outcome of screening different proton sources for the reduction of α-heterosubstituted sulfone **139** is illustrated in table 3.3. The initial result is that obtained previously during studies on the effect of the leaving group (table 3.3, entry 1). In this reaction we achieved 13 % ee, and obtained the same selectivity during studies into the reduction of α,β-unsaturated lactone **246** using CPA **210** (table 3.2, entry 1). However, the reduction of **139** in the presence of other proton sources failed to follow the trend. Using biphenol derived CPA **211** we saw selectivities drop from 10 % ee (unsaturated lactone **246**) to an essentially racemic 1 % ee (sulfone **139**, table 3.3, entry 2), whilst in the case of our most promising proton source, xylene-derived **212**, we saw the enantiomeric excess drop from 41 % ee (**246**) to 16 % ee (**139**, table 3.3, entry 3). Attempting the reduction in the presence of (*S*)-(+)-pantolactone **248** and camphorsultam **249** resulted in racemic product (table 3.3, entries 4 and 5). Conversely, the reduction of **139** in the presence of aminoalcohol-derived CPA's **213**, **214** and **215** led to a rise in the enantioselectivity of the reaction with an increase from 7 % ee, 6 % ee and 4 % ee (**246**) to 20 % ee, 19 % ee and 10 % ee (**139**) respectively (table 3.3, entries 6, 7 and 8). In addition, there was a rather surprising switch in the sign of the optical rotation of the product indicating we were observing an opposite sense of asymmetric induction. Finally, the reaction was completed in the presence of commercially available (*R*)-(+)-BINOL **250** which led to **121** in 6 % ee and in low yield (table 3, entry 9).

entry	CPA	Isolated yield of **121** (%)	ee of **121** (%)
1	**210**	76	13 (–)
2	**211**	69	1 (–)
3	**212**	71	16 (–)
4	**248**	86	0
5	**249**	77	0
6	**213**	62	20 (+)
7	**214**	67	19 (+)
8	**215**	71	10 (+)
9	**250**	29	6 (–)

Table 3.3

The next question we asked was why the reduction-asymmetric protonation of **246** using SmI_2 and a CPA gave different results to the reduction-asymmetric protonation of **139** using the same conditions. In particular, why did reduction-asymmetric protonation of **246** using CPA **212** give **121** in 41 % ee whilst reduction-asymmetric protonation of **139** using CPA **212** give **121** in only 16 % ee.

The main difference between those two processes, aside from the presence of an expelled group, is the number of protons needed for the transformation. Reduction of **139** requires only a single proton, while conjugate reduction of **246** requires two (scheme 3.42).



Scheme 3.42

As shown earlier, any protons in the reaction come from the chiral proton source (chapter 3.4). The result is that during the conjugate reduction-asymmetric protonation sequence, the chiral proton source is modified by an initial protonation at the β-carbon leading to enolate **A** (figure 3.4). Reduction of sulfone **139** however may generate enolate **B**.

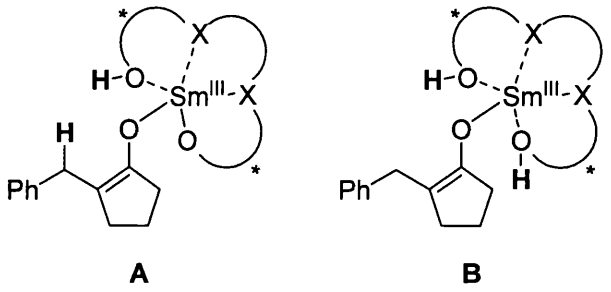


Figure 3.4

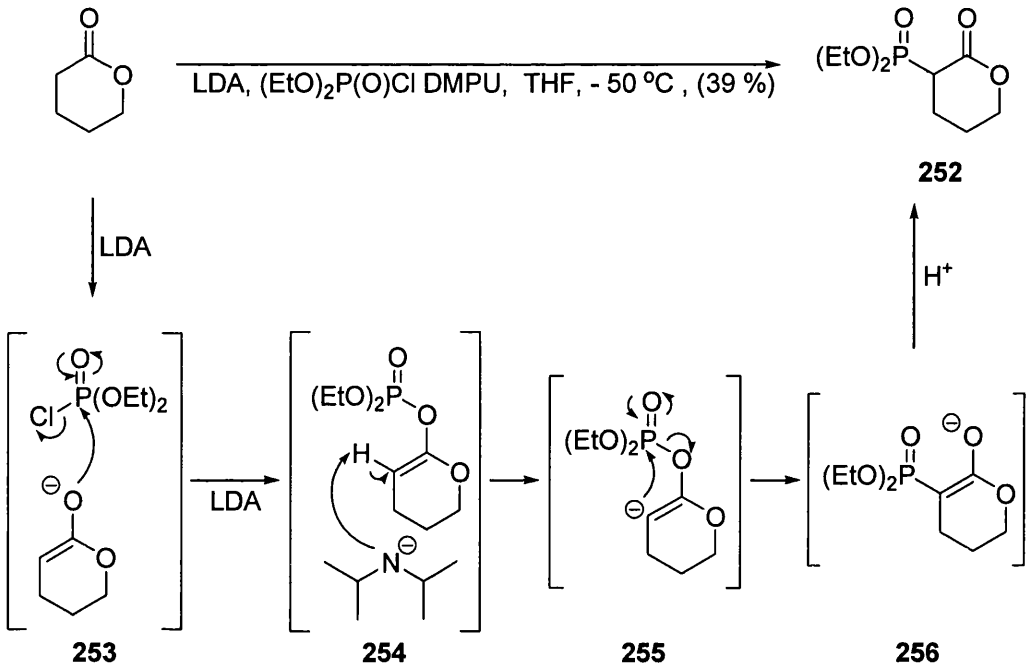
As the samarium(III) enolate is involved at the critical point of the reaction when enantioselectivity is introduced, it is conceivable that this minor difference in the enolate is leading to increased enantioselectivities in the cases of protonating agents **210**, **211** and **212** and could possibly also lie behind the switch in the sense of induction in the cases where the protonating agents are **213**, **214** and **215**.

To summarise, we have made some interesting observations in the reduction-asymmetric protonation sequence. It is clear that using a tetradentate proton source leads to greater enantioselectivities than mono- or bidentate proton sources, presumably because multidentate proton sources better co-ordinate to samarium(III).

3.6 Investigating the effect of ring size on enantioselectivity

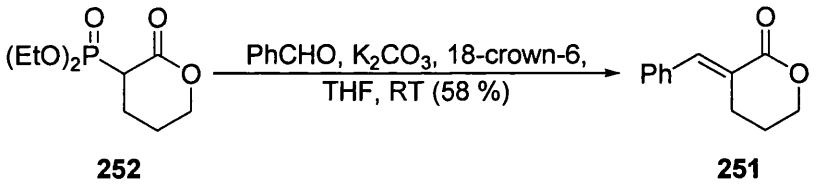
One major difference in the substrates investigated by Takeuchi and our model substrate is ring size. Whilst we have concentrated our efforts on five-membered lactones, Takeuchi's examples are all on cyclic six-membered ketones and lactones. Ring size and type may be crucial in affecting the enantioselectivity of the reaction. In order to ascertain whether this was the case, we decided to prepare the analogous six-membered α,β-unsaturated lactone **251** and carry out the conjugate reduction with SmI_2 in the presence of chiral proton sources.

Our synthesis of α,β-unsaturated-δ-valerolactone **251** began with the preparation of phosphonate **252** using LDA and diethyl chlorophosphonate in 39 % yield (scheme 3.43).[129, 130] The mechanism for the transformation is illustrated in scheme 3.44. First, one equivalent of LDA deprotonates the lactone α-to the carbonyl to give enol **253** which reacts with diethyl chlorophosphonate leading to enolate **254**. A second equivalent of LDA then abstracts a proton from the α-position in **254** to afford anion **255**. The phosphonate group then migrates to the α-position to afford structure **256**. Aqueous work up finally releases **252**.



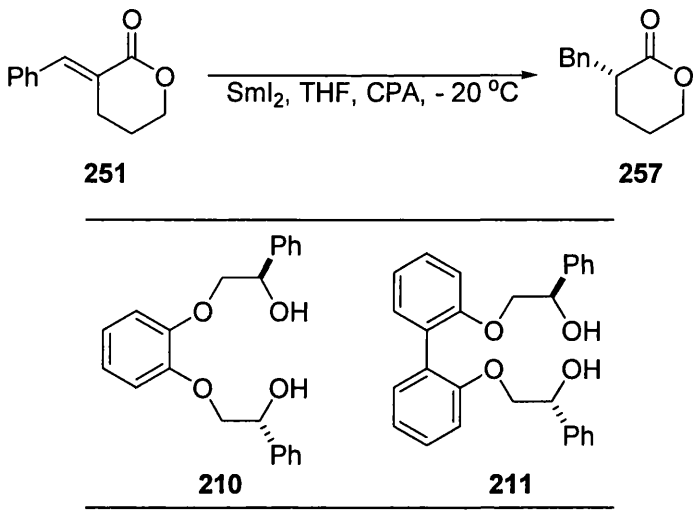
Scheme 3.43

Phosphonate **252** was then converted to α,β-unsaturated-δ-valerolactone **251** via a Horner-Wadsworth-Emmons reaction with benzaldehyde. Unsaturated lactone **251** was obtained as a single isomer in 58 % yield (scheme 3.44).



Scheme 3.44

We employed our standard conditions for the reduction and these are outlined below (scheme 3.45).



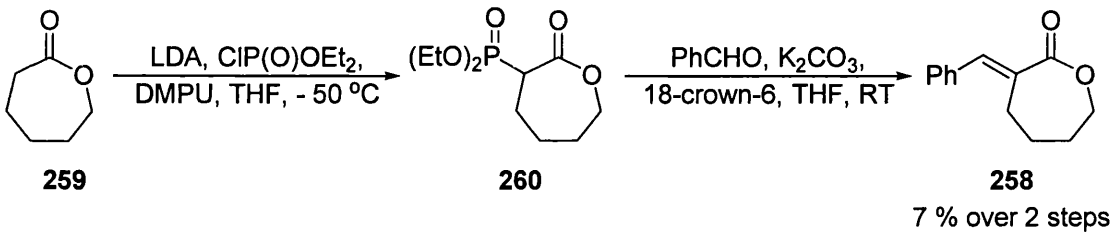
Scheme 3.45

Two of Takeuchi's proton sources; catechol-derived proton source **210** and biphenol-derived proton source **211** were used in the reduction of the **251** (figure 3.5). Conjugate reduction in the presence of chiral proton source **210** led to the saturated product **257** in 42 % yield and in 7 % ee (table 3.4, entry 1). Reduction in the presence of biphenol-derived proton source **211** led to lactone **257** with slightly lower selectivity (table 3.4, entry 2). In both cases, reduction-asymmetric protonation of **251** gave rise to the product with *R*-configuration.[131, 132] It should be pointed out that in the case of lactone product **257**, enantiomeric excess was determined by optical rotation and comparison made with the literature rotation. As a result, there is a greater error associated with the enantioselectivities reported, particularly as the rotations were measured on small quantities (< 10 mg) of **257**.

entry	CPA	Isolated yield of **257** (%)	ee of **257** (%)	Config.
1	**210**	42	7	*R* (+)
2	**211**	38	6	*R* (+)

Table 3.4

These results seem to suggest that ring size, certainly a difference of one methylene unit, does not have an effect on the enantioselectivity of the sequence. However, we had also planned to attempt the conjugate reduction-asymmetric protonation of the analogous seven-membered unsaturated lactone **258**. Synthesis began from ε-caprolactone **259** which was converted to phosphonate **260** (scheme 3.46). Due to difficulties in removing DMPU from the crude mixture, **260** was used without further purification for the Horner-Wadsworth-Emmons reaction with benzaldehyde. This led to α,β-unsaturated-ε-caprolactone **258** in a disappointingly low 7 % yield over the two steps.

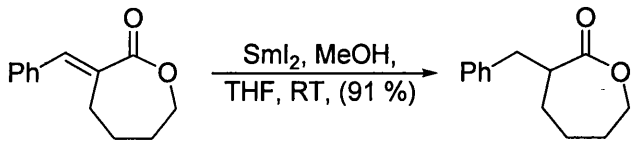


259 **260** **258**

7 % over 2 steps

Scheme 3.46

Conjugate reduction of **258** was first carried out using methanol to obtain racemic **261** for the determination of chiral HPLC conditions. This led to α-benzyl-ε-caprolactone **261** in an excellent 91 % (scheme 3.47). However, when the same transformation was carried out at -20 °C in the presence of chiral proton source **210**, we failed to observe any of the reduced lactone, although starting material **258** was recovered. Unfortunately, we had insufficient time to repeat the reduction of this substrate.



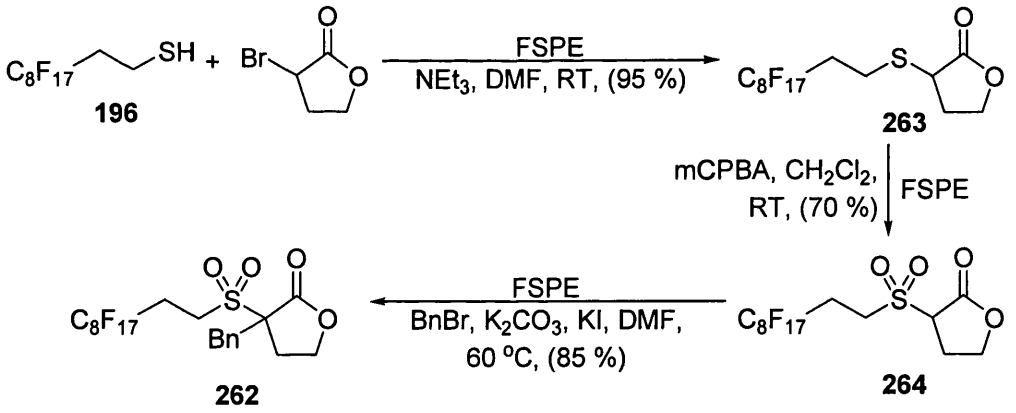
258 **261**

Scheme 3.47

3.7 Phase-tag assisted synthesis

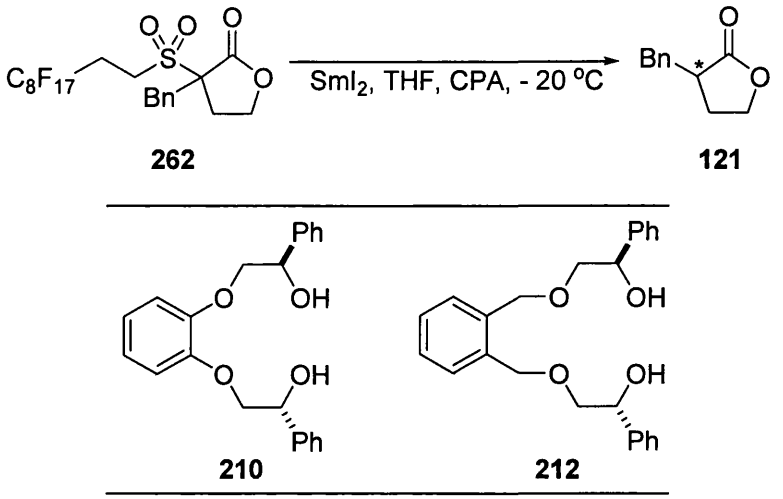
Having ascertained that a sequential cleavage-asymmetric protonation strategy should be feasible for use in sulfone linker systems, we sought to illustrate the concept in a phase tag-assisted synthesis. Having previously encountered many problems with solid phase synthesis, we opted to demonstrate our methodology in the cleavage of a fluorous phase tag from a simple butyrolactone substrate.

Synthesis of fluorous-tagged butyrolactone **262** began with the coupling of the fluorous thiol, $C_8F_{17}CH_2CH_2SH$ **196**, and α-bromo-γ-butyrolactone using triethylamine to afford **263** in 95 % yield (scheme 3.48). This was oxidised in 70 % yield using *m*CPBA to give sulfone **264**. Benzylation was accomplished through the use of benzyl bromide and potassium carbonate and gave alkylated sulfone **262** in good yield. Fluorous solid phase extraction (FSPE) was used successfully throughout this synthesis for the purification of intermediates.



Scheme 3.48

Reductive cleavage of the phase tag proceeded well under identical conditions to those used in previous reduction-asymmetric protonation studies. The cleavage was attempted in the presence of our better proton sources, and the general scheme for the reaction is illustrated below (scheme 3.49).



Scheme 3.49

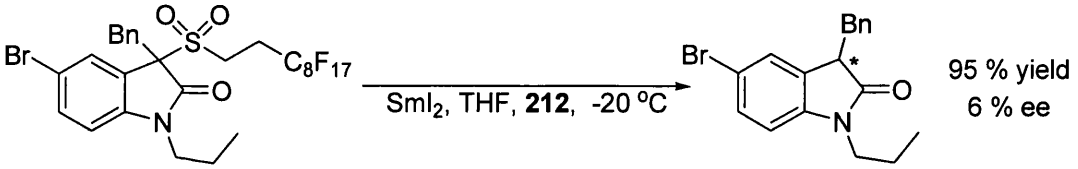
The two proton sources employed for this reaction are illustrated above, with the results obtained shown in the table 3.5. Cleavage of fluorous-tagged lactone **262** in the presence of proton source **210** led to lactone **121** in 78 % yield and in 14 % ee (table 3.5, entry 1). Attempting the reduction with the best proton source **212** led to **121** this time in a yield of 82 % and in 18 % ee (table 3.5, entry 2). Whilst these enantioselectivities are low, we believe this is the first instance of asymmetry being introduced in the final step of a phase-tag assisted synthesis and as such our results are significant and show the feasibility of the cleavage-asymmetric protonation strategy.

entry	CPA	Isolated yield of **121** (%)	ee of **121** (%)
1	**210**	78	14
2	**212**	82	18

Table 3.5

During our studies into the cleavage of a phase tag and our preceding investigations into the asymmetric protonation of samarium enolates, we often felt that the lack of selectivity encountered might simply be due to an unfortunate choice of model substrate for the development of our methodology. Accordingly, we decided to attempt the cleavage-asymmetric protonation on fluorous-tagged oxindole **265**, which had been prepared by

another member of the group (scheme 3.50).[133] We first found chiral HPLC conditions for the separation of the two enantiomers of **266**. The reduction-protonation proceeded in excellent yield, unfortunately, chiral HPLC analysis revealed **266** was isolated with an enantiomeric excess of only 6 %.



265 **266**

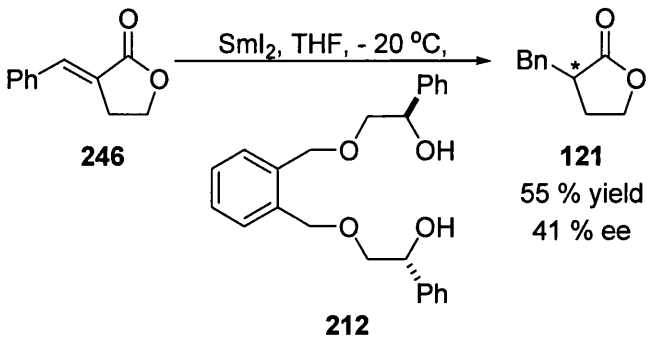
Scheme 3.50

Whilst we have not achieved satisfactory selectivities in these reactions, we have demonstrated that cleavage of our linker in the presence of a CPA yields enantiomerically enriched carbonyl compounds after a phase tag assisted synthesis. Future screening of other proton sources as well as attempting the reduction on other fluorous-tagged carbonyl compounds might result in higher selectivities and a better understanding of the process.

3.8 Conclusions

Whilst these studies have thrown up more questions than answers, some important points and conclusions can be drawn from the results. Firstly, it is apparent that the nature of the leaving group does have an effect on the reduction-asymmetric protonation of α-substituted butyrolactones. We have advanced the theory that the isolation of racemic products is due to proton transfer from the CPA to the samarium(III) complex of the expelled group, leading to generation of an achiral proton source and non-selective protonation of the samarium(III) enolate.

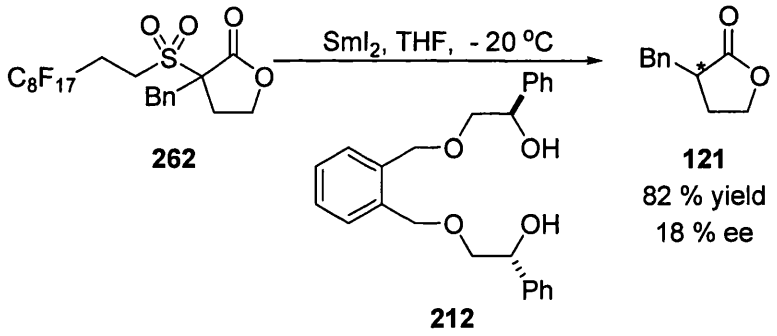
Secondly, comparisons between the different proton sources employed gave insights into ligand design for this and similar processes. We obtained enantioselectivities of up to 41 % ee using tetradentate oxygen proton sources (scheme 3.51). Using aminoalcohol-derived proton sources with two oxygen and two nitrogen atoms available for co-ordination, led to enantioselectivities up to 20 % ee. However, the use of bidentate (*R*)-(+)-BINOL led to a maximum enantiomeric excess of only 6 % ee, whilst attempts made using mono-dentate (*S*)-(+)-pantolactone and camphorsultam resulted in racemic product. This implies that the reaction relies upon a structured transition state in which maximum co-ordination between the protonating ligand and the samarium(III) enolate is necessary to give any enantioselectivity.



Scheme 3.51

We have also proposed a theory as to why enantioselectivities obtained in the reduction of α-sulfonyl-γ-butyrolactones such as **139** and **245** give different levels of enantioselectivity compared to conjugate reduction of α,β-unsaturated lactone **246**. This theory is based once again on the nature of the protonating species: In the conjugate reduction-asymmetric protonation of unsaturated lactone **246**, the CPA is modified by an initial protonation of the substrate prior to the key protonation of the samarium(III) enolate. We believe the modified nature of the CPA leads to different enantioselectivities.

Finally, we have developed a strategy for the phase-tag assisted synthesis of enantiomerically enriched carbonyl compounds where asymmetry is introduced in the final cleavage step (scheme 3.52). Despite the low enantioselectivities observed, the methodology is still in its infancy and may yet prove advantageous for library synthesis.



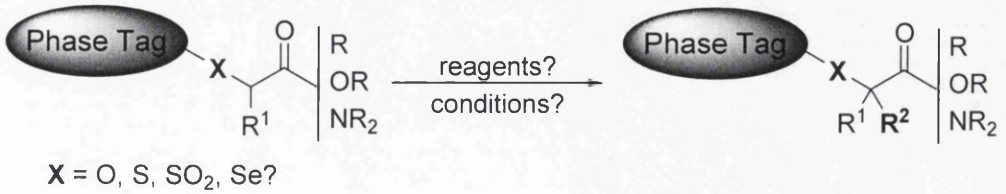
Scheme 3.52

Chapter 4: Future work

The nature of the project and the results obtained has left numerous directions that future work might take. In both chapters 2 and 3, we saw studies towards the construction of functionalised azepinones using our linker and phase tag methodology, as well as the potential for introducing chirality into a phase tag assisted synthesis. The ultimate aim for any future work would attempt to encompass both these disciplines and apply them to create a small library of enantiomerically enriched pharmaceutically important molecules or building blocks. However, the realisation of this would require further exhaustive studies into the optimisation of either a solid or fluorous phase route to azepinones as well as the screening of a larger, more diverse array of chiral proton sources. In the short term, future aims will involve responding to some of the more pressing questions thrown up by the research, particularly regarding the cleavage-enantioselective protonation work.

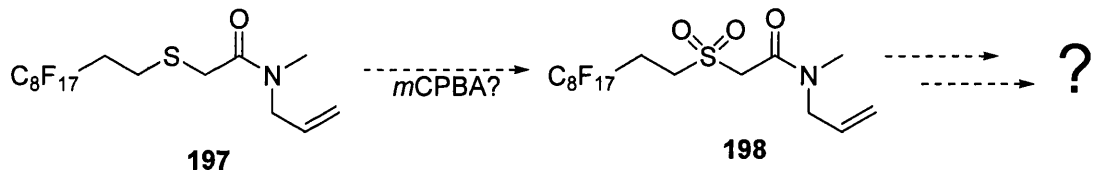
Limited success has been achieved thus far on solid phase, and only when using an ether linker. The identification of thiol resins better suited to the reaction conditions employed in our synthesis of azepinones might provide more satisfactory results on solid phase.

One of the initial goals of this project was to investigate the potential for the alkylation of substrates bound to a phase tag using our linker. Although we made some progress towards our goal, we were generally unable to transfer promising solution studies to solid phase. We believe this was largely due to the reagents employed for the transformation, and as such, further studies to identify a more 'resin friendly' means of alkylation is an area well worth investigating (scheme 4.1). Also, would using a selenium linking atom offer any advantages in the transformation?



Scheme 4.1

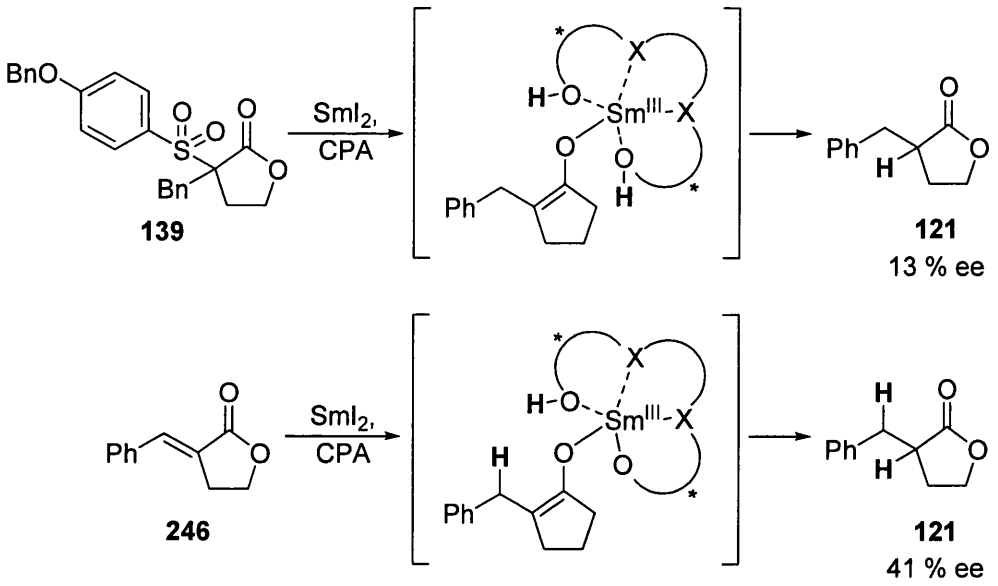
The work thus far undertaken into the construction of azepinones on solid phase has been fraught with complications, largely due to the nature of the starting resin as mentioned earlier. However, a number of solution phase routes towards such templates have been successful and attempting to perform these on other polymer backbones may afford a more positive outcome. At present a route utilising a fluorous tag appears the most promising. Although this route ultimately failed, a lack of time meant we were unable to optimise any of the reactions attempted. For instance, the use of *m*CPBA to change the oxidation state of the linking sulfur atom in **197** as opposed to oxone, could be investigated as previous experience showed that a more selective reaction can be obtained using *m*CPBA when the substrate also contains an alkene (scheme 4.2).



197 **198**

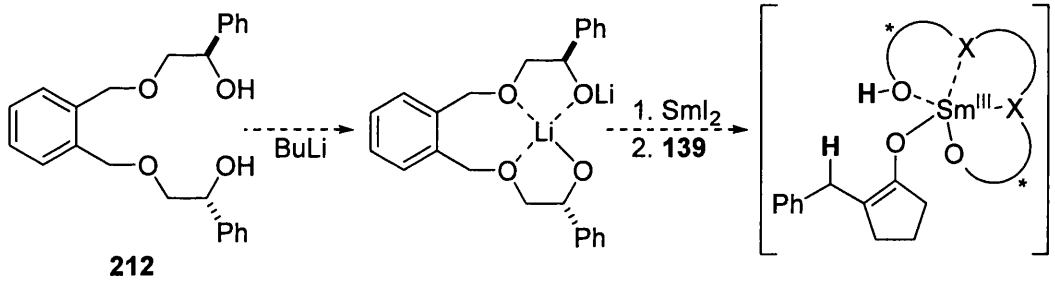
Scheme 4.2

In the second part of my work, whilst screening a large number of diverse, tetradentate chiral proton sources may eventually yield a suitable proton source for the construction of enantiomerically enriched lactones, understanding the process is of more importance. Therefore, further mechanistic studies should take priority. In particular, the nature of the protonating species must be investigated. This would help us to explain the different selectivities observed in the reduction of **139** and **246** in the presence of the same CPA (scheme 4.3).



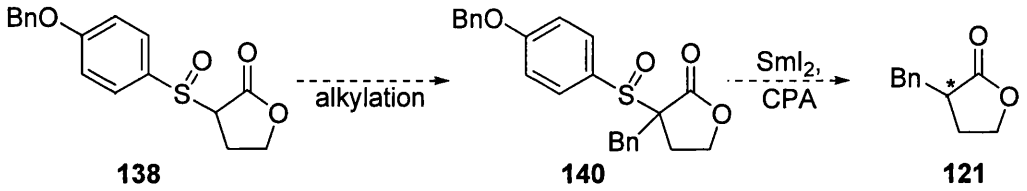
Scheme 4.3

An attempt should be made to independently prepare the protonating species that we believe is present in the reduction of α,β-unsaturated lactones. One such way would be to deprotonate the CPA initially using ^{n}butyllithium then displacing the lithium ion with the larger samarium ion (scheme 4.4). Would this lead to a similar CPA to that generated in the conjugate reduction of **246**? Would this lead to enhanced enantioselectivities?



Scheme 4.4

Another interesting study would be to carry out the reduction of benzylated sulfoxide **140** (scheme 4.5). Would the reduction of this lead to 0 % ee, as observed for the corresponding sulfide or 13 % ee, as observed for the corresponding sulfone?



138 **140** **121**

Scheme 4.5

Introducing chirality at the final point in a phase tag assisted synthesis via a cleavage-enantioselective protonation strategy will allow access to enantiomerically enriched carbonyl compounds. When the final cleavage-enantioselective protonation sequence is optimised it will be applied to a range of immobilised (or tagged) substrates, thus allowing the asymmetric synthesis of libraries of pharmaceutically relevant classes.

Chapter 5: Experimental section

5.1 General experimental

All experiments were carried out under an atmosphere of nitrogen or argon using anhydrous solvents unless otherwise stated. Reactions were carried out using oven-dried glassware. THF was distilled from sodium and benzophenone. CH_2Cl_2, toluene and diisopropylamine were distilled from CaH_2 under Ar/N_2. NEt_3 and DMSO were distilled from CaH_2 and stored over KOH and under Ar/N_2. Reagents were purchased and used without purification unless stated. Distilled water was used throughout.

Samarium (II) iodide was prepared by the method of Imamoto[134] with the modification that the samarium-iodine solution was heated at 60 °C rather than at reflux.

Column chromatography was carried out using Fischer Matrix silica gel 60 and FluoroFlash silica. Macherey-Nagel aluminium backed plates, pre-coated with silica gel 60 (UV_{254}), were used for thin layer chromatography and were visualized by illumination with UV light or staining with alkali $KMnO_4$.

^1H and ^{13}C NMR spectra were recorded on both Varian 300 and Bruker DPX-400 and DPX-500 Fourier transform spectrometers with chemical shift values being reported in ppm relative to residual chloroform ($\delta_H = 7.27$ or $\delta_C = 77.0$) as an internal standard unless otherwise stated. NMR signals were assigned using DEPT 45, 90 and 135, HMQC and COSY spectra. All coupling constants are reported in Hertz (Hz). Rationalisation of coupling constants has been carried out where required. Peaks associated with the perfluoro chain in fluorous tagged compounds were not recorded as they were too weak to be visible in the ^{13}C spectra.

IR spectra (KBr/NaCl) were recorded using a JASCO FT/IR 410 and Impact 400 spectrometer. ATR IR spectra were recorded on a Bio-Rad Merlin Excaliber spectrometer. Mass Spectra were recorded at the University of Glasgow and the University of Manchester

using a JEOL JMS-700 spectrometer. Melting points were recorded on Kofler hot stage apparatus and are uncorrected. GC analysis of **121** was carried out using a Supelco column β-dex 110. 50 °C to 230 °C at 1 °Cmin^{-1} with a flow rate of 20 mls^{-1}. Approximate retention times: 105.2 (- enantiomer), 106.8 (+ enantiomer).

Solid phase reactions were carried out in round bottom flasks and were performed with gentle stirring. In some cases reactions were performed in polypropylene bond elute cartridges which were placed in a carousel and rotated, such reactions are indicated within the experimental. Commercially available bromo-Wang resin with a loading of 1.40 mmol/g was used. Solvents and soluble reagents were removed by high pressure water suction after transferral of the reaction suspension into polypropylene bond elute cartridges (25 ml or 50 ml fitted with a polyethylene porous disc), using approximately 50 ml solvent per gram of resin for each wash.

THF used for washing resin was distilled prior to use. The resin was washed with THF (30 ml), THF:H_2O (3:1) (3 × 30 ml), THF:H_2O (1:1) (3 × 30 ml), THF:H_2O (1:3) (3 × 30 ml), THF (2 × 30 ml), then alternate washings with CH_2Cl_2 (3 × 30 ml) and MeOH (3 × 30 ml), finishing with THF (2 × 30 ml). The resin was then left to dry for 10 min under water pump pressure before being dried for at least 6 h under high vacuum.

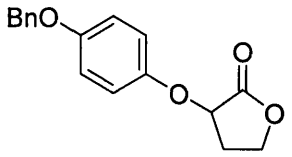
Calculation of the theoretical loading of resins was carried out according to the equation:

$S_{(th)}$ - Theoretical substitution
$S_{(s)}$ - Starting substitution mmol/g
Wt - g/mol added to resin

$$S_{(th)} = \frac{S_{(s)}}{1 + \left(\frac{S_{(s)} \times \Delta\ Wt}{1000}\right)}$$

5.2 Experimental

3-(4-Benzyloxyphenoxy)dihydro-furan-2-one 117[36]

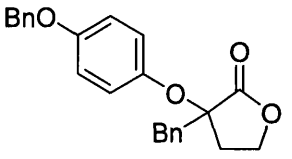


117

K_2CO_3 (3.45 g, 25.0 mmol) was added to a solution containing α–bromo-γ-butyrolactone (1.85 ml, 20.0 mmol) and 4-benzyloxyphenol **115** (1.00 g, 4.99 mmol) in DMF (75 ml) and the mixture was stirred at room temperature for 48 h. The reaction mixture was quenched with aqueous saturated NH_4Cl (5 ml) followed by H_2O (10 ml) and then extracted with 30 % EtOAc/pet. ether (3 × 10 ml). The organic layers were then dried ($MgSO_4$) and concentrated. The crude mixture was purified by column chromatography (silica, 80 % EtOAc/pet. ether) to give 3-(4-benzyloxyphenoxy)dihydro-furan-2-one **117** (951 mg, 3.35 mmol, 67 %).

^{1}H NMR: δ_H (400 MHz, $CDCl_3$) 2.46 (1H, dt, J = 8.0, 13.3 Hz, CH_AH$_B$CH), 2.64-2.70 (1H, m, CH$_A$$H_B$CH), 4.34 (1H, m, C$H_AH_B$O), 4.52 (1H, dt, J = 8.0, 4.1, CH$_A$$H_B$O), 4.84 (1H, t, J = 8.0 Hz, CH), 5.04 (2H, s, $PhCH_2$), 6.93 (2H, d, J = 6.9 Hz, 2 × ArH), 7.00 (2H, d, J = 6.9 Hz, 2 × ArH), 7.44-7.31 (5H, m, ArH).

3-Benzyl-3-(4-benzyloxyphenoxy)dihydro-furan-2-one 119



119

To a solution of diisopropylamine (345 µl, 2.46 mmol), in THF (10 ml) that had been cooled to -45 °C was added ^{n}BuLi (985 µl, 2.46 mmol, 2.5 M in hexane). The reaction

mixture was then stirred for 30 min. A solution of **117** (500 mg, 1.76 mmol) in THF (10 ml) was then added dropwise by cannula and the reaction was stirred for a further 30 min. Finally, benzyl bromide (837 µl, 7.04 mmol) was added dropwise to the solution and the reaction mixture was allowed to warm slowly to -20 °C and stirred for 1.5 h. The reaction mixture was quenched with aqueous saturated NH_4Cl (3 ml) followed by H_2O (5 ml) and the aqueous layer extracted with 40 % EtOAc/pet. ether (3 × 5 ml). The organic layer was then dried ($MgSO_4$), and concentrated. The crude mixture was purified by column chromatography (silica, 100 % CH_2Cl_2) to give 3-benzyl-3-(4-benzyloxyphenoxy)dihydro-furan-2-one **119** as a white solid (461 mg, 1.20 mmol, 68 %).

^{1}H NMR: δ_H (400 MHz, $CDCl_3$) 2.30-2.23 (1H, m, C*H*$_A$H$_B$CH$_2$OC=O), 2.48-2.41 (1H, m, CH$_A$*H*$_B$CH$_2$OC=O), 3.23 (1H, apparent d, J = 13.6 Hz, PhCH$_2$C), 3.32 (1H, apparent d, J = 13.6 Hz, PhCH$_2$C), 3.80-3.74 (1H, m, 1 H from CH$_2$OC=O), 4.11-4.05 (1H, m, 1 H from CH$_2$OC=O), 5.03 (2H, s, PhCH$_2$O), 7.01-6.87 (4H, m, 4 × ArH), 7.50-7.32 (10H, m, 10 × ArH).

^{13}C NMR: δ_C (100 MHz, $CDCl_3$) 30.2 (*C*H$_2$CH$_2$O), 41.4 (Ph*C*H$_2$C), 65.0 (CH$_2$*C*H$_2$O), 70.4 (PhCH$_2$O) 83.2 (ArC), 115.3 (2 × ArCH), 127.1 (2 × ArCH), 127.3 (2 × ArCH), 127.6 (ArCH), 127.9 (2 × ArCH), 128.1 (ArCH), 130.2 (2 × ArCH), 130.4 (2 × ArCH), 134.5 (O*C*C=O), 136.8 (ArC), 147.9 (ArCO), 155.6 (ArCO), 175.9 (C=O).

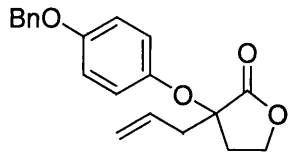
ν_{max} KBr/ cm^{-1} 3529 br, 1776 m (C=O), 1504 s, 1454 s, 1379 s, 1207 br, 1025 m, 845 s, 759 m.

MS (EI): *m/z* 374 (M$^+$, 16 %), 200, 131, 91 (Bn$^+$, 100 %).

HRMS: Found 374.1517, $C_{24}H_{22}O_4$, requires 374.1518.

MP: 83.8 – 85.2 °C.

3-Allyl-3-(4-benzyloxyphenoxy)dihydro-furan-2-one 120



120

To a solution of diisopropylamine (69.0 μl, 0.49 mmol), in THF (2 ml) that had been cooled to -45 °C was added ^{n}BuLi (221 μl, 0.49 mmol, 2.5 M in hexane). The reaction mixture was then stirred for 30 min. A solution of **117** (100 mg, 0.35 mmol) in THF (3 ml) was then added dropwise via cannula and the reaction was stirred for a further 30 min. Finally, allyl bromide (152 μl, 1.76 mmol) was added dropwise to the solution and the reaction mixture was allowed to warm slowly to -20 °C and stirred for 1 h. The reaction mixture was quenched first with aqueous saturated NH_4Cl (3 ml) followed by H_2O (5 ml) and the aqueous layer extracted with 40 % EtOAc/pet. ether (3 × 5 ml). The organic layer was then dried ($MgSO_4$), and concentrated. The crude mixture was purified by column chromatography (silica, 100 % CH_2Cl_2) to give 3-allyl-3-(4-benzyloxyphenoxy)dihydro-furan-2-one **120** as a clear oil (87 mg, 0.25 mmol, 73 %).

^{1}H NMR: δ_H (400 MHz, $CDCl_3$) 2.66-2.29 (1H, m, CH_AH$_B$CH$_2$O), 2.59-2.49 (2H, m, CH_2CH=CH$_2$), 2.82-2.76 (1H, m, CH$_A$$H_BCH_2$O), 4.28-4.19 (2H, m, CH$_2$O), 5.02 (2H, s, PhCH$_2$O), 5.14 (1H, dd, J = 1.5, 10.3 Hz, CH=CH_AH$_B$), 5.16 (1H, dd, J = 1.5, 15.5 Hz, CH=CH$_A$$H_B$), 5.94-5.84 (1H, m, C$H$=CH$_2$), 7.01-6.88 (4H, m, 4 × ArH), 7.50-7.32 (5H, m, 2 × ArH).

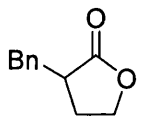
^{13}C NMR: δ_C (100 MHz, $CDCl_3$) 31.2 (*C*H$_2$CH$_2$O), 39.2 (*C*H$_2$CH), 65.1 (CH$_2$*C*H$_2$O), 70.3 (PhCH$_2$O), 82.1 (ArC), 115.4 (2 × ArCH), 120.3 (CH=*C*H$_2$), 123.0 (2 × ArCH), 127.2 (2 × ArCH), 127.7 (ArCH), 128.3 (2 × ArCH), 131.0 (*C*H=CH$_2$), 136.8 (O*C*C=O), 147.8 (ArCO), 155.6 (ArCO), 175.2 (C=O).

ν_{max} KBr/ cm^{-1} 3536 br, 2918 m, 1778 m (C=O), 1504 m, 1378 s, 1207 br, 1024 m, 843 s, 741 s.

MS (EI): *m/z* 324 (M$^+$, 44 %), 200, 125, 91 (Bn$^+$, 100 %).

HRMS: Found 324.1360, $C_{20}H_{20}O_4$, requires 324.1362.

3-Benzyldihydro-2(3*H*)-furanone 121



121

A solution of SmI_2 (7.38 ml, 0.74 mmol, 0.1 M in THF), was added to a solution of 3-benzyl-3-(4-benzyloxyphenoxy)dihydro-furan-2-one **119** (115 mg, 0.31 mmol) in MeOH (2.5 ml) and THF (2.5 ml) that had been cooled to 0 °C. The mixture was then stirred before being allowed to warm to room temperature. After 1 h, a further 2.4 equivalents of SmI_2 (7.38 ml, 0.74 mmol, 0.1 M in THF) was added and the reaction was allowed to stir for another 4 h. The reaction mixture was quenched first with aqueous saturated NH_4Cl (2 ml) followed by H_2O (2 ml) and the aqueous layer extracted with Et_2O (3 × 20 ml). The organic layer was then dried ($MgSO_4$), and concentrated. The crude mixture was purified by column chromatography (silica, 100 % CH_2Cl_2) to give 3-benzyldihydro-2(3*H*)-furanone **121** as a yellow oil (46 mg, 0.26 mmol, 84 %).

^{1}H NMR: δ_H (400 MHz, $CDCl_3$) 2.12-2.02 (1H, m, CH_AH$_B$CH$_2$O), 2.36-2.28 (1H, m, CH$_A$$H_BCH_2$O), 2.83 (1H, dd, J = 9.4, 13.6 Hz, PhCH_AH$_B$), 2.96-2.88 (1H, m, CH) 3.19 (1H, dd, J = 4.0, 13.6 Hz, PhCH$_A$$H_B$), 4.33-4.19 (2H, m, CH_2O), 7.40-7.29 (5H, m, 5 × ArH).

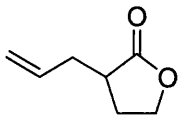
^{13}C NMR: δ_C (100 MHz, $CDCl_3$) 27.0 (*C*H$_2$CH$_2$O), 35.1 (CH_2Ph), 40.1 (CH), 65.5 (CH_2O), 125.7 (ArCH), 127.7 (2 × ArCH), 127.9 (2 × ArCH), 137.4 (ArC), 177.7 (C=O).

ν_{max} KBr/ cm^{-1} 3510 br, 1774 m (C=O), 1497 s, 1454 s, 1375 s, 1149 m, 1022 m, 802 s, 750 s, 702 s.

MS (EI): *m/z* 176 (M^+, 53 %), 148, 91 (Bn^+, 100 %), 83.

HRMS: Found 176.0837, $C_{11}H_{12}O_2$, requires 176.0837.

3-Allyldihydro-2(3*H*)-furanone 122



122

A solution of SmI_2 (7.20 ml, 0.72 mmol, 0.1 M in THF), was added to a solution of 3-allyl-3-(4-benzyloxyphenoxy)dihydro-furan-2-one **120** (97 mg, 0.28 mmol) and MeOH (2.3 ml) in THF (2.0 ml) that had been cooled to 0 °C. The mixture was then stirred before being allowed to warm to room temperature. After 1 h, a further 2.4 equivalents of SmI_2 (7.20 ml, 0.72 mmol, 0.1 M in THF) was added and the reaction was allowed to stir for another 4 h. The reaction mixture was quenched first with aqueous saturated NH_4Cl (5 ml) then H_2O (10 ml) and the aqueous layer extracted with Et_2O (3 × 20 ml). The organic layer was then dried ($MgSO_4$), and concentrated. The crude mixture was purified by column chromatography (silica, 20 % pet. ether/CH_2Cl_2) to give 3-allyldihydro-2(3*H*)-furanone **122** as a yellow oil (4 mg, 0.03 mmol, 9 %).

^1H NMR: δ_H (400 MHz, $CDCl_3$) 2.06-1.96 (1H, m, $CH_AH_BCH_2O$), 2.32-2.24 (1H, m, $CH_AH_BCH_2O$), 2.41-2.33 (1H, m, CHC=O), 2.69-2.59 (2H, m, $CHCH_2CH$), 4.33-4.19 (2H, m, CH_2O), 5.14 (1H, dd, J = 1.5, 10.2 Hz, $CH=CH_AH_B$), 5.16 (1H, dd, J = 1.5, 15.3 Hz, $CH=CH_AH_B$), 5.80 (1H, m, $CH=CH_2$).

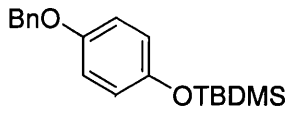
^{13}C NMR: δ_C (100 MHz, $CDCl_3$) 29.8 (CH_2CH_2O), 34.4 ($CHCH_2CH$), 37.8 (*C*HC=O), 66.5 (CH_2O), 117.8 ($CH=CH_2$), 134.4 ($CH=CH_2$), 178.8 (C=O).

ν_{max} KBr/ cm^{-1} 3510 br, 1774 m (C=O), 1497 s, 1454 s, 1375 s, 1149 m, 1022 m, 802 s, 750 s, 702 s.

MS (EI): *m/z* 176 (M^+, 53 %), 148, 91 (Bn^+, 100 %), 83.

HRMS: Found 176.0837, $C_{11}H_{12}O_2$, requires 176.0837.

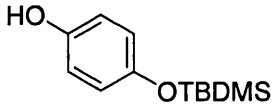
O-*tert*-Butyldimethylsilyl benzyloxyphenol 123[36]



123

Imidazole (6.38 g, 93.6 mmol) and TBDMSCl (9.03 g, 59.9 mmol) were added to a solution of benzyloxyphenol **115** (6.00 g, 30.0 mmol) in DMF (30 ml) at room temperature and the mixture was stirred for 4 h. The reaction was quenched with aqueous saturated $NaHCO_3$ (30 ml) and H_2O (20 ml). The aqueous layer was extracted with 30 % EtOAc/pet. ether (3 × 50 ml). The organic layer was then dried ($MgSO_4$), and concentrated to give O-*tert*-butyldimethylsilyl benzyloxyphenol **123** as a white solid (8.66 g, 27.6 mmol, 92 %).
^1H NMR: δ_H (400 MHz, $CDCl_3$) 0.18 (6H, s, $(CH_3)_2Si$), 0.98 (9H, s, $(CH_3)_3CSi$), 5.00 (2H, s, $PhCH_2O$), 6.75-6.87 (4H, m, 4 × ArH), 7.30-7.52 (5H, m, 5 × ArH).

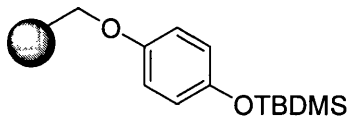
4-(*tert*-Butyldimethylsilyloxy)phenol 124[36]



124

To a solution of **123** (8.66 g, 27.6 mmol) in EtOH (70 ml) was added 10 % Pd/C (1.30 g, 15 % weight) under hydrogen (balloon) and the reaction was stirred at room temperature for 5 h. The reaction mixture was then poured onto a short column of silica gel and eluted with 40 % EtOAc/pet. ether, which upon concentration gave 4-(*tert*-butyldimethylsilyloxy)phenol **124** as a white crystalline solid (6.11 g, 27.3 mmol, 99 %).
^1H NMR: δ_H (400 MHz, $CDCl_3$) 0.17 (6H, s, $(CH_3)_2Si$), 0.98 (9H, s, $(CH_3)_3CSi$), 4.56 (1H, br s, OH), 6.74-6.68 (4H, apparent s, 4 × ArH).

Wang-supported 4-(*tert*-butyldimethylsilanyloxy)-phenol 126

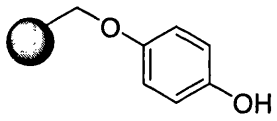


126

4-(*tert*-Butyldimethylsilanyloxy)-phenol **124** (13.4 g, 59.5 mmol) was added to a flask containing a suspension of bromo-Wang resin **125** (1.40 mmol/g, 8.50g, 11.9 mmol) which had been pre-swollen in DMF (80 ml) for 20 min. NaH (1.43 g, 59.5 mmol) was added and the mixture was stirred slowly at room temperature. After 12 h, the resin was filtered, washed and dried according to the standard washing procedure to give Wang-supported 4-(*tert*-butyldimethylsilanyloxy)-phenol **126**.

ν_{max} KBr/cm^{-1} 3029 w, 2918 w, 1601 m, 1509 s, 1218 s (C-O).

Wang-supported hydroquinone 116

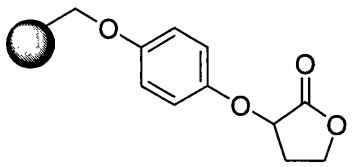


116

Wang-supported 4-(*tert*-butyldimethylsilanyloxy)-phenol **126** (1.17 mmol/g, 8.50 g, 9.95 nmol) was swollen in THF (100 ml) for 20 min. TBAF (59.7 ml, 59.7 mmol, 1.0 M in THF) was then added and the mixture was rotated at room temperature. After 24 h, the resin was filtered, washed and dried according to the standard washing procedure to give Wang-supported hydroquinone **116**.

ν_{max} KBr/cm^{-1} 3027 w (OH), 2915 w, 1600 m, 1506 s, 1218 m (C-O).

Wang-supported 3-(4-hydroxy-phenoxy)dihydro-furan-2-one 118

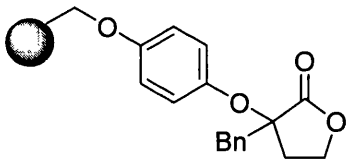


118

Wang-supported hydroquinone **116** (1.35 mmol/g, 0.96 g, 1.30 mmol) was swollen in DMF (35 ml) for 20 min. α-Bromo-γ-butyrolactone (1.92 ml, 20.8 mmol) was then added followed by K_2CO_3 (1.80 g, 13.0 mmol), and the reaction mixture was stirred slowly at 60 °C. After 36 h, the resin was filtered, washed and dried according to the standard washing procedure to give Wang-supported 3-(4-hydroxy-phenoxy)dihydro-furan-2-one **118**.

ν_{max} KBr/cm^{-1} 3025 w, 2917 w, 1788 s (C=O), 1611 s, 1507 s, 1217 s (C-O).

Wang-supported 3-benzyl-3-(4-hydroxy-phenoxy)dihydro-furan-2-one 127

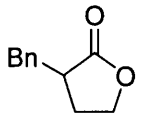


127

^{n}BuLi (2.11 ml, 5.86 mmol, 2.8 M in hexane) was added dropwise to a solution of diisopropylamine (821 µl, 5.86 mmol), in THF (4 ml) that had been cooled to -45 °C and the solution was stirred for 30 min. Wang-supported 3-(4-hydroxy-phenoxy)dihydro-furan-2-one **118** (1.22 mmol/g, 600 mg, 0.73 mmol) that had been pre-swollen in THF (10 ml) was then added dropwise by cannula to the LDA. After 30 min, benzyl bromide (697 µl, 5.86 mmol) was added dropwise to the solution and the reaction mixture was allowed to warm slowly to -20 °C and stirred for a further 1.5 h. The reaction mixture was first quenched with H_2O (20 ml), before being filtered, washed and dried according to the standard washing procedure to give Wang-supported 3-benzyl-3-(4-hydroxy-phenoxy)dihydro-furan-2-one **127**.

ν_{max} KBr/cm^{-1} 3023 m, 2920 m, 1783 s (C=O), 1599 s, 1493 m, 1221 (C-O).

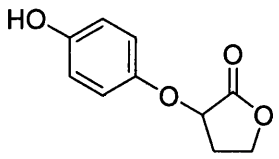
3-Benzyldihydro-2(3*H*)-furanone 121 cleaved from Wang-supported 3-benzyl-3-(4-hydroxy-phenoxy)dihydro-furan-2-one **127**



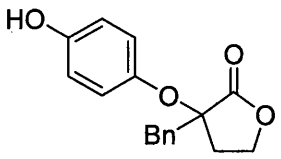
121

A solution of MeOH (5.42 ml) and SmI_2 (15.7 ml, 1.57 mmol, 0.1 M in THF) was added to a solution of Wang-supported 3-benzyl-3-(4-hydroxy-phenoxy)dihydro-furan-2-one **127** (1.09 mmol/g, 600 mg, 0.65 mmol) in THF (6.00 ml) and the reaction mixture was stirred slowly at room temperature for 1 h. A further 2.4 equivalents of SmI_2 (15.7 ml, 1.57 mmol, 0.1 M in THF) were then added and the reaction mixture was stirred for a further 2 h. The resin was drained, washed with THF (3 × 100 ml) and then concentrated. The crude mixture was purified by column chromatography (silica, 100 % CH_2Cl_2) to give 3-benzyldihydro-2(3*H*)-furanone **121** as a yellow oil (6 mg, 0.03 mmol, 5 % over 5 steps). Spectroscopic data corresponded to that reported earlier in this section.

3-(4-Hydroxyphenoxy)dihydro-furan-2-one 128 and **3-benzyl-3-(4-hydroxyphenoxy) dihydro-furan-2-one 129**



128



129

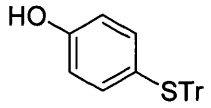
Wang-supported 3-benzyl-3-(4-hydroxy-phenoxy)dihydro-furan-2-one **127** (1.09 mmol/g, 600 mg, 0.65 mmol) was swollen in CH_2Cl_2 (6 ml) for 20 min. TFA (6 ml) was then added and the mixture was stirred slowly at room temperature for 24 h. The suspension was then filtered and the resin washed with CH_2Cl_2 (3 × 20 ml) and the washings were collected and

concentrated. The crude product was purified by column chromatography (silica, 60 % EtOAc/pet. ether) to give a mixture of 3-(4-hydroxyphenoxy)dihydro-furan-2-one **128** as a light brown oil (23 mg, 0.03 mmol, 5 %) and 3-benzyl-3-(4-hydroxyphenoxy)dihydro-furan-2-one **129** as a brown solid (48 mg, 0.12 mmol, 18 %).

For **128**: δ_H (400 MHz, $CDCl_3$) 2.46 (1H, apparent dq, J = 8.1, 13.2 Hz, CH_AH_BCHO), 2.72-2.64 (1H, m, CH_AH_BCHO), 4.34 (1H, ddd, J = 6.8, 8.1, 15.2 Hz, CH_AH_BO), 4.52 (1H, ddd, J = 4.0, 8.6, 15.2 Hz, CH_AH_BO), 4.83 (1H, apparent t, J = 7.8 Hz, CHC=O), 7.01-6.76 (4H, m, 4 × ArH).

For **129**: δ_H (400 MHz, $CDCl_3$) 2.25 (1H, ddd, J = 5.9, 7.9, 14.0 Hz, $CH_AH_BCH_2O$), 2.43 (1H, ddd, J = 6.0, 7.9, 14.0 Hz, $CH_AH_BCH_2O$), 3.21 (1H, d, J = 13.6 Hz, Ph CH_AH_B), 3.30 (1H, d, J = 13.6 Hz, Ph CH_AH_B), 3.78 (1H, dt, J = 6.0, 8.5 Hz, CH_AH_BO), 4.08 (1H, dt, J = 5.9, 8.5 Hz, CH_AH_BO), 4.99 (1H, br s, OH), 6.75 (2H, d, J = 8.9 Hz, 2 × ArH), 6.92 (2H, d, J = 8.9 Hz, 2 × ArH), 7.35-7.29 (5H, m, 2 × ArH).

4-Tritylsulfanyl phenol 133[99]

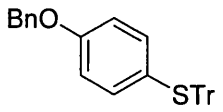


133

Trityl chloride (4.42 g, 15.9 mmol) was added to a solution of 4-mercaptophenol **132** (2.00 g, 15.9 mmol) and pyridine (1.28 ml, 15.9 mmol) in CH_2Cl_2 (10 ml) and the reaction mixture was stirred at room temperature for 4 h. The crude mixture concentrated then purified by column chromatography (60 % EtOAc/pet. ether) to give 4-tritylsulfanyl phenol **133** as a white solid (14.2 g, 15.6 mmol, 98 %).

^{1}H NMR: δ_H (400 MHz, $CDCl_3$) 4.72 (1H, br, OH), 6.50 (2H, d, J = 8.4 Hz, 2 × ArH), 6.87 (2H, d, J = 8.4 Hz, 2 × ArH), 7.28-7.18 (9H, m, 9 × ArH), 7.44-7.42 (6H, m, 6 × ArH).

1-Benzyloxy-4-tritylsulfanyl-benzene 134



134

Sodium hydride (548 mg, 22.8 mmol) was added to a solution of 4-tritylsulfanyl phenol **133** (4.21 g, 11.4 mmol) in THF (30 ml) that had been cooled to 0 °C. TBAI (84.0 mg, 0.23 mmol) and benzyl bromide (2.72 ml, 22.8 mmol) were then added and the reaction mixture was stirred at room temperature for 2 h. The reaction mixture was quenched with aqueous saturated NH_4Cl (5 ml), then H_2O (10 ml), the organic layer was then extracted with 30 % EtOAc/pet. ether (3 × 10 ml), dried ($MgSO_4$) and concentrated. The crude mixture was purified by recrystalisation from pet. ether/CH_2Cl_2 to give 1-benzyloxy-4-tritylsulfanyl-benzene **134** as a white solid (4.43 g, 9.69 mmol, 85 %).

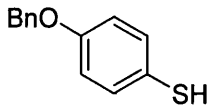
^1H NMR: δ_H (400 MHz, $CDCl_3$) 4.99 (2H, s, CH_2), 6.62 (2H, d, J = 8.9 Hz, 2 × ArH), 6.90 (2H, d, J = 8.9 Hz, 2 × ArH), 7.43-7.18 (20H, m, 20 × ArH).

^{13}C NMR: δ_C (100 MHz, $CDCl_3$) 69.8 (CH_2), 70.8 (CPh_3), 114.6 (2 × ArCH), 124.6 (ArC), 126.5 (3 × ArCH), 127.4 (2 × ArCH), 127.5 (ArCH), 127.9 (6 × ArCH), 128.0 (ArCH), 130.0 (ArCH), 132.5 (6 × ArCH), 136.6 (3 × ArC), 137.7 (2 × ArCH), 144.7 (ArCO), 159.2 (ArCS).

ν_{max} KBr/cm^{-1} 3450 br, 3054 s, 1589 m, 1491 m,1250 m, 1026 m, 831 s, 700 s.

MP: 129.5 – 132.6 °C.

4-Benzyloxy-benzenethiol 135



135

TFA (1 ml) was added to a solution of 1-benzyloxy-4-tritylsulfanyl-benzene **134** (190 mg, 0.41 mmol) and triethylsilane (132 µl, 0.83 mmol) in CH_2Cl_2 (1 ml) and the reaction

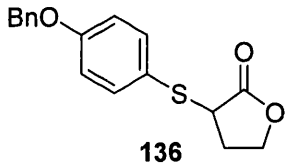
mixture was stirred at room temperature for 1 h. The reaction mixture was quenched with aqueous saturated NH_4Cl (2 ml), then H_2O (5 ml), the organic layer was then extracted with 30 % EtOAc/pet. ether (3 × 5 ml). The organic layers were then dried ($MgSO_4$) and concentrated. The crude mixture was purified by column chromatography (silica, 5 % EtOAc/pet. ether) to give 4-benzyloxy-benzenethiol **135** as a yellow oil (60.0 mg, 0.27 mmol, 67 %).

^{1}H NMR: δ_H (400 MHz, $CDCl_3$) 4.96 (2H, s, CH_2), 6.80 (2H, d, J = 9.8, 2 × ArH), 7.27-7.14 (5H, m, 5 × ArH), 7.35-7.29 (2H, m, 2 × ArH).

^{13}C NMR: δ_C (100 MHz, $CDCl_3$) 70.1 (CH_2), 115.7 (2 × ArCH), 132.3 (2 × ArCH), 128.0 (ArCH), 128.3 (2 × ArCH), 128.6 (2 × ArCH), 133.9 (ArC), 136.7 (ArCO), 157.7 (ArCS).

ν_{max} KBr/cm^{-1} 3345 br, 2557 s (S-H), 1222 m, 819 m.

3-(4-Benzyloxy-benzenesulfanyl)dihydro-furan-2-one 136



136

α-Bromo-γ-butyrolactone (87.0 μl, 0.94 mmol) was added to a solution of 4-benzyloxy-benzenethiol **135** (51.0 mg, 0.24 mmol) and NEt_3 (99.0 μl, 0.71 mmol) in DMF (2 ml), and the reaction mixture was stirred at room temperature for 1.5 h. The reaction mixture was quenched with H_2O (2 ml) and the aqueous layer was extracted with 30 % EtOAc/pet. ether (3 × 5 ml). The organic layer was then dried ($MgSO_4$) and concentrated. The crude mixture was purified by kugelrohr distillation to remove excess α-bromo-γ-butyrolactone and gave 3-(4-benzyloxy-benzenesulfanyl)dihydro-furan-2-one **136** as a clear oil (47.0 mg, 0.16 mmol, 66 %).

^{1}H NMR: δ_H (400 MHz, $CDCl_3$) 2.30-2.22 (1H, m, CH_AH$_B$CH$_2$O), 2.68-2.59 (1H, m, CH$_A$$H_BCH_2$O), 3.72 (1H, dd, J = 5.9, 8.7 Hz, CH), 4.26-4.11 (2H, m, CH$_2$CH_2O), 5.07 (2H, s, PhCH$_2$O), 6.96 (2H, d, J = 8.8 Hz, 2 × ArH), 7.44-7.29 (5H, m, 5 × ArH), 7.53 (2H, d, J = 8.8 Hz, 2 × ArH).

^{13}C NMR: δ_C (100 MHz, $CDCl_3$) 29.5 (CH_2CH_2O), 45.0 (CH), 66.4 (CH_2CH_2O), 70.1 ($PhCH_2O$), 115.7 (2 × ArCH), 121.8 (ArC), 127.5 (2 × ArCH), 128.1 (2 × ArCH), 128.6 (ArCH), 136.4 (ArCO), 136.9 (2 × ArCH), 159.9 (ArCS), 175.1 (C=O).

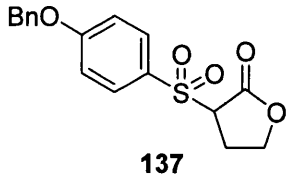
ν_{max} KBr/cm^{-1} 3462 br, 1781 s (C=O), 1220 m, 830 m.

MS (EI): *m/z* 300 (M^+, 50 %), 91 (Bn^+, 100 %).

HRMS: Found 300.0821, $C_{17}H_{16}O_3S$, requires 300.0820.

MP: 85.9 – 87.1 °C.

3-(4-Benzyloxy-benzenesulfonyl)dihydro-furan-2-one 137



137

*m*CPBA (1.15 g, 6.66 mmol) was added to a solution of 3-(4-benzyloxy-benzenesulfanyl)dihydro-furan-2-one **136** (500 mg, 1.67 mmol) in CH_2Cl_2 (15 ml) and the reaction mixture was stirred at room temperature for 1.5 h. The reaction mixture was quenched with aqueous saturated $NaHCO_3$ (5 ml), and then H_2O (5 ml) and the aqueous layer was then washed with CH_2Cl_2 (3 × 10 ml). The organic layers were then dried ($MgSO_4$), and concentrated. The crude mixture was purified by column chromatography (silica, 40 % EtOAc/pet. ether) to give 3-(4-benzyloxy-benzenesulfonyl)dihydro-furan-2-one **137** as a white solid (511 mg, 1.54 mmol, 92 %).

^1H NMR: δ_H (400 MHz, $CDCl_3$) 2.79-2.68 (1H, m, $CH_AH_BCH_2O$), 3.08-3.00 (1H, m, $CH_AH_BCH_2O$), 4.01 (1H, dd, J = 4.3, 10.0, Hz, CH), 4.39 (1H, dt, J = 4.0, 8.3 Hz, CH_AH_BO), 4.50 (1H, apparent q, J = 8.3 Hz, CH_AH_BO), 5.16 (2H, s, $PhCH_2O$), 7.05 (2H, d, J = 9.0 Hz, 2 × ArH), 7.45-7.35 (5H, m, 5 × ArH), 7.88 (2H, d, J = 9.0 Hz, 2 × ArH).

^{13}C NMR: δ_C (100 MHz, $CDCl_3$) 24.1 (CH_2CH_2O), 63.7 (CH), 67.1 (CH_2O), 70.5 ($PhCH_2O$), 115.3 (2 × ArCH), 127.6 (2 × ArCH), 128.1 (ArC), 128.5 (2 × ArCH), 128.8 (ArCH), 131.7 (2 × ArCH), 163.8 (ArCS), 165.5 (ArCO), 168.5 (C=O).

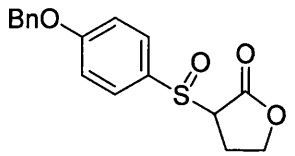
ν_{max} KBr/cm^{-1} 3442 br, 1764 m (C=O), 1591 s, 1497 s, 831 m.

MS (EI): *m/z* 332 (M^+, 6 %), 91 (Bn^+, 100 %).

HRMS: Found 332.0720, $C_{17}H_{16}O_5S$, requires 332.0718.

MP: 110.4 – 112.5 °C.

3-(4-Benzyloxy-benzenesulfinyl)dihydro-furan-2-one 138



138

H_2O_2 (46.0 µl, 0.41 mmol) was added to a solution of the 3-(4-benzyloxy-benzenesulfanyl)dihydro-furan-2-one **136** (30.0 mg, 0.10 mmol) in CH_2Cl_2 (1 ml) and HFIP (0.5 ml) and the reaction mixture was stirred at room temperature for 18 h. The reaction mixture was quenched with H_2O (2 ml) and the organic layer was then extracted with CH_2Cl_2 (3 × 5 ml). The organic layers were then dried ($MgSO_4$) and concentrated. The crude mixture was purified by column chromatography (silica, 50 % EtOAc/pet. ether) to give 3-(4-benzyloxy-benzenesulfinyl)dihydro-furan-2-one **138** as a white solid (22.0 mg, 0.07 mmol, 70 %).

Approx. 1:1 mixture of diastereoisomers; ^{1}H NMR: δ_H (400 MHz, $CDCl_3$) 2.18-2.02 (1H, m, $CH_AH_BCH_2O$, one diastereoisomer), 2.60-2.50 (1H, m, $CH_AH_BCH_2O$, one diastereoisomer), 2.74-2.66 (1H, m, $CH_AH_BCH_2O$, one diastereoisomer), 2.90-2.81 (1H, m, $CH_AH_BCH_2O$, one diastereoisomer), 3.44 (1H, apparent q, J = 8.4 Hz, CH, one diastereoisomer), 3.64 (1H, dd, J = 7.2, 9.6 Hz, CH, one diastereoisomer), 4.13 (1H, dd, J = 3.8, 10.0 Hz, $CH_2CH_AH_BO$, one diastereoisomer), 4.20 (1H, dt, J = 3.8, 9.6 Hz, $CH_2CH_AH_BO$, one diastereoisomer), 4.32 (1H, dd, J = 8.8, 15.3 Hz, $CH_2CH_AH_BO$, one diastereoisomer), 4.43 (1H, dt, J = 5.3, 8.8 Hz, $CH_2CH_AH_BO$, one diastereoisomer), 5.12 (4H, s, $PhCH_2$, both diastereoisomers), 7.14 (4H, d, J = 8.7 Hz, 4 × ArH, both diastereoisomers), 7.43-7.36 (10H, m, 10 × ArH, both diastereoisomers), 7.61 (4H, d, J = 9.2 Hz, 4 × ArH, both diastereoisomers).

^{13}C NMR: δ_H (100 MHz, $CDCl_3$) 18.9 (CH_2CH_2O, one diastereoisomer), 20.8 (CH_2CH_2O, one diastereoisomer), 62.3 (CH, one diastereoisomer), 63.9 (CH, one diastereoisomer), 67.5 (CH_2CH_2O, one diastereoisomer), 67.6 (CH_2CH_2O, one diastereoisomer), 70.3 (2 × $PhCH_2O$, both diastereoisomers), 115.8 (2 × ArCH, one diastereoisomer), 115.9 (2 × ArCH, one diastereoisomer), 125.8 (4 × ArCH both diastereoisomers), 127.5 (4 × ArCH both diastereoisomers), 127.6 (2 × ArCH both diastereoisomers), 128.7 (4 × ArCH both diastereoisomers), 129.6 (2 × ArC, both diastereoisomers), 135.9 (ArCO, one diastereoisomer), 135.9 (ArCO, one diastereoisomer), 161.6 (ArCS, one diastereoisomer), 162.1 (ArCS, one diastereoisomer), 170.4 (C=O, one diastereoisomer), 171.7 (C=O, one diastereoisomer).

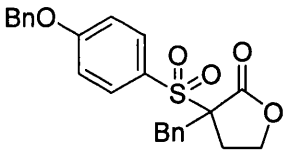
ν_{max} KBr/cm^{-1} 3446 br, 1770 m (C=O), 1592 s, 1497 s, 1242 m, 835 m.

MS (EI): *m/z* 316 (M^+, 1 %), 91 (Bn^+, 100 %).

HRMS: Found 316.0770, $C_{17}H_{16}O_4S$, requires 316.0769.

MP: 106.1 – 108.7 °C.

3-Benzyl-3-(4-benzyloxy-benzenesulfonyl)dihydro-furan-2-one 139



139

3-(4-Benzyloxy-benzenesulfonyl)dihydro-furan-2-one **137** (100 mg, 0.30 mmol) was added to a solution of NaH (14.0 mg, 0.60 mmol) in DMF (2 ml) that had been cooled to 0 °C, and the reaction mixture was stirred for 15 min. Benzyl bromide (72.0 µl, 0.60 mmol) was then added dropwise and the reaction mixture was stirred at room temperature for 3 h. The reaction mixture was quenched with acetic acid (1 ml), then H_2O (3 ml), and then extracted with Et_2O (3 × 5 ml). The organic layers were then combined, dried ($MgSO_4$) and concentrated. The crude mixture was purified by column chromatography (silica, 20 % EtOAc/pet. ether) to give 3-benzyl-3-(4-benzyloxy-benzenesulfonyl)dihydro-furan-2-one **139** as a white solid (122 mg, 0.29 mmol, 96 %).

^{1}H NMR: δ_H (400 MHz, $CDCl_3$) 2.36 (1H, dd, J = 8.0, 9.0, Hz, CH_AH$_B$CH$_2$O), 3.02-2.95 (1H, m, CH$_A$$H_BCH_2$O), 3.02 (1H, d, AB system, J = 13.1 Hz, CCH$_2$Ph), 3.18 (1H, d, AB system, J = 13.1 Hz, CCH$_2$Ph), 3.61 (1H, dt, J = 3.9, 9.0 Hz, CH$_2$CH_AH$_B$O), 4.21 (1H, m, CH$_2$CH$_A$$H_B$O), 5.09 (2H, s, PhCH$_2$O), 7.04-7.01 (2H, m, 2 × ArH), 7.09-7.05 (2H, m, 2 × ArH), 7.38-7.17 (8H, m, 8 × ArH), 7.84-7.80 (2H, m, 2 × ArH).

^{13}C NMR: δ_C (100 MHz, $CDCl_3$) 25.9 (*C*H$_2$CH$_2$O), 37.6 (C*C*H$_2$Ph), 65.9 (CH$_2$*C*H$_2$O), 70.5 (PhCH$_2$O), 72.6 (*C*C=O), 115.0 (2 × ArCH), 125.6 (ArCS), 127.6 (2 × ArCH), 127.9 (ArCH), 128.5 (2 × ArCH), 128.8 (2 × ArCH), 129.0 (2 × ArCH), 130.2 (2 × ArCH), 133.3 (ArCH), 135.5 (2 × ArC), 163.9 (ArCO), 172.0 (C=O).

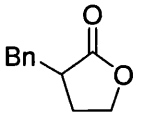
ν_{max} KBr/cm^{-1} 3435 br, 1761 m (C=O), 1591 m, 1319 s (SO_2), 1261 m, 1140 m (SO_2), 831 s, 704 s.

MS (EI): *m/z* 422 (M^+, 3 %), 91 (Bn^+, 100 %).

HRMS: Found 422.1187, $C_{24}H_{22}O_5S$, requires 422.1188.

MP: 154.2 – 157.1 °C.

3-Benzyldihydro-2(3*H*)-furanone 121 from 3-benzyl-3-(4-benzyloxy-benzenesulfonyl)dihydro-furan-2-one **139**



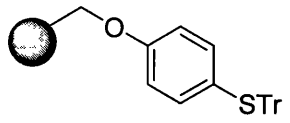
121

A solution of SmI_2 (3.90 ml, 0.39 mmol, 0.1 M in THF), was added to a solution of 3-benzyl-3-(4-benzyloxy-benzenesulfonyl)dihydro-furan-2-one **139** (69.0 mg, 0.16 mmol) in MeOH (1.1 ml) and THF (0.5 ml) that had been cooled to 0 °C. The mixture was then allowed to warm to room temperature and stirred for 1 h. The reaction mixture was quenched first with aqueous saturated NH_4Cl (2 ml) followed by H_2O (2 ml) and the aqueous layer extracted with 40 % EtOAc/pet. ether (3 × 10 ml). The organic layer was then dried ($MgSO_4$), and concentrated. The crude mixture was purified by column

chromatography (silica, 20 % EtOAc/pet. ether) to give 3-benzyldihydro-2(3*H*)-furanone **121** as a yellow oil (15 mg, 0.08 mmol, 52 %).

Spectroscopic data corresponded to that reported earlier in this section.

Wang-supported protected thiol 142

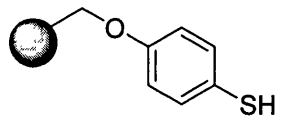


142

Bromo-Wang resin **125** (2.00 g, 1.40 mmol/g, 2.80 mmol) was swollen in DMF (25 ml) for 20 min. 4-Tritylsulfanyl phenol **133** (5.16 g, 14.0 mmol) was then added followed by NaH (336 mg, 14.0 mmol) and the reaction mixture was stirred at room temperature. After 24 h, the resin was filtered, washed and dried according to the standard washing procedure to give Wang-supported protected thiol **142**.

ν_{max} KBr/cm^{-1} 3442 br, 2922 br, 1589 m, 1491 s, 1223 m, 1005 br, 822 m.

Wang-supported thiol 141

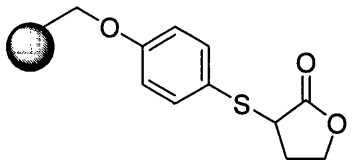


141

Wang-supported protected thiol **142** (1.90 g, 1.00 mmol/g, 1.90 mmol) was swollen in CH_2Cl_2 (10 ml) for 20 min. Then triethylsilane (1 ml) and TFA (9 ml) were added and the reaction mixture was stirred at room temperature. After 1 h, the resin was filtered, washed and dried according to the standard washing procedure to give Wang-supported thiol **141**.

ν_{max} KBr/cm^{-1} 3529 br, 2922 br, 2599 s (S-H), 1599 br, 1493 s, 1221 m, 1014 s, 822 m, 758 m.

Wang-supported lactone 143

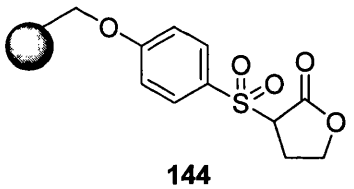


143

Wang-supported thiol **141** (1.90 g, 1.32 mmol/g, 2.51 mmol) was swollen in DMF (20 ml) for 20 min. α-Bromo-γ-butyrolactone (3.71 ml, 40.1 mmol) was added to the solution, followed by NEt_3 (3.52 ml, 25.1 mmol) and the reaction mixture was heated to 60 °C. After 24 h, the resin was filtered, washed and dried according to the standard washing procedure to give Wang-supported lactone **143**.

ν_{max} KBr/cm^{-1} 3417 br, 2920 br, 1787 br (C=O), 1601 m, 1493 s, 1223 br, 824 m, 758 m.

Wang-supported sulfone 144

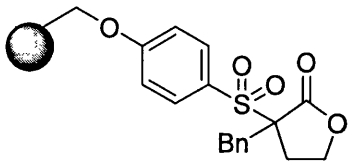


144

Wang-supported lactone **143** (2.00 g, 1.19 mmol/g, 2.38 mmol) was swollen in CH_2Cl_2 (20 ml) for 20 min. *m*CPBA (1.64 g, 9.52 mmol) was added and the solution was stirred at room temperature. After 17 h, the resin was filtered, washed and dried according to the standard washing procedure to give Wang-supported sulfone **144**.

ν_{max} KBr/cm^{-1} 3435 br, 3024 m, 2922 s, 1788 s (C=O), 1603 m, 1452 s, 1146 w (SO_2), 758 m.

Wang-supported benzylated sulfone 145

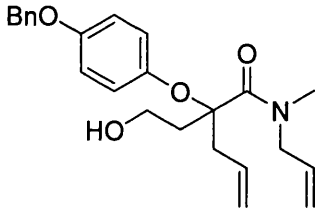


145

NaH (166 mg, 6.90 mmol) was added dropwise via cannula to a solution of Wang-supported sulfone **144** (600 mg, 1.15 mmol/g, 0.69 mmol) that had been pre-swollen in DMF (6 ml) for 20 min, at 0 °C. After 1 h, benzyl bromide (821 μl, 6.90 mmol) was added dropwise and the mixture was allowed to warm to room temperature. After 24 h, the resin was filtered, washed and dried according to the standard washing procedure to give resin **145**.

ν_{max} KBr/cm^{-1} 3433 br, 3025 w, 2922 m, 1788 m (C=O), 1493 m, 1320 w (SO_2), 1148 w (SO_2), 699 s.

2-(4-Benzyloxyphenoxy)-2-(2-hydroxyethyl)-pent-4-enoic acid-*N*-allyl-*N*-methyl amide 153



153

$AlMe_3$ (1.69 ml, 3.39 mmol, 2.0 M in hexane) was added to a solution of *N*-methylallylamine (1.30 ml, 13.5 mmol) in toluene (2.5 ml) at room temperature and the mixture was stirred for 20 min. A solution of 3-allyl-3-(4-benzyloxyphenoxy)dihydro-furan-2-one **120** (366 mg, 1.13 mmol) in toluene (10 ml) was then added dropwise via cannula and the reaction mixture was stirred for 24 h. The reaction mixture was quenched with HCl (2 ml, 1.0 M) then H_2O (5 ml) dropwise before being extracted with CH_2Cl_2 (3 ×

20 ml). The organic layers were then dried ($MgSO_4$), and concentrated. The crude mixture was purified by column chromatography (silica, 40 % EtOAc/pet. ether) to give the 2-(4-benzyloxyphenoxy)-2-(2-hydroxyethyl)-pent-4-enoic acid-*N*-allyl-*N*-methyl amide **153** as a clear oil (343 mg, 0.87 mmol, 77 %).

Approx 3:1 mixture of rotamers; ^{1}H NMR: δ_H (400 MHz, $CDCl_3$) 1.58 (2H, br, CH_2OH, both rotamers), 2.21 (2H, dt, J = 5.6, 14.7 Hz, $CH_AH_BCH_2OH$, both rotamers), 2.41-2.31 (2H, m, $CH_AH_BCH_2OH$, both rotamers), 2.87-2.79 (4H, m, $CCH_2CH{=}CH_2$, both rotamers), 2.91 (3H, s, NMe, one rotamer), 3.19 (3H, s, NMe, one rotamer), 3.80-3.71 (4H, m, CH_2OH, both rotamers), 4.01 (2H, d, J = 4.8 Hz, NCH_AH_B, one rotamer), 4.39 (2H, d, J = 5.3 Hz, NCH_AH_B, one rotamer), 5.01 (4H, s, $PhCH_2O$, both rotamers), 5.20-5.10 (8H, m, $CCH_2CH{=}CH_2$, $NCH_2CH{=}CH_2$, both rotamers), 5.57-5.48 (2H, m, $CCH_2CH{=}CH_2$, both rotamers), 5.75-5.70 (2H, m, $NCH_2CH{=}CH_2$, both rotamers), 6.78 (4H, dd, J = 7.8, 9.0 Hz, 4 × ArH, both rotamers), 6.89-6.84 (4H, m, 4 × ArH, both rotamers), 7.44-7.32 (10H, m, 10 × ArH, both rotamers).

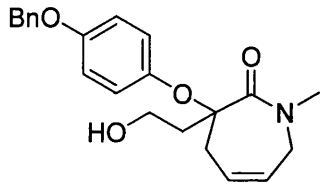
Approx 3:1 mixture of rotamers; ^{13}C NMR: δ_C (100 MHz, $CDCl_3$) 34.8 (NMe, one rotamer), 35.0 (NMe, one rotamer), 37.3 (CH_2CH_2OH, one rotamer), 37.2 (CH_2CH_2OH, one rotamer), 38.4 ($CH_2CH{=}CH_2$, one rotamer), 38.7 ($CH_2CH{=}CH_2$, one rotamer), 52.1 (NCH_2, one rotamer), 52.6 (NCH_2, one rotamer), 58.3 (2 × CH_2OH, both rotamers), 70.5 (2 × $PhCH_2O$, both rotamers), 84.2 (2 × $CC{=}O$, both rotamers), 115.7 (4 × ArCH, both rotamers), 118.1 (2 × $CH_2{=}CH$, both rotamers), 118.4 (4 × ArCH, both rotamers), 118.9 (4 × ArCH, both rotamers), 119.2 (2 × $CH_2{=}CH$, both rotamers), 127.5 (2 × ArCH, both rotamers), 128.6 (4 × ArCH, both rotamers), 132.1 (2 × $NCH_2CH{=}CH_2$, both rotamers), 132.2 (2 × $CCH_2CH{=}CH_2$, both rotamers), 137.0 (2 × ArC, both rotamers), 148.5 (2 × ArCO, both rotamers), 153.8 (2 × ArCO, both rotamers), 172.9 (2 × C=O, both rotamers).

ν_{max} KBr/ cm^{-1} 3454 br, 1620 s (tertiary amide), 1506 s, 1207 s, 1080 m, 829 m, 700 s.

MS (EI): *m/z* 395 (M^+, 22 %), 196, 166, 91 (Bn^+, 100 %).

HRMS: Found 395.2097, $C_{24}H_{29}O_4N$, requires 395.2097.

3-(4-Benzyloxyphenoxy)-3-(2-hydroxyethyl)-1-methyl-1,3,4,7-tetrahydro-azepin-2-one 154



154

Grubbs 1st generation catalyst ($(PCy_3)_2Cl_2Ru$=CHPh, 31 mg, 0.04 mmol) was added to a solution of 2-(4-benzyloxyphenoxy)-2-(2-hydroxyethyl)-pent-4-enoic acid-*N*-allyl-*N*-methyl amide **153** (151 mg, 0.38 mmol) in CH_2Cl_2 (5 ml) at room temperature and the solution was heated at reflux for 48 h. The reaction mixture was purified by filtration (silica, 60 % EtOAc/pet. ether) and concentrated. The reaction mixture was further purified by column chromatography (silica, 60 % EtOAc/pet. ether) to give 3-(4-benzyloxyphenoxy)-3-(2-hydroxyethyl)-1-methyl-1,3,4,7-tetrahydro-azepin-2-one **154** as a brown oil (86 mg, 0.24 mmol, 62 %).

^{1}H NMR: δ_H (400 MHz, $CDCl_3$) 2.02-1.96 (1H, m, CH_AH$_B$CH=CH), 2.60-2.52 (1H, m, CH$_A$$H_B$CH=CH), 2.67-2.63 (2H, m, CH_2CH$_2$O), 3.10 (3H, s, NMe), 3.30 (1H, dd, J = 7.4, 17.4 Hz, CH_AH$_B$N), 3.81-3.71 (2H, m, CH_2OH), 4.01 (1H, br s, OH), 4.66-4.68 (1H, m, CH$_A$$H_B$N), 4.93 (2H, s, PhCH$_2$O) 5.74-5.68 (1H, m, C*H*=CH), 5.87-5.81 (1H, m, CH=C*H*), 6.70-6.81 (4H, m, 4 × ArH), 7.44-7.32 (5H, m, 5 × ArH).

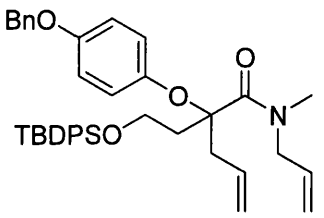
^{13}C NMR: δ_C (100 MHz, $CDCl_3$) 35.2 (*C*H$_2$CH$_2$OH), 38.6 (NMe), 38.8 (C*C*H$_2$CH=CH), 49.1 (NCH$_2$), 58.0 (CH$_2$OH), 70.5 (PhCH$_2$O), 83.7 (ArC), 115.7 (2 × ArCH), 119.4 (*C*H=CH), 124.6 (2 × ArCH), 127.1 (ArCH), 127.5 (2 × ArCH), 127.9 (CH=*C*H), 128.6 (2 × ArCH), 137 (O*C*C=O), 148.3 (ArCO), 154.2 (ArCO), 173.7 (C=O).

ν_{max} KBr/ cm^{-1} 3433 br, 2927 br, 1627 m (tertiary amide), 1504 s, 1207 m, 735 s.

MS (EI): *m/z* 367 (M$^+$, 49 %), 200, 168, 150, 138, 91 (Bn$^+$, 100 %).

HRMS: Found 367.1782, $C_{22}H_{25}O_4N$, requires 367.1784.

2-(4-Benzyloxyphenoxy)-2-[2-(*tert*-butyldiphenylsilanyloxy)ethyl]-pent-4-enoic acid-*N*-allyl-*N*-methyl-amide 156



156

TBDPSCl (132 µl, 0.51 mmol) and imidazole (69.0 mg, 1.01 mmol) were added to a solution of 2-(4-benzyloxyphenoxy)-2-(2-hydroxyethyl)-pent-4-enoic acid-*N*-allyl-*N*-methyl amide **153** (100 mg, 0.25 mmol) in DMF (1 ml) and the reaction mixture was allowed to stir at room temperature for 3 h. The reaction mixture was quenched first with aqueous saturated NH_4Cl (2 ml), then H_2O (2 ml), the organic layer was then extracted with 30 % EtOAc/pet. ether (3 × 10 ml). The organic layers were then dried ($MgSO_4$) and concentrated. The crude mixture was purified by column chromatography (silica, 40 % EtOAc/pet. ether) to give 2-(4-benzyloxyphenoxy)-2-[2-(*tert*-butyldiphenylsilanyloxy) ethyl]-pent-4-enoic acid-*N*-allyl-*N*-methyl-amide **156** as a clear oil (114 mg, 0.18 mmol, 71 %).

Approx 3:1 mixture of rotamers; ^1H NMR: δ_H (400 MHz, $CDCl_3$) 1.02 (18H, s, 2 × $C(CH_3)_3$, both rotamers), 2.38-2.30 (2H, m, 2 × $CH_AH_BCH_2OSi$, both rotamers), 2.48-2.46 (2H, m, 2 × $CH_AH_BCH_2OSi$, both rotamers), 2.69 (2H, dd, J = 8.1, 14.9 Hz, 2 × $CCH_AH_BCH=CH_2$, both rotamers), 2.83 (3H, s, NMe, one rotamer), 2.95-2.91 (2H, m, 2 × $CCH_AH_BCH=CH_2$, both rotamers), 3.07 (3H, s, NMe, one rotamer), 3.77 (4H, t, J = 7.1 Hz, 2 × CH_2OSi, both rotamers), 3.84 (2H, AB system, J = 6.3, 14.5 Hz, NCH_AH_B, both rotamers), 4.01 (2H, AB system, J = 6.3, 14.5 Hz, NCH_AH_B, both rotamers), 4.99 (4H, s, 2 × $PhCH_2O$, both rotamers), 5.12-5.92 (8H, m, 2 × $CCH_2CH=CH_2$, 2 × $NCH_2CH=CH_2$, both rotamers), 5.48-5.37 (2H, m, 2 × $CCH_2CH=CH_2$, both rotamers), 5.70-5.62 (2H, m, 2 × $NCH_2CH=CH_2$, both rotamers), 6.74-6.70 (4H, m, 4 × ArH, both rotamers), 6.82-6.79 (4H,

m, 2 × ArH, both rotamers), 7.44-7.31 (20H, m, 20 × ArH, both rotamers), 7.67-7.61 (8H, m, 8 × ArH, both rotamers), 7.74-7.72 (2H, m, 2 × ArH, both rotamers).

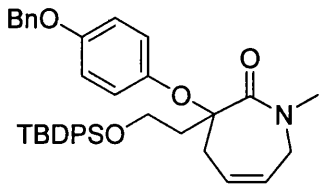
Approx 3:1 mixture of rotamers; ^{13}C NMR: δ_C (100 MHz, $CDCl_3$) 19.1 (2 × $C(CH_3)_3$, both rotamers), 26.6 (3 × $C(CH_3)_3$, one rotamer), 26.8 (3 × $C(CH_3)_3$, one rotamer), 34.5 (NMe, one rotamer), 34.6 (NMe, one rotamer), 35.6 (CH_2CH_2OH, one rotamer), 36.1 (CH_2CH_2OH, one rotamer), 37.7 ($CH_2CH{=}CH_2$, one rotamer), 37.8 ($CH_2CH{=}CH_2$, one rotamer), 51.6 (NCH_2, one rotamer), 52.3 (NCH_2, one rotamer), 59.6 (2 × CH_2OSi, both rotamers), 70.5 (2 × $PhCH_2O$, both rotamers), 83.6 (2 × $CC{=}O$, both rotamers), 115.6 (4 × ArCH, both rotamers), 117.8 (2 × $CCH_2CH{=}CH_2$, both rotamers), 117.9 (4 × ArCH, both rotamers), 118.1 (2 × ArCH, both rotamers), 118.9 (2 × $NCH_2CH{=}CH_2$, both rotamers), 127.5 (4 × ArCH, both rotamers), 127.6 (4 × ArCH, both rotamers), 127.7 (4 × ArCH, both rotamers), 127.9 (4 × ArCH, both rotamers), 128.6 (2 × ArCH, both rotamers), 129.5 (4 × ArCH, both rotamers), 129.7 (2 × ArCH, both rotamers), 132.3 (2 × $CCH_2CH{=}CH_2$, both rotamers), 132.5 (2 × $NCH_2CH{=}CH_2$, both rotamers), 133.6 (2 × ArC, both rotamers), 134.8 (2 × ArC, both rotamers), 135.6 (4 × ArCH, both rotamers), 136.6 (2 × ArC, both rotamers), 149.3 (2 × ArCO, both rotamers), 153.6 (2 × ArCO, both rotamers), 173.1 (2 × C=O, both rotamers).

ν_{max} NaCl/ cm^{-1} 3436 br, 1633 m (tertiary amide), 1504 s, 1207 m, 1111 s, 737 m, 702 m.

MS (EI): *m/z* 633 (M^+, 3 %), 356, 135, 91 (Bn^+, 100 %).

HRMS: Found 633.3270, $C_{40}H_{47}O_4NSi$, requires 633.3274.

3-(4-Benzyloxyphenoxy)-3-[2-(*tert*-butyldiphenylsilanyloxy)ethyl]-1-methyl-1,3,4,7-tetrahydro-azepin-2-one 157



157

Grubbs 1st generation catalyst ($(PCy_3)_2Cl_2Ru$=CHPh, 27.0 mg, 0.03 mmol) was added to a solution of 2-(4-benzyloxyphenoxy)-2-[2-(*tert*-butyldiphenylsilanyloxy)ethyl]-pent-4-enoic acid allyl-methyl-amide **156** (104 mg, 0.16 mmol) in CH_2Cl_2 (3.5 ml) at room temperature and the solution was heated at reflux for 24 h. The reaction mixture was purified by column chromatography (silica, 15 % EtOAc/pet. ether) to give 3-(4-benzyloxyphenoxy)-3-[2-(*tert*-butyldiphenylsilanyloxy)ethyl]-1-methyl-1,3,4,7-tetrahydro-azepin-2-one **157** as a dark grey oil (83 mg, 0.13 mmol, 84 %).

^{1}H NMR: δ_H (400 MHz, $CDCl_3$) 1.00 (9H, s, $C(CH_3)_3$), 2.34-2.27 (1H, m, CH_AH_BCH), 2.44-2.38 (1H, m, $CH_AH_BCH_2O$), 2.68-2.61 (1H, m, CH_AH_BCH), 2.96-2.91 (1H, m, $CH_AH_BCH_2O$), 3.03 (3H, s, NMe), 3.13 (1H, dd, J = 7.5, 17.3 Hz, CH_AH_BN), 3.69-3.64 (1H, m, $CH_2CH_AH_BO$), 3.87-3.81 (1H, m, $CH_2CH_AH_BO$), 4.37 (1H, dt, J = 2.8, 17.3 Hz, CH_AH_BN), 5.06 (2H, s, $PhCH_2O$), 5.63-5.59 (1H, m, CH=CH), 5.80-5.75 (1H, m, CH=CH), 6.76 (2H, d, J = 9.3 Hz, 2 × ArH), 6.81 (2H, d, J = 9.3 Hz, 2 × ArH), 7.45-7.30 (11H, m, 11 × ArH), 7.57 (2H, d, J = 8.0 Hz, 2 × ArH), 7.64 (2H, d, J = 7.9 Hz, 2 × ArH).

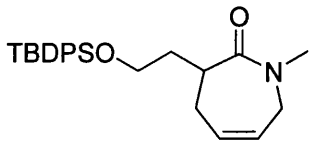
^{13}C NMR: δ_C (100 MHz, $CDCl_3$) 19.1 ($C(CH_3)_3$), 26.8 (3 × $C(CH_3)_3$), 36.4 (CH_2CH_2O), 36.5 (CCH_2CH), 38.3 (NMe), 48.6 (NCH_2), 59.5 (CH_2OSi), 70.5 ($PhCH_2O$), 82.3 (ArC), 115.6 (2 × ArCH), 117.8 (2 × ArCH), 124.4 (CH=CH), 127.5 (2 × ArCH), 127.5 (4 × ArCH), 127.6 (ArCH), 127.9 (CH=CH), 128.6 (4 × ArCH), 129.5 (2 × ArCH), 133.6 (ArC), 133.9 (ArC), 135.6 (2 × ArCH), 137.2 (OCC=O), 149.0 (ArCO), 153.5 (ArCO), 172.9 (C=O).

ν_{max} KBr/cm^{-1} 3450 br, 2929 m, 1643 s (tertiary amide), 1504 m, 1209 m 823 s.

MS (EI): *m/z* 605 (M^+, 11 %), 548, 406, 328, 261, 197, 150, 91 (Bn^+, 95 %).

HRMS: Found 605.2962, $C_{38}H_{43}NO_4Si$, requires 605.2961.

3-[2-(*tert*-Butyldiphenylsilanyloxy)ethyl]-1,3,4,7-tetrahydro-azepin-2-one 158



158

A solution of SmI_2 (4.00 ml, 0.40 mmol, 0.1 M in THF) was added to a solution of 3-(4-benzyloxyphenoxy)-3-[2-(*tert*-butyldiphenylsilanyloxy)ethyl]-1-methyl-1,3,4,7-tetrahydro-azepin-2-one **157** (82.0 mg, 0.14 mmol) and DMPU (261 μl, 2.16 mmol) in THF (1.1 ml) at room temperature and the reaction mixture was stirred for 12 h. The reaction mixture was quenched first with aqueous saturated NH_4Cl (2 ml) followed by H_2O (2 ml) and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 ml). The organic layer was then dried (Na_2SO_4), and concentrated. The crude mixture was purified by column chromatography (silica, 15 % EtOAc/pet. ether) to give 3-[2-(*tert*-butyldiphenylsilanyloxy)ethyl]-1,3,4,7-tetrahydro-azepin-2-one **158** as an orange oil (26.0 mg, 0.07 mmol, 47 %).

^{1}H NMR: δ_H (400 MHz, $CDCl_3$) 1.06 (9H, s, $C(CH_3)_3$), 1.58-1.54 (1H, m, $CH_AH_BCH_2O$), 2.22-2.17 (3H, m, $CHCH_2CH$, $CH_ACH_BCH_2O$), 3.02 (3H, s, NMe), 3.18 (1H, dd, J = 7.5, 17.4 Hz, NCH_AH_B), 3.43-3.42 (1H, m, CHC=O), 3.79-3.76 (2H, m, CH_2O), 4.45 (1H, d, J = 17.4 Hz, NCH_ACH_B), 5.78-5.73 (2H, m, CH=CH), 7.42-7.38 (6H, m, 6 × ArH), 7.67-7.64 (4H, m, 4 × ArH).

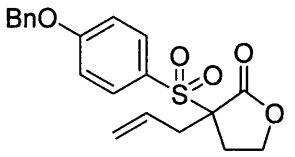
^{13}C NMR: δ_C (100 MHz, $CDCl_3$) 19.3 ($C(CH_3)_3$), 26.9 (3 × $C(CH_3)_3$), 32.1 ($CHCH_2CH$), 34.4 (CH_2CH_2O), 35.9 (NMe), 36.3 (CH), 47.4 (CH_2N), 61.8 (CH_2O), 124.1 (CH=CH), 127.6 (2 × ArCH), 129.5 (4 × ArCH), 131.7 (CH=CH), 133.9 (ArC), 134.0 (ArC), 135.5 (4 × ArCH), 175.5 (C=O).

ν_{max} ATR/ cm^{-1} 2929 w, 1643 s (tertiary amide), 1427 m, 1096 s, 814 m.

MS (CI): *m/z* 408 ($(M+H)^+$, 100 %), 350, 199.

HRMS: Found 408.2358, $C_{25}H_{34}O_2NSi$, requires 408.2353.

3-Allyl-3-(4-benzyloxybenzenesulfonyl)dihydro-furan-2-one 159



159

Allyl bromide (82.0 μl, 0.95 mmol) was added to a solution of 3-(4-benzyloxybenzenesulfonyl)dihydro-furan-2-one **137** (79.0 mg, 0.24 mmol), K_2CO_3 (165 mg, 1.19 mmol) and KI (8.00 mg, 0.05 mmol) in DMF (1 ml). The reaction mixture was then heated to 60 °C for 3 h. The reaction mixture was quenched with aqueous saturated NH_4Cl (2 ml) followed by H_2O (2 ml) and then extracted with 40 % EtOAc/pet. ether (3 × 10 ml). The organic layers were then dried ($MgSO_4$) and concentrated. The crude mixture was purified by column chromatography (silica, 30 % EtOAc/pet. ether) to give 3-allyl-3-(4-benzyloxy-benzenesulfonyl)dihydro-furan-2-one **159** as a white solid (63.0 mg, 0.17 mmol, 71 %).

^{1}H NMR: δ_H (400 MHz, $CDCl_3$) 2.65-2.57 (3H, m, CH_2CH, CH_AH$_B$CH$_2$O), 3.09 (1H, ddd, J = 2.9, 7.9, 14.8 Hz, CH$_A$$H_BCH_2$O), 4.31 (1H, dt, J = 2.9, 8.9 Hz, CH$_2$CH_AH$_B$O), 4.47 (1H, dd, J = 8.9, 14.8 Hz, CH$_2$CH$_A$$H_B$O), 5.16 (2H, s, PhCH$_2$O), 5.13 (1H, dd, J = 1.6, 15.7 Hz, CH=CH_AH$_B$), 5.15 (1H, dd, J = 1.6, 10.3 Hz, CH=CH$_A$$H_B$), 5.60-5.50 (1H, m, CH$_2$=C$H$), 7.12 (2H, d, J = 9.0 Hz, 2 × ArH), 7.45-7.35 (5H, m, 5 × ArH), 7.83 (2H, d, J = 9.0 Hz, 2 × ArH).

^{13}C NMR: δ_C (100 MHz, $CDCl_3$) 26.6 (*C*H$_2$CH$_2$O), 36.5 (*C*H$_2$CH), 66.3 (CH$_2$O), 70.5 (PhCH$_2$O), 70.9 (ArC), 115.0 (2 × ArCH), 122.2 (*C*H$_2$=CH), 125.4 (ArCS), 127.6 (2 × ArCH), 128.5 (2 × ArCH), 128.8 (CH$_2$=*C*H), 129.7 (ArCH), 133.1 (2 × ArCH), 135.5 (ArCO), 163.9 (*C*C=O), 171.6 (C=O).

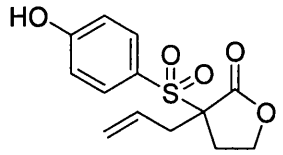
ν_{max} KBr/cm^{-1} 3483 br, 2939 s, 1756 m (C=O), 1591 s, 1495 s, 1321 (SO_2), 1146 (SO_2), 831 m.

MS (EI): m/z 372 (M^+, 6 %), 91 (Bn^+, 95 %).

Acc. Mass: Found 372.1031, $C_{38}H_{43}NO_4Si$ requires 372.1031.

MP: 107.9 – 110.1 °C.

3-(4-Hydroxybenzenesulfonyl)-3-allyl-dihydrofuran-2(3H)-one 162

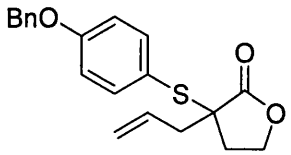


162

N-Methylallylamine (254 µl, 2.64 mmol) was added dropwise to a solution of 3-allyl-3-(4-benzyloxy-benzenesulfonyl)dihydro-furan-2-one **159** (82.0 mg, 0.22 mmol) and $AlCl_3$ (176 mg, 1.32 mmol) in CH_2Cl_2 (3 ml) that had been cooled to 0 °C. The reaction mixture was then allowed to warm to room temperature and stirred for 6 h. The reaction mixture was quenched first with 1M HCl (2 ml) and then H_2O (2 ml), and the aqueous layer was then extracted with CH_2Cl_2 (3 × 10 ml). The organic layers were then dried ($MgSO_4$) and concentrated. The crude mixture was purified by column chromatography (silica, 30 % EtOAc/pet. ether) to give 3-(4-hydroxybenzenesulfonyl)-3-allyl-dihydrofuran-2(3H)-one **162** as a clear oil (43 mg, 0.15 mmol, 69 %).

^{1}H NMR: δ_H (400 MHz, $CDCl_3$) 2.68-2.55 (3H, m, C*H*$_2$CH=CH$_2$, C*H*$_A$H$_B$CH$_2$O), 3.10 (1H, ddd, J = 2.8, 7.9, 14.8 Hz, CH$_A$*H*$_B$CH$_2$O), 4.36 (1H, dt, J = 2.8, 8.8 Hz, C*H*$_A$H$_B$O), 4.51 (1H, dd, J = 8.8, 17.1 Hz, CH$_A$*H*$_B$O), 5.21 (1H, dd, J = 1.3, 15.6 Hz, CH=C*H*$_A$H$_B$), 5.29 (1H, dd, J = 1.3, 9.6 Hz, CH=CH$_A$*H*$_B$), 5.60-5.49 (1H, m, C*H*=CH$_2$), 6.93 (2H, d, J = 8.5 Hz, 2 × ArH), 7.72 (2H, d, J = 8.5 Hz, 2 × ArH).

3-Allyl-3-(4-benzyloxy-benzenesulfanyl)dihydro-furan-2-one 163



163

To a solution of diisopropylamine (196 µl, 1.40 mmol), in THF (1 ml) that had been cooled to -45 °C was added ^{n}BuLi (633 µl, 1.40 mmol, 2.21 M in hexane). The reaction mixture

was then stirred for 30 min. A solution of 3-(4-benzyloxy-benzenesulfanyl)dihydro-furan-2-one **136** (300 mg, 1.00 mmol) in THF (4 ml) was then added dropwise by cannula and the reaction was stirred for a further 30 min. Finally allyl bromide (432 µl, 4.99 mmol) was added dropwise to the solution and the reaction mixture was stirred for 7 h. The reaction mixture was quenched first with aqueous saturated NH_4Cl (5 ml) followed by H_2O (5 ml) and the aqueous layer was extracted with 40 % EtOAc/pet. ether (3 × 10 ml). The organic layer was then dried ($MgSO_4$), and concentrated. The crude mixture was purified by column chromatography (silica, 10 % EtOAc/pet. ether) to give 3-Allyl-3-(4-benzyloxy-benzenesulfanyl)dihydro-furan-2-one **163** as a clear oil (271 mg, 0.80 mmol, 80 %).

^{1}H NMR: δ_H (400 MHz, $CDCl_3$) 2.21-2.15 (1H, m, CH_AH$_B$CH$_2$O), 2.57-2.47 (3H, m, CH$_A$$H_BCH_2O, CH_2$CH), 4.27 (2H, apparent dd, J = 8.9, 10.4 Hz, CH$_2$CH_2O), 5.08 (2H, s, PhCH$_2$O), 5.24-5.18 (2H, m, CH_2=CH), 5.87-5.77 (1H, m, CH$_2$=CH), 6.97 (2H, d, J = 8.8 Hz, 2 × ArH), 7.46-7.34 (5H, m, 5 × ArH), 7.49 (2H, d, J = 8.8 Hz, 2 × ArH).

^{13}C NMR: δ_C (100 MHz, $CDCl_3$) 33.2 (*C*H$_2$CH$_2$O), 39.2 (*C*H$_2$CH), 52.8 (*C*C=O), 65.0 (CH$_2$O), 70.1 (PhCH$_2$O), 115.4 (2 × ArCH), 119.9 (ArCS), 120.0 (*C*H$_2$=CH), 127.6 (2 × ArCH), 128.2 (ArCH), 128.7 (CH$_2$=*C*H), 132.2 (2 × ArCH), 136.4 (ArC), 138.9 (2 × ArCH), 160.5 (ArCO), 175.7 (C=O).

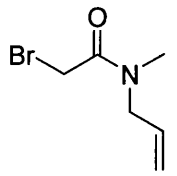
ν_{max} ATR cm^{-1} 2903 br, 2330 w, 1759 s (C=O), 1578 m, 996 m, 679 s.

MS (EI): m/z 340 (M$^+$, 36 %), 91 (Bn$^+$, 100 %).

Acc. Mass: Found 340.1132, $C_{20}H_{20}O_3S$, requires 340.1133.

MP: 87.8 – 89.9 °C.

***N*-Allyl-2-bromo-*N*-methyl-acetamide 168**



168

To a solution of *N*-methylallylamine (675 μl, 7.03 mmol) in CH_2Cl_2 (10 ml) that had been cooled to 0 °C was added NEt_3 (1.19 ml, 8.44 mmol) and bromoacetylbromide (737 μl, 8.44 mmol). The reaction mixture was allowed to warm to room temperature and stirred for 2 h. The reaction mixture was quenched with aqueous saturated NH_4Cl (5 ml), then H_2O (5 ml) and then extracted with CH_2Cl_2 (3 × 10 ml). The organic layers were then combined, dried ($MgSO_4$) and concentrated. The crude mixture was purified by column chromatography (silica, 30 % EtOAc/pet. ether) to give *N*-allyl-2-bromo-*N*-methyl-acetamide **168** as a yellow oil (1.18 g, 6.12 mmol, 87 %).

Approx. 1:1 mixture of rotamers; ^{1}H NMR: δ_H (400 MHz, $CDCl_3$) 2.97 (3H, s, CH_3, one rotamer), 3.06 (3H, s, CH_3, one rotamer), 3.84 (2H, s, CH_2Br, one rotamer), 3.88 (2H, s, CH_2Br, one rotamer), 4.02-4.00 (4H, m, 2 × CH_2N, both rotamers), 5.31-5.18 (4H, m, 2 × CH_2=CH, both rotamers), 5.90-5.72 (2H, m, 2 × CH_2=C*H*, both rotamers).

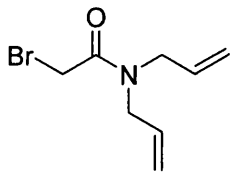
Approx. 1:1 mixture of rotamers; ^{13}C NMR: δ_C (100 MHz, $CDCl_3$) 25.5 (CH_2Br, one rotamer), 26.0 (CH_2Br, one rotamer), 34.1 (CH_3, one rotamer), 35.5 (CH_3, one rotamer), 50.4 (CH_2N, one rotamer), 52.3 (CH_2N, one rotamer), 117.4 (CH_2=CH, one rotamer), 117.8 (CH_2=CH, one rotamer), 130.9 (CH_2=CH, one rotamer), 131.7 (CH_2=CH, one rotamer), 167.0 (C=O, one rotamer), 167.4 (C=O, one rotamer).

ν_{max} NaCl cm^{-1} 3449 br, 2934 br, 1727 s, 1650 s (tertiary amide), 1405 m, 1280 m, 1090 m, 929 m, 633 w.

MS (CI): *m/z* 192 (M^+, 50 %), 154 (31).

HRMS: Found 192.0019 192 $C_6H_{11}ONBr$ requires.0019.

***N*,*N*-Diallyl-2-bromoacetamide 169**



169

To a solution of diallylamine (634 µl, 5.15 mmol) in CH_2Cl_2 (10 ml) that had been cooled to 0 °C was added NEt_3 (868 µl, 6.18 mmol) and bromoacetylbromide (540 µl, 6.18 mmol). The reaction mixture was allowed to warm to room temperature and stirred for 2 h. The reaction mixture was quenched with aqueous saturated NH_4Cl (5 ml), then H_2O (5 ml) and then extracted with CH_2Cl_2 (3 × 10 ml). The organic layers were then combined, dried ($MgSO_4$) and concentrated to give *N*,*N*-diallyl-2-bromoacetamide **169** as a brown oil (1.09 g, 5.10 mmol, 99 %).

^1H NMR: δ_H (400 MHz, $CDCl_3$) 3.85 (2H, s CH_2Br), 3.99 (4H, apparent dt, J = 1.5, 3.3 Hz, 2 × CH_2N), 5.27-5.17 (4H, m, 2 × CH_2=CH), 5.88-5.72 (2H, m, CH).

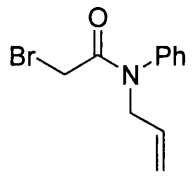
^{13}C NMR: δ_C (100 MHz, $CDCl_3$) 26.1 (CH_2Br), 48.4 (NCH_2), 50.0 (NCH_2), 117.1 (CH_2=CH), 117.6 (CH_2=CH), 132.1 (CH), 132.6 (CH), 166.8 (C=O).

ν_{max} NaCl/cm^{-1}: 3494 w, 2983 w, 1656 s (tertiary amide), 1415 s, 1210 m, 928 s, 617 w.

MS (EI): *m/z* 217 (M^+, 9 %), 138 (100), 41 (44).

HRMS: Found 217.0103, $C_8H_{12}ONBr$ requires 217.0102.

***N*-Allyl-2-bromo-*N*-phenyl-acetamide 170**



170

To a solution of *N*-allylaniline (509 μl, 3.75 mmol) in CH_2Cl_2 (10 ml) that had been cooled to 0 °C was added NEt_3 (633 μl, 4.51 mmol) and bromoacetylbromide (394 μl, 4.51 mmol). The reaction mixture was allowed to warm to room temperature and stirred for 2 h. The reaction mixture was quenched with aqueous saturated NH_4Cl (5 ml), then H_2O (5 ml) and then extracted with CH_2Cl_2 (3 × 10 ml). The organic layers were then combined, dried ($MgSO_4$) and concentrated. The crude mixture was then purified by column chromatography (10 % EtOAc/pet. ether) to give *N*-allyl-2-bromo-*N*-phenyl-acetamide **170** as an orange oil (935 mg, 3.71 mmol, 99 %).

^{1}H NMR: δ_H (400 MHz, $CDCl_3$) 3.68 (2H, s, CH_2Br), 4.32 (2H, d, J = 6.4 Hz, CH_2N), 5.12 (1H, dd, J = 1.4, 10.3 Hz, CH=CH_AH$_B$), 5.18 (1H, dd, J = 1.4, 15.9 Hz, CH=CH$_A$$H_B$), 5.93-5.83 (1H, m, CH_2=C*H*), 7.28-7.21 (2H, m, 2 × ArH), 7.49-7.37 (3H, m, 3 × ArH).

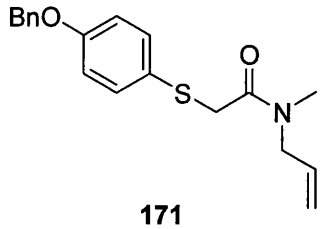
^{13}C NMR: δ_C (100 MHz, $CDCl_3$) 27.0 (CH_2Br), 52.9 (CH_2N), 118.7 (*C*H_2=CH), 128.0 (2 × ArCH), 128.7 (ArCH), 129.8 (2 × ArCH), 132.0 (CH_2=*C*H), 141.3 (ArCN), 166.3 (C=O).

ν_{max} NaCl/cm^{-1}: 3062 br, 1668 s (tertiary amide), 1210 m, 928 m, 700 s.

MS (CI): *m/z* 254 ((M+H)$^+$, 82 %), 176 (100).

HRMS: Found 254.0180, $C_{11}H_{12}ONBr$ requires 254.0181.

***N*-Allyl-2-(4-benzyloxyphenylsulfanyl)-*N*-methyl-acetamide 171**



171

N-Allyl-2-bromo-*N*-methyl-acetamide **168** (888 mg, 4.62 mmol) was added to a solution of 4-benzyloxybenzenethiol **135** (200 mg, 0.93 mmol) and NEt_3 (650 µl, 4.62 mmol) in DMF (4 ml) and the reaction mixture was stirred at room temperature for 12 h. The reaction mixture was quenched with aqueous saturated NH_4Cl (2 ml), then H_2O (2 ml) and then extracted with CH_2Cl_2 (3 × 10 ml). The organic layers were then combined, dried ($MgSO_4$) and concentrated. The crude mixture was purified by column chromatography (silica, 20 % EtOAc/pet. ether) to give *N*-allyl-2-(4-benzyloxyphenylsulfanyl)-*N*-methyl-acetamide **171** as a green/yellow oil (168 mg, 0.51 mmol, 55 %).

Approx. 1:1 mixture of rotamers; ^1H NMR: δ_H (400 MHz, $CDCl_3$) 2.93 (3H, s, CH_3, one rotamer), 2.95 (3H, s, CH_3, one rotamer), 3.63 (2H, s, CH_2S, one rotamer), 3.67 (2H, s, CH_2S, one rotamer), 3.90 (2H, m, CH_2N, one rotamer), 3.98 (2H, m, CH_2N, one rotamer), 5.06 (4H, s, 2 × CH_2O, both rotamers), 5.24-5.12 (4H, m, 2 × CH_2=CH, both rotamers), 5.81-5.70 (2H, m, 2 × CH_2=C*H*, both rotamers), 6.92 (4H, apparent dd J = 2.1, 5.2 Hz, 4 × ArH, both rotamers), 6.94 (4H, apparent dd J = 2.1, 5.2 Hz, 4 × ArH, both rotamers), 7.48-7.32 (10H, m, 10 × ArH, both rotamers).

Approx. 1:1 mixture of rotamers; ^{13}C NMR: δ_C (100 MHz, $CDCl_3$) 33.8 (CH_3, one rotamer), 35.1 (CH_3, one rotamer), 38.2 (CH_2S, one rotamer), 38.5 (CH_2S, one rotamer), 50.2 (CH_2N, one rotamer), 52.6 (CH_2N, one rotamer), 70.0 (2 × CH_2O, both rotamers), 115.3 (8 × ArCH, both rotamers), 116.9 (CH_2=CH, one rotamer), 117.4 (CH_2=CH, one rotamer), 125.2 (ArCS, one rotamer), 125.3 (ArCS, one rotamer), 127.4 (4 × ArCH, both rotamers), 128.1 (4 × ArCH, both rotamers), 128.5 (2 × ArCH, both rotamers), 132.4 (CH_2=CH, one rotamer), 132.6 (CH_2=CH, one rotamer), 134.1 (ArCO, one rotamer), 134.2

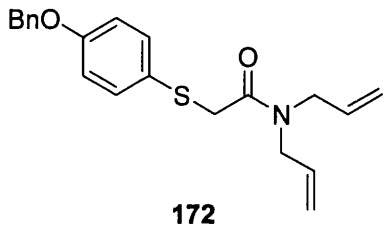
(ArCO, one rotamer), 136.6 (2 × ArC, both rotamers), 168.4, (C=O, one rotamer), 168.8 (C=O, one rotamer).

ν_{max} NaCl/cm^{-1}: 2926 br, 1648 s (tertiary amide), 1492 m, 1242 m, 1008 m, 828 m.

MS (EI): *m/z* 327 (M^+, 66 %), 236 (27), 112 (43), 91 (Bn^+, 100).

HRMS: Found 327.1292, $C_{19}H_{21}O_2NS$ requires 327.1293.

_N,N_-Diallyl-2-(4-benzyloxyphenylsulfanyl)-acetamide 172



172

N,N-Diallyl-2-bromoacetamide **169** (2.15 g, 9.85 mmol) was added to a solution of 4-benzyloxybenzenethiol **135** (1.42 g, 6.54 mmol) and NEt_3 (1.38 ml, 9.85 mmol) in DMF (15 ml) and the reaction mixture was stirred at room temperature for 12 h. The reaction mixture was quenched with aqueous saturated NH_4Cl (5 ml), then H_2O (5 ml) and then extracted with CH_2Cl_2 (3 × 20 ml). The organic layers were then combined, dried ($MgSO_4$) and concentrated. The crude mixture was purified by kugelrohr distillation to remove excess amide. This gave *N,N*-diallyl-2-(4-benzyloxyphenylsulfanyl)-acetamide **172** as a yellow oil (1.53 g, 4.32 mmol, 66 %).

^{1}H NMR: δ_H (400 MHz, $CDCl_3$) 3.63 (2H, s, CH_2S), 3.90 (2H, d, J = 5.7 Hz, CH_2N), 3.99 (2H, d, J = 5.7 Hz, CH_2N), 5.06 (2H, s, CH_2O), 5.27-5.13 (4H, m, 2 × C*H*$_2$=CH), 5.83-5.69 (2H, m, 2 × CH_2=C*H*), 6.93 (2H, dd, J = 1.8, 6.8 Hz, 2 × ArH), 7.43-7.30 (5H, m, 5 × ArH), 7.45 (2H, dd, J = 1.8, 6.8 Hz, 2 × ArH).

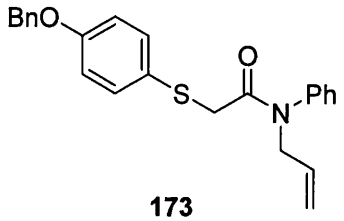
^{13}C NMR: δ_C (100 MHz, $CDCl_3$) 38.3 (CH_2S), 48.0 (CH_2N), 49.5 (CH_2N), 70.0 ($PhCH_2O$), 115.5 (2 × ArCH), 116.8 (*C*H_2=CH), 117.4 (*C*H_2=CH), 125.2 (ArCS), 127.4 (2 × ArCH), 128.0 (ArCH), 128.5 (2 × ArCH), 132.7 (CH_2=*C*H), 132.8 (CH_2=*C*H) 134.2 (2 × ArCH), 136.6 (ArC), 158.7 (ArCO), 168.7 (C=O).

ν_{max} NaCl/cm^{-1}: 3450 w, 2923 w, 1651 s (tertiary amide), 1493 s, 1454 m, 1243 s, 996 m, 827 m.

MS (EI): *m/z* 353 (M^+, 52 %), 262 (23), 138 (52), 91 (Bn^+, 100).

HRMS: Found 353.1451, $C_{21}H_{23}O_2NS$ requires 353.1450.

_N_-Allyl-2-(4-benzyloxyphenylsulfanyl)-_N_-phenyl-acetamide 173



173

N-Allyl-2-bromo-*N*-phenyl-acetamide **170** (2.50 g, 9.85 mmol) was added to a solution of 4-benzyloxybenzenethiol **135** (1.42 g, 6.54 mmol) and NEt_3 (1.38 ml, 9.85 mmol) in DMF (15 ml) and the reaction mixture was stirred at room temperature for 12 h. The reaction mixture was quenched with aqueous saturated NH_4Cl (5 ml), then H_2O (5 ml) and then extracted with CH_2Cl_2 (3 × 20 ml). The organic layers were then combined, dried ($MgSO_4$) and concentrated. The crude mixture was purified by kugelrohr distillation to remove excess amide. This gave *N*-allyl-2-(4-benzyloxyphenylsulfanyl)-*N*-phenyl-acetamide **173** as a yellow oil (1.41 g, 3.60 mmol, 55 %).

^{1}H NMR: δ_H (400 MHz, $CDCl_3$) 3.40 (2H, s, CH_2S), 4.29 (2H, d, J = 6.3 Hz, CH_2N), 5.07 (2H, s, CH_2O), 5.08 (1H, dd, J = 1.3, 15.9 Hz, CH=CH_AH$_B$), 5.12 (1H, dd, J = 1.3, 10.4 Hz, CH=CH$_A$$H_B$), 5.90-5.80 (1H, m, CH_2=C*H*), 6.90 (2H, dd, J = 5.0, 6.9 Hz, 2 × ArH), 7.07-7.05 (2H, m, 2 × ArH), 7.45-7.31 (10H, m, 10 × ArH).

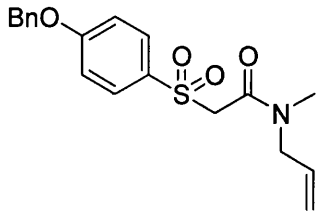
^{13}C NMR: δ_C (100 MHz, $CDCl_3$) 38.9 (CH_2S), 52.6 (CH_2N), 70.0 (CH_2O), 115.4 (2 × ArCH), 118.1 (*C*H_2=CH), 125.8 (ArCH), 127.4 (ArCS), 128.0 (2 × ArCH), 128.1 (ArCH), 128.3 (2 × ArCH), 128.6 (2 × ArCH), 129.6 (2 × ArCH), 132.7 (CH_2=*C*H), 134.2 (2 × ArCH), 136.7 (ArC), 141.8 (ArCN), 158.6 (ArCO), 168.5 (C=O).

ν_{max} NaCl/cm^{-1}: 3062 br, 1656 s (tertiary amide), 1494 s, 1240 s, 1007 m, 827 m.

MS (EI): *m/z* 389 (M^+, 88 %), 298 (45), 91 (Bn^+, 100).

HRMS: Found 389.1451, $C_{24}H_{23}O_2NS$ requires 389.1450.

_N_-Allyl-2-(4-benzyloxyphenylsulfonyl)-_N_-methyl-acetamide 174



174

Oxone (796 mg, 1.22 mmol) was added to a solution of *N*-allyl-2-(4-benzyloxyphenylsulfanyl)-*N*-methyl-acetamide **171** (106 mg, 0.31 mmol) in DMF (2 ml) and H_2O (0.5 ml) and the reaction mixture was stirred at room temperature for 3 h. The reaction mixture was quenched with aqueous saturated NH_4Cl (1 ml), then H_2O (1 ml) and then extracted with CH_2Cl_2 (3 × 5 ml). The organic layers were then combined, dried ($MgSO_4$) and concentrated. The crude mixture was purified by kugelrohr distillation to remove DMF. This gave *N*-allyl-2-(4-benzyloxyphenylsulfonyl)-*N*-methyl-acetamide **174** as a brown oil (115 mg, 0.31 mmol, 99 %).

Approx. 1:1 mixture of rotamers; ^{1}H NMR: δ_H (400 MHz, $CDCl_3$) 2.95 (3H, s, CH_3, one rotamer), 3.14 (3H, s, CH_3, one rotamer), 3.99 (2H, d, J = 5.8 Hz, CH_2N, one rotamer), 4.13 (2H, d, J = 4.8 Hz, CH_2N, one rotamer), 4.18 (2H, s, CH_2S, one rotamer), 4.25 (2H, s, CH_2S, one rotamer), 5.15 (4H, s, 2 × CH_2O, both rotamers), 5.29-5.18 (4H, m, 2 × CH_2=CH, both rotamers), 5.89-5.68 (2H, m, 2 × CH_2=C*H*, both rotamers), 7.11 (4H, dd, J = 2.0, 9.0 Hz, 4 × ArH, both rotamers), 7.45-7.35 (10H, m, 10 × ArH, both rotamers), 7.89-7.84 (4H, m, 2 × ArH, both rotamers).

Approx. 1:1 mixture of rotamers; ^{13}C NMR: δ_C (100 MHz, $CDCl_3$) 34.3 (CH_3, one rotamer), 36.2 (CH_3, one rotamer), 50.5 (CH_2N, one rotamer), 53.1 (CH_2N, one rotamer), 59.9 (CH_2S, one rotamer), 60.2 (CH_2S, one rotamer), 70.4 (2 × CH_2O, both rotamers), 115.1 (4 × ArCH, both rotamers), 117.2 (*C*H_2=CH, one rotamer), 117.8 (*C*H_2=CH, one rotamer), 127.5 (2 × ArCH, both rotamers), 128.4 (4 × ArCH, both rotamers), 128.7 (4 ×

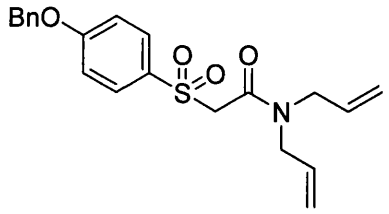
ArCH, both rotamers), 130.5 (ArCO, one rotamer), 130.6 (ArCO, one rotamer), 130.8 (4 × ArCH, both rotamers), 131.8 (CH_2=*C*H, one rotamer), 132.0 (CH_2=*C*H, one rotamer), 135.7 (2 × ArC, both rotamers), 161.4 (C=O, one rotamer), 161.8 (C=O, one rotamer), 163.2 (2 × ArCS, both rotamers).

ν_{max} KBr/cm^{-1}: 3429 w, 1648 s (tertiary amide), 1262 m, 1084 m, 1013 w, 934 w, 725 m.

MS (EI): *m/z* 359 (M^+, 10 %), 295 (24), 112 (84), 91 (Bn^+, 100).

HRMS: Found 359.1193, $C_{19}H_{21}O_4NS$ requires 359.1191.

_N,N_-Diallyl-2-(4-benzyloxyphenylsulfonyl)-acetamide 175



175

Oxone (779 mg, 1.27 mmol) was added to a solution of *N,N*-diallyl-2-(4-benzyloxyphenylsulfanyl)-acetamide **172** (112 mg, 0.32 mmol) in DMF (2 ml) and H_2O (0.5 ml) and the reaction mixture was stirred at room temperature for 3 h. The reaction mixture was quenched with aqueous saturated NH_4Cl (2 ml), then H_2O (2 ml) and then extracted with CH_2Cl_2 (3 × 10 ml). The organic layers were then combined, dried ($MgSO_4$) and concentrated. The crude mixture was purified by kugelrohr distillation to remove DMF. This gave *N,N*-diallyl-2-(4-benzyloxyphenylsulfonyl)-acetamide **175** as a white solid (117 mg, 0.31 mmol, 96 %).

^{1}H NMR: δ_H (400 MHz, $CDCl_3$) 3.99 (2H, d, J = 5.5 Hz, C*H*$_A$H$_B$N), 4.16-4.13 (2H, m, CH$_A$*H*$_B$N), 4.19 (2H, s, CH_2S), 5.15 (2H, s, CH_2O), 2.30-5.19 (4H, m, 2 × C*H*$_2$=CH), 5.88-5.70 (2H, m, 2 × CH_2=C*H*), 7.10 (2H, d, J = 9.0 Hz, 2 × ArH), 7.45-7.36 (5H, m, 5 × ArH), 7.85 (2H, d, J = 9.0 Hz, 2 × ArH).

^{13}C NMR: δ_C (100 MHz, $CDCl_3$) 48.5 (CH_2N), 50.1 (CH_2N), 60.1 (CH_2S), 70.4 (CH_2O), 115.1 (2 × ArCH), 117.1 (*C*H_2=CH), 117.6 (*C*H_2=CH), 127.6 (2 × ArCH), 128.4 (2 ×

ArCH), 128.7 (ArCH), 130.4 (ArCO), 130.9 (2 × ArCH), 132.0 (CH_2=*C*H), 132.3 (CH_2=*C*H), 135.7 (ArC), 161.8 (C=O), 163.5 (ArCS).

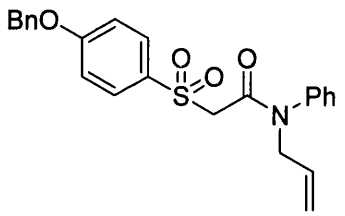
ν_{max} KBr/cm^{-1}: 3431 w, 1649 s (tertiary amide), 1450 m, 1144 s, 925 m, 733 m.

MS (EI): *m/z* 385 (M^+, 13 %), 138 (71), 91 (Bn^+, 100).

HRMS: Found 385.1346, $C_{21}H_{23}O_4NS$ requires 385.1348.

MP: 84.5 – 86.1 °C.

_N_-Allyl-2-(4-benzyloxyphenylsulfonyl)-_N_-phenyl-acetamide 176



176

Oxone (644 mg, 1.05 mmol) was added to a solution of *N*-allyl-2-(4-benzyloxyphenylsulfanyl)-*N*-phenyl-acetamide **173** (102 mg, 0.26 mmol) in DMF (2 ml) and H_2O (0.5 ml) and the reaction mixture was stirred at room temperature for 3 h. The reaction mixture was quenched with aqueous saturated NH_4Cl (2 ml), then H_2O (2 ml) and then extracted with CH_2Cl_2 (3 × 10 ml). The organic layers were then combined, dried ($MgSO_4$) and concentrated. The crude mixture was purified by kugelrohr distillation to remove DMF. This gave *N*-allyl-2-(4-benzyloxyphenylsulfonyl)-*N*-phenyl-acetamide **176** as a yellow oil (103 mg, 0.24 mmol, 94%).

^{1}H NMR: δ_H (400 MHz, $CDCl_3$) 3.97 (2H, s, CH_2O), 4.28 (2H, d, J = 6.2 Hz, CH_2N), 5.12 (1H, dd, J = 1.7, 9.9 Hz, CH=CH_AH$_B$), 5.15 (1H, dd, J = 1.7, 15.0 Hz, CH=CH$_A$$H_B$), 5.16 (2H, s, CH_2S), 5.87-5.77 (1H, m, CH_2=C*H*), 7.11 (2H, dd, J = 2.0, 7.0 Hz, 2 × ArH), 7.19-7.16 (2H, m, 2 × ArH), 7.46-7.38 (8H, m, 8 × ArH), 7.85 (2H, dd, J = 2.0, 7.0 Hz, 2 × ArH).

^{13}C NMR: δ_C (100 MHz, $CDCl_3$) 52.6 (CH_2N), 59.4 (CH_2O), 70.4 (CH_2S), 114.9 (2 × ArCH), 118.5 (*C*H_2=CH), 126.3 (ArCH), 127.5 (2 × ArCH), 128.4 (ArCO), 128.4 (2 ×

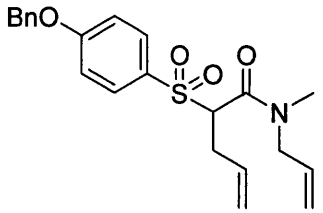
ArCH), 128.8 (2 × ArCH), 130.0 (2 × ArCH), 130.9 (ArCH), 131.1 (2 × ArCH), 131.9 (CH_2=*C*H), 135.7 (ArC), 141.2 (ArCN), 161.3 (C=O), 163.1 (ArCS).

ν_{max} ATR/cm^{-1} 3682 br, 2904 m, 1655 s (tertiary amide), 1586 m, 1492 m, 1306 m, 1150 m, 1000 w, 689 s.

MS (EI): *m/z* 421 (M^+, 9 %), 174 (100), 91 (Bn^+, 100).

HRMS: Found 421.1350, $C_{24}H_{23}O_4NS$ requires 421.1348.

2-(4-Benzyloxybenzenesulfonyl)-pent-4-enoic acid-*N*-allyl-*N*-methyl-amide 177



177

Allyl bromide (333 µl, 3.85 mmol) was added to a solution of *N*-allyl-2-(4-benzyloxyphenylsulfonyl)-*N*-methyl-acetamide **174** (346 mg, 0.96 mmol), K_2CO_3 (665 mg, 4.81 mmol) and KI (32.0 mg, 0.19 mmol) in DMF (10 ml) and the reaction mixture was stirred at room temperature for 12 h. The reaction mixture was quenched with aqueous saturated NH_4Cl (5 ml), then H_2O (5 ml) and then extracted with CH_2Cl_2 (3 × 20 ml). The organic layers were then combined, dried ($MgSO_4$) and concentrated. The crude mixture was purified by kugelrohr distillation to remove excess allyl bromide. This gave 2-(4-benzyloxybenzenesulfonyl)-pent-4-enoic acid-*N*-allyl-*N*-methyl-amide **177** as a white solid (254 mg, 0.85 mmol, 89 %).

Approx. 1:1 mixture of rotamers; ^{1}H NMR: δ_H (400 MHz, $CDCl_3$) 2.72-2.56 (4H, m, 2 × CH_2CHC=O, both rotamers), 2.97 (3H, s, CH_3, one rotamer), 3.13 (3H, s, CH_3, one rotamer), 3.80 (1H, dd, J = 4.4, 13.0 Hz, NC$H_A$$H_B$, one rotamer), 3.97 (1H, dd, J = 5.5, 15.3 Hz, NC$H_A$$H_B$, one rotamer), 4.08 (1H, dd, J = 5.5, 15.3 Hz, NC$H_A$$H_B$, one rotamer), 4.24 (1H, t, J = 10.8 Hz, CHC=O, one rotamer), 4.39 (1H, t, J = 10.8 Hz, CHC=O, one rotamer), 4.52-4.46 (1H, m, NC$H_A$$H_B$, one rotamer), 5.08-5.03 (4H, m, 2 × $CHCH_2CH$=CH_2, both rotamers), 5.09 (4H, s, 2 × CH_2O, both rotamers), 5.27-5.13 (4H, m, 2 × NCH_2CH=CH_2,

both rotamers), 5.59-5.53 (2H, m, 2 × $CHCH_2CH$=CH_2, both rotamers) , 5.83-5.67 (2H, m, 2 × NCH_2CH=CH_2, both rotamers), 7.09 (4H, dd, J = 2.8, 8.9 Hz, 4 × ArH, both rotamers), 7.45-7.35 (10H, m, 10 × ArH, both rotamers), 7.80-7.76 (4H, m, 4 × ArH, both rotamers).

Approx. 1:1 mixture of rotamers; ^{13}C NMR: δ_C (100 MHz, $CDCl_3$) 32.6 (CH_2CHC=O, one rotamer), 32.9 (CH_2CHC=O, one rotamer), 34.6, (CH_3, one rotamer), 35.9 (CH_3, one rotamer), 50.9 (CH_2N, one rotamer), 52.6 (CH_2N, one rotamer), 66.0 (2 × CHC=O, both rotamers), 70.4 (2 × CH_2O, both rotamers), 114.7 (2 × ArCH, one rotamer), 114.8 (2 × ArCH, one rotamer), 117.3 (2 × $CHCH_2CH$=CH_2, both rotamers), 118.8 (NCH_2CH=CH_2, one rotamer), 119.0 (NCH_2CH=CH_2, one rotamer), 127.6 (2 × ArCH, both rotamers), 128.8 (4 × ArCH, both rotamers), 132.1 (4 × ArCH, both rotamers), 132.2 (2 × $CHCH_2CH$=CH_2, both rotamers), 132.2 (4 × ArCH, both rotamers), 132.4 (2 × NCH_2CH=CH_2, both rotamers) 135.7 (2 × ArC, both rotamers), 138.2 (2 × ArCO, both rotamers), 163.3 (2 × ArCS, both rotamers), 164.6 (C=O, one rotamer), 165.5 (C=O, one rotamer).

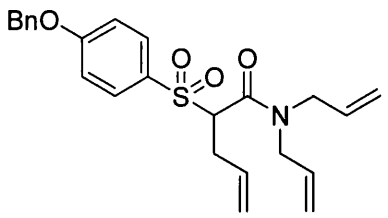
ν_{max} KBr/cm^{-1}: 3438 w, 2925 m, 1659 m (tertiary amide), 1251 m, 1144 s, 1007 m, 727 m.

MS (EI): *m/z* 399 (M^+, 6 %), 152 (46), 91 (Bn^+, 100).

HRMS: Found 399.1505, $C_{22}H_{25}O_4NS$ requires 399.1504.

MP: 106.3 – 108.2 °C.

2-(4-Benzyloxybenzenesulfonyl)-pent-4-enoic acid-*N*,*N*-diallylamide 178



178

Allyl bromide (260 μl, 3.00 mmol) was added to a solution of *N*,*N*-diallyl-2-(4-benzyloxyphenylsulfonyl)-acetamide **175** (289 mg, 0.75 mmol), K_2CO_3 (518 mg, 3.75 mmol) and KI (25.0 mg, 0.15 mmol) in DMF (10 ml) and the reaction mixture was stirred at room temperature for 24 h. The reaction mixture was quenched with aqueous saturated NH_4Cl (2 ml), then H_2O (2 ml) and then extracted with CH_2Cl_2 (3 × 20 ml). The organic layers were then combined, dried ($MgSO_4$) and concentrated. The crude mixture was purified by kugelrohr distillation to remove excess allyl bromide. This gave 2-(4-benzyloxybenzenesulfonyl)-pent-4-enoic acid-*N*,*N*-diallylamide **178** as a clear oil (201 mg, 0.47 mmol, 63 %).

^{1}H NMR: δ_H (400 MHz, $CDCl_3$) 2.60-2.52 (1H, m, CH_AH$_B$CHC=O), 2.70-2.64 (1H, m, CH$_A$$H_B$CHC=O), 3.64 (1H, dd, J = 5.9, 15.6 Hz, NCH_AH$_B$), 3.84 (1H, apparent dt, J = 2.4, 18.3 Hz, NCH_AH$_B$), 4.26 (1H, dd, J = 3.7, 10.9 Hz, CHC=O), 4.35 (1H, apparent dt, J = 2.0, 15.6 Hz, NCH$_A$$H_B$), 4.49 (1H, apparent dt, J = 2.0, 18.3 Hz, NCH$_A$$H_B$), 5.14-5.04 (2H, m, CHCH$_2$CH=CH_2), 5.15 (2H, s, PhCH$_2$O), 5.33-5.17 (4H, m, NCH$_2$CH=CH_2), 5.62-5.52 (1H, m, CHCH$_2$CH=CH$_2$), 5.84-5.72 (2H, m, NCH$_2$CH=CH$_2$), 7.09 (2H, dd, J = 2.0, 7.1 Hz, 2 × ArH), 7.44-7.35 (5H, m, 5 × ArH), 7.76 (2H, dd, J = 2.0, 7.1 Hz, 2 × ArH).

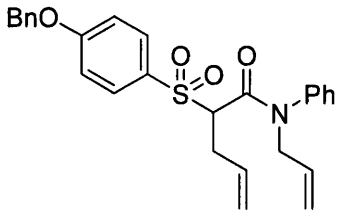
^{13}C NMR: δ_C (100 MHz, $CDCl_3$) 33.0 (*C*H$_2$CHC=O), 48.8 (CH$_2$N), 49.7 (CH$_2$N), 66.2 (CHC=O), 70.4 (PhCH$_2$O), 114.7 (2 × ArCH), 117.3 (NCH$_2$CH=*C*H$_2$), 117.3 (NCH$_2$CH=*C*H$_2$), 119.1 (CHCH$_2$CH=*C*H$_2$), 127.6 (2 × ArCH), 128.4 (2 × ArCH), 128.7 (ArCH), 130.4 (ArCO), 132.2 (2 × NCH$_2$*C*H=CH$_2$), 132.3 (CHCH$_2$*C*H=CH$_2$), 132.6 (2 × ArCH), 135.7 (ArC), 163.4 (ArCS), 164.6 (C=O).

ν_{max} NaCl/cm^{-1}: 3628 w, 3080 m, 1654 s (tertiary amide), 1316 s, 1146 s, 925 m, 700 m.

MS (EI): *m/z* 425 (M$^+$, 6 %), 210 (20), 178 (81), 91 (Bn$^+$, 100).

HRMS: Found 425.1660, $C_{24}H_{27}O_4NS$ requires 425.1661.

2-(4-Benzyloxybenzenesulfonyl)-pent-4-enoic acid-*N*-allyl-*N*-phenyl-amide 179



179

Allyl bromide (278 μl, 3.21 mmol) was added to a solution of *N*-allyl-2-(4-benzyloxyphenylsulfonyl)-*N*-phenyl-acetamide **176** (338 mg, 0.80 mmol), K_2CO_3 (554 mg, 4.01 mmol) and KI (27.0 mg, 0.16 mmol) in DMF (10 ml) and the reaction mixture was stirred at room temperature for 7 h. The reaction mixture was quenched with aqueous saturated NH_4Cl (3 ml), then H_2O (3 ml) and then extracted with CH_2Cl_2 (3 × 20 ml). The organic layers were then combined, dried ($MgSO_4$) and concentrated. The crude mixture was purified by kugelrohr distillation to remove excess allyl bromide. This gave 2-(4-benzyloxybenzenesulfonyl)-pent-4-enoic acid-*N*-allyl-*N*-phenyl-amide **179** as a yellow oil (335 mg, 0.73 mmol, 91 %).

^{1}H NMR: δ_H (400 MHz, $CDCl_3$) 2.58-2.51 (2H, m, C*H*$_2$CHC=O), 4.03 (1H, dd, J = 5.9, 9.2 Hz, CHC=O), 4.29 (2H, dd, J = 2.1, 5.1 Hz, CH_2N), 5.18-5.08 (4H, m, C*H*$_2$=CHCH$_2$CH, C*H*$_2$=CHCH$_2$N), 5.17 (2H, s, PhCH$_2$O), 5.59-5.48 (1H, m, CH$_2$=C*H*CH$_2$CH), 5.89-5.79 (1H, m, CH$_2$=C*H*CH$_2$N), 7.10 (2H, dd, J = 2.0, 7.0 Hz, 2 × ArH), 7.47-7.36 (10H, m, 10 × ArH), 7.77 (2H, dd, J = 2.0, 7.0 Hz, 2 × ArH).

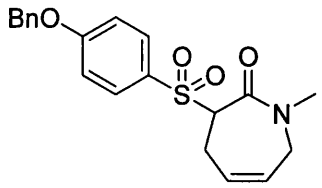
^{13}C NMR: δ_C (100 MHz, $CDCl_3$) 33.2 (*C*H$_2$CHC=O), 52.9 (CH_2N), 66.2 (*C*HC=O), 70.4 (PhCH$_2$O), 114.6 (2 × ArCH), 118.3 (*C*H$_2$=CHCH$_2$N), 119.4 (*C*H$_2$=CHCH$_2$CH), 127.5 (3 × ArCH), 128.4 (2 × ArCH), 128.6 (2 × ArCH), 128.8 (3 × ArCH), 129.7 (ArCO), 131.8 (CH$_2$=*C*HCH$_2$N), 132.2 (CH$_2$=*C*HCH$_2$CH), 132.4 (2 × ArCH), 135.7 (ArC), 141.1 (ArCN), 163.2 (ArCS), 164.2(C=O).

ν_{max} NaCl/cm^{-1}: 3066 br, 1661 s (tertiary amide), 1495 s, 1259 s, 1146 s, 834 m, 701 m.

MS (EI): *m/z* 461 (M^+, 7 %), 214 (66), 91 (Bn^+, 100).

HRMS: Found 461.1662, $C_{27}H_{27}O_4NS$ requires 461.1661.

3-(4-Benzyloxybenzenesulfonyl)-1-methyl-1,3,4,7-tetrahydro-azepin-2-one 180



180

Grubbs 1st generation catalyst ($(PCy_3)_2Cl_2Ru$=CHPh, 50.0 mg, 0.06 mmol), was added to a solution of 2-(4-benzyloxybenzenesulfonyl)-pent-4-enoic acid-*N*-allyl-*N*-methyl-amide **177** (244 mg, 0.61 mmol) in CH_2Cl_2 (5 ml) and the reaction mixture was heated to reflux for 24 h. The reaction mixture was purified by filtration (silica, 100 % CH_2Cl_2). The crude mixture was then purified by column chromatography (silica, 20 % EtOAc/pet. ether) to give 3-(4-benzyloxybenzenesulfonyl)-1-methyl-1,3,4,7-tetrahydro-azepin-2-one **180** as a brown oil (171 mg, 0.46 mmol, 76 %).

^{1}H NMR: δ_H (400 MHz, $CDCl_3$) 2.54-2.46 (1H, m, CH_AH$_B$CHC=O), 2.99 (3H, s, CH_3), 3.04-3.00 (1H, m, CH$_A$$H_B$CHC=O), 3.43-3.37 (1H, m, NCH_AH$_B$), 4.42-4.37 (1H, m, NCH$_A$$H_B$), 4.67 (1H, dd, J = 3.3, 13.0 Hz, CHC=O), 5.15 (2H, s, CH_2O), 5.81 (2H, m, CH=CH), 7.10 (2H, d, J = 9.0 Hz, 2 × ArH), 7.45-7.37 (5H, m, 5 × ArH), 8.05 (2H, d, J = 9.0 Hz, 2 × ArH).

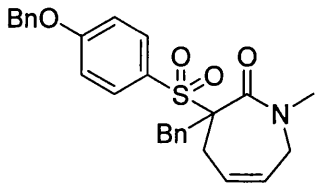
^{13}C NMR: δ_C (100 MHz, $CDCl_3$) 27.3 (CH_2CHC=O), 36.0 (CH_3), 47.3 (CH_2N), 66.2 (*C*HC=O), 70.4 (PhCH_2O), 114.6 (2 × ArCH), 124.4 (*C*H=CH), 127.5 (3 × ArCH), 128.4 (CH=*C*H), 128.7 (2 × ArCH), 129.4 (ArCO), 132.9 (2 × ArCH), 135.8 (ArC), 163.1 (ArCS), 167.0 (C=O).

ν_{max} ATR/cm^{-1} 2922 br, 1652 s (tertiary amide), 1587 m, 1491 w, 1250 m, 1128 m, 996 w, 829 w.

MS (EI): *m/z* 372 (M^+, 100 %), 152 (65).

HRMS: Found 372.1270, $C_{20}H_{22}O_4NS$ requires 372.1270.

3-Benzyl-3-(4-benzyloxybenzenesulfonyl)-1-methyl-1,3,4,7-tetrahydro-azepin-2-one 181



181

LiHMDS (0.11 ml, 0.11 mmol), was added to solution of **180** (20.0 mg, 0.05 mmol) in THF (0.5 ml) that had been cooled to -78 °C and the reaction mixture was stirred for 30 min. Benzyl bromide (26.0 μl, 0.22 mmol) was then added dropwise and the reaction mixture was stirred at -78 °C for 16 h. The reaction mixture was quenched first with aqueous saturated NH_4Cl (2 ml) followed by H_2O (2 ml) and the aqueous layer extracted with CH_2Cl_2 (3 × 10 ml). The organic layers were then dried ($MgSO_4$), and concentrated. The crude mixture was purified by column chromatography (silica, 30 % EtOAc/pet. ether) to give 3-benzyl-3-(4-benzyloxybenzenesulfonyl)-1-methyl-1,3,4,7-tetrahydro-azepin-2-one **181** as a clear oil (23.0 mg, 0.05 mmol, 93 %).

^{1}H NMR: δ_H (400 MHz, $CDCl_3$) 2.73 (1H, dd, J = 6.9, 15.2 Hz, CCH_AH$_B$CH=CH), 2.81 (1H, d, J = 12.4 Hz, PhCH_AH$_B$C), 3.08 (3H, s, NMe), 3.27 (1H, dd, J = 6.5, 15.2 Hz, CCH$_A$$H_B$CH=CH), 3.36 (1H, dd, J = 6.9, 15.2 Hz, NCH_2), 3.67 (1H, d, J = 12.4 Hz, PhCH$_A$$H_B$C), 3.87 (1H, dd, J = 7.0, 15.2 Hz, NCH_2), 5.14 (2H, s, $PhCH_2O$), 5.63 (1H, dt, J = 6.5, 9.2 Hz, CCH_2C*H*=CH), 5.92 (1H, dt, J = 6.9, 9.2 Hz, NCH_2C*H*=CH), 7.12-7.07 (4H, m, 4 × ArH), 7.25-7.19 (3H, m, 3 × ArH), 7.45-7.34 (5H, m, 5 × ArH), 7.88-7.84 (2H, m, 2 × ArH).

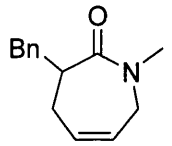
^{13}C NMR: δ_C (100 MHz, $CDCl_3$) 27.7 (CCH_2CH=CH), 39.4 (NMe), 42.9 ($PhCH_2C$), 46.5 (NCH_2), 70.3 ($PhCH_2O$), 79.1 (*C*C=O), 114.2 (2 × ArCH), 126.2 (ArC), 127.2 (ArCH), 127.6 (2 × ArCH), 128.3 (2 × ArCH), 128.4 (2 × ArCH), 128.7 (2 × ArCH), 129.5 (ArCH), 130.4 (*C*H=CH), 131.3 (ArC), 132.4 (*C*H=CH), 133.2 (2 × ArCH), 135.4 (ArCO), 135.8 (ArCS), 163.0 (C=O).

ν_{max} ATR/cm^{-1} 3666 br, 2925 br, 1650 s (tertiary amide), 1249 m, 1130 m, 714 s.

MS (CI): *m/z* 372 ($(M+H)^+$, 54 %), 231 (33), 214 (38), 124 (100).

HRMS: Found 462.1735, $C_{27}H_{28}O_4NS$ requires 462.1734.

3-Benzyl-1-methyl-1,3,4,7-tetrahydro-azepin-2-one 182



182

A solution of SmI_2 (2.59 ml, 0.26 mmol, 0.1 M in THF), was added to a solution of 3-benzyl-3-(4-benzyloxybenzenesulfonyl)-1-methyl-1,3,4,7-tetrahydro-azepin-2-one **181** (50.0 mg, 0.11 mmol) and MeOH (0.8 ml) in THF (0.4 ml) that had been cooled to 0 °C. The mixture was then allowed to warm to room temperature and stirred for 1 h. The reaction mixture was quenched first with aqueous saturated NH_4Cl (2 ml) followed by H_2O (2 ml) and the aqueous layer extracted with CH_2Cl_2 (3 × 5 ml) dried ($MgSO_4$), and concentrated. The crude mixture was purified by column chromatography (silica, 30 % EtOAc/pet. ether) to give 3-benzyl-1-methyl-1,3,4,7-tetrahydro-azepin-2-one **182** as a yellow oil (19.0 mg, 0.09 mmol, 81 %).

^1H NMR: δ_H (400 MHz, $CDCl_3$) 2.21-2.05 (2H, m, $PhCH_2$), 2.52 (1H, apparent dd, J = 7.6, 13.6 Hz, CHC=O), 2.95 (3H, s, NMe), 3.28-3.19 (3H, m, $CHCH_2C$, $CHCH_AH_BN$), 4.41-4.36 (1H, m, $CHCH_AH_BN$), 5.68-5.58 (2H, m, CH=CH), 7.23-6.91 (5H, m, 5 × ArH).

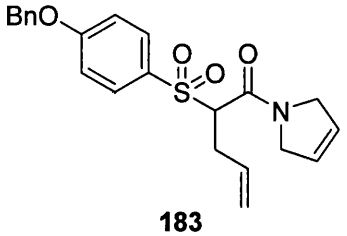
^{13}C NMR: δ_C (100 MHz, $CDCl_3$) 31.4 ($CHCH_2CH$), 36.1 (NMe), 37.6 (CH_2Ph), 42.4 (CH), 47.4 (NCH_2), 124.0 (CH=CH), 126.0 (2 × ArCH), 128.3 (ArCH), 129.3 (CH=CH), 131.6 (2 × ArCH), 140.4 (ArC), 162.3 (C=O).

ν_{max} KBr/cm^{-1} 2929 br, 1644 m (tertiary amide), 1490 w, 1219 w, 804 w, 342 m.

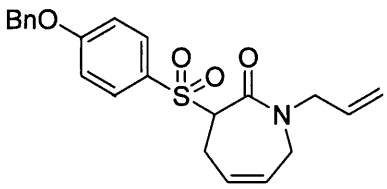
MS (CI): *m/z* 216 ($(M+H)^+$, 100 %), 124 (100), 91 (92).

HRMS: Found 216.1380, $C_{14}H_{18}ON$, requires 216.1383.

2-(4-Benzyloxyphenylsulfonyl)-1-(2H-pyrrol-1(5H)-yl)pent-4-en-1-one 183 and **3-(4-benzyloxyphenylsulfonyl)-1-allyl-3,4-dihydro-1H-azepin-2(7H)-one 184**



183



184

Grubbs 1st generation catalyst ($(PCy_3)_2Cl_2Ru$=CHPh, 6.00 mg, 0.01 mmol), was added to a solution of 2-(4-benzyloxybenzenesulfonyl)-pent-4-enoic acid-*N*,*N*-diallylamide **178** (30.0 mg, 0.07 mmol) in CH_2Cl_2 (2 ml) and the reaction mixture was heated at reflux for 2 h. The reaction mixture was purified by filtration (silica, 100 % CH_2Cl_2). The crude mixture was then purified by column chromatography (silica, 20 % EtOAc/pet. ether) to give a mixture of 2-(4-benzyloxyphenylsulfonyl)-1-(2H-pyrrol-1(5H)-yl)pent-4-en-1-one **183** as a dark grey oil (5.57 mg, 0.01 mmol, 20 %) and 3-(4-benzyloxyphenylsulfonyl)-1-allyl-3,4-dihydro-1H-azepin-2(7H)-one **184** as a brown oil (15.9 mg, 0.04 mmol, 57 %).

For **183**: ^{1}H NMR: δ_H (400 MHz, $CDCl_3$) 2.72-2.57 (2H, m, CH_2CHC=O), 4.13 (1H, dd, J = 3.9, 11.0 Hz, CHC=O), 4.32-4.22 (3H, m, NCH_2, NCH_AH$_B$), 4.67-4.61 (1H, m, NCH$_A$$H_B$), 5.07 (2H, apparent dd, J = 1.2, 10.1, CH=CH_2), 5.15 (2H, s, CH_2O), 5.70-5.59 (1H, m, CH=CH_2), 5.81-5.78 (1H, m, CH=CH), 5.88-5.86 (1H, m, CH=CH), 7.07 (2H, dd, J = 2.0, 6.9 Hz, 2 × ArH), 7.45-7.36 (5H, m, 5 × ArH), 7.81 (2H, dd, J = 2.0, 6.9 Hz, 2 × ArH).

^{13}C NMR: δ_C (100 MHz, $CDCl_3$) 32.3 (*C*H_2CHC=O), 53.5 (NCH_2), 54.0 (NCH_2), 68.3 (CHC=O), 70.4 (CH_2O), 114.7 (2 × ArCH), 118.9 (CH=*C*H_2), 124.8 (*C*H=CH), 125.8 (CH=*C*H), 127.6 (2 × ArCH), 127.8 (ArCO), 128.4 (2 × ArCH), 128.6 (*C*H=CH_2), 128.8 (ArCH), 132.2 (2 × ArCH), 135.7 (ArC), 162.6 (ArCS), 163.4 (C=O).

ν_{max} KBr/cm^{-1}: 3431 w, 2923 w, 1659 s (tertiary amide), 1437 m, 1145 m, 1002 m, 737 m.

MS (EI): *m/z* 397 (M^+, 1 %), 150 (100), 91 (Bn^+, 87), 68 (46).

HRMS: Found 397.1350, $C_{22}H_{23}O_4NS$ requires 397.1348.

For **184**: ^{1}H NMR: δ_H (400 MHz, $CDCl_3$) 2.49-2.56 (1H, m, CH_AH$_B$CHC=O), 3.03 (1H, dd, J = 3.2, 17.8 Hz, CH$_A$$H_B$CHC=O), 3.42 (1H, dd, J = 5.5, 17.5 Hz, NCH_AH$_B$CH), 3.86 (1H, dd, J = 6.3, 15.4 Hz, NCH_AH$_B$CH=CH$_2$), 4.16 (1H, dd, J = 5.5, 15.4 Hz, NCH$_A$$H_B$CH=CH$_2$), 4.27-4.22 (1H, m, NCH$_A$$H_B$CH), 4.67 (1H, dd, J = 3.2, 13.0 Hz, CHC=O), 5.15 (2H, s, CH$_2$O), 5.17-5.13 (2H, m, CH_2=CH), 5.67-5.63 (1H, m, CH$_2$=C*H*), 5.82-5.76 (2H, m, C*H*=C*H*), 7.02 (2H, dd, J = 2.1, 7.0 Hz, 2 × ArH), 7.45-7.38 (5H, 5 × ArH), 8.04 (2H, dd, J = 2.1, 7.0 Hz, 2 × ArH).

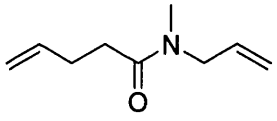
^{13}C NMR: δ_C (100 MHz, $CDCl_3$) 27.3 (CH*C*H$_2$CH), 44.3 (N*C*H$_2$CH=CH$_2$), 50.2 (NCH$_2$CH=CH), 66.3 (CH), 70.3 (PhCH$_2$O), 114.6 (2 × ArCH), 118.1 (CH=*C*H$_2$), 125.0 (*C*H=CH), 127.5 (2 × ArCH), 127.9 (ArCO), 128.4 (2 × ArCH), 128.5 (CH=*C*H), 128.7 (ArCH), 132.7 (*C*H=CH$_2$), 132.8 (2 × ArCH), 133.8 (ArC), 159.3 (ArCS), 161.9 (C=O).

ν_{max} KBr/cm^{-1}: 2922 br, 1655 s (tertiary amide), 1465 w, 1249 m, 997 m, 727 m.

MS (CI): *m/z* 398 ((M+H)$^+$, 22 %), 164 (100), 150 (46), 91 (Bn$^+$, 100).

HRMS: Found 398.1422, $C_{22}H_{24}O_4NS$ requires 398.1421.

_N_-Allyl-_N_-methylpent-4-enamide 186



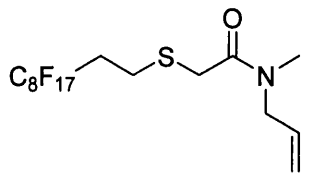
186

NEt_3 (461 µl, 4.55 mmol) and 4-pentenoyl chloride (503 µl, 4.55 mmol) were added to a solution of *N*-methylallylamine (270 µl, 3.80 mmol) in CH_2Cl_2 (10 ml) that had been cooled to 0 °C. The mixture was then allowed to warm to room temperature and stirred for 12 h. The reaction mixture was quenched with aqueous saturated NH_4Cl (5 ml) then H_2O (5 ml). The aqueous layer was then extracted with CH_2Cl_2 (3 × 10 ml). The organic layers were then dried (Na_2SO_4) and concentrated to give *N*-allyl-*N*-methylpent-4-enamide **186** as a brown oil (547 mg, 3.57 mmol, 94 %)

Approx. 1:1 mixture of rotamers; ^{1}H NMR: δ_H (500 MHz, $CDCl_3$) 2.43-2.17 (8H, m, 2 × CH_2CH_2C=O, both rotamers), 2.93 (3H, s, NMe, one rotamer), 2.95 (3H, s, NMe, one

rotamer), 3.90 (2H, d, J = 6.0 Hz, NCH_2, one rotamer), 4.00 (2H, d, J = 6.0 Hz, NCH_2, one rotamer), 5.22-5.03 (8H, m, 2 × $CH_2CH_2CH=CH_2$, 2 × $NCH_2CH=CH_2$, both rotamers), 5.88-5.75 (4H, m, 2 × $CH_2CH_2CH=CH_2$, 2 × $NCH_2CH=CH_2$, both rotamers).

2-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-Heptadecafluorodecylsulfanyl)-*N*-allyl-*N*-methylacetamide 197



197

N-Allyl-2-bromo-*N*-methyl-acetamide **168** (2.45 g, 12.8 mmol) was added via cannula to a solution of 3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecane-1-thiol **196** (2.49 ml, 8.50 mmol) and NEt_3 (1.80 ml, 12.8 mmol) in DMF (20 ml) and the reaction mixture was stirred at room temperature for 16 h. The reaction mixture was quenched with aqueous saturated NH_4Cl (5 ml) then H_2O (5 ml). The aqueous layer was then extracted with CH_2Cl_2 (3 × 20 ml). The organic layers were then dried (Na_2SO_4) and then concentrated. The crude product was then purified using fluorous silica (eluting with 80 % MeCN/H_2O then MeCN) to give 2-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecylsulfanyl)-*N*-allyl-*N*-methylacetamide **197** as a white solid (4.32 g, 7.31 mmol, 86 %).

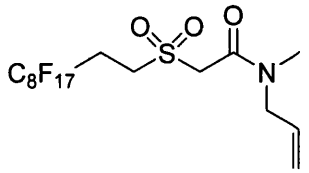
Approx. 1:1 mixture of rotamers; ^1H NMR: δ_H (500 MHz, $CDCl_3$) 2.51-2.45 (4H, m, 2 × CH_2CF_2, both rotamers), 2.92-2.89 (4H, m, 2 × $CH_2CH_2CF_2$, both rotamers), 2.95 (3H, s, NMe, one rotamer), 3.03 (3H, s, NMe, one rotamer), 3.32 (2H, s, $CH_2C=O$, one rotamer), 3.36 (2H, s, $CH_2C=O$, one rotamer), 4.01-3.97 (4H, m, 2 × NCH_2, both rotamers), 5.28-5.16 (4H, m, 2 × $CH=CH_2$, both rotamers), 5.87-5.70 (2H, m, 2 × $CH=CH_2$, both rotamers).

Approx. 1:1 mixture of rotamers; ^{13}C NMR: δ_C (75 MHz, $CDCl_3$) 22.6 (2 × $CH_2CH_2CF_2$, both rotamers), 31.4 (2 × CH_2CF_2, both rotamers), 32.7 ($CH_2C=O$, one rotamer), 33.1 ($CH_2C=O$, one rotamer), 33.7 (NCH_3, one rotamer), 35.1 (NCH_3, one rotamer), 50.0 (NCH_2, one rotamer), 52.4 (NCH_2, one rotamer), 116.7 ($CH=CH_2$, one rotamer), 117.1

(CH=CH_2, one rotamer), 132.1 (CH=CH_2, one rotamer), 132.2 (CH=CH_2, one rotamer), 168.2 (C=O, one rotamer), 168.7 (C=O, one rotamer).

ν_{max} ATR/cm^{-1}: 2930 br, 1650 s (tertiary amide), 1489 m, 1241 m, 996 m, 823 m.

2-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-Heptadecafluorodecylsulfonyl)-*N*-allyl-*N*-methylacetamide 198



198

Oxone (8.32 g, 13.5 mmol) was added to a solution of 2-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecylsulfanyl)-*N*-allyl-*N*-methylacetamide **197** (2.00 g, 3.38 mmol) in DMF (22 ml) and H_2O (5.5 ml) and the reaction mixture was stirred at room temperature for 2 h. The reaction mixture was diluted with H_2O (10 ml) and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 ml). The organic layers were then dried (Na_2SO_4) and then concentrated. The crude product was then purified using fluorous silica (eluting with 80 % MeCN/H_2O then MeCN) to give 2-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecylsulfonyl)-*N*-allyl-*N*-methylacetamide **198** as a white solid (695 mg, 1.16 mmol, 33 %).

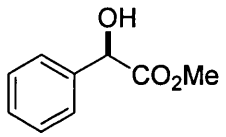
Approx. 1:1 mixture of rotamers; ^{1}H NMR: δ_H (500 MHz, $CDCl_3$) 2.74-2.70 (4H, m, 2 × CH_2CF_2, both rotamers), 3.03 (3H, s, NMe, one rotamer), 3.14 (3H, s, NMe, one rotamer), 3.63-3.58 (4H, m, 2 × C$H_2$$CH_2CF_2$, both rotamers), 4.09-4.06 (6H, m, CH_2C=O, one rotamer and 2 × NCH_2, both rotamers), 4.15 (2H, m, CH_2C=O, one rotamer), 5.33-5.18 (4H, m, 2 × CH=CH_2, both rotamers), 5.87-5.73 (2H, m, 2 × CH=CH_2, both rotamers).

Approx. 1:1 mixture of rotamers; ^{13}C NMR: δ_C (75 MHz, $CDCl_3$) 24.5 (2 × CH_2CF_2, both rotamers), 34.5 (NCH_3, one rotamer), 36.3 (NCH_3, one rotamer), 45.6 (2 × $CH_2CH_2CF_2$, both rotamers), 50.7 (NCH_2, one rotamer), 53.1 (NCH_2, one rotamer), 56.4 (CH_2C=O, one rotamer), 56.7 (CH_2C=O, one rotamer), 117.6 (CH=CH_2, one rotamer), 118.1 (CH=CH_2,

one rotamer), 131.3 (*C*H=CH_2, one rotamer), 131.5 (*C*H=CH_2, one rotamer), 161.5 (C=O, one rotamer), 162.0 (C=O, one rotamer).

ν_{max} ATR/cm^{-1}: 2929 br, 1644 s (tertiary amide), 1487 m, 1239 m, 996 m, 819 m.

_R_-(-)-Methyl mandelate 267[124]

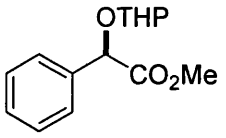


267

R-(-)-Mandelic acid **207** (10.0 g, 65.7 mmol), was dissolved in MeOH (70 ml), and the mixture was cooled to -10 °C before thionyl chloride (5.28 ml, 72.3 mmol) was added dropwise. The reaction was then allowed to warm to room temperature and stirred for 3 h. The solvent was then evaporated and the reaction mixture was diluted with iced H_2O (60 ml) and Et_2O (100 ml). The organic layer was then extracted with H_2O (3 × 20 ml), dried ($MgSO_4$), and concentrated to give *R*-(-)-methyl mandelate **267** as a white solid (8.50 g, 51.3 mmol, 78 %).

^{1}H NMR: δ_H (400 MHz, $CDCl_3$) 3.44 (1H, d, J = 6.5 Hz, OH), 3.78 (3H, s, CH_3), 5.19 (1H, d, J = 6.5 Hz, CH), 7.45-7.32 (5H, m, 5 × ArH).

_R_-(-)-Methyl-2-phenyl-2-(tetrahydropyranyloxy) acetate 208[124]



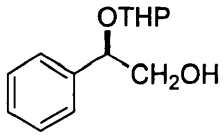
208

To a solution containing *R*-(-)-methyl mandelate **267** (12.9 g, 77.4 mmol) and dihydropyran (29.7 ml, 354 mmol) in CH_2Cl_2 (200 ml) at 0 °C, was added pyridinium *p*-toluene sulfonate (2.26 g). The reaction was stirred at 0 °C for 10 min before being stirred for a further 43 h

at room temperature. The reaction mixture was quenched with aqueous saturated NH_4Cl (10 ml) then H_2O (40 ml). The aqueous layer was then extracted with CH_2Cl_2 (3 × 40 ml). The organic layers were then dried (Na_2SO_4) and concentrated. The crude product was purified by column chromatography (silica, 30 % EtOAc/pet. ether) to give *R*-(-)-methyl-2-phenyl-2-(tetrahydropyranyloxy) acetate **208** as a clear oil (18.8 g, 75.1 mmol, 97 %).

Approx. 1:1 mixture of diastereoisomers; ^1H NMR: δ_H (400 MHz, $CDCl_3$) 1.95-1.47 (12H, m, 3 × CH_2 of THP, both diastereoisomers), 3.54-3.48 (4H, m, 2 × CH_2O, both diastereoisomers), 3.72 (6H, s, 2 × CH_3, both diastereoisomers), 4.59 (1H, t, J = 3.5 Hz, OCHO, one diastereoisomer), 4.97-4.82 (1H, m, OCHO, one diastereoisomer), 5.25 (1H, s, CHC=O, one diastereoisomer), 5.34 (1H, s, CHC=O, one diastereoisomer), 7.51-7.31 (10H, m, 10 × ArH, both diastereoisomers).

_R_-(-)-2-Phenyl-2-(tetrahydropyranyloxy) ethanol 206[124]



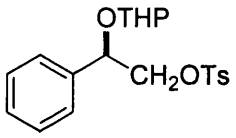
206

A solution of *R*-(-)-methyl-2-phenyl-2-(tetrahydropyranyloxy) acetate **208** (6.76 g, 27.0 mmol) in THF (70 ml) was added dropwise to a stirred suspension of $LiAlH_4$ (2.05 g, 54.0 mmol) in THF (70 ml) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min before being allowed to warm to room temperature and stirred for a further 2 h. The reaction mixture was then cooled and quenched with the consecutive addition of aqueous saturated NH_4Cl (10 ml), 10 % aqueous NaOH (10 ml), and H_2O (10 ml). The resulting white precipitate was then filtered and extracted with THF (2 × 50 ml). The organic layer was then dried ($MgSO_4$), and concentrated. The crude mixture was purified by column chromatography (silica, 40 % EtOAc/pet. ether) to give *R*-(-)-2-phenyl-2-(tetrahydropyranyloxy) ethanol **206** as a clear oil (4.64 g, 20.8 mmol, 77 %).

Approx. 1:1 mixture of diastereoisomers; ^1H NMR: δ_H (400 MHz, $CDCl_3$) 1.91-1.44 (12H, m, 3 × CH_2 of THP, both diastereoisomers), 2.40 (1H, broad, OH, one diastereoisomer),

3.13 (1H, broad, OH, one diastereoisomer), 3.33-3.28 (2H, m, 2 × CH_AH$_B$OH, both diastereoisomers), 3.62-3.53 (2H, m, 2 × CH$_A$$H_B$OH, both diastereoisomers), 4.08-4.01 (2H, m, 2 × CH_AH$_B$OC, both diastereoisomers), 4.54 (1H, apparent q, J = 2.8 Hz, OCHO, one diastereoisomer), 4.76-4.73 (2H, m, 2 × CH$_A$$H_B$OC, both diastereoisomers), 4.85-4.82 (2H, m, CHCH$_2$O, both diastereoisomers), 4.93 (1H, t, J = 3.6 Hz, OCHO, one diastereoisomer), 7.42-7.28 (10H, m, 10 × ArH, both diastereoisomers).

R-(-)-2-Phenyl-2-(tetrahydropyranyloxy)-1-p-toluenesulfonyloxyethane 209[46]

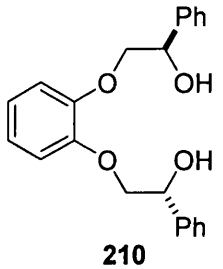


209

p-TsCl (8.85 g, 46.4 mmol) was added to a solution containing R-(-)-2-phenyl-2-(tetrahydropyranyloxy) ethanol **206** (9.38 g, 42.2 mmol), in pyridine (28.9 ml). The mixture was stirred at room temperature for 7 h. The reaction mixture was quenched first with aqueous saturated NaCl (10 ml) and then with H_2O (20 ml) and the organic layer extracted with $CHCl_3$ (3 × 20 ml). The organic layer was then further washed with aqueous saturated $CuSO_4$ (0.5 M, 5 × 20 ml) to remove excess pyridine. The organic layer was then dried ($MgSO_4$), and concentrated. The crude mixture was purified by recrystallisation from pet. ether/CH_2Cl_2 to give R-(-)-2-phenyl-2-(tetrahydropyranyloxy)-1-p-toluenesulfonyloxy ethane **209** as white crystals (10.9 g, 28.7 mmol, 68 %).

Approx. 1:1 mixture of diastereoisomers; ^{1}H NMR: δ_H (400 MHz, $CDCl_3$) 1.88-1.49 (12H, m, 3 × CH_2 of THP, both diastereoisomers), 2.45 (6H, s, 2 × CH_3, both diastereoisomers), 3.52-3.50 (1H, m, OCHPh, one diastereoisomer), 3.98 (1H, dt, J = 3.1, 10.5, OCHO, one diastereoisomer), 4.16-4.07 (4H, m, 2 × CH_2OC, both diastereoisomers), 4.22 (1H, dd, J = 8.0, 10.5, OCHPh, one diastereoisomer), 4.50 (1H, t, J = 3.1, OCHO, one diastereoisomer), 4.96-4.87 (4H, m, 2 × CH_2OS, both diastereoisomers), 7.32-7.24 (14H, m, 14 × ArH, both diastereoisomers), 7.75 (4H, dd, J = 2.7, 8.4 Hz, 4 × ArH, both diastereoisomers).

1,2-Di[(*S*)-2-hydroxy-2-phenylethoxy] benzene 210[46]



210

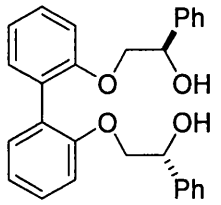
To a suspension of Cs_2CO_3 (1.50 g, 4.60 mmol), in DMF (2.5 ml) was added catechol (0.23 g, 2.09 mmol) and the reaction mixture was stirred vigorously for 30 min. *R*-(-)-2-Phenyl-2-(tetrahydropyranyloxy)-1-*p*-toluenesulfonyloxy ethane **209** (1.73 g, 4.60 mmol) was then added to the suspension which was then heated to 80 °C and stirred for 23 h. After cooling the reaction mixture was diluted with Et_2O (50 ml) and then washed with aqueous saturated NaCl (10 ml), and H_2O (2 × 10 ml). The organic layer was then dried ($MgSO_4$), concentrated and used without further purification.

A solution of the residue and *p*-toluenesulfonic acid (0.14 g, 0.73 mmol) in MeOH (15 ml) was stirred at room temperature for a further 2.5 h. The MeOH was then removed in the presence of $NaHCO_3$ (1.00 g), and the resulting residue was diluted with Et_2O (50 ml), the solids filtered off, and the filtrate concentrated. The crude mixture was purified by column chromatography (silica, 30 % EtOAc/pet. ether), and then further purified by recrystallisation from pet. ether/CH_2Cl_2 to give 1,2-di[(*S*)-2-hydroxy-2-phenylethoxy] benzene **210** as off white crystals (580 mg, 1.59 mmol, 76 %).

^{1}H NMR: δ_H (400 MHz, $CDCl_3$) 3.81 (2H, s, OH), 4.08 (2H, m, CH_AH_BO), 4.18 (2H, dd, J = 3.0, 10.0, CH_AH_BO), 5.13 (2H, dd, J = 3.0, 8.9, CHO), 6.98 (4H, s, 4 × ArH), 7.42 (10H, m, 10 × ArH).

$[\alpha]_D$ = – 86.1°, Lit. value = + 85.7° *R*-isomer ($CHCl_3$).

2,2'-Di[(*S*)-2-hydroxy-2-phenylethoxy]-1,1'-biphenyl 211[46]



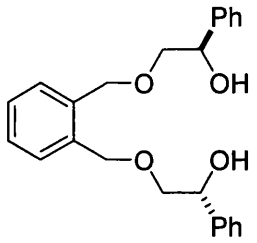
211

According to the procedure described for **210**, 2,2'-diphenol (1.50 g, 8.06 mmol) and tosylate **209** (6.67 g, 17.7 mmol) were reacted with Cs_2CO_3 (6.36 g, 17.7 mmol) in DMF (20 ml) for 15 h at 80 °C. The crude mixture was purified by column chromatography (silica, 20 % EtOAc/pet. ether), to give 2,2'-di[(*S*)-2-hydroxy-2-phenylethoxy]-1,1'-biphenyl **211** as an orange oil (2.33 g, 5.48 mmol, 68 %).

^{1}H NMR: δ_H (400 MHz, $CDCl_3$) 3.73 (2H, broad singlet, OH), 4.05 (2H, apparent t, J = 9.3 Hz, CH_AH$_B$O), 4.17-4.13 (2H, m, CH$_A$$H_B$O), 4.92 (2H, d, J = 8.9 Hz, C*H*OH), 7.04 (2H, d, J = 8.3 Hz, ArCH), 7.16 (2H, t, J = 7.6 Hz, 2 × ArCH), 7.35-7.30 (14H, m, 14 × ArH).

$[\alpha]_D$ = – 40.5°, Lit. value = + 40.1° *R*-isomer ($CHCl_3$).

1,1'-Di [(*S*)-2-hydroxy-2-phenylethyl]-*o*-xylenedioxide 212[40]



212

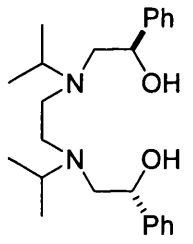
R-(-)-2-Phenyl-2-(tetrahydropyranyloxy) ethanol **206** (8.58 g, 0.04 mmol) was added to a suspension of NaH (0.94 g, 0.04 mmol) in THF (140 ml) that had been cooled to 0 °C, and the reaction mixture was stirred for 30 min. 1,1'-*o*-Xylenedibromide (4.63 g, 0.02 mmol) was then added and the reaction mixture was allowed to warm to room temperature before being stirred for 17 h. The reaction mixture was quenched with acetic acid (10 ml), then

H_2O before being extracted with Et_2O (3 × 20 ml). The organic layers were then dried (Na_2SO_4) and concentrated to give 1,1'-bis[(*R*)-2-tetrahydropyranyloxy-2-phenylethyl]-*o*-xylenedioxide which was used without further purification.

A solution of the residue and *p*-toluenesulfonic acid (9.97 g, 0.04 mmol) in MeOH (60 ml) was stirred at room temperature for a further 2.5 h. The MeOH was then removed in the presence of $NaHCO_3$ (1.00 g), and the resulting residue was diluted with CH_2Cl_2 (30 ml), the precipitate filtered off, and the filtrate concentrated. The crude mixture was purified by column chromatography (silica, 30 % EtOAc/pet. ether) to give 1,1'-di [(*S*)-2-hydroxy-2-phenylethyl]-*o*-xylenedioxide **212** as a white solid (4.23 g, 0.01 mmol, 56 %).

^{1}H NMR: δ_H (500 MHz, $CDCl_3$) 3.47-3.43 (2H, m, OCH_AH$_B$CHOH), 3.49 (2H, broad singlet, OH), 3.62 (2H, dd, J = 3.0, 9.9 Hz, OCH$_A$$H_B$CHOH), 4.57 (2H, d, J = 11.6 Hz, PhCH_AH$_B$O), 4.65 (2H, d, J = 11.6 Hz, PhCH$_A$$H_B$O), 4.85 (2H, dd, J = 3.0, 9.1 Hz, C*H*OH), 7.30-7.18 (14H, m, 14 × ArH).

_N,N'_-Di[(S)-2-hydroxy-2-phenylethyl]-_N,N'_-diisopropylethylenediamine 213[46]



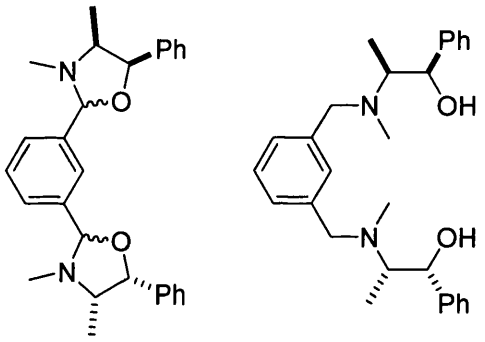
213

A solution of *N,N'*-diisopropylethylenediamine (1.20 g, 8.32 mmol) and (*R*)-styrene oxide (2.00 g, 16.6 mmol) was stirred in DMF : H_2O (9:1, 6.60 ml) and the reaction mixture was heated to 100 °C and stirred for 18 h. The reaction mixture was quenched with aqueous saturated NaCl (5 ml) and then extracted with EtOAc (3 × 15 ml). The organic layer was then dried (Na_2SO_4), and concentrated. The crude mixture was purified by column chromatography (silica, 5 % EtOAc/pet. ether) to give *N,N'*-di[(*S*)-2-hydroxy-2-phenylethyl]-*N,N'*-diisopropylethylene diamine **213** as a clear oil (771 mg, 2.66 mmol, 32 %).

^{1}H NMR: δ_H (500 MHz, $CDCl_3$) 0.93 (6H, d, J = 6.6 Hz, CH_3), 0.96 (6H, d, J = 6.6 Hz, CH_3), 2.32 (2H, dd, J = 10.5, 13.7 Hz, NCH_AH_BCH), 2.43-2.55 (4H, m, NCH_2CH_2N), 2.67 (2H, dd, J = 3.0, 13.7 Hz, NCH_AH_BCH), 2.98-2.93 (2H, m, NCH), 4.67 (2H, dd, J = 3.0, 10.5 Hz, C*H*OH), 5.84 (2H, br, OH), 7.28-7.09 (10H, m, 10 × ArH).

$[\alpha]_D$ = – 137.5°, Lit. value = – 137.0° ($CHCl_3$).

(2*S*/2*R*,4S,5R)-3,4-dimethyl-2-(3-((2*S*/2*R*,4S,5R)-3,4-dimethyl-5-phenyloxazolidin-2-yl)phenyl)-5-phenyloxazolidine 217 and **(+)-(1*S*,2*R*)-bis[*N*-methyl-*N*-(2-hydroxy-2-phenyl-1-methyl)-ethyl]-*m*-xylenediamine 214**[122, 123]



217 **214**

Isophthaldialdehyde **216** (1.69 g, 12.6 mmol) and (-)-ephedrine (4.16 g, 25.2 mmol) were stirred in CH_2Cl_2 (50 ml) in the presence of 3 Å molecular sieves (3 g) at room temperature for 24 h. The crude mixture was filtered through a pad of celite to give (2*S*/2*R*,4S,5R)-3,4-dimethyl-2-(3-((2*S*/2*R*,4S,5R)-3,4-dimethyl-5-phenyloxazolidin-2-yl)phenyl)-5-phenyloxazolidine **217** which was used without further purification.

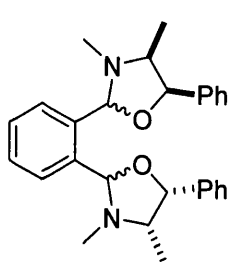
^{1}H NMR: δ_H (500 MHz, $CDCl_3$) 0.86 (6H, d, J = 6.0 Hz, $CHCH_3$), 2.26 (6H, s, NMe), 3.05 (2H, dq, J = 6.0, 9.0 Hz, C*H*CH_3), 4.82 (2H, s, NCHO), 5.22 (2H, d, J = 9.0 Hz, PhCHO), 7.94-7.30 (14H, m, 14 × ArH).

The crude mixture in THF (40 ml) was added dropwise to a suspension of $LiAlH_4$ (944 mg, 24.9 mmol) in THF (80 ml) and the reaction mixture was heated to reflux for 17 h. Upon cooling, the reaction mixture was treated sequentially with H_2O (0.9 ml), 15 % NaOH (2.7 ml) and H_2O (0.9 ml) before being stirred for 2 h. The white solids were removed by filtration, and the filtrate was dried (Na_2SO_4) and then concentrated. The crude mixture was

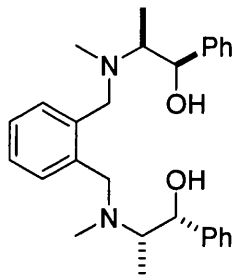
purified by column chromatography (silica, 48 % EtOAc /48 % pet. ether/4 % NEt_3) to give (+)-(1*S*,2*R*)-bis[*N*-methyl-*N*-(2-hydroxy-2-phenyl-1-methyl)-ethyl]-*m*-xylenediamine **214** as a clear oil (4.92 g, 11.3 mmol, 90 % over 2 steps).

^{1}H NMR: δ_H (500 MHz, $CDCl_3$) 0.86 (6H, d, J = 7.0 Hz, CHC*H*$_3$), 2.02 (6H, s, NMe), 2.76 (2H, dt, J = 4.9, 7.0 Hz, C*H*CH_3), 3.43 (4H, s, NCH_2), 4.68 (2H, d, J = 4.9 Hz, C*H*OH), 6.97-6.92 (3H, m, 3 × ArH), 7.12-7.06 (3H, m, 3 × ArH), 7.17-7.14 (8H, m, 8 × ArH).

(2*S*/2*R*,4*S*,5*R*)-3,4-dimethyl-2-(2-((2*S*/2*R*,4*S*,5*R*)-3,4-dimethyl-5-phenyloxazolidin-2-yl)phenyl)-5-phenyloxazolidine 219 and **(+)-(1*S*,2*R*)-bis[*N*-methyl-*N*-(2-hydroxy-2-phenyl-1-methyl)-ethyl]-*o*-xylenediamine 215**[122, 123]



219



215

According to the procedure described for **217**, phthaldialdehyde **218** (1.69 g, 12.6 mmol) was stirred with (-)-ephedrine (4.16 g, 25.2 mmol) and 3 Å molecular sieves (3 g) in CH_2Cl_2 (50 ml) to give (2*S*/2*R*,4*S*,5*R*)-3,4-dimethyl-2-(2-((2*S*/2*R*,4*S*,5*R*)-3,4-dimethyl-5-phenyloxazolidin-2-yl)phenyl)-5-phenyloxazolidine **219** which was used without further purification.

^{1}H NMR: δ_H (500 MHz, $CDCl_3$) 0.85 (6H, d, J = 6.0 Hz, CHC*H*$_3$), 2.23 (6H, s, NMe), 3.11-3.06 (2H, m, C*H*CH_3), 5.25 (2H, d, J = 9.0 Hz, PhCHO), 5.42 (2H, s, NCHO), 8.12-7.30 (14H, m, 14 × ArH).

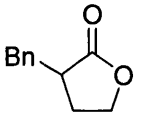
According to the procedure described for **214**, the crude mixture was treated with $LiAlH_4$ (944 mg, 24.9 mmol) to give (+)-(1*S*,2*R*)-bis[*N*-methyl-*N*-(2-hydroxy-2-phenyl-1-methyl)-ethyl]-*o*-xylenediamine **215** as a clear oil (3.52 g, 8.32 mmol, 66 %).

^{1}H NMR: δ_H (500 MHz, $CDCl_3$) 0.82 (6H, d, J = 12.6 Hz, CHC*H*$_3$), 1.93 (6H, s, NMe), 2.61 (2H, dq, J = 6.0, 12.6 Hz, C*H*CH_3), 3.22 (2H, d, AB system J = 13.3 Hz, NC*H*$_A$H$_B$),

3.37 (2H, d, AB system J = 13.3 Hz, NCH_AH_B), 3.56 (2H, br, OH), 4.54 (2H, d, J = 6.0 Hz, C*H*OH), 7.12-7.00 (14H, m, 14 × ArH).

General procedure A for the reduction of α-heterosubstituted lactones:

3-Benzyldihydro-2(3*H*)-furanone 121 from the reduction-protonation of 3-benzyl-3-(4-benzyloxyphenoxy)dihydro-furan-2-one **119** using 1,2-di[(*S*)-2-hydroxy-2-phenylethoxy] benzene **210**

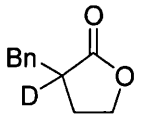


121

A solution of SmI_2 (8.0 ml, 0.80 mmol, 0.1 M in THF) was added to a solution of 1,2-di[(*S*)-2-hydroxy-2-phenylethoxy] benzene **210** (281 mg, 0.80 mmol) in THF (1 ml) that had been cooled to -20 °C. 3-Benzyl-3-(4-benzyloxyphenoxy)dihydro-furan-2-one **119** (100 mg, 0.27 mmol) in THF (1.5 ml) was then added dropwise via cannula and the reaction mixture was stirred at -20 °C for 18 h. The reaction mixture was allowed to decolourise in air before being quenched with aqueous saturated NaCl (5 ml). The aqueous layer was then extracted with 30 % EtOAc/pet. ether (3 × 5 ml). The organic layer was then dried (Na_2SO_4), and concentrated. The crude mixture was purified by column chromatography (silica, 15 % EtOAc/pet. ether) to give 3-benzyldihydro-2(3*H*)-furanone **121** as a yellow oil (22 mg, 0.13 mmol, 47 %, 0 % ee).

Spectroscopic data corresponded to that reported earlier in this section.

3-Benzyldihydro-2(3*D*)-furanone 234 from the reduction-protonation of 3-benzyl-3-(4-benzyloxyphenoxy)dihydro-furan-2-one **119** in the presence of MeOD

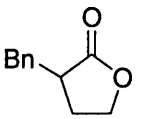


234

A solution of SmI_2 (9.60 ml, 0.96 mmol, 0.1 M in THF), was added to a solution of 3-benzyl-3-(4-benzyloxyphenoxy)dihydro-furan-2-one **119** (150 mg, 0.40 mmol) and MeOD (3.2 ml) in THF (3 ml) that had been cooled -20 °C. The mixture was then stirred at -20 °C. After 1 h, a further 2.4 equivalents of SmI_2 (7.38 ml, 0.74 mmol, 0.1 M in THF) was added and the reaction was allowed to stir for another 4 h. The reaction mixture was quenched first with aqueous saturated NH_4Cl (3 ml) followed by H_2O (3 ml) and then extracted with Et_2O (3 × 10 ml). The organic layer was then dried ($MgSO_4$), and concentrated. The crude mixture was purified by column chromatography (silica, 100 % CH_2Cl_2) to give 3-benzyldihydro-2(3*D*)-furanone **234** as a yellow oil (7.6 mg, 0.04 mmol, 11 %).

^{1}H NMR: δ_H (400 MHz, $CDCl_3$) 2.16-2.06 (1H, m, CH_AH$_B$CH$_2$O), 2.40-2.33 (1H, m, CH$_A$$H_BCH_2$O), 2.90 (1H, d, J = 14.0 Hz, PhCH_AH$_B$), 3.37 (1H, d, J = 14.0 Hz, PhCH$_A$$H_B$), 4.36-4.23 (2H, m, CH_2O), 7.53-7.31 (5H, m, 5 × ArH).

3-Benzyldihydro-2(3*H*)-furanone 121 from the reduction-protonation of 3-benzyl-3-(4-benzyloxyphenoxy)dihydro-furan-2-one **119** in the presence of BnOH

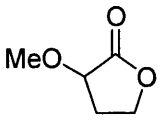


121

A solution of SmI_2 (3.20 ml, 0.32 mmol, 0.1 M in THF), was added to a solution of 3-benzyl-3-(4-benzyloxyphenoxy)dihydro-furan-2-one **119** (50.0 mg, 0.13 mmol) and BnOH (55.0 µl) in THF (1 ml) that had been cooled -20 °C. The mixture was then stirred at -20 °C

for 2h. The reaction mixture was quenched with D_2O (3 ml) and then extracted with 30 % EtOAc/pet. ether (3 × 5 ml). The organic layer was then dried ($MgSO_4$), and concentrated. The crude mixture was purified by column chromatography (silica, 100 % CH_2Cl_2) to give 3-benzyldihydro-2(3*D*)-furanone **121** as a yellow oil (4.23 mg, 0.06 mmol, 42 %).
Spectroscopic data corresponded to that reported earlier in this section.

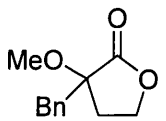
3-Methoxy-dihydro-furan-2-one 237[135]



237

To a solution of α-hydroxy-γ-butryolactone (2.50 g, 24.3 mmol) in DMF (15 ml) was added silver oxide (8.97 g, 72.9 mmol) and MeI (3.02 ml, 48.6 mmol) and the reaction mixture was stirred at room temperature for 22 h. 20 % EtOAc/pet. ether (3 × 20 ml) was added to the reaction mixture and it was passed through a plug column and concentrated. The crude mixture was purified by column chromatography (silica, 30 % EtOAc/pet. ether) to give 3-methoxy-dihydro-furan-2-one **237** as a clear oil (1.93 g, 16.5 mmol, 68 %).
^1H NMR: δ_H (500 MHz, $CDCl_3$) 2.32 (1H, dd, J = 6.8, 8.1 Hz, $CH_AH_BCH_2O$), 2.66-2.59 (1H, m, $CH_AH_BCH_2O$), 3.63 (3H, s, OMe), 4.14 (1H, t, J = 8.1 Hz, CH), 4.33 (1H, ddd, J = 6.8, 8.4, 9.3 Hz, $CH_2CH_AH_BO$), 4.49 (1H, dt, J = 8.4, 9.3 Hz, $CH_2CH_AH_BO$).
^{13}C NMR: δ_C (75 MHz, $CDCl_3$) 29.1 (CH_2CH_2O), 57.9 (OMe), 65.2 (CH_2CH_2O), 74.8 (CH), 174.7 (C=O).
ν_{max} KBr/cm^{-1} 2925 w, 1776 s (C=O), 1362 w, 1157 m.
MS (CI): *m/z* 134 (((M+H)+NH3)$^+$, 100 %), 86 (60).
HRMS: Found 134.0808, $C_5H_{12}O_3N$ requires 134.0812.

3-Benzyl-3-methoxy-dihydro-furan-2-one 236



236

To a solution of diisopropylamine (2.41 ml, 17.2 mmol), in THF (4 ml) that had been cooled to -45 °C was added ^{n}BuLi (6.89 ml, 17.2 mmol, 2.5 M in hexane). The reaction mixture was then stirred for 30 min at -45 °C. A solution of 3-methoxy-dihydro-furan-2-one **237** (1.00 g, 8.61 mmol) in THF (6 ml) was then added dropwise by cannula and the reaction was stirred for a further 30 min. Finally, benzyl bromide (7.37 ml, 43.1 mmol) was added dropwise to the solution and the reaction mixture stirred for 8 h. The reaction mixture was quenched first with aqueous saturated NH_4Cl (5 ml) then H_2O (5 ml) and extracted with CH_2Cl_2 (3 × 10 ml). The organic layers were then dried ($MgSO_4$) and concentrated. The crude mixture was purified by column chromatography (silica, 20 % EtOAc/pet. ether) to give 3-benzyl-3-methoxy-dihydro-furan-2-one **236** as a yellow oil (629 mg, 3.01 mmol, 35 %).

^{1}H NMR: δ_H (500 MHz, $CDCl_3$) 2.25 (1H, t, J = 6.4 Hz, CH_AH$_B$CH$_2$O), 2.26 (1H, t, J = 7.3 Hz, CH$_A$$H_BCH_2$O), 3.11 (1H, d, AB system, J = 14.0 Hz, PhCH$_2$C), 3.21 (1H, d, AB system, J = 14.0 Hz, PhCH$_2$C), 3.49 (3H, s, OMe), 3.89 (1H, dt, J = 6.4, 8.8 Hz, CH_AH$_B$O), 4.30 (1H, dt, J = 7.3, 8.8 Hz, CH$_A$$H_B$O), 7.36-7.25 (5H, m, 5 × ArH).

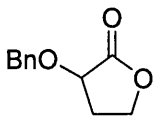
^{13}C NMR: δ_C (75 MHz, $CDCl_3$) 31.9 (*C*H$_2$CH$_2$O), 38.5 (CH$_2$Ph), 52.1 (OMe), 65.4 (CH$_2$*C*H$_2$O), 80.2 (ArC), 127.1 (ArCH), 128.5 (2 × ArCH), 130.0 (2 × ArCH), 134.9 (*C*C=O), 175.1 (C=O).

ν_{max} KBr/cm^{-1} 2936 w, 2330 s, 1759 s (C=O), 1142 w, 633 w.

MS (CI): *m/z* 224 (((M+H)+NH$_3$)$^+$, 100 %), 91 (100).

HRMS: Found 224.1280 $C_{12}H_{18}O_3N$ requires 224.1281.

3-Benzyloxy-dihydro-furan-2-one 238



238

To a solution of α-hydroxy-γ-butryolactone (2.02 g, 19.8 mmol) in DMF (15 ml) was added silver oxide (7.30 g, 59.4 mmol) and benzyl bromide (4.71 ml, 39.6 mmol) and the reaction mixture was stirred at room temperature for 24 h. 40 % EtOAc/pet. ether (3 × 20 ml) was added to the reaction mixture and it was passed through a plug column and concentrated. The crude mixture was purified by column chromatography (silica, 20 % EtOAc/pet. ether) to give 3-benzyloxy-dihydro-furan-2-one **238** as a yellow oil (2.86 g, 14.9 mmol, 75 %).

^{1}H NMR: δ 2.33-2.24 (1H, m, CH_AH$_B$CH$_2$O), 2.51-2.43 (1H, m, CH$_A$$H_BCH_2$O), 4.25-4.15 (2H, m, CH$_2$$H_ACH_B$O and CH), 4.41 (1H, ddd, J = 4.1, 8.2, 9.1 Hz, CH$_2$CH$_A$$H_B$O), 4.74 (1H, d, AB system, J = 11.8 Hz, PhCH$_2$O), 4.95 (1H, d, AB system, J = 11.8 Hz, PhCH$_2$O), 7.45-7.28 (5H, m, 5 × ArH).

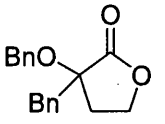
^{13}C NMR: δ 29.8 (CH$_2$CH$_2$O), 65.3 (CH$_2$CH$_2$O), (CH$_2$Ph), 72.3 (CH), 128.1 (2 × ArCH), 128.8 (3 × ArCH), 136.9 (ArC), 175.0 (C=O).

ν_{max} KBr/cm^{-1} 3536 br, 2915 m, 1772 br (C=O), 1454 s, 1025 m, 744 m.

MS (CI): *m/z* 193 (M$^+$, 97 %), 91 (Bn$^+$, 100 %).

HRMS: Found 193.0866, $C_{11}H_{12}O_3$, requires 193.0865.

3-Benzyl-3-benzyloxy-dihydro-furan-2-one 239



239

To a solution of diisopropylamine (729 µl, 5.20 mmol), in THF (1 ml) that had been cooled to -45 °C was added ^{n}BuLi (2.25 ml, 5.20 mmol, 2.24 M in hexane). The reaction mixture

was then stirred for 30 min at -45 °C. A solution of 3-benzyloxy-dihydro-furan-2-one **238** (500 mg, 2.60 mmol) in THF (4 ml) was then added dropwise by cannula and the reaction was stirred for a further 30 min. Finally, benzyl bromide (1.55 ml, 13.0 mmol) was added dropwise to the solution and the reaction mixture stirred for 8 h. The reaction mixture was quenched with aqueous saturated NH_4Cl (5 ml) then H_2O (5 ml) and the aqueous layer was extracted with 40 % EtOAc/pet. ether (3 × 5 ml). The organic layer was then dried ($MgSO_4$), and concentrated. The crude mixture was purified by column chromatography (silica, 10 % EtOAc/pet. ether) to give 3-benzyl-3-benzyloxy-dihydro-furan-2-one **239** as a clear oil (289 mg, 1.01 mmol, 39 %).

^{1}H NMR: δ_H (400 MHz, $CDCl_3$) 2.25-2.13 (2H, m, CH_2CH_2O), 3.12 (1H, d, AB system, J = 13.9 Hz, PhCH_2C), 3.17 (1H, d, AB system, J = 13.9 Hz, PhCH_2C), 3.78 (1H, ddd, J = 5.0, 7.4, 8.8 Hz, CH_2CH_AH$_B$O), 4.20 (1H, dt, J = 7.3, 8.8 Hz, CH_2CH$_A$$H_B$O), 4.56 (1H, d, AB system, J = 11.1 Hz, PhCH_2O), 4.65 (1H, d, AB system, J = 11.1 Hz, PhCH_2O), 7.30-7.15 (10H, m, 10 × ArH).

^{13}C NMR: δ_C (100 MHz, $CDCl_3$) 32.7 (*C*H_2CH_2O), 39.0 (CH_2Ph), 65.5 (CH$_2$*C*H$_2$O), 66.7 (PhCH_2O), 126.5 (ArC), 127.6 (ArCH), 127.7 (ArCH), 127.9 (ArCH), 128.1 (ArCH), 128.4 (ArCH), 128.5 (ArCH), 128.8 (ArCH), 129.8 (ArCH), 130.1 (ArCH), 130.3 (ArCH), 134.9 (*C*C=O), 137.5 (ArCO), 175.3 (C=O).

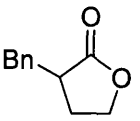
ν_{max} KBr/cm^{-1} 2919 m, 1772 br (C=O), 1454 s, 1024 m, 700 s.

MS (CI): *m/z* 283 (M^+, 100 %), 91 (Bn^+, 9 %).

HRMS: Found 283.1334, $C_{18}H_{19}O_3$, requires 283.1334.

MP: 100.9 – 102.1 °C.

3-Benzyldihydro-2(3*H*)-furanone 121 from reduction-protonation of 3-benzyl-3-methoxy-dihydro-furan-2-one **236** using 1,2-di[(*S*)-2-hydroxy-2-phenylethoxy] benzene **210**



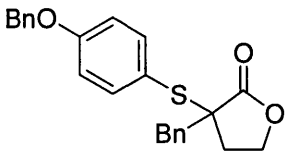
121

According to general procedure A. 3-Benzyl-3-methoxy-dihydro-furan-2-one **236** (50.0 mg, 0.26 mmol) was reduced using SmI_2 (7.90 ml, 0.79 mmol, 0.1 M in THF) in the presence of 1,2-di[(*S*)-2-hydroxy-2-phenylethoxy] benzene **210** (276 mg, 0.79 mmol) to give 3-benzyldihydro-2(3*H*)-furanone **121** (8.97 mg, 0.05 mmol, 20 %, 0 % ee).
Spectroscopic data corresponded to that reported earlier in this section.

3-Benzyldihydro-2(3*H*)-furanone 121 from reduction-protonation of 3-benzyl-3-benzyloxy-dihydro-furan-2-one **239** using 1,2-di[(*S*)-2-hydroxy-2-phenylethoxy] benzene **210**

According to general procedure A. 3-Benzyl-3-benzyloxy-dihydro-furan-2-one **239** (100 mg, 0.35 mmol) was reduced using SmI_2 (8.50 ml, 0.85 mmol, 0.1 M in THF) in the presence of 1,2-di[(*S*)-2-hydroxy-2-phenylethoxy] benzene **210** (248 mg, 0.71 mmol) to give 3-benzyldihydro-2(3*H*)-furanone **121** (22.8 mg, 0.13 mmol, 37 %, 0 % ee).
Spectroscopic data corresponded to that reported earlier in this section.

3-Benzyl-3-(4-benzyloxy-phenylsulfanyl)dihydro-furan-2-one 240



240

To a solution of diisopropylamine (196 µl, 1.40 mmol), in THF (2 ml) that had been cooled to -45 °C was added ^{n}BuLi (624 µl, 1.40 mmol, 2.24 M in hexane). The reaction mixture was then stirred for 30 min at -45 °C. A solution of 3-(4-benzyloxy-phenylsulfanyl)dihydro-furan-2-one **136** (300 mg, 1.00 mmol) in THF (6 ml) was then added dropwise by cannula and the reaction was stirred for a further 30 min. Finally, benzyl bromide (594 µl, 4.99 mmol) was added dropwise to the solution and the reaction mixture was allowed to warm slowly and stirred for 3.5 h. The reaction mixture was quenched with aqueous saturated NH_4Cl (5 ml), H_2O (10 ml), and then diluted with 40 % EtOAc/pet. ether (3 × 10 ml). The organic layer was then dried ($MgSO_4$) and concentrated. The crude mixture was purified by column chromatography (silica, 10 % EtOAc/pet. ether) to give 3-benzyl-3-(4-benzyloxy-phenylsulfanyl)dihydro-furan-2-one **240** as an off-white solid (317 mg, 0.81 mmol, 81 %).

^{1}H NMR: δ_H (400 MHz, $CDCl_3$) 2.14 (1H, ddd, J = 2.2, 6.7, 13.8 Hz, CH_AH$_B$CH$_2$O), 2.49-2.41 (1H, m, CH$_A$$H_BCH_2$O), 3.03 (1H, d, AB system, J = 13.8 Hz, CCH$_2$Ph), 3.33 (1H, d, AB system, J = 13.8 Hz, CCH$_2$Ph), 3.93 (1H, dt, J = 2.2, 8.8 Hz, CH_AH$_B$O), 4.17-4.12 (1H, m, CH$_A$$H_B$O), 5.10 (2H, s, PhCH$_2$O), 7.00 (2H, d, J = 8.8 Hz, 2 × ArH), 7.47-7.21 (10H, m, 5 × ArH), 7.55 (2H, d, J = 8.8 Hz, 2 × ArH).

^{13}C NMR: δ_C (100 MHz, $CDCl_3$) 32.2 (*C*H$_2$CH$_2$O), 41.4 (CCH$_2$Ph), 54.6 (*C*C=O), 64.9 (CH$_2$*C*H$_2$O), 70.1 (PhCH$_2$O), 115.4 (2 × ArCH), 120.2 (ArCS), 127.2 (2 × ArCH), 127.6 (2 × ArCH), 128.2 (2 × ArCH), 128.6 (ArCH), 128.7 (2 × ArCH), 130.4 (ArCH), 135.8 (ArC), 136.4 (ArC), 138.9 (2 × ArCH), 160.6 (ArCO), 175.8 (C=O).

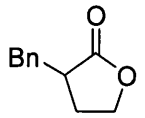
ν_{max} KBr/cm^{-1} 1749 m (C=O), 1245 m, 1002 s, 831 s, 704 m.

MS (EI): *m/z* 390 (M$^+$, 27 %), 91 (Bn$^+$, 100 %).

HRMS: Found 390.1292, $C_{24}H_{22}O_3S$, requires 390.1290.

MP: 131.9 – 133.2 °C.

3-Benzyldihydro-2(3*H*)-furanone 121 from reduction-protonation of 3-benzyl-3-(4-benzyloxy-phenylsulfanyl)dihydro-furan-2-one **240** using 1,2-di[(*S*)-2-hydroxy-2-phenylethoxy] benzene **210**



121

According to general procedure A. 3-Benzyl-3-(4-benzyloxy-phenylsulfanyl)dihydro-furan-2-one **240** (100 mg, 0.26 mmol) was reduced using SmI_2 (7.70 ml, 0.77 mmol, 0.1 M in THF) in the presence of 1,2-di[(*S*)-2-hydroxy-2-phenylethoxy] benzene **210** (269 mg, 0.77 mmol) to give 3-benzyldihydro-2(3*H*)-furanone **121** (19.0 mg, 0.12 mmol, 46 %, 0 % ee).

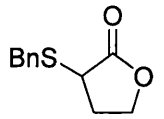
Spectroscopic data corresponded to that reported earlier in this section.

3-Benzyldihydro-2(3*H*)-furanone 121 from reduction-protonation of 3-benzyl-3-(4-benzyloxy-benzenesulfonyl)dihydro-furan-2-one **139** using 1,2-di[(*S*)-2-hydroxy-2-phenylethoxy] benzene **210**

According to general procedure A. 3-Benzyl-3-(4-benzyloxy-benzenesulfonyl)dihydro-furan-2-one **139** (100 mg, 0.24 mmol) was reduced using SmI_2 (5.70 ml, 0.57 mmol, 0.1 M in THF) in the presence of 1,2-di[(*S*)-2-hydroxy-2-phenylethoxy] benzene **210** (166 mg, 0.47 mmol) to give 3-benzyldihydro-2(3*H*)-furanone **121** (32.0 mg, 0.18 mmol, 76 %, 13 % ee).

Spectroscopic data corresponded to that reported earlier in this section.

3-Benzylsulfanyl-dihydro-furan-2-one 243



243

α-Bromo-γ-butyrolactone (3.72 ml, 40.3 mmol) was added to a solution of benzylmercaptan (945 μl, 8.05 mmol) and NEt_3 (5.64 ml, 40.3 mmol) in DMF (20 ml), and the reaction mixture was stirred at room temperature for 1.5 h. The reaction mixture was quenched with aqueous saturated NH_4Cl (5 ml), then H_2O (10 ml), and the organic layer was then extracted with CH_2Cl_2 (3 × 20 ml). The organic layer was then dried ($MgSO_4$) and concentrated. The crude mixture was purified by column chromatography (silica, 30 % EtOAc/pet. ether) to give 3-benzylsulfanyl-dihydro-furan-2-one **243** as a clear oil (1.32 g, 6.23 mmol, 78 %).

^{1}H NMR: δ_H (500 MHz, $CDCl_3$) 2.08-2.02 (1H, m, CH_AH$_B$CH), 2.56 (1H, apparent dq, J = 8.6, 13.5 Hz, CH$_A$$H_B$CH), 3.33 (1H, dd, J = 4.5, 8.6 Hz, CH), 3.84 (1H, AB system J = 13.5 Hz, PhCH_2S), 4.13 (1H, AB system J = 13.5 Hz, PhCH_2S), 4.32-4.28 (1H, m, CH_AH$_B$O), 4.43-4.38 (1H, m, CH$_A$$H_B$O), 7.43-7.28 (5H, m, 5 × ArH).

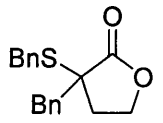
^{13}C NMR: δ_C (75 MHz, $CDCl_3$) 29.5 (*C*H$_2$CH), 35.1 (CH$_2$S), 37.6 (*C*HC=O), 66.8 (CH$_2$O), 127.4 (2 × ArCH), 128.6 (2 × ArCH), 129.2 (ArCH), 137.0 (ArC), 175.5 (C=O).

ν_{max} KBr/cm^{-1} 2912 w, 1760 s (C=O), 1373 w, 1155 m, 699 s.

MS (CI): *m/z* 226 (((M+H)+NH_3)$^+$, 100 %), 91 (59).

HRMS: Found 226.0896, $C_{11}H_{16}O_2NS$ requires 226.0896.

3-Benzyl-3-benzylsulfanyl-dihydro-furan-2-one 241



241

To a solution of diisopropylamine (471 µl, 3.36 mmol), in THF (2 ml) that had been cooled to -45 °C was added ^{n}BuLi (1.34 ml, 3.36 mmol, 2.5 M in hexane). The reaction mixture was then stirred for 30 min. A solution of 3-benzylsulfanyl-dihydro-furan-2-one **243** (500 mg, 2.40 mmol) in THF (3 ml) was then added dropwise by cannula and the reaction was stirred for a further 30 min. Finally, benzyl bromide (1.14 ml, 9.60 mmol) was added dropwise to the solution and the reaction mixture stirred for 6 h. The reaction mixture was quenched with aqueous saturated NH_4Cl (2 ml), then H_2O (10 ml) and then extracted with CH_2Cl_2 (3 × 5 ml). The organic layers were then dried (Na_2SO_4), and concentrated. The crude mixture was purified by column chromatography (silica, 20 % EtOAc/pet. ether) to give 3-benzyl-3-benzylsulfanyl-dihydro-furan-2-one **241** as a clear oil (660 mg, 2.33 mmol, 97 %).

^{1}H NMR: δ_H (500 MHz, $CDCl_3$) 1.95-1.91 (1H, m, CH_AH$_B$CH$_2$O), 2.47-2.44 (1H, m, CH$_A$$H_BCH_2$O), 3.11 (1H, AB system, J = 14.0 Hz, PhCH$_2$C), 3.45 (1H, AB system, J = 14.0 Hz, PhCH$_2$C), 4.01 (1H, AB system J = 12.1 Hz, PhCH$_2$S), 4.09 (1H, AB system J = 12.1 Hz, PhCH$_2$S), 4.13-4.10 (1H, m, CH_AH$_B$O), 4.40-4.36 (1H, m, CH$_A$$H_B$O), 7.50-7.23 (10H, m, 10 × ArH).

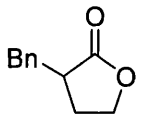
^{13}C NMR: δ_C (75 MHz, $CDCl_3$) 33.3 (*C*H$_2$CH$_2$O), 33.9 (Ph*C*H$_2$S), 40.9 (Ph*C*H$_2$C), 51.4 (*C*C=O), 65.2 (CH$_2$O), 127.2 (2 × ArCH), 127.4 (2 × ArCH), 128.5 (2 × ArCH), 128.7 (ArCH), 129.3 (2 × ArCH), 130.3 (ArCH), 135.7 (ArC), 136.6 (ArC), 175.4 (C=O).

ν_{max} ATR/cm^{-1} 1758 s (C=O), 1451 w, 1170 m, 707 s.

MS (CI): *m/z* 316 ((M+H)$^+$, 6 %), 176, 91 (59).

HRMS: Found 316.1359, $C_{18}H_{22}O_2NS$ requires 316.1366.

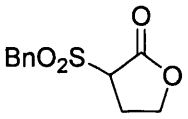
3-Benzyldihydro-2(3*H*)-furanone 121 from reduction-protonation of 3-benzyl-3-benzylsulfanyl-dihydro-furan-2-one **241** using 1,2-di[(*S*)-2-hydroxy-2-phenylethoxy] benzene **210**



121

According to general procedure A. 3-Benzyl-3-benzylsulfanyl-dihydro-furan-2-one **241** (25.0 mg, 0.08 mmol) was reduced using SmI_2 (2.50 ml, 0.25 mmol, 0.1 M) in the presence of 1,2-di[(*S*)-2-hydroxy-2-phenylethoxy] benzene **210** (88.0 mg, 0.25 mmol) to give 3-benzyldihydro-2(3*H*)-furanone **121** (15.4 mg, 0.04 mmol, 51 %, 0 % ee).
Spectroscopic data corresponded to that reported earlier in this section.

3-Benzylsulfonyl-dihydro-furan-2-one 244



244

*m*CPBA (4.57 g, 26.5 mmol) was added to a solution of 3-benzylsulfanyl-dihydro-furan-2-one **243** (1.38 g, 6.63 mmol) in CH_2Cl_2 (20 ml) and the reaction mixture was stirred at room temperature for 3 h. The reaction mixture was quenched with aqueous saturated $NaHCO_3$ (10 ml), and then H_2O (10 ml). The aqueous layer was then extracted with CH_2Cl_2 (3 × 15 ml) before being dried ($MgSO_4$) and then concentrated. The crude mixture was purified by column chromatography (silica, 30 % EtOAc/pet. ether) to give 3-benzylsulfonyl-dihydro-furan-2-one **244** as a white solid (1.19 g, 4.97 mmol, 75 %).
^1H NMR: δ_H (500 MHz, $CDCl_3$) 2.59-2.55 (1H, m, $CH_AH_BCH_2O$), 2.94-2.90 (1H, m, $CH_AH_BCH_2O$), 3.92 (1H, dd, J = 5.6, 10.4 Hz, CHC=O), 4.40 (1H, AB system, J = 14.1 Hz,

$PhCH_2$), 4.43-4.39 (1H, m, CH_AH_BO), 4.60-4.55 (1H, m, CH_AH_BO), 4.96 (1H, AB system, J = 14.1 Hz, $PhCH_2$), 7.46-7.42 (3H, m, 3 × ArH), 7.60-7.56 (2H, m, 2 × ArH).

^{13}C NMR: δ_C (75 MHz, $CDCl_3$) 21.6 (CH_2CH_2O), 57.2 ($CHC{=}O$), 57.7 ($PhCH_2$), 67.5 (CH_2O), 127.2 (ArC), 128.2 (2 × ArCH), 129.4 (ArCH), 131.2 (2 × ArCH), 169.5 (C=O).

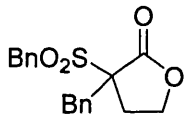
ν_{max} KBr/cm^{-1} 2938 s, 1757 s (C=O), 1306 m, 1130 s, 658 m 610 s.

MS (CI): *m/z* 258 $(((M+H)+NH_3)^+$, 100 %), 176 (52), 91 (Bn^+, 100 %).

HRMS: Found 258.0798, $C_{11}H_{16}O_4NS$, requires 258.0795.

MP: 125.7 – 128.2 °C.

3-Benzyl-3-benzylsulfonyl-dihydro-furan-2-one 245



245

Benzyl bromide (229 µl, 1.92 mmol) was added to a solution of 3-benzylsulfonyl-dihydro-furan-2-one **244** (100 mg, 0.48 mmol), K_2CO_3 (332 mg, 2.40 mmol) and KI (16.0 mg, 0.10 mmol) in DMF (2 ml), and the reaction mixture was heated to 60 °C for 5 h. The reaction mixture was quenched with aqueous saturated $NaHCO_3$ (2 ml), and then H_2O (2 ml). The aqueous layer was extracted with CH_2Cl_2 (3 × 5 ml) before being dried (Na_2SO_4), and then concentrated. The crude mixture was purified by column chromatography (silica, 15 % EtOAc/pet. ether) to give 3-benzyl-3-benzylsulfonyl-dihydro-furan-2-one **245** as a white solid (126 mg, 0.42 mmol, 88 %).

^1H NMR: δ_H (500 MHz, $CDCl_3$) 2.41-2.36 (1H, m, $CH_AH_BCH_2O$), 3.01-2.97 (1H, m, $CH_AH_BCH_2O$), 3.21 (1H, AB system, J = 13.1 Hz, $PhCH_2$), 3.69-3.64 (1H, m, $PhCH_2$), 3.69 (1H, apparent d, J = 13.0 Hz, CH_AH_BO), 4.34 (1H, m, CH_AH_BO), 4.59 (1H, AB system, J = 13.2 Hz, $PhCH_2SO_2$), 4.82 (1H, AB system, J = 13.2 Hz, $PhCH_2SO_2$), 7.23-7.22 (2H, m, 3 × ArH), 7.39-7.35 (6H, m, 6 × ArH), 7.50-7.49 (2H, m, 2 × ArH).

^{13}C NMR: δ_C (75 MHz, $CDCl_3$) 25.2 (CH_2CH_2O), 37.6 (CCH_2Ph), 54.7 ($PhCH_2SO_2$), 66.6 (CH_2O), 72.5 ($CC{=}O$), 125.5 (ArC), 127.0 (ArCH), 127.7 (2 × ArCH), 128.2 (ArCH),

128.6 (ArCH), 128.9 (ArCH), 129.2 (ArCH), 130.1 (2 × ArCH), 131.7 (ArCH), 132.9 (ArC), 173.2 (C=O).

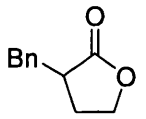
ν_{max} KBr/cm^{-1} 1751 s (C=O), 1381 w, 1311 m, 1018 m, 692 s.

MS (CI): *m/z* 348 (((M+H)+NH_3)$^+$, 97 %), 194, 96.

HRMS: Found 348.1267, $C_{18}H_{22}O_4NS$, requires 348.1264.

MP: 137.7 – 139.1 °C.

3-Benzyldihydro-2(3*H*)-furanone 121 from reduction-protonation of 3-benzyl-3-benzylsulfonyl-dihydro-furan-2-one **245** using 1,2-di[(*S*)-2-hydroxy-2-phenylethoxy] benzene **210**

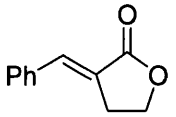


121

According to general procedure A. 3-Benzyl-3-benzylsulfonyl-dihydro-furan-2-one **245** (25.0 mg, 0.08 mmol) was reduced using SmI_2 (2.30 ml, 0.23 mmol, 0.1 M) in the presence of 1,2-di[(*S*)-2-hydroxy-2-phenylethoxy] benzene **210** (80.0 mg, 0.23 mmol) to give 3-benzyldihydro-2(3*H*)-furanone **121** (7.00 mg, 0.04 mmol, 53 %, 13 % ee).

Spectroscopic data corresponded to that reported earlier in this section.

3-[1-Phenyl-meth-(*E*)-ylidene]-dihydro-furan-2-one 246[136]



246

1-Butyrolactone-triphenyl phosphorane **247** (500 mg, 1.44 mmol) was added to a solution of benzaldehyde (0.11 ml, 1.11 mmol) in CH_2Cl_2 (10 ml) and the reaction mixture was stirred at room temperature for 4 h. The reaction mixture was quenched with aqueous

saturated NH_4Cl (5 ml), then H_2O (5 ml) and extracted with CH_2Cl_2 (3 × 10 ml). The organic layers were then dried ($MgSO_4$) and concentrated. The crude mixture was purified by column chromatography (silica, 30 % EtOAc/pet. ether) to give 3-[1-phenyl-meth-(*E*)-ylidene]-dihydro-furan-2-one **246** as a white solid (192 mg, 1.10 mmol, 99 %).

^1H NMR: δ_H (400 MHz, $CDCl_3$) 3.28 (2H, dt, J = 2.9, 7.4 Hz, C*H*$_2$C=CH), 4.49 (2H, t, J = 7.4 Hz, CH_2O), 7.55-7.42 (5H, m, 5 × ArH), 7.60 (1H, t, J = 2.9 Hz, CH_2C=C*H*).

^{13}C NMR: δ_C (100 MHz, $CDCl_3$) 27.4 (*C*H_2C=CH), 65.4 (CH_2O), 109.7 (ArC), 123.5 (2 × ArCH), 128.9 (ArCH), 129.8 (ArCH), 130.0 (ArCH), 134.6 (*C*C=O), 136.6 (C=*C*H), 172.5 (C*C*=O).

ν_{max} ATR/cm^{-1} 3441 w, 2922 w, 1729 s (C=O, α,β-unsaturated lactone), 1173 m, 1003 w, 758 w, 673 m.

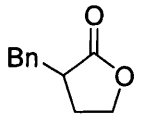
MS (CI): *m/z* 192 $(((M+H)+NH3)^+$, 100 %), 175 (32).

HRMS: Found 192.1020 $C_{11}H_{14}O_2N$ requires 192.1019.

MP: 109.7 – 111.9 °C.

General procedure B for the reduction of α,β-unsaturated lactones:

3-Benzyldihydro-2(3*H*)-furanone 121 from reduction-protonation of 3-[1-phenyl-meth-(*E*)-ylidene]-dihydro-furan-2-one **246** using 1,2-di[(*S*)-2-hydroxy-2-phenylethoxy] benzene **210**



121

A solution of SmI_2 (8.60 ml, 0.86 mmol, 0.1 M) was added to a solution of 1, 2-di[(*S*)-2-hydroxy-2-phenylethoxy] benzene **210** (302 mg, 0.86 mmol) in THF (1 ml) that had been cooled to -20 °C. 3-[1-Phenyl-meth-(*E*)-ylidene]-dihydro-furan-2-one **246** (50.0 mg, 0.29 mmol) in THF (1.5 ml) was then added dropwise via cannula and the reaction mixture was stirred at -20 °C for 18 h. The reaction mixture was allowed to decolourise in air before

being quenched with aqueous saturated NaCl (5 ml). The aqueous layer was then extracted with 30 % EtOAc/pet. ether (3 × 5 ml). The organic layer was then dried (Na_2SO_4), and concentrated. The crude mixture was purified by column chromatography (silica, 15 % EtOAc/pet. ether) to give 3-benzyldihydro-2(3*H*)-furanone **121** as a yellow oil (40.9 mg, 0.24 mmol, 81 %, 13 % ee).
Spectroscopic data corresponded to that reported earlier in this section.

3-Benzyldihydro-2(3*H*)-furanone 121 from reduction-protonation of 3-[1-phenyl-meth-(*E*)-ylidene]-dihydro-furan-2-one **246** using 1,2-di[(*S*)-2-hydroxy-2-phenylethoxy] benzene **211**

According to general procedure B. 3-[1-Phenyl-meth-(*E*)-ylidene]-dihydro-furan-2-one **246** (23.0 mg, 0.13 mmol) was reduced using SmI_2 (3.90 ml, 0.39 mmol, 0.1 M in THF) in the presence of 2,2'-di[(*S*)-2-hydroxy-2-phenylethoxy]-1,1'-biphenyl **211** (168 mg, 0.39 mmol) to give 3-benzyldihydro-2(3*H*)-furanone **121** (11.1 mg, 0.06 mmol, 47 %, 10 % ee).
Spectroscopic data corresponded to that reported earlier in this section.

3-Benzyldihydro-2(3*H*)-furanone 121 from reduction-protonation of 3-[1-phenyl-meth-(*E*)-ylidene]-dihydro-furan-2-one **246** using 1,2-di[(*S*)-2-hydroxy-2-phenylethoxy] benzene **212**

According to general procedure B. 3-[1-Phenyl-meth-(*E*)-ylidene]-dihydro-furan-2-one **246** (25.0 mg, 0.14 mmol) was reduced using SmI_2 (4.30 ml, 0.43 mmol, 0.1 M in THF) in the presence of 1,1'-di-[(*S*)-2-hydroxy-2-phenylethyl]-o-xylenedioxide **212** (163 mg, 0.43 mmol) to give 3-benzyldihydro-2(3*H*)-furanone **121** (14.1 mg, 0.08 mmol, 55 %, 41 % ee).
$[\alpha]_D = -17.8^\circ$
Spectroscopic data corresponded to that reported earlier in this section.

3-Benzyldihydro-2(3*H*)-furanone 121 from reduction-protonation of 3-[1-phenyl-meth-(*E*)-ylidene]-dihydro-furan-2-one **246** using 1,2-di[(*S*)-2-hydroxy-2-phenylethoxy] benzene **213**

According to general procedure B. 3-[1-Phenyl-meth-(*E*)-ylidene]-dihydro-furan-2-one **246** (27.0 mg, 0.16 mmol) was reduced using SmI_2 (4.70 ml, 0.47 mmol, 0.1 M in THF) in the presence of *N,N'*-di[(*S*)-2-hydroxy-2-phenylethyl]-*N,N'*-diisopropylethylene diamine **213** (181 mg, 0.47 mmol) to give 3-benzyldihydro-2(3*H*)-furanone **121** (12 mg, 0.07 mmol, 43 %, 7 % ee).

Spectroscopic data corresponded to that reported earlier in this section.

3-Benzyldihydro-2(3*H*)-furanone 121 from reduction-protonation of 3-[1-phenyl-meth-(*E*)-ylidene]-dihydro-furan-2-one **246** using 1,2-di[(*S*)-2-hydroxy-2-phenylethoxy] benzene **214**

According to general procedure B. 3-[1-Phenyl-meth-(*E*)-ylidene]-dihydro-furan-2-one **246** (19.0 mg, 0.11 mmol) was reduced using SmI_2 (3.30 ml, 0.33 mmol, 0.1 M in THF) in the presence of (+)-(1*S*,2*R*)-bis[*N*-methyl-*N*-(2-hydroxy-2-phenyl-1-methyl)-ethyl]-*o*-xylenediamine **214** (142 mg, 0.33 mmol) to give 3-benzyldihydro-2(3*H*)-furanone **121** (12.0 mg, 0.07 mmol, 62 %, 6 % ee).

Spectroscopic data corresponded to that reported earlier in this section.

3-Benzyldihydro-2(3*H*)-furanone 121 from reduction-protonation of 3-[1-phenyl-meth-(*E*)-ylidene]-dihydro-furan-2-one **246** using 1,2-di[(*S*)-2-hydroxy-2-phenylethoxy] benzene **215**

According to general procedure B. 3-[1-Phenyl-meth-(*E*)-ylidene]-dihydro-furan-2-one **246** (30.0 mg, 0.17 mmol) was reduced using SmI_2 (5.10 ml, 0.51 mmol, 0.1 M in THF) in the presence of (+)-(1*S*,2*R*)-bis[*N*-methyl-*N*-(2-hydroxy-2-phenyl-1-methyl)-ethyl]-*m*-xylenediamine **215** (221 mg, 0.51 mmol) to give 3-benzyldihydro-2(3*H*)-furanone **121** (21.0 mg, 0.18 mmol, 69 %, 4 % ee).

Spectroscopic data corresponded to that reported earlier in this section.

3-Benzyldihydro-2(3*H*)-furanone 121 from reduction-protonation of 3-benzyl-3-(4-benzyloxy-benzenesulfonyl)dihydro-furan-2-one **139** using 2,2'-di[(*S*)-2-hydroxy-2-phenylethoxy]-1,1'-biphenyl **211**

According to general procedure A. 3-Benzyl-3-(4-benzyloxy-benzenesulfonyl)dihydro-furan-2-one **139** (40.0 mg, 0.10 mmol) was reduced using SmI_2 (2.80 ml, 0.28 mmol, 0.1 M in THF) in the presence of 2,2'-di[(*S*)-2-hydroxy-2-phenylethoxy]-1,1'-biphenyl **211** (121 mg, 0.28 mmol) to give 3-benzyldihydro-2(3*H*)-furanone **121** (12.1 mg, 0.07 mmol, 69 %, 1 % ee).
Spectroscopic data corresponded to that reported earlier in this section.

3-Benzyldihydro-2(3*H*)-furanone 121 from reduction-protonation of 3-benzyl-3-(4-benzyloxy-benzenesulfonyl)dihydro-furan-2-one **139** using 1,1'-di [(*S*)-2-hydroxy-2-phenylethyl]-*o*-xylenedioxide **212**

According to general procedure A. 3-Benzyl-3-(4-benzyloxy-benzenesulfonyl)dihydro-furan-2-one **139** (32.0 mg, 0.08 mmol) was reduced using SmI_2 (2.30 ml, 0.23 mmol, 0.1 M in THF) in the presence of 1,1'-di [(*S*)-2-hydroxy-2-phenylethyl]-*o*-xylenedioxide **212** (87.0 mg, 0.23 mmol) to give 3-benzyldihydro-2(3*H*)-furanone **121** (10.2 mg, 0.07 mmol, 71 %, 16 % ee).
Spectroscopic data corresponded to that reported earlier in this section.

3-Benzyldihydro-2(3*H*)-furanone 121 from reduction-protonation of 3-benzyl-3-(4-benzyloxy-benzenesulfonyl)dihydro-furan-2-one **139** using (*S*)-(+)-pantolactone **248**

According to general procedure A. 3-Benzyl-3-(4-benzyloxy-benzenesulfonyl)dihydro-furan-2-one **139** (50.0 mg, 0.12 mmol) was reduced using SmI_2 (3.60 ml, 0.36 mmol, 0.1 M in THF) in the presence of (*S*)-(+)-pantolactone **248** (46.0 mg, 0.36 mmol) to give 3-benzyldihydro-2(3*H*)-furanone **121** (18.0 mg, 0.10 mmol, 86 %, 0 % ee).
Spectroscopic data corresponded to that reported earlier in this section.

3-Benzyldihydro-2(3*H*)-furanone 121 from reduction-protonation of 3-benzyl-3-(4-benzyloxy-benzenesulfonyl)dihydro-furan-2-one **139** using camphorsultam **249**

According to general procedure A. 3-Benzyl-3-(4-benzyloxy-benzenesulfonyl)dihydro-furan-2-one **139** (50.0 mg, 0.12 mmol) was reduced using SmI_2 (3.60 ml, 0.36 mmol, 0.1 M in THF) in the presence of camphorsultam **249** (77.0 mg, 0.36 mmol) to give 3-benzyldihydro-2(3*H*)-furanone **121** (16.0 mg, 0.09 mmol, 77 %, 0 % ee).
Spectroscopic data corresponded to that reported earlier in this section.

3-Benzyldihydro-2(3*H*)-furanone 121 from reduction-protonation of 3-benzyl-3-(4-benzyloxy-benzenesulfonyl)dihydro-furan-2-one **139** using *N,N'*-di[(*S*)-2-hydroxy-2-phenylethyl]-*N,N'*-diisopropylethylenediamine **213**

According to general procedure A. 3-Benzyl-3-(4-benzyloxy-benzenesulfonyl)dihydro-furan-2-one **139** (23.0 mg, 0.05 mmol) was reduced using SmI_2 (1.60 ml, 0.16 mmol, 0.1 M in THF) in the presence of *N,N'*-di[(*S*)-2-hydroxy-2-phenylethyl]-*N,N'*-diisopropylethylenediamine **213** (63.0 mg, 0.16 mmol) to give (+)-3-benzyldihydro-2(3*H*)-furanone **121** (7.00 mg, 0.04 mmol, 74 %, 20 % ee). $[\alpha]_D = +10^\circ$.
Spectroscopic data corresponded to that reported earlier in this section.

3-Benzyldihydro-2(3*H*)-furanone 121 from reduction-protonation of 3-benzyl-3-(4-benzyloxy-benzenesulfonyl)dihydro-furan-2-one **139** using (+)-(1*S*,2*R*)-bis[*N*-methyl-*N*-(2-hydroxy-2-phenyl-1-methyl)-ethyl]-*o*-xylenediamine **214**

According to general procedure A. 3-Benzyl-3-(4-benzyloxy-benzenesulfonyl)dihydro-furan-2-one **139** (25.0 mg, 0.06 mmol) was reduced using SmI_2 (1.80 ml, 0.18 mmol, 0.1 M in THF) in the presence of (+)-(1*S*,2*R*)-bis[*N*-methyl-*N*-(2-hydroxy-2-phenyl-1-methyl)-ethyl]-*o*-xylenediamine **214** (77.0 mg, 0.18 mmol) to give (+)-3-benzyldihydro-2(3*H*)-furanone **121** (7 mg, 0.04 mmol, 71 %, 10 % ee).
Spectroscopic data corresponded to that reported earlier in this section.

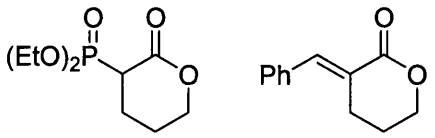
3-Benzyldihydro-2(3*H*)-furanone 121 from reduction-protonation of 3-benzyl-3-(4-benzyloxy-benzenesulfonyl)dihydro-furan-2-one **139** using (+)-(1*S*,2*R*)-bis[*N*-methyl-*N*-(2-hydroxy-2-phenyl-1-methyl)-ethyl]-*m*-xylenediamine **215**

According to general procedure A. 3-Benzyl-3-(4-benzyloxy-benzenesulfonyl)dihydro-furan-2-one **139** (26.0 mg, 0.06 mmol) was reduced using SmI_2 (1.90 ml, 0.19 mmol, 0.1 M in THF) in the presence of (+)-(1*S*,2*R*)-bis[*N*-methyl-*N*-(2-hydroxy-2-phenyl-1-methyl)-ethyl]-*m*-xylenediamine **215** (80.0 mg, 0.19 mmol) to give (+)-3-benzyldihydro-2(3*H*)-furanone **121** (7.00 mg, 0.04 mmol, 67 %, 19 % ee).
Spectroscopic data corresponded to that reported earlier in this section.

3-Benzyldihydro-2(3*H*)-furanone 121 from reduction-protonation of 3-benzyl-3-(4-benzyloxy-benzenesulfonyl)dihydro-furan-2-one **139** using (*R*)-(+)-BINOL **250**

According to general procedure A. 3-Benzyl-3-(4-benzyloxy-benzenesulfonyl)dihydro-furan-2-one **139** (50.0 mg, 0.12 mmol) was reduced using SmI_2 (3.60 ml, 0.36 mmol, 0.1 M in THF) in the presence of (*R*)-(+)-BINOL **250** (102 mg, 0.36 mmol) to give 3-benzyldihydro-2(3*H*)-furanone **121** (6.00 mg, 0.04 mmol, 29 %, 6 % ee).
Spectroscopic data corresponded to that reported earlier in this section.

Diethyl 2-oxo-tetrahydro-2*H*-pyran-3-yl-phosphonate 252 and **3-[1-phenyl-meth-(*E*)-ylidine]-tetrahydro-pyran-2-one 251**



252 **251**

To a solution of diisopropylamine (1.55 ml, 11.0 mmol), in THF (30 ml) that had been cooled to -50 °C was added ^{n}BuLi (4.40 ml, 11.0 mmol, 2.5 M in hexane). The reaction mixture was then stirred for 30 min at -50 °C. A solution of δ-valerolactone (1.0 g, 9.99

mmol) in THF (5 ml) was then added dropwise by cannula and the reaction was stirred for a further 30 min at -50 °C. A solution of DMPU (1.33 ml, 11.0 mmol) and diethylchlorophosphate (1.59 ml, 11.0 mmol) in THF (5 ml) was then added dropwise by cannula and the reaction was allowed to warm to room temperature and stirred for 1 h. The reaction mixture was then cooled to -50 °C and a solution of LDA (2.2 eq; diisopropylamine (3.10 ml, 21.98 mmol), ^{n}BuLi (8.80 ml, 22.0 mmol), THF (20 ml)) was added and the reaction mixture was stirred overnight at -50 °C. The reaction mixture was quenched with AcOH (10 ml, 1M in Et_2O) and the crude product was purified by plug column (100 % Et_2O) and concentrated to give diethyl 2-oxo-tetrahydro-2*H*-pyran-3-yl-phosphonate **252** as a yellow oil which was used without further purification.

^{1}H NMR: δ_H (500 MHz, $CDCl_3$) 1.33 (6H, m, 2 x OCH_2CH_3), 1.86-1.77 (1H, m, $CH_AH_BCH_2O$), 2.08-2.00 (1H, m, $CH_AH_BCH_2O$), 2.30-2.14 (2H, m, CH_2CH), 3.13 (1H, dt, J = 27.3, 7.3Hz, CHP), 4.27-4.14 (4H, m, 2 × CH_2CH_3), 4.38-4.32 (1H, m, CH_AH_BO), 4.47-4.43 (1H, m, CH_AH_BO).

K_2CO_3 (357 mg, 2.59 mmol) and 18-crown-6 (621 mg, 2.35 mmol) were added to a solution of diethyl 2-oxo-tetrahydro-2*H*-pyran-3-yl-phosphonate **252** (555 mg, 2.35 mmol) in THF (10 ml) and the reaction mixture was stirred at room temperature for 2 h. Benzaldehyde (287 µl, 2.82 mmol) was then added dropwise and the reaction mixture was stirred at room temperature for 17 h. The reaction mixture was quenched with aqueous saturated NH_4Cl (5 ml), then H_2O (5 ml) and the aqueous layer was extracted with CH_2Cl_2 (3 × 5 ml). The organic layer was then dried (Na_2SO_4) and concentrated. The crude mixture was purified by column chromatography (silica, 20 % EtOAc/pet. ether) to give 3-[1-phenyl-meth-(*E*)-ylidine]-tetrahydro-pyran-2-one **251** as a clear oil (259 mg, 5.79 mmol, 58 % over 2 steps).

^{1}H NMR: δ_H (500 MHz, $CDCl_3$) 2.01 (2H, m, CH_2CH_2O), 2.90 (2H, dt, J = 2.4, 6.6 Hz, CH=CCH_2), 4.41 (2H, t, J = 5.3 Hz, CH_2O), 7.60-7.37 (5H, m, 5 × ArH), 7.94-7.93 (1H, t, J = 2.4 Hz, CH=C).

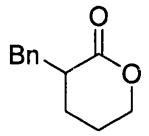
^{13}C NMR: δ_C (75 MHz, $CDCl_3$) 23.0 (CH=CCH_2), 26.3 (CH_2CH_2O), 68.7 (CH_2O), 125.7 (*C*C=O), 128.5 (2 × ArCH), 129.1 (2 × ArCH), 130.2 (ArCH), 134.9 (ArC), 141.6 (C=*C*H), 166.9 (C=O).

ν_{max} KBr/cm^{-1} 2968 br, 1705 s (C=O, α,β-unsaturated lactone), 1612 m, 1257 m, 1168 m, 771 w, 694 w.

MS (CI): *m/z* 189 ((M+H)$^+$, 100 %).

HRMS: Found 189.0911 $C_{12}H_{13}O_2$ requires 189.0910.

3-Benzyl-tetrahydropyran-2-one 257 from reduction-protonation of 3-[1-phenyl-meth-(*E*)-ylidine]-tetrahydro-pyran-2-one **251** using 1, 2-di[(*S*)-2-hydroxy-2-phenylethoxy] benzene **210**



257

According to general procedure B. 3-[1-Phenyl-meth-(*E*)-ylidine]-tetrahydro-pyran-2-one **251** (25.0 mg, 0.13 mmol) was reduced using SmI_2 (3.90 ml, 0.39 mmol, 0.1 M in THF) in the presence of 1, 2-di[(*S*)-2-hydroxy-2-phenylethoxy] benzene **210** (164 mg, 0.39 mmol) to give 3-benzyl-tetrahydropyran-2-one **257** (9.61 mg, 0.06 mmol, 42 %, 7 % ee).

^{1}H NMR: δ_H (500 MHz, $CDCl_3$) 1.58-1.30 (1H, m, CH_AH$_B$CHC=O), 1.83-1.82 (1H, m, CH$_A$$H_B$CHC=O), 1.92-1.88 (2H, m, CH_2CH$_2$O), 2.75-2.72 (2H, m, PhCH$_2$), 3.31 (1H, d, J = 9.6 Hz, CH), 4.32-4.27 (2H, m, CH$_2$O), 7.33-7.20 (5H, m, 5 × ArH).

^{13}C NMR: δ_C (75 MHz, $CDCl_3$) 21.9 (*C*H$_2$CHC=O), 24.0 (*C*H$_2$CH$_2$O), 37.2 (CH$_2$Ph), 41.5 (CH), 68.5 (CH$_2$O), 126.5 (2 × ArCH), 128.5 (2 × ArCH), 129.2 (ArCH), 138.9 (ArC), 174.0 (C=O).

ν_{max} ATR/ cm^{-1} 2920 br, 1737 s (C=O), 1259 w, 1151 m, 1054 w.

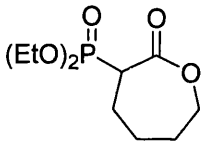
MS (CI): *m/z* 208 (((M+H)+NH$_3$)$^+$, 100 %), 190, 91 (Bn$^+$, 100 %).

HRMS: Found 208.1336, $C_{12}H_{18}O_2N$, requires 208.1332.

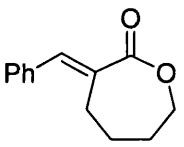
3-Benzyl-tetrahydropyran-2-one 257 from reduction-protonation of 3-[1-phenyl-meth-(*E*)-ylidine]-tetrahydro-pyran-2-one **251** using 2,2'-di[(*S*)-2-hydroxy-2-phenylethoxy]-1,1'-biphenyl **211**

According to general procedure B. 3-[1-Phenyl-meth-(*E*)-ylidine]-tetrahydro-pyran-2-one **251** (25.0 mg, 0.13 mmol) was reduced using SmI_2 (3.90 ml, 0.39 mmol, 0.1 M in THF) in the presence of 2,2'-di[(*S*)-2-hydroxy-2-phenylethoxy]-1,1'-biphenyl **211** (164 mg, 0.39 mmol) to give 3-benzyl-tetrahydropyran-2-one **257** (8.69 mg, 0.05 mmol, 38 %, 6 % ee). Spectroscopic data corresponded to that reported earlier in this section.

Diethyl 2-oxo-oxepan-3-yl-phosphonate 260 and **3-[1-phenyl-meth-(*E*)-ylidine]-oxepan-2-one 258**



260



258

To a solution of diisopropylamine (1.36 ml, 9.64 mmol), in THF (30 ml) that had been cooled to -50 °C was added ^{n}BuLi (4.10 ml, 9.64 mmol, 2.5 M in hexane). The reaction mixture was then stirred for 30 min at -50 °C. A solution of ε-caprolactone **259** (1.00 g, 8.76 mmol) in THF (5 ml) was then added dropwise by cannula and the reaction was stirred for a further 30 min at -50 °C. A solution of DMPU (1.17 ml, 9.64 mmol) and diethylchlorophosphate (1.39 ml, 9.64 mmol) in THF (5 ml) was then added dropwise by cannula and the reaction was allowed to warm to room temperature and stirred for 1 h. The reaction mixture was then cooled to -50 °C and a solution of LDA (2.2 eq in THF) was added and the reaction mixture was stirred overnight at -50 °C. The reaction mixture was quenched with aqueous saturated NH_4Cl (10 ml) then H_2O (10 ml). The organic layers were extracted with CH_2Cl_2 (3 × 15 ml), dried (Na_2SO_4), and concentrated to give diethyl 2-oxo-oxepan-3-yl-phosphonate **260** as an orange oil which was used without further purification.

^{1}H NMR: δ_H (500 MHz, $CDCl_3$) 1.20-1.11 (1H, m, CH_AH$_B$CH), 1.29 (3H, t, J = 4.3 Hz, CH_3), 1.32 (3H, t, J = 7.1 Hz, CH_3), 1.67-1.60 (1H, m, CH$_A$$H_B$CH), 1.80-1.72 (2H, m, C$H_2CH_2CH_2$O), 2.09-2.02 (1H, m, C$H_AH_BCH_2$O), 2.32-2.21 (1H, m, CH$_A$$H_BCH_2$O), 3.20-

3.14 (1H, m, CH), 4.11-4.05 (1H, m, CH_AH_BO), 4.26-4.15 (4H, m, 2 × CH_2CH_3), 4.45-4.40 (1H, m, CH_AH_BO).

K_2CO_3 (1.59 g, 11.5 mmol) and 18-crown-6 (2.77 g, 10.5 mmol) were added to a solution of diethyl 2-oxo-oxepan-3-yl-phosphonate **260** (2.62 g, 10.5 mmol) in THF (10 ml) and the reaction mixture was stirred at room temperature for 2 h. Benzaldehyde (1.28 ml, 12.6 mmol) was then added dropwise and the reaction mixture was stirred at room temperature for 17 h. The reaction mixture was quenched with aqueous saturated NH_4Cl (5 ml) and then extracted with CH_2Cl_2 (3 × 10 ml) before being dried (Na_2SO_4), and then concentrated. The crude mixture was purified by column chromatography (silica, 20 % EtOAc/pet. ether) to give 3-[1-phenyl-meth-(*E*)-ylidine]-oxepan-2-one **258** as a white solid (295 mg, 1.49 mmol, 17 % over 2 steps).

^{1}H NMR: δ_H (500 MHz, $CDCl_3$) 1.98-1.89 (4H, m, $CH_2CH_2CH_2O$), 2.64-2.62 (2H, m, $CH_2CC=O$), 4.31-4.29 (2H, m, CH_2O), 7.37-7.32 (1H, m, CH=C), 7.41-7.38 (5H, m, 5 × ArH).

^{13}C NMR: δ_C (75 MHz, $CDCl_3$) 25.2 ($CH_2CH_2CH_2O$), 27.1 ($CH_2CC=O$), 28.2 ($CH_2CH_2CH_2O$), 68.3 (CH_2O), 128.4 (2 × ArCH), 128.5 (2 × ArCH), 129.2 (ArCH), 134.8 (ArC), 135.0 ($CC=O$), 137.2 ($CH=C$), 174.0 (C=O).

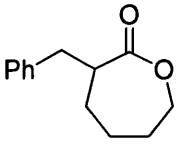
ν_{max} KBr/cm^{-1} 2924 m, 1697 s (C=O, α,β-unsaturated lactone), 1151 m, 1033 m, 773 m.

MS (CI): *m/z* 220 ($((M+H)+NH_3)^+$, 100 %), 203 ($(M+H)^+$, 53 %).

HRMS: Found 220.1332, $C_{13}H_{18}O_2N$, requires 220.1332.

MP: 79.8 – 81.2 °C.

3-Benzyloxepan-2-one 261



261

A solution of SmI_2 (3.71 ml, 0.37 mmol, 0.1 M in THF), was added to a solution of 3-[1-phenyl-meth-(*E*)-ylidine]-oxepan-2-one **258** (25 mg, 0.12 mmol) in THF (0.25 ml) and

MeOH (1 ml) at room temperature, and the mixture was stirred. The reaction mixture was quenched first with aqueous saturated NH_4Cl (2 ml) followed by H_2O (2 ml) and then extracted with Et_2O (3 × 5 ml). The organic layer was then dried ($MgSO_4$), and concentrated. The crude mixture was purified by column chromatography (silica, 20 % EtOAc/pet. ether) to give 3-benzyloxepan-2-one **261** as a clear oil (23.0 mg, 0.11 mmol, 91 %).

^{1}H NMR: δ_H (500 MHz, $CDCl_3$) 1.33-1.28 (2H, m, CH_2CH$_2$CH$_2$O), 1.49-1.44 (2H, m, CH_2CH$_2$O), 1.62-1.59 (2H, m, CH_2CH$_2$CH$_2$CH$_2$O), 2.65-2.60 (1H, m, CHC=O), 2.67 (1H, dd, J = 6.8, 13.5 Hz, CH_AH$_B$Ph), 2.87 (1H, dd, J = 8.2, 13.5 Hz, CH$_A$$H_B$Ph), 3.55-3.53 (2H, m, CH$_2$O), 7.22-7.07 (5H, m, 5 × ArH).

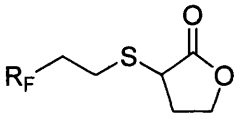
^{13}C NMR: δ_C (75 MHz, $CDCl_3$) 23.5 (*C*H$_2$CH$_2$CH$_2$O), 31.7 (*C*H$_2$CH$_2$CH$_2$CH$_2$O), 32.5 (*C*H$_2$CH$_2$O), 38.5 (CH$_2$Ph), 47.6 (CH), 62.6 (*C*H$_2$O), 126.3 (ArCH), 128.4 (2 × ArCH), 128.8 (2 × ArCH), 139.3 (ArC), 176.1 (C=O).

ν_{max} ATR/ cm^{-1} 2938 s, 1733 m (C=O), 1163 s, 700 m.

MS (EI): *m/z* 222 (((M+H)+NH$_3$)$^+$, 4 %), 91 (Bn$^+$, 100 %).

HRMS: Found 222.1479, $C_{13}H_{20}O_2N$, requires 222.1489.

3-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-Heptadecafluorodecylsulfanyl)dihydrofuran-2(3H)-one 263



263

α-Bromo-γ-butyrolactone (480 μl, 5.21 mmol) was added to a solution of 3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecane-1-thiol **196** (500 mg, 1.04 mmol and NEt_3 (732 μl, 5.21 mmol) in DMF (10 ml) and the reaction mixture was stirred at room temperature for 17 h. The reaction mixture was quenched with aqueous saturated NaCl (5 ml) and then H_2O (5 ml), before being extracted with 10 % EtOAc/pet. ether (3 × 10 ml), dried (Na_2SO_4) and then concentrated. The crude product was purified by fluorous

chromatography to give 3-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecylsulfanyl)dihydrofuran-2(3H)-one **263** as a white solid (556 mg, 0.99 mmol, 95 %).

^{1}H NMR: δ_H (500 MHz, $CDCl_3$) 2.10 (1H, apparent dd, J = 7.5, 13.7 Hz, CH_AH$_B$CH$_2$O), 2.53-2.40 (2H, m, CH_2CF_2), 2.68 (1H, dd, J = 8.4, 13.7 Hz, CH$_A$$H_BCH_2$O), 2.91-2.87 (1H, m, C$H_AH_B$S), 3.14-3.04 (1H, m, C$H_AH_B$S), 3.55 (1H, dd, J = 4.9, 8.4 Hz, CH), 4.34-4.31 (1H, m, CH_AH$_B$O), 4.33-4.19 (1H, dt, J = 7.5, 9.0 Hz, CH$_A$$H_B$O).

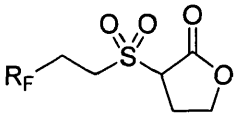
^{13}C NMR: δ_C (75 MHz, $CDCl_3$) 22.3 (CH_2S), 29.6 (CH$_2$CH$_2$O), 31.7 (CH$_2$CF$_2$), 39.3 (CH), 66.8 (CH_2O), 174.9 (C=O).

ν_{max} ATR/ cm^{-1} 1762 m (C=O), 1332 w, 1144 s, 955 m.

MS (CI): *m/z* 582 (M+NH_3)$^+$, 22 %), 121, 104.

HRMS: Found 582.0389, $C_{14}H_{13}O_2NF_{17}S$, requires 582.0390.

3-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-Heptadecafluorodecylsulfonyl)dihydrofuran-2(3H)-one 264



264

*m*CPBA (431 mg, 1.92 mmol) was added to a solution of 3-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecylsulfanyl)dihydrofuran-2(3H)-one **263** (543 mg, 0.96 mmol) in CH_2Cl_2 (10 ml) and the reaction mixture was stirred at room temperature for 2 h. The reaction mixture was quenched with aqueous saturated NaCl (5 ml) and then H_2O (5 ml), before being extracted with CH_2Cl_2 (3 × 10 ml). The organic layers were then dried (Na_2SO_4) and then concentrated. The crude product was then purified using fluorous silica (eluting with 80 % MeCN/H_2O then MeCN) to give 3-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecylsulfonyl)dihydrofuran-2(3H)-one **264** as a white solid (400 mg, 0.67 mmol, 70 %).

^{1}H NMR: δ_H (500 MHz, $CDCl_3$) 2.80-2.73 (3H, m, CH_2CF$_2$, CH_AH$_B$CH$_2$O), 3.05-3.02 (1H, m, CH$_A$$H_BCH_2$O), 3.58-3.66 (1H, m, C$H_AH_B$S), 3.79-3.86 (1H, m, CH$_A$$H_B$S), 4.07 (1H, dd,

J = 5.3, 10.2 Hz, CH), 4.51 (1H, dt, J = 4.8, 8.5 Hz, CH_AH$_B$O), 4.61 (1H, dd, J = 8.5, 9.8 Hz, CH$_A$$H_B$O).

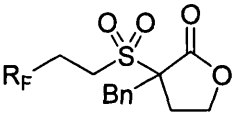
^{13}C NMR: δ_C (75 MHz, $CDCl_3$) 29.6 (CH_2CH_2O), 31.7 (CH_2CF_2), 39.8 (CH_2S), 40.5 (CH), 69.2 (CH_2O), 175.0 (C=O).

ν_{max} ATR/ cm^{-1} 1760 s (C=O), 1298 w, 1200 m, 1139 s, 958 m.

MS (CI): *m/z* 614 (M^+, 56 %), 295, 185, 102.

HRMS: Found 614.0279, $C_{14}H_{13}O_4F_{17}S$, requires 614.0288.

3-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-Heptadecafluorodecylsulfonyl)-3-benzyl-dihydrofuran-2(3H)-one 262



262

Benzyl bromide (297 µl, 2.50 mmol) was added to a solution of 3-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecylsulfonyl)dihydrofuran-2(3H)-one **264** (372 mg, 0.62 mmol), K_2CO_3 (431 mg, 3.12 mmol) and KI (21 mg, 0.13 mmol) in DMF (10 ml), and the reaction mixture was heated to 60 °C for 18 h. The reaction mixture was quenched with aqueous saturated NH_4Cl (5 ml), and then extracted with CH_2Cl_2 (3 × 5 ml) before being dried (Na_2SO_4), and then concentrated. The crude product was then purified using fluorous silica (eluting with 80 % MeCN/H_2O then MeCN) to give 3-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecylsulfonyl)-3-benzyl-dihydrofuran-2(3H)-one **262** as a white solid (362 mg, 0.53 mmol, 85 %).

^{1}H NMR: δ_H (500 MHz, $CDCl_3$) 2.45-2.40 (1H, m, CH_AH$_B$CH$_2$O), 2.84-2.68 (2H, m, CH_2CF_2), 3.03-3.01 (1H, m, CH$_A$$H_BCH_2$O), 3.25 (1H, d, J = 13.1 Hz, CH_AH$_B$Ph), 3.55-3.46 (1H, m, CH_AH$_B$S), 3.64-3.60 (1H, m, CH_AH$_B$O), 3.66 (1H, d, J = 13.1 Hz, CH$_A$$H_B$Ph), 3.98-3.94 (1H, m, CH$_A$$H_B$S), 4.32 (1H, dt, J = 1.9, 8.8 Hz, CH$_A$$H_B$O), 7.23-7.22 (2H, m, 2 × ArH), 7.39-7.34 (3H, m, 3 × ArH).

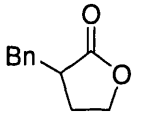
^{13}C NMR: δ_C (75 MHz, $CDCl_3$) 23.7 (CH_2CF_2), 24.7 (CH_2CH_2O), 37.6 (CH_2Ph) 40.6 (CH_2S), (CH_2O), 72.3 ($CC{=}O$), 128.5 (ArCH), 129.4 (2 × ArCH), 130.1 (2 × ArCH), 132.2 (ArC), 172.4 (C=O).

ν_{max} ATR/ cm^{-1} 1751 s (C=O), 1299 w, 1203 s, 1134 s, 1027 m, 968 m.

MS (EI): *m/z* 686 (M^+, 4 %), 193, 174, 91 (Bn^+, 100 %).

HRMS: Found 686.0416, $C_{21}H_{15}O_4F_{17}S$, requires 686.0414.

3-Benzyldihydro-2(3*H*)-furanone 121 from reduction-protonation of 3-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecylsulfonyl)-3-benzyl-dihydrofuran-2(3H)-one **262** using 1,2-di[(*S*)-2-hydroxy-2-phenylethoxy] benzene **210**



121

According to general procedure A. 3-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-Heptadecafluorodecylsulfonyl)-3-benzyl-dihydrofuran-2(3H)-one **262** (100 mg, 0.15 mmol) was reduced using SmI_2 (4.40 ml, 0.44 mmol, 0.1 M in THF) in the presence of 1,2-di[(*S*)-2-hydroxy-2-phenylethoxy] benzene **210** (153 mg, 0.44 mmol) to give 3-benzyldihydro-2(3*H*)-furanone **121** (20 mg, 0.12 mmol, 78 %, 14 % ee).

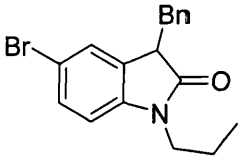
Spectroscopic data corresponded to that reported earlier in this section.

3-Benzyldihydro-2(3*H*)-furanone 121 from reduction-protonation of 3-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecylsulfonyl)-3-benzyl-dihydrofuran-2(3H)-one **262** using 1,1'-di [(*S*)-2-hydroxy-2-phenylethyl]-*o*-xylenedioxide **212**

According to general procedure A. 3-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-Heptadecafluorodecylsulfonyl)-3-benzyl-dihydrofuran-2(3H)-one **262** (79.0 mg, 0.12 mmol) was reduced using SmI_2 (3.50 ml, 0.35 mmol, 0.1 M in THF) in the presence of

1,1'-di [(*S*)-2-hydroxy-2-phenylethyl]-*o*-xylenedioxide **212** (131 mg, 0.35 mmol) to give 3-benzyldihydro-2(3*H*)-furanone **121** (17 mg, 0.01 mmol, 82 %, 18 % ee).
Spectroscopic data corresponded to that reported earlier in this section.

3- Benzyl-5-bromo-1-propyl-1,3-dihydro-indol-2-one 266[137]



266

According to general procedure A. 3-Benzyl-5-bromo-3-(3,3,4,4,5,5,6,6,7,7,8,8, 9,9,10,10,10-heptadecafluorodecylsulfonyl)-1-propyl-1,3-dihydro-indol-2-one **265** (60.0 mg, 0.07 mmol) was reduced using SmI_2 (2.20 ml, 0.22 mmol, 0.1 M in THF) in the presence of 1,1'-di[(*S*)-2-hydroxy-2-phenylethyl]-*o*-xylenedioxide **212** (83.0 mg, 0.22 mmol) to give 3- benzyl-5-bromo-1-propyl-1,3-dihydro-indol-2-one **266** (24.0 mg, 0.07 mmol, 95 %, 6 % ee).

^{1}H NMR: δ_H (500 MHz, $CDCl_3$) 0.75 (3H, t, J = 7.4 Hz, CH_3), 1.41-1.53 (2H, m, CH_2CH_3), 2.90 (1H, dd, J = 13.7, 8.5 Hz, $PhCH_AH_B$), 3.33-3.43 (2H, m, $PhCH_AH_B$, CH_AH_BN), 3.54-3.64 (1H, m, CH_AH_BN, CH), 6.53 (1H, d, J = 8.3 Hz, ArH), 6.92 (1H, s, ArH), 7.03-7.07 (2H, m, 2 × ArH), 7.10-7.19 (3H, m, 3 × ArH), 7.24 (1H, d, J = 8.3 Hz, ArH).

HPLC analysis for **266** was obtained using an AD column using a hexane : IPA mixture (90 : 10) with a flow rate of 0.5 $mlmin^{-1}$ at 230 nm. Retention times = 12.53 min, 12.56 min.

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