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Novel Thermally Cleavable Safety-Catch Linkers for Combinatorial Chemistry

by

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ABSTRACT

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Two novel thermally cleavable safety-catch linkers were developed for solid phase organic synthesis, based on the sulfoxide/selenoxide pericyclic elimination reaction. The linkers were evaluated using various substrates; both peptides and small organic molecules.

Activation of the safety-catch was achieved *via* selective oxidation of the sulfide/selenide to the corresponding sulfoxide/selenoxide. A novel oxidation method for the solid phase oxidation of sulfides to sulfoxides was developed whereby hydrogen peroxide was used in hexafluoroisopropanol (HFIP) thus preventing undesirable over-oxidation to the sulfone.

Cleavage of the sulfoxide linker was only possible using high temperatures (100°C) and an activated substrate. In contrast, the selenoxide elimination occurred at room temperature, hence allowing milder cleavage conditions. The selenoxide linker was synthesised with a number of substrates, both peptides and small organic molecules. Cleavage was successful at room temperature, although further optimisation is required.

Table of Contents

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Abbreviations

AcOH	Acetic acid
AIBN	Azobisisobutyronitrile
aq	Aqueous
BCG	Bromocresol green (TLC stain)
Boc	*Tert*-butoxycarbonyl
^{t}Bu	*Tert*-butyl
^{13}C	Carbon-13
$CDCl_3$	Chloroform-∂
CD_3OD	Methanol-∂_3
CI	Chemical ionisation
conc	Concentration
δ	Chemical shift (ppm)
d	Doublet
DBU	1,8-Diazabicyclo[5.4.0]undecene-7
DCM	Dichloromethane
DIC	*N,N'*-Diisopropylcarbodiimide
DIPEA	Diisopropylethylamine
DMAP	4-Dimethylaminopyridine
DMF	*N,N'*-Dimethylformamide
DMSO	Dimethylsulfoxide
D_2O	Deuterium oxide
EI	Electron impact
eq	Equivalents
ES	Electrospray
Et_2O	Diethyl ether
EtOAc	Ethyl acetate
EtOH	Ethanol
FAB	Fast atom bombardment

Fmoc	9-Fluorenylmethoxycarbonyl
FPLC	Fast protein liquid chromatography
FT-IR	Fourier transform infra-red
^1H	Proton
h	Hour
HF	Hydrogen fluoride
HFIP	1,1,1,3,3,3- Hexafluoroisopropanol
HOBt	1-Hydroxybenzotriazole
HRMS	High resolution mass spectroscopy
Hz	hertz
IR	Infra-red
J	Coupling constant (Hz)
LDA	Lithium diisopropylamide
m-CPBA	*meta*-chloroperbenzoic acid
MAS	Magic angle spinning (NMR)
MeCN	Acetonitrile
MeOH	Methanol
mg	Milligram
$MgSO_4$	Magnesium sulfate (anhydrous)
min	Minute
m.p.	Melting point
MS	Mass spectrometry
3-NBA	3-Nitrobenzyl alcohol (FAB matrix)
NBS	*N*-Bromosuccinimide
NMF	*N*-Methylformamide
NMR	Nuclear magnetic resonance
PEG	Polyethylene glycol
q	Quartet
quint	Quintet
R_f	Retention factor
RP HPLC	Reverse phase high performance liquid chromatography

RT	Room temperature
s	Singlet
sat.	Saturated
SPOS	Solid phase organic synthesis
SPPS	Solid phase peptide synthesis
t	Triplet
^{t}BuOH	*Tert*-butanol
TEBA	Benzyltriethylammonium chloride
tert	Tertiary
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TIS	Triisopropylsilane
TLC	Thin layer chromatography
UV	Ultra violet
MW	Molecular weight

The standard three letter codes are used for amino acids.

To Mum and Dad with all my love

Chapter 1: Introduction

1.1 Combinatorial Chemistry

Combinatorial chemistry[1] has revolutionised the drug discovery process since it was first introduced to the pharmaceutical industry in the early 1990s. Whereas traditionally drug design was used to optimise target compounds, combinatorial chemistry has been implemented as an alternative method for lead identification and lead optimisation. The main driving force behind this new technology was the development of high throughput screening (HTS) which permits enormous numbers of compounds to be evaluated in biochemical assays against molecules of therapeutic relevance.

Combinatorial chemistry is a technique whereby large numbers of structurally distinct molecules may be synthesised in a time and resource efficient manner, thus satisfying the demand from the high throughput screens. The main feature of combinatorial chemistry is that each synthesis is designed such that a range of analogues can be produced using similar reaction conditions. Thus, the technique is amenable to automation and in this way, one chemist can produce hundreds or thousands of novel compounds in the time usually taken to prepare only a few using conventional methods.

Combinatorial chemistry may be used to prepare many compounds simultaneously, either as mixtures, or more commonly as individual compounds *via* parallel synthesis routes. The syntheses may be carried out using solution or solid phase chemistry. Solid phase techniques will be the focus of this thesis.

1.2 Solid Phase Chemistry

The solid phase is an insoluble polymeric support or resin onto which the molecule of interest is covalently attached. Merrifield[2] pioneered the technique of solid phase chemistry in the 1960s for the synthesis of peptides. Since then, solid supported chemistry has been applied to the synthesis of other oligomers such as nucleotides[3] and oligosaccharides[4] and, more recently, for the synthesis of small organic molecules (solid phase organic synthesis, SPOS). The reason for this widespread implementation of solid phase chemistry is the number of advantages it offers over conventional solution phase synthesis.

The product is attached to a polymer support and thus may be separated from unreacted reagents and side-products by filtration. Therefore, high concentrations of reagents may be used to drive reactions to completion because the purification of intermediates can be effected simply by washing extensively. The repetitive nature of the washing steps makes the procedure particularly amenable to automation, thus shortening synthesis time. In addition, toxic or malodorous chemicals are made less noxious by covalent attachment to the polymeric support.

However, there are certain disadvantages associated with the use of solid phase chemistry, namely the lack of analytical techniques available to monitor reactions and the time required to optimise a chemical synthesis. Also, the use of a linker increases the length of the synthesis by two steps (addition and cleavage), much as a protecting group would, and so it is often not practical to use solid phase chemistry for very short reaction sequences.

1.3 Monitoring Reactions on the Solid Phase

A major hindrance to the development of solid phase chemistry has been the lack of available analytical techniques to monitor reactions and characterise intermediates. The traditional tools of the solution chemist, TLC and NMR, can no longer be employed. Thus, when a reaction is low-yielding, the optimisation process is no longer a trivial one. Over the last decade, however, there has been much research into overcoming these problems by the adaptation of spectroscopic techniques for the analysis of resin-bound compounds.

1.3.1 Cleavage and analysis

Until quite recently, cleavage and analysis was the only effective way to identify intermediates and hence was the favoured method. The linker was cleaved to release the resin-bound product into solution and analysis was performed using the conventional analytical tools of NMR, MS, IR and HPLC. However, every cleavage takes time, potentially alters the product, is irreversible and lowers the overall yield, so this is a wasteful approach.

1.3.2 Mass spectrometry

Although mass spectrometry (MS) is a destructive technique, it is still widely used for monitoring solid phase reactions, as it is one of the most sensitive analytical tools available.[5] Commonly, MS is used following linker cleavage in a cleavage and analysis strategy of reaction monitoring. It is possible to cleave material from beads *in situ* and perform MS analysis using matrix-assisted laser desorption ionisation time-of-flight (MALDI-TOF) MS.[6,7] Other MS techniques, namely imaging time-of-flight secondary ion MS (TOF-SIMS) and electrospray MS (ES-MS) are routinely used for the direct analysis of material from small numbers of resin beads.[8]

1.3.3 Colorimetric tests

In 1970, Kaiser[9] described a colorimetric method to determine the quantity of free amine on the resin. This method, which became known as the Kaiser or ninhydrin test, uses ninhydrin to bind free amines on the resin, resulting in a complex called Ruhemann's purple being formed. The UV absorbance of this complex can be measured at 570 nm and the concentration of amine sites on the resin determined using the Beer-Lambert law. This technique is very sensitive; for example, quantities of amine as low as 5 μmol/g can be accurately determined. Sarin[10] later reported a modification, which increased the accuracy of the results. This method continues to be used extensively, most frequently for following peptide couplings on the resin either qualitatively or quantitatively.

Alternatively, the bromophenol blue test[11] is a method that allows for the non-invasive determination of free amines, like the ninhydrin test, but the use of bromophenol blue enables the detection of secondary amines in addition to primary amines.

Another colorimetric test often used in solid phase peptide synthesis is the Fmoc test.[12] UV analysis of the fulvene-piperidine adduct (UV maximum at 301 nm), released upon Fmoc-deprotection with piperidine/DMF, provides a reliable and quantitative method of determining resin loading.

Other colorimetric tests include the Ellman[13] test for thiols and the Volhard titration,[14] which is used to detect chlorides quantitatively. However, colorimetric tests tend to be suitable in only very specific cases, where a particular functional group is present, e.g. peptide couplings. Therefore more general techniques which would provide structural information on a wider range of resin-bound compounds were sought.

1.3.4 Gel phase NMR

Analysis of organic molecules by NMR is possible if there is good spectral resolution i.e. narrow line widths. This is achieved in solution by using physically homogeneous samples and then "shimming" the static field of the magnet to make the sample magnetically homogeneous. A resin-bound sample is heterogeneous and as such has areas of different magnetic susceptibilities that are not correctable by shimming. The resin bound sample would therefore need to be cleaved from the resin into solution before NMR analysis.

If a resin-bound compound is analysed by NMR in its dry state, very broad lines are formed due to chemical shift anisotropy and dipolar couplings, so no structural information can be deduced. However, on addition of a suitable solvent, e.g. $CDCl_3$ or C_6D_6, the resin swells, allowing increased molecular movement and thus narrowing the observed linewidths. The resin is neither a solid nor a liquid in this state, instead having the consistency of a slurry or gel and hence the technique of gel phase NMR evolved.

1.3.4.1 ^1H Gel phase NMR

^1H gel phase NMR has been made possible through the use of magic angle spinning (MAS) which further increases the spectral resolution, giving almost solution quality spectra. Many examples of gel phase MAS ^1H NMR have been published, including the determination of e.e. following a solid phase Sharpless epoxidation.[15]

The most significant advance in this field has been the development of the Nanoprobe.[16] By placing the entire sample (max. 40 μL) inside the receiver coil, the highest possible detection sensitivity is obtained. It is even possible to acquire spectra (^1H and HMQC NMR) from a single bead using the Nanoprobe.[17] Wehler used the Nanoprobe to establish which was the best resin for gel phase ^1H NMR, concluding that the long PEG chains of TentaGel meant this resin was the best solvated and therefore had the narrowest linewidths.[18]

1.3.4.2 ^{13}C Gel phase NMR

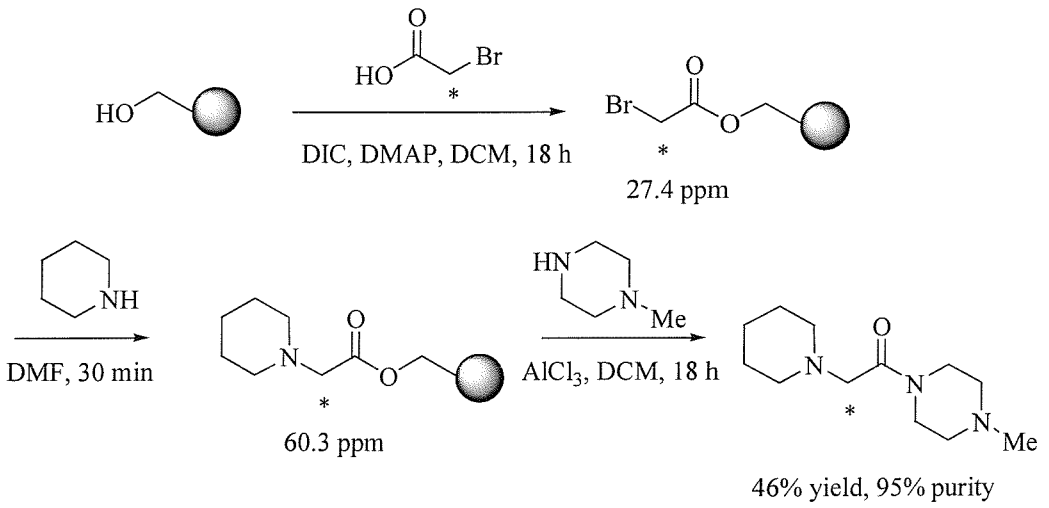
Despite the broader linewidths of ^{13}C NMR spectra (typically 25-75 Hz, compared to ~5 Hz for ^{1}H NMR), the resolution is significantly better due to the increased chemical shift dispersion of ^{13}C NMR. Satisfactory ^{13}C NMR spectra can therefore be obtained using a conventional spectrometer, without the need to use MAS.

In 1980, Epton[19] investigated the ^{13}C NMR of peptides on a poly(acryloylmorpholine) based resin. This particular resin was chosen for its excellent swelling properties, which contributed to the narrow linewidths observed. In this instance, ^{13}C NMR was used to follow the removal of the Boc protecting group in solid phase peptide synthesis. The methyl carbons were particularly visible due to the presence of nine equivalent hydrogens. It was observed that the amino acids furthest from the matrix had the narrowest signals because they were experiencing the most "solution-like" environment. Giralt[20] observed that the solvation of a compound on resin or in solution was almost identical, thus explaining the similar reactivity observed for equivalent reactions, whether carried out in solution or on the solid phase.

Gel phase ^{13}C NMR has since been used in many aspects of solid phase chemistry – from determining the chemical process used to synthesise chloromethyl resin[21,22] to monitoring the reactions of resin-bound steroids.[23] Unfortunately, this technique suffers from the low sensitivity of ^{13}C, which means that large quantities of resin and long experiment times are necessary. This problem has been partly addressed by Lorgé[24] who optimised the NMR parameters to reduce the typical experiment time from several hours to 7.5 min.

Enriched ^{13}C building blocks have also been used as an alternative way to overcome the problems of low sensitivity and long acquisition times. Enrichment enables high quality spectra to be obtained without interference from unenriched peaks and solvent. Although ^{13}C enriched materials are expensive, they are typically only used in reaction optimisation and commonly only 20-25% of the label is incorporated. The labeled atom itself need not be directly involved in the reaction as changes in the electronic environment of adjacent atoms will still affect the chemical shift of the labeled atom. For example, Barn[25] esterified 20% bromoacetic-2-^{13}C acid onto a

spacer unit and then displaced the bromide with an amine (Figure 1.1). Monitoring the reaction was achieved in real-time using ^{13}C gel phase NMR, enabling the reaction time to be reduced from 18 hours to 30 min.



* denotes ^{13}C enriched position (20%)

Figure 1.1: The use of ^{13}C enriched building blocks for monitoring reactions with gel phase ^{13}C NMR

The introduction of ^{13}C isotopes allows the ^{13}C NMR to be acquired in the same time as a solution sample, without any specialised equipment and gives excellent results. Look[26] successfully acquired a ^{13}C NMR spectrum on only 20 mg resin through the use of ^{13}C enriched building blocks and NMR tube inserts.

Gel phase ^{13}C NMR has proved popular for monitoring solid phase reactions because the technique is non-destructive, provides large amounts of structural information and requires no specialist equipment.

1.3.4.3 Gel phase ^{31}P, ^{15}N and ^{19}F NMR

Other nuclei have also been investigated for gel phase NMR, namely ^{31}P, ^{15}N and ^{19}F.[27,28] The advantage of these nuclei is that they have high sensitivities so acquisition times are shorter and polymer signals no longer dominate the spectra.

These techniques allow the rapid monitoring of solid phase reactions but again are only useful for specific problems, e.g. ^{31}P for solid phase oligonucleotide synthesis.[29]

1.3.5 Infra-red spectroscopy

Fourier transform infra-red (FT-IR) is a very useful technique for solid phase organic chemistry, but is limited in terms of structural discrimination, requiring a change in an IR chromophore. Historically, FT-IR was a destructive method as KBr discs of resin were prepared for analysis, however, since the advent of microspectroscopy, a spectrum can be obtained from a single bead, so IR has been compared favourably to TLC.

Yan[30] has shown that a single bead can be representative of the entire reaction and demonstrated that the kinetics of a reaction could be studied in real-time using single bead IR. The quality of the IR spectrum is not always ideal as often the peaks are broad and flat-topped. Flattening the bead provides a more uniform pathlength for radiation and hence gives better peak resolution and improved spectral quality.[31] Yan has also used single bead FT-IR to investigate site-site interactions and site separation effects[32] and to compare rates of reaction on different resins.[33]

As well as microspectroscopy, there are other IR techniques available such as diffuse reflectance infra-red FT (DRIFT) which is particularly useful for observing data in the "OH" spectral region, photoacoustic FT-IR, which provides cleaner spectra, free of baseline artifacts caused by sample inhomogeneity and light scattering and also FT Raman, which allows the monitoring of different functional groups. Yan carried out a comprehensive comparison of various FT-IR and FT Raman methods, concluding that single-bead IR was a superb FT-IR technique for monitoring solid phase reactions, but the equipment was expensive, so the beam-condenser method provided a cheaper alternative.[34]

Although IR does not always provide vast amounts of structural information, it should be remembered that normally the compounds are not unknowns so often the structure simply needs to be confirmed rather than assigned. In summary, IR is a very simple, sensitive and convenient method of analysis and is almost a replacement for TLC when studying solid phase reactions.

1.3.6 Elemental analysis

Yan[35] described the use of combustion elemental analysis for quantifying reactions on the solid phase. Elemental analysis provides information on the CHN content of compounds by combustion in oxygen, producing carbon dioxide, water and nitrogen. Typically only 2 mg of resin is needed for analysis but it is vitally important that samples are thoroughly dried, as the presence of solvents causes errors.

1.3.7 Summary of solid phase spectroscopic methods

Spectroscopic methods are needed to identify different functional groups on the resin, thus providing an alternative to the cleavage and analysis procedure, which is a rigorous and time-consuming method. The main problems that result from on-resin analysis are due to the polymeric matrix, which tends to dominate the spectra. By adapting traditional analytical techniques such as NMR and IR, along with the introduction of new instrumentation e.g. FT-IR microspectrometers and Nanoprobe technology, routine analysis of resin-bound samples has become a reality. As with so many things, the best results are achieved when a combination of techniques are used together to provide information on the resin-bound compound, rather than relying on any one method in isolation.

1.4 Resins

There are two main classes of resins used in solid phase chemistry – polystyrene and polystyrene-polyethylene glycol grafts (PS-PEG). Polystyrene resins are typically formed by suspension polymerisation of styrene with divinylbenzene (usually 1%) as a co-polymer to crosslink the resin, thus conferring increased mechanical strength to the resulting polymer without reducing its swelling properties. Polystyrene is completely hydrophobic in nature and hence swells in solvents such as DMF and DCM but exhibits very little swelling in alcoholic solvents and water. This limits the type of chemistry which can be carried out using polystyrene resins, and hence PS-PEG resins are routinely used when aqueous conditions are required.

PS-PEG resins, of which TentaGel is the most well-known,[36] consist of approximately 70% polyethylene glycol (MW 3000-4000) grafted onto a central polystyrene core (Figure 1.2). The PEG chain enables the resin to swell in polar solvents such as water, MeOH and EtOH, enabling a broad range of chemistry to be carried out.

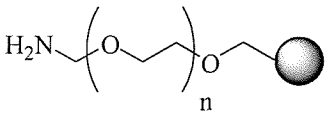


Figure 1.2: TentaGel resin

The choice of resin used in any synthesis depends mainly on the reaction conditions which are to be used, but the loading requirements should also be considered. (TentaGel has a substitution of 0.3 mmol/g whereas the substitution of polystyrene typically ranges from 0.5 to 2 mmol/g). Another factor which should be taken into account is the cost – TentaGel is significantly more expensive than polystyrene.

1.5 Linkers[37]

A linker is a bifunctional molecule, which attaches the compound of interest to the solid phase *via* a labile chemical bond. The linker itself is joined to the resin through a robust or chemically inert bond. The labile bond between the molecule and linker may be cleaved under (preferably) mild conditions, to release the molecule of interest into solution (Figure 1.3).

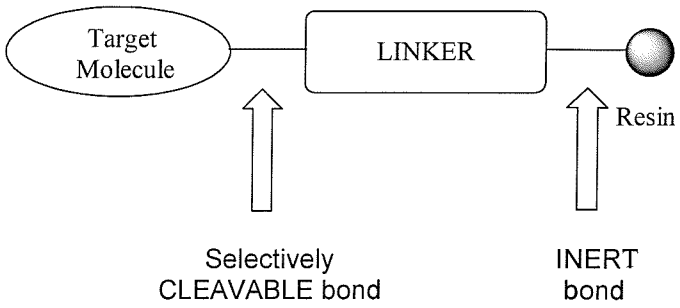
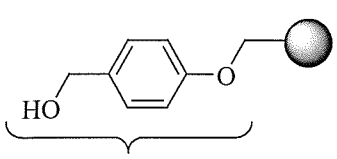


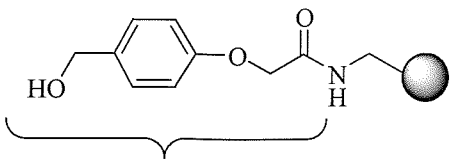
Figure 1.3: Schematic of a linker

If this linking strategy is to be successful, a linker must possess similar properties to that of a protecting group. It is necessary to achieve quantitative loading of the linker/protecting group, chemical stability during the synthesis sequence, i.e. orthogonality, and quantitative cleavage of the substrate from the linker without product degradation. It is thus not surprising that many linkers have been derived from protecting groups.

The most well-known and commonly used linker is the Wang linker,[38] which was originally developed for solid phase peptide synthesis (Figure 1.4). The Wang linker bears a free hydroxy group to which a molecule with a terminal acid group is esterified. At the end of the synthesis, the Wang linker is cleaved by a protic acid, usually TFA, to release the molecule with its restored carboxylic acid functionality. Frequently 4-hydroxymethylphenoxyacetic acid (HMPA) is used as an alternative to the Wang linker (Figure 1.4). Indeed, HMPA is often referred to as a "Wang-type linker", because its mechanism of cleavage is identical.



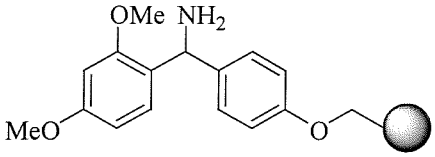
Wang linker



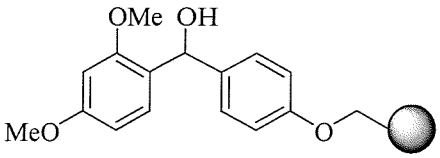
HMPA linker

Figure 1.4: Wang and HMPA linkers (shown attached to the solid support)

Like the Wang linker, the Rink linker[39] is used to attach carboxylic acids to the resin and may be cleaved under acidic conditions (TFA) to release the molecule into solution with either a terminal acid or, if the Rink amide linker is used, a terminal amide (Figure 1.5).



Rink amide linker



Rink acid linker

Figure 1.5: Rink acid and Rink amide linkers (shown attached to the solid support)

Traditional linkage methods rely heavily on acids or esters to attach compounds to the resin, having been originally used for solid phase peptide synthesis. These methods of attachment are suitable in some cases, but it may not always be useful to have a reactive group remaining after cleavage, especially if that cleavage occurs under harsh conditions, e.g. TFA. New linkers which cleave under milder conditions are constantly being developed, such as photolabile linkers which cleave simply on exposure to light (λ = 350 nm) and traceless silicon linkers, which cleave without leaving any trace of attachment other than a C-H bond in the released molecule. However, as speed is of the essence within the pharmaceutical industry, there remains a need for linkers that will permit the *in situ* biological screening of compounds for drug discovery applications.

1.6 Safety-Catch Linkers[40]

Safety-catch linkers rely on a two-step cleavage process: the first step is activation of the linker, followed by a second step, which effects the actual cleavage (Figure 1.6). In this way, the safety-catch linker may be released (activated) then the resin beads transferred to a different vessel, e.g. a 96-well plate, for cleavage. Provided the cleavage is achieved under mild conditions, e.g. warming or mildly acidic/basic conditions, the compounds are ready for immediate biological screening, without the need for any further chemical transformations or sample manipulation.

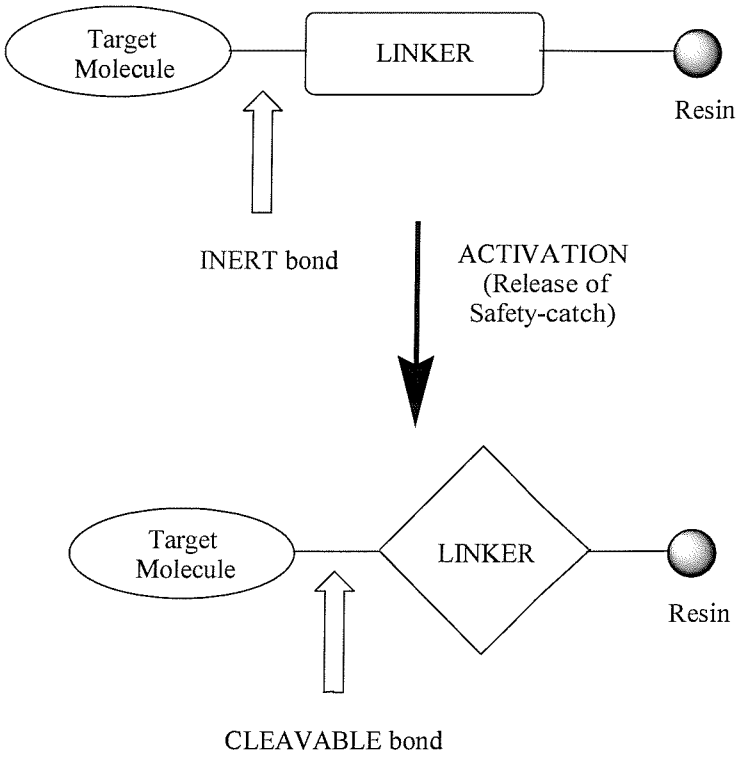


Figure 1.6: Schematic of a safety-catch linker

1.6.1 Kenner's safety-catch linker

The safety-catch principle was first applied by Kenner in 1971, who described an acylsulfonamide linker for peptide synthesis.[41] *N*-Acylsulfonamides are resistant to alkaline hydrolysis, as basic attack simply results in the deprotonation of the acidic

sulfonamide proton (pk_a ~ 2.5). However, once the linker is activated *via* *N*-methylation (diazomethane), cleavage may be effected by nucleophilic displacement using NaOH, ammonia or hydrazine, thus forming the carboxylic acid, amide or hydrazide functionalised products respectively (Figure 1.7).

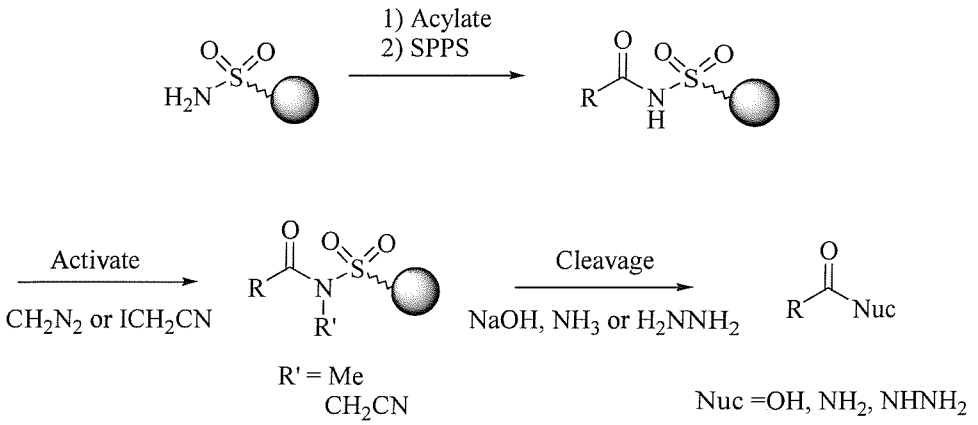


Figure 1.7: Kenner's acylsulfonamide safety-catch linker

Unfortunately, the low reactivity of the *N*-alkylsulfonamide requires the use of excess amine to achieve cleavage, and non-nucleophilic or sterically hindered amines fail to cleave the linker at all. Thus Backes[42] described an alternative activation step employing iodoacetonitrile instead of diazomethane, for the activation step, leading to an *N*-cyanomethyl derivative (Figure 1.7). This is much more labile to nucleophilic displacement, thus limiting the quantities of amine which were used in the cleavage step and allowing target compounds to be isolated without requiring additional purification.

1.6.2 Frank's safety-catch linker

Hoffmann and Frank reported a safety-catch linker, which would cleave in aqueous solution to release peptide acids.[43,44] The linker was based on a glycolic acid linker, and could be cleaved with 10 mM NaOH (pH 12). By incorporating a basic group, the hydrolysis of the ester bond could be enhanced by intramolecular catalysis, allowing cleavage to occur under mild conditions (Figure 1.8).

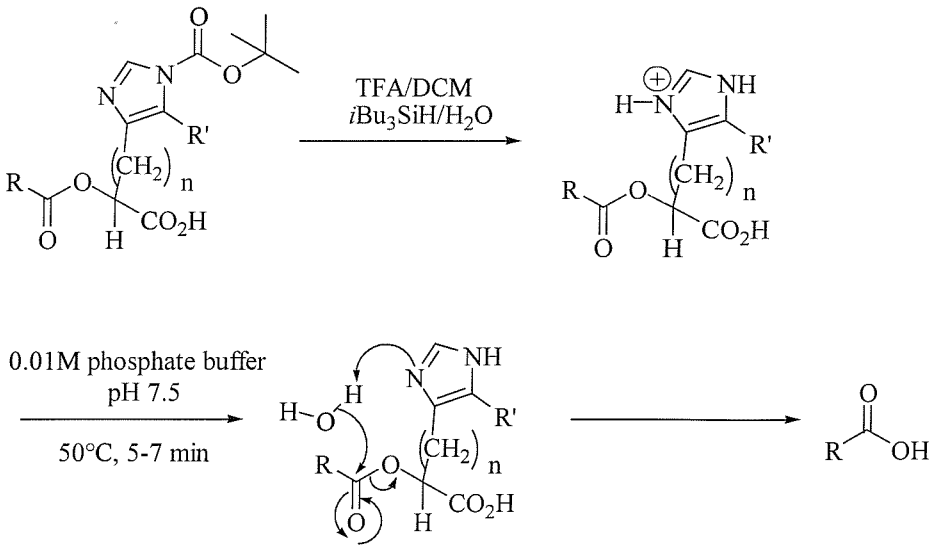
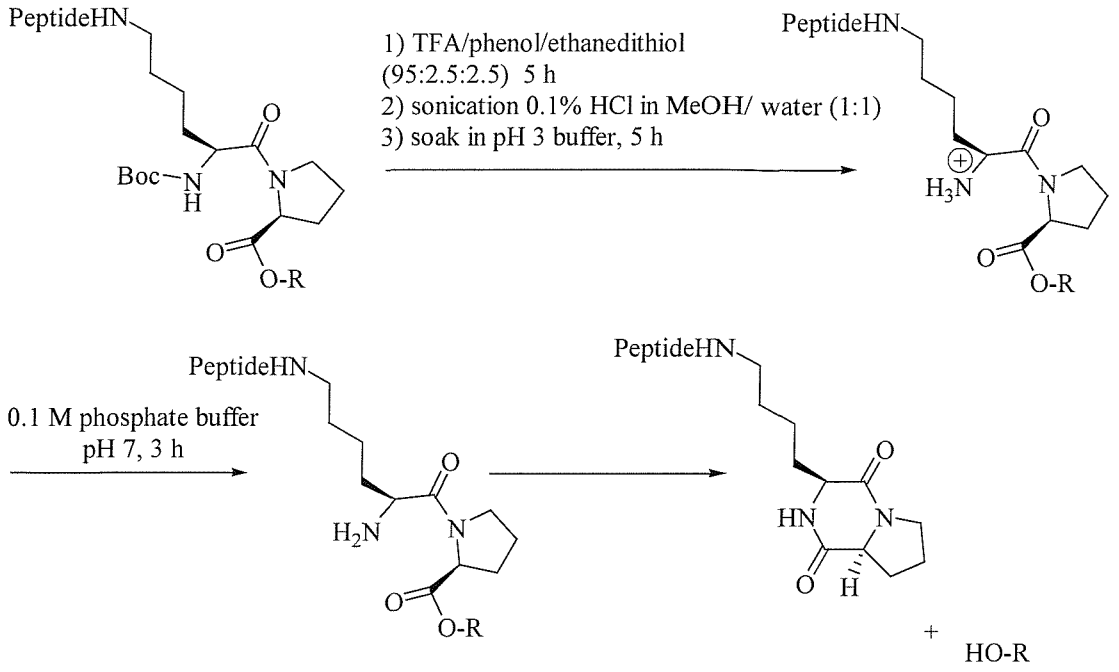


Figure 1.8: Frank's safety-catch linker cleaves via *intramolecular catalysis under basic conditions*

The basic group needed to be "turned off" during peptide synthesis, to prevent premature cleavage; thus a Boc group was employed for imidazole protection. Acid treatment removes the Boc group, and simultaneously "turns on" the catalytic effect, although cleavage does not occur until the resin is placed in basic solution and the imidazole is finally deprotonated. The optimum conditions were 0.01 M phosphate buffer at pH 7.5, heated to 50°C, which enabled the linker to be cleaved in only 5-7 min.

1.6.3 Diketopiperazine (DKP) based linkers

Geyson developed a diketopiperazine-based safety-catch linker to release peptides into aqueous solution for biological screening.[45,46] In the same manner as above, activation was accomplished by Boc-removal (TFA) with cleavage occurring once the resin was transferred to pH 7 buffer (Figure 1.9).



R = CH_2CO-NH-$(CH_2)_2CO$-NH-$(CH_2)_6NH$-{polyacrylic acid}--{polyethylene rod}

Figure 1.9: A diketopiperazine-based safety-catch linker

Unfortunately, all the peptides had a C-terminal diketopiperazine moiety, so in order to obtain the free peptide, Bradley[47] developed a safety-catch linker whereby cleavage still resulted in the formation of a diketopiperazine but it remained bound to the resin and thus was not incorporated in the final product. As above, the safety-catch comprised a Boc group, the removal of which led to intramolecular formation of a diketopiperazine, once the amine had been deprotonated by treatment with base (Et_3N). Diketopiperazine formation led to the release of a derivatised hydroxyphenylmethylester, which underwent facile 1,6-elimination to give the product and a quinone methide by-product (Figure 1.10). It was demonstrated that this linker was suitable for use in both solution phase and solid phase screens, releasing the molecule of interest in yields of over 70% within a few hours.

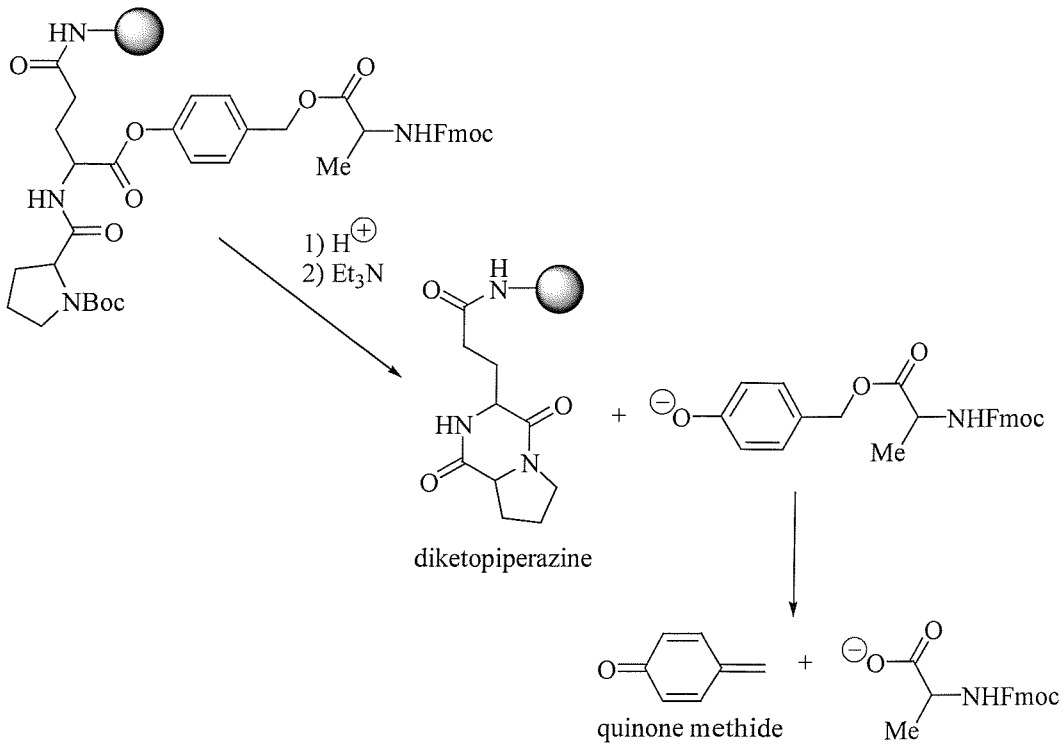


Figure 1.10: A modified diketopiperazine-based safety-catch linker

A similar cleavage strategy was described by Lebl for the multiple release of peptides from a polymeric support.[48] He designed a symmetrical linker based on two molecules of iminodiacetic acid, which cleaved in two distinct steps, giving two equimolar portions of peptide. The first stage of release was spontaneous formation of a diketopiperazine, which was only possible after activation by Boc-removal (TFA). The structure was stable in acidic pH, but once the proton was removed from the secondary amine group (pH 7-9) the diketopiperazine was formed spontaneously. The release of the second peptide was accomplished by application of higher pH (3-12 h in 0.05-0.2% NaOH) or by exposure to gaseous ammonia. Even after both peptide portions were cleaved, an identical peptide remained bound to the resin to serve as a reference for structural determination (Figure 1.11).

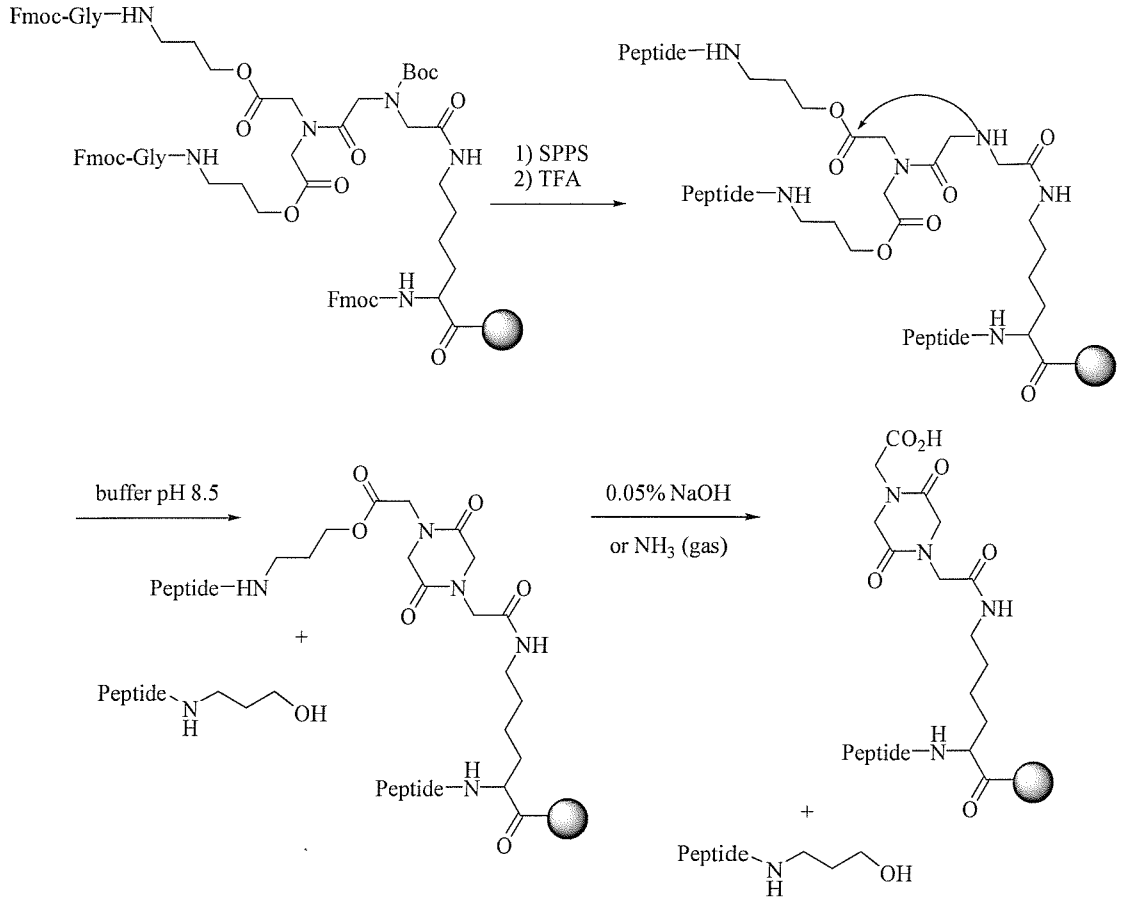


Figure 1.11: A safety-catch linker for multiple product release

1.6.4 Dpr(Phoc) linker

A 2-amino-3-*N*-phenoxycarbonylaminopropionic acid (Dpr(Phoc)) based linker has been shown to permit the use of aqueous conditions in solid phase peptide synthesis.[49] The Dpr(Phoc) residue was chosen because of the resistance of phenyl carbamates to acidolysis, the ready access to the linker and its straightforward attachment to a support, the ease with which isocyanates are generated at alkaline pH and the anticipated fast and selective intramolecular addition of this electrophile to a nearby amide. In addition, the residue is incorporated *via* an amide bond, rather than the more commonly used ester linkage, therefore conferring extra stability on the linker.

Cleavage occurs only after activation *via* alkaline hydrolysis (pH 10), creating an isocyanate *in situ* which is then trapped by the adjacent amide, thus forming a

5-membered cyclic intermediate. This cyclic urea can be cleaved either by alkaline hydrolysis to give the peptide acid, or aminolysis to give the corresponding peptide amide (Figure 1.12).

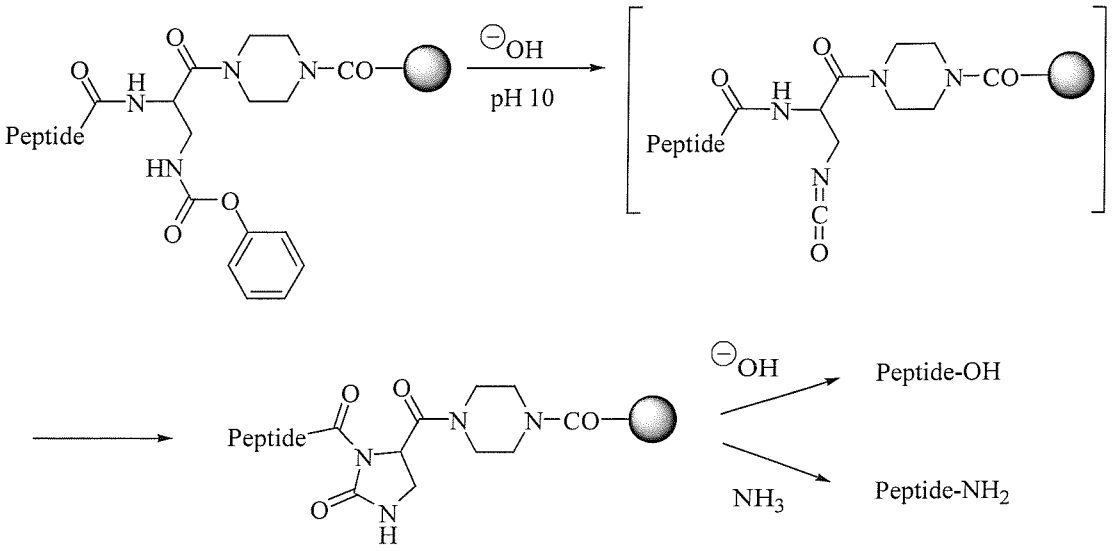


Figure 1.12: The Dpr(phoc) safety-catch linker

1.6.5 Ugi/De-Boc/Cyclisation (UDC) safety-catch linker

The Ugi multi-component reaction is an efficient route for the synthesis of complex molecules in a single step, so is frequently used in combinatorial chemistry. Hulme[50] described the synthesis of a resin-bound isonitrile, which was used to perform a solid-supported Ugi reaction. The safety-catch could be released through Boc-activation of the benzamide carbonyl to permit cleavage of the Ugi product under mild conditions. Lithium hydroxide or sodium methoxide were used to effect the cleavage, giving the corresponding acids or methyl esters respectively (Figure 1.13).

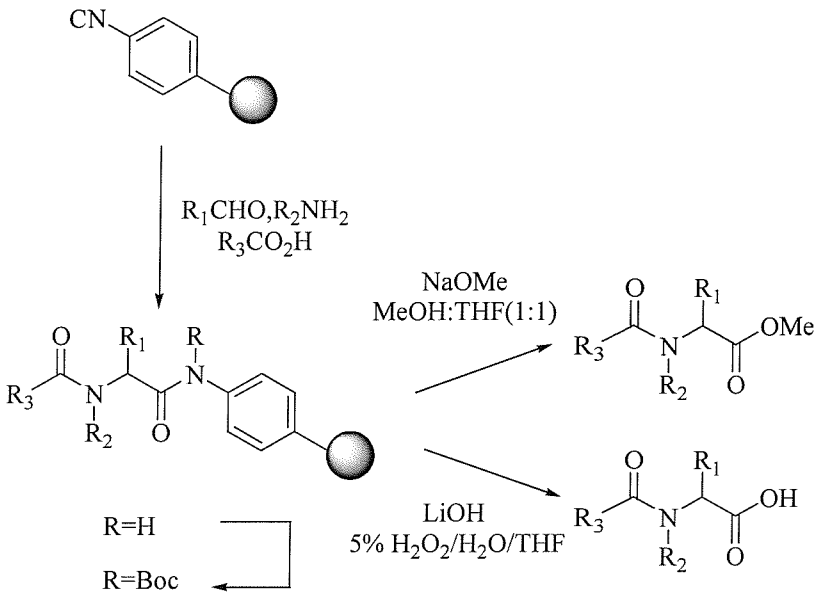


Figure 1.13: Ugi/De-Boc/Cyclisation (UDC) safety-catch linker

1.6.6 Benzyl hydrazide safety-catch linker

Wieland[51] developed a safety-catch linker based on the benzyl hydrazide functionality, which he used for solid phase peptide synthesis. The oxidation of a hydrazide produces a diazene. Subsequent nucleophilic attack of the diazene with *n*-benzylamine released nitrogen, a polymer-bound toluene and the substrate as its acyl derivative (Figure 1.14).

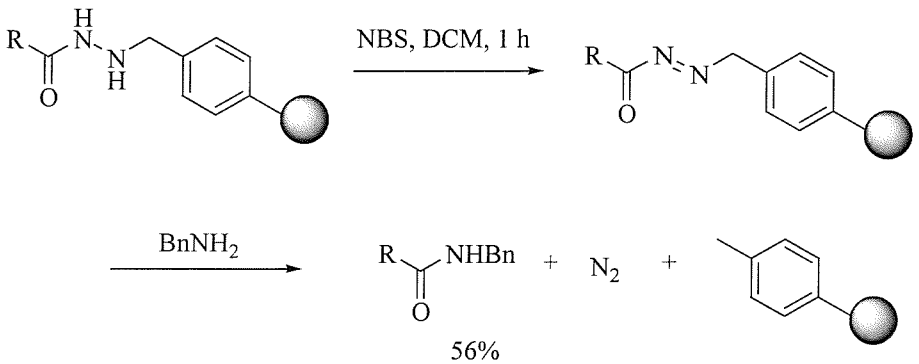


Figure 1.14: A benzyl hydrazide safety-catch linker activated by oxidation

A phenyl hydrazide linker, compatible with acid-, base- and reduction-labile protecting groups, was later described by Semenov.[52] Copper (II) complexes with nitrogen containing ligands were employed as a catalyst for the oxidation step, which was carried out using the atmosphere as an oxidant. The phenylazo intermediate decomposed *in situ* to afford the protected tripeptide 83% pure (HPLC) after 16 h (Figure 1.15).

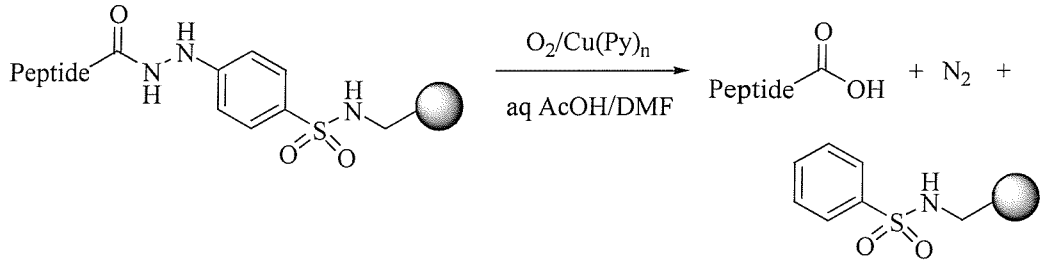


Figure 1.15: A phenyl hydrazide safety-catch linker

Waldmann demonstrated the compatibility of the phenyl hydrazide linker with many different reactions, e.g. Heck and Suzuki reactions, Sonogashira coupling and Stille reactions.[53] The aromatic products were cleaved in excellent yields (> 90%) after oxidation with *N*-bromosuccinimide (NBS) or $Cu(OAc)_2$ followed by reaction with a nucleophile (e.g. MeOH) (Figure 1.16).

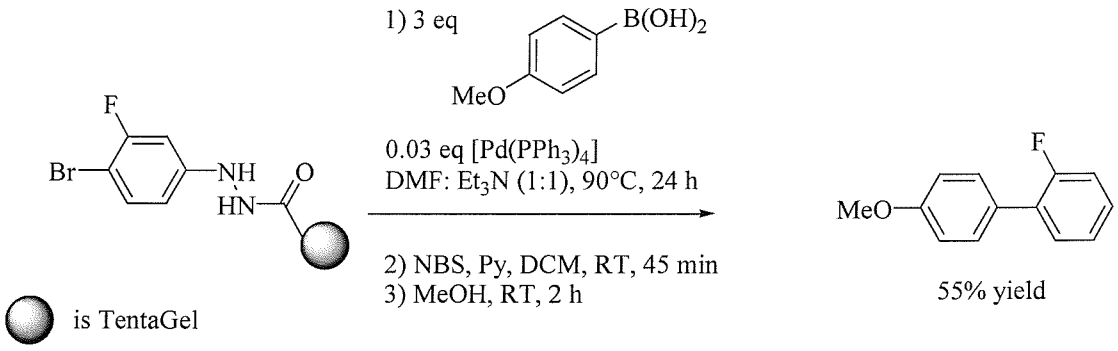
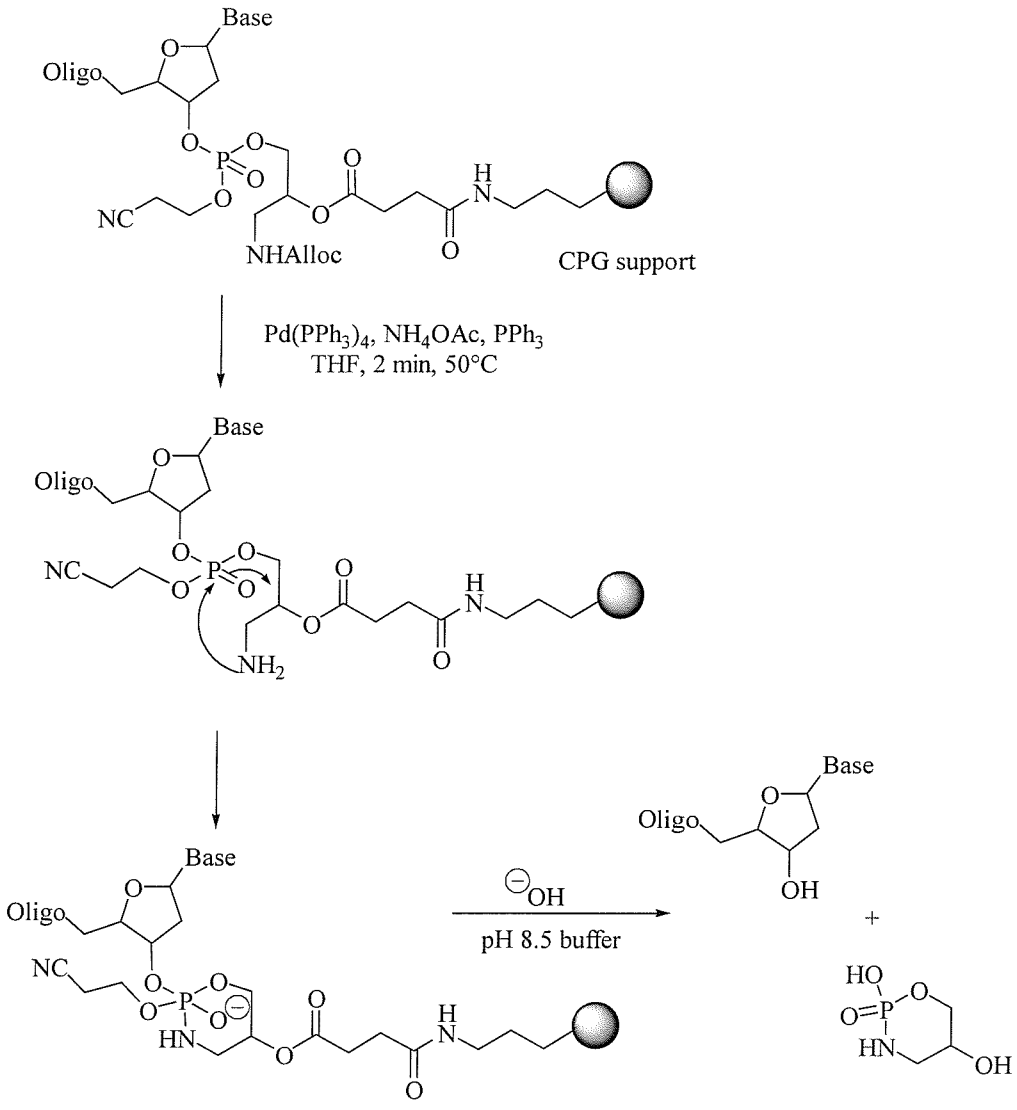


Figure 1.16: Use of the phenyl hydrazide safety-catch linker for Suzuki reactions

1.6.7 Lyttle safety-catch linker

A safety-catch linker based on the 3-amino-1,2-dihydroxypropane group has been designed for solid phase oligonucleotide synthesis by Lyttle and co-workers.[54] Following activation by removal of the alloc protecting group, the amine nitrogen attacks the phosphorus atom, thus forming a 6-membered ring. Upon treatment with base, both the cyanoethanol moiety and the 3'-hydroxynucleotide are cleaved from the resin *via* nucleophilic displacement.



CPG support = controlled pore glass

Figure 1.17: A safety-catch linker for oligonucleotide synthesis

1.6.8 Redox-sensitive safety-catch linker

A redox-sensitive linker has been designed by Wang and co-workers which takes advantage of a "trimethyl lock"-facilitated cyclic ether formation to allow the preparation of peptides with a free acid at the C-terminus.[55] The peptide can be cleaved at the end of the synthesis by a two-step process. Firstly, the quinone is reduced with a mild reducing reagent, thus releasing (activating) the safety-catch. Then the actual cleavage is effected by treatment with tetrabutylammonium fluoride (TBAF) which catalyses cyclic ether formation with concomitant release of the peptide (Figure 1.18).

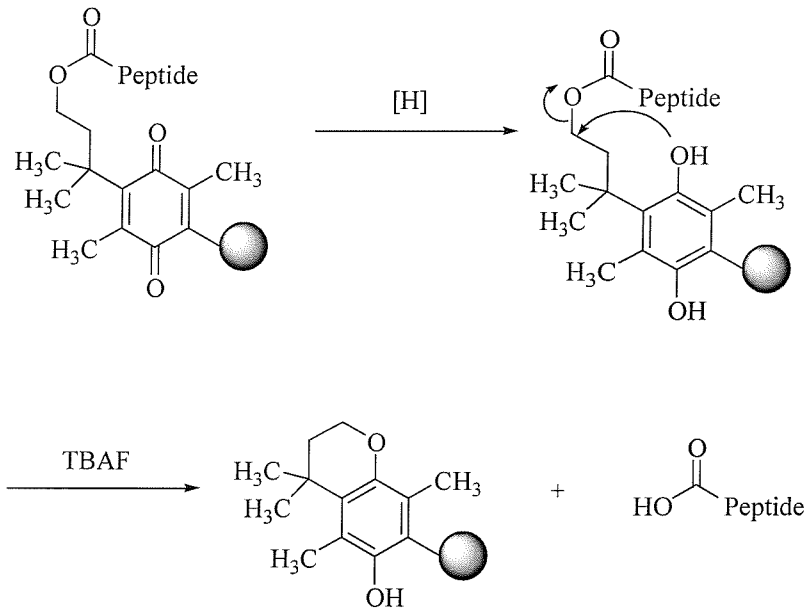


Figure 1.18: A redox-sensitive safety-catch linker based on a "trimethyl lock"-facilitated cyclic ether formation

1.6.9 Photolabile linkers

Although all photolabile linkers are orthogonal to normal synthetic chemistry, and hence may be considered as safety-catch linkers, some specific examples of photolabile linkers, which cleave only after activation have recently been described. *Ortho*-nitrobenzyl esters, the most common class of photolabile linkers, suffer from slow cleavage kinetics and the generation of a reactive chromogenic nitroso aldehyde on the resin. Balasubramanian described the synthesis of a dithiane protected

benzoin photolabile safety-catch linker that would not suffer from these drawbacks. In addition, the use of a safety-catch linker prevented premature cleavage, enabling easier sample manipulation throughout the synthesis.[56]

Benzoin esters undergo photosolvolytic cleavage at 350 nm, rearranging to form the isomeric benzofurans. The new photolabile linker was designed around a 3-alkoxybenzoin core, the substrate being esterified to the hydroxyl group and the carbonyl being protected as a dithiane until cleavage was desired. Deprotection of the dithiane could be effected with bis[(trifluoroacetoxy)iodo]benzene, mercury perchlorate or periodic acid, but periodic acid was found to be the reagent of choice. The resin was then exposed to light (λ= 350 nm) to release the molecule (Figure 1.19). Lower resin substitutions were found to result in faster cleavage times (92% yield, 2 h).[57]

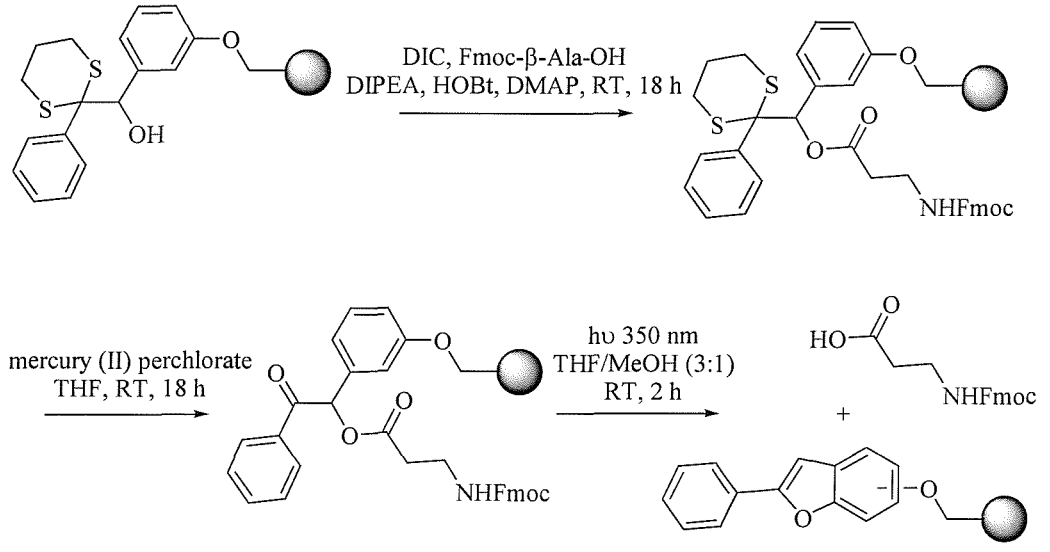


Figure 1.19: A photolabile safety-catch linker

1.6.10 Sulfide/sulfone safety-catch linkers

Marshall described the synthesis of a modified solid support to allow the preparation of protected peptide fragments.[58] An oxidation step converted the stable sulfide into an activated sulfone, capable of acylating an amine. Cleavage of the peptide from the support was effected *via* acylation with an amino acid salt, thus lengthening the peptide by one residue at the carboxy terminus (Figure 1.20).

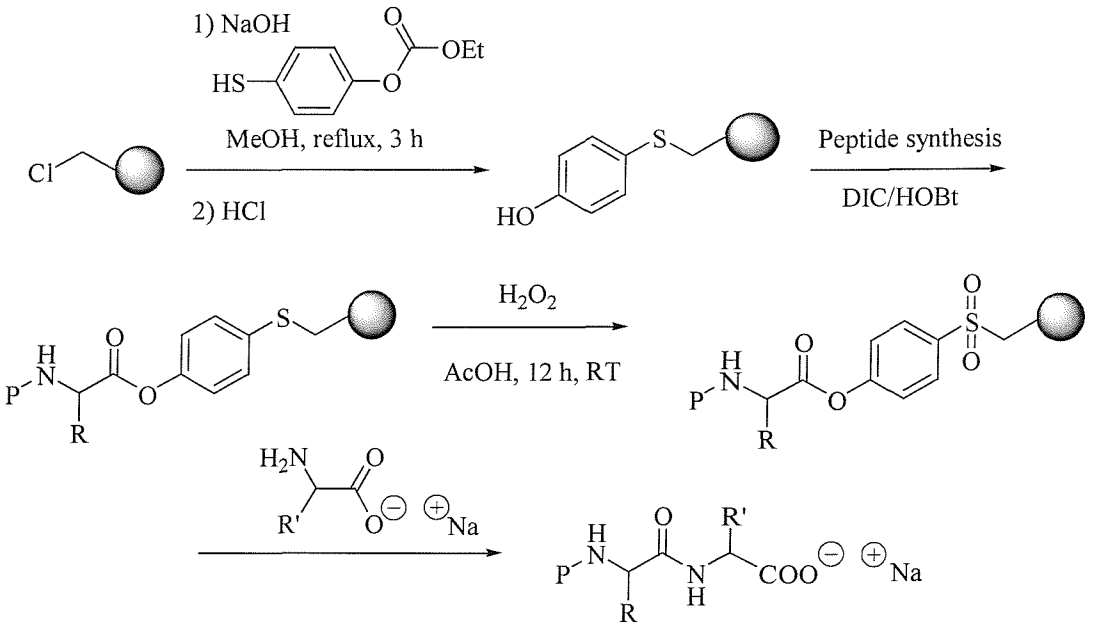


Figure 1.20: Synthesis of protected peptide fragments using a sulfide/sulfone safety-catch linker

However, several groups have recently demonstrated that cleavage can be achieved without the oxidation (activating) step. Breitenbucher[59] and co-workers employed excess *n*-butylamine in pyridine to ensure that the cleavage was complete within 24 hours. The piperazine-2-carboxamide products were obtained in high yields. Alternatively, Dressman[60] favoured using 4 equivalents of amine in acetonitrile while Yager[61] used a limiting amount of the primary amine (0.5 equivalents) in DCM.

During the synthesis of a library of pyrimidines, Obrecht also demonstrated cleavage *via* nucleophilic displacement with amines.[62] The safety-catch was activated by sulfide to sulfone oxidation (3 equivalents *m*-CPBA, DCM), and nucleophilic aromatic substitution of the sulfone group by primary or secondary amines (1.5 equivalents) resulted in the release of substituted pyrimidines from the resin. Very high levels of purity (typically > 96-99%) were obtained and the cleavage step also allowed additional diversity to be introduced (Figure 1.21).

This linking strategy has also been used by Masquelin[63] to synthesise a library of trisubstituted triazines and by Suto,[64] who effected the cleavage with a limiting quantity of amine (0.95 equivalents) to improve product purity.

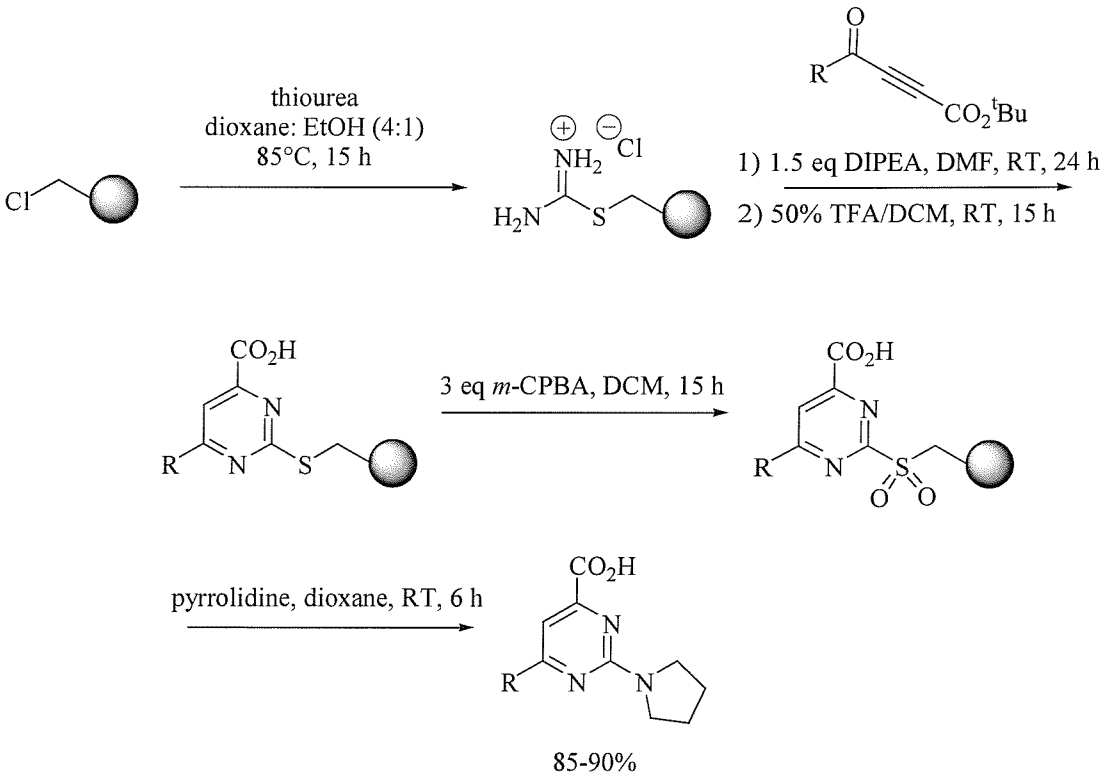


Figure 1.21: Synthesis of pyrimidines using a sulfide/sulfone safety-catch mechanism

Janda and co-workers developed an alternative traceless linker on a soluble polymeric support.[65] The safety-catch was again released (activated) by oxidation of the sulfide to the sulfone, but then cleavage was effected reductively with

sodium/mercury. By employing the chemoselective reagent Oxone® ($KHSO_5$), olefins and ketones remained unaffected (Figure 1.22).

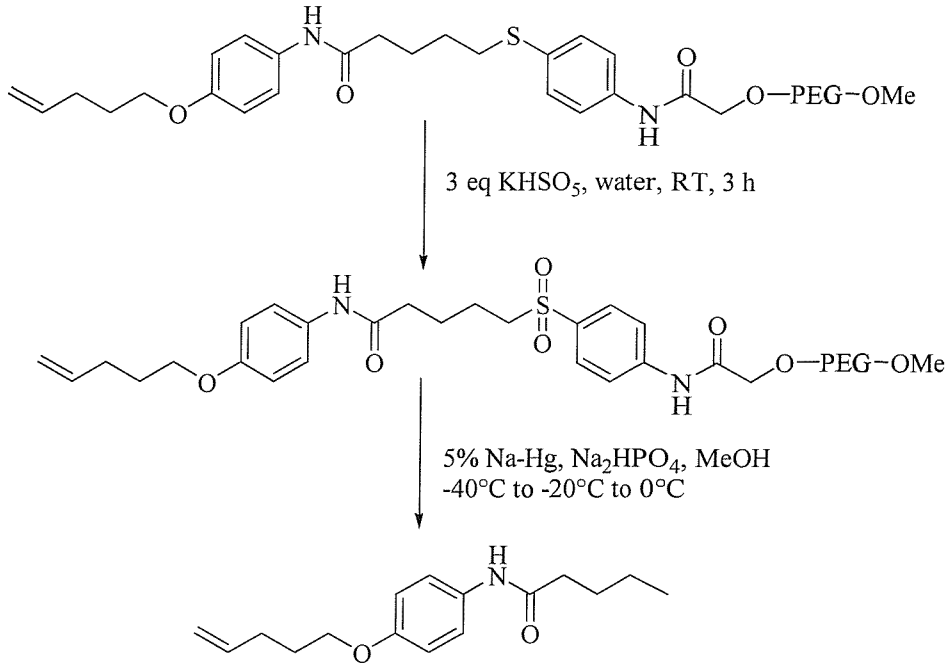


Figure 1.22: A "traceless" sulfone safety-catch linker cleaved by Na/Hg (after activation by oxidation)

1.6.11 Sulfide/sulfoxide safety-catch linkers

The *p*-(methylsulfinyl) benzyl (Msib) safety-catch protecting group for carboxylic acids was described by Samanen and Brandeis.[66] The Msib ester could be readily activated by reduction to *p*-(methylthio) benzylester (Mtb), which cleaved on exposure to anhydrous acid (TFA) (Figure 1.23).

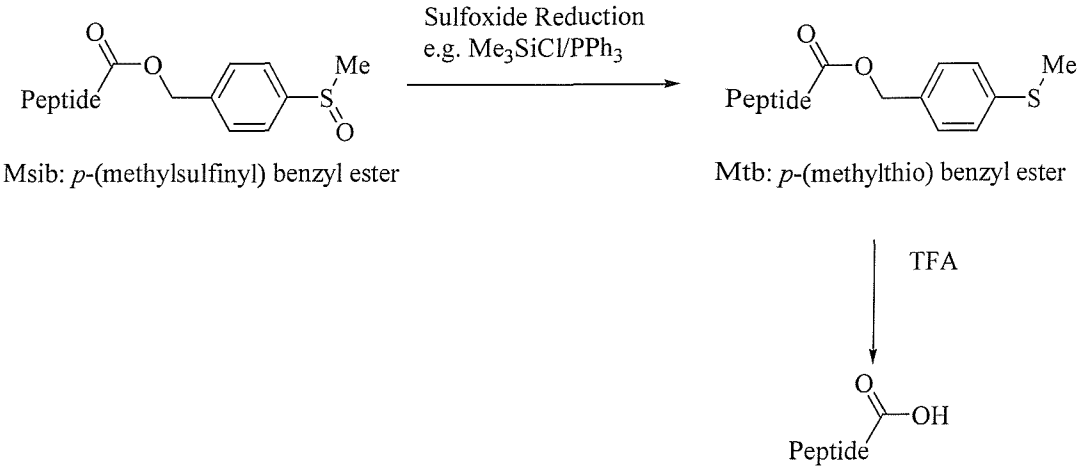


Figure 1.23: The Msib/Mtb safety-catch protecting group for carboxylates

Kiso adapted the Msib/Mtb safety-catch for the protection of amines, creating the *p*-(methylsulfinyl) benzyloxycarbonyl (Msz) protecting group[67] which was then developed into a safety-catch linker, 4-(4-methoxyphenyl-Boc-amino)methyl-3-methoxyphenylsulfinyl-6-hexanoic acid (DSA handle) using the same sulfide/sulfoxide strategy, but on a benzhydrylamine skeleton (Figure 1.24).[68]

It was deduced that two electron donating groups were necessary on the aromatic rings for the smooth release of the peptide amide by mild acidolysis, as the Rink and peptide amide (PAL) linkers are substituted in this way, and also cleave under mild conditions. Thus, the DSA handle was designed with two alkoxy groups and one alkylsulfinyl group, which could be reduced to an electron donating alkylthio group. Cleavage then occurred under acidic conditions (TFA). It was discovered, however, that activation and cleavage could be achieved in a one-pot reaction using $SiCl_4$ in TFA with a suitable scavenger (anisole). The utility of the DSA handle was demonstrated by the synthesis of an 11-amino acid peptide amide, buccalin, in 40% overall yield (Figure 1.24).

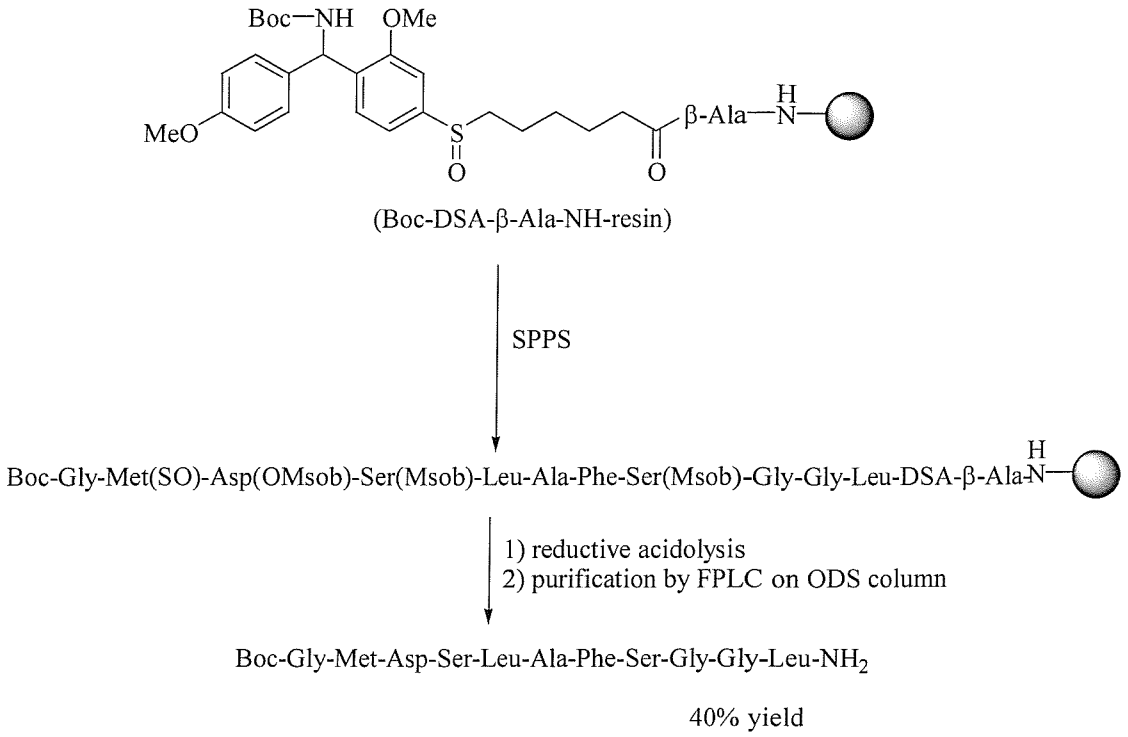


Figure 1.24: Synthesis of buccalin on the DSA safety-catch linker

The same authors have also reported the synthesis and application of an almost identical handle, 4-(2,5-dimethyl-4-sulfinylphenyl)-4-hydroxybutanoic acid (DSB), which is also cleaved *via* reductive acidolysis.[69]

Pátek and Lebl independently investigated the synthesis and application of a benzhydryl linker based on the Msib/Mtb safety-catch strategy.[70] It was confirmed that the sulfinyl variant was stable to the acidic conditions required for Boc-removal (50% TFA/DCM-anisole) and hence had potential as a safety-catch linker for the synthesis of C-terminal amides. The activation and cleavage could again be achieved in one-pot by reductive acidolysis ($SiCl_4$/TFA/scavenger or Me_3SiCl/TFA/scavenger). By introducing an alkoxy group and thus permitting attachment of the linker to the solid support, Pátek and Lebl created the safety-catch acid labile (SCAL) handle (Figure 1.25).[71]

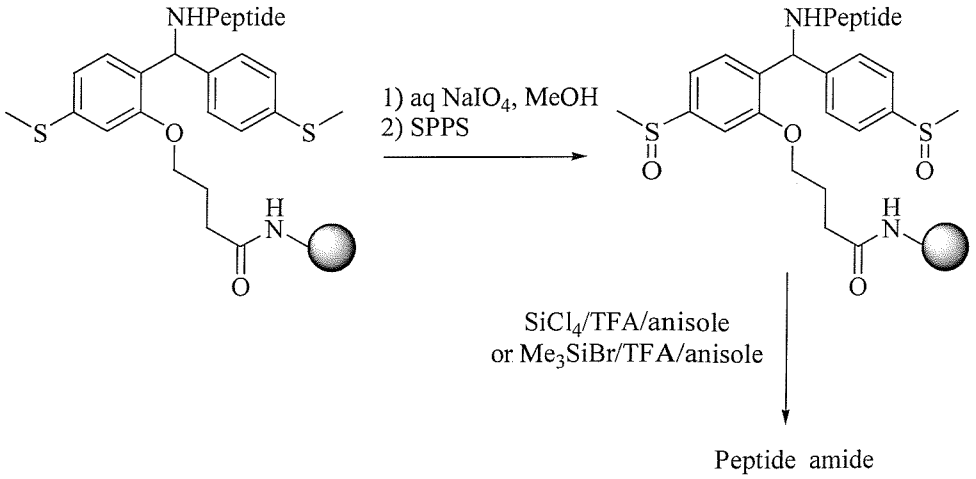


Figure 1.25: Synthesis of peptide amides using the safety-catch acid labile (SCAL) handle

1.6.12 Selenium-based safety-catch linkers

The first example of solid phase selenium chemistry dates back to 1976. Michels and co-workers prepared selenium-containing polymers from the co-polymerisation of divinylbenzene and 4-vinylbenzene-1-selenol.[72] The selenol was converted to selenenyl chloride by treatment with SO_2Cl_2, and then reacted with a ketone (4-methylcyclohexanone). Oxidation with hydrogen peroxide provided the unsaturated ketone (4-methylcyclohexenone) in 91% yield (Figure 1.26). However little more was published in this area until recently.

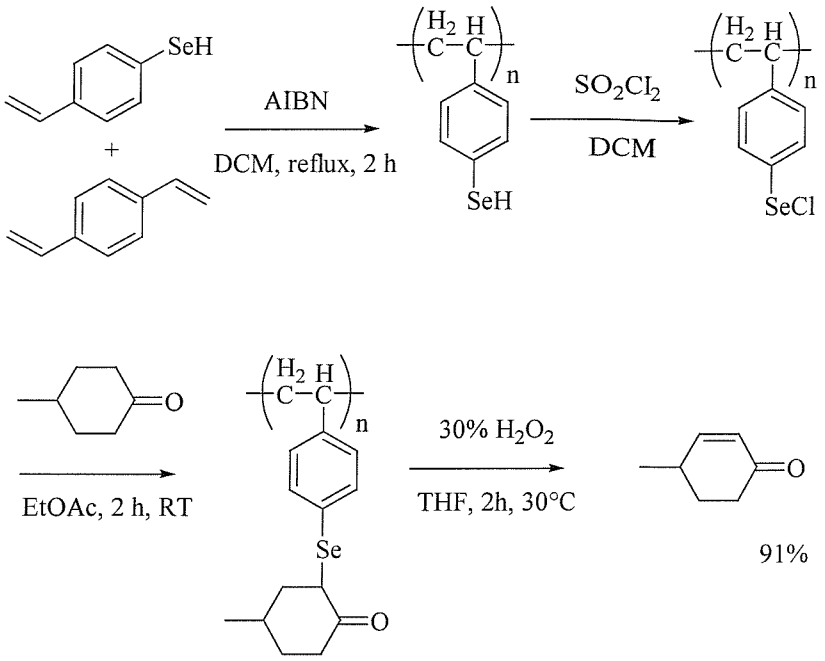


Figure 1.26: Synthesis of 4-methylcyclohexenone using a polymer-supported selenium reagent

Nicolaou[73] described the synthesis of polymer-supported selenium reagents, which were prepared from polystyrene resin *via* lithiation and quenching with dimethyldiselenide. An alkyl iodide was then efficiently loaded onto the polymer using mild alkylation conditions and cleaved with hydrogen peroxide to release the unsaturated analogue (2,2-dimethyl-1-(pent-4-enyloxy)-1,1-diphenyl-1-silapropane) in 78% yield (Figure 1.27). An alternative free radical cleavage method was demonstrated using tributyltin hydride and AIBN to release the corresponding alkyl compound in 89% yield.

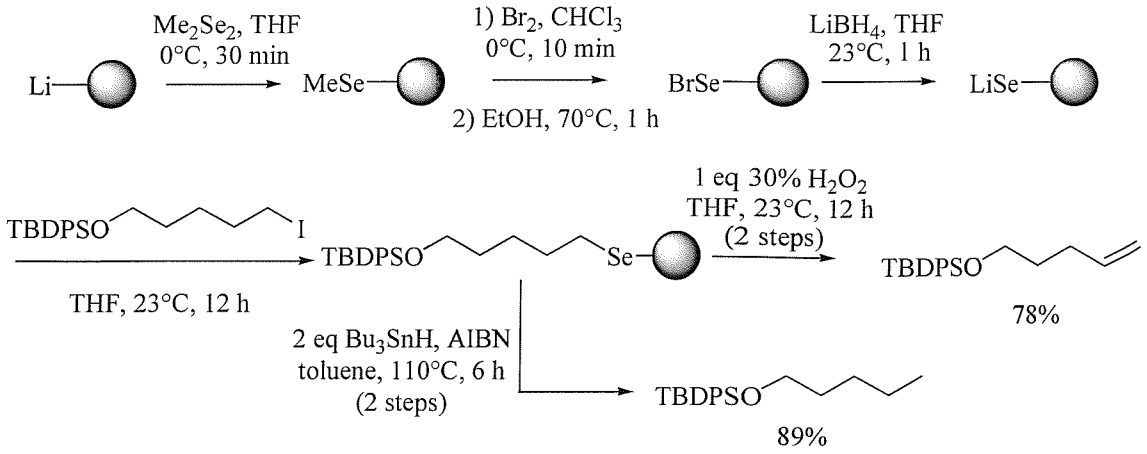


Figure 1.27: Synthesis and application of a selenoxide linker

Fujita has also described the use of polymer-supported selenium reagents to effect oxyselenenylation-deselenenylation and produce unsaturated carbonyl compounds.[74] He prepared selenocyanates by reacting Merrifield resin with potassium selenocyanate. (*E*)-4-Phenyl-3-butenoic acid was coupled to the polymer in the presence of copper (II) chloride, undergoing an intramolecular oxyselenenylation (selenolactonisation). Oxidation was achieved with *m*-CPBA at room temperature, which led to simultaneous release of the unsaturated lactone in 56% yield (from the selenocyanate) (Figure 1.28).

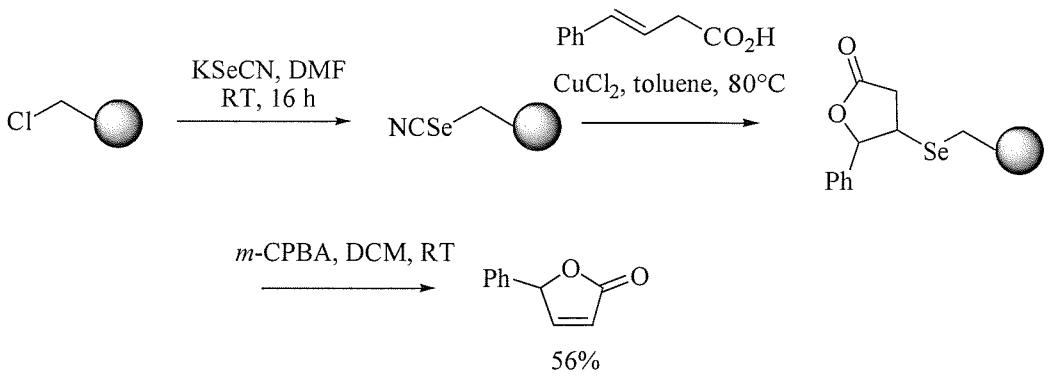


Figure 1.28: Solid-phase oxyselenenylation-deselenenylation

1.6.13 Aims

The aim of this research was to develop a safety-catch linker based on the sulfoxide/selenoxide pericyclic elimination reaction. Oxidation of the sulfide/selenide to the corresponding sulfoxide/selenoxide would constitute the activation step. Cleavage was then possible by increasing the temperature appropriately – sulfoxides usually undergo elimination at ~100°C in solution, in contrast to the selenoxide analogues which eliminate at much lower temperatures, typically around room temperature. The scope and utility of the linkers were demonstrated using a range of peptide and small organic molecules as models.

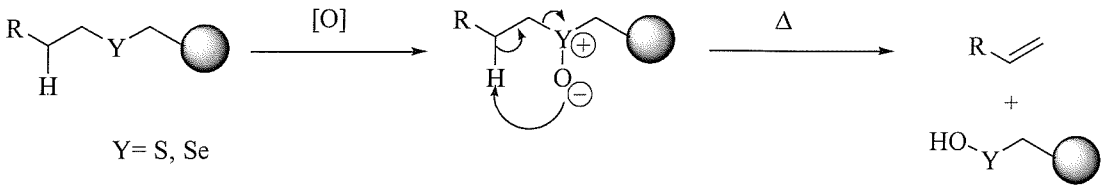


Figure 1.29: Design of a novel thermally cleavable safety-catch linker

Chapter 2: The Oxidation of Sulfides to Sulfoxides

This chapter describes the synthesis of sulfoxides from their corresponding sulfides under a range of different oxidation conditions, both in solution and then subsequently on the solid phase.

2.1 Solution Oxidation of Sulfides to Sulfoxides

Sulfoxides continue to be an important class of compound, involved in the metabolism of sulfur-containing natural products e.g. amino acids and vitamins. In addition, they are often used as intermediates in C-C bond formation reactions,[75] being used to stabilise anions at adjacent carbons. Sulfoxides are typically prepared from the corresponding sulfide by oxidation.[76] The first recorded synthesis, using nitric acid as an oxidant, was by Märcker in 1865.[77] Since then, a wide variety of reagents have been developed to effect this transformation including peroxides,[78] peracids,[79] ozone,[80] sodium metaperiodate,[81] dioxiranes,[82] nitrogen dioxide,[83] chromium trioxide,[84] manganese dioxide,[84] hypervalent iodine reagents[85,86] and sodium perborate,[87] in addition to numerous photochemical,[88] electrochemical[89] and enzymatic methods.[90,91] There is also considerable interest in the stereoselective oxidation of achiral sulfides to chiral sulfoxides[92,93] as chiral sulfoxides play an important role in asymmetric synthesis, particularly asymmetric C-C bond formation. The most frequently used methods for the oxidation of sulfides in organic synthesis are discussed in more detail below.

2.1.1 Sodium metaperiodate

Leonard and Johnson[81] first described the oxidation of a sulfide using aqueous sodium metaperiodate in 1961. The temperature was critical – at 0°C, sulfoxides were isolated in almost quantitative yields, while increasing the temperature to 60°C produced exclusively the sulfone.

In recent years, various modifications have been made to this method. Tetrabutylammonium periodate [$(n\text{-}C_4H_9)_4N^+IO_4^-$] has been used, which enabled the isolation of sulfoxides despite the raised temperature, by employing phase transfer conditions.[94] There have also been numerous examples of periodate on solid supports i.e. alumina[95] and silica[96] and on amberlyst resin.[97] Supported reagents have gained popularity in organic synthesis because of their manipulative convenience. They also allow the oxidation to be performed in organic solvents, thus increasing its scope.

By utilising sodium metaperiodate, over-oxidation to the sulfone can be avoided, providing the temperature is strictly controlled. In addition, the reaction conditions are mild and sodium metaperiodate is cheap, safe and easy to handle. The main disadvantages of this oxidation are the aqueous conditions required, which limit the generality of the method.

2.1.2 Oxone® ($KHSO_5$)

The active ingredient of Oxone® is potassium hydrogen persulfate, but it also contains potassium sulfate and potassium hydrogen sulfate. Originally used to synthesise sulfones chemoselectively,[98] the intermediate sulfoxides may be isolated by carefully controlling the oxidation conditions. Webb[99] used low temperatures, a limiting quantity of Oxone® (0.65 equivalents) and a short reaction time (5 min) to halt the oxidation at the sulfoxide oxidation state, and obtain the sulfoxides in good yields (46-99%). In a similar way, Trost[98] also isolated the sulfoxides by using a very short reaction time (2 min) and implementing a reductive work-up. Evans[100] used a phase-transfer catalyst ($Bu_4N^+Br^-$) in DCM/water (1:1) to prevent over oxidation, and in this way was able to isolate pure sulfoxides even after long reaction times (5 h).

Like sodium metaperiodate, Oxone® is commercially available and easy to use. However, it remains predominantly a method for the oxidation of sulfides to sulfones and hence the synthesis of sulfoxides requires very stringent control measures.

2.1.3 *Meta*-chloroperbenzoic acid (*m*-CPBA)

Organic peroxyacids such as *m*-CPBA are stronger oxidants than hydrogen peroxide or any of its derivatives. The effectiveness of peroxyacids as oxidants is the result of strong polarisation due to their disymmetry about the O–O bond. Overberger[79] postulated that the mechanism for these peroxyacids involved a cyclic intramolecular H-bonded species as an intermediate in the oxidation of sulfides (Figure 2.1).

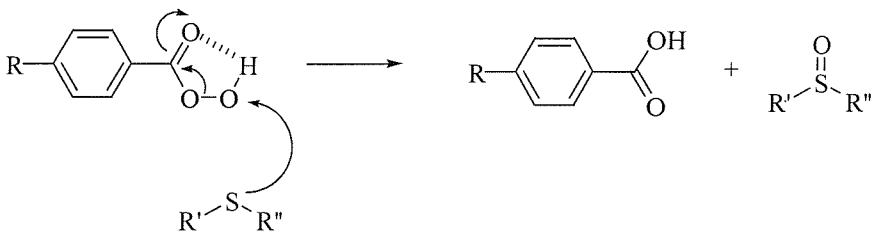


Figure 2.1: The mechanism of sulfide oxidation with m-*CPBA*

A major disadvantage of *m*-CPBA is its shock-sensitive nature. An alternative reagent for the oxidation of sulfides to sulfoxides is magnesium monoperoxyphthalate hydrate[101] (MMPP), a non-shock sensitive crystalline solid which is used stoichiometrically (Figure 2.2). The major disadvantage is its low solubility in organic solvents; hence recent reports of supported MMPP.[102,103]

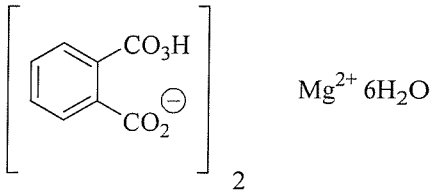


Figure 2.2: The structure of magnesium monoperoxyphthalate hydrate (MMPP)

2.1.4 Hydrogen peroxide

Hydrogen peroxide is the most widely used oxidising agent for sulfoxide synthesis. It has a low molecular weight, yet contains a high proportion of active oxygen (47% by weight). It has the advantage of being very environmentally friendly, producing only water as the oxidation by-product, and is very cheap. However, over-oxidation to the sulfone can easily occur. Gazdar[78] first utilised hydrogen peroxide when looking for a milder oxidation method than the nitric acid method used by Märcker.

The mechanism is widely thought to involve the substitution of the hydrogen atom in hydrogen peroxide with another atom e.g. a transition metal, or a group of atoms e.g. acyl group, thus forming the hydroperoxide as the active intermediate. This hydroperoxide reacts with the substrate (R) more easily than with hydrogen peroxide, if OX is a better leaving group than OH, to form the oxidised product (RO) (Figure 2.3).

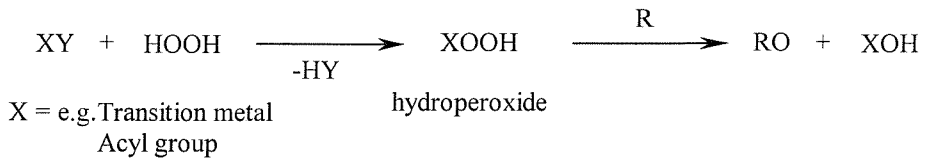


Figure 2.3: The mechanism of sulfide oxidation with hydrogen peroxide

Hydrogen peroxide is often used in conjunction with a catalyst[104] e.g. acetic or formic acids or V_2O_5, SeO_2, $TiCl_3$, TeO_2. For example, Hulea *et al.* used a titanium-zeolite catalyst to increase the reaction rate, but discovered that the oxidation with or without a catalyst was very solvent-dependent, preferring protic solvents such as

MeOH, EtOH to MeCN or THF. [105] Hydrogen peroxide is especially useful for the oxidation of hindered sulfides. Payne[106] developed the acetonitrile/hydrogen peroxide system, which at basic pH forms a peroxyimidic acid intermediate, which is a very powerful oxidising agent. Page[107] used potassium carbonate as the basic component and found that sulfoxides could be selectively formed if the temperature was maintained at 0°C.

Ravikumar *et al.* investigated the oxidation with the classical oxidising agent hydrogen peroxide using hexafluoroisopropanol (HFIP). [108] Using an excess of hydrogen peroxide (2 equivalents), they were able to ensure complete consumption of the sulfide and yet detected no sulfone. They postulated that the strong electron withdrawing nature of the trifluoro groups enabled the hydroxyl proton of the HFIP to form a hydrogen bond with the peroxide, thus activating the hydroxyl-leaving group. However, HFIP is an excellent solvent for stabilising cations, thus the positive sulfur atom could be solvated by HFIP, preventing further oxidation to the sulfone.

2.2 Solid Phase Oxidation of Sulfides

Literature on the solid phase oxidation of sulfides to sulfoxides is scarce, with only a handful of examples known. The most commonly used oxidising agent for this transformation is *m*-CPBA, which should selectively yield the sulfoxide, providing the oxidation is carried out at low temperatures (around 0°C). There are slightly more examples of the sulfide to sulfone transformation being carried out on the solid phase.

Mata[109] synthesised both the sulfoxide and sulfone derivatives of penicillins using *m*-CPBA as the oxidant. To synthesise the sulfoxide, 1.4 equivalents of *m*-CPBA were used and the temperature was kept at 0°C for the entire reaction (20 h). As could be anticipated, the sulfone was obtained using a larger excess of *m*-CPBA (5 equivalents) and an increased reaction time (96 h). Yields for the sulfoxides ranged from 66-97%, whereas the sulfones were often obtained in quantitative yield (Figure 2.4).

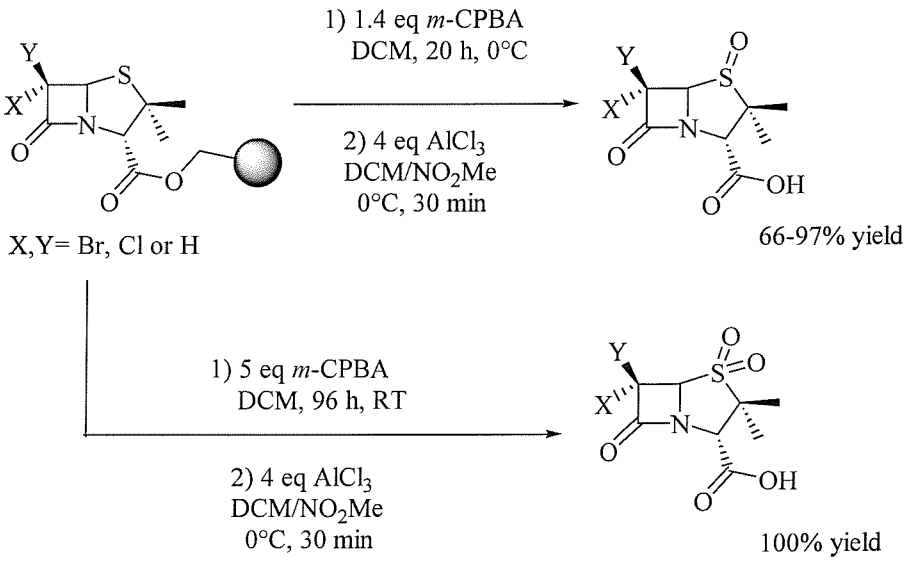
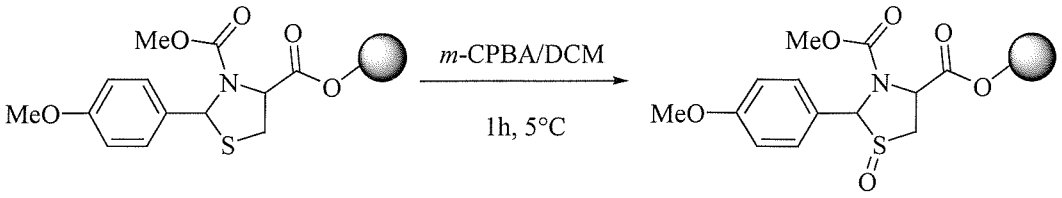


Figure 2.4: Oxidation of penicillins on the solid phase

Pátek[110] also used cold *m*-CPBA to oxidise a sulfide to a sulfoxide selectively on the solid phase (Figure 2.5). However, problems were encountered when attempting to oxidise the sulfoxide further to the sulfone. Reagents such as hydrogen peroxide in acetic acid (4 h, reflux) and 10% Na_2WO_4 in H_2O_2/H_2O/dioxane and $^{i}Pr_4N^{+}RuO_4^{-}$ /NMMO/MeCN (the latter two reagents 8 h, room temperature) failed to produce any sulfone. The reason for this was not suggested but was likely to be as a result of reagent inaccessibility on the solid phase.



Cleavage gave the sulfoxide in 94% yield (6 steps)

Figure 2.5: Oxidation of thiazolidines on the solid phase

Czarnik[111] found the oxidation of sulfide to sulfoxide on the resin to be problematic. Typically, in solution a stoichiometric amount of oxidant would be employed to avoid over-oxidation to the sulfone, but usually the ability to use a large excess of reagent and remove it easily is considered an advantage of SPOS. The problem was solved with the use of *N*-(phenylsulfonyl)-3-phenyloxaziridine, after various oxidants had been investigated. By carefully controlling the amount of reagent used and limiting the reaction time, the sulfoxide could be obtained selectively (Figure 2.6). The benzisothiazolones were then cleaved from the resin by activation with trichloroacetic anhydride, as described by Wright.[112] The same group has also used $NaBrO_2$ as an alternative oxidation method, again for the synthesis of benzisothiazolones.[113]

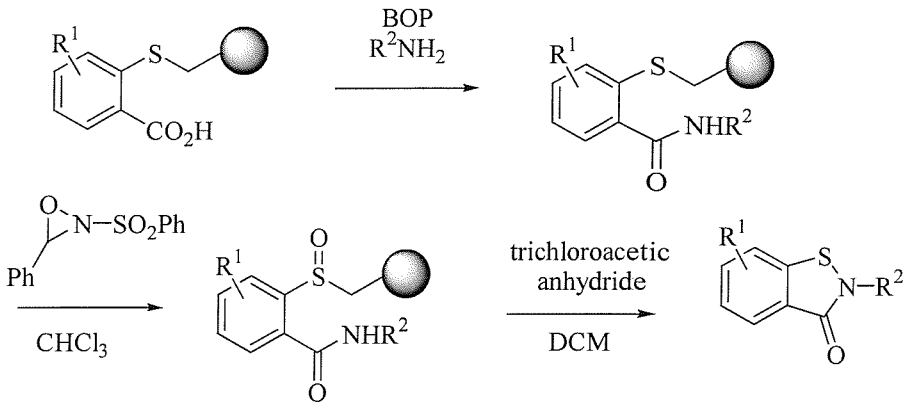
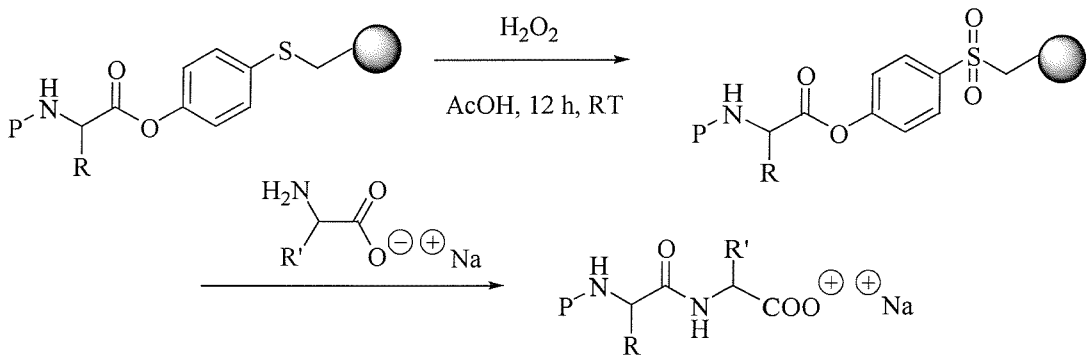


Figure 2.6: Sulfide oxidation on the resin using oxaziridine

The first example of the transformation of a sulfide being oxidised to a sulfone on the resin utilised hydrogen peroxide (Figure 2.7).[58] This oxidation converted the anchoring ester linker into an activated ester capable of acylating an amino acid and was thus used to synthesise protected peptide fragments, although later other groups observed that oxidation was not necessary.



Where P is a suitable protecting group

Figure 2.7: Oxidation of resin-bound sulfides with hydrogen peroxide

In an almost identical procedure, Marshall[114] used the same ester linker to synthesise cyclic peptides on the resin, although in this case the oxidation of sulfide to sulfone was effected with *m*-CPBA (3 equivalents) in dioxane.

A library of heterocycles was synthesised by Gayo using an excess (10 equivalents) of *m*-CPBA to oxidise a sulfide to a sulfone, which was then cleaved from the resin by nucleophilic displacement with secondary amines, to give a variety of heterocyclic products (50-93% yield) (Figure 2.8).[64] This same cleavage mechanism was also employed by Obrecht,[62] who effected the sulfide to sulfone oxidation in 15 hours at room temperature using only 3 equivalents of *m*-CPBA. In this case, the heterocyclic products were obtained in very good yields (85-90%).

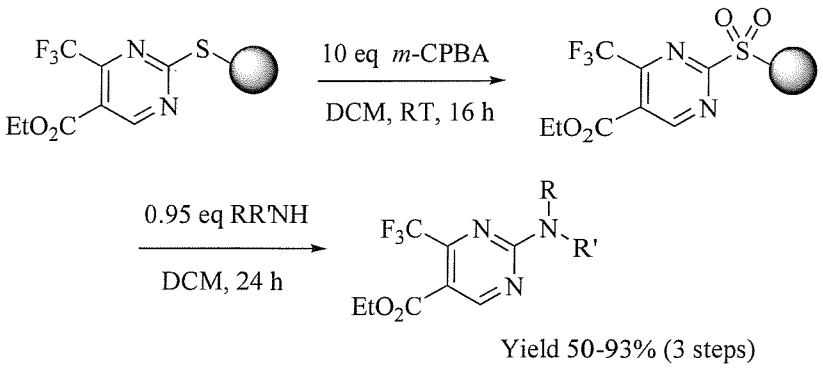


Figure 2.8: Synthesis of a resin-bound sulfone using m-*CPBA*

Another example of the use of *m*-CPBA to effect the sulfide to sulfone oxidation was by Nieuwstad.[115] In this instance, the reversible binding of sulfur dioxide to a polymer-bound 1,3-diene acceptor was being investigated (Figure 2.9).

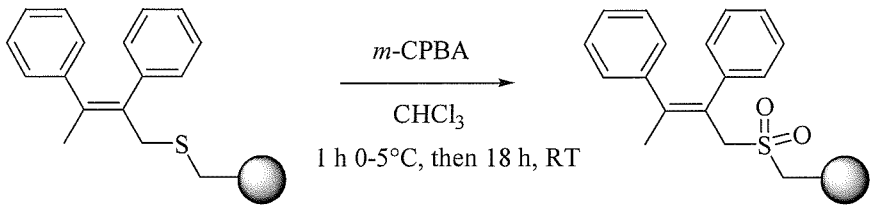


Figure 2.9: Nieuwstad used m-*CPBA to synthesise sulfones on the resin*

Similarly, Ganesan[116] used excess *m*-CPBA (10 equivalents) to effect the sulfide to sulfone transformation on the resin to synthesise a solid phase version of *p*-tolylsulfonylmethyl isocyanide, which was then used to synthesise several oxazoles (Figure 2.10).

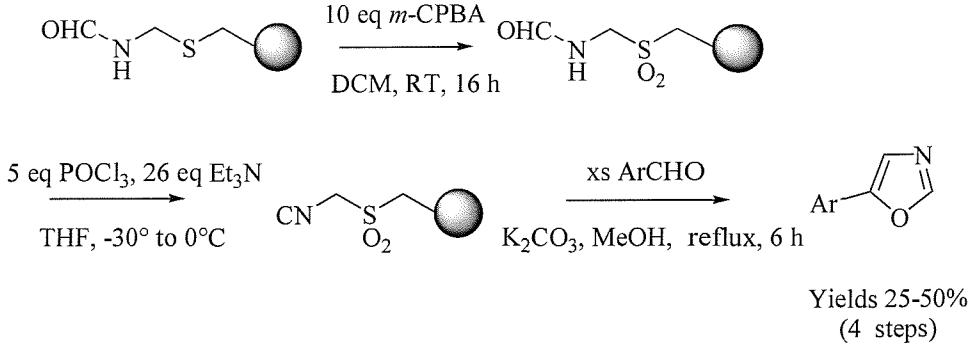


Figure 2.10: Preparation of a resin-bound sulfone for the synthesis of oxazoles

In contrast, Panek[117] achieved the same sulfide to sulfone oxidation but using milder conditions; only 2.5 equivalents *m*-CPBA in DCM for 6 h at room temperature (Figure 2.11).

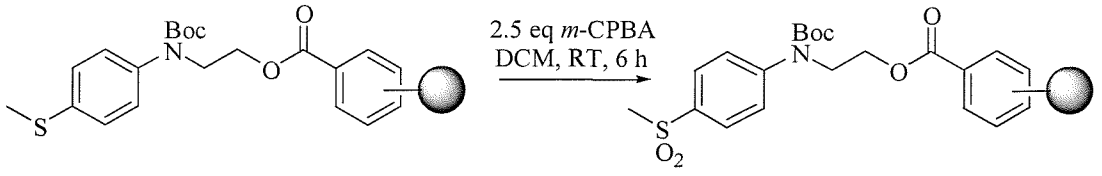


Figure 2.11: Synthesis of resin-bound sulfones using only 2.5 equivalents of m-CPBA

Alternatively, sulfones can undergo β-elimination, which provides a route for the synthesis of dehydroamino acids. Kelly-Basetti[118] used Oxone® for oxidation to the sulfone and then DBU to effect the cleavage in solution, as had been previously shown by Pyne (Figure 2.12).[119] Yamada[120] performed the analogous reactions on the solid phase, oxidising with *m*-CPBA to the sulfone and then treating the resin

with DBU to eliminate the sulfone and simultaneously release dehydroamino acids into solution.

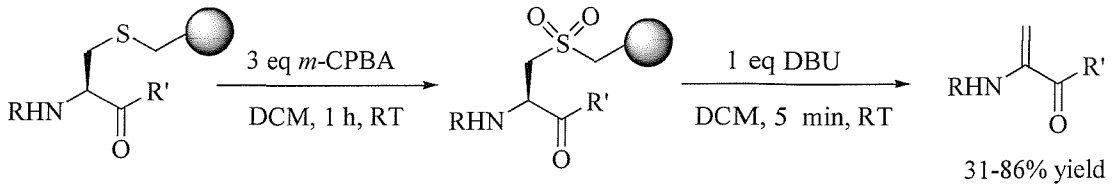


Figure 2.12: Synthesis of dehydroamino acids via *oxidation and β-elimination*

Using similar chemistry, Gosselin[121] prepared resin-bound dehydroamino acids having achieved the oxidation of sulfide to sulfone with excess *m*-CPBA (Figure 2.13). The sequence of reactions was followed using photoacoustic FTIR spectroscopy, monitoring the appearance/disappearance of the strong sulfone (O=S=O) stretch at 1140cm^{-1}.

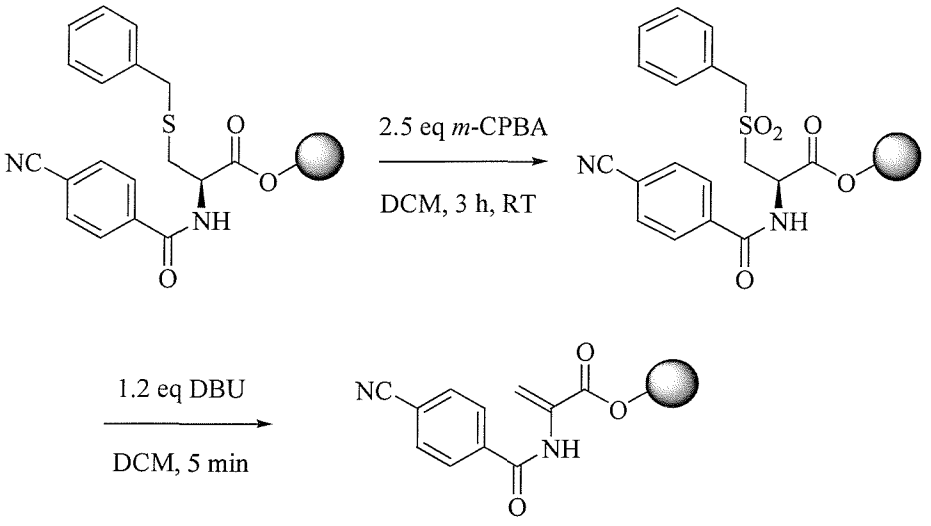


Figure 2.13: Synthesis of resin-bound dehydroamino acids

Gani described the synthesis of a new traceless linker based on an aryl vinyl sulfone.[122] Oxidation of the sulfide to the sulfone on the resin was achieved using either an excess of *m*-CPBA or an excess of Oxone® (Figure 2.14). The same oxidation conditions (excess *m*-CPBA in DCM) have also been used by Barco[123] to

synthesise substituted piperidin-4-one derivatives in around 75% yield, *via* displacement of the resin-bound sulfone with benzylamine.

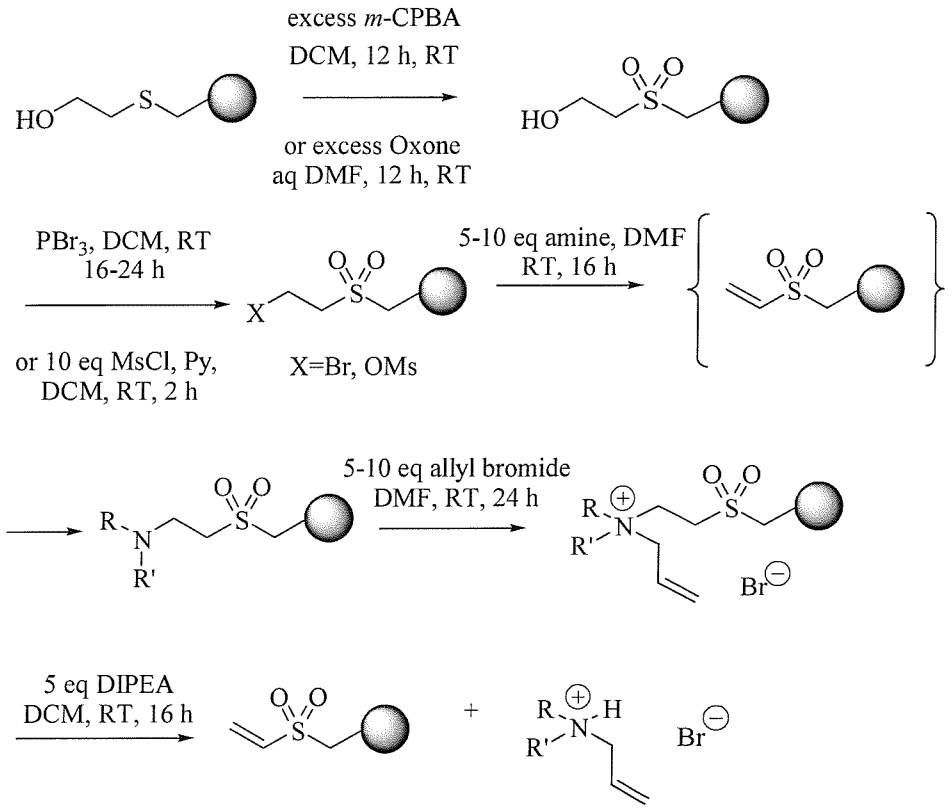


Figure 2.14: Synthesis of a traceless linker using excess Oxone® or m-*CPBA to oxidise the sulfide to the sulfone*

Aqueous Oxone® (4 equivalents) has also been used to effect this transformation on soluble PEG polymers.[124] The sulfone was then cleaved in a traceless manner using Na-Hg to give the alkyl product (Figure 2.15).

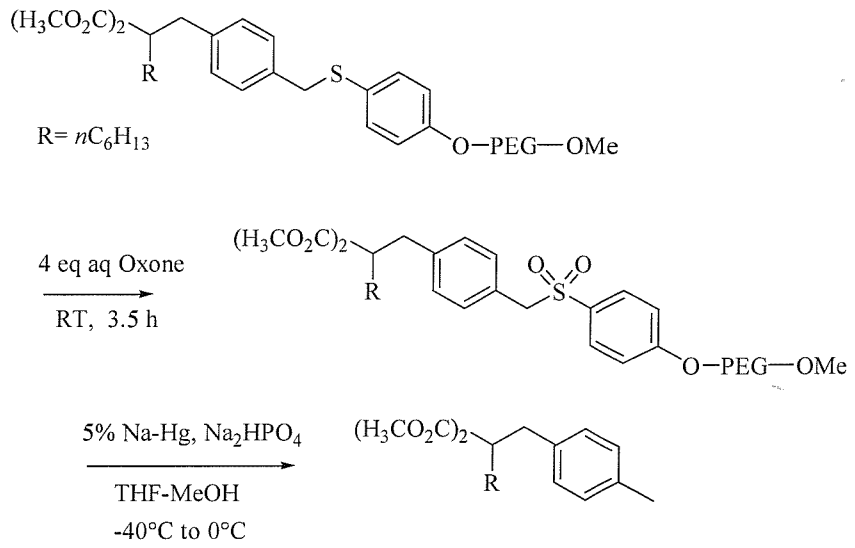


Figure 2.15: Oxidation of the sulfide to the sulfone releases the safety-catch and activates the linker for subsequent reductive cleavage

Jiang[125] demonstrated the same cleavage strategy for oligosaccharide synthesis, but chose to oxidise the sulfide using dioxirane instead of Oxone® (Figure 2.16).

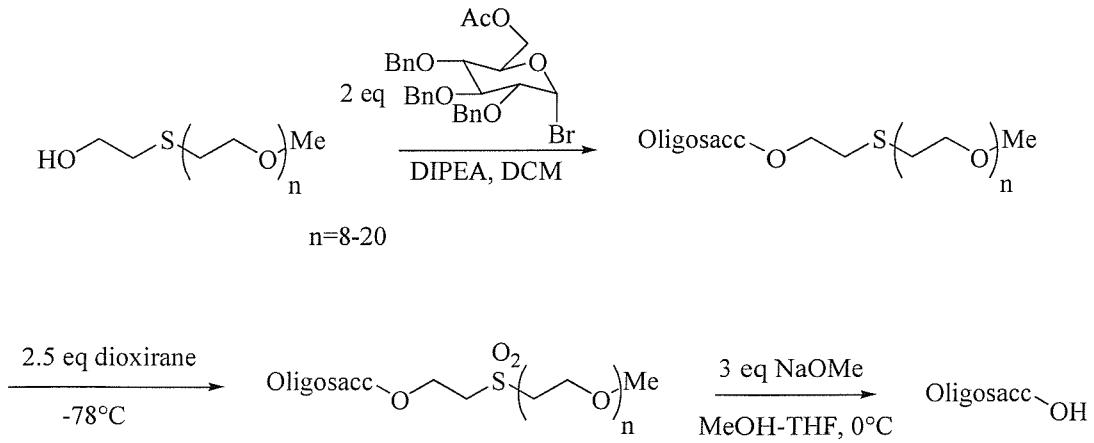


Figure 2.16: Synthesis of oligosaccharides on soluble PEG polymers

2.3 Results and Discussion

2.3.1 Oxidation of sulfides with sodium metaperiodate in solution

The oxidation of a sulfide to its corresponding sulfoxide was crucial to the implementation of the safety-catch linker, which was to be based upon the sulfoxide/selenoxide pericyclic elimination reaction. It was critical that this oxidation step occurred in quantitative yield, allowing subsequent thermal elimination to proceed quantitatively.

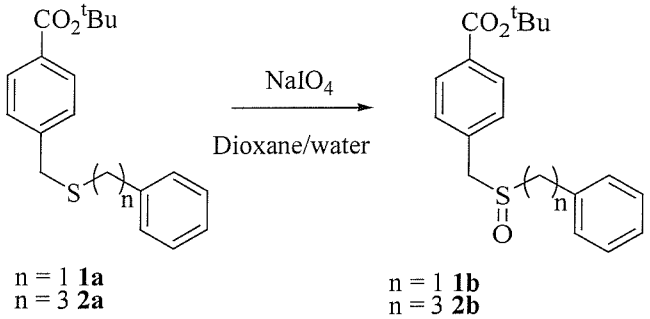


Figure 2.17: The oxidation of benzylic sulfides with sodium metaperiodate

Initially, the oxidation was effected using sodium metaperiodate (Figure 2.17). The substrate chosen to test the oxidation procedure was *tert*-butyl 4-[(phenylmethylthio)methyl]benzoate (**1a**). Four different reaction conditions were evaluated (see Table 2.1).

Method A was attempted using 1.1 equivalents of sodium metaperiodate. Although the reaction appeared complete after 18 hours, NMR showed residual sulfide (approximately 8% by integration).

Method	Reaction Time/h	Equivalents of $NaIO_4$	Temperature/°C (after initial cold addition)	% Yield (**1b**)	% Sulfide remaining (NMR integration)
A	18	1.1	RT	90	8
B	5.5	1.1	40	70	<1
C	5.5	1.2	RT	78	14
D	4	1.2	40	91	0

Table 2.1: A comparison of different reaction conditions for the sodium metaperiodate oxidation of benzylic sulfides

Three reactions were carried out in parallel to investigate the best way to increase the yield of the oxidation – Method B involved using 1.1 equivalents of $NaIO_4$ and warming to 40°C, whereas Method C used a larger excess of the oxidant (1.2 equivalents) but was carried out at room temperature. Method D used an excess of $NaIO_4$ in addition to warming the reaction at 40°C. After 10 min at 0°C, Method C was warmed up slowly as before. Both Methods B and C were worked-up after 5.5 hours, but Method D was deemed complete (TLC) after only 4 hours.

Method B was slightly lower yielding (70% compared to 78% for Method C), but the product showed very little sulfide contamination by NMR, compared to Method C which had approximately 14% sulfide remaining (by integration). Method D gave excellent results – a very high yield of the sulfoxide (**1b**) (91%) and yet no contamination from unreacted sulfide or indeed any visible over-oxidation products (Table 2.1).

The two best methods, Methods B and D, were then applied to an alternative sulfide, *tert*-butyl 4-[(3-phenylpropylthio)methyl]benzoate (**2a**) to ensure the oxidation was compatible with other substrates. Method B, using less oxidant, resulted in a yield of 80% of the sulfoxide, but it was contaminated with approximately 11% of the starting sulfide. Method D required an increased reaction time of 6 hours to reach completion (TLC), but after work-up more than one product was observed.

Chromatography allowed the purification and identification of these products and resulted in the isolation of the *tert*-butyl 4-{[(3-phenylpropyl)sulfinyl]methyl}benzoate (**2b**) (56%) but also the corresponding sulfone (15%).

It was necessary for the oxidation to proceed cleanly and homogeneously so that the reaction might be transferred to the solid phase and hence an alternative oxidation method was sought.

2.3.2 A comparison between $NaIO_4$ and H_2O_2 for the oxidation of sulfides in solution

The oxidation was thus effected using hydrogen peroxide in hexafluoroisopropanol (HFIP) as described by Ravikumar[108] and compared to the sodium metaperiodate method using two sulfide substrates – phenyl 3-phenylpropylsulfide (**3a**) and *tert*-butyl 4-[(2-methyl-1-oxoindan-2-ylthio)methyl]benzoate (**4a**) (Figure 2.18, Table 2.2).

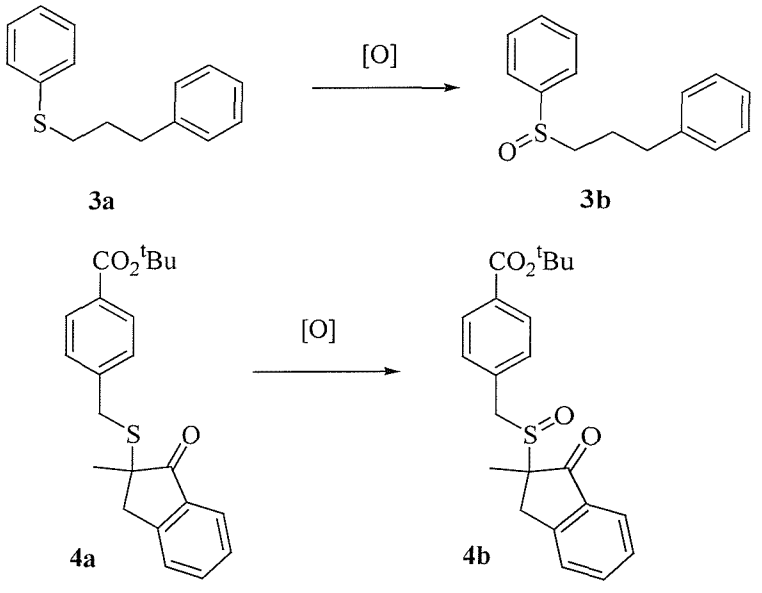


Figure 2.18: Oxidation of the phenylsulfide and indanone substrates using either sodium metaperiodate or hydrogen peroxide

Substrate	Oxidation Method	Temperature/°C	Time/h	Isolated Yield/%
Phenyl 3-phenylpropyl sulfide (**3a**)	$NaIO_4$/ Dioxane: water	1) RT 2) 40°C	1) 2 h 2) 4 h	62
	H_2O_2/ HFIP	RT	1.5	82
tert-butyl 4-[(2-methyl-1-oxoindan-2-ylthio)methyl]benzoate (**4a**)	$NaIO_4$/ Dioxane: water	RT	6	50
	H_2O_2/ HFIP	RT	1.5	84

Table 2.2: A comparison between sodium metaperiodate and hydrogen peroxide oxidation methods

These results clearly showed the advantages in using the H_2O_2/HFIP method –the sulfoxide was obtained quickly, selectively, in high yield using mild and totally homogeneous reaction conditions.

2.3.3 Use of HFIP/H_2O_2 method for further sulfide oxidations

A further substrate was oxidised, phenylmethyl 2-[4-(acetylamino)phenylthio]acetate (**7a**), using a resin attachment point mimic (amide) with the aim of transferring the oxidation onto the solid phase. The sulfide was prepared from 4-acetamidothiophenol (**6**), which was alkylated with benzyl bromoacetate (**5**) using caesium carbonate in DMF, which gave the sulfide (**7a**) in 40% yield. The oxidation was effected using the HFIP method, which gave the sulfoxide (**7b**) in 92% yield after only 1 hour at room temperature (Figure 2.19).

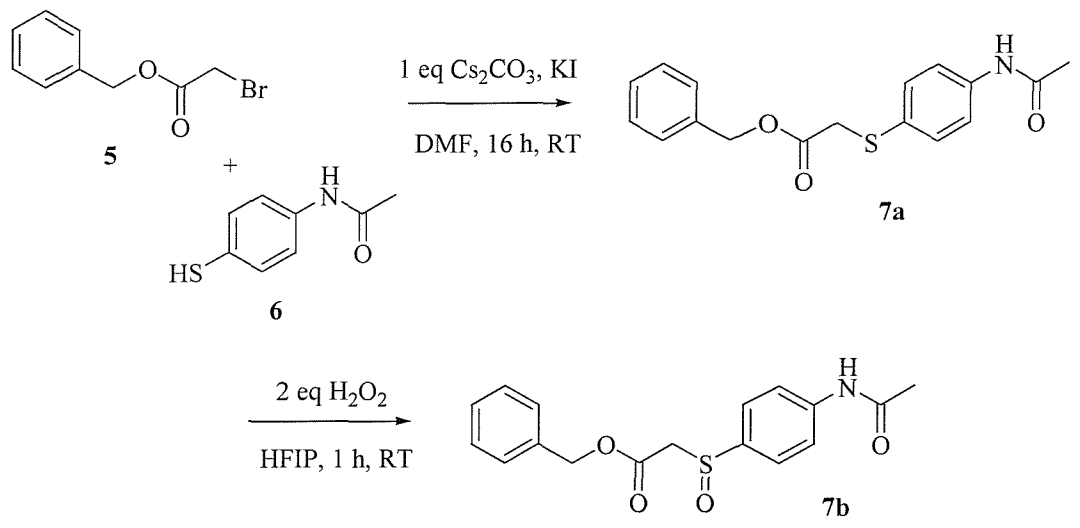


Figure 2.19: Synthesis of a solution model for the solid phase oxidation of sulfides

2.3.4 Effect of solvent and acid on the hydrogen peroxide oxidation of sulfides

Drabowicz[126] demonstrated that sterically hindered sulfides were easily oxidised to the corresponding sulfoxides using hydrogen peroxide in isopropanol with sulfuric acid as a catalyst. Given the similarity of this method to the HFIP one, it was decided to compare the two oxidation methods. It was postulated that perhaps the HFIP oxidation was successful due to its intrinsic acidity, thus it simply catalysed the reaction.

The same sulfide substrate as above was used, phenylmethyl 2-[4-(acetylamino)phenylthio]acetate (**7a**). The sulfone (**7c**) was prepared from the sulfide (**7a**) using Oxone® (3 equivalents in aqueous MeOH), as an HPLC standard. RP HPLC was used to compare the relative proportions of sulfide, sulfoxide and sulfone during the oxidation reactions. The retention times were as follows: sulfide (**7a**) 15.3 min, sulfoxide (**7b**) 12.3 min and sulfone (**7c**) 13.9 min.

Three oxidation reactions were carried out; all employed two equivalents of hydrogen peroxide as the oxidant, but used different solvent systems – Reaction A: HFIP (1 mL), Reaction B: ^{i}PrOH (1 mL) and Reaction C: ^{i}PrOH (1 mL) together with catalytic conc. H_2SO_4. The sulfide (**7a**) was dissolved in the appropriate solvent for 15 min at room temperature, before the addition of the hydrogen peroxide. The

reactions were then monitored by TLC and quantified by RP HPLC over a 24 hour time period (Table 2.3).

Time/h	% sulfide, sulfoxide and sulfone in the reaction mixture by RP HPLC at 254nm*								
	Reaction A (HFIP)			**Reaction B (^{i}PrOH)**			**Reaction C (^{i}PrOH and catalytic H^{+})**		
	S	**SO**	SO_2	S	SO	SO_2	S	SO	SO_2
1	6	**86**	2	82	14	1.5	4	83	0
2.5	0	**93**	1.5	65	26	9	0	78	9
7	0	**94**	2	59	27	11	0	61	19
24 (isolated)	0	**97**	0	70	30	0	0	40	31

* Only relative proportions of the sulfide, sulfoxide and sulfone were considered; other impurities were disregarded.

Table 2.3: The relative proportions of sulfide, sulfoxide and sulfone present during oxidation reaction as determined by RP HPLC at 254 nm

From the table above, it can be seen that Reaction A, using HFIP as the solvent, was the most efficient reaction, with over 90% of the sulfoxide formed in 2.5 hours, compared with just 26% (Reaction B) and 78% (Reaction C). The use of HFIP also gave the cleanest reaction with less than 2.5% of the over-oxidised sulfone detected. In fact, the sulfone was not detected at all following aqueous work-up. The addition of catalytic acid (Reaction C) clearly had an effect on the rate of the oxidation reaction. For example, without the acid (B), only 14% of the sulfoxide was detected after 1 hour, yet in Reaction B, this figure was 83%.

The best results were achieved using HFIP as the solvent. Its effectiveness was probably due, at least in part, to its innate acidity (pK_a = 9.30 HFIP in water, compared to pK_a ~ 17 isopropanol). These results showed that HFIP was still the

solvent of choice over acidic ^{i}PrOH due to the large proportion of sulfone formed in Reaction C over longer periods.

In summary, the hydrogen peroxide/HFIP method provides a much cleaner route to sulfoxides than sodium metaperiodate. The oxidation was achieved at room temperature and yet the reaction time was shorter. Purification by flash chromatography was still necessary to obtain completely pure sulfoxides, but the HFIP oxidation was much cleaner than both the hydrogen peroxide in acidic isopropanol and the sodium metaperiodate oxidation. More importantly, no sulfone was detected during the hydrogen peroxide/HFIP oxidation.

It was for these reasons that the hydrogen peroxide/HFIP oxidation was chosen as the oxidation method of choice to be transferred to the solid phase.

2.3.5 HFIP/H_2O_2 oxidation method on the solid phase

Commercially available 4-(methylthio)benzoic acid (**12**) was the model chosen to investigate the use of the hydrogen peroxide/HFIP method for a resin-bound sulfide. Aminomethyl resin (**8**) was synthesised from the commercially available chloromethyl resin using the standard procedure.[127] Then 4-hydroxymethylphenoxyacetic acid (HMPA) (**9**) (a Wang-type linker) was attached to the resin (**8**) *via* amide bond formation using standard DIC/HOBt[128] coupling conditions and then Fmoc-Gly-OH was esterified to the resin-bound Wang linker (**10**), similarly using standard DIC/DMAP reaction conditions.[129] Following Fmoc deprotection with 20% piperidine in DMF, 4-(methylthio)benzoic acid (**12**) was coupled to the resin (**11**) *via* an amide bond using standard DIC/HOBt coupling conditions. A portion of this resin (**13a**) (100 mg) was then subjected to a mixture of 95% TFA/2.5% water/2.5% TIS to cleave the Wang linker and release the unmodified sulfide as a conjugate with glycine (**14a**). This enabled the starting sulfide (**14a**) to be characterised and used as a control before the oxidation reaction was attempted (Figure 2.20).

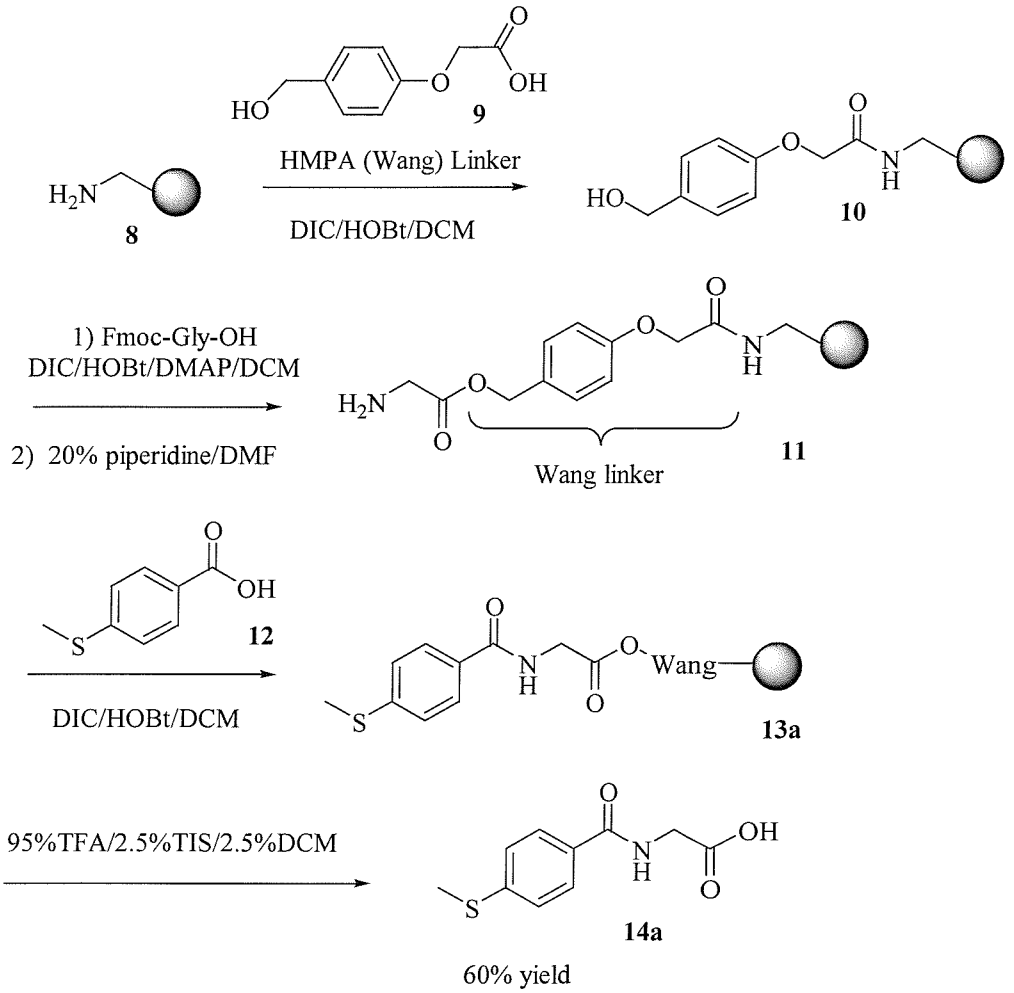


Figure 2.20: Synthesis of a model sulfide for solid phase oxidation trials

The oxidation was then effected with hydrogen peroxide and HFIP as before. The resin (**13a**) was initially swollen in DCM before the HFIP was added as the solvent (approx. 1 mL per 100 mg resin was used), followed by the hydrogen peroxide. The reaction was then shaken at room temperature for four hours. At this time, the resin (**13b**) was thoroughly washed and then a portion (250 mg) cleaved as above. RP HPLC and subsequent MS analysis showed the sulfoxide (**14b**) had been obtained (86% yield over three steps) (Figure 2.21).

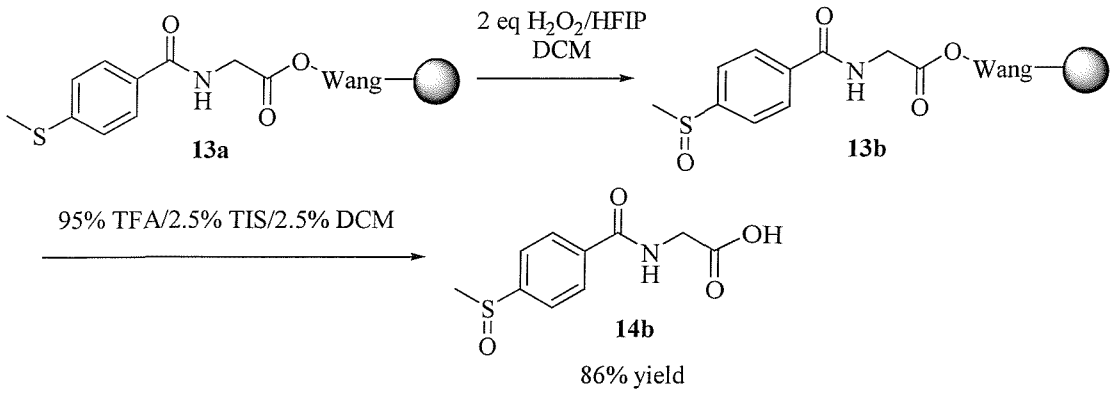


Figure 2.21: Oxidation of a resin-bound sulfide with H_2O_2/HFIP

This model reaction proved that the hydrogen peroxide in HFIP oxidation method was easily adaptable for the solid phase oxidation of sulfides selectively to the corresponding sulfoxides.

2.3.6 Solid phase HFIP/H_2O_2 oxidation monitored by gel phase ^{13}C NMR

The H_2O_2/HFIP oxidation was then attempted on the solid phase using the previously utilised 4-acetamidothiophenol (**6**). To solve the problem of monitoring the oxidation reaction on the resin, a ^{13}C-enriched building block, bromoacetic-2-^{13}C acid, was introduced. Thus, the resin oxidation reaction was monitored by the change in chemical shift using routine ^{13}C gel phase NMR.

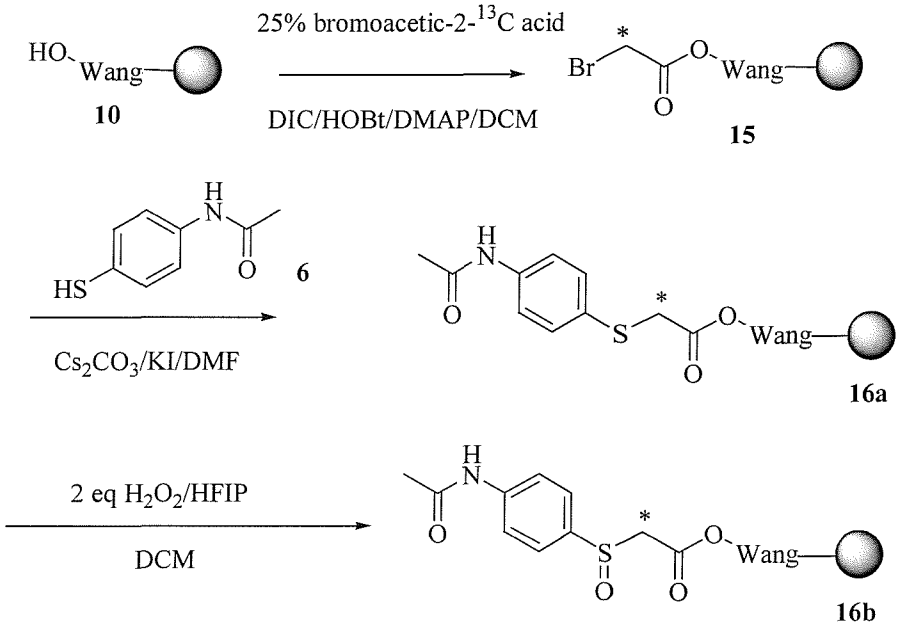


Figure 2.22: Synthesis of a resin-bound sulfoxide, monitored by gel phase ^{13}C NMR

Polystyrene aminomethyl resin (**8**) was reacted with the Wang linker (**9**) under standard DIC/HOBt coupling conditions to give resin-bound linker (**10**). Esterification with 25% bromoacetic-2-^{13}C-acid was then accomplished using DIC/DMAP/HOBt. Gel phase ^{13}C NMR at this stage clearly showed the enriched carbon to have a chemical shift of 26.0 ppm (**15**). Excess 4-acetamidothiophenol (**6**) (5 equivalents) was used to displace the resin-bound bromide, in a reaction analogous to the earlier solution phase preparation of the sulfide (Figure 2.22). Gel phase ^{13}C NMR of the resin (**16a**) showed the enriched ^{13}C to have moved downfield to 37.7 ppm. No peak was visible at 26.0 ppm; thus the alkylation had proceeded quantitatively (Figure 2.23).

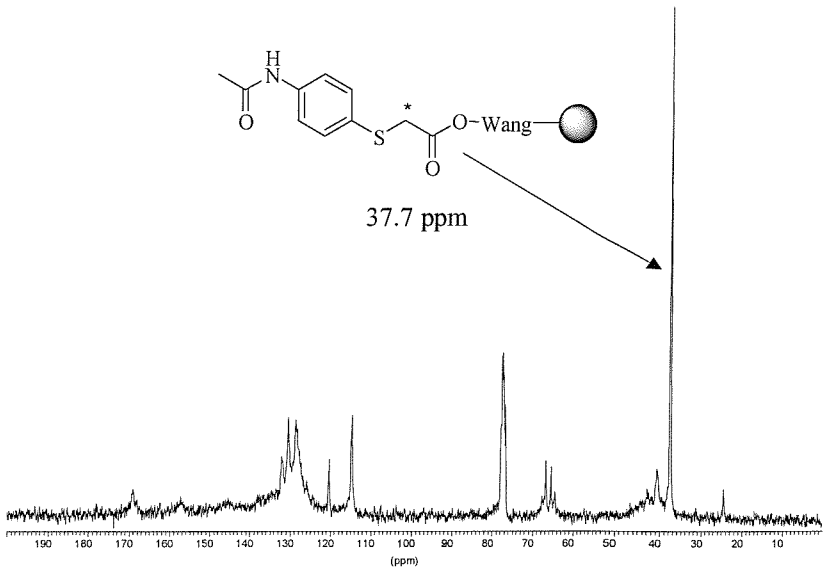


*Figure 2.23: Gel phase ^{13}C NMR (75 MHz, $CDCl_3$) of the resin-bound sulfide (**16a**) (NS=512)*

Sulfide (**16a**) was then oxidised as previously described. After the resin had been thoroughly washed and dried, a gel phase ^{13}C NMR was obtained of the resin (**16b**). This clearly showed the major enriched peak to have shifted significantly downfield to 62.7 ppm (Figure 2.24). This was in good agreement with the solution analogue (**7b**) (61.6 ppm) and, more importantly, no signal corresponding to unreacted sulfide was observed. Unfortunately, the solution studies showed that the enriched carbon of the sulfoxide (**7b**) and the sulfone (**7c**) had very similar chemical shifts (61.6 ppm and 61.5 ppm respectively). Therefore, the product from the H_2O_2/HFIP oxidation reaction was cleaved as before and analysed by RP HPLC and MS, which confirmed the only product was the sulfoxide (**17b**) (Figures 2.25 and 2.26).

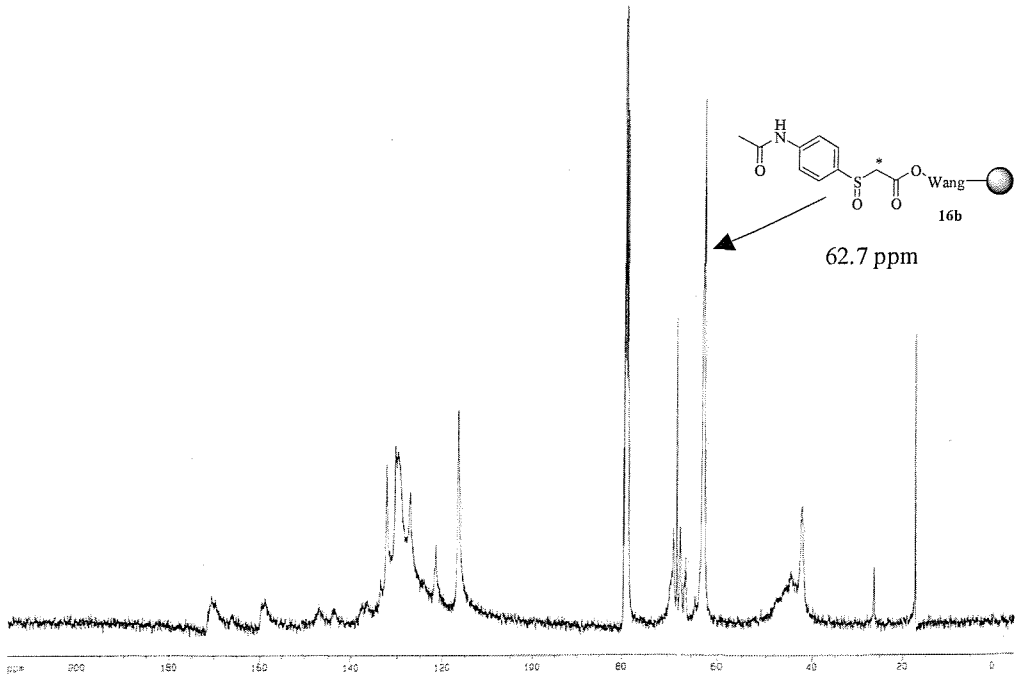


*Figure 2.24: Gel phase ^{13}C NMR (100 MHz, $CDCl_3$) of the resin-bound sulfoxide **(16b)** (NS=6144)*

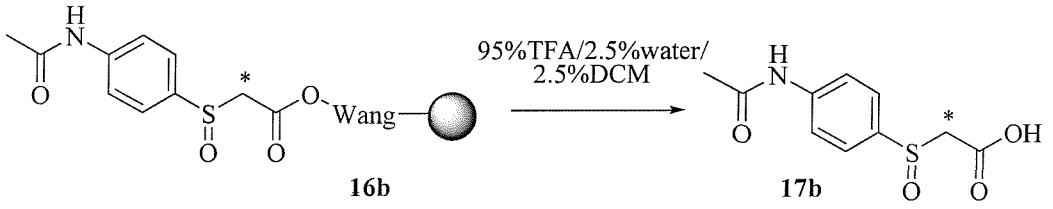


Figure 2.25: Cleavage of the sulfoxide from the resin

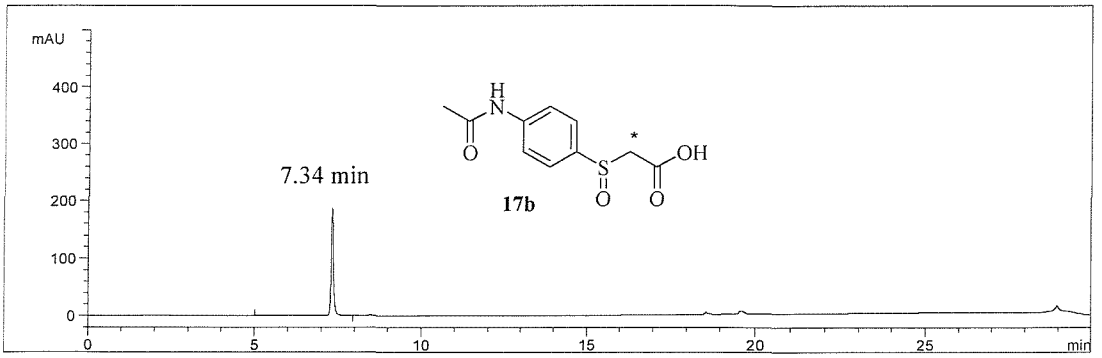


*Figure 2.26: RP HPLC spectrum of 2-{[4-(acetylamino)phenyl]sulfinyl}acetic acid **(17b)** after cleavage from the resin*

2.3.7 Monitoring the oxidation using non-enriched substrates

Enriched ^{13}C building blocks have been shown to be very useful for monitoring solid phase reactions by ^{13}C NMR, however, these chemicals are expensive and limit the chemistry that can be carried out. It was therefore decided to investigate gel phase ^{13}C NMR for non-enriched substances to see if the oxidation reaction could still be monitored in this way. The indanone substrate (**4a**), which had previously been oxidised in solution with both sodium metaperiodate and the novel hydrogen peroxide/HFIP method, was chosen as a model (Figure 2.27).

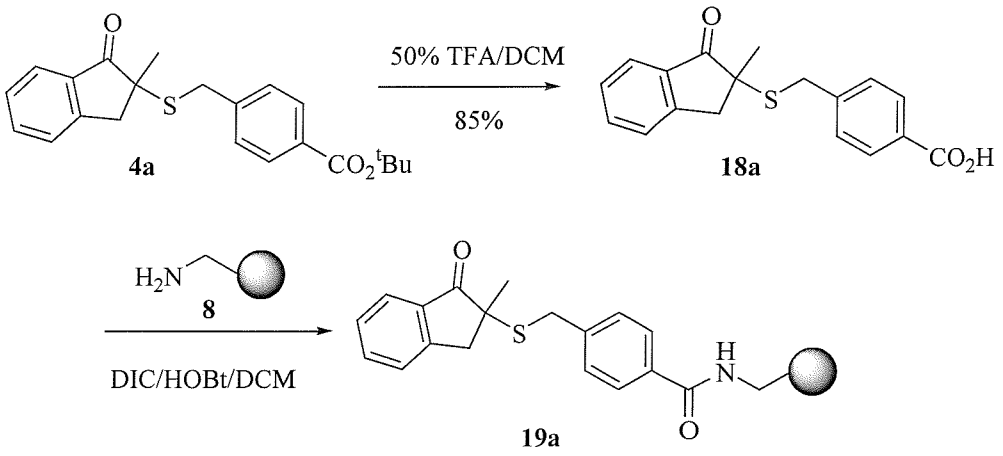


Figure 2.27: Synthesis of a resin-bound indanone

The *tert*-butyl ester was removed from (**4a**) by treatment with 50% TFA/DCM for 2 hours at room temperature to give the free acid (**18a**) in 85% yield. This acid was coupled to aminomethyl polystyrene resin (**8**) with DIC/HOBt. A gel phase ^{13}C NMR spectrum was obtained for the resin-bound sulfide (**19a**). Obviously, the number of scans required was significantly increased compared to the samples which used enriched building blocks, but the spectrum (Figure 2.29) obtained after 5 hours, gave good correlation with the solution spectrum obtained previously.

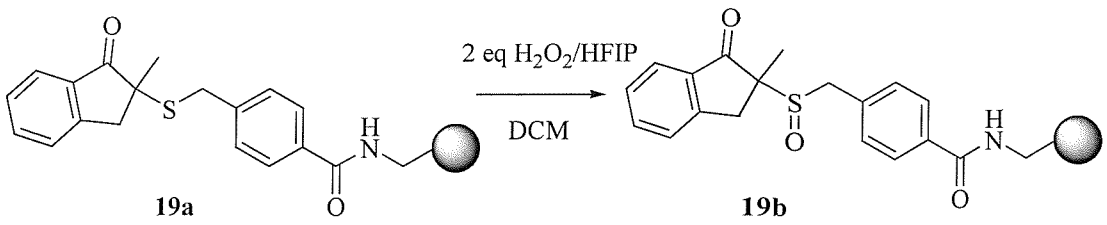


Figure 2.28: Oxidation of a resin-bound indanone

The resin-bound sulfide (**19a**) was oxidised as before (Figure 2.28) and analysed by gel phase ^{13}C NMR (Figure 2.30). The shift of the benzylic methylene was clearly visible from 34 ppm (sulfide) to 66 ppm in the resin-bound sulfoxide (**19b**). No starting material was visible; therefore the oxidation had occurred in over 90% yield. The NMR spectrum was compared with that of the sulfoxide indanone in solution (**4b**) and found to be in good agreement. The methyl group (^{9}C) had two signals (at 13 and 17 ppm) as a result of the diastereomers produced, indicating that only the sulfoxide had been formed (Figure 2.30).

No linker was used in this instance, so cleavage and analysis of products was impossible. However, the success of the hydrogen peroxide/HFIP oxidation reaction was further confirmed by the subsequent pericyclic elimination of the indanone (Chapter 3) which would only have been possible if the sulfoxide had been formed.

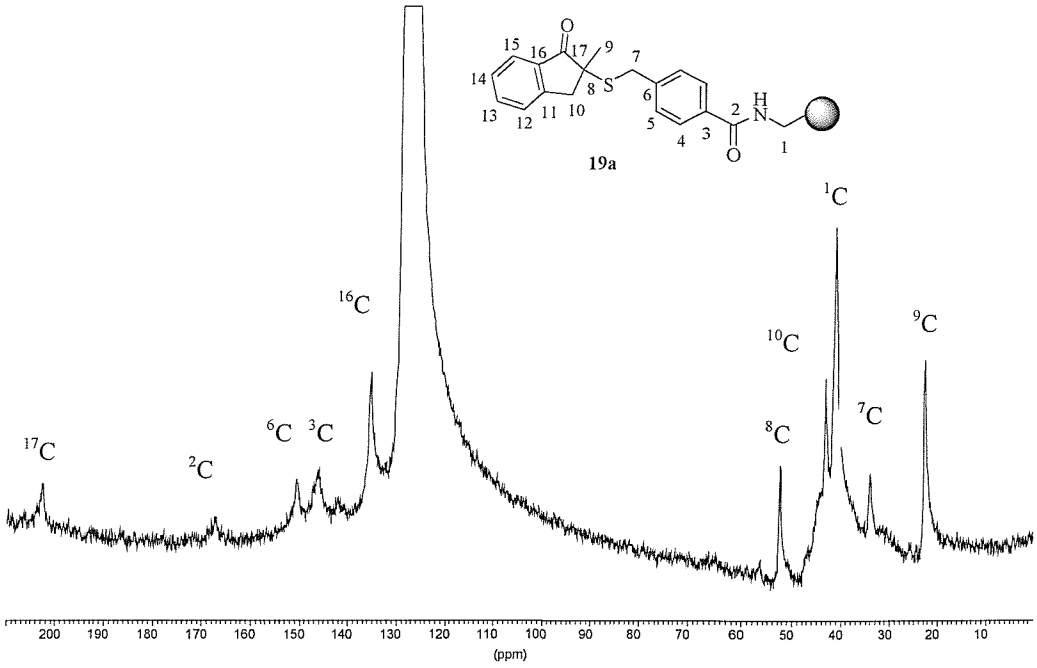


*Figure 2.29: Gel phase ^{13}C NMR (100 MHz, C_6D_6) of the resin-bound sulfide (**19a**) (NS = 37470)*

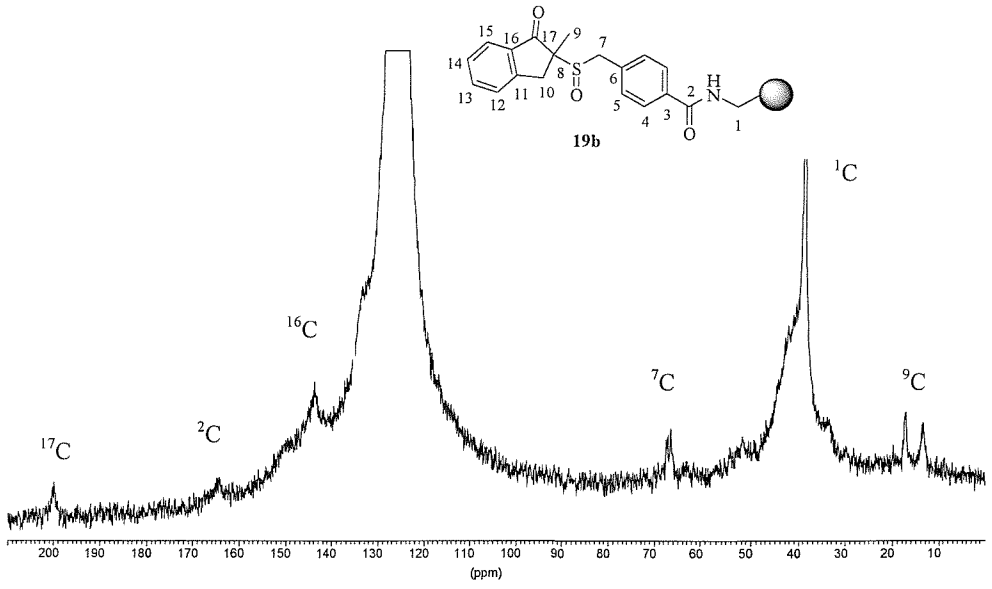


*Figure 2.30: Gel phase ^{13}C NMR (100 MHz, C_6D_6) of the resin-bound sulfoxide (**19b**) (NS=29750)*

2.3.8 Applications

2.3.8.1 Heterocycles

Pyrimidine heterocycle (**20a**) (Figure 2.31) was synthesised on aminomethyl polystyrene resin using the Rink amide linker by another member of the research group.[130] In this instance, it was used to demonstrate the applicability of the novel hydrogen peroxide/HFIP oxidation method to a wide range of chemistries.

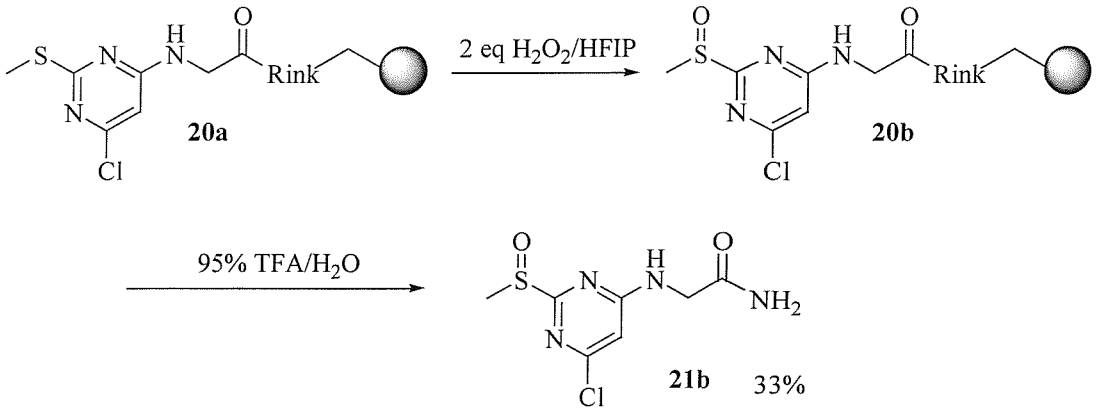


Figure 2.31: The oxidation of a pyrimidine heterocycle on the solid phase

Resin-bound sulfide (**20a**) (10 mg) was cleaved with 95% TFA/5% water to provide a standard sulfide (**21a**) for HPLC. Resin-bound sulfide (**20a**) was then oxidised using excess hydrogen peroxide in HFIP. The oxidation was shaken for 4 hours at room temperature and then the resin (**20b**) washed thoroughly. The Rink amide linker was cleaved with 95% TFA/5% water and the cleaved material analysed by RP HPLC and mass spectroscopy. HPLC showed only sulfoxide (**21b**) and sulfide (**21a**). No sulfone was detected (Figure 2.32).

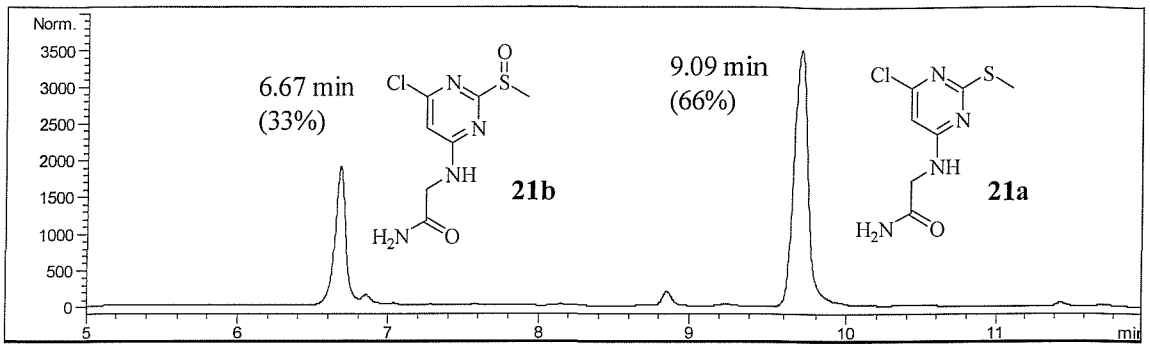


Figure 2.32: The RP HPLC spectrum showing oxidation of the pyrimidine heterocycle

2.3.8.2 Dehydroamino acids

Previous work in the research group[131] has demonstrated the synthesis of dehydroamino acids *via* the oxidation of a sulfide with sodium metaperiodate and then subsequent basic elimination (DBU). Current work is in progress to investigate the use of the H_2O_2/HFIP oxidation method in this synthesis (Figure 2.33).[132]

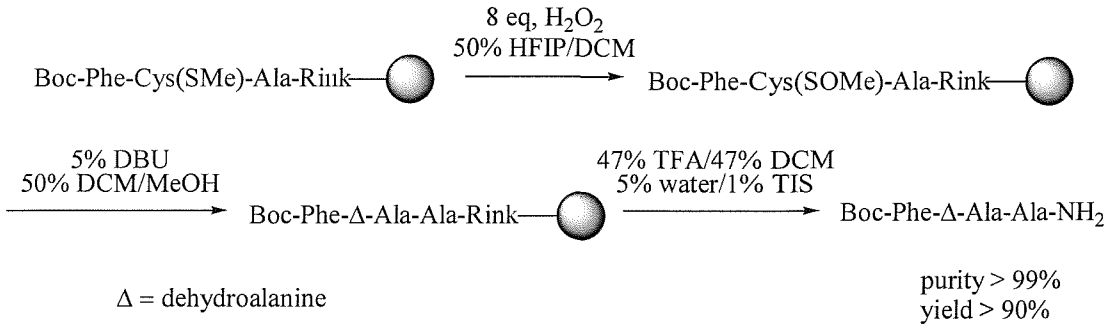


Figure 2.33: Synthesis of dehydroamino acids using HFIP/H_2O_2 oxidation step

2.3.8.3 Penicillins

Penicillins remain an interesting class of biologically active molecule, with continuing interest in their synthesis both in solution and on the resin. It is for this reason that the H_2O_2/HFIP oxidation method has been applied to the synthesis of penicillin sulfoxides. Penicillin G was attached to Merrifield resin by reflux with KF in DMF over 24 hours. [109] ATR FT-IR was used to monitor the reaction and showed the presence of two carbonyl stretches at 1784 and 1747 cm^{-1}, in agreement with

previous studies by Mata[109] and indicative of the penicillin β-lactam ring system (Figure 2.34). Gel phase ^{13}C NMR confirmed the reaction was successful (Figure 2.35).

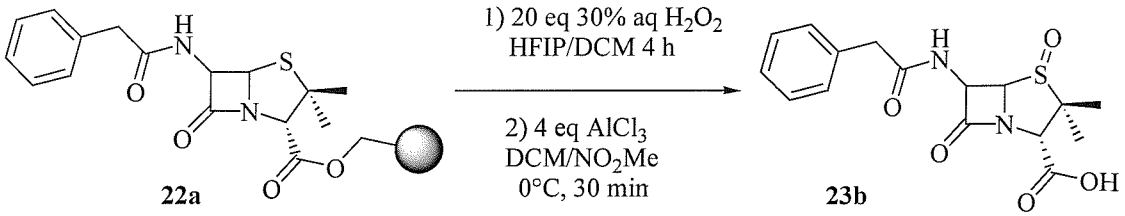


Figure 2.34: Solid phase oxidation of penicillin G using the H_2O_2/HFIP method

Oxidation was then effected as before using H_2O_2/HFIP. However, a very large excess (20 equivalents) of the oxidant was required to ensure the oxidation went to completion. The oxidation was monitored by gel phase ^{13}C NMR; the methyl groups shifted significantly from 27 and 32 ppm to 18 and 19 ppm as the sulfoxide was formed (Figures 2.35 and 2.36).

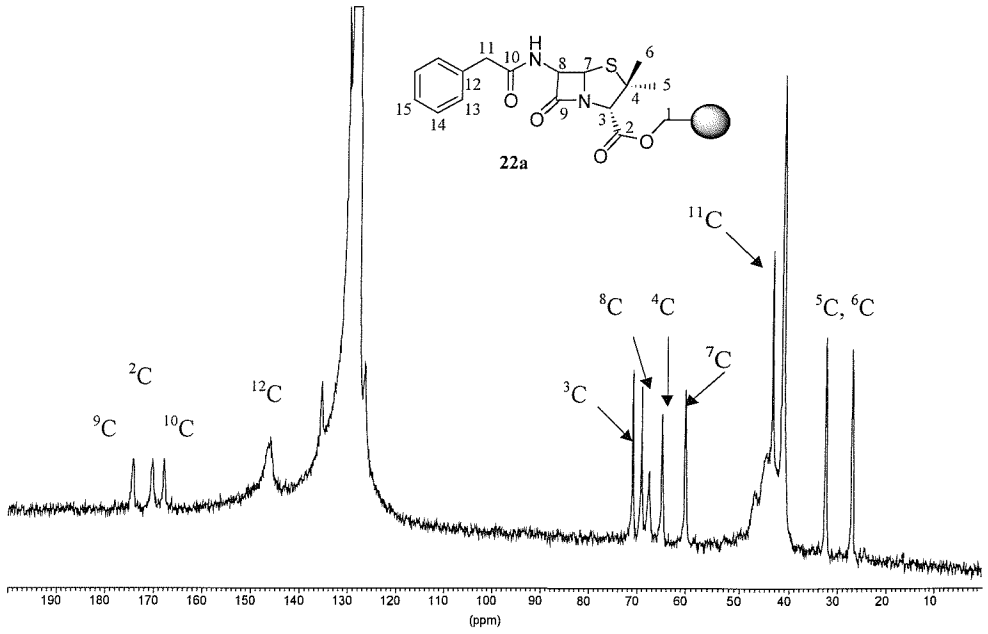


*Figure 2.35: ^{13}C Gel phase NMR (100 MHz, C_6D_6) of the unoxidised resin-bound penicillin (**22a**) (NS= 9216)*

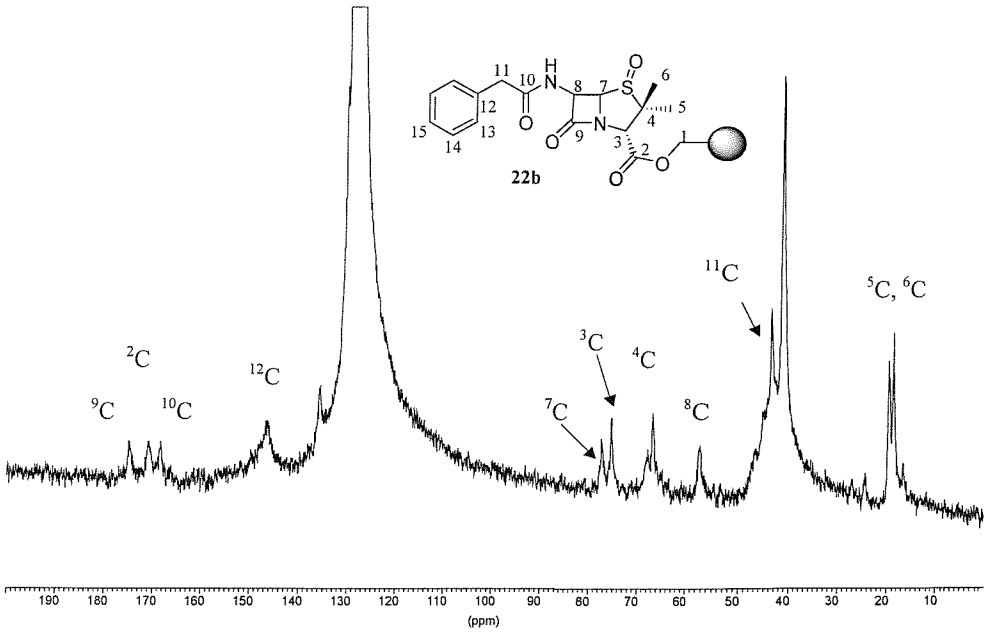


*Figure 2.36: Gel phase ^{13}C NMR (100 MHz, C_6D_6) of the oxidised resin-bound penicillin (**22b**) (NS= 12288)*

Unfortunately, the aluminium chloride mediated cleavage described by Mata[109] failed to release the penicillin, but the oxidation can still be deemed successful because of the changes in chemical shift observed in the gel phase NMR, which compared to calculated ^{13}C NMR shifts.

2.4 Conclusions

It has been demonstrated that the HFIP/H_2O_2 oxidation method which oxidises sulfides to their corresponding sulfoxides without over-oxidation to the sulfone, has many advantages over traditional oxidation methods e.g. sodium metaperiodate, and is ideal for solid phase organic synthesis. The oxidation proceeds much faster, at room temperature, and is generally much cleaner than the reaction with sodium metaperiodate. Several sulfoxides have been synthesised using this new method.

The procedure has been adapted for use on the solid phase, thus providing, as far as we are aware, the only truly selective means of oxidising a sulfide to the sulfoxide on the resin.

Chapter 3: Development of a Sulfoxide Safety-Catch Linker

3.1 Introduction

Despite the broad range of linkers available for solid phase organic synthesis, there is still a need for linkers which cleave under biologically compatible conditions. The aim of this research was to develop a novel linker, capable of simple cleavage in aqueous media, allowing immediate biological screening. In order for a range of chemistries to be carried out, and to prevent premature cleavage, it was important that cleavage only occurred after a selective and mild activation step. Therefore, a linker was designed to exploit the sulfoxide pericyclic elimination reaction, with a view to also investigating the analogous selenoxide linker, as the elimination temperature would be lower.

3.1.1 Sulfoxide pericyclic eliminations [133]

The synthesis of α,β-unsaturated carbonyl compounds can be readily achieved using the sulfoxide pericyclic elimination reaction. The sulfur is introduced by enolate formation followed by reaction with a disulfide, commonly diphenyldisulfide. Oxidation of the thioether to the sulfoxide is achieved using the methods described in Chapter 2. The subsequent elimination reaction is effected in one of two ways – either *via* base-catalysed β-elimination[134] (Figure 3.1) or simple pyrolysis.

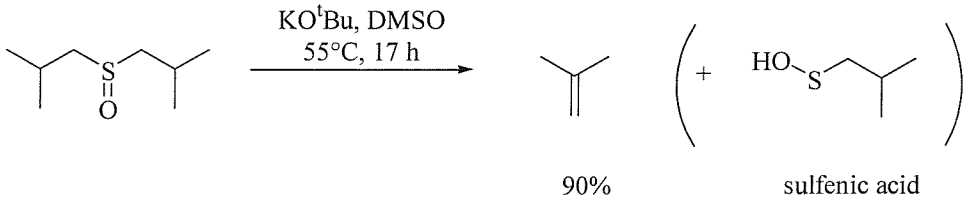


Figure 3.1: Base-catalysed elimination of sulfoxides

Pyrolysis requires higher temperatures for elimination, but the reaction is generally cleaner. Typically, aryl sulfoxides eliminate between 25-80°C, whereas the less activated alkyl sulfoxides require higher temperatures, usually 110-130°C.[135] The procedure is extremely mild and a wide range of functionalities are tolerated, e.g. acetals, epoxides, silyl ethers and even alkenes, depending on the selectivity of the oxidation.

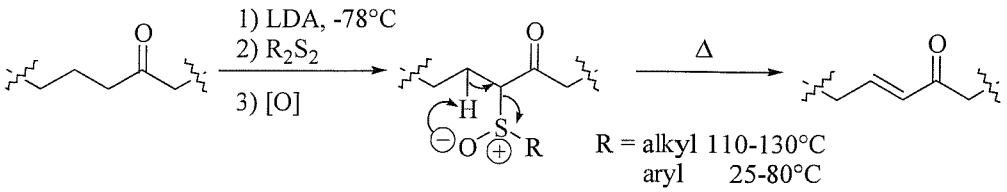


Figure 3.2: General procedure for the sulfoxide pericyclic elimination

The mechanism of pyrolytic elimination was first elucidated by Kingsbury and Cram in 1960.[136] In fact, they noticed the presence of two different mechanisms, which seemed to be temperature-dependent. The first occurred at low temperatures (~120°C) and was a cyclic elimination, analogous to the Cope reaction of amine-oxides.[137] Kinetic, structural and stereochemical studies confirmed the presence of a single cyclic transition state in which the sulfoxide oxygen abstracted a β-hydrogen, leading to the formation of an alkene and a sulfenic acid (Figure 3.3). The second mechanism observed was a free radical process involving C-S bond cleavage, but this process was only detected at high temperatures (~ 180°C).

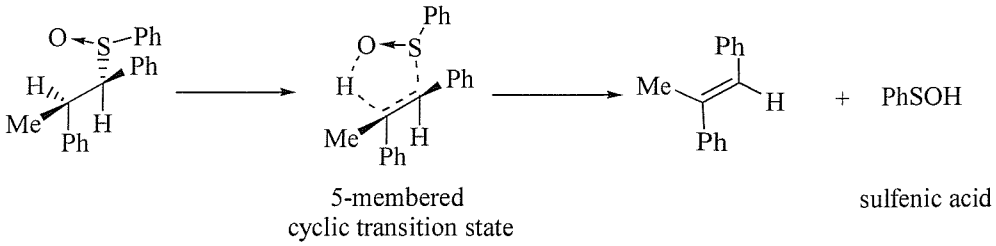


Figure 3.3: The sulfoxide pericyclic elimination proceeds through a 5-membered cyclic transition state

The sulfoxide pericyclic elimination reaction leads preferentially to the formation of the *E* alkene (Figure 3.4), with the exception of compounds that have similar β,β-disubstitution or if the geometry is unattainable.[138]

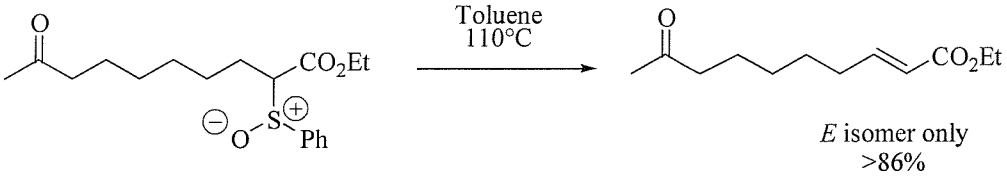


Figure 3.4: Synthesis of the Queen's substance (a bee pheromone) via *pyrolytic sulfoxide elimination*

In molecules with more than one β-hydrogen, the elimination reaction will always abstract the proton such that the more stable alkene is formed; protons that lead to conjugation with a carbonyl or phenyl ring will be abstracted preferentially. The regiochemistry for the abstraction of the β-hydrogen in non-cyclic systems follows the series $C{=}CCH_2 \approx C{\equiv}CCH_2 > ArCH_2 \approx CH_3 > C\text{-}CH_2 >> C\text{-}H$.

Emerson[139] investigated the regiochemistry of the elimination reaction using an unsymmetrical sulfoxide with three different types of β-hydrogen present – *a*, *b* and *c* (Figure 3.5).

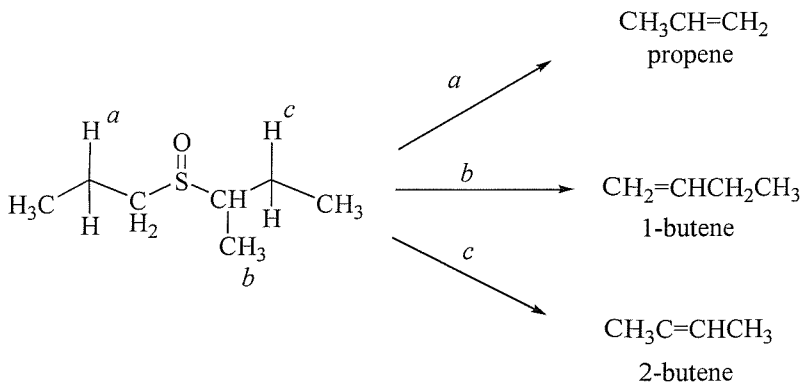


Figure 3.5: Elimination reaction with an unsymmetrical sulfoxide

If proton *a* was abstracted, propene was formed, whereas *b* produced 1-butene and *c* 2-butene (*cis* and *trans*). By comparing the ratios of alkenes formed, it could be determined which factors controlled the choice of proton, e.g. inductive effect and electronic factors. The ratio of propene:isomeric butene formed, showed that a C-S bond was easier to cleave if the carbon atom was secondary rather than primary. Statistics predicted the ratio of 1-butene:2-butene would be 3:2, however a 7:3 ratio was actually observed, signifying the relative acidity of the abstracted proton did not have a critical rôle in the elimination.

Cyclic systems prefer to eliminate to produce the *endo*-isomer, given the restraint that the elimination is a *syn* process, for example, the synthesis of carvone (Figure 3.6).[140] Although there are two different types of β-hydrogen present, the elimination favours the formation of the *endo*-product because the proton abstracted must be *cis* to the sulfoxide. In the synthesis of carvone, if the sulfoxide is axial, the proton to be abstracted must be equatorial, and therefore the methylene proton is removed rather than the methyl proton, which is not in the correct conformation. The transition state conformation for *endo*-alkene is thought to preferred over the transition state conformation leading to the *exo*-alkene, due to the more favourable alignment of the C=O and S=O dipoles.[138]

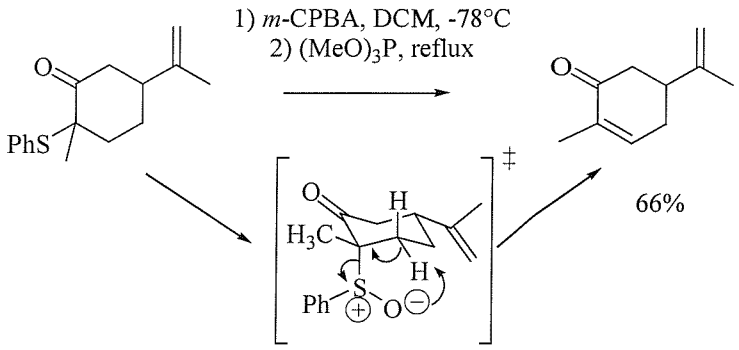


Figure 3.6: Synthesis of carvone via endo-*alkene formation*

During the elimination, the sulfur moiety is released as a sulfenic acid (RSOH) which is very unstable, making its isolation and characterisation difficult. Disproportionation to the disulfide (RSSR) occurs, unless the sulfenic acid is stabilised by the presence of an electron withdrawing R group, hydrogen bonding or is sterically hindered, all of which impede intermolecular reaction. There is also a possibility of sulfenic acid re-addition to the alkene, reversing the elimination reaction.[141] Typically, this side-reaction can be prevented by trapping the sulfenic acid, for example with trimethoxyphosphine (Figure 3.6).

The synthesis of dehydroamino acids illustrates the synthetic value of the sulfoxide elimination. In this example (Figure 3.7), base-catalysed elimination was not feasible due to the sensitivity of the peptide substrate; hence the thermal elimination was employed. [141] The typical temperature of elimination varied from 114-140°C for individual amino acid residues, which was too high for the synthesis of larger peptides as they would denature and the dehydroamino acids would polymerise. *N*-Methylation of the amine disrupted hydrogen bonding to the sulfoxide and enabled the elimination to be effected at only 80°C (3-7 h) (Figure 3.7). Substitution at the β-position of the amino acid was also found to disrupt hydrogen bonding and thus also lower the elimination temperature.

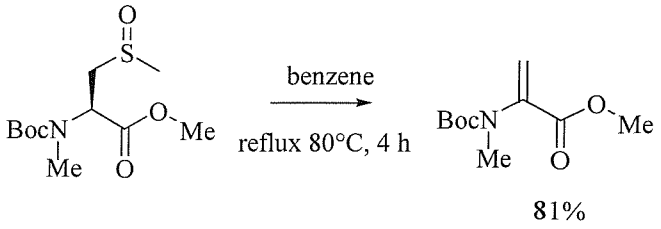


Figure 3.7: Preparation of dehydroalanines

Rapoport[142] synthesised β,γ-unsaturated dehydroamino acids using Kugelrohr distillation of the sulfoxide to effect pyrolytic elimination and produced the desired β,γ-unsaturated isomer in 95% crude yield, with only 5% of the contaminating α,β-isomer (Figure 3.8). The increased temperature required for elimination (148°C, under a vacuum of 3 mmHg) was a reflection of the decreased acidity of the β-proton compared to the α-proton; an α-proton which is activated by virtue of being adjacent to a carbonyl, has a 15000-fold increased rate of abstraction.

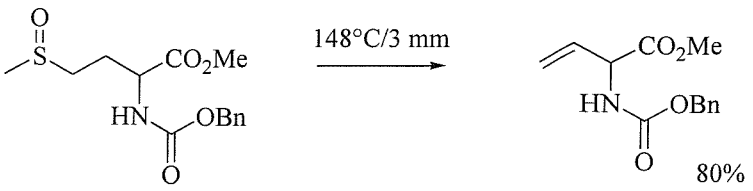


Figure 3.8: Synthesis of a β,γ-unsaturated dehydroamino acid

The sulfoxide pericyclic elimination is extremely useful in organic synthesis, allowing a range of unsaturated compounds such as esters, ketones, lactones and nitriles to be synthesised under mild conditions and in high yields. The mildness of the reaction, i.e. absence of strongly basic or acidic conditions, and the ease of elimination, achieved only by heating, have led us to design a safety-catch linker for solid phase organic synthesis based on the sulfoxide pericyclic elimination reaction. The linker would be resistant to cleavage until selectively activated *via* oxidation to the sulfoxide, at which point thermal elimination would occur, releasing the desired unsaturated products.

3.1.2 Previous work [143]

The safety-catch sulfoxide (selenoxide) linker was originally designed with solid phase peptide synthesis in mind, providing a novel method for the production of vinylic and allylic peptidic esters upon cleavage from the resin. Preliminary work in the group investigated the elimination conditions required using amino acids and small peptides as model compounds.

Merrifield resin was alkylated with 2-mercaptoethanol, and subsequently esterified with Boc-Ala-OH to produce an initial solid phase model. Oxidation ($NaIO_4$) gave the sulfoxide, which was heated in MeOH under N_2 (5 h), to give Boc-Ala-OMe in quantitative yield (Figure 3.9).

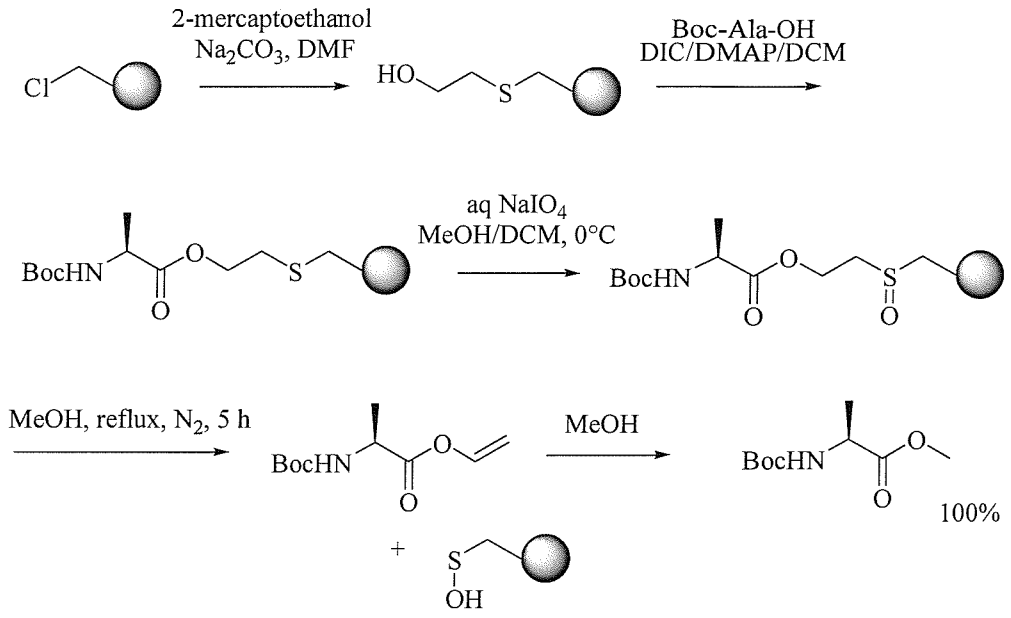


Figure 3.9: Synthesis of Boc-Ala-OMe using the sulfoxide safety-catch linker

The cleavage mechanism was thought to produce a vinyl ester as the initial product of the sulfoxide pericyclic elimination reaction, but this immediately underwent transesterification in MeOH to give the corresponding methyl ester. The sulfenic acid was assumed to remain attached to the resin. However, the exact mechanism of the methyl ester formation was in some doubt, as will be shown in the subsequent sections.

3.2 Results and Discussion

3.2.1 Synthesis of tripeptide standards

Following on from initial work on amino acids, a tripeptide was synthesised for further evaluation of the safety-catch sulfoxide linker. The tripeptide (H-Phe-Ile-Ala-OH) (**25**) and its corresponding methyl ester (H-Phe-Ile-Ala-OMe) (**26**) were synthesised as standards to investigate the elimination reactions. Tripeptide (**25**) was synthesised by standard Fmoc chemistry using the Wang linker on polystyrene resin (**10**). Cleavage with 95% TFA/2.5% TIS/2.5% DCM provided tripeptide (H-Phe-Ile-Ala-OH) (**25**) in 74% yield. Methyl ester (**26**) was prepared in 76% yield by reaction with thionyl chloride (4 equivalents) in MeOH (Figure 3.10).

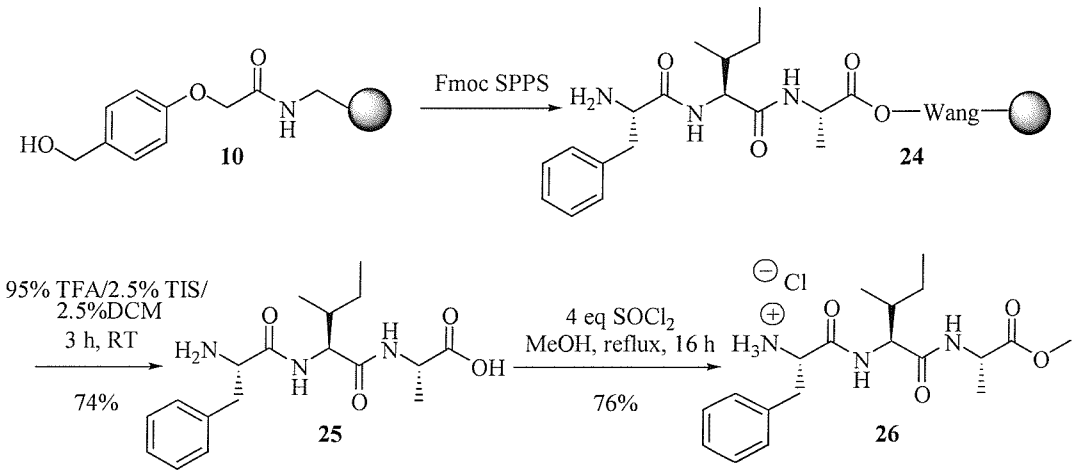


*Figure 3.10: Synthesis of the standard tripeptide (**25**) and the corresponding methyl ester (**26**)*

3.2.2 Synthesis of the tripeptide (25) using the sulfoxide linker

Aminomethyl TentaGel resin was reacted with 25% bromoacetic-2-^{13}C acid and the bromide displaced with 2-mercaptoethanol. The first residue of the tripeptide, alanine, was esterified onto the linker using DIC/DMAP,[129] and the remaining two residues (Ile, Phe) were added using standard Fmoc chemistry. The resin-bound sulfide was oxidised with $NaIO_4$ (1.1 equivalents) (Figure 3.11). Gel phase ^{13}C NMR

showed the change in chemical shift of the enriched atom from 29.4 ppm for the bromide (**27**), to 36.4 ppm for the sulfide (**28**) and then to 56.2 ppm upon oxidation to the sulfoxide (**30b**).

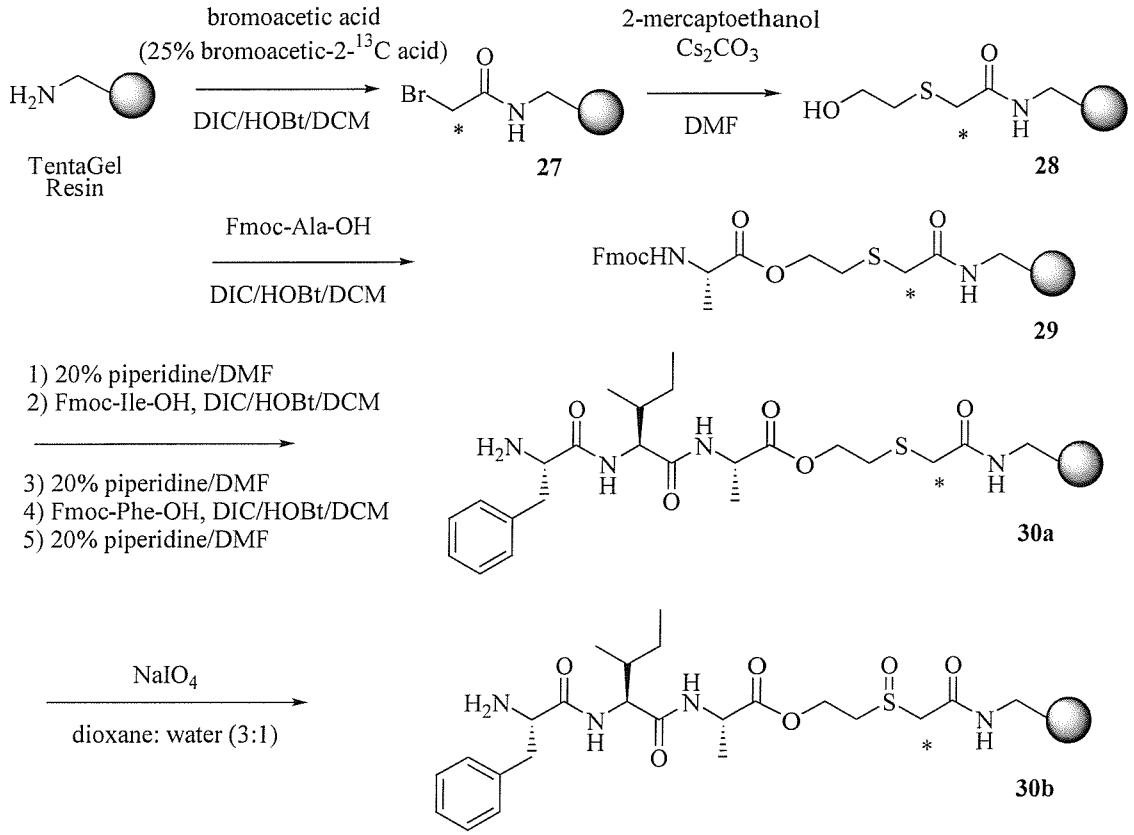


Figure 3.11: Solid phase synthesis of a tripeptide

3.2.3 Thermolysis of the tripeptide model

The resin-bound tripeptide (**30b**) was heated overnight in a number of solvents (MeOH, water, dioxane, toluene and ^{t}BuOH) to investigate the effects of solvent and temperature on the sulfoxide pericyclic elimination reaction (Figure 3.12). For each solvent the resin (**30b**) was heated overnight, then filtered and the filtrate analysed by mass spectrometry. It was expected that thermolysis with toluene, dioxane and ^{t}BuOH would produce the vinyl ester of the peptide, but in fact no peptide was detected in any of these solvents. Sulfoxide resin (**30b**), heated in water overnight, was expected to produce the carboxylic acid of the peptide, *via* hydroxyl

displacement of the vinyl ester (**31**), but again no peptide was detected. The elimination reaction was also attempted using microwave activation – the resin was swollen in water (400 μL), placed into a reaction tube and exposed to microwave irradiation (1.5 min, 950 Watts), but again no peptide was detected.

However, when the resin-bound tripeptide (**30b**) was subjected to MeOH reflux overnight (16 h), the methyl ester of the tripeptide (**26**) was obtained in quantitative yield (Figure 3.12). It appeared that MeOH was necessary for cleavage to occur and therefore previously the tripeptide must have been released from the resin *via* a simple transesterification mechanism. This result was unexpected, as normally ester cleavage requires base catalysis (e.g. Et_3N, NaOMe, DBU).[144,145]

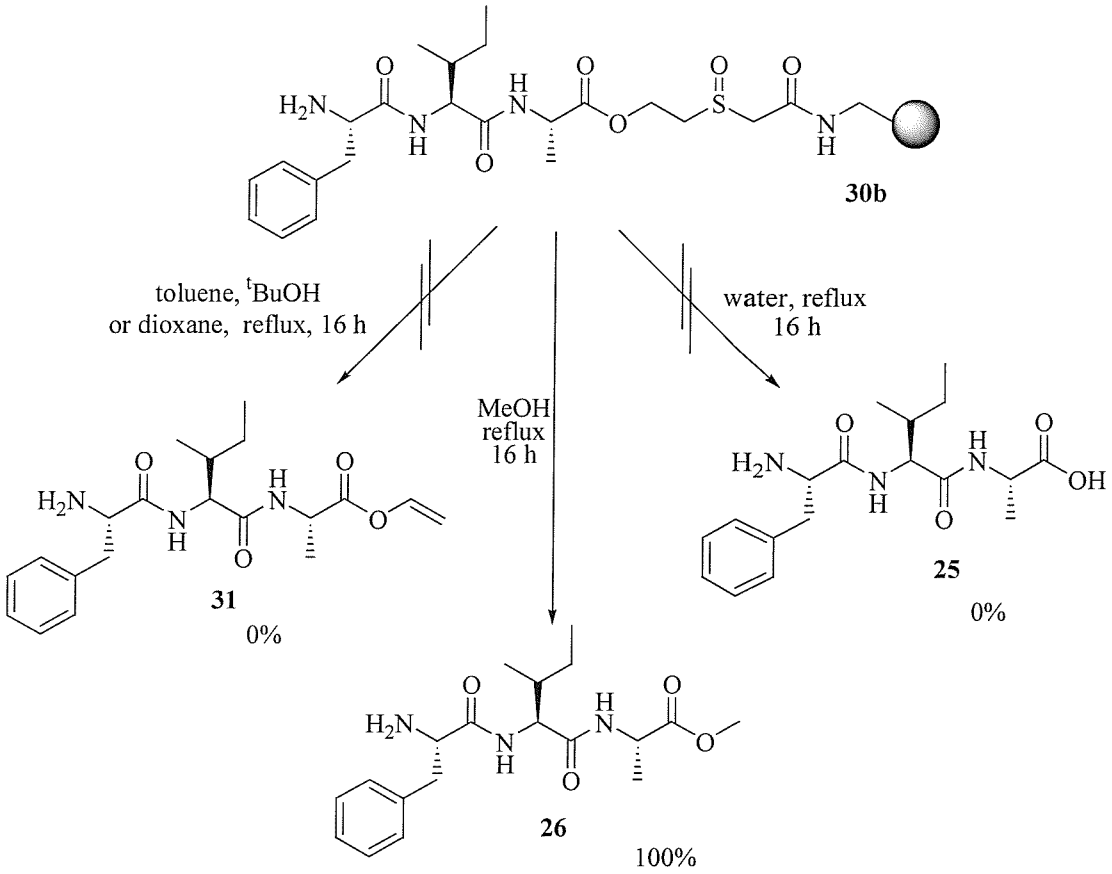


Figure 3.12: Thermolysis reactions of the resin-bound tripeptide

3.2.4 Control reactions – methanolysis of the sulfide and sulfone analogues

Control reactions were carried out using the sulfide (**30a**) and sulfone (**30c**) variants of the tripeptide resin (**30b**). If the only means of cleavage was *via* the sulfoxide pericyclic elimination reaction, no peptide should be detected. If, however, the tripeptide methyl ester (**26**) had been released from the resin by a simple methanolysis reaction, tripeptide (**26**) should be obtained in quantitative yield when the sulfide and sulfone resins were heated in MeOH.

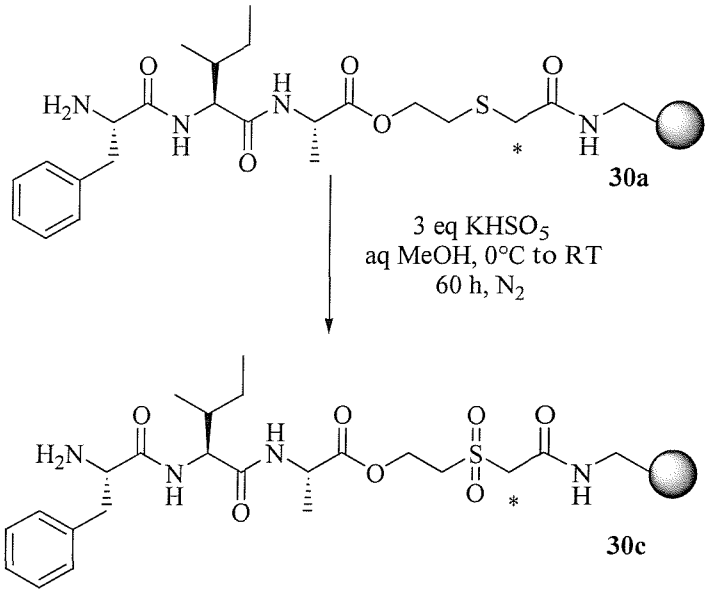


Figure 3.13: Oxidation of the sulfide to the sulfone with Oxone®

The sulfone was synthesised from the ^{13}C-enriched sulfide resin (**30a**) using Oxone® (3 equivalents in aqueous MeOH) (Figure 3.13) with the reaction being monitored by gel phase ^{13}C NMR. A change in chemical shift was observed from 36.1 ppm (**30a**) to 60.6 ppm (**30c**) upon oxidation.

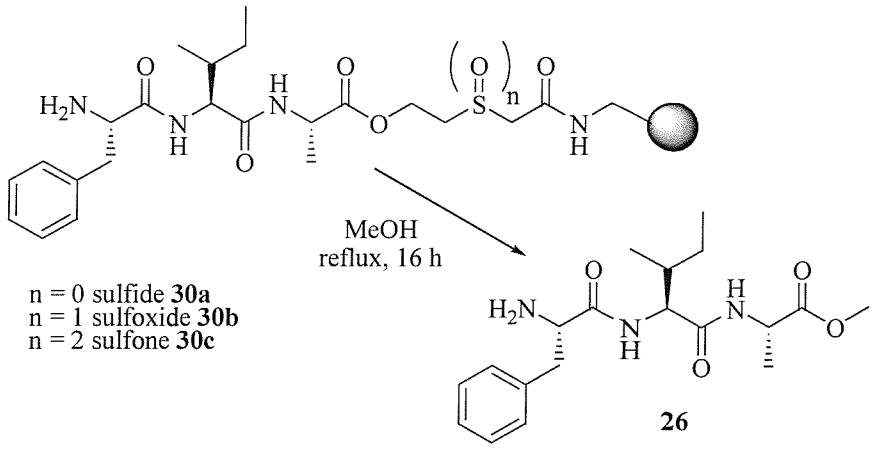


Figure 3.14: Methanolysis of the sulfide, sulfoxide and sulfone analogues

Sulfide resin (**30a**) and sulfone resin (**30c**) were heated in MeOH overnight (Figure 3.14). Unfortunately, in both cases the peptide methyl ester (**26**) was obtained quantitatively, signifying the transesterification reaction was occurring. The elimination of the sulfide demonstrates that oxidation was not necessary for cleavage and hence the linker cannot be considered a safety-catch linker.

3.2.5 Methanolysis of a tripeptide from the Wang linker

To demonstrate that the methanolysis was a general reaction, the same tripeptide (H-Phe-Ile-Ala-OH) was synthesised using the Wang linker on polystyrene resin, then heated in MeOH overnight (16 h). As anticipated, the tripeptide methyl ester (**26**) was obtained in quantitative yield, confirming a simple transesterification reaction had occurred (Figure 3.15), somewhat contrary to literature reports for tranesterification.

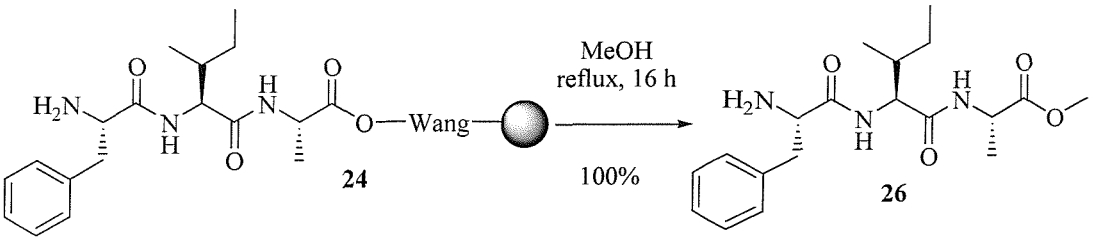


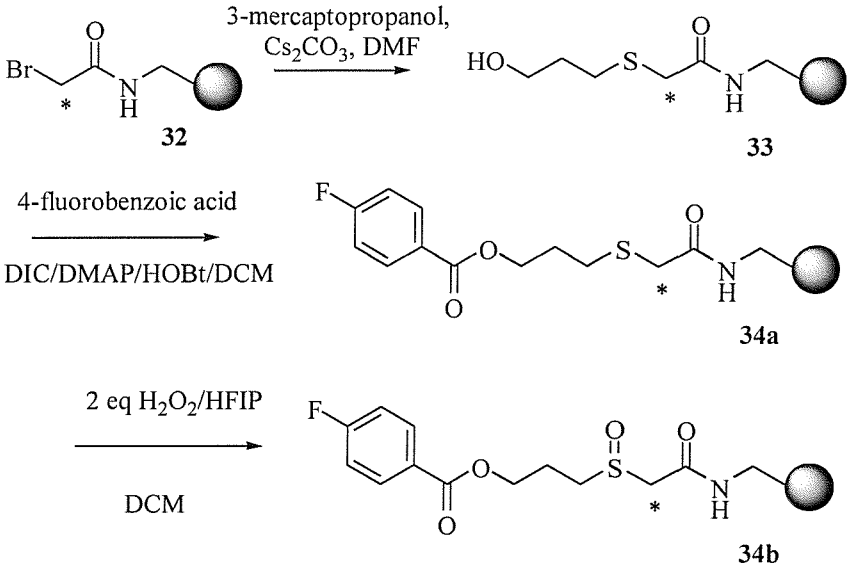
Figure 3.15: Methanolysis of the tripeptide from the Wang linker

3.2.6 Limitations

The sulfoxide linker cannot be considered a safety-catch linker, as cleavage did not require any prior activation (oxidation). The cleavage reaction did not proceed *via* the anticipated pericyclic mechanism, but was a simple transesterification reaction. This was proven by the methanolysis of the sulfide analogue (**30a**), and confirmed by the synthesis of the standard tripeptide using the Wang linker, which were both simply transesterified in MeOH to form the methyl esters.

3.2.7 Attempted synthesis of allyl esters using the sulfoxide linker

There is some literature precedent that an alcohol or ester moiety β to the sulfoxide would retard the pericyclic elimination reaction.[146] Therefore a model was developed with the ester γ to the sulfoxide which, on cleavage, would produce allyl esters. Bromoacetamidomethyl polystyrene resin (**32**) was synthesised as previously and the bromide displaced with 3-mercaptopropanol (Figure 3.16). 4-Fluorobenzoic acid was esterified onto the alcohol resin using standard DIC/DMAP coupling conditions.[129] The fluorinated substrate was chosen to allow monitoring of the esterification step by gel phase ^{19}F NMR, which indeed showed that the fluorobenzoic acid had been successfully coupled (Figure 3.18). Sulfide (**34a**) was oxidised using the H_2O_2/HFIP method, and the success of this reaction was confirmed by gel phase ^{13}C NMR (Figure 3.19).



* ^{13}C enriched position (25%)

Figure 3.16: Synthesis of a resin-bound fluorinated model

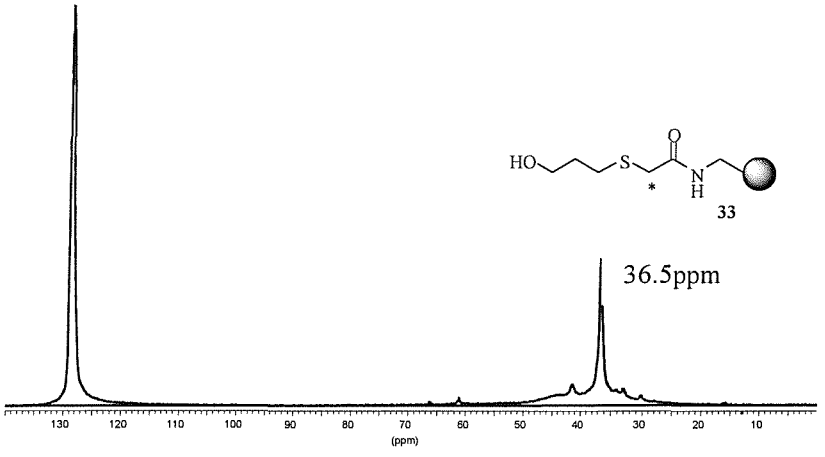


Figure 3.17: Gel phase ^{13}C NMR (75 MHz, C_6D_6) of the resin-bound sulfide
The peak observed at 36.5 ppm corresponds to the ^{13}C-enriched atom (NS=2048)

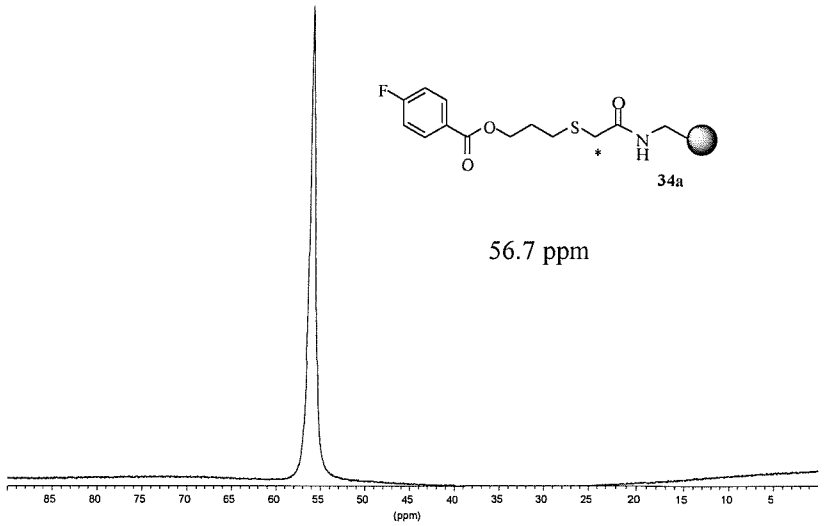


Figure 3.18: Gel phase ^{19}F NMR (282 MHz, $CDCl_3$) of the esterified fluorobenzoic acid. The peak observed corresponds to the fluorine atom (56.7 ppm) (NS=256)

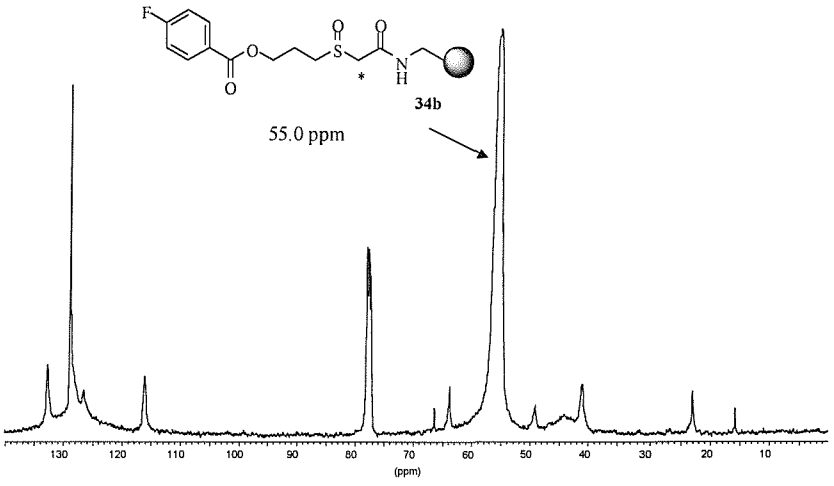


Figure 3.19: Gel phase ^{13}C NMR (75 MHz, $CDCl_3$) of the resin-bound sulfoxide. The major peak observed at 55.0 ppm shows the ^{13}C-enriched atom (NS=2048)

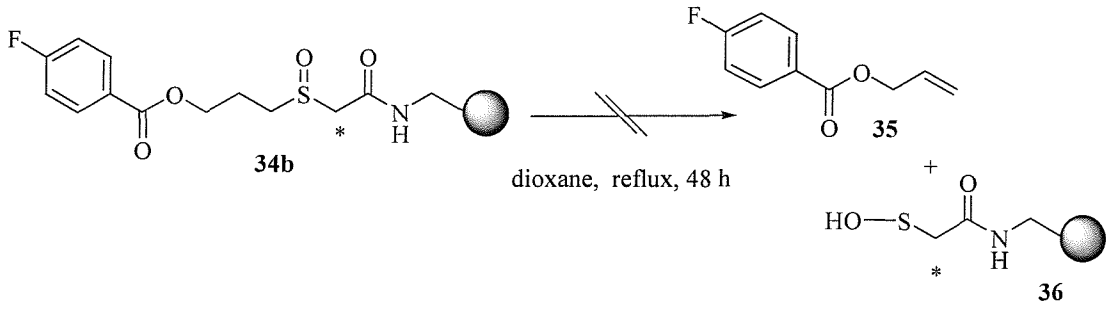


Figure 3.20: Attempted cleavage of the sulfoxide linker to produce an allyl ester

The sulfoxide pericyclic elimination was attempted by refluxing sulfoxide resin (**34b**) in dioxane (24 h) (Figure 3.20). No allyl benzoate product (**35**) was detected by TLC or HPLC, even after a further 24 hours reflux, while gel phase ^{19}F NMR established the presence of resin-bound fluorine. As the resin reactions had produced unexpected difficulties, a new solution model was chosen to optimise the elimination conditions.

3.3 Development of a Solution-Phase Model

A non-peptidic model was used to further investigate the sulfoxide pericyclic elimination reaction. The core of the model was chosen to be *tert*-butyl 4-(bromomethyl)benzoate (**39**). The bromide could be alkylated with a range of thiols to provide access to many different model compounds, while the *tert*-butyl ester could be easily deprotected to allow attachment to aminomethyl resin. All reactions were accomplished in solution thereby allowing easy monitoring and full characterisation of intermediates, but could be transferred to the solid phase at any point, to allow the eliminations to be attempted both in solution and on the resin.

3.3.1 Synthesis of the core structure

Tert-butyl 4-(bromomethyl)benzoate (**39**), the core structure, was prepared from *p*-toluoyl chloride (**37**) in two steps.[147] *Tert*-butyl ester (**38**) was prepared from the acid chloride with ^{t}BuOH and pyridine in DCM (64 h), while the bromide was introduced using *N*-bromosuccinimide (NBS) and benzoyl peroxide in carbon tetrachloride, giving the *tert*-butyl 4-(bromomethyl)benzoate (**39**) in 74% overall yield (Figure 3.21).

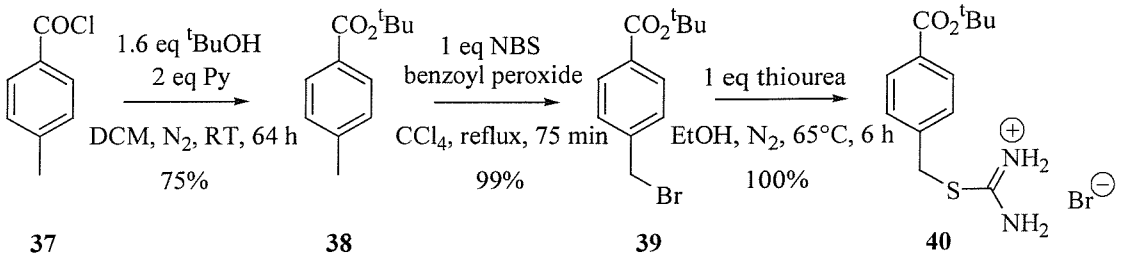


Figure 3.21: Preparation of the isothiouronium salt

Introduction of the thioether could be achieved *via* simple alkylation. However, an alternative method, reaction with thiourea, was used, giving the isothiouronium salt (**40**) in quantitative yield.[148] The main advantage of this method was the ease of

manipulation of the air-sensitive and malodorous compounds (not only for sulfides but also the analogous selenides). More significantly, it provided a means of introducing selenium using selenourea, thereby avoiding the isolation of toxic and air-sensitive selenols, and allowed a large range of halides to be readily coupled (Chapter 4).

3.3.2 Study of the sulfoxide elimination employing a phenylpropane substrate

3.3.2.1 Synthesis of tert-*butyl 4-[(3-phenylpropylthio)methyl]benzoate*

The first model chosen was *tert*-butyl 4-[(3-phenylpropylthio)methyl]benzoate (**2a**), which should undergo pericyclic elimination to release allylbenzene. This elimination had already been demonstrated in the literature with allylbenzene being obtained in 30% yield, after heating at 130°C for 24 h, but it increased to 90% if microwave irradiation was used.[149]

Isothiouronium salt (**40**) was hydrolysed using 10% aqueous NaOH and then alkylated with 1-bromo-3-phenylpropane (1.2 equivalents) to give sulfide (**2a**) in a disappointing 30% yield. An alternative two-step synthesis, whereby the thiol intermediate was isolated, gave the sulfide (**2a**) in only 38% overall yield (Figure 3.22).

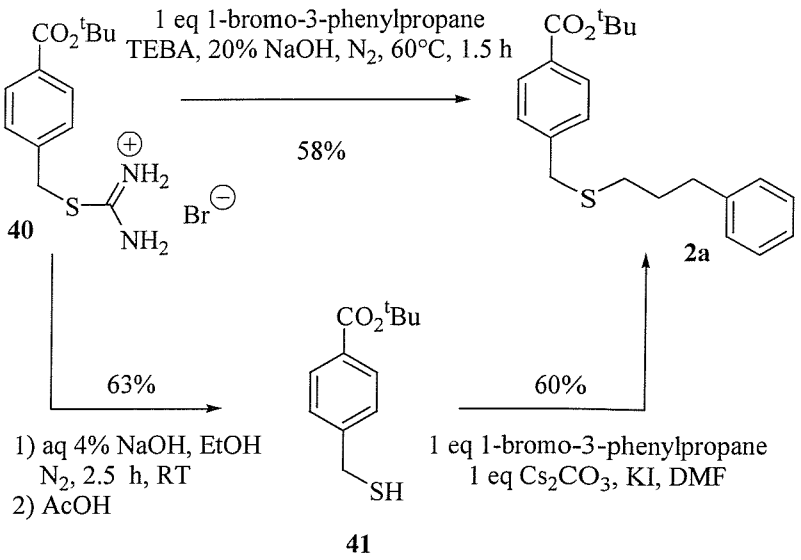


Figure 3.22: Synthesis of tert-*butyl 4-[(3-phenylpropylthio)methyl]benzoate*

The yield of alkylation was significantly improved using a phase transfer catalyst, benzyltriethylammonium chloride (TEBA)[150] in a one-pot procedure, which produced sulfide (**2a**) in 58% yield.

3.3.2.2 Thermal elimination of tert-*butyl 4-[(3-phenylpropylthio)methyl]benzoate*

Sulfide (**2a**) was oxidised in 56% yield using sodium metaperiodate (1.2 equivalents) in dioxane/water. Alkyl sulfoxides are difficult to eliminate, requiring temperatures of 110-130°C and several hours of heating. Typically, aprotic solvents such as dioxane, toluene, benzene are used for the pyrolysis of sulfoxides; therefore reflux in dioxane (16 h) was used (Figure 3.23).[136]

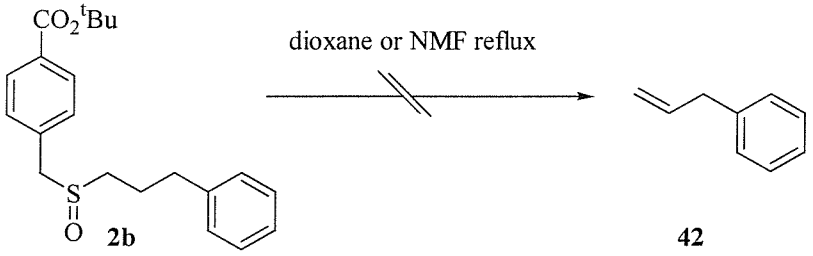


*Figure 3.23: Attempted thermal elimination of sulfoxide (**2b**)*

Dioxane was chosen for its high boiling point and its general inertness. However, the reaction failed to produce any allylbenzene despite recent literature precedent.[149] Sulfoxide (**2b**) was heated in *N*-methylformamide (NMF) at 130°C for 30 hours, then heated overnight (b.p. 199°C) as this solvent had been used successfully by Moghaddam.[149] No allylbenzene was detected. The only products observed and isolated at this stage were 3-phenylpropyldisulfide (**43**) (12 mg, 13%) and sulfone (**44**) (8 mg, 9%) (Figure 3.24).

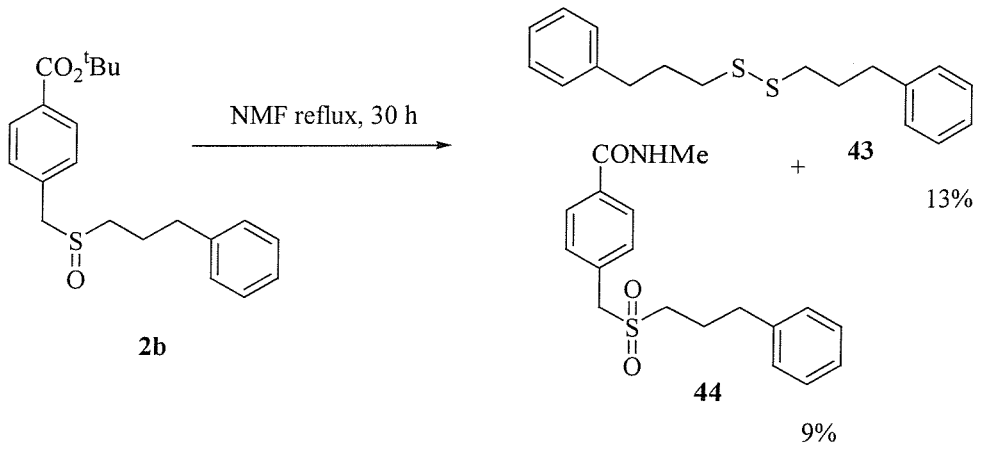


Figure 3.24: Products isolated from the attempted thermal elimination of sulfoxide

As no allylbenzene had been detected, a control reaction was devised whereby allylbenzene was heated in dioxane (16 h) and then re-isolated. Allylbenzene was successfully re-isolated in 75% yield, proving that the volatility of allylbenzene was not hindering its isolation from the elimination reaction conditions. It was concluded that the problem was due to the elimination reaction rather than the properties of the product.

3.3.2.3 Microwave elimination of tert*-butyl 4-[(3-phenylpropylthio)methyl]benzoate*

Sulfoxide (**2b**) was exposed to microwave radiation with the aim of effecting the elimination, as had previously been reported.[149] The substrate (**2b**) was dissolved in NMF and placed into a specially designed condenser filled with solid CO_2 (Figure 3.25) and irradiated for 7 min (950 W). No starting sulfoxide remained, but equally

no allylbenzene was detected, only 3-phenylpropyldisulfide (**43**) (14 mg, 11%) and sulfide (**2a**) (17 mg, 12%) were identified (Figure 3.26).

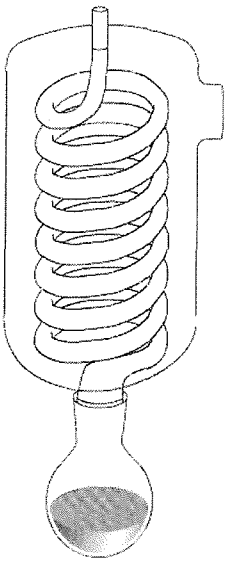


Figure 3.25: Apparatus used for microwave experiments. (Condenser was cooled with dry-ice.)

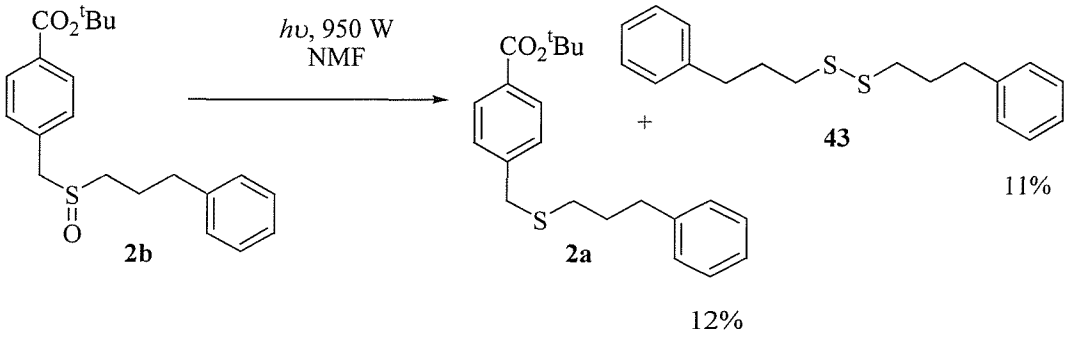


*Figure 3.26: Products isolated from the attempted microwave elimination of sulfoxide (**2b**)*

The presence of the disulfide (**43**), which was detected in both elimination reactions, suggested that some C-S bond cleavage was occurring. This phenomenon had previously been observed by Cram[136] in thermal eliminations at high temperatures (~

180°C), where a free radical elimination mechanism was postulated to occur. This C-S cleavage was also prevalent in the photochemical cleavage reactions of sulfoxides.[151]

From these results, it was concluded that sulfoxide pericyclic elimination was not possible with this model, either thermally or with the use of microwaves. It was postulated that the molecule was not activated enough towards elimination, due to the benzylic position of the sulfoxide, despite a recent report (1993) to the contrary.[149] Hence a new model was designed.

*3.3.2.4 Eliminations with [(3-phenylpropyl)sulfinyl]benzene (**3b**)*

The phenyl analogue, phenyl 3-phenylpropylsulfide (**3a**), of sulfide (**2a**) was oxidised to give the sulfoxide (**3b**) in 82% yield (Chapter 2). Thermal pericyclic elimination was again attempted by heating in NMF at 130°C for 24 hours and also in toluene (reflux, 24 h). Neither reaction produced any of the anticipated allylbenzene elimination product; only starting material was isolated (64% from NMF reaction, 65% from toluene) (Figure 3.27).

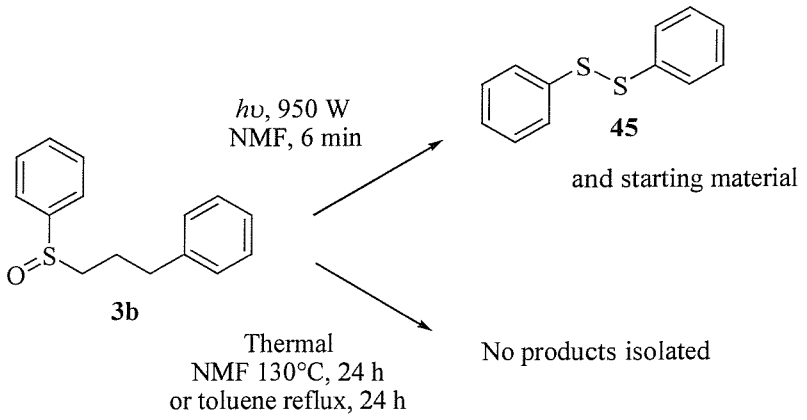


Figure 3.27: Thermal and microwave elimination of [(3-phenylpropyl)sulfinyl]benzene

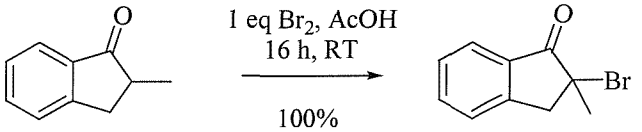
The elimination was attempted using microwaves. However, the only compounds isolated following chromatographic separation were sulfoxide (**3b**) (17%) and diphenyldisulfide (**45**) (7%) (Figure 3.27).

The pericyclic elimination was unsuccessful when attempted with microwaves or thermally and with a benzylic (**2b**) or phenyl sulfoxide (**3b**). The benzylic position for the sulfoxide is unactivated compared to the phenyl. It is known that alkyl sulfoxides require higher temperatures to eliminate than phenyl ones,[135] therefore the failure of the benzylic sulfoxide to eliminate was unsurprising. However, literature[138] suggests that phenyl sulfoxides cleave very easily, so the reason for this model failing to eliminate under thermal or microwave activation is unclear.

3.3.3 Study of the sulfoxide elimination employing an indanone substrate

3.3.3.1 Synthesis of tert-*butyl 4-{[(2-methyl-1-oxoindan-2-yl)sulfinyl]methyl}benzoate*

A new model was designed based on the indanone structure. On elimination, this compound should release an indenone, and the α,β-unsaturated ketone formed should help to drive the reaction while the presence of the chromophore would allow UV detection.



46 **47**

Figure 3.28: Synthesis of 2-bromo-2-methylindanone

The model indanone (**4a**) was synthesised from the isothiouronium salt (**40**) and 2-bromo-2-methylindanone (**47**). The bromide (**47**) was prepared, in quantitative yield, from bromine and 2-methylindanone (**46**) (Figure 3.28). However, the sulfide (**4a**) proved difficult to synthesise. Several different methods were attempted, but the best yield was a disappointing 27%, obtained under the phase transfer conditions

used previously.[150] Sulfide (**4a**) was oxidised very efficiently using the H_2O_2/HFIP method to give the sulfoxide (**4b**) in 84% yield (Figure 3.29).

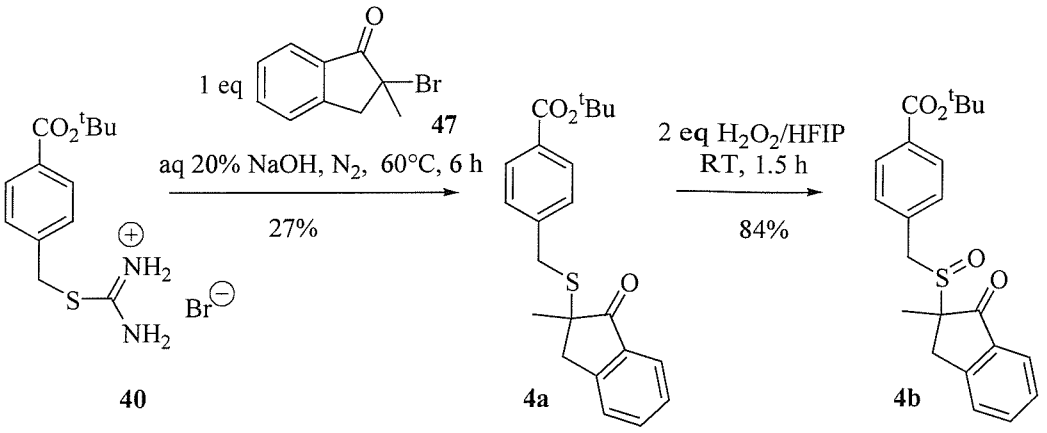


Figure 3.29: Synthesis of the indanone model

3.3.3.2 Synthesis of the standard indenones

The pericyclic elimination of sulfoxide (**4b**) was expected to give predominantly the *endo*-indenone, based on previous observations,[140] but theoretically, the *exo*-indenone could also be formed. Therefore both products, the *exo*-indenone and the *endo*-indenone, were synthesised as standards. The *exo*-indenone was prepared *via* a Mannich reaction:[152] 1-indanone was reacted with dimethylamine hydrochloride and paraformaldehyde in EtOH with catalytic HCl, to give a dimethylamino ketone. This product was not isolated but immediately alkylated with methyl iodide. The elimination was effected with aqueous sodium hydrogen carbonate to give the desired *exo*-indenone (**49**) in 32% yield (Figure 3.30).

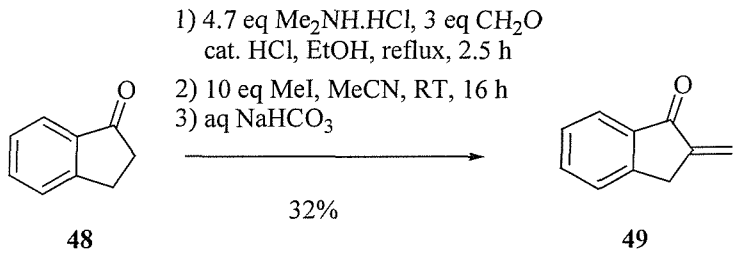


Figure 3.30: Synthesis of the standard exo-*indenone*

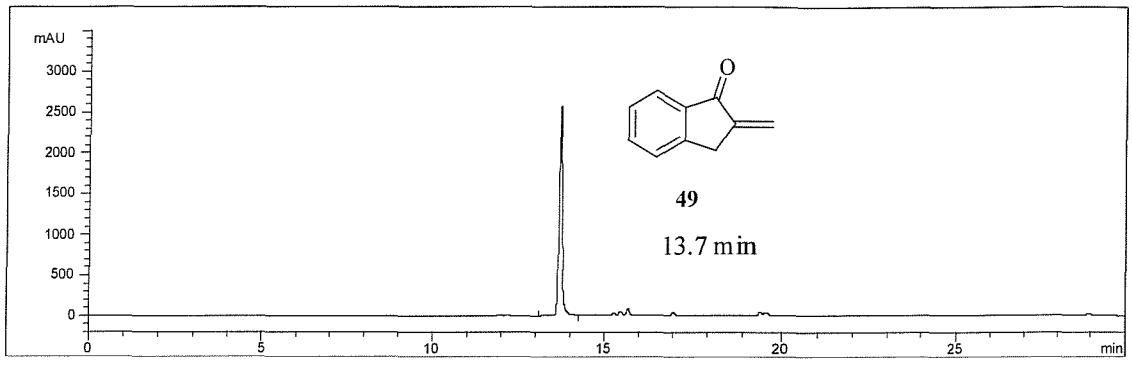


Figure 3.31: RP HPLC standard exo-indenone

The *endo*-indenone (**52**) was prepared following a literature preparation by Floyd and Allen.[153] Benzaldehyde and propionic acid (**50**) were condensed to give hydroxy acid (**51**), which was converted into the acid chloride using thionyl chloride, and cyclised *via* an intra-molecular Friedel-Crafts reaction, to give the *endo*-indenone (**52**) in 17% yield (Figure 3.32).

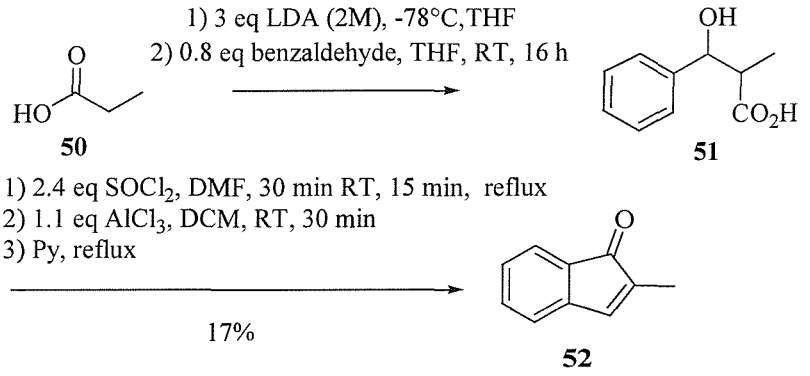


Figure 3.32: Synthesis of the standard endo-*indenone*

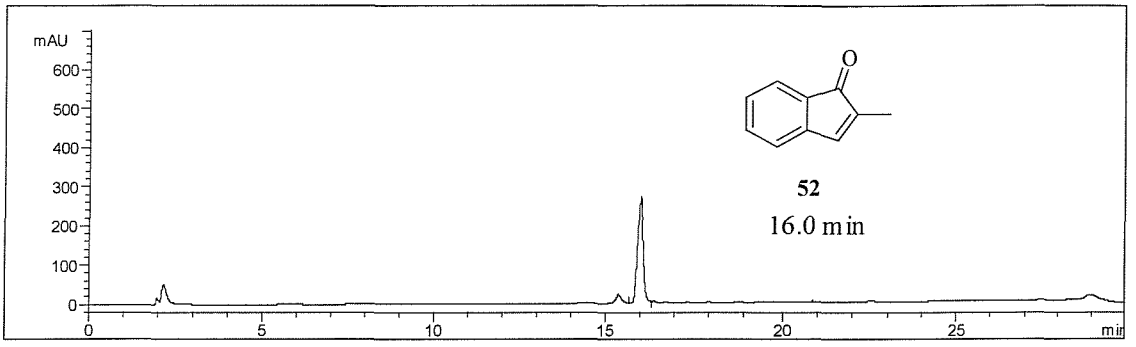


Figure 3.33: RP HPLC of the standard endo-*indenone*

3.3.3.3 Indanone eliminations in solution

Sulfoxide (**4b**) was heated in dioxane overnight (22 h) to effect pericyclic elimination and release the indenone products (Figure 3.34).

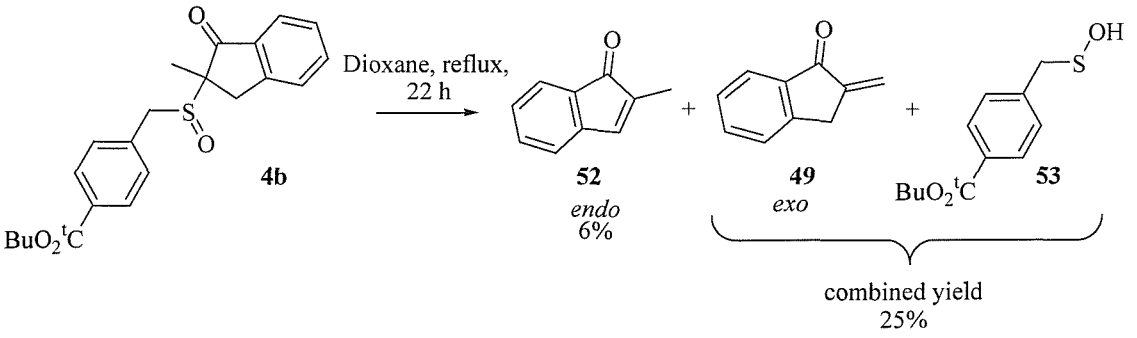


Figure 3.34: Thermal elimination of the solution indanone model

The crude reaction was analysed by RP HPLC, which showed the *exo*-indenone was the major compound (13.9 min) and the *endo*-indenone was the minor compound at 15.9 min (Figure 3.35). The ratio of *exo:endo*-indenone was found to be 9:1, in contrast to the expected result, which was that the *endo* isomer would be favoured, due to the previous predictions on cyclic eliminations.[140] Another major peak was present at 17.6 min, which was assumed to be the sulfenic acid (**53**). Unfortunately, it proved impossible to separate the *exo*-indenone from the sulfenic acid, despite extensive attempts using flash chromatography, semi-preparative RP HPLC and preparative TLC techniques. NMR analysis of the *exo*-indenone and sulfenic acid mixture appeared to confirm the sulfenic acid structure by the presence of a benzylic CH_2 at 3.78 ppm and an S-OH at 10.10 ppm. MS analysis identified the corresponding disulfide, which seemed the likely decomposition product of the sulfenic acid.

Although the solution phase elimination was successful and the *exo* and *endo*-indenones were successfully characterised, the isolated yields were disappointing. It was postulated that the sulfenic acid, a reactive species, might have been involved in side reactions, thus resulting in a decreased yield.

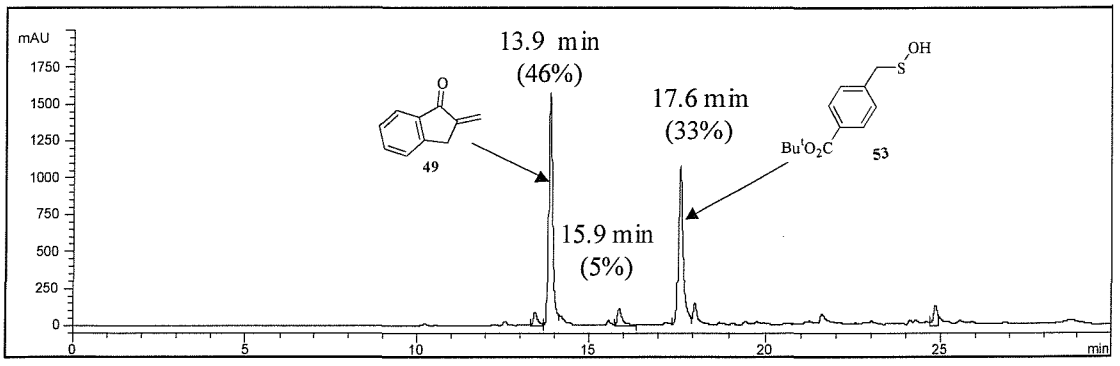


Figure 3.35: Crude products from the solution elimination of the indanone model (9:1 exo:endo)

3.3.3.4 Indanone eliminations on the resin

Indanone (**4a**) was deprotected, coupled to aminomethyl resin and oxidised as described previously. To effect elimination, the resin bound sulfoxide (**19b**) was

heated in dioxane overnight (22 h) (Figure 3.36). The expected indenone products were observed by TLC and RP HPLC. The resin was heated in dioxane again (16 h) to ensure complete elimination, releasing only the *exo*-indenone (**49**) on this occasion, while further heating failed to afford any additional products.

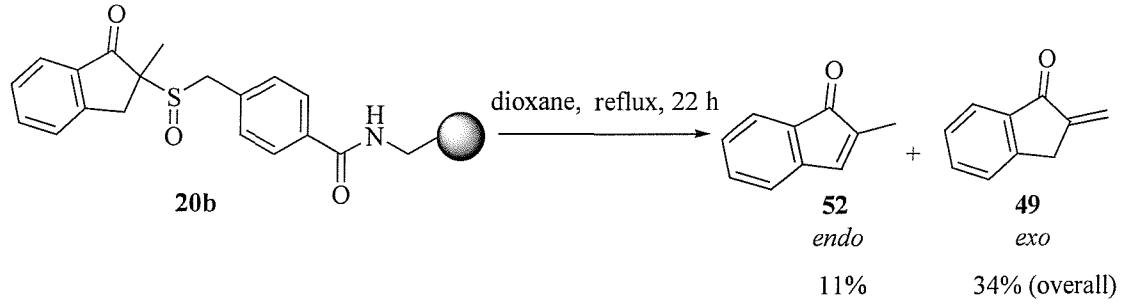


Figure 3.36: Solid phase elimination of indenones

The proportion of *exo*:*endo* indenone obtained was interesting as the *exo*-isomer (**49**) dominated the crude RP HPLC trace (13:1), to a greater extent than in the solution elimination (Figure 3.37). After separation of the indenone isomers by flash chromatography, the *exo*-isomer (**49**) remained the major product (9.2 mg, 34%), *endo* (3 mg, 11%) (**52**). The elimination proceeded very cleanly as expected, with the indenones being the only products detected, although the isolated yield (45% combined yield of *exo*- and *endo*-indenones) was still disappointing.

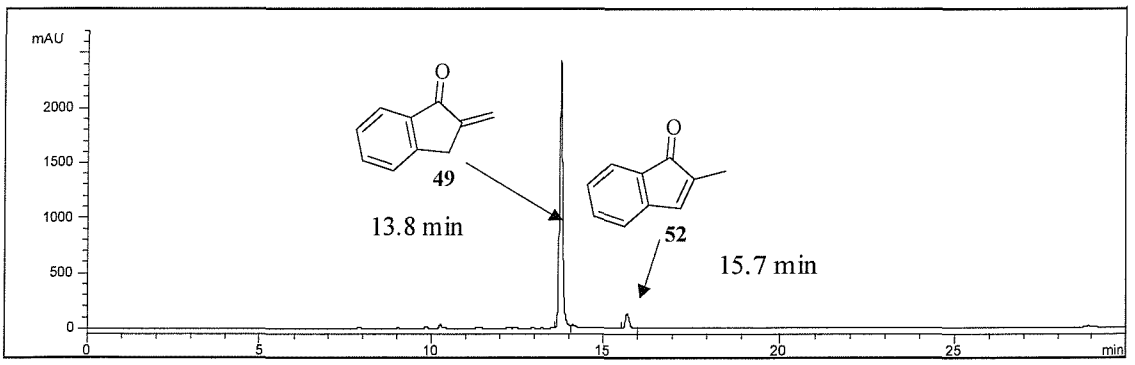


Figure 3.37: Crude RP HPLC trace from the thermal elimination of the resin-bound indanone (13:1 exo:endo*)*

3.3.3.5 Discussion

Elimination studies have shown that the sulfoxide pericyclic elimination reaction will occur both in solution and on the solid phase, at temperatures of ~ 100°C, but only when a suitably activated substrate is present, e.g. the indanone model. The indanone eliminated to give two possible products, the *endo*- and *exo*-indenones. In each elimination, solution phase and solid phase, the *exo* isomer was clearly the dominant isomer. Although there is a statistical preference for the *exo*-isomer (3 methyl protons: 2 methylene protons) the observed ratios do not reflect this (9:1 and 13:1).

Crystals of sulfoxide (**4b**) were grown from $CHCl_3$/hexane and the crystal structure is shown below (Figure 3.36). The crystal structure describes the position of atoms in space when in the solid state. It is not necessarily the same arrangement as when the compound is dissolved in solution. However, it enables certain observations to be made which might explain the *exo:endo* ratio observed. From modelling the indanone substrate, steric interactions seem to be an important factor to explain the increased selectivity observed.

The time-averaged single crystal structure of the sulfoxide (**4b**) (Figure 3.36) would seem to depict a sulfone, however it should be noted that the sulfoxide oxygen is present in equal proportions in either one of two different conformations, represented by oxygen atoms O4 and O5, describing the two diastereoisomers of this sulfoxide.

If the sulfoxide oxygen (O4 or O5) is placed so as to remove one of the CH_2 (C22) protons (and lead to the *endo* compound (**52**)), the methyl group (C14) eclipses the benzylic hydrogens (C12) on the other side of the sulfoxide (similar to 1, 3-diaxial interactions in cyclohexanes). The indanone will therefore adopt a conformation to minimise steric interactions; thus the *exo*-compound (**49**) is produced because of the unfavourable position of the protons and the sulfoxide oxygen.

The crystal structure obtained does not disagree with this argument; the compound assumes a fairly linear structure, with the sulfoxide occupying a position more suited to the removal of a proton from the exocyclic methyl than the methylene group. However, the relative bond strengths of C-H bonds [primary C-H (~ 98 $kJmol^{-1}$) > secondary C-H (~ 94 $kJmol^{-1}$)], the general belief that the *endo*-isomer of cyclic

compounds is the more stable[140] and also Saytzeff's rule[154] all favour the formation of the *endo*-indenone.

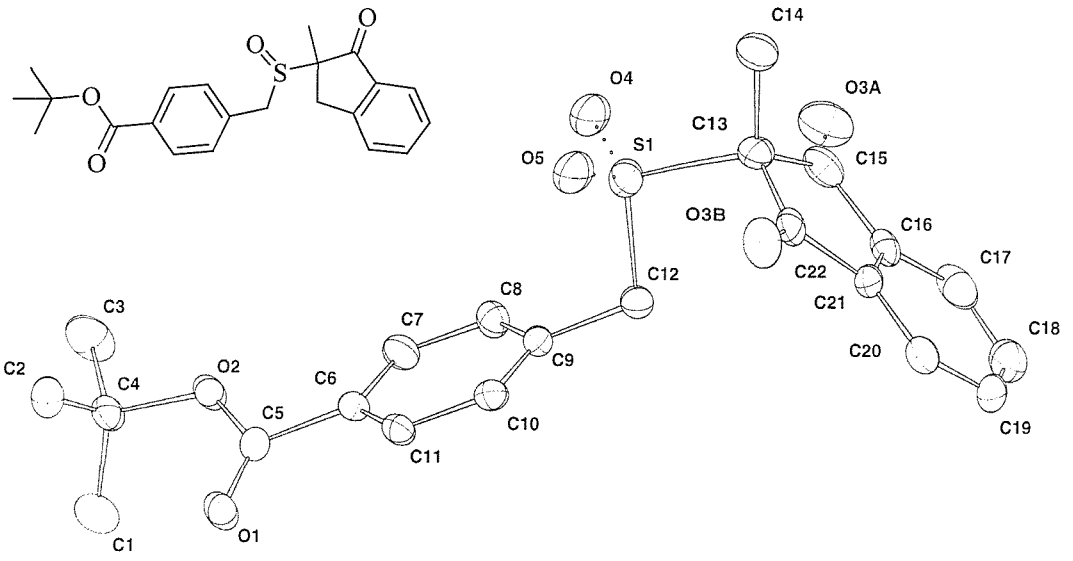


Figure 3.36: Single crystal structure refinement of tert-*butyl 4-{[(2-methyl-1-oxoindan-2-yl)sulfinyl]methyl}benzoate* ***(4b)***

3.4 Conclusions

A safety-catch linker based on the sulfoxide pericyclic elimination reaction is not a viable possibility, due to its limited scope. Although the pericyclic elimination was successful, using both solution and solid phase substrates, it is dependent on the presence of an activated product being formed e.g. α,β–unsaturated ketone. If the substrate is simply an alkane, the activation energy barrier appears too high for the elimination to occur. Surprisingly, the sulfoxide elimination also failed when a more activated phenyl sulfoxide was used instead of the benzylic sulfoxide, despite a recent report stating otherwise.[149]

Chapter 4: Development of a Selenium Safety-Catch Linker

Following the limited success of attempts to develop a safety-catch linker based on the sulfoxide pericyclic elimination reaction, this chapter investigates the synthesis and potential applications of a selenoxide safety-catch linker.

4.1 The Selenium Pericyclic Elimination Reaction[155]

The selenium pericyclic elimination reaction is analogous to the sulfoxide pericyclic elimination. The significant difference between the two reactions is the bond energy of C-Se (234 $kJmol^{-1}$) compared to C-S (272 $kJmol^{-1}$), facilitating elimination at much lower temperatures; typically 100°C lower than the corresponding sulfoxide elimination. This should enable a selenium safety-catch linker to be cleaved at or below room temperature, following selective oxidation. Therefore the oxidation to the selenoxide would need to occur at reduced temperatures ~ 0°C, in order for the linker to remain a safety-catch linker.

As with the sulfoxide elimination, the selenoxide elimination can be formally divided into three steps – the introduction of the selenium (by selenenylation adjacent to a carbonyl), oxidation to the selenoxide and then fragmentation of the selenoxide to release the olefin. However, in practise, the oxidation and elimination steps occur almost simultaneously in a one-pot reaction.

4.1.1. Introduction of the selenium moiety

There are three major routes for the introduction of the selenium compound. The most commonly used method involves forming the lithium enolate of the ketone, ester, lactam or lactone, which is then quenched with an electrophilic selenium reagent, i.e. phenyl selenyl chloride or bromide (PhSeCl, PhSeBr) or diphenyldiselenide (PhSeSePh).[156]

α-Phenylselenyl ketones must be synthesised using PhSeCl or PhSeBr as the source of electrophilic selenium because diphenyldiselenide cannot react with ketone enolates due to an unfavourable equilibrium (Figure 4.1). Aldehydes are simply reacted with acidic PhSeCl to achieve α-selenylation.

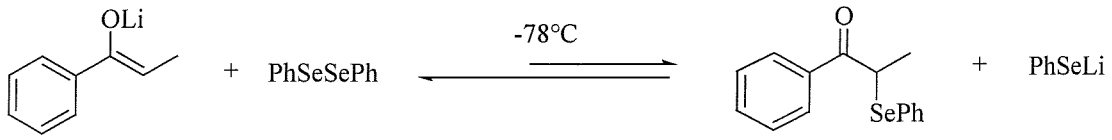


Figure 4.1: The equilibrium for the addition of diphenyldiselenide to a ketone lithium enolate is disfavoured

For unsymmetrical ketones, the kinetic enolate is formed on reaction with LDA but the isomeric enolate can be obtained *via* the corresponding enol acetate. The third method for α-selenylation involves addition of benzeneselenyl trifluoroacetate ($PhSeOC(O)CF_3$) to an alkyne, followed by basic hydrolysis with potassium hydroxide (Figure 4.2).[157]

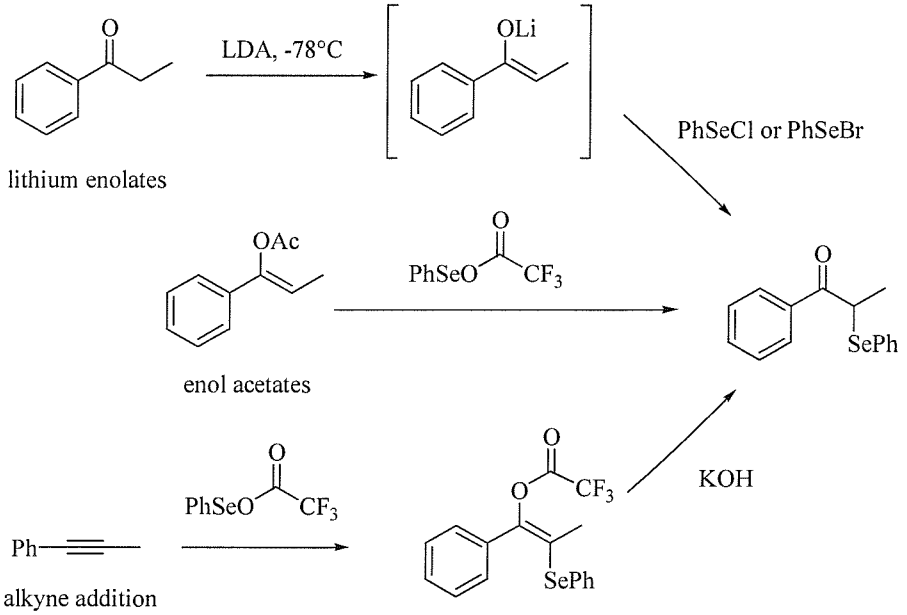


Figure 4.2: Methods for the preparation of α-selenylated ketones

Most selenium compounds used in synthesis have at least a phenyl, methyl or benzyl group attached to the selenium atom. The phenylseleno series of compounds have the lowest volatility and hence the least pungent smell, and are used most frequently. Substituting the phenyl with electron-withdrawing groups, e.g. *o*-nitrophenyl, can increase the rate of elimination further.[158] The use of methylseleno compounds enables the eliminated selenenic acid products to be removed simply by applying a vacuum whereas benzylseleno compounds are used less frequently, despite having a similar reactivity to the methylseleno analogues. The main advantage of benzylseleno compounds is that they can be cleaved with sodium in ammonia, giving rise to an alternative to the selenoxide elimination reaction.

4.1.2 Oxidation to the selenoxide

Selenides are oxidised to the selenoxides more easily than the corresponding sulfide to sulfoxide transformation, but it is very difficult to oxidise selenoxides further to selenones. Thus, the oxidation of selenide to selenoxide can be effected using an excess of the chosen oxidant. Usually a cheap reagent such as hydrogen peroxide,[159,160] ozone or *m*-CPBA is used for the oxidation. Selenoxides are more polar and more basic than the corresponding sulfoxides and the stereochemical lability of selenoxides is much greater than sulfoxides; selenoxides are readily racemised in neutral or weakly acidic solutions (Figure 4.3).[161]

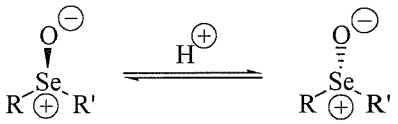


Figure 4.3: Selenoxides racemise in neutral or weakly acidic media

4.1.3 Selenoxide fragmentation

The first recognised selenoxide eliminations to form olefins were reported in 1967[162] and 1970,[163] well after the related sulfoxide elimination had been discovered and extensively studied. Sharpless confirmed the *syn* stereochemistry of the selenoxide

elimination reaction, proving it was analogous to the sulfoxide elimination reaction.[164] Several research groups then reported applications of the selenoxide elimination reaction almost simultaneously.[164,165]

After the oxidation of the selenide, the elimination can either be effected slowly by warming to room temperature or very rapidly by the addition of the cold selenoxide to refluxing carbon tetrachloride or hexane. An alkylamine (e.g. diethylamine or pyridine) is sometimes added to trap out the selenenic acid, although in contrast to the sulfoxide elimination, the selenoxide reaction is not reversible, i.e. selenenic acid will not undergo re-addition to the olefin.[159]

4.1.3.1 Selectivity of the selenoxide elimination

The preference for which β-proton is abstracted is in the order allylic > benzylic > CH_3 > CH_2 > CH > propargylic. If β and β' hydrogens are available, a regioisomeric mixture of products results, in which often the least substituted alkene prevails, albeit only marginally. Elimination resulting in the formation of conjugated alkenes is always highly favoured.

If disubstituted olefins are formed, the *E* alkene is the major isomer, as for the sulfoxide elimination, and endocyclic alkenes tend to be preferred to exocyclic ones, (unless there is no *syn* hydrogen available). The selenoxide elimination is frequently used for the synthesis of allyl alcohols (Figure 4.4) as selenoxides always eliminate away from an adjacent hydroxyl group, thus forming allylic rather than vinylic alcohols.[166]

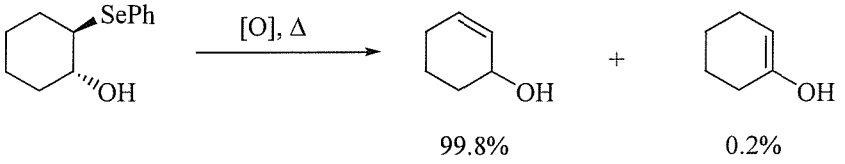
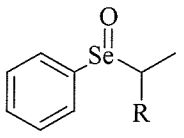
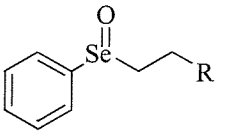


Figure 4.4: Selenoxide elimination to form allyl alcohols

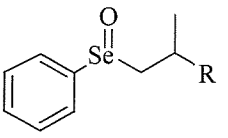
Branching α to the selenoxide has been observed to increase the rate of elimination, in the order 3° > 2° > 1°, and especially if the substituent is phenyl.[146] In contrast, branching at the β-position decreases the rate of elimination (Figure 4.5).



	$t_{1/2}$ (min)
R = H	360
Me	38
Ph	<1



	$t_{1/2}$ (min)
R = H	360
Me	675
OMe	4000
Ph	9



	$t_{1/2}$ (min)
R = H	675
Me	1800
Ph	72

Figure 4.5: Effect of α- and β-branching on the rate of selenoxide elimination measured at 38°C in $CDCl_3$ (with 1.5 equivalents dimethylamine added to suppress β-hydroxy selenide formation)

The selenoxide elimination proceeds more slowly in protic solvents compared to aprotic solvents; e.g. AcOH reduces the rate of elimination by a factor of five. The reason for this is assumed to be an increase in hydrogen bonding which hampers the intramolecular pericyclic elimination.[146]

Elimination to form endocyclic alkenes is usually favoured over exocyclic elimination; the precise ratio of *exo*:*endo*-isomers observed has been attributed to the relative stabilities of the two transition state conformations involved (Figure 4.6). The *endo* isomer tends to be favoured because its transition state conformation minimises dipole-dipole repulsion between the C=O and Se=O bonds.[167]

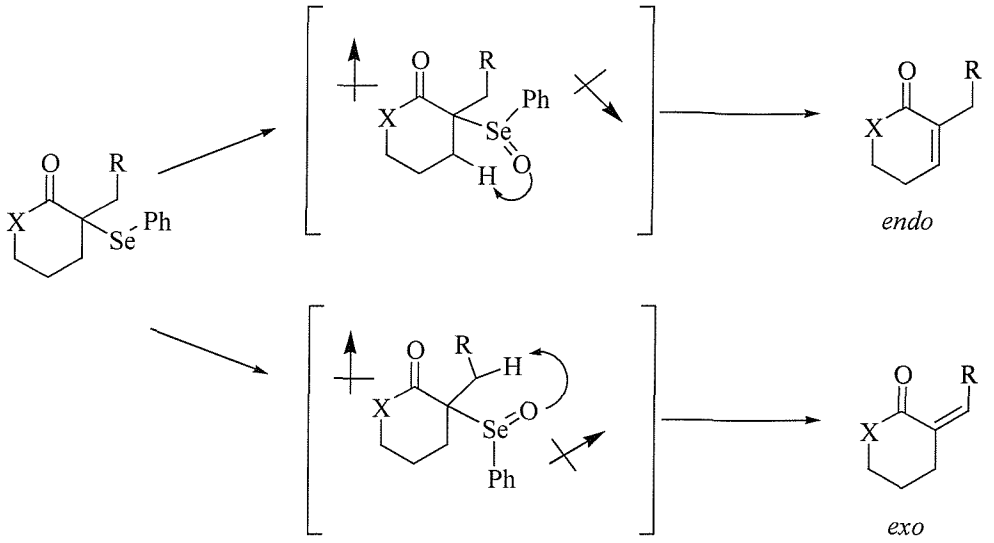


Figure 4.6: Possible transition states in the selenoxide elimination reaction

However, the *exo*-isomer can be favoured by taking advantage of an unfavourable arrangement for *syn* elimination (Figure 4.7). If methylation is performed after α-selenylation, the exocyclic methyl group can be formed exclusively. This is due to the selenoxide no longer having a *cis* relationship to the bridgehead proton; thus no β-hydrogen is available to form the *endo*-isomer. Choice of solvent is also thought to play a rôle in the ratio of *exo*:*endo*-isomers observed, with polar solvents favouring the more polar exocyclic transition state.

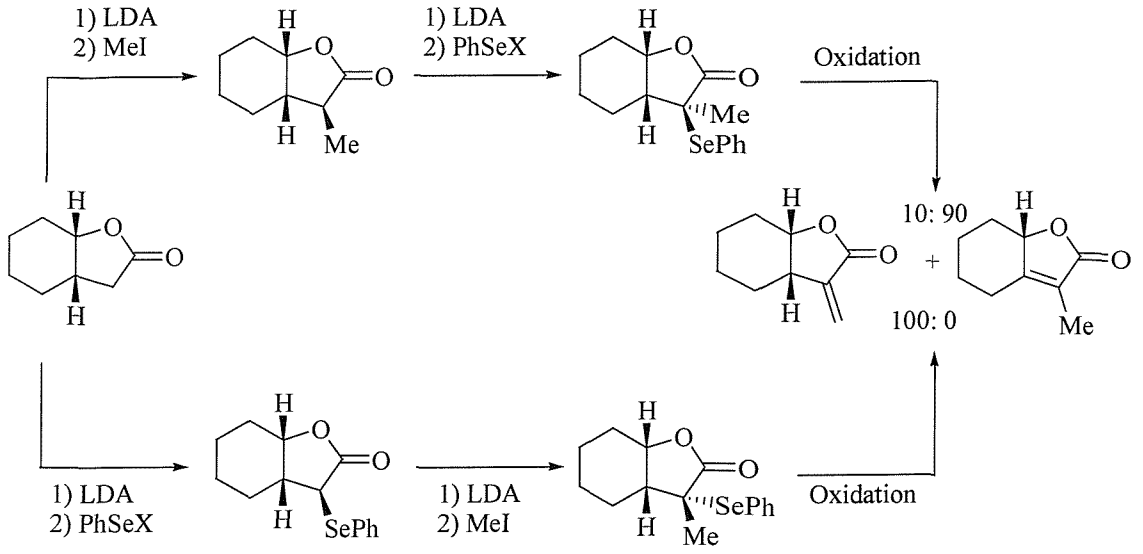


Figure 4.7: Synthesis of exo *and* endo *lactones*

4.1.3.2 Reactions of selenenic acid

The selenoxide fragments at temperatures as low as –50°C, producing the olefin and selenenic acid. Selenenic acids are very unstable and only arylselenenic acids stabilised by electron withdrawing groups have been successfully isolated.[168] However, the fate of the selenium extruded during the elimination depends on the oxidation conditions used. If one equivalent of oxidant is used, the selenenic acid eliminated disproportionates into the diselenide (RSeSeR) and a seleninic acid ($RSeO_2H$). However if an excess of oxidant is used, the only product is the seleninic acid. This is non-volatile and can be easily removed from the olefin product by base extraction during the aqueous work-up. It has been postulated that the oxidation of selenides to selenoxides and subsequent elimination, is autocatalytic – catalysed by perseleninic acid which is formed from the eliminated selenenic acid and excess oxidant.[159] This assumption comes from the observation that selenides that are unable to form the seleninic acid are oxidised very slowly in H_2O_2.

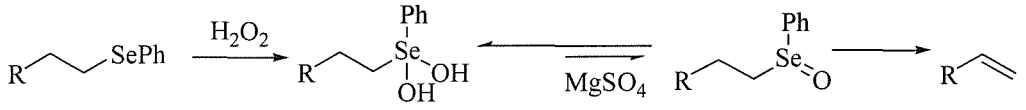
4.1.3.3 Side reactions of the selenoxide elimination

There are a number of selenides for which simple oxidation and elimination give an unsatisfactory yield of α,β-unsaturated compounds, but often the side-products have not been characterised so the exact reason for failure remains unclear. The most problematic reactions involve systems where the alkene formed is strained or there is poor alignment of the selenoxide and proton during elimination.

a) Acid-catalysed seleno-Pummerer reactions have been observed, especially when there is an acidic α-hydrogen present, resulting in the formation of α-diketone compounds.[169] These can be avoided by carrying out the elimination under basic conditions.

b) If the system gives rise to a stabilised carbonium ion, heterolytic cleavage of the C-Se bond may occur, particularly under acidic conditions, when the selenoxide would be protonated.

c) Primary selenoxides do not behave in the same manner as secondary selenoxides (Figure 4.8). After 16 hours only 6% of 1-decene had been formed, whereas secondary selenoxides had eliminated to form olefins in only 3 hours. The addition of magnesium sulfate after the oxidant, increased the rate of reaction and the olefin was obtained in 77% yield after only 2.5 hours at room temperature,[164] the rationale being that the primary selenoxides apparently exist as the hydrate, and thus require dehydration before selenoxide elimination can occur (Figure 4.8).



R = *n*-decyl

Figure 4.8: Primary selenoxides exist as the hydrate, but can be dehydrated with $MgSO_4$

d) It has been observed that selenoxides, particularly if they are primary, are rapidly reduced to the starting selenide, on standing at room temperature overnight. This

may account for the low yields of olefin obtained from the elimination of primary selenoxides. It is thought that the seleninic acid produced upon elimination catalyses reduction in this instance.[170] The problem can be overcome by using *o*-nitrophenyl selenides, which undergo elimination much more rapidly, and avoidance of acidic reaction conditions.[158]

e) Baeyer-Villiger oxidation of starting selenide, intermediate selenoxide or product by hydrogen peroxide has been observed. Grieco[171] reported that benzeneperselenenic acid generated *in situ* from selenenic acid and hydrogen peroxide could be used to effect the Baeyer-Villiger reaction. A variety of ketones were reacted with benzeneperselenenic acid under homogeneous (THF) or heterogeneous (DCM) conditions at room temperature, to give the corresponding lactones in yields of 50-83%.

Polymer-bound selenenic acid[172] was used successfully in catalytic amounts with hydrogen peroxide and ketone substrates to effect the Baeyer-Villiger reaction, therefore confirming that selenenic acid can catalyse this reaction.

4.1.3.4 Solid phase selenoxide eliminations

Kurth synthesised polyisoxazolines on the solid phase in an iterative fashion using nitrile oxide 1,3-dipolar cycloadditions to an alkene, followed by a selenoxide elimination to regenerate the alkene.[144] The isoxazoline was cleaved with sodium methoxide but these conditions led to isomerisation of the alkene (Figure 4.9). The two-step elongation procedure was repeated three times, using a variety of R_x substituents, to form a library of sixty-four triisoxazolines.

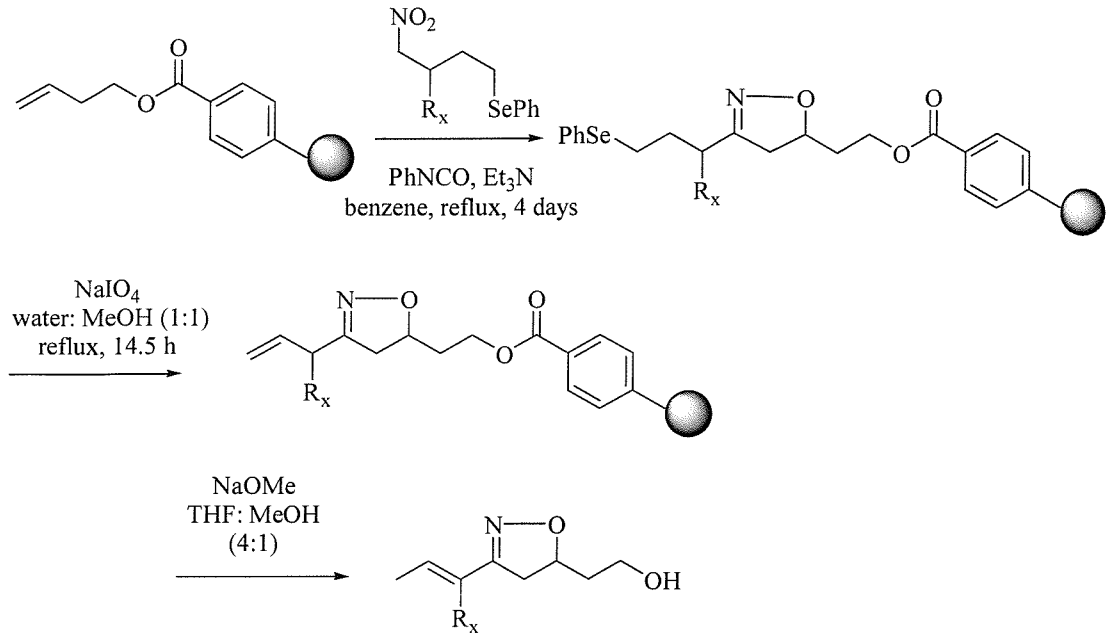


Figure 4.9: Synthesis of polyisoxazolines (one iteration shown)

4.1.4 Selenoxide vs. sulfoxide elimination

Selenium is more expensive and more toxic than sulfur, but these disadvantages are far outweighed by the advantages the selenoxide elimination reaction has over the sulfoxide equivalent. The introduction of selenium is easy, as phenylselenenyl chloride is stable whereas phenylsulfenyl chloride (PhSCl) is not. Selenium forms weaker (and longer) σ bonds than sulfur, therefore reactions involving C-Se or O-Se bond cleavage are much faster e.g. alkyl selenoxides undergo *syn* elimination ~1000 faster than sulfoxides.[146] Selenium is more easily oxidised to selenium (IV) but it is very difficult to obtain Se (VI) in contrast to sulfoxides, which are easily oxidised to sulfones. Hence a wider range of oxidising agents are accessible for the selenide to selenoxide oxidation.

4.2 Results and Discussion

Tert-butyl 4-(2-amidino-2-selenaethyl)benzoate (**54**) was prepared in quantitative yield from *tert*-butyl 4-(bromomethyl)benzoate (**39**) and selenourea, in an analogous manner to the synthesis of isothiouronium salt (**40**) (Chapter 3). Isoselenouronium salt (**54**) was hydrolysed with aqueous NaOH and then alkylated *in situ* with a suitable bromide (Figure 4.10), thus avoiding isolation of the extremely air-sensitive selenols.

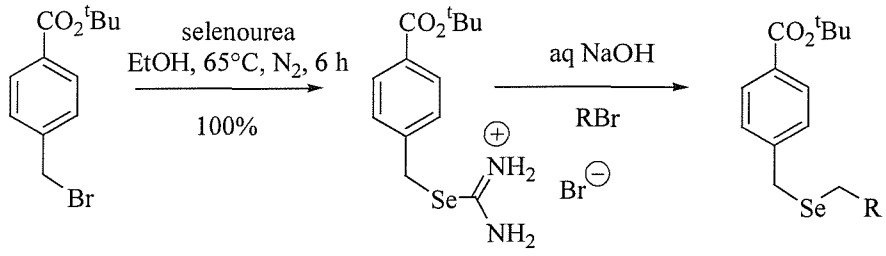


Figure 4:10: Synthesis of selenides via *hydrolysis of an isoselenouronium salt*

4.2.1 Study of the selenoxide elimination employing a phenylpropane substrate

Isoselenouronium salt (**54**) was alkylated with 1-bromo-3-phenylpropane to give the selenide (**56**) in 33% yield. The alkylation was achieved in one pot but in two discrete steps – the hydrolysis was effected first with 4% aqueous NaOH, then the solution was concentrated to give the intermediate selenolate (**55**) before the bromide was added in EtOH (Figure 4.11).

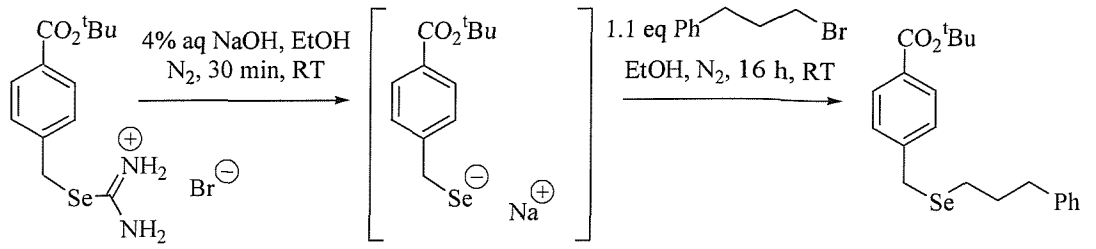


*Figure 4.11: Synthesis of selenide (**56**)*

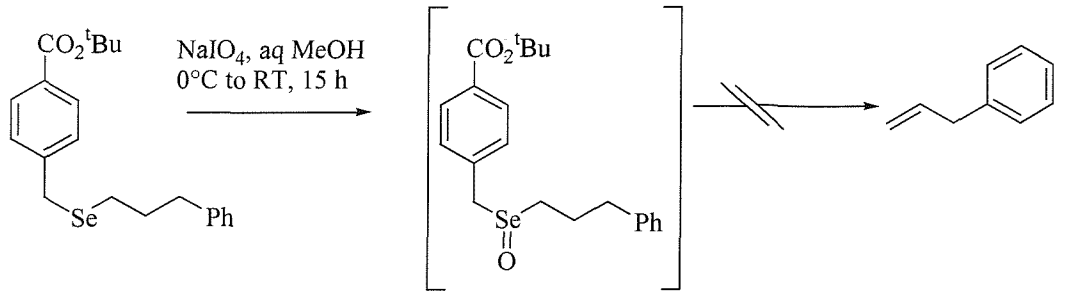
*4.2.1.1 Oxidation of selenide (**56**)*

Oxidation of selenide (**56**) to the selenoxide (**57**) was attempted with an excess of 60% aqueous H_2O_2 in THF, initially at 0°C for 2.5 hours, after which the solution was allowed to warm up to room temperature (23°C). Selenoxides are very unstable molecules and hence it was predicted that immediate fragmentation would occur upon warming to room temperature, giving the allylbenzene product (**42**) and a selenenic acid. However, even after 4 hours at room temperature, no allylbenzene (**42**) was detected (TLC, HPLC).

Cumene hydroperoxide (1 equivalent) was employed as an alternative oxidant as this had previously been used to generate allylbenzene *via* selenoxide elimination.[173] After 48 hours at room temperature, no allylbenzene was detected (TLC) and selenide (**56**) remained; hence the mixture was heated at 45°C for 24 hours, but without success. Another equivalent of cumene hydroperoxide was added and the reaction heated for a further 24 hours. The reaction was halted at this time even though selenide (**56**) still remained, because decomposition products began to appear. No allylbenzene (**42**) was observed.

An alternative oxidant, sodium metaperiodate, was used in aqueous MeOH (Figure 4.12). Again, the initial addition of oxidant was at 0°C, but then the reaction was allowed to warm up slowly to room temperature overnight (15 h). No starting selenide (**56**) remained, but equally, no allylbenzene (**42**) was visible. Crude analysis of the product suggested selenoxide (**57**) had been formed, which was surprising as selenoxides are usually too unstable to be isolated. The selenoxide structure was

substantiated by RP HPLC/MS and the presence of non-equivalent benzylic protons in the ^{1}H NMR spectrum, as had been observed for the sulfoxide analogue (**2b**).



56 **57** **42**

*Figure 4.12: Oxidation and elimination of selenide (**56**) failed to produce allylbenzene*

4.2.1.2 Attempted elimination of allylbenzene

Selenoxide (**57**) was heated in MeOH at 40°C to effect *syn* elimination. After 28 hours, no selenoxide remained and yet no allylbenzene (**42**) was detected either (Figure 4.13). After work-up and analysis, it was found that the only product was selenide (**56**). These inadvertent reductions have been observed previously when a selenenic acid or a selenol was present during the elimination. Clark[170] noted that primary selenoxides in particular were slow to undergo thermolysis. Thus during extended reaction times, the small quantities of selenenic acid produced from the elimination catalyse the reduction of the remaining selenoxide to the selenide, and hence the yield of the olefins were low. Usually, this reduction can be prevented by using an excess of oxidant or by trapping the selenenic acid as it is formed.

4.2.1.3 Attempted elimination of allylbenzene from a resin-bound selenide

Selenide (**56**) was dissolved in formic acid to effect removal of the *tert*-butyl ester and give acid (**58**) in 74% yield.[174] Acid (**58**) was attached to aminomethyl polystyrene resin (**8**) using DIC/HOBt coupling conditions. Resin (**59**) was oxidised with sodium metaperiodate (2 equivalents) in aqueous MeOH overnight. TLC proved

no concomitant elimination had occurred, therefore the resin was heated in MeOH overnight. No products were detected (TLC, HPLC) (Figure 4.13).

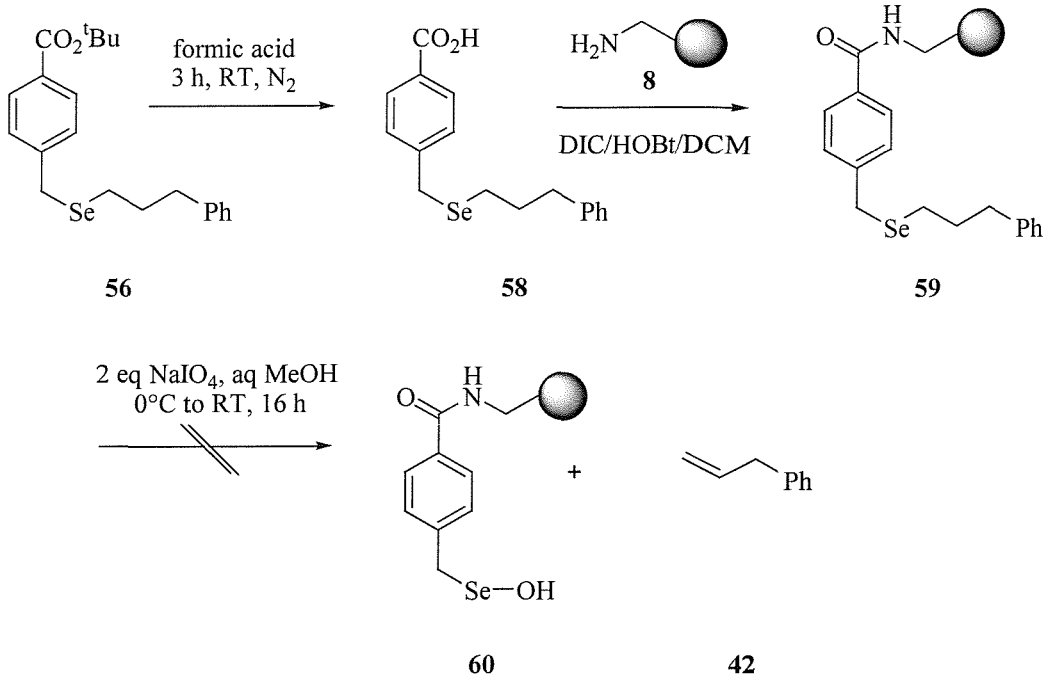


*Figure 4.13: Synthesis and attempted elimination of resin-bound phenylpropane selenide (**59**)*

Previously, the sulfoxide analogue (**2b**) had failed to eliminate (Chapter 3), but it was thought that the selenoxide (**57**) would undergo the pericyclic elimination more easily (at room temperature). As this proved not to be the case, the more reactive indanone derivative of the selenide was prepared because of the prior success enjoyed with the sulfoxide-indanone (**4b**).

4.2.2 Synthesis of an indanone analogue of the selenide

Indanone (**61**) was prepared in 22% yield from isoselenouronium salt (**54**) and 2-bromo-2-methylindanone (**47**) in a one-pot, two-step reaction involving initial hydrolysis using NaOH, followed by alkylation using caesium carbonate in DMF (Figure 4.14).

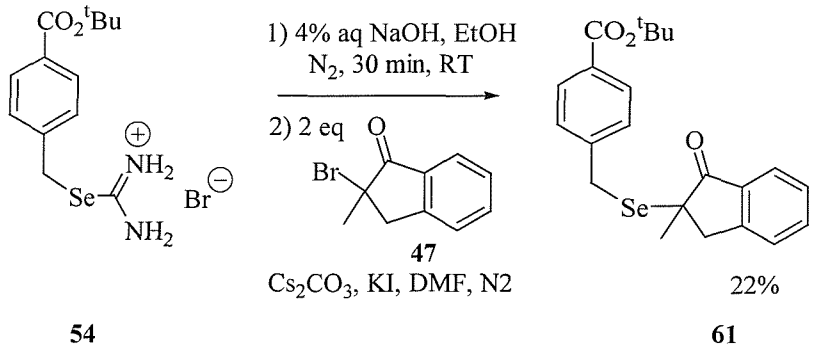


*Figure 4.14: Synthesis of an indanone-substituted selenide (**61**)*

The reason for the disappointing yield can be partly attributed to the formation of diselenide (**62**), which was isolated despite the use of stringent oxygen-free conditions. However, diselenides can be converted to unsymmetrical selenides by reduction with sodium borohydride[175] and subsequent alkylation with a suitable bromide, hence the material could be recovered (Figure 4.15).

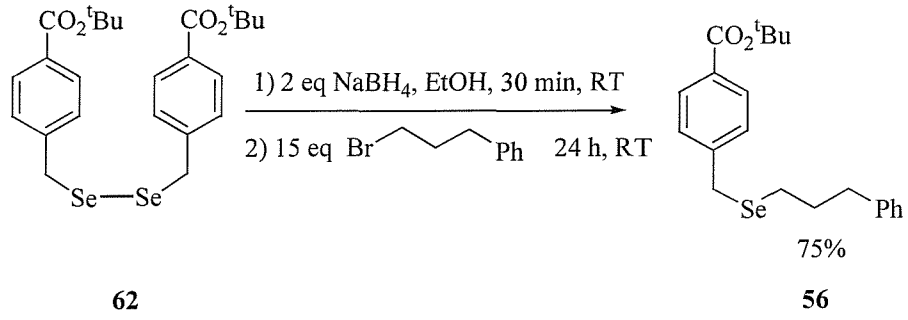
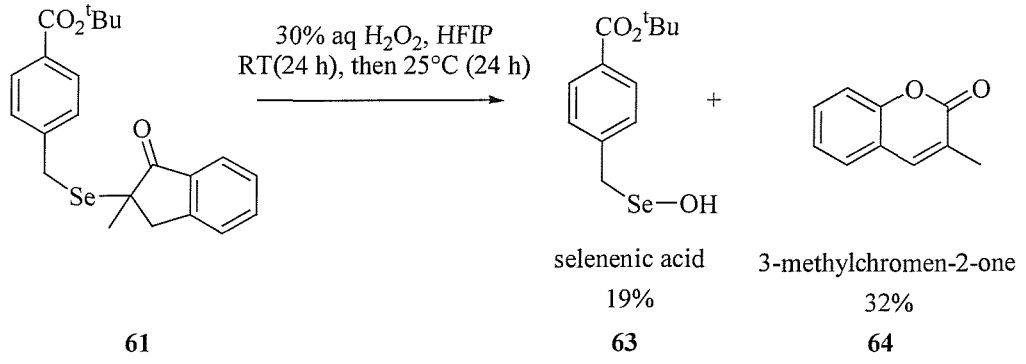


Figure 4.15: Reduction of a diselenide with sodium borohydride

Selenide (**61**) was oxidised with 30% aq H_2O_2 in HFIP. No reaction was observed after 24 hours at room temperature (18°C) so the reaction was warmed to 25°C overnight. The crude ratio of products was analysed by RP HPLC and found to be a 10:1 mixture of *exo*:*endo*-indenones. However, following purification by flash chromatography, the isolated products obtained were not the anticipated *exo* and *endo*-indenones but 3-methylchromen-2-one (**64**) (33% yield), which resulted from elimination followed by a Baeyer-Villiger reaction, and selenenic acid (**63**), isolated

in 19% yield (Figure 4.16). The isolation of selenenic acid (**63**) was surprising, as selenenic acids are notoriously unstable. However its presence indicated that the desired selenoxide pericylic elimination must have occurred.



selenenic acid 19% **63**

3-methylchromen-2-one 32% **64**

61

Figure 4.16: Solution phase oxidative elimination of indenones

A resin-bound selenide-indanone model was synthesised by deprotecting the *tert*-butyl ester and coupling acid (**65**) to aminomethyl polystyrene resin (**8**) using DIC/HOBt.

tert-Butyl deprotection of selenide (**61**) was initially attempted with 50% TFA/DCM as had been employed previously for the deprotection of the analogous sulfide (**4a**). However, the desired acid was obtained in only 54% yield. During the hydrolysis, the reaction mixture changed colour from yellow to red, which was indicative of polymeric selenium compounds being formed, despite the inert atmosphere used. 2-Methylindanone (**46**) was also isolated from this reaction in 46% yield, suggesting that C-Se cleavage was occurring. This observation implies an alternative linkage strategy may be developed in time that exploits this hitherto unexpected reaction.

An alternative deprotection strategy was thus employed, using neat formic acid. This method proved successful, affording acid (**65**) in 77% yield (Figure 4.17). The acid was then coupled to aminomethyl polystyrene resin (**8**) with DIC/HOBt to form resin-bound selenide (**66**) (Figure 4.18). The coupling reaction was monitored by gel phase ^{13}C NMR which clearly showed the presence of three methylenes, and the chemical shifts were in good agreement with the solution ^{13}C NMR of selenide (**61**).

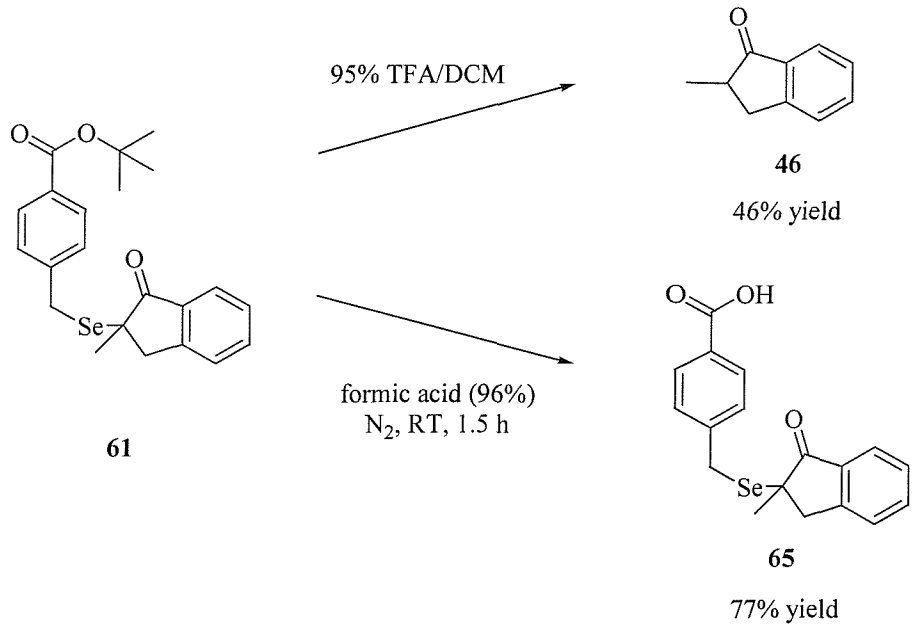


Figure 4.17: Deprotection of tert-*butyl 4-[2-(2-methyl-1-oxoindan-2-yl)-2-selenaethyl]benzoate* ***(61)***

Oxidation and concomitant elimination of *exo* and *endo*-indenones was then achieved by oxidation with hydrogen peroxide overnight (Figure 4.18). The yield of products was 56% overall (over 2 steps) and the *exo*-indenone (**49**) dominated as before (4:2.5 *exo*:*endo*), although not to the same extent. In addition, a small amount of 3-methylchromen-2-one (**64**) was isolated, resulting from the Baeyer-Villiger reaction.

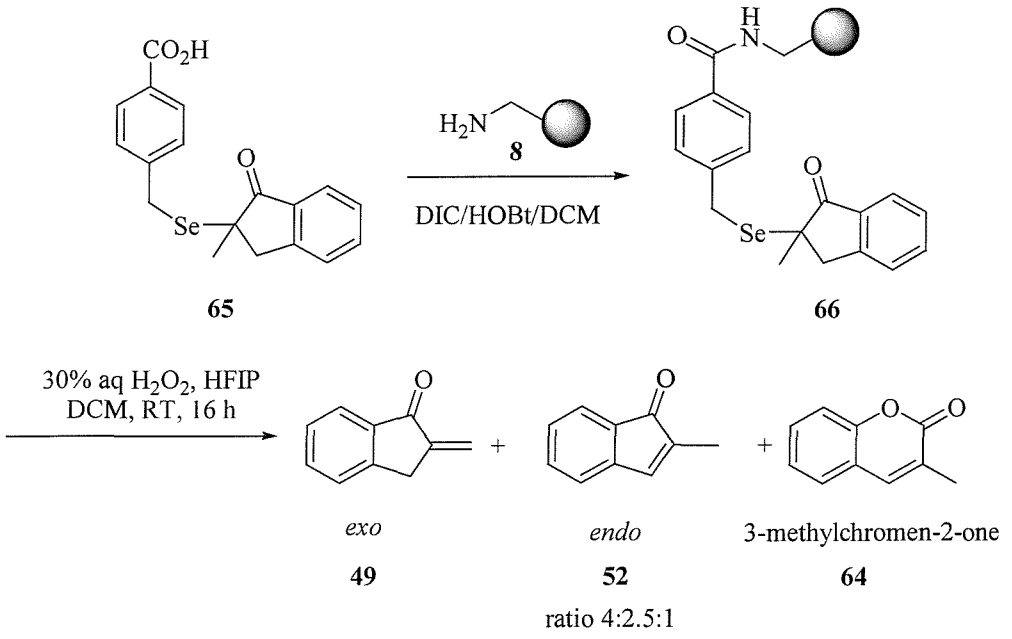


*Figure 4.18: Initial synthetic route to a resin-bound selenide-indanone (**66**) and subsequent oxidative cleavage*

During initial solid phase experiments, the resin-bound selenide-indanone was formed by coupling the entire selenide-indanone moiety (**65**) to the resin in one step. It was now decided to synthesise the resin-bound selenide-indanone in a stepwise manner, in a route analogous to the synthesis of the sulfoxide linker for peptide eliminations (Chapter 3).

Bromoacetic acid was coupled onto TentaGel resin using DIC/HOBt and then the bromide was displaced with selenourea to form the resin-bound isoselenouronium salt (**67**). Hydrolysis was effected simply by washing the resin with 2% then 10% aq NaOH, followed by immediate treatment with 2-bromo-2-methylindanone (**47**) and caesium carbonate in DMF to achieve alkylation of the intermediate selenol.

Resin-bound selenide (**68**) was then heated in MeOH overnight to confirm its stability prior to the activating oxidation step. As anticipated, no cleavage of material from the resin was observed. Oxidation to the selenoxide was effected with aqueous sodium metaperiodate in dioxane, in contrast to previous experiments, where H_2O_2 had been employed. Spontaneous elimination of the selenoxide was observed during

the oxidation step, leading to the formation of *exo* and *endo*-indenones (Figure 4.19). The indenones were identified by RP HPLC, which gave the *exo*:*endo* ratio as 21:1. The dominance of the *exo* isomer was observed before when H_2O_2 was the oxidant used to effect elimination, but the ratio was only 4:2.5 *exo*:*endo*. It is possible that the use of sodium metaperiodate has somehow favoured the *exo*-isomer, but it is more likely that the altered position of the selenium on the resin has enhanced selectivity for the *exo*-indenone.

The overall isolated yield from the sodium metaperiodate oxidation and elimination was 32% (5 steps from TentaGel resin). Unsurprisingly, no Baeyer-Villiger product was detected.

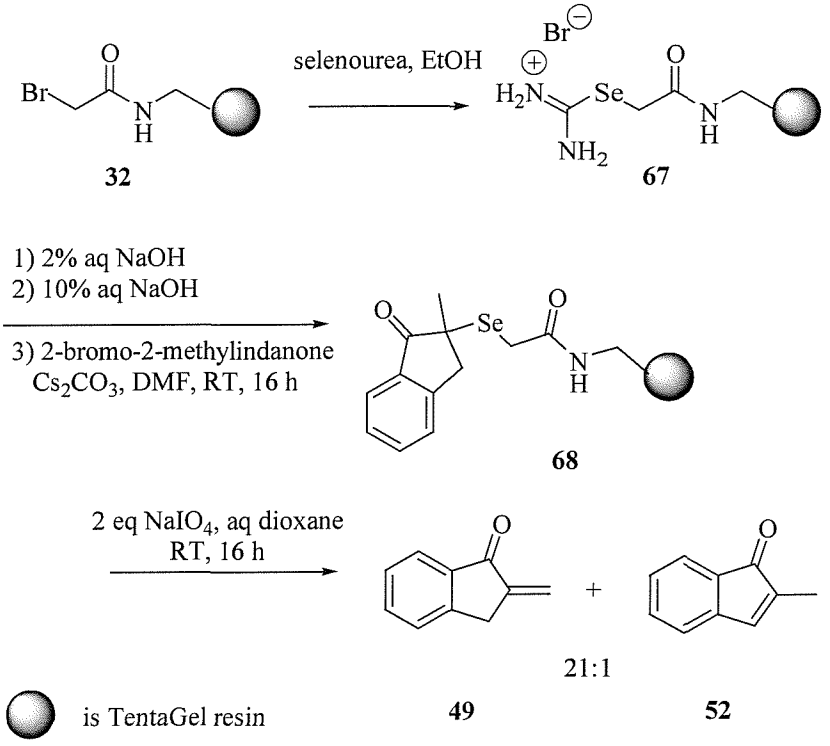


*Figure 4.19: Alternative synthesis of resin-bound selenide-indanone (**68**)*

Crystals of selenide (**61**) were grown from $CHCl_3$/hexane (Figure 4.20).

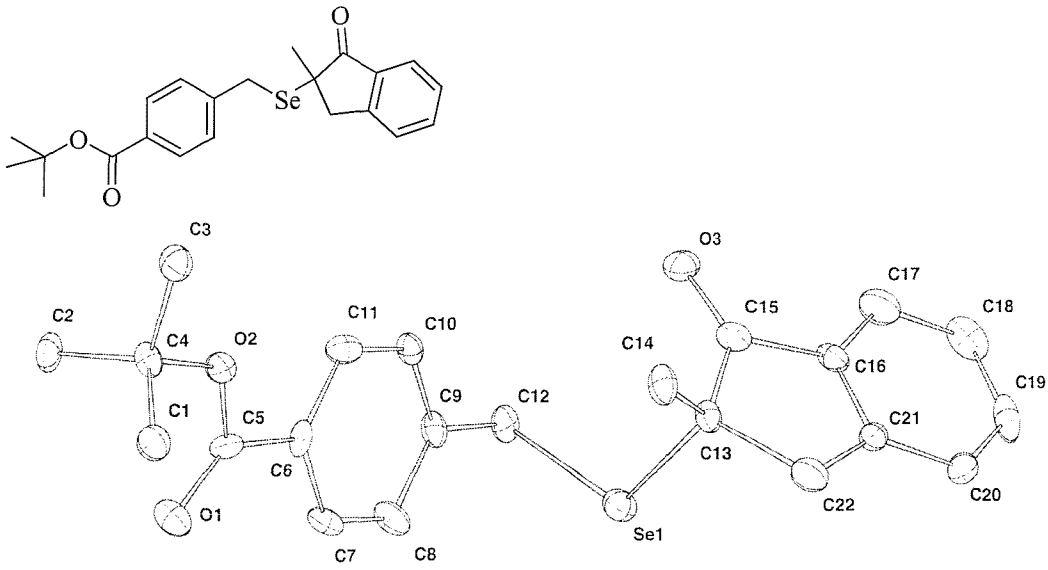


Figure 4.20: Single crystal structure refinement of
tert-*butyl 4-[2-(2-methyl-1-oxoindan-2-yl)-2-selenaethyl]benzoate* (***61***)

4.2.3 Comparison of sulfur and selenium analogues

The studies carried out on the selenoxide elimination reaction have demonstrated that the process is not as facile as was originally thought. Unactivated alkyl sulfoxides were previously shown to be unreactive towards the pericyclic elimination (Chapter 3), but it was thought that the more reactive selenium analogues would eliminate at room temperature. Investigations into the elimination of analogous selenoxides in solution demonstrated that these eliminations were not straightforward and were unsuccessful at room temperature. In contrast, both the sulfoxide and selenoxide indanone analogues have been shown to eliminate in the desired pericyclic manner. The selenoxide indanone is more reactive than the analogous sulfoxide (**4b**) because of the lower bond energy of the C-Se bond. Typically, a C-Se bond has an energy of 272 $kJmol^{-1}$ compared to 234 $kJmol^{-1}$ for a C-S bond, thus resulting in the selenium-

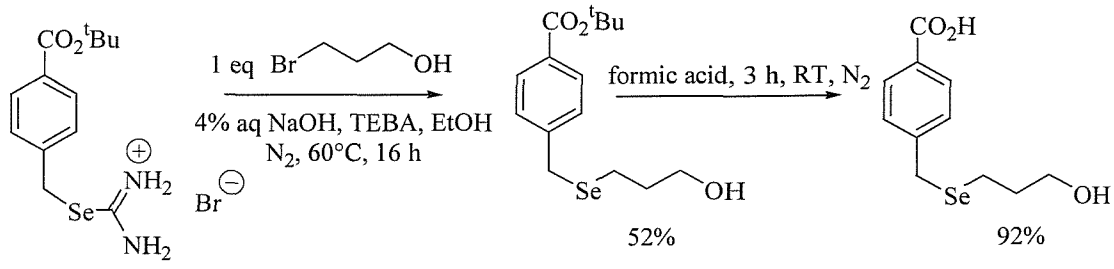
containing compound having a lower stability. Therefore, as anticipated, the selenoxide underwent elimination at significantly reduced temperatures; room temperature as opposed to 100°C for the sulfoxide.

As discussed in Chapter 3, the crystal structure of the sulfoxide (Figure 3.36) enabled some conclusions to be drawn about the predominance of the *exo*-indenone (**49**) isomer. It was thought that the conformation where the sulfoxide removed a methyl proton, thus forming the *exo*-indenone (**49**), was more favourable since steric interactions would be minimised. Although the analogous selenoxide was not isolated, it seems likely that the same explanation holds true and hence the observed predominance of the *exo*-indenone (**49**) upon elimination was not surprising.

Selenium is a larger atom than sulfur and may thus force the indanone substrate into a slightly altered conformation, positioning the selenoxide oxygen so that a proton may be abstracted more easily.

4.2.4 Ester model

The original aim of this research was to develop a linker, which would release allyl and vinyl esters upon cleavage. With this goal in mind, another selenide model was synthesised, with a terminal alcohol for subsequent esterification of acids. Selenide (**69**) was prepared in 52% yield from isoselenouronium salt (**54**) and 1-bromopropanol under phase transfer conditions (Figure 4.21).



54 **69** **70**

*Figure 4.21: Synthesis of selenide (**69**)*

The *tert*-butyl ester was deprotected with formic acid in 92% yield to allow the carboxylic acid (**70**) to be coupled to polystyrene aminomethyl resin (**8**). Fmoc-Phe-OH was chosen to be esterified onto the resin-bound alcohol, to investigate applications of the selenoxide linker for peptide synthesis.

Esterification of Fmoc-Phe-OH was achieved using DIC/DMAP coupling conditions[129] to give the resin-bound Fmoc-Phe-OH (**72**) in 32% yield. A trial cleavage was performed whereby the resin was reacted with sodium metaperiodate (2 equivalents) in dioxane/water overnight to effect elimination and release Fmoc-Phe-OAllyl. Previously, an authentic standard of Fmoc-Phe-OAllyl (**73**) had been synthesised *via* the esterification of Fmoc-Phe-OH with allyl bromide and caesium carbonate in DMF. RP HPLC/MS analysis confirmed the successful elimination of Fmoc-Phe-OAllyl (**73**) by comparison with the known standard (Figure 4.22).

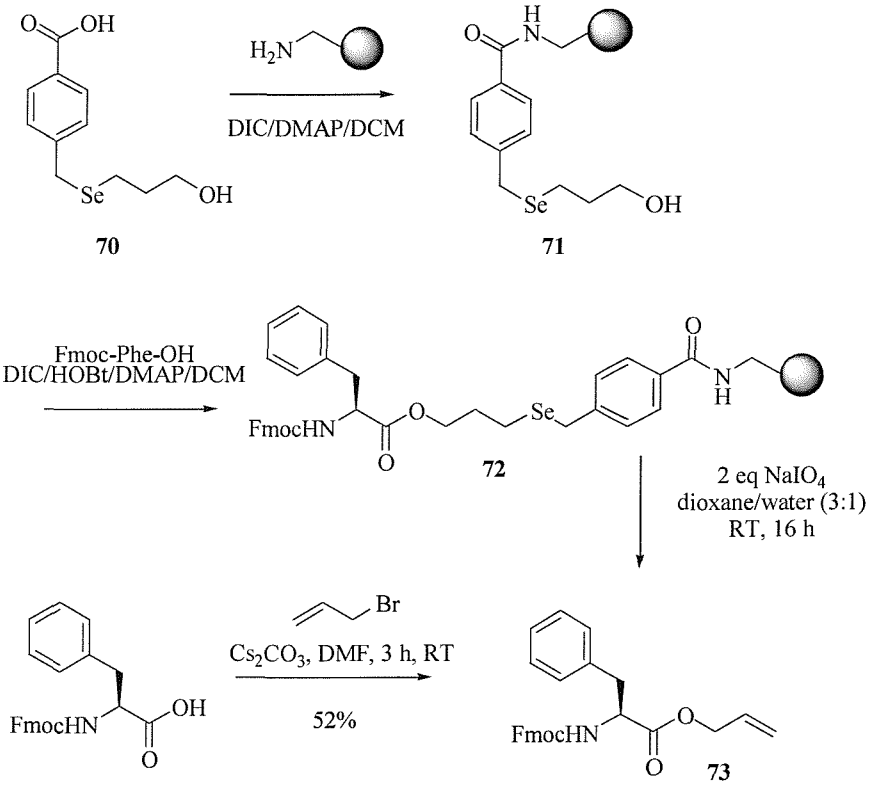


Figure 4.22: Synthesis of Fmoc-Phe-OAllyl (73)

4.3 Conclusions

It has been demonstrated that the selenoxide based linker eliminated at a significantly lower temperature than that required for elimination in the sulfoxide analogue. In addition, the sulfoxide linker only cleaved successfully if an activating substrate was present to drive the elimination, even then high temperatures (100°C) were necessary. In contrast, the selenoxide analogue has been shown to eliminate even "unactivated" substrates at room temperature, for example, to form allyl esters. The selenoxide elimination reactions are not fully optimised, but show the selenoxide linker has potential, in particular for the synthesis of unsaturated molecules, e.g. allyl esters.

Chapter 5: Experimental

5.1 General Information

5.1.1 Instrumentation

Nuclear magnetic resonance (NMR) spectra were recorded using a Bruker AC 300 spectrometer operating at 300 MHz for ^{1}H, 75 MHz for ^{13}C and 282 MHz for ^{19}F, a Bruker AM 360 operating at 69 MHz for ^{77}Se and a Bruker DPX 400 spectrometer operating at 400 MHz for ^{1}H and 100 MHz for ^{13}C (δ scale in parts per million). Coupling constants (*J*) were measured in Hertz (Hz). ^{77}Se NMR were referenced to dimethylselenide and recorded with proton decoupling. ^{19}F NMR were referenced to hexafluorobenzene.

ESI mass spectra were recorded using a VG Platform Quadrupole Electrospray Ionisation mass spectrometer, measuring mono-isotopic masses. FAB mass spectra were recorded on a VG analytical 70-250-SE normal geometry double focusing mass spectrometer using argon as a bombarding gas in a 3-nitrobenzyl alcohol (3-NBA) matrix. High resolution accurate mass measurements were carried out at 10,000 resolution using mixtures of polyethylene glycols and/or polyethylene glycolmethylethers as mass calibrants for FAB.

Infra-red spectra were recorded on a Bio-Rad Golden Gate FTS 135 spectrophotometer; all samples being run neat as oils or solids.

Melting points were determined using a Gallenkamp melting point apparatus and are uncorrected.

UV-VIS spectra were measured on a Hewlett Packard 8452A diode array spectrophotometer.

Microwave experiments were carried out using a domestic microwave oven manufactured by Matsui (model MC199TC), [950 W, 2450 Hz].

Aluminium backed silica plates - 0.25 mm layer silica gel 60 with fluorescent indicator (Alugram® SIL G/UV_{254}) were used for thin layer chromatography (TLC). UV (λ = 254 nm) and $KMnO_4$ stain [$KMnO_4$ (3.00 g), K_2CO_3 (20.0 g), 5% aq NaOH (5 mL) in water (300 mL)] were used to visualise compounds unless otherwise stated. Other stains used were bromocresol green (BCG), ninhydrin and polymolybic acid (PMA).

Reverse phase analytical HPLC (RP HPLC) was performed using a Hewlett Packard HP1100 Chemstation, using a Phenomenex C_{18} prodigy 5μ (150 mm x 3.0 mm i.d.) column. The gradients used are described in the table below.

Solvent 1: water with 0.1% TFA

Solvent 2: acetonitrile with 0.042% TFA

	Starting conditions	Finishing conditions	Time/min
Gradient A	Solvent 1	Solvent 2	20
Gradient B	50% Solvent 1	Solvent 2	20
Gradient C	Solvent 1	Solvent 2	40

Table 5.1: Gradients used for RP HPLC purification

Preparative RP HPLC was achieved using a Hewlett Packard HP 1100 Chemstation equipped with an automatic fraction collector using a Phenomenex C_{18} prodigy 5μ (250 mm x 10.0 mm i.d.) column and eluting with Gradient C.

Single crystal data were collected using an Enraf Nonius KappaCCD diffractometer. The structures were solved using SHELXS97 and refined using SHELXL97.[176,177]

5.1.2 Reagents

Dry solvents were prepared as follows: DCM and pyridine were distilled from CaH_2, THF was distilled from sodium and benzophenone. ^{t}BuOH was dried over 4 Å molecular sieves.

5.2 General Experimental Methods

5.2.1 Quantitative ninhydrin test[9]

A known mass of resin (*ca.* 5 mg) was weighed into a small test tube and treated with 6 drops of Reagent A (preparation described below) and 2 drops of Reagent B (preparation described below) and heated in an oil bath at 110°C for 10 min. The test tube was cooled and 60% aq EtOH (2 mL) was added. The resin was removed by filtration through glass wool and the deep blue filtrate collected in a 25 mL volumetric flask. The resin was washed with a solution of tetraethylammonium chloride (0.5 M in DCM, 2 x 0.5 mL), and the volume made up to 25 mL with 60% aq EtOH. The absorbance at 570 nm was then measured against a reagent blank. The level of amine present was calculated using the equation below:

Quantity of amine present (mmol/g) = $[(A_{570} \times V)/ (E_{570} \times W)] \times 10^3$

Where E_{570} is an average extinction coefficient suitable for most peptides with the value of 1.5×10^4 $M^{-1}cm^{-1}$, V is the final volume of the solution (25 mL), W is the weight of the resin sample (mg) and A_{570} is the recorded absorbance at 570 nm.

Reagent A:
Solution 1. Reagent grade phenol (40.0 g) was dissolved in absolute EtOH (10 mL) with warming and then stirred over Amberlite mixed-bed resin MB-3 (4.00 g) for 45 min. The mixture was then filtered.
Solution 2. Potassium cyanide (65 mg) was dissolved in water (100 mL). A 2 mL aliquot of this solution was diluted with pyridine (freshly distilled from ninhydrin) and stirred over Amberlite mixed-bed resin MB-3 (4.00 g). The solution was filtered and mixed with Solution 1 to give Reagent A.

Reagent B:
Ninhydrin (2.50 g) was dissolved in absolute EtOH (50 mL).

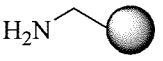
5.2.2 Quantitative Fmoc test[12]

A known quantity of resin (*ca.* 5 mg) was treated with a solution of 20% piperidine in DMF (1 mL) for 15 min. The solution was filtered through glass wool and the volume of the filtrate made up to 10 mL with 20% piperidine in DMF. The absorbance at 302 nm was measured against a blank of 20% piperidine in DMF. The resin substitution was calculated from the following equation:

$$\text{Substitution (mmol/g)} = [(A_{302} \times V)/ (E_{302} \times W)] \times 10^3$$

where A_{302} is the absorbance of the piperidyl-fulvene adduct, V is the final volume of the solution (10 mL), W is the weight of the resin sample (mg) and E_{302} is the extinction coefficient of the adduct at 302 nm (7800 $M^{-1}cm^{-1}$).

5.2.3 Preparation of aminomethyl resin[127] (8)



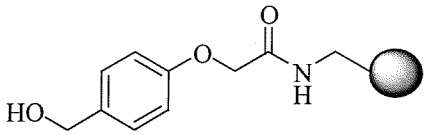
Chloromethyl resin (Merrifield resin) (1.0 eq, 5.00 g, 1.40 mmol/g, 7.0 mmol) was swollen in DMF (100 mL) for 20 min, then potassium phthalimide (1.6 eq, 11.2 mmol, 2.08 g) was added portionwise and the mixture heated at 120°C (16 h). The resin was cooled, filtered and then washed thoroughly with hot DMF (2 x 50 mL), DMF/water (1:1) (2 x 50 mL), water (2 x 50 mL), dioxane/water (1:1) (2 x 50 mL), dioxane (2 x 50 mL), EtOH (2 x 50 mL), MeOH (2 x 50 mL), and Et_2O (2 x 50 mL) and dried *in vacuo* to yield phthalimidomethyl resin.

The phthalimidomethyl resin (1.0 eq, 5.20 g, 0.87 mmol/g, 5.00 mmol) was suspended in EtOH (50 mL) and hydrazine hydrate (8.0 eq, 40.0 mmol, 3.31 g, 3.22 mL) was added. The mixture was refluxed overnight, cooled and the resin filtered and washed with hot DMF (2 x 100 mL), hot water (2 x 100 mL), hot DCM (2 x 100 mL), hot water (2 x 100 mL), DMF (2 x 100 mL), DCM (2 x 100 mL), EtOH (2 x

100 mL), MeOH (2 x 100 mL) and Et_2O (2 x 100 mL) and dried *in vacuo* to yield the title compound.

A quantitative ninhydrin test gave the resin loading as 1.20 mmol/g (86% yield).

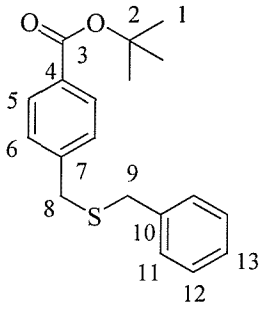
5.2.4 Preparation of Wang polystyrene resin[38] (10)



Aminomethyl resin (**8**) (5.00 g, 1.25 mmol/g, 6.25 mmol) was swollen in DCM (10 mL). HMPA linker (**9**) (a Wang-type linker) (2.0 eq, 12.5 mmol, 2.28 g) and HOBt[129] (2.0 eq, 12.5 mmol, 1.69 g) were dissolved in DCM (5 mL) and stirred for 10 min. After this time, DIC (2.2 eq, 13.8 mmol, 1.73 g, 2.15 mL) was added and the solution stirred for a further 10 min, before it was added to the pre-swollen resin. The resin was shaken at room temperature (48 h) and then a ninhydrin test was performed. This gave the expected negative result so the resin was washed with DMF (2 x 50 mL), DCM (2 x 50 mL), MeOH (2 x 50 mL) and Et_2O (2 x 50 mL) and dried *in vacuo* to yield the title compound.

5.3 Experimental for Chapter 2

5.3.1 *Tert*-butyl 4-[(phenylmethylthio)methyl]benzoate (1a)



Tert-butyl 4-(amidinothiomethyl)benzoate (**40**) (1 eq, 1.87 mmol, 500 mg) was dissolved in water (2 mL) and EtOH (2 mL) under nitrogen. To this solution was added 4% aq NaOH (5 mL) and a white precipitate was formed. The mixture was stirred for 30 min and then benzyl bromide (1.2 eq, 2.24 mmol, 360 mg, 250 μL) was added and the solution left to stir at room temperature (16 h). The product was extracted with $CHCl_3$ (2 x 10 mL), washed with water (2 x 10 mL), brine (1 x 15 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give a yellow oil. The product was purified by flash chromatography on silica gel eluting with 0% to 10% diethyl ether in hexane to give the title compound (441 mg, 75%) as a yellow oil.

R_f: 0.4 (10% Et_2O: hexane)

RP HPLC (λ=254 nm) Gradient A: 22.4 min (100%)

IR (ν_{max}/cm^{-1}): 1711 C=O (s)

m/z (EI): 314 (94%, $M^{+\cdot}$)

HRMS (EI): $C_{19}H_{22}O_2S$ Calc. 314.1341 Found 314.1353

δ_H (300 MHz, $CDCl_3$): 1.62 (9H, s, $^1CH_3$); 3.59, 3.63 (2 x 2H, s, $^8CH_2$, $^9CH_2$); 7.28-7.36 (7H, m, ^6CH, ^{11}CH, ^{12}CH, ^{13}CH); 7.94 (2H, d, *J* 8, ^5CH)

δ_C (75 MHz, $CDCl_3$): 28.2 (^1C); 35.3, 35.5 (^8C, ^9C); 80.9 (^2C); 127.1, 128.5, 128.8, 129.0, 129.6, (^5C, ^6C, ^{11}C, ^{12}C, ^{13}C); 130.7, 137.8, 143.0 (^4C, ^7C, ^{10}C); 165.5 (^3C)

5.3.2 Solution phase oxidation of sulfides with $NaIO_4$

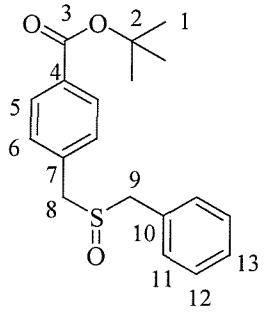
Sodium metaperiodate (1.1 eq, 0.92 mmol, 0.20 g) was dissolved in water (1 mL) and cooled (ice/water bath). *Tert*-butyl 4-[(phenylmethylthio)methyl]benzoate (**1a**) (1.0 eq, 0.84 mmol, 0.26 g) was dissolved in dioxane (3 mL) and added dropwise to the oxidant. The reaction was allowed to warm up to room temperature and left to stir (18 h). The product was extracted with DCM (2 x 2 mL) and washed with water (1 x 2 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give sulfoxide (**1b**) as an off-white solid in 90% crude yield.

Methods B, C and D followed the above protocol, but with the specific conditions outlined in the table below.

Method	Equivalents of $NaIO_4$	Temperature/°C	Reaction Time/h	Crude Yield/%
A	1.1	RT	18	90
B	1.1	40	5.5	70
C	1.2	RT	5.5	78
D	1.2	40	4	91

Table 5.2: Conditions used for the oxidation of sulfides with $NaIO_4$

5.3.3 *Tert*-butyl 4-{[benzylsulfinyl]methyl}benzoate (1b)



Sulfoxide (**1b**) was prepared using the procedure described above (Method D, Section 5.3.2). After work-up, the title compound was isolated as an off-white solid (189 mg, 91%).

R_f: 0.60 (EtOAc: hexane: AcOH 3: 6.5: 0.5)

RP HPLC (λ=254 nm) Gradient A: 17.1 min (100%)

IR (ν_{max}/cm^{-1}): 1033 S=O (s); 1714 C=O (s)

m/z (ES$^+$): 331 (100%, $[M+H]^+$); 661 (54%, $[2M+H]^+$)

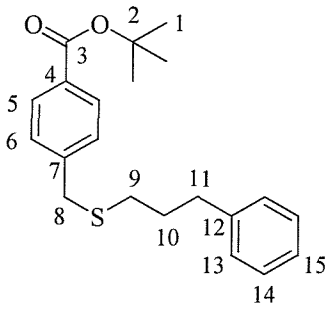
HRMS (FAB, 3-NBA): $C_{19}H_{23}O_3S$ Calc. 331.1368 Found 331.1370

m.p.: 110-114°C

δ_H (300 MHz, $CDCl_3$): 1.60 (9H, s, $^1CH_3$); 3.84-4.02 (4H, m, $^8CH_2$, $^9CH_2$); 7.30-7.38 (7H, m, ^6CH, ^{11}CH, ^{12}CH, ^{13}CH); 8.00 (2H, d, *J* 8, ^5CH)

δ_C (75 MHz, $CDCl_3$): 28.1 ($^1CH_3$); 57.0, 57.6 ($^9CH_2$, $^8CH_2$); 81.2 (^2C); 128.5, 129.0, 130.0, 130.0, 130.1 (^5C, ^6C, ^{11}C, ^{12}C, ^{13}C); 129.8, 132.0, 134.7 (^4C, ^7C, ^{10}C); 165.4 (^3C)

5.3.4 *Tert*-butyl 4-[(3-phenylpropylthio)methyl]benzoate[150] (2a)



Tert-butyl 4-(amidinothiomethyl)benzoate (**40**) (1.0 eq, 2.0 mmol, 0.53 g), 1-bromo-3-phenylpropane (1.0 eq, 2.0 mmol, 0.40 g, 306 μL) and benzyltriethylammonium chloride (TEBA) (0.05 eq, 0.1 mmol, 22 mg) were dissolved in 20% aq NaOH (6 mL) under nitrogen. The mixture was stirred vigorously at 60°C for 1.5 hours. The product was extracted with EtOAc (2 x 10 mL) and then washed with water (2 x 10 mL), brine (1 x 10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give a yellow oil. The product was purified by flash chromatography on silica gel eluting with 0% to 5% diethyl ether in hexane to give the title compound (398 mg, 58%) as a colourless oil.

R_f: 0.36 (10% Et_2O: hexane)

RP HPLC (λ=254 nm) Gradient B: 20.1 min (100%)

IR (ν_{max}/cm^{-1}): 1709 C=O (s)

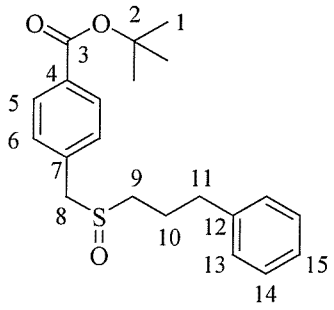
m/z (EI): 342 (54%, [$M^{+\cdot}$])

HRMS (EI): $C_{21}H_{26}O_2S$ Calc. 342.1654 Found 342.1670

δ_H (300 MHz, $CDCl_3$): 1.62 (9H, s, $^1CH_3$); 1.87 (2H, quint, *J* 7, $^{10}CH_2$); 2.41 (2H, t, *J* 7, $^9CH_2$); 2.68 (2H, t, *J* 7, $^{11}CH_2$); 3.73 (2H, s, $^8CH_2$); 7.14 (2H, d, *J* 8, ^6CH); 7.19-7.35 (5H, m, ^{13}CH, ^{14}CH, ^{15}CH); 7.93 (2H, d, *J* 8, ^5CH)

δ_C (75 MHz, $CDCl_3$): 28.2 (^{1}C); 30.6, 30.7 (^{9}C, ^{11}C); 34.7 (^{10}C); 35.9 (^{8}C); 81.0 (^{2}C); 126.0, 128.4, 128.5, 128.7, 129.6 (^{5}C, ^{6}C, ^{13}C, ^{14}C, ^{15}C); 130.7, 141.4, 143.4 (^{4}C, ^{7}C, ^{12}C); 165.6 (^{3}C)

5.3.5 *Tert*-butyl 4-{[(3-phenylpropyl)sulfinyl]methyl}benzoate (2b)



Sulfide (**2a**) was oxidised with sodium metaperiodate using Method D as described in the general procedure (Section 5.3.2), but with an increased reaction time (6 h). After work-up, the title compound was obtained as a colourless oil (100 mg, 56%).

R_f: 0.19 (50% EtOAc: hexane)

RP HPLC (λ=254 nm) Gradient A: 18.1 min (100%)

IR (ν_{max}/cm^{-1}): 1699 C=O (s)

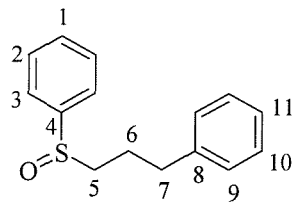
m/z (ES$^+$): 359 (100%, $[M+H]^+$); 717 (50%, $[2M+H]^+$)

HRMS (EI): $C_{21}H_{27}O_3S$ Calc. 359.1681 Found 359.1670

δ_H (300 MHz, $CDCl_3$): 1.61 (9H, s, $^1CH_3$); 2.02-2.15 (2H, m, $^{10}CH_2$); 2.56 (2H, t, *J* 8, $^{11}CH_2$); 2.65-2.82 (2H, m, $^9CH_2$); 3.94, 4.01 (2 x 1H, d, *J* 13, $^8CH_2$); 7.12 (2H, d, J 8, ^{6}CH); 7.16-7.32 (5H, m, ^{13}CH, ^{14}CH, ^{15}CH); 7.97 (2H, d, *J* 8, ^{5}CH)

δ_C (75 MHz, $CDCl_3$): 28.1 (^{1}C); 24.0, 34.5 (^{10}C, ^{11}C); 50.5 (^{9}C); 57.8 (^{8}C); 81.3 (^{2}C); 126.3, 128.5, 128.6, 130.0, 130.0 (^{5}C, ^{6}C, ^{13}C, ^{14}C, ^{15}C); 132.0, 134.3, 140.3 (^{4}C, ^{7}C, ^{12}C); 165.6 (^{3}C)

5.3.6 [(3-Phenylpropyl)sulfinyl]benzoate[149] (3b)



To a stirred solution of phenyl 3-phenylpropyl sulfide (1.0 eq, 2.0 mmol, 0.46 g) in 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) (2.5 mL) was added 30% aq H_2O_2 (2.0 eq, 4.0 mmol, 450 μL). The reaction was stirred at room temperature (1.5 h). The product was extracted with DCM (3 x 10 mL), washed with water (1 x 15 mL), brine (1 x 15 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The product was purified by flash chromatography on silica gel, eluting with 20% ethyl acetate in hexane, followed by 100% ethyl acetate, to give the title compound as colourless crystals (402 mg, 82%).

Sulfoxide (**3b**) was also synthesised using sodium metaperiodate as outlined in the general procedure (Method B, Section 5.3.2) to furnish the title compound as colourless crystals (1.52 g, 62%).

R_f: 0.25 (50% EtOAc: hexane)

RP HPLC (λ=254 nm) Gradient B: 5.92 min (95%)

IR (ν_{max}/cm^{-1}): 1040 S=O (s)

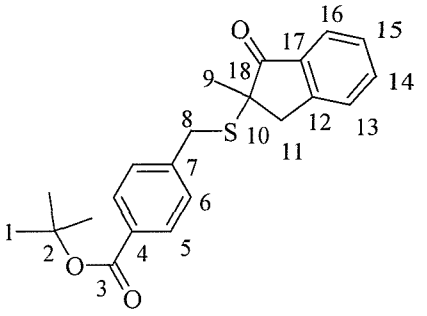
m/z (ES$^+$): 245 (100%, $[M+H]^+$)

m.p.: 37-41°C (Lit. 44-45°C)[149]

δ_H (400 MHz, $CDCl_3$): 1.82-1.93, 1.97-2.08 (2 x 1H, m, $^6CH_2$); 2.66 (2H, ddd, *J* 2, 8, 8, $^7CH_2$); 2.68-2.76 (2H, ddd, *J* 2, 8, 8, $^5CH_2$); 7.03-7.22 (5H, m, ^8CH, ^9CH, ^{11}CH); 7.38-7.55 (5H, m, ^1CH, ^2CH, ^3CH)

δ_C (100 MHz, $CDCl_3$): 24.0 (^6C); 34.9 (^7C); 56.7 (^5C); 124.5, 126.7, 128.9, 129.0, 129.7, 131.4 (^1C, ^2C, ^3C, ^9C, ^{10}C, ^{11}C); 140.8 (^8C); 144.2 (^4C)

5.3.7 *Tert*-butyl 4-[(2-methyl-1-oxoindan-2-ylthio)methyl]benzoate (4a)



Sulfide (**4a**) was synthesised from 2-bromo-2-methylindanone (**47**) and the isothiouronium salt (**40**) using the phase transfer conditions described above for sulfide (**2a**) (Section 5.3.4), but with an increased reaction time (heated at 60°C for 6 h). After work-up, the title compound was obtained as an off-white solid (98 mg, 27%).

R_f: 0.35 (10% Et_2O: hexane)

RP HPLC (λ=254 nm) Gradient A: 21.8 min, 87%

IR (ν_{max}/cm^{-1}): 1709 C=O (s, br)

m/z (EI): 368 (7%, [$M^{+\cdot}$])

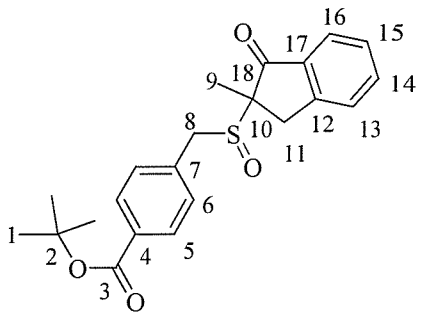
HRMS (EI): $C_{22}H_{24}O_3S$ Calc. 368.1446 Found 368.1433

m.p.: 91-94°C

δ_H (400 MHz, $CDCl_3$): 1.49 (9H, s, $^1CH_3$); 1.55 (3H, s, $^9CH_3$); 3.07, 3.17 (2 x 1H, d, *J* 18, $^{11}CH_2$); 3.81, 3.86 (2 x 1H, d, *J* 13, $^8CH_2$); 7.23 (2H, d, *J* 8, ^6CH); 7.31 (1H, d, *J* 8, ^{13}CH); 7.33, 7.52 (2 x 1H, dd, *J* 8, 8, ^{14}CH, ^{15}CH); 7.74 (1H, d, *J* 8, ^{16}CH); 7.79 (2H, d, *J* 8, ^5CH)

δ_C (100 MHz, $CDCl_3$): 22.8 (^9C); 28.6 (^1C); 33.9 (^8C); 43.3 (^{11}C); 52.5 (^{10}C); 81.3 (^2C); 125.6, 126.6, 128.4, 129.4, 130.0, 135.5 (^5C, ^6C, ^{13}C, ^{14}C, ^{15}C, ^{16}C,); 131.2, 134.9 (^{12}C, ^{17}C); 142.7 (^4C); 150.4 (^7C); 166.0 (^3C); 203.2 (^{18}C)

5.3.8 *Tert*-butyl 4-{[(2-methyl-1-oxoindan-2-yl)sulfinyl]methyl}benzoate (4b)



Tert-butyl 4-[(2-methyl-1-oxoindan-2-ylthio)methyl]benzoate (**4a**) (1.0 eq, 0.51 mmol, 0.18 g) was dissolved in HFIP (1.25 mL) and 30% aq H_2O_2 (2.0 eq, 1.02 mmol, 113 μL) was added. The reaction was stirred at room temperature (1.5 h) and then the product was extracted with DCM (2 x 5 mL), washed with water (1 x 5 mL), brine (1 x 5 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the title compound as a white solid. Recrystallisation from $CHCl_3$/hexane gave white needles of compound (**4b**) (162 mg, 84%).

Sulfoxide (**4b**) was also synthesised according to the sodium metaperiodate procedure, as outlined above (Method C, Section 5.3.2). After work-up, the title compound was obtained as colourless needles (238 mg, 50%).

R_f: 0.41 (50% EtOAc: hexane)

RP HPLC (λ=254 nm) Gradient A: 17.6 min (100%)

IR (ν_{max}/cm^{-1}): 1700 C=O (s, br)

m/z (ES$^+$): 385 (20%, $[M+H]^+$); 791 (100%, $[2M+H]^+$)

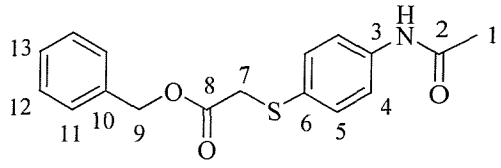
HRMS (EI): $C_{22}H_{24}O_4S$ Calc. 384.1395 Found 384.1395

m.p.: 112-115°C

δ_H (400 MHz, $CDCl_3$): diastereoisomers; * denotes major isomer 1.59 (9H, s, $^1CH_3$); 1.74* + 1.75 (3H, s, $^9CH_3$); 3.06, 3.94 + 3.12, 3.84* (2 x 1H, 2 x d, *J* 13, $^{11}CH_2$); 3.62 and 3.78 + 3.84 and 3.40* (2 x 1H, 2 x d, *J* 13, $^8CH_2$); 7.21-8.01 (8H, m, ^5CH, ^6CH, ^{13}CH, ^{14}CH, ^{15}CH, ^{16}CH)

δ_C (100 MHz, $CDCl_3$): diastereoisomers; * denotes major isomer 15.3* +20.4 (^9C); 28.6 (^1C); 35.7 + 37.8* (^{11}C); 54.2 + 55.1* (^8C); 68.7 + 69.1* (^{10}C); 81.1 (^2C); 125.1 + 125.2*, 126.9 + 127.1*, 128.8 + 128.8*, 130.3 + 130.4*, 130.5* + 130.6, 136.6 + 137.0* (^5C, ^6C, ^{13}C, ^{14}C, ^{15}C, ^{16}C,); 131.9* + 132.0, 135.3, 135.6+ 135.8* (^4C, ^{12}C, ^{17}C); 151.4 + 152.2* (^7C); 165.3 (^3C); 201.7 (^{18}C)

5.3.9 Phenylmethyl 2-[4-(acetylamino)phenylthio]acetate (7a)



4-Acetamidothiophenol (**6**) (1.0 eq, 25.0 mmol, 4.18 g), Cs_2CO_3 (1.0 eq, 25.0 mmol, 8.15 g) and KI (catalytic) were dissolved in DMF (12 mL) under nitrogen, to give a black solution, which became olive green after a few minutes. Benzyl bromoacetate (**5**) (1.0 eq, 25.0 mmol, 5.72 g, 3.96 mL) was added and a white precipitate formed. The reaction was stirred under nitrogen (16 h), the solution changing in colour from white to orange/yellow. Water (70 mL) was added and then the product was extracted with EtOAc (4 x 40 mL). The combined organic layers were washed with $NaHCO_3$ (40 mL), 1M HCl (1 x 40 mL), water (1 x 40 mL) and brine (1 x 40 mL), then dried over $MgSO_4$, filtered and concentrated *in vacuo*. The product was purified by flash chromatography on silica gel, eluting with 5% to 100% ethyl acetate in hexane then 1% MeOH in ethyl acetate, to give the title compound as an off-white solid (3.02 g, 40%).

R_f: 0.63 (EtOAc)

RP HPLC (λ=254 nm) Gradient A: 15.3 min (100%)

IR (ν_{max}/cm^{-1}): 1655 C=O (s) amide; 1733 C=O (s) ester

m/z (ES$^+$): 316 (7%, $[M+H]^+$); 338 (100% $[M+Na]^+$)

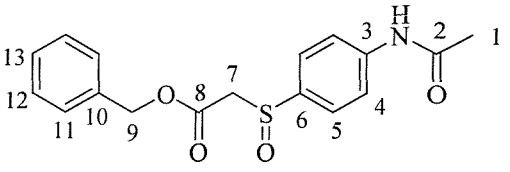
HRMS (EI): $C_{17}H_{17}NO_3S$ Calc. 315.0929 Found 315.0945

m.p.: 63-66°C

δ_H (300 MHz, $CDCl_3$): 2.23 (3H, s, $^1CH_3$); 3.69 (2H, s, $^7CH_2$); 5.20 (2H, s, $^9CH_2$); 7.34-7.51 (9H, m, ^4CH, ^5CH, ^{11}CH, ^{12}CH, ^{13}CH)

δ_C (100 MHz, $CDCl_3$): 25.0 (^1C); 38.0 (^7C); 67.6 (^9C); 120.8, 128.7, 128.8, 129.0, 132.5, (^4C, ^5C, ^{11}C, ^{12}C, ^{13}C); 129.8, 135.7, 138.0 (^3C, ^6C, ^{10}C); 168.9 (^2C); 170.1 (^8C)

5.3.10 Phenylmethyl 2-[4-(acetylamino)phenylsulfinyl}acetate (7b)



Sulfide (**7a**) (1.0 eq, 1.0 mmol, 0.32 g) was dissolved in HFIP (1.25 mL) and 30% aq H_2O_2 (2.0 eq, 2.0 mmol, 225 μL) was added. The solution was stirred at room temperature for 1 hour and the product extracted with DCM (3 x 5 mL). The combined organic layers were washed with water (1 x 10 mL), brine (1 x 10 mL) and dried over $MgSO_4$, filtered and concentrated *in vacuo* to yield the title compound as an off-white foam (304 mg, 92%).

R_f: 0.4 (10% MeOH: DCM)

RP HPLC (λ=254 nm) Gradient A: 12.3 min (100%)

IR (ν_{max}/cm^{-1}): 1257 S=O (s); 1684 C=O (s) amide; 1730 C=O (s) ester

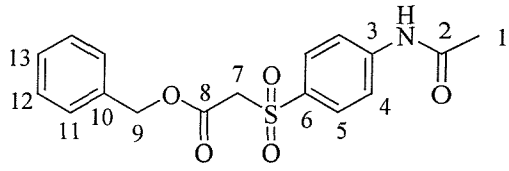
m/z (ES$^+$): 332 (55%, $[M+H]^+$); 354 (100%, $[M+Na]^+$)

HRMS (EI): $C_{17}H_{17}NO_4S$ Calc. 331.0878 Found 331.0899

δ_H (300 MHz, $CDCl_3$): 2.18 (3H, s, $^1CH_3$); 3.70, 3.91 (2 x 1H, d, *J* 13, $^7CH_2$); 5.11 (2H, s, $^9CH_2$); 7.27-7.36 (5H, m, ^{11}CH, ^{12}CH, ^{13}CH); 7.55, 7.68 (2 x 2H, d, *J* 9, ^4CH, ^5CH); 8.24 (1H, s, br, NH)

δ_C (100 MHz, $CDCl_3$): 24.8 (^1C); 61.6 (^7C); 67.9 (^9C); 119.2, 124.3, 127.5, 127.6, 127.7 (^4C, ^5C, ^{11}C, ^{12}C, ^{13}C); 134.8, 136.8, 141.9 (^3C, ^6C, ^{10}C); 164.6 (^2C); 169.2 (^8C)

5.3.11 Phenylmethyl 2-{[(4-acetylamino)phenyl]sulfonyl}acetate (7c)



Sulfide (**7a**) (1.0 eq, 2.0 mmol, 0.63 g) was dissolved in MeOH (8 mL) and cooled to 0°C. To this was added a solution of Oxone® (3.0 eq, 6.0 mmol, 3.68 g) in water (8 mL) and the resulting suspension stirred (16 h) at room temperature. The product was extracted with $CHCl_3$ (3 x 20 mL) and the combined organic layers washed with water (1 x 20 mL), brine (1 x 20 mL), and dried over $MgSO_4$, filtered and concentrated *in vacuo*. The product was purified by flash chromatography on silica gel, eluting with 10% to 100% ethyl acetate, to give the title compound as a white solid (213 mg, 31%).

R_f: 0.16 (50% EtOAc: hexane)

RP HPLC (λ=254 nm) Gradient A: 13.9 min (100%)

IR (ν_{max}/cm^{-1}): 1135 S=O (s); 1317 S=O (s); 1678 C=O (s) amide; 1737 C=O (s) ester

m/z (APCI$^+$): 348 (56%, $[M+H]^+$)

HRMS (EI): $C_{17}H_{17}NO_5S$ Calc. 347.0827 Found 347.0825

m.p.: 99-102°C

δ_H (300 MHz, $CDCl_3$): 2.21 (3H, s, $^1CH_3$); 4.15 (1H, s, $^7CH_2$); 5.11 (2H, s, $^9CH_2$); 7.27-7.34 (5H, m, ^{11}CH, ^{12}CH, ^{13}CH); 7.66, 7.74 (2 x 2H, d, *J* 9, ^4CH, ^5CH); 8.11 (1H, s, br, NH)

δ_C (100 MHz, $CDCl_3$): 25.1 (^1C); 61.5 (^7C); 68.5 (^9C); 119.7, 129.0, 129.1, 129.1, 130.2 (^4C, ^5C, ^{11}C, ^{12}C, ^{13}C); 133.1, 134.8, 144.1 (^3C, ^6C, ^{10}C); 162.7 (^2C); 169.5 (^8C)

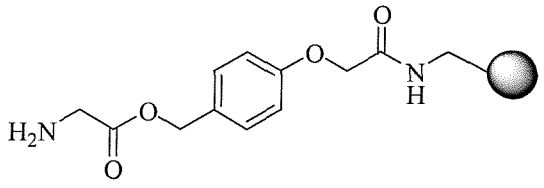
5.3.12 Effect of solvent and acid on the oxidation of sulfides

Sulfide (**7a**) (1.0 eq, 0.5 mmol, 0.16 mg) was dissolved in the appropriate solvent (1 mL) (Table 5.3) at room temperature for 15 min and 30% aq H_2O_2 (3.0 eq, 1.5 mmol, 170 μL) was added. The solution was stirred at room temperature, the progress of each reaction being monitored by TLC and RP HPLC. An aliquot (10 μL) was removed from the reaction at specific times (1 h, 2.5 h, 7 h, 22.5 h). To this aliquot was added water (500 μL) and MeCN (500 μL). 15 μL of this mixture was analysed by RP HPLC (Gradient A) and the absorbance measure at 254 nm. After 24 hours, the products were extracted with DCM (3 x 5 mL), the combined organic layers were washed with water (1 x 10 mL), brine (1 x 10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to yield the title compound as an off-white foam.

Reaction	Solvent	Additional solvent(s)	Isolated Yield (Crude)
A	HFIP	10 drops MeOH	153 mg, 92% colourless oil
B	^{i}PrOH	10 drops MeOH	147 mg, 89% colourless oil
C	^{i}PrOH	5 drops conc. HCl (catalytic)	137 mg, 83% pink oil

*Table 5.3: Conditions used for the oxidation of sulfide (**7a**) with 30% H_2O_2*

5.3.13 Preparation of Gly-Wang polystyrene resin (11)

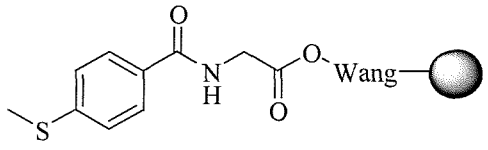


Wang polystyrene resin (**10**) (1.0 eq, 0.50 g, 0.70 mmol/g, 0.35 mmol) was swollen in DCM (1 mL). Fmoc-Gly-OH (2.0 eq, 0.70 mmol, 0.20 mg) and HOBt (2.0 eq, 0.70 mmol, 95 mg) were dissolved in DCM (2 mL) at room temperature. After 10 min, DIC (2.2 eq, 0.77 mmol, 97 mg, 121 μL) was added and the solution stirred for a further 10 min before it was added to the pre-swollen resin. The resin was then shaken at room temperature (4 h). The resin was filtered and washed with DMF (2 x 30 mL), DCM (2 x 30 mL), MeOH (2 x 30 mL) and Et_2O (2 x 30 mL). A qualitative ninhydrin test was negative.

A quantitative Fmoc test was performed in duplicate, which gave the substitution of the resin to be 0.23 mmol/g.

The Fmoc group was removed with 20% piperidine/DMF (2 x 20 mL). A qualitative ninhydrin test was positive.

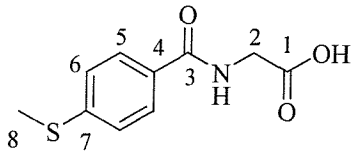
5.3.14 Preparation of a resin-bound sulfide (13a)



Gly-Wang-resin (**11**) (1.0 eq, 0.50 g, 0.23 mmol/g, 0.12 mmol) was pre-swollen with DCM (1 mL). 4- (Methylthio)benzoic acid (**12**) (2.0 eq, 0.23 mmol, 39 mg) and HOBt (2.0 eq, 0.23 mmol, 31 mg) were dissolved in DCM (2 mL). After 10 min, DIC (2.2 eq, 0.25 mmol, 32 mg, 40 μL) was added and the solution stirred for a further 10 min before it was added to the pre-swollen resin. The resin was shaken at

room temperature (4 days). The resin was washed with DMF (2 x 30 mL), DCM (2 x 30 mL), MeOH (2 x 30 mL) and Et_2O (2 x 30 mL). A qualitative ninhydrin test was negative.

5.3.15 2-[(4-Methylthiophenyl)carbonylamino]acetic acid (14a)

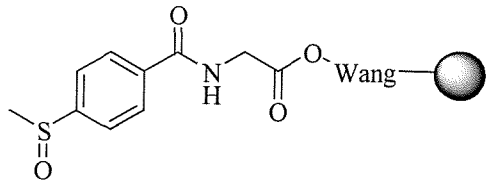


Resin (**13a**) (100 mg) was swollen in DCM (1 mL), a solution of 2.5% water/2.5% TIS/95% DCM was added and the resin shaken for 3 hours at room temperature. The filtrate was collected and the resin washed with DCM (2 x 10 mL), the filtrate was concentrated *in vacuo* and the residue re-dissolved in DCM and precipitated with hexane to give an off-white powder (3.1 mg, 60% over two steps – coupling and cleavage).

R_f: 0.0 (50% EtOAc: hexane) [stained BCG]
RP HPLC (λ=254 nm) Gradient A: 10.8 min (100%)
IR (ν_{max}/cm^{-1}): 1703 C=O (s) amide; 1728 C=O (s) acid
m/z (APCI$^-$): 224 (100%, $[M-H]^-$)
HRMS (EI): $C_{10}H_{11}NO_3S$ Calc. 225.0460 Found 225.0465

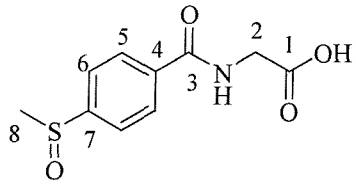
δ_H (400 MHz, CD_3OD): 2.42 (3H, s, $^8CH_3$); 3.98 (2H, s, $^2CH_2$); 7.21, 7.67 (2 x 2H, d, *J* 8, ^5CH, ^6CH)
δ_C (100 MHz, CD_3OD): 13.6 (^8C); 41.1 (^2C); 125.1, 127.6 (^5C, ^6C); 129.9 (^4C); 144.5 (^7C); 168.8 (^3C); 172.0 (^1C)

5.3.16 Synthesis of sulfoxide resin (13b)



Sulfide resin (**13a**) (1.0 eq, 0.40 g, 0.23 mmol/g, 0.092 mmol) was swollen in DCM (1 mL) and then HFIP (4 mL) was added, followed by 30% aq H_2O_2 (2.0 eq, 0.18 mmol, 23 μL). The resin was shaken at room temperature for 4 hours, then washed with DMF (2 x 20 mL), DCM (2 x 20 mL), MeOH (2 x 20 mL) and Et_2O (2 x 20 mL) and dried *in vacuo*. Sulfoxide (**13b**) was used without analysis.

5.3.17 2-{[4-(Methylsulfinyl) phenyl]carbonylamino}acetic acid (14b)



Sulfoxide resin (**13b**) (1 eq, 0.23 mmol/g, 0.25 g, 0.058 mmol) was swollen in DCM (1 mL) and a solution of 2.5% water/2.5% TIS/95% DCM was added and the resin shaken for 3 hours at room temperature. The filtrate was collected and the resin washed with DCM (2 x 10 mL), then concentrated ***in vacuo*** and the residue re-dissolved in TFA and precipitated with DCM to give a white powder (12 mg, 86% over three steps – coupling, oxidation and cleavage).

R_f: 0.1 (1% MeOH in EtOAc) [stained BCG]

RP HPLC (λ=254 nm) Gradient A: 6.94 min (100%)

IR (ν_{max}/cm^{-1}): 1640 C=O (s) amide; 1723 C=O (s) acid; 3352 OH (m, br)

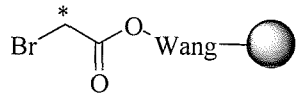
m/z (APCI$^+$): 242 (35%, $[M+H]^+$)

m.p.: 144-147°C

δ_H (400 MHz, DMSO-d_6): 2.90 (3H, s, $^8CH_3$); 4.08 (2H, d, J 5, $^2CH_2$); 7.89, 8.17 (2 x 2H, d, J 8, ^5CH, ^6CH); 9.10 (1H, t, J 5, NH)

δ_C (100 MHz, DMSO-d_6): 41.8 (^2C); 43.5 (^8C); 124.1, 128.5 (^5C, ^6C); 136.3 (^4C), 150.1 (^7C); 166.1 (^3C); 171.6 (^1C)

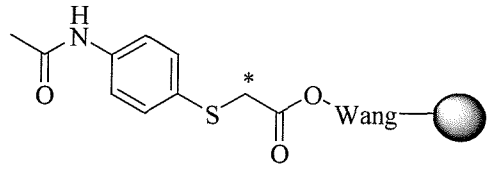
5.3.18 Preparation of ^{13}C-labeled bromoacetamidomethyl polystyrene resin (15)



Bromoacetic acid (1.5 eq, 9.38 mmol, 1.30 g) and bromoacetic-2-^{13}C acid (99 atom-%) (0.5 eq, 3.13 mmol, 437 mg) were dissolved in DCM (20 mL) with HOBt (2.0 eq, 12.5 mmol, 1.69 g) and DMAP (0.3 eq, 1.88 mmol, 0.23 g).[128] After stirring for 10 min, DIC (2.2 eq, 1.73 g, 2.15 mL) was added and the mixture stirred for a further 10 min, before it was added to the resin (**10**) (1.0 eq, 5.00 g, 1.25 mmol/g, 6.25 mmol) pre-swollen in DCM (2 mL). The reaction was shaken at room temperature for 2 days and then the resin filtered, washed with DMF (2 x 30 mL), DCM (2 x 30 mL), MeOH (2 x 30 mL) and Et_2O (2 x 30 mL) and dried *in vacuo*.

δ_C (100 MHz, $CDCl_3$) [Gel phase]: 26.0 (*C)

5.3.19 Alkylation of bromide resin (16) with 4-acetamidothiphenol (16a)

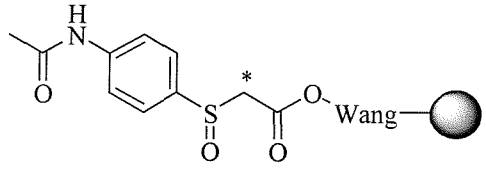


4-Acetamidothiophenol (**6**) (7.0 eq, 31.3 mmol, 5.22 g) caesium carbonate (3.0 eq, 12.5 mmol, 4.07 g) and KI (catalytic) were dissolved in DMF (15 mL) and stirred for 30 min at room temperature. The solution was then added to ^{13}C-labeled bromoacetamidomethyl Wang resin (**15**) (1.0 eq, 5.00 g, 0.93 mmol/g, 4.61 mmol) which had been pre-swollen in DMF (2 mL). The resin was shaken at room temperature (16 h). The resin was filtered and washed with DMF (2 x 50 mL), hot water (3 x 50 mL), DCM (2 x 50 mL), MeOH (2 x 50 mL), Et_2O (2 x 50 mL) and dried *in vacuo*.

IR (ν_{max}/cm^{-1}): 1668 C=O (s) amide; 1740 C=O (s) ester

δ_C (75 MHz, $CDCl_3$) [Gel phase]: 37.7 (*C)

5.3.20 Synthesis of sulfoxide resin (16b)

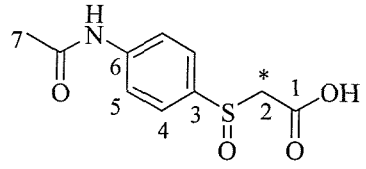


Sulfide resin (**16a**) (1.0 eq, 0.25 g, 0.84 mmol/g, 0.21 mmol) was swollen in DCM (1 mL) and then HFIP (2.5 mL) was added, followed by 30% aq H_2O_2 (3.0 eq, 0.63 mmol, 68 μL). The reaction was shaken at room temperature for 4 hours, the resin was then filtered and washed with DCM (2 x 10 mL), DMF (2 x 10 mL), DCM (2 x

10 mL), MeOH (2 x 10 mL), and Et_2O (2 x 10 mL) and dried *in vacuo* to give the title compound.

δ_C (100 MHz, $CDCl_3$) [Gel phase]: 62.7 (*C)

5.3.21 2-{[4-Acetylamino)phenyl]sulfinyl}acetic acid (17b)

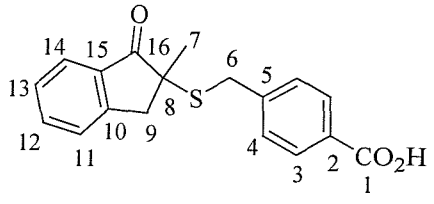


2-{[4-acetylamino)phenyl]sulfinyl}acetic acid (**17b**) was obtained from sulfoxide resin (**16b**) (1.0 eq, 0.25 g, 0.84 mmol/g, 0.21 mmol) by cleavage of the Wang linker as previously described (Section 5.3.17). The title compound was obtained as an off-white solid (20 mg, 40%) after precipitation with TFA/Et_2O.

R_f: 0.1 (EtOAc) [stained BCG]
RP HPLC (λ=254 nm) Gradient A: 7.34 min (100%)
IR (ν_{max}/cm^{-1}): 1708 C=O (s) acid; 1630 C=O (s) amide
m/z (ES$^+$): 242 (54%, $[M+H]^+$); 505 (100%, $[2M+Na]^+$)
m.p.: 121-124°C

δ_H (300 MHz, ∂_4-MeOH): 1.47 (3H, s, $^7CH_3$); 3.22 (2H, s, $^2CH_2$); 7.04 (2H, d, *J* 8, ^4CH); 7.13 (2H, d, *J* 8, ^5CH)
δ_C (75 MHz, ∂_4-MeOH): 23.9 (^8C); 62.0 (^2C); 121.2, 126.9 (^4C, ^5C); 137.5 (^3C); 143.8 (^6C); 167.9 (^7C); 171.9 (^1C)

5.3.22 4-[(2-Methyl-1-oxoindan-2-ylthio)methyl]benzoic acid (18a)



Tert-butyl 4-[(2-methyl-1-oxoindan-2-ylthio)methyl]benzoate (**4a**) (1.0 eq, 0.50 g, 1.36 mmol) was dissolved in DCM (5 mL) and then TFA (5 mL) was added and the solution stirred at room temperature (1 h). The solvents were removed *in vacuo* and then the residue re-dissolved in DCM and precipitated with hexane, to afford the title compound as an off-white powder (361 mg, 85%).

R_f: 0.0 (20% Et_2O: hexane) [stained BCG]

RP HPLC (λ=254 nm) Gradient A: 15.7 min (100%)

IR (ν_{max}/cm^{-1}): 1681 C=O (s) acid; 1703 C=O (s)

m/z (APCI$^-$): 311 (50%, $[M-H]^-$)

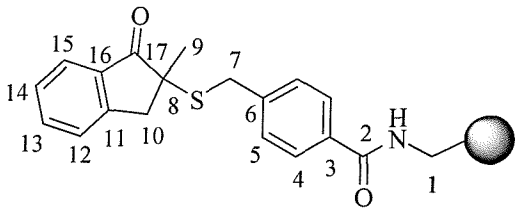
HRMS (EI): $C_{18}H_{16}O_3S$ Calc. 312.0820 Found 312.0822

m.p.: 180-182°C

δ_H (300 MHz, $CDCl_3$ + TFA): 1.66 ($^7CH_3$); 3.18, 3.28 (2 x 1H, d, *J* 18, $^9CH_2$); 3.92, 3.97 (2 x 1H, d, *J* 13, $^6CH_2$); 7.36-7.48 (4H, m, ^4CH, ^{11}CH, ^{13}CH); 7.64 (1H, dd, *J* 7, 7, ^{12}CH); 7.83 (1H, d, *J* 7, ^{14}CH); 7.99 (2H, d, *J* 8, ^4CH); 8.99 (1H, br, s, $^1CO_2H$)

δ_C (75 MHz, $CDCl_3$ + TFA): 22.5 (^7C); 33.7 (^9C); 43.0 (^6C); 52.4 (^8C); 125.4, 126.4, 128.3, 129.5, 130.6, 135.7 (^3C, ^4C, ^{11}C, ^{12}C, ^{13}C, ^{14}C); 134.4, 127.8, 144.3, 150.4 (^2C, ^5C, ^{10}C, ^{15}C); 172.1 (^1C); 203.8 (^{16}C)

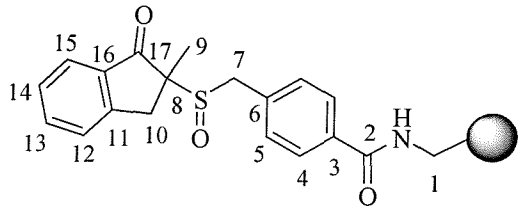
5.3.23 Preparation of resin-bound indanone (19a)



4-[(2-methyl-1-oxoindan-2-ylthio)methyl]benzoic acid (**18**) (1.2 eq, 0.78 mmol, 0.24 g) and HOBt (1.5 eq, 0.98 mmol, 132 mg) were dissolved in DCM (2 mL) and DMF (1 mL) and stirred at room temperature for 10 min. DIC (1.5 eq, 0.98 mmol, 123 mg, 153 μL) was then added and the solution stirred for a further 10 min. The solution was then added to aminomethyl polystyrene resin (**8**) (1.0 eq, 0.50 g, 1.3 mmol/g, 0.65 mmol), pre-swollen in DCM (2 mL), and the reaction shaken at room temperature (64 h). The resin was filtered and washed with DMF (2 x 10 mL), DCM (2 x 10 mL), MeOH (2 x 10 mL) and Et_2O (2 x 10 mL) and then dried *in vacuo* to give the title compound.

δ_C (100 MHz, C_6D_6) [Gel phase]: 22.3 (^{9}C); 33.7 (^{7}C); 42.9 (^{10}C); 52.0 (^{8}C); 145.5 (^{3}C) 150.2 (^{6}C); 166.9 (^{2}C); 202.1 (^{17}C)

5.3.24 Synthesis of sulfoxide resin (19b)

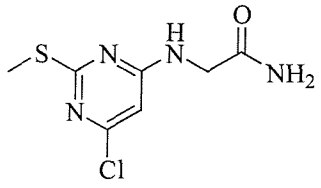


Resin (**19a**) (1.0 eq, 0.50 g, 0.94 mmol/g, 0.47 mmol) was swollen in DCM (1 mL) and HFIP (4 mL) was added, followed by 30% aq H_2O_2 (3.0 eq, 1.3 mmol, 147 μL) and the reaction was shaken at room temperature (4 h). The resin was then filtered

and washed with DCM (2 x 10 mL), DMF (2 x 10 mL), DCM (2 x 10 mL), MeOH (2 x 10mL) and Et_2O (2 x 10mL) and dried *in vacuo* to give the title compound.

δ_C (100 MHz, C_6D_6) [Gel phase]: diastereoisomers; * denotes major isomer; 13.5 + 17.3* (^{9}C); 39.1 (^{1}C); 66.5* + 67.3 (^{7}C); 143.9 (^{16}C); 164.3 (^{2}C); 199.9 (^{17}C)

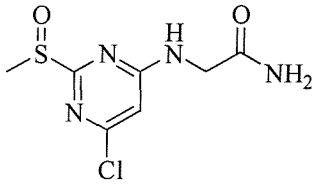
5.3.25 Synthesis of a sulfide HPLC standard (21a)



Resin-bound pyrimidine (**20a**) was synthesised on Rink polystyrene resin by another member of the group.[130] The Rink amide linker was then cleaved to provide sulfide (**21a**) as a standard for HPLC. Resin-bound sulfide (**20a**) (1.0 eq, 0.18 mmol/g, 10 mg, 1.80 μmol) was swollen in DCM (5 drops) then 95% TFA/water (0.5 mL) was added and the resin shaken at room temperature (1 h). [The resin was observed to turn red in colour during this time]. The resin was then filtered and washed with DCM (2 x 1 mL) and the filtrate concentrated *in vacuo*. The residue was dissolved in water/MeCN and analysed by RP HPLC and mass spectrometry.

RP HPLC (λ=254 nm) Gradient A: 9.92 min (21%)
m/z (ES$^+$): 233 (100%, $[M+H]^+$)

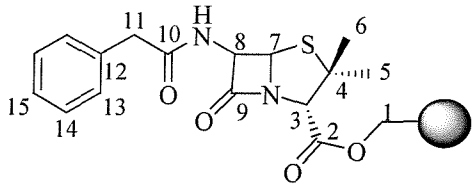
5.3.26 Synthesis of sulfoxide (21b)



Resin-bound sulfide (**20a**) (1.0 eq, 0.18 mmol/g, 10 mg, 1.8 μmol) was swollen in DCM (5 drops) then HFIP (5 drops) was added, followed by 30% aq H_2O_2 (5 eq, 8.80 μmol, 1 μL) and the resin was shaken at room temperature for 4 hours. The resin was filtered and washed with DCM (2 x 1 mL), DMF (1 x 1 mL), DCM (1 x 1 mL), MeOH (1 x 1 mL) and Et_2O (1 x 1 mL) and dried *in vacuo*. The Rink amide linker was then cleaved as described above to give the product (**21b**) in 33% yield (RP HPLC).

RP HPLC (λ=254 nm) Gradient A: 6.67 min (33%)
m/z (ES^+): 249 (72%, $[M+H]^+$)

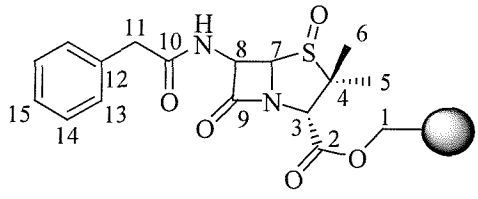
5.3.27 Preparation of resin-bound penicillin[109] (22a)



Merrifield resin (1.0 eq, 1.00 g, 1.40 mmol/g, 1.40 mmol) was swollen in DMF (7 mL) for 30 min. Then penicillin G (sodium salt) (1.5 eq, 2.10 mmol, 0.75 g) in DMF (1 mL) and KF (1.75 eq, 2.45 mmol, 0.25 g) were added to the resin at room temperature under nitrogen. The reaction was stirred at 60°C (24 h), then filtered, washed with EtOH (3 x 10 mL), water (3 x 10 mL), MeOH (3 x 10 mL), DCM (3 x 10 mL) and dried *in vacuo*. The reaction was then repeated.

IR (ν_{max}/cm^{-1}): 1687 C=O amide (s); 1747 C=O ester (s); 1784 C=O (s) β-lactam amide

5.3.28 Preparation of resin-bound penicillin sulfoxide (22b)

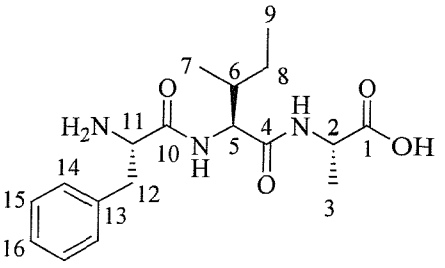


Resin-bound penicillin sulfide (**22a**) (1.0 eq, 0.99 mmol/g, 0.25 mmol, 0.25 g) was swollen in DCM (1 mL) and then HFIP (3 mL) was added, followed by 30% aq H_2O_2 (10.0 eq, 2.5 mmol, 280 μL) and the resin was shaken at room temperature (4 h). Gel phase ^{13}C NMR indicated sulfide remained so the reaction was repeated with 30% aqueous H_2O_2 (20.0 eq, 5.0 mmol, 560 μL) and again shaken at room temperature (4 h).

δ_C (100 MHz, C_6D_6) [Gel phase]: 18.7, 19.6 (^5C, ^6C); 43.7 (^{11}C); 57.3 (^8C); 66.7 (^4C); 75.2 (^3C); 77.2 (^7C); 146.3 (^{12}C); 168.3 (^{10}C); 170.7 (^2C); 174.8 (^9C)

5.4: Experimental for Chapter 3

5.4.1 Synthesis of the standard tripeptide H-Phe-Ile-Ala-OH (25)



Wang polystyrene resin (**10**) (1.0 eq, 1.50 g, 0.70 mmol/g, 1.05 mmol) was swollen in DCM (2 mL). Fmoc-Ala-OH (2.0 eq, 2.10 mmol, 0.65 g) and HOBt (2.0 eq, 2.10 mmol, 0.28 g) were dissolved in DCM (5 mL) and stirred at room temperature for 10 min. DIC (2.2 eq, 2.31 mmol, 361 μL) was added and the solution stirred for a further 10 min, then added to the pre-swollen resin and shaken (3 h). A qualitative ninhydrin test was negative. Fmoc removal was achieved with 20% piperidine in DMF (2 x 15 mL), and the resin was filtered, washed with DMF (2 x 15 mL), DCM (2 x 15 mL), MeOH (2 x 15 mL) and Et_2O (2 x 15mL) and dried *in vacuo.*

Fmoc-Ile-OH (2.0 eq, 2.10 mmol, 0.74 g) and then Fmoc-Phe-OH (2.0 eq, 2.10 mmol, 0.81 g) were coupled in the same way. Fmoc removal was achieved with 20% piperidine in DMF (2 x 15 mL), and the resin was filtered, washed with DMF (2 x 15 mL), DCM (2 x 15 mL), MeOH (2 x 15 mL) and Et_2O (2 x 15mL) and dried *in vacuo*.

The Wang linker was cleaved with 95% TFA/2% TIS/3% DCM (25 mL) shaken at room temperature (3 h). The filtrate was concentrated, the residue dissolved in MeOH (1 mL) and precipitated with Et_2O (30 mL) to yield the title compound as a white solid (164 mg, 74%).

R_f: 0.74 (50% MeOH: $CHCl_3$) [stained ninhydrin]

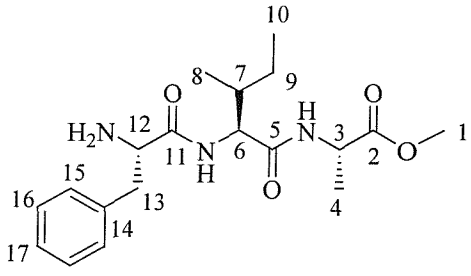
RP HPLC (λ=220 nm) Gradient A: 9.2 min (16%)

m/z (ES^+): 350 (75%, $[M+H]^+$); 372 (32%, $[M+Na]^+$)

δ_H (300 MHz, CD_3OD): 0.95 (3H, t, *J* 7, $^9CH_3$); 1.00 (3H, d, *J* 7, $^7CH_3$); 1.14-1.24, 1.55-1.64 (2 x 1H, m, $^8CH_2$); 1.42 (3H, d, *J* 7, $^3CH_3$); 1.77-1.88 (1H, m, ^6CH); 3.03, 3.28 (2 x 1H, dd, *J* 8, 14, $^{12}CH_2$); 4.10 (1H, m, ^{11}CH); 4.22 (1H, t, *J* 8, ^5CH); 4.39 (1H, q, *J* 7, ^2CH); 7.31 (5H, m, ^{14}CH, ^{15}CH, ^{16}CH)

δ_C (75 MHz, CD_3OD): 11.3 (^9C); 13.6 (^7C); 17.5 (^3C); 25.7 (^8C); 38.3 (^6C); 38.5 (^{12}C); 49.4 (^2C); 55.3 (^5C); 59.0 (^{11}C); 128.7 (^{16}C); 129.9, 130.8 (^{14}C, ^{15}C); 135.4 (^{13}C); 169.4 (^4C); 172.7 (^{10}C), 175.6 (^1C)

5.4.2 Synthesis of the tripeptide methyl ester H-Phe-Ile-Ala-OMe (26)



Tripeptide (**25**) (1.0 eq, 0.23 g, 0.64 mmol) was dissolved in MeOH (20 mL), then $SOCl_2$ (4.0 eq, 2.56 mmol, 0.31 g, 187 μL) was added dropwise (care: violent reaction!). The reaction was refluxed (16 h), then concentrated *in vacuo* to yield the title compound as a white solid (184 mg, 76%).

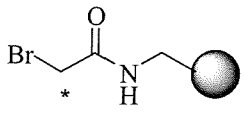
R_f: 0.81 (50% MeOH: $CHCl_3$) [stained ninhydrin]
RP HPLC (λ=220 nm) Gradient A: 10.4 min (42%)
m/z (ES^+): 364 (72%, $[M+H]^+$); 386 (52%, $[M+Na]^+$)

δ_H (300 MHz, CD_3OD): 0.95 (3H, t, *J* 7, $^{10}CH_3$); 1.00 (3H, d, *J* 7, $^8CH_3$); 1.12-1.30, 1.58-1.66 (2 x 1H, m, $^9CH_2$); 1.70-1.89 (1H, m, ^7CH); 1.42 (3H, d, *J* 7, $^4CH_3$); 2.65

(3H, s, $^{1}CH_3$); 3.02, 3.24 (2 x 1H, dd, *J* 8, 14 $^{13}CH_2$); 4.22 (1H, m, ^{12}CH); 4.28 (2H, d, *J* 8, $^{6}CH_2$); 4.39 (1H, q, *J* 8, ^{3}CH); 7.25-7.35 (5H, m, ^{15}CH, ^{16}CH, ^{17}CH)

δ_C (75 MHz, CD_3OD): 11.3 (^{10}C); 15.5 (^{8}C); 17.3 (^{4}C); 25.7 (^{9}C); 35.3 (^{7}C); 38.8 (^{13}C); 50.1 (^{1}C); 52.9 (^{3}C); 55.6 (^{6}C); 59.4 (^{12}C); 129.0 (^{17}C); 130.3, 130.9 (^{15}C, ^{16}C); 135.7 (^{14}C); 169.7 (^{2}C); 173.1 (^{5}C); 174.6 (^{11}C)

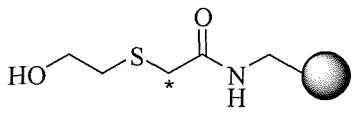
5.4.3 Bromoacetamidomethyl TentaGel resin (27)



Bromoacetic acid (1.5 eq, 0.45 mmol, 63 mg), bromoacetic-2-^{13}C acid (99 atom-%) (0.5 eq, 0.15 mmol, 21 mg) and HOBt (2.0 eq, 0.60 mmol, 81 mg) were dissolved in DCM (5 mL) at room temperature. After 10 min, DIC (2.2 eq, 0.66 mmol, 76 mg, 103 μL) was added and the solution stirred for a further 10 min. This solution was then added to aminomethyl TentaGel resin (1.00 g, 0.30 mmol/g, 0.30 mmol) (**25**) pre-swollen in DCM (1 mL) and the resin shaken overnight at room temperature. The resin was filtered and washed with DMF (2 x 15 mL), DCM (2 x 15 mL), MeOH (2 x 15 mL) and Et_2O (2 x 15 mL) and dried *in vacuo*. A qualitative ninhydrin test was negative.

δ_C (75 MHz, $CDCl_3$) [Gel phase]: 29.4 (*C)

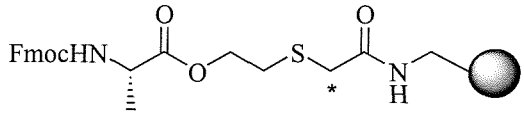
5.4.4 (1-Hydroxy-2-mercapto)-*S*-acetamidomethylethyl TentaGel resin (28)



Bromoacetamidomethyl TentaGel resin (**27**) (1.00 g, 0.30 mmol/g, 0.30 mmol) was swollen in DMF (2 mL). 2-Mercaptoethanol (10.0 eq, 3.0 mmol, 0.23 g, 210 μL), Cs_2CO_3 (2.0 eq, 0.60 mmol, 63 mg) and KI (~ 1 mg, catalytic) were dissolved in DMF (15 mL) and stirred at room temperature for 10 min. The solution was added to the resin and then shaken at room temperature (65 h). The resin was filtered and washed with DMF (2 x 15 mL), DCM (2 x 15 mL), MeOH (2 x 15 mL) and Et_2O (2 x 15 mL) and dried *in vacuo*.

δ_C (75 MHz, $CDCl_3$) [Gel phase]: 36.4 (*C)

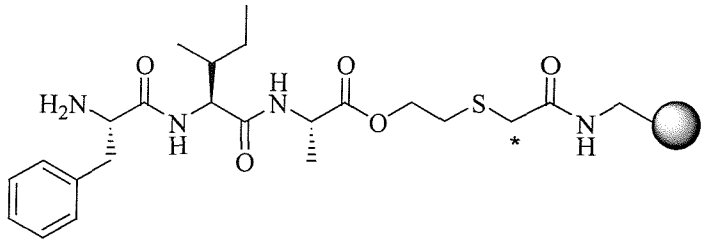
5.4.5 Esterification of Fmoc-Ala-OH onto the resin with DIC/DMAP (29)



Resin (**28**) (1.00 g, 0.30 mmol/g, 0.30 mmol) was swollen in DCM (1 mL). Fmoc-Ala-OH (2.0 eq, 0.60 mmol, 0.19 mg), HOBt (2.0 eq, 0.60 mmol, 81 mg) and DMAP (0.3 eq, 0.09 mmol, 11 mg) were dissolved in DCM (10 mL) and stirred at room temperature for 10 min. The solution was then added to the pre-swollen resin and shaken at room temperature for 3.5 hours. The resin was filtered and washed with DMF (2 x 15 mL), DCM (2 x 15 mL), MeOH (2 x 15 mL) and Et_2O (2 x 15 mL) and dried *in vacuo*. Quantitative Fmoc test (performed in duplicate) gave the resin substitution as 0.80 mmol/g (56% yield over three steps).

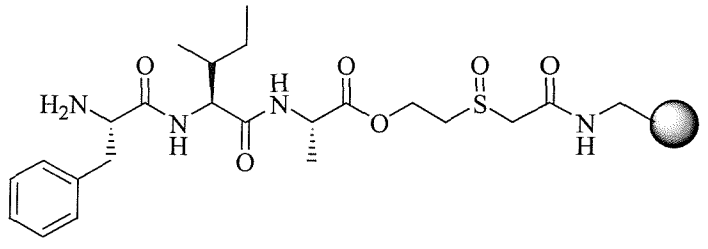
δ_C (75 MHz, $CDCl_3$) [Gel phase]: 36.3 (*C)

5.4.6 Synthesis of the resin-bound tripeptide (H-Phe-Ile-Ala-OH) (30a)



Fmoc was removed from resin (**29**) with 20% piperidine in DMF (2 x 15 mL). A qualitative ninhydrin test was positive. Fmoc-Ile-OH (2.0 eq, 0.60 mmol, 0.21 g) and Fmoc-Phe-OH (2.0 eq, 0.60 mmol, 0.21 g) were then coupled as described above, but without DMAP (Section 5.4.5). After removal of the Fmoc group as before, a qualitative ninhydrin test confirmed the reaction was complete. Resin (**30a**) was used without further analysis.

5.4.7 Synthesis of the sulfoxide analogue (30b)



Sulfide TentaGel resin (**30a**) (1.00 g, 0.27 mmol/g, 0.27 g) was swollen in dioxane (1 mL). $NaIO_4$ (2.0 eq, 0.53 mmol, 0.11 g) was dissolved in water (0.5 mL) and dioxane (0.5 mL) and then the solution was added dropwise to the pre-swollen resin. The reaction was shaken at room temperature (24 h) and then the resin was filtered and washed with DMF (2 x 15 mL), DCM (2 x 15 mL), MeOH (2 x 15 mL) and Et_2O (2 x 15 mL) and dried *in vacuo*.

δ_C (75 MHz, $CDCl_3$) [Gel phase]: 56.2 (*C)

5.4.8 Thermolysis of the peptide (30b)

Sulfoxide resin (1.0 eq, 0.15 mmol/g, 120 mg, 0.018 mmol) (**30b**) was suspended in MeOH (5 mL) and refluxed (16 h). The resin was filtered and the filtrate concentrated *in vacuo*, to yield the tripeptide methyl ester in quantitative yield (6.36 mg).

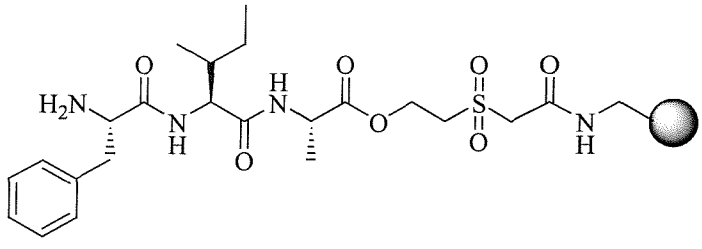
The thermolysis was repeated with the other solvents (water, dioxane, toluene and ^{t}BuOH). No tripeptide was detected.

This thermolysis was repeated for sulfide (**30a**) and sulfone (**30c**) and in each case the tripeptide methyl ester was obtained in quantitative yield.

5.4.9 Microwave elimination of the peptide (30b)

Sulfoxide resin (**30b**) (1.0 eq, 20 mg, 0.74 mmol/g, 0.015 mmol) was placed in an Eppendorf tube with water (400 μL). This was placed (unsealed) in a microwave [Matsui 950 W] and exposed to microwave radiation on full power for 5 min. No tripeptide was detected.

5.4.10 Synthesis of the sulfone analogue (30c)



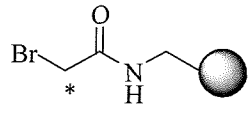
Sulfide TentaGel resin (**30a**) (0.20 g, 0.30 mmol/g, 0.06 mmol) was swollen in MeOH (10 mL) and then cooled to 0°C (ice/water bath). Potassium hydrogen persulfate (Oxone®) (3.0 eq, 0.18 mmol, 0.11 g) was dissolved in water (10 mL) and

then added to the resin. The mixture was allowed to warm up to room temperature and shaken under nitrogen (60 h). The resin was filtered and washed DMF (2 x 15 mL), DCM (2 x 15 mL), MeOH (2 x 15 mL) and Et_2O (2 x 15 mL) and dried *in vacuo*.

δ_C (300 MHz, $CDCl_3$) [Gel phase]: 60.6 (*C)

Cleavage of sulfone (**30c**) was effected by methanolysis, as for the sulfide analogue (**30a**) above, to give tripeptide methyl ester (**26**) in quantitative yield.

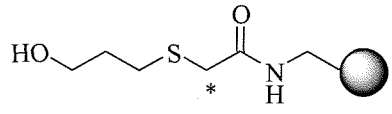
5.4.11 Synthesis of bromoacetamidomethyl polystyrene resin (32)



Synthesised according to the procedure above for bromide (**27**) (Section 5.4.3), but with 50% bromoacetic-2-^{13}C acid (99 atom-%) and using aminomethyl polystyrene resin instead of TentaGel.

δ_C (75 MHz, $CDCl_3$) [Gel phase]: 29.3 (*C)

5.4.12 Synthesis of the resin-bound sulfide (33)

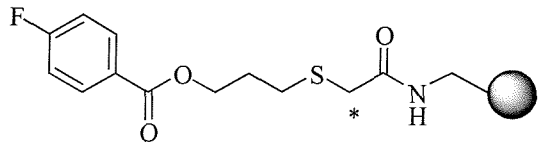


Bromoacetamidomethyl polystyrene resin (**32**) (50% ^{13}C enriched) (1.0 eq, 1.30 mmol/g, 0.50 g, 0.65 mmol) was swollen in DMF (1 mL). 3-Mercaptopropanol (10.0 eq, 6.50 mmol, 0.60 g) and Cs_2CO_3 (2.0 eq, 1.3 mmol, 0.42 g) were dissolved in

DMF (5 mL), stirred for 15 min, then added to the pre-swollen resin and shaken at room temperature (16 h). The resin was filtered and washed with DMF (2 x 15 mL), DCM (2 x 15 mL), MeOH (2 x 15 mL) and Et_2O (2 x 15 mL) and dried *in vacuo*.

δ_C (75 MHz, $CDCl_3$) [Gel phase]: 36.5 (*C)

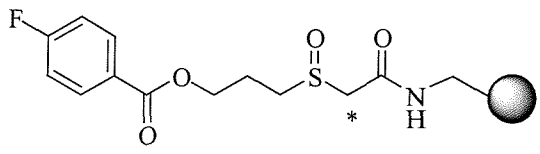
5.4.13 Esterification of 4-fluorobenzoic acid to the resin (34a)



HOBt (2.0 eq, 1.14 mmol, 0.15 g), 4-fluorobenzoic acid (2.0 eq, 1.14 mmol, 0.16 mg) and DMAP (2.0 eq, 1.14 mmol, 0.14 mg) were dissolved in DCM (5 mL) at room temperature. After 10 min, DIC (2.2 eq, 1.25 mmol, 0.16 mg, 196 μL) was added and the mixture stirred for a further 10 min. The solution was then added to resin (**33**) (1.0 eq, 1.13 mmol/g, 0.50 g, 0.57 mmol) pre-swollen in DCM (1 mL), and shaken overnight at room temperature. The resin was filtered and washed with DMF (2 x 15 mL), DCM (2 x 15 mL), MeOH (2 x 15 mL) and Et_2O (2 x 15 mL) and dried *in vacuo*.

δ_C (75 MHz, $CDCl_3$) [Gel phase]: 35.6 (*C)
δ_F (282 MHz, $CDCl_3$) [Gel phase]: 56.7

5.4.14 Synthesis of sulfoxide resin (34b)



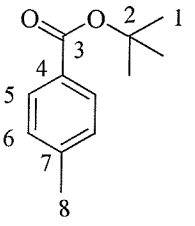
Sulfide resin (**34a**) (0.50 g, 0.98 mmol/g, 0.49 mmol) was swollen in DCM (1 mL), then HFIP (3 mL) and 30% aq H_2O_2 (2.5 eq, 1.23 mmol, 139 μL) were added and the resin shaken at room temperature (4 h). The resin was filtered, washed with DCM (2 x 15 mL), DMF (2 x 15 mL), DCM (2 x 15 mL), MeOH (2 x 15 mL) and Et_2O (2 x 15 mL) and dried *in vacuo*.

δ_C (75 MHz, $CDCl_3$) [Gel phase]: 55.0 (*C)

5.4.15 Elimination of sulfoxide resin (34b)

Sulfoxide resin (**34b**) (0.98 mmol/g, 0.20 g, 0.20 mmol) was refluxed in dioxane (2 x 24 h). No prop-2-enyl 4-fluorobenzoate was detected and gel phase ^{19}F NMR confirmed the presence of fluorine on the resin.

5.4.16 *Tert*-butyl 4-methyl benzoate[147] (38)



Dry ^{t}BuOH (1.6 eq, 0.052 mol, 3.84 g, 4.96 mL) and dry pyridine (2.0 eq, 0.064 mol, 5.13 g, 5.25 mL) were dissolved in dry DCM (20 mL) under nitrogen and cooled to 0°C. *p*-Toluoyl chloride (1.0 eq, 0.032 mol, 5.00 g, 4.27 mL) (**37**) was added dropwise and the reaction was stirred at room temperature (64 h). The reaction was diluted with DCM (20 mL) and the organic layer washed with 1M HCl (1 x 30 mL) and water (2 x 30 mL), then dried over $MgSO_4$, filtered and concentrated *in vacuo*. The product was purified by vacuum distillation (160°C, 4-5 Torr) to give the title compound as a colourless liquid (4.65 g, 75%).

R_f: 0.58 (6.5: 3: 0.5 hexane: EtOAc: AcOH)

RP HPLC (λ=254 nm) Gradient A: 20.2 min (100%)

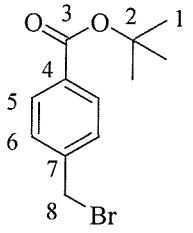
IR (ν_{max}/cm^{-1}): 1703 C=O (s)

m/z (EI): 193 (100%, $[M+H]^+$)

δ_H (300 MHz, $CDCl_3$): 1.58 (9H, s, $^{1}CH_3$); 2.39 (3H, s, $^{8}CH_3$); 7.20 (2H, d, *J* 8, ^{6}CH); 7.88 (2H, d, *J* 8, ^{5}CH)

δ_C (100 MHz, $CDCl_3$): 21.6 (^{8}C); 28.2 (^{1}C); 80.6 (^{2}C); 128.8, 129.4 (^{5}C, ^{6}C); 129.3 (^{4}C); 142.9 (^{7}C); 165.9 (^{3}C)

5.4.17 *Tert*-butyl 4-(bromomethyl)benzoate[147] (39)



Tert-butyl 4-methylbenzoate (**38**) (1.0 eq, 2.60 mmol, 0.50 g) *N*-bromosuccinimide (1.0 eq, 2.6 mmol, 0.46 g) and benzoyl peroxide (0.008 eq, 0.02 mmol, 5.2 mg) were dissolved in CCl_4 (5 mL), brought to reflux and heated for 75 min. The solvent was removed *in vacuo* and the yellow liquid solidified when stirred under vacuum overnight. The solid was triturated with petroleum ether (40-60) and the decantate evaporated to give a yellow oil. This crystallised when stirred under vacuum (2 h) and the solid was recrystallised from MeOH to give pale yellow needles (696 mg, 99%).

R_f: 0.24 (10% Et_2O: hexane)

RP HPLC (λ=254 nm) Gradient A: 20.1 min (88%)

IR (ν_{max}/cm^{-1}): 1695 C=O (s)

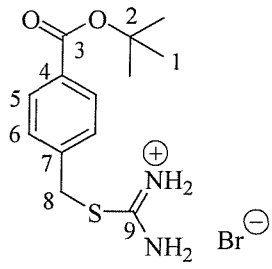
m/z (EI): 269 (100%, $M^{+\cdot}$); 271 (100%, $M^{+\cdot}$)

m.p.: 48-50°C (Lit. 50-52°C)[147]

δ_H (300 MHz, $CDCl_3$): 1.58 (9H, s, $^1CH_3$); 4.23 (2H, s, $^8CH_2$); 7.42 (2H, d, *J* 8, ^6CH); 7.97 (2H, d, *J* 8, ^5CH)

δ_C (100 MHz, $CDCl_3$): 26.2 (^1C); 30.3 (^8C); 79.2 (^2C); 124.4 (^4C); 126.8, 127.8 (^5C, ^6C); 140.0 (^7C); 163.2 (^3C)

5.4.18 *Tert*-butyl 4-(amidinothiomethyl)benzoate[148] (40)



Tert-butyl 4-(bromomethyl)benzoate (1.2 eq, 1.2 mmol, 0.32 g) (**39**) and thiourea (1.0 eq, 1.0 mmol, 76 mg) were dissolved in EtOH (1 mL) with stirring. The solution was then heated at 65°C (6 h). EtOH was removed *in vacuo* and the white residue suspended in Et_2O (10 mL). The resulting precipitate was filtered and dried *in vacuo* to yield the title compound as a white powder in quantitative yield (347 mg).

R_f: 0.19 (20% MeOH: DCM)

RP HPLC (λ=254 nm) Gradient A: 11.7 min (100%)

IR (ν_{max}/cm^{-1}): 1711 C=O (s)

m/z (ES$^+$): 267 (100%, $[M+H]^+$)

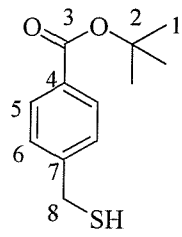
HRMS (FAB, 3-NBA): $C_{13}H_{19}N_2O_2S$ Calc. 267.1137 Found 267.1154

m.p.: 238-240°C

δ_H (300 MHz, DMSO-δ_6): 1.52 (9H, s, $^1CH_3$); 4.55 (2H, s, $^8CH_2$); 7.52 (2H, d, *J* 8, ^6CH); 7.88 (2H, d, *J* 8, ^5CH); 8.99, 9.19 (2 x 2H, s br, NH_2)

δ_C (100 MHz, DMSO-δ_6): 28.4 (^1C); 35.9 (^8C); 82.9 (^2C); 130.9, 131.3 (C^5, C^6); 133.1 (^4C); 140.4 (^7C); 166.7 (^3C); 171.8 (^9C)

5.4.19 *Tert*-butyl 4-(sulfanylmethyl)benzoate (41)



Tert-butyl 4-(amidinothiomethyl)benzoate (1.0 eq, 3.0 mmol, 1.04 g) (**40**) was dissolved in EtOH (6 mL) under nitrogen. To this solution was added 4% aq NaOH (9 mL) and the reaction was stirred at room temperature (2.5 h). AcOH (0.5 mL) was added dropwise to adjust the pH of the reaction to pH 5. The solvents were removed *in vacuo* and the residue extracted with $CHCl_3$ (2 x 10 mL). The combined organic layers were washed with water (1 x 15 mL), brine (1 x 15 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield the title compound as a yellow solid (424 mg, 63%).

R_f: 0.85 (50% EtOAc: hexane)
RP HPLC (λ=254 nm): 19.0 min (85%)
IR (ν_{max}/cm^{-1}): 1710 C=O (s)
m/z (EI): 224 (8%, $M^{+\cdot}$)
HRMS (EI): $C_{12}H_{16}O_2S$ Calc. 224.0871 Found 224.0863
m.p.: 28-30°C

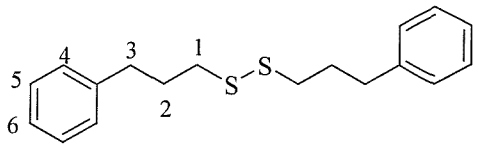
δ_H (300 MHz, $CDCl_3$): 1.55 (9H, s, $^1CH_3$); 1.68 (1H, t, *J* 7, SH); 3.69 (2H, d, *J* 7, $^8CH_2$); 7.40 (2H, d, *J* 8, ^6CH); 7.87 (2H, d, *J* 8, ^5CH)
δ_C (75 MHz, $CDCl_3$): 28.4 (^1C); 28.8 (^8C); 81.2 (^2C); 128.0, 130.0 (^5C, ^6C); 129.2 (^4C); 146.0 (^7C); 165.5 (^3C)

5.4.20 Synthesis of sulfide (2a) using *tert*-butyl 4-(sulfanylmethyl)benzoate (41)

Thiol (**41**) (1 eq, 0.74 mmol, 0.17 mg), caesium carbonate (1 eq, 0.74 mmol) and KI (catalytic) were dissolved in DMF (2 mL) under nitrogen. 1-Bromo-3-phenylpropane (1 eq, 0.74 mmol, 0.15 mg, 112 μL) was added and the reaction stirred at room temperature (16 h). The reaction was diluted with water (1 x 25 mL) then the organic layer was extracted with EtOAc (4 x 10 mL). The combined organic layer was washed with water (1 x 20 mL), brine (1 x 20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield the crude sulfide. The product was purified by flash chromatography on silica gel eluting with 0% to 5% diethyl ether in hexane to furnish sulfide (**2a**) as a colourless oil in 60% yield. (For data see Section 5.3.4).

5.4.21 Thermal elimination of *tert*-butyl 4-{[(3-phenylpropyl)sulfinyl]methyl}benzoate (2b)

Sulfoxide (**2b**) (1.0 eq, 0.28 mmol, 0.10 g) was dissolved in *N*-methylformamide (NMF) (1.5 mL) and heated at 130°C for 24 h. Sulfoxide remained (TLC) and so the reaction was refluxed (16 h). The product was extracted with EtOAc (1 x 10 mL), washed with water (4 x 20 mL), brine (1 x 20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The product was purified by flash chromatography on silica gel eluting with 50% to 0% hexane in EtOAc. The only products isolated were 3-phenylpropyldisulfide (12 mg, 13%) (**43**) and a sulfone (**8** mg, 9%) (**44**) (see below). None of the expected product, allylbenzene, was detected.

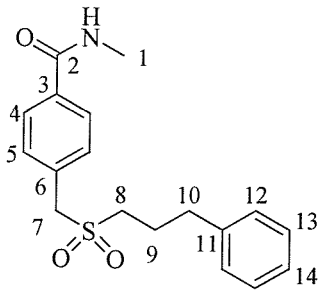


43

R_f: 0.97 (50% EtOAc: hexane)

m/z (EI): 302 (72%, $M^{+\cdot}$)

δ_H (300 MHz, $CDCl_3$): 2.00 (2H, m, $^2CH_2$); 2.62-2.77 (4H, m, $^1CH_2$, $^3CH_2$); 7.12-7.31 (5H, m, ^4CH, ^5CH, ^6CH)



44

R_f: 0.5 (EtOAc)

m/z (ES^+): 332 (100%, $[M+H]^+$); 354 (9%, $[M+Na]^+$)

δ_H (300 MHz, $CDCl_3$): 2.13 (2H, m, $^9CH_2$); 2.72 (2H, t, *J* 7, $^{10}CH_2$); 2.82 (2H, t, *J* 7, $^8CH_2$); 3.02 (3H, d, *J* 5, $^1CH_3$); 4.20 (2H, s, $^7CH_2$); 6.18 (1H, br, s, NH); 7.12 (2H, d, *J* 8, $^5CH_2$); 7.17-7.42 (5H, m, ^{12}CH, ^{13}CH, ^{14}CH); 8.06 (2H, d, *J* 8, $^4CH_2$)

5.4.22 Microwave elimination of *tert*-butyl 4-{[(3-phenylpropyl)sulfinyl]methyl}benzoate (2b)

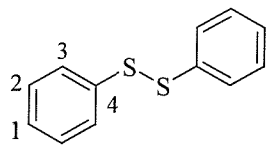
Sulfoxide (1.0 eq, 0.42 mmol, 0.15 g) (**2b**) was dissolved in *N*-methylformamide (3 mL) in a round-bottom flask fitted with a dry-ice condenser (Figure 3.25). The solution was irradiated for 7 minutes [950 W, power level 7]. The reaction was cooled and diluted with a large excess of water (50 mL) and the product was extracted with EtOAc (4 x 10 mL). The combined organic layers were washed with water (2 x 20 mL), brine (1 x 20 mL), then dried over $MgSO_4$, filtered and concentrated *in vacuo* to yield a yellow oil. The product was purified by flash chromatography on silica gel, eluting with 25% EtOAc in hexane. No allylbenzene, the expected product, was isolated. Some starting material (**2b**) was recovered (2%), and two new products were identified. The first was 3-phenylpropyldisulfide (11%) (**43**) and the other was the sulfide (**2a**) of the starting material (12%).

5.4.23 Thermal elimination of [(3-phenylpropyl)sulfinyl]benzene (3b)

Sulfoxide (**3b**) (1.0 eq, 1.0 mmol, 0.24 g) was refluxed in toluene (5 mL) or *N*-methylformamide (NMF) (5mL), heating at 130°C, for 24 h. The product was extracted with EtOAc (4 x 10 mL) after quenching the reaction with a large excess of water (1 x 30 mL). The combined EtOAc layers were washed with water (2 x 10 mL), brine (1 x 10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to yield a yellow oil. The product was purified by flash chromatography on silica gel, eluting with 0% to 10% EtOAc in hexane. The anticipated product, allylbenzene, was not detected. Starting material (**3b**) was recovered (160 mg, 65% (toluene); 157 mg, 64% (NMF)).

5.4.24 Microwave elimination of [(3-phenylpropyl)sulfinyl]benzene (3b)

Sulfoxide (**3b**) (1.0 eq, 0.41 mmol, 0.10 g) was dissolved in *N*-methylformamide (1.5 mL) in a round-bottomed flask fitted with a dry-ice condenser. The solution was irradiated on full power [950 W, power level 10] for 1 min. TLC showed starting material remained and hence it was irradiated again (2 min at power level 5, then 3 x 1 min at power level 7). The reaction was quenched with a large excess of water (1 x 20 mL) and the product was extracted with EtOAc (4 x 10 mL). The combined organic layers were washed with water (1 x 20 mL), brine (1 x 20 mL) dried over $MgSO_4$, filtered and concentrated *in vacuo* to yield a yellow oil. No allylbenzene was detected. Starting material (**3b**) was isolated (17 mg, 17%) along with a single new product which was identified as diphenyldisulfide (**45**) (6.8 mg, 7%).



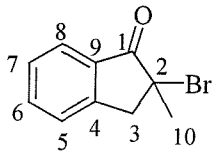
45

R_f: 0.73 (10% Et_2O: hexane)

m/z (ES^+): 218 (100%, $[M+H]^+$)

δ_H (300 MHz, $CDCl_3$): 7.21-7.37 (6H, m, ^{1}CH, ^{2}CH); 7.38-7.52 (4H, d, *J* 8, ^{3}CH)

5.4.25 2-Bromo-2-methylindanone[178] (47)

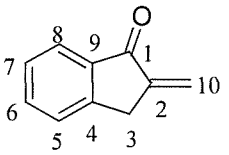


2-Methylindanone (1.0 eq, 6.80 mmol, 1.00 g) (**46**) was dissolved in glacial acetic acid (20 mL) and the solution cooled to 0°C. Bromine (1.0 eq, 6.80 mmol, 1.10 g, 353 μL) was added, the solution warmed up to room temperature and stirred (16 h). The product was extracted with $CHCl_3$ (2 x 20 mL), the combined organic layers washed with saturated aq $NaHCO_3$ (2 x 20 mL), water (1 x 20 mL), brine (1x 20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to yield the title compound as yellow plates in quantitative yield (1.53 g).

R_f: 0.61 (50% EtOAc: hexane)
RP HPLC (λ=254 nm) Gradient A: 15.1 min (92%)
IR (ν_{max}/cm^{-1}): 1715 C=O (s)
m/z (EI): 224 (^{79}Br, 25%, $M^{+\cdot}$); 226 (^{81}Br, 25%, $M^{+\cdot}$)
m.p.: 52-54°C (Lit. 57-59°C)

δ_H (300 MHz, $CDCl_3$): 1.93 (3H, s, $^{10}CH_3$); 3.46, 3.76 (2 x 1H, d, *J* 18, $^3CH_2$); 7.39-7.43 (2H, m, ^{5}CH, ^{6}CH); 7.64 (1H, dd, *J* 7, 7, ^{7}CH); 7.81 (1H, d, *J* 7, ^{8}CH)
δ_C (75 MHz, $CDCl_3$): 26.9 (^{10}C); 46.4 (^{3}C); 59.9 (^{2}C); 125.7, 126.6, 128.4, 136.1 (^{5}C, ^{6}C, ^{7}C, ^{8}C); 132.7, 149.2 (^{4}C, ^{9}C); 200.5 (^{1}C)

5.4.26 Synthesis of the standard *exo*-indenone (49)[179]



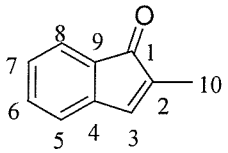
1-Indanone (**48**) (1.0 eq, 2.00 g, 15.2 mmol), paraformaldehyde (3.0 eq, 45.0 mmol, 4.05 g) and dimethylamine hydrochloride (4.7 eq, 70.0 mmol, 5.67 g) were dissolved in EtOH (150 mL) with conc. HCl (1 mL). The suspension was refluxed for 2.5 h, then cooled and the solution diluted with acetone (50 mL). The precipitate that formed was filtered and treated with saturated aq Na_2CO_3 (50 mL). The amine product was extracted with Et_2O (2 x 30 mL), the organic layers combined and washed with water (30 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to yield a yellow oil (858 mg). The oil was treated with MeI (10.0 eq, 0.045 mol, 6.44 g, 2.83 mL) in MeOH (3 mL) and stirred at room temperature (16 h). The excess MeI and MeOH were removed *in vacuo* and then saturated aq $NaHCO_3$ (2 mL) was added. The product was extracted with EtOAc (2 x 2.5 mL), washed with brine (1 x 5 mL) dried over $MgSO_4$, filtered and concentrated *in vacuo*. The product was purified by flash chromatography on silica gel, eluting with 20% EtOAc in hexane, then 10% MeOH in EtOAc to give the title compound as a yellow oil (700 mg, 32%).

R_f: 0.29 (20% EtOAc: hexane)
RP HPLC (λ=254 nm) Gradient A: 13.7 min (100%)
IR (ν_{max}/cm^{-1}): 1702 C=O (s)
m/z (EI): 144 (100%, $M^{+\cdot}$)

δ_H (300 MHz, $CDCl_3$): 3.78 (2H, s, $^3CH_2$); 5.67, 6.39 (2 x 1H, s, $^{10}CH_2$); 7.43 (1H, t, *J* 8, ^{7}CH); 7.51, (1H, d, *J* 8, ^{5}CH); 7.63 (1H, t, *J* 8, ^{6}CH); 7.89 (1H, d, *J* 8, ^{8}CH)

δ_C (75 MHz, $CDCl_3$): 32.5 (^3C); 119.4 (^{10}C); 124.7, 136.5, 127.6, 135.0 (^5C, ^6C, ^7C, ^8C); 138.3, 143.4, 150.0 (^2C, ^4C, ^9C); 193.6 (^1C)

5.4.27 Synthesis of the standard *endo*-indenone[153] (52)



Propionic acid (1.2 eq, 0.023 mol, 1.70 g, 1.69 mL) (**50**) was dissolved in dry THF (5 mL) under nitrogen and cooled to 0°C before the addition of lithium diisopropylamide (LDA) (2M solution in THF) (3.0 eq, 28 mL, 0.057 mol). The reaction was stirred at 0°C for 30 min and then cooled to -78°C. Benzaldehyde (1.0 eq, 0.019 mol, 2.0 g, 1.92 mL) in THF (5 mL) was added and the reaction was allowed to warm to room temperature and stirred at room temperature (16 h). 15% Aqueous NaOH (1 x 50 mL) was added and the aqueous layer washed once with Et_2O.

The aqueous phase was acidified with 10% HCl (1 x 30 mL) to pH 2, and extracted with Et_2O (5 x 20 mL). The combined extracts were washed with brine (1 x 30 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to yield the hydroxyacid intermediate (**51**) as a yellow/orange oil (1.34 g, 40%).

Hydroxyacid (**51**) (1.0 eq, 7.50 mmol, 1.34 g) was dissolved in DCM (8 mL) and added to a stirred solution of $SOCl_2$ (2.4 eq, 18 mmol, 1.31 mL) and DMF (0.03 eq, 0.23 mmol, 17.4 μL) in DCM (4 mL) *via* cannula over 30 min. The reaction was stirred at room temperature for 30 min, then refluxed for 15 min before the solvent was removed *in vacuo* to give the crude acid chloride.

The acid chloride was added to a solution of $AlCl_3$ (1.1 eq, 8.25 mmol, 1.09 g) in DCM (6 mL) at room temperature. After stirring for 30 min, the reaction was poured onto water (1 x 30 mL) and then extracted with Et_2O (4 x 25 mL). The combined extracts were washed with water (1 x 30 mL), saturated $NaHCO_3$ (2 x 50 mL) and brine (1 x 50 mL), then dried over $MgSO_4$, filtered and concentrated *in vacuo*.

The crude cyclised compound was dissolved in pyridine (30 mL) and heated to 70°C for 2.5 h. The reaction was cooled and poured onto water (30 mL), extracted with Et_2O (3 x 50 mL) and then the combined extracts washed with 10% HCl (2 x 100 mL), water (1 x 100 mL), sat. $NaHCO_3$ (1 x 50 mL), brine (1 x 50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to yield a yellow oil. The product was purified by column chromatography on silica gel, eluting with 0% to 100% EtOAc in hexane, to yield the title compound as yellow crystals (469 mg, 17% overall yield).

R_f: 0.67 (50% EtOAc: hexane)
RP HPLC (λ=254 nm) Gradient A: 16.0 min (100%)
IR (ν_{max}/cm^{-1}): 1705 C=O (s)
m/z (EI): 144 (100%, $M^{+\cdot}$)
m.p.: 43-45°C (Lit. 44-46°C)[153]

δ_H (300 MHz, $CDCl_3$): 1.83 (3H, s, $^{10}CH_3$); 6.87 (1H, d, *J* 7, ^{5}CH); 7.02-7.10 (2H, m, ^{3}CH, ^{6}CH); 7.22 (1H, t, *J* 7, ^{7}CH); 7.31 (1H, d, *J* 7, ^{8}CH)
δ_C (75 MHz, $CDCl_3$): 10.1 (^{10}C); 121.2, 122.6, 127.9, 133.9, 143.4 (^{3}C, ^{5}C, ^{6}C, ^{7}C, ^{8}C); 130.8, 136.2, 145.0 (^{2}C, ^{4}C, ^{9}C); 198.8 (^{1}C)

5.4.28 Solution phase elimination of indanone model (4b)

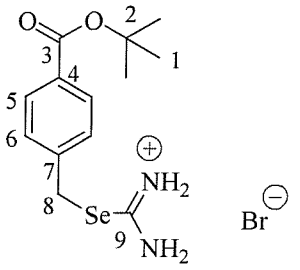
Sulfoxide (**4b**) (1.0 eq, 0.22 mmol, 85 mg) was dissolved in dioxane (2 mL) and refluxed (22 hours). The dioxane was removed *in vacuo* and the residue purified by flash chromatography on silica gel, eluting with hexane to 7% Et_2O in hexane, to give the *endo*-indenone (**52**) (2 mg, 6%) and the *exo*-indenone (**49**), which could not be separated from the sulfenic acid (**53**) (combined yield 9.6 mg, 25%). Semi-preparative RP HPLC (Gradient C) was also attempted to separate these compounds, but without success.

5.4.29 Solid phase elimination of indanone model (19b)

Sulfoxide resin (**19b**) (1.0 eq, 0.93 mmol/g, 0.20 g, 0.19 mmol) was suspended in dioxane (2 mL) and refluxed (22 hours). The resin was filtered and washed with DCM (5 mL), MeOH (5 mL) and Et_2O (5 mL) and the filtrate concentrated *in vacuo.* The cleavage was then repeated to ensure complete elimination. On this occasion, only *exo*-indenone was detected. The residues were combined and purified by flash chromatography on silica gel, eluting with hexane to 7% Et_2O in hexane, to give the *endo*-indenone (3 mg, 11%) (**52**) and the *exo*-indenone (9.2 mg, 34%) (**49**).

5.5 Experimental for Chapter 4

5.5.1 *Tert*-butyl 4-(2-amidino-2-selenaethyl)benzoate (54)



Tert-butyl 4-(bromomethyl)benzoate (**41**) (1.2 eq, 1.20 mmol, 0.32 g) and selenourea (1.0 eq, 1.00 mmol, 0.12 g) were dissolved in EtOH (2 mL) under nitrogen. The solution was heated at 65°C (6 h). EtOH was removed *in vacuo* and the residue suspended in Et_2O (10 mL). The resulting precipitate was filtered and dried *in vacuo* to yield the title compound as a white powder in quantitative yield (395 mg).

R_f: 0.20 (20% MeOH: DCM)

RP HPLC (λ=254 nm) Gradient A: 11.3 min (97%)

IR (ν_{max}/cm^{-1}): 1705 C=O (s)

m/z (ES$^+$): 315 (^{79}Se, 100%, $[M+H]^+$)

HRMS (FAB, 3-NBA): $C_{13}H_{19}N_2O_2Se$ Calc. 315.0612 Found 315.0596

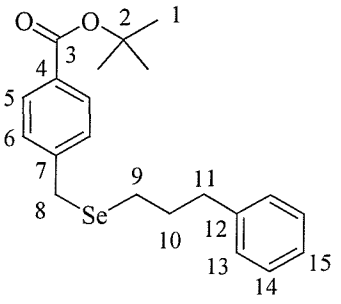
m.p.: 225-228°C

δ_H (300 MHz, CD_3OD): 1.52 (9H, s, $^1CH_3$); 3.24 (1H, s, br, NH); 3.88 (2H, s, $^8CH_2$); 7.51 (2H, d, *J* 8, ^5CH); 7.92 (2H, d, *J* 8, ^6CH)

δ_C (75 MHz, CD_3OD): 28.3 (^1C); 31.4 (C^8); 82.4 (^2C); 130.2, 130.8 (^5C, ^6C); 132.6, 142.4 (^7C, ^4C); 166.7, 171.8 (^3C, ^9C)

δ_{Se} (69 MHz, CD_3OD): 439.7

5.5.2 *Tert*-butyl 4-(5-phenyl-2-selenapentyl)benzoate (56)



Tert-butyl 4-(2-amidino-2-selenaethyl)benzoate (bromide salt) (**54**) (1.0 eq, 0.85 mmol, 0.27 g) was dissolved in N_2-purged EtOH (3 mL) under nitrogen. Aqueous 4% NaOH (N_2-purged) (3 mL) was added and the solution stirred for 30 min at room temperature, then the solvents were removed *in vacuo*. 1-Bromo-3-phenylpropane (1.3 eq, 1.10 mmol, 0.22 g) in N_2-purged EtOH (3 mL) was added and the solution stirred overnight at room temperature. EtOH was removed *in vacuo* and the residue partitioned between water (10 mL) and EtOAc (5 mL). The aqueous layer was extracted with EtOAc (2 x 10 mL), and the combined extracts washed with water (2 x 15 mL), brine (1 x 15 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The product was purified by flash chromatography on silica gel, eluting with 0% to 5% EtOAc in hexane to give the title compound as a yellow oil (111 mg, 33%).

R_f: 0.43 (50% EtOAc: hexane)

RP HPLC (λ=254 nm) Gradient A: 23.4 min (100%)

IR (ν_{max}/cm^{-1}): 1708 C=O (s)

m/z (EI): 390 (^{79}Se, 100%, $M^{+\cdot}$)

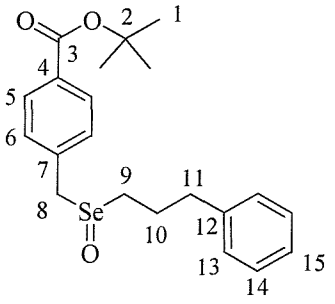
HRMS (EI): $C_{21}H_{26}O_2Se$ Calc. 390.1098 Found 390.1088

δ_H (400 MHz, $CDCl_3$): 1.62 (9H, s, $^{1}CH_3$); 1.87-1.99 (2H, m, $^{10}CH_2$); 2.49 (2H, t, *J* 7, $^{9}CH_2$); 2.68 (2H, t, *J* 7, $^{11}CH_2$); 3.78 (2H, s, $^{8}CH_2$); 7.14-7.35 (7H, m, ^{13}CH, ^{14}CH, ^{15}CH, ^{6}CH); 7.82 (2H, d, *J* 9, ^{5}CH)

δ_C (100 MHz, $CDCl_3$): 23.7 (^9C); 26.9 (^8C); 31.8 (^{10}C); 28.7 (^1C); 35.8 (^{11}C); 81.3 (^2C); 126.2, 126.4, 128.7, 128.8, 128.9, 129.8, 130.1, 130.4, 130.8 (^5C, ^6C, ^{13}C, ^{14}C, ^{15}C); 141.7, 144.9 (^7C, ^{12}C); 166.0 (^3C)

δ_{Se} (69 MHz, $CDCl_3$): 261.1

5.5.3 Oxidation of *t*ert-butyl 4-(5-phenyl-2-selenapentyl)benzoate (56)



Selenide (1.0 eq, 0.50 mmol, 0.20 g) (**56**) was dissolved in MeOH (1 mL) and cooled to 0°C. $NaIO_4$ (1.1 eq, 0.55 mmol, 0.12 g) was dissolved in water (1 mL) and MeOH (2 mL) was added slowly. The sodium metaperiodate solution was then added (in one portion) to the selenide. The solution was allowed to warm up to room temperature whilst stirring overnight. Insoluble $NaIO_3$ was removed by filtration, then the solution was concentrated *in vacuo*. The residue was re-dissolved in Et_2O (2 x 5 mL) and transferred to a separating funnel. The organic layer was washed with water (1 x 5 mL), brine (1 x 5 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to yield the crude selenoxide (**57**) as a yellow/orange oil (202 mg, 99%).

R_f: 0.05 (20% Et_2O: hexane) [PMA]

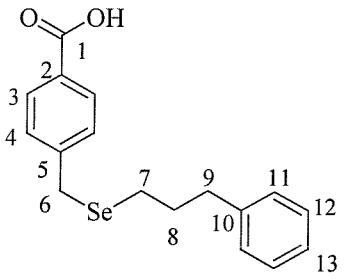
RP HPLC (λ=254 nm) Gradient A: 14.5 min (95%)

m/z (ES^+): 407 (^{79}Se, 28%, $[M+H]^+$); 813 (^{79}Se, 100%, $[2M+H]^+$)

δ_H (400 MHz, $CDCl_3$): 1.52 (9H, s, $^1CH_3$); 1.91-2.03 (2H, m, $^{10}CH_2$); 2.42-2.52, 2.53-2.69 (2 x 2H, m, $^9CH_2$, $^{11}CH_2$); 3.93, 4.03 (2 x 1H, d, *J* 11, $^8CH_2$); 7.01 (2H, d, J 7, ^6CH); 7.10-7.22 (5H, m, ^{13}CH, ^{14}CH, ^{15}CH); 7.86 (2H, d, *J* 7, ^5CH)

δ_C (100 MHz, $CDCl_3$): 28.6 (^{1}C); 35.7 (^{8}C); 24.7, 46.4, 52.8 (^{9}C, ^{10}C, ^{11}C); 81.8 (^{2}C); 126.8, 128.5, 128.8, 128.9, 130.0, 130.1 (^{5}C, ^{6}C, ^{13}C, ^{14}C, ^{15}C); 132.3, 135.3 (^{4}C, ^{12}C); 140.4 (^{7}C); 165.5 (^{3}C)

5.5.4 4-(5-Phenyl-2-selenapentyl)benzoic acid (58)



Tert-butyl 4-(5-phenyl-2-selenapentyl)benzoate (**56**) (1.0 eq, 0.64 mmol, 0.25 g) was dissolved in N_2-purged formic acid (5 mL) under nitrogen and stirred at room temperature (3 h). The formic acid was removed *in vacuo* and the residue was re-dissolved in warm DCM and precipitated with hexane to give the title compound as a pale yellow powder (157 mg, 74%).

R_f: 0.84 (EtOAc)

RP HPLC (λ=254 nm) Gradient A: 18.5 min (100%)

IR (ν_{max}/cm^{-1}): 2931 OH (br, m); 1700 C=O (s)

m/z (APCI$^-$): 333 (^{79}Se, 100%, [M-H]$^-$)

HRMS (EI): $C_{17}H_{18}O_2Se$ Calc. 334.0472 Found 334.0474

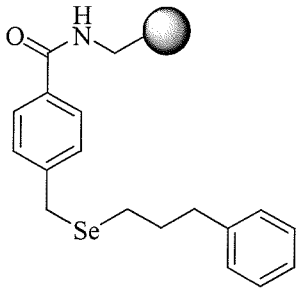
m.p.: 81-84°C

δ_H (300 MHz, $CDCl_3$ +TFA): 1.89-2.01 (2H, m, $^8CH_2$); 2.51 (2H, t, *J* 8, $^7CH_2$); 2.69 (2H, t, *J* 8, $^9CH_2$); 3.80 (2H, s, $^6CH_2$); 7.10-7.38 (7H, m, ^{4}CH, ^{11}CH, ^{12}CH, ^{13}CH); 8.02 (2H, d, *J* 8, ^{3}CH)

δ_C (75 MHz, $CDCl_3$ +TFA): 23.5 (^{7}C); 26.6 (^{8}C); 32.0 (^{6}C); 36.0 (^{9}C); 126.2, 128.6, 128.7, 129.0, 130.7 (^{3}C, ^{4}C, ^{11}C, ^{12}C, ^{13}C); 127.7 (^{2}C); 141.4 (^{10}C); 146.3 (^{5}C); 172.0 (^{1}C)

δ_{Se} (69 MHz, $CDCl_3$ +TFA): 261.2

5.5.5 Preparation of resin-bound 4-(5-phenyl-2-selenapentyl)benzoic acid (59)

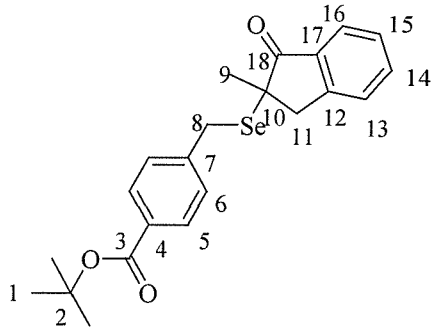


Aminomethyl resin (1.3 mmol/g, 0.20 g, 0.26 mmol) was swollen in DCM (1 mL). Acid (**58**) (1.5 eq, 0.39 mmol, 0.13 g) and HOBt (1.5 eq, 0.39 mmol, 53 mg) were dissolved in DCM (4 mL) and stirred at room temperature for 10 min. DIC (1.7 eq, 0.43 mmol, 54 mg, 67 μL) was added to the solution and the reaction was stirred for a further 10 min before being added to the pre-swollen resin. The resin was shaken at room temperature (48 h). The resin was filtered and washed with DMF (2 x 10 mL), DCM (2 x 10 mL), MeOH (2 x 10 mL) and Et_2O (2 x 10 mL) and dried *in vacuo*. A ninhydrin test was negative. Resin (**59**) was used without further analysis.

5.5.6 Oxidative elimination of resin-bound 4-(5-phenyl-2-selenapentyl)benzoic acid (59)

The selenide resin (**59**) (0.92 mmol/g, 0.20 g, 0.18 mmol) was swollen in DCM (1 mL). HFIP (2 mL) was added, followed by 30% aq H_2O_2 (2.0 eq, 0.37 mmol, 42 μL). The resin was shaken at room temperature (24 h). The resin was filtered and washed with DCM (2 x 10 mL) and the filtrate concentrated *in vacuo*. Analysis (TLC, HPLC, MS) showed no allylbenzene (**42**) was detected.

5.5.7 *Tert*-butyl 4-[2-(2-methyl-1-oxoindan-2-yl)-2-selenaethyl]benzoate (61)



Tert-butyl 4-(2-amidino-2-selenaethyl)benzoate (bromide salt) (**54**) (1.0 eq, 2.50 mmol, 0.79 g) was dissolved in N_2-purged EtOH (3 mL) under nitrogen and then N_2-purged 4% NaOH (5 mL) was added and the solution stirred at room temperature (30 min), during which time the solution changed colour from purple to yellow. The solvent was removed *in vacuo*, to leave a yellow/white residue. To this was added Cs_2CO_3 (1.0 eq, 2.50 mmol, 0.82 g), KI (catalytic amount) and DMF (5 mL) and the resulting mixture was stirred vigorously under nitrogen. Then 2-bromo-2-methylindanone (**47**) (2.0 eq, 5.00 mmol, 1.13 g) was added as a solution in DMF (3 mL) and the solution was stirred under nitrogen (16 h). The mixture was diluted with water (30 mL) and the product was extracted with EtOAc (4 x 20 mL). The combined organic layers were washed with water (2 x 30 mL), brine (1 x 30 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to yield a yellow oil. The product was purified by flash chromatography on silica gel, eluting with 0% to 4% Et_2O in hexane to give the title compound (**61**) as colourless plates (222 mg, 21%).

R_f: 0.32 (20% Et_2O: hexane)

RP HPLC (λ=254 nm) Gradient A: 22.1 min (92%)

IR (ν_{max}/cm^{-1}): 1701 C=O (s)

m/z (EI): 416 (^{79}Se, 85%, [$M^{+\cdot}$])

HRMS (EI): $C_{22}H_{24}O_3Se$ Calc. 416.0891 Found 416.0898

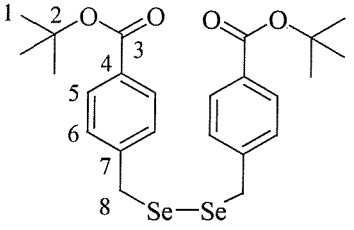
m.p.: 96-98°C

δ_H (400 MHz, $CDCl_3$): 1.50 (9H, s, $^1CH_3$); 1.72 (3H, s, $^9CH_3$); 3.09, 3.20 (2 x 1H, d, *J* 18, $^{11}CH_2$); 3.92, 3.98 (2 x 1H, d, *J* 12, $^8CH_2$); 7.32 (2H, d, *J* 8, ^4CH); 7.38 (1 H, d, *J* 8, ^{13}CH); 7.43 (1H, dd, *J* 8, 8, ^{14}CH); 7.60 (1H, dd, *J* 8, 8, ^{15}CH); 7.80-7.91 (3H, m, ^5CH, ^{16}CH)

δ_C (100 MHz, $CDCl_3$): 23.3 (^9C); 27.7 (^8C); 28.6 (^1C); 43.1 (^{11}C); 48.8 (^{10}C); 81.5 (^2C); 125.5, 126.5, 128.4, 129.5, 130.4, 135.2 (^5C, ^6C, ^{13}C, ^{14}C, ^{15}C, ^{16}C); 130.9, 134.9, 143.4, 149.7 (^4C, ^7C, ^{12}C, ^{17}C); 166.0 (^3C); 203.2 (^{18}C)

δ_{Se} (69 MHz, $CDCl_3$): 464.0

5.5.8 *Tert*-butyl 4-(4-{4-[(*tert*-butyl)oxycarbonyl]phenyl}-2,3-diselenabutyl)benzoate (62)



Tert-butyl 4-(4-{4-[(*tert*-butyl)oxycarbonyl]phenyl}-2,3-diselenabutyl)benzoate (**62**) was a side-product during the alkylation reaction described above (Section 5.5.7) for the synthesis of *tert*-butyl 4-[2-(2-methyl-1-oxoindan-2-yl)-2-selenaethyl]benzoate (**61**).

Tert-butyl 4-(4-{4-[(*tert*-butyl)oxycarbonyl]phenyl}-2,3-diselenabutyl)benzoate (**62**) was obtained as a yellow oil (88 mg, 13%).

R_F: 0.68 (50% Et_2O: hexane)

RP HPLC (λ=254 nm) Gradient A: 24.3 min (90%)

IR (ν_{max}/cm^{-1}): 1705 C=O (s)

m/z (EI): 542 (^{79}Se, 2%, [$M^{+\cdot}$])

δ_H (300 MHz, $CDCl_3$): 1.60 (9H, s, $^1CH_3$); 3.85 (2H, s, $^8CH_2$); 7.25 (2H, d, *J* 7, ^6CH); 7.93 (2H, d, *J* 7, ^5CH)

δ_C (75 MHz, $CDCl_3$): 28.4 (^1C); 32.1 (^8C); 81.2 (^2C); 128.9, 129.7 (^5C, ^6C); 130.9 (^4C); 143.8 (^7C); 165.6 (^3C)

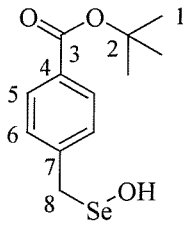
δ_{Se} (69 MHz, $CDCl_3$): 412.1

5.5.9 Reduction of *tert*-butyl 4-(4-{4-[(*tert*-butyl)oxycarbonyl]phenyl}-2,3-diselenabutyl)benzoate (62) with $NaBH_4$

Tert-butyl 4-(4-{4-[(*tert*-butyl)oxycarbonyl]phenyl}-2,3-diselenabutyl)benzoate (**62**) (1.0 eq, 0.54 g, 1.00 mmol) was dissolved in EtOH (15 mL) under nitrogen. $NaBH_4$ (2.0 eq, 2.00 mmol, 76 mg) in EtOH (5 mL) was added dropwise over 30 min, then 1-bromo-3-phenylpropane (10.0 eq, 10.0 mmol, 1.28 mL) was added and the reaction stirred at room temperature (10 h). TLC confirmed intermediate selenolate present, thus 1-bromo-3-phenylpropane (5.0 eq, 5.00 mmol, 0.60 mL) was added and the reaction stirred overnight at room temperature. EtOH was removed *in vacuo*, then the residue re-dissolved in EtOAc (5 mL) and partitioned with water (5 mL). The organic layer was washed with 2 M $KHSO_4$ (2 x 5 mL), brine (1 x 5 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The product was purified by flash chromatography on silica gel, eluting with 0% to 5% Et_2O in hexane to afford *t*ert-butyl 4-(5-phenyl-2-selenapentyl)benzoate (**56**) as a yellow oil (583 mg, 75%). (See Section 5.5.2 for data).

5.5.10 Solution phase oxidative elimination of selenide-indanone (61) (H_2O_2)

Selenide (1.0 eq, 0.2 mmol, 83 mg) (**61**) was dissolved in HFIP (2.5 mL). 30% aq H_2O_2 was added and the solution stirred at room temperature (24 h). No products were detected (TLC), thus the reaction was warmed to 25°C (16 h). The product was extracted with DCM (2 x 3 mL), washed with water (1 x 2 mL), brine (1 x 2 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The products were purified by flash chromatography on silica gel, eluting with 0% to 20% EtOAc in hexane.
Selenenic acid (**63**) was isolated as a yellow oil (11.0 mg, 19%).



63

R_f: 0.11 (20% Et_2O: hexane)

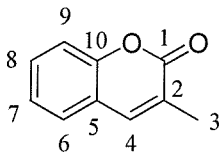
RP HPLC (λ=254 nm) Gradient A: 14.8 min (100%)

m/z (EI): 288 (^{79}Se, 2%, $M^{+\cdot}$)

δ_H (300 MHz, $CDCl_3$): 1.61 (9H, s, $^1CH_3$); 4.77 (2H, s, $^8CH_2$); 7.41 (2H, d, *J* 8, ^6CH); 7.98 (2H, d, *J* 8, ^5CH)

δ_C (75 MHz, $CDCl_3$): 27.2 (^1C); 63. 8 (^8C); 80.8 (^2C); 126.0, 128.7 (^5C, ^6C); 131.6 (^4C); 144.4 (^7C); 167.9 (^3C)

The Baeyer-Villiger product, 3-methylchromen-2-one (**64**), was isolated as a white solid (9.4 mg, 33%).



64

R_f: 0.44 (20% Et_2O: hexane)

RP HPLC (λ=254 nm) Gradient A: 14.4 min (82%)

IR (ν_{max}/cm^{-1}): 1704 C=O (s)

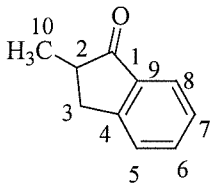
m/z (EI): 160 (100%, $M^{+\cdot}$)

m.p.: 89-91°C (Lit. 91°C)[180]

δ_H (300 MHz, $CDCl_3$): 2.23 (3H, s, $^3CH_3$); 7.04-7.17, 7.40-7.51 (2 x 2H, m, ^6CH, ^7CH, ^8CH, ^9CH); 7.42 (1H, s, ^4CH)

δ_C (100 MHz, $CDCl_3$): 17.6 (^3C); 116.9, 120.0, 124.7, 126.3, 127.3 (^2C, ^6C, ^7C, ^8C, ^9C); 130.9 (^5C); 139.6 (^4C); 153.7 (^{10}C); 162.6 (^1C)

5.5.11 2-Methylindanone[181] (46)



During the attempted *tert*-butyl deprotection of selenide (**61**) (1 eq, 0.28 g, 0.68 mmol) with 50% TFA/DCM (5 mL), 2-methylindanone (**46**) was obtained as a yellow oil (47 mg, 46%) yield.

R_f: 0.33 (20% Et_2O: hexane)

RP HPLC (λ=254 nm) Gradient A: 14.4 min (95%)

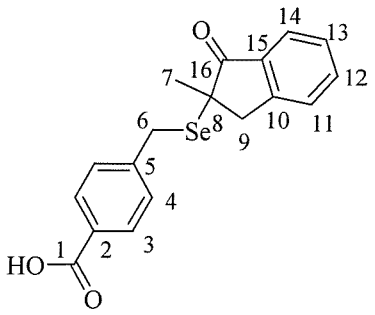
IR (ν_{max}/cm^{-1}): 1706 C=O (s)

m/z (EI): 146 (47%, [$M^{+\cdot}$])

δ_H (300 MHz, $CDCl_3$): 1.31 (3H, d, *J* 7, $^{10}CH_3$); 2.68-2.89 (2H, m, $^3CH_2$); 3.41 (1H, q, *J* 7, ^2CH); 7.35 (1H, dd, *J* 8, 8, ^7CH); 7.45 (1H, d, *J* 8, ^5CH); 7.59 (1H, dd, *J* 8, 8, ^6CH); 7.76 (1H, d, *J* 8, ^8CH)

δ_C (75 MHz, $CDCl_3$): 16.4 (^{10}C); 35.1 (^3C); 42.1 (^2C), 124.1, 126.7, 127.5, 134.9, 136.5 (^4C, ^5C, ^6C, ^7C, ^8C); 153.7 (^9C); 209.7 (^1C)

5.5.12 4-[2-(2-Methyl-1-oxoindan-2-yl)-2-selenaethyl]benzoic acid (65)



4-[2-(2-Methyl-1-oxoindan-2-yl)-2-selenaethyl]benzoic acid (**65**) was obtained from selenide (**61**) (1 eq, 0.55 mmol, 0.23 g) by removal of the *tert*-butyl ester as previously described (Section 5.5.4) but with a reduced reaction time of 1.5 h. After precipitation, the title compound was furnished as a white powder (153 mg, 77%).

R_f: 0.36 (50% EtOAc: hexane) [BCG stain]

RP HPLC (λ=254 nm) Gradient A: 16.1 min (100%)

IR (ν_{max}/cm^{-1}): 3050 OH (br, m); 1693 C=O (s)

m/z (APCI$^-$): 359 (^{79}Se, 18%, [M-H]$^-$)

HRMS (EI): $C_{18}H_{16}O_3Se$ Calc. 360.0265 Found 360.0262

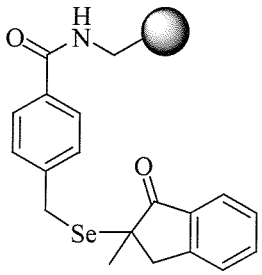
m.p.: 154-156°C

δ_H (300 MHz, $CDCl_3$ +TFA): 1.80 (3H, s, $^7CH_3$); 3.24 (2 x 1H, d, *J* 18, $^9CH_2$); 4.06 (2 x 1H, d, *J* 12, $^6CH_2$); 7.36-7.44 (4H, m, ^4CH, ^{11}CH, ^{13}CH); 7.62 (1H, dd, *J* 7, ^{12}CH); 7.85 (1H, d, *J* 7, ^{14}CH); 7.97 (2H, d, *J* 9, ^3CH); 8.93 (1H, s, br, OH)

δ_C (75 MHz, $CDCl_3$ +TFA): 22.9 (^7C); 27.8 (^6C); 43.1 (^9C); 47.7 (^8C); 125.7, 126.6, 128.6, 129.8, 131.0, 135.8 (^3C, ^4C, ^{11}C, ^{12}C, ^{13}C, ^{14}C); 127.3, 133.5, 144.1, 148.7 (^2C, ^5C, ^{10}C, ^{15}C); 171.1 (^1C); 202.5 (^{16}C)

δ_{Se} (69 MHz, $CDCl_3$ +TFA): 473.4

5.5.13 Preparation of resin-bound selenide-indanone (66)

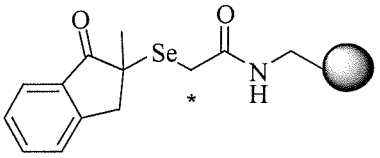


Aminomethyl polystyrene resin (1.0 eq, 0.20 g, 1.30 mmol/g, 0.26 mmol) (**8**) was swollen in DCM (1 mL). HOBt (1.5 eq, 0.39 mmol, 53 mg) and acid (**65**) (1.5 eq, 0.39 mmol, 0.14 g) were dissolved in DCM (2 mL) and stirred for 10 min at RT. DIC (1.7 eq, 0.43 mmol, 54 mg, 67 μL) was added, then the solution added to the pre-swollen resin and shaken overnight at RT. A ninhydrin test showed the reaction was not complete, hence HOBt (1.0 eq, 0.26 mmol, 35 mg) and DIC (1.0 eq, 0.26 mmol, 33 mg, 41 μL) were added to the coupling solution and the resin left to shake overnight at room temperature. The resin was filtered and washed with DMF (2 x 10 mL), DCM (2 x 10 mL), MeOH (2 x 10 mL), and Et_2O (2 x 10 mL) and dried *in vacuo*. A ninhydrin test showed the reaction was complete. Resin (**66**) was used without further analysis.

5.5.14 Solid phase oxidative elimination of selenide-indanone (66) (with H_2O_2)

Resin (**66**) (1.0 eq, 0.90 mmol/g, 0.20 g, 0.18 mmol) was swollen in DCM (1 mL), then HFIP (2 mL) and 30% aq H_2O_2 (2.0 eq, 0.36 mmol, 41 μL) were added and the resin left to shake at room temperature (16 h). The resin was filtered off, washed with DCM (2 x 10 mL), MeOH (1 x 5 mL) and Et_2O (1 x 5 mL), then the filtrate concentrated *in vacuo* to yield a yellow oil. The product was purified by flash chromatography on silica gel, eluting with 0% to 5% Et_2O in hexane to give *exo*-indenone (7.8 mg, 30%), *endo*-indenone (4.9 mg, 19%) (identified by RP HPLC) and 3-methylchromen-2-one (**64**) (1.9 mg, 7%) in the ratio 4:2.5:1 and in 56% overall yield (over 2 steps).

5.5.15 Stepwise preparation of resin-bound selenide-indanone (68)



Resin-bound bromoacetic acid (25% ^{13}C enriched) (1.00 g, 0.29 mmol/g, 0.29 mmol) (**32**) was stirred in EtOH (10 mL) under nitrogen at RT. Selenourea (1.5 eq, 0.44 mmol, 55 mg) was added and stirred for a further 15 min at RT, heated to 50°C for 1 h and then refluxed for a further 15 min. The reaction was cooled, and the resin washed with 2% aq NaOH (2 x 20 mL), 10% aq NaOH (1 x 20 mL), DCM (2 x 20 mL), MeOH (2 x 20 mL) and Et_2O (2 x 20 mL) and dried *in vacuo* to give resin-bound selenol.

Selenol resin was immediately swollen in DMF (2 mL). A solution of caesium carbonate (3.0 eq, 0.87 mmol, 0.27 g) and 2-bromo-2-methylindanone (5.0 eq, 1.45 mmol, 0.33 g) (**47**) in DMF (10 mL) was immediately added to the pre-swollen resin. The reaction was then shaken under nitrogen at room temperature overnight (16 h). The resin was filtered off and washed with DMF (2 x 30 mL), DCM (2 x 30 mL), MeOH (2 x 30 mL), and Et_2O (2 x 30 mL) and dried *in vacuo*.

δ_C (75 MHz, $CDCl_3$) [Gel phase]: 26.5 (*C)

5.5.16 Control reaction: attempted thermal elimination of selenide-indanone (66)

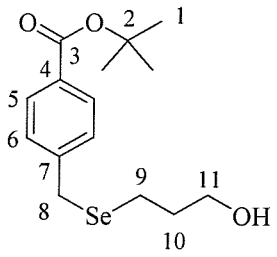
Resin-bound selenide-indanone (1.0 eq, 0.10 g, 0.28 mmol/g, 0.028 mmol) (**66**) was refluxed in MeOH (10 mL) overnight. The resin was filtered off, washed with DCM (2 x 2 mL), MeOH (2 x 2 mL) and Et_2O (2 x 2 mL) and the filtrate was concentrated *in vacuo*. No products were detected (TLC, MS).

5.5.17 Solid phase oxidative elimination of selenide-indanone (68) (with $NaIO_4$)

Resin-bound selenide-indanone (1.0 eq, 0.50 g, 0.28 mmol/g, 0.14 mmol) (**68**) was swollen in dioxane (2 mL). Sodium metaperiodate (2.0 eq, 0.28 mmol, 64 mg) was dissolved in water (2 mL) and cooled to 0°C. Dioxane (5 mL) was added, then the oxidant was added to the pre-swollen resin and left to shake at room temperature overnight (16 h). The resin was filtered off and washed with DCM (2 x 15 mL). The filtrate was transferred to a separating funnel and the organic layer was washed with water (5 mL) and then dried over $MgSO_4$, filtered and concentrated *in vacuo* to yield yellow crystals (6.4 mg, 32% over 5 steps).

The presence of both *exo* and *endo* indenones were confirmed by RP HPLC (21:1 *exo*:*endo* ratio) and EI (two compounds with mass 144).

5.5.18 *Tert*-butyl 4-(5-hydroxy-2-selenapentyl)benzoate (69)



Tert-butyl 4-(2-amidino-2-selenaethyl)benzoate (bromide salt) (**54**) (1.0 eq, 4.10 mmol, 1.28 g), 3-bromopropan-1-ol (2.4 eq, 1.39 g, 900 μL) and TEBA (0.5 eq, 2.21 mmol, 50 mg) were dissolved in N_2-purged 4% aq NaOH (20 mL) under nitrogen and heated at 60°C (16 h). The product was extracted with EtOAc (4 x 15 mL) and then the combined organic layers were washed with water (2 x 25 mL), brine (1 x 25 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The product was purified by flash chromatography on silica gel, eluting with 5% to 20% EtOAc in hexane, to give the title compound (**69**) as a pale yellow oil (1.34 g, 96%).

R_f: 0.16 (20% EtOAc: hexane)

RP HPLC (λ=254 nm) Gradient A: 17.2 min (98%)

IR (ν_{max}/cm^{-1}): 1710 C=O (s)

m/z (EI): 330 (^{79}Se, 32%, [M$^{+\cdot}$])

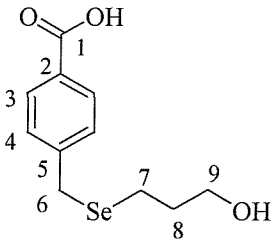
HRMS (EI): $C_{15}H_{22}O_3Se$ Calc. 330.0734 Found 330.0738

δ_H (300 MHz, $CDCl_3$): 1.51 (9H, s, $^1CH_3$); 1.71-1.84 (3H, m, *J* 7, $^{10}CH_2$, OH); 2.50 (2H, t, *J* 7, $^9CH_2$); 3.61 (2H, t, *J* 7, $^{11}CH_2$); 3.71 (2H, s, $^8CH_2$); 7.24 (2H, d, *J* 8, ^6CH); 7.83 (2H, d, *J* 8, ^5CH)

δ_C (75 MHz, $CDCl_3$): 20.5 (^9C); 26.4 (^8C); 32.7 (^{10}C); 28.4 (^1C); 62.4 (^{11}C); 81.2 (^2C); 128.8, 129.8 (^5C, ^6C); 130.5 (^4C); 144.5 (^7C); 165.8 (^3C)

δ_{Se} (69 MHz, $CDCl_3$): 253.2

5.5.19 4-(5-Hydroxy-2-selenapentyl)benzoic acid (70)



4-(5-hydroxy-2-selenapentyl)benzoic acid (**70**) was obtained from selenide (**69**) (1 eq, 1.70 g, 5.15 mmol) by removal of the *tert*-butyl ester as previously described (Section 5.5.4, reaction time 2 h). After precipitation, the title compound was furnished as an off-white powder (1.30 g, 92%).

R_f: 0.79 (EtOAc) [BCG stain]

RP HPLC (λ=254 nm) Gradient A: 13.9 min (100%)

IR (ν_{max}/cm^{-1}): 1700 C=O (s)

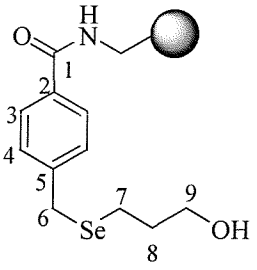
m/z (APCI$^-$): 273 (^{79}Se, 32%, [M-H$^-$])

m.p.: 84-86°C

δ_H (300 MHz, CD_3OD): 1.79 (2H, quint, *J* 7, $^8CH_2$); 2.53 (2H, dd, *J* 7, 7, $^7CH_2$); 3.55 (2H, dd, *J* 7, 7, $^9CH_2$); 3.80 (2H, s, $^6CH_2$); 7.30 (2H, d, *J* 8, ^3CH); 7.85 (2H, d, *J* 8, ^4CH); 8.03 (1H, s, br, OH)

δ_C (75 MHz, CD_3OD): 20.7 (^8C); 27.0 (^7C); 34.0 (^6C); 62.3 (^9C); 129.5, 130.5 (^3C, ^4C); 135.2 (^2C); 144.5 (^5C); 166.1 (^1C)

5.5.20 Preparation of resin-bound selenide (71)

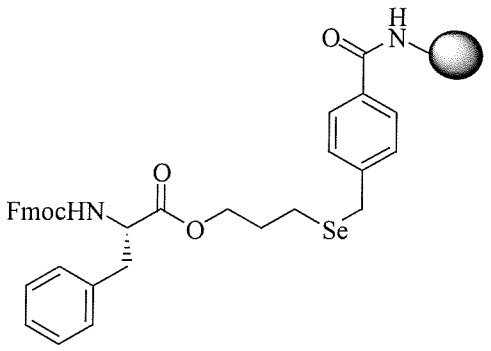


4-(5-Hydroxy-2-selenapentyl)benzoic acid (**70**) (1.2 eq, 1.56 mmol, 0.55 g) and HOBt (1.5 eq, 1.95 mmol, 0.26 g) were dissolved in DCM (5 mL). After 10 min, DIC (1.5 eq, 1.95 mmol, 0.25 g, 305 μL) was added and the solution stirred for a further 10 min, before it was added to aminomethyl polystyrene resin (1.00 g, 1.30 mmol/g, 1.30 mmol), pre-swollen in DCM (2 mL). The resin was then shaken at room temperature (48 h). The resin was filtered and washed with DMF (2 x 20 mL), DCM (2 x 20 mL), MeOH (2 x 20 mL) and Et_2O (2 x 20 mL) and dried *in vacuo*. A qualitative ninhydrin test was negative.

IR (ν_{max}/cm^{-1}): 1720 C=O (s)

δ_C (100 MHz, C_6D_6) [Gel phase]: 20.2 (^7C); 26.9, 29.7 (^6C, ^8C); 63.4 (^9C); 143.7, 146.3 (^2C, ^5C); 160.9 (^1C)

5.5.21 Preparation of resin-bound Fmoc-Phe-OH (72)



Alcohol resin (**71**) (1.0 eq, 0.75 mmol/g, 0.25 g, 0.19 mmol) was swollen in DCM (1 mL). Fmoc-Phe-OH (2.0 eq, 0.38 mmol, 0.15 g), HOBt (2.0 eq, 0.38 mmol, 51 mg) and DMAP (0.3 eq, 0.056 mmol, 6.8 mg) were dissolved in DCM (3 mL) and stirred at room temperature for 10 min. DIC (2.2 eq, 0.42 mmol, 52 mg, 65 μL) was added and the solution stirred for a further 10 min before it was added to the pre-swollen resin. The resin was shaken at room temperature for 44 h, then the resin was filtered and washed with DMF (2 x 10 mL), DCM (2 x 10 mL), MeOH (2 x 10 mL) and Et_2O (2 x 10 mL) and dried *in vacuo* to yield resin-bound selenide (**72**). The coupling reaction was repeated. A quantitative Fmoc test gave the substitution as 0.19 mmol/g (32%).

5.5.22 Oxidative elimination of resin-bound Fmoc-Phe-OH (72)

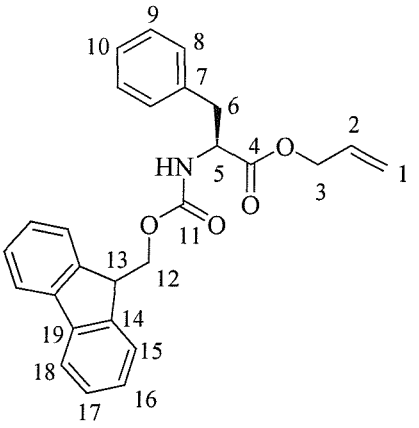
Resin (1.0 eq, 0.15 mmol/g, 50 mg, 7.5 μmol) (**72**) was swollen in dioxane (0.5 mL). $NaIO_4$ (10.0 eq, 75 μmol, 16 mg) was dissolved in water (0.5 mL) and cooled to 0°C. Dioxane (1 mL) was added to the $NaIO_4$ solution and then the mixture was added to the resin and shaken at room temperature (18 h). The resin was filtered and washed with DCM (2 x 5 mL). The filtrate was concentrated *in vacuo* and then re-dissolved in water (5 mL) and DCM (5 mL). The organic layer was washed with water (1 x 5 mL), brine (1 x 5 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*.

Analysis by RP HPLC/MS confirmed Fmoc-Phe-OAllyl (1.0 mg, 31%) (**73**) had been successfully cleaved from the resin.

RP HPLC (λ=254 nm) Gradient A: 20.2 min (96%)

m/z (ES^+): 428 (9%, $[M+H]^+$)

5.5.23 Preparation of standard Fmoc-Phe-OAllyl (73)



Fmoc-Phe-OH (1.0 eq, 1.00 g, 2.58 mmol) and caesium carbonate (1.0 eq, 2.58 mmol, 0.84 g) were dissolved in DMF (15 mL). Allyl bromide (5.0 eq, 12.9 mmol, 1.56 g) was added and the solution stirred at room temperature (3 h). DMF was removed *in vacuo* and the residue re-dissolved in water (10 ml) and EtOAc (10 mL). The organic layer was washed with sat. $NaHCO_3$ (1 x 15 mL), water (1 x 15 ml) and brine (1 x 15 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo.* The product was purified by flash chromatography on silica gel, eluting with 0% to 10% EtOAc in hexane, to afford the title compound (**73**) as an off-white waxy solid (0.57 g, 52%).

R_f: 0.31 (20% EtOAc: hexane)

RP HPLC (λ=254 nm) Gradient A: 20.2 min (100%)

IR (ν_{max}/cm^{-1}): 1702 C=O (s) ester; 1722 C=O (s) carbamate

m/z (ES^+): 428 (3%, $[M+H^+]$); 450 (100%, $[M+Na^+]$); 466 (64%, $[M+K^+]$);

m.p.: 91-93°C (Lit. 92-95°C)[182]

δ_H (300 MHz, $CDCl_3$): 2.96 (1H, br, s, NH); 3.12-3.28 (2H, m, $^6CH_2$); 4.27 (1H, t, *J* 6, ^{13}CH); 4.41, 4.51 (2 x 1H, dd, *J* 7,11, $^3CH_2$); 4.68 (2H, d, *J* 6, $^{12}CH_2$); 4.77 (1H, dd, *J* 6, 14, ^5CH); 5.35 (2H, dd, *J* 10, 17, $^1CH_2$); 5.93 (1H, m, ^2CH); 7.18 (2H, d, *J* 7, ^8CH); 7.28-7.41 (5H, m, ^9CH, ^{10}CH, ^{17}CH); 7.46 (2H, t, *J* 7, ^{16}CH); 7.63 (2H, t, *J* 7, ^{18}CH); 7.82 (2H, d, *J* 7, ^{15}CH)

δ_C (100 MHz, $CDCl_3$): 38.7 (^6C); 47.6 (^{13}C); 55.3 (^5C); 66.5 (^{12}C); 67.4 (^3C); 119.6 (^1C), 128.8, 133.0, 136.1, 141.8, 144.2 (^7C, ^{14}C, ^{19}C); 120.4, 125.5, 125.5, 127.5, 127.6, 128.1, 129.0, 129.8, 129.8, 131.8 (^2C, ^5C, ^8C, ^9C, ^{10}C, ^{13}C, ^{15}C, ^{16}C, ^{17}C, ^{18}C)

5.6 Crystallographic Data

5.6.1 Crystallographic data for *tert*-butyl 4-{[(2-methyl-1-oxoindan-2-yl)sulfinyl]methyl}benzoate (4b)

Empirical formula	$C_{22}H_{24}O_4S$
Formula weight	384.47
Temperature	298(2) K
Wavelength	0.71073 Å
Crystal system	Orthorhombic
Space group	$Pna2_1$
Unit cell dimensions	a = 19.173(2) Å
	b = 17.7818(17) Å
	c = 6.0797(4) Å
Volume	2072.8(3) Å^3
Z	4
Density (calculated)	1.232 Mg / m^3
Absorption coefficient	0.179 mm^{-1}
F(000)	816
Crystal	Colourless needle
Crystal size	0.20 × 0.05 × 0.05 mm^3
θ range for data collection	3.12 – 23.24°
Index ranges	$-21 \le h \le 21$, $-19 \le k \le 19$, $-6 \le l \le 6$
Reflections collected	11105
Independent reflections	2904 [R_{int} = 0.1151]
Completeness to θ = 23.24°	99.7 %
Absorption correction	Empirical, SORTAV
Max. and min. transmission	0.9911 and 0.9650
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2904 / 3 / 261
Goodness-of-fit on F^2	0.997
Final R indices [$F^2 > 2\sigma(F^2)$]	$R1$ = 0.0633, $wR2$ = 0.1299
R indices (all data)	$R1$ = 0.1221, $wR2$ = 0.1498
Absolute structure parameter	–0.01(18)
Extinction coefficient	0.0068(19)
Largest diff. peak and hole	0.270 and –0.188 e Å^{-3}

*Table 5.4: Crystal data and structure refinement for sulfoxide (**4b**)*

S1–O5	1.304(13)	C13–C22	1.518(8)
S1–O4	1.410(10)	C13–C15	1.519(9)
S1–C12	1.817(5)	C21–C16	1.362(8)
S1–C13	1.837(6)	C21–C20	1.389(9)
O2–C5	1.342(6)	C21–C22	1.481(8)
O2–C4	1.479(7)	C9–C10	1.354(7)
C12–C9	1.512(7)	C9–C8	1.393(8)
C6–C7	1.358(7)	C10–C11	1.399(7)
C6–C11	1.383(7)	C15–C16	1.452(9)
C6–C5	1.500(8)	C7–C8	1.376(7)
O1–C5	1.199(7)	C19–C18	1.353(13)
C4–C2	1.482(9)	C19–C20	1.376(11)
C4–C1	1.498(8)	C16–C17	1.413(9)
C4–C3	1.524(8)	C17–C18	1.381(12)
C13–C14	1.503(8)		

O5–S1–O4	109.4(6)	C16–C21–C20	120.5(6)
O5–S1–C12	111.7(5)	C16–C21–C22	110.7(6)
O4–S1–C12	113.4(5)	C20–C21–C22	128.7(6)
O5–S1–C13	108.0(5)	C10–C9–C8	119.1(5)
O4–S1–C13	113.2(5)	C10–C9–C12	120.1(6)
C12–S1–C13	100.9(3)	C8–C9–C12	120.8(5)
C5–O2–C4	121.2(4)	C9–C10–C11	121.1(5)
C9–C12–S1	108.4(4)	C21–C22–C13	107.2(5)
C7–C6–C11	119.0(5)	C16–C15–C13	108.9(5)
C7–C6–C5	123.6(5)	C6–C7–C8	121.8(5)
C11–C6–C5	117.4(5)	C7–C8–C9	119.5(5)
O2–C4–C2	109.3(5)	O1–C5–O2	125.4(5)
O2–C4–C1	110.6(6)	O1–C5–C6	123.8(5)
C2–C4–C1	113.3(6)	O2–C5–C6	110.8(5)
O2–C4–C3	101.2(5)	C18–C19–C20	121.5(9)
C2–C4–C3	111.6(6)	C21–C16–C17	120.9(7)
C1–C4–C3	110.2(6)	C21–C16–C15	109.8(5)
C14–C13–C22	112.9(6)	C17–C16–C15	129.1(7)
C14–C13–C15	113.9(6)	C19–C20–C21	118.4(7)
C22–C13–C15	103.1(5)	C6–C11–C10	119.5(5)
C14–C13–S1	106.5(4)	C18–C17–C16	117.2(8)
C22–C13–S1	109.7(4)	C19–C18–C17	121.5(9)
C15–C13–S1	110.8(4)		

Symmetry transformations used to generate equivalent atoms.

Table 5.5: Bond lengths (Å) and angles (°) for sulfoxide ***(4b)***

5.6.2 Crystallographic data for *tert*-butyl 4-[2-(2-methyl-1-oxoindan-2-yl)-2-selenaethyl]benzoate (61)

Empirical formula	$C_{22}H_{24}O_3Se$
Formula weight	415.37
Temperature	150(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	*Pn*
Unit cell dimensions	$a = 6.0387(6)$ Å
	$b = 17.283(3)$ Å $\quad \beta = 95.888(9)°$
	$c = 9.4669(15)$ Å
Volume	982.8(2) Å^3
Z	2
Density (calculated)	1.404 Mg / m^3
Absorption coefficient	1.928 mm^{-1}
F(000)	428
Crystal	Colourless plate
Crystal size	0.20 × 0.10 × 0.02 mm^3
θ range for data collection	3.20 – 23.04°
Index ranges	$-6 \le h \le 6$, $-18 \le k \le 18$, $-10 \le l \le 10$
Reflections collected	5614
Independent reflections	2596 [$R_{int} = 0.1085$]
Completeness to $\theta = 23.04°$	95.1 %
Absorption correction	Empirical, SORTAV
Max. and min. transmission	0.9625 and 0.6990
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2596 / 2 / 241
Goodness-of-fit on F^2	0.930
Final *R* indices [$F^2 > 2\sigma(F^2)$]	*R1* = 0.0530, *wR2* = 0.0893
R indices (all data)	*R1* = 0.0886, *wR2* = 0.1002
Absolute structure parameter	0.025(18)
Extinction coefficient	0.0058(14)
Largest diff. peak and hole	0.410 and –0.297 e Å^{-3}

*Table 5.6: Crystal data and structure refinement for selenide (**61**)*

Se1–C12	1.962(7)	C4–C3	1.516(10)
Se1–C13	2.006(8)	C4–C2	1.523(11)
O1–C5	1.234(13)	C7–C6	1.385(10)
C12–C9	1.512(11)	C6–C11	1.396(11)
C21–C16	1.381(10)	C6–C5	1.480(13)
C21–C20	1.389(11)	C9–C10	1.366(10)
C21–C22	1.513(12)	O2–C5	1.332(12)
C8–C7	1.372(12)	C11–C10	1.391(11)
C8–C9	1.385(12)	C20–C19	1.392(14)
C13–C14	1.502(10)	C16–C17	1.380(14)
C13–C15	1.507(11)	C16–C15	1.464(11)
C13–C22	1.550(12)	O3–C15	1.229(8)
C4–O2	1.484(10)	C17–C18	1.385(16)
C4–C1	1.512(10)	C19–C18	1.377(14)

C12–Se1–C13	100.8(3)	C11–C6–C5	121.0(8)
C9–C12–Se1	117.0(5)	C10–C9–C8	118.5(8)
C16–C21–C20	119.9(9)	C10–C9–C12	121.1(7)
C16–C21–C22	111.5(8)	C8–C9–C12	120.4(8)
C20–C21–C22	128.6(8)	C5–O2–C4	121.7(7)
C7–C8–C9	119.7(8)	O1–C5–O2	122.9(10)
C14–C13–C15	116.0(7)	O1–C5–C6	123.3(9)
C14–C13–C22	115.2(7)	O2–C5–C6	113.8(10)
C15–C13–C22	104.2(7)	C10–C11–C6	117.3(7)
C14–C13–Se1	111.0(6)	C21–C20–C19	117.4(9)
C15–C13–Se1	104.2(5)	C17–C16–C21	122.4(10)
C22–C13–Se1	105.0(6)	C17–C16–C15	128.5(10)
O2–C4–C1	113.1(6)	C21–C16–C15	109.1(8)
O2–C4–C3	101.8(6)	C21–C22–C13	104.4(7)
C1–C4–C3	112.3(7)	C9–C10–C11	123.3(7)
O2–C4–C2	108.0(7)	C16–C17–C18	118.1(12)
C1–C4–C2	111.9(7)	C18–C19–C20	122.5(11)
C3–C4–C2	109.2(7)	O3–C15–C16	127.8(8)
C8–C7–C6	121.6(8)	O3–C15–C13	122.8(8)
C7–C6–C11	119.5(8)	C16–C15–C13	109.3(7)
C7–C6–C5	119.4(9)	C19–C18–C17	119.7(10)

Symmetry transformations used to generate equivalent atoms.

Table 5.7: Bond lengths (Å) and angles (°) for selenide ***(61)***

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