UNIVERSITY OF SOUTHAMPTON

DEVELOPMENT OF A 1,3-DITHIANE LINKER FOR THE SOLID PHASE SYNTHESIS OF PODOPHYLLUM LIGNANS

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ABSTRACT

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In recent years the fight against disease has led the scientists to look for new drugs to fight the infections so prevalent in society today. One such new group of compounds are the podophyllum lignans, which have been shown to have cytotoxic activity against many common cancers. Their main problem are the toxic side effects they exhibit. In order to counteract this scientists have been looking at ways of modifying the peripheral structure of these compounds whilst keeping the central core of the molecule intact.

We describe a number of routes to synthesise a 1,3-dithiane linker which will allow the solid phase synthesis of many compounds based upon the podophyllotoxin skeleton. This will allow the rapid determination of the key structural motifs necessary for cytotoxicity, whilst minimising toxic side effects.

Contents

Abbreviations

APCI	atmospheric pressure chemical ionisation
ATR	attenuated total reflectance
br	broad
CI	chemical ionisation
d	doublet
δ	chemical shift (ppm)
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCM	dichloromethane
DIAD	diisopropyl azodicarboxylate
DIBAL-H	diisobutylaluminium hydride
DIC	*N*, *N*-diisopropylcarbodiimide
DCC	*N*, *N*-dicyclohexylcarbodiimide
DCU	*N*, *N*-dicyclohexylurea
DIPEA	*N*, *N*-diisopropylethylamine
DMAP	4-dimethylaminopyridine
DMF	*N*, *N*-dimethylformamide
DMSO	dimethylsulfoxide
EI	electron impact
ES	electrospray

Fmoc	9*H*-fluorenylmethoxycarbonyl
HOBt	1-hydroxybenzotriazole
HPLC	high performance liquid chromatography
IR	infra-red
J	coupling constant (Hz)
LDA	lithium diisopropylamide
m	multiplet, medium
MIRC	Michael initiated ring closure
M. Pt.	melting point
MS	mass spectrometry
NMR	nuclear magnetic resonance
PS	polystyrene
q	quartet
R.T.	retention time
r.t.	room temperature
R_f	retention factor
RP	reversed phase
s	singlet, strong
SPS	solid phase synthesis
t	triplet
^{t}Bu	*tert*-butyl

TFA	trifluoroacetic acid
TLC	thin layer chromatography
Ts	*p*-toluenesulfonyl
UV	ultra-violet
w	weak

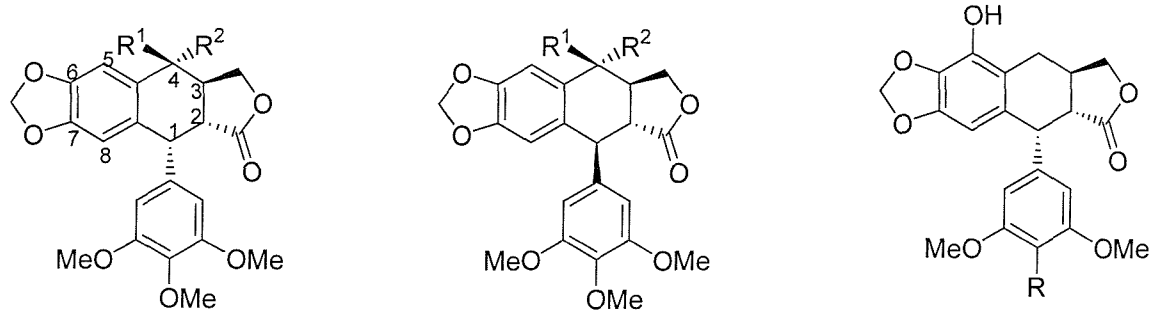
1. Podophyllum Lignans

1.1 Introduction

Podophyllum lignans are a class of natural products, which have become increasingly important in modern medicine as more of their cytotoxic activities are discovered[1]. This series of compounds can be extracted from various *Podophyllum sp.* (May apple, American mandrake). The aryl tetralin lignan lactones which have been isolated from these plants, of which podophyllotoxin is the main active constituent, have been used in the indigenous medicine of the North American and Himalayan people.[1]

1.2 The cytotoxic nature of podophyllum lignans

In 1946 the anti-mitotic properties of podophyllotoxin were discovered and interest in this class of compounds grew. The stereoisomers of podophyllotoxin **1**, of which epipodophyllotoxin **2** is one of the best documented, also show cytotoxic activity.[2]



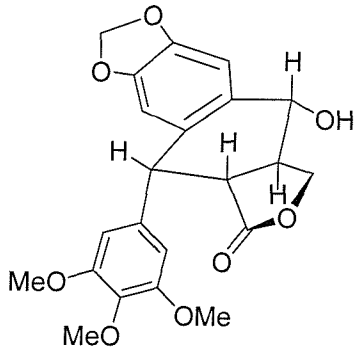
Podophyllotoxin **1**	R^1 = H R^2 = OH	Isopodophyllotoxin **3**	R^1 = H R^2 = OH	α-pelatin **5**	R = OH
Epipodophyllotoxin **2**	R^1 = OH R^2 = H	Epiisopodophyllotoxin **4**	R^1 = OH R^2 = H	β-pelatin **6**	R = OMe

Figure 1: Podophyllotoxin and structurally related compounds which show varying levels of cytotoxicity.[2-3]

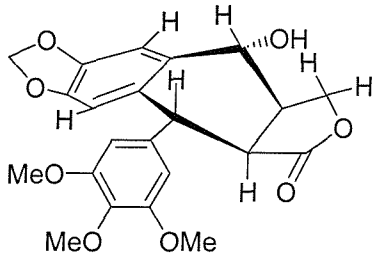
Extracts of podophyllotoxin, its demethyl derivative and two structurally similar compounds α and β peltatin **5**, **6** have all been shown to have powerful and specific cytotoxicity (Figure 1). These substances have been employed in the treatment of genital warts.[3]

However, although the initial anti-tumour activity of these compounds appeared promising, they have in most cases failed to pass clinical trials due to toxic side effects.[4] This led groups to attempt the construction of semi-synthetic derivatives of podophyllotoxin **1** which would exhibit fewer side effects.

It was found by modification of the peripheral substitution pattern of the ring system, and also by alteration of the stereochemistry, that certain functionalities are important for anti-mitotic activity. The compound requires polyoxygenation of the aromatic ring, and for the lactone ring junction to be *trans*. This stereochemistry is very difficult to generate as the molecule prefers the less strained *cis* ring junction as found in picropodophyllin **7** (Figure 2).



Podophyllotoxin **1** - Trans lactone ring junction



Picropodophyllin **7** - Cis lactone ring junction

Figure 2 : The structures of podophyllotoxin and picropodophyllin showing the different conformations adopted for the lactone ring junction.

Using the knowledge gained from these experiments, two semi-synthetic derivatives of podophyllotoxin **1** were developed. Etoposide (VP-16) **8** and tenoposide (VM-26) **9** are glycosidal derivatives of podophyllotoxin which exhibit strong anti-tumour activity (Figure 3). Having passed clinical trials, they are both in use for the treatment of small cell lung cancer, testicular cancer and bladder cancer.[2,3]

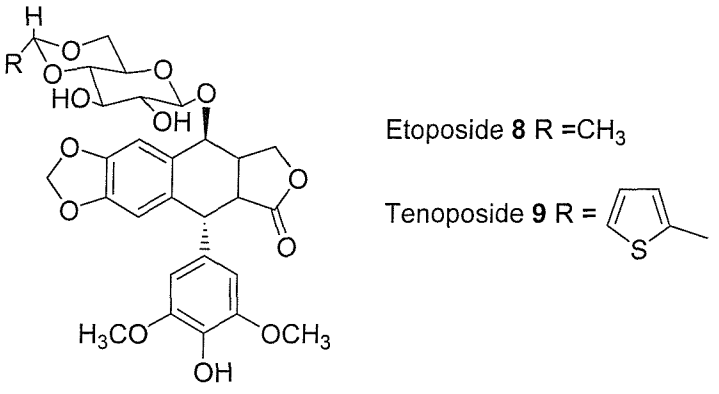


Figure 3 : The glycocidal derivatives of podophyllotoxin etoposide and tenoposide have shown strong anti-tumour activity and are now in use as anti-cancer agents for the treatment of small cell lung cancer, testicular cancer and bladder cancer.[2-3]

The mode of action of etoposide and tenoposide is *via* inhibition of the catalytic activity of type II DNA topoisomerase with concurrent enzyme mediated strand cleavage of DNA.[7] The strand breaks are generated by formation of a cleavable complex between DNA, the drug and DNA topoisomerase II.[5-6] Podophyllotoxin does not exhibit the same traits, but acts through inhibition of microtubule polymerisation.[7]

Since the discovery of these two derivatives, many more analogues of podophyllotoxin have been synthesised. Justicidin B and diphyllin (isolated from *Justicia hayatai* and *Diphylleia grayi* respectively[8]) have been synthesised as ring-A opened lignans. These two derivatives have been found to be more active than podophyllotoxin against Sindbis virus.[9]

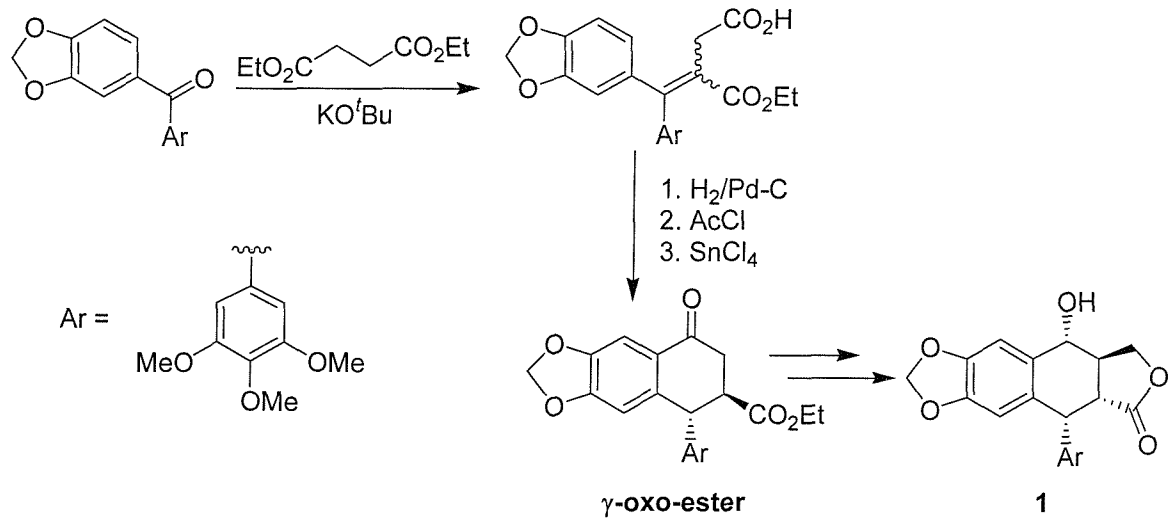
Other modifications of the podophyllum skeleton have led to the production of many compounds which show varying levels of cytotoxicity. Examples include the oxazolidinones, where skeletal atom replacement results in compounds which retain anti-mitotic activity.[10] Another class of compounds, the arylnaphthones, also tend to show biological activity, although not all compounds in this class are active.[11] The cytotoxic arylnaphthalene lignan, Taiwanin E (isolated from *Taiwania cryptomerioides* Hayata (taxodiaceae))[12], a compound with the functionality of podophyllotoxin around a central aromatic ring, has now been synthesised using a

Michael initiated ring closure (MIRC) procedure (see section 1.3.4)[18]. This procedure should allow a large number of similar compounds to be synthesised.

1.3 Synthesis of podophyllotoxin derivatives

Podophyllotoxin, containing four contiguous chiral centres, a rigid and strained *trans* B/C ring fusion and an axially locked C-1 aryl substituent has been a target for synthetic chemists for a long time.[1-2] Four main routes have been used to synthesise podophyllotoxin and its structurally similar derivatives. These approaches are discussed below.

1.3.1 The oxo-ester route



Scheme 1 : Synthesis of podophyllotoxin using the oxo-ester approach.

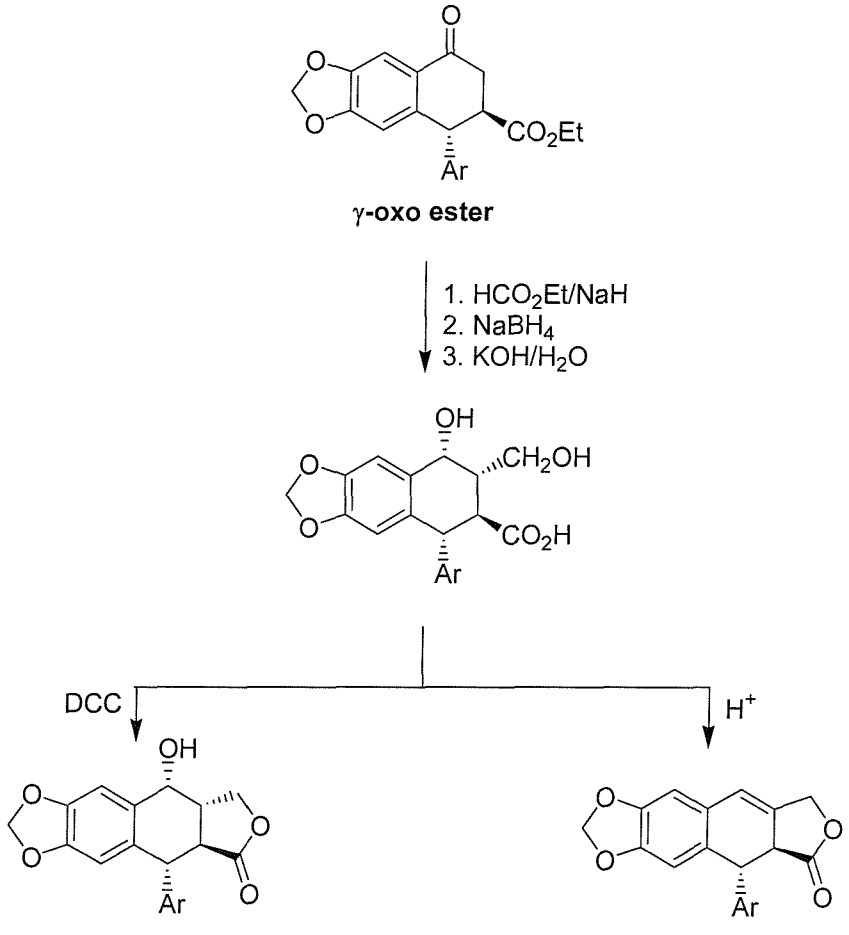
The pioneering work for this route was completed by Gensler,[13] who used a Stobbe condensation on a benzophenone derivative followed by reduction and cyclisation to give the γ-oxo-ester. A stereoselective aldol condensation and lactonisation followed to generate the product.

The main problem with this synthetic route is the number of steps required to generate the starting oxo-ester. The remaining drawback to this route is the difficulty

in generating the correct relative stereochemistry at C-1, C-2 and C-3 in the podophyllotoxin skeleton.

1.3.2 The dihydroxyacid route

Once again the initial work on this synthesis was accomplished by Gensler.[13] Using the γ-oxo-ester as a starting point, he converted this to the dihydroxyester. Dehydration of this ester generated an unsaturated lactone, which gave the desired product upon rehydration. Alternatively, treatment of the dehydrated ester with DCC gave another derivative of podophyllotoxin.[4]



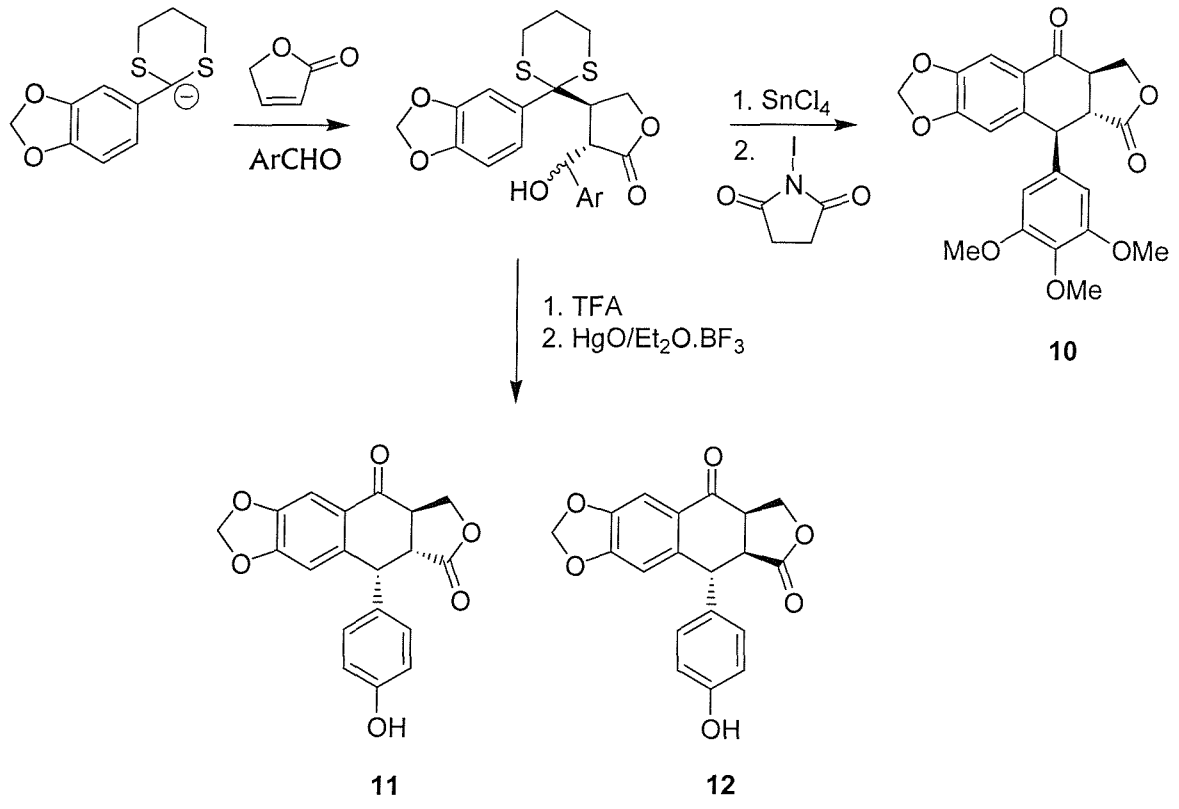
Scheme 2 : Synthesis of podophyllotoxin and its derivatives using a dihydroxyacid intermediate.

The distinction between the γ-oxo-ester route and the dihydroxyacid method was shown by Rodrigo *et al.* when they used a Diels-Alder reaction to generate the

dihydroxy acid fixing the relative configuration at up to four chiral centres.[4] The advantage of this sequence is the establishment of the correct stereochemistry at C-1, C-2 and C-3, which was proving problematic with the oxo-ester route. The stereochemistry of the dihydroxyacid pre-determines the stereochemistry of the product and hence which isomer of podophyllotoxin is created.

1.3.3 Tandem conjugate addition

Both the previous syntheses have a main disadvantage, whether it is a kinetic protonation or another process to generate the required 2,3-*trans* configuration. The tandem conjugate addition route overcomes these problems by forming the *trans*-dibenzylbutyrolactone framework upon which many lignans are based.



Scheme 3 : Tandem conjugate addition reactions developed by Zeigler and Gonzalez.

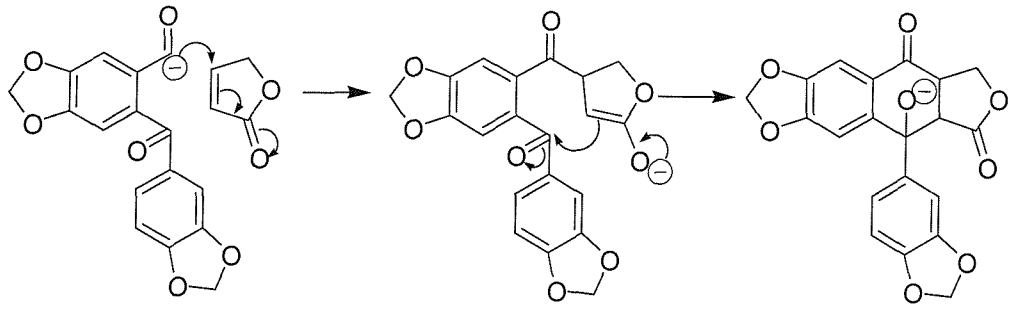
Ziegler used this theory to make isopodophyllone **10**[14] and Gonzalez synthesised podophyllone **11** and picropodophyllone **12** analogues using the same strategy.[15] The same general approach has been extended to perform an asymmetric synthesis of aryltetralin lignans such as deoxyisopodophyllotoxin.[16]

This synthetic strategy appears upon first consideration to overcome all the problems previously encountered with other methods, such as length of synthesis and the stereochemistry of the lactone ring. However, in general this path gives the 1,2-*trans* configuration present in isopodophyllotoxin as opposed to the 1,2-*cis* configuration of podophyllotoxin.

Kutney has furthered this approach by using a cell free enzyme preparation from *Catharanthus roseus* to afford the oxidative phenolic coupling of a diphenolic dibenzylbutyrolactone. This method combines the stereoselectivity of an enzyme coupling with simplicity of the tandem conjugate addition route.[17]

1.3.4 Michael Initiated Ring Closure (MIRC)

Harrowven and co-workers developed a new approach to the problem.[18-19] Michael initiated cyclisations have long been used to generate both simple and complex substrates.[20] This work has now been adapted to the synthesis of podophyllins *via* a type II MIRC. The viability of this work has been shown by the synthesis of taiwanin E[18] and chinensinaphthol,[19] both naturally occurring arylnaphthalenes possessing all the functionality of podophyllotoxin around a central aromatic ring.



Scheme 4 : Synthesis of podophyllotoxin based arylnaphthalenes using a Michael initiated ring closure.

The reaction mechanism works *via* an acyl anion equivalent, which is subjected to intermolecular Michael addition. The resulting ester enolate undergoes an intramolecular aldol condensation to give a 6-membered ring closed product (Scheme 4).

Kamal and Daneshtalab have utilised the MIRC, which when followed by desulfurisation, in the presence of a nickel containing complex reducing agent (NiCRA), and then aromatization, produces ring-A opened podophyllum lignans which can be used as DNA topoisomerase inhibitors.[9]

The MIRC procedure not only overcomes the problem of lengthy syntheses but also generates the correct podophyllotoxin stereochemistry.[18] Therefore it would seem that this route is the ideal opening for the synthesis of podophyllotoxin derivatives.

1.4 Lignans - An ideal target for SPS

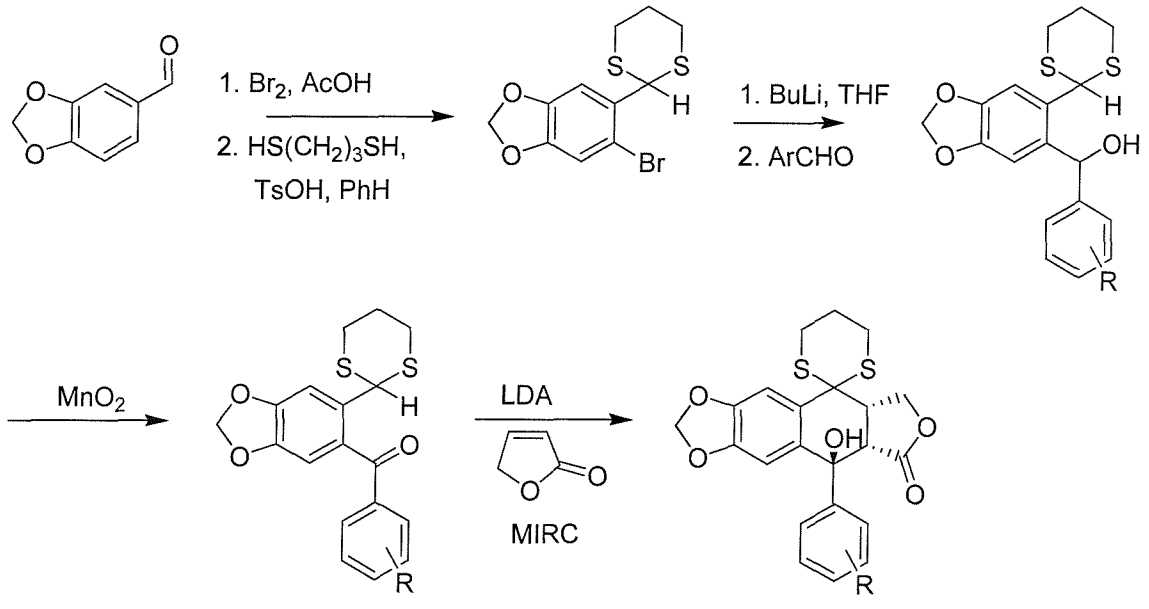
The podophyllum lignans are an ideal target for solid phase reactions for a number of reasons. The synthesis of podophyllotoxin and its derivatives is typified by long and complicated reactions. The intermediates are numerous, leading to many purification steps, making the process time consuming and difficult.

Solid phase synthesis, although not affecting the number of steps in the overall sequence, would allow for easier purification of intermediates. This is accomplished

by a simple washing procedure as opposed to more traditional time consuming processes (for example column chromatography).

Another advantage of SPS is the ability to use an excess of reagents in most of the steps which would force the reactions to completion, generating better yields.

The presence of a keto group at position C-4 (for numbering scheme see Figure 1) on the podophyllotoxin skeleton provides an ideal attachment point to resin. During the MIRC synthesis this group is protected as a 1,3-dithiane which can be inserted at the start of the sequence by coupling piperonal with 1,3-propanedithiol (Scheme 5).[19]



Scheme 5 : Synthesis of podophyllotoxin precursors using a MIRC approach.

It is this functionality which is to be used for the linkage to resin in the course of this project. The advantage of a 1,3-dithiane link is that upon cleavage it produces a ketone functionality directly and cleanly. The ketone can be reduced to an alcohol concurrently with dehydration at position C-1.

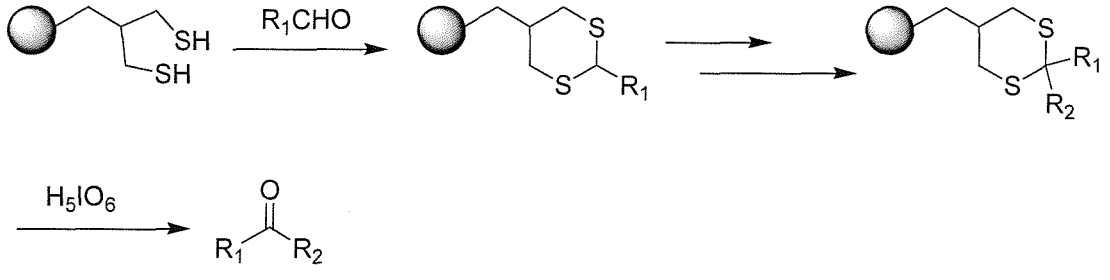
1.5 Linkers

Linkers allow the products of solid phase syntheses to be cleaved from the resin. There are two important functions a linker must possess. It must be stable to all the reaction conditions it will be exposed to during the course of the synthesis and must be easily, quantitatively and selectively cleaved under mild conditions at the end of the synthesis to release the target molecule.

The 1,3-dithiane linkage can be cleaved at the end of the synthesis with periodic acid to generate a ketone functionality in the final product.[23]

1.6 Aims of the project

The aim of this project was to develop a 1,3-dithiane linker for use in the synthesis of structurally similar lignans based around the podophyllum skeleton. This linker would allow cleavage to yield a ketone functionality in the final product. The idea was to form the linker directly on Merrifield resin to negate the need for additional linkage to the resin. However this proved not to be possible, thus, an amide linkage was generated. It was then intended to synthesise podophyllotoxin *via* a MIRC procedure following documented work by Harrowven.[18-19]



Scheme 6 : General scheme to show the projected outcome of the project.

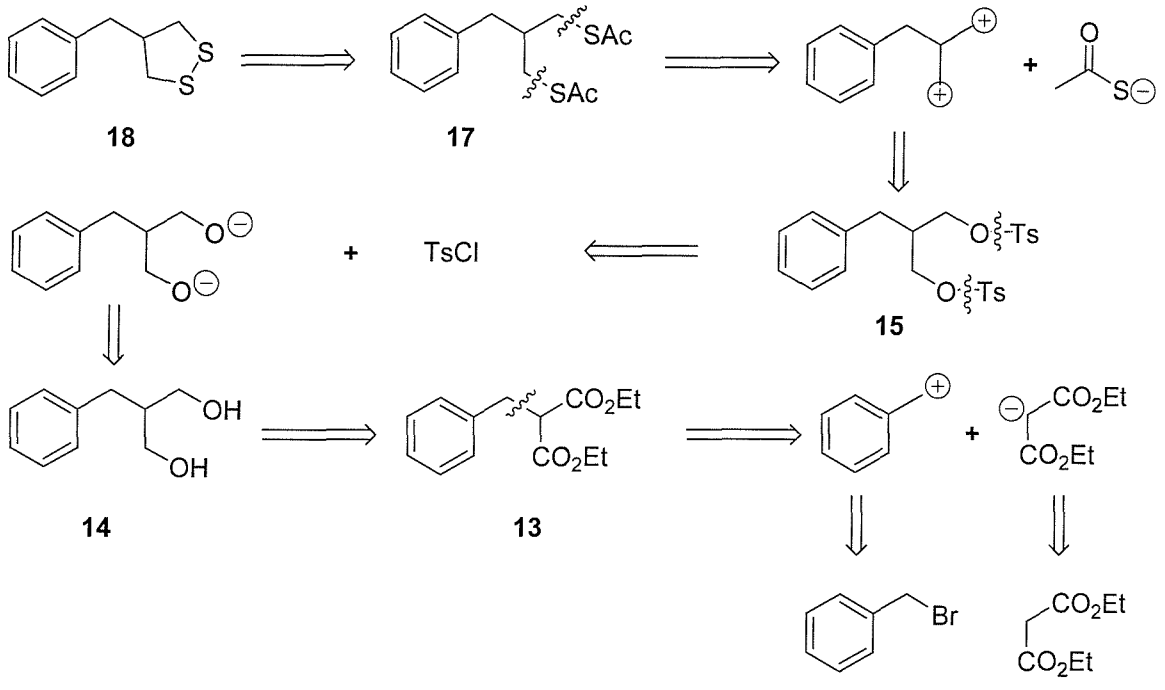
2. Preparation of a 1,3-Dithiane linker using Malonate Chemistry

2.1 Introduction

The aim of this project was to produce a 1,3-dithiane linker, which could be utilised for the solid phase synthesis of lignans based around the podophyllum skeleton. This would allow a rapid entry into a class of compounds which have proved time consuming to make and difficult to purify by solution methods.[4]

Although the project was based around a solid phase objective, it was necessary to use solution phase analogues throughout the work, to validate the methodology, due to difficulties in detecting the dithiane moiety on the solid phase by conventional spectroscopic means.

2.2 Solution Phase Diethyl Malonate Synthesis.

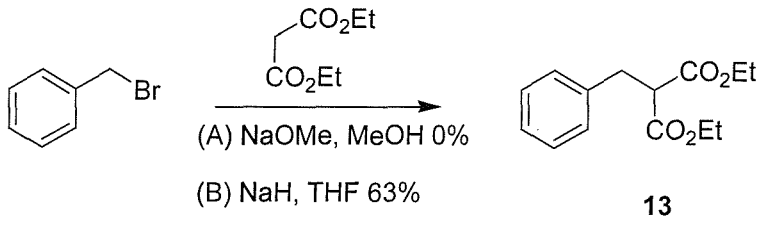


Retrosynthetic Scheme 1 : Retrosynthesis for the diethylmalonate synthon.

The first route attempted in the quest for an easily attainable 1,3-dithiane linker was *via* the diethyl malonate synthon. This approach was chosen because diethyl malonate already had in place a 1,3-diester moiety, which could be easily converted to the corresponding diol and hence to the dithiol.

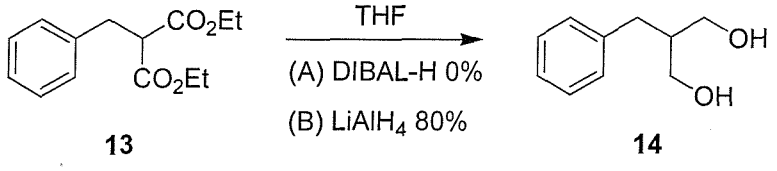
2.2.1 Synthesis of a benzylic 1,3-diol

To mimic the resin, benzyl bromide was used as it could be easily alkylated and also displays similar reactivity to the chloromethyl polystyrene resin used in the project (Scheme 7).



Scheme 7 : Coupling of benzyl bromide to diethyl malonate.

1.1eq of sodium hydride was used to deprotonate diethyl malonate,[21] which was then alkylated with benzyl bromide. Upon purification it could be seen that the desired benzylic diester **13** was obtained in 63% yield.



Scheme 8 : Synthesis of 2-benzylpropane-1,3-diol.

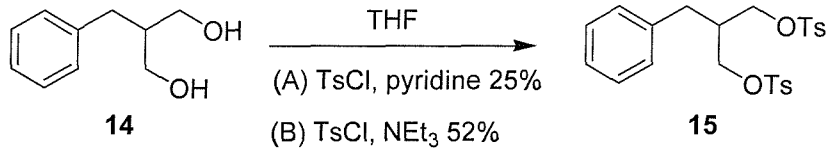
Diester **13** then provided a starting point for the 1,3-dithiol synthesis. The first step was to effect the reduction of both the malonate esters to alcohol functions, two methods were tried to achieve this (Scheme 8). The method of choice was reduction using 3 eq of DIBAL,[22] a liquid source of hydride, and therefore highly compatible

for use with resin. DIBAL can access all parts of the resin easily and quickly, it is also readily washed away at the end of the reaction unlike some of the solid hydrides which are poorly soluble. However, even after prolonged reaction times only unreacted starting material could be detected in the reaction mixture (TLC).

The second choice of reagent was the solid $LiAlH_4$, a more reactive reducing agent. The reduction reaction was performed using the standard procedure of dropwise addition of the ester, as a solution in anhydrous THF, cooled to 0°C, followed by warming to room temperature, with reduction to **14** taking place in 24h (monitored by TLC). This reaction proceeded in good yield (80%).

2.2.2 Tosylation as a route to a 1,3-dithiol

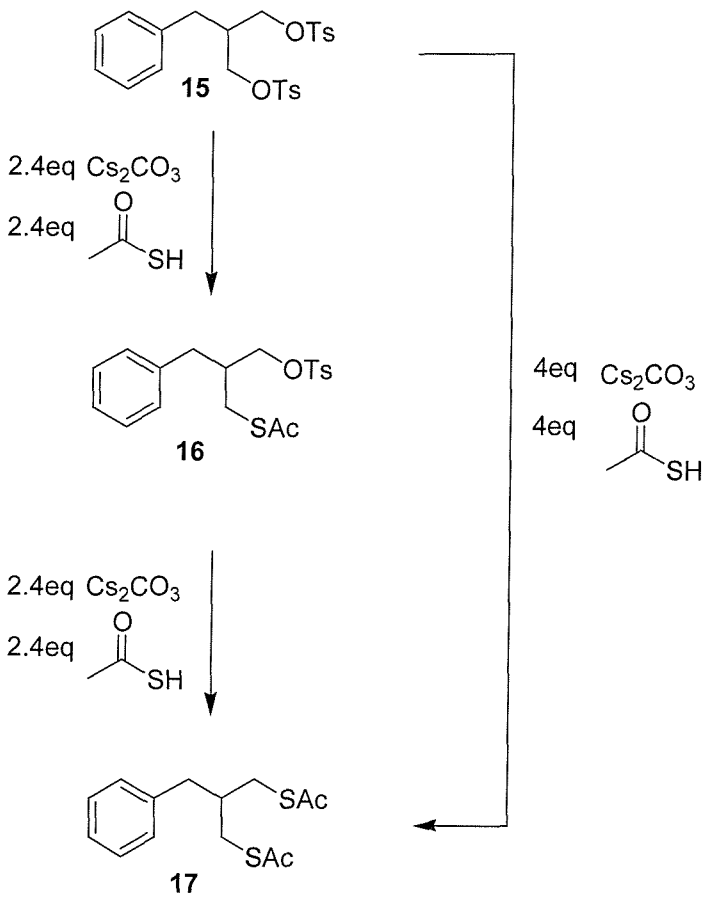
2-Benzylpropane-1,3-diol **14** was derivatised using TsCl and pyridine following the method of Bertini *et al.*[23] (Scheme 9) However, this led to a very poor yield of **15** (25%) even after overnight reaction. An alternative tosylation procedure was followed which utilised triethylamine as the base instead of pyridine.[24]



14 **15**

Scheme 9 : Tosylation procedures used on 2-benzylpropane-1,3-diol.

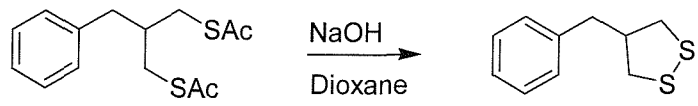
When attempted, this reaction used 3 eq of TsCl and 4 eq of triethylamine and was left overnight. Although the yield for this was still only moderate (52%) it was a significant improvement upon the pyridine coupling, and sufficient that the methodology could be transferred to the solid phase where the reaction could be forced to completion by the use of excess reagents.



Scheme 10 : Synthesis of 2-benzylpropane-1,3-dithioacetate.

The tosyl groups of **15** were displaced by reaction with cesium thioacetate, generated *in situ* by reaction of thiolacetic acid and cesium carbonate (Scheme 10). The reaction was heated to 70°C for 1.5h, at which time all the starting material had been consumed (TLC). However, upon work up, NMR and MS identified the product of the reaction as O-tosyl-S-acetyl-2-benzyl-1-hydroxypropane-3-thiol **16**. The reaction was repeated utilising **16** as the starting substrate, but the desired product, 2-benzylpropane-1,3-dithioacetate **17** was only obtained in low yield (28%).

The direct conversion of **15** to **17** was again attempted, using a greater excess of thiolacetic acid and cesium carbonate. This resulted in the desired compound, **17**, after 4h reaction time in a much greater yield (53%) than previously obtained.



17 18

Scheme 11 : Hydrolysis of both thioesters to give 4-benzyl-1,2-dithiolane **18**.

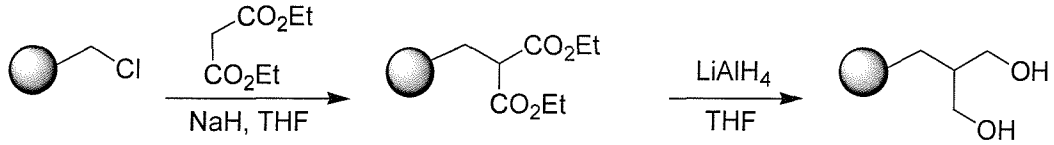
The final step in the solution synthesis was the hydrolysis of the thioester, with concomitant disulfide formation, using sodium hydroxide in dioxane (Scheme 11). This reaction proceeded very slowly, requiring in total 12 equivalents of sodium hydroxide and an overnight reaction in the presence of air for the consumption of **17**. The product when isolated from the impurities by column chromatography was found to be the ring closed disulfide **18** (30mg, 47%).

2.3 Resin Bound Diethyl Malonate work

Having established that the chemistry worked in solution, an attempt was made to transfer the methodology onto resin. Polystyrene resin (substitution 1.3-1.4mmolg^{-1}) was used for all syntheses described.

2.3.1 Synthesis of a resin bound 1,3-diol

The initial coupling of diethyl malonate with chloromethyl resin to make diester **19** was achieved using sodium hydride as base[25] (Scheme 12). The reaction was analysed by IR and the appearance of the ester C=O peak at 1715cm^{-1} monitored.

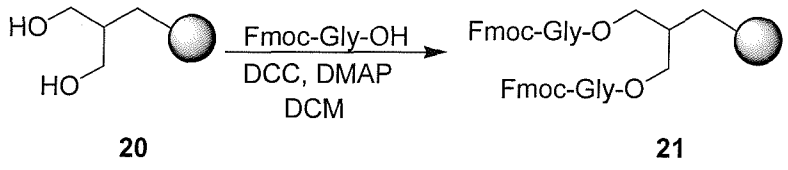


19 20

Scheme 12 : Route to a resin bound 1,3-diol.

Diol **20** was afforded by the reduction of resin bound diethylpropane-1,3-dioate **19** with $LiAlH_4$ following a literature preparation (Scheme 12).[25]

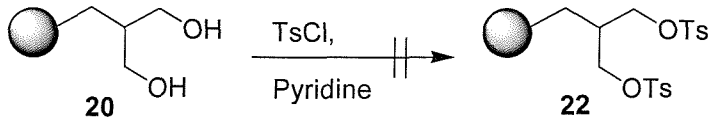
To determine the substitution of resin **20**, commercially available Fmoc-Gly-OH was coupled to a small portion of the resin using DCC and DMAP *via* a symmetric anhydride approach[26] (Scheme 13). The coupling procedure was repeated twice, with washing of the resin in between the two couplings.



Scheme 13 : Coupling of Fmoc-Gly-OH to diol resin **20**.

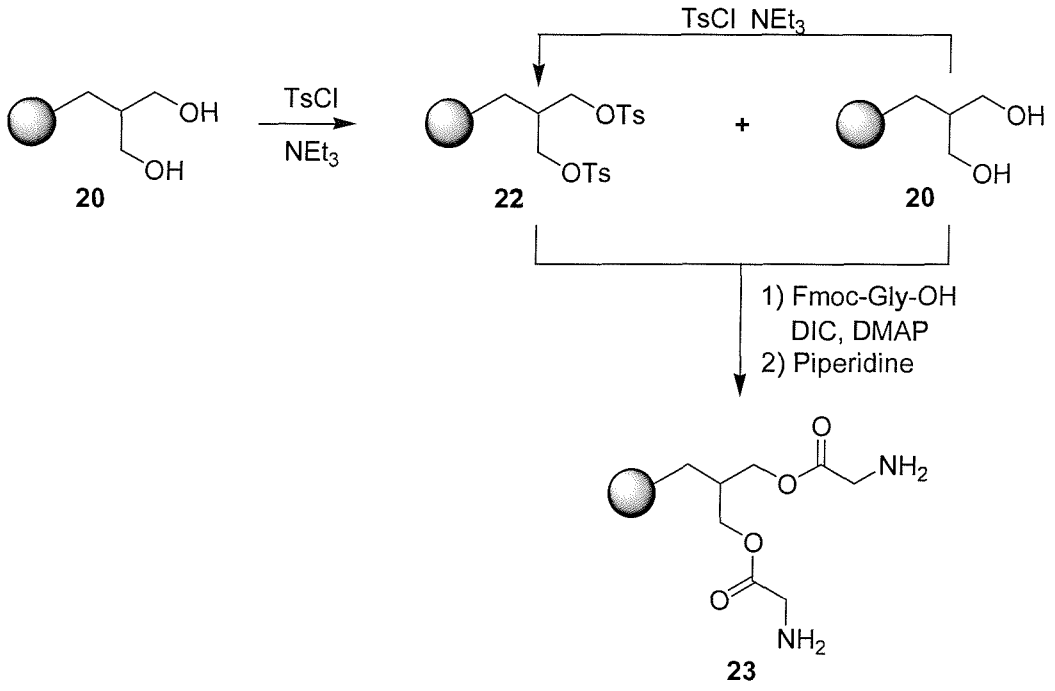
A quantitative Fmoc test was performed on the resin **21** following a standard procedure (Appendix 1).[26] The calculated substitution was $1.94 mmol g^{-1}$ for Fmoc-resin, implying a substitution of $1.24 mmol g^{-1}$ for the diol resin.

2.3.2 Synthesis of resin bound 1,3-ditosylates



Scheme 14 : Tosylation of a resin bound 1,3-diol.

An attempt to tosylate the resin bound propane-1,3-diol **20** using TsCl and pyridine, following a literature preparation,[23] led to inconclusive results as the tosyl group did not have an easily identifiable IR peak on the resin (Scheme 14).

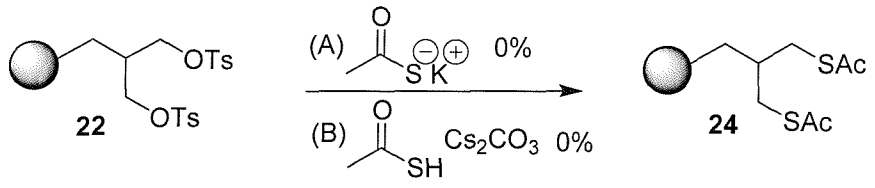


Scheme 15 : Successful tosylation of resin **20**.

The tosylation reaction was repeated using the TsCl/triethylamine method.[24] Following an overnight coupling, resin **22** was washed and dried and a small portion coupled to Fmoc-Gly-OH using HOBt and DIC to determine whether the coupling had gone to completion. If the reaction had gone to completion then there would be no OH groups left and so no Fmoc-Gly-OH would couple. The Fmoc groups were removed by treatment with 20% piperidine in DMF and a qualitative ninhydrin test performed on resin **23**. The ninhydrin test was positive indicating that the tosylation reaction had not gone to completion.

The coupling with TsCl and triethylamine was repeated and a small portion of the resin coupled to Fmoc-Gly-OH. This time the ninhydrin test, performed once the Fmoc groups had been removed, was negative showing that the tosylation reaction had gone to completion (Scheme 14).

Bertini *et al.*[23] detailed a preparation for the conversion of tosyl groups to thioester, using potassium thioacetate. To this end we attempted the substitution of **22** with 20 eq of potassium thioacetate. However, upon work up of the resin **24** no carbonyl peak could be detected by IR (Scheme 16).



Scheme 16 : Attempted synthesis of resin bound propane-1,3-dithioacetate **24**.

A second attempt was made to make resin bound propane-1,3-dithioacetate, this time using the cesium salt of thiolacetic acid generated *in situ*. Again upon work up no C=O peak was detectable by IR suggesting that the reaction had failed.

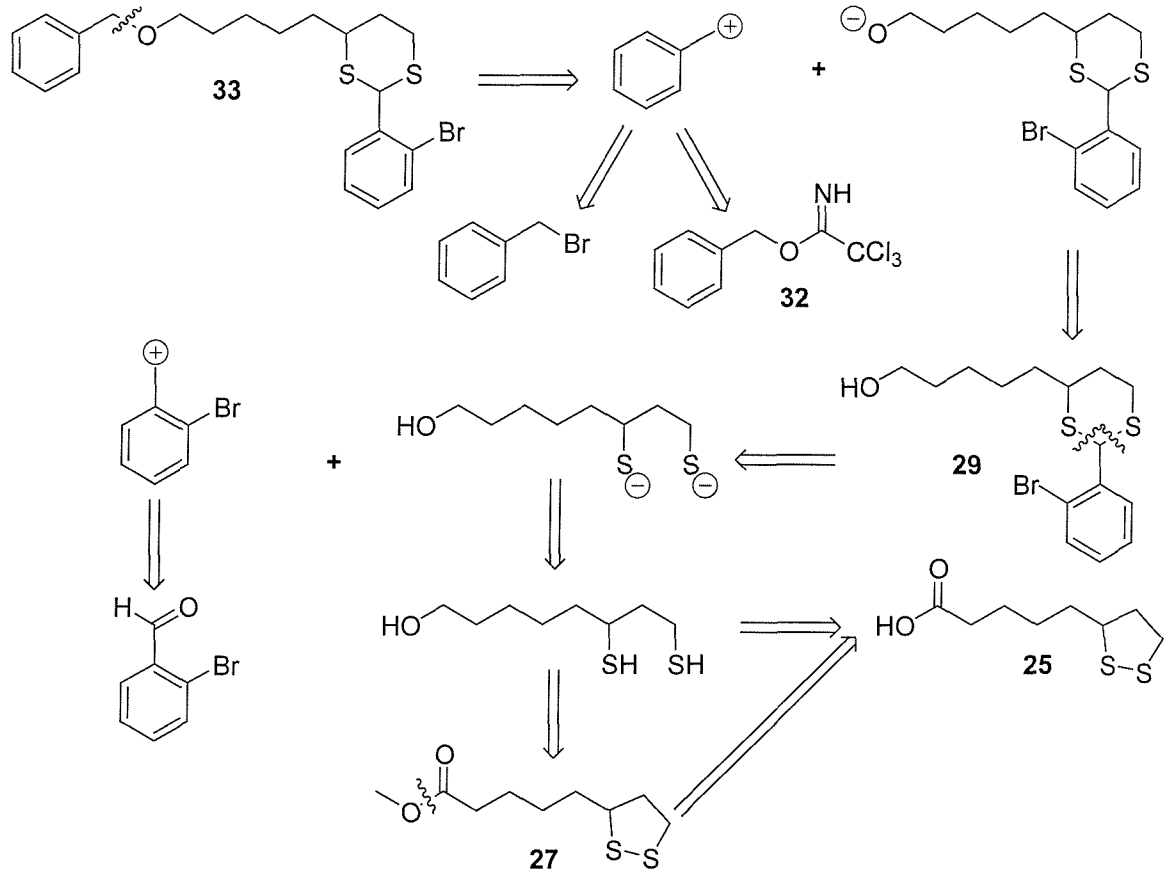
As this approach to the 1,3-dithiol was encountering so many problems an alternative synthetic scheme was sought.

3. Synthesis of a Lipoic Acid Linker

3.1 Introduction

The naturally occurring compound lipoic acid contains a 1,3-disulfide ring, which can be readily opened to a dithiol.[35] This compound seemed an ideal starting point as its 1,3-disulfide ring could be opened and coupled to aldehydes, obviating the need for malonyl synthons. The only problem with this approach would be the attachment of lipoic acid to the resin. An ether was the preferred method of attachment as this would provide a relatively inert link to the resin which would withstand the reaction conditions required for the rest of the natural product synthesis.

3.2 Solution phase lipoic acid ether work

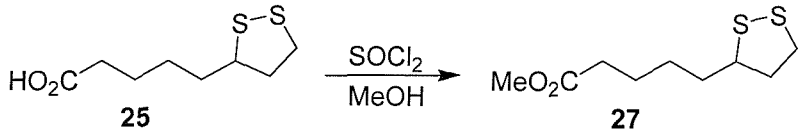


Retrosynthetic Scheme 2 : Retrosynthesis for lipoic acid ether work.

Once again a solution analogue was prepared to allow optimisation of the chemistry before it was transferred to the resin.

3.2.1 Synthesis of 6,8-disulfanyloctan-1-ol

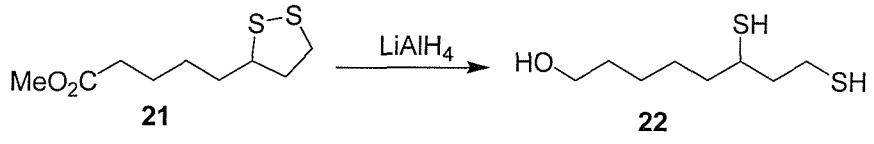
Literature methods suggested that the best way to achieve reduction of the carboxylic acid of lipoic acid to the alcohol was *via* the methyl ester. Methyl-5-(1,2-dithiolan-3-yl)pentanoate **27** was afforded by the reaction of **25** with thionyl chloride and refluxing overnight in methanol (Scheme 17).[27] Initial attempts to generate this compound resulted in poor yields due to difficulties in recovery of pure product from the column during purification (20-30%)



25 **27**

Scheme 17 : Methylation of lipoic acid using thionyl chloride and methanol.

As the reaction yielded only minor impurities, it was used crude in the following reaction and purified at the next stage.



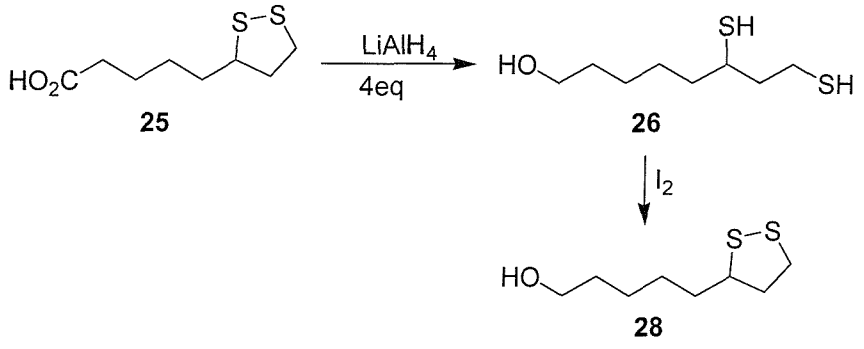
21 **22**

Scheme 18 : $LiAlH_4$ reduction of methyl-5-(1,2-dithiolan-3-yl)pentanoate **27**.

$LiAlH_4$ reduction of **27** afforded 6,8-disulfanyloctan-1-ol **26**, the ring opened dithiol (Scheme 18). This reaction proceeded well, however purification of the product again proved tricky. Stirring in air only partially oxidised the dithiol so an alternative was sought.

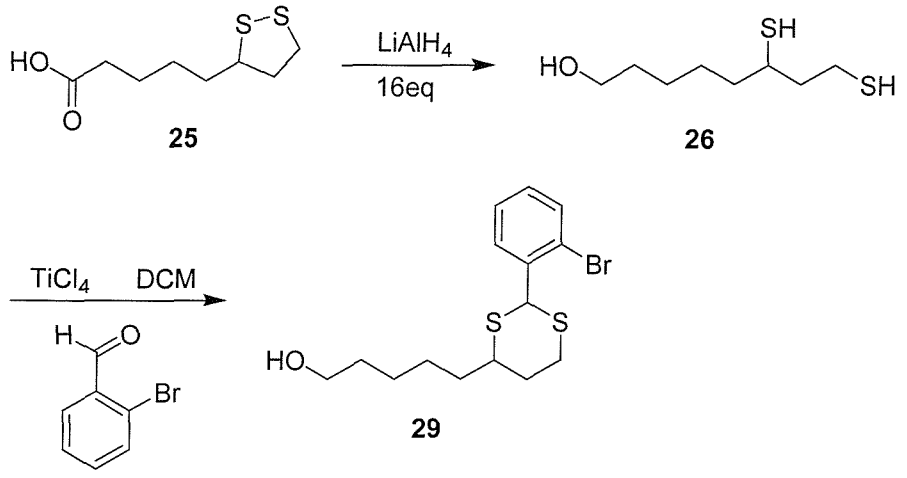
A literature preparation [28] suggested that it would be possible to reduce lipoic acid **25** directly to **26** using 16 equivalents of hydride (from $LiAlH_4$) in refluxing THF overnight. This method proved successful, yielding **26** in a single step from **25.** However, the problem of purification still remained due to the presence of partially oxidised dithiol, resulting in a poor yield of **26** (25%) following column chromatography.

In a new attempt to synthesise the alcohol, following $LiAlH_4$ reduction of **25** the product, **26**, was ring closed by the addition of I_2 until a brown colour persisted. The solution was washed extensively and the solvent removed *in vacuo*. However, on standing **28** polymerised (Scheme 19).



Scheme 19 : Iodine treatment of the reduction product **26**.

Due to problems with the isolation or complete oxidation of **26**, it was carried through to the next reaction without characterisation. The product, **26**, was reacted directly with 2-bromobenzaldehyde using titanium tetrachloride according to a literature method.[29] **29** was isolated and purified by column chromatography (55% for 2 steps from **25**) (Scheme 20).

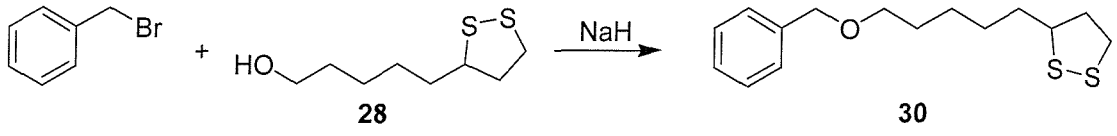


Scheme 20 : Synthesis of a lignan precursor for attachment to a 1,3-dithiane linker *via* an ether link.

3.3 Generating the ether link

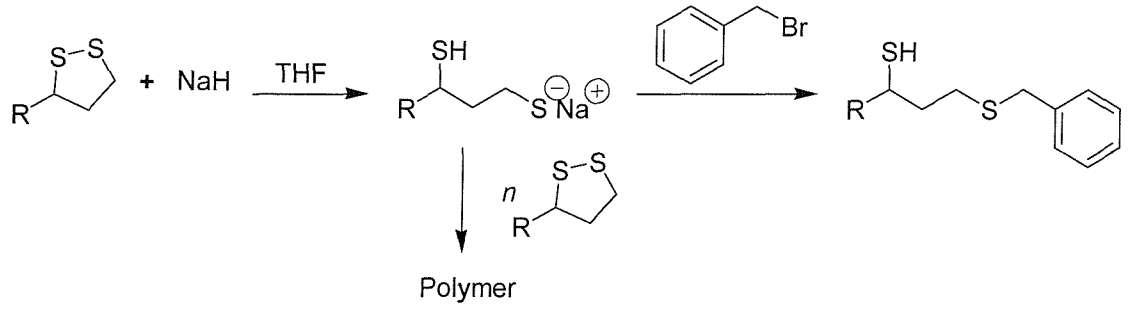
3.3.1 Benzylic alkylations

Using some of the previously isolated 5-(1,2-dithiolan-3-yl)pentan-1-ol **28**, a number of experiments were performed in an attempt to generate a benzylic ether linkage which would serve as a model for solid phase applications.



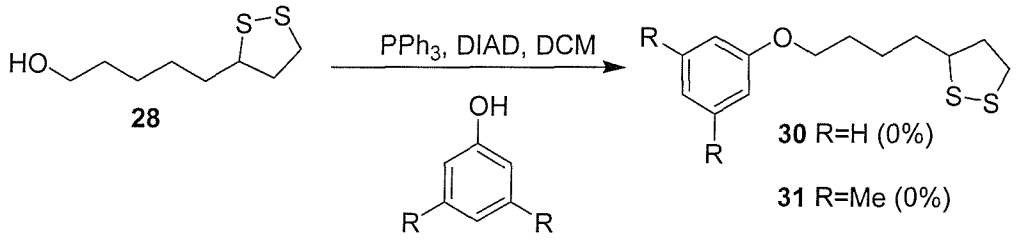
Scheme 21 : Attempted alkylation reaction between benzyl bromide and **28**.

The first method attempted was the alkylation of benzyl bromide using sodium hydride to deprotonate the alcohol of **28** (Scheme 21). Even with an excess of sodium hydride and a 48h coupling time none of the desired product was obtained. The failure of the etherification was attributed to the competing disulfide reduction reaction, which affords the dithiol species. This molecule is then more susceptible to benzyl bromide alkylation, alternatively it is capable of forming a polymer (Scheme 22).[30]



Scheme 22 : Possible alkylation products.

3.3.2 Mitsunobu couplings[31-32]

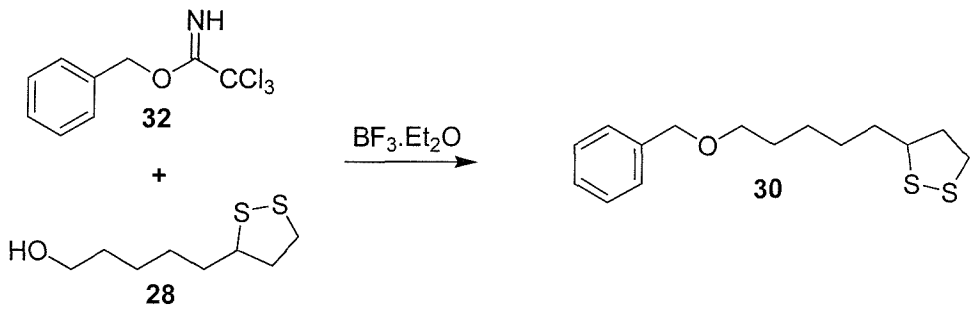


Scheme 23 : Phenolic ether couplings

The alcohol **28** was considered to be a possible candidate for a Mitsunobu reaction[31-32] as it could be coupled to a phenol to produce the desired ether link in **30**. The reaction was carried out using 1.1 eq of triphenylphosphine and 1.1 eq of diisopropyl azodicarboxylate to couple **28** to phenol (Scheme 23). However, no product could be detected by TLC, the triphenylphosphine was suspected to be attacking the disulfide in preference to the alcohol due to the order of addition.

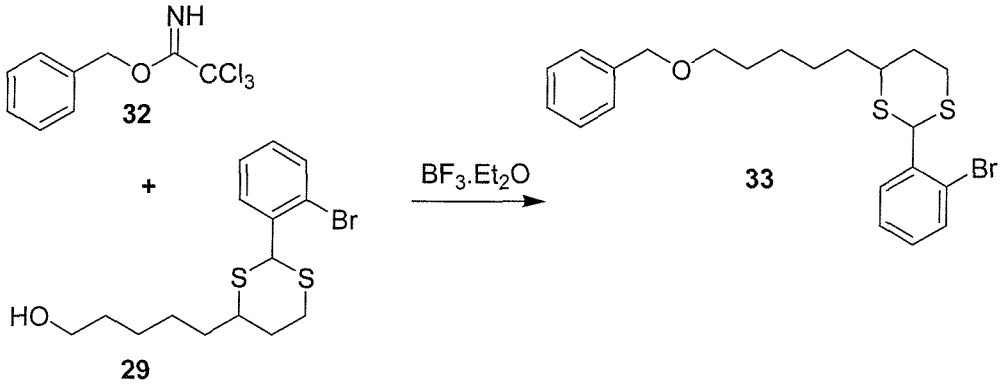
The reaction was repeated, this time using a less hygroscopic phenol as the acidic component. Diisopropyl azodicarboxylate and triphenylphosphine were mixed and this solution added to the 3,5-dimethylphenol prior to the addition of **28** (Scheme 23). This reaction also failed to generate any product **31** and the methodology was abandoned.

3.3.3 Creating an ether link using benzyl-2,2,2-trichloroacetimidate



Scheme 24 : Use of benzyl-2,2,2-trichloroacetimidate to create an ether link.

In an effort to generate an ether link, trichloroacetimidate activation *via* a commonly used and well documented reaction[33] was considered. For the solution model, benzyl-2,2,2-trichloroacetimidate **32** was utilised along with boron trifluoride diethyletherate (Scheme 24). Following an overnight coupling the product **30**, purified by column chromatography, was isolated in moderate yield (53%).

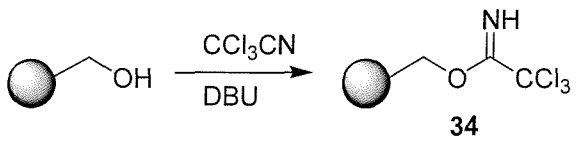


Scheme 25 : Trichloroacetimidate coupling of **29**.

Following the same preparation as used previously[33] 5-(2-(2-bromophenyl)-1,3-dithian-4-yl)pentan-1-ol **29** was coupled to **32** using boron trifluoride diethyletherate (Scheme 25). This reaction appeared to proceed well, by TLC, however the product proved problematic to purify, even after subjecting the crude material to extensive column chromatography it was not possible to obtain the product pure. The coupling

was repeated using 2 equivalents of **32** to force the reaction, however upon purification by column chromatography no pure product could isolated. Given the success of the previous trichloroacetimidate coupling, it was decided to attempt the reaction on the solid phase to simplify the purification procedure.

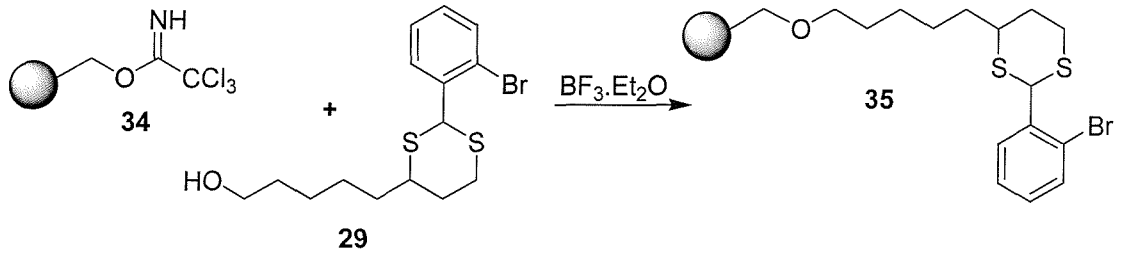
3.4 Solid phase synthesis of trichloroacetimidate ethers.



34

Scheme 26 : Synthesis of resin bound trichloroacetimidate **34**.

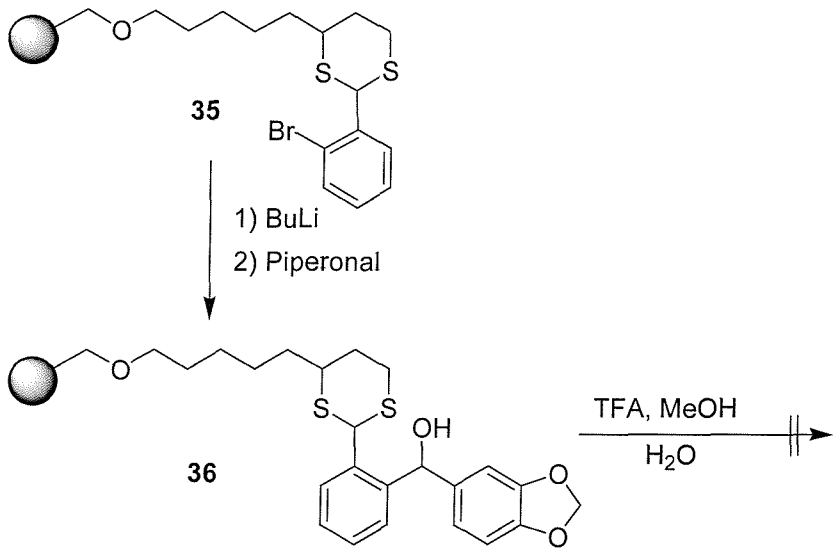
Resin bound trichloroacetimidate **34** was prepared from hydroxymethyl polystyrene resin using a literature preparation (Scheme 26).[34] For this part of the synthesis, resin functionalised with a Wang linker was used, as this would allow cleavage of the entire dithiane linker during synthesis to facilitate monitoring of the reactions. Trichloroacetonitrile was coupled to the resin using DBU. To determine whether the reaction had gone to completion IR spectroscopy was used, and the presence of a peak at 1664cm^{-1} corresponding to C=N was found.



Scheme 27: Creating an ether link to resin bound trichloroacetimidate.

To test the methodology, **29** was coupled to the resin **34** with boron trifluoride diethyletherate, using the method published by Hanessian *et al* (Scheme 27).[34] After

2h, IR spectroscopy showed the disappearance of the characteristic trichloroacetimidate C=N band at 1664cm^{-1}, indicating completion of the reaction.



Scheme 28 : Cleavage of the Wang linker.

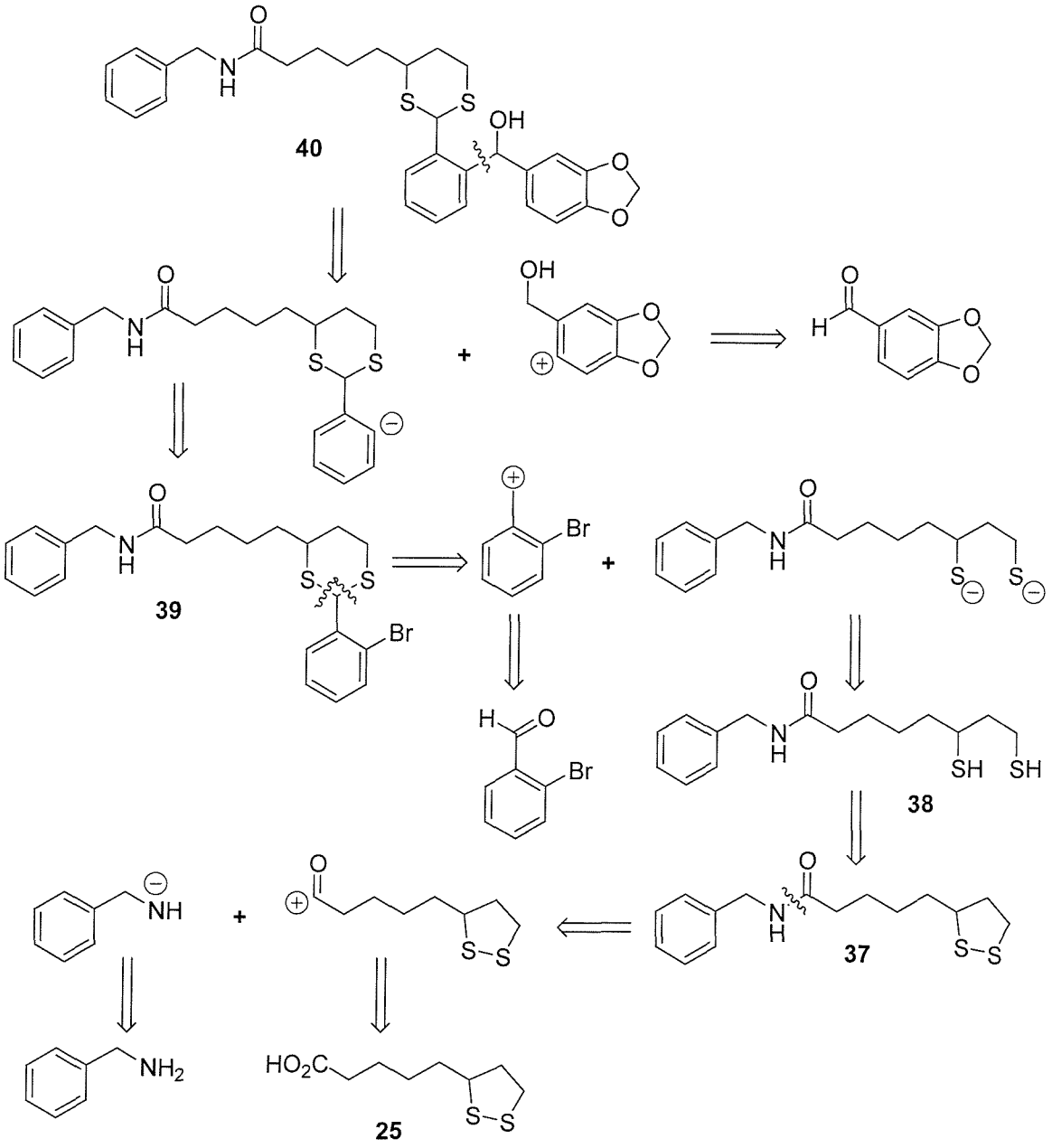
Resin **35** was subjected to an *n*-BuLi transmetallation reaction[18-19] in order to couple piperonal to the aromatic ring of **35**. Due to the difficulty in distinguishing the OH bend for this compound by IR spectroscopy, a portion of the Wang linker attached to the resin **36** was cleaved using 96% TFA, 2% methanol and 2% water. This displaced the dithiane linker and its attached product into solution for analysis.

After 3h the solution was filtered and concentrated *in vacuo*, upon analysis the desired product could not be found (Scheme 28). It was suspected that the *n*-BuLi mediated coupling had not occurred. This linker methodology was abandoned and an alternative sought.

4. Synthesis of a Lipoamide Linker

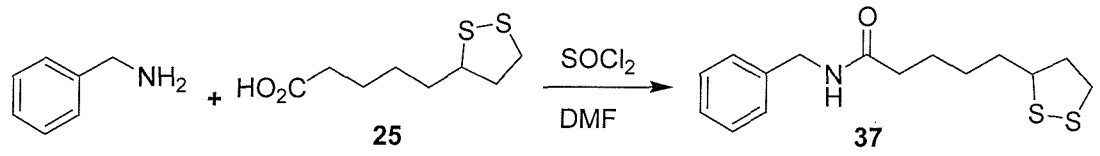
4.1 Introduction

An amide bond was the second method of choice to link lipoic acid to the resin quickly and cleanly. This approach would not require the reduction of the carboxylic acid moiety of lipoic acid, therefore making the synthesis less time consuming.



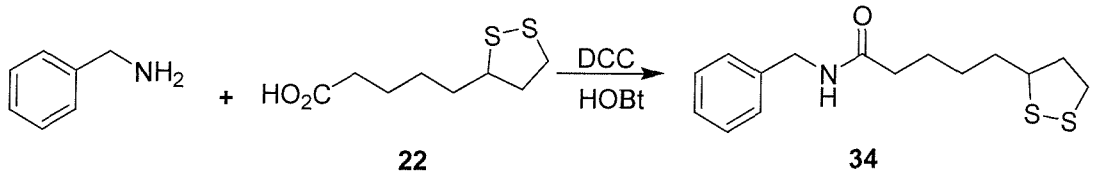
Retrosynthetic Scheme 3 : Retrosynthesis of lipoamide chemistry.

4.2 Solution phase formation of amides with lipoic acid.



Scheme 29 : Thionyl chloride coupling of benzylamine with **25.**

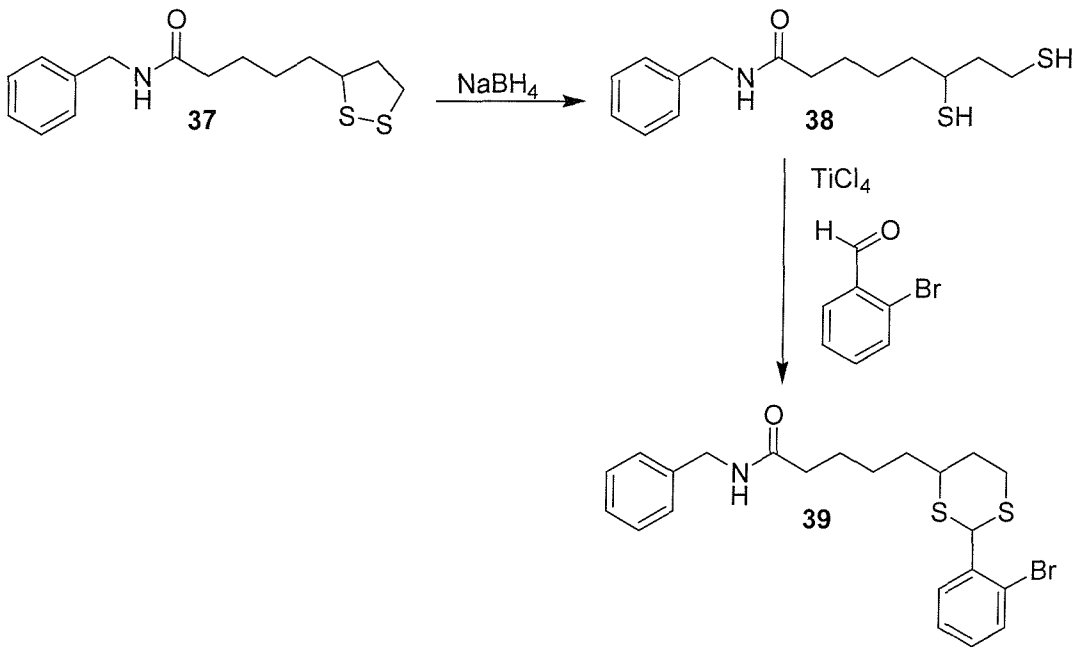
For the solution phase model, benzylamine was coupled to lipoic acid **25.** The first method attempted using the activating conditions of thionyl chloride in DMF (Scheme 29).[35] The product **37** was extracted and the solvent removed *in vacuo* whereupon the product polymerised. The reaction was repeated but not left overnight. However, upon work-up the product again polymerised so the method was abandoned.



Scheme 30 : Successful coupling of benzylamine with **25** using DCC and HOBt.

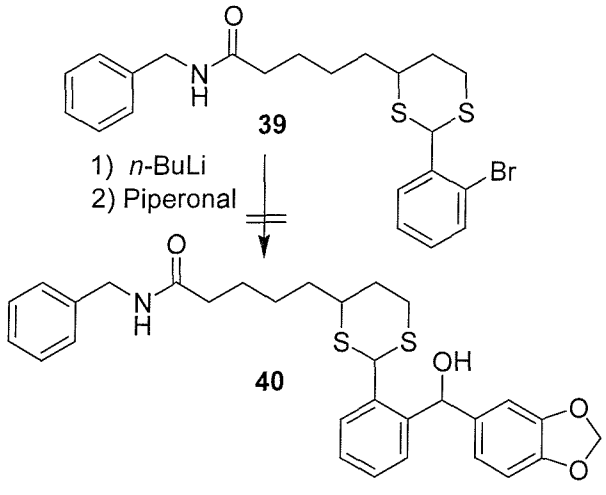
The coupling of benzylamine and lipoic acid **25** was achieved using DCC and HOBt. This route afforded the amide **37** in good yield (78%) (Scheme 30). The product was purified easily by extraction followed by column chromatography. By pre-forming the activated ester using HOBt, polymerisation of the dithiane was eliminated.

A literature method[35] was used for the sodium borohydride reduction of **37** to dithiol **38.** To prevent the product from oxidising, purification by extraction with degassed solvents was completed under a nitrogen atmosphere. **38** was used immediately in the subsequent reaction without characterisation (Scheme 31).



Scheme 31 : Synthesis of a dithiane link between **38** and 2-bromobenzaldehyde.

The next reaction in the sequence was the production of a dithiane link to 2-bromobenzaldehyde using titanium tetrachloride (Scheme 31).[29] The product **39** was afforded by extraction of the organic phase, followed by solvent removal and purification by column chromatography in reasonable yield (69% for 2 steps from **37**).



Scheme 32 : Attempted synthesis of **40** from **39** using an *n*-BuLi transmetallation reaction followed by a coupling with piperonal.

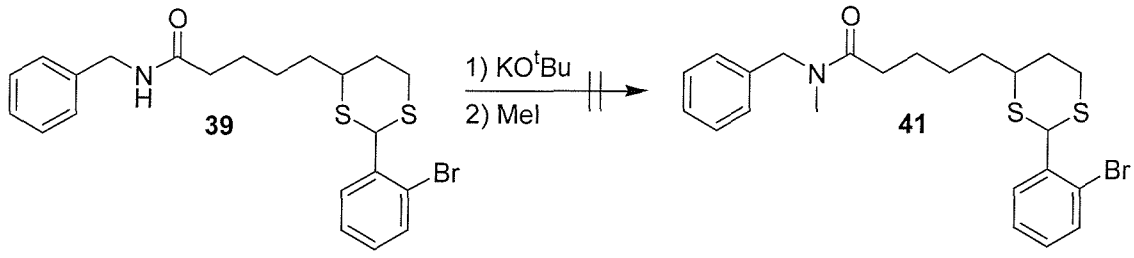
The subsequent step in the synthesis was the transmetallation of **39** with piperonal using *n*-BuLi[18-19] (Scheme 32). This reaction was performed under a variety of conditions in an attempt to optimise the coupling (Table 1).

Eq. of *n*-BuLi	**Temperature during trans-metallation**	**Duration of trans-metallation**	**Eq. of piperonal**	**Temperature during coupling**	**Duration of coupling**
1.1	-30°C	0.5h	1	-78°C	1h
2.2	0°C	0.5h	1	-78°C	1h
2.2	0°C	1.25h	1	-78°C	12h
2.2	0°C	2.5h	1.1	-78°C	24h
3.3	25°C	4h	2	25°C	36h
3.3	25°C	12h	2	60°C	48h

Table 1 *n*-BuLi transmetallation reactions

No product could be detected by TLC after using any of the above reaction conditions. In the last reaction a product was detected by TLC, but upon purification and NMR analysis this proved to be reduced piperonal. It was thought that the reason for this was that the build up of charge on the molecule during transmetallation was too great, thus preventing the reaction from taking place.

4.3 *N*-Methylation of 39

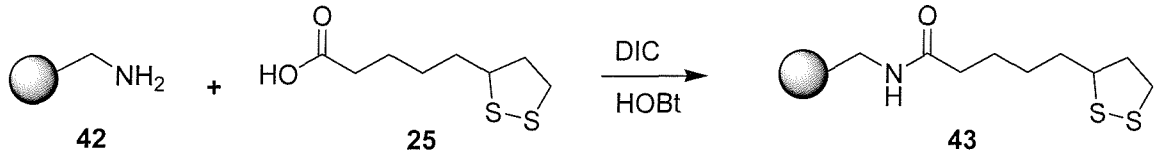


Scheme 33 : *N*-Methylation of lipoamide **39**.

It was postulated that *N*-methylation of **39** would reduce the charge build up on the molecule during transmetallation, thus enabling the reaction to proceed. Potassium *tert*-butoxide was used as base to deprotonate the nitrogen as this would not affect any of the other base labile protons. Methyl iodide was then added and the reaction left to stir for 2.5h (Scheme 33). Upon workup only starting material was obtained.

4.4 Solid phase synthesis of lipoic acid amides

For this series of reactions, aminomethyl polystyrene resin **42** was used, this was synthesised from chloromethyl polystyrene resin in two steps *via* phthalimide resin (Appendix 3). A quantitative ninhydrin test was performed on the dried resin **42**, following a literature method (Appendix 2).[36]

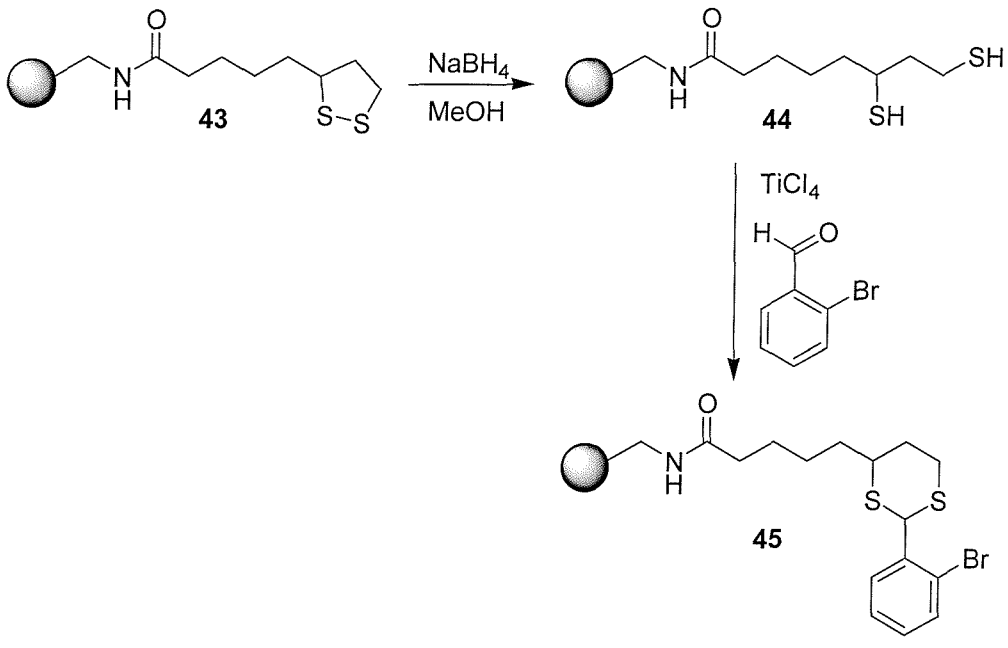


Scheme 34 : Resin bound lipoamide.

Aminomethyl resin **42** was coupled to lipoic acid **25** using DIC and HOBt *via* an activated ester approach (Scheme 34). A qualitative ninhydrin test was performed on

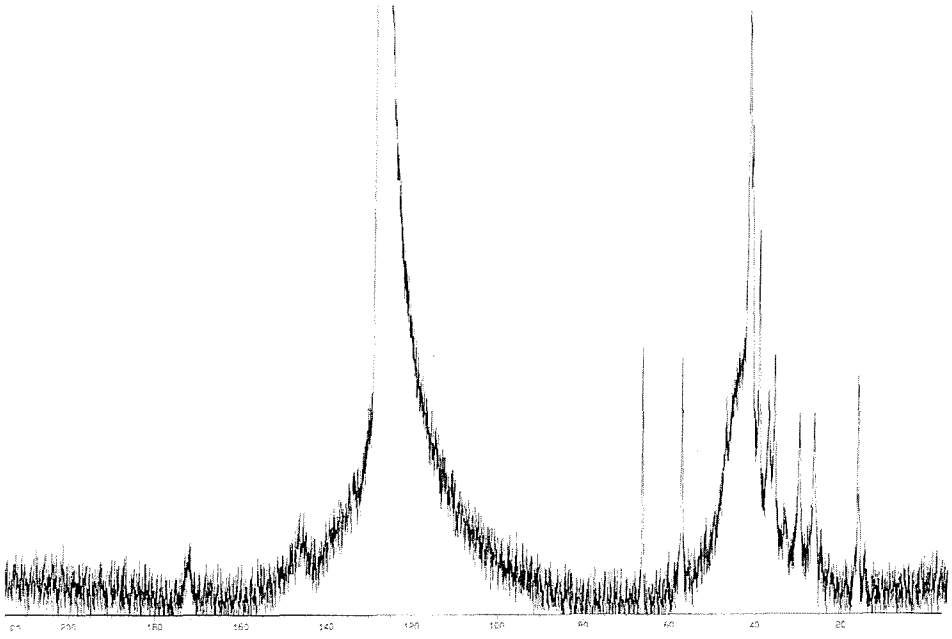
the dry resin **43**, after exhaustive washing, to determine whether the reaction had gone to completion.

The disulfide bond in resin **43** was reduced using sodium borohydride[35] in a 5h reaction to give resin bound 6,8-disulfanyloctanamide **44** (Scheme 35). This reaction was carried out under nitrogen and the product washed and dried under nitrogen to prevent oxidation back to the disulfide **43**.

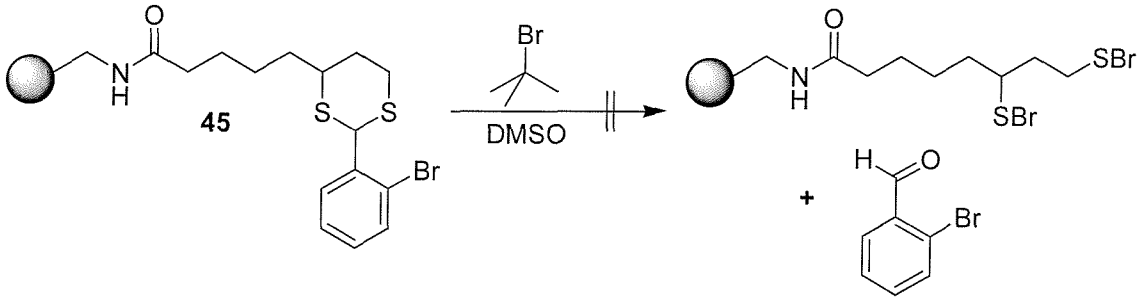


Scheme 35 : Synthesis of a 1,3-dithiane link between **44** and 2-bromobenzaldehyde.

Resin **44** was immediately coupled to 2-bromobenzaldehyde using titanium tetrachloride following the same protocol as the solution reaction.[29] The reaction was quenched with water after 2.5h and the resin **45**, filtered off from the solution and washed thoroughly before drying. ^{13}C Gel-phase NMR showed that the coupling had been successful, as it was possible to see the appearance of a dithiane carbon resonance in the ^{13}C NMR spectrum (see Picture 1). For full assignment see Chapter 5.

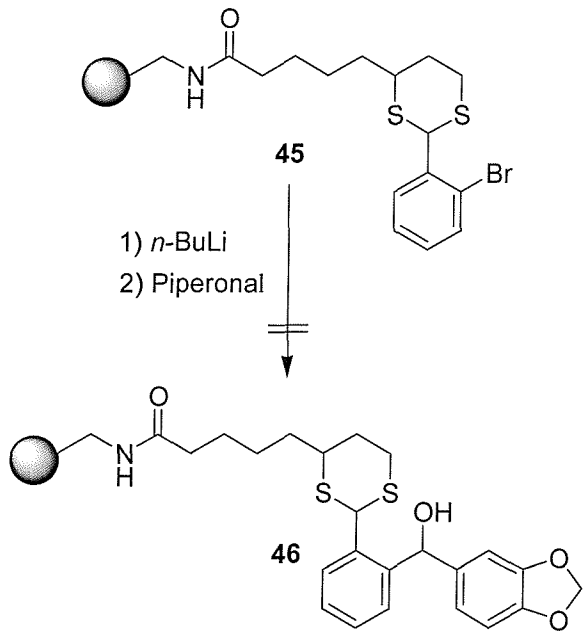


Picture 1 : Gel phase NMR showing the coupled lipoamide linker complete with dithiane linkage.



Scheme 36 : Literature method cleavage of resin **45**.[38]

Cleavage of the dithiane using a literature method was attempted.[37-38] The resin **45** was swollen in DCM and a solution of *tert*-butylbromide in DMSO added, the reaction was heated to 80°C overnight and the resin filtered and washed (Scheme 36). The filtrate was concentrated and subjected to mass spectroscopy. No ion was found which corresponded to the product of the cleavage, because of this it was assumed that the cleavage reaction had not worked.



Scheme 37 : Resin transmetallation reaction.

Transmetallation of resin **45** with piperonal (2 eq) using 3.3 eq of *n*-BuLi as base was attempted[18-19] (Scheme 37). After an overnight coupling a small portion of the dithiane linker on resin **46** was cleaved using periodic acid,[23] to determine whether the reaction had worked.

HPLC analysis of the product from the cleavage reaction showed it to be 2-bromobenzaldehyde (R.T. = 15.2 min. cf. 2-bromobenzaldehyde 15.2 min.), this indicated that the transmetallation reaction had not worked. As the bromide was recovered, not the alcohol, this suggested that halogen-metal exchange had not transpired.

The coupling was repeated with heating (70°C) and after 24h the resin was washed and ^{13}C gel phase NMR carried out. This showed the product to be **45** not **46** as expected.

5. Experimental

5.1 General

NMR spectra were obtained at 298 K using a Bruker AC-300 spectrometer (300 MHz for ^{1}H NMR and 75 MHz for ^{13}C NMR) and a Bruker DPX-400 spectrometer (400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR). Chemical shifts (δ) were referenced to the residual protio signals of the solvents used. Coupling constants (J) are given in Hz. Spectra were solved using DEPT, COSY and HMQC experiments as required.

ES-MS was performed on a VG Platform quadrupole electrospray ionisation mass spectrometer.

Infra-red spectra were recorded on a Bio-Rad Golden Gate FTS 135 spectrophotometer.

Melting points were determined using open capillaries on Gallenkamp apparatus and remain uncorrected.

TLC was performed using Alugram® silica gel 60 F_{254} (0.25mm) plates. Spots were detected using UV, phosphomolybdic acid, permanganate and bromocresol green.

RP-HPLC was effected using a Hewlett-Packard HP1100 Chemstation, using a Phenomenex Prodigy C_{18} 5μ column (150mm x 3.0mm) eluting from 0.1%TFA/H_2O to 0.042% TFA/CH_3CN over 20 min. UV detection was carried out at 220nm, 254nm and 270nm.

DCM, DIPEA, pyridine and triethylamine were distilled freshly from CaH_2 under N_2 prior to use. THF was distilled freshly from sodium benzophenone ketyl under N_2. DMF was of peptide synthesis grade and was purchased from Rathburn UK.

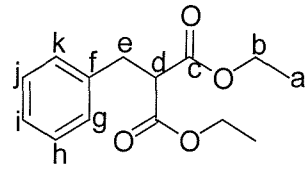
5.2 Experimental for Chapter 2.

Diethyl-2-benzylpropane-1,3-dioate (13)[21]

The title compound was prepared using the method of Guijarro and Yus.[21] Diethyl malonate (6.83mL, 45mmol, 1eq) was added dropwise, to a suspension of sodium hydride (1.09g, 50mmol, 1.1eq) in anhydrous THF (50mL). When gas evolution had ceased benzyl bromide (5.95mL, 50mmol, 1.1eq) was added and the solution left stirring for 3h. The reaction was followed by TLC (10% EtOAc in hexane). After 3h the resulting mixture was quenched with a saturated solution of ammonium chloride and extracted with ethyl acetate (3 x 50mL). The organics were combined, dried over $MgSO_4$ and the solvent removed *in vacuo*. The product was purified by column chromatography (SiO_2, 10% EtOAc in hexane), to give 7.04g of the title compound as a colourless oil (63%).

R_f: 0.2 (10% EtOAc in hexane)

m/z (APCI): 250 (M^+), 251 $(M+H)^+$



δ_H (300MHz, $CDCl_3$): 1.21 (6H, t, J = 7, H^a), 3.23 (2H, d, J = 8, H^e), 3.66 (1H, t, J = 8, H^d), 4.17 (4H, q, J = 7, H^b), 7.17-7.33 (5H, m, H^{g-k}).

δ_C (75MHz, $CDCl_3$): 14.2 (C^a), 34.8 (C^e), 54.0 (C^d), 61.6 (C^b), 126.9 (C^i), 127.1 (C^g), 128.4(C^k), 128.6 (C^j), 129.0 (C^h), 138.0 (C^f), 169.0 (C^c).

IR: ν cm^{-1} (neat): 2987 (C-H stretch), 1730 (ester C=O), 1229 (ester C-H).

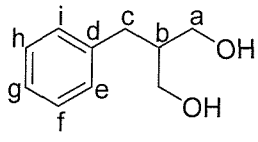
2-Benzylpropane-1,3-diol (14)[25]

The title compound was prepared according to the method of Chandrasekhar and Padmaja.[25] Diethyl-2-benzylpropane-1,3-dioate (**13**) (0.5g, 2mmol, 1eq), dissolved in anhydrous THF (20mL) was added dropwise to a suspension of $LiAlH_4$ (0.15g, 4mmol, 2eq) in anhydrous THF (20mL) at 0°C. The reaction was allowed to warm to room temperature over 1h and was then left to stir overnight. Two spots were detected by TLC, one the product and the other partially reduced starting material. Ether (100mL) was added to the reaction and excess $LiAlH_4$ quenched by the dropwise addition of 4M NaOH until a white precipitate was observed. The reaction mixture was filtered through celite to remove the white aluminium salts and the residue washed with ether. The solvent was removed *in vacuo* and the residue taken up in ethyl acetate (50mL), and then washed with water (2 x 30mL) and brine (30mL) before being dried over $MgSO_4$. The solvent was removed *in vacuo* to yield crude product as a clear oil. The product was crystallised from ethyl acetate with hexane to give 0.27g of the title compound as fine white crystals (80%).

R_f: 0.07 (1:1 EtOAc : hexane)

M. Pt.: 67-69°C

m/z (APCI): 167 $(M+H)^+$, 189 $(M+Na)^+$, 205 $(M+K)^+$



δ_H (300MHz, $CDCl_3$): 2.05 (1H, ttt, J = 7, 4, 4, H^b), 2.60 (2H, d, J = 7, H^c), 3.77 (4H, 2 x d, J = 4, 4, H^a), 7.15-7.33 (5H, m, H^{e-i}).

δ_C (75MHz, $CDCl_3$): 34.4 (C^c), 44.0 (C^b), 65.4 (C^a), 126.3 (C^g), 126.5 (C^e), 128.3 (C^i),128.6 (C^h),129.2 (C^f), 140.0 (C^d).

IR: ν cm^{-1} (solid): 3322 (OH bend, H bonded), 2926 (C-H stretch).

HPLC: (254nm): 10.4 minutes

Ditosyl-2-benzylpropane-1,3-diol (15)

Method A: Synthesis using TsCl and pyridine.[23]

The title compound was prepared according to the method of Bertini *et al.*[23] 2-Benzylpropane-1,3-diol (**14**) (1.0g, 6.02mmol,1eq) was dissolved in anhydrous THF (10mL) and pyridine (0.97mL, 12.05mmol, 2eq) added. The solution was cooled to –10°C and *p*-toluenesulfonyl chloride (2.30g, 12.05mmol, 2eq) in anhydrous THF (10mL) added. The solution was warmed to room temperature and left to stir overnight. The solvent was removed *in vacuo* and the residue taken up in ethyl acetate. This was washed with 1M $CuSO_4$ to remove excess pyridine, the organic phase was then washed with 1M $KHSO_4$ (2 x 50mL), 1M $NaHCO_3$ (2 x 50mL) and brine (2 x 50mL) before being concentrated *in vacuo*. The product was purified by column chromatography (SiO_2, 1:1 EtOAc : hexane) to remove *p*-toluenesulfonyl chloride. The title compound was isolated in 0.70g yield as a white solid (25%)

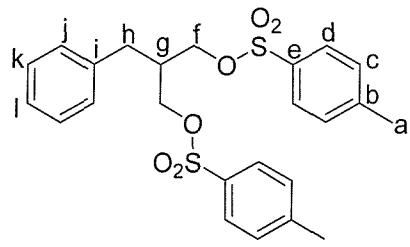
Method B: Synthesis using TsCl and triethylamine.[24]

The title compound was prepared according to the method of Tanabe *et al.*[24] 2-Benzylpropane-1,3-diol (**14**) (0.60g, 3.61mmol, 1eq) was dissolved in anhydrous THF (2mL). Triethylamine (2.02mL, 0.14mol, 4eq) was added and the solution placed under nitrogen prior to cooling on an ice/salt slush. *p*-Toluenesulfonyl chloride (2.07g, 0.11mol, 3eq) was dissolved in anhydrous THF (5mL) and was added to the solution of 2-benzylpropane-1,3-diol (**14**). The reaction was allowed to warm to room temperature and was left to stir at room temperature overnight. The solvent was removed *in vacuo* and the residue suspended in ethyl acetate. The organic layer was extracted with 1M $KHSO_4$ (2 x 15mL), 1M $NaHCO_3$ (2 x 15mL), water (1 x 15mL) and brine (2 x 15mL). The organic layer was dried over $MgSO_4$ and the solvent removed *in vacuo* to yield a white solid. The solid was seen by TLC to be two spots and was purified by column chromatography (SiO_2, 3:1 hexane : EtOAc). The two spots were found to be *O*-tosyl-2-benzylpropane-1,3-diol and the desired product. 0.88g of the title compound were isolated as a white solid (52%)

R_f: 0.43 (1:1 EtOAc : hexane)

M. Pt.: 78-80°C

m/z (APCI): 475 $(M+H)^+$, 492 $(M+NH_4)^+$, 497 $(M+Na)^+$



δ_H (300MHz, $CDCl_3$): 2.19-2.31 (1H, m, H^g), 2.48 (6H, s, H^a), 2.59 (2H, d, J = 8, H^h), 3.86-4.01 (4H, 2 x dd, J = 5, 5, H^f), 6.94-6.97 (2H, m, H^j), 7.18-7.20 (3H, m, H^{k+l}), 7.34-7.75 (8H, 2 x d, J = 8, 8, H^{c+d}).

d_C (75MHz, $CDCl_3$): 21.7 (C^a), 33.2 (C^f), 40.0 (C^g), 68.2 (C^h), 126.7 (C^l), 127.9 (C^k), 128.6 (C^d), 128.9 (C^j), 129.9 (C^c), 132.3 (C^e), 137.3 (C^i), 145.1 (C^b).

HPLC: (254nm): 20.0 minutes

IR: ν cm^{-1} (solid): 1598 (aromatic C-C), 1358 (O-SO_2), 1173 (O-SO_2), 812 (*p*-substituted aromatic C-H), 750 (aromatic C-H), 699 (aromatic C-H).

2-Benzylpropane-1,3-dithioacetate (17)[23]

Method A: Synthesis using 2.4eq cesium thioacetate.

The title compound was prepared according to a modified method using the work of Bertini *et al.*[23] Ditosyl-2-benzylpropane-1,3-diol (**15**) (0.70g, 1.48mmol, 1eq) was dissolved in a minimum of anhydrous DMF (~3mL). A solution of Cs_2CO_3 (1.16g, 3.54mmol, 2.4eq) in anhydrous DMF (5mL) was added to thiolacetic acid (253μL, 3.54mmol, 2.4eq) and the mixture stirred for 30min at room temperature before being added to the solution of ditosyl-2-benzylpropane-1,3-diol (**15**). The reaction was

heated to 70°C for 1.5h after which time no starting material could be observed by TLC (1:1 EtOAc : hexane). Ethyl acetate (20mL) was added to the cooled reaction mixture and the DMF removed by washing with water (2 x 100mL). The organic layer was washed with brine (5 x 50mL) and dried over $MgSO_4$ prior to solvent removal *in vacuo*. The product was purified by column chromatography (SiO_2, 2:1 hexane : EtOAc). The solvent was removed *in vacuo,* to give a sticky cream oil (0.26g). Upon NMR analysis it could be seen that the product, although appearing as one spot by TLC, contained an impurity, this was found to be O-tosyl-S-acetyl-2-benzyl-1-hydroxypropane-3-thiol (**16**) (Figure 4).

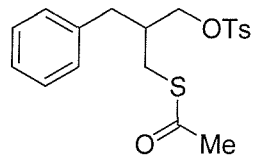


Figure 4 : *O*-Tosyl-*S*-acetyl-2-benzyl-1-hydroxypropane-3-thiol. (**16**)

To force the reaction to completion another coupling was performed. Ditosyl-2-benzylpropane-1,3-diol (**15**) (0.35g, 0.74mmol, 1eq) was dissolved in the minimum of anhydrous DMF (1mL). A solution of Cs_2CO_3 (580mg, 1.77mmol, 2.4eq) in anhydrous DMF (3mL) was added to thiolacetic acid (127μL, 1.77mmol, 2.4eq) and the mixture stirred for 30min at room temperature before being added to the ditosyl-2-benzylpropane-1,3-diol solution. The reaction was heated to 70°C for 1.5h after which time TLC showed the reaction to have gone to completion. The product was purified by column chromatography (SiO_2, 2:1 hexane : EtOAc) to give 0.116g of the title compound as a yellow oil (28%).

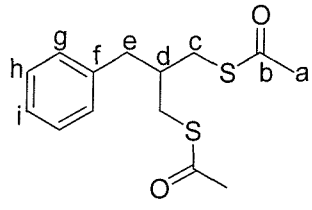
Method B: Synthesis using 4eq cesium thioacetate.[23]

The title compound was prepared according to a modified method using the work of Bertini *et al.*[23] Ditosyl-2-benzylpropane-1,3-diol (**15**) (0.70g, 1.48mmol, 1eq) was dissolved in a minimum of anhydrous DMF (2mL) with stirring under nitrogen. Cesium carbonate (1.92g, 5.91mmol, 4eq) was dissolved in anhydrous DMF (5mL)

with stirring, thiolacetic acid (0.42mL, 5.91mmol, 4eq) was added to the solution (vigorous bubbling occurred), to give a bright orange solution. This was allowed to stir for 30min before being added to the solution containing ditosyl-2-benzylpropane-1,3-diol. The solution was left stirring at 70°C for 4h after which time all the starting material could be seen to have been consumed. The reaction was cooled and ethyl acetate (10mL) added. The DMF was removed by washing with water (3 x 15mL), the organic layer was then washed with water (4 x 15mL) and brine (2 x 15mL) before being dried over $MgSO_4$, and solvent removed *in vacuo*. The product was purified by column chromatography (SiO_2, 9:1 hexane : EtOAc), to give 220mg of the title compound as a yellow oil (53%).

R_f: 0.59 (1:1 hexane : EtOAc)

m/z: (CI): 283 $(M+H)^+$, 300 $(M+NH_4)^+$



δ_H (300MHz, $CDCl_3$): 2.10-2.23 (1H, m, H^d), 2.38 (6H, s, H^a), 2.69 (2H, d, J = 7, H^e), 2.80-3.05 (4H, 2 x dd, J = 6, H^c), 7.11-7.35 (5H, m, H^{g-i}).

δ_C (75MHz, $CDCl_3$): 30.8 (C^a), 32.0 (C^c), 39.2 (C^d), 40.5 (C^e), 126.6 (C^i), 128.6 (C^h), 129.3 (C^g), 138.9 (C^f), 195.5 (C^b).

HPLC: (254nm) 19.5 min.

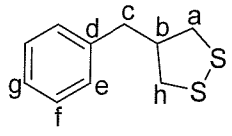
IR: ν cm^{-1} (neat): 2923 (alkyl C-H), 1688 (R-CO-S-R), 1129 (C=O), 1102 (C=O), 743 (aromatic C-H), 699 (aromatic C-H).

4-Benzyl-1,2-dithiolane (18)

2-Benzylpropane-1,3-dithioacetate (**17**) (0.12g, 0.41mmol, 1eq) was dissolved in dioxane (1mL) and placed under nitrogen. Sodium hydroxide (0.07g, 1.65mmol, 4eq) dissolved in dioxane (2mL) was added to the solution containing 2-benzylpropane-1,3-dithioacetate. The reaction was stirred under nitrogen for 6h after which time starting material was still visible by TLC, a further 8eq of sodium hydroxide were added to force the reaction to completion and the reaction was left to stir overnight. The solvent was removed *in vacuo* and the residue suspended in 2M HCl (5mL), the product was extracted under nitrogen into ethyl acetate (2 x 20mL) and dried over $MgSO_4$. The solvent was removed *in vacuo* to give 30mg of the title compound as a yellow oil (47%).

R_f: 0.15 (2:1 Hexane : EtOAc)

m/z (CI): 196 (M^+ Disulfide)



δ_H (300MHz, $CDCl_3$): 2.05-2.28 (1H, m, H^b), 2.56-2.81 (4H, m, H^a), 3.43-3.67 (2H, m, H^c), 7.03-7.27 (5H, m, H^{e-g}).

δ_C (75MHz, $CDCl_3$): 36.9 (C^a), 40.0 (C^h), 42.5 (C^b), 63.5 (C^c), 126.5 (C^g), 128.8 (C^e), 129.5 (C^f), 139.9 (C^d).

HPLC: (254nm) 17.9 min.

IR: ν cm^{-1} ($CHCl_3$): 2922 (alkyl C-H); 1603 (aromatic C-C); 1494 (aromatic C-C); 740 (aromatic C-H); 699 (aromatic C-H).

Resin bound diethylpropane-1,3-dioate (19)[25]

The title compound was prepared according to the method (modified for resin work) of Chandrasekhar and Padmaja.[25] To a stirred solution of sodium hydride (991mg, 41.29mmol, 3eq) in DMF (2mL) was added diethyl malonate (4.41g, 27.53mmol, 2eq) at 0°C. The mixture was stirred at room temperature for 30min. Merrifield resin (10g, 1.37mmolg^{-1}, 13.77mmol, 1eq) was added portionwise at 0°C and the mixture allowed to stir at room temperature for 4h. The reaction mixture was quenched with ethyl acetate (15mL) to remove residual sodium hydride. The resin was collected and washed with water (3 x 20mL), ethyl acetate (2 x 10mL), acetone (2 x 10mL) and ether (2 x 10mL). The resin was dried under vacuum.

IR: ν cm^{-1} (ATR): 2909 (polystyrene C-H), 1713 (C=O stretch), 1492 (polystyrene C=C), 1451 (polystyrene C=C), 750 (polystyrene), 696 (polystyrene).

Resin bound propane-1,3-diol (20)[25]

The title compound was prepared according to the method of Chandrasekhar and Padmaja.[25] To a stirred solution of $LiAlH_4$ (0.16g, 4.14mmol, 3eq) in anhydrous THF (5mL) was added **19** (1g, 1.38mmol, 1eq) at 0°C. The contents of the flask were allowed to stir at 30°C for 6h under nitrogen. The resin was collected and washed with 5% HCl (2 x 30mL), acetone (2 x 10mL) and ether (2 x 10mL). The resulting resin bound propane-1,3-diol was dried under vacuum.

IR: ν cm^{-1} (ATR): 3500 (OH stretch), 3025 (polystyrene C-H), 2917 (polystyrene C-H), 1601 (polystyrene C-H), 1492 (polystyrene C-H), 1451 (polystyrene C=C), 750 (polystyrene), 696 (polystyrene).

Coupling of Fmoc-Gly-OH to resin bound propane-1,3-diol. (21)

Fmoc-Gly-OH (0.67g, 2.26mmol, 8eq) was dissolved in DCM (10mL) and DMF (1mL), to this solution was added DCC (58mg, 0.28mmol, 1eq). The solution was left to stir for 30min, after this time the DCU formed was removed by filtration. The solvent was removed *in vacuo* to yield the anhydride of Fmoc-Gly-OH as a white

solid. The anhydride (1.30g, 2.26mmol) was dissolved in DMF and the solution added to the pre-swollen resin bound propane-1,3-diol (**20**) (100mg), DMAP (28mg, 0.23mmol, 0.8eq) was added and the resin shaken overnight. The solution was removed by filtration and the resin washed with DMF (3 x 10mL), DCM (3 x 10mL), methanol (3 x 10mL) and ether (3 x 10mL). The coupling was repeated using the same amount of reagents but this time leaving the reaction for 48h to ensure that all available sites were coupled. A quantitative Fmoc test (Appendix 1.) was performed to determine the substitution of the resin.

IR: ν cm^{-1} (ATR): 3028 (polystyrene C-H), 2921 (polystyrene C-H), 2850 (polystyrene C-H), 1706 (ester linkage C=O), 1493 (polystyrene C=C), 1452 (polystyrene C=C), 700 (polystyrene).

Substitution = 1.94mmolg^{-1}

Resin bound ditosylpropane-1,3-diol (22)

Method A: Synthesis using TsCl and pyridine.[23]

The title compound was prepared according to the method (modified for resin work) of Bertini *et al.*[23] Resin bound propane-1,3-diol (**20**) (500mg, 1.94mmolg^{-1}, 0.97mmol, 1eq) was pre-swollen in anhydrous DCM (2mL) and pyridine (0.78mL, 9.7mmol, 10eq) was added. The solution was placed under nitrogen prior to being cooled on an ice/salt slush. *p*-Toluenesulfonyl chloride (1.85g, 9.7mmol, 10eq) in anhydrous DCM (5mL) was added and the solution warmed to room temperature, the reaction was allowed to shake overnight. The solvent was removed by filtration and the resin washed with DMF (3 x 10mL), DCM (3 x 10mL), methanol, (3 x 10mL) and ether (3 x 10mL) before being dried under vacuum.

IR: ν cm^{-1} (ATR): 3032 (polystyrene C-H), 2922 (polystyrene C-H), 2851 (polystyrene C-H), 1360 (-O-SO_2-), 1174 (-O-SO_2-).

Method B: Synthesis using TsCl and triethylamine.[24]

The title compound was prepared according to the method (modified for resin work) of Tanabe *et al.*[24] The resin bound propane-1,3-diol (**20**) (1.00g, 1.94mmolg^{-1}, 1.94mmol, 1eq) was swollen in minimum anhydrous THF (3mL), triethylamine (5.41mL, 38.8mmol, 20eq) was added and the resin placed under nitrogen prior to cooling on an ice/salt slush. *p*-Toluenesulfonyl chloride (7.40g, 38.8mmol, 20eq) was dissolved in the minimum of anhydrous THF (7mL) and added to the resin. The reaction was allowed to warm to room temperature and was stirred slowly overnight. The reaction mixture was removed from the resin by filtration under reduced pressure and the resin washed in DMF (3 x 15mL), DCM (3 x 15mL), methanol (3 x 15mL) and ether (2 x 15mL). The resin was dried under vacuum. To determine if the reaction had gone to completion 50mg of the resin was coupled to Fmoc-Gly-OH, this was necessary as the infra red stretch for a tosyl group is very hard to see and therefore not an accurate test of whether the reaction had worked.

Coupling of Fmoc-Gly-OH to resin bound propane-1,3-diol (20)

Fmoc-Gly-OH (0.12g, 0.39mmol, 4eq) was dissolved with HOBt (50mg, 0.39mmol, 4eq) in a minimum of DCM (1mL) and DMF (1mL). The solution was left to stir for 10min before the addition of DIC (66.8μL, 0.43mmol, 4.4eq), the solution was left to stir for a further 10min. DMAP (7.11mg, 0.06mmol, 0.6eq) was added and the solution added to the pre-swollen resin (**20**) (50mg, 0.10mmol, 1eq). The reaction was left to shake for 2h. After this time the resin was washed with DMF (3 x 3mL), DCM (3 x 3mL), methanol (3 x 3mL) and ether (2 x 3mL) before being dried under vacuum. The Fmoc group was removed by shaking the resin for 10min with a 20% solution of piperidine in DMF (2mL). The resin (**23**) was washed and dried using the same procedure as previously described. A qualitative ninhydrin test was performed on the dried resin, the resin beads turned blue indicating the presence of free amine groups. This showed that there were still free hydroxyl groups present on the resin, allowing Fmoc-Gly-OH to couple, and hence that the tosylation reaction had not gone to completion. The coupling with *p*-toluenesulfonyl chloride was repeated using the same quantities of reagents as before. After 24h the reaction was

stopped and the resin washed with DMF (3 x 10mL), DCM (3 x 10mL), methanol (3 x 10mL) and ether (2 x 10mL) before being dried under vacuum. Again a coupling with Fmoc-Gly-OH was performed to enable the extent of the tosylation reaction to be determined. Following coupling of Fmoc-Gly-OH and the subsequent removal of the Fmoc group the result of the qualitative ninhydrin test was negative showing that no Fmoc-Gly-OH had coupled and hence that the tosylation reaction had gone to completion.

IR: ν cm^{-1} (ATR): 2917 (alkyl C-H), 1492 (aromatic C-C), 1450 (aromatic C-C), 750 (aromatic C-H), 696 (aromatic C-H).

Resin bound propane-1,3-dithioacetate. (24)

Method A: Synthesis using potassium thioacetate.[23]

The title compound was prepared according to the method of Bertini *et al.*[23] The resin bound ditosylpropane-1,3-diol (**22**) (300mg, 1.94mmolg^{-1}, 0.58mmol, 1eq) was swollen in a minimum of anhydrous DMF (2mL) under nitrogen. Potassium thioacetate (0.27g, 2.33mmol, 4eq) was dissolved in anhydrous DMF (1mL) and was added to the resin. The reaction was heated to 70°C and left with slow stirring for 4h. The resin was washed with DMF (3 x 10mL), DCM (3 x 10mL), methanol (3 x 10mL) and ether (2 x 10mL) before being dried under vacuum.

IR: ν cm^{-1} (ATR): 2918 (alkyl C-H), 1600 (aromatic C-C), 1492 (aromatic C-C), 1451 (aromatic C-C).

Method B: Synthesis using cesium thioacetate.[23]

The title compound was prepared using the modified method of Bertini *et al.*[23] Cesium carbonate (9.48g, 29.1mmol, 15eq) was dissolved with stirring in a minimum of anhydrous DMF (10mL), thiolacetic acid (2.08mL, 29.1mmol, 15eq) was added to the solution (vigorous bubbling occurred), to give a bright orange solution. This was left to stir for 30min before being added to the pre-swollen resin bound

ditosylpropane-1,3-diol (**22**) (1.00g, 1.94mmol, 1eq). The resin was left stirring at 70°C for 24h by which time the solution had turned a dark brown colour. The solution was removed and the resin washed with DMF (3 x 15mL), DCM (3 x 15mL), methanol (3 x 15mL) and ether (3 x 15mL) and was then dried under vacuum overnight.

IR: ν cm^{-1} (ATR): 2950 (alkyl C-H), 1492 (aromatic C-C), 1451 (aromatic C-C), 755 (aromatic C-H), 696 (aromatic C-H).

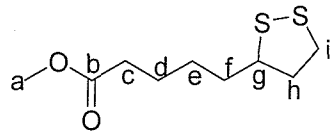
5.3 Experimental for Chapter 3.

Methyl-5-(1,2-dithiolan-3-yl) pentanoate (27)

Thioctic acid (**25**) (5.0g, 24.2mmol, 1eq) was dissolved in methanol (15mL) and the solution cooled to -10°C. Thionyl chloride (1.95mL, 26.7mmol, 1.1eq) was added dropwise down a condenser. The solution was refluxed at 80°C overnight until TLC showed that the reaction had gone to completion. The reaction was cooled and the solvent removed *in vacuo* to yield a sticky orange oil (5.60g), which was used in the subsequent reaction without further purification.

R_f: 0.59 (1:1 hexane : EtOAc)

m/z (EI): 220 (M^+)



δ_H (300MHz, $CDCl_3$): 1.36-1.46 (2H, m, H^e), 1.56-1.64 (4H, m, H^{d+i}), 1.88-1.94 (2H, m, H^c), 2.26 (2H, dt, $J = 7$, H^f), 2.68-2.79 (3H, m, H^{g+h}), 3.60 (3H, s, H^a).

δ_C (75MHz, $CDCl_3$): 25.3 (C^d), 26.8 (C^e), 33.9 (C^c), 34.2 (C^f), 35.0 (C^i), 36.8 (C^h), 50.7 (C^g), 51.9 (C^a).

IR: ν cm^{-1} (neat): 2925 (C-H stretch), 2855 (C-H stretch), 1729 (ester C=O), 1433 ($OCOCH_3$), 1168 ($OCOCH_3$).

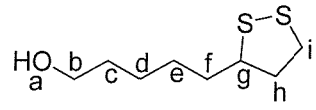
5-(1,2-Dithiolan-3-yl)pentan-1-ol (28)

A suspension of $LiAlH_4$ (0.69g, 18.2mmol, 1eq) in anhydrous THF (100mL), was cooled on an ice bath and placed under nitrogen. A solution of methyl-5-(1,2-dithiolan-3-yl)pentanoate (**27**) (4.0g, 18.2mmol, 1eq) in anhydrous THF (50mL) was

added dropwise with stirring to the $LiAlH_4$ suspension. The reaction was allowed to warm to room temperature and was left to stir overnight. Upon TLC analysis it was found that the reaction had not gone to completion. A second equivalent of $LiAlH_4$ was added to the reaction, which was then left to stir for a further 24h. The reaction was cooled and then quenched by the dropwise addition of water. The solvent was removed *in vacuo* to yield a white residue. This was dissolved in 2M HCl (100mL) and the product extracted into ethyl acetate (2 x 100mL). The organics were combined and extracted with water (2 x 100mL) and brine (2 x 100mL) before being dried over $MgSO_4$ and solvent removal *in vacuo* to yield a pale yellow oil. The product was purified by column chromatography, (SiO_2, 3:2 hexane : EtOAc) to give 2.05g of the title compound as a clear yellow oil (57%).

R_f: 0.36 (1:1 hexane : EtOAc)

m/z (EI): 192 (M^+)



δ_H (400MHz, $CDCl_3$): 1.25-1.43 (2H, m, H^e), 1.45-1.65 (4H, m, H^{d+i}), 1.80-1.96 (2H, m, H^c), 2.52-2.75 (2H, m, H^f), 2.79-2.92 (3H, m, H^{g+h}), 3.27 (1H, brs, H^a), 3.50-3.62 (2H, m, H^b).

δ_C (100MHz, $CDCl_3$): 22.5 (C^e), 25.7 (C^d), 27.0 (C^c), 32.8 (C^f), 39.3 (C^i), 39.7 (C^h), 43.1 (C^g), 63.1 (C^b).

IR: ν cm^{-1} (neat): 3346 (OH bend), 2930 (C-H stretch), 2855 (C-H stretch).

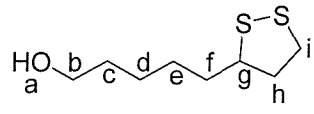
$LiAlH_4$ reduction of thioctic acid (25) to give 5-(1,2-dithiolan-3-yl)pentan-1-ol (28)

Method A: Ring closure by stirring in air.

Thioctic acid (**25**) (800mg, 3.9mmol, 1eq) was dissolved in anhydrous THF (2mL), this solution was added dropwise, with cooling on an ice bath, to a suspension of $LiAlH_4$ (589mg, 15.5mmol, 4eq) in anhydrous THF (8mL). The reaction was then heated to reflux under nitrogen for 24h. The reaction was cooled and the excess $LiAlH_4$ was quenched by pouring the reaction mixture slowly, with stirring, onto crushed ice. The quenched reaction was stirred for 2h in air. The reaction mixture was acidified by the addition of 2M HCl (50mL) and the product extracted with ethyl acetate (3 x 200mL). The organics were combined and washed with 1M $KHSO_4$ (3 x 100mL), 1M $NaHCO_3$ (3 x 100mL) and brine (3 x 100mL), before being dried over $MgSO_4$ and concentrated *in vacuo*. The product was purified by column chromatography, (SiO_2, 2:1 hexane : EtOAc) to give 180mg of the title compound as a pale yellow oil (24%).

R_f: 0.32 (1:1 hexane : EtOAc)

m/z (EI): 192 (M^+)



δ_H (400MHz, $CDCl_3$): 1.25-1.43 (2H, m, H^e), 1.45-1.65 (4H, m, H^{d+i}), 1.80-1.96 (2H, m, H^c), 2.52-2.75 (2H, m, H^f), 2.79-2.92 (3H, m, H^{g+h}), 3.27 (1H, brs, H^a), 3.50-3.62 (2H, m, H^b).

δ_C (100MHz, $CDCl_3$): 22.5 (C^e), 25.7 (C^d), 27.0 (C^c), 32.8 (C^f), 39.3 (C^i), 39.7 (C^h), 43.1 (C^g), 63.1 (C^b).

IR: ν cm^{-1} (liquid film): 3341 (OH bend), 2925 (C-H stretch), 2850 (C-H stretch).

Method B: Ring closure using I_2.

The reduction was achieved using the same procedure as given in Method A. Following quenching of the excess $LiAlH_4$, the lithium salts were extracted by washing with 1M $KHSO_4$ (3 x 100mL), 1M $NaHCO_3$ (3 x 100mL) and brine (3 x 100mL). Iodine was added until colour persisted, the residue was taken up in EtOAc and washed with $Na_2S_2O_3$ (2 x 100mL), 1M $KHSO_4$ (50mL), 1M $NaHCO_3$ (50mL) and brine (50mL), before being dried over $MgSO_4$ and concentrated *in vacuo*. This procedure resulted in a single spot plus some salts on the baseline of the TLC plate. The residue was taken up in chloroform and salts were removed by filtration. The solution was concentrated *in vacuo*, NMR analysis showed the product to be pure and the desired one. Upon leaving this pure compound it took on a firm jelly like appearance and became insoluble in all common laboratory solvents.

6,8-Disulfanyloctan-1-ol (26)[28]

The title compound was prepared using the method of Field and Khim.[28] A suspension of $LiAlH_4$ (3.68g, 97.1mmol, 4eq) in anhydrous THF (100mL), was placed under nitrogen and cooled on an ice bath to 0°C. To this was added dropwise, with stirring, a solution of thioctic acid (**25**) (5.0g, 24.2mmol, 1eq) in anhydrous THF (10mL). The reaction was allowed to warm to room temperature and was then heated to reflux for 24h. The reaction was cooled on an ice bath and the excess $LiAlH_4$ quenched by the dropwise addition of 2M HCl. When all the $LiAlH_4$ was quenched the solvent was removed *in vacuo* (maintaining a nitrogen atmosphere). The residue was taken up in degassed ethyl acetate (100mL) and the salts extracted with degassed 1M $KHSO_4$ (3 x 50mL), before being dried over $MgSO_4$ and concentrated *in vacuo*. TLC analysis showed the product to be the desired one and so it was used directly in the next reaction without further purification to prevent the dithiol being oxidised.

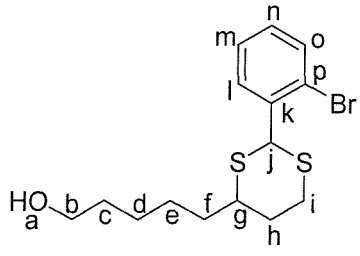
R_f: 0.33 (1:1 hexane : EtOAc)

5-(2-(2-Bromophenyl)-1,3-dithian-4-yl)pentan-1-ol (29)[29]

The title compound was prepared according to the method of Muzard and Portella.[29] 2-Bromobenzaldehyde (2.83mL, 24.2mmol, 1eq) was dissolved in anhydrous, degassed DCM (30mL). 6,8-Disulfanyloctan-1-ol (**25.**) (4.6g, 24.2mmol, 1eq) in anhydrous, degassed DCM (25mL) was added and the reaction cooled to –20°C. A solution of $TiCl_4$ (7.98mL, 72.6mmol, 3eq) in anhydrous, degassed DCM (15mL) was added dropwise to the reaction with stirring. The reaction turned bright orange and a solid formed. The reaction was warmed to room temperature and allowed to stir for 2.5h. The reaction was cooled on an ice bath and water (100mL, 1eq) added to quench any excess $TiCl_4$. The organic layer was decanted and dried over $MgSO_4$, prior to solvent removal *in vacuo*. The product was purified by column chromatography, (SiO_2, 2:1 hexane : EtOAc) to give 4.79g of the title compound as a clear oil (55%, 2 steps from **25**).

R_f: 0.26 (1:1 hexane : EtOAc)

m/z (APCI): 362 $(M+H)^+$, 402 $(M+K)^+$



δ_H (300MHz, $CDCl_3$): 1.30-1.65 (6H, m, $H^{d,e+i}$), 1.66-1.77 (2H, m, H^c), 2.12-2.39 (2H, dt, J = 14, 2, H^f), 2.91-3.17 (3H, m, H^{g+h}), 3.63 (2H, t, J = 7, H^b), 5.09 (1H, s, H^j), 7.19 (1H, dd, J = 7, 7, H^l), 7.30 (1H, dd, J = 7, 7, H^n), 7.55 (1H, d, J = 7, H^m), 7.70 (1H, d, J = 7, H^o).

δ_C (75MHz, $CDCl_3$): 25.7 (C^d), 26.5 (C^e), 32.6 (C^c), 32.7 (C^f), 32.8 (C^i), 36.3 (C^h), 46.5 (C^j), 51.6 (C^g), 62.8 (C^b), 123.1 (C^p), 128.3 (C^m), 129.9 (C^n), 130.0 (C^l), 133.1 (C^o), 138.1 (C^k).

HPLC: (254nm) 18.6 min

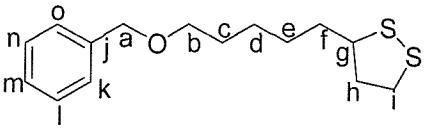
IR: ν cm^{-1} (neat): 3336 (OH bend), 2930 (C-H stretch), 2855 (C-H stretch), 1463 (alkane C-H bend), 742 (aromatic C-H).

5-(1,2-Dithiolan-3-yl)-1-(phenylmethoxy)pentane (30)[33]

The title compound was prepared according to the method of Bundle *et al.*[33] 5-(1,2-Dithiolan-3-yl)pentan-1-ol (**28**) (100mg, 0.52mmol, 1eq) and benzyl-2,2,2-trichloroacetimidate (**32**) (194μL, 1.04mmol, 2eq) were dissolved in anhydrous DCM (7mL). To this was added boron trifluoride diethyl etherate (33μL, 0.26mmol, 0.5eq) dropwise with cooling on an ice bath. The system was placed under nitrogen, warmed to room temperature and left to stir overnight. The trichloroacetamide, which formed during the reaction, was filtered off and the filtrate extracted with 1M $NaHCO_3$ (3 x 15mL), water (3 x 15mL) and brine (3 x 15mL) before being dried over $MgSO_4$ and the solvent removed *in vacuo*. The product was purified by column chromatography (SiO_2, 2:1 hexane : EtOAc) to give 77.2mg of the title compound as a yellow oil (53%).

R_f: 0.19 (2:1 hexane : EtOAc)

m/z (EI): 283 $(M+H)^+$



δ_H (300MHz, $CDCl_3$): 1.12-1.31 (2H, m, H^e), 1.33-1.53 (4H, m, H^{d+i}), 1.57-1.75 (2H, m, H^c), 2.39-2.58 (2H, m, H^f), 3.48-3.69 (3H, m, H^{g+h}), 4.61 (2h, s, H^a), 7.09-7.33 (5H, m, H^{j-n}).

δ_C (75MHz, $CDCl_3$): 25.7 (C^d), 26.5 (C^e), 32.7 (C^c), 34.5 (C^f), 35.2 (C^i), 36.5 (C^h), 44.4 (C^g), 63.0 (C^b), 67.2 (C^a), 127.0 (C^m), 127.1 (C^j), 128.6 (C^l), 128.7 (C^n), 129.0 (C^o), 129.1 (C^k).

HPLC: (254nm) 20.8 min

IR: ν cm^{-1} (neat): 2930 (C-H stretch), 2855 (C-H stretch), 1608 (aryl), 1243 (C-O stretch), 1047 (C-O stretch).

5-(2-(2-Bromophenyl)-(1,3-dithian-4-yl))-1-(phenylmethoxy)pentane) (33)[33]

The title compound was prepared according to the method of Bundle *et al.*[33] 5-(2-(2-Bromophenyl)1,3-dithian-4-yl)pentan-1-ol (**29**) (200mg, 0.55mmol, 1eq) and benzyl-2,2,2-trichloroacetimidate (**32**) (204μL, 1.1mmol, 2eq) were dissolved in anhydrous DCM (10mL). To this was added boron trifluoride diethyl etherate (34μL, 0.275mmol, 0.5eq) dropwise with cooling. The reaction was warmed to room temperature and allowed to stir for 48h. The trichloroacetamide formed during the reaction was filtered off and the filtrate washed with 1M $NaHCO_3$ (3 x 20mL), water (3 x 20mL) and brine (3 x 20mL) before being dried over $MgSO_4$ and concentrated *in vacuo*. An attempt was made to purify the compound (**33**) by column chromatography (SiO_2, 2:1 hexane : EtOAc), however this proved not to be possible.

R_f: 0.46 (2:1 hexane : EtOAc)

Acetimidate resin (34)[34]

The title compound was prepared according to the method of Hanessian and Xie.[34] HO-Wang Linker-PS resin (500mg, 0.32mmol, 0.64mmolg^{-1}, 1eq) was swollen in anhydrous DCM (7mL), to this was added trichloroacetonitrile (640μL, 6.4mmol, 20eq). The reaction was placed under nitrogen and cooled to 0°C on an ice bath. DBU (48μL, 0.32mmol, 1eq) was added dropwise over a period of 5min, the reaction was left to stir gently on ice for a period of 40min. After this time the reaction had turned from clear to a tan/brown colour. The resin was filtered and washed with DCM (3 x 5mL), DMSO (2 x 5mL), THF (2 x 5mL) and ether (3 x 5mL), before being dried in a stream of nitrogen.

IR: ν cm^{-1} (ATR): 3027 (C -H stretch), 2919 (C-H stretch), 2852 (C-H stretch), 1664 (C=N).

Resin bound 5-(2-(2-bromophenyl)-1,3-dithian-4-yl)pentan-1-ol (35)[34]

The title compound was prepared according to the method of Hanessian and Xie.[34] Trichloroacetimidate resin (**34**) (400mg, 0.26mmol, 1eq) was washed with anhydrous DCM (2mL) to remove any moisture and then suspended in anhydrous DCM (2mL). 5-(2-(2-Bromophenyl)1,3-dithian-4-yl)pentan-1-ol (**29**) (185mg, 0.51mmol, 2eq), dissolved in anhydrous DCM (1mL), was added and the reaction stirred gently at room temperature for 5min. Boron trifluoride diethyl etherate (16μL, 0.13mmol, 0.5eq) was added and the reaction stirred for 2h. The resin was washed with DCM (3 x 10mL), methanol (2 x 10mL) and ether (3 x 10mL) before being dried and stored under nitrogen.

IR: ν cm^{-1} (ATR): 3026 (C-H stretch), 2920 (C-H stretch), 2855 (C-H stretch).

Cleavage of Wang linker with TFA

A solution of TFA (4.8mL), water (0.1mL) and methanol (0.1mL) was added to the resin (300mg, 0.192mmol, 1eq) (**35**) (pre-swollen in DCM (2mL)). The resin was shaken for 3h. The cleavage cocktail was removed by filtration and the resin washed with DCM (3 x 4mL). The filtrate and DCM washings were combined and the solvent removed *in vacuo*. Analysis by TLC, mass spectrometry and NMR showed none of the expected product and from this we deduced that the original coupling reaction to produce the ether link must have failed.

5.4 Experimental for Chapter 4.

5-(1,2-Dithiolan-3-yl)-*N*-benzylpentanamide (37)

Method A: Synthesis using thionyl chloride.[35]

The title compound was prepared according to the method of Nambu, Endo and Okawara.[35] Thionyl chloride (354μL, 4.85mmol, 1eq) was added dropwise to a solution of thioctic acid (**25**) (1g, 4.85mmol, 1eq) in DMF (5mL) at -10°C. Benzylamine (529μL, 4.85mmol, 1eq) was added and the solution stirred at room temperature overnight. Ether was added to the reaction mixture to extract the product (3 x 15mL). The organic layers were combined and dried over $MgSO_4$ prior to solvent removal *in vacuo*. During the extraction, polymeric biproducts could be seen adhering to the walls of the separating funnel. Upon solvent removal the product polymerised preventing further purification of the product. For this reason it was decided to attempt the coupling in a different manner.

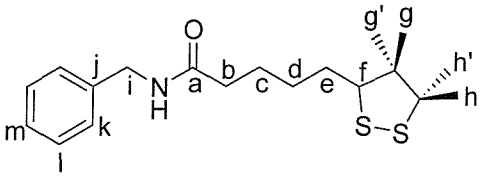
Method B: Synthesis using an activated ester approach.

Thioctic acid (**25**) (6.68g, 32.40mmol, 1.1eq) was dissolved in anhydrous DCM (10mL) and DMF (1mL). HOBt (4.38g, 32.40mmol, 1.1eq) was added and the solution stirred for 15min. DCC (7.28g, 35.23mmol, 1.2eq) was added and the reaction stirred for 45min. The reaction was filtered to remove the DCU formed, benzylamine (3.21mL, 29.46mmol, 1eq) added and the reaction stirred overnight. The solvent was removed *in vacuo* and the product taken up in ethyl acetate (30mL), the product was washed with water (3x20mL) and brine (3 x 20mL) and then dried over $MgSO_4$ prior to solvent removal *in vacuo*. The product still contained residual salts and these were removed by further washing with 1M $KHSO_4$ (1 x 20mL), 1M $NaHCO_3$ (1 x 20mL), water (2 x20mL) and brine (2 x 20mL) the product was recrystallised from ethyl acetate with hexane. The product was filtered off from the solvent and dried under vacuum to give 6.76g of the title compound as a white solid (78%).

R_f: 0.24 (1:1 hexane : EtOAc)

M. Pt.: 62-64°C

m/z (ES^+): 296 $(M+H)^+$, 318 $(M+Na)^+$, 334 $(M+K)^+$, 613 $(2M+Na)^+$



δ_H (400MHz, $CDCl_3$): 1.52 (2H, tt, J = 7, 8, H^d), 1.68-1.78 (4H, m, H^{c+e}), 1.95 (1H, ddd, J = 7, 7, 14, H^g), 2.26 (2H, t, J = 7, H^b), 2.48 (1H, ddd, J = 7, 7, 12, $H^{g'}$), 3.11-3.24 (2H, m, $H^{h+h'}$), 3.60 (1H, ddd, J = 7, 7, 13, H^f), 4.47 (2H, d, J = 6, H^i), 5.93 (1H, s, NH), 7.30-7.40 (5H, m, H^{k-m}).

δ_C (100MHz, $CDCl_3$): 25.5 (C^c), 29.1 (C^d), 34.8 (C^e), 36.6 (C^b), 38.6 (C^h), 40.4 (C^g), 43.7 (C^i), 56.6 (C^f), 127.7 (C^m), 128.0 (C^l), 128.9 (C^k), 138.5 (C^j), 172.7 (C^a).

HPLC: (254nm) 10.7min

IR: ν cm^{-1} (solid): 3293 (NH amide), 2920 (C-H stretch), 2840 (C-H stretch), 1634 (C=O amide), 1528 (secondary amide), 1495 (alkane), 1452 (alkane), 1255 (C-O stretch)

N-Benzyl-6,8-disulfanyloctanamide(38)[35]

The title compound was prepared according to the method of Nambu, Endo and Okawara.[35] 5-(1,2-Dithiolan-3-yl)-*N*-benzylpentanamide (**37**) (6.76g, 22.9mmol, 1eq) was dissolved in degassed methanol (40mL), the solution was cooled to 0°C and sodium borohydride (2.60g, 68.7mmol, 3eq) added portionwise. The reaction was warmed to room temperature and allowed to stir for 2.5h. The solution was acidified to pH 2 with degassed 2M HCl. The product was extracted under nitrogen with degassed chloroform (3 x 50mL). The organics were combined and, dried over

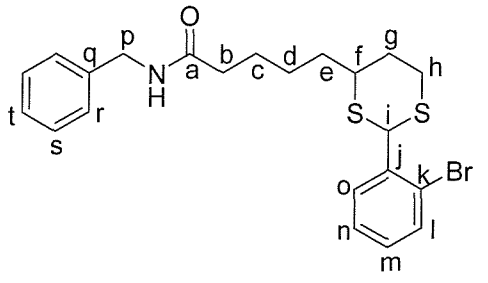
$MgSO_4$ and concentrated *in vacuo*. Due to the air sensitive nature of the product it was used immediately without further purification.

5-(2-(2-Bromophenyl)(1,3-dithian-4-yl)-*N*-benzylpentanamide (39)[29]

The title compound was prepared according to the method of Muzard and Portella.[29] *N*-Benzyl-6,8-disulfanyloctanamide (**38**) (6.80g, 22.9mmol, 1eq) was dissolved in anhydrous degassed DCM (15mL), to this was added a solution of 2-bromobenzaldehyde (2.67mL, 22.9mmol, 1eq) in anhydrous degassed DCM (5mL), the reaction was then cooled to -20°C. A solution of $TiCl_4$ (7.55mL, 68.7mmol, 3eq) in anhydrous degassed DCM (10mL) was added dropwise with stirring. The reaction was warmed to room temperature and left to stir for 2.5h. After this time an orange solid had formed on the bottom of the flask. The reaction was cooled to 0°C and water (30mL) was added to quench the reaction. The solution was left stirring until all the orange solid had dissolved. The organic layer was decanted, dried over $MgSO_4$ and concentrated *in vacuo*. The product was purified by column chromatography (SiO_2, 2:1 hexane : EtOAc) to give 6.28g of the title compound as a clear oil (59%, 2 steps from **37**).

R_f: 0.30 (1:1 hexane : EtOAc)

m/z (ES^+): 465 $(M+H)^+$, 487 $(M+Na)^+$, 503 $(M+K)^+$



δ_H (300MHz, $CDCl_3$): 1.30-1.71 (6H, m, H^{c-e}), 2.05-2.20 (4H, m, H^{b+g}), 2.83-3.07 (3H, m, H^{f+h}), 4.39 (2H, d, J = 6, H^p), 5.53 (1H, s, H^i), 5.77 (1H, brs, NH), 7.09 (1H, t, J = 8, H^m), 7.13-7.31 (6H, m, H^{n+r-t}),7.50 (1H, d, J =8, H^o), 7.60 (1H, d, J = 8, H^l).

δ_C (75MHz, $CDCl_3$): 25.6 (C^c), 25.9 (C^d), 32.7 (C^e), 32.8 (C^b), 36.0 (C^h), 36.6 (C^g), 43.7 (C^p), 46.3 (C^i), 51.7 (C^f), 123.2 (C^k), 127.7 (C^t), 128.0 (C^r), 128.3 (C^n), 128.9 (C^s), 129.9 (C^m), 133.1 (C^{l+o}), 138.1 (C^j), 138.5 (C^q), 172.7 (C^a).

IR: ν cm^{-1} (neat): 3302 (NH amide), 2926 (C-H stretch), 2884 (C-H stretch), 1626 (C=O amide), 1527 (2^o amide)

HPLC: (254nm) 19.3 min

Resin bound 5-(1,2-dithiolan-3-yl)pentanamide (43)

Thioctic acid (**25**) (680mg, 3.3mmol, 1.1eq) was dissolved in DCM (5mL), to this was added HOBt (446mg, 3.3mmol, 1.1eq). The solution was left to stir for 5min. DIC (564μL, 3.6mmol, 1.2eq) was added and the solution left to stir for 15min. Aminomethyl resin (**42**) (3g, $1mmolg^{-1}$, 3mmol, 1eq) was pre-swollen with DCM (10mL). The coupling solution was added and the reaction left shaking overnight. The coupling solution was removed by filtration and the resin washed with DMF (3 x 30mL), DCM (3 x 30mL), methanol (3 x 30mL) and ether (3 x 30mL) prior to being dried under vacuum. A qualitative ninhydrin test was performed and a negative result obtained indicating that the reaction had gone to completion.

IR: ν cm^{-1} (ATR): 3026 (polystyrene C-H), 2920 (polystyrene C-H), 2840 (polystyrene C-H), 1654 (amide C=O), 1491 (alkane C-H), 1449 (alkane C-H)

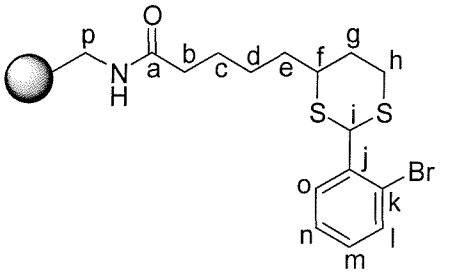
Resin bound 6,8-disulfanyloctanamide (44)[35]

Th title compound was prepared according to the method (modified for resin work) of Nambu, Endo and Okawara.[35] Resin bound 5-(1,2-dithiolan-3-yl)pentanamide (**43**) (3g, $1mmolg^{-1}$, 3mmol, 1eq) was suspended in degassed methanol (30mL). The reaction mixture was cooled to 0°C and sodium borohydride (1.13g, 30mmol, 10eq) added portionwise. The reaction was warmed to room temperature and allowed to stir under nitrogen for 5h. The solution was removed whist maintaining a nitrogen atmosphere, and the resin washed with degassed methanol (3 x 30mL) and anhydrous degassed DCM (3 x 30mL). Due to the air

sensitivity of 6,8-disulfanyloctanamide, the resin was used immediately to the next reaction.

Resin bound 5-(2-(2-bromophenyl)(1,3-dithian-4-yl)pentanamide (45)[29]

The title compound was prepared according to the method (modified for resin work) of Muzard and Portella.[29] Resin bound 6,8-disulfanyloctanamide (**44**) (3g, 1mmolg^{-1}, 3mmol, 1eq) was pre-swollen in anhydrous degassed DCM (30mL), 2-bromobenzaldehyde (700μL, 6mmol, 2eq) dissolved in anhydrous degassed DCM (30mL) was added to the resin, and the reaction cooled to -20°C. A solution of $TiCl_4$ (1.98mL, 18mmol, 6eq) in anhydrous, degassed DCM (15mL) was added dropwise with stirring. The reaction was warmed to room temperature and allowed to stir for 2.5h. The reaction was cooled to 0°C and water (75mL, 1eq) was added, the solution was decanted and the resin washed with DCM (3 x 30mL), methanol (3 x 30mL) and ether (2 x 20mL) before being dried under vacuum.



δ_C (100MHz, C_6D_6): 26.2 (C^c), 29.7 (C^d), 33.3 (C^e), 35.3 (C^b), 36.7 (C^h), 38.9 (C^g), 41.4 (C^p), 46.6 (C^i), 51.4 (C^f), 145.5 (C^j), 172.0 (C^a).

IR: ν cm^{-1} (ATR): 3024 (NH amide), 2919 (C-H stretch), 2845 (C-H stretch), 1656 (C=O amide), 1491 (alkane), 1449 (alkane).

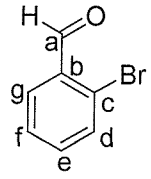
Cleavage of the dithiane of resin bound 5-(2-(2-bromophenyl)(1,3-dithian-4-yl)pentanamide (45)[23]

The title cleavage was afforded according to the method of Bertini *et al.*[23] Resin bound 5-(2-(2-bromophenyl)(1,3-dithian-4-yl)pentanamide (**45**) (100mg, 0.074mmol, 1eq) was swollen in anhydrous THF (3mL) and cooled to 0°C. Periodic acid (64mg, 0.28mmol, 3.8eq) was dissolved in anhydrous THF (2mL), and added to the resin the reaction was left to stir for 5h at room temperature. The reaction was quenched by the addition of water (10mL), the solution was removed from the resin by filtration and the resin washed with DCM (1 x 5mL). The filtrate and resin washings were combined and the solvent removed *in vacuo*. The residue was taken up in ethyl acetate and washed with water (3 x 10mL) and brine (3 x 10mL) before being dried over $MgSO_4$ and concentrated *in vacuo* to give the crude product as a deep orange oil.

R_f: 0.29 (1:1 hexane : EtOAc)

Yield: 9.6mg (70%)

m/z (EI): 184 (M^+)



δ_H (300MHz, $CDCl_3$): 7.41-7.48 (2H, m, H^{e-f}), 7.64-7.67 (1H, m, H^d), 7.91-7.94 (1H, m, H^g), 10.38 (1H, s, H^a).

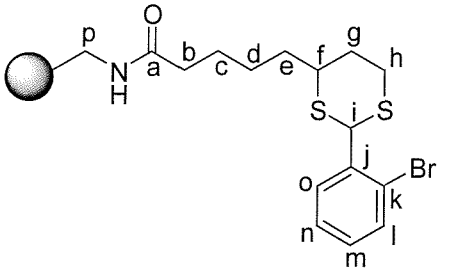
δ_C (75MHz, $CDCl_3$): 127.3 (C^c), 128.1 (C^f), 130.1 (C^g), 134.1 (C^d), 135.5 (C^e), 192.0 (C^a).

HPLC: (254nm): 15.2 min

Attempted synthesis of resin bound 5-(2-(2-(2H-benzo[d]-1,3-dioxolan-5-yl-hydroxymethyl)phenyl)-(1,3-dithian-4-yl)pentanamide (46)[18-19]

An attempt to make the title compound was carried out according to the method of Harrowven.[18-19] Resin bound 5-(2-(2-bromophenyl)(1,3-dithian-4-yl)pentanamide (**45**) (2.0g, 2.0mmol, 1eq) was swollen in anhydrous THF (10mL) and cooled to -78°C. *n*-BuLi (622μL, 6.6mmol, 3.3eq) was added dropwise to the cooled resin, the reaction was warmed to room temperature and allowed to stir overnight. The solution was cooled to -20°C and a solution of piperonal (601mg, 4mmol, 2eq) in anhydrous THF (5mL) added dropwise, the reaction was then heated to 60°C and left stirring at this temperature for 36h. The reaction was quenched by the addition of water (10mL), the resin was removed by filtration and was washed with alternating DMF (10mL) and water (10mL) for 10 washes, it was then washed with DCM (3 x 10mL), methanol (3 x 10mL) and ether (3 x 10mL). The resin was analysed using gel-phase NMR to determine whether the reaction had worked.

IR: ν cm^{-1} (ATR): 3361 (OH stretch), 3026 (NH amide), 2920 (C-H stretch), 2845 (C-H stretch), 1656 (C=O amide), 1491 (alkane), 1449 (alkane).



δ_C (100MHz, C_6D_6): 26.1 (C^c), 29.5 (C^d), 32.6 (C^e), 35.3 (C^b), 36.6 (C^h), 39.0 (C^g), 41.4 (C^p), 46.7 (C^i), 51.0 (C^f), 146.4 (C^j), 173.0 (C^a).

As can be seen from the gel-phase NMR, the transmetallation reaction did not work and the piperonal could not couple to the resin.

Appendix 1.

Quantitative Fmoc Test.[26]

A known mass of dry resin was weighed into an Eppendorf tube, 20% piperidine in DMF (1mL) was added to the tube and the tube shaken for 10min. The resin was filtered through a glass wool plug in a pipette and the filtrate made up to 10mL with 20% piperidine in DMF.

The absorbance was measured at 302nm against a blank.

The substitution was calculated using the following formula:

Sub^{n} ($mmolg^{-1}$) = A_{302} x Volume (mL) x 10^3 / 7800 x mass (mg)

10^3 converts from mg to g

7800 = extinction coefficient

Appendix 2.

Quantitative Ninhydrin Test.[36]

To a known quantity of dry resin (3-5mg) was added 6 drops of ninhydrin solution A and two drops of ninhydrin solution B. The suspension of resin was then heated to 100°C for 5min. The solution was cooled and 2mL 60% aqueous ethanol added. The resin was removed by filtration and washed with NH_4Cl solution in DCM (2 x 0.5mL), the washings were collected, combined with the reaction mixture and made up to 25mL with 60% aqueous ethanol. A blank was made in the same way but without the resin. The absorbance at 570nm was recorded against the blank.

The substitution can be calculated using the following formula:

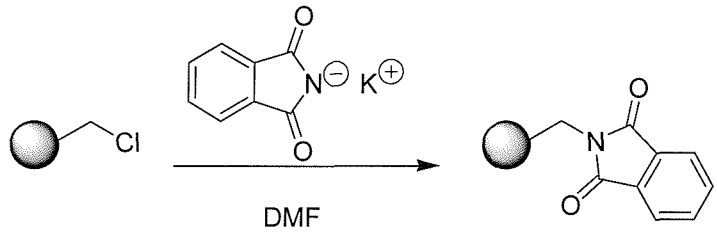
Sub^n ($mmolg^{-1}$) = A_{570} x Volume (mL) x 10^3 / E x Mass (mg)

10^3 converts from mg to g.

E = extinction coefficient at 570nm = 1.5×10^4.

Appendix 3.

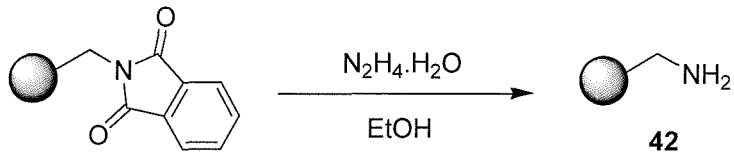
Phthalimide resin



Scheme 37 : Synthesis of phthalimide resin.

Polystyrene chloromethyl resin (20g, 1.4mmolg^{-1}, 28mmol, 1eq) and potassium phthalimide (25g, 140mmol, 5eq) were heated to 120°C overnight in DMF (300mL). The solution was removed by filtration and the resin washed with DMF (3 x 300mL), DMF : H_2O (1:1) (3 x 300mL), water (3 x 300mL), dioxane (2 x 200mL), methanol (2 x 200mL) and ether (2 x 200mL). The resin was dried under vacuum.

Aminomethyl resin



Scheme 38 : Synthesis of aminomethyl resin **42**.

Phthalimide resin (20g, 1.4mmolg^{-1}, 28mmol, 1eq) was suspended in ethanol (400mL), hydrazine (34mL, 0.7mol, 20eq) was added and the reaction left to reflux overnight. A thick white precipitate formed which was removed by washing with hot DMF (3 x 300mL), hot DMF : H_2O (1:1) (3 x 300mL), hot water (3 x 300mL), dioxane (3 x 300mL), methanol (3 x 300mL) and ether (2 x 300mL). The resin was

dried under vacuum and a quantitative ninhydrin test performed (Appendix 2.) to determine the substitution of the resin.

Substitution: 1.0mmolg^{-1}

IR: ν cm^{-1} (ATR): 3025 (NH amine), 2919 (C-H stretch), 1493 (alkane C-H), 1451 (alkane C-H).

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