UNIVERSITY OF SOUTHAMPTON

Investigation of Keteniminium-Olefin Cycloadditions on the Solid-Phase

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ABSTRACT

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INVESTIGATION OF KETENIMINIUM-OLEFIN CYCLOADDITIONS ON THE SOLID-PHASE

By James Dudley Hart

The [2+2] keteniminium-olefin cycloaddition reaction has proven to be a powerful method for the synthesis of cyclobutanones. These cyclobutanones are important synthetic intermediates and can be easily converted into a range of heterocyclic and carbocyclic structures. Many derivatives of these compounds display significant biological activities.

This research deals with the synthesis and subsequent chemical manipulation of resin-bound cyclobutanones, with a view to using them as a core unit for the design of libraries. The cycloadditions have been combined with the use of a nucleophile cleavable sulfonyl linker, allowing the introduction of an extra element of diversity in the cleavage step.

Contents

Acknowledgements

I would like to thank my supervisor Dr. Richard Brown for his help, support and tolerance throughout this period of work.

All the members of all the research groups both past and present who have in any way contributed to keeping me sane (the get-out clause in case I forget to mention anyone).

Particular mentions should go to Martyn, Phil and Mike for being good friends, JD for being JD, Nigel and John for the beers, Faye and Julie for listening to me whinge and feeding me pizza, and Mum and Dad for their unconditional love and support ... oh, and of course for the money as well!

Abbreviations

1°	Primary
2°	Secondary
Ac	Acetyl
Boc	*tert*-Butoxycarbonyl
br	Broad (NMR and IR)
Bu	Butyl
c	Concentrated
CAS	Chemical Abstracts
Cbz	Carbobenzoxy (benzyloxycarbonyl, Z)
d	Doublet (NMR)
DCC	1,3-Dicyclohexylcarbodiimide
DCE	1,2-Dichloroethane
DIC	1,3-Diisopropylcarbodiimide
DIPEA	*N*,*N*-Diisopropylethylamine
DMA	*N*,*N*-Dimethylacetamide
DMAP	4-Dimethylaminopyridine
DMF	*N*,*N*-Dimethylformamide
eq.	Equivalents
Et	Ethyl
Fmoc	9-Fluorenylmethoxycarbonyl
HOBt	1-Hydroxybenzotriazole
i	Iso
IR	Infra-red
J	Coupling constant
KOTMS	Potassium trimethylsiloxide
Leu	Leucine
m	Multiplet (NMR)
mCPBA	Meta-chloroperbenzoic acid
Me	Methyl
MPS	Multiple Parallel Synthesis
N	Normal solution of reagent
NMP	*N*-Methylpyrrolidine
NMR	Nuclear Magnetic Resonance
Nu	Nucleophile
PEG	Polyethyleneglycol
Ph	Phenyl
Pr	Propyl
q	Quartet (NMR)
rt	Room temperature
s	Singlet (NMR) or Strong (IR)
t	Tertiary
t	Triplet (NMR)
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
Tf	Trifluoromethanesulfonyl (triflyl)
Ts	Toluene-4-sulfonyl (tosyl)
w	Weak (IR)

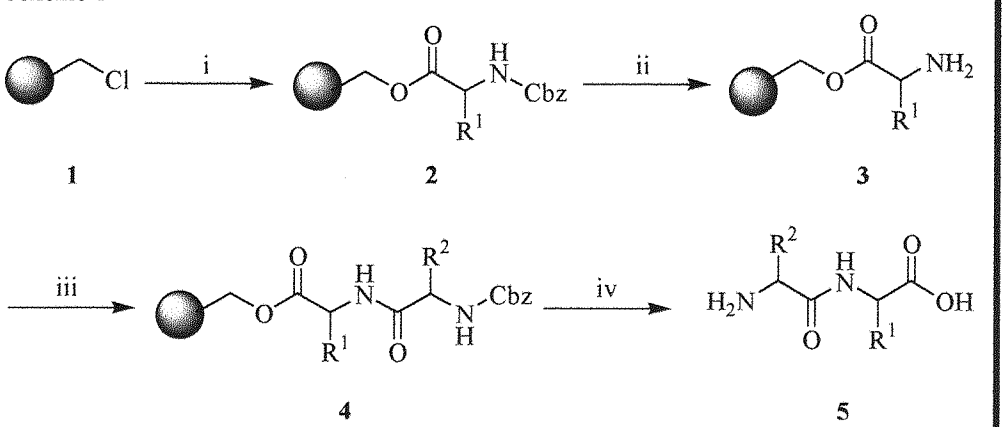
1. Introduction

1.1 Solid-Phase Chemistry

1.1.1 Genesis

In 1963 the first example of a solid-phase synthesis was reported,[1] it demonstrated the synthesis of a tetrapeptide using a totally new approach. The initial concept was uncomplicated, simply attach the starting amino acid to an insoluble support by means of a covalent bond, then assemble the peptide and cleave from the support (scheme 1).

Scheme 1



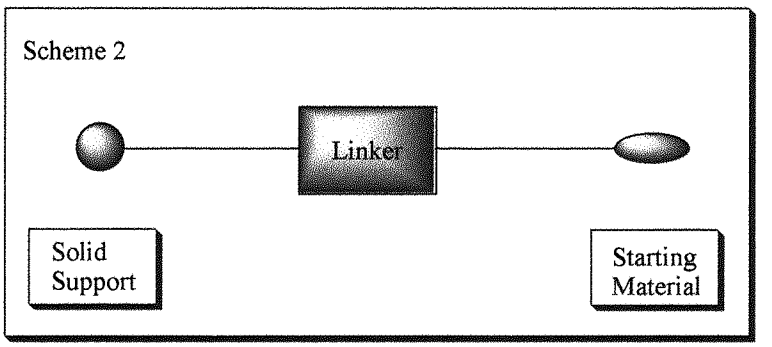
Reagents/Conditions: i) Amino Acid ii) HBr-AcOH iii) DCC iv) NaOH

The solid support used was made from a chloromethylated copolymer of vinylbenzene and divinylbenzene in the form of 200 – 400 mesh beads. These beads had a porous structure, that when in the presence of a suitable solvent would swell, thus allowing the diffusion of reagents into the support.[2] Supports of this type have become known as resins.

This seemingly trivial theory has revolutionised the way we look at chemistry and triggered a massive amount of research in the area of solid-phase peptide chemistry, and more recently in the solid-phase synthesis of small molecules. Indeed a number of excellent reviews have been recently published detailing the scope of solid-phase

chemistry.[3-6] The current growing use of solid-phase synthesis is to a large extent due to the ease of manipulation when compared to classical solution phase chemistry techniques. It is now possible to carry out a range of solid-phase procedures without the need to purchase unnecessary, expensive equipment, leading to the isolation of relatively large amounts of product after cleavage. The typical solid-phase synthesis of a small molecule[α] can now be carried out by the same basic method of immobilisation of the starting material to a solid support (scheme 2) and subsequent reaction sequence that was originally used by Merrifield over 35 years ago.

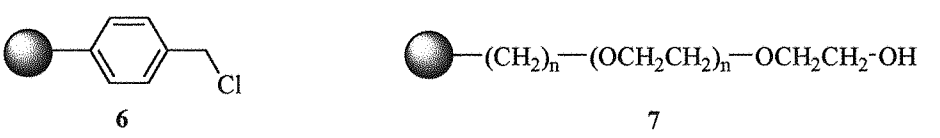
Scheme 2



1.1.2 The Resin

The first point of development of solid-phase synthesis lies with the resin itself. There is a wide range of resins available for the immobilisation of molecules onto the solid phase, and the nature of that molecule can dictate the choice of resin (scheme 3).

Scheme 3



6 **7**

Resin **6** has now become universally known as Merrifield's resin and will swell[7] in a range of organic solvents and as such is not suitable for an aqueous reaction. Resin **7** is

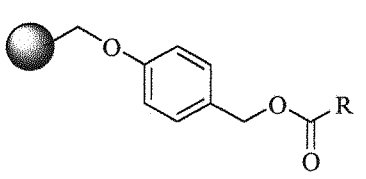
[α] For the purpose of this work, the term small molecule refers to any organic molecule with molecular mass under 1 kDa.

made from polyethylene glycol (PEG) grafted onto polystyrene and will swell in protic and aprotic solvents, but unsurprisingly is a lot more expensive, so for most conventional organic syntheses a derivative of the original Merrifield's resin is utilised.

1.1.3 The Linker

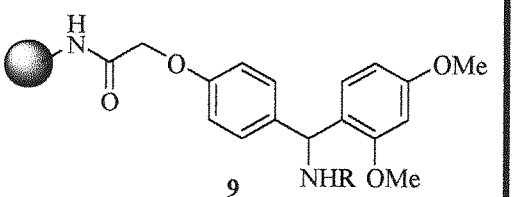
Today most solid-phase syntheses require the substrate to be attached to the resin *via* a small molecule known as a linker. This linker has properties similar to that of any protecting group used in synthesis, it must be stable to all the reaction conditions and also has to be easily cleavable at the end of the reaction sequence. There are a large number of commonly used linkers for this purpose, a few are shown below (scheme 4).[8-10]

Scheme 4



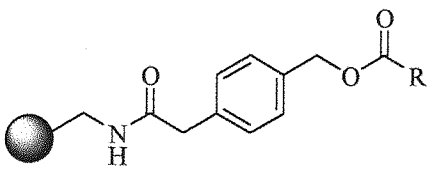
8

Wang linkage. Cleaved with 50 % TFA / CH_2Cl_2



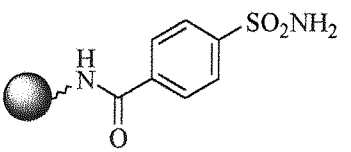
9

Rink amide linkage. Cleaved with TFA



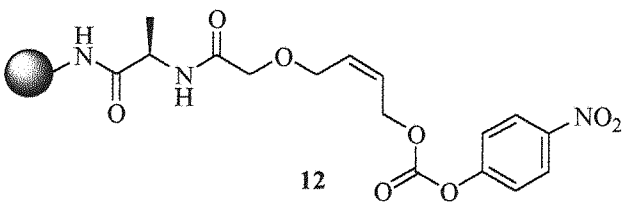
10

PAM linkage. Cleaved with HF



11

Kenner's "safety catch linker".
Cleaved with ICH_2CN, then Nu^-



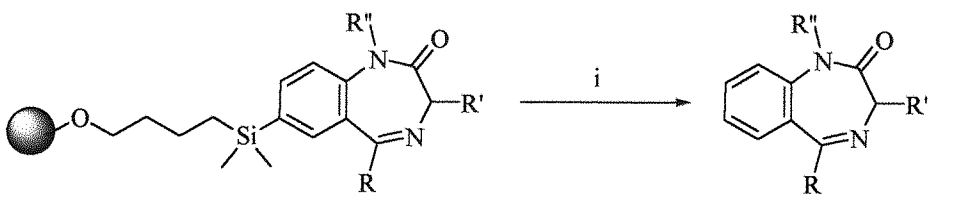
12

Allyl linker developed by Unden.

Based on the Alloc protecting group, cleavage is Pd-catalysed

Linkers can be specifically tailored for cleavage under set conditions, so before any solid-phase synthesis can be undertaken it is essential that the correct type be chosen. Most are either acid or base labile, but there are ranges of photolabile linkers that can be simply cleaved with light.[10] There is another classification of linkers known as traceless linkers, these involve the formation of a C-H bond upon cleavage, a well-known example is the silyl linker (scheme 5).[4]

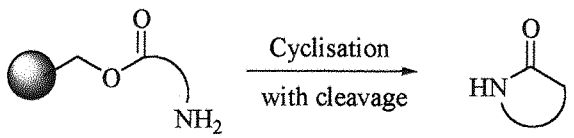
Scheme 5



Reagents/Conditions: i) HF

If the bond attaching the molecule to the resin is the bond broken in an intramolecular reaction, then it is possible to achieve both cyclisation and cleavage in the one step. These cyclative cleavage linkers will therefore release a cyclic product when submitted to the cleavage conditions (scheme 6).[5]

Scheme 6

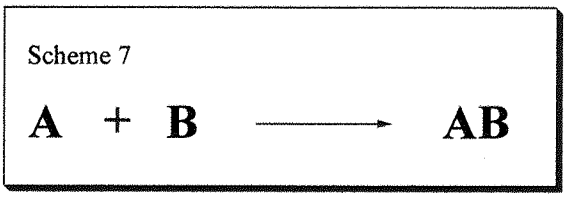


There are another range of linkers known as nucleophile cleavable or react and release linkers, these will be covered in greater depth at a later stage (section 1.2).

1.1.4 Combinatorial Chemistry

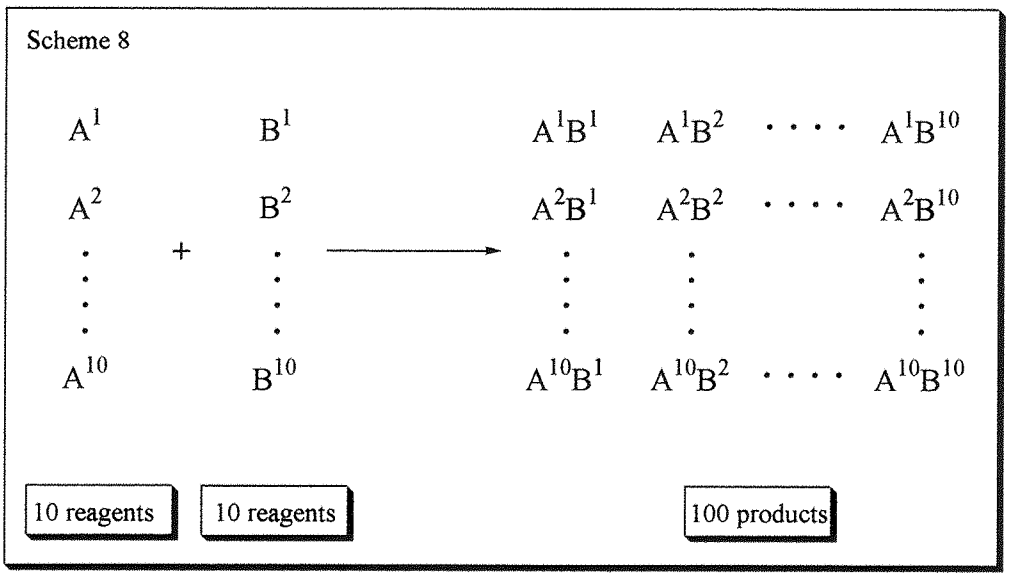
The one main goal of combinatorial chemistry is to simultaneously produce many different compounds with defined structures. The aim is to produce many different structures at the same time, and is based on a very simple principle. Conventional organic synthesis uses two compounds reacting together to give us one product (scheme 7).

Scheme 7

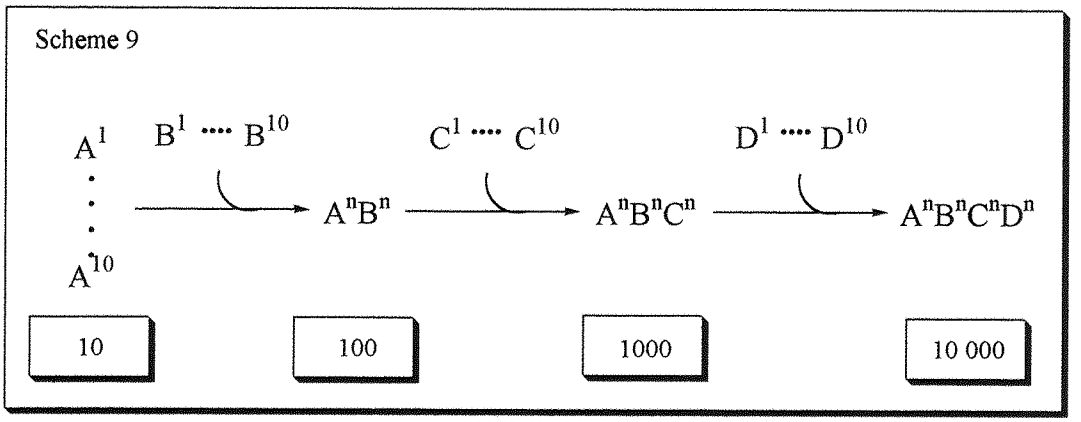


The premise of combinatorial chemistry[11] and also multiple parallel synthesis (MPS)[12], is to use different building blocks of types A(A_1-A_{10}) (e.g. Acid chlorides) and B(B_1-B_{10}) (e.g. Amines), and then react each substance with all of the other reactants (scheme 8).

Scheme 8



The difference between the two methods is that combinatorial chemistry can be used to synthesise enormous numbers of compounds, usually as a mixture (although they can be formed as separate entities). With only 3 synthetic steps and 10 molecules of each type A, B, C and D it is therefore possible to obtain 10,000 compounds (scheme 9).



Indeed a combination of all 20 naturally occurring amino acids to give every possible hexapeptide would give a staggering 20^6 compounds. The collective term for the set of compounds produced in a combinatorial synthesis is a library.

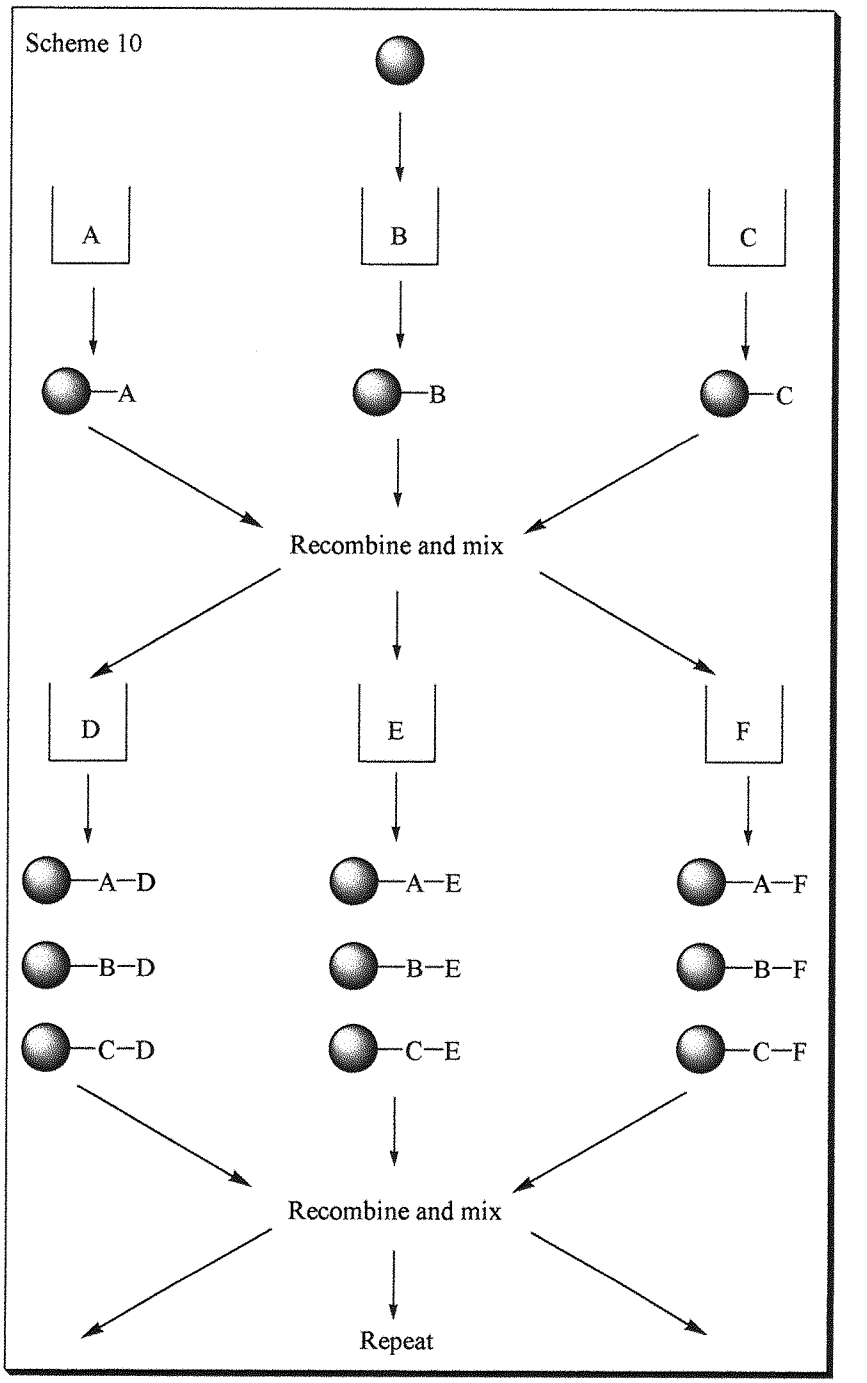
When developing a pharmaceutical agent, one of the key initial steps is the identification of lead compounds. Once this has been accomplished, many analogues of those lead compounds have to be synthesised in order to maximise the desirable and minimise the undesirable properties. It is therefore unsurprising that the demand for more and more novel chemical entities is astronomical. In order to address this increasingly huge demand, methods have been developed so that we are able to create combinatorial libraries.[13] These combinatorial libraries can then be screened to identify the presence of any activity. Currently there are a number of methods available suitable for the synthesis of a large library of compounds.[14-16]

1.1.5 Discrete Compounds

Seemingly the most straightforward method of synthesising a library is to produce multiple compounds in parallel, whilst keeping each of the compounds in a separate reaction vessel (multiple parallel synthesis). In this way it is possible at any time exactly what compounds are present in the various vessels, the compound being identified by its location. A successful way of accomplishing this is by the use of 96 well plates. These consist of a supporting reservoir block with 96 holes or "wells". Utilising these plates it is possible to place 96 pins into the wells, each pin being coated

with some suitable polymeric material for conducting a solid-phase synthesis, such as *N,N*-dimethylacrylamide. Into each of these wells different reactants can be added, thus synthesising 96 discrete compounds each on its own pin. At the end of the synthesis these compounds can then be cleaved so that each is contained in its own individual well.

1.1.6 Split Synthesis

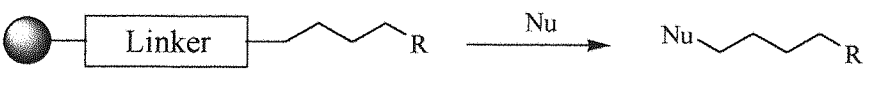


An excellent method for the synthesis of libraries of compounds is split and mix synthesis.[13] In this technique a quantity of resin is split into separate reaction vessels. In each vessel an excess of all reagents are used in order to ensure the reaction is driven to completion. The resin is recombined and mixed thoroughly, then split into the requisite number of reaction vessels for the next step (scheme 10). This second step provides compounds that contain all the possible combinations of the two sets of reagents. It is easy to see that by repeating the split, react, and mix strategy a huge number of compounds can be produced in a relatively short space of time. This method has now found widespread use in the field of combinatorial chemistry.[17,18]

1.2 Nucleophile Cleavable Linkers

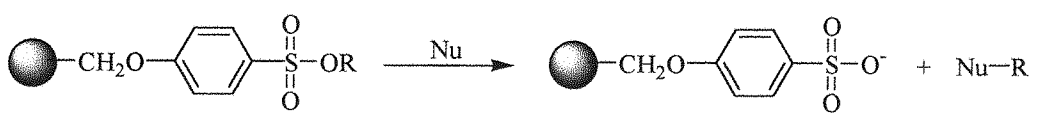
Cleavage of a substrate from the solid support using an intermolecular nucleophile can provide us with a great opportunity to introduce an extra element of diversity into a compound collection (scheme 11).[19]

Scheme 11



An excellent example of this involves the use of arylsulfonate esters in solid-phase organic synthesis (scheme 12).[20,21]

Scheme 12

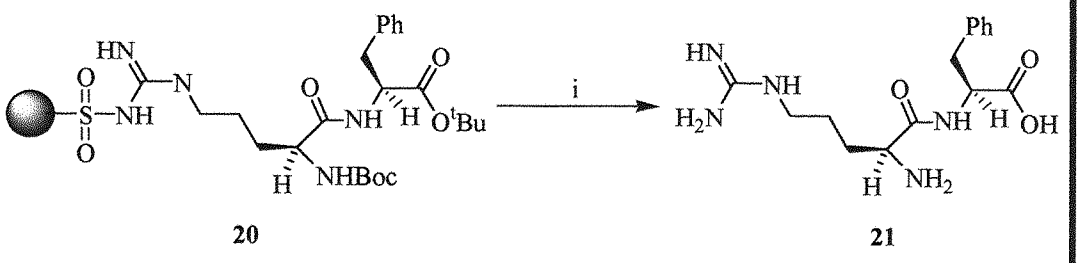


17 18 19

Where Nu = R_3N, $R_3S^-Na^+$, Imidazole

This was itself based on a linker developed by Maryanoff *et al*[22], involving the synthesis of arginine-containing peptides (scheme 13).

Scheme 13

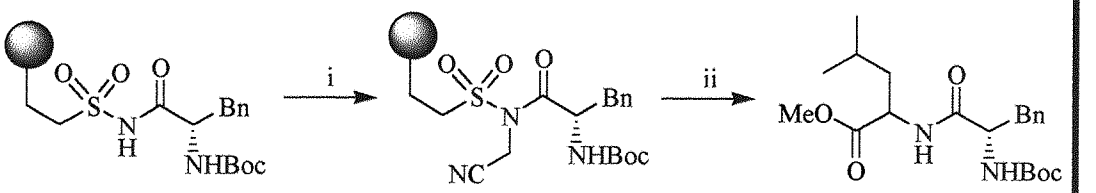


20 **21**

Reagents/conditions: i) HF, anisole, 0 °C, 4 h

A further derivative of these react and release linkers are the "safety-catch" linkers. These cannot be directly cleaved from the resin, and instead must first be activated toward nucleophilic attack (scheme 14).[19]

Scheme 14



22 **23** **24**

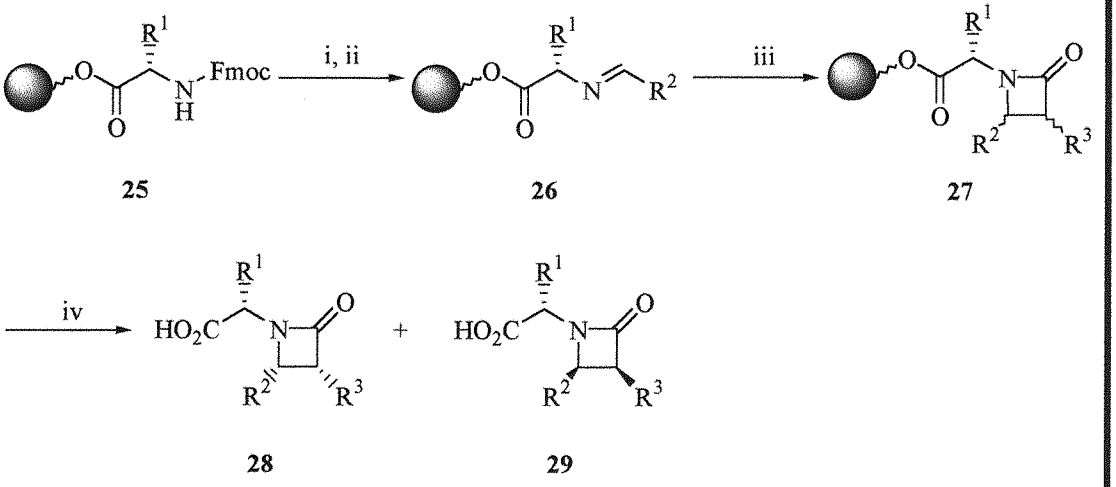
Reagents/conditions: (i) ICH_2CN, *i*-Pr_2NEt; (ii) Leu-OMe

This confers the obvious advantage that nucleophilic substitution reactions can be safely carried out on the resin without running the risk of prematurely cleaving any product.

1.3 [2+2] Cycloaddition Reactions

The β-lactam pharmacophore has for some time been of great clinical value as precursors of both monocyclic and bicyclic antibiotics. It is possible to form libraries of these compounds using the [2+2] cycloaddition reactions of ketenes with imines (scheme 15).[23]

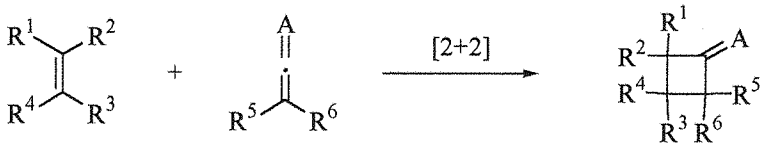
Scheme 15



Reagents/conditions: i) 30 % piperidine in NMP 45 minutes;
ii) 0.8 M R^2CHO in 1:1 $(MeO)_3CH:CH_2Cl_2$, 3 hours;
iii) 0.8 M R^3CH_2COCl, 1.1 M NEt_3 in CH_2Cl_2, 0 °C to 25 °C, 16 hours;
iv) 3 % TFA in CH_2Cl_2, 45 minutes.

[2+2] Cycloadditions can also be used to make other types of compound, indeed the reaction between ketenes or keteniminium salts and alkenes to form cyclobutanone containing species is well documented (scheme 16).[24] Satisfactory results can be achieved with ketene derivatives[25], but the best yields are often obtained with keteniminium salts due to their higher reactivity.[26-28]

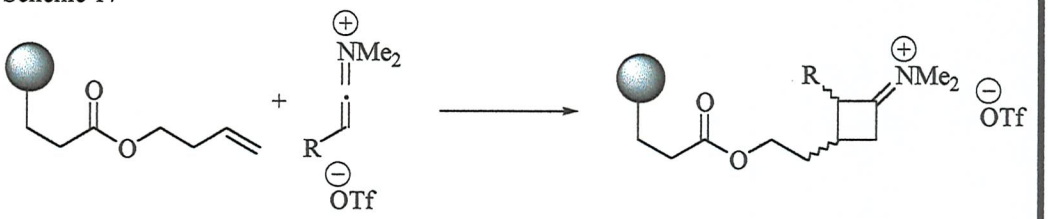
Scheme 16



The cyclobutane rings formed from these reactions have been the subject of great interest recently, compounds containing this cyclobutane moiety could provide new templates for the design of novel synthetic libraries. The [2+2] reaction detailed above provides us with an excellent entry point into the synthesis of highly derivatised cyclobutanones, cyclobutanols and cyclobutylamines. This synthetic pathway works

well in solution phase chemistry but it can also be effectively utilised on the solid-phase (scheme 17).

Scheme 17



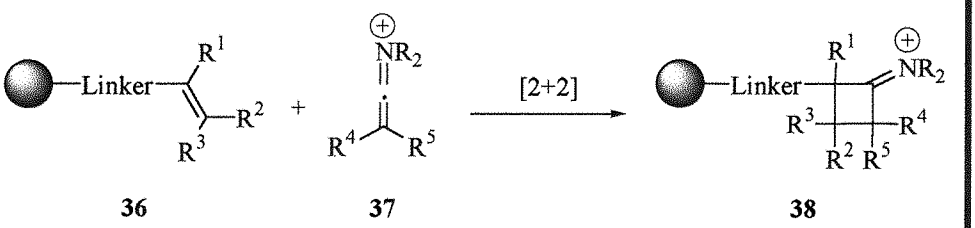
33 34 35

Compounds of this type can be very important synthetic intermediates and indeed derivatives of these intermediates can display significant biological activities, ranging from potential anti-cancer agents[29] to antibody peptidases[30] and many others. Therefore the availability of libraries based on these novel structures could have a large impact on the search for new therapeutic agents.

2. Aims and Objectives

The main objective of this research was to look into the ways in which we could manipulate resin-bound cyclobutanone containing compounds, with a view to using them as a core for library design. However, before this could be done it was necessary to optimise keteniminium-olefin [2+2] cycloaddition reactions on the solid-phase (scheme 18).

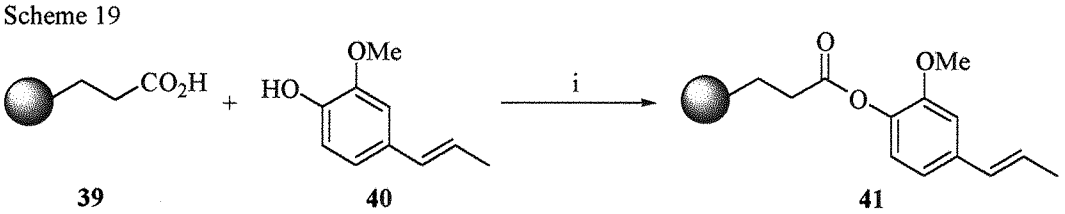
Scheme 18



36 **37** **38**

Work conducted previously within the research group has shown that an ester linkage will be stable to all the reaction conditions, and can be easily cleaved at the end of the synthesis. This ester linkage can be formed by the reaction of a carboxylated resin **39** with an alkenol **40** in order to make the alkene resin **41** (scheme 19).

Scheme 19



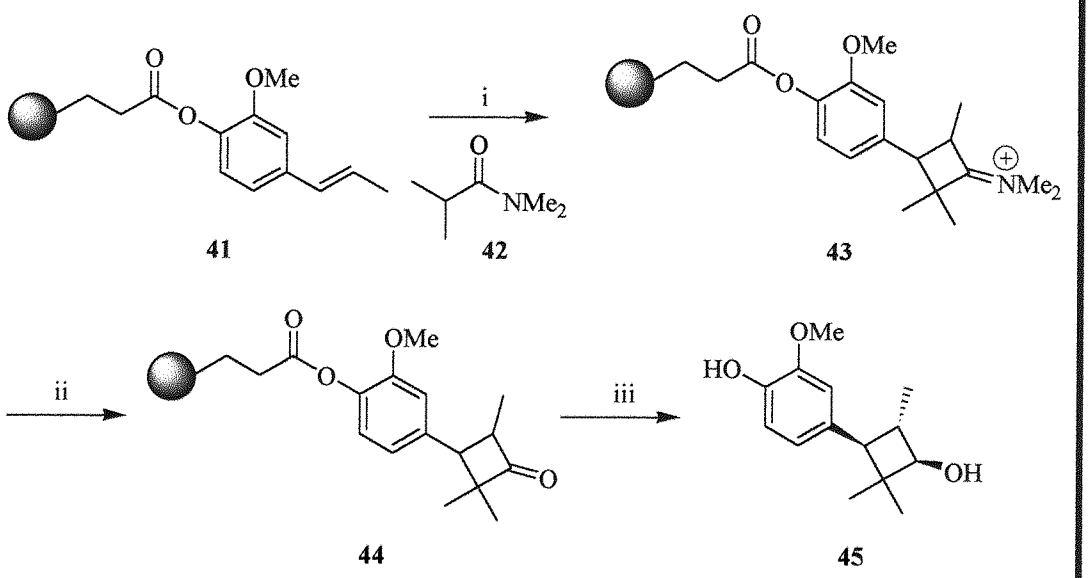
39 **40** **41**

Reagents/conditions: i) DIC, DMAP, CH_2Cl_2

In the long term, the objective will be to utilise the optimised [2+2] reaction sequence derived from Ghosez's keteniminium-olefin cycloaddition, to produce an array of compounds containing the cyclobutane moiety. Products such as these could provide interesting new templates to aid in the design of novel synthetic libraries.

Initial studies were to be carried out on the *iso*eugenol resin **41** (scheme 20) to demonstrate the effectiveness and viability of these reactions. At a later date it was hoped modifications could be made to increase the scope of the cycloadditions.

Scheme 20



Reagents/Conditions: i) Tf_2O, 2,6-di-*tert*-butylpyridine, CH_2Cl_2; (ii) $NaHCO_3$, THF; (iii) $LiBH_4$, MeOH, THF.

We decided to pursue two main approaches to increase the scope of the solid-phase [2+2] cycloaddition chemistry.

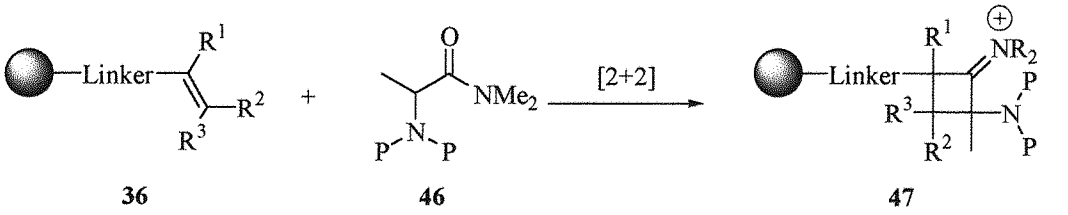
- Utilisation of a selection of amides in the formation of the keteniminium salt intermediate.
- Transformation of the linker used to increase diversity in the cleavage step.

2.1 Utilisation of Different Amides in [2+2] Cycloadditions

It can be imagined that if the amide used in the formation of the keteniminium salt intermediate has suitable functional groups, then it could serve as an excellent handle for further chemical manipulations of the cycloadducts **38** (scheme 18). For example, if instead of simply using *N,N*-dimethyl-isobutyramide, we were to replace one of the

methyl groups on the α-carbon with a protected amine, then we could envisage the deprotection and subsequent reaction of that group in the cycloadduct **47** (scheme 21).

Scheme 21

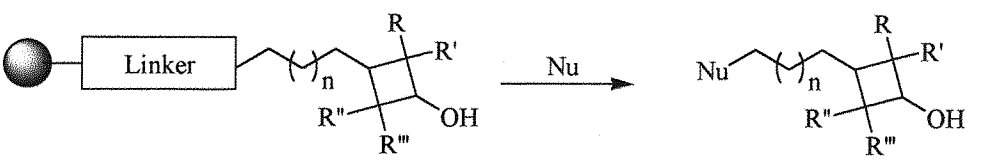


36 **46** **47**

2.2 Development of Linker Technologies

As previously mentioned it was our aim to modify existing linker technologies, in order to combine the cleavage step with the introduction of an additional position of variability. This should further increase the scope of these reactions, then we would have an effective method for the fast, simple formation of many different compounds (scheme 22).

Scheme 22



48 **49**

Nu = 1° and 2° amines, imidazole, NaSEt

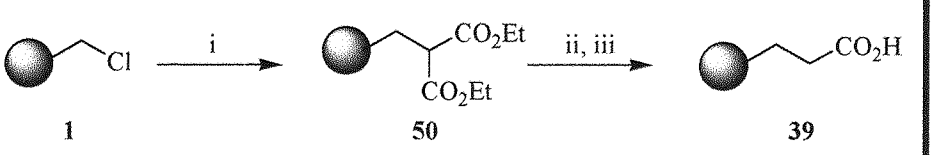
It is easy to see that by combining these two methodologies it is possible to generate a vast series of compounds with relatively few chemical manipulations, based on a novel template.

3. Results and Discussion

3.1 Preliminary Work

It was decided that a suitable entry point into this research would be to synthesise a sample of the acid resin **39** (scheme 23) and optimise the route towards 4-(3-hydroxy-2,2,4-trimethylcyclobutyl)-2-methoxyphenol (**45**) (scheme 20).

Scheme 23



1 **50** **39**

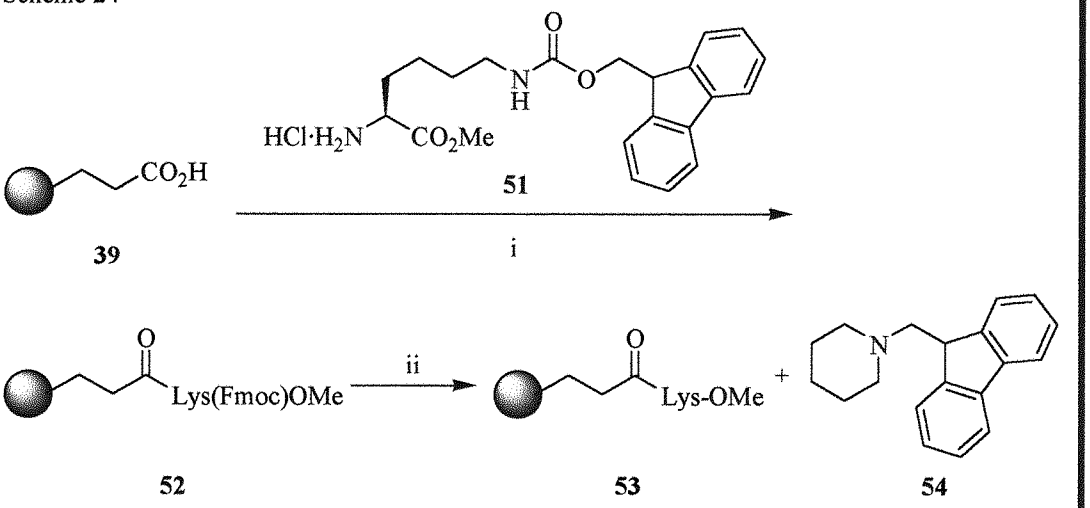
Reagents/conditions: i) Diethylmalonate, NaH, DMF; ii) KOH, THF; iii) HCl, THF

The acid resin **39** was synthesised with little difficulty, but before any quantitative results could be obtained for the cycloadditions, it was necessary to determine the resin loading. This was achieved using two methods:

- Analysis by Fmoc method with UV quantification of the fulvene adduct.
- Analysis of a cleaved sample using Gas Chromatography.

In order to accomplish this, acid resin **39** was coupled with *N*-ε-Fmoc-L-lysine methyl ester (**51**) and the Fmoc group subsequently cleaved with piperidine (scheme 24). In each of two 20 mL volumetric flasks, between 5 and 10 mg of resin **52** was accurately weighed out and suspended in approximately 10 mL of a solution of 20 % piperidine/DMF, then left to stand for 20 minutes. Each flask was then made up to 20 mL using more of the 20 % piperidine/DMF. A "blank" cuvette (control) was filled with the 20 % piperidine/DMF solution, whilst a second was filled with the mixture in one of the volumetric flasks. A sample of the reaction mixture could then be scanned for the presence of the tertiary amine **54** by measuring the UV absorbance at 302 nm against the control cuvette.

Scheme 24



Reagents/conditions: i) DIC, HOBt, DIPEA, NMP, CH_2Cl_2; ii) 20% piperidine/DMF

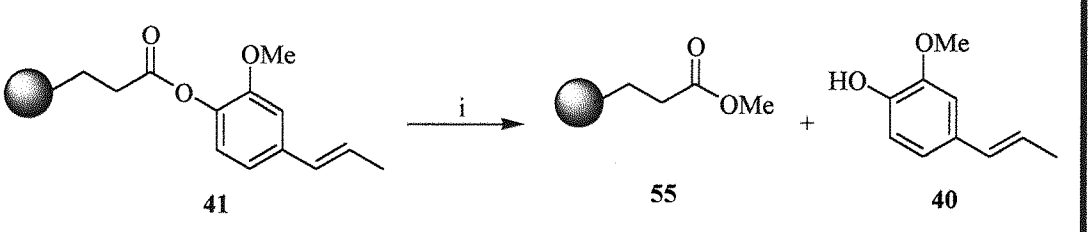
Using the Beer-Lambert law, this absorbance value can then be used to calculate the concentration of amine **54** in solution. Which can in turn be converted to a value for the loading of acid resin **39**.

$$[\text{Fmoc}]\ \text{mmol/g} = \frac{\text{Absorbance (302 nm) x Volume (mL) x 1000}}{\text{Mass (mg) x 7800 (extinction coefficient)}}$$

This method gave us a value for the loading of acid resin **39** of 0.38 mmol/g.

The second method of loading determination involved the utilisation of gas chromatography. In this example *iso*eugenol resin **41** was transesterified with methanol and potassium trimethylsiloxide (scheme 25).

Scheme 25



Reagents/conditions: i) KOTMS, MeOH, CH_2Cl_2

A known amount of naphthalene used as an internal standard can then be added to the reaction mixture, and the solution analysed by GC. The concentration of the released *iso*eugenol (**40**) in solution can then be compared to the naphthalene concentration in order to determine the resin loading, this method gave a loading of 0.64 mmol/g for the same batch of resin. It was decided that this second method was likely to be more accurate, and so the higher value was taken for the loading.

3.2 Solid-Phase [2+2] Cycloaddition Reactions

The carboxylated resin **39** was coupled with *iso*eugenol (**40**) to give the alkene resin **41**. This was to be the first system upon which all cycloadditions were to be carried out. Initial experiments were targeted at the formation of 4-(3-hydroxy-2,2,4-trimethylcyclobutyl)-2-methoxyphenol (**45**) as previously detailed (scheme 20). The *N*,*N*-dimethyl-isobutyramide (**42**) was synthesised in reasonable yield (62 %) from the isobutyryl chloride and was easily purified by vacuum distillation.

The formation of the iminium species **43** demonstrated that the cycloaddition of the alkene resin **41** with a keteniminium species (for results see table 1) was proceeding, analysis of resin **43** by on bead IR confirmed the presence of the iminium moiety. Originally the reaction was carried out at reflux, but subsequent optimisation has indicated that equally high yields are obtained at rt. For this particular reaction it seems that the highest yields are, unsurprisingly, realised with a great excess of solution reagents. The most cost-effective method though, seems to be with using 5 equivalents of the reagents, giving a yield of around the same figure but avoiding using large quantities of the expensive reagents Tf_2O and 2,6-di-*tert*-butylpyridine.

The next step in the synthesis was the hydrolysis of the immobilised iminium salt **43** to furnish the resin-bound cyclobutanone **44**. This was achieved readily by the use of aqueous $NaHCO_3$ over 3 hours at rt. Analysis of the filtrate by TLC indicated that none of the cyclobutanone species had been cleaved from the resin, subsequent on bead IR of the resin confirmed the presence of the C=O moiety (1767 cm^{-1}).

The final phase of the synthesis was the formation of the cyclobutanol **45**. This was accomplished by a $LiBH_4$ reduction of both the cyclobutanone group and also the ester linkage. The reaction proceeded in high yield (70 %), affording **45** as a mixture of 2 isomers. On bead IR analysis of the residual resin confirmed that there was no ester or ketone present, and analysis of the reaction mixture by TLC and NMR confirmed that none of the unreacted cyclobutanone had been released (table 1).[β]

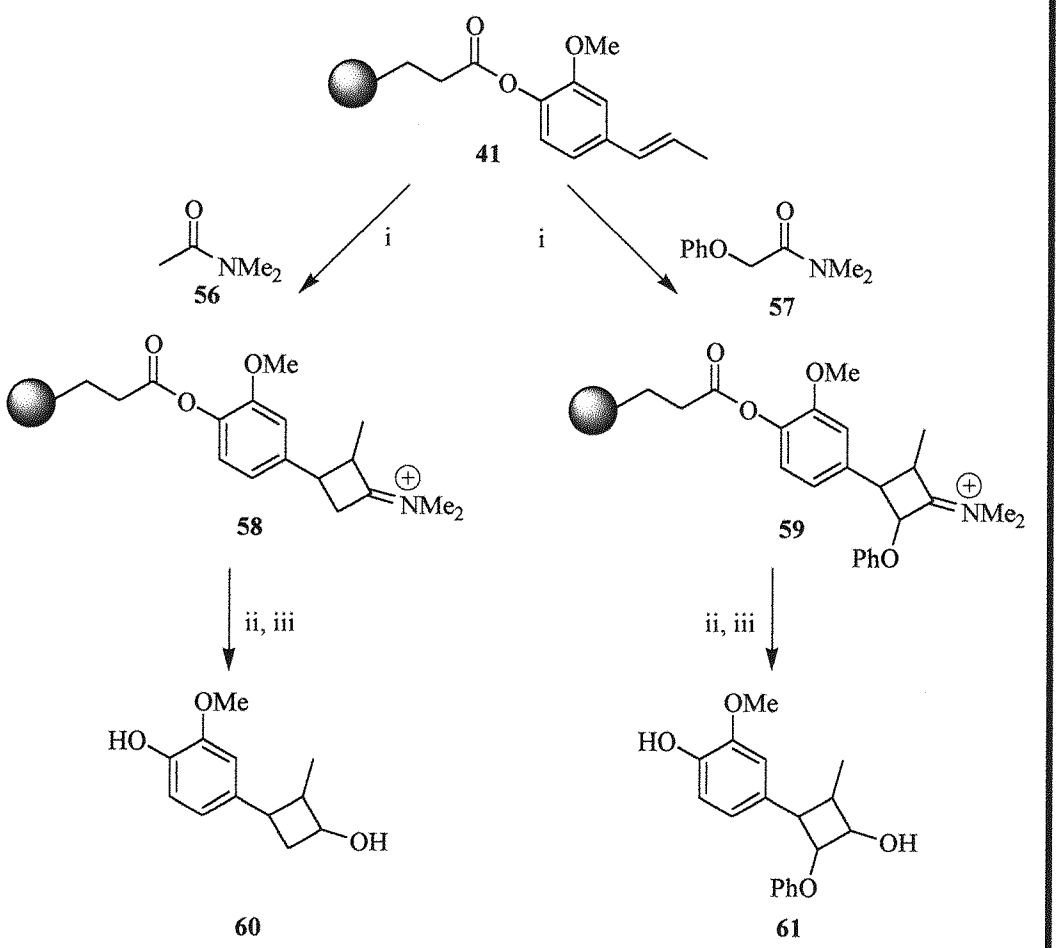
Table 1: Yields/conditions of reaction leading to the formation of cyclobutanol **45**

Cycloaddition reaction	**Hydrolysis of iminium salt**	**Cleavage ($LiBH_4$, MeOH)**	**Overall Yield**
25 eq. of all reagents, 16 hours, reflux	$NaHCO_3$ - 1 mL THF - 5 mL, 3 hours	4 eq. of all reagents, 22 hours, rt	73 %
10 eq. of all reagents, 16 hours, reflux	$NaHCO_3$ - 1 mL THF - 5 mL, 3 hours	2.5 eq. of all reagents, 22 hours, rt	70 %
10 eq. of all reagents, 16 hours, rt	$NaHCO_3$ - 1 mL THF - 5 mL, 3 hours	2.5 eq. of all reagents, 22 hours, rt	70 %
5 eq. of all reagents, 16 hours, rt	$NaHCO_3$ - 1 mL THF - 5 mL, 3 hours	2.5 eq. of all reagents, 22 hours, rt	69 %
2 eq. of all reagents, 16 hours, rt	$NaHCO_3$ - 1 mL THF - 5 mL, 3 hours	2.5 eq. of all reagents, 22 hours, rt	66 %

The next logical step was to continue the cycloadditions on the same resin, but making use of different amides in the first step. We decided to make use of *N,N*-dimethylacetamide (**56**) and *N,N*-dimethyl-2-phenoxyacetamide (**57**) (scheme 26).

[β] [2+2] Reactions were conducted using 250 mg of resin **41** in dichloromethane (3 mL)

Scheme 26



Reagents/conditions: i) Tf_2O, 2,6-di-*tert*-butylpyridine, CH_2Cl_2;

ii) $NaHCO_3$, THF; iii) $LiBH_4$, MeOH, THF.

The reaction conditions for this sequence were the same as those used for the previous [2+2] cycloaddition, and "on-bead" IR spectra taken of the iminium resin **58-59** indicated the possibility of the C=N stretch being visible. Likewise when hydrolysed, the corresponding cyclobutanone resins contained peaks that could be attributed to the ketone moiety. However when it came to the final step, that of the reductive cleavage, none of the desired products **60** or **61** was observed in the ^{1}H-NMR spectrum. The synthesis was therefore repeated using a higher concentration of reagents, and more forcing conditions. In the first step the solvent was changed from dichloromethane to dichloroethane (in order to raise the internal temperature), and the reaction stirred at 80

°C. Unfortunately though, there was still no product apparent in the ^{1}H-NMR. The range of conditions used in these reactions can be seen below (table 2).

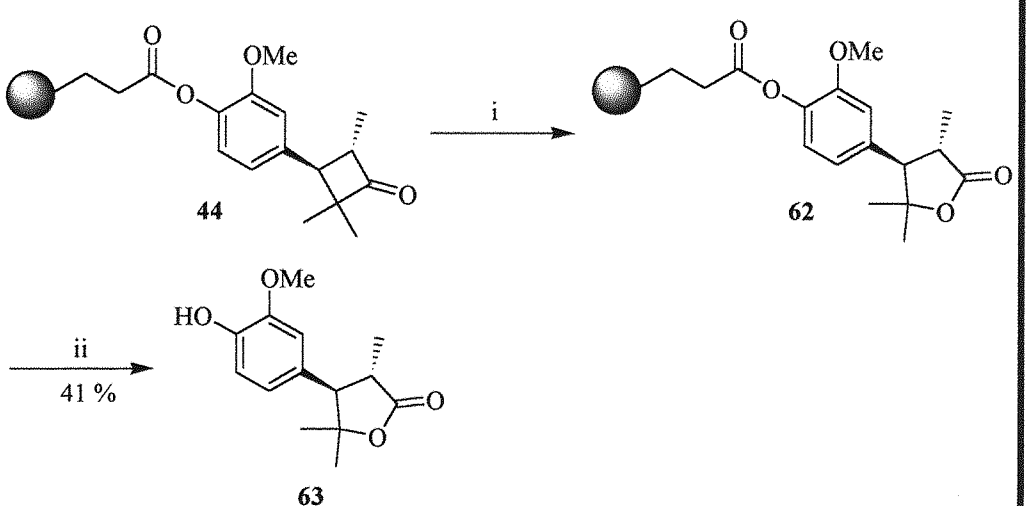
Table 2: Yields/conditions of reactions leading to the attempted formation of cyclobutanols **60** and **61**

Amide	[2+2]	Cleavage	Yield
2-Phenoxy	2.5 eq. all reagents	1.3 eq. $LiBH_4$	0 %
2-Phenoxy	5 eq. all reagents	1.3 eq. $LiBH_4$	0 %
2-Phenoxy	5 eq. all reagents DCE, 80 °C	2 eq. $LiBH_4$	0 %
2-Phenoxy	10 eq. all reagents DCE, 80 °C	5 eq. $LiBH_4$	0 %
DMA	5 eq. all reagents	2 eq. $LiBH_4$	0 %
DMA	5 eq. all reagents DCE, 80 °C	2 eq. $LiBH_4$	0 %

3.3 Developing the Range of Reactions

We wanted to demonstrate the fact that these cyclobutanone containing species could be used as intermediates in the formation of other compounds. To this end it was decided to investigate the synthesis of lactone **62** (scheme 27).

Scheme 27

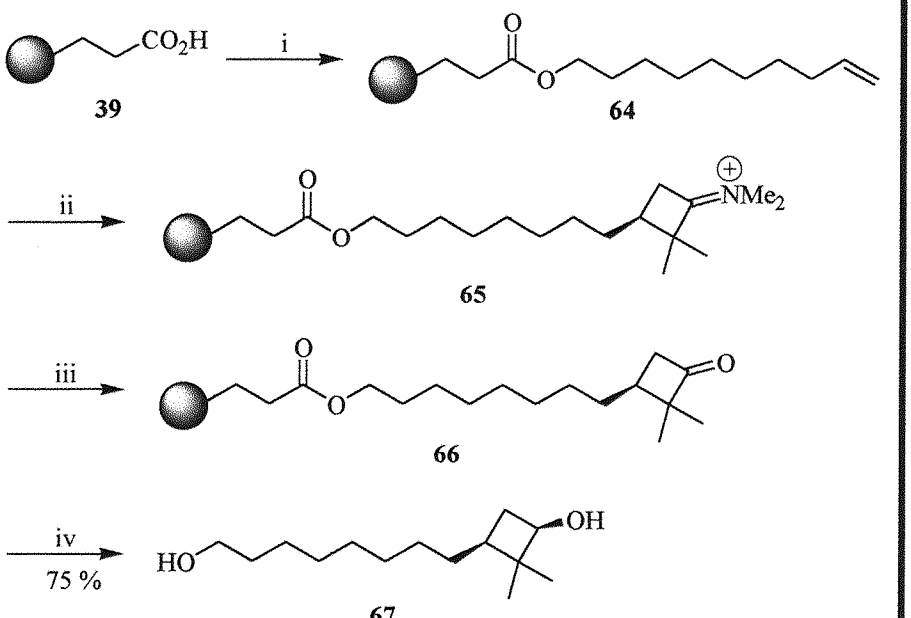


Reagents/conditions: i) mCPBA, CH_2Cl_2; ii) KOTMS, MeOH, CH_2Cl_2

Reaction of resin **44** with mCPBA in CH_2Cl_2 successfully gave the lactone **62**, as confirmed by the shift in the C=O signal in the IR from 1780 to 1764 cm^{-1}. This was then cleaved from the resin using KOTMS and MeOH, initial analysis of the reaction mixture indicated that there was no product present, but on repetition of the reaction the correct product **63** was obtained in reasonable yield (41 %).

It was our further intention to show that these cycloadditions would be viable using other alkenes as well. In order to achieve this, resin **64** was synthesised and taken through to form cyclobutanol **67** (scheme 28).

Scheme 28



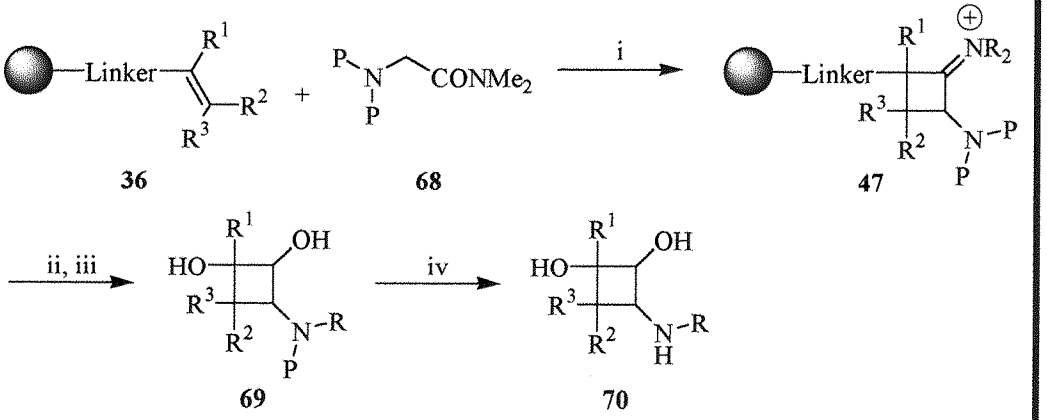
Reagents/conditions: i) DIC, 9-decen-1-ol, DMAP, CH_2Cl_2;
ii) Tf_2O, *N*, *N*-dimethyl-isobutyramide, 2,6-di-*tert*-butylpyridine, CH_2Cl_2;
iii) $NaHCO_3$, THF; iv) $LiBH_4$, MeOH, THF

The reaction sequence proceeded as expected, and analysis by ^{1}H-NMR confirmed that the desired cyclobutanol **67** was indeed present. This successfully demonstrated that we could synthesise these types of compounds on different resin systems. Therefore at this point it was decided to focus our efforts on synthesising further examples of cyclobutanols.

3.4 Expansion of the Diversity of the Cycloadditions

Now that the viability of these cycloadditions had been shown, it was predicted that if we could introduce some protected functionality into the cycloadditions using these amides, then at a later date the cycloadducts could be deprotected and used in further reactions (scheme 29).

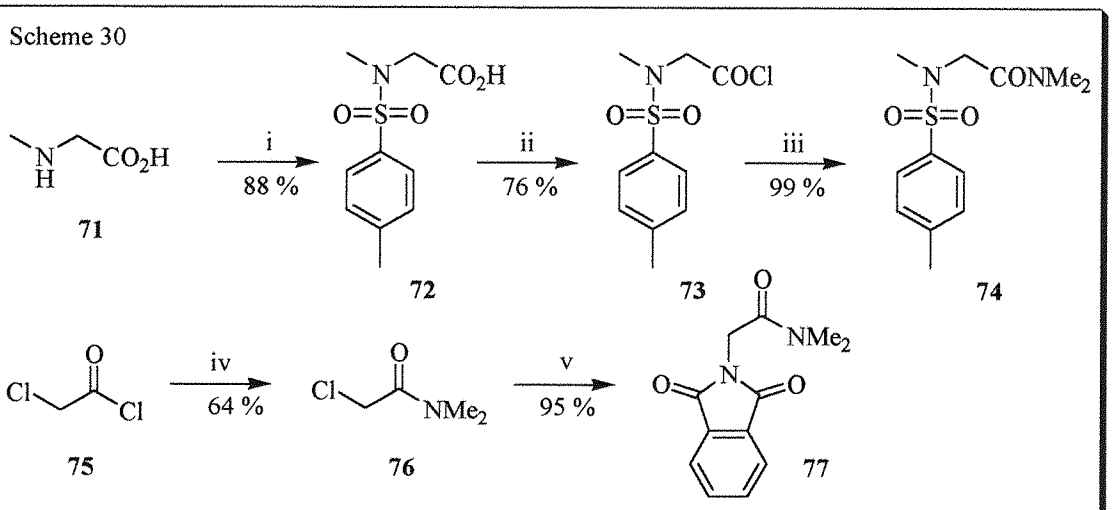
Scheme 29



Reagents/conditions: i) [2+2]; ii) Hydrolysis; iii) Cleavage; iv) Deprotection

It was therefore decided to synthesise two different amides for use in [2+2] cycloadditions, utilising the tosyl and phthalimide protecting groups, which could hopefully be removed at the end of the synthesis (scheme 30).

Scheme 30



Reagents/conditions: i) Tosyl chloride, *N,N*-diisopropylethylamine, CH_2Cl_2;
ii) PCl_5, DMF; iii) Dimethylammonium chloride, NEt_3, CH_2Cl_2;
iv) Dimethylammonium chloride, NEt_3, toluene; v) Potassium phthalimide, DMF.

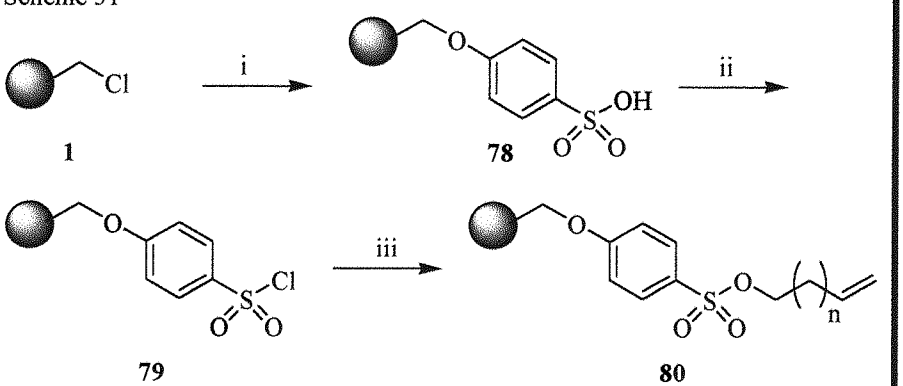
The synthesis of the phthalimide **77** was attempted first. The initial formation of the amide **76** proceeded in moderate yield (64 %) with the crude product easily purified by vacuum distillation.[29] The reaction of amide **76** with potassium phthalimide gave the desired compound **77** as a white solid, in high yield (95 %).[30]

The attempted synthesis of amide **74** began with the reaction of tosyl chloride with the amino acid sarcosine, using triethylamine as the base. The reaction provided a number of different products, and the resulting brown sludge proved difficult to purify, therefore it was necessary to try alternative conditions to synthesise compound **74**. The reaction between sarcosine (**71**) and tosyl chloride in aqueous NaOH, generated *N*-tosylsarcosine (**72**) as a white solid (88 %).[31] The acid **72** was then converted to the acid chloride **73** with PCl_5 in good yield (76 %). It was then a simple matter to react acid chloride **73** with dimethylamine hydrochloride, affording amide **74** as an off-white solid in excellent yield (99 %).

3.5 Nucleophile Cleavable Linkers

One of the main aspects to this research involved the synthesis and utilisation of a nucleophile cleavable linker. It was decided that the linker we would attempt to use would be the sulfonyl linker **78** detailed below (scheme 31).[22]

Scheme 31



Reagents/conditions: i) Base, 4-hydroxybenzenesulfonic acid sodium salt, DMA; ii) PCl_5, DMF; iii) Alkenol, NEt_3, CH_2Cl_2

The first step in the synthesis involved the reaction of Merrifield resin (**1**) with 4-hydroxybenzenesulfonic acid sodium salt. The commercial sodium salt was bought as

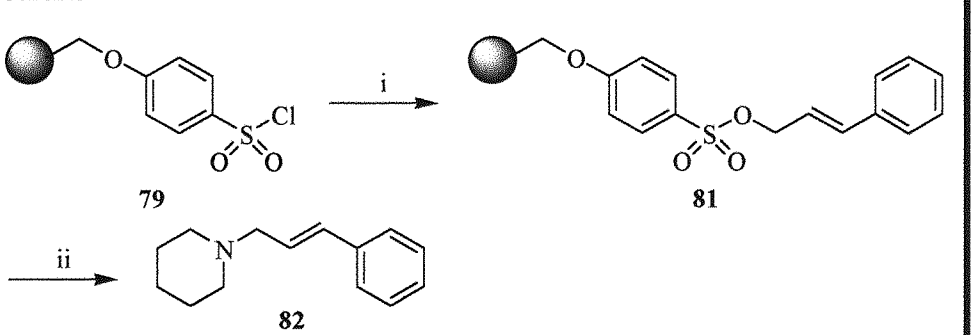
the dihydrate, and subsequently dehydrated and used in the reaction. Initial attempts at the synthesis of resin **78** using a solution of sodium methoxide in methanol as the base, however analysis of the resin by "on bead" IR did not show the presence of any S=O bands. So the reaction was repeated using a range of bases (table 3).

Table 3: Bases used in attempted synthesis of resin **78**

Base	**S=O present in IR**
NaOMe / MeOH	No
NaOMe powder	No
KI, K_2CO_3	No
NaH	No
KO^tBu	No

Although there were no S=O peaks present in any of the IR spectra, it remained a possibility that the reactions had worked to some extent but for some reason the peaks were very weak. Due to this fact it was decided to continue the synthesis of the linker forward with a batch of the resin **78**, form the sulfonyl chloride, couple it with an alcohol and then immediately cleave with piperidine. If the correct product was present in the resulting reaction mixture, it would indirectly prove that the linker had been successfully made. The literature[22] claimed that the best method for the formation of the sulfonic acid resin **78** used NaOMe powder, so it was this batch of resin that was reacted with PCl_5 in an attempt to make the sulfonyl chloride resin **79**. Once again there were no S=O peaks present in the IR, but nonetheless resin **79** was reacted with cinnamyl alcohol and then piperidine to determine for certain whether or not the reaction sequence had been successful (scheme 32).

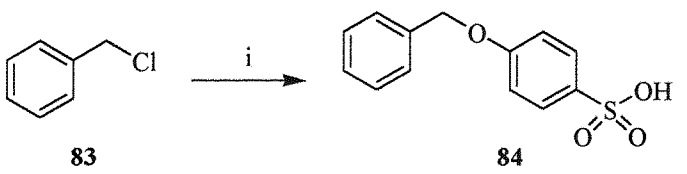
Scheme 32



Reagents/conditions: i) Cinnamyl alcohol, NEt_3, CH_2Cl_2;
ii) Piperidine, CH_3CN

Analysis of the reaction mixture by ^{1}H-NMR indicated that none of the desired cleaved product **82** was present, instead the only observable peaks belonged to the piperidine. This can be explained by the fact that the previous steps in the synthesis had as previously feared been unsuccessful, as had been initially surmised by the IR. This result was further confirmed by the equivalent solution phase reaction (scheme 33), none of the desired product **84** was observable in the ^{1}H-NMR.

Scheme 33



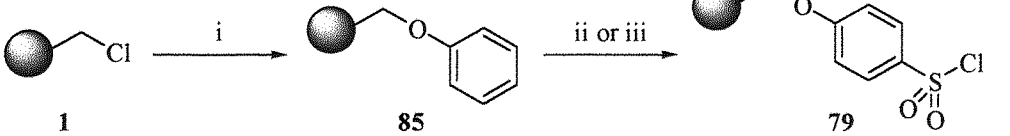
83 **84**

Reagents/conditions: i) NaH, 4-hydroxybenzenesulfonic acid, DMA

It is possible that the failure of this synthesis can be attributed to the fact that the 4-hydroxybenzenesulfonic acid sodium salt may not have been anhydrous, resulting in any water present being deprotonated in favour of the phenolic proton due to the presence of the sulfonate anion.

At this point it was decided that we were unlikely to get this reaction sequence to work to any satisfactory degree. Therefore it became necessary to discover another route to a nucleophile cleavable linker of this type, there were three viable options proposed. The first two involved the formation of resin **85** in order to insert a spacer into the linker, followed by lithiation and subsequent reaction with sulfuryl chloride, or by direct sulfonation of resin **85**, leading straight to the sulfonyl chloride **79** (scheme 34).[32]

Scheme 34

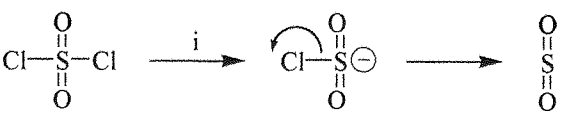


1 **85** **79**

Reagents/conditions: i) Phenol, NaI, Cs_2CO_3, DMF; ii) SO_2Cl_2, DMF; iii) ^{n}BuLi, then SO_2Cl_2, DMF

It was decided that it would be logical to initially attempt the direct sulfonation of resin **85** due to the instability of sulfuryl chloride (**86**) when exposed to organolithium compounds (scheme 35). The sulfuryl chloride undergoes a lithium-halogen exchange with the organolithium to give intermediate **87**, which then loses chloride to form sulfur dioxide **88**.

Scheme 35



86 **87** **88**

Reagents/conditions: i) R-Li

The reaction between resin **85** and sulfuryl chloride (**86**) was analysed by "on bead" IR, which established that there were no S=O groups attached to the resin. This led to the need to resort to the third option to form the linker, the direct sulfonation of polystyrene resin. The literature[34] showed that cross-linked polystyrene resin could be directly sulfonated by reaction with chlorosulfonic acid (scheme 36).

Scheme 36

89 **90**

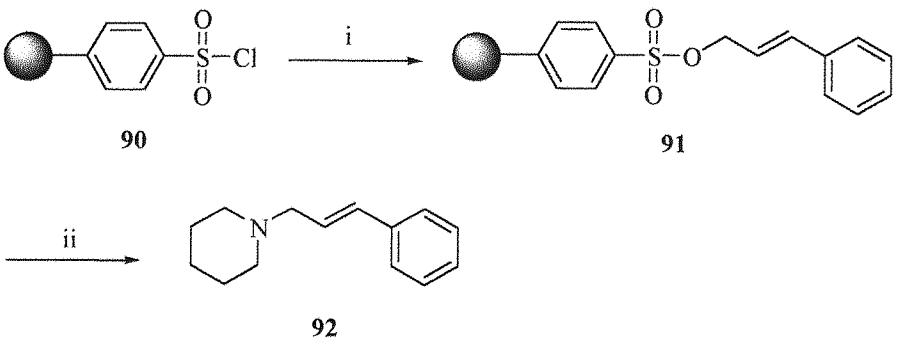
Reagents/conditions: i) $ClSO_3H$, CCl_4.

In this method, a portion of 1 % cross-linked polystyrene resin was suspended in carbon tetrachloride and carefully treated with chlorosulfonic acid. An instant colour change in the resin from white to orange/brown was observed, and subsequent analysis of the sample by on bead IR was dominated by the presence of two very strong bands at 1368 and 1168 cm^{-1}. These corresponded to the S=O bands, confirming that sulfonation of the resin had been successful.

Before any cycloaddition chemistry could be carried out on resin **90**, it was important to ascertain whether or not a suitable molecule could be coupled to the resin and

subsequently cleaved. If this were to prove problematic it would mean that an alternative source of linker would have to be found. In order to test the viability of this resin for our needs, a small sample was coupled with cinnamyl alcohol and then cleaved with piperidine in acetonitrile (scheme 37).

Scheme 37

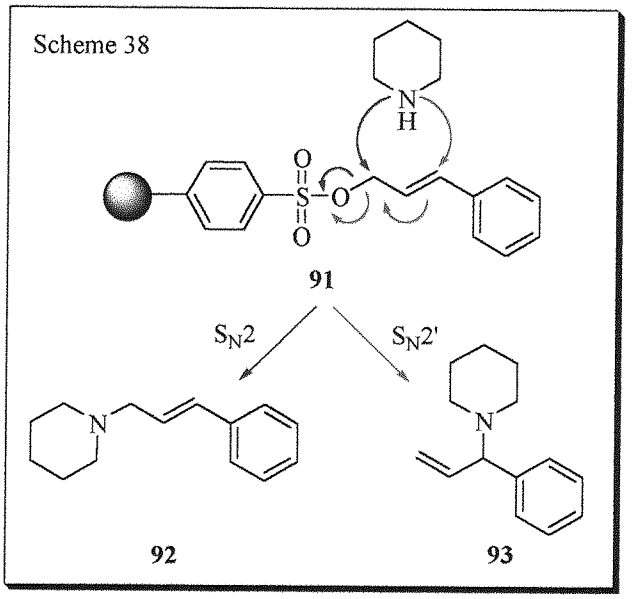


90 **91** **92**

Reagents/conditions: i) Cinnamyl alcohol, Et_3N, CH_2Cl_2; ii) Piperidine, CH_3CN.

Analysis of the sulfonate resin **91** by on bead IR revealed a shift in the S=O bands to 1211 and 1175 cm^{-1}, indicating that the coupling had been successful. The cleavage step suggested a mixture of two products **92** and **93**, corresponding to the point of attack by the nucleophile (scheme 38), however, the NMR was not clean and the exact nature of the products was not certain.

Scheme 38

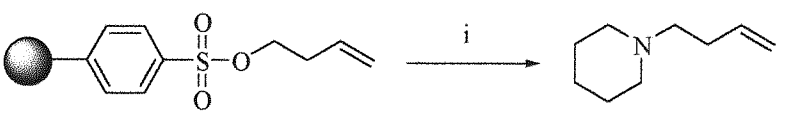


91 **92** **93**

This result proved that the nucleophile cleavable linker was indeed cleavable by nucleophiles, although it was unfortunate that the alcohol chosen for the coupling gave

a mixture of products when cleaved. Therefore the logical stage to proceed with was to couple the sulfonyl chloride resin **90** with a different alcohol that would only grant one product, in this case 3-buten-1-ol was chosen (scheme 39).

Scheme 39

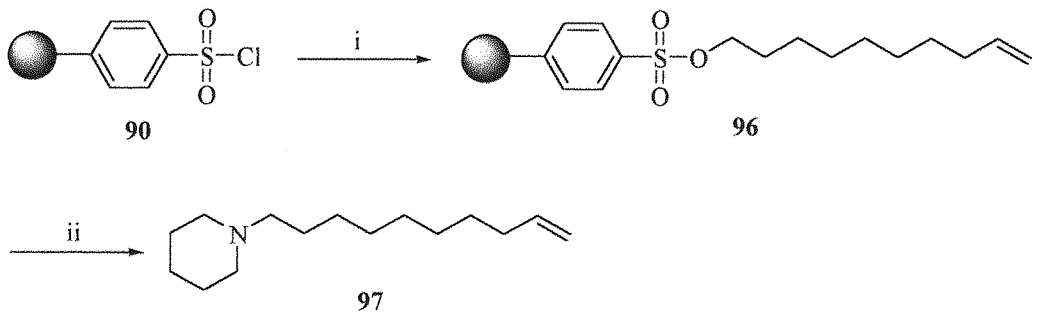


94 **95**

Reagents/conditions: i) Piperidine, CH_3CN.

However, none of the desired product was observed in the ^{1}H-NMR spectrum. This could be explained by the fact that in the presence of base (piperidine), resin **94** could be deprotonated leading to the elimination of 1,3-butadiene. This meant that neither resin **91** nor resin **94** would be suitable linkers upon which to carry out [2+2] cycloaddition reactions, therefore another alkenol had to be used. It was postulated that coupling of 9-decen-1-ol onto sulfonyl chloride resin **90** would provide us with a linker that should only give one product on cleavage, and serve as an effective system on which to investigate cycloaddition reactions (scheme 40).

Scheme 40



90 **96**

97

Reagents/conditions: i) 9-Decen-1-ol, Et_3N, CH_2Cl_2; i) Piperidine, CH_3CN.

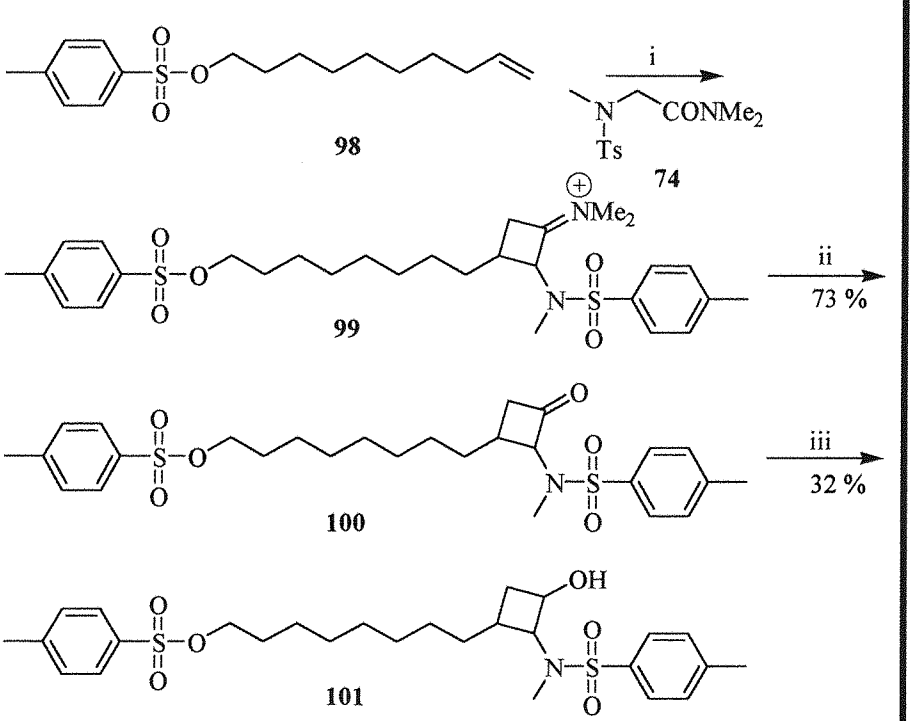
Reaction of sulfonyl chloride resin **90** with 9-decen-1-ol successfully gave resin **96**, the IR showed the presence of S=O peaks at 1348 and 1171 cm^{-1}. The subsequent cleavage of the tertiary amine *N*-(9-decenyl)piperidine (**97**) was also successful and analysis by ^{1}H-NMR indicated that only one compound had been released into

solution. The yield for this reaction was taken as being 100 %, thus enabling us to calculate yields for any other reactions using the nucleophile cleavable linker. This meant that we now had a linker that would be suitable for our [2+2] cycloadditions.

3.6 Solid-Phase [2+2] Cycloaddition Reactions with Nucleophile Cleavable Linkers

We now knew that our linker could be successfully cleaved with nucleophiles, but before we subjected it to any [2+2] cycloadditions, we wanted to investigate the equivalent solution phase reactions. In order to accomplish this, toluene-4-sulfonic acid dec-9-enyl ester (**98**) was synthesised in high yield (78 %), which could then be used in our cycloadditions (scheme 41).

Scheme 41

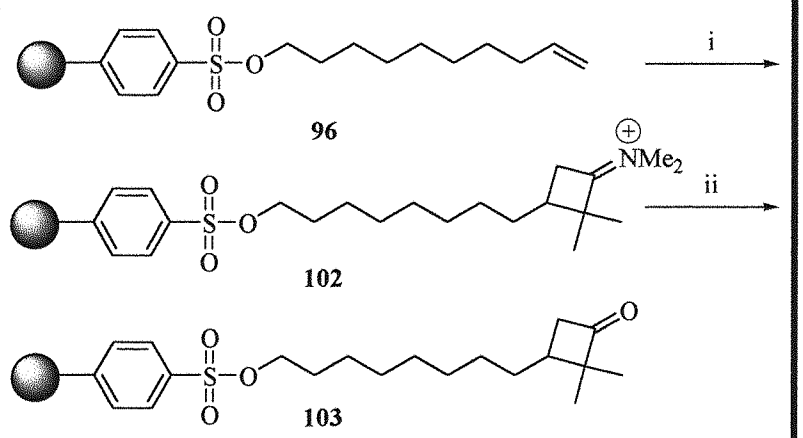


Reagents/conditions: i) Tf_2O, 2,6-di-*tert*-butylpyridine, CH_2Cl_2; ii) H_2O; iii) $NaBH_4$, $CeCl_3$, MeOH, THF

Cyclobutanone **100** was successfully synthesised from alkene **98** in high yield (73 %), the ^{1}H-NMR spectrum indicating the presence of the desired compound. The corresponding reduction of the ketone to the cyclobutanol **101** was also achieved,

providing **101** in poor yield (32 %). The success of these reactions meant that we could attempt the equivalent sequence on the solid-phase. The first cycloaddition to be attempted on the nucleophile cleavable linker, was with *N*,*N*-dimethyl-isobutyramide (**42**) (scheme 42).

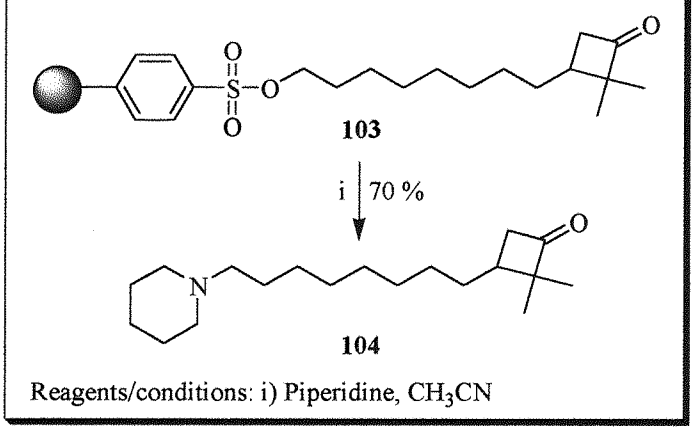
Scheme 42



Reagents/conditions: i) *N*, *N*-dimethyl-isobutyramide, Tf_2O, 2,6-di-*tert*-butylpyridine, CH_2Cl_2; ii) $NaHCO_3$, THF

The sulfonyl linker **96** was reacted with amide **42** in the presence of Tf_2O and 2,6-di-*tert*-butylpyridine in CH_2Cl_2, analysis of the resin by IR indicated that an iminium species was definitely present. The hydrolysis to the ketone also proceeded without problems, the next step was to attempt to cleave both the cyclobutanone species from the resin (scheme 43).

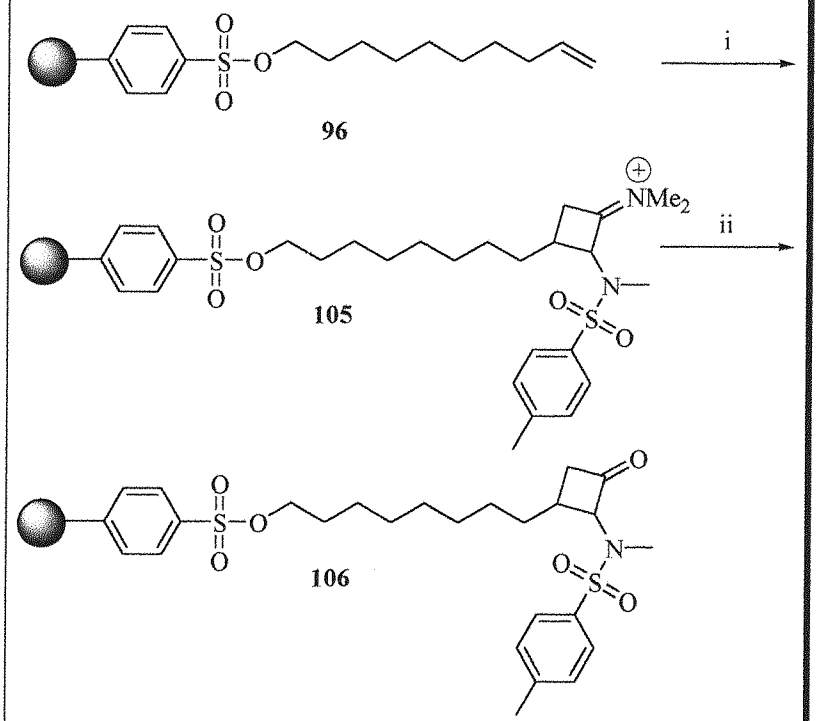
Scheme 43



Reagents/conditions: i) Piperidine, CH_3CN

Analysis of the resulting reaction mixture by ^{1}H-NMR and IR (1774 cm^{-1}, C=O) showed that we had indeed successfully synthesised the correct product, in good yield (70 %). The logical choice for the next sequence to attempt, was the [2+2] cycloaddition between the sulfonate resin **96** and one of the amides with a protected nitrogen functionality, initially 2-(toluene-4-sulfonyl-methyl-amino)-*N*,*N*-dimethylacetamide (**74**) (scheme 44).

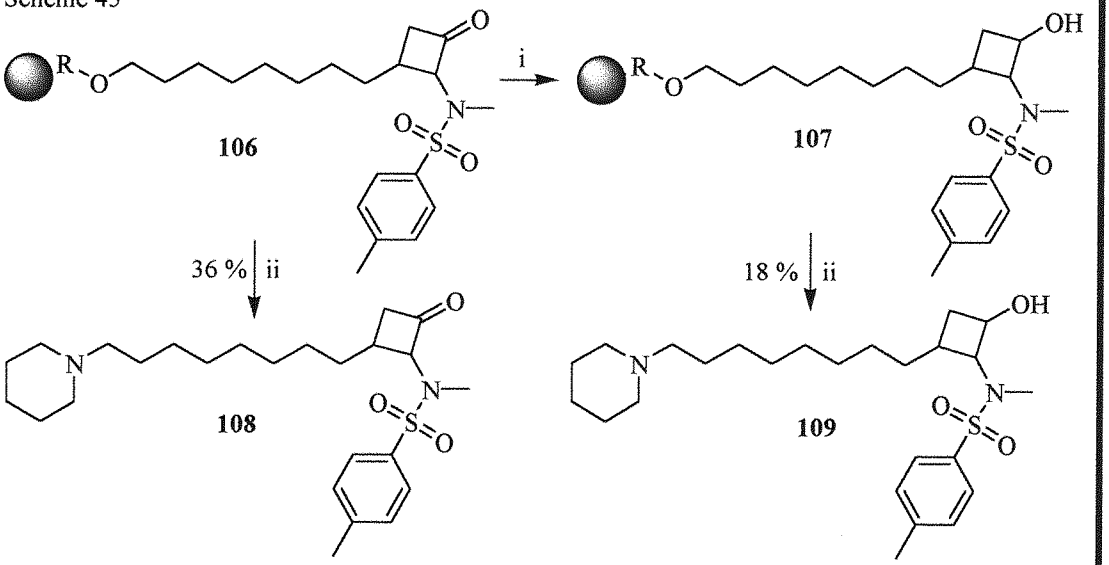
Scheme 44



Reagents/conditions: i) *N*,*N*-dimethyl-isobutyramide, Tf_2O, 2,6-di-*tert*-butylpyridine, CH_2Cl_2; ii) $NaHCO_3$, THF

Once again we were pleased to note that on bead IR confirmed that resins **105** and **106** had been synthesised. This time it was decided to attempt to release not only the cyclobutanone **108** but the corresponding cyclobutanol **109** as well (scheme 45). Unfortunately, the cleavage of these two compounds proved partially to be problematic. The ^{1}H-NMR of both compounds suggested that the reactions had been successful albeit in modest yield (36 % and 18 %), but we were unable to purify either compound to any satisfactory degree. A possible explanation of the low yield of cyclobutanol **109** could be the premature cleavage of resin **107** under the basic reaction conditions.

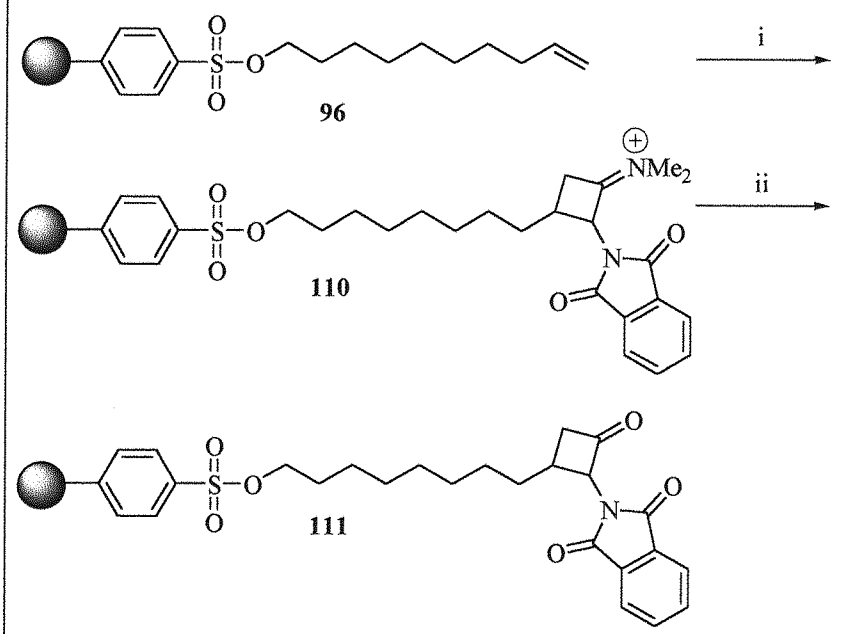
Scheme 45



Reagents/conditions: i) $NaBH_4$; ii) Piperidine, CH_3CN R = -$PhSO_2$-

We also wanted to attempt the equivalent [2+2] cycloadditions using phthalimide **77** synthesised earlier (scheme 46). However, analysis of both the cyclobutanone iminium species **110** and the corresponding ketone **111** by on bead IR, indicated that in each case the desired functional groups (C=N and C=O) were not present. It seems likely

Scheme 46



Reagents/conditions: i) 2-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-*N*, *N*-dimethylacetamide, Tf_2O, 2,6-di-*tert*-butylpyridine, CH_2Cl_2; ii) $NaHCO_3$, THF

that the explanation for this lies in the phthalimide group interfering with the initial cycloaddition reaction.

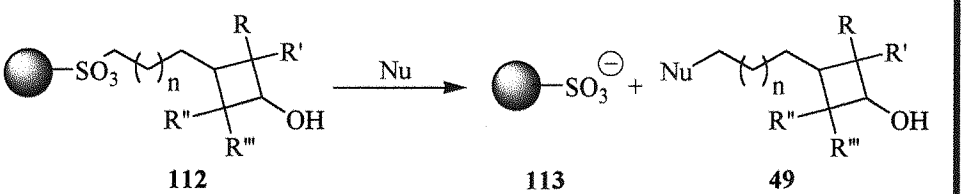
4. Conclusions

Throughout the course of this research we have illustrated that keteniminium-olefin [2+2] cycloaddition reactions can be achieved in high yield on the solid-phase. A range of different cyclobutanones and cyclobutanols has been successfully synthesised and by subtly changing the structure of the reactants, it should be relatively facile to produce a large number of these compounds.

It has been shown that when compared to the solution-phase cycloadditions, the corresponding solid-phase reactions are often much higher yielding, and display several other key advantages. Specifically, these are the much greater ease of purification of the compounds, and many of the reactions can be forced to completion if we use a large excess of reagents. A further interesting advantage displayed by the solid-phase route, is the ability it gives us to isolate the cyclobutanone iminium species, something not possible using solution-phase methods.

We have demonstrated the successful use of a nucleophile cleavable sulfonyl linker, and have proven that [2+2] cycloadditions are compatible with such a linker (scheme 47).

Scheme 47

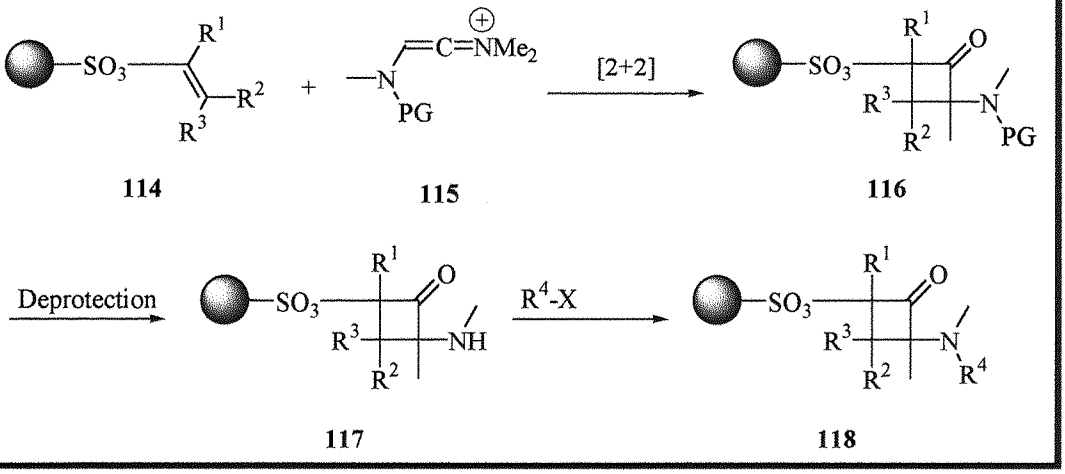


112 **113** **49**

Nu = 1^{o} and 2^{o} amines, imidazole, NaSEt

We have shown that by modifying the amide used in the cycloaddition, it is possible to introduce protected functional groups into the cyclobutanones. This protecting group can then be subsequently removed, allowing further chemical derivatisation using this newly introduced functionality (scheme 48).

Scheme 48



114 **115** **116**

117 **118**

5. Experimental

5.1 General Procedures

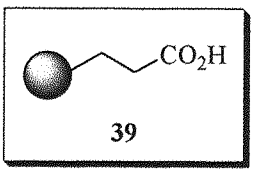
IR spectra were recorded on a Perkin-Elmer FT-IR spectrometer. A Bio-Rad FTS 135 spectrometer was used to record "on bead" spectra. The abbreviations s (strong), m (medium), w (weak) and br (broad) are used when reporting the data. ^{1}H-NMR and ^{13}C-NMR spectra were recorded in $CDCl_3$ solution using a Bruker AC300 (300 and 75 MHz respectively), a Bruker AM300 (as for the AC300) or a Bruker DPX400 (400 and 100 MHz respectively). Chemical shifts are reported in δ units with $CHCl_3$ being used as an internal standard. The abbreviations s (singlet), d (doublet), t (triplet), q (quartet) and m (multiplet) are used when reporting the data. Coupling constants (*J*) are reported in Hz. Mass spectra were recorded on a Fisons VG platform single quadrupole mass spectrometer in electron spray ionisation mode, relative abundances are reported in brackets after the mass. Merck Kieselgel 60 was used for column chromatography. Thin layer chromatography was performed using Merck silica gel 60 F_{254}, and visualised under UV, with iodine, or by staining with solutions of potassium permanganate or phosphomolybdic acid. UV absorbance spectra were recorded on a Hewlett Packard 8452A diode array spectrophotometer. All solvents were purified and dried using standard techniques.

5.2 Synthesis

5.2.1 Purification of Polystyrene Resin

Following the method of Farrall *et al*,[36] polystyrene resin (5 g, 1 % cross-linked) was washed with 60-80 °C solutions of aqueous 1N NaOH, aqueous 1N HCl, aqueous 2N NaOH/1,4-dioxane (1:2), aqueous 2N HCl/1,4-dioxane (1:2), H_2O and DMF. The resin was then washed with rt solutions of aqueous 2N HCl/MeOH (1:1), H_2O, MeOH, MeOH/CH_2Cl_2 (1:3), MeOH/CH_2Cl_2 (1:10) (50 mL of each). The resin was then collected by filtration and dried *in vacuo* at 50 °C for 2 days.

5.2.2 Resin 39

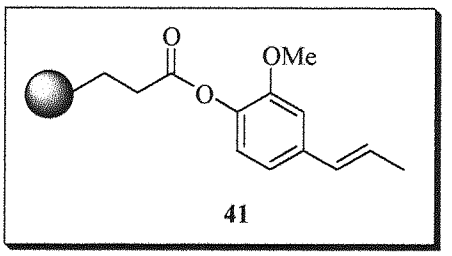


39

To a suspension of resin **50** (5 g), in THF (75 mL) was added aqueous 2N KOH (7.5 mL) and the reaction stirred at reflux for 20 hours. The resin was collected by filtration and washed with H_2O, MeOH and CH_2Cl_2 (40 mL of each). The resin (5 g) was then re-suspended in THF (75 mL) and aqueous 2N HCl (7.5 mL) was added and the reaction stirred at reflux for 4 hours then cooled to rt. The resin was collected by filtration and washed with H_2O, MeOH and CH_2Cl_2 (40 mL of each) then dried *in vacuo* at 50 °C.

IR (on bead) ν/cm^{-1}: 3026 (w), 2916 (m), 2851 (w), 1714 (s), 1599 (m), 1494 (s), 1444 (s).

5.2.3 Resin 41

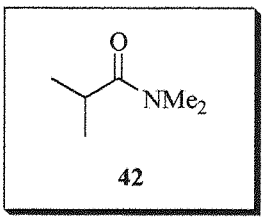


41

To a suspension of the carboxylated resin **39** (4 g) in CH_2Cl_2 (20 mL) was added *iso*eugenol (31) (3.28 g, 20 mmol), DMAP (122 mg, 1mmol) and DIC (3.13 mL, 20 mmol). The reaction was then stirred at rt for 20 hours, filtered and washed with CH_2Cl_2, MeOH, H_2O and CH_2Cl_2 (all 25 mL) then dried *in vacuo* at 50 °C to yield resin **41** (4.5 g).

IR (on bead) ν/cm^{-1}: 3025 (m), 2921 (s), 1735 (m), 1600 (m), 1508 (m), 1493 (m), 1451 (m).

5.2.4 *N,N*-Dimethyl-isobutyramide 42



42

To a solution of dimethylamine hydrochloride (11.5 g, 141 mmol), CH_2Cl_2 (50 mL) and NaOH (2 N, 187 mL) was added isobutyryl chloride (9.83 mL, 94 mmol) dropwise at 0 °C. The reaction was then stirred at rt for 20 hours, at which time ether (150 mL) was added, the layers separated and the organic phase washed with brine (50 mL), aqueous 2N HCl (25 mL), brine (50 mL) and $NaHCO_3$ (50 mL, sat. solution). The organic phase was dried ($MgSO_4$) and the solvent removed *in vacuo*. The crude mixture was then purified by vacuum distillation, to furnish the product **42** as a colourless oil (6 g, 52.2 mmol, 62 %).

Spectroscopic data were in agreement with that reported in the literature.[35]

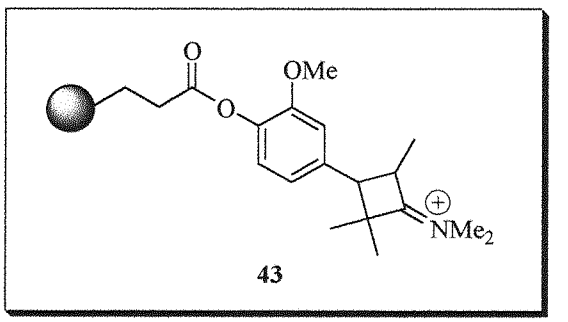
^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 2.98 (3H, s, -N(C**H**$_3$)(CH$_3$)), 2.87 (3H, s, -N(CH$_3$)(C**H**$_3$)), 2.75 (1H, septet, -C**H**(CH$_3$)$_2$, *J*=6.5 Hz), 1.01 (6H, d, -CH(C**H**$_3$)$_2$, *J*=6.5 Hz).

^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 177.1 (**C**=O), 37.1 (-N(**C**H$_3$)(CH$_3$)), 35.6 (-N(CH$_3$)(**C**H$_3$)), 30.2 (-**C**H(CH$_3$)$_2$), 19.3 (-CH(**C**H$_3$)$_2$).

IR (neat) ν/cm^{-1}: 3483 (m), 3276 (w), 2970 (m), 2934 (m), 2874 (m), 1644 (s), 1505 (m), 1399 (m).

MS (ES$^+$; MeCN) *m/z*: 253.4 (2M+Na)$^+$, 231.3 (2M+H)$^+$. Calculated for $C_6H_{13}NO$, m=115.

5.2.5 Resin 43

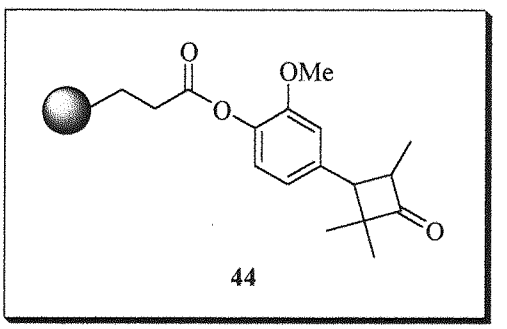


43

To a solution of *N,N*-dimethyl-isobutyramide (**42**) (575 mg, 5 mmol) in CH_2Cl_2 (8 mL) was added trifluoromethanesulfonic anhydride (840 μL, 5 mmol) dropwise at 0 °C under N_2. After 2 minutes 2,6-di-*tert*-butylpyridine (1.12 mL, 5 mmol) was added followed by the alkene resin **41** (500 mg) and the reaction was stirred for 20 hours at rt. The brown suspension was then filtered and washed with CH_2Cl_2 (20 mL), THF (10 mL), H_2O (5 mL) and CH_2Cl_2 (10 mL), then dried *in vacuo* at 50 °C to yield the iminium resin **43** (500 mg).

IR (on bead) ν/cm^{-1}: 3024 (w), 2926 (m), 1763 (cyclobutanone C=O, m), 1729 (m), 1602 (m), 1511 (m), 1493 (m), 1452 (s).

5.2.6 Resin 44

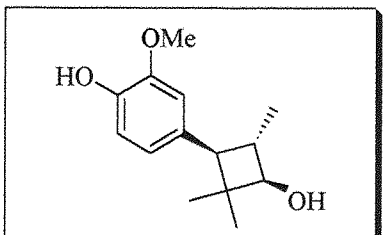


44

To a suspension of the iminium resin **43** (500 mg) in THF (5 mL) was added $NaHCO_3$ (1 mL, sat. aqueous solution) and the reaction stirred for 3 hours at rt. The reaction was then filtered and washed with CH_2Cl_2, THF, H_2O and CH_2Cl_2 (2 x 7 mL of each), then dried *in vacuo* at 50 °C to yield the cyclobutanone resin **44** (450 mg).

IR (on bead) ν/cm^{-1}: 3022 (w), 2922 (m), 1767 (s), 1732 (m), 1602 (m), 1493 (m), 1451 (m).

5.2.7 4-(3-Hydroxy-2,2,4-trimethylcyclobutyl)-2-methoxyphenol (45)



45

To a suspension of the cyclobutanone resin **44** (260 mg) in THF (4 mL) at –78 °C was added $LiBH_4$ (250 µL, 2 M solution in THF, 0.5 mmol) followed by MeOH (20 µL, 0.5 mmol). The mixture was allowed to warm to rt in the cold bath over a period of 1 hour and then stirred for a further 20 hours. The reaction was then filtered and washed with NH_4Cl (15 mL, sat. solution) and CH_2Cl_2 (15 mL), the phases were separated and extracted with CH_2Cl_2. The organic phase was then dried (Na_2SO_4) and the solvent removed *in vacuo*, yielding the crude product as a mixture of 2 isomers (20 mg). The residue was then purified by column chromatography (SiO_2, 1.5 x 21 cm, ether/hexane 1:1) to yield the 2 diastereoisomers.

Isomer 1: R_f = 0.135 {ether/hexane 1:1}, 6 mg, 0.025 mmol, 21 %.
Isomer 2: R_f = 0.270 {ether/hexane 1:1}, 14 mg, 0.059 mmol, 48 %.

Isomer 1:

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 6.86 (1H, d, C**H** aromatic, *J*=8.0 Hz), 6.63 (1H, d, C**H** aromatic, *J*=8.0 Hz), 6.59 (1H, s, C**H** aromatic), 5.54 (1H, s, -O**H**), 3.89 (3H, s, -OC**H**$_3$), 3.43 (1H, d, -C**H**(OH), *J*=6.5 Hz), 2.32 (2H, m, -C**H**(CH_3) & -C**H**(Ar)), 1.22 (3H, s, -C(C**H**$_3$)CH_3), 1.21 (3H, d, -CH(C**H**$_3$), 0.66 (3H, s, -C(CH_3)(**C**H_3).

^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 146.5 (**C**(OCH_3) aromatic), 144.1 (**C**(OH) aromatic), 131.3 (**C** aromatic), 120.1 (**C**H aromatic), 114.3 (**C**H aromatic), 110.1 (**C**H aromatic), 79.5 (-**C**H(OH)), 56.0 (-**C**H(Ar)), 49.9 (-O**C**H_3), 44.7 (-**C**(CH_3)$_2$), 40.2 (-**C**H(CH_3)), 28.7 (-CH(**C**H_3)), 17.7 (-C(**C**H_3)(CH_3)), 16.4 (-C(CH_3)(**C**H_3)).

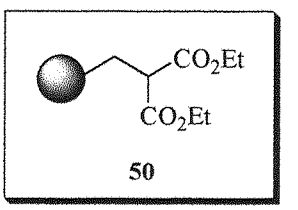
Isomer 2:

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 6.85 (1H, d, C**H** aromatic, *J*=8.0 Hz), 6.63 (1H, d, C**H** aromatic, *J*=8.0 Hz), 6.60 (1H, s, C**H** aromatic), 5.50 (1H, s, -O**H**), 3.91 (1H, d, -C**H**(OH)), 3.89 (3H, s, -OC**H**$_3$), 2.96 (1H, d, C**H**R_2(Ar)), 2.78 (1H, m, C**H**(CH_3)), 1.15 (3H, s, -C(C**H**$_3$)CH_3), 1.11 (3H, d, -CH(C**H**$_3$)), 0.73 (3H, s, -C(CH_3)C**H**$_3$).

^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 146.5 (**C**(OCH_3) aromatic), 144.1 (**C**(OH) aromatic), 131.3 (**C** aromatic), 120.0 (**C**H aromatic), 114.1 (**C**H aromatic), 110.1 (**C**H aromatic), 75.5 (-**C**H(OH)), 56.0 (-**C**(CH_3)$_2$), 54.1 (-O**C**H_3), 33.6 (**C**H(Ar)), 29.9 (-**C**(CH_3)$_2$), 22.8 (-CH(**C**H_3)), 22.7 (-C(**C**H_3)(CH_3)), 12.6 (-C(CH_3)(**C**H_3)).
IR (neat) ν/cm^{-1}: 3422 (br s), 2951 (m), 2926 (m), 2866 (m), 1604 (w), 1514 (s), 1459 (m), 1258 (s).

MS (ES^+; MeCN) *m/z*: 238.1 (9), 237.1 (61) $(M+H)^+$. Calculated for $C_{14}H_{20}O_3$, m=236.

5.2.8 Resin 50

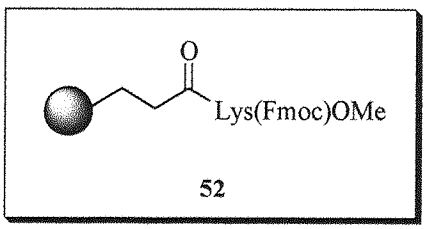


50

Diethylmalonate (3.80 mL, 25 mmol) was added dropwise to a suspension of NaH (1.00 g, 25 mmol) in DMF (25 mL) over a period of 30 minutes at 0 °C with evolution of H_2. After 10 minutes Merrifield's resin (5 g, 5 mmol, 1mmol/g) was added and the reaction stirred at 60 °C for 18 hours. The resin was collected by filtration and washed with CH_2Cl_2, MeOH, H_2O and CH_2Cl_2 (2 x 20 mL of each), then dried *in vacuo* at 50 °C.

IR (on bead) ν/cm^{-1}: 3021 (w), 2921 (m), 2851 (w), 1724 (s), 1599 (m), 1499 (s), 1444 (s).

5.2.9 Resin 52

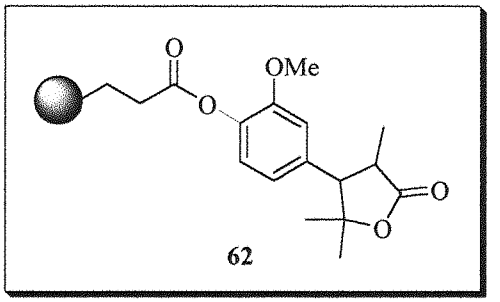


52

To a suspension of the carboxylated resin **39** (100 mg) in CH_2Cl_2 (1 mL) was added DIC (50 μL, 0.3 mmol) and HOBt (40 mg, 0.3 mmol) and the reaction stirred for 30 minutes at rt. A solution of H-Lys(Fmoc)-OMe.HCl (**51**) (130 mg, 0.35 mmol) in NMP (1 mL) and DIPEA (50 μL, 0.3 mmol) was then added and the reaction stirred at rt for 20 hours under nitrogen. The resin was collected by filtration and washed with CH_2Cl_2, DMF, CH_2Cl_2, MeOH and CH_2Cl_2 (15 mL of each), then dried *in vacuo* at 50 °C to give resin **52** as a yellow solid.

IR (on bead) ν/cm^{-1}: 2922 (m), 1726 (s), 1675 (s), 1600 (m), 1490 (s), 1445 (s).

5.2.10 Resin 62

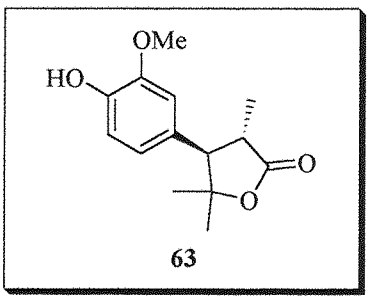


62

To a suspension of the cyclobutanone resin **39** (500 mg) in CH_2Cl_2 (5 mL) was added mCPBA (720 mg, 70 %, 2.5 mmol) and the reaction stirred at rt for 20 hours. The resin was collected by filtration and washed with CH_2Cl_2, H_2O, MeOH and CH_2Cl_2 (2 x 20 mL).

IR (on bead) ν/cm^{-1}: 3026 (w), 2926 (m), 1764 (s), 1727 (s), 1599 (m), 1499 (m), 1444 (m).

5.2.11 4-(4-Hydroxy-3-methoxyphenyl)-3, 5, 5-trimethyltetrahydro-2-furanone (63)



63

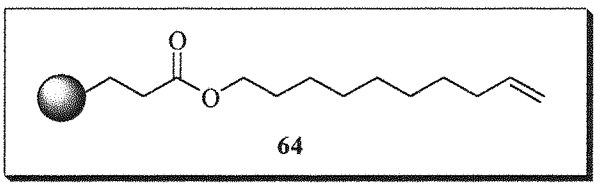
To a suspension of the lactone resin **62** (200 mg) in CH_2Cl_2 (2 mL) was added KOTMS (130 mg, 1 mmol) then MeOH (200 μL, 4 mmol) and the reaction stirred at rt for 20 hours. The resin was collected by filtration and washed with CH_2Cl_2, MeOH, H_2O and CH_2Cl_2 (2 x 5 mL of each), the filtrate was concentrated *in vacuo* to give the lactone **63** as a colourless oil (12 mg, 0.048 mmol, 41 %).

^{1}H-NMR (300 MHz, $CDCl_3$) δ/ppm: 7.71 (1H, dd, C**H** aromatic, *J*=6.0, 3.5 Hz), 7.54 (1H, dd, C**H** aromatic, *J*=6.0, 3.5 Hz), 4.23 (4H, m, -OC**H**$_3$ & -C**H**(Ar)), 1.68 (1H, quintet, -C**H**(CH_3), *J*=6.2 Hz), 0.93 (3H, s, -C**H**$_3$), 0.91 (3H, s, -C**H**$_3$).

^{13}C-NMR (75 MHz, $CDCl_3$) δ/ppm: 131.0 (aromatic **C**H), 130.0 (aromatic **C**H), 68.3 (-**C**(CH_3)$_2$), 38.9 (-O**C**H_3), 30.5 (-**C**H(Ar)), 29.1 (-**C**H(CH_3)), 23.9 (-C(CH_3)(**C**H_3)), 23.2 (-C(**C**H_3)(CH_3)), 11.1 (-CH(**C**H_3)). Unable to visualise carbonyl and quaternary aromatic carbons.

IR (neat) ν/cm^{-1}: 2961 (m), 2931 (m), 2861 (w), 1733 (s), 1464 (w), 1268 (s), 1123 (m), 1068 (m).

5.2.12 Resin 64

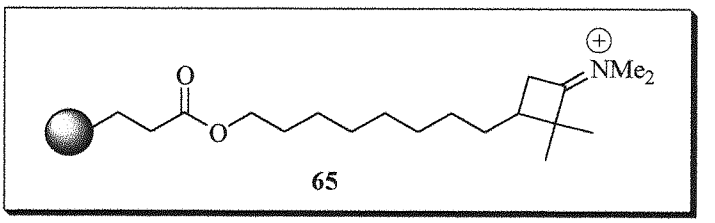


64

To a suspension of the acid resin **39** (800 mg) in CH_2Cl_2 (6 mL) was added 9-decen-1-ol (720 μL, 4 mmol), DMAP (25 mg, 0.2 mmol) and DIC (625 μL, 4 mmol) and the reaction stirred at rt for 24 hours. The resin was collected by filtration and washed with CH_2Cl_2, MeOH, H_2O and CH_2Cl_2 (2 x 20 mL of each) then dried *in vacuo* at 50 °C.

IR (on bead) ν/cm^{-1}: 3024 (w), 2920 (m), 1730 (s), 1601 (m), 1492 (s), 1450 (s).

5.2.13 Resin 65

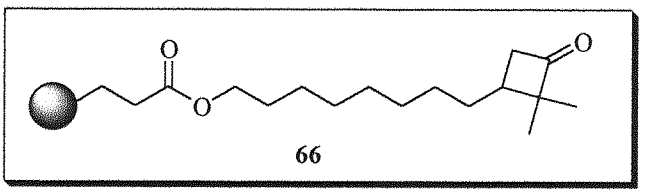


65

To a solution of *N*,*N*-dimethyl-isobutyramide (**42**) (115 mg, 1mmol) in CH_2Cl_2 (3 mL) at 0 °C under nitrogen was added Tf_2O (170 μL, 1 mmol) with stirring. After 2 minutes 2,6-di-*tert*-butylpyridine (225 μL, 1 mmol) was added followed by resin **64** (200 mg). The reaction was allowed to warm to rt over a period of 30 minutes and then stirred at rt for a further 20 hours. The resin was collected by filtration and washed with CH_2Cl_2, MeOH, H_2O and CH_2Cl_2 (2 x 15 mL of each) then dried *in vacuo* at 50 °C.

IR (on bead) ν/cm^{-1}: 3021 (w), 2921 (m), 2851 (w), 1769 (w), 1729 (s), 1494 (s), 1444 (s).

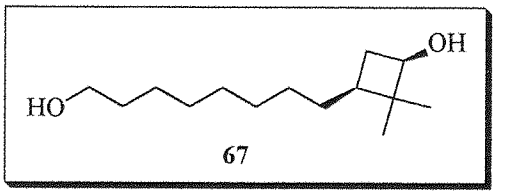
5.2.14 Resin 66



66

To a suspension of resin **65** (200 mg) in THF (3 mL) was added $NaHCO_3$ (1 mL, sat. aqueous solution) and the reaction stirred at rt for 4 hours. The resin was collected by filtration and washed with CH_2Cl_2, H_2O, MeOH and CH_2Cl_2 (2 x 10 mL of each) then dried *in vacuo* at 50 °C.

IR (on bead) ν/cm^{-1}: 3021 (w), 2921 (m), 2851 (w), 1769 (s), 1729 (s), 1494 (s), 1444 (s).



67

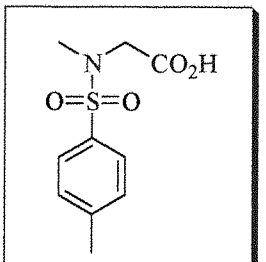
To a suspension of resin **66** (50 mg) in THF (1 mL) was added $LiBH_4$ (160 μL, 2N soln. In THF, 0.313 mmol) then MeOH (13 μL, 0.313 mmol) at 0 °C. The reaction was allowed to warm to rt over a period of 30 minutes and then stirred at rt for a further 20 hours. The reaction was collected by filtration and washed with NH_4Cl (sat. aqueous solution) and THF (2 x 20 mL). The phases were separated and the aqueous phase extracted with CH_2Cl_2 (3 x 10 mL). The organic phases were combined, dried (Na_2SO_4) and the solvent removed *in vacuo* granting cyclobutanone **67** as a colourless oil (4 mg, 0.018 mmol, 75 %).

^{1}H-NMR (300 MHz, $CDCl_3$) δ/ppm: 3.70 (1H, t, -C**H**(OH), *J*=8.0 Hz), 3.66 (2H, t, -C**H**$_2$OH, *J*=6.6 Hz), 2.28-2.35 (2H, m, -C**H**$_A$**H**$_B$CH(OH)), 1.88-1.95 (1H, m, -C**H**-C(CH_3)(CH_3)), 1.25-1.40 (12H, m, -C**H**$_2$), 1.07 (3H, s, -C**H**$_3$), 0.94 (3H, s, -C**H**$_3$).

^{13}C-NMR (75 MHz, $CDCl_3$) δ/ppm: 72.5 (**C**H(OH)), 63.2 (**C**H_2OH), 37.1 (-**C**(CH_3)$_2$), 35.2 (-**C**H_2CH(OH)), 32.9 (-**C**$H_2$$CH_2$OH), 30.2 (-**C**$H_2$-), 29.9 (-**C**$H_2$-), 29.7 (-**C**$H_2$-), 29.5 (-**C**$H_2$-), 28.4 (-**C**$H_2$-), 28.2 (-**C**$H_2$-), 25.9 (**C**H-C($CH_3$)$_2$), 22.6 (-**C**$H_3$), 14.9 (-**C**$H_3$).

IR (neat) ν/cm^{-1}: 3392 (br w), 2926 (m), 2851 (m), 1649 (m), 1459 (m), 1404 (m), 1338 (m), 1263 (m), 1163 (m), 1008 (m).

5.2.16 *N*-Methyl-*N*-(toluene-4-sulfonyl) glycine (72)



72

Following the method of DeRuiter *et al*,[33] a solution of sarcosine (**71**) (2.67 g, 30 mmol) and NaOH pellets (2.40 g, 60 mmol) in H_2O (30 mL) was added tosyl chloride (5.72 g, 30 mmol) portionwise over a period of 30 minutes at 60 °C. After complete addition the reaction was stirred for an additional 30 minutes at 60 °C then cooled to 0 °C, and acidified to pH 1 with cHCl yielding the crude product as a thick, white precipitate isolated by filtration. This was purified by recrystallisation (EtOH) granting the product **72** as a white solid (6.40 g, 26 mmol, 88 %).

^{1}H-NMR (300 MHz, $CDCl_3$) δ/ppm: 7.70 (2H, d, aromatic C**H**, *J*= 8.4 Hz), 7.32 (2H, d, aromatic C**H**, *J*= 8.4 Hz), 3.97 (2H, s, -NC**H**$_2$-), 2.87 (3H, s, -NC**H**$_3$), 2.44 (3H, s, ArC**H**$_3$).

^{13}C-NMR (75 MHz, $CDCl_3$) δ/ppm: 173.8 (**C**=O), 144.0 (aromatic **C**), 135.0 (aromatic **C**), 129.9 (aromatic **C**H), 127.6 (aromatic **C**H), 51.1 (-N**C**H$_2$-), 36.0 (-N**C**H$_3$), 21.7 (Ar**C**H$_3$).

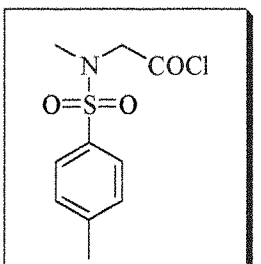
IR (neat) ν/cm^{-1}: 3171-2400 (br m), 1722 (s), 1598 (m), 1433 (m), 1338 (s), 1243 (m), 1158 (s), 1088 (m), 1022 (m), 936 (s).

MPt.: 147-149 °C, slightly lower than the literature values.[37]

MS (ES$^-$) *m/z*: 486.3 (26), 485.3 (100, (2M-H)$^-$). Calculated for $C_{10}H_{13}NO_4S$, m=243.

CAS No.: 2644-99-7.

5.2.17 *N*-Methyl-*N*-(toluene-4-sulfonyl) glycyl chloride (73)



73

To a stirred suspension of PCl_5 (4.11 g, 19.8 mmol) in toluene (40 mL) at 0 °C was added *N*-methyl-*N*-(toluene-4-sulfonyl) glycine (**72**) (4.00 g, 16.5 mmol) and the mixture stirred for 2 hours, and then for a further hour at rt. The reaction was then concentrated *in vacuo* to one-third volume and hexane (30 mL) added, the resulting suspension was filtered through celite to furnish the crude product as an off-white solid. This was purified by recrystallisation (EtOH) yielding the pure acid chloride **73** as a white solid (3.30 g, 12.6 mmol, 76 %).

^{1}H-NMR (300 MHz, $CDCl_3$) δ/ppm: 7.69 (2H, d, aromatic C**H**, *J*= 8.4 Hz), 7.34 (2H, d, aromatic C**H**, *J*= 8.4 Hz), 4.44 (2H, s, -NC**H**$_2$-), 2.90 (3H, s, -NC**H**$_3$), 2.45 (3H, s, ArC**H**$_3$).

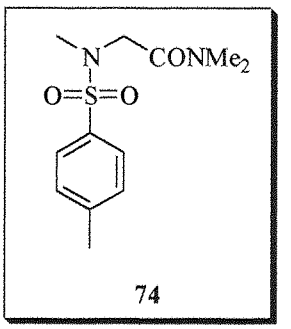
^{13}C-NMR (300 MHz, $CDCl_3$) δ/ppm: 170.3 (**C**=O), 144.4 (aromatic **C**), 135.0 (aromatic **C**), 130.0 (aromatic **C**H), 127.5 (aromatic **C**H), 60.3 (-N**C**H$_2$-), 35.6 (-N**C**H$_3$), 21.7 (Ar**C**H$_3$).

IR (neat) ν/cm^{-1}: 3061 (m), 2987 (w), 1802 (s), 1607 (m), 1465 (w), 1350 (s), 1270 (s), 1167 (s).

MPt.: 109-111 °C

CAS No.: 95631-21-3

5.2.18 2-(Toluene-4-sulfonyl-methyl-amino)-*N*,*N*-dimethylacetamide (74)



74

To a solution of the acid chloride (**73**) (3.00 g, 11.5 mmol) in CH_2Cl_2 (30 mL) was added dimethylamine hydrochloride (1.70 g, 20.7 mmol) then triethylamine (2.90 mL, 20.7 mmol) and the reaction stirred for 18 hours. The reaction was then washed with aqueous 2N HCl (2 x 20 mL) and the organic phase dried (Na_2SO_4) and the solvent removed *in vacuo*, to furnish the product as a colourless oil which solidified on standing to give an off-white solid (3.07 g, 11.4 mmol, 99 %).

^{1}H-NMR (300 MHz, $CDCl_3$) δ/ppm: 7.65 (2H, d, aromatic C**H**, *J*= 7.9 Hz), 7.30 (2H, d, aromatic C**H**, *J*= 7.9 Hz), 3.84 (2H, s, -NC**H**$_2$-), 3.09 (3H, s, -NC**H**$_3$CH$_3$), 2.90 (3H, s, -NC**H**$_3$), 2.73 (3H, s, -NCH$_3$C**H**$_3$), 2.40 (3H, s, ArC**H**$_3$).

^{13}C-NMR (75 MHz, $CDCl_3$) δ/ppm: 167.2 (**C**=O), 144.0 (aromatic **C**), 133.7 (aromatic **C**), 129.9 (aromatic **C**H), 127.8 (aromatic **C**H), 52.5 (-N**C**H$_2$-), 37.3 (-N**C**H$_3$), 36.0 (-N**C**H$_3$CH$_3$), 35.6 (-NCH$_3$**C**H$_3$), 21.7 (Ar**C**H$_3$).

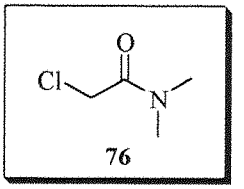
IR (neat) ν/cm^{-1}: 2976 (w), 2921 (w), 2866 (w), 1654 (s), 1489 (m), 1404 (m), 1334 (s), 1263 (m), 1153 (s), 1088 (s), 1011 (s), 928 (s).

MS (ES$^+$; MeCN) *m/z*: 272.1 (10), 271.1 (71). Calculated for $C_{12}H_{18}N_2O_3S$, m=270.

MPt.: 96-97 °C

CAS No.: 115901-76-3

5.2.19 *N,N*-Dimethyl-2-chloroacetamide (76)



76

Following the procedure of Suzuki *et al*,[31] a solution of dimethylamine hydrochloride (6.10 g, 75 mmol) and triethylamine (21 mL, 150 mmol) in toluene (72 mL) was added a solution of α-chloroacetylchloride (**75**) (6.00 mL, 75 mmol) in toluene (18 mL) with vigorous stirring at 0 °C. The reaction was stirred for 2 hours at 0 °C then the solid triethylamine hydrochloride was collected by filtration, the filtrate was washed with aqueous 2N HCl (50 mL) and the organic phase dried (Na_2SO_4). The solvent was removed *in vacuo* to give the crude product as a brown oil which was purified by vacuum distillation (98-100 °C, 11 mmHg), furnishing the pure amide as a colourless oil (7.30 g, 60 mmol, 80 %).

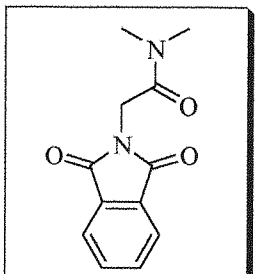
^{1}H-NMR (300 MHz, $CDCl_3$) δ/ppm: 3.95 (2H, s, -C**H**$_2$Cl), 2.93 (3H, s, -NCH$_3$C**H**$_3$), 2.80 (3H, s, -NC**H**$_3$CH$_3$).

^{13}C-NMR (75 MHz, $CDCl_3$) δ/ppm: 166.1 (**C**=O), 40.6 (-**C**H$_2$Cl), 37.0 (-N**C**H$_3$CH$_3$), 35.4 (-NCH$_3$**C**H$_3$).

IR (neat) ν/cm^{-1}: 2947 (m), 2885 (w), 1654 (s), 1506 (m), 1406 (m), 1258 (m), 1153 (m).

CAS No.: 2675-89-0.

5.2.20 2-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-*N,N*-dimethylacetamide(77)



77

Following the method of Toda *et al*,[32] a solution of *N*,*N*-dimethyl-2-chloroacetamide (**76**) (500 mg, 4.1 mmol) in DMF (5 mL) was added potassium phthalimide (1.14 g, 6.2 mmol) and the reaction stirred at reflux for 12 hours. The reaction was then poured onto ice water, extracted with $CHCl_3$ (2 x 20 mL) and washed with aqueous 2N KOH, H_2O, aqueous 2N HCl and H_2O (2 x 20 mL of each). The organic phase was dried

(Na_2SO_4) and the solvent removed *in vacuo* to leave the product **77** as a white solid which was purified by recrystallisation (EtOH) (900 mg, 3.9 mmol, 95 %).

^{1}H-NMR (300 MHz, $CDCl_3$) δ/ppm: 7.87 (2H, dd, aromatic C**H**, *J*= 5.5, 3.0 Hz), 7.72 (2H, dd, aromatic C**H**, *J*= 5.5, 3.2 Hz), 4.49 (2H, s, -NC**H**$_2$), 3.11 (3H, s, -NC**H**$_3$CH$_3$), 2.98 (3H, s, -NCH$_3$C**H**$_3$).

^{13}C-NMR (75 MHz, $CDCl_3$) δ/ppm: 168.3 (**C**=O), 165.5 (**C**=O), 134.2 (aromatic **C**H), 132.4 (aromatic **C**), 123.6 (aromatic **C**H), 39.4 (-N**C**H$_2$-), 36.4 (-N**C**H$_3$CH$_3$), 36.0 (-NCH$_3$**C**H$_3$).

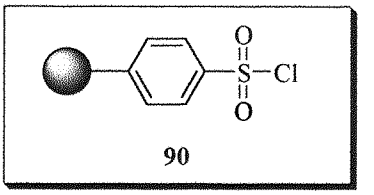
IR (CH_2Cl_2 solution cell) ν/cm^{-1}: 3056 (m), 2987 (m), 1722 (s), 1670 (s), 1436 (m), 1401 (m), 1270 (m).

MS (EI) *m/z* (rel. intensity): 154.1 (11), 153.0 (63). Calculated for $C_{12}H_{12}N_2O_3$, m=152.

MPt.: 176-177 °C

CAS No.: 13648-32-3.

5.2.21 Resin 90

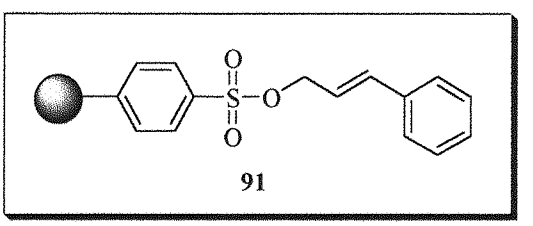


90

Following the method of Roush *et al*,[34] polystyrene resin (1 % cross-linked, 1 g) was suspended in CCl_4 (30 mL) at 0 °C and chlorosulfonic acid (3.2 mL, 48 mmol) was cautiously added with vigorous stirring. After the addition was complete, the reaction was stirred at reflux for 2 hours. The mixture was then cooled to 0 °C and treated with ice water (40 mL), the resin was collected by filtration and washed with CCl_4, acetone and toluene (2 x 30 mL) then dried *in vacuo* at 50 °C. The resin was then suspended in dry DMA (5 mL) was added PCl_5 (520 mg, 2.5 mmol) portionwise and the reaction stirred at rt for 4 hours. The resin was collected by filtration and washed with DMF and CH_2Cl_2 (2 x 50 mL of each) then dried *in vacuo* at 50 °C for 24 hours.

IR (on bead) ν/cm^{-1}: 3031 (w), 2926 (m), 1594 (m), 1494 (w), 1414 (m), 1366 (s), 1166 (s), 1078 (m).

5.2.22 Resin 91

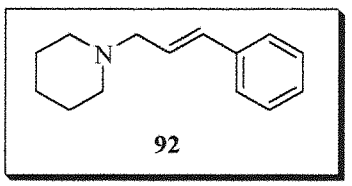


91

To a suspension of the sulfonyl chloride resin **90** (500 mg) in CH_2Cl_2 (7 mL) was added cinnamyl alcohol (670 mg, 5 mmol), DMAP (60 mg, 0.5 mmol) the triethylamine (700 μL, 5 mmol) and the reaction stirred at rt for 24 hours. The resin was collected by filtration and washed with CH_2Cl_2 (4 x 20 mL).

IR (on bead) ν/cm^{-1}: 3022 (w), 2917 (m), 2847 (w), 1600 (m), 1490 (m), 1445 (s), 1400 (m), 1211 (s), 1175 (s), 1122 (s), 1033 (s).

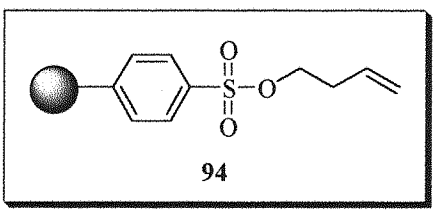
5.2.23 1-(3-Phenylallyl)piperidine (92)



92

To a suspension of the sulfonate resin **91** (200 mg) in CH_3CN (3 mL) was added piperidine (100 μL, 1 mmol) and the reaction stirred at 60 °C for 18 hours. The resin was then collected by filtration and washed with CH_3CN (3 x 10 mL), the filtrate was concentrated *in vacuo* providing the product **92** as a colourless oil (12 mg, 0.060 mmol).

5.2.24 Resin 94

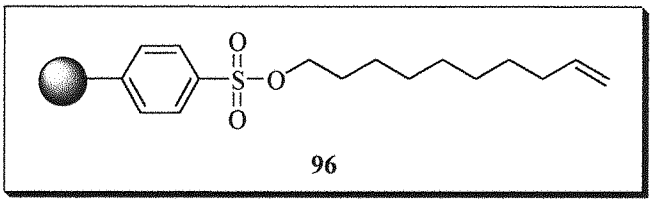


94

To a suspension of the sulfonyl chloride resin **90** (500 mg) in CH_2Cl_2 (7 mL) was added 3-buten-1-ol (430 μL, 5 mmol), DMAP (60 mg, 0.5 mmol) and triethylamine (700 μL, 5 mmol) and the reaction stirred at rt for 24 hours. The resin was collected by filtration and washed with CH_2Cl_2 (4 x 20 mL).

IR (on bead) ν/cm^{-1}: 3022 (w), 2917 (m), 2847 (w), 1600 (m), 1490 (m), 1445 (s), 1400 (m), 1349 (s), 1230 (s), 1169 (s), 1122 (s), 1033 (s).

5.2.25 Resin 96

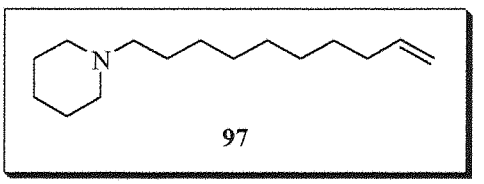


96

To a suspension of the sulfonyl chloride resin **90** (1 g) in CH_2Cl_2 (10 mL) was added 9-decen-1-ol (1.78 mL, 10 mmol) and triethylamine (1.40 mL, 10 mmol) and the reaction stirred at rt for 24 hours. The resin was collected by filtration and washed with CH_2Cl_2, MeOH, H_2O, MeOH and CH_2Cl_2 (2 x 25 mL of each) then dried *in vacuo* at 50 °C.

IR (on bead) ν/cm^{-1}: 2926 (m), 2851 (w), 1599 (w), 1454 (m), 1409 (m), 1348 (m), 1171 (s).

5.2.26 *N*-(9-Decenyl)piperidine (97)



97

To a suspension of the sulfonate resin **96** (250 mg) in CH_3CN (3 mL) was added piperidine (125 μL, 1.25 mmol) and the reaction stirred at 60 °C for 18 hours. The resin was then collected by filtration and washed with CH_3CN (4 x 15 mL), the filtrate was concentrated *in vacuo* giving the product as a colourless oil (50 mg, 0.22 mmol).

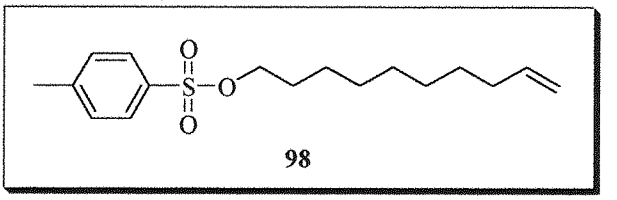
^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 5.81 (1H, ddt, >C**H**=CH_2, *J*=17.4, 10.4, 6.5 Hz), 5.02-4.90 (2H, m, >CH=C**H**$_2$), 2.48 (4H, br s, -C**H**$_2$NC**H**$_2$), 2.38 (2H, t, ($H_{10}C_5$)NC**H**$_2$-, *J*=5.1 Hz), 2.03 (2H, q, -C**H**$_2$CH=CH_2, *J*=6.5 Hz), 1.67 (4H, quintet, -NCH_2C**H**$_2$-, *J*=5.5 Hz), 1.42-1.60 (6H, m, -NCH_2C**H**$_2$C**H**$_2$C**H**$_2$-) 1.30-1.40 (10H, m, -C**H**$_2$-).

^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 139.3 (-<u>C</u>H=CH_2), 114.2 (-CH=<u>C</u>H_2), 59.4 (-N<u>C</u>H_2-), 54.5 (-N<u>C</u>H_2-), 33.9 (-<u>C</u>H_2-CH=CH_2), 29.6 (-<u>C</u>H_2-), 29.5 (-<u>C</u>H_2-), 29.2 (-<u>C</u>H_2-), 29.0 (-<u>C</u>H_2-), 27.7 (-<u>C</u>H_2-), 26.4 (-<u>C</u>H_2-), 25.5 (-<u>C</u>H_2-), 24.2 (-<u>C</u>H_2-).

IR (neat) ν/cm^{-1}: 2931 (s), 2856 (m), 1639 (w), 1454 (m), 1258 (s), 1153 (m), 1028 (m), 903 (m).

MS (EI) *m/z*: 225.3 (15), 224.3 (100) $(M+H)^+$. Calculated for $C_{15}H_{29}N$, m=223.

5.2.27 Toluene-4-sulfonic acid dec-9-enyl ester (98)



98

To a solution of 9-decen-1-ol (2 mL, 11.2 mmol) in CH_2Cl_2 (10 mL) was added tosyl chloride (3.20 g, 16.8 mmol), DMAP (140 mg, 1.1 mmol) and triethylamine (3.13 mL, 22.4 mmol) and the mixture stirred for 24 hours. The reaction was then washed with aqueous 2N HCl, brine and aqueous 2N NaOH (2 x 20 mL of each), the organic phase dried (Na_2SO_4) and the solvent removed *in vacuo*. This gave the sulfonic ester **98** as a colourless oil, which solidified on standing to a white crystalline solid (2.43 g, 7.83 mmol, 78 %).

Spectroscopic data were in agreement with that reported in the literature.[38]

^{1}H-NMR (300 MHz, $CDCl_3$) δ/ppm: 7.77 (2H, d, aromatic C<u>H</u>, *J*=8.1 Hz), 7.33 (2H, d, aromatic C<u>H</u>, *J*=8.1 Hz), 5.78 (1H, ddt, -C<u>H</u>=CH_2, *J*=16.9, 10.3, 6.6 Hz), 4.88-5.02 (2H, m, -CH=C<u>H</u>$_2$), 4.00 (2H, t, -SO_3C<u>H</u>$_2$-, *J*=6.6 Hz), 2.43 (3H, s, -C<u>H</u>$_3$), 2.01 (2H, q, -C<u>H</u>$_2$CH=CH_2, *J*=6.6 Hz), 1.62 (2H, quintet, -SO_3CH_2C<u>H</u>$_2$, *J*=6.6 Hz), 1.20-1.40 (10H, m, -C<u>H</u>$_2$-).

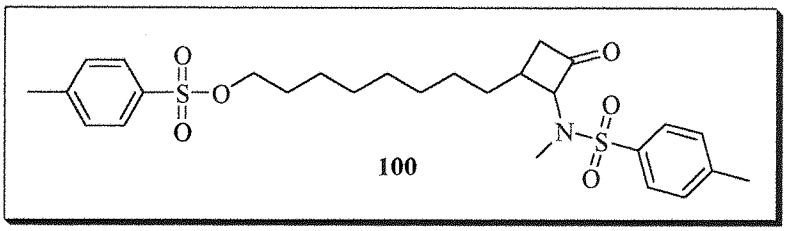
^{13}C-NMR (75 MHz, $CDCl_3$) δ/ppm: 144.8 (aromatic C), 139.2 (-CH=CH_2), 133.3 (aromatic C), 130.0 (aromatic CH), 128.0 (aromatic CH), 114.3 (-CH=CH_2), 70.8 (-SO_3CH_2-), 33.9 (-CH_2CH=CH_2), 29.3 (-CH_2-), 29.1 (-CH_2-), 29.0 (-CH_2-), 28.9 (-CH_2-), 25.4 (-$SO_3CH_2CH_2$-), 21.8 (-CH_3).

IR (neat) ν/cm^{-1}: 2979 (w), 2920 (m), 2852 (m), 1642 (w), 1596 (w), 1479 (w), 1354 (s), 1172 (s), 1097 (m), 952 (s).

MPt.: 31-33 °C

CAS No.: 66605-77-4

5.2.28 8-(2-{Methyl[(4-methylphenyl)sulfonyl]amino}-3-oxocyclobutyl)octyl-4-methyl-1-benzenesulfonate (100)



100

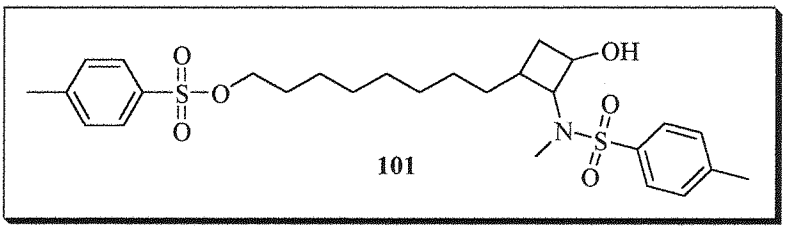
To a solution of 2-(Toluene-4-sulfonyl-methyl-amino)-*N*,*N*-dimethylacetamide (**74**) (250 mg, 0.840 mmol) in CH_2Cl_2 (5 mL) at 0 °C was added Tf_2O (140 μL, 0.840 mmol) and the reaction stirred for 2 minutes. The 2,6-di-*tert*-butylpyridine (190 μL, 0.840 mmol) was then added followed by toluene-4-sulfonic acid dec-9-enyl ester (**98**) (260 mg, 0.840 mmol). The reaction was allowed to warm to rt over a period of 30 minutes and stirred for 20 hours. H_2O (10 mL) was added and the reaction stirred for a further 16 hours. The phases were separated and the aqueous phase extracted with CH_2Cl_2 (3 x 10 mL), the organic phases were combined, dried (Na_2SO_4) and the solvent removed *in vacuo*, granting the cyclobutanone **100** as a colourless oil (315 mg, 0.59 mmol, 73 %).

^{1}H-NMR (300 MHz, $CDCl_3$) δ/ppm: 7.78 (2H, d, aromatic C**H**, *J*=8.1 Hz), 7.70 (2H, d, aromatic C**H**, *J*=8.1 Hz), 7.34 (2H, d, aromatic C**H**, *J*=8.1 Hz), 7.30 (2H, d, aromatic C**H**, *J*=8.1 Hz), 4.89 (1H, d, -C**H**(N(Ts)), *J*=5.9 Hz), 4.01 (2H, t, -$SO_3C\underline{H}_2$-, *J*=6.6 Hz), 2.73 (3H, s, -N($C\underline{H}_3$)), 2.70-2.80 (1H, m, -C**H**(H)-CO-), 2.44 (3H, s, -$C\underline{H}_3$), 2.41 (3H, s, -$C\underline{H}_3$), 2.35-2.45 (1H, m, -(CH(**H**)-CO-), 1.73-1.81 (1H, m, -C**H**-CH_2-CO), 1.62 (2H, quintet, -$SO_3CH_2C\underline{H}_2$-, *J*=7.4 Hz), 1.10-1.40 (12H, m, -$C\underline{H}_2$-).

IR (neat) ν/cm^{-1}: 2925 (m), 2854 (m), 1772 (s), 1598 (m), 1494 (w), 1457 (m), 1335 (br s), 1173 (s), 1157 (s), 1090 (s), 1019 (w), 971 (m).

MS (ES^+; MeCN) *m/z*: 559.5 (23), 558.4 (84). Calculated for $C_{27}H_{37}NO_6S_2$, m=534.

5.2.29 8-(3-Hydroxy-2-{methyl[(4-methylphenyl)sulfonyl]amino}cyclobutyl)octyl-4-methyl-1-benzenesulfonate (101)



101

To a solution of the cyclobutanone **100** (250 mg, 470 mmol) in THF was added a solution of $CeCl_3$ (700 mg, 1.87 mmol) in MeOH (4.5 mL). $NaBH_4$ (71 mg, 1.87 mmol) was then added portionwise and the reaction stirred at rt for 16 hours. When the reaction was complete, H_2O (10 mL) was added and the phases separated. The aqueous phase was washed with THF (3 x 10 mL) the organic phase dried (Na_2SO_4) and the solvent removed *in vacuo*, providing the cyclobutanol **69** as a colourless oil (80 mg, 0.15mmol, 32 %).

^{1}H-NMR (300 MHz, $CDCl_3$) δ/ppm: 7.79 (2H, d, aromatic C**H**, *J*=8.0 Hz), 7.70 (2H, d, aromatic C**H**, *J*=8.0 Hz), 7.34 (4H, d, aromatic C**H**, *J*=8.0Hz), 4.12 (1H, q, -C**H**(OH), *J*=8.4 Hz), 4.01 (2H, t, -$SO_3C\underline{H}_2$-, *J*=6.5 Hz), 2.96 (1H, t, -C**H**-N(Ts), *J*=8.0

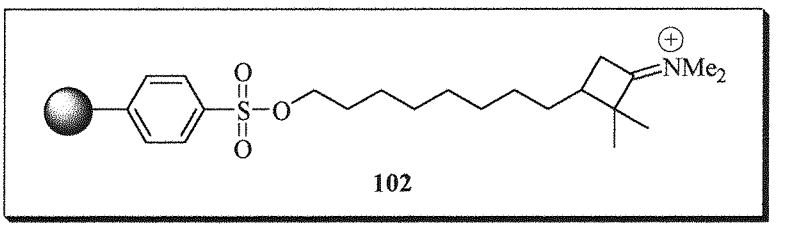
Hz), 2.62 (3H, s, -N(C**H**$_3$)), 2.45 (6H, s, -C**H**$_3$), 2.33 (2H, q, -C**H**$_2$-CH(OH), *J*=7.9 Hz), 1.74 (1H, m, -C**H**-CH$_2$-CH(OH)), 1.62 (2H, quintet, -SO$_3$CH$_2$C**H**$_2$-, *J*=6.5 Hz), 1.10-1.30 (12H, m, -C**H**$_2$-).

^{13}C-NMR (75 MHz, $CDCl_3$) δ/ppm: 143.8 (aromatic **C**), 129.9 (aromatic **C**H), 129.8 (aromatic **C**H), 128.0 (aromatic **C**H), 128.0 (aromatic **C**H), 70.8 (-SO$_3$**C**H$_2$-), 68.5 (-**C**H(OH)), 67.7 (-**C**H-N(Ts)), 35.2 (-**C**H$_2$CH(OH)), 33.0 (-**C**H-CH-N(Ts)), 31.2 (-**C**H$_2$-), 30.6 (-**C**H$_2$-), 29.4 (-**C**H$_2$-), 29.3 (-**C**H$_2$-), 29.0 (-**C**H$_2$-), 27.0 (-**C**H$_2$-), 25.4 (-N(**C**H$_3$)), 21.8 (-**C**H$_3$), 21.7 (-**C**H$_3$).

IR (neat) ν/cm^{-1}: 2925 (m), 2854 (m), 1598 (m), 1494 (w), 1457 (m), 1335 (br s), 1173 (s), 1157 (s), 1090 (s), 1019 (w), 971 (m).

MS (ES$^+$; MeCN) *m/z*: 539.1 (8), 538.1 (43). Calculated for $C_{27}H_{39}NO_6S_2$, m=537

5.2.30 Resin 102

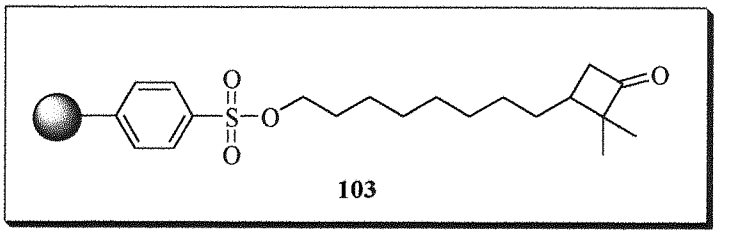


102

To a solution of *N,N*-dimethyl-isobutyramide (**42**) (115 mg, 1mmol) in CH_2Cl_2 (3 mL) at 0 °C under nitrogen was added Tf_2O (170 μL, 1 mmol) with stirring. After 2 minutes 2,6-di-*tert*-butylpyridine (225 μL, 1 mmol) was added followed by resin **96** (200 mg). The reaction was allowed to warm to rt over a period of 30 minutes and then stirred at rt for a further 20 hours. The resin was collected by filtration and washed with CH_2Cl_2, MeOH, H_2O and CH_2Cl_2 (2 x 15 mL of each) then dried *in vacuo* at 50 °C.

IR (on bead) ν/cm^{-1}: 2928 (m), 2856 (w), 1766 (w, C=O), 1724 (m), 1596 (m), 1459 (m), 1412 (m), 1350 (s), 1260 (s), 1171 (s), 1029 (s).

5.2.31 Resin 103

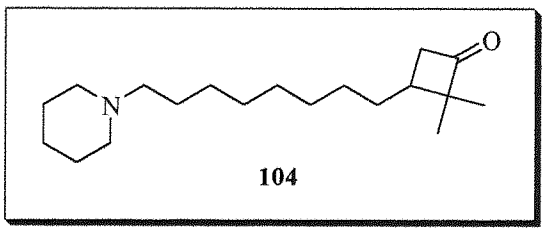


103

To a suspension of resin **102** (200 mg) in THF (3 mL) was added $NaHCO_3$ (1 mL, sat. aqueous solution) and the reaction stirred at rt for 4 hours. The resin was collected by filtration and washed with CH_2Cl_2, H_2O, MeOH and CH_2Cl_2 (2 x 10 mL of each) then dried *in vacuo* at 50 °C.

IR (on bead) ν/cm^{-1}: 2924 (m), 2854 (w), 1767 (s), 1596 (w), 1461 (m), 1411 (m), 1352 (s), 1172 (s), 1036 (m), 1009 (m), 920 (m).

5.2.32 2, 2-Dimethyl-3-(8-Piperidinooctyl)-1-cyclobutanone (104)



104

To a suspension of resin **103** (50 mg) in CH_3CN (1 mL) was added piperidine (25 μL, 0.250 mmol) and the reaction stirred at 60 °C for 5 hours. The resin was collected by filtration and washed with CH_3CN and CH_2Cl_2 (2 x 10 mL of each), the filtrate was concentrated *in vacuo* to grant the cyclobutanone **104** as a colourless oil (9 mg, 0.031 mmol, 70 %).

^{1}H-NMR (300 MHz, $CDCl_3$) δ/ppm: 3.02 (1H, dd, C**H**(H)-CO-, *J*=17.6, 9.0 Hz), 2.57 (1H, dd, CH(**H**)-CO-, *J*=17.6, 7.5 Hz), 2.41 (4H, br s, -C**H**$_2$NC**H**$_2$-), 2.33 (2H, m, -

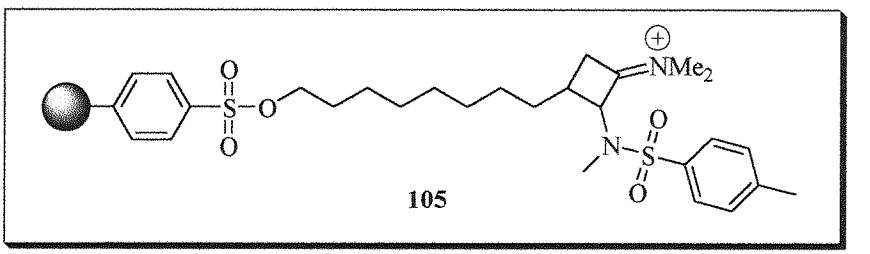
$SO_3C\underline{H}_2$-), 2.00 (1H, m, -C<u>H</u>-C$(CH_3)_2$), 1.40-1.70 (14H, m, -C<u>H</u>$_2$-), 1.20-1.40 (6H, br s, -NCH_2C<u>H</u>$_2$C<u>H</u>$_2$C<u>H</u>$_2$-), 1.19 (3H, s, -C<u>H</u>$_3$), 1.08 (3H, -C<u>H</u>$_3$).

^{13}C-NMR ($CDCl_3$) δ/ppm: 60.8 (-<u>C</u>H_2N<u>C</u>H_2-), 58.1 (-<u>C</u>$(CH_3)_2$), 53.9 (-<u>C</u>H_2-NR_2), 48.7 (<u>C</u>H_2-CO-), 36.6 (-<u>C</u>H_2CH_2NCH_2<u>C</u>H_2-), 29.8 (-<u>C</u>H_2-), 29.6 (-<u>C</u>H_2-), 29.3 (-<u>C</u>H_2-), 29.1 (-<u>C</u>H_2-), 28.6 (-<u>C</u>H_2-), 26.7 (-<u>C</u>H_2-), 23.9 (-<u>C</u>H_2-), 23.8 (-<u>C</u>H_2-), 22.8 (-<u>C</u>H_2-), 22.1 (-<u>C</u>H_3), 17.2 (-<u>C</u>H_3). Unable to visualise carbonyl carbon.

IR (neat) ν/cm^{-1}: 2933 (s), 2857 (w), 1774 (s), 1636 (m), 1464 (w), 1384 (w).

MS (ES^+; MeCN) *m/z*: 295.3 (18), 294.2 (100, $(M+H)^+$). Calculated for $C_{19}H_{35}NO$, m=293

5.2.33 Resin 105

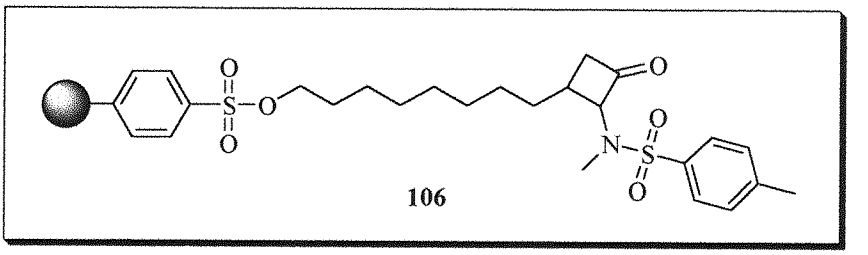


105

To a solution of *N,N*-dimethyl-isobutyramide (**42**) (520 mg, 1.75 mmol) in DCE (5 mL) at 0 °C was added Tf_2O (300 μL, 1.75 mmol) and the reaction stirred for 2 minutes. 2,6-di-*tert*-butylpyridine (400 μL, 1.75 mmol) was added followed by resin **96** (250 mg). The reaction was then stirred at reflux for 20 hours, the resin was collected by filtration, washed with CH_2Cl_2, MeOH, H_2O and CH_2Cl_2 (2 x 10 mL) then dried *in vacuo* at 50 °C.

IR (on bead) ν/cm^{-1}: 2926 (m), 2851 (w), 1780 (m, C=O), 1721 (m), 1596 (m), 1460 (m), 1411 (m), 1344 (s), 1168 (s), 1029 (m), 1006 (m).

5.2.34 Resin 106

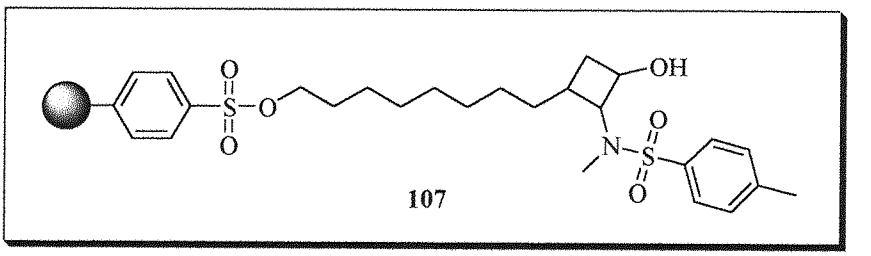


106

To a suspension of resin **105** (250 mg) in THF (5 mL) was added $NaHCO_3$ (1 mL, sat. aqueous solution) and the reaction stirred for 5 hours. The resin was collected by filtration, washed with CH_2Cl_2, MeOH, H_2O and CH_2Cl_2 (2 x 10 mL of each) and dried *in vacuo* at 50 °C.

IR (on bead) ν/cm^{-1}: 2931 (m), 2856 (w), 1779 (s), 1599 (m), 1454 (w), 1413 (m), 1338 (s), 1173 (s).

5.2.35 Resin 107

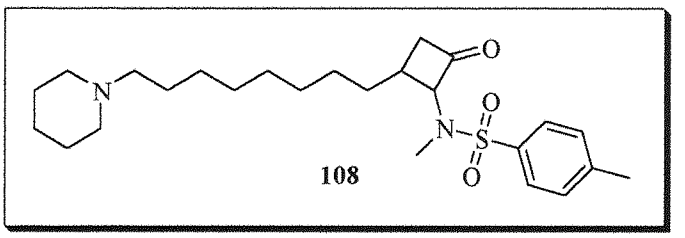


107

To a suspension of resin **106** (250 mg) in THF (2 mL) was added a solution of $CeCl_3$ (373 mg, 1 mmol) in MeOH (2.25 mL). $NaBH_4$ (40 mg, 1 mmol) was then added portionwise and the reaction stirred at rt for 12 hours. The resin was collected by filtration, washed with CH_2Cl_2, MeOH, H_2O and CH_2Cl_2 (2 x 10 mL of each) then dried *in vacuo* at 50 °C.

IR (on bead) ν/cm^{-1}: 3400-3300 (br m), 2933 (m), 2852 (w), 1601 (m), 1470 (w), 1413 (m), 1352 (s), 1178 (s).

5.2.36 *N*1,4-Dimethyl-*N*1-[2-oxo-4-(8-piperidinooctyl)cyclobutyl]-1-benzenesulfonamide (108)



108

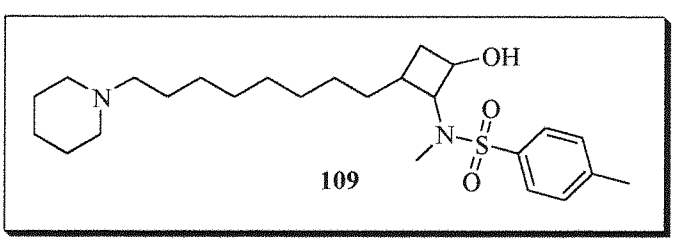
To a suspension of resin **106** (250 mg) in CH_3CN (3 mL) was added piperidine (125 μL, 1.25 mmol) and the reaction stirred at 60 °C for 6 hours. The resin was collected by filtration and washed with CH_3CN and CH_2Cl_2 (3 x 5 mL), the filtrate was concentrated *in vacuo* to give the cyclobutanone **108** as a colourless oil (18 mg, 0.04 mmol, 36 %).

^{1}H-NMR (300 MHz, $CDCl_3$) δ/ppm: 7.64-7.79 (2H, m, aromatic C**H**), 7.28-7.38 (2H, m, aromatic C**H**), 1.10-2.50 (36H, m).

^{13}C-NMR (75 MHz, $CDCl_3$) δ/ppm: Too little sample to obtain carbon NMR.

IR (neat) ν/cm^{-1}: 2928 (m), 2853 (w), 1775 (s), 1596 (m), 1460 (w), 1412 (m), 1350 (s), 1168 (s).

5.2.37 *N*1-[2-Hydroxy-4-(8-piperidinooctyl)cyclobutyl]-*N*1,4-dimethyl-1-benzenesulfonamide (109)



109

To a suspension of resin **107** (250 mg) in CH_3CN (3 mL) was added piperidine (125 μL, 1.25 mmol) and the reaction stirred at 60 °C for 6 hours. The resin was collected by filtration and washed with CH_3CN and CH_2Cl_2 (3 x 5 mL), the filtrate was concentrated *in vacuo* to give the cyclobutanone **109** as a colourless oil (12 mg, 0.027 mmol, 18 %).

^{1}H-NMR (300 MHz, $CDCl_3$) δ/ppm: 7.64-7.79 (2H, m, aromatic C**H**), 7.28-7.38 (2H, m, aromatic C**H**), 5.38 (1H, br s, -O**H**), 2.90-4.70 (3H, m, C**H**(OH) & -C**H**$_2$CH(OH)), 2.77 (1H, t, -C**H**-N(Ts), *J*=3.5 Hz), 2.34-2.45 (10H, m, -C**H**$_2$NC**H**$_2$- & -C**H**$_3$ & -NC**H**$_3$), 1.40-1.70 (11H, m, -NCH$_2$C**H**$_2$C**H**$_2$C**H**$_2$- & -C**H**CH$_2$CH(OH) & (-C**H**$_2$-)$_2$), 0.90-1.40 (12H, m, -C**H**$_2$-).

^{13}C-NMR (75 MHz, $CDCl_3$) δ/ppm: 129.8 (aromatic **C**H), 128.0 (aromatic **C**H), 127.4 (aromatic **C**), 126.1 (aromatic **C**), 59.4 (-**C**H(OH)), 54.5 (-**C**H-N(Ts)), 29.5 (-**C**H$_2$CH$_2$NCH$_2$**C**H$_2$-), 29.4 (-**C**H$_2$CH(OH)), 29.3 (-**C**H-CHN(Ts)), 26.4 (-**C**H$_2$N**C**H$_2$-), 25.6 (-**C**H$_2$-), 25.6 (-**C**H$_2$-), 25.5 (-**C**H$_2$-), 25.5 (-**C**H$_2$-), 25.4 (-**C**H$_2$-), 24.3 (-**C**H$_2$-), 24.2 (-**C**H$_2$-), 23.2 (-**C**H$_2$-), 21.7 (-N**C**H$_3$), 21.6 (-**C**H$_3$), 20.6 (-**C**H$_3$).

IR (neat) ν/cm^{-1}: 3400-3300 (br m), 2935 (m), 2857 (w), 1597 (m), 1464 (w), 1418 (m), 1355 (s), 1172 (s).

MS (ES$^+$; MeCN) *m/z*: 451.5 (9, (M+H)$^+$), 224.2 (100, (M-$C_{10}H_{13}NO_3S$)$^+$). Calculated for $C_{25}H_{42}N_2O_3S$, m=450.

6. References

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