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Solid-Phase Synthesis of Cyclic Sulfonamides and Sulfamides Employing a Ring-Closing Metathesis Cleavage Strategy

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ABSTRACT

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SOLID-PHASE SYNTHESIS OF CYCLIC SULFONAMIDES AND SULFAMIDES EMPLOYING A RING-CLOSING METATHESIS CLEAVAGE STRATEGY

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A series of novel 7-membered cyclic sulfonamides and sulfamides were prepared in good to excellent yields using a ring-closing metathesis (RCM) approach. Model studies in solution indicated the sulfonamides were suitable substrates for RCM and they were thus employed on the solid-phase. A strategy that involved simultaneous cyclisation and cleavage from the resin was developed and applied to the synthesis of cyclic sulfonamides.

The solid supports used included commercially available Merrifield resin and a carboxyethyl resin derived from the former. The effect of three different linkers upon the efficiency of the reaction was investigated: a relatively inflexible allylic linker, a flexible linker and a novel double armed linker. Whereas the RCM cleavage strategy failed when using the inflexible linker, cyclisative release from the more flexible single and double armed linkers proceeded efficiently using 5 mol% of catalyst. In fact, the double armed linker was successfully employed even with 1 mol% of catalyst.

Following a similar strategy, the synthesis of 7-membered cyclic sulfamides met with success in the solution-phase but preliminary efforts to transfer it to the solid-phase failed in part due to lack of time. Methods for hydroxylation of the double bond on the sulfamides were developed leading to potential HIV protease inhibitors.

To a few good friends

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On ne voit bien qu'avec le coeur. L'essentiel est invisible pour les yeux.
Le Petit Prince; Antoine de Saint-Exupéry

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Abbreviations

Ac	Acetyl
acac	Acetylacetonate
ADMET	Acyclic diene metathesis
AIBN	2,2'-Azobisisobutyronitrile
APCI	Atmospheric pressure chemical ionisation
Ar	Aryl
binap	2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
Bn	Benzyl
Boc	*tert*-Butoxycarbonyl
BOP	[(Benzotriazol-1-yl)oxy] tris(dimethylamino)phosphonium hexafluorophosphate
b.p.	Boiling point
br	Broad
BSTFA	Bis(trimethylsilyl)trifluoroacetamide
Bu	Butyl
CAN	Ceric ammonium nitrate
cat.	Catalytic
CI	Chemical ionisation
CIP	2-Chloro-1,3-dimethylimidazolidinium hexafluorophosphate
CSI	Chlorosulfonyl isocyanate
Cy	Cyclohexyl
d	Doublet
DBN	1,5-Diazabicyclo[4.3.0]non-5-ene
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	1,3-Dicyclohexylcarbodiimide
DEAD	Diethylazodicarboxylate
DIBAL	Diisobutylaluminium hydride
DIC	1,3-Diisopropylcarbodiimide
DMA	Dimethylacetamide
DMAD	Dimethylacetylenedicarboxylate
DMAP	4-Dimethylaminopyridine
DME	1,2-Dimethoxyethane
DMF	*N*,*N*-Dimethylformamide
DMFP	1,3-Dimethyl-2-fluoropyridinium 4-toluenesulfonate
DMSO	Dimethylsulfoxide
DMT	4,4'-Dimethoxytriphenylmethyl

dppe	1,2-Bis(diphenylphosphino)ethane
dppp	1,3-Bis(diphenylphosphino)propane
EI	Electron impact
eq.	Equivalents
Et	Ethyl
EtOAc	Ethyl acetate
Fmoc	9-Fluorenylmethoxycarbonyl
fs	Fine splitting
GC	Gas chromatography
HMDS	Hexamethyl disilazane
HOAt	7-Aza-*N*-hydroxybenzotriazole
HOBt	1-Hydroxybenzotriazole
HPLC	High performance liquid chromatography
hr	Hour
HRMS	High resolution mass spectrometry
hrs	Hours
i	iso
IBX	1-Hydroxy-1,2-benziodoxol-3(1*H*)-one
IR	Infra red
J	Coupling constant
L	Any metal ligand
LDA	Lithium diisopropylamide
M	Molecular ion
m	Multiplet
MBHA	4-Methylbenzhydrylamine resin
mCPBA	3-Chloroperbenzoic acid
Me	Methyl
Mes	2,4,6-trimethylphenyl (mesityl)
min	Minute(s)
m.p.	Melting point
MS	Mass spectrometry
Ms	Methanesulfonyl
m.w.	Molecular weight
m/z	Mass / charge (ratio)
n	normal
NMM	*N*-Methylmorpholine
NMO	*N*-Methylmorpholine oxide
NMP	1-Methyl-2-pyrrolidinone
NMR	Nuclear magnetic resonance

o	ortho
p	para
PAM	Phenylacetamidomethyl (resin)
Ph	Phenyl
PMB	4-Methoxybenzyl
PMP	4-Methoxyphenyl
Pr	Propyl
*p*TSA	*para*-Toluenesulfonic acid
PyBOP	[(Benzotriazol-1-yl)oxy]-tris(pyrrolidino)phosphonium hexafluorophosphate
PyBrop	Bromo-tris(pyrrolidino)phosphonium hexafluorophosphate
q	Quadruplet
R	Any substituent
rel.	Relative
RCM	Ring-closing metathesis
ROMP	Ring-opening metathesis polymerisation
s	Singlet
t	Triplet
t	tert
TBAF	Tetrabutylammonium fluoride
TBDMS	*tert*-Butyldimethylsilyl
Tf	Trifluoromethanesulfonyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
THP	Tetrahydropyran
tlc	Thin layer chromatography
TMS	Trimethylsilyl
Trt	Triphenylmethyl (trityl)
Ts	Toluenesulfonyl
UV	Ultra violet
v/v	mixture ratio by volume
X	Any halogen
Y	Any amine protecting group

Cyclisation Cleavage in Solid-Phase Organic Synthesis

1- Solid-Phase Organic Synthesis and General Considerations

Since Merrifield's pioneering work to improve the synthesis of peptides employing a solid support in 1963,[1] much effort has been put into developing solid-phase techniques from which not only peptide synthesis but as well small organic molecule synthesis could benefit. Nowadays, the widespread use of solid-phase techniques in academic research groups and in the pharmaceutical industry, particularly when applied to combinatorial chemistry, clearly demonstrates the success of the method. This can be explained by speed, simplicity, and the efficiency of this methodology characterised e.g. by removal of solvent and excess reagents by a simple filtration, as opposed to a time consuming work-up and extraction; excess reagents affording high yields by driving the reaction to completion; pseudo-dilution phenomenon or site isolation enabling macrocyclisation and avoiding unwanted intermolecular reactions.[2]

Merrifield Resin[3]

There are a wide variety of commercially available resins, each with different characteristics such as hydrophilicity, loading level, bead size and shape, functionalisation. The resin that was used exclusively during this work was Merrifield resin, commercially prepared by cross-linking polystyrene with divinylbenzene and functionalised with chloromethyl groups (introduced either by copolymerisation with vinylbenzyl chloride or polystyrene alkylation with chloromethyl methyl ether). On an average, there are up to 2,000,000 beads of 100-200 mesh polystyrene per gram. Merrifield resin displays excellent swelling properties (in mL/g) in toluene (7), dichloromethane (7) and THF (8) but it does not swell in polar solvents such as DMF (3), methanol (2) or water (-).

Reaction Monitoring[4]

The current shortage of reliable and non-destructive analytical techniques for monitoring on-resin reactions is the major drawback of solid-phase synthesis. Possible solutions are the use of gel phase ^{13}C NMR, possibly on ^{13}C enriched material, IR spectroscopy, cleavage of an aliquot followed by conventional analysis in solution, and elemental analysis; the last two ones being destructive methods. Although the information contained in an IR spectrum is

often limited, no sample preparation is required when machines equipped for on-bead IR are used. Traditional IR instruments can also be used although minor crushing into KBr discs is necessary. During the thesis, on-bead IR was used routinely, as well as combustion analysis and cleavage of an aliquot and subsequent standard analysis.

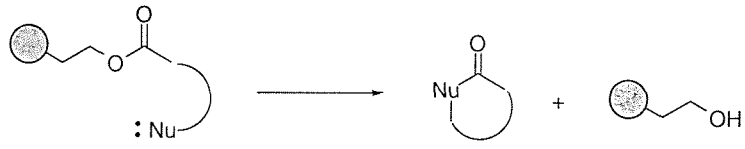
Choice of a Linker[5]

On the solid-phase, linkers temporarily connect the substrate to the solid-support. As a consequence, the choice of an appropriate linker is crucial. A 'good' linker should enable quantitative loading of the substrate onto the resin and should allow an efficient release of the product at the last step while the substrate-linker bond should be chemically stable during all the synthetic steps. If possible, the linker should also be cheap, readily available and should not complicate rapid isolation of the product.

Cyclisation Cleavage as a Means of Release of the Target Molecule

In certain cases, when the bond linking the substrate to the polymer core is broken with concomitant ring closure, a cyclic molecule is released from the resin. This is illustrated by attack of a nucleophile, e.g. an alcohol or an amine, onto an ester moiety at the site of attachment to the support (Figure 1).

Figure 1



In addition to nucleophilic attack, other examples of cyclisation cleavage include intermolecular cyclisation (e.g. Diels-Alder cycloaddition) and olefin metathesis. All these strategies will be discussed below in more details. As we will see, all reports claimed high product purity. In fact, this major advantage of the cyclisation cleavage strategy can be easily explained. Only the beads bearing substrates with the exact requirements for the cyclisation will lead to the product.

The following report covers the literature to July 2000. The different sections were classified according to the type of bond that is formed during the cyclisation. Examples of on-resin cyclisation followed by a separate cleavage, or solution-phase cyclisation after cleavage, or

even cyclisation of the linker to release a linear product will not be discussed in this report. However, both cyclic peptide and small organic molecule examples will be presented.

2- Cyclisation with Formation of an Amide Bond

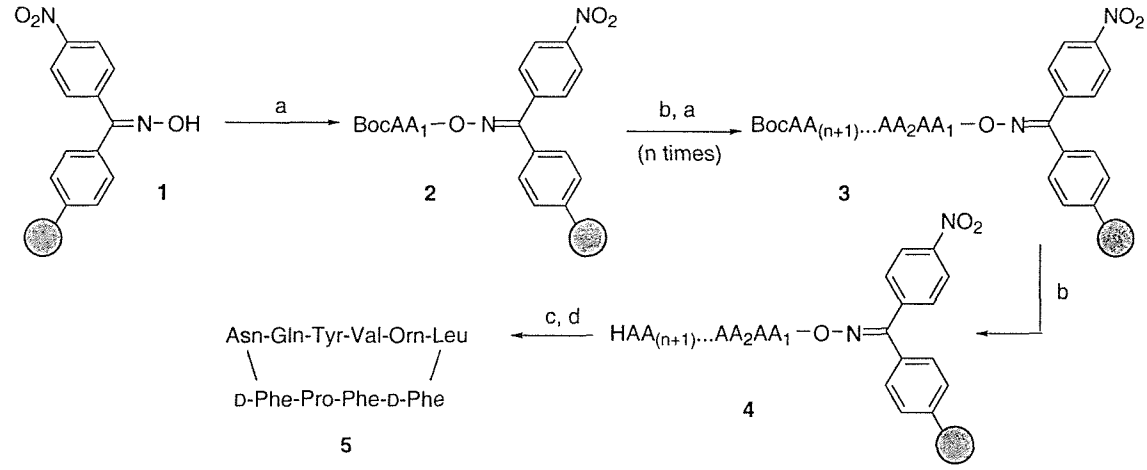
Cyclisation with formation of an amide bond is by far the most common method for the cyclisative cleavage strategy. There are numerous examples of synthesis of cyclic peptides and small organic molecules using this method.

2.1- Application to the Synthesis of Cyclic Peptides and Peptoids

Cyclic peptides present specific characteristics that make them quite interesting in terms of their biological properties. Solid-phase chemistry was originally designed for the synthesis of peptides. It then seems natural that the cyclisation cleavage approach was also used for the formation of peptides.

More than ten years ago, Ösapay *et al.* reported the solid-phase synthesis of cyclic peptides.[6] They employed an intramolecular nucleophilic attack onto an ester of Kaiser's oxime resin **1**. The concept arose after Kaiser observed the formation of a cyclic dipeptide during the development of the oxime solid-support.[7] Subsequently, the same group reported improvements and other applications of this method, including the syntheses of a cyclic decapeptide, tyrocidine A,[8] (55% yield, >95% purity) and lanthionine peptides (50-82% yield, 90-95% purity).[9,10] To illustrate the use of the strategy, the early synthesis of tyrocidine (**5**) is presented below (Scheme 1).[10] The peptide chain was assembled using Boc chemistry and BOP activation. After the appropriate peptide sequence was assembled on the resin by solid-phase synthesis, the deprotected terminal amino group was reacted with the anchoring active ester to close the ring under acidic conditions. Supplementary work on exocyclic amino acids and deprotection were carried out in solution.

Scheme 1



Reagents and conditions: a) $BocAA_xOH$, BOP, EtN^iPr_2, CH_2Cl_2; b) TFA, CH_2Cl_2; c) AcOH, CH_2Cl_2, DMF, 24 hrs; d) side chain deprotection.

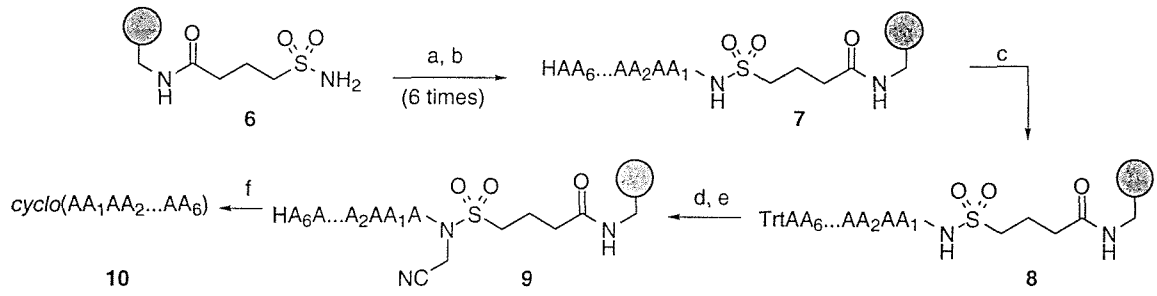
Also employing cyclisation onto Kaiser's oxime resin **1** and a similar Boc and BOP strategy, Nishino published a series of papers on solid-phase cyclic peptide synthesis, studying the influence of the peptide sequence and the substitution on Kaiser's resin on cyclisation.[11-16] Similarly to Ösapay's work, cyclisation occurred by action of acetic acid and triethylamine in DMF. It should be mentioned that in some publications, the solvent or the coupling reagent might differ, but the general strategy stayed the same. Comparing the yields obtained on the solid-phase with the those obtained in solution clearly demonstrates the superiority of the former method, e.g. Nishino obtained a tetrapeptide in an overall 65% yield as opposed to 10% by conventional synthesis in solution.[11] Some of Nishino's co-workers published the synthesis of cyclic peptide libraries.[17]

Lee also employed the oxime resin **1** for the synthesis of a cyclooctadepsipeptide but the cleavage conditions were significantly different.[18,19] Initially a tetradepsipeptide was coupled to the oxime resin under standard conditions and the remaining residues were added employing PyBrop and Hünig's base. Cyclisative cleavage of the terminal unprotected amino acid onto the ester linkage was achieved in good yield and purity refluxing in ethyl acetate for two days. Surprisingly, Lee reported that, among other systems, the conditions used by Nishino and Ösapay, dichloromethane with acetic acid, did not afford the desired cyclic product.

Finally, Taylor and Kapurniotu also employed oxime resin **1** for the synthesis of a cyclopeptide.[20] They reported that, in addition to the sequence dependence of the cyclisation, yield and purity could significantly vary according to the nature of the protecting groups used.

A different approach for a head-to-tail cyclisation cleavage of two hexapeptides was that of Yang.[21] In order to use Fmoc solid-phase synthesis and therefore piperidine for the deprotection of the amino groups, the authors used a safety-catch sulfonamide linker, stable to piperidine while still allowing nucleophilic attack by the terminal amine (Scheme 2).

Scheme 2

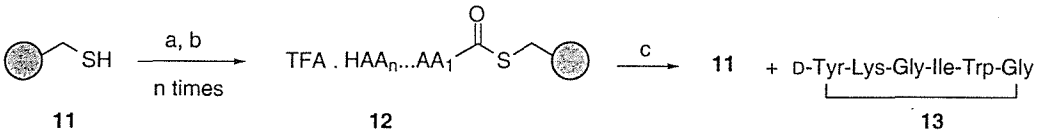


Reagents and conditions: a) FmocAA$_x$OH, PyBOP, EtN^{i}Pr$_2$, DMF; b) piperidine, DMF; c) Ph_3CCl, EtN^{i}Pr$_2$, CH_2Cl_2; d) ICH_2CN, EtN^{i}Pr$_2$, NMP; e) TFA, ^{i}Pr$_3$SiH, CH_2Cl_2; f) EtN^{i}Pr$_2$, THF.

Double coupling of the first Fmoc protected amino acid to the sulfonamide resin **6** was achieved in the presence of Hünig's base and PyBOP. The remaining amino acids were assembled following standard Fmoc protocol. The final amino acid had to be protected with trityl after coupling, affording **8**, in order to ensure stability to the conditions used for the sulfonamide linker activation. After cyanomethylation to activate the linker, the trityl group was removed by action of substoichiometric amounts of TFA and triisopropylsilane. The resulting resin **9** was treated with Hünig's base affording the cyclisation cleavage to the hexapeptide **10**. Deprotection of the side chains was achieved in solution. Like Nishino, the authors found that the yield of cyclised material was highly dependent on the amino acid sequence on the solid-phase just like in the solution synthesis.

Richter appeared rather critical of the use of Kaiser's oxime resin as it led to the formation of dimers.[22] He and his group reported the synthesis of cyclic peptides **13**. Thiol resin **11** was prepared in a few steps from commercially available MBHA resin (Scheme 3).

Scheme 3



Reagents and conditions: a) BocAA$_x$OH, DIC, EtN^{i}Pr$_2$ or NMM; b) TFA, CH_2Cl_2; c) DMAP, DMA, EtN^{i}Pr$_2$, 2-7 days.

The linear peptide was assembled using standard Boc solid-phase protocol, with *in situ* neutralisation of the TFA salts. Cyclisation from the thioester resin **12** to eight different peptides like **13** was achieved in 15-35% yield at room temperature in the presence of catalytic DMAP and three equivalents of Hünig's base. The authors then demonstrated that the Kaiser's oxime supported synthesis of two of the eight peptides afforded the desired material in comparable yield but inferior purity.

Peptides are not the only compounds to benefit from the advantages of solid-phase synthesis. Because of their medicinal significance, the solid-phase synthesis of small organic molecules has also been widely investigated, and cyclisation cleavage has often been used as a cleavage method.

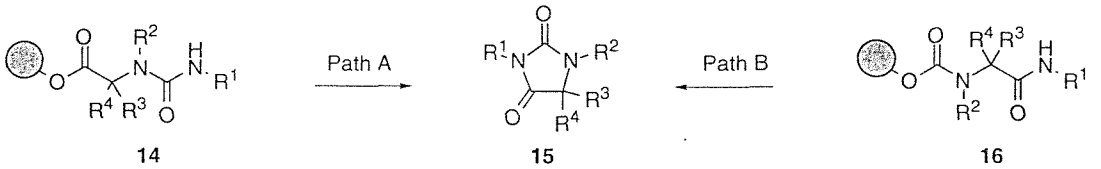
2.2- Application to the Synthesis of Non-Peptidic Organic Molecules

Cyclisation cleavage with formation of an amide bond applied to the synthesis of small organic molecules is doubtless the most studied area of research as demonstrated by the number of publications on the subject. Different classes of heterocycles have been synthesised using this method, and are presented below.

Hydantoins and Derivatives[23-42]

Numerous examples of hydantoin synthesis were reported in the literature. A closer look at the structure and the various strategies reveal that two different cyclisation cleavage methods have been employed (Figure 2).

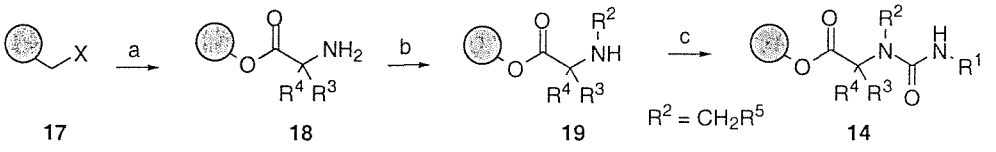
Figure 2



Path B was exploited by only one research group.[24] The authors assembled **16** by *N*-coupling a selection of *N*-substituted amino acids to an activated carbonate resin and reacting the resulting terminal free carboxylic acid with a series of amines (R^1NH_2) under standard conditions. The cyclisative cleavage was achieved in high purity in the presence of triethylamine in methanol with heating for two days. The method was used to prepare an 800-member library. The authors emphasised the advantage resulting from the greater commercial availability of amines over the isocyanates used in most of the hydantoin solid-phase syntheses so far, as we will see below.

All the other reports followed path A. Two examples of cyclisation in acidic conditions were reported.[23,33] However these rather harsh conditions made the method unattractive and restricted it to the use of acid-stable substituents. Thus, the majority of the subsequent reported syntheses relied on milder method of cleavage, mainly the use of base to effect the cyclisative release.[26-30,32,34-36,39,40,42] Two research groups reported cyclisation by simple warming of the resin.[37-39,41] The various reagents and conditions to effect cyclisation are summarised in table 1 at the end of this section. The general procedure for the assembling of the hydantoin precursor on the solid-phase relied on 1) coupling of an amino acid to an appropriately functionalised resin **17**, 2) if required, introduction of a substituent R^2 on the amine moiety by reductive amination, and 3) acylation with isocyanates to give **14** (Scheme 4).

Scheme 4



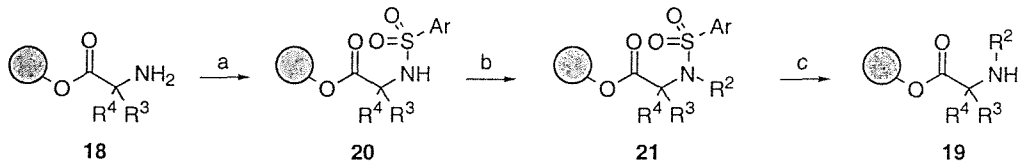
Reagents and conditions: a) 1) $HO_2CCR^3R^4NHY$, 2) deprotection; b) R^5CHO, $NaBH_3CN$, AcOH; c) R^1NCO.

A few variations to the general scheme 4 were reported:

1) the use of an *N*-substituted amino acid to give **19** directly.[29,31]
2) the coupling of a haloacid $HO_2CCR^3R^4X$ and subsequent *N*-alkylation with R^2NH_2 to yield resin-bound amine **19**.[31]
3) the alternative two-step introduction of R^2 under Fukuyama-Mitsunobu conditions (Scheme 5). Thus, amine **18** was reacted with a sulfonyl chloride to allow further coupling

with alcohols R^2OH under Mitsunobu conditions. The sulfonyl moiety on **21** was subsequently removed by reaction with a thiolate.[29,33]

Scheme 5

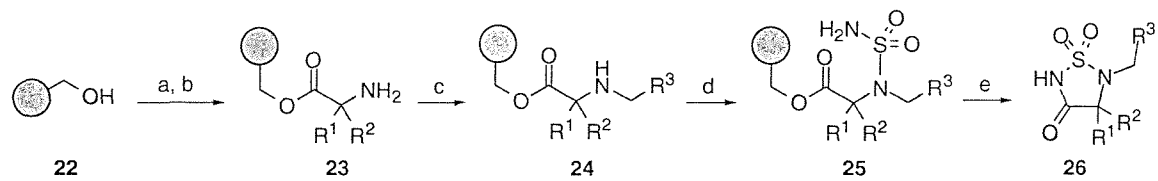


Reagents and conditions: a) $ArSO_2Cl$, base, CH_2Cl_2; b) R^2OH, DEAD (or equivalent), PPh_3, CH_2Cl_2; c) RSH, base, CH_2Cl_2.

4) the formation of an imine intermediate from **18** by transimination and further reduction to **19**.[32]
5) the formation of a resin-bound isocyanate or carbonyl chloride by exposure of **19** to phosgene or triphosgene and subsequent reaction with amine R^1NH_2 to form urea **14**.[28,29,40]
6) the reaction of amine **19** with an activated chloroformate followed by displacement with amine R^1NH_2 to yield urea **14**.[31]

In addition, by replacing isocyanates with thioisocyanates on the procedure depicted in scheme 4, Park and Kurth carried out the automated synthesis of several thiohydantoins in 30-40% yield.[37,39] Similarly, Matthews and Rivero obtained a series of thiohydantoins and noted that the cyclisation occurred in yields higher than those obtained with the corresponding hydantoins upon action of base or heat.[28] The synthesis reported by Wu presented more dissimilarity, and enabled the formation of not only hydantoins but as well hydrouracils together with their thio derivatives.[41] Finally, Albericio *et al.* recently reported the synthesis of ten sulfahydantoins in five steps (Scheme 6).[42]

Scheme 6

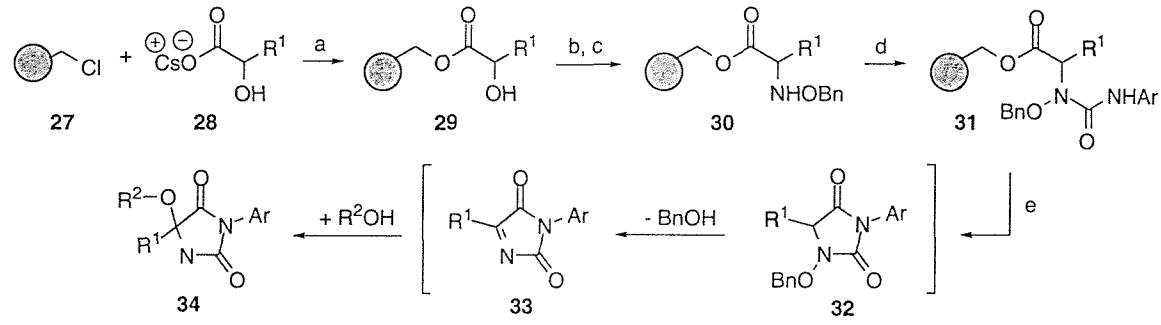


Reagents and conditions: a) $FmocNHCR^1R^2CO_2H$, DIC, DMAP, CH_2Cl_2, DMF, 2hrs; b) piperidine, DMF, 20min; c) 1) R^3CHO, AcOH, $(MeO)_3CH$, CH_2Cl_2, 5hrs, 2) $NaCNBH_3$, $(MeO)_3CH$, CH_2Cl_2, 3x2hrs; d) H_2NSO_2Cl, 2,4,6-collidine, CH_2Cl_2, 4hrs; e) DBU, CH_2Cl_2, 5hrs.

Fmoc protected amino acids were coupled to Wang resin or functionalised MBHA resin under standard conditions. Deprotection of the amine to give **23** and subsequent reductive amination with aromatic aldehydes afforded resin-bound amines **24**. Freshly prepared sulfamoyl chloride, from the reaction of formic acid with chlorosulfonyl isocyanate, was then reacted. The resulting resin-bound sulfamides **25** were treated with DBU at room temperature to release the desired cyclised sulfahydantoins **26** in low yield (7-31%) but good purity (60-100%) after purification on Amberlyst resin.

Although globally similar to the path A strategy represented in figure 2, an interesting alternative was reported by Hanessian.[25] The cyclisation cleavage occurred with introduction of further functionalisation (Scheme 7).

Scheme 7

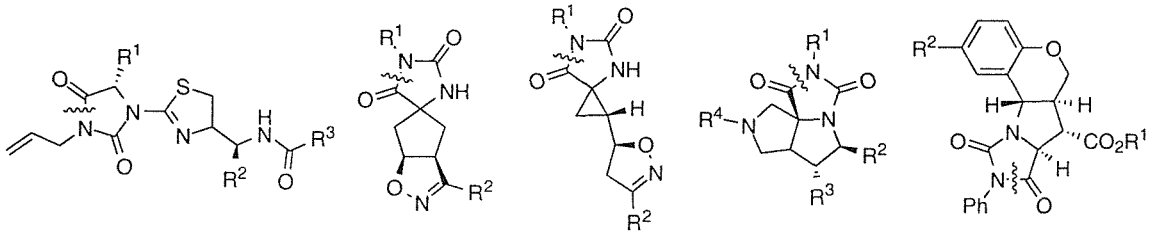


Reagents and conditions: a) DMF, 80°C, 8hrs; b) Tf_2O, lutidine, CH_2Cl_2; c) $BnONH_2$, 0°C; d) ArNCO, $ClCH_2CH_2Cl$, reflux, 24hrs; e) ^tBuOK, R^2OH.

After the solution-phase synthesis of 50 hydantoins, the authors coupled an α-hydroxyacid to Merrifield resin (**27**) *via* its caesium salt **28**. Activation of the hydroxy as the corresponding triflate and reaction with *O*-benzylhydroxylamine afforded ester **30**. Subsequent reaction with isocyanates afforded resin-bound ureas **31**. Cyclisation cleavage was achieved with further functionalisation when resin **31** was treated with an alcoholic solution of potassium *tert*-butoxide. Purity of the cleaved products **34** was high (89-96%), and the yields in purified products ranged from 23% to 72%.

Finally, some reports described the preparation of more complex polycyclic hydantoins. Thus, the synthesis of thiazolylhydantoins **35**,[34] spiro compounds **36** and **37**,[35] triaza tricycles **38**,[40] and hexahydro-1*H*-pyrrolo[1,2-c]imidazoles[30] were reported (Figure 3).

Figure 3



35 36 37 38 39

Note: ~~~ indicates where the cyclisation occurred

To conclude on the cyclisation cleavage applied to the synthesis of hydantoins and their derivatives, table 1 summarises all the reagents used to effect cyclisation and gives the yield and purity obtained.

Table 1: Cyclisation cleavage to hydantoins and their derivatives

Entry[a]	Cyclisation conditions	Resin	Yield (%)	Purity (%)
	acidic conditions			
1[23]	6N HCl; 85-100°C	Wang	4-81	--
2[28]	6N HCl; 94°C	Wang	16	--
3[33]	TFA in CH_2Cl_2[b]	Wang	--	--
	tertiary amines			
4[28]	Et_3N in $CHCl_3$	Wang	48-100	>90
5[29]	Et_3N in MeOH; 40-100°C	Tentagel S-OH	40-100	'purification was not necessary'
6[24]	Et_3N in MeOH; 55-90°C	Hydroxymethyl polystyrene	12-74	65-99
7[34]	Et_3N in dioxane; 60°C	Benzhydrylamine modified with 6-aminohexanoic acid	69-191[c]	--
8[35, 36]	Et_3N in THF; 60°C	Merrifield	20-35	--
9[30]	EtN^iPr_2 in DMF; 110°C	Merrifield modified with 1,3-propanediol	6-15	--

Table 1: Cyclisation cleavage to hydantoins and their derivatives (continued)

Entry[a]	Cyclisation conditions	Resin	Yield (%)	Purity (%)
	other bases			
10[26, 27]	neat $^{i}Pr_2NH$[d]	Wang	79-92	'1 peak by HPLC'
11[32]	neat $^{i}PrNH_2$	2-(1-Methyl)hydroxyethyl polystyrene	12-98	>90
12[42]	DBU in CH_2Cl_2	Wang and MBHA modified with 4-alkoxybenzylalcohol	7-31	60-100
13[40]	^{t}BuOK in THF	Hydroxymethyl polystyrene	14-34	>90
	heat			
14[37, 38]	THF; 60°C	Merrifield modified with 1,3-propanediol	20-40	>95
15[41]	DMF; 60-90°C	Hydroxymethyl polystyrene	21-69	66-98
	other conditions			
16[25]	^{t}BuOK, ROH	Merrifield	23-72	89-96
17[31]	BSTFA in 1,2-dichloroethane; 70-80°C	Hydroxymethyl polystyrene	15-58	--

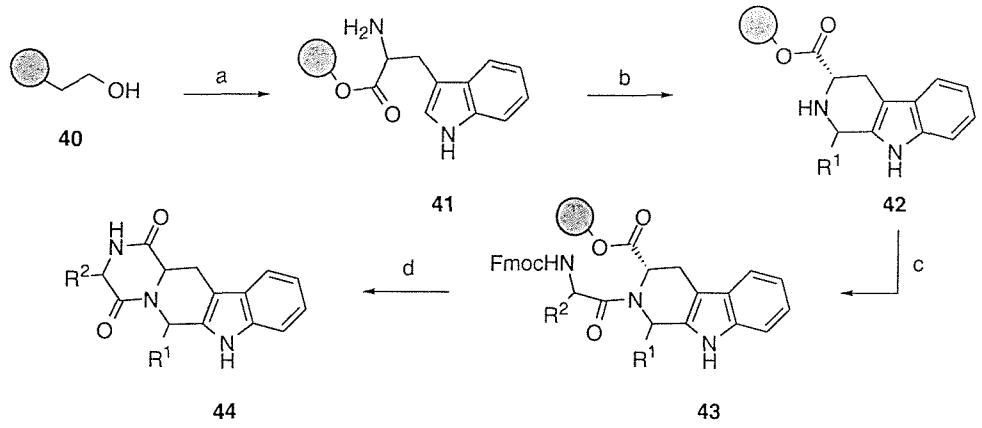
Notes: a) reference number; b) autocleavage also occurred, depending on reactivity; c) based on milligrams of product per gram of resin; d) triethylamine, pyrrolidine and piperidine were also reported to effect cyclisation.

Noteworthy are entries 2 and 4, for which Matthews compared the cyclisative acidic conditions reported by Hobbs DeWitt with the base-promoted cyclisation release. The desired hydantoin was recovered in a much lower yield with the former method (16% vs. 64%). Also, during the preparation of this report, Kurth and Park published a paper which summarised the cyclisative cleavage differences observed for the hydantoin synthesis on Merrifield and Wang resins.[39] Assembling the linear hydantoin precursor according to the procedure described in scheme 4, the authors observed that when R^2=H, cyclisation cleavage was observed in 95% yield, in the presence of triethylamine, from the Merrifield resin only. In contrast, for R^2=Bn, cyclisation occurred in 92% and 94% yield respectively for the Merrifield and the Wang based synthesis. Nevertheless, the cleavage conditions were harsher for the latter requiring elevated temperature. In contrast, the analogous thioureas did not require base to effect the cyclisative release.

Diketopiperazines and Related Compounds[43-46]

Diketopiperazines display interesting biological properties and have been the target of numerous solid-phase syntheses. In order to create a general solid-phase method to the synthesis of indolyl diketopiperazine alkaloids **44**, Koomen *et al.* chose a cyclisation cleavage strategy (Scheme 8).[43]

Scheme 8

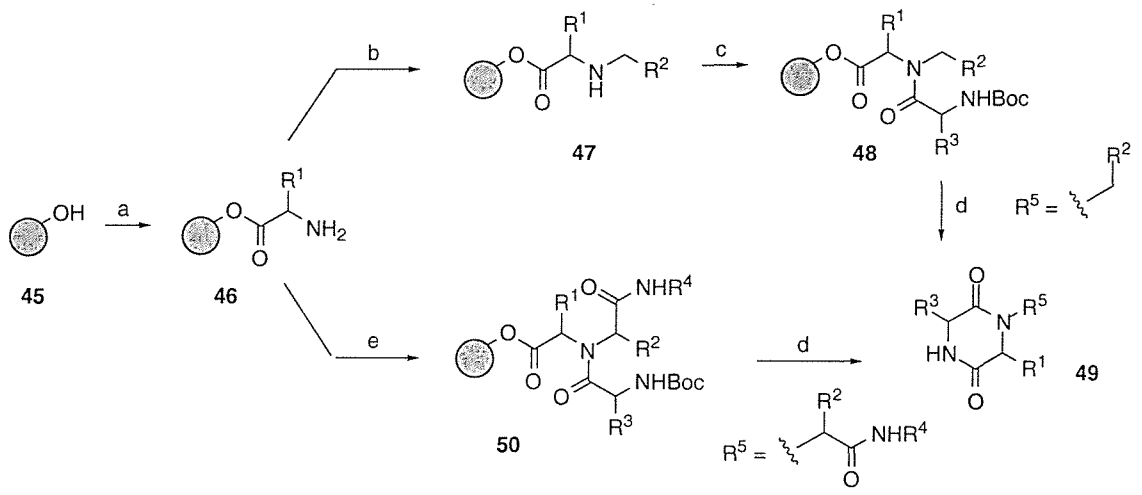


Reagents and conditions: a) L-tryptophan, see reference therein; b) R^1CHO, TFA, CH_2Cl_2; c) CIP, EtN^iPr_2, $FmocNHCH(R^2)CO_2H$, NMP, 16hrs; d) piperidine, THF, 16hrs.

Hydroxyethyl polystyrene (**40**) was loaded with tryptophan. Subsequent Pictet-Spengler condensation with a series of aldehydes afforded resin **42**. Reaction with highly reactive Fmoc protected amino acid chlorides, prepared *in situ* from the corresponding Fmoc amino acids and CIP, was followed by Fmoc deprotection. Instantaneous cyclisation cleavage of the free amino intermediate took place, releasing pure products **44** in 50%-99% yield after removal of the piperidine by-product. The method was applied to the automated synthesis of a 42-member library.

Szardenings *et al.* reported the synthesis of diketopiperazines **49** following two complementary strategies (Scheme 9).[44] First, a linear synthesis was employed (steps b, c, d). It consisted in resin attachment of a protected amino acid fluoride generated *in situ*, deprotection, reductive alkylation with aldehydes, acylation of the thus formed secondary amine **47** under standard conditions, removal of all the acid labile protecting groups, and cyclisation cleavage to **49**. The second method relied on a Ugi multi-component condensation (steps e and d). The carbonyl component was added first to the TentaGel bound amino acid in order to induce the formation of the imine.

Scheme 9



Reagents and conditions: a) 1) YNHCH(R^1)CO_2H, DMFP, Et$N^i Pr_2$, 2) deprotection; b) R^2CHO, $(MeO)_3CH$, MeOH or R^2CHO, AcOH, $NaCNBH_3$, THF; c) BocNHCH(R^3)CO_2H, DIC, HOAt; d) 1) TFA, CH_2Cl_2, 2) AcOH or Et_3N, toluene, EtOH; e) R^2CHO, BocNHCH(R^3)CO_2H, R^4NC, MeOH.

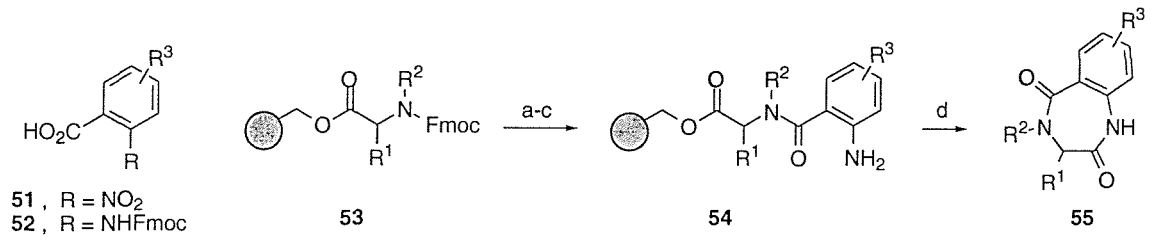
Nevertheless, the cleavage step remained the same. Cyclisation was induced by treatment of the resin-bound substrates **48** and **50** with a mixture of toluene and ethanol under either acidic or basic conditions. The purity of the released diketopiperazines was usually greater than 90%. The yields of isolated material ranged from 8% to 37% for the linear synthesis while almost quantitative cleavages were obtained with the Ugi four component condensation.

Finally, another Ugi multi-component condensation was later reported in the literature, starting from hydroxymethyl resin bound amino acids.[46] Upon treatment with TFA, cyclisation cleavage released the desired diketopiperazines in moderate purity and yield.

1,4-Benzodiazepine-2,5-diones and 1,4-Benzodiazepine-2-ones[46,47]

Among the several methods reported in the literature for the solid-phase synthesis of benzodiazepinediones, the one by Mayer *et al.* was based on a cyclisative cleavage (Scheme 10).[47]

Scheme 10

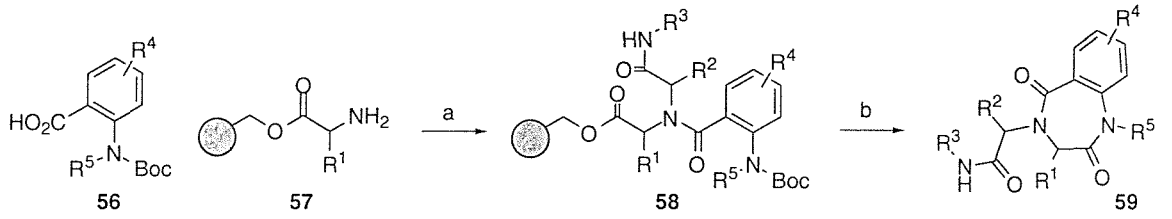


Reagents and conditions: a) piperidine, DMF; b) **51** or **52**, DCC, HOBt, 2-4hrs; c) (R = NHFmoc) piperidine, DMF // (R = NO_2) $SnCl_2$, DMF, 5hrs; d) ^tBuONa, THF, 60°C, 24hrs.

Commercially available Fmoc amino acid derivatised Wang resin **53** was deprotected and coupled to nitrobenzoic or protected anthranilic acid, **51** and **52**, under standard conditions. Fmoc removal or nitro reduction afforded the free anilines **54** that were reacted with sodium *tert*-butoxide in refluxing THF to induce cyclisative cleavage affording compounds **55** in 45-80% yield and over 81% purity.

In the previous chapter we presented the work by Hulme *et al.* on the formation of diketopiperazines using a multi-component condensation strategy. The authors also reported in the same article the synthesis of benzodiazepinones using a similar strategy (Scheme 11).[46]

Scheme 11



Reagents and conditions: a) R^2CHO, R^3NC, **56**, MeOH, CH_2Cl_2, 24hrs; b) TFA, CH_2Cl_2.

Fmoc protected amino acids were coupled to Wang or hydroxymethyl resins and subsequently deprotected with piperidine to give **57**. Ugi condensation afforded resin **58** that was treated with TFA to afford the desired benzodiazepines **59** in good to excellent yield by simultaneous deprotection, cyclisation and cleavage. Purity ranged from 67% to 100%. Encouraged with these results, the authors set up an automated synthesis, benefiting from the four points of diversity, culminating in the synthesis of a 9750-member library.

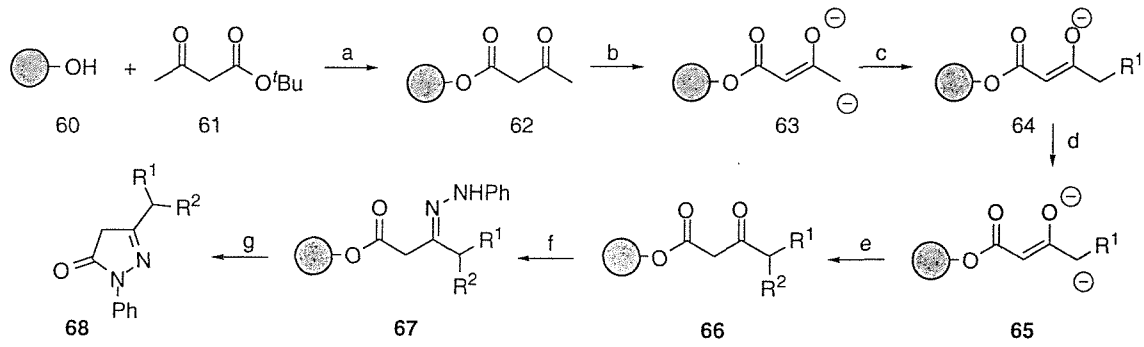
Finally, in an early paper, together with the first reported synthesis of hydantoins using a new apparatus to automate synthesis, Hobbs DeWitt and co-workers reported the two step synthesis of a library of forty benzodiazepines.[23] Boc-protected amino acid functionalised

Merrifield resin was deprotected and reacted with a series of 2-aminobenzophenones. Cyclisation was induced upon treatment with TFA. The desired benzodiazepinones were obtained in low to moderate yield and high purity.

Pyrazolones[48-50]

While studying resin-bound 1,3-dicarbonyl compounds, Tietze developed a solid-phase procedure for the synthesis of biologically active pyrazolones **68** (Scheme 12).[48]

Scheme 12



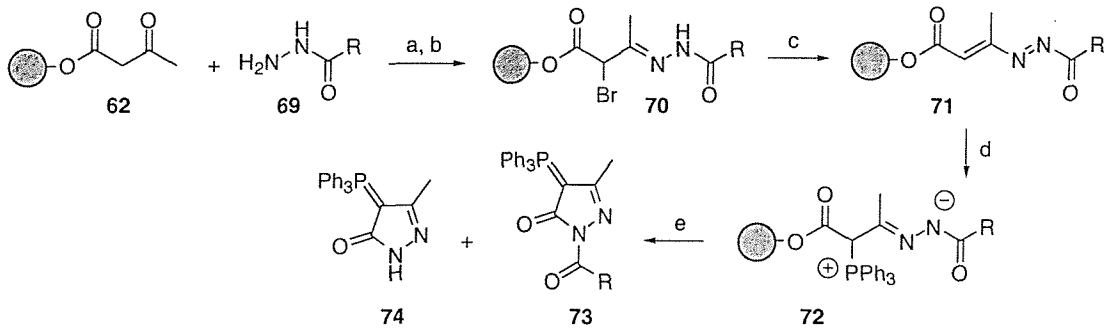
Reagents and conditions: a) toluene, 100°C, 3hrs; b) LDA, THF, 0°C, 1hr; c) R^1X, THF; d) *n*BuLi, THF, 0°C, 0.5hr; e) 1) R^2X, THF, 2) 2N HCl, THF; f) $PhNHNH_2$, THF, 3hrs; g) toluene, 100°C, 5hrs.

The key step involved the reaction of phenylhydrazine with a set of polymer-bound β-ketoesters **66** previously prepared on the solid-phase. Cyclisation cleavage was performed upon heating resin **67** in toluene. It should be mentioned that the second alkylation (step e) was carried out only on two compounds out of the nine examples reported. Overall yields of **68** ranged from 40-76% and purity was greater than 90%.

Further developments and improvements of the procedure were subsequently reported.[49] They involved in particular the functionalisation of the α-carbon atom of the resin-bound β-ketoesters, the latter being synthesised by reaction of several acid chlorides, Meldrum's acid and hydroxy resin **60**. The conditions for the cyclisation cleavage were changed to 2% TFA in acetonitrile at room temperature over half an hour. This effected the cyclisative release of twelve pyrazolones in overall yields ranging from 56% to 95% and high purity. The authors also reported one example of synthesis of *N*-unsubstituted pyrazolone in 84% yield, obtained by reaction with hydrazine hydrate instead of phenylhydrazine.

Finally, in collaboration with Attanasi, the synthesis of pyrazolone Wittig ylides was reported (Scheme 13).[50] The cyclisative release of ylides **73** relied on the ring formation by nucleophilic attack of betaine **72** onto the ester linker.

Scheme 13



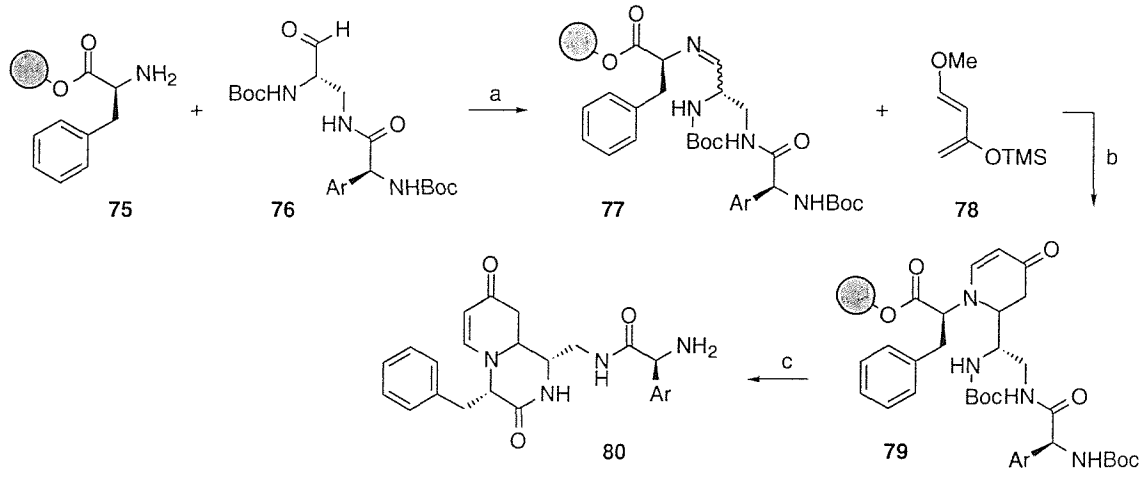
Reagents and conditions: a) DMF, 4hrs; b) $PhNMe_3^+Br_3^-$, CH_2Cl_2, 3hrs; c) EtN^iPr_2, CH_2Cl_2; d) PPh_3, EtOAc, 1hr; e) MeOH, 60°C, 10-12hrs.

The formation of the betaine on the solid-phase presented no particular difficulty. However, it should be noted that the cyclisation occurred with concomitant release of the methanolysed *N*-unsubstituted pyrazolone **74** in a 1:1 ratio with the desired ylides **73**. The isolated yields in the combined products ranged from 12% to 42%.

Pyridopyrazines[51]

Recently, Goodman *et al.* reported the solid-phase synthesis of complex opioids using a [4+2] cycloaddition with Danishefsky diene **78**. The report first described the synthesis of pyridones cleaved under standard acidic conditions. Subsequently, the authors presented the cyclisation cleavage to pyridopyrazine **80** by action of TFA (Scheme 14).

Scheme 14



Reagents and conditions: a) $(MeO)_3CH$, CH_2Cl_2; b) $ZnCl_2$, THF, 4°C, 24hrs; c) TFA, CH_2Cl_2, 12hrs.

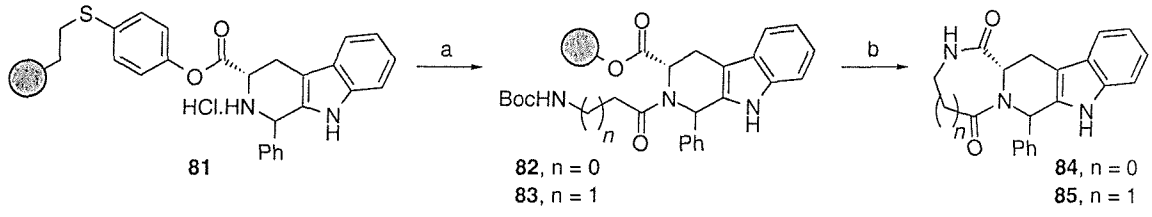
The solid-phase assembly of the building blocks to both the pyridone and pyridopyrazine **80** followed a similar strategy. Hence, coupling of peptidic aldehyde **76** to phenylalanine Wang resin **75** in the presence of trimethyl orthoformate and subsequent reaction of the resulting

resin-bound imine **77** with Danishefsky diene in the presence of zinc chloride afforded dihydropyridone **79**. Upon treatment with TFA, removal of the Boc protecting groups initiated cyclisation cleavage. The desired material was released in 45% overall yield, with elevated purity and d.e. (>95%).

Tetrahydro-β-carboline-2,3-bis-lactams[52]

In order to illustrate the advantages of the acid-stable and amine-cleavable 4-hydroxythiophenol linker, Yager and Fantauzzi reported its use for the synthesis of a 345-member library of biologically active tetrahydro-β-carbolines. They also demonstrated that the thiophenol linker could allow cyclisation cleavage if the amine was suitably placed on the resin-bound substrate (Scheme 15).

Scheme 15



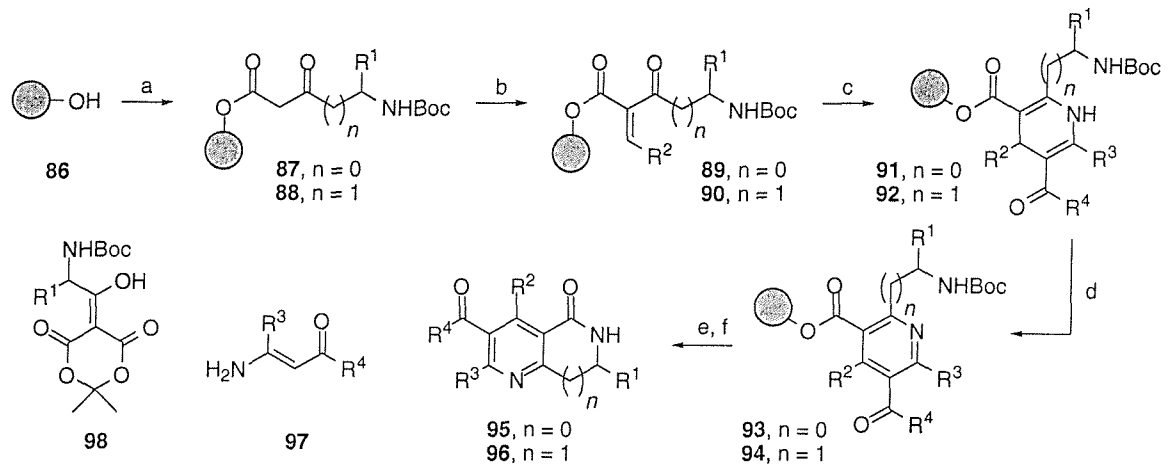
Reagents and conditions: a) Boc-Gly or Boc-β-Ala, PyBOP, NMM, DMF, 17hrs; b) 1) HCl, MeOH, 4hrs, 2) CH_2Cl_2, 4hrs.

Resin **81** was prepared in two steps by reaction of tryptophan with 4-hydroxythiophenol functionalised Merrifield resin, and subsequent Pictet Spengler ring formation with benzaldehyde in toluene. Acylation of the secondary amine with Boc-glycine and Boc-β-alanine under standard conditions provided **82** and **83**. Removal of the Boc group was achieved by action of methanolic hydrochloric acid and thorough washings of the resin. Treatment of the resulting hydrochloride salts with triethylamine resulted in the cyclisative release of the desired tetrahydro-β-carboline-2,3-bis-lactams. Whereas the exact yield of **84** was not reported, compound **85** was obtained in 66% yield.

Pyridine-Fused Heterocycles[53]

As an extension of their solid-phase work on the Knoevenagel and Hantzsch condensation reactions to synthesise nicotinic acid derivatives, Bhandari *et al.* envisaged that the introduction of an amine would enable cyclisative cleavage to take place by nucleophilic attack of this amine onto the linking ester (Scheme 16).

Scheme 16



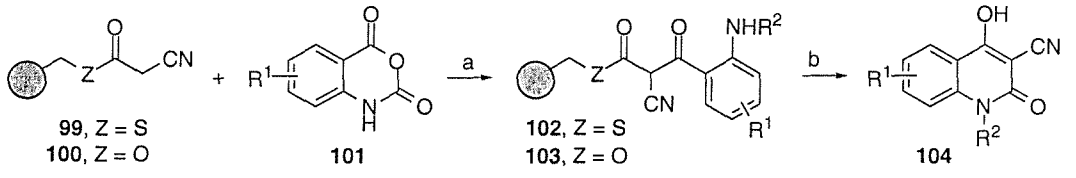
Reagents and conditions: a) **98**, toluene, 70°C, 12hrs; b) R^2CHO, $CH(OMe)_3$, piperidine, DMF, 65°C, 6hrs; c) **97**, $CH(OMe)_3$, DMF, 80°C, 12hrs; d) CAN, DMA; e) 1) further functionalisation on R^4, 2) TFA, CH_2Cl_2; f) Et_3N, CH_2Cl_2.

Two different types of alcohol resin **86** were reacted with α-amino acyl Meldrum's acids **98** to yield the corresponding resin-bound acylacetylate **87**. Knoevenagel condensation with aromatic aldehydes was followed by Hantzsch heterocyclisation with enamines. The resulting resin **91** was aromatised upon treatment with CAN and underwent cyclisation cleavage after Boc deprotection of the amine to give **95**. An alternative one-pot synthesis of **91** was also reported. Using this method, the authors prepared a library of 4800 compounds, by reacting together 16 acyl Meldrum's acids, 20 aldehydes and 15 enamines. Finally, they also described the synthesis of the corresponding naphthyridinones **96** using acyl Meldrum's acids derived from β-amino acids and following the same procedure.

4-Hydroxyquinolin-2(*1H*)-ones[54]

While developing new tools for combinatorial chemistry, Ganessan *et al.* loaded cyanoacetic acid on Wang and TentaGel-SH resins to give **99** and **100** (Scheme 17). *C*-Acylation using isatoic anhydride (**101**) in the presence of a base was then performed.

Scheme 17



Reagents and conditions: a) Et_3N, DMF; b) toluene, 80°C, 24hrs.

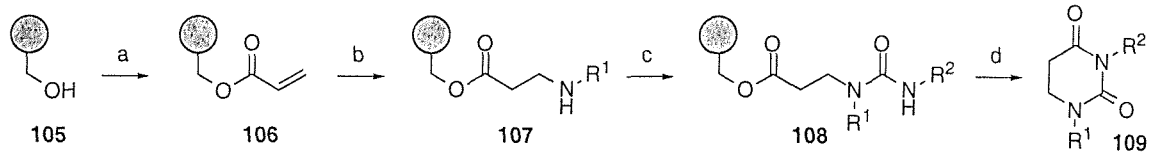
Upon heating, cyclisation cleavage took place, affording the desired hydroxyquinolines **104** as their triethylamine salts in yields ranging from 22% to 65% and purity from 72% to 99%.

Traces of an acyclic by-product were sometimes detected. Comparison of the efficiency of the acylation and the cyclisation depending on which resin was used was reported.

5,6-Dihydropyrimidine-2,4-diones[55]

In order to ease the preparation of 5,6-dihydropyrimidinedione libraries that could be used for biological screenings, Hamper and Kolodziej treated Wang resin (**105**) with acryloyl chloride (Scheme 18). Subsequent Michael addition of primary amines afforded resin **107** which was reacted with a series of isocyanates. The resulting resin-bound ureas **108** were first treated with an aqueous solution of TFA and afforded mainly the linear β-ureido acids.

Scheme 18



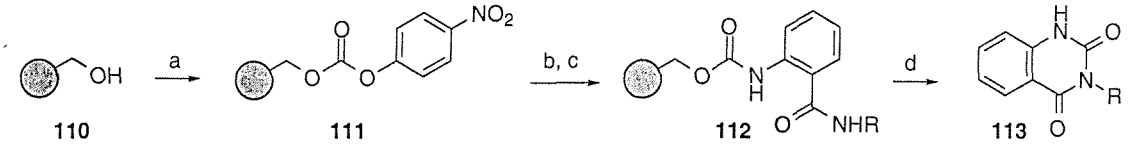
Reagents and conditions: a) H_2C=CHCOCl, Et_3N, CH_2Cl_2; b) R^1NH_2, DMSO, >24hrs; c) R^2NCO, CH_2Cl_2, 4hrs; d) HCl, toluene, 95°C, 4hrs.

However, when treated with HCl in ethanol at higher temperature and under pressure, the desired pyrimidinediones **109** were obtained, albeit in poor yield. After optimisation of the conditions of the cyclisative cleavage and contaminant removal by filtration through silica, the isolated yields in heterocycles **109** ranged from 13% to 76%.

Quinazolin-4-ones and Quinazolin-2,4-diones[56,57]

Following a solution-phase study to find out the optimal cyclisation conditions to form quinazolinediones, Martinez *et al.* decided to apply their method to the solid-phase in order to benefit from the advantages of combinatorial chemistry (Scheme 19).[57]

Scheme 19



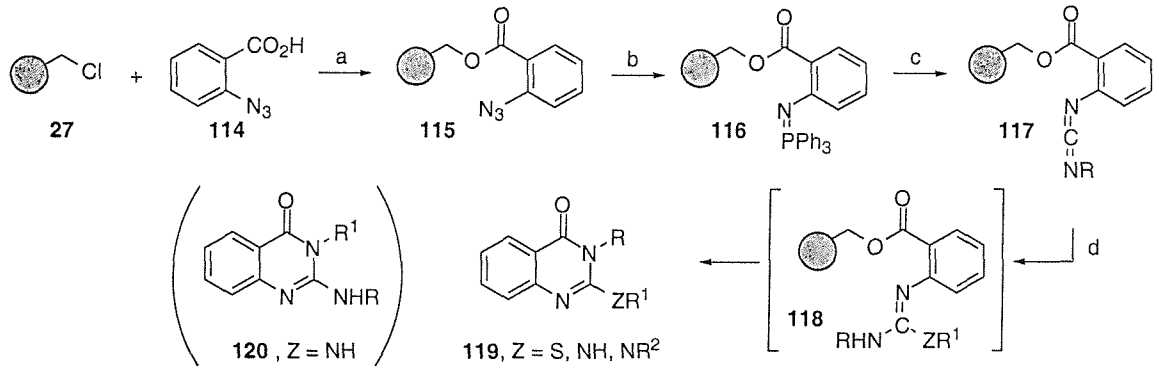
Reagents and conditions: a) 4-nitrophenyl chloroformate, NMM, CH_2Cl_2, 0°C; b) anthranilic acid, HOBt, EtN^iPr_2, DMF, CH_2Cl_2, 6hrs; c) RNH_2, BOP, EtN^iPr_2, CH_2Cl_2, 12hrs; d) Et_3N, MeOH, 60°C, 24hrs.

Hydroxymethyl polystyrene **110** was activated as the corresponding carbonate **111**. Subsequent reaction with anthranilic acid afforded resin **112** which was coupled to eight

amines under standard conditions. Final treatment with excess triethylamine in methanol led to cyclisative cleavage of quinazolinediones **113** in high purity and moderate to good yield.

The strategy followed by Villalgordo relied on aza Wittig-mediated annulation.[56] Azidobenzoic acid (**114**) was coupled to Merrifield resin *via* its caesium salt (Scheme 20).

Scheme 20



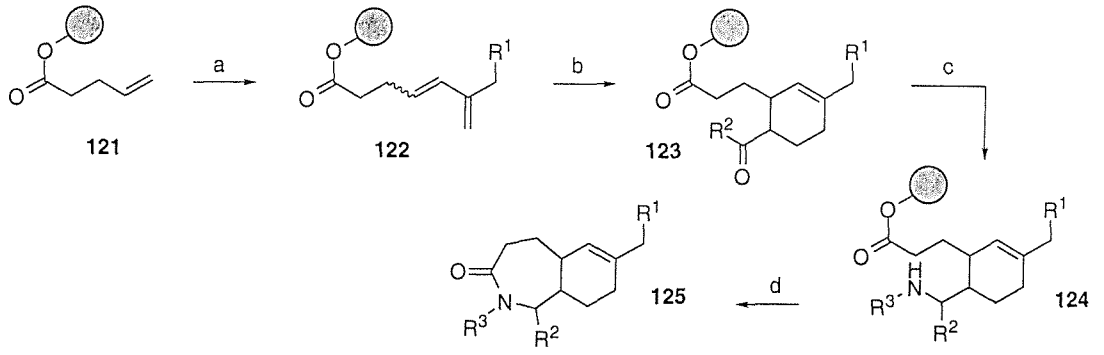
Reagents and conditions: a) Cs_2CO_3, KI, DMF, 80°C, 8hrs; b) PPh_3, THF, 6hrs; c) RNCO, CH_2Cl_2, 8hrs; d) R^1ZH, THF, 50°C, 4hrs.

Subsequent reaction with triphenylphosphine afforded resin-bound iminophosphorane **116** that was reacted with isocyanates. The authors then treated the resulting resin **117** with thiols, primary and secondary amines. Concomitant cyclisation cleavage of **118** occurred, leading to the desired quinazolines **119** in good yield and purity greater than 90%. Notably, unhindered primary amines led to the formation of the two possible regioisomers, **119** and **120**, in a 1:1 ratio.

Octahydrobenzazepinones[58]

Blechert and Schürer reported the solid-phase cross-coupling reaction of a terminal alkene and a terminal alkyne leading to the formation of 1,3-butadiene **122**, enabling a subsequent Diels-Alder reaction to take place. After investigating the feasibility of the reaction on Wang resin, with release of the cyclised product by transesterification, the authors decided to incorporate the nucleophile into the substrate leading to cyclisation cleavage (Scheme 21).

Scheme 21



Reagents and conditions: a) $R^1CH_2C{\equiv}CH$, Grubbs catalyst, CH_2Cl_2, 45°C, 24hrs; b) $R^2COCH{=}CH_2$, $MeAlCl_2$, toluene, CH_2Cl_2, -35°C, 18hrs; c) 1) R^3NH_2, $(MeO)_3CH$, CH_2Cl_2, 2hrs, 2) Bu_4NBH_4, AcOH, DMF, 12hrs; d) 1) Me_3Al, toluene, CH_2Cl_2, 0.5hr, 2) Et_3N, toluene, CH_2Cl_2, 60°C, 24hrs.

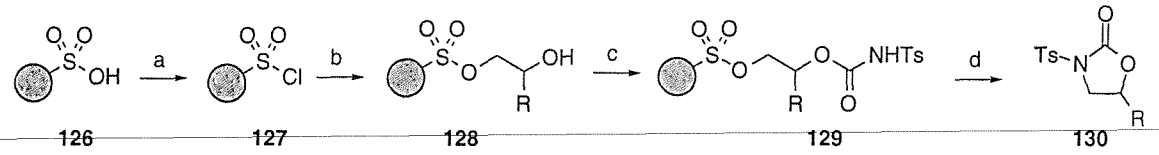
Reductive amination on resin-bound ketone or aldehyde **123** afforded amine **124**. Cyclisation cleavage was achieved in the presence of catalytic amount of Lewis acid and triethyl amine at room temperature, thus affording the desired heterocycles **125** in an average 20% yield but with high purity.

3- Cyclisation with Formation of a C-N Bond Other than an Amide

1,3-Oxazolidin-2-ones[59]

The starting resin was prepared from commercially available resin **126** according to a method established by the authors (Scheme 22). 1,2-Diols were subsequently coupled, attaching selectively *via* the primary alcohol. Reaction of secondary alcohol **128** with isocyanate proceeded without the need of a catalyst.

Scheme 22



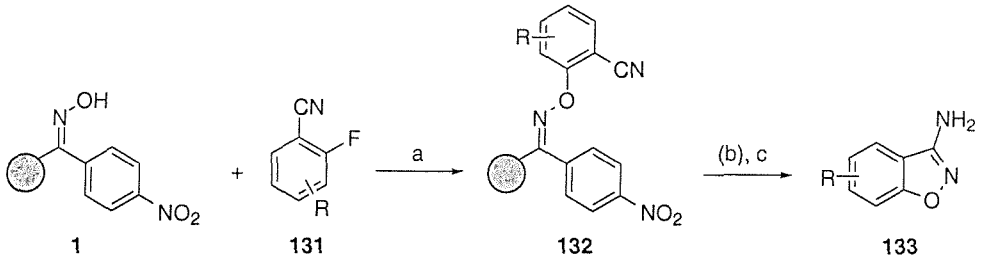
Reagents and conditions: a) $SOCl_2$, DMF, 5min; b) 1,2 diol, Et_3N, CH_2Cl_2, 15hrs; c) TsNCO, CH_2Cl_2, 5hrs; d) DBN, CH_2Cl_2, 15hrs.

Upon reaction with DBN, cyclisation cleavage occurred, thus affording the target oxazolidinones **130** in overall 70% yield. The authors were pleased to observe that no racemisation took place on enantiomerically pure diols.

3-Aminobenzisoxazoles[60]

To take advantage of parallel synthesis techniques, Wiley *et al.* sought to develop a method for the solid-phase synthesis of 3-aminobenzisoxazoles **133**. To implement Shutske's use of a two step process involving acetone oxime addition to 2-fluorobenzonitrile followed by a subsequent acid-mediated cyclisation, the authors decided to employ Kaiser's oxime resin **1**, already presented above. After preliminary studies in solution, the authors moved on to the solid-phase (Scheme 23). Coupling of benzonitrile **131**, carried out at 55°C or at room temperature in the presence of an electron-withdrawing group, was followed by optimisation of the cleavage conditions.

Scheme 23



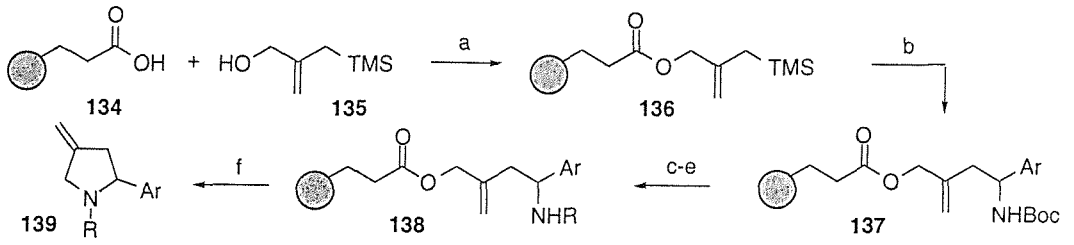
Reagents and conditions: a) KO^{t}Bu, THF, 55°C, 12hrs; b) further functionalisation; c) TFA, HCl, 55°C, 2hrs.

Higher yields were observed for the cyclisation step when THF was used as the solvent, probably due to its resin swelling properties. Also, the presence of aqueous HCl was found to give markedly better results and shorter reaction times than the TFA/water mixture initially employed. Crude cyclisation products were generally quite pure. Further functionalisation was carried out, using Boc protected amines, thus demonstrating the stability of the oxime resin towards anhydrous acid.

Pyrrolidines[61]

Several linkers that rely upon the palladium-catalysed cleavage of allylic systems have been reported in the literature. However, Brown and Fisher designed a reversed allylic linker, activated by palladium, to afford an electrophilic π-allyl palladium species that could be trapped with nucleophiles to release cyclic products. They applied this strategy to the synthesis of pyrrolidines **139** (Scheme 24). After investigating the chemistry on a solution-phase model, where some of the yields were rather low, the authors decided to optimise their approach directly on the solid-phase.

Scheme 24



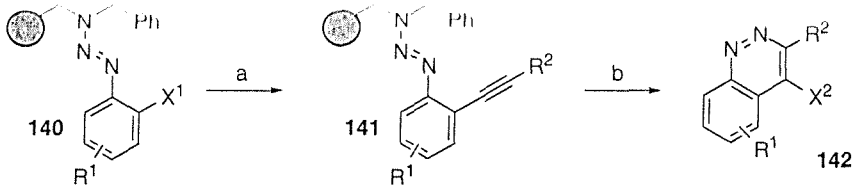
Reagents and conditions: a) DIC, DMAP, CH_2Cl_2; b) ArCH=NBoc, $BF_3.OEt_2$, CH_2Cl_2; c) TFA, CH_2Cl_2; d) RCHO, AcOH, $ClCH_2CH_2Cl$; e) $Me_4NB(OAc)_3H$, $ClCH_2CH_2Cl$; f) $Pd(acac)_2$, dppe, THF.

A set of six different pyrrolidines **139** were synthesised by coupling under standard conditions alcohol **135** to a carboxyethylated polystyrene resin **134** prepared in-house in three steps. The ester linkage enabled cleavage from the resin to check the reaction progress after each step. The authors found that the optimised conditions for the next step, an imino Sakurai reaction requiring a large excess of boron trifluoride etherate, gave better yields than the analogous work carried out in solution. Removal of the protecting group from **137** and further reductive alkylation then preceded catalytic cyclisation cleavage. It should be noted that the crude cyclised products were cleaner than their acyclic precursors released by reductive cleavage.

Cinnolines[62]

After having developed a triazene linker that enabled traceless cleavage of arenes, Bräse *et al.* were interested in its use as a component of the Richter cyclisation hence releasing heterocycles in a cyclisative cleavage fashion (Scheme 25).

Scheme 25



Reagents and conditions: a) $R^2C{\equiv}CH$, $Pd(OAc)_2$, Et_3N, DMF, 80°C, 12hrs; b) HX^2 (X^2= Br or Cl), H_2O, acetone.

Starting from benzylaminomethyl polystyrene, three different haloaryl resins **140** were prepared in good yield. Subsequent palladium catalysed cross-coupling reaction with four alkynes under standard conditions afforded resins **141**. Finally, the cyclisative cleavage took place in the presence of aqueous HCl or HBr in acetone at room temperature. Cinnolines **142** were obtained in good yield (47-95%) and purity (60-95%). More dilute acid or longer

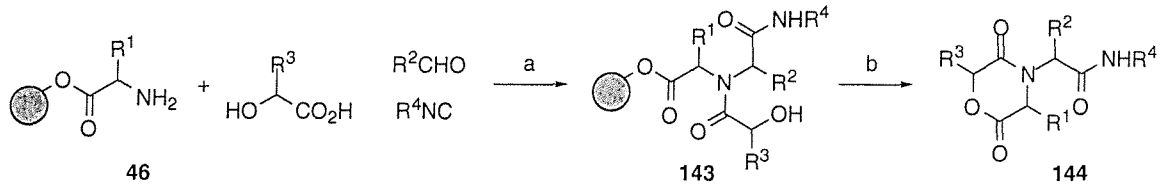
reaction times led to a hydrolysis reaction thus affording the corresponding 4-hydroxycinnolines.

4- Cyclisation with Formation of a C-O Bond

Diketomorpholines[45]

The synthesis of diketomorpholines **144** was reported in the same paper as the diketopiperazines **49** and represented in fact an adaptation of it.[45] Szardenings and co-workers decided to use a series of α-hydroxy functionalised acids in the Ugi four component condensation to give **143** (Scheme 26).

Scheme 26



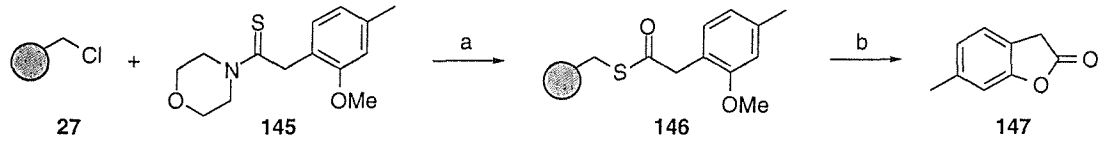
Reagents and conditions: a) MeOH; b) 1) TFA, CH_2Cl_2, 2) AcOH or Et_3N, toluene, EtOH.

Cyclisation under mild conditions afforded the desired products **144** in 16% to 56% yield after purification. Notably, TentaGel resin was superior to Wang or PAM resin with respect to purity of the released diketomorpholines.

Benzofuranones[63]

Bradley and Harrowven disclosed a method for the cyclisative cleavage of thioester **146** to benzofuranone **147** in the presence of boron trichloride in 95% yield (Scheme 27).

Scheme 27



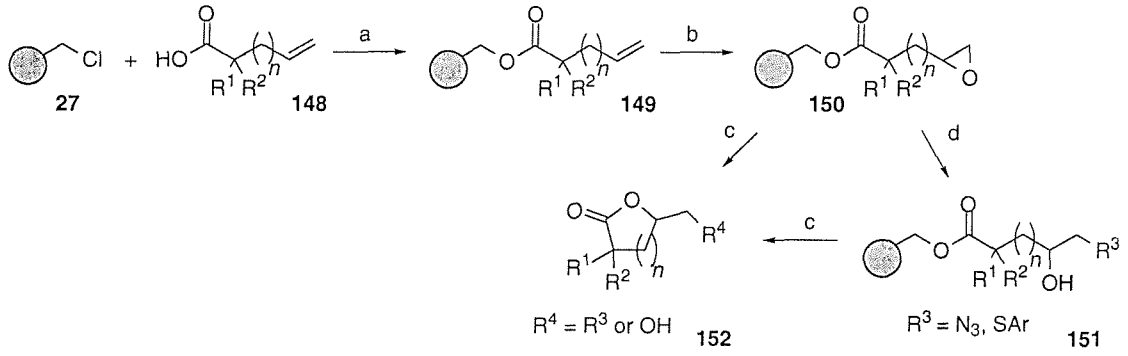
Reagents and conditions: a) NaI, DMF, 100°C, 48hrs; b) BCl_3, CH_2Cl_2, 0°C, 5hrs.

The authors reported only one example and underlined the limited scope of this reaction, its main interest being its novelty.

γ- and δ-Lactones[64]

French researchers reported investigations on the synthesis of polymer-bound epoxides **150** by oxidation of alkenes and their subsequent use in the formation of lactones, the interest being their widespread occurrence in natural products (Scheme 28).

Scheme 28



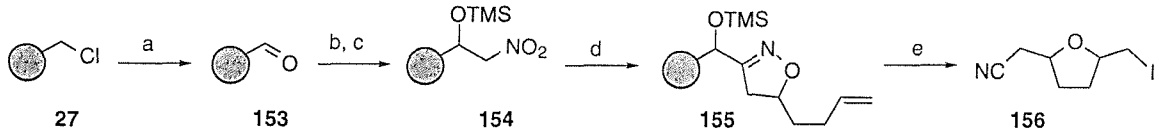
Reagents and conditions: a) Cs_2CO_3, KI, DMF, 80°C; b) mCPBA, CH_2Cl_2; c) TFA, CH_2Cl_2; d) NaN_3, NH_4Cl or ArSNa.

Coupling of four different alkenoic acids **148** to Merrifield resin was achieved using caesium carbonate. Subsequent epoxidation with 3-chloroperbenzoic acid in methylene chloride at room temperature afforded resin **150**. Reaction of resin-bound epoxides with azide or sodium thiolate as the nucleophile opened the epoxides and the resulting alcohols spontaneously cyclised off the resin upon treatment with TFA. Likewise, eight lactones **152** were obtained in good yields (45-67%) and purities (>75%). In addition, the authors reported that the epoxides also cyclised upon treatment with TFA in dichloromethane, yielding four lactones **152** (R^4 = OH) in comparable yields (56-60%) and purity (>70%).

Tetrahydrofurans, Tetrahydrofuroisoxazolines and γ-Butyrolactones[65-67]

2,5-Disubstituted tetrahydrofurans are present in many natural products including polyether antibiotics. As an approach to solving the problem of bis cycloaddition on an α,ω-diene that occurred during a solution-phase method to form tetrahydrofurans, the authors considered the potential benefits of attachment of the substrate to a solid-support (Scheme 29).[65]

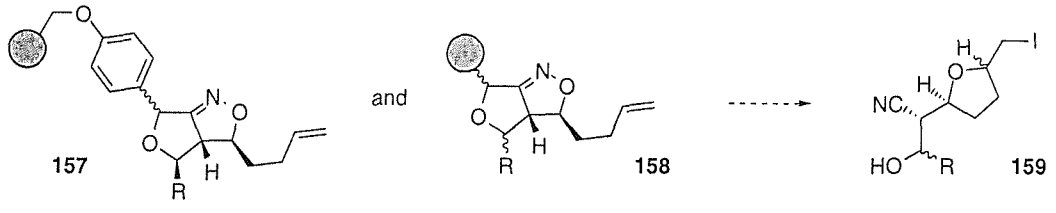
Scheme 29



Reagents and conditions: a) DMSO, $NaHCO_3$, 155°C, 6hrs; b) CH_3NO_2, Et_3N, THF, EtOH, 14hrs; c) TMSCl, Et_3N, THF, 24hrs; d) PhNCO, 1,5-hexadiene, Et_3N, C_6H_6, 80°C, 96hrs; e) ICl, CH_2Cl_2, -78°C, 1.5hrs.

After carrying out the chemistry using a solution-phase model, the authors decided to use Merrifield resin. Oxidation of Merrifield resin to the corresponding polymer-bound aldehyde **153**, condensation with nitromethane and protection of the hydroxyl group afforded resin **154**. In fact, the protection was necessary for the subsequent dehydration of the nitroalkane in the presence of phenyl isocyanate, followed by cycloaddition with 1,5-hexadiene to take place. Finally, electrophilic cyclisation of isoxazole **155** with iodine monochloride at -78°C afforded the desired cyclic product and regenerated the polymer bound aldehyde **153**. The overall yield of **156**, much higher than that obtained in solution, was found to be 40% when using 3 equivalents of hexadiene instead of 29% when using 2 equivalents. When recovered and recycled through the synthetic sequence, polymer-bound aldehyde afforded another 11-17% of product. Three years later, modifications of the original linker were published leading to the formation of resins **157** and **158** from Merrifield resin (Figure 4).[66]

Figure 4

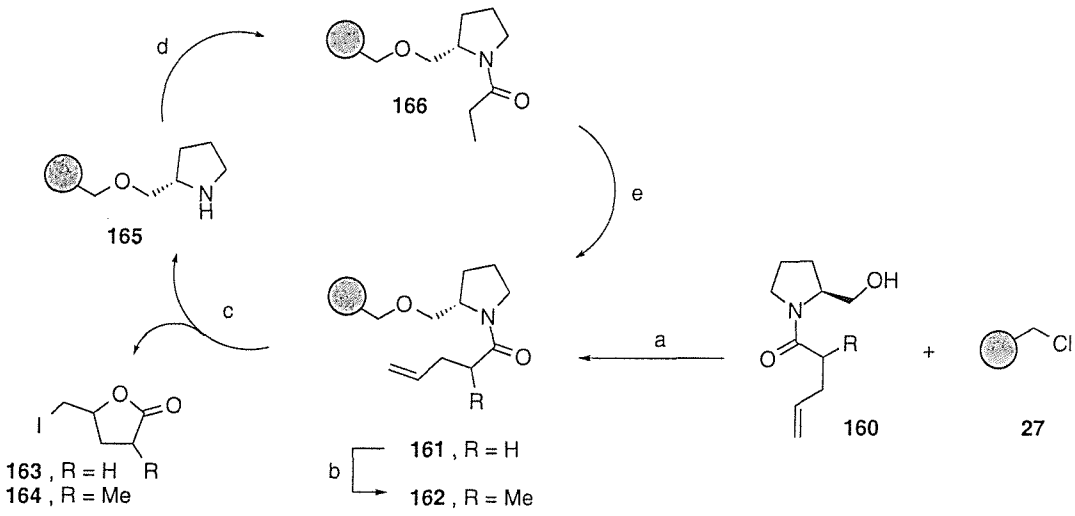


Nevertheless, the electrophilic cyclisation to induce the cleavage off the resin of the expected tetrahydrofuran **159** occurred in a similar manner as that reported previously. The best result was obtained with IBr in dichloromethane on a high loading resin. Surprisingly, homologation of the side chain did not lead to the formation of the expected tetrahydropyrans.

Using an iodolactonisation to induce the cyclisation cleavage, Kurth and co-workers were able to synthesise optically active butyrolactones **164** (Scheme 30).[67] Merrifield resin was linked *via* an ether linkage to functionalised L-prolinol **160**. Initially the latter was prepared previously in solution and coupled under standard conditions. Later, the chiral linker was assembled on the resin, thus offering the remarkable advantage of being regenerated upon

cleavage. In order to investigate the magnitude of asymmetric induction by the resin-bound chiral auxiliary, alkylation was carried out affording resin **162**. Treatment of resins **161** and **162** with iodine in a mixture of THF and water provided all the possible isomeric lactones in good overall yield.

Scheme 30



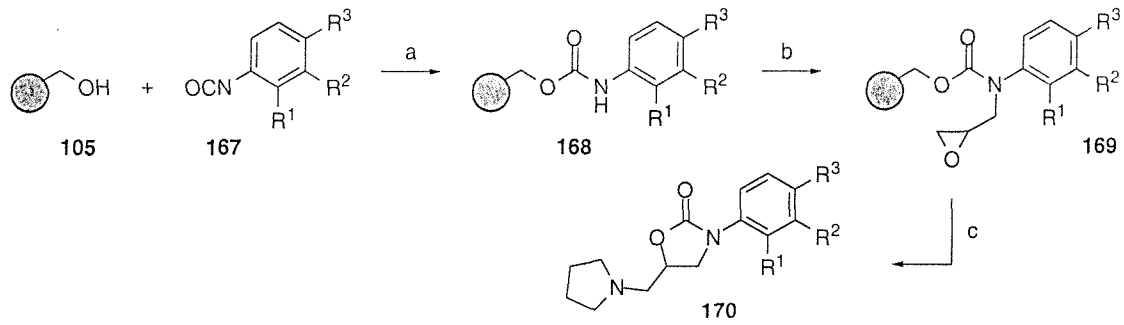
Reagents and conditions: a) KH, 18-crown-6, DMF, THF, 80°C, 3 days; b) LDA, MeI, THF; c) I_2, THF, H_2O, 3 days; d) propionyl chloride, Et_3N, THF, 2 days; e) LDA, allyl iodide, THF.

The authors were pleased to observe that the enantiomeric ratios obtained closely matched those obtained in solution and thus demonstrated the potential of the method.

Oxazolidinones[68]

The *N*-aryloxazolidinone scaffold is present in numerous compounds of biological interest. Buchstaller reported a three-step synthesis starting from eleven commercially available isocyanates **167** and Wang resin **105** (Scheme 31).

Scheme 31



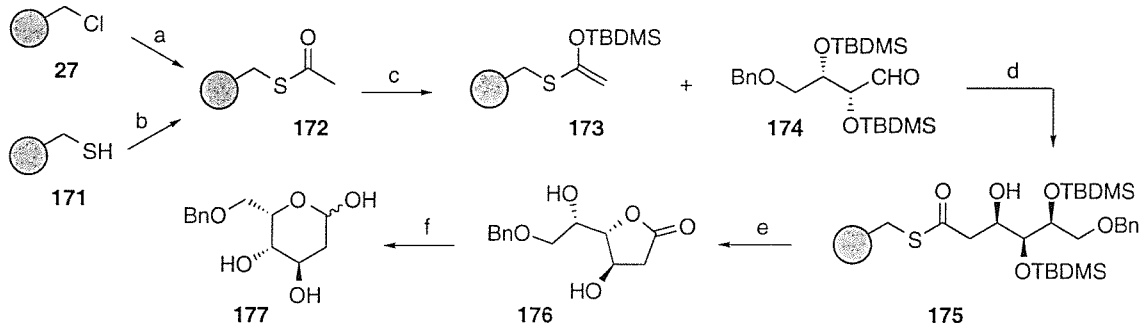
Reagents and conditions: a) Et_3N, CH_2Cl_2, 0.5hrs; b) $LiN(SiMe_3)_2$, LiI, glycidyltosylate, NMP, THF, 24hrs; c) pyrrolidine, $LiClO_4$, THF.

Thus, resin-bound carbamates **168** were obtained using 6 equivalents of isocyanates **167** in the presence of catalytic amounts of triethylamine. Subsequent *N*-alkylation upon treatment with 2 equivalents of lithium amide and excess of alkylating agent afforded resins **169**. The final cyclisative cleavage occurred after nucleophilic opening of the epoxides with 5 equivalents of pyrrolidine at ambient temperature, thus leading to the corresponding aminoalcohols that spontaneously cyclised off the resin. Lithium perchlorate was added to the reaction mixture to facilitate the epoxide ring opening. Oxazolidinones **170** were obtained in excellent purity (>97%, apart from 3 compounds) and good yield (71-100%).

Monosaccharide Derivatives[69]

In view of the biological importance of sugars, Kobayashi *et al.* investigated a new method for the solid-phase synthesis of diverse monosaccharide derivatives (Scheme 32). Initially one monosaccharide was prepared using a four-step synthesis on the solid-phase, followed by a fifth step in solution. Then, varying the reagents to react with the resin-bound substrate, the authors produced about twenty different sugars.

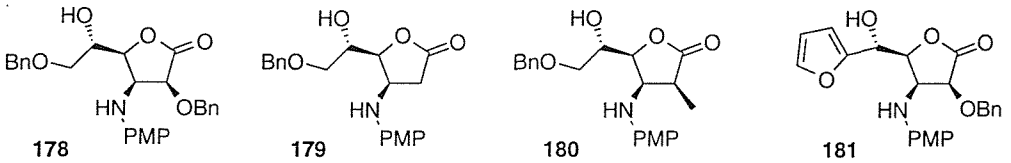
Scheme 32



Reagents and conditions: a) CH_3COSK, Bu_4NI, DMF; b) CH_3COCl, Et_3N, CH_2Cl_2; c) TBDMSOTf, Et_3N, CH_2Cl_2; d) $BF_3.OEt_2$, CH_2Cl_2, -78°C; e) TBAF, AcOH, THF, 40°C; f) DIBAL, CH_2Cl_2, -78°C.

Either chloromethylated or thiol resins were converted to the resin-bound thioester **172**. Formation of the silyl enol ether at room temperature was followed by aldol condensation with chiral aldehyde **174** in the presence of a Lewis acid. Deprotection of the silyl group induced spontaneous cyclisation with release from the resin. The overall yield was determined to be 61%. Final reduction of **176** was carried out in solution in good yield. Some of the other sugars synthesised similarly are depicted below (Figure 5).

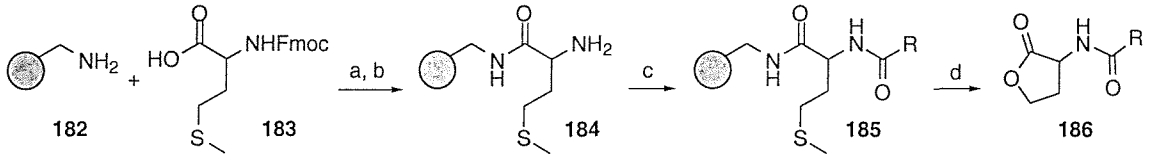
Figure 5



Homoserine Lactones[70]

With a view to explore a mild cleavage method for the solid-phase synthesis of homoserine lactone libraries, Moon *et al.* reported the use of a four-step process (Scheme 33). The reaction sequence involved coupling of Fmoc protected methionine **183** to aminoethyl polystyrene resin **182** using standard conditions, deprotection with a 20% solution of piperidine in dichloromethane, subsequent *N*-coupling with a carboxylic acid and final cyclisation cleavage to give lactones **186**.

Scheme 33



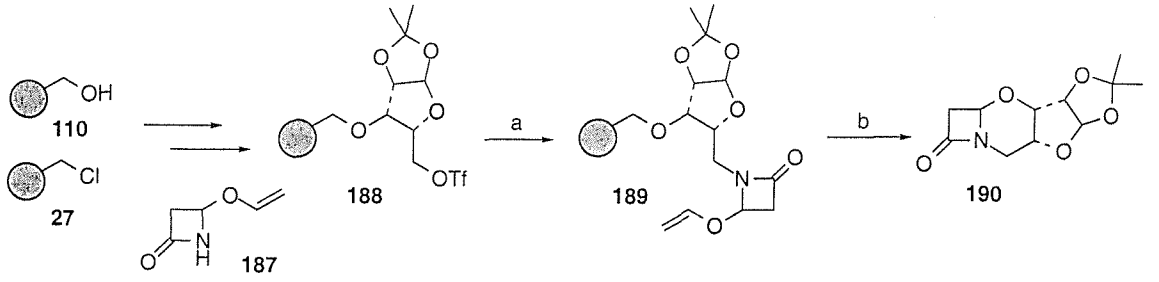
Reagents and conditions: a) HOBt, DIC, *N*-ethylmorpholine, DMF; b) 20% piperidine/DMF; c) RCO_2H, HOBt, DIC, *N*-ethylmorpholine, DMF; d) BrCN, TFA, $CHCl_3$, H_2O.

The cleavage step was achieved by treating the resin with a large excess of cyanogen bromide and catalytic amount of TFA in a 5:2 (v/v) mixture of chloroform and water, at room temperature over 24 hours. The cyclisative cleavage occurred with retention of stereochemistry. The title compounds **186** were obtained in 32-53% overall yield.

1-Oxacephams[71,72]

In two papers, Chmielewski *et al.* described a cyclisation cleavage to oxacephams. They both relied on the same cleavage method but differed in the method of preparation of the intermediate resins (Scheme 34).

Scheme 34



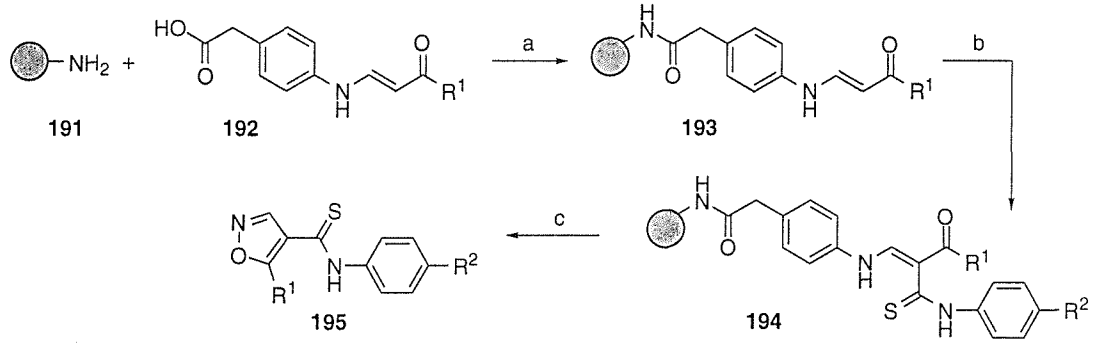
Reagents and conditions: a) **187**, *n*BuLi, Bu_4NHSO_4, THF, 12hrs; b) $BF_3.Et_2O$, CH_2Cl_2, 3hrs.

N-Alkylation of 4-vinyloxyazetidin-2-one (**187**) with triflate **188** in the presence of two equivalents of butyllithium afforded the resin-bound β-lactams **189**. The latter were treated with a Lewis acid at room temperature for three hours to give the desired heterocycles **190** in 30% overall yield over six steps for the first linker described by the authors, and 20% yield over five steps for the second linker. In both cases high diastereomeric purity was observed.

Isoxazolylthioamides[73]

Albert *et al.* at Novartis decided to synthesise 24 thioamides analogous to leflunomide and its metabolite in order to gain insight into the modulation of their biological activities (Scheme 36). Coupling of a series of 6 different acids **192** to amino TentaGel resin **191** was achieved using standard techniques. Acids **192** were synthesised in solution as they are generally obtained in low yields, thus avoiding an initial low loading of the resin. Further functionalisation with 4 variously *p*-substituted phenylisothiocyanates was carried out under reflux in THF.

Scheme 36



Reagents and conditions: a) DCC, HOBt; b) phenylisothiocyanate, THF, reflux; c) $H_2NOH.HCl$, $NaHCO_3$, H_2O, EtOH.

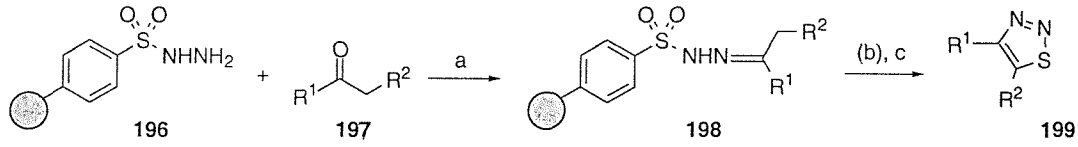
Cyclisation cleavage of the isoxazolyl thioamides **195** from the resin was achieved by treating resin **194** with hydroxylamine hydrochloride in aqueous ethanol. The yields were rather low (12-20%) but the purity was greater than 95% in most cases.

5- Cyclisation with Formation of a C-S Bond

1,2,3-Thiadiazoles[74]

1,2,3-Thiadiazoles are an important class of biologically active compounds. After preparing a gel-type polystyrene-sulfonylhydrazine resin **196**, Porco *et al.* felt they could use it as a linker for carbonyl compounds in solid-phase synthesis (Scheme 35).

Scheme 35



Reagents and conditions: a) AcOH, THF, 50°C, 4hrs; b) further functionalisation *via* Suzuki coupling; c) $SOCl_2$, $ClCH_2CH_2Cl$, 60°C, 5hrs.

The formation of sulfonylhydrazone **198** was complete in a couple of hours at 50°C in the presence of acetic acid using 2.5 equivalents of seven different ketones **197**. The cleavage step, carried out in parallel on the seven substrates, was achieved using thionyl chloride. The cleavage solution of 1,2,3-thiadiazoles **199** required purification using an aqueous saturated solution of sodium carbonate. The authors also described a method for further functionalisation under Suzuki conditions in cases when aryl halides were present on the resin-bound substrate **198** prior to the cyclisation.

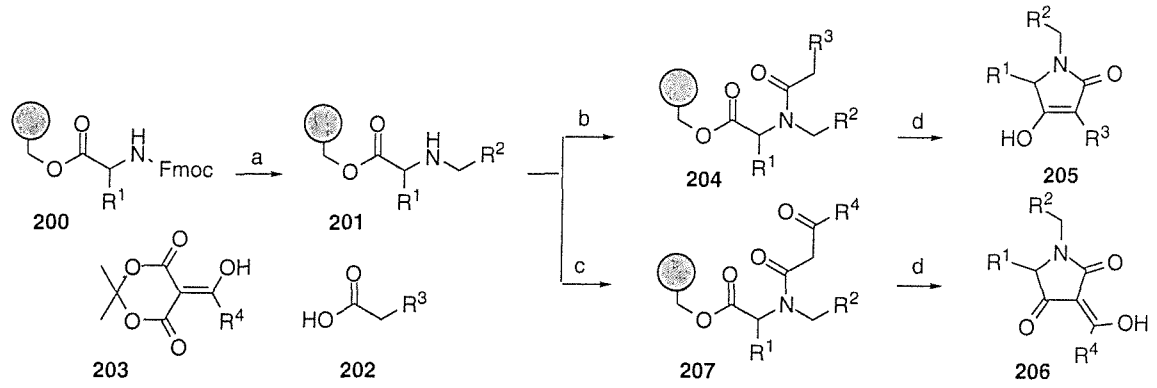
6- Cyclisation with Formation of a C-C Bond

Tetramic Acids[75-78]

3-Acyl tetramic acid has attracted significant attention over the last years as a result of its biological activity. Four different syntheses were reported in the literature in 1998. They mainly differed in the reaction conditions used to effect the final Dieckmann cyclisative cleavage. Several resin-bound aminoacids, either purchased as such on Merrifield resin or attached to any kind of hydroxymethyl resins (e.g. Wang or TentaGel) using standard techniques, were further functionalised to give resins **201** by reductive amination with a variety of aldehydes, unless the resin-bound amino acids were purchased already *N*-alkylated

(Scheme 37). Subsequent acylation was carried out using Meldrum's acid **203**, synthesised according to the needs of the authors, or using malonates or substituted acetic acids **202** in the case of Matthews's and Ganessan's works. Subsequent cyclisation under the different conditions described below afforded the desired 5-membered rings **205** or **206**.

Scheme 37



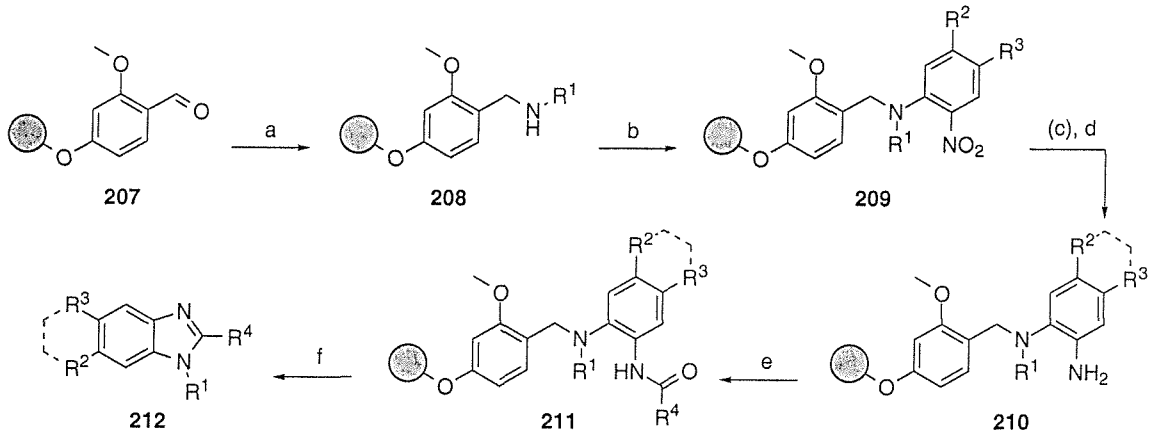
Reagents and conditions: a) 1) piperidine, DMF, 2) R^2CHO, $NaBH_3CN$, AcOH, $(MeO)_3CH$, CH_2Cl_2; b) **202**, DIC, HOBt, CH_2Cl_2 or **202**, DIC, DMF; c) **203**, toluene, 65 or 120°C; d) KOH, MeOH or EtN^iPr_2, dioxane or NaOEt or Bu_4NOH.

Weber *et al.* employed a series of common bases to find out the best conditions for the cyclisative cleavage. Favouring purity (>83%) over yield (11-38%) of the final products **206**, they reported the use of diisopropylethyl amine at 80°C in dioxane over 16 hours. Romoff used a different base, KOH in methanol, which allowed cyclisation to **206** at room temperature in less than 30 minutes. The corresponding potassium salts were obtained in excellent purity (>95%) and higher yields (43-92%). Matthews preferred the use of a 0.1M solution of sodium ethoxide at 85°C for one day and obtained a small library of compounds **205** in excellent yields and purity (>95%). Both authors were pleased to discover that little racemisation occurred. Finally, Ganessan tested potassium *tert*-butoxide and lithium hexamethyldisilazide but preferred the use of tetrabutylammonium hydroxide since it could be easily removed by treatment with Amberlyst. The reported yields of **205** ranged from 68% to 91% and the purity was generally high.

Benzimidazoles and Related Structures[79,80]

Krchnák and Smith developed a solid-phase sequence with final cyclisation cleavage to benzimidazoles (Scheme 38). At about the same time Mazurov published a very similar strategy leading to related structures, namely 5,6,7,8-tetrahydro-1*H*-imidazo[4,5-g] quinoxalin-ones.

Scheme 38



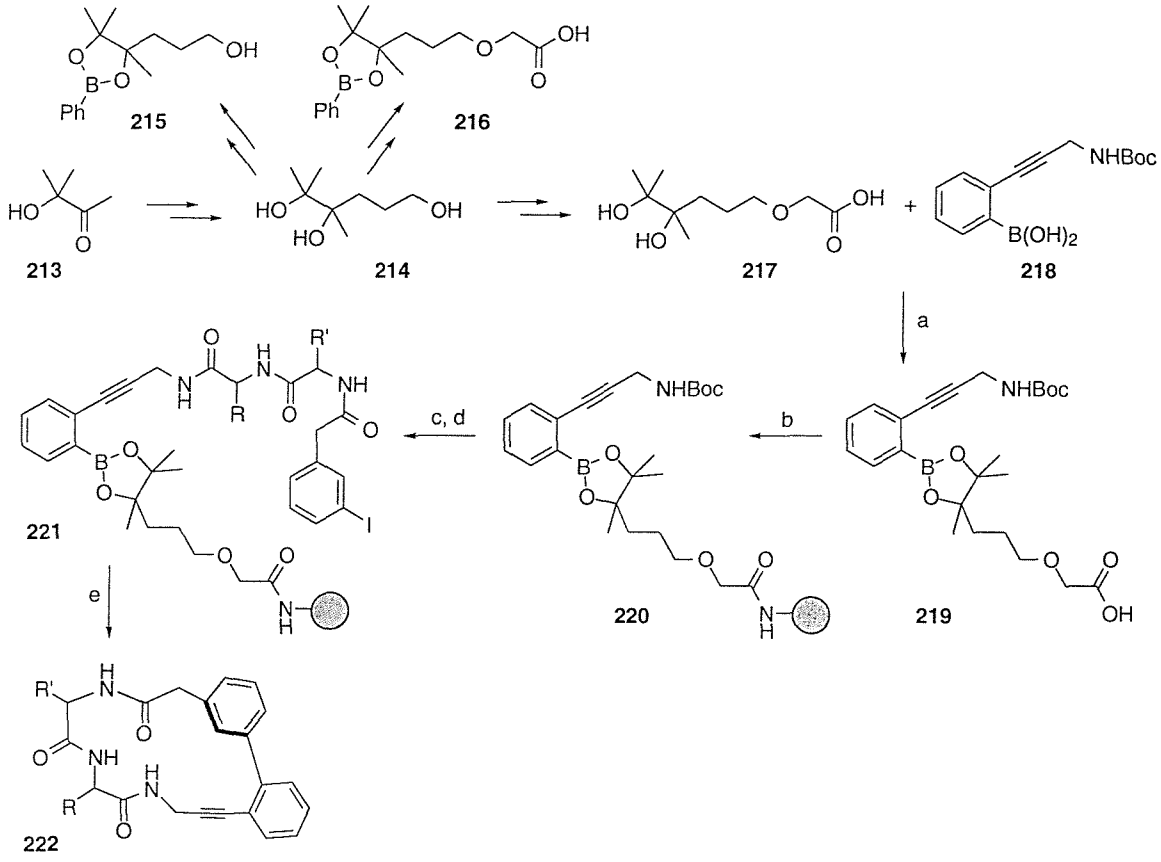
Reagents and conditions: a) R^1NH_2, hydride source; b) *o*-fluoronitrobenzene, DMSO or 1,5-difluoro-2,4-dinitrobenzenes, Et_3N; c) further functionalisation on R^2 and R^3; d) $SnCl_2$, base; e) R^4COCl, EtN^iPr_2, CH_2Cl_2 or R^4CO_2H, DIC; f) AcOH or HCl, dioxane, methanol, 80°C.

In both cases, commercially available aldehyde resin **207**, enabling cleavage of an aliquot to check the reaction progress, was reacted with a series of amines and the resulting imines were reduced *in situ*. Subsequent reaction with several fluoronitrobenzenes or difluorodinitrobenzenes afforded resins **209**. At this stage Mazurov carried out further functionalisation of the resin-bound substrate, taking advantage of the second fluorine to couple several amino esters. The nitro groups were reduced to the corresponding anilines **210** upon treatment with tin (II) chloride, with simultaneous ring closing in Mazurov's case. Resin-bound anilines **210** were subsequently acylated. Krchnák initially obtained the desired cyclised product **212** as the major component of a mixture, the minor being acylated phenylenediamine. The latter could be transformed into the target molecule by cyclisation in acetic acid at 80°C. Later, Krchnák was able to obtain only the desired benzimidazoles **212** by simultaneous cyclisation and cleavage in hot acetic acid. A small set of benzimidazoles was obtained in good purity (82-96%) and yield (30-74%). Mazurov also obtained partial cyclisation when using a mixture of TFA, dichloromethane and triethyl silane. The mixture of target molecule **212** and diaminobenzene could be transformed into product only by further reaction with hot methanolic hydrochloric acid in dioxane. Alternatively, using this mixture as the cleavage cocktail resulted in complete cyclisative cleavage of **212**. However, Mazurov reported that while the yield of crude material was essentially the same with both methods (ca 80%), the purity was higher when using the two step procedure. A library of sixty compounds was synthesised. Notably, the same year but in another journal, Mazurov published another report on solid-phase synthesis of benzimidazoles, stating that the cleavage occurred with concomitant ring closure only when R^4 was a methyl group.[81]

β-Turn Biaryl Macrocycles[82]

During their studies on β-turn mimics, Burgess and co-workers discovered from molecular modelling studies that the biaryl structure **222** holds the two aminoacids rigidly in a β-turn conformation. The authors decided to investigate the cyclisation release of **222** with simultaneous formation of the biaryl bond under Suzuki conditions (Scheme 39).

Scheme 39



Reagents and conditions: a) $MgSO_4$, CH_2Cl_2, 12hrs; b) TentaGel or MBHA, DIC, HOBt, EtN^iPr_2, DMF; c) deprotection conditions not reported; d) dipeptide, DIC, HOBt, EtN^iPr_2, DMF; e) $PdCl_2$binap, K_3PO_4, DMF, 60°C, 24hrs.

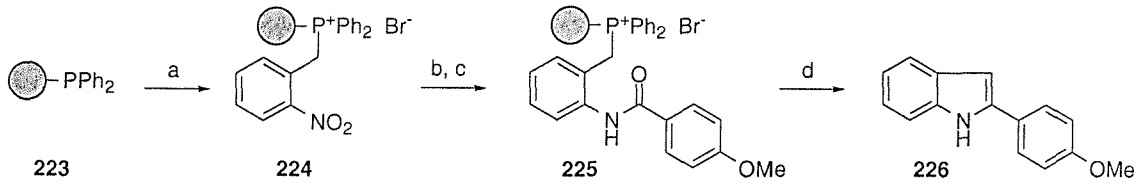
In order to do so, they developed in solution a new boron linker from diol **217**, the synthesis of which was reported in the literature. After several unsuccessful attempts to couple **215** to a phenolic resin, the authors decided to modify their initial linker. Introduction of a carboxylic acid group allowed efficient coupling of **216** to Rink amide resin, and optimisation of the Suzuki conditions was carried out on the resulting resin-bound boronic ester. Further modification of the linker was carried out in order to introduce the alkyne, thus leading to **219**. For its preparation, the required boronic acid **218** was obtained in four steps from 2-bromoiodobenzene. Subsequent coupling of **219** to an amine resin was achieved under

standard conditions. Unfortunately, the peptide chain could not be assembled directly on the resin, and therefore had to be prepared in solution and then coupled to the resin, giving resin **221**. Cyclisation of **222** occurred in high purity and in about 30% yield for both R=R'=H and R=H, R'=L-CH_2CONH_2.

Indoles and Indolines[83,84]

As one example of the possible use of a resin-bound phosphonium salt, Hughes reported a cyclisation cleavage to the 2-substituted indole **226** (Scheme 40).[83]

Scheme 40



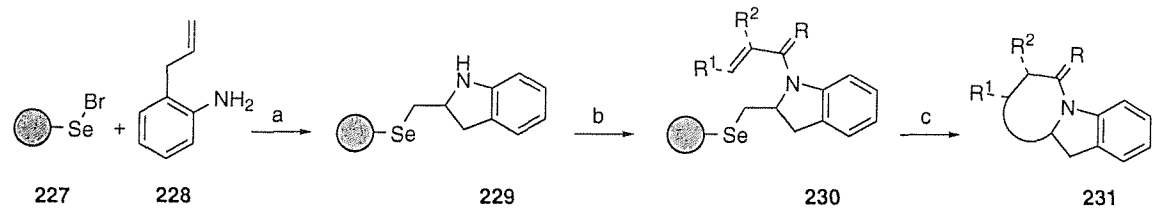
223 224 225 226

Reagents and conditions: a) 2-nitrobenzyl bromide, DMF, 70°C, 48hrs; b) 1) $Na_2S_2O_4$, EtOH, reflux, 1.5hrs, 2) HBr, MeOH, dioxane; c) 4-methoxybenzoyl chloride, pyridine, CH_2Cl_2, 5hrs; d) 1) toluene, DMF, 2) KO'Bu, reflux, 45min.

The phosphonium salt resin was prepared from commercially available polymer-bound triphenylphosphine **223**. Formation of the phosphonium salt and reduction of the nitro group was followed by acylation, thus affording anilide **225**. Intramolecular Wittig reaction under strictly anhydrous conditions was achieved in 78% yield, provided DMF was used as a co-solvent probably to help solvation and/or swelling.

Nicolaou *et al.* reported two possible ways of utilisation of selenium linker to synthesise indolines.[84] They first reported the use of the selenium linker as a traceless linker leading to the formation of 1-methyl substituted indolines. The second use of the selenium linker was based on its ability to generate a carbon-centred radical. The close proximity of a radical acceptor led to cyclisative cleavage (Scheme 50). Functionalisation of selenyl bromide polystyrene **227** with allyl aniline in the presence of tin chloride afforded resin **229**. The secondary amine was subsequently coupled to a series of olefins either by amide formation or alkylation under standard conditions. Treatment of resin **230** with radical initiator AIBN and tributyltin hydride provided the desired polycyclic indolines **231** in yields ranging from 13% to 36% and high purity.

Scheme 50



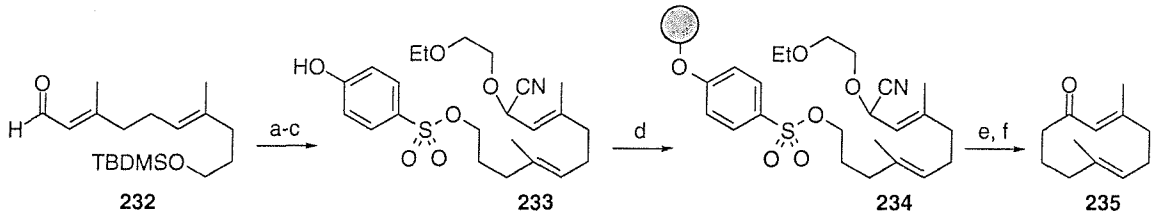
227 228 229 230 231

Reagents and conditions: a) $SnCl_4$, CH_2Cl_2; b) R=O: $R^1CH{=}CHR^2CO_2H$, DCC, DMAP, CH_2Cl_2, 24hrs, R=H_2: $R^1CH{=}CHCH_2Br$, NaH, DMF, 60°C; c) Bu_3SnH, AIBN, toluene, 90°C, 4hrs.

Macrocyclic Ketones and Lactones[85,86]

Employing a Multipin system, Takahashi *et al.* used 4-hydroxybenzenesulfonate as a linker to enable the introduction of a nucleophile upon cleavage.[85] They decided to apply an intramolecular nucleophilic attack to the formation of cyclic ketones from resin-bound cyanohydrins (Scheme 51).

Scheme 51



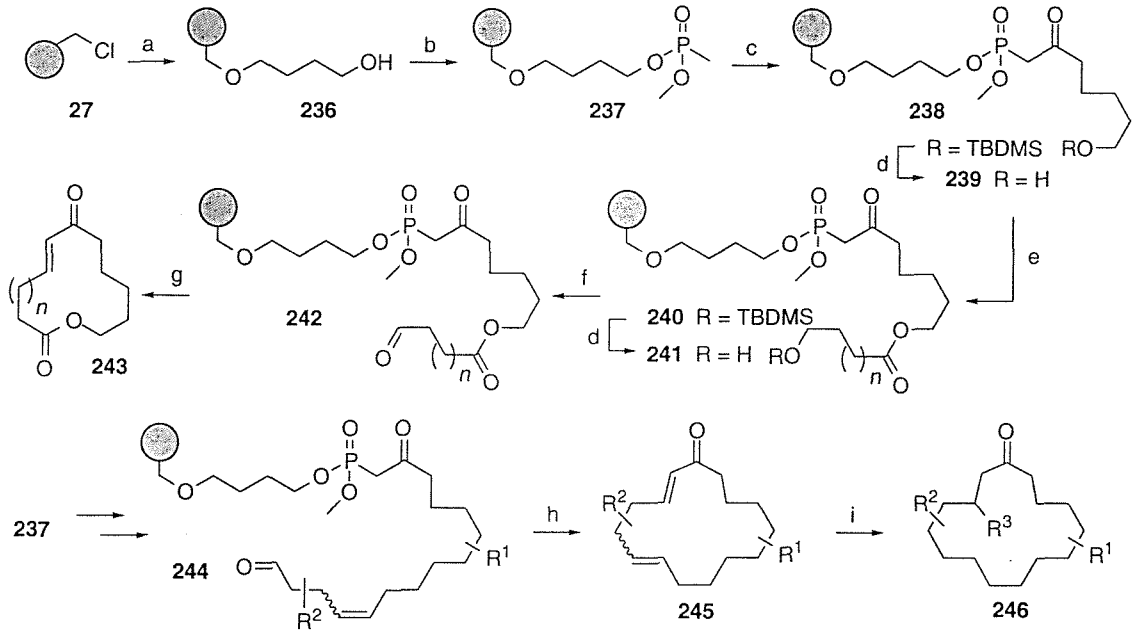
232 233 234 235

Reagents and conditions: a) 1) TMSCN, 18-crown-6, KCN, 2) HCl, THF, 3) ethyl vinyl ether, *p*TSA, CH_2Cl_2; b) TBAF, THF; c) 4-hydroxybenzenesulfonyl chloride, pyridine, $CHCl_3$; d) trityl crown resin, EtN^iPr_2, 24hrs; e) LiHMDS, dioxane, 100°C; f) 1) H^+, 2) OH^-.

The synthesis of the cyanohydrin derived from **232** was previously reported by the authors. Its solution-phase reaction with 4-hydroxysulfonyl chloride afforded phenol **233** that was subsequently loaded on the trityl resin in 50% yield. Treatment of resin **234** with insoluble bases did not induce any cleavage from the solid-support. Nevertheless, when **234** was reacted with lithium hexamethyldisilazide in THF, the expected macrocycle was obtained in moderate yield. Optimisation of the solvent system, reaction temperature and quantity of base improved the yield to 46%. Conversion to the corresponding ketone **235** was carried out in solution following a known procedure.

Nicolaou and co-workers decided to investigate the ketophosphonate-aldehyde condensation reaction as a means of cyclisative release of macrocyclic ketones **246** and lactones **243** (Scheme 52).[86]

Scheme 52



Reagents and conditions: a) 1,4-butanediol, NaH, Bu_4NI, DMF, 12hrs; b) $CH_3P(O)(OCH_3)Cl$, Et_3N, CH_2Cl_2, 12hrs; c) *n*BuLi, $MeO_2C(CH_2)_5OTBDMS$, 40min; d) TBAF, THF, 12hrs; e) $HO_2C(CH_2)_mOTBDMS$ (m=9 or 11; n=m-2), DCC, DMAP, CH_2Cl_2, 12hrs; f) Dess Martin periodinane, CH_2Cl_2, 6hrs; g) K_2CO_3, 18-crown-6, toluene, 65°C, 12hrs; i) 1) $LiCu(R^3)_2$, Et_2O, 0°C, 1hr, 2) H_2, Pd-C, MeOH, 2hrs.

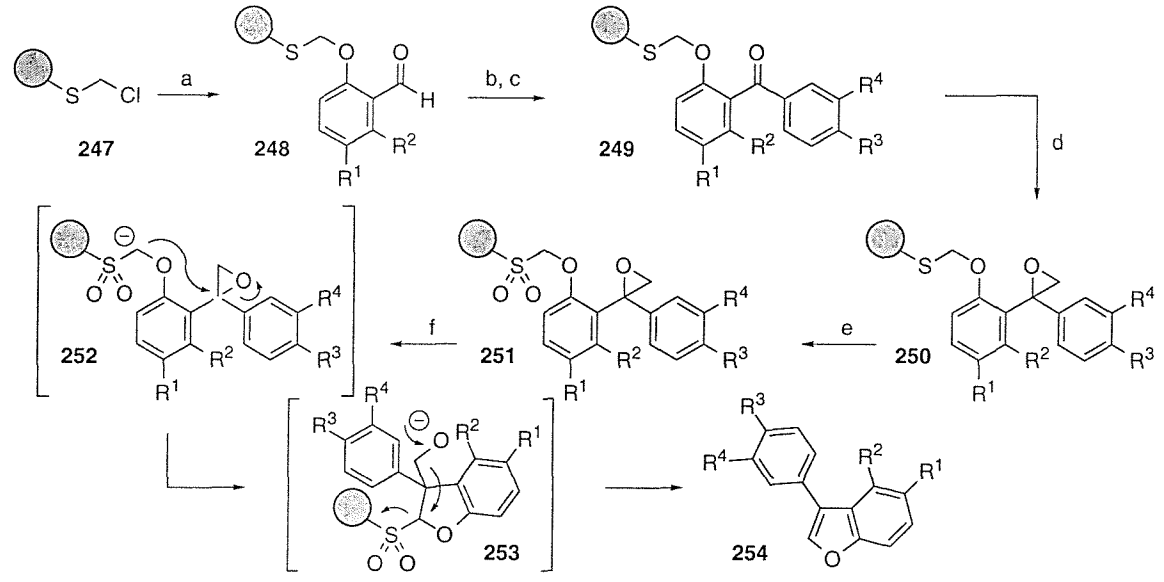
The resin-bound methylphosphonate **237** was synthesised in two steps from Merrifield resin. The phosphonate resin **237** was then treated with butyl lithium and a methyl heptanoate derivative to give ketone **238**. First desilylation, coupling with two functionalised acids and second desilylation under standard conditions afforded resin-bound alcohols **241** (n=7 or 9) that were subsequently oxidised to the corresponding aldehydes **242** under Dess-Martin conditions. Addition of a base to a suspension of the resin in toluene caused the release of the macrocyclic lactones **243** in about 60% yield and high purity. The authors then decided to apply their method to the automated synthesis of a library of muscone derivatives **246**. Replacing ester formation with a cross metathesis reaction between two terminal olefins but maintaining the same conditions for the cyclisation cleavage, they produced a series of cyclic ketones **245**.Further functionalisation was achieved in solution by action of organocuprates and hydrogenation.

Benzofurans[87]

Finally, in a report about a solution and solid-phase synthesis of arylbenzofurans **254**, Nicolaou *et al.* described a novel reaction cascade that could be considered as a cyclisative cleavage (Scheme 53). Initial studies in the solution phase validated the method. The starting resin, resin-bound chloromethylphenyl sulfide **247**, was prepared from polystyrene. Initially,

to test the solid-phase strategy, 2-hydroxybenzophenones were coupled to the resin. The resulting compounds **249** were transformed into the corresponding epoxides **250** and the linker was subsequently oxidised to sulfone **251** upon treatment with mCPBA. Reaction with potassium *tert*-butoxide afforded the expected benzofurans **254** in high purity.

Scheme 53



Reagents and conditions: a) salicylaldehydes, Cs_2CO_3, DMF, 95°C, 12hrs; b) aryl magnesium bromides, 3hrs; c) IBX, THF, DMSO, 2hrs; d) trimethylsulfonyl iodide, ^{t}BuOK, THF, DMSO, 2hrs; e) mCPBA, $NaHCO_3$, CH_2Cl_2, 12hrs; f) ^{t}BuOK, DMF, 15min.

Next, the authors sought to extend their methodology and decided to build the resin bound benzophenone intermediates **249** in three steps (a, b, c), thus enabling a wider set of compounds to be introduced on the final molecules. Epoxide formation, oxidation to the sulfone and cyclisative cleavage afforded the desired benzofurans **254** in high purity and good overall yield (an average 70% yield per step was achieved).

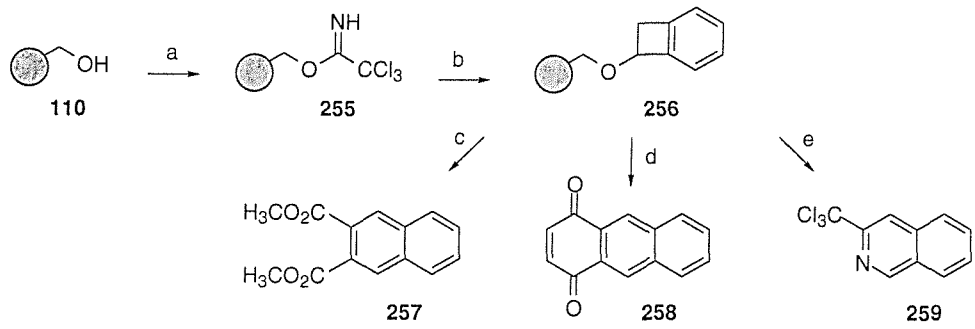
7- Multiple Bond Formation and Cycloaddition

Naphthalenes, Isoquinolines and Naphthoquinones[88]

During their studies on [4+2] cycloaddition reactions amenable to the solid-phase, Craig *et al.* developed the use of resin-bound *o*-quinodimethane that was obtained by attachment of benzocyclobutenol to trichloroacetimidate resin **255** (Scheme 54). Three Diels-Alder reactions were carried out on resin **256** by adding a 1M solution of the dienophile in toluene and refluxing for 14 hours. The yields obtained were low to moderate, ranging from 13% for

259 to 39% for **258** and 41% for **257**. No reaction was observed with methyl propiolate as the dienophile.

Scheme 54



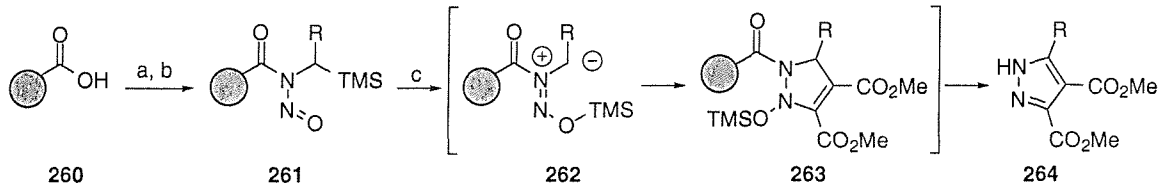
Reagents and conditions: a) 1) NaHMDS, THF, 1hr, 2) Cl_3CCN, 16hrs; b) benzocyclobutenol, TfOH, hexane, CH_2Cl_2, 16hrs; c) DMAD, toluene, 105°C, 14hrs; d) benzoquinone, toluene, 105°C, 14hrs; e) Cl_3CCN, toluene, 105°C, 14hrs.

The authors did not wish to increase the amount of dienophile since an excess would contaminate the cleaved product thus rendering purification necessary. Therefore they looked into reactions of **256** that would provide material still attached to the resin, thus enabling the excess dienophile to be removed prior to cyclisation, but the release strategy they used was no longer a cyclisation cleavage.

Pyrazoles[89]

Komatsu *et al.* found that cycloaddition reactions could be performed by action of dipolarophiles on α-silylnitrosoamides to give *N*-unsubstituted pyrazoles in excellent yields. Preparation of resin-bound α-silylnitrosoamides **261** was first investigated (Scheme 55).

Scheme 55

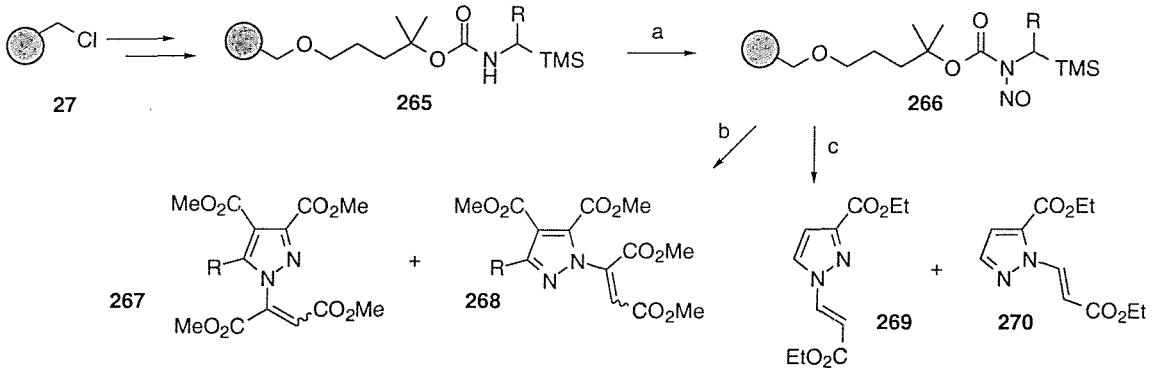


Reagents and conditions: a) $H_2NCH(R)SiMe_3$, DIC, CH_2Cl_2, 20hrs; b) N_2O_4, AcONa, CCl_4, 20hrs; c) DMAD, toluene, 80°C, 1hr.

However, subsequent reaction with two equivalents of dimethylacetylenedicarboxylate as the dipolarophile afforded the corresponding pyrazoles **264** in very low yields. Ruling out the possibility of a side reaction thanks to previous solution-phase studies, the authors imputed the failure to the short distance between the polymer support and the substrate. They therefore

designed the extended linker **265**, adapted from a work by Hernández and Hodges [90] (Scheme 56).

Scheme 56



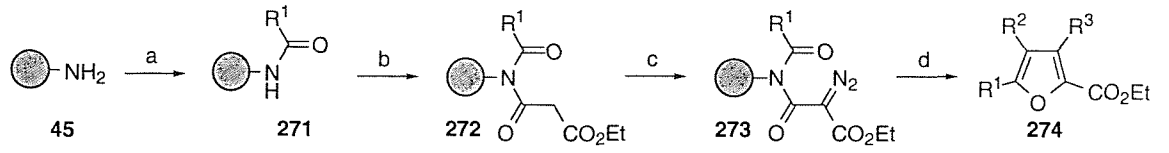
Reagents and conditions: a) N_2O_4, pyridine; b) DMAD, toluene, 80°C, 48hrs; c) $HC{\equiv}CCO_2Et$, toluene, 80°C, 48hrs.

Nitrosation of **265** afforded the resin-bound α-silylnitrosoamide **266** which was subsequently reacted with four equivalents of DMAD. Since the reaction rate was slow, extended reaction times were used thus leading to further reaction of the cleaved material with excess alkyne. Whereas increased reaction times tripled the quantity of pyrazole that was recovered, increased reaction temperature did not seem to have any effect on the yield. Hence the best results in yield (70%) for **267+268** (R=H) were obtained when heating the resin at 80°C for 48 hours. Two regioisomers in a 1:1 ratio were obtained for R≠H as well as when **266** was reacted with ethyl propiolate and gave pyrazole **269+270**.

Furans[91,92]

Gallop and Gowravaram used the ability of diazocarbonyls **273** to react with electron-deficient acetylenes in the presence of rhodium catalyst to yield tetrahydrofurans **274**.[91] The starting diazocarbonyls were readily obtained from primary amines, carboxylic acids and malonic or acetoacetic acids. Solution-phase mechanistic studies showed that the amine was not incorporated into the final tetrahydrofurans. It was therefore clearly not a means of introduction of structural diversity and the authors decided to use it as the attachment point. Resin-bound diazoimides **273** were built on the solid-phase in three steps from TentaGel resin **45** (Scheme 57).

Scheme 57



Reagents and conditions: a) R^1CO_2H, DIC, DMAP, DMF; b) ethyl malonyl chloride, benzene, 60°C, 1.5hrs; c) TsN_3, Et_3N, CH_2Cl_2, 18hrs; d) $R^2C{\equiv}CR^3$, Rh_2L_4, benzene, 80°C, 2hrs.

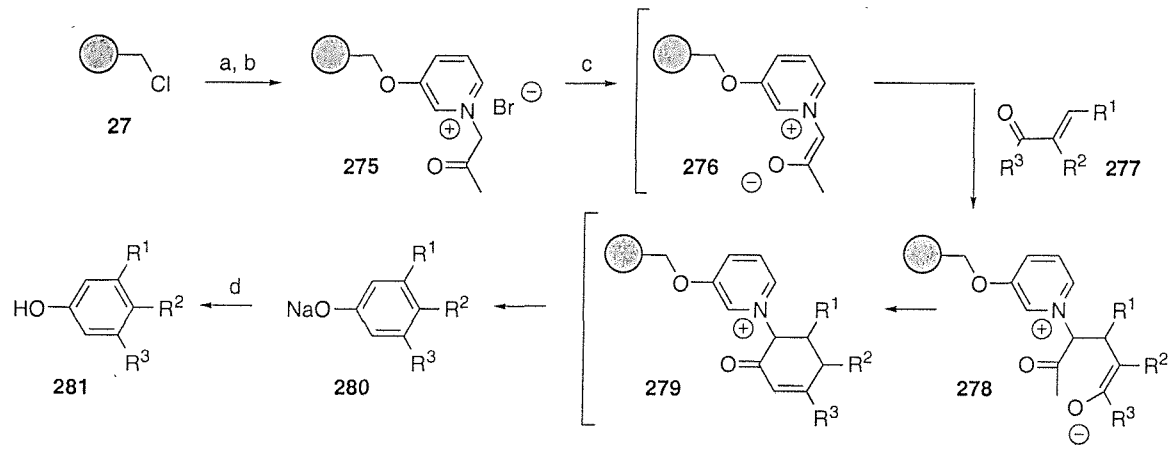
Subsequent reaction with five acetylenes in the presence of $Rh_2(OAc)_4$ afforded nine substituted tetrahydrofurans **274** in good purified yield. In order to avoid the purification step to remove excess acetylene from the product, the authors investigated the reaction at room temperature and found that the bicyclic intermediates could be isolated. Thus, excess acetylene could be removed by washing prior to promoting the cycloreversion and release of the desired tetrahydrofurans **274**. It was found that the acetylenes which were not reactive enough to allow reaction at room temperature were nevertheless volatile enough to be removed from the product *in vacuo*. A 32-member library of furans was built using this technique.

A very similar procedure was reported by another group in the same year.[92] Diazoester **273** was assembled in a different manner, from Wang resin in three steps and with the introduction of two points of diversity. Under the conditions used, the cycloadduct intermediate, obtained by reaction of substituted acetylenes in the presence of a different rhodium catalyst, could be isolated. Nine furans were obtained upon action of heat in benzene, in 70% yield and over 98% purity.

Phenols[93]

Katritzky *et al.* described the synthesis of a small selection of substituted phenols **281** on Merrifield resin **27** proposing the mechanism depicted in scheme 58. Reaction of the sodium salt of 3-hydroxypyridine with Merrifield resin and subsequent alkylation afforded the resin bound pyridinium salt **275**.

Scheme 58



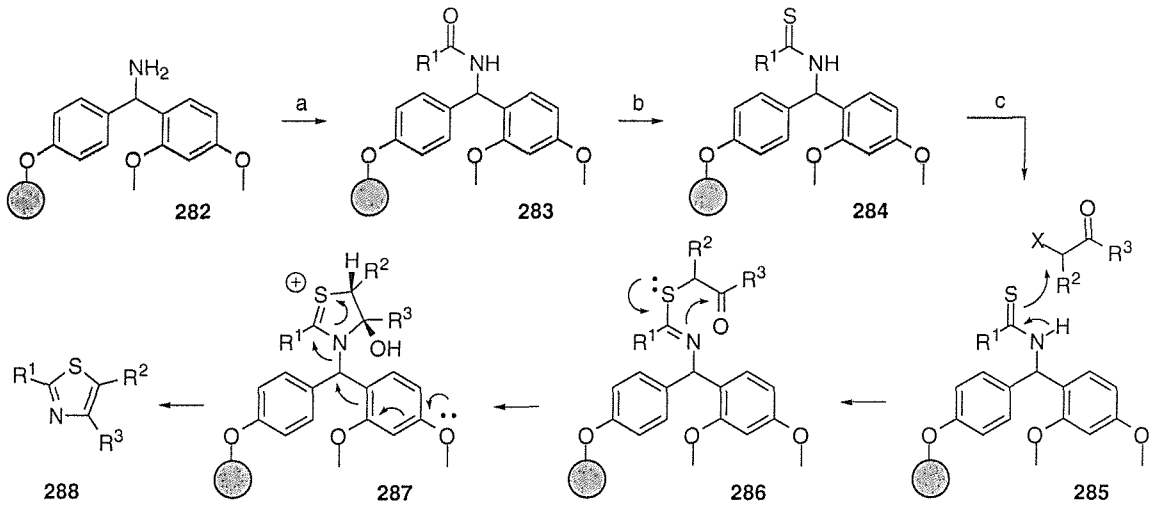
Reagents and conditions: a) 3-hydroxypyridine sodium salt, DMA, 65°C, 15hrs; b) 2-bromoacetone, acetonitrile, 75°C, 40hrs; c) **277**, NaOH, EtOH, reflux, 1hr; d) HCl.

Under the optimised conditions previously determined, resin **275** was reacted with a series of chalcones **277** in ethanolic sodium hydroxide to release the desired phenols **281**, after treatment with acid, in good yield (52-85%) and purity (72-100%).

Thiazoles[94]

A small library of 25 thiazoles **288** was prepared in three steps from Rink amide resin **282** (Scheme 59).

Scheme 59



Reagents and conditions: a) DIC, DMAP; b) Lawesson's reagent, THF, 65°C, 4hrs; c) $XCHR^2COR^3$ (X = Br or Cl), THF, 65°C, 16hrs.

Coupling of five acids to the resin under standard conditions was followed by reaction with Lawesson's reagent to give the corresponding thioamides **284**. Subsequent reaction of **284**

with a series of five α-haloketones in refluxing THF led to the cyclisative cleavage of the desired thiazoles **288** in good yield, as claimed by the authors. Notably, the average purity of the cleaved material was improved with the use of bromoketones as opposed to chloroketones. The authors also detailed the possible mechanism for the cyclisation depicted above.

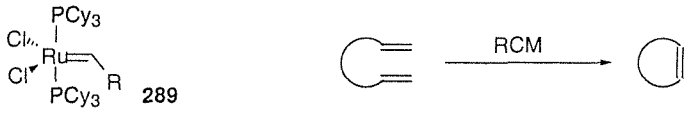
8- Cyclisation Cleavage by Ring-Closing Metathesis

As we will see below, ring-closing metathesis (RCM) was also used as a cyclisative cleavage procedure to release heterocycles from the resin. As this was the method we chose to study during our research work, RCM will be presented in more detail in the next chapter.[95]

8.1- Ring-Closing Metathesis: A Brief Overview

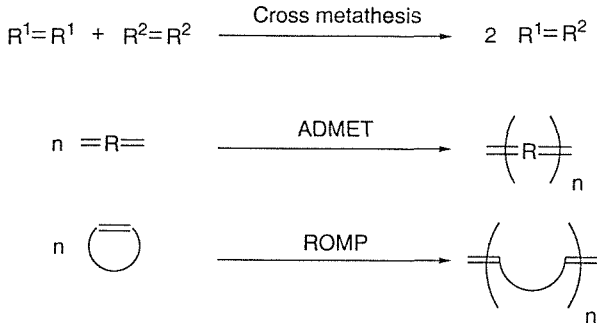
In this chapter we will mainly focus on the well-defined ruthenium carbene complexes of type **289** introduced by Grubbs and co-workers in the early 1990s and their use in RCM reactions to efficiently provide carbocycles and heterocycles of almost any ring size from a linear diene (Figure 6). Some more general aspects of olefin metathesis and the use of other well-defined metathesis catalysts will also be covered.

Figure 6



RCM is just one particular sub-class of a wider class of reactions known as olefin metathesis that originated several decades ago in polymer chemistry using the early Re-, W- or Tl-based metathesis catalysts. The other fundamental reactions that belong to the olefin metathesis - namely cross metathesis, acyclic diene metathesis and ring opening polymerisation - are depicted in figure 7.

Figure 7

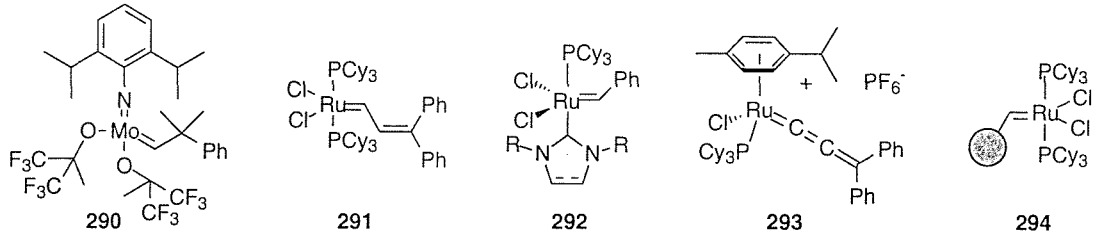


All the olefin metathesis reactions given above proceed *via* a catalytic cyclisation of an olefin with a transition metal alkylidene complex in a [2+2] fashion. The thus formed intermediate metalacyclobutane is unstable and decomposes in another [2+2] reaction. All the possible reactions are generally reversible and one can imagine that all the possible olefins will be formed. The overall result depends on reaction rates and displacement of equilibrium when volatile or insoluble products are generated.

Synthesis and Structure

The discovery and development of new stable and functional group tolerant ruthenium and molybdenum catalysts allowed the wide use of olefin metathesis in organic synthesis. In fact, shortly after Schrock's report of a molybdenum imido catalyst **290** that could be used in organic synthesis, Grubbs and co-worker disclosed the preparation of a ruthenium-based catalyst **291** that combined high activity, good reproducibility and high yields with an excellent tolerance toward most of the common functional groups (Figure 8).

Figure 8



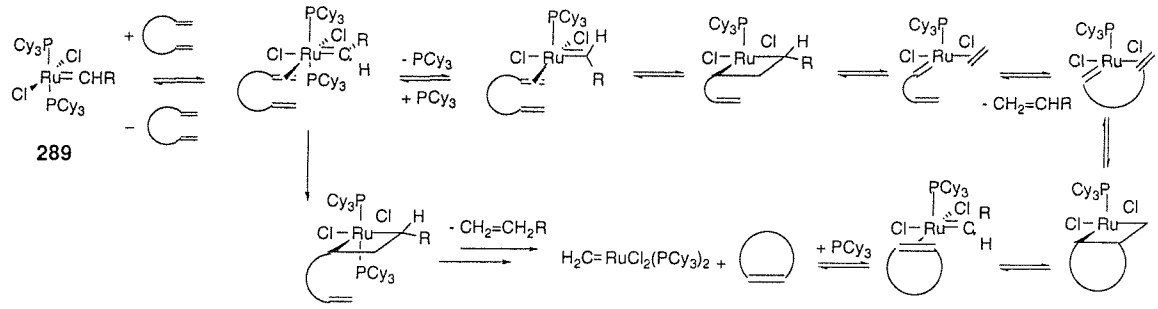
The ruthenium catalysts offer the advantage of a greater compatibility with polar functional groups at the sacrifice of reactivity. In contrast, the molybdenum catalyst **290** has the advantage of being able to form rings that are sterically more demanding but suffers from high sensitivity to air and water. Over the years, in addition to the further development of the initial catalysts, new catalysts were also introduced, e.g. **292** and **293**.[96-100] They display similar good activity and tolerance toward functional groups but are often much easier to

prepare than the original catalysts.[101-104] Hoveyda *et al.* reported a ruthenium catalyst that could be recovered at the end of a reaction using flash chromatography.[105] Remarkably, only the imidazole and dihydroimidazole derivative catalyst **292**, among the most active catalysts reported so far, have met with popularity.[106-109] In addition to these homogeneous catalysts, resin-bound ruthenium alkylidenes **294** were also reported.[110-112] The main advantages were a better handling of the catalyst, which could be recycled, and the tendency to lead to less product contamination by highly coloured ruthenium residues, which is generally recognised as an important issue.[113,114] Due to their success, several of these catalysts are now commercially available. Catalyst **289** (R = Ph) is commonly known as Grubbs catalyst, and we will follow this usage in this report.

Mechanism and Activity

During our research project we used exclusively the neutral 16-electron 5-coordinate ruthenium (II) complex **289** (R = Ph). Formally, **289** (R = Ph) is not the propagating species but the latter, ruthenium methylidene **289** (R = H), is formed in the first turn of the catalytic cycle.[103] Grubbs and co-workers proposed a mechanism which is generally accepted.[115] They established that two different pathways - associative and dissociative - take place simultaneously but are of different importance. In the associative pathway, the olefin simply co-ordinates to the catalyst to form an intermediate 18-electron olefin complex. All the subsequent intermediates have either 16 or 18 electrons. In the dissociative however, upon binding to the olefin, a phosphine ligand is displaced from the metal to form a 16-electron complex. Once the metathesis reaction is complete, the catalyst is regenerated upon co-ordination of the phosphine. The metallacyclobutane intermediate, the formation of which is the rate-determining step, has only 14 electrons. The dissociative pathway is believed to account for >90-95% of the RCM mechanism (Figure 9).

Figure 9



To support this hypothesis, it was also demonstrated that excess phosphine in the reaction mixture slowed the reaction whereas addition of CuCl, a known phosphine scavenger, dramatically increased the catalyst activity.[115]

Further rules and observations regarding the catalyst longevity,[116] the outcome of a reaction in function of the size of the ring to be formed and the substitution pattern of the starting alkene for a given catalyst were deduced from the numerous examples found in the literature (see below). For example, Fürstner showed that the number of carbon atoms between the olefin and a carbonyl group on the molecule could dramatically influence the reaction rate and outcome.[118b] It was also shown that the Thorpe-Ingold effect played a role when a *gem*-dimethyl group is present on the substrate by contributing substantially to the thermodynamic stability of the ensuing ring and/or the transition state leading to ring closure.[117]

RCM in the Solution-Phase: Synthetic Applications

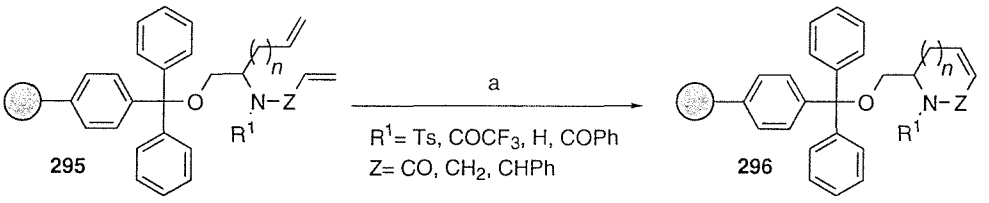
Numerous applications have been reported.[118] Examples of common organic structures and more complex natural products that were synthesised by RCM included epothilones,[119,120] sugars,[121] non natural cyclic amino acids,[122] and bicyclic lactams.[123] Typical procedures involved refluxing a 20 mM solution of diene in dichloromethane for two to eight hours in the presence of 5 mol% of catalyst. If required, benzene and toluene allowed reactions to proceed at higher temperature, although room temperature was not uncommon. A useful summary of failure and success with respect to the functional group tolerability and ring size formed can be found in the literature.[95c]

Metathesis in Solid-Phase Organic Synthesis

In addition to several cross-metathesis examples,[124-127] RCM reactions were soon employed on the solid-phase. Initially, cyclic molecules were formed on the resin in high yield and

cleaved later. For example, Blechert *et al.* demonstrated the feasibility of the RCM reaction on a solid support (TentaGel and trityl polystyrene) by synthesising a small collection of 5 to 8 member azacycles.[128,129] The target molecules were first cyclised on the resin in high yield (70%-91%) using 8-15mol% of ruthenium catalyst to give resin **296** and were subsequently released into solution (Scheme 60).

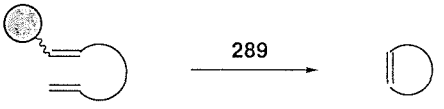
Scheme 60



Reagents and conditions: a) **289** (R = Ph) or **291**, benzene or CH_2Cl_2.

Van Maarseveen then suggested that RCM reaction could be used for the cyclisative release of target molecules from the solid-phase.[130] Thus, if the substrate were to be attached to the polymer core through one of the two double bonds, the RCM reaction would simultaneously form the ring and effect the cleavage from the resin in one step (Figure 10).

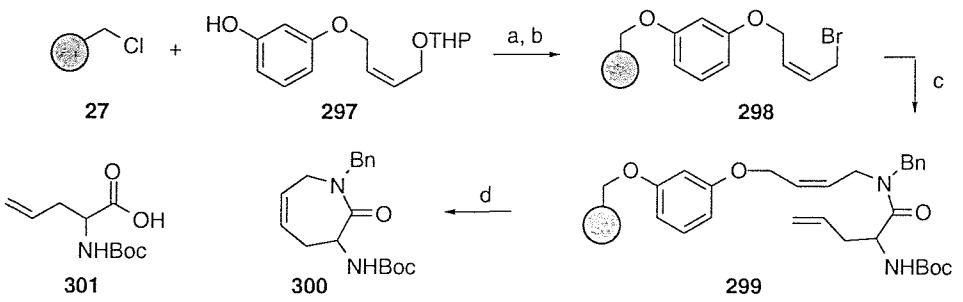
Figure 10



8.2- Cyclisation Cleavage Reactions Employing RCM

Van Maarseveen and co-workers were the first to report the use of RCM for the cyclisation cleavage of heterocycles, namely 7-membered lactams **300** (Scheme 61).[130] A close look at the accepted reaction mechanism revealed that the first catalytic cycle would cause the ruthenium alkylidene to be immobilised onto the solid support (Figure 12 below, and further discussion in chapter 2.3). As a solution, the authors suggested the use of an olefin co-factor to regenerate the catalyst and keep the catalytic cycle working.

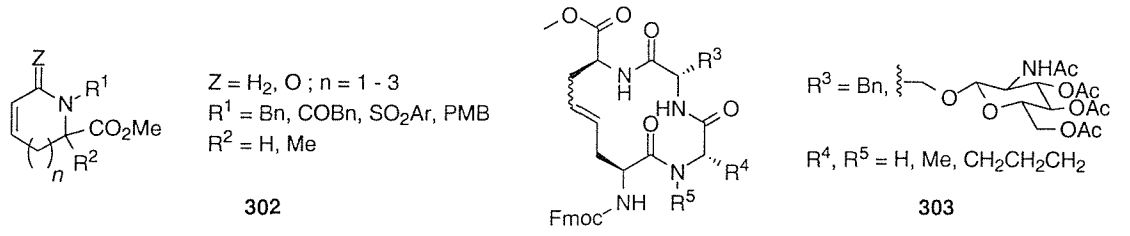
Scheme 61



Reagents and conditions: a) NaH, NMP; b) PPh_3Br_2, CH_2Cl_2; c) 1) $BnNH_2$, NMP, 50°C, 2) **301**, PyBrop, EtN^iPr_2, NMP; d) Grubbs catalyst, 1-octene, toluene.

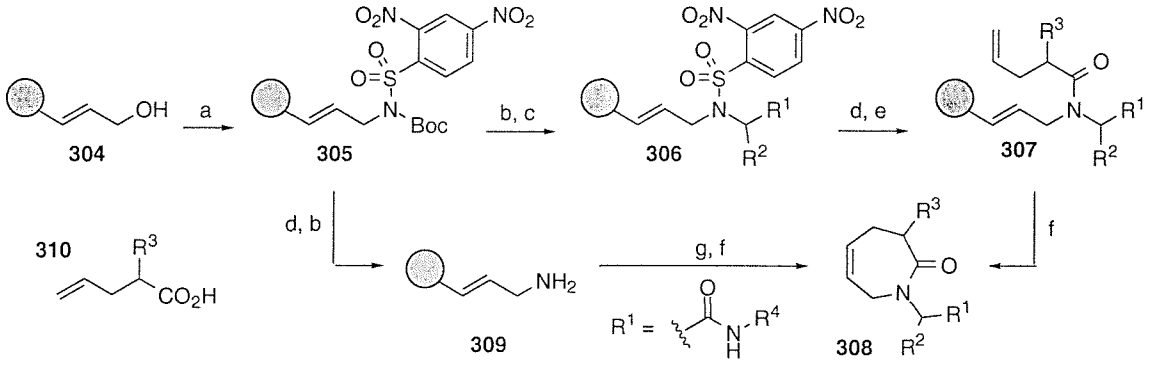
The linear precursor **299** was assembled on Merrifield resin in four steps, following a successful solution-phase study. However, subsequent reaction of resin **299** with various amounts of Grubbs catalyst at different temperatures and in the presence of two different co-factors (1-octene and ethylene) afforded the product in low yield. Only 5% yield of lactam **300** was recovered after 7 days with 14 mol% of catalyst in the presence of ethylene, and 37% yield with 12 mol% of catalyst after 2 hours in the presence of 1-octene. Since using an equimolar amount of Grubbs catalyst afforded **300** in 54% yield only, the authors suggested that the poor yields were due to an intermolecular dimerisation - although the phenomenon could not be detected by spectroscopy - rather than the irreversible immobilisation of the ruthenium complex. As a consequence, they concluded that future work should concentrate on the use of a resin of lower loading in order to prevent intermolecular reactions or alternatively, on the better use of the olefin co-factors. In fact, in collaboration with another research group, they later reported the results obtained for the latter option.[131] Thus, the use of stoichiometric amounts of styrene as the co-factor was successfully applied to the synthesis of medium ring lactams **302** in good yield and purity (Figure 11). The work also described the influence of the ring size and of the various protecting groups and substituents, R^1, R^2 and Z, over the cyclisation. Notably, cyclisation cleavage occurred in yields up to 97% for one example, and the authors were able to obtain an 8-membered ring **302** in 12% yield whereas the corresponding solution-phase cyclisation failed.

Figure 11



In contrast, Piscopio *et al.* published a series of papers on the cyclisation cleavage of lactam β-turn mimetics **308** without the use of a co-factor.[132-134] The publication first described the 2-step synthesis of a dihydropyran in 43% yield as a proof of concept, followed by the synthesis of lactam **308**. About four steps were conducted on Fréchet's cinnamyl alcohol resin **304** before the cleavage took place (Scheme 62).

Scheme 62



Reagents and conditions: a) 1,1-dimethylethyl *N*-(2,4-dinitrobenzenesulfonyl) carbamate, DEAD, PPh_3, THF, 16hrs; b) TFA, CH_2Cl_2, 16hrs; c) $R^1CH(OH)R^2$, DEAD, PPh_3, THF, 16hrs; d) nBuNH$_2$, CH_2Cl_2, 2hrs; e) **310**, PyBrop, EtN^iPr$_2$, DMF, 48hrs; f) Grubbs catalyst (5 mol%), CH_2Cl_2, 80°C, 16hrs; g) **310**, R^2CHO, R^4NC, CH_2Cl_2, MeOH, 48hrs.

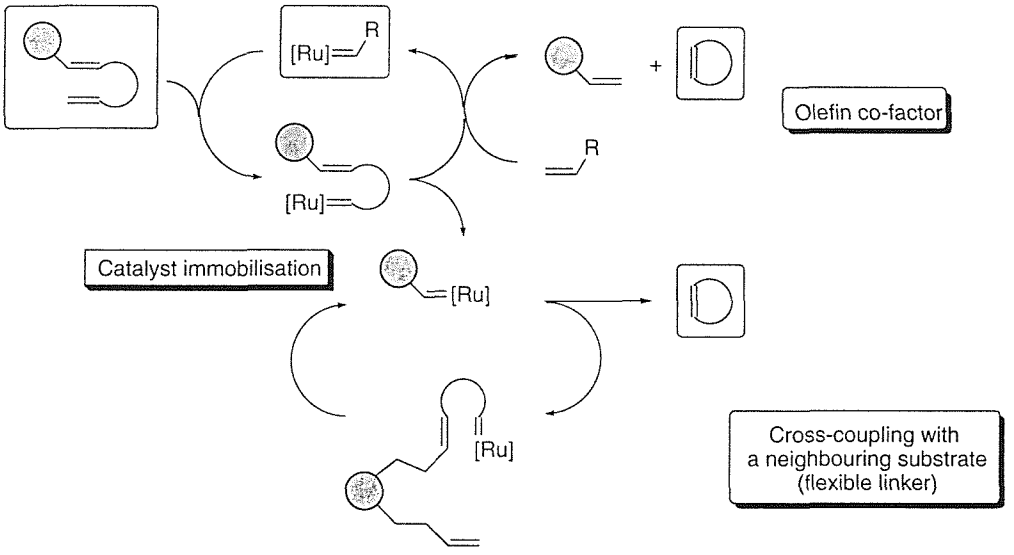
Purity of the crude material was high and overall yields ranged from 15% to 36%. When a multi-component reaction was employed to build the RCM precursor (step g), the yields improved to about 60%.

A noteworthy fact was reported by Blechert and co-workers.[135] They noticed that the cyclisation cleavage to cyclic tetrapeptide **303** off Wang resin was achieved in 30% yield (Figure 11, above). However, when an 8-carbon long spacing arm between the polymer core and the first double bond was employed, the yield significantly increased to 70%, without the need for an olefin co-factor. This seems to underline the flexibility requirements that the solid-support should provide for the cross-coupling reaction with a neighbouring olefin to take place, as suggested by the work by Piscopio reported in the previous paragraph (Figure 12, below). The authors then studied the influence of the linear peptide conformation on the

cyclisation cleavage rate and showed that it was found to be 7-50 times slower for non-proline containing dienes.

Figure 12 summarises the RCM cyclisation cleavage strategies to maintain a catalytic cycle - olefin co-factor or flexible linker - as a consequence of the catalyst immobilisation.

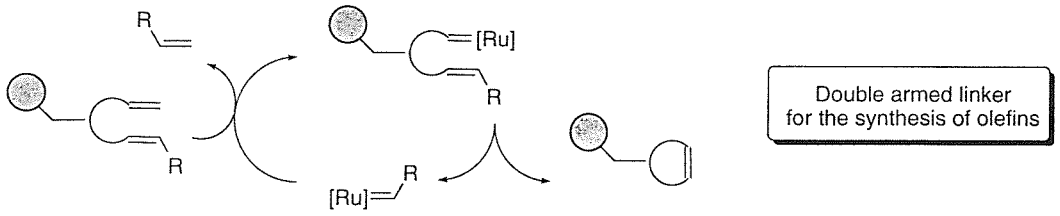
Figure 12



Finally, Nicolaou reported the successful cyclisation cleavage using RCM applied to the preparation of a library of epothilone A derivatives.[119] However, taking into account that amounts of ruthenium carbene as high as 75 mol% were used and given that the average yield in released product was 20%, we can establish that the process was hardly catalytic.

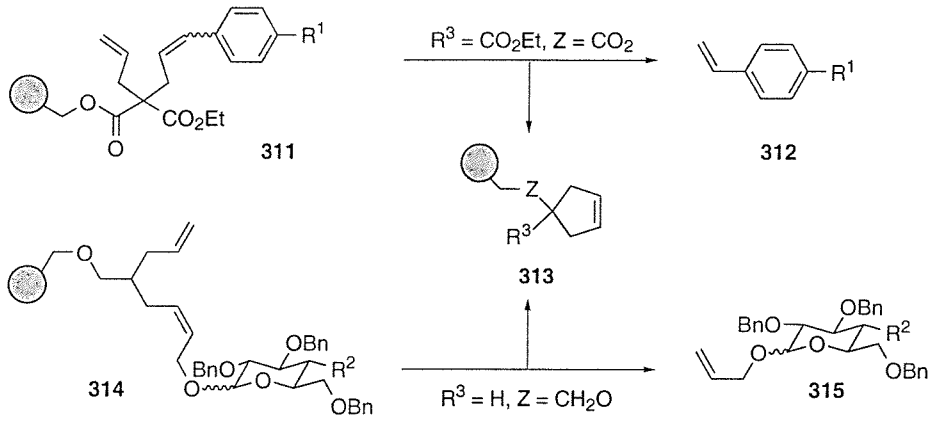
Shortly after the report by van Maarseveen, another concept arose regarding the use of RCM as a cyclisation cleavage method (Figure 13). However, it was no longer the product which cyclised, but the linker, thus releasing a linear olefin product. The important feature, though, was that this method enabled moderate yields to be obtained with catalytic amounts of the Grubbs ruthenium complex **289** (R = Ph).

Figure 13



To the best of our knowledge, there are only two reported applications of this method: the synthesis of styrene derivatives[136] and the synthesis of sugars[137] (Figure 14).

Figure 14



Aims of the Project and General Guidelines

In order to extend the repertoire of solid-phase synthetic methodology, we were interested in strategies that would provide an efficient ring closure and cleavage from the solid support in a single operation. We expected that the use of the mild reaction conditions of the RCM reaction, combined with the ease of preparation and stability of the intended intermediates would provide a general strategy for the solid-phase synthesis of cyclic alkenes.

A close look at the RCM cyclisation cleavage reaction underlined the striking difference between its rather efficient use in the solution-phase and the moderate yields obtained on the solid-phase. Unfortunately, it seemed that in order to obtain high yields employing a RCM cyclisative release strategy on solid-phase, the use of an olefin co-factor or a spacer was almost mandatory. As a matter of fact, the cyclisation cleavage strategy was repeatedly described by all the research groups that used it as a means to release highly pure compounds, by the very nature of the reaction that took place. The use of a co-factor is then contradictory

with the whole process, as it can lead to the formation of additional by-products that have to be separated from the target molecule, in addition to the inevitable catalyst residues.

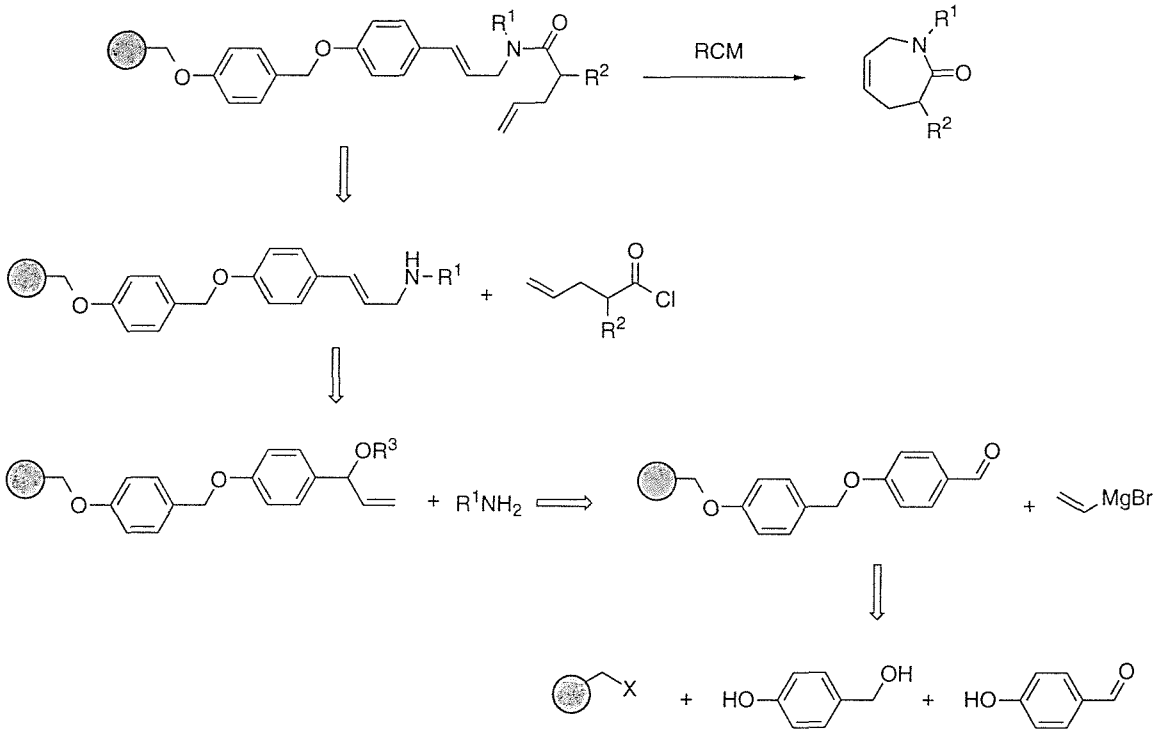
We felt that we could improve the RCM cyclisation cleavage and retain high yields of cyclic product while keeping the catalyst amount low and without making use of an olefin co-factor. In particular, we hoped to reach quantities of catalyst lower than 5 mol% in order to maintain low product contamination by residual ruthenium. We therefore decided to investigate the use of a double armed linker, related to resins **311** and **314**, but that would allow the release of cyclic molecules instead of linear olefins.

To start with, we decided to investigate the solid-phase synthesis of medium-size lactams. We were attracted by their widespread occurrence in biologically active compounds, including natural products and conformationally restricted peptidomimetics. In order to get a better understanding of the RCM process, before beginning the study of our new double armed linker, we wished to first investigate the RCM cyclisation cleavage from a Wang linker. We then planned to directly compare the efficiency of the cyclisation cleavage from a series of linkers, including the Wang linker, with that obtained from the double armed linker. In the event of success, further application would include the preparation of a collection of cyclic lactams and/or their incorporation into peptidomimetics as a means to demonstrate the viability of the strategy.

1- The Synthesis of Medium-Ring Lactams: Initial Solution-Phase Model, Analogous Solid-Phase Synthesis and Preliminary Ring-Closing Metathesis Studies

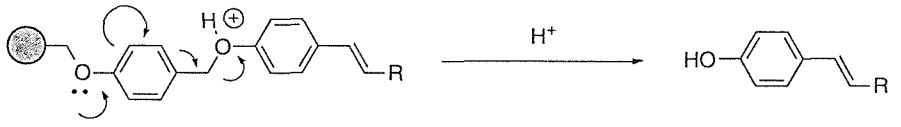
As discussed in the introduction, we felt that the existing RCM cyclisation-cleavage strategies published in the literature needed to be improved, in particular with respect to the amount of catalyst used. Thus, we wanted to achieve the solid-phase synthesis of medium-ring lactams using lower amounts of Grubbs catalyst than those employed in earlier work.[119,130-135] The first synthetic target was a modified Wang linker for which we designed the short retrosynthesis presented in figure 1.1.

Figure 1.1



Although ultimately we wanted to rely solely on a RCM reaction to effect the cleavage of the final compounds, we introduced an acid cleavable linker to allow us to monitor reaction progress throughout the solid-phase synthesis. Participation of the oxygen lone pair renders the Wang linker cleavable under acidic conditions (Figure 1.2). As a consequence, we anticipated that cleavage of a resin sample would permit the identification of the attached compounds and hence allow us to determine the success or the failure of each reaction step.

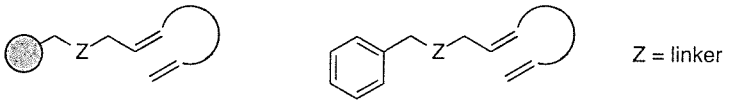
Figure 1.2



1.1- Synthesis of a Solution-Phase Model

In view of the shortcomings of analytical techniques for monitoring the progress of the solid-phase organic reactions, we decided to conduct the synthesis of a solution-phase model prior to starting any work on the resin. The model study would be used to validate the chemistry involved, and to gain a better understanding on how the reactions would proceed on the solid-phase. Based on structural similarities, we decided to replace the polymeric core by a simple benzyl group (Figure 1.3).

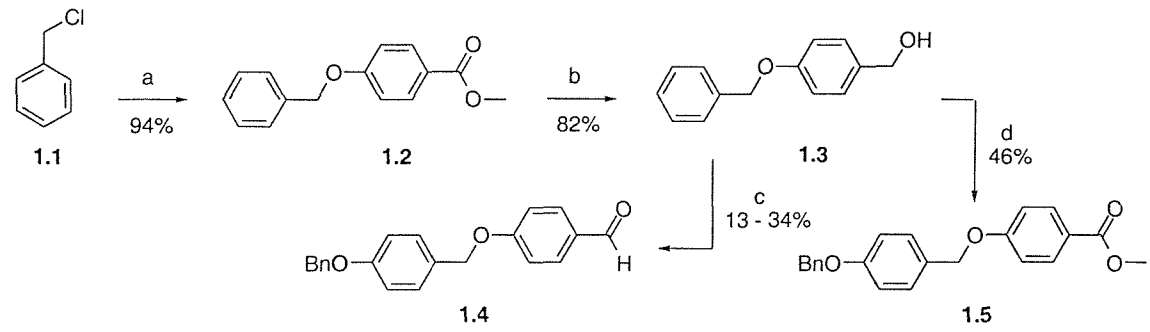
Figure 1.3



Solid-phase substrate Solution-phase model

We established that 4-benzyloxybenzyl alcohol (**1.3**) was a convenient starting materiel for the synthesis of the solution model (Scheme 1.1). Although **1.3** is commercially available, its synthesis was still informative bearing in mind that we would need to assemble a related structure on the solid-phase. The first step, which involved the nucleophilic substitution of chloride **1.1** by the sodium alkoxide of methyl 4-hydroxybenzoate, proceeded in good yield. The presence of a benzylic electron donating group *para* to the ester moiety lowered the reactivity of the resulting ester **1.2**. As a consequence, reduction of ester **1.2** to alcohol **1.3** was slow using lithium borohydride, even under reflux. However, the reduction proceeded smoothly using lithium aluminium hydride.

Scheme 1.1



Reagents and conditions: a) methyl 4-hydroxybenzoate, NaH, DMF; b) $LiAlH_4$, Et_2O; c) 4-hydroxybenzaldehyde, DEAD, PPh_3, THF or C_6H_6; d) methyl 4-hydroxybenzoate, DEAD, PPh_3, THF.

Due to the formation of inorganic salts, we anticipated increased difficulty when working on the solid-phase with $LiAlH_4$. Nevertheless, due to the simplicity of this method we decided not to change strategy and moved onto the next step, investigating the synthesis of aldehyde **1.4** using a Mitsunobu reaction.[138,139] Unfortunately, the yields ranged from 13% to 34%, under a variety of conditions examined (Table 1.1). Numerous unidentified by-products were formed, thus accounting for the fact that almost no starting material could be recovered.

Table 1.1: Mitsunobu reactions for the formation of benzyl aryl ether **1.4**

Entry	Reagents[a]	Solvent	Method[b]	Reaction time	Yield (%)
1	1 eq.	THF	A	7 days	14
2	1 eq.	THF	B	15 hours	32
3	1 eq.	THF	B	3 days	34
4	2 eq.	C_6H_6	C	1 day	33
5	2 eq.	C_6H_6	A	3 days	22

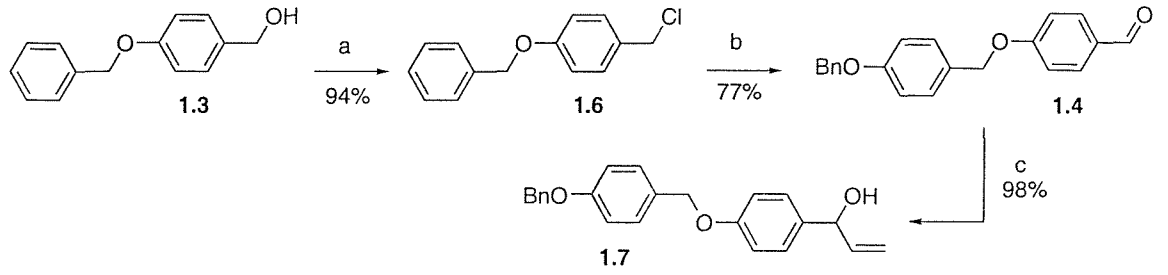
Notes: a) number of equivalents of DEAD, triphenyl phosphine and phenol for 1 eq. of alcohol **1.3**; b) the following methods were used: A) alcohol and phenol were added in one portion to a mixture of DEAD and triphenyl phosphine; B) DEAD and alcohol were added slowly to a mixture of phenol and triphenyl phosphine; C) DEAD was added to a mixture containing all the other reagents.

We therefore adopted a slight change of tact, using methyl 4-hydroxybenzoate instead of the aldehyde. The yield improved to 46% thus affording ester **1.5**. However this modification introduced two additional steps to return to the desired aldehyde **1.4**, namely reduction of an aryl ester and oxidation to the corresponding aldehyde. This appeared unattractive to us for the solid-phase sequence so the route was abandoned.

As an alternative, we chose to investigate the conversion of alcohol **1.3** into the corresponding chloride **1.6** following a known procedure.[140] Subsequent nucleophilic substitution by the

sodium alkoxide of 4-hydroxybenzylaldehyde provided an efficient synthesis of aldehyde **1.4** (Scheme 1.2).

Scheme 1.2



Reagents and conditions: a) MsCl, EtN^iPr_2, CH_2Cl_2; b) 4-hydroxybenzylaldehyde, NaH, DMF; c) vinylmagnesium bromide, THF.

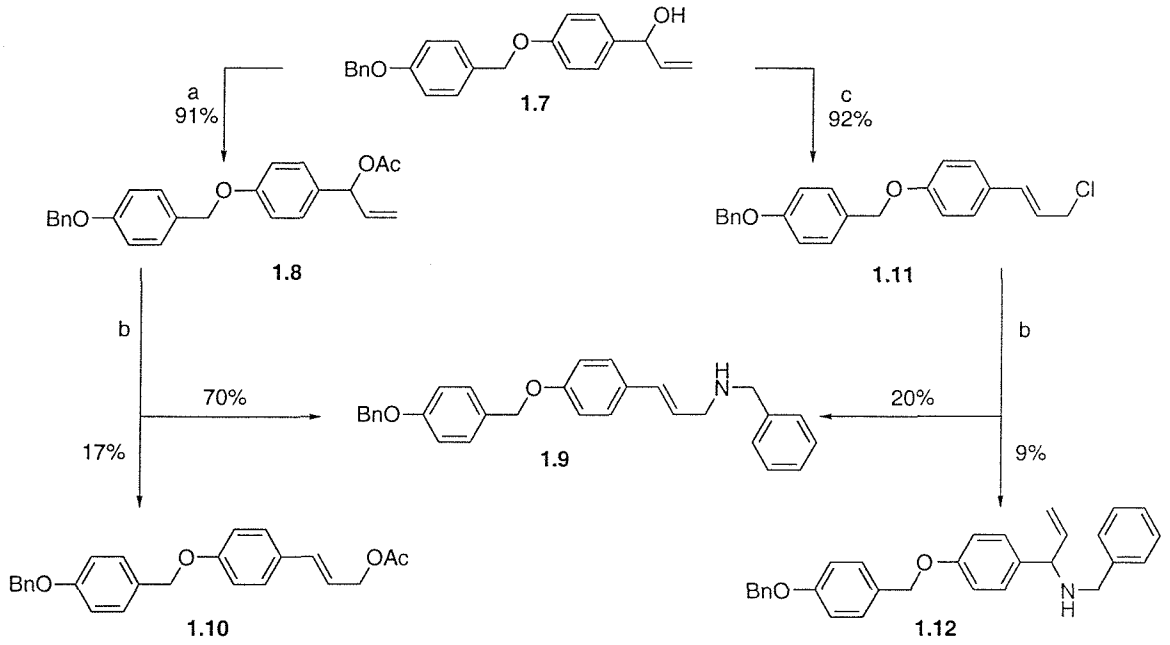
The first of the two double bonds required for the RCM reaction was introduced by nucleophilic addition of vinylmagnesium bromide to aldehyde **1.4**.[141] The Grignard reaction proceeded smoothly and afforded alcohol **1.7** in 98% yield. Conversion of **1.7** into the corresponding acetate **1.8** was achieved in excellent yield, providing a substrate for coupling with an amine under palladium catalysis (Scheme 1.3). Following a literature report,[142] we investigated the use of palladium chemistry to effect the conversion of allylic acetate **1.8** into allylic amine **1.9**. Using different ligands - dppe, dppp or triphenyl phosphine - trial reactions were carried out in THF in the presence of palladium acetylacetonate. The results are reported in table 1.2. The system using dppe turned out to be the most efficient.

Table 1.2: yields of **1.9** obtained by varying the nature of the ligands

Ligand	dppe	dppp	PPh_3
Yield (%)	70	43	38

Amine **1.9** was obtained with an *E* configuration, as shown by the coupling constants observed in the ^{1}H-NMR spectrum (J = 16.2 Hz between the two olefinic protons). No significant quantity of the *Z* isomer was observed. Based on spectroscopic data, it seemed that the major by-product observed was the isomerised acetate **1.10**, obtained in 17% yield despite the large excess of benzylamine.

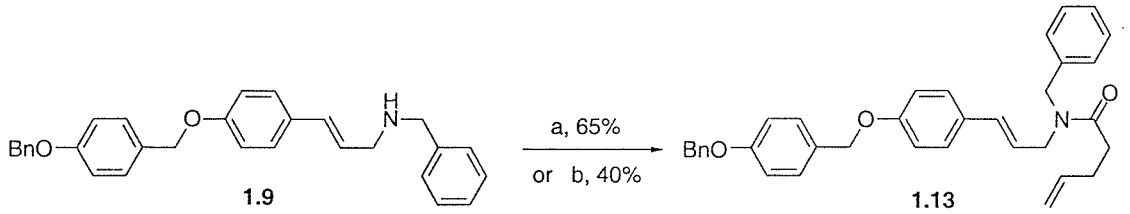
Scheme 1.3



Reagents and conditions: a) acetic anhydride, DMAP, Et_3N; b) benzylamine, $Pd(acac)_2$, dppe, THF; c) MsCl, EtN^iPr_2, CH_2Cl_2.

In order to increase the yield of **1.9** and avoid the formation of the isomerised acetate **1.10**, we investigated the direct nucleophilic substitution of chloride **1.11**. The latter was readily synthesised in 92% yield from allylic alcohol **1.7** following the procedure previously applied to the conversion of **1.3** into **1.6**.[140] Only the *E* configuration was obtained as supported by ^{1}H-NMR (J = 15.6 Hz between the two olefinic protons). However, no reaction was observed between **1.11** and benzylamine in the presence of Hünig's base, even at reflux of THF. When the $Pd(acac)_2$/dppe system was employed with chloride **1.11** the reaction proceeded poorly, giving amine **1.9** in 20% yield. Spectroscopic data surprisingly showed that the major isolated by-product was presumably the isomerised amine **1.12**, obtained in 9% yield. Despite our failure to further improve the yield for the formation of **1.9** from **1.7** we decided to push forward and investigate the key RCM reaction. Hence, the next step was to introduce the second double bond required for the RCM reaction, by forming an amide bond. We compared two methods to activate 4-pentenoic acid:- formation of the corresponding acyl chloride and use of a coupling reagent (Scheme 1.4).

Scheme 1.4



Reagents and conditions: a) 4-pentenoic acid, DCC, HOBt, EtN^iPr_2, CH_2Cl_2; b) 1) 4-pentenoic acid, NaH, CH_2Cl_2, 2) oxalyl chloride, 3) **1.9**, EtN^iPr_2, CH_2Cl_2.

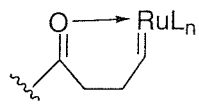
In both cases the reactions proceeded with moderate yields. The better yields obtained with the peptide coupling reagent were counterbalanced by the increased purification problems. Although isolation and characterisation of the acid chloride was possible, the reaction sequence 'b' to **1.13** was carried out in one pot. At room temperature, the NMR spectra of amide **1.13** showed a 3:2 ratio of rotamers. A high temperature NMR experiment was carried out in order to determine the energy barrier to rotation about the C-N bond ($\Delta G^{\ddagger}$). Unfortunately, the required temperature was too high. At 60°C, the two *N*-benzylic methylene singlets and the two allylic methylene doublets had still not coalesced. Typical values for $\Delta G^{\ddagger}$ for amide rotation range between 50 and 100 kJ/mol.

1.2- Solution-Phase Ring-Closing Metathesis on Amide 1.13

Following standard procedures,[123] RCM on amide **1.13** was attempted using 10 mol% of the ruthenium catalyst. After 24 hours, only starting material could be detected by tlc. The reaction mixture was therefore heated at reflux temperature for another 15 hours. However, no change was observed. Mechanistic studies carried out by Grubbs concluded that addition of copper chloride increased the activity of the catalyst.[113] Excess copper chloride was therefore added to a solution of amide **1.13** and Grubbs catalyst in CH_2Cl_2 but again after 15 hours, only starting material was recovered.

We were quite surprised by this negative results since all the literature reports showed the success of RCM reactions on tertiary amides and on the formation of 7-membered rings, using Grubbs catalyst.[123] In our case, the problem may arise from the formation of a stable complex where co-ordination between the carbonyl and the metal carbene occurs, as described by Fürstner,[115] thus causing the catalytic cycle to stop (Figure 1.4).

Figure 1.4

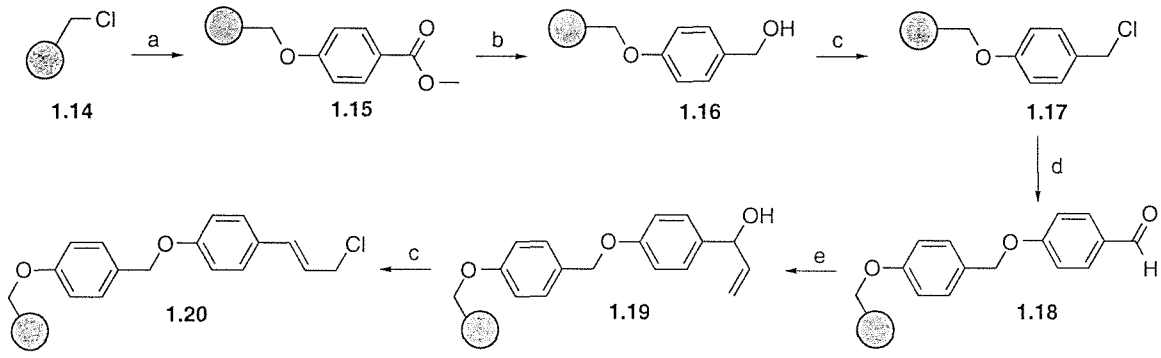


1.3- Transferring the Solution Chemistry to the Solid-Phase

Some of the solid-phase work was already underway during the optimisation of the solution-phase model synthesis. As a consequence, in spite of the failure of the final amide cyclisation, we had started assembling the rather complex linker on the solid-phase, benefiting from the results obtained in solution with the model, and thus carrying out only the most efficient reactions.

Nucleophilic substitution of commercially available, Merrifield resin (**1.14**) with methyl 4-hydroxybenzoate afforded the resin-bound methyl ester **1.15**, which was subsequently reduced using excess lithium borohydride to alcohol **1.16** (Scheme 1.5). Despite problems encountered with the reduction in solution, successful reaction on the solid-phase was indicated by IR spectroscopy, which showed the disappearance of the carbonyl peak.

Scheme 1.5



Reagents and conditions: a) methyl 4-hydroxybenzoate, NaH, DMF, 60°C; b) $LiBH_4$, MeOH, THF; a) MsCl, EtN^iPr_2, DMF; d) 4-hydroxybenzaldehyde, NaH, DMF; e) vinylmagnesium bromide, THF.

Benzylic alcohol **1.16** was then activated by mesylation and subsequent displacement by chloride to give benzylic chloride resin **1.17**. Subsequent nucleophilic attack by the sodium phenoxide of 4-hydroxybenzaldehyde prepared *in situ* afforded resin-bound aldehyde **1.18**. Grignard reaction between aldehyde **1.18** and vinylmagnesium bromide afforded allylic alcohol **1.19**. Finally, activation of the hydroxy group in **1.19** with mesyl chloride afforded allylic chloride **1.20**. At this stage we did not carry out any further steps to the solid-phase

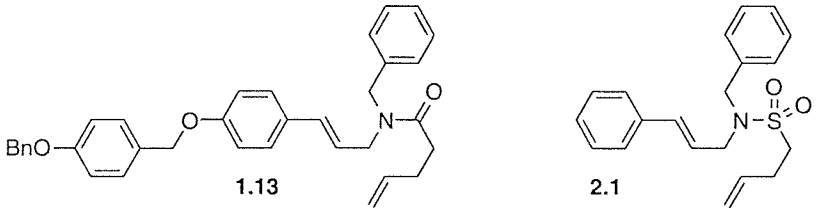
analogue of benzylic amide **1.13** since its solution-phase cyclisation had failed. Resin **1.20** was stored for further use.

Upon reviewing the current literature, it became clear that this work need not be pursued any further as similar successful solid-phase strategies had already been published.[130,131,134,143] As a result, we looked into possible carbonyl isosters and were delighted to observe that very little had been published on medium-ring monocyclic sulfonamides, either in solution or on the solid-phase.[¶] In fact, the literature reported several examples of peptidomimetics containing sulfonamides[146-149] but almost no examples of small monocyclic organic molecules.[150] There was therefore a whole class of novel compounds, with potential interest to the pharmaceutical industry, that could be synthesised by RCM. We anticipated that sulfonamide bond would be compatible with Grubbs ruthenium catalyst as several examples of successful cyclisations of substrates with tosyl protecting groups were found in the RCM literature.[123,143]

2- The Synthesis of Medium-Ring Cyclic Sulfonamides: Simplified Solution-Phase Model, Analogous Solid-Phase Synthesis and Further RCM Studies

In order to speed up the reaction sequence to the sulfonamide equivalent to **1.13**, we decided to use a simplified solution-phase model. In practice, **2.1** was obtained by leaving out the 4-(benzyloxy)benzyloxy *para* substituent on **1.13** but keeping the same synthetic strategy (Figure 2.1).

Figure 2.1

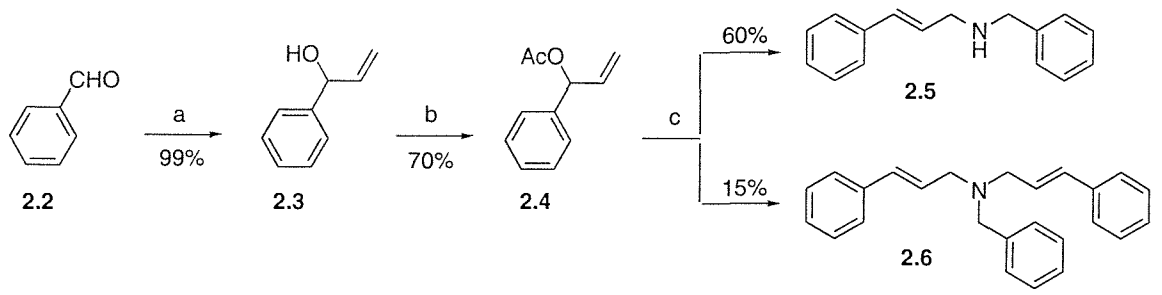


[¶] Eventually two reports on medium ring sulfonamides were published, the first one[144] around the time of our work and the second one[145] during the preparation of the thesis.

2.1- A Simplified Solution-Phase Model: RCM of Sulfonamides

Secondary amine **2.5**, the simplified analogue to amine **1.9**, was synthesised in three steps from benzaldehyde (**2.2**) under the same reaction conditions used during our initial model (Scheme 2.1).

Scheme 2.1



Reagents and conditions: a) vinylmagnesium bromide, THF; b) Ac_2O, DMAP, Et_3N, CH_2Cl_2; c) benzylamine, dppe, $Pd(acac)_2$, THF.

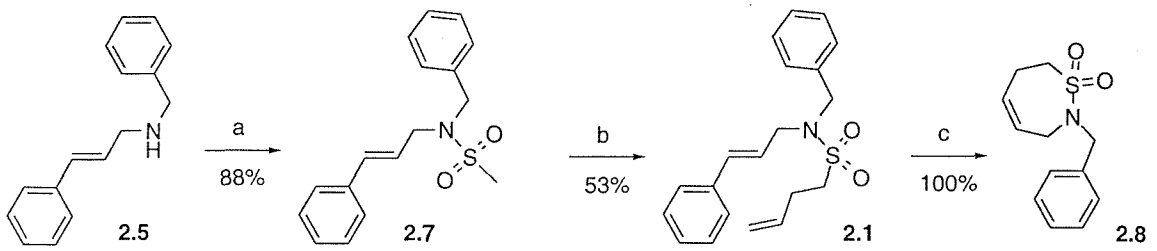
Palladium *N*-alkylation of benzylamine with acetate **2.4** afforded amine **2.5** with an *E*-configuration as demonstrated by ^{1}H-NMR (J = 15.8 Hz between the two olefinic protons). Spectroscopic evidence implied that the major by-product **2.6** obtained in 15% yield resulted from a double alkylation.

With amine **2.5** in hand we needed to introduce the *N*-butene sulfonyl group to produce the RCM precursor **2.1**. Two approaches were considered:- direct introduction of the entire butene sulfonyl side-chain on secondary amine **2.5** or *N*-mesylation of **2.5** followed by *C*-alkylation to assemble the group in a linear manner. Initially we decided to pursue the second approach.

2.1.1- Stepwise Assembly of the Sulfonyl Moiety and RCM

N-Mesyl amine **2.7** was obtained from amine **2.5** in 88% yield, providing careful temperature control was employed (Scheme 2.2).

Scheme 2.2

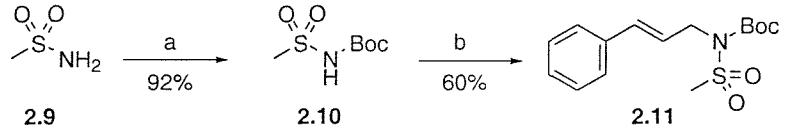


Reagents and conditions: a) MsCl, CH_2Cl_2; b) 1) BuLi, THF, -78°C, 2) allyl bromide; c) Grubbs catalyst, CH_2Cl_2.

Deprotonation of **2.7** was achieved with butyl lithium by adaptation of a literature procedure.[151,152] Subsequent allylation with allyl bromide afforded sulfonamide **2.1** in an unoptimised 53% yield. We were delighted to observe that the RCM reaction to sulfonamide **2.8** proceeded quantitatively in two hours using 5 mol% of the Grubbs ruthenium catalyst. This first successful ring closure led to the first molecule of a novel class of compounds.

With a view to eventually introduce various substituents on the nitrogen (see section 4), we decided to change the benzyl group for a more easily removed protecting group. Among the different protecting groups we considered, the Boc group seemed an ideal candidate. It is not only easy to remove but as well displays electron withdrawing properties that we thought would facilitate deprotonation of the sulfonamide and hence facilitate the *C*-alkylation. Due to poor reactivity, we were unable to form the Boc analogue of **2.5** from acetate **2.4** and *tert*-butyl carbamate under similar conditions. Alternative nucleophilic substitution of cinnamyl chloride with *tert*-butyl carbamate also failed. Further attempts to introduce the mesylate group prior to the *tert*-butyl ester were unsuccessful. As a consequence, we imagined that the formation of a Boc-protected sulfonamide prior to coupling with cinnamyl chloride by *N*-alkylation would provide an interesting alternative route to **2.11**, the Boc analogue of **2.7** (Scheme 2.3).

Scheme 2.3

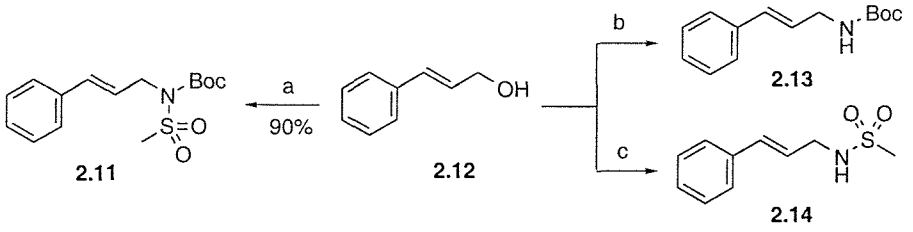


Reagents and conditions: a) Boc_2O, Et_3N, DMAP, CH_2Cl_2; b) cinnamyl chloride, K_2CO_3, DMF.

Following a literature procedure,[153] methanesulfonyl carbamate **2.10** was obtained in 92% yield by reaction of methane sulfonamide (**2.9**) and di-*tert*-butyl dicarbonate. *N*-Allylation of

2.10 with cinnamyl chloride afforded sulfonyl carbamate **2.11** in moderate yield. In order to increase the yield of the last reaction, we studied the feasibility of a Mitsunobu reaction between cinnamyl alcohol (**2.12**) and sulfonamide **2.10** (Scheme 2.4). Gratifyingly, the reaction proceeded smoothly and sulfonyl carbamate **2.11** was obtained in substantially higher yield than previously achieved.

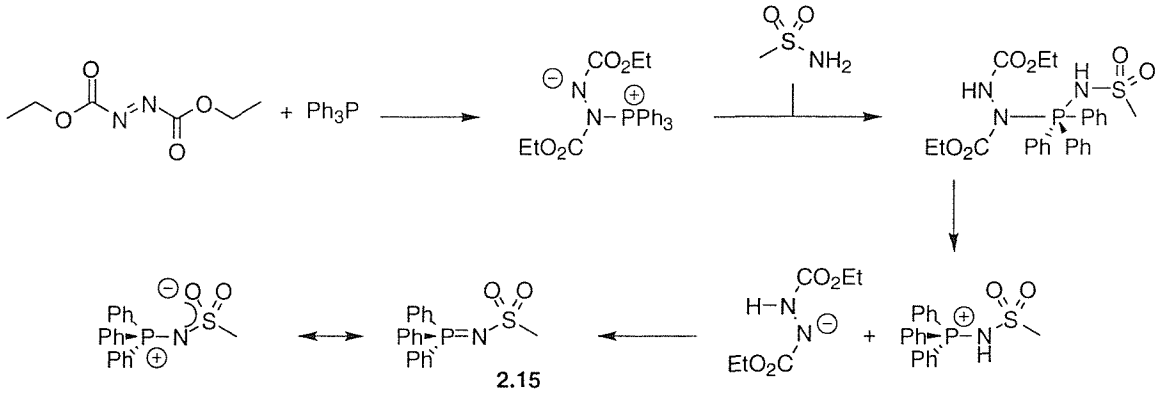
Scheme 2.4



Reagents and conditions: a) sulfonamide **2.10**, DEAD, PPh_3, THF; b) $BocNH_2$, DEAD, PPh_3, THF; c) $MsNH_2$, DEAD, PPh_3, THF.

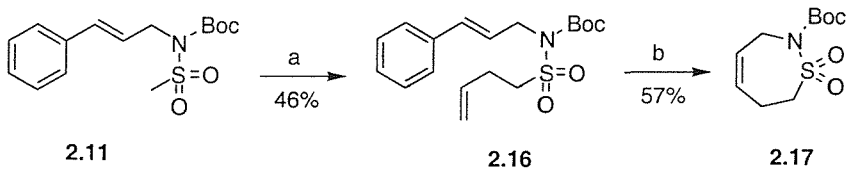
Remarkably, when we attempted to assemble the various building blocks under the same conditions but in a different order, compounds **2.13** and **2.14** were not obtained. In the case of the attempted formation of *tert*-butyl carbamate **2.13**, only starting material was recovered thus underlining the proton acidity requirements of the Mitsunobu reaction. More interesting was the case of the unsuccessful synthesis of methanesulfonamide **2.14**: the standard conditions led to the formation of *N*-(1,1,1-triphenyl-λ^5-phosphanylidene) methanesulfonamide (**2.15**) the stability of which prevented the reaction from continuing. A mechanism for the formation of **2.15** has been proposed in the literature (Figure 2.2).[154]

Figure 2.2



Alkylation of **2.11** with allyl bromide introduced the second double bond required for the RCM (Scheme 2.5). Lithium diisopropyl amide was preferred to *n*-butyl lithium, as the formation of the α-alkanesulfonamide anion using the latter was capricious. Contrary to our expectations, the yield for the deprotonation/alkylation remained low in spite of the presence of the electron withdrawing carbamate group.

Scheme 2.5



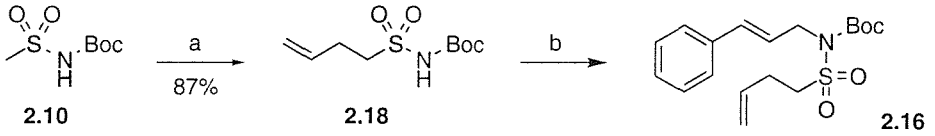
Reagents and conditions: a) 1) LDA, THF, -78°C, 2) allyl bromide; b) Grubbs catalyst, CH_2Cl_2.

The best alkylation results were obtained when reacting 1 equivalent of LDA, allyl bromide and substrate. An excess of base afforded considerably more degraded material. RCM of **2.16** proceeded less efficiently than its benzyl analogue **2.1**. Under similar conditions, the 7-membered ring **2.17** was obtained in only 31% yield as opposed to quantitative yield for **2.1**. A yield of 57% was achieved by extending the reaction time and increasing the temperature.

2.1.2- Improved Synthesis of Sulfonamide 2.16

So far, the *C*-alkylations leading to RCM precursors **2.1** and **2.16** were carried out in a linear fashion. We anticipated major difficulties in performing the same carbanion chemistry on the solid-phase. As a result, we investigated the formation of the entire olefinic sulfonamide **2.18** by *C*-alkylation of **2.10** prior to reaction with cinnamyl alcohol (**2.12**) to give **2.16** leading to a more convergent approach (Scheme 2.6). Under the conditions previously employed, alkylation of sulfonamide **2.10** produced **2.18** in significantly improved yield. Nevertheless, the alkylation reaction turned out to be quite difficult to achieve on a large scale.

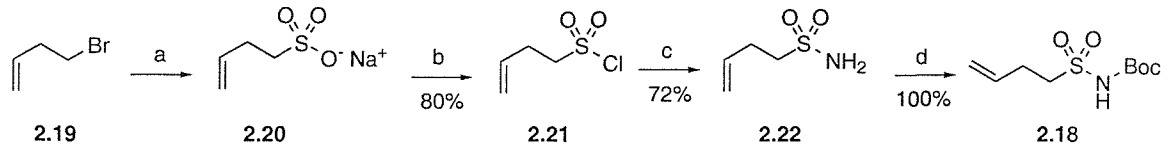
Scheme 2.6



Reagents and conditions: a) 1) LDA, THF, -78°C, 2) allyl bromide; b) alcohol **2.12**, DEAD, PPh_3, THF.

Subsequent Mitsunobu coupling was therefore not investigated at that time, as we felt the synthesis of **2.18** could be further improved (Scheme 2.7). After several unsuccessful attempts,[155] sulfonyl chloride **2.21** was obtained from 4-bromobutene (**2.19**) in 80% yield over two steps following a procedure reported in the literature.[156,157] The key to a successful synthesis was that the intermediate sodium salts **2.20** required thorough drying prior to treatment with phosphorus oxychloride.

Scheme 2.7



2.19 2.20 2.21 2.22 2.18

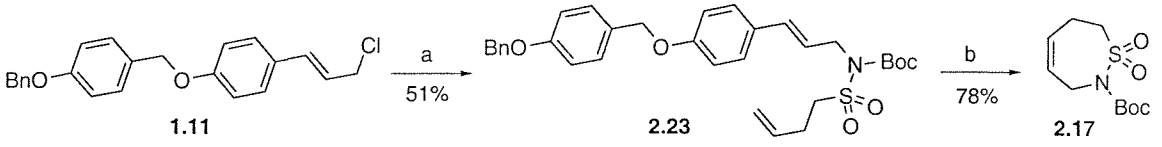
Reagents and conditions : a) Na_2SO_3, H_2O, 60°C; b) $POCl_3$, 105°C; c) NH_4OH; d) Boc_2O, CH_2Cl_2.

Direct reaction between sulfonyl chloride **2.21** and *tert*-butyl carbamate in the presence of a base failed. However, following a two step procedure reported in the literature,[158] the Boc protected sulfonamide **2.18** was obtained in good yield by action of neat aqueous ammonia on **2.21** and subsequent Boc protection of the resulting free sulfonamide **2.22**. The overall yield from 4-bromobutene was somewhat lower than the one obtained when using the LDA alkylation method, but this new route provided clear advantages of cost, scale and purification.

2.2- Returning to the Extended Linker: Solution- and Solid-Phase RCM of Sulfonamides

With the synthesis of the sulfonamide moiety now optimised and efficient, we decided to check the feasibility of the RCM reaction on the extended solution model **1.11**, as it was still the strategy we would pursue initially on the solid-phase. Nucleophilic substitution of allylic chloride **1.11** with sulfonamide **2.18** afforded the desired RCM precursor **2.23** in moderate yield (Scheme 2.8).

Scheme 2.8

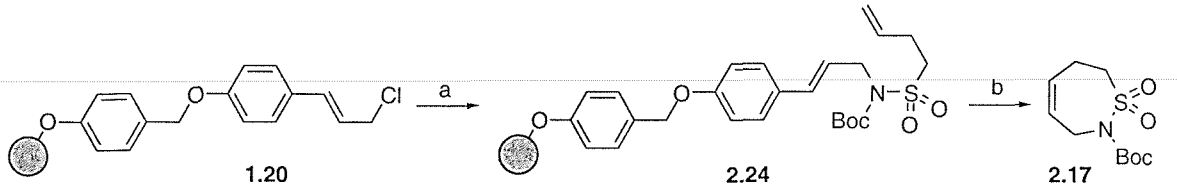


1.11 2.23 2.17

Reagents and conditions : a) sulfonamide **2.18**, K_2CO_3, DMF; b) Grubbs catalyst, CH_2Cl_2.

We were pleased to see that RCM of diene **2.23** carried out at 40°C over 15 hours returned the desired 7-membered sulfonamide **2.17** in 78% yield. This represented a substantial increase in yield compared to the RCM achieved on the simple cinnamyl model **2.16**, perhaps suggesting some electronic influence on the RCM reaction. In view of the excellent result on the solution model, we carried out the reaction sequence on the solid-phase. Thus, after *N*-allylation of chloride **1.20** with the Boc protected sulfonamide **2.18**, resin **2.24** was submitted to the RCM conditions (Scheme 2.9). Surprisingly, the results were somehow different on the solid-phase.

Scheme 2.9



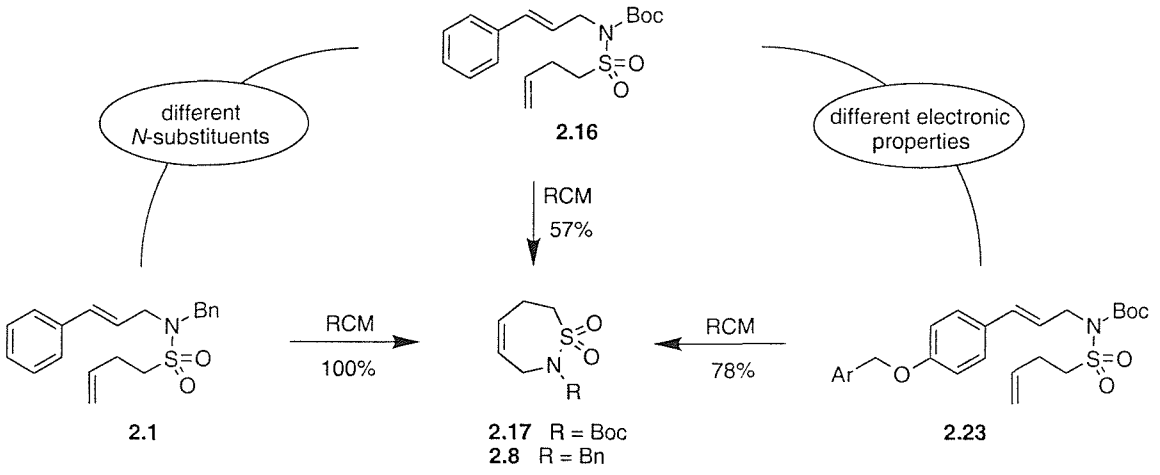
Reagents and conditions: a) sulfonamide **2.18**, K_2CO_3, DMF; b) Grubbs catalyst, CH_2Cl_2.

Only traces of cyclic sulfonamide **2.17** were observed by H^1-NMR after 24 hours in refluxing CH_2Cl_2 and in the presence of 10 mol% catalyst. We concluded that somehow the catalyst had been deactivated, perhaps by formation of a resin-bound complex (see introduction and below).

2.3- Solution- and Solid-Phase RCM of Sulfonamides: Early Conclusions

So far, the RCM reactions to cyclic sulfonamides **2.8** and **2.17** had been successful only in solution (Figure 2.3).

Figure 2.3

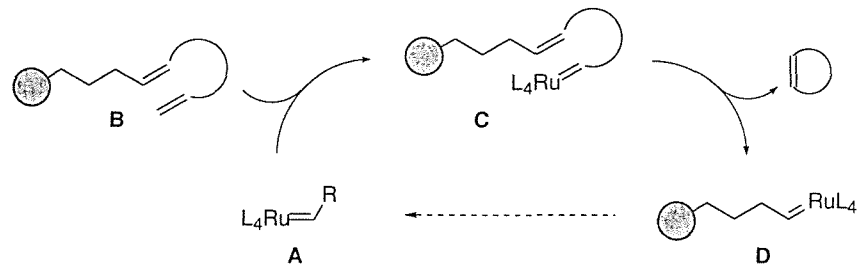


We observed that substantially higher yields were obtained for an electron rich styrenic double bond (**2.23** vs. **2.16**) or *N*-benzyl rather than an *N*-Boc sulfonamide (**2.1** vs. **2.16**). The same effects were expected on the solid-phase but were not necessarily observed, as reported below. It should be stressed, however, that these reactions were one-off experiments and it is consequently unwise to read too much into the results.

There could be several reasons why the solid-phase attempts failed. First, any of the synthetic steps could have gone wrong, but IR spectra supported their success and, in spite of being

time-consuming, the solution-phase model synthesis helped validate the overall approach before transfer to the solid-phase. Secondly, as mentioned in the introduction to this work, closer inspection of possible mechanistic pathways for the cyclisative cleavage reaction revealed a potentially more complex situation (Figure 2.4).

Figure 2.4



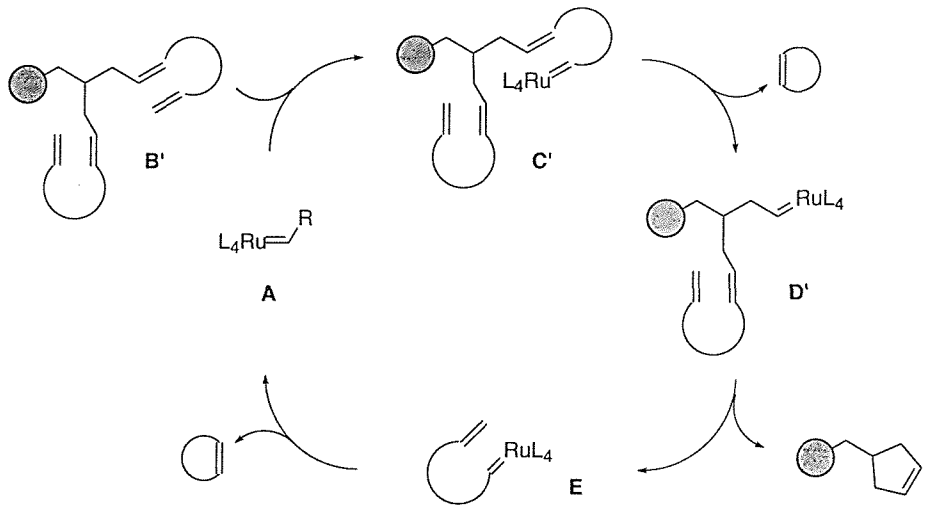
Initial attack by the metal alkylidene **A** upon resin-bound diene **B** leads to the formation of **C** which further reacts to release a cyclic molecule. Since the resulting polymer-bound ruthenium alkylidene compound **D** can not diffuse freely in solution, it may not be able to continue to participate in the catalytic process. As discussed earlier and with the exception of the work reported by Piscopio,[132-134] this phenomenon could explain our failure as well as the low yields reported by others.[130,135] As discussed in the introduction, the possible solutions reported in the literature to improve the efficiency of RCM cyclisation cleavage were the use of an alkene co-factor which was expected to undergo cross-metathesis with **D** to regenerate a ruthenium complex **A**,[130,131,134,143] or the use of a flexible spacer that could allow interaction with another resin-bound diene in close proximity on the same bead.[135]

As a result, and as the solution-phase RCM looked quite promising, we decided to move on to the introduction of a new linker strategy which was expected to increase the efficiency of the ruthenium catalysed cyclisative cleavage approach.

3- A New Concept: a Double Armed Linker

We suggested the use of a double armed linker to provide a solution to the low catalyst turnover for the RCM cleavage, represented on figure 3.1.

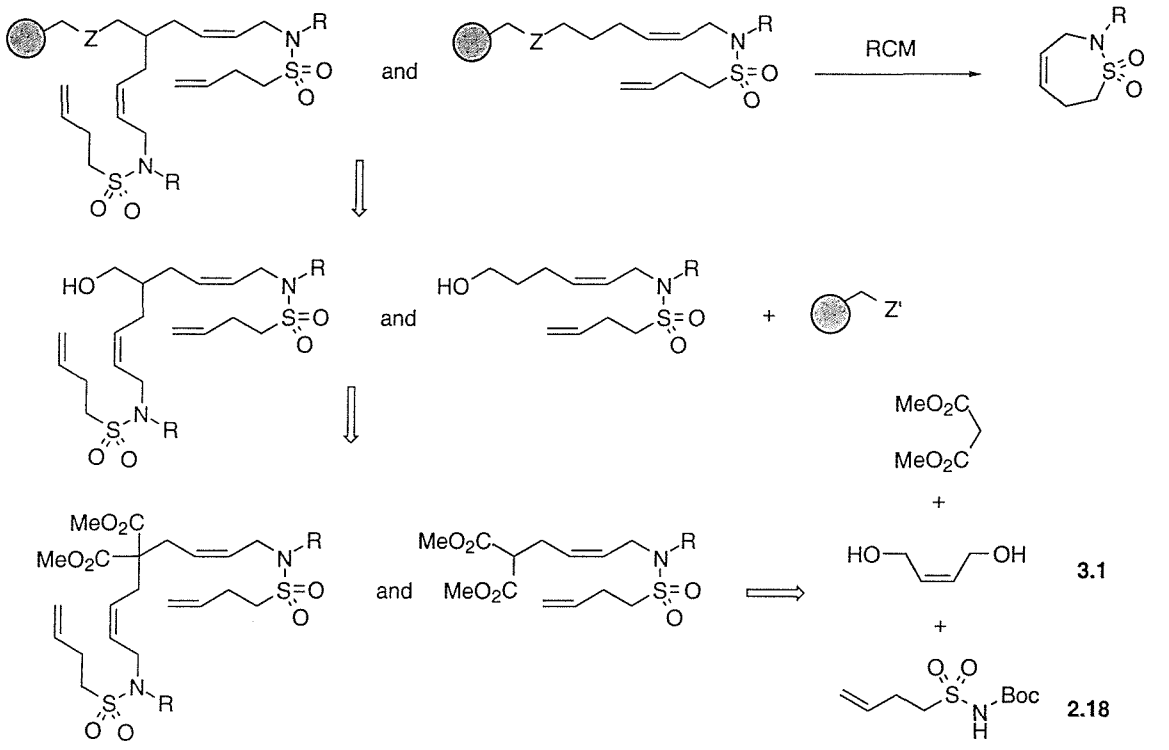
Figure 3.1



Thus, on a double armed linker, resin-bound ruthenium complex **D'** possesses in very close proximity a molecule with which further metathesis is possible and easy. In addition, as the second metathesis is completed on diene **E**, free ruthenium catalyst **A** is regenerated without requiring a cofactor, and the catalytic cycle can continue with no breakdown except for the loss of activity of the catalyst itself depending on its longevity. We therefore expected the new linker strategy to exhibit improved kinetics. We wished to compare the efficiency of our proposed double armed linker with that of the corresponding single armed, and decided to start the syntheses of both from a common intermediate. It should be reminded that, as seen in the introduction, a related double armed linker had been used for the metathesis cleavage of acyclic olefins.[136,137]

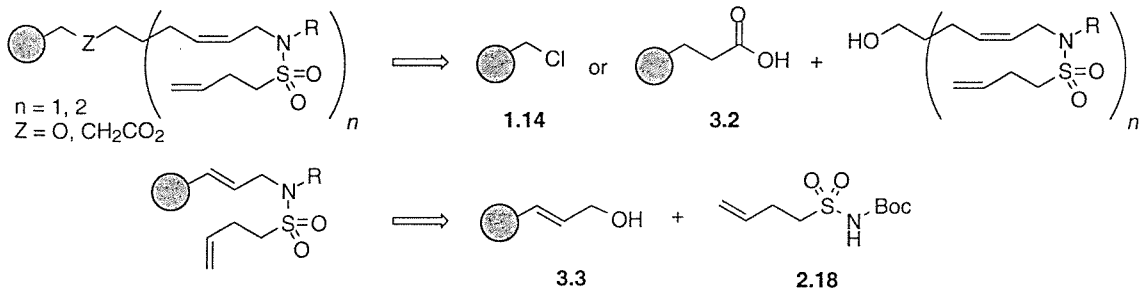
The revised immobilised substrates and an approach to their synthesis is outlined below (Figure 3.2). Malonate chemistry seemed extremely appropriate as it would allow introduction of the second arm when reacting the activated methylene with two equivalents of alkylating agent whereas reaction with only one equivalent would led to the formation of the single armed linker. In addition, taking into account the observations made during the synthesis of the previous extended and simplified linkers, we chose an allylic alcohol for coupling of sulfonamide **2.18** under Mitsunobu conditions. Finally, *cis*-2-butene-1,4-diol (**3.1**) was chosen as a valuable building block, although the double bond geometry would present the opposite configuration to the one obtained so far.

Figure 3.2



The problem of monitoring the reactions on the solid-phase discussed above was still an issue which we decided to address by a stepwise approach. Thus, we would initially synthesise the whole linker and substrate in solution prior to coupling the resulting material to the resin, as represented in figure 3.2. Our final approach would ultimately require the linker to be directly assembled on the solid-phase (section 3.2.2). Although the final aim would be to use the more robust Merrifield resin (**1.14**) with linkage through an ether, which would exclude all methods of cleavage but RCM, the problem of monitoring the progress of the solid-phase reactions could be resolved by employing an ester linker (Figure 3.3). With this aim, carboxyethyl resin **3.2**, the synthesis of which was achieved in our laboratories[59] and is reported in chapter 6, seemed the ideal candidate. The carboxylic functionality of **3.2** should not only ease the coupling of the linkers but as well the resulting ester anchoring point could be cleaved at any time to check reaction efficiency. In addition, in order to compare the efficiency of the double armed linker with other linkers as well as with the single armed linker, we planned to prepare resin **3.3**. Indeed, **3.3** had already been employed successfully in a solid-phase RCM cleavage strategy by another research group.[132-134] The synthesis of this third type of resin is described in chapter 6.[159]

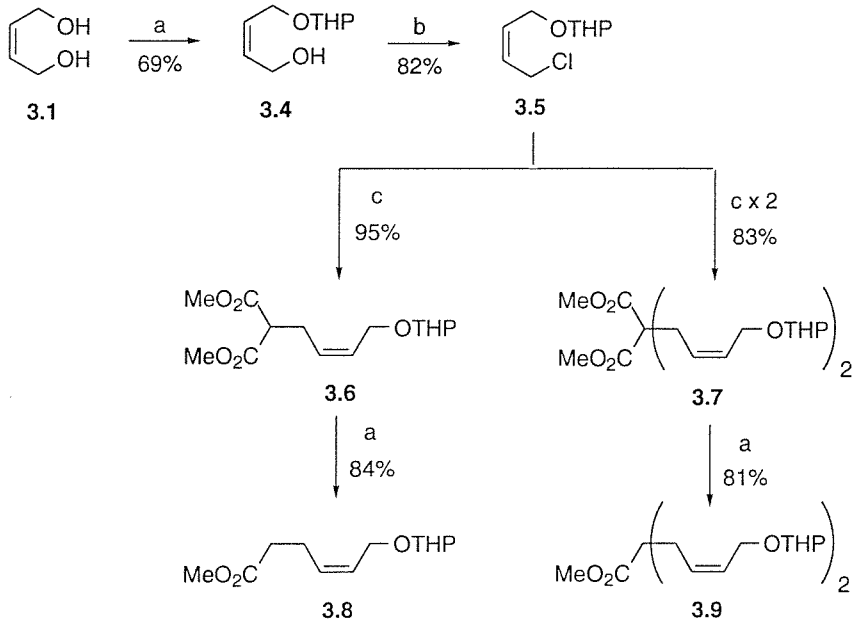
Figure 3.3



3.1- Solution-Phase Synthesis of the Single and Double Armed Linkers and Substrates

Following a literature report,[160] treatment of *cis*-2-butene-1,4-diol (**3.1**) with dihydropyran in the presence of a catalytic amount of acid afforded a mixture of di-, monoprotected and unreacted diol (Scheme 3.1). This did not constitute a major disadvantage as the deprotected and unreacted diols could be collected and equilibrated to afford further monoprotected diol **3.4**. Alcohol **3.4** was then converted in 82% yield into chloride **3.5**. Good yields were also obtained for the monoalkylation and dialkylation of dimethyl malonate with **3.5** thus affording malonates **3.6** and **3.7**.

Scheme 3.1



Reagents and conditions: a) dihydropyran, *p*TSA, THF, CH_2Cl_2; b) MsCl, EtN^iPr_2, CH_2Cl_2; c) dimethyl malonate, NaH, DMF; d) KOAc, DMSO, 140°C.

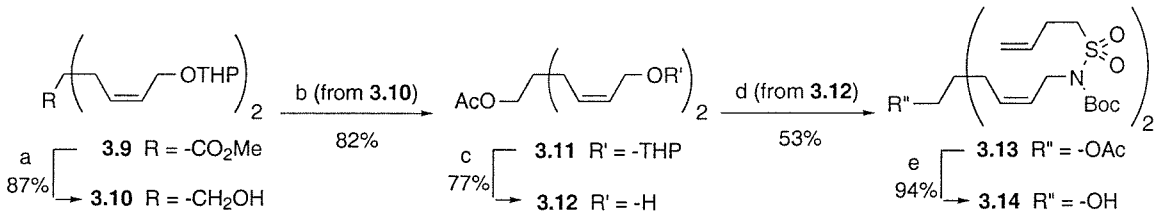
The best results for the dialkylation of the malonate were obtained when carried out in two steps, with isolation of the intermediate monoalkylated malonate **3.6**. In the first step, excess

dimethylmalonate favoured the formation of **3.6** which was subsequently converted to the dialkylated compound **3.7** using excess chloride **3.5**. Krapcho reactions[161] on the mono- and dialkylated malonates afforded the monoesters **3.8** and **3.9** in 84% and 81% yield respectively. In order to improve the selectivity of the monoprotection of **3.1**, the use of a silicon protecting group (TBDMS) in place of the pyranyl ether was investigated thus affording exclusively the monoprotected diol in 93% yield. However, the harsh conditions required for the Krapcho reaction led to extensive decomposition and the alternative route was not investigated further.

3.1.1- Towards the Double Armed Linker

We then decided to further elaborate ester **3.9** by first providing the resin anchoring point prior to forming the sulfonamide. Thus, reduction of **3.9** employing $LiAlH_4$ afforded alcohol **3.10** in 87% yield (Scheme 3.2). Subsequent protection as the corresponding acetate **3.11** and deprotection of the THP group by transacetalation[162] afforded diol **3.12**. Sulfonamide **2.18** was coupled to **3.12** under Mitsunobu conditions to give sulfonyl carbamate **3.13**. Deacetylation of **3.13** led to alcohol **3.14** which was ready for attachment to the appropriate resins.

Scheme 3.2

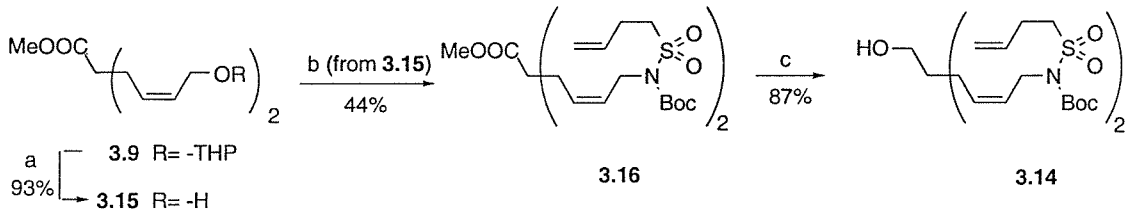


Reagents and conditions: a) $LiAlH_4$, Et_2O; b) Ac_2O, DMAP, Et_3N, CH_2Cl_2; c) *p*TSA, MeOH; d) sulfonamide **2.18**, DEAD, PPh_3, THF; e) MeOH, K_2CO_3.

With the acetylated product **3.13** in hand, we were able to investigate the efficiency of the RCM on our new system. After one day at room temperature using 20 mol% of Grubbs catalyst a mixture of cyclic product and unreacted starting material was obtained, in a ratio 2:1. Although the conversion was incomplete, the trial reaction did show that RCM from this type of 'double armed' substrate was viable.

To avoid unnecessary protection and deprotection of the hydroxy group as the corresponding acetate, we decided to explore the synthesis of **3.14** by formation of the sulfonamide in place of the tetrahydropyranyl ether first and then reduction of the ester (Scheme 3.3).

Scheme 3.3



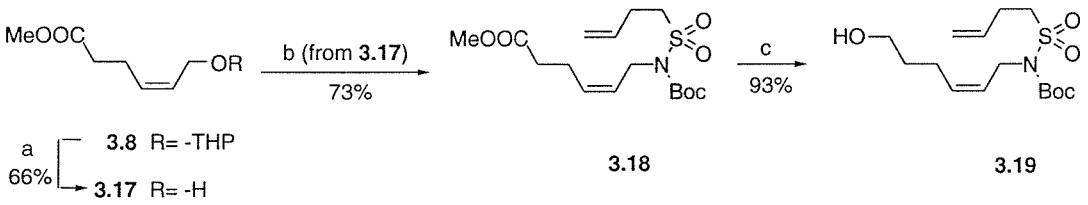
Reagents and conditions: a) *p*TSA, MeOH; b) sulfonamide **2.18**, DEAD, PPh_3, THF; c) $LiAlH_4$, Et_2O.

Deprotection of the tetrahydropyranyl ether **3.9**, followed by double Mitsunobu coupling of Boc sulfonamide **2.18** with the resulting diol **3.15** afforded ester **3.16** in 41% overall yield. Reduction of **3.16** to alcohol **3.14** proceeded without event. This sequence of reactions was used to prepare multigram quantities of alcohol **3.14**, which was ready for coupling to the solid-phase, allowing us to explore the solid-phase RCM reactions.

3.1.2- Towards the Single Armed Linker

The three step reaction sequence presented above was repeated on the single armed substrate. Thus THP deprotection of ester **3.8**, Mitsunobu coupling of the resulting alcohol **3.17** with sulfonamide **2.18** and final ester reduction of **3.18** afforded the desired Boc protected sulfonamide **3.19** in 45% overall yield (Scheme 3.4).

Scheme 3.4



Reagents and conditions: a) *p*TSA, MeOH; b) sulfonamide **2.18**, DEAD, PPh_3, THF; c) $LiAlH_4$, Et_2O.

Multigram quantities of alcohol **3.19** were prepared, placing us in a good position to synthesise the resin-bound RCM precursors.

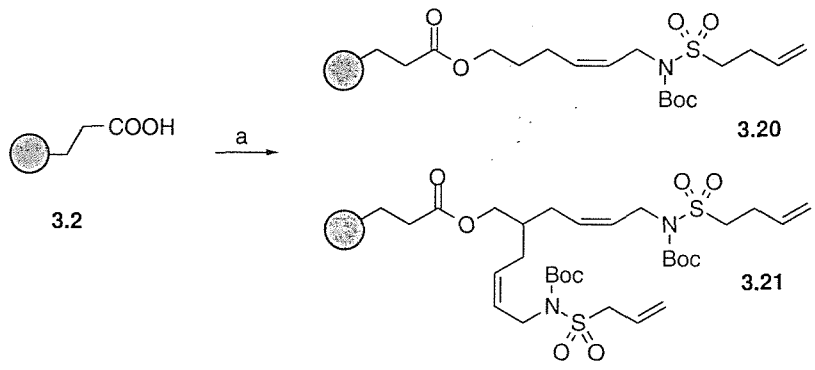
In addition, we made the most of the availability of **3.18** to determine the apparent influence of concentration on the RCM yield. Trial solution-phase RCM reactions on **3.18** at concentrations of 0.1, 0.5 and 1mM in CH_2Cl_2 and in the presence of 1 mol% of catalyst were conducted. The reactions were quantitative in all cases.

3.2- Formation of RCM Precursors and Subsequent Cyclisative Cleavage

3.2.1- Initial One-Step Solid-Phase Synthesis on Carboxyethyl Resin 3.2

As mentioned in the introduction to this chapter, we decided to first employ the carboxyethyl resin **3.2** to enable reaction monitoring by reductive cleavage of an aliquot. Resin-bound RCM precursors **3.20** and **3.21** were obtained by coupling alcohols **3.14** and **3.19** to resin **3.2**, using a mixture of DIC and DMAP (Scheme 3.5).

Scheme 3.5



Reagents and conditions: a) DIC, DMAP, alcohol **3.14** or **3.19**, CH_2Cl_2.

IR spectroscopy and lithium borohydride reduction confirmed completion and success of the couplings. In addition, the reductive cleavage allowed us to determine the loading, as explained in section 6.

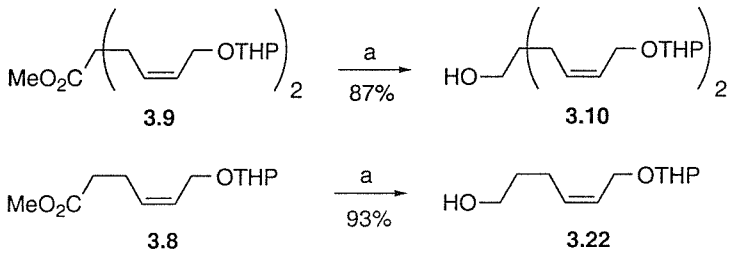
Resins **3.20** and **3.21** were submitted to 50 mol% Grubbs catalyst in refluxing dichloromethane. We were pleased to observe formation of the desired 7-membered sulfonamide **2.17** but felt that we ought to bring further improvement to the synthesis, in particular with respect to the number of steps carried out on the resin. We therefore decided not to optimise the RCM conditions at this point, although we were sure that we could go to levels of catalyst much lower than 50 mol%.

3.2.2- A More Expedient Solution-Phase Synthesis

Since the solution-phase synthesis of the linker and substrate was rather time-consuming and presented purification problems upon scale-up, we felt that we could prepare an earlier intermediate and complete the synthesis on the solid-phase. Alcohol **3.10**, which had been previously obtained in 87% yield from the reduction of the double armed ester **3.9** seemed a

promising candidate. Similarly **3.8**, the single armed ester obtained from the Krapcho reaction, afforded alcohol **3.22** upon reduction (Scheme 3.6).

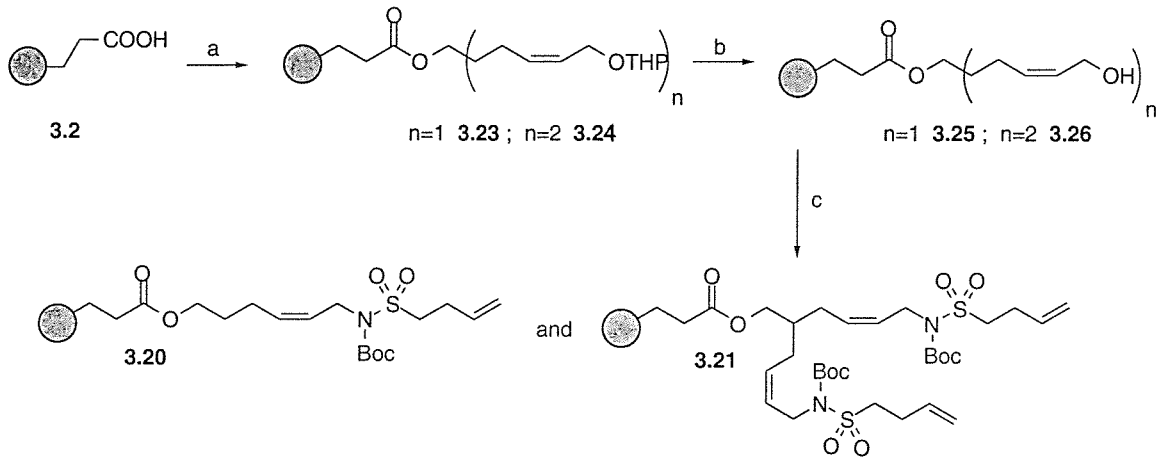
Scheme 3.6



Reagents and conditions: a) $LiAlH_4$, THF.

Alcohols **3.10** and **3.22** were subsequently coupled to the carboxyethyl resin **3.2** under standard conditions (Scheme 3.7). Consecutive THP deprotection and Mitsunobu reaction afforded the resin-bound RCM precursors **3.20** and **3.21**.

Scheme 3.7



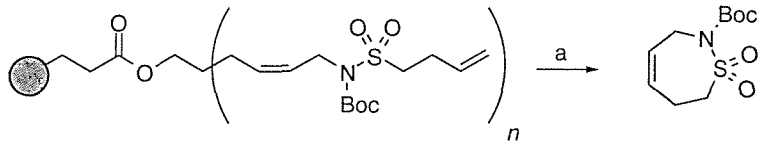
Reagents and conditions: a) DIC, DMAP, alcohols **3.22** or **3.10**, CH_2Cl_2; b) *p*TSA, MeOH, DME; c) sulfonamide **2.18**, DEAD, PPh_3, THF.

IR spectroscopy or lithium borohydride reduction confirmed completion and success of the different reactions through out the sequence. In addition, lithium borohydride cleavage of a small sample of resins **3.25** and **3.26** allowed us to optimise the THP deprotection. Four different methods were investigated (TFA/H_2O,[163] *p*TSA / MeOH / DME,[131] AcOH / CH_2Cl_2,[164] HCl / THF). We thus observed that acetic acid and hydrochloric acid failed to effect efficient deprotection whereas TFA and the transacetalation method did. However, the risk of transesterification with the resin in the presence of TFA was a concern. As a result, transacetalation using *p*TSA and methanol was retained for all subsequent syntheses as it was convenient and efficient.

3.2.3- RCM Cyclisation Cleavage on Resins 3.20 and 3.21

The resin-bound RCM precursors **3.20** and **3.21** were submitted to different amounts of Grubbs catalyst at different concentrations, temperatures and in different solvents (Scheme 3.8). We had already found during the solution-phase study that concentration had little apparent effect on the yield. Refluxing dichloromethane was the solvent of choice. In addition, a co-factor, namely 1-octene, was also added to the single armed resin as had been suggested in the solid-phase RCM literature to improve the yields. The results obtained varying the quantities of catalyst are reported in table 3.1.

Scheme 3.8



n=1, **3.20** ; n=2, **3.21** **2.17**

Reagents and conditions: a) Grubbs catalyst, CH_2Cl_2, 15 hours.

Table 3.1: results for RCM cyclisation cleavage[a] to the Boc protected sulfonamide **2.17**

Entry	Catalyst (mol%)	Yield[b] (%)		
		Resin **3.20**	Resin **3.20** with co-factor[c]	Resin **3.21**
1	2.5	66	53	61
2	5	61	38	43
3	10	62	56	52
4	50	41	--[d]	55

Notes: a) the reactions were conducted as suspensions of resin (100-300 mg) in refluxing CH_2Cl_2 (2-4 mL) in the presence of the catalyst; b) yields refer to purified material; c) 1-octene (1 eq.); d) the reaction was not carried out.

Aside from the fact that the yields were generally good, we were surprised to observe no fundamental difference of behaviour between the single armed and the double armed resins. However, the use of a co-factor turned out to be a disadvantage since we sometimes obtained unidentified impurities which had to be separated from the desired sulfonamide **2.17**. To establish the origin of these impurities, two reactions were carried out. In the first, a solution of **2.17** and ruthenium catalyst in CH_2Cl_2 was heated at reflux for one week. In the second, a duplicate reaction containing also 1-octene was carried out under the same conditions. After one week we were pleased to see that no degradation of the cyclic sulfonamide had occurred in the absence of 1-octene. However, in its presence unidentified cross-coupling impurities were formed. This experiment also showed that prolonged reaction times did not have a

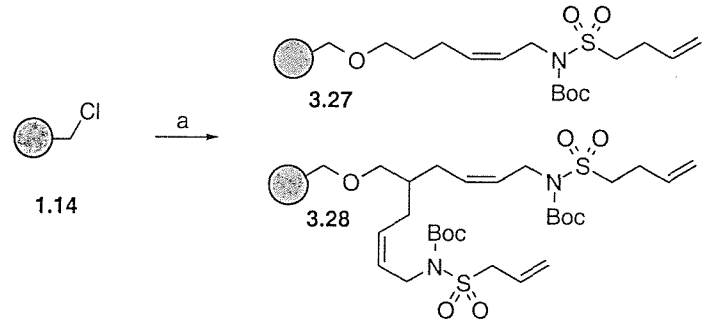
negative effect on the yield of cyclic cleaved material in case the necessary reaction time for quantitative RCM cleavage reactions was shorter than in practice (15 hours). To conclude, comparable yields of cleaner products were obtained in the absence of co-factor, and the products were typically of higher purity.

3.2.4- Synthesis of Ether-Linked RCM Substrates

The carboxyethyl resin had proved useful in the early studies but its base-lability limited the reaction conditions that could be used. The success of the trial RCM reactions on the carboxyethyl resin led us to study the feasibility of the reaction on the more robust Merrifield resin (**1.14**). It is important to bear in mind that on **1.14**, the substrate would be linked to the polymer *via* an ether linkage with no possibility of cleavage of the material until the final RCM cyclisation release, but as such, increasing the range of reaction conditions that could ultimately be used.

The first RCM precursors on Merrifield resin were synthesised from alcohols **3.14** and **3.19** prepared in solution. Thus, action of NaH on **3.14** and **3.19** in DMF with heating afforded the corresponding sodium alkoxides which were coupled to **1.14** (Scheme 3.9). In order to improve the efficiency of the coupling, both addition of 1 equivalent of 15-crown-5 to the sodium alkoxides[165] and the use of ^{t}BuOK instead of NaH[88] were investigated. Combustion analysis on sulfur carried out on batches of resin prepared by each of the different methods returned similar values. Sodium hydride in DMF was retained as the method of choice.

Scheme 3.9



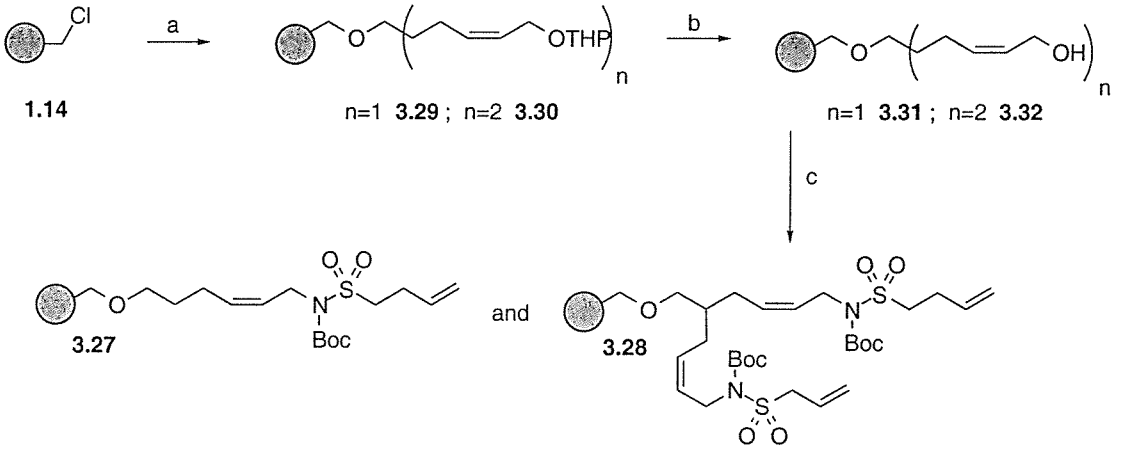
Reagents and conditions: a) alcohols **3.14** or **3.19**, NaH, THF, 60°C.

To check the feasibility of RCM cleavage on our new substrates, resins **3.27** and **3.28** were submitted to 5 mol% of ruthenium catalyst in refluxing dichloromethane. Gratifyingly,

sulfonamide **2.17** was obtained in quantitative yield. We were then in a position to investigate the solid-phase synthesis of the substrates **3.27** and **3.28**.

Alcohols **3.22** and **3.10** were coupled to Merrifield resin (**1.14**) by reaction of the corresponding sodium alkoxides in DMF at 60°C (Scheme 3.10). The resin-bound free alcohol **3.31** and diol **3.32** were obtained by cleavage of the tetrahydropyranyl ethers **3.29** and **3.30** under the conditions used on the carboxyethyl resin-bound pyranyl ethers **3.23** and **3.24**. Finally Mitsunobu coupling with sulfonamide **2.18** afforded the RCM precursors **3.27** and **3.28**.

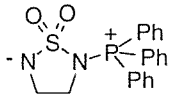
Scheme 3.10



Reagents and conditions: a) **3.22** or **3.10**, NaH, THF, 60°C; b) *p*TSA, MeOH, DME; c) sulfonamide **2.18**, DEAD, PPh_3, THF.

In some instances, IR analyses of resins **3.27** and **3.28** indicated that no Mitsunobu coupling had occurred. We first believed that reactivity problems resulted in this failure. Therefore, we carried out a series of coupling reactions using the supposedly more reactive dimethyl diathiazine triphenyl phosphorane (**3.33**) as an alternative to the classical Mitsunobu conditions (Figure 3.4).[166]

Figure 3.4

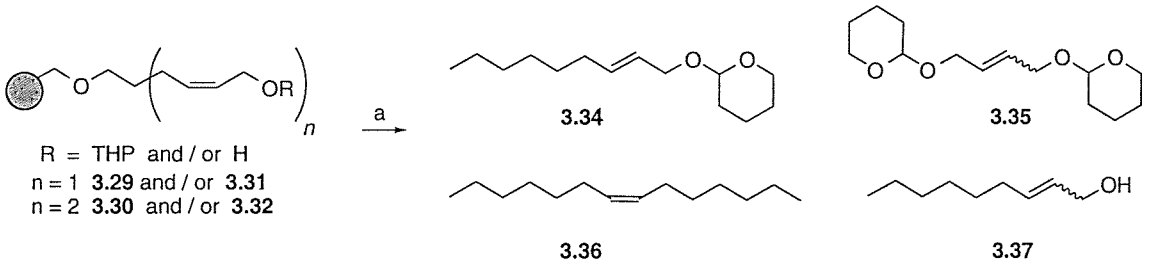


3.33

Disappointingly, no improvement was observed. Further investigation showed that the absence of coupling problem could be traced to an inefficient THP deprotection, since resubmission of the resins to *p*TSA and methanol and subsequent coupling under standard

Mitsunobu conditions eventually worked. We therefore designed a method to monitor the cleavage of the THP groups. In the event of incomplete deprotection, cross-metathesis reaction of the resins with 1-octene under standard metathesis conditions afforded olefin **3.34** (Scheme 3.11). Olefin **3.35** and (*E*)-7-tetradecene (**3.36**), the two possible homodimers, were also recovered from the cross-coupling reaction. In contrast, if the deprotection was complete, we expected the formation of alcohol **3.37**. However, only homodimer **3.36** was observed in this case, suggesting perhaps catalyst poisoning which prevented the formation of **3.37**. When the cross-metathesis showed that the deprotection was incomplete, the resin was resubmitted to the THP deprotection conditions.

Scheme 3.11



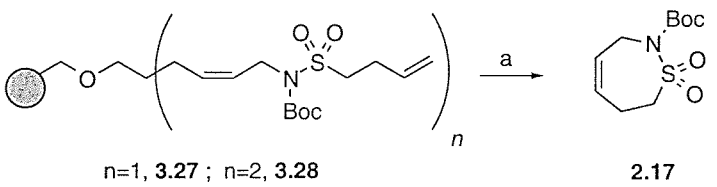
Reagents and conditions: a) 1-octene, Grubbs catalyst, CH_2Cl_2.

Surprisingly, spectral evidence seemed to indicate that the double bond conformation was *Z* for **3.36**[167] and *E* for **3.34**. It was reported in the literature that the alkene substitution outcome for cross-metathesis reactions could be either *E* and *Z* depending on the nature of the substrate.[143]

3.2.5- RCM Cyclisation Cleavage on Resins 3.27 and 3.28

Resins **3.27** and **3.28** were then submitted to different amount of Grubbs catalyst in refluxing dichloromethane (Scheme 3.12).

Scheme 3.12



Reagents and conditions: a) Grubbs catalyst, CH_2Cl_2, 15 hours.

The results obtained varying the quantities of catalyst are reported in table 3.2. The olefin co-factor was not used with **3.27** since it had not provided any advantage on the carboxyethyl resin.

Table 3.2: results for RCM cyclisation cleavage[a] to the Boc protected sulfonamide **2.17**

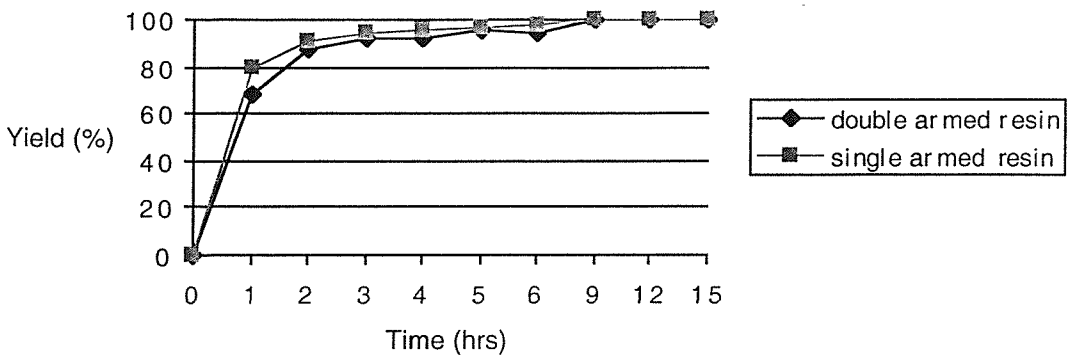
Entry	Catalyst (mol%)	Yield[b] [Yield][c] (%)	
		Resin **3.27**	Resin **3.28**
1	1	[31]	[91]
2	2.5	[45]	[100]
3	5	100 [100]	100 [100]
4	50	60 [53]	84 [78]

Notes: a) the reactions were conducted as suspensions of resin (100-300 mg) in refluxing CH_2Cl_2 (2-4 mL) in the presence of the catalyst; b) isolated yield; c) yield determined by GC (see below).

RCM cyclisation cleavage from Merrifield resins **3.27** and **3.28** proceeded in better yields than those seen for carboxyethyl resins **3.20** and **3.21**. We were delighted to obtain quantitative cleavage in some instances (entries 2 and 3). But the most striking fact was that when less than 5 mol% of catalyst was used (entry 1), better yields in the cyclisative cleavage were obtained for the double armed resin. Thus, the double armed linker seemed to be more efficient than the single armed linker only with small amounts of catalyst.

To get an approximate idea of when the RCM cleavage reactions were reaching completion, we decided to monitor by GC the product formation over time using phenanthrene as an internal standard. The choice of phenanthrene relied on physico-chemical properties such that the retention time on the GC column was close to the that of the cyclic sulfonamides and that phenanthrene was inert under the RCM conditions. A known quantity of phenanthrene was therefore introduced in the reaction mixture and samples were regularly taken from the reaction mixture and injected into the GC. A curve representing the increase in cyclic sulfonamide concentration was plotted against time (Graph 3.1). We observed a plateau after about three hours for the RCM cyclisative cleavage from single and double armed ether linked resins **3.27** and **3.28** in refluxing CH_2Cl_2 employing 5 mol% of catalyst.

Graph 3.1: yield (%) in Boc-protected sulfonamide **2.17** against time (hour) during cyclisation cleavage off double and single armed resins **3.27** and **3.28**



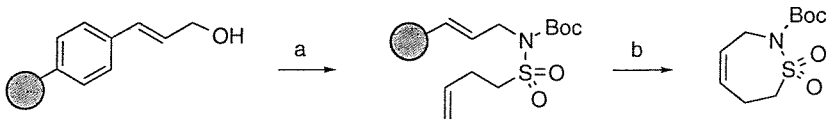
After product isolation, we found that in fact quantitative cleavage had been reached. We also demonstrated that there was a good agreement between isolated yields and GC yields and decided to preferentially use the latter method whenever possible since it was less time consuming. It should be mentioned that GC was chosen as the analytical tool due to the absence of a strong chromophore in the RCM product **2.17**, which was required for the HPLC equipment that was available.

3.2.6- Resin 3.3 Functionalisation and Subsequent Cyclisation Cleavage

As mentioned earlier, in addition to the comparison between the single and the double armed linker, we felt that better conclusions on the RCM cyclisation release mechanistic pathway could be drawn by comparison with a third type of resin. The literature reported the use of resin **3.3** in an efficient RCM cyclisative cleavage of small organic heterocycles.[132-134] Resin **3.3** was characterised by a lack of flexibility in the linking chain, which made it even more interesting to compare with the other resins since the flexible, several carbon long chain of the single armed linker on resins **3.20** and **3.27** seemed to lead to quite high yields.

Mitsunobu coupling of **3.3** with sulfonamide **2.18** under standard conditions or employing phosphorane **3.33** provided RCM precursor **3.38**. Under the optimised conditions identified in our earlier studies, RCM cyclisation cleavage from resin **3.38** turned out to be extremely inefficient, yielding only traces of cyclic compound **2.17**. Even when a high quantity of Grubbs catalyst was used, no improvement in yield was observed.

Scheme 3.11



3.3 3.38 2.17

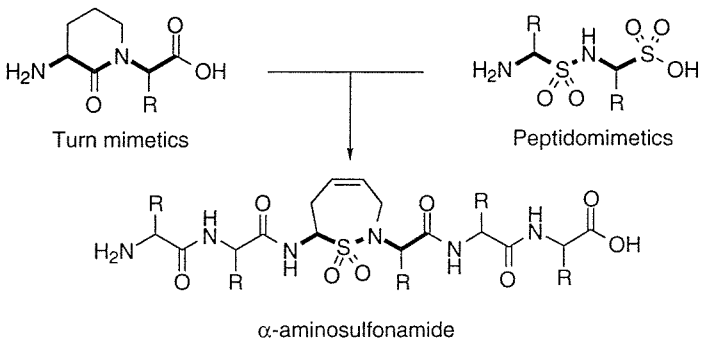
Reagents and conditions: a) **2.18**, DEAD, PPh_3, THF or **2.18**, **3.3**, THF; b) Grubbs catalyst, CH_2Cl_2.

Due to the inadequacies of the solid-phase analytical methods, we were never able to unambiguously determine that resins and **3.3** or **3.38** were formed efficiently. Unfortunately, due to time constraints, we were unable to probe this question further. If time had been available we would have looked at the oxidative cleavage of **3.38**. The RCM cyclisation cleavage off resin **3.3** was abandoned.

4- Further Functionalisation of our Initial Sulfonamide Scaffold

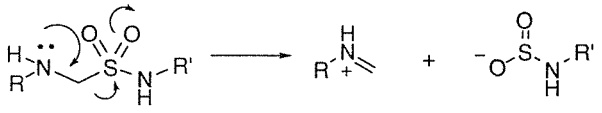
After having developed an efficient synthetic approach to some simple cyclic sulfonamides, we were keen to expand the scope of this methodology to the synthesis of more elaborate molecules. Initially, we had in mind the synthesis of peptidomimetics that would incorporate our cyclic sulfonamide scaffold. In particular, we wanted to prove the feasibility of growing peptide chains from the sulfonamide core, relying on the ring to induce conformational restriction, thus forming β or γ-turn mimetics (Figure 4.1).[146,168-170] The stage had already been partially set for this further elaboration of the cyclic core. An acid-labile *N*-protecting group had been incorporated, permitting further functionalisation at that position by alkylation. In addition, as mentioned previously, the use of the sulfonamide as a replacement for the amide bond found in natural peptides was reported in the literature.[147-149] The resulting combination of these two characteristics appeared to us as an interesting goal.

Figure 4.1



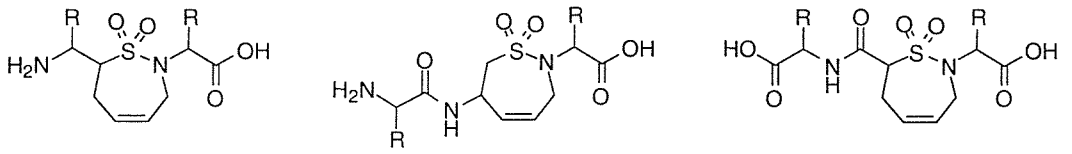
However, a review of the literature on the numerous attempts to synthesise α-amino sulfonamides suggested that the formation of such molecules had been elusive, due to their instability.[171] An elimination process cleaves the C-S bond (Figure 4.2).

Figure 4.2



Nevertheless, access to the β-aminosulfonamides was possible.[148,172] Investigation into the possible syntheses of peptidomimetics **A**, **B** and **C** led us to focus on the preparation of the latter (Figure 4.3).

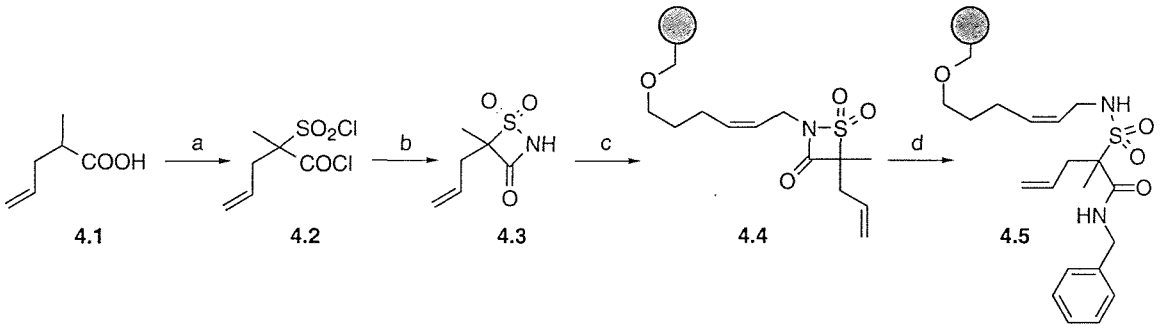
Figure 4.3



A **B** **C**

Prior to investigation of the feasibility of introducing various substituents on the nitrogen, we decided to first study how to achieve functionalisation α to the sulfur. Several methods for the synthesis of α-carboxylic sulfonyl chlorides and derivatives have been described in the literature.[173-177] Attempts to reproduce one of them, starting from the commercially available 2-methyl-4-pentenoic acid (**4.1**), were unsuccessful as preparation of **4.3** failed (Scheme 4.1).

Scheme 4.1



4.1 **4.2** **4.3** **4.4** **4.5**

Reagents and conditions: a) SO_3, $POCl_3$; b) NH_3, Et_2O; c) resin **3.32**, DEAD, PPh_3, THF; d) benzylamine, CH_2Cl_2.

Due to a lack of time, we were unable to pursue other routes to attempt functionalisation of the carbon next to the sulfonamide group. It should be mentioned, however, that during the preparation of this thesis a successful solution-phase synthesis of templates similar to **C** employing RCM was published in the literature.[145]

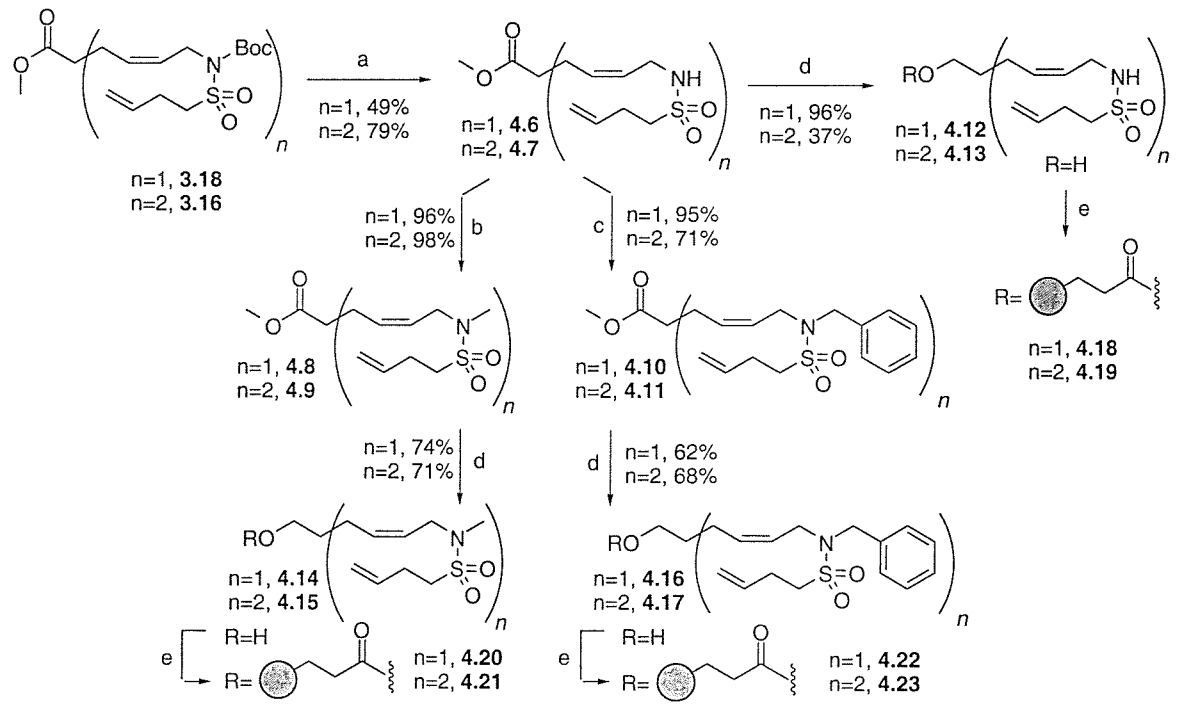
In spite of our failure in functionalising β to the sulfur, we investigated the feasibility of further chemistry on the nitrogen. As a consequence, even if the more elaborated peptidomimetics could not be obtained, we would still access to a collection of novel

medium-ring sulfonamides. We believed that a small collection of cyclic sulfonamides might be of interest since, as far as we knew, there were no examples of tetrahydro-2-thiazepine-1,1-dione ring systems such as **2.8** and **2.17** in the literature. At a later time, however, a paper reported the use of RCM to form the corresponding 6-membered ring sulfonamides in solution.[144]

4.1- Solution- and Solid-Phase Synthesis of RCM Precursors

The presence of the ester group as the anchoring point on the carboxyethyl resin **3.2** prevented us from removing the Boc group and carry out the *N*-alkylation directly on the solid-phase. A solution-phase synthesis with final coupling to the resin was therefore necessary. Starting from either esters **3.16** or **3.18**, Boc deprotection by transesterification using K_2CO_3 in MeOH afforded sulfonamides **4.6** and **4.7**, which were subsequently reacted with methyl iodide or benzyl bromide in the presence of NaH to give the *N*-alkylated products **4.8-4.11** (Scheme 5.1). Reduction of the ester group afforded the corresponding alcohols **4.12-4.17**, which were subsequently coupled to the carboxyethyl resin **3.2** under standard DIC conditions.

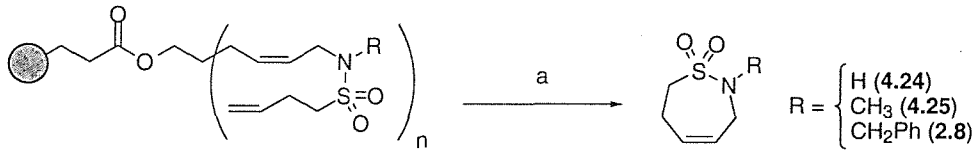
Scheme 4.2



Reagents and conditions: a) K_2CO_3, MeOH, CH_2Cl_2, 60°C; b) methyl iodide, NaH, CH_2Cl_2; c) benzyl bromide, NaH, CH_2Cl_2; d) $LiAlH_4$, THF; e) resin **3.2**, DIC, DMAP, CH_2Cl_2.

Resins **4.18-4.23** were submitted to Grubbs catalyst under the previous optimised conditions (Scheme 4.3).

Scheme 4.3



n=1, **4.18** (R=H), **4.20** (R=Me), **4.22** (R=Bn)
n=2, **4.19** (R=H), **4.21** (R=Me), **4.23** (R=Bn)

Reagents and conditions: a) Grubbs catalyst, CH_2Cl_2, 15 hours.

Running up to 12 reactions in parallel with rapid GC analyses using the internal standard method facilitated the whole process. Due to its convenient retention time, phenanthrene was chosen as the internal standard after it was established that GC yields were in good agreement with isolated yields. The results are reported in table 4.1.

Table 4.1: RCM cyclisation cleavage[a] off carboxyethyl resins **4.18-4.23**

Entry	R	Catalyst (mol%)	Yield[b] [Yield][c] (%)	
			Single armed	Double armed
1	H	5	5	23
2	CH_3	5	70 [86]	100 [100]
3	CH_2Ph	5	84 [100]	76 [100]

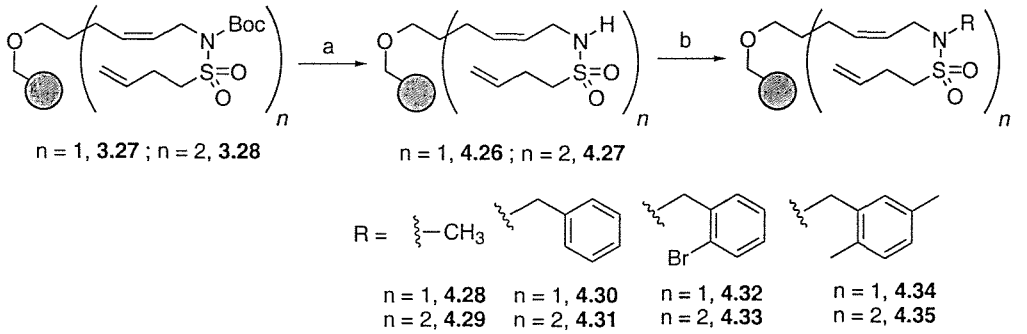
Notes: a) the reactions were carried out as suspension of the resin (100-300 mg) in refluxing CH_2Cl_2 (2-4 mL) in the presence of the catalyst; b) isolated yield; c) yield determined by GC (see below).

Surprisingly, we observed a significant difference between the yields calculated by GC and those determined by product isolation. We presumed the GC yield more representative since we were working on small quantities of cleaved material when a slight variation in weight caused an important difference in yield. Disappointingly, the free sulfonamide did not cyclise in good yield (entry 1). This might have resulted from catalyst poisoning or from attachment of the substrates **4.12** and **4.13** *via* the sulfonamide instead of the hydroxy group thus resulting in on-resin cyclisation and no cleavage. The other cyclic sulfonamides were obtained in good to excellent yield and high purity (entries 2 and 3). In addition, the yields of *N*-alkylated material were significantly better than those obtained for the Boc protected sulfonamide (see table 3.1).

As the *N*-alkylations occurred in high yields on the solution-phase, we did not anticipate problems transferring the chemistry to the solid-phase on the more robust Merrifield resin (Scheme 4.4). However base-catalysed transesterification on resins **3.27** and **3.28** did not appear to lead to satisfactory deprotection, even after long reaction times or refluxing as

indicated by the presence of a carbonyl peak on IR. Gratifyingly complete removal of the Boc group was achieved using a 50% solution of TFA in CH_2Cl_2. Subsequent alkylation with several halides in the presence of base afforded a set of *N*-alkylated RCM precursors.

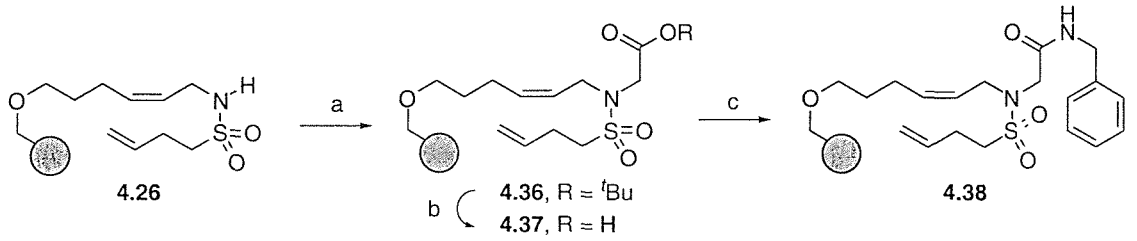
Scheme 4.4



Reagents and conditions: a) TFA, CH_2Cl_2; b) ^{t}BuOK, methyl iodide or benzyl bromide or 2-bromobenzyl bromide or 2,5-dimethylbenzyl chloride, THF.

Comparison of the efficiency of two *N*-alkylation methods reported in the literature[178,179] was made possible by carrying out the RCM cleavage of the resin-bound substrates. After a single alkylation with the reactive alkylating agent methyl iodide in the presence of DBU,[178] the cleaved crude product from the RCM of resin **4.28** contained about 20% of the desired methylated compound **4.25** and 80% of the unsubstituted cyclic sulfonamide **4.24**. This ratio increased to 1:1 when a double *N*-alkylation was carried out. Replacing DBU with ^{t}BuOK[179] afforded a quantitative *N*-alkylation. As a result, the ^{t}BuOK method was used in all future alkylation reactions. In order to demonstrate that several steps could be carried out on our resin-bound sulfonamides and more particularly with a view to growing a peptide chain from our substrate, we investigated *N*-alkylation with *tert*-butylbromoacetate (Scheme 4.5). Removal of the resulting *tert*-butyl ester **4.36** with TFA afforded the free carboxylic acid **4.37**, which was then coupled to benzylamine using standard amide bond formation methods.

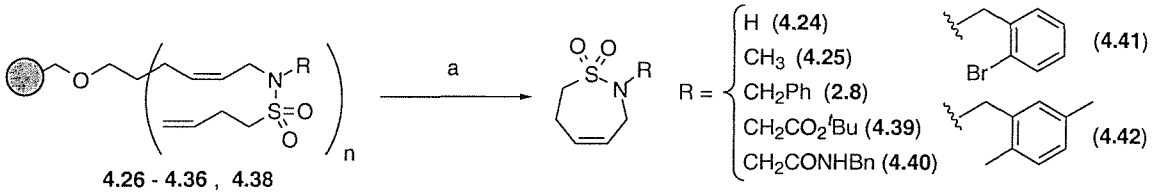
Scheme 4.5



Reagents and conditions: a)*tert*-butyl bromoacetate, ^{t}BuOK, THF; b) TFA, CH_2Cl_2; c) DIC, DMAP, benzylamine, CH_2Cl_2.

Resins **4.26**-**4.36** and **4.38** were then submitted to Grubbs catalyst (Scheme 4.6). Like resins **4.18**-**4.23**, the use of a 12 reactions block and a GC with the method of internal standard were beneficial. The results are reported in table 4.2.

Scheme 4.6



Reagents and conditions: a) Grubbs catalyst, CH_2Cl_2, 15 hours.

Table 4.2: RCM cyclisation cleavage[a] off resins **4.26**-**4.36** and **4.38**

Entry	R	Catalyst (mol%)	Yield[b] [Yield][c] (%)	
			Single armed	Double armed
1	H	5	98	97
2	CH_3	5	[74]	--[d]
3	CH_2Ph	1	[45]	[100]
4	CH_2Ph	2.5	[94]	[100]
5	CH_2Ph	5	[100]	[100]
6	$CH_2(o\text{-Br})C_6H_4$	5	58	92
7	$CH_2(2,5\text{-}(CH_3)_2)C_6H_4$	5	59	58
8	$CH_2CO_2{}^tBu$	2.5	95	--[d]
9	$CH_2CO_2{}^tBu$	5	95	--[d]
10	$CH_2CONHCH_2Ph$	5	92	--[d]

Notes: a) the reactions were conducted as suspensions of resin (100-300 mg) in refluxing CH_2Cl_2 (2-4 mL) in the presence of the catalyst; b) isolated yield; c) yield determined by GC (see below); d) the reaction was not carried out.

Unlike the carboxyethyl resins **4.18** and **4.19**, RCM cleavage from resins **4.26** and **4.27** afforded the free sulfonamide **4.24** in almost quantitative yield (entry 1). It should be emphasise that the yield of sulfonamide **4.40** was still excellent, even after the three step reaction sequence of the resin-bound substrate (entry 10). Entry 3 confirmed the superior efficiency of the double armed linker over the single armed with lower amount of catalyst.

4.2- General Conclusions on Ring-Closing Metathesis to Cyclic Sulfonamides

A few other observations were made during the study of the RCM cyclisation cleavage. First, at the end of a RCM reaction, the resins were typically coloured brown purple, often correlating with the amount of catalyst that had been used for the reaction and thus suggesting that some ruthenium species were trapped within the resin. The entrapment of the catalyst

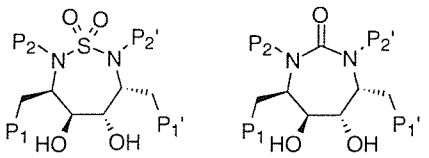
might corroborate the proposed explanation for the breakdown of the catalytic cycle described in section 2.3. To demonstrate this possibility, the coloured resins were reacted with 1-octene in refluxing CH_2Cl_2. In all the experiments (*E*)-7-tetradecene (**3.35**), the cross-metathesis product of 1-octene with itself, was isolated. In addition, the resin-bound catalyst turned out to be more stable to air than the original Grubbs catalyst, as the coloured resins retained the cross-metathesis ability even after several weeks to air exposure. Secondly, in some instances, IR spectra of the resins which did not afford quantitative cleavage showed characteristic peaks for the Boc carbonyl and the sulfonamide group. To see if further product could be obtained from these recovered resin, they were resubmitted to the RCM conditions. Only small quantities (5% or less) of the cyclic sulfonamides were obtained, suggesting that the material remaining on the resin was somehow deactivated towards RCM cleavage. Interestingly, similar observations were reported by van Maarseveen.[130]

As a conclusion, we were pleased to observe that the yields for the cyclisation cleavage to the cyclic sulfonamides were generally excellent. We also demonstrated that a series of reactions could be carried out on the resin prior to the cyclisative release without reduction in yield of cyclised product. Moreover, we generally observed that for very low amounts of catalyst, the single armed resin was less efficient towards RCM than the double armed resin, on both the carboxyethyl and Merrifield resins. For this reason, the introduction of the double armed linker appeared to have been justified as its cleavage efficiency was greatly superior when amount of catalyst lower than 5 mol% were used. Reduced amount of catalyst was clearly an advantage as residual traces of ruthenium were systematically observed in the cleaved products when higher catalyst quantities were employed. Product purity was reported as one of the major problems associated with the RCM reaction.[111,112] In addition we have demonstrated the importance of the linker's flexibility. Indeed our single armed resins, which possessed 5 or 7 atoms between the polymer core and the first double bond, showed an excellent cleavage efficiency without the help of a co-factor. In the future it might be interesting to determine the minimum number of atoms required to get a good yield for the cyclisation cleavage by varying the length of the single armed linker.

5- Cyclic Sulfamides: Further Developments of the RCM Cyclisation Cleavage

In view of the closely related work published on the synthesis of cyclic sulfonamides by RCM[144] and in order to further extend the possible applications of the RCM cyclisative cleavage, we became highly interested in the synthesis of cyclic sulfamides **5.1** that we judged easily accessible by slight modification of our original strategy. The sulfamide group (R-NH-SO_2-NH-R') has been known for a long time and several syntheses have been described.[180-182] Recently, further interest in cyclic sulfamides emerged due to the discovery of HIV protease inhibitors **5.1** analogous to **5.2** (Figure 5.1).[183-187] Nevertheless, this class of compounds remained relatively unexplored.

Figure 5.1

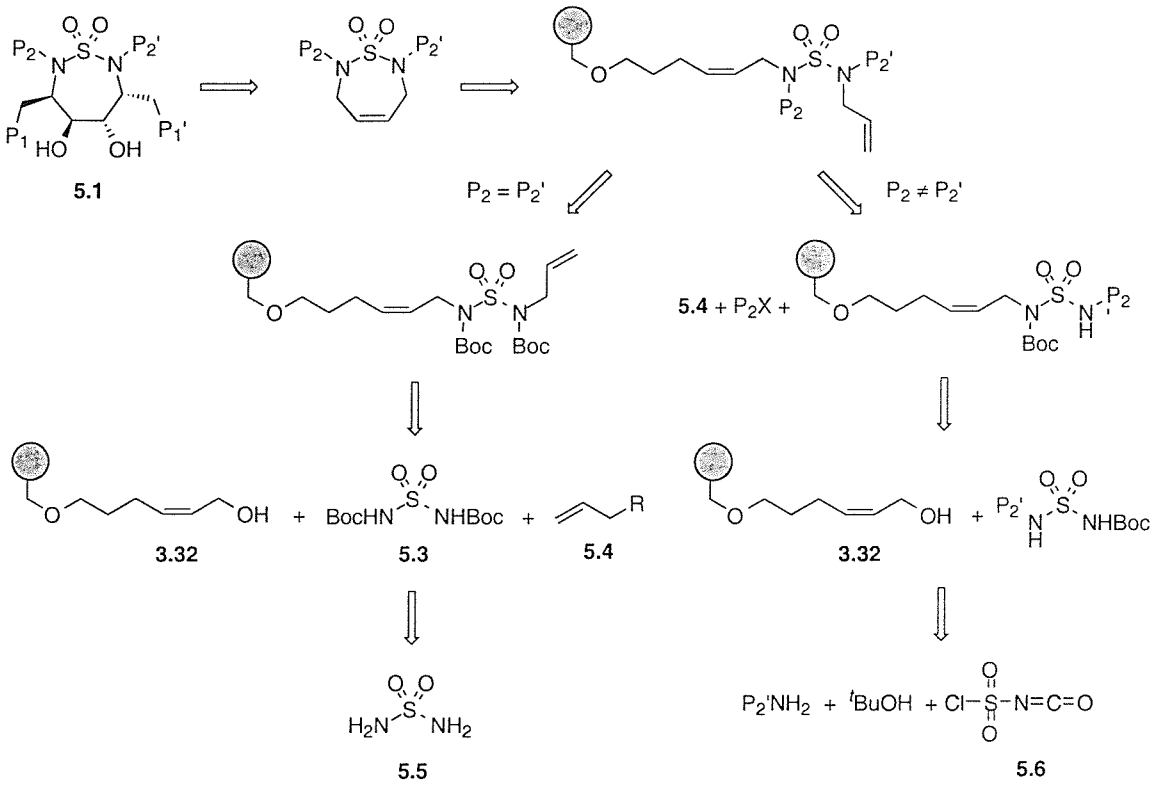


5.1 **5.2**

P_1, P_1' = Ph, CH_2Ph, OPh
P_2, P_2' = CH_2Ph, CH_2*m*-C_6H_4OH, CH_2*m*-$C_6H_4NH_2$, CH_2*m*-$C_6H_4CH_2OI$

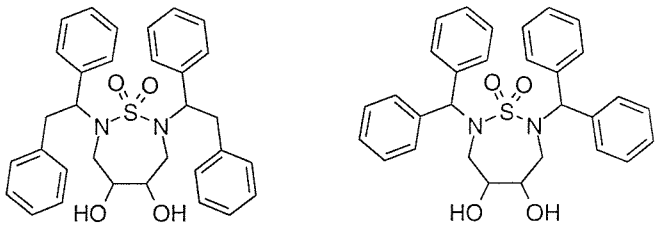
Retrosynthetic analysis led us to consider two solid-phase approaches to cyclic sulfamides analogous to HIV inhibitor **5.1** from commercially available sulfamide (**5.5**) and chlorosulfonyl isocyanate (**5.6**) (Figure 5.2). The first approach would afford symmetrical sulfamides, whereas the second route would give the possibility to introduce different P_2 and P_2' substituents.

Figure 5.2



The synthetic strategy used so far for the preparation of cyclic sulfonamides did not allow the introduction of the P_1 and P_1' substituents α to the nitrogens. We therefore wanted to chose P_2 and P_2' to fill in the position normally occupied in space by the substituents P_1 and P_1' and hence mimic their effect, e.g. as on sulfamides **5.7** and **5.8** (Figure 5.3).

Figure 5.3



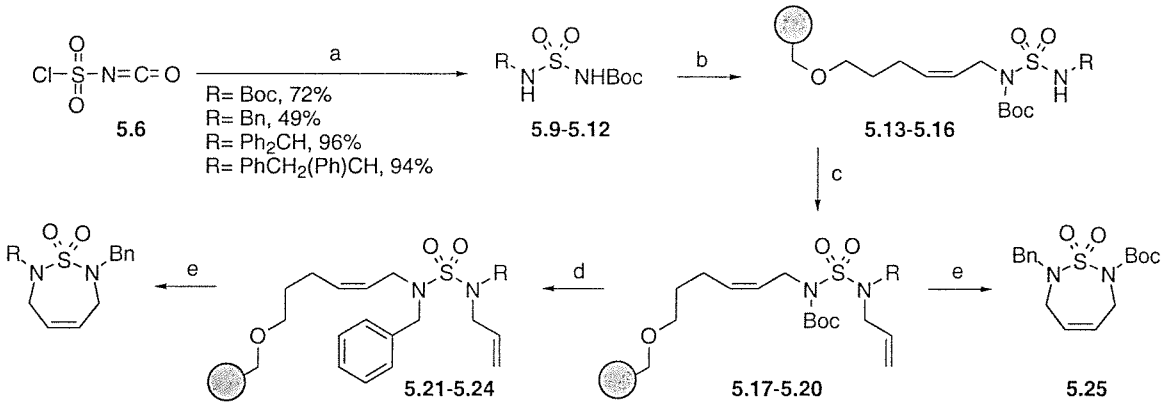
5.7 **5.8**

Finally, it should be mentioned that we were confident not to plan any solution-phase study as all the steps carried out on the resin would employ reactions already conducted and optimised during the solid-phase synthesis of cyclic sulfonamides.

5.1- Solid-Phase Cyclisation Cleavage of HIV Protease Inhibitor Precursors

Following a literature procedure, one-pot reaction of commercially available chlorosulfonyl isocyanate (**5.6**) with *tert*-butanol and one of four different amines afforded the corresponding four sulfamides **5.9**-**5.12** in high yields with no purification required (Scheme 5.1).[181]

Scheme 5.1

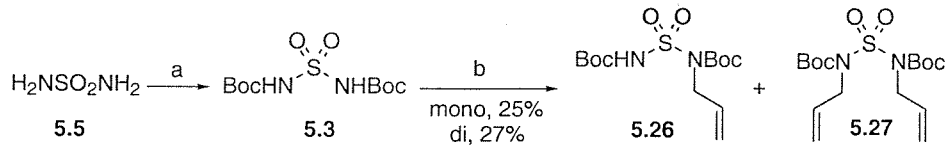


Reagents and conditions: a) 1) ^{t}BuOH, CH_2Cl_2, 2) RNH_2, CH_2Cl_2; b) resin **3.31**, DEAD, PPh_3, THF; c) allyl bromide, ^{t}BuOK, THF; d) 1) TFA, CH_2Cl_2, 2) benzyl bromide, ^{t}BuOK, THF; e) Grubbs catalyst, CH_2Cl_2.

The lower yield for the benzylic compound was due to an uncontrolled warming of the reaction mixture. Employing the Mitsunobu conditions, sulfonamides **5.9**-**5.12** were subsequently coupled to the single armed ether resin **3.31** *via* the most acidic nitrogen. The secondary amine of resins **5.13**-**5.16** was alkylated with allyl bromide under the *N*-alkylation conditions previously established for the sulfonamides. Prior to carrying out Boc deprotection and a second *N*-alkylation with benzyl bromide on **5.17**-**5.20** towards benzylated resins **5.21**-**5.24**, resins **5.17**-**5.20** were submitted to the RCM conditions. Unfortunately, only the resin-bound *N*-Boc,*N'*-benzylated sulfamide afforded traces of the corresponding cyclic compound **5.25**. The other resins gave no reaction and the synthetic strategy was not further investigated.

In view of the failure, we looked into the second strategy, i.e. towards symmetric sulfamides. Double Boc-protection of commercially available sulfamide (**5.5**) afforded **5.3** which was not isolated (Scheme 5.2). Mitsunobu reaction with allyl alcohol failed to afford compound **5.26**. However the latter was obtained by *N*-alkylation with allyl bromide in the presence of sodium hydride, albeit in low yield. A substantial amount of diallylated sulfonamide **5.27** was also obtained.

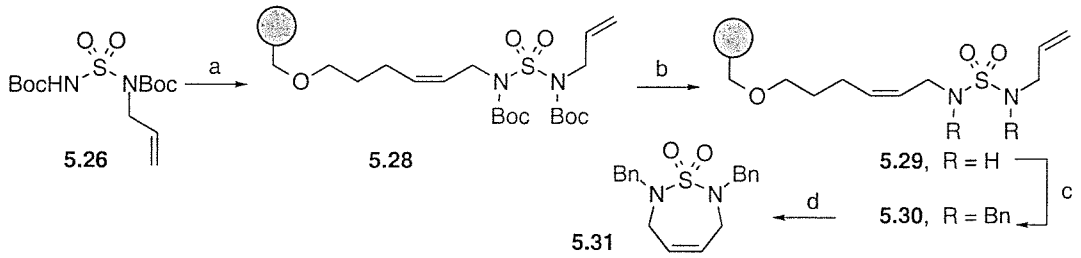
Scheme 5.2



Reagents and conditions: a) Boc_2O, DMAP, Et_3N, CH_2Cl_2; b) allyl bromide, NaH, THF.

Sulfamide **5.26** was then coupled to the ether-linked single armed resin **3.31** under Mitsunobu conditions (Scheme 5.3). The success of the coupling was demonstrated by on-bead IR. Subsequent Boc deprotection and double *N*-alkylation with benzyl chloride employing the same reaction conditions as described during the cyclic sulfonamide synthesis afforded RCM precursor **5.30**.

Scheme 5.3



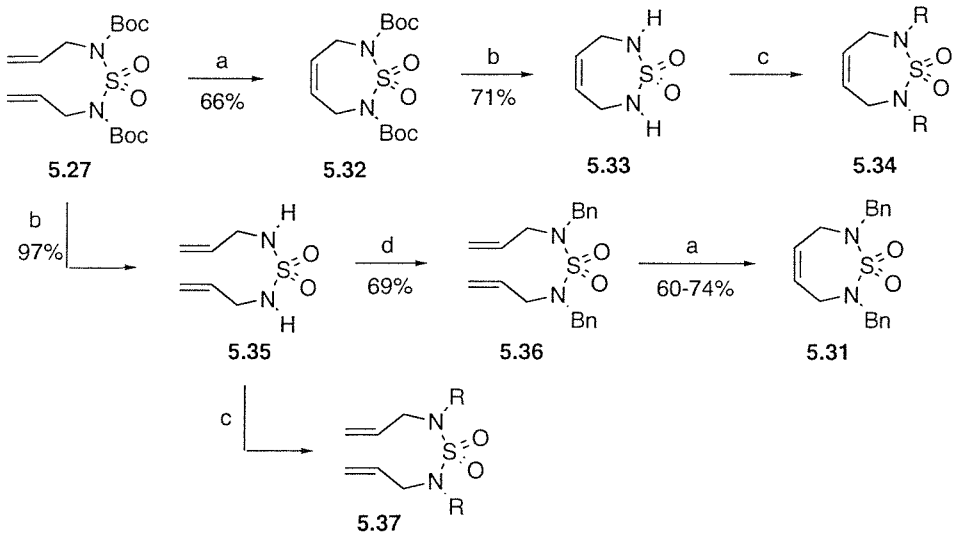
Reagents and conditions: a) resin **3.31**, DEAD, PPh_3, THF; b) TFA, CH_2Cl_2; c) benzyl bromide, ^tBuOK, THF; d) Grubbs catalyst, CH_2Cl_2.

Unfortunately, as in the previous attempts, the RCM cyclisation cleavage failed to afford the corresponding cyclic sulfamide **5.31**. A possible explanation for the failure of the cyclisation cleavage was some functional group incompatibility, which we decided to investigate by conducting RCM reactions in solution.

5.2- Solution-Phase RCM to HIV Protease Inhibitor Precursors

To the best of our knowledge, no ring-closing metathesis reaction had been carried out in the presence of the sulfamide functional group. We decided to take advantage of the diallylated compound **5.27** obtained as a by-product to investigate the tolerance of Grubbs catalyst towards the sulfamide functional group (Scheme 5.4). We were pleased to see that the corresponding 7-membered ring **5.32** was obtained in 66% yield when **5.27** was submitted to 2 mol% of catalyst at room temperature.

Scheme 5.4



Reagents and conditions: a) Grubbs catalyst, CH_2Cl_2; b) TFA, CH_2Cl_2; c) $PhCH_2CH_2Br$ or Ph_2CHBr, ^tBuOK, THF; d) benzylbromide, ^tBuOK, THF.

Solution-phase deprotection of the two Boc groups of **5.32** afforded another novel cyclic sulfamide **5.33**. In addition, further functionalisation prior to the RCM reaction was proved to be feasible in solution as double Boc deprotection and *N*-alkylation with benzyl bromide of **5.27** afforded the RCM precursor **5.36**. Under RCM conditions, **5.36** yielded the corresponding dibenzylated cyclic sulfamide **5.31**. Notably, no significant variation in yield of **5.31** was observed when **5.36** was submitted to various amount of catalyst (Table 5.1).

Table 5.1: RCM cyclisation cleavage[a] to sulfamide **5.31**

Catalyst (mol%)	1	2	2.5
Yield (%)	74	60	69

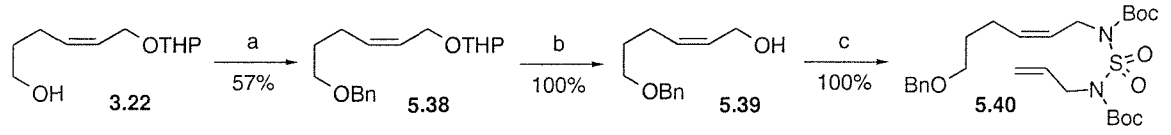
Note: a) the reaction was carried out as a 1mM solution of diolefin in CH_2Cl_2 in the presence of catalyst, at room temperature, for 15 hours.

Attempted *N*-alkylations of cyclic **5.33** or acyclic **5.35** with (2-bromoethyl)benzene or bromodiphenyl methane failed to produce **5.34** or **5.37**, probably due to steric reasons and/or reactivity of the alkylating agents. Sulfamides **5.34** and **5.37** could not be obtained either when investigating *N*-alkylation of **5.3** with the more steric demanding groups prior to Boc deprotection and *N*-allylation with allyl bromide. Nevertheless, it should be also mentioned that we were unable to recover any unreacted starting material from the unsuccessful *N*-alkylated reactions. We concluded that not only the steric and/or electronic properties of the alkylating agents but as well the marked instability of the sulfamide functional group towards the alkylation conditions were responsible for the failure to obtain the desired *N*-alkylated

RCM precursors with a substituent other than benzyl or Boc. The formation of complex *N*-substituted compounds was therefore abandoned.

Yet, this still did not explain why the reaction sequence had failed on the solid-phase. For even if no *N*-alkylation with bulky groups had occurred, IR spectra demonstrated the attachment of the sulfamide group to the functionalised Merrifield resin **3.31** and as a result, submission of the different resins to the RCM conditions should have released some cyclic sulfamides. Since we had demonstrated the compatibility of Grubbs catalyst with the sulfamide functional group, there was a contradiction between the relative success of the solution-phase RCM of terminal diolefins **5.27** and **5.36** and the absence of notable cyclisative cleavage from the resins. We therefore decided to synthesise a solution-phase model to closely mimic the resin-bound compounds replacing the polymer core with a benzyl group (Scheme 5.5).

Scheme 5.5

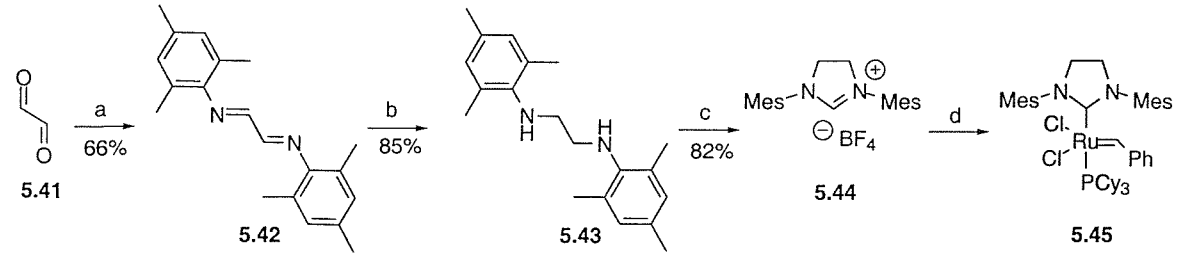


Reagents and conditions: a) NaH, benzyl bromide, THF; b) methanol, *p*TSA; c) DEAD, triphenylphosphine, sulfamide **5.26**, THF.

Protection of the hydroxy group on single armed linker **3.22** as the corresponding benzyl ether followed by THP deprotection and Mitsunobu coupling afforded the solution-phase model **5.40**. When submitted to 1 mol% of catalyst in CH_2Cl_2 at room temperature, only starting material was recovered. By increasing the quantity of catalyst to 5 mol% and using refluxing dichloromethane, cyclic sulfamide **5.32** was obtained in a ratio 2:5 to the unreacted starting material. Under more forcing conditions, i.e. refluxing dichloroethane, the ratio was only 1:3, probably due to increased catalyst decomposition. We had therefore evidence for a reactivity problem, which could account for the failure of all the attempts of solid-phase RCM to form cyclic sulfamides so far.

We believed that a more active catalyst, such as **5.45**, would provide an efficient RCM cleavage from the resin and on the solution-phase model. We decided to synthesise catalyst **5.45** following methods reported in the literature (Scheme 5.6).[105,188]

Scheme 5.6



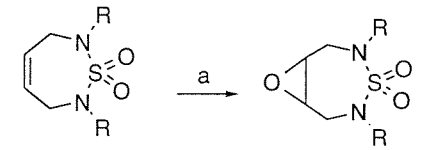
Reagents and conditions: a) 2,4,6-trimethylaniline, H_2O, acetone; b) $NaBH_3CN$, methanol; c) triethylorthoformate, NH_4BF_4; d) 1) ^tBuOK, THF, 2) Grubbs catalyst, toluene, THF.

All the synthetic steps to salt **5.44** proceeded smoothly. Unfortunately, the various attempts to substitute one of the phosphine ligands of Grubbs catalyst by the hydroimidazole group failed. The synthesis of the active catalyst was not pursued any further due to lack of time. Unfortunately, we were also unable to obtain the commercially available catalyst before the end of the Ph.D. programme.

5.3- Alkene Oxidation

In spite of the absence of a method for the cyclisative cleavage of sulfamides off the resin, we decided to investigate the oxidation of the alkene bond in order to introduce a binding site as required for the synthesis of potential HIV protease inhibitor analogues.[183] A small array of oxidation reactions, namely epoxidation, hydroboration and dihydroxylation, was set up. First, attempted epoxidation of **5.31** and **5.32** in the presence of mCPBA proved unsuccessful, returning some unreacted starting material in the best cases, regardless of the temperatures and solvents used (Scheme 5.7).

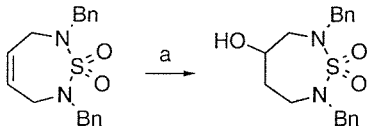
Scheme 5.7



Reagents and conditions: a) mCPBA, CH_2Cl_2 or $ClCH_2CH_2Cl$.

As an alternative to the epoxidation, hydroboration of the double bond and subsequent oxidation of the resulting borane was also performed (Scheme 5.8).[189] Gratifyingly, ^{1}H-NMR spectra of the crude reaction demonstrated the presence of alcohol **5.48** after 3 hours but the reaction yield was not quantified due to lack of time.

Scheme 5.8

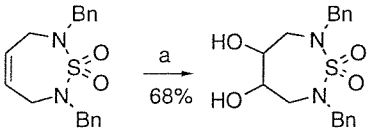


5.31 **5.48**

Reagents and conditions: a) 1) $BH_3.(CH_3)_2S$, hexane, 2) H_2O_2, NaOH, H_2O.

Finally, olefin **5.31** was reacted with a catalytic amount of osmium tetroxide in the presence of *N*-methylmorpholine-*N*-oxide for 16 hours at room temperature (Scheme 5.9).

Scheme 5.9



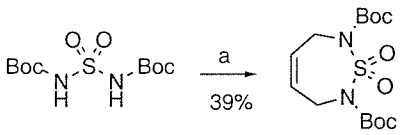
5.31 **5.49**

Reagents and conditions: a) OsO_4, NMO, acetone, H_2O.

We were pleased to see that the crude material was of high purity, with diol **5.49** isolated in good yield.

Last but not least, we also designed an expedient one-step synthesis of cyclic sulfamide **5.32** from **5.3** albeit in moderate yield (Scheme 5.10). Multigram Mitsunobu reactions between butenediol and sulfamide **5.3** were achieved. If required, sulfamide **5.32** could be subsequently deprotected and *N*-alkylated.

Scheme 5.10



5.3 **5.32**

Reagents and conditions: a) 1,4-butenediol, DEAD, PPh_3, THF.

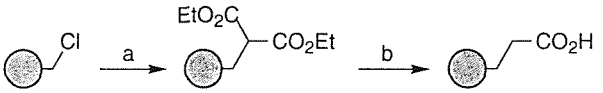
6- Resin Synthesis and Loading Calculations

The synthesis of resins **3.2** and **3.3** from commercially available Merrifield resin as well as the loading calculation methods employed to determine the yields discussed in the previous chapters are presented below.

6.1- Synthesis of the Carboxyethyl Resin 3.2

Carboxyethyl resin **3.2** was prepared in two steps following a procedure established in our laboratories and involving alkylation of diethyl malonate, ester hydrolysis and decarboxylation (Scheme 6.1).[59]

Scheme 6.1



1.14 6.1 3.2

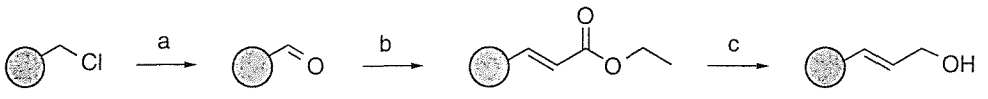
Reagents and conditions: a) diethyl malonate, NaH, DMF; b) 1) THF, NaOH, 60°C, 2) THF, HCl, 60°C.

The loading level of resin **3.2** was determined to be 1 mmol/g using the method described below.

6.2- Synthesis of the Allylic Alcohol Resin 3.3

Initially, attempted synthesis of aldehyde resin **6.2** by direct lithiation of polystyrene,[190] reaction with bromoacetaldehyde diethyl acetal and hydrolysis to the unmasked aldehyde failed, as indicated by the absence of carbonyl peak on the on-bead IR. This three step method was abandoned and an alternative synthesis involving oxidation of Merrifield resin with DMSO in the presence of base, following a procedure reported in the literature,[159] eventually afforded aldehyde resin **6.2** (Scheme 6.2).

Scheme 6.2



1.14 6.2 6.3 3.3

Reagents and conditions: a) DMSO, $NaHCO_3$, 155°C; b) $(EtO)_2P(O)CH_2CO_2Et$, THF, NaHMDS; c) DIBAL, MeOH, THF.

Solid-phase Horner-Wadsworth-Emmons reaction on aldehyde resin **6.2** with triethyl phosphonoacetate and reduction of the resulting ester afforded the resin-bound allylic alcohol **6.3**. The stereochemistry of the double bond was likely to be *E* as reported for solid-phase Horner reactions.[191] The loading of resin **3.3** was determined to be of 2 mmol/g using the method described below involving dihydrocinnamic acid.

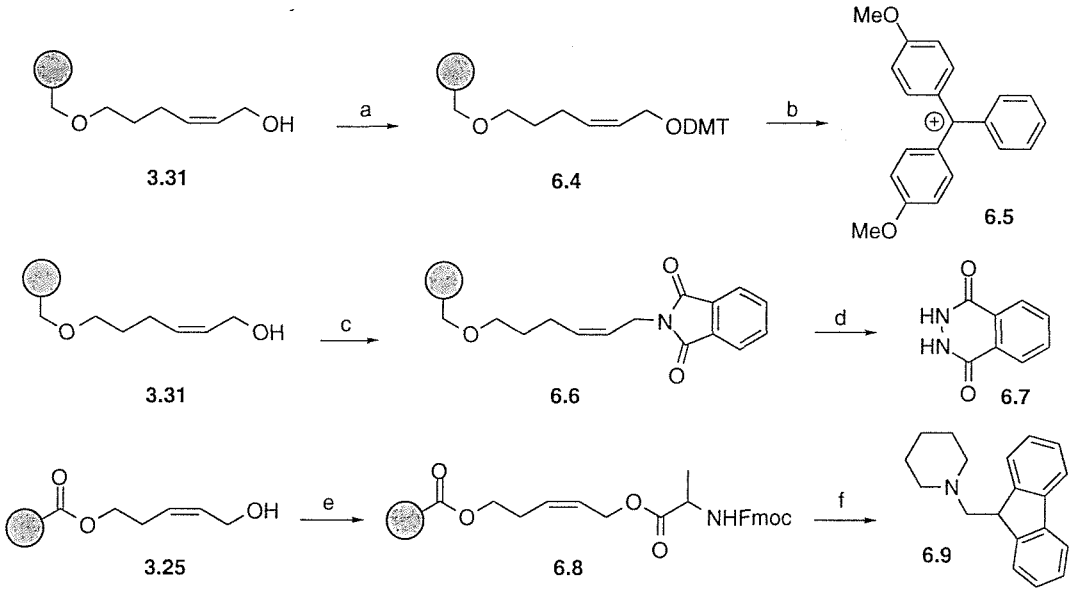
6.3- Loading Calculations

A reliable measurement of the loading level of the resins was necessary, in order to base both quantities of reagents used in each step of the synthesis and the yield of the RCM cleavages. Among the different methods routinely used in solid-phase synthesis, we chose to investigate and compare the three methods described below.

6.3.1- Determination of Loading by Cleavage and UV Quantification

Based on the linear relation between concentration and UV absorbance, the method was described by Krchnák for quantifying secondary Fmoc protected amines.[77] Since there was no chromophore on any of our resins, we decided to use well-known high-yielding chemistry on diols **3.26** and **3.32**, alcohols **3.3**, **3.25** and **3.31** and carboxylic acid **3.2** to introduce a suitable group that would led to a chromophoric species upon cleavage (Scheme 6.3). The literature reported that the trityl group or its derivatives could be efficiently coupled to and removed from the solid-phase. We decided to use DMT cation **6.5** for a loading determination by UV spectrometry. We therefore reacted alcohol resin **3.31** with 4,4'-dimethoxytrityl chloride. However, all attempts to remove the DMT group upon addition of hydrochloric acid in ethanol, including heating, vigorous shaking, and the addition of triethylsilane, a known trityl group scavenger,[192] were unsuccessful perhaps due to the poor swelling of the resin in ethanol.

Scheme 6.3



Reagents and conditions: a) 4,4'-dimethoxytrityl chloride, Et_3N, DMAP, CH_2Cl_2; b) HCl/EtOH 3:2 (v/v); c) phthalimide, DEAD, PPh_3, THF; d) hydrazine, EtOH; e) DIC, DMAP, *N*-α-Fmoc-L-alanine, CH_2Cl_2; f) piperidine/DMF 1:5 (v/v).

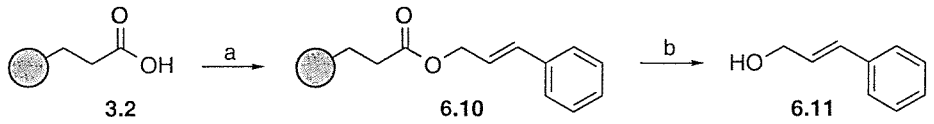
We therefore looked into the possible use highly UV active phthalhydrazide **6.7** for the loading calculation. A linear UV absorbance calibration curve was plotted for different concentrations of phthalhydrazide. Reaction of the hydroxy group of **3.31** with phthalimide under Mitsunobu conditions and subsequent hydrazine cleavage afforded phthalhydrazide **6.7**,[193] the UV absorbance of which was measured in solution. Inconsistent values were obtained, and similarly with resins **3.32**, **3.25** and **3.26**. A possible explanation may be found in the poor solubility of **6.7**. The method was abandoned. Finally, high-yielding DIC coupling of an Fmoc-protected alanine to resin **3.25** and subsequent deprotection of the Fmoc group of **6.8** using 20% piperidine in DMF released UV active **6.9** in solution. The loading values we obtained were abnormally low and the method was also abandoned.

6.3.2- Coupling and Cleavage of a Cinnamic Acid Derivative

Alternatively, we decided to take advantage of the hydroxy or carboxy groups on resins **3.2**, **3.3**, **3.25**, **3.26**, **3.31** and **3.32** to form esters using carbodiimide coupling reagents and subsequently hydrolyse the ester bond. Quantification of the cleaved moiety was achieved by means other than its UV absorbance, namely isolation and GC analysis using an internal standard.

Cinnamyl alcohol (**6.11**) was coupled to resin **3.2**, the completion of the reaction being supported by IR (Scheme 6.4).

Scheme 6.4

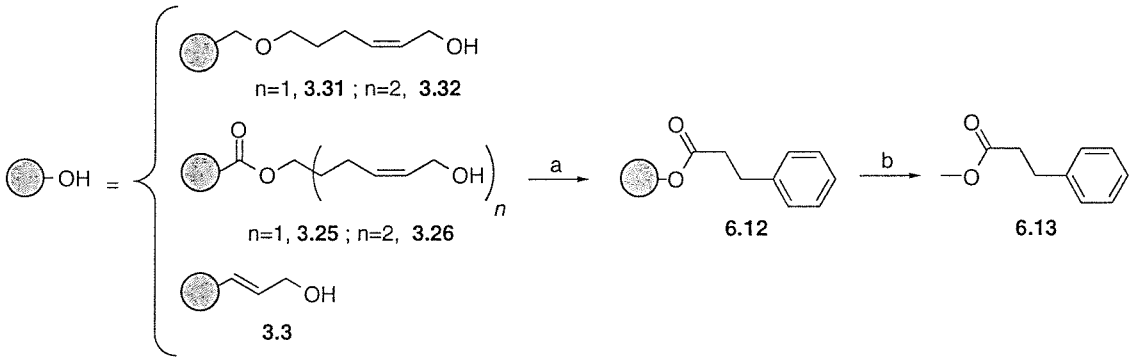


Reagents and conditions: a) DIC, cinnamyl alcohol, DMAP, CH_2Cl_2; b) naphthalene, TMSOK, MeOH, CH_2Cl_2, 50°C, 15hrs.

Cinnamyl alcohol was then released from resin **6.10** using a cleavage cocktail of potassium trimethylsilanolate and methanol and quantified by GC using naphthalene as an internal standard. As mentioned previously, the loading value of **3.2** was found to be 1 mmol/g.

A reversed method was applied to the resins possessing a terminal hydroxy group (Scheme 6.5). Thus, dihydrocinnamic acid was coupled to **3.3**, **3.25**, **3.26**, **3.31** and **3.32**. The formation of the corresponding resin-bound esters was monitored by IR.

Scheme 6.5



Reagents and conditions: a) DIC, dihydrocinnamic acid, DMAP, CH_2Cl_2; b) naphthalene, Et_3N/MeOH 9:1 (v/v), 50°C, 15hrs.

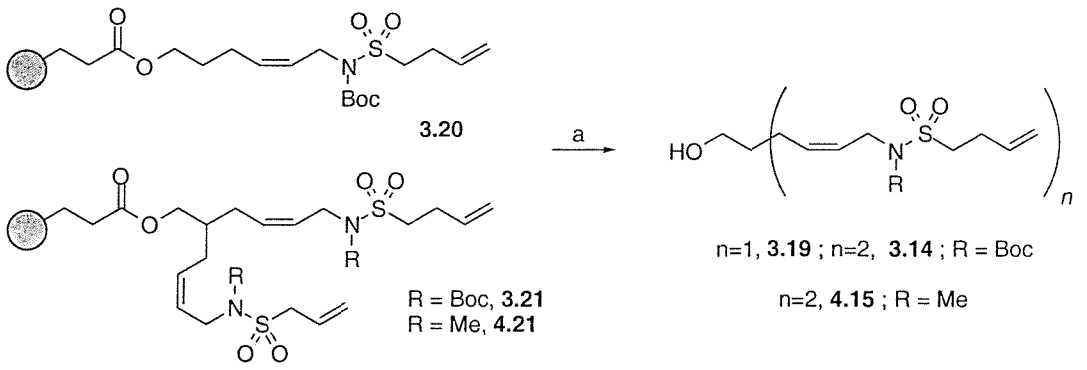
Transesterification under the conditions reported in the literature[194] afforded ester **6.13** which was quantified by GC analysis. The different loading values are reported in table 6.1 below.

6.3.3- Reductive Cleavage of Functionalised Carboxyethyl Resin Samples

It should be remembered that the carboxyethyl resin was introduced in our earlier work with a view to monitor the reaction progress by reductive cleavage of aliquots of functionalised

resin. As a result, isolation of the cleaved alcohols **3.14**, **3.19** and **4.15** off resins **3.20**, **3.21** and **4.21** was a means of determining the loading levels (Scheme 6.6).

Scheme 6.6



Reagents and conditions: a) $LiBH_4$, MeOH, THF.

The amounts of product recovered from this reductive cleavage allowed the determination of the loading for the three resins concerned (Table 6.1).

6.3.4- Combustion Analysis

Finally, several samples of the RCM precursor resins were sent to microanalysis on sulfur. The results were generally reproducible, even on different batches of resin (Table 6.1).

Table 6.1: comparison of the loading values obtained by different method

Entry	Resin	Loading (meq./g)[a] Determination Method		
		Cleavage[b]	Combustion	Theoretical[c]
1	**3.3**	2.0	--	--
2	**3.2**	1.0	--	--
3	**3.20**	[0.73]	0.72	0.76[d]
4	**4.20**	--	0.97	0.81[d]
5	**4.22**	--	1.00	0.77[d]
6	**3.21**	[0.55]	0.58	0.62[d]
7	**4.21**	[0.69]	0.80	0.70[d]
8	**4.23**	--	0.64	0.63[d]
9	**3.31**	1.02	--	--
10	**3.27**	--	0.88	0.82[e]
11	**3.32**	0.97	--	--
12	**3.28**	--	0.68	0.69[f]

Notes: Commercially available Merrifield resin stated 2.3 mCl/g; a) meq./g stands for the number of functional groups concerned per gram of resin, e.g. loading values determined by combustion analysis were based on sulfur and/or nitrogen, whereas the cleavage method reflected the number of hydroxy groups present on the resin; b) loading values were determined by transesterification of a cinnamic derivative except for the values in square brackets determined by reductive cleavage; c) by theoretical loading is meant the value calculated from the

known loading of the starting resins **3.2**, **3.21** and **3.22** assuming a 100% yield for all the subsequent steps; d) from resin **3.2** (1.0 meq./g); e) from **3.31** (1.02 meq./g); f) from **3.32** (0.97 meq./g).

Since different techniques afforded the same values for most of the resins, we concluded that these loading levels were reliable enough to be used to determine the percentages of catalyst to be employed and the yield of cyclic products. In addition, the theoritical values indicated that the solid-phase Mitsunobu coupling reactions from **3.31** and **3.32** to **3.27** and **3.28** occurred in almost quantitative yields. Similarly, the DIC coupling reactions to give the variously *N*-alkylated carboxyethyl resins **4.20-4.23** turned out to be rather high yielding.

7- Conclusions and Further Work

To summarise, I first presented our preliminary studies on the solution-phase synthesis of medium size lactams and the corresponding cyclic sulfonamides, ultimately leading to the successful solid-phase synthesis of the latter employing a ring-closing metathesis cyclisation cleavage strategy. Next, I reported the failure in the attempted use of a short allylic linker. Finally, I disclosed the successful results we obtained as for the solution-phase synthesis of cyclic sulfamides.

As discussed previously, the initial idea from which the project originated was to provide a general solid-phase method that would allow efficient RCM cleavage using amounts of Grubbs catalyst lower than 5 mol%. The introduction of the new concept of double armed linker relied on its capacity to regenerate the ruthenium catalyst thus keeping the catalytic cycle working. We were therefore delighted to observe that cyclisative cleavage was achieved in good yield with as little as 2.5 and even 1 mol% of catalyst using the double armed linker. Nevertheless, using higher catalyst loading the corresponding single armed linker was as efficient as the double armed. We concluded that a flexible linker was required to facilitate some of the steps involved in the catalytic cycle, and that employing either the double armed linker or a flexible linker made the use of a co-factor unnecessary. The risks of contamination by cross-coupling products were therefore reduced.

We believe that the mild reaction conditions that were used and the ease with which the various moieties were assembled on the solid-support constitute two major advantages that would allow us to generalise our synthetic method. In fact, it is likely that other cyclic

medium size sulfonamides can be obtained in the same manner either by parallel synthesis or using combinatorial chemistry techniques. Further work should also focus on the incorporation of cyclic sulfonamides into peptidomimetics, and more particularly to optimise the introduction of side chains on our initial scaffold, although, as we have already mentioned, research work in the area has now attracted some attention from other academic and industrial groups.[144, 145] From a practical point of view, in order to avoid supplementary steps on loading calculation, future work should also concentrate on improving the protecting group strategy used on the solid-phase. Thus, replacing the existing THP group by a group which possesses a chromophore should save time by enabling simultaneous loading determination and deprotection.

As for the solid-phase synthesis of cyclic sulfamides, unfortunately, the project could not be completed. In fact, the failure can presumably be explained by a lack of activity of the catalyst towards the substrates. Taking into account the certain biological potential that those molecules possess, we believe that the project should be pursued. In particular, the synthesis of novel HIV protease inhibitors should be a major objective. As a result, prior to being extended to the solid-phase, further work should allow cyclisation of a solution model in the presence of the more stable catalysts recently described in the literature.[104-107]

1- General Methods

All reactions requiring anhydrous conditions were performed in dry glassware under an atmosphere of nitrogen or argon. Methylene chloride, 1,2-dichloroethane, DMF and triethylamine were distilled from calcium hydride.[195] Tetrahydrofuran was freshly distilled from sodium wire and benzophenone.[195] Grubbs catalyst was purchased from Strem Chemicals or Fluka. Other reagents were purchased from Sigma/Aldrich, Fisher, Novabiochem or Lancaster and used as such. Merrifield resin (1.3 or 2.3 meq. Cl/g) was purchased from Aldrich.

Column flash chromatography[196] was carried out using Merck 60 mesh silica. Column dimensions are reported as width x height of silica. Thin layer chromatography was carried out on glass backed Merck Kiesegel 60 silica plates. Compounds were visualised by irradiation at 254 nm or staining with one or more of the following reagents: iodine; potassium permanganate (1.5 g) in water (150 mL); phosphomolybdic acid (12 g) in ethanol (250 mL); ninhydrin (0.5 g) in ethanol (100 mL). For flash chromatography as well as thin layer chromatography, eluent systems A-G are described:

A: Hexane
B: Hexane/Et_2O 1:1
C: Hexane/Et_2O 1:2
D: Hexane/Et_2O 1:3
E: Et_2O
F: Hexane/EtOAc 5:1
G: CH_2Cl_2

IR spectra were recorded on a Perkin-Elmer 1600 FT-IR instrument using samples supported on sodium chloride cells, a Bio-Rad FTS 135 instrument using a Golden Gate adapter or a Nicolet Impact 400 instrument using a Thunderdome adapter. Absorptions are described as strong (s), medium (m), weak or broad (br).

UV studies were carried out on a Perkin-Elmer Lambda 2 UV/VIS spectrometer or a Hewlett-Packard 8452A diode array spectrophotometer.

^{1}H-NMR and ^{13}C-NMR spectra were recorded as $CDCl_3$ solutions, on a JEOL GX270, a Bruker AC300, a Bruker AM300 or a Bruker DPX400 spectrometer. Chemical shifts are reported in δ units with $CHCl_3$ as internal standard. Coupling constants (*J*) are reported in Hertz.

Low resolution mass spectra were obtained on a Fisons VG platform single quadrupole mass spectrometer in electron spray ionisation mode. The relative intensity of a peak and its

probable assignment to a fragment ion are reported between parentheses after the m/z value for that peak.

Melting points were measured on a Gallenkamp electrothermal melting point apparatus.

GC analyses for sample purity, yields and loading calculations were carried out on a Varian 3800 fitted with a 30 m x 0.25 mm DB120 fused silica column and connected to a Hewlett Packard 3396 Series II integrator. The following settings were used: both the injector and the detector were set at 220°C. Two different temperature programs were used, depending on the application:- (A) for the calculation of the yields of cyclic sulfonamides **2.8**, **2.17** and **4.25**, the column was heated at 160°C for 4.5 minutes, followed by an increase in temperature by 5°C/min to 220°C; - (B) for the loading determination with the methyl ester of dihydrocinnamic acid and with cinnamyl alcohol, the column was heated at 150°C for 5 minutes. The two internal standard used, phenanthrene and naphthalene, possessed the following retention times: 11.2 min (temperature program A) and 2.2 min (temperature program B) respectively.

Microanalyses were obtained from University College, London or MEDAC Ltd, Egham.

Chemical Abstract registry numbers of previously known compounds are written between square brackets.

Naming of the compounds according to the IUPAC rules was assisted by the ACD/Name software version 2.51 (January 1997) designed by Advanced Chemistry Development Inc., Canada. The functional group -SO_2-NH-COO- was not recognised by the software.

2- Solution-Phase Chemistry

In order to condense the experimental section, procedures that were routinely used are shown below.

Preparation of Lithium Diisopropyl Amine (1 mmol):[151]

To a solution of diisopropyl amine (140 µL, 1 mmol) in THF (0.5 mL) at -78°C was added dropwise under an inert atmosphere a 1.6M solution of *n*-butyl lithium in hexane (625 µL, 1 mmol). The colourless mixture was stirred at room temperature for 15 minutes and cooled to -78°C. At this stage, the other reagents were added as reported in the corresponding experimental procedures.

Reduction of Esters (1 mmol) Using Lithium Aluminium Hydride:[197]

To an ice cooled solution of lithium aluminium hydride (46 mg, 1.2 mmol) in ether (2 mL) was added dropwise a solution of ester (1 mmol) in ether (2 mL). The ice bath was removed and the solution was stirred at room temperature for between 10 minutes and 6 hours until completion of the reaction as indicated by tlc. Excess $LiAlH_4$ was carefully destroyed at 0°C with vigorous stirring by addition of water (0.5 mL), a 15% aqueous solution of NaOH (0.5 mL) and after 5 minutes water (1.5 mL). The reaction mixture was stirred for several minutes. The product was then extracted twice with ether (5 mL) and dichloromethane (5 mL). The combined organic layers were washed with brine (5 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification methods are given in the respective procedures.

Mitsunobu Coupling of Allylic Alcohols and Diols (1 mmol) to Boc-protected Sulfonamides and Sulfamides:[138,139,198]

To a solution of alcohol / diol (1 mmol), triphenyl phosphine (262 mg, 1 mmol / 524 mg, 2 mmol) and sulfonamide or sulfamide (1 mmol / 2 mmol) in THF (10 mL / 20 mL) was added dropwise a solution of diethylazodicarboxylate (160 µL, 1 mmol / 320 µL, 2 mmol) in THF (2 mL / 4 mL) at room temperature. Upon completion, as indicated by tlc, the solvent was removed *in vacuo*. Triphenylphosphine oxide was precipitated by addition of ether and collected by filtration. The filtrate was concentrated *in vacuo* to give a yellow oil. Purification by flash chromatography is reported in each procedure.

N-*Alkylation of Sulfonamides and Sulfamides (1 mmol):*

To a solution of free sulfonamide or sulfamide (1 mmol) in DMF (10 mL) was added a 60% suspension of sodium hydride in mineral oil (44 mg, 1.1 mmol). When the gas evolution stopped, the alkylating agent (1 mmol) was added. The solution was kept under an inert atmosphere at 60°C for 15 hours. The reaction mixture was quenched with NH_4Cl (10 mL). The product was extracted three times with CH_2Cl_2 (10 mL). The combined organic layers were washed with brine (20 mL), dried ($MgSO_4$) and concentrated to give an oil. Purification by flash chromatography is reported in each procedure.

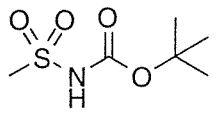
Formation of Unsymmetrical Sulfamides:[181]

To an ice cooled solution of chlorosulfonyl isocyanate (2.4 mL, 27.5 mmol) in CH_2Cl_2 (60 mL) was added *tert*-butanol (4.4 mL, 27.5 mmol). The mixture was stirred for 5 minutes.

Triethylamine (4.2 mL) was added, followed by a solution of amine (25 mmol) in CH_2Cl_2 (25 mL) maintaining the reaction temperature low. The ice bath was removed and the reaction mixture was stirred at room temperature for 1 hour, diluted with CH_2Cl_2 (50 mL) and washed three times with 2N HCl (20 mL). The organic layer was dried ($MgSO_4$) and concentrated to give the corresponding sulfamides as white solids which did not require purification.

Specific Procedures

i. 1,1-Dimethylethyl *N*-(methanesulfonyl) carbamate <u>2.10</u> [147751-16-4]



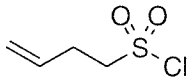
$C_6H_{13}NO_4S$
m.w.= 195.23 g/mol
White solid; m.p.= 109-112°C

To an ice cooled solution of methane sulfonamide (0.95 g, 10 mmol), triethylamine (1.5 mL, 11 mmol) and 4-dimethylaminopyridine (0.12 g, 1 mmol) in CH_2Cl_2 (20 mL) was added dropwise over 2 minutes a solution of di-*tert*-butyl dicarbonate (2.5 g, 11.5 mmol) in CH_2Cl_2 (12 mL). The reaction mixture was stirred for 2.5 hours and was then concentrated *in vacuo*. The residue was partitioned between ethyl acetate (60 mL) and a 1N aqueous solution of HCl (40 mL). The organic layer was washed with water (20 mL) and brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give a white solid which was recrystallised from hexane (1.8 g, 9.2 mmol, 92%).

The spectroscopic data (NMR, IR) and the melting point (107.5-108°C) were consistent with those reported in the literature.[151,153]

- **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 7.51 (br s, 1H, NH), 3.27 (s, 3H, SO_2CH_3), 1.52 (s, 9H, $C(CH_3)_3$)
- **^{13}C NMR** (75 MHz, $CDCl_3$) δ: 150.0 (CO), 84.6 ($OC(CH_3)_3$), 41.3 (SO_2CH_3), 28.1 ($C(CH_3)_3$)
- **IR** (neat) ν_{max}: 3076, 2942, 1700 (s, CO), 1431 (m), 1408, 1354 (s, SO_2), 1326 (s), 1261, 1145 (s, SO_2), 1067 (m), 1033 cm^{-1}
- **MS** (EI) m/z (%): 213 ($[M+NH_4]^+$, 23)

ii. 3-Butene-1-sulfonyl chloride 2.21 [33994-36-4]



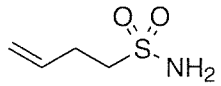
$C_4H_7ClO_2S$
m.w.= 154.61 g/mol
Colourless oil; b.p.= 48-50°C / 0.5 mmHg

To a solution of sodium sulfite (10 g, 80 mmol) in water (100 mL) was added 3-bromobutene (10 g, 74 mmol). The solution was heated at 60°C with vigorous stirring for 2 hours, until the oily droplets of the bromide completely disappeared. The water was evaporated. The solid residue was thoroughly dried at 100°C under reduced pressure for 24 hours in the presence of phosphorus pentoxide to afford a white solid. The solid was powdered and phosphorus oxychloride (14 mL, 150 mmol) was added. The mixture was heated at 105°C for 4 hours. After cooling to room temperature, excess phosphorus oxychloride was carefully removed *in vacuo*. The solid residue was collected by filtration and washed three times with CH_2Cl_2 (15 mL). The filtrate was purified by distillation to give the title compound as a colourless oil (9.15 g, 59 mmol, 80%).

The boiling point was consistent with that reported in the literature (45-50°C / 0.7 mmHg).[157]

- Rf (E): 0.81
- **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 5.82 (ddt, 1H, J = 16.9, 10.3, 6.6, C**H**=CH_2), 5.25-5.19 (m, 2H, CH=C**H**$_2$), 3.77-3.72 (m, 2H, CH_2SO_2), 2.83-2.75 (m, 2H, C**H**$_2$$CH_2SO_2$)
- **^{13}C NMR** (75 MHz, $CDCl_3$) δ: 131.9 (**C**H=CH_2), 118.8 (CH=**C**H$_2$), 64.4 (CH_2SO_2), 28.4 (**C**$H_2CH_2SO_2$)
- **IR** (neat) ν_{max}: 3086, 2986, 2923, 1643, 1367 (s, SO_2), 1237 (m), 1161 (s, SO_2), 993 (m), 924 (m), 751, 701 cm^{-1}

iii. 3-Butene-1-sulfonamide 2.22

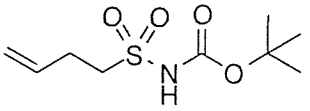


$C_4H_9NO_2S$
m.w.= 135.18 g/mol
White solid; m.p.= 41-42°C

Sulfonyl chloride **2.21** (4 g, 26 mmol) was added to an ice cooled 30% solution of ammonia in water (40 mL). The reaction mixture was stirred for 10 minutes. The product was extracted with CH_2Cl_2 (20 mL), ether (20 mL) and EtOAc (20 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give the title compound as a white solid (2.53 g, 19 mmol, 72%). No purification was required.

- Rf (E): 0.50
- **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 5.84 (ddt, 1H, *J* = 16.9, 10.4, 6.5, C**H**=CH_2), 5.18 (dd, 1H, *J* = 17.6, 1.5, CH=C**H**H), 5.14 (dd, 1H, *J* = 10.3, 1.5, CH=CH**H**), 4.93 (brs, 2H, NH_2), 3.25-3.19 (m, 2H, CH_2SO_2), 2.65-2.58 (m, 2H, $CH_2CH_2SO_2$)
- **^{13}C NMR** (75 MHz, $CDCl_3$) δ: 134.1 (**C**H=CH_2), 117.4 (CH=**C**H_2), 54.4 (CH_2SO_2), 28.2 ($CH_2CH_2SO_2$)
- **IR** (neat) ν_{max}: 3346 (m), 3255 (m), 3070, 2986, 1640, 1535, 1453, 1301 (s, SO_2), 1276 (s), 1242 (m), 1133 (s, SO_2), 1101 (m), 992 (m), 933 (s), 892 (s), 785 (m) cm^{-1}
- **MS** (EI) m/z (%): 144 ($[2M+NH_4]^{2+}$, 100)
- $C_4H_9NO_2S$ requires (%) C: 35.54; H: 6.71; N: 10.36. Found C: 35.70; H: 6.77; N: 10.40

iv. 1,1-Dimethylethyl *N*-(3-butene-1-sulfonyl) carbamate 2.18



$C_9H_{17}NO_4S$
m.w.= 235.30 g/mol
Colourless oil

Note: this compound was prepared following two different methods, either from **2.10** or **2.22**.

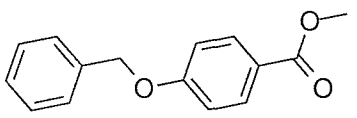
Method A: A solution of LDA (40 mmol) was prepared following the general procedure described previously. A solution of sulfonyl carbamate **2.10** (3.9 g, 20 mmol) in THF (15 mL) was then added over 15 minutes. The solution was stirred at -78°C for 6 minutes and transferred *via* a cannula into a solution of allyl bromide (1.9 mL, 21 mmol) in THF (10 mL) at -78°C over 15 minutes. The reaction mixture was stirred at -78°C for 1.5 hours, allowed to warm to room temperature and stirred for another 1.5 hours. Excess LDA was cautiously destroyed with water (5 mL). The mixture was then poured into a 2N aqueous solution of HCl (25 mL) and the product was extracted three times with CH_2Cl_2 (10 mL). The combined organic layers were washed with a saturated aqueous solution of NH_4Cl (15 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash chromatography through a column of silica (4x10 cm; eluent system A, B) afforded the title compound as a colourless oil (4.09 g, 17 mmol, 87%).

Method B: To an ice cooled solution of sulfonamide **2.22** (1.35 g, 10 mmol), 4-dimethylaminopyridine (12 mg, 0.1 mmol) and diisopropylethylamine (1.73 mL, 12 mmol) in CH_2Cl_2 (100 mL) was added dropwise a solution of di-*tert*-butyl dicarbonate (2.5 g, 11 mmol) in CH_2Cl_2 (10 mL). The ice bath was removed. The reaction mixture was stirred for 2.5 hours and was then concentrated in vacuo. The residue was partitioned between ethyl acetate (60 mL) and a 1N aqueous solution of HCl (40 mL). The organic layer was washed with water

(20 mL) and brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give an oil. Purification by flash chromatography (3x5 cm, eluent system A, B) afforded the title compound as a colourless oil (2.35 g, 10 mmol, 100%).

- Rf (B): 0.36, (C): 0.57
- **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 7.78 (brs, 1H, NH), 5.79 (ddt, 1H, J = 16.9, 9.9, 6.6, C**H**=CH_2), 5.18-5.08 (m, 2H, CH=C**H$_2$**), 3.49-3.43 (m, 2H, CH_2SO_2), 2.61-2.53 (m, 2H, $CH_2CH_2SO_2$), 1.52 (s, 9H, $C(CH_3)_3$)
- **^{13}C NMR** (75 MHz, $CDCl_3$) δ: 150.1 (CO), 133.7 (**C**H=CH_2), 117.7 (CH=**C**H_2), 84.4 ($OC(CH_3)_3$), 52.2 (CH_2SO_2), 28.1 ($C(CH_3)_3$), 27.6 ($CH_2CH_2SO_2$)
- **IR** (solution, CH_2Cl_2) ν_{max}: 3236 (br, NH), 2982, 1740 (s, CO), 1643, 1434 (m), 1346 (s, SO_2), 1245, 1135 (s, SO_2), 1061 cm^{-1}
- **MS** (EI) m/z (%): 493 ($[2M+Na]^+$, 22)

v- Methyl 4-benzyloxybenzoate <u>1.2</u> [32122-11-5]



$C_{15}H_{14}O_3$
m.w.= 242.26 g/mol
White solid; m.p.= 97-98°C

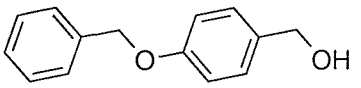
To a solution of methyl 4-hydroxybenzoate (228 mg, 1.5 mmol) in DMF (2 mL) was added a 60% dispersion of sodium hydride in mineral oil (60 mg, 1.5 mmol). When the gas evolution stopped, a solution of benzylchloride (126 mg, 1 mmol) in DMF (2 mL) was added to the mixture which was then stirred at 80°C for 15 hours. The mixture was carefully quenched with water (5 mL) and the product was extracted three times with ether (5 mL). The combined organic layers were washed with brine (15 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give an off-white solid. Recrystallisation from petroleum ether afforded the title compound as a white solid (227 mg, 0.94 mmol, 94%).

The spectroscopic data (IR, ^{1}H NMR) and the melting point (94-96°C) were in good agreement with those reported in the literature.[199,200]

- Rf (B): 0.57
- **^{1}H NMR** (270 MHz, $CDCl_3$) δ: 8.01 (d, 2H, J = 8.7, $C_6H_2H_2$), 7.43-7.37 (m, 5H, C_6H_5), 7.01 (d, 2H, J = 8.9, $C_6H_2H_2$), 5.13 (s, 2H, CH_2O), 3.90 (s, 3H, OCH_3)
- **^{13}C NMR** (75 MHz, $CDCl_3$) δ: 167.0 (CO), 162.6 (C), 136.4 (C), 131.8 (CH), 128.8 (CH), 128.4 (CH), 127.6 (CH), 123.0 (C), 114.6 (CH), 70.2 (CH_2O), 52.0 (OCH_3)

• **IR** (nujol) ν_{max}: 1717 (s, CO), 1605 (m), 1515, 1250 (s), 1171 (s), 1111 (s), 1011 (s), 916, 856 (m), 771 (s), 749 (s), 699 (s) cm^{-1}

vi. 4-(Benzyloxy)benzyl alcohol 1.3 [836-43-1]



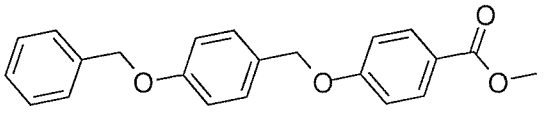
$C_{14}H_{14}O_2$
m.w.= 214.25 g/mol
White solid; m.p.= 87-89°C

Reduction of ester **1.2** (242 mg, 1 mmol) to the corresponding alcohol using lithium aluminium hydride (46 mg, 1.2 mmol) was carried out as reported in the general method. Purification by recrystallisation from petroleum ether afforded the title compound as a white solid (175 mg, 0.82 mmol, 82%).

The spectroscopic data and the melting point (86-87°C) were consistent with those of the commercially available material.

• Rf (B): 0.26
• **^{1}H NMR** (270 MHz, $CDCl_3$) δ: 7.46-7.29 (m, 7H, C_6H_5 & $C_6\mathbf{H}_2H_2$), 6.98 (d, 2H, J = 8.7, $C_6H_2\mathbf{H}_2$), 5.09 (s, 2H, CH_2O), 4.62 (s, 2H, $\mathbf{CH}_2OH$), 1.68 (brs, 1H, OH)
• **^{13}C NMR** (68 MHz, $CDCl_3$) δ: 158.4 (C), 137.0 (C), 133.4 (C), 128.6 (CH), 128.5 (CH), 128.0 (CH), 127.4 (CH), 115.0 (CH), 70.1 (CH_2O), 65.0 (CH_2O)
• **IR** (nujol) ν_{max}: 3201 (br, OH), 1512 (m), 1248 (m), 1172, 1112, 1008 (m), 809 (m), 736 (s) cm^{-1}

vii. Methyl 4-[4-(benzyloxy)benzyl]oxybenzoate 1.5



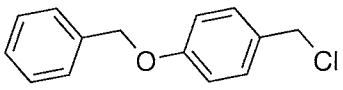
$C_{22}H_{20}O_4$
m.w.= 348.38 g/mol
White solid; m.p.= 127-128°C

To a mixture of triphenylphosphine (262 mg, 1 mmol), alcohol **1.3** (214 mg, 1 mmol), and methyl 4-hydroxybenzoate (152 mg, 1 mmol) in THF (5 mL) was added dropwise a solution of diethylazodicarboxylate (174 mg, 1 mmol) in THF (5 mL). After 48 hours, the reaction was quenched with a saturated aqueous solution of Na_2CO_3 (5 mL) and the product was extracted twice with ether (5 mL). The combined organic layers were washed with brine (5 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash chromatography through a short

column of silica (2x5 cm; eluent system A-E) afforded the title compound as a white solid (160 mg, 0.46 mmol, 46%).

- Rf (B): 0.60
- **^{1}H NMR** (270 MHz, $CDCl_3$) δ: 8.00 (d, 2H, J = 8.9, $C_6\mathbf{H}_2H_2$), 7.46-7.34 (m, 7H, C_6H_5 & $C_6H_2\mathbf{H}_2$), 7.03-6.98 (m, 4H, $C_6\mathbf{H}_2H_2$ & $C_6H_2\mathbf{H}_2$), 5.12 (s, 2H, CH_2O), 5.05 (s, 2H, CH_2O), 3.88 (s, 3H, OCH_3)
- **^{13}C NMR** (68 MHz, $CDCl_3$) δ: 167.0 (CO), 162.7 (C), 159.0 (C), 137.0 (C), 131.8 (CH), 129.5 (C), 128.8 (CH), 128.2 (CH), 127.6 (CH), 127.4 (CH), 122.9 (C), 115.1 (CH), 114.5 (CH), 70.2 (CH_2O), 70.0 (CH_2O), 52.0 (OCH_3)
- **IR** (nujol) ν_{max}: 1721 (s, CO), 1601, 1511, 1312 (m), 1244 (m), 1175 (m), 1104 (m), 1037 (m), 1002 (m), 849 (m), 768 (m), 730 (s), 691 cm^{-1}
- **MS** (CI) m/z (rel. intensity): 197 ($[BnOC_6H_4CH_2]^+$, 30), 152 (18), 121 (32), 91 ($[C_6H_5CH_2]^+$, 100)

viii. 4-(Benzyloxy)benzyl chloride <u>1.6</u> [836-42-0]



$C_{14}H_{13}ClO$
m.w.= 232.71 g/mol
White solid; m.p.= 76-79°C

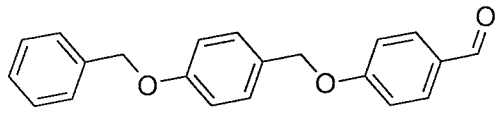
To a solution of diisopropylethylamine (191 µL, 1.1 mmol) in CH_2Cl_2 (5 mL) was added alcohol **1.3** (214 mg, 1 mmol). The mixture was cooled to 0°C and mesyl chloride (81 µL, 1.05 mmol) was added. The ice bath was removed and the mixture was stirred for 3 hours at room temperature. The mixture was diluted with ether (5 mL), washed with water (5 mL), a 1N aqueous solution of HCl (3 mL), brine (3 mL) and a saturated aqueous solution of $NaHCO_3$ (3 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo* to give a yellow solid. Purification by flash chromatography through a short column of silica (4x3 cm; eluent system A, B) afforded the title compound as a white solid (219 mg, 0.94 mmol, 94%).

The spectroscopic data and the melting point (77-79°C) were in good agreement with those of the commercially available material.

- Rf (B): 0.68
- **^{1}H NMR** (270 MHz, $CDCl_3$) δ: 7.44-7.28 (m, 7H, C_6H_5 & $C_6H_2\mathbf{H}_2$), 6.98 (d, 2H, J = 8.7, $C_6H_2\mathbf{H}_2$), 5.08 (s, 2H, CH_2O), 4.57 (s, 2H, CH_2Cl)
- **^{13}C NMR** (68 MHz, $CDCl_3$) δ: 158.5 (C), 136.2 (C), 130.1 (CH), 130.0 (C), 128.6 (CH), 128.0 (CH), 127.4 (CH), 115.1 (CH), 70.1 (CH_2O), 46.2 (CH_2Cl)

- **IR** (nujol) ν_{max}: 1615, 1580, 1515 (m), 1299 (m), 1252 (m), 1174 (m), 1109, 1081, 1006 (m), 918, 837 (m), 818, 741 (s), 697 (s), 667(m) cm^{-1}
- **MS** (CI) m/z (rel. intensity): 197 ($[BnOC_6H_4CH_2]^+$, 24), 91 ($[C_6H_5CH_2]^+$, 100), 77 (10)

ix. 4-[4-(Benzyloxy)benzyl]oxybenzaldehyde 1.4 [88015-49-0]

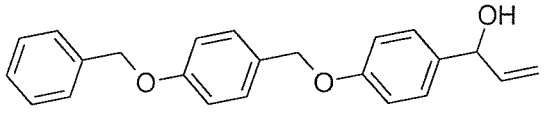


$C_{21}H_{18}O_3$
m.w.= 318.35 g/mol
White solid; m.p.= 110-112°C

To a stirred solution of 4-hydroxybenzaldehyde (160 mg, 1.05 mmol) in DMF (5 mL) was added a 60% dispersion of sodium hydride in mineral oil (42 mg, 1.05 mmol). When the gas evolution stopped, a solution of chloride **1.6** (233 mg, 1 mmol) in DMF (2 mL) was added dropwise. The mixture was heated to 80°C for 4 hours. The mixture was carefully quenched with water (10 mL) and the product was extracted three times with ether (10 mL). The combined organic layers were washed with brine (25 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash chromatography through a short column of silica (2x5 cm; eluent system A, B) afforded the desired aldehyde as a white solid (245 mg, 0.77 mmol, 77%).

- Rf (B): 0.47, (C): 0.66
- **^{1}H NMR** (270 MHz, $CDCl_3$) δ: 9.82 (s, 1 H, CHO), 7.76 (d, 2H, J = 8.4, $C_6\mathbf{H}_2H_2$), 7.40-7.22 (m, 7H, C_6H_5 & $C_6H_2\mathbf{H}_2$), 6.99 (d, 2H, J = 8.4, $C_6\mathbf{H}_2H_2$), 6.94 (d, 2H, J = 8.1, $C_6H_2\mathbf{H}_2$), 5.01 (s, 2H, CH_2O), 4.97 (s, 2H, CH_2O)
- **^{13}C NMR** (68 MHz, $CDCl_3$) δ: 190.7 (CHO), 163.8 (C), 158.9 (C), 136.8 (C), 131.9 (CH), 130.1 (C), 129.2 (CH), 128.6 (CH), 128.2 (C), 128.0 (CH), 127.4 (CH), 115.1 (CH), 115.0 (CH), 70.2 (CH_2O), 70.1 (CH_2O).
- **IR** (nujol) ν_{max}: 1693 (s, CO), 1601 (m), 1573, 1510 (m), 1303 (m), 1246 (s), 1164 (s), 1110 (m), 1035 (m), 996 (m), 845 (m), 814 (m), 728 (s) cm^{-1}

x. 1-(4-{[4-(Benzyloxy)benzyl]oxy}phenyl)-2-propen-1-ol 1.7



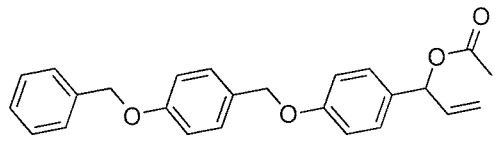
$C_{23}H_{22}O_3$
m.w.= 346.62 g/mol
White solid; m.p.= 110-111°C

To a 1.0M solution of vinylmagnesium bromide in THF (1 mL, 1 mmol) was added dropwise at -10°C a solution of substituted benzaldehyde **1.4** (318 mg, 1 mmol) in THF (5 mL). The

mixture was allowed to warm to room temperature and stirred for 2 hours. The mixture was cooled in an ice bath and stirred vigorously while a saturated aqueous solution of NH_4Cl (15 mL) was added. The product was extracted twice with ether (5 mL). The combined organic layers were washed with brine (25 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash chromatography through a short column of silica (4x3 cm; eluent system A-E) afforded the desired alcohol as a white solid (339 mg, 0.98 mmol, 98%).

- Rf (B): 0.33
- **^{1}H NMR** (270 MHz, $CDCl_3$) δ: 7.46-7.27 (m, 9H, C_6H_5 & 2x$C_6\mathbf{H}_2H_2$), 6.98 (t fs, 4H, J = 8.8, 2x$C_6H_2\mathbf{H}_2$), 6.06 (ddd, 1H, J = 17.6, 10.3, 5.9, C**H**=CH_2), 5.38 (dt, 1H, J = 17.6, 1.5, CH=CH**H**), 5.21 (dt, 1H, J = 10.3, 1.5, CH=CH**H**), 5.19-5.11 (m, 1H, C**H**OH), 5.09 (s, 2H, CH_2O), 5.00 (s, 2H, CH_2O), 1.97 (brs, 1H, OH)
- **^{13}C NMR** (68 MHz, $CDCl_3$) δ: 158.7 (C), 158.5 (C), 140.4 (CH), 136.9 (C), 135.1 (C), 129.3 (C), 129.1 (CH), 128.6 (CH), 128.0 (CH), 127.7 (CH), 127.4 (CH), 115.0 (CH), 114.9 (CH), 114.7 (CH=**C**H_2), 74.8 (CHOH), 70.1 (CH_2O), 69.8 (CH_2O)
- **IR** (nujol) ν_{max}: 1625, 1601, 1293 (m), 1245 (m), 1008 (m), 730 (s) cm^{-1}
- $C_{23}H_{22}O_3$ requires (%) C: 79.74; H: 6.40. Found C: 79.78; H: 6.60

xi. 1-(4-{[4-(Benzyloxy)benzyl]oxy}phenyl) allyl acetate <u>1.8</u>



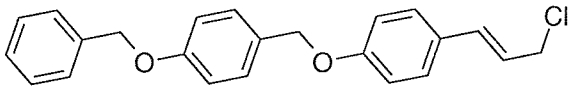
$C_{25}H_{24}O_4$
m.w.= 388.47 g/mol
White solid; m.p.= 71-73°C

To a stirred solution of alcohol **1.7** (346 mg, 1 mmol) in CH_2Cl_2 (5 mL) was added triethylamine (146 µL, 1.05 mmol), 4-dimethylamino pyridine (12 mg, 0.1 mmol), and acetic anhydride (100 µL, 1.05 mmol). The reaction was stirred for 1 hour. The mixture was diluted with ether (5 mL), washed with a saturated aqueous solution of $NaHCO_3$ (3 mL) and brine (3 mL). The organic layer was dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash chromatography through a short column of silica (4x4 cm; eluent system A-C) or recrystallisation from petroleum ether afforded the title compound as a white solid (353 mg, 0.91 mmol, 91%).

- Rf (B): 0.52
- **^{1}H NMR** (270 MHz, $CDCl_3$) δ: 7.46-7.28 (m, 9H, C_6H_5 & 2x$C_6\mathbf{H}_2H_2$), 7.02-6.94 (m, 4H, 2x$C_6H_2\mathbf{H}_2$), 6.24 (brd, 1H, J = 5.6, C**H**OAc), 6.02 (ddd, 1H, J = 16.9, 10.3, 5.8, C**H**=CH_2), 5.29 (dt, 1H, J = 16.9, 1.5, CH=CH**H**), 5.25 (dt, 1H, J = 10.3, 1.5, CH=CH**H**), 5.10 (s, 2H, CH_2O), 4.98 (s, 2H, CH_2O), 2.08 (s, 3H, $COCH_3$)

- **^{13}C NMR** (68 MHz, $CDCl_3$) δ: 169.9 (CO), 158.8 (C), 158.7 (C), 136.9 (C), 136.4 (CH), 131.2 (C), 129.1 (CH), 128.9 (C), 128.7 (CH), 128.6 (CH), 127.9 (CH), 127.4 (CH), 116.4 ($CH=CH_2$), 115.0 (CH), 114.9 (CH), 75.8 (**C**HOAc), 70.0 (CH_2O), 69.8 (CH_2O), 21.2 ($COCH_3$)
- **IR** (nujol) ν_{max}: 1731 (s, CO), 1608, 1583, 1511 (m), 1302 (m), 1227 (m), 1171 (m), 1011 (m), 929 (m), 803 (m), 739 (m), 695 cm^{-1}

xii. 1-(Benzyloxy)-4-({4-[(*E*)-3-chloro-1-propenyl]phenyloxy}methyl) benzene <u>1.11</u>

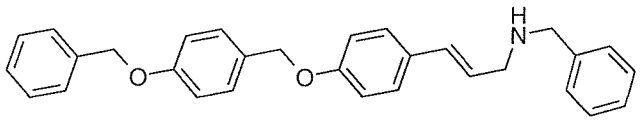


$C_{23}H_{21}ClO_2$
m.w.= 364.85 g/mol
White solid; m.p.= 141-142°C

To a solution of allylic alcohol **1.7** (1 g, 2.9 mmol) in CH_2Cl_2 (20 mL) was added diisopropylethylamine (826 µL, 3.2 mmol). The mixture was cooled to 0°C in an ice bath and mesyl chloride (236 µL, 3 mmol) was added. The reaction was allowed to warm to room temperature and stirred for 3 hours. The reaction mixture was poured into a 2N aqueous solution of HCl (20 mL). The organic layer was washed with a saturated aqueous solution of $NaHCO_3$ (20 mL), brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give a white solid (97 mg, 2.7 mmol, 92%). No further purification was required.

- Rf (B): 0.57
- **^{1}H NMR** (270 MHz, $CDCl_3$) δ: 7.47-7.32 (m, 9H, C_6H_5 & $2xC_6H_2H_2$), 7.02-6.92 (m, 4H, $2xC_6H_2H_2$), 6.61 (d, 1H, J = 15.6, ArC**H**=CH), 6.20 (dt, 1H, J = 15.6, 7.3, ArCH=C**H**), 5.09 (s, 2H, CH_2O), 5.00 (s, 2H, CH_2O), 4.25 (d fs, 2H, J = 7.3, CH_2Cl)
- **^{13}C NMR** (75 MHz, $CDCl_3$) δ: 159.1 (C), 158.9 (C), 137.0 (C), 134.0 (CH), 129.4 (CH), 129.2 (C), 128.9 (C), 128.8 (CH), 128.2 (CH), 127.6 (CH), 122.9 (CH), 115.1 (CH), 70.2 (CH_2O), 70.0 (CH_2O), 46.1 (CH_2Cl)
- **IR** (solution, CH_2Cl_2) ν_{max}: 3053 (m), 2986, 2930, 1605 (m), 1583, 1511 (m), 1452, 1422, 1386, 1288 (m), 1265 (s), 1174 (m), 1113, 1006 (m), 975 (m), 896, 839, 813 (m), 738 (s) cm^{-1}

xiii. *N*-Benzyl-*N*-[(*E*)-3-(4-{[4-(benzyloxy)benzyl]oxy}phenyl)-2-propenyl] amine 1.9

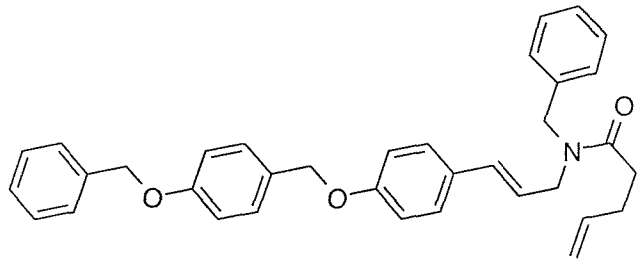


$C_{30}H_{29}NO_2$
m.w.= 435.54 g/mol
White solid; m.p.= 105-106°C

To a solution of allylic acetate **1.8** (50 mg, 0.13 mmol) in THF (3 mL) were added benzylamine (70 µL, 0.64 mmol), a solution of palladium acetylacetonate (4 mg, 0.013 mmol) in THF (0.5 mL), and a solution of 1,2-bis(diphenylphoshino)ethane (7.5 mg, 0.019 mmol) in THF (0.2 mL). The mixture was stirred for 15 hours at room temperature. The reaction was quenched with a saturated solution of $NaHCO_3$ (5 mL). The product was extracted twice with ether (10 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash chromatography through a short column of silica (2x4 cm; eluent system A-E) afforded the title compound as a white solid (39 mg, 0.09 mmol, 70%).

- Rf (E): 0.25
- **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 7.50-7.28 (m, 14H, 2xC_6H_5 & 2x$C_6\mathbf{H}_2H_2$), 7.00 (dd, 4H, *J* = 8.7, 2.3, 2x$C_6H_2\mathbf{H}_2$), 6.54 (d, 1H, *J* = 16.2, ArC**H**=CH), 6.24 (dt, 1H, *J* = 16.2, 5.9, ArCH=C**H**), 5.11 (s, 2H, CH_2O), 5.02 (s, 2H, CH_2O), 3.89 (s, 2H, Ph$\mathbf{CH}_2$NH), 3.47 (d, 2H, *J* = 5.9, $\mathbf{CH}_2$NHBn), 1.73 (s, 1H, NH)
- **^{13}C NMR** (75 MHz, $CDCl_3$) δ: 158.8 (C), 158.5 (C), 140.5 (C), 137.1 (C), 131.1 (CH), 130.3 (C) 129.4 (CH), 128.8 (CH), 128.6 (CH), 128.4 (CH), 128.2 (CH), 127.7 (C), 127.6 (CH), 127.2 (CH), 126.4 (CH), 115.1 (CH), 70.2 (CH_2O), 70.0 (CH_2O), 53.5 (CH_2N), 51.5 (CH_2N)
- **IR** (solution, CH_2Cl_2) ν_{max}: 3052, 2985, 2872, 1606 (m), 1510 (s), 1453, 1421, 1380, 1265 (s), 1237 (m), 1173 (m), 1111, 1010, 969, 895, 827, 741 (s), 704 (s) cm^{-1}
- **MS** (EI) m/z (rel. intensity): 436 ($[M+H]^+$, 32), 329 (100)
- **HRMS** (EI) m/z : 436.22660. $C_{30}H_{30}NO_2$ requires 436.22765

xiv. *N*1-Benzyl-*N*1-[(*E*)-3-(4-{[4-(benzyloxy)benzyl]oxy}phenyl)-2-propenyl]-4-pentenamide 1.13



$C_{35}H_{35}NO_3$
m.w.= 517.66 g/mol
White solid; m.p.= 75-78°C

Note: this compound was prepared from amine **1.9** by using either peptide coupling reagents (Method A) or nucleophilic substitution (Method B).

Method A: To an ice bath cooled solution of amine **1.9** (50 mg, 0.12 mmol) in CH_2Cl_2 (2.5 mL) was added dropwise 4-pentenoic acid (11 μL, 0.11 mmol), diisopropylethyl amine (19 μL, 0.11 mmol), 1,3-dicyclohexylcarbodiimide (22 mg, 0.11 mmol), and 1-hydroxybenzotriazole hydrate (16 mg, 0.11 mmol). The mixture was stirred for 10 minutes at 0°C and for 24 hours at room temperature. The reaction mixture was diluted with ether (5 mL), the solid precipitate collected by filtration and the filtrate poured into a saturated aqueous solution of $NaHCO_3$ (2 mL). The product was extracted twice with ether (5 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo* to give a coloured solid. Purification by flash chromatography through a short column of silica (2x4 cm; eluent system A, B) afforded the title compound as a white solid (35 mg, 0.07 mmol, 65%).

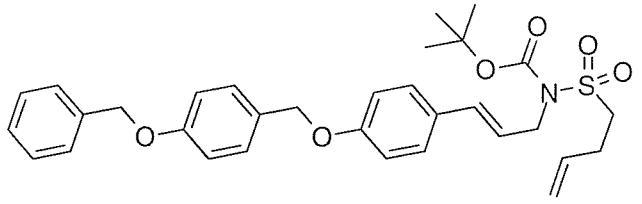
Method B: To a solution of 4-pentenoic acid (25 μL, 0.23 mmol) in CH_2Cl_2 (5 mL) was added a 60% dispersion of sodium hydride in mineral oil (10 mg, 0.24 mmol). When the gas evolution stopped, oxalyl chloride (20 μL, 0.23 mmol) was added, followed by a solution of diisopropylethylamine (65 μL, 0.25 mmol) and amine **1.9** (100 mg, 0.23 mmol) in CH_2Cl_2 (5 mL). The reaction mixture was stirred for 24 hours and was quenched by addition of a saturated aqueous solution of $NaHCO_3$ (10 mL). The product was extracted twice with ether (15 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give a solid. Purification by flash chromatography through a column of silica (4x2 cm; eluent system A, B) afforded the title compound as a white solid (48 mg, 0.09 mmol, 40%).

Note: as previously mentioned, the NMR spectra showed the presence of two rotamers.

- Rf (B): 0.42

- **^{1}H NMR** (270 MHz, $CDCl_3$), 20°C, δ: 7.49-7.34 (m, 14H, 2xC_6H_5 & 2x$C_6H_2H_2$), 7.03-6.92 (m, 4H, 2x$C_6H_2H_2$), 6.38 and 6.37 (*rotamers A and B*, 2d, 1H, *J* = 15.9, ArC**H**=CH), 6.08-5.82 (m, 2H, ArCH=C**H** & C**H**=CH_2), 5.17-5.09 (m, 3H, CH_2O & CH=CH**H**), 5.07-5.00 (m, 3H, CH_2O & CH=CH**H**), 4.66 (*rotamer A*, s, 2H, Ph**C**H_2N) and 4.56 (*rotamer B*, s, 2H, Ph**C**H_2N), 4.16 (*rotamer B*, d, 2H, *J* = 5.4, CH_2N) and 3.98 (*rotamer A*, d, 2H, *J* = 5.4, CH_2N), 2.57-2.49 (m, 4H, CH_2CH_2)
- **^{1}H NMR** (360 MHz, $CDCl_3$),.60°C, δ: 7.49-7.34 (m, 14H, 2xC_6H_5 & 2x$C_6H_2H_2$), 7.03-6.92 (m, 4H, 2x$C_6H_2H_2$), 6.38 (d, 1H, *J* = 15.9, ArC**H**=CH), 6.08-5.82 (br m, 2H, ArCH=C**H** & C**H**=CH_2), 5.17-5.09 (br s, 3H, CH_2O & CH=CH**H**), 5.07-5.00 (br s, 3H, CH_2O & CH=CH**H**), 4.66 (*rotamer A*, s, 2H, Ph**C**H_2N), 4.56 (*rotamer B*, s, 2H, Ph**C**H_2N), 4.16 (*rotamer B*, s fs, 2H, CH_2N), 3.98 (*rotamer A*, s fs, 2H, CH_2N), 2.57-2.49 (m, 4H, CH_2CH_2)
- **^{13}C NMR** (75 MHz, $CDCl_3$) δ: 172.7 (CO), 158.8 (C), 137.9 (C), 137.7 (C), 137.0 (C), 132.8 (CH), 131.6 (CH), 129.4 (C), 129.2 (C), 129.1 (CH), 128.8 (CH), 128.4 (CH), 128.2 (CH), 127.7 (CH), 127.6 (CH), 127.5 (CH), 126.5 (CH), 122.5 (C), 121.9 (CH), 115.5 (CH=**C**H_2), 115.2 (CH), 115.1 (CH), 70.2 (CH_2O), 70.0 (CH_2O), 50.0 (CH_2), 48.9 (CH_2), 48.3 (CH_2), 47.7 (CH_2), 32.8 (CH_2), 32.6 (CH_2), 29.6 (CH_2), 29.5 (CH_2)
- **IR** (solution, CH_2Cl_2) ν_{max}: 1634 (s, CO), 1514, 1173 (m), 1113 (m), 1077, 1021 (m), 907, 780, 736 (m), 695 cm^{-1}
- **MS** (EI) m/z (rel. intensity): 1575 ($[3M+Na]^+$, 4), 1057 ($[2M+Na]^+$, 24); 540 ($[M+Na]^+$, 100)
- $C_{35}H_{35}NO_3$ requires (%) C: 81.21; H: 6.81; N: 2.70. Found C: 81.23; H: 6.84; N: 2.69

xv. 1,1-Dimethylethyl *N*1-(3-butene-1-sulfonyl) *N*1-[(*E*)-3-(4-{[4-(benzyloxy)benzyl]oxy} phenyl)-2-propenyl] carbamate 2.23



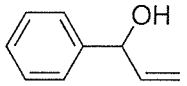
$C_{32}H_{37}NO_6S$
m.w.= 563.71 g/mol
White solid; m.p.= 100-102°C

To a solution of sulfonyl carbamate **2.18** (134 mg, 0.57 mmol) in DMF (10 mL) was added potassium carbonate (83 mg, 0.6 mmol). The mixture was stirred for five minutes at room temperature. A solution of allylic chloride **1.11** (200 mg, 0.55 mmol) in DMF (10 mL) was then added dropwise. The reaction mixture was heated at 70°C for 18 hours. The reaction mixture was allowed to cool to room temperature and the reaction was quenched with a saturated aqueous solution of $NaHCO_3$ (10 mL). The product was extracted twice with ether (10 mL). The combined organic layers were washed with brine (20 mL), dried ($MgSO_4$) and

concentrated *in vacuo* to give a yellow oil. Purification by flash chromatography through a column of silica (3.5x4 cm; eluent system A, B) afforded the title compound as a colourless oil (160 mg, 0.28 mmol, 51%).

- Rf (C): 0.63
- **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 7.46-7.30 (m, 9H, C_6H_5 & 2x$C_6\mathbf{H}_2H_2$), 7.02-6.91 (m, 4H, 2x$C_6H_2\mathbf{H}_2$), 6.57 (d, 1H, J = 15.4, ArC**H**=CH), 6.08 (dt, 1H, J = 15.4, 6.6, ArCH=C**H**), 5.80 (ddt, 1H, J = 16.9, 10.3, 6.6, C**H**=CH_2), 5.17-5.09 (m, 4H, CH=C$\mathbf{H}_2$ & CH_2O), 5.00 (s, 2H, CH_2O), 4.39 (d, 2H, J = 6.6, CH_2N), 3.57-3.53 (m, 2H, CH_2SO_2), 2.60-2.52 (m, 2H, $\mathbf{CH}_2CH_2SO_2$), 1.56 (s, 9H, C($\mathbf{CH}_3$)$_3$)
- **^{13}C NMR** (75 MHz, $CDCl_3$) δ: 158.8 (C), 151.6 (CO), 137.0 (C), 135.3 (C), 133.8 (CH), 133.7 (CH), 129.4 (CH), 128.8 (CH), 128.2 (CH), 127.9 (CH), 127.6 (CH), 121.9 (CH), 117.6 (CH=**C**H_2), 115.1 (CH), 84.7 (O**C**(CH_3)$_3$), 70.2 (CH_2O), 70.0 (CH_2O), 53.6 (CH_2), 48.5 (CH_2), 28.2 (C(**C**H_3)$_3$), 27.7 (**C**$H_2CH_2SO_2$)
- **IR** (solution, CH_2Cl_2) ν_{max}: 2981 (m), 2928, 1722 (s, CO), 1641, 1606 (m), 1510 (s), 1454 (m), 1420 (m), 1354 (s, SO_2), 1263 (s), 1237 (s), 1173 (s), 1146 (s, SO_2), 1007 (m), 968, 925, 895, 826 (m), 734 (m) cm^{-1}
- **MS** (EI) m/z (rel. intensity): 1149 ([2M+Na]$^+$, 8), 586 ([M+Na]$^+$, 34), 581 ([M+NH_4]$^+$, 100)
- **HRMS** (EI) m/z : 586.224718. $C_{32}H_{37}NO_6SNa$ requires 586.223379

xvi. 1-Phenyl-2-propen-1-ol 2.3 [4393-06-0]



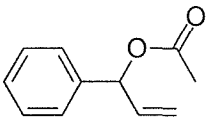
$C_9H_{10}O$
m.w.= 134.18 g/mol
Colourless oil

To a solution of benzaldehyde (2 mL, 20 mmol) in THF (5 mL) was added dropwise under an inert atmosphere at 0°C and with vigorous stirring a 1.0M solution of vinyl magnesium bromide in THF (25 mL, 25 mmol). The mixture was allowed to warm to room temperature and was stirred for 5 hours. The reaction mixture was cooled to 0°C and vigorously stirred as a saturated aqueous solution of NH_4Cl (20 mL) was added. The product was extracted twice with ether (10 mL). The combined organic layers were washed with brine (5 mL), dried ($MgSO_4$) and concentrated *in vacuo* to afford the title compound as a colourless oil (2.66 g, 20 mmol, 99%). No further purification was required.

The spectroscopic data (NMR, IR) were consistent with those reported.[201,202]

- Rf (B): 0.49
- **^{1}H NMR** (270 MHz, $CDCl_3$) δ: 7.39-7.26 (m, 5H, C_6H_5), 6.13-6.00 (m, 1H, **CH**=CH_2), 5.40-5.19 (m, 3H, **CH**OH & CH=**CH_2**), 2.20 (br s, 1H, OH)
- **^{13}C NMR** (75 MHz, $CDCl_3$) δ: 142.7 (CH), 140.9 (CH), 128.7 (CH), 127.9 (C), 126.5 (CH), 115.3 (CH=CH_2), 75.5 (CHOH)
- **IR** (neat) ν_{max}: 3361 (br, OH), 3062, 2979, 1673, 1641, 1601, 1493 (m), 1451 (m), 1281, 1196 (m), 1117, 1024 (m), 988 (m), 838, 699 (m) cm^{-1}
- **MS** (CI) m/z (rel. intensity): 133 ($[M-H]^+$, 46), 117 (100), 91 (35), 77 (50), 63 (14), 51 (20)

xvii. 1-Phenylallyl acetate 2.4 [7217-71-2]



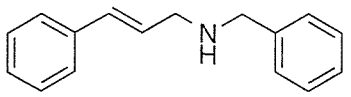
$C_{11}H_{12}O_2$
m.w.= 176.21 g/mol
Colourless oil; b.p.= 61°C / 0.7 mmHg

To a solution of allylic alcohol **2.3** (2.55 g, 19 mmol) in CH_2Cl_2 (20 mL) was added triethylamine (2.8 mL, 20 mmol), 4-dimethylaminopyridine (116 mg, 1.95 mmol) and acetic acid (1.9 mL, 20 mmol). After 3 hours, the reaction mixture was quenched with a saturated aqueous solution of $NaHCO_3$ (10 mL). The product was extracted twice with ether (20 mL). The combined organic layers were washed with brine (5 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give a yellow oil. Distillation under reduced pressure afforded the title compound as a colourless oil (2.32 g, 13 mmol, 70%).

The ^{1}H-NMR data were consistent with those reported in the literature (67°C / 0.3 mmHg).[203]

- Rf (B): 0.66
- **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 7.38-7.28 (m, 5H, C_6H_5), 6.29 (dt, 1H, *J* = 5.9, 1.5, **CH**OAc), 6.04 (ddd, 1H, *J* =16.9, 10.3, 5.9, **CH**=CH_2), 5.32 (dt, 1H, *J* =17.6, 1.5, CH=CH**H**), 5.27 (dt, 1H, *J* =10.3, 1.5, CH=CH**H**), 2.14 (s, 3H, $COCH_3$)
- **^{13}C NMR** (75 MHz, $CDCl_3$) δ: 170.1 (CO), 139.0 (CH), 136.4 (CH), 128.7 (CH), 128.3 (C), 127.3 (CH), 117.1 (CH=CH_2), 76.3 (**CH**OAc), 21.4 ($CO\mathbf{C}H_3$)
- **IR** (neat) ν_{max}: 1740 (s, CO), 1495, 1455, 1371 (m), 1231 (s), 1021 (m), 983, 937, 759, 700 (m) cm^{-1}
- **MS** (CI) m/z (rel. intensity): 176 (M^+, 6), 134 (94), 115 (100), 91 (28), 77 (27)

xviii. *N*-Benzyl-*N*-[(*E*)-3-phenyl-2-propenyl] amine 2.5 [40032-55-1]



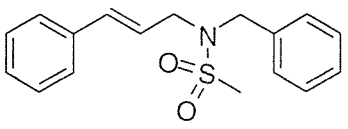
$C_{16}H_{17}N$
m.w.= 223.32 g/mol
Colourless oil

To a solution of acetate **2.4** (2.27 g, 13 mmol) in THF (5 mL) was added benzyl amine (7.1 mL, 65 mmol), palladium acetylacetonate (304 mg, 1 mmol), and 1,2-bis (diphenylphosphino)ethane (206 mg, 0.5 mmol) under an inert atmosphere. The mixture was stirred for 24 hours at room temperature. The reaction mixture was quenched with a saturated aqueous solution of $NaHCO_3$ (30 mL). The product was extracted twice with ether (20 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo* to give an oil. Purification by flash chromatography through a column of silica (4.5x6.5 cm; eluent system A-E) afforded the title compound as a colourless oil (1.76 g, 7.9 mmol, 60%).

The spectroscopic data (NMR, IR) were consistent with those reported.[204,205]

- Rf (B): 0.14, (C): 0.25
- **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 7.45-7.29 (m, 10H, C_6H_5), 6.60 (d, 1H, J = 15.8, PhC**H**=CH), 6.37 (dt, 1H, J = 15.8, 6.2, PhCH=C**H**), 3.88 (s, 2H, NC**H**$_2$Ph), 3.48 (dd, 2H, J = 6.2, 1.2, C**H**$_2$NBn), 1.61 (s, 1H, NH)
- **^{13}C NMR** (75 MHz, $CDCl_3$) δ: 140.4 (C), 137.3 (C), 131.6 (CH), 129.0 (CH), 128.7 (CH), 128.6 (CH), 128.4 (CH), 127.5 (CH), 127.2 (CH), 126.4 (CH), 53.5 (CH_2N), 51.4 (CH_2N)
- **IR** (neat) ν_{max}: 3306 (br, NH), 3021 (m), 2814 (m), 1609 (s), 1573 (s), 1492 (s), 1452 (s), 1356 (m), 1292 (m), 1236, 1202, 1117 (m), 1070 (m), 1027 (m), 967, 909, 737 cm^{-1}
- **MS** (EI) m/z (rel. intensity): 224 ([M+H]$^+$, 100)

xix. *N*-Benzyl-*N*-[(*E*)-3-phenyl-2-propenyl] methanesulfonamide 2.7



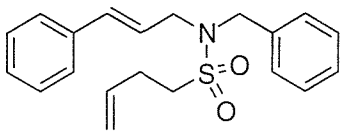
$C_{17}H_{19}NO_2S$
m.w.= 301.41 g/mol
White solid; m.p.= 94-95°C

A solution of amine **2.5** (1 g, 4.5 mmol) in CH_2Cl_2 (10 mL) was cooled to -78°C. Methanesulfonyl chloride (365 μL, 4.7 mmol) and diisopropylethyl amine (820 μL, 4.7 mmol) were added dropwise under an inert atmosphere. The mixture was allowed to warm to

room temperature and stirred for 15 hours. The reaction was quenched with a saturated aqueous solution of $NaHCO_3$ (10 mL). The product was extracted twice with ether (10 mL). The combined organic layers were washed with a 2N aqueous solution of HCl (5 mL) and brine (5 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Recrystallisation from petroleum ether afforded the title compound as a white solid (1.19 g, 4 mmol, 88%).

- Rf (C): 0.47
- **^{1}H NMR** (270 MHz, $CDCl_3$) δ: 7.39-7.31 (m, 10H, C_6H_5), 6.52 (d, 1H, J = 15.8, PhC**H**=CH), 6.15 (dt, 2H, J = 15.8, 6.9, PhCH=C**H**), 4.45 (s, 2H, N**C**H_2Ph), 3.96 (d, 2H, J = 6.8, **C**H_2NBn), 2.90 (s, 3H, SO_2CH_3)
- **^{13}C NMR** (75 MHz, $CDCl_3$) δ: 136.2 (C), 135.9 (C), 135.1 (CH), 128.9 (CH), 128.8 (CH), 128.7 (CH), 128.3 (CH), 128.2 (CH), 126.7 (CH), 123.2 (CH), 50.2 (CH_2N), 48.8 (CH_2N), 40.3 (SO_2CH_3)
- **IR** (solution, CH_2Cl_2) ν_{max}: 3063 (m), 3030 (m), 2926 (m), 2856, 1495 (m), 1455, 1332 (s, SO_2), 1270 (m), 1149 (s, SO_2), 1068, 1028, 962 (m), 927 (m), 903, 787 (m) cm^{-1}
- **MS** (EI) m/z (rel. intensity): 620 ($[2M+NH_4]^+$, 100), 319 ($[M+NH_4]^+$, 40); (APCI): 302 ($[M+H]^+$, 15), 301 (M^+, 6), 222 (100)

xx. *N*1-Benzyl-*N*1-[(*E*)-3-phenyl-2-propenyl]-3-butene-1-sulfonamide 2.1



$C_{20}H_{23}NO_2S$
m.w.= 341.45 g/mol
White solid; m.p.= 62-63°C

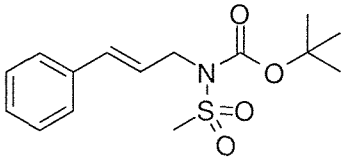
To a solution of sulfonamide **2.7** (100 mg, 0.33 mmol) in THF (10 mL) at -78°C was added dropwise a 2.2M solution of *n*-butyl lithium in hexane (150 µL, 0.33 mmol). The reaction mixture was stirred for 10 minutes at room temperature and cooled to -78°C. Allyl bromide (30 µL, 0.35 mmol) was added. The mixture was allowed to warm to room temperature and stirred for two hours. Water (5 mL) was cautiously added to the reaction mixture, followed by a saturated aqueous solution of $NaHCO_3$ (10 mL). The product was extracted twice with ether (10 mL). The combined organic layers were washed with brine (5 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash chromatography through a short column of silica (4x4 cm; eluent system A, B) afforded the title compound as a white solid (59 mg, 0.17 mmol, 53%).

- Rf (B): 0.52
- **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 7.38-7.28 (m, 10H, C_6H_5), 6.49 (d, 1H, J = 15.8, PhC**H**=CH), 6.14 (dt, 1H, J = 15.8, 6.6, PhCH=C**H**), 5.82 (ddt, 1H, J = 16.9, 10.3, 6.6,

CH=CH_2), 5.14-5.09 (m, 2H, CH=CH_2), 4.48 (s, 2H, NCH_2Ph), 3.97 (d, 2H, J = 6.6, CH_2NBn), 3.12-3.07 (m, 2H, CH_2SO_2), 2.64-2.57 (m, 2H, $CH_2CH_2SO_2$)

- **^{13}C NMR** (75 MHz, $CDCl_3$) δ: 136.0 (C), 135.9 (C), 134.7 (CH), 134.2 (CH), 128.7 (CH), 128.6 (CH), 128.4 (CH), 128.1 (CH), 127.9 (CH), 126.4 (CH), 123.4 (CH), 117.0 (CH=CH_2), 52.6 (CH_2), 50.1 (CH_2), 48.7 (CH_2), 27.7 (CH_2)
- **IR** (solution, CH_2Cl_2) ν_{max}: 2926, 1642, 1495 (m), 1455, 1335 (s, SO_2), 1269 (s), 1143 (s, SO_2), 969 (m), 926 (m), 807 cm^{-1}
- **MS** (APCI) m/z (rel. intensity): 342 ($[M+H]^+$, 34), 341 (M^+, 48), 222 (100)
- **HRMS** (EI) m/z : 341.14646. $C_{20}H_{23}NO_2S$ requires 341.14495

xxi. 1,1-Dimethylethyl *N*-(methanesulfonyl) *N*-[(*E*)-3-phenyl-2-propenyl] carbamate 2.11



$C_{15}H_{21}NO_4S$
m.w.= 311.39 g/mol
Colourless oil

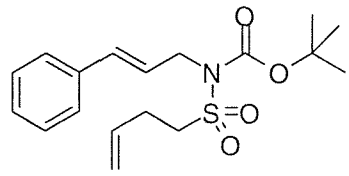
Note: this compound was prepared following two different methods, either by Mitsunobu coupling (Method A) or by nucleophilic substitution (Method B).
Method A: The coupling between cinnamyl alcohol (673 mg, 5 mmol) and methanesulfonyl carbamate **2.10** (980 mg, 5 mmol) was carried out by a Mitsunobu reaction following the general procedure reported above. Purification by flash chromatography through a short column of silica (4x6 cm; eluent system A-E) afforded the title compound as a colourless oil (1.4 g, 4.5 mmol, 90%).

Method B: To a solution of methanesulfonyl carbamate **2.10** (490 mg, 2.5 mmol) in DMF (10 mL) was added potassium carbonate (690 mg, 5 mmol). The mixture was stirred for five minutes at room temperature. A solution of cinnamyl chloride (**2.12**) (150 mg, 3.75 mmol) in DMF (10 mL) was then added dropwise. After 3 hours, the reaction mixture was cooled to 0°C and carefully quenched with a 2N aqueous solution of HCl (10 mL). The product was then extracted twice with ether (10 mL). The combined organic layers were washed with brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give a yellow oil. Purification by flash chromatography through a short column of silica (3.5x4 cm; eluent system A-E) afforded the title compound as a colourless oil (460 mg, 1.48 mmol, 60%).

- Rf (C): 0.41
- **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 7.38-7.20 (m, 5H, C_6H_5), 6.61 (d, 1H, J = 16.2, PhCH=CH), 6.21 (dt, 1H, J = 15.4, 6.6, PhCH=CH), 4.43 (d, 2H, J = 6.6, CH_2N), 3.24 (s, 3H, SO_2CH_3), 1.55 (s, 9H, $C(CH_3)_3$)

- **^{13}C NMR** (75 MHz, $CDCl_3$) δ: 151.6 (CO), 136.4 (C), 134.2 (CH), 128.8 (CH), 128.2 (CH), 126.7 (CH), 123.7 (CH), 84.9 ($OC(CH_3)_3$), 48.2 (CH_2N), 42.6 (SO_2CH_3), 28.2 ($C(CH_3)_3$)
- **IR** (solution, CH_2Cl_2) ν_{max}: 2978, 1723 (s, CO), 1450, 1349 (s, SO_2), 1318 (m), 1277 (m), 1256 (m), 1134 (s, SO_2), 1071, 1020 cm^{-1}
- **MS** (EI) m/z: 645 ($[2M+Na]^+$, 28)

xxii. 1,1-Dimethylethyl *N* 1-(3-butene-1-sulfonyl) *N* 1-[(*E*)-3-phenyl-2-propenyl] carbamate <u>2.16</u>

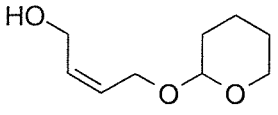


$C_{18}H_{25}NO_4S$
m.w.= 351.46 g/mol
Colourless oil

A solution of LDA (2 mmol) was prepared as described in the general procedures. A solution of sulfonyl carbamate **2.11** (622 mg, 2 mmol) in THF (3 mL) was then added dropwise. The solution was stirred at -78°C for 15 minutes and then rapidly transferred *via* a cannula into a solution of allyl iodide (185 μL, 2 mmol) in THF (3 mL) at -78°C. The reaction mixture was stirred at -78°C for 5 minutes. It was then allowed to warm up to room temperature over 30 minutes and stirred for 15 hours. The mixture was cautiously poured into a 2N aqueous solution of HCl (10 mL) and the product was extracted three times with CH_2Cl_2 (10 mL). The combined organic layers were washed with a saturated aqueous solution of NH_4Cl (15 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give an orange oil. Purification by flash chromatography through a column of silica (4x10 cm; eluent system A-E) afforded the title compound as a colourless oil (323 mg, 0.9 mmol, 46%).

- Rf (C): 0.62
- **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 7.41-7.24 (m, 5H, C_6H_5), 6.64 (d, 1H, J = 16.2, PhC**H**=CH), 6.22 (dt, 1H, J = 16.2, 6.6, PhCH=C**H**), 5.80 (ddt, 1H, J = 16.9, 10.3, 6.6, C**H**=CH_2), 5.14-5.10 (m, 2H, CH=CH_2), 4.42 (d, 2H, J = 6.6, CH_2N) 3.59-3.50 (m, 2H, CH_2SO_2), 2.60-2.53 (m, 2H, C$H_2CH_2SO_2$), 1.55 (s, 9H, $C(CH_3)_3$)
- **^{13}C NMR** (75 MHz, $CDCl_3$) δ: 151.6 (CO), 136.5 (C), 134.1 (CH), 133.8 (CH), 128.7 (CH), 128.1 (CH), 126.7 (CH), 124.1 (CH), 117.6 (CH=CH_2), 84.8 ($OC(CH_3)_3$), 53.6 (CH_2), 48.4 (CH_2), 28.2 ($C(CH_3)_3$), 27.8 ($CH_2CH_2SO_2$)
- **IR** (solution, CH_2Cl_2) ν_{max}: 2979, 1723 (S, CO), 1642, 1578, 1449, 1354 (S, SO_2), 1318 (m), 1301, 1277 (m), 1255 (m), 1132 (s, SO_2), 1071, 1045 cm^{-1}
- **MS** (EI) m/z (rel. intensity): 725 ($[2M+Na]^+$, 29), 352 ($[M+H]^+$, 4)

xxiii. (*Z*)-4-Tetrahydro-2*H*-2-pyranyloxy)-2-buten-1-ol 3.4 [57323-06-5]



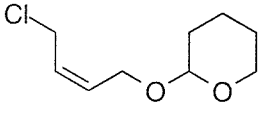
$C_9H_{16}O_3$
m.w.= 172.22 g/mol
Colourless oil

To an ice cooled solution of 2-buten-1,4-diol (**3.1**) (9.4 mL, 114 mmol) and dihydropyran (10.4 mL, 114 mmol) in a 2:5 (v/v) mixture of CH_2Cl_2 and THF (350 mL) was added 4-toluene sulfonic acid monohydrate (1.5 g, 8 mmol) with vigorous stirring. The reaction mixture was stirred at 0°C for 90 minutes, then at room temperature for a further 90 minutes. The reaction was quenched with a saturated aqueous solution of $NaHCO_3$ (50 mL) and the product was extracted twice with ether (75 mL). The combined organic layers were washed with brine (25 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give an oil. Purification by flash chromatography through a column of silica (5x11 cm; eluent system A-E) afforded the title compound as a colourless oil (13.55 g, 79 mmol, 69%).

The spectroscopic data (NMR, IR) were consistent with those reported in the literature.[160,206]

- Rf (D): 0.27, (B): 0.10
- **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 5.81 (dt, 1H, *J* = 11.0, 6.6, C**H**=CH), 5.67 (dt, 1H, *J* = 11.7, 6.6, CH=C**H**), 4.62 (t, 1H, *J* = 3.3, OCHO), 4.25-4.05 (m, 4H, CH_2O), 3.85-3.77 (m, 1H, C**H**HO), 3.50-3.47 (m, 1H, CH**H**O), 2.92 (brs, 1H, OH), 1.79-1.51 (m, 6H, $CH_2CH_2CH_2$)
- **^{13}C NMR** (75 MHz, $CDCl_3$) δ: 132.4 (**C**H=CH), 128.0 (CH=**C**H), 97.6 (OCHO), 62.5 (CH_2O), 62.1 (CH_2O), 58.3 (CH_2O), 30.5 (CH_2), 25.3 (CH_2), 19.2 (CH_2)
- **IR** (neat) ν_{max}: 3389 (OH, br), 2942 (m), 1441, 1387, 1353, 1321, 1262, 1202 (m), 1183, 1157, 1117 (m), 1075 (m), 1020 (s) cm^{-1}

xxiv. (*Z*)-4-Chloro-2-butenyl tetrahydro-2*H*-2-pyranyl ether 3.5 [41793-29-7]



$C_9H_{15}ClO_2$
m.w.= 190.67 g/mol
Colourless oil; b.p.= 68-72°C / 0.45 mbar

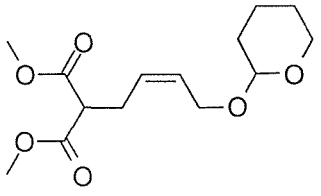
To an ice cooled solution of alcohol **3.4** (4 g, 23 mmol) and diisopropylethylamine (6.8 mL, 26 mmol) in CH_2Cl_2 (20 mL) was added dropwise methanesulfonyl chloride (1.86 mL, 24 mmol). The reaction mixture was stirred at 0°C for 5 minutes, then at room temperature for a further 2 hours. The reaction was quenched with a saturated aqueous solution of $NaHCO_3$ (10 mL) and the product was extracted twice with ether (20 mL). The combined organic layers

were washed with brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give a yellow oil. Purification by distillation or by flash chromatography through a column of silica (3x5 cm; eluent system A) afforded the title compound as a colourless oil (3.6 g, 19 mmol, 82%).

The spectroscopic data (NMR, IR) were consistent with those reported.[160]

- Rf (C): 0.60
- **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 5.83-5.72 (m, 2H, CH=CH), 4.63 (t, 1H, *J* = 3.3, OCHO), 4.31 (dd, 1H, *J* = 13.6, 4.0, CHH), 4.18-4.11 (m, 3H, CH_2 & CHH), 3.90-3.83 (m, 1H, CHH), 3.57-3.50 (m, 1H, CHH), 1.87-1.51 (m, 6H, $CH_2CH_2CH_2$)
- **^{13}C NMR** (75 MHz, $CDCl_3$) δ: 130.6 (CH=CH), 128.5 (CH=CH), 98.1 (CH), 62.4 (CH_2O), 62.2 (CH_2O), 39.3 (CH_2Cl), 30.7 (CH_2), 25.5 (CH_2), 19.5 (CH_2)
- **IR** (neat) ν_{max}: 2943, 1441, 1387, 1340, 1322, 1259 (m), 1202 (m), 1183, 1156, 1119 (s), 1075 (m), 1059 (m), 1024 (s) cm^{-1}
- **MS** (CI) m/z (rel. intensity): 155 ($[M-Cl]^+$, 8), 85 (100)

xxv. Dimethyl 3-[(*Z*)-4-(tetrahydro-2*H*-2-pyranyloxy)-2-butenyl] pentanedioate 3.6
[93915-02-7]



$C_{14}H_{22}O_6$
m.w.= 286.32 g/mol
Colourless oil

To a solution of dimethyl malonate (1.14 mL, 10 mmol) in DMF (100 mL) was added a 60% dispersion of sodium hydride in mineral oil (440 mg, 11 mmol). When the gas evolution stopped, chloride **3.5** (1.72 g, 9 mmol) was added and the reaction mixture was stirred at room temperature for 15 hours. The reaction was carefully quenched with water (50 mL) and the product was extracted three times with ether (50 mL). The combined organic layers were washed with brine (25 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give an oil. Purification by flash chromatography through a column of silica (5x5 cm; eluent system A, B) afforded the title compound as a colourless oil (2.43 g, 8.5 mmol, 95%).

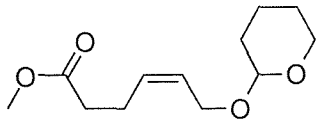
The spectroscopic data (NMR, IR) were consistent with those reported in the literature.[160]

- Rf (D): 0.59
- **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 5.71-5.62 (m, 1H, CH=CH), 5.53-5.44 (m, 1H, CH=CH), 4.59 (t, 1H, *J* = 3.3, OCHO), 4.28-4.22 (m, 1H, CHHO), 4.10-4.03 (m, 1H, CHHO), 3.87-

3.81 (m, 1H, CHHO), 3.70 (s, 6H, OCH_3), 3.51-3.35 (m, 2H, CHHO & $CH(CO_2Me)_2$), 2.66 (t, 2H, J = 7.3, $CH_2CH(CO_2Me)_2$), 1.81-1.51 (m, 6H, $CH_2CH_2CH_2$)

- **^{13}C NMR** (75 MHz, $CDCl_3$) δ: 169.3 (CO), 129.5 (CH=CH), 128.0 (CH=CH), 98.1 (OCHO), 62.7 (CH_2O), 62.3 (CH_2O), 52.7 (OCH_3), 51.6 ($CH(CO_2Me)_2$), 30.7 (CH_2), 27.1 (CH_2), 25.5 (CH_2), 19.6 (CH_2)
- **IR** (neat) ν_{max}: 2951, 1738 (s, CO), 1438 (m), 1342, 1234 (m), 1201 (m), 1157 (m), 1120, 1026 (m) cm^{-1}
- **MS** (CI) m/z (rel. intensity): 203 (19), 185 (88), 125 (27), 85 (100)

xxvi. Methyl (*Z*)-6-(tetrahydro-2*H*-2-pyranyloxy)-4-hexenoate 3.8 [112181-30-3]



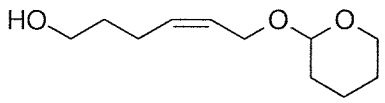
$C_{12}H_{20}O_4$
m.w.= 228.28 g/mol
Colourless oil

To a solution of malonate **3.6** (3.15 g, 11 mmol) and water (400 µL) in DMSO (30 mL) was added potassium acetate (2.15 g, 22 mmol). The mixture was stirred at 140°C for 5 hours. The solution was then allowed to cool to room temperature, poured into water (250 mL) and the product was extracted three times with a 1:1 (v/v) mixture of ether and hexane (100 mL). The combined organic layers were washed with water (75 mL), a saturated aqueous solution of $NaHCO_3$ (75 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give a yellow oil. Purification by flash chromatography through a column of silica (4x5 cm; eluent system A-C) afforded the title compound as a colourless oil (2.11 g, 9.2 mmol, 84%).

The spectroscopic data (NMR, IR) were consistent with those reported in the literature.[160]

- Rf (C): 0.54
- **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 5.61-5.46 (m, 2H, CH=CH), 4.58 (t, 1H, J = 3.3, OCHO), 4.22 (dt, 1H, J = 11.9, 5.5, CHHO), 4.04 (dd, 1H, J = 12.4, 6.4, CHHO), 3.86-3.79 (m, 1H, CHHO), 3.62 (s, 3H, OCH_3), 3.49-3.45 (m, 1H, CHHO), 2.38-2.31 (m, 4H, $CH_2CH_2CO_2Me$), 1.82-1.48 (m, 6H, $CH_2CH_2CH_2$)
- **^{13}C NMR** (75 MHz, $CDCl_3$) δ: 173.4 (CO), 131.2 (CH=CH), 127.6 (CH=CH), 98.0 (OCHO), 62.7 (CH_2O), 62.3 (CH_2O), 51.7 (OCH_3), 34.0 (CH_2), 30.7 (CH_2), 25.6 (CH_2), 23.1 (CH_2), 19.6 (CH_2)
- **IR** (neat) ν_{max}: 2946, 1738 (s, CO), 1439 (m), 1354 (m), 1230 (m), 1200 (m), 1165, 1118 (m), 1024 (m), 905, 869, 815, 735 cm^{-1}
- **MS** (CI) m/z (rel. intensity): 127 (55), 85 (100)

xxvii. (*Z*)-6-(Tetrahydro-2*H*-2-pyranyloxy)-4-hexen-1-ol 3.22 [34625-34-8]



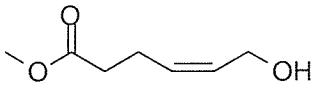
$C_{11}H_{20}O_3$
m.w.= 200.27 g/mol
Colourless oil

Lithium aluminium hydride reduction of ester **3.8** (2.58 g, 11.3 mmol) was carried out as described in the general procedures. Purification by flash chromatography through a column of silica (5x6 cm, eluent system A, B) afforded the title compound as a colourless oil (2.10 g, 10.5 mmol, 93%).

The spectroscopic data were in good agreement with those reported in the literature.[207]

- Rf (C): 0.33
- **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 5.68-5.52 (m, 2H, CH=CH), 4.62 (t, 1H, *J* = 3.3, OCHO), 4.28-4.22 (m, 1H , C**H**HOTHP), 4.06-3.86 (m, 1H, CH**H**OTHP), 3.90-3.81 (m, 1H, $CH_2CH_2CH_2CHHO$), 3.59 (t, 2H, *J* = 6.3, CH_2OH), 3.53-3.48 (m, 1H, $CH_2CH_2CH_2CHHO$), 2.41 (brs, 1H, OH), 2.28-2.13 (m, 2H, $CH_2CH_2CH_2OH$), 1.89-1.48 (m, 8H, CH_2CH_2OH & $CH_2CH_2CH_2$)
- **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 133.8 (**C**H=CH), 126.4 (CH=**C**H), 97.8 (OCHO), 62.5 (CH_2O), 62.4 (CH_2O), 61.4 (CH_2OH), 32.0 (CH_2), 30.7 (CH_2), 25.5 (CH_2), 23.6 (CH_2), 19.5 (CH_2)
- **IR** (neat) ν_{max}: 3396 (br, OH), 2938 (m), 1656, 1440, 1340, 1261, 1201, 1182, 1158, 1116 (m), 1056 (m), 1021 (s), 971 (m), 902 (m), 868 (m), 813 cm^{-1}
- **MS** (EI) m/z (rel. intensity): 363 (5), 227 (100), 172 (80), 154 (35); (CI): 85 (100)
- $C_4H_9NO_2S$ requires (%) C: 65.97; H: 10.07. Found C: 65.10; H: 10.22

xxviii. Methyl (*Z*)-6-hydroxy-4-hexenoate 3.17



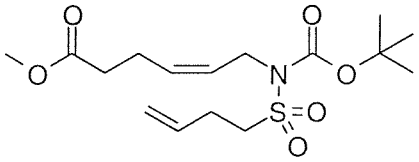
$C_7H_{12}O_3$
m.w.= 144.17 g/mol
Colourless oil

To an ice cooled solution of ester **3.8** (200 mg, 0.88 mmol) in methanol (10 mL) was added 4-toluensulfonic acid (36 mg, 0.18 mmol). The ice bath was removed and the solution was stirred for 3 hours. The reaction was quenched with a saturated aqueous solution of $NaHCO_3$ (20 mL) and the product was extracted twice with ether (25 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give an

oil. Purification by flash chromatography through a short column of silica (1.5x3 cm; eluent system B) afforded the title compound as a colourless oil (84 mg, 0.58 mmol, 66%).

- Rf (C): 0.15
- **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 5.71-5.62 (m, 1H, C**H**=CH), 5.50-5.41 (m, 1H, CH=C**H**), 4.17 (d, 2H, *J* = 6.6, C**H**$_2$OH), 3.44 (s, 3H, OCH_3), 2.92 (brs, 1H, OH), 2.40-2.38 (m, 4H, $CH_2CH_2CO_2Me$)
- **^{13}C NMR** (75 MHz, $CDCl_3$) δ: 173.9 (CO), 130.6 (CH), 130.2 (CH), 58.2 (CH_2OH), 51.8 (OCH_3), 33.7 (CH_2), 22.7 (CH_2)
- **IR** (neat) ν_{max}: 3411 (br, OH), 2953, 1736 (s, CO), 1438 (m), 1365, 1166 (m), 1094, 1025 (m), 984, 850 cm^{-1}
- **MS** (CI) m/z (rel. intensity): 162 ($[M+NH_4]^+$, 25), 145 ($[M+H]^+$, 12)

xxix. Methyl (Z)-6-((3-butenylsulfonyl){[(1,1-dimethylethyl)oxy]carbonyl}amino)-4-hexenoate 3.18

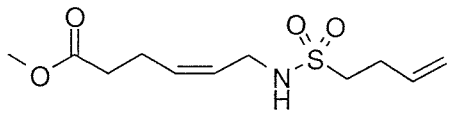


$C_{16}H_{27}NO_6S$
m.w.= 361.45 g/mol
Colourless oil

Mitsunobu coupling between alcohol **3.17** (91 mg, 0.63 mmol) and sulfonyl carbamate **2.18** (148 mg, 0.63 mmol) was carried out following the general procedure reported above. Purification by flash chromatography through a short column of silica (2x4 cm; eluent system A, B) afforded the title compound as a colourless oil (166 mg, 0.46 mmol, 73%).

- Rf (C): 0.50, (B): 0.45
- **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 5.76 (ddt, 1H, *J* = 16.9, 10.3, 6.6, C**H**=CH$_2$), 5.52 (dt, 1H, *J* = 10.3, 5.9, C**H**=CH), 5.49 (dt, 1H, *J* = 10.3, 5.9, CH=C**H**), 5.19-5.08 (m, 2H, CH=C**H**$_2$), 4.31 (d, 2H, *J* = 5.9, CH_2N), 3.67 (s, 3H, OCH_3), 3.53-3.45 (m, 2H, CH_2SO_2), 2.60-2.36 (m, 6H, C**H**$_2$CH$_2$SO$_2$ & C**H**$_2$CH$_2$CO$_2$Me), 1.52 (s, 9H, $C(CH_3)_3$)
- **^{13}C NMR** (75 MHz, $CDCl_3$) δ: 173.5 (COO), 151.5 (NCO), 133.8 (**C**H=CH$_2$), 131.5 (**C**H=CH), 126.2 (CH=**C**H), 117.6 (CH=**C**H$_2$), 84.7 (**O**C(CH$_3$)$_3$), 53.5 (CH_2SO_2), 51.7 (OCH_3), 43.3 (CH_2N), 33.7 (CH_2), 28.1 (C(**C**H$_3$)$_3$), 27.7 (**C**H$_2$CH$_2$SO$_2$), 22.9 (CH_2)
- **IR** (neat) ν_{max}: 1727 (s, CO), 1438, 1357 (s, SO_2), 1276 (m), 1147 (s, SO_2), 917, 851 cm^{-1}
- **MS** (EI) m/z: 745 ($[2M+Na]^+$, 10), 400 ($[M+K]^+$, 27), 384 ($[M+Na]^+$, 28), 379 ($[M+NH_4]^+$, 100)
- **HRMS** (CI) m/z : 362.16303. $C_{16}H_{28}NO_6S$ requires 362.16373

xxx. Methyl (*Z*)-6-[(3-butenylsulfonyl)amino]-4-hexenoate 4.6

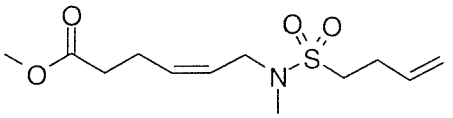


$C_{11}H_{19}NO_4S$
m.w.= 261.33 g/mol
Colourless oil

To a solution of sulfonamide **3.18** (950 mg, 2.6 mmol) in methanol (25 mL) was added potassium carbonate (360 mg, 2.6 mmol). The reaction mixture was heated to 60°C for 15 hours. After cooling to room temperature, the reaction was quenched by adding water (5 mL). The product was extracted twice with CH_2Cl_2 (10 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo* to give an oil. Purification by flash chromatography (5x6 cm; eluent system A-E) afforded the title compound as a colourless oil (333 mg, 1.3 mmol, 49%).

- Rf (C): 0.19, (E): 0.50
- **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 5.83 (ddt, 1H, *J* = 16.9, 10.4, 6.9, C**H**=CH_2), 5.60-5.49 (m, 2H, CH=CH), 5.18-5.06 (m, 2H, CH=C**H**$_2$), 4.80 (brs, 1H, NH), 3.80-3.76 (m, 2H, CH_2N), 3.65 (s, 3H, OCH_3), 3.14-3.02 (m, 2H, CH_2SO_2), 2.62-2.51 (m, 2H, C**H**$_2CO_2$Me), 2.46-2.34 (m, 4H, C**H**$_2CH_2CO_2$Me & C**H**$_2CH_2SO_2$)
- **^{13}C NMR** (75 MHz, $CDCl_3$) δ: 173.7 (CO), 134.5 (**C**H=CH_2), 132.3 (**C**H=CH), 126.4 (CH=**C**H), 117.2 (CH=**C**H$_2$), 52.1 (CH_2SO_2), 51.9 (OCH_3), 39.9 (CH_2N), 33.3 (CH_2), 28.0 (**C**H$_2CH_2SO_2$), 22.6 (CH_2)
- **IR** (film) ν_{max}: 3286 (br, NH), 2952, 1731 (s, CO), 1642, 1437 (m), 1316 (s, SO_2), 1236 (m), 1201 (m), 1139 (s, SO_2), 1063 (m), 996, 920 (m), 857, 731 cm^{-1}
- **MS** (EI) m/z (rel. intensity): 540 ($[2M+NH_4]^+$, 30), 279 ($[M+NH_4]^+$, 100), 262 ($[M+H]^+$, 55)
- **HRMS** (CI) m/z : 262.11070. $C_{11}H_{20}NO_4S$ requires 262.11131

xxxi. Methyl (*Z*)-6-[(3-butenylsulfonyl)(methyl)amino]-4-hexenoate 4.8



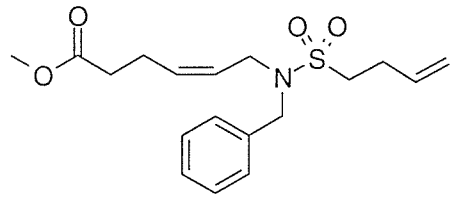
$C_{12}H_{21}NO_4S$
m.w.= 275.36 g/mol
Colourless oil

Sulfonamide **4.6** (180 mg, 0.69 mmol) was *N*-alkylated with methyl iodide (43 µL, 0.69 mmol) following the method reported in the general procedures. Purification by flash

chromatography (1.5x2 cm; eluent system A-E) afforded the title compound as a colourless oil (182 mg, 0.66 mmol, 96%).

- Rf (D): 0.45
- **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 5.85 (ddt, 1H, *J* = 16.5, 10.0, 6.5, C**H**=CH_2), 5.68-5.62 (m, 1H, C**H**=CH), 5.54-5.48 (m, 1H, CH=C**H**), 5.18-5.10 (m, 2H, CH=C**H$_2$**), 3.90 (d, 2H, *J* = 7.0, CH_2N), 3.67 (s, 3H, OCH_3), 3.05-3.00 (m, 2H, CH_2SO_2), 2.86 (s, 3H, NCH_3), 2.61-2.55 (m, 2H, C**H$_2$**CO_2Me), 2.47-2.40 (m, 4H, C**H$_2$**CH_2CO_2Me & C**H$_2$**CH_2SO_2)
- **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 173.5 (CO), 134.8 (**C**H=CH_2), 132.9 (**C**H=CH), 126.0 (CH=**C**H), 117.3 (CH=**C**H_2), 52.1 (OCH_3), 50.1 (CH_2SO_2), 46.8 (CH_2N), 34.5 (NCH_3), 34.3 (CH_2), 27.9 (**C**$H_2CH_2SO_2$), 23.0 (CH_2)
- **IR** (film) ν_{max}: 2952, 1736 (s, CO), 1643, 1601, 1439 (m), 1335 (s, SO_2), 1275, 1200 (m), 1149 (s, SO_2), 1084, 997 (m), 920 (m), 814 cm^{-1}
- **MS** (EI) m/z: 573 ($[2M+Na]^+$, 25), 314 ($[M+K]^+$, 12), 298 ($[M+Na]^+$, 17), 276 ($[M+H]^+$, 8)
- **HRMS** (CI) m/z : 276.12686. $C_{12}H_{22}NO_4S$ requires 276.12696

xxxii. Methyl (*Z*)-6-[benzyl(3-butenylsulfonyl)amino]-4-hexenoate <u>4.10</u>



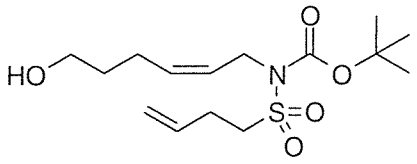
$C_{18}H_{25}NO_4S$
m.w.= 351.46 g/mol
Colourless oil

Sulfonamide **4.6** (193 mg, 0.74 mmol) was *N*-alkylated with benzyl bromide (88 μL, 0.74 mmol) following the method reported in the general procedures. Purification by flash chromatography (1.5x4 cm; eluent system A-C) afforded the title compound as a colourless oil (247 mg, 0.70 mmol, 95%).

- Rf (D): 0.62
- **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.42-7.31 (m, 5H, C_6H_5), 5.85 (ddt, 1H, *J* = 17.0, 10.0, 6.5, C**H**=CH_2), 5.64-5.48 (m, 2H, CH=CH), 5.20-5.11 (m, 2H, CH=C**H$_2$**), 4.42 (s, 2H, N**CH$_2$**Ph), 3.90 (d, 2H, *J* = 7.0, **CH$_2$**NBn), 3.68 (s, 3H, OCH_3), 3.10-3.04 (m, 2H, CH_2SO_2), 2.64-2.58 (m, 2H, C**H$_2$**CO_2Me), 2.41-2.24 (m, 4H, C**H$_2$**CH_2CO_2Me & C**H$_2$**CH_2SO_2)
- **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 173.7 (CO), 134.8 (C), 132.8 (**C**H=CH), 129.1 (CH), 128.7 (CH), 128.3 (CH), 127.9 (CH), 125.7 (CH=**C**H), 117.4 (CH=**C**H_2), 52.8 (CH_2SO_2), 52.0 (OCH_3), 50.9 (N**C**H_2Bn), 43.6 (CH_2N), 33.9 (CH_2), 27.9 (**C**$H_2CH_2SO_2$), 23.0 (CH_2)

- **IR** (film) ν_{max}: 2924, 1734 (s, CO), 1642, 1602, 1495, 1438 (m), 1336 (s, SO_2), 1235 (m), 1202 (m), 1140 (s, SO_2), 1056 (m), 997, 920 (m), 816, 735 cm^{-1}
- **MS** (EI) m/z (rel. intensity): 725 ($[2M+Na]^+$, 20), 390 ($[M+K]^+$, 9), 374 ($[M+Na]^+$, 21), 369 ($[M+NH_4]^+$, 11), 352 ($[M+H]^+$, 7)
- **HRMS** (CI) m/z : 352.15806. $C_{18}H_{26}NO_4S$ requires 352.15826

xxxiii. Methyl (Z)-6-((3-butenylsulfonyl){[(1,1-dimethylethyl)oxy] carbonyl}amino)-4-hexen-1-ol 3.19

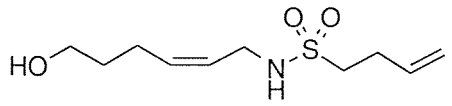


$C_{15}H_{27}NO_5S$
m.w.= 333.44 g/mol
Colourless oil

Lithium aluminium hydride reduction of ester **3.18** (200 mg, 0.55 mmol) was carried out following the procedure given in the general methods. Alcohol **3.19** was obtained as a colourless oil (170 mg, 0.51 mmol, 93%) which required no further purification.

- Rf (C): 0.18
- **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 5.79 (ddt, 1H, *J* = 16.9, 10.3, 6.6, C**H**=CH_2), 5.58-5.48 (m, 2H, CH=CH), 5.18-5.09 (m, 2H, CH=C**H**$_2$), 4.31 (d, 2H, *J* = 5.9, CH_2N), 3.63 (t, 2H, *J* = 6.2, C**H**$_2$OH), 3.54-3.48 (m, 2H, CH_2SO_2), 2.57-2.50 (m, 2H, C**H**$_2$$CH_2SO_2$), 2.26 (q, 2H, *J* = 6.6, C**H**$_2$$CH_2CH_2OH$), 2.05 (brs, 1H, OH), 1.66 (quintuplet, 2H, *J* = 6.6, C**H**$_2$$CH_2OH$), 1.53 (s, 9H, $C(CH_3)_3$)
- **^{13}C NMR** (75 MHz, $CDCl_3$) δ: 151.6 (CO), 133.8 (CH), 133.3 (CH), 125.4 (CH), 117.6 (CH=C**H**$_2$), 85.0 (O**C**$(CH_3)_3$), 61.6 (CH_2OH), 53.6 (CH_2SO_2), 43.5 (CH_2N), 32.1 (**C**H_2CH_2OH), 28.1 ($C(\mathbf{C}H_3)_3$), 27.7 (**C**$H_2CH_2SO_2$), 23.4 (**C**$H_2CH_2CH_2OH$)
- **IR** (film) ν_{max}: 3424 (br, OH), 2935, 1725 (s, CO), 1642, 1476, 1440, 1395, 1357 (s, SO_2), 1314 (m), 1275 (m), 1259 (m), 1147 (s, SO_2), 1058 (m), 921 (m), 850, 817 cm^{-1}
- **MS** (EI) m/z: 689 ($[2M+Na]^+$, 23), 684 ($[2M+NH_4]^+$, 8), 372 ($[M+K]^+$, 15), 351 ($[M+NH_4]^+$, 100)
- $C_{15}H_{27}NO_5S$ requires (%) C: 54.03; H: 8.16; N: 4.20. Found C: 53.59; H: 8.19; N: 4.14

xxxiv. *N*1-[(Z)-6-Hydroxy-2-hexenyl]-3-butene-1-sulfonamide 4.12

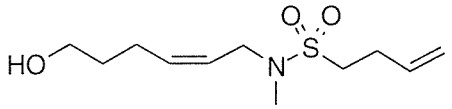


$C_{10}H_{19}NO_3S$
m.w.= 233.32g/mol
Colourless oil

Ester **4.6** (205 mg, 0.78 mmol) was reduced in the presence of lithium aluminium hydride following the procedure reported in the general methods. Purification by flash chromatography (1.5x2 cm; eluent system A-E) afforded the title compound as a colourless oil (176 mg, 0.75 mmol, 96%).

- Rf (E): 0.22
- **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 5.83 (ddt, 1H, *J* = 16.9, 10.2, 6.6, C**H**=CH_2), 5.62-5.51 (m, 2H, CH=CH), 5.18-5.08 (m, 2H, CH=C**H$_2$**), 4.80 (brs, 1H, NH), 3.74 (t, 2H, *J* = 5.9, **CH_2**NH), 3.62 (t, 2H, *J* = 6.2, **CH_2**OH), 3.14-3.06 (m, 2H, CH_2SO_2), 2.62-2.51 (m, 2H, **CH_2**CH_2SO_2), 2.22 (q, 2H, *J* = 6.6, **CH_2**$CH_2$$CH_2$OH), 2.02 (brs, 1H, OH), 1.63 (quintuplet, 2H, *J* = 6.6, **CH_2**CH_2OH)
- **^{13}C NMR** (75 MHz, $CDCl_3$) δ: 134.4 (CH), 134.1 (CH), 125.6 (CH), 117.2 (CH=**CH_2**), 61.2 (**CH_2**OH), 52.2 (**CH_2**SO_2), 39.8 (**CH_2**N), 31.5 (**CH_2**CH_2OH), 28.1 (**CH_2**CH_2SO_2), 23.4 (**CH_2**$CH_2$$CH_2$OH)
- **IR** (film) ν_{max}: 3287 (br, OH), 2923 (m), 1644, 1455, 1315 (s, SO_2), 1230, 1139 (s, SO_2), 1063 (m), 919 cm^{-1}
- **MS** (EI) m/z (rel. intensity): 489 ($[2M+Na]^+$, 14)

xxxv. *N*1-[(Z)-6-Hydroxy-2-hexenyl]-*N*1-methyl-3-butene-1-sulfonamide 4.14



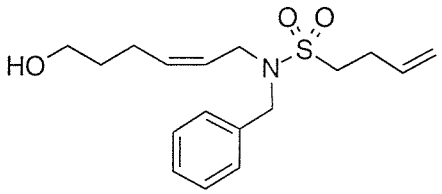
$C_{11}H_{21}NO_3S$
m.w.= 247.35 g/mol
Colourless oil

Ester **4.8** (183 mg, 0.66 mmol) was reduced in the presence of lithium aluminium hydride following the procedure reported in the general methods. Purification by flash chromatography (1.5x3 cm; eluent system A-E) afforded the title compound as a colourless oil (121 mg, 0.49 mmol, 74%).

- Rf (E): 0.25

- **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 5.62 (ddt, 1H, *J* = 17.0, 10.0, 6.5, C**H**=CH_2), 5.51-5.44 (m, 1H, C**H**=CH), 5.32-5.25 (m, 1H, CH=C**H**), 4.96-4.89 (m, 2H, CH=C**H$_2$**), 3.67 (d, 2H, *J* = 7.0, CH_2N), 3.44 (t, 2H, *J* = 6.0, **CH_2**OH), 2.83-2.79 (m, 2H, CH_2SO_2), 2.65 (s, 3H, NCH_3), 2.39-2.33 (m, 2H, **CH_2**CH_2SO_2), 2.01 (q, 2H, *J* = 7.5, **CH_2**CH_2CH_2OH), 1.84 (brs, 1H, OH), 1.45 (quintuplet, 2H, *J* = 7.0, **CH_2**CH_2OH)
- **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 135.4 (**C**H=CH_2), 135.3 (CH), 125.2 (CH), 118.0 (CH=**C**H_2), 62.7 (CH_2OH), 50.7 (CH_2SO_2), 47.4 (CH_2N), 35.2 (NCH_3), 33.1 (**C**H_2CH_2OH), 28.4 (**C**$H_2CH_2SO_2$), 24.5 (**C**$H_2CH_2CH_2OH$)
- **IR** (film) ν_{max}: 3397 (br, OH), 2922 (m), 1643, 1455, 1322 (s, SO_2), 1203 (m), 1147 (s, SO_2), 1059, 995 (m), 921 (s), 799 (m) cm^{-1}
- **MS** (EI) m/z (rel. intensity): 248 ($[M+H]^+$, 6)

xxxvi. *N*1-Benzyl-*N*1-[(*Z*)-6-hydroxy-2-hexenyl]-3-butene-1-sulfonamide 4.16

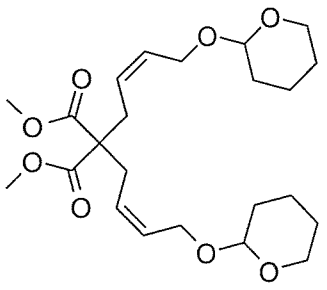


$C_{17}H_{25}NO_3S$
m.w.= 323.45 g/mol
Colourless oil

Ester **4.10** (211 mg, 0.60 mmol) was reduced in the presence of lithium aluminium hydride following the procedure reported in the general methods. Purification by flash chromatography (1.5x3 cm; eluent system A-E) afforded the title compound as a colourless oil (120 mg, 0.37 mmol, 62%).

- Rf (E): 0.41
- **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 7.40-7.30 (m, 5H, C_6H_5), 5.81 (ddt, 1H, *J* = 16.5, 10.2, 6.3, C**H**=CH_2), 5.68-5.54 (m, 1H, C**H**=CH), 5.52-5.41 (m, 1H, CH=C**H**), 5.17-5.08 (m, 2H, CH=C**H$_2$**), 4.43 (s, 2H, NC**H$_2$**Ph), 3.87 (d, 2H, *J* = 7.0, **CH_2**NBn), 3.56 (t, 2H, *J* = 6.0, **CH_2**OH), 3.09-3.01 (m, 2H, CH_2SO_2), 2.65-2.54 (m, 2H, **CH_2**CH_2SO_2), 2.04 (q, 2H, *J* = 7.3, **CH_2**CH_2CH_2OH), 1.80 (brs, 1H, OH), 1.58 (quintuplet, 2H, *J* = 7.0, **CH_2**CH_2OH)
- **^{13}C NMR** (75 MHz, $CDCl_3$) δ: 136.3 (C), 134.5 (CH), 134.4 (CH), 128.8 (CH), 128.4 (CH), 128.1 (CH), 124.3 (CH), 117.2 (CH=**C**H_2), 61.9 (CH_2OH), 52.6 (NCH_2Bn), 50.6 (CH_2SO_2), 43.4 (CH_2N), 32.2 (**C**H_2CH_2OH), 27.8 (**C**$H_2CH_2SO_2$), 23.5 (**C**$H_2CH_2CH_2OH$)
- **IR** (neat) ν_{max}: 3287 (br, OH), 2929, 1495, 1455, 1337 (s, SO_2), 1276, 1140 (s, SO_2), 1061 (m), 1029 (m), 923 (m), 813 cm^{-1}
- **MS** (EI) m/z (rel. intensity): 324 ($[M+H]^+$, 7)

xxxvii. Dimethyl 3,3-di[(*Z*)-4-tetrahydro-2*H*-2-pyranyloxy)-2-butenyl] pentanedioate 3.7

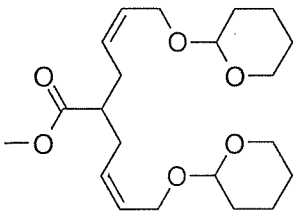


$C_{23}H_{36}O_8$
m.w.= 440.52 g/mol
Colourless oil

To a solution of dimethyl malonate (1.1 mL, 10 mmol) in DMF (100 mL) was added a 60% dispersion of sodium hydride in mineral oil (1 g, 25 mmol). When the gas evolution stopped, chloride **3.5** (5.75 g, 30 mmol) was added and the reaction mixture was stirred at room temperature for 15 hours. The reaction was carefully quenched with water (50 mL) and the product was extracted three times with ether (50 mL). The combined organic layers were washed with brine (25 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give an oil. Purification by flash chromatography through a column of silica (5x5 cm; eluent system A, B) afforded the title compound as a colourless oil (3.65 g, 8.3 mmol, 83%).

- Rf (B): 0.43, (C): 0.51
- **^{1}H NMR** (300MHz, $CDCl_3$) δ: 5.71-5.63 (m, 2H, C**H**=CH), 5.43-5.34 (m, 2H, CH=C**H**), 4.58 (t, 2H, *J* = 3.3, OCHO), 4.21 (dd, 2H, *J* = 12.5, 5.9, C**H**HO), 4.01 (dd, 2H, *J* = 12.5, 7.3, CH**H**O), 3.87-3.79 (m, 2H, C**H**HO), 3.68 (s, 6H, OCH_3), 3.48-3.43 (m, 2H, CH**H**O), 2.66 (d, 4H, *J* = 8.1, $(CH_2)_2C(CO_2Me)_2$), 1.83-1.46 (m, 12H, $CH_2CH_2CH_2$)
- **^{13}C NMR** (75MHz, $CDCl_3$) δ: 171.3 (CO), 130.4 (**C**H=CH), 125.9 (CH=**C**H), 98.2 (OCHO), 62.8 (CH_2O), 62.3 (CH_2O), 57.4 ($C(CO_2Me)_2$), 52.7 (OCH_3), 30.9 (CH_2), 30.7 (CH_2), 25.5 (CH_2), 19.6 (CH_2)
- **IR** (neat) ν_{max}: 2944, 1734 (s, CO), 1439, 1318, 1288, 1201 (m), 1183 (m), 1117 (m), 1077, 1058, 1024 (m) cm^{-1}

xxxviii. Methyl (Z)-6-(tetrahydro-2*H*-2-pyranyloxy)-2-[(Z)-4-(tetrahydro-2*H*-2-pyranyloxy)-2-butenyl]-4-hexenoate 3.9

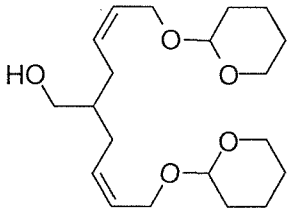


$C_{21}H_{34}O_6$
m.w.= 382.49 g/mol
Colourless oil

To a solution of malonate **3.7** (4.79 g, 10.8 mmol) and water (400 µL) in DMSO (30 mL) was added potassium acetate (2.15 g, 22 mmol). The mixture was stirred at 140°C for 5 hours. The solution was then allowed to cool to room temperature and poured into water (250 mL). The product was extracted three times with a 1:1 (v/v) mixture of ether and hexane (100 mL). The combined organic layers were washed with water (75 mL), a saturated aqueous solution of $NaHCO_3$ (75 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give a yellow oil. Purification by flash chromatography through a column of silica (4x5 cm; eluent system A, B) afforded the title compound as a colourless oil (3.35 g, 8.7 mmol, 81%).

- Rf (C): 0.48
- **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 5.67-5.56 (m, 2H, C**H**=CH), 5.55-5.45 (m, 2H, CH=C**H**), 4.60 (s, 2H, OCHO), 4.22 (dt, 2H, *J* = 12.4, 6.4, C**H**HO), 4.13-3.99 (m, 2H, CH**H**O), 3.88-3.81 (m, 2H, C**H**HO), 3.68 (s, 3H, OCH_3), 3.51-3.47 (m, 2H, CH**H**O), 2.49-2.23 (m, 5H, CH_2CHCO_2Me), 1.85-1.50 (m, 12H, $CH_2CH_2CH_2$)
- **^{13}C NMR** (75 MHz, $CDCl_3$) δ: 175.2 (CO), 129.4 (**C**H=CH), 128.6 (CH=**C**H), 98.0 (OCHO), 62.7 (CH_2O), 62.2 (CH_2O), 51.7 (OCH_3), 45.5 (**C**HCO_2Me), 30.7 (CH_2), 29.7 (CH_2), 25.6 (CH_2), 19.6 (CH_2)
- **IR** (neat) ν_{max}: 2942, 1735 (s, CO), 1439 (m), 1373, 1261, 1165, 1118 (m), 1024 (m), 972, 807 (m), 869, 814 cm^{-1}

xxxix. Methyl (*Z*)-6-(tetrahydro-2*H*-2-pyranyloxy)-2-[(*Z*)-4-(tetrahydro-2*H*-2-pyranyloxy)-2-butenyl]-4-hexenoate 3.10

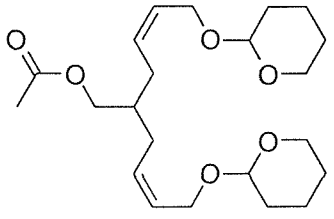


$C_{20}H_{34}O_5$
m.w.= 354.48 g/mol
Colourless oil

Lithium aluminium hydride reduction of ester **3.9** (3.24 mg, 8.5 mmol) was carried out following the method reported in the general procedures. Purification by flash chromatography through a column of silica (3.5x4 cm; eluent system A, C) afforded the title compound as a colourless oil (2.63 g, 7.4 mmol, 87%).

- Rf (C): 0.20, (B): 0.35
- **^{1}H NMR** (400 MHz, ($CDCl_3$) δ: 5.71-5.57 (m, 4H, CH=CH), 4.66-4.62 (m, 2H, OCHO), 4.32-4.19 (m, 2H, CHHOTHP), 4.14-4.01 (m, 2H, CHHOTHP), 3.90-3.82 (m, 2H, $CH_2CH_2CH_2CHHO$), 3.52-3.49 (m, 4H, $CH_2CH_2CH_2CHHO$ & CH_2OH), 2.96 (brs, 1H, OH), 2.26-2.07 (m, 4H, CH_2CHCH_2OH), 1.85-1.51 (m, 13H, $CH_2CH_2CH_2$ & $CHCH_2OH$)
- **^{13}C NMR** (100 MHz, ($CDCl_3$) δ: 132.7 (CH=CH), 127.2 (CH=CH), 98.3 (OCHO), 63.4 (CH_2O), 62.6 (CH_2O), 62.3 (CH_2O), 41.1 ($CHCH_2OH$), 30.6 (CH_2), 28.9 (CH_2), 25.5 (CH_2), 19.5 (CH_2)
- **IR** (neat) ν_{max}: 3461 (br, OH), 2939 (m), 1440, 1320, 1261, 1200, 1115 (m), 1076 (m), 1020 (s), 971 (m), 903 (m), 868 (m), 811, 719 cm^{-1}
- $C_{20}H_{34}O_5$ requires (%) C: 67.77; H: 9.67. Found C: 67.29; H: 9.77

xl. (*Z*)-6-(Tetrahydro-2*H*-2-pyranyloxy)-2-[(*Z*)-4-(tetrahydro-2*H*-2-pyranyloxy)-2-butenyl]-4-hexenyl ethanoate 3.11



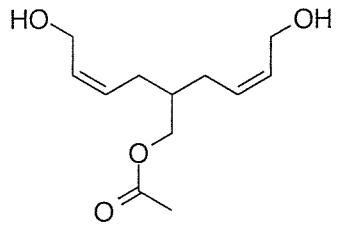
$C_{22}H_{36}O_6$
m.w.= 396.51 g/mol
Colourless oil

To a solution of alcohol **3.10** (300 mg, 0.84 mmol) in CH_2Cl_2 (30 mL) were added triethylamine (130 μL, 0.9 mmol), 4-dimethylaminopyridine (10 mg, 0.09 mmol), and acetic anhydride (84 μL, 0.9 mmol). The reaction mixture was stirred at room temperature for 1 hour, diluted with ether (5 mL), washed with a saturated aqueous solution of $NaHCO_3$ (5 mL),

brine (5 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give an oil. Purification by flash chromatography through a column of silica (2x4.5 cm; eluent system A, C) afforded the title compound as a colourless oil (274 mg, 0.69 mmol, 82%).

- Rf (C): 0.35
- **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 5.70-5.51 (m, 4H, CH=CH), 4.63-4.59 (m, 2H, OCHO), 4.23 (dd, 2H, *J* = 12.5, 5.8, C**H**HO), 4.07-4.00 (m, 2H, CH**H**O), 3.99 (d, 2H, *J* = 5.9, CH_2OAc), 3.90-3.82 (m, 2H, C**H**HO), 3.54-3.46 (m, 2H, CH**H**O), 2.13 (t, 4H, *J* = 7.0, CH_2CHCH_2OAc), 2.05 (s, 3H, $OCOCH_3$), 1.85-1.49 (m, 13H, $CH_2CH_2CH_2$ & $CHCH_2OAc$)
- **^{13}C NMR** (75 MHz, $CDCl_3$) δ: 171.2 (CO), 130.4 (**C**H=CH), 128.2 (CH=**C**H), 98.1 (OCHO), 66.2 (CH_2O), 62.8 (CH_2O), 62.3 (CH_2O), 38.3 (**C**HCH_2OAc), 30.8 (CH_2), 29.1 (CH_2), 25.6 (CH_2), 21.0 ($OCOCH_3$), 19.6 (CH_2)
- IR (film) ν_{max}: 2940, 1740 (s, CO), 1440, 1366, 1236 (m), 1201, 1117 (m), 1078 (m), 1024 (s), 973, 905, 869 cm^{-1}

xli. (Z)-6-Hydroxy-2-[(Z)-4-hydroxy-2-butenyl]-4-hexenyl ethanoate <u>3.12</u>



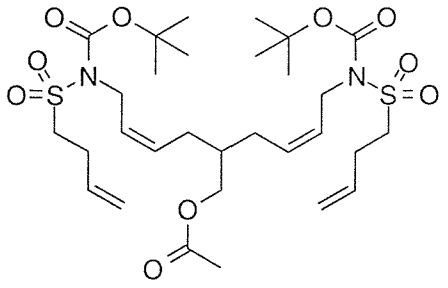
$C_{12}H_{20}O_4$
m.w.= 228.28 g/mol
Colourless oil

To an ice cooled solution of acetate **3.11** (1.2 g, 3 mmol) in methanol (30 mL) was added 4-toluenesulfonic acid (114 mg, 0.6 mmol). The ice bath was removed and the solution was stirred for 3 hours. The reaction was quenched with a saturated aqueous solution of $NaHCO_3$ (20 mL). The product was extracted twice with EtOAc and CH_2Cl_2 (25 mL). The combined organic layers were washed with brine (25 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give an oil. Purification by flash chromatography through a column of silica (3.5x3 cm; eluent system A-E) afforded the title compound as a colourless oil (527 mg, 2.3 mmol, 77%).

- Rf (E): 0.23
- **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 5.70-5.60 (m, 2H, C**H**=CH), 5.47-5.39 (m, 2H, CH=C**H**), 4.09 (d, 4H, *J* = 6.6, CH_2OH), 3.97 (d, 2H, *J* = 7.0, CH_2OAc), 2.11-2.06 (m, 4H, CH_2CHCH_2OAc), 2.26 (s, 2H, OH), 2.03 (s, 3H, $OCOCH_3$), 1.95-1.84 (m, 1H, C**H**CH_2OAc)
- **^{13}C NMR** (75 MHz, $CDCl_3$) δ: 171.6 (CO), 131.0 (**C**H=CH), 129.1 (CH=**C**H), 66.2 (CH_2O), 58.3 (CH_2O), 39.7 (**C**HCH_2OAc), 28.4 (CH_2), 21.1 ($OCOCH_3$)
- IR (neat) ν_{max}: 3327 (br, OH), 2875, 1736 (s, CO), 1716 (s), 1437, 1388, 1367, 1236 (m), 1032 (s), 638 cm^{-1}

- **MS** (EI) m/z: 341 ([M+TFA]-, 58), 299 (100)

xlii. (Z)-6-((3-Butenylsulfonyl){[(1,1-dimethylethyl)oxy]carbonyl}amino)-2-[(Z)-4-((3-butenylsulfonyl){[(1,1-dimethylethyl)oxy]carbonyl}amino)-2-butenyl]-4-hexenyl ethanoate 3.13

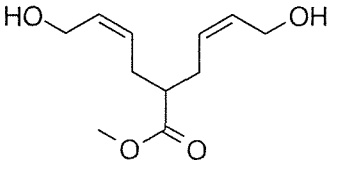


$C_{30}H_{50}N_2O_{10}S_2$
m.w.= 662.85 g/mol
Colourless oil

The Mitsunobu coupling of diol **3.12** (91 mg, 0.63 mmol) and sulfonyl carbamate **2.18** (153 mg, 0.65 mmol) was carried out following the method reported in the general procedures. Purification by flash chromatography through a column of silica (2x4 cm; eluent system A, B) afforded the title compound as a colourless oil (220 mg, 0.33 mmol, 53%).

- Rf (B): 0.24
- **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 5.76 (ddt, 2H, *J* = 16.9, 10.3, 6.6, C**H**=CH_2), 5.57-5.45 (m, 4H, CH=CH), 5.14-5.05 (m, 4H, CH=C**H$_2$**), 4.25 (d, 4H, *J* = 5.1, CH_2N), 3.93 (d, 2H, *J* = 5.9, **CH_2**OAc), 3.50-3.43 (m, 4H, CH_2SO_2), 2.52-2.45 (m, 4H, **CH_2**CH_2SO_2), 2.20-2.16 (m, 4H, **CH_2**$CHCH_2OAc$), 2.02 (s, 3H, $OCOCH_3$), 1.85-1.77 (m, 1H, **CH**CH_2OAc), 1.49 (s, 18H, $C(CH_3)_3$)
- **^{13}C NMR** (75 MHz, $CDCl_3$) δ: 171.2 (COO), 151.5 (NCO), 133.8 (CH), 130.7 (CH), 126.8 (CH), 117.5 (CH=**CH_2**), 84.7 (**O**$C(CH_3)_3$), 66.2 (CH_2O), 53.5 (CH_2O), 43.3 (CH_2), 38.2 ($OCOCH_3$), 28.9 (CH_2), 28.1 ($C(CH_3)_3$), 27.6 (CH_2), 21.1 (**CH**CH_2OAc)
- **IR** (neat) ν_{max}: 2978, 1724 (s, CO), 1643, 1439, 1354 (s, SO_2), 1312 (m), 1274 (m), 1236 (m), 1132 (s, SO_2), 1035 (m), 996, 917 (m), 849 cm^{-1}
- **MS** (EI) m/z: 1342 ($[2M+NH_4]^+$, 7), 701 ($[M+K]^+$, 12), 685 ($[M+Na]^+$, 45), 680 ($[M+NH_4]^+$, 100)

xliii. Methyl (Z)-6-hydroxy-2-[(Z)-4-hydroxy-2-butenyl]-4-oate 3.15

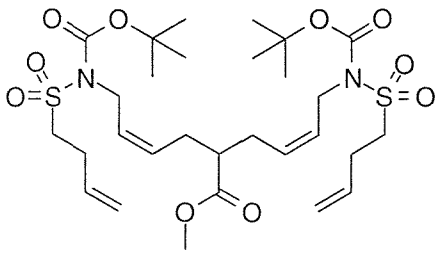


$C_{11}H_{18}O_4$
m.w.= 214.25 g/mol
Colourless oil

To an ice cooled solution of ester **3.9** (3.44 g, 9 mmol) in methanol (70 mL) was added 4-toluenesulfonic acid (340 mg, 1.8 mmol). The ice bath was removed and the solution stirred for 3 hours. The reaction was quenched with a saturated aqueous solution of $NaHCO_3$ (10 mL). The product was extracted three times with ether (10 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo* to give an oil. Purification by flash chromatography (3x5 cm; eluent system A-E) afforded the title diol as a colourless oil (1.79 g, 8.4 mmol, 93%).

- Rf (E): 0.26
- **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 5.72-5.60 (m, 2H, C**H**=CH), 5.47-5.11 (m, 2H, CH=C**H**), 4.06 (d, 4H, J = 6.6, C**H$_2$**OH), 3.72 (s, 3H, OCH_3), 3.13 (brs, 2H, OH), 2.68-2.22 (m, 5H, CH_2CHCO_2Me)
- **^{13}C NMR** (75 MHz, $CDCl_3$) δ: 175.9 (CO), 131.3 (CH), 128.6 (CH), 58.0 (CH_2OH), 52.0 (OCH_3), 44.8 (**C**HCO$_2$Me), 28.9 (**C**H$_2$CHCO$_2$Me)
- **IR** (film) ν_{max}: 3348 (br, OH), 2953, 1725 (s, CO), 1659, 1437 (m), 1291 (m), 1199 (m), 1181 (m), 1111, 1013 (s), 862 cm^{-1}
- **MS** (EI) m/z (rel. intensity): 249 ([M+NH_4OH]$^+$, 100)

xliv. (Z)-6-((3-Butenylsulfonyl){[(1,1-dimethylethyl)oxy]carbonyl}amino)-2-[(Z)-4-((3-butenylsulfonyl){[(1,1-dimethylethyl)oxy]carbonyl}amino)-2-butenyl]-4-hexenyl ethanoate 3.16



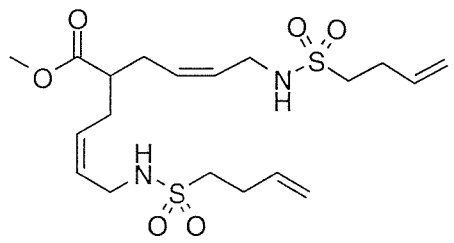
$C_{29}H_{48}N_2O_{10}S_2$
m.w.= 648.83 g/mol
Colourless oil

Mitsunobu coupling between diol **3.15** (1.7 g, 8 mmol) and sulfonyl carbamate **2.18** (3.76 g, 16 mmol) was carried out as reported in the general procedures. Purification by flash

chromatography through a column of silica (4x8 cm; eluent system A, B) afforded the title compound as a colourless oil (2.28 g, 3.5 mmol, 44%).

- Rf (C): 0.64
- **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 5.79 (ddt, 2H, *J* = 16.9, 10.3, 6.6, C**H**=CH_2), 5.54-5.51 (m, 4H, CH=CH), 5.17-5.09 (m, 4H, CH=C**H**$_2$), 4.37-4.20 (m, 4H, CH_2N), 3.66 (s, 3H, OCH_3), 3.53-3.48 (m, 4H, CH_2SO_2), 2.56-2.34 (m, 9H, C**H**$_2$CHCO$_2$Me & C**H**$_2$CH$_2$SO$_2$), 1.53 (s, 18H, $C(CH_3)_3$)
- **^{13}C NMR** (75 MHz, $CDCl_3$) δ: 175.3 (COO), 151.5 (NCO), 133.8 (**C**H=CH_2), 129.9 (**C**H=CH), 127.2 (CH=**C**H), 117.6 (CH=**C**H$_2$), 84.8 (O**C**(CH$_3$)$_3$), 53.6 (CH_2SO_2), 51.8 (OCH_3), 45.3 (**C**HCO$_2$Me), 43.3 (CH_2N), 29.7 (**C**H$_2$CHCO$_2$Me), 28.2 (C(**C**H$_3$)$_3$), 27.7 (**C**H$_2$CH$_2$SO$_2$)
- **IR** (neat) ν_{max}: 2978, 1724 (s, CO), 1643, 1437, 1354 (s, SO_2), 1312 (m), 1257 (m), 1239 (m), 1144 (s, SO_2), 1132 (s), 913 (m), 849, 728 (m) cm^{-1}
- **MS** (EI) m/z (rel.intensity): 687 ($[M+K]^+$, 13), 671 ($[M+Na]^+$, 100), 666 ($[M+NH_4]^+$, 83)
- **HRMS** (CI) m/z : 671.263761. $C_{29}H_{48}N_2O_{10}S_2Na$ requires 671.264258

xlv. Methyl (Z)-6-[(3-butenylsulfonyl)amino]-2-{(Z)-4-[(3-butenylsulfonyl)amino]-2-butenyl}-4-hexenoate 4.7



$C_{19}H_{32}N_2O_6S_2$
m.w.= 448.59 g/mol
Colourless oil

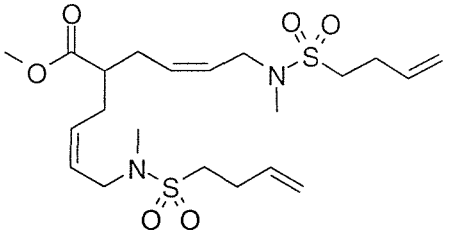
To a solution of sulfonamide **3.16** (2.05 mg, 3.1 mmol) in methanol (25 mL) was added potassium carbonate (830 mg, 6 mmol). The reaction mixture was stirred for 15 hours at 60°C. After cooling to room temperature, the reaction was quenched by addition of water (10 mL). The product was extracted twice with CH_2Cl_2 (20 mL). The combined organic layers were dried ($MgSO_4$) and concentrated to give an oil. Purification by flash chromatography (5x6 cm; eluent system A-E) afforded the title compound as a colourless oil (1.1 g, 2.4 mmol, 79%).

- Rf (E): 0.35
- **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 5.82 (ddt, 2H, *J* = 16.9, 10.2, 6.4, C**H**=CH_2), 5.62-5.43 (m, 4H, CH=CH), 5.18-5.09 (m, 4H, CH=C**H**$_2$), 4.67 (brs; 2H, NH), 3.74 (t, 4H, *J* = 6.2,

CH_2N), 3.67 (s, 3H, OCH_3), 3.13-3.08 (m, 4H, CH_2SO_2), 2.60-2.23 (m, 7H, $\mathbf{CH_2}CH_2SO_2$ & $CHHCHCO_2Me$), 2.31-2.23 (m, 2H, $CH\mathbf{H}CHCO_2Me$)

- **^{13}C NMR** (75 MHz, $CDCl_3$) δ: 175.6 (CO), 134.4 ($\mathbf{C}H=CH_2$), 130.4 ($\mathbf{C}H=CH$), 127.5 ($CH=\mathbf{C}H$), 117.3 ($CH=\mathbf{C}H_2$), 52.3 (CH_2SO_2), 52.1 (OCH_3), 45.1 ($\mathbf{C}HCO_2Me$), 39.9 (CH_2N), 29.6 ($\mathbf{C}H_2CHCO_2Me$), 28.1 ($\mathbf{C}H_2CH_2SO_2$)
- **IR** (neat) ν_{max}: 3284 (br, NH), 2953, 1730 (s, CO), 1643, 1437 (m), 1316 (s, SO_2), 1276 (m), 1234, 1141 (s, SO_2), 1065 (m), 997, 918 (m), 855, 734 cm^{-1}
- **MS** (EI) m/z (rel. intensity): 914 ($[2M+NH_4]^+$, 18), 466 ($[M+NH_4]^+$, 48), 449 ($[M+H]^+$, 22)
- **HRMS** (CI) m/z : 449.176560. $C_{19}H_{33}N_2O_6S_2$ requires 449.177454

xlvi. Methyl (Z)-6-[(3-butenylsulfonyl)(methyl)amino]-2-{(Z)-4-[(3-butenyl sulfonyl)(methyl)amino]-2-butenyl}-4-hexenoate 4.9

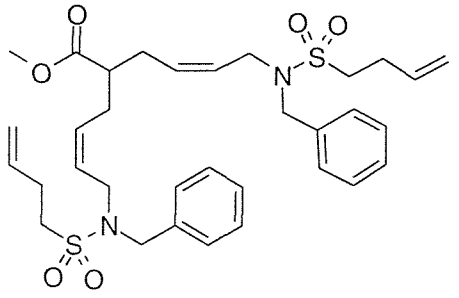


$C_{21}H_{36}N_2O_6S_2$
m.w.= 476.64 g/mol
Colourless oil

Sulfonamide **4.7** (380 mg, 0.85 mmol) was *N*-alkylated with methyl iodide (110 μL, 1.7 mmol) following the method reported in the general procedures. Purification by flash chromatography (1.5x1.5 cm; eluent system A-E) afforded the title compound as a colourless oil (370 mg, 0.83 mmol, 98%).

- Rf (D): 0.15
- **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 5.82 (ddt, 2H, J = 16.9, 10.2, 6.5, $\mathbf{C}H=CH_2$), 5.64-5.48 (m, 4H, CH=CH), 5.18-5.07 (m, 4H, $CH=\mathbf{C}H_2$), 3.94-3.72 (m, 4H, CH_2N), 3.66 (s, 3H, OCH_3), 3.03-2.98 (m, 4H, CH_2SO_2), 2.81 (s, 6H, NCH_3), 2.60-2.22 (m, 9H, $\mathbf{C}H_2CH_2SO_2$ & $CH_2\mathbf{C}HCO_2Me$)
- **^{13}C NMR** (75 MHz, $CDCl_3$) δ: 175.1 (CO), 134.5 ($\mathbf{C}H=CH_2$), 131.0 ($\mathbf{C}H=CH$), 126.7 ($CH=\mathbf{C}H$), 117.2 ($CH=\mathbf{C}H_2$), 51.9 (OCH_3), 49.7 (CH_2SO_2), 46.5 (CH_2N), 45.2 ($\mathbf{C}HCO_2Me$), 34.3 (NCH_3), 29.7 ($\mathbf{C}H_2CHCO_2Me$), 27.6 ($\mathbf{C}H_2CH_2SO_2$)
- **IR** (neat) ν_{max}: 2949, 1731 (s, CO), 1642, 1439 (m), 1329 (s, SO_2), 1275 (m), 1228 (m), 1199 (m), 1145 (s, SO_2), 1133 (s), 994 (m), 916 (m), 796, 696 cm^{-1}
- **MS** (EI) m/z (rel. intensity): 515 ($[M+K]^+$, 12), 499 ($[M+Na]^+$, 78), 494 ($[M+NH_4]^+$, 14), 477 ($[M+H]^+$, 6)
- **HRMS** (CI) m/z : 477.207974. $C_{21}H_{37}N_2O_6S_2$ requires 477.208754

xlvii. Methyl (Z)-6-[benzyl(3-butenylsulfonyl)amino]-2-{(Z)-4-[benzyl(3-butenyl sulfonyl)amino]-2-butenyl}-4-hexenoate 4.11

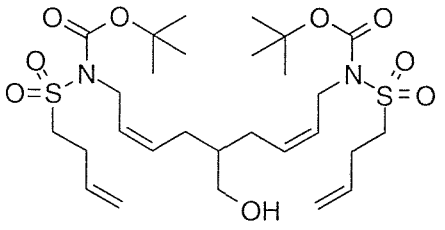


$C_{33}H_{44}N_2O_6S_2$
m.w.= 628.84g/mol
Colourless oil

Sulfonamide **4.7** (100 mg, 0.22 mmol) was *N*-alkylated with benzyl bromide (53 μL, 0.44 mmol) following the method reported in the general procedures. Purification by flash chromatography (1.5x2 cm; eluent system A-E) afforded the title compound as a colourless oil (101 mg, 0.16 mmol, 71%).

- Rf (D): 0.37
- **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.28-7.19 (m, 10H, C_6H_5), 5.72 (ddt, 2H, J = 16.5, 10.0, 6.5, C**H**=CH_2), 5.43-5.35 (m, 4H, CH=CH), 5.06-4.95 (m, 4H, CH=C**H$_2$**), 4.30 (s, 4H, NC**H$_2$**Ph), 3.77-3.65 (m, 4H, C**H$_2$**NBn), 3.51 (s, 3H, OCH_3), 2.97-2.90 (m, 4H, CH_2SO_2), 2.51-2.45 (m, 4H, C**H$_2$**CH_2SO_2), 2.28-2.20 (m, 1H, C**H**CO_2Me), 2.11-2.04 (m, 2H, C**H**HCHCO_2Me), 1.97-1.90 (m, 2H, CH**H**CHCO_2Me)
- **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 175.5 (CO), 136.0 (C), 134.7 (**C**H=CH_2), 131.0 (**C**H=CH), 129.1 (CH), 128.7 (CH), 128.3 (CH), 126.8 (CH=**C**H), 117.4 (CH=**C**H_2), 52.8 (CH_2SO_2), 52.1 (OCH_3), 50.2 (N**C**H_2Ph), 45.4 (**C**HCO_2Me), 43.6 (**C**H_2NBn), 29.8 (**C**H_2CHCO_2Me), 19.5 (**C**$H_2$$CH_2SO_2$)
- **IR** (film) ν_{max}: 2949, 1732 (s, CO), 1642, 1495, 1438 (m), 1335 (s, SO_2), 1275 (m), 1229 (m), 1202 (m), 1140 (s, SO_2), 1058 (m), 1028, 997, 921 (m), 815, 734, 700 cm^{-1}
- **MS** (EI) m/z (rel. intensity): 651 ($[M+Na]^+$, 23), 646 ($[M+NH_4]^+$, 7)
- **HRMS** (CI) m/z : 651.252973. $C_{33}H_{44}N_2O_6S_2Na$ requires 651.253299

xlviii. (Z)-6-((3-Butenylsulfonyl){[(1,1-dimethylethyl)oxy]carbonyl}amino)-2-[(Z)-4-((3-butenylsulfonyl){[(1,1-dimethylethyl)oxy]carbonyl}amino)-2-butenyl]-4-hexen-1-ol 3.14



$C_{28}H_{48}N_2O_9S_2$
m.w.= 620.81 g/mol
Colourless oil

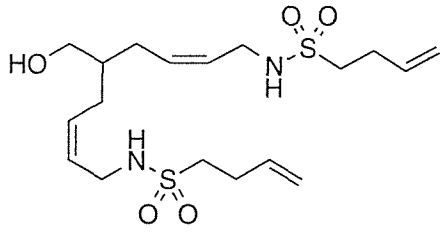
Note: this product was synthesise either by deprotection of acetate **3.13** (Method A) or reduction of ester **3.16** (Method B).

Method A: To an ice cooled solution of acetate **3.13** (420 mg, 0.63 mmol) in methanol (6 mL) was added potassium carbonate (90 mg, 0.65 mmol). The reaction mixture was stirred at 0°C for 1.5 hours and then at room temperature for another 4.5 hours. Brine (10 mL) was added to the reaction mixture and the product was extracted twice with ether (20 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo* to give a colourless oil (368 mg, 0.59 mmol, 94%). No further purification was required.

Method B: Lithium aluminium hydride reduction of ester **3.16** (620 mg, 0.95 mmol) was carried out following the method given in the general procedures. Purification by flash chromatography (2x4 cm; eluent system A-E) afforded the title compound as a colourless oil (513 mg, 0.83 mmol, 87%).

- Rf (C): 0.25
- **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 5.79 (ddt, 2H, *J* = 16.9, 10.3, 6.6, C**H**=CH_2), 5.61-5.47 (m, 4H, CH=CH), 5.18-5.10 (m, 4H, CH=C**H$_2$**), 4.40-4.25 (m, 4H, CH_2N), 3.54-3.48 (m, 6H, CH_2SO_2 & **CH_2**OH), 2.57-2.50 (m, 4H, **$CH_2CH_2SO_2$**), 2.36-2.26 (m, 2H, C**H**HCHCH_2OH), 2.18-2.09 (m, 2H, CH**H**CHCH_2OH), 1.99 (br s, 1H, OH), 1.69-1.59 (m, 1H, C**H**CH_2OH), 1.54 (s, 18H, $C(CH_3)_3$)
- **^{13}C NMR** (75 MHz, $CDCl_3$) δ: 151.6 (CO), 133.8 (**C**H=CH_2), 131.8 (**C**H=CH), 126.3 (CH=**C**H), 117.6 (CH=**C**H_2), 85.0 (**O**$C(CH_3)_3$), 63.5 (CH_2OH), 53.6 (CH_2SO_2), 43.7 (CH_2N), 41.3 (**C**HCH_2OH), 28.8 (**C**H_2CHCH_2OH), 28.2 (C(**C**H_3)$_3$), 27.7 (**C**$H_2CH_2SO_2$)
- **IR** (neat) ν_{max}: 3538 (br, OH), 2979, 1722 (s, CO), 1642, 1438, 1395, 1353 (s, SO_2), 1313 (m), 1257 (m), 1144 (s, SO_2), 1132 (s), 1049 (m), 918 (m), 848, 812, 734 (m), 703 cm^{-1}
- **MS** (EI) m/z: 1263 ([2M+Na]$^+$, 30), 1258 ([2M+NH_4]$^+$, 28), 659 ([M+K]$^+$, 15), 643 ([M+Na]$^+$, 100)

xlix. *N*1-[(2Z,7Z)-9-[(3-Butenylsulfonyl)amino]-5-(hydroxymethyl)-2,7-nonadienyl]-3-butene-1-sulfonamide 4.13

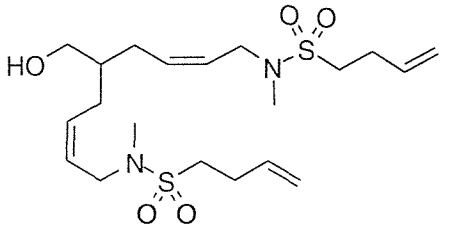


$C_{18}H_{32}N_2O_5S_2$
m.w.= 420.58 g/mol
Colourless oil

Ester **4.7** (430 mg, 0.96 mmol) was reduced in the presence of lithium aluminium hydride following the procedure reported in the general methods. Purification by flash chromatography (1.5x3 cm; eluent system A-E) afforded the title compound as a colourless oil (139 mg, 0.35 mmol, 37%).

- Rf (E): 0.12
- **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 5.91-5.81 (m, 2H, C**H**=CH_2), 5.67-5.59 (m, 4H, CH=CH), 5.34 (brs, 2H, NH), 5.19-5.11 (m, 4H, CH=C**H**$_2$), 3.86-3.55 (m, 6H, CH_2N & C**H**$_2$OH), 3.15-3.11 (m, 4H, CH_2SO_2), 2.89 (brs, 1H, OH), 2.61-2.57 (m, 4H, C**H**$_2$$CH_2SO_2$), 2.34-2.29 (m, 2H, C**H**HCHCH_2OH), 2.13-2.08 (m, 2H, CH**H**CHCH_2OH), 1.73-1.66 (m, 1H, C**H**CH_2OH)
- **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 134.7 (**C**H=CH_2), 132.8 (**C**H=CH), 126.9 (CH=**C**H), 117.5 (CH=**C**H_2), 62.7 (CH_2OH), 52.5 (CH_2SO_2), 40.7 (**C**HCH_2OH), 40.1 (CH_2N), 29.2 (CH_2**C**HCH_2OH), 28.2 (CH_2**C**H_2SO_2)
- **IR** (neat) ν_{max}: 3287 (br, NH), 2922, 1644, 1435, 1314 (s, SO_2), 1232, 1139 (s, SO_2), 1066 (m), 997, 920 (m), 853 cm^{-1}
- **MS** (EI) m/z (rel. intensity): 421 ($[M+H]^+$, 4)

l. *N*1-[(2Z,7Z)-9-[(3-Butenylsulfonyl)(methyl)amino]-5-(hydroxymethyl)-2,7-nonadienyl]-*N*1-methyl-3-butene-1-sulfonamide 4.15



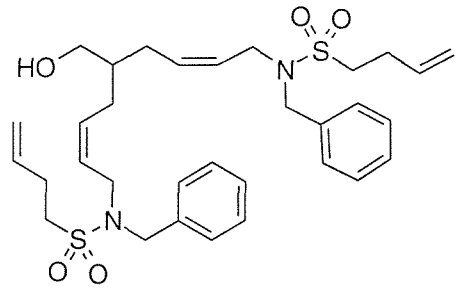
$C_{20}H_{36}N_2O_5S_2$
m.w.= 448.63 g/mol
Colourless oil

Ester **4.9** (580 mg, 1.2 mmol) was reduced in the presence of lithium aluminium hydride following the procedure reported in the general methods. Purification by flash

chromatography (1.5x3 cm; eluent system A-E) afforded the title compound as a colourless oil (356 mg, 0.85 mmol, 71%).

- Rf (E): 0.23
- **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 5.85 (ddt, 2H, *J* = 16.6, 10.0, 6.5, C**H**=CH_2), 5.74-5.67 (m, 2H, **CH**=CH), 5.62-5.55 (m, 2H, CH=**CH**), 5.20-5.12 (m, 4H, CH=C**H$_2$**), 3.96 (dd, 2H, *J* = 15.1, 7.5, **CH**HN), 3.85 (dd, 2H, *J* = 15.1, 6.5, CH**H**N), 3.57 (d, 4H, *J* = 4.5, **CH$_2$**OH), 3.07-3.03 (m, 4H, CH_2SO_2), 2.89 (s, 6H, NCH_3), 2.63-2.57 (m, 4H, **CH$_2$**CH_2SO_2), 2.30 (dt, 2H, *J* = 14.6, 7.5, **CH**HCHCH_2OH), 2.14 (dt, 2H, *J* = 14.5, 7.0, CH**H**CHCH_2OH), 1.91 (brs, 1H, OH), 1.72-1.68 (m, 1H, C**H**CH_2OH)
- **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 134.8 (**CH**=CH_2), 133.1 (**CH**=CH), 125.8 (CH=**CH**), 117.4 (CH=**C**H_2), 63.9 (CH_2OH), 50.0 (CH_2SO_2), 47.0 (CH_2N), 41.4 (**C**HCH_2OH), 34.7 (CH_3), 29.0 (**C**H_2CHCH_2OH), 27.9 (**C**$H_2CH_2SO_2$)
- **IR** (neat) ν_{max}: 3537 (br, OH), 2921, 1642, 1446, 1322 (s, SO_2), 1276, 1202, 1147 (s, SO_2), 1135 (s), 996 (m), 921 (m), 759, 694 cm^{-1}
- **MS** (EI) m/z (rel. intensity): 471 ([M+Na]$^+$, 11), 449 ([M+H]$^+$, 11)

li. *N*1-Benzyl-*N*1-[(2Z,7Z)-9-[benzyl(3-butenylsulfonyl)amino]-5-(hydroxy methyl)-2,7-nonadienyl]-3-butene-1-sulfonamide 4.17



$C_{32}H_{44}N_2O_5S_2$
m.w.= 600.83 g/mol
Colourless oil

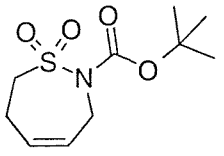
Ester **4.11** (544 mg, 0.87 mmol) was reduced in the presence of lithium aluminium hydride following the procedure reported in the general methods. Purification by flash chromatography (1.5x3 cm; eluent system A-E) afforded the title compound as a colourless oil (354 mg, 0.59 mmol, 68%).

- Rf (E): 0.50
- **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.24-7.19 (m, 10H, C_6H_5), 5.71 (ddt fs, 2H, *J* = 17.0, 10.5, 6.5, C**H**=CH_2), 5.47-5.34 (m, 4H, CH=CH), 5.04-4.98 (m, 4H, CH=C**H$_2$**), 4.30 (s, 4H, NC**H$_2$**Ph), 3.78 (dd, 2H, *J* = 16.1, 7.0, **CH**HNBn), 3.68 (dd, 2H, *J* = 16.1, 6.0, CH**H**NBn), 3.26 (d, 2H, *J* = 3.5, **CH$_2$**OH), 2.96-2.94 (m, 4H, CH_2SO_2), 2.49-2.44 (m, 4H, **CH$_2$**CH_2SO_2),

1.90 (brdt, 3H, J = 14.0, 7.0, CHHCHCH$_2$OH & OH), 1.76 (dt, 2H, J = 14.0, 6.5, CHHCHCH$_2$OH), 1.40-1.38 (m, 1H, CHCH$_2$OH)

- **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 135.1 (C), 133.3 (CH=CH$_2$), 131.3 (CH=CH), 127.6 (CH), 127.2 (CH), 126.9 (CH), 124.3 (CH=CH), 116.0 (CH=CH$_2$), 62.5 (CH$_2$OH), 51.3 (CH$_2$SO$_2$), 49.6 (NCH$_2$Ph), 42.5 (CH$_2$NBn), 39.9 (CHCH$_2$OH), 27.6 (CH$_2$CHCH$_2$OH), 26.6 (CH$_2$CH$_2$SO$_2$)
- **IR** (neat) ν_{max}: 3540 (br, OH), 2919, 1643, 1495, 1455, 1337 (s, SO$_2$), 1276, 1204, 1140 (s, SO$_2$), 1085, 1060 (m), 1028, 922 (m), 808 (m), 735, 700 (m) cm^{-1}
- **MS** (EI) m/z (rel. intensity): 623 ([M+Na]$^+$, 8), 601 ([M+H]$^+$, 7)

lii. 1,1-Dimethylethyl 1,1-dioxo-2,3,6,7-tetrahydro-1*H*-1λ^6,2-thiazepine-2-carboxylate 2.17



$C_{10}H_{17}NO_4S$
m.w.= 247.31 g/mol
Colourless oil

Note: for the solid-phase cyclisation cleavage procedure leading to the formation of the title compound, see below section G in the solid-phase chemistry experimental section.

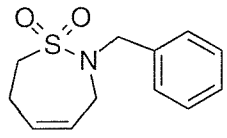
Method A: To a solution of sulfonyl carbamate **2.16** (120 mg, 0.34 mmol) in CH_2Cl_2 (5 mL) was added a solution of bis(tricyclohexylphosphine)benzylidene ruthenium (IV) dichloride (14 mg, 0.017 mmol) in CH_2Cl_2 (5 mL) under an atmosphere of argon. The reaction mixture was refluxed for 15 hours. The reaction mixture was filtered through a short pad of silica eluting with ether (5 mL). The filtrates were concentrated *in vacuo*. Purification by flash chromatography through a short column of silica (1.5x3 cm; eluent system A, B) afforded the title compound as a colourless oil (48 mg, 0.19 mmol, 57%).

Method B: To a solution of sulfonyl carbamate **2.23** (100 mg, 0.18 mmol) in CH_2Cl_2 (5 mL) was added a solution of bis(tricyclohexylphosphine)benzylidene ruthenium (IV) dichloride (7 mg, 0.0085 mmol) in CH_2Cl_2 (5 mL) under an atmosphere of argon. The reaction mixture was refluxed for 15 hours. The reaction mixture was filtered through a short pad of silica eluting with ether. The filtrates were concentrated *in vacuo*. Purification by flash chromatography through a short column of silica (1.5x4 cm; eluent system A, B) afforded the title compound as a colourless oil (33 mg, 0.13 mmol, 78%).

- Rf (B): 0.26, (C): 0.50

- **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 5.93 (dt, 1H, *J* = 11.5, 5.0, C**H**=CH), 5.86 (dt, 1H, *J* = 11.5, 6.2, CH=C**H**), 4.25 (d, 2H, *J* = 4.5, CH_2N), 3.30-3.26 (m, 2H, CH_2SO_2), 2.51-2.46 (m, 2H, $CH_2CH_2SO_2$), 1.50 (s, 9H, $C(CH_3)_3$)
- **^{13}C NMR** (75 MHz, $CDCl_3$) δ: 151.6 (CO), 131.7 (CH), 130.4 (CH), 84.5 ($OC(CH_3)_3$), 51.6 (CH_2), 45.0 (CH_2), 28.1 ($C(CH_3)_3$), 22.2 ($CH_2CH_2SO_2$)
- **IR** (solution, CH_2Cl_2) ν_{max}: 2926, 1732 (s, CO), 1457, 1362 (s, SO_2), 1293 (m), 1237 (m), 1140 (s, SO_2) cm^{-1}
- **MS** (EI) m/z (rel. intensity): 517 ($[2M+Na]^+$, 45), 270 ($[M+Na]^+$, 68)
- **HRMS** (CI) m/z : 270.077671. $C_{10}H_{17}NO_4SNa$ requires 270.077049
- **UV** λ_{max}: 253, 206 nm
- **GC** (temperature program A): 10.4 min

liii. 2-Benzyl-2,3,6,7-tetrahydro-1*H*-1λ^6,2-thiazepine-1,1-dione 2.8



$C_{12}H_{15}NO_2S$
m.w.= 237.32 g/mol
Colourless oil

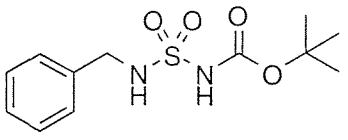
Note: for the solid-phase cyclisation cleavage procedure leading to the formation of the title compound, see below section G in the solid-phase chemistry experimental section.

To a solution of diolefin **2.1** (35 mg, 0.1 mmol) in CH_2Cl_2 (2 mL) under an inert atmosphere of argon was added a solution of bis(tricyclohexyl phosphine)benzylidene ruthenium (IV) dichloride (4 mg, 0.005 mmol) in CH_2Cl_2 (1 mL). The reaction mixture was stirred for 2 hours at room temperature. The mixture was then filtered through a short plug of silica eluting with ether (5 mL). The filtrates were then concentrated *in vacuo* and purified by flash chromatography through a short column of silica (1.5x2 cm; eluent system A, B) to give the title compound as a colourless oil (23 mg, 0.1 mmol, 100%).

- Rf (D): 0.43, (F): 0.29
- **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 7.43-7.21 (m, 5H, C_6H_5), 6.16 (dt, 1H, *J* = 11.2, 5.5, CH=CH), 5.87 (dt, 1H, *J* = 11.0, 5.9, CH=C**H**), 4.24 (s, 2H, NCH_2Ph), 3.63 (d, 2H, *J* = 6.0, CH_2NBn), 3.14-3.10 (m, 2H, CH_2SO_2), 2.61-2.55 (m, 2H, $CH_2CH_2SO_2$)
- **^{13}C NMR** (75 MHz, $CDCl_3$) δ: 135.5 (C), 133.7 (CH), 130.4 (CH), 128.8 (CH), 128.7 (CH), 128.2 (CH), 50.5 (CH_2), 49.1 (CH_2), 42.0 (CH_2), 22.3 ($CH_2CH_2SO_2$)
- **IR** (neat) ν_{max}: 2926, 1455 (m), 1347 (s), 1330 (s, SO_2), 1293, 1157 (s), 1140 (s, SO_2), 897 (s), 791, 737 (s), 701 (s) cm^{-1}
- **MS** (APCI) m/z (rel. intensity): 238 ($[M+H]^+$, 28), 172 (27), 132 (100)

- **HRMS** (EI) m/z : 237.08235. $C_{12}H_{15}NO_2S$ requires 237.08235
- **GC** (temperature program A): 11.9 min

liv. (Benzylamino) [(*tert*-butoxycarbonyl)amino]dioxo-λ^6-sulfane 5.10



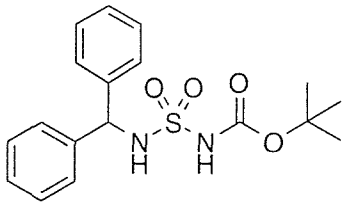
$C_{12}H_{18}N_2O_4S$
m.w.= 286.34 g/mol
White solid; m.p.= 124°C

The procedure reported in the general methods was carried out, using benzylamine (2.7 mL, 25 mmol), thus affording the title compound (3.49 g, 12 mmol, 49%).

The spectroscopic data were in good agreement with those reported in the literature.[181]

- Rf (G): 0.05
- **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 7.39-7.30 (m, 5H, C_6H_5), 7.16 (brs, 1H, SO_2NHBoc), 5.43 (brs, 1H, SO_2NHBn), 4.25 (d, 2H, J = 6.4, $NHCH_2Ph$), 1.46 (s, 9H, $C(CH_3)_3$)
- **^{13}C NMR** (75 MHz, $CDCl_3$) δ: 150.4 (CO), 135.2 (C), 129.0 (CH), 128.4 (CH), 128.3 (CH), 84.1 ($OC(CH_3)_3$), 48.2 (CH_2N), 28.1 ($C(CH_3)_3$)
- **IR** (neat) ν_{max}: 3278 (br, NH), 1705 (s, CO), 1457 (m), 1414, 1351 (s, SO_2), 1255, 1144 (s, SO_2), 1087, 1053, 823, 727 cm^{-1}
- **MS** (EI) m/z (rel. intensity): 595 ($[2M+Na]^+$, 30)

lv. (Benzhydrylamino) [(*tert*-butoxycarbonyl)amino]dioxo-λ^6-sulfane 5.11



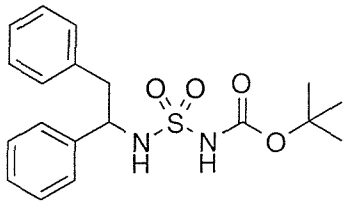
$C_{18}H_{22}N_2O_4S$
m.w.= 362.44 g/mol
White solid; m.p.= 164°C

The procedure reported in the general methods was carried out, using diphenylmethylamine (4.3 mL, 25 mmol), thus affording the title compound (8.70 g, 24 mmol, 96%).

- Rf (G): 0.11

- **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 7.38-7.25 (m, 11H, $C_6\mathbf{H}_5$ & $SO_2N\mathbf{H}Boc$), 5.94 (brd, 1H, *J* = 7.4, $SO_2N\mathbf{H}Bn$), 5.71 (d, 1H, *J* = 7.3, $C\mathbf{H}(Ph)_2$), 1.34 (s, 9H, $C(CH_3)_3$)
- **^{13}C NMR** (75 MHz, $CDCl_3$) δ: 149.9 (CO), 140.4 (C), 128.9 (CH), 128.0 (CH), 127.5 (CH), 83.8 ($O\mathbf{C}(CH_3)_3$), 62.0 ($\mathbf{C}H(Ph)_2$), 28.0 ($C(\mathbf{C}H_3)_3$)
- **IR** (neat) ν_{max}: 3278 (br, NH), 1702 (s, CO), 1496, 1429 (s), 1352 (s, SO_2), 1255 (m), 1137 (s, SO_2), 1087, 1059, 747, 722 cm^{-1}
- **MS** (EI) m/z (rel. intensity): 747 ($[2M+Na]^+$, 15)

lvi. [(*tert*-Butoxycarbonyl)amino][(1,2-diphenylethyl)amino]dioxo-λ^6-sulfane 5.12

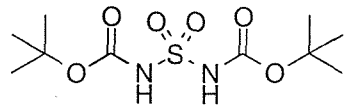


$C_{19}H_{24}N_2O_4S$
m.w.= 376.47 g/mol
White solid; m.p.= 132°C

The procedure reported in the general methods was carried out, using 1,2-diphenylethylamine (4.8 mL, 25 mmol), thus affording the title compound (8.85 g, 23.5 mmol, 94%).

- Rf (G): 0.12
- **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 7.29-7.01 (m, 11H, C_6H_5 & $SO_2N\mathbf{H}Boc$), 5.91 (d, 1H, *J* = 7.3, $BocNHSO_2N\mathbf{H}$), 4.69 (q, 1H, *J* = 7.4, $NHC\mathbf{H}(Ph)CH_2Ph$), 3.20 (dd, 1H, *J* = 13.4, 6.4, $CH(Ph)C\mathbf{H}HPh$), 3.06 (dd, 1H, *J* = 13.4, 7.6, $CH(Ph)CH\mathbf{H}Ph$), 1.33 (s, 9H, $C(CH_3)_3$)
- **^{13}C NMR** (75 MHz, $CDCl_3$) δ: 150.0 (CO), 139.9 (C), 136.5 (C), 129.7 (CH), 128.8 (CH), 128.5 (CH), 128.0 (CH), 127.0 (CH), 126.9(CH), 83.6 ($O\mathbf{C}(CH_3)_3$), 60.3 ($NH\mathbf{C}HPh$), 43.8 (CH_2Ph), 28.1 ($C(\mathbf{C}H_3)_3$)
- **IR** (neat) ν_{max}: 3267 (br, NH), 1701 (s, CO), 1497, 1435 (s), 1342 (s, SO_2), 1251 (m), 1140 (s, SO_2), 1172, 1059, 823 (m), 725 cm^{-1}
- **MS** (EI) m/z (rel. intensity): 775 ($[2M+Na]^+$, 12)

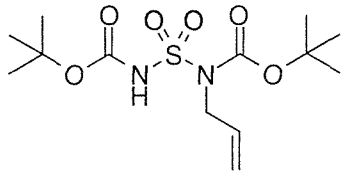
lvii. *N,N'*-Di(*tert*-butoxycarbonyl)sulfamide 5.3



$C_{10}H_{20}N_2O_6S$
m.w.= 296.34 g/mol
No pure sample available

Method A: The procedure reported in the general methods was carried out, using *tert*-butylcarbamate (2.9 g, 25 mmol), thus affording the title compound (5.33 g, ca 18 mmol, ca 72%), impure, which was used as such in the subsequent reaction.
Method B: To an ice cooled solution of sulfamide (**5.5**) (2 g, 21 mmol), dimethylaminopyridine (240 mg, 2 mmol) and triethylamine (6.9 mL, 50 mmol) in CH_2Cl_2 (20 mL) was added dropwise a solution of di-*tert*-butyl dicarbonate (10.5 g, 48 mmol) in CH_2Cl_2 (10 mL). The ice bath was removed. The reaction mixture was stirred for 20 hours and was then concentrated in vacuo. The residue was partitioned between ethyl acetate (30 mL) and a 1N aqueous solution of HCl (20 mL). The organic layer was washed with water (10 mL) and brine (10 mL), dried ($MgSO_4$) and concentrated in vacuo to give a solid (6.22 g, ca 21 mmol, ca 100%), impure, which was used as such in the subsequent reaction.

lviii. [Allyl(*tert*-butoxycarbonyl)amino][(*tert*-butoxycarbonyl)amino]dioxo-λ^6-sulfane 5.26



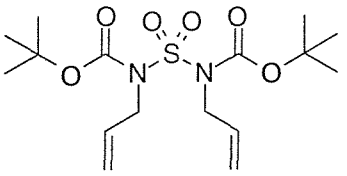
$C_{13}H_{24}N_2O_6S$
m.w.= 336.40 g/mol
White solid; m.p.= 91-94°C

Sulfamide **5.3** (12 g, 42 mmol) was *N*-alkylated as reported in the general procedure, using allyl bromide (3.60 mL, 42 mmol) as the alkylating agent. Purification by flash chromatography (5x4 cm; eluent system A-E) afforded the title compound as a white solid (3.53 g, 10.5 mmol, 25%).

- Rf (B): 0.38
- **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 7.49 (brs, 1H, NH), 5.92 (ddt, 1H, *J* = 17.5, 10.6, 5.5, CH=CH_2), 5.28 (dd, 2H, *J* = 17.4, 1.0, CH=CH**H**), 5.21 (dd, 2H, *J* = 10.4, 1.0, CH=CH**H**), 4.39 (d, 2H, *J* = 5.4, CH_2N), 1.52 (s, 9H, $C(CH_3)_3$), 1.51 (s, 9H, $C(CH_3)_3$)
- **^{13}C NMR** (75 MHz, $CDCl_3$) δ: 151.3 (CO), 149.6 (CO), 133.0 (**C**H=CH_2), 117.6 (CH=**C**H_2), 85.0 ($OC(CH_3)_3$), 84.5 ($OC(CH_3)_3$), 51.6 (CH_2N), 28.1 ($C(CH_3)_3$)

- **IR** (neat) ν_{max}: 3204 (br, NH), 1744 (s, CO), 1714 (s, CO), 1440, 1368 (s, SO_2), 1332, 1140 (s, SO_2), 926, 831, 801, 730 (m) cm^{-1}
- **MS** (EI) m/z (rel. intensity): 695 ($[2M+Na]^+$, 100)
- $C_{13}H_{24}N_2O_6S$ requires (%) C: 46.42; H: 7.19; N: 8.33. Found C: 47.01; H: 7.39; N: 8.29

lix. Di[allyl(*tert*-butoxycarbonyl)amino](dioxo)-λ^6-sulfane 5.27

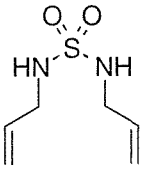


$C_{16}H_{28}N_2O_6S$
m.w.= 376.46 g/mol
White solid; m.p.= 98-101°C

The title compound (4.2 g, 11.3 mmol, 27%) was obtained as a by-product from the previous reaction.

- Rf (B): 0.67
- **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 5.86 (ddt, 2H, *J* = 16.9, 10.3, 5.1, C**H**=CH_2), 5.23 (d, 2H, *J* = 7.9, CH=C**H**H), 5.13 (d, 2H, *J* = 10.3, CH=CH**H**), 4.34 (d, 4H, *J* = 5.1, CH_2N), 1.45 (s, 18H, $C(CH_3)_3$)
- **^{13}C NMR** (75 MHz, $CDCl_3$) δ: 150.6 (CO), 133.2 (**C**H=CH_2), 117.1 (CH=**C**H_2), 84.5 ($OC(CH_3)_3$), 51.9 (CH_2N), 28.0 ($C(CH_3)_3$)
- **IR** (neat) ν_{max}: 1715 (s, CO), 1440, 1368 (s, SO_2), 1319, 1277, 1256, 1140 (s, SO_2), 933, 830, 800, 774, 731 (m) cm^{-1}
- **MS** (EI) m/z (rel. intensity): 776 (32), 775 ($[2M+Na]^+$, 100), 399 ($[M+Na]^+$, 4)
- $C_{16}H_{28}N_2O_6S$ requires (%) C: 51.05; H: 7.50; N: 7.44. Found C: 51.14; H: 7.63; N: 7.43

lx. *N,N'*-Diallylsulfamide 5.35 [6104-14-9]



$C_6H_{12}N_2O_2S$
m.w.= 176.23 g/mol
White solid; m.p.= 68-69°C

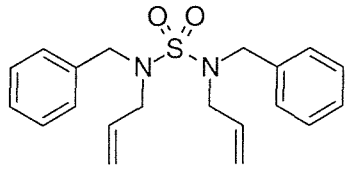
To a solution of sulfamide **5.27** (3.16 g, 8.4 mmol) in CH_2Cl_2 (10 mL) was added 1:3 (v/v) mixture of trifluoroacetic acid and CH_2Cl_2 (7 mL). After 3 hours, tlc indicated the reaction was not complete. Neat trifluoroacetic acid (2 mL) was added. A saturated aqueous solution

of $NaHCO_3$ (15 mL) was added. The product was extracted three times with EtOAc (20 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give a yellow oil which solidified upon standing. Recrystallisation from hexane afforded the title compound as a white oil (1.43 g, 8.1 mmol, 97%).

The spectroscopic data (IR, NMR, MS) were in good agreement with those reported in the literature.[208]

- Rf (B): 0.13
- **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 5.89 (ddt, 2H, J = 17.4, 10.0, 5.4, C**H**=CH_2), 5.30 (dt, 2H, J = 17.4, 1.5, CH=C**H**H), 5.21 (dd, 2H, J = 10.4, 1.5, CH=CH**H**), 4.25 (brs, 2H, NH), 3.69 (brs, 4H, CH_2N)
- **^{13}C NMR** (75 MHz, $CDCl_3$) δ: 133.5 (**C**H=CH_2), 118.0 (CH=**C**H_2), 45.9 (CH_2N)
- **IR** (neat) ν_{max}: 3278 (m, NH), 1466, 1437, 1339, 1314 (s, SO_2), 1203, 1147 (s, SO_2), 1061 (m), 1012, 986, 931 (m) cm^{-1}

lxi. *N,N'*-Diallyl-*N,N'*-dibenzylsulfamide <u>5.36</u>



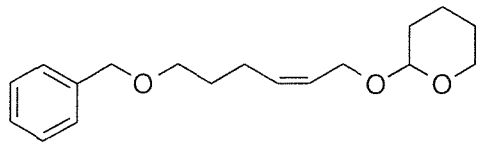
$C_{20}H_{24}N_2O_2S$
m.w.= 356.48 g/mol
Colourless oil

To a solution of sulfamide **5.35** (500 mg, 2.8 mmol) and potassium *tert*-butoxide (640 mg, 5.7 mmol) in THF (30 mL) was added benzyl bromide (680 µL, 5.7 mmol). The reaction mixture was stirred at room temperature for 18 hours. The reaction was quenched with water (10 mL). The product was extracted three times with EtOAc (10 mL). The combined organic layers were washed with brine (20 mL), dried ($MgSO_4$) and concentrated to give an oil. Purification by flash chromatography (4x2.5 cm; eluent system A) afforded the title compound as a white solid (689 mg, 1.9 mmol, 69%).

- Rf (B): 0.60
- **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 7.40-7.28 (m, 10H, C_6H_5), 5.84 (ddt, 2H, J = 16.9, 9.9, 6.4, C**H**=CH_2), 5.23 (dd, 2H, J = 9.9, 1.0, CH=C**H**H), 5.15 (dd, 2H, J = 16.9, 1.4, CH=CH**H**), 4.41 (s, 4H, N**C**$\mathbf{H_2}$Ph), 3.73 (d, 4H, J = 6.9, N**C**$\mathbf{H_2}$Bn)
- **^{13}C NMR** (75 MHz, $CDCl_3$) δ: 136.4 (C), 132.8 (CH), 128.8 (CH), 128.6 (CH), 127.9 (CH), 119.6 (CH=**C**H_2), 50.5 (CH_2N), 49.6 (CH_2N)

- **IR** (neat) ν_{max}: 1495, 1455, 1324 (s, SO_2), 1204, 1145 (s, SO_2), 1047, 992, 923 (m), 888 (m), 794 (m), 738 cm^{-1}

lxii. 2-{[(Z)-6-(Benzyloxy)-2-hexenyl]oxy}tetrahydro-2*H*-pyran 5.38

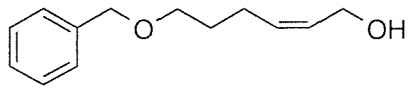


$C_{18}H_{26}O_3$
m.w.= 290.40 g/mol
Colourless oil

To a solution of alcohol **3.22** (2.5 g, 12 mmol) in DMF (50 mL) was added a 60% suspension of NaH in mineral oil (600 mg, 15 mmol). When the gas evolution stopped, benzyl bromide (1.42 mL, 12 mmol) was added. The reaction mixture was stirred at room temperature for 16 hours. The reaction was quenched with water (10 mL). The product was extracted three times with ether (15 mL). The combined organic layers were washed with brine (15 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash chromatography (5x4 cm; eluent system A-E) afforded the title compound as a colourless oil (1.98 g, 6.8 mmol, 57%).

- Rf (B): 0.63
- **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 7.38-7.25 (m, 5H, C_6H_5), 5.65-5.54 (m, 2H, CH=CH), 4.63 (t, 1H, J = 3.0, OCHO), 4.51 (s, 2H, OCH_2Ph), 4.30-4.25 (m, 1H, CHHO), 4.12-4.06 (m, 1H, CHHO), 3.92-3.84 (m, 1H, CHHO), 3.54-3.52 (m, 1H, CHHO), 3.49 (t, 2H, J = 6.4, CH_2O), 2.20 (q, 2H, J = 6.9, $CH_2CH_2CH_2OBn$), 1.87-1.53 (m, 8H, CH_2CH_2OBn & $CH_2CH_2CH_2$)
- **^{13}C NMR** (75 MHz, $CDCl_3$) δ: 138.7 (C), 133.0 (CH), 128.5 (CH), 127.8 (CH), 127.7 (CH), 126.6 (CH), 98.1 (OCHO), 73.1 (CH_2O), 69.8 (CH_2O), 62.9 (CH_2O), 62.4 (CH_2O), 30.8 (CH_2), 29.7 (CH_2), 25.6 (CH_2), 24.4 (CH_2), 19.7 (CH_2)
- **IR** (neat) ν_{max}: 2928, 2852, 1453, 1363, 1201 (m), 1115 (m), 1077 (m), 1023 (s), 905, 735 (m) cm^{-1}

lxiii. (Z)-6-(Benzyloxy)-2-hexen-1-ol 5.39



$C_{13}H_{18}O_2$
m.w.= 206.28 g/mol
Colourless oil

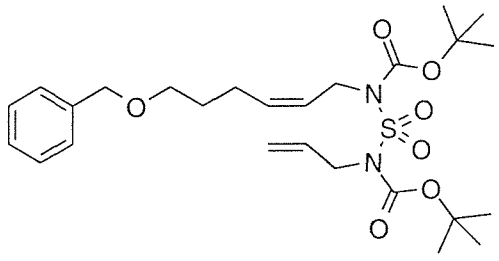
To a solution of acetal **5.38** (1.70 g, 5.8 mmol) in methanol (30 mL) was added 4-toluenesulfonic acid (114 mg, 0.6 mmol) and the solution was stirred at room temperature for 2 hours. The reaction mixture was diluted with CH_2Cl_2 (20 mL) and water (10 mL) was

added. The product was extracted three times with CH_2Cl_2 (15 mL). The combined organic layers were washed with brine (15 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give a slightly coloured oil. Purification by flash chromatography (3.5x3 cm; eluent system A-E) afforded the title compound as a colourless oil (1.19 g, 5.8 mmol, 100%).

The ^{1}H NMR and IR spectra were in good agreement with those reported in the literature for the (*E*) isomer.[209]

- Rf (B): 0.23
- **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 7.40-7.29 (m, 5H, C_6H_5), 5.73-5.62 (m, 1H, C**H**=CH), 5.61-5.49 (m, 1H, CH=C**H**), 4.51 (s, 2H, OC**H**$_2$Ph), 4.17 (d, 1H, *J* = 7.7, C**H**$_2$OH), 3.52 (t, 2H, *J* = 6.5, C**H**$_2$OBn), 2.23-2.18 (q, 2H, *J* = 6.4, C**H**$_2$CH$_2$CH$_2$OBn), 1.90 (brs, 1H, OH), 1.74-1.65 (quintuplet, 2H, *J* = 6.5, C**H**$_2$CH$_2$OBn)
- **^{13}C NMR** (75 MHz, $CDCl_3$) δ: 138.5 (C), 132.3 (CH), 129.4 (CH), 128.6 (CH), 127.9 (CH), 127.8 (CH), 73.0 (CH_2O), 69.3 (CH_2O), 58.4 (CH_2O), 29.4 (CH_2), 24.0 (CH_2)
- **IR** (neat) ν_{max}: 3375 (br, OH), 2934, 2856 (m), 1495, 1454 (m), 1364, 1206, 1099 (m), 1028 (m), 736 (m) cm^{-1}

lxiv. [Allyl (*tert*-butoxycarbonyl)amino][[(Z)-6-(Benzyloxy)-2-hexenyl](*tert*-butoxycarbonyl)amino] dioxo-λ^6-sulfane 5.40



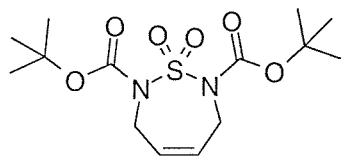
$C_{26}H_{40}N_2O_7S$
m.w.= 524.67 g/mol
Colourless oil

The Mitsunobu coupling reported in the general procedures was carried out with the following reagents: alcohol **5.39** (516 mg, 2.5 mmol), triphenylphosphine (655 mg, 2.5 mmol), sulfonamide **5.26** (815 mg, 2.5 mmol), and DEAD (340 μL, 2.5 mmol). Purification by flash chromatography (3.5x3 cm; eluent system A, B) afforded the title compound as a colourless oil (1.31 g, 2.5 mmol, 100%).

- Rf (B): 0.58
- **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.39-7.31 (m, 5H, C_6H_5), 5.96 (ddt, 1H, *J* = 16.2, 12.0, 4.1, C**H**=CH$_2$), 5.61-5.58 (m, 2H, CH=CH), 5.33 (dd, 1H, *J* = 17.1, 1.5, CH=C**H**H), 5.24 (dd, 1H, *J* = 10.5, 1.5, CH=CH**H**), 4.55 (s, 2H, OC**H**$_2$Ph), 4.51-4.49 (m, 2H, CH=CHC**H**$_2$N), 4.43 (dt, 2H, *J* = 5.5, 1.5, CH$_2$=CHC**H**$_2$N), 3.54 (t, 2H, *J* = 6.5, C**H**$_2$OBn), 2.31-2.27 (m, 2H, C**H**$_2$CH$_2$CH$_2$OBn), 1.76 (quintuplet, 2H, *J* = 4.9, C**H**$_2$CH$_2$OBn), 1.55 (s, 18H, C(CH$_3$)$_3$)

- **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 150.7 (CO), 150.6 (CO), 138.8 (C), 133.3 (**C**H=CH_2), 132.7 (**C**H=CH), 128.5 (CH), 127.8 (CH), 127.6 (CH), 125.5 (CH=**C**H), 117.2 (CH=**C**H_2), 84.5 (O**C**$(CH_3)_3$), 73.0 (OCH_2Ph), 69.9 (**C**H_2OBn), 51.9 (NCH_2CH=CH_2), 47.1 (NCH_2CH=CH), 29.6 (**C**$H_2$$CH_2$OBn), 28.2 (C(**C**$H_3$)$_3$), 28.1 (C(**C**$H_3$)$_3$), 24.2 ($CH_2$**C**$H_2$$CH_2$OBn)
- **IR** (neat) ν_{max}: 2929, 1737 (s, CO), 1455, 1386 (s, SO_2), 1370 (s, SO_2), 1315 (m), 1249 (m), 1147 (s, SO_2), 930, 848 (m), 810 (m), 730 (m) cm^{-1}

lxv. Di(*tert*-butyl) 1,1-dioxo-2,3,6,7-tetrahydro-1*H*-1λ^6,2,7-thiadiazepine-2,7-dicarboxylate 5.32



$C_{14}H_{24}N_2O_6S$
m.w.= 348.41 g/mol
White solid; m.p.= 71-74°C

Note: two different procedures were followed for the preparation of the title compound.

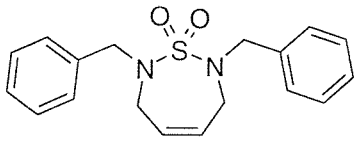
Method A: To a solution of sulfamide **5.27** (155 mg, 0.4 mmol) in CH_2Cl_2 (10 mL) under an inert atmosphere of argon was added bis(tricyclohexyl phosphine)benzylidene ruthenium (IV) dichloride (6 mg, 0.008 mmol). The reaction mixture was stirred for 15 hours at room temperature. The mixture was then filtered through a short plug of silica eluting with ether (10 mL). The filtrates were then concentrated *in vacuo* and purified by flash chromatography through a short column of silica (0.5x3 cm; eluent system A, B) to give the title compound as a white solid (92 mg, 0.26 mmol, 66%).

Method B: The Mitsunobu coupling reported in the general procedures was carried out with 1,4-butenediol (1.65 mL, 20 mmol), triphenylphosphine (10.5 g, 40 mmol), sulfonamide **5.3** (6.11 g, 20 mmol), and DEAD (6.3 mL, 40 mmol). Purification by flash chromatography (3.5x4 cm; eluent system A, B) afforded the title compound as a colourless oil (2.72 g, 7.8 mmol, 39%).

- Rf (B): 0.38
- **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 5.79 (t, 2H, J = 2.4, CH=CH), 4.37 (d, 4H, J = 2.5, CH_2N), 1.51 (s, 18H, C$(CH_3)_3$)
- **^{13}C NMR** (75 MHz, $CDCl_3$) δ: 150.6 (CO), 126.7 (CH=CH), 85.2 (O**C**$(CH_3)_3$), 45.2 (CH_2N), 28.0 (C(**C**H_3)$_3$)
- **IR** (neat) ν_{max}: 1728 (s, CO), 1456, 1389 (s, SO_2), 1369 (m), 1325 (m), 1302 (m), 1254 (m), 1181 (m), 1143 (s, SO_2), 1082 (m), 937, 889, 847, 804, 767 cm^{-1}

- **MS** (EI) m/z (rel. intensity): 719 ($[2M+Na]^+$, 42)
- $C_{14}H_{24}N_2O_6S$ requires (%) C: 48.26; H: 6.94; N: 8.14. Found C: 48.66; H: 7.07; N: 7.86

lxvi. 2,7-Dibenzyl-2,3,6,7-tetrahydro-1*H*-1λ^6,2,7-thiadiazepine-1,1-dione 5.31

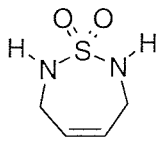


$C_{18}H_{20}N_2O_2S$
m.w.= 328.43 g/mol
White solid; m.p.= 95-96°C

To a solution of sulfamide **5.36** (228 mg, 0.64 mmol) in CH_2Cl_2 (10 mL) under an inert atmosphere of argon was added bis(tricyclohexyl phosphine)benzylidene ruthenium (IV) dichloride (5 mg, 0.006 mmol). The reaction mixture was stirred for 15 hours at room temperature. The mixture was then filtered through a short plug of silica eluting with ether (10 mL). The filtrates were then concentrated *in vacuo* and purified by flash chromatography through a short column of silica (3x4 cm; eluent system A-E) to give the title compound as a white solid (165 mg, 0.47 mmol, 74%).

- Rf (B): 0.40
- **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 7.38-7.32 (m, 10H, C_6H_5), 5.86 (t, 2H, J = 3.0, CH=CH), 4.50 (s, 4H, NCH_2Ph), 3.71 (d, 4H, J = 3.0, CH_2NBn)
- **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 136.2 (C), 129.5 (CH), 128.6 (CH), 128.2 (CH), 127.8 (CH), 52.3 (CH_2N), 43.4 (CH_2N)
- **IR** (neat) ν_{max}: 2982, 1389 (m), 1369 (s, SO_2), 1325 (m), 1303 (m), 1254 (m), 1181 (m), 1143 (s, SO_2), 1082 (m), 937, 847, 804, 767, 733 cm^{-1}
- $C_{14}H_{24}N_2O_6S$ requires (%) C: 65.83; H: 6.14; N: 8.53. Found C: 65.69; H: 5.99; N: 8.42

lxvii. 2,3,6,7-Tetrahydro-1*H*-1λ^6,2,7-thiadiazepine-1,1-dione 5.33



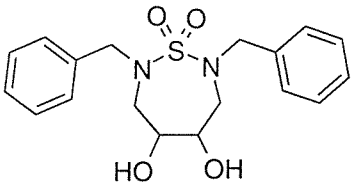
$C_4H_8N_2O_2S$
m.w.= 148.18 g/mol
White solid; m.p.= 254-257°C

To sulfamide **5.32** (2.7 g, 7.7 mmol) was added 1:1 (v/v) mixture of trifluoroacetic acid and CH_2Cl_2 (10 mL). After 30 minutes, tlc indicated the reaction was not complete. Neat trifluoroacetic acid (8 mL) was added. After 30 minutes, upon completion, the reaction

mixture was concentrated *in vacuo* to give a solid. Purification by recrystallisation from ether afforded the title compound as a white solid (815 mg, 5.5 mmol, 71%).

- Rf (C): 0.12
- **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 5.84 (s, 2H, CH=CH), 4.81 (br, 2H, NH), 3.63 (s, 4H, CH_2N)
- **^{13}C NMR** (75 MHz, $CDCl_3$) δ: 130.3 (CH), 40.8 (CH_2N)
- **IR** (neat) ν_{max}: 3278 (s, NH), 1436 (m), 1416, 1305 (s, SO_2), 1235 (m), 1139 (s, SO_2), 1096 (m), 1071 (s), 1022, 956, 788 (m) cm^{-1}
- $C_4H_8N_2O_2S$ requires (%) C: 32.42; H: 5.44; N: 18.90. Found C: 32.55; H: 5.52; N: 18.77

lxviii. 2,7-Dibenzyl-4,5-dihydroxyperhydro-1λ^6,2,7-thiadiazepine-1,1-dione 5.49

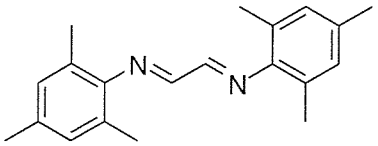


$C_{18}H_{22}N_2O_4S$
m.w.= 362.44 g/mol
Colourless oil

To a solution of cyclic sulfamide **5.31** (407 mg, 1.24 mmol) in acetone (20 mL), water (5 mL) and a 60% solution of *N*-methylmorpholine oxide in water (245 mg, 1.25 mmol) was cautiously added osmium tetroxide (15 mg, 0.06 mmol). The reaction mixture was stirred at room temperature for 16 hours. The solution was diluted with CH_2Cl_2 (10 mL) and sodium metabisulfite was added. The reaction mixture was left stirring for 1 hour. Sodium sulfate was added. The product was extracted twice with CH_2Cl_2 (10 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash chromatography through a short column of silica (3.5x4 cm; eluent system A-E) afforded the title compound as a white solid (305 mg, 0.84 mmol, 68%).

- Rf(D): 0.20
- **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 7.39-7.27 (m, 10H, C_6H_5), 4.63 (d, 2H, *J* = 5.1, NCHHPh), 4.55 (d, 2H, *J* = 5.1, NCHHPh), 3.66 (d fs, 2H, *J* = 6.4, CHOH), 3.41 (dd, 2H, *J* = 14.9, 6.4, CHHNBn), 3.08 (d, 2H, *J* = 14.9, CHHNBn), 2.62 (br, 2H, OH)
- **^{13}C NMR** (75 MHz, $CDCl_3$) δ: 136.9 (C), 129.0 (CH), 128.3 (CH), 128.1 (CH), 69.7 (CHOH), 53.7 (CH_2N), 46.6 (CH_2N)
- **IR** (neat) ν_{max}: 3458 (s, OH), 1496, 1455 (m), 1346 (s, SO_2), 1293 (m), 1153 (s, SO_2), 1095, 1047 (m), 939 (m), 798 cm^{-1}

lxix. *N*1-[(*E*)-2-(Mesitylimino)ethylidene]-2,4,6-trimethylaniline 5.42 [56222-36-7]



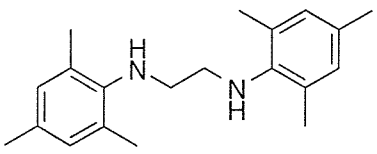
$C_{20}H_{24}N_2$
m.w.= 292.42 g/mol
Yellow solid; m.p.= 156-157°C

To a solution of 2,4,6-trimethylaniline (1.4 mL, 10 mmol) in acetone (5 mL) was added a 40% solution of glyoxal (**5.41**) in water (725 mg, 5 mmol). The reaction mixture was stirred at room temperature for one hour during which yellow crystals precipitated. The crystals were collected by filtration and rapidly washed with ice cooled acetone. The title compound was obtained as bright yellow crystals which required no further purification (965 mg, 3.3 mmol, 66%)

The NMR spectroscopic data and the metling point (157-158°C) were in good agreement with those reported in the literature.[188]

- Rf (C): 0.75
- **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 8.12 (s, 2H, C**H**=NMes), 6.93 (s, 4H, $C_6\mathbf{H}_2(CH_3)_3$), 2.31 (s, 6H, 4-(CH_3)), 2.18 (s, 12H, CH_3)
- **^{13}C NMR** (75 MHz, $CDCl_3$) δ: 163.6 (**C**H=NMes), 147.5 (C), 134.4 (C), 129.1 (CH), 126.7 (C), 20.9 (CH_3), 18.4 (CH_3)
- **IR** (neat) ν_{max}: 2916, 1617 (m), 1477, 1375 (m), 1275 (m), 1260 (m), 1202 (m), 1141, 1031, 850 (s), 764 (s), 750 (s) cm^{-1}
- **MS** (EI) m/z (rel. intensity): 294 (16), 293 ($[M+H]^+$, 74)

lxx. *N*1,*N*2-Dimesityl-1,2-ethanediamine 5.43 [n/a]



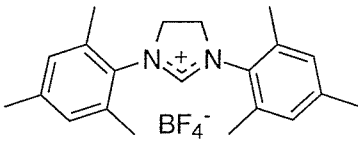
$C_{20}H_{28}N_2$
m.w.= 296.45 g/mol
Yellow oil

To a suspension of imine **5.42** (2.57 g, 8.8 mmol) in methanol (30 mL) was added sodium cyanoborohydride (1.64 g, 26.4 mmol). The reaction mixture was then cooled to 0°C and a 2N aqueous solution of HCl (ca. 4 mL) was added dropwise until pH<4. The ice bath was removed and the reaction mixture was kept under stirring at room temperature for 15 hours. The reaction mixture was diluted with CH_2Cl_2 (10 mL) and a 2N aqueous solution of NaOH

was added to bring the pH to 9. The product was extracted twice with CH_2Cl_2 (10 mL) and twice with Et_2O (10 mL). The combined organic layers were dried ($MgSO_4$) and concentrated to give amine **5.43** as a white solid (2.22 g, 7.5 mmol, 85%) which required no further purification.

- Rf (C): 0.44
- **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 6.86 (s, 4H, $C_6\mathbf{H}_2(CH_3)_3$), 3.19 (s, 4H, $\mathbf{CH}_2$NMes), 2.32 (s, 12H, CH_3), 2.27 (brs, 8H, 4-(CH_3) & NH)
- **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 137.6 (C), 136.8 (C), 131.5 (C), 130.5 (CH), 48.9 ($\mathbf{CH}_2$NMes), 21.0 (CH_3), 19.1 (CH_3)
- **IR** (neat) ν_{max}: 3428 (br, NH), 1668, 1612 (m), 1484 (m), 1149 (m), 977, 851 (m) cm^{-1}
- **MS** (EI) m/z (rel. intensity): 298 (20), 297 ([M+H]$^+$, 100)

lxxi. 1,3-Dimesityl-4,5-dihydro-1*H*-imidazol-3-ium tetrafluoroborate 5.44 [n/a]



$C_{21}H_{27}N_2.BF_4$
m.w.= 394.26 g/mol
White solid; m.p.> 250°C

To a solution of ammonium tetrafluoroborate (600 mg, 5.7 mmol) and amine **5.43** (1.67 g, 5.6 mmol) in enough ethanol to dissolve them was added triethyl orthoformate (950 μL, 5.7 mmol). The reaction mixture was heated to 120°C for 3 hours. Upon cooling the reaction mixture to room temperature, a colourless solid precipitated which was collected by filtration and washed with ethanol. Recrystallisation from acetone / ether afforded the title compound as a white solid (1.8 g, 4.7 mmol, 82%) which required no further purification.

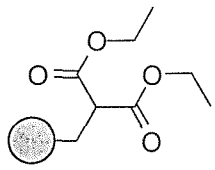
- **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 8.50 (s, 1H, NCHN), 6.89 (s, 4H, $C_6\mathbf{H}_2(CH_3)_3$), 4.36 (s, 4H, $\mathbf{CH}_2$NMes), 2.24 (s, 12H, CH_3), 2.20 (s, 6H, 4-(CH_3))
- **^{13}C NMR** (75 MHz, $CDCl_3$) δ: 160.0 (C), 140.8 (C), 135.0 (C), 130.1 (CH), 51.5 ($\mathbf{CH}_2$NMes), 21.1 (NCHN), 17.7 (CH_3), 17.6 (CH_3)
- **IR** (neat) ν_{max}: 1627 (m), 1486, 1268 (m), 1214, 1093, 1053 (s), 1037 (m), 966 cm^{-1}
- **MS** (EI) m/z (rel. intensity): 309 (21), 308 ([M-BF_4]$^+$, 100)

3- Solid-Phase Chemistry

A. Preparation of the Various Starting Resins from Commercially Available Merrifield Resin

i. Carboxyethyl Resin 3.2

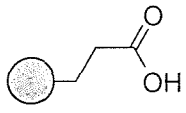
*Step 1: Alkylation (Resin **6.1**)*



DMF (100 mL) was added to a 60% suspension of sodium hydride in mineral oil (5.23 g, 132 mmol) under nitrogen. The mixture was cooled to 0°C and diethyl malonate (20 mL, 132 mmol) was added dropwise over 30 minutes. When the gas evolution stopped, Merrifield resin (**1.14**) (12 g, 2.3 mmol Cl/g, 28 mmol) was added to the solution and the reaction mixture stirred at 60°C for 15 hours. The reaction mixture was cooled to room temperature. Resin **6.1** was collected by filtration, thoroughly washed with DMF, H_2O, THF, CH_2Cl_2 (2x25 mL each) and dried at 50°C *in vacuo* for 5 hours.

IR (neat) ν_{max}: 1729 (s), 1603, 1492, 1449 (m), 1368, 1148 (m), 1030 (m), 757 (m), 698 (s) cm^{-1}

*Step 2: Hydrolysis and Decarboxylation (Resin **3.2**)*

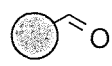


Resin **6.1** (6 g, unknown loading) was suspended in THF (100 mL) and a 2N aqueous solution of NaOH (10 mL) was added. The reaction mixture was heated at reflux temperature for 15 hours. After cooling to room temperature, the resin was collected by filtration and washed with H_2O, MeOH, CH_2Cl_2 (25 mL each). The resin was suspended in THF (100 mL) and a 2N aqueous solution of HCl (15 mL) was added. The reaction mixture was heated to reflux temperature for 3 hours. After cooling to room temperature, resin **3.2** was collected by filtration, washed with H_2O, THF, CH_2Cl_2 (25 mL each) and dried at 50°C *in vacuo* for 5 hours.

Loading (transesterification): 1 mmol OH/g

IR (neat) ν_{max}: 1719 (s), 1602, 1492, 1449 (m), 842, 697 (s) cm^{-1}

ii. Aldehyde Resin 6.2

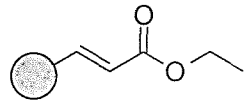


To a suspension of Merrifield resin (**1.14**) (2 g, 2.3 mmol Cl/g, 4.6 mmol) in DMSO (75 mL) was added either sodium bicarbonate or potassium carbonate (7 g and 11 g respectively, 80 mmol). The reaction mixture was heated at 155°C for 6 hours. The resin was collected by filtration, washed with H_2O, MeOH, CH_2Cl_2 (2x20 mL each) and dried at 50°C *in vacuo* for 5 hours.

IR (neat) ν_{max}: 1697 (s), 1603 (m), 1492, 1450 (m), 1306, 1270, 1212, 1167, 1027, 841, 827, 754 (m), 696 (s) cm^{-1}

iii. Allylic Alcohol Resin 3.3

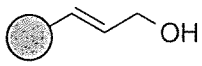
*Step 1: Horner Emmons Reaction (Resin **6.3**)*



To a solution of triethyl phosphonoacetate (0.3 mL, 1.5 mmol) in THF (2 mL) at -78°C was added dropwise a 1.0M solution of sodium hexamethyldisilane in THF (1.3 mL, 1.3 mmol). The reaction mixture was stirred at room temperature for 1 hour and added via a cannula to a suspension of the resin bound aldehyde **6.2** (250 mg, unknown loading) in THF (1 mL). Resin **6.3** was collected by filtration, washed with H_2O, THF, CH_2Cl_2 (2x10 mL each) and dried at 50°C *in vacuo* for 5 hours.

IR (neat) ν_{max}: 2919, 1708 (s), 1603, 1492, 1450 (m), 1366, 1306, 1264 (m), 1172 (m), 1025 (m), 977, 755 (m), 697 (s) cm^{-1}

*Step 2: Ester Reduction (Resin **3.3**)*

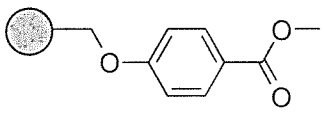


To a suspension of resin **6.3** (250 mg, unknown loading) in THF (3 mL) was added dropwise under an inert atmosphere a 2M solution of lithium borohydride in THF (1 mL, 2 mmol) followed by methanol (80 μL, 2 mmol). The reaction mixture was stirred for 13 hours. The excess lithium borohydride was carefully quenched with water (5 mL). Resin **3.3** was collected by filtration, washed with H_2O, MeOH, CH_2Cl_2 (2x10 mL each), and dried at 50°C *in vacuo* for 5 hours.

Loading (transesterification): 2.0 mmol OH/g
IR (neat) ν_{max}: 3341 (br), 2918, 1601, 1492, 1450 (m), 965 (m), 697 (s) cm^{-1}

B. Assembling Resin 2.24

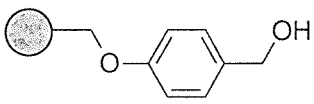
*Step 1: Resin-bound Methyl 4-Hydroxybenzoate **1.15***



To a solution of methyl 4-hydroxybenzoate (715 mg, 4.7 mmol) in DMF (4 mL) was added a 60% solution of sodium hydride in mineral oil (188 mg, 4.7 mmol). When the gas evolution stopped, Merrifield resin (2 g, 1.34 mmol Cl/g, 2.7 mmol) was added and the mixture was stirred at 80°C for 26 hours. The resin was collected by filtration, washed with DMF, dioxan, CH_2Cl_2, THF, CH_2Cl_2 (10 mL each) and dried *in vacuo* at 50°C for 5 hours.

IR (neat) ν_{max}: 3021, 2920, 1720 (s), 1600, 1510 (m), 1453 (m), 754 (m), 697 (s) cm^{-1}

*Step 2: Reduction (Resin **1.16**)*

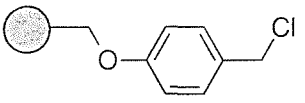


To a suspension of resin **1.15** (2 g, unknown loading) in THF (15 mL) was added methanol (1.1 mL, 27 mmol) and a 2.0M solution of lithium borohydride in THF (13.4 mL, 27 mmol).

The reaction mixture was stirred for 30 hours. The resin was collected by filtration, washed with H_2O, MeOH, CH_2Cl_2 (2x15 mL each) and dried *in vacuo* at 50°C for 5 hours.

IR (neat) ν_{max}: 3021, 2918, 1600, 1508 (m), 1453 (m), 1223 (m), 1008 (m), 896, 741 (m), 697 (s) cm^{-1}

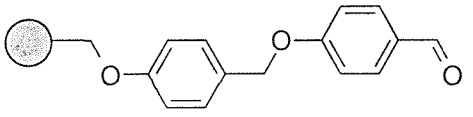
*Step 3: Chlorination (Resin **1.17**)*



To a suspension of resin **1.16** (2 g, unknown loading) in CH_2Cl_2 (10 mL) was added dropwise diisopropylethylamine (3.50 mL, 13.4 mmol) and mesyl chloride (1 mL, 13.4 mmol). The reaction mixture was stirred for 15 hours. Resin **1.17** was collected by filtration, washed with H_2O, MeOH, CH_2Cl_2 (2x20 mL each) and dried *in vacuo* at 50°C for 5 hours.

IR (neat) ν_{max}: 3022, 2925, 1601, 1512 (m), 1493, 1453 (m), 1242 (m), 1174, 757 (m), 697 (s) cm^{-1}

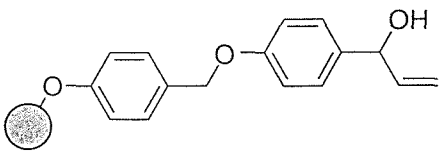
*Step 4: Nucleophilic Substitution (Resin **1.18**)*



To a suspension of resin bound chloride **1.17** (2 g, unknown loading) in DMF (10 mL) was added a solution of 4-hydroxybenzaldehyde (1.5 g, 10 mmol) and a 60% solution of sodium hydride in mineral oil (400 mg, 10 mmol) in DMF (5 mL). The reaction mixture was heated at 80°C for 28 hours. Resin **1.18** was collected by filtration, washed with H_2O, MeOH, CH_2Cl_2 (2x20 mL each) and dried *in vacuo* at 50°C for 5 hours.

IR (neat) ν_{max}: 3027, 2922, 1733 (m), 1601, 1493, 1452 (m), 757 (m), 697 (s) cm^{-1}

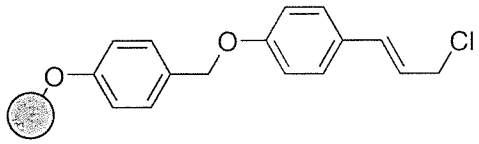
*Step 5: Grignard Reaction (Resin **1.19**)*



To a suspension of aldehyde resin **1.18** (2 g, unknown loading) in THF (10 mL) was added dropwise a 1.0M solution of allylmagnesium bromide in THF (14 mL, 14 mmol) at -78°C. The reaction was stirred at -78°C for 10 minutes, allowed to warm to room temperature and stirred for another 30 minutes. Resin **1.19** was collected by filtration, washed with H_2O, THF, CH_2Cl_2 (2x20 mL each) and dried *in vacuo* at 50°C for 5 hours.

IR (neat) ν_{max}: 3337 (br), 3027, 2922, 1602, 1510 (s), 1493 (s), 1452 (s), 1222 (m), 1173 (m), 699 (s) cm^{-1}

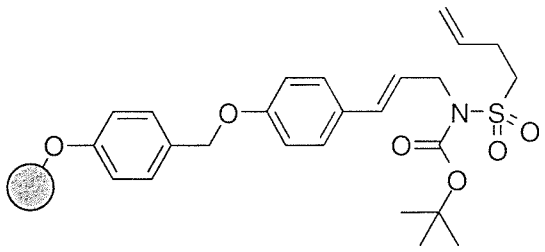
*Step 6: Chlorination (Resin **1.20**)*



To a suspension of resin **1.19** (2 g, unknown loading) in DMF (10 mL) was added diisopropyl ethylamine (1.9 mL, 11 mmol). After 5 minutes, methanesulfonyl chloride (0.7 mL, 8 mmol) was added dropwise over 1 minute. The mixture was stirred at room temperature for 15 hours. Resin **1.20** was collected by filtration, washed with water, MeOH, THF, CH_2Cl_2 (15 mL each) and dried *in vacuo* at 50°C for 5 hours.

IR (neat) ν_{max}: 3024, 2923, 1605, 1511 (s), 1493, 1452 (m), 1222 (s), 762 (m), 698 (s) cm^{-1}

*Step 7: Nucleophilic Substitution (Resin **2.24**)*

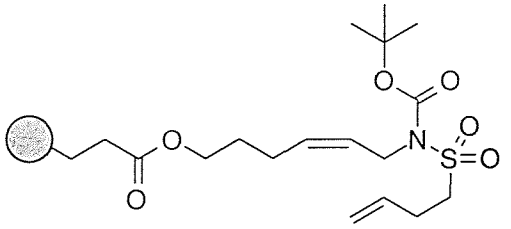


To a suspension of potassium carbonate (1.8 g, 13 mmol) in DMF (10 mL) was added sulfonyl carbamate **2.18** (3 g, 13 mmol). The mixture was stirred for 10 minutes and transferred *via* a cannula to a suspension of resin **1.20** (2 g, unknown loading) in DMF (10 mL). The mixture was heated at 60°C overnight. Resin **2.24** was collected by filtration, washed with DMF, water, MeOH, DMF, CH_2Cl_2 (15 mL each) and dried *in vacuo* at 50°C for 5 hours.

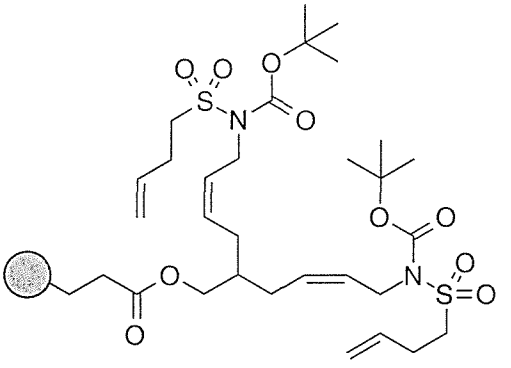
IR (neat) ν_{max}: 3026, 2923, 1673 (s), 1603, 1510 (s), 1493, 1452, 1383 (s), 1225, 1173 (s), 1089, 697 (s) cm^{-1}

C. General Procedure to the N*-Functionalised Carboxyethyl Resins 3.20, 3.21 and 4.18-4.23*

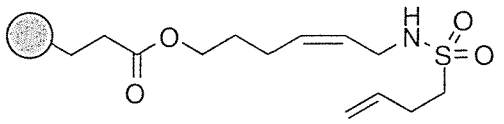
Method A (direct coupling of the sulfonamides synthesised in the solution-phase): To a suspension of carboxyethyl resin **3.2** (200 mg, 1.0 mmol OH/g, 0.2 mmol) in CH_2Cl_2 (4 mL) were added diisopropylcarbimide (100 μL, 0.6 mmol), 4-dimethylaminopyridine (74 mg, 0.6 mmol) and alcohol **3.19**, **3.14** and **4.12-4.17** (respectively 200 mg, 372 mg, 140 mg, 252 mg, 148 mg, 269 mg, 194 mg and 360 mg, 0.6 mmol). The mixture was stirred for 15 hours. The resin was collected by filtration, washed three times with CH_2Cl_2 (10 mL) and dried *in vacuo* at 50°C for 5 hours.



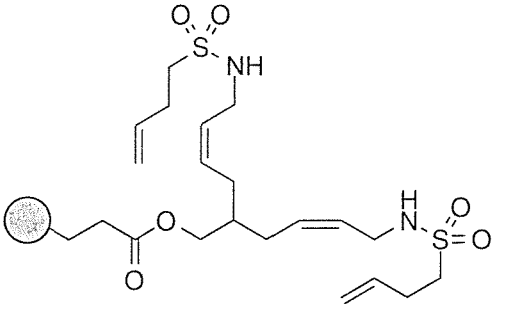
Loading (combustion analysis): 0.72 mmol S/g; (reductive cleavage): 0.73 mmol S/g
IR (neat) ν_{max}: 2922, 1727 (s), 1602, 1492, 1450 (m), 1360 (s), 1147 (s), 912, 755 (m), 697 (s) cm^{-1}



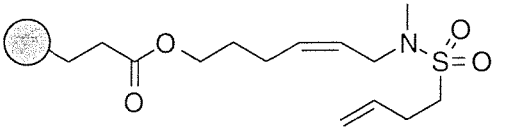
Loading (combustion analysis): 0.58 mmol S/g; (reductive cleavage): 0.55 mmol S/g
IR (neat) ν_{max}: 2922, 1730 (s), 1602, 1492, 1450 (m), 1362 (s), 1147 (s), 909, 755 (m), 697 (s) cm^{-1}



IR (neat) ν_{max}: 2919, 1727 (s), 1645, 1601, 1492, 1448 (m), 1332 (s), 1143 (s), 697 (s) cm^{-1}

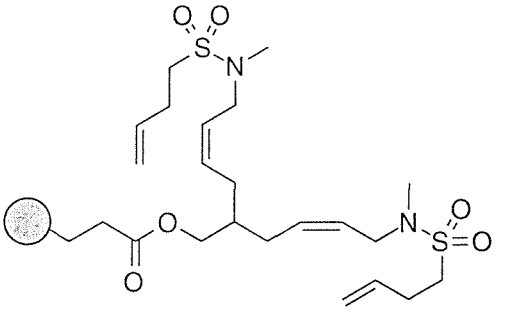


IR (neat) ν_{max}: 2919, 1727 (s), 1645, 1601, 1492, 1447 (m), 1314 (s), 1140 (s), 697 (s) cm^{-1}



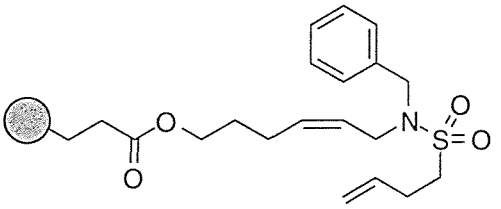
Loading (combustion analysis): 0.97 mmol S/g

IR (neat) ν_{max}: 2920, 1728 (s), 1601, 1492, 1449 (m), 1333 (s), 1148 (s), 993, 916, 757 (m), 697 (s) cm^{-1}



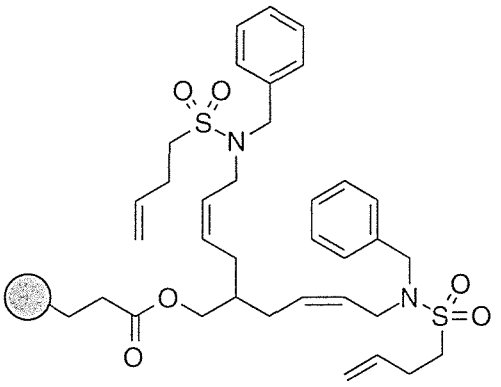
Loading (combustion analysis): 0.80 mmol S/g; (reductive cleavage): 0.69 mmol S/g

IR (neat) ν_{max}: 2920, 1728 (s), 1601, 1492, 1449 (m), 1331 (s), 1137 (s), 994, 917, 797 (m), 698 (s) cm^{-1}



Loading (combustion analysis): 1.00 mmol S/g

IR (neat) ν_{max}: 2920, 1728 (s), 1602, 1492, 1449 (m), 1334 (s), 1140 (s), 918 (m), 756, 697 (s) cm^{-1}



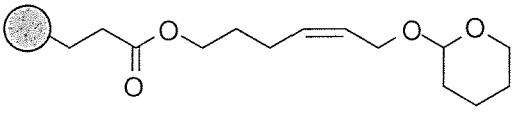
Loading (combustion analysis): 0.64 mmol S/g

IR (neat) ν_{max}: 2920, 1728 (s), 1602, 1492, 1450 (m), 1334 (s), 1140 (s), 919 (m), 756, 697 (s) cm^{-1}

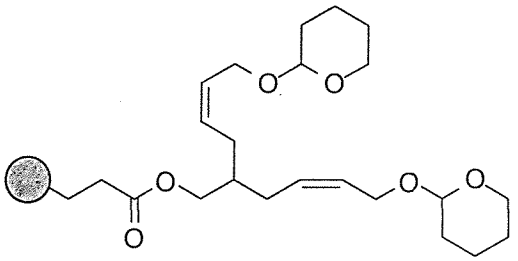
Method B (by assembling stepwise the different building blocks on the solid-phase):

*Step 1: Coupling Reaction (Resins **3.23** and **3.24**)*

Carboxyethyl resin **3.2** (750 mg, 1.0 mmol OH/g, 0.75 mmol) was swollen in CH_2Cl_2 (5 mL). Alcohol **3.22** or **3.10** (respectively 450 mg and 797 mg, 2.25 mmol), DIC (350 µL, 2.25 mmol) and 4-dimethylaminopyridine (280 mg, 2.25 mmol) were added. The reaction was stirred at room temperature for 15 hours. The resin was collected by filtration, washed three times with CH_2Cl_2 (10 mL) and dried *in vacuo* at 50°C for 5 hours.



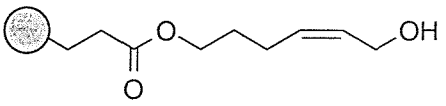
IR (neat) ν_{max}: 2920, 1731 (s), 1601, 1492, 1450 (m), 1023 (m), 697 (s) cm^{-1}



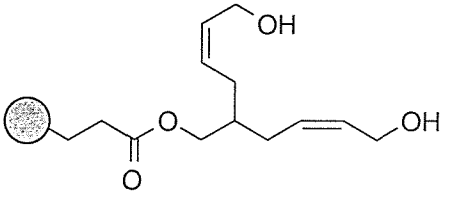
IR (neat) ν_{max}: 2926, 1731 (s), 1601, 1493, 1452 (m), 1023 (m), 697 (s) cm^{-1}

*Step 2: THP Deprotection (Resins **3.25** and **3.26**)*

To a suspension of the THP-protected resins **3.23** and **3.24** (740 mg, unknown loading) swollen in a 5:1 (v/v) mixture of DME and MeOH (6 mL) was added 4-toluenesulfonic acid (250 mg, 1.5 mmol). The mixture was stirred at room temperature for 15 hours. The resin was collected by filtration, washed twice with MeOH and CH_2Cl_2 (10 mL each) and dried *in vacuo* at 50°C for 5 hours.



IR (neat) ν_{max}: 3335 (br), 2922, 1729 (s), 1602, 1492, 1449 (m), 1028 (m), 697 (s) cm^{-1}



IR (neat) ν_{max}: 3336 (br), 2920, 1730 (s), 1601, 1492, 1449 (m), 1026 (m), 697 (s) cm^{-1}

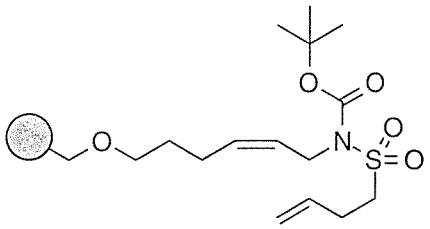
*Step 3: Mitsunobu Coupling (Resins **3.20** and **3.21**)*

To a suspension of the free hydroxy resins **3.25** and **3.26** (200 mg, unknown loading) swollen in THF (3 mL) was added triphenylphosphine (respectively 140 mg, 0.5 mmol and 280 mg, 1 mmol) and sulfonyl carbamate **2.18** (respectively 166 mg, 0.5 mmol and 235 mg, 1 mmol). Diethylazodicarboxylate (respectively 80 µL, 0.5 mmol and 160 µL, 1 mmol) was added dropwise. The mixture was stirred at room temperature 15 hours. The resin was collected by filtration, washed twice with MeOH and CH_2Cl_2 (10 mL each) and dried *in vacuo* at 50°C for 5 hours.

The IR data of resins **3.20** and **3.21** have already been disclosed above.

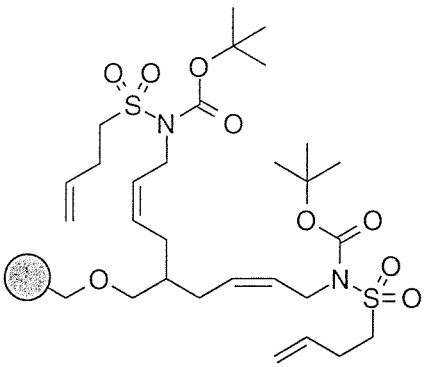
D. General Procedure to the N-*Functionalised Merrifield Resins 3.27, 3.28 and 4.26-4.38*

Method A (direct coupling of the sulfonamides synthesised in the solution-phase): To a solution of alcohols **3.14** and **3.19** (respectively 460 mg and 857 mg, 1.38 mmol) in DMF (10 mL) was added sodium hydride (60 mg, 1.5 mmol). When the gas evolution stopped, the solution was added dropwise to Merrifield resin (200 mg, loading 2.3 mmol Cl/g, 0.5 mmol) swollen in THF (5 mL). The reaction mixture was stirred at 60 °C for 15 hours. Excess sodium hydride was carefully quenched with water. The resin was collected by filtration and thoroughly washed with DMF, H_2O, DMF, CH_2Cl_2 (10 mL each). The resin was then dried *in vacuo* at 50°C for 5 hours.



Loading (combustion analysis): 0.88 mmol S/g

IR (neat) ν_{max}: 2921, 1723 (s), 1601, 1493, 1452 (m), 1358 (s), 1148 (s), 912, 850, 698 (s) cm^{-1}



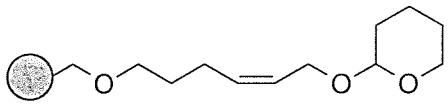
Loading (combustion analysis): 0.68 mmol S/g

IR (neat) ν_{max}: 2925, 1724 (s), 1602, 1492, 1450 (m), 1358 (s), 1145 (s), 910, 847 cm^{-1}

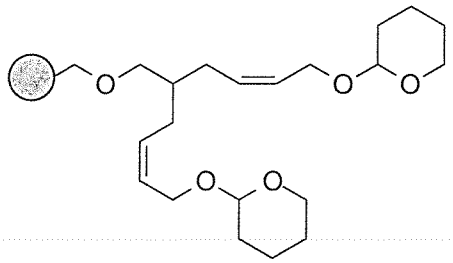
Method B (by stepwise assembling the different building blocks on the solid-phase):

*Step 1: Coupling Reaction (Resins **3.29** and **3.30**)*

To a solution of alcohols **3.22** and **3.10** (respectively 280 mg and 490 mg, 1.38 mmol) in DMF (10 mL) was added sodium hydride (60 mg, 1.5 mmol). When the gas evolution stopped, the solution was added dropwise to Merrifield resin (200 mg, loading 2.3 mmol Cl/g, 0.5 mmol) swollen in THF (5 mL). The reaction mixture was stirred at 60 °C for 15 hours. Excess sodium hydride was carefully quenched with water. The resin was collected by filtration and thoroughly washed with DMF, H_2O, DMF, CH_2Cl_2 (10 mL each). The resin was then dried *in vacuo* at 50°C for 5 hours.



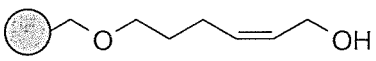
IR(neat) ν_{max}: 2921, 1601, 1493, 1451 (m), 1023 (m), 904, 756, 697 (s) cm^{-1}



IR (neat) ν_{max}: 2921, 1601, 1492, 1450 (m), 1021 (m), 904, 756, 697 (s) cm^{-1}

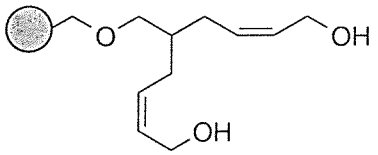
*Step 2: THP Deprotection (Resins **3.31** and **3.32**)*

To a suspension of the THP-protected resin **3.29** or **3.30** (respectively 300 mg and 325 mg, unknown loading) in MeOH (respectively 5 mL and 10 mL) was added *p*TSA (respectively 180 mg, 0.95 mmol and 360 mg, 1.9 mmol). The mixture was stirred at room temperature for 15 hours. The resin was collected by filtration, washed with CH_2Cl_2, MeOH, CH_2Cl_2 (10 mL each) and dried *in vacuo* at 50°C for 5 hours.



Loading (transesterification): 1.02 mmol OH/g

IR (neat) ν_{max}: 3340 (br), 2920, 1601, 1492, 1451 (m), 1031 (m), 1010 (m), 752, 697 (s) cm^{-1}



Loading (transesterification): 0.97 mmol OH/g

IR (neat) ν_{max}: 3334 (br), 2920, 1601, 1492, 1449 (m), 1026 (m), 754, 697 (s) cm^{-1}

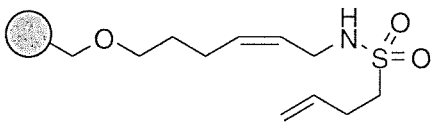
*Step 3: Mitsunobu Reaction (Resins **3.27** and **3.28**)*

To a suspension of the free hydroxy resin **3.31** or **3.32** (150 mg, respectively 1.02 mmol OH/g and 0.97 mmol OH/g, 0.15 mmol and 0.14 mmol) swollen in THF (5 mL) was added triphenylphosphine (165 mg, 0.6 mmol) and sulfonyl carbamate **2.18** (150 mg, 0.6 mmol). Diethylazodicarboxylate (0.1 mL, 0.6 mmol) was added dropwise. The mixture was stirred at room temperature for 15 hours. The resin was collected by filtration, washed three times with CH_2Cl_2 (10 mL) and dried *in vacuo* at 50°C for 5 hours.

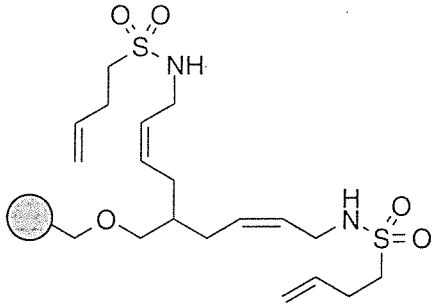
The IR data of resins **3.27** and **3.28** have already been disclosed above.

*Step 4: Boc Deprotection (Resins **4.26** and **4.27**)*

To a suspension of resins **3.27** and **3.28** (150 mg, unknown loading) swollen in CH_2Cl_2 (2 mL) was added a 50% solution of trifluoroacetic acid in CH_2Cl_2 (5mL). The mixture was stirred at room temperature for 30 minutes. The resin was collected by filtration, washed twice with H_2O, Et_3N and CH_2Cl_2 (5 mL each) and dried *in vacuo* at 50°C for 5 hours.



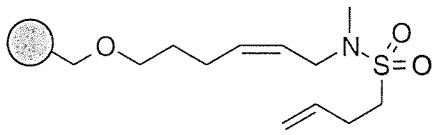
IR (neat) ν_{max}: 2915, 1601, 1492, 1449 (m), 1321 (s), 1218 (m), 1143 (s), 907 (m), 697 (s) cm^{-1}



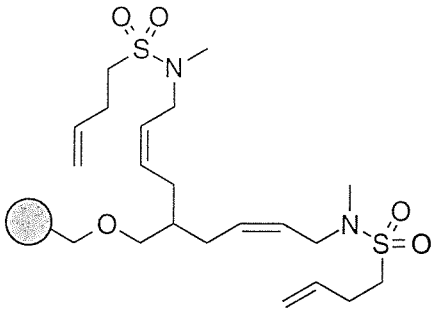
IR (neat) ν_{max}: 2914, 1601, 1492, 1450 (m), 1321 (s), 1216 (m), 1141 (s), 907 (m), 696 (s) cm^{-1}

*Step 5: Alkylation (Resins **4.28-4.36**)*

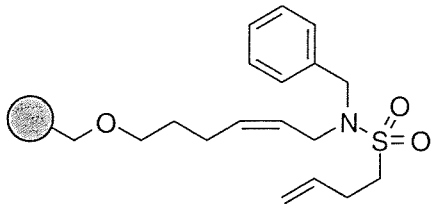
Resins **4.26** and **4.27** (150 mg, unknown loading) was swollen in THF (5 mL). Potassium *tert*-butoxide (167 mg, 1.5 mmol) was added followed by methyl iodide, benzyl bromide, 2,5-dimethylbenzyl chloride or 2-bromobenzyl bromide (respectively 90 µL, 180 µL, 220 µL or 375 mg, 1.5 mmol). The reaction mixture was stirred at room temperature for 15 hours. The resin was collected by filtration, washed three times with CH_2Cl_2 (10 mL) and dried *in vacuo* at 50°C for 5 hours.



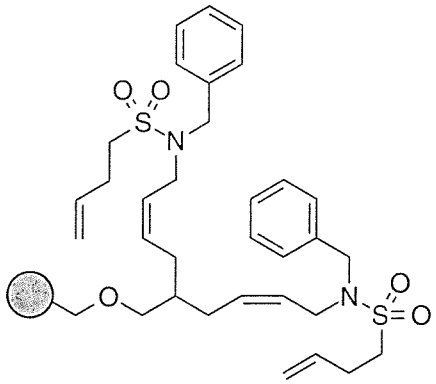
IR (neat) ν_{max}: 2918, 1601, 1492, 1449 (m), 1321 (s), 1139 (s), 915 (m), 755, 696 (s) cm^{-1}



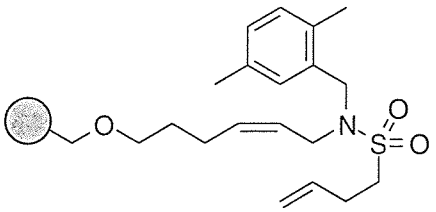
IR (neat) ν_{max}: 2916, 1601, 1492, 1449 (m), 1320 (s), 1137 (s), 915 (m), 755, 697 (s) cm^{-1}



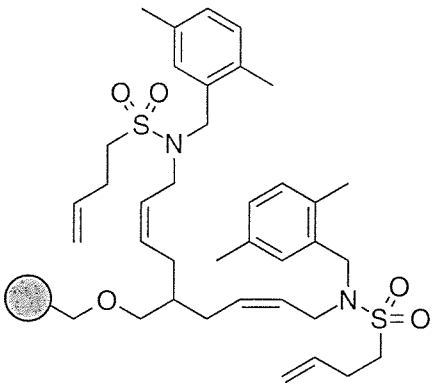
IR (neat) ν_{max}: 2918, 1600, 1492, 1450 (m), 1328 (s), 1141 (s), 754, 696 (s) cm^{-1}



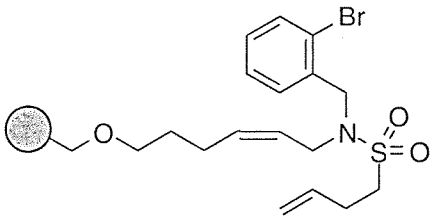
IR (neat) ν_{max}: 2920, 1600, 1492, 1450 (m), 1337 (s), 1141 (s), 742, 697 (s) cm^{-1}



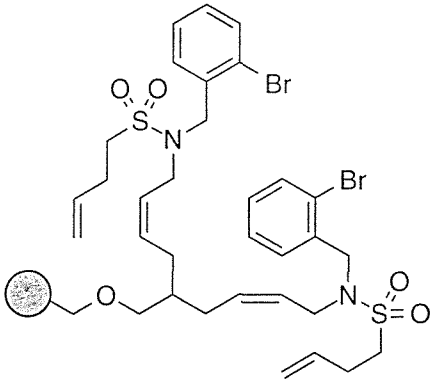
IR (neat) ν_{max}: 2915, 1603, 1492, 1449 (m), 1319 (s), 1141 (s), 912 (m), 697 (s) cm^{-1}



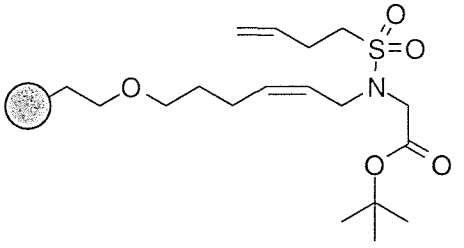
IR (neat) ν_{max}: 2908, 1602, 1492, 1450 (m), 1327 (s), 1140 (s), 910 (m), 697 (s) cm^{-1}



IR (neat) ν_{max}: 2922, 1601, 1493, 1446 (m), 1321 (s), 1140 (s), 1026, 911 (m), 697 (s) cm^{-1}



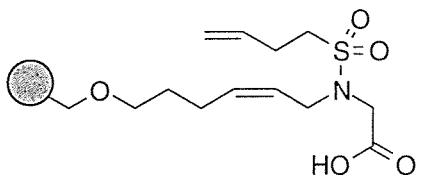
IR (neat) ν_{max}: 2922, 1601, 1492, 1448 (m), 1318 (s), 1140 (s), 1026, 910 (m), 697 (s) cm^{-1}



IR (neat) ν_{max}: 2915, 1735 (s), 1601, 1492, 1450 (m), 1338 (s), 1230 (m), 1140 (s), 912, 750, 697 (s) cm^{-1}

Step 6: Removal of tert-*Butyl Ester (Resin* ***4.37****)*

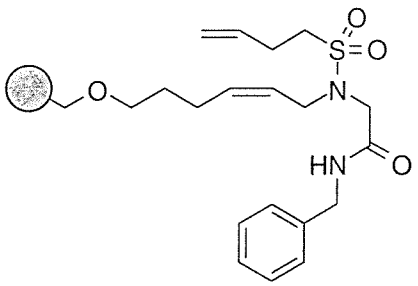
To a suspension of resin-bound *tert*-butyl ester **4.36** (150 mg, unknown loading) swollen in CH_2Cl_2 (2 mL) was added a 50% solution of trifluoroacetic acid in CH_2Cl_2 (5mL). The mixture was stirred at room temperature for 3 hours. The resin was collected by filtration, washed twice with CH_2Cl, Et_3N and CH_2Cl_2 (5 mL each) and dried *in vacuo* at 50°C for 5 hours.



IR (neat) ν_{max}: 2907, 1727 (s), 1600, 1492, 1449 (m), 1337 (s), 1216, 1141 (s), 920, 697 (s) cm^{-1}

*Step 7: DIC Coupling (Resin **4.38**)*

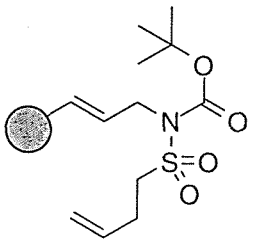
Benzylamine (186 µL, 1.7 mmol) was added to a suspension of resin **4.37** (160 mg, unknown loading) in THF (5 mL) in the presence of 4-dimethylaminopyridine (200 mg, 1.7 mmol). DIC (260 µL, 1.7 mmol) was then added dropwise. The reaction mixture was left to react at room temperature for 15 hours. The resin was collected by filtration, washed twice with CH_2Cl_2 (10 mL) and dried *in vacuo* at 50°C for 5 hours.



IR (neat) ν_{max}: 2918, 1673 (s), 1602, 1492, 1450 (m), 1324 (s), 1141 (s), 1078 (m), 697 (s) cm^{-1}

E. Preparation of Resin 3.38

Resin **3.3** (250 mg, loading 2.0 mmol OH/g, 0.5 mmol) was suspended in THF (10 mL). Triphenyl phosphine (1.31 g, 5 mmol) and sulfamide **2.18** (1.17 g, 5 mmol) were added. Diethylazodicarboxylate (0.8 mL, 5 mmol) was then added dropwise and the reaction mixture was stirred at room temperature for 15 hours. The resin was collected by filtration and washed three times with CH_2Cl_2 (20 mL). The resin was dried in the oven at 40°C *in vacuo*. The coupling was repeated a second time under the same conditions.

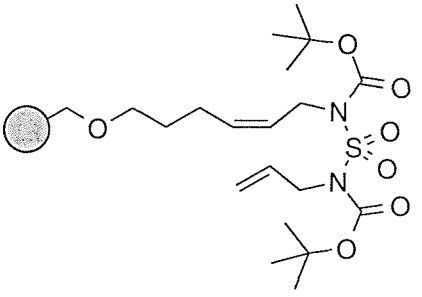


IR (neat) ν_{max}: 2919, 1726 (s), 1600, 1492, 1450 (m), 1356 (s), 1143 (s), 963 (m), 753, 696 (s) cm^{-1}

F. General Procedure for the Preparation of Resin-bound Sulfamides 5.28-5.30

Step 1: Mitsunobu Coupling (Resin 5.28)

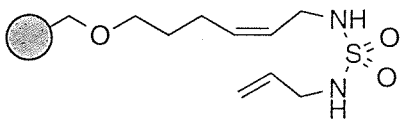
Resin **3.31** (250 mg, loading 1.02 mmol OH/g, 0.25 mmol) was suspended in THF (2 mL). Triphenyl phosphine (131 mg, 0.5 mmol) and sulfamide **5.26** (170 mg, 0.5 mmol) were added. Diethylazodicarboxylate (80 µL, 0.5 mmol) was then added dropwise and the reaction mixture was stirred at room temperature for 15 hours. The resin was collected by filtration and washed three times with CH_2Cl_2 (20 mL). The resin was dried in the oven at 40°C *in vacuo*. The coupling was repeated a second time under the same conditions.



IR (neat) ν_{max}: 2928, 1737 (s), 1601, 1492, 1453 (m), 1388 (s), 1369 (s), 1316 (m), 1249 (m), 1148 (s), 923, 847, 809 (m), 759 (m), 697 (s) cm^{-1}

Step 2: Deprotection (Resin 5.29)

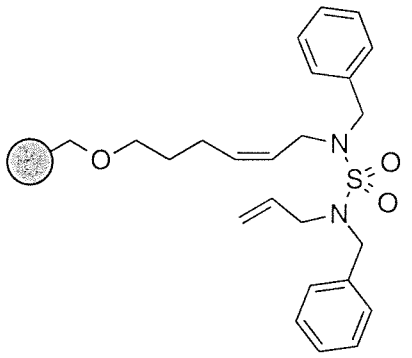
To a suspension of resins **5.28** (150 mg, unknown loading) swollen in CH_2Cl_2 (2 mL) was added a 50% solution of trifluoroacetic acid in CH_2Cl_2 (5mL). The mixture was stirred at room temperature for 30 minutes. The resin was collected by filtration, washed twice with H_2O, Et_3N and CH_2Cl_2 (5 mL each) and dried *in vacuo* at 50°C for 5 hours.



IR (neat) ν_{max}: 2952, 1600, 1492, 1451 (m), 1323 (s), 1144 (s), 857, 734 (m), 696 (s) cm^{-1}

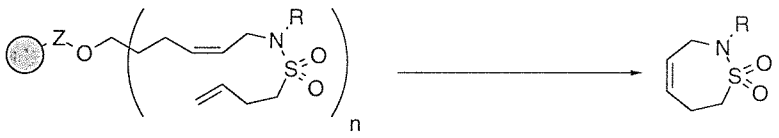
*Step 3: Alkylation (Resin **5.30**)*

Resins **5.29** (100 mg, unknown loading) was swollen in THF (5 mL). Potassium *tert*-butoxide (167 mg, 1.5 mmol) was added followed by benzyl bromide (180 μL, 1.5 mmol). The reaction mixture was stirred at room temperature for 15 hours. The resin was collected by filtration, washed three times with CH_2Cl_2 (10 mL) and dried *in vacuo* at 50°C for 5 hours.



IR (neat) ν_{max}: 2919, 1600, 1492, 1450 (m), 1343 (s), 1322 (m), 1146 (s), 1077, 1026, 888, 754 (m), 696 (s) cm^{-1}

G. General Procedure for the Solid-phase RCM Cyclisation Cleavage to Cyclic Sulfonamides



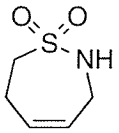
Z = CH_2 or CH_2CH_2CO
n = 1 or 2

To a suspension of resin (100-300 mg, 0.5-1 mmol S/g) in CH_2Cl_2 was added bis (tricyclohexylphosphine)benzylidene ruthenium (IV) dichloride (1, 2.5, 10 or 50 mol% accordingly). The reaction mixture was heated to reflux for 15 hours. The resin was collected by filtration, washed twice with CH_2Cl_2 (5 mL). The filtrates were purified through a short pad of silica eluting with ether. The filtrates were then concentrated *in vacuo* and purified by flash chromatography through a short column of silca (1x3 cm) elutiung with hexane to

hexane/ether (1:1) to give the cyclic sulfonamides as a white solid or a colourless oil accordingly (20-50 mg, 1-5 mmol, 10-100%).

Note: the spectroscopic data for sulfonamides **2.17** (R = Boc) and **2.8** (R = Bn) was already given among the solution-phase experimentals (Procedures lii and liii).

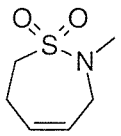
i. 2,3,6,7-Tetrahydro-1*H*-1λ^6,2-thiazepine-1,1-dione 4.24



$C_5H_9NO_2S$
m.w.= 147.20 g/mol
White solid; m.p.= 66-67°C

- Rf (D): 0.21
- **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 6.09-5.96 (m, 2H, CH=CH), 4.58 (brs, 1H, NH), 3.67 (dd, 2H, *J* = 6.6, 5.15, **CH_2**NH), 3.16-3.12 (m, 2H, CH_2SO_2), 2.58-2.53 (m, 2H, **CH_2**CH_2SO_2)
- **^{13}C NMR** (75 MHz, $CDCl_3$) δ: 132.6 (**C**H=CH), 132.3 (CH=**C**H), 52.7 (CH_2), 42.0 (CH_2), 22.1 (**CH_2**CH_2SO_2)
- **IR** (neat) ν_{max}: 3274 (NH), 2930, 1455, 1412 (m), 1316 (s, SO_2), 1284 (s), 1241, 1202 (m), 1158 (m), 1135 (s, SO_2), 1227 (s), 1068 (m), 1037 (m), 995, 937, 896 cm^{-1}
- $C_5H_9NO_2S$ requires (%) C: 40.80; H: 6.16; N: 9.52. Found C: 41.01; H: 6.35; N: 9.01

ii. 2-Methyl-2,3,6,7-tetrahydro-1*H*-1λ^6,2-thiazepine-1,1-dione 4.25

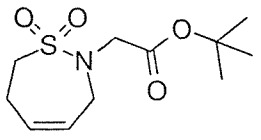


$C_6H_{11}NO_2S$
m.w.= 161.22 g/mol
Colourless oil

- Rf (D): 0.33
- **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 6.17-6.08 (m, 1H, **C**H=CH), 5.95 (dt, 1H, *J* = 11.8, 5.9, CH=**C**H), 3.80 (d, 2H, *J* = 6.6, **CH_2**NMe), 3.04-2.99 (m, 2H, CH_2SO_2), 2.77 (s, 3H, NCH_3), 2.56-2.50 (m, 2H, **CH_2**CH_2SO_2)
- **^{13}C NMR** (75 MHz, $CDCl_3$) δ: 133.5 (CH), 130.1 (CH), 47.0 (CH_2), 46.4 (CH_2), 35.1 (NCH_3), 22.2 (**CH_2**CH_2SO_2)
- **IR** (neat) ν_{max}: 2954 (s), 1471 (m), 1382 (m), 1346 (s), 1332 (s, SO_2), 1294 (m), 1209, 1158 (s), 1139 (s, SO_2), 1117, 1096, 980 cm^{-1}
- **MS** (APCI) m/z (rel. intensity): 162 ([M+H]$^+$, 100)
- **HRMS** (EI) m/z : 161.05032. $C_6H_{11}NO_2S$ requires 161.05105

- **GC** (temperature program A): 11.8 min

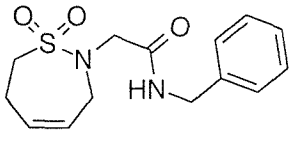
iii. *tert*-Butyl 2-(1,1-dioxo-2,3,6,7-tetrahydro-1*H*-1λ^6,2-thiazepin-2-yl) acetate 4.39



$C_{11}H_{19}NO_4S$
m.w.= 261.33 g/mol
Colourless oil

- Rf (B): 0.25
- **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 6.11 (dt, 1H, *J* = 11.0, 6.6, C**H**=CH), 5.95 (dt, 1H, *J* = 11.0, 5.1, CH=C**H**), 3.92 (d, 2H, *J* = 5.9, C**H$_2$**NCH$_2$CO$_2$^{t}Bu), 3.80 (s, 2H, NC**H$_2$**CO$_2$^{t}Bu), 3.13-3.09 (m, 2H, CH$_2$SO$_2$), 2.59-2.53 (m, 2H, C**H$_2$**CH$_2$SO$_2$), 1.48 (s, 9H, C(C**H$_3$**)$_3$)
- **^{13}C NMR** (75 MHz, $CDCl_3$) δ: 133.7 (**C**H=CH), 130.1 (CH=**C**H), 82.4 (O**C**(CH$_3$)$_3$), 50.5 (CH$_2$), 49.5 (CH$_2$), 44.4 (CH$_2$), 28.2 (C(**C**H$_3$)$_3$), 22.3 (**C**H$_2$CH$_2$SO$_2$)
- **IR** (neat) ν_{max}: 2977, 1744 (s, CO), 1455, 1368 (m), 1348 (s), 1331 (s, SO$_2$), 1296, 1228 (m), 1137 (s, SO$_2$), 1094, 1012, 950, 913, 802 cm^{-1}
- **MS** (EI) m/z (rel. intensity): 279 ([M+NH$_4$]$^+$, 12)
- **HRMS** (CI) m/z : 284.093042. $C_{11}H_{19}NO_4SNa$ requires 284.092699

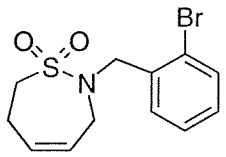
iv. *N*1-Benzyl-2-(1,1-dioxo-2,3,6,7-tetrahydro-1*H*-1λ^6,2-thiazepin-2-yl) acetamide 4.40



$C_{14}H_{18}N_2O_3S$
m.w.= 294.37 g/mol
Colourless oil

- Rf (C): 0.05
- **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 7.34-7.21 (m, 5H, C$_6$H$_5$), 6.93 (brs, 1H, NH), 6.09 (dt, 1H, *J* = 13.2, 5.9, C**H**=CH), 5.94 (dt, 1H, *J* = 11.0, 5.5, CH=C**H**), 4.43 (d, 2H, *J* = 5.8, NC**H$_2$**Ph), 3.73 (d, 2H, *J* = 6.0, C**H$_2$**NBn), 3.68 (s, 2H, NC**H$_2$**CONH), 3.03-2.98 (m, 2H, CH$_2$SO$_2$), 2.54-2.43 (m, 2H, C**H$_2$**CH$_2$SO$_2$)
- **^{13}C NMR** (75 MHz, $CDCl_3$) δ: 171.8 (CO), 137.8 (C), 134.4 (CH), 129.8 (CH), 128.5 (CH), 127.8 (CH), 51.0 (CH$_2$), 49.5 (CH$_2$), 44.9 (CH$_2$), 43.6 (CH$_2$), 22.1 (**C**H$_2$CH$_2$SO$_2$)
- **IR** (neat) ν_{max}: 3251 (br, NH), 2933, 1650 (s, CO), 1531 (m), 1454, 1427, 1325 (s, SO$_2$), 1297, 1226, 1158 (s), 1138 (s, SO$_2$), 1097, 1021, 920 (m) cm^{-1}
- **MS** (EI) m/z (rel. intensity): 295 ([M+H]$^+$, 17)
- $C_{14}H_{18}N_2O_3S$ requires (%) C: 57.12; H: 6.16; N: 9.51. Found C: 56.92; H: 6.28; N: 9.19

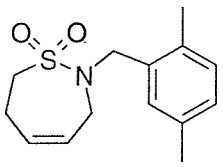
v. 2-(2-Bromobenzyl)-2,3,6,7-tetrahydro-1*H*-1λ^6,2-thiazepine-1,1-dione 4.41



$C_{12}H_{14}BrNO_2S$
m.w.= 316.21 g/mol
White solid; m.p.= 96-97°C

- Rf (D): 0.59, (B): 0.26
- **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 7.57 (t fs, 2H, *J* = 8.1, $C_6\mathbf{H}_2H_2$), 7.36 (t fs, 1H, *J* = 7.4, $C_6\mathbf{H}H_3$), 7.18 (t fs, 1H, *J* = 8.1, $C_6\mathbf{H}H_3$), 6.18 (dt, 1H, *J* = 13.2, 6.6, **CH**=CH), 6.00 (dt, 1H, *J* = 11.0, 5.9, CH=C**H**), 4.39 (s, 2H, NC$\mathbf{H}_2$Ph), 3.69 (d, 2H, *J* = 5.9, C$\mathbf{H}_2$NAr), 3.18-3.14 (m, 2H, CH_2SO_2), 2.64-2.58 (m, 2H, C$\mathbf{H}_2$CH_2SO_2)
- **^{13}C NMR** (75 MHz, $CDCl_3$) δ: 135.3 (C), 133.7 (CH), 133.0 (CH), 130.8 (CH), 130.3 (CH), 129.5 (CH), 128.1 (CH), 123.6 (C), 50.3 (CH_2), 49.8 (CH_2), 42.8 (CH_2), 22.3 ($CH_2CH_2SO_2$)
- **IR** (neat) ν_{max}: 2931, 1440 (m), 1350 (s), 1331 (s, SO_2), 1297, 1241, 1209 (m), 1155 (s), 1139 (s, SO_2), 1025 (m), 913 (m), 791 cm^{-1}
- **MS** (APCI) m/z (rel. intensity): 318 (50), 316 (M^+, 100), 314 (50)
- $C_{12}H_{14}BrNO_2S$ requires (%) C: 45.58; H: 4.46; N: 4.43. Found C: 45.67; H: 4.39; N: 4.24

iv. 2-(2,5-Dimethylbenzyl)-2,3,6,7-tetrahydro-1*H*-1λ^6,2-thiazepine-1,1-dione 4.42

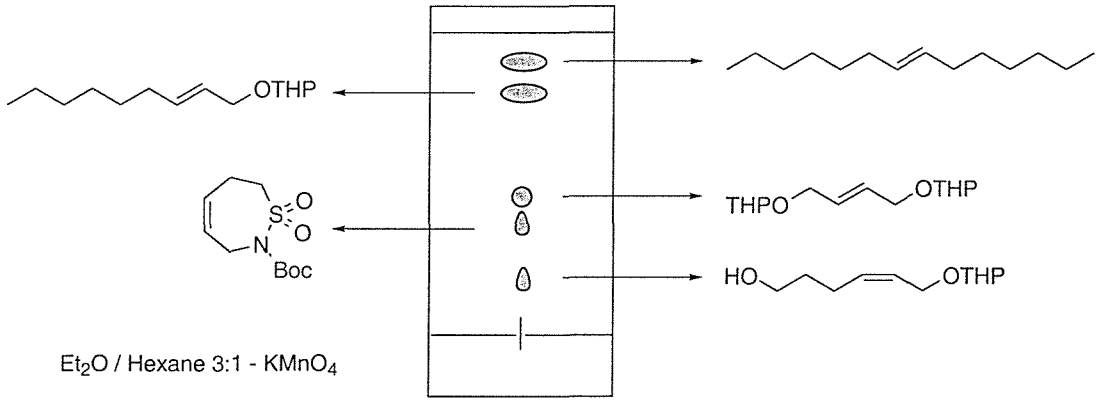


$C_{14}H_{19}NO_2S$
m.w.= 265.37 g/mol
White solid; m.p.= 118°C

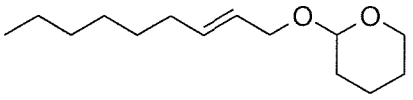
- Rf (D): 0.55, (B): 0.20
- **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 7.11-7.04 (m, 3H, C_6H_3), 6.19 (dt, 1H, *J* = 13.2, 6.6, CH=CH), 5.88 (dt, 1H, *J* = 11.0, 5.9, CH=C**H**), 4.22 (s, 2H, NC$\mathbf{H}_2$Ph), 3.58 (d, 2H, *J* = 6.6, CH_2NBn), 3.15-3.12 (m, 2H, CH_2SO_2), 2.62-2.56 (m, 2H, C$\mathbf{H}_2$CH_2SO_2), 2.35 (s, 3H, CH_3), 2.33 (s, 3H, CH_3)
- **^{13}C NMR** (75 MHz, $CDCl_3$) δ: 135.6 (C), 134.7 (C), 133.7 (CH), 132.7 (C), 130.9 (CH), 130.5 (CH), 129.0 (CH), 48.6 (CH_2), 48.5 (CH_2), 41.7 (CH_2), 22.2 ($\mathbf{CH}_2CH_2SO_2$), 20.9 (CH_3), 18.7 (CH_3)
- **IR** (neat) ν_{max}: 2959, 1348 (s), 1329 (s, SO_2), 1208 (m), 1158 (s), 1140 (s, SO_2), 1083 (m), 1028, 909 (m), 818, 797 cm^{-1}
- $C_{14}H_{19}NO_2S$ requires (%) C: 63.37; H: 7.22; N: 5.28. Found C: 63.31; H: 7.33; N: 5.21

H. Cross-coupling Reaction with 1-Octene

Resins **3.31** or **3.32** (100 mg, unknown loading) was suspended in CH_2Cl_2 (2 mL) and 1-octene (65 μL, 0.4 mmol) was added. The reaction mixture was refluxed for 9 hours. The resin was collected by filtration and washed three times with CH_2Cl_2 (20 mL). The filtrates were concentrated and analysed by ^{1}H-NMR and tlc for traces of **3.34**, their absence indicating the complete THP deprotection of resins **3.31** and **3.32**.



i. (*E*)-2-Nonenyl tetrahydro-2*H*-2-pyranyl ether 3.34



$C_{14}H_{26}O_2$
m.w.= 226.36 g/mol
Colourless oil

- Rf(A): 0.27, (B): 0.59, (D): 0.72
- **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 5.72 (dt, 1H, *J* = 15.4, 6.6, CH), 5.62-5.51 (m, 1H, CH), 4.64 (t, 1H, *J* = 3.2, OCHO), 4.25-4.16 (m, 1H, C**H**HO), 3.97-3.84 (m, 2H, CH**H**O & C**H**HO), 3.56-3.46 (m, 1H, CH**H**O), 2.50 (q, 2H, *J* = 6.6, C**H**$_2$CH=CH), 1.90-1.26 (m, 14H, C**H**$_2$C**H**$_2$C**H**$_2$C**H**$_2$CH$_3$ & CH$_2$CH$_2$CH$_2$), 0.89 (t, 3H, *J* = 7.0, CH$_3$)
- **^{13}C NMR** (75 MHz, $CDCl_3$) δ: 135.1 (CH), 126.1 (CH), 97.8 (OCHO), 68.0 (CH_2O), 62.4 (CH_2O), 32.5 (CH_2), 31.8 (CH_2), 30.8 (CH_2), 29.2 (CH_2), 29.0 (CH_2), 25.6 (CH_2), 22.8 (CH_2), 19.7 (CH_2), 14.2 (CH_3)
- **IR** (neat) ν_{max}: 2925 (s), 2854 (m), 1455, 1365 (m), 1201 (m), 1118 (m), 1078, 1024 (s), 968 (m), 905, 869, 816 cm^{-1}
- **MS** (CI) m/z (rel. intensity): 102 (25), 85 (100), 69 (34)

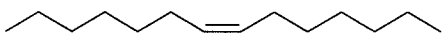
ii. 2-{[4-(Tetrahydro-2*H*-2-pyranyloxy)-2-butenyl]oxy}tetrahydro-2*H*-pyran 3.35 [18107-53-4]

$C_{14}H_{24}O_4$
m.w.= 256.34 g/mol
Colourless oil

The ^{1}H NMR spectrum was in good agreement with that reported in the literature.[210]

- Rf(B): 0.37, (D): 0.55
- **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 5.87 (t, 2H, *J* = 2.9, CH), 4.66 (t, 2H, *J* = 2.9, OCHO), 4.29-4.24 (m, 2H, CHHO), 4.01-3.97 (m, 2H, CHHO), 3.92-3.84 (m, 2H, CHHO), 3.55-3.48 (m, 2H, CHHO), 1.89-1.52 (m, 12H, $CH_2CH_2CH_2$)
- **^{13}C NMR** (75 MHz, $CDCl_3$) δ: 129.3 (CH), 98.1 (OCHO), 67.2 (CH_2O), 62.3 (CH_2O), 30.7 (CH_2), 25.6 (CH_2), 19.6 (CH_2)
- **IR** (neat) ν_{max}: 2940, 1365 (m), 1217 (m), 1134, 1025 (m), 818 cm^{-1}
- **MS** (EI) m/z (rel. intensity): 172 ([M-THP]$^+$, 32); (CI): 155 (15), 102 (14), 85 (100)

iii. 7-(*Z*)-Tetradecene 3.36 [10374-74-0]



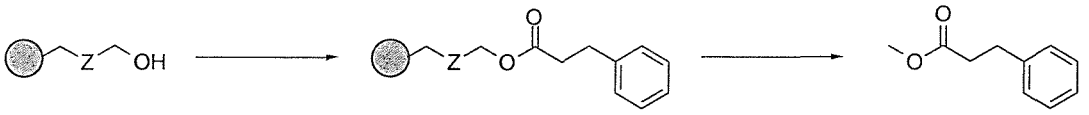
$C_{14}H_{28}$
m.w.= 196.37 g/mol
Colourless oil

The ^{1}H NMR and MS data were in good agreement with those reported in the literature.[167]

- Rf(A): 0.78, (D): 0.83
- **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 5.41-5.33 (m, 2H, CH=CH), 2.04-1.95 (m, 4H, CH_2CH=CH), 1.39-1.22 (m, 16H, $CH_2CH_2CH_2CH_2CH_3$), 0.89 (t, 6H, *J* = 6.6, CH_3)
- **^{13}C NMR** (75 MHz, $CDCl_3$) δ: 130.5 (CH), 32.8 (CH_2), 31.9 (CH_2), 29.8 (CH_2), 29.0 (CH_2), 22.8 (CH_2), 14.3 (CH_3)
- **IR** (neat) ν_{max}: 2956 (m), 2923 (s), 2854 (m), 1456 (m), 1377 (m), 1217, 965 (m), 722 cm^{-1}
- **MS** (CI) m/z (rel. intensity): 196 (M^+, 15), 97 (33), 83 (54), 69 (50), 55 (74)
- **GC** (temperature program A): 2.3 min

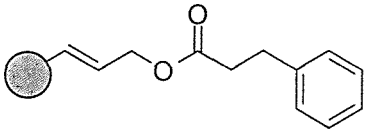
I. Loading Calculations by Esterification/Transesterification

i. Alcohol Resins 3.3, 3.26, 3.27, 3.32, and 3.33

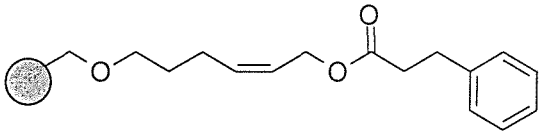


*Step 1: Esterification (Resin **6.12**)*

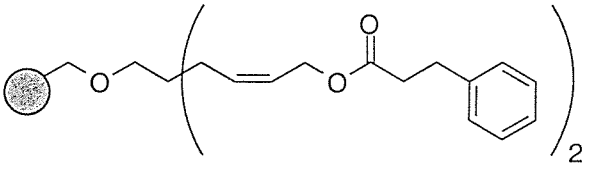
To a suspension of resin (100 mg, unknown loading) in CH_2Cl_2 (2 mL) was added diisopropylcarbamide (160 µL, 1 mmol), 4-dimethylaminopyridine (120 mg, 1 mmol) and dihydrocinnamic acid (150 mg, 1 mmol). The reaction mixture was stirred at room temperature for 15 hours. The resin was collected by filtration and washed three times with CH_2Cl_2 (10 mL). The resin was dried in the oven at 40°C *in vacuo*. The coupling was repeated a second time under the same conditions.



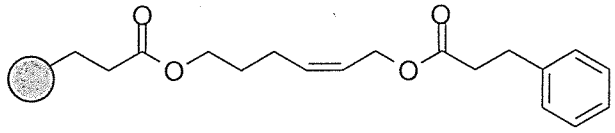
IR (neat) ν_{max}: 2920, 1732 (s), 1601, 1493, 1450 (m), 1148 (m), 1024, 750 (m), 697 (s) cm^{-1}



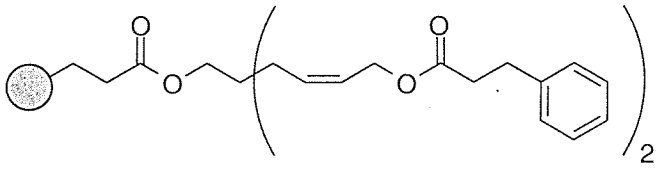
IR (neat) ν_{max}: 2916, 1732 (s), 1601, 1492, 1450 (m), 1365 (m), 1100, 1025, 905, 758 (m), 697 (s) cm^{-1}



IR (neat) ν_{max}: 2916, 1731 (s), 1600, 1492, 1451 (m), 1365 (m), 1025, 758 (m), 697 (s) cm^{-1}



IR (neat) ν_{max}: 2916, 1732 (s), 1601, 1492, 1450 (m), 1365 (m), 1100, 1025, 905, 758 (m), 697 (s) cm^{-1}

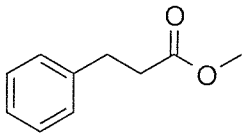


IR (neat) ν_{max}: 2916, 1731 (s), 1600, 1492, 1451 (m), 1365 (m), 1025, 758 (m), 697 (s) cm^{-1}

Step 2: Transesterification

A suspension of resin (100 mg, unknown loading) in a 9:1 (v/v) mixture of triethylamine and methanol (3mL) was heated at 50°C for 15 hours. The resin was collected by filtration and washed three times with CH_2Cl_2 (20 mL). The filtrates were concentrated and analysed by GC for the quantities of methyl 3-phenylpropanoate they contained.

Methyl 3-phenylpropanoate <u>6.13</u> [103-25-3]

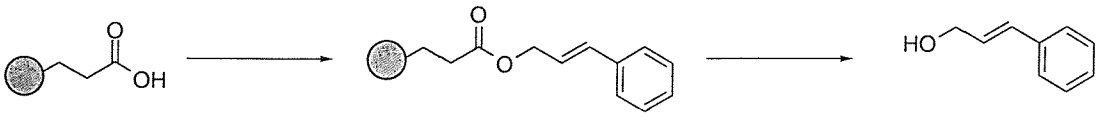


$C_{10}H_{12}O_2$
m.w.=164.20 g/mol
Colourless oil

All spectroscopic data were in good agreement with those reported in the literature.[211]

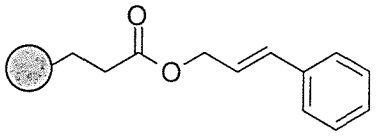
- **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 7.24-7.05 (m, 5H, C_6H_5), 3.58 (s, 3H, OCH_3), 2.84 (t, 2H, J = 7.6, CH_2), 2.52 (t, 2H, J = 8.1, CH_2)
- **^{13}C NMR** (75 MHz, $CDCl_3$) δ: 173.5 (CO), 140.7 (C), 128.7 (CH), 128.5 (CH), 126.4 (CH), 51.8 (OCH_3), 35.9 (CH_2), 31.1 (CH_2)
- **IR** (neat) ν_{max}: 2951, 1737 (s, CO), 1496, 1454, 1436 (m), 1365, 1196 (m), 1162 (m), 1079, 1029, 986, 837, 752 cm^{-1}
- **MS** (CI) m/z (rel. intensity): 182 (14), 164 (34), 104 (100), 91 (51), 77 (22)
- **GC** (temperature program B): 2.8 min

ii. Carboxilic Acid Resin 3.2



*Step 1: Esterification (Resin **6.10**)*

To a suspension of resin **3.2** (100 mg, unknown loading) in CH_2Cl_2 (2 mL) was added diisopropylcarbamide (160 µL, 1 mmol), 4-dimethylaminopyridine (120 mg, 1 mmol) and cinnamyl alcohol (134 mg, 1 mmol). The reaction mixture was stirred at room temperature for 15 hours. The resin was collected by filtration and washed three times with CH_2Cl_2 (10 mL). The resin was dried in the oven at 40°C *in vacuo*. The coupling was repeated a second time under the same conditions.

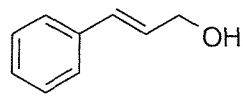


IR (neat) ν_{max}: 2916, 1730 (s), 1601, 1492, 1450 (m), 1025, 750 (m), 697 (s)

Step 2: Transesterification

A suspension of resin (100 mg, unknown loading) was swollen in a 4:1 (v/v) mixture of CH_2Cl_2 and methanol (2.5 mL). A known quantity of naphthalene (10-30 mg) and potassium trimethylsilanolate (641 mg, 5 mmol) were added. The reaction mixture was stirred at 50°C for 15 hours. The resin was collected by filtration and washed five times with CH_2Cl_2 (10 mL). The filtrates were concentrated and analysed by GC for quantities of cinnamyl alcohol.

Cinnamyl alcohol 6.11 [104-54-1]



$C_9H_{10}O$
m.w.=134.18 g/mol
White solid; m.p.= 33-35°C

The GC trace was compared with a sample of commercially available cinnamyl alcohol. No further characterisation was carried out.

GC (temperature program B): 4.3 min

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