UNIVERSITY OF SOUTHAMPTON

Novel Methodologies for the Construction of Polyether Libraries

by

Nathalie Sylvie Bouloc

Doctor of Philosophy

Department of Chemistry
Faculty of Science

June 2000

UNIVERSITY OF SOUTHAMPTON

ABSTRACT

FACULTY OF SCIENCE

CHEMISTRY

Doctor of Philosophy

NEW METHODOLOGIES FOR THE CONSTRUCTION OF POLYETHER LIBRARIES

by Nathalie Sylvie Bouloc

Polyether antibiotics are a class of natural products obtained by the fermentation of *Streptomyces sp*. They display a broad range of biological properties and are of commercial importance in the veterinary field as anticoccidial agents and growth promoters. Due to the complexity of their structures, the discovery of new leads and access to analogues is restricted to semi-synthetic modifications of the natural products. This thesis describes an iterative approach aimed at the synthesis of unnatural polyether libraries. A new method of *O*-alkylation using cyclic sulfate chemistry has been developed. Reaction of resin bound 1,4-benzenedimethanol with representative 1,2-, 1,3- and 1,4-cyclic sulfates gave the ether products in satisfactory yields. The scope of the reaction was shown to be limited by the predisposition of some cyclic sulfates to elimination. Good regioselectivity was obtained. Hydrolysis of the intermediate sulfate ester under mild acidic conditions allowed the regeneration of the hydroxyl group and was shown to proceed with retention of configuration. The methodology was successfully applied to the synthesis of tetramer library using two 1,2-cyclic sulfates and a trimer library using 4 cyclic sulfates by multiple parallel synthesis. Cyclic sulfate chemistry was shown to be a convenient method for solid phase *O*-alkylation and polyether synthesis, allowing activation of the hydroxyl group while at the same time avoiding the synthesis of monoprotected diols and bifunctionalised building blocks.

CONTENTS

ACKNOWLEDGEMENTS

I would like to thank my supervisor, professor Mark Bradley for his guidance and extreme patience throughout my PhD, faith in this project and for a couple of memorable 'animated discussions'.
I would like to thank Dr Nigel Walshe for his help and enthusiasm during the course of this project and Pfizer central research for financial support.

My thanks go also to John Langley and Julie Herminan for running mass spec samples but also for their disposability toward students. Also many thanks to Joan Street for running NMR samples.

But most of all, "merci beaucoup" to the past and present members of the Bradley group, students and post-docs who have been part of this story. All my gratitude goes to *Patrick* and *Jo* for their friendship and support; *Vin* for proof reading, dealing me chocolate in difficult times and sharing a common love for chemistry (no really...); *Neil* "Dr HPLC emeritus" for top quality sarcasm and a very happy time in the red lab; *JD* and *Andrea* for looking after me so nicely these past two years.

ABBREVIATIONS

α	observed optical rotation in degrees
$[\alpha]$	specific optical rotation
Ac	acetyl
APCI	atmospheric pressure chemical ionisation
ATR	attenuated total reflectance
aq.	aqueous
Ar	aryl
Bn	benzyl
Boc	Butoxycarbonyl
bp	boiling point
br	broad (spectral assignment)
δ	chemical shift in parts per million (ppm) downfield from tetramethylsilane
δ_C	carbon-13
δ_H	proton
cat.	catalytic
CI	chemical ionisation
DIEA	diisopropylethylamine
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	*N,N'*-dicyclohexylcarbodiimide
DCM	dichloromethane
DCU	dicyclohexyl urea
DEPT	distortionless enhancement by polarisation transfer
DIBAL	diisobutylaluminium hydride
DIC	diisopropylcarbodiimide
Dod	4,4'-dimethoxybenzhydryl
DMAP	4-dimethylaminopyridine
DMF	*N,N'*-dimethylformamide
DMSO	dimethylsulfoxide
DVB	divinylbenzene
ee	enantiomeric excess
EEDQ	2-ethoxy-1-ethoxycarbonyl-1,2-dihydro-quinoline
Et	ethyl
EI	electron impact

EtOAc	ethyl acetate
EtOH	ethanol
ES	electrospray
ES +ve	electrospray (positive ion mode)
ES -ve	electrospray (negative ion mode)
FAB	fast atom bombardment
Fmoc	9-fluorenylmethoxycarbonyl
HATU	2-(1H-9-azabenzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
HOBt	*N*-hydroxybenzotriazole
HPLC	high-performance liquid chromatography
RP-HPLC	reverse phase high performance liquid chromatography
NP-HPLC	normal phase high performance liquid chromatography
HRMS	high-resolution mass spectrometry
IR	infra-red
FTIR	fourier transform infra-red
J	coupling constant (Hz)
LHDMS	lithium hexamethyldisilazide.
MALDI-TOF MS	matrix assisted laser desorption time of flight mass spectrometry
Me	methyl
MHz	megahertz
MeOH	methanol
mp	melting point
MS	mass spectrometry
$[M+H]^+$	protonated molecular ion
$[M+Na]^+$	sodiated molecular ion
$[2M+H]^+$	protonated molecular ion dimer
m/z	mass to charge ratio
NBA	nitrobenzyl alcohol
NMO	*N*-methylmorpholine oxide
NMR	nuclear magnetic resonance
ArC	quaternary aromatic carbon
ArCH	aromatic CH
C	quaternary carbon
s	singlet
d	doublet
dd	doublet of doublets
dt	doublet of triplets

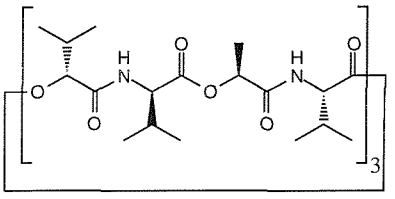
t	triplet
q	quartet
quin	quintet
m	multiplet
Nu	nucleophile
O/N	overnight
PE	petroleum ether
PEG	polyethylene glycol
Ph	phenyl
ppm	parts per million
PS	polystyrene
PyBOP	benzotriazole-1-yl-oxy-tris-pyrrolidino-phosphonium hexafluorophosphate.
PyBroP	bromo-tris-pyrrolidino-phosphonium hexafluorophosphate
$\mathbf{R_f}$	retention factor
$\mathbf{t_R}$	retention time
rt	room temperature
SPS	solid phase synthesis
tert: (*t*-)	tertiary
***t*-Bu**	*tert*-butyl
***t*-BuOH**	*tert*-butyl alcohol
TFA	trifluoroacetic acid
THHF	tetramethyl fluoroformamidinium hexafluorophosphate
TIS	triisopropylsilane
TG	TentaGel
THF	tetrahydrofuran
TLC	thin layer chromatography
UV	ultraviolet

Chapter 1: Introduction

1.1. Polyether ionophores

1.1.1. Natural and synthetic ionophore structures

The term ionophore was first used by Pressman[1] to describe the ability of a molecule to complex an ion and assist its transport through a lipophilic interface, such as a natural or artificial membrane. These ionophoric properties are shared by a wide range of natural products: peptides,[2] cyclic depsipeptides,[3] macrotetrolides,[4] acetogenins[5] and polyether antibiotics.[6] Representative members of these different families are shown in figure 1.1.



Valinomycin

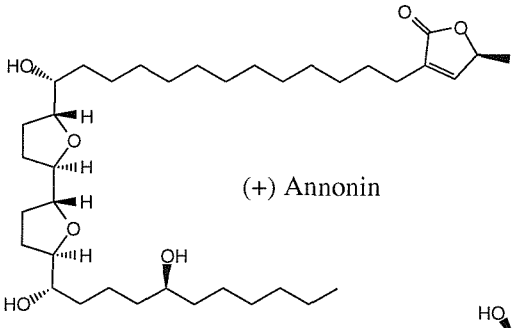
Cyclic Depsipeptides

HC(=O)-Val-Gly-Ala-D-Leu-Ala-D-Val-Val-D-Val

$HOCH_2CH_2NH$-Trp-D-Leu-Trp-D-Leu-Trp-D-Leu-Trp

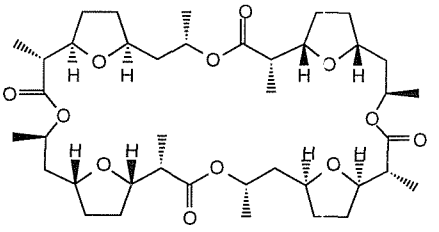
Gramicidin A

Peptides



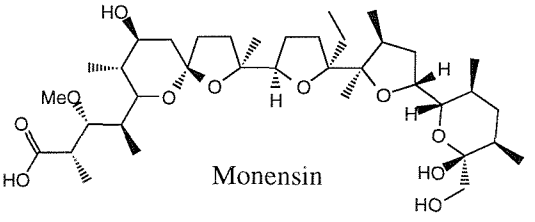
(+) Annonin

Acetogenins



Nonactin

Macrotetrolides



Monensin

Polyether antibiotics

Figure 1.1: Naturally occurring ionophores

Although very diverse in structure,[7] a common feature is the presence of heteroatoms placed at strategic positions and capable of acting as ligands for the ion. In all cases, the biological activity of these compounds is closely linked to their ionophoric properties. They form lipid soluble complexes with physiologically important cations and can participate in ion transport across cell membranes. They can thereby play many roles in biological processes.[1,7]

Discovery of the ionophoric properties of crown compounds by Pederson[8] led the way to the design and synthesis of an array of synthetic ionophores and later, in the more general context of supramolecular chemistry,[9] to the synthesis of ionic receptors. In order to access compounds with new or specific ionophoric properties, cyclic structures with increasing complexity (e.g. lariats, cryptands and spherands) as well as open-chain frameworks (podands) have been prepared[10] (Figure 1.2).

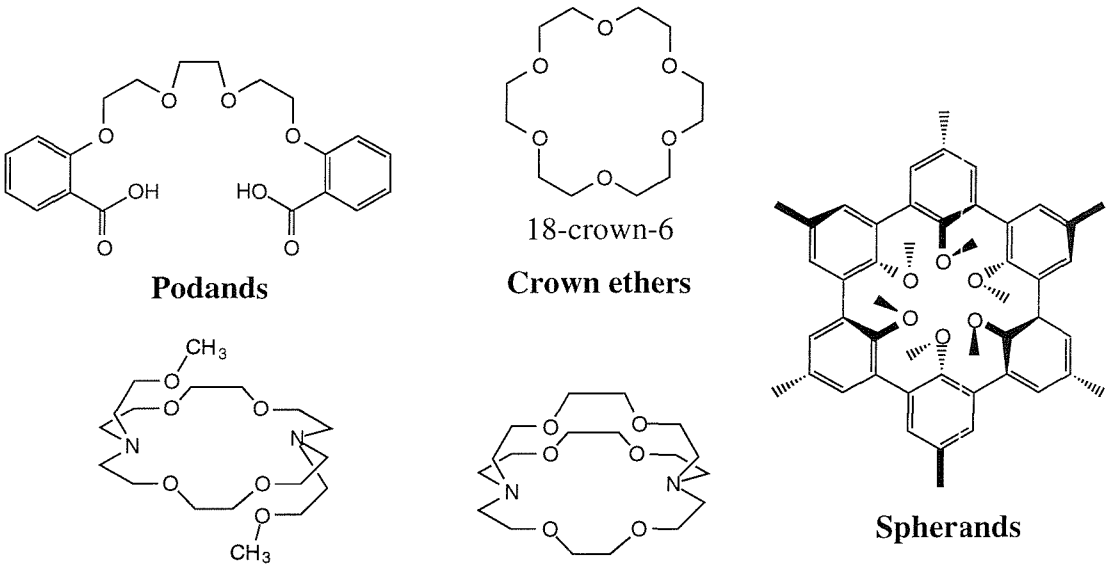


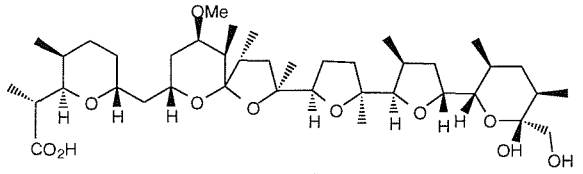
Figure 1.2: Synthetic ionophores

Synthetic ionophores have found a wide range of applications from phase transfer agents and catalysts in chemical processes[10b] to molecular sensors,[11] and more recently pharmaceutical applications as contrast agents.[12]

More importantly, the extensive work carried out in the field has allowed the comprehensive study of the structural parameters controlling complex stability and selectivity, as well as an understanding of the complexation and transport mechanisms[13] involved in many biological processes.

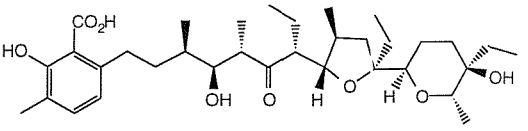
1.1.2. The polyether antibiotics

Among the natural ionophores, the polyether antibiotics[4] particularly stand out both by the intriguing complexity of their structures and the wide range of biological properties they display. Also known as 'carboxylic ionophores' or 'Nigericin-type ionophores', they constitute a large class of structurally related compounds (Figure 1.3). To date, more than 120 compounds have been isolated from the fermentation broths of *Streptomyces* cultures.[14]



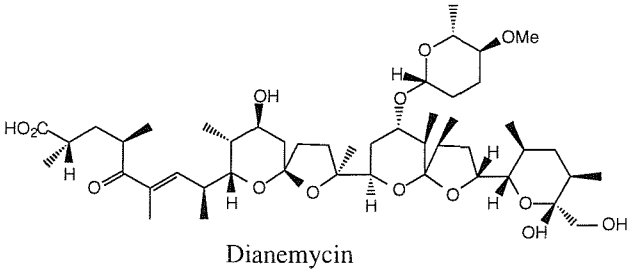
Nigericin

a. Monovalent Polyether Antibiotics



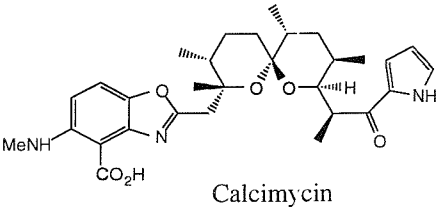
Lasolactic A

b. Divalent Polyether Antibiotics



Dianemycin

c. Monovalent Monoglycoside Polyethers



Calcimycin

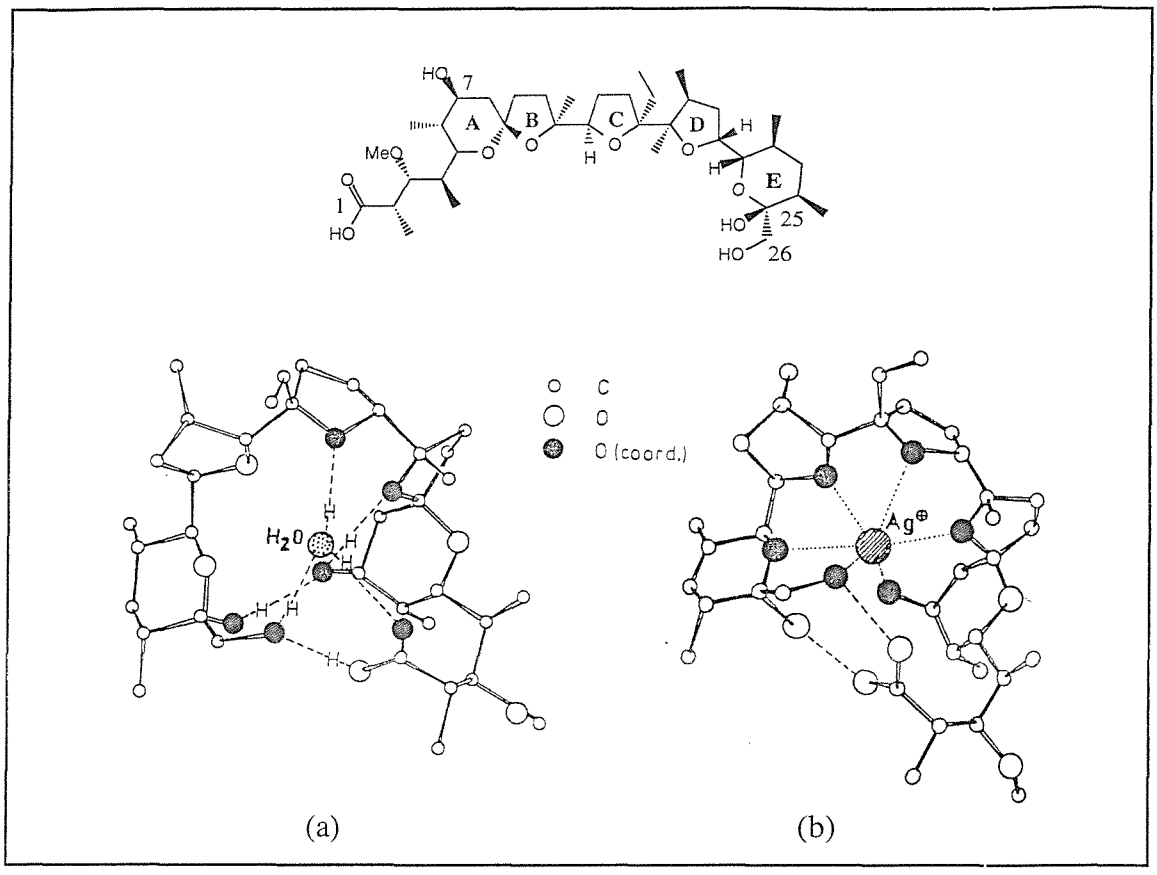
d. Divalent Pyrrole Ether Antibiotics

Figure 1.3: Representative members of the 4 sub-classes of polyether antibiotics

Interest in this class of compounds, initially isolated for their antibiotic activity grew with the discovery of their anticoccidial properties. Several compounds have found commercial applications in the veterinary field as anticoccidial agents and growth promoters. Monensin (Figure 1.4) has been one of the leading anticoccidial agents on the market for the last 30 years. Polyether antibiotics are generally active against gram positive bacteria and fungi. Some compounds have also been found to be powerful insecticides or pesticides.[15] Although their parental toxicity has prevented clinical applications, they have also been shown to be potential cardiovascular agents.[16] Due to their high ion selectivity, they have proved very useful tools in cellular biochemistry and physiology to probe the roles of cations in various biological systems.[1,17] More recently, they have been used in the design of ion selective electrodes.[18]

As illustrated by figure 1.3, the structure of the polyether antibiotics is very characteristic. They are open-chain molecules, terminated at one end by a hydroxyl group and at the other end by a carboxylic acid function. The backbone is dominated by the presence of substituted tetrahydrofuran and tetrahydropyran rings often fused into spiroketal systems, giving rise to a large number of asymmetric centers.

Though linear, these molecules adopt, both in the free and complexed states, a cyclic conformation by head to tail hydrogen bonding between the terminal hydroxyl and carboxyl groups (Figure 1.4).



X-ray crystal structure of (a) free monensin hydrate complex. H-bond are dashed lines. (b) Ag^{+}-monensin complex. Metal/oxygen contacts are shown as dotted lines. Two H-bond (dashed lines) are responsible for the pseudocyclic conformation.

Figure 1.4

Pre-organisation and stabilisation of the binding conformation is induced by the twists and steric constraints brought about by the ring systems and asymmetric centers in the backbone. Work by Still *et al.*[19] has shown that acyclic segments are rigidified by particular arrays of chiral centers which destabilise undesired rotamers by avoidance of +gauche/-gauche interactions, pushing the molecule into specific conformations. The resulting complex possesses a hydrophilic central cavity with the oxygen atoms pointing inwards and serving as ligands for the encapsulated cation. The carbon backbone with alkyl groups pointing outwards creates a lipophilic exterior.

As illustrated in the case of monensin, X-ray analysis has shown that the free and complexed forms present very similar conformations with subtle though important differences in the hydrogen bonding scheme (Figure 1.4). The free acid is held in a cyclic conformation by three intramolecular hydrogen bonds.

Three additional hydrogen bonds occur with a water molecule located on one side of the molecule. The Ag^+-complex exists with two hydrogen bonds between the terminal carboxyl group and the hydroxyl group at the carbon C-25 and C-26. The Ag^+ cation is co-ordinated in an irregular arrangement by six oxygen atoms. To explain the formation of the complex, it has been postulated[20] that the free molecule possesses two sides, one being tightly drawn in by intramolecular hydrogen bonds, the other being widened up by the water molecule. As a solvated cation approaches from this latter side, the water molecule goes into the solvation sphere of the cation and is displaced, possibly as H_3O^+. While one side of the cation is still solvated, the other becomes co-ordinated by the monensin oxygens. Thus, with minimal conformational reorganisation, the cation is enveloped; the water molecule acting as a signal to direct the ion into the hydrophilic cavity. Comparison of the X-ray crystal structures of different metal complexes of a same molecule but also of different members of this family shows the basic skeletons to adopt essentially a same conformation. Cations of different radii can be accommodated with only small changes in the overall conformation suggesting that the ion selectivity is the results of only subtle changes in the carbon backbone.

All members of this family possess the ability to complex monovalent cations such as Na^+ or K^+. Additionally a sub-group, the 'divalent polyether antibiotics', can form complexes with divalent cations such as Ca^{2+} or Ba^{2+}. These compounds of the lasalocid or calcymicin type (Figure 1.3 (b), (d)) possess shorter backbones, preventing encapsulation of the cation. Complexation is therefore achieved by formation of dimeric complexes of the form $[M^+L^-]_2$ or $M^{2+}[L^-]_2$. The polar side of two molecules face each other, forming a sandwich structure around either a divalent cation and a water molecule (Figure 1.5), or two monovalent cations. The ion selectivity and the creation of an hydrophilic pocket is achieved by differing the arrangement of the two ligands L around the cation.

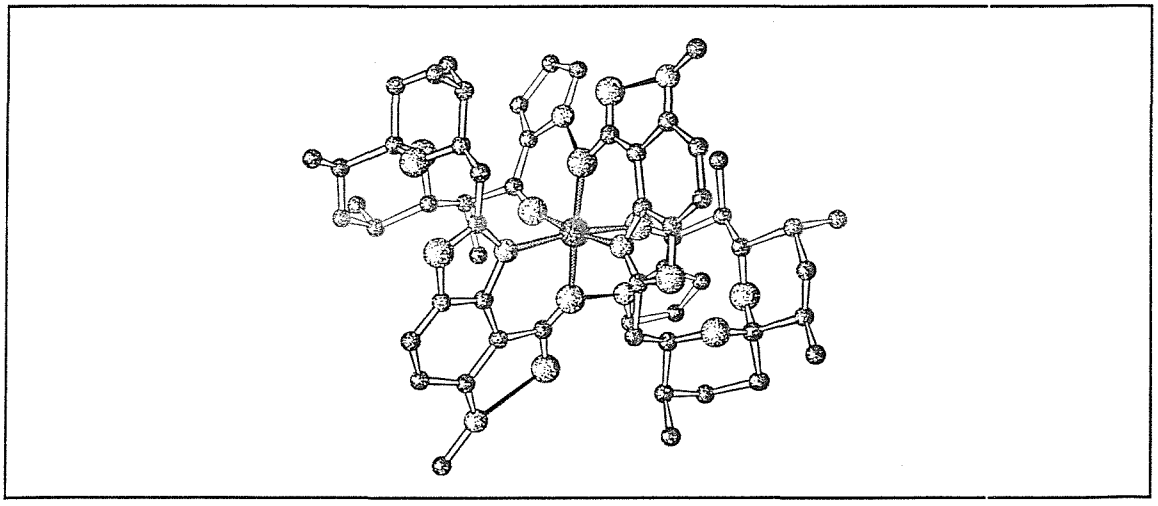
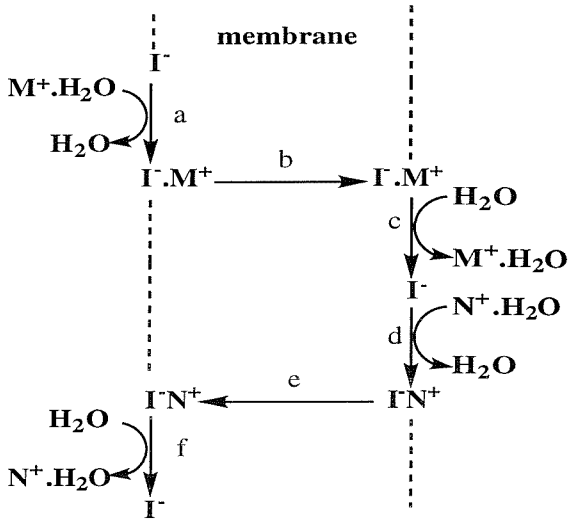


Figure 1.5: X-ray crystal structure of Ag^+ - lasalocid complex

At physiological pH, the terminal carboxyl group is deprotonated. The resulting neutral and nonpolar complexes ($[M^+L^-]$ or $[M^+L^-]_2$) are therefore thought of as being soluble in the non polar lipid bilayer interior of the membrane, allowing passive diffusion from one aqueous/membrane interface to the other and transport of the cation across the membrane. A simplistic view of the mode of transport of the polyether antibiotics is shown in figure 1.6.



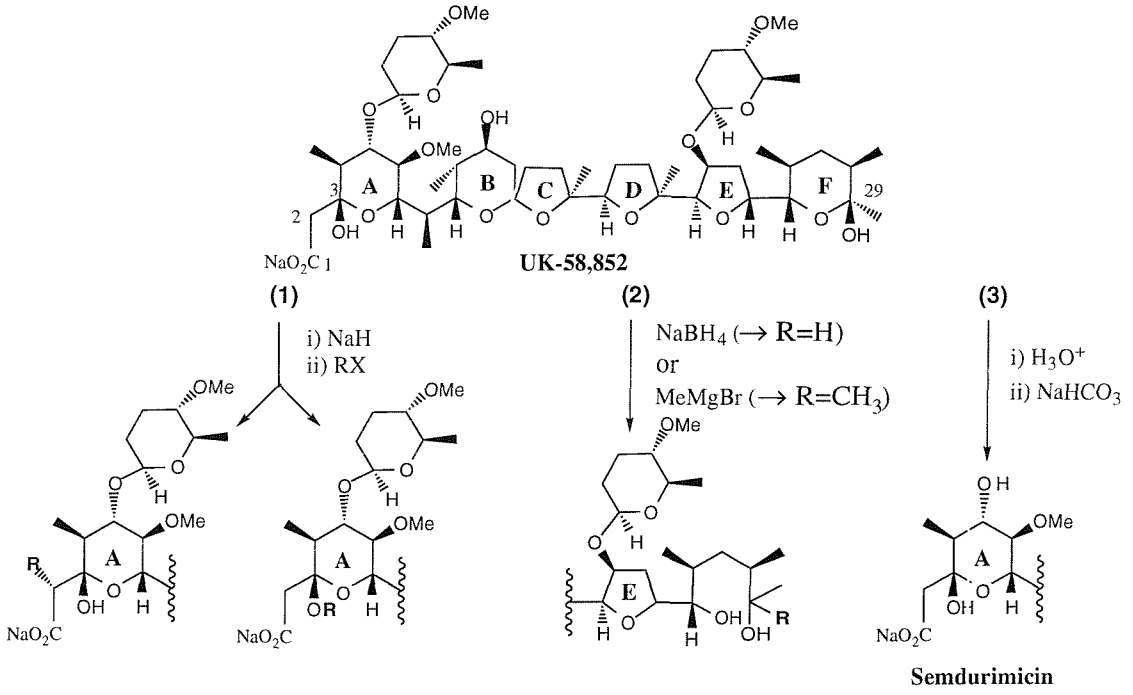
(a) The ionophore is trapped at the polar face of the membrane in its anionic form I^-. The ionophore encounters a complexible cation M^+ and proceeds to engulf it, displacing its water of solvation through the lowest energy mechanism. (b) The resulting neutral complex $[I^-M^+]$ is now capable of passively diffusing across the apolar membrane interior to the opposite interface. (c) Release of the cation, coincident with resolvation. (d,e,f) The anionic ionophore I^- is now able to combine with a cation N^+ and return by the same process to the initial membrane interface where the cation N^+ is released.

Figure 1.6

The transport cycle results in the electroneutral exchange of one cation for another down a concentration gradient and is independant of the membrane potential. The carboxylic ionophores are therefore refered to as "exchange diffusion" carriers. Since membrane potentials play an important role in regulating excitable cells (e.g. nerves, muscles), an electrical neutral transport appears to be an essential requirement for tolerance of pharmacologically active concentration of ionophores. For this reason, carboxylic ionophores have considerably greater potential as therapeutic agents than neutral ionophores which alter membrane potentials and tend to be exceedingly toxic.

The extreme complexity of the polyether antibiotic structures represent a real challenge for synthetic chemists. A number of total syntheses have been achieved[21] and an abundant literature deals with stereocontrolled routes to the key structural fragments[22] but production for commercial applications is still restricted to large scale fermentation processes.

Semi-synthetic modifications[23] of the natural products has therefore remained the major tool for understanding structure-activity relationships and enhancing biological activity. In combination with an X-ray knowledge of the complex structure, a series of single step synthetic transformation can be carried out, aimed at modifying either the lipophilicity of the carbon backbone or altering the structure of the ion binding cavity. A successful example is shown in scheme 1.1. A lead structure, compound UK58-852, was transformed into a finished drug.



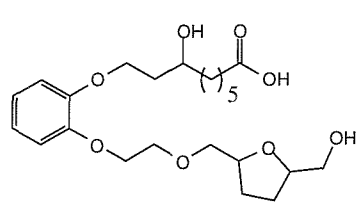
Modification of the ion-binding cavity by (1) etherification of the C-3 hydroxyl or alkylation at C-2. (2) cleavage of the F-ring ketal. (3) Modification of the lipophilic scaffold by selective hydrolytic cleavage of the deoxy sugars.

Scheme 1.1

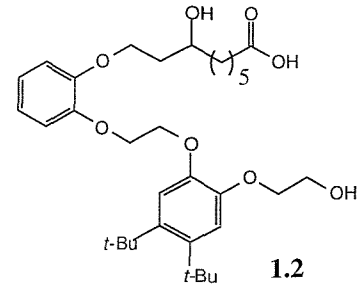
Selective removal of one of the sugar moieties gave a semi-synthetic derivative, semduramicin, with increased anticoccidial activity and additional growth promoter properties. Semduramicin is now obtained by direct fermentation of a mutant strain of the organism which originally produced UK58-852 and has been commercialised by Pfizer under the name Aviax.

However, the range of chemical modifications theoretically possible remains limited in scope and often results in a loss or decrease of activity compared to the parent molecule. Access to synthetic analogues is therefore of particular importance. In this direction, a range of open chain synthetic ionophores have been designed by direct analogy to the polyether antibiotic framework. The following examples illustrate the difficulty in achieving carrier and biological activity other than simple complexation properties. The proposed structures must allow for appropriate rate of complexation and decomplexation and result in a suitable lipophilicity of the complex.[13b,24]

Among early examples, Garder *et al.*[25] incorporated in the design of the compounds **1.1** and **1.2**, key structural features shared by the polyether antibiotics (i.e. carboxyl and hydroxyl end groups, presence of 6 oxygen atoms available for co-ordination, separation of the carboxyl group from the first oxygen donor by 5 carbon atoms, 1,2-glycol arrangement of the oxygen's) (Figure 1.7). The compounds were expected to have the potential for forming a pseudo-cyclic hydrogen-bonded array that could encompass actions. However, they failed to form organic soluble complexes and no biological activity was detected in a coccidiosis screen.



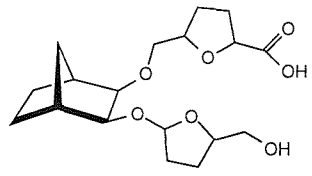
1.1



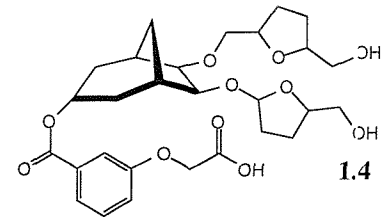
1.2

Figure 1.7

In a similar approach, Wieranga *et al.*[26] used the bicyclo[2.2.1]heptane and bicyclo[3.2.1]octane units to confer a three-dimensional organisation upon the structures **1.3** and **1.4** (Figure 1.8). Although biological activity was not examined, **1.4** compared favourably to lasolactid and calcimycin in transporting Ca^{2+}.



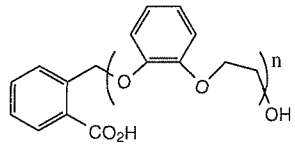
1.3



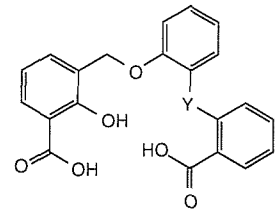
1.4

Figure 1.8

Acyclic oligo-ether structures with various terminal end groups inducing a pseudo cyclic conformation have been extensively studied by Vögtle *et al.* [27] and have been shown to form complexes with various alkali and alkaline earth cations. Based on this concept, Yamagushi *et al.*[28] have reported the synthesis of a series of linear α-carboxy-ω-hydroxy polyethers **1.5** (Figure 1.9).



1.5



Y = $O(CH_2)_3O$, $O(CH_2CH_2O)_2$
$O(CH_2CH_2O)_3$

1.6

Figure 1.9

The backbone was composed of repeating units derived from catechol and ethylene glycol replacing the THF and THP rings found in the polyether antibiotics. Good ion selectivity and transport activity were observed.

The polyether antibiotics are relevant compounds in many therapeutic areas. Access to a wider range of synthetic analogues would allow comprehensive structure-activity relationship studies and access to compounds with a broader range of physicochemical and biological properties. Polyether based ionophore compounds appear therefore as interesting targets for combinatorial chemistry.

1.1.3. Aims

In the past decade, the practice of combinatorial chemistry has profoundly transformed the drug discovery process. Traditionally, lead discovery relied on the isolation of new biologically active natural products and screening of corporate compound databases. Optimisation of lead structures was carried out using rational design, traditional solution phase methodologies and focused on the synthesis of one compound at a time. Combinatorial chemistry introduced a much more 'empirical' approach and aimed at the simultaneous synthesis of a collection of compounds or 'library'. Submitted in a variety of formats (single compounds, mixtures), a large number of compounds can therefore be screened in a much more cost and time efficient manner.

Combinatorial chemistry takes its roots in the pioneering work of Merrifield on solid phase peptide synthesis[29] followed by the introduction of the 'mix and split' concept by Furka.[30] Work in the field focused therefore initially on the solid phase synthesis of natural oligomers (peptides, oligonucleotides) and their mimetics. The interest of the pharmaceutical industry in the synthesis of small organic molecules based on known pharmacophores boosted the development of solid phase organic chemistry and the adaptation of the main repertoire of organic reactions to solid phase.[31] Recent advances in solid supported reagents,[32] resin scavengers,[33] and purification strategies[34] have narrowed the gap between solution and solid phase approaches to library synthesis.

Combinatorial chemistry in a broad sense embraces now a variety of fields, techniques and applications[35]. Whilst the primary focus of combinatorial chemistry was on drug discovery and optimisation, the wide potential of this approach is now applied in fields as diverse as material science and catalyst development[36] or genetic engineering.[37]

Synthesis of polyether libraries

We wished to develop new solid phase synthetic methodologies to allow access to libraries of polyether antibiotic analogues. As shown in figure 1.10, the repetive nature of the polyether framework can be capitalised by the design of a new class of unnatural oligomers.

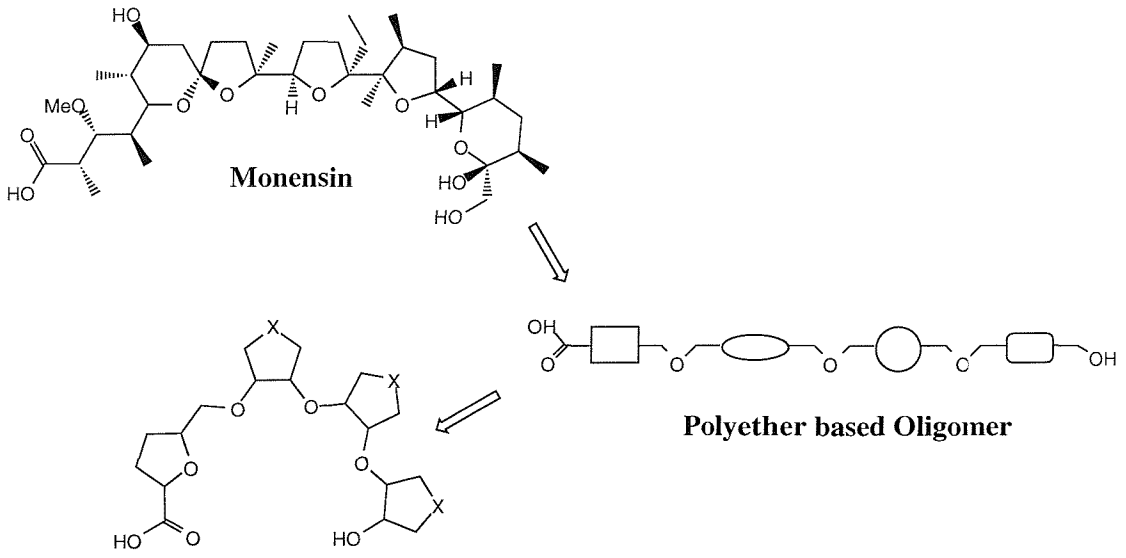


Figure 1.10

The general backbone of the natural polyether antibiotic is re-created in a simplified manner but keeping the key features intact (e.g. terminal hydroxyl and carboxylic acid groups, separation of the oxygens by two methylene units). Considerable variations can be introduced into the carbon backbone. The parameters conferring the ionophore properties can therefore be easily varied. Ion selectivity can, for example, be tuned by varying the chain length and the number of oxygen available for coordination. Lipophilicity can be altered by changing the nature of the building block (e.g. aromatic residue, presence of heteroatoms). Although the proposed structure may lack the rigidity and preorganisation observed in the natural products, structural constraints can be introduced into the chain using rigid and/or turn inducing building blocks.

1.2 Solid phase synthesis

Various issues must be addressed when planning a solid phase combinatorial synthesis: choice of the synthetic strategy, format and size of the library, choice of the solid support (linker and resin), reaction monitoring and finally screening process. A comprehensive treatment can be found in many reviews.[35] Specific aspects will be covered in the following paragraphs.

1.2.1 Synthetic methodology - specificity of oligomer synthesis

Oligomeric structures composed of repeating sub-units connected together by the same type of linkage are well suited for combinatorial approaches. Due to their central role in many biological process, extensive work has focused on the synthesis of natural oligomers such as peptides, oligonucleotides and oligosaccharides. Access to unnatural analogs mimicking either the primary sequence or secondary structure is an active area of research[38] (Figure 1.11).

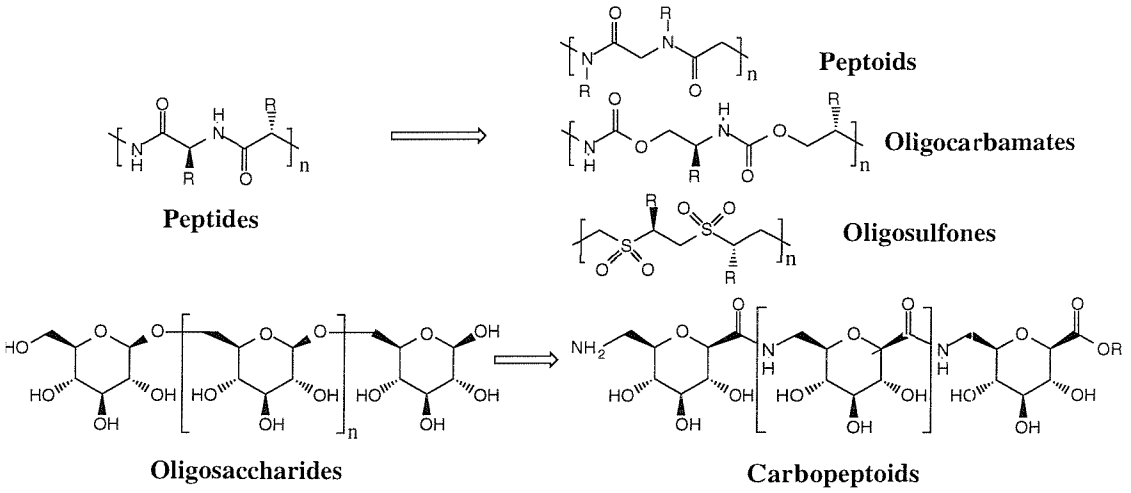
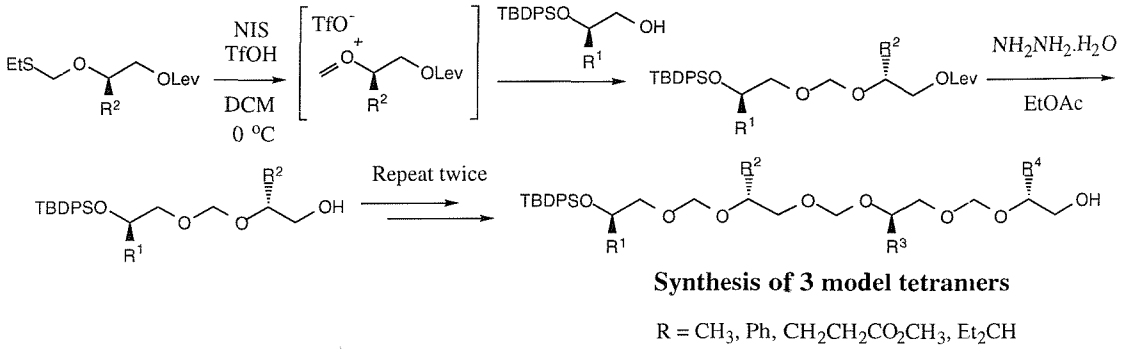


Figure 1.11: Example of natural oligomers and their mimetics

More recently, solid phase combinatorial approaches to the synthesis of non classical oligomeric structures such as polyketides,[39,40] polyisoxazolines,[41] oligothiophenes[42] have been explored. Close to our own target, a convergent strategy has been reported in solution directed to the synthesis of oligo-THF libraries as synthetic analogues of the Acetogenins.[43] Oligo-THF peptides have also been prepared to form potential polyether helices with ion channel activity.[44] In an effort towards the development of unnatural biopolymers capable of selective metal ion coordination, Schultz *et al.*[45] developed a two step iterative protocol for the solution phase synthesis of ethoxyformacetal oligomers libraries (Scheme 1.2).

A set of 4 O,S-thioformacetal donor monomers, with diverse chiral side chains were coupled using NIS/TfOH activation. The methodology was demonstrated by the synthesis of 3 tetramers.



Scheme 1.2

Solid phase approaches are often preferred to solution phase approaches due to the ease of purification and the advantage of pushing the reaction to completion by use of excess reagents. Moreover, the procedures are more easily amenable to automation and can therefore allow access to larger libraries. Oligomer synthesis is traditionally carried out by the iterative coupling of bifunctional building blocks (Figure 1.12). Following the tethering of the first monomer on the solid support, the oligomer chain is elongated by a series of deprotection and activation/coupling steps.

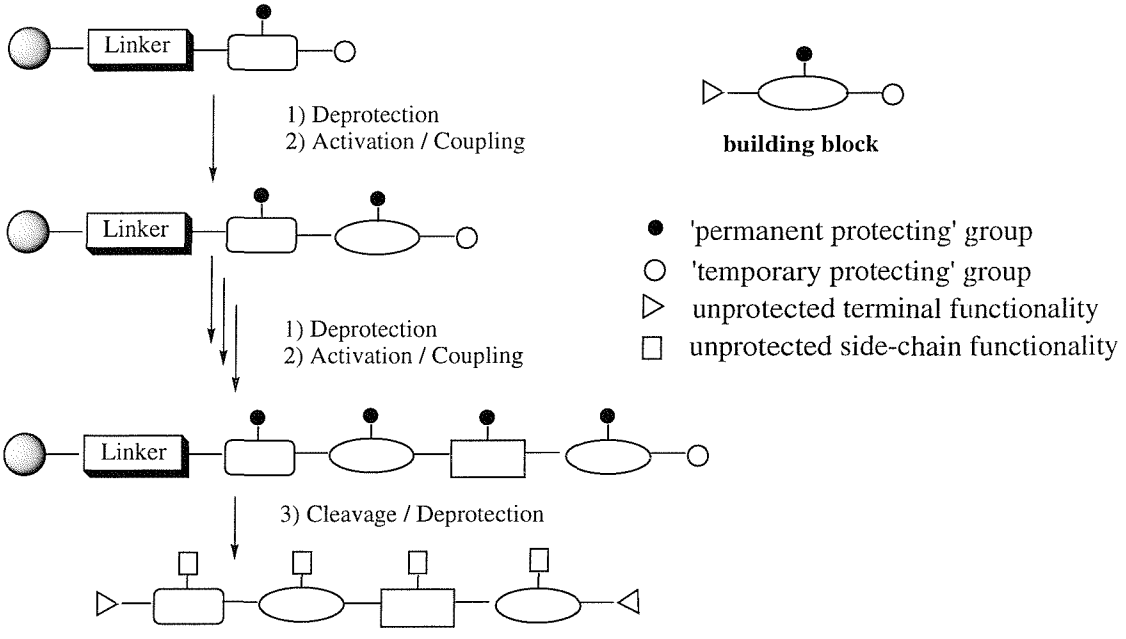
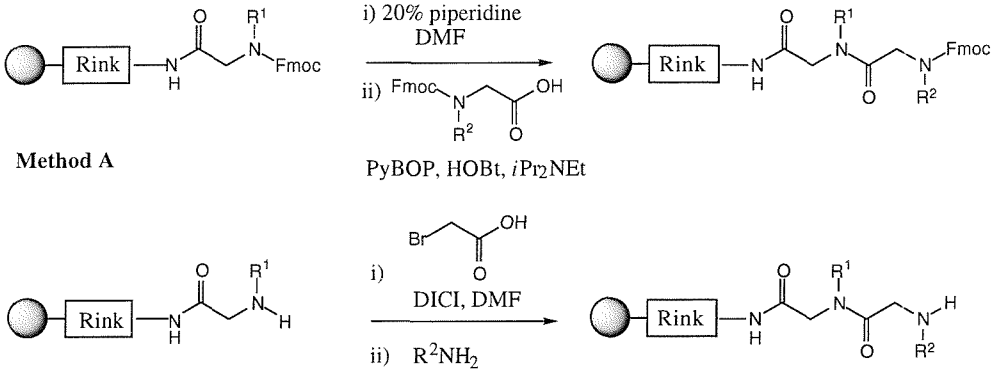


Figure 1.12

Approaches in which the activated species are generated on the resin are usually disfavoured as any side reactions at the reactive center would terminate the growth of the chain. Anchoring can be considered *via* the oligomer terminus or *via* a backbone functionality. The latter allows access to a wider range of termini and is of particular interest in the case of cyclic structures. Complex protecting group strategies are required to avoid branching or side reactions of monomers possessing additional functionalities. Protecting schemes based on graduated lability have been used (e.g. Boc chemistry in SPPS) although orthogonal strategies are usually preferred as they benefit from a more flexible array of protecting group allowing the construction of more complex structures. As illustrated in the case of peptoid synthesis, choice of a suitable monomer set is a determinant issue in terms of diversity generation but also in terms of availability of reactants (Scheme 1.3). The original approach reported by Simon *et al.*[46] employed standard peptide synthesis methods with Fmoc-protected *N*-alkylglycine monomers preformed in solution (Method A, Scheme 1.3).



Method B: Submononer approach

Scheme 1.3

The submonomer approach (Method B, Scheme 1.3) developed subsequently by Zuckermann *et al.*[47] allowed the direct incorporation of commercially available amines and bromoacetic acid as building blocks; thereby eliminating costly, time consuming monomer synthesis and obviating the need for amine protection.

Due to the high number number of synthetic steps and the impossibility of intermediate purification, development of high yielding (typically ≥ 99%) and stereospecific coupling procedures is essential. Separation of the target sequence from the family of deletion impurities lacking one or more residue is often difficult to achieve by conventional purification techniques due to their similar chemical and physical properties. An additional capping step is therefore often introduced to prevent the formation of deletion sequence due to non quantitative coupling. This is typically achieved in peptide and oligonucleotide synthesis by acylation.

As shown in figure 1.13, purification from the now family of 'terminated sequence' can be in turn facilitated by 'reversible labelling'[48] of the final target sequence.

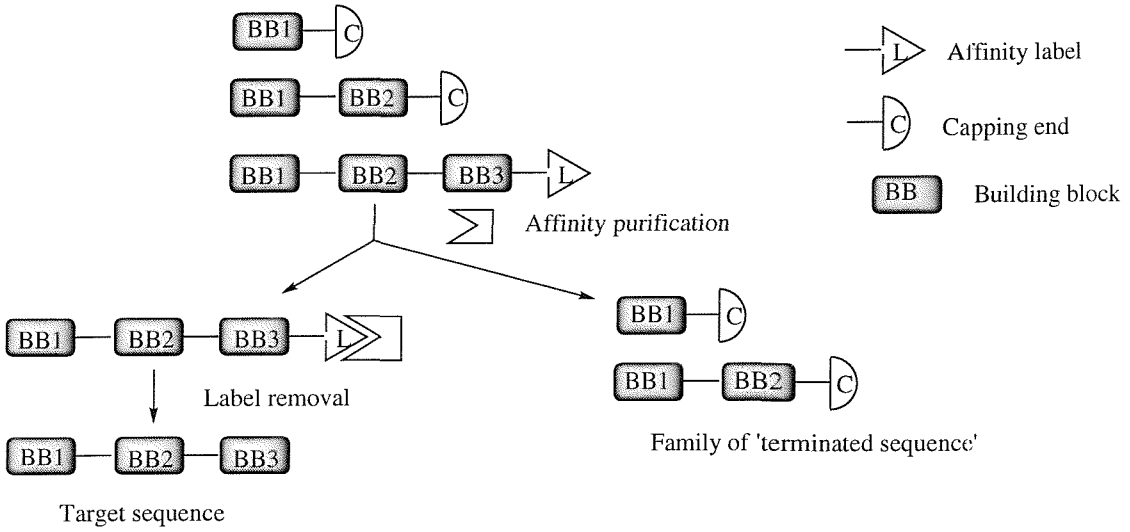


Figure 1.13

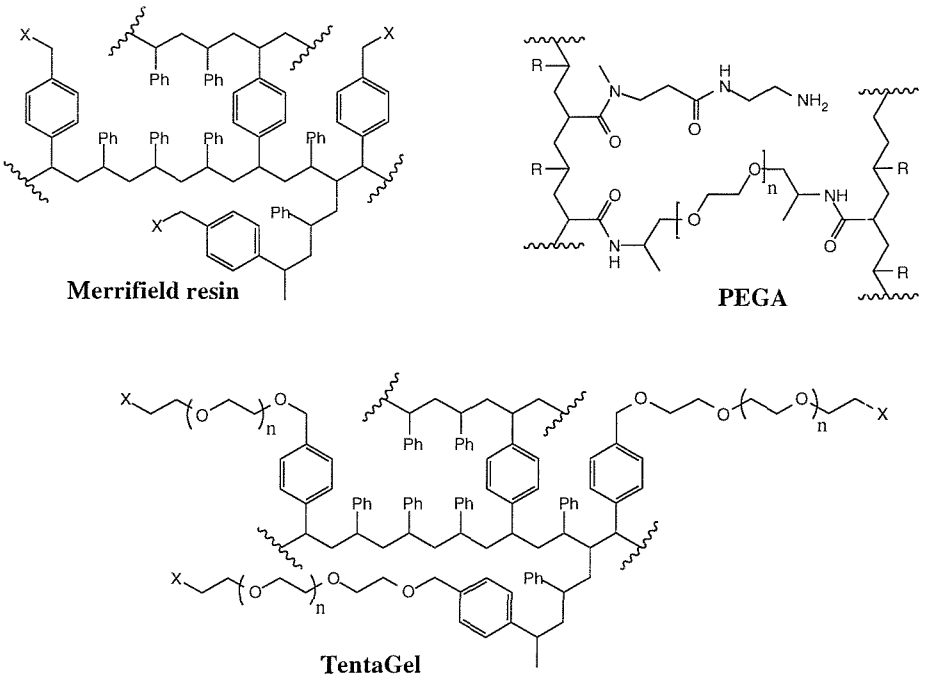
Various 'affinity label' have been proposed for the selective purification of synthetic proteins. For example, Fmoc based probes[49] were used for reverse phase HPLC purification. Use of benzo-fused Fmoc derivatives (Tbfmoc) allowed purification by porous graphitised carbon (PGC) chromatography. Biotinylated peptides were separated by avidin/agarose-affinity chromatography. For the synthesis of large oligomers, convergent strategies can alternatively be envisaged. Such 'segment condensation' approaches have been exploited mainly in peptides synthesis using partially protected peptides (5 to 15 residues in length) made by either solution or solid phase procedures.[50]

1.2.2 Solid supports

a. 'Gel type' resins and 'Macroporous resins

Insoluble cross-linked polymers constitute the type of support the most commonly used in solid phase organic chemistry. Recent years have seen the development of a increasing number of polymer supports[51] in order to accommodate the now wide range of chemistries carried out, emphasizing the influence of the polymer support on the success of the reaction.[52] Reaction kinetics on solid phase are diffusion controlled. Variables such as swelling capacity, bead size, degree of cross-linking and nature of the core polymer will affect the diffusion of the reagents to the reactive sites within the polymer matrix and hence the overall reaction rate. Initial work by Merrifield on solid phase peptide synthesis was carried out on lightly cross-linked (1-2% divinylbenzene) polystyrene resin beads. The hydrophobic nature of the polystyrene matrix and its limited swelling capacity in polar solvent was taken responsible for sequence dependant

coupling difficulties[53] and led to the development of more hydrophilic supports, in particular, PEG grafted supports (e.g. TentaGel[54], ArgoGel[55]) and PEG-based resins (e.g. CLEAR,[56] PEGA[57], POEPOP[58]).[59]



(a) Merrifield resin = 1-2% cross-linked (DVB) polystyrene. (b) TentaGel = PS resin grafted with PEG. (c) PEGA = polyethyleneglycol-poly-(*N*,*N*-dimethylacrylamide) copolymer.

Figure 1.14: Chemical structure of representative polymer supports

The widely used TentaGel resin, obtained by grafting polyethylene glycol chains on polystyrene resin, provides a hydrophilic support swelling in both polar and non polar solvents. Due to the flexibility and the good solvatation properties of the PEG chains, the reactions can be performed under quasi homogeneous conditions.[60] Reactive sites located at the end of the PEG spacer have been shown to behave kinetically like in solution.[61] A second group of support is constituted by the macroporous resins.[62] They are highly cross-linked polymer (≥ 20%) prepared by polymerisation in the presence of a non-reactive diluent that phase separates during the polymerisation and defines a permanent pore structure. In contrast to the 'gel type' resins previously mentioned (e.g. Merrifield resin), rapid diffusion of the reagents to the reactive sites located at the pore surface is possible in a broad range of solvent despite a low swelling of the polymer. Greater site accessibility under anionic reactions have been observed in macroporous resins than with standard 'gel type' resins.[63]

b. Site isolation versus site-site interaction

The overall concentration of the reactive group within the beads being relatively high and the polymer chain of lightly cross-linked polymer having a high mobility, a certain

proportion of the reactive sites can reach each other. Site-site interactions are found to occur frequently and can lead to side reactions such as double binding of substrates.[64] The ability to achieve site isolation is dependant on a number of factors and is quite case specific. The use of resins with low functional group loading and higher cross-linking levels generally increases site isolation. Site isolation has been successfully exploited in certain cases, for example ring closing methatesis.[65]

1.2.3 Linkers

The function of the linker is to act as a selectively cleavable 'bridge' between the solid support and the molecule synthesised. A wide range of linkers,[66] very often based on known solution phase protecting groups, have now been developed to allow attachment and/or release of most functionalities. New features have recently been introduced in the design of linkers[67] which can now play additional roles in the library generation and the screening processes. *'Linkers based on a chiral auxillary'*[68] allow asymmetric induction and become part of the synthetic process itself. *'Diversification linkers'*[69] allow the generation of a range of functionalities depending on the cleavage conditions chosen and can thus be used to introduce another point of diversity in the target molecule. Cleavage based on *cyclisation*[70] during the last step of the synthesis provide an internal mode of purification. *'Multi-cleavable linkers'*[71] allow the release of a controlled amount of compound and can therefore be used for monitoring reactions or in deconvolution processes when screening mixtures. *'Biocompatible linkers'* such as photocleavable linkers or pH-cleavable linkers[72] allow the direct screening of the compounds upon release.

The choice of the linker must be based on several considerations: (1) choice of the attachment point on the target molecule (e.g. alcohol, amine group), (2) stability of the linker to the chemistries being carried out, (3) existence of an efficient method of loading the starting building block onto the linker, (4) cleavage conditions allowing release in high yields and without damage to the target molecule. A final issue resides in the attachment point of the linker to the resin. Some linkers or 'integral linkers' are part of the polymer matrix itself.[73] They are introduced during the polymerisation process (as a co-mononer) or by post-functionalisation of the polystyrene/DVB resin.[74] Most often, the linkers or 'grafted linkers' are synthesised first in solution then coupled to the resin. This approach is more versatile as it can allow the introduction of a spacer and leave the alternative to carry out the coupling of the first building block in solution ('pre-loading') to ensure a high loading or to avoid side reactions. The type of linkage between the linker and the resin (traditionally an amide or ether bond) must be chosen so as to avoid interference with subsequent chemistry.[75]

1.2.4 Analytical methods for solid phase reaction monitoring

Efficient monitoring[76] is crucial both at the development stage and for final characterisation of the library members. Cleavage and analysis by classical solution phase techniques remain by far the most common method of solid phase reaction monitoring, but the process is time consuming and more importantly destructive. Moreover, some intermediates can prove unstable to the cleavage conditions. Important efforts have therefore been made in the development of 'non-destructive methods' (e.g. gel phase NMR, IR) allowing direct characterisation of resin bound molecules.

a. Colorimetric assays

A variety of UV and colorimetric assays have been developed for the selective detection and quantification of resin bound functional groups: ninhydrin[77] and Fmoc[78] tests for primary amines,[79] Ellman's test for thiols,[80] bromophenol blue test for basic nitrogens,[81] chloranil test for secondary amines,[82] DMT test for alcohols.[83,84] They are used routinely for loading and yield determination and to assess reaction completion. They are essential in oligomer synthesis where they are often integrated to the automated synthesis procedures.

b. FTIR spectroscopy

FTIR spectroscopy allows the structural analysis of resin bound molecules and the rapid assessment of the success and completion of solid phase reactions by simply following the appearance (or disappearance) of characteristic IR chromophores. A range of FTIR methods[85] involving different sampling and acquisition modes are now routinely used. Acquisition of spectra is possible by the traditional KBr pellet method[86] using a conventional IR-spectrometer. Single bead FTIR microspectroscopy,[87] ATR[88] (attenuated total reflectance) spectroscopy, RAMAN[89] spectroscopy, DRIFT[90] (diffuse reflectance FTIR), and photoaccoustic FTIR[91] constitute more recent and superior techniques. Only 1-10 mg of resin is typically required for routine analysis. Use of an FTIR microscope or an ATR objective allows single bead analysis. Single bead FTIR microscopy has proved a valuable tool for real time monitoring and kinetic determination and was used for example by Yan *et al.* for the study of the effect of polymer support (e.g. site-site interaction,[92] nature of the resin[93]) and reaction conditions (e.g. effect of mixing methods[94]). With the use of a specialised flow-through infrared cell, Pivonka *et al.*[95] have achieved real time IR analyses of SPOC reactions, the reactions being carried out in the infrared cell itself, giving a direct insight into reagent diffusion rates and reactivity within the microenvironment of single beads.

c. Gel Phase NMR spectroscopy [96]

Using conventional probes, NMR spectra of resin bound molecules can be acquired from a resin sample (50 to 100 mg) fully swollen in a deuterated solvent, thus creating a semi-solution like environment or 'gel phase'. The restricted mobility of the tethered molecule and the non-homogeneity of the sample results in a strong NMR linewidth broadening. Satisfactory spectra are however obtained for nuclei with wide spectral dispersion such as ^{31}P,[97] ^{19}F [98] or ^{13}C.[99] Due to the low abundance of the ^{13}C nucleus, prolonged acquisition times are necessary to obtain satisfactory signal to noise ratios. Alternatively, the use of ^{13}C enriched building blocks allows 'fast ^{13}C gel phase NMR'.[100] ^{1}H NMR has become feasible with the use of magic-angle spinning (MAS) but requires use of a specific probe ('nanoprobe'[101]). MAS NMR techniques (^{1}H MAS, ^{13}C MAS, TOCSY MAS, HMQC MAS) though requiring specific equipment yield high quality spectra and allow direct structure elucidations.[102]

d. Mass Spectroscopy[103]

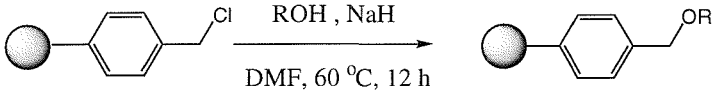
Very high sensitivity and speed of analysis are the two advantages of mass spectroscopy over other analytical techniques. Though a destructive method, mass spectroscopy is often the method of choice in conjunction with HPLC analysis both for reaction monitoring and library characterisation. Electrospray MS and MALDI TOF MS can both be used with adequate sensitivity for single-bead analysis. *In Situ* cleavage followed by MALDI-TOF analysis has been achieved with acid-labile linkers cleaved with TFA vapors[104] and with photolabile linkers[105] allowing real time monitoring.

1.3 Choice of synthetic strategy

1.3.1 Ether bond formation: solid phase methodologies

A high yielding and general method of ether bond formation on the solid phase is crucial for successful access to polyether libraries. A large repertoire of synthetic methods[106] have been developed in solution for the synthesis of linear and cyclic ethers. A range of reactions has now been translated to the solid phase.

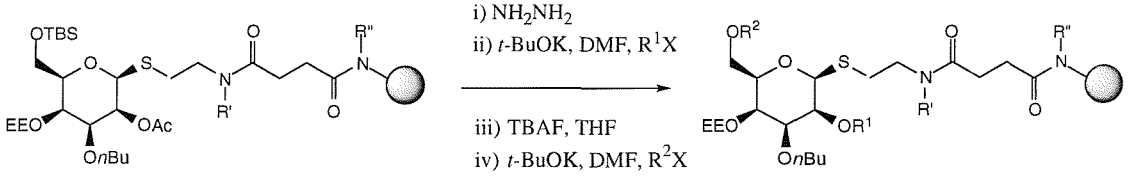
The Williamson reaction, a traditional method of ether synthesis in solution, has found utility mainly in the case of *O*-benzylation for the coupling of alcohols and phenols onto Merrifield resin or chlorinated Wang linker[107] (Scheme 1.4).



R = $Ph(CH_2)_2$, $PhCH_2CHCH_2CH_3$, $PhCH_2C(CH_3)_2$, 2-*t*-butylphenyl, 4-*t*-butylphenyl, 2-fluorophenyl, $CHF_2(CF_2)_3CH_2$

Scheme 1.4

Typical procedures[108] involve pre-formation of the alkoxide using soluble bases such as *t*-BuOK or KHDMS followed by addition of the resin. Heterogeneous bases (NaH, KH) have also been used in the presence of a crown ether or a phase transfer catalyst[109] (e.g. $Bu_4N^+Cl^-$). Use of iodomethylated polystyrene appeared to offer no advantages over chloromethylated resin.[110] Excess benzyl chloride groups have been removed by treatment with NaI and subsequent reaction with Bu_3SnH.[111] The direct coupling of symmetrical diols has been achieved by taking advantage of site isolation.[112] Though coupling of both primary and secondary alcohols has been reported in good yields, prolonged reaction times and heating is usually required. Formation of the alkoxide on the resin has been reported in only a limited number of cases. For example, Kunz *et al.*[113] have performed the alkylation of a carbohydrate scaffold with a range of primary alkyl halides (Scheme 1.5).

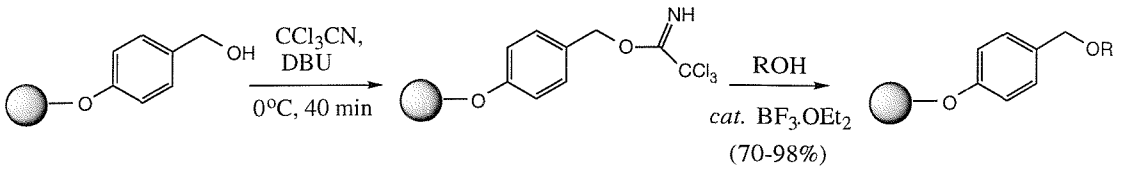


R^1X = CH_3I, *n*BuI, *n*HeptI, $PhCH_2Br$, o-$CNC_6H_4CH_2Br$
R^2X = CH_3I, *i*PrI, *n*HeptI, $PhCH_2Br$, o-$CNC_6H_4CH_2Br$, *cyclo*-$C_6H_{11}CH_2Br$

Scheme 1.5

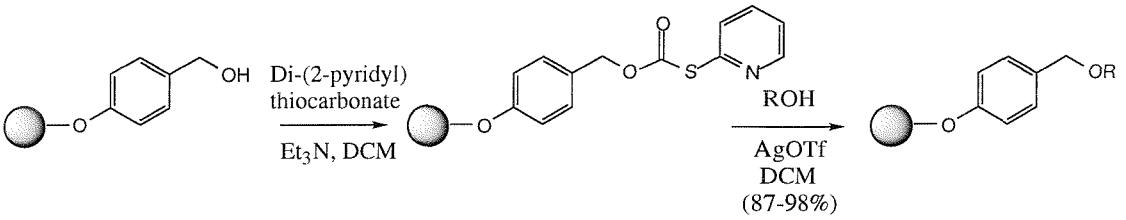
Alkylation of a resin bound secondary alcohol with benzyl halide derivatives has been successfully carried out by Furth *et al.*[114] during the synthesis of amino ether derivatives. Activation by the formation of a resin bound tosylated derivative has been reported by Fréchet *et al.*[115]

Alternative *O*-benzylation procedures under non-basic conditions have been developed by Hannessian *et al.*[116,117] The coupling of representative primary, secondary, and tertiary alcohols bearing a range of functionalities (ester, acetals) proceeded in good to excellent yields under mild Lewis acidic conditions by activation of the Wang linker *via* a trichloroacetimidate derivative[116] (Scheme 1.6).



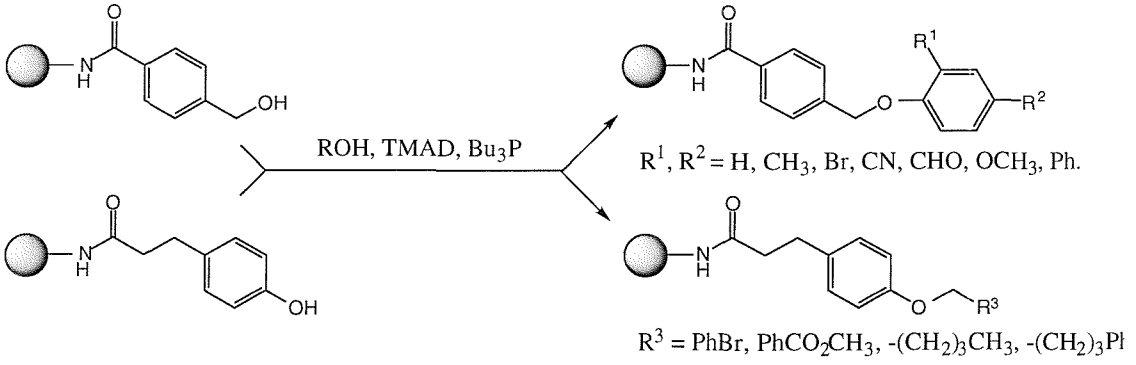
Scheme 1.6

Alternatively, activation of the Wang linker by formation of a 2-pyridylthiocarbonate derivative allowed etherification under neutral conditions[117] (Scheme 1.7).



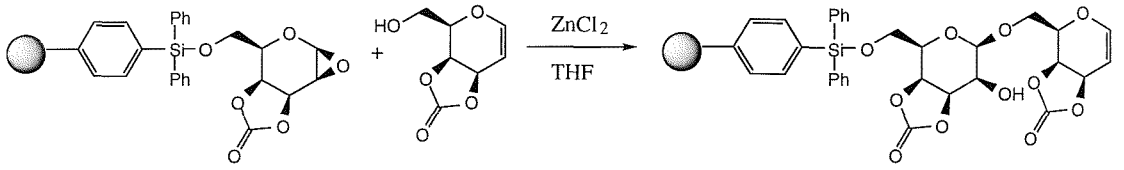
Scheme 1.7

O-Alkylation of resin bound phenols has been achieved using Cs_2CO_3 in DMF[118] or under homogeneous conditions using the neutral Schwesinger base P1-*t*-Bu.[119] However, the method of choice for the solid phase synthesis of alkyl aryl ethers remains the Mitsunobu reaction and has been successfully applied in library synthesis.[120] Both the alkylation of resin bound alcohols with a phenol derivative in solution and the reverse process have been reported[121] (Scheme 1.8).



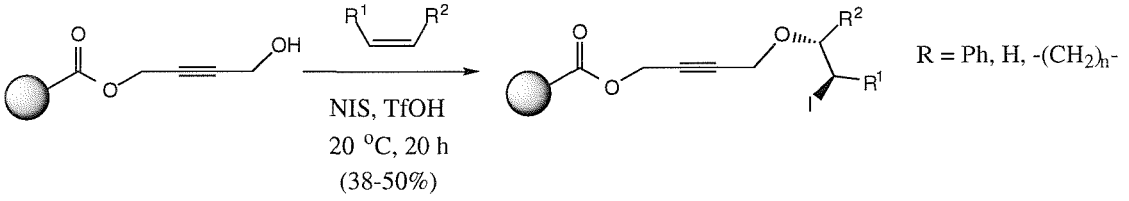
Scheme 1.8

Danishefsky *et al.*[122] used an epoxide opening strategy under Lewis acid conditions for the solid phase synthesis of oligosaccharides (Scheme 1.9). Solid phase synthesis of levoglucan derivatives was performed by epoxide opening with a range of alcohols in the presence of *t*-BuOK or the Schwesinger base P_4-*t*-Bu.[123] Specific solid phase *O*-glycosylation methods and strategies have been extensively reviewed.[124]



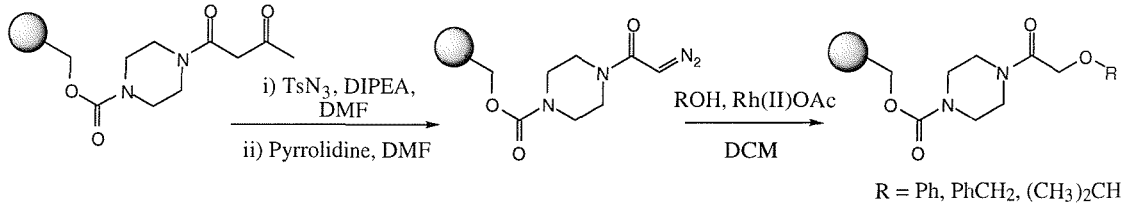
Scheme 1.9

Resin bound ethers have also been prepared by iodoetherification. Treatment of a resin bound diol with styrene derivatives[125] or alkenes[126] in the presence of *N*-iodosuccinimide provided an iodoether derivative; the iodide group could be used subsequently to introduce further diversity (Scheme 1.10)



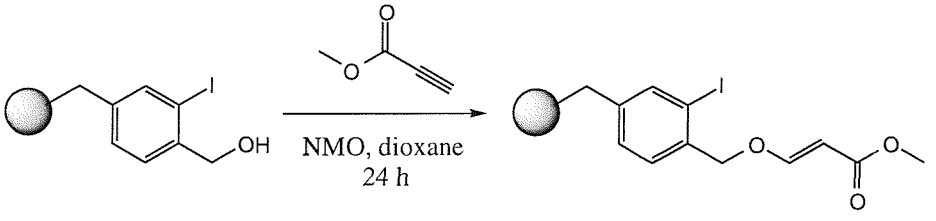
Scheme 1.10

Ether bond formation by carbene OH-insertion has been reported by Zaragoza *et al.*[127] (Scheme 1.11). Treatment of a resin bound diazoacetamide with rhodium (II) acetate generated an intermediate rhodium carbenoid, which could then undergo OH insertion with a series of alcohols. The ether products were obtained in low yields but high purity.



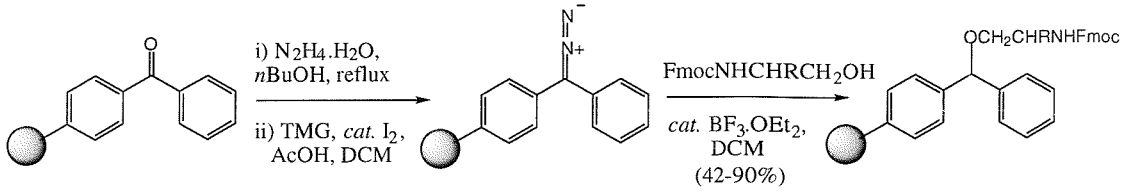
Scheme 1.11

Ethers have been prepared by Michael addition of resin bound diols onto divinyl sulfones,[128] electron poor acetylenes[129] and alkenes[130] (Scheme 1.12).



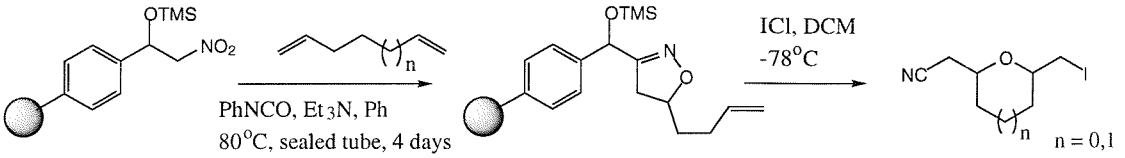
Scheme 1.12

Anchoring of *N*-Fmoc amino alcohols onto a benzhydryl resin has been achieved in good yields *via* etherification with the diphenyldiazomethane derivative[131] in the presence of a Lewis acid catalyst (Scheme 1.13).



Scheme 1.13

The synthesis of 2,5-disubstituted tetrahydrofurans and tetrahydropyran rings was performed by Kurth *et al.* by electrophilic cyclisation of isoxazolines[132] and tetrahydrofuroisoxazolines[130] (Scheme 1.14).



Scheme 1.14

Solid supported cyclic ether synthesis has also been achieved by radical cyclisations,[126] or as part of a cyclisation cleavage strategy *via* an iodine-magnesium exchange.[133]

Use of diols as building blocks for the solid phase synthesis of oligoethers

Diols appear the most straightforward set of building blocks for the construction of polyethers. A wide range are commercially available or can be easily synthesised in optically pure form by asymmetric dihydroxylation.[134] However the use of diols imposes two problems: firstly the low reactivity of the alcohol functionality requires alternate activation of the O-H bond to enhance the nucleophilicity of the oxygen or activation of the C-O bond to convert the alcohol into a reactive alkylating agent. Secondly, synthetic differentiation between the two alcohol functionalities must be achieved. Recent methods for the selective manipulation of diols either by selective monoprotection[135] and/or conversion into electrophilic building blocks (e.g. epoxide,[136] cyclic sulfites and sulfates,[137] halohydrins, stannylene acetals[138]) have been reviewed.[134] Our choice turned to the use of cyclic sulfates.

1.3.2 Cyclic sulfate chemistry

a. Reactivity

1,2-, 1,3- and 1,4-Cyclic sulfates are versatile electrophilic building blocks. Their formation and synthetic applications have been extensively reviewed.[137] They undergo substitution reactions with a wide range of nitrogen, sulphur, carbon, halogen and oxygen nucleophiles. Selected examples, given in figure 1.15, illustrate the scope and versatility of cyclic sulfate chemistry.

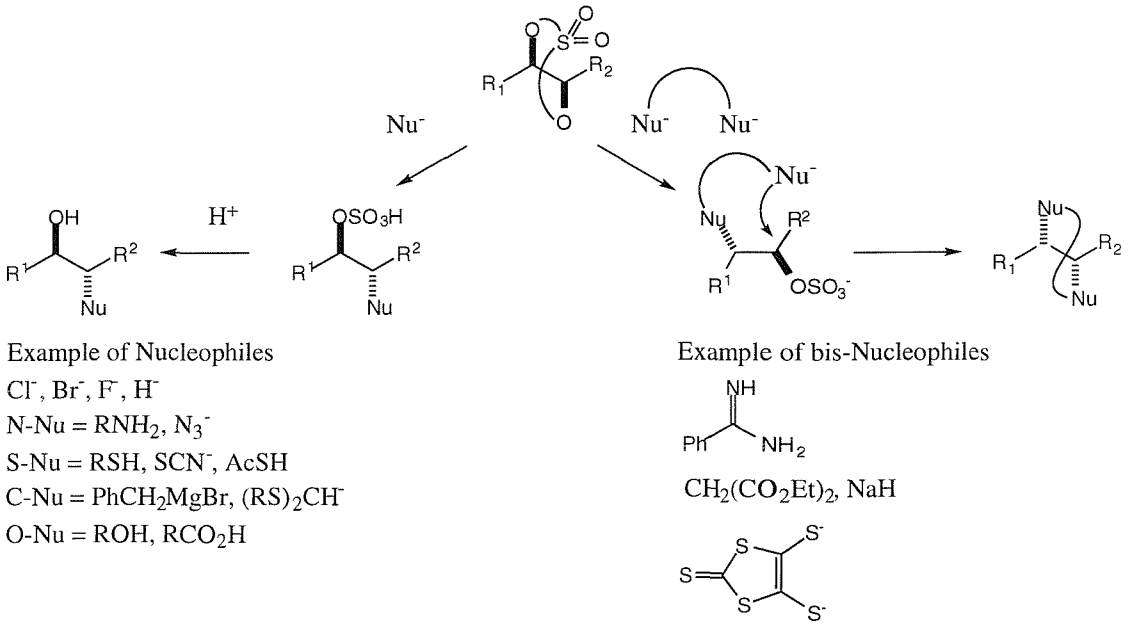
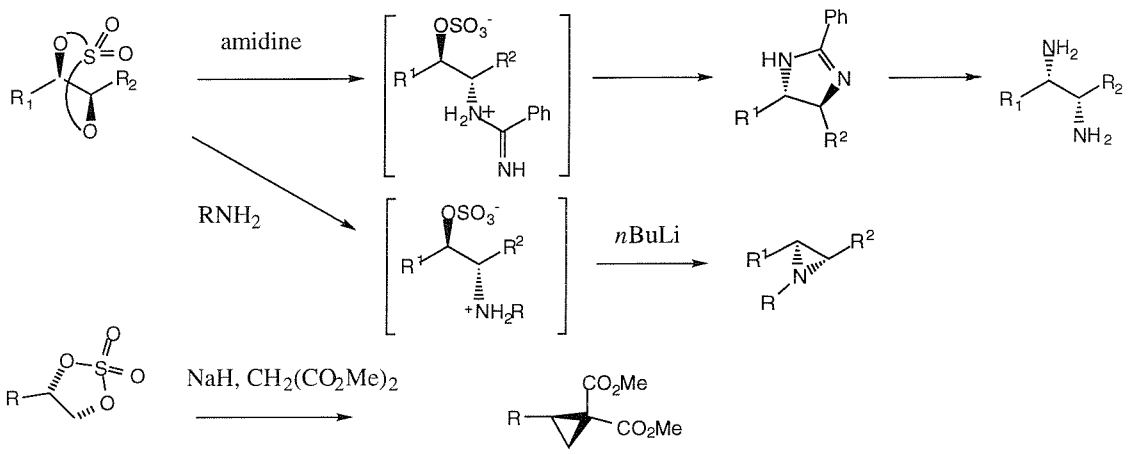


Figure 1.15: Some representative reactions of 1,2-cyclic sulfates.

The high reactivity of the cyclic sulfates has been attributed to the ring strain and the good leaving group ability of the $ROSO_3^-$ moiety. The reaction proceeds *via* an S_N2 mechanism with clean inversion at the stereogenic center. Excellent regioselectivity is achieved in most cases, the reaction being very sensitive to steric and electronic directions.

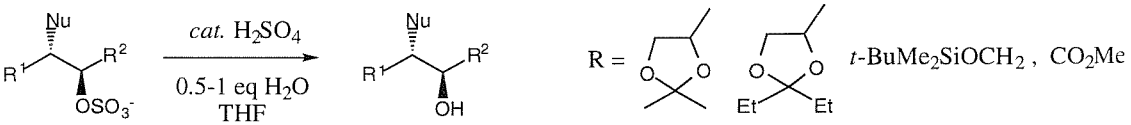
Unlike the β-hydroxyl group generated during epoxide opening, the corresponding sulfate ester moiety can act as a leaving group leading to disubstituted products (Figure 1.15). However, since the dianion SO_4^{2-} is a much poorer leaving group than $ROSO_3^-$ the second displacement is more difficult and has been observed mainly in an intramolecular fashion. Only two examples of intermolecular displacement[139] by sodium mercaptide and dimethylamine have been reported recently and required vigorous reaction conditions ($NaSCH_3$, DMF, 80 °C; or Me_2NH, THF, autoclave).

Double displacements[140] have been exploited for example in the synthesis of cyclopentanediacids,[140a] aziridines,[140c] chiral imidazoline and diamines[140d] (Scheme 1.15).



Scheme 1.15

In most cases, the sulfate ester moiety acts as a protecting group and is later hydrolysed to allow further transformations. Whereas sulfate esters are notably resistant to hydrolysis in neutral or acidic aqueous conditions, they are rapidly hydrolysed in relatively non polar nucleophilic solvents (especially moist ether, dioxane or THF), in the presence of a trace amount of acid.[141] Chemoselective hydrolysis of the sulfate ester moiety has been achieved in the presence of acid sensitive functionalities such as acetonide or silyloxy protecting groups using a catalytic amount of H_2SO_4 (0.1-0.4 eq) in moist THF[142] (Scheme 1.16).



Scheme 1.16

The hydrolysis proceeds with sulphur-oxygen bond scission resulting in complete retention of configuration.[143]

b. 1,2-cyclic sulfates as 'epoxide equivalents'

1,2-cyclic sulfates have often been exploited as epoxide equivalents[137a-b] (Table 1.1). They are often more reactive but can show a different regioselectivity.

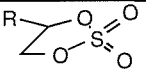
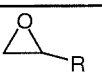
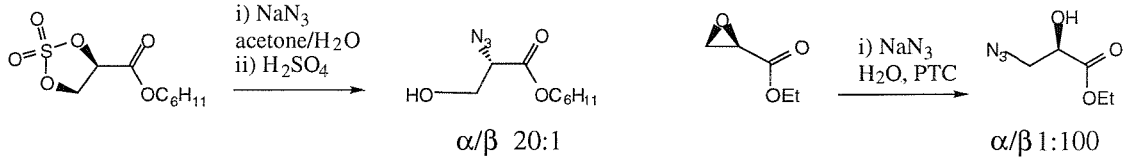
	Cyclic sulfate	Epoxide
Basic structure		
Ring strain	ca. 5-6 Kcal/mol	ca. 27-28 Kcal/mol
Reaction type	S_N2	S_N2
Product type	β-substituted alcohol	β-substituted alcohol
Leaving group	$ROSO_3^-$, good	RO^-, poor
Reactivity	reacts under acidic, basic and neutral conditions without the help of any catalyst	much less reactive, Lewis acid catalysed reaction
Regioselectivity	attack at the less hindered carbon α-substitution preferred if $R=CO_2R$	attack at the less hindered carbon
Stereochemistry	inversion	inversion
Double Nu-displacement	possible	not possible

Table 1.1: Comparison between cyclic sulfates and epoxides

For example, the presence of an ester substituent strongly directs attack at the α position even in the case of monosubstituted cyclic sulfates.[144] Whereas the cyclic sulfate of cyclohexyl glycerate was found to react with azides, benzoates, chloride and fluoride ions predominantly or exclusively at C-2, the epoxide analogue either failed to react or gave the product from attack at C-3 (Scheme 1.17).



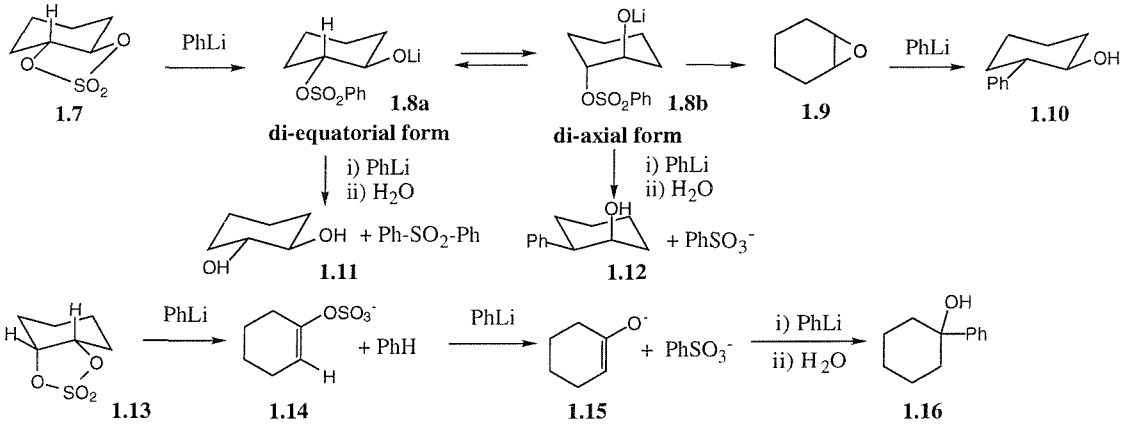
Influence of steric and electronic factors on the regioselectivity - comparison with epoxide

Scheme 1.17

c. Comparison with the parent cyclic sulfites

Cyclic sulfites[137] have found fewer synthetic applications. They are less reactive and in contrast with cyclic sulfates, the sulfur atom is still a potent electrophilic centre leading to competing attack at the sulfur.[145] Whereas nucleophiles such as amines, bromide,[146] thiocyanate and azide[147] tend to add at the carbon center, organolithium, Grignard reagents,[148] and fluoride ions add predominantly to the sulfur. However, cyclic sulfites can constitute interesting alternatives when the cyclic sulfates cannot be easily prepared or are too unstable.[149]

In the case of cyclic sulfates, attack at the sulfur is likely to occur only if approach of the nucleophile to the carbon is hindered. Only rare examples have been reported. Upon reaction of *trans*-1,2-cyclohexanediol cyclic sulfate **1.7** with phenyl lithium Anderson *et al.*[150] isolated a mixture of products (Scheme 1.18). It was postulated that the di-equatorial form imposed by the *trans* stereochemistry prevented substitution by phenyl lithium at the carbon center. Addition at the sulfur gave instead the intermediate **1.8**. The di-axial form **1.8b** could then further undergo either back-attack of the hydroxy group to give the epoxide **1.9** or substitution by PhLi to give **1.12**, whereas the di-equatorial form **1.8a** underwent a second attack at the sulphur to give **1.11** and phenyl sulfone. Reaction of *cis*-1,2-cyclohexanediol cyclic sulfate **1.13** gave 1-phenylcyclohexanol **1.16** suggesting that 1,2-elimination to form **1.14** occured, followed by nucleophilic attack on the sulfur to give the enolate **1.15** which then added phenyl lithium. Likewise *cis*-1,2-cyclopentanediol cyclic sulfate gave 1-phenylcyclopentanol.

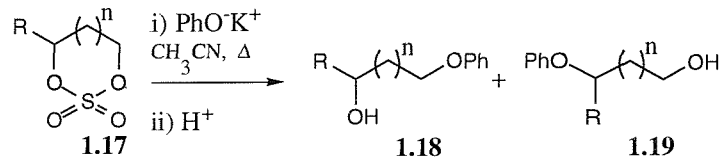


Scheme 1.18

Similarly, attack at the sulfur was observed by Berridge *et al.*[151] upon reaction of cyclic sulfate sugar derivatives with phenoxide and fluoride nucleophiles.

d. Examples of O-alkylation using cyclic sulfates

Cyclic sulfates have proved to be very efficient *O*-alkylating agents in a number of reactions. Berridge *et al.*[151] studied the reactivity of a series of 1,2-, 1,3- and 1,4- cyclic sulfates toward *O*-alkylation. In all cases, reactions with phenoxide were rapid, high yielding and proceeded with excellent regioselectivity (Table 1.2). No double substitutions were observed. Other examples of reactions with phenolate derivatives have been reported.[152]

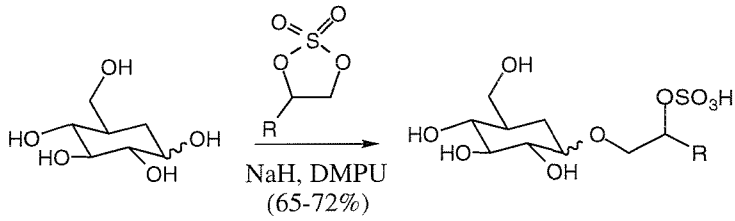


1.17 **1.18** **1.19**

cyclic sulfate **1.17**	Phenyl ether Yield (**1.18** + **1.19**)	ratio **1.18:1.19**
butane 1,2-	80 %	100:0
butane 1,3-	80 %	100:0
propane 1,2	85 %	75:25
butane 1,4-	83 %	na

Table 1.2

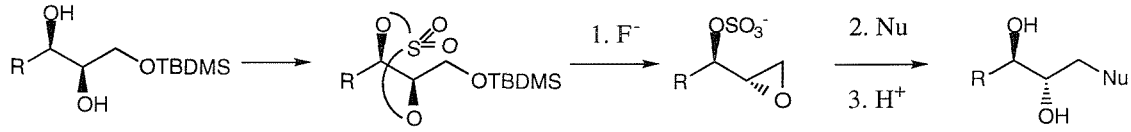
Cyclic sulfates have been used in the preparation of surfactants.[153] Schmidt *et al.*[154] have reported for example the selective anomeric *O*-alkylation of glucose with cyclic sulfates of long chain diols (Scheme 1.19).



R = $C_{10}H_{21}$, $C_{12}H_{25}$, $C_{14}H_{29}$

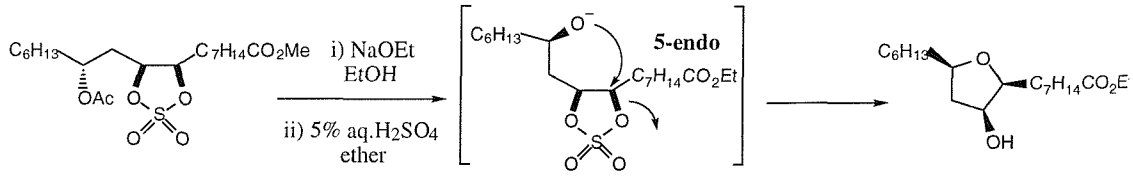
Scheme 1.19

The capacity of the sulfate ester moiety to act as an *in situ* protecting group allowed the synthesis of erythro-diols *via* an irreversible Payne rearrangement[155] (Scheme 1.20), later used as a key step in the synthesis of the natural product (+)-disparlure.[156]



Scheme 1.20

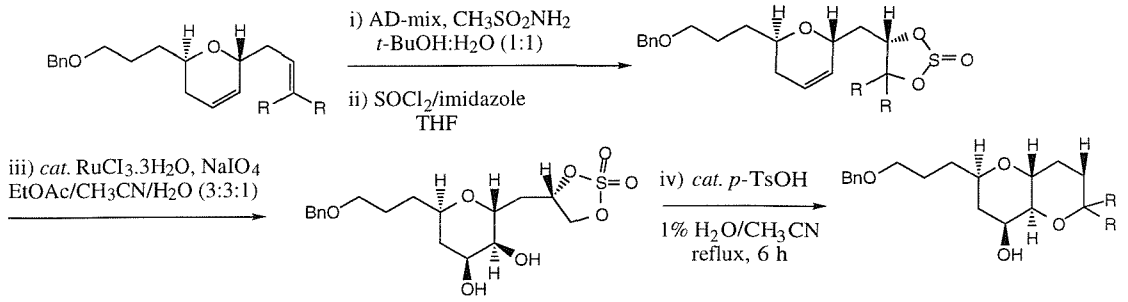
Cyclic sulfates have been exploited in the stereoselective synthesis of ether rings, key fragments of many natural polyethers. For example, 5-endo cyclisation of hydroxy cyclic sulfate **1.21** formed *in situ* by saponification of acetate **1.20**, lead to optically active tetrahydrofurans **1.22** with clean inversion of configuration at the reacting center[157,158] (Scheme 1.21).



1.20 **1.21** **1.22**

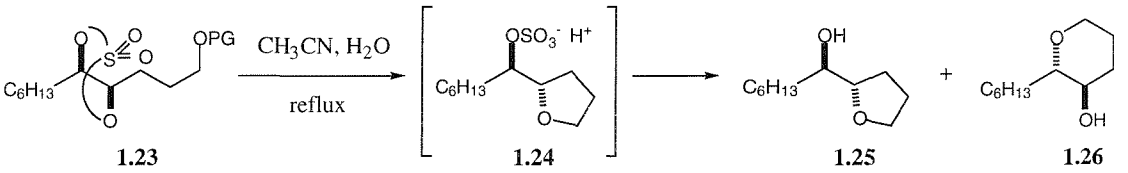
Scheme 1.21

A similar strategy allowed the synthesis of fused *bis*-pyran systems[159] (Scheme 1.22).



Scheme 1.22

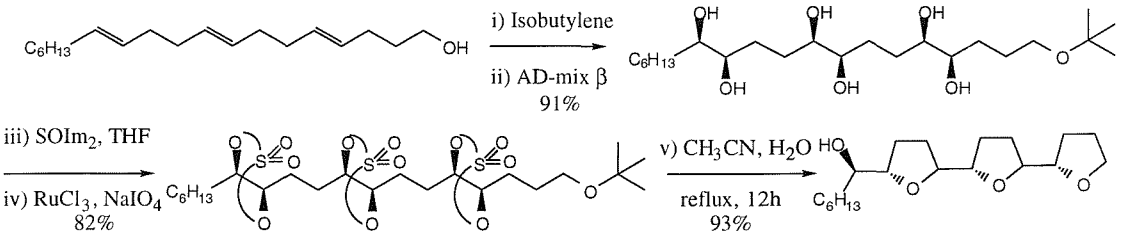
Searching for an epoxide equivalent that would favor 6-*endo-tet* cyclisation over normally favored 5-*exo-tet* cyclisation, Rychnovsky *et al.* [160] investigated the solvolysis of the cyclic sulfates **1.23** (Scheme 1.23). All substrates favored the 5-*exo-tet* cyclisation to give the THP derivative **1.25** as the major product. Interestingly, direct obtention of the free alcohol other than the intermediate sulfate ester **1.24** was observed.



PG	**1.25/1.26**	yield (**1.25+1.26**)
Bn	> 50	97%
MOM	32	90%
TBS	10	98%
t-Bu	32	91%

Scheme 1.23

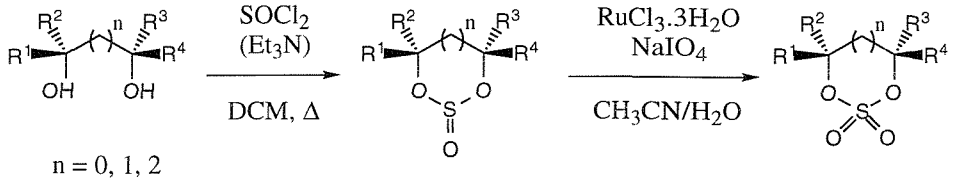
This feature was exploited further to an elegant cascade cyclisation to give 2,5-oligo-THF, the reaction proceeding by a serie of cyclisations and *in situ* sulfate ester hydrolyses (Scheme 1.24).[160]



Scheme 1.24

e. Synthesis of cyclic sulfates

1,2-, 1,3-, and 1,4-cyclic sulfates are most conveniently obtained in optically pure form and in high yields from the corresponding diols using the two step procedure reported by Sharpless *et al.*[142a] (Scheme 1.25).



n = 0, 1, 2
R = H, Aryl, Alkyl, CO_2R, CONHR, Sugar, ketal, etc.

Scheme 1.25

The diol is first converted to the cyclic sulfite by treatment with thionyl chloride in refluxing DCM or CCl_4. The crude sulfite is then oxidised[161] in a biphasic mixture of DCM/acetonitrile/water in presence of a catalytic amount of $RuCl_3.3H_2O$ (*ca.* 0.1-1 mol%) using a slight excess of $NaIO_4$ as the co-oxidant. In the case of substrates having acid labile substituents, synthesis of the cyclic sulfites can be carried out in presence of Et_3N or pyridine to scavenge the HCl evolved. Since tertiary amines inhibit the oxidation catalyst, isolation of the cyclic sulfite by simple aqueous work up is carried out prior to oxidation. The oxidation step can be performed in the presence of acid and base labile functional groups such as acetals or ketals, although it fails in the presence of functional groups (e.g. amide) which can bind ruthenium tetroxide and thus stop the catalytic turnover.[162]

Direct synthesis of 1,2-cyclic sulfates from the diol has been reported using SO_2Cl_2. Low yields are generally obtained in the case of acyclic diols. However, the reaction proceeds in satisfacty yields when the 1,2-diol moiety is *syn* in a 5- or 6-membered ring (e.g. in carbohydrate systems[151,163]) or possesses strongly electron withdrawing substituents,[152c] thus overcoming the competing S_N2 displacement by chloride.

1.3.3 Proposed strategy for the solid phase synthesis of oligo-ether libraries

Using cyclic sulfate chemistry, the construction of the polyether chain was envisaged by a two step iterative process akin to peptide synthesis (Figure 1.16). The proposed strategy involved first *O*-alkylation of a resin bound alcohol with a cyclic sulfate followed by hydrolysis of the intermediate sulfate ester moiety to regenerate a hydroxyl functionality which could undergo another iteration. The sulfate ester moiety acting as a protecting group would allow repeated couplings to push the reaction to completion or alternatively the selective capping of the unreacted alcohol.

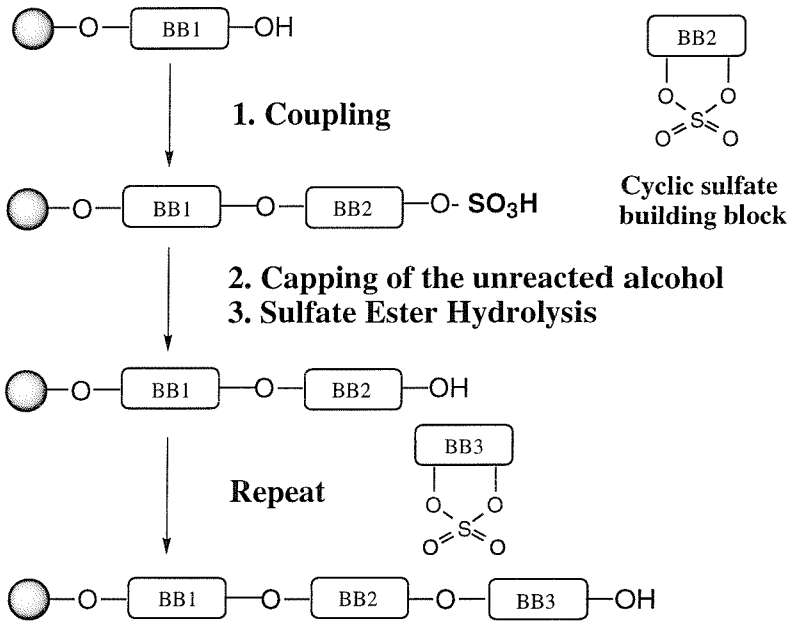


Figure 1.16

Use of cyclic sulfates would thereby serve the dual purpose of activating one hydroxyl group while protecting the adjacent hydroxyl group avoiding the synthesis of monoprotected diols or bifunctionalised building blocks. Moreover, being readily available in optically pure form from the corresponding diols, they would allow access to a very diverse monomer set. Additionally, spacing between the oxygens could be varied from 2 to 4 methylene units using 1,2- 1,3- or 1,4-cyclic sulfates. Though not investigated here, ether bond formation could be extended to the introduction of other heteroatoms (N, S) using thiols and amines as nucleophiles.

The development of the *O*-alkylation and sulfate ester hydrolysis procedures will be presented in chapter 2. Application of cyclic sulfate chemistry to the synthesis of polyether libraries will be described in chapter 3. Due to the particular structural features of the target molecules, monitoring constituted a major issue throughout the project and

Chapter 2: Cyclic Sulfate Chemistry

Due to the novelty of the solid phase approach, a model reaction was chosen to allow the study of the reaction conditions in solution prior to the transfer and optimisation of the reaction onto the solid phase (Figure 2.1).

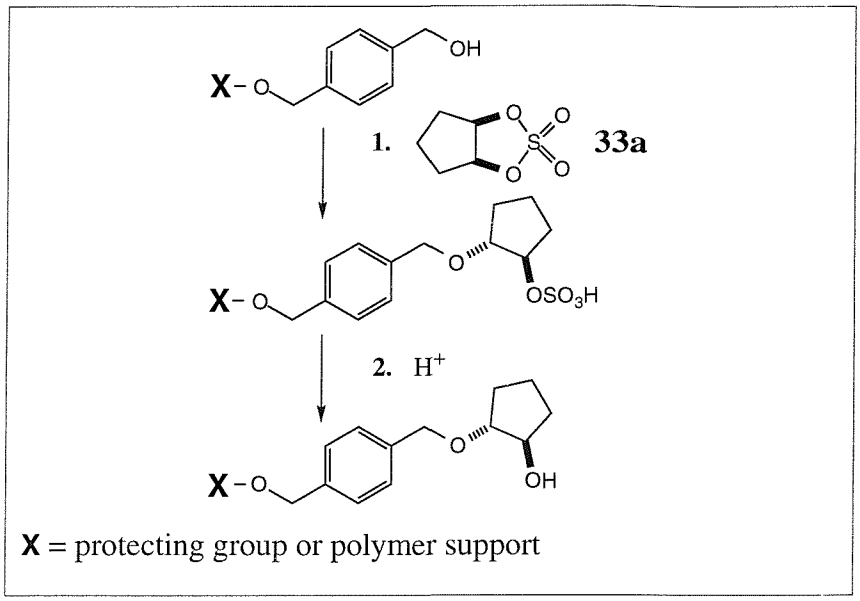


Figure 2.1: Model reaction for the solution and solid phase studies

The terminal carboxylic acid and hydroxyl groups present in the target polyether mimics provide two possible attachment points of the first monomer onto the support. The linker selected must however be stable to both the basic conditions of the *O*-alkylation step and the mild acidic conditions used for the sulfate ester hydrolysis. A wide range of linkers has been developed for the tethering of alcohols through ester,[164] silyl ether,[165] alkyl ether (trityl linker,[166] Wang linker,[107b,116,117] Rink linker[167]), ketal (Ellman's linker,[168] vinyloxy linker[169]), aminal[170] and carbonate[171] functionalities. Most linkers designed for anchoring carboxylic acids[172] involve the coupling of the acid onto the linker through an ester bond and can give trans-esterification side reactions during the *O*-alkylation step. Attachment of the first building block *via* a more stable ether bond using the terminal hydroxyl functionality was therefore preferred. Trityl linkers allowing both the tethering and release of primary alcohols under relatively mild conditions had been extensively used by Fréchet *et al.*[173] for the manipulation of symmetrical diols. A trityl linker was therefore envisaged for the initial studies. 1,4-Benzenedimethanol was selected as the first building block. The benzylic alcohol would constitute a relatively reactive nucleophile and at the same time provide a chromophore for the target molecules, allowing monitoring by HPLC-UV analysis. By analogy to the ether rings found in the natural polyethers, 1,2-cyclopentanediol cyclic sulfate **33a** was chosen as the model cyclic sulfate monomer.

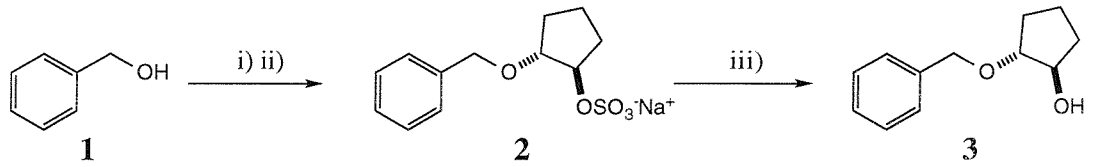
2.1 *O*-alkylation using cyclic sulfate chemistry

2.1.1 Solution phase model

2.1.1.1 Qualitative study

The reactions were first examined in solution to assess their feasibility for solid phase synthesis. The choice of the reaction conditions was directed both by literature procedures in solution and the constraints of solid phase synthesis.

A typical procedure used in *O*-alkylation reactions with cyclic sulfates involves pre-formation of the alkoxide by treatment of the alcohol with bases such as NaH or *t*-BuOK, followed by addition of the cyclic sulfate. Best results are generally obtained in polar aprotic solvents (acetonitrile,[151] DMF, THF or DMPU[154]). To provide the starting conditions for the solid phase, a qualitative study was carried out with different solvents (THF and DMF) and bases (NaH and two soluble bases, *t*-BuOK and LHDMS, more compatible with the solid phase). Benzyl alcohol **1** was treated with a slight excess of base (1.2 eq) for 30 min, followed by addition of 1,2-cyclopentane cyclic sulfate **33a** (1.5 eq). The reactions proceeded extremely slowly in THF, but were close to completion (TLC) in DMF in less than 15 min. Identical results were obtained with the 3 bases selected. The reaction carried out with NaH proceeded in 71% yield (Scheme 2.1).



1 **2** **3**

Reagents and conditions: i) NaH (1.2 eq), 15-crown-5 (0.1 eq), DMF, 30 min. ii) **33a** (1.2 eq), DMF, 30 min, 71%. iii) H_2SO_4 (0.1 eq), H_2O (0.01 eq), dioxane, 30 min, 60%.

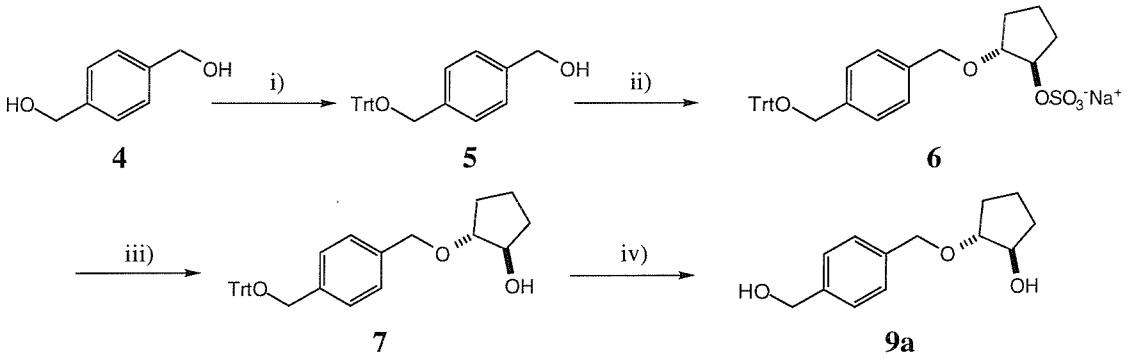
Scheme 2.1

For comparison, synthesis of *trans*-2-benzyloxycyclopentanol **3** has been reported by epoxide opening[174] of cyclopentene oxide with benzyl alcohol in the presence of $BF_3.OEt_2$ in 32% yield. The reaction was accompanied by formation of a mixture of *trans*-2-(*trans*-2-benzyloxycyclopentyloxy)cyclopentanol isomers by side reaction of **3** with the epoxide.

Hydrolysis of the sulfate ester was then attempted using the procedure reported by Sharpless *et al.*[142] After removal of the solvent, direct treatment of the crude product **2** with a small amount of H_2SO_4 (0.1 eq) and water (0.01 eq) in dioxane resulted in the rapid hydrolysis of the sulfate ester moiety to give the free alcohol **3**.

2.1.1.2 Synthesis of two model compounds

A key issue for the viability of the solid phase approach was the stability of the trityl linker to the acidic conditions necessary for the sulfate ester hydrolysis step. Using a trityl protecting group as an equivalent of the trityl linker, the complete synthetic scheme was therefore first performed in solution, simultaneously allowing the synthesis and complete characterisation of the sulfate ester intermediate **8a** and ether product **9a** (Scheme 2.2 and 2.3).

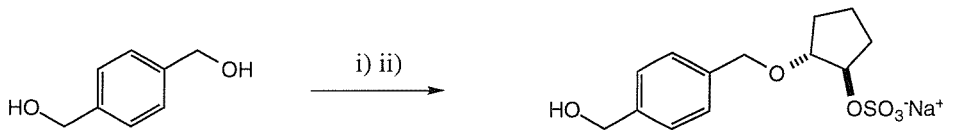


Reagents and conditions: i) Trityl chloride (1 eq), 1,4-benzenedimethanol **4** (2 eq), DBU (1.2 eq), DCM/THF 1:1, O/N, 65%. ii) NaH (1.3 eq), DMF, 15 min then 1,2-cyclopentane cyclic sulfate **33a** (1 eq), DMF, 79%. iii) H_2SO_4 (0.2 eq), dioxane/ 0.2% H_2O, 98%. iv) 15% TFA/MeOH, 1 h, 87%.

Scheme 2.2

Trityl protection of 1,4-benzenedimethanol **4** was carried out by a standard literature procedure.[175,176] Slow addition of trityl chloride in DCM to a concentrated solution of 1,4-benzenedimethanol (2 eq) and DBU (1.2 eq) afforded the monoprotected diol **5** in 65% yield. *O*-alkylation was carried out by treating **5** with a slight excess of NaH (1.3 eq) in DMF for 15 min, followed by addition of the cyclic sulfate **33a** (1 eq). The reaction proceeded rapidly (15 min) and afforded the intermediate sulfate ester **6** in good yield (79%). Treatment of **6** with a catalytic amount of sulfuric acid (0.2 eq) in moist dioxane achieved the rapid and selective hydrolysis of the sulfate ester moiety. No trityl deprotection was observed. Final cleavage of the trityl protecting group was performed with 15% TFA in MeOH and gave **9a** in 87% yield.

The intermediate sulfate ester **8a** was prepared by direct addition of cyclic sulfate **33a** to an excess of 1,4-benzenedimethanol (2 eq) and NaH (0.5 eq) in DMF (37% yield) (Scheme 2.3).



4 **8a**

Reagents and conditions: i) 1,4-benzenedimethanol **4** (2 eq), NaH (0.5 eq), DMF, 10 min. ii) 1,2-cyclopentanediol cyclic sulfate **33a** (1 eq), DMF, 1.5 h, 37%.

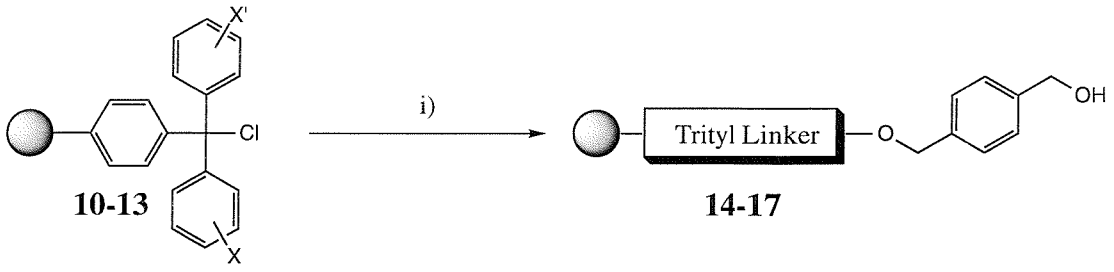
Scheme 2.3

The products **8a** and **9a** were fully characterised and used as analytical standards for the following studies.

2.1.2 Solid phase model

2.1.2.1 Optimisation of the Loading and cleavage conditions on trityl resins

Having demonstrated in solution the possibility of achieving the selective hydrolysis of the sulfate ester moiety in the presence of a trityl protecting group, the 2% cross-linked polystyrene 2-chlorotrityl resin **10** was selected for the initial studies, the chloro substituent slightly increasing the acid stability of the linker. PS/1%DVB 2-Chlorotrityl chloride resin **11**, and two TentaGel resins, NovaSyn® TGT alcohol resin **12** and NovaSyn® Dichloro TGT resin **13** were later used during the course of the reaction optimisation process (Scheme 2.4).



10-13 **14-17**

10, **14** X = H, X' = 2-Cl; 2-Chlorotrityl chloride resin (PS/2% DVB)
11, **15** X = H, X' = 2-Cl; 2-Chlorotrityl chloride resin (PS/1% DVB)
12, **16** X = X' = H; NovaSyn® TGT alcohol resin (TentaGel)
13, **17** X = X' = 4,4'-Cl; NovaSyn® Dichloro TGT resin (TentaGel)

Reagents and conditions: i) 1,4-benzenedimethanol **4** (10 eq), pyridine, (20 eq), DCM/THF 1:1, 48 h. **14** loading = 0.2 mmol/g (30%), **15** loading = 0.5 mmol/g (38%), **16** loading = 0.07 mmol/g (31%). **17** loading = 0.17 mmol/g (85%).

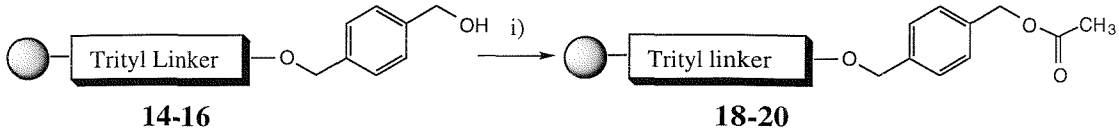
Scheme 2.4

Coupling of diol **4** was carried out by a standard procedure.[177] The resins **10-13** were treated with a concentrated solution of 1,4-benzenedimethanol **4** and pyridine in a mixture of DCM/THF (1:1) for 48 h. A large excess of diol (10 eq, 1-1.5 M) was used to ensure both a satisfactory loading and to avoid cross-linking. However, only moderate yields (30-38%) were obtained. Replacement of pyridine by DBU[174] did not significantly improve the yields. Due to the high moisture sensitivity of the resin, use of freshly chlorinated resin was found later to be the most important factor and allowed us to achieve a yield of 85% on resin **13**.

Typical procedures for the cleavage of alcohols from trityl and 2-chlorotrityl resins use 1 to 50% TFA in DCM containing 5% TIS.[178] The use of acetic acid or formic acid[166a] has also been reported. In all cases, the formation of ester by-products is a major side reaction. Hydrolysis of the esters is generally achieved by treatment of the crude product with aqueous $NaHCO_3$ and organic extraction but was not applicable here due to the water solubility of the products. TFA ester formation was however avoided by reducing the amount of TFA to 3% (without affecting the yields of cleavage) and most importantly by concentration of the filtrates at room temperature with co-evaporation of the TFA by repeated addition of CH_3CN. Treatment of the residue in CH_3CN with a small amount of NH_3 followed by evaporation of the solvent could additionally ensure complete hydrolysis of the esters. Rapid and complete cleavage requires the addition of a scavenger to quench the trityl cation and displace the equilibrium in favour of the free alcohol. Triisopropylsilane was not always effective; while addition of methanol[179] was found to be more efficient and less expensive especially for large scale cleavages. To avoid the formation of TFA ester by-products, the use of HCl in dioxane[180] or dry HBr[181] had also been reported though in the latter case bromination was a potential side reaction. Cleavage with a commercial solution of 4M HCl in dioxane was therefore attempted. Longer treatments (1 h) were required to ensure satisfactory cleavage whilst avoiding by-product formation due to the cleavage conditions. A 30 min treatment with 4M HCl/dioxane was therefore adopted for routine small scale cleavage as it simplified the cleavage procedure and reduced considerably the time needed for analysis.

Determination of the loading was achieved by small scale cleavage and HPLC-UV analysis using a calibration curve for the alcohol **4**. Direct quantification of the resin bound diol was not attempted by a colorimetric test. The only test reported at the time was based on the release and quantification of the dimethoxytrityl protecting group[83] and was therefore not compatible with the linker used. Nicolaou *et al.*[109] reported later the quantification of resin bound alcohols by capping with Fmoc-Cl, followed by treatment of the resin with 10% Et_3N in DCM and standard Fmoc test.

The extent of cross linking was assessed by capping the resin bound diol **14-16** with acetic anhydride[182] (Scheme 2.5).



14-16 **18-20**

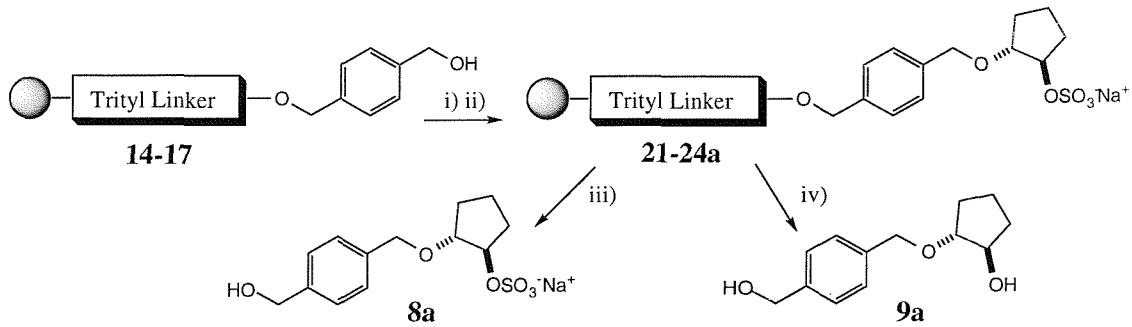
Reagents and conditions: i) Ac_2O (10 eq), Et_3N (10 eq), DMAP (1 eq), DCM, O/N, twice.

Scheme 2.5

Cleavage and HPLC analysis showed incomplete conversion to the monoacetylated product. As no analytical methods were available to confirm completion of the esterification, the capping was repeated a second time. However no changes were observed by HPLC analysis. Quantification of **4** by HPLC-UV analysis using a calibration curve indicated that on the polystyrene resins **14** and **15** 20% of the diol was left unesterified and 15% on TentaGel resin **16**. Examples of double binding of bifunctional substrates, resulting from site-site interactions, have been previously reported on trityl resins.[64,183] However, such percentages are unlikely to result only from cross-linking of the diol as the bulk of the trityl linker reduces the conformational mobility of the reactive sites and should thereby favours site isolation.[64] Incomplete esterification or reduced site accessibility probably contribute to these results.

2.1.2.2 Development of the O-alkylation procedure.

O-alkylation of the resin bound diol with cyclic sulfate **33a** was then attempted (Scheme 2.6).



14-17 **21-24a** **8a** **9a**

Reagents and conditions: i) base (*t*-BuOK or NaH). ii) cyclic sulfate **33a**. iii) 3% TFA/ 5% TIS/ DCM, 30 min. iv) 4M HCl/dioxane, 1h.

Scheme 2.6

a. Monitoring Issues

Monitoring of the reaction proved troublesome. The absence of a colorimetric test for the alcohol and sulfate ester functionalities was a major problem. FTIR analysis was expected to provide an alternative way to assess the success of the reaction and allow kinetic studies by following the disappearance of the OH band and appearance of the OSO_3H band. ATR FTIR spectra were recorded on a Bio-Rad FTS-135 spectrometer with a Golden gate accessory. As shown in figure 2.2, for polystyrene resin **15** the characteristic sharp band of the free OH at ~ 3500 cm^{-1} and broad band of the hydrogen bonded hydroxyl groups at ~ 3400 cm^{-1} could be clearly observed.

With resin **22a**, the appearance of the strong $O\text{-}SO_2\text{-}O$ bands were clearly visible at 1260 and 1217 cm^{-1} and could be used for kinetic studies. However, as the strong broad SO-H band overlapped with the hydroxyl band, IR analysis did not allow to determine the extend of completion of the reaction.

Gel phase NMR of resin and **11**, **15** and **22** was attempted in various solvent (d^6-benzene, $CDCl_3$) and with an extended number of scans. The NMR spectra obtained were very broad and no signal from the tethered molecule could be discerned (whereas with later work on TentaGel Wang resin, the cyclopentane moiety gave rise to characteristic signals). The quality of the gel phase NMR spectra (line widths) depends principally on the mobility of the tethered molecule and, as demonstrated in different studies,[184] is strongly affected by the polymer support chosen (% cross linking, swelling). The low mobility of the compound associated with the trityl linker, which is an integral part of the polystyrene resin can therefore probably account for these results.

The low molecular weight and absence of readily ionisable functional groups prevented the detection of diol **4** by either ES MS or APCI MS. Similarly the ether product **8a** could not be detected at low concentrations. Detection by ESMS (+ve mode) proved even more difficult when TentaGel resin **16** or **17** were used due to the leakage of PEG from the resin upon acid treatment. Detection of the sulfate ester **8a** was easily achieved by ES MS (-ve mode) but was very often swamped by the presence of residual TFA from the cleavage or from the HPLC solvent. Replacement of TFA by NH_4OAc to buffer the HPLC solvents later allowed the successful use of LC-ESMS (-ve).

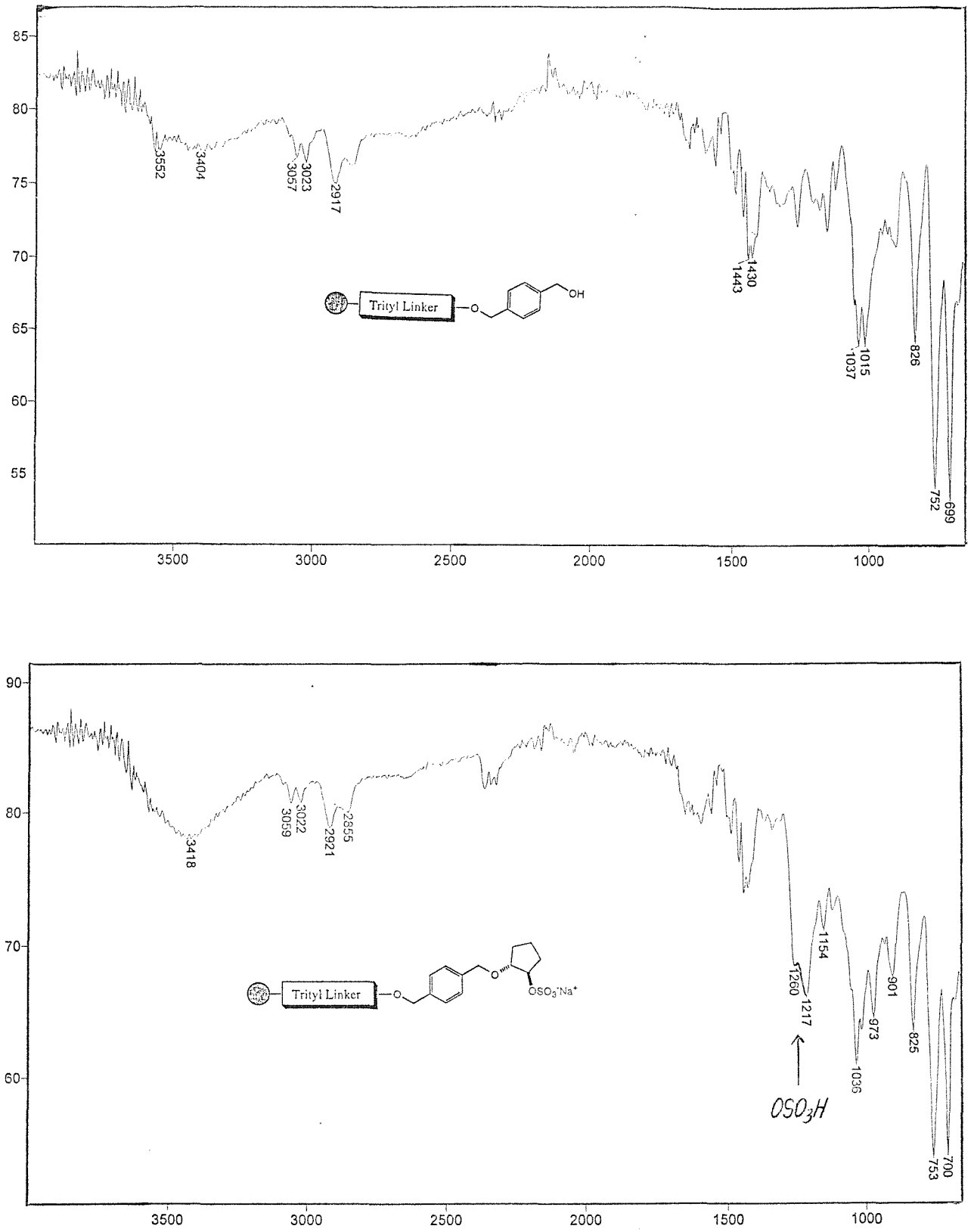
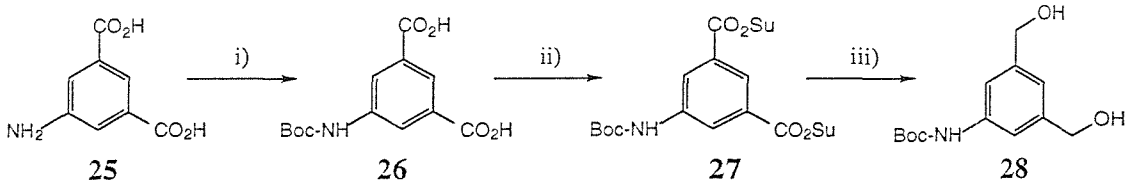


Figure 2.2: FTIR spectra of resin **15** and **22a**

To assist detection of both the starting material and products (or by-products) by mass spectrometry, use of building block **28** bearing an additional amine functionality was investigated (Scheme 2.7). Boc protection of the amine was required to avoid side reaction with the cyclic sulfate. **28** was synthesised in 3 steps from commercially available 5-amino isophthalic acid **25**.



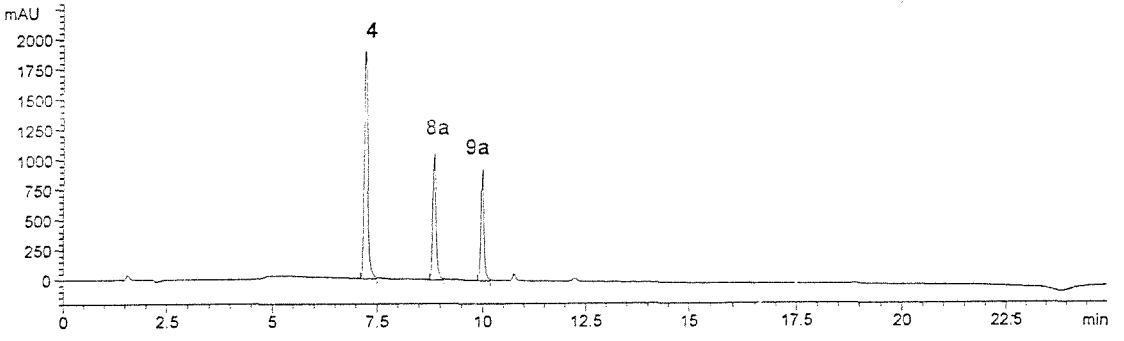
25 **26** **27** **28**

Reagents and conditions: i) Boc_2O (1.1 eq), NaOH (2 eq), dioxane, 78%. ii) *N*-hydroxy succinimide (2 eq), DCC (2 eq), DMF/THF, 65%. iii) DIBAL (7 eq), THF, 83%.

Scheme 2.7

Boc protection with Boc_2O under standard conditions[185] gave **26** in 78% yield. Direct reduction of the dicarboxylic acid **26** with BH_3.THF under various conditions (addition of trimethylborate,[186] heating at 40 °C) gave the diol **28** in poor yield (50%). The *N*-hydroxysuccinic ester **27** was therefore prepared by reaction of **26** with *N*-hydroxysuccinimide and DCC (65% yield). Subsequent reduction with DIBAL[187] afforded the diol **28** in 83% yield. Coupling of **28** onto the trityl resin **11** was achieved under the conditions previously described for 1,4-benzenedimethanol. Unfortunately upon cleavage with 4M HCl/dioxane, partial Boc deprotection was observed leading to complicated HPLC chromatograms, thus further complicating reaction monitoring. Use of **28** was therefore abandoned and the optimisation study was carried out with 1,4-benzenedimethanol as the first building block.

Monitoring of the reaction was therefore mainly limited to small scale cleavage and HPLC analysis by comparison with the reference compounds **8a** and **9a** made in solution (Figure 2.3).



HPLC chromatogram of the reference compounds: diol **4** t_R = 7.3 min, ether compound **9a** t_R = 9.1 min, sulfate ester **8a** t_R = 8.4 min. λ = 220 nm. 20 min gradient from 100% [H_2O/0.1% TFA] to 100% [CH_3CN/0.04% TFA].

Figure 2.3

Characterisation of any side-products required large scale synthesis, cleavage and analysis by conventional methods, considerably slowing down the optimisation process. Cleavage of resins **21-24** with 4M HCl/dioxane took place with concomitant hydrolysis of the sulfate ester whereas cleavage with TFA left the sulfate ester moiety untouched. The extent of conversion of the diol **4** to the ether product was determined by HPLC comparison of the percentage area of the peaks corresponding to diol **4** and product **9a** (or **8a**). It must be noted that this method is not strictly accurate due to the slight difference of extinction coefficient of the compounds **4**, **8a** and **9a** but provided a good estimate (± 5%).

b. Development and Optimisation of the Solid Phase O-Alkylation Procedure

In order to determine the optimum conditions of ether bond formation, a number of variables were investigated, including the choice of base, solvent, resin, concentrations of reagents, and reaction times. Consecutive rounds of optimisation were carried out. The reaction conditions and results obtained are summarised in the tables 2.1-2.8.

A first set of experiments was carried out on the 2% cross-linked polystyrene resin **14**. Despite varying all possible parameters the yields did not go above 38% and proved difficult to reproduce (Table 2.1). Attempts to drive the reaction by heating at 50 °C resulted in degradation of the cyclic sulfate and complete failure of the reaction.

Exp.*	i) Alkoxide formation				ii) Alkylation			% conversion	
	Base	crown ether	solvent	time	33a	solvent	time	1st / 2nd coupling	
1	*t*-BuOK 5 eq	×	THF	1 h	5 eq	DMF	O/N	10%	16%
2	*t*-BuOK 5 eq	×	THF/DMF 1:1	1 h	5 eq	DMF	O/N	35%	38%
3	*t*-BuOK 5 eq	×	THF/DMSO	1 h	5 eq	DMSO	O/N	5%	10%
	t-BuOK 5 eq	×	THF/DMPU	1 h	5 eq	DMPU	O/N	10%	11%
4	*t*-BuOK 5 eq	1 eq	THF	1 h	5 eq	DMF	O/N	14%	16%
5	*t*-BuOK 20 eq + filter	×	THF	1 h	5 eq	DMF	O/N	8%	10%

* Reaction carried out on resin PS/2%DVB resin **14**.

Table 2.1

Repeated couplings afforded only a slight increase in yield but satisfactorily was not associated with the formation of side products. HPLC analysis showed only the presence of the unreacted alcohol **4** and the ether product **8a** confirming that the sulfate ester moiety acted successfully as a protecting group. It was postulated that the reduced swelling capacity associated with the high degree of cross-linking of resin **14** (2% DVB) could be responsible for the low yields obtained. The study was therefore repeated on the more lightly cross-linked (1% DVB) polystyrene resin **15** and initially concentrated on the use of NaH as the base.

As shown in table 2.2, DMF proved to be the best solvent. The combination of DMSO and NaH to form the soluble methylsulfinyl carbanion[188] also gave satisfactory results. The reaction failed with DMPU, probably due a lower swelling of the resin.

Exp*	i) Alkoxide formation				ii) Alkylation			% conversion
	NaH (eq)	crown ether	solvent	time	33a (eq)	solvent	time (h)	1srt/2nd / 3rd coupling
1	5 eq c = 0.6M	×	DMF	1.5 h	5 eq c = 0.3M	DMF	O/N	46% 56% 62%
2	5 eq c = 0.6M	×	DMSO	1.5 h	5 eq c = 0.3M	DMSO	O/N	46% 48% ×
3	5 eq c = 0.6M	×	DMPU	1.5 h	5 eq c = 0.3M	DMPU	O/N	2% 11% ×

* Experiment carried out on 1%DVB/PS resin **15**.

Table 2.2

Efficient formation of the alkoxide is crucial for the success of the reaction. As shown in table 2.3, addition of crown ether to promote NaH solubility successfully improved the yields. Use of 1eq of 15-crown-5 (0.2 eq/NaH) proved to be optimal.

Exp*	i) Alkoxide formation				ii) Alkylation			% conversion
	NaH	crown ether	solvent	time	33a	solvent	time	(HPLC)[a]
1	5 eq c = 0.6M	×	DMF	2 h	5 eq c = 0.3M	DMF	O/N	46%
2	5 eq c = 0.6M	0.2 eq	DMF	2 h	5 eq c = 0.3M	DMF	O/N	54%
3	5 eq c = 0.6M	1 eq	DMF	2 h	5 eq c = 0.3M	DMF	O/N	60%
4	5 eq c = 0.6M	5 eq	DMF	2 h	5 eq c = 0.3M	DMF	O/N	55%

* Experiment carried on 1%DVB/PS resin **15**. [a] one coupling.

Table 2.3

The reactions failed when simultaneous addition of the base and cyclic sulfate was conducted. Efficient formation of the alkoxide required the treatment of the resin with NaH for a minimum of 1 h. Longer treatments were unnecessary or resulted in lower yields (Table 2.4).

Exp*	i) Alkoxide formation				ii) Alkylation			% conversion (HPLC)[a]
	NaH	crown ether	solvent	time	33a	solvent	time	
1	3 eq c = 0.4M	1 eq	DMF	2 h	6 eq c = 0.2M	DMF	O/N	50%
2	3 eq c = 0.4M	1 eq	DMF	6 h	6 eq c = 0.2M	DMF	O/N	48%
3	3 eq c = 0.4M	1 eq	DMF	O/N	6 eq c = 0.2M	DMF	O/N	29%

* Experiment carried on 1%DVB/PS resin **15**. [a] one coupling.

Table 2.4

Use of a very large excess of reagents (20 eq) had little effect but a high concentration of reagents (c = 0.3-0.6M) was found to be determinant (Table 2.5).

Exp*	i) Alkoxide formation				ii) Alkylation			% conversion (HPLC)[a]
	NaH	crown ether	solvent	time	33a	solvent	time	
1	5 eq c = 0.6M	1 eq	DMF	2 h	5 eq c = 0.3M	DMF	O/N	56%
2	20 eq c = 0.6M	2 eq	DMF	2 h	20 eq c = 0.3M	DMF	O/N	61%
3	5 eq c = 0.6M	2 eq	DMF	2 h	10 eq c = 0.6M	DMF	O/N	53%

* Experiment carried on 1%DVB/PS resin **15**. [a] one coupling.

Table 2.5

Cyclic sulfate **33a** was found to degrade quickly under the alkylation conditions (*t* BuOK/DMF or NaH/ 15-crown-5/DMF). To circumvent this problem, the reaction was attempted with an excess of cyclic sulfate with respect to the base (Table 2.5 Exp. 3, Table 2.6, Exp. 2). Alternatively, the resin was treated with an excess of *t*-BuOK which was filtered off under N_2 prior to addition of the cyclic sulfate (Table 2.6, Exp. 3). However, in both cases, the yields remained unchanged.

Exp*	i) Alkoxide formation				ii) Alkylation			% conversion (HPLC)[a]
	t-BuOK	crown ether	solvent	time	33a	solvent	time	
1	5 eq	×	THF/DMF 1:1	1.30 h	5 eq	DMF	O/N	52%
2	5 eq	×	THF/ DMF 1:1	1.30 h	10 eq	DMF	O/N	50%
3	10 eq + filter	×	THF/ DMF 1:1	1.30 h	5 eq	DMF	O/N	53%

* Experiment carried on 1%DVB/PS resin **15**. [a] one coupling.

Table 2.6

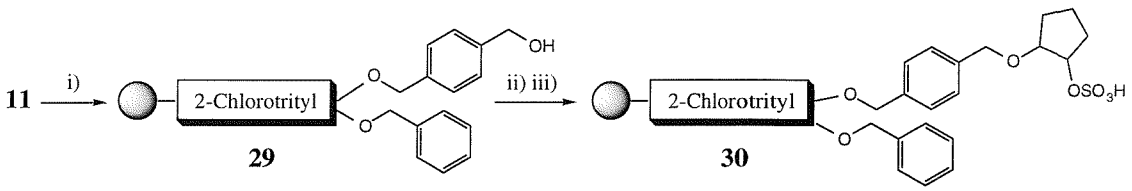
A study of the kinetics of the reaction was carried out. The reaction was performed by treating resin **15** with NaH (5 eq), 15-crown 5 (1 eq) in DMF for 1 h, followed by the addition of cyclic sulfate **33a** (5 eq). Samples were taken at regular time intervals. IR analysis of the resin **22a** showed that the appearance of the sulfate ester band at 1225 cm^{-1} was immediate. Cleavage and HPLC analysis confirmed that the reaction was taking place extremely quickly. No changes were observed after 10 min suggesting that as in solution, the substitution reaction was proceeding extremely rapidly.

The choice of the resin proved to be the most important parameter. As shown in table 2.7, dramatic improvements in the yields could be observed by changing from the 2% cross-linked polystyrene resin **14** (37% yield) to the more lightly cross-linked (1% DVB) polystyrene resin **15** (62% yield) and finally by using TentaGel resin **16** (72% yield).

resin	i) Alkoxide formation				ii) Alkylation			% conversion		
	NaH	crown ether	solvent	time	33a	solvent	time	1srt	/2nd	/3rd couplings
14 PS/ 2%DVB	5 eq c = 0.3M	1 eq	DMF	2 h	5 eq c =0.15M	DMF	O/N	37%	×	×
15 PS/ 1%DVB	5 eq c = 0.6M	1 eq	DMF	2 h	5 eq c = 0.3M	DMF	O/N	60%	64%	69%
15 PS/ 1%DVB	20eq c = 0.6M	2 eq	DMF	2 h	20 eq c = 0.3M	DMF	O/N	61%	×	×
16 TentaGel	20 eq c = 0.4M	2 eq	DMF	2 h	20 eq c = 0.2M	DMF	O/N	72%	81%	82%

Table 2.7

The reaction proceeds via the generation of negative charges (alkoxide) then involves the formation of ionic groups (sulfate esters). The hydrophobic nature of the polystyrene matrix is thus not ideally suited for such a reaction. The swelling capacity of the polystyrene resin is likely to be affected by the appearance of the ionic groups. Such an effect is markedly stronger with a higher degree of cross-linking and is probably responsible for the difference in yields observed between resins **14** and **15**. The build up of negative charges might be responsible for the difficulty observed in driving the reactions to completion. It was therefore expected that decreasing the loading of the alcohol on the resin should be beneficial. To test this hypothesis, a range of loadings, decreasing from 0.82 mmol/g to 0.07 mmol/g were obtained by coupling mixtures of benzyl alcohol **1** and 1,4-benzenedimethanol **4** at different ratios onto polystyrene resin **11** (Scheme 2.8).



Reagents and condition: i) 1,4-benzenedimathanol **4**, benzyl alcohol **1**, pyridine, DCM/THF 1:1, 48 h. ii) NaH , 15-crown-5 , DMF, 1 h. iii) **33a**, DMF, 1 h.

Scheme 2.8

O-alkylation was then performed with a fixed concentration of reagents (c_{NaH} = 0.6M, c_{33a} = 0.4 M) although resulting in a different number of equivalent. Cleavage and HPLC analysis surprisingly indicated a percentage of conversion constant for the whole series (46-50%) (Table 2.8).

Entry	Loading 29[a] (mmol/g)	% conversion
1	0.82	46
2	0.63	48
3	0.40	50
4	0.29	49
5	0.13	47
6	0.07	47

[a] Determined by small scale cleavage and HLPC/UV analysis using a calibration curve for 1,4-benzene dimethanol. [b] Based on HPLC analysis, % area **8b**.

Table 2.8

The use of TentaGel was initially forsaken as it was thought that difficulties in drying the resin and its chelation properties would impede the synthesis. However, the hydrophilic environment provided by the PEG chains and its excellent swelling properties seemed to be a critical factor in the success of the reaction. To ensure the removal of traces of moisture, the resin was dried *in vacuo* over P_2O_5 for 24 h or washed with freshly distilled THF under N_2 prior to addition of the reagents.

Conclusions

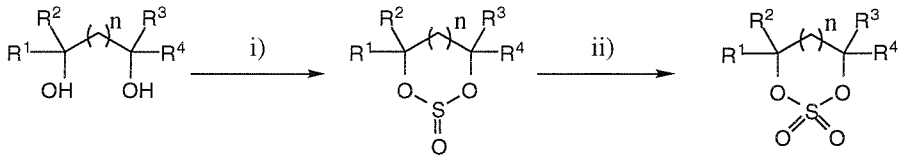
Optimum conditions for ether bond formation were found to be treatment of the resin bound diol with NaH (5eq), 15-crown-5 (1eq) in DMF at room temperature for 1-2h followed by addition of the cyclic sulfate (5eq) in DMF. However, yields were strongly dependent on the solid support chosen. The best results have been obtained on TentaGel resin and subsequent work was carried out on this support. Surprisingly, the degree of loading was not observed to affect the yield of the alkylation reaction. Further studies on lower cross-linked resin or macroporous resins could be beneficial.

2.1.3 Study of the scope of the reaction

2.1.3.1 Choice and synthesis of the cyclic sulfates

Having successfully developed the conditions for *O*-alkylation with one model cyclic sulfate, the reaction was then attempted with a range of representative 1,2-, 1,3- and 1,4-cyclic sulfates in order to assess the scope and limitations of the reaction in terms of library synthesis. Unsymmetrical cyclic sulfates (**33c**, **33d**, **33e** and **33f**) bearing various alkyl, phenyl and ester groups were selected to determine the degree of regioselectivity which could be achieved as a function of the steric and electronic demands of the substituents. It was envisaged that the use of cyclic sulfates bearing an ester group (**33d** and **33e**) would allow the introduction of the terminal carboxylic function. The electron withdrawing effect of the ester group normally directs the attack to the α center leading to the formation of β-hydroxy ester derivatives.[144] In the case of cyclic sulfate **33e**, it was hoped that the disubstitution would force the attack at the β center giving rise to the desired α-hydroxy ester moiety, a structural feature dominant in the natural polyethers. Cyclic sulfates **33b**, and **33h** were chosen by analogy to the ether rings present in the natural products. Such cyclic building blocks should prove useful in introducing a certain degree of rigidity into the polyether backbone. To allow the study of the stereoselectivity of the reaction, the cyclic sulfates were prepared, where possible, in enantiomerically pure form (**33d**, **33i**).

The cyclic sulfates **33a-i** were synthesised from the corresponding diols by the Sharpless procedure[140a] (Scheme 2.9)

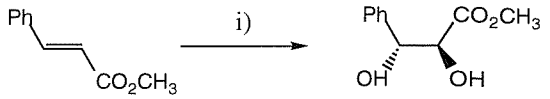


31a-i **32a-i** **33a-i**

Reagents and conditions: i) $SOCl_2$ (1.2 eq), DCM, reflux, 1 h. ii) $NaIO_4$ (1.5 eq), *cat.* $RuCl_3$, $DCM/CH_3CN/H_2O$.

Scheme 2.9

Diols **31a,b,c,f,g,h,i** are commercially available. Following a literature procedure,[189] diol **31d** was prepared as the 2*S*,3*R* enantiomer from *trans*-methyl cinnamate by catalytic asymmetric dihydroxylation with AD-mix β (Scheme 2.10)

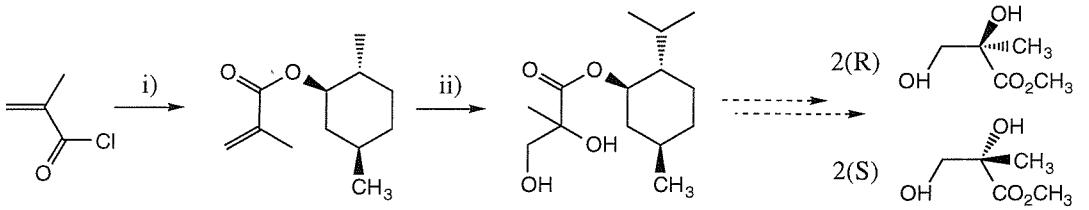


34 **31d**

Reagents and conditions: AD-mix β, *t*-BuOH/H_2O 1:1, $MeSO_2NH_2$ (1 eq), 0 °C 12 h, then rt, 12 h, 64%.

Scheme 2.10

Preparation of diol **31e** in optically pure form by catalytic asymmetric dihydroxylation of methyl methacrylate usually proceeds in low *ee*. An alternative approach reported by Rodriguez *et al.*,[190] based on the resolution of menthol derivatives was therefore attempted (Scheme 2.11).

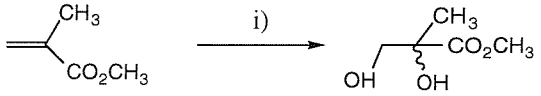


35 **36** **37** **31e**

Reagents and conditions: i) (-)-menthol, (1.5 eq), Et_3N (1.2 eq), DCM, 72%. ii) *cat.* OsO_4 (0.01 eq), NMO (1.1 eq), H_2O/acetone/*t*-BuOH 10:4:2, 75%.

Scheme 2.11

Esterification of methacryloyl chloride with (-)menthol in presence of Et_3N, followed by dihydroxylation of the resulting alkene **36** by a standard OsO_4/NMO procedure afforded the expected diol **37** as a diastereomeric mixture (10% *de* by NMR). Unfortunately, the two diastereoisomers proved impossible to resolve on a large scale by chromatography on silica gel. The process was therefore abandoned and diol **31e** was prepared as a racemic mixture, by *syn* dihydroxylation of methyl methacrylate[191] with OsO_4 (Scheme 2.12).

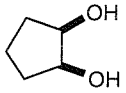
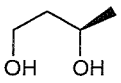
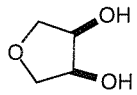
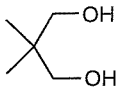
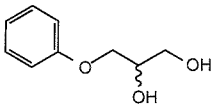
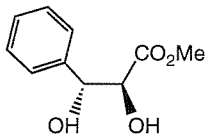
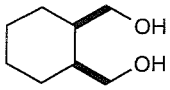
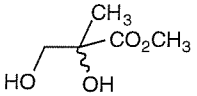
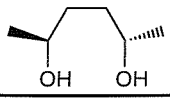


38 **31e**

Reagents and conditions: i) NMO (1.1 eq), *cat.* OsO_4 (0.03 mol%), acetone/*t*-BuOH/H_2O 3:1:6, 68%.

Scheme 2.12

The synthesis of the cyclic sulfates **33a-h** proceeded in high yields (Table 2.9).

Entry	31	33 Yield (%)	Entry	31	33 Yield (%)
a		81[a]	**f**		69[a]
b		73[a]	**g**		93[a]
c		84[a]			
d		50[b]	**h**		83[a]
e		51[b]	**i**		82[a]

[a] One pot procedure. [b] Overall yield. Two steps synthesis with purification of the intermediate cyclic sulfite **32**.

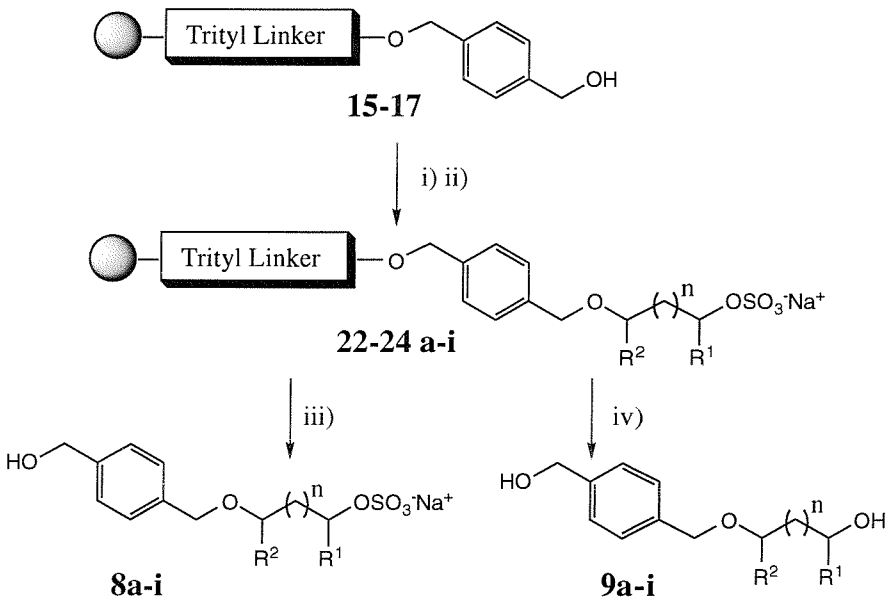
Table 2.9

High purity was obtained after simple aqueous work up. The compounds proved to be relatively stable and could be stored for several months without noticeable degradation (NMR). Only cyclic sulfate **33d** bearing two strongly activating substituents (phenyl and ester group) degraded quickly.[192] The cyclic sulfite intermediate **32d** was however stable. Oxidation was therefore carried out just prior to the use of **33d**.

2.1.3.2 O-alkylation

To complete the study of the influence of the polymer support, the reactions were performed on 3 different supports: polystyrene resin **11** and the TentaGel resins **12** and **13**. TentaGel resins often suffer from poor substitutions (e.g. resin **12** 0.22 mmol/g, resin **13** 0.17 mmol/g) requiring synthesis on a large scale to allow isolation of sufficient material for full characterisation of the products. It was therefore investigated if sufficient yields could be obtained with this new series of compounds on polystyrene resin. NovaSyn TGT resin **12** is derived from TentaGel amino resin by acylation with Bayer's 4-carboxytrityl linker. The amide bond is susceptible to deprotonation upon treatment with NaH and *N*-alkylation side reactions. Any side product formed should be trapped on the resin and therefore should not affect the synthesis in term of purity. We were however concerned that after repeated cycles of synthesis, the physical integrity of the resin could be altered. Therefore, a final set of reactions used NovaSyn® dichlorotrityl TG resin **13** which is prepared by derivatisation of TentaGel bromo resin with (di-4-chlorophenyl)(4-hydroxyphenyl)methanol, thus providing attachment of the linker *via* a more inert ether bond (but resulting in a more acid labile support).

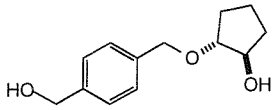
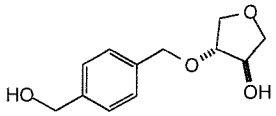
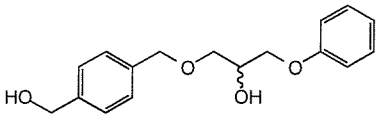
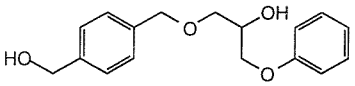
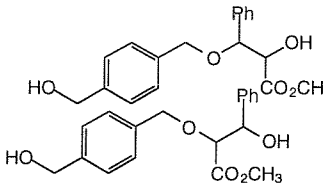
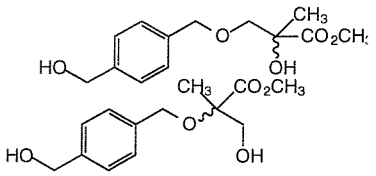
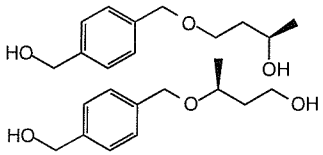
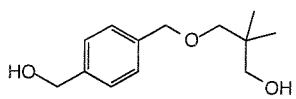
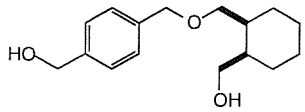
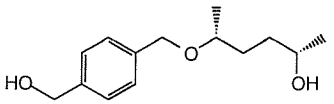
Following coupling of the model diol **4** to give the resin bound diol **15**, **16** and **17**, *O*-alkylation with the cyclic sulfates **33a-i** was attempted using the optimised conditions previously developed (Scheme 2.13).



Reagents and conditions: i) NaH (5 eq), 15-crown-5 (1 eq), 2 h, DMF. ii) **33 a-i** (5 eq), DMF, O/N. iii) 3% TFA/ 5% TIS/DCM, 30 min. iv) 4M HCl in dioxane/DCM, 30 min.

Scheme 2.13

Results obtained on the 3 supports are presented in table 2.10.

Ether products 9		Resin 22	Resin 23	Resin 24	
		% conversion[a] (purity)[b]	% conversion[a] (purity)[b]	% conversion[a] (purity)[b]	Isolated Yield[c] (%)
a		60 (60)	83 (83)	74 (74)	59
b		60 (60)	76 (76)	63 (63)	50
c		54[e] (33)	87[e] (42)	62[e] (60)	51
		0	0	0	0
d		0	×[d]	0	0
e		0	×[d]	0	0
f		0	0	0	0
g		56 (56)	×[d]	54 (54)	21
h		58 (58)	82 (82)	70 (70)	39
i		×[d]	×[d]	53 (53)	36

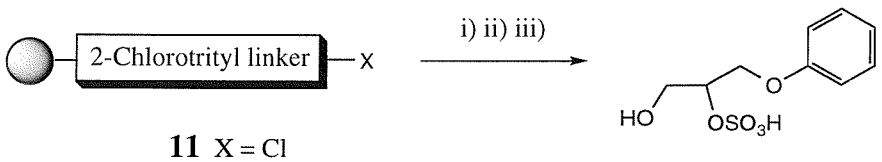
[a] Estimated by HPLC/UV analysis. %conversion = % area **9** /(% area 1,4-benzenedimethanol **4** + %area **9**). [b] % area product **9**. [c]After semi prepreparative HPLC purification, based on recovery of pure compound **9** (Overall yield starting from resin **12-14**). [d] reaction not performed on this support.

Table 2.10

As previously observed with the model cyclic sulfate **33a**, higher yields were obtained for the whole series on TentaGel resin **24** and **23** compared to polystyrene resins **22**. A marked difference was observed between the two TentaGel resin **24** and **23**. On resin **24**, the reactions proceeded with difficulty and 4 couplings were necessary to reach satisfactory yields, whereas on resin **23** higher yields were already obtained after 2 couplings. These results are likely to arise from the larger bead size of resin **24** (130 μm) compared to resin **23** (90 μm). The rate of diffusion of the reagents is inversely proportional to the bead diameter (α 1/r). For large particle sizes, diffusion of the reagents to the active sites within the complete polymer network is slower and more difficult, the effect being markedly more pronounced with heterogeneous reagents such NaH.

Good yields were obtained with the 1,2-cyclic sulfates **33a**, **33b**, and **33c**. *O*-alkylation with the unsymmetrical cyclic sulfate **33c** proceeded with complete regioselectivity. Formation of a single regioisomer was observed. NMR analysis showed the attack to have selectively taken place at the primary position. Reasonable conversion was obtained with 1,3-cyclic sulfate **33g** whereas S_N2 reactions on neopentylglycol derivatives are usually difficult due to the steric hindrance caused by the β-substituants. Satisfactory yields were also obtained with 1,4-cyclic sulfates **33h** and **33f** showing that, although 1,4-cyclic sulfates lack the ring strain of the 1,2-cyclic sulfates, the activation remains efficient. As expected, the substitution reaction was more difficult with **33i** (53% conversion) than with **33h** (70% conversion) due to the steric hindrance.

In the case of cyclic sulfate **33c**, formation of a side product in variable amount was observed on each support (resin **15** 29% area, resin **16** 31% area, resin **17** 22% area). The diol **31c** (t_R = 9.7 min) was isolated upon HCl cleavage and the sulfate ester **40** upon TFA cleavage (t_R = 8.7 min, ESMS (-ve mode) 247.1 $[M-H]^-$). A control reaction performed by treatment of the trityl resin **39** with **33c** suggested that these side products resulted from the reaction of the cyclic sulfate with the unreacted trityl linker (Scheme 2.14). With the other cyclic sulfates, absence of a UV chromophore prevented the detection of this side reaction by HPLC-UV analysis.



11 X = Cl
39 X = OH

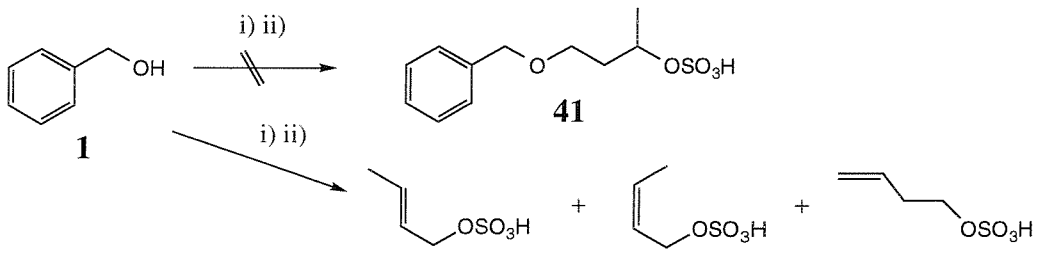
40

Reagents and conditions: i) NaH (5 eq), 15-crown-5 (1 eq), DMF, 2 h. ii) **33c** (5 eq), DMF, O/N. iii) 3% TFA/ 5% TIS/DCM.

Scheme 2.14

The reaction failed with the 1,2-cyclic sulfates **33d** and **33f**. Despite several attempts and repeated couplings, HPLC analysis showed only the presence of the unreacted diol **4**. No product of *O*-alkylation or side reaction was detected. The presence of the strongly activating phenyl or ester substituents particularly favours 1,2-elimination or degradation under the strong basic conditions necessary for the alkoxide formation. The cyclic sulfate of dimethyl tartrate has for example been reported to undergo 1,2-elimination in presence of pyridine[193] or DBU.[194]

More surprisingly, *O*-alkylation failed with the 1,3-cyclic sulfate **33f** on all 3 supports. (±) 1,3-butanediol cyclic sulfate **33f** is commercially available and has been successfully used in substitution reactions with a range of nucleophiles[195] including alcohols and phenols.[196,151] The reaction was therefore investigated in solution under the conditions used for the solid phase approach (Scheme 2.15).



Reagents and conditions: i) NaH (5 eq), 15-crown 5 (1 eq), DMF, 1h. ii) **33f** (5 eq), DMF, 1h.

Scheme 2.15

Benzyl alcohol **1**was treated with an excess of NaH (5 eq) and 15-crown-5 (1eq) in DMF (c= 0.3 M) for 30 min followed by addition of cyclic sulfate **33f** (5 eq). After 10 min, TLC showed the presence of benzyl alcohol **1**, and complete disappearance of the cyclic sulfate **33f**. Excess NaH was quenched by addition of MeOH and DMF was removed *in vacuo*. Purification of the crude product by chromatography on silica gel allowed complete recovery of the benzyl alcohol and isolation of a mixture of the elimination products **42**, suggesting that the strongly basic conditions and the use of DMF as solvent had favoured β-elimination.[197]

To circumvent degradation of the cyclic sulfates, *O*-alkylation with cyclic sulfates **33d**, **33e**, **33f** was attempted by treatment of the resin bound diol **15** with *t*-BuOK and filtration of the excess base under N_2 prior to addition of the cyclic sulfates. However, the reactions remained unsuccessful in the three cases.

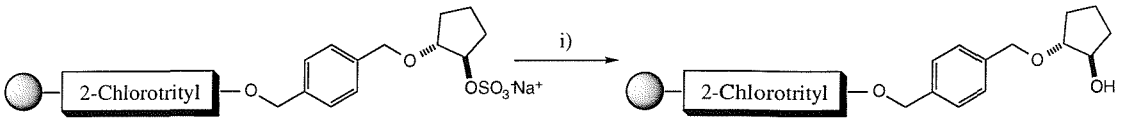
Conclusions

We have shown that the chemistry developed on the resin for one cyclic sulfate can be transferred to a variety of other cyclic sulfates. The scope of the reaction is only limited by the predisposition of very activated cyclic sulfates to undergo elimination.

The *O*-alkylation reaction is expected to proceed with inversion of configuration and hydrolysis of the sulfate ester moiety with retention of configuration. NMR analysis of **9i** indicated the presence of only one stereoisomer suggesting that reaction with the enantiomerically pure cyclic sulfate **33i** had proceeded stereoselectively. Reaction with the *meso* cyclic sulfates **33a**, **33b**, and **33h** should result in the formation of the two *trans* enantiomers in a 1:1 ratio. Due to the isolation of small amount of the ether product **9**, further study of the stereochemical aspect of the reaction and determination of the absolute configuration of the product was not carried out at this stage but is treated in section 2.3.

2.2. Development of the sulfate hydrolysis conditions

To allow the construction of the polyether chain, the development of conditions for sulfate ester hydrolysis was required. Based on the solution phase procedure,[140] hydrolysis of the sulfate ester moiety was first attempted by treating the resin bound sulfate ester **22** with a range of dilute solutions of HCl in dioxane containing 1% H_2O (Scheme 2.16).



22 **43a**

Reagents and conditions: HCl/ 1% H_2O/ dioxane, 24 h.

Scheme 2.16

TFA cleavage of resin **43a** and HPLC analysis showed that complete hydrolysis of the sulfate ester moiety took place with concentrations of 0.01 and 0.001M HCl after 24 h but analysis of the filtrate by HPLC showed that partial cleavage from the resin was occurring simultaneously (Table 2.12).

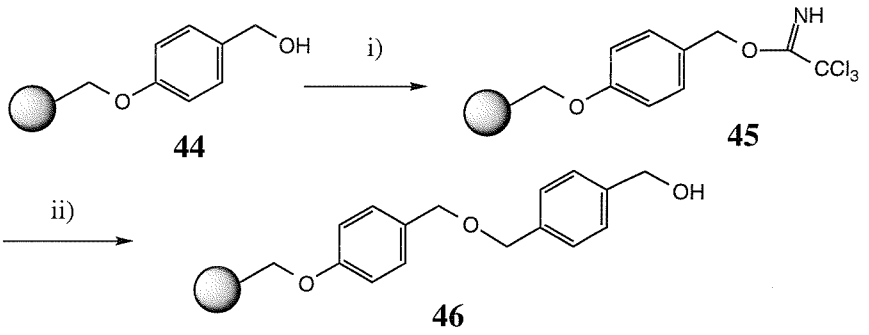
Entry	cHCl (mol/l)	resin 43a[a] % sulfate ester hydrolysis	resin 43a % cleavage[b]
1	0.01	100	20
2	0.001	100	20
3	0.0001	0	0

[a] determined by HPLC-UV analysis based on % area **8a** and **9a**. [b] quantification of **4** was carried out by HPLC-UV analysis using a calibration curve.

Table 2.12

We therefore turned to the use of the more acid stable Wang linker. Coupling of diol **4** onto the Wang linker was achieved by the method reported by Hanessian *et al.*[116]

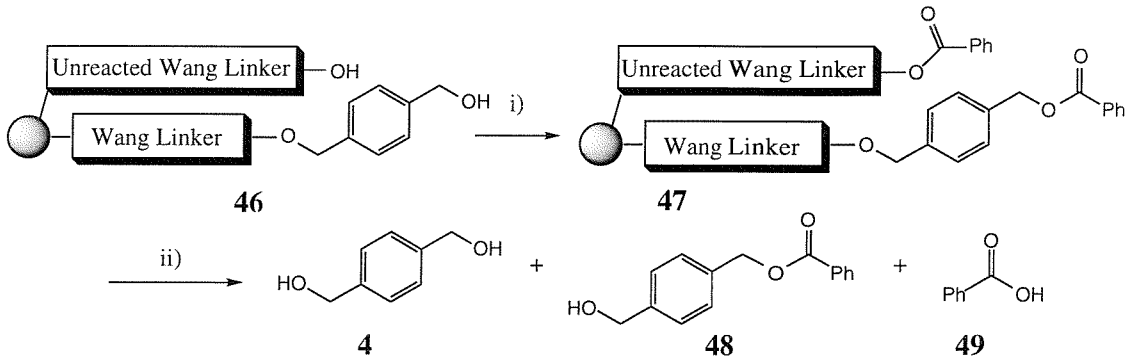
The trichloroacetimidate derivative **45** was prepared by treatment of NovaSyn®TG HMP resin **44** with CCl_3CN (20 eq) and DBU (1 eq) at 0 °C for 1 h (Scheme 2.17).



Reagents and conditions: i) CCl_3CN (20 eq), DBU (1 eq), DCM, 0 °C, 1 h. ii) 1,4-benzenedimethanol **4** (10 eq), $BF_3.OEt_2$ (0.5 eq), DCM/THF 1:1, 24 h.

Scheme 2.17

Although the appearance of the strong C=N stretching band at 1664 cm^{-1} was clearly observed, the OH band was barely discernible on either resin **44** and **46**. Thus, FTIR could not be used to determine the extent of completion of the reaction. The trichloroacetimidate resin **45** was then treated with a concentrated solution of 1,4-benzenedimethanol **4** (10 eq) in the presence of a small amount of $BF_3.OEt_2$ (0.5 eq) for 24 h. The reaction proceeded in 70 % yield (two steps from resin **44**). The presence of unreacted Wang linker was a potential problem as *O*-alkylation of the linker could take place with the cyclic sulfates. In order to determine the amount of unreacted linker and the percentage of double binding, resin **46** was treated with benzoyl chloride (Scheme 2.18).



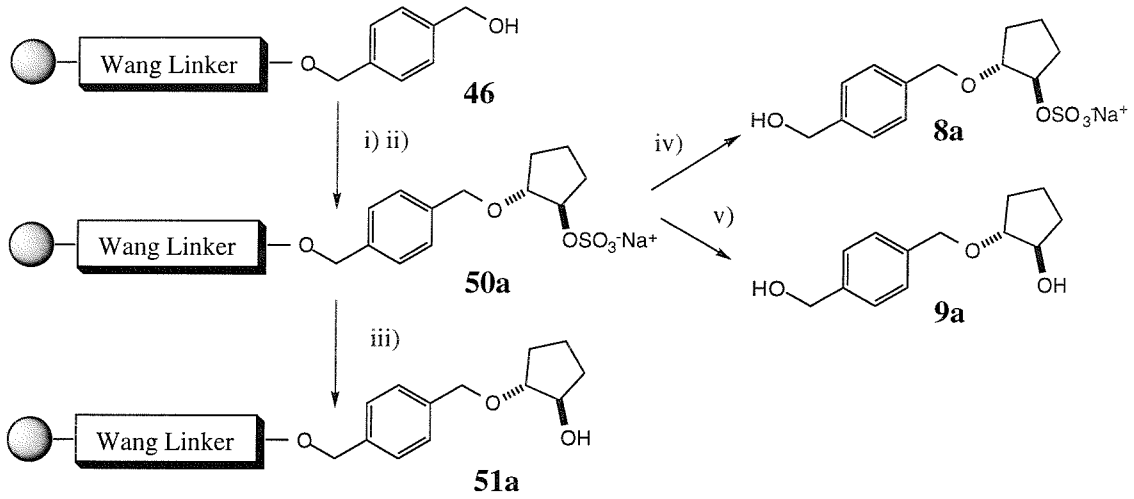
Reagents and conditions: i) Benzoyl chloride (10 eq), Pyridine (20 eq), DCM, 6 h. ii) 50% TFA/DCM.

Scheme 2.18

Quantification of the amount of diol **4** and benzoic acid released upon cleavage was achieved by HPLC-UV analysis using a calibration curve for each compound. A negligible amount of benzoic acid was detected suggesting that the Wang linker had completely reacted. However as previously observed on the Trityl resins **10-13**, a non negligible amount of diol was left unesterified (15%), suggesting that cross-linking of **4** was occuring.[116]

The release of alcohols from the Wang linker is typically carried out with 50% TFA/DCM although the use of only 1-10% has also been reported.[116] As with the trityl linker, optimisation of the cleavage conditions was carried out to avoid the formation of TFA esters. Optimum conditions for routine analysis were found to be a 15 min treatment with 50% TFA/DCM followed by concentration of the filtrates at room temperature and for large scale cleavages two treatment of 30 min with 50% TFA/DCM and co-addition of MeOH. However in the latter case, formation of TFA esters was difficult to avoid and after evaporation of the filtrates, treatment of the crude product with NH_3 was usually necessary.

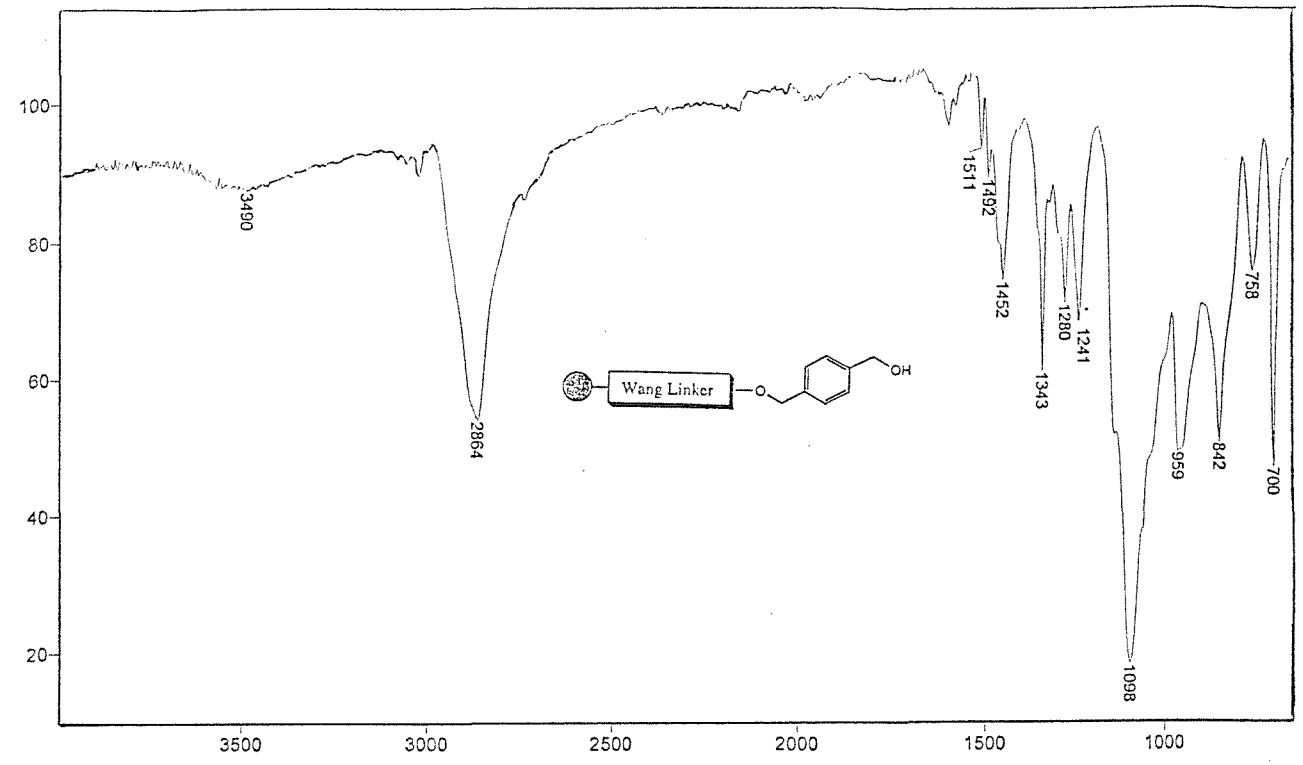
Synthesis of the resin bound sulfate ester **50a** was carried out using the *O*-alkylation procedure previously developed (Scheme 2.19). Upon cleavage of resin **50a** with 50% TFA, the sulfate ester moiety remained unaffected allowing the release of **8a**. Cleavage with 4M HCl/dioxane to give **9a** was possible but required prolonged cleavage times and gave relatively poorer yields. Hydrolysis of the sulfate ester moiety was then attempted with dilute solutions of HCl in 1% H_2O/dioxane.



Reagents and conditions: i) NaH (5 eq), 15-crown-5 (1 eq), DMF, 2 h. ii) **33a** (5 eq), DMF, 6 h. iii) 4M HCl/dioxane, 2 h. iv) 50% TFA/DCM, 30 min v) 0.01M HCl/ 1% H_2O/ dioxane , 24 h.

Scheme 2.19

As shown in figure 2.4, monitoring of the reaction by FTIR was difficult as the sulfate ester band was partially masked by a strong band resulting from the PEG chains. Due to the use of TentaGel resin, ^{13}C gel phase NMR gave excellent spectra and proved extremely useful for the monitoring of the sulfate ester hydrolysis step. As shown in figure 2.5, the significant changes of chemical shifts of the CH and CH_2 in the cyclopentane ring could be clearly observed allowing the unambiguous confirmation of the completion of the reaction.



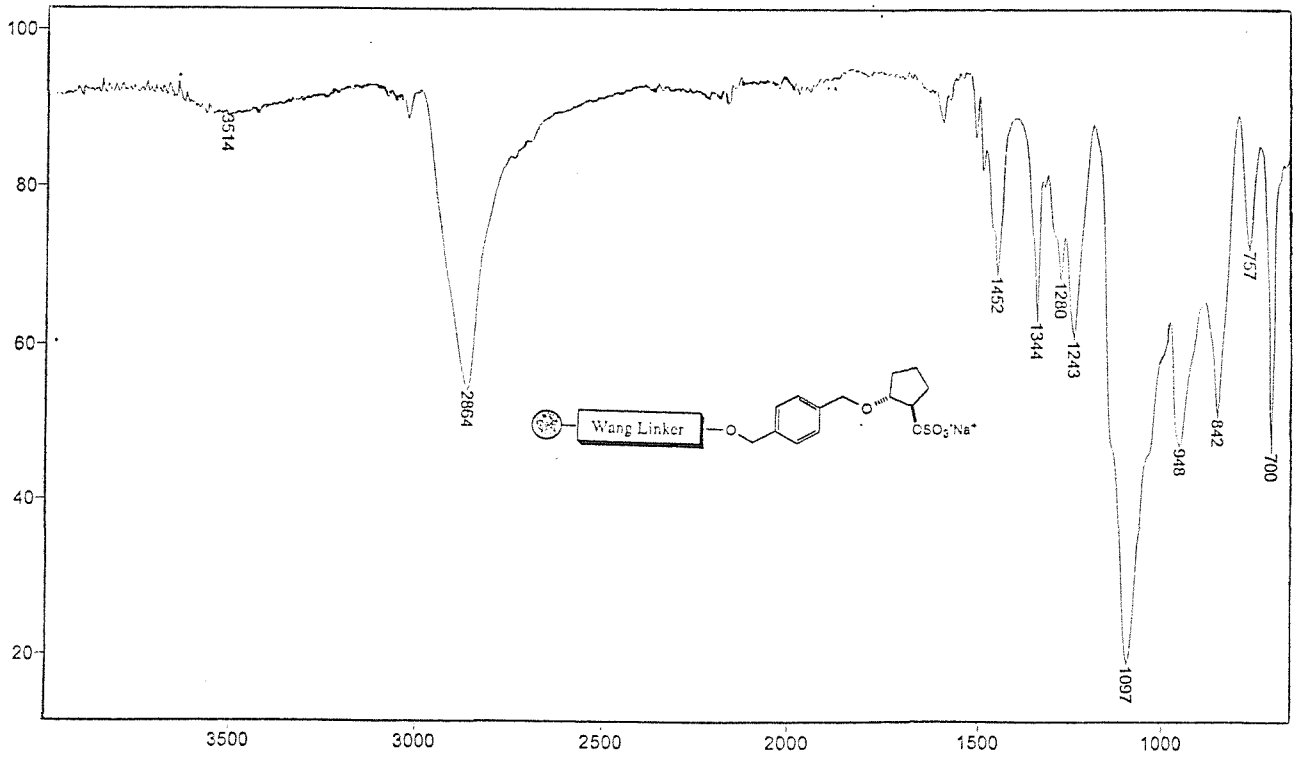
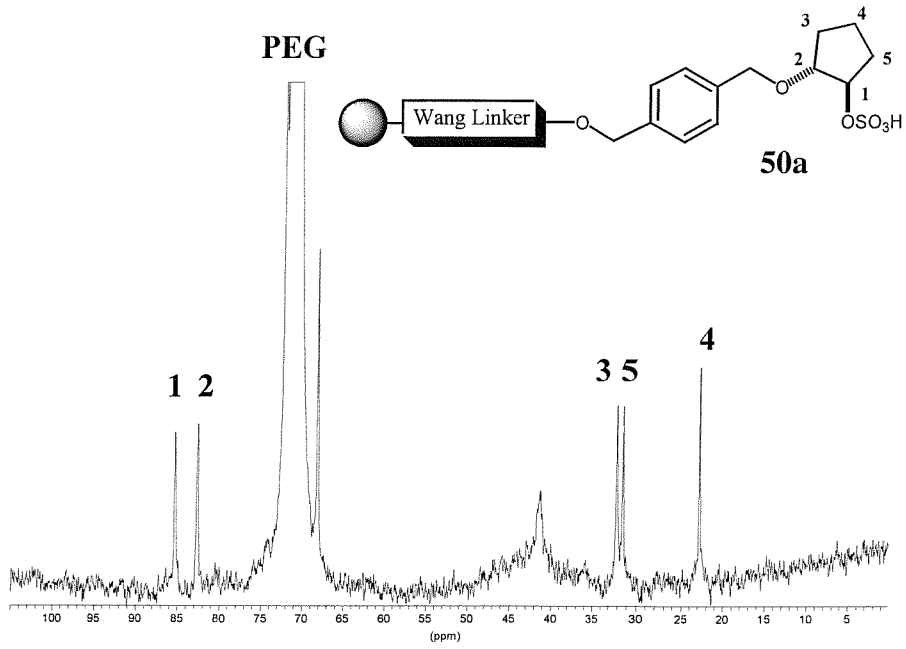


Figure 2.4: FTIR spectra of resin **50a** and **51a**



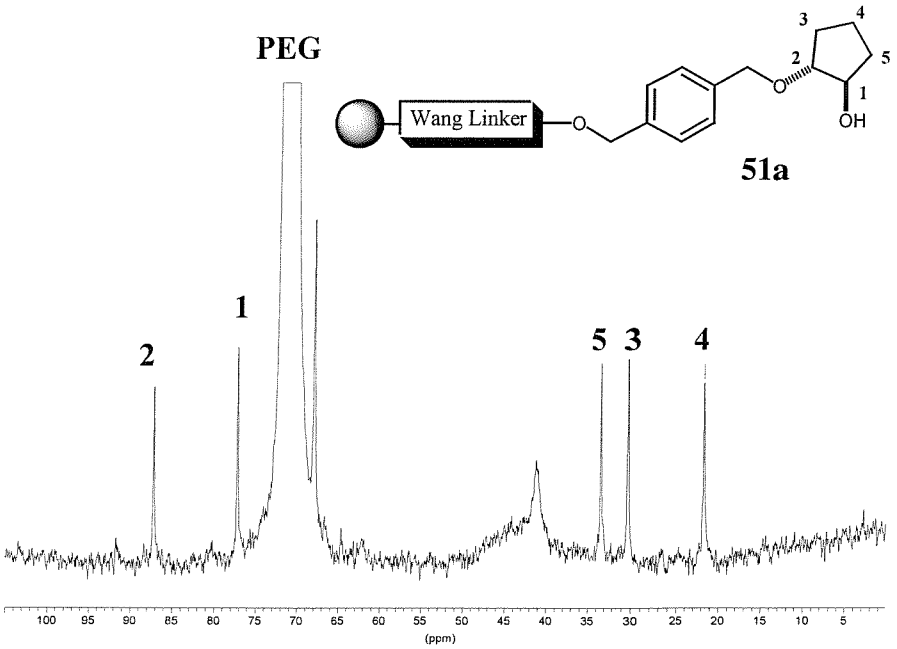


Figure 2.5: Gel phase NMR of resin **50a** and **51a**

Kinetic investigation of the reaction was carried out by cleavage and HPLC analysis of samples taken at regular time intervals. Hydrolysis with a 0.001 M HCl solution in 1% H_2O/dioxane proceeded extremely slowly and was not complete after 24 h (Figure 2.6). With a 0.01M HCl solution in 1% H_2O/dioxane, the rate of hydrolysis was considerably faster and the reaction complete after 4 h. Presence of diol **4** in the filtrate was not detected by HPLC-UV analysis upon treatment of resin **50a** with 0.01M HCl/1% H_2O/dioxane for 24 h and confirmed that the Wang linker was completely stable to the sulfate ester hydrolysis conditions.

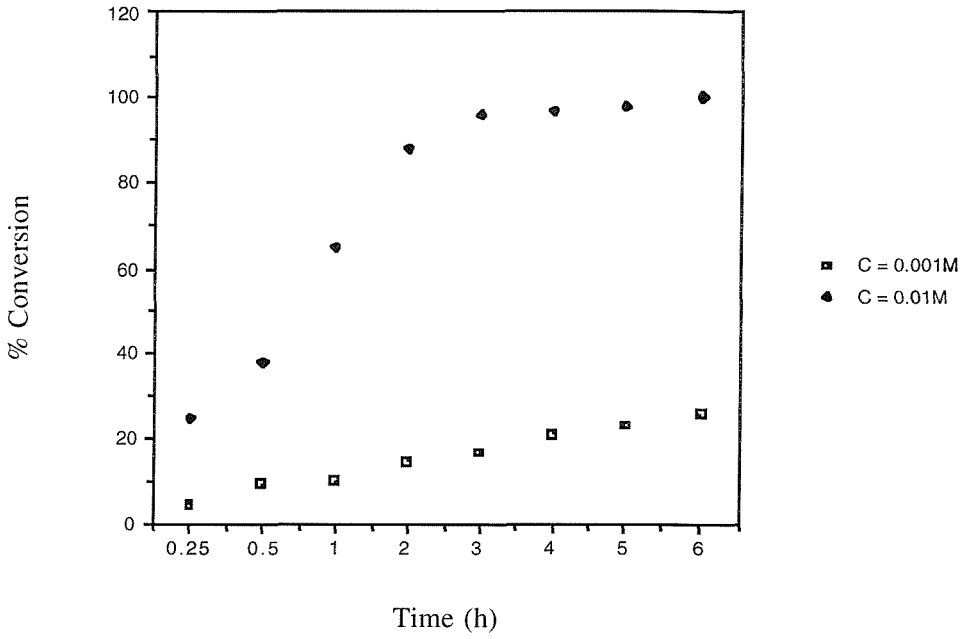
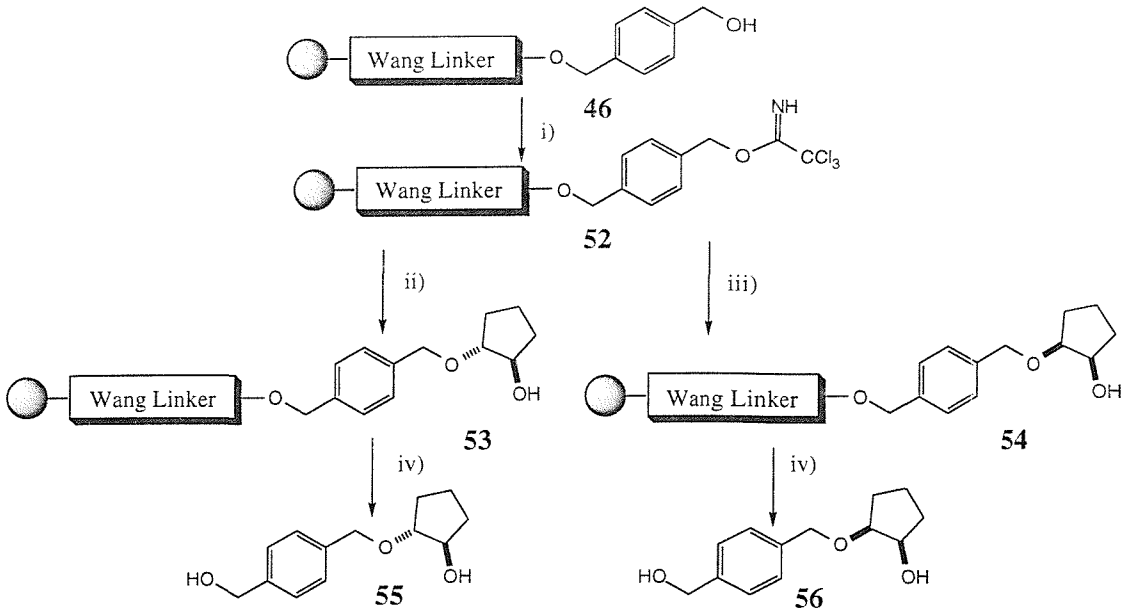


Figure 2.6

2.3. Determination of stereochemistry

O-alkylation should take place with complete inversion at the stereogenic center and hydrolysis of the sulfate ester under mild acidic conditions with retention of configuration. Coupling with the *meso* cyclic sulfate **33a** should therefore lead to the formation of a racemic mixture of the two *trans* enantiomers.

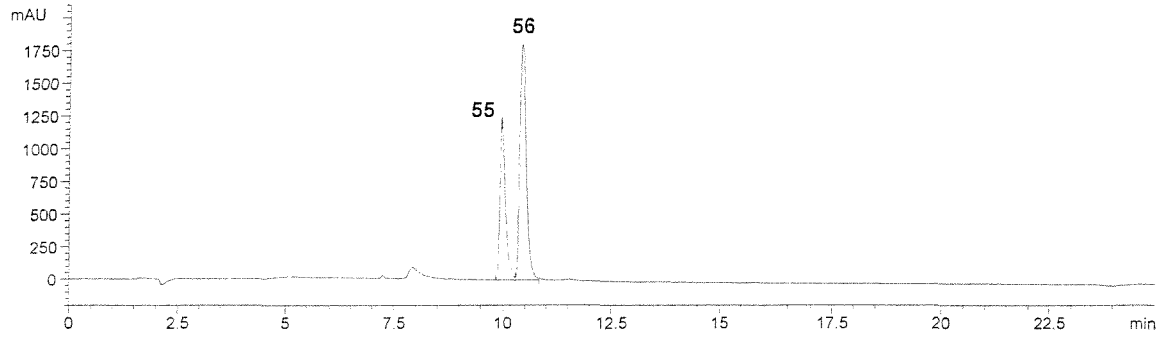
To confirm that both steps proceeded in a steoreoselective manner, the two possible pairs of *cis* and *trans* enantiomers were synthesised by a different route and fully characterised (Scheme 2.20).



Reagents and conditions: i) CCl_3CN (20 eq), DBU (1 eq), DCM, 0 °C, 1 h. ii) *trans* 1,2-cyclopentane diol (10 eq), $BF_3.OEt_2$ (0.5 eq), DCM, 6 h. ii) *cis* 1,2-cyclopentane diol (10 eq), $BF_3.OEt_2$ (0.5 eq), DCM, 6 h.

Scheme 2.20

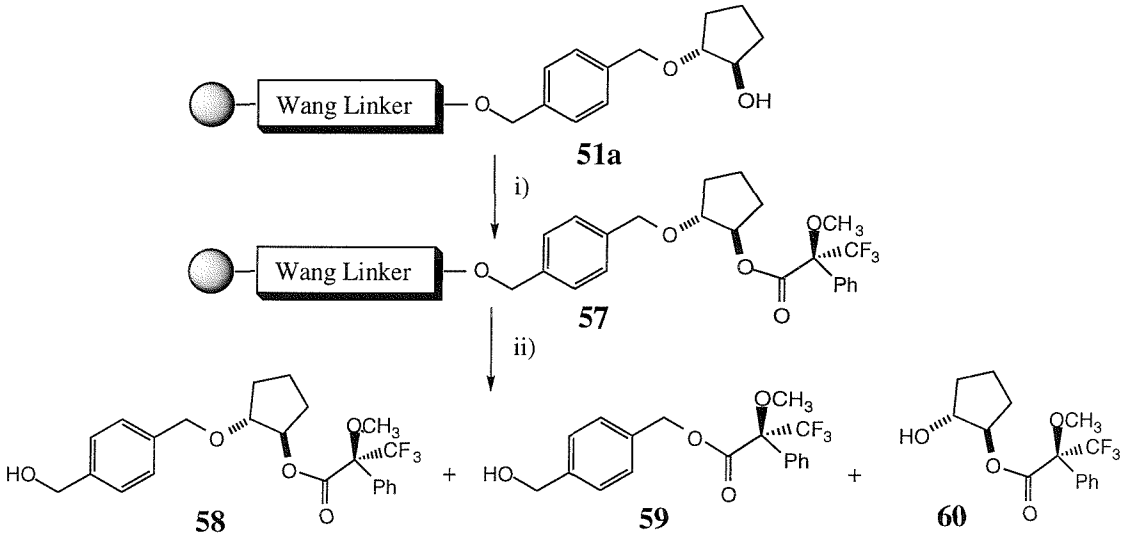
Formation of the tricloroacetimidate derivative **52**, followed by reaction with *cis*-1,2-cyclopentadiol and *trans*-1,2-cyclopentane diol gave respectively the *cis* and *trans* diastereoisomers **55** and **56** in 50% and 57% yield (3 steps from resin **44**). The two diastereoisomers possessed distinctive NMR data and HPLC retention times (Figure 2.7). Comparison with the data obtained for **9a** clearly allowed us to assign **9a** as the *trans* isomer, demonstrating that both the *O*-alkylation and sulfate hydrolysis step proceeded stereoselectively.



Conditions: λ = 220 nm, 20 min gradient from 100% [H_2O/ 0.1% TFA] to 100% [CH_3CN/ 0.04% TFA]. **55** t_R = 9.9 min, **56** t_R = 10.3 min.

Figure 2.7: HPLC trace of the *cis* and *trans* isomers **55** and **56**

To further confirm by NMR, the Mosher ester derivative **58** were prepared by treatment of the resin bound ether products **51a** with MTPA-Cl (Scheme 2.21).

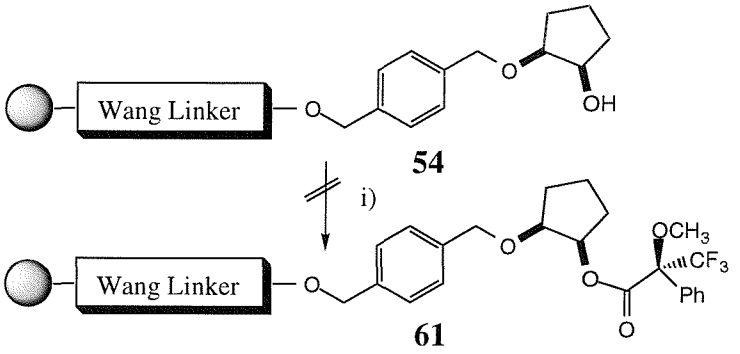


Reagents and conditions: i) MTPA-Cl (2 eq), Et_3N (10 eq), DMAP (0.1 eq), DCM, O/N. ii) 50% TFA/DCM

Scheme 2.21

Cleavage of resin **57** and HLPC analysis showed complete conversion to the Mosher ester derivatives **58**. NMR analysis of the isolated product **58** showed a 1:1 ratio of the trans diastereoisomers. The side products **59** and **60** were also isolated and resulted respectively from the reaction of MTPA-Cl with unreacted alcohol **46** and from the side reaction of the free Wang linker **44** with cyclic sulfate **33a.**

The reaction failed with the resin bound ether product **54**, despite several attempts using either the acid chloride and pyridine, or by a standard coupling of the acid with DIC/HOBt, due probably to steric congestion.



Reagents and conditions: i) MTPA-Cl (2 eq), Et_3N (10 eq), DMAP (0.1 eq), DCM, O/N. or MTPA-OH (5 eq), DIC (10 eq), HOBt (10 eq), DMAP (1 eq), DCM, O/N.

Scheme 2.22

Conclusions

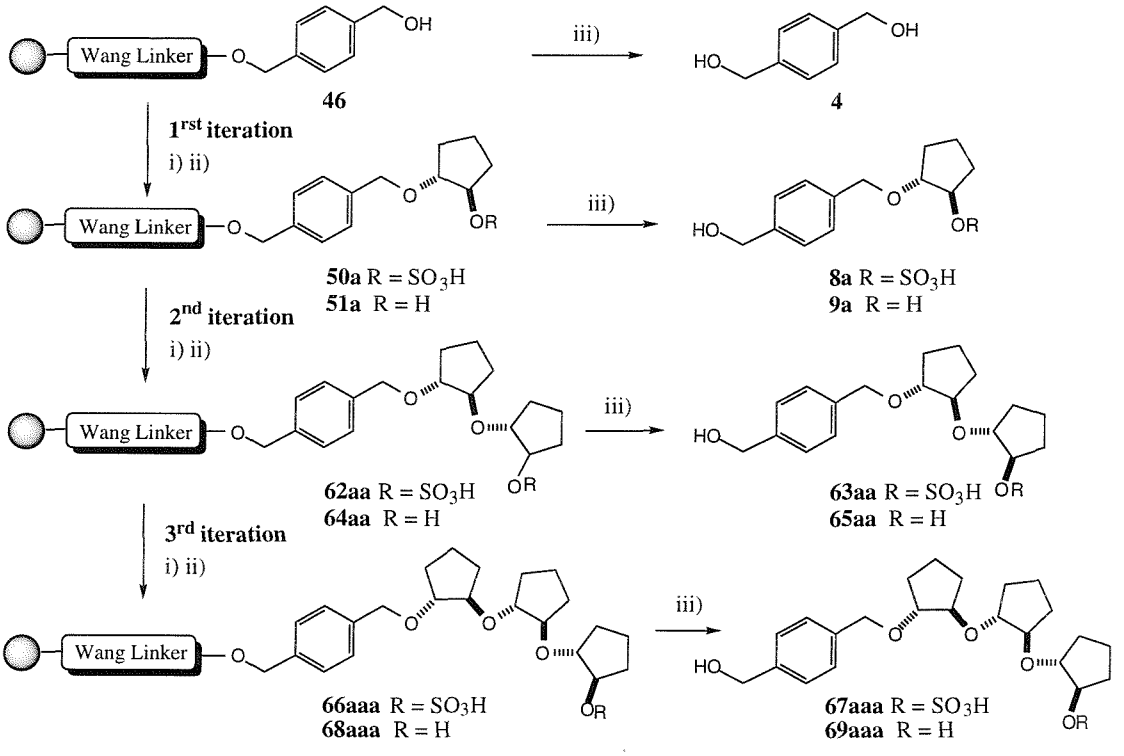
A new method of ether bond formation on the solid phase has been developed. Using cyclic sulfate derivatives, 1,2-, 1,3- and 1,4-diols can be coupled in moderate to good yield without the need for monoprotection. The yields obtained compare favourably with examples reported for solid phase *O*-alkylation by the Williamson synthesis. Reaction of the alkoxide with the cyclic sulfate proceeded extremely quickly and prolonged reaction times were not necessary. Excellent regioselectivity has been observed with the cyclic sulfate **33c**. This single example does not allow to draw general conclusions but based on literature precedents in solution, a same level of regioselectivity should be obtained. Hydrolysis of the sulfate ester moiety is performed under relatively mild acid conditions and allows regeneration of the hydroxyl functionality. The free alcohols can also be obtained directly by cleavage from the resin with HCl. The two step process was shown to proceed in a stereoselective manner.

Chapter 3: Polyether Synthesis

3.1 Library synthesis

3.1.1 Model reaction

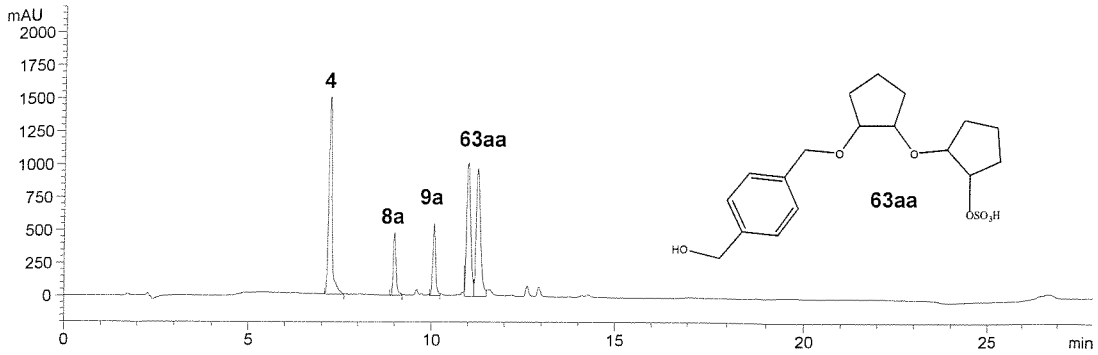
Having established the procedures of *O*-alkylation and sulfate ester hydrolysis, the possibility of constructing a polyether chain by a two step iterative process was investigated with the synthesis of the tetramer **69aaa**. Using the model cyclic sulfate **33a**, three successive iterations were carried out (Scheme 3.1).



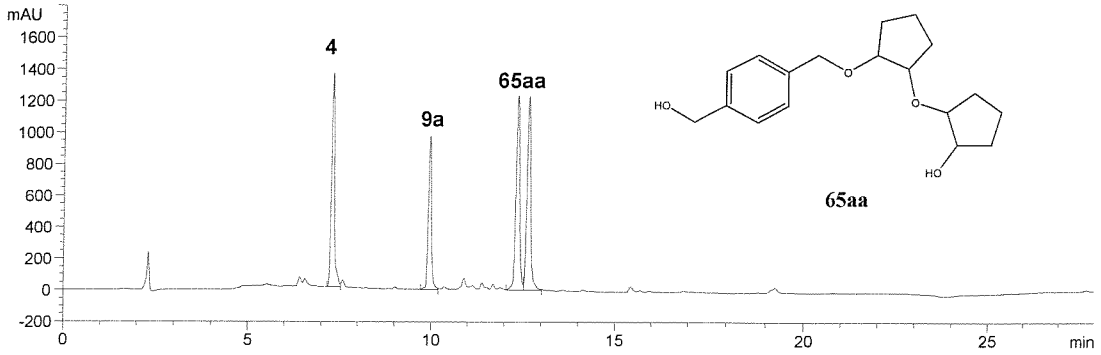
Reagents and conditions: i) NaH (5 eq), 15-crown-5 (1 eq), DMF, 1 h then **33a** (5 eq), DMF, 4 h. R = SO_3H. ii) 0.01 M HCl/1% H_2O/dioxane, 12 h. R = H. iii) 50% TFA/DCM.

Scheme 3.1

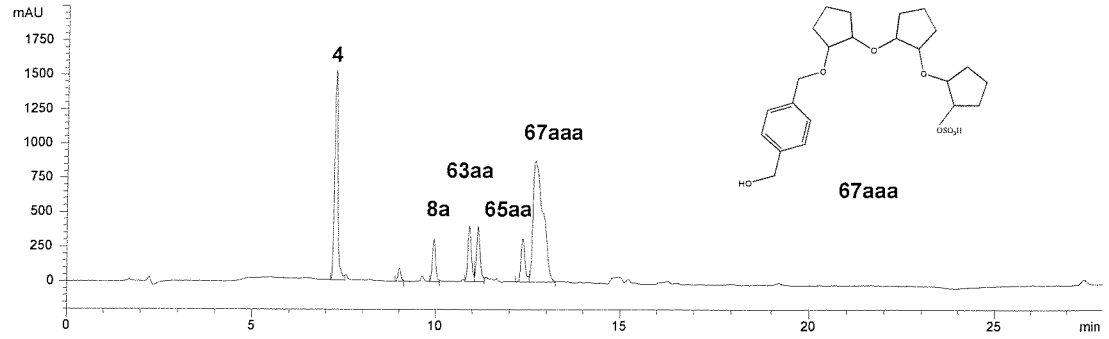
The dimer **9a** was formed in 64% after two couplings. *O*-alkylation of the resin bound secondary alcohol **51a** proved more difficult. However, relatively high conversion to the trimer **63aa** was obtained after 3 couplings (ratio **9a/63aa** 15:85). A side reaction occurred with the unreacted alcohol **46** to reform a small amount of the sulfate ester **8a** (8% area) (Figure 3.1 (a)). After hydrolysis of the sulfate ester moiety, a mixture of the diol **4** (27% area), dimer **9a** (18% area) and trimer **65aa** (55% area) was obtained (Figure 3.1 (b)).



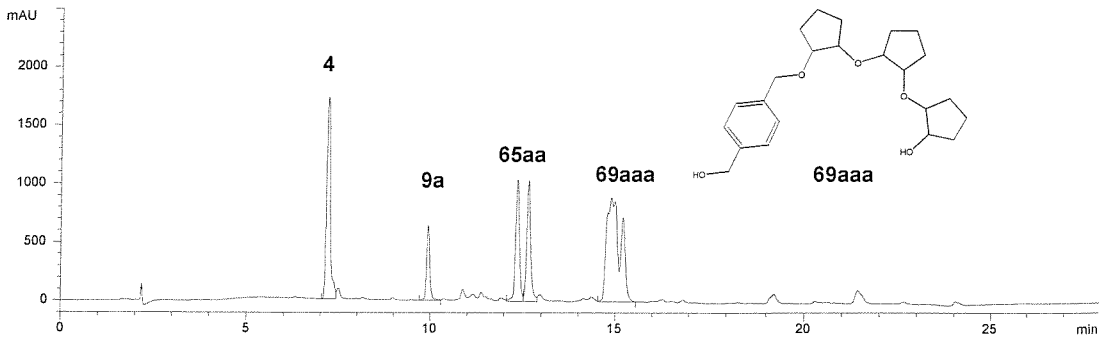
(a) Resin **62aa**: **4** t_R = 7.2 min (32%), **8a** t_R = 8.7 min (8%), **9a** t_R = 9.9 min (9%), **63aa** t_R = 11.0-11.3 min (51%).



(b) Resin **64aa**: **4** t_R = 7.2 min (27%), **9a** t_R = 9.9 min (18%), **65aa** t_R = 12.3-12.6 min (55%).



(c) Resin **66aaa**: **4** t_R = 7.2 min (27%), **8a** t_R = 8.7 min (1%), **9a** t_R = 9.9 min (5%), **63aa** t_R = 11.0-11.3 min (15%), **65aa** (diast. 1) t_R = 12.3 min (6%), **65aa** (diast. 2) + **67aaa** 12.4-12.8 min (46%).



(d) Resin **68aaa**: **4** t_R = 7.2 min (24%), **9a** t_R = 9.9 min (7%), **65aa** t_R = 12.3-12.4 min (27%), **69aaa** tR = 14.5-15.5 min (42%).

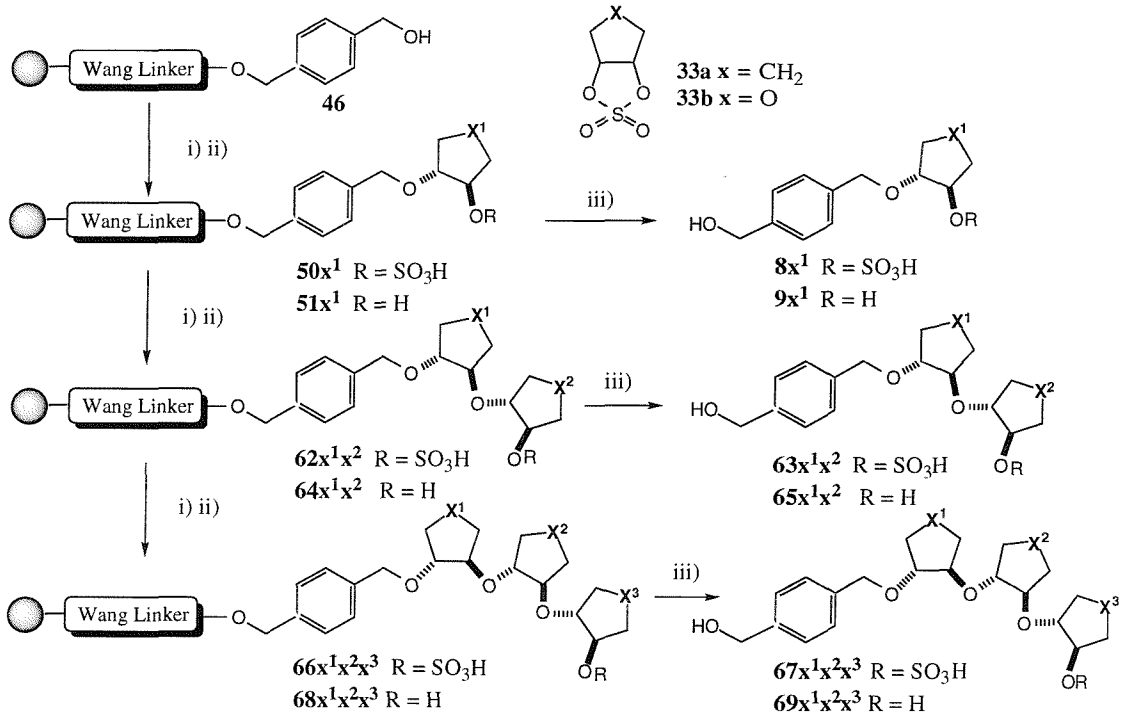
Figure 3.1

The percentage of diol **4** remained constant during the third iteration, suggesting that the remaining unreacted diol **4** was cross-linked. *O*-alkylation of the trimer **65aa** proceeded with increasing difficulty but gave satisfactory results after 4 couplings (ratio trimer **65aa**/tetramer **66aaa** 23:77). A side reaction was observed with the unreacted dimer **9a** which reformed the sulfate ester **63aa** in small amount (15% area) (Figure 3.1 (c)). Following hydrolysis of the sulfate ester moiety, a mixture of the diol **4** (24% area), dimer **9a** (7% area), trimer **65aa** (27% area) and tetramer **69aaa** (42% area) was finally obtained (Figure 3.1 (d)). Due to the use of a *meso* cyclic sulfate, the trimer **65aa** was obtained as two pairs of diastereoisomers in a 1:1 ratio (t_R = 12.3 and 12.6 min) and the tetramer **69aaa** as four pairs of diastereoisomers (four partially resolved peaks, t_R = 14.6-15.2 min). After cleavage and purification by semi-preparative RP-HPLC, the tetramer **69aaa** was obtained in 13% overall yield (7 steps from resin **44**). The separation of the four pairs of diastereoisomers was not achieved.

As the polyether chain grows, *O*-alkylation become markedly more difficult. During the first iteration, *O*-alkylation took place predominantly during the first coupling (e.g. 1st coupling **8a** 46% area, 2nd coupling **8a** 60% area, 3rd coupling **8a** 64% area). During the second and third iterations, each coupling proceeded comparitively lower yields but similar overall conversion to the ether products could however be obtained after 4 to 6 couplings. Repeated couplings did not allow to drive the *O*-alkylation to completion. However, after hydrolysis of the sulfate ester moiety, further alkylation of previously unreacted alcohols was observed. These results tend to suggest that formation of a charge build up due to the presence of the anionic sulfate ester group prevented the *O*-alkylation proceeding to completion.

3.1.2 Synthesis of a tetramer library

The validity of the methodology was demonstrated by the synthesis of an 8 member library of tetramers **69x^{1}x^{2}x^3**, by multiple parallel synthesis, using the two cyclic sulfates **33a** and **33b** (Scheme 3.2).



Reagents and conditions: i) NaH (5 eq), 15-crown-5 (1 eq), DMF, 1 h. then **33a** or **33b** (5 eq), DMF, 4 h. R = SO_3H. ii) 0.01M HCl/1% H_2O/dioxane, O/N. R = H. iii) 50% TFA/DCM.

Scheme 3.2

The synthesis of the library was carried out as previously described for the model compound **69aaa**. Repeated couplings were required to achieve satisfactory yields of *O*-alkylation. Incomplete *O*-alkylation and further reaction of the alcohol at the following step led to the formation of by-products. Moreover, due to the use of two *meso*-cyclic sulphates, the synthesis gave rise to complex mixtures of stereoisomers. However, as confirmed by HPLC and ESMS analysis, the 8 tetramers **69x^{1}x^{2}x^3** were successfully obtained in moderate yields (35 to 51% area, 7 steps from resin **44**) (Table 3.1).

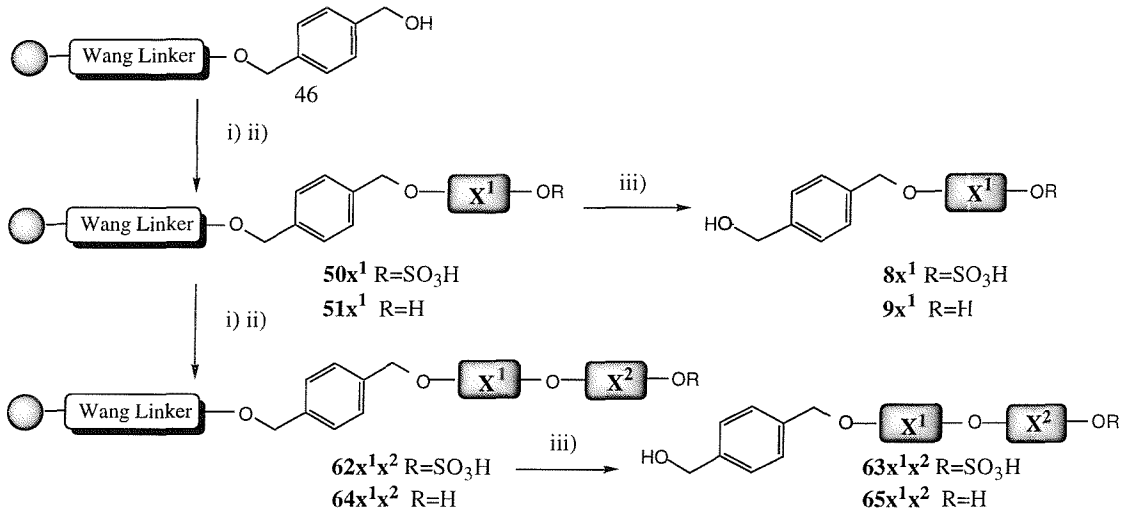
69x^{1}x^{2}x^3	**Purity**[a]
69aaa	43
69aab	33
69aba	43
69abb	35
69baa	40
69bab	36
69bba	51
69bbb	42

[a] Determined by HPLC analysis, % area **69x^{1}x^{2}x^3**

Table 3.1

3.1.3 Synthesis of a trimer library

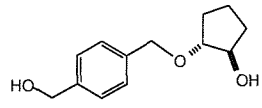
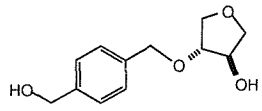
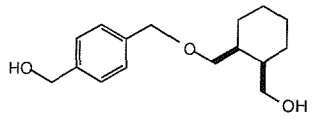
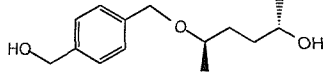
The methodology was then applied to the synthesis of a 16 member library of trimers **65x^{1}x^2** by multiple parallel synthesis using 4 cyclic sulfates (**33a**, **33b**, **33h**, **33i**) (Scheme 3.3).



Reagents and conditions: i) NaH (5 eq), 15-crown-5 (1 eq), DMF, 1 h then **33a**, **33b**, **33h** or **33i** (5 eq), DMF, 4 h. R = SO_3H. ii) 0.01 M HCl/1% H_2O/dioxane. R = H. iii) 50% TFA DCM.

Scheme 3.3

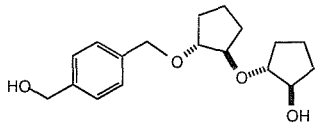
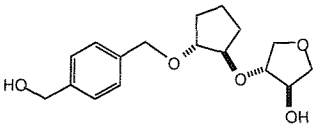
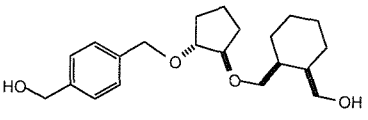
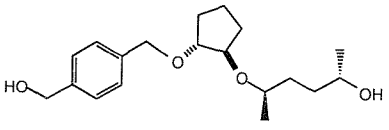
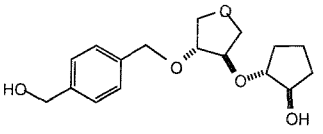
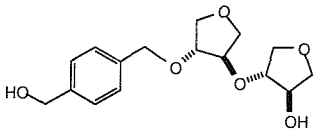
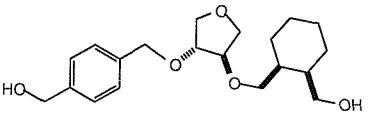
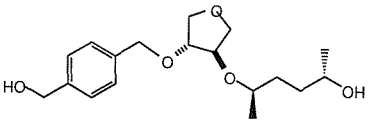
Conversion to the dimers **8a** and **8b** was observed in 78% and 64% yield respectively (Table 3.2). Surprisingly, *O*-alkylation failed with the cyclic sulfates **33h** and **33i** whereas etherification had been successfully achieved on polystyrene and TentaGel trityl resins. HPLC analysis showed only the presence of the unreacted diol **4**.

Cyclic sulfate	9x^1		% conversion[a] (purity)[b]
33a	**9a**		78 (78)
33b	**9b**		64 (64)
33h	**9h**		0
33i	**9i**		0

[a] Determined by HPLC analysis (λ = 220 nm). % conversion = % area **9x^1**/ (% area **4** + % area **9x^1**) [b] % area **9x^1**.

Table 3.2

A second iteration was carried out on resin **51a** and **51b**. On resin **51b**, *O*-alkylation was successful with the 4 cyclic sulfates. Excellent conversion to the trimers **65bh** and **65bbi** was observed (ratio **9b/65bh** 9/91, ratio**9b/65bi** 20/80). The different trimers were obtained in moderate yields after HPLC purification (Table 3.3). For reasons which remain unclear, the coupling of the cyclic sulfates **33h** and **33i** failed on resin **51a**. No evident steric or electronic factors provide a satisfactory explanation for these results.

65x^{1}x^2		**Purity**[a] (%)	**Yield**[b] (%)
65aa		50	28
65ab		45	24
65ah		0	0
65ai		0	0
65ba		48	19
65bb		49	28
65bh		40	17
65bi		59	35

[a] % area **65x^{1}x^2**. [b]isolated product **65x^{1}x^2** after RP-HPLC purification. overall yield from resin **44** (5 steps)

Table 3.3

3.2 Capping strategy

As observed during the synthesis of the trimer and tetramer libraries, the difficulty encountered in forcing the reaction to completion as the chain is growing led to the formation of an increasing number of by-products and obtention of complex mixtures. Thus, development of an efficient and general method for capping the unreacted hydroxyl group was therefore necessary for the viability of the approach. As previously demonstrated in peptide and oligonucleotide synthesis,[48] capping could be integrated as part of a more general purification strategy.[198]

The choice of a capping agent orthogonal both to synthesis and cleavage conditions was however difficult. Alcohol protecting groups[199] such as acetals and silyl ethers were not compatible with the acidic conditions of the sulfate ester hydrolysis and cleavage steps, while most ester based protecting groups were likely to be labile under the strongly basic conditions used for the *O*-alkylation. Methyl, benzyl or allyl ether protection appeared therefore the more suitable options. However, capping of the unreacted alcohol must be achieved selectively in presence of the sulfate ester group. The sulfate ester group can act as a nucleophile under strong alkylating conditions. Methylation of sulfate esters has for example been achieved by treatment with NaH/MeI[200] or diazomethane.[201] The resulting dialkyl sulfates are highly reactive and could undergo either nucleophilic attack at the sulfur or carbon centers depending on the steric and electronic directions of the alkyl substituents[202] or promote elimination (Figure 3.2).

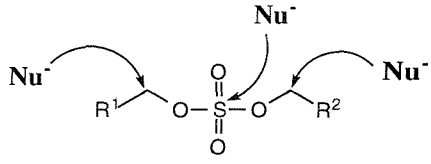


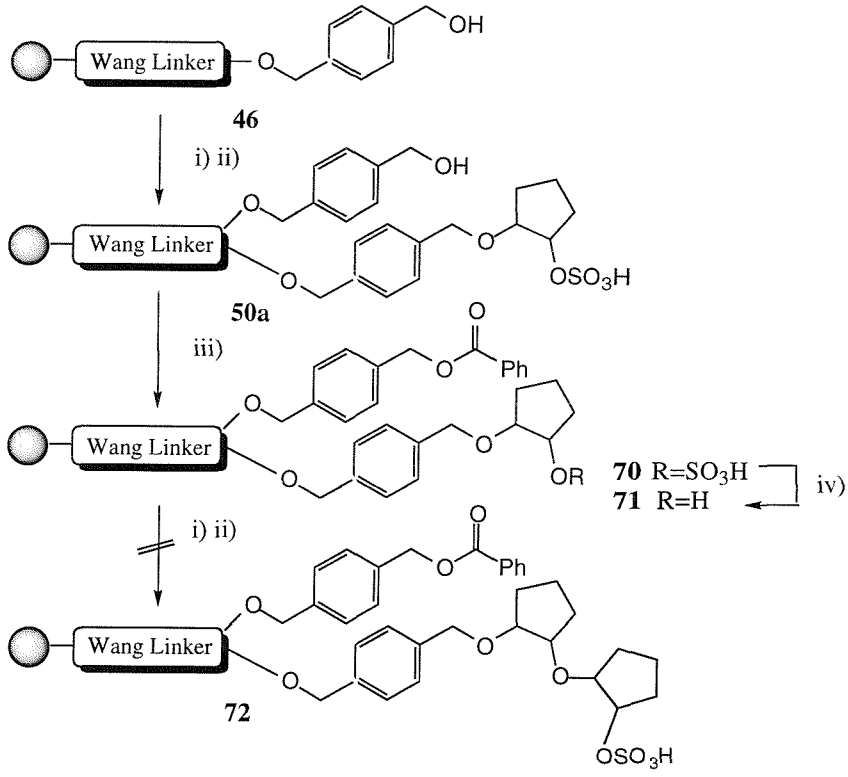
Figure 3.2

Free sulfates or their salts are difficult to handle due to their high polarity. Hence sulfatation is usually carried out as the last step of a synthesis and protection of the sulfate ester moiety has only been reported in a few cases. Perlin *et al.*[203] have described the use of phenyl sulfates introduced directly from the alcohol using phenyl chlorosulfate. The phenyl sulfates were found to be stable to NaOMe and NH_4OH. Removal of the phenyl protecting group was achieved by hydrogenation to give a cyclohexyl sulfate which was then susceptible to base hydrolysis. More interestingly, use of the 2,2,2-trifluoroethyl group has been studied by Flitsch *et al.*[204] for the protection of sulfate esters in carbohydrates. The trifluoroethyl esters were formed by treatment of the sulfate monoesters with 2,2,2-trifluodiazoethane and could be selectively introduced in the presence of free alcohols.[205] The trifluoroethyl esters were found to be stable to strong organic acids (TFA:EtOH 4:1, 25 °C, 2h), catalytic

hydrogenolysis, TBAF, refluxing methanol and NaOMe/MeOH. Refluxing with *t*-BuOK/*t*-BuOH lead to the removal of the protecting group. Treatment with dilute sulfuric acid resulted in the cleavage of the entire sulphate moiety. Selective protection of the sulfate ester moiety, followed by capping of the unreacted alcohol and finally removal of the sulfate ester protecting group could be envisaged, although this would introduce an additional step.

Corbett *et al.*[206] have reported the selective alkylation of a carboxylic acid with various alkyl halides (MeI, Br-C_6H_4-CH_2Br, NO_2-C_6H_4-CH_2Br, Br-$C_6H_4COCH_2Br$) in the presence of a sulfate ester moiety. Selective capping with MeI was therefore attempted. A single coupling was performed on resin **46** with the cyclic sulfate **33a**, leaving the alcohol **4** partially unreacted. Resin **50a** was then treated with NaH (5eq) and MeI (5eq) in DMF. Cleavage and HPLC analysis showed only a small percentage of conversion of the alcohol **4** to the methyl ether and complete hydrolysis of the sulfate ester **8a** to give **9a**. Subsequent work did not allow these results to be reproduced and to determine if methylation of the sulfate ester was taking place.

Capping was attempted with benzoyl chloride (5 eq) in the presence of a large excess of Et_3N (10 eq) under rigorously dry conditions. Cleavage of resin **70** and HPLC analysis showed that esterification of the alcohol **4** to the benzoyl ester could be achieved while leaving the sulfate ester **8a** unaffected (Figure 3.3).

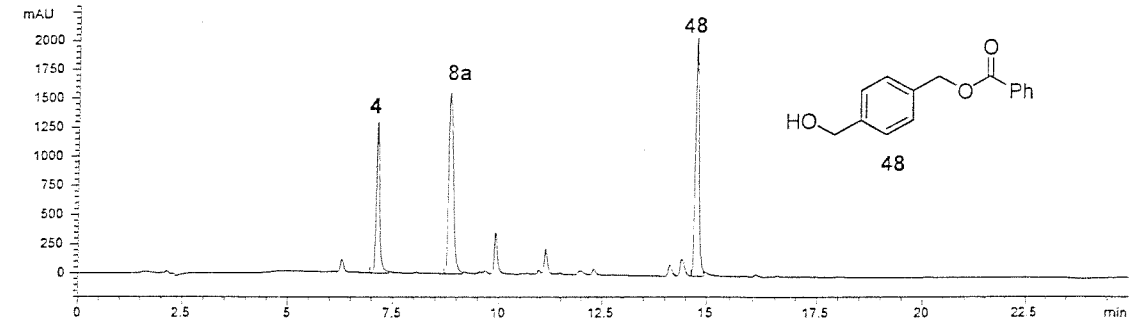


Reagents and conditions: i) NaH (5 eq), 15-crown-5 (1 eq), DMF, 1 h ii) **33a** (5 eq), DMF, 4 h. R = SO_3H. iii) Benzoyl chloride (5 eq), Et_3N (10 eq), DMAP (0.5 eq), DCM, 5 h. iv) 0.01 M HCl/ 1% H_2O/ dioxane, 12 h. R = H.

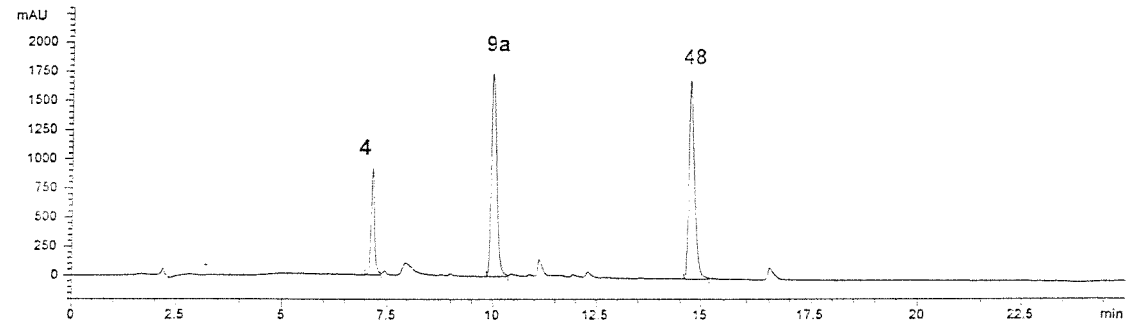
Scheme 3.4

Following hydrolysis of the sulfate ester moiety, *O*-alkylation of the resin bound dimer **71** with cyclic sulfate **33a** was then attempted. Complete hydrolysis of the benzoyl ester was observed and may have resulted from traces of NaOH in the reaction mixture or due to the formation of NaOMe during the washing step upon addition of MeOH to quench the excess NaH.

(a) Resin 70



(b) Resin 71



(c) Resin 72

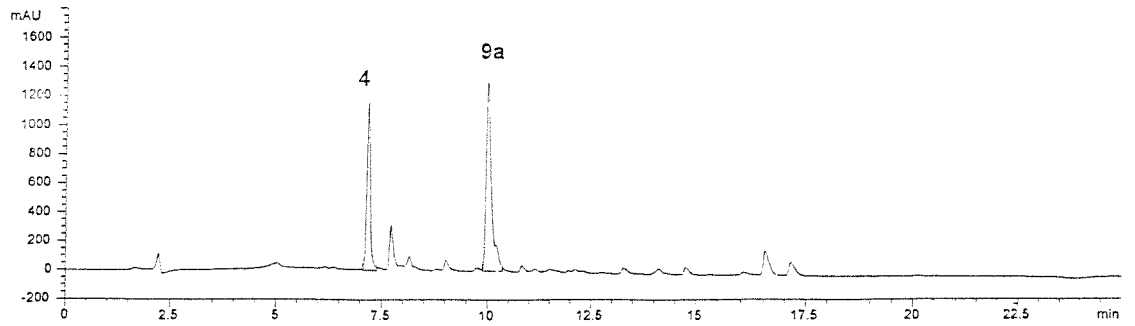
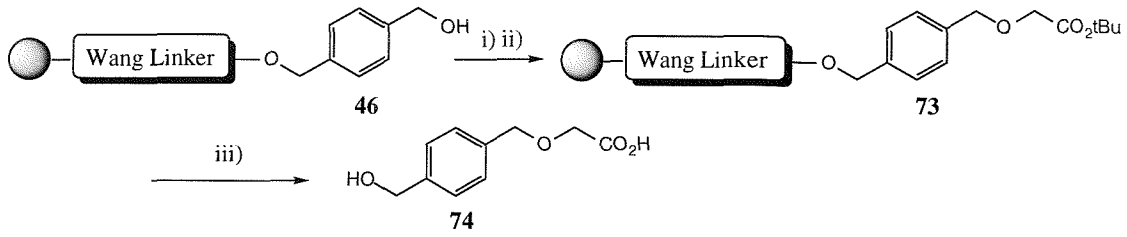


Figure 3.3

3.3 Introduction of the terminal carboxylic acid

Introduction of the terminal carboxylic acid was attempted by a standard Williamson reaction using *t*-butyl bromoacetate[207] (Scheme 3.5).



Reagents and conditions: i) *t*-BuOK (5 eq), THF, 1h then filtration under N_2. ii) $BrCH_2CO_2t$-Bu (10 eq), DMF, O/N.

Scheme 3.5

The resin bound diol **46** was first treated with *t*-BuOK. The excess base was then filtered off under N_2 prior to addition of *t*-butyl bromoacetate. Success of the reaction was confirmed by analysis of resin **73** by FTIR (appearance of the C=O band at 1730 cm^{-1}) and gel phase ^{13}C NMR ($(\underline{C}H_3)_3C$ 28 ppm). TFA cleavage proceeded with concomitant hydrolysis of the *t*-butyl ester to give the free carboxylic acid **74**. HPLC analysis showed conversion to the acid **74** in 53% yield. Attempts to push the reaction to completion by a second and third coupling resulted in the formation of an increasing number of side products of lower polarity. This might be due to the relative high acidity of the methylene protons α to the carbonyl which are thus likely to undergo deprotonation under the strong basic conditions followed by alkylation with *t*-butyl bromoacetate. Cleavage and purification by semi-preparative RP-HPLC gave **74** in 25% (2 steps from **44**). Other alternatives based on literature procedures are shown in figure 3.4 and could constitute the basis for further work to allow the introduction of diverse terminal building blocks.

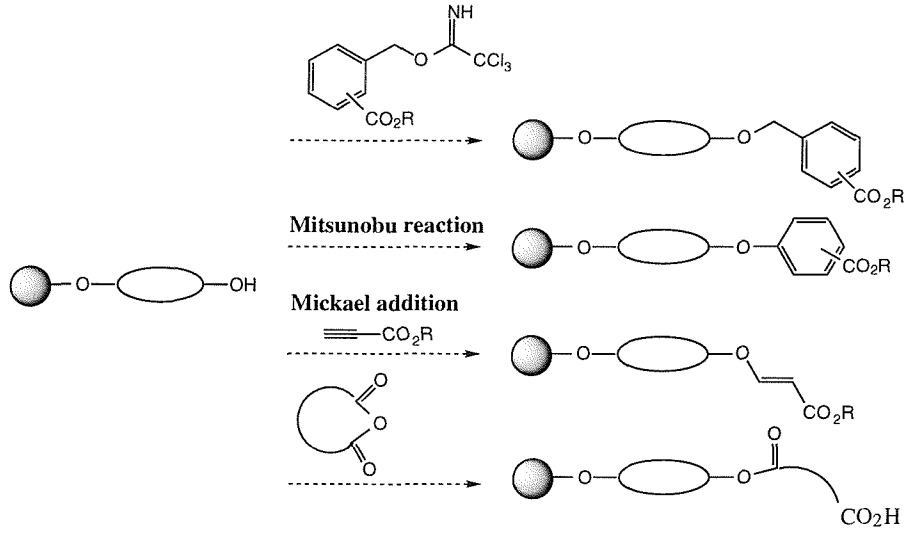


Figure 3.4

Conclusions

The methodology developed allows the construction of oligo-ethers by a simple two step procedure. The principle has been demonstrated by the synthesis of two small libraries. However, ether bond formation becomes increasingly difficult as the chain grows and requires extensive couplings to reach satisfactory yields of *O*-alkylation. Moreover, as observed with the synthesis of the trimer library, success of the *O*-alkylation seems to be highly dependent on the combination of building blocks used.
The *O*-alkylation and sulfate ester hydrolysis reactions have been shown to proceed with overall clean inversion of configuration. However, the generation of an increasing number of stereoisomers associated with the use of *meso* cyclic sulfates can be considered as a weakness of the methodology as it severely complicates the analysis and purification of the libraries. The use of NaH was preferred to *t*-BuOK as it was initially found to give more reproducible results but has impeded automation of the procedure. For that purpose, use of *t*-BuOK could be reconsidered. Consequently, the methodology developed so far is applicable to the synthesis of short length oligo-ethers (3-4 residues) and small size libraries only. Development of an efficient and general method for capping the unreacted diols is crucial to extend the approach to the synthesis of longer oligo-ether chains and facilitate purification.

Chapter 4: Monitoring Using A Dual Linker System

As previously discussed in chapters 2 and 3, monitoring of the reactions and rapid characterisation of the compounds proved difficult and was a major limitation for the development of the reactions on the solid phase. Monitoring by HPLC-UV analysis imposed the choice of a first building block possessing a UV chromophore. However, the side reactions between the cyclic sulfates and the unreacted trityl linker only became apparent with the cyclic sulfate **33f** possessing a chromophore. Monitoring by ESMS analysis was especially difficult during the first steps of the synthesis, as the target molecules possessed a low molecular weight and lacked sufficient protonation/deprotonation sites to effect ionisation by ESMS. Detection only became possible when the oligoethers reached a sufficient length to display ionophoric properties allowing their detection as sodiated molecular ions.

Such issues have been addressed by Fitzgerald *et al.*[208] with the development of a dual linker system (Figure 4.1).

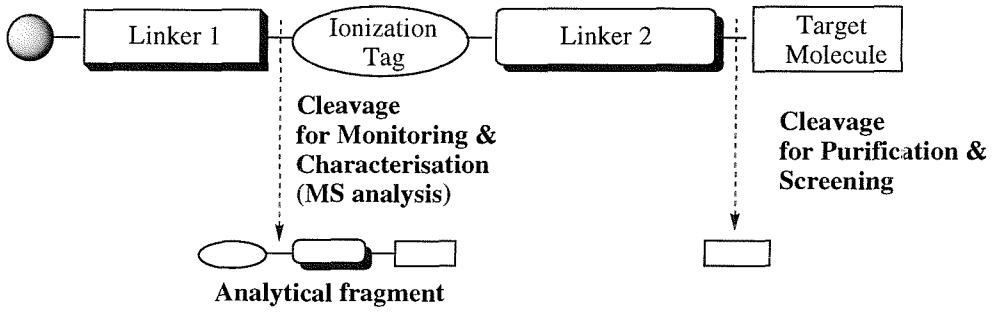


Figure 4.1: principle of the dual linker system.

The dual linker system consists of two linkers cleavable under orthogonal conditions, and connected one to the other by an ionisation tag. Upon cleavage of the first linker, an 'analytical fragment' is released. The ionisation tag, containing a readily ionisable functionality such as an amine ensures that any compound cleaved off can be characterised independently of its ability to fly by mass spectrometry. Cleavage of the second linker allows the release of the target molecule in a 'traditional manner', leaving the tag and first linker bound to the resin. The modular nature of this approach allows the choice of a variety of linkers and ionisation tags in function of the chemistry carried out.

The original construct developed by Fitzgerald[201] used the photocleavable *o*-nitrobenzyl linker and a short peptide as an ionisation tag allowing real time monitoring by MALDI TOF MS (Figure 4.2).

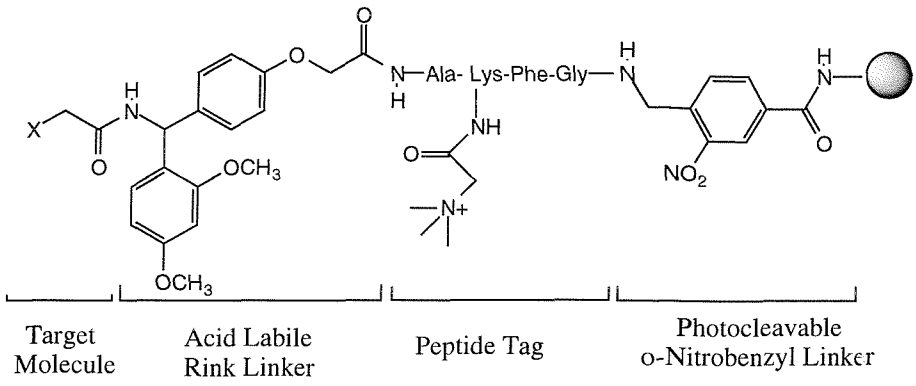


Figure 4.2

The UV laser was used to simultaneously promote the photolytic cleavage of the analyte from the solid support and its gas phase ionisation for subsequent mass spectral analysis. The additional mass of the peptide and Rink linker ensured that the analyte peaks were not obscured by the matrix peaks.

During the course of this project, Carr *et al.*[209] reported the synthesis of various dual linker systems using for example the orthogonal acid labile Rink linker and hydrazine labile Dde linker or the thiol sensitive 2-nitrosulfonamide linker (Figure 4.3). Isotopically enriched diamines (50% ^{15}N enriched or doubly labelled with deuterium) were used as ionisation tags giving rise to characteristic doublet signals ($[M+H]^+$ and $[M+H+2]^+$), the mass splitting facilitating the identification of the relevant signals in the ESMS spectra.

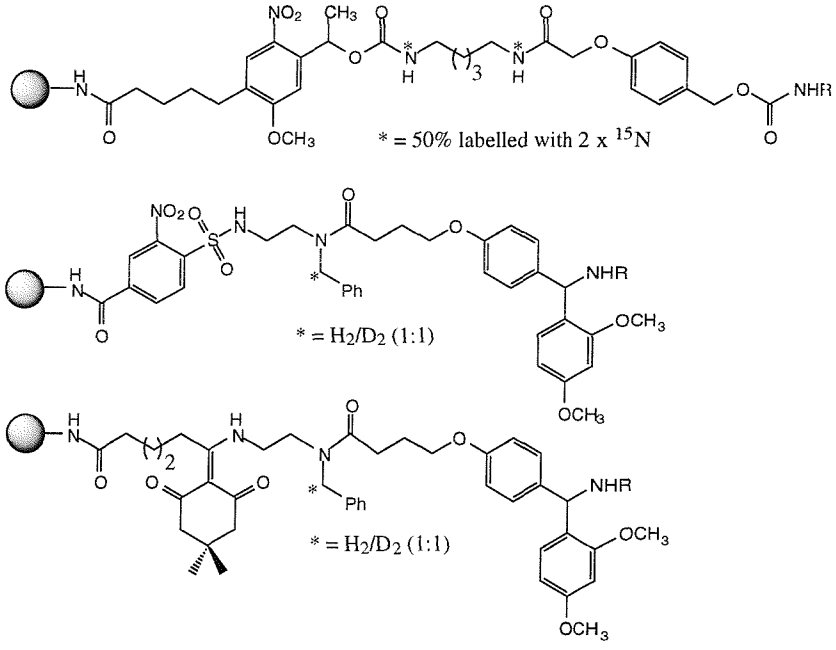


Figure 4.3

A new dual linker system shown in figure 4.4 was designed to facilitate the monitoring of the solid phase synthesis of polyether libraries using cyclic sulfate chemistry.

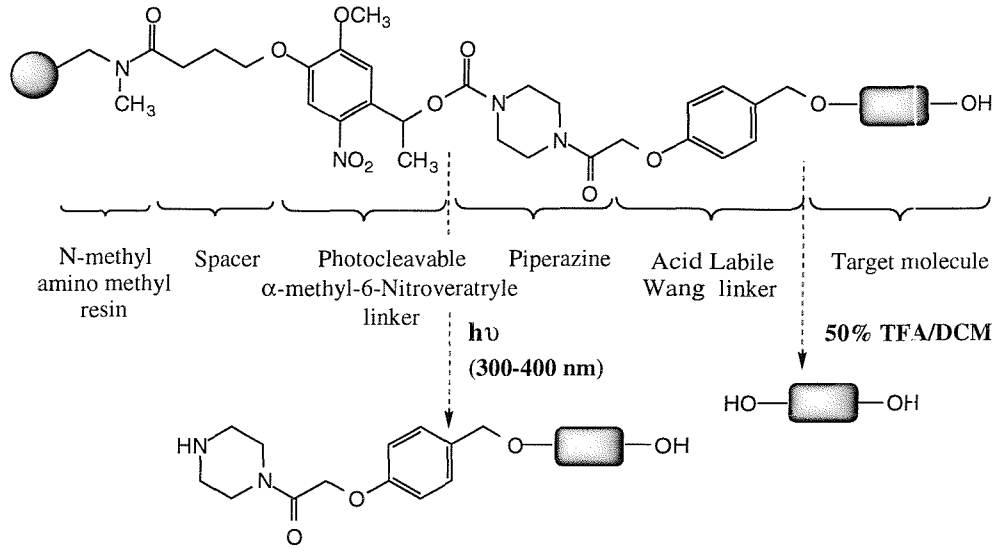


Figure 4.4

Difficulty resided in the construction of a dual linker linker system stable to the synthetic conditions. The choice of the first linker turned to the use of a photolabile linker.[210] Photolysis offers a mild method of cleavage under neutral conditions. Photocleavage is orthogonal to acidic and basic reactions and provides compatibility with the reaction conditions used during polyether synthesis.

The choice of the Wang linker, imposed by the synthetic strategy adopted, provided a chromophore in the analytical fragment. Piperazine was selected as the ionisation tag. The use of a secondary diamine prevented *N*-alkylation side reactions in the presence of the cyclic sulfates and avoided the use of additional protecting groups. Similarly, the use of *N*-methyl aminomethyl resin allowed the attachment of the photocleavable linker *via* an inert *N*-methylated amide bond.

4.1 Synthesis of the dual linker system

Assembly of the dual linker system could in theory be performed directly on the solid phase. However, complete control of the reactions is essential at this stage to ensure the integrity of the dual linker system. It was therefore decided for the initial studies to pre-load the amine on the photocleavable linker. Likewise, to ensure a good loading of the first building block and absence of unreacted Wang linker, coupling of the model diol **4** was performed in solution (Figure 4.5).

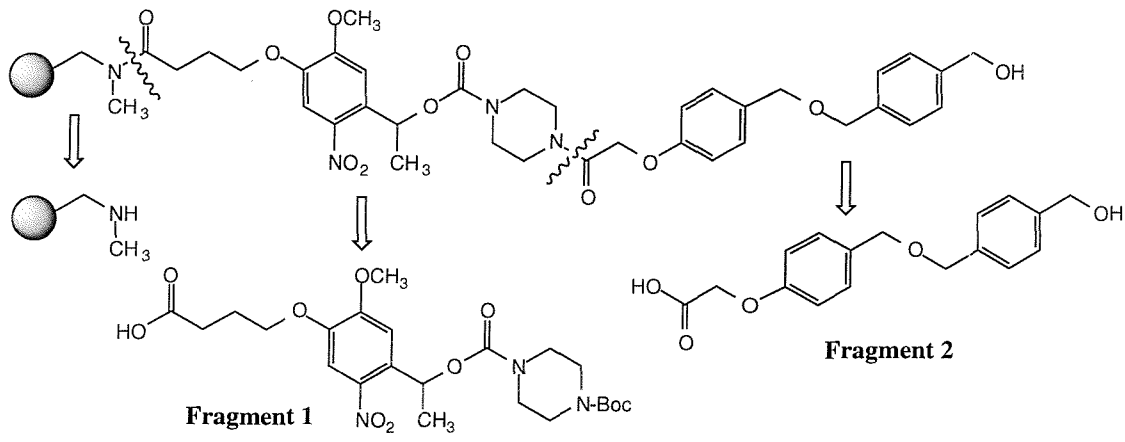
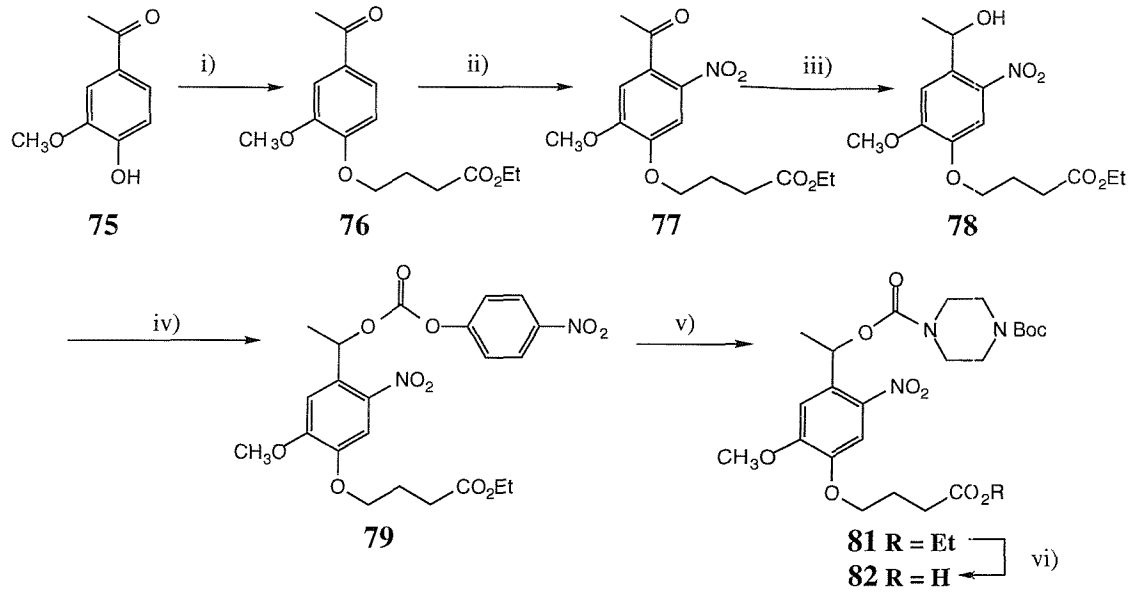


Figure 4.5

4.1.1 Synthesis of the first fragment

Multigram synthesis of the α-methyl nitroveratryl linker **78** was achieved by a 3 step procedure[211,210a] starting from commercially available acetovanillone **75** (Scheme 4.1). Alkylation of **75** with ethyl 4-bromobutyrate under standard conditions gave the ketone ester **76** in 70% yield. Regioselective nitration of **76** was performed with fuming nitric acid in dry DCM.[210a] Despite careful monitoring of the temperature (T<-10 °C), formation of the *ipso* substitution by-product was observed in 10% yield. Subsequent reduction of **77** with $NaBH_4$ gave the photocleavable linker **78** in 60% overall yield (3 steps).



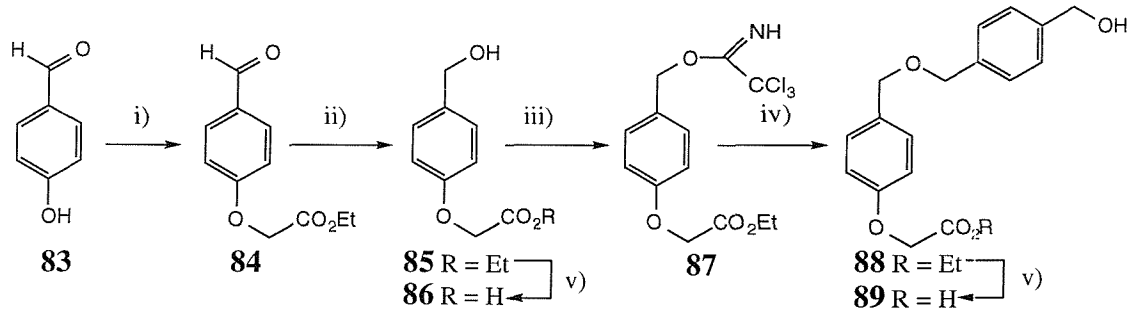
Reagents and conditions: i) $Br(CH_2)_3CO_2Et$ (1.2 eq), K_2CO_3 (2 eq), KI (0.02 eq), CH_3CN, reflux, 6 h, 70%. ii) Fuming nitric acid, DCM, -10 °C, 1 h. iii) $NaBH_4$ (0.25 eq), THF/EtOH 4:1, 0 °C→ rt, 6 h, 86% (two steps). iv) 4-nitrophenylchloroformate (1.1 eq), pyridine (1.5 eq), DCM, 0 °C → rt, O/N, 89%. v) Boc-piperazine **80** (1.1 eq), Et_3N (1.5 eq), CH_3CN, 75%. vi) 2M NaOH (2 eq), dioxane/H_2O 2:1, 2 h, 90%.

Scheme 4.1

Synthesis of mono-protected Boc piperazine **80** was achieved following a literature procedure.[212] Coupling on the photocleavable linker was performed *via* the activated *p*-nitrophenol carbamate **79** and gave the urethane derivative **81** in 75% yield. Final hydrolysis of the ester with NaOH in dioxane gave the first part of the dual linker system **82**.

4.1.2 Synthesis of the second fragment

The Wang linker **86** was synthesised from *p*-hydroxybenzaldehyde following a literature procedure.[213] Coupling of the diol **4** was performed under mild Lewis acid conditions *via* the trichloroacetimidate derivative **87**. (Scheme 4.2).



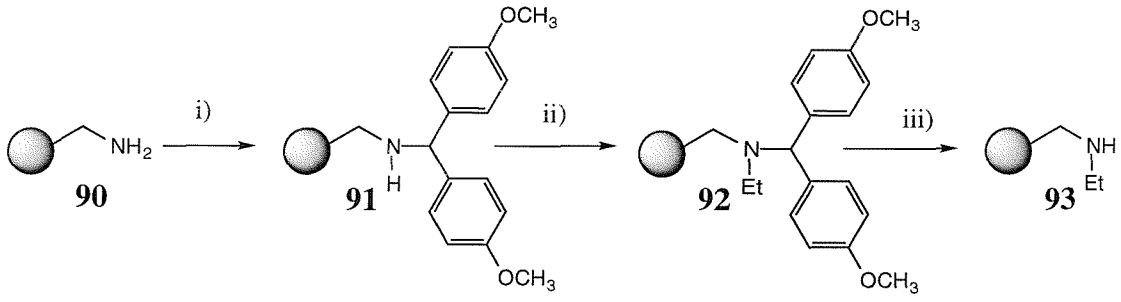
Reagents and conditions: i) $BrCH_2CO_2Et$ (1.2 eq), K_2CO_3 (2 eq), KI (0.02 eq), CH_3CN, reflux, 80%. ii) $NaBH_4$ (0.25 eq), EtOH, 0 °C → rt, 2 h, 93%. iii) CCl_3CN (1.2 eq), *cat.* DBU (0.2 eq), ether, 92%. iv) **4** (3 eq), $BF_3.OEt_2$ (0.1 eq), DCM/THF 1:1, 0 °C, 84%. v) 2M NaOH (2 eq), dioxane/H_2O 2:1, 90%.

Scheme 4.2

Synthesis of **87** was carried out by modification of a literature procedure[214] and proceeded in good yields (92%). Initial attempts to couple 1,4-benzenedimethanol to **87** resulted in formation of a large amount of *bis*-alkylated product (30%) despite the use of a large excess of diol and its slow addition.[215] Optimisation of the reaction by variation of different parameters[216] (temperature, Lewis acid, solvent (DCM, THF, cyclohexane)) finally allowed us to reduce the percentage of *bis*-alkylation and gave the product **88** in 84% yield. Subsequent ester hydrolysis provided the second fragment **89** of the dual linker system.

4.1.3 Synthesis of the *N*-alkylated amino-methyl resin

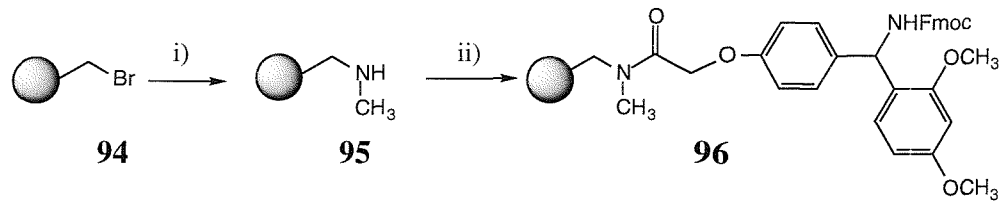
Synthesis of *N*-alkylated aminomethyl resin **93** was first attempted by reductive alkylation of amino methyl resin **90** by modification of a literature procedure.[217] (Scheme 4.3)



Reagents and conditions: i) Dod-Cl (1.5 eq), DIEA (3 eq), DCM, O/N. ii) CH_3CHO (10 eq), 1% AcOH, DMF/TMOF 1:1, 1 h then $NaBH(OAc)_3$ (10 eq), O/N. iii) 50% TFA / 5% TIS / DCM.

Scheme 4.3

To avoid *bis*-alkylation, aminomethyl resin **90** was first protected with the Dod group. The reaction was monitored by the ninhydrin test. Reductive amination of resin **91** was then carried out under standard conditions.[218] Due to the bulk of the Dod group, the bromophenol test was negative on resin **91** and therefore could not be used to monitor the completion of the reaction. Removal of the Dod group proved difficult. After extensive treatments with 50% TFA/ 5% TIS /DCM, presence of the pink Dod cation could be still observed in the filtrates. Although a quantitative ninhydrin test on resin **90** showed the reductive alkylation to be successful, a more direct and simpler method was sought. Hence, resin **95** was conveniently prepared by treatment of brominated TentaGel resin **94** with a large excess of $MeNH_2$ (20 eq) in THF in the presence of KI (2 eq) (Scheme 4.4).



94 **95** **96**

Reagents and conditions: i) CH_3NH_2 (20 eq), KI (2 eq), THF/DMF 9:1, O/N. ii) (a) DIC (2 eq), HOBt (2 eq). (b) HATU (2 eq), DIEA (4 eq). (c) PyPOP (2 eq), DIEA (4 eq). (d) PyBrop (2 eq), DIEA (4 eq). (e) THHF (2 eq), DIEA (4 eq) in DCM, DMF 9:1, O/N.

Scheme 4.4

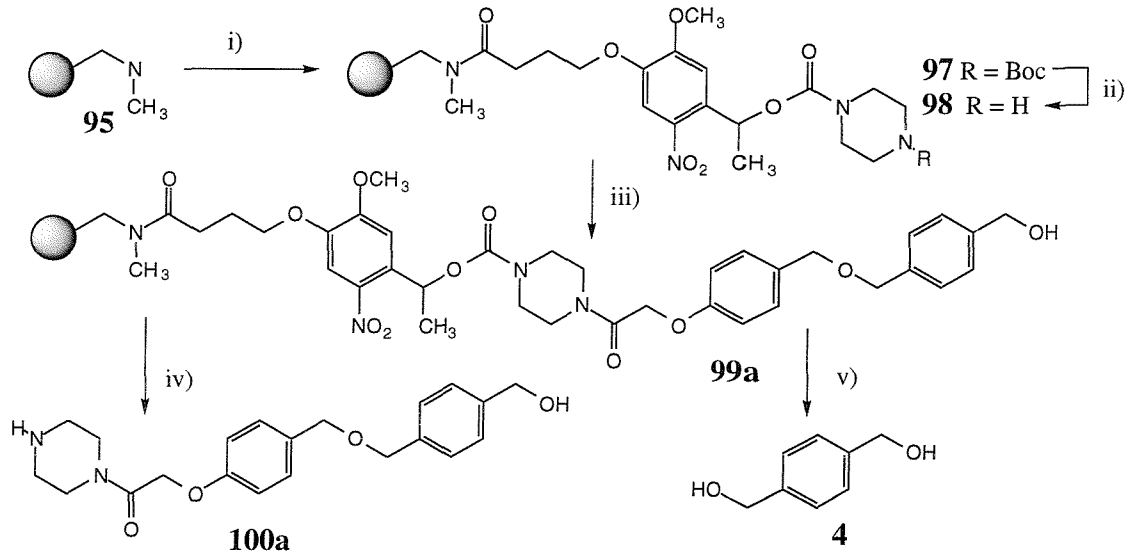
Success of the reaction was confirmed by Gel phase NMR of resin **95** with the complete disappearance of the $\underline{C}H_2Br$ peak (31 ppm) and appearance of two new peaks at 36 ppm ($N\underline{C}H_3$) and 51 ppm ($\underline{C}H_2NHCH_3$). A quantitative bromophenol test[81] indicated a loading of 0.23 mmol/g (76% yield).

Resin **95** was derivatised with the Fmoc Rink linker to provide a model study of the coupling conditions on the *N*-methylated resin. The coupling was first attempted under standard conditions using HOBt/DIC. After two couplings, a qualitative bromophenol blue test was still positive. Reagents recommended for the coupling of hindered or *N*-methyl amino acids[219] (HATU/DIEA[220], PyBOP/DIEA, PyBroP/DIEA[221], THHF/DIEA[222]) were therefore investigated. In all cases, an Fmoc test indicated that the reactions were complete or close to completion after one coupling though the qualitative bromophenol blue tests remained weakly positive in all cases.

4.1.4 Assembly of the dual linker system

Attachment of the first part of the dual linker system **82** on *N*-methyl aminomethyl resin **95** was carried out with PyBroP (Scheme 4.5). FTIR showed the appearance of the NO_2 band at 1551 cm^{-1} and C=O band (Boc) at 1691 cm^{-1}. The characteristic structural features of **82** could be clearly observed by gel phase NMR: $\underline{C}(CH_3)_3$ at 79 ppm, $(\underline{C}H_3)_3C$ at 28 ppm, aromatic CH of the photocleavable linker at 109 and 108 ppm, $O\underline{C}H_3$ at 56 ppm (Figure 4.6). Small scale cleavage by photolysis and ESMS analysis gave the expected peak at 187 $[M+H]^+$ for Boc-piperazine. A qualitative bromophenol test was however still weakly positive after two couplings. A quantitative bromophenol test was carried out and indicated the presence of 16% unreacted amine. Resin **97** was therefore capped with a large excess of acetyl chloride (10 eq) in presence of pyridine. No change in the gel phase NMR and IR spectra were however observed and the bromophenol blue test remained positive.

Removal of the Boc protecting group was achieved by treatment of resin **97** with 50% TFA/DCM. Disappearance of the $(\underline{C}H_3)_3C$ peak at 28 ppm in the gel phase NMR spectra of resin **98** and the disappearance of the C=O (Boc) band at 1692 cm^{-1} confirmed completion of deprotection.



Reagents and conditions: i) **82** (1.5 eq), PyBroP (2 eq), DIEA (4 eq), DCM, O/N. ii) 50% TFA/DCM. iii) **89** (1.1 eq), EEDQ (1.2 eq), DCM/DMF 9:1, O/N. iv) hυ, CH_3CN, 2 h. v) 50%/ TFA/ DCM.

Scheme 4.5

Amide bond formation between the resin bound piperazine moiety **98** and **89** was first attempted using standard DIC/HOBt conditions. Small scale photolysis and HPLC-UV analysis showed the presence of the expected adduct **100a** (t_R = 9.6 min, ESMS (+ve) 371 $[M+H]^+$) along with ester by-products resulting from the self-condensation of **89** (t_R = 13.2 min, 654 $[M'+H]^+$; t_R = 15.7 min, 938 $[M''+H]^+$). Coupling of **89** with EEDQ allowed us to reduce the formation of the ester by-products. Treatment of resin **99a** with 2M NaOH in dioxane (2 eq) finally ensured the complete hydrolysis of the ester by-products. Cleavage with 50% TFA and quantification of 1,4-benzenedimethanol **4** by HPLC-UV analysis indicated however a poor loading (0.08 mmol/g, 32% yield). A quantitative bromophenol blue test indicated a percentage of unreacted secondary amine identical to the previous step.

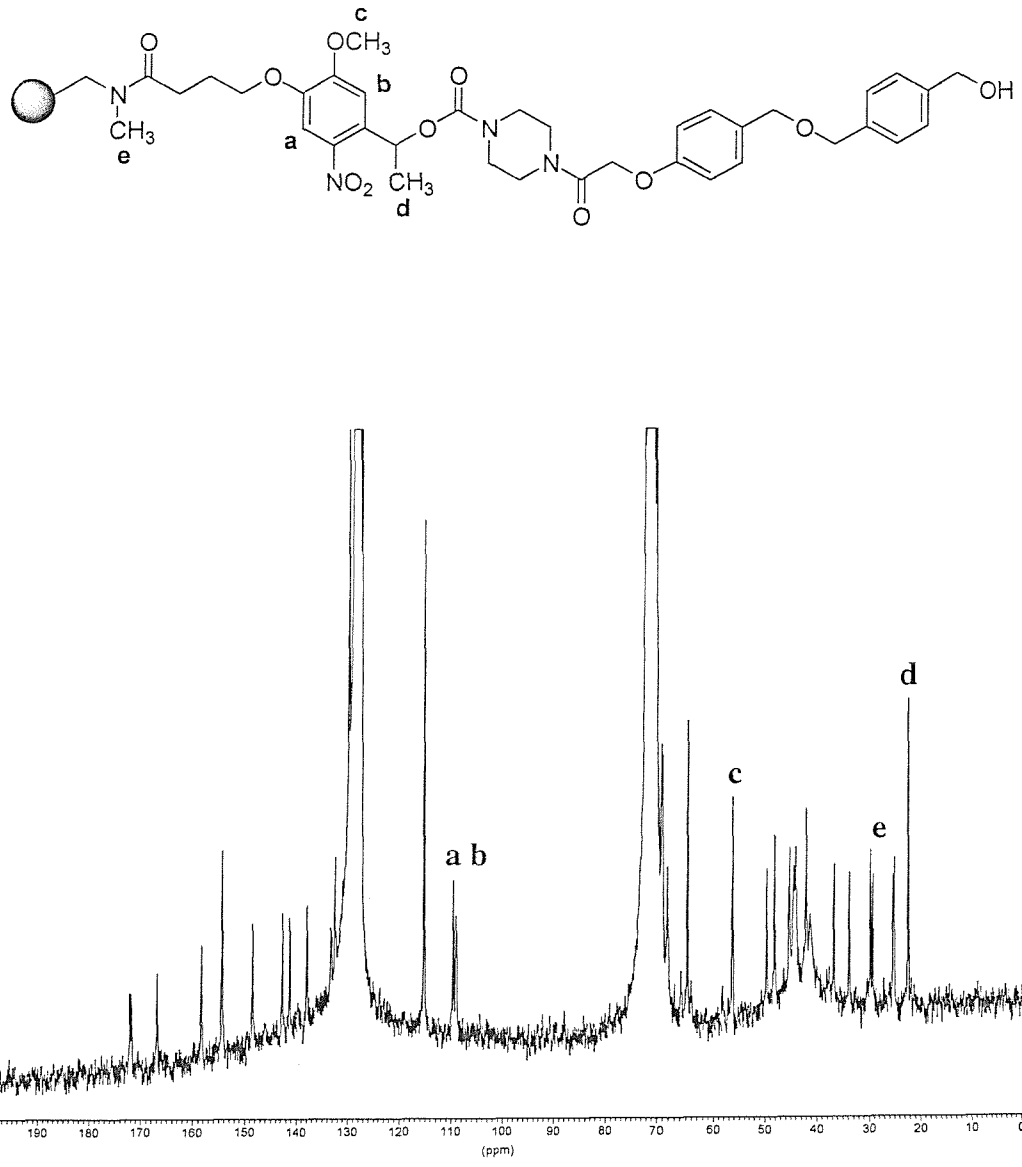
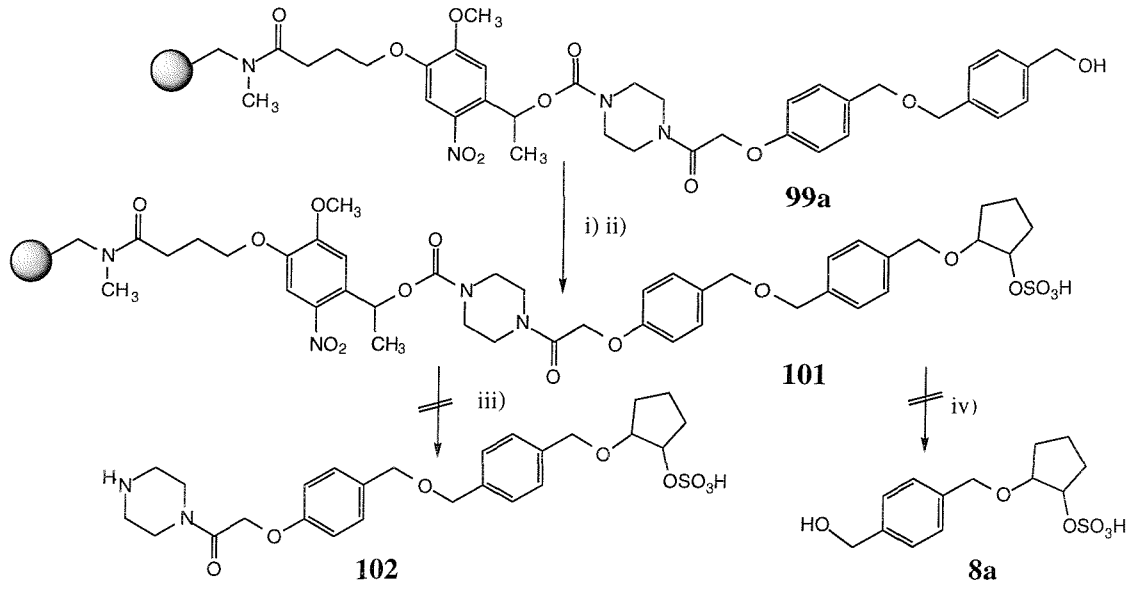


Figure 4.6: Gel phase NMR of resin **99a**

4.2 Monitoring

4.2.1 Monitoring of the *O*-alkylation reaction using cyclic sulfate chemistry

Having constructed the dual linker **99a**, *O*-alkylation of the resin bound diol **99a** with the model cyclic sulfate **33a** was then attempted (Scheme 4.6). After addition of the cyclic sulfate, samples were taken at regular time intervals.

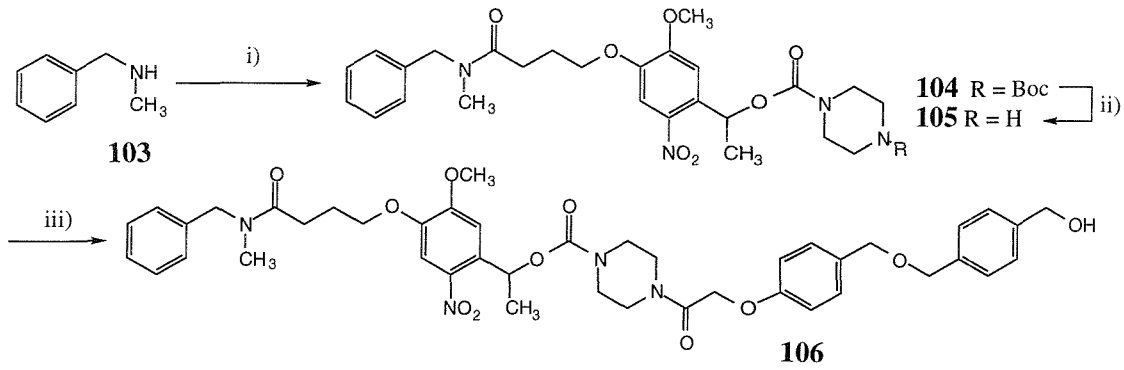


Reagents and conditions: i) NaH (5 eq), 15-crown 5 (1 eq), DMF, 1 h. ii) **33a** (5 eq), DMF, 6 h. iii) hυ, 2 h, CH_3CN. iv) 50% TFA/DCM, 30 min.

Scheme 4.6

Photolysis and HPLC analysis showed the presence of unreacted **100a** (t_R = 9.7 min) and the appearance of a new product (t_R = 10.7 min). However, ESMS analysis did not confirm the formation of the expected sulfate ester **102**. TFA cleavage and HPLC-UV analysis showed the presence of unreacted diol **4**, absence of the sulfate ester **8a** and appearance of a new peak (t_R = 10.7 min) with a molecular weight of 414.

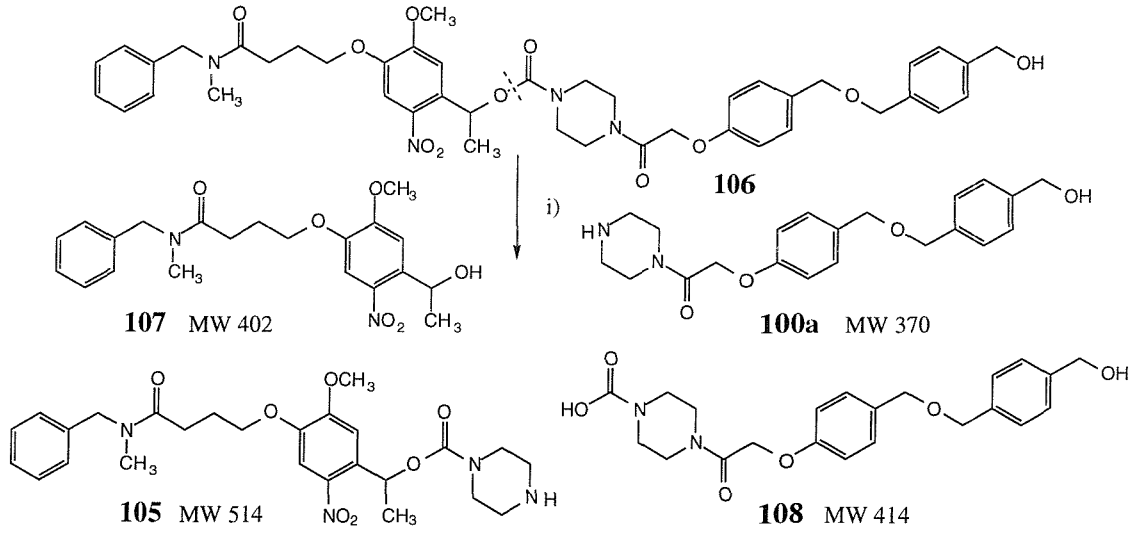
A control reaction by treatment of resin **99a** with NaH (5 eq) gave identical results and confirmed that the products observed did not result from *O*-alkylation with the cyclic sulfate **33a**, but from a side reaction following treatment with NaH. Moreover, TFA cleavage and quantification of the released diol **4** indicated a strong decrease in loading from 0.08 mmol/g to 0.03 mmol/g. Analysis of the filtrate confirmed the leakage of products from the resin during the reaction. To test the stability of the dual linker system, the solution analogue **106** was synthesised (Scheme 4.7).



Reagents and conditions : i) DCC (1.1 eq), HOBt (1.1 eq), DMAP (0.1 eq), *N*-methylbenzylamine (1.2 eq), O/N, 81%. ii) TFA/DCM, 90%. iii) **89** (1 eq), EEDQ (1.2 eq), DCM, O/N, 49%.

Scheme 4.7

As an equivalent of the attachment point to the resin, **82** was coupled with *N*-methyl benzylamine *via* a standard DCC/HOBt reaction and gave the *N*-methyl amide **104** in 81% yield. Boc deprotection with TFA to give the free amine **105** followed by coupling of the adduct **89** with EEDQ gave the model compound **106**. **104** was first submitted to the reaction conditions used for the solid phase *O*-alkylation (NaH (5 eq), 15-crown 5 (1 eq), DMF (c = 0.2 M), rt, 2h). No noticeable degradation of **104** was observed by TLC. NaH was quenched by addition of D_2O. After removal of the solvent *in vacuo*, the crude product was analysed by HPLC. No degradation of **104** was detected. After aqueous work up, analysis of the crude product by NMR did not show any change in the spectra. **106** was then submitted to the same conditions. The reaction was quenched by addition of MeOH. Following removal of the solvent *in vacuo*, analysis by HPLC showed degradation of **106** to give a mixture of compounds (Scheme 4.8): t_R= 9.7 min (**100a**, 371 $[M+H]^+$); 10.8 min (**108**, 415.2 $[M+H]^+$), 12.3-12.6 min (**105**, 515 $[M+H]^+$), 14.8 min (**107**, 403.3 $[M+H]^+$), 16.8 min (**106**, 799 $[M+H]^+$)

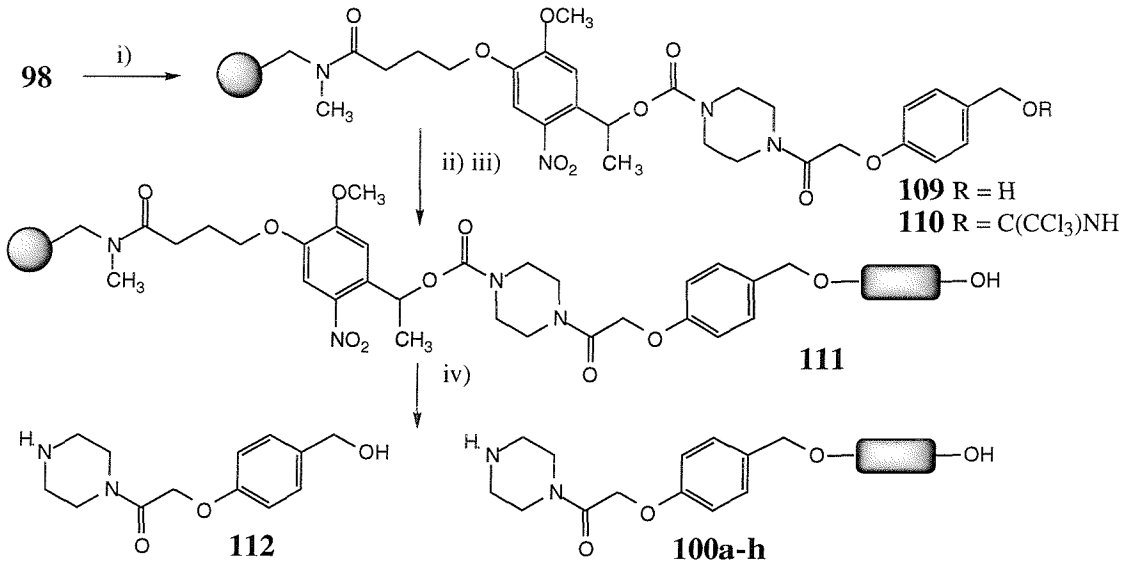


Scheme 4.8

Though the different products could not be fully characterised, these different results suggest that the carbamate linkage between the photocleavable linker and piperazine moiety is unstable to the *O*-alkylation conditions either due to internal reaction with the alkoxide or during the washing step due to the formation of NaOMe upon addition of MeOH to quench the excess of NaH.

4.2.2. Coupling of non UV-active diols on the Wang linker.

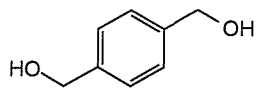
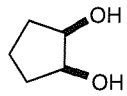
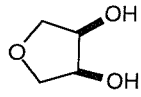
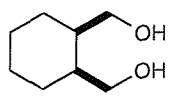
The dual linker system was used to monitor the coupling of non UV-active diols on the Wang linker (Scheme 4.9). Coupling of the model diol **4** and three non UV-active diols **31-a,b,h** was carried out using the conditions reported by Hannessian *et al.*[108]



Reagents and conditions: i) CCl_3CN (15 eq), DBU (1 eq), DCM, 1 h, 0 °C. ii) diol **4**, **31a**, **31b**, or **31h** (5 eq), $BF_3.OEt_2$ (0.4 eq), THF. iii) hυ, CH_3CN, 2 h.

Scheme 4.9

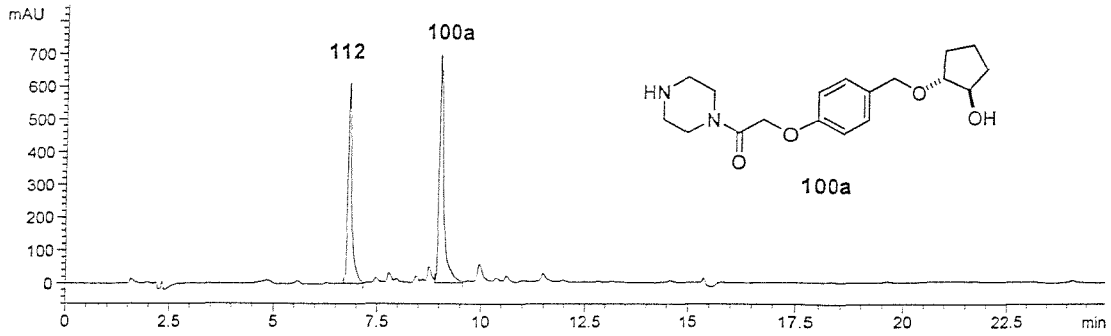
Upon photolysis, the diols **31-a,b,h** could be easily detected and characterised as their analytical fragments **100-a,b,h.** The yield of the reaction could be estimated by comparison of the percentage of **112** and **100**. In all cases, presence of the adduct **112** indicated that the reaction had not proceeded to completion (Table 4.1).

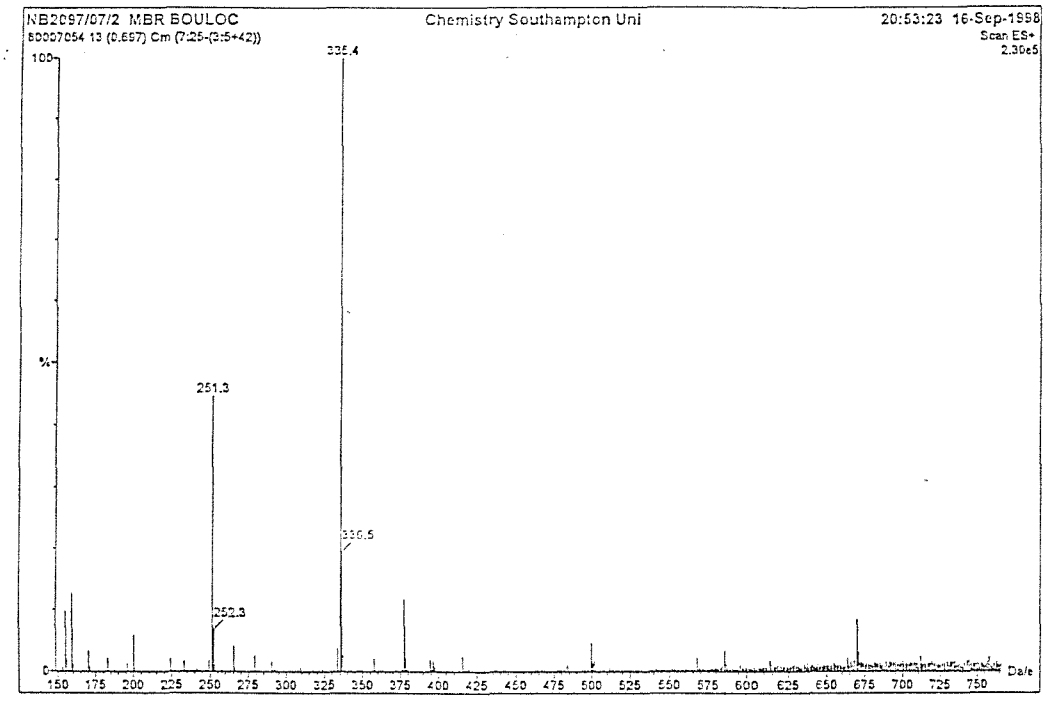
diol	 **4**	 **31a**	 **31b**	 **31h**
% conversion[a] (purity)	85[b] (85) 70[c]	68 (68)	58 (58)	60 (60)

[a] Based on photolysis and HPLC analysis (% area **100**/(% area **100** + % area **112**)). [b] taking in account the difference of ε. [c] Based on TFA cleavage and HPLC analysis using a calibration curve.

Table 4.1

However no product resulting from cross-linking of the diols was detected. As shown in figure 4.7, photolysis of 5 mg of resin **99** was sufficient to obtain good ESMS(+ve) and HPLC data.





ESMS (+ve): 335.4 (**100a**, $[M+H]^+$), 251.3 (**112**, $[M+H]^+$)

Figure 4.7

Conclusions

The design and synthesis of a new dual linker system was carried out. However, the construct chosen proved to be unstable to the reaction conditions used during the polyether synthesis. The carbamate linkage between the photocleavable linker and the amine tag appeared susceptible to hydrolysis and nucleophilic attack under the strong basic conditions required by the *O*-alkylation step. The dual linker system was successfully used to monitor the coupling of non UV active diols onto the Wang linker allowing rapid characterisation of side products and detection of side reactions.

Chapter 5: Experimental

5.1 General Information

5.1.1 Instrumentation

Nuclear magnetic resonance spectra were recorded on a Bruker AC300 spectrometer at 300 MHz for ^{1}H and 75 MHz for ^{13}C, and on a Bruker AM400 spectrometer at 400 MHz for ^{1}H and 100 MHz for ^{13}C (δ scale in parts per million).

Infra-red spectra were recorded on an FTIR microspectrometer BioRad FTS-135 equipped with a golden gate accessory and are recorded neat as oils or solids. The following abbreviations have been used to denote intensity and peak shape: s, strong; m, medium; w, weak; br, broad.

Fast Atom Bombardment mass spectra were recorded on an Analytical 70-250-SE normal geometry double focusing mass spectrometer (using argon gas and a NBA matrix). Electrospray mass spectra were recorded using a VG Platform Quadrupole Electrospray Ionisation mass spectrometer.

UV-Vis spectra were recorded on a Hewlett Packard 8452A Diode Array spectrophotometer.

Melting points were recorded on a Gallenkamp melting point apparatus and are uncorrected.

Thin layer chromatography was carried out on 0.25 mm Kieselgel 60G/UV254 pre-coated aluminium foil plates and were visualised with a 254 nm UV lamp. Column chromatography on silica gel used Kielesgel 60 230.

5.1.2 Reagents

Solvents were freshly distilled from CaH_2 for hexane, toluene and CH_2Cl_2, from sodium/benzophenone under nitrogen atmosphere for THF and ether. Pyridine and triethylamine were distilled from CaH_2. Dry DMF was purchased from Aldrich. Solvents used for photolysis experiments were degassed by N_2 bubbling for 1 h.

Moisture sensitive reactions were carried out using oven-dried glassware (12 h) under a nitrogen atmosphere. Nitrogen was dried by passage over $CaCl_2$ pellets and silica gel.

Cis 1,2-cyclopentanediol **31a**, 1,4-anhydroerythritol **31b**, 3-phenoxy 1,2-propanediol **31b**, *cis* 1,2-cyclohexanedimethanol **31h**, (*R*)-(-)-1,3-butanediol **31f**, (2*S*,5*S*)-(+)-hexanediol **31i** are commercially available (Aldrich). Commercial 1,4-benzenedimethanol **4** was recrystallized from EtOAc and dried *in vacuo* over KOH. Resins were purchased from Novabiochem.

5.1.3 General procedures

5.1.3.1 Cleavage procedures for Trityl based resins

Procedure 1 (Small scale TFA cleavage)

The resin (10 mg) was placed in an Eppendorf tube, swollen in DCM (200 µL) and treated with 3% TFA / 5% TIS / DCM (1 mL) for 30 min. The resin was filtered and washed with CH_3CN (10 mL). The filtrates were evaporated *in vacuo* (without heating). The residue was dissolved in CH_3CN/H_2O 2:8 (1 mL) and analysed by analytical RP HPLC.

Procedure 2 (Small scale HCl cleavage)

As above. The TFA cleavage cocktail was replaced by a commercial solution of 4M HCl in dioxane (1 mL).

Procedure 3 (Large scale cleavage HCl cleavage)

The resin was placed in a glass peptide vessel, swollen in DCM (2 mL), and treated with a mixture of 4M HCl in dioxane (3 mL), MeOH (1 mL) and TIS (100 µL) for 30 min with occasional stirring. The resin was filtered, washed with DCM/MeOH 1:3 (6 x 3 mL) and the cleavage repeated a second time using the same conditions. The combined washings were evaporated *in vacuo* (without heating). The residue was taken up in CH_3CN/H_2O 2:8 (c = 10 mg/mL) and purified by semi-preparative RP-HPLC.

5.1.3.2 Cleavage procedures for Wang based resin

Procedure 4 (Small scale TFA cleavage)

The resin (10 mg) was placed in an Eppendorf tube, swollen in DCM (0.5 mL) and treated with TFA (0.5 mL) for 30 min. The resin was filtered and washed with CH_3CN (10 mL). The filtrates were evaporated *in vacuo* (without heating). TFA was co-evaporated by repeated addition of CH_3CN. The residue was dissolved in CH_3CN/H_2O 2:8 (1 mL).

Procedure 5 (Large scale TFA cleavage)

The resin was placed in a glass peptide vessel, swollen in DCM (5 mL/g), and treated with 50% TFA (5 mL/g) and MeOH (1 mL/g) for 30 min with occasional stirring. The resin was filtered, washed with DCM/MeOH 3:1 (6 x 3 mL), and the cleavage was repeated a second time using the same conditions. The washings were evaporated *in vacuo* (without heating). The residue was taken up in CH_3CN/H_2O 2:8 (c = 10 mg/mL) and purified by semi-preparative HPLC.

5.1.3.3 HPLC analysis

Reverse phase analytical HPLC

HPLC analysis was carried out using a HP1100 Hewlett Packard HPLC system equipped with a C18 column (Prodigy 5µ ODS3 100Å, size 150 x 3 mm) using H_2O/0.1% TFA (solvent A) and CH_3CN/0.04%TFA (solvent B). Flow rate 0.5 mL/min. λ = 220, 254 nm. V_{inj} = 25 µL. All HPLC samples were prepared in H_2O/CH_3CN 8:2.

Gradient 1			**Gradient 2**			**Gradient 3**			**Gradient 4**		
t (min)	A (%)	B (%)	t (min)	A (%)	B (%)	t (min)	A (%)	B (%)	t (min)	A (%)	B (%)
0	100	0	0	100	0	0	100	0	0	100	0
20	0	100	5	75	25	5	75	25	4	80	20
25	0	100	35	70	30	35	75	25	35	80	20
30	100	0	40	0	100	40	0	100	40	0	100
			45	0	100	45	0	100	45	0	100
			50	100	0	50	100	0	50	100	0

Reverse phase semi preparative HPLC.

Purification was carried out using a HP1100 Hewlett Packard HPLC system equipped with a C18 column (Phenomenex ODG-4097-NO, Prodigy 5µ ODS3 100A, size 250 x 10 mm) using H_2O/0.1% TFA and CH_3CN/0.04% TFA as solvents. Flow rate 2.5 mL/min. Detection λ = 220 nm.

Quantification by HPLC-UV analysis using a calibration curve

A calibration curve for 1,4-benzenedimethanol was obtained by injection of standard solutions (c = 8 mM, 5 mM, 2 mM, 1 mM, 0.5 mM).

C (mmol/L) = 1 10^{-3} x Area. (λ = 254 nm, V_{inj} = 50 µL)

A calibration curve for benzoic acid was obtained by injection of standard solutions (c = 8 mM, 5 mM, 2 mM, 1 mM, 0.5 mM)

C (mmol/L) =0.58 10^{-3} x Area (λ = 282 nm, V_{inj} = 25 µL)

5.1.3.4 Gel phase NMR

Prior to preparation of the NMR samples, the resins were dried *in vacuo* for 24 h for TentaGel resins or until constant weight for polystyrene resins and introduced dry (100-200 mg) in a silylated 5 mm o.d. NMR tube. d^6-Benzene (1-2 mL) was added. Homogeneous slurries were obtained by swirling the tubes with a vortex shaker or by carefully stirring the resin with a fine capillary to remove the air bubbles and allowing the resin to swell and equilibrate with the solvent for 30 min. The NMR spectra were acquired at 75 MHz with 28000 scans or at 100 MHz with 9812 scans. Spectra were referenced to the center d^6-benzene peak at 128.2 ppm or to the PEG peak at 71.2 ppm. Data were processed applying GB = 0 and LB = 5 Hz to the FID prior to Fourier transformation.

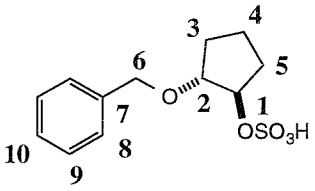
5.1.4 Experimental style

Compounds were named using standard IUPAC nomenclature. The compounds are illustrated in full structural form with progressive numbering of each carbon atom. It should be pointed out that the numbering system is arbitrary and was done primarily for ease and clarity of NMR data assignment and does not necessarily follow the nomenclature given. In cases where more than one known group is present in a resonance, the signals are characterised by quoting the appropriate signals separated by a comma, e.g. 2.74 (m, 6H, H-3,4,5). In cases where there is ambiguity in assigning two or more very similar resonances, which have not been satisfactorily determined by 1D or 2D NMR or cannot be distinguished by comparison with theorical data obtained using a NMR prediction software, the signals are characterised by quoting the appropriate signals separated by a slash, e.g. 30.2 (CH_2-8/3).

5.2 Experimental chapter 2

5.2.1 Solution phase model

(1*R*, 2*R*) and (1*S*, 2*S*) 2-(Phenylmethoxy)cyclopentyl hydroxysulfonate (2)



NaH (0.180 g, 60% in oil, 4.5 mmol) was washed under N_2 with dry hexane (2 mL) then suspended in dry DMF (10 mL). 15-Crown-5 (60 μL, 0.3 mmol) and anhydrous benzyl alcohol (300 μL, 3 mmol) were added and the mixture was stirred for 15 min. Cyclic sulfate **33a** (0.492 g, 3 mmol) in dry DMF (5 mL) was added and the reaction mixture was stirred at room temperature for 1 h. Excess NaH was quenched by the addition of MeOH and the solvents were removed *in vacuo*. The residue was purified by chromatography on silica gel (DCM/MeOH 9:1 to 8.5:1.5) to afford **2** as a white waxy solid (0.587 g, 71% yield).

TLC: R_f = 0.30 (DCM/MeOH 8.5:1.5).

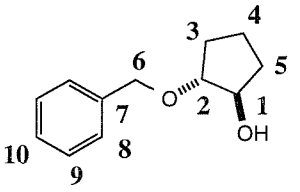
δ_H (300 MHz, CD_3OD): 7.37 (m, 5H, ArH), 4.85 (ddd, 1H, J = 2.9, 2.9, 5.8 Hz, H-1), 4.68 (d, 1H, J_{AB} = 12.1 Hz, H_A-6), 4.58 (d, 1H, J_{AB} = 12.1 Hz, H_B-6), 4.14 (ddd, 1H, J = 2.9, 2.9, 5.8 Hz, H-2), 2.20-1.60 (m, 6H, H-3,4,5).

δ_C (75 MHz, CD_3OD): 139.8 (ArC-7), 129.2 (ArCH-9), 128.8 (ArCH-8), 128.4 (ArCH-10), 85.5 (CH-1), 84.7 (CH-2), 72.0 (CH_2-6), 31.7 (CH_2-3), 31.0 (CH_2-5), 22.4 (CH_2-4).

IR: υ_{max} 3397 (OH), 1253 (OSO_3H), 1204 (OSO_3H) cm^{-1}.

MS (ES -ve): *m/z* (%) 271 ($[M-H]^-$, 100).

(1*R*, 2*R*) and (1*S*, 2*S*) 2-(Phenylmethoxy)cyclopentan-1-ol (3)[174,223]



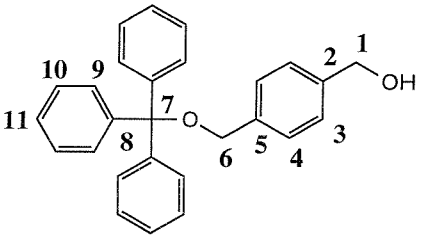
To a solution of **2** (50 mg, 0.18 mmol) in dioxane (2 mL) was added 0.01M H_2SO_4 in 1% H_2O/dioxane (1.8 mL, 0.018 mmol). The reaction mixture was stirred at room temperature for 1 h then concentrated *in vacuo*. The residue was dissolved in EtOAc (10 mL) and washed with brine (3 mL). The organic phase was dried over $MgSO_4$ and evaporated *in vacuo* to give **3** as a colourless oil (20 mg, 60% yield). Experimental data were in agreement with reported literature data.[174,223]

TLC: R_f = 0.60 (DCM/MeOH 9:1).

δ_H (300 MHz, $CDCl_3$): 7.36 (m, 5H, ArH), 4.58 (s, 2H, H-6), 4.16 (ddd, 1H, *J* = 2.9, 2.9, 5.8 Hz, H-1), 3.81 (ddd, 1H, *J* = 2.9, 2.9, 5.8 Hz, H-2), 2.20-1.50 (m, 6H, H-3,4,5).

δ_C (75 MHz, $CDCl_3$): 139.9 (ArC-7), 129.2 (ArCH-9), 128.7 (ArCH-8), 128.4 (ArCH-10), 87.6 (CH-2), 77.8 (CH-1), 65.1 (CH_2-6) 33.1 (CH_2-5), 30.5 (CH_2-3), 21.8 (CH_2-4).

{4-[(Triphenylmethoxy)methyl]phenyl]}methan-1-ol (5)



To a solution of 1,4-benzenedimethanol **4** (1.20 g, 8.6 mmol) and DBU (0.75 mL, 5.1 mmol) in dry THF (20 mL) was added dropwise a solution of trityl chloride (1.21 g, 4.3 mmol) in dry DCM (20 mL). The reaction mixture was stirred at room temperature for 24 h then evaporated *in vacuo*. The residue was purified by chromatography on silica gel (PE/EtOAc 7:3 + 0.1% Et_3N) to afford **5** as a colorless oil (1.06 g, 65% yield).

TLC: R_f = 0.41 (PE/EtOAc 7:3).

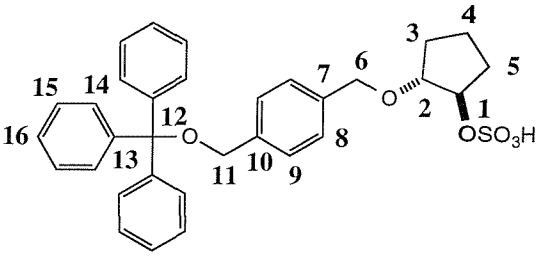
δ_H (300 MHz, CD_3CN 9:1): 7.55-7.20 (m, 19H, ArH), 4.63 (s, 2H, H-1), 4.15 (s, 2H, H-6).

δ_C (75 MHz, CD_3CN): 145.4 (ArC), 141.5 (ArC), 139.2 (ArC), 129.7 (ArCH), 128.7 (ArCH), 128.0 (ArCH), 127.9 (ArCH), 88.2 (C-7), 66.7 (CH_2-6), 64.9 (CH_2-1).

IR: υ_{max} 3311 (OH) cm^{-1}.

MS (FAB, NBA): *m/z* (%) 243 (trityl group, $[M'+H]^+$, 100), 403 ($[M+Na]^+$, 10).

(1*R*, 2*R*) and (1*S*, 2*S*) 2-({4-[(Triphenylmethoxy) methyl]phenyl} phenyl} methoxy) cyclopentyl hydroxysulfonate (6)



NaH (16 mg, 0.39 mmol) was washed under N_2 with dry hexane (2 mL) then suspended in dry DMF (2 mL). A solution of **5** (0.123 g, 0.3 mmol) in dry DMF (2 mL) was added and the reaction mixture was stirred for 15 min. A solution of cyclic sulfate **33a** (51 mg, 0.3 mmol) in dry DMF (2 mL) was added dropwise and the mixture stirred at room temperature for 6 h. Excess NaH was quenched by the addition of MeOH and the solvents were removed *in vacuo*. Purification of the residue by chromatography on silica gel (DCM/MeOH 8.5:1.5 + 0.01% Et_3N) gave **6** as a waxy solid (0.129 g, 79% yield).

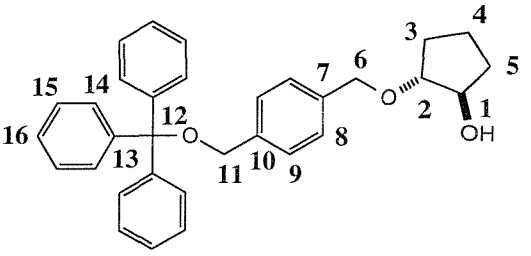
TLC: R_f = 0.38 (DCM/MeOH 8.5:1.5)

δ_H (300 MHz, CD_3CN/CD_3OD): 7.55-7.20 (m, 19H, ArH), 4.71 (ddd, 1H, J = 3.1, 3.1, 6.2 Hz, H-1), 4.58 (d, 1H, J_{AB} = 11.8 Hz, H_A-6), 4.50 (d, 1H, J_{AB} = 11.8 Hz, H_B-6), 4.09 (s, 2H, H-11), 4.03 (ddd, 1H, J = 3.1, 3.1, 6.2 Hz, H-2), 2.10-1.50 (m, 6H, H-3,4,5).

δ_C (75 MHz, CD_3CN/CD_3OD): 144.6 (ArC-13), 139.3 (ArC), 139.0 (ArC), 128.9 (ArCH), 128.4 (ArCH), 128.3 (ArCH), 127.6 (ArCH), 127.5 (ArCH), 87.9 (C-12), 84.6 (CH-1), 83.3 (CH-2), 70.8 (CH_2-6), 65.8 (CH_2-11), 31.0 (CH_2-3), 30.2 (CH_2-5), 21.6 (CH_2-4).

MS (ES -ve): *m/z* (%) 543 ($[M-H]^-$, 100).

(1*R*, 2*R*) and (1*S*, 2*S*) 2-({4-[(Triphenylmethoxy) methyl] phenyl} methoxy) cyclopentan-1-ol (7)



To a solution of **6** (0.118 g, 0.21 mmol) in dioxane (10 mL) was added H_2O (20 μL) and 10% H_2SO_4 in dioxane (20 μL, 0.04 mmol). The resultant mixture was stirred for 1.5 h, diluted with EtOAc (15 mL), washed with brine (10 mL), dried over $MgSO_4$ and evaporated *in vacuo* to give **7** as a colourless oil (96 mg, 98% yield).

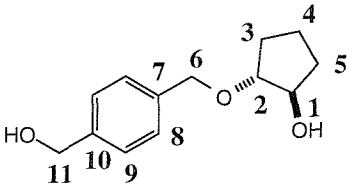
TLC: R_f = 0.90 (DCM/MeOH 8.5:1.5).

δ_H (300 MHz, CD_3CN): 7.55-7.20 (m, 19H, ArH), 4.52 (s, 2H, H-6), 4.13 (s, 2H, H-11), 4.07 (ddd, 1H, *J* = 3.1, 3.1, 6.2 Hz, H-2), 3.71 (ddd, 1H, *J* = 3.1, 3.1, 6.2 Hz, H-1), 2.00-1.45 (m, 6H, H-3,4,5).

δ_C (75 MHz, CD_3CN): 145.2 (ArC), 139.4 (ArC), 139.0 (ArC), 129.5 (ArCH), 129.0 (ArCH), 128.7 (ArCH), 128.2 (ArCH), 128.1 (ArCH), 87.9 (C-12), 87.4 (CH-2), 77.4 (CH-1), 71.3 (CH_2-6), 66.4 (CH_2-11), 33.2 (CH_2-5), 30.4 (CH_2-3), 21.7 (CH_2-4).

MS (ES +ve): *m/z* (%) 243 ($[M']^+$, trityl, 100), 482 ($[M+NH_4]^+$, 50), 487 ($[M+Na]^+$, 5), 946 ($[2M+NH_4]^+$, 15), 951 ($[2M+Na]^+$, 5).

(1*R*, 2*R*) and (1*S*, 2*S*) 2-{[4-(Hydroxymethyl) phenyl] methoxy} cyclopentan-1-ol (9a)



To a solution of **7** (96 mg, 0.2 mmol) in MeOH (3 mL) was added 15% TFA in MeOH (800 μL). The mixture was stirred for 1 h. Following removal of the solvent *in vacuo*, purification of the residue by chromatography on silica gel (PE/EtOAc 1:1) afforded **9a** as a colourless oil (40 mg, 87% yield).

TLC: R_f = 0.36 (PE/EtOAc 1:1).

δ_H (400 MHz, $CDCl_3$): 7.32 (s, 4H, ArH), 4.64 (s, 2H, H-11), 4.56 (d, 1H, J_{AB}= 12.0 Hz, H_A-6), 4.50 (d, 1H, J_{AB} = 12.0 Hz, H_B-6), 4.15 (ddd, 1H, J = 4.0, 5.2, 6.5 Hz, H-1), 3.75 (ddd, 1H, J = 4.0, 5.2, 6.5 Hz, H-2), 2.0-1.4 (m, 6H, H-3,4,5).

δ_C (100 MHz, $CDCl_3$): 140.5 (ArC-10), 138.1 (ArC-7), 128.0 (ArCH-8), 127.2 (ArCH-9), 86.7 (CH-2), 77.5 (CH-1), 71.2 (CH_2-6), 65.1 (CH_2-11), 32.2 (CH_2-5), 29.5 (CH_2-3), 20.6 (CH_2-4).

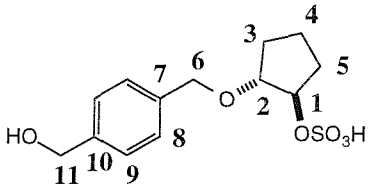
IR: υ_{max} 3320 (OH) cm^{-1}.

MS (ES +ve): *m/z* (%) 240.2 ($[M+NH_4]^+$, 100), 462.4 ($[2M+NH_4]^+$, 50).

RP-HPLC (λ_{220}, gradient 1): t_R = 9.9 min.

HRMS (EI): 222.1257 ($[M^{\cdot+}]$, $C_{13}H_{18}O_3$ requires 222.1255).

(1*R*, 2*R*) and (1*S*, 2*S*) 2-{[4-(Hydroxymethyl)phenyl]methoxy} cyclopentyl hydroxysulfonate (8a)



NaH (5 mg, 0.18 mmol) was washed under N_2 with dry hexane (2 mL) and suspended in dry DMF (2 mL). A solution of 1,4-benzenedimethanol **4** (0.100 g, 0.72 mmol) in dry DMF (3 mL) was added and the mixture was stirred for 10 min. A solution of cyclic sulfate **33a** (60 mg, 0.36 mmol) in dry DMF (3 mL) was added dropwise and the reaction mixture was stirred at room temperature for 1.5 h. The solvent was removed *in vacuo*. Purification of the residue by chromatography on silica gel (DCM/MeOH 8.5:1.5) afforded **8a** as a white solid (40 mg, 37% yield).

TLC: R_f = 0.32 (DCM/MeOH 8.5:1.5).

mp: 140 °C (*dec.*).

δ_H (400 MHz, CD_3OD): 7.52 (d, 2H, J = 8.5 Hz, ArH), 7.50 (d, 2H, J = 8.5 Hz, ArH), 4.84 (ddd, 1H, J = 3.1, 3.1, 6.2 Hz, H-1), 4.84 (d, 1H, J_{AB} = 11.8 Hz, H_A-6), 4.77 (s, 2H, H-11), 4.73 (d, J_{AB} = 11.8 Hz, H_B-6), 4.29 (ddd, 1H, J = 3.1, 3.1, 6.2 Hz, H-2), 2.3-1.8 (m, 6H, H-3,4,5).

δ_C (100 MHz, CD_3OD): 142.3 (ArC-10), 139.4 (ArC-7), 129.3 (ArCH-8), 128.3 (ArCH-9), 86.0 (CH-1), 84.9 (CH-2), 72.3 (CH_2-6), 65.4 (CH_2-11), 32.3 (CH_2-5), 31.6 (CH_2-3), 22.9 (CH_2-4).

IR: υ_{max} 3270 (OH), 1252 (OSO_3H), 1204 (OSO_3H) cm^{-1}.

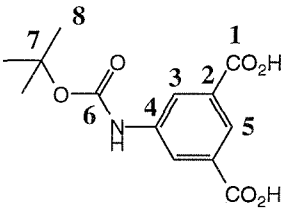
MS (ES-ve): 301.2 (100%, $[M-H]^-$). Not detected under the conditions used for HRMS.

RP-HPLC (λ_{220}, gradient 1): t_R = 8.9 min.

5.2.2 Solid phase model

5.2.2.1 monomer synthesis

5-[(*tert*-Butoxy)carbonyl)amino]benzene-1,3-dicarboxylic acid (26)



To an ice cold solution of 5-aminoisophthalic acid **25** (1.00 g, 5.5 mmol) in a mixture of dioxane (10 mL), water (10 mL) and 1M NaOH (11 mL, 11 mmol) was added dropwise a solution of di-*tert*-butyl pyrocarbonate (1.32 g, 6 mmol) in dioxane (10 mL). The reaction mixture was stirred for 4 h. A further 0.1 eq of di-*tert*-butyl pyrocarbonate (0.120 g, 0.55 mmol) in dioxane (2 mL) was added and the reaction mixture left stirring overnight. The solution was concentrated *in vacuo*. The residual solution was diluted with water (10 mL) and washed with EtOAc (3 x 20 mL). The aqueous phase was acidified to pH 3 with 2M $KHSO_4$. The precipitated compound was collected by filtration, washed with water and dried in a dessicator *in vacuo* to afford **26** as a white solid (0.30 g, 78% yield).

TLC: R_f = 0.25 (DCM/MeOH 9:1).

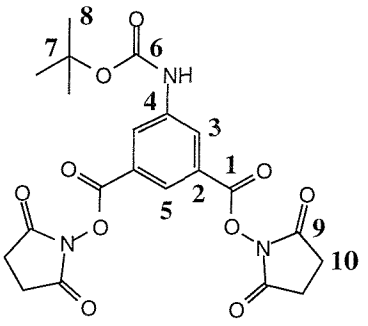
δ_H (300 MHz, d^6-DMSO): 8.31 (d, 2H, J =1.1 Hz, ArH-3), 8.08 (t, 1H, J = 1.1 Hz, ArH-5), 1.48 (s, 9H, H-8).

δ_C (75 MHz, d^6-DMSO): 166.4 (C-1), 152.6 (C-6), 140.2 (ArC-4), 131.5 (ArC-2), 123.4 (ArCH-5), 122.4 (ArCH-3), 79.6 (C-7), 27.9 (CH_3-8).

IR (KBr disk): υ_{max} 3342 (NH), 3000-2500 (OH), 1710 (CO_2H), 1680 (CONH) cm^{-1}.

MS (ES, +ve): *m/z* (%) 580.3 ($[2M+NH_4]^+$, 10), 585.3 ($[2M+Na]^+$, 5).

2,5-Dioxopyrrolidinyl 3-[(*tert*-butoxy)carbonyl)amino] -5- [(2,5-dioxopyrrolidinyl) oxycarbonyl] benzoate (27)



To a solution of **26** (0.50 g, 1.78 mmol) in dry DMF (5 mL) and dry THF (5 mL) was added *N*-hydroxysuccinimide (41 mg, 3.56 mmol). The mixture was cooled to 0 °C and DCC (0.733 g, 3.56 mmol) was added. The reaction mixture was left stirring at room temperature for 5 h. DCU was removed by repetitive cooling and filtration of the solution. The filtrate was washed with saturated $NaHCO_3$ (3 x 15 mL), brine (20 mL), dried over $MgSO_4$ and evaporated *in vacuo*. Recrystallisation of the crude product from EtOH/EtOAc 1:1 afforded **27** as a white solid (0.547 g, 65% yield).

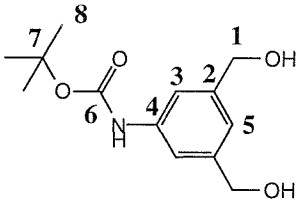
TLC: R_f= 0.80 (DCM/MeOH 9:1).

δ_H (300 MHz, CD_3CN): 8.56 (d, 2H, J = 1.1 Hz, ArCH-3), 8.32 (t, 1H, J = 1.1 Hz, ArCH-5), 2.85 (s, 8H, H-10), 1.50 (s, 9H, H-8).

δ_C (75 MHz, CD_3CN): 171.0 (C-1), 162.0 (C-9), 153.9 (C-6), 142.7 (AIC-4), 127.8 (ArC-2), 125.7 (ArCH-3/5), 125.6 (ArCH-3/5), 81.9 (C-7), 28.5 (CH_3-8), 26.5 (CH_2-10).

MS (ES +ve): *m/z* (%) 493.2 ($[M+NH_4]^+$, 35), 968.0 ($[2M+NH_4]^+$, 100).

***N*-[3,5-*bis*(Hydroxymethyl)phenyl](*tert*-butoxy)carboxamide (28)**



To a solution of *N*-hydroxysuccinimide ester **27** (0.100 g, 0.21 mmol) in dry THF (5 mL) at 0 °C was added dropwise DIBAL (1M in toluene, 0.9 ml, 0.9 mmol). The resultant mixture was stirred at 0 °C for 2 h. A further 2 eq of DIBAL (0.4 mL) then 1 eq (0.2 mL) were added. The reaction mixture was quenched with MeOH (2 mL) and allowed to warm to room temperature. 30% KNa-tartrate (4 mL) was added. The mixture was stirred for 15 min then extracted with EtOAc (3 x 15 mL). The combined organics were washed with saturated $NaHCO_3$ (15 mL), brine (10 mL), dried over

$MgSO_4$ and evaporated *in vacuo*. The crude product was recrystallised from MeOH to afford of **28** as a white solid (0.044 g, 83% yield).

TLC: R_f= 0.48 (DCM/MeOH 9:1).

δ_H (300 MHz, CD_3OD): 7.35 (s, 2H, ArH-3), 7.04 (s, 1H, ArH-5), 4.6 (s, 4H, H-1), 1.55 (s, 9H, H-8).

δ_C (75 MHz, CD_3OD): 155.2 (C-6), 143.4 (ArC-2), 140.6 (ArC-4), 120.6 (ArCH-5), 117.1 (ArCH-3), 80.7 (C-7), 65.1 (CH_2-1), 28.6 (CH_3-8).

IR (KBr disk): 3100 (OH), 1684 (C=O) cm^{-1}.

MS (ES +ve): 271.3 ($[M+NH_4]^+$, 100), 524.5 ($[2M+NH_4]^+$, 35).

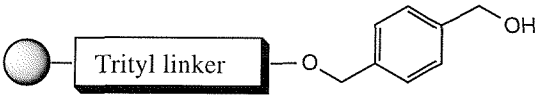
RP-HPLC (λ_{220}, gradient 1): t_R = 8 min.

5.2.2.2 Optimisation of the loading and cleavage conditions on trityl resins

General procedure for the chlorination of trityl alcohol resins

Trityl alcohol resins (Novasyn TGT Alcohol resin **12**, NovaSyn dichlorotrityl alcohol TG resin **13**) were placed in a peptide vessel, washed under N_2 with dry DCM (3 x 10 mL/g), dry toluene (3 x 10 mL/g), then suspended in dry toluene (5 mL/g) and the slurry transferred to an oven-dried silylated round bottom flask. Acetyl chloride (1 mL/g) was added and the mixture was heated at 60 °C under N_2 with gentle stirring for 3 h. The slurry was transferred into an oven-dried peptide vessel, washed under N_2 with dry toluene (3 x 10 mL/g) and dry DCM (3 x 10 mL/g). The freshly chlorinated resins **12** and **13** were used immediately.

General procedure for the coupling of 1,4-benzenedimethanol on trityl based resins



Chlorinated trityl resin (**10**, **11**, **12**, **13**) was washed under N_2 with dry DCM (3 x 10 mL/g) then suspended in dry DCM (5 mL/g). A solution of 1,4-benzenedimethanol (10 eq) and dry pyridine (20 eq) in a minimum of dry THF was added. The resin was shaken for 48 h, then washed with DCM (3 x 10 mL/g), MeOH (3 x 10 mL/g), DMF (3 x 10 mL/g), DCM (3 x 10 mL/g), MeOH (3 x 10 mL/g) and dried *in vacuo* for 48 h in a dessicator over KOH. The loading of 1,4-benzenedimethanol **4** was determined by small scale cleavages (method 1) and HPLC-UV analysis using a calibration curve.

Resin (14)

Coupling of 1,4-benzenedimethanol **4** onto resin **10** (0.5 g) using the general procedure described above gave resin **14** with a loading of 0.2 mmol/g (30% yield). [1 step from Novabiochem 2-chlorotrityl chloride resin, 200-400 mesh, 2% DVB, 0.67 mmol/g].

Resin (15)

Coupling of 1,4-benzenedimethanol onto resin **11** (1 g) using the general procedure described above gave resin **15** with a loading of 0.5 mmol/g (38% yield). [1 step from Novabiochem 2-chlorotrityl chloride resin, 200-400 mesh, 1% DVB, 1.3 mmol/g].

IR: υ_{max} 3500 (sharp, free OH), 3400 (OH) cm^{-1}.

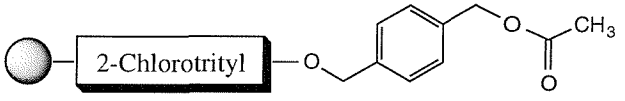
Resin (16)

Coupling of 1,4-benzenedimethanol onto resin **12** (0.5 g) using the general procedure described above gave resin **15** with a loading of 0.07 mmol/g (31% yield). [2 steps from NovaSyn® TGT alcohol resin, 90 μm beads, 0.22 mmol/g].

Resin (17)

Coupling of 1,4-benzenedimethanol onto resin **13** (4 g) using the general procedure described above gave resin **17** with a loading of 0.17 mmol/g (85% yield). [2 steps from NovaSyn® dichlorotrityl TG alcohol resin, 130 μm beads, 0.17 mmol/g].

General procedure for the determination of the percentage of cross-linking



Resin (**10**, **11** or **12**) (50 mg) was suspended in dry DMF (1.5 mL). DMAP (1 eq), dry Et_3N (10 eq), acetic anhydride (10 eq) were added consecutively and the resin was shaken at room temperature overnight. The resin was filtered, washed with DMF (3 x 3 mL), DCM (3 x 3 mL), MeOH (3 x 3 mL), dried *in vacuo* overnight and the acetylation was repeated a second time. The percentage unreacted 1,4-benzenedimethanol **4** was determined by cleavage of resin (**18, 19** or **20**) (procedure 1) and calibrated HPLC-UV analysis by comparison with the loading of **4** the starting resin.

Resin (18): 20% of unreacted diol **4** was recovered after acylation of resin **11.**
Resin (19): 20% of unreacted diol **4** was recovered after acylation of resin **12.**
Resin (20): 15% of unreacted diol **4** was recovered after acylation of resin **13.**

5.2.2.3 Optimisation of the O-alkylation

a. Study of the influence of the loading on the *O*-alkylation reaction. Resin (29)

2-Chlorotrityl chloride resin **11** (200 mg, 0.24 mmol, 1.2 mmol/g) was suspended in dry DCM (0.5 mL). Pyridine (200 µL, 2.4 mmol) was added followed by mixture of 1,4-benzenedimethanol **4** (0.5 M in DCM/DMF 9:1) and anhydrous benzyl alcohol **1** (1 M in DCM) (see table below). The resin was shaken at room temperature for 48 h, then filtered, washed with DMF (3 x 5 mL), DCM (3 x 5 mL), MeOH (3 x 5 mL) and dried *in vacuo* over KOH for 12 h. The loading was determined by small scale cleavage (procedure 1) and calibrated HPLC-UV analysis (see table below).

Resin (30)

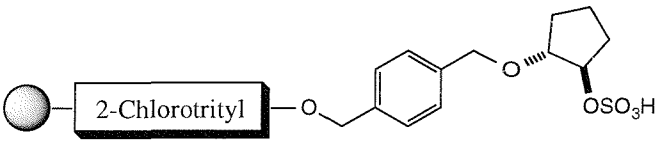
Resin **29** (0.150 g) was washed with dry THF (3 x 2 mL), dry DMF (1 mL) then suspended in dry DMF (1 mL). 15-Crown-5 (37 µL, 0.18 mmol) and NaH (36 mg, 0.92 mmol) were added and the resin was shaken at room temperature for 2 h. Cyclic sulfate **33b** (0.153 g, 0.92 mmol) in dry DMF (1 mL) was added and the resin shaken at room temperature for 1 h. The resin was filtered, washed with DMF (3 x 2 mL), MeOH (3 x 2 mL), DCM (3 x 2 mL) and MeOH (3 x 2 mL), then dried *in vacuo* for 1 h. Percentage conversion to the ether product **8b** was determined by small scale cleavage (procedure 1) and HPLC-UV analysis (λ_{220}) (see table below).

Entry	**4** (eq)	**1** (eq)	**4** (0.5M) V (µL)	**1** (1M) V (µL)	**Loading of diol 4** (mmol/g)	**% conversion to 9b**
1	5	0	2400	0	0.82	46
2	3	2	1500	490	0.63	48
3	1.6	3.4	780	840	0.40	50
4	0.7	4.3	460	1060	0.29	49
5	0.3	4.7	160	1150	0.13	47
6	0.1	4.9	60	1200	0.07	47

b. General procedure for *O*-alkylation using cyclic sulfate chemistry

Dry resin bound diol (**14**, **15**, **16** or **17**) was placed in an oven-dried peptide vessel and washed under N_2 with dry THF (3 x 5 mL/g) and dry DMF (1 x 5 mL/g). The resin was suspended in dry DMF (5 mL/g) then 15-crown-5 (1 eq) and NaH (5 eq) were added under N_2. The resin was shaken at room temperature for 2 h. Cyclic sulfate **33a** (5 eq) in a minimum amount of DMF was added and the resin was shaken at room temperature overnight. The resin was filtered, washed with DMF (3 x 10 mL/g), MeOH (3 x 10 mL/g), DCM (3 x 10 mL/g), MeOH (3 x 10 mL/g), DCM (3 x 10 mL/g), MeOH (3 x 10 mL/g) and dried overnight *in vacuo* in a dessicator over KOH.

Resin (22)

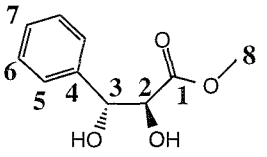


IR: υ_{max} 3418 (OH), 1260-1217 (OSO_3H) cm^{-1}.

5.2.3 Scope of the reaction

5.2.3.1 Synthesis of the diols

Methyl (2*S*, 3*R*)-2,3-dihydroxy-3-phenylpropanoate (31d)[189]



t-BuOH (80 mL), H_2O (80 mL), and AD-mix-β (22 g) were stirred until two clear phases were obtained. $MeSO_2NH_2$ (1.52 g, 16 mmol) was added and the reaction mixture was cooled to 0 °C. Methyl cinnamate (2.60 g, 16 mmol) was added in one portion and the heterogeneous slurry stirred at 0 °C for 12 h then at room temperature for 12 h. The mixture was cooled to 0 °C and Na_2SO_3 (24 g, 190 mmol) was added. The mixture was allowed to warm to room temperature and stirred for 1 h. The reaction mixture was concentrated *in vacuo*, then extracted with EtOAc (4 x 80 mL). The combined organics were washed with water (50 mL), brine (3 x 30 mL), dried over $MgSO_4$ and evaporated *in vacuo*. The crude product was purified by chromatography on silica gel (PE/EtOAc 6:4) to afford **31d** as a white solid (2 g, 64% yield). Experimental data were in agreement with reported literature data.[189]

TLC: R_f = 0.43 (PE/EtOAc 1:1).

mp= 79-80 °C (EtOAc/Hexane) [lit.[189] 80-81 °C (EtOAc/hexane)].

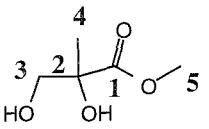
δ_H (300 MHz, $CDCl_3$): 7.45-7.29 (m, 5H, ArH), 5.02 (d, 1H, *J* = 2.9 Hz, H-3), 4.37 (d, 1H, *J* = 2.9 Hz, H-2), 3.81 (s, 3H, H-8).

δ_C (75 MHz, $CDCl_3$): 173.3 (C-1), 140.0 (ArC-4), 128.6 (ArCH-6), 128.2 (ArCH-7), 126.3 (ArCH-5), 74.8 (CH-2), 74.5 (CH-3), 53.0 (CH_3-8).

IR: υ_{max} 3483 (free OH), 3373 (br, OH), 1711 (C=O) cm^{-1}.

MS (CI, NH_3): *m/z* (%) 196 ($[M]^+$, 20), 214 ($[M+NH_4]^+$, 100).

Methyl 2,3-dihydroxy-2-methyl propanoate (31e)[191,224]



Methyl methacrylate (1 mL, 10 mmol) was added dropwise at 0 °C to a solution of NMO (1.28 g, 11 mmol) and OsO_4 (7 mg, 0.003 mmol) in acetone (2.5 mL), *t*-BuOH (1 mL) and water (6 mL). The mixture was stirred at room temperature for 24 h. Na_2SO_3 (1.89 g, 15 mmol) and hydrated magnesium silicate (1 spatula) were added. The mixture was stirred for 15 min and filtered through celite. The filtrate was acidified to pH 7 with 10% aqueous H_2SO_4. The organic solvents were removed *in vacuo*. The residual solution was acidified to pH 2 with 10% H_2SO_4, saturated with NaCl and extracted with EtOAc (9 x 25 mL). The combined organics were dried over $MgSO_4$ and evaporated *in vacuo*. Purification by chromatography on silica gel (PE/EtOAc 3:7) gave **31e** as a colourless oil (0.92 g, 68% yield). Experimental data were in agreement with reported literature data.[191,224]

TLC: R_f = 0.32 (PE/EtOAc 3:7).

δ_H (300 MHz, $CDCl_3$): 3.76 (s, 3H, H-5), 3.76 (d, 1H, J_{AB} = 11.4 Hz, H_A-3), 3.62 (s, OH), 3.53 (d, 1H, J_{AB} = 11.4 Hz, H_B-3), 1.31 (s, 3H, H-4).

δ_C (75 MHz, $CDCl_3$): 176.1 (C-1), 75.9 (C-2), 68.5 (CH_2-3), 53.0 (CH_3-5). 21.8 (CH_3-4).

IR: υ_{max} 3426 (br, OH), 1730 (C=O) cm^{-1}.

MS (CI, NH_3): *m/z* (%) 135 ($[M+H]^+$, 5), 152 ($[M+NH_4]^+$, 100).

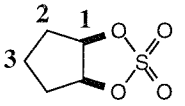
5.2.3.2 Synthesis of the cyclic sulfates

General procedure for the synthesis of cyclic sulfate 33a-i[142a]

Thionyl chloride (1.2 eq) was added dropwise to a solution of the diol (10 mmol) in dry DCM (1 mL/mmol) and the mixture was refluxed for 30 min. The reaction mixture was either evaporated *in vacuo* and the intermediate cyclic sulphite **32** purified by chromatography on silica gel or oxidation of the sulphite carried out in one pot.

To an ice cold solution of cyclic sulphite **32** in DCM (1 mL/mmol) and CH_3CN (1 mL/mmol) were added $RuCl_3.3H_2O$ (1 mg/mmol) and $NaIO_4$ (1.5 eq) followed by water (1.5 mL/mmol). The mixture was stirred vigorously for 1 h at 0 °C then extracted with ether (4 x 30 mL). The organics were washed with water (30 mL), saturated $NaHCO_3$ (3 x 30 mL) and brine (2 x 30 mL), dried over $MgSO_4$ and evaporated *in vacuo* to afford pure cyclic sulfate **33**.

(5S,1R)-2,4-Dioxa-3-thiabicyclo[3.3.0]octane-3,3-dione (33a)[225]



20 mmol scale reaction (one pot) from *cis*-1,2-cyclopentanediol **31a** gave **33a** as a colourless solid (2.69 g, 81% yield). Experimental data were in agreement with reported literature data.[225]

TLC: R_f = 0.30 (Hexane/EtOAc 7:3).
mp = 24-25 °C (ether) [lit.[225] 22-23 °C (ether)].

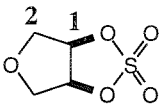
δ_H (300 MHz, $CDCl_3$): 5.30 (dd, 2H, *J* = 1.4, 3.6 Hz, H-1), 2.29-1.75 (m, 6H, H-2,3).

δ_C (75 MHz, $CDCl_3$): 85.9 (CH-1), 32.6 (CH_2-2) 22.3 (CH_2-3).

IR: υ_{max} 1198 (SO_2) cm^{-1}.

MS (CI, NH_3): *m/z* (%) 182 ($[M+NH_4]^+$, 100), 346 ($[2M+NH_4]^+$, 70).

(3αS,6αR) 4H,6H,3αH,6αH-Oxolano[3,4-δ]1,3,2-dioxathiolane-2,2-dione (33b)



19 mmol scale reaction (one pot) gave **33b** as a white crystalline solid (2.3 g, 73% yield).

TLC: R_f = 0.13 (PE/EtOAc 7:3).
mp = 61-68 °C (ether).

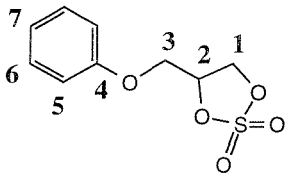
δ_H (300 MHz, $CDCl_3$): 5.42 (dd, 2H, *J* = 2.5, 1.1 Hz, H-1), 4.32 (dd, 2H, *J* = 12.8, 1.1 Hz, H-2), 3.72 (ddd, 2H, *J* = 12.8, 1.1, 2.2 Hz, H'-2).

δ_C (75 MHz, $CDCl_3$): 83 5 (CH-1), 72.2 (CH_2-2).

IR: υ_{max} 1198 (SO_2) cm^{-1}.

MS (CI, NH_3): *m/z* (%) 184 ($[M+NH_4]^+$, 100), 350 ($[2M+NH_4]^+$, 30).
HRMS (CI, NH_3): *m/z* 184.0294 ($[M+NH_4]^+$, $C_4H_{10}NO_5S$ requires 184.0279).

4-(Phenoxymethyl)-1,3,2-dioxathiolane-2,2-dione (33c)



12 mmol scale reaction (two steps) gave **33c** as a white solid (2.37 g, 84% yield).

TLC: R_f = 0.54 (hexane/EtOAc 7:3).

mp = 33-34 °C (ether).

δ_H (300 MHz, $CDCl_3$): 7.34 (2H, dd, *J* = 7.3, 8.8 Hz, ArH-6), 7.06 (1H, tt, *J* = 1.1, 7.3 Hz, ArH-7), 6.94 (dd, 2H, *J* = 1.1, 8.8 Hz, ArH-5), 5.26 (dddd, 1H, *J* = 6.6, 6.6, 5.1, 5.1 Hz, H-2), 4.85 (1H, dd, *J* = 6.6, 8.8 Hz, H-1), 4.74 (1H, dd, *J* = 6.6, 8.8 Hz, H'-1), 4.31 (1H, dd, *J* = 10.6, 5.1 Hz, H-3), 4.27 (dd, 1H, *J* = 10.6, 5.1 Hz, H'-3).

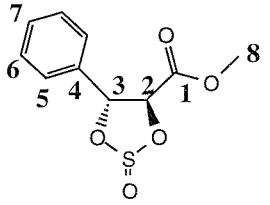
δ_C (75 MHz, $CDCl_3$): 157.6 (C-4), 129.9 (ArCH-6), 122.4 (ArCH-7), 114.7 (ArCH-5), 79.0 (CH-2), 69.8 (CH_2-3), 65.7 (CH_2-1).

IR: υ_{max} 1202 (SO_2) cm^{-1}.

MS (CI, NH_3): *m/z* (%) 230 ($[M]^+$, 25), 248 ($[M+NH_4]^+$, 100).

HRMS (CI, NH_3): *m/z* 248.063 ($[M+NH_4]^+$, $C_9H_{14}NO_5S$ requires 248.0592).

Methyl (4*S*,5*R*)-2-oxo-5-phenyl-1,3,2-dioxathiolane-4-carboxylate (32d)[226]



4.4 mmol scale reaction from **31d** gave after chromatographic purification (PE/EtOAc 8.5:1.5) **32d** as a colourless oil (0.71 g, 66% yield). Mixture of 2 diastereoisomers in a 1:1 ratio. Experimental data were in agreement with reported literature data.[226]

TLC: R_f = 0.50 (hexane/EtOAc 8:2).

δ_H (300 MHz, $CDCl_3$): 7.40-6.70 (m, 10H, ArH), 6.17 (1H, d, *J* = 7.3 Hz, H-3), 5.60 (d, 1H, *J* = 8.0 Hz, H-3), 5.21 (d, 1H, *J* = 8.0 Hz, H-2), 4.84 (d, 1H, *J* = 7.3 Hz, H-2), 3.86 (s, 3H, H-8), 3.85 (s, 3H, H-8).

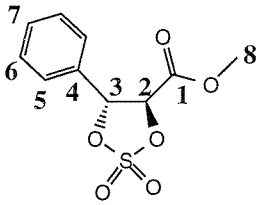
δ_C (75 MHz, $CDCl_3$): 167.6 (C-1), 166.7 (C-1), 134.1 (ArC-4), 133.8 (ArC-4), 130.0 (ArCH-7), 129.7 (ArCH-7), 129.3 (ArCH-6), 129.2 (ArCH-6), 127.7 (ArCH-5),

127.0 (ArCH-5), 88.0 (CH-2), 83.5 (CH-2), 83.3 (CH-3), 81.4 (CH-3), 53.5 (CH_3-8).

IR: υ_{max} 1742 (C=O), 1205 (S=O) cm^{-1}.

MS (CI, NH_3): *m/z* (%) 260 ($[M+NH_4]^+$, 100), 502 ($[2M+NH_4]^+$, 10).

Methyl (4*S*,5*R*)-2,2-dioxo-5-phenyl-1,3,2-dioxathiolane-4-carboxylate (33d)[226,227]



1.44 mmol scale reaction from **32d** gave **33d** as a colourless oil (0.28 g, 75% yield). Washing with saturated $NaHCO_3$ was not carried out during the aqueous work up to avoid hydrolysis. The compound degraded rapidly and could not be stored (under N_2 at -20 °C) more than two days. Experimental data were in agreement with reported literature data.[226,227]

TLC R_f = 0.40 (hexane/EtOAc 8:2).

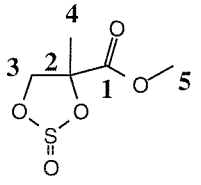
δ_H (300 MHz, $CDCl_3$): 7.50 (m, 5H, ArH), 5.95 (d, 1H, *J* = 8.0 Hz, H-3), 5.18 (d, 1H, *J* = 8.0 Hz, H-2), 3.89 (s, 3H, H-8).

δ_C (75 MHz, $CDCl_3$): 164.8 (C-1), 132.1 (ArC-4), 131.0 (ArCH-7), 129.5 (ArCH-6), 127.2 (ArCH-5), 84.5 (CH-2), 81.5 (CH-3), 53.9 (CH_3-8).

IR: υ_{max} 1747 (C=O), 1206 (SO_2) cm^{-1}.

$[\alpha]_D$ and MS were not recorded due to the rapid degradation of **33d**.

Methyl 4-methyl-2-oxo-1,3,2-dioxathiolane-4-carboxylate (32e)



3 mmol scale reaction from **31e** gave after chromatographic purification (PE/EtOAc 6:4), **32e** as an oil (0.43 g, 79% yield). Mixture of two diastereoisomers in a 1:2 ratio.

TLC: R_f = 0.5 (hexane/EtOAc 7:3).

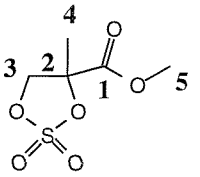
δ_H (300 MHz, $CDCl_3$): 4.85 (d, 1H, *J* = 9.1 Hz, H-3), 4.50 (d, 1H, *J* = 9.1 Hz, H'-3), 3.81 (s, 3H, H-5), 1.83 (s, 3H, H-4). Minor diastereoisomer 5.06 (d, 1H, *J* = 8.8 Hz, H-3), 4.27 (d, 1H, *J* = 8.8 Hz, H-3), 3.85 (s, 3H, H-5), 1.65 (s, 3H, H-4).

δ_C (75 MHz, $CDCl_3$): 170.7 (C-1), 87.7 (C-2), 73.9 (CH_2-3), 53.6 (CH_3-5), 21.8 (CH_3-4). Minor diasteroisomer 170.3 (C-1), 86.2 (C-2), 73.9 (CH_2-3), 53.6 (CH_3-5), 23.3 (CH_3-4).

IR: υ_{max} 1740 (C=O), 1208 (S=O) cm^{-1}.

MS (CI, NH_3): *m/z* (%) 198 ($[M+NH_4]^+$, 100).

Methyl 4-methyl-2,2-dioxo-1,3,2-dioxathiolane-4-carboxylate (33e)[228]



2.4 mmol scale reaction from **32e** gave **33e** as a colourless oil (0.31 g, 65% yield).

TLC: R_f = 0.45 (hexane/EtOAc 7:3).

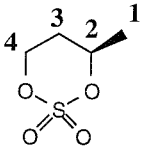
δ_H (300 MHz, $CDCl_3$): 5.02 (d, 1H, *J* = 9.1 Hz, H-3), 4.49 (d, 1H, *J* = 9.1 Hz, H'-3), 3.90 (s, 3H, H-5), 1.82 (s, 3H, H-4).

δ_C (75 MHz, $CDCl_3$): 168.5 (C-1), 86.4 (C-2), 75.0 (CH_2), 54.1 (CH_3-5), 22.4 (CH_3-4).

IR: υ_{max} 1746 (C=O), 1210 (SO_2) cm^{-1}.

MS (CI, NH_3): *m/z* (%) 214 ($[M+NH_4]^+$, 100), 410 ($[2M+NH_4]^+$, 15).

(4*R*)-4-Methyl-1,3,2-dioxathiane-2,2-dione (33f)[229]



5 mmol scale reaction (one pot) from (*R*)-1,3-butanediol **31f** gave **33f** as a white solid (0.52 g, 69% yield). Experimental data were in agreement with reported literature data.[229]

TLC: R_f = 0.4 (hexane/EtOAc 7:3).

mp = 44 °C (ether) [lit.[229] 45-47 °C (EtOAc/hexane)].

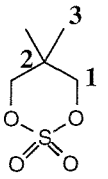
δ_H (300 MHz, $CDCl_3$): 5.06 (ddq, 1H, *J* = 2.5, 12.5, 6.2 Hz, H-2), 4.79 (ddd, 1H, *J* = 2.5, 11.4, 12.8 Hz, H-4), 4.57 (ddd, 1H, *J* = 1.4, 5.1, 11.4 Hz, H'-4), 2.15 (dddd, 1H, *J* = 5.1, 12.5, 12.8, 14.7 Hz, H-3), 1.88 (dddd, 1H, *J* =1.4, 14.7, 2.5, 2.5 Hz, H'-3), 1.49 (d, 3H, *J* = 6.2 Hz, H-1).

δ_C (75 MHz, $CDCl_3$): 82.8 (CH-2), 72.1 (CH_2-4), 30.9 (CH_2-3), 20.9 (CH_3-1).

IR: υ_{max} 1187 (SO_2) cm^{-1}.

MS (CI, NH_3): *m/z* (%) 170 ($[M+NH_4]^+$, 100), 322 ($[2M+NH_4]^+$, 75).

5,5-Dimethyl-1,3,2-dioxathiane-2,2-dione (33g)[230]



10 mmol scale reaction (one pot) from neopentyl glycol **31g** gave **33g** as a white solid (1.50 g, 93% yield). Experimental data were in agreement with reported literature data.[230]

TLC: R_f = 0.6 (hexane/EtOAc 7:3).

mp = 78-79 °C (ether) [lit.[231] 79-80 °C (ether)].

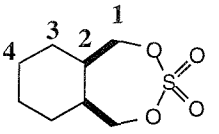
δ_H (300 MHz, $CDCl_3$): 4.30 (s, 4H, H-1), 1.10 (s, 6H, H-3).

δ_C (75 MHz, $CDCl_3$): 81.9 (CH_2-1), 30.9 (C-2), 20.9 (CH_3-3).

IR: υ_{max} 1197 (SO_2) cm^{-1}.

MS (CI, NH_3): *m/z* (%) 184 ($[M+NH_4]^+$, 100).

(1*S*,7*R*)-3,5-dioxa-4-thiabicyclo[5.4.0]undecane-4,4-dione (33g)[232]



13.8 mmol scale reaction (one pot) from *cis*-1,2-cyclohexanedimethanol **31g** gave **33g** as a white solid (2.36 g, 83% yield). Experimental data were in agreement with reported literature data.[232]

TLC: R_f = 0.72 (hexane/EtOAc 8:2).

mp = 58-59 °C (ether/hexane) [lit.[232] 58-59 °C (hexane)].

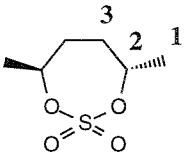
δ_H (300 MHz, $CDCl_3$): 4.44 (2H, dd, *J* = 12.1, 6.6 Hz, H-1), 4.34 (2H, dd, *J* = 12.1, 2.2 Hz, H'-1), 2.22-2.10 (2H, m, H-2), 1.89-1.71 (2H, m, H-3), 1.69-1.54 (2H, m, H'3), 1.53-1.40 (4H, m, H-4).

δ_C (75 MHz, $CDCl_3$): 74.4 (CH_2-1), 38.1 (CH-2), 26.3 (CH_2-4), 23.7 (CH_2-3).

IR: υ_{max} 1195 (SO_2) cm^{-1}.

MS (CI, NH_3): *m/z* (%) 224 ($[M+ NH_4]^+$, 100), 430 ($[2M+ NH_4]^+$, 20).

(4*S*,7*S*)-4,7-dimethyl-1,3,2-dioxathiepane-2,2-dione (33h)[233]



5 mmol scale reaction (one pot) from (2*S*,5*S*)-(+)-1,5-hexanediol **31h** gave **33h** as a white crystalline solid (0.74 g, 82% yield). Experimental data were in agreement with reported literature data.[233]

TLC: R_f = 0.64 (hexane/EtOAc 7:3).

mp = 104-105 °C (ether) [Lit.[233] 109-110 °C (ether/hexane)].

δ_H (300 MHz, $CDCl_3$): 4.80 (m, 2H, H-2), 2.09-1.82 (m, 4H, H-3), 1.43 (d, 6H, J = 6.2 Hz, H-1).

δ_C (75 MHz, $CDCl_3$): 81.6 (CH-2), 34.6 (CH_2-3), 21.7 (CH_3-3).

IR: υ_{max} 1190 (SO_2) cm^{-1}.

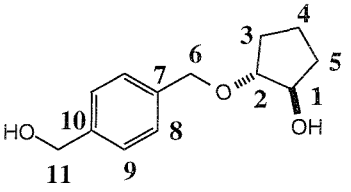
MS (CI, NH_3): *m/z* (%) 198 ($[M+ NH_4]^+$, 100).

5.2.3.3 Scope of the reaction

Resin (24a-i)

Each reaction was performed on resin **17** (0.5 g) using the general *O*-alkylation procedure described above. The couplings were repeated 4 times. Cleavage with 4 M HCl/dioxane (procedure 4) gave with concomitant sulfate ester hydrolysis the ether product **9a-i**.

(1*S*,2*S*) and (1*R*,2*R*)-2-{[4-(Hydroxymethyl)phenyl]methoxy}cyclopentane-1-ol (9a)



Cleavage of resin **24a** (0.33 g) gave after semi-preparative RP-HPLC purification **9a** as a colourless oil (8 mg, 59% yield, two steps from **13**, two enantiomers).

RP-HPLC (λ_{220}, gradient 1): t_R = 9.9 min.

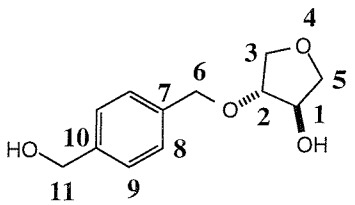
δ_H (400 MHz, $CDCl_3$): 7.33 (s, 4H, ArH), 4.66 (s, 2H, H-11), 4.57 (d, 1H, J_{AB} = 12.0 Hz, H_A-6), 4.51 (d, 1H, J_{AB} =12.0 Hz, H_B-6), 4.16 (ddd, 1H, J = 4.0, 5.2, 6.5 Hz, H-1), 3.76 (ddd, 1H, J = 4.0, 5.2, 6.5 Hz, H-2), 2.05-1.90 (m, 2H, H-3,5), 1.78-1.67 (m, 2H, H-4), 1.70-1.60 (m, 1H, H'-3), 1.61-1.50 (m, 1H, H'-5).

δ_C (100 MHz, $CDCl_3$): 140.5 (ArC-10), 138.1 (ArC-7), 128.1 (ArCH-8), 127.2 (ArCH-9), 86.7 (CH-2), 77.6 (CH-1), 71.3, (CH_2-6), 65.2 (CH_2-11), 32.3 (CH_2-5), 29.5 (CH_2-3), 20.6 (CH_2-4).

IR: υ_{max} 3317 (OH) cm^{-1}.

MS (EI): *m/z* (%) 222 ([M^{+}], 5), 137 (35), 121 (43), 104 (100), 91 (20), 77 (20).
HRMS (EI): 222.1238 ([M^{+}], $C_{13}H_{18}O_3$ requires 222.1255).

(3*S*,4*S*) and (3*R*,4*R*)-4-{[4-(Hydroxymethyl)phenyl]methoxy} oxolan-3-ol (9b)



Cleavage of resin **24b** (0.30 g) gave after semi-preparative RP-HPLC **9b** as a colourless oil (6.4 mg, 50% yield, two steps from **13**).

RP-HPLC (λ_{220}, gradient 1): t_R = 8.1 min.

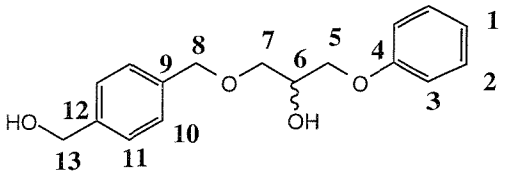
δ_H (400 MHz, $CDCl_3$): 7.36 (d, 2H, *J* = 8.2 Hz, ArH), 7.33 (d, 2H, *J* = 8.2 Hz, ArH), 4.69 (s, 2H, H-11), 4.58 (s, 2H, H-6), 4.33 (ddd, 1H, *J* = 4.0, 1.5, 1.5 Hz, H-1), 4.08 (dd, 1H, *J* = 10.0, 4.7 Hz, H-3), 3.98 (m (overlapped by H-5), 1H, H-2), 3.98 (dd, 2H, *J* = 4.0, 9.8 Hz, H-5), 3.81 (dd, 1H, *J* = 10.0, 2.1 Hz, H'-3), 3.74 (dd, 1H, *J* = 9.8, 1.5 Hz, H'-5).

δ_C (100 MHz, $CDCl_3$): 140.7 (ArC-10), 137.3 (ArC-7), 128.1 (ArCH-8), 127.3 (ArCH-9), 84.9 (CH-2), 75.7 (CH-1), 74.1 (CH_2-5), 71.7 (CH_2-3), 71.5 (CH_2-6), 65.2 (CH_2-11).

IR: υ_{max} 3337 (OH) cm^{-1}.

MS (EI): *m/z* (%) 224 ([M^{+}], 30), 137 (35), 121 (100), 104 (80), 91 (30), 77 (20).
HRMS (EI): *m/z* 224.1051 ([M^{+}], $C_{12}H_{16}O_4$ requires 224.1048).

1-{[4-(Hydroxymethyl)phenyl]methoxy}-3-phenoxypropan-2-ol (9c)



Cleavage of resin **24c** (0.35 g) gave after semi-preparative HPLC purification **9c** as a colourless oil (9.8 mg, 51% yield, two steps from **13**).

RP-HPLC (λ_{220}, gradient 1): t_R = 13.1 min.

δ_H (400 MHz, $CDCl_3$): 7.34 (s, 4H, ArH-10,11), 7.29 (dd, 2H, *J* = 8.7, 7.5 Hz, ArH-2), 6.97 (tt, 1H, *J* = 7.5, 1.0 Hz, ArH-1), 6.91 (dd, 2H, *J* = 1.0, 8.7 Hz, ArH-3), 4.68 (2H, s, H-13), 4.58 (2H, s, H-8), 4.19 (dddd, 1H, *J* = 4.7, 4.7, 6.0, 6.0 Hz, H-6), 4.04 (dd, 1H, *J* = 9.5, 4.7 Hz, H-5), 4.02 (dd, 1H, *J* = 9.5, 6.0 Hz, H'-5), 3.69 (dd, 1H, *J* = 9.5, 4.7 Hz, H-7), 3.64 (dd, 1H, *J* = 9.5, 6.0 Hz, H'-7).

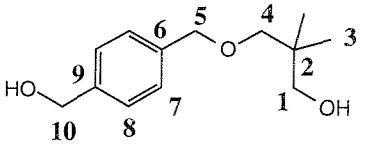
δ_C (100 MHz, $CDCl_3$): 158.7 (ArC-4), 140.7 (ArC-12), 137.4 (ArC-9), 129.6 (ArCH-2), 128.2 (ArCH-10), 127.3 (ArCH-11), 121.3 (ArCH-1), 114.7 (ArCH-3), 73.4 (CH_2-8), 71.1 (CH_2-7), 69.3 (CH-6), 69.0 (CH_2-5), 65.2 (CH_2-13).

IR: υ_{max} 3342 (OH) cm^{-1}.

MS (EI): *m/z* (%) 288 ([M^+], 75), 271 (8), 257 (3), 177 (5), 163 (5), 134 (20), 121 (100), 104 (25), 91 (30), 77 (35).

HRMS (EI): *m/z* 288.1342 ([M^{+}], $C_{17}H_{20}O_4$ requires 288.1361).

3-{[4-(Hydroxymethyl)phenyl]methoxy}-2,2-dimethylpropan-1-ol (9g)



Cleavage of resin **24g** (0.30 g, mmol) gave after semi-preparative HPLC purification **9g** as a colourless oil (12 mg, 21% yield, two steps from **13**).

RP-HPLC (λ_{220}, gradient 1): t_R = 11.4 min.

δ_H (400 MHz, $CDCl_3$): 7.36 (d, 2H, *J* = 8.3 Hz, ArH), 7.32 (d, 2H, *J* = 8.3 Hz, ArH), 4.70 (s, 2H, H-10), 4.51 (s, 2H, H-5), 3.66 (br s, OH), 3.46 (s, 2H, H-1), 3.32 (s, 2H, H-4), 0.93 (s, 6H, H-3).

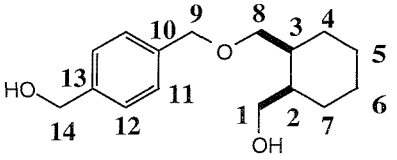
δ_C (100 MHz, $CDCl_3$): 140.5 (ArC-9), 137.8 (ArC-6), 127.9 (ArCH-7), 127.3 (ArCH-8), 79.6 (CH_2-4), 73.5 (CH_2-1), 71.9 (CH_2-5) 65.3 (CH_2-10).

IR: υ_{max} 3351 (OH) cm^{-1}.

MS (CI, ammonia): *m/z* (%) 225 ($[M+H]^+$, 40), 242 ($[M+NH_4]^+$, 20).

HRMS (CI, ammonia): *m/z* 242.1756 ($[M+NH_4]^+$, $C_{16}H_{22}O_2$ requires 246.1619).

(1S,2R) and (1R,2S)-2-({[4-(hydroxymethyl)phenyl)methoxy}methyl)cyclohexyl] methanol-1-ol (9h)



Cleavage of resin **24g** (0.38 g) gave after semi-preparative RP-HPLC purification **9 g** as a colourless oil (7.5 mg, 39% yield, two steps from **13**).

RP-HPLC (λ_{220}, gradient 1): t_R =13.2 min.

δ_H (400 MHz): 7.36 (d, 2H, *J* = 8.2 Hz, ArH), 7.30 (d, 2H, *J* = 8.2 Hz, ArH), 4.69 (s, 2H, H-14), 4.51 (s, 2H, H-9), 3.68 (dd, 1H, *J* = 9.2, 9.2 Hz, H-8), 3.56 (dd, 1H, *J* = 8.7, 11.5 Hz, H-1), 3.49 (dd, 1H, *J* = 5.5, 11.5 Hz, H'-1), 3.41 (dd, 1H, *J* = 9.2, 3.5 Hz, H'-8), 2.15 (m, 1H, H-3), 1.89 (m, 1H, H-2), 1.70-1.20 (m, 8H, H-4,5,6,7).

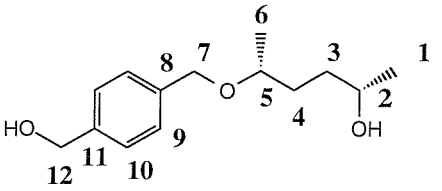
δ_C (100 MHz, $CDCl_3$): 140.7 (ArC-13), 137.3 (ArC-10), 128.3 (ArCH-11), 127.3 (ArCH-12), 73.3 (CH_2-9), 72.1 (CH_2-8), 65.2 (CH_2-14), 64.8 (CH_2-1), 40.8 (CH-2), 36.5 (CH-3), 28.9 (CH_2), 26.0 (CH_2), 24.8 (CH_2), 23.6 (CH_2).

IR: υ_{max} 3385 (OH) cm^{-1}.

MS (EI): *m/z* (%) 264 ($[M^{\cdot+}]$, 3), 246 ($[M-H_2O]^+$, 8) 137 (100), 121 (65), 104 (70), 91 (28), 77 (20).

HRMS (EI): *m/z* 246.1628 ($[M-H_2O]^+$, $C_{16}H_{22}O_2$ requires 246.1619).

(2*S*,5*R*)-5-{[4-(Hydroxymethyl)phenyl]methoxy}hexan-2-ol (9i)



Cleavage of resin **24i** (0.33 g) gave after semi-preparative RP-HPLC purification **9i** as a colourless oil (5.5 mg, 36% yield, two steps from **13**). Due to the small amount of product recovered the $[\alpha]_D$ could not be recorded.

RP-HPLC (λ_{220}, gradient 1): t_R = 10.9 min.

δ_H (400 MHz, $CDCl_3$): 7.25 (s, 4H, ArH), 4.60 (s, 2H, H-12), 4.51 (d, 1H, J_{AB} = 11.7 Hz, H_A-7), 4.37 (d, 1H, J_{AB} = 11.7 Hz, H_B-7), 3.71 (m, 1H, H-2), 3.50 (m, 1H, H-5), 1.59-140 (m, 4H, H-3,4), 1.14 (d, 3H, J = 6.0 Hz, H-6), 1.10 (d, 3H, J = 6.3 Hz, H-1).

δ_C (100 MHz, $CDCl_3$): 140.4 (ArC-11), 138.3 (ArC-8), 128.1 (ArCH-10), 127.2 (ArCH-9), 75.1 (CH-5), 70.3 (CH_2-7), 68.2 (CH-2), 65.3 (CH_2-14), 35.2 (CH_2-3), 33.0 (CH_2-4), 23.6 (CH_2-1), 19.6 (CH_3-6).

IR : υ_{max} 3332 (OH) cm^{-1}.

MS (EI): *m/z* (%) 220 ($[M-H_2O]^+$, 8), 202 (25), 137 (35), 121 (100), 107 (25), 91 (30), 77 (20).

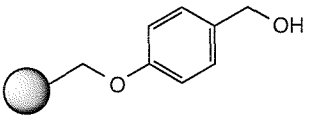
HRMS (EI): *m/z* 220.1468 ($[M-H_2O]^+$, $C_{14}H_{20}O_2$ requires 220.1463).

5.2.3 Development of the sulfate ester hydrolysis procedure

General procedure for the coupling of diol on Wang based resin - Synthesis of resin (46)

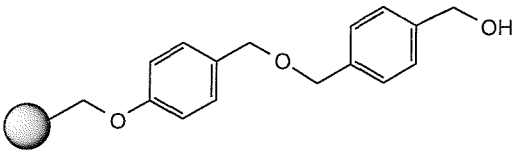
NovaSyn® TG HMP resin **44** (0.26 mmol/g) was placed in a peptide vessel and washed under N_2 with dry THF (3 x 10 mL) and dry DCM (3 x 10 mL). The resin was then suspended in dry DCM (10 mL/g). The slurry was transferred to a flask and cooled to 0 °C. CCl_3CN (20 eq) was added followed by DBU (1 eq). The resin was stirred gently at 0 °C for 2 h then transferred to an oven-dried peptide vessel and washed under N_2 with dry DCM (3 x 10 mL/g) and dry THF (4 x 10 mL/g). The freshly made trichloroacetimidate Wang derivative **45** was suspended in dry DCM (5 mL/g) and a solution of 1,4-benzenedimethanol **4** (5 eq) in dry THF (5 ml/g) was added. The resin was shaken for 10 min then $BF_3.OEt_2$ (0.5 eq) was added and the resin was shaken at room temperature for 24 h. The resin was filtered, washed with MeOH (5 x 20 mL/g), DMF (5 x 20 mL/g), MeOH (5 x 20 mL/g), DCM (5 x 20 mL/g), MeOH (2 x 20 mL/g) and dried *in vacuo* over P_2O_5 for 48 h.

NovaSyn® TG HMP resin (44)



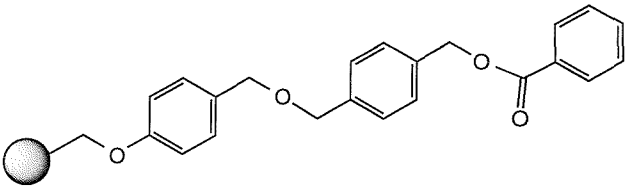
δ_C (75 MHz, d^6-benzene): 159.2 (ArC), 135.7 (ArC), 130.7 (ArC), 129.0 (ArCH), 129.0, 128.7, 114.6 (ArCH), 71.2 (br, PEG), 70.5 (CH_2), 68.3 (CH_2), 64.9 (CH_2), 41.6 (br, resin).

Resin (46)



δ_C (75 MHz, d^6-benzene): 158.7 (ArC), 142.0 (ArC), 137.5 (ArC), 130.9 (ArCH), 129.9 (ArCH), 129.0, 128.7, 114.6 (ArCH), 71.6 (CH_2), 71.2 (br, PEG), 69.7 (CH_2), 67.5 (CH_2), 64.1 (CH_2), 40.7 (br, resin).

General procedure for the determination of the percentage of cross-linking and unreacted Wang linker - Synthesis of resin (47)



Resin **46** (50 mg, 0.013 mmol) was placed in a 3 mL Supelco syringe, washed under N_2 with dry DCM (3 x 1 mL) then suspended in dry DCM (1 mL). Dry pyridine (15 µL, 0.19 mmol) was added followed by benzoyl chloride (15 µL, 0.13 mmol). The resin was shaken at room temperature for 6 h. The resin was filtered, washed with DCM (3 x 3 mL), DMF (5 x 3 mL), MeOH (5 x 3 mL), DCM (3 x 3 mL), and MeOH (3 x 3 mL) and dried *in vacuo* over P_2O_5 for 12 h. The percentage of cross-linking was determined by TFA cleavage (procedure 4) and quantification of the unreacted 1,4-benzenedimethanol **4** by HPLC-UV analysis using a calibration curve. The percentage of unreacted Wang linker was determined by quantification of released benzoic acid by HPLC analysis using a calibration curve.

Study of the rate of sulfate ester hydrolysis

Resin **50a** (200 mg) was suspended in a solution of HCl in dioxane (2 mL) (c_1 = 0.001M (1% H_2O); c_2 = 0.01M (1% H_2O)). The resin was stirred gently at room temperature for 12 h. Samples were taken at regular intervals, filtered, washed with dioxane/H_2O 9:1 (3 x 2 mL), dioxane (3 x 2 mL), DCM (3 x 2 mL) and MeOH (3 x 2 mL). The resin samples were dried *in vacuo* then cleaved with TFA (procedure 4) and analysed by RP-HPLC. % hydrolysis = % area **9a** / (% area **8a** + % area **9a**).

Time (h)	0.001M HCl/1%H_2O/dioxane % hydrolysis	0.01 M HCl/1%H_2O/dioxane % hydrolysis
0.25	5	25
0.5	9.5	38
1	10	65
2	15	88
3	17	96
4	21	97
5	23	98
6	26	100

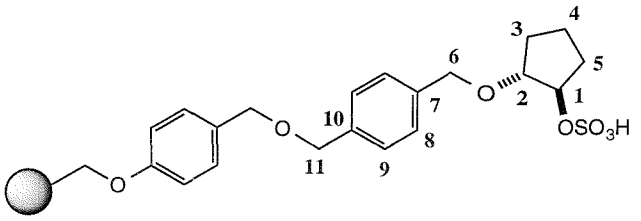
Study of the stability of the wand linker to the sulfate ester hydrolysis conditions

Resin **50a** (10 mg) was placed in an Eppendorf tube and treated with solutions of HCl in dioxane (c1 = 0.001M (1% H_2O); c2 = 0.01M (1% H_2O); c3 = 0.1M (10% H_2O)) at room temperature for 12 h. The resin was filtered and washed with dioxane (5 mL). The filtrates were evaporated *in vacuo* and analysed by RP-HPLC. In the 3 cases, diol **4** was not detected in the filtrates.

General procedure for hydrolysis of the Sulfate Ester moiety

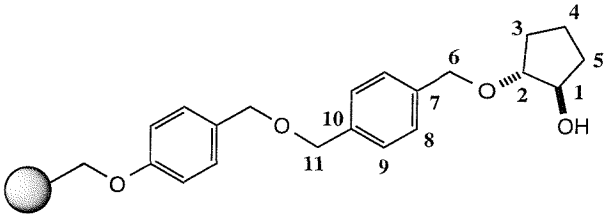
Resin **50a** was washed with DCM (3 x 10 mL/g), dioxane (3 x 10 mL/g) then suspended in dioxane (5 mL/g). A solution of 0.01M HCl in 1% H_2O/dioxane (1 mL/g) was added and the resin was shaken at room temperature overnight. The resin was filtered, washed with DMF (3 x 10 mL/g), MeOH (3 x 10 mL/g), DCM (3 x 10 mL/g), MeOH (3 x 10 mL/g), DCM (3 x 10 mL/g), MeOH (3 x 10 mL/g) and dried *in vacuo* over P_2O_5 for 12 h.

Resin (50a)



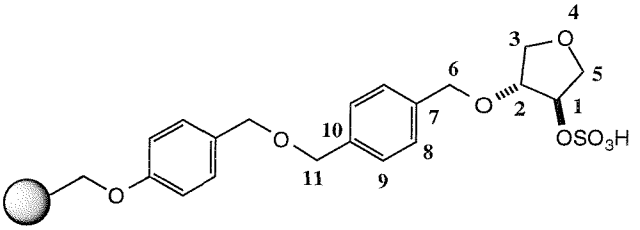
δ_C (75 MHz, d^6-benzene): 159.1 (ArC), 139.4 (ArC), 138.0 (ArC), 129.6 (ArCH), 128.5, 128.2, 114.9 (ArCH), 85.1 (CH-1), 82.4 (CH-2), 72.0 (CH_2), 71.2 (br, PEG), 70.0 (CH_2), 67.9 (CH_2), 41.0 (br, resin), 31.9 (CH_2-3), 31.2 (CH_2-5), 22.5 (CH_2-4).

Resin (51a)



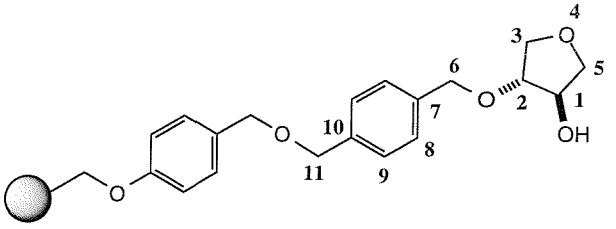
δ_C (75MHz, d^6-benzene): 159.6 (ArC), 139.5 (ArC), 138.8 (ArC), 129.6 (ArCH), 128.5, 128.2, 115.4 (ArCH), 87.6 (CH-2), 77.6 (CH-1), 72.3 (CH_2), 71.2 (br, PEG), 70.5 (CH_2), 68.3 (CH_2), 41.0 (br, resin), 33.7 (CH_2-5), 30.2 (CH_2-3), 22.1 (CH_2-4).

Resin (50b)



δ_C (100 MHz, d^6-benzene): 138.8, 131.5, 129.9, 115.2, 84.1 (CH-1), 80.9 (CH-2), 72.9, 72.2, 71.2 (br, PEG), 70.3, 68.2, 41.5 (br, resin).

Resin (51b)



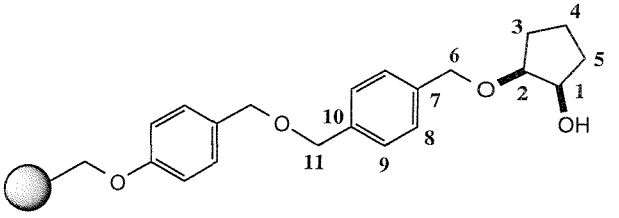
δ_C (100 MHz, d^6-benzene): 159 2, 138.6, 131.3, 129.7, 115.0, 86.0 (CH-2), 75.8, 74.7, 71.2 (br, PEG), 68.0, 41.1(br, resin).

5.2.4 Determination of stereochemistry

Synthesis of resin (53) and (54) - general procedure

Resin **46** was washed under N_2 with dry THF (3 x 5 mL/g) and dry DCM (3 x 5 mL/g) then suspended in dry DCM (5 mL/g). The slurry was transferred to a round bottom flask and cooled to 0 °C. CCl_3CN (20 eq) was added followed by (DBU (1 eq). The resin was stirred gently at 0 °C for 2 h then transferred to an oven-dried peptide vessel and washed under N_2 with dry DCM (3 x 5 mL/g) and dry THF (4 x 5 mL/g). The freshly made trichloroacetimidate derivative was suspended in dry DCM (5 mL/g) and a solution of *cis*-1,2-cyclopentanediol (resin **54**) or *trans*-1,2-cyclopentanediol (resin **53**) (5 eq) in dry DCM (1 mL/mmol) was added. The resin was shaken for 10 min then $BF_3.OEt_2$ (0.5 eq) was added and the resin was shaken at room temperature for 24 h. The resin was filtered, washed with MeOH (5 x 10 mL/g), DMF (5 x 10 mL/g), MeOH (5 x 10 mL/g), DCM (5 x 10 mL/g), MeOH (2 x 10 mL/g) and dried *in vacuo* over P_2O_5 for 48 h.

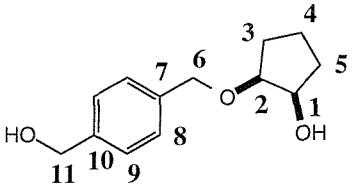
Resin (54)



RP-HPLC (λ_{220}, gradient 1): t_R = 7.1 min (**4**, 34% area), t_R = 10.4 min (**56**, 66% area).

δ_C (100 MHz, d^6-benzene): 159.2, 138.7, 138.4, 131.2, 130.3, 129.7, 115.0, 82.0 (CH-2), 72.4 (CH-1), 72.1, 71.2 (br, PEG), 70.1, 67.9, 41.1 (br, resin), 31.7 (CH_2-5), 28.3 (CH_2-3), 20.1 (CH_2-4).

(1*R*,2*S*) and (1*S*,2*R*)-2-{[4-(Hydroxymethyl)phenyl]methoxy}cyclopentane-1-ol (56)



Cleavage from resin **54** (0.3 g) with 50% TFA (procedure 5) gave after RP-HPLC purification **56** as a colourless oil (8.6 mg, 50%, 2 steps from **44**).

RP-HPLC (λ_{220}, gradient 1): t_R = 10.3 min.

δ_H (400 MHz, $CDCl_3$): 7.36 (s, 4H, ArH), 4.69 (s, 2H, H-11), 4.61 (d, 1H, J_{AB} = 11.8 Hz, H_A-6), 4.53 (d, 1H, J_{AB} = 11.8 Hz, H_B-6), 4.09 (ddd, 1H, J = 4.3, 4.3, 5.3 Hz, H-1), 3.81 (ddd, 1H, J = 4.3, 6.5, 6.5 Hz, H-2), 1.90-1.40 (m, 6H, H-3,4,5).

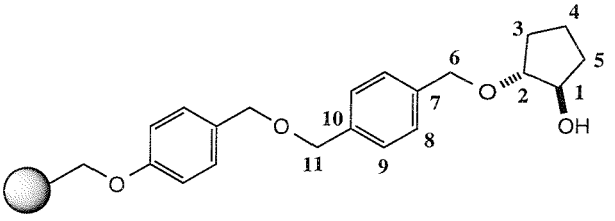
δ_C (100 MHz, $CDCl_3$): 140.7 (ArC-10), 137.7 (ArC-7), 128.1 (ArCH-8), 127.3 (ArCH-9), 81.5 (CH-2), 72.4 (CH-1), 71.4 (CH_2-6), 65.2 (CH_2-11), 31.3 (CH_2-5), 28.0 (CH_2-3), 19.8 (CH_2-4).

IR : υ_{max} 3374 (OH) cm^{-1}.

MS (CI, NH_3): *m/z* (%) 240.1 ($[M+NH_4]^+$, 60), 205.1 ($[M+H-H_2O]^+$, 10), 138.0 (100), 105.1 (80), 84.1 (10).

HRMS (EI): *m/z* 222.1257 ($[M^+]$, $C_{13}H_{18}O_3$ requires 222.1255).

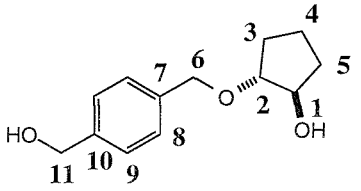
Resin (53)



RP-HPLC (λ_{220}, gradient 1): t_R = 7.0 min (**4**, 26% area), t_R = 9.8 min (**55**, 74% area).

δ_C (100 MHz, d^6-benzene): 159.2 (ArC), 139.2, 138.2, 131.3, 130.3, 129.7, 115.0 (ArCH), 87.2 (CH-2), 77.2 (CH-1), 71.2 (br, PEG), 70.1, 68.0, 41.2 (br, resin), 33.4 (CH_2-5), 30.3 (CH_2-3), 21.7 (CH_2-4).

(1*R*,2*R*) and (1*S*,2*S*)-2-{[4-(hydroxymethyl)phenyl]methoxy}cyclopentane-1-ol (55)



Cleavage from resin **53** (0.3 g) with 50% TFA (procedure 5) gave after semi-preparative RP-HPLC purification **55** as a colourless oil (10 mg, 57%, 2 steps from **44**).

RP-HPLC (λ_{220}, gradient 1): t_R = 9.8 min.

δ_H (400 MHz, $CDCl_3$): 7.32 (s, 4H, ArH), 4.66 (s, 2H, H-11), 4.56 (d, 1H, J_{AB} = 12.0 Hz, H_A-6), 4.50 (d, 1H, J_{AB} = 12.0 Hz, H_B-6), 4.15 (ddd, 1H, J = 4.0, 5.2, 6.4 Hz, H-1), 3.74 (ddd, 1H, J = 4.0, 5.2, 6.4 Hz, H-2), 2.05-1.50 (m, 6H, H-3,4,5).

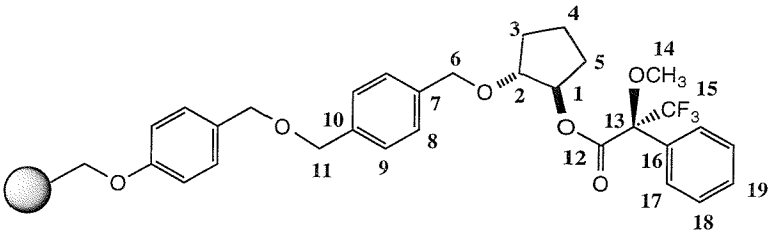
δ_C (100 MHz, $CDCl_3$): 140.4 (ArC-10), 138.2 (ArC-7), 128.1 (ArCH-8), 127.2 (ArCH-9), 86.7 (CH-2), 77.6 (CH-1), 71.3 (CH_2-6), 65.3 (CH_2-11), 32.3 (CH_2-5), 29.5 (CH_2-3), 20.6 (CH_2-4).

IR : υ_{max} 3311 (OH) cm^{-1}.

MS (CI, NH_3): *m/z* (%) 240.1 ($[M+NH_4]^+$, 70), 222.1 ($[M]^+$, 30), 205 ($[M+H-H_2O]^+$, 15), 138.0 (95), 122.1 (100), 105.0 (80), 84.1 (25).

HRMS (EI): *m/z* 222.1258 ($[M^+]$, $C_{13}H_{18}O_3$ requires 222.1255).

Resin (57)



Resin **51a** (0.5 g, 0.13 mmol) was washed under N_2 with dry THF (5 x 3 mL), dry DCM (5 x 3 mL) then suspended in dry DCM (2 mL). Dry Et_3N (180 µL, 0.13 mmol) and DMAP (16 mg, 0.013 mmol) were added followed by (*R*)-(-)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (48 µL, 0.26 mmol). The resin was shaken at room temperature overnight then filtered, washed with MeOH (5 x 3 mL), DMF (5 x 3 mL), MeOH (5 x 3 mL), DCM (5 x 3 mL), MeOH (5 x 3 mL) and dried *in vacuo*.

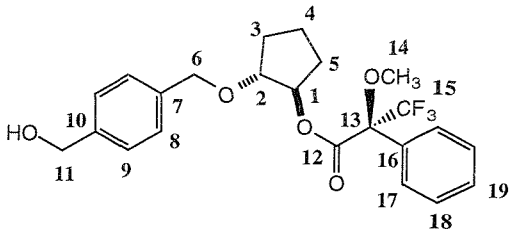
RP-HPLC (λ_{220}, gradient 1): t_R = 7.2 min (**4**, 30%), t_R = 16.7 min (**59** + **60**, 27% area), t_R = 18.7 min (**58**, 43%).

δ_C (100 MHz, d^6-benzene): 166.3 , 159.3 (C-12), 138.9, 138.2, 133.2, 129.8, 129.0, 123.1 (CH_3-14), 115.1, 83.6 (CH-2), 82.0 (CH-1), 70.2, 68.1, 55.6 (CH_3-14), 41.3 (br, resin), 30.7 (CH_2-3/5), 30.5 (CH_2-3/5), 30.2 (CH_2-3/5), 22.1 (CH_2-4), 21.8 (CH_2-4).

δ_F (300 MHz, $CDCl_3$): 90.4 (CF_3).

IR: υ_{max} 1717 (C=O) cm^{-1}.

(1*R*,2*R*) and (1*S*,2*S*)-2-{[4-(hydroxymethyl)phenyl]methoxy}cyclopentyl (2S)-3,3,3-trifluoro-2-methoxy-2-phenyl propanoate (58)



Cleavage from resin **57** (0.5 g) with 50% TFA (procedure 5) gave after semi-preparative RP-HPLC purification **58** as an oil (15 mg, 28% yield, 4 steps from resin **44**). 2 enantiomers in a 1:1 ratio.

δ_H (400 MHz, $CDCl_3$): 7.60-7.25 (m, 18H, ArCH-8,9,17,18,19), 5.39-5.33 (m, 2H, H-1), 4.69 (s, 4H, H-11), 4.60 (d, 1H, J_{AB} = 12.0 Hz, H_A-6), 4.58 (d, 1H, J_{AB} = 12.0 Hz, H_B-6), 4.56 (d, 1H, J_{AB} = 12.0 Hz, H_A-6), 4.48 (d, 1H, J_{AB} = 12.0 Hz, H_B-6), 3.98 (ddd, 1H, J = 2.5, 4.5, 6.5 Hz, H-2), 3.89 (ddd, 1H, J = 2.5, 3.0, 5.8 Hz, H-2), 3.54 (qua, 3H, J = 1.2 Hz, H-14), 3.53 (q, 3H, J = 1.2 Hz, H-14), 2.30-1.60 (m, 12 H, H-3,4,5).

δ_C (100 MHz, $CDCl_3$): 166.16 (C-12), 166.14 (C-12), 140.5 (ArC-10), 140.4 (ArC-10), 137.79 (ArC-7), 137.76, (ArC-7), 132.4 (ArC-16), 132.3 (ArC-16), 130.0, 129.7, 128.6, 128.0, 127.5, 127.45, 127.44, 127.26, 127.23, 126.6 (10 ArCH), 124.9 (C-15), 122.0 (C-13), 83.48 (CH-2), 83.46 (CH-2), 81.83 (CH-1), 81.79 (CH-1), 71.3 (CH_2-6), 71.2 (CH_2-6), 65.33 (CH_2-11), 65.31 (CH_2-11), 55.49 (CH_3-15), 55.46 (CH_3-15), 30.5 (CH_2-3), 30.3 (CH_2-3), 30.2 (CH_2-5), 29.9 (CH_2-5), 21.7 (CH_2-4), 21.5 (CH_2-4).

δ_F (300 MHz, $CDCl_3$): 90.2 (CF_3), 90.1 (CF_3).

IR : υ_{max} 3356 (OH), 1743 (C=O) cm^{-1}.

MS (CI, NH_3): *m/z* (%) 456 ($[M+NH_4]^+$, 20), 403 (3), 337 (5), 301 (3), 34 (5), 189 (18), 121 (100), 105 (98), 84 (30).

HRMS (EI): *m/z* 438.1660 ($[M^{\cdot+}]$, $C_{23}H_{25}O_5F_3$ requires 438.1654).

5.3 Experimental chapter 3

5.3.1 Synthesis of the tetramer library

General procedure for the synthesis of the dimer ($9x^1$)

Resin **46** (4 g, 1.04 mmol) was placed in a peptide vessel and washed under N_2 with dry THF (3 x 20 mL), dry DMF (20 mL) and suspended in DMF (35 mL). 15-Crown-5 (210 μL, 1.04 mmol) and NaH (0.200 g, 5.2 mmol) were added under N_2. The resin was shaken at room temperature for 2 h. Cyclic sulfate **$33x^1$** (5.2 mmol; **33a** 0.852 g, **33b** 0.863 g, **33h** 1.07 g, **33i** 0.936 g) in dry DMF (5 mL) was added and the resin was shaken at room temperature overnight. The resin was filtered, washed with DMF (3 x 20 mL), MeOH (3 x 20 mL), DCM (3 x 20 mL) and MeOH (3 x 20 mL). The reaction was repeated three times.

Resin **$50x^1$** (4 g) was washed with DCM (3 x 20 mL) and dioxane (3 x 20 mL). 0.01M HCl in 1% H_2O/dioxane (40 mL) was added and the resin was shaken at room temperature overnight. The resin was washed with dioxane (3 x 20 mL), MeOH (3 x 20 mL), DCM (3 x 20 mL) and MeOH (3 x 20 mL) and dried *in vacuo* overnight.

General procedure for the synthesis of the trimer ($65x^1x^2$)

Resin **$51x^1$** (1.0 g, 0.26 mmol) was placed in a peptide vessel and washed under N_2 with dry THF (3 x 10 mL), dry DMF (2 x 5 mL) and suspended in dry DMF (9 mL). 15-crown-5 (52 μL, 0.26 mmol) and NaH (52 mg, 1.3 mmol) were added under N_2. The resin was shaken at room temperature for 2 h. Cyclic sulfate **$33x^2$** (1.3 mmol; **33a** 0.213 g, **33b**, 0.215 g, **33h** 0.267 g, **33i** 0.234 g) in dry DMF (1 mL) was added and the resin was shaken at room temperature overnight. The resin was filtered, washed with DMF (3 x 10 mL), MeOH (3 x 10 mL), DCM (3 x 10 mL) and MeOH (3 x 10 mL). The reaction was repeated four times.

Resin **$62x^1x^2$** (1.0 g) was washed with DCM (3 x 10 mL) and dioxane (3 x 10 mL). 0.01M HCl in 1% H_2O/dioxane (10 mL) was added and the resin was shaken at room temperature overnight. The resin was washed with dioxane (3 x 10 mL), MeOH (3 x 10 mL), DCM (3 x 10 mL), MeOH (3 x 10 mL) and dried *in vacuo* overnight.

General procedure for the synthesis of the tetramer ($69x^1x^2x^3$)

Resin **$64x^1x^2$** (0.4 g, 0.1 mmol) was placed in a peptide vessel and washed under N_2 with dry THF (3 x 5 mL), dry DMF (5 mL) and suspended in dry DMF (4 mL). 15-crown-5 (21 μL, 0.1 mmol) and NaH (42 mg, 1 mmol) were added under N_2. The resin was shaken at room temperature for 2 h. Cyclic sulfate **$33x^3$** (1 mmol; **33a** 0.164 g, **33b** 0.166 g) in dry DMF (1 mL) was added and the resin was shaken at room

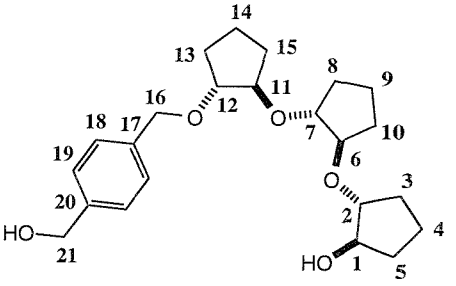
temperature for 4 h. The resin was filtered, washed with DMF (3 x 5 mL), MeOH (3 x 5 mL), DCM (3 x 5 mL) and MeOH (3 x 5 mL). The reaction was repeated eight times. Resin **66x^{1}x^{2}x^3** (0.4 g) was washed with DCM (3 x 5 mL) and dioxane (3 x 5 mL). 0.01M HCl in 1% H_2O/dioxane (5 mL) was added and the resin was shaken at room temperature overnight. The resin was washed with dioxane (3 x 5 mL), MeOH (3 x 5 mL), DCM (3 x 5 mL), MeOH (3 x 5 mL) and dried *in vacuo* overnight.

Resin (68aaa).

RP-HPLC (λ_{220}, gradient 1): t_R = 7.2 min (**4**, 23%), t_R = 9.9 min (**9a**, 7%), t_R = 12.3 min (**65aa**, 13%), t_R = 12.6 min (**65aa**, 13%), t_R = 14.6-15.2 min (**69aaa**, 4 peaks, 43%).

2- [2- (2-{[4-(hydroxymethyl)phenyl] methoxy} cyclopentyloxy) cyclopentyloxy] cyclopentan-1-ol (69aaa)

Cleavage of resin **68aaa** (0.80 g) with 50% TFA (procedure 5) gave after semi-preparative RP-HPLC purification **69aaa** as a colourless oil (11.7 mg, 13% yield, 7 steps from resin **44**). Mixture of 4 pairs of diastereoisomers in a 1:1:1:1 ratio which could not be separated by RP-HPLC.



RP-HPLC (λ_{220}, gradient 1): t_R = 14.6-15.2 min (4 peaks).

δ_H (400 MHz, $CDCl_3$): 7.35 (m, 4H, ArH), 4.67 (br s, 2H, H-21), 4.61-4.48 (m, 2H, H-16), 4.08-3.63 (m, 6H, H-1,2,6,7,11,12), 1.95-1.20 (m, 18H, H-3,4,5,8,9,10,13,14,15).

δ_C (100 MHz, $CDCl_3$): 140.53, 140.47, 140.42, 140.37 (4 ArC-20), 138.32, 138.26, 138.23, 138.15 (4 ArC-17), 128.24, 128.19, 128.13, 128.08 (4 ArCH-18), 127.36, 127.33, 127.27 (3 ArCH-19), 87.51, 87.20, 85.39, 85.31, 85.24, 85.12, 85.07, 84.65, 84.45, 84.34, 84.20, 84.15, 84.10, 83.96, 83.70, 83.51, 83.38, 78.12, 78.06, 77.42, 77.39 (21 CH), 71.21, 71.17, 71.11 (3 CH_2-16), 65.30 (CH_2-21), 32.30, 31.09, 31.03, 30.98, 30.84, 30.73, 30.64, 30.54, 30.46, 30.44, 30.37, 30.32, 30.21, 29.97, 29.85, 29.83, 29.76, 29.67, 21.53, 21.51 (2 CH_2), 21.39, 21.37, 21.27, 21.21 , 20.82, 20.72, 20.41, 20.26, 19.55, 19.37 (31 CH_2-3,4,5,8,9,10,13,14,15).

IR: υ_{max} 3366 (OH) cm^{-1}.

MS (ES +ve): *m/z* (%) 373.4 ($[M+H-H_2O]^+$, 5), 391.4 ($[M+H]^+$, 100), 408.2 ($[M+NH_4]^+$, 80), 413 ($[M+Na]^+$, 95), 492 ($[M+K]^+$, 5).
HRMS (EI): *m/z* 391.2470 ($[M+H]^+$, $C_{23}H_{35}O_5$ requires 391.2484).

Resin (68aab)

RP-HPLC (λ_{220}, gradient 2): t_R = 7.2 min (**4**, 12%), t_R = 10.4 min (**9a**, 18%), t_R = 12.8 min (**65ab**, 21%, MS (ES +ve) 326.1 ($[M+NH_4]^+$, 100)), t_R = 20.4 min (**65aa**, 7%, MS (ES +ve) 307.2 ($[M+H]^+$, 100)), t_R = 22.4 min (**65aa**, 7%, ES MS (+ve) 307.2 ($[M+H]^+$, 100)), t_R = 26.4 min (**69aab**, 18%, MS (ES +ve) 410.1 ($[M+NH_4]^+$, 100)), t_R = 28.9 min (**69aab**, 17%, MS (ES +ve) 410.1 ($[M+NH_4]^+$, 100)).

Resin (68aba)

RP-HPLC (λ_{220}, gradient 2): t_R = 7.2 min (**4**, 12%), t_R = 10.4 min (**9a**, 15%), t_R = 11.5 min (**65ab**, 5%), t_R = 12.6 min (4%), t_R = 20.3 min (**65aa**, 10%, MS (ES +ve) 348.4 ($[M+CH_3CN+H]^+$, 100)), t_R = 22.2 min (**65aa**, 11%, MS (ES +ve) 307.2 ($[M+H]^+$, 100)), t_R = 24.3-25.1 min (**69aba**, 43%, MS (ES +ve) 410.2 ($[M+NH_4]^+$, 100)).

Resin (68abb)

RP-HPLC (λ_{220}, gradient 3): t_R = 7.2 min (**4**, 12%), t_R = 8.1 min (2%), t_R = 8.8 min (**9a**, 5%), t_R = 10.4 min (**9b**, 18%), t_R = 13.1 min (**65ab**, 27%, ES MS (+ve) 326.2 ($[M+NH_4]^+$, 100)), t_R = 15.1 min (**69abb**, 18%, MS (ES +ve) 412.2 ($[M+NH_4]^+$, 100)), t_R = 15.7 min (**69abb**, 18%, MS (ES +ve) 412.2 ($[M+NH_4]^+$, 100)).

Resin (68baa)

RP-HPLC (λ_{220}, gradient 2): t_R = 6.2 min (5%), t_R = 7.2 min (**4**, 12%), t_R = 10.3 min (**9a**, 7%), t_R = 11.4 min (**65ba**, 22%), t_R = 15.2 min (4%), t_R = 20.1 min (3%), t_R = 20.6 min (**69baa**, 10%, MS (ES +ve) 410.2 ($[M+NH_4]^+$, 100)), 21.5 min (**69baa**, 10%, MS (ES +ve) 393.2 ($[M+H]^+$, 100)), 22.2 min (4%), 23.4 min (**69baa**, 10%, MS (ES +ve) 410.2 ($[M+NH_4]^+$, 100)), 24.8 min (**69baa**, 10%, MS (ES +ve) 393.2 ($[M+H]^+$, 100)).

Resin (68bab)

RP-HPLC (λ_{220}, gradient 4): t_R = 6.2 min (5%), t_R = 7.2 min (**4**, 12%), t_R = 8.1 min (**9b**, 3%), t_R = 9.3 min (5%), t_R = 12.4 min (6%), t_R = 15.5-15.9 min (**65ba**, 20%, ES MS (+ve) 326.2 ($[M+NH_4]^+$, 100)), t_R = 19.8 min (8%), t_R = 23.0-25.7 min (**69bab**, 4 peaks, 37%, ES MS (+ve) 412.1 ($[M+NH_4]^+$, 100), t_R = 26.6 min (4%).

Resin (68bba)

RP-HPLC (λ_{220}, gradient 4): t_R = 6.2 min (5%), t_R = 7.2 min (**4**, 12%), t_R = 8.1 min (**9b**, 2%), t_R = 9.4 min (**65bb**, 4%), t_R = 12.5 min (3%), t_R = 15.4-15.9 min (**65ba**, 23%), t_R = 18.2-20.1 min (**69bba**, 4 peaks, 51%, ES MS (+ve) 412.1 ($[M+NH_4]^+$, 100)).

Resin (68bbb)

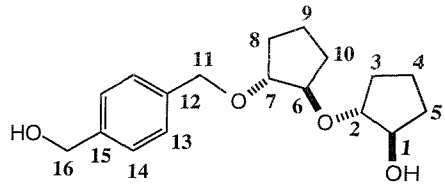
RP-HPLC (λ_{220}, gradient 3): t_R = 6.1 min (6%), t_R = 7.2 min (**4**, 15%), t_R = 8.1 min (**9b**, 10%),t_R = 8.8 min (**65bb**, 27%), t_R = 9.4 min (**69bbb**, 42%, ES MS (+ve) 414.1 ($[M+NH_4]^+$, 100)).

5.3.2 Synthesis of the trimer library

Resin (64aa)

RP-HPLC (λ_{220}, gradient 1): t_R = 7.1min (**4**, 15%), t_R = 10.0 min (**9a**, 35%), t_R = 12.5 min (**9a**, 25%), t_R = 12.8 min (**65aa**, 25%).

2-(2-{[4-(hydroxymethyl)phenyl]methoxy}cyclopentyloxy)cyclopentane-1-ol (65aa).



Cleavage from resin **64aa** (0.95 g) with 50% TFA (procedure 5) gave after semi preparative RP-HPLC purification **65aa** as a colourless oil. Two pairs of enantiomers in a 1:1 ratio. The diastereoisomers were separated by RP-HPLC [diastereoisomer 1 (10 mg), diastereoisomer 2 (11 mg); 28% yield, 5 steps from **44**].

Diastereoisomer 1 (2 enantiomers)

RP-HPLC (λ_{220}, gradient 1): t_R = 12.3 min.

δ_H (400 MHz, $CDCl_3$): 7.34 (s, 4H, ArH-13,14), 4.67 (s, 2H, H-16), 4.56 (d, 1H, J_{AB} = 11.8 Hz, H_A-11), 4.52 (d, 1H, J_{AB} = 11.8 Hz, H_B-11), 4.07 (ddd, 1H, J = 4.0, 5.5, 7.0 Hz, H-1), 3.96 (ddd, 1H, J = 3.5, 5.0, 6.5 Hz, H-6), 3.85 (ddd, 1H, J = 3.5, 4.5, 7.0 Hz, H-7), 3.74 (ddd, 1H, J = 4.0, 5.5, 7.0 Hz, H-2), 2.02-1.89 (m, 4H, 4 H-3,5,8,10), 1.74-1.64 (m, 4H, H-4,9), 1.64-1.48 (m, 4H, H'-3,5,8,10).

δ_C (100 MHz, $CDCl_3$): 140.4 (ArC-15), 138.1 (ArC-12), 128.1 (ArCH-13), 127.2 (ArCH-14), 85.4 (CH-2), 85.0 (CH-7), 83.6 (CH-6), 77.5 (CH-1), 71.1 (CH_2-11), 65.2 (CH_2-16), 32.2 (CH_2-5), 30.7 (CH_2-10), 30.2 (CH_2-3/8), 30.1 (CH_2-3/8), 21.4 (CH_2-4/9), 20.7 (CH_2-4/9).

IR: υ_{max} 3350 (OH) cm^{-1}.

HRMS (EI): *m/z* 288.1703 ($[M-H_2O]^+$, $C_{18}H_{24}O_3$ requires 288.1725).

Diastereoisomer 2 (2 enantiomers)

RP-HPLC (λ_{220}, gradient 1): t_R = 12.7 min.

δ_H (400 MHz, $CDCl_3$): 7.34 (s, 4H, ArH-13,14), 4.66 (s, 2H, H-16), 4.59 (d, 1H, J_{AB} = 12.0 Hz, H_A-11), 4.49 (d, 1H, J_{AB} = 12.0 Hz, H_B-11), 3.98 (ddd, 1H, J = 4.5, 6.5, 6.5 Hz, H-1), 3.91 (ddd, 1H, J = 4.0, 7.0, 7.0 Hz, H-6), 3.85 (ddd, 1H, J = 5.0, 7.0, 7.0 Hz, H-7), 3.66 (ddd, 1H, J = 5.0, 7.0, 7.0 Hz, H-2), 2.02-1.88 (m, 4H, H-3,5,8,10), 1.72-1.60 (m, 4H, H-4,9), 1.60-1.44 (m, 4H, H'-3,5,8,10).

δ_C (100 MHz, $CDCl_3$): 140.6 (ArC-15), 137.9 (ArC-12), 128.3 (ArCH-13), 127.3 (ArCH-14), 86.8 (CH-2), 85.2 (CH-7), 84.8 (CH-6), 77.9 (CH-1), 71.4 (CH_2-11), 65.2 (CH_2-16), 31.5 (CH_2-5), 30.9 (CH_2-10), 30.1 (CH_2-3/8), 29.7 (CH_2-3/8), 20.8 (CH_2-4/9), 20.0 (CH_2-4/9).

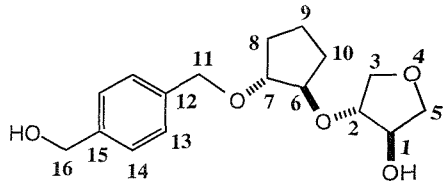
IR: υ_{max} 3343 (OH) cm^{-1}.

HRMS (EI): *m/z* 288.1700 ($[M-H_2O]^+$, $C_{18}H_{24}O_3$ requires 288.1725).

Resin (64ab)

RP-HPLC (λ_{220}, gradient 1): t_R = 7.1min (**4**, 16%), t_R = 8.1 min (**9b**, 7%), t_R = 10.0 min (**9a**, 32%), t_R = 10.9 min (**65ab**, 45%).

4-(2-{[4-(hydroxymethyl)phenyl]methoxy}cyclopentyloxy)oxolan-3-ol (65ab)



Cleavage from resin **64ab** (0.75 g) with 50% TFA (procedure 5) gave after semi-preparative HPLC purification **65** as a colourless oil (15 mg, 24% yield, 5 steps from **44**). Mixture of two pairs of enantiomers in a 1:1 ratio. Separation of the diastereoisomers could not be achieved by RP-HPLC.

RP-HPLC (λ_{220}, gradient 1): t_R = 10.9 min.

δ_H (400 MHz, $CDCl_3$): 7.34 (s, 4H, ArCH-13,14), 4.66 (s, 2H, H-16), 4.52 (2 AB quartet, 2H, H-11) [diastereoisomer 1: 4.60 (d, J_{AB} = 12.0 Hz, H_A), 4.45 (d, J_{AB} = 12.0 Hz, H_B); diastereoisomer 2: 4.58 (d, J_{AB} = 11.7, H_A), 4.47 (d, J_{AB} = 11.7 Hz, H_B)], 4.21 (ddd, 1H, J = 4.0, 1.6, 1.6 Hz, H-1), 4.11 (ddd, 1H, J = 4.0, 2.0, 2.0 Hz, H-1), 4.04-3.81 (m, 5H, H-2,6,7 + H-3,5), 3.70-3.60 (m, 2H, H'-3,5), 2.10-1.90 (m, 2H, H-8,10), 1.74-1.64 (m, 2H, H-9), 1.65-1.50 (m, 2H, H'-8,10).

δ_C (100 MHz, $CDCl_3$): 140.6 (ArC-15), 137.90, 137.89 (ArC-12), 128.37, 128.35 (ArCH-13), 127.48, 127.40 (ArCH-14), 85.0, 84.9 (CH-2), 84.8, 84.7 (CH-7), 84.1, 84.0 (CH-6), 76.0, 75.8 (CH-1), 73.9, 73.7 (CH_2), 72.1 (CH_2), 71.5, 71.3 (CH_2-11), 70.7 (CH_2), 65.2 (CH_2-16), 30.7, 30.4 (CH_2-10), 30.0, 29.8 (CH_2-8)., 21.3, 20.9 (CH_2-9).

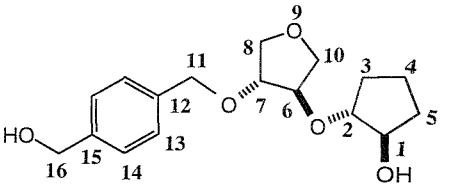
IR: υ_{max} 3367 (OH) cm^{-1}.

HRMS (EI): *m/z* 290.1504 ([M-H_2O]$^+$, $C_{18}H_{24}O_3$ requires 290.1518).

Resin (64ba)

RP-HPLC (λ_{220}, gradient 1): t_R = 6.4 min (7%), t_R = 7.3 min (**4**, 14%), t_R = 8.2 min (**9a**, 7%), t_R = 10.1 min (**9b**, 15%), t_R = 10.5 min (**65ba**, 48%), t_R = 10.9 min (4%), t_R = 11.6 min (5%).

2-(4-{[4-(hydroxymethyl)phenyl]methoxy}oxolan-3-yloxy)cyclopentan-1-ol (65ba)



Cleavage of resin **65ba** (0.90 g) with 50% TFA (procedure 5) gave after semi-preparative RP-HPLC purification **65ba** as a colourless oil (14 mg, 19% yield, 5 steps from **44**). Mixture of two pairs of enantiomers in a 1:1 ratio. Separation of the diastereoisomers could not be achieved by RP-HPLC.

RP-HPLC (λ_{220}, gradient 1): t_R = 10.5 min.

δ_H (400 MHz, $CDCl_3$): 7.40 (s, 4H, ArH-13,14), 4.68 (s, 2H, H-16), 4.63-4.50 (2 AB qua, 2H, H-11) [diastereoisomer 1: 4.60 (d, J_{AB} = 12.0 Hz, H_A), 4.52 (d, J_{AB} = 12.0 Hz, H_B); diastereoisomer 2: 4.59 (d, J_{AB} = 12.0 Hz, H_A), 4.55 (d, J_{AB} = 12.0 Hz, H_B)], 4.10-3.92 (m, 4H, H-6,7,1+ H-8/10) [m= 4.10-4.02 (m, H-8/10), 4.04-3.98 (m, H-8/10), 4.04-3.96 (m, H-1), 3.98-3.92 (m, H-8/10)], 3.80-3.56 (m, 4H, H-2 + H-8,10) [m= 3.80 (dd, J = 2.0, 9.5 Hz, H-8/10), 3.77 (dd, 1H, J = 2.0, 9.5 Hz, H'-8/10), 3.70 (dd, 1H, J = 2.0, 9.5 Hz, H'-8/10), 3.67-3.59 (m, 1H, H-2)], 2.00-1.58 (m, 2H, H-3,5), 1.74-1.62 (m, 2H, H-4), 1.58-1.45 (m, 2H, H'-3,5).

δ_C (100 MHz, $CDCl_3$): 140.89, 140.84 (ArC-15), 137.39, 137.35 (ArC-12), 128.35, 128.26 (ArCH-13), 127.46, 127.39 (ArCH-14), 86.0, 85.8 (CH-2), 83.2 (CH-7), 82.3, 82.0 (CH-6), 77.6 (CH-1), 72.3, 72.0 (CH_2-8/10), 71.8, 71.5 (CH_2-8/10), 70.7 (CH_2-11), 65.1 (CH_2-16), 32.08, 32.01 (CH_2-5), 29.9, 29.6 (CH_2-3), 20.5, 20.3 (CH_2-4).

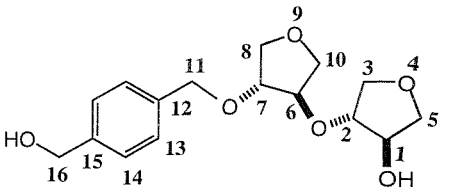
IR: υ_{max} 3366 (OH) cm^{-1}.

HRMS (EI): *m/z* 290.1487 ($[M-H_2O]^+$, $C_{17}H_{22}O_4$ requires 290.1518).

Resin (64bb)

RP-HPLC (λ_{220}, gradient 1): t_R = 6.4 min (6%), t_R = 7.3 min (**4**, 17%), t_R = 8.2 min (**9b**, 28%), t_R = 8.9 min (**65bb**, 49%).

4-(4-{[4-(hydroxymethyl)phenyl]methoxy}oxolan-3-yloxy)oxolan-3-ol (65bb)



Cleavage of resin **64bb** (1g) with 50% TFA (procedure 5) gave after semi-preparative HPLC purification **65bb** as a colourless oil (14 mg, 28% yield, 5 steps from **44**). Mixture of two pairs of enantiomers in a 1:1 ratio. Separation of the diastereoisomers could not be achieved by RP-HPLC.

RP-HPLC (λ_{220}, gradient 1): t_R = 8.9 min.

δ_H (400 MHz, $CDCl_3$): 7.36 (m, 4H, ArH) [m = diastereoisomer 1: 7.38 (d, *J* = 8.5 Hz, ArH), 7.34 (d, *J* = 8.5 Hz); diastereoisomer 2: 7.37 (d, *J* = 8.5 Hz), 7.35 (d, *J* = 8.5 Hz)] , 4.66 (s, 2H, H-16), 4.55 (m, 2H, H-11), 4.14-3.60 (m, 16H, H-1,2,6,7+ H-3,5,8,10).

δ_C (100 MHz, $CDCl_3$): 141.0, 140.9 (ArC-15), 137.3, 137.1 (ArC-12), 128.5, 128.4 (ArCH-13), 127.2, 127.5 (ArCH-14), 84.1, 84.0 (CH), 83.1, 82.9 (CH), 82.5, 82.3 (CH), 75.6, 75.5 (CH), 73.9, 73.8 (CH_2), 71.85, 71.81 (CH_2), 71.77 (CH_2), 71.74, 71.72 (CH_2), 65.0 (CH_2-16).

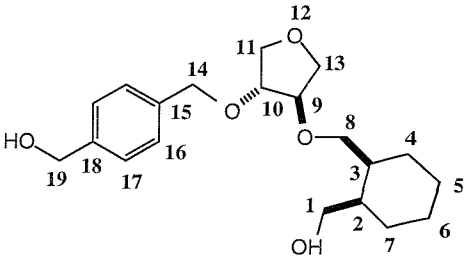
IR: 3355 (OH) cm^{-1}.

HRMS (EI): 292.1285 ($[M-H_2O]^+$, $C_{16}H_{20}O_5$ requires 292.1310).

Resin (64bh)

RP-HPLC (λ_{220}, gradient 1): t_R = 6.3 min (7%), t_R = 7.3 min (**4**, 20%), t_R = 8.2 min (**9b**, 4%), t_R = 10.9 min (15%), t_R = 11.6 min (7%), t_R = 12.8 min (**65bh**, 18%), t_R = 13.0 min (**65bh**, 22%), t_R = 13.1 min (7%).

{4- [(4-{[2-(hydroxymethyl) cyclohexyl] methoxy} oxolan-3-yloxy) methyl] phenyl} methan-1-ol (65bh)



Cleavage of resin **64bh** (0.83 g) with 50% TFA (procedure 5) gave after semi-preparative RP-HPLC purification **65** as a colourless oil. Mixture of two pairs of enantiomers in a 1:1 ratio. The diastereoisomers were separated [diastereoisomer 1 (7.4 mg) and diastereoisomer 2 (5.7 mg), 17% yield, 5 steps from **44**].

Diastereoisomer 1 (2 enantiomers)

RP-HPLC (λ_{220}, gradient 1): t_R = 12.8 min.

δ_H (400 MHz, $CDCl_3$): 7.41 (d, 2H, *J* = 8.2 Hz, ArH), 7.38 (d, 2H, *J* = 8.2 Hz, ArH), 4.74 (s, 2H, *J* = 8.2 Hz, ArH), 4.74 (s, 2H, H-19), 4.64 (d, 1H, J_{AB} = 4.6 Hz, H_A-14), 4.58 (d, 1H, J_{AB} = 4.6 Hz, H_B-14), 4.06 (m, 1H, *J* = Hz, H-9/10), 4.01-3.95 (overlapping m, 4H, H-11,13 + H9/10), 3.64 (dd, 1H, *J* = 9.3, 8.2 Hz, H-8), 3.54 (dd, 1H, *J* = 11.5, 8.2 Hz, H-1), 3.50 (dd, 1H, *J* = 11.5, 10.3 Hz, H'-1), 3.96 (dd, 1H, *J* = 9.3, 4.5 Hz, H'-8), 2.10 (m, 1H, H-3), 1.89 (ddddd, *J* = 4.0, 4.0, 6.2, 8.2, 8.2 Hz, H-2), 1.70-1.30 (m, 8H, H-4,5,6,7).

δ_C (100 MHz, $CDCl_3$): 140.8 (ArC-18), 137.1 (ArC-15), 128.2 (ArCH-16), 127.3 (ArCH-17), 83.8 (CH-9/10), .82.4 (CH-9/10), 71.6 (CH_2-11/13), 71.4 (CH_2-14), 71.3 (CH_2-11/13), 70.8 (CH_2-8), 65.1 (CH_2-19), 64.6 (CH_2-1), 40.6 (CH-2), 36.3 (CH-3), 28.5 (CH_2), 25.9 (CH_2), 24.6 (CH_2), 23.5 (CH_2).

IR: 3372 (OH) cm^{-1}.

HRMS (EI): *m/z* 368.2426 ($[M+NH_4]^+$, $C_{20}H_{34}O_5N$ requires 368.2437).

Diastereoisomer 2 (2 enantiomers)

RP-HPLC (λ_{220}, gradient 1): t_R = 13.0 min.

δ_H (400 MHz, $CDCl_3$): 7.38 (d, 2H, *J* = 8.3 Hz, ArH), 7.35 (d, 2H, *J* = 8.3 Hz, ArH), 4.70 (s, 2H, H-19), 4.61 (d, 1H, J_{AB} = 12.0 Hz, H_A-14), 4.53 (d, 1H, J_{AB} = 12.0 Hz, H_B-14), 4.05-3.92 (overlapping m, 4H, H-9,10,11,13), 3.82 (dd, 1H, *J* = 2.2, 9.8 Hz, H'-11/13), 3.78 (dd, 1H, *J* = 4.7, 12.0 Hz, H'-11/13), 3.54 (dd, 1H, *J* = 8.3, 9.0 Hz, H-8), 3.46 (s (AB quartet degenerated), 1H, H-1), 3.44 (s (AB quartet

degenerated), 1H, H'-1), 3.34 (dd, 1H, J = 9.0, 4.5 Hz, H'-8), 2.04 (m, 1H, H-3), 1.83 (m, 1H, H-2), 1.63-1.26 (m, 8H, H-4,5,6,7).

δ_C (100 MHz, $CDCl_3$): 140.8 (ArC-18), 137.1 (ArC-15), 128.3 (ArCH-16), 127.3 (ArCH-17), 84.0 (CH-9), 82.3 (CH-10), 71.7 (CH_2-11/13), 71.4 (CH_2-11/13), 71.4 (CH_2-14),70.9 (CH_2-8), 65.1 (CH_2-19), 64.6 (CH_2-1), 40.6 (CH_2-2), 36.4 (CH_2-3), 28.5 (CH_2), 25.9 (CH_2), 24.6 (CH_2), 23.5 (CH_2).

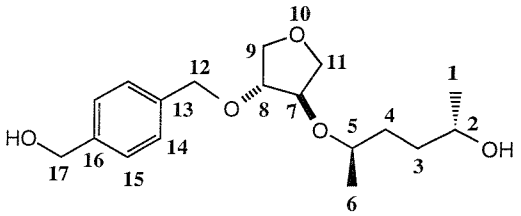
IR: 3372 (OH) cm^{-1}.

HRMS (EI): *m/z* 368.2416 ($[M+NH_4]^+$, $C_{20}H_{34}O_5N$ requires 368.2437).

Resin (64bi)

RP-HPLC (λ_{220}, gradient 1): t_R = 6.3 min (6%), t_R = 7.3 min (**4**, 15%), t_R = 8.2 min (**9b**, 12%), t_R = 10.8 min (**65bi**, 22%), t_R = 10.9 min (**65bi**, 39%), t_R = 11.6 min (6%).

5-((3S,4S)-4-{[4-(hydroxymethyl)phenyl]methoxy}oxolan-3-yloxy)(2S,5R)hexan-2-ol and 5-((3R,4R)-4-{[4-(hydroxymethyl)phenyl]methoxy}oxolan-3-yloxy)(2S,5R) hexan-2-ol (65bi)



Cleavage from resin **64bi** (0.82 g) with 50% TFA (procedure 5) gave after semi-preparative RP-HPLC purification **65bi** as a colourless oil. Mixture of two diastereoisomers in a 1:1 ratio. The diastereoisomers were separated [diastereoisomer 1 (10 mg) and diastereoisomer 2 (14.3 mg), 35% yield, 5 steps from **44**].

Diastereoisomer 1 (single enantiomer)

RP-HPLC (λ_{220}, gradient 1): t_R = 10.8 min.

δ_H (400 MHz, $CDCl_3$): 7.35 (d, 1H, J = 8.2 Hz, ArH), 7.33 (d, 1H, J = 8.2 Hz, ArH), 4.68 (s, 2H, H-17), 4.60 (d, 1H, J_{AB} = 12.0 Hz, H_A-12), 4.50 (d, 1H, J_{AB} = 12 Hz, H_B-12), 4.06-3.99 (m overlapping, 2H, H-7+ H-11), 3.95-3.90 (m overlapping, 2H, H-8 + H-9), 3.84 (dd, 1H, J = 3.7, 11.5 Hz, H'-9), 3.75-3.65 (m overlapped, 1H, H-2), 3.67 (dd, 1H, J = 8.5, 1.7 Hz, H'-11), 3.43 (qdd, 1H, J = 6.2, 6.2, 6.2 Hz, H-5), 1.55-1.20 (m, 4H, H-3,4), 1.15 (d, J = 6.6 Hz, 3H, H-1), 1.13 (d, J = 6.0 Hz, 3H, H-6).

δ_C (100 MHz, $CDCl_3$): 140.9 (ArC-16), 137.2 (ArC-13), 128.3 (ArCH-14), 127.3 (ArCH-15), 82.8 (CH-8), 81.2 (CH-7), 74.8 (CH-5), 72.6 (CH_2-11), 71.5 (CH_2-9), 71.2 (CH_2-12), 68.1 (CH-2), 65.1 (CH_2-17), 35.2 (CH_2-3), 33.1 (CH_2-4), 23.6 (CH_3-1), 20.1 (CH_3-6).
HRMS (EI): *m/z* 325.2008 ($[M+H]^+$, $C_{18}H_{29}O_5$ requires 325.2015).

Diastereoisomer 2 (single enantiomer)

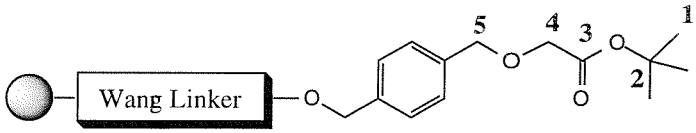
RP-HPLC (λ_{220}, gradient 1): t_R = 10.9 min.

δ_H (400 MHz, $CDCl_3$): 7.36 (d, 2H, *J* = 8.5 Hz, ArH), 7.33 (d, 2H, *J* = 8.5 Hz, ArH), 4.68 (s, 2H, H-17), 4.58 (d, 1H, J_{AB} = 11.3 Hz, H_A-12), 4.54 (d, 1H, J_{AB} = 11.3 Hz, H_B-12), 4.07 (ddd, 1H, *J* = 4.5, 1.5, 1.5 Hz, H-7), 3.99 (ddd, 1H, J = 4.5, 1.5, 1.5 Hz, H-8), 3.95 (dd, 1H, *J* = 9.7, 0.7 Hz, H-11), 3.94 (dd, 1H, *J* = 9.5, 0.7 Hz, H-9), 3.82 (dd, 1H, *J* = 9.5, 2.0 Hz, H'-9), 3.77 (m (overlapped by other signals), 1H, H-2), 3.75 (dd, 1H, *J* = 9.7, 2.2 Hz, H'-11), 3.50 (m, 1H, H-5), 1.68-1.40 (m, 4H, H-3,4), 1.18 (d, 3H, *J* = 6.2 Hz, H-1), 1.15 (d, 3H, *J* = 6.2 Hz, H-6).

δ_C (100 MHz, $CDCl_3$): 140.7 (ArC-16), 137.4 (ArC-13), 128.1 (ArCH-14), 127.2 (ArCH-15), 83.8 (CH-8), 80.9 (CH-7), 74.5 (CH-5), 71.7 (CH_2-12), 71.6 (CH_2-9/11), 71.4 (CH_2-9/11), 68.1 (CH-2), 65.1 (CH_2-17), 35.2 (CH_2-3), 33.1 (CH_2-4), 23.6 (CH_3-1), 20.1 (CH_3-6).
HRMS (EI): *m/z* 325.2001 ($[M+H]^+$, $C_{18}H_{29}O_5$ requires 325.2015).

5.3.1 Introduction of the terminal carboxylic acid

Resin (74)

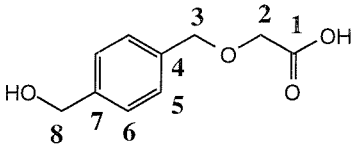


Resin **46** (0.5 g, 0.13 mmol) was washed under N_2 with dry THF (5 x 5mL) then suspended in dry THF (1 mL). *t*-BuOK (1M in THF, 0.65 mL, 0.65 mmol) was added. The resin was shaken for 1 h then filtered under N_2. Dry DMF (3 mL) was added followed by *t*-butyl bromoacetate (192 µL, 1.3 mmol) and the resin was shaken overnight. The resin was filtered, washed with DMF (5 x 5 mL), DCM (5 x 5 mL), MeOH (5 x 5 mL) and dried *in vacuo*.

RP-HPLC (λ_{220}, gradient 1): t_R = 7.1 min (**4**, 28%), t_R = 8.4 min (**75**, 53%), t_R = 9.2 min (7%), t_R = 11.6 min (12%).

δ_C (100 MHz, d^6-benzene): 159.2, 130.4, 115.0, 73.1, 72.1, 70.1, 68.0, 64.6, 41.2 (br, resin), 28.3 (CH_3-1).

2-{[4-hydroxymethyl)phenyl]methoxy}acetic acid (75)



Cleavage from resin **74** (0.45 g) with 50% TFA (procedure 5) gave after semi preparative RP-HPLC purification **75** as a white solid (5 mg, 25%, 2 steps from **44**).

mp = 84-85 °C.

RP-HPLC (λ_{220}, gradient 1): t_R = 8.4 min.

δ_H (400 MHz, CD_3CN/D_2O 9:1): 7.32 (s, 4H, ArH-5,6), 4.55 (s, 4H, H-3,8), 4.07 (s, 2H, H-2).

δ_C (100 MHz, CD_3CN/D_2O 9:1): 172.0, (C-1), 141.7 (ArC), 136.7 (ArC), 128.2 (ArCH), 127.0 (ArCH), 72.7 (CH_2-3), 66.9 (CH_2-2), 63.5 (CH_2-8).

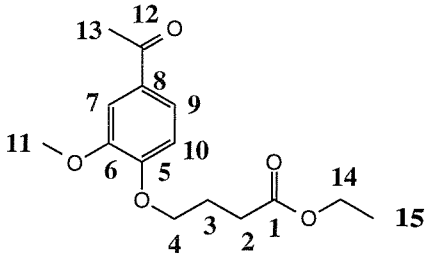
IR: υ_{max} 3500 (OH alcohol), 2600 (br, OH acid), 1731 (C=O) cm^{-1}.

MS: not detected under the conditions used for HRMS.

5.4 Experimental chapter 4

5.4.1 Synthesis of the dual linker system

Ethyl 4-{[4-acetyl-2-(methyloxy)phenyl]oxy}butanoate (76)[210c]



To a solution of acetovanillone **75** (10.0 g, 60 mmol) in CH_3CN (125 mL) was added K_2CO_3 (16.5 g, 12 mmol) and KI (0.200 g, 1.2 mmol). Ethyl 4-bromobutyrate (10.3 mL, 72 mmol) was added dropwise and the mixture was refluxed for 6 h. After cooling, the inorganic salts were removed by filtration and washed with EtOAc (3 x 25 mL). Following removal of the solvents *in vacuo* the crude product was recrystallized from EtOAc/PE to afford **76** as a white solid (11.7 g, 70% yield). Experimental data were in agreement with reported literature data.[210c]

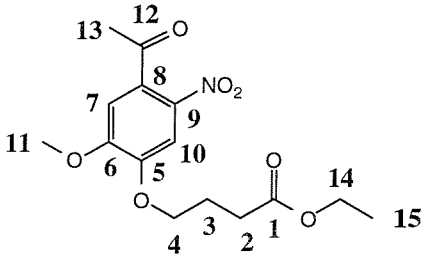
TLC: R_f = 0.33 (Hexane/EtOAc 7:3).

δ_H (300 MHz, $CDCl_3$): 7.54 (dd, 1H, *J* = 2.2, 8.4 Hz, ArH-9), 7.51 (d, 1H, *J* = 2.2 Hz, ArH-7), 6.89 (d, 1H, *J* = 8.4 Hz, ArH-10), 4.14 (qua, 2H, *J* = 6.2 Hz, H-14), 4.13 (t, 2H, *J* = 6.6 Hz, H-4) 3.90 (s, 3H, H-11), 2.55 (s, 3H, H-13), 2.53 (t, 2H, *J* = 6.6 Hz, H-2), 2.20 (quin, 2H, *J* = 6.6 Hz, H-3), 1.25 (t, 3H, *J* = 7.3 Hz, H-15).

δ_C (75 MHz, $CDCl_3$): 196.8 (C-12), 173.0 (C-1), 152.6 (ArC-6), 149.2 (ArC-5), 130.4 (ArC-8), 123.3 (ArCH-9), 111.2 (ArCH-10), 110.4 (ArCH-7), 67.7 (CH_2-4), 60.4 (CH_2-14), 55.9 (CH_3-11), 30.5 (CH_2-2), 26.2 (CH_3-13), 24.2 (CH_2-3), 14.3 (CH_3-15).

IR: υ_{max} 1728 (C=O ester), 1667 (C=O ketone) cm^{-1}.

Ethyl 4-{[4-acetyl-2-(methyloxy)-5-nitrophenyl] oxy}butanoate (77) [210a,210b]



Fuming nitric acid (2 mL, 47 mmol) was added dropwise at -10 °C to a solution of **76** (1.0 g, 3.57 mmol) in dry DCM (50 mL). The reaction was stirred at -10 °C for 2 h.

The mixture was poured into ice/water (25 mL) and extracted with DCM (3 x 25 mL). The combined organics were washed with saturated $NaHCO_3$ (2 x 25 mL), brine (25 mL), dried over $MgSO_4$ and evaporated *in vacuo*. The crude product (1.1 g) was carried through to the next step without further purification. NMR analysis of the crude product indicated the presence of the *ipso* substitution by-product in 20% yield. A small sample was purified further by chromatography on silca gel (hexane/EtOAc 7:3) for characterisation purposes and gave **77** as a pale yellow solid.

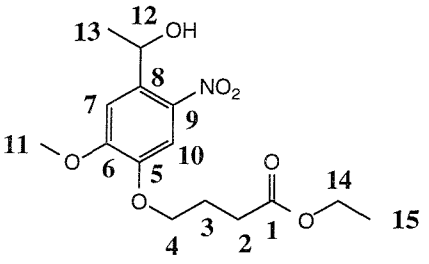
TLC: $R_f = 0.23$ (hexane/EtOAc 7:3).

δ_H (300 MHz, $CDCl_3$): 7.59 (s, 1H, ArH-10), 6.74 (s, 1H, ArH-7), 4.14 (t, 2H, J = 7.3 Hz H-4), 4.14 (qua, 2H, J = 6.2 Hz, H-14), 3.94 (s, 3H, H-11), 2.53 (t, 2H, J = 7.3 Hz, H-2), 2.48 (s, 3H, H-13), 2.19 (quin, 2H, J = 6.6 Hz, H-3), 1.28 (t, 3H, J = 7.3 Hz, H-15).

δ_C (75 MHz, $CDCl_3$): 200.2 (C-12), 172.9 (C-1), 154.4 (ArC-6), 148.9 (ArC-5), 138.4 (ArC-9), 132.9 (ArC-8), 108.8 (ArCH), 108.1 (ArCH), 68.6 (CH_2-4), 60.7 (CH_2-14), 56.7 (CH_3-11), 30.6 (CH_2-2), 30.5 (CH_3-13), 24.3 (CH_2-3) 14.3 (CH_3-15).

IR: υ_{max} 1728 (C=O ester), 1704 (C=O ketone), 1575, 1514 (NO_2) cm^{-1}.

Ethyl 4-{[4-(1-hydroxyethyl)-2-(methyloxy)-5-nitrophenyl] oxy} butanoate (78)[210a,210b]



To a solution of **77** (5.29 g, 16 mmol) in THF (160 mL) and EtOH (30 mL) was added $NaBH_4$ (0.615 g, 16 mmol) portionwise at 0 °C. The mixture was stirred at room temperature for 6 h. The reaction mixture was quenched by addition of 2M HCl in EtOH (25 mL). The solvents were removed *in vacuo*. The residue was resuspended in H_2O (35 mL) and the solution acidified to pH 3 with 2M $KHSO_4$, then extracted with EtOAc (3 x 50 mL). The combined organics were washed with brine (50 mL), dried over $MgSO_4$ and evaporated *in vacuo*. The crude product was recrystallised from EtOAc to give **78** as a yellow solid (4.50 g, 86% yield).

TLC: R_f = 0.12 (Hexane/EtOAc 7:3).

mp: 70-72 °C (EtOAc).

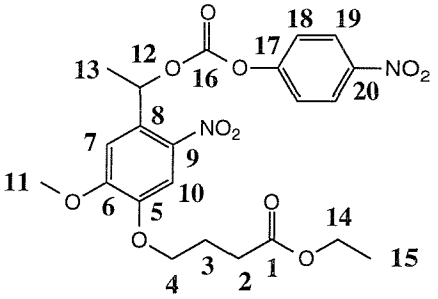
δ_H (300 MHz, $CDCl_3$): 7.54 (s, 1H, ArH-10), 7.29 (s, 1H, ArH-7), 5.53 (qua, 1H, *J* = 6.2 Hz, H-12), 4.14 (qua, 2H, *J* = 7.0 Hz, H-14), 4.09 (t, 2H, *J* = 6.6 Hz, H-4), 3.96 (s, 3H, H-11), 2.52 (t, 2H, *J* = 7.3 Hz, H-2), 2.16 (quin, 2H, *J* = 6.6 Hz, H-3), 1.42 (d, 3H, *J* = 6.5 Hz, H-13), 1.25 (t, 3H, *J* = 7.3 Hz, H-15).

δ_C (75 MHz, $CDCl_3$): 173.1 (C-1), 154.2 (ArC-6), 147.0 (ArC-5), 139.6 (ArC-9), 137.1 (ArC-8), 109.1 (ArCH-7), 108.8 (ArCH-10), 68.4 (CH_2-4), 65.8 (CH-12), 60.7 (CH_2-14), 56.4 (CH_3-11), 30.7 (CH_2-2), 24.4 (CH_3-13), 24.1 (CH_2-3), 14.3 (CH_3-15).

IR: υ_{max} 3287 (OH), 1722 (C=O ester), 1502 (NO_2) cm^{-1}.

MS (CI, NH_3): *m/z* (%) 345 ($[M+NH_4]^+$, 20), 310 ($[M+H-H_2O]^+$, 100), 280 (20), 103 (90).

Ethyl 4-({2-(methyloxy)-5-nitro-4-[1-({[4-nitrophenyl)oxy]carbonyl} oxy)ethyl] phenyl} oxy) butanoate (79)



4-Nitrophenyl chloroformate (1.93 g, 9.5 mmol) in dry DCM (25 mL) was added dropwise to a solution of **78** (2.80 g, 8.7 mmol) and pyridine (1 mL, 13 mmol) in dry DCM (50 mL) at 0 °C. The reaction mixture was stirred at room temperature overnight. The solvent was evaporated *in vacuo*. The crude compound was purified by chromatography on silica gel (PE/EtOAc 8:2 to 7:3) to give **79** as pale yellow solid (3.32 g, 89% yield).

TLC: R_f = 0.47 (PE/EtOAc 7:3).

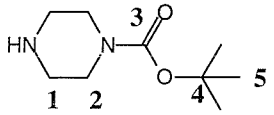
δ_H (300 MHz, $CDCl_3$): 8.25 (d, 2H, *J* = 9.2 Hz, ArH-19), 7.60 (s, 1H, ArH-10), 7.34 (d, 2H, *J* = 9.2 Hz, ArH-18), 7.10 (s, 1H, ArH-7), 6.52 (qua, 1H, *J* = 6.2 Hz, H-12), 4.15 (qua, 2H, *J* = 7.3 Hz, H-14), 4.12 (t, 2H, *J* = 6.9 Hz, H-4), 3.99 (s, 3H, H-11), 2.54 (t, 2H, *J* = 6.9 Hz, H-2), 2.21 (quin, 2H, *J* = 6.2 Hz, H-3), 1.77 (d, 3H, *J* = 6.2 Hz, H-13), 1.25 (t, 3H, *J* = 7.3 Hz, H-15).

δ_C (75 MHz, $CDCl_3$): 173.0 (C-1), 155.4 (C-16), 154.3 (ArC-17), 151.5 (ArC-6), 147.8 (ArC-20), 145.5 (ArC-5), 139.9 (ArC-9), 131.4 (ArC-8), 125.4 (ArCH-19) 121.8 (ArCH-18), 109.0 (ArCH-7), 108.1 (ArCH-10), 73.9 (CH-12), 68.4 (CH_2-4). 60.5 (CH_2-14), 56.6 (CH_3-11), 30.7 (CH_2-2), 24.3 (CH_2-3), 22.1 (CH_3-13), 14.3 (CH_3-15).

IR: υ_{max} 1755 (C=O carbamate), 1725 (C=O ester), 1516 (NO_2) cm^{-1}.

MS (ES +ve): *m/z* (%) 510.6 ($[M+NH_4]^+$, 100), 515.5 ($[M+Na]^+$, 20), 531.4 ($[M+K]^+$, 5), 556.5 ($[M+CH_3CN+Na]^+$, 5), 1002.8 ($[2M+NH_4]^+$, 50), 1007.8 ($[2M+Na]^+$, 30).

_N_-tert-butoxycarbonyl piperazine (80)[212]



A solution of Boc_2O (5.0 g, 23 mmol) in dry DCM (100 mL) was added dropwise over 1 h to an ice cold solution of piperazine (5.9 g, 68 mmol) in dry DCM (50 mL). The reaction mixture was stirred at room temperature overnight. The solvent was removed *in vacuo*. The residue was taken up in water (30 mL) and extracted with EtOAc (3 x 50 mL). The combined organics were washed with brine (2 x 50 mL), dried over $MgSO_4$ and removed *in vacuo*. The crude product was purified by chomatography (DCM/MeOH 9:1 to 8:2) to give **80** as a white waxy solid (3.24 g, 75% yield).

TLC: R_f = 0.29 (DCM/MeOH 9:1).

mp = 45 °C (EtOAc) [Lit[212] 45-46 °C (EtOAc/Et_2O 1:1)].

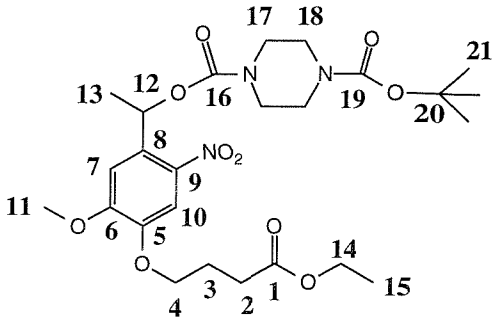
δ_H (300 MHz, $CDCl_3$): 3.35 (t, 4H, *J* = 5.1 Hz, H-2), 2.75 (t, 4H, *J* = 5.1 Hz, H-1) , 2.14 (1H, br s, NH), 1.41 (s, 9H, H-5).

δ_C (75 MHz, $CDCl_3$): 154.9 (C-3), 79.7 (C-4), 45.9 (CH_2), 45.0 (broad, CH_2), 28.5 (CH_3-5).

IR: υ_{max} 3325 (NH), 1686 (C=O Boc) cm^{-1}.

MS (ES +ve): *m/z* (%) 187.2 ($[M+H]^+$, 100), 228.3 ($[M+CH_3CN+H]^+$, 60), 373.7 ($[2M+H]^+$, 20).

1-(1,1-dimethylethyl)4-{1-[4-{4-(ethyloxy)-4-oxybutyl] oxy} -5-(methyloxy) -2-nitrophenyl} ethyl} hexahydro-1,4-pyrazine dicarboxylate (81)



To a solution of **79** (3.23 g, 6.5 mmol) in CH_3CN (60 mL) and Et_3N (1.35 mL, 7.2 mmol) was added dropwise a solution of **80** (1.34 g, 7.2 mmol) in CH_3CN (30 mL). The mixture was heated at 50 °C overnight. After cooling, the solvent was removed *in vacuo*. The residue was taken up in EtOAc (60 mL) and washed with saturated $NaHCO_3$ (2 x 20 mL), brine (20 mL), dried over $MgSO_4$ and evaporated *in vacuo*. The crude product was purified by chromatography on silica gel (PE/EtOAc 7:3) to give **81** as a green solid (2.58 g, 75% yield).

TLC: R_f = 0.23 (PE/EtOAc 7:3).

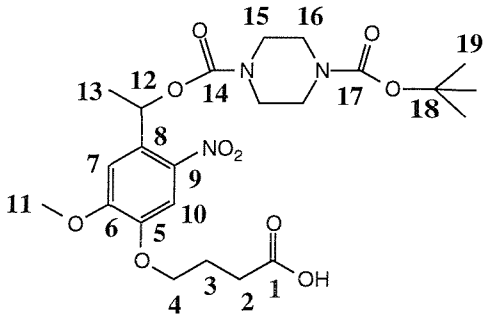
δ_H (300 MHz, $CDCl_3$): 7.56 (s, 1H, ArH-10), 6.93 (s, 1H, ArH-7), 6.38 (qua, 1H, *J* = 6.6 Hz, H-12), 4.15 (qua, 2H, *J* = 6.9 Hz, H-14), 4.10 (t, 2H, *J* = 6.2 Hz, H-4), 3.92 (s, 3H, H-11), 3.60-3.30 (m broad, 8H, H-17,18), 2.53 (t, 2H, *J* = 7.3 Hz, H-2), 2.17 (quin, 2H, *J* = 6.6 Hz, H-3), 1.63 (d, 3H, *J* = 6.6 Hz, H-13), 1.46 (s, 9H, H-21), 1.26 (t, 3H, *J* = 6.9 Hz, H-15).

δ_C (75 MHz, $CDCl_3$): 173.0 (C-1), 154.7 (C-19), 154.1 (C-16), 153.8 (ArC-6), 147.1 (ArC-5), 139.8 (ArC-9), 133.6 (ArC-8), 108.9 (ArCH-7), 107.9 (ArCH-10), 80.3 (C-20), 69.7 (CH-12), 68.2 (CH_2-4), 60.5 (CH_2-14), 56.2 (CH_3-11), 43.5 (broad CH_2-17,18), 30.5 (CH_2-2), 28.3 (CH_3-21), 24.2 (CH_2-3), 22.1 (CH_3-13), 14.2 (CH_3-15).

IR: υ_{max} 1729 (C=O ester), 1689 (C=O Boc), 1510 (NO_2) cm^{-1}.

MS (ES +ve): *m/z* (%) 540.7 ($[M+H]^+$, 10), 557.7 ($[M+NH_4]^+$, 100), 562.7 ($[M+Na]^+$, 70).

4-{[4-(1-{[(4- {[(1,1-dimethylethyl)oxy]oxy}carbonyl} hexahydro -1-pyrazinyl) carbonyl] oxy}ethyl) -2-(methyloxy) -5-nitrophenyl] oxy} butanoic acid (82)



To a solution of **81** (1.07 g, 2 mmol) in dioxane/water 1:1 (20 mL) was added 2 M NaOH (2 mL, 4 mmol). The reaction mixture was left stirring at room temperature for 1 h then concentrated *in vacuo*. The reaction mixture was acidified to pH 4 with 2M $KHSO_4$. The reaction mixture was saturated with NaCl and extracted with EtOAc (2 x 75 mL). The combined organics were washed with brine and evaporated *in vacuo*. The crude product was recrystallised from EtOAc to give **82** as a pale yellow solid (0.97 g, 95% yield).

TLC: R_f= 0.21 (DCM/MeOH 9:1).

δ_H (300 MHz, $CDCl_3$): 7.56 (s, 1H, ArH), 6.84 (s, 1H, ArH), 6.38 (qua, 1H, *J* = 6.2 Hz, H-12), 4.10 (t, 2H, *J* = 6.2 Hz, H-4), 3.92 (s, 3H, H-11), 3.41 (m broad, 8H, H-14,15), 2.58 (t, 2H, *J* = 6.9 Hz, H-2), 2.16 (quin, 2H, *J* = 6.6 Hz, H-3), 1.63 (d, 3H, *J* = 6.2 Hz, H-13), 1.46 (s, 9H, H-18).

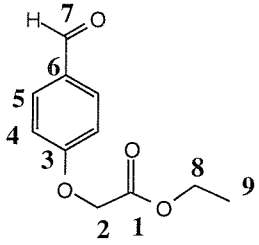
δ_C (75 MHz, $CDCl_3$): 177.7 (C-1), 154.6 (C-16/13), 154.2 (C-16/13), 153.8 (ArC-6), 147.1 (ArC-5), 139.8 (ArC-9), 133.5 (ArC-8), 109.0 (ArCH-7), 107.9 (ArCH-10), 80.5 (C-17), 69.8 (CH-12), 67.0 (CH_2-4), 56.2 (CH_3-11), 43.6 (broad, CH_2-15,16), 30.1 (CH_2-2), 28.3 (CH_3-19), 23.9 (CH_2-3), 22.0 (CH_3-13).

IR: υ_{max} 3110 (br, OH acid), 1727 (C=O acid), 1693 (C=O) cm^{-1}.

MS (ES +ve): *m/z* (%) 512.2 ($[M+H]^+$, 5), 529.3 ($[M+NH_4]^+$, 70) 534.3 ($[M+Na]^+$, 65), 550.2 ($[M+K]^+$, 15), 1040.4 ($[2M+NH_4]^+$, 100), 1045.3 ($[2M+Na]^+$, 50), 1061.2 ($[2M+K]^+$, 10).

HRMS (FAB): *m/z* 511.2166 ($[M]^+$, $C_{23}H_{33}O_{10}N_3$ requires 511.2165).

Ethyl-(4-formyl-1-phenoxy) ethanoate (84)[234]



K_2CO_3 (1.30 g, 0.49 mmol) and KI (0.136 g, 0.082 mmol) were added to a solution of 4-hydroxybenzaldehyde **83** (5.0 g, 41 mmol) in CH_3CN (50 mL). Ethyl bromoacetate (5.4 mL, 49 mmol) was added and the mixture was refluxed for 6 h. After cooling, the inorganic salts were removed by filtration and washed with EtOAc (3 x 20 mL). The filtrate was concentrated *in vacuo*. The crude product was recrystallised from EtOAc to give **84** a white solid (6.82 g, 80% yield).

mp = 43 °C (EtOAc) [lit.[234] 42 °C (EtOH)].

TLC: R_f = 0.42 (PE/EtOAc 7:3).

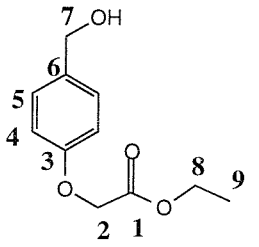
δ_H (300 MHz, $CDCl_3$): 9.88 (s, 1H, H-7), 7.83 (d, 2H, J = 9.2 Hz, ArH-5), 7.00 (d, 2H, J = 9.2 Hz, ArH-4), 4.70 (s, 2H, H-2), 4.27 (qua, 2H, J = 7.3 Hz, H-8), 1.29 (t, 3H, J = 7.3 Hz, H-9).

δ_C (75 MHz, $CDCl_3$): 190.8 (C-7), 168.2 (C-1), 162.7 (ArC-3), 132.1 (ArCH-5), 130.8 (ArC-6), 115.0 (ArCH-4), 65.3 (CH_2-2), 61.8 (CH_2-8), 14.2 (CH_3-9).

IR: υ_{max} 2988, 1750 (C=O ester), 1671 (C=O aldehyde) cm^{-1}.

MS (CI, ammonia): *m/z* (%) 226 ($[M+NH_4]^+$, 20), 208 ($[M^+]$, 100).

Ethyl-(4-hydroxymethyl-1-phenoxy)ethanoate (85)



$NaBH_4$ (0.272 g, 7.2 mmol) was added portionwise to a solution of **84** (5.0 g, 24 mmol) in EtOH (50 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 2 h then quenched by dropwise addition of 2M HCl in EtOH (5 mL). The solvent was removed *in vacuo*. The residue was taken up in EtOAc (75 mL), washed with brine (3 x 20 mL),

dried over $MgSO_4$ and evaporated *in vacuo*. The crude compound was recrystallised from EtOAc to give **85** as a white solid (4.33 g, 86% yield).

TLC: R_f = 0.37 (PE/EtOAc 7:3).

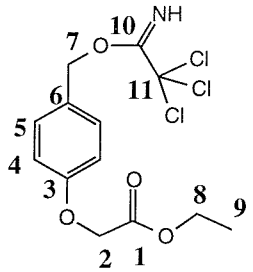
δ_H (300 MHz, $CDCl_3$): 7.25 (d, 2H, *J* = 8.8 Hz, ArH-5), 6.85 (d, 2H, *J* = 8.8 Hz, ArH-4), 4.60 (s, 2H, H-2), 4.58 (s, 2H, H-7), 4.25 (qua, 2H, *J* = 6.9 Hz, H-8), 2.1 (broad s, 1H, OH), 1.30 (t, 3H, *J* = 6.9 Hz, H-9).

δ_C (75 MHz, $CDCl_3$): 168.9 (C-1), 157.4 (ArC-3), 134.4 (ArC-6), 128.7 (ArCH-5), 114.8 (ArCH-4), 65.5 (CH_2-2), 64.9 (CH_2-7), 61.5 (CH_2-8). 14.3 (CH_3-9).

IR: 3321 (br, OH), 1739 (C=O ester) cm^{-1}.

MS (CI, NH_3): *m/z* (%) 212 ($[M+2]^+$, 50), 193 ($[M+H-H_2O]^+$, 100).

Ethyl 2-[(4-{[2,2,2-trichloroethanimidoyl) oxy] methyl} phenyl) oxy] ethanoate (87)



To a solution of **85** (2 g, 9.5 mmol) in dry ether (80 mL) was added DBU (284 µL, 1.9 mmol). The mixture was stirred at room temperature for 30 min then cooled to 0°C. A solution of CCl_3CN (1.1 mL, 14 mmol) in dry ether (20 mL) was added dropwise. The reaction mixture was stirred at room temperature for 4 h. The reaction mixture was diluted with ether (50 mL), washed with saturated $NaHCO_3$ (3 x 30 mL), brine (20 mL), dried over $MgSO_4$ and evaporated *in vacuo* to give **87** as a colourless oil (3.12 g, 92 % yield).

TLC: R_f = 0.55 (PE/EtOAc 7:3).

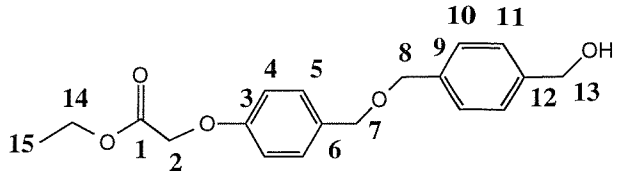
δ_H (300 MHz, $CDCl_3$): 8.37 (s, 1H, NH), 7.38 (d, 2H, *J* = 8.9 Hz, ArH-5), 6.92 (d, 2H, *J* = 8.9 Hz, ArH-4), 5.28 (s, 2H, H-7), 4.64 (s, 2H, H-2), 4.28 (q, 2H, *J* = 6.9 Hz, H-8), 1.31 (t, 3H, *J* = 6.9 Hz, H-9).

δ_C (75 MHz, $CDCl_3$): 168.9 (C-1), 162.7 (C-10), 158.0 (ArC-3), 129.8 (ArCH-5), 128.7 (ArC-6), 114.8 (ArCH-4), 70.6 (CH_2-2), 65.5 (CH_2-7), 61.5 (CH_2-8). 14.3 (CH_3-9).

IR: υ_{max} 1756 (C=O ester), 1662 (C=N) cm^{-1}.

MS: unstable under MS analysis conditions.

Ethyl 2-({4-[({[4-(hydroxymethyl)phenyl] methyl}oxy) methyl] phenyl} oxy) ethanoate (88)



To a solution of 1,4-benzenedimethanol **4** (1.94 g, 14 mmol) in dry THF (70 mL) was added $BF_3.OEt_2$ (0.2 M in THF, 1.4 mL, 0.28 mmol). The solution was cooled to 0 °C and a solution of **87** (1.0 g, 2.8 mmol) in dry DCM (140 mL) was added dropwise over 5 h. After completion of the reaction, the solvents were evaporated *in vacuo*. The crude product was purified by chromatography on silica gel to afford **88** as a white solid (0.78 g, 84% yield).

TLC: R_f = 0.33 (PE/EtOAc 6:4).

mp = 52 °C (EtOAc).

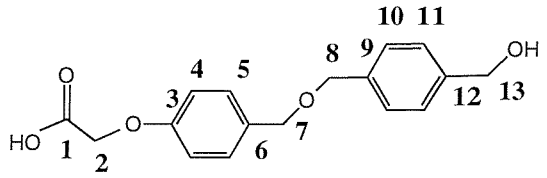
δ_H (300 MHz, $CDCl_3$): 7.34 (s, 4H, ArH-10,11), 7.29 (d, 2H, *J* = 8.8 Hz, ArH-5), 6.89 (d, 2H, *J* = 8.8 Hz, ArH-4), 4.67 (s, 2H, H-13), 4.62 (s, 2H, H-2), 4.53 (s, 2H, H-7), 4.48 (s, 2H, H-8), 4.27 (qua, 2H, *J* = 7.0 Hz, H-14), 1.30 (t, 3H, *J* = 7.0 Hz, H-15).

δ_C (75 MHz, $CDCl_3$): 169.1 (C-1), 157.5 (ArC-3), 140.5 (ArC-12), 137.8 (ArC-9), 131.6 (ArC-6) , 129.5 (ArCH-5), 128.2 (ArCH-10), 127.2 (ArCH-11), 114.7 (ArCH-4), 71.8 (CH_2-8/7), 71.7 (CH_2-8/7) 65.6 (CH_2-2), 65.2 (CH_2-13), 61.5 (CH_2-14), 14.3 (CH_3-15).

IR: υ_{max} 3307 (OH), 1743 (C=O) cm^{-1}.

MS (ES +ve): *m/z* (%) 348.3 ($[M+NH_4]^+$, 100), 353.3 ($[M+Na]^+$, 20), 369.3 ($[M+K]^+$, 5), 678.5 ($[2M+NH_4]^+$, 10), 683.5 ($[2M+Na]^+$, 5).
HRMS (CI, NH_3): *m/z* 348.1818 ($[M+NH_4]^+$, $C_{19}H_{26}NO_5$ requires 348.1811).

2-[4-({[4-(hydroxymethyl)phenyl]methoxy)phenoxy] acetic acid (89)



To a solution of **88** (0.82 g, 2.5 mmol) in dioxane/water 3:2 (25 mL) was added 2 M NaOH (5 mL). The mixture was stirred at room temperature for 30 min. The reaction

mixture was acidified to pH 3, saturated with NaCl then extracted with EtOAc (3 x 30 mL). The combined organics were washed with brine (2 x 20 mL), dried over $MgSO_4$ and evaporated *in vacuo* to give **89** as a white solid (0.69 g, 84%).

mp = 88 °C.
δ_H (300 MHz, $CDCl_3$): 7.29 (d, 2H, J = 8.8 Hz, ArH-10/11), 7.26 (d, 2H, J = 8.8 Hz, ArH-10/11), 7.21 (d, 2H, J = 8.8 Hz, ArH-5), 6.84 (d, 2H, J = 8.8 Hz, ArH-4), 4.59 (s, 2H, H-2), 4.52 (s, 2H, H-13), 4.45 (s, 2H, H-8/7), 4.40 (s, 2H, H-8/7).
δ_C (75 MHz, $CDCl_3$):170.9 (C-1), 157.4 (ArC-3), 140.9 (ArC-12), 137.2 (ArC-9), 131.2 (ArC-6), 129.3 (ArCH-5), 127.8 (ArCH-10), 126.9 (ArCH-11), 114.4 (ArCH-4), 71.6 (CH_2-2), 71.5 (CH_2-13), 65.0 (CH_2-7/8), 64.4 (CH_2-7/8).
IR: υ_{max} 3340 (OH alcohol), 2800 (OH acid), 1729 (C=O acid) cm^{-1}.
MS (ES +ve): *m/z* (%) 320 ($[M+NH_4]^+$, 40), 622 ($[2M+NH_4]^+$, 100), 924 ($[3M+NH_4]^+$, 25).
HRMS (EI): *m/z* 302.1150 ($[M^{\cdot+}]$, $C_{17}H_{18}O_5$ requires 302.1154).

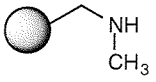
Photolysis - general procedure.
The resin (10 mg) was placed in a pyrex test tube under N_2. Degassed CH_3CN (0.5 mL) was added. Photolysis was carried out under N_2 for 2 h with stirring. The resin was filtered. The filtrate was either directly submitted for MS analysis or evaporated *in vacuo*. The residue was taken up in CH_3CN/H_2O 2:8 (1 mL) and analysed by RP-HPLC.

Qualitative Bromophenol Blue test.
The resin (2 mg, 0.6 µmol) was placed in a test tube and suspended in DCM (0.5 mL). A 0.01 mM solution of bromophenol blue in dioxane (60 µl, 0.006 µmol, 1% of the sites) was added. Abscence of blue coloration of the solution indicated the completion of the reaction.

Quantitative Bromophenol Blue test[81]
The resin (5 mg, 1.5 µmol) was placed in a 1 mL Supelco syringe, washed with DCM (3 x 1 mL) then treated with a 0.01 M bromophenol blue solution in 9:1 DCM/EtOH until the resin turned orange. Excess bromophenol blue was washed off with 9:1 DCM/EtOH until the resin turned back to blue. The resin was washed with 5% DIEA/DCM until the beads became colourless. The solution was adjusted to 25 mL with EtOH then diluted 1/10 and assayed spectrophotometrically at 600 nm against a blank.

$$c\ (mmol/g) = (Abs_{600} \times 250) \times 1\ 10^3/(91800 \times m(mg)).$$

_N_-Methyl aminomethyl TentaGel resin (95).

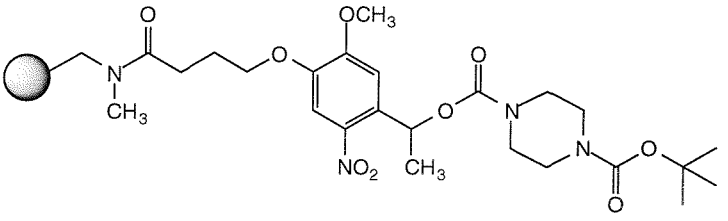


NovaSyn TG Bromo resin (3 g, 0.3 mmol/g, 0.9 mmol) was placed in an oven-dried peptide vessel and washed with dry THF (4 x 20 mL). The resin was suspended in dry THF (20 mL). Methylamine (2 M in THF) (9 mL, 18 mmol) and KI (0.149 g, 0.9 mmol) were added under N_2 and the resin was shaken at room temperature overnight. The resin was filtered, washed with THF (4 x 20 mL), DMF (4 x 20 mL), DCM (4 x 20 mL), MeOH (4 x 20 mL) and dried *in vacuo* for 48 h in a dessicator. A quantitative bromophenol blue test gave a loading of 0.23 mmol/g.

δ_C (100 MHz, d^6 benzene): 71.2 (PEG), 51.6 (CH_2), 36.2 (CH_3)

(Novasyn TG bromo resin: δ_C (100 MHz, d^6 benzene): 71.2 (PEG), 31.3 (CH_2Br)).

Resin (97).



A solution of **82** (0.23 g, 0.45 mmol), DIEA (200 μL, 1.2 mmol) and PyBroP (0.279 g, 0.6 mmol) in dry DCM (3 mL) and dry DMF (0.2 mL) was added to resin **95** (1 g, 0.3 mmol) suspended in dry DCM (5 mL). The resin was shaken at room temperature overnight, then filtered, washed with DCM (3 x 10 mL), DMF (3 x 10 mL), MeOH (3 x 10 mL), DCM (3 x 10 mL), and MeOH (3 x 10 mL). The resin was dried overnight *in vacuo* over P_2O_5. A qualitative bromophenol blue test was still positive after a second coupling with **82** (0.076 g, 0.15 mmol), PyBroP (0.139 g, 0.3 mmol) and DIEA (100 μL, 0.6 mmol). A quantitative bromophenol blue test indicated 0.04 mmol/g unreacted amine.

IR: υ_{max} 1691 (C=O), 1641 (C=O), 1515 (NO_2), cm^{-1}.

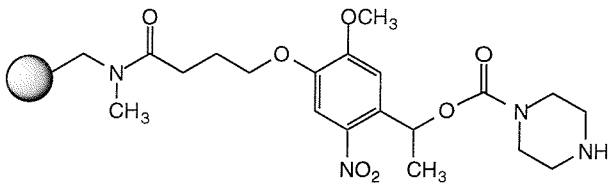
δ_C (100 MHz, d^6-benzene): 172.0, 171.7, 154.7, 154.3, 148.4, 141.2, 133.3, 109.5, 108.8, 79.9, 71.2 (PEG), 70.2, 70.1, 69.3, 69.0, 56.2, 49.6, 48.2, 44.1, 41.3, 36.7, 33.9, 29.8, 28.7.

Small scale photolysis and ES-MS analysis: 187.2 ($[M+H]^+$, 100), 228.3 ($[M+CH_3CN+H]^+$, 50).

Capping unreacted secondary amines.

Resin **97** (1 g, 0.3 mmol) was suspended in dry DCM (5 mL). Pyridine (0.5 mL, 60 mmol), and acetyl chloride (0.2 mL) were added. The resin was shaken at room temperature overnight, filtered, washed with DCM (5 x 5 mL), DMF (5 x 5 mL), DCM (5 x 5 mL), MeOH (5 x 5 mL), and dried *in vacuo*.

Resin (98).



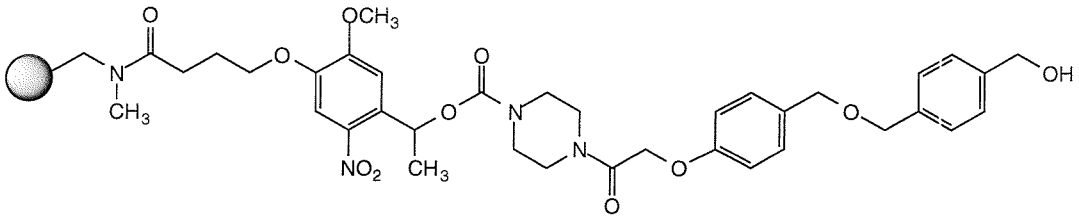
Boc deprotection was carried with 50% TFA/DCM (20 mL/g) with two treatments of 30 min. The resin was filtered, washed with DCM (5 x 20 mL), DMF (3 x 5 mL) and DCM (3 x 5 mL), DMF (5 x 20 mL), 10% DIEA/DCM (3 x 20 mL), DCM (5 x 20 mL), MeOH (5 x 20 mL) and dried *in vacuo* in over P_2O_5.

IR: υ_{max} 1691 (C=O), 1641 (C=O), 1518 (NO_2) cm^{-1}.

δ_C (100 MHz, d^6 benzene): 171.9, 171.6, 154.3, 148.2, 141.0, 133.7, 109.4, 108.7, 71.2 (PEG), 70.2, 69.7, 69.2, 68.9, 56.2, 49.6, 48.1, 46.3, 45.4, 41.2, 36.6, 33.8, 29.8, 29.2.

Small scale photolysis and ES-MS analysis: No peak corresponding to Boc piperazine was detected.

Resin (99a).



A solution of **82** (0.049 g, 0.16 mmol) and EEDQ (0.044 g, 0.17 mmol) in DCM (2.5 mL) and DMF (0.5 mL) was added to the resin **98** (0.5 g, 0.15 mmol) suspended in DCM (5 mL). The resin was shaken at room temperature overnight, washed with DCM (5 x 5 mL), DMF (5 x 10 mL), DCM (5 x 10 mL), MeOH (5 x 10 mL) and dried *in vacuo* over P_2O_5 for 48 h.

Small scale photolysis and HPLC/MS analysis: t_R = 9.6 min.

MS (ES +ve): *m/z* 371.3 ($[M+H]^+$, 100), 741.4 ($[2M+H]^+$, 60).

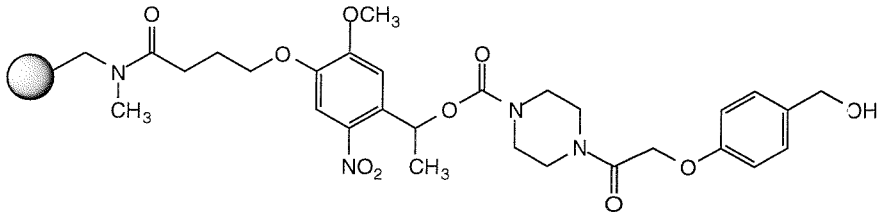
TFA cleavage: **4**, t_R =7.3 min

IR: υ_{max} 1691 (C=O), 1642 (C=O), 1516 (NO_2) cm^{-1}.

δ_C (100 MHz, d^6 benzene): 172.0, 171.7, 166.7, 158.2, 154.3, 148.2, 142.6, 137.8, 133.8, 132.3, 129.8, 115.1, 109.4, 108.9, 71.2 (PEG), 70.2, 69.2, 69.2, 68.1, 64.6, 56.3, 49.6, 48.2, 45.2, 44.4, 44.0, 42.0, 41.2, 36.6, 33.8, 29.7, 29.2, 25.3, 25.1, 22.3.

5.4.2 Monitoring of the coupling of non-UV active diols

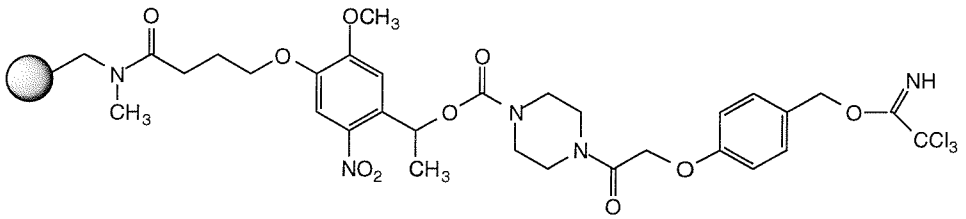
Resin (109).



A solution of Wang linker **86** (0.027 g, 0.15 mmol) and EEDQ (0.04 g, 0.17 mmol) in dry DCM/DMF 9:1 (2 mL) was added to the resin **98** (0.5 g, 0.12 mmol) suspended in dry DCM (2 mL). The resin was shaken at room temperature overnight, filtered, washed with DMF (5 x 5 mL), MeOH (5 x 5 mL), DCM (5 x 5 mL), and MeOH (5 x 5 mL) and dried *in vacuo* over P_2O_5.

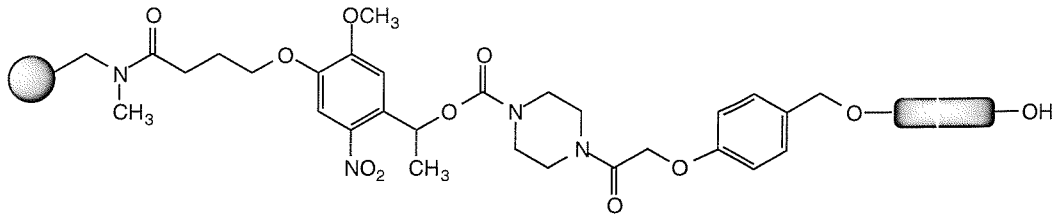
Small scale photolysis and HPLC/MS analysis: t_R = 6.8 min.
MS (ES +ve): *m/z* 251.3 ($[M+H]^+$, 100).

Resin (110)



Dry resin **109** (0.5 g, 0.12 mmol) was placed in an oven-dried silylated flask and suspended in dry DCM (10 mL). The slurry was cooled to 0 °C. CCl_3CN (188 µL, 1.8 mmol) was added followed by DBU (19 µL, 0.12 mmol). The resin was stirred gently at 0 °C for 1 h then filtered under N_2, washed with dry DCM (3 x 10 mL) and dried *in vacuo* overnight.

Resin (111)



Coupling of the diol - general procedure

Dry resin **110** (0.100 g, 0.025 mmol) was washed under N_2 with dry THF then suspended in THF (0.5 mL). Diols **4, 31a**, **31b**, **31h** (5 eq) in dry THF (1 mL) were added to the resin followed by $BF_3.OEt_2$ (0.2 M in THF) (50 µL, 0.01 mmol). The resin was shaken at room temperature overnight, then filtered, washed with DCM (5 x 3 mL), THF (5 x 3 mL), DMF (5 x 3 mL), MeOH (5 x 3 mL), DCM (5 x 3 mL), MeOH (5 x 3 mL), and dried *in vacuo* overnight.

Resin (111-4)

RP-HPLC (λ_{220}, gradient A): t_R = 6.7 min (**112**, 8%), t_R = 9.6 min (**100-4**, 92%)

t_R = 9.6 min: MS (ES +ve): *m/z* (%) 353.3 ($[M+H-H_2O]^+$, 100), 371.5 ($[M+H]^+$, 100), 393.3 ($[M+Na]^+$, 5).

Resin (111-a)

RP-HPLC (λ_{220}, gradient A): t_R = 6.7 min (**112**, 42%), t_R = 9.0 min (**100a**, 58%)

t_R = 9.0 min: MS (ES +ve): 335.4 ($[M+H]^+$, 100), 357.5 ($[M+Na]^+$, 25).

Resin (111-b)

RP-HPLC (λ_{220}, gradient A): t_R = 6.7 min (**112**, 40%), t_R = 7.5 min (**100b**, 60%)

t_R = 7.5 min: MS (ES +ve): 337.4 ($[M+H]^+$, 100), 359.4 ($[M+H]^+$, 20).

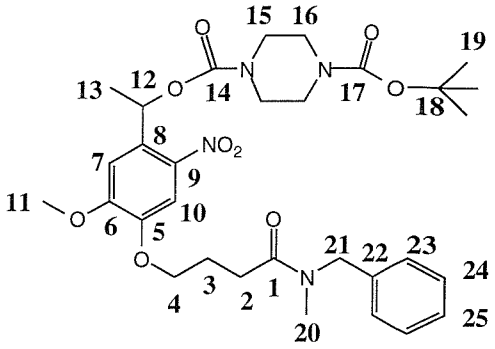
Resin (111-h)

RP-HPLC (λ_{220}, gradient A): t_R = 6.7 min (**112**, 32%), t_R = 10.6 min (**100h**, 68%)

t_R = 10.6 min: MS (ES +ve): 377.6 ($[M+H]^+$, 100).

5.4.3 Solution model

Tert-butyl 4-{[(5-methoxy-4-{3-[N-methyl-N-benzylcarbamoyl] propoxy} -2-nitrophenyl) ethyl] oxycarbonyl} piperazine carboxylate (104)



To a solution of **82** (0.511 g, 1 mmol) in DCM (15 mL) and DMF (0.5 mL) was added HOBt (0.148 g, 1.1 mmol), DCC (0.227 g, 1.1 mmol) and DMAP (12 mg, 0.1 mmol). The mixture was stirred for 15 min. *N*-Methyl benzylamine **102** (218 µl, 2 mmol) was added and the mixture was stirred overnight. The precipitated urea was removed by filtration. The filtrate was washed with saturated $NaHCO_3$ (3 x 10 mL), 1% citric acid (3 x 10 mL), brine (3 x 10 mL), dried over $MgSO_4$ and evaporated *in vacuo*. Purification by chromatography on silica gel gave **104** as a yellow oil (0.509 g, 82%). Two rotamers in a 1:1 ratio.

TLC: R_f = 0.3 (EtOAc/PE 7:3).

RP-HPLC (λ_{220}, gradient 1): t_R = 18.6 min.

δ_H (300 MHz, $CDCl_3$): 7.60 and 7.56 (s, 1H, ArH-10), 7.40-7.10 (m, 5H, ArH-23,24,25), 6.93 and 6.90 (s, 1H, ArH-7), 6.39 (qua, 1H, *J* = 6.2 Hz, H-12), 4.60 (m, 2H, H-21), 4.17 and 4.11 (t, 2H, *J* = 6.6 Hz, H-4), 3.92 and 3.82 (s, 3H, H-13), 3.60-3.30 (br m, 8H, H-15,16), 2.97 and 2.94 (s, 3H, H-20), 2.60 (t, 2H, *J* = 6.6 Hz, H-2), 2.26 (quin, 2H, *J* = 6.6 Hz, H-3), 1.64 and 1.65 (d, 3H, *J* = 6.2 Hz, H-13), 1.47 (s, 9H, H-19).

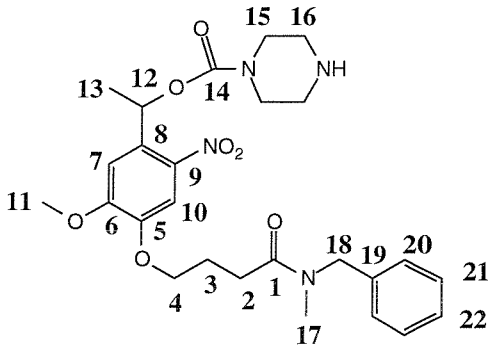
δ_C (75 MHz, $CDCl_3$): 172.5 and 172.1 (C-1), 154.7 (14/17), 154.2 (14/17), 153.9 (ArC), 147.4 (ArC), 140.4 (ArC), 140.1 (ArC), 137.5 (ArC), 133.5 (ArC), 129.0 (ArCH), 128.7 (ArCH), 128.2 (ArCH), 127.7 (ArCH), 127.5 (ArCH), 126.4 (ArCH), 109.2 (ArCH-7), 108.0 (ArCH-10), 80.4 (C-18), 69.0 (C-12), 68.7, 68.6 (CH_2-4), 56.3, 56.2 (CH_3-11), 53.4 (CH_2-21), 51.0 (CH_2), 43.8 (CH_2-15,16), 34.8 (CH_2), 34.2 (CH_2-20), 29.6, 29.1 (CH_2-2), 28.5 (CH_3-19), 24.7, 24.6 (CH_2-3), 22.2 (CH_3-13).

IR: υ_{max} 1692 (C=O), 1642 (C=O), 1580 (C=O), 1519 (NO_2) cm^{-1}.

MS (ES +ve): *m/z* (%) 615.3 ($[M+H]^+$, 75), 632.3 ($[M+NH_4]^+$, 100), 1229.1 ($[2M+H]^+$, 10), 1246.1 ($[2M+NH_4]^+$, 50).

HRMS (FAB): *m/z* 615.3056 ($[M+H]^+$, $C_{31}H_{43}O_9N_4$ requires 615.3030).

(5-methoxy -4-{3-[N-methyl-N-benzylcarbamoyl] propoxy} -2-nitrophenyl) ethyl piperazine carboxylate (105)



To a solution of **104** (0.45 g, 0.73 mmol) in DCM (5 mL) was added TFA (1 mL). The mixture was stirred at room temperature for 2 h then concentrated *in vacuo*. The residue was taken in water (20 mL). The solution was basified to pH 9 with 2M NaOH then extracted with EtOAc (3 x 30 mL). The combined organics were washed with brine (2 x 10 mL), dried over $MgSO_4$ and evaporated *in vacuo*. Purification by chromatography on silica gel (DCM:MeOH 9:1) gave **105** as a foamy yellow solid (0.360 g, 95% yield). Two rotamers in 1:1 ratio.

TLC: R_f = 0.5 (DCM/MeOH 9:1).

RP-HPLC (λ_{220}, gradient 1): t_R = 12.2 min.

δ_H (300 MHz, $CDCl_3$): 7.59 and 7.55 (s, 1H, H-7), 7.35-7.10 (m, 5H, ArH-20,21,22), 6.94 and 6.91 (s, 1H, ArH-10), 6.387 and 6.382 (qua, 1H, J = 6.2 Hz, H-12), 4.63 (d, 1H, J_{AB} = 14.8 Hz, H_A-18), 4.57 (d, 1H, J_{AB} = 14.8 Hz, H_B-18), 4.55 (s, 2H, H-18), 4.16 (t, 2H, J = 6.2 Hz, H-4), 3.92 and 3.84 (s, 3H, H-17), 3.48 (br s, 4H, H-15/16), 2.96 (s, 3H, H-17), 2.93 (s, 3H, H-17), 2.84 (br s, 4H, H-15/16), 2.60 (t, 2H, H-2), 2.25 (quin, 2H, J = 6.2 Hz, H-3), 1.63 and 1.62 (d, 3H, J = 6.2 Hz, H-13).

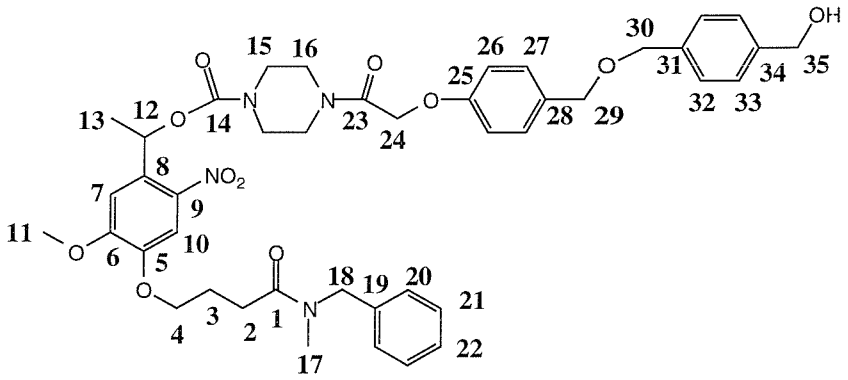
δ_C (75 MHz, $CDCl_3$): 172.6 and 172.2 (C-1), 154.2 and 153.9 (C-14), 147.3 (ArC), 139.9 (ArC), 137.4 (ArC), 136.6 (ArC), 133.9 (ArC), 129.0 (ArCH), 128.7 (ArCH), 128.1 (ArCH), 127.6 (ArCH), 127.4 (ArCH), 126.4 (ArCH), 109.2 (ArCH-7), 108.0 (ArCH-10), 69.7 (CH-12), 68.7 and 68.5 (CH_2-4), 56.29 and 56.21 (CH_3-11), 53.3 (CH_2-18), 45.7 (CH_2-15/16), 44.6 (CH_2-15/16), 34.8 and 34.1 (CH_3-17), 29.6 and 29.1 (CH_2-2), 24.7 and 24.5 (CH_2-3), 22.2 (CH_3-13).

IR: υ_{max} 1692 (C=O), 1637 (C=O), 1515 (NO_2) cm^{-1}.

MS (ES +ve): *m/z* (%) 515.2 ($[M+H]^+$, 100), 537.2 ($[M+Na]^+$, 20), 553 ($[M+K]^+$, 5), 573 ($[M+CH_3CN+NH_4]^+$, 5).

HRMS (FAB): *m/z* 515.2500 ($[M+H]^+$, $C_{26}H_{35}O_7N_4$ requires 515.2505).

(5- methoxy -4-{3-[N-mehyl-N-benzylcarbamoyl] propoxy} -2-nitrophenyl) ethyl 4-{2-[4-({[4-(hydroxymethyl)phenyl] methoxy}methyl) phenoxy} acetyl} piperazine carboxylate (106)



To a solution of **105** (0.141 g, 0.27 mmol) in DCM (3 mL) was added **89** (91 mg, 0.30 mmol) and EEDQ (74 mg, 0.3 mmol) in DCM (0.5 mL) and DMF (0.5 mL). The reaction mixture was stirred at room temperature overnight. The solvents were removed *in vacuo*. The residue was taken in EtOAc (20 mL), washed with saturared $NaHCO_3$ (10 mL), 1 % citric acic (10 mL), brine (10 mL), dried over $MgSO_4$, and evaporated *in vacuo*. Purification by chromatography on silica gel gave **106** as a yellow oil (0.150 g, 58%).

TLC: R_f= 0.5 (DCM/MeOH 9:1).

RP-HPLC (λ_{220}, gradient 1): t_R = 16.7 min.

δ_H (300 MHz, $CDCl_3$): 7.49 and 7.46 (s, 1H, ArC-10), 7.30-7.15 (m,), 7.00 (d, 1H, ArH-), 6.84 (d, 2H, J = 6.7 Hz, ArH-), 6.82 and 6.80 (s, 1H, ArH-7), 6.30 (qua, 1H, J = 6.2 Hz H-), 4.62 - 4.40 (m, H, H-18, 24, 29, 30, 35), 4.07 and 4.02 (t, 2H, J = 6.2 Hz, H-4), 3.82 and 3.75 (s, 3H, H-13), 3.52 (br s, 4H, H-15/16), 3.40 (br s, 4H, H-15/16), 2.88 and 2.85 (s, 3H, H-17), 2.51 (t, 2H, J = 6.2 Hz, H-2), 2.15 (quin, 2H, J = 6.2 Hz, H-3), 1.56 and 1.56 (d, 3H, J = 6.2 Hz, H-13)

δ_C (75 MHz, $CDCl_3$):172.6 and 172.23 (C-1), 166.9, 157.3, 154.1 and 153.8 (C-14), 147.4, 140.8, 140.1, 137.5, 137.4, 136.6, 133.1 (ArC and C), 129.6, 129.0, 128.1, 128.1, 127.5, 127.1, 126.4, 126.4, 114.5 (ArCH), 109.2 (ArCH-7), 108.1 (ArCH-10), 71.9 (CH_2), 71.7 (CH_2), 70.1 (CH-12), 68.8, 68.7, 68.1, 65.2, 56.38 and 56.31 (CH_3-11), 53.4, 51.0, 45.4, 44.1, 44.1, 43.7, 42.1 (CH_2), 34.8 and 34.2 (CH_3-17), 29.6 and 29.1 (CH_2-2), 24.7 and 24.6 (CH_2-3), 22.2 (CH_3-13).

IR: υ_{max} 3415 (OH), 1638 (C=O), 1511 (NO_2), cm^{-1}.

MS (ES +ve): *m/z* (%) 799.2 ($[M+H]^+$, 100), 816.2 ($[M+NH_4]^+$, 20).

HRMS (FAB): *m/z* 799.3592 ($[M+H]^+$, $C_{43}H_{51}O_{11}N_4$ requires 799.3554).

REFERENCES

(1) Pressman, B.C. *Annu. Rev. Biochem.* **1976**, *45*, 501-530.

(2) Hassall, C.H.; Thomas, W.A. *Chem. Ber.* **1971**, *7*, 145-148 and references cited therein.

(3) Burgermeister, W.; Winkler-Oswatitsch, R. *Top. Curr. Chem.* **1977**, *69*, 91-103.

(4) Beck, J.; Gerlach, H.; Prelog, V.; Voser, W. *Helv. Chem. Acta* **1962**, *45*, 620-625.

(5) (a) Zeng, L.; Ye, Q.; Oberlies, N.H.; Shi, G.; Gu, Z.M.; He, K.; McLaughlin, J.L. *Nat. Prod. Report* **1996**, 275-291. (b) Hoppe, R.; Scharf, H.D. *Synthesis* **1995**, 1447-1463.

(6) (a) Westley, J.W *Adv. Appl. Microbiol.* **1977**, *22*, 177-222. (b) Westley, J.W. In *Polyether Antibiotics: Naturally Occuring Ionophores*; Westley, J.W., Ed.; Marcel Dekker: New York, 1982; Vol 1. (c) Westley, J.W. In *Polyether Antibiotics: Naturally Occuring Ionophores*; Westley, J.W., Ed.; Marcel Dekker: New York, 1983; Vol 2. (d) Omura, S. In *Macrolide Antibiotics* Academic Press: Orlando, 1984.

(7) (a) Dobler, M. In *Ionophores and their structures*; Wiley-Interscience: New York, 1981. (b) Hilgenfeld, R.; Saenger, W. *Top. Curr. Chem.* **1982**, *101*, 81-109. (c) Dobler, M. In *Comprehensive Supramolecular Chemistry*; Gokel, G.W., Ed.; Elsevier: Oxford, 1996; Vol 1, p 267-313.

(8) Pedersen, C.J. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1021-1027.

(9) (a) Lehn, J.M. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 89-112. (b) Lehn, J.M. In *Supramolecular Chemistry: Concepts and Perspectives*; VCH: Weinheim, 1995.

(10) (a) Weber, E.; Toner, J.L.; Goldberg, I.; Vögtle, F.; Laidler, D.A.; Stoddart, J.F.; Bartsch, R.A.; Liotta, C.L. 'Crown Ethers and Analogues', In *The Chemistry of Functional Groups*; Patai, S.; Rappoport, Z., Eds.; John Wiley and Sons: Chichester, 1989. (b) Hiraoka, M. In *Crown compounds, their characteristic and applications'*; Elsevier: 1982. (c) Gokel, G. In *Crown Ethers and Cryptands*; Monograph In Supramolecular Chemistry N° 3, RSC: Cambridge, 1991.

(11) Beer, P.D.; Gale, P.A.; Chen, Z. *Adv. Phys. Org. Chem.* **1998**, *31*, 1-90.

(12) Knopp, M.V. *J. Magn. Res. Imaging* **1999**, *10*, 314-316.

(13) (a) Jong, F.; Visser, H.C.F. In *Comprehensive Supramolecular Chemistry*; Reinhoudt, D.N., Ed.; Elsevier: Oxford, 1996; Vol 10. (b) Painter, G.R.; Pressman B.C. *Top. Curr. Chem.* **1982**, *101*, 83 -109.

(14) Dutton, C.J.; Banks, B.J.; Cooper, C.B. *Nat. Prod. Report* **1995**, 165-181.

(15) Westley, J.W. *Annu. Rep. Med. Chem.* **1975**, *10*, 246-250.

(16) Pressman, B.C. *Annu. Rev. Biochem.* **1976**, *45*, 4925-4950.

(17) Reed, P.W. *Meth. Enzymol.* **1979**, *55*, 435-440.

(18) Suzuki, K.; Tohda, K. *Trends Anal. Chem.* **1993**, 12, 287-295.

(19) (a) Still, W.C.; Hauck, P.; Kempf, D. *Tetrahedron Lett.* **1987**, 28, 2817-2820. (b) Smith, P.W.; Still, W.C. *J. Am. Chem. Soc.* **1988**, *110*, 7917-7919.

(20) (a) Dobler, M. In *Comprehensive Supramolecular Chemistry*; Gokel, G.W., Ed.; Elsevier: Oxford, 1996; Vol. 1, p 292-313. (b) Steinrauf, L.K.; Sabesan, M.N. In *Organic Chemistry and Biochemistry;* Pullman, B.; Goldblum, N., Eds.; Dorddrecht: D. Reidel, 1977; Part 2, p 43-57.

(21) Vaillancourt, V.; Pratt, N.E.; Perron, F.; Albizati, K.F. In *Total Synthesis of Natural Products*; John Wiley and Sons: New York, 1992; Vol 8, p 533.

(22) (a) Boivin, T.L.B. *Tetrahedron* **1987**, *43*, 3309-3362. (b) Harmange, J.C.; Figadere, B. *Tetrahedron: Asymmetry* **1993**, *4*, 1711-1754. (c) Koert, U. *Synthesis*, **1995**, 115-132.

(23) (a) Glazer, E.A.; Koss, D.A.; Olson, J.A.; Ricketts, A.P.; Schaaf, T.K.; Wiscount, R.J. *J. Med. Chem.* **1992**, *35*, 1839-1844 and references cited therein. (b) Still, W.C.; Hauk, P.; Kempf, D. *Tetrahedron Lett.* **1989**, 6947-48. (c) Smith, P.W.; Still, W.C. *J. Am. Chem. Soc.* **1988**, *110*, 7917-7919.

(24) (a) Eisenman, G.; Krasne, S.J. In *The ion selectivity of carriers molecules, membranes, and enzymes*; Chap 2. (b) Epsein, M. In *MTP Int. Rev. of Science, Biochemistry series'*; Butterworth: London, Vol. 2, Chap 10.

(25) Gardner, O.J.; Beard, C.C. *J. Med. Chem.* **1978**, *21*, 357-361

(26) Wieranga, W.; Evans, B.R.; Woltersom, J.A. *J. Am. Chem. Soc.* **1979**, *101*, 1334-1336.

(27) Vögtle, F.; Weber, E. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 753-776.

(28) (a) Kasuga, C.N.; Kuboniwa, H.; Nakahama, S.; Yamaguchi, K. *J. Am. Chem. Soc.* **1995**, *117*, 7238-7244. (b) Hiratani, K.; Taguchi, K. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 3827-3833.

(29) Merrifield, R.B. *J. Am. Chem. Soc.* **1963**, *85*, 2149-2154.

(30) Furka, A.; Sebestyen, F; Asgedom, M.; Dibo, G. *Int. J. Pept. Protein Res.* **1991**, *37*, 487-493.

(31) (a) Hermkens, P.H.H.; Ottenheijm, H.C.J.; Rees, D. *Tetrahedron* **1996**, *52*, 4527-4554. (b) Hermkens, P.H.H.; Ottenheijm, H.C.J.; Rees, D. *Tetrahedron* **1997**, *53*, 5643-5678. (c) Booth, S.; Hermkens, P.H.H.; Ottenheijm, H.C.J.; Rees, D. *Tetrahedron* **1998**, *54*, 15385-15443.

(32) Ley, S.V.; Schucht, O.; Thomas, A.W.; Murray, P.J. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1251-1252.

(33) Booth, R.J.; Hodges, J.C *Acc. Chem. Res.* **1999**, *32*, 18-26.

(34) Curran, D.P. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 1174-1196.

(35) (a) *Combinatorial Chemistry and Molecular Diversity in Drug Discovery*; Gordon E.M.; Kerwin, J.F. Eds.; Wiley-Liss, 1998. (b) *Annual Report in Combinatorial Chemistry and Molecular Diversity;* Moos, W.H.; Pavia, M.R.; Ellington, A.D.; Kay, B.K., Eds.; ESCOM: Leiden, 1997; Vol 1. (c) *A Practical Guide to Combinatorial Chemistry;* Czarnik, A.W.; DeWitt, S.H., Eds.; ACS professional reference book, 1997. (d) *Combinatorial Chemistry*; Wilson, S.R.; Czarnik A.W. Eds.; Wiley-Interscience, 1997.

(36) Jandeleit, B.; Schaefer, D.J.; Powers, T.S.; Turner, H.W.; Weinberg, W.H. *Angew. Chem., Int. Ed. Engl.* **1999**, *18*, 2494-2532.

(37) Bechthold, A.; Fernandez, J.A.S. In *Combinatorial Chemistry;* Jung, G., Ed.; Wiley-VCH, 1999; p 381-407.

(38) (a) Soth, M.J.; Nowick, J.S. *Curr. Opin. Chem. Biology* **1997**, *1*, 120-129. (b) Bianco, A. In *'Combinatorial Chemistry'*, Jung, G. Eds.; Wiley-VCH, 1999, 257-290.

(39) Reggelin, M.; Brening, V. *Tetrahedron Lett.* **1996**, *37*, 6851-6852.

(40) Peterson, I.; Scott, J.P. *Tetrahedron Lett.* **1997**, *38*, 7441-7448.

(41) Kurth, M.J.; Ahlberg, L.A.; Takenouchi, K. *J. Org. Chem.* **1996**, *61*, 8755-8761.

(42) Malenfant, P.R.L.; Fréchet, J.M. *J. Chem. Soc., Chem. Commun.* **1998**, 2657-2658.

(43) Sinha, S.C.; Sinha, A.; Yazbak, A.; Keinan, E. *J. Org. Chem.* **1996**, *61*, 7640-7641.

(44) (a) Wagner, H.; Harms, K.; Koert, U.; Meder, S.; Boheim, G. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2643-2646.

(45) Hall, D.G.; Schultz, P.G. *Tetrahedron Lett.* **1997**, *38*, 7825-7828.

(46) Simon, R.J.; Kania, R.S.; Zuckermann, R.N.; Huebner, V.D.; Jewell, D.A.; Banville, S.; Ng, S.; Wang, L.; Rosenberg, S.; Marlowe, C.K.; Spellmeyer, D.C.; Frankel, A.D.; Santi, D.V.; Cohen, F.E.; Bartlett, P.A. *Proc. Natl. Acad. Sci. U.S.A.* **1992**, *89*, 9367-9371.

(47) Zuckermann R.N.; Kerr, J.M.; Kent, S.B.H.; Moos, W.H. *J. Am. Chem. Soc.* **1992**, *114*, 10646-10647.

(48) Mascagni, P.; Ball, H.L.; Bertolini, G. *Anal. Chim. Acta.* **1997**, *352*, 375-385.

(49) (a) Merrifield, R.B.; Batch, A.E. *J. Org. Chem.* **1978**, *43*, 25-29. (b) Mutter, M.; Bellof, D. *Helv. Chim. Acta* **1984**, 67, 2009-2016.

(50) Lloyd-Williams, P.; Albercio, F.A.; Giralt, E. *Tetrahedron* **1993**, *49*, 11065-11133.

(51) Labadie, J.W. *Curr. Opin. Chem. Bio.* **1998**, *2*, 346-352.

(52) (a) Sherrington, D.C. *Chem. Commun.* **1998**, 2275-2286. (b) Sherrington D.C. In *Polymer Supported Reactions in Organic Synthesis;* Hodge, P; Sherrington, D.C., Eds.; Wiley: Chichester, 1980; p 59-74. (c) Hodge, P. *Chem. Soc. Rev.* **1997**, 417-424.

(53) Atherton, E.; Sheppard, R.C. In *Perspectives in Peptide Chemistry*; 1981, p 101-117.

(54) Bayer, E. *Angew. Chem. Int., Int. Ed. Engl.* **1991**, *30*, 113-129.

(55) Gooding, O. W.; Baudart, S.; Deegan, T.L.; Heisler, K.; Labadie, J.F.; Newcomb, W.S.; Porco, J.A.; Eikeren, P. *J. Comb. Chem.* **1999**, *1*, 113-122.

(56) Kempe, M.; Barany, G. *J. Am. Chem. Soc.* **1996**, *118*, 7083-7093.

(57) Meldal, M, *Tetrahedron Lett.* **1992**, *33*, 3077-3080.

(58) Renil, M.; Meldal, M. *Tetrahedron Lett.* **1996**, *37*, 6185-6188.

(59) Barany, G.; Albericio, F.; Kates, S.A.; Kempe, M. *ACS Symp. Series*, 1997; Vol 680, 239-264.

(60) Lerh, B.; Egelhaaf, H.J.; Fritz, H.; Rapp, W.; Bayer, E.; Oelkrug, D. *Macromolecules* **1996**, *29*, 7931-7936.

(61) Quarrell, R.; Claridge, T.D.W.; Weaver, G.W.; Lowe, G. *Mol. Diversity* **1995**, *1*, 223-232

(62) Hori, M.; Gravert, D.J.; Wentwortth, P.; Janda, K.D. *Bioorg. Med. Chem. Lett.* **1998**, *6*, 2363-2368.

(63) (a) Farrall, M.J.; Fréchet, J.M. *J. Org. Chem.* **1976**, 41, 3877. (b) Backes, B.J.; Ellman, J.A. *J. Am. Chem. Soc* **1994**, *116*, 11171.

(64) (a) Frechet, J.M.J. *Tetrahedron* **1981**, *37*, 663-683 and references cited therein..

(65) (a) Spitzer, J.L.; Kurth, M.J.; Score, N.E.; Nadji, S.D. *Tetrahedron* **1997**, *53*, 6791-6808. (b) Schuster, M.; Pernerstorfer, J.; Blechert, S. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1979-1980.

(66) For reviews on linkers and cleavage strategies see: (a) James, I.W. *Tetrahedron* **1999**, *55*, 4855-4946. (b) Guillier, F.; Orain, D.; Bradley, M. *Acc. Chem. Res.* **1999** in press.

(67) Gordon, K.; Balasubramanian, S. *J. Chem. Technol. Biotechnol.* **1999**, *74*, 835-851.

(68) (a) Moon, H.; Shore, N.E.; Kurth, M.J. *Tetrahedron Lett.* **1994**, *35*, 8915-8918. (b) Allin, S.M.; Shuttleworth, S.J. *Tetrahedron Lett.* **1996**, *37*, 8023-8026.

(69) (a) Ley, S.V.; Mynett, D.M.; Koot, W.J. *Synlett* **1995**, *10*, 17-20. (b) Gayo, L.M.; Suto, M.J. *Tetrahedron Lett.* **1997**, *38*, 211-214. (c) Schurer, S.C.; Blechert, S. *Synlett* **1998**, *2*, 166-170.

(70) (a) Fridkin, M.; Patchornik, A.; Kathalski, E. *J. Am. Chem. Soc.* **1965**, *87*, 464-468. (b) Dressman, B.A.; Spangle, L.A.; Kaldor, S.W. *Tetrahedron Lett.* **1996**, *37*, 937-940. (c) Buchstaller, H.P. *Tetrahedron* **1998**, *54*, 3465-3470. (d) Van Maarseveen, J.H.; Denhartog, J.A.J.; Engelen, V.; Finner, E.; Visser, G.; Kruse, C.G. *Tetrahedron Lett.* **1996**, *37*, 8249-8252.

(71) Pátek, M.; Lebl, M. *Biopolymers (Pept. Sc.)* **1998**, *47*, 353-363.

(72) Atrash, B.; Bradley, M. *J. Chem. Soc., Chem. Comm.* **1997**, *15*, 1397-1398.

(73) Borhan, B.; Wilson, J.A.; Gash, M.J.; Ko, Y.; Kurth, M.J. *J. Org. Chem.* **1995**, *60*, 7375-7378.

(74) (a) Ajayaghosh, A.; Pillai, V.N.R. *Tetrahedron* **1988**, *44*, 6661-6666. (b) Fyles, T. M.; Leznoff, C.C. *Can J. Chem.* **1976**, *54*, 935-939. (c) Wang, S.S. *J. Org. Chem.* **1976**, *41*, 3258-3260.

(75) (a) Whitehouse, D.L.; Sanisov, S.N.; Austin, D.J. *Tetrahedron Lett.* **1997**, *38*, 7851-7852. (b) Kobayashi, S.; Moriwaki, M. *Tetrahedron Lett* **1997**, *38*, 4251-4254.

(76) For reviews on analytical techniques for solid phase and combinatorial chemistry see: (a) Egner, J. E.; Bradley, M. *Drug Disc. Today* **1997**, *3*, 102-108. (b) Gallop. M.A.; Fitch, W.L. *Curr. Op. Chem. Biol.* **1997**, *1*, 94-100. (c) Swali, V.; Bradley, M. *Anal. Commun.* **1997**, *34*, 15H-18H. (d) Fitch, W. L. *Mol. Diversity* **1999**, *4*, 39-45.

(77) (a) Kaiser, E.; Colescott, R.L.; Bossinger, C.D.; Cook, P.I. *Anal. Biochem.* **1970**, *34*, 595-598. (b) Sarin, V.K.; Kent, S.B.H.; Tam, J.P.; Merrifield, R.B. *Anal. Biochem.* **1981**, *117*, 147-157.

(78) Bernatowicz, M.S.; Daniels, S.B.; Koster, H. *Tetrahedron Lett.* **1989**, *30*, 4645-4648.

(79) Other amine tests: (a) Chu, S.S.; Reich, S.H. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 1053-1058 (NPIT test). (b) Hodge, R.S.; Merrifield, R.B. *Anal. Biochem.* **1975**, *65*, 241-272 (picrate test). (c) Handcock, W.S.; Battersby, J.E. *Anal. Biochem.* **1976**, *71*, 260-264 (2,4,6-trinitrobenzenesulphonic acid test).

(80) Virgilio, A.A.; Ellman J.A. *J. Am. Chem. Soc.* **1994**, *116*, 11580-11581.

(81) Krchňák, V.; Vágner, J.; Safár, P.; Lebl, M. *Collect. Czech. Chem. Commun.* **1998**, *53*, 2542-2548.

(82) Vojkovsky, T. *Peptide Res.* **1995**, *8*, 236-237.

(83) Reddy, M.P.; Voelker, P.J. *J. Int. Pept. Protein Res.* **1988**, *31*, 345-348.

(84) Kuisle, O.; Lolo, M.; Quiñoá, E.; Riuera, R. *Tetrahedron* **1999**, *55*, 14807-14812.

(85) For a comparison between various IR techniques see: (a) Yan, B.; Gremlich, H.U.; Moss, S.; Coppolla, G.M.; Sun, Q.; Liu, L. *J. Comb. Chem.* **1999**, *1*, 46-54. (b) Gremlich, H.U. *Am. Lab.* **1998**, 33-38. (d) Bandel, H.; Haap, W.; Jung, G. In *Combinatorial Chemistry;* Jung, G., Ed.; Wiley-VCH, 1999; p 478-498.

(86) Crowley, J.I.; Rapoport, H. *J. Org. Chem.* **1980**, *45*, 3215-3227

(87) Yan, B.; Kumaravel, G.; Anjaria, H.; Wu, A.; Petter, R.C.; Jewell, C.F. Wareing, J.R. *J. Org. Chem.* **1995**, *60*, 5736-5738.

(88) (a) Yan, B.; Fell, J.B.; Kumaravel, G. *J. Org. Chem.* **1996**, *61*, 7467-7472. (b) Gremlich, H.U.; Berets, S. *Appl. Spectrosc.* **1996**, *50*, 532-536.

(89) Larsen, B. D.; Christensen, D.H.; Holm, A.; Zillmer, R.; Nielsen, O.F. *J. Am. Chem. Soc.* **1993**, *115*, 6247-6253.

(90) (a) Chan, T.Y.; Chen, R.; Sofia, M.J.; Smith, B.C.; Glennon, D. *Tetrahedron Lett.* **1997**, *38*, 2821-2824. (b) Deben, I.; Goorden, J.; Van Doornum, E.; Ovaa, H.; Kellenbach, E. *Eur. J. Org. Chem.* **1998**, 697-700.

(91) Gosselin, F.; Di Renzo, M.; Ellis, T.H.; Lubell, W.D. *J. Org. Chem.* **1996**, *61*, 7980-7981.

(92) Yan, B.; Sun, Q.; Wareing, J.M.; Jewell, C.F. *J. Org. Chem.* **1998**, *63*, 55-58.

(93) (a) Yan, B. *Acc. Chem. Res.* **1998**, *31*, 621-630. (b) Yan, B. *J. Org. Chem.* **1998**, *63*, 4092-4097.

(94) Li, W.; Yan, B. *Tetrahedron Lett.* **1997**, *38*, 6485-6488.

(95) (a) Pivonka, D.E.; Russel, K.; Gero, T. *Appl. Spectrosc.* **1996**, *12*, 1471-1478. (b) Pivonka, D.E.; Simpson, T. R. *Anal. Chem.* **1997**, *69*, 3851-3853.

(96) (a) Keifer, P.A. *Drug Disc. Today* **1997**, *2*, 468-479. (b) Orge, F.; Wagner, A.; Mioskowski, C. *J. Comb. Chem.* **1999**, *1*, 25-27. (c) Keifer, P.A. *Curr. Opin. Biotech.* **1999**, *10*, 34-41.

(97) (a) Johnson, C.R.; Zhang, B. *Tetrahedron Lett.* **1995**, *36*, 9253-9256. (b) Bardella, F.; Eritja, R.; Pedroso, E.; Giralt, E. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 2793-2796.

(98) Fex, T.; Kihlberg, J. *Tetrahedron Lett.* **1996**, *37*, 7649-7652.

(99) Blossey, E.C.; Cannon, R.G. *J. Org. Chem.* **1990**, *55*, 4664-4668.

(100) Look, G.C.; Holmes, C.P.; Chinn, J.P.; Gallop, M.A. *J. Org. Chem.* **1994**, *59*, 7588-7590.

(101) Fitch, W.L.; Detre, G.; Holmes, C.P.; Shoolery, J.N.; Keifer, P.A. *J. Org. Chem.* **1994**, *59*, 7055-7956.

(102) (a) Riedl, R.; Tappe, R.; Berkessel, A. *J. Am. Chem. Soc.* **1998**, *120*, 8994-9000. (b) Seeberger, P.H.; Beebe, X.; Sukenick, G.D.; Pochapsky, S.; Danishefsky, S.J. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 491-493. (c) Op,

I.E.; Dhalluin, C.F.; Deprez, B.P.; Melnyk, P.C.; Lippens, G.M.; Tartar, A.L. Tetrahedron **1996**, *52*, 12209-12222. (d) Warrass, R.; Lippens, G. In *Combinatorial Chemistry;* Jung, G., Ed.; Wiley-VCH, 1999; p 533-542.

(103) Süßmuth, R.; Trautwein, A.; Ritcher, H.; Nicholson, G.; Jung, G. In *Combinatorial Chemistry;* Jung, G., Ed.; Wiley-VCH, 1999; p 499-532.

(104) Egner, B.J.; Cardno, M.; Bradley, M. *J. Chem. Soc., Chem. Commun.* **1995**, *21*, 2163-2164.

(105) Fitzgerald, M.C.; Harris, K.; Shevlin, C.G.; Siuzdak, G. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 9709-982.

(106) (a) *The chemistry of the ether linkage;* Patai, S., Ed.; Interscience, 1967. (b) Larock, R.C. In *Comprehensive Functional Group Transformations;* Wiley-VCH, 1989; p 443-462. (c) Baggett, N. In *Comprehensive Organic Chemistry'*; Barton, D.; Ollis, D.W., Eds.; p 799-852. (d) Houben-Weyl. *'Methoden der Organischen Chemie'*, 4th Ed., Vol VI/3, G. Thieme: Stuttgart, 1965; part 1.

(107) (a) Stones, D.; Miller, D.J.; Beaton, M.W.; Rutherford, T.J.; Gani, D. *Tetrahedron Lett.* **1998**, *39*, 4875-4878. (b) Deegan, T. L.; Gooding, O.W.; Baudart, S.; Porco, J.A. *Tetrahedron Lett.* **1997**, *38*, 4973-4976.

(108) (a) Leznoff, C.C.; Wong, J.Y. *Can. J. Chem.* **1973**, *51*, 3756-3759. (b) McArthur, C.R.; Worster, P.M.; Jiang, J.L.; Leznoff, C.C. *Can. J. Chem*, **1982**, *60*, 1836-1841. (c) Hernandez, A.S.; Hodges, J.C. *J. Org. Chem.* **1997**, *62*, 3153-3157.

(109) Nicolaou, K.C.; Winssinger, N.; Vourloumis, D.; Ohshima, T.; Kim, S.; Pfefferkorn, J.; Xu, J.Y.; Li, T. *J. Am. Chem. Soc.* **1998**, *120*, 1084-10826.

(110) Moon, H.S.; Schore, N.E.; Kurth, M.J. *J. Org. Chem.* **1992**, *57*, 6088-6089.

(111) Worster, P.M.; McArthur, C.R.; Leznoff, C.C. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 221-223.

(112) (a) Moon, H.S.; Schore, N.E.; Kurth, M.J. *Tetrahedron Lett.* **1994**, *35*, 8915-8917.

(113) Wunberg, T.; Kallus, C.; Opatz, T.; Henke, S.; Schimdt, W.; Kunz, H. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 2503-2505.

(114) (a) Furth, P.S.; Reitman, M.S.; Cook, A.F. *Tetrahedron Lett.* **1997**, *38*, 5403-5406. (b) Furth, P.S.; Reitman, M.S.; Gentle, R.; Cook, A.F. *Tetrahedron Lett.* **1997**, *38*, 6643-6645.

(115) Fréchet, J.M.J.; Kelly, J.; Sherington, D.C. *Polymer* **1984**, *25*, 1491-1498.

(116) Hanessian, S.; Xie, F. *Tetrahedron Lett.* **1998**, *39*, 733-736.

(117) Hanessian, S.; Ma, J.; Wang, W. *Tetrahedron Lett.* **1999**, *40*, 4631-4634.

(118) Nicolaou, K.C.; Winssinger, N.; Pastor, J.; DeRoose, F. *J. Am. Chem. Soc.* **1997**, *119*, 449-450.

(119) Du, X.; Armstrong, R.W. *J. Org. Chem.* **1997**, *62*, 5678-5679.

(120) (a) Krchňák, V.; Flegelová, Z.; Weichsel, A.S.; Lebl, M. *Tetrahedron Lett.* **1995**, *36*, 6193-6196. (b) Valerio, R.M.; Bray, A.M.; Patsiouras, H. *Tetrahedron Lett.* **1996**, 37, 3019-3022.

(121) (a) Rano, T.A.; Chapman, K.T. *Tetrahedron Lett.* **1995**, *36*, 3789-3792. (b) Richter, L.S.; Gadek, T.R. *Tetrahedron Lett.* **1994**, *35*, 4705-4706.

(122) Danishesfsky, S.J.; McClure, K.F.; Randolph, J.T.; Ruggeri, R.B. *Science* **1993**, *260*, 1307-1309.

(123) Brill, W.K-D.; DeMesmaeker, A.; Wendeborn, S. *Synlett* **1998**, 1085-1090.

(124) (a) Fréchet, J.M.M. In *Polymer Supported Reactions in Organic Synthesis;* Hodge, P; Sherrington, D.C., Eds.; John Wiley and sons, 1980; p 407-434. (b) Seeberger, P.H.; Bilodeau, M.T., Danishefski, S.J. *Aldrichimica Acta* **1997**, *30*, 75-92. (c) Osborn, H.M.I.; Khan, T.H. *Tetrahedron* **1999**. *55*, 1807-1850.

(125) Tortolani, D.R.; Biller, S.A. *Tetrahedron Lett.* **1996**, *37*, 5687-5690.

(126) Routledge, A.; Abell, C.; Balasubramanian, S. *Synlett* **1997**, 61-62.

(127) Zaragoza, F.; Vejle Petersen, S. *Tetrahedron* **1996**, *52*, 5999-6002.

(128) Heinonen, P.; Lönnberg, H. *Tetrahedron Lett.* **1997**, *38*, 8569-8572.

(129) Berteina, S.; Wendeborn, S.; De Mesmaeker, A. *Synlett* **1998**, 1231-1233.

(130) Beebe, X.; Chiappari, C.L.; Kurth, M.J.; Schore, N.E. *J. Org. Chem.* **1995**, *60*, 4204-4212.

(131) Mergler, M.; Dick, F.; Gosteli, J.; Nyfeler, R. *Tetrahedron Lett.* **1999**, *40*, 4663-4664.

(132) (a) Beebe, X.; Shore, N.E.; Kurth, M.J. *J. Am. Chem. Soc.* **1992**, *114*, 10061-10062. (b) Beebe, X.; Shore, N.E.; Kurth, M.J. *J. Org. Chem.* **1995**, *60*, 4196-4203.

(133) Rottlander, M.; Knochel, P. *J. Comb. Chem.* **1999**, *1*, 181-183.

(134) Kolb, H.C.; VanNieuwenhze, M.S.; Sharpless, K.B. *Chem. Rev.* **1994**, *94*, 2483-2547.

(135) Kunz, H.; Waldmann, H. In *Comprehensive Organic Synthesis;* Trost, B.M.; Fleming, I., Eds.; Pergamon Press:New York, 1991; Vol 6, p 631-701.

(136) (a) Rossiter, B.E. In *Asymmetric Synthesis;* Morrison, J.D. Ed.; Academic Press: New York, 1986; Vol 5, p 193. (b) Gorzynski Smith, J. *Synthesis* **1984**, 629-630.

(137) (a) Lorhay, B.B. *Synthesis* **1992**, 1035-1052. (b) Andersen, K.K. In *Comprehensive Organic Chemistry;* Barton, D.; Ollis, D.W., Eds.; Pergamon Press: New York, 1979; Vol 3, 367-372. (c) Marko, I.E.; Svendsen, J.S. In *Comprehensive Organometallic Chemistry;* Abel, E.D.; Gordon, F.; Stone, A.; Wilkinson, G., Eds.; Pergamon Press: New York, 1995; Vol 12, p 1169-1176.

(138) (a) David, S.; Hanessian, S. *Tetrahedron* **1985**, *41*, 643-663. (b) Peyrere, M.; Quintard, J.P.; Rahm, A. In *Tin in Organic Synthesis;* Butterworths:London, 1987; p 261-285.

(139) Fraser, A.S.; Kawasaki, A.M.; Jung, M.E.; Manoharan, M. *Tetrahedron Lett.* **2000**, *41*, 1523-1526.

(140) Exemples of double displacement with C-nucleophiles: (a) Gao, Y.; Sharpless, K.B. *J. Am. Chem. Soc.* **1988**, *110*, 7538-7539. (b) Ramaswamy, S.; Prasad, K.; Repic, O. *J. Org. Chem.* **1992**, 57, 6344-6347. N-nucleophiles: (c) Lorhay, B.B.; Gao, Y.; Sharpless, K.B. *Tetrahedron Lett.* **1989**, *3*, 2623-2626. (d) Oi, R.; Sharpless, K.B. *Tetrahedron Lett.* **1991**, *32*, 999-1002. S-Nucleophiles: (d) Ozturk, T.; Povey, D.C.; Wallis, J.D. *Tetrahedron* **1994**, *5*, 11205-11212.

(141) Goren, M.B.; Kochansky, M.E. *J. Org. Chem.* **1973**, *38*, 3510-3513.

(142) Kim, B.M.; Sharpless, K.B. *Tetrahedron Lett.* **1989**, *30*, 655-658.

(143) (a) Burstein, S.; Lieberman, S. *J. Am. Chem. Soc.* **1958**, *80*, 5235-5237. (b) Batts, B.B. *J. Chem. Soc. B, Phys. Org.* **1966**, 547-555. (c) Benkovic, S.J. *J. Am. Chem. Soc.* **1966**, *88*, 5511-5513. (d) Benkovic, S.J.; Dunikoski, L.K. *Biochemistry* **1970**, *9*, 1390-1392. (d) Benkovic, S.J. In *Comprehensive Chemical Kinetics;* Bamford, C.H.; Tipper, C.F.H., Eds.; Elservier: Amsterdam, 1972; Vol 10, p 39-51.

(144) Gao, Y.; Sharpless, K.B. *J. Am. Chem. Soc.* **1988**, *110*, 7538-7539.

(145) Fisher, G.W.; Zimmermann, T. In *Comprehensive Heterocyclic Chemistry;* Katriski, A.R.; Rees, C.W., Eds.; Pergamon Press: New York, 1984; Vol 6, p 851-895.

(146) Gao, Y.; Zepp, C.M. *Tetrahedron Lett.* **1991**, *32*, 3155-3158.

(147) Lorhay, B.B.; Ahuja, J.R. *J. Chem. Soc., Chem. Commun.* **1991**, 95-97.

(148) Rebeire, F.; Kagan, H.B. *Tetrahedron Lett.* **1989**, *30*, 3659-3662.

(149) Jeong, L.S.; Marquez, V.E. *Tetrahedron Lett.* **1996**, *37*, 2353-2356.

(150) Andersen, K.K.; Fenton, S.W. *J. Org. Chem.* **1964**, *29*, 3270-3273.

(151) Berridge, M.S.; Franceschini, M.P.; Rosenfield, E.; Tewson, T.J. *J. Org. Chem.* **1990**, *55*, 1211-1217.

(152) (a) Tomalia, D.A.; Falk, J.C. *J. Heterocyclic Chem.* **1972**, *9*, 891-894. (b) Massonneau, V.; Radisson, X.; Mulhauser, M.; Michel, N.; Buforn, A.; Botannet, B. *New J. Chem.* **1992**, *16*, 107-112. (c) Vanhessche, K.P.M.; Sharpless, K.B. *Chem. Eur. J.* **1997**, *3*, 517-522.

(153) Gautun, O.R.; Carlsen, P.H.J.; Maldal, T.; Vikane, O.; Gilje, E. *Acta Chem. Scand.* **1996**, *50*, 170-177.

(154) Klotz, W.; Schmidt, R.R. *Synthesis* **1996**, 687-689.

(155) Ko, S.Y.; Malik, M.; Dickinson, A.F. *J. Org. Chem.* **1994**, *59*, 2570-2576.

(156) Ko, S.Y. *Tetrahedron Lett.* **1994**, *35*, 3601-3604.

(157) Kalantar, T.H.; Sharpless, K.B. *Acta Chem. Scand.*, **1993**, *47*, 307-313.

(158) Brimble, M.A.; Prabaharan, H. *Tetrahedron* **1998**, *54*, 2113-2128.

(159) McDonald, F.E.; Vadapally, P. *Tetrahedron Lett.* **1999**, *40*, 2235-2238.

(160) Beauchamp, T. J.; Powers, J.P.; Rychnovsky, S.D. *J. Am. Chem. Soc.* **1995**, *117*, 12873-12874.

(161) For earlier methods of oxidation of cyclic sulfite under stoichiometric conditions see: (a) Gardner, H.K.; Lucas, H.J. *J. Am. Chem. Soc.* **1950**, *72*, 5497-5499. (b) Lowe, G.; Salamone, S.J. *J. Chem. Soc., Chem. Commun.*, **1983**, 1392-1394.

(162) Kim, B.M.; Sharpkless, K.B. *Tetrahedron Lett.* **1990**, *31*, 4317-4320.

(163) (a) Tewson, T.J. *J. Org. Chem.* **1983**, *48*, 3507-3510. (b) Von der Klein, P.A.M.; Boons, G.J.P.H.; Veeneman, G.H.; Van der Marel, G.A. *Tetrahedron Lett.* **1989**, *30*, 5477-5480.

(164) (a) Swistok, J.; Tiley, J.W.; Danho, W.; Wagner, R.; Mulkerins, K. *Tetrahedron Lett.* **1989**, *30*, 5045-5048. (b) Panek, J.S.; Zhu, B. *Tetrahedron Lett.* **1996**, *37*, 8151-8154.

(165) (a) Hu, Y.; Porco, J.A.J.; Labadie, J.W.; Gooding, O.W. *J. Org. Chem.* **1998**, *63*, 4518-4521. (b) Stranix, B.R.; Liu, H.Q.; Darling, G.D. *J. Org. Chem.* **1997**, *62*, 6183-6186. (c) Randolph, J.T.; McClure, K.F.; Danishefsky, S.J. *J. Am. Chem. Soc.* **1995**, *117*, 5712-5719. (d) Chan, T.H.; Huang, W.Q. *J. Chem. Soc., Chem. Commun.* **1985**, 909-911.

(166) (a) Li, Z.; Ganesan, A. *Synlett* **1998**, 405-406. (b) Chen, C.; Ahlberg Randall, L.A.; Miller, R.B.; Jones, A.D.; Kurth, M.J. *J. Am. Chem. Soc.* **1994**, *116*, 2661-2662.

(167) Garigipati, R.S. *Tetrahedron Lett.* **1997**, *38*, 6807-6810.

(168) Thompson, L.A.; Ellman, J.A. *Tetrahedron Lett.* **1994**, *35*, 9333-9336.

(169) Wang, G.T.; Li, S.; Wideburg, N.; Krafft, G.A.; Kempf, D.J. *J. Med. Chem.* **1995**, *38*, 2995-3002.

(170) Bohm, G.; Dowden, J.; Rice, D.C.; Burgess, I.; Pilard, J.; Guilbert, B.; Haxton, A.; Hunter, R.C.; Turner, N.J.; Flitsch, S.L. *Tetrahedron Lett.* **1998**, *39*, 3819-3822.

(171) (a) Alsina, J.; Chiva, C.; Ortiz, M.; Rabanal, F.; Giralt, E.; Albericio, F. *Tetrahedron Lett.* **1997**, *38*, 883-886. (b) Routledge, A.; Stock, H.T.; Flitsch, S.L.; Turner, N.J. *Tetrahedron Lett.* **1997**, *38*, 8287-8290. (c) Sauerbrei, B.; Jungmann, V.; Waldmann, H. *Angew. Chem. Int. Ed. Engl.* **1998**, *37*, 1143-1146.

(172) Linkers for carboxylic acids: see references 58a and 58b and references cited therein.

(173) For examples of the use of trityl based resins for the immobilisation of diols see: (a) Fyles, T.M. *Can. J. Chem.* **1978**, *56*, 1031-1035. (b) Leznoff, C.C. *Tetrahedron Lett.* **1982**, *23*, 3023-3027. (c) Leznoff, C.C. *Can. J. Chem.* **1977**, *55*, 1143-1150. (d) Leznoff, C.C. *J. Chem. Soc. Chem Comm.* **1976**, 251-252.

(174) Liboska, R.; Masojídková, M.; Rosenberg, I. *Collect. Czech. Chem. Commun.* **1996**, *61*, 779-790.

(175) Chaudhary, S.K.; Hernadez, O. *Tetrahedron Lett.* **1979**, *2*, 95-98.

(176) Colin-Messager, S.; Girard, J.P.; Rossi, J.C. *Tetrahedron Lett.* **1992**, *33*, 2689-2692.

(177) (a) Frechet, J.M.; Nuyens, L.J. *Can. J. Chem.* **1976**, *54*, 926-934. (b) Novabiochem 'The Combinatorial Chemistry Catalogue', March 1999, S15. (c) 'Advanced Chemtech Handbook of Combinatorial and Solid Phase Organic Chemistry', 1998, 340-342.

(178) Wenschuh, H.; Beyermann, M.; Haber, H.; Seydel, J.K.; Klaus, E.; Bienert, M.; Carpino, L.A.; Elfaham, A.; Albericio, F. *J. Org. Chem.* **1995**, *60*, 405-410.

(179) Wenschuh, H.; Beyermann, M.; Haber, H.; Seydel, J.K.; Krause, E.; Bienert, M. *J. Org. Chem.* **1995**, *60*, 405-410.

(180) (a) Borhan, B.; Wilson, J.A.; Gasch, M.J.; Ko, Y.; Kurth, D.M.; Kurth, M.J. *J. Org. Chem.* **1995**, *60*, 7375-7378.

(181) Fréchet, J.M.; Nuyens, L.J. *Can. J. Chem.* **1976**, 926-934.

(182) Atherton, E.; Sheppard, R.C. In 'Solid Phase Peptide Synthesis', Rickwood, D.; Hames, B. Eds., IRL Press, 1989, p 136.

(183) Leznoff, C.C. *Acc. Chem. Res.* **1978**, *11*, 327-335.

(184) Keifer, P.A. *J. Org. Chem.* **1996**, *61*, 1558-1559.

(185) Bodanszky, M.; Bodanszky, A. In *The Practice of Peptide Synthesis;* Springer-Verlag: Berlin Heidelberg, 1994.

(186) Lane, C.F.; Myatt, H.L.; Daniels, J.; Hopps, H.B. *J. Org. Chem.* **1974**, *39*, 3052-3054.

(187) Shimamoto, K.; Ishida, M.Shinozaki, H.; Ohfune, Y. *J. Org. Chem.* **1991**, *56*, 4167-4176.

(188) Sjoberg, B.; Sjoberg, K. *Acta Chem. Scan.* **1972**, *26*, 275-278.

(189) Deng, J.; Hamada, Y.; Shiori, T. *Synthesis* **1998**, 627-638.

(190) Rodriguez, J.B.; Markey, S.P.; Ziffer, H. *Tetrahedron: Asymmetry* **1993**, *4*, 101-108.

(191) Shishido, K.; Yamashita, A.; Hiroya, K.; Fukumoto, K. *J. Chem. Soc., Perkin Trans 1* **1990**, 469-475.

(192) Nymann, K.; Svendsen, J.S. *Acta Chem.Scand.* **1994**, *48*, 183-186.

(193) Kim, K.S.; Lee, G.W.; Cho, I.H.; Joo, Y.H. *Bull. Korean Chem. Soc.* **1993**, *14*, 660-661.

(194) Kim. J. *J. Med. Chem.* **1998**, *41*, 2451-2460.

(195) Lichtenberg, Duerr, *Bull. Chem. Soc. Chim. Fr.*, **1956**, 664-671. Lowe, G. *J. Chem. Soc., Chem. Commun.* **1985**, *16*, 1075-1078.

(196) Lichtenberg, Kircher, *C.R. Hebd. Seances Acad. Sci*, **1949**, *229*, 1346-1449.

(197) Lichtenberg, *Bull. Soc. Chim. Fr.*, **1948**, 1009-1012.

(198) Curran, D.P. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 1174-1196.

(199) Kociénski, P.J. In *Protecting Groups*; Enders, D.; Noyori, R.; Trost, B.M., Eds.; Thieme: New York, 1994.

(200) Krebbs, H.; Komori,T.; Kawaski, T. *Liebigs Ann. Chem.* **1984**, 2, 296-305.

(201) (a) Tiecco, M.; Testafferri, L.; Tingilo, M. *Tetrahedron* **1993**, *49*, 5351-5358. (b) Ogawa, K.; Terada, T.; Mukurama, Y.; Hamakawa, T.; Hashimoto, S.; Fuji, S. *Chem. Pharm. Bull.* **1986**, *34*, 1118-1127.

(202) Kaiser, E.T. In *The Organic Chemistry of Sulfur;* Oae, S., Ed.; Plenum Press:New York, 1944; p 48-74.

(203) Penney, C.L.; Perlin A.S. *Carbohydrate Res.* **1981**, 93, 241-246.

(204) Proud, A.D.; Prodger, J.C.; Flitsch, S.L. *Tetrahedron Lett.* **1997**, *38*, 7243-7246.

(205) Meese, C.O. *Synthesis* **1984**, 1041-1042.

(206) Brown, A.G.; Corbett, D.F.; Eglington, A.J.; Howarth, T.T. *Tetrahedron* **1983**, *39*, 2551-2562.

(207) Lu, Y.A.; Felix, A.M. *Int. J. Pept. Protein Res.* **1994**, *43*, 127-129.

(208) Carrasco, M.R.; Fitzgerald, M.C.; Oda, Y.; Kent, S.B.H. *Tetrahedron Lett.* **1997**, *38*, 6331-6334.

(209) (a) McKeown, S.C.; Wason, S.P.; Carr, R.A.E.; Marshall, P. *Tetrahedron Lett.* **1999**, *40*, 2007-2410. (b) Murray, P.J.; Kay, C.; Scicinski, J.J.; McKeown, S.C.; Watson, S.P.; Carr, R.A.E. *Tetrahedron Lett.* **1999**, *40*, 5609-5612.

(210) (a) Teague, S.J. *Tetrahedron Lett.* **1996**, *37*, 5751-5754. (b) Holmes, C.P. *J. Org. Chem.*, **1997**, *62*, 2370-2380. (c) Whitehouse, D.L.; Savinov, S. N.; Austin, D.J. *Tetrahedron Lett.* **1997**, *38*, 7851-7852. (d) Gordeev, M.F.; Gordon, E.M.; Patel, D.V. *J. Org. Chem.* **1997**, *62*, 8177-8181.

(211) Bouloc, N. M.Phil.; Southampton University, **1996**.

(212) Bradbury, J.B.; Baumgold, J.; Paek, R.; Kammula, U.; Zimmet, J.; Jacobson, K. A. *J. Med. Chem.* **1991**, *34*, 1073-1079.

(213) Robertson, D.N.*J. Org. Chem* **1957**, *21*, 1190-1194.

(214) (a) Wessel, H.P.; Iversen, T.; Bundle, D.R. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2247-2250. (b) Audia, J. E. A.; Boisvert, L.; Patten, A. V., Danishesky, S. *J. Org. Chem.* **1989**, *54*, 3738-3740.

(215) Walkup, R.D.; Mosher, M.D.; *Tetrahedron*, **1993**, *49*, 9285-9294.

(216) (a) Nakajima, N.; Horita, K.; Abe, R.; Yonemitsu, O. *Tetrahedron Lett.* **1988**, *29*, 4139-4142. (b) Evans, D.A.; Kaldor, S.W.; Jones, T.K.; Clardy, J.; Stout, T. J. *J. Am. Chem. Soc.* **1990**, *112*, 7001-7031.

(217) McDonald, F.E.; Vadapally, P. *Int. J. Pept. Protein Res.* **1993**, *42*, 118-124

(218) (a) Cushman, M. *J. Org. Chem.* **1996**, *61*, 9368-9372. (b) Campbell, D.A. *J. Org. Chem. 61*, **1996**, 6720-6722. (c) Ellman, J.A. *J. Org. Chem.* **1996**, *61*, 4494-4495. (d) *Tetrahedron Lett.* **1998**, *39*, 935-938.

(219) Spencer, J. R.; Antonenko, V. V.; Delaet, N. G.J.; Goodman, M. *Int. J. Pept. Protein Res.* **1992**, *40*, 282-293.

(220) Albericio, F. *Tetrahedron Lett.* **1997**, *38*, 4853-4856.

(221) (a) Coste, J. *Tetrahedron Lett.* **1990**, *31*, 669-672. (b) Coste, J. *Tetrahedron* **1991**, *47*, 259-270.

(222) Boas, U.; Pedersen, B.; Christensen, J.B. *Synth. Commun.* **1998**, *28*, 1223-1231.

(223) Peterson, P. E.; Stephanian, M. S. *J. Org. Chem.* **1988**, *53*, 1903-1907.

(224) Wang, Z.M.; Kolb, H. C.; Sharpless, K. B. *J. Org. Chem.* **1994**, *59*, 5104-5105.

(225) (a) Anderson, K.K.; Fenton, S.W. *J. Org. Chem.* **1964**, *29*, 3270-3273. (b) Perunal, P.T. *Synth. Comm.* **1990**, *20*, 1353-1356.

(226) Koskinen, A.M.P.; Karvinen, E.K.; Siirilae, J.P. *J. Chem. Soc., Chem. Commun.* **1994**, *1*, 21-22

(227) Jang, D.O.; Joo, Y.H. *Synth. Commun.* **1998**, *28*, 871-878.

(228) Zefirov, N.S.; Sorokin, V.D.; Zandankin, V.V.; Kozmin, A.S. *J. Org. Chem. (Engl. Transl.)* **1986**, *22*, 398-399.

(229) Berridge, M.S.; Franceschini, M.P.; Rosenfeld, E.; Tewson, T.J. *J. Org. Chem.* **1990**, *55*, 1211-1217.

(230) Hellier, D.G.; Liddy, H.G. *Magn. Reson. Chem.* **1988**, *26*, 671-674. Edmunson, R.S. *Tetrahedron* **1964**, *20*, 2781-2795.

(231) Brimacombe, J.S. *J. Chem. Soc* **1960**, 201-211.

(232) Yokomatsu, T.; Nakabayashi, N.; Matsumuto, K.; Shibuya, S. *Tetrahedron: Asymmetry* **1995**, *6*, 3055-3062.

(233) Burk, M.J.; Feaster, J.E.; Nugent, W.A.; Harlow, R.L. *J. Am. Chem. Soc.* **1993**, *115*, 10125-10138.

(234) Robertson *J. Org. Chem* .**1957**, *21*, 1190-1195.