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Use of Polymeric Supports for the Synthesis of Structurally Defined Oligomers

A Thesis Presented by

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In Partial Fulfilment of the Requirements
For the Award of the Degree of

Doctor of Philosophy

of the

University of London

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Abstract

The aims of this project were firstly to develop a protocol for the iterative synthesis of polyethers on a polymeric support, using suitably protected monomers. The synthesis of cyclic ethers by an intramolecular cyclisation/cleavage from the polymeric support, utilising a sulfonyl chloride linker, was also desired. The final aim was to develop a method for reductive amination on a polymeric support, with a view to forming mixed amine/ether oligomers.

Chapter 1 is a review of the range of polymers that have been used as supports in organic synthesis, various linkers that have been used to immobilise molecules onto supports, the synthesis of polyethers and cyclic ethers in solution and on polymeric supports, and reductive amination in solution and on polymeric supports. Chapter 2 describes the protecting group strategies that were developed for the synthesis of linear, singly branched and dibranched monomers. These strategies gave monomers in very high yields, which were suitably protected for use in the synthesis of oligomers and cyclic ethers in later chapters. Chapter 3 describes the synthesis of novel linkers on a soluble PEG support; PEG sulfonyl chloride and PEG Wang trichloroacetimidate. Both linkers were synthesised in high yields, and were successfully utilised in the PEG supported reactions described in later chapters. Chapter 4 describes the synthesis of oxetanes by mono-activation of a branched diol as a sulfonate ester in solution, on cross-linked polystyrene and on PEG, followed by intramolecular cyclisation/cleavage. Oxetanes were afforded in good yields, under mild conditions, with rapid purification. Chapter 5 describes the development of an iterative polyether synthesis, initially on cross-linked polystyrene, and then on a PEG support. This provided access to a range of structurally defined oligoethers and avoided the laborious purification techniques associated with classical solution based methods. Chapter 6 describes the mild and selective oxidation of an immobilised alcohol to an aldehyde on a PEG support, followed by reductive amination with secondary amines. A strategy is also proposed for the synthesis of mixed amine/ether oligomers. The final chapter describes the experimental techniques employed.

Table of Contents

Results and Discussion

Abbreviations

ACE	=	Active Chain End
AM	=	Activated Monomer
BAP	=	Borane-Pyridine Complex
Bn	=	Benzyl
Boc	=	*tert*-Butoxycarbonyl
d	=	Doublet
Dan	=	Dansyl
DBU	=	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	=	Dicyclohexylcarbodiimide
Dde	=	1-(4,4-Dimethyl-2,6-dioxocyclohexylidene)ethyl
DDQ	=	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DHP	=	Dihydropyran
DIPEA	=	Di*iso*propylethylamine
DMAP	=	4-Dimethylamino Pyridine
DMF	=	N,N-Dimethylformamide
DMSO	=	Dimethyl sulfoxide
Dod	=	4,4'-Dimethoxy-trityl
EDC	=	*N*-(3-Dimethylaminopropyl)-*N'*-ethyl carbodiimide
EI	=	Electron Ionisation
eq.	=	Molar Equivalents
FAB	=	Fast Atom Bombardment
Fmoc	=	9-Fluorenylmethoxycarbonyl
HPLC	=	High Performance Liquid Chromatography
HRMS	=	High Resolution Mass Spectrometry
Hz	=	Hertz
IR	=	Infrared
IBX	=	*o*-Iodoxybenzoic Acid
LPOS	=	Liquid Phase Organic Synthesis
(m)	=	Medium
m	=	Multiplet

m	=	Meta
m.p.	=	Melting Point
mCPBA	=	*meta*-Chloroperoxybenzoic Acid
MHz	=	Megahertz
Mmd	=	4-Methoxy-dityl
mol.	=	Mole
Ms/Mesyl	=	Methanesulfonyl
NMR	=	Nuclear Magnetic Resonance
NMO	=	N-Methylmorpholine N-Oxide
o	=	Ortho
^{o}C	=	Centigrade
OCbz	=	Carbobenzoxy
p	=	Para
PAMAM	=	Polyamidoamine
Pfb	=	Perfluorobutyrate
PS	=	Cross-Linked Polystyrene
PS-PEG	=	Poly(styrene-oxyethylene) Graft Copolymer
PEG	=	Poly(ethylene glycol)
PEGA	=	Acrylolated *O*,*O'*-bis(2-Aminopropyl)polyethylene Glycol
POEPS	=	Polyoxyethylene-polystyrene
POEPOP	=	Polyoxyethylene-polyoxypropylene
PPTS	=	Pyridinium p-toluenesulfonate
PTC	=	Phase Transfer Catalysis
q	=	Quartet
quin	=	Quintet
r.t.	=	Room Temperature
(s)	=	Strong
s	=	Singlet
sept	=	Septet
SLURPS	=	Superior Liquid-Uptake Resins for Polymer-Supported Synthesis
S_N2	=	Nucleophilic Substitution Bimolecular
SPOS	=	Solid Phase Organic Synthesis
t	=	Triplet
t/*tert*	=	Tertiary

TBA	=	Tetrabutylammonium
TBAAc	=	Tetrabutylammonium Acetate
TBAI	=	Tetrabutylammonium Iodide
TBAOH	=	Tetrabutylammonium Hydroxide
TBDPS	=	*tert*-Butyldiphenylsilyl
TBS	=	*tert*-Butyldimethylsilyl
TFA	=	Trifluoroacetic Acid
THF	=	Tetrahydrofuran
THP	=	Tetrahydropyran
TLC	=	Thin Layer Chromatography
TME	=	Trimethylolethane
TMS	=	Trimethylsilyl
TOPCAT	=	2-Pyridylthiocarbonate
TPAP	=	Tetrapropylammonium Perruthenate
Ts/Tosyl	=	*p*-Toluenesulfonyl
UV	=	Ultraviolet
(w)	=	Weak

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Chapter 1

1.0 Introduction

This review will discuss aspects of polymer supported organic synthesis, including the different types of polymer that have been used as supports, from Merrifield's groundbreaking work on cross-linked polystyrene resins to recent work using soluble dendrimers. Methods of linking small molecules to these supports, with a specific focus on methods which utilise hydroxyl functionalities as the point of immobilisation, are also discussed. The introduction will then go on to present syntheses of polyethers and cyclic ethers, both in solution and on polymer supports and the use of reductive amination for the synthesis of polyamines in solution and on solid supports.

1.1 Polymer Supported Synthesis

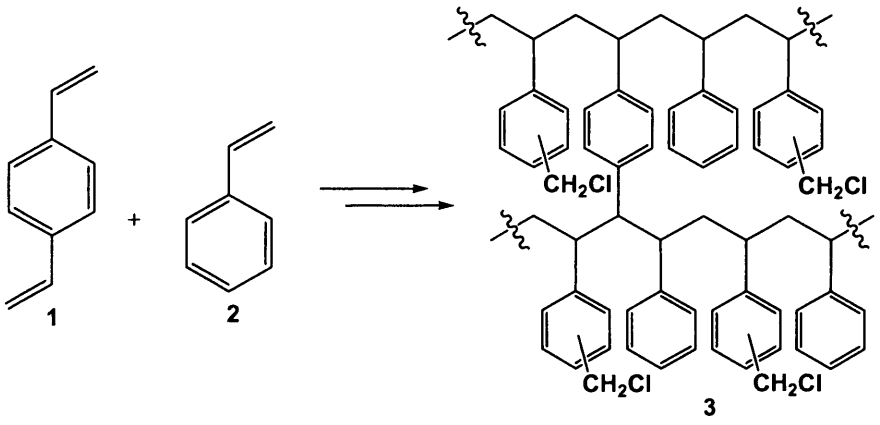
Polymers have been used as supports in organic synthesis for over 40 years. [1] The most frequently used approach involves the covalent attachment of a small molecule to the support, one or more transformations, followed by cleavage of the desired product. The use of polystyrene as a solid support was first reported by Merrifield, in the field of peptide synthesis.[1] By covalently attaching the first protected amino acid of the chain to a completely insoluble polymer, a peptide can be built up iteratively on the support, washing away excess reagents at each stage. This has been extensively used as an alternative to the more time consuming recrystallization techniques after each step to purify products, usually associated with classical solution phase peptide synthesis. While Merrifield and other groups have developed many other novel syntheses on polymer supports, these were mainly iterative oligomers syntheses such as those of oligonucleotides [2, 3] and oligosaccharides.[4] It is only fairly recently that polymer supported synthesis has really become a commonly used alternative to solution based methodologies. The increased use of polymer supported chemistry in recent years is largely due to the rise in popularity of

combinatorial chemistry within the pharmaceutical industry where advantages of such strategies lend themselves perfectly to the clean and simple construction of vast compound libraries.

The major advantage that this approach to organic synthesis has over an analogous solution based synthesis is that the high molecular weight of the support can be utilised to isolate it from low molecular weight reagents used to carry out the transformations using very straightforward procedures, such as washing with appropriate solvents. This not only avoids the sometimes complex and often time consuming purification of intermediates associated with solution based reactions (e.g. flash chromatography) but it also means that an excess of reagents can be used to drive the polymer supported reaction to completion without making purification more arduous.

1.1.1 Influence of Polymer Structure on Utility as a Support

For many years reactions of this type were almost exclusively carried out on cross-linked polystyrene (PS) resins, which remain the most widely used support to this day. When initially designing a polymer supported peptide synthesis, Merrifield considered various polymers including cellulose, polyvinyl alcohol, and polymethyl acrylate, but had the most success using a chloromethylated copolymer (**3**) synthesised from styrene (**2**) and divinylbenzene (**1**, scheme 1.1.1.1), in the form of 200-400 mesh beads.[1]



Scheme 1.1.1.1 Synthesis of a Chloromethylated PS Resin (**3**)

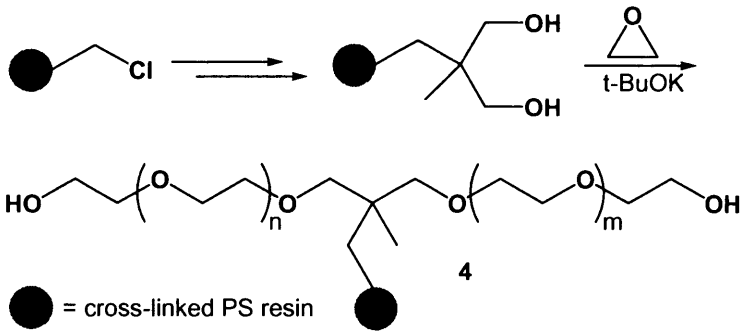
In appropriate swelling solvents, reagents can diffuse through the polystyrene matrix and access reactive end groups. While reaction rates are generally slower than the analogous solution based reactions, due to steric hindrance and environmental effects caused by the polymer matrix, PS resins have been used as supports for a very diverse range of transformations. More recently, functionalised PS resins have also been widely used as electrophilic and nucleophilic scavengers,[5-9] as well as providing supports for catalysts.[10]

While the properties of PS resins can be adjusted by modifying the polymeric structure (e.g. adjusting the level of cross-linking to control the flexibility of the polymer) there are several problems associated with the use of PS resins. The apolar nature of the polystyrene can make it an unsuitable environment for certain reactions, such as ether synthesis (chapter 1.2.5).[11] Also, polar protic solvents such as methanol and water cause the resin to shrink, and thus hinder access to the active sites, making it inappropriate for syntheses carried out in these solvents.[12] Furthermore, the monitoring of on-resin intermediates is not straightforward on polystyrene as in solution. However, solid and gel phase NMR have been achieved, giving some information as to the structure of the resins end groups.[13, 14] A standard method used for on-resin monitoring is by infrared (IR) spectrometry, but this is only useful if the transformation involves a characteristic functional group change.[15-17] Bead staining tests have also been developed for various modifications, which can indicate if a reaction has gone to completion.[18-20] A further problem is that the integrity of the beads can be damaged by mechanical force, so the standard method of stirring the reaction with a rotating magnet and a follower bead is not suitable. Various methods for agitating the reaction mixture have been employed; gentle overhead stirring, shakers, gas bubblers,[21] and rotating ovens (for heated reactions) [22]. Beads can also be cracked by sudden, large changes in volume caused by swelling or shrinkage, which is known as osmotic shock.[23]

In recent years, a lot of research in the area has focused on making novel polymers for use as supports, which provide a more solution-like environment. There are now a wide range of commercially available supports, from PS resins with a modified end structure, to alternative dendrimers with very different architectures. The most commonly used of these modified polystyrene resins are poly(styrene-oxyethylene)

graft copolymers (PS-PEG) resins.[19, 24] The first reported resins of this type had PEG chains grafted to the polystyrene *via* benzylic ether linkages, and are commonly known by their commercial name; Tentagel resins.[24] Due to the polar nature of PEG chains, these resins swell in a both polar and apolar solvents, and generally display greater swelling than standard polystyrene resins. The resins compatibility with reactions carried out in water and aqueous enzymatic reactions has been shown to be limited however.[25] The more solution-like environment provided by PS-PEG resins has been shown to give much improved reaction kinetics in various reactions e.g. peptide synthesis [26] and polyether synthesis.[27]

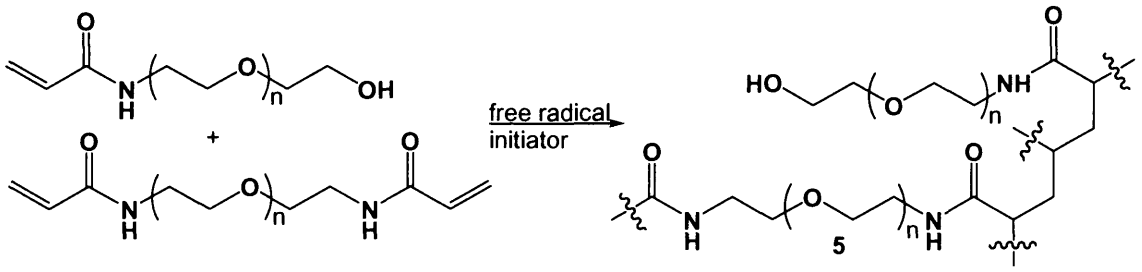
The gel like nature of the Tentagel resin whilst swollen allows resin supported intermediates to be studied by standard NMR techniques, which provides a useful tool for monitoring on-resin reactions.[24] Tentagel resins, however, have the disadvantage of having considerably lower loadings than PS resins (0.2-0.3 mmol g-1 compared to 0.6-2.0 mmol g^{-1} for 1 % cross-linked PS). Also, the instability of the benzylic ether linkage in strong acid makes the resin incompatible with these conditions. New PS-PEG resins have been developed to address these problems. For instance, PS-PEG resins, known commercially as Argogel^{TM} (**4**) have been developed with the benzylic ether linkage replaced with an aliphatic linkage to improve acid stability and with a bifunctional PS-PEG linkage to double the loading capacity (scheme 1.1.1.2).[19] As with PS resins, PS-PEG resins have the disadvantage that beads can be damaged by mechanical pressure or osmotic shock.



Scheme 1.1.1.2 Synthesis of Argogel^{TM} Resin (**4**) [19]

Another interesting class of PS resins that have been used in solid-phase synthesis are macroporous resins.[28] Unlike standard gel-type PS resins, which have low cross-linking (1-2 %), macroporous resins have a more rigid structure and the beads contain a network of small pores, through which small molecules in solution can diffuse in order to reach the reactive sites. Resins with between 10 and 85 % cross-linking were investigated for use as macroporous resins, with a composition near the middle of the range ultimately being selected for further development.[28] Because of its' rigidity, this resins was not significantly swollen by solvents and as a result reactions could be carried out in any solvent. Macroporous resins have the advantage over PS-PEG resins that the loading is similar to that of standard PS-resins. The structure also makes the beads more resistant to osmotic shock, although beads can still be damaged by mechanical pressure. Macroporous resins display disadvantages when it comes to reaction analysis, as the increased rigidity makes them unsuitable for monitoring by NMR. As with standard PS resins however, they can be monitored by IR spectrometry.[28]

Recently there has been an increased focus in developing solid supports that do not include polystyrene in their structure, in an attempt to find a polymeric support that is more universally applicable. An important class of this type of support are resins formed by the cross-linking of PEG chains. The first of these resins to be utilised as a solid support was PEGA (**5**) formed by the radical polymerization of acrylamide substituted PEG (scheme 1.1.1.3).[29, 30]

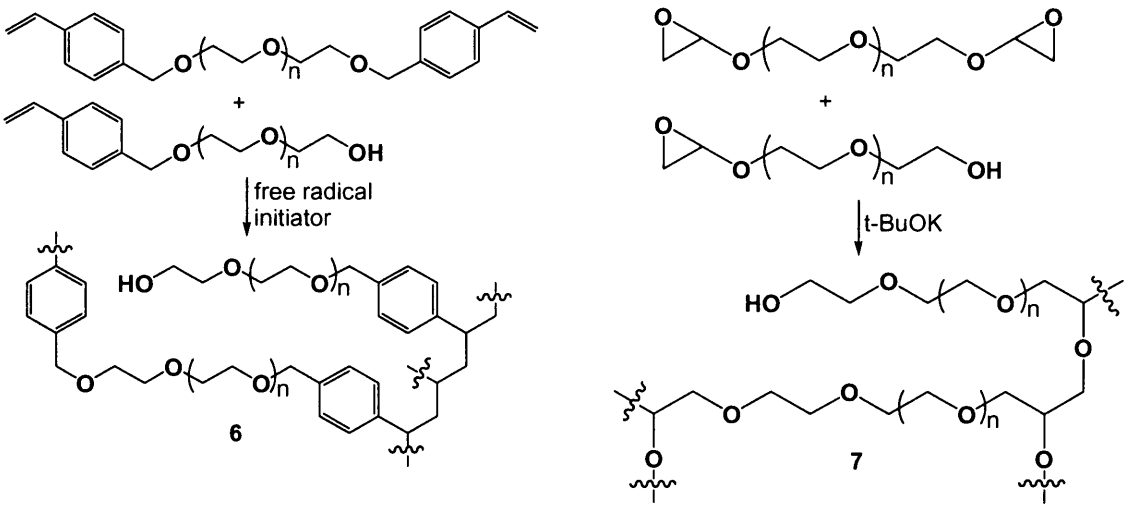


Scheme 1.1.1.3 Synthesis of PEGA (**5**) [29]

PEGA has shown high swelling volumes in both organic solvents and water. It has been successfully utilised in the synthesis of difficult peptide sequences and due to its more accessible reactive sites and compatibility with water it has been

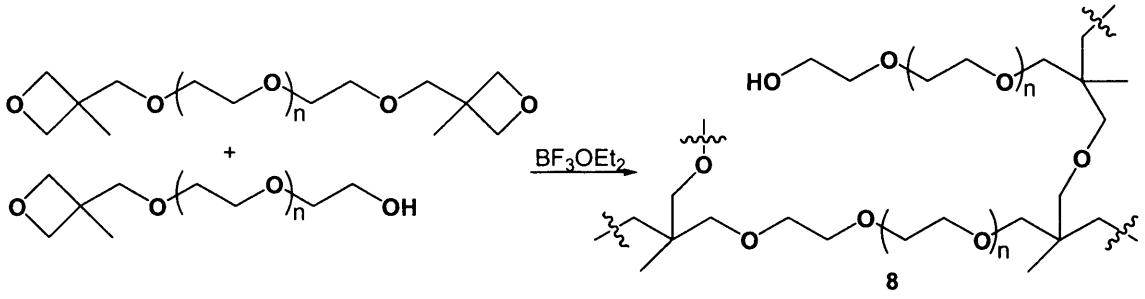
successfully utilised in enzymatic reactions carried out in aqueous media.[25, 31] However, PEGA has its limitations when it comes to chemical stability of the polymer backbone. Due to the large number of amide functionalities, it is not compatible with certain reaction conditions, for example reactions with Lewis acids or strong bases.[32]

In an attempt to form cross-linked PEG resins with more stable linkages than **5**, POEPS (**6**) and POEPOP (**7**) resins were developed.[32] Resin **6** (scheme 1.1.1.4) was formed by the homopolymerisation of vinylbenzyl ether terminated PEG chains, to give a polymer with a PEG backbone of PEG chains, linked by benzylic ether linkages. Due to the nature of these linkages, the resin has the disadvantage that there is the possibility of cleavage with Lewis acids or hydrogenation. A modified version of resin **6** was developed with three methylene units between the PEG molecule and the polystyrene backbone in order to give a more stable polymer, known as POEPS-3.[33] Resin **7** also has a more stable structure, as it is formed by the homo-polymerisation of epoxy terminated PEG chains, giving a structure that is linked by more stable allyl ether linkages.[33] Both types of resin have similar swelling properties to resin **5** in both organic and aqueous solvents. Hydroxyl group capacities can be varied from 0.1 to 0.6 mmol g^{-1} by adjusting the monomer composition, giving reasonable loading levels. Both **6** and **7** resins were successfully utilised for a high yielding supported peptide synthesis, as well as carbenium and carbanion reactions in organic solvents and biochemical reactions in aqueous solvents.[33]



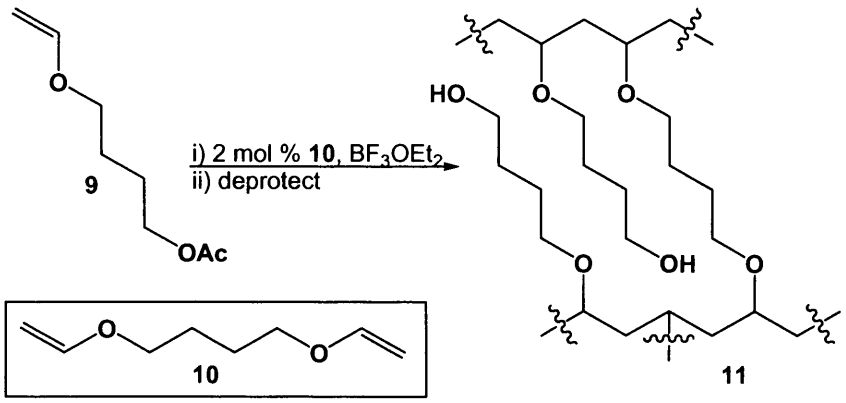
Scheme 1.1.1.4 Synthesis of POEPS (**6**) and POEPOP (**7**) [33]

It has been observed that the structure of the POEPOP resin contains an equal number of primary and secondary alcohols, as well as containing both primary and secondary ether linkages.[34] Not only does this mean that the polymer does not have a uniform structure, but secondary ether linkages are less stable than primary, making the polymer susceptible to degradation in extremely strong acidic or basic conditions. In an attempt to avoid these problems, the SPOCC (**8**) resin was developed.[34] This resin is formed by the Lewis acid catalysed polymerization of PEG chains functionalised with oxetane rings (Scheme 1.1.1.5), giving a polymer with exclusively primary ethers and alcohols. The high stability of **8** was demonstrated by subjecting it to various strongly acidic conditions, for example it was found to be unchanged by refluxing in toluene with 20 equivalents of thionyl chloride for 72 h, conditions which caused **7** to degrade and then dissolve within minutes.[34] Again, the swelling properties of the resin in all solvents were similar to those of **5**. Resin **8** was successfully utilised as a polymer support for various chemical reactions, including peptide and glycopeptide synthesis, nucleophilic reactions and enzymatic reactions in aqueous media.[34]



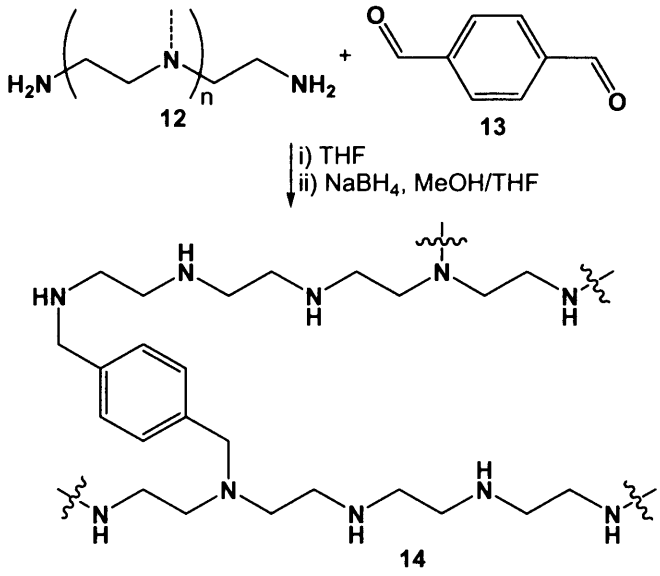
Scheme 1.1.1.5 Synthesis of SPOCC (**8**) [34]

Steinke's group have reported the synthesis of novel polyether resins, for which they have coined the name SLURPS (**11**, scheme 1.1.1.5).[35] These are synthesised by the cationic polymerisation of monovalent monomers with a small percentage of divalent monomer present. In this case the monomers used are vinyl ethers, with the hydroxyl functionalities of the monovalent monomer protected as acetates (**9**). This allows deprotection following polymerisation, revealing free hydroxyl groups that can then be widely functionalised (construction of a Wang linker followed by Mitsunobu functionalization being given as an example).[35] These supports, which take the form of gels, have been synthesised with high loading levels (up to 8.5 mmol g^{-1}) that could be tuned by adjustment of the monomer ratio. They were also observed to be swollen to a greater degree than both PS and Tentagel resins in all solvents (with the exception of water compared to Tentagel reins), and to display a high degree of chemical stability. NMR and IR can also be routinely used to monitor on-resin reactions.[35]



Scheme 1.1.1.5 Synthesis of SLURPS (**11**) [35]

An alternative method of synthesising solid supports is to cross-link soluble polymers that have a high density of functional groups. Polyethylimines (**12**) can be cross-linked by reductive amination with dialdehydes, such as compound **13**, giving supports with many free secondary amines that can be further functionalised (scheme 1.1.1.6).[36] These supports are known as Ultragels and Ultraresins (**14**) because they can have very high loading levels (up to 13.8 mmol g^{-1}). Resins displayed good swelling in a range of both polar and non-polar solvents, including diethyl ether, which is known to shrink both polystyrene and PEG containing resins.[36] It was noted however that the addition of a hydroxyacetimide linker led to reduced swelling properties in polar and non-polar solvents, whereas addition of a hydrophobic Rink amide linker led to strongly improved swelling properties in nonpolar solvents.[36] This strong influence of chemical modifications on the properties displayed by the support is an undesirable aspect. With the high density of functional groups, there could also be a greater chance of side reactions between adjacent reactive sites.



Scheme 1.1.1.6 Synthesis of Ultragels/Ultraresins (**14**) [36]

Despite advances in SPOS, the heterogeneous nature of reactions can be problematic due to nonlinear kinetic behaviour, unequal distribution, unequal access to reactive sites, and solvation problems.[37] This has lead to increasing interest in the use of soluble polymers as supports, known as liquid-phase organic synthesis (LPOS). There are several exhaustive reviews of the area,[37, 38] so an overview of the main

polymer supports that have been utilised in LPOS will be presented in this chapter. Soluble polymer supports can provide homogeneous reaction conditions and straightforward techniques for purification of intermediates can be used due to the high molecular weight of the polymer. Purification techniques include recrystallization, dialysis (involving filtration through a selective permeable membrane), nanofiltration, and size exclusion chromatography.[37]

The origins of this type of synthesis are again found in the field of peptide synthesis. The first reported soluble polymer supported peptide synthesis used linear polystyrene as the support; chloromethylated polystyrene with an average molecular weight of 200 000 and a loading capacity of 0.91 mmol g^{-1}.[39] Reactions were carried out in DMF or dioxane, and purification of the polymer bound intermediates was achieved by precipitation with water. There were problems with the use of this support, however; precipitation of the support, upon addition of water, caused co-precipitation of some reagents and in later steps the support became less soluble due to bridging between unreacted chloromethyl groups. In fact, when using a higher loading polymer (1.49 mmol g^{-1}) some resin bound intermediates were completely insoluble and later reactions had to be carried out under heterogeneous conditions.[39]

Since then, various polymers have been investigated for their suitability as supports in LPOS.[37] A soluble polymer that has been used in the many applications is PEG (figure 1.1.1.1). Large PEG chains have been widely used to modify biologically active molecules, altering and controlling biodistribution, pharmacokinetics, and toxicity.[40, 41] Using similar chemistries, it is possible to attach smaller substrates to the hydroxyl functionalities of the PEG chain and carry out polymer supported syntheses.[37, 38]

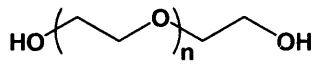


Figure 1.1.1.1 Poly(ethylene glycol)

The structure and properties of PEG make it ideal for use as a support. It is soluble in a wide range of polar and apolar organic solvents, as well as water and the polyether

backbone is excellent at solubilising polymer supported intermidiates.[37] Also, the helical structure adopted by PEG chains makes them readily crystallize when diethyl ether, or *tert*-butyl methyl ether are added to a concentrated solution, or when solutions of PEG in various alcohols (e.g. methanol, ethanol, propan-2-ol) are cooled.[42] PEG is commercially available, either in a mono-methoxy form or with 2 free hydroxyl functionalities, over a range of molecular weights. For use as a soluble polymer support, an average mass of 2000 g mol^{-1} or greater is required as PEGs below this molecular weight are less able to adopt a crystalline form.[37] PEG chains have a hydroxyl group at each end (or at one end when using the mono-methyl form), which can undergo many chemical modifications and thus be utilised as the point of attachment for small molecules. The structure of PEG does not interfere with spectroscopic techniques, so IR, UV, and NMR spectrometry can be routinely used to monitor polymer bound intermediates.[37] Also, due to the homogeneous nature of reactions on PEG, damage to the polymer by mechanical force or osmotic shock is no longer a concern.

PEG has been successfully used as a soluble support for a range of chemical transformations and the construction of small molecules.[43-47] An example of PEG overcoming some limitations of heterogeneous Tentagel supported reactions is in asymmetric dihydroxylation.[48] Here, PEG supported reactions were seen to have improved yields and a greater enantiomeric excess than the corresponding Tentagel supported reaction.[48] There are now several highly successful PEG supported peptide syntheses in the literature, for example, the synthesis of a pentapeptide on PEG 10 000, following linkage of the first amino acid to the PEG with DCC, with coupling yields greater than 99 % and no observed racemization.[49] Purification was initially achieved by ultrafiltration, but it was found that precipitation of the PEG from solutions in methylene chloride, by addition of diethyl ether, gave faster and more efficient purification. Kinetic studies of peptide synthesis have demonstrated that PEG supported reactions are similar to those carried out in solution, with the coupling step being faster in some cases for the PEG supported reaction (table 1.1.1.1),[50] unlike linear or cross-linked PS supported reactions, where the rate of the coupling reaction is significantly slower than the analogous solution reaction (table 1.1.1.2).[51]

R	k_2 ($M^{-1} s^{-1}$)
ethyl	0.013
2-methoxyethyl	0.008
PEG (molecular weight 2000)	0.018
PEG (4000)	0.019
PEG (10 000)	0.014

Table 1.1.1.1 Measured Rates of *p*-Nitrophenyl (Np) Release from Boc-Ala-ONp by H_2N-Gly-OR in CH_3CN [50]

R	k_2 ($M^{-1} s^{-1}$)
phenyl	0.081
polystyrene, soluble (20 400)	0.047
Polystyrene, insoluble (cross-linked)	0.030

Table 1.1.1.2 Measured Rates of *p*-Nitrophenyl (Np) Release from Boc-Ala-ONp by H_2N-Gly-OR in $CHCl_3$ [51]

The degree of loading with PEG chains is lower than that of the cross-linked resins that have been discussed previously in this chapter. Also, because each chain is at most bifunctional, the highest loading possible is 1.00 mmol g^{-1} (for PEG 2000). In order to maintain desirable aspects of linear PEG supports; high solubility in a range of solvents, good chemical stability and facile analysis of intermediates, whilst increasing the potential loading level of the support, PEG based oligomers have been made with between 4 and 32 PEG side arms, each with a hydroxyl end group (e.g. figure 1.1.1.2).[52] Purification of oligomers of this size are generally by size exclusion chromatography or ultrafiltration, which whilst more time consuming than recrystallization, are efficient methods of separation. For example, a 4-armed PEG star (**15**) was successfully converted to the tetramine, followed by the attachment of 4 Rink handles, and this support was used in the synthesis of a library of di- and tri-substituted guanidines.[52] Separation was achieved using size exclusion chromatography and high purity products were obtained in many cases.

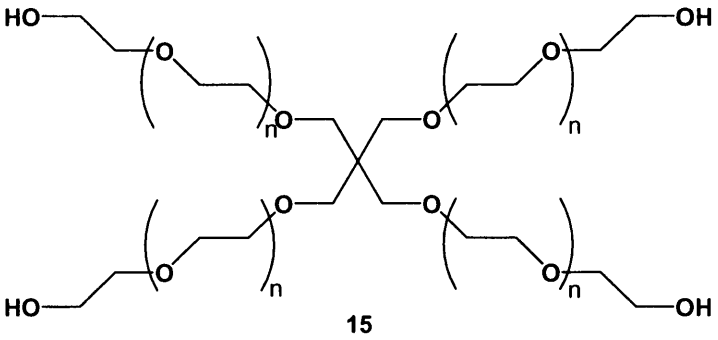
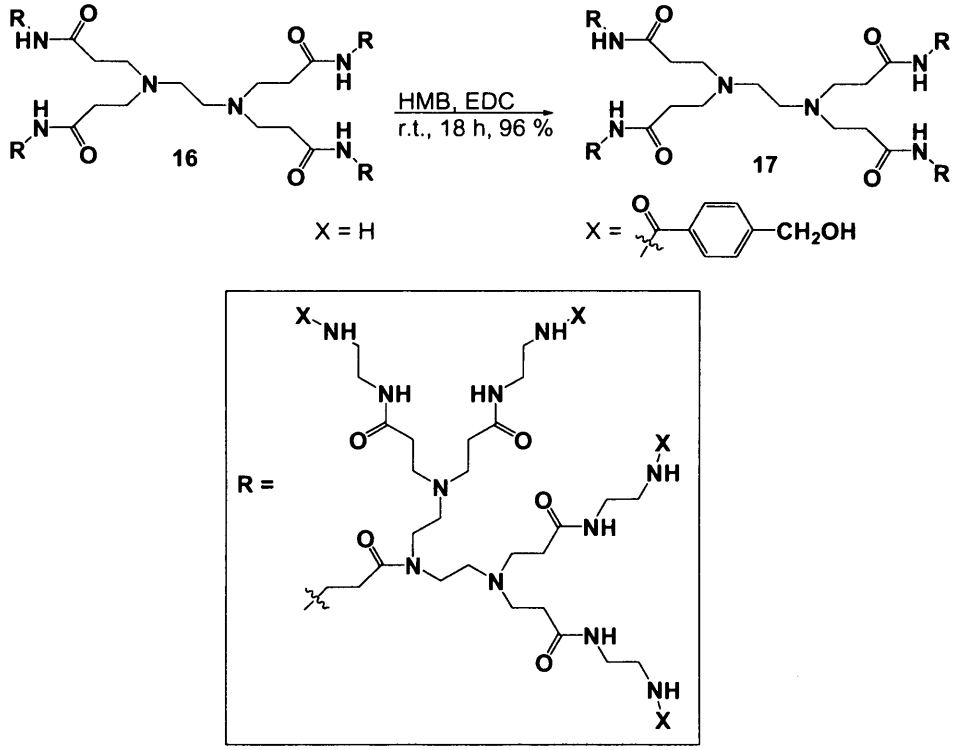


Figure 1.1.1.2 PEG Star with 4 Side Arms (**15**)

Some classes of dendrimer have also been successfully utilised as soluble polymer supports. Dendrimers are polymers which branch out from a central core, and can be built up in generations. Kim's group have reported the use of Starburst polyamidoamine (PAMAM) generation 1 dendrimer (**16**) as a soluble polymer support, which they stated as meeting their requirements due to its ability to exist in an extended form, giving good access to the majority of the reactive end groups. [50] Reaction of **16** and 4-hydroxymethylbenzoic acid, using EDC, to give functionalised dendrimer **17** (scheme 1.1.1.7).[53]



Scheme 1.1.1.7 Coupling of HMB Linker onto PAMAM Generation 1 (**16**) [53]

They also reported the successful use of **17** in the synthesis of a small combinatorial library using Fischer indole methodology.[53] This was an efficient process, with indoles prepared in HPLC purities of between 84 % and 99 %. Due to the discrete nature of these dendrimers, they can be fully characterised by standard techniques including NMR and mass spectrometry, allowing for excellent analysis of the polymer bound intermediates.[53]

Parquette's group have proposed the use of a hyperbranched polyester (**18**) as an alternative soluble polymer support to the PAMAM dendrimer.[54] This provides a low cost support, since it is made by a one step synthesis. Although the polymer does not exist in the form shown in an idealised representation (figure 1.1.1.3), enough of the end groups are situated near the polymer surface to give good accessibility for reagents. The support also has the advantage that it can be precipitated by methanol after each reaction, giving a more rapid purification method. Using this support, the group successfully carried out a polysaccharide synthesis, with routine monitoring of the polymer bound intermediates by NMR and MS. However, the support has the major limitation that the ester linkages are susceptible to cleavage by nucleophilic reagents, and as a result its use as a soluble polymeric support is not widely applicable.[54]

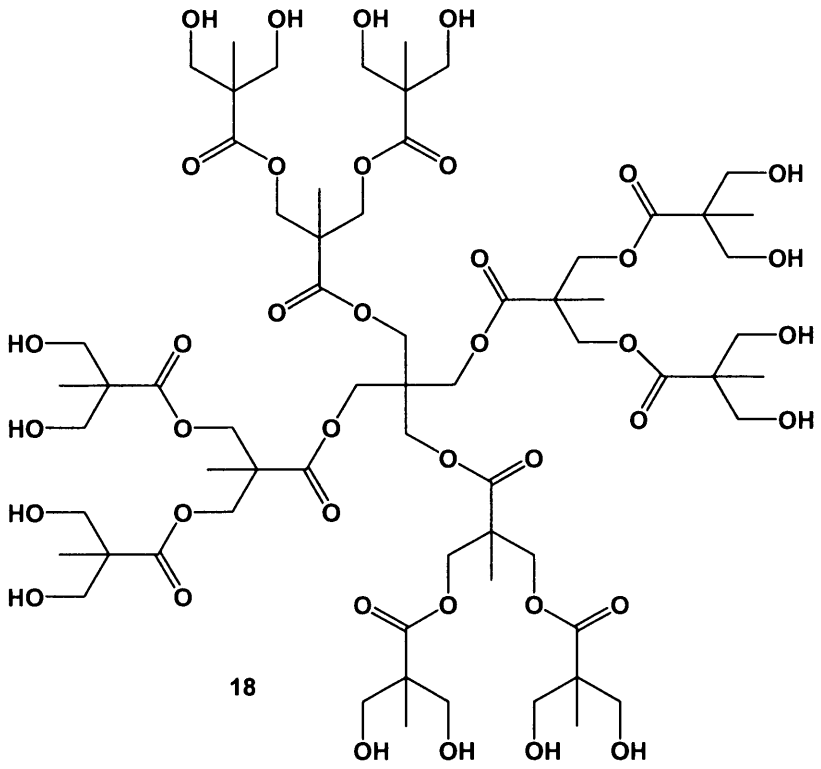
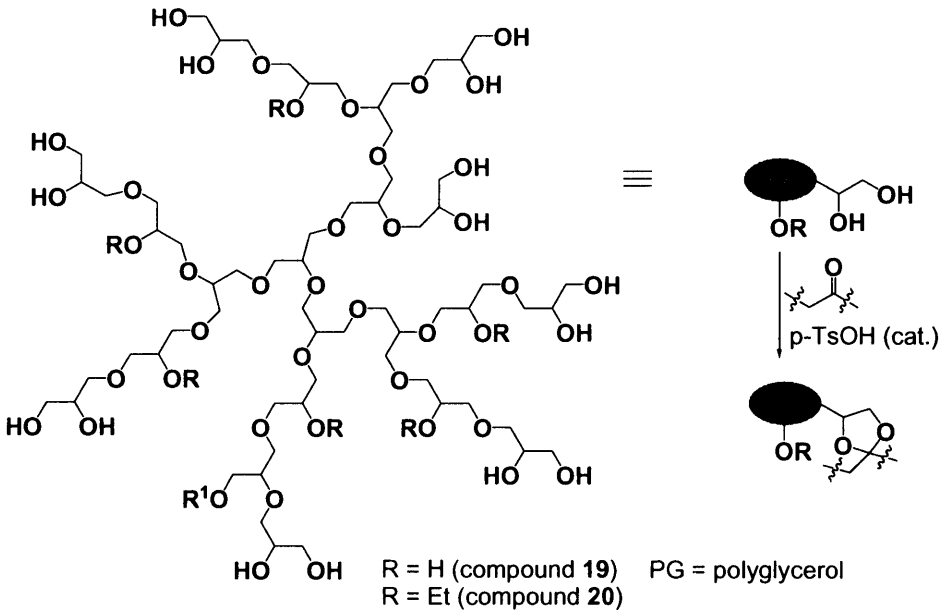


Figure 1.1.1.3 Idealised Depiction of Hyperbranched Polyester (**18**)[54]

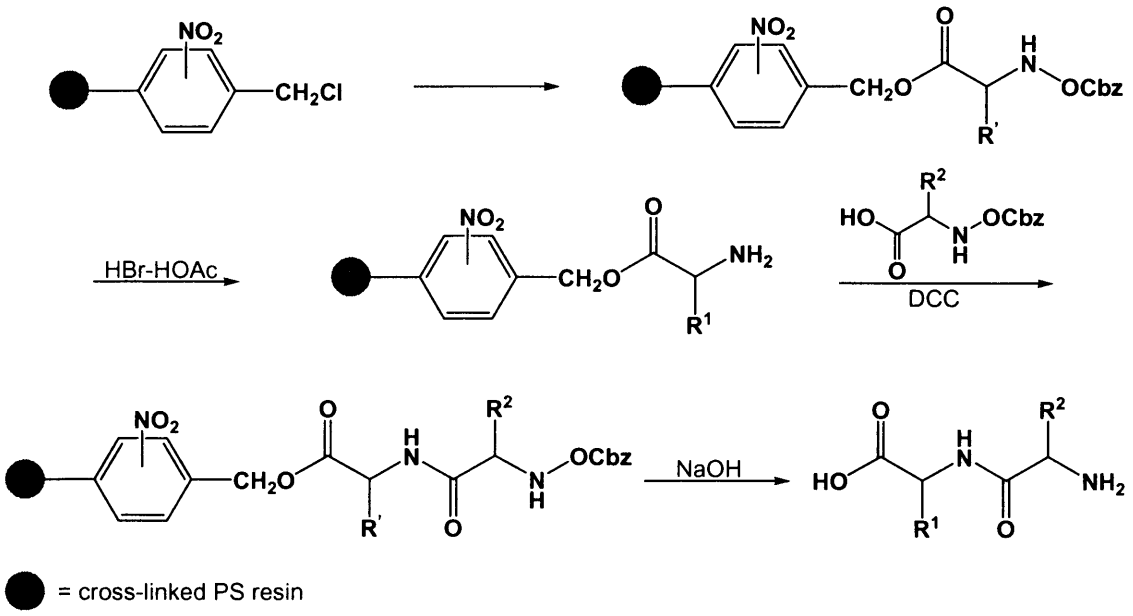
A more stable alternative to this type of support was reported by Haag's group; their chosen supports being hyperbranched polyglycerols.[55] The aliphatic polyether backbone of this type of support is stable to both strongly acidic and basic conditions, as well as various oxidants. It is also thermally stable up to 300 °C under anaerobic conditions (250 °C under oxygen). The supports exhibits high solubility in a range of solvents, with the core hydroxyl support (**19**) being soluble in many polar solvents (both protic and aprotic e.g. DMF, methanol, water), and the core alkylated support (**20**) also being soluble in various non-polar solvents (e.g. toluene, dichloromethane). These supports also have the advantage of relatively high loading for both core alkylated (3.5 mmol g^{-1}) and core hydroxyl (4.1 mmol g^{-1}) species. A limitation of the support is that, due to the reactive sites being 1,2-diols, its use thus far has exclusively been in immobilising carbonyl compounds as acetals (scheme 1.1.1.8).[55] Nevertheless, following the loading of suitably functionalised carbonyl compounds, Haag *et al.* demonstrated that the nucleophilic displacement of halides, as well as Suzuki cross-coupling reactions could be successfully achieved on the support.[55] The strictly di-functional nature of these end groups, however, is likely to limit the general utility of the support on steric grounds.



Scheme 1.1.1.8 Loading Carbonyl Compounds onto Hyperbranched Polyglycerols [55]

1.1.2 The Use of Linkers in Polymer Supported Synthesis

Another important consideration when planning a polymer supported synthesis is method of attachment and cleavage of products from the support. Linkers are therefore often used to aid the immobilisation of small molecules. In Merrifield's seminal peptide synthesis, the first protected amino acid (as its triethylammonium salt) was attached to the PS resin by a reaction with the chloromethylated form (scheme 1.1.2.1).[1] The resin was also nitrated, as this was seen to minimise the cleavage of intermediates from the resin under the strongly acidic conditions required to deprotect the carbobenzoxy group used to protect the amino acid. Following the peptide forming step, using dicyclohexylcarbodiimide (DCC), the product was cleaved from the resin by saponification with sodium hydroxide.[1]

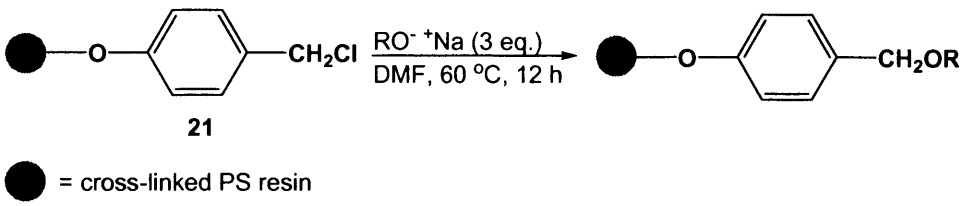


Scheme 1.1.2.1 Merrifield's Peptide Synthesis [1]

The chloromethyl polystyrene derivative, commonly known as the Merrifield resin, can also be used as a linker for carboxylic acids, secondary amines, phenols and thiols.[19] Since the development of this basic linker, many novel techniques have been utilised for the immobilisation of molecules to supports, through a variety of functional groups. Here the focus is on some of the linkers that are used to anchor molecules *via* hydroxyl functionalities. The linkers discussed in this chapter are used to attach small molecules to PS resins, as this type of support has had the greatest volume of research carried out into its use. Some of the linkage methods could equally be useful on the other types of polymer support discussed in Chapter 1.1.1, and indeed some have been successfully used on alternative supports.

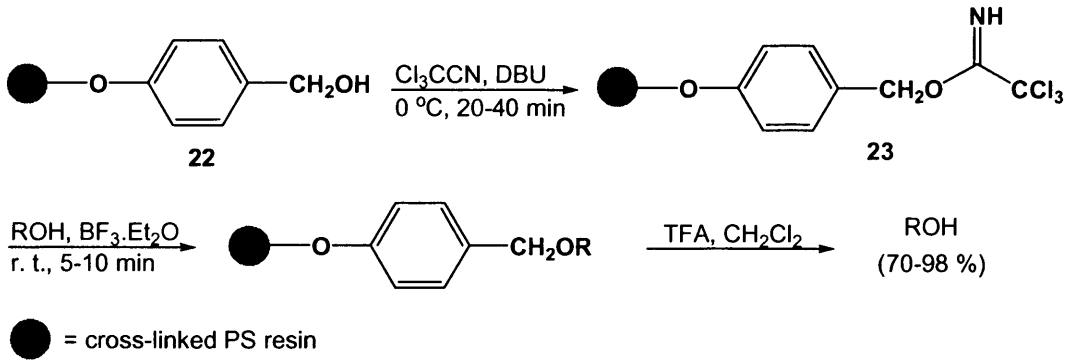
A popular method of attaching alcohols to solid supports is *via* 4-alkoxybenzyl linkers, known as Wang linkers; the resin bound equivalent of a p-methoxybenzyl protecting group. Various methods have been developed for reacting alcohols with this type of linker to give the corresponding resin bound ether and this can now be achieved under basic, acidic or neutral conditions making the linker compatible with a wide range of protecting groups. Loading of an alcohol can be achieved under basic conditions by reacting a PS bound Wang chloride (**21**) with an excess of the sodium alkoxide in a suitable solvent, such as DMF (scheme 1.1.2.2).[56] The disadvantage of

this method is that, being a Williamson's type ether synthesis it has associated problems, such as high temperatures and reduced reactivities for secondary and tertiary alkoxides (see chapter 1.2 for further discussion of Williamson's type ether synthesis).



Scheme 1.1.2.2 Loading of Alcohol onto PS Wang Chloride (**21**) [56]

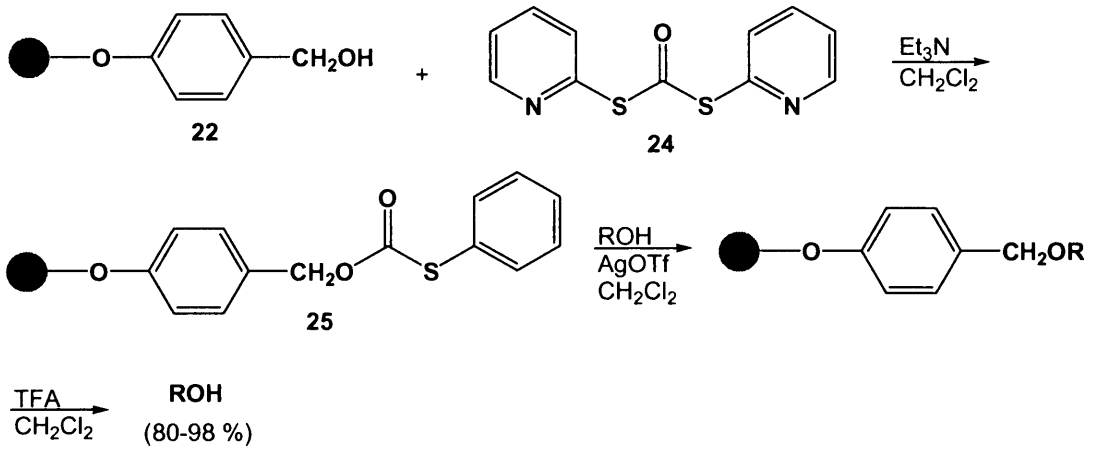
More recently a method has been developed for the formation of resin bound Wang ethers using acid catalysed conditions. Rather than using the Wang chloride (**21**) the reactive species is the Wang trichloroacetimidate (**23**).[57] This was rapidly formed from the corresponding resin bound Wang alcohol (**22**) by reaction with a large excess of trichloroacetonitrile and DBU at 0 °C in quantitative yield (scheme 1.1.2.3).[57] Resin **23** was then reacted with an alcohol and a Lewis acid catalyst at room temperature, such as boron trifluoride diethyl etherate, to give the corresponding Wang ether. Following acidic cleavage the products were obtained in high yields (70-98 %) even for more hindered secondary and tertiary alcohols.[57]



Scheme 1.1.2.3 Formation and Loading of Wang Trichloroacetimidate Resin (**23**) [57]

Hanessian's group have also reported a method of forming resin bound Wang ethers under neutral conditions, via a 2-pyridylthiocarbonate (TOPCAT) resin (**25**).[58] Resin

25 is formed by the reaction of the resin bound Wang alcohol (**22**) with di-(2-pyridyl)thiocarbonate (**24**) using triethylamine as a base (scheme 1.1.2.4). Resin **25** was then reacted with an alcohol and silver triflate to give the corresponding Wang ether. Following acidic cleavage the products were obtained in good yields (80-98 %), even for secondary and tertiary alcohols, with the recovered yield of a tertiary alcohol being 10 % higher than when the trichloroacetimidate protocol was used.[58]

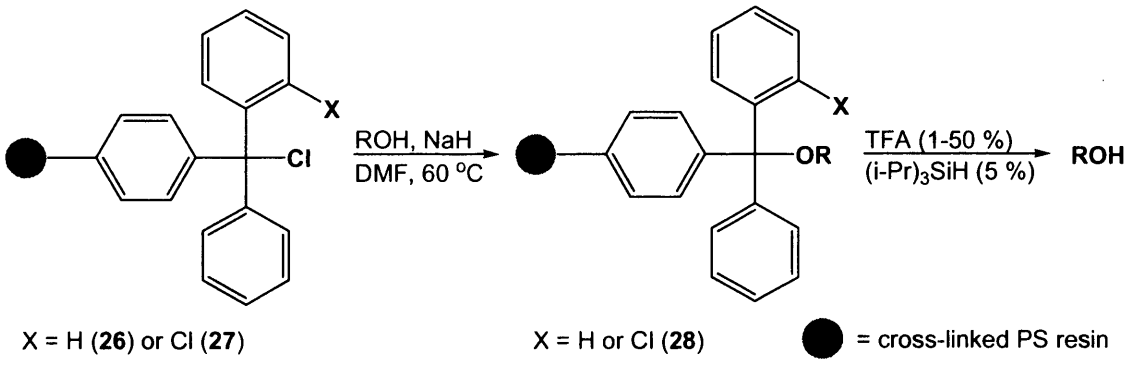


Scheme 1.1.2.4 Formation and Loading of TOPCAT Resin (**25**)[58]

As demonstrated by the two previous examples, the general method of cleavage for Wang ethers is by treatment with a strong acid, such as 20 % TFA in chloroform. This method often gives alcohol products contaminated with the corresponding trifluoroacetate esters (20-30 %). An alternative, non-acidic cleavage method has been reported; oxidative cleavage using DDQ.[56] Unlike TFA cleavage, the products are obtained by DDQ cleavage with no indication of impurities by HPLC and in yields greater than 70 %.

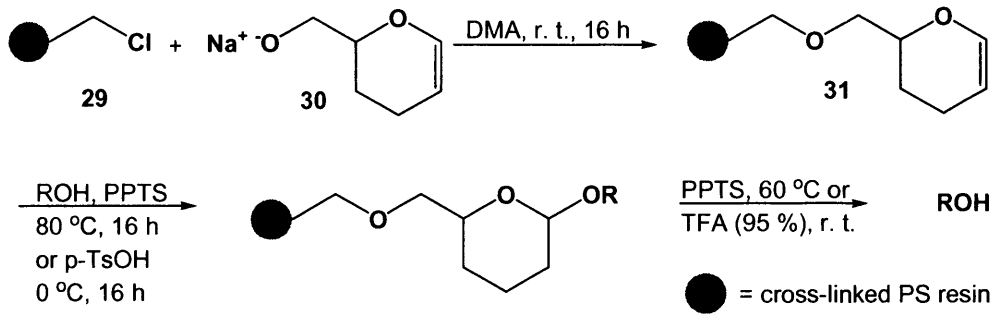
Another commonly used protecting group in classical synthesis, for which a resin bound analogue has been developed, is the trityl group.[59] Due to the site of the ether linkage being particularly hindered, especially for the 2-chlorotrityl linker (**28**), it is very stable to nucleophilic attack, as well as basic conditions. Alcohols can be immobilised by reacting their alkoxides with trityl (**26**) and chlorotrityl (**27**) PS resins, using pyridine as a base (scheme 1.1.2.5).[59] The linker is slightly more acid labile than a Wang linker, with cleavage being generally achieved using 1-50 % TFA

in dichloromethane, using triisopropylsilane (5 %) as a cation scavenger. Wenschuh *et al.* have reported the successful immobilisation of Fmoc-amino alcohols in this way as a precursor to a PS supported peptide synthesis.[59]



Scheme 1.1.2.5 Loading and Cleavage of Trityl Resin (**26** and **27**) [59]

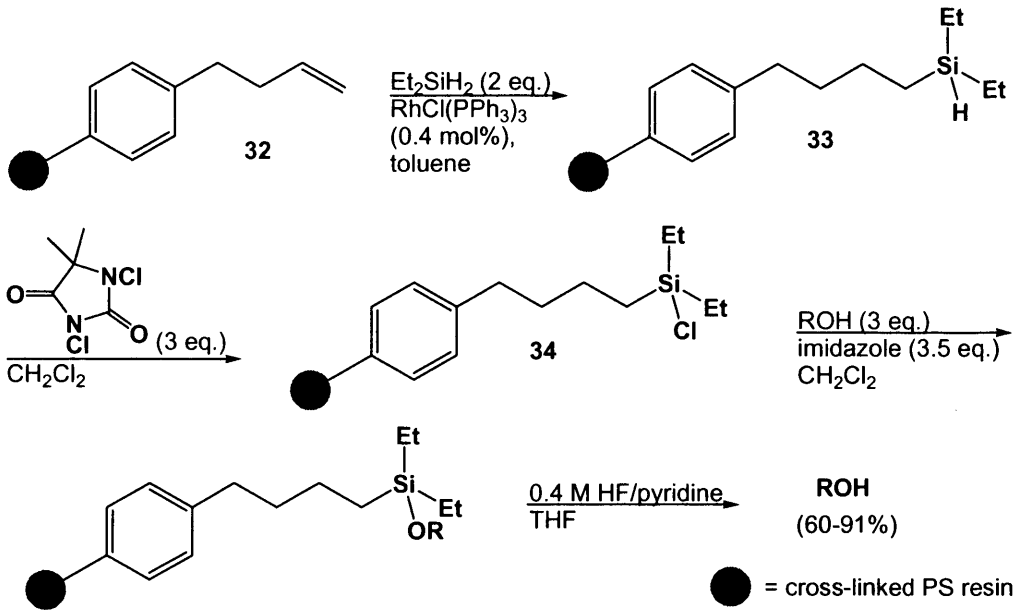
In order to develop a linker on a PS resin with properties similar to those of the widely used tetrahydropyran (THP) protecting group, Ellman's group reacted a Merrifield resin (**29**) with the sodium salt of (6-hydroxymethyl)3,4-dihydro-2*H*-pyran (**30**), scheme 1.1.2.6).[60] The novel dihydropyran (DHP) resin (**31**) could be reacted with an alcohol, using either pyridinium p-toluenesulfonate (PPTS) or p-toluenesulfonic acid as a catalyst, to form a THP ether linkage. Yields for the loading step were generally good for primary and secondary alcohols (66 %-95 %), although the yield for the loading of a tertiary was very low (10 %). While the reason for the low yield of the latter loading was not suggested, a tertiary alcohol could eliminate water under acidic conditions due to the stabilising inductive effect of the three methyl groups on the carbocation intermediate. Following the loss of a proton from the carbocation, the resulting alkene would be gaseous and could escape the reaction mixture.



Scheme 1.1.2.6 DHP Resin (**31**): Synthesis, Loading and Cleavage [60]

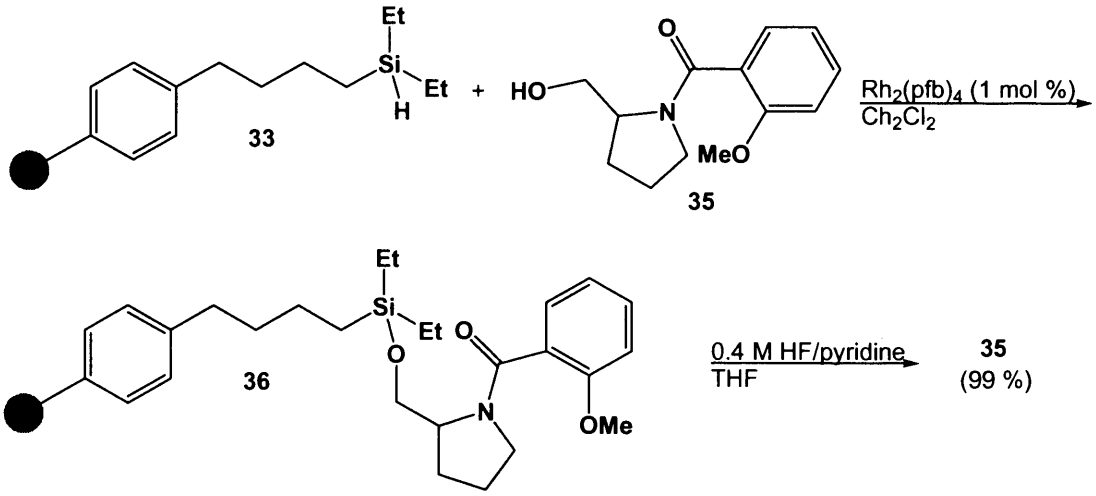
Like its classical solution based counterpart, this linkage was very stable to nucleophilic attack and basic conditions. Complete cleavage of the THP ether was achieved either by treatment of the resin with PPTS in 1:1 butanol/1,2-dichloroethane at 60 °C, or with 95:5 TFA/H_2O at room temperature.[60]

A range of silyl based linkers have also been developed in order to utilise the properties that are commonly associated with silyl protecting groups in solution. These protecting groups are stable to a range of transformations and can be cleaved by acid hydrolysis or in the presence of the fluoride ion.[61, 62] Methods of synthesising such linkers include the lithiation of polystyrene, followed by trapping of the intermediate with dialkyldichlorosilanes,[63-65] or by hydrosilylation of a resin bound olefin with dialkylchlorosilane derivatives.[66] Both of these methods form silyl chloride resins which are fairly unstable and cannot be stored for long periods. To avoid this problem, several groups have developed the far more stable resin bound silane derivatives. Hu *et al.* have reported hydrosilylation of a resin-bound olefin (**32**) with disubstituted silanes (scheme 1.1.2.7).[62] The resin bound silane (**33**) could then be activated as the silyl chloride (**34**) followed by the loading of various primary and secondary alcohols, using imidazole as a base. Following cleavage of the alcohol in HF/pyridine, products were obtained in yields ranging from 60-91 %.[62]



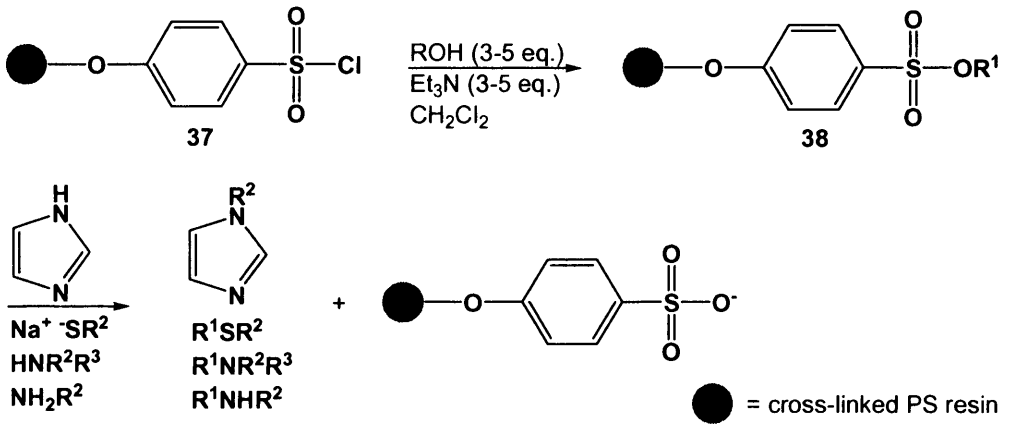
Scheme 1.1.2.7 Alkyl Silane Resin (**33**): Synthesis, Activation, Loading and Cleavage [62]

They also demonstrated that a primary alcohol (**35**) could be attached directly to the resin bound silane (**33**) using a catalytic amount of rhodium(II) perfluorobutyrate (scheme 1.1.2.8).[62] The resin bound intermediate (**36**) could then be cleaved, again with HF/pyridine, in a near quantitative yield of 99 %.



Scheme 1.1.2.8 Loading and Cleavage of Silane Resin (**33**) [62]

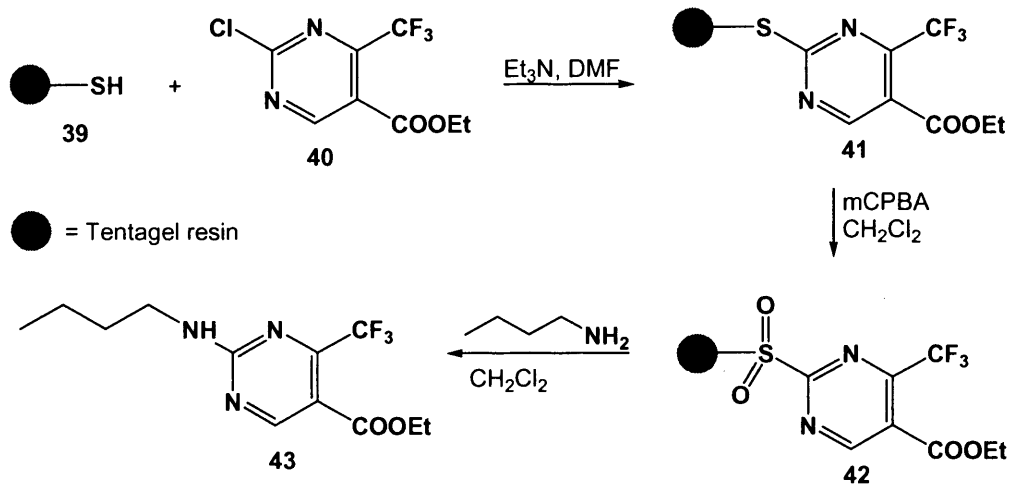
All of the examples of linkers discussed thus far are cleaved in such a way that the hydroxyl group of the initial substrate is recovered. Sulfonate linkers provide an alternative to this type of solid phase methodology, allowing for a cleavage step that can be used to add functionality into the product.[67-71] The most commonly used resin of this type is the commercially available Sulfonyl Chloride (Polymer Bound) (**37**) which can be seen as the PS supported equivalent of tosyl chloride. As such, it can readily be used to immobilise alcohols as the corresponding sulfonate ester, with an amine base such as triethylamine (scheme 1.1.2.8).[67] Like tosyl esters, the resin bound sulfonate ester (**38**) is an efficient leaving group and can be displaced by attack from various nucleophiles. This nucleophilic attack breaks the C-O bond of the immobilised substrate, so as well as being cleaved from the support, the product also has the nucleophile incorporated into its structure. Examples of nucleophiles that have been successfully used to cleave immobilised sulfonate esters include amines, thiols, imidazole (scheme 1.1.2.8) [69] and iodide.[67] All of these methods incorporate a potentially useful functionality into the final product.



Scheme 1.1.2.8 Loading and Cleavage of Sulfonate Resin (**37**) [69]

The synthesis of a traceless sulphur-based linker has also been reported.[68] Here a Tentagel thiol resin (**39**) was used to immobilise 2-chloro-4-trifluoromethyl pyrimidine-5-carboxylate (**40**, scheme 1.1.2.9). Unlike a sulfonate linker, thiol linkages are not susceptible to nucleophilic attack and are resistant to a range of reaction conditions including saponification, conversion to the acid chloride, reduction to the alcohol, and Mitsunobu conditions. Treatment of the resin bound

intermediate (**41**) with mCPBA converted it to the resin bound sulfone (**42**), from which the amine product (**43**) could be cleaved by reaction with an excess of n-butylamine (scheme 1.1.2.9).[68]



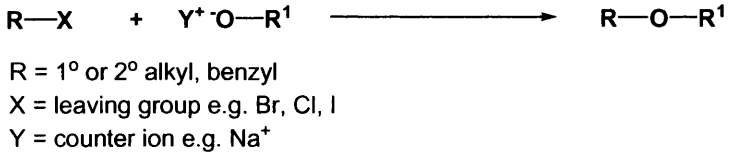
Scheme 1.1.2.9 Loading, Oxidation and Cleavage of Thiol Resin (**39**) [68]

1.2 Ether Synthesis

Polymer supports have been shown to be a very useful tool when carrying out iterative synthesis of oligomers. [1-3, 65] The repetitive nature of such syntheses, with larger oligomers requiring the same few steps to be carried out a number of times, makes the often time consuming purification associated with solution-based chemistries increasingly arduous. This problem is compounded by the excess of reagents that may be required when attempting to drive the chain extension step to completion.[1] A desire to avoid the production bottleneck caused by lengthy purification steps makes a polymer bound approach attractive. In addition, polymer supported synthesis also lends itself well to automated approach to synthesis.[21] In the literature there are numerous examples of iterative polymer supported syntheses of peptides,[1] oligonucleotides,[2, 3] oligosaccharides [65] and polyamines (see chapter 1.3.2 for a discussion of polyamine synthesis on solid supports). Another important class of oligomers are polyethers, the solution based syntheses of which have been reported in countless studies. On polymeric supports however, there are very few reported ether syntheses, and even fewer attempts to synthesise polyethers.[11]

1.2.1 Ether Synthesis in Solution

The most commonly used method of ether synthesis in solution is the Williamson reaction, which has been used for over a century. The mechanism of the reaction is generally S_N2, with the alkoxide displacing a halide (scheme 1.2.1.1).



Scheme 1.2.1.1 Williamson's Ether Synthesis

In this basic form the reaction is fairly limited in that branching at the α carbon, or to a lesser extent at the β carbon of the alkyl halide can dramatically effect the rate of reaction, as well as promoting competing elimination reactions. As a result, there is low reactivity with secondary alkyl halides and in most cases tertiary alkyl halides are not compatible with the Williamson reaction.[72]

The basic Williamson reaction has been modified in several ways over the years, in an attempt to make it a more effective method of ether synthesis. One method of improving the reaction is to replace alkyl halides with better leaving groups. Popular alternative leaving groups to halides are reactive sulfonate esters. These have the advantage of being more reactive than the corresponding halides [73] and can also be easily prepared directly from alcohols. The most commonly used sulfonate esters for this purpose are the esters of *p*-toluenesulfonic acid (tosylates) and methanesulfonic acid (mesylates, figure 1.2.1.1). Fluorinated sulfonate esters are even more reactive leaving groups, with tresylates giving around 100 times greater reactivity than tosylates, and triflates giving about 400 times greater reactivity than the latter.[74] Triflate esters can give the corresponding ester in very high yields when used as the leaving group in the Williamson reaction.[75, 76]

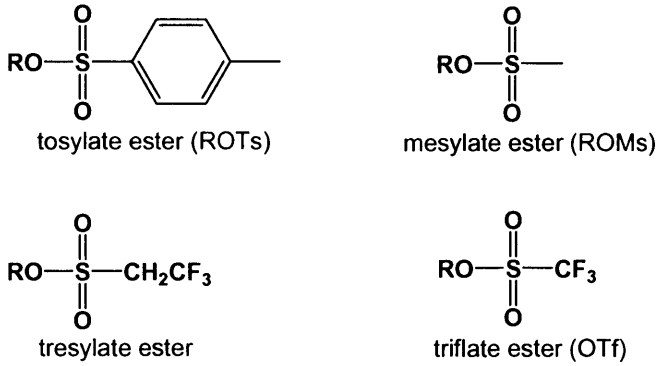
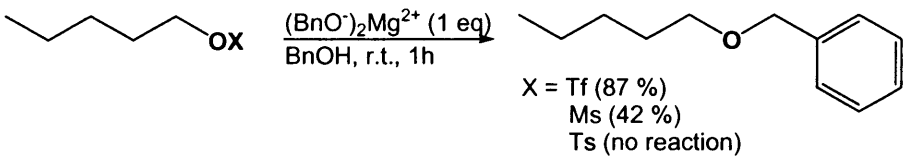


Figure 1.2.1.1 Examples of Reactive Sulfonate Esters

Nishiyama's group found that alkyl triflates could be successfully reacted with various magnesium alkoxides, at low temperatures and with short reaction times, giving a range of unsymmetrical ethers in generally very high yields.[76] The reaction between pentyl triflate and the magnesium alkoxide of benzyl alcohol in ether proceeded at room temperature, giving 87 % of the corresponding ether after one hour (scheme 1.2.1.2).[76] Comparatively, pentyl mesylate gave the ether in a 42 % yield when reacted under these conditions, and there was no reaction at all when pentyl tosylate was used.

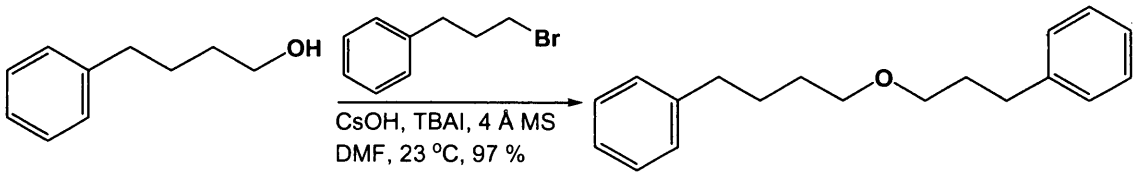


Scheme 1.2.1.2 Reaction of Magnesium Alkoxides with Sulfonate Esters [76]

The use of various additives has also enhanced reactivity in S_N2 ether syntheses. A method that has been widely used to increase reactivity is phase transfer catalysis (PTC).[77] As alkoxides have in general high solubility in water but low solubility in organic solvents and the opposite is often the case for the substrate, there can be a low concentration of both reactive species in the same phase.[77] This can be overcome in some cases by the use of dipolar aprotic solvents (*e.g.* DMF, DMSO), which can solubilise both species, however, there are problems with the use of these solvents, associated with the difficulty of their removal and toxicity. Alternatively, a phase

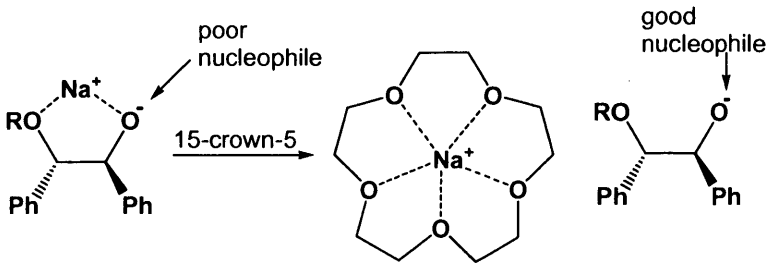
transfer catalyst can be added, which can help to solubilise the alkoxide in standard organic solvents.

One class of phase transfer catalysts are salts that have bulky cations with a diffuse charge, for example, quaternary ammonium (R_4N^+) and phosphonium (R_4P^+) salts.[78] The most common R groups on the quaternary cation are propyl or butyl groups. These large, diffuse cations, unlike metal cations, are not readily solubilised by water and are better solvated by other polar solvents. When a phase transfer catalyst is added to a metal alkoxide in a biphasic system, equilibrium is established, where by the quaternary cation can exchange for the metal ion of the alkoxide and transfer it to the organic phase. This can lead to high concentrations of alkoxide ions in solvents which they would otherwise be insoluble in.[78] Freedman *et al.* has successfully used tetrabutylammonium (TBA) salts to catalyse ether synthesis in a two phase system of this nature, resulting in the complete alkylation of aliphatic chlorides under conditions where yields would otherwise have been far lower.[79] The optimum conditions were achieved with a two phase system with at least a 5 fold excess of sodium hydroxide (50%, aqueous) over alcohol, an excess of alkyl chloride and 3-5 molar % of TBAB, giving the desired ethers in yields of 82-97 %.[79] Similarly, Dueno's group used a combination of TBA iodide (TBAI) and caesium hydroxide to give ethers in very high yield from a reaction between alkyl bromides and alcohols (scheme 1.2.1.3).[80] The TBAI was postulated to convert the alkyl bromide to the more reactive iodide *in situ*, in addition to having an effect by phase transfer catalysis. They also suggested that the fairly large and diffuse caesium ion would generate alkoxides that were less strongly associated with the cation, resulting in the formation of more reactive "naked anions".[80]



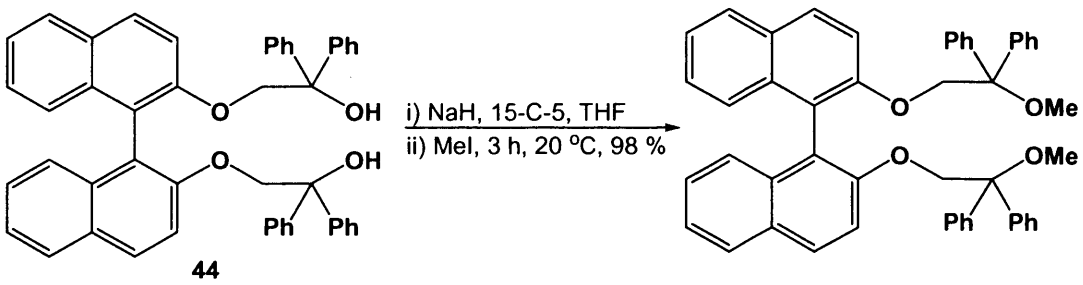
Scheme 1.2.1.3 Use of TBAI and Caesium Hydroxide to Promote Ether Synthesis [80]

The other main class of PTCs are cryptands, a class of compound which includes crown ethers. These cyclic polyethers act by complexing metal anions within their inner cavity. This causes the ions to have a larger form, with a more diffuse charge, and as a result they are less solubilised by water, and more so by organic solvents. The diffuse nature of the ion, once complexed, also causes it to have less association with the alkoxide ion, giving a more reactive nucleophile (scheme 1.2.1.4).[81]



Scheme 1.2.1.4 Use of 15-Crown-5 for Complexing Metal Cations[81]

Greeves *et al.* were successful in using crown ethers as catalysts for various challenging ether syntheses, including the methylation of a very hindered tertiary alcohol (**44**), which had previously proven to be a problematical transformation. The reaction proceeded smoothly at room temperature, with 15-crown-5 (15-C-5) as an additive, to give the product in a 98 % yield (scheme 1.2.1.5).[81]

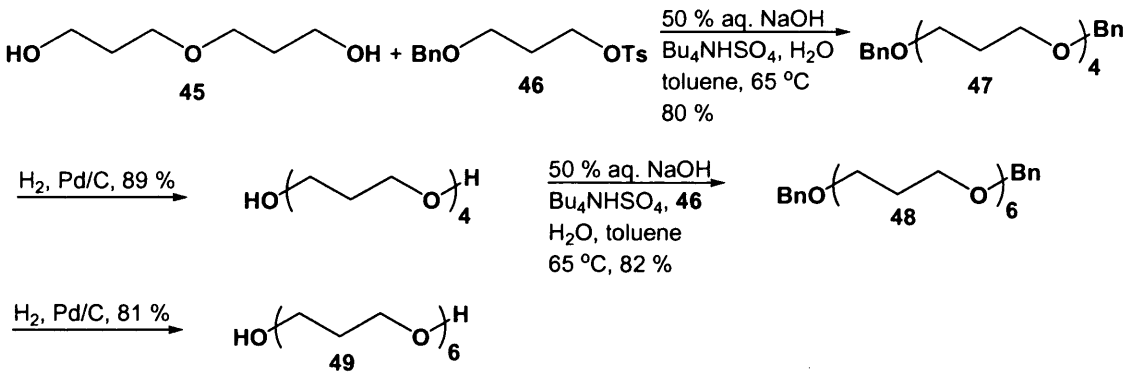


Scheme 1.2.1.5 15-Crown-5 Assisted Methylation of a Tertiary Alcohol[81]

1.2.2 Oligoether Synthesis in Solution

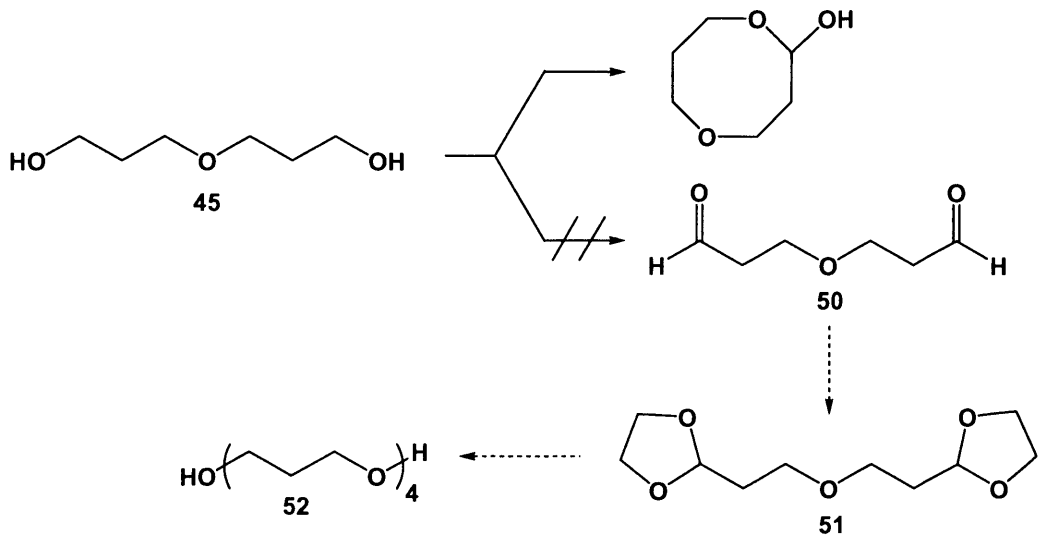
In general the Williamson reaction is not favoured for the formation of large polyethers, as many repetitive steps would be required, and the overall synthesis

would be low yielding. However, there are some examples in the literature of the use of this reaction for the synthesis of small oligoethers. Such an approach was attractive to Gin *et al.* because they intended to utilise oligomers as membrane-spanning chains in synthetic transmembrane ion channels and for this purpose discrete, monodisperse oligoethers were required.[82] Dimer **45** was reacted with a 3-benzyloxypropyl tosylate (**46**) with 50 % sodium hydroxide and TBA hydrogensulfate, giving the benzyl protected tetramer (**47**) in an 80 % yield (scheme 1.2.2.1). Deprotection of the benzyl protecting groups by hydrogenation, followed by a repetition of the ether forming step afforded the benzyl protected hexamer (**48**), which was then deprotected to give the desired hexapropylene glycol (**49**) in a yield of 47 % over all steps.[82]



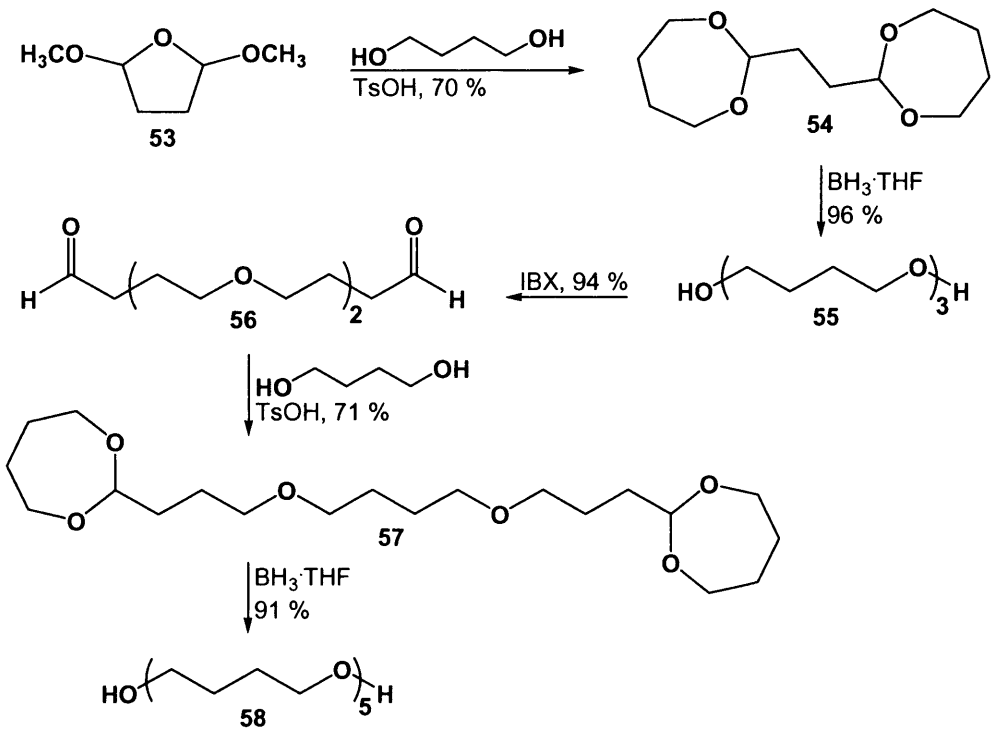
Scheme 1.2.2.1 Synthesis of Hexapropylene Glycol (**49**)[82]

Gin *et al.* also envisaged synthesising propylene glycol oligomers by oxidising the dimer (**45**) to the dialdehyde (**50**), which could be reacted with 1,3-propanediol to give the diacetal (**51**), followed by a reductive ring opening to give the tetramer (**52**, scheme 1.2.2.2).[82] This approach failed, however, due to a competing intramolecular cyclisation during the oxidation step.



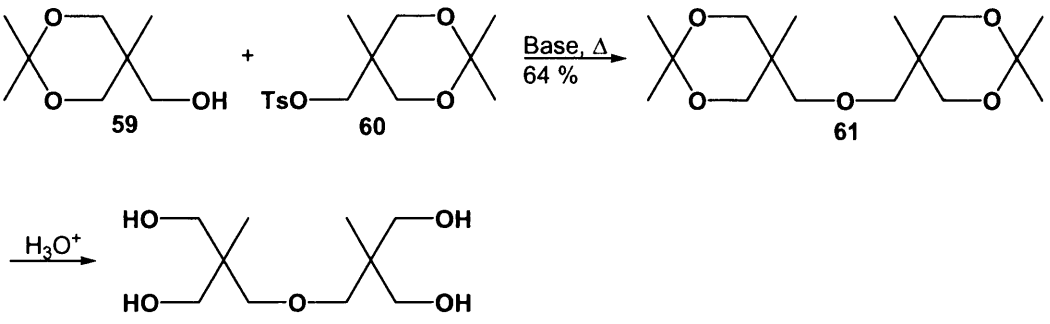
Scheme 1.2.2.2 Unsuccessful Approach to Tetrapropylene Glycol (**52**) Synthesis[82]

A similar approach was successful, however, when utilised for the synthesis of pentabutylene glycol. Here masked dialdehyde **53** was reacted with 1,4-butanediol, using *p*-tosic acid as a catalyst, to afford diacetal **54** as the sole product in a 70 % yield (scheme 1.2.2.3).[82] Reductive ring opening was achieved by reacting **54** with a borane-THF complex, giving tributylene glycol (**55**) in a 96 % yield. Unlike the previous example, **55** could be cleanly oxidised to the aldehyde (**56**) by treatment with *o*-iodoxybenzoic acid (IBX) in a 94 % yield. Repetition of the acetal forming step and reductive ring opening afforded pentabutylene glycol (**58**) with a yield of 65 % over these two steps.[82]



Scheme 1.2.2.3 Synthesis of Pentabutylene Glycol (**58**) [82]

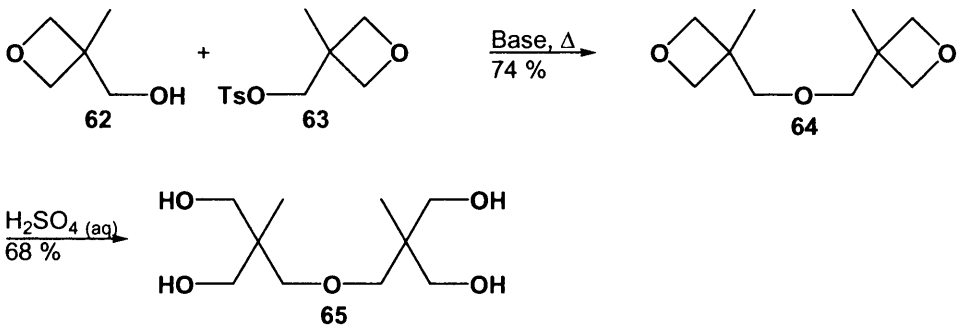
Gash has described the synthesis of a dimer from monomers based on trimethylolethane (TME).[83] The ketal protected derivative (**59**) was reacted with the corresponding tosylate (**60**) to give the protected dimer (**61**) in a 64 % yield (scheme 1.2.2.4). The dimer was then deprotected by acid hydrolysis to reveal hydroxyl groups that could be further functionalised.[83]



Scheme 1.2.2.4 Synthesis of Dimer with Pendant Hydroxyl Groups [83]

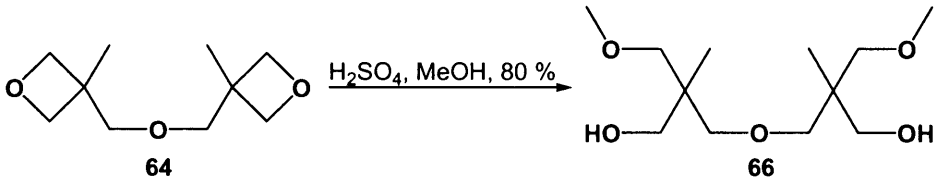
Dale and Fredriksen have carried out much research into designing polyether ligands for the selective complexation of small molecules.[84-89] They reported an alternative

synthesis of the Gash's dimer; reacting 3-hydroxymethyl-3-oxetane (**62**) with its tosylate (**63**), under similar conditions, to give bis-(3-methyloxetan-3-ylmethyl) ether (**64**) in a 74 % yield (scheme 1.2.2.5). This was then hydrolysed with dilute sulfuric acid to give dimer **65** in a 68 % yield.[86]



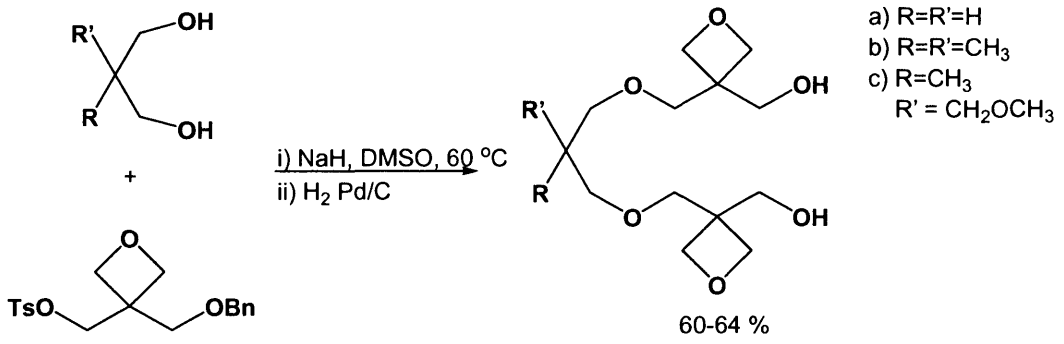
Scheme 1.2.2.5 Alternative Synthesis of Dimer with Pendant Hydroxyl Groups[86]

By carrying out the hydrolysis step using concentrated sulfuric acid in methanol, an alternative dimethylated product (**66**) was formed in an 80 % yield (scheme 1.2.2.6).[86] By masking 2 pendant hydroxyl groups in this way, the dimer could be further reacted in a linear fashion.



Scheme 1.2.2.6 Synthesis of Dimer with Pendant Methoxy Groups[86]

Dale and Fredriksen also reported the formation of trimers by reacting tosylates, similar to **60** and **63**, with various 1,3 – diols (scheme 1.2.2.7), with yields ranging from 60-64 %.[88]



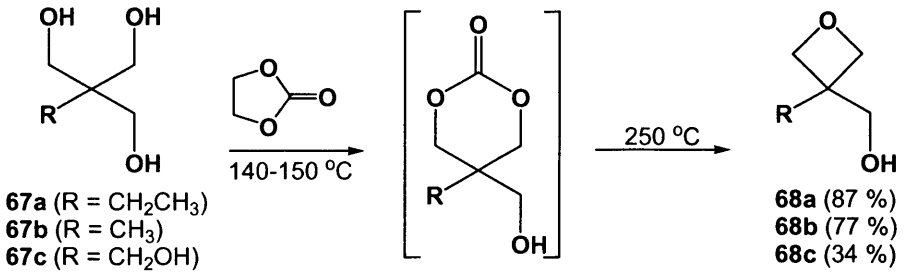
Scheme 1.2.2.7 Synthesis of Trimers with Pendant Oxetane Functionalities [88]

1.2.3 Cyclic Ether Synthesis in Solution

There has been much interest in forming cyclic ethers and polyethers. Oxetanes are four membered cyclic ethers and, as with their three membered analogues, epoxides (figure 1.2.3.1), have been found to be important monomers for polyether synthesis through acid catalysed ring opening (chapter 1.2.4).[90-93] They can also be polymerised by anionic ring opening.[94]

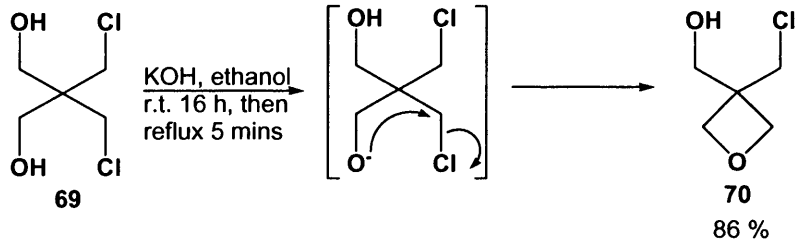
Figure 1.2.3.1 Examples of Cyclic Ethers

Oxetanes have been used in the formation of ligands for the selective complexation of small molecules (schemes 1.2.2.5 and 1.2.2.7),[85, 86, 88] as well as oxetane moieties being found in many natural products.[95, 96] A method widely used to synthesise oxetanes (as well as three, four and five membered cyclic ethers) on an industrial scale is the pyrolysis of cyclic carbonate esters with one or more pendant hydroxyl group. Pattison reported the synthesis of oxetanes with pendant functionalities (**68a**, **68b**, **68c**) from the corresponding triols (**67a**, **67b**) or tetraol (**67c**) using this method (scheme 1.2.3.1).[97] The yields for the conversion of triols **67a** and **67b** were 87 % and 77 % respectively, but the conversion of the tetraol (**67c**) was much lower (34 %). This method has the disadvantage that high temperatures and pressures are required to drive the reaction.



Scheme 1.2.3.1 Oxetane Synthesis by Pyrolysis of Cyclic Carbonate Esters [97]

Less commonly used methods of oxetane synthesis include treatment of cyclic sulfate esters with hot conc. alkali,[98] and [2 + 2] cycloaddition of an alkene and an aldehyde.[99] The most popular method of oxetane synthesis is by an intramolecular nucleophilic substitution of a good leaving group by an alkoxide ion. Using this method, Farthing was able to cyclise the di-chlorinated derivative of pentaerythritol (**69**) to the corresponding oxetane (**70**) in an 86 % yield (scheme 1.2.3.2).[92]

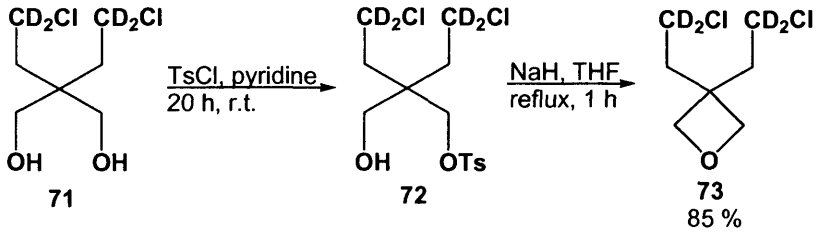


Scheme 1.2.3.2 Oxetane Synthesis by Intramolecular Cyclisation [92]

There are problems associated with such intramolecular cyclisations, however, with possible side reactions including fragmentation of the alkoxide into alkenes and carbonyl compounds, as well as competing elimination.[85]

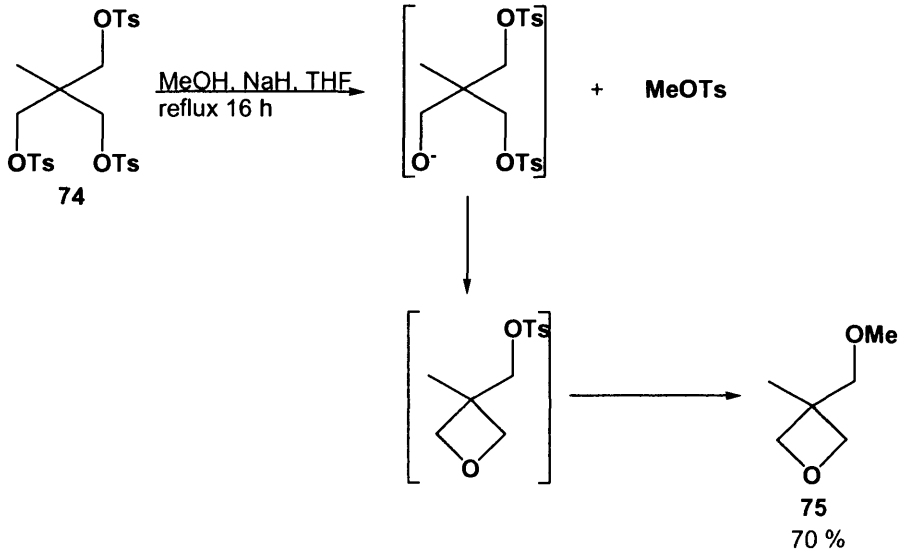
More recently, sulfonate esters have been used instead of halogens for this type of oxetane synthesis. Kawakami *et al.* reported the selective mono-tosylation of a partially deuterated, di-chlorinated species of pentaerythritol (**71**), by treatment with tosyl chloride in pyridine (scheme 1.2.3.3).[100] The mono-tosyl derivative (**72**) was then converted to the corresponding oxetane (**73**), using sodium hydride, in an 85 % yield.[100] As the monomer also had pendant chloride groups in equivalent positions to

the tosylate, this reaction demonstrates the greater reactivity of sulfonate esters as leaving groups in S_N2 reactions.



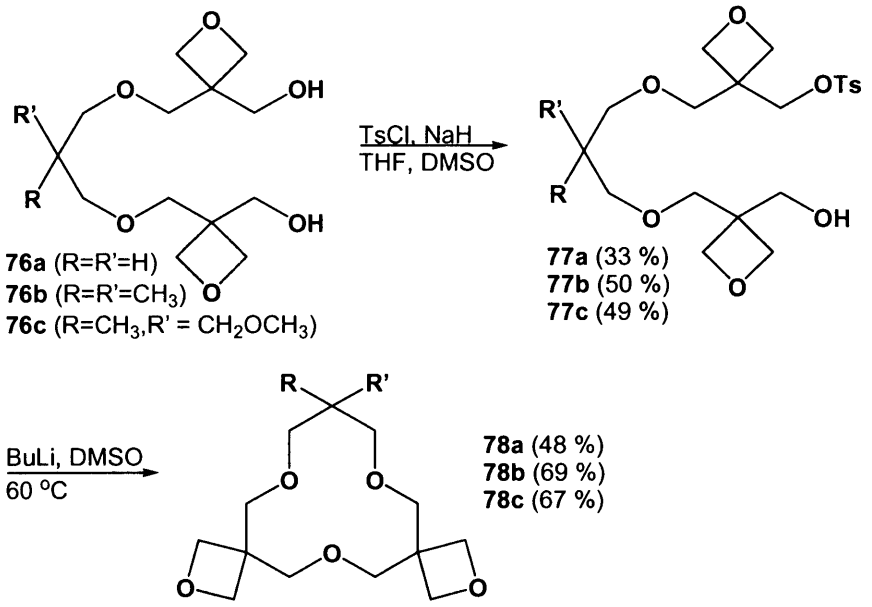
Scheme 1.2.3.3 Mono-tosylation of Diol (**71**) and Intramolecular Cyclisation [100]

Dale and Fredriksen found that when reacting a tri-tosylate (**74**) with methoxide, rather than forming the tri-alkylated product, an intermediate alkoxide was formed that cyclised to the corresponding oxetane (**75**) in a 70 % yield (scheme 1.2.3.4).[87]



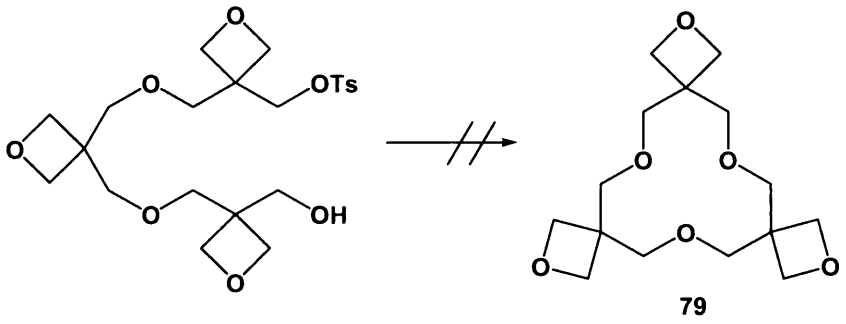
Scheme 1.2.3.4 Tosylate Exchange and Intramolecular Cyclisation [87]

By selectively converting trimeric polyethers (**76a**, **76b**, **76c**) to the corresponding tosylates (**77a**, **77b**, **77c** in 33 %, 50 % and 49 % yield respectively), Dale and Fredriksen were then able to effect an intramolecular cyclisation reaction by treatment with butyl lithium (scheme 1.2.3.5).[88] This gave the cyclic trimers **78a**, **78b**, and **78c** in yields of 48 %, 69 % and 67 % respectively, the molecules with bulkier R groups giving a higher yielding cyclisation.



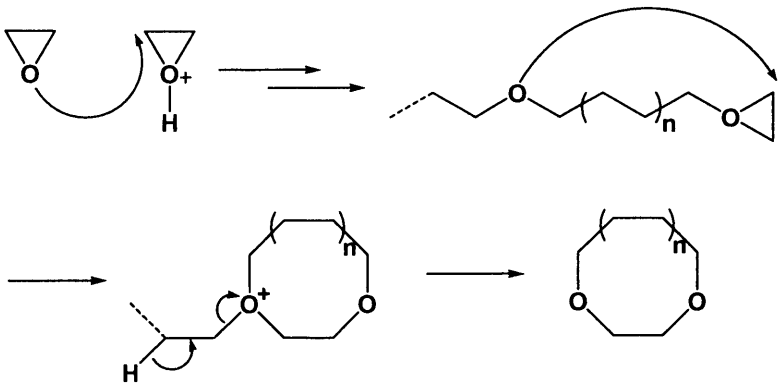
Scheme 1.2.3.5 Synthesis of Cyclic Trimers by Intramolecular Cyclisation [88]

However, an attempt to form a cyclic trimer with three pendant oxetane functionalities (**79**) failed "due to the ring strain of the system" (scheme 1.2.3.6). [88]



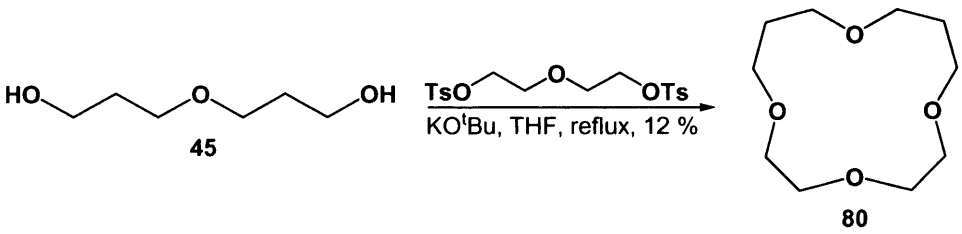
Scheme 1.2.3.6 Unsuccessful Synthesis of Cyclic Trimer (**79**) [88]

The ability to form cyclic polyethers by intramolecular cyclisation is also evidenced by the ring-chain equilibrium that exists when forming larger polyethers by acid catalysed polymerisation of epoxides (chapter 1.2.4). While these "back-biting" reactions can occur to form relatively small cyclic polyethers (scheme 1.2.3.7), increasing the chain length decreases the probability of cyclisation and increases the probability of a reaction with another molecule. [101]



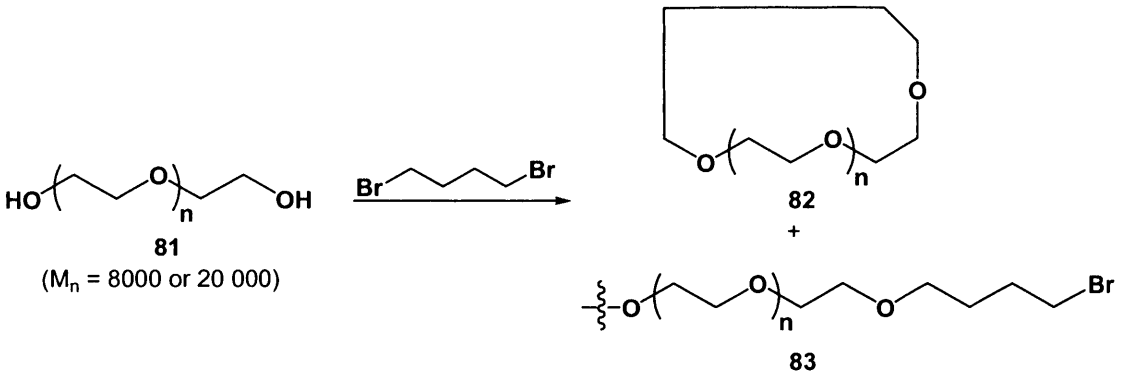
Scheme 1.2.3.7 Back-Biting During Oxetane Polymerisation [101]

Cyclic polyethers can also be synthesised by end-to-end ring closure of an α,ω-dicarbanionic molecule, using an appropriate difunctional electrophile.[102] This synthesis has been used extensively to form cyclic polyethers such as crown ethers, which have been found to be useful for complexing metal ions, although yields are generally low. For example, Buchanan *et al.* synthesised 1,4,7,11-tetracyclotetradecane (**80**) by reacting 4-oxa-1,7-heptanediol (**45**) with diethylene glycol ditosylate, in a 12 % yield (scheme 1.2.3.8).[102]



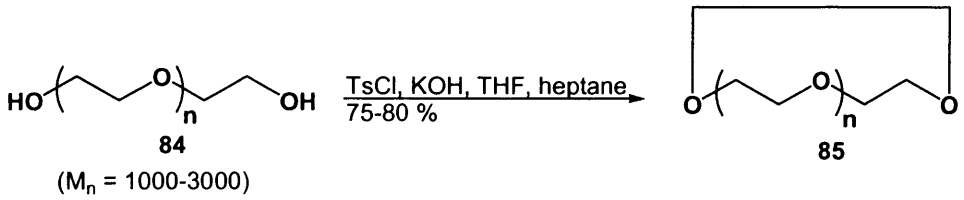
Scheme 1.2.3.8 Synthesis of Cyclic Tetramer (**80**) [102]

Using end-to-end ring closure, much larger cyclic polyethers have also been formed. For example, Ishuizu *et al.* reported the synthesis of cyclic polyethers (**82**) by reacting the alkoxides of PEGs (**81**, average mass 8000 and 20 000) with 1,4-dibromobutane (scheme 1.2.3.8).[103] Although the extent of products arising from a competing condensation reaction (**83**) was increased with increasing reaction time and decreasing PEG alkoxide concentration, the ratio of cyclisation to condensation remained at around 100 %.[103]



Scheme 1.2.3.8 Formation of Cyclic PEGs by End-to-End Ring Closure [103]

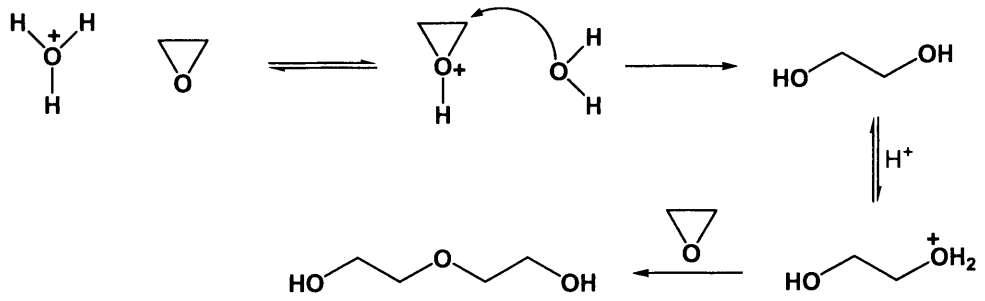
The intramolecular cyclisation of mono-functional PEG chains has also been reported.[104] For example, Yu *et al.* reacted PEG chains (**84**, average mass 1000 to 3000) with tosyl chloride in the presence of potassium hydroxide, affording cyclic PEG products (**85**) in 75-80 % yields (scheme 1.2.3.9).[103] Here, the ratio of cyclic products to linear products was kept high by ensuring that the molar concentration of reactive end groups was low ($<10^{-5}$ mol dm^{-3}).



Scheme 1.2.3.9 Intramolecular Cyclisation of PEG Chains (**84**) [104]

1.2.4 Synthesis of Larger Polyethers in Solution

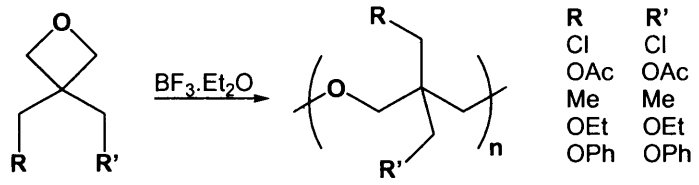
For the synthesis of larger polyethers, the preferred method is by cationic activated polymerisation of oxygen containing heterocycles (see review by Kubisa *et al.*).[101] The Activated Monomer (AM) mechanism, using oxirane, gives straight chain polyethers under mild acid catalysis (scheme 1.2.4.1).[101]



Scheme 1.2.4.1 Cationic Activated Polymerisation of Oxirane [101]

If the concentration of the terminal hydroxyl moiety in solution is too low, the competing Active Chain End (ACE) mechanism becomes more favourable, making the polymerisation cease. A low concentration of the terminal hydroxyl moiety can also encourage "back biting" to form cyclic polyethers (scheme 1.2.3.7).[101] In reality all of these mechanisms are in competition, but conditions can be manipulated to favour the AM mechanism. Concentration of the monomer at any one time must be low for AM to be favoured, so the monomer should be added slowly to the solution.[101] This is a useful method for the synthesis of linear polyethers and hyperbranched polyethers (schemes 1.2.2.5 and 1.2.2.6). However, while conditions can be controlled to give polyethers in a narrow molecular weight range, it is not possible to synthesise polyethers of a uniform molecular weight using this method.

An example of Lewis acid catalysed polyether synthesis was reported by Farthing. Here cationic activated polymerisation of oxetane monomers with 2,2-bis substituents gave polyethers with pendant functionalities (scheme 1.2.4.2).[92]

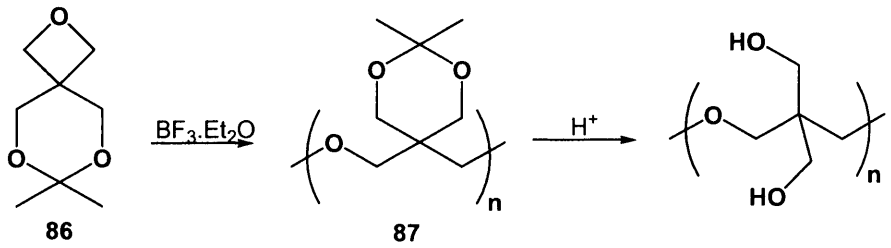


R	R'
Cl	Cl
OAc	OAc
Me	Me
OEt	OEt
OPh	OPh

Scheme 1.2.4.2 Cationic Activated Polymerisation of Oxetane Monomers [92]

2,2-Bishydroxymethyl oxetane (R=R'=OH) could not be polymerised directly to give a straight chain polymer, as the free hydroxyl groups caused branching. In order to synthesise straight chain polyethers with pendant hydroxyl functional groups, a ketal

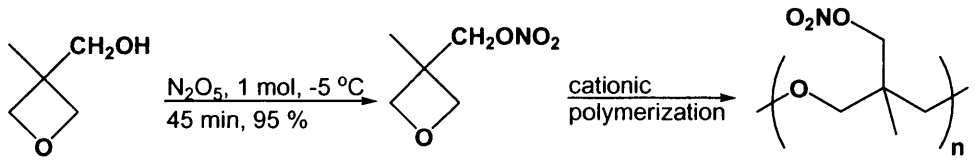
protected oxetane monomer (**86**) was polymerised, followed by deprotection of polymer **87** by acid hydrolysis (scheme 1.2.4.3).[92] As the hydroxyl groups became available, the polymer became increasingly tough and rigid, due to strong hydrogen bonding between chains. This also made the deprotected polymer insoluble even in highly polar solvents.[92]



86 87

Scheme 1.2.4.3 Synthesis of Polyether with Pendant Hydroxyl Groups [92]

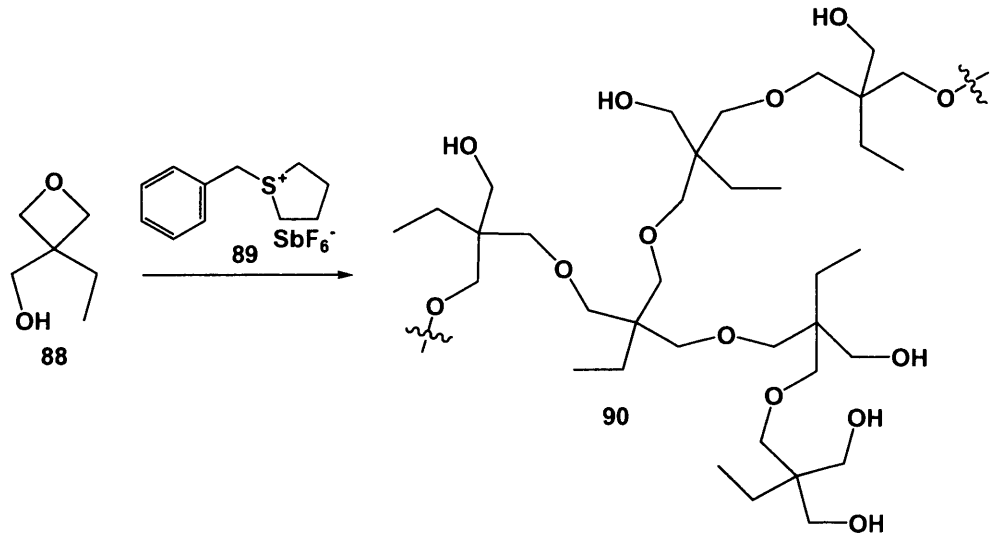
Polyethers with pendant nitro-functionalities are known to be highly energetic materials. Millar *et al.* have reported a nitrating system that is particularly suited to forming nitrate esters from pendant hydroxyl functionalities on oxygen containing heterocycles, using dinitrogen pentoxide in organic solvents, which can then be cationically polymerised (scheme 1.2.4.4).[105]



Scheme 1.2.4.4 Synthesis of Polyether with Pendant Nitrate Esters [105]

This synthesis can also be applied to epoxides with pendant hydroxyl functionalities to form PEG-like polyethers with pendant nitrate esters. Conditions can be controlled to give polyethers of a desired molecular weight range, which is particularly important for this type of energetic materials, as the energy of the polyether is directly related to their molecular weight. If suitable hydroxyl functionalities are also included in the polyethers, they can be cross-linked to a polyurethane rubber. These energetic rubbers have been widely used as propellants and explosives.

If cationic ring opening polymerisation is carried out using oxetanes with unprotected pendant hydroxyl functionalities, hyperbranched polyethers are formed. [87, 88, 103-105] Unlike the dendritic polymers discussed previously, hyperbranched polymers are polydisperse and some monomer units are incorporated in a linear fashion giving a less defined structure.[90] Hult *et al.* reported a high yielding hyperbranched polyether synthesis using 3-ethyl-3(hydroxymethyl)oxetane (**88**) as the monomer and benzyl tetramethylenesulfonium hexafluoroantimonate (**89**) as the initiator (scheme 1.2.2.5).[90]

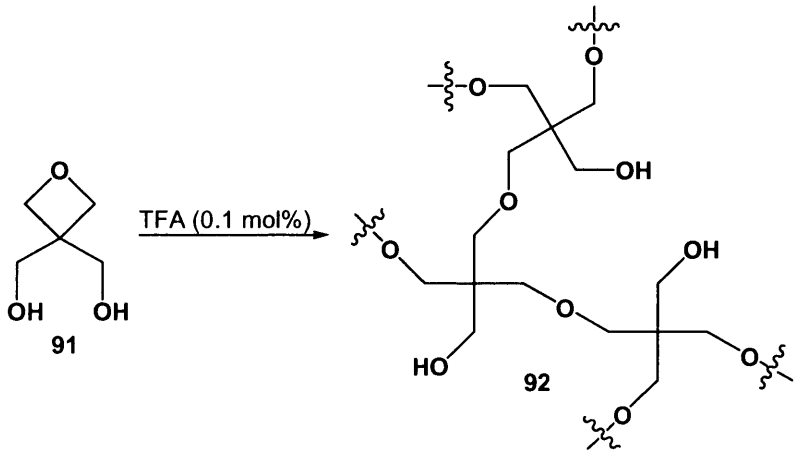


Scheme 1.2.2.5 Cationic Ring Opening to Give a Hyperbranched Polyether (**90**) [90]

The hyperbranched polyethers formed (**90**) were of relatively narrow weight distribution and low molecular weight for this type of polymerisation, for example, after polymerisation at 120 °C size exclusion chromatography indicated that a hyperbranched polyether with a distribution of 1.26 and an average molecular weight of 5251 g mol^{-1} had been formed.[90] However, the structure proposed for **90** has since been shown to be an idealised view of a hyperbranched polyether, with a limiting factor in the formation of hyperbranched polyether being intramolecular chain transfer, which terminates the polymerisation giving cyclic fragments. [106] Processes of this nature are thought to become more prevalent as the concentration of hydroxyl groups increases, increasing the degree of hydrogen bonding in the system and changing the conformation of the polymer, making the hydroxyl groups become less available. Attempts to control the degree of branching in hyperbranched polyethers

have shown that the type of initiator used and the reaction temperature do not have an effect on the structural build up of the polymer. The degree of conversion of the monomer did have an effect on the branching, however, with the polyether mainly being linear at low conversion.

Chen *et al.* have explored the synthesis of a hyperbranched polymer using an alternative monomer, 3,3-bis(hydroxymethyl)oxetane (**91**) and trifluoroacetic acid (TFA) as the initiator (scheme 1.2.2.6).[108] Unlike the polymers formed using compound **88**, where there was no branching at most monomer units, the hyperbranched polyethers formed by this reaction (**92**) were singly branched at nearly every monomer unit. The increased ratio of hydroxyl groups in this polymer led to a more rigid structure.[108]



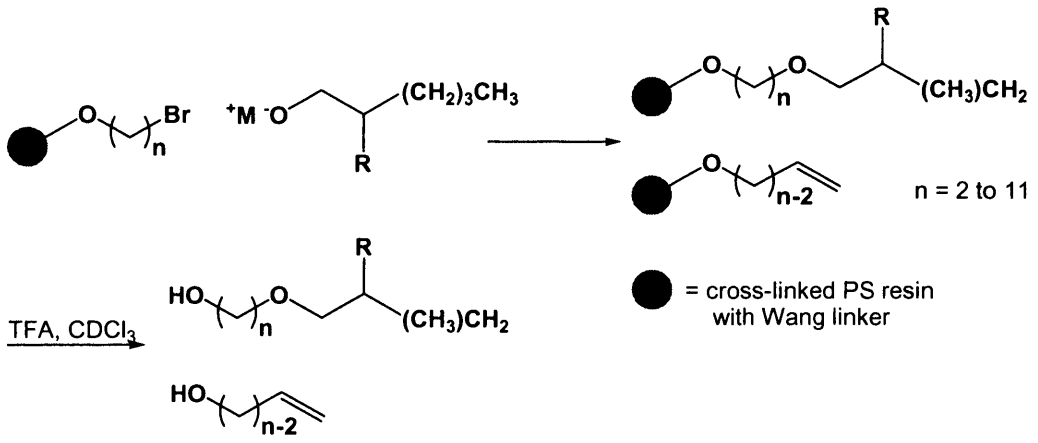
Scheme 1.2.2.6 Cationic Ring Opening to Give a Hyperbranched Polyether (**92**) [108]

They went on to synthesise a hyperbranched co-polymer using a 1:1 mixture of **88** and **91**.[108] In this polyether, most of the units of monomer **88** were seen to be linear, whereas most units of monomer **91** were singly branched. It was therefore hypothesised that the degree of branching in these co-polymers could be controlled as desired by changing the monomer ratio.[108]

1.2.5 Ether Synthesis on Polymeric Supports

Examples of ether synthesis on solid supports are somewhat limited. The majority involve protecting group strategies, for example the conversion of a hydroxyl group to a benzyl ether on a PS support.[109] Perhaps part of the reason for this lack of ether synthesis on solid supports is that the harsh reaction conditions that are often associated with the classical Williamson's ether synthesis would not be compatible with PS supports.

In response to an observed lack of studies into the general applicability of Williamson's type ether synthesis to PS bound substrates, Weissberg *et al.* have studied the effects of varying reaction parameters for the conversion of PS supported alkyl bromides to their corresponding ethers (scheme 1.2.5.1).[11] Alkyl bromides were attached to the support by means of a Wang linker.



Scheme 1.2.5.1 Ether Synthesis and Competing Elimination on a Solid Support [11]

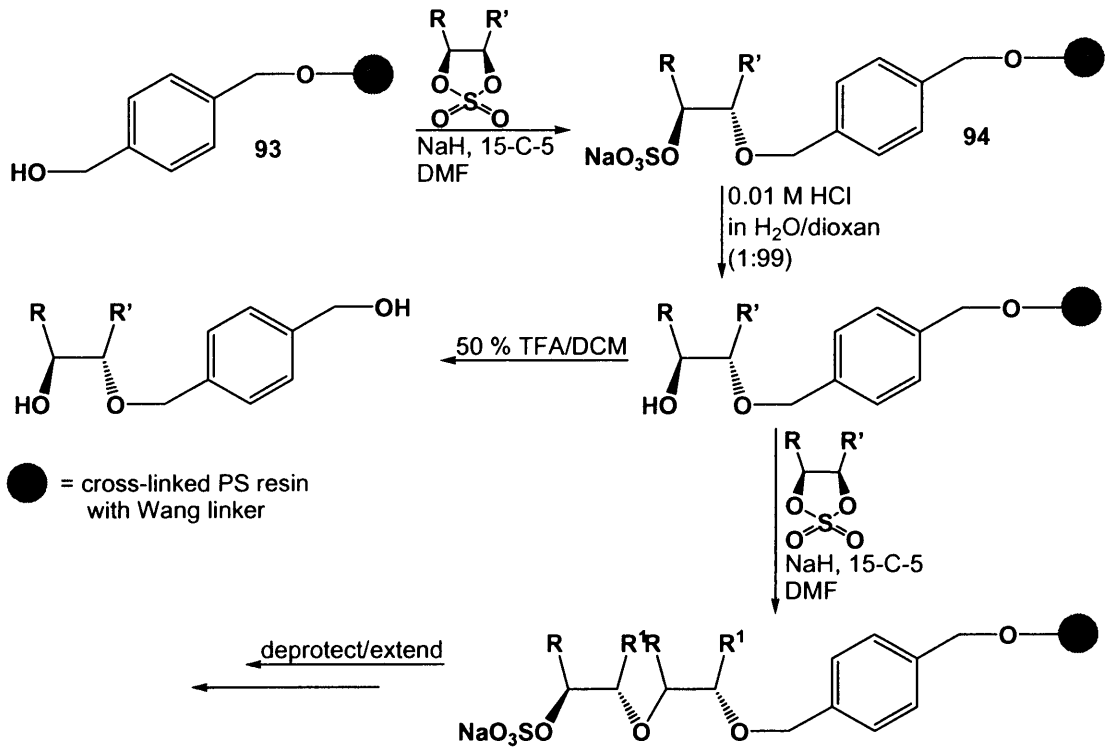
Initial reactions between immobilised 3-bromopropanol or 6-bromohexanol and alkoxides in solution highlighted that competing elimination of hydrogen bromide, to give an alkene, was far more prevalent than with the analogous solution based reactions.[11] In solution, elimination is usually only observed for secondary and tertiary alkyl halides, whereas on the support there was substantial elimination even with primary alkyl halides. The substitution/elimination ratio was found to be strongly dependant on reaction conditions. For example, increasing the nucleophile size by using β-branched alkoxides was seen to decrease the ratio, decreasing selectivity for the desired extension.[11]

In order to get complete conversion of the supported alkyl bromides, various additives were used. Of the crown ethers used to facilitate the reaction, 15-crown-5 was seen to give the best rate of bromide conversion and in the absence of this additive there was a significant drop in selectivity (2.11 to 1.69).[11] Little difference in selectivity or bromide conversion was observed between the use of potassium iodide and TBAI as the iodide salt, suggesting that their main role in facilitating the reaction was not as a phase transfer catalyst, but perhaps for in-situ conversion of the bromide to a more reactive iodide. The best rates of conversion and selectivity were obtained when both 15-crown-5 and an iodide salt were used.

A key factor that determined the substitution/elimination ratio was the length of the immobilised alkyl bromide. Longer alkyl bromides (greater n value) were subject to a far lesser degree of hydrogen bromide elimination.[11] As there were no factors associated directly with the alkyl bromide to explain this phenomenon, they hypothesised that it was due to a polymer matrix "proximity" effect. They speculated that for shorter alkyl halides, fewer reactive sites were solvated, but were instead in the apolar environment of the polystyrene. This is a logical explanation of the greater degree of elimination with shorter alkyl halides, because it is known that an apolar environment favours elimination over subsitution.[110]

Recently Bradley's group have reported an iterative approach to the synthesis of polyethers on a solid support.[27] This was carried out using a functionalised PS resin (**93**) from which an alkoxide could be generated using sodium hydride. Various cyclic sulfates were reacted with the resin bound alkoxide via a nucleophilic ring opening reaction, with inversion of stereochemistry, to give the corresponding ether with a terminal sulfate ester (scheme 1.2.5.2).[27] The sulfate ester (**94**) was hydrolysed in mild acid and resin bound products were then either cleaved from the resin with TFA, or the extension step and ester hydrolysis were repeated to give higher oligomers. Unlike Weissberg's studies, the electrophile (here a cyclic sulfate rather than an alkoxide) was in solution rather than bound to the PS resin, and as a result no competing elimination observed. Initial reactions, carried out on a 2 % cross-linked PS resin gave very low conversion of the alkoxide to the ether using these conditions. This was improved by moving to a 1 % cross-linked support, thought to be due to the

removal of charge-charge interactions, but the best results were obtained using a Tentagel resin.[27]

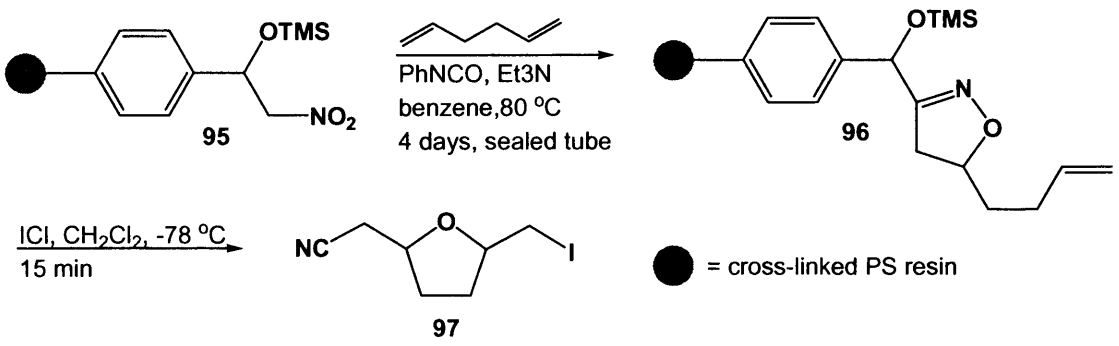


Scheme 1.2.5.2 Iterative Polyether Synthesis on a Solid Support [27]

Using a Tentagel resin, various cyclic sulfates, prepared from both cyclic and acyclic diols, were converted to the corresponding diol, with HPLC indicating % conversions to the dimer ranging from 53-74 %. Using the methodology they were able to carry out iterative extensions up to the tetramer in a 13 % purified yield. A limitation to this methodology is that because the extension step was not quantitative, higher oligomers were obtained in mixtures with the lower molecular weight oligomers, e.g. the tetramer was obtained in a mixture with the monomer, dimer and trimer.

There have been even fewer 'on resin' syntheses of cyclic ethers. Beebe *et al.* reported a synthesis of tetrahydrofurans on a PS resin via a 1,3-dipolar addition of a resin bound nitrile oxide (**95**) to an α,ω-diene, to give an isooxazoline with a terminal olefin (**96**), which can then undergo electrophilic cyclisation/cleavage to give a

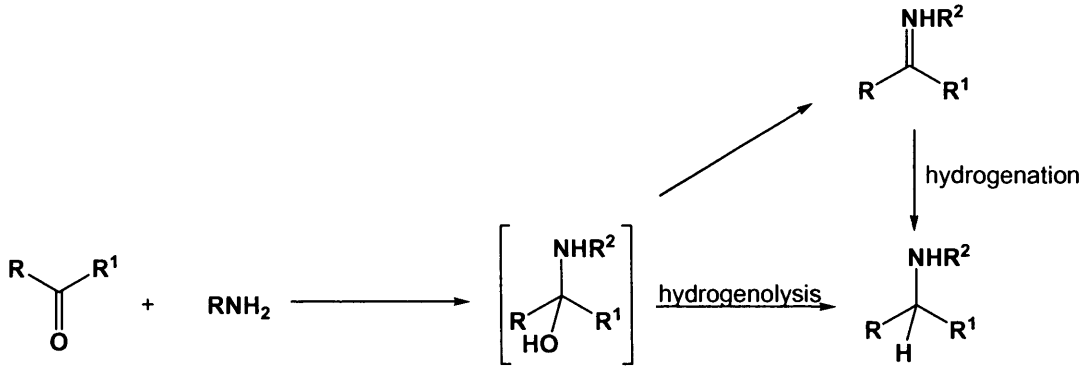
cyclic ether (**97**, scheme 22).[111] This is an efficient process, although it is as yet limited to the formation of 5-membered rings.



Scheme 22 PS Supported Synthesis of 5-Membered Cyclic Ether (**95**) [111]

1.3 Reductive Amination

The methods discussed in chapter 1.2 have exclusively been directed towards synthesising polyethers. Another important class of polymers, which have been synthesised in solution and on polymer supports are polyamines. Reductive amination (also known as reductive alkylation) has been shown to be a very useful method of forming C-N amine bonds in iterative polyamine syntheses. Reactions of this type involve the condensation of aldehydes or ketones with amines, followed by either hydrogenolysis of the intermediate (for ammonia, primary, or secondary amines) or imine formation followed by hydrogenation (for ammonia, or primary amines) to give the alkylated amine (scheme 1.3.0.1). [112, 113]



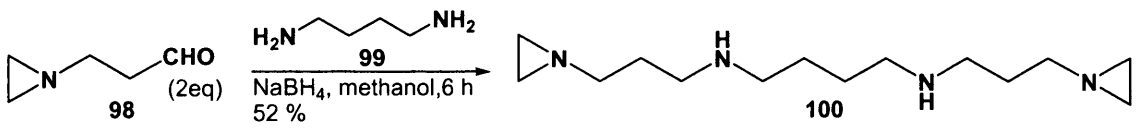
Scheme 1.3.0.1 Pathways for Reductive Amination [113]

In order to effect a hydrogenolysis or hydrogenation reaction, some kind of reducing agent is required. Suitable reducing agents include hydrogen with a nickel catalyst, zinc and hydrogen chloride, sodium cyanoborohydride and sodium borohydride. [112, 113] Where amines and aldehydes/ketones are suitably functionalised, reductive alkylation has been successfully utilised as a method of forming polyamines, both in solution and on polymeric supports.

1.3.1 Reductive Amination in Solution

There are several comprehensive reviews of the biological importance and synthesis of polyamines in the literature.[114] Polyamine analogues have a role in a range of cell processes and as a result naturally occurring polyamines can be modified to give potent enzyme inhibitors, ion-channel blockers and cytotoxic agents. Due to the very high level of polyamine biosynthesis in cancerous cells, polyamine analogues that can disrupt cell processes are potential anti-tumour agents. They have also been explored as potential treatments for neurological disorders such as Alzheimer's.[114]

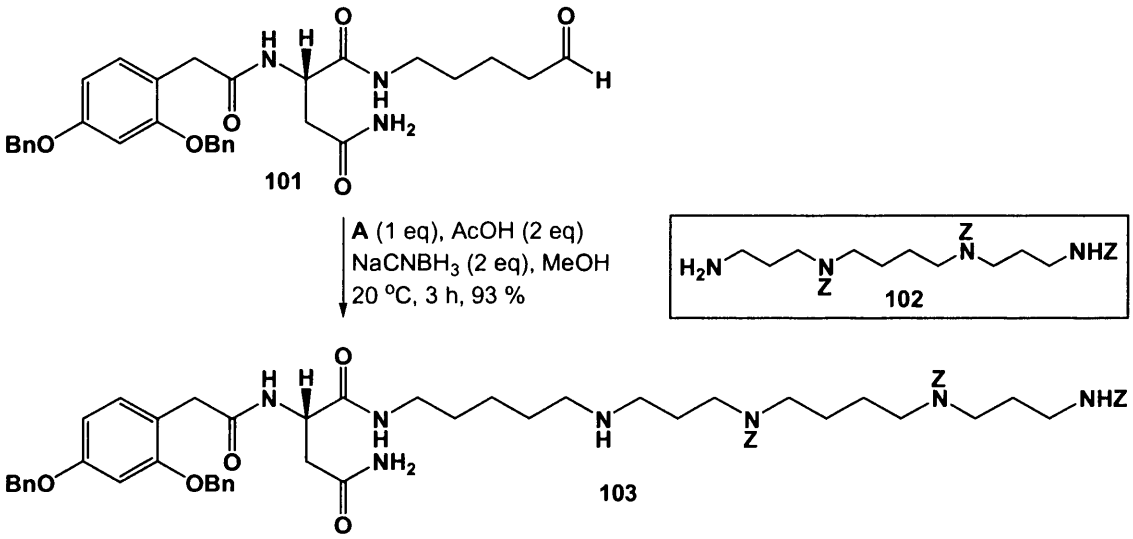
Several groups have successfully utilised reductive amination in the solution-based synthesis of polyamine analogues.[115-120] For example, Li *et al.* were interested in the design of anti-cancer agents that incorporated a polyamine for the targeting of DNA and an alkylating group to give cytotoxic activity.[119] The polyamine part of the molecule was synthesised by a reductive amination reaction between 1,4-diaminobutane (**99**) and an 3-aziridinylpropanal (**98**) in the presence of sodium borohydride, affording polyamine **100** in a 52 % yield (scheme 1.3.1.1).[119]



Scheme 1.3.1.1 Polyamine Synthesis by Reductive Amination [119]

Blagbrough's group also utilised a reductive alkylation for the joining of the two fragments of a modified spider toxin that has potential uses as an ion-channel blocker.[117] A reaction between protected polyamine **102** and aldehyde **101** in the

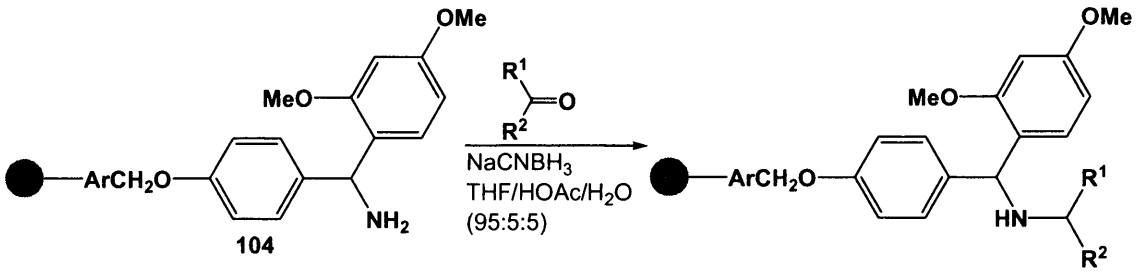
presence of glacial acetic acid (to maintain a neutral pH) and sodium cyanoborohydride gave the desired product (**103**) in a 93 % yield (scheme 1.3.1.2).[117]



Scheme 1.3.1.2 Synthesis of Modified Spider Toxin (**103**) by Reductive Amination [117]

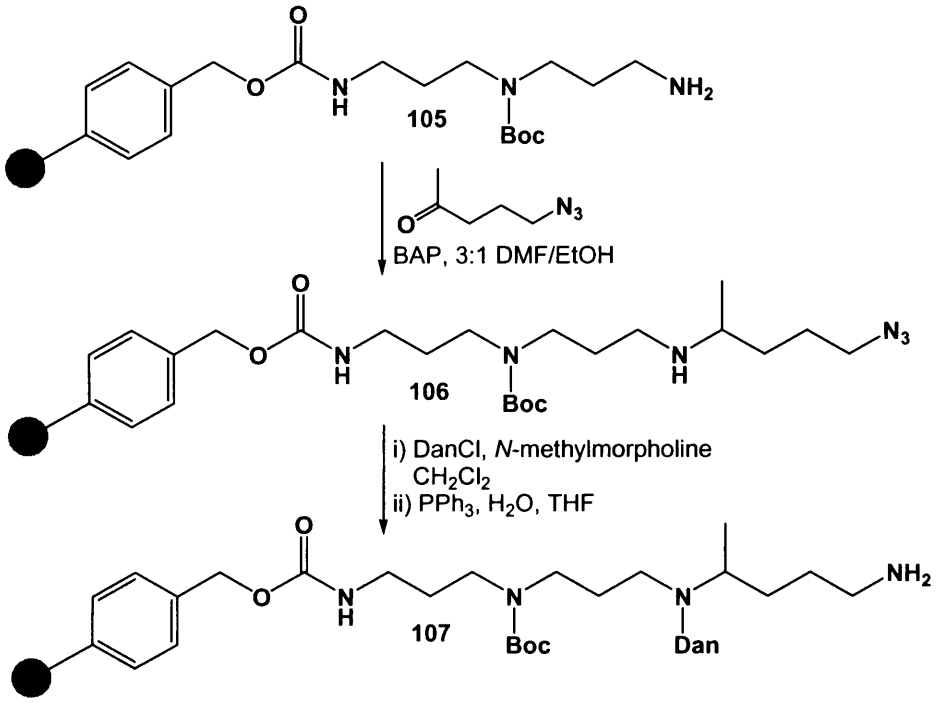
1.3.2 Reductive Amination on Polymeric Supports

Reductive amination has also been used as a method of attaching molecules to polymeric supports. For example, Brown *et al.* were able to immobilise a range of aldehydes and ketones by reacting them with a Rink amide linker on a PS support (**104**) and sodium cyanoborohydride (scheme 1.3.3.1).[121] The alkylation reaction proceeded nearly to completion (>95 %) after around 3 hours at room temperature, but after this the remaining sites could not be reacted further due to severe steric hindrance.



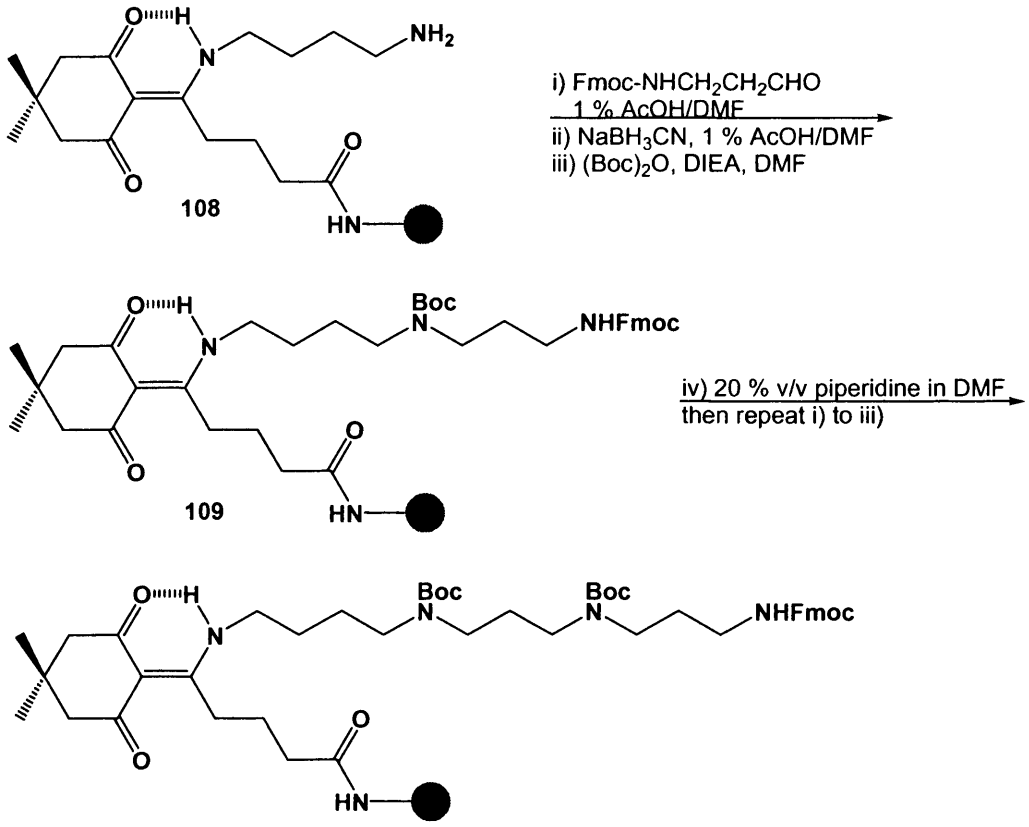
Scheme 1.3.2.1 Loading of Aldehydes or Ketones onto Rink Amine Resin (**104**) [121]

As with some other iterative polymer syntheses, it has been a logical step to develop polymer supported syntheses of polyamines. This has allowed the rapid method for the preparation of large combinatorial libraries of polyamine analogues. A number of these polymer supported syntheses have successfully used reductive amination for the extension step. For example, Blagbrough *et al.* employed such an approach when developing a library of linear polyamine analogues to be tested as potential glutamate receptor antagonists.[122] Here the extension step was a reaction between an immobilised diamine, attached to a PS support through a Wang linker (**105**), and a ketone, with a borane-pyridine complex (BAP) as the reducing agent (scheme 1.3.2.1). Reductive amination was followed by *N*-dansylation of the secondary amine on resin **106**. As the ketone used for the reductive amination was functionalized with an azide, this group could be reduced to amines following the extension step by reaction with triphenyl phosphine. Following *N*-dansylation of the newly formed primary amine on resin **107**, the product was cleaved from the support and obtained in a yield of 35 % over all steps.[122]



Scheme 1.3.2.1 Reductive Alkylation and Azide Reduction on a Solid Support [122]

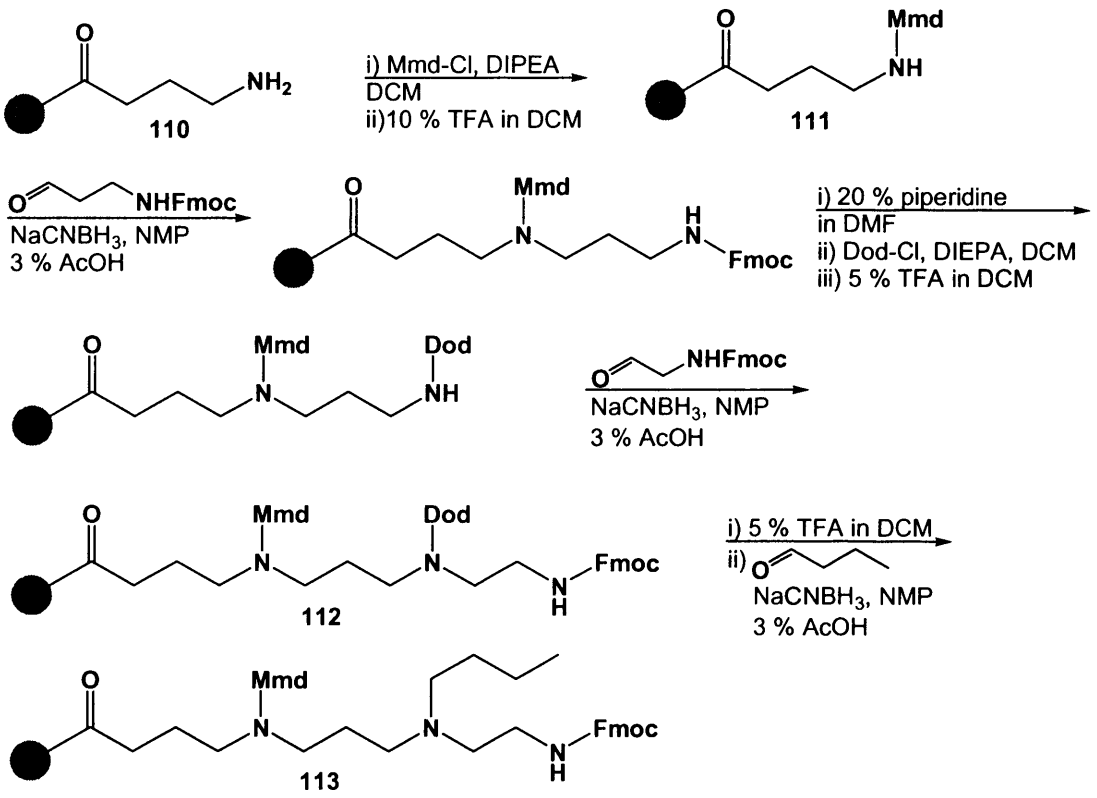
Bycroft's group have also reported reductive alkylation on a solid support in their strategies towards the synthesis of glutamate receptors.[123, 125] Here they used a Dde group as a linker to the support, due to its selectivity for primary amines. The supported diamine (**108**) was extended by a reaction with an aldehyde, isolation of the imine, and reduction with sodium cyanoborohydride (scheme 1.3.2.2).[123] Cleavage of the Fmoc group from resin **109** allowed a second extension step by the same reductive amination protocol. After further deprotections and cleavage from the support, the polyamine product was obtained in a yield of 65 % over all steps and in 90 % purity.[123]



Scheme 1.3.2.2 Iterative Polyamine Synthesis by Reductive Alkylation [123]

Jönsson *et al.* have developed a solid supported synthesis of branched polyamines by reductive amination, taking advantages of the relative stabilities of various protecting groups.[125] Resin bound amine (**110**) was mono-protected with a 4-methoxy-dityl (Mmd) group by reacting with Mmd chloride and diisopropylethylamine (DIPEA), followed by exposing the resin to 5 % TFA for 10 second periods (scheme 1.3.2.3). The Mmd protected product (**111**) was then reacted with Fmoc-amino propanal and sodium cyanoborohydride to give the extended product. The Fmoc group was deprotected and the resin was mono-protected with a 4,4'-dimethoxy dityl (Dod) group by a reaction with Dod chloride and DIPEA, followed by several 10 second exposures to 5 % TFA. A second reductive amination was then carried out using Fmoc-amino ethanal under the previous conditions to give the resin bound trimer (**112**).[125] Due to the differences in acid stabilities between MMd and Dod groups, the Dod group could then be selectively deprotected by treatment with 5 % TFA for 15 minutes. This exposed one of the secondary amines, which could be reacted with butraldehyde and sodium cyanoborohydride to give the branched product (**113**).

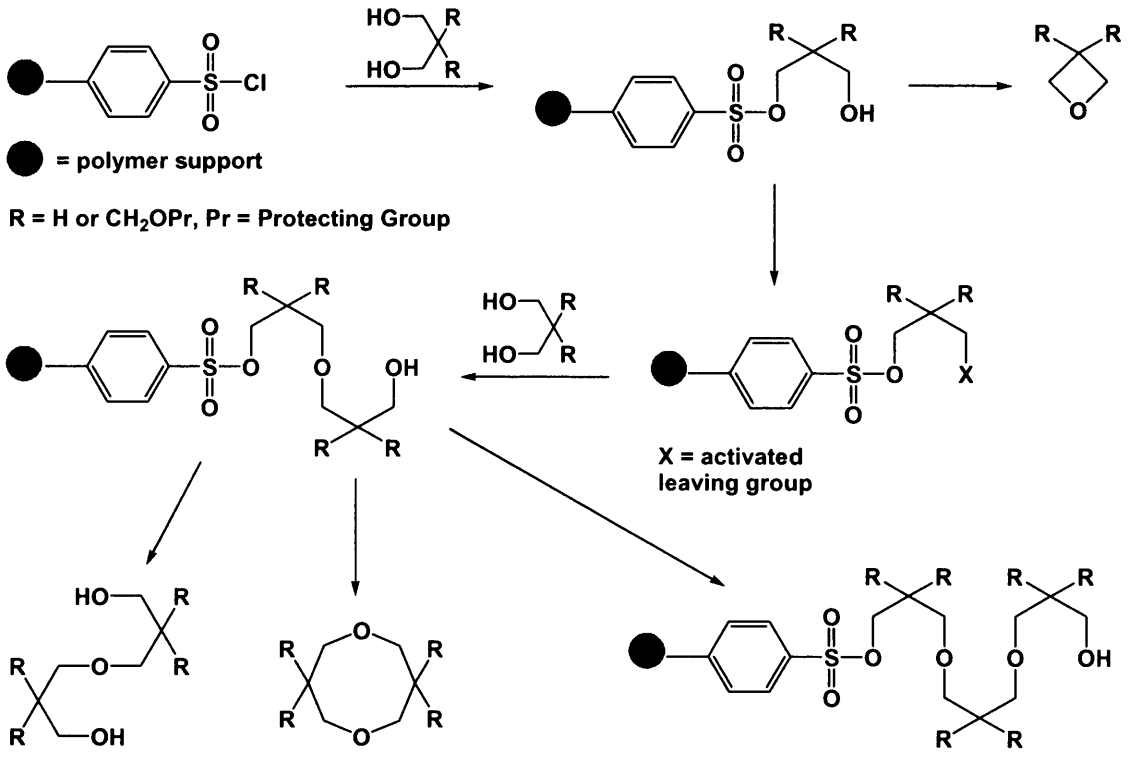
Using this methodology the group were able to synthesise and cleave a selectively branched tetramer in a 40 % yield over all steps and in 80 % purity.[125]



Scheme 1.3.2.3 Solid Supported Synthesis of a Selectively Branched Polyamine [125]

1.4 Project Aims

The aims of this project were firstly to develop an iterative ether synthesis that could be carried out on a polymeric support (scheme 1.4.1). To this end, the synthesis of a range of suitably protected monomers was required. A sulfonyl type linker would be used as the linker to the support, which would allow the formation of both cylic polyethers and straight chain polyethers. Cyclic polyethers would be afforded by an intramolecular cyclisation reaction upon cleavage of the product from the support. It was hoped that extension of the method, from simple linear monomers to branched monomers with protected hydroxyl groups, would allow access to a wide range of functionalised polyethers. The development of a complementary iterative polyamine synthesis was also desired, as a further means of adding diversity to the polymers. Secondary amine linkages in the final oligomer could be a potential site for the addition of alkyl chains or other desired functional groups.



Scheme 1.4.1 Proposed Iterative Ether Synthesis

Chapter 2

2.0 Monomer Synthesis

The availability of suitably protected and functionalized monomers is essential to the success of any oligomer synthesis. The following chapter describes the synthesis of the monomers that were later used to synthesise polyethers, cyclic ethers and in reductive amination strategies. Three main classes of monomers were studied; linear monomers based on 1,3-propanediol (**114**), singly branched monomers based on 2-methoxy-1,3-propanediol (**115**) and dibranched monomers based on pentaerythritol (**116,** figure 2.0.1).

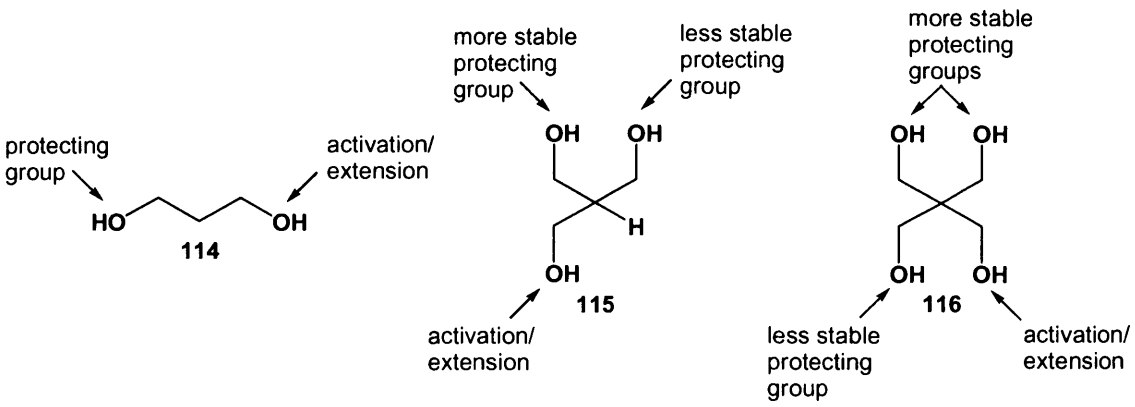


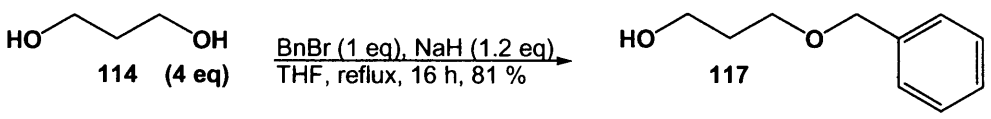
Figure 2.0.1 Monomer Precursors

Important considerations when planning protecting group strategies included the suitability of deprotection conditions for "on-resin" reactions, with respect to the stability of the chosen polymeric support and linker. The protecting groups also had to be stable to all other reaction conditions. For singly branched and dibranched monomers, the relative stabilities of the different protecting groups used was also a consideration; one hydroxyl group was required to be masked by a protecting group which could be cleaved "on-resin" by conditions that would not cleave the other protected hydroxyls.

2.1 Synthesis of Linear Monomers

For the development of chain extension strategies (chapter 4; polyether synthesis, chapter 5; amine synthesis), all preliminary test reactions were carried out using linear monomers based on 1,3-propanediol (**114**). Using the least sterically hindered of the 3 classes of monomer, the aim was to establish the general reaction conditions of the chain extension strategy, before any attempts to adapt conditions for use with the more hindered monomers.

Key to the synthesis of linear monomers was the selective mono-protection of one of the functional groups. This was important for their utility in iterative chain extensions, where only one monomer unit addition was sought per extension step. For use in the synthesis of acyclic ethers (chapter 4) 1,3-propanediol (**114**) was initially converted to its mono-benzyl protected derivative. Benzyl ethers have been widely used as protecting groups for hydroxyl functionalities due to their high stability to both acidic and basic conditions, generally requiring catalytic hydrolysis for their cleavage.[126] This was ideal for initial test reactions, as a robust protecting group would avoid unwanted deprotection by the extension conditions. Also, the characteristic λ_{max} of benzyl groups could help in monitoring reactions. In an HPLC run of a mixture of benzyl functionalised compounds, the benzyl group would give a handle for UV detection, giving the relative amount of each component. The presence of benzyl groups could also help in TLC analysis, where shining UV radiation on the plate would reveal which compounds contained UV active groups. The reaction of a large excess of 1,3-propanediol (**114**) with sodium hydride to form the alkoxide *in situ*, and addition of benzyl bromide gave the desired mono-benzylated product (**117**) after heating at reflux in an 81 % yield (scheme 2.1.1).



Scheme 2.1.1 Mono-benzylation of 1,3-Propanediol (**114**)

The benzyl protected monomer (**117**) was initially ideal for test reactions, but the conditions required for deprotection would not be useful for "on-resin" deprotections on polystyrene based resins (which was our initially chosen support), as they would either be too strongly acidic, or require heterogeneous reaction conditions (e.g. hydrogenation with palladium on carbon [126]) that would make purification problematical following the reaction. A mono-protected monomer was therefore also required that had a protecting group that could be removed using milder conditions and would be compatible with our chosen polymeric supports. A silyl protected monomer was ideal, as silyl removal is completely achieved by treatment with TBAF, as well as by acid hydrolysis.[127] A *tert*-butyldimethylsilyl (TBS) protecting group was selected as the relatively unstable, less hindered trimethylsilyl (TMS) groups seemed unlikely to be stable to all reaction conditions, but the more hindered tri*iso*propylsilyl (TIPS) and *tert*-butyldiphenylsilyl (TBDPS) groups could be too acid stable for compatibility with acidic cleavage conditions and too sterically hindered to give high reactivities (figure 2.1.1).[128]

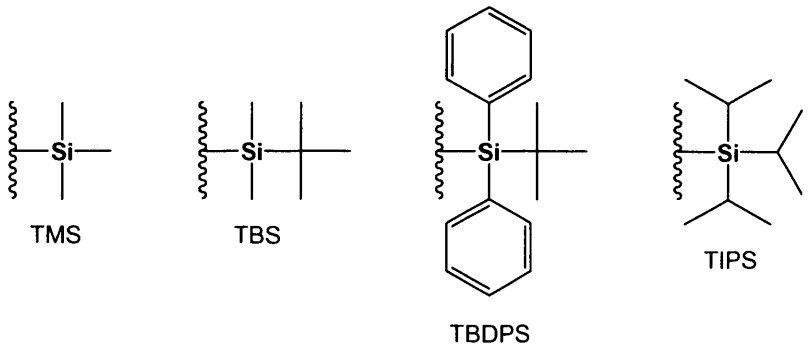
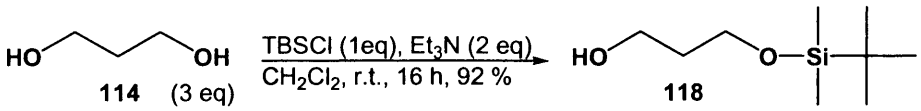


Figure 2.1.1 Examples of Silyl Protecting Groups

By reacting a large excess of 1,3-propanediol, **114**, with TBS chloride, using triethylamine as a base, the mono-TBS protected monomer (**118**) was generated in a 92 % yield (scheme 2.1.2). Analysis by TLC indicated that no corresponding di-silyl protected product had been formed and therefore this reaction was completely selective towards the mono-protected product.

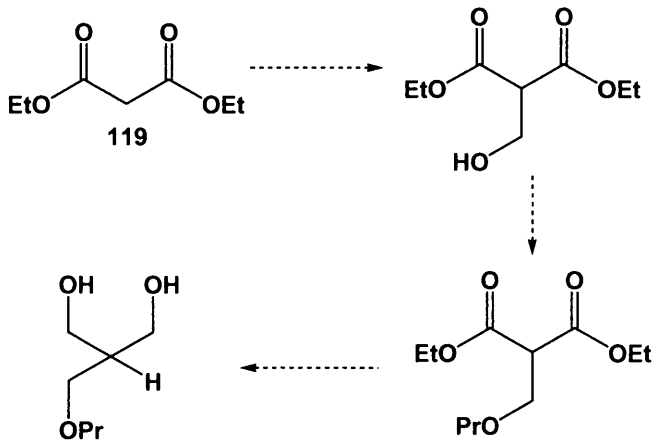


Scheme 2.1.2 Mono-TBS Protection of 1,3-Propanediol (**114**)

2.2 Synthesis of Singly Branched Monomers

At a later stage in the project the development of singly branched monomers based on 2-methoxy-1,3-propanediol (**115**) was initiated. Such monomers could have greater reactivity than analogous dibranched monomers, due to reduced steric hinderance, but still had a pendant hydroxyl group for further functionalization following oligomer synthesis.

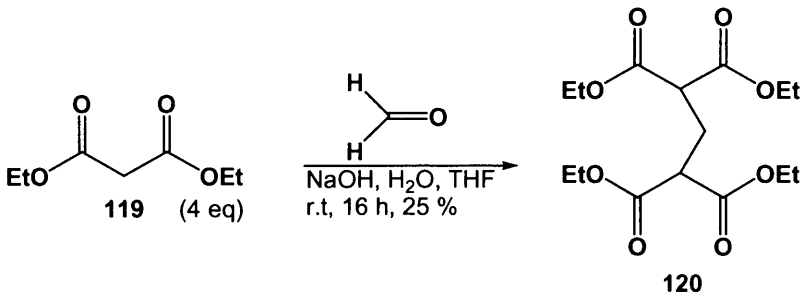
Triol **115** is commercially available, but its cost is very high. Therefore, rather than attempting to selectively mono-protect the triol (**115**), the synthesis of singly branched monomers was investigated starting with the electrophilic addition of a hydroxymethyl group to diethyl malonate (**119**). This was followed by suitable protection of the hydroxyl group and subsequent reduction to generate a 1,3-diol (scheme 2.2.1).



Scheme 2.2.1 Proposed Synthesis of Singly Branched Monomers

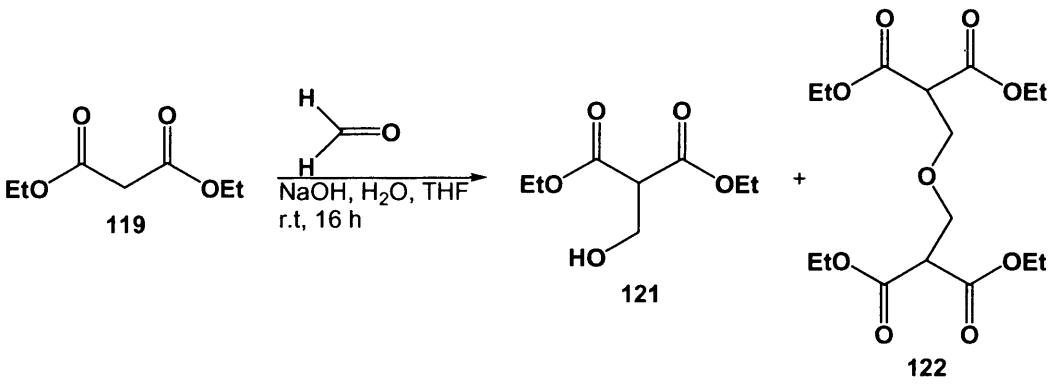
Diethyl malonate (**119**) was reacted with formaldehyde and sodium hydroxide as a base at room temperature. Initially the reaction was carried out with excess of **119** in

the hope that this would favour mono-addition over di-addition. In fact the main product isolated was neither product, but the dimalonate (**120**), obtained in a 25 % yield (scheme 2.2.2). A study of the literature revealed that the formation of this product under similar conditions had been documented.[129]



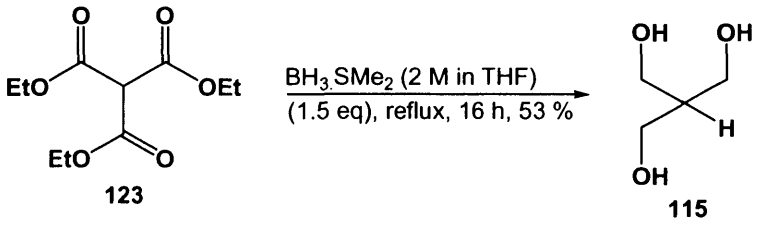
Scheme 2.2.2 Failed Addition of Hydroxymethyl Group onto Diethyl Malonate (**119**)

To favour the formation of the desired product (**121**) and reduce the formation of the dimalonate species (**120**), an equimolar amount of **119** was reacted with formaldehyde, and sodium hydroxide (scheme 2.2.3). However, analysis of the crude product by mass spectrometry indicated a complex mixture of products could have been formed. Products with an m/z of 191 (M^+) and 213 (M + Na) could correspond to the desired product (**121**), with a peaks at 363, 385 (+ Na) possibly indicating an alternative di-malonate product (**122**). It was extremely difficult to separate the mixture by flash column chromatography since the products had similar Rf values. Due to the mixture of products formed the yield of **121** was likely to be low, so an alternative synthesis of singly branched monomers was considered.



Scheme 2.2.3 Addition of Hydroxymethyl Group onto Diethyl Malonate (**119**)

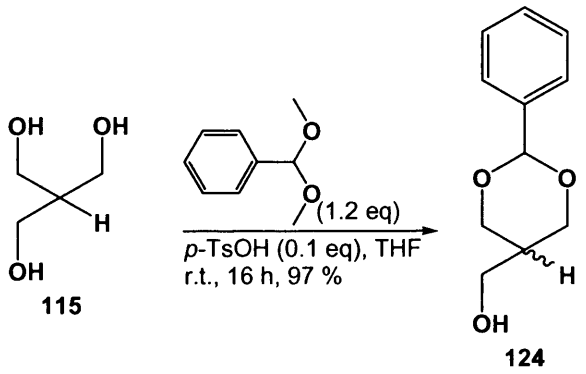
An alternate strategy was then considered using triol **115** directly to synthesise the protected monomer. The reduction of triethyl methanetricarboxylate (**123**), which was commercially available at relatively low cost, was carried out with a borane-methyl sulphide complex (scheme 2.2.4).[130] During the reaction dimethyl sulfide was removed using a Dean-Stark trap, as it has been reported in the literature that this drives the reaction forward, substantially improving the yield.[130] Using this method, the triol (**115**) was obtained in a 53 % yield.



Scheme 2.2.4 Reduction of Triethyl Methane Tricarboxylate (**123**)

Direct mono-protection of the triol (**115**) was not attempted because such a reaction would be likely to require an excess of the triol, give a mixture of products, and be relatively low yielding. As an alternative, two of the hydroxyl groups were tethered using an acetal protecting group. As this could only give one possible product it was feasible that the reaction could be driven to give complete consumption of **115**. The chosen protecting group was a benzylidene acetal, which could potentially be subject to a reductive ring opening, freeing one hydroxyl group and converting the other to a highly stable benzyl ether.[131] Compound **115** was reacted with benzaldehyde

dimethyl acetal, using tosic acid as a catalyst, to give the corresponding benzylidene protected product (**124**) in a 97 % yield (scheme 2.2.5).



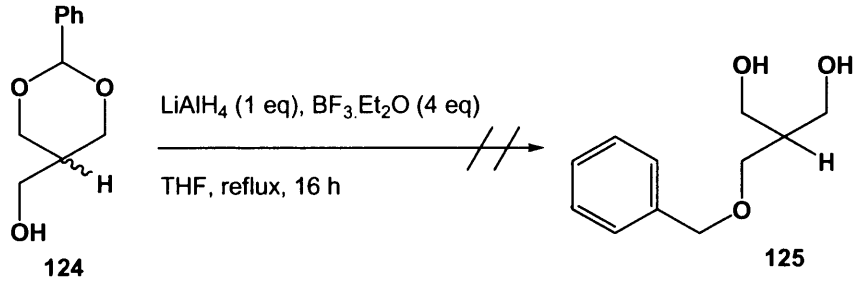
Scheme 2.2.5 Benzylidene Protection of Triol (**115**)

Compound **124** was obtained as a mixture of stereoisomers, due to the axial or equatorial position that could be adopted by the hydroxymethyl group on the six membered ring (figure 2.2.1). It has been shown in the literature that these isomers can be separated on a silica column.[132] For the monomer synthesis, however, the mixture of stereoisomers was reacted on without further separation, as both isomers would give the same non-chiral product following deprotection of the acetal.

Figure 2.2.1 cis and trans-2-Phenyl-5-(hydroxymethyl)-1,3-dioxane

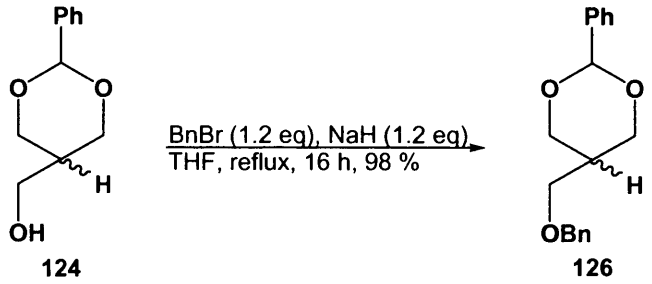
The reductive ring opening of the benzylidene acetal was then attempted, to give the mono-benzylated product (**125**). For this reaction a methodology which had successfully ring opened the benzylidene acetals of a dibenzylidene protected tetraol was used.[131] Compound **124** was reacted with a complex of lithium aluminium hydride and boron tifluoride diethyl etherate at reflux (scheme 2.2.6), however, after sixteen hours the desired product was not isolated. It is not clear as to why these conditions do not give a successful ring opening reaction for this particular substrate.

The only substantial difference between this reaction and the literature example is the presence of a free hydroxyl group in the substrate (**124**). It has been shown that the cis isomer of **124** complexes with lithium ions, so perhaps these interactions can inhibit the ring opening reaction.



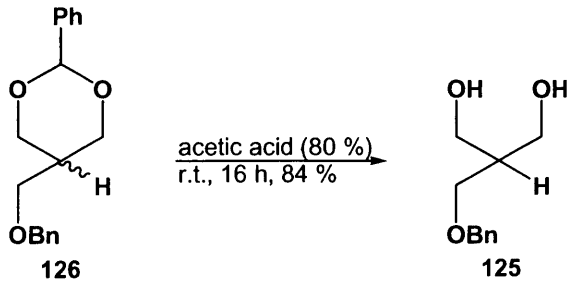
Scheme 2.2.6 Failed Reductive Ring Opening of Benzylidene Protected Triol (**124**)

Benzylidene acetals are acid labile and can be selectively converted back to the corresponding diol by hydrolysis in fairly weak acid in the presence of a benzyl group.[133] An alternative mono-protection strategy was therefore the formation of a benzyl ether on the free hydroxyl of **124**, followed by the selective deprotection of the benzylidene acetal. To this end, **124** was reacted with benzyl bromide, using sodium hydride as the base, to give the benzyl protected product (**126**) in a 98 % yield (Scheme 2.2.7).



Scheme 2.2.7 Benzyl Protection of Benzylidene Protected Triol (**124**)

Removal of the benzylidene group was achieved in 80 % acetic acid at room temperature to afford diol **125** in an 84 % yield (scheme 2.2.8). It is hoped that this monomer could be further functionalised and successfully utilised in iterative ether syntheses.

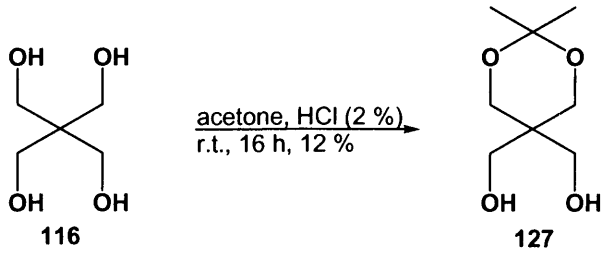


Scheme 2.2.8 Deprotection of Benzylidene Group on Protected Triol (**126**)

2.3 Synthesis of Dibranched Monomers

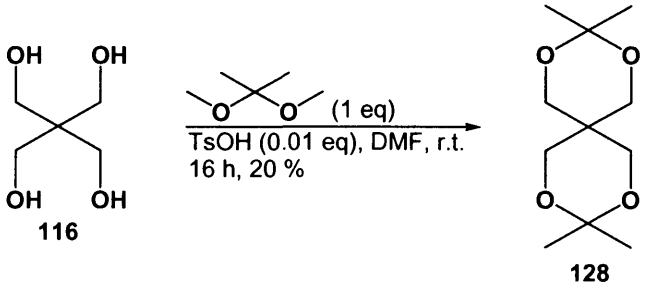
Monomers with an architecture based on pentaerythritol (**116**) were also studied as potential building blocks for polyethers. This tetraol was attractive because it is the equivalent of a 1,3-diol with two pendant hydroxyl groups and monomers formed from it could therefore potentially give oligomers with many sites for further modification. Also, monomers based on pentaerythritol had previously been successfully used in oxetane forming cyclisation reactions.[92, 100] It is believed that pentaerythritol based monomers are particularly suitable for oxetane synthesis because the steric bulk of the two side branches at the quaternary centre enhances the proximity of the activated leaving group and the alkoxide. Pentaerythritol (**116**) has very limited solubility in non-polar organic solvents, however, protected products have high solubility in a range of organic solvents [134] making them useful for a range of transformations.

Initial attempts to di-protect **116** involved the tethering of two of the hydroxyl groups as acetals or ketals. Protecting groups of this nature tether two adjacent hydroxyl groups, protecting the diol against basic and nucleophilic attack, and can be hydrolysed under mildly acidic conditions.[135] Stirring **116** in acetone, with hydrochloric acid as a catalyst, Bladon and Owen have reported the formation of the mono-ketal product (**127**) in a 25 % yield.[136] Using this procedure **127** was synthesised in a yield of only 12 % (scheme 2.3.1). This lower yield reflects the fact that the reaction was attempted very early in the project and that the purification stage was not optimised, due to higher yielding alternative methods quickly discovered in the literature.



Scheme 2.3.1 Mono-Ketal Protection of Pentaerythritol (**116**)

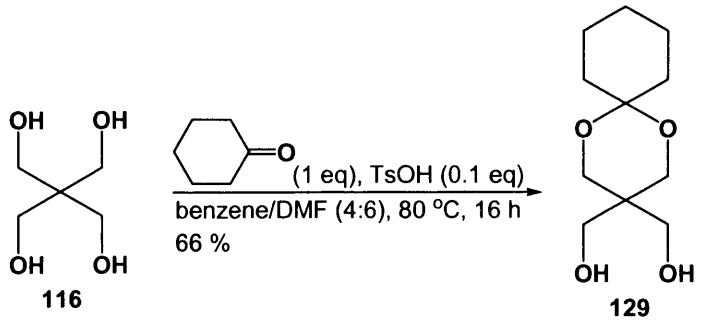
Due to the very low solubility of pentaerythritol (**116**) and its ketal protected derivative (**127**) in acetone at room temperature there is fairly low reactivity using this method, but this in turn allows the mono-protected species (**127**) to be formed in preference to the di-protected species (**128**). An attempt was then made to improve the yield of **127** by reacting **116** with an equimolar amount 2,2-dimethoxypropane, known to be an effective reagent for ketal formation,[135] using *p*-toluenesulfonic acid as the catalyst. It was hoped that formation of the mono-ketal species (**127**) could be favoured by controlling the molar equivalents of the reagents. However, this reaction led to the exclusive formation of **128** in a 20 % yield (scheme 2.3.2). This is most likely because the mono-protected species (**127**) has much higher solubility in DMF than **116**, so it quickly reacts further to give the di-protected species (**128**).



Scheme 2.3.2 Di-Ketal Protection of Pentaerythritol (**116**)

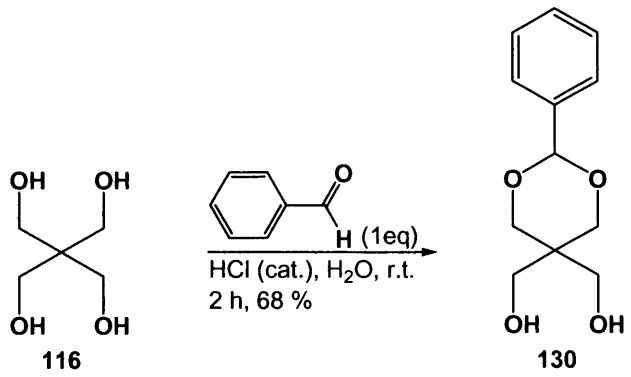
From studying the literature we found that mono-ketal derivatives of pentaerythritol derivatives could be synthesised more effectively at high temperatures in organic solvents, so as to give full dissolution of the pentaerythritol.[137] It is well known that water can promote the reverse reaction in ketal type protections, so azeotropic removal of the water can also greatly improve the yield. By reacting **116** with an

equimolar amount of cyclohexanone, in a mixture of DMF and benzene, at 115 °C, whilst distilling water into a Dean-Stark trap, using tosic acid as the catalyst, Grau *et al.* formed the corresponding mono-protected product, **129**, in a 92 %.[137] Using this procedure, **129** was formed in a 66 % yield (scheme 2.2.3).



Scheme 2.2.3 Mono-Ketal Protection of Pentaerythritol (**116**)

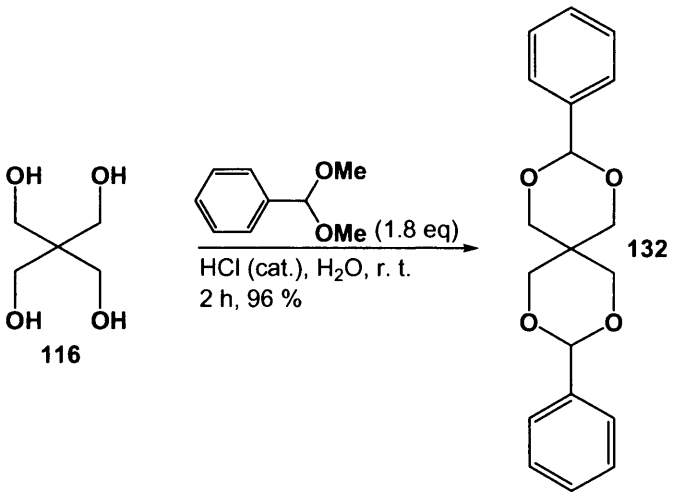
An alternative mono-acetal protection has been reported by Issidorides and Gulen, in this case incorporating a benzylidene protecting group.[138] By reacting **116** with benzaldehyde, using hydrochloric acid as the catalyst and water as the solvent, they were able to exclusively form the mono-benzylidene product (**130**) in a yield of 77 %. Unlike the previous method, the presence of water did not have a detrimental effect on the yield of the reaction. Here the favourable equilibrium was driven by the product (**116**) precipitating from solution as it is formed. Using this method **130** was synthesised in a 68 % yield (Scheme 2.3.4). The workup was also relatively straightforward, requiring recrystallization from hot, slightly alkaline water and then from hot toluene.



Scheme 2.3.4 Mono-Benzylidene Protection of Pentaerythritol (**116**)

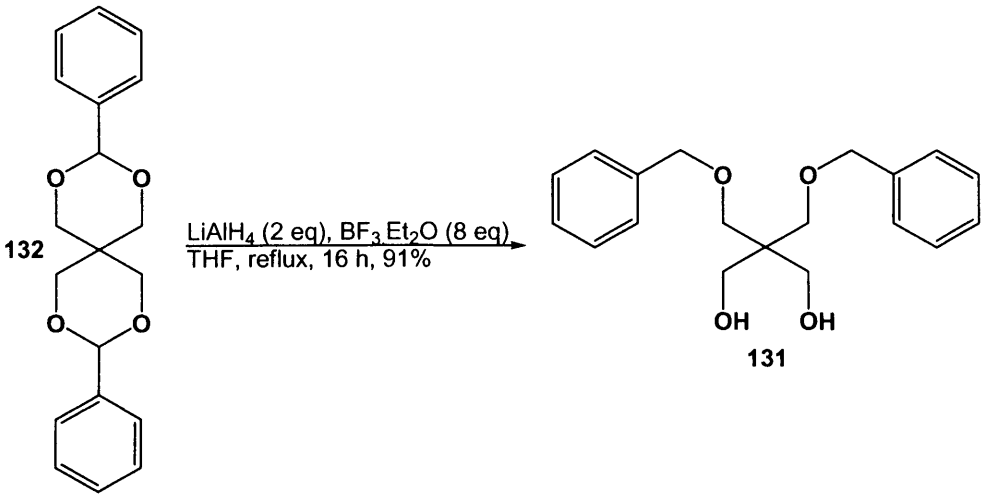
While the use of these mono-protected species in oxetane forming cyclisation reactions is discussed later (chapter 4), their relative acid lability precluded them from being used in polymer supported ether synthesis, because the protecting groups would not be stable to all reaction conditions utilised (see chapter 5). A more acid stable protecting group was therefore required. Benzyl protection seemed to be an attractive strategy because, as previously discussed, benzyl ethers are known to be very stable to acidic hydrolysis [126] and the characteristic λ_{max} of benzyl groups could help monitoring of reactions.

It has been reported that selective alkylation of pentaerythritol can be problematic, due to the low solubility of mono and di-alkoxides in organic solvents.[135] A high yielding, 2-step synthesis of the dibenzyl protected pentaerythritol (**131**) has been reported however and this approach was investigated.[131] In the first step compound **116** is reacted with the dimethyl acetal of benzaldehyde, using a tosic acid catalyst. For ease of purification when using this method, a slight excess of **116** was used in order to ensure that all of the benzaldehyde dimethyl acetal was consumed. Excess unreacted pentaerythritol (**116**) was simply removed by filtration following the reaction. Using this approach, the dibenzylidene protected derivative (**132**) was formed in a 96 % yield (scheme 2.3.5).



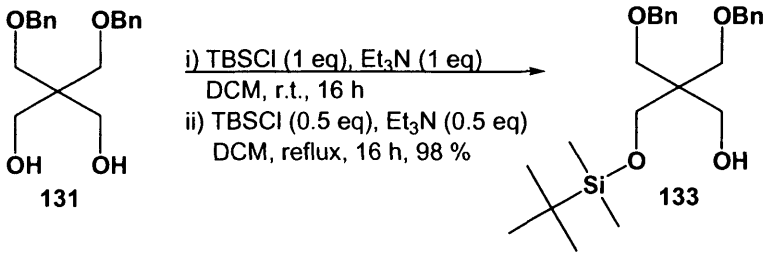
Scheme 2.3.5 Di-Benzylidene Protection of Pentaerythritol (**116**)

The literature reports the reductive ring opening of the benzylidene acetal using a complex of lithium aluminium hydride and borontrifluoride-diethyl etherate, giving the dibenzyl protected product (**131**) in an 82 % yield.[131] Using this method, synthesis of **131** was achieved in a 91 % yield (scheme 2.3.6).



Scheme 2.3.6 Reductive Ring Opening of Di-Benzylidene Pentaerythritol (**132**)

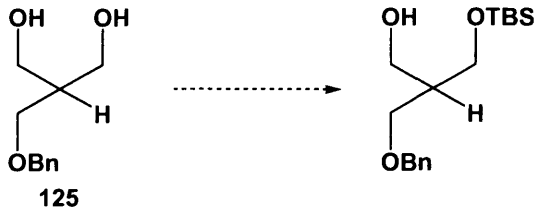
As with the linear monomers, it was envisaged that an "on-resin" deprotection step could be used in the polymer supported ether syntheses in order to allow iterative extension. Again, a TBS protecting group was selected for this purpose. Initially the TBS protection was carried out at room temperature using equimolar amounts of TBS chloride and triethylamine. However, after sixteen hours, TLC analysis indicated that significant amounts of unreacted **131** remained. Factors contributing to the incomplete reaction could be the relative steric hindrance at the position of the hydroxyl groups and the possibility of water present reacting with some of the TBS chloride. By adding a further portion of TBS chloride and triethylamine after 16 h at room temperature and then heating to reflux for a further sixteen hours, the mono-silyl protected product (**133**) was formed in a near quantitative yield (98 %, scheme 2.3.7) with no formation of the di-TBS protected product.



Scheme 2.3.7 Mono-TBS Protection of Di-Benzyl Pentaerythritol (**131**)

2.4 Conclusions and Future Work

In summary, a range of mono and dibranched monomers have been synthesised, which are suitably protected for the syntheses of cyclic and acyclic ethers and polyethers (see chapters 4 and 5). The synthesis of a selectively monobenzyl protected triol (**125**) has also been achieved. If one of the remaining hydroxyl groups of this compound could be protected with a more acid labile protecting group, such a TBS group (scheme 2.4.1) it is likely that it could provide a useful monomer for polyether synthesis.



Scheme 2.4.1 Mono-TBS Protection of Benzyl Protected Triol (**125**)

Chapter 3

3. Linker Synthesis on PEG

Increasingly, soluble polymer supports have been used in preference to solid supports in polymer supported synthesis due to the more favourable reaction kinetics afforded by homogenous reaction conditions.[37, 38] PEG has been used in a number of cases, due to its solubility in a range of solvents, high solubilising power, and easy access of small molecules to active sites. This chapter describes investigations into the attachment of suitable linkers to PEG supports for the immobilisation of substrates and cleavage of final products. The synthesis of two novel PEG supported linkers are described; an aryl sulfonyl chloride linker and a Wang trichloroacetimidate linker (figure 3.0.0.1), both of which have been utilised in later reactions.

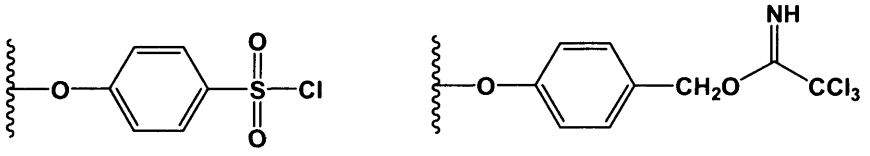


Figure 3.0.0.1 Linkers for PEG Supported Syntheses

3.1 Synthesis of PEG Sulfonyl Chloride

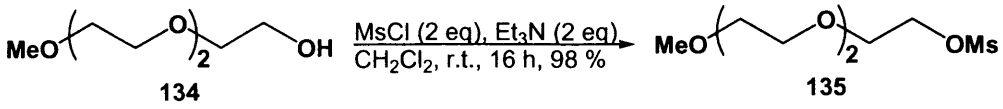
The use of aryl sulfonate linker attached to a PS type resin, known commercially as Sulfonyl Chloride (Polymer Bound), for the immobilisation of small molecules through free hydroxyl and amine moieties has been reported.[69, 70] An interesting feature of this linker is that, being the resin bound equivalent of a tosyl group, resin bound substrates can be cleaved by nucleophilic attack, substituting the immobilised sulfonate ester with other functionalities, such as amines. Previous preliminary investigations within the group explored the use of an intramolecular

cyclisation/cleavage strategy using this resin that can convert immobilised 1,3-diols to oxetanes.[139] Building upon this preliminary data, the use of this strategy was explored (see chapter 4) as well as use of the linker as a method of attachment for polymer supported polyether syntheses (see chapter 5). However, it later became apparent that a PS support did not provide an ideal environment for ether synthesis due to the apolar nature of the support. A PEG support was therefore desired to give a more polar, solution-like environment. As a PEG supported equivalent of the PS based sulfonyl chloride (polymer bound) had not been previously reported, the synthesis of a PEG bound sulfonyl chloride linker was explored.

3.1.1 Test Reactions on a Small PEG

Initial synthetic investigations into the PEG sulfonyl chloride synthesis were tested on mono-methoxy PEG 3 (**134**) as a simple model to assess the feasibility of the approach. Reaction conditions could then be applied to a much larger PEG that would act as the soluble support. The approach used when constructing the linker on PEG was analogous to the method used to synthesise sulfonyl chloride (polymer bound),[140] but it had to be modified in various ways to make all steps compatible with the PEG support.

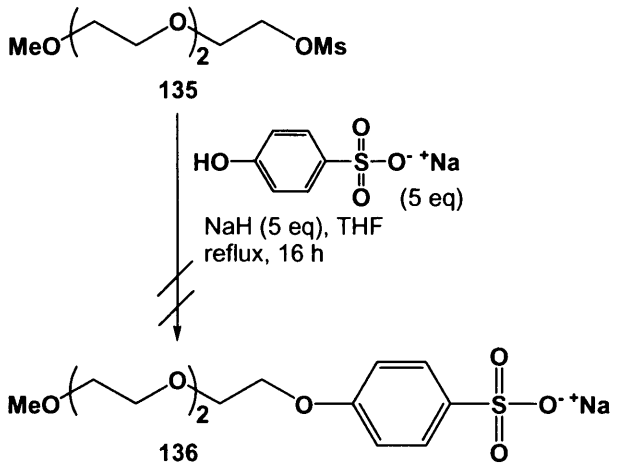
Initially, activation of the PEG hydroxyl groups was required in order that the sulfonyl linker could be attached by nucleophilic substitution. Mesylate activation was selected as this is known to be a highly reactive leaving group which would hopefully drive a nucleophilic displacement to completion even when using a much larger PEG mesylate. Compound **134** was successfully converted to the corresponding mesylate (**135**) in a 98 % yield by reaction with mesyl chloride, using triethylamine as the base (scheme 3.1.1.1). As purity was established by NMR analysis, compounds can be considered to have 95-98 % purity.



134 135

Scheme 3.1.1.1 Mesylation of Methoxy PEG 3 (**134**)

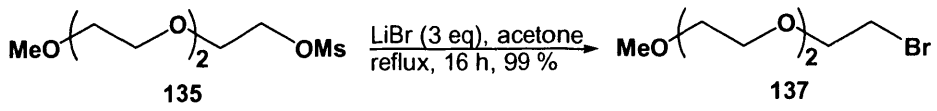
The reaction of mesylate **135** with 4-hydroxybenzene sulfonic acid (sodium salt) in THF, using sodium hydride as a base (scheme 3.1.1.2) was attempted. However, the insolubility of the sulfonic acid salt in THF prevented the reaction from proceeding, even at high temperatures. The sulfonic acid salt seemed to be largely insoluble in all solvents except water, but attempts to react it with mesylate **135** in an aqueous solvent system predictably led to hydrolysis of the mesylate.



Scheme 3.1.1.2 Attempted Reaction of Benzene Sulfonic Acid Salt with Methoxy PEG 3 Mesylate (**135**)

Synthesis of the more water stable PEG bromide (**137**) was then carried out so that a solvent system could be utilised that was compatible with both the activated PEG and the sulfonic acid salt. The conversion of compound **134** directly to the bromide by heating at reflux in aqueous hydrobromic acid was initially attempted; however, NMR spectroscopic analysis of the crude product indicated that cleavage of the methoxy group had occurred. Another commonly used method of converting a hydroxyl group to a bromide is by reacting the alcohol with carbon tetrabromide and triphenylphosphine.[141] This method was avoided, however, as it has been reported that triphenylphosine oxide has a tendency to strongly complex with PEG making

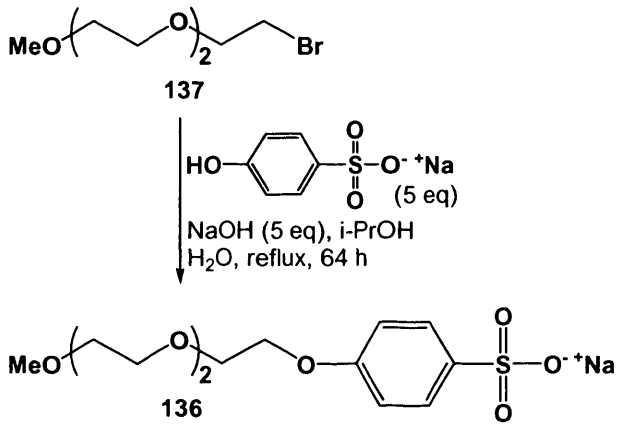
purifications difficult.[140] The PEG bromide (**137**) was prepared by reacting mesylate **135** with lithium bromide in refluxing acetone, giving the product in a quantitative yield (scheme 3.1.1.3).



135 137

Scheme 3.1.1.3 Bromination of Methoxy PEG 3 Mesylate (**135**)

With the PEG bromide (**137**) in hand, suitable conditions were determined for the nucleophilic substitution reaction. Compound **137** was reacted with an excess of sulfonic acid sodium salt in water and propan-2-ol (1:1), using sodium hydroxide as a base (scheme 3.1.1.4), conditions which had previously been reported to give a successful reaction between the sulfonic acid salt and an alternative alkyl bromide.[139] NMR spectroscopic analysis of the crude product indicated that we the desired PEG sulfonic acid salt (**136**) was formed. However, the product could not be separated from excess of 4-hydroxybenzenesulfonic acid sodium salt due to the two compounds having very similar properties in terms of solubilities and RF values.



Scheme 3.1.1.4 Reaction of Benzenesulfonic Acid Salt with Methoxy PEG 3 Bromide (**137**)

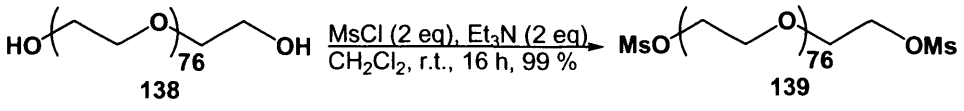
Due to these problems it was decided to move onto the synthesis of the linker on a higher molecular weight PEG support. It was envisaged that the difficulty which arose in the separation of PEG sulfonic acid from the excess of benzene sulfonic acid

salt would not be an issue using large PEG. It was postulated that long chain PEG sulfonic salt would be far more soluble in organic solvents, such as dichloromethane, which would not dissolve the benzene sulfonic acid salt, allowing separation by simple filtration.

3.1.2 Synthesis on a PEG Support

Synthesis of a sulfonyl chloride linker on mono-methoxy PEG 5000 (average molecular weight of 5000 g mol^{-1}) was initially carried out. However, all subsequent reactions were carried out on PEG 3400 (**138**). The latter PEG support has a greater loading capacity due to its lower molecular weight and the difunctional nature of the molecule. Since the synthetic steps and associated issues for the construction of a PEG sulfonyl chloride linker were extremely similar for both methoxy PEG 5000 and PEG 3400, only the reactions carried out on the latter support are described in detail.

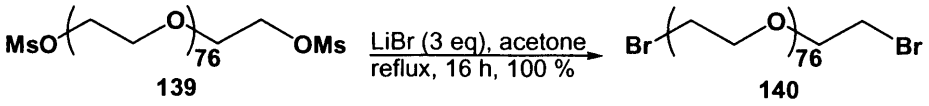
Mesylation of PEG 3400 (**138**) was carried out using the same conditions that had been used with methoxy PEG 3 (**134**), but with twice the number of equivalents to allow for the difunctional nature of the PEG chain. PEG 3400 (**138**) was successfully converted to the dimesylate (**139**) with quantitative recovery of the PEG product (scheme 3.1.2.1). Over the course of these reactions a range of recrystallation methods were attempted to purify PEG supported products. The most commonly used of these was to dissolve the crude product in hot propan-2-ol, remove any insoluble impurities (such as salts) by filtration, then cool the solution to ~5 °C to precipitate the PEG compound. The precipitate was then collected by filtration and washed with propan-2-ol then diethyl ether. Following the mesylation and purification, ^{1}H NMR spectroscopic analysis of the product suggested that there had been quantitative conversion to **139**.



Scheme 3.1.2.1 Mesylation of PEG 3400 (**138**)

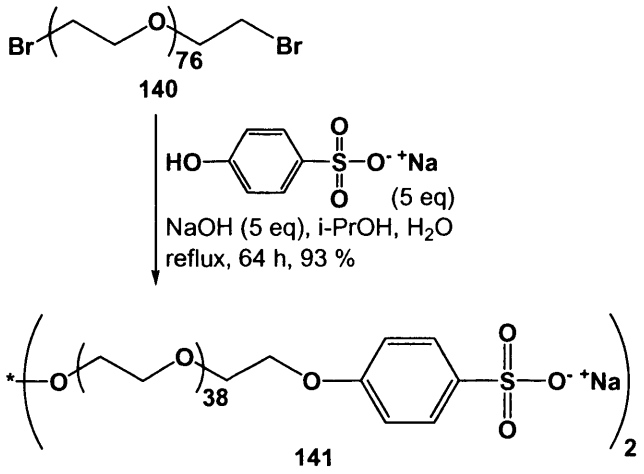
Throughout this report, where reactions are carried out on PEG 3400 or methoxy PEG 5000, the percentages given in reaction schemes indicate % recovery (by mass) of the PEG support, rather than the % yield or conversion. Unless otherwise stated, characteristic shifts in the signals of the ^{1}H NMR spectra of the supports indicated that all end groups had been converted to the desired product. The purity of the PEG supports is therefore accurate to within 1 %. The molar equivalents indicated in scheme 3.1.2.1 are given with respect to the loading of the PEG (0.59 mmol g^{-1}) rather than the molecular weight.

As the bromination conditions developed on the smaller PEG chain had given quantitative conversion to the desired product these conditions were utilised to convert PEG dimesylate (**139**) to the corresponding bromide. The bromination conditions were indeed applicable for use on the PEG support, converting **139** to the PEG bromide (**140**) again with quantitative recovery of the material (scheme 3.1.2.2).



Scheme 3.1.2.2 Bromination of PEG 3400 Mesylate (**139**)

The conversion of the PEG bromide (**140**) to its corresponding PEG sulfonic acid salt (**141**) was then carried out by reaction with 4-hydroxybenzenesulfonic acid (sodium salt) in propan-2-ol and water, using sodium hydroxide as a base (scheme 3.1.2.3). Unlike the much smaller PEG sulfonic acid, compound **141** was highly soluble in a range of organic solvents including dichloromethane, chloroform, acetonitrile and hot toluene. The product was removed from excess of sulfonic acid sodium salt by dissolving the crude product in hot propan-2-ol (following the evaporation of water) and removal of any insoluble impurities by filtration, before cooling the solution to room temperature to precipitate the pure PEG sulfonic acid (**141**) with 93 % recovery of the product.



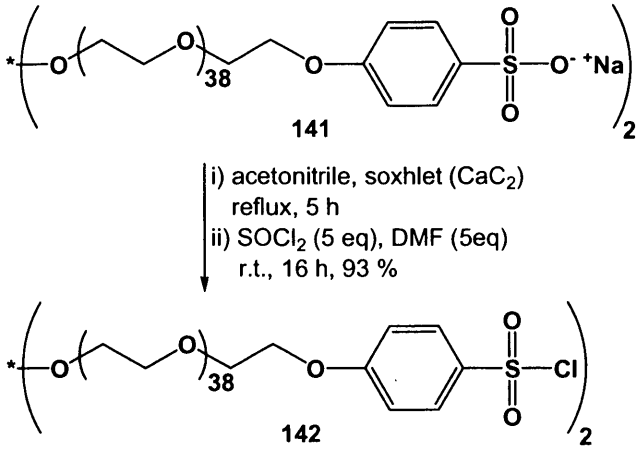
Scheme 3.1.2.3 Reaction of Benzenesulfonic Acid Salt with PEG 3400 Bromide (**140**)

The final step of the synthesis was to activate **141** as the corresponding PEG sulfonyl chloride so that it could be used to immobilise alcohols or amines. However, the chlorination of the PEG sulfonic acid salt proved to be the most problematic step in the synthesis, not surprisingly because of the tendency for PEG to complex water. The chlorination was attempted at various temperatures with thionyl chloride, both neat and in solution with a base (triethylamine), as well as with a complex of thionyl chloride and DMF,[144] but all methods gave very limited conversion to PEG sulfonyl chloride **142**. Further analysis of **141** by ^{1}H NMR spectrometry confirmed that there was water trapped within the crystalline structure associated with the recrystallization step.

A method was therefore sought to dry the PEG prior to chlorination. Precipitating the PEG product from a concentrated solution in dichloromethane by dilution with diethyl ether, following precipitation from hot propan-2-ol gave a PEG with less encapsulated water, but a small amount of water that still remained hindered the reaction. An attempt to dry the PEG *in vacuo* over a period of time also failed and was not helped by the fact that heating the crystalline PEG caused it to melt, even at fairly low temperatures, and solidify in a sticky, less manageable form.

It was decided that azeotropic drying of the PEG immediately prior to the reaction may be effective. Use of a Soxhlet adaptor on the reaction vessel, containing a

porous thimble of calcium carbide, was explored with use of a suitable solvent (toluene or acetonitrile) that could be distilled through the Soxhlet, continuously removing water from the PEG in the vessel below. PEG sulfonic acid sodium salt (**141**) was completely dry after about 5 hours. At this point the reaction could be cooled to room temperature and reagents for subsequent steps could be added directly. Using acetonitrile as the solvent/azeotrope, followed by reaction with a thionyl chloride/DMF complex,[144] PEG sulfonic acid salt (**141**) was cleanly converted to PEG sulfonyl chloride (**142**, scheme 3.1.2.4). Purification of the product required two recrystallizations from hot propan-2-ol to give the pure product. Despite this the desired product was obtained in a high percentage recovery of 93 %.



Scheme 3.1.2.4 Chlorination of PEG Sulfonic Acid Salt (**141**)

Care had to be taken when storing PEG sulfonyl chloride (**142**), as water trapped in the matrix of the crystalline form eventually could convert the product back to its corresponding sulfonic acid form. In its crystalline form compound **142** could be stored for a month successfully, but as a solution in a suitable solvent, such as dichloromethane, it was stored over molecular sieves for much longer periods.

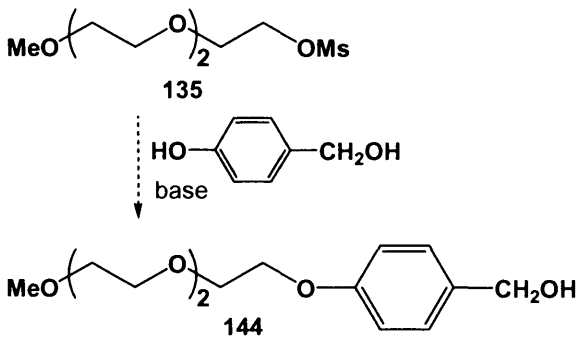
3.2 Synthesis of PEG Wang Linker

While the PEG sulfonyl chloride linker described in chapter 3.1 proved to be useful for various PEG supported ether syntheses, it was not compatible with our desire to carry out PEG supported reductive alkylation (see chapter 6) because sulfonate esters

are known to be cleaved under reducing conditions.[145] An alternative linker was required that would be stable to these conditions, yet also allow cleavage by a suitable method. Wang linkers on PS resins have been widely as a way of immobilising substrates *via* a free hydroxyl moiety and supported Wang ethers can be cleaved by acidic cleavage or oxidative cleavage using DDQ.[56] It was desired to construct an analogous Wang linker on a PEG chain and activate it in such a way that it could be used to immobilise alcohols.

3.2.1 Test Reactions on a Small PEG

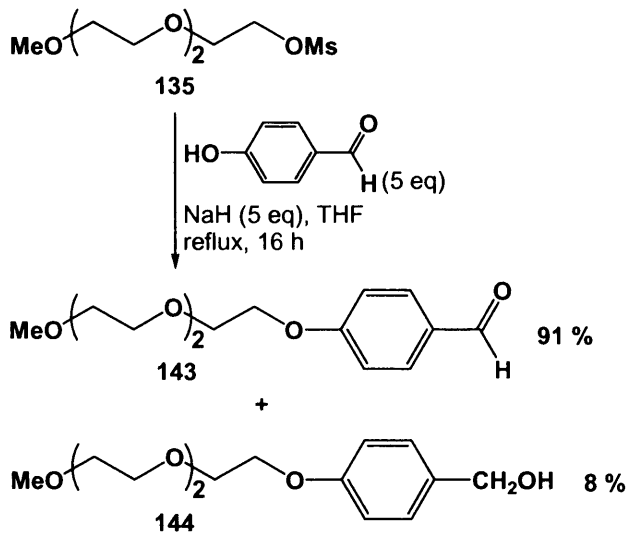
As with the sulfonyl chloride linker, the initial steps in the synthesis of a PEG supported Wang linker were tested on methoxy PEG 3 (**134**). The first step was to activate the free hydroxyl group as a potential leaving group so that the linker could be added by nucleophilic substitution. Since a procedure had been used to give the corresponding mesylate ester (**135**) in a very high yield of 98 % (scheme 3.1.1.1), this material was used for the nucleophilic substitution. The most direct route to the PEG Wang alcohol from **135** would be the nucleophilic substitution of the mesylate group with the phenoxide of 4-hydroxy benzyl alcohol (scheme 3.2.1.1).



Scheme 3.2.1.1 Direct Attachment of a Wang Alcohol Linker onto a PEG Support

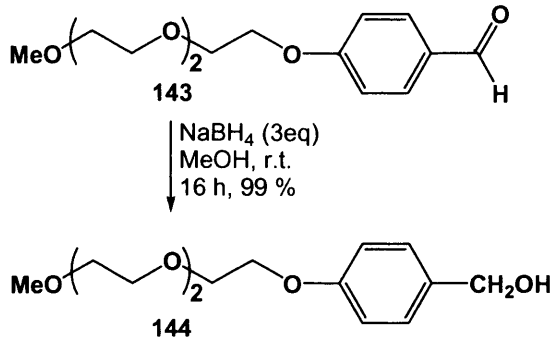
This direct approach was not used however, because of the possibility of alkoxide formation at the benzylic position, which could potentially lead to the linker being attached to the PEG chain from the wrong end or even cause bridging between two PEG chains.

As a uniform PEG product is very desirable when working with the larger PEG supports due to the extreme difficulty in separating mixtures of large PEG products, a two step approach was envisaged. Therefore, instead of using 4-hydroxy benzyl alcohol, the attachment of 4-hydroxy benzaldehyde to the PEG chain was explored. The reaction of the PEG mesylate (**135**) with an excess of 4-hydroxy benzaldehyde, using sodium hydride as a base, led to the formation of the desired PEG benzaldehyde (**143**), recovered in a 91 % yield (scheme 3.2.1.2). Although the product was not obtained in a quantitative yield, the PEG mesylate (**135**) was completely consumed by the reaction. Further product analysis revealed that the lower than expected yield was due to the formation of the PEG Wang alcohol (**144**) in a low yield of 8 %. This product was probably due to either an impurity present in 4-hydroxy benzaldehyde, or *via* reduction of the aldehyde by an excess of sodium hydride. The formation of **144** could be undesirable, as it gives a potential site for reaction with a second molecule of PEG mesylate (**135**) to give a bridged product. However, as no other side products were detected, the reaction was still useful for transfer to the large PEG because a uniform PEG product would be obtained following the reduction of the aldehyde.



Scheme 3.2.1.2 Reaction of 4-Hydroxy Benzaldehyde with Methoxy PEG 3 Mesylate (**135**)

Reduction of PEG benzaldehyde (**143**) to the alcohol (**144**) was carried out using an excess of sodium borohydride to give the product in a 99 % yield (scheme 3.2.1.3).

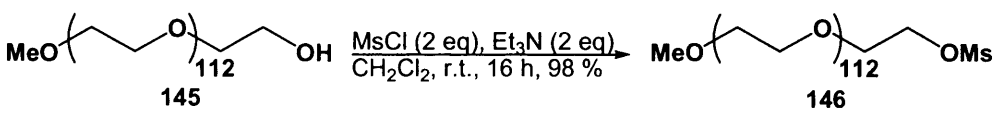


Scheme 3.2.1.3 Reduction of Methoxy PEG 3 Benzaldehyde (**144**)

3.2.2 Synthesis on a PEG Support

With the synthesis of a Wang linker on a small PEG in hand, the reaction procedures were applied to a large PEG support. As with the synthesis of the PEG sulfonyl chloride linker, all of the following transformations were successfully carried out on both methoxy PEG 5000 and PEG 3400. In this case however, only syntheses carried out on methoxy PEG 5000 are discussed here because this support was exclusively used in the subsequent development of a reductive alkylation protocol (see chapter 6).

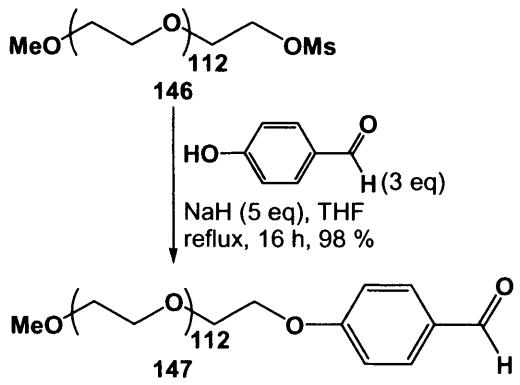
Methoxy PEG 5000 (**145**) was converted to the corresponding mesylate by reaction with an excess of mesyl chloride and triethylamine in dichloromethane, giving the desired PEG mesylate (**146**) with 98 % recovery (scheme 3.2.2.1). As before, ^{1}H NMR suggested that there had been quantitative conversion to the PEG mesylate.



Scheme 3.2.2.1 Mesylation of Methoxy PEG 5000 (**145**)

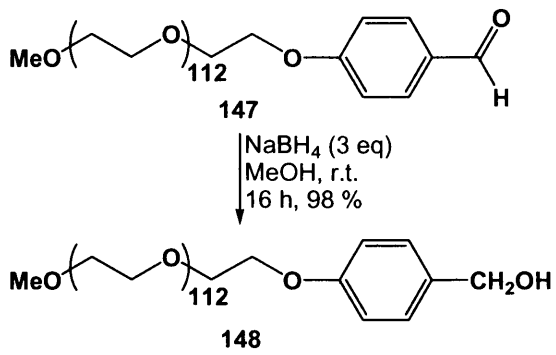
There was a concern that a small amount of water trapped in the matrix of the PEG could have a potentially detrimental effect on the attachment of 4-hydroxy benzaldehyde to the PEG chain. However reaction of the PEG mesylate (**146**) with

excess of 4-hydroxy benzaldehyde, using sodium hydride as a base led to the formation of the PEG aldehyde (**147**, scheme 3.2.2.2) without the need for a special pre-drying step beyond the usual removal of solvents *in vacuo*. This is most likely because the excess of sodium hydride used can react with any water present, drying the PEG, and the small amount of sodium hydroxide formed does not affect the reaction. Another interesting observation was that, unlike the analogous reaction on the smaller PEG, ^{1}H NMR spectroscopic analysis of the product did not reveal the formation of any of the Wang alcohol. The most likely explanation for this is the consumption of excess sodium hydride by water, so it is unavailable for the reduction of the aldehyde. The PEG aldehyde product (**147**) was afforded as a pink solid, suggesting that it may have complexed to small amount of 4-hydroxy benzaldehyde. Nevertheless this was not detected by NMR spectrometry and did not seem to affect future reactions.



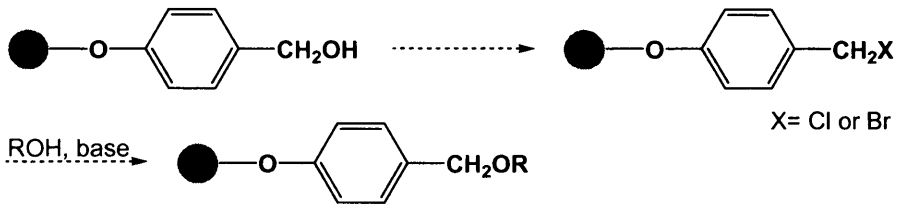
Scheme 3.2.2.2 Reaction of 4-Hydroxy Benzaldehyde with Methoxy PEG 5000 Mesylate (**146**)

The conversion of compound **147** to the alcohol was achieved using the conditions that were previously used for the small PEG and the PEG Wang alcohol (**148**) was obtained with quantitative recovery (scheme 3.2.2.3). ^{1}H NMR spectroscopic analysis indicated complete conversion to the Wang alcohol (**148**) as evidenced by the disappearance of the signal corresponding to the proton on the aldehyde (δ_H = 9.87) and the appearance of a signal corresponding to the protons of the benzylic CH_2 (4.60). This product no longer had a pink hue, suggesting that if there was an impurity present in the starting material, it too had been reduced.



Scheme 3.2.2.3 Reduction of Methoxy PEG 5000 Benzaldehyde (**147**)

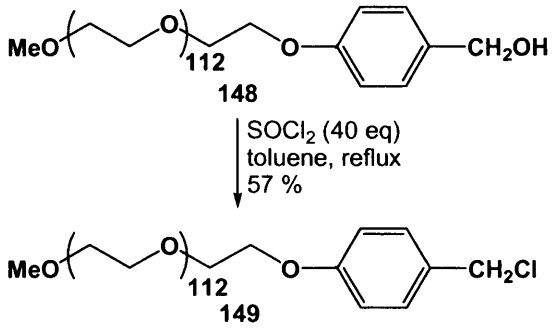
With the PEG Wang alcohol (**148**) in hand a method to activate the alcohol, so that it could be used for the immobilisation of small molecules with free hydroxyl moieties, was investigated. Wang linkers are often activated as the chloro or bromo species.[56] These halogenated Wang linkers can then be reacted with alcohols by a Williamson reaction, linking the small substrate to the support *via* an ether linkage (scheme 3.2.2.4). As with previous brominations on PEG (see chapter 3.1.1), the standard method of reacting the alcohol with carbon tetrabromide and triphenylphosphine [141], was avoided due to the tendency of PEG chains to complex strongly with triphenylphosphine oxide.[142]



Scheme 3.2.2.4 Activation and Loading of a Wang Linker

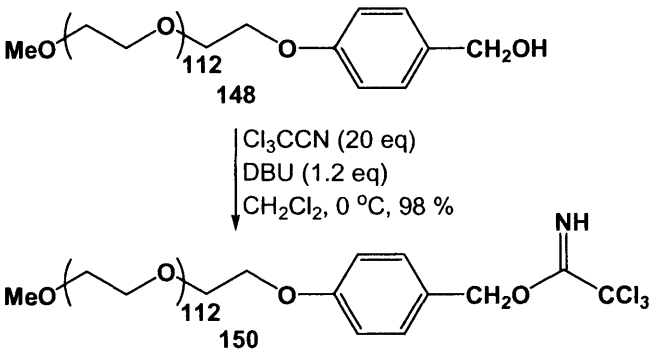
Several attempts were made to convert PEG Wang alcohol (**148**) to the corresponding chloride using thionyl chloride, however, under fairly mild conditions, such as at room temperature in dichloromethane, both with and without triethylamine, full conversion to the alkyl chloride could not be achieved. Only by reacting **148** with a very large excess of thionyl chloride in toluene at reflux was full conversion to the corresponding PEG Wang chloride (**149**) achieved (scheme

3.2.2.5). The recovery of the product was low however (53 %), possibly due to degradation of some of the PEG under such harsh conditions. Due to these problems, it was decided that a halide activation of this nature was not a suitable method of activation.



Scheme 3.2.2.5 Chlorination of a Methoxy PEG 5000 Wang Alcohol (**148**)

A much milder method of activating PS bound Wang alcohols had been reported in the literature, involving conversion the hydroxyl group to a trichloroacetimidate. The Wang trichloroacetimidate could then be reacted with an alcohol in the presence of an acid catalyst to give the corresponding ether (see chapter 1, scheme 1.1.2.3).[57] This method was attractive as both reactions proceed at low temperatures with short reaction times. Reaction of the PEG Wang alcohol (**148**) with a large excess of trichloroacetonitrile and DBU at 0 °C for 1 hour gave the PEG Wang trichloroacetimidate (**150**) with a near quantitative recovery of 98 % (scheme 3.2.2.6). With this product in hand, the loading of desired monomers onto the support *via* their hydroxyl groups was then possible (see chapter 6).



Scheme 3.2.2.6 Activation of a Methoxy PEG 5000 Wang Alcohol (**148**) to the Trichloroacetimidate (**150**)

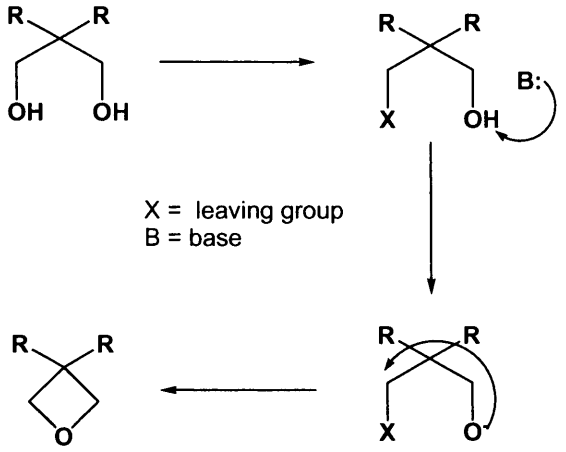
3.3 Conclusions

In summary we have developed two novel linkers both on PEG 3400 and methoxy PEG 5000. Both are analogous to linkers that have been successfully utilised to load small molecules onto PS supports. In later chapters, uses of these linkers as well as cleavage methods developed are described.

Chapter 4

4.0 Cyclic Ether Synthesis; Oxetanes

Oxetanes are four membered cyclic ethers. Due to the strain in the system, they can undergo homopolymerisation in the presence of an acid catalyst,[90-93] but they are fairly resistant to nucleophilic attack,[85, 88] unlike three membered epoxides. These features have made them an important precursor in the synthesis of both straight chained and hyperbranched polyethers (see chapter 1). This chapter describes a study into the synthesis of oxetanes by a cyclisation reaction, possible for substrates which have a hydroxyl group in a 1,3 relationship with a good leaving group. A suitable base can be used to deprotonate the hydroxyl group and the alkoxide formed can effect an intramolecular nucleophilic substitution reaction (scheme 4.0.1). The synthesis of oxetanes was approached using three methods: in solution using tosylate esters; on a PS support using a sulfonate linker and on a PEG support using a novel sulfonate linker. Building upon preliminary studies carried out in our group previously,[139] the aim was to establish what advantages a polymer supported approach to this kind of oxetane synthesis has over the analogous solution based method both in terms of yield and ease of purification.



Scheme 4.0.1 Mechanism of Intramolecular Cyclisation

4.1 Oxetane Synthesis in Solution

Oxetane synthesis *via* an intramolecular cyclisation reaction in solution has been known for many years. Initially most cyclisation reactions of this type where carried out using halides as the leaving group,[91] but recently more reactive sulfonate esters have been used to successfully promote oxetane synthesis.[100] Branching at the 2-position has been found to have a significant effect upon the degree of cyclisation. Indeed, derivatives of pentaerythritol are useful oxetane precursors where steric bulk caused by 2,2'-pendant groups, is thought to enhance reactivity by forcing the alkoxide and the leaving group to be closer in space (figure 4.1.1).

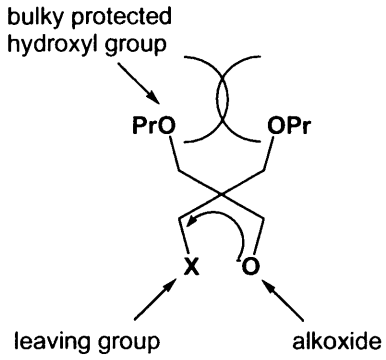
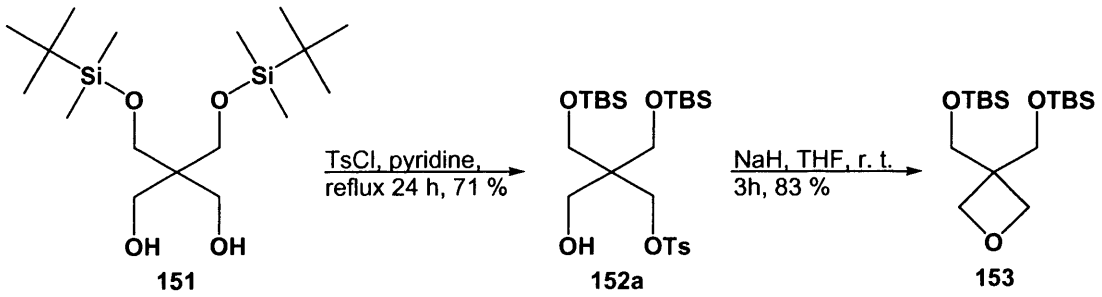


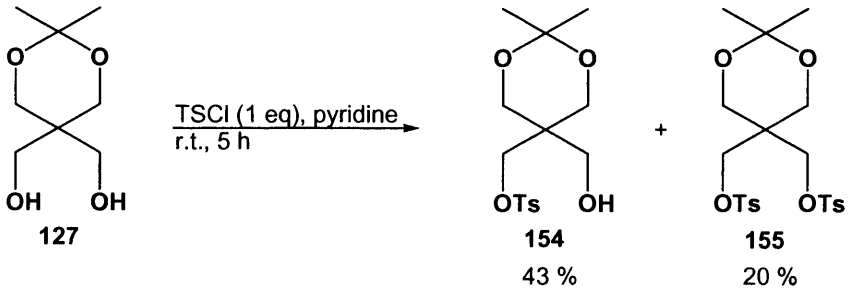
Figure 4.1.1; Influence of Bulky Pendant Groups on Oxetane Synthesis

Preliminary studies into oxetane synthesis carried out in our group had exclusively used the di-TBS protected form of pentaerythritol (**151**). These bulky protecting groups were useful in terms of increasing the proximity of the alkoxide to the leaving group. As such, cyclisation of the mono-tosylate (**152a**) with sodium hydride proceeded quickly at room temperature to give the oxetane (**153**) in an 83 % yield (scheme 4.1.1). While the steric bulk of this monomer makes it useful for the cyclisation reaction, it may prove to be too hindered for desired uses of the oxetane (**153**) e.g. in acid catalysed self-polymerisation. It was therefore desired to investigate the effectiveness of this type of oxetane synthesis for monomers based on pentaerythritol that had less bulky protecting groups.



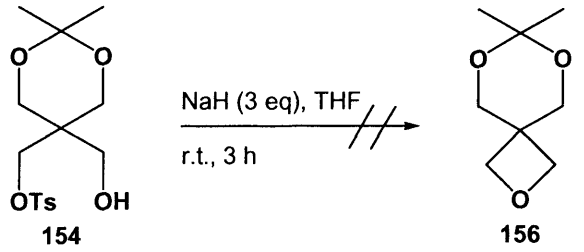
Scheme 4.1.1 Oxetane Synthesis Using a TBS Protected Monomer (**151**)

The first monomer that was used as an oxetane precursor was mono-ketal protected pentaerythritol (**127**). The synthesis of the corresponding oxetane was desirable, as it has been successfully used in acid catalysed self-polymerisation to form polyethers (see chapter 1, scheme 1.2.4.3).[91] The mono-tosylation of this compound, using tosyl chloride in an excess of pyridine, has been reported by Fitt and Owen in a 48 % yield.[146] Using this method the mono-tosyl compound (**154**) was isolated in a 43 % yield (scheme 4.1.2). The corresponding di-tosyl compound (**155**) was also isolated in a 20 % yield with separation of the products requiring time consuming recrystallization techniques.



Scheme 4.1.2 Selective Tosylation of Ketal Protected Pentaerythritol (**127**)

The cyclisation of **154** to form the corresponding oxetane (**156**) was then attempted, by reaction with sodium hydride (scheme 4.1.2). While TLC analysis indicated that the starting material had been converted to another species, analysis by NMR spectrometry was uninformative and the oxetane (**156**) could not be isolated. Synthesis of this oxetane has previously been reported, where it was found to be rather volatile (bp 81.5-82 °C).[92] Since small scale reactions were envisaged, it was decided to attempt the synthesis of a less volatile oxetane for ease of handling.



Scheme 4.1.3 Attempted Cyclisation of Mono-Tosylate (**154**)

By studying the literature it was found that benzylidene protected oxetane **157** (figure 4.1.2) was a solid at room temperature (mp 78-79 °C).[147] Synthesis of this oxetane was therefore attempted *via* the monotosylate.

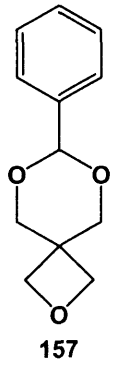
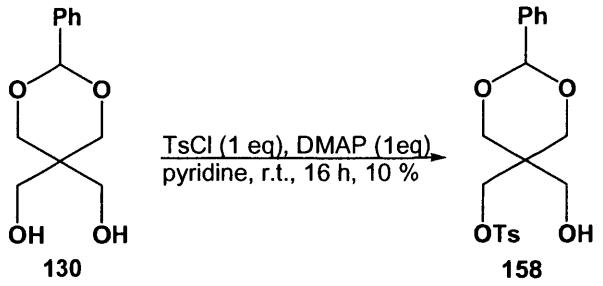


Figure 4.1.2 Benzylidene Protected Oxetane

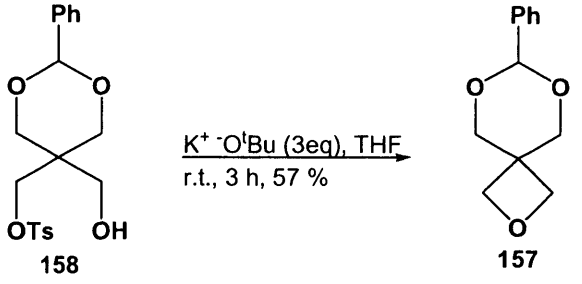
Initially, synthesis of the mono-tosylate (**158**) from the corresponding diol (**130**) was attempted using the previous conditions, but this reaction failed to give the desired product. As there was a large amount of unreacted diol in the reaction mixture, it seemed that there was very low reactivity when using this monomer. It has been widely reported in the literature that DMAP can give far greater reactivity than pyridine for reactions of this nature, even when used as a catalyst.[148] The reaction did not proceed using DMAP catalytically with an equimolar amount of tosyl chloride and pyridine as a solvent. However, by using a stoichiometric amount of DMAP, again with pyridine as a solvent, the mono-tosylate (**158**) was obtained in a 10 % yield (scheme 4.1.2), with isolation of the product requiring flash silica chromatography



Scheme 4.1.2 Selective Tosylation of Benzylidene Protected Pentaerythritol (**130**)

A higher yielding synthesis of the mono-tosylate (**158**) was attempted using pyridine as a solvent and heating at reflux. However, this approach led only to decomposition of the products. Ultimately a more efficient synthesis was not achieved, but nevertheless cyclisation was attempted with this material.

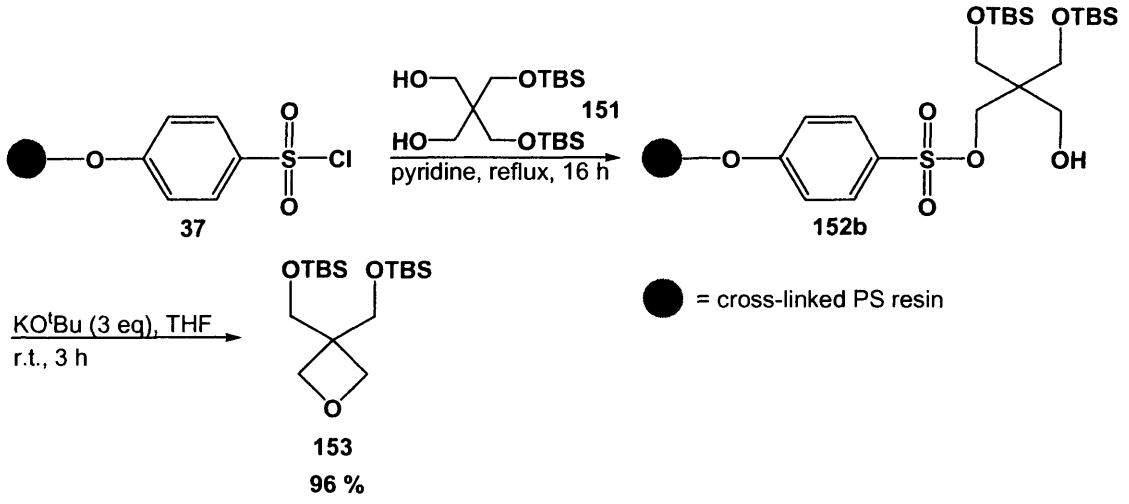
By reacting compound **158** with an excess of potassium *tert*-butoxide, the corresponding oxetane (**157**) was isolated in a 57 % yield (scheme 4.1.3). This may be lower yielding than the synthesis of the TBS protected oxetane (**153**), but compound **158** is substantially less hindered, with the benzylidene acetal tethering the protected pendant hydroxyl groups. This could make it a useful precursor for the synthesis of polyethers by acid catalysed self-polymerisation.



Scheme 4.1.3 Intramolecular Cyclisation of Mono-Tosylate (**158**)

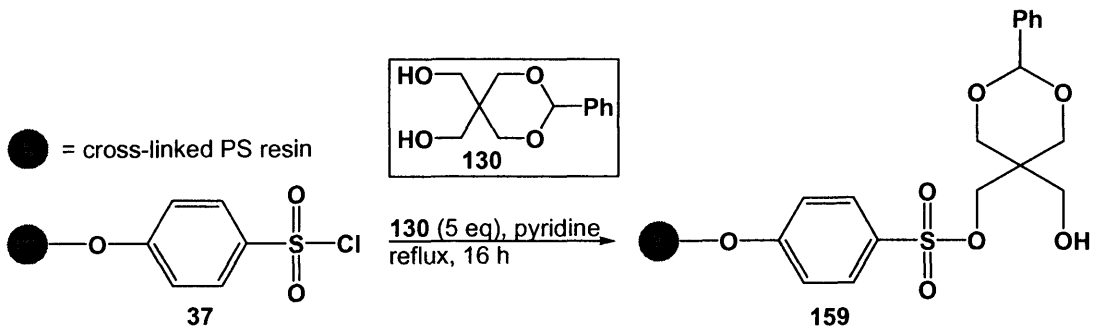
4.2 Oxetane Synthesis on a Polystyrene Support

Preliminary work carried out in our group had demonstrated that a PS resin with a sulfonate linker, known commercially as sulfonyl chloride (polymer bound) (**37**) could be used to both immobilise and mono-activate di-TBS protected pentaerythritol (**151**).[139] The evidence given for the successful formation of **152b** was that elemental analysis of the polymer showed that it did contain any chlorine atoms. Deprotonation of the free hydroxyl group on the resin bound intermediate (**152b**) led to an intramolecular cyclisation/cleavage reaction to give the desired oxetane product (**153**) in a yield of 96 % over both steps (scheme 4.2.1). It was hoped that this method would be applicable for a rapid and high yielding synthesis of the less hindered, benzylidene protected oxetane (**157**).



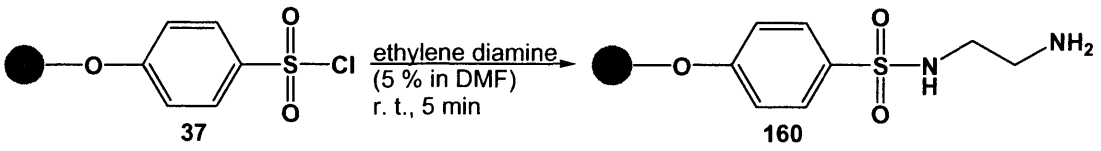
Scheme 4.1.2 Loading and Cyclisation/Cleavage of TBS Protected Pentaerythritol (**151**) with Sulfonyl Chloride (Polymer Bound) (**37**)

The first step in the procedure was to mono activate and immobilise benzylidene protected pentaerythritol (**130**) using sulfonyl chloride (polymer bound) (**37**). This loading procedure was attempted using the conditions developed previously; reacting resin **37** with an excess of **130**, using pyridine as both the solvent and the base (scheme 4.2.2).



Scheme 4.2.2 Loading onto Sulfonyl Chloride (Polymer Bound) (**37**)

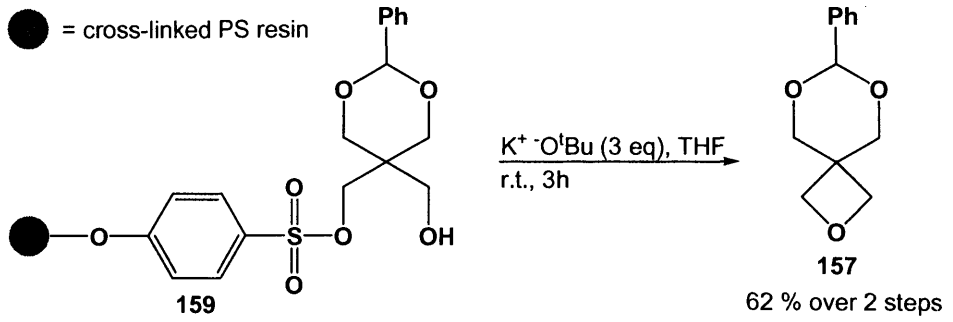
In order to agitate the mixture, the reaction was stirred very slowly with a magnetic follower that was as small as possible, so as to avoid damage to the resin. A positive result from a bead staining test suggested that all sites on the resin had been loaded.[21] This test was carried out as follows; following the loading reaction, a small amount of resin was treated with 5 % ethylene diamine in DMF for 5 minutes, which would convert any remaining sulfonyl chloride groups to a sulphonamide linked to a primary amine (scheme 4.2.3). The beads were then washed (DMF; THF; dichloromethane) and stained with bromophenol blue (1 % in DMF). Following further washing with DMF, a white or off-white colouring of the beads indicated an absence of primary amine and therefore a complete loading reaction.[21] It was not, however, possible to determine the degree, if any, of bridging between adjacent sites on the resin.



Scheme 4.2.3 Treatment of Resin **37** with Diamine Prior to Bead Staining Test

In order to initiate a cyclisation/cleavage reaction of resin bound intermediate **159** was required a suitable base to deprotonate the free hydroxyl group of the resin bound intermediate. To get a direct comparison with the solution based cyclisation, as well as the previous solid supported oxetane synthesis, resin **159** was reacted with potassium *tert*-butoxide affording the oxetane (**157**) in a 62 % yield over both steps (scheme 4.2.4). Again, increasing the reaction time failed to increase the yield of the

oxetane product. This yield was significantly higher than the analogous solution based method and purification of the intermediate was by straightforward and rapid washing of the resin with suitable solvents. The lower yield than for the TBS protected oxetane (**157**) could again be reflective of the reduced steric bulk of oxetane **161**.



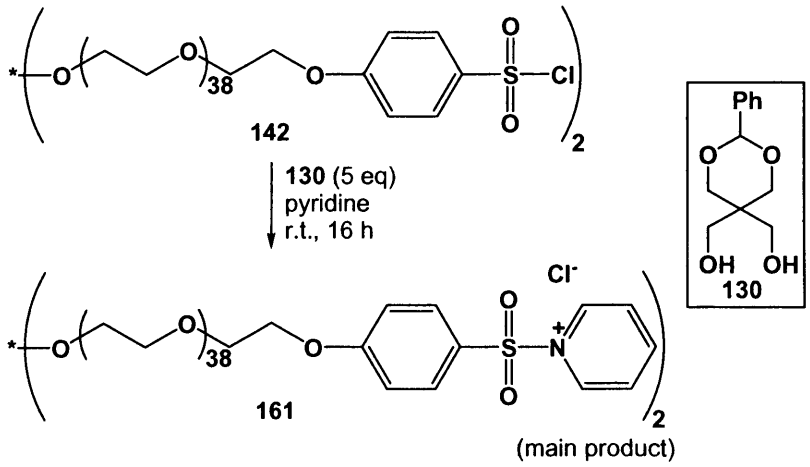
Scheme 4.2.3 Cyclisation/Cleavage of PS Bound Sulfonate Ester (**159**)

4.3 Oxetane Synthesis on a PEG Support

Having shown that the cyclisation/cleavage method was compatible with the chosen monomer, use of the novel PEG sulfonyl chloride (**142**) was explored. PEG supports have been shown to give a more solution-like environment for reactions, which can improve reaction kinetics. It was hoped that the more polar nature of the PEG environment could encourage the cyclisation step by stabilising the ion pair of the alkoxide. PEG supported intermediates can also be routinely monitored by NMR spectrometry, so it was hoped that more information could be gained about the loading step by the use of such a support.

Initially loading of benzylidene protected pentaerythritol (**130**) onto the PEG support (**142**) was attempted using an excess of **130** in pyridine, at room temperature (scheme 4.3.1). ^{1}H NMR spectroscopic analysis of the recovered PEG indicated that the major species formed was the PEG sulphonamide (**161**), with signals at δ_H 7.97, 8.47 and 8.92 ppm corresponding to the aromatic protons of the pyridine ring. This analysis also indicated the formation of a small amount of the loaded product being

formed, with a signal at δ_H 7.31 ppm corresponding to the aromatic protons of the benzylidene acetal.

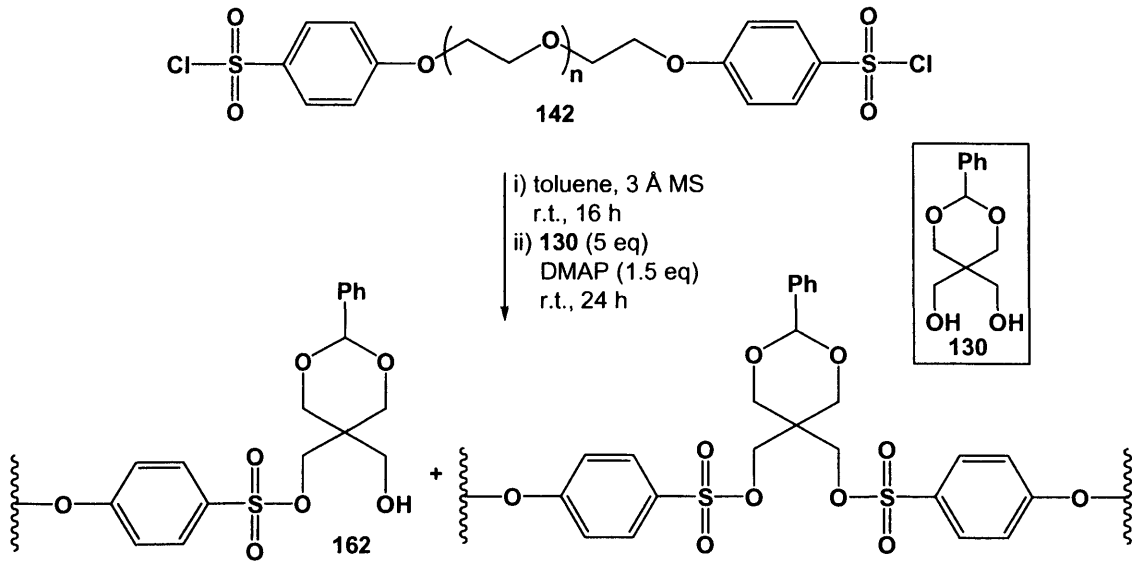


Scheme 4.3.1 Attempted Loading of Protected Pentaerythritol (**130**) onto PEG 3400 Sulfonyl Chloride (**142**)

Conversion of the intermediate PEG sulphonamide (**161**) to the desired loaded adduct was investigated further by increasing the reaction temperature to reflux, as with the PS resin. However, ^{1}H NMR spectroscopic analysis of the product indicated that while there was a slight increase in formation of the loaded product, the main product was PEG sulfonic acid formed by competing hydrolysis of the intermediate sulphonamide (**161**) and there still remained a fair amount of the sulphonamide. Sulfonic acid formation was due to the presence of water, trapped in the polymer matrix of the PEG chain during recrystallization. Attempts were made to dry PEG sulfonyl chloride (**142**) under vacuum for long periods (up to several weeks), but this approach was unsuccessful, due to the high affinity for PEG to complex with water through strong hydrogen bonding.

Whilst attempting to load 1,3-propanediol (**114**) onto PEG sulfonyl chloride (**142**, see chapter 5, scheme 5.3.1.1), it was found that competing sulfonic acid formation could be avoided if the PEG support was first pre-dried over molecular sieves. In order to incorporate a similar pre-drying step for the loading of the benzylidene protected monomer (**130**), the use of pyridine as the solvent would be precluded, as the drying step would require an inert solvent. The use of toluene as the solvent was

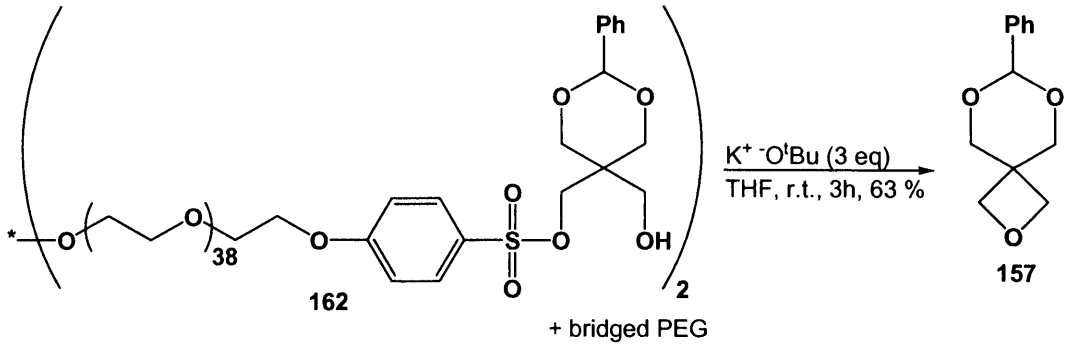
therefore explored; pre-drying a solution of **142** in this solvent for sixteen hours, prior to addition of a large excess of **130** and the strong base DMAP to drive the loading reaction (scheme 4.3.2). Following recovery of the PEG, propan-1-ol used as the recrystallization solvent was concentrated *in vacuo* and, following straightforward flash column chromatography, all unreacted monomer (**130**) was recovered.



Scheme 4.3.2 Loading of Protected Pentaerythritol (**130**) onto PEG 3400 Sulfonyl Chloride (**142**)

^{1}H NMR spectroscopic analysis of this product indicated that there had been full conversion of the intermediate sulphonamide to a loaded product and that competing sulfonic acid formation had been avoided. There were, however, four signals for the aromatic protons of the Wang linker (δ_H 7.03, 7.05, 7.83 and 7.86 ppm), indicating that two products had been formed. It is likely that the recovered PEG was a mixture of the desired terminal loaded product and a bridged product with several PEG chains linked by the monomer unit. Attempts to avoid the formation of a bridged product by using more equivalents of the monomer (**130**) were unsuccessful. Due to the complex ^{1}H NMR (see appendix A), it was difficult to ascertain the exact ratio of these products, but as the bridged product could not react further under the cyclisation conditions, the material was reacted further.

Using the previous cyclisation conditions; reaction of the PEG supported intermediate (**162**) with potassium *t*-butoxide, very little of the corresponding oxetane (**157**) was formed. However, by adding molecular sieves to the reaction, and stirring overnight, **157** was isolated in a 63 % yield (scheme 4.3.3). For ease of calculation, the yield of **157** was calculated assuming that **162** was the pure, unbridged species. The purity of the oxetane (**157**) was determined by NMR spectrometry.



Scheme 4.3.3 Cyclisation/Cleavage of PEG Bound Sulfonate Ester (**162**)

Following the reaction, the PEG support was recovered and ^{1}H NMR spectroscopic analysis suggested that it was composed of a mixture of PEG sulfonic acid and some loaded product; presumably the bridged sites. These observations indicated that the ratio of bridged to non-bridged PEG was around 2:3. While direct loading of dibranched monomers is problematic for PEG sulfonyl chloride (**142**), cyclisation/cleavage from this support seems to very efficient.

4.4 Conclusions and Future Work

In conclusion, oxetane formation has been explored in solution, on a PS support, and on a PEG support, using benzylidene protected pentaerythritol (**130**) activated with sulfonate esters. The solution based reaction, using a mono-tosylate as the intermediate, was the least effective of the three methods. While the cyclisation step occurred in a yield of 57 %, the intermediate was only isolated in a far lower yield of 10 %, giving an overall yield of 6 % making this method not synthetically useful. Also, purification of the intermediate was more complicated than with the alternative

methods, requiring flash column chromatography. The PS resin supported oxetane synthesis was achieved in a higher overall yield of 62 %. While a bead staining test indicated that there had been full loading, limited methods of analysing the resin bound intermediate made it difficult to determine the yield at each step. Purification of the intermediate was far more straightforward, requiring simple washing procedures. The PEG supported reaction had a very similar overall yield of 63 %. Due to the ability to use ^{1}H NMR spectrometry to monitor the PEG based intermediate it was possible to establish that the loading method had a side product, probably caused by bridging between two PEG chains. The non-bridged product seemed to be fully cleaved from the support, suggesting that the cyclisation reaction was very high yielding. Purification of the PEG bound intermediate was again straightforward, requiring recrystallization from hot propan-2-ol followed by a simple washing procedure. With some further optimisation it seems likely that both the PS supported and PEG supported oxetane syntheses could provide useful methods for synthesising many different oxetanes, that is superior to the solution based reaction.

Future work, as far as the PEG supported reaction is concerned, would be to improve the loading reaction in order to avoid the formation of a bridged side product. A method of achieving this is discussed in a later chapter, involving the use of a tri-protected monomer and the inclusion of an "on PEG" deprotection step (see chapter 5, scheme 5.2.3.1 and scheme 5.2.3.2). If the formation of a bridged product could be avoided as far as possible, the overall process would be likely to be very high yielding. With either the PS supported or PEG supported reaction, it is likely that an automated system could be set up in order to synthesise a library of oxetanes in a very efficient manner. It is also likely that the method could be applied to cyclic ethers of various sizes.

Chapter 5

5.0 Polyether Synthesis on Polymeric Supports

Since the conception of polymer supported synthesis, the technique has been widely used for the iterative synthesis of oligomers. Polymer supports lend themselves ideally to such iterative polymer syntheses because the simple purification of polymer supported intermediates compared to analogous solution reactions makes the process less time consuming. As discussed in chapter 1.2.5, Bradley's group have reported an iterative synthesis of polyethers on a Tentagel support, reacting supported alkoxides with cyclic sulfonates (scheme 1.2.5.2).[27] While this strategy afforded rapid access to a range of small polyethers, it had the limitation that the cleaved products were obtained as mixtures of different sized oligomers which still required HPLC separation.

In an attempt to provide access to oligoethers in higher purity, an alternative polymer supported strategy has been explored. Prior to this, a short study was carried out in solution in order to find conditions that would afford ethers in high yields (ideally >99 %) using an extension of the Williamson method.

5.1 Ether Synthesis in Solution

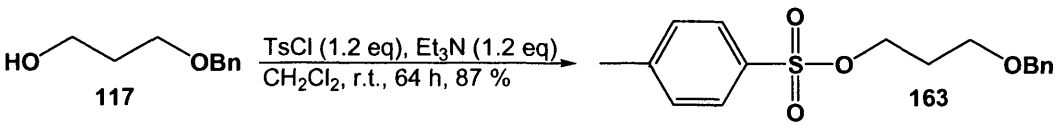
Williamson ether synthesis has been known for over a century and involves the reaction between an alkoxide and an alkyl halide in a suitable solvent (often an excess of the halide). Due to limitations of the Williamson reaction, such as reactivities and competing elimination when using secondary or tertiary alkyl halides, many modifications have been reported. Methods to improve the Williamson reaction include the use of more reactive leaving groups, [75, 76] the use of additives, such as phase transfer catalysts [79, 80] and cryptands,[81] and the use of dipolar aprotic solvents to improve the solubility of reagents. Using these modifications, ether

formation can be very high yielding, even for fairly hindered nucleophiles or electrophiles.

5.1.1 Activation of Monomers

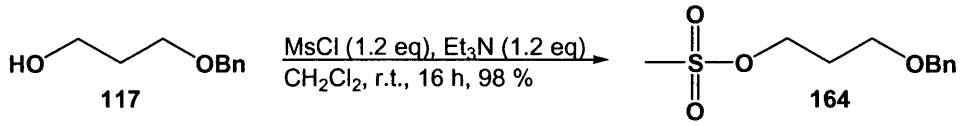
Sulfonate esters have been found to be a useful alternative to alkyl halides in Williamson ether syntheses. They can be readily prepared from the corresponding alcohol and are generally more reactive than alkyl halides.[73, 74] This method of activation was therefore explored when developing a high yielding ether synthesis. In a previous chapter the use of sulfonyl chloride (polymer bound) for the loading of alcohols followed by a cyclisation/cleavage reaction affording cyclic ether was described (see chapter 4, schemes 4.2.2 and 4.2.4). It was intended that this linker would again be used when developing a PS supported ether synthesis, in order to enable the use of these unique cyclisation/cleavage properties. To avoid a competing side-reaction (e.g. cleavage of the product), when carrying out ether synthesis on this support a more active sulfonate ester than the linker would be required for the extension step.

The solution based equivalent of the PS bound sulfonate linker is a *p*-toluene sulfonate (tosylate) ester. A tosylate was therefore used in solution based test reactions when exploring the relative reactivities of various sulfonate esters. Initially, linear monomers based on 1,3-propanediol (**114**, see chapter 2) were used in test reactions, in order to establish reaction conditions for a relatively unhindered system, before moving on to more substituted monomers. Benzyl protected monomer (**117**) was selected because it is relatively robust and the UV signal of the benzyl group could aid analysis by TLC or HPLC. Reacting compound **117** with a slight excess of tosyl chloride and triethylamine afforded the corresponding tosylate (**163**) in an 87 % yield (scheme 5.1.1.1).



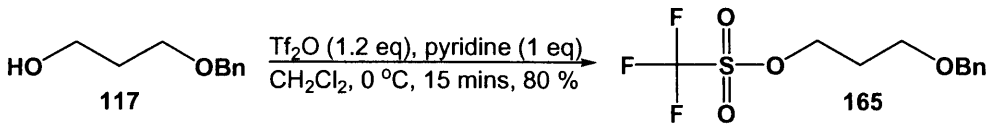
Scheme 5.1.1.1 Tosylation of Benzyl Protected Monomer (**117**)

Ether synthesis using methane sulfonate (mesylate) activation has been reported using conditions that afforded no extension when using the corresponding tosylate.[75] It was therefore hoped that the conversion of **117** to the corresponding mesylate ester (**164**) would afford a species that would be significantly more reactive than the tosylate (**163**). Compound **117** was reacted with a slight excess of mesyl chloride and triethylamine to give **164** in a 98 % yield (scheme 5.1.1.2).



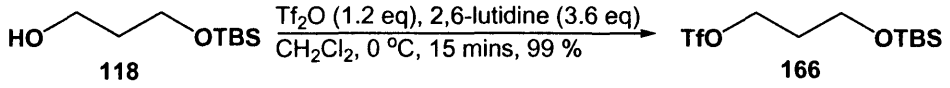
Scheme 5.1.1.2 Mesylation of Benzyl Protected Monomer (**117**)

In order to ensure a high degree of chain extension when carrying out polymer supported ether syntheses we also intended to use the highly reactive triflate esters. Due to the high reactivity of triflates esters, the conditions for their preparation must be carefully controlled to avoid both hydrolysis back to the alcohol and side reactions, such as a reaction between the product and the amine base used in the reaction.[149] The use of triethylamine and diisopropylamine were both found to be unsuitable for triflate formation, as the crude NMR spectrum revealed extensive side product formation, presumably due to reactions between base and triflate. However, by reacting alcohol **117** with an equimolar amount of pyridine and a slight excess of triflic anhydride at 0 °C, triflate **165** was formed in an 80 % yield (scheme 5.1.1.3). Purification of the product when using this method was by an aqueous work-up, requiring repeated washing steps to completely remove an excess of triflate-pyridine salt formed. While conversion of the alcohol to the triflate was likely to have been quantitative, some of the product was probably lost by hydrolysis during the aqueous work up .



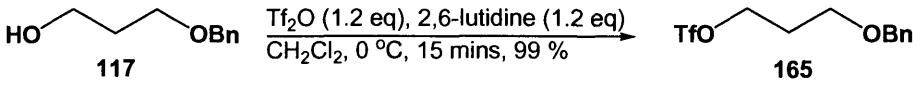
Scheme 5.1.1.3 Triflate Formation on Benzyl Protected Monomer (**117**)

Synthesis of a triflate from the TBS protected monomer (**118**) was also required. Using this activated monomer it was hoped that chain extension on a polymeric support could be followed by an "on-resin" deprotection, allowing further iterations of the oligoether. When synthesising the triflate using the reaction conditions that had successfully converted alcohol **117** to triflate **165**, deprotection of the TBS group occurred due to the acidity of triflic anhydride. To ensure that all of the acidic triflic anhydride was neutralised a slight excess of pyridine was used, but the triflate product had a tendency to alkylate the excess pyridine. The use of alternative bases was explored and by reacting **117** and triflic anhydride with an excess of the more hindered base 2,6-lutidine, triflate **166** was readily generated (scheme 5.1.1.4). Due to the low R_F values of 2,6-lutidine and its triflate salt running in dichloromethane, the purification of **166** was straightforwardly achieved by filtering the crude reaction mixture through a short pad of silica (~2"). As this method of purification avoided the need for an aqueous work up, the product was isolated in quantitative yield.



Scheme 5.1.1.4 Triflate Formation on TBS Protected Monomer (**118**)

As this purification procedure was a significant improvement to that used for the formation of **165**, a similar approach was attempted to improve the yield of the benzyl protected triflate. Following a reaction between **117** and triflic anhydride, using 2,6-lutidine rather than pyridine, the crude product could be filtered through a short pad of silica (~2") instead of using an aqueous work up, affording **165** in a quantitative yield (scheme 5.1.1.5).

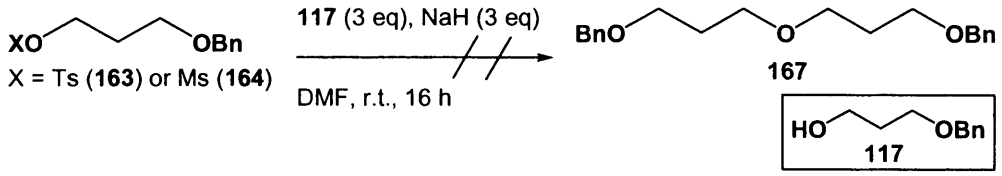


Scheme 5.1.1.5 Optimised Triflate Formation on Benzyl Protected Monomer (**117**)

5.1.2 Test Reactions in Solution

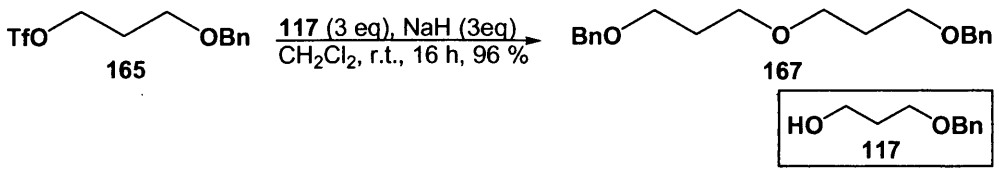
In order to identify ether forming conditions that would be sufficiently mild for later use with polymeric supports, ether synthesis in solution, at room temperature was required. The conditions developed would need to be high yielding for mesylates and/or triflates, but give low reactivities for tosylates. Application of these conditions to a solid support would then give chain extension without cleaving products from the support by reaction with the tosyl sulfonate linker.

Initial test reactions were carried out at room temperature, using sodium hydride as a base. Sodium hydride was selected because it is compatible with a range of aprotic solvents and is often used in ether syntheses. For reactions with tosylate and mesylate activation, ether synthesis was attempted in DMF, as this dipolar aprotic solvent can aid ether synthesis by efficiently solubilising both the alkoxide and the electrophile. When tosylate **163** or mesylate **164** were reacted with an excess of alcohol **117** under these conditions, no reaction was observed after sixteen hours (scheme 5.1.2.1).



Scheme 5.1.2.1 Attempted Ether Synthesis with Tosylate (**163**) or Mesylate (**164**)

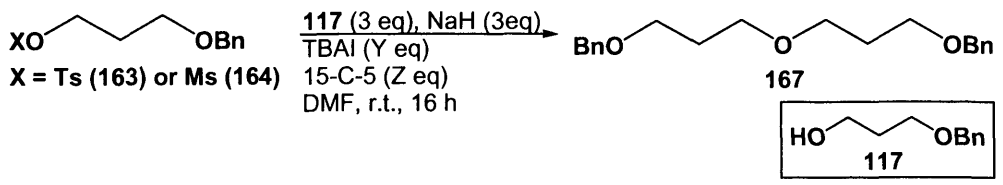
Upon reacting triflate **165** with alcohol **117** under these conditions, a deeply coloured solution was formed upon addition of the triflate. It soon became apparent that this was due to a reaction between the triflate and DMF.[149] Due to the high reactivity of the triflate, an inert solvent was therefore required. Reacting **165** with an excess of **117** and sodium hydride in dichloromethane, at room temperature, afforded the symmetrical ether (**167**) in a 96 % yield (scheme 5.1.2.2), despite the low solubility of the alkoxide in this solvent. The use of dichloromethane was also advantageous, because it is known to cause a high degree of swelling with PS resins, giving good access to the reactive sites.



Scheme 5.1.2.2 Ether Synthesis with Triflate (**165**)

In an attempt to improve the reactivity of mesylate **164**, the use of several additives was also considered. Phase transfer catalysts are known to help facilitate Williamson type reactions by transporting the alkoxide into the organic phase of the reaction, thus giving a higher concentration of both reactive species in the same phase.[77] As well as being able to transport the alkoxide from an aqueous phase to an organic phase, phase transfer catalysts can also be used to transport an insoluble alkoxide from the solid phase to an organic phase in the absence of an aqueous phase.[151] Quaternary amine salts are known to be effective phase transfer agents because the large, diffuse ammonium cation readily solubilises ion pairs in the organic phase. A commonly used reagent of this class is tetrabutylammonium iodide (TBAI).[79, 80]

In order to determine comparable reactivities between the means of activation, tosylate **163** and mesylate **164** were reacted with an excess of alcohol **117** using sodium hydride, with TBAI as an additive (scheme 5.1.2.2). Under these conditions, the tosylate (**163**) reacted to give ether **167** in a 10 % yield (table 5.1.2.1, entry 1), whereas the mesylate (**164**) gave the same ether in a 39 % yield (table 5.1.2.1, entry 2). This suggested that chain extension on a polymer support, using mesylate activation, in the presence of the sulfonate linker was possible.



Scheme 5.1.2.2 Influence of Additives on Ether Synthesis

Entry	Sulfonate Ester (X)	Compound	Eq. of TBAI (Y)	Eq. of 15-C-5 (Z)	Yield
1	Ts	**163**	1	-	10 %
2	Ms	**164**	1	-	39 %
3	Ms	**164**	-	1	49 %
4	Ms	**164**	1	1	94 %

Table 5.1.2.1 Influence of Additives on Ether Synthesis

Ideally, for mesylates to be suitable leaving groups in ether synthesis on a polymeric support, chain extension yields would need to be quantitative, so further reaction optimisation was required. In an attempt to improve yields, further additives were considered, in particular 15-crown-5. These cyclic polyethers can complex cations such as K^+ and Na^+ by electrostatic interactions with the lone pairs of its oxygen atoms. This can enhance the Williamson reaction by complexing the metal ion of an alkoxide, dissociating the ion pair and giving a more reactive species.[81] Due to the diffuse nature of the complexed metal ion, it is also thought that the alkoxide is more readily solubilised in organic solvents.

By reacting mesylate **164** with an excess of alcohol **117** in DMF, using sodium hydride as a base and 15-crown-5 as an additive, ether **167** was formed in a 49 % yield (scheme 5.1.2.2, table 5.1.2.1, entry 3). However, when using both TBAI and 15-crown-5, ether **167** was obtained in a much higher yield of 94 % (scheme 5.1.2.2, table 5.1.2.1, entry 4). TLC analysis of the reaction showed no trace of the mesylate (**164**) after sixteen hours under these conditions so these reaction conditions had the potential to give quantitative chain extensions on a polymer support.

5.2 Polyether Synthesis on a PS Support

Initially the polymer supported ether synthesis was investigated using a PS resin. These resins, comprised of polystyrene cross-linked with a divinyl benzene copolymer, have been extensively used in polymer supported synthesis, including the iterative synthesis of oligomers.[1] Since they are completely insoluble in all solvents, the purification of intermediates can be rapidly achieved with washing procedures. However, they can be swollen to various degrees by organic solvents, allowing small molecules in solution to diffuse through the polymer matrix and access the reactive sites.

Due to the interesting cyclisation/cleavage strategy that could be afforded by sulfonate linkers (see chapter 4), sulfonyl chloride (polymer bound) (**37**) was used for the immobilisation of the substrate. This was obtained in a 1 % cross-linked form, since previous work reported that resins of this nature gave significantly better yields for ether synthesis than 2% cross linked resins.[27] The loading level of the chosen support was 1.5-2.0 mmol g^{-1}.

5.2.1 Development of a Mild Cleavage Reaction

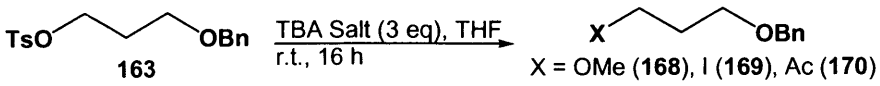
For ease of monitoring test reactions on the support a cleavage method that could be performed at room temperature, converting the resin bound intermediate to a suitable product for purification and analysis was required. Existing cleavage conditions reported in the literature generally involved a reaction with amines at high temperatures and pressures,[69] and so were not suitable for our purposes.

In order to find conditions that may be suitable to cleave a product from the resin, solution phase analogous reactions were carried out using a tosylate ester. Benzyl protected tosylate **163** was selected as a substrate for ease of UV analysis. The most useful transformation from a synthetic viewpoint would have been hydrolysis of the tosylate ester to give a hydroxyl group in the cleaved product. However, metal hydroxide salts (e.g. NaOH, KOH) usually have limited solubilities, and therefore reactivities, in organic solvents and such reactions are generally carried out in polar

protic solvents. Polar protic solvents (e.g. methanol) are known to shrink PS resins, limiting access to the reactive sites. Caesium hydroxide has higher solubility in organic solvents due to the larger, more diffuse nature of the metal counterion.[79] However, treatment of tosylate **163** with an excess of caesium hydroxide in THF, at room temperature, gave no reaction. Use of a phase transfer catalyst to facilitate the hydrolysis of the tosylate ester was explored by reacting sodium hydroxide and 15-crown-5 with **163** in THF, at room temperature, however, the reaction failed.

Several further attempts to achieve the hydrolysis reaction using alternative reagents were carried out. It had been reported that the use of hydrogen peroxide to generate the peroxide anion can give higher reactivity in nucleophilic substitution reactions.[150] However, following the reaction between tosylate **163**, lithium hydroxide and hydrogen peroxide (50 % in water) in THF, at room temperature, only starting materials were recovered. Another method which can generate a more reactive species is the use of potassium *t*-butoxide, with a drop of water, to generate a highly reactive hydroxide species which is not associated with the metal counterion (known as "anhydrous hydroxide"). This method also failed to hydrolyse tosylate **163** at room temperature.

Due to previous observations that tetrabutylammonium (TBA) salts could effect the Williamson reaction at room temperature, a hydrolysis reaction between tosylate **163** and an excess of TBA hydroxide in THF, at room temperature was attempted (scheme 5.2.1.1, table 5.2.1.1, entry 1). TBA hydroxide is available as a 1 M solution in methanol, so the corresponding alcohol was not isolated, but the tosylate was instead converted to the corresponding methyl ether (**168**) in an 81 % yield. Following this result, tosylate **163** was reacted with several other TBA salts to establish whether the tosylate ester could be converted into a range of functional groups. Reacting **163** with TBAI under the same conditions gave the corresponding iodide (**169**) in a 59 % yield (scheme 5.2.1.1, table 5.2.1.1, entry 2). The highest yield, however, was for the conversion of **163** to acetate **170** using TBA acetate in a 93 % yield (scheme 5.2.1.1, table 5.2.1.1, entry 3).

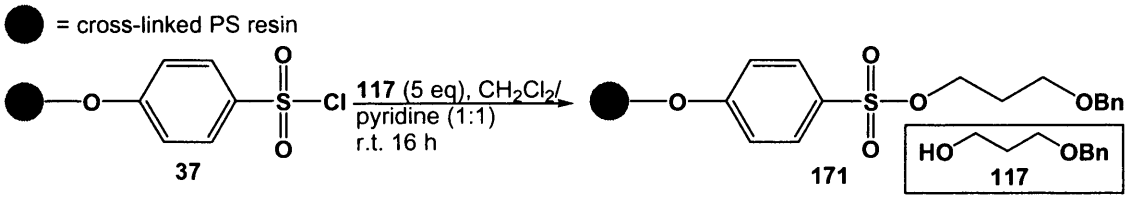


Scheme 5.2.1.1 Cleavage of Tosylate (**163**) with TBA Salts

Entry	TBA Salt	Product	Yield
1	TBAOH in methanol (1M)	**168**	81 %
2	TBAI	**169**	59 %
3	TBAAc	**170**	93 %

Table 5.2.1.1 Cleavage of Tosylate (**163**) with TBA Salts

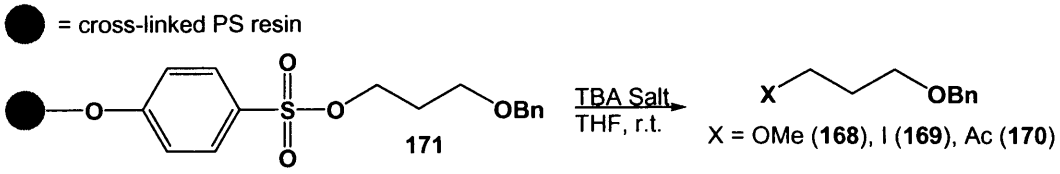
In order to establish whether TBA salts could cleave products from a PS linked sulfonate ester, the resin bound equivalent of tosylate **163** was synthesised. A previous literature procedure had reported the successful loading of a range of alcohols onto resin **37** in a 1:1 mixture of dichloromethane and pyridine at room temperature.[20] Alcohol **117** was reacted with resin **37** in this solvent system at room temperature (scheme 5.2.1.2). IR analysis of resin **37** and the resin bound intermediate **171** was not informative, as there were no distinctive differences in the IR signals of both resins. However, a bead staining test (see chapter 4) gave a positive result, suggesting that all sites on the resin had reacted.



Scheme 5.2.1.2 Loading of Benzyl Protected Monomer (**117**) onto Sulfonyl Chloride (Polymer Bound) (**37**)

With resin bound intermediate **171** in hand, cleavage reactions were attempted with the three TBA salts that had successfully cleaved tosylate **163**. Resin **171** was shaken at room temperature, with an excess of each TBA salt (scheme 5.2.1.3, table 5.2.1.2). Both TBAI and TBAAc reacted with resin **171** to give products **169** and **170** in yields of 39 % (table 5.2.1.2, entry 2) and 43 % (table 5.2.1.2, entry 2) respectively. Yields were calculated from the original loading value of sulfonyl chloride (polymer

bound), taking that value to be 2.0 mol g^{-1}. When TBA hydroxide (1M in methanol) was used, no product was isolated. This was probably because the methanol present can shrink the PS resin, limiting access to the reactive sites. The reaction could possibly have been more successful by dissolving TBA hydroxide in an aprotic solvent system (which would give the product as an alcohol rather than with a methoxy functionality), but this was not explored further due to the success of the alternative cleavage methods.



Scheme 5.2.1.3 Cleavage of PS Bound Sulfonate Ester (**171**) with TBA Salts

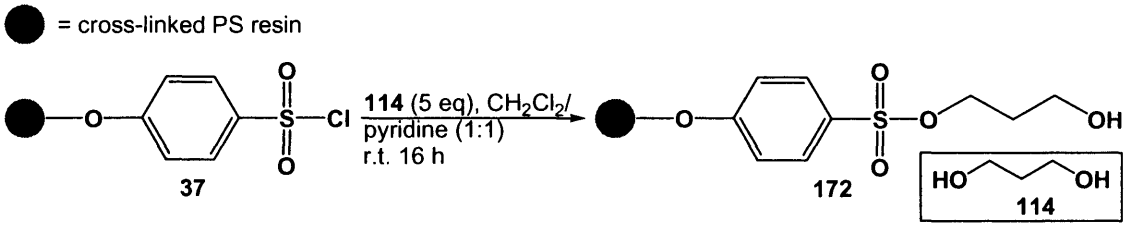
Entry	Reagents	Product	Equivalents	Time	Yield
1	TBAOH/MeOH (1M)	**168**	3	16 h	-
2	TBAI	**169**	8	64 h	39 %
3	TBAAc	**170**	3	16 h	43 %

Table 5.2.1.2 Cleavage of PS Bound Sulfonate Ester (**171**) with TBA Salts

The iodide (**169**) was formed in lower yields than the acetate (**170**) and required more equivalents of TBA salt and longer reaction times. Attempts were made to improve the isolated yield of **169** by increasing the equivalents of the TBAAc, but this had little effect. Whilst the yields are not high, as a means of monitoring PS supported reactions, they were regarded as sufficient. Incorporating an acetate functionality had the potential advantage that it would provide characteristic signals for both NMR and UV spectroscopic techniques, unlike iodide and hydroxide groups. It was therefore decided to use TBAAc as the main cleavage method for test reactions.

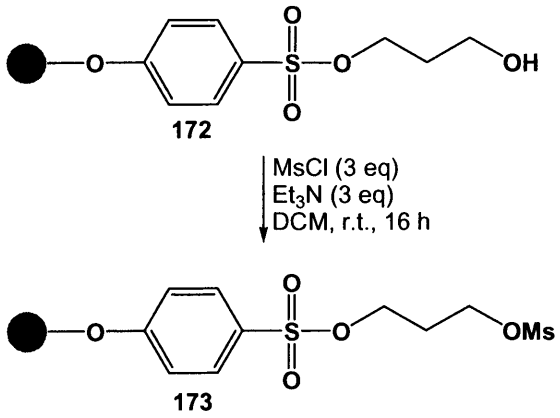
5.2.2 Test Reactions with Linear Monomers

With a mild, convenient cleavage reaction in hand for the monitoring of test reactions, an "on resin" ether synthesis was carried out. The first step involved loading of a suitable monomer onto the support that, once immobilised, would have a free hydroxyl group, either for activation as a leaving group or deprotonation to form an alkoxide. Again, linear monomers were used in these preliminary reactions. To immobilise the substrate, resin **37** was reacted with an excess of 1,3-propanediol (**114**) in pyridine and dichloromethane, at room temperature (scheme 5.2.2.1). Again, analysis by IR was uninformative as small amounts of water in the starting resin and the product masked the hydroxyl signal, but the recovered resin gave a positive result with the bead staining test, suggesting that it had been converted to resin bound intermediate **172**.



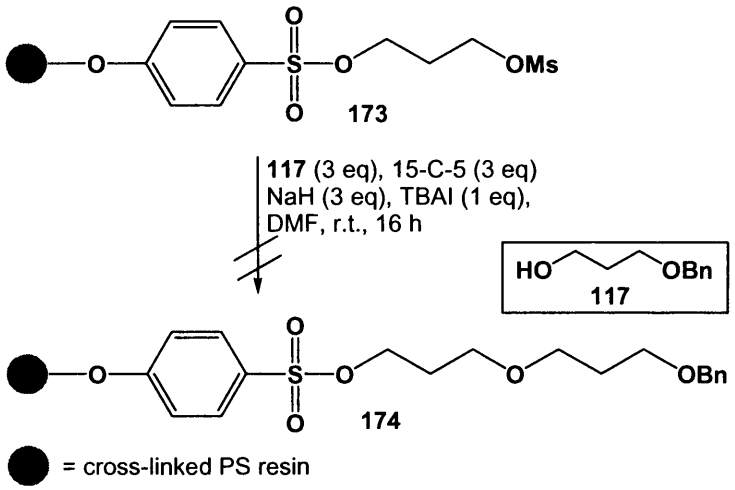
Scheme 5.2.2.1 Loading of 1,3-Propanediol (**114**) onto Sulfonyl Chloride (Polymer Bound) (**37**)

"On resin" chain extension was first attempted using mesylate activation, in conjunction with the use of additives. For this type of reaction there were two alternatives; activating resin bound alcohol **172** as a mesylate and reacting with an alkoxide in solution, or reacting the alkoxide of **172** with a mesylate in solution. In order to test the first approach, resin **172** was reacted with an excess of mesyl chloride and triethylamine in dichloromethane (scheme 5.2.2.2).



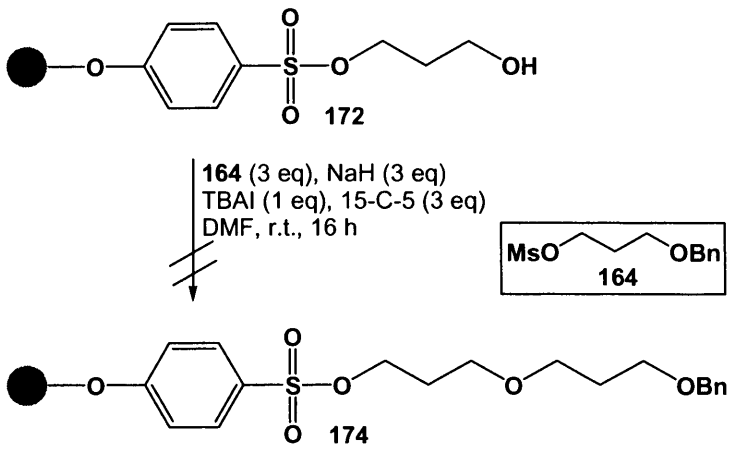
Scheme 5.2.2.2 Mesylation of PS Bound Alcohol (**172**)

Assuming complete conversion to the mesylate **173**, this was reacted with an excess of the benzyl protected monomer (**117**) in DMF, with sodium hydride, TBAI and 15-crown-5 (scheme 5.2.2.3). Sodium hydride was selected rather than a soluble base, as Bradley's group had demonstrated that it could be successfully used to form an alkoxide on a PS resin.[27] It was decided that the reaction would be monitored by cleaving the product, rather than attempting gel state NMR. The resin bound product was subjected to TBA acetate cleavage conditions (see 5.2.1). Analysis of the cleavage products by mass spectrometry showed no trace of a dimeric product, suggesting that there had been no chain extension.



Scheme 5.2.2.3 Attempted Chain Extension with PS Bound Mesylate (**173**)

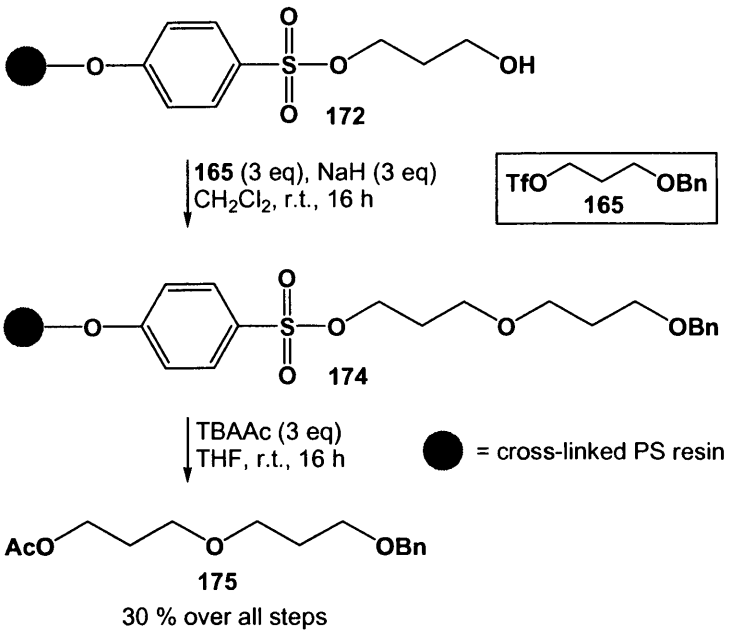
To test the alternative approach, resin **172** was shaken with an excess of mesylate **164** in DMF with sodium hydride, TBAI and 15-crown-5 (Scheme 5.2.2.4). Unfortunately, analysis of the products following TBA acetate cleavage showed no trace of a dimeric product. As there was a possibility of TBAI present causing a competing cleavage reaction, both methods of chain extension were also attempted with only 15-crown-5 as an additive, but again there was no trace of an extended product.



Scheme 5.2.2.4 Attempted Chain Extension with PS Bound Alcohol (**172**) and Mesylate (**164**)

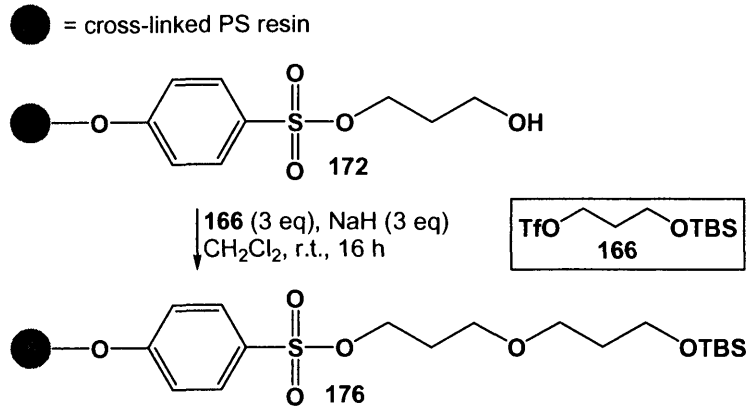
As mesylate activation did not give a sufficiently reactive leaving group to promote ether synthesis on a PS support, even in the presence of phase transfer catalysts, the use of triflate esters as the leaving group was then explored. Since a PS supported triflate would be unstable in terms of storage and the washing procedures required for purification, the reaction was attempted with an immobilised alkoxide and a triflate in solution. The resin bound alcohol (**172**) was shaken with triflate **165** and sodium hydride in dichloromethane (scheme 5.2.2.5). Mass spectrometry analysis of the TBA acetate cleavage product indicated that some of the dimeric product (**175**) had been formed, although there was also a peak corresponding to the unreacted monomer. In an attempt to assess the reaction more fully, the reaction was scaled up (77 mg of extended resin were cleaved) and the dimer was isolated by flash column chromatography in a 30 % yield over all steps. This was encouraging given that the test cleavage reaction yield was 43 %. Unfortunately it was not possible to isolate any monomeric product from the crude reaction mixture. It was later found that with

TBA acetate cleavages of products containing free hydroxyl groups that product isolation was not possible, perhaps due to deprotonation and complexation of these products with the TBA salts.



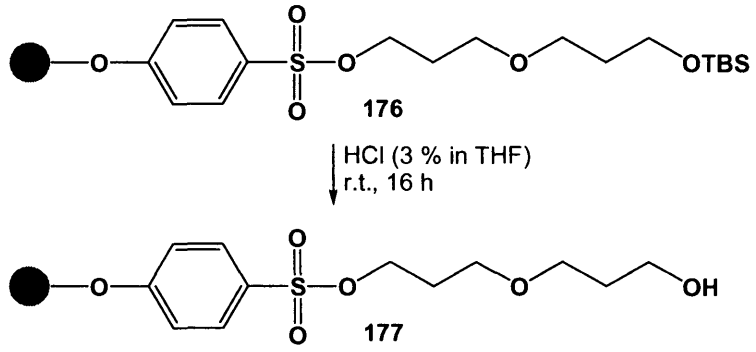
Scheme 5.2.2.5 Chain Extension with Triflate (**165**) and Cleavage from PS Support

Since the ratio between monomeric and dimeric products could not be established using TBAAc cleavage, the iterative synthesis to the trimer was carried out. In order to make the process iterative, an "on resin" deprotection step was required. The previous chain extension reaction was therefore carried out with the alternative TBS protected triflate (**166**, scheme 5.2.2.6). Mass spectrometry analysis of the products following a small scale (5 mg of resin) TBA acetate cleavage indicated that, while there was monomeric product present, there had again been some chain extension to give the resin bound intermediate **176**.



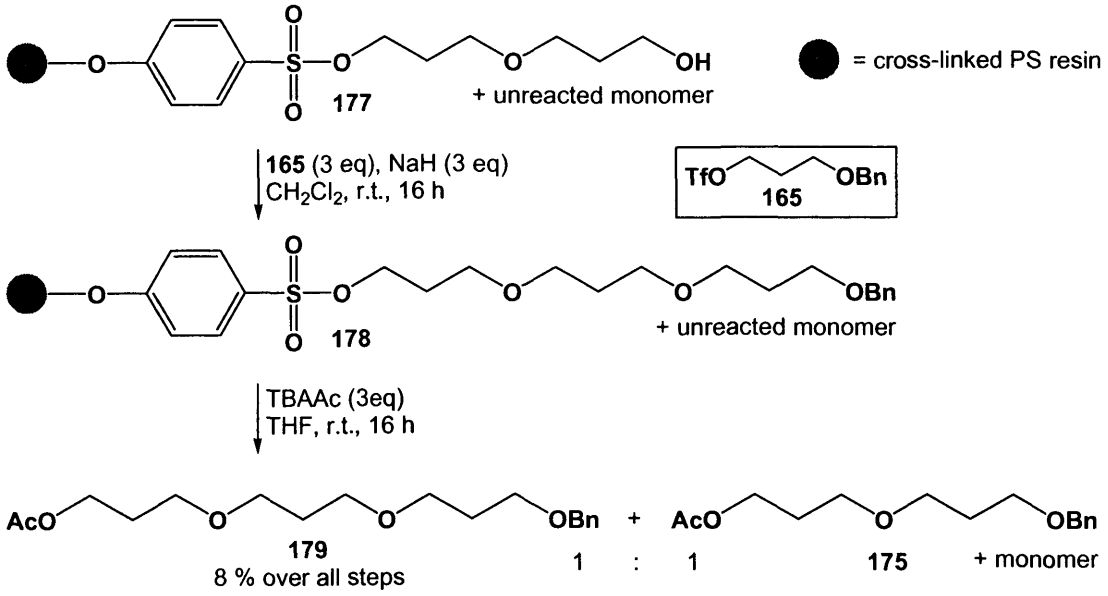
Scheme 5.2.2.6 Chain Extension with PS Bound Alcohol (**172**) and Triflate (**166**)

The use of TBAF to cleave the TBS protecting group, led to cleavage the sulfonyl linker. The acid lability of the TBS was explored by reacting resin **176** with a 3 % solution of hydrochloric acid in THF (scheme 5.2.2.7). When the resin was washed following deprotection, the cleaved TBS group was detected in the wash solution, but no other cleavage products.



Scheme 5.2.2.7 Deprotection of TBS group on PS Resin (**176**)

For the second chain extension, resin **177** was shaken with an excess of triflate **165** under the previous chain extension conditions (scheme 5.2.2.8). Mass spectrometry analysis of the crude TBA acetate cleavage products indicated a mixture of the monomer, the benzyl protected dimer (**175**) (formed by further extension of the previously unreacted monomer), and benzyl protected trimer (**179**). Dimer **175** and trimer **179** were isolated by flash chromatography and were found to be in a molar ratio of 1:1. Trimer **179** was isolated in a yield of 8 % over all steps.



Scheme 5.2.2.8 Second Chain Extension and Cleavage on PS Resin

The absence of deprotected dimer, according to mass spectrometry analysis of the cleavage products, suggested that the second chain extension was quantitative and that it was the first addition step that was most problematical. The first extension step was carried out using more equivalents of triflate and also treating resin **172** twice with the triflate, but neither approach gave complete extension. All of these factors suggested that a limiting factor was the proximity of the reactive site to the matrix of the resin. The apolar environment of PS resins has, for example, been observed to increase the prevalence of competing elimination when ether syntheses were attempted on PS supported alkyl bromides. This apolar matrix effect could also be destabilising to an ion pair during alkoxide formation. For the second extension step there is a spacer between the hydroxyl group and the resins matrix, so any destabilising effects are decreased. As the first extension step on this resin could not be improved, it was decided to transfer the reaction conditions to a polymeric support that would provide a more solution-like environment, facilitating the process.

5.3 Polyether Synthesis on a PEG Support

In an attempt to give a more solution-like environment for ether forming reactions to be carried out, PS resins have been modified by grafting PEG chains to the end groups, with commercially available examples of these resins including Tentagel [24]

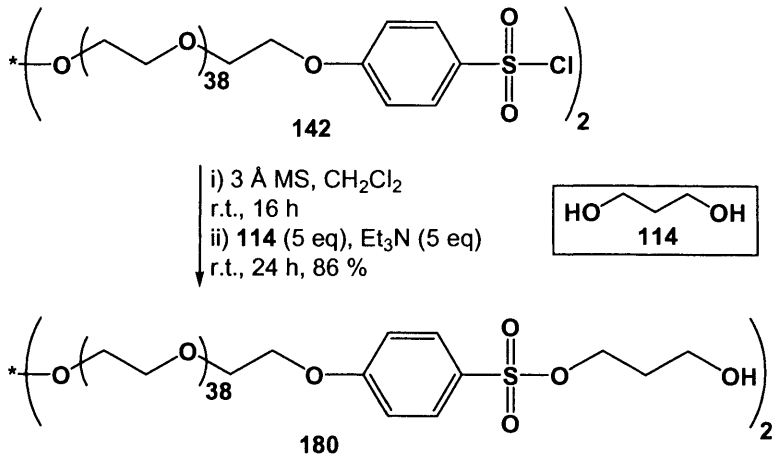
and Argogel.[19] However, these reactions still have the problems associated with other PS resins, with heterogeneous reaction conditions giving rise to nonlinear kinetic behaviour, unequal distribution, unequal access to the reactive sites, and solvation problems.[37] PEG grafted PS resins are also susceptible to damage by mechanical force, limiting the methods that can be used to stir reactions.

Increasingly in the literature soluble polymer supports have been used in preference to solid supports, due to the more solution like environment afforded by homogenous reaction conditions. PEG has been used in a number of cases, due to solubility in a range of solvents, high solubilising power, and easy access of small molecules to active sites. It was envisaged that the more solution like and polar environment of the PEG chain could help to stabilise alkoxide formation and that steric problems would be reduced. An additional attractive feature of the PEG was that reactions could be monitored by ^{1}H NMR spectrometry. This would be particularly useful, as attempts at monitoring chain extensions by IR on the PS support had proved uninformative and cleavage at each stage in the synthesis was required for the analysis of intermediates. Using the novel PEG sulfonyl chloride support (**142**, see Chapter 3) a direct comparison between the chain extension conditions on a PS support and a PEG support could be ascertained.

5.3.1 Test Reactions with Linear Monomers

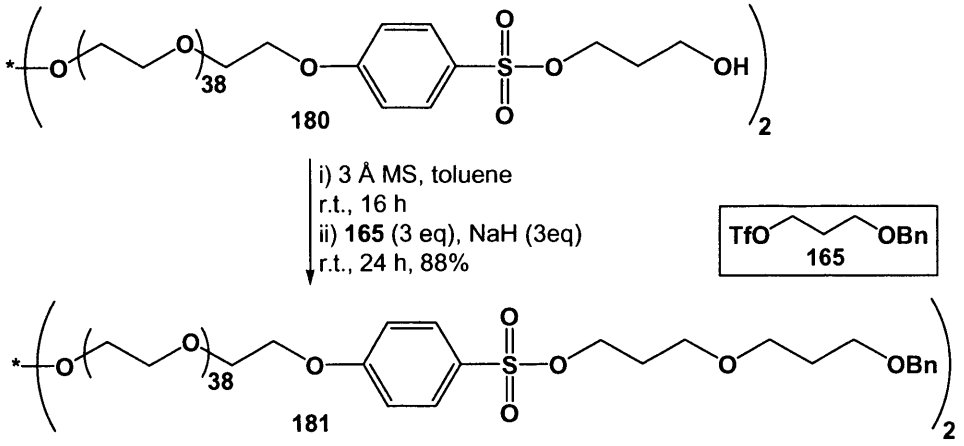
In order to test the suitability of the PEG support (**142**) for an iterative polyether synthesis, preliminary reactions were again carried out with linear monomers, using the triflate method of activation that had successfully given some chain extension on the PS support. For ease of purification, 1,3 propanediol (**114**) was loaded onto the support using 3 equivalents of triethylamine as the base, rather than the larger excess of pyridine used previously. ^{1}H NMR spectroscopic analysis of the recovered PEG revealed that water trapped in the PEG had caused some conversion to PEG sulfonic acid. As the reaction required the use of dichloromethane as the solvent (reactions in acetonitrile and toluene were found to give incomplete loading), azeotropic removal of water was not a possibility (see chapter 3, scheme 3.1.2.4) and an alternative method of drying the PEG was required. Stirring a solution of PEG sulfonyl chloride

(**142**) in dichloromethane with 3 Å molecular sieves overnight, prior to addition of a fivefold excess of diol **114** and triethylamine was found to be an effective method of drying the PEG and the reaction then proceeded cleanly with no PEG sulfonic acid formation (scheme 5.3.1.1). Furthermore, ^{1}H NMR spectroscopic analysis indicated that there was no bridging between PEG chains through the diol, as evidenced by the presence of only one signal corresponding to the CH_2CH_2OH protons of the loaded product (quintet, $\delta_H = 1.87$).



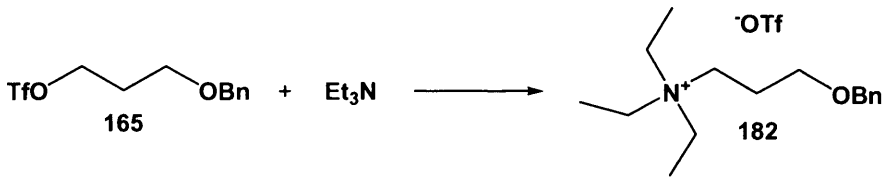
Scheme 5.3.1.1 Loading 1,3-Propanediol (**114**) onto PEG 3400 Sulfonyl Chloride (**142**)

The conditions developed on the PS support (scheme 5.2.2.5) initially seemed to give very little chain extension using the PEG support. This was probably due to encapsulation of water by the PEG. The problem was again solved by drying with 3 Å molecular sieves before adding the reagents. Compound **180** was initially reacted with an excess of the benzyl protected triflate (**165**) and sodium hydride (scheme 5.3.1.2). ^{1}H NMR spectroscopic analysis indicated very high conversion to the dimer, as evidenced by the appearance of a multiplet corresponding to the aromatic protons of the benzyl group (δ_H = 7.27-7.35) and a singlet corresponding to the benzylic CH_2 (4.46), as well as a slight shift in the position of the peaks corresponding to the aromatic protons of the linker (7.03 and 7.83 to 6.99 and 7.80). It was not possible, however, to determine whether extension was achieved in a quantitative yield solely by this method of analysis.



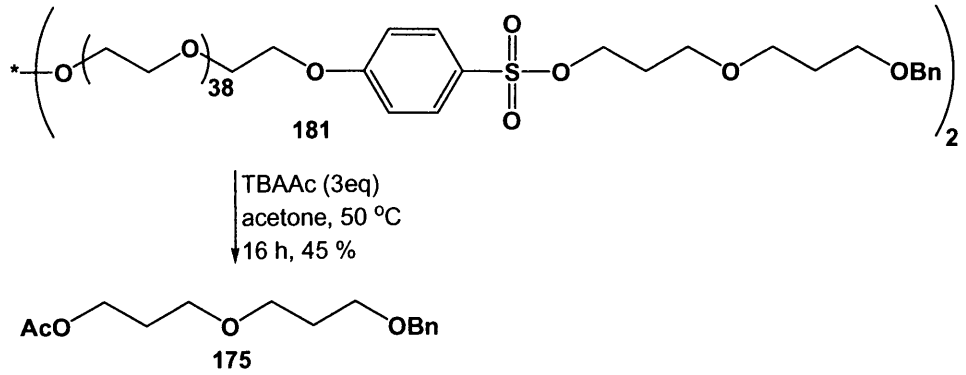
Scheme 5.3.1.2 Chain Extension of PEG Supported Alcohol (**180**) with Triflate (**165**)

Excess triflate present in the crude product seemed to complex strongly with the PEG, initially causing a low % recovery during purification. However, when triethylamine was added prior to recrystallization, the PEG product was recovered in a much higher yield of 88 %. This was presumably due to the excess triflate alkylating the triethylamine and being converted to a quaternary ammonium salt (**182**, scheme 5.3.1.3),[147] which complexes less strongly to the PEG.



Scheme 5.3.1.3 Alkylation of Triethylamine with Triflate (**165**)

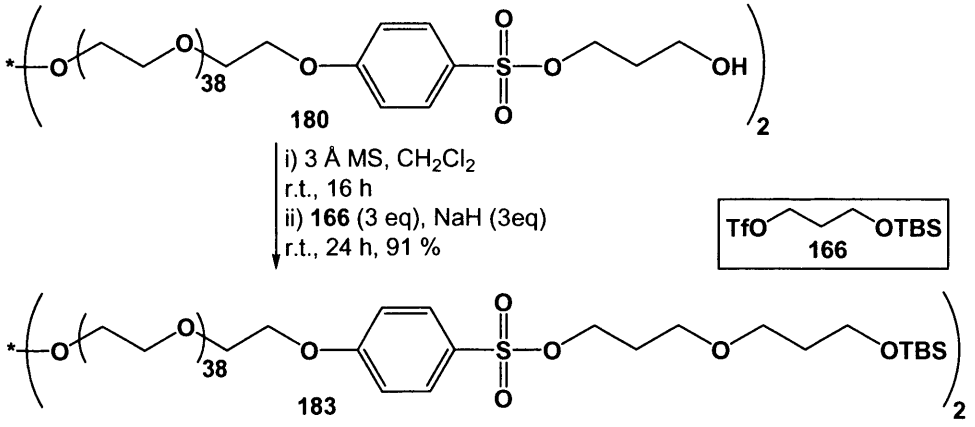
Cleavage of the product from the support using the conditions developed for the PS support was then attempted using TBAAc (see 5.2.1). However, the reaction did not proceed. Compatibility of the PEG support with polar protic solvents was not a problem and therefore cleavages were attempted using sodium hydroxide in water, and sodium methoxide in methanol, but these reactions were also unsuccessful. Eventually it was found that the reaction between **181** with TBAAc in acetone, at 50 °C, led to cleavage of the dimer (**175**) from the PEG support (scheme 5.3.1.3).



Scheme 5.3.1.3 Cleavage of PEG Bound Sulfonate Ester (**181**) with TBA Acetate

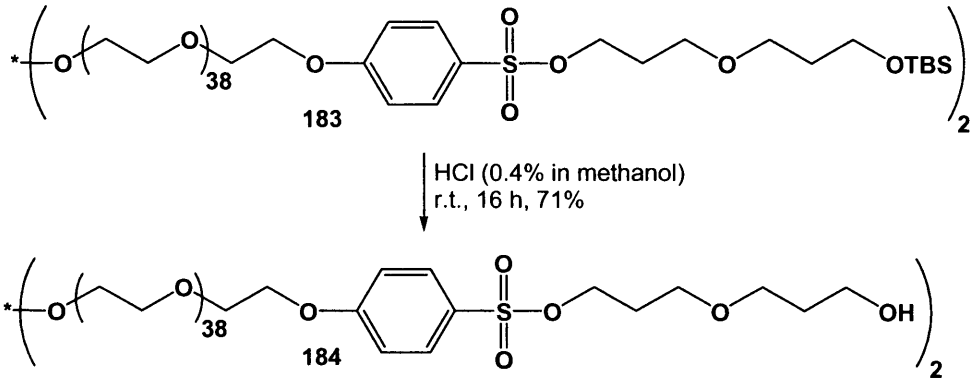
The cleaved PEG support was recovered and ^{1}H NMR spectroscopic analysis showed that it had predominantly been converted to PEG sulfonic acid. The isolated yield of **175** (45 %) contradicted the evidence provided by ^{1}H NMR analysis of **181**, which suggested a greater degree of chain extension had occurred. The problem could be isolation of the product from the support during the work up. The method of extracting the product was to precipitate the PEG from the crude product by slowly adding diethyl ether to a concentrated solution in methanol. It is possible that some of the product was complexing with the PEG support and was precipitated with it. An alternative method attempted was dissolving the crude product in water and attempting to extract **175** with diethyl ether, however this was not a straightforward process, as there was a tendency for an emulsion to form between the layers making separation of the organic and aqueous phases difficult. Ultrafiltration, dialysis or size exclusion chromatography could prove to be more effective methods of separating cleaved products from the PEG support in future work.

In order to obtain further information on the extent of ether synthesis, iterative trimer synthesis on the PEG support was carried out. The PEG bound alcohol (**180**) was reacted with the TBS protected triflate (**166**) under the standard chain extension conditions (scheme 5.3.1.4). Again ^{1}H NMR spectroscopic analysis of the product (**183**) indicated a very high degree of chain extension, as evidenced by peaks corresponding to the protons on the TBS group (δ_H = 0.01 and 0.03; 0.80 and 0.85), as well as a slight shift in the position of the peaks corresponding to the aromatic protons of the linker (7.03 and 7.83 to 7.00 and 7.80). The unexpected splitting of the signals corresponding to the TBS protons was thought to be due to restricted rotation.



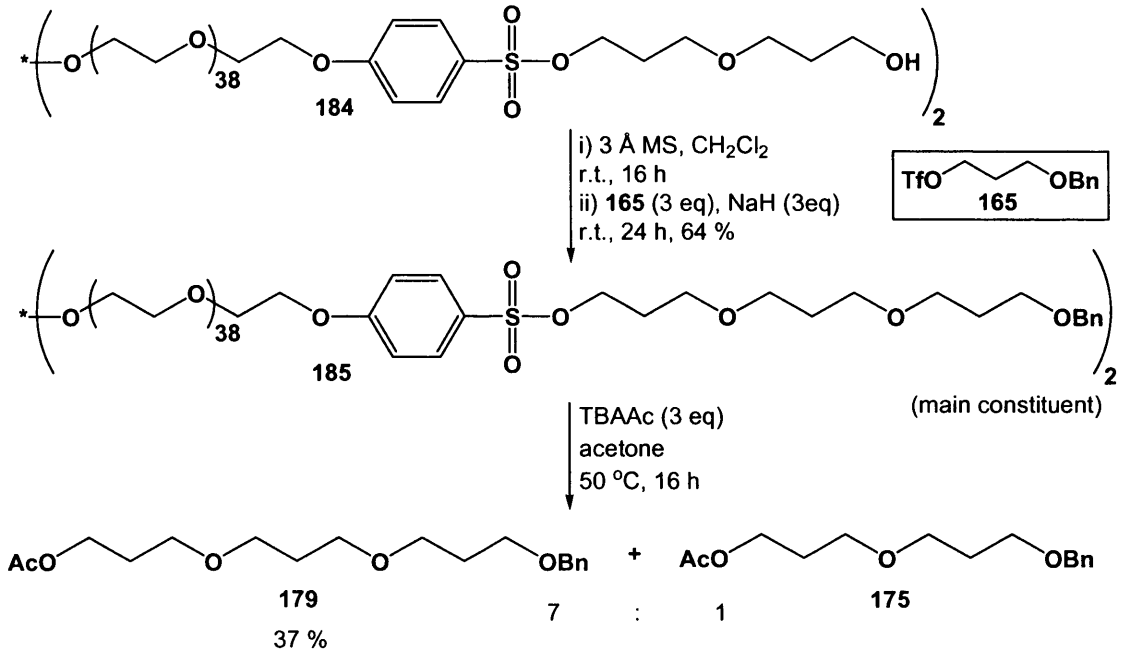
Scheme 5.3.1.4 Chain Extension of PEG Supported Alcohol (**180**) with Triflate (**166**)

The extended PEG (**183**) was then deprotected, assuming complete chain extension for ease of calculation. This was achieved by stirring **183** in a 0.4 % solution of hydrochloric acid in methanol for 16 hours (scheme 5.3.1.4). The PEG could be recrystallized directly, following the evaporation of methanol, however, the best % recovery of **184** was achieved by neutralisation of the solution with Amberlyst® A21 ion-exchange resin prior to recrystallization, giving the product in a 71 % yield. It is not clear why the % recovery of the support was as low as 71 % when separating from the excess of HCl, but this was also the case for similar deprotections (see scheme 5.3.2.2). ^{1}H NMR spectroscopic analysis indicated that the deprotection had gone to completion, as there were no signals corresponding to the protons of the TBS group.



Scheme 5.3.1.4 Deprotection of TBS Group on PEG Support

Deprotected PEG **184** was then reacted with benzyl protected triflate **165** under the standard chain extension conditions (scheme 5.3.1.5). ^{1}H NMR spectroscopic analysis again indicated that there had again been a high degree of chain extension. Following TBA acetate cleavage, two products were isolated by silica column chromatography; trimer **179** and dimer **175**, in a ratio of 7:1. The trimer (**179**) was the major product and was isolated in a yield of 37 %. This indicated a far greater degree of chain extension than was achieved on the PS resin, where the ratio of trimer **179** to dimer **175** was 1:1 for the analogous reactions.



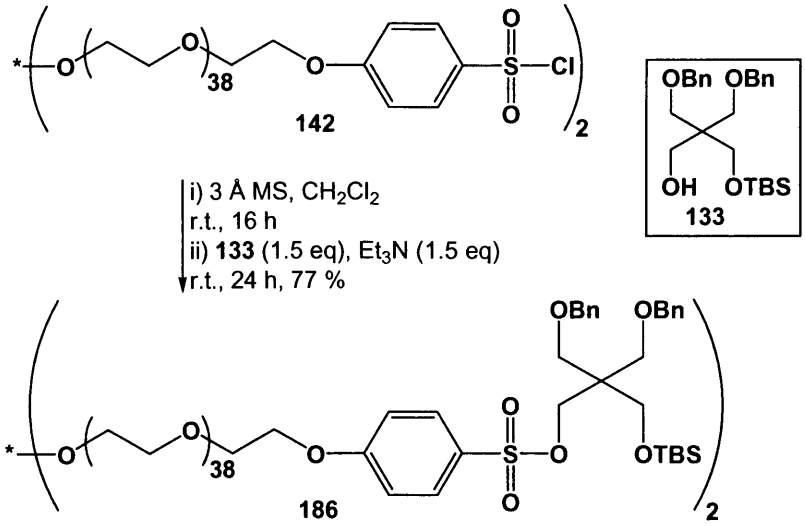
Scheme 5.3.1.5 Second Chain Extension and Cleavage on PEG Support

These results support the hypothesis that the more polar, solution-like environment provided by the PEG support is far more suitable for Williamson's type ether syntheses by stabilising alkoxide formation. As with the previous cleavage reaction it is likely that a much higher yield could be achieved by improving the separation of the PEG support from the cleaved product. Clearly a high degree of chain extension can be achieved on a PEG support using linear monomers, even for the first extension when the active site is closer to the polymer.

5.3.2 Polyether Synthesis with Dibranched Monomers

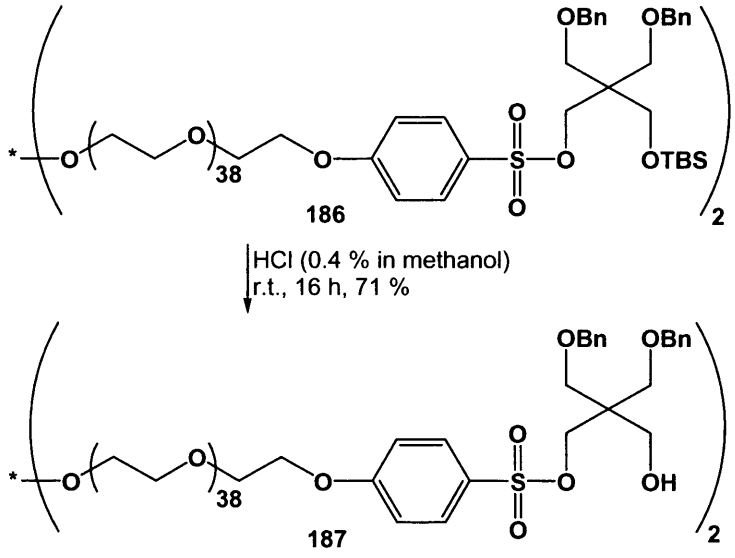
The polyethers formed with linear monomers would be relatively limited in their uses, as there are only two terminal sites for further functionalization after cleavage. In order to synthesise polyethers that could be extensively functionalised, the use of branched monomers with suitably protected pendant hydroxyl groups was envisaged. As a high yielding synthesis of a dibranched monomer (**131**, see chapter 2) had been developed, this monomer was used to test the scope of the iterative polyether synthesis approach.

The first step was to immobilise the monomer with PEG sulfonyl chloride (**142**). From the methods established with the branched diol **130** (chapter 4, scheme 4.3.2) it was likely that the method of loading used for 1,3-propanediol (**114**), with triethylamine as the base (scheme 5.3.1.1), may not be applicable. It had also been established that the use of a stronger base, DMAP, increased the extent of loading, but also caused some bridging between PEG chains. It was therefore decided to load the mono-TBS species (**133**) onto **142** and then deprotect the TBS group, in order to get a uniform first unit product. By pre-drying **142** in dichloromethane with molecular sieves, then reacting it with an excess of **133**, using DMAP as a base (scheme 5.3.2.1), the alcohol was loaded onto the support with a 77 % recovered yield. ^{1}H NMR spectroscopic analysis indicated complete conversion of to the loaded product (**186**), as evidenced by signals corresponding to the protons of the TBS group (δ_H -0.03 and 0.81 ppm) and the benzyl protecting groups (δ_H 7.19-7.29 ppm) and a shift in the position of signals corresponding to the aromatic protons of the linker (δ_H 7.06 and 7.95 to 6.91 and 7.85 ppm). The reaction sometimes also formed a small amount of PEG sulfonic acid through hydrolysis, despite pre-drying, but it was considered that the presence of this by-product should not affect the overall purity of the final cleaved product.



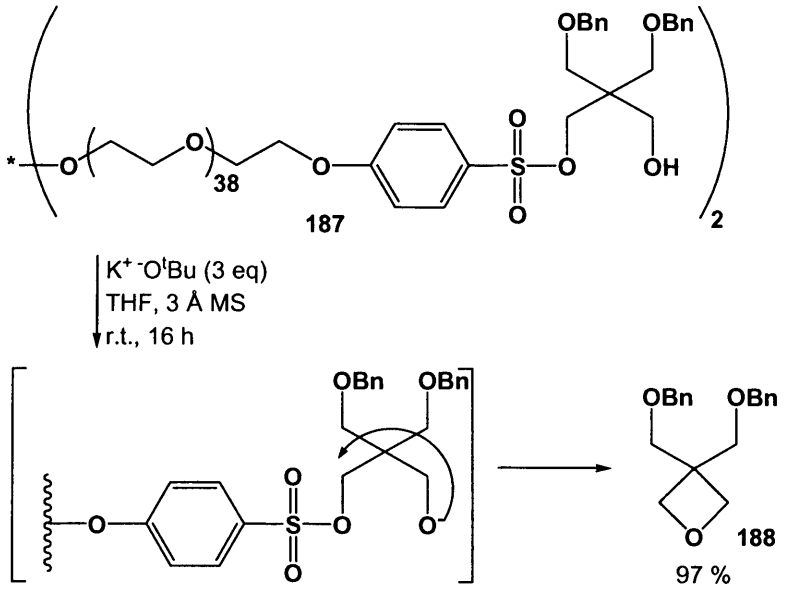
Scheme 5.3.2.1 Loading of Dibranched Monomer (**133**) onto PEG 3400 Sulfonyl Chloride (**142**)

As the TBS protected product was loaded onto the support, an extra deprotection step was required. The TBS group of the loaded PEG (**186**) was deprotected by treatment with a 0.4 % solution of hydrochloric acid in methanol (scheme 5.3.2.2). Following neutralisation with Amberlyst® A21 ion-exchange resin, the deprotected product (**187**) was recovered in a 71 % yield. ^{1}H NMR spectroscopic analysis indicated that the TBS group had been completely removed.



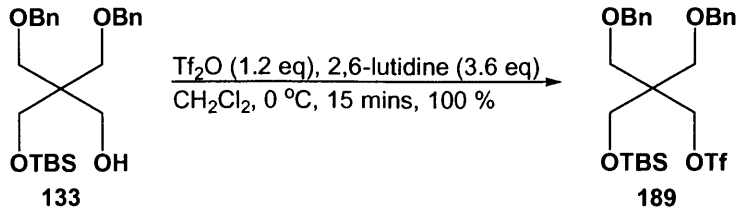
Scheme 5.3.2.2 Deprotection of TBS Group on PEG Support

Due to the steric bulk of the branched O-benzyl groups, it was envisaged that an intramolecular cyclisation/cleavage strategy could be used to cleave the product from the support (see chapter 4, scheme 4.3.3). Using the conditions developed previously, the PEG bound alcohol (**187**) was reacted with potassium *t*-butoxide to give the corresponding oxetane (**188**) in an isolated yield of 97 % (scheme 5.3.2.3). The crude product obtained was quite clean, merely requiring filtration through a short pad of silica in a suitable eluent to give the pure product. The isolated yield of the oxetane product was significantly higher than the previous cyclisation reaction on the PEG support that had given oxetane **157** in a 63 % yield (see chapter 4, scheme 4.3.3). This gives a further indication that the lower yield of **157** was due to a competing bridging reaction during the loading step.



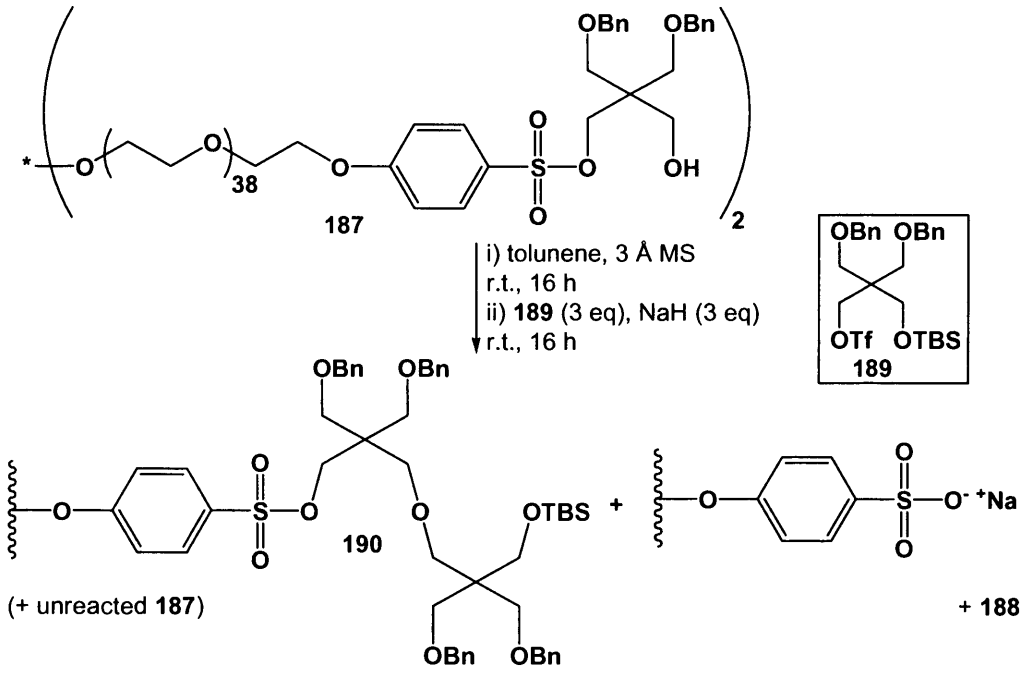
Scheme 5.3.2.3 Cyclisation/Cleavage on PEG Support

Before the synthesis of a polyether with branching at every unit could be achieved, activation of monomer **133** as a triflate ester was required. This was successfully achieved in a quantitative yield by reacting with triflic anhydride and an excess of 2,6-lutidine (scheme 5.3.2.4).



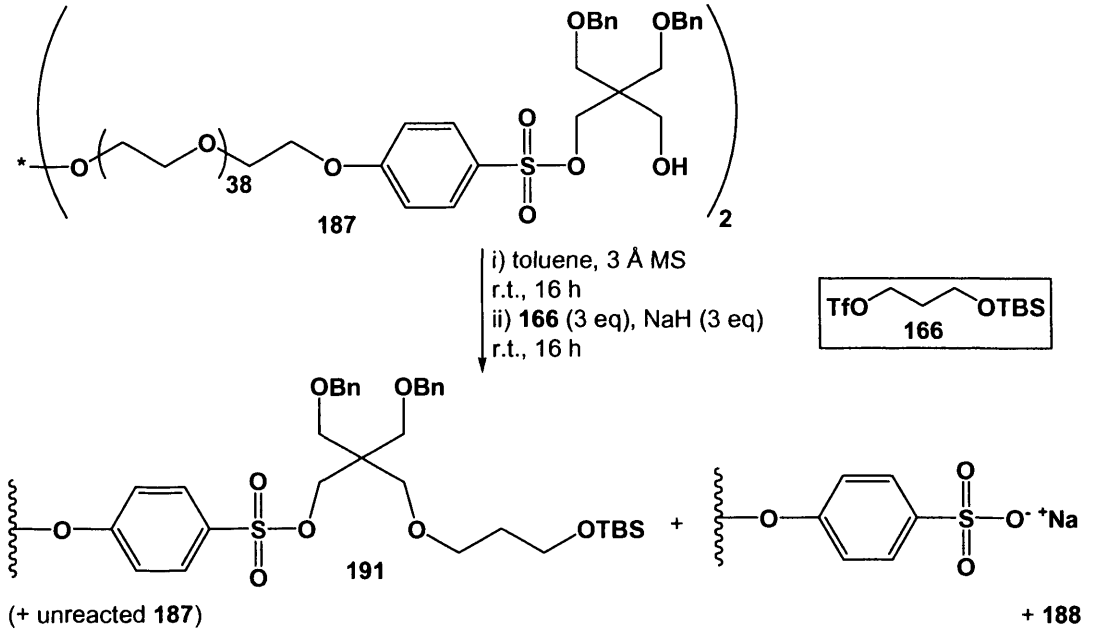
Scheme 5.3.2.4 Triflate Formation on Dibranched Monomer

Initially the PEG bound alcohol (**187**) was reacted with an excess of triflate **189** under the standard conditions (scheme 5.3.2.5). ^{1}H NMR analysis indicated that as well as apparent chain extension, sulfonic acid formation had also occurred (see appendix). This side reaction was presumably due to the greater affinity of the loaded monomer for cyclisation and cleavage from the support. Due to complexity of the ^{1}H NMR spectrum of the recovered PEG, it was also difficult to ascertain the degree of extension. There appeared to be multiple overlapping signals corresponding to the aromatic protons of the sulfonate linker in the spectrum due to incomplete extension, so a direct comparison between the integration of these signals and the signals corresponding to the TBS protecting group would not provide information as to the degree of chain extension.



Scheme 5.3.2.5 Chain Extension of PEG Supported Alcohol (**187**) with Dibranched Triflate (**189**)

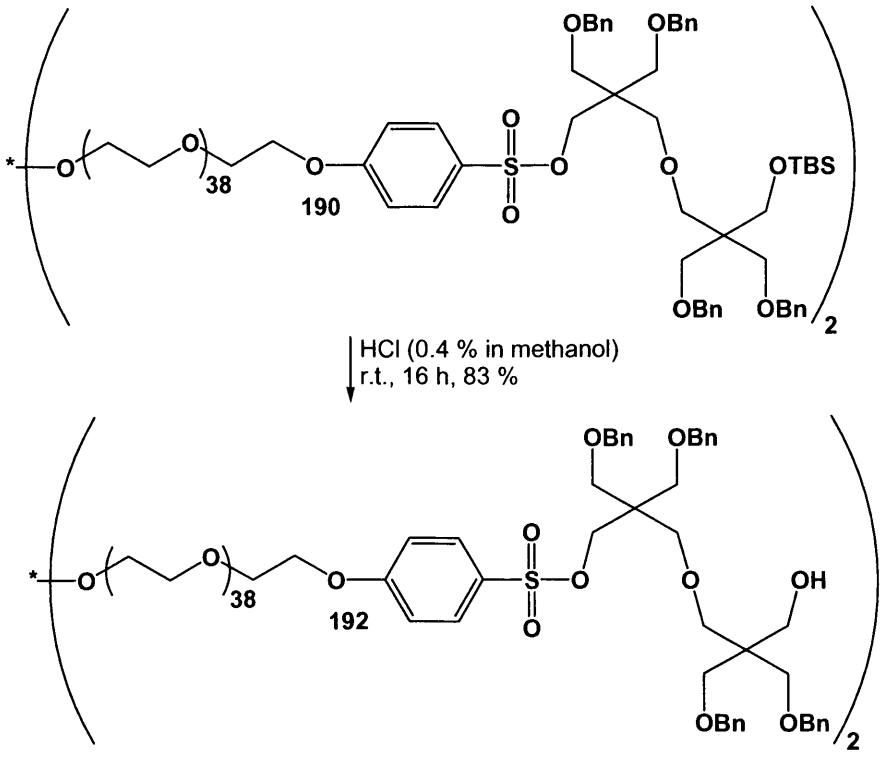
Compound **187** was also reacted with the linear TBS protected triflate (**166**), scheme 5.3.2.6) to establish whether cyclisation can be reduced by using a less hindered triflate. The high degree of sulfonic acid formation in this reaction suggested the steric hindrance of the triflate is not a key factor in the side reaction observed.



Scheme 5.3.2.6 Chain Extension of PEG Supported Alcohol (**187**) with Linear Triflate (**166**)

As using a less hindered triflate seemed to have little effect in avoiding the cyclisation side reaction, it was attempted to overcome the problem by increasing the equivalents of triflate **189** from 3 to 6 in the chain extension reaction with the PEG supported alcohol (**187**). Using this large excess of the triflate, ^{1}H NMR spectroscopic analysis showed far less sulfonic acid formation. Again, due to the increasing complexity of the ^{1}H NMR spectra (see appendix B), cleavage of the products from the support was required to ascertain the degree of extension.

Prior to cyclisation/cleavage, deprotection of the TBS group was required. For ease, the amounts of reagent were calculated as if the PEG bound substrate (**190**) was solely composed of the extended product. Compound (**190**) was treated with 0.4 % HCl in methanol to give the deprotected product (**192**), recovered in an 83 % yield (scheme 5.3.2.7). ^{1}H NMR spectroscopic analysis indicated that the TBS group had been completely removed (see appendix C).

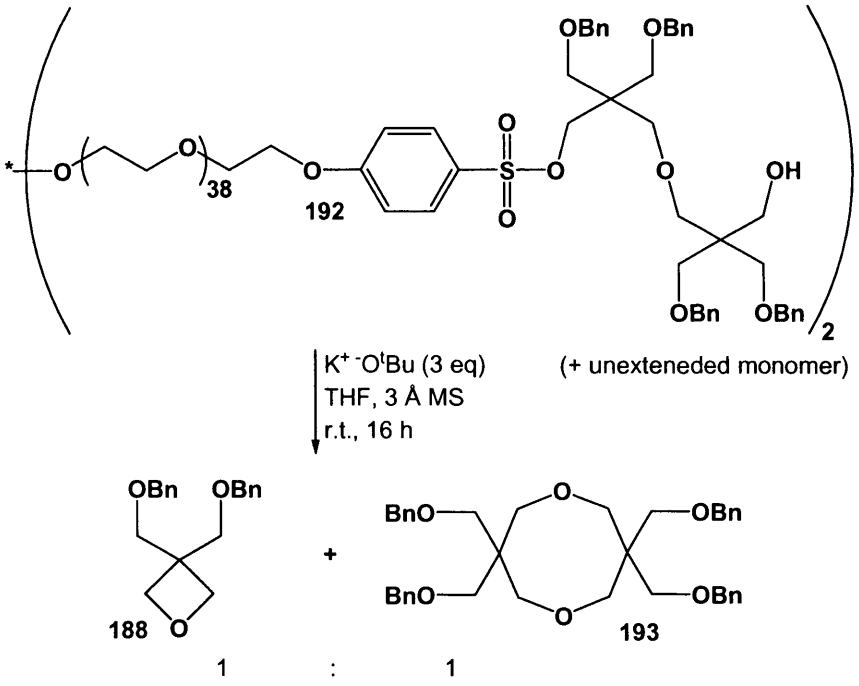


Scheme 5.3.2.7 Deprotection of TBS Group on PEG Support

The cyclisation/cleavage of the product from the deprotected PEG (**192**) was then attempted (scheme 5.3.2.8) using the conditions that had successfully cleaved the monomer. Analysis of the crude product by ^{1}H and ^{13}C NMR spectrometry indicated that the cyclisation had been successful, but it could not be established whether the product was the oxetane (**188**), the cyclic dimer (**193**), or a mixture of them both because both molecules gave rise to very similar NMR signals. Mass spectrometry analysis of the crude product had peaks corresponding to both **188** (321, $[M + Na]^+$, $C_{19}H_{22}O_3$) and **193** (619, $[M + Na]^+$, $C_{38}H_{44}O_6$). To determine the ratio of the products, analysis of the crude mixture obtained from the cyclisation/cleavage of **192** was carried out by reverse phase HPLC.

Using a gradient (100 % water to 100 % acetonitrile over 30 minutes) and UV detection (260 nm), the HPLC trace indicated two main products, the first with a retention time of 19.9 minutes and the second with a retention time of 25.7 minutes with the area under the peaks in a 1:1 ratio. In order to establish which of these peaks was caused by the oxetane monomer (**188**), an HPLC on the pure sample of **188** gave rise to a peak with a retention time of 19.8 minutes. This indicated that the product

with a retention time of 25.7 minutes was the cyclic dimer (**193**). The synthesis of this cyclic dimer demonstrates extension of the methodology developed in chapter 4 for the synthesis of four-membered oxetanes and provides access to a cyclic oligomer with four potential sites for deprotection and further functionalization.



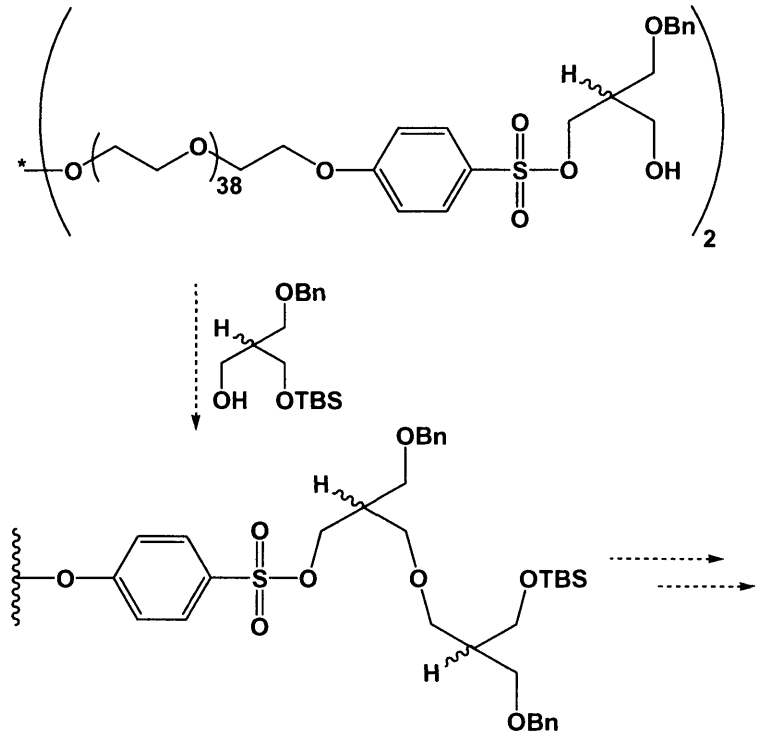
Scheme 5.3.2.8; Cyclisation/Cleavage on PEG Support

5.4 Conclusions and Future Work

A successful reaction between polymer supported alkoxides and triflates to give ethers has been developed. It has been shown that use of an acid labile TBS protecting group allows chain extension using monomers with masked hydroxyls, which can be deprotected "on-resin" allowing iterative ether synthesis. Conversion of PS supported alcohols to ethers was relatively low yielding due to the unfavourable apolar environment of the support. Despite this, using linear monomers, the dimer and the trimer could be formed. Using a PEG support to provide a more polar, solution-like environment, the ether forming step proceeded in a much higher yield for dimer and trimer synthesis, using linear monomers. The first chain extension step on a PEG support using the more hindered dibranched monomer gave less

conversion to the dimer than with linear monomers, although it did provide a novel route to a cyclic oligoether with multiple sites for further functionalization.

As steric hindrance has an effect on the ether forming step, it would be desirable to explore ether synthesis using the singly branched monomer developed in chapter 2. This should provide higher yielding access to oligoethers with masked pendant hydroxyl functionalities (scheme 5.4.1).



Scheme 5.4.1 Chain Extension with Singly Branched Monomers

While the monomers utilised here for oligoether synthesis have all been 1,3-diols, it is very likely that the methodology could be extended to a wide range of diols. It is also likely that further deprotections and chain extensions could afford higher oligomers such as tetramers and pentamers. There is therefore the potential for a wide range of polyethers, both cyclic and acyclic to be formed using this methodology.

Chapter 6

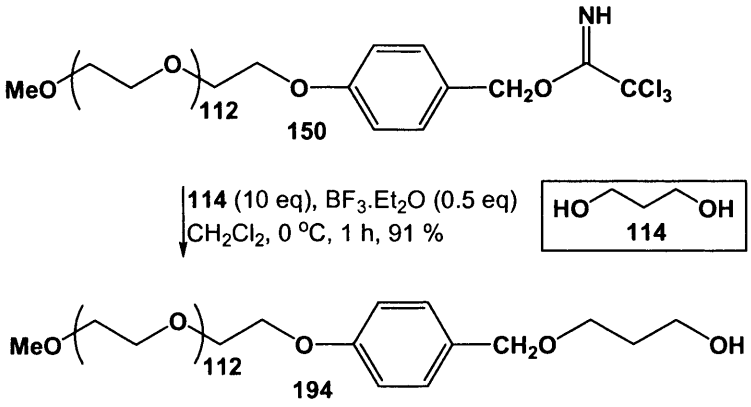
6.0 Reductive Amination

The development of a reductive amination strategy on a PEG support was desired, with a view to forming mixed amine/ether oligomers. Not only would the incorporation of amine linkages give the polymers different properties, but having secondary amines in the structure would also provide a site for branching, as demonstrated by Jönsson *et al.* (chapter 1, scheme 1.3.2.3). [125] There are several examples of iterative polyamine syntheses by reductive amination, on PS supports, in the literature. Reductive amination has also been used as a method of attaching PEG aldehydes to biological systems, through an amine group, conferring the useful properties of PEG chains such as solubility. Studies into reductive alkylation using the novel PEG Wang trichloroacetimidate (**150**) were therefore undertaken.

6.1 Oxidation and Amination on a PEG Support

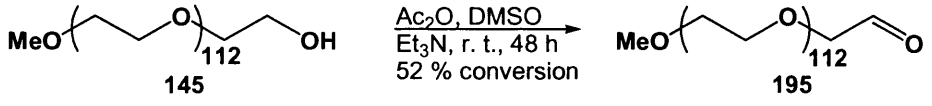
The initial step to investigate the reductive amination strategy was the loading of a suitable monomer onto the polymer support. 1,3-Propanediol was chosen for this purpose, as this would give the possibility of either oxidising to the aldehyde for a reductive amination, or generating an alkoxide and reacting with a triflate to form an ether linkage using the conditions developed previously. The loading of diol onto PS supports using a Wang trichloroacetimidate has previously been reported, using an excess of the diol and borontrifluoride diethyl etherate as a catalyst.[57] Using these conditions, 1,3-propanediol was successfully reacted with PEG Wang trichloroacetimidate (**150**) to give the loaded PEG product (**194**) with 91 % recovery (scheme 6.1.1). ^{1}H NMR of the product suggested full conversion to the loaded product, as evidenced by shifts in the position of the aromatic protons (from δ_H at 6.90 and 7.34 to 6.87 and 7.22 ppm) and disappearance of the signal corresponding to the imine proton (δ_H at 8.35 ppm), as well as the appearance of signals

corresponding to the protons of the loaded diol (δ_H at 1.83 ppm, others masked by the signal for the PEG protons).



Scheme 6.1.1 Loading of 1,3-Propanediol (**114**) with Methoxy PEG 5000 Wang Trichloroacetimidate (**150**)

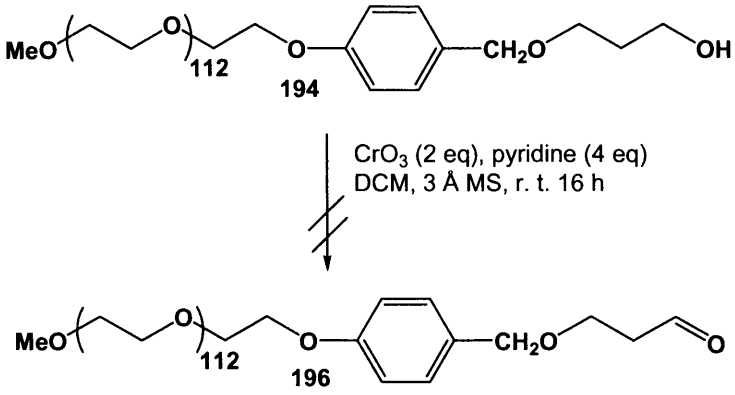
In order to successfully carry out a reductive amination step, controlled oxidation of the free hydroxyl moiety to an aldehyde was required. The more successful of the methods of synthesising PEG aldehydes in the literature have not been through direct oxidation of a terminal hydroxyl group but instead, for example, by addition of a 1,2-diol followed by periodate oxidation or coupling with bromoacetaldehyde diethyl acetal, followed by aldehyde deprotection (for a review see ref. 38).[153] Chamow *et al.* reported the direct oxidation of methoxy PEG 5000 (**145**) by reacting with acetic anhydride, DMSO and triethylamine at room temperature, known as the Moffat procedure (scheme 6.1.2).[154] However, the yield for conversion to the aldehyde (**195**) was reported as only 52 %, which would be unacceptable for a high purity polymer supported synthesis.



Scheme 6.1.2 Oxidation of Methoxy PEG 5000 (**145**) by Chamow *et al.* [154]

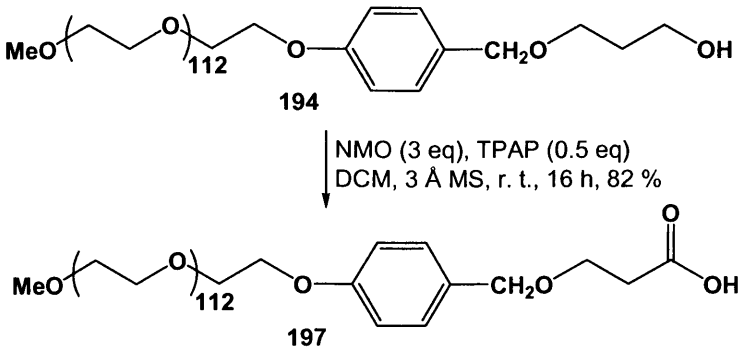
Clearly a higher yielding oxidation to the aldehyde was required. Oxidation of PEG alcohol **194** was attempted by reaction with chromium trioxide and pyridine, over

molecular sieves in an attempt to form the desired PEG aldehyde (**196**, scheme 6.1.2). Following the reaction, recovery of the PEG by the standard recrystallization techniques was problematic and low yielding (50 %), presumably due to complexation between the PEG and the chromium species. ^{1}H NMR spectroscopic analysis of the recovered PEG also indicated that only the starting PEG alcohol (**194**) was recovered. An alternative oxidation method was therefore explored.



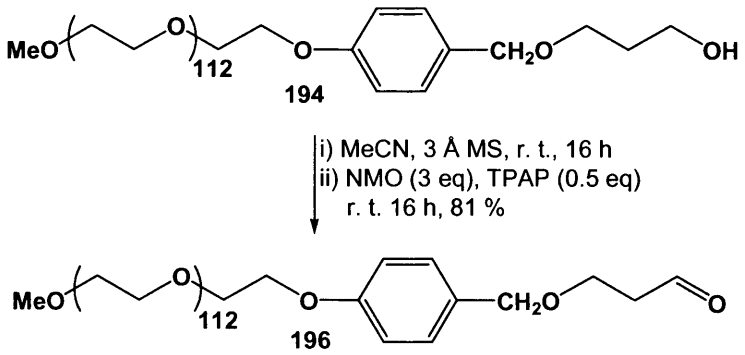
Scheme 6.1.2 Failed Oxidation of PEG bound Alcohol (**194**) with Pyridine-Chromium Complex

More recently, Ley's group have developed a reagent for the mild, selective oxidation of primary alcohols to aldehydes; tetrapropylammonium perruthenate (TPAP).[155] This reagent can be used in catalytic amounts, when used in conjunction with another oxidising agent, such as methylmorpholine *N*-oxide (NMO), to regenerate the catalyst. However, when **194** was reacted with a catalytic amount of TPAP and an excess of NMO, over molecular sieves (scheme 6.1.3), ^{1}H NMR spectroscopic analysis of the product did not indicate that an aldehyde had been formed. There were shifts in the position of the aromatic protons, however, suggesting that the PEG had undergone conversion to an alternative product. It has been reported that in the presence of water, TPAP oxidation can give the corresponding carboxylic acid as the product,[155] so it is possible that the PEG carboxylic acid (**197**) had been formed with 82 % recovery of the product.



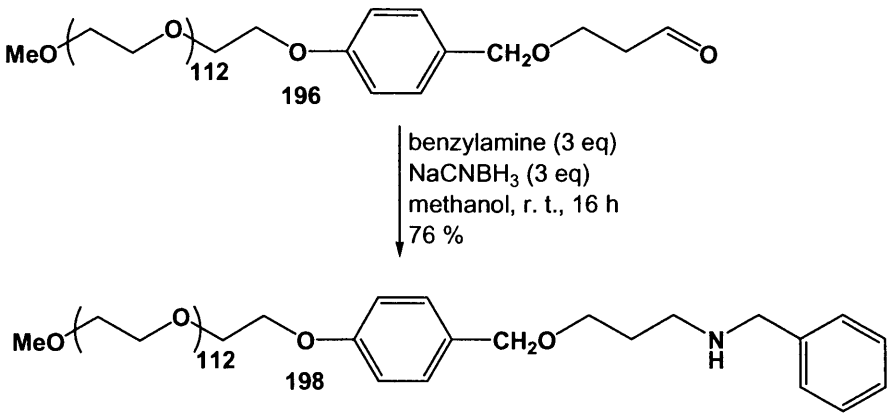
Scheme 6.1.3 Oxidation of PEG Bound Alcohol (**194**) to a Carboxylic Acid (**197**)

The presence of water was most likely to be due to water trapped in the polymer matrix of the PEG during recrystallization. Previously when this problem had arisen, it had been solved by pre-drying the PEG, either by azeotropic removal of water or molecular sieves (see chapters 3 and 5). The reaction was therefore repeated with **194** being stirred over molecular sieves for 16 hours prior to the addition of TPAP and NMO (scheme 6.1.3.4). ^{1}H NMR spectroscopic analysis then suggested that the product was the desired PEG aldehyde (**196**), with a triplet at 9.77 ppm corresponding to the aldehyde proton. ^{1}H NMR analysis also suggested quantitative conversion to **196** as there was a complete shift in the CH_2 protons adjacent to the aldehyde from a quintet at 1.83 ppm to a doublet of triplets at 2.67 ppm. The product was obtained with 81 % recovery. The product (**196**) had a grey colouring, no doubt due to some of the TPAP catalyst being co-precipitated by the PEG chain. As this impurity was not observed in the ^{1}H NMR spectrum of **196**, the amount of TPAP present will be very low (<1 %).



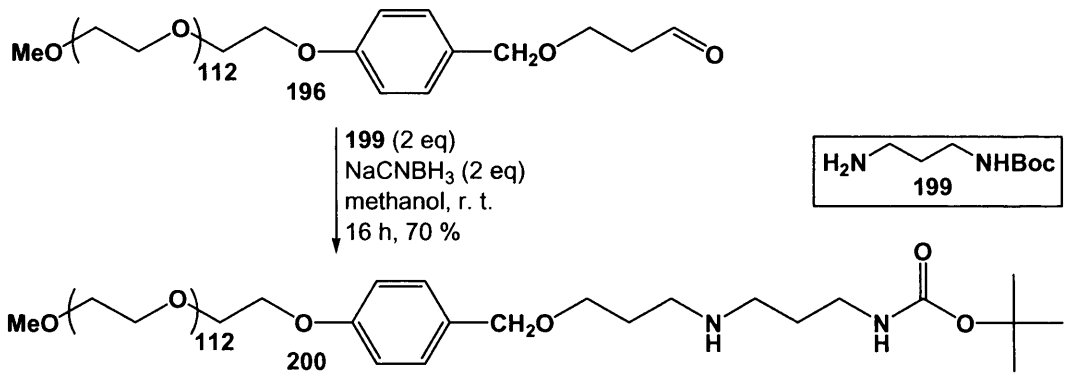
Scheme 6.1.3 Oxidation of PEG Bound Alcohol (**194**) to an Aldehyde (**196**)

With the PEG aldehyde (**196**) in hand, conditions were sought that would effect a reductive amination when reacted with an amine. A commonly used reducing agent for reductive amination on PS supports in the literature is sodium cyanoborohydride, so this reagent was used for the PEG supported reactions. In a simple test reaction, compound **196** was reacted with an excess of benzylamine and sodium cyanoborohydride for 16 hours (scheme 6.1.4). ^{1}H NMR analysis suggested that a reductive amination had successfully been carried out; the signals associated with the aldehyde (δ_H 2.67 and 9.77 ppm) were no longer present and there was now a multiplet at 7.32 ppm that could correspond to the aromatic protons of the benzylamine. It was, however, unclear whether the product consisted exclusively of the aminated product (**198**) as the signals for the aromatic protons of the Wang linker were more complex than would be expected. A side reaction could be the aldehyde being reduced to the alcohol, but the peaks for the aromatic and C*H*$_2$ protons of the Wang linker are not at the same position as when the corresponding alcohol was made previously, so this cannot be the case. It could be a bridged side product, caused by the secondary amine being alkylated by a second molecule of **196** to form a tertiary amine, although this is perhaps unlikely due to the steric bulk of the monoalkylated product and the excess of benzylamine used. It is possible that the more complex than expected NMR signals are caused by conformational effects of the PEG rather than being due to a side product. The product (**198**) had a brown colouring, most likely due to some of the benzylamine being oxidised to the corresponding N-oxide by the trace amount of TPAP impurity.



Scheme 6.1.4 Reductive Amination of PEG Supported Aldehyde (**196**) with Benzylamine

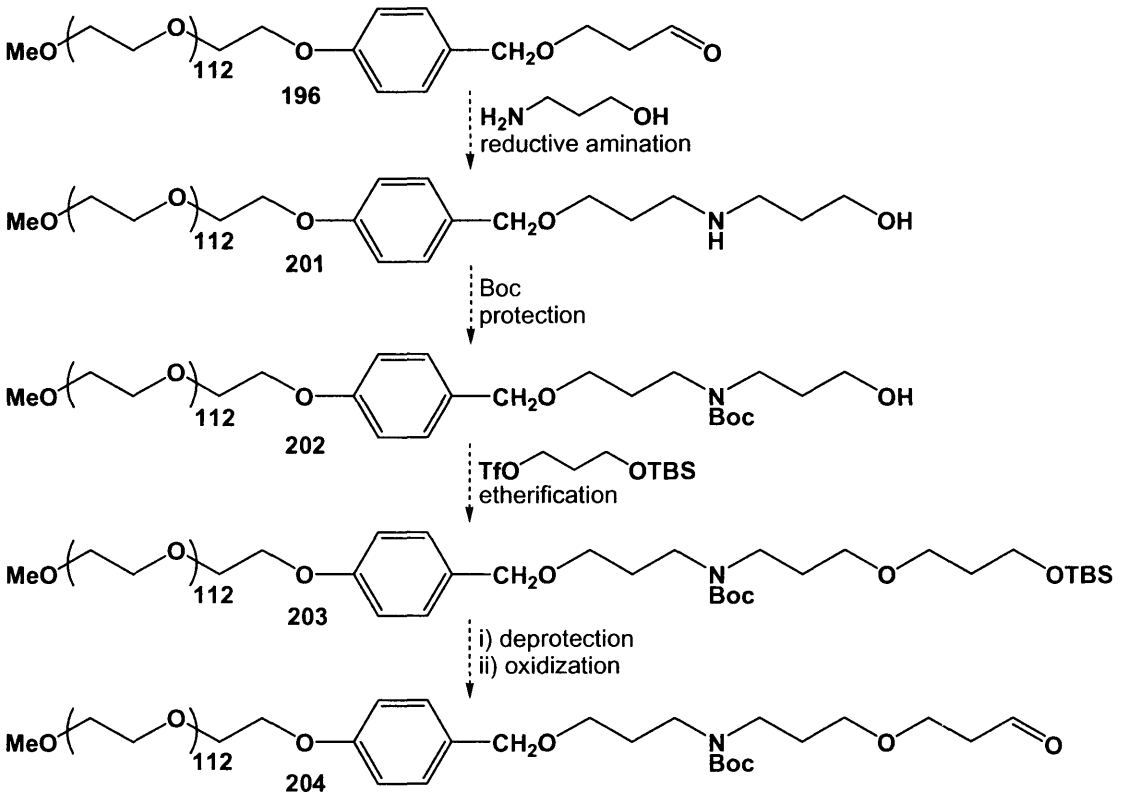
In order to carry out further iterations, reductive amination with difunctional monomers was required. A mono-Boc protected form of 1,3-propanediamine (**199**) [152] was reacted with **196** under the same conditions (scheme 6.1.5). Again, ^{1}H NMR analysis suggested that there was none of the PEG aldehyde species (**196**) present in the product, and a singlet at 1.42, corresponding to the protons of the Boc group, suggested that there had been a successful reductive alkylation. As with the previous reaction, the aromatic protons of the Wang linker gave more complex peaks than would be expected, so there could be a bridged side product. The product (**200**) was isolated with a 70 % recovery. Product **200** had a brown colouring, which is again likely to be due to N-oxide formation by the trace amount of TPAP present.



Scheme 6.1.5 Reductive Amination of PEG Supported Aldehyde (**196**) with Mono-Boc Protected 1,3-Propanediamine (**199**)

6.2 Conclusions and Future Work

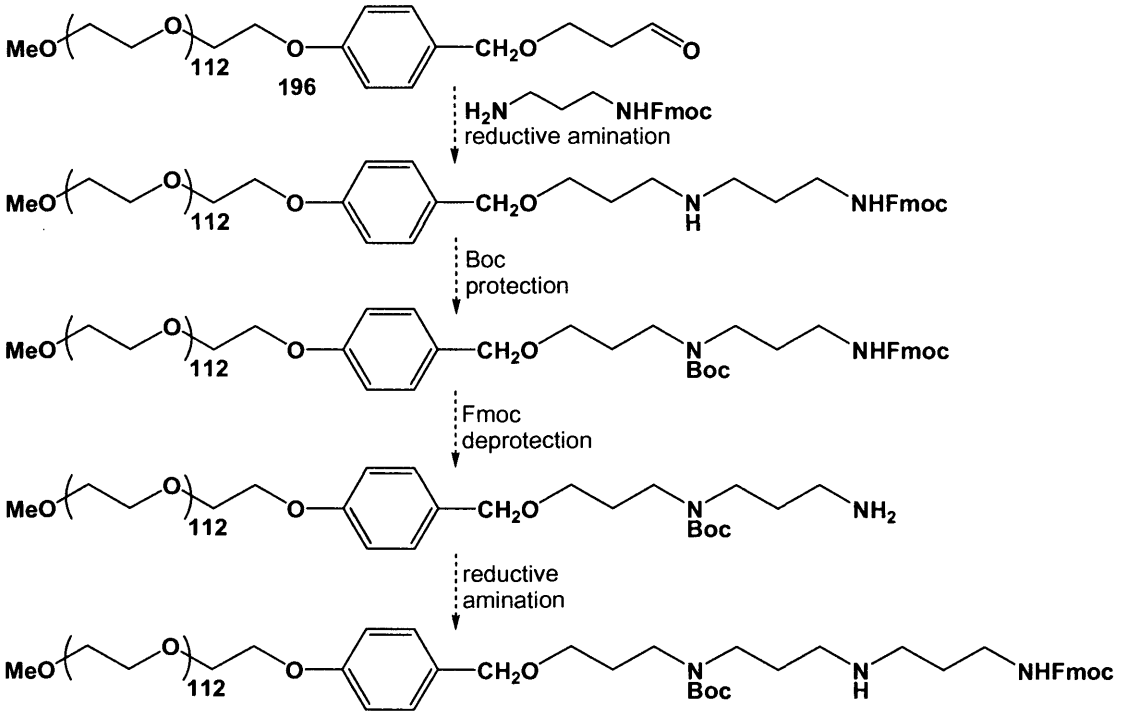
In order to develop a strategy for the synthesis of mixed ether/amine oligomers, reductive amination of **196** with amino alcohols could be envisaged (scheme 6.2.1). This would provide a free hydroxyl group in the dimer (**201**) which, once suitably protected, could be extended using the methodology developed for etherification on a PEG support previously, using a suitable triflate and sodium hydride (see chapter 5). Following deprotection of the hydroxyl protecting group of the trimer (**203**), it could then be subject to either a further etherification, or be oxidised to the aldehyde (**204**) to allow a further reductive amination. A strategy of this nature should allow the synthesis of mixed amine/ether polymers, with direct control over the ratio and position of each type of linkage, giving access to a class of polymers with potentially very interesting structural properties.



Scheme 6.2.1 Synthetic Strategy Towards Mixed Amine/Ether Polymers

Iterative amination strategies to form polyamines should also be possible on a PEG support, using methodologies similar to those which have been successfully utilised

on PS supports. To allow further iterations, a suitable protection strategy would be required, such as Bycroft *et al.*'s reductive alkylation strategy on a PS support, which utilised the relative acid and base labilities of Fmoc and Boc protecting groups (see chapter 1, scheme 1.3.2.2).[121, 122] Such a strategy should allow the synthesis of a linear polyamine, avoiding branching at the secondary amine positions (scheme 6.2.1).



Scheme 6.2.1 Synthetic Strategy Towards Linear Polyamines on PEG

Chapter 7

7.0 General Procedures

Chemicals and ion exchange resins were purchased from the Aldrich Chemical Company Ltd and were used as without further purification. Unless otherwise stated, water refers to the use of deionised water. Solvents were purchased from BDH Ltd., apart from anhydrous dimethylformamide (Aldrich), and were used as received. Anhydrous solvents were HPLC grade and were distilled over potassium hydroxide (pyridine), calcium hydride (dichloromethane), phosphorus pentoxide (acetonitrile), or sodium with benzophenone (THF). All anhydrous reactions were performed under nitrogen. Ether refers to diethyl ether, ethanol refers to absolute ethanol (>99.7 %) and was used as received.

Analytical thin layer chromatography was performed on precoated, aluminium backed plates purchased from BDH. TLC plates were visualised using UV light, phosphomolybdic acid or potassium permanganate. Flash chromatography was performed using silica, purchased from BDH, as a stationary phase. For flash chromatography, reported eluent ratios are given by volume with respect to each solvent.

For all compounds, NMR spectroscopy is the general method for assessing purity, and therefore compounds can be taken as being at 95-98 % pure. The chemical shift (δ) of each peak is given relative to tetramethylsilane (TMS), where $\delta = 0$.

For all PEG supported reactions, % recovery of the product are reported and conversion was indicated as quantitative by ^{1}H NMR spectroscopy unless otherwise stated. For reactions carried out on a difunctional PEG support, moles are calculated from the loading level of the support rather than the molecular weight.

The term *in vacuo* refers to removal of solvents by means of evaporation under reduced pressure, provided by an air pump, using a Buchi® rotary evaporator.

Instrumentation

^{1}H and ^{13}C NMR Spectroscopy: Bruker Avance-500, AMX-400 and AMX-300.

Mass spectrometry: VG-7070 and VG ZAB 2SE.

Infrared Spectroscopy: Shamadazu FTIR-8700

HPLC: Varian 410.

Melting Points: Gallenkamp.

Chemical grades (Aldrich)

Acetic acid, glacial, 99.99+ %

Benzaldehyde, redistilled, 99.5+ %

Benzaldehyde dimethyl acetal, 99 %

tert-Butyldimethylsilyl Chloride, 97 %

Cyclohexanone, 99.8 %

4-(Dimethylamino)pyridine, 99+ %

N,N-Dimethylformamide, anhydrous, 99.8 %

Formaldehyde, 37 wt. % solution in water

Hydrochloric acid, 37 wt. % in water

4-Hydroxybenzenesulfonic acid, sodium salt dehydrate, 98 %

Lithium aluminium hydride, powder, 95 %

Lithium bromide, 99+ %

2,6-Lutidine, redistilled, 99+ %

Magnesium sulfate, 97+ %

4-Methylmorpholine *N*-oxide, 97 %

Pentaerythritol, 98 %

Potassium *tert*-butoxide, 95 %

1,3-Propanediol, 99.6+ %

Sodium borohydride, powder, 98 %

Sodium hydride, 60 % in mineral oil

Sodium hydrogencarbonate, 99 %

Sodium hydroxide, 98 %

Sulfuric acid, 95-98 %

Tetrabutylammonium acetate, 97 %

Tetrabutylammonium hydroxide, 1.0 M solution in methanol

Thionyl chloride, 99+ %

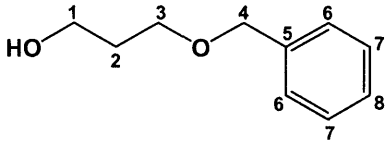
p-Toluenesulfonic acid monohydrate, 98+ %

p-Toluenesulfonyl chloride, 98 %

Triethyl methanetricarboxylate, 98 %

7.1 Monomer Synthesis

3-Benzyloxy propan-1-ol (117) [157]



To a solution of 1,3-propanediol (**114**) (8.45 mL, 117 mmol) in anhydrous THF (100 mL) was added, with caution, sodium hydride (60 % in mineral oil, 1.22 g, 30.5 mmol), and benzyl bromide (3.48 mL, 29.1 mmol). The reaction mixture was stirred at reflux for 16 hours, and then cooled to 5 °C in an ice bath. Methanol (5 mL), was cautiously added (1 mL min^{-1}), followed by water (100 mL). The solution was extracted with ethyl acetate (100 mL), and the organic extracts were washed with water (2 x 100 mL), dried over magnesium sulfate, filtered, and the solvent was removed *in vacuo*. Flash chromatography of the crude product (3:1, hexane/ethyl acetate) afforded the title compound as a clear oil (3.92 g, 23.6 mmol, 81 %). (Lit. 92 % yield, methodology uses TBAI as a catalyst.)

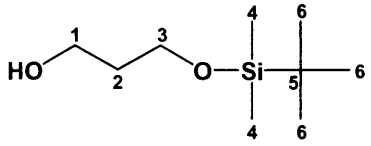
ν_{max} (KBr)/cm^{-1} 3406 (br), 2868 (m), 1719 (w), 1452 (m), 1074 (s)

δ_H (300 MHz; $CDCl_3$) 1.78 (2H, quin, *J* 5.8 Hz, H-2), 2.12 (1H, s, CH_2OH), 3.58 (2H, t, *J* 5.8 Hz, H-1/H-3), 3.69 (2H, t, *J* 5.8 Hz, H-1/H-3), 7.19-7.29 (5H, m, Ph)

δ_C (75 MHz; $CDCl_3$) 32.1 (C-2), 61.8, 69.3, 73.2 (C-4), 127.6 (Ph), 127.7 (Ph), 128.4 (Ph), 138.0 (C-5)

m/z (ES+) 189 ($[M + Na]^+$, $C_{10}H_{14}O_2$, 100 %),167 (20 %)

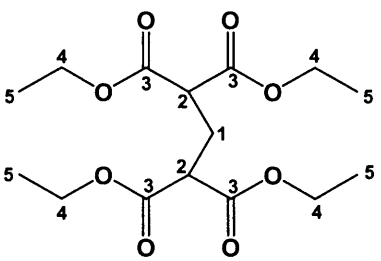
3-(*tert*-Butyl-dimethyl-silanyloxy)-propan-1-ol (118) [158]



To a solution of 1,3-propanediol (**114**, 8.00 mL, 111 mmol), in dichloromethane (50 mL), was added TBS chloride (6.04 g, 443 mmol), followed by careful addition of triethylamine (11.2 mL, 886 mmol, 1 mL min^{-1}). The reaction mixture was stirred at room temperature for 16 hours, and then washed with water (3 x 50 mL). The organic layer was separated and dried over magnesium sulfate, filtered, and the solvent was removed *in vacuo*. Flash chromatography of the crude product (3:1, hexane/ethyl acetate) afforded the title compound as a clear oil (7.00 g, 815 mmol, 92 %). (Lit. 90 % yield, alternative methodology using sodium hydride as the base.)

ν_{max} (KBr)/cm^{-1} 3337 (br), 2957 (s), 1472 (m), 1257 (s), 1097 (s)
δ_H (300 MHz; $CDCl_3$) 0.03 (6H, s, H-4), 0.89 (9H, s, H-6), 1.77 (2H, quin, *J* 5.6 Hz, H-2), 2.16 (1H, s, CH_2OH), 3.79 (2H, t, *J* 5.6 Hz, H-1/H-3), 3.82 (2H, t, *J* 5.6 Hz, H-1/H-3)
δ_C (75 MHz; $CDCl_3$) -5.5 (C-4), 18.2 (C-5), 25.6 (C-6), 34.1 (C-2), 62.5, 63.0
m/z (CI+) 191 ($[M + H]^+$, $C_9H_{22}O_2Si$, 100 %)

2-(2,2-Bis-ethoxycarbonyl-ethyl)-malonic acid diethyl ester (120) [129]

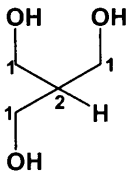


To a solution of diethyl malonate (**119**) (1.00 mL, 6.59 mmol) in THF (10 mL) and water (1 mL) was added formaldehyde (0.12 mL, 1.7 mmol) and sodium hydroxide (65.9 mg, 1.65 mmol) and the reaction mixture was stirred at room temperature for 16 hours. Water (10 mL) was added and the solution was extracted with diethyl ether

(3 x 20 mL). The combined organic extracts were dried over magnesium sulfate, filtered, and the solvent was removed *in vacuo*. Flash chromatography of the crude product (19:1 then 3:1, hexane/ethyl acetate) afforded the title compound as clear oil (120. mg, 4.00 x 10^{-1} mmol, 25 %). (Lit. does not include full experimental details).

δ_H (300 MHz; $CDCl_3$) 1.25 (12H, t, *J* 7.1 Hz, H-5), 2.44 (2H, t, *J* 7.6 Hz, H-1), 3.44 (2H, t, *J* 7.6 Hz, H-2), 4.18 (8H, q, *J* 7.1 Hz, H-4)
δ_C (75 MHz; $CDCl_3$) 14.0 (C-5), 27.3 (C-1), 49.4 (C-2), 61.6 (C-4), 168.6 (C-3)

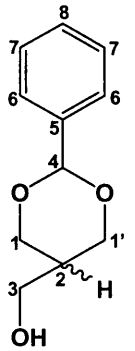
2-Hydroxymethyl-propane-1,3-diol (115) - Literature Procedure Used Unmodified [130]



Compound **115** was synthesised according to a procedure published by Harnden.[130] Yield 53 %, Lit. yield 83 %. All spectroscopic data is in full agreement with the published data. Compound **115** is commercially available from Aldrich Ltd).

δ_H (300 MHz; D_2O) 1.76 (1H, sept, *J* 6.0 Hz, H-2), 3.52 (6H, d, *J* 6.0 Hz, H-1)

2-Phenyl-[1,3]dioxan-5-yl)-methanol (124) [132]

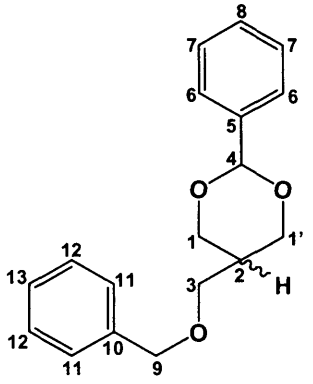


To a solution of **115** (80 mg, 0.75 mmol) in THF (5 mL) was added benzaldehyde dimethyl acetal (0.14 mL, 0.90 mmol) and *p*-toluenesulfonic acid, and the reaction

mixture was stirred, at room temperature, for 16 hours. Water (10 mL) was added and the solution was extracted with diethyl ether (3 x 10 mL). The combined organic extracts were washed with saturated sodium hydrogen carbonate (3 x 10 mL), dried over magnesium sulfate, filtered, and the solvent was removed *in vacuo*. Flash chromatography of the crude product (1:0, then 39:1, chloroform/ methanol) afforded the title compound as a pair of stereoisomers that were colourless solids (142 mg, 7.30 x 10^{-1} mmol, 97 %). (Lit. gives alternative synthesis of **124**).

ν_{max} (KBr)/cm^{-1} 3308 (br), 2837 (s), 1462 (s), 1389 (s), 1096 (m)
δ_H (300 MHz; $CDCl_3$) 1.60 (1H, m), 2.19 (1H, s), 2.30 (1H, sept, *J* 6.1 Hz), 2.53 (1H, s), 3.36 (2H, d, *J* 6.1 Hz), 3.66 (2H, t, *J* 11.4 Hz), 3.97 (2H, d, *J* 7.5 Hz), 4.06-4.28 (6H, m), 5.39 (1H, s), 5.50 (1H, s), 7.31-7.61 (10H m)
δ_C (75 MHz; $CDCl_3$) 36.4, 36.8, 60.8, 61.4, 67.7, 69.6, 101.4, 101.8, 125.9, 126.0, 128.2, 128.9, 128.9, 138.1, 138.3
m/z (ES+) 217 ($[M + Na]^+$, $C_{11}H_{14}O_3$, 100 %), 195 ($[M + H]^+$, 20 %)

5-Benzyloxymethyl-2-phenyl-[1,3]dioxane (126)

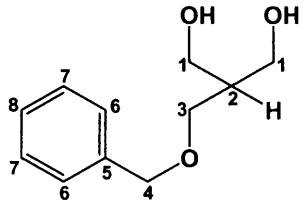


To a solution of **124** (820. mg, 4.22 mmol) in anhydrous THF (10 mL) was added benzyl bromide (0.60 mL, 5.1 mmol) and sodium hydride (203 mg, 60 % in mineral oil, 5.07 mmol), and the reaction mixture was stirred, at reflux, for 16 hours. The reaction mixture was allowed to cool to room temperature, followed by cautious addition of methanol (5 mL, 1 mL min^{-1}), then water (10 mL). The solution was extracted with ethyl acetate (3 x 10 mL), the combined organic extracts were dried over magnesium sulfate, filtered, and the solvent was removed *in vacuo*. Flash

chromatography of the crude product (19:1, ethyl acetate/ hexane) afforded the title compound as a pair of stereoisomers that were colourless solids (1.18 g, 4.14 mmol, 98 %), m.p. 40-42 °C.

ν_{max} (KBr)/cm^{-1} 2855 (w), 1454 (m), 1385 (m), 1099 (s), 746 (s)
δ_H (300 MHz; $CDCl_3$) 1.57 (1H, m), 2.54 (1H, sept, *J* 5.9 Hz), 3.32 (2H, dd, *J* 3.4 Hz and 5.9 Hz), 3.76 (2H, t, *J* 10.9 Hz), 3.90 (2H, dd, *J* 3.4 Hz, and 7.5 Hz), 4.17 (2H, d, *J* 11.7 Hz), 4.24-4.32 (4H, m), 4.48 (2H, s), 4.58 (2H, s), 5.43 (1H, s), 5.51 (1H, s), 7.30-7.49 (20H, m)
δ_C (75 MHz; $CDCl_3$) 34.9, 35.0, 68.1, 68.3, 69.3, 69.9, 73.2, 73.4, 101.5, 101.9, 126.0, 126.0, 127.5, 127.7, 128.3, 128.4, 128.4, 128.9
m/z (ES+) 307 ([*M* + Na]$^+$, $C_{18}H_{20}O_3$, 100 %), 285 ([*M* + H]$^+$, 10 %)
HRMS (ES+) $C_{18}H_{20}O_3$ [*M* + Na]$^+$ requires 307.13047, found 307.13053

2-Benzyloxymethyl-propane-diol (125) [159]



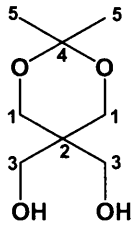
A solution of **126** (100. mg, 3.50 x 10^{-1} mmol) in acetic acid (80 % solution in water by volume, 3 mL) was stirred, at room temperature, for 16 hours. Acetic acid was removed *in vacuo*, and the crude residue was dissolved in ethyl acetate (10 mL). The solution was washed with saturated sodium hydrogen carbonate solution (3 x 10 mL), dried over magnesium sulfate, filtered, and the solvent was removed *in vacuo*. Flash chromatography of the crude product (1:9, hexane/ ethyl acetate) afforded the title compound as a white solid (58. mg, 3.0 x 10^{-1} mmol, 84 %). (Lit. reports alternative synthesis of **125**).

ν_{max} (KBr)/cm^{-1} 3364 (br), 2881 (m), 1703 (m), 1278 (m), 1028 (m)
δ_H (300 MHz; $CDCl_3$) 2.03 (1H, sept, *J* 5.6 Hz, H-2), 2.30 (2H, s, O*H*), 3.62 (2H, d, *J* 5.6 Hz, H-3), 3.80 (4H, d, *J* 5.6 Hz, H-1), 4.51 (2H, s, H-4), 7.26-7.37 (5H, m, Ph)

δ_C (75 MHz; $CDCl_3$) 42.8 (C-2), 63.3 (C-1), 70.5 (C-3), 73.5 (C-4), 127.6 (Ph), 127.8 (Ph), 128.5 (Ph), 137.8 (C-5)

m/z (ES+) 219 ($[M + Na]^+$, $C_{11}H_{16}O_3$, 100 %)

(5-Hydroxymethyl-2,2-dimethyl-[1,3] dioxin-5-yl)-methanol (127) – Literature Procedure Used Unmodified [136]



Compound **127** was synthesised according to a procedure published by Bladen and Owen. [136] Yield 12 %, Lit. yield 25 %. All spectroscopic data is in full agreement with the published data.

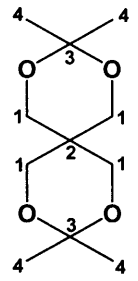
ν_{max} (KBr)/cm^{-1} 3261 (br), 2993 (s), 2876 (s), 1458 (m), 1369 (s)

δ_H (300 MHz; $CDCl_3$) 1.41 (6H, s, H-5), 2.46 (2H, s, CH_2OH), 3.72 (4H, s, H-1), 3.74 (4H, s, H-3)

δ_C (75 MHz; $CDCl_3$) 23.7 (C-5), 39.0 (C-2), 62.7 (C-3), 65.0 (C-1), 98.6 (C-4)

m/z (CI+) 177 ($[M + H]^+$, $C_8H_{16}O_4$, 20 %), 161 (100 %)

3,3,9,9-Tetramethyl-2,4,8,10-tetraoxa-spiro [5.5] undecane (128) [136]

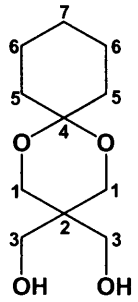


To **116** (3.40 g, 25.0 mmol), partially dissolved in anhydrous DMF (15 mL), was added 2,2-dimethoxypropane (2.70 mL, 25.0 mmol) and *p*-toluenesulfonic acid (60. mg, 0.25 mmol). The mixture was stirred at room temperature for 16 hours, and then

unreacted pentaerythritol was removed by filtration. The reaction mixture was washed with a saturated solution of sodium hydrogencarbonte (3 x 20 mL), dried over magnesium sulfate, filtered, and DMF was removed *in vacuo*. Recrystallization of the crude product from diethyl ether afforded the title compound as a colourless solid (1.05 g, 4.85 mmol, 20 %). (Lit. reports an alternative synthesis of **128**).

ν_{max} (KBr)/cm^{-1} 2868 (s), 1454 (m), 1373 (s), 1028 (m), 837 (s)
δ_H (300 MHz; $CDCl_3$) 1.38 (12H, s, H-4), 3.71 (8H, s, H-1)
δ_C (75 MHz; $CDCl_3$) 23.6 (C-4), 32.7 (C-2), 64.1 (C-1), 98.6 (C-3)
m/z (CI+) 217 ([*M* + H]$^+$, $C_{11}H_{20}O_4$, 40 %), 201 (95 %), 143 (100 %)

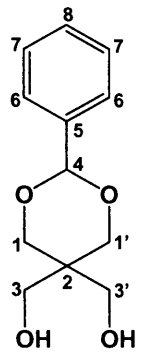
(3-Hydroxymethyl-1,5-dioxan-spiro [5.5] undec-3-yl)-methanol (129) – Literature Procedure Used Unmodified [137]



Compound **129** was synthesised according to a procedure published by Murguia *et al.* [137] Yield 66 %, Lit. yield 92 %. All spectroscopic data is in full agreement with the published data.

ν_{max} (KBr)/cm^{-1} 3279 (br), 2922 (m), 1146 (w), 1107 (w), 1038 (m)
δ_H (300 MHz; $CDCl_3$) 1.47-1.53 (6H, m, H-7 and H-6), 1.73 (4H, m, H-5), 2.04 (2H, s, CH_2OH), 3.73 (4H, s), 3.75 (4H, s)
δ_C (75 MHz; $CDCl_3$) 22.5, 25.6, 32.5, 39.2 (C-2), 61.9 (C-3), 65.2 (C-1), 98.6 (C-4)
m/z (CI+) 217 ([*M* + H]$^+$, $C_{11}H_{20}O_4$, 100 %)

(5-Hydroxymethyl-2-phenyl-[1,3]dioxin-5-yl)-methanol (130) – Literature Procedure Used Unmodified [138]



Compound **130** was synthesised according to a procedure published by Issidorides *et al.* [138] Yield 68 %, Lit. yield 77 %. All spectroscopic data is in full agreement with the published data.

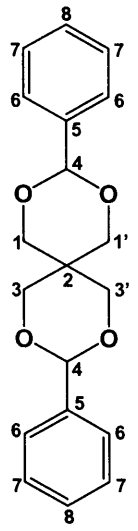
ν_{max} (KBr)/cm^{-1} 3269 (br), 2963 (s), 1387 (s), 1038 (s), 762 (s)

δ_H (300 MHz; $CDCl_3$) 2.05 (2H, s, CH_2OH), 3.54 (2H, s), 3.76 (2H, d, *J* 12.0 Hz), 4.13 (2H, s), 4.16 (2H, d, *J* 12.0 Hz), 5.43 (1H, s, H-4), 7.33-7.39 (3H, m, Ph), 7.43-7.48 (2H, m, Ph)

δ_C (75 MHz; $CDCl_3$) 38.9 (C-2), 64.3, 65.7, 70.0 (C-1 and C-1'), 102.1 (C-4), 126.0 (Ph), 128.3 (Ph), 129.1 (Ph), 138.0 (C-5)

m/z (ES+) 247 ($[M + Na]^+$, $C_{12}H_{16}O_4$, 100 %)

3,9-Biphenyl-2,4,8,10-tetraoxa-spiro [5.5] undecane (132) [131]



To **116** (7.35 g, 54.0 mmol), partially dissolved in THF (200 mL), was added benzaldehyde dimethyl acetal (13.5 mL, 97.2 mmol), and *p*-toluenesulfonic acid (760. mg, 4.00 mmol), and the reaction mixture was stirred at room temperature for 40 hours. Amberlyst® A21 ion-exchange resin (1 g) was added, and the reaction mixture was stirred for a further hour. Unreacted pentaerythritol and the ion-exchange resin were removed by filtration, and the solvent was removed *in vacuo* to afford the title compound as a colourless solid (13.0 g, 41.5 mmol, 96 %). (Lit. does not give experimental procedure). The compound was not further purified, and was used as isolated in the next step.

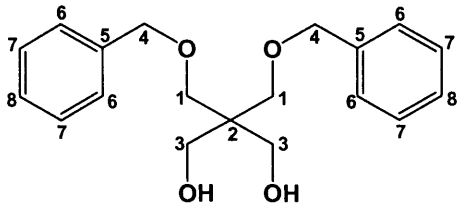
ν_{max} (KBr)/cm^{-1} 3037 (s), 2856 (s), 1387 (s), 1078 (s), 748 (s)

δ_H (300 MHz; $CDCl_3$) 3.59 (2H, d, *J* 11.0 Hz), 3.82-3.88 (4H, m), 4.89 (2H, d, *J* 11.0 Hz), 5.47 (2H, s, H-5), 7.36-7.43 (6H, m, Ph), 7.49-7.52 (4H, m, Ph)

δ_C (75 MHz; $CDCl_3$) 32.5 (C-2), 70.6, 71.1, 102.3 (C-4), 126.1 (Ph), 128.3 (Ph), 129.1 (Ph), 138.0 (C-5)

m/z (CI+) 313 ([*M* + H]$^+$, $C_{15}H_{22}O_6S$, 90 %)

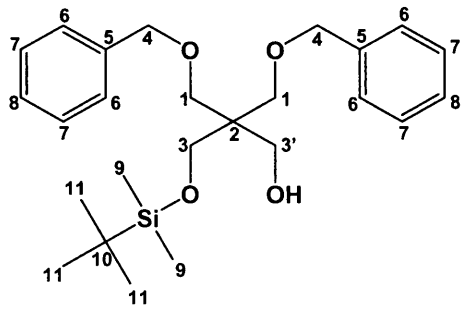
2,2-Bis-benzyloxymethyl-propane-1,3-diol (131) – Literature Procedure Used Unmodified [131]



Compound **131** was synthesised according to a procedure published by Abdun-Nur *et al.* [131] Yield 91 %, Lit. yield 82 %. All spectroscopic data is in full agreement with the published data.

ν_{max} (KBr)/cm^{-1} 3300 (br), 2856 (m), 1454 (m), 1119 (s), 733 (s)
δ_H (300 MHz; $CDCl_3$) 2.50 (2H, t, *J* 6.2 Hz, CH_2OH), 3.56 (4H, s, H-1), 3.69 (4H, d, *J* 6.2 Hz, H-3), 4.49 (4H, s, H-4), 7.27-7.37 (10H, m, Ph)
δ_C (75 MHz; $CDCl_3$) 45.0 (C-2), 65.1 (C-3), 72.0 (C-1), 73.8 (C-4), 127.6 (Ph), 127.8 (Ph), 128.5 (Ph), 137.9 (C-5)
m/z (ES+) 339 ([*M* + Na]$^+$, $C_{19}H_{24}O_4$, 100 %)

3-Benzyloxy-2-benzyloxymethyl-2-(*tert*-butyl-dimethyl-silanyloxymethyl)-propan-1-ol (133)



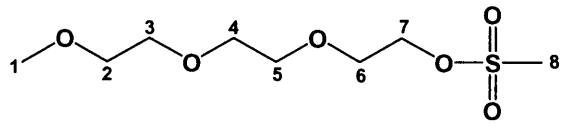
To a solution of **131** (2.46 g, 7.87 mmol) in dichloromethane (75 mL), was added TBS chloride (1.19 g, 7.87 mmol), and triethylamine (1.25 mL, 9.44 mmol), and the reaction mixture was stirred at room temperature for 16 h. A further portions of TBS chloride (574 mg, 3.94 mmol), and triethylamine (0.52 mL, 3.9 mmol) were added, and the reaction mixture was stirred at reflux for 16 hours. The reaction was allowed

to cool to room temperature, and was then washed with water (3 x 75 mL), dried over magnesium sulfate, filtered, and the solvent was removed *in vacuo*. Flash chromatography of the crude product (3:1, hexane/ethyl acetate) afforded the title compound as a clear oil (3.29 g, 7.71 mmol, 98 %).

ν_{max} (KBr)/cm^{-1} 3450 (br), 2856 (s), 2341 (m), 1454 (m), 1092 (s)
δ_H (300 MHz; $CDCl_3$) 0.03 (6H, s, H-9), 0.87 (9H, s, H-11), 2.87 (1H, t, *J* 6.1 Hz, CH_2OH), 3.49 (4H, s, H-1), 3.68 (2H, s, H-3), 3.74 (2H, d, *J* 6.1 Hz, H-3'), 4.48 (4H, s, H-4), 7.26-7.34 (10H, m, Ph)
δ_C (75 MHz; $CDCl_3$) -5.7 (C-9), 18.2 (C-10), 25.8 (C-11), 45.5 (C-2), 63.6, 66.3, 70.7 (C-1), 73.6 (C-4), 127.5, 127.5, 128.3, 138.4
m/z (ES+) 453 ($[M + Na]^+$, $C_{25}H_{38}O_4Si$, 100 %), 431 (10 %)
HRMS (CI+) $C_{25}H_{38}O_4Si$ $[M + H]^+$ requires 431.26175, found 431.26107

7.2 Linker Synthesis on PEG

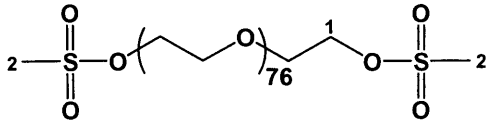
Methanesulfonic acid 2-[2-(2-methoxy-ethoxy)-ethoxy]-ethyl ester (135) [160] – Literature Procedure Was Used Unmodified



Compound **135** was synthesised according to a procedure published by Schmidt *et al.* [160] Yield 98 %, Lit. yield 78 %. All spectroscopic data is in full agreement with the published data.

δ_H (300 MHz; $CDCl_3$) 2.98 (3H, s, H-8), 3.29 (3H, s, H-1), 3.46 (2H, m, PEG CH_2), 3.54-3.60 (6H, m, PEG CH_2), 3.69 (2H, m, PEG CH_2), 4.30 (2H, m, H-7)
δ_C (75 MHz; $CDCl_3$) 37.5 (C-8), 53.3 (C-1), 58.7 (C-7), 68.8 (PEG CH_2), 69.2 (PEG CH_2), 70.3 (PEG CH_2), 70.3 (PEG CH_2), 70.4 (PEG CH_2), 71.7 (PEG CH_2)
m/z (ES+) 265 ($[M + Na]^+$, $C_8H_{18}O_6S$, 100 %)

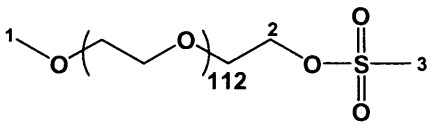
PEG 3400 Mesylate (139)



To a solution of PEG 3400 (**138**) (10.0 g, 5.88 mmol) in dichloromethane (20 mL), was added methanesulfonyl chloride (0.91 mL, 12. mmol), followed by cautious addition of triethylamine (1.39 mL, 11.8 mmol, 1 mL min^{-1}). The reaction mixture was stirred at room temperature for 16 hours. The solvent was removed *in vacuo*, and the crude product was dissolved in hot propan-2-ol (50 mL). The solution was cooled to 5 °C, and the precipitate was collected by filtration, washed with propan-2-ol (10 mL), and diethyl ether (50 mL), and dried *in vacuo*, affording the title compound as a white solid (10.4 g, 5.84 mmol, 99 %).

δ_H (300 MHz; $CDCl_3$) 3.07 (6H, s, H-2), 3.39-3.89 (m, PEG CH_2), 4.36 (4H, m, H-1)

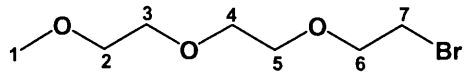
Methoxy PEG 5000 Mesylate (146)



To a solution of Methoxy-PEG 5000 (**145**) (10.0 g, 2.00 mmol) in dichloromethane (10 mL), was added methanesulfonyl chloride (0.31 mL, 4.0 mmol), followed by cautious addition of triethylamine (0.56 mL, 4.0 mmol, 0.05 mL min^{-1}). The reaction mixture was stirred at room temperature for 16 hours. The solvent was removed *in vacuo*, and the crude product was dissolved in hot propan-2-ol (100 mL). The solution was cooled to 5 °C in a refrigerator, and the precipitate was collected by filtration, washed with propan-2-ol (20 mL), and diethyl ether (100 mL), and dried *in vacuo*, affording the title compound as a colourless solid (10.0 g, 1.97 mmol, 98 %).

δ_H (300 MHz; $CDCl_3$) 3.07 (3H, s, H-3), 3.37 (3H, s, H-1), 3.38-3.89 (m, PEG CH_2), 4.36 (2H, m, H-2)

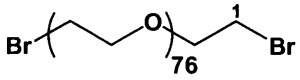
1-[2-(2-Bromo-ethoxy)-ethoxy]-2-methoxy-ethane (137)



To a solution of **135** (100. mg, 3.90 x 10^{-1} mmol) in acetone (5 mL) was added lithium bromide and the reaction mixture was stirred at reflux for 16 hours. The solution was allowed to cool to room temperature, water (10 mL) was added and the solution was extracted with diethyl ether (3 x 10 mL). The combined organic extracts were dried over magnesium sulfate, filtered, and the solvent was removed *in vacuo* to afford the title compound as a clear oil (92. mg, 0.38 mmol, 97 %).

δ_H (400 MHz; $CDCl_3$) 3.34 (3H, s, H-1), 3.43 (2H, t, *J* 6.3 Hz, H-7), 3.52 (2H, m, PEG CH_2), 3.60-3.64 (6H, m, PEG CH_2), 3.77 (2H, t, *J* 6.3 Hz, PEG CH_2)
δ_C (100 MHz; $CDCl_3$) 30.2 (C-7), 58.9 (C-1), 70.4 (PEG CH_2), 70.5 (PEG CH_2), 71.1 (PEG CH_2), 71.8 (PEG CH_2)

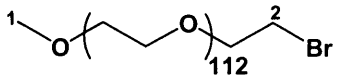
PEG 3400 Bromide (140)



To a solution of **139** (10.0 g, 5.62 mmol) in acetone (50 mL), was added lithium bromide (1.47 g, 16.9 mmol). The reaction mixture was stirred at reflux for 16 hours. The solution was allowed to cool to room temperature, and a white solid was removed by filtration. The filtrate was collected, and the solvent was removed *in vacuo*. The crude product was dissolved in hot propan-2-ol (50 mL), and the solution cooled to 5 °C in a refrigerator. The precipitate was collected by filtration, washed with propan-2-ol (10 mL), and diethyl ether (50 mL), and dried *in vacuo* to afford the title compound as a white solid (9.86 g, 5.60 mmol, 99 %).

δ_H (300 MHz; $CDCl_3$) 3.38-3.85 (m, PEG CH_2), 3.45 (4H, t, *J* 6.3 Hz, H-1)

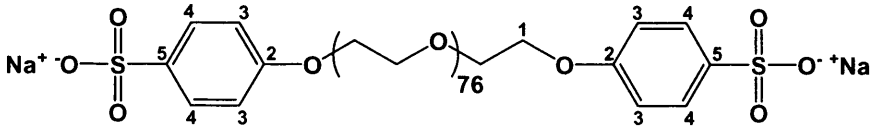
Methoxy PEG 5000 Bromide (205)



To a solution of **146** (9.00 g, 1.77 mmol) in acetone (50 mL), was added lithium bromide (461 mg, 5.31 mmol). The reaction mixture was stirred at reflux for 16 hours. The solution was allowed to cool to room temperature, and a white solid was removed by filtration. The filtrate was collected, and the solvent was removed *in vacuo*. The crude product was dissolved in hot propan-2-ol (50 mL), and the solution cooled to 5 °C in a refrigerator. The precipitate was collected by filtration, washed with propan-2-ol (10 mL), and diethyl ether (50 mL), and dried *in vacuo* to afford the title compound as a white solid (8.87 g, 1.75 mmol, 99 %).

δ_H (300 MHz; $CDCl_3$) 3.35 (3H, s, H-1), 3.36-3.89 (m, PEG CH_2), 3.45 (4H, t, *J* 6.3 Hz, H-2)

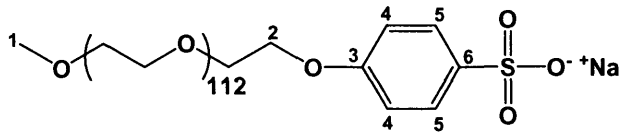
PEG 3400 Sulfonic Acid (Sodium Salt) (141)



To a solution of **140** (8.30 g, 4.70 mmol) in propan-2-ol (50 mL) and water (50 mL), was added 4-hydroxybenzenesulfonic acid, sodium salt (5.46 g, 23.5 mmol), and sodium hydroxide (940. mg, 23.5 mmol). The reaction mixture was stirred at reflux for 64 hours and was then allowed to cool to room temperature. The solvent was removed *in vacuo*, and the crude product was dissolved in hot propan-2-ol (100 mL), which was filtered to remove insoluble white solid. The solution was cooled to 5 °C in a refrigerator, and the precipitate was collected by filtration, washed with propan-2-ol (30 mL), and diethyl ether (50 mL), and dried *in vacuo* to afford the title compound as a white solid (8.25 g, 4.40 mmol, 93 %).

δ_H (300 MHz; $CDCl_3$) 3.39-3.84 (m, PEG CH_2), 4.13 (4H, t, *J* 5.1 Hz, H-1), 6.84 (4H, d, *J* 8.8 Hz, H-3), 7.83 (4H, d, *J* 8.8 Hz, H-4)

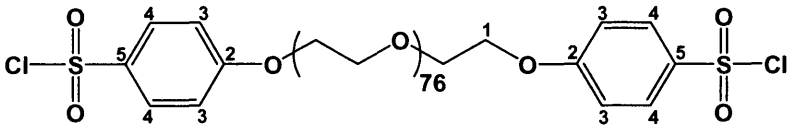
Methoxy PEG 5000 Sulfonic Acid (Sodium Salt) (206)



To a solution of **205** (3.00 g, 5.90 x 10^{-1} mmol) in propan-2-ol (20 mL) and water (20 mL), was added 4-hydroxy benzenesulfonic acid, sodium salt (687 mg, 2.96 mmol), and sodium hydroxide (118 mg, 2.96 mmol). The reaction mixture was stirred at reflux for 64 hours and was then allowed to cool to room temperature. The solvent was removed *in vacuo*, and the crude product was dissolved in hot propan-2-ol (50 mL), which was filtered to remove insoluble white solid. The solution was cooled to 5 °C in a refrigerator, and the precipitate was collected by filtration, washed with propan-2-ol (30 mL), and diethyl ether (50 mL), and dried *in vacuo* to afford the title compound as a white solid (2.75 g, 5.30 x 10^{-1} mmol, 90 %).

δ_H (300 MHz; $CDCl_3$) 3.35 (3H, s, H-1), 3.35-3.86 (m, PEG CH_2), 4.11 (2H, t, *J* 5.0 Hz, H-2), 6.82 (2H, d, *J* 8.6 Hz, H-4), 7.80 (2H, d, *J* 8.6 Hz, H-5)

PEG 3400 Sulfonyl Chloride (142)

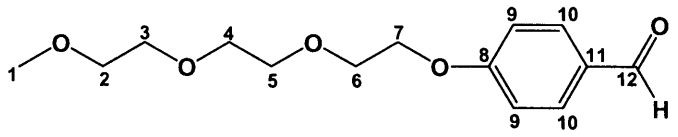


A solution of **141** (23.2 g, 12.4 mmol), in acetonitrile (500 mL), was stirred at reflux, allowing the solvent to distil through a soxhlet adaptor with a porous thimble containing calcium carbide (2 g), for 5 hours, under an atmosphere of nitrogen. The reaction mixture was allowed to cool to room temperature, followed by the addition of sulfonyl chloride (4.01 mL, 61.8 mmol), and DMF (4.78 mL, 61.8 mmol). The reaction mixture was stirred for a further 16 hours at room temperature. The solvent

was removed *in vacuo* and the crude product was dissolved in hot propan-2-ol (100 mL). The solution was cooled to 5 °C in a refrigerator and the precipitate was collected by filtration. The precipitation step was repeated and the precipitate was collected by filtration. The crude product was washed with propan-2-ol (10 mL) and diethyl ether (50 mL), and dried *in vacuo* to afford the title compound as a white solid (21.6 g, 11.5 mmol, 93 %).

δ_H (300 MHz; $CDCl_3$) 3.37-3.89 (m, PEG CH_2), 4.22 (4H, t, *J* 4.6 Hz, H-1), 7.06 (4H, d, *J* 9.0 Hz, H-3), 7.95 (4H, d, *J* 9.0 Hz, H-4)

4-{2-[2-(2-Methoxy-ethoxy)-ethoxy]-ethoxy}-benzaldehyde (143) [161]



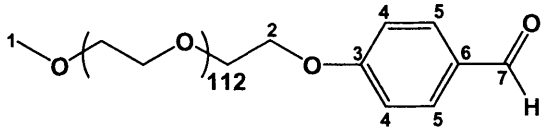
To a solution of **135** (100. mg, 3.90 x 10^{-1} mmol) in THF (5 mL) was added 4-hydroxybenzaldehyde (238 mg, 1.95 mmol), followed by cautious addition of sodium hydride (78.0 mg, 60 % in mineral oil, 1.95 mmol), at room temperature, with stirring. The reaction mixture was stirred at reflux for 16 hours and was then allowed to cool to room temperature, followed by cautious addition of methanol (3 mL, 0.05 mL min^{-1}), then water (10 mL). The solution was extracted with diethyl ether (2 x 20 mL), the combined organic extracts were dried over magnesium sulfate, filtered, and the solvent was removed *in vacuo*. Flash chromatography of the crude product (4:1, then 2:1, then 1:1, hexane/ ethyl acetate) afforded the title compound as a clear oil (95 mg, 0.35 mmol, 91 %), as well as **144** as a clear oil (8 mg, 0.3 x 10^{-1} mmol, 8 %). (Lit. 63 % yield, reports an alternative method using the PEG tosylate rather than **135**).

δ_H (300 MHz; $CDCl_3$) 3.34 (3H, s, H-1), 3.52 (2H, m, PEG CH_2), 3.61-3.67 (4H, m, PEG CH_2), 3.71 (2H, m, PEG CH_2), 3.86 (2H, t, *J* 5.1 Hz, H-7), 4.19 (2H, t, *J* 4.6 Hz), 7.00 (2H, d, *J* 8.7 Hz, H-9), 7.82 (2H, d, *J* 8.7 Hz, H-10), 9.85 (1 H, s, H-12)

δ_C (75 MHz; $CDCl_3$) 58.8 (C-1), 67.5 (PEG CH_2), 69.2 (PEG CH_2), 70.3 (PEG CH_2), 70.4 (PEG CH_2), 70.7 (PEG CH_2), 71.7 (PEG CH_2), 114.6 (C-9), 129.8 (C-11), 131.7 (C-10), 163.6 (C-8), 190.5 (C-12)

m/z (ES+) 307 ($[M + K]^+$, $C_{14}H_{20}O_5$, 100 %), 291 ($[M + Na]^+$, 95 %)

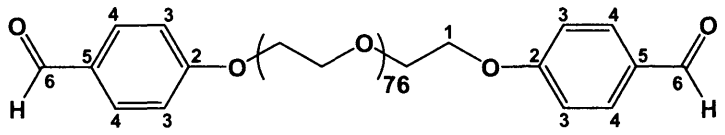
Methoxy PEG 5000 Benzaldehyde (147)



To a solution of **146** (10.0 g, 1.97 mmol) in anhydrous THF (50 mL) was added 4-hydroxybenzaldehyde (722 mg, 5.91 mmol), followed by cautious addition of sodium hydride (236 mg, 60 % in mineral oil, 5.91 mg) with stirring, at room temperature. The reaction mixture was stirred at reflux for 16 hours and was then allowed to cool to room temperature, followed by the cautious addition of methanol (10 mL, 1 mL min^{-1}). The solvent was removed *in vacuo*, and the crude product was dissolved in hot propan-2-ol (100 mL) and filtered to remove insoluble impurities. The solution was cooled to 5 °C, and the precipitate was collected by filtration, washed with propan-2-ol (10 mL), and diethyl ether (100 mL), and dried *in vacuo*, affording the title compound as a pink solid (6.53 g, 1.28 mmol, 98 %).

δ_H (300 MHz; $CDCl_3$) 3.31 (3H, s, H-1), 3.39-3.89 (m, PEG CH_2), 4.20 (2H, t, *J* 5.1 Hz, H-2), 7.02 (2H, d, *J* 8.8 Hz, H-4), 7.82 (2H, d, *J* 8.8 Hz, H-5), 9.87 (1H, s, H-7)

PEG 3400 Benzaldehyde (207)

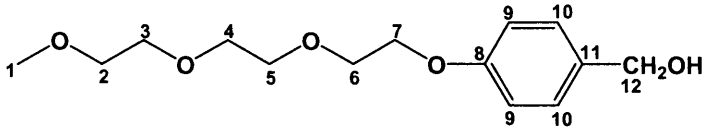


To a solution of **139** (14.0 g, 7.88 mmol) in anhydrous THF (100 mL) was added 4-hydroxy benzaldehyde (4.81 g, 39.4 mmol), followed by cautious addition of sodium hydride (1.57 g, 60 % in mineral oil, 39.4 mg) with stirring, at room temperature.

The reaction mixture was stirred at reflux for 16 hours and was then allowed to cool to room temperature, followed by the cautious addition of methanol (10 mL, 1 mL min^{-1}). The solvent was removed *in vacuo*, and the crude product was dissolved in hot propan-2-ol (100 mL) and filtered to remove insoluble impurities. The solution was cooled to 5 °C, and the precipitate was collected by filtration, washed with propan-2-ol (10 mL), and diethyl ether (100 mL), and dried *in vacuo*, affording the title compound as a pink solid (5.03 g, 1.38 mmol, 35 %).

δ_H (300 MHz; $CDCl_3$) 3.38-3.89 (m, PEG CH_2), 4.19 (4H, t, *J* 5.9 Hz, H-1), 7.00 (4H, d, *J* 8.9 Hz, H-3), 7.81 (4H, d, *J* 8.9 Hz, H-4), 9.87 (2H, s, H-6)

(4-{2-[2-(2-Methoxy-ethoxy)-ethoxy]-ethoxy)-phenyl)-methanol (144)



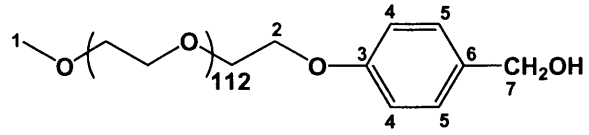
To a solution of **143** (25 mg, 0.90 x 10^{-1} mmol) in methanol was added, with caution, sodium borohydride (10. mg, 0.27 mmol) and the reaction mixture was stirred at room temperature for 16 hours. Water (10 mL) was added, and the solution was extracted with diethyl ether (3 x 10 mL). The combined organic extracts were dried over magnesium sulfate, filtered, and the solvent was removed *in vacuo* to afford the title compound as a clear oil (24 mg, 0.89 x 10^{-1} mmol, 99 %).

δ_H (400 MHz; $CDCl_3$) 3.36 (3H, s, H-1), 3.54 (2H, m, PEG CH_2), 3.62-3.67 (4H, m, PEG CH_2), 3.72 (2H, m, PEG CH_2), 3.84 (2H, t, *J* 5.2 Hz, PEG CH_2), 4.11 (2H, t, *J* 4.5 Hz, H-7), 4.59 (2H, s, H-12), 6.88 (2H, d, *J* 8.4 Hz, H-9), 7.26 (2H, d, *J* 8.0 Hz, H-10)

δ_C (75 MHz; $CDCl_3$) 59.0 (C-1), 65.0 (PEG CH_2), 67.5 (PEG CH_2), 69.7 (PEG CH_2), 70.5 (PEG CH_2), 70.6 (PEG CH_2), 70.8 (PEG CH_2), 71.9 (PEG CH_2), 114.7 (C-8), 128.5 (C-10), 133.3 (C-11), 158.0 (C-8)

m/z (ES+) 293 ($[M + Na]^+$, $C_{14}H_{22}O_5$, 100 %)

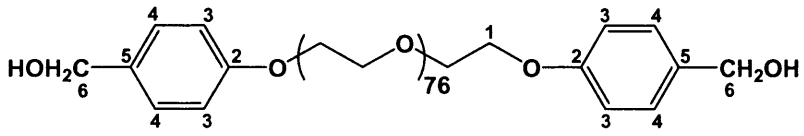
Methoxy PEG 5000 Wang Alcohol (148)



To a solution of **147** (10.0 g, 1.96 mmol) in methanol (50 mL) was added, with caution, sodium borohydride (224 mg, 5.88 mmol) with stirring, at room temperature. The reaction mixture was stirred at room temperature for a further 16 hours. The solvent was removed *in vacuo*, and the crude product was dissolved in hot propan-2-ol (100 mL). The solution was cooled to 5 °C in a refrigerator, and the precipitate was collected by filtration, washed with propan-2-ol (20 mL), and diethyl ether (100 mL), and dried *in vacuo*, affording the title compound as a colourless solid (10.0 g, 1.96 mmol, 99 %).

δ_H (300 MHz; $CDCl_3$) 1.89 (1H, t, *J* 5.7 Hz, CH_2OH), 3.37 (3H, s, H-1), 3.40-3.88 (m, PEG CH_2), 4.12 (2H, t, *J* 5.7 Hz, H-2), 4.60 (2H, d, *J* 5.7 Hz, H-7), 6.90 (2H, d, *J* 8.7 Hz, H-4), 7.27 (2H, d, *J* 8.7 Hz, H-5)

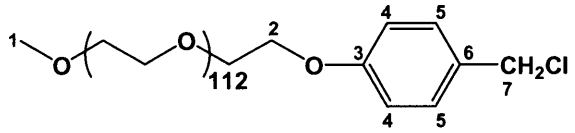
PEG 3400 Wang Alcohol (208)



To a solution of **207** (5.03 g, 2.78 mmol) in methanol (25 mL) was added, with caution, sodium borohydride (212 mg, 5.58 mmol) with stirring, at room temperature. The reaction mixture was stirred at room temperature for a further 16 hours. The solvent was removed *in vacuo*, and the crude product was dissolved in hot propan-2-ol (50 mL). The solution was cooled to 5 °C in a refrigerator, and the precipitate was collected by filtration, washed with propan-2-ol (20 mL), and diethyl ether (50 mL), and dried *in vacuo*, affording the title compound as a colourless solid (4.10 g, 1.14 mmol, 82 %).

δ_H (300 MHz; $CDCl_3$) 3.37-3.88 (m, PEG CH_2), 4.12 (4H, t, *J* 5.1 Hz, H-1), 4.60 (4H, d, *J* 5.1 Hz, H-6), 6.89 (4H, d, *J* 8.7 Hz, H-3), 7.27 (4H, d, *J* 8.7 Hz, H-4)

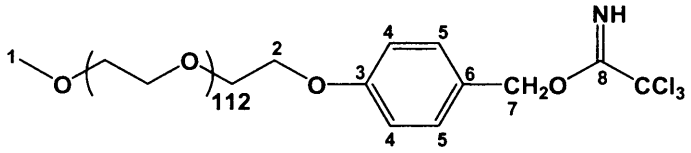
Methoxy PEG 5000 Wang Chloride (149)



To a solution of **148** (3.53 g, 6.92 x 10^{-1} mmol) in toluene (10 mL) was added thionyl chloride (2.00 mL, 27.7 mmol) and the reaction mixture was stirred at reflux, for 16 hours. The reaction mixture was allowed to cool to room temperature followed by removal of the solvent *in vacuo*, and the crude product was dissolved in hot propan-2-ol (50 mL). The solution was cooled to 5 °C in a refrigerator, and the precipitate was collected by filtration, washed with propan-2-ol (10 mL), and diethyl ether (50 mL), and dried *in vacuo*, affording the title compound as a colourless solid (2.02 g, 3.94 x 10^{-1} mmol, 57 %).

δ_H (300 MHz; $CDCl_3$) 3.35 (3H, s, H-1), 3.36-3.85 (m, PEG CH_2), 4.10 (2H, t, *J* 5.0 Hz, H-2), 4.53 (2H, s, H-7), 6.87 (2H, d, *J* 8.7 Hz, H-4), 7.27 (2H, d, *J* 8.7 Hz, H-5)

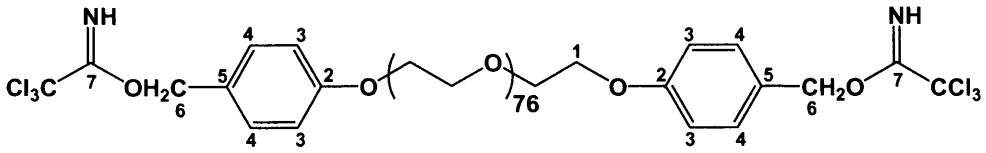
Methoxy PEG 5000 Wang Trichloroacetimidate (150)



To a solution of **148** (6.35 g, 1.24 mmol) in anhydrous dichloromethane (50 mL), at 0 °C, was added trichloroacetonitrile (2.49 mL, 24.8 mmol) and DBU (0.22 mL, 1.5 mmol), and the reaction mixture was stirred, at 0 °C, for 1 hour. The solvent was removed *in vacuo*, and the crude product was dissolved in hot propan-2-ol (75 mL). The solution was cooled to 5 °C in a refrigerator, and the precipitate was collected by filtration, washed with propan-2-ol (20 mL), and diethyl ether (75 mL), and dried *in vacuo*, affording the title compound as a colourless solid (6.35 g, 1.21 mmol, 98 %).

δ_H (300 MHz; $CDCl_3$) 3.36 (3H, s, H-1), 3.43-3.80 (m, PEG CH_2), 4.12 (2H, t, *J* 4.7 Hz, H-2), 5.25 (2H, s, H-7), 6.90 (2H, d, *J* 8.8 Hz, H-4), 7.34 (2H, d, *J* 8.8 Hz, H-5), 8.35 (1H, s, N*H*)

PEG 3400 Wang Trichloroacetimidate (209)

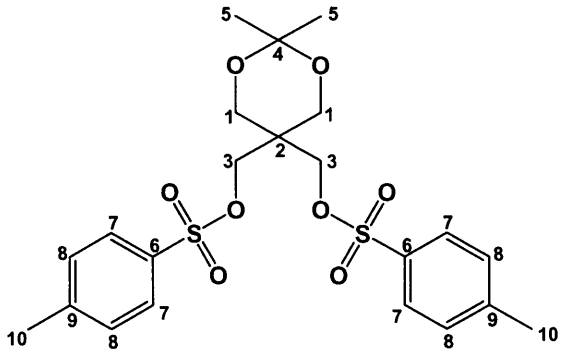


To a solution of **208** (3.10 g, 1.72 mmol) in anhydrous dichloromethane (50 mL), at 0 °C, was added trichloroacetonitrile (2.70 mL, 34.0 mmol) and DBU (0.31 mL, 2.0 mmol), and the reaction mixture was stirred, at 0 °C, for 1 hour. The solvent was removed *in vacuo*, and the crude product was dissolved in hot propan-2-ol (50 mL). The solution was cooled to 5 °C in a refrigerator and the precipitate was collected by filtration, washed with propan-2-ol (20 mL) and diethyl ether (50 mL), and dried *in vacuo*, affording the title compound as a colourless solid (2.54 g, 1.30 mmol, 71 %).

δ_H (300 MHz; $CDCl_3$) 3.38-3.87 (m, PEG CH_2), 4.11 (4H, t, *J* 4.9 Hz, H-1), 5.24 (2H, s, H-6), 6.90 (4H, d, *J* 8.7 Hz, H-3), 7.33 (4H, d, *J* 8.7 Hz, H-4), 8.33 (2H, s, N*H*)

7.3 Cyclic Ether Synthesis; Oxetanes

2,2-Dimethyl-5,5-bis-(toluene-4-sulfonyloxymethyl)-[1,3]dioxan (155) [146]



To a solution of **127** (2.50 g, 14.2 mmol) in dry pyridine (10 mL), at 0 °C, was added a solution of *p*-toluenesulfonyl chloride (2.67 g, 14.2 mmol) in dry pyridine (10 mL), dropwise, over 1 hour. The solution was stirred at room temperature for a further 5 hours, and pyridine was removed *in vacuo*. The crude product was dissolved in dichloromethane (20 mL), and the solution was washed with water (5 x 20 mL). The solution was dried over magnesium sulfate, filtered, and dichloromethane was removed *in vacuo*. Recrystallization of the crude product from methanol, followed by filtration, afforded the title compound as a colourless solid (1.60 g, 3.30 mmol, 20 %), and the filtrate was put to one side.

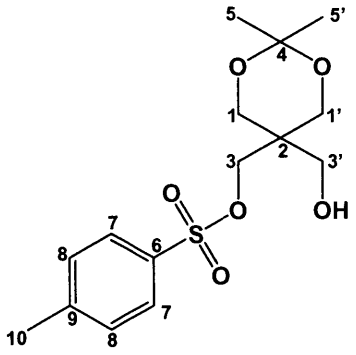
ν_{max} (KBr)/cm^{-1} 2993 (m), 2874 (m), 1597 (m), 1360 (s), 1177 (s)

δ_H (300 MHz; $CDCl_3$) 1.24 (6H, s, C-5), 2.45 (6H, s, C-10), 3.58 (4H, s), 3.95 (4H, s), 7.35 (4H, d, *J* 8.2 Hz, C-8), 7.74 (4H, d, *J* 8.2 Hz, C-7)

δ_C (75 MHz; $CDCl_3$) 21.6 (C-5), 23.3 (C-10), 38.1 (C-2), 61.3 (C-1), 68.0 (C-3), 98.8 (C-4), 128.0 (Ph), 130.0 (Ph), 132.2 (C-6), 145.2 (C-9)

m/z (ES+) 507 ([*M* + Na]$^+$, $C_{22}H_{28}O_4S_2$, 100 %)

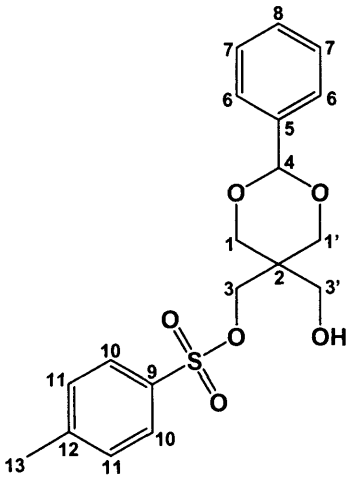
Tolune-4-sulfonic acid 5-hydroxymethyl-2,2-dimethyl-[1,3] dioxin-5-yl methyl ester (154) [146] - Literature Procedure Was Used Unmodified



The methanol filtrate from the previous procedure was concentrated *in vacuo*. The crude product was recrystallized from ethyl acetate to afford the title compound as a colourless solid (2.10 g, 6.35 mmol, 43 %). (Lit. 48 % yield, lit. reports alternative purification procedure).

ν_{max} (KBr)/cm^{-1} 3460 (s), 2949 (m), 2889 (m), 1356 (s), 1171 (s)
δ_H (300 MHz; $CDCl_3$) 1.29 (3H, s, H-5/H-5'), 1.37 (3H, s, H-5/H-5'), 1.83 (1H, t, J 5.9 Hz, CH_2OH), 2.44 (3H, s, H-10), 3.57 (2H, d, *J* 5.9 Hz, H-3'), 3.65 (2H, s), 3.67 (2H, s), 4.15 (2H, s, H-3), 7.35 (4H, d, *J* 8.1 Hz, H-8), 7.80 (4H, d, *J* 8.3 Hz, H-7)
δ_C (75 MHz; $CDCl_3$) 21.7, 21.9, 25.3 (C-10), 39.3 (C-2), 61.7, 62.0, 69.1 (C-3), 98.6 (C-4), 128.0 (Ph), 130.0 (Ph), 132.6 (C-6), 145.1 (C-9)
m/z (CI+) 331 ([*M* + H]$^+$, $C_{15}H_{22}O_6S$, 5%), 315 (75 %), 83 (100 %)

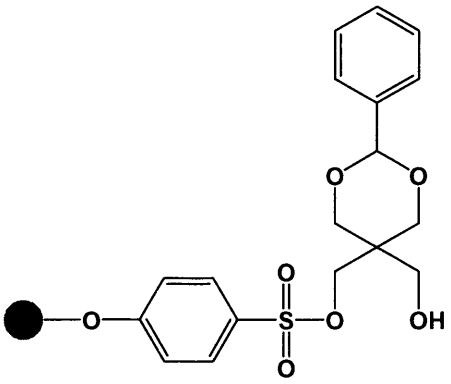
Toluene-4-sulfonic acid 5-hydroxymethyl-2-phenyl-[1,3]dioxin-5-ylmethyl ester (158)



To a solution of **130** (200. mg, 8.92 x 10^{-1} mmol) and DMAP (109 mg, 8.92 x 10^{-1} mmol) in anhydrous pyridine (5 mL), was added a solution of tosyl chloride (170. mg, 8.92 x 10^{-1} mmol) in anhydrous pyridine (5 mL), dropwise, with stirring, at 0 °C, over 1 hour. The reaction mixture was then stirred at room temperature for 16 hours, followed by the addition of water (10 mL). The solution was extracted with ethyl acetate (3 x 5 mL) and the organic extracts were combined. The solvent was then removed *in vacuo*, using water (3 x 5 mL) to form an azeotrope, and thus aid evaporation of pyridine. The crude product was dissolved in ethyl acetate (10 mL), the solution was dried over magnesium sulfate, filtered, and the solvent was removed *in vacuo*. Flash chromatography of the crude product (2:1, ethyl acetate/hexane) afforded the title compound as a colourless solid (34 mg, 0.90 x 10^{-1} mmol, 10 %).

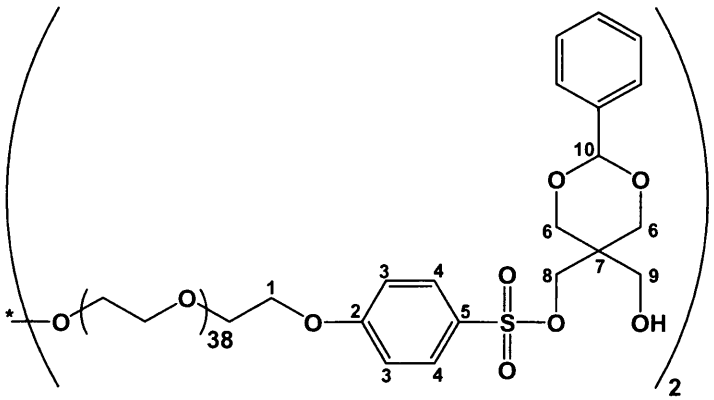
δ_H (300 MHz; $CDCl_3$) 1.97 (1H, t, *J* 5.9 Hz, CH_2OH), 2.43 (3H, s, H-13), 3.49 (2H, d, *J* 5.9 Hz, H-3'), 3.77 (2H, d, *J* 12.1 Hz), 4.08 (2H, d, *J* 12.1 Hz), 4.44 (2H, s), 5.35 (1H, s, H-4), 7.29-7.46 (7H, m and d, Ph and H-11), 7.82 (2H, d, *J* 8.2 Hz, H-10)
δ_C (75 MHz; $CDCl_3$) 21.6 (C-13), 39.3 (C-2), 61.8, 68.6, 69.5, 102.0 (C-4), 126.0, 128.0, 128.2, 129.1, 130.0, 132.5, 137.7, 145.1 (C-12)
m/z (ES+) 378 ($[M + Na]^+$, $C_{19}H_{22}O_6S$, 100 %)

Loading Monomer onto Cross-Linked Polystyrene Support (159)



To a suspension of sulfonyl chloride (polymer bound, **37**) (100. mg, 2.00 x 10^{-1} mmol) in anhydrous pyridine (5.0 mL), was added **130** (224 mg, 1.00 mmol), and the reaction mixture was stirred gently at reflux for 16 hours. The resin was collected by filtration, washed with dichloromethane (3 x 5 mL), dimethyl formamide (3 x 5 mL), dimethyl formamide/water (5:1, 3 x 5 mL), THF (3 x 5 mL), and dichloromethane (3 x 5 mL), and dried *in vacuo* (102 mg recovered).

Loading Monomer onto PEG Support (162)



A solution of **142** (500. mg, 2.60 x 10^{-1} mmol) in toluene (20 mL) was stirred at room temperature for 16 hours, over 3 Å molecular sieves. Compound **130** (299 mg, 1.33 mmol) and DMAP (47.6 mg, 3.90 x 10^{-1} mmol) were added, and the reaction mixture was stirred for a further 24 hours at room temperature). The solvent was removed *in vacuo*, and the crude product was dissolved in hot propan-2-ol (20 mL). The solution was cooled to 5 °C in a refrigerator, and the precipitate was collected by

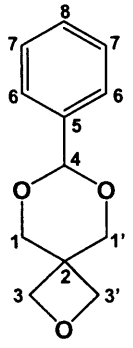
filtration, washed with propan-2-ol (5 mL), and diethyl ether (50 mL), and dried *in vacuo*, affording a mixture of the loaded product and bridged product (820 mg).

(*n. b.* The material was reacted on without further purification, taking it to be the pure unbridged product for the purposes of molar calculations).

δ_H (500 MHz; $CDCl_3$) 3.47-4.20 (m, PEG), 4.20 (t, H-1), 4.41 (s), 5.39 (s, H-10), 7.04 (d, *J* 8.9 Hz, H-3), 7.31-7.42 (m, Ph), 7.82 (d, *J* 8.9 Hz, H-4)

(See appendix A for ^{1}H NMR spectrum)

7-Phenyl-2,6,8-trioxa-spiro [3.5] nonane (157) [147]



In Solution

To a solution of **158** (28 mg, 0.70 x 10^{-1} mmol) in THF (1 mL) was added potassium *t*-butoxide (24 mg, 2.10 x 10^{-1} mmol) and the reaction mixture was stirred at room temperature for 3 hours. Water (5 mL) was added, and the solution was extracted with ethyl acetate (3 x 5 mL). The combined organic extracts were dried over magnesium sulfate, filtered, and the solvent was removed *in vacuo*. Flash chromatography of the crude product (3:1, hexane/ethyl acetate) afforded the title compound as a white solid (8 mg, 0.4 x 10^{-1} mmol, 57 %).

On Resin

To a suspension of **159** (50.0 mg, 0.70 x 10^{-1} mmol) in THF (2 mL), was added potassium *tert*-butoxide (23.6 mg, 2.10 x 10^{-1} mmol), and the reaction mixture was shaken at room temperature for 3 hours. The resin was separated by filtration, and washed with tetrahydrofuran/water (5:1, 3 x 5 mL), tetrahydrofuran (3 x 5 mL), and dichloromethane (3 x 5 mL). The combined filtrates were washed with water (5 mL), dried over magnesium sulfate, filtered, and the solvent was removed *in vacuo*. The crude product was filtered through a short pad of silica in ethyl acetate/hexane (2:3) to give the title compound as a white solid (9 mg, 0.4 x 10^{-1} mmol, 62 %).

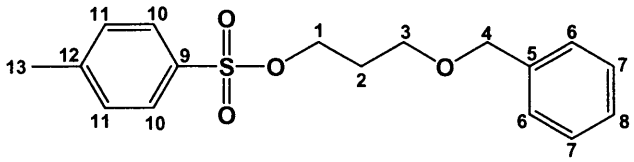
On PEG

To a solution of **162** (212 mg, 1.00 x 10^{-1} mmol) in THF, over 3 Å molecular sieves, was added potassium *tert*-butoxide (37 mg, 0.30 mmol). The reaction mixture was stirred at room temperature for 16 hours. The solvent was removed *in vacuo*, and the crude product was dissolved in a minimum of methanol. Diethyl ether (20 mL) was added to precipitate a white solid, which was removed by filtration. The solvent was removed *in vacuo*, and the crude product was filtered through a short pad of silica, eluting with ethyl acetate/hexane (1:3) to afford the title compound as a white solid (13 mg, 0.63 x 10^{-1} mmol, 63 %). (Lit. reports the use of an alternative methodology).

δ_H (300 MHz; $CDCl_3$) 3.89 (d, 2H, *J* 10.9 Hz), 4.27 (s, 2H), 4.56 (d, 2H, 10.9 Hz), 5.43 (s, 1H, H-4), 7.31-7.38 (m, 5H, Ph)
δ_C (75 MHz; $CDCl_3$) 38.0 (C-2), 73.1, 73.8 (, 81.3, 101.3 (C-4), 126.0 (Ph), 128.3 (Ph), 129.0 (Ph), 137.7 (C-5)

7.4 Polyether Synthesis on Polymeric Supports

Toluene-4-sulfonic acid 3-benzyloxy-propyl ester (163) – Literature Procedure Was Used Unmodified [157]



Compound **163** was synthesised according to a procedure published by Schomaker *et al.* [157] Yield 87 %, Lit. yield 88 %. All spectroscopic data is in full agreement with the published data.

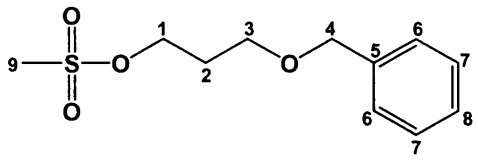
ν_{max} (KBr)/cm^{-1} 1599 (w), 1454 (w), 1360 (s), 1177 (s), 1097 (m)

δ_H (300 MHz; $CDCl_3$) 1.84 (2H, quin, *J* 6.1 Hz, H-2), 2.42 (3H, s, H-13), 3.40 (2H, t, *J* 6.1 Hz, H-3), 4.06 (2H, t, *J* 6.1 Hz, H-1), 4.31 (2H, s, H-4), 7.13 (2H, d, *J* 8.3 Hz, H-11), 7.15-7.25 (5H, m, Ph), 7.69 (2H, d, *J* 8.3 Hz, H-10)

δ_C (75 MHz; $CDCl_3$) 21.6 (C-13), 29.3 (C-2), 65.6, 67.7, 73.0 (H-4), 127.5, 127.6, 127.9, 128.3, 129.8, 133.0, 138.1, 144.7

m/z (ES+) 343 ([*M* + Na]$^+$, $C_{17}H_{18}O_4S$, 100 %)

Methane sulfonic acid 3-benzyloxypropyl ester (164) [162]

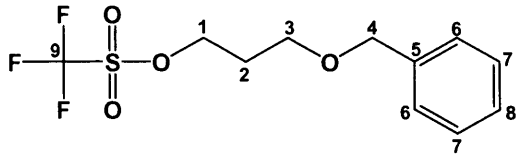


To a solution of **117** (100. mg, 6.02 x 10^{-1} mmol) in dichloromethane (2 mL) was added methanesulfonyl chloride (0.07 mL, 0.9 mmol). The solution was cooled to 5 °C in an ice bath and triethylamine (0.12 mL, 0.90 mmol) was added with caution (0.01 mL min^{-1}). The reaction mixture was stirred at room temperature for 16 hours, and then washed with water (5 x 5 mL). The organic layer was dried over magnesium sulfate, filtered, and the solvent was removed *in vacuo* to afford the title

compound as a yellow oil (144 mg, 5.90 x 10^{-1} mmol, 98 %). (Lit. 88 % yield, alternative methodology was used with pyridine as the base).

ν_{max} (KBr)/cm^{-1} 2885 (m), 1352 (s), 1174 (s), 1103 (m)
δ_H (300 MHz; $CDCl_3$) 2.03 (2H, quin, *J* 6.1 Hz, H-2), 2.95 (3H, s, H-9), 3.59 (2H, t, *J* 6.1 Hz, H-3), 4.35 (2H, t, *J* 6.1 Hz, H-1), 4.51 (2H, s, H-4), 7.26-7.37 (5H, m, Ph)
δ_C (75 MHz; $CDCl_3$) 29.6 (C-2), 37.2 (C-9), 65.5, 67.3, 73.2 (C-4), 127.7 (Ph), 127.7 (Ph), 128.4 (Ph), 138.1 (C-5)
m/z (ES+) 267 ([*M* + Na]$^+$, $C_{11}H_{16}O_4S$, 100 %), 245 (20 %)

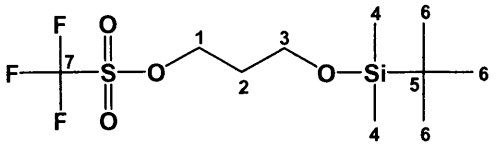
1,1,1-Trifluoro-methanesulfonic acid 3-benzyloxy-propyl ester (165) [163]



To a solution of **117** (85.0 mg, 5.11 x 10^{-1} mmol) in anhydrous dichloromethane (3 mL), was added 2,6-lutidine (0.07 mL, 0.6 mmol). The reaction mixture was cooled in an ice bath, and trifluoromethanesulfonic anhydride (0.10 mL, 0.61 mmol), was added dropwise, over 10 minutes, with stirring. The reaction mixture was stirred at 5 °C for a further 5 minutes, and then filtered through a short pad of silica, to afford the title compound as an orange oil (120. mg, 5.06 x 10^{-1} mmol, 99 %). (Lit., full experimental procedure not reported in the literature).

δ_H (300 MHz; $CDCl_3$) 2.11 (2H, quin, *J* 6.0 Hz, H-2), 3.59 (2H, t, *J* 6.0 Hz, H-3), 4.52 (2H, s, H-4), 4.69 (2H, t, *J* 6.0 Hz, H-1), 7.27-7.36 (5H, m, Ph)
δ_C (75 MHz; $CDCl_3$) 29.8 (C-2), 64.9 (C-3), 73.3 (C-1), 74.6 (C-4), 127.7 (Ph), 127.8 (Ph), 128.5 (Ph), 137.8 (C-5)
m/z (ES+) 321 ([*M* + Na]$^+$, $C_{11}H_{13}O_4SF_3$, 100 %)

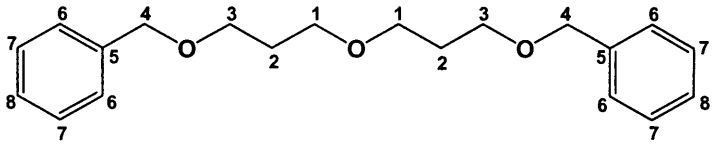
1,1,1-Trifluoro-methanesulfonic acid 3-(*tert*-butyl-dimethyl-silanyloxy)-propyl ester (166) [163]



To a solution of **118** (1.05 g, 5.50 mmol) in anhydrous dichloromethane (10 mL), was added 2,6-lutidine (2.31 mL, 19.8 mmol). The reaction mixture was cooled in an ice bath, and trifluoromethanesulfonic anhydride (1.11 mL, 6.60 mmol), was added dropwise, over 10 minutes, with stirring. The reaction mixture was stirred at 5 °C for a further 5 minutes, and then filtered through a short pad of silica, to afford the title compound as an orange oil (1.42 g, 5.48 mmol, 99 %). (Lit., full experimental procedure not reported).

ν_{max} (KBr)/cm^{-1} 2960 (m), 1414 (s), 1248 (s), 1207 (s), 1148 (s)
δ_H (300 MHz; $CDCl_3$) 0.01 (6H, s, H-4), 0.88 (9H, s, H-6), 1.99 (2H, quin, *J* 5.9 Hz, H-2), 3.72 (2H, t, *J* 5.9 Hz, H-3), 4.66 (2H, t, *J* 5.9 Hz, H-1)
δ_C (75 MHz; $CDCl_3$) -5.6 (C-4), 18.2 (C-5), 25.8 (C-6), 32.3 (C-2), 57.8 (C-3), 74.5 (C-1), 112.6 (C-7), 116.6 (C-7), 120.8 (C-7), 124.6 (C-7)

1-Benzyloxy-3-(3-benzyloxy-propoxy)propane (167)



With Mesylate

To a solution of **117** (110. mg, 6.62 x 10^{-1} mmol) in anhydrous DMF (3 mL), was added, with caution, sodium hydride (60 % in mineral oil, 26.4 mg, 6.62 x 10^{-1} mmol). Compound **164** (53.8 mg, 2.21 x 10^{-1} mmol) was added followed by TBAI (81 mg, 0.22 mmol) and 15-crown-5 (0.04 ml, 0.2 mmol), and the reaction mixture was stirred at room temperature for 16 hours. Methanol (1 mL, 0.1 mL min^{-1}) was

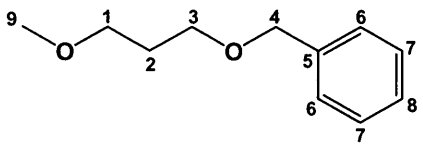
added and the solvent was removed *in vacuo*. Flash chromatography of the crude product (9:1, hexane/ethyl acetate), afforded the title compound as a clear oil (65 mg, 0.21 mmol, 94 %).

With Triflate

To a solution of **117** (107 mg, 64.4 x 10^{-1} mmol) in anhydrous dichloromethane (3 mL) was added, with caution, sodium hydride (60% in mineral oil, 26 mg, 0.64 mmol) followed by **165** (50. mg, 0.21 mmol), and the reaction mixture was stirred at room temperature for 16 hours. Methanol (1 mL, 0.1 mL min^{-1}) was added and the solvent was removed *in vacuo*. Flash chromatography of the crude product (9:1, hexane/ethyl acetate), afforded the title compound as a clear oil (63 mg, 0.21 mmol, 96 %).

δ_H (300 MHz; $CDCl_3$) 1.89 (4H, quin, *J* 6.4 Hz, H-2), 3.53 (4H, t, *J* 6.4 Hz, H-1/H-3), 3.57 (4H, t, *J* 6.4 Hz, H-1/H-3), 4.51 (4H, s, H-4), 7.27-7.38 (10H, m, Ph)
δ_C (75 MHz; $CDCl_3$) 30.2 (C-2), 67.4, 67.8, 73.0 (C-4), 127.5 (Ph), 127.6 (Ph), 128.3 (Ph), 138.6 (C-5)
m/z (ES+) 337 ($[M + Na]^+$, $C_{20}H_{26}O_3$, 100 %)

(3-Methoxy-propoxymethyl)-benzene (168)

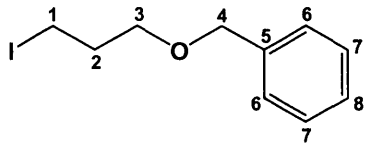


To a solution of **163** (100. mg, 31.2 x 10^{-1} mmol) in THF (5 mL) was added TBA-hydroxide (1M in MeOH, 0.93 mL, 0.94 mmol). The reaction mixture was stirred at room temperature for 16 hours. Water (5 mL) was added, and the solution was extracted with ethyl acetate (3 x 5 mL). The combined organic extracts were dried over magnesium sulfate, filtered, and the solvent was removed *in vacuo*. Flash chromatography of the crude product (9:1 hexane/ethyl acetate), afforded the title compound as a clear oil (45 mg, 0.25 mmol, 81 %).

δ_H (300 MHz; $CDCl_3$) 1.81 (2H, quin, *J* 6.4 Hz, H-2), 3.25 (3H, s, H-9), 3.41 (2H, t, *J* 6.4 Hz, H-1/H-3), 3.49 (2H, t, *J* 6.4 Hz, H-1/H-3), 4.50 (2H, s, H-4), 7.18-7.32 (5H, m, Ph)

δ_C (75 MHz; $CDCl_3$) 30.1 (C-2), 58.6 (C-9), 67.3, 69.8, 73.0 (C-4), 127.5 (Ph), 127.6 (Ph), 128.3 (Ph), 138.6 (C-5)

(3-Iodo-propoxymethyl)-benzene (169)



In Solution

To a solution of **163** (90 mg, 0.28 mmol) in THF (5 mL) was added TBAI (311 mg, 8.40 x 10^{-1} mmol). The reaction mixture was stirred at room temperature for 16 hours. Water (5 mL) was added, and the solution was extracted with ethyl acetate (3 x 5 mL). The combined organic extracts were dried over magnesium sulfate, filtered, and the solvent was removed *in vacuo*. Flash chromatography of the crude product (8:2, hexane/ethyl acetate), afforded the title compound as a yellow oil (46 mg, 0.17 mmol, 59 %).

On Resin

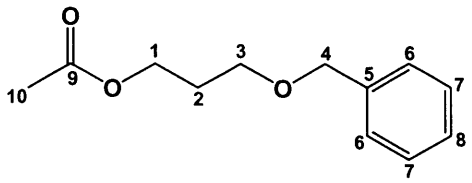
To a suspension of **171** (100. mg, 2.00 x 10^{-1} mmol) in THF (3 mL) was added TBAI (591 mg, 1.60 mmol). The reaction mixture was shaken at room temperature for 16 hours and then the resin was collected by filtration. The resin was washed with THF (3 x 3 mL) and DCM (3 x 3 mL). The combined filtrates were collected and the solvent was removed *in vacuo*. Flash chromatography of the crude product (8:2, hexane/ethyl acetate), afforded the title compound as a clear oil (10. mg, 0.78 x 10^{-1} mmol, 39 %).

δ_H (300 MHz; $CDCl_3$) 2.03 (2H, quin, *J* 6.4 Hz, H-2), 3.22 (2H, t, *J* 6.4 Hz, H-1), 3.46 (2H, t, *J* 6.4 Hz, H-3), 4.44 (2H, s, H-4), 7.20-7.30 (5H, m, Ph)

δ_C (75 MHz; $CDCl_3$) 3.3 (C-1), 33.6 (C-2), 69.6 (C-3), 73.5 (C-4), 127.7 (Ph), 128.4 (Ph), 138.6 (C-5)

m/z (ES+) 299 ($[M + Na]^+$, $C_{10}H_{13}OI$, 100 %)

Acetic acid 3-benzyloxy-propyl ester (170)



In Solution

To a solution of **163** (100. mg, 3.12 x 10^{-1} mmol) in THF (5 mL) was added TBA-acetate (280. mg, 9.36 x 10^{-1} mmol). The reaction mixture was stirred at room temperature for 16 hours. The reaction mixture was cooled to 5 °C in a refrigerator and the white precipitate was filtered and washed with ethyl acetate (3 x 5 mL). The filtrate was collected and the solvent was removed *in vacuo*. Flash chromatography of the crude product (9:1, hexane/ethyl acetate), afforded the title compound as a clear oil (52 mg, 0.25 mmol, 81 %).

On Resin

To a suspension of **171** (100. mg, 2.00 x 10^{-1} mmol) in THF (3 mL) was added TBA-acetate (181 mg, 6.00 x 10^{-1} mmol). The reaction mixture was shaken at room temperature for 16 hours and then filtered. The resin was washed with THF (3 x 3 mL) and DCM (3 x 3 mL). The combined filtrates were collected and the solvent was removed *in vacuo*. Flash chromatography of the crude product (9:1, hexane/ethyl acetate), afforded the title compound as a clear oil (17 mg, 0.82 x 10^{-1} mmol, 41 %).

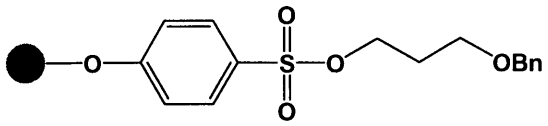
ν_{max} (KBr)/cm^{-1} 1740 (s), 1366 (w), 1242 (m), 1047 (w)

δ_H (300 MHz; $CDCl_3$) 1.93 (2H, quin, *J* 6.3 Hz, H-2), 2.01 (3H, s, H-10), 3.54 (2H, t, *J* 6.3 Hz, H-3), 4.17 (2H, t, *J* 6.3 Hz, H-1), 4.50 (2H, s, H-4), 7.27-7.37 (5H, m, Ph)

δ_C (75 MHz; $CDCl_3$) 20.9 (C-10), 29.0 (C-2), 61.7, 66.6, 73.0 (C-4), 127.6 (Ph), 128.3 (Ph), 138.3 (C-5), 171.0 (C-9)

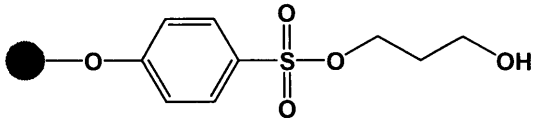
m/z (ES+) 231 ($[M + Na]^+$, $C_{12}H_{16}O_3$, 100 %)

Loading of Monomer onto Cross-Linked Polystyrene Support (171)



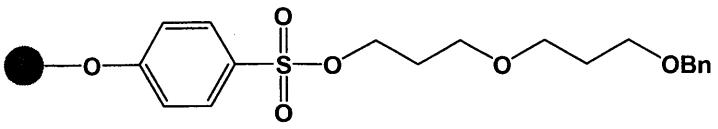
To a suspension of sulfonyl chloride (polymer bound, **37**) (300. mg, 6.00 x 10^{-1} mmol) in anhydrous dichloromethane (1.5 mL) and pyridine (1.5 mL) was added **117** (500 mg, 3.00 mmol) and the reaction mixture was shaken, at room temperature, for 16 hours. The resin was collected by filtration, washed with dichloromethane (3 x 5 mL), dimethyl formamide (3 x 5 mL), dimethyl formamide/water (5:1, 3 x 5 mL), THF (3 x 5 mL), and dichloromethane (3 x 5 mL), and dried *in vacuo* (330 mg recovered).

Loading of Diol onto Cross-Linked Polystyrene Support (172)



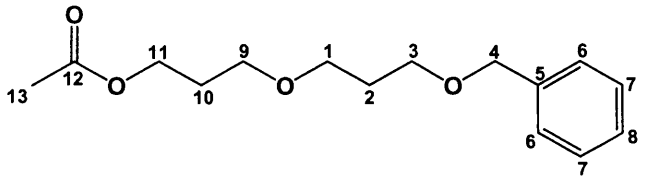
To a suspension of sulfonyl chloride (polymer bound, **37**) (1.02 g, 2.04 mmol) in anhydrous dichloromethane (1.5 mL) and pyridine (1.5 mL) was added 1,3-propanediol (**114**) (0.74 ml, 0.10 x 10^{-1} mol) and the reaction mixture was shaken, at room temperature, for 16 hours. The resin was collected by filtration, washed with dichloromethane (3 x 5 mL), dimethyl formamide (3 x 5 mL), dimethyl formamide/water (5:1, 3 x 5 mL), THF (3 x 5 mL), and dichloromethane (3 x 5 mL), and dried *in vacuo* (1.18 g recovered).

Chain Extension on Cross-Linked Polystyrene (174)



To a suspension of **172** (98 mg, 0.20 mmol) in anhydrous dichloromethane (1 mL) was added **165** (176 mg, 5.90 x 10^{-1} mmol), followed by sodium hydride (24 mg, 60 % in mineral oil, 0.59 mmol) and the reaction mixture was shaken at room temperature for 16 hours. The resin was collected by filtration, washed with dichloromethane (3 x 5 mL), dimethyl formamide (3 x 5 mL), dimethyl formamide/water (5:1, 3 x 5 mL), THF (3 x 5 mL), and dichloromethane (3 x 5 mL), and dried *in vacuo* (100 mg recovered).

Acetic acid 3-(3-benzyloxy-propoxy)-propyl ester (175)



On Resin

To a suspension of **174** (77 mg, 0.15 mmol) in THF (1 mL) was added TBA acetate (136 mg, 4.50 x 10^{-1} mmol), and the reaction mixture was shaken at room temperature for 16 hours. The resin was filtered off and washed with dichloromethane (3 x 5 mL), THF (3 x 5 mL), and THF/methanol (3:1, 3 x 5 mL). The filtrate and washes were combined, and the solvent was removed *in vacuo*. Flash chromatography of the crude product (9:1, hexane/ethyl acetate) afforded the title compound as a clear oil (12 mg, 0.45 x 10^{-1} mmol, 30 %).

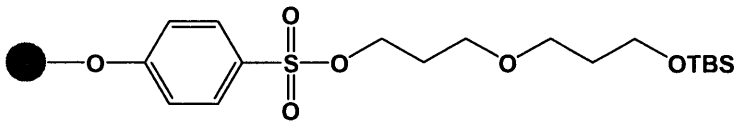
On PEG

To a solution of **181** (800. mg, 3.80 x 10^{-1} mmol), in acetone (100 mL), was added TBA acetate (175 mg, 5.80 x 10^{-1} mmol), and the reaction mixture was stirred at 50 ^{o}C for 16 hours. The solution was concentrated *in vacuo*, to a volume of ~ 1 mL, and

diethyl ether (100 mL) was added. The precipitated white solid was removed by filtration, and the filtrate was washed with water (3 x 50 mL). The organic layer was separated and dried over magnesium sulfate, filtered, and the solvent was removed *in vacuo*. Flash chromatography of the crude product (85:15, hexane/ethyl acetate) afforded the title compound as a clear oil (46 mg, 1.71 x 10^{-1} mmol, 45 %).

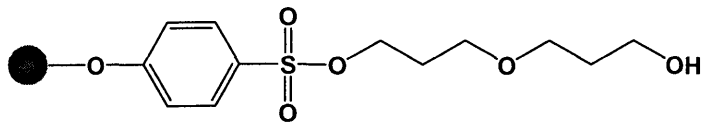
δ_H (300 MHz; $CDCl_3$) 1.87 (4H, quin, *J* 6.3 Hz, H-2 and H-10), 2.04 (3H, s, H-13), 3.47 (2H, t, *J* 6.3 Hz), 3.51 (2H, t, *J* 6.3 Hz), 3.55 (2H, t, *J* 6.3 Hz), 4.13 (2H, t, *J* 6.3 Hz, H-11), 4.49 (2H, s, H-4), 7.27-7.37 (5H, m, Ph)
δ_C (75 MHz; $CDCl_3$) 21.0 (C-13), 29.0, 30.1, 61.8, 67.2, 67.9, 73.0 (C-4), 127.5 (Ph), 127.6 (Ph), 128.3 (Ph), 138.5 (C-5), 171.1 (C-12)
m/z (CI+) 289 ([*M* + Na]$^+$, $C_{15}H_{22}O_4$, 100 %)
HRMS (CI+) $C_{15}H_{22}O_4$ [*M* + Na]$^+$ requires 289.14103, found 289.14123

Chain Extension on Cross-Linked Polystyrene (176)



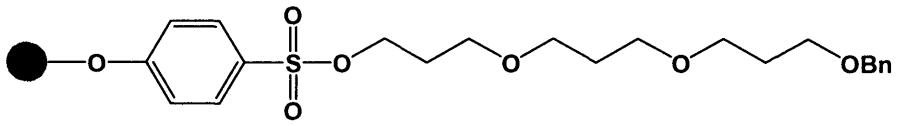
To a suspension of **172** (110. mg, 2.20 x 10^{-1} mmol) in anhydrous dichloromethane (1 mL) was added **166** (171 mg, 6.60 x 10^{-1} mmol), followed by sodium hydride (23 mg, 60 % in mineral oil, 0.66 mmol) and the reaction mixture was shaken at room temperature for 16 hours. The resin was collected by filtration, washed with dichloromethane (3 x 5 mL), dimethyl formamide (3 x 5 mL), dimethyl formamide/water (5:1, 3 x 5 mL), THF (3 x 5 mL), and dichloromethane (3 x 5 mL), and dried *in vacuo* (122 mg recovered).

Deprotection on Cross-Linked Polystyrene (177)



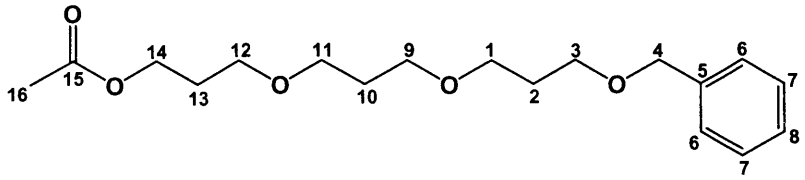
To a suspension of **176** (150. mg, 3.00 x 10^{-1} mmol) in THF (0.92 mL) was added hydrochloric acid (0.08 mL), and the reaction mixture was shaken at room temperature for 16 hours. The resin was collected by filtration, washed with dichloromethane (3 x 5 mL), dimethyl formamide (3 x 5 mL), dimethyl formamide/water (5:1, 3 x 5 mL), THF (3 x 5 mL), and dichloromethane (3 x 5 mL), and dried *in vacuo* (121 mg recovered).

Second Chain Extension on Cross-Linked Polystyrene (178)



To a suspension of **177** (120. mg, 2.40 x 10^{-1} mmol) in anhydrous dichloromethane (1 mL) was added **165** (169 mg, 7.20 x 10^{-1} mmol), followed by sodium hydride (29 mg, 60 % in mineral oil, 0.72 mmol) and the reaction mixture was shaken at room temperature for 16 hours. The resin was collected by filtration, washed with dichloromethane (3 x 5 mL), dimethyl formamide (3 x 5 mL), dimethyl formamide/water (5:1, 3 x 5 mL), THF (3 x 5 mL), and dichloromethane (3 x 5 mL), and dried *in vacuo* (122 mg recovered).

Acetic acid 3-[3-(3-benzyloxy-propoxy)-propoxy]-propyl ester (179)



On Resin

To a suspension of **178** (118 mg, 2.40 x 10^{-1} mmol) in THF (1 mL) was added TBA acetate (21 mg, 0.70 x 10^{-1} mmol), and the reaction mixture was shaken at room temperature for 16 hours. The resin was filtered off and washed with dichloromethane (3 x 5 mL), THF (3 x 5 mL), and THF/methanol (3:1, 3 x 5 mL). The filtrate and washes were combined, and the solvent was removed *in vacuo*. Flash chromatography of the crude product (9:1, hexane/ethyl acetate) afforded the title compound as a yellow oil (5 mg, 0.02 mmol, 8 %), as well as **175** (4 mg, 0.02 mmol, 8 %).

On PEG

To a solution of **185** (400. mg, 1.80 x 10^{-1} mmol), in acetone (50 mL), was added TBA acetate (84 mg, 0.28 mmol), and the reaction mixture was stirred at 50 °C for 16 hours. The solution was concentrated *in vacuo*, to a volume of ~ 1 mL, and diethyl ether (100 mL) was added. The precipitated white solid was removed by filtration, and the filtrate was washed with water (3 x 50 mL). The organic layer was separated and dried over magnesium sulfate, filtered, and the solvent was removed *in vacuo*. Flash chromatography of the crude product (85:15 then 1:1, hexane/ethyl acetate) afforded the title compound as a yellow oil (22 mg, 0.67 x 10^{-1} mmol, 37 %), as well as **175** (3 mg, 0.01 mmol, 6 %).

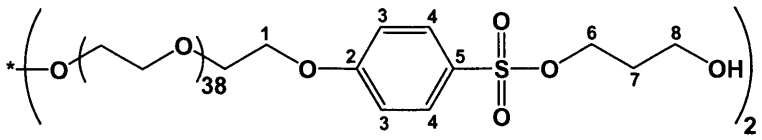
δ_H (300 MHz; $CDCl_3$) 1.80 (2H, quin, *J* 6.4 Hz), 1.87 (4H, quin, *J* 6.4 Hz), 2.04 (3H, s, H-16), 3.46 (8H, t, *J* 6.2 Hz), 3.50 (2H, t, *J* 6.3 Hz), 3.55 (2H, t, *J* 6.4 Hz), 4.13 (2H, t, *J* 6.5 Hz, H-14), 4.49 (2H, s, H-4), 7.25-7.35 (5H, m, Ph)

δ_C (75 MHz; $CDCl_3$) 21.0 (C-16), 29.0, 30.0, 30.1, 61.8, 67.2, 67.4, 67.8, 67.8, 67.9, 72.9 (C-4), 127.5 (Ph), 127.6 (Ph), 128.3 (Ph), 138.5 (C-5), 171.1 (C-15)

m/z (CI+) 347 ($[M + Na]^+$, $C_{18}H_{28}O_5$, 20 %), 217 (35 %), 176 (100 %)

HRMS (CI+) $C_{18}H_{28}O_5$ $[M + Na]^+$ requires 347.18343, found 347.18392

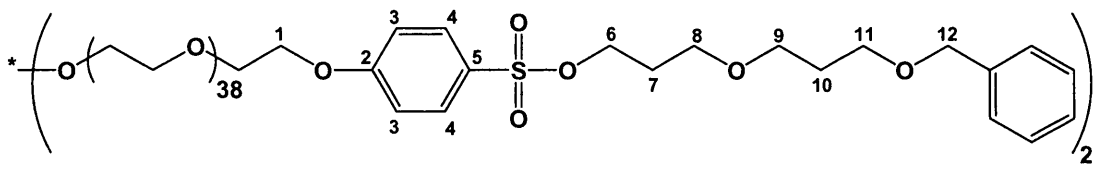
Loading of Diol onto PEG Support (180)



To a solution of **142** (5.00 g, 2.67 mmol) in anhydrous dichloromethane (50 mL), over 3 Å molecular sieves (1 g), was added propane-1,3-diol (**114**) (0.96 mL, 13 mmol) and the reaction mixture was stirred at room temperature for 16 hours. Triethylamine (1.86 mL, 13.3 mmol) was added and the reaction mixture was stirred for a further 24 hours. The molecular sieves were removed by filtration through celite, the solvent was removed *in vacuo*, and the crude product was dissolved in hot propan-2-ol (50 mL). The solution was cooled to 5 °C in a refrigerator, the precipitate was collected by filtration. The crude product was washed with propan-2-ol (20 mL) and diethyl ether (50 mL), and dried *in vacuo* to afford the title compound as a colourless solid (4.37 g, 2.28 mmol, 86 %).

δ_H (300 MHz; $CDCl_3$) 1.87 (4H, quin, *J* 6.0 Hz, H-7), 3.38-3.88 (m, PEG CH_2), 4.17-4.20 (m, PEG CH_2), 7.03 (4H, d, *J* 9.1 Hz, H-3), 7.83 (4H, d, *J* 9.1 Hz, H-4)

Chain Extension on PEG (181)

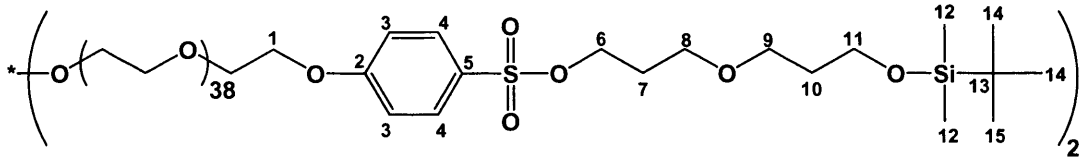


A solution of **180** (2.00 g, 1.04 mmol) in anhydrous dichloromethane (10 mL), over 3 Å molecular sieves (500 mg) was stirred at room temperature, for 16 hours. Compound **165** (364 mg, 1.57 mmol) was added, followed by cautious addition of sodium hydride (63 mg, 60 % in mineral oil, 1.6 mmol), and the reaction mixture

was stirred for a further 24 hours. Triethylamine (0.44 mL, 3.1 mmol) was added, and the reaction mixture was stirred for a further hour. The molecular sieves were removed by filtration through celite, the solvent was removed *in vacuo*, and the crude product was dissolved in hot propan-2-ol (50 mL). The solution was cooled to 5 °C in a refrigerator, the precipitate was collected by filtration. The crude product was washed with propan-2-ol (30 mL) and diethyl ether (50 mL), and dried *in vacuo* to afford the title compound as a colourless solid (1.89 g, 9.20 x 10^{-1} mmol, 88 %).

δ_H (300 MHz; $CDCl_3$) 1.79 (4H, quin, *J* 6.3 Hz), 1.85 (4H, quin, *J* 6.2 Hz), 3.38-3.86 (m, PEG CH_2), 4.07-4.17 (m, PEG CH_2), 4.46 (4H, s, H-12), 6.99 (4H, d, *J* 9.0 Hz, H-3), 7.27-7.35 (5H, m, Ph), 7.80 (4H, d, *J* 9.0 Hz, H-4)

Chain Extension on PEG (183)

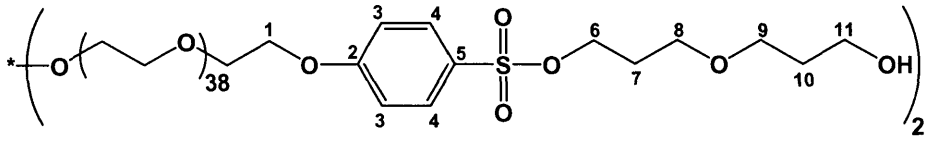


A solution of **180** (3.00 g, 1.56 mmol) in anhydrous dichloromethane (15 mL), over 3 Å molecular sieves (1 g) was stirred at room temperature, for 16 hours. Compound **166** (608 mg, 2.35 mmol) was added, followed by cautious addition of sodium hydride (94 mg, 60 % in mineral oil, 2.4 mmol), and the reaction mixture was stirred for a further 24 hours. Triethylamine (0.66 mL, 4.7 mmol) was added, and the reaction mixture was stirred for a further hour. The molecular sieves were removed by filtration through celite, the solvent was removed *in vacuo*, and the crude product was dissolved in hot propan-2-ol (80 mL). The solution was cooled to 5 °C in a refrigerator and the precipitate was collected by filtration. The crude product was washed with propan-2-ol (50 mL) and diethyl ether (80 mL), and dried *in vacuo* to afford the title compound as a colourless solid (2.99 g, 1.42 mmol, 91 %).

δ_H (300 MHz; $CDCl_3$) -0.03 and 0.01 (6H, s, H-12), 0.80 and 0.85 (9H, s, H-14), 1.67 and 1.80 (4H, quin, *J* 6.0 Hz), 1.86 (4H, quin, *J* 6.2 Hz), 3.38-3.87 (m, PEG

CH_2), 4.08-4.18 (m, PEG CH_2), 7.00 (4H, d, *J* 8.9 Hz, H-3), 7.80 (4H, d, *J* 8.9 Hz, H-4)

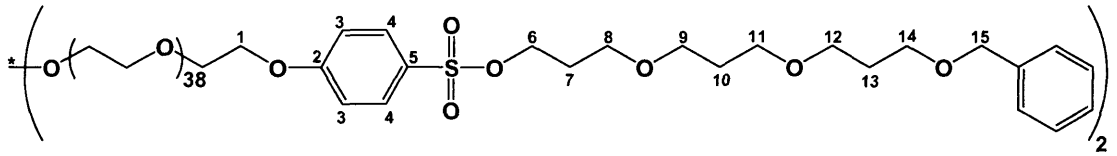
Deprotection on PEG (184)



To a solution of **183** (2.00 g, 9.60 x 10^{-1} mmol) in methanol (100 mL) was added hydrochloric acid (1 mL, 14.4 mmol) and the reaction mixture was stirred at room temperature for 16 hours. Amberlyst® A21 ion-exchange resin (5 g) was added and the reaction mixture was stirred for a further hour. The resin was removed by filtration, the solvent was removed *in vacuo*, and the crude product was dissolved in hot propan-2-ol (30 mL). The solution was cooled to 5 °C in a refrigerator and the precipitate was collected by filtration. The crude product was washed with propan-2-ol (10 mL) and diethyl ether (30 mL), and dried *in vacuo* to afford the title compound as a colourless solid (1.35 g, 6.82 x 10^{-1} mmol, 71 %)

δ_H (300 MHz; $CDCl_3$) 1.74 (4H, quin, *J* 6.0 Hz), 1.89 (4H, quin, *J* 5.7 Hz), 3.40-3.88 (m, PEG CH_2), 4.08-4.21 (m, PEG CH_2), 7.03 (4H, d, *J* 8.5 Hz, H-3), 7.83 (4H, d, *J* 8.5 Hz, H-4)

Second Chain Extension on PEG (185)

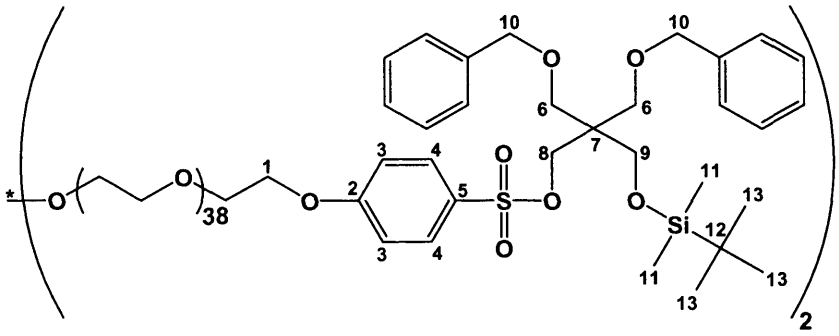


A solution of **184** (1.35 g, 6.82 x 10^{-1} mmol) in anhydrous dichloromethane (5 mL), over 3 Å molecular sieves (500 mg) was stirred at room temperature, for 16 hours. Compound **165** (236 mg, 1.02 mmol) was added, followed by cautious addition of sodium hydride (41 mg, 60 % in mineral oil, 1.0 mmol), and the reaction mixture was stirred for a further 24 hours. Triethylamine (0.28 mL, 2.0 mmol) was added,

and the reaction mixture was stirred for a further hour. The molecular sieves were removed by filtration through celite, the solvent was removed *in vacuo*, and the crude product was dissolved in hot propan-2-ol (30 mL). The solution was cooled to 5 °C in a refrigerator and the precipitate was collected by filtration. The crude product was washed with propan-2-ol (10 mL) and diethyl ether (30 mL), and dried *in vacuo* to afford the title compound as a colourless solid (938 mg, 4.36 x 10^{-1} mmol, 64 %)

δ_H (300 MHz; $CDCl_3$) 1.73 (4H, quin, *J* 6.4 Hz), 1.85 (4H, quin, *J* 6.3 Hz), 1.86 (4H, quin, *J* 6.1 Hz), 3.39-3.87 (m, PEG CH_2), 4.09-4.47 (m, PEG CH_2), 7.01 (4H, d, *J* 9.0 Hz, H-3), 7.28-7.35 (10H, m, Ph), 7.81 (4H, d, *J* 9.0 Hz, H-4)

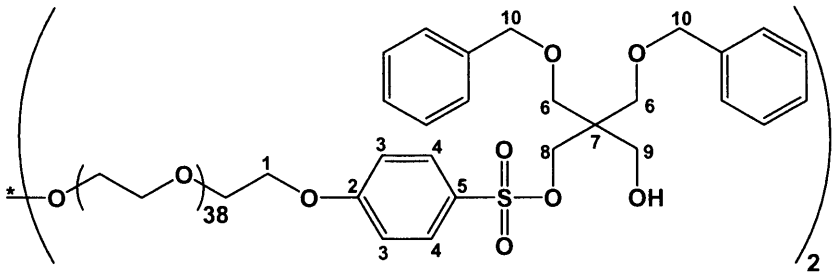
Loading of Monomer onto PEG Support (186)



To a solution of **142** (3.00 g, 1.60 mmol) in anhydrous dichloromethane (10 mL), over 3 Å molecular sieves (500 mg), was added **133** (1.02 g, 2.40 mmol) and the reaction mixture was stirred at room temperature for 16 hours. DMAP (293 mg, 2.40 mmol) was added and the reaction mixture was stirred for a further 24 hours. The molecular sieves were removed by filtration through celite, the solvent was removed *in vacuo*, and the crude product was dissolved in hot propan-2-ol (20 mL). The solution was cooled to 5 °C in a refrigerator and the precipitate was collected by filtration. The crude product was washed with propan-2-ol (10 mL) and diethyl ether (20 mL), and dried *in vacuo* to afford the title compound as a colourless solid (2.80 g, 1.24 mmol, 77 %)

δ_H (300 MHz; $CDCl_3$) -0.03 (12H, s, H-11), 0.81 (18H, s, H-13), 3.38 (8H, s, H-6), 3.39-3.88 (m, PEG CH_2), 4.05 (4H, s), 4.10 (4H, t, *J* 4.5 Hz, H-1), 4.38 (8H, s, H-10), 6.91 (4H, d, *J* 8.3 Hz, H-3), 7.19-7.29 (20H, m, Ph), 7.85 (4H, d, *J* 8.3 Hz, H-4)

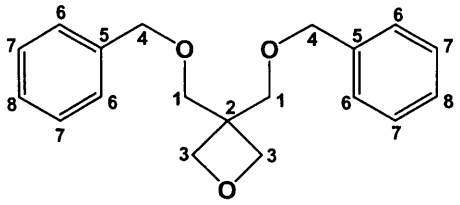
Deprotection on PEG (187)



To a solution of **186** (2.75 g, 1.21 mmol) in methanol (125 mL) was added hydrochloric acid (1.25 mL, 15.3 mmol) and the reaction mixture was stirred at room temperature for 16 hours. Amberlyst® A21 ion-exchange resin (5 g) was added and the reaction mixture was stirred for a further hour. The resin was removed by filtration, the solvent was removed *in vacuo*, and the crude product was dissolved in hot propan-2-ol (20 mL). The solution was cooled to 5 °C in a refrigerator and the precipitate was collected by filtration. The crude product was washed with propan-2-ol (10 mL) and diethyl ether (20 mL), and dried *in vacuo* to afford the title compound as a colourless solid (2.59 g, 1.20 mmol, 99 %)

δ_H (300 MHz; $CDCl_3$) 3.38-3.85 (m, PEG CH_2), 3.43 (8H, s, H-6), 4.09 (4H, s), 4.10 (4H, t, *J* 4.5 Hz, H-1), 4.39 (8H, s, H-10), 6.94 (4H, d, *J* 9.0 Hz, H-3), 7.17-7.20 (8H, m, Ph), 7.26-7.32 (12H, m, Ph), 7.77 (4H, d, *J* 9.0 Hz, H-4)

3,3-Bis-benzyloxymethyl-oxetane (188) [87]



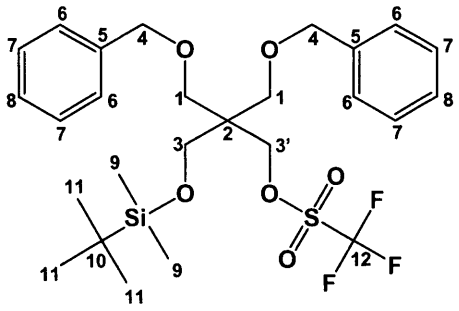
To a solution of **187** (200. mg, 1.00 x 10^{-1} mmol) in anhydrous THF (5 mL), over 3 Å molecular sieves (500 mg), was added potassium *tert*-butoxide (16 mg, 0.14 mmol) and the reaction mixture was stirred at room temperature for 16 hours. The sieves were removed by filtration, and the solution was concentrated *in vacuo* to a volume of ~1 mL. Diethyl ether (10 mL) was added and the precipitated white solid was removed by filtration. The solvent was removed *in vacuo*, and the crude product was filtered through a short pad of silica, eluting with ethyl acetate/ hexane (1:3) to afford the title compound as a clear oil (29 mg, 9.7 x 10^{-1} mmol, 97 %). (Lit. reports the synthesis of **188** using alternative methodology).

δ_H (300 MHz; $CDCl_3$) 3.70 (4H, s, H-1), 4.48 (4H, s, H-4), 4.54 (4H, s, H-3), 7.27-7.36 (10 H, m, Ph)

δ_C (75 MHz; $CDCl_3$) 43.8 (C-2), 71.4 (C-1), 73.4 (C-3 and C-4), 127.6 (Ph), 127.6 (Ph), 128.4 (Ph), 138.2 (C-5)

m/z (ES+) 321 ($[M + Na]^+$, $C_{19}H_{22}O_3$, 100 %)

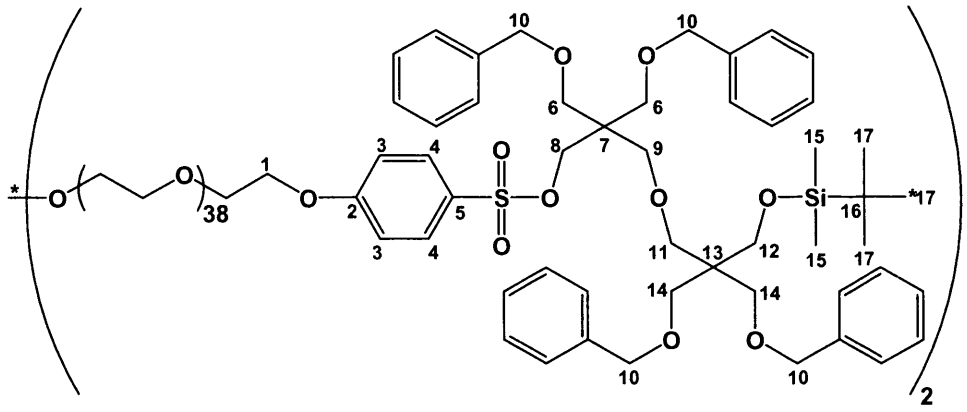
1,1,1-Trifluoro-methanesulfonic acid 3-benzyloxy-2-benzyloxymethyl-2(*tert*-butyl-dimethyl-silanyloxymethyl)-propyl ester (189)



To a solution of **133** (128 mg, 2.97 x 10^{-1} mmol) in anhydrous dichloromethane (3 mL), was added 2,6-lutidine (0.13 mL, 1.1 mmol). The reaction mixture was cooled in an ice bath and trifluoro-methanesulfonic anhydride (0.06 mL, 0.4 mmol), was added dropwise, over 10 minutes, with stirring. The reaction mixture was stirred at 5 °C for a further 5 minutes, and then filtered through a short pad of silica, to afford the title compound as a pink oil (161 mg, 28.5 x 10^{-1} mmol, 96 %)

ν_{max} (KBr)/cm^{-1} 3032 (w), 2930 (s), 1414 (s), 1207 (s), 949 (s)
δ_H (300 MHz; $CDCl_3$) 0.02 (6H, s, H-9), 0.86 (9H, s, H-11), 3.46 (4H, s, H-1), 3.57 (2H, s, H-3), 4.47 (4H, s, H-4), 4.58 (2H, s, H-3), 7.25-7.35 (10H, m, Ph)
m/z (FAB+) 563 ($[M + H]^+$, $C_{26}H_{37}O_4FSSi$, 100 %), 307 (30 %), 154 (100 %)
HRMS (FAB+) $C_{26}H_{37}O_4FSSi$ $[M + H]^+$ requires 563.21103, found 563.2

Chain Extension on PEG (190)

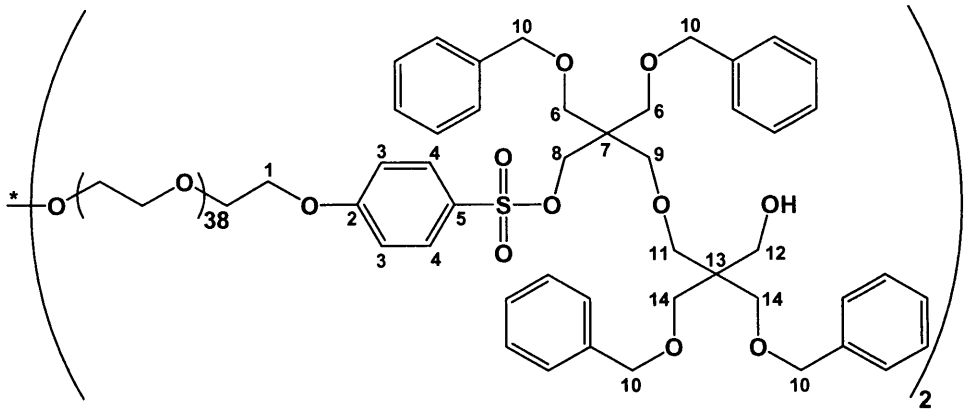


A solution of **187** (200. mg, 9.31 x 10^{-2} mmol) in anhydrous dichloromethane (5 mL), over 3 Å molecular sieves (100 mg) was stirred at room temperature, for 16 hours. Compound **189** (156 mg, 2.79 x 10^{-1} mmol) was added, followed by cautious addition of sodium hydride (6 mg, 60 % in mineral oil, 0.1 mmol), and the reaction mixture was stirred for a further 24 hours. Triethylamine (0.04 mL, 0.3 mmol) was added, and the reaction mixture was stirred for a further hour. The molecular sieves were removed by filtration through celite, the solvent was removed *in vacuo*, and the crude product was dissolved in hot propan-2-ol (10 mL). The solution was cooled to 5 °C in a refrigerator and the precipitate was collected by filtration. The crude product was washed with propan-2-ol (5 mL) and diethyl ether (10 mL), and dried *in vacuo* to afford the title compound as a colourless solid (169 mg, 7.16 x 10^{-2} mmol, 77 %). ^{1}H NMR also indicated that a small amount of **141** had been formed.

δ_H (300 MHz; $CDCl_3$) -0.02 (12H, s, H-15), 0.82 (18H, s, H-17), 3.39-3.88 (m, PEG CH_2), 3.42 (8H, s), 3.49 (8H, s), 4.06 (4H, s), 4.13 (4H, t, *J* 4.7 Hz, H-1), 4.40 (16H, s, H-10), 6.93 (4H, d, *J* 8.9 Hz, H-3), 7.20-7.23 (16H, m, Ph), 7.27-7.33 (24H, m, Ph), 7.78 (4H, d, *J* 8.9 Hz, H-4)

(See appendix B for ^{1}H NMR spectrum)

Deprotection on PEG (192)

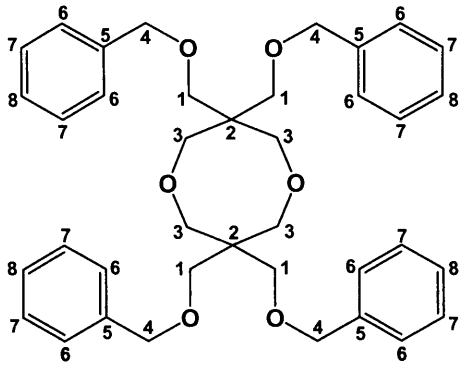


To a solution of **190** (750. mg, 1.21 mmol) in methanol (30 mL) was added hydrochloric acid (0.33 mL, 4.0 mmol) and the reaction mixture was stirred at room temperature for 16 hours. Amberlyst® A21 ion-exchange resin (2 g) was added and the reaction mixture was stirred for a further hour. The resin was removed by filtration, the solvent was removed *in vacuo*, and the crude product was dissolved in hot propan-2-ol (10 mL). The solution was cooled to 5 °C in a refrigerator and the precipitate was collected by filtration. The crude product was washed with propan-2-ol (5 mL) and diethyl ether (10 mL), and dried *in vacuo* to afford the title compound as a colourless solid (449 mg, 1.00 x 10^{-1} mmol, 83 %)

δ_H (300 MHz; $CDCl_3$) 3.38-3.88 (m, PEG CH_2), 3.44 (16H, s, H-6 and H-14), 4.10 (4H, s), 4.13 (4H, t, *J* 4.7 Hz, H-1), 4.40 (16H, s, H-10), 6.95 (4H, d, *J* 9.0 Hz, H-3), 7.19-7.21 (24H, m, Ph), 7.27-7.34 (24H, m, Ph), 7.78 (4H, d, *J* 9.0 Hz, H-4)

(See appendix C for ^{1}H NMR spectrum)

3,3,7,7-Tetrakis-benzyloxymethyl-[1,5]dioxocane (193)



To a solution of **192** (250. mg, 1.11 x 10^{-1} mmol) in anhydrous THF (5 mL), over 3 Å molecular sieves (500 mg), was added potassium *tert*-butoxide (18.7 mg, 0.17 mmol) and the reaction mixture was stirred at room temperature for 16 hours. The sieves were removed by filtration, and the solution was concentrated *in vacuo* to a volume of ~1 mL. Diethyl ether (10 mL) was added and the precipitated white solid was removed by filtration, followed by the removal of solvent *in vacuo* to afford the crude product as a yellow oil (38 mg). NMR and mass spectroscopic analysis of the crude product indicated a mixture of the title compound and **188**. HPLC analysis indicated that the products were in a 1:1 ratio.

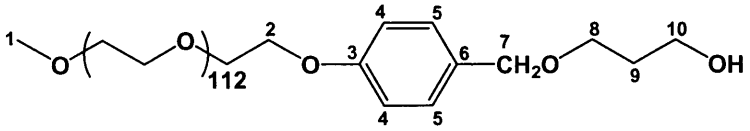
δ_H (300 MHz; $CDCl_3$) 3.70 (4H, s, H-1), 4.48 (4H, s, H-4), 4.54 (4H, s, H-3), 7.27-7.36 (10 H, m, Ph)

δ_C (75 MHz; $CDCl_3$) 43.8 (C-2), 71.4 (C-1), 73.4 (C-3 and C-4), 127.6 (Ph), 127.6 (Ph), 128.4 (Ph), 138.2 (C-5)

m/z (ES+) 619 ($[M + Na]^+$, $C_{38}H_{44}O_6$, 5 %), 321 (100 %)

7.5 Reductive Amination

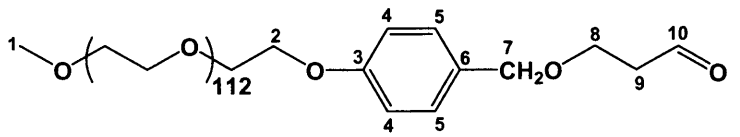
Loading of Diol onto PEG Support (194)



To a solution of **150** (500. mg, 1.00 x 10^{-1} mmol) in anhydrous dichloromethane (50 mL), at 0 °C, was added 1,3-propanediol (**114**) (0.07 mL, 1 mmol) and boron trifluoride diethyl etherate (0.01 mL, 0.05 mmol), and the reaction mixture was stirred, at 0 °C, for 1 hour. The solvent was removed *in vacuo*, and the crude product was dissolved in hot propan-2-ol (10 mL). The solution was cooled to 5 °C in a refrigerator, and then the precipitate was collected by filtration and washed with propan-2-ol (5 mL), and diethyl ether (10 mL), and dried *in vacuo*, affording the title compound as a colourless solid (470. mg, 9.10 x 10^{-1} mmol, 91 %)

δ_H (300 MHz; $CDCl_3$) 1.83 (2H, quin, *J* 5.8 Hz, H-9), 3.36 (3H, s, H-1), 3.39-3.88 (m, PEG CH_2 and H-8 and H-10), 4.10 (2H, t, *J* 4.7 Hz, H-2), 4.42 (2H, s, H-7), 6.87 (2H, d, *J* 8.7 Hz, H-4), 7.22 (2H, d, *J* 8.7 Hz, H-5)

Oxidation to Aldehyde on PEG (196)



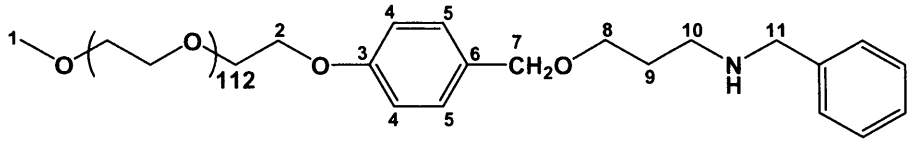
A solution of **194** (3.00 g, 5.81 x 10^{-1} mmol) in anhydrous acetonitrile (20 mL), over 3 Å molecular sieves (500 mg) was stirred at room temperature, for 16 hours. NMO (136 mg, 1.16 mmol) and TPAP (20. mg, 0.58 x 10^{-1} mmol) were added, and the reaction mixture was stirred for a further 24 hours. The molecular sieves were removed by filtration through celite, the solvent was removed *in vacuo*, and the crude product was dissolved in hot propan-2-ol (50 mL). The solution was cooled to 5 °C in a refrigerator and the precipitate was collected by filtration. The crude product was

washed with propan-2-ol (20 mL) and diethyl ether (50 mL), and dried *in vacuo* to afford the title compound as a grey solid (2.43 g, 4.71 x 10^{-1} mmol, 81 %)

δ_H (300 MHz; $CDCl_3$) 2.67 (2H, dt, *J* 6.1 Hz and 1.9 Hz, H-9), 3.37 (3H, s, H-1), 3.39-3.88 (m, PEG CH_2), 4.11 (2H, t, *J* 4.9 Hz, H-2), 4.44 (2H, s, H-7), 6.88 (2H, d, *J* 8.9 Hz, H-4), 7.22 (2H, d, *J* 8.9 Hz, H-5), 9.77 (1H, t, *J* 1.9 Hz, H-10)

(See appendix D for ^{1}H NMR spectrum)

Reductive Amination on PEG (198)

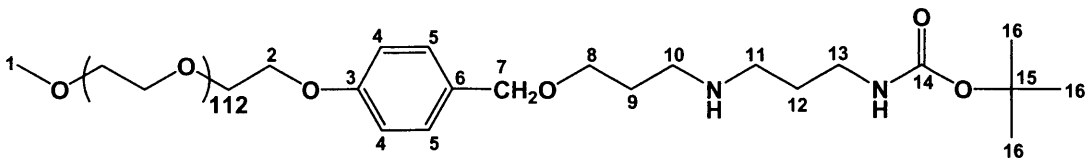


To a solution of **196** (200. mg, 3.87 x 10^{-2} mmol) in methanol was added benzylamine (0.01 mL, 0.08 mmol) and sodium cyanoborohydride (4.87 mg, 7.75 x 10^{-2} mmol) and the reaction mixture was stirred at room temperature for 16 hours. The solvent was removed *in vacuo* and the crude product was dissolved in hot propan-2-ol (10 mL). The solution was cooled to 5 °C in a refrigerator and the precipitate was collected by filtration. The crude product was washed with propan-2-ol (5 mL) and diethyl ether (10 mL), and dried *in vacuo* to afford the title compound as a brown solid (158 mg, 2.94 x 10^{-2} mmol, 76 %)

δ_H (300 MHz; $CDCl_3$) 3.37 (m, H-1), 3.38-3.88 (m, PEG CH_2), 4.12 (t, *J* 5.3 Hz, H-2), 4.35 (s), 4.59 (s), 6.86 (m, H-4), 7.21 (m, H-5), 7.33 (m, Ph)

(See appendix E for ^{1}H NMR spectrum)

Reductive Amination on PEG (200)



To a solution of **196** (725 mg, 14.0 x 10^{-1} mmol) in methanol was added **199** (49 mg, 0.28 mmol) and sodium cyanoborohydride (18 mg, 0.28 mmol) and the reaction mixture was stirred at room temperature for 16 hours. The solvent was removed *in vacuo*, and the crude product was dissolved in hot propan-2-ol (20 mL). The solution was cooled to 5 °C in a refrigerator and the precipitate was collected by filtration. The crude product was washed with propan-2-ol (10 mL) and diethyl ether (20 mL), and dried *in vacuo* to afford the title compound as a brown solid (520. mg, 9.83 x 10^{-1} mmol, 70 %)

δ_H (300 MHz; $CDCl_3$) 1.42 (s, H-15), 2.16 (s), 3.37 (m, H-1), 3.38-3.88 (m, PEG CH_2), 4.10 (m, H-2), 4.42 (m), 4.59 (s), 6.86 (m, H-4), 7.21 (m, H-5)

(See appendix F for ^{1}H NMR spectrum)

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156. Thank you to Dr Anne-Cécile Hérve for the synthesis of compound **199**.

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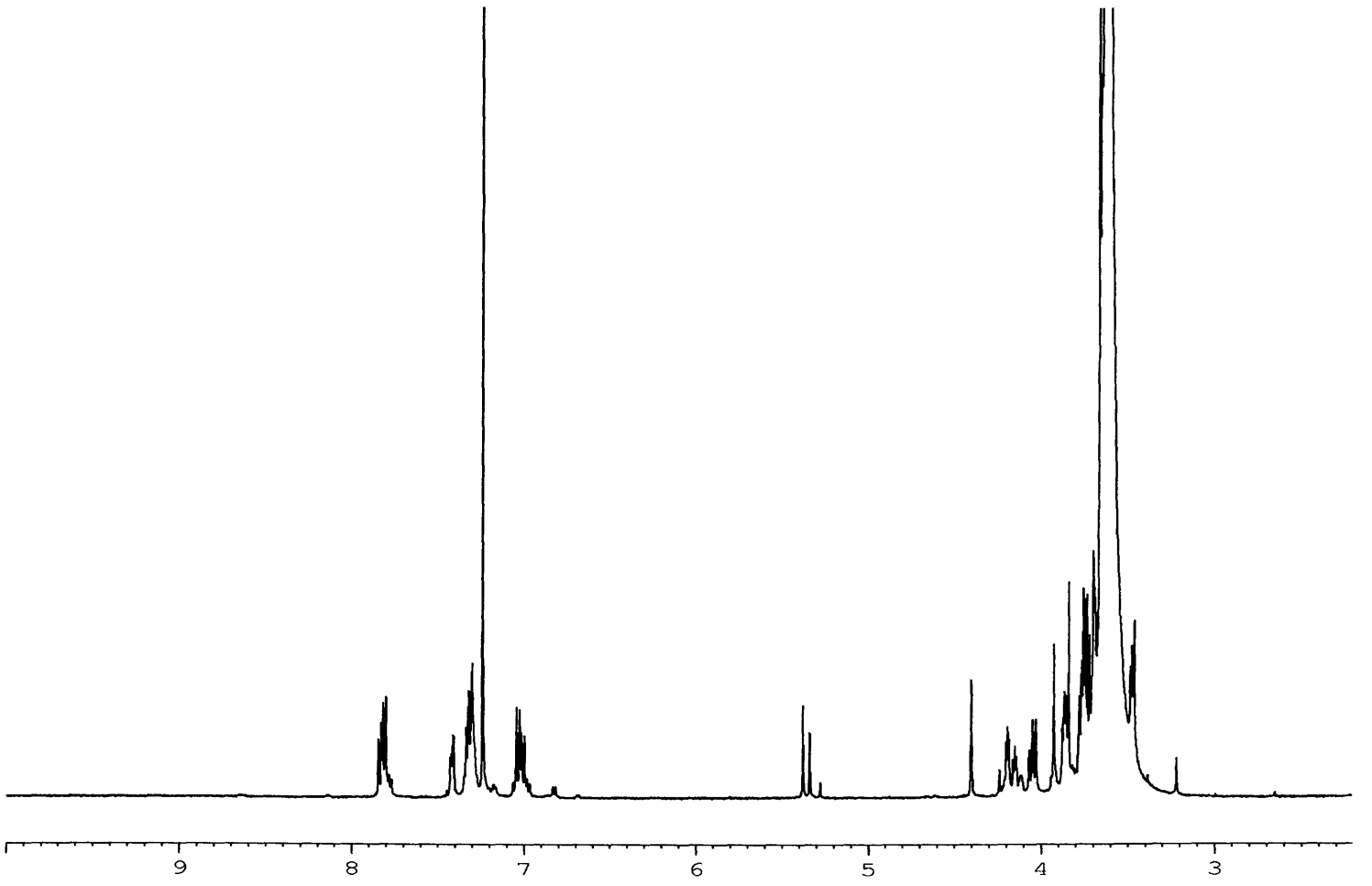
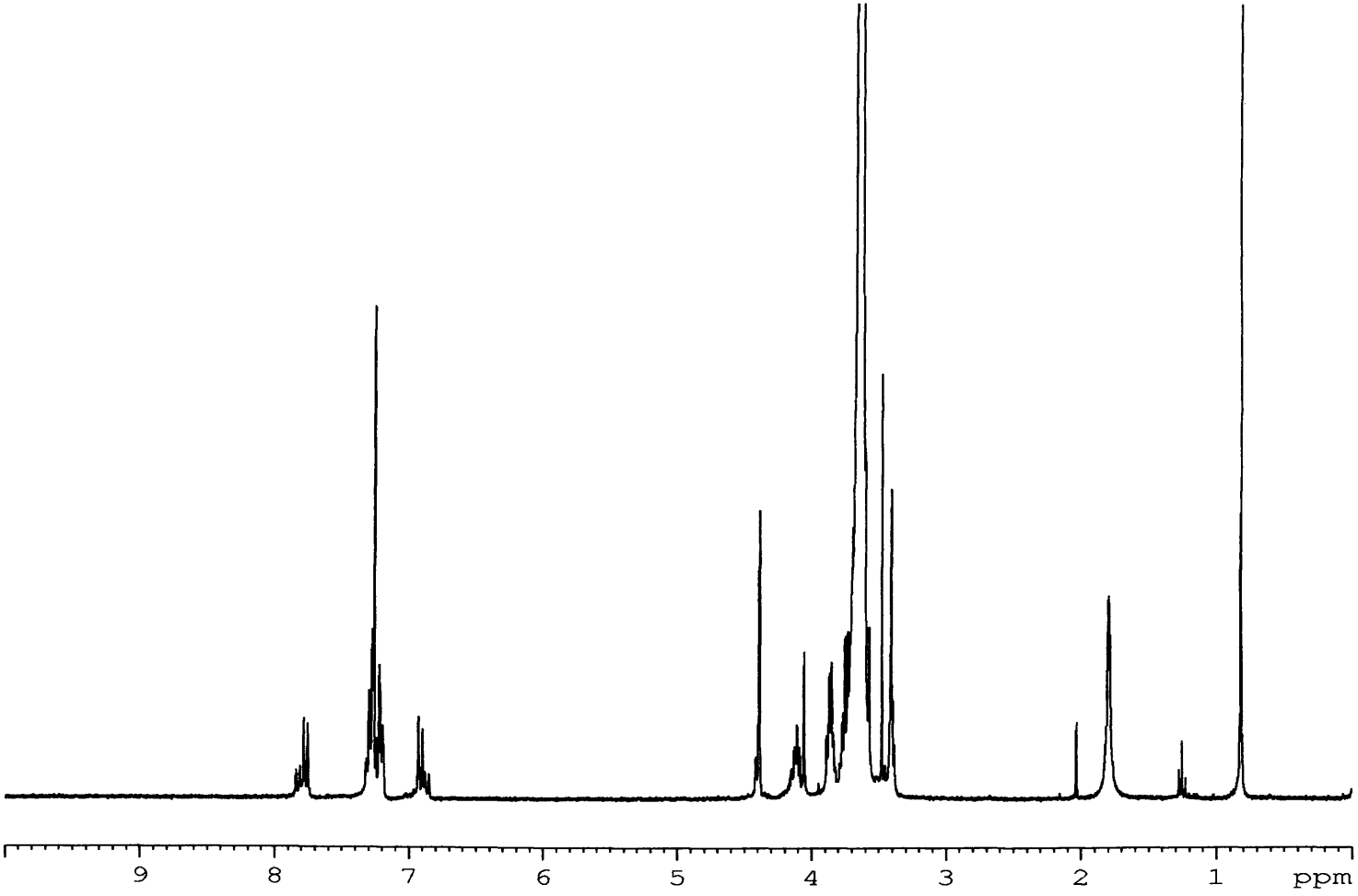
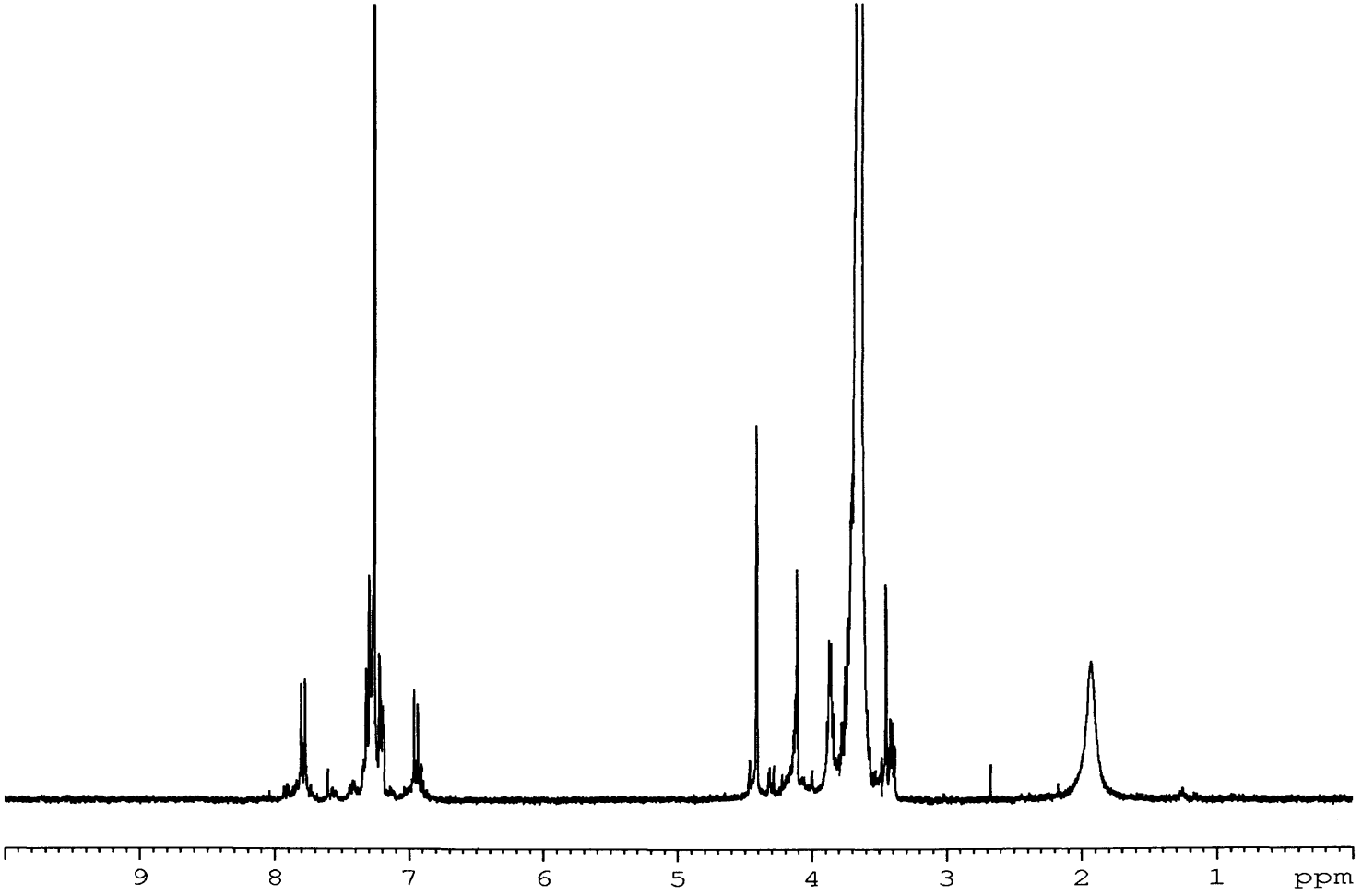
Appendix A ^{1}H NMR of **162**



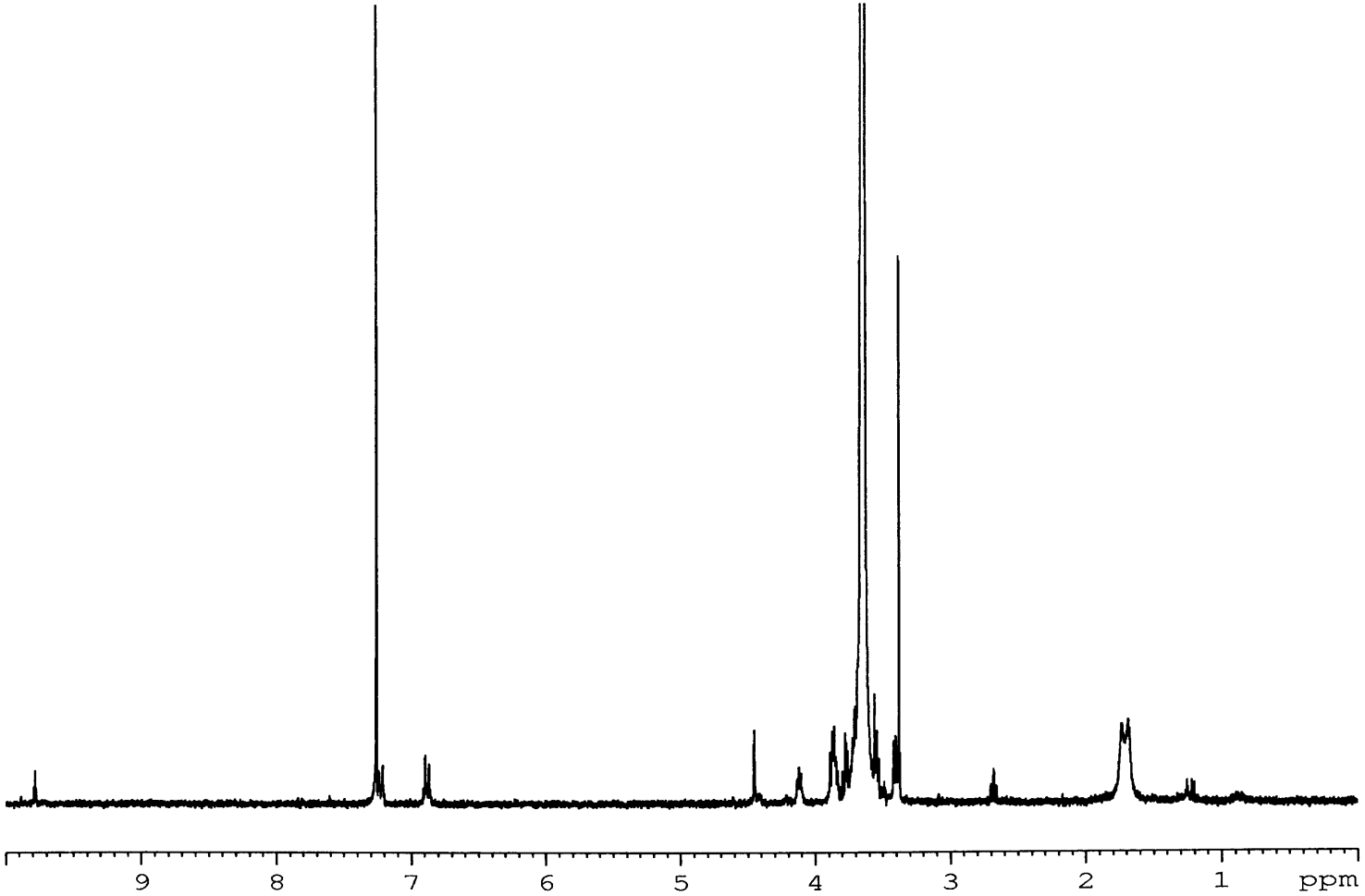
Appendix B ^{1}H NMR of **190**



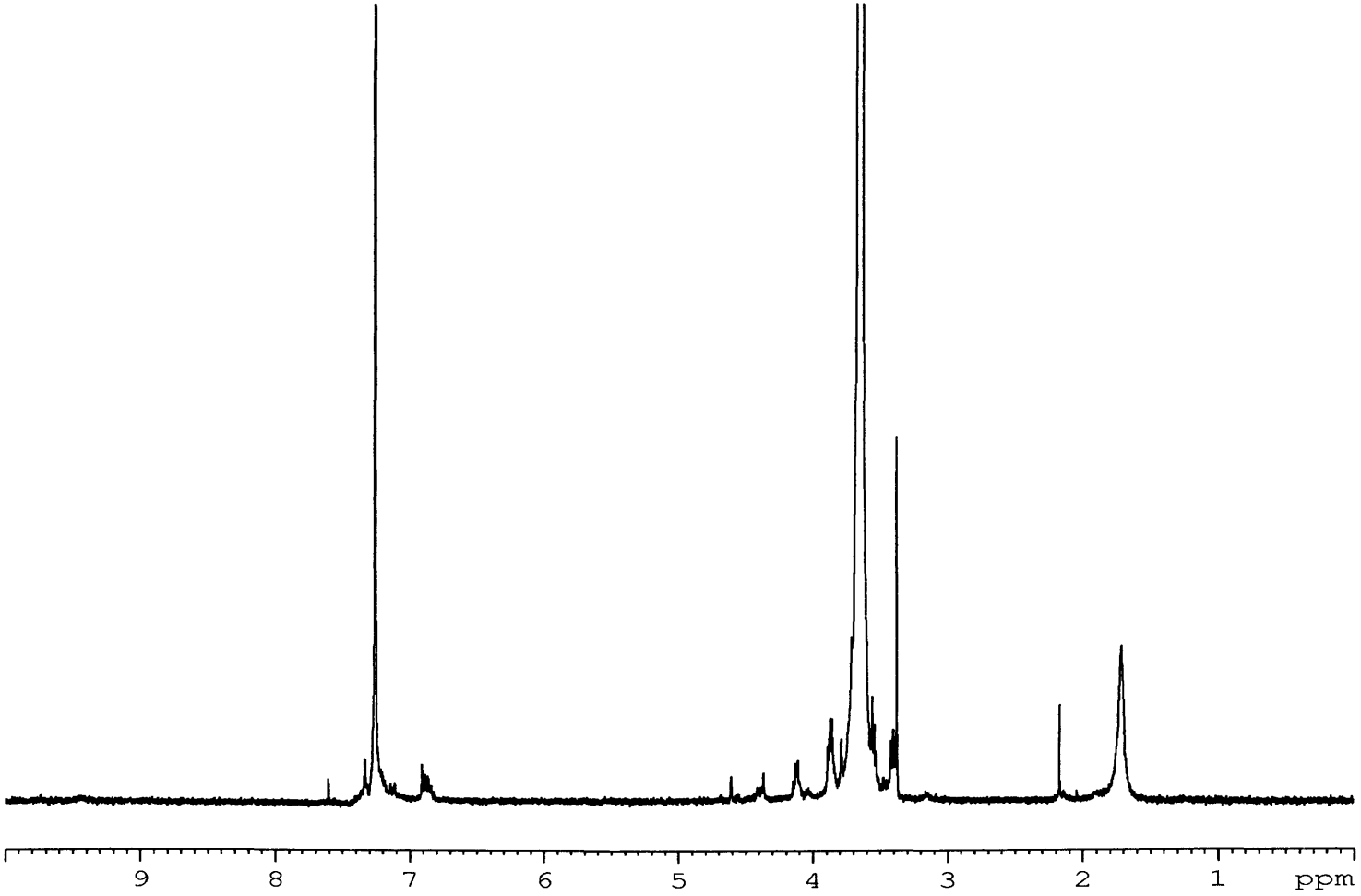
Appendix C ^{1}H NMR of **192**



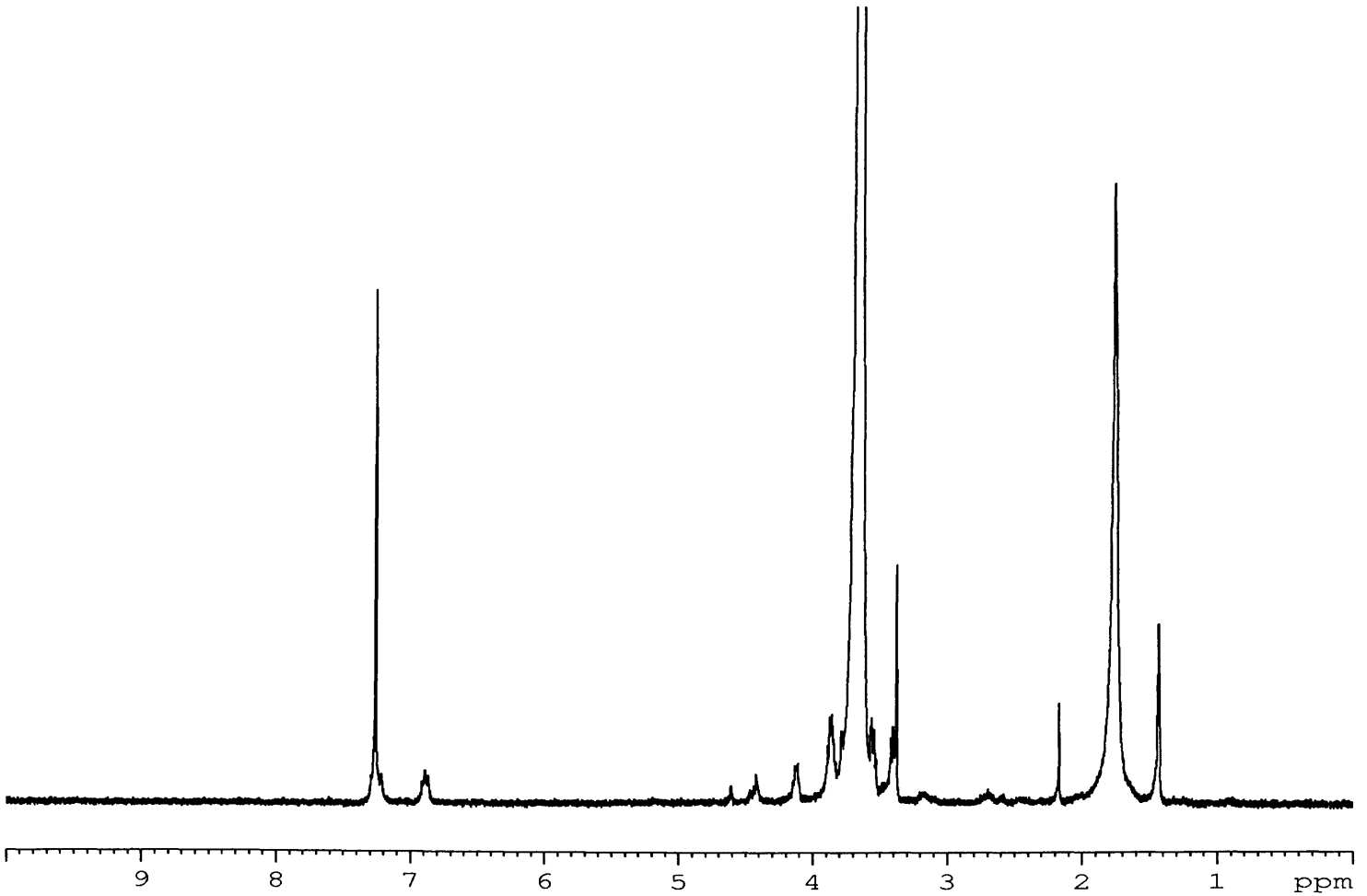
Appendix D ^{1}H NMR of **196**



Appendix E ^{1}H NMR of **198**



Appendix F ^{1}H NMR of **200**



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Oxetane synthesis via cyclisation of aryl sulfonate esters on polystyrene and PEG polymeric supports

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