Isotopically enriched crosslinked epoxy polymers

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Isotopically Enriched Crosslinked Epoxy Polymers

Jeffrey Robert White, B.Sc. (Hons)

Ph.D. Thesis

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Declaration

The work contained in this thesis was carried out in the Department of Chemistry at the University of Durham between October 1991 and September 1994. All the work is my own, unless otherwise indicated. It has not been previously submitted for a degree at this or any other university.

To Mum and Dad,
for giving me the chance

"Its a bleedin edyercayshin livin up heer, I tel u"

- Bascule

Feersum Endjinn
by Iain M. Banks

Acknowledgements

"No man does it all by himself"

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Finally, a huge 'thank you' goes to Mum, Dad and Peter, without whom...

Abbreviations

●	: carbon isotope label (^{13}C or ^{14}C)
Ac	: acetyl
Ar	: aryl group
b.p.	: boiling point
BADGE	: bisphenol-A diglycidyl ether
Bu	: butyl
CI	: chemical ionisation
CP	: cross polarisation
d	: doublet
DDS	: diaminodiphenylsulfone
DMAP	: N,N-dimethylaminopyridine
DMF	: N,N-dimethylformamide
DMSO	: dimethylsulfoxide
ee	: enantiomeric excess
EI	: electron impact
Et	: ethyl
GC	: gas chromatography
GC-MS	: gas chromatography - mass spectroscopy
Hal	: halogen
HPPD	: high power proton decoupling
hplc	: high performance gas chromatography
IR	: infra red
LDA	: lithium diisopropylamide
m	: multiplet
MAS	: magic angle spinning
*m*CPBA	: 3-chloroperoxybenzoic acid
Me	: methyl
Ms	: methanesulfonyl
MS	: mass spectroscopy

m.p.	: melting point
NCS	: N-chlorosuccinimide
NMR	: nuclear magnetic resonance
NQS	: non-quaternary suppression
p	: pentet
Ph	: phenyl
py	: pyridine
q	: quartet
R	: alkyl group
s	: singlet
t	: triplet
TBDMS	: *tert*-butyldimethylsilyl
TBDPS	: *tert*-butyldiphenylsilyl
Tg	: glass transition temperature
TGDDM	: tetraglycidyldiaminodiphenylmethane
THF	: tetrahydrofuran
tlc	: thin layer chromatography
TMED	: N,N,N',N'-tetramethylethylenediamine
Ts	: *p*-toluenesulfonyl
Tr	: triphenylmethyl
X	: leaving group

Abstract

Isotopically Enriched Crosslinked Epoxy Polymers

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The epoxy resin system based on tetraglycidyldiaminodiphenylmethane (TGDDM) and diaminodiphenylsulfone (DDS) is widely used for high performance aerospace applications.

The desirable macroscopic properties of the TGDDM/DDS resin are dependant upon the microscopic network formed during resin curing, but to date work aimed at clarifying the structure of this network has proved inconclusive. This work further investigates the epoxy resin network structure, using the techniques of isotopic labelling and solid state nuclear magnetic resonance (NMR).

The synthesis of labelled TGDDM and DDS by known and original protocols has been investigated. A majority of the work was aimed at the unambiguous labelling with carbon-13 and deuterium of TGDDM, the success of which has led to the discovery of a versatile and convenient method of labelling epichlorohydrin. Nitrogen-15 labelled TGDDM and DDS were also synthesised, the latter using an original protocol.

Cured epoxy resins containing isotopic labels were produced, and investigated using solid state NMR. The presence of both linear and cyclised structures was observed, and their relative contributions to the network estimated. Unambiguous assignment of the solid state NMR spectrum was also made.

Finally, using samples and methodologies from the isotopic labelling syntheses, further small scale studies were carried out. A range of α-ketosulfonate compounds was synthesised to probe the formation reaction. The crystal structures of three related compounds containing different halogen substituents were compared. Two further epoxide compounds were synthesised and evaluated as potential epoxy resin additives. A bis-α-chloroketone was evaluated as a substrate for baker's yeast reduction, and yielded a diol with a high enantiomeric excess.

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CHAPTER 1

Introduction

Introduction

1.1 Epoxy Resins

The term 'epoxy resin' is a generic term[1,2], used to refer to any compound that contains two or more epoxide moieties and which can be reacted, or cured, to produce a three dimensional crosslinked matrix. The term refers to both the monomer and the polymer.

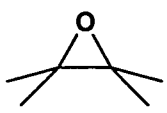


Figure 1.1 *An epoxide group*

The epoxide groups of the uncured resin may be polymerised to generate a homopolymer, but the more usual procedure is to use a hardener in conjunction with the epoxy resin. The hardener is generally a compound containing reactive groups such as alcohols, amines, or other nucleophilic groups, which react easily with the epoxide rings of the resin, opening the rings to give an alcohol.

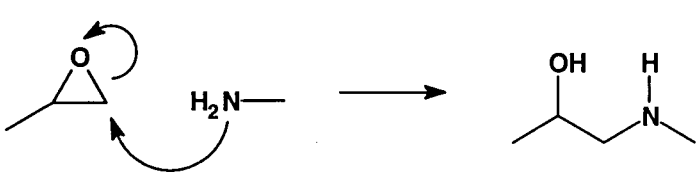


Figure 1.2 *Typical reaction of an epoxide group with an amine.*

While the initial work on epoxy based resin systems was carried out as early as 1920[1,2,3], the first compounds to be given the name of "epoxy resin", based on the reaction of bisphenol-A (2,2-di(4'-hydroxy-phenyl)propane) **(1)** and epichlorohydrin **(2)**, were made in the mid to late 1930's. The credit for their production is given jointly to two men,

Dr. Pierre Castan, working in Switzerland, and Dr O.S. Greenlee, working in the United States. Their uncured resins were of the type shown in Figure 1.3, consisting of a mixture of species of differing molecular weight. The molecular weight of the epoxy resin **(3)**, produced from the reaction of bisphenol-A **(1)** and epichlorohydrin **(2)** in the presence of a base such as NaOH, could be controlled by varying the conditions, in particular the amount of epichlorohydrin added. The larger the excess of the epoxide, the lower the molecular weight, with almost pure monomeric bisphenol-A diglycidyl ether (BADGE) (n=0) being produced when a tenfold excess was used.

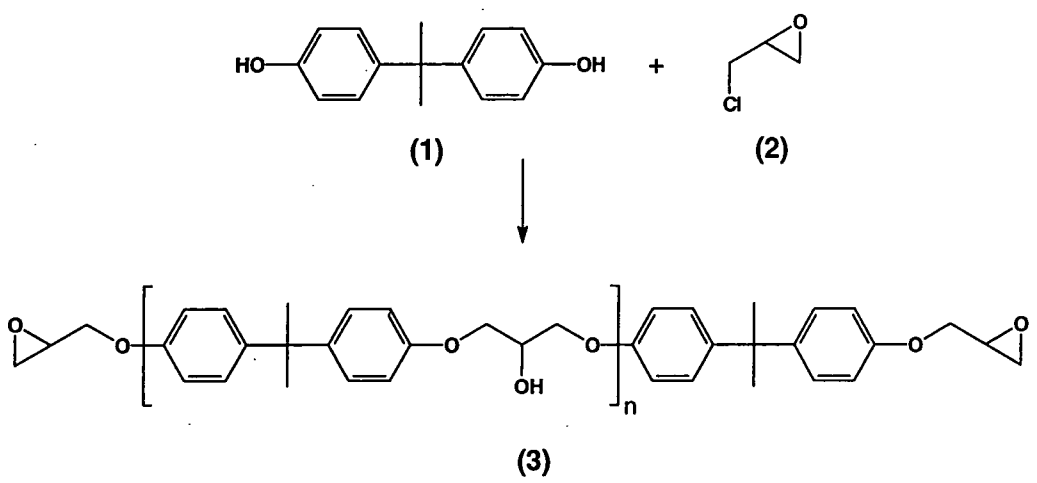


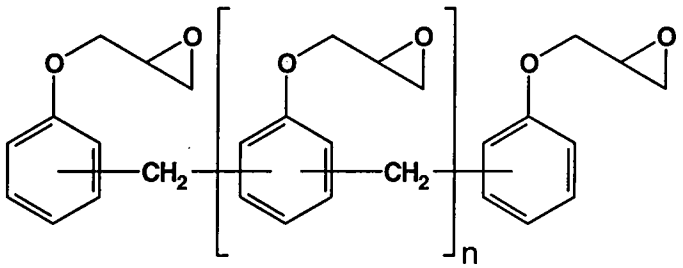
Figure 1.3 *Reaction of bisphenol-A (1) and epichlorohydrin (2) to give bisphenol-A diglycidyl ether (BADGE) (3)*

The use of several different types of hardeners was also explored during this early research. Castan used phthalic anhydride to cure his resins[1], while Schlack reported the use of a number of different hardeners, including organic and inorganic acids, amines and mercaptans.

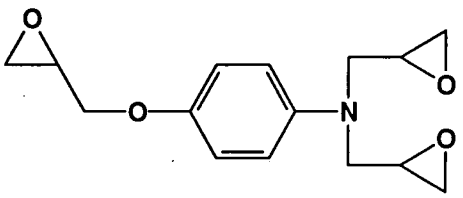
The commercial exploitation of these epoxy resins began in earnest in the late 1940's. In 1948 the production of bisphenol-A resins in the United States was virtually zero, but by 1957, 30 million pounds

weight was being consumed. By the end of 1965 over 110 million pounds was being used, with an annual increase of 10% in the following years[1].

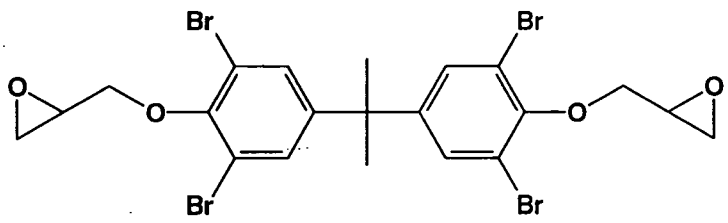
The rapid increase in consumption of epoxy resins was in part due to the introduction in the 1950's and 1960's of a number of new compounds based on species other than bisphenol-A. Figure 1.4 shows three such resins. The Novolac resins[2] **(4)** are an obvious progression from the bisphenol derivatives, but with an extended chain of aromatic rings and an increased number of epoxide groups. The N,N,O-triglycidyl *p*-aminophenol[5] **(5)** is just one of a family of resins based on aromatic amines rather than alcohols. Tetrabromobisphenol-A



Novolac Resins (4)



N,N,O-Triglycidyl *p*-aminophenol (5)



Tetrabromobisphenol-A diglycidyl ether (6)

Figure 1.4 *Three epoxy resins introduced in the 1950's and 1960's*

diglycidyl ether[1] **(6)** is produced by adding bromine to the normal synthesis of the bisphenol-A epoxy resin, and the bromide groups give the cured epoxy resin greatly increased flame resistance.

Epichlorohydrin **(2)** was still used as the epoxidising agent for the most part, but the relative expense of this compound was forcing research into other epoxidising methodology. Work by Dr Daniel Swern[1] into epoxidation of alkenes using peracids was utilised in the 1950's to produce epoxidised soyabean oil, and by 1963 some 5 million pounds weight of resin were being produced using peracids.

The rapid success of epoxy resins can be explained when their properties are examined[1-7]. Firstly, they are convenient to handle on a large scale, with many having low viscosity before cure, and convenient curing temperatures (5-150°C). These are both important considerations if the resin is to be used on an industrial scale, removing the need for specialist handling techniques and costly high temperature curing ovens.

Perhaps the most important feature of these materials is the low shrinkage and lack of volatile by-products when the resin is cured with the hardener. Non-uniform shrinkage of the resin would cause stress inside the matrix, weakening it and making it more likely to fail. The lack of shrinkage and volatile by-products ensures that the casting can be accomplished without any distortion or volatile-induced voids in the structure, and the lack of internal stress imparts high mechanical strength as a result. Another advantage is that when the low internal stress is combined with the large number of polar groups in the cured resin, it leads to very high adhesive strength.

Other attractive features of epoxy resins include their high electrical insulation properties, and their good chemical resistance, although the latter can depend on which hardeners are used.

With such properties as these, epoxy resins have found a number of applications, the most important of which is as an adhesive.

Araldite, made by Ciba-Gigy, is used for household adhesive purposes, while other specialist resins are used for high performance applications such as the aerospace industry[6,7]. The excellent adhesion, chemical resistance and electrical insulation properties also make epoxy resins attractive as surface coatings, paint additives and sealants, as well as encapsulation compounds and varnishes for the electrical and electronic industries. Epoxy resins have also found a role as casting compounds for short run and prototype moulds, stamping dies, patterns and such.

Epoxy resins have found a particularly significant use in the aerospace industry in the last 30 years, with the introduction epoxy resin based composite materials[6,7]. The combined properties of the epoxy matrix and the reinforcing fibres give a material that is both light and strong, and which offers an attractive alternative to established aircraft building materials.

1.2 Epoxy Resin Composite Materials

A composite material is generally defined as a system created from a reinforcing element and a compatible resin binder or matrix, to obtain specific properties[2,6,7]. The two elements retain their separate chemical and physical properties, and can be identified in the final product along with the interface between them. The reinforcing and matrix elements act in concert to produce the desired results, with the former as the load bearer and the latter acting as the load transfer agent, as well as giving rigidity and providing environmental protection.

Conventional materials such as metal alloys are often described as isotropic, as they behave identically no matter in which orientation their properties are tested. Composites, on the other hand, are anisotropic because their behaviour depends on which direction they are being tested in[6]. To illustrate, consider a composite reinforced with carbon fibres, all of which are laid out in the same direction. The strength of this material will be much greater along the direction of the fibres than it will be "across the grain", in much the same way as a plank of wood. This factor makes composite elements much harder to design and manufacture, but also provides the possibility of shaping them to fit exact design requirements.

Reinforced materials have been around since primitive man first used straw to strengthen buildings made of mud, but the first composites based on reinforced synthetic resins date from around the turn of the century, with Dr Leo Baekland's production of the reinforced phenol-aldehyde matrix called Bakelite[2]. Formica, another widely used material, was first made at around the same time, using the same phenol-aldehyde resins reinforced with layers of paper[2].

The use of these and other synthetic composite materials increased through the First World War and the interwar period up to

1939, helped in no small way by the growing radio industry, which consumed large amounts of such materials. By the end of this period, reinforced resin laminates were also appearing as parts for mechanical applications in cars, washing machines, vacuum cleaners, refrigerators etc., the lower cost of manufacture in comparison to conventional metal parts making them preferable.

The advent of the Second World War once more forced the pace of composite research. In particular, the need to protect delicate radar equipment from the elements without blocking their signals, made the search for suitable materials vitally important. It was for this purpose that glass fibres were first used, to reinforce a polyester resin and give the first "fibreglass" material.

It was during the Second World War that composites had their first application as aerospace components. The all-plywood Mosquito bomber was a practical demonstration of the benefits of reinforced composites[2], even if the reinforcing material was wood rather than the more advanced glass fibres. Less spectacular but perhaps more important was the successful testing in 1944 of the BT-15 aircraft, which had an experimental glass fibre reinforced plastic fuselage[2].

The use of epoxy resin composites began in earnest in the years after the war, especially those made with glass fibres, which found a number of applications in the aerospace industry. However, while the strength-to-weight ratios of these materials compare well with metals, the stiffness-to-weight ratios do not, which limited their use to non-loadbearing structures such as control surfaces, internal fittings and fairings. The event that changed this was the almost simultaneous development in the 1960's of boron fibres in the United States, and carbon fibres in the United Kingdom. When either of these are combined with an epoxy matrix to make a composite, they are superior to conventional aircraft building materials in both strength and stiffness, while still maintaining their light weight[5].

The development of the boron-epoxy composites in the US was more rapid than that of the carbon-epoxy composites in the UK, and the boron based system was the first to be incorporated into high performance military aircraft. The F-14 Tomcat carrier based fighter for example, went into production in 1969, and incorporated horizontal stabilisers with a boron-epoxy composite skin that had a 19% weight saving over a metal skin[5,6]. Boron-epoxy composites were also used in the tail section of the F-15 Eagle in 1975[6,7], but by the time the F-16 was going into production in 1977, carbon-epoxy composites were favoured on cost grounds over boron. The F-16 also had sections of it's tail fin assembly manufactured from composite materials[6,7].

A more extensive use of composite materials came in 1978, with the introduction of the F/A-18 Hornet, as shown in Figure 1.5, with composites making up approximately 35% of the surface area, and 9% of the mass of the aircraft[6,7]. The AV-8B (Harrier) took the trend even further, using composites as structural members as well as external skin, and making up 26% of the mass of the entire aircraft[6,7]. The most recent example shown is the new European Fighter Aircraft (EFA), which is presently at the prototype stage and due to go into production in the near future. Carbon fibre-epoxy resin composites make up about 80% of the surface area and 40% of the mass of this advanced design, figures which are broadly similar to those for the new US Advanced Tactical Fighter[5].

The use of epoxy composites for civilian aerospace applications has lagged behind those for military applications considerably, although composites are soon expected to make up as much as 15% of the mass of new civilian aircraft[5]. The delay in application of composites is partly due to the much larger structures need for large airliners, which are more difficult to manufacture and suffer from greater stresses due to their size.

Epoxy composites are of particular use for the rotor blades of

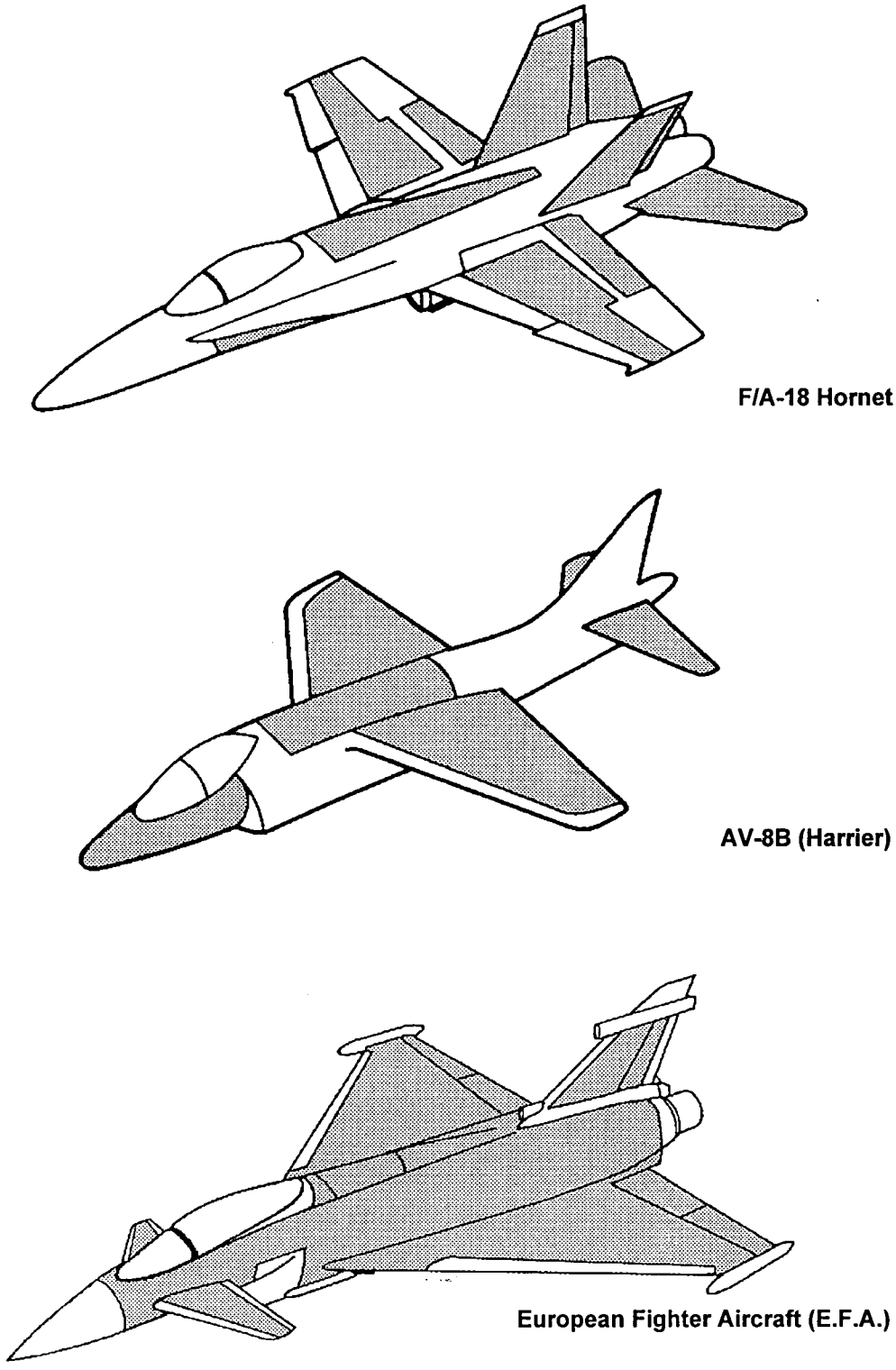


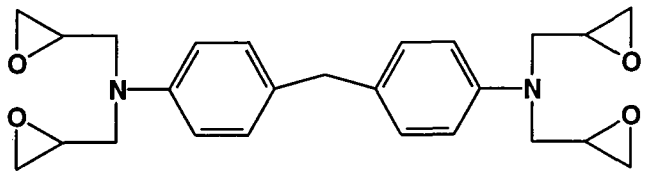
Figure 1.5 *Epoxy composite usage in three military aircraft*

helicopters, for in addition to being lighter than metal, the composite can have it's structure tailored to suit the needs of the blade[6]. The density and orientation of the carbon fibres can be altered to change the dynamic frequencies of the blade, and control it's crucial twisting and flopping frequencies.

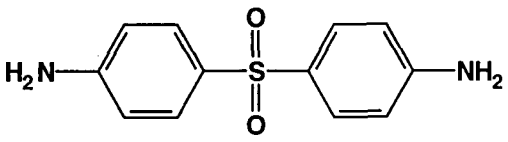
Composites have found many other applications where strength and low weight are advantageous, including missile casings[6], the cargo bay doors on the space shuttle[7], car chassis[6], and sporting goods such as tennis rackets[6]. The other properties of composites, such as vibration damping, design flexibility, chemical and environmental resistance and relative cheapness have produced a huge array of potential uses, which would take several volumes to describe and catalogue.

1.3 Epoxy Resins and Curing Mechanisms

The epoxy resins used for the manufacture of high performance composites have to meet exacting standards of strength, stiffness and temperature resistance, due to the extreme conditions they will have to endure as part of an aircraft fuselage. For example, when an aircraft flies at 40,000ft at a velocity of Mach 2.2, the leading edges of the wings can reach a temperature of 200°C[5]. The well known systems based on phenol epoxies, such as the diglycidyl ether of bisphenol-A **(3)** and the Novolac **(4)** epoxy resins, are unable to meet these standards, and other epoxies have had to be developed. The epoxy resin/hardener combination that is most favoured at the present time is that of tetraglycidyldiaminodiphenylmethane (TGDDM) **(7)** and diaminodiphenylsulfone (DDS) **(8)**, as shown in Figure 1.6.



Tetraglycidyldiaminodiphenyl methane (TGDDM) (7)



Diaminodiphenyl sulfone (DDS) (8)

Figure 1.6 *The two components of an epoxy resin system*

The tetra-epoxide[8,9] **(7)**, a viscous amber liquid, and the amine hardener **(8)**, a white powder, cure to give a brown, glassy resin with excellent mechanical properties and a glass transition temperature (Tg) in the region of 255-275°C[5], depending on the exact formulation. A

considerable amount of research has been carried out into the system's properties and behaviour, and it is the one regarded as the standard by which improvements in resin technology are measured.

While the macroscopic behaviour of the TGDDM/DDS resin has been studied extensively and is well understood, the chemical structure of the matrix is still not fully characterised. In order to improve the mechanical properties of the resin, the chemical structure of the matrix, and it's relationship to the behaviour of the cured resin must be investigated and clarified. Several different possible mechanisms for the curing reaction of TGDDM with DDS have been proposed[10], as shown in Figure 1.7.

The reaction pathway starts with the nucleophilic attack of a primary amine from the hardener at the terminal carbon of one of the epoxide groups from the epoxy resin. This gives a secondary amine and a secondary alcohol group which can then go on to react with either the second epoxide group of the resin molecule, or another epoxide group from a different epoxy resin molecule. During the early stages of the cure, when the matrix is only partially crosslinked and relatively mobile, it is expected that the various cyclisation reactions would be disfavoured, but as the reaction continues the resin will become less mobile, forcing the intramolecular reaction of the remaining free epoxide groups with nearby amine and alcohol groups. Another factor to take into consideration is that the number of alcohol groups will increase as the reaction proceeds, so increasing the probability of their taking a part in the curing.

Investigations carried out into the possible curing pathways have taken two approaches to the problem. The first involves the synthesis of model compounds, which are much easier to handle and characterise, and from which data on the full system may theoretically be inferred. The second method of investigation attempts to look directly at the cured resin with various spectroscopic techniques, and

thus gain information about how it has reacted.

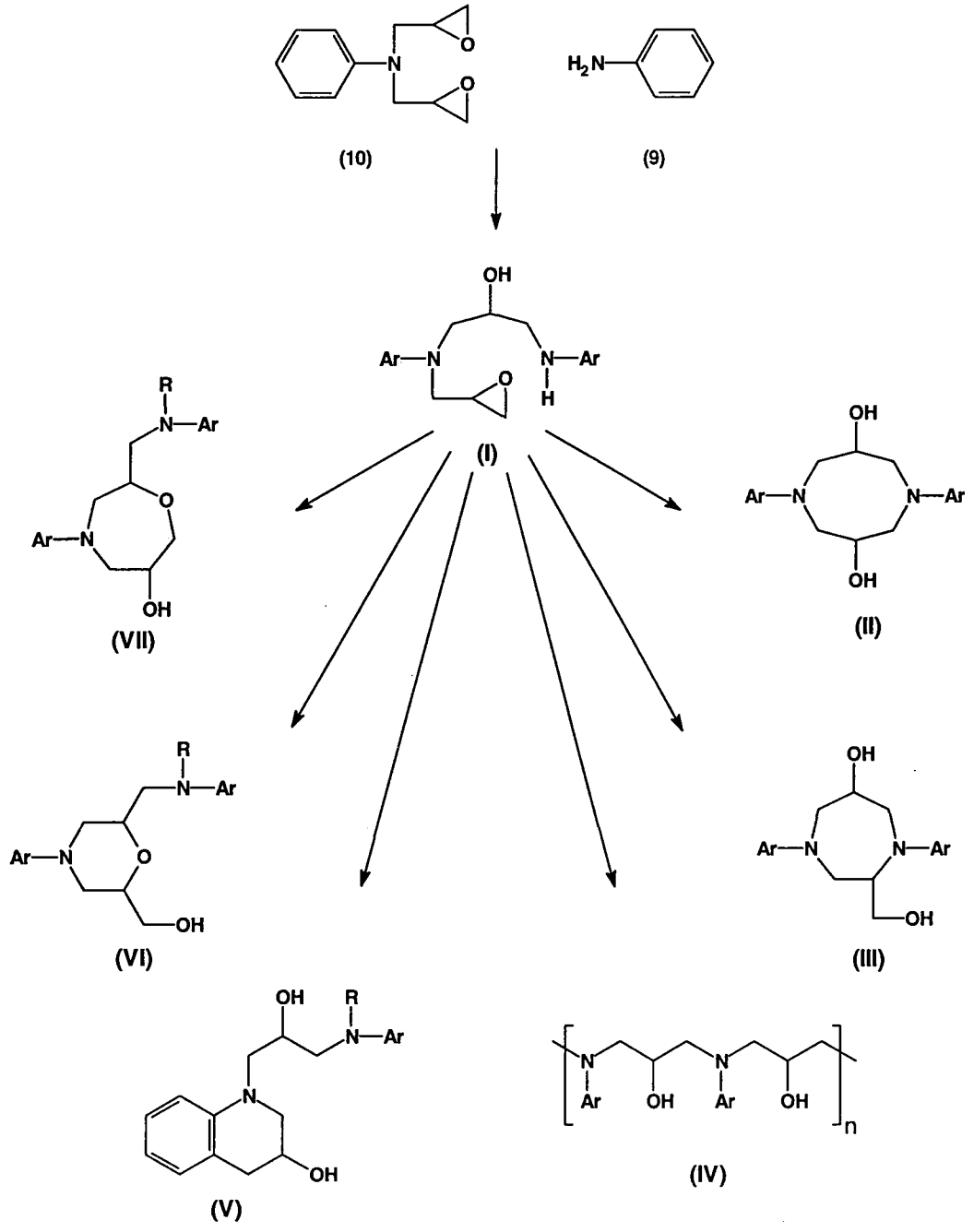


Figure 1.7 *Possible reaction pathways for the TGDDM / DDS epoxy resin system*

Work[10-14] using aniline **(9)** and diglycidyl aniline **(10)** to model the reaction of TGDDM **(7)** and DDS **(8)** has shown evidence for the

formation of the cyclic systems shown in Figure 1.7. A sample of the eight-membered ring system (II) was isolated by high performance liquid chromatography[10], and it was found to exist in two forms, as *cis* and *trans* isomers, as shown in Figure 1.8. The two isomers have major differences in their chemical shifts, and can be clearly distinguished.

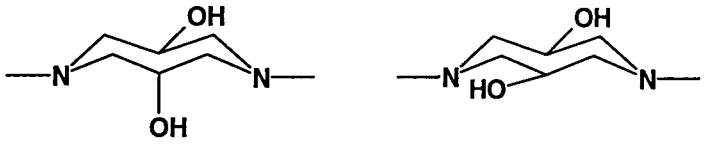


Figure 1.8 *The* cis *and* trans *isomers of the model compounds containing eight-membered rings.*

Evidence for the tetrahydroquinoline (V), and the six and seven-membered ring systems (VI & VII) was found in unpurified samples characterised by ^{13}C NMR[11]. When heated to remove any volatile components, samples of the same crude polymer mixture also showed evidence of thermal instability[11,15], the ^{13}C NMR spectra showing increased contributions from the resonances attributed to the ether and tetrahydroquinoline containing ring systems[11]. Two cyclisation reactions were proposed to account for these observations, as shown in Figures 1.9 and 1.10.

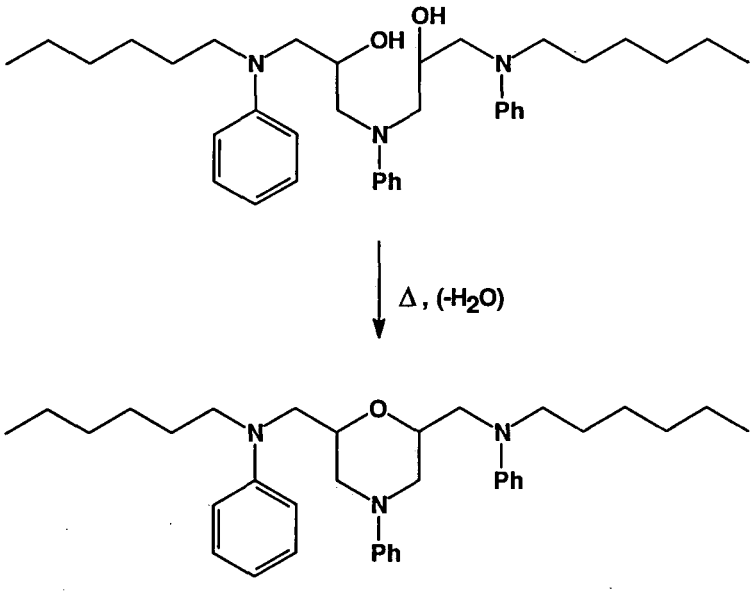


Figure 1.9 *Proposed thermal cyclisations of aniline / diglycidyl aniline model system to form ether linkage*

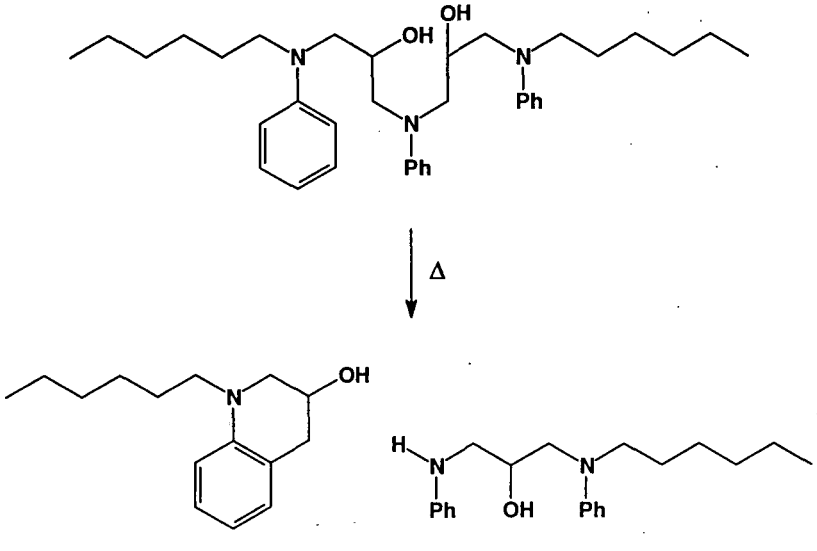


Figure 1.10 *Proposed thermal fragmentation of aniline / diglycidyl aniline model system*

The same work[10,11] also identifies the linear polymer (IV), and shows that the polymer has random tacticity. It is interesting to note that no evidence is found for the seven-membered ring system (III), even though Baldwin's rules[16] might suggest that the 7-exo-trig closure would be favoured over the observed 8-endo-trig closure to give the eight-membered ring (II) (epoxides have been treated as alkene analogues in this case).

The presence of rings in the cured resin was investigated[17] by using the model system based on diglycidylaniline and aniline by monitoring the rate of gelation of the system. The formation of a gel in a curing system is delayed by ring formation, which inhibits network formation. The study, which combined a theoretical study of the various reaction rates in the curing resin, showed a definite delay in gelation due to ring formation.

Model compounds have been used for purposes other than straight forward structure investigation. The effect of autocatalysis of the resin curing has also been studied[18] using a theoretical model system of ammonia and ethylene oxide. The epoxide groups react more rapidly if they are protonated, or hydrogen bonded to groups such as alcohols, and the study attempted to quantify the effect on the cure rate of the proton donors such as the alcohol groups formed during the curing process. The plasticising effect of water on the resin has also been examined[19].

Direct spectroscopic examination of the cured resin is difficult, largely due to the nature of the material. The very properties that make it an attractive matrix material for composites also make it very awkward to handle. Attempts have been made to use solid state ^{13}C NMR to characterise the cured resin[20,21], but to date the results have been less than satisfactory. Below the Tg of the sample, solid state NMR spectra tend to have broad linewidths and poor resolution. By heating the sample to well above it's glass transition temperature, the

linewidths can clearly be reduced and resolution improved, but as the TGDDM/DDS resin has such a high Tg (250-270°C), the temperatures required to induce line narrowing also degrade the resin.

Some groups have used data from model compounds to try and understand the broad and overlapping lines of the room temperature solid state ^{13}C NMR of the TGDDM/DDS resin[22]. They synthesised small molecules containing groups that were similar to the structures expected, and then obtained both the solution and solid state ^{13}C NMR spectra of the samples. This information was then used to help deconvolute the complex solid state ^{13}C NMR spectrum of the cured resin, and thus determine the presence or absence of any of the possible structures. It is reported that peaks corresponding to structures (II), (IV) and (VI) were found, although these results must be viewed as slightly suspect. Computer based deconvolution of solid state spectra is known to be unreliable, particularly when applied to systems such as the TGDDM/DDS resin where there are large numbers of peaks involved. It also does not necessarily follow that the chemical shifts of the model compounds correlate exactly to those of the bulk resin, which may exist in very different chemical environments.

Fourier Transform Infra Red (FT-IR) spectroscopy has also been used[23] to investigate thin films of the epoxy resin as it cures. Although it is not possible to identify specific structures in the polymer matrix, the appearance and disappearance of functional groups such as amines, alcohols and epoxides can be followed, and data gathered about rate constants and rates of reaction as well as the relative proportions of each in the resin at any time during the curing process. The reaction kinetics of the system have also been investigated using Differential Scanning Calorimetry[24].

To date, data gathered into the nature of the TGDDM/DDS epoxy resin system is either indirect, based only on model studies, or inconclusive and open to question. The need for further investigation

in order to gain hard evidence about the matrix microstructure is obvious, in order to increase the understanding of epoxy resin composite materials and their behaviour.

1.4 Aims of the Project

One of the most promising potential approaches to the problem of ascertaining the microstructure of the TGDDM/DDS epoxy resin was the use of selective isotopic enrichment. Isotopes active to NMR (^{2}H, ^{13}C, ^{15}N) could be introduced selectively into positions in the TGDDM and DDS monomers, the resin cured, and the resultant solid examined by solid state NMR. The enriched sites would then give more intense resonances, making them obvious amongst the many other peaks in the spectrum, and rendering the assignment easier and more reliable.

The atoms in the monomers initially identified as appropriate sites for isotopic enrichment were those most directly involved in the polymerisation reaction, and which would be involved in the different possible reaction productions. As such, the carbon atoms of the glycidyl side chains, and the nitrogen atoms in both the epoxy resin and the amine hardener, were targeted for enrichment. Therefore five labelled molecules emerged as potential targets for synthesis, and these are shown in Figure 1.11.

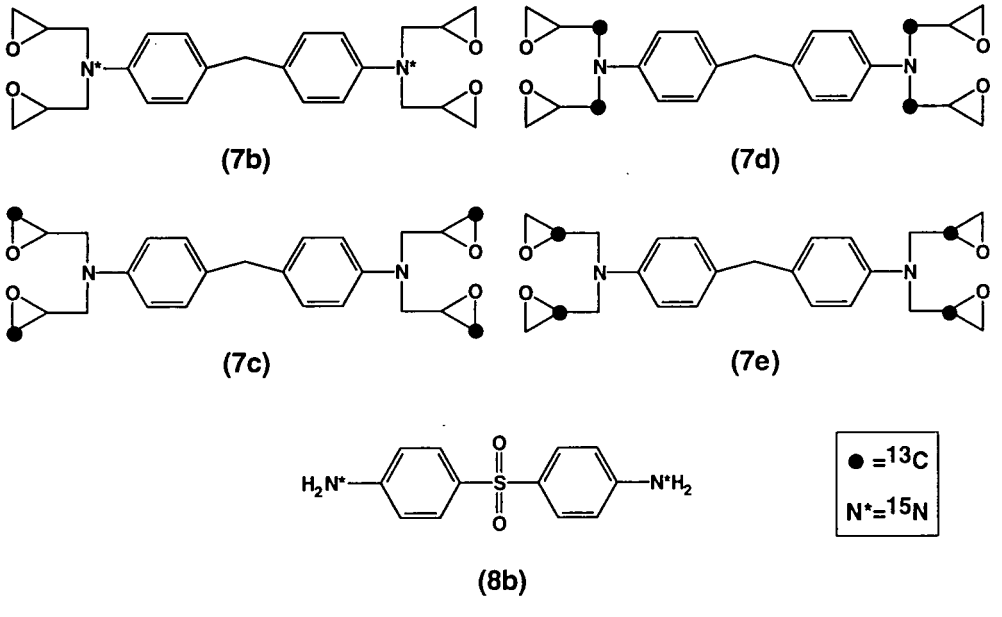


Figure 1.11 *The five initial target molecules*

The synthesis of these isotopically labelled monomers was the primary objective of the research and is described in the next chapter. Only the nitrogen-15 labelled form of TGDDM (**7b**) could be accessed using currently available labelled material and established synthetic procedures[8,9]. The regioselective labelling of the glycidyl moieties was clearly the greater challenge, particularly as there were no established literature syntheses which could be deployed. Therefore, new synthetic strategies to achieve this had to be developed.

CHAPTER 2

Selective Isotopic Labelling of the Glycidyl Moiety

2.6 Synthetic Route 3

2.6.1 Proposed Route

2.6.2 Experimental Results

2.6.3 Conclusion

Selective Isotopic Labelling of the Glycidyl Moiety

2.1 Introduction

The discipline of unambiguous isotopic labelling of organic molecules produces problems and difficulties not often met in mainstream synthetic organic chemistry. A whole selection of general principles apply, which stem from the unusual nature of this kind of organic synthesis.

The biggest limiting factor in isotopic labelling chemistry is the highly restricted number of possible starting materials. While the synthetic organic chemist has generally thousands of chemicals available from the chemical suppliers, the number of suitable isotopically labelled starting materials is severely limited. The separation of different isotopes of an element is difficult and expensive, making the compounds containing the labels expensive as a result, and it is uneconomic for companies to keep large stocks. Synthetic routes designed for isotopic labelling often have to be initiated from less than ideal starting materials as a result of this.

Often the compounds which are required to be labelled have been known for many years, and there are well documented and accepted methods of preparing them. However, with the limited number of available labelled starting materials, it is unusual for these known routes to be amenable to the use of labels, and it is often necessary for a new method to be established in order to achieve the desired labelled product.

The expense of the labelled material also demands that the synthetic route should be efficient, with as little label as possible being lost to poor yields and side products. Some of the cheapest carbon-13

labelled compounds cost in the region of £100 per gram.

Side products also have to be avoided for another reason. Labelling of molecules is often carried out such that the progress of the label can be followed in a later experiment via techniques such as NMR and MS. The presence of impurities and side products containing labels could seriously interfere with the interpretation of results, as even very low levels of impurity can show up because of isotopic enrichment. The process of purifying the sample also means the inevitable loss of some of the desired product.

The nature of the compounds formed during synthesis is also important. Crystalline solids and easily distilled liquids are much more convenient to handle, and therefore remove the need for specialist equipment and handling techniques which often lower the yields. Gases and volatile liquids are best avoided if at all possible.

To sum up, a good method for isotopic labelling should conform to the following points.

- Few synthetic steps
- High yields
- Clean reactions with no side products and impurities
- A cheap source of label
- Easily handled compounds at all stages in the synthesis

2.2 The TGDDM monomer

In order to place isotopic labels unambiguously in the glycidyl side chains of the TGDDM monomer, it was useful to examine their origins in the widely used synthesis of the unlabelled material. The commercial route[8,9] is shown in Figure 2.1, and it can be seen that the glycidyl groups are created by the addition of epichlorohydrin **(2a)** to aniline **(9a)**.

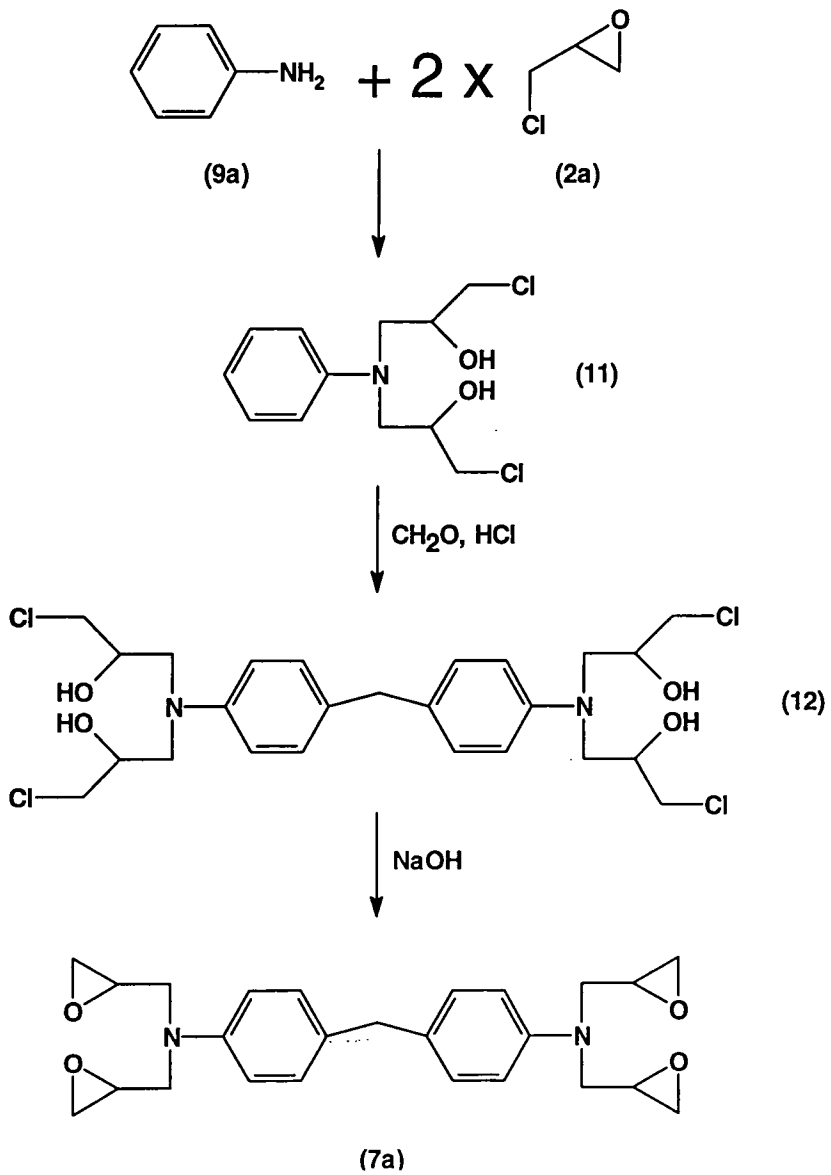


Figure 2.1 *Synthesis of TGDDM (7a)*

It is useful to note that all of the carbon and hydrogen atoms of the incorporated epichlorohydrin molecules remain intact in the final TGDDM molecule. It would therefore be sensible to approach the synthesis of labelled TGDDM with the intention of producing labelled epichlorohydrin, or an analogue of epichlorohydrin, which could then be used in the established synthesis shown in Figure 2.1. If an analogue of epichlorohydrin were to be used, it would have to have a leaving group (X) which behaved in a similar fashion to the chloro- group of epichlorohydrin.

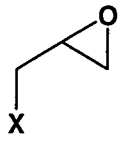


Figure 2.2 *Epichlorohydrin analogue (X = leaving group)*

The possible choices for the leaving group (X), apart from the chloro- group, include a whole range of organic leaving groups. The most useful might be those large groups with relatively high mass, such as the sulfonate or carboxylate esters, which would make the potentially small intermediates larger and easier to handle, and might also confer crystallinity.

These analogues might also be accessible through synthetic routes different to epichlorohydrin, and may make labelling simpler. In particular it would be useful to consider routes based around derivatives of allyl alcohol **(13a)** and glycidol **(14)**, as shown in Figure 2.3, as these emerge as obvious intermediates for a labelled epichlorohydrin analogue.

Allyl Alcohol (13a) **Glycidol (14)**

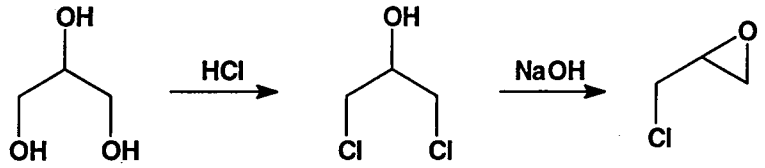
Figure 2.3 *Possible intermediates towards an epichlorohydrin analogue*

Before addressing our approaches to the synthesis of the desired labelled molecules, the established syntheses of epichorohydrin **(7a)** and possible intermediates are reviewed.

2.3 Syntheses of Epichlorohydrin

2.3.1 Unlabelled Epichlorohydrin

Epichlorohydrin **(2a)** is prepared commercially[25,26,27] from 1,3-dichloropropan-2-ol **(16a)**, by a method which has been known and used since the latter half of the last century. The starting material is glycerol **(15a)**, which is treated first with hydrochloric acid, and then with a base such as sodium or calcium hydroxide. The reaction scheme is shown in Figure 2.4.



(15a) (16a) (2a)

Figure 2.4 *Synthesis of epichlorohydrin (2a) from glycerol (15a)*

The basic treatment of the dichlorohydrin **(16a)** is variously carried out in an ethereal solution[25], or as an aqueous solution[27] or slurry[26] with the epichlorohydrin forming as an immiscible organic layer. In either case, the product **(2a)** is purified by careful distillation to separate out the solvents.

The success of the glycerol based synthesis has meant that research into other ways of making epichlorohydrin has been somewhat limited. The simplicity, convenience and high yields (>80%) of the reaction has tended, for commercial purposes at least, to put other work at a disadvantage, although other routes have been reported.

Apart from the base treatment of chlorohydrins, another classic way of making epoxides is to react alkenes with peracids. Such an

approach has tended in recent years to concentrate on the potential catalytic effects of transition metals on the reaction of peracids on allyl chloride, and a number of systems have been studied. Titanium/ silica gel[28,29,30], rhenium[31], molybdenum[32], tungsten[33,34] and iron/copper[35] systems have all been examined, although in general the yields of epichlorohydrin are medium to low, making these systems unsuitable for use in a labelling regime.

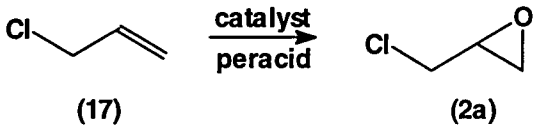


Figure 2.5 *Catalytic epoxidation of allyl chloride*

Another method for the formation of epichlorohydrin, shown in Figure 2.6, was established in 1978 which used D-mannitol (18), a naturally occurring compound, as a starting material[36].

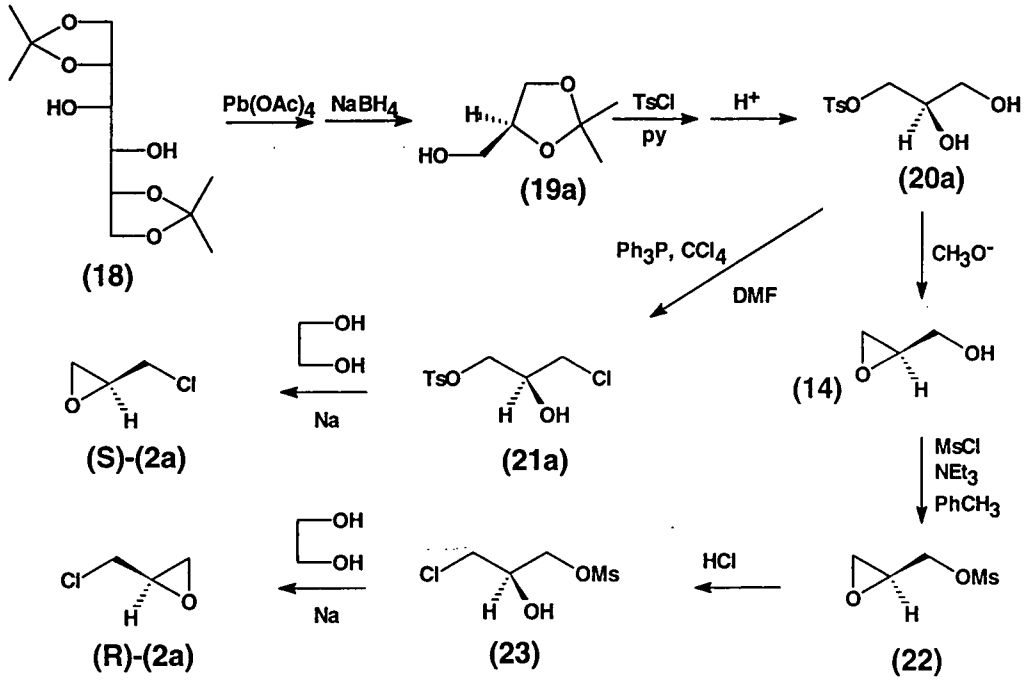


Figure 2.6 *Synthesis of (R)- and (S)-epichlorohydrin (2a)*

The synthesis of epichlorohydrin based on D-mannitol was designed as a method of accessing both chiral forms of the product on a large and economic scale, due to the increasing use of chiral epichlorohydrin in organic synthesis. D-Mannitol provides the chiral centres in a form that can be used to make selectively protected glycerol analogues, which can later be turned into the desired end product.

2.3.2 Carbon-13 Labelled Epichlorohydrin

Specific and unambiguous labelling of epichlorohydrin using different carbon isotopes has been achieved by two separate synthetic routes to date, one utilising the established glycerol synthesis and another based on a nickel/acetylene reaction.

The first route starts from labelled acetic acid **(24a)**[37], one of the cheaper forms of carbon label available, and is shown in Figure 2.7 below.

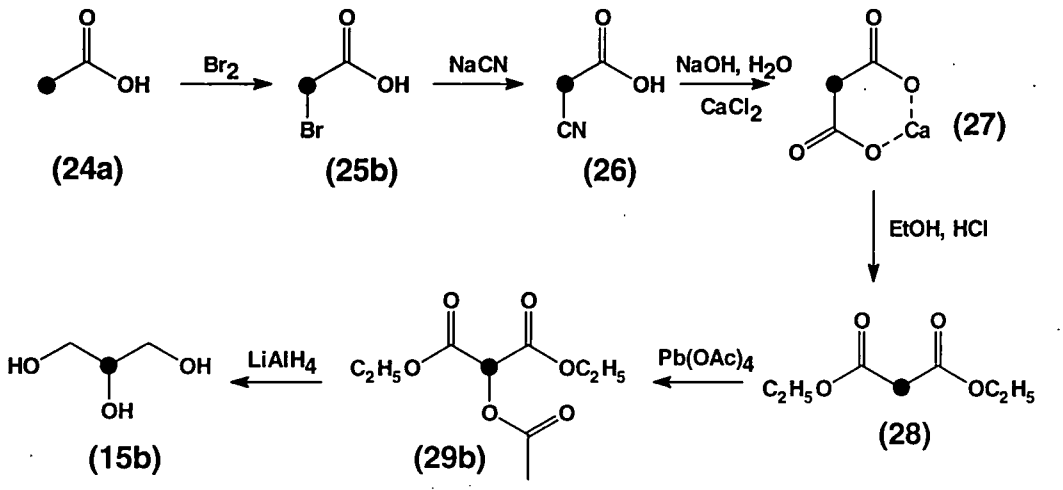


Figure 2.7 *Synthesis of C-2 labelled glycerol* ***(15b)*** *from acetic acid*

The diagram shows the synthesis up to the production of C-2

labelled glycerol (**15b**), which can then be treated to form C-2 labelled epichlorohydrin (**2b**). Epichlorohydrin doubly labelled in both the C-1 and C-3 positions (**2e**) can also be made by this methodology[38], using C-1 labelled acetic acid (**24b**) and labelled KCN, but separate C-1 or C-3 labelling is not possible, because of the scrambling that would occur at the final, base catalysed epoxide closure step, to give a mixture of (**2c**) and (**2d**).

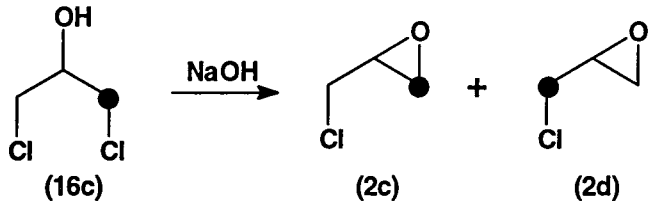


Figure 2.8 *Label scrambling during epichlorohydrin formation*

This route has been utilised on several occasions, and has been exploited commercially by a number of companies to produce small amounts of labelled epichlorohydrin[39,40,41], although it doesn't appear to be widely applicable.

The second route[42,43] involves the use of a nickel catalyst and provides a method of synthesising C-2,3 labelled epichlorohydrin (**2f**) from labelled acetylene (**30**). The route is shown in Figure 2.9. The methodology uses a base catalysed epoxide closure similar to that in the glycerol based synthesis, but in this case there is only one possible method of ring closure, and label scrambling is avoided. This synthesis is also specific to the particular species formed, and could not easily be adapted to give different, singly labelled alternatives.

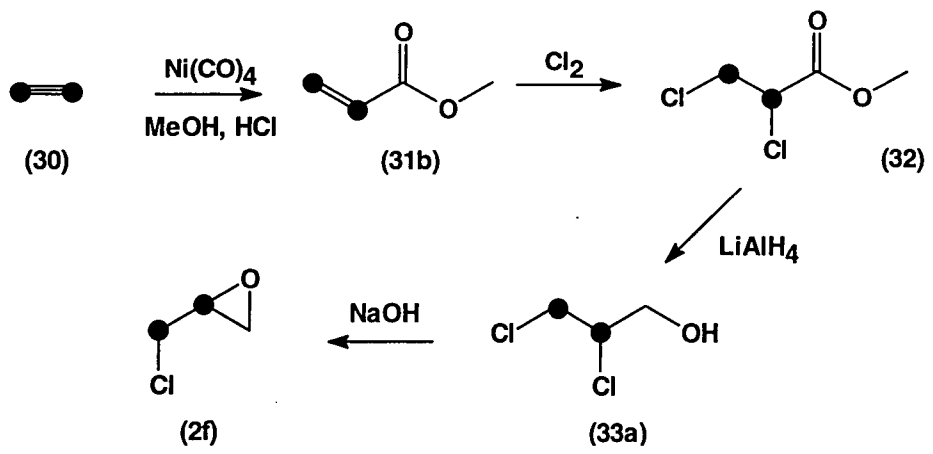


Figure 2.9 *Synthesis of C-2,3 labelled epichlorohydrin (2f)*

Both of the methodologies presented above are unsatisfactory as potential methods of making the required singly labelled epichlorohydrins for the labelling of TGDDM. While it would be possible to produce C-2 labelled epichlorohydrin **(2b)** from the first of the two routes shown above, the synthesis is long and would certainly involve a considerable loss of label in the process of synthesis. As the labelled compounds are required in gram quantities for further reaction to TGDDM, this wastage would render the synthesis prohibitively expensive, and illustrates the requirement for a more convenient synthesis.

2.3.3 Carbon-13 Labelling of Potential Intermediates

While the established routes to labelled epichlorohydrin are unsuitable for the required products, it may be possible to use other literature preparations to achieve the final outcome. If an epichlorohydrin analogue were to be used in the TGDDM synthesis instead of epichlorohydrin, as suggested in Section 2.2 and shown in Figure 2.2, different starting materials and different label sources

might be considered.

Perhaps the most important potential intermediate is allyl alcohol **(13a)** which, if it can be esterified and epoxidised successfully, would make a useful epichlorohydrin analogue. Several protocols for synthesising labelled allyl alcohol exist in the literature, some of which may be of use in the production of unambiguous, singly labelled TGDDM.

Several of the reported syntheses of carbon labelled allyl alcohol are rather similar, sharing a first step that features an anionic acetylene species and a compound with a single electrophilic carbon. The first, shown in Figure 2.10, uses ethynylmagnesium bromide **(34)** and carbon-13 labelled carbon dioxide in a two step synthesis of C-1 labelled allyl alcohol **(13b)**[44].

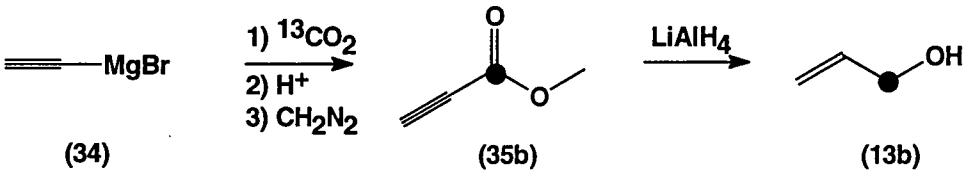


Figure 2.10 *C-1 labelling of allyl alcohol **(13b)** using ethynyl-magnesium bromide **(34)** and labelled carbon dioxide*

While this synthetic route is attractive in that it is short and simple, the literature source gives no details of the yields for each of the steps. The handling of labelled carbon dioxide might also pose problems if loss of label were to be avoided.

The second route is very similar to that shown in Figure 2.10, using acetylene **(30)**, doubly labelled with carbon-14, and formaldehyde[45]. In this case the desired labelled product was [2,3-$^{14}C_2$] allyl alcohol **(13f)**, and the change of reagents was probably forced by the availability or otherwise of the necessary labelled materials. The modified scheme is shown in Figure 2.11

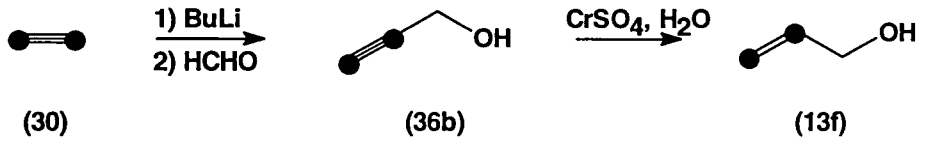


Figure 2.11 *C-2,3 labelling of allyl alcohol* ***(13f)*** *using carbon-14 labelled acetylene* ***(30)*** *and formaldehyde*

As before, the reaction scheme is short and appears at first sight to be simple, but the gaseous nature of both the acetylene **(30)** and the formaldehyde is problematic. The yield quoted is based on the radio-activity of the final product, which is moderate at 50%.

Another literature source outlines a synthesis of C-1 labelled allyl alcohol **(13b)**, using barium carbonate-^{14}C as a starting material[46]. Although the reference gives no details of how the synthesis was accomplished or what the final yield was, it is likely that the barium carbonate was converted into carbon dioxide, formaldehyde or some similar compound, and treated in a similar way to that shown in Figures 2.10 and 2.11.

A final method for carbon labelling of allyl alcohol is shown in Figure 2.12, which uses labelled potassium cyanide to produce **(13b)**[47].

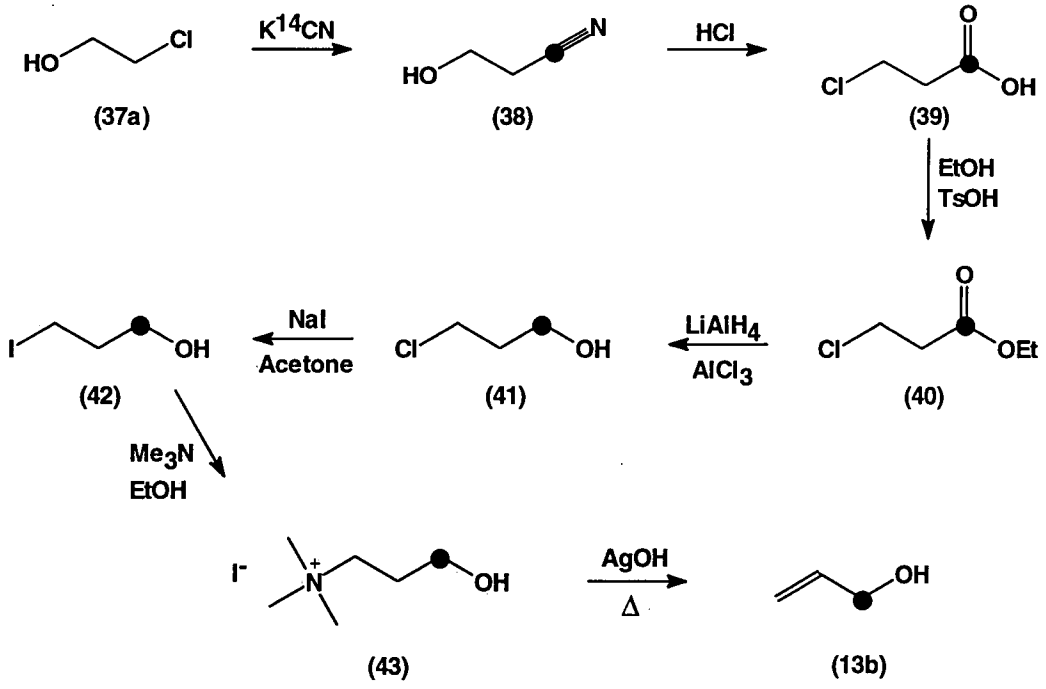


Figure 2.12 *Labelling of allyl alcohol* ***(13b)*** *using labelled cyanide*

The same route can be used to synthesise C-3 labelled allyl alcohol **(13d)** if sodium [1-^{14}C] acetate **(44a)** is used to produce labelled chloroethanol **(37b)**, as shown in Figure 2.13.

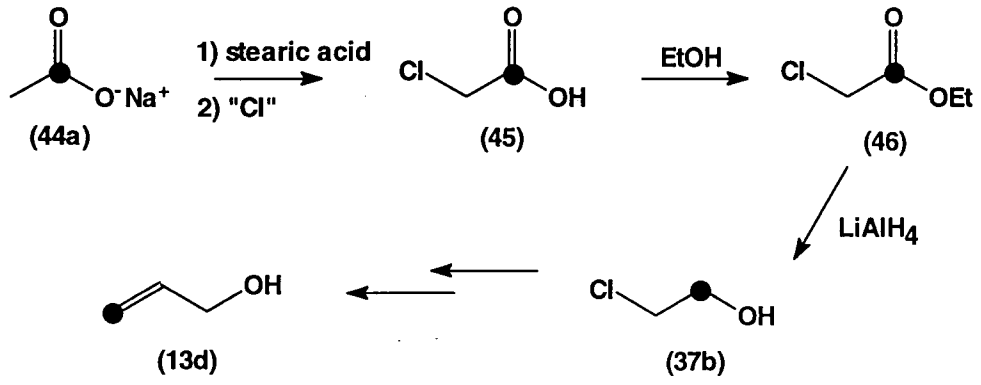


Figure 2.13 *Labelling chloroethanol for production of C-3 labelled allyl alcohol* ***(13d)***

These routes to labelled allyl alcohol are much longer than those shown previously, with seven and eleven steps respectively, and the yields suffer as a result. [1-^{13}C]-Allyl alcohol **(13b)** is produced with an overall yield of 33%, while [3-^{13}C]-allyl alcohol **(13d)** is produced in only 10% yield. The large wastage of label this implies is only partly offset by the relatively cheap sources of label used (acetate and cyanide). However, this methodology does have the advantage that it should also be possible, by using C-2 labelled acetate **(44b)** instead of C-1, to synthesise C-2 labelled allyl alcohol **(13c)**. This would mean that all of the three forms of singly labelled allyl alcohol could be accessed unambiguously.

It appears that all of the requirements for carbon labelling of allyl alcohol can be met by using established synthetic protocols from the literature. However, this on its own is of no use if it proves impossible to transform allyl alcohol into a glycidol based epichlorohydrin analogue. It is interesting to note that although a relatively large body of work exists for the carbon labelling of allyl alcohol as detailed above, there is no record of any work that successfully labelled any of the carbons of glycidol. The utility of the labelled allyl alcohol-based analogue as an intermediate would also be doubtful if the analogue fails to behave in a manner similar to epichlorohydrin itself in reacting to form the TGDDM monomer.

2.3.4 Deuterium Labelled Epichorohydrin

Deuterium labelling of epichlorohydrin has been achieved by three different synthetic routes in the past, using a number of readily available starting materials. In all cases the deuterium atoms are introduced in a reduction reaction, using either lithium aluminium deuteride or sodium borodeuteride. Both of these agents have been widely used as a source of label in the past, and as such are relatively

cheap and easily available.

The three routes illustrate possibly the simplest method of introducing deuterium into the epichlorohydrin molecule, by reducing a carbonyl group to give an alcohol, as shown in Figure 2.14.

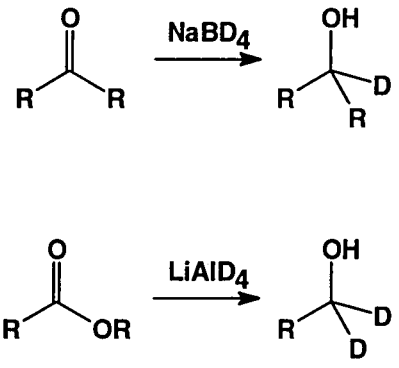


Figure 2.14 *Reductive insertion of deuterium labels*

If the molecule chosen for reduction in this manner is provided with chloro- substituents in the correct positions, it is a simple matter to treat the reduced product with base to give the required epichlorohydrin. The first route[48] uses a 2,3-dichloropropanoate ester **(47)**, as shown in Figure 2.15, with an overall yield of 55%.

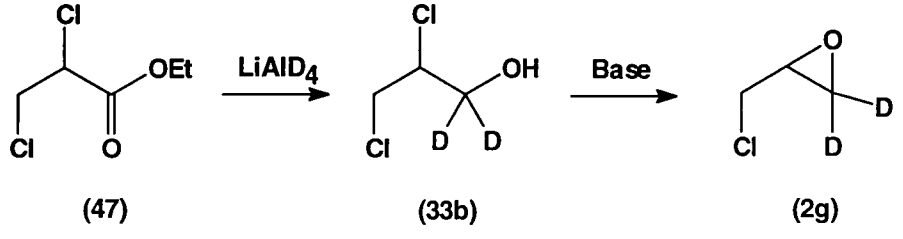
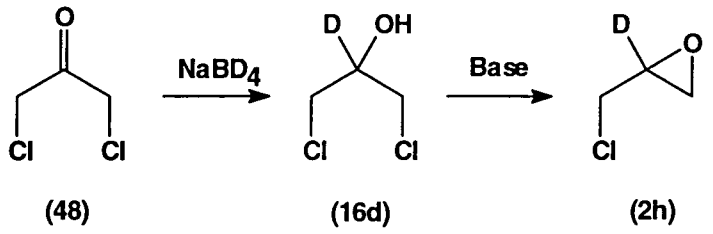


Figure 2.15 *Synthesis of deuterium labelled epichlorohydrin* ***(2g)***

The second route[49] is just as short and simple, with a starting material, 1,3-dichloropropanone **(48)**, that is readily available, as shown in Figure 2.16. The dichloropropanol species **(16d)** can then

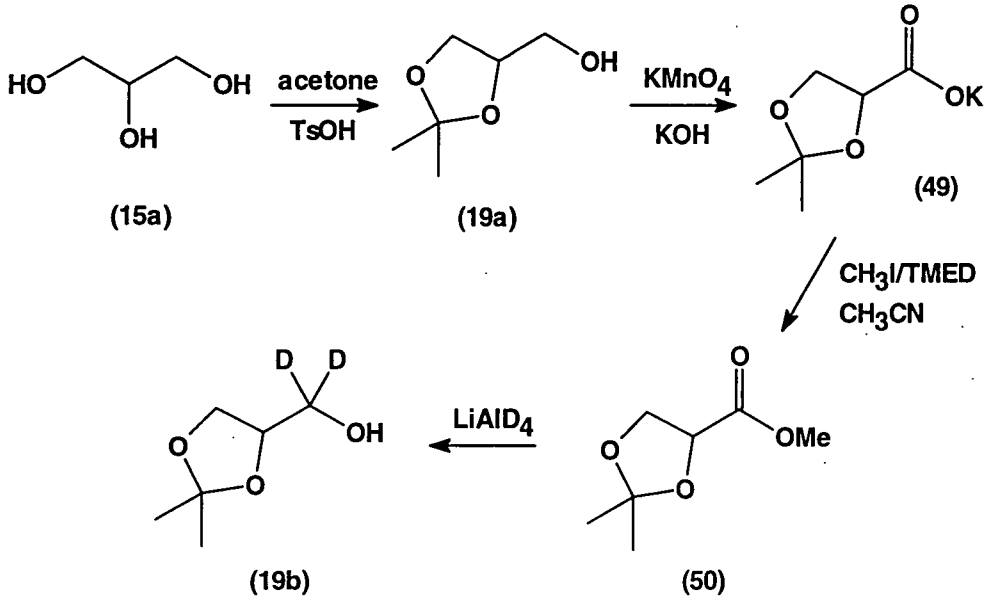
eliminate HCl to give the epoxide (**2h**) at either of the chloro-substituents. The molecule is symmetric in this case, so no scrambling of the label occurs.



(48) (16d) (2h)

Figure 2.16 *Synthesis of deuterium labelled epichlorohydrin* ***(2h)***

The third and final route[50-53] also exploits a lithium aluminium deuteride reduction of an ester to insert the deuterium isotopes.



(15a) (19a) (49) (50) (19b)

Figure 2.17 *Synthesis of a deuterium labelled acetal protected glycerol* ***(19b)***

Although it leads to both C-1 and C-3 deuterium labelled epichlorohydrin (**2h**) and (**2i**), it is a much longer synthetic procedure.

The first half of the protocol, shown in Figure 2.17, converts glycerol **(15a)** in four steps into a deuterium labelled acetal species **(19b)**. This species can then be treated in one of two ways to produce either **(2h)** or **(2i)**, as shown below in Figure 2.18.

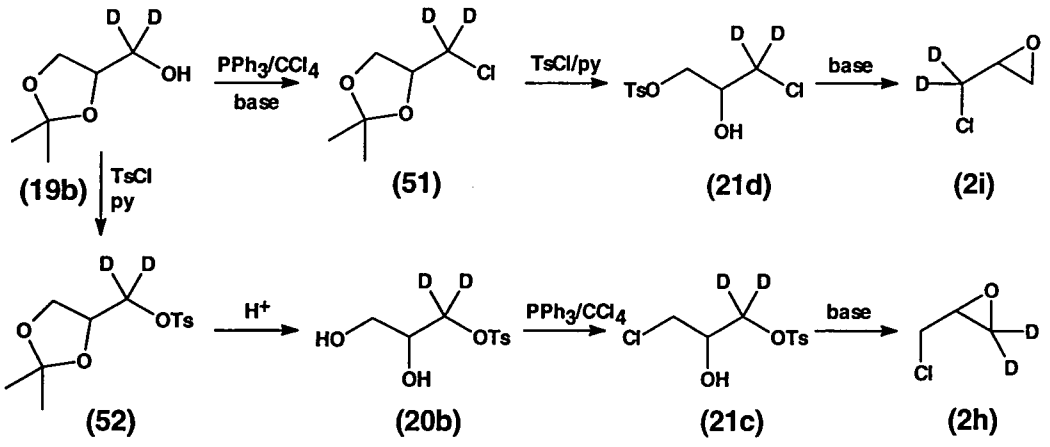


Figure 2.18 *Transformation of a deuterium labelled acetal (**19b**) into (**2h**)* and **(2i)**

The overall yields of the deuterium labelled epichlorohydrins **(2h)** and **(2i)**, from the insertion of the label with lithium aluminium deuteride, was approximately 36% for **(2h)** (top route), and 27% for **(2i)**.

Potentially useful labelling strategies have also been used to prepare deuterium labelled glycerols[54-58], as glycerol can be readily converted into epichlorohydrin *via* the scheme outlined in Figure 2.4 shown earlier. The only difficulty in using glycerol as an intermediate is that asymmetric labelling (i.e. at C-1 or C-3) becomes scrambled, as previously discussed, rendering several established synthetic routes unusable in our case. However, two situations remain that are of potential use in the synthesis of **(2j)**[59] and **(2h)**[60], as shown in Figure 2.19

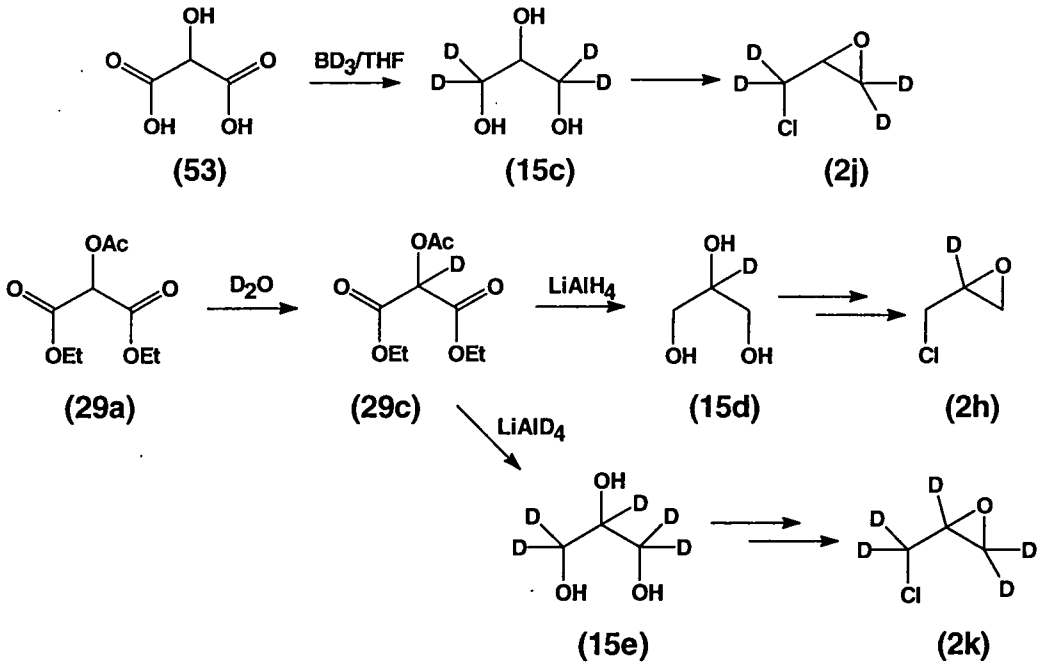


Figure 2.19 *Synthesis of deuterium labelled glycerols*

Both of the reaction schemes shown above are short and straightforward, and high yields of epichlorohydrin might be expected from them. No yield is quoted for the top scheme, but that for the second is quoted at 42% overall. It would seem likely that lithium aluminium deuteride could be substituted in the latter reaction shown in Figure 2.19 to produce a fully deuterium labelled glycerol **(15e)** and hence a fully deuterium labelled epichlorohydrin **(2k)**. Fully deuterium labelled epichlorohydrin has been reported as being commercially available[61], and while no protocol was reported it is possible that a route similar to that shown above was used.

This section has shown that established syntheses provide routes to a number of deuterium labelled epichlorohydrins, shown in Figure 2.20, although some of these routes are long and have low yields associated with them. These problems have made it necessary for us to develop an original protocol to produce the required labelled compounds in large enough amounts for our study.

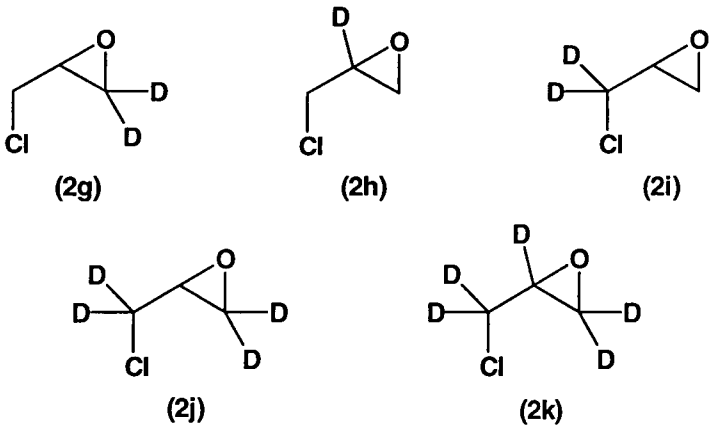


Figure 2.20 *Deuterium labelled epichlorohydrins available by established synthetic routes*

2.3.5 Deuterium Labelling of Potential Intermediates

If the glycidyl ester analogues of epichlorohydrin are to be deployed, it is useful to examine previous labelling strategies to these potential intermediates, and in particular allyl alcohol **(13a)** and glycidol **(14)**. As discussed earlier, these are the most promising potential intermediates for a labelled glycidyl ester.

Examples of deuterium labelled allyl alcohols can be synthesised by a number of different synthetic routes, allowing access to almost any of the possible labelled compounds. Discounting the hydroxyl hydrogen, there are five possible sites for deuterium labelling in the allyl alcohol molecule. If the two hydrogens of the CH_2 group are counted as equivalent, this gives four sites for deuterium labelling, as shown in Figure 2.21.

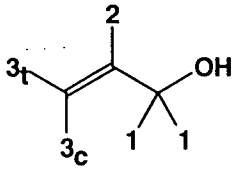


Figure 2.21 *The four sites for deuterium labelling in allyl alcohol*

Protocols have already been described for the selective labelling of all the possible sites, although some are only partly successful in that they are not completely regioselective.

The first route is very similar to that described in Section 2.3.3, using a labelled form of formaldehyde and a Grignard reagent **(54)**[62]. This is an efficient reaction giving a yield of 79% of the desired alcohol, and is shown in Figure 2.22.

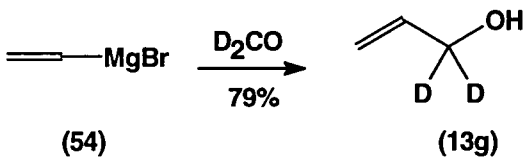


Figure 2.22 *Synthesis of [1-$^2H_2$]-allyl alcohol **(13g)** from labelled formaldehyde and vinylmagnesium bromide **(54)***

An alternative strategy for introducing deuterium into allyl alcohol at the same site involves the reduction of a carbonyl group with lithium aluminium deuteride[63]. Unusually, however, the yields are moderate (~45%) and render this route problematical.

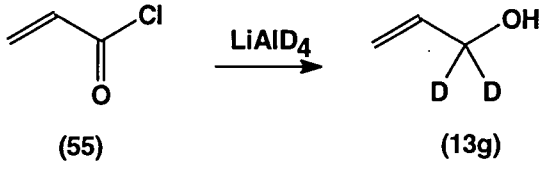
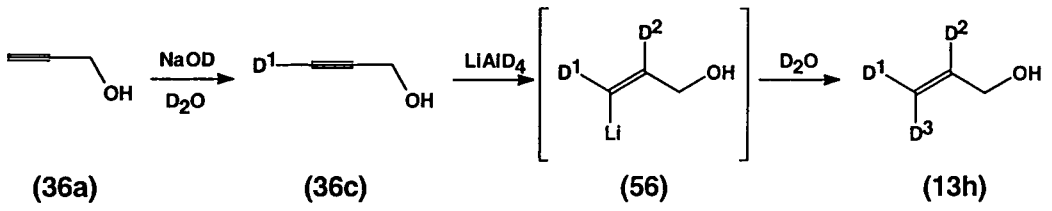


Figure 2.23 *Synthesis of deuterium labelled allyl alcohol **(13g)** from acrylyl chloride **(55)** and lithium aluminium deuteride*

Deuterium labelling of allyl alcohol in positions 2, 3_t and 3_c (Figure 2.21) has been investigated by a number of groups[64-67], and has led to a unified strategy for inserting the label at each individual site. The synthesis starts with 2-propyn-1-ol **(36a)**, and the deuterium

labels are added one at a time as required, as shown in Figure 2.24.



(36a) (36c) (56) (13h)

Figure 2.24 *Insertion of deuterium atoms at positions 2, 3_t and 3_c of allyl alcohol*

The label at the 3_t (D^1) position is inserted first, by exchanging the acetylenic proton with deuterium oxide and sodium deuteroxide. Reduction with lithium aluminium deuteride inserts the label at position 2 (D^2), and quenching the reduction with deuterium oxide inserts the label at position 3_c (D^3). If a lesser degree of labelling is required, of course, the labelled reagents at any stage can be replaced with unlabelled material to give a mono- or di-labelled product instead, and if 3_t labelling is not require the first step is eliminated.

If all three labels are inserted during the reaction, the overall yield is approximately 40%, although this increases to around 60% if the first step is omitted. The biggest drawback to this method of labelling is that the reduction/quench step isn't 100% regiospecific. As much as 20% of the final product can be left unlabelled or incorrectly labelled by this route. Impurities for certain labelling patterns can be reduced by cooling the reaction, but the difficulty still remains for many of the other combinations, so rendering this methodology of limited use[67].

Some of these selectivity problem can be overcome by using a protected species[68-70], such as that shown in Figure 2.25. The route takes methyl acrylate **(31a)** and generates and adduct **(57)** with anthracene to protect the double bond. The ester group is then reduced with lithium aluminium hydride to insert two deuterium atoms. Such

protection also stops the reactants from polymerising and compromising the yield.

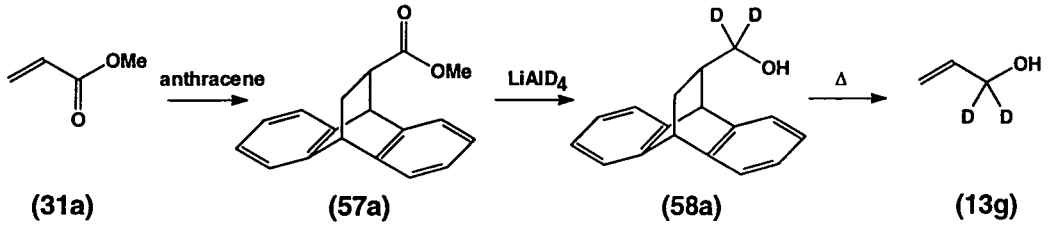


Figure 2.25 *Reduction of methyl acrylate / anthracene adduct (**57a**) with lithium aluminium deuteride*

This strategy can also be used with methyl propiolate **(35a)**[71,72], to give an adduct **(59)** with a double bond bridging the anthracene. This now allows the stereoselective insertion of deuterium atoms at sites 1, 2 and 3_t because the double bond is locked by the complex. This is shown in Figure 2.26.

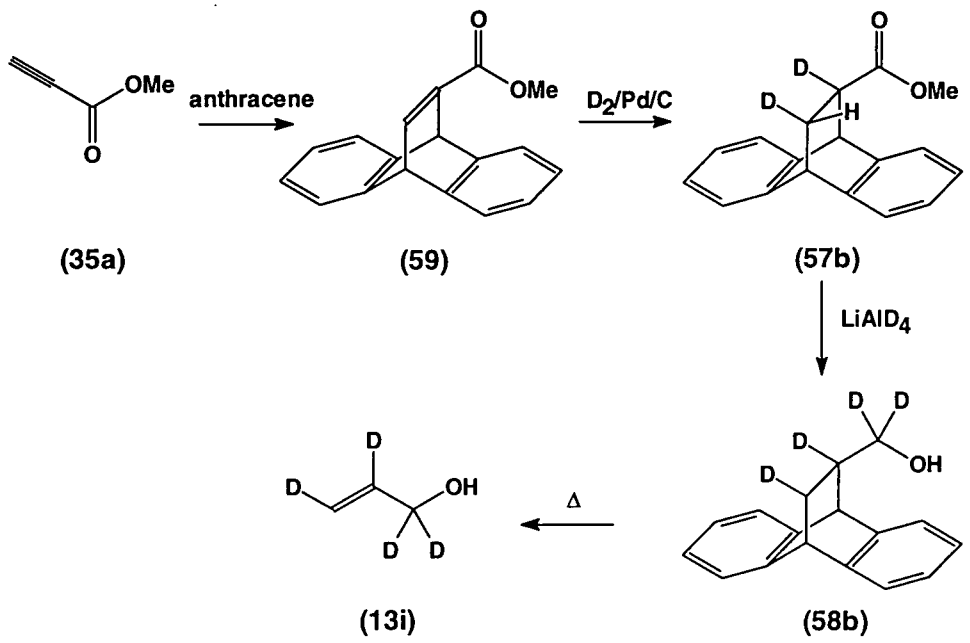


Figure 2.26 *Selective deuterium insertion at sites 1, 2 and 3_t of the complex of 2-propyn-1-ol (**59**) using D_2 and $LiAlD_4$*

It would be possible to use methyl [3-^{2}H]-propiolate (**35c**), labelled with deuterium from D_2O in a similar fashion to that described in Figure 2.24, and so introduce a label at the 3_c position as well. As before, the three different sets of labelled reagents can be interchanged to produce different labelling patterns. The only limitation of this technique is that the 2 and 3_t positions are labelled in the same step and cannot be accomplished separately. However, since most of the steps in this synthesis are carried out in high yield (>95%), it is very attractive as a labelling strategy.

While the syntheses of deuterium labelled allyl alcohol are relatively numerous in the scientific literature, similar syntheses of deuterium labelled glycidol are almost non-existent. Whether this is a reflection on the difficulty of the task, or simply a lack of demand for labelled glycidol, isn't clear.

2.4 Synthetic Route 1

2.4.1 Proposed Route

At the outset of the project, the objective of labelling the carbon atoms of the TGDDM monomer was given top priority, as it was judged the best strategy for elucidating the polymer macrostructure. A number of considerations combined to suggest the first approach to labelling these carbons, such as simplicity, expected ease of handling and short synthetic route. The proposed pathway generates an epichlorohydrin analogue, glycidyl *p*-toluenesulfonate **(62b)**, and is shown in Figure 2.27.

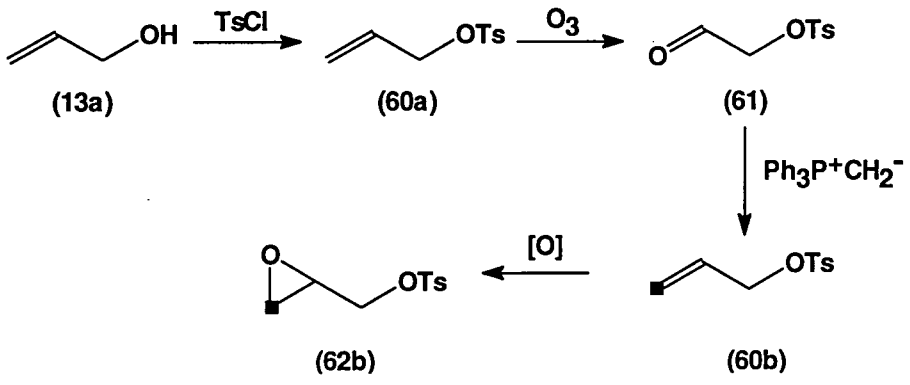


Figure 2.27 *Proposed route to labelled glycidyl* tosylate ***(62b)***

Ideally, the glycidyl sulfonate ester **(62b)** will have a similar reactivity to epichlorohydrin in the synthesis of the TGDDM monomer, while the use of an allyl based system will allow selectivity in labelling between the C-1 and C-3 carbons. The use of tosylate esters should also convert small, difficult to handle intermediates into larger molecules and more readily handled materials, possibly with a degree of crystallinity.

The investigations for this synthetic route are in three distinct areas; insertion of the label, epoxidation of the double bond, and

exploration of the reaction of glycidyl tosylate **(62b)** with aniline **(9a)** as a model system for the formation of the TGDDM monomer. Perhaps the most important of the three is the last one, as the analogue is of no use if it behaves differently from epichlorohydrin. In many cases, having the last step of a synthesis as the most difficult is unattractive, but because of the nature of isotopic synthesis many of the intermediates are readily available in unlabelled form. This allows investigations to take place into several stages at the same time, and allowed the three separate synthetic areas to be addressed simultaneously.

2.4.2 Experimental Results

The first area addressed was the insertion of the carbon label into allyl tosylate **(60a)**. This is in many ways the least important of the three, as a number of routes already exist for this, as described in section 2.3.3. While they are in some cases long and low yielding synthetic protocols, their existence means that failure to find a shorter route need not be a major problem.

The planned route involved the tosylation of allyl alcohol **(13a)** with tosyl chloride[63], followed by cleavage of the double bond with ozone[74] to generate an aldehyde **(61)**. The label could then be inserted using a Wittig reagent[75] formed in a standard manner from triphenylphosphine and labelled methyl iodide. All of the steps have a literature precedent, and were expected to have a reasonable chance of success.

The tosylation of allyl alcohol proceeded readily, from a mixture of allyl alcohol, tosyl chloride and concentrated sodium hydroxide solution shaken at room temperature. The tosylate ester **(60a)** was a clear oil rather than a solid, but could be easily purified over silica gel, and thus allowed the ozonolysis step to be investigated.

Treatment of the alkene with ozone initially proved problematic, and little product was isolated unless very carefully distilled dichloromethane was used as a solvent. However, once this was realised, and methyl sulfide was chosen to reduce the ozonide intermediate, the required product **(61)** was recovered in good yield (99%). The aldehyde was also an oil rather than a solid, and proved to be unstable at room temperature, slowly breaking down in a matter of days. Thus it was necessary to make this compound and use it immediately.

The first serious problem occurred with the insertion of the isotopic label, using the Wittig reagent $CH_3(Ph)_3P^+Br^-$. The reaction was conducted in the normal manner, with the phosphonium salt treated with lithium diisopropylamide (LDA) at –78°C to generate the ylide. The aldehyde **(61)** was then added, and the reaction stirred and left to warm to room temperature. However, work-up generated a complex product which contained only residual tosylate resonances as determined by ^{1}H-NMR. The desired alkene **(60b)** could not be identified by NMR or thin layer chromatography (TLC) using a reference sample.

In an attempt to solve this problem, and circumvent the subsequent epoxidation step, the phosphorus ylide was replaced with the sulfur ylide[76], $(CH_3)_2OS{=}CH_2$. This would in principle convert the aldehyde **(61)** to the epoxide **(62b)** directly. In the event a similar result emerged, giving a mixture of tosylate containing fragments but none of the expected product.

The failure of the phosphorus and sulfur ylide reagents posed a serious problem for the synthetic route. The choice of ylide reagents was limited to those that could be made from labelled methyl iodide, using established synthetic routes. The complete failure of the reaction also seemed to indicate a problem that couldn't be solved by choosing a milder form of ylide reagent. Indeed, it is possible that the

problem is inherent in the aldehyde **(61)**, which is already proven to be unstable and contains an excellent leaving group in the shape of the tosylate functionality. One rationale is that the nucleophilic ylides attack preferentially the carbon containing the tosylate group rather than the aldehyde, as shown in Figure 2.28, and is consistent with the residual tosylate resonances in the ^{1}H-NMR spectra.

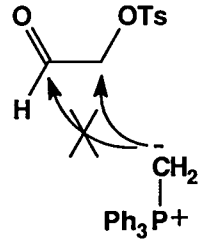


Figure 2.28 *Possible method of attack of the ylide on the aldehyde*

In an attempt to solve this problem, it was decided to protect the alcohol group with a much poorer leaving group. An obvious candidate was one of the family of silyl protection groups, because they are very easily removed using mild conditions. The species chosen was the *t*-butyldimethylsilyl (TBDMS) group[77], and the modified synthetic route is shown in Figure 2.29

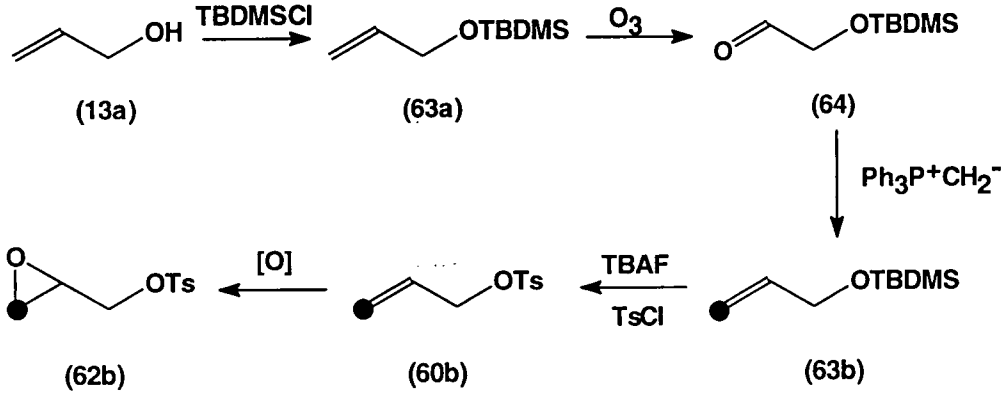


Figure 2.29 *The modified route to labelled glycidyl tosylate* ***(62b)***

While the route has increased from four to six synthetic steps, the lower reactivity of the silyl ether should allow the Wittig reaction to proceed normally.

Stirring the allyl alcohol with the corresponding silyl chloride (TBDMSCl) and imidazole in DMF gave the desired silyl ether **(63a)** in excellent yield. Unfortunately, ozonolysis of the silyl ether failed to produce the desired aldehyde **(64)**, and instead fragmentation dominated once more. No product could be detected in the reaction work-up as judged by ^{1}H-NMR, with the only identifiable peaks being associated with the silyl protecting group.

To investigate the possibility that the protecting group was in some way vulnerable to ozone, another attempt was made using an almost identical method, except that the TBDMS group was replaced with a *t*-butyldiphenylsilyl (TBDPS) group[78,79,80]. Again, the corresponding silyl ether **(65a)** was prepared in excellent yield using an analogous procedure. Treatment of this alkene with ozone did generate the required aldehyde **(66)** in moderate yield (50%). This seemed to indicate that the failure of the ozonolysis reaction with the TBDMS derivative was due to the instability of the protecting group to the experimental conditions, and ozone in particular. The TBDPS-aldehyde was, however, unstable at room temperature, and had to be used immediately.

The next step was to attempt the Wittig reaction once more, on the TBDPS protected aldehyde **(66)**. Treatment with the phosphorus ylide was carried out as before, but once again, analysis by ^{1}H-NMR of the product mixture was disappointing, with no sign of the desired allyl alcohol derivative **(65b)**. The only identifiable resonances came from the remains of the silyl protecting group.

The search for a suitable protecting group now moved on, this time to the triphenylmethyl (trityl) group[81,82]. The trityl ether **(67)** was formed easily by stirring allyl alcohol with triphenylmethyl

chloride, in a solution of triethylamine and dimethylaminopyridine in dichloromethane. Unfortunately, as in the case of the TBDMS ether, exposure to ozone caused fragmentation of the starting material, with no evidence for the generation of the required product **(68)**.

The behaviour of the variously protected species seems to suggest an inherent instability in the aldehyde system itself, rendering it prone to fragmentation. It has either proved impossible to make, as in the TBDMS **(64)** and trityl **(68)** cases, or unstable and prone to rapid break down, as in the case of the tosyl **(61)** and TBDPS **(66)** derivatives.

The second area under investigation was the epoxidation to convert the allyl tosylate species **(60b)** to a glycidyl derivative **(62b)**. The first approach involved treatment of the allyl species with *m*-chloroperoxybenzoic acid (*m*CPBA) in the presence of sodium bicarbonate[83,84]. The reactants were first stirred together in dichloromethane at room temperature, but after work-up, the product mixture showed only traces of epoxide **(62b)** dominated by unreacted starting material **(60b)**. Longer reaction times (>24hrs) did not improve the situation. For example, t.l.c. analysis of the reaction in refluxing dichloromethane for forty-eight hours, showed that the starting material had almost disappeared. However, the amount of material recovered from the reaction was extremely small, making this method unusable as part of a labelling protocol. It appears that the epoxide **(62b)** is either only formed as a minor product, with another water soluble species being the major component, or that the epoxide reacts a second time to generate some other compound, possibly the diol. Clearly the diol could disappear into the aqueous washes during work-up.

The concurrent investigation of the label insertion, described earlier, had moved on to the use of the silyl protecting groups at this time, so it was decided to attempt the epoxidation of the TBDPS

protected allyl alcohol **(65a)** in order to avoid the problems of the allyl tosylate epoxidation. Treatment of the silyl allyl ether with *m*CPBA and sodium bicarbonate gave, on work-up, the desired epoxide **(69)** in good yield (68%).

The third area of investigation focused on the chemistry of the epichlorohydrin analogue glycidyl tosylate **(62a)**[73], and in particular to establish whether it behaves in the same manner as epichlorohydrin with amines. The possible modes of reaction for the tosylate analogue are shown in Figure 2.30.

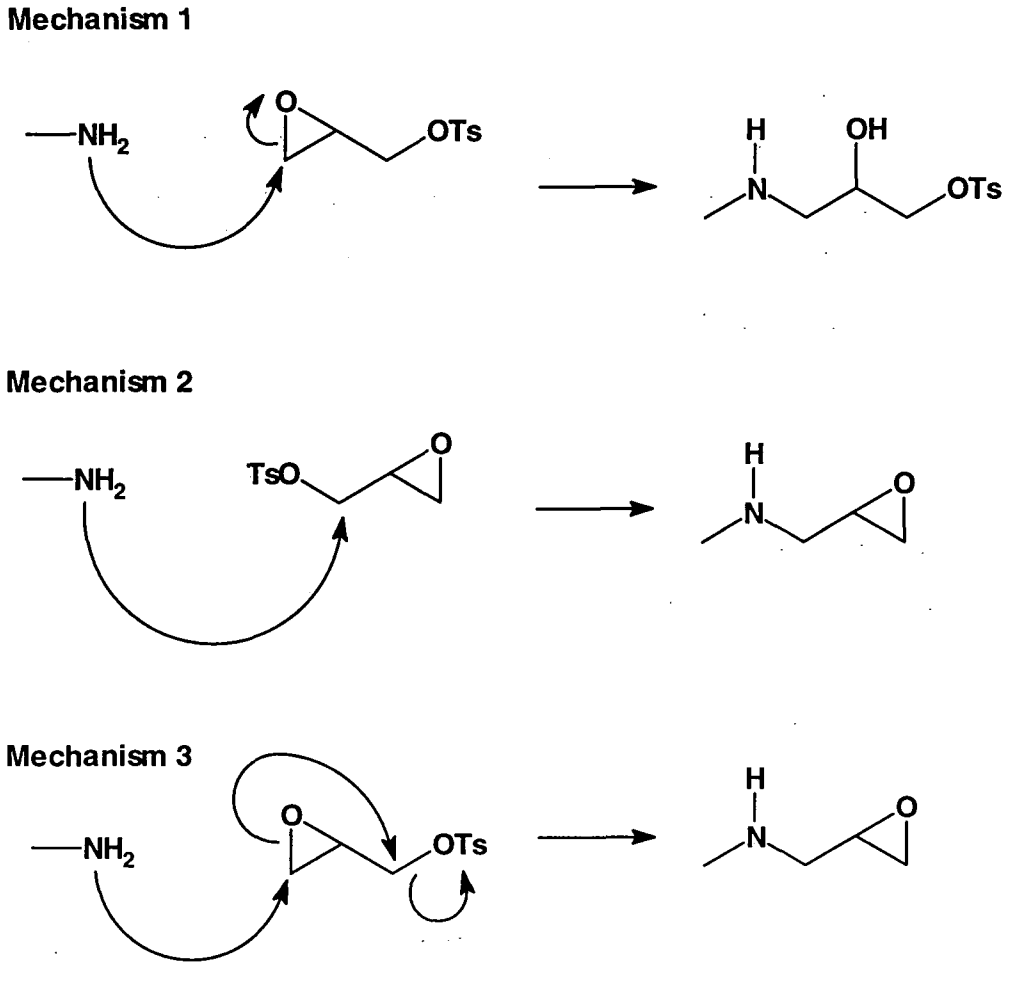


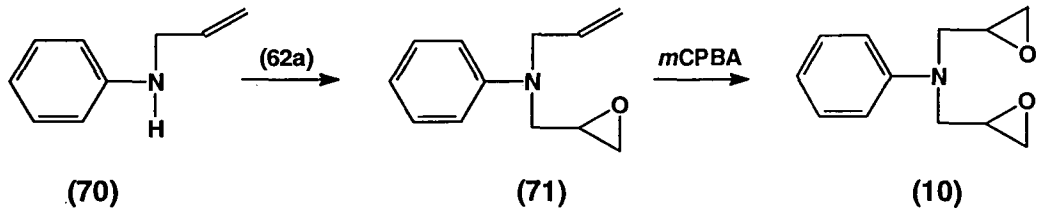
Figure 2.30 *Possible mechanisms for amine attack on glycidyl tosylate*

In principle any of the three processes above could be used as part of a labelling regime, assuming that further reaction doesn't take place. If different aniline molecules become linked together by a second amine reacting with the epoxide formed in process 2 or 3, the polymeric product formed would clearly be of no use.

Initial studies on the tosylate analogue **(62a)** were not encouraging. Use of the epichlorohydrin analogue in the first step of the TGDDM synthesis[7,8] produced an unidentifiable, intractable solid. Even when a very large excess of **(62a)** was used to try and reduce the possibility of intermolecular crosslinking, none of the desired product could be identified by ^{1}H-NMR, amongst the numerous unidentifiable resonances. It seemed likely that some form of further reaction is taking place.

In order to try to probe the mechanism of the aniline/glycidyl tosylate reaction the protocol was repeated using diisopropylamine in place of the aniline and a large excess of the analogue **(62a)**. This was judged an appropriate strategy to try and isolate intermediate species, by removing the possibilities for further reaction with the second reactive site at the amine. When the reaction product was analysed it showed clearly by ^{1}H-NMR analysis the presence of an epoxide ring still intact in the side chain, while the tosylate resonances are completely absent. This seems to confirm that either one or both of processes 2 or 3, shown in Figure 2.30 is operating, which would leave an epoxide moiety for further reaction with other amines. Only a labelled reaction could delineate between the two processes.

Such behaviour is clearly problematic for the whole synthetic strategy, as it would seem to be impossible to use the glycidyl tosylate as a direct replacement for epichlorohydrin. However, it might be possible to change the TGDDM synthesis to accommodate the behaviour of the glycidyl species. A model study was carried out to test this, as shown in Figure 2.31.



(70) (71) (10)

Figure 2.31 *Model for an alternative synthesis of TGDDM from glycidyl* p-*toluenesulfonate* ***(62a)***

The first step would involve coupling the secondary amine **(70)** and glycidyl tosylate **(62a)** to give **(71)**, followed by epoxidation of the double bond, to give the diepoxide **(10)**. The N-allyl aniline **(70)** was chosen because of it's ready availability, to determine if such a strategy is feasible. If the model worked out successfully, attempts would be made to apply the methodology to a TGDDM producing system. Although the revised route only allows one of the glycidyl groups of TGDDM to be labelled, this was seen as more than adequate as the glycidyl groups are equivalent and the level of carbon labelling necessary was expected to be about 25%.

Treatment of N-allyl aniline with n-butyllithium, followed by addition to a solution of the glycidyl tosylate **(62a)** gave a 53% yield of the required product. However, treatment of the N-allyl-N-glycidyl aniline **(71)** with *m*CPBA[83,84] gave a low yield of the N-oxide derivative rather than the desired diepoxide **(10)**. A combination of mass spectral and ^{1}H-NMR data confirmed that, although the mass of the product was correct, the oxygen had attached itself to the nitrogen atom. There was no spectral evidence to suggest generation of the diepoxide **(10)**.

2.4.3 Conclusion

The synthetic route outlined at the beginning of this section was chosen for a number of reasons, including the short protocol, the

relatively large body of work on the labelling of allyl alcohol, and the anticipation that tosylate derivatives would make the compounds in the scheme easy to handle and purify. The work carried out on the route has revealed a number of problems both major and minor, and compromised the route. The scheme which started as a short series has grown to try to accommodate the synthetic difficulties, and the crystallinity of the intermediates is only partly realised. Attempts to label the allyl species foundered on the apparent instability of the derivatised α-hydroxyaldehydes, and the key epoxidation step to generate glycidyl groups from allyl groups has proven very difficult to achieve.

Perhaps the most serious problem is the difference in behaviour between epichlorohydrin **(2a)** and the tosylate analogue **(62a)** designed to replace it. The much better leaving group capacity of the tosylate group has greatly effected the experimental results, and shown that it would be very difficult to use the analogue in its originally devised role.

While any one of these problems might individually be solved, all of them together combine to make this synthetic route untenable. The way forward lies in designing and exploiting an entirely different synthetic protocol.

2.5 Synthetic Route 2

2.5.1 Proposed Route

The second synthetic route to be investigated in an attempt to introduce isotopic labels into the TGDDM monomer was designed to overcome a number of problems which emerged in the last section. In particular, the route is designed to produce labelled epichlorohydrin itself, rather than glycidyl *p*-toluenesulfonate **(62a)**. The route also allows direct generation of the epichlorohydrin in a base induced ring closure similar to those used in commercial preparations. Another important point is that the label originates from labelled acetic acid **(24)** which is relatively cheap and readily available. The route is shown in Figure 2.32

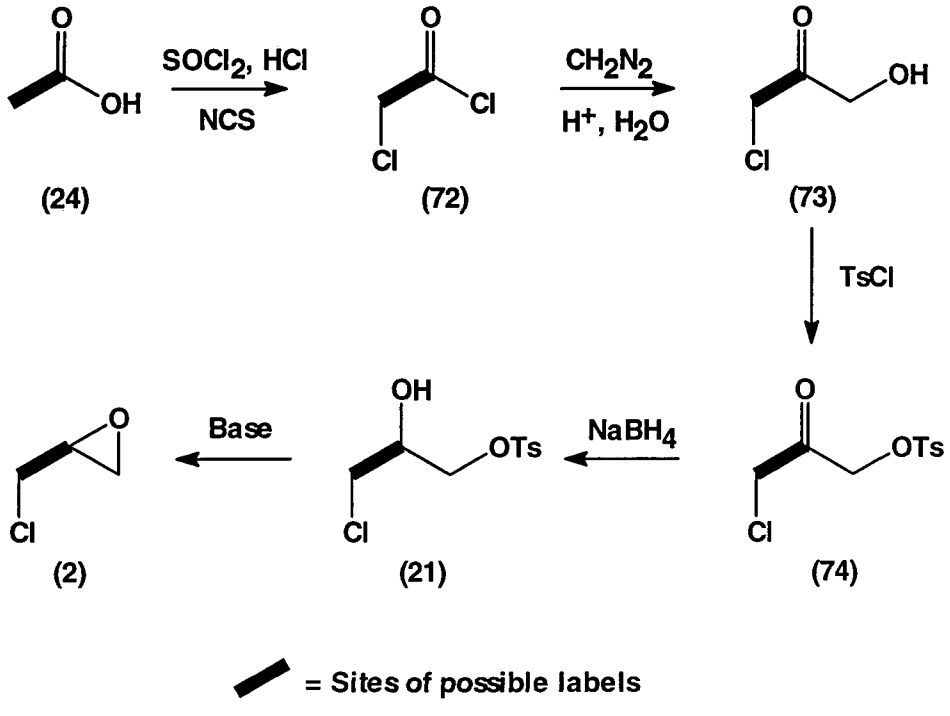


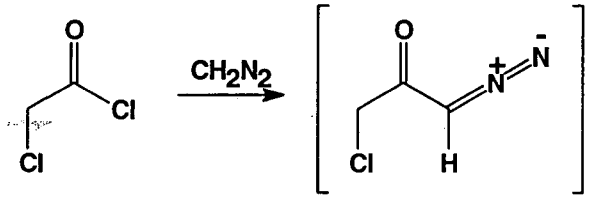
Figure 2.32 *The proposed synthetic route to labelled epichlorohydrin*

The first and last steps of this synthesis are also established in the literature[36,85], and are known to proceed with good yields. The only uncertainty at the outset was the transformation of the acid chloride (**72**) into an α-hydroxyketone (**73**), by formation and then hydrolysis of a diazoketone.

2.5.2 Experimental Results

The generation of 2-chloroacetyl chloride (**72**) proceeded as expected according to a literature precedent[85]. Heating a solution of acetic acid in thionyl chloride for thirty minutes, followed by addition of N-chlorosuccinimide and continued heating gave the desired compound, which could be isolated by careful distillation in good yield (60%). While some difficulties were initially experienced in completely removing all of the residual thionyl chloride from the product, the problem was solved by careful distillation, and investigation of the formation and hydrolysis of the diazoketone could proceed.

Addition of the chloroacetyl chloride (**72**) to an equimolar solution of diazomethane[86] produced a pale yellow solution which was confirmed by ^{1}H-NMR and mass analysis to be the diazoketone (**75**) shown in Figure 2.33.



(72) (75)

Figure 2.33 *Formation of the diazoketone (75)*

The diazoketone (**75**) proved remarkably stable, and is resistant to hydrolysis. If the diazoketone is heated under reflux in a wet

ethereal solution with a few drops of sulfuric acid, the compound is left almost completely untouched. Similarly, if the ethereal solution is added to an equal volume of 1M sulfuric acid and the biphasic mixture heated, the diazoketone remains untouched as before. When, in a separate reaction, the ether is distilled from the biphasic solution and the aqueous solution refluxed for two days, no organic material can be recovered from the mixture, even after several days of continuous extraction into organic solvents.

In an attempt to mediate the hydrolysis, several different acids were tried in place of the sulfuric acid. All were ineffective, with one exception. The use of hydrochloric acid, while not producing the desired alcohol, did however have the effect of increasing the size of one product signal in the ^{1}H-NMR. This was attributed to the presence of 1,3-dichloropropanone (**48**)[87-89].

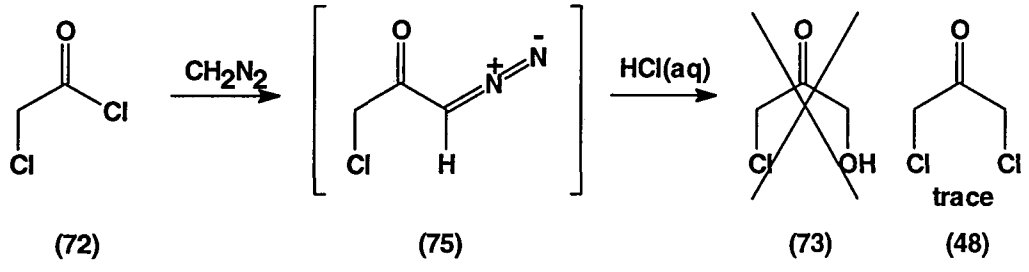


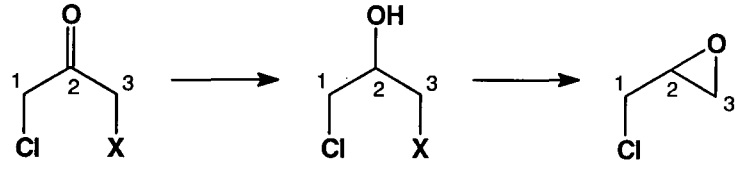
Figure 2.34 *Formation of a trace of 1,3-dichloropropanone (48)*

The dichloropropanone (**48**) could clearly be a useful intermediate for labelled epichlorohydrin, as outlined in section 2.3.4 and Figure 2.16, since specific carbon labelling at C-2 would be possible. In order to explore this result further, the aqueous HCl used in the reaction was replaced with anhydrous HCl in ether[89]. ^{1}H-NMR of the product showed a single peak, which further analysis confirmed to be 1,3-dichloropropanone (**48**), formed in good yield (99%).

The route to epichlorohydrin (**2**) from 1,3-dichloropropanone (**48**)

was therefore established, and became the focus for subsequent study. Sodium borohydride was used to reduced the ketone to an alcohol **(16)**, and a sodium hydroxide wash used to close the epoxide ring. Thus it was shown that C-2 carbon and deuterium (from sodium borodeuteride) labelling of epichlorohydrin can be achieved easily using acetic acid as a starting material.

The dichloropropanone-based synthesis of epichlorohydrin described is clearly of use, but there are still limitations. If the acid chloride **(72)** and diazomethane are present in an uneven stoichiometry, and this is normally the case bearing in mind the nature of diazomethane, then the HCl quench generates impurities, which are difficult to remove without lowering the yield significantly. Additionally, this route doesn't allow unique labelling at C-1 or C-3 of epichlorohydrin with either carbon-13 or deuterium, because of the random nature of the epoxide closure in the symmetrical dichloropropanol system. Rather than introducing chloride from HCl, it was judged preferable to introduce another, better leaving group. This would then provide the selectivity required for C-1 labelling as well as C-2, as shown in Figure 2.35.



X = Leaving group (> Cl)

Figure 2.35 *Insertion of a better leaving group at C-3*

The originally proposed scheme deployed a tosylate group to achieve selectivity, and so this was where the investigation began. Instead of adding anhydrous HCl to the diazoketone solution, a direct substitution was attempted, and solid *p*-toluenesulfonic acid was added

in its place[89-92]. The solution effervesced as expected, and following work-up a crude white solid was isolated, and recrystallised. When analysed this proved to be the tosylate derivative (**74**), generated in approximately 55% yield, as shown in the Figure below. Thus, although its synthesis was devised ultimately by a convoluted route, it can be synthesised easily, and with the added benefit of reducing the overall scheme by one step.

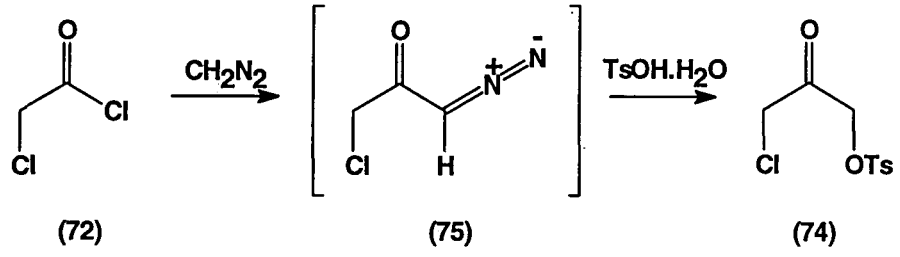


Figure 2.36 *Synthesis of 3-chloro-2-oxopropyl p-toluenesulfonate (74)*

While the tosylation of a diazoketone with tosic acid may seem unusual, there is some precedent in the literature[89,90]. The reaction is driven by protonation of the diazoketone, breaking up the delocalisation and allowing the weak tosylate nucleophile to displace the dinitrogen group as nitrogen gas.

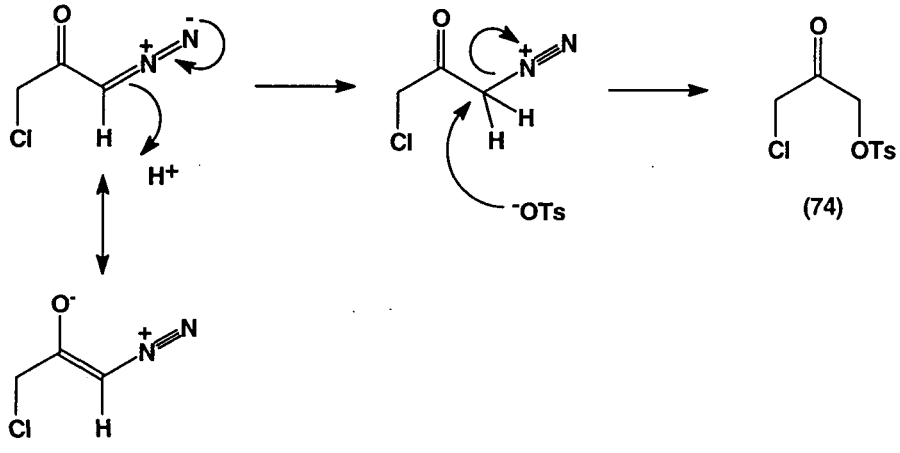
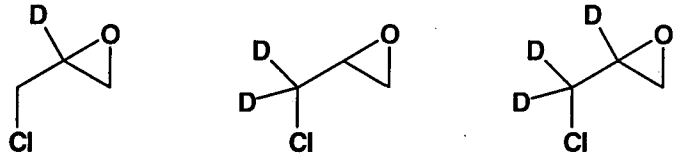


Figure 2.37 *Proposed mechanism of the tosylation reaction*

The last two steps in the proposed route (Figure 2.32) proceeded as expected, using sodium borohydride to reduce the ketone **(74)**[93], and then treating the resultant alcohol **(21)** with sodium ethylene glycolate in ethylene glycol[36], to produce epichlorohydrin **(2)**. The product was removed from the ethylene glycol solution by distillation under reduced pressure. The selectivity which is now introduced allows unambiguous labelling at both C-1 and C-2, with an approximate overall yield of 20% from the acetic acid.

Deuterium labelled compounds are generally cheaper than their carbon-13 counterparts, and as such allowed exploration of the versatility of the synthetic route. To this end the three deuterium labelled forms of epichlorohydrin shown in Figure 2.38 were synthesised.



(2h) (2i) (2l)

Figure 2.38 *Deuterium labelled forms of epichlorohydrin prepared by the diazoketone route*

The compound **(2h)** was prepared using sodium borodeuteride, **(2i)** from [2-$^{2}H_3$]-acetic acid, and **(2l)** from a combination of both of these reagents. The ^{13}C-NMR spectra of all three of these samples, plus the spectrum of unlabelled epichlorohydrin, are shown in Figure 2.39. The splitting patterns due to the nuclear spin (I=1) of deuterium can be clearly seen, indicating that the compounds have been labelled unambiguously as expected, with no scrambling or dilution of the label.

Having clearly demonstrated the success and versatility of this route with deuterium labelled reagents, a carbon-13 labelled form **(2b)**

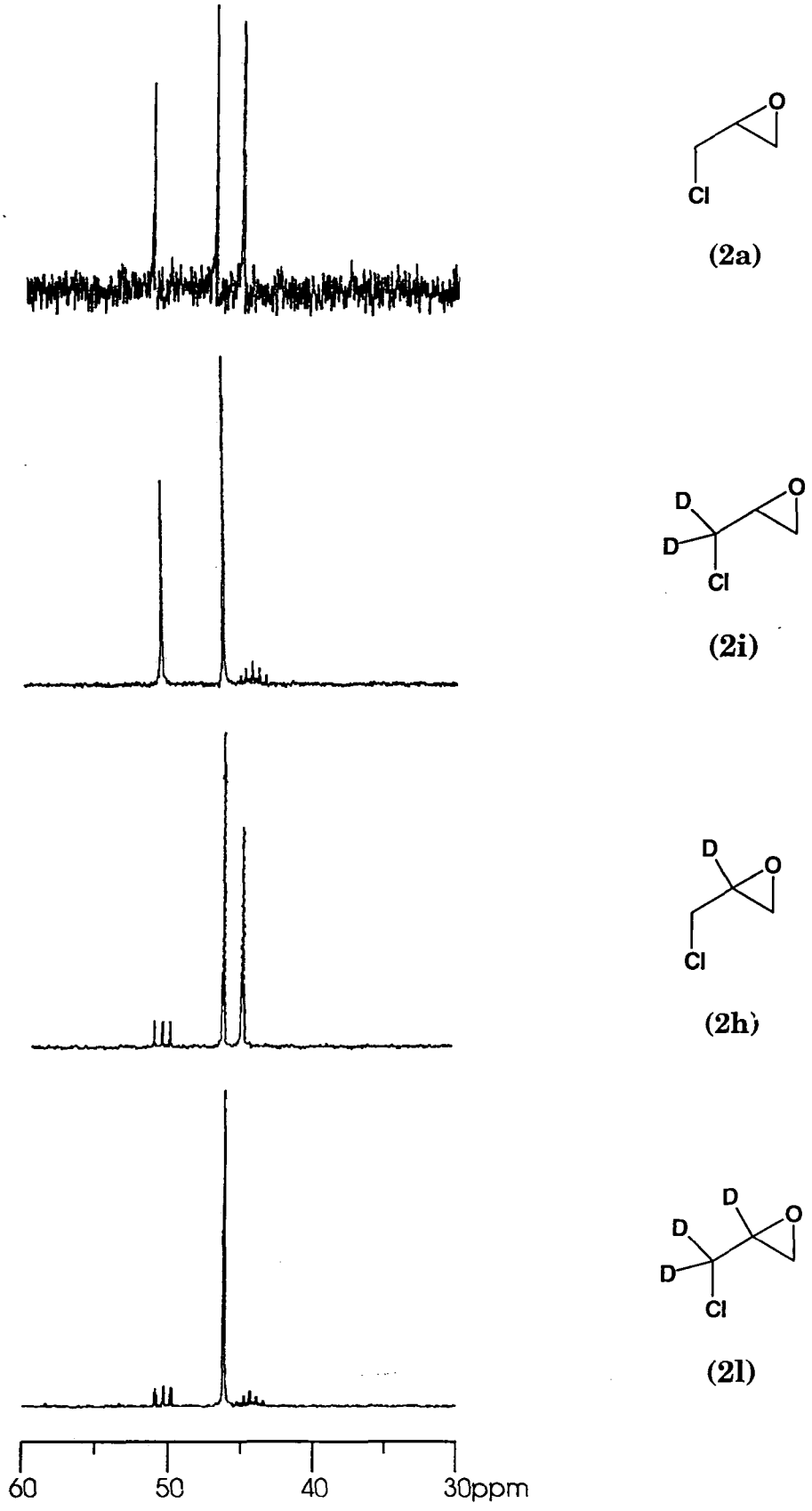


Figure 2.39 *^{13}C-NMR spectra for selected epichlorhydrins*

was then prepared. [1-^{13}C]-Acetic acid (4g) was used as a starting material to prepare [2-^{13}C]-epichlorohydrin **(2b)** (1g), for use in the synthesis of labelled TGDDM **(7d)**.

2.5.3 Conclusion

The second synthetic route to labelled epichlorohydrin, after modification was therefore successful. Thus the route, shown in Figure 2.40, is the most straightforward and most versatile described to date for the synthesis of isotopically labelled epichlorohydrin.

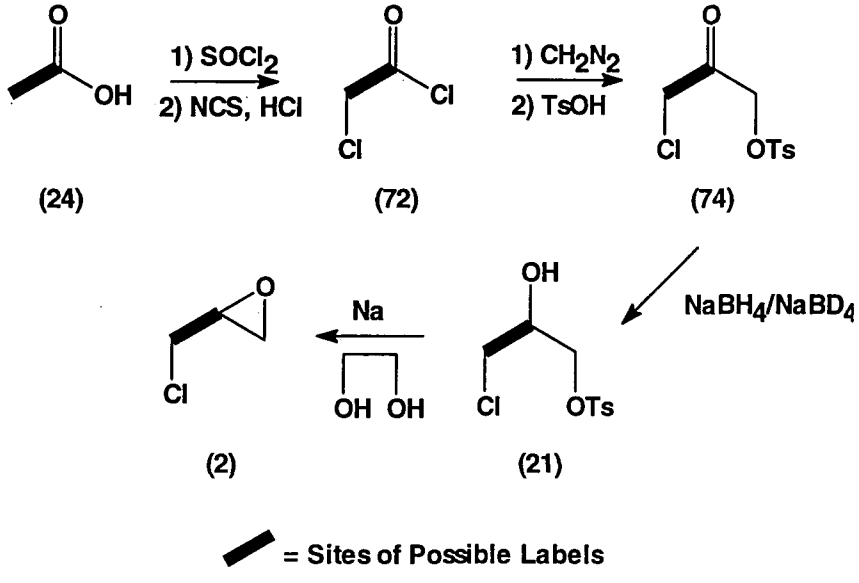


Figure 2.40 *Synthetic route to C-1 and C-2 labelled epichlorohydrins*

This methodology uses a short route with moderate to high yields throughout, and a good overall yield of approximately 20%. It also exploits two relatively cheap sources of isotope, acetic acid and sodium borodeuteride, which are readily available from chemical suppliers. The reaction scheme itself uses simple chemistry without the need for awkward handling techniques or exotic chemicals, and is very amenable to the synthesis of gram quantities of isotopically labelled

material if necessary. The synthetic route also involves very little in the way of purification, thus avoiding unnecessary handling and loss of the label.

The only disadvantage of this route is that it doesn't allow easy access to C-3 labelled epichlorohydrin (**2c**). It would be technically possible to use labelled diazomethane to synthesise such compounds, but the cost of the labelled starting material is prohibitive, especially for the gram quantities that would be required. This deficiency is addressed in the next section.

2.6 Synthetic Route 3

2.6.1 Proposed Route

The only remaining problem for the labelling of epichlorohydrin is unambiguous labelling at C-3. Bearing in mind the success of the synthetic procedure described in section 2.5, it was proposed to adapt this chemistry, and to start from another readily available, labelled starting material. The adapted scheme is shown in Figure 2.41.

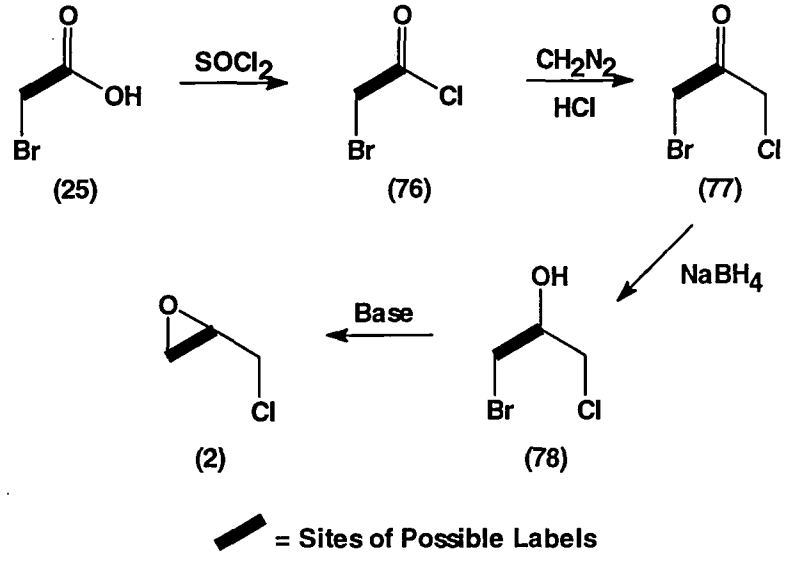


Figure 2.41 *Route to C-2,3 labelled epichlorohydrins*

This route exploits bromide, which is a better leaving group than chloride. The route starts with bromoacetic acid **(25)**, which can be synthesised in a straightforward manner by literature methods[94] from labelled sodium acetate, but it is also readily available commercially. This was then reacted with thionyl chloride to form the acid chloride **(76)**[85], and was then treated with diazomethane[86] and anhydrous HCl[89] in diethyl ether, to form 1-bromo-3-chloropropanone **(77)**. This was treated in the same manner as before, reducing the ketone to an

alcohol (**78**) with sodium borohydride[93] and the closing the epoxide and displacing the bromide with sodium ethylene glycolate in ethylene glycol[36] to give the desired epichlorohydrin (**2**).

2.6.2 Experimental Results

Treatment of bromoacetic acid (**25**) with thionyl chloride, followed by distillation, led to the bromoacetyl chloride (**76**) in almost quanititative yield. Addition of diazomethane to the acid chloride, followed by quenching with HCl in diethyl ether, gave 1-bromo-3-chloropropanone (**77**) in almost 90% yield. No trace of any bromide displacement by chloride could be observed in the product mixture. Sodium borohydride reduction to give (**78**) was completed cleanly (73% yield). The final, base-induced epoxide closure was carried out using sodium ethylene glycolate as before to give a yield of about 60%. Treatment with base produced the desired epoxide ring closure to give exclusively epichlorohydrin (**2**), with absolutely no trace of epibromohydrin by ^{1}H- and ^{13}C-NMR. The overall yield for the reaction scheme is approximately 40%.

2.6.3 Conclusion

The route outlined in this section makes an excellent compliment to that of the previous section, allowing isotopic labelling of the C-3 site of epichlorohydrin. It is also possible to label epichlorohydrin in the C-2 position by this route, further increasing its versatility.

CHAPTER 3

Synthesis of Isotopically Labelled Monomers

Synthesis of Isotopically Labelled Monomers

3.1 Introduction

Five different isotopically labelled forms of the TGDDM and DDS monomers were synthesised to use as probes to investigate the macrostructure of the cured resin system. Of the four TGDDM variants, one was regiospecifically labelled with carbon-13 **(7d)**, two with deuterium **(7f)** and **(7g)**, and one with nitrogen-15 isotopes **(7b)**. A nitrogen-15 labelled form of DDS **(8b)** was also prepared. The sites of isotope incorporation into these labelled monomers are shown in Figure 3.1.

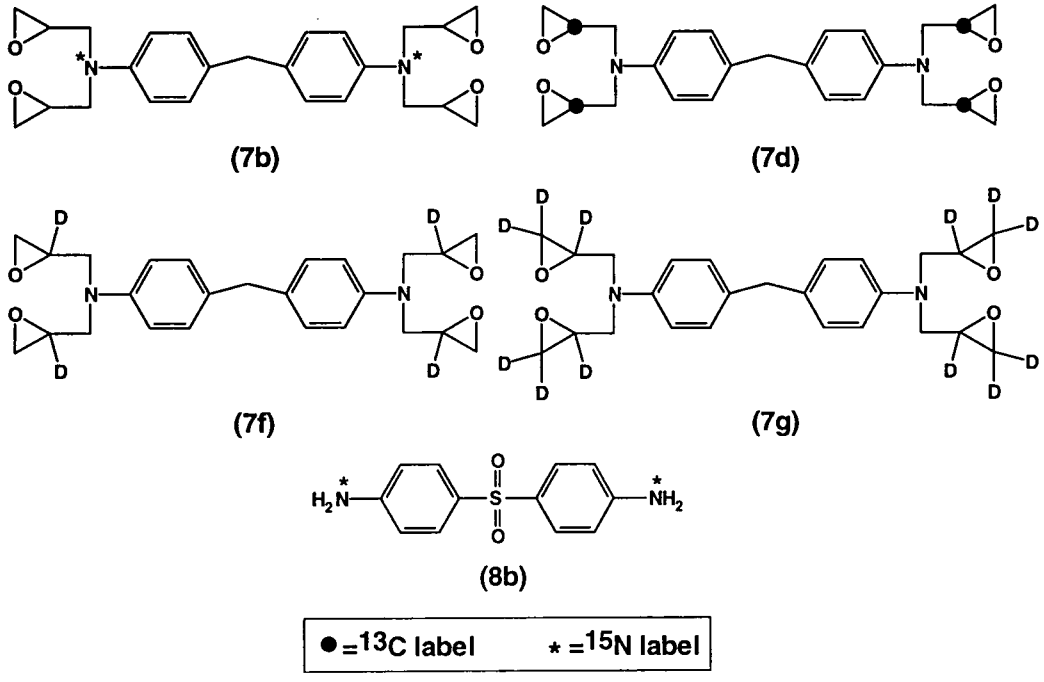


Figure 3.1 *The regiospecific location of isotopes in the five target monomers*

The carbon-13 and nitrogen-15 labelled monomers were synthesised with the aim of increasing the intensity of the labelled atoms resonances in the solid state ^{13}C-NMR spectrum, and thus make the spectra easier to assign and interpret. In order to generate selective and unambiguous enhancements, isotope enrichment of approximately 20-30% was judged adequate for carbon-13. Of course the greater the percentage enrichment, the more expensive the synthesis, and this consideration must be taken into account.

The labelling of TGDDM with deuterium on the other hand was approached differently, because of the different effect that the labelling was hoped to produce. While the nitrogen-15 and carbon-13 labelling was aimed at *increasing* the intensity of certain peaks in the solid state NMR spectra, the deuterium labelling was aimed at selectively altering the nature of particular carbon atoms to force them to behave as if they were quaternary carbons. It was hoped that this technique would aid assignment of the carbon-13 NMR spectrum, as greater simplicity would result. This effect is only observed for carbon-13 atoms completely labelled with deuterium, so a maximum effect will be observed when the deuterium content is as close to 100% as possible.

3.2 Synthesis of Isotopically Labelled Tetraglycidyldiamino-diphenylmethane (TGDDM)

3.2.1 Introduction

The syntheses of the different labelled forms of TGDDM prepared in the study were carried out by the protocol described in Chapter 2[8,9,95]. The route involve the preparation of TGDDM from aniline **(9a)** and epichlorohydrin **(2a)**, and thus isotopes can be introduced from labelled forms of these starting material. The reaction scheme is shown in Figure 3.2.

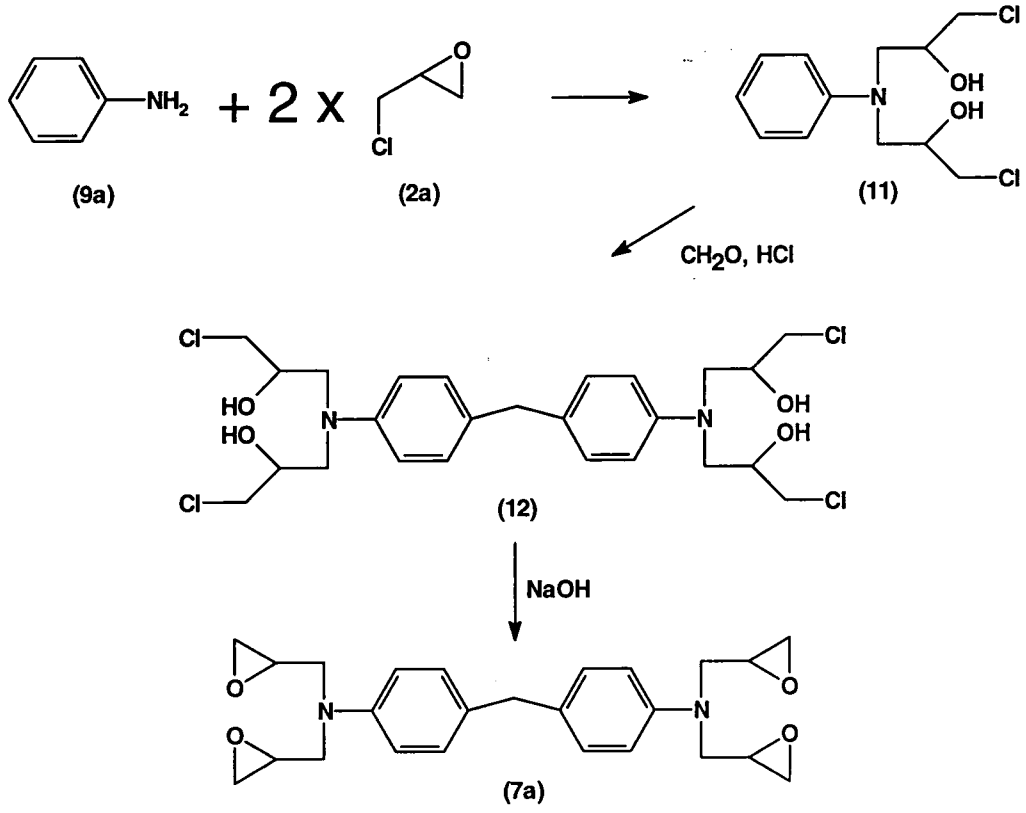


Figure 3.2 *The synthesis of TGDDM (**7a**) from aniline (**9a**) and epichlorohydrin (**2a**)*

Chapter 2 describes the development of a new route to isotopically labelled forms of epichlorohydrin labelled with carbon-13 and

deuterium. With nitrogen-15 labelled aniline **(9b)** available commercially, it is only a case of deploying the correctly labelled starting materials to generate the required labelled monomers.

3.2.2 Carbon-13 Labelling

The [2-^{13}C]-epichlorohydrin **(2b)** was prepared at 99 atom% using the method described in Chapter 2, starting with [1-^{13}C]-acetic acid **(24b)**. This material was then diluted to 20 atom%, a level considered adequate to show a discernible level of resonance enhancement at specific sites in the carbon-13 solid state NMR spectrum. The labelled TGDDM **(7d)** was thus prepared in a straightforward manner[95], and gave carbon-13 and ^{1}H-NMR spectra entirely consistent with the level of isotopic incorporation.

3.2.3 Deuterium labelling

The same route to the TGDDM monomer was used to produce the deuterium labelled versions **(7f)** and **(7g)**[95], although no dilution of the isotopically labelled epichlorohydrin was carried out. Appropriate amounts of [2-^{2}H]- and [2,3,3-^{2}H$_3$]-epichlorohydrin **(2h)** and **(2l)** (4.0g and 3.2g respectively) where synthesised by the route described in Chapter 2.

Figures 3.3 and 3.4 show the carbon-13 NMR spectra of the two deuterium labelled TGDDM samples **(7f)** and **(7g)**. The ^{1}J ^{2}H-^{13}C coupling patterns due to deuterium labelling can clearly be seen. Both spectra show two overlaid triplets for the carbon at the C-2" position, while Figure 3.4 also shows two pentets for the carbon at C-3", as well as two singlets which correspond to a small amount of unlabelled carbon at the same position.

Examination of the expansions in the spectra shows a doubling of

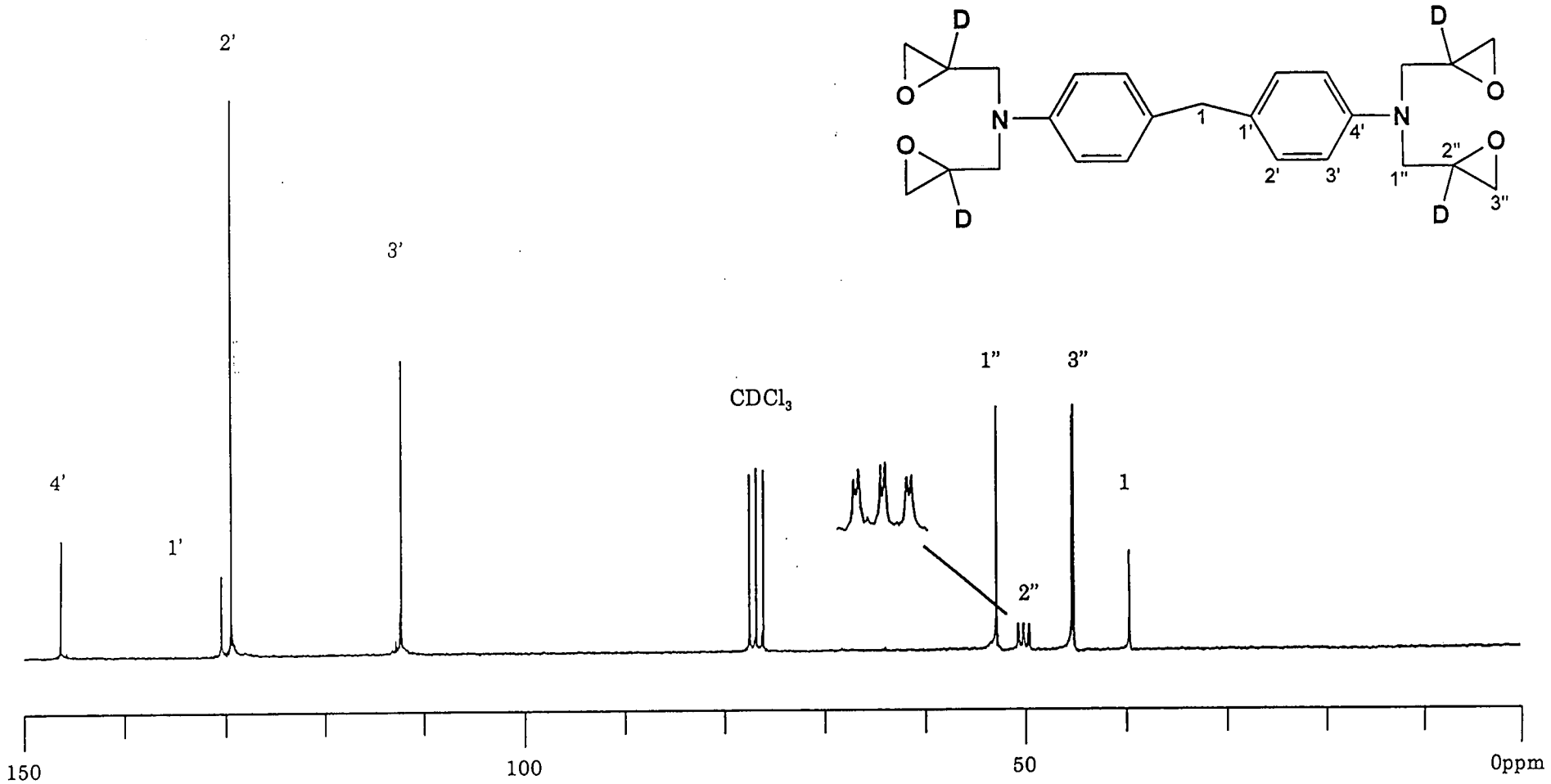


Figure 3.3 50MHz Carbon-13 NMR spectrum of [2"-$^2D_4$]-Tetraglycidyldiaminodiphenylmethane (TGDDM) (7f)

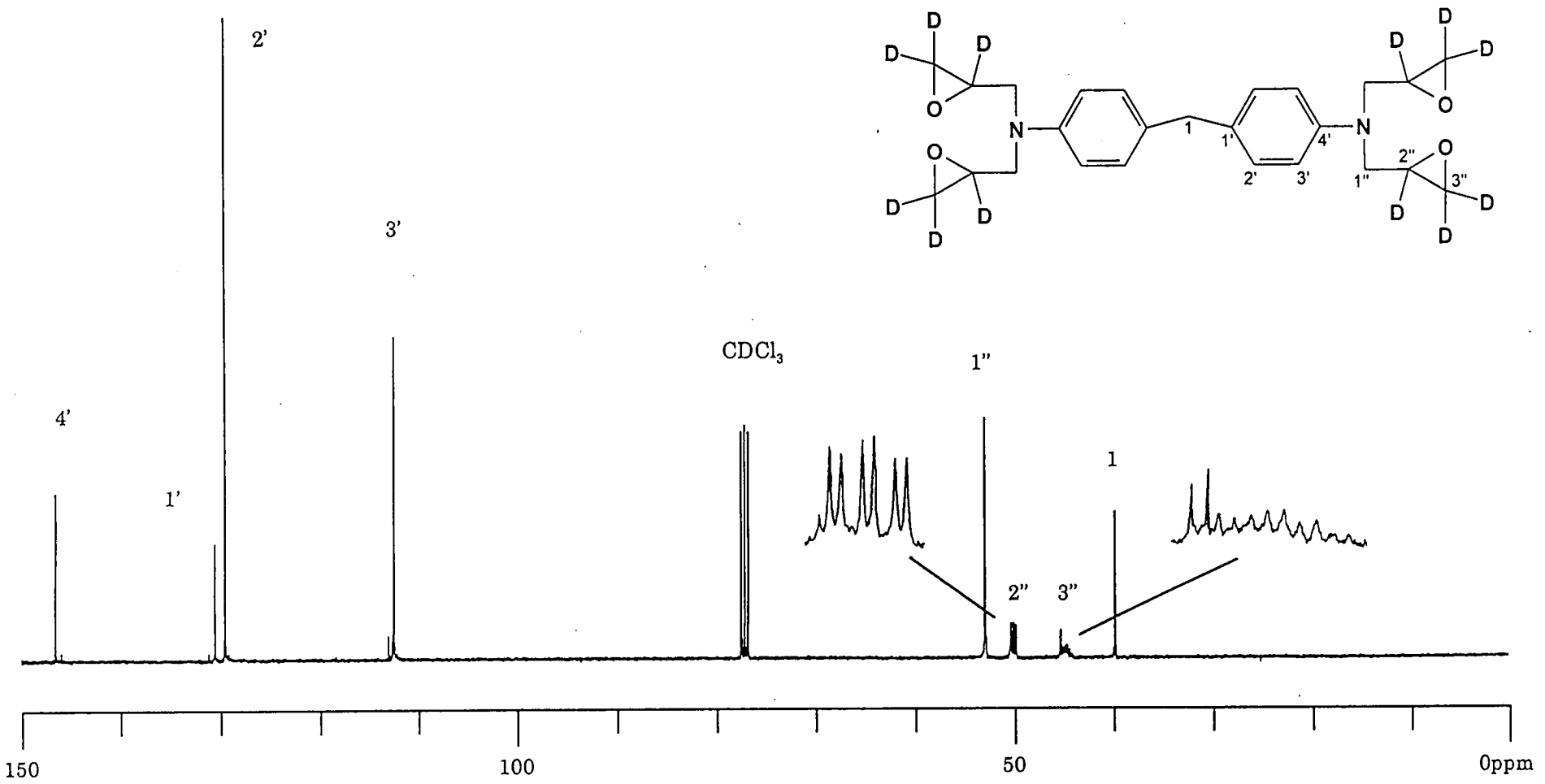


Figure 3.4 100MHz Carbon-13 NMR spectrum of [2".3"-$^2D_{12}$]-Tetraglycidyldiaminodiphenylmethane (TGDDM) (7g)

all the signals is due to diastereomeric interactions present in the sample, which induce small differences in the chemical shift. All four of the glycidyl groups present in the TGDDM monomer contain a chiral centre, which in theory gives 2^4 (=16) different stereoisomers, although some of these are equivalent to each other. However, in the NMR spectrum this is simplified for several reasons. The first is due to the relatively large distance between the two ends of the molecule. The chiral centres cannot 'feel' each other over this distance, and allows each end of the monomer to be treated independently. Thus interpretation of the diastereomeric interactions in TGDDM are similar to those observed for diglycidyl aniline, as shown in Figure 3.5.

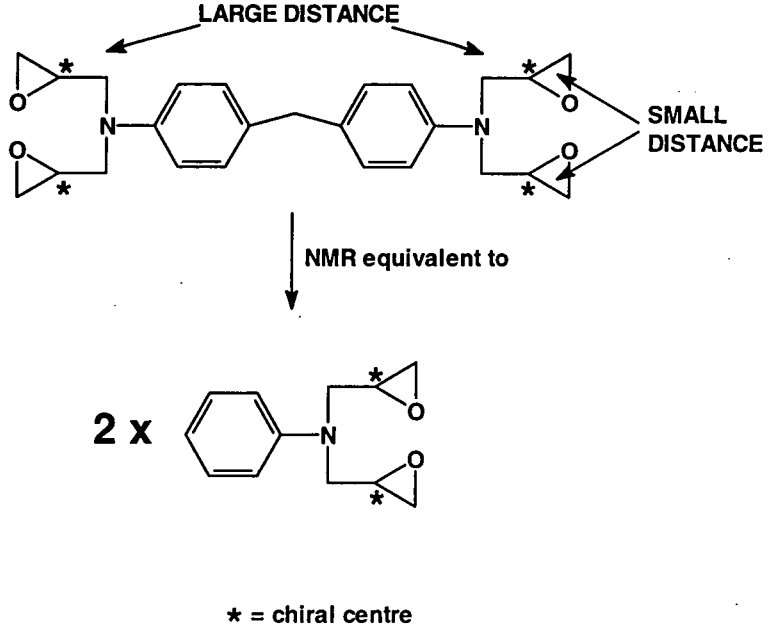


Figure 3.5 *Simplification of the TGDDM carbon-13 NMR due to distance between chiral centres*

The diglycidyl aniline model has only two chiral centres, which produce three stereoisomers (*D-*, *L-*, and *meso-*), and simplifies the resonances in the NMR to just two peaks for each carbon environment. This is why the carbon-13 resonances in the TGDDM monomer

spectrum show very fine splittings for atoms close to the chiral centres, such as those that have been labelled with deuterium in this case.

The appearance of a small amount of unlabelled C-3" carbon can be seen in the spectrum in Figure 3.4, and merits some comment. The two unlabelled C-3" carbon peaks which appear at 45.2ppm, and have a slightly larger chemical shift value than the two pentets due to the deuterium labelled carbons, are approximately one tenth the height of the C-1" carbon resonance on the same spectrum. This indicates that somewhere in the region of 10% of the C-3" carbons contain protons rather than the desired deuterium atoms. The epichlorohydrin added to the reaction was 99 atom% at both C-2 and C-3, and no protons were detectable by NMR at these sites. It is reasonable to assume that the dilution/scrambling occurred during the condensation reaction. The 10% of deuterium at C-1" would be undetectable due to its very weak intensity.

A possible mechanism for the label dilution or scrambling can be inferred from a number of observations. Firstly, while there is clear evidence for both two protons at C-3" (10%) and two deuteriums at C-3" (90%), there is no sign of any mixed proton/deuterium labelling. Secondly, while the C-3" carbon has been subject to label dilution, the C-2" carbon is unaffected.

The lack of mixed proton/deuterium labelling in particular seems to indicate a partial loss of regiochemical control as illustrated in Figure 3.6.

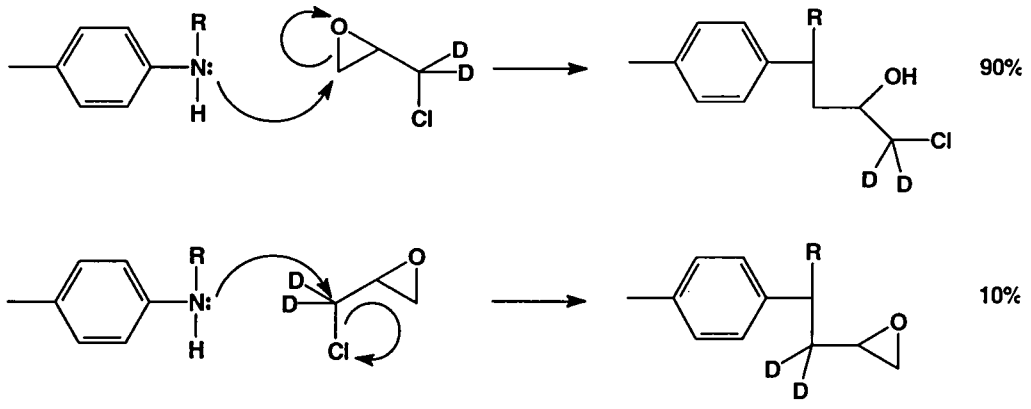


Figure 3.6 *Possible mechanism for label scrambling in the TGDDM monomer*

The first pathway in the Figure shows the expected reaction pathway, with opening of the epoxide to give a chlorohydrin derivative. The second pathway can account for the scrambling of the label, where the amine displaces the chloride, leaving the epoxide intact. The eventual result of this would be location of the deuteriums at C-1" rather than C-3" as desired, but at an insufficient level to be detectable by carbon NMR due to coupling and weak signal intensity. This mechanism could also explain why the C-2" labelling is unaffected.

The occurrence of this small amount of label scrambling also shows up the phenomenon of the α- and β-shifts[96], which produce a small decrease in the chemical shift of carbons containing deuteriums when compared to the protonated versions. The α-shift is the larger of the two, caused by deuteriums directly bonded to the carbon being observed, and is of the order of 0.3-0.6ppm per deuterium. The β-shift is smaller at approximately 0.1ppm per deuterium, and is caused by deuteriums attached to carbon atoms vicinal to the one being observed.

The glycidyl carbons of the [2",3"-$^{2}D_{12}$]-TGDDM (**7g**) exhibit clear α- and β-shifts. C-1" feels a β-shift due to the deuterium on C-2", moving from 53.1 to 52.9ppm. C-2" feels β-shifts from both the

deuteriums of C-3", plus a much larger α-shift from the directly attached deuterium, resulting in a shift from 50.6 to 50.0ppm. C-3" feels a β-shift from the deuterium on C-2", plus a large α-shift from the two deuteriums directly attached, shifting the signal from 45.4 to 44.6ppm. It is interesting to note that the 10% of unlabelled C-3", showing up as the two largest peaks in the expansion in Figure 3.4, does not have the large α-shift of the other 90%, due to the missing deuteriums. This results in a small shift from 45.4 to 45.2ppm.

3.2.4 Nitrogen-15 labelling

The nitrogen-15 labelled TGDDM **(7b)** was synthesised[8,9] with an isotopic enrichment of 26 atom%. Nitrogen-15 aniline **(9b)** was admixed with natural abundance aniline **(9a)** to give the desired level of enrichment, and this was then converted by the standard synthetic method for the preparation of TGDDM. The product **(7b)** was successfully prepared, and nitrogen-15 NMR showed the label very clearly. However, it proved impossible to detect the influence of the nitrogen-15 labels in the carbon NMR spectrum, due to the low intensity of the appropriate signals. It might be reasonable to expect to see a splitting caused by the interaction of nitrogen-15 (I=1/2) and carbon-13 (I=1/2) for the carbon next to the nitrogen, but the already weak quaternary signal is made even harder to observe due to coupling, and because only 26% of the carbons actually 'see' a labelled nitrogen.

3.3 Synthesis of Isotopically Labelled Diaminodiphenyl-sulfone (DDS)

3.3.1 Introduction

Diaminodiphenylsulfone (DDS) **(8a)** is the 'hardener' that is reacted with TGDDM **(7a)** to give the cured resin under investigation. The amine groups of DDS react with the epoxide moieties of TGDDM, and thus DDS is an integral part of the structures of the cured material. It was therefore judged appropriate to label the nitrogen atoms of the DDS amine groups with nitrogen-15, in an attempt to elucidate the structures formed by solid state nitrogen-15 NMR.

The availability of nitrogen-15 labelled starting materials is extremely limited, and was the major factor in designing a synthetic approach to DDS. Previous literature syntheses of DDS[97,98] use unsuitable reaction schemes or limiting reaction conditions such as high temperature and pressure, and as such were not used. The most promising approach, based on availability of starting materials, and a practical synthetic route, was the use of the Gabriel reaction[99].

The Gabriel synthesis is a classic method for the preparation of primary amines, in both unlabelled and labelled forms. An alkyl halide, typically a fluoride, is reacted with potassium phthalimide to give an alkyl phthalimide, which is converted to an amine by hydrolysis or hydrazinolysis. This methodology has been used for the synthesis of nitrogen labelled species in the past, one of the more recent examples being the production of labelled nylon-12 for solid state NMR studies[100]. The proposed route to DDS is shown in Figure 3.7.

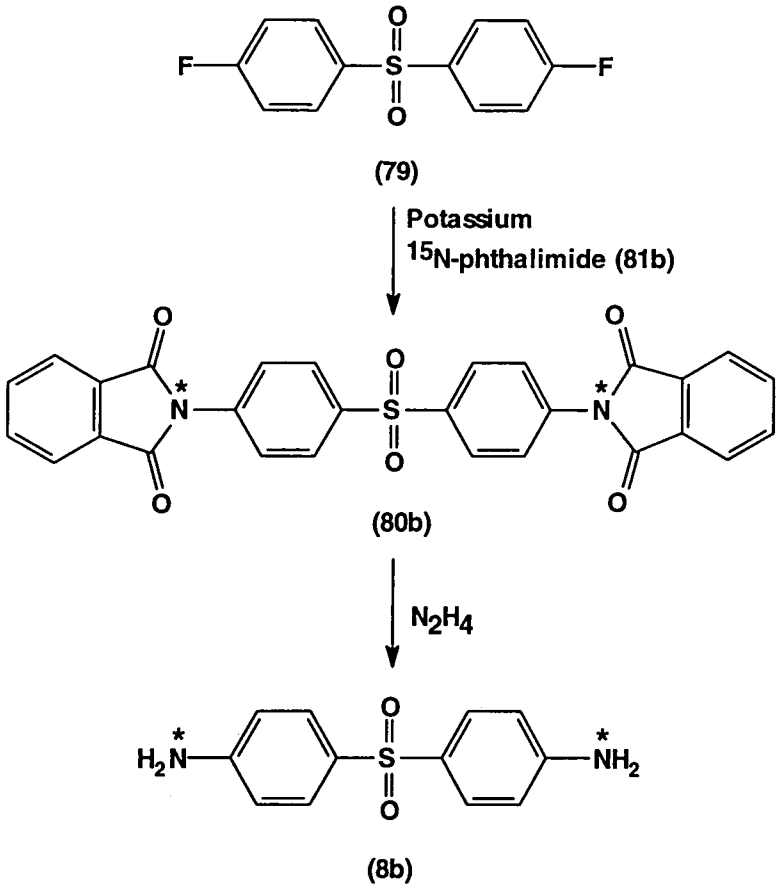


Figure 3.7 *Route to nitrogen-15 labelled DDS (**8b**)*

3.3.2 Nitrogen-15 labelling

Experimental investigations into the synthetic pathway initially met with problems. Following a literature precedent[100], the difluorophenylsulfone (**79**) was reacted with unlabelled potassium phthalimide (**81a**) in dry DMF at 100°C, but upon workup the only product that was isolated was the monosubstituted species, with one fluoro- and one phthalimido- substituent. However it was soon found that by increasing the temperature to DMF reflux the reaction proceeded to the required diphthalimido- substituted species (**80a**).

The second step proceeded very much as expected, in a straightforward manner. The diphthalimide (**80a**) was heated to

reflux with hydrazine in methanol, and worked up with strong acid, followed by neutralisation with base to give the required diamine **(8a)**.

Nitrogen-15 labelling of DDS was carried out using a sample of nitrogen-15 potassium phthalimide **(81b)** (99 atom%), diluted with natural abundance material to give a final level of enrichment of 30 atom%. The presence of the label in the final product **(8b)** can be seen clearly in the proton NMR of the sample, where the amine protons emerge as both a singlet (unlabelled) and a doublet (labelled, J=87.1Hz) in the expected ratio, as shown in Figure 3.8.

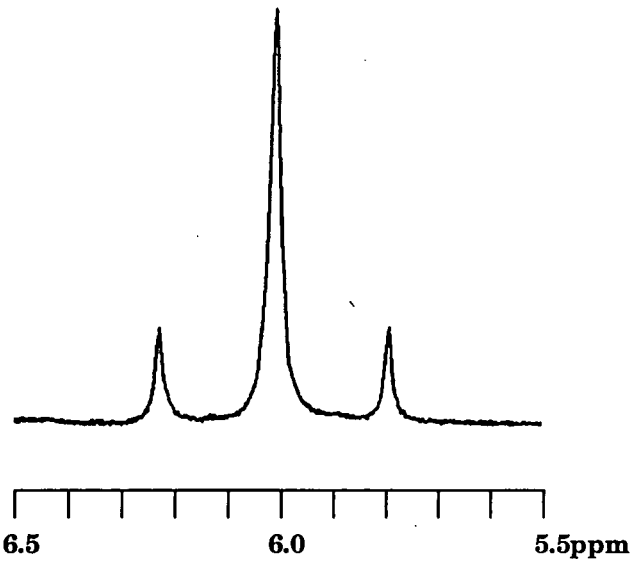


Figure 3.8 *^{1}H-NMR of the amine protons in labelled DDS (8b) (30 atom% ^{15}N)*

3.4 Conclusion

Two conclusions can be drawn from the work described in this chapter concerning the synthesis of labelled monomer units. Perhaps the most obvious point to be drawn is that it is possible at all to synthesise these compounds, especially in the case of the nitrogen-15 labelled form of DDS **(8b)**. The protocol used to produce **(8b)** was devised from a classic synthetic method, but it was applied to a previously untried case with no certainty of success. The five isotopically labelled monomers are all new compounds, and may have other potential uses beyond the current programme.

The second point brought to light by the work is concerned with the mechanism of formation of the TGDDM **(7)** monomer from aniline **(9)** and epichlorohydrin **(2)**, as shown in Figure 3.6. The 10% loss in regioselectivity illustrates an aspect of the reaction mechanism not previously appreciated in unlabelled systems, indicating that not all of the aniline-epichlorohydrin reactions result in a chlorohydrin type intermediate. Labelling has suggested that at least some of these reactions proceed to give a glycidyl group directly via chloride displacement. This reaction is used by industry to produce large amounts of epoxy resin for the aerospace industry, and the importance of this seemingly small experimental point should be seen in this context.

CHAPTER 4

Solid State Nuclear Magnetic Resonance Analysis

Solid State Nuclear Magnetic Resonance Analysis

4.1 Solid State Nuclear Magnetic Resonance

4.1.1 Introduction[104-106]

Solid state NMR poses a number of problems for anyone wanting to use this technique to probe the structure of solids. While nuclei in solution state samples undergo rapid tumbling and motion in the magnetic field, solids are locked in position and are unable to move. Line broadening due to shielding anisotropy and heteronuclear dipolar interactions, and long relaxation times all contribute to make solid state NMR a difficult technique to use. Some explanation of the methods used to overcome these problems is required before the experimental results are examined.

Shielding anisotropy is caused by different orientations of the nuclear environment to the applied magnetic field, giving broad spectral lines, and can be overcome using a technique known as Magic Angle Spinning. Heteronuclear interactions, which are very strong in the solid state, will also cause the resonances in the spectrum to be broad and flat, but can be eliminated using High Power Proton Decoupling. The carbon nuclei in the solid lattice have long relaxation times because of the rigid state of the lattice but this problem can be avoided by using a method known as Cross Polarisation (CP).

Three other techniques used also need an explanation. Non-quaternary Suppression (NQS) and spectrum deconvolution are methods used to simplify spectra and make them easier to interpret. Resolution Enhancement involves mathematical manipulation of the free induction decay signal to boost the resolution of the spectrum.

4.1.2 Magic Angle Spinning

A molecule is made up of charged particles which are in motion, and thus there will be a magnetic field associated with the molecule. Moreover, depending on the symmetry of the molecule or fragment of the molecule, this magnetic field will be unsymmetric and will interact with the applied magnetic field of an NMR spectrometer in a different fashion depending upon orientation. These interactions are normally averaged out by rapid tumbling in the solution state, but in solids the molecular arrangements are fixed, and so are visible as line broadening in the spectrum. The effect is known as shielding anisotropy, and the three typical line shapes for a powder are shown in Figure 4.1.

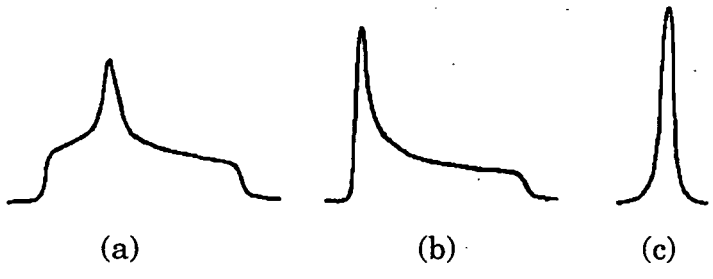


Figure 4.1 *Three powder patterns caused by shielding anisotropy; (a) general (b) axially symmetric (c) isotropic*

The general case (a) occurs when the molecule lacks spherical or axial symmetry, and has different degrees of interaction with the applied magnetic field in all three dimensions. An example of this would be a carbon with four different substituents attached to it. Case (b) is caused by a system with axial symmetry, similar to the chloroform molecule, while case (c) is produced by a spherically symmetric system which has a completely uniform magnetic field in all directions.

In order to find out how to reduce or remove this effect, the general case of a spinning sample has to be examined, as shown in Figure 4.2.

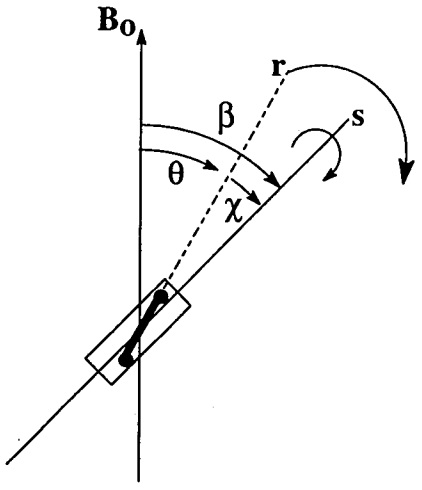


Figure 4.2 *Geometric relationships in macroscopic sample rotation at an angle to the applied magnetic field*

Consider a molecule in a sample that is being spun around an axis, **S**, which is set at an angle β, to the applied magnetic field $\mathbf{B_o}$. In a powdered sample, there will be random orientation of the molecular axes, so all values of χ, and thus all values of θ , will exist. The broadening of the NMR resonances is dependant on the factor of $(3\cos^2\theta - 1)$, which is derived form the dipolar Hamiltonian equation. Therefore to eliminate the effect, the average $\langle\ 3\cos^2\theta - 1\ \rangle$ must equal zero. Expanding the factor into a fuller version, it now looks like this:-

$$\langle\ 3\cos^2\theta - 1\ \rangle = 1/2\ (\ 3\cos^2\beta - 1)\ (\ 3\cos^2\chi - 1\ )$$

If we require:- $\langle\ 3\cos^2\theta - 1\ \rangle = 0$

then:- $(\ 3\cos^2\beta - 1) = 0$

$\therefore \beta = 54.7°$

If a powdered sample is placed in a container and spun about an axis at an angle of 54.7° to the applied magnetic field, the effects of shielding anisotropy are removed from the final spectrum. This angle is called the Magic Angle, and the technique is generally known as Magic Angle Spinning.

The only problems with MAS occurs if the sample is spun at too slow a rate to properly average the shielding anisotropy. Spin rates in the kilohertz region are normally required for complete averaging, and slower rates produce satellite resonances in the spectrum. These resonances are called spinning sidebands, and can be seen as smaller versions of the main resonance, situated either side of the main peaks and at equal distances from them.

4.1.3 High Power Proton Decoupling

It is often necessary in solution state NMR to decouple one type of nucleus while observing another, in order to enhance the signal to noise ratio or probe structural aspects of the sample under examination. This is done using a double resonance procedure, by irradiating the sample in the region of the first nuclei with appropriate radio-frequencies while observing the second nuclei. This has the effect of removing any coupling due to the first nuclei. A typical example of this is the observation of carbon-13 in the solution state, during which all protons are decoupled to simplify the spectrum and improve the signal to noise ratio.

Heteronuclear dipolar interactions are observed in the solid state. The fact that the molecules in the sample are conformationally fixed means that intermolecular as well as intramolecular couplings are observed. This further complicates the spectrum and reduces the signal to noise ratio further. In order to decouple the protons in the solid state, higher power radio-frequency irradiation is necessary than

is normally used for solution state NMR. This procedure is known as High Power Proton Decoupling (HPPD).

4.1.4 Cross Polarisation

The rigidity of solids and their component molecules produces the problem of relatively long relaxation rates for spin systems such as carbon-13 and nitrogen-15. After the magnetisation and free induction decay of such systems, it can take a period of many seconds for the system to relax back to a Boltzmann-like energetic distribution, and become amenable to another magnetisation/free induction decay cycle. This renders the modern technique of Fourier Transform NMR inefficient and slow.

To get around the problem of long carbon-13 relaxation times, the technique of Cross Polarisation is used. The pulse sequence for this process is shown in Figure 4.3.

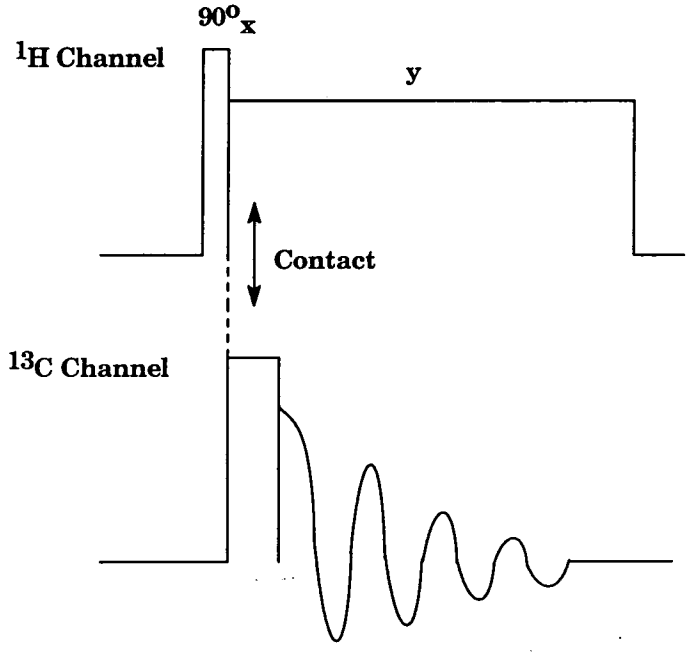


Figure 4.3 *The pulse sequence for Cross Polarisation from the proton to the carbon-13 nuclei*

The initial magnetisation of the system is to the proton nuclei, with a ninety degree radio frequency pulse, followed by spin locking and high power decoupling of the protons in the y-axis of the rotating frame of reference. The spin locking has the effect of keeping the proton magnetisation coherent and slowing down its free induction decay. At the end of the ninety degree proton pulse, the radio frequency in the carbon-13 channel is switched on, and the power of the radio frequency adjusted so that the *Hartmann-Hahn matching condition* is satisfied:-

$$\gamma_H B_{1H} = \gamma_C B_{1C}$$

The Magnetogyric Ratio (γ_x) is a constant for a given nucleus, while the magnetic field in the rotating frame of reference (B_{1X}) can be altered by varying the amplitude of the applied radio-frequency. When the matching condition is satisfied, the magnetisation of the protons can be transferred to the carbon-13 nuclei, during the *contact period.* The large magnetogyric ratio of protons and relatively small magnetogyric ratio of carbon-13 nuclei means that when the system equilibrates, the carbons will have gained a large degree of magnetisation, larger than would have been gained by direct carbon magnetisation. At the end of the contact period, the radio-frequency is switched off and a free induction decay recorded as normal.

The advantage of cross polarisation becomes apparent at this point, as the next cycle of magnetisation/cross polarisation/decay begins once the *protons* have relaxed, rather than the carbons. The proton relaxation time is much shorter than the carbon relaxation time, which allows faster and more efficient collection of data from the sample.

This technique is amenable to use with other low abundance NMR active isotopes. As well as carbon-13 spectra, Nitrogen-15

spectra are also accumulated using this process, due to the increased magnetisation and shorter cycle times.

4.1.5 Non-quaternary Suppression

While the techniques of magic angle spinning, high power proton decoupling and cross polarisation make solid state NMR practical, the spectra produced are often complex and difficult to interpret. However, manipulation of the pulse sequence used to obtain the data can simplify the spectrum considerably, as in the case of Non-quaternary Suppression.

Removal of the protonated carbons from a spectrum to leave only the quaternary species is made possible due to the fact that the magnetisation of carbon nuclei coupled to proton nuclei decays faster than that of uncoupled carbon nuclei. A pulse sequence that exploits this is shown in Figure 4.4.

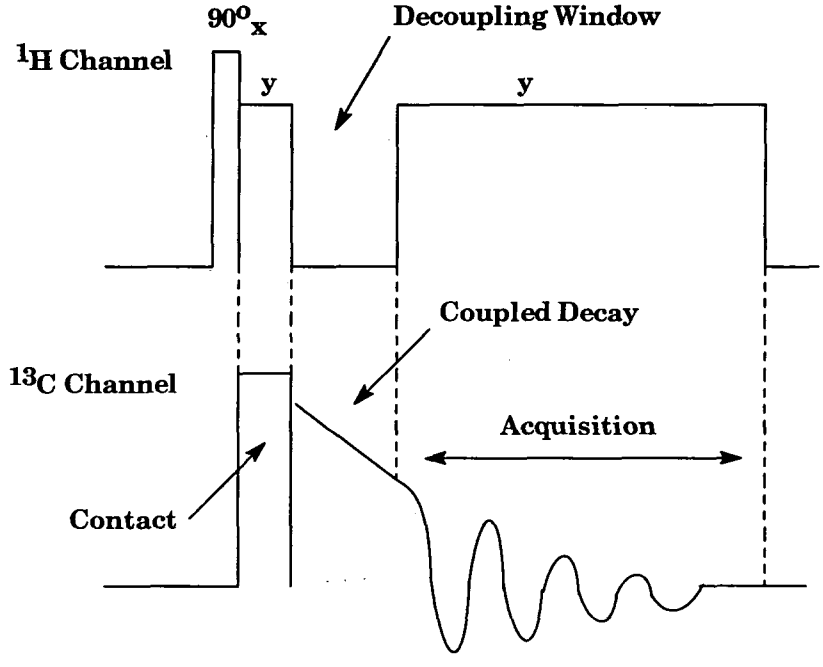


Figure 4.4 *Pulse sequence for Non-quaternary Suppression (NQS)*

The pulse sequence is very similar to that for normal cross polarisation of nuclei. The protons are magnetised with a ninety degree radio frequency pulse, and then spin locked and decoupled during the contact period. However, once the contact period is over, proton decoupling is switched off for a short time, typically 40μs, while the carbon magnetisation is decaying. During this decoupling 'window', the CH and CH_2 carbons decay quickly to zero, while the quaternary carbons decay slowly. The decay rate of CH_3 groups is of an intermediate rate due to their mobility by internal rotation. At the end of the decoupling 'window', the only significant magnetisation left in the sample resides in the quaternary carbons, which continue to decay during the subsequent acquisition period. Thus the spectrum gained from using such a pulse sequence will be made up of strong, narrow resonances for quaternary carbons, with weaker peaks for any methyl carbons present in the sample.

In addition to producing a spectrum containing only unprotonated carbon resonances, it is also possible to obtain a spectrum for protonated carbons. This is achieved computationally by subtracting the result of the NQS experiment from the full spectrum. This technique provides another way of probing the chemical structure of the sample under examination.

4.1.6 Deconvolution of Solid State NMR Spectra

The complex peak shapes of some solid state NMR spectra ares often due to the overlapping of several broad resonances. In theory, it is possible to work out the constituent resonances from the shape of these composite peaks, using computerised statistical methods. This technique is called Deconvolution, and can be useful for the interpretation of complex spectra.

The software used as part of this project allows the user to set the

number of peaks to be fitted to a complex peak-shape. It then uses a simplex algorithm[104] based on non-linear least square fitting to find the best fit it can for the specified number of peaks. This fit also gives a numerical value to the least squares fit, which can be compared with other values for fits with different numbers of peaks. The operator can then decide, on the basis of these values, which number of peaks has produced the most meaningful fit, and is most likely to be correct.

It should be noted, however, that conclusions drawn from deconvolution treatments of complex peaks are not completely reliable. The more complex a peak, the more inaccurate the final answer is likely to be, particularly if there is an appreciable amount of background noise. A complex peak shape will always be fitted best with a large number of constituent peaks, even when in reality it is the result of a smaller number. In addition to the absolute numeric value given to the least squares fit for x number of peaks, the difference between this value and that for x-1 peaks should be examined. If there is a significant improvement in the least squares fit for x peaks, the result is probably meaningful. If not, the result is probably not useful.

4.1.7 Resolution Enhancement

Resolution Enhancement relies on the properties of the free induction decay that is emitted by the sample in an NMR spectrometer. In particular, it is easier to distinguish closely grouped resonances by examining the end of the decay rather than nearer the beginning. It is possible to scale the free induction decay by multiplying by an exponential factor, so that this region of the decay is accentuated disproportionately and makes a greater than normal contribution to the spectrum, enhancing its resolution. However, as the signal to noise ratio is higher in this region of the spectrum, it will also be increased in the final spectrum.

4.2 Synthesis and Treatment of Cured Resins

The curing of TGDDM with DDS requires care if the resultant solid resin is to be prepared correctly. The procedure described below is designed to give fully cured samples in a reproducible fashion[5,105].

TGDDM (**7**) was warmed to 60°C to render it more mobile, and then a stoichiometric amount of the DDS (**8**) hardener was added. The mixture was stirred until the hardener dissolved, and was then degassed under vacuum to remove any volatile components. Fifteen minutes after the first addition of the DDS, while still mobile, the mixture was poured into a pre-warmed mould at 150°C.

The mould comprises two layers of inert, non-stick fabric cut into a squared off' U-shape pattern, and sandwiched between two glass plates treated with a commercial non-stick separating agent. The result is a thin, rectangular, open topped mould, into which the uncured resin mixture is poured, as shown in Figure 4.5.

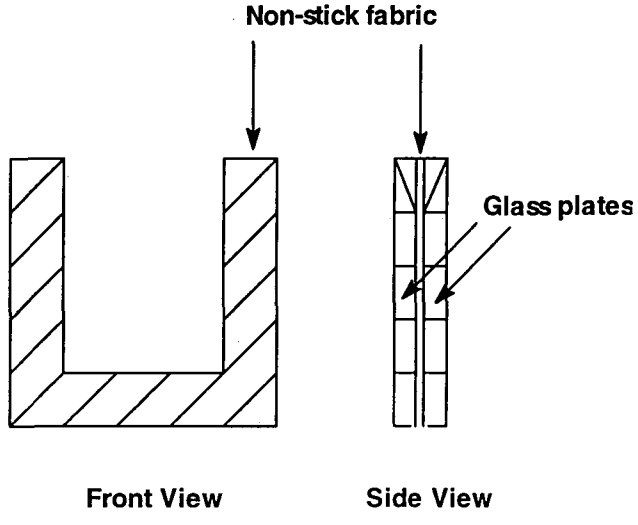


Figure 4.5 *Epoxy resin curing mould*

Once in the mould, the resin was placed in an oven, and heated for five hours at 150°C. The mould was then transferred to another

sealed oven, and heated in an inert atmosphere for three hours at 180°C and three hours at 200°C. The mould was then allowed to cool, and broken open to give the solid resin as a golden brown, translucent material.

In order to carry out the solid state NMR analysis of the sample, the resin was reduced to a fine powder, which could then be packed into a small sample vial for insertion into the NMR spectrometer probe.

4.3 Solid State NMR of labelled samples

4.3.1 Carbon-13 labelled sample

The spectrum for the resin prepared from [2"-$^{13}C_4$]-TGDDM (**7d**) (20 atom%) is shown in Figure 4.6, and the effect of the carbon-13 enrichment can be seen clearly. The region of the spectrum containing the aliphatic carbon resonances is dominated by what appears to be a single broad peak, while the only other distinguishable features are the aromatic resonances between 100 and 160ppm.

Resolution enhancement of the spectrum reveals that this single large peak has two shoulders, indicating two smaller peaks on either side of the main resonance. Deconvolution of the peak reveals a best fit with a major peak at 69.4ppm, and two smaller peaks on either side at 64.3 and 76.6ppm. The resolution enhanced peak, the deconvolution best fit and the difference of the two are shown in Figure 4.7.

4.3.2 Deuterium labelled samples

Two deuterium labelled resins were prepared using [2"-$^{2}D_4$]- and [2",3"-$^{2}D_{12}$]- labelled TGDDM monomers (**7f**) and (**7g**). The spectra of these samples were collected, and while the full spectra appeared unchanged, the effect of the deuterium labels can be seen if the NQS non-protonated spectrum is examined. This spectrum has a group of new peaks between 40 and 80ppm, which are due to the carbons labelled with deuterium. A spectrum of an unlabelled sample of cured TGDDM/DDS has no such quaternary resonances. It is therefore possible to identify the deuterium-labelled carbon resonances in this non-protonated spectrum, separating them from overlapping resonances from other carbons in the full spectrum. Figures 4.8 and 4.9 show the full, protonated and non-protonated spectra of the two

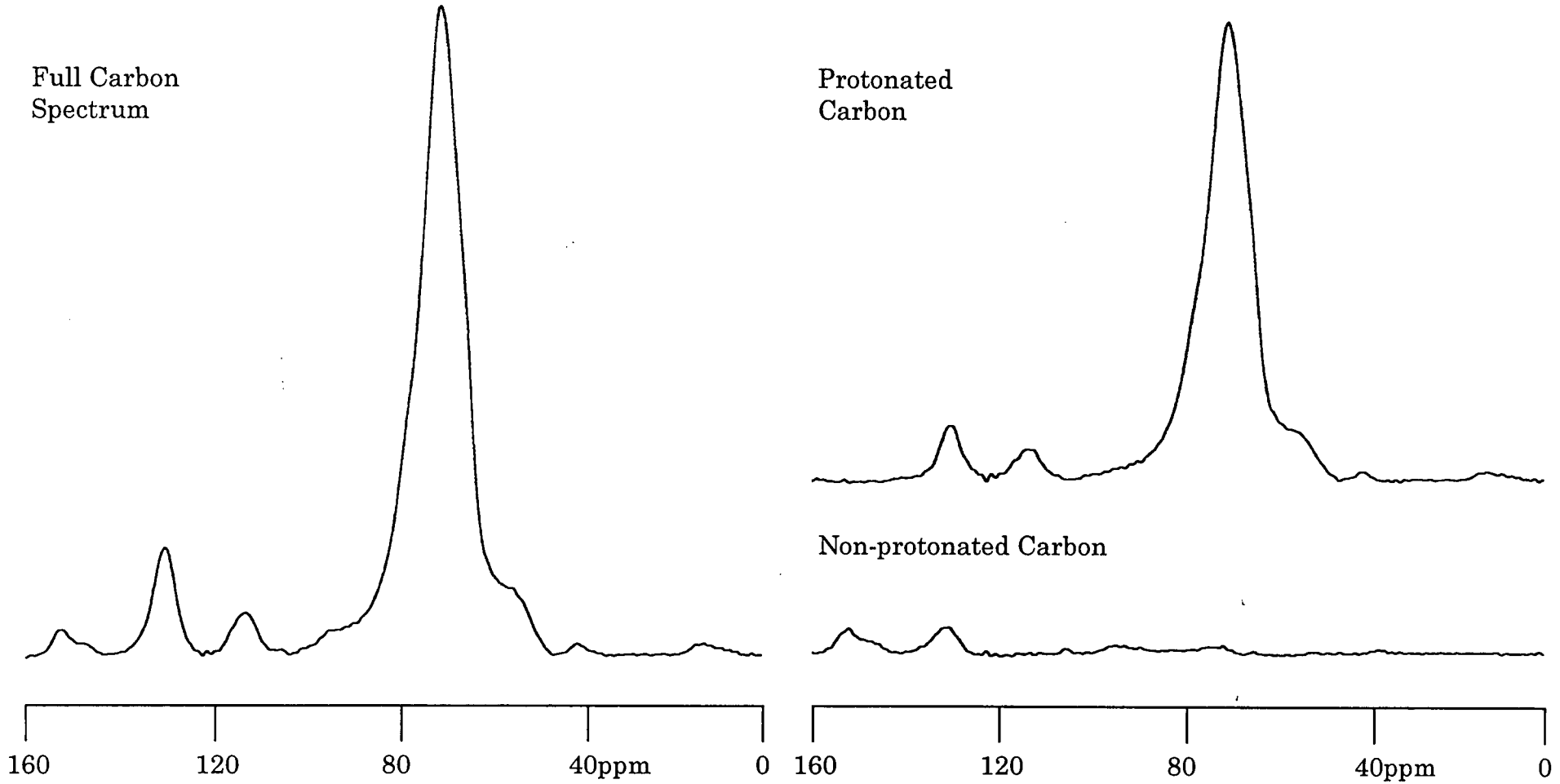


Figure 4.6 *Solid state carbon-13 NMR spectrum of [2"-$^{13}C_4$]-TGDDM/DDS* ***(7d)/(8a)*** *epoxy polymer*

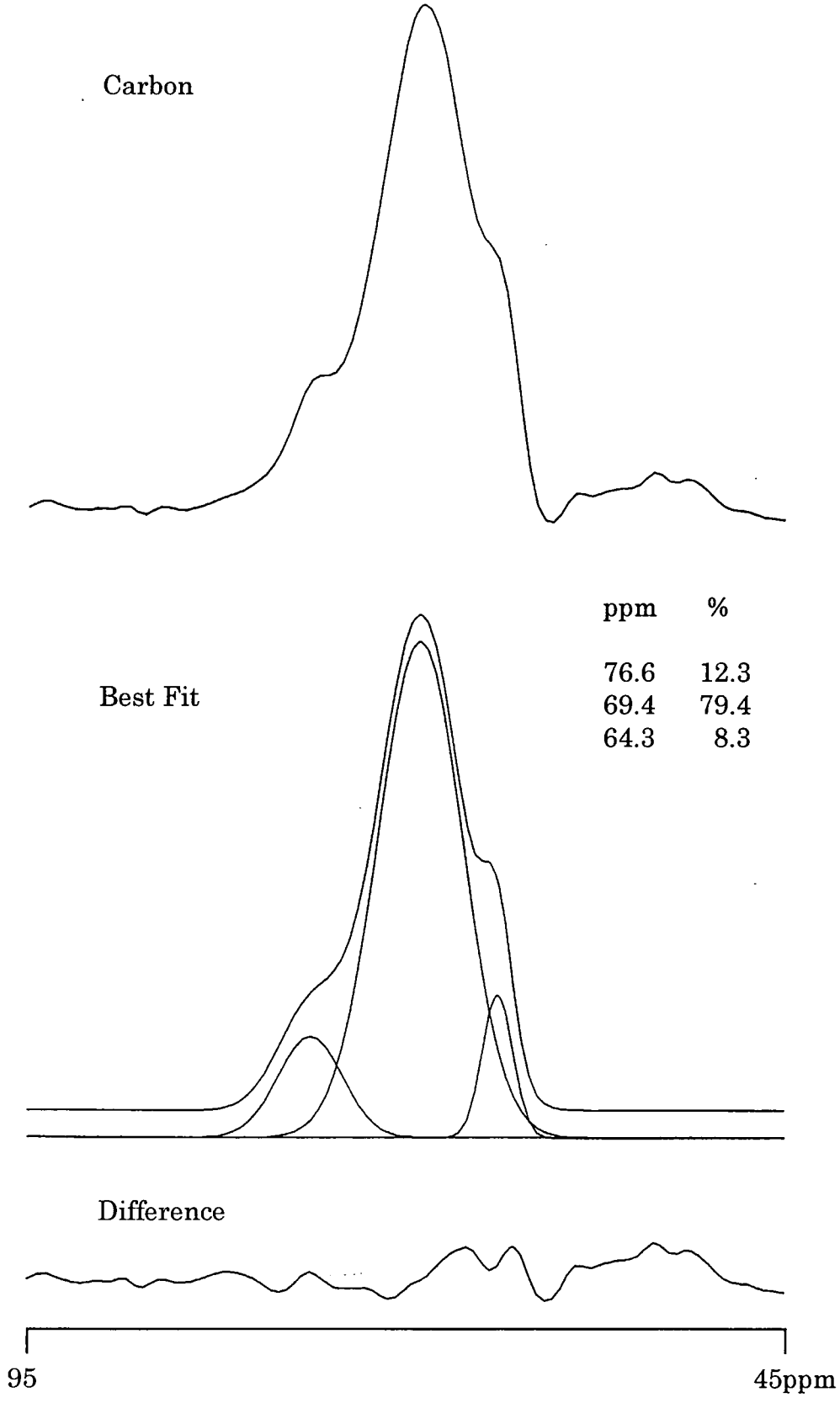


Figure 4.7 *Deconvolution of labelled carbon resonance for [2"-$^{13}C_4$]-TGDDM/DDS* ***(7d)/(8a)*** *cured resin*

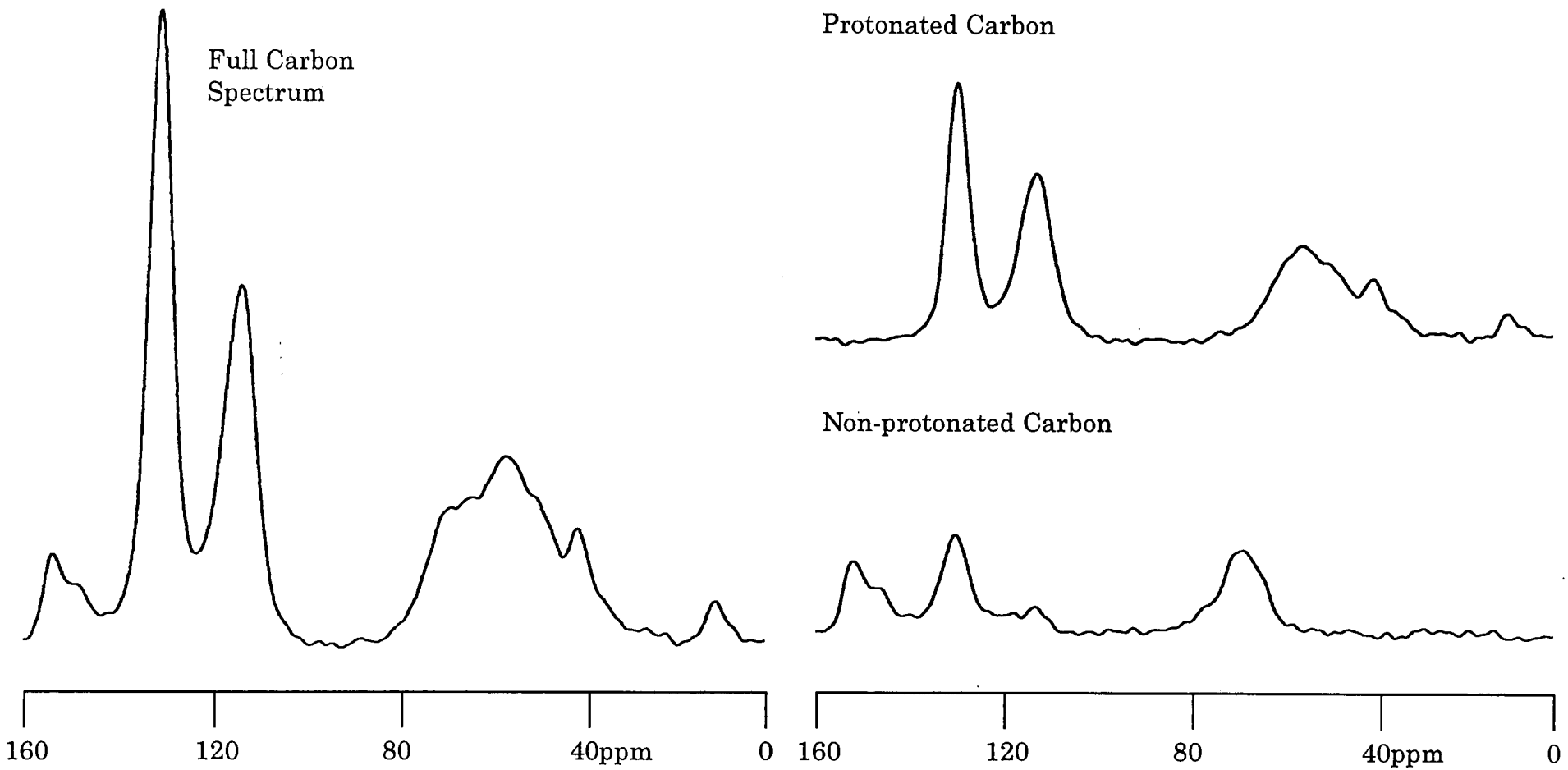


Figure 4.8 *Solid state carbon-13 NMR spectrum of [2"-$^2D_4$]-TGDDM/DDS* ***(7f)/(8a)*** *epoxy polymer*

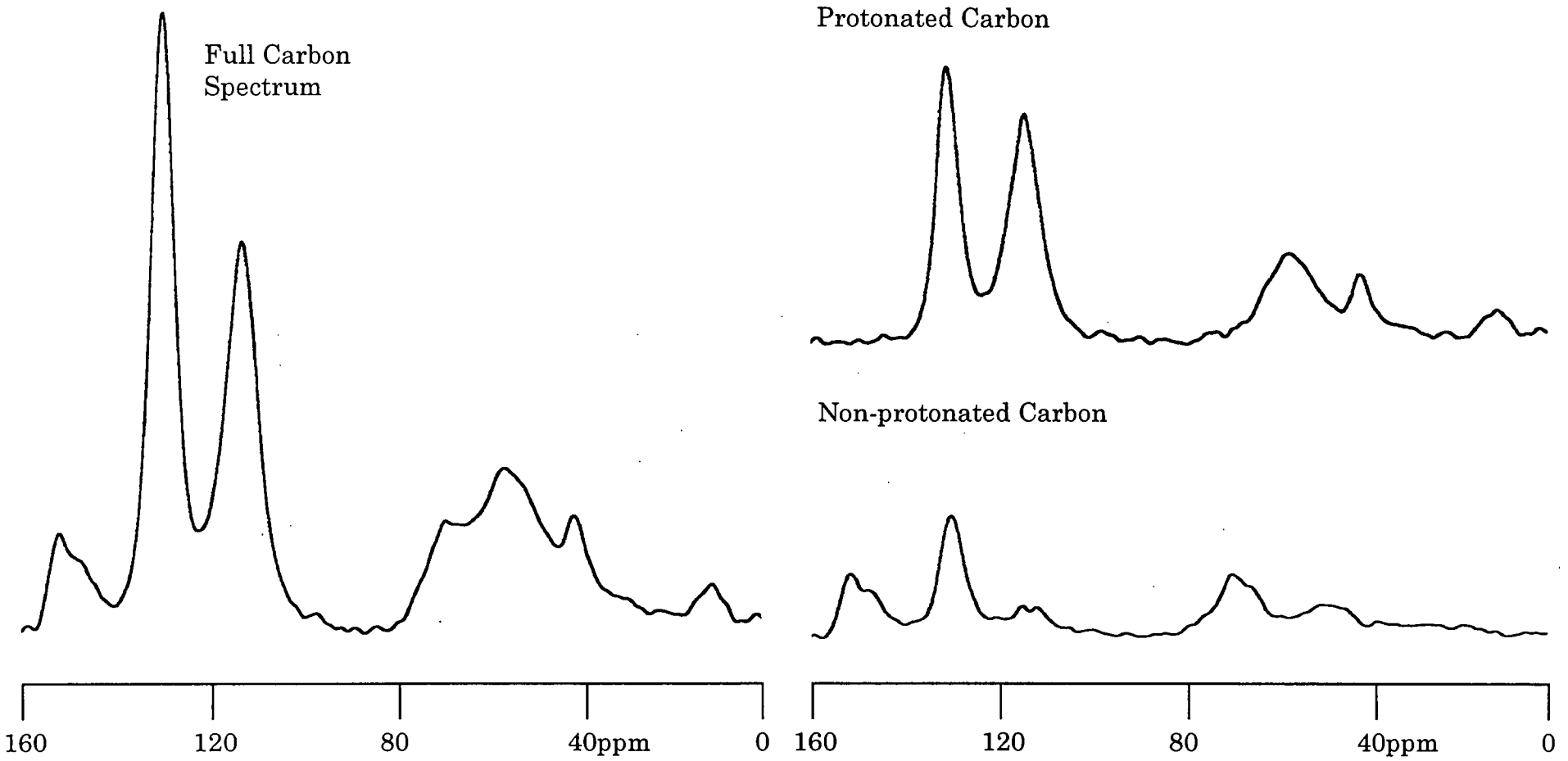


Figure 4.9 *Solid state carbon-13 NMR spectrum of [2",3"-$^{2}D_{12}$]-TGDDM/DDS* ***(7g)/(8a)*** *epoxy polymer*

labelled samples, and the new peaks in the non-protonated spectra can be clearly seen.

Clearly there are fewer constituent peaks in these isolated resonances, due to the deuterium labelled carbon atoms, than there are in the full spectrum. It follows that any deconvolution that is carried out on these peaks is much more likely to give meaningful information than that derived from the unlabelled spectrum. Figure 4.10 shows the deconvolution of the resonance that corresponds to the deuterium labelled carbon in the [2"-$^{2}D_{4}$]-TGDDM/DDS **(7f)/(8a)** resin. This gives a best-fit that has three peaks at 64.4, 69. and 75.9ppm, in an approximately 1:3:1 ratio. These peak positions reinforce the data gained from the carbon-13 labelling experiment, which has analogous peak positions and approximately similar relative peak intensities.

Deconvolution of the non-protonated spectrum of the [2",3"-$^{2}D_{12}$]-TGDDM/DDS **(7g)/(8a)** resin between 40 and 90ppm was attempted, but the broad resonance at 50ppm, due to the C-3" carbons, was too weak to give any meaningful information. Figure 4.9 shows that these C-3" carbons have a lower intensity overall when compared to the C-2" carbons. This effect is caused by the way the cross polarisation pulse sequence interacts with the deuterium labelled carbon atoms. As stated before, the magnetisation of the carbon-13 nuclei is derived from magnetisation of the protons during the contact period. Non-protonated carbon-13 nuclei have to obtain their magnetisation from the protons of neighbouring carbon atoms, which is less efficient and results in lower peak intensities in the NMR spectrum. The further away the nearest protons are to the carbon-13 nuclei in question, the lower the efficiency of the cross polarisation, and hence the lower the intensity of the resultant resonance. In the case in question, the C-2" carbon-13 atoms are closer to the nearest protons (at C-1") than the C-3" carbon-13 atoms, and therefore give the stronger resonance of the two.

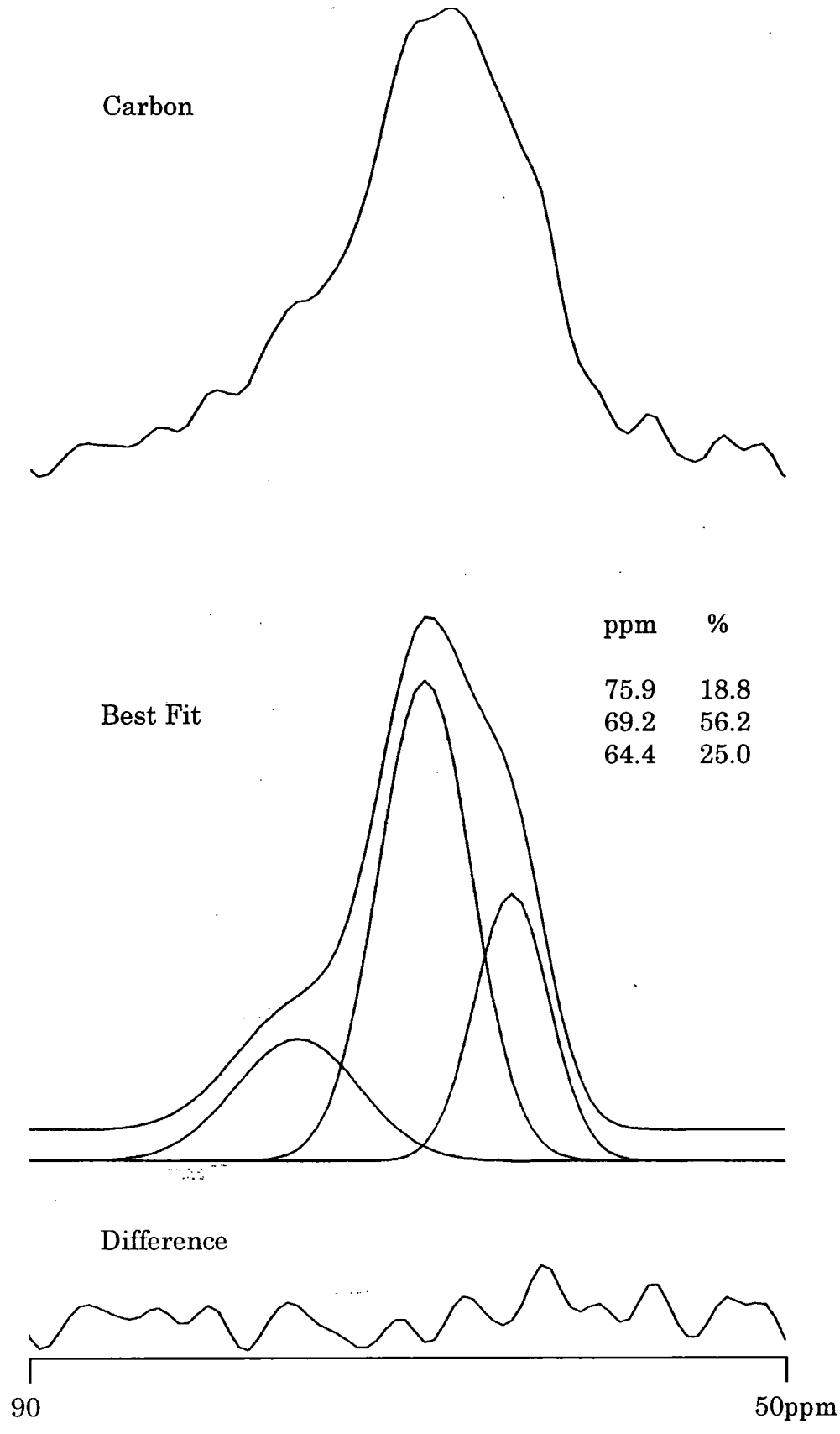


Figure 4.10 *Deconvolution of labelled carbon resonance for [2"-$^2D_4$]-TGDDM/DDS* ***(7f)/(8a)*** *cured resin*

4.3.3 Nitrogen-15 labelled samples

Nitrogen-15 labelling was carried out for two samples, one with the label inserted in the TGDDM monomer **(7b)**, and one with the label in the DDS hardener **(8b)**. Each was cured with an unlabelled sample of the other monomer, and analysed using solid state ^{15}N-NMR spectroscopy. A mixture of these two powdered resin samples was also analysed in a separate experiment, as was an unlabelled resin. The results are shown in Figure 4.11.

The natural abundance spectrum (a) shows two peaks, one at –304.5 and another at –319.9ppm. The spectrum of the sample made from nitrogen-15 labelled TGDDM **(7b)** (b) shows a peak at –319.8ppm, while the sample made from nitrogen-15 labelled DDS **(8b)** (c) shows a peak at –305.0ppm. The final spectrum, of the add-mix of the (b) and (c), shows a spectrum very similar to the natural abundance trace shown in (a), with peaks at –304.8 and –319.1ppm.

4.3.4 Conclusion

The labelling experiments described in this chapter were designed to provide information concerning the structures formed during TGDDM/DDS resin cure. It was hoped to establish whether various ring systems played a part in the resin curing, and to attempt to quantify their contribution to the overall crosslinked structure. The various proposed curing pathways were described in chapter 1[10-14,106], and are outlined again in Figure 4.12.

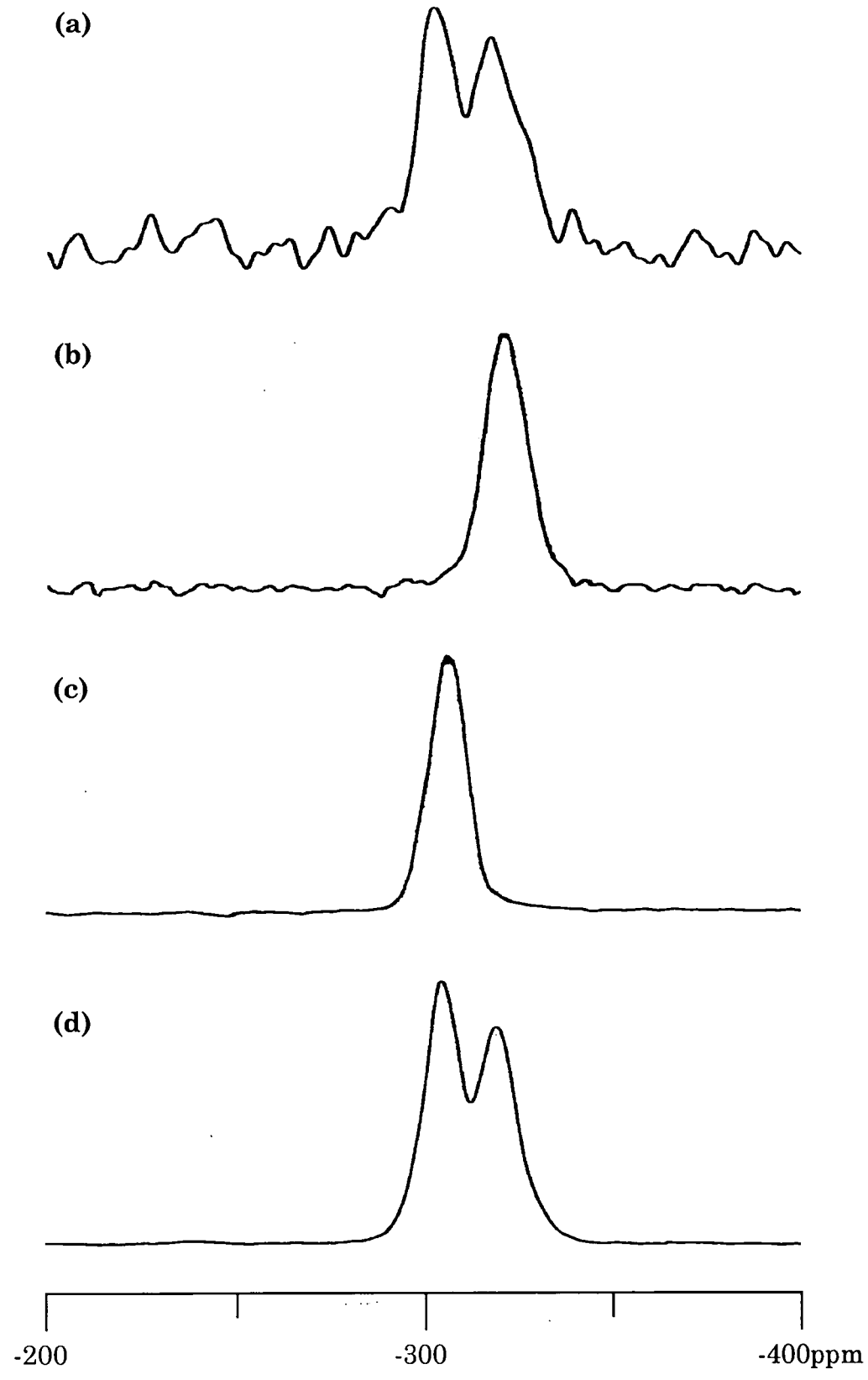


Figure 4.11 *Nitrogen-15 NMR spectra of TGDDM/DDS cured resins*
(a) *natural abundance* ***(b)*** *26% ^{15}N TGDDM* ***(7b)***
(c) *30% ^{15}N DDS* ***(8b)*** ***(d)*** *add mixture of (b) and (c)*

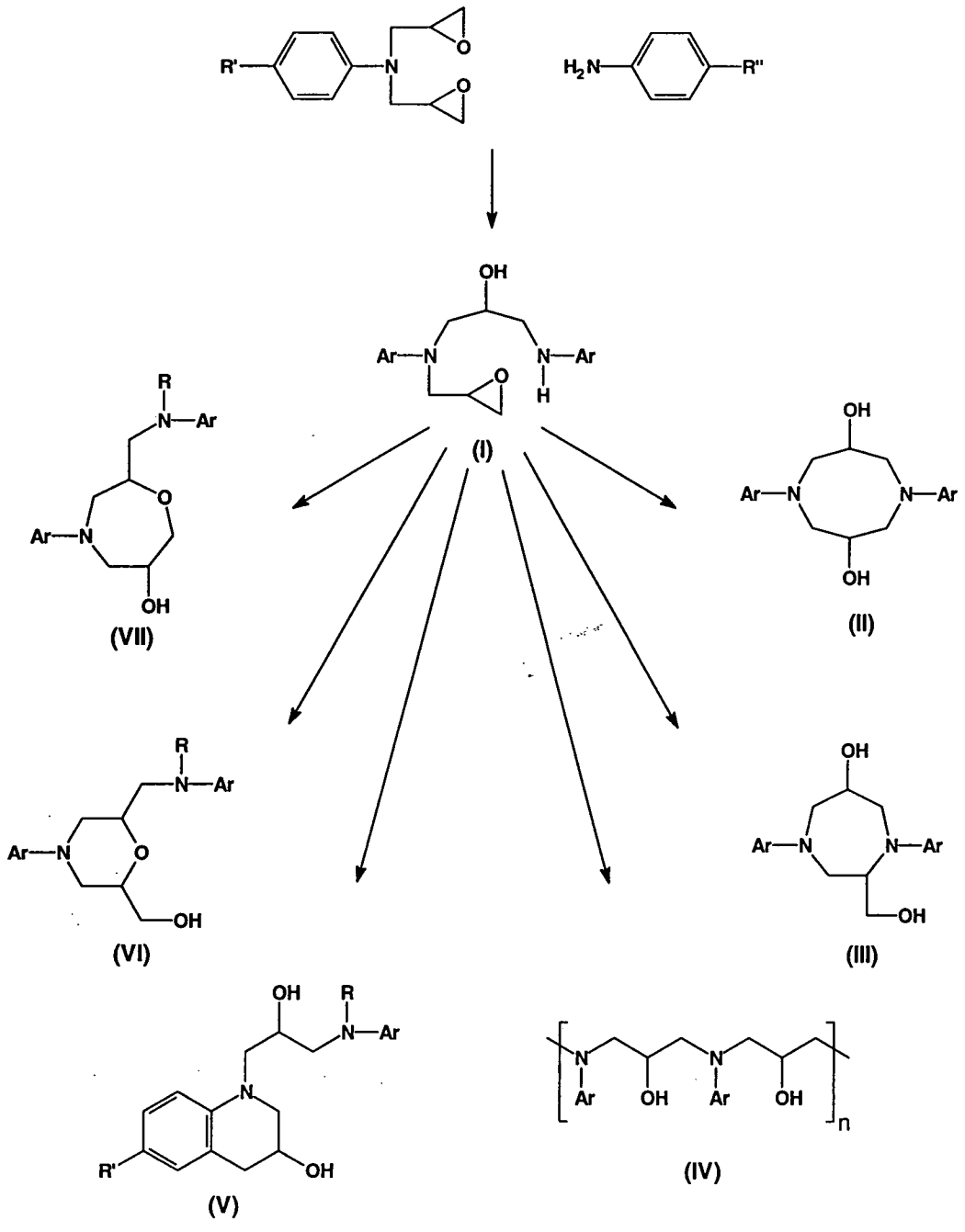


Figure 4.12 *Possible reaction pathways for the TGDDM / DDS epoxy resin system*

The carbon and deuterium labelling experiments provide information for the C-2" carbons of the TGDDM molecule. The chemical shift of this carbon atom is particularly sensitive to the different environments of the cured structures, because of its proximity

to the site of reaction in all cases.

Model studies have been carried out[10,11,106], using aniline **(9a)** and diglycidylaniline **(10)**, to try and probe which reactions are likely to occur, and NMR data has been gathered about the chemical shifts of the C-2" carbon in the various resultant structures[10,11,106,107]. It was found that the eight membered ring system (II), which exists as *cis* and *trans* diastereomers, exhibits two peaks, one at 63ppm, (*cis*) and another at 70ppm (*trans*). The linear polymer (IV) gives a tight triplet of peaks at 68ppm, while the tetrahydroquinoline ring gives a peak at 64ppm. The six and seven membered ring systems (VI) and (VII) give a selection of peaks between 70 and 80ppm.

The carbon and deuterium labelling experiments gave, after resolution enhancement and deconvolution, a set of one major and two minor peaks in both cases. The intensities of these three peaks varies somewhat between the two experiments, but this is to be expected considering that the process of deconvolution gives at best only approximate answers. However, it is reasonable to say from the experimental results that the labelled carbon is present as three peaks at approximately 65, 70 and 75ppm, in a ratio of about 1:8:1. It can also be suggested that the peak at 70ppm is the most intense of the three, while the other two are weaker resonances corresponding to less abundant connectivities in the resin.

A comparison of the model data for the aniline/diglycidylaniline system[10,11,106] with the experimental results of the solid state NMR forces a number of conclusions. For instance, the large central peak at about 70ppm is likely to be the linear polymer (model data 68ppm), although there may well be some contribution from *trans*-eight membered rings (model data 70ppm) in the resin. The lesser of the smaller peaks at 65ppm is consistent with either some *cis*-eight membered rings (model data 63ppm) or tetrahydroquinoline rings (model data 64ppm). The higher of the smaller peaks at 75ppm is

consistent with six and seven membered rings systems (model data 70-80ppm) in the resin.

The nitrogen-15 labelling study allowed an unambiguous assignment of the ^{15}N-spectrum to be made. However, each spectrum shows only one regular Gaussian peak, with no fine structure at all. While an assignment is now made, the failure of the labelling to produce any further structural information is disappointing. This is particularly so in the case of the nitrogen-15 labelled DDS hardener, the label of which should be intimately involved in any structural variation in the polymer, and might have been expected to show a chemical shift variation. However, this proved not to be the case.

The resolution of the solid state NMR spectra used to probe the structures present in the cured resin is unfortunately insufficient to provide further insight into the resin structure. Line narrowing techniques which involve heating the sample to promote matrix motion and thus environment averaging have been attempted, with no success. The very high Tg of the resin (260-270°C) means that sample decomposition occurs before any noticeable line narrowing effects were seen.

Despite these limitations, it has been established that the majority (~70%) of the epoxide units in the resin react to give a linear polymer, and thus good crosslinking. However, it is likely that a significant proportion (~30%) of the epoxide units react to give ring systems of one type or another. Moreover, it should be possible to use this labelling methodology as an analytical tool to quantify the success of any attempts to reduce this ring formation, and improve the physical properties of the cured resin.

Carbon-13 labelling of TGDDM has also established that there is no significant amount of uncured epoxide units in the final resin, as uncured epoxide groups be apparent as an enriched peak at about 50ppm. This is absent from the spectrum of the cured resin.

CHAPTER 5

Applications of Diazoketone Chemistry

Applications of Diazoketone Chemistry

5.1 α-Ketosulfonates

5.1.1 Introduction

The reaction of acyl chlorides with diazomethane and *p*-toluenesulfonic acid to form α-ketosulfonates has received very little attention in the past, and there are only a few examples of it's synthetic use[90-92]. The reaction, shown in Figure 5.1, has been described, and a few example compounds have been produced, but it appears that for the most part this useful protocol has been neglected.

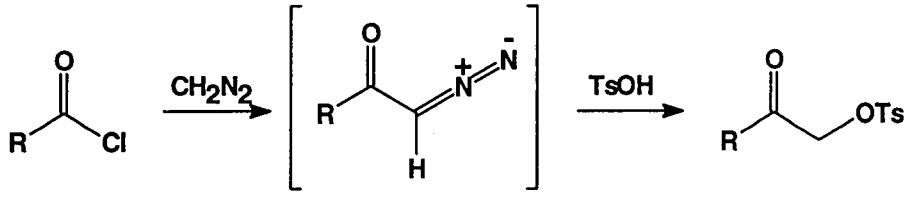


Figure 5.1 *Reaction of acyl halides with diazomethane and* p-*toluenesulfonic acid to give an α-ketosulfonate.*

The crystalline compound, **(78)** (R=CH_2Cl) was synthesised using this methodology during the preparation of isotopically labelled epichlorohydrin described in Chapter 2. As an extension of this work, it was decided to attempt a short series of reactions to prepare a selection α-keto-*p*-toluenesulfonates using this methodology. The aim of the work was to explore the effect of different substituents and/or multiple acid chloride moieties. The syntheses of the fluoro-, bromo-, and iodo- analogues of **(74)** were also investigated. Finally, as the

crystal structure of **(74)** had already been obtained (Chapter 2), a comparison of this structure with those of its analogues was of interest.

5.1.2 Experimental Results

The α-ketosulfonates were all generated using a similar protocol, from different acid chlorides. The protocol involved the addition of the acid chloride to an ethereal diazomethane solution followed by addition of *p*-toluenesulfonic acid[90]. An aqueous workup and crystallisation generated the α-ketosulfonates in the yields shown in the table in Figure 5.2.

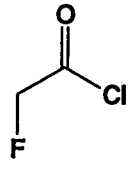
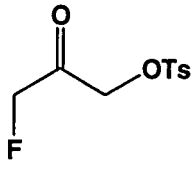
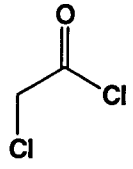
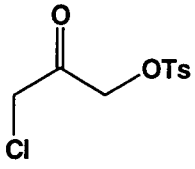
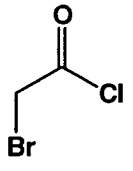
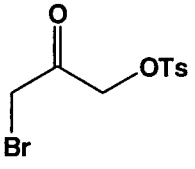
Acid chloride	α-Ketosulfonate	Yield (%)
 **(83)**	 **(84)**	9%
 **(72)**	 **(74)**	54%
 **(76)**	 **(85)**	49%

Figure 5.2 *Table of acid chlorides, α-ketosulfonate products and yields (continued overleaf)*

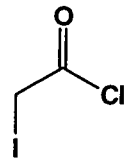
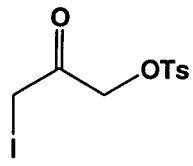
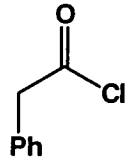
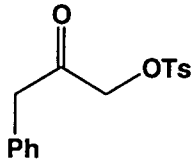
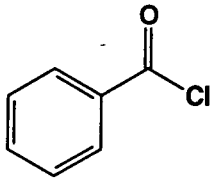
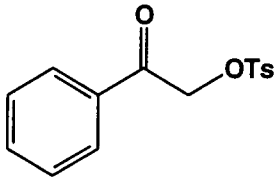
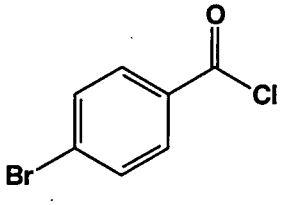
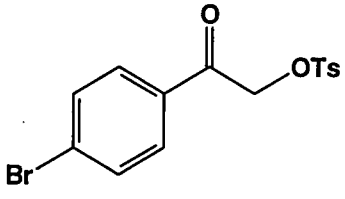
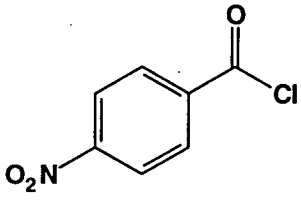
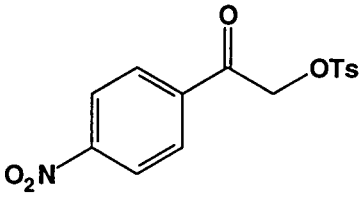
Acid chloride	α-Ketosulfonate	Yield
		42%
(86)	(87)	
		55%
(88)	(89)	
		49%
(90)	(91)	
		47%
(92)	(93)	
		61%
(94)	(95)	

Figure 5.2 *Table of acid chlorides, α-ketosulfonate products and yields (continued overleaf)*

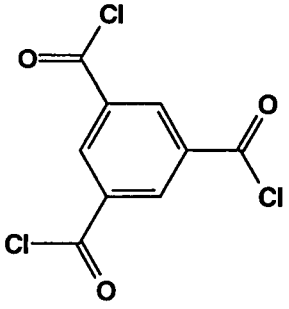
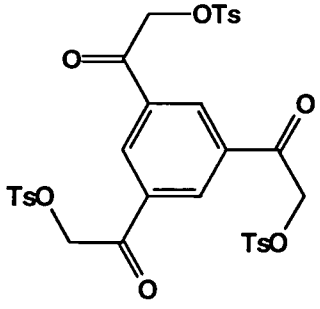
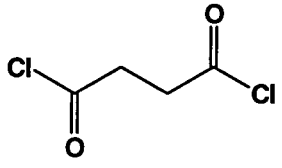
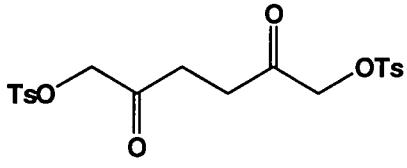
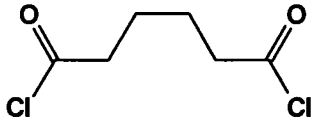
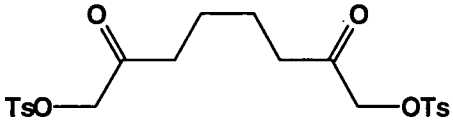
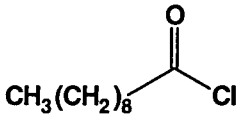
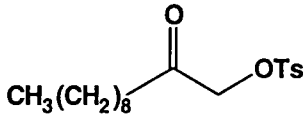
Acid chloride	α-Ketosulfonate	Yield
 (98)	 (99)	Not Formed
 (100)	 (101)	Not Formed
 (102)	 (103)	41%
 (104)	 (105)	60%

Figure 5.2 *Table of acid chlorides, α-ketosulfonate products and yields (continued)*

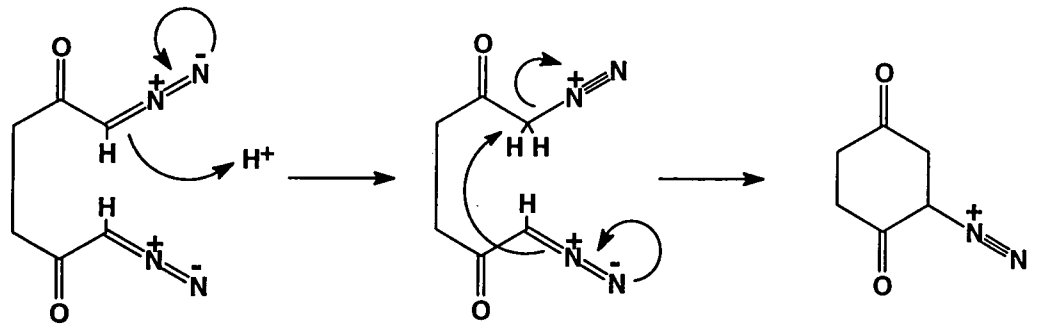
It can be seen that the products generally form in yields of about 50% under normal conditions, with certain exceptions. This moderate yield is almost certainly due to the fact that the *p*-toluenesulfonic acid used in the reaction was in the form of its monohydrate. It is possible that the water is competing with the tosylate anion in the reaction with the protonated diazoketone, forming some of the free alcohol instead of the tosylate derivative. However, none of this free alcohol was observed, although this could be due to it being removed from the reaction mixture during the aqueous workup.

The fluoro- derivative **(84)** was formed in a very low yield of only 9%, which may be due to several different factors. Fluoroacetyl chloride **(83)**, unlike all of the other starting materials, was not available commercially and had to be prepared from fluoroacetic acid **(82)**[108]. Rather than carry out excessive purification on a very toxic compound, the acid chloride **(83)** was produced in a crude form, and used directly. Although no impurities could be detected by ^{1}H-NMR and other techniques, their presence could not be ruled out. It has also been noted[109] that α-fluoroketones are unstable under certain conditions and can readily self-condense, and clearly this would further reduce the yield.

The lower yield of the di-tosylate compounds is to be expected because of the cumulative effect of two moderate yielding reactions on one molecule. This may also explain why no tri-tosylate **(99)** was recovered, with the cumulative effect of three reactions. Contrary to this however is the di-tosylate **(103)** which was produced in 41% yield. It might be that the starting material is a particularly good substrate for this reaction.

An anomalous result concerns the reaction of succinyl dichloride. While the reaction would be expected to give only a low yield of **(101)**, the absence of any product was unexpected. Observation of the reaction appeared to indicate that the bis-(α-diazoketone) **(106)** was

formed as an intermediate. However, an unusual discoloration occurred during the addition of the *p*-toluenesulfonic acid. A possible mechanism can be suggested to account for the lack of product, and is shown in Figure 5.3.



(106)

Figure 5.3 *A possible decomposition mechanism for the diazoketone intermediate of succinyl dichloride*

The Figure shows that the bis-(α-diazoketone) **(106)** can condense to generate a six membered ring as a result of intra-molecular reaction between the two diazoketone moieties.

5.1.3 Crystal Structure Analysis

The synthesis of the fluoro-, bromo- and iodo- versions of 3'-chloro-2'-oxopropyl *p*-toluenesulfonate **(74)** was outlined in the previous section. It was hoped to grow crystals of all three of these compounds to compare their structures, after X-ray analysis, with that of the chloro- derivative, already obtained as part of earlier work. However, while adequate crystals of the bromo- and iodo- analogues, **(85)** and **(87)**, were obtained it proved impossible to grow a suitable crystal for the fluorinated compound **(84)**, due to its tendency to form very fine needles. The three crystals obtained were analysed using X-ray

crystallography, and their structures were solved. These are shown in Figure 5.4, with the sulfonate SO_3 moiety orientated identically.

It can be seen from the Figure that while the chloro- derivative **(74)** (a) and the bromo- derivative **(85)** (b) have essentially identical solid state conformations, the iodo- compound **(87)** (c) is very different. In particular, while the C-X and C=O bonds in (a) and (b) are very nearly eclipsed, the same torsional angle for the C-I and C=O bonds of (c) is 92.7°. The planarity of the α-halogenoketone moiety of both (a) and (b) can be explained by a combination of the relatively small van der Waals radii of chloride and bromide (1.75Å and 1.85Å) and O····X charge transfer bonds between the halogen atoms and the oxygen atoms of the neighbouring carbonyl groups[110,111]. This is an extension of the well described 'Cis-effect'[112,113]. The iodide, on the other hand, appears large enough to cause steric problems, forcing it to orientate away from the carbonyl group. Presumably also charge transfer between the 'soft' iodine and 'hard' oxygen is of less significance. The O-C-C-C conformation for both (a) and (b) is sterically unfavourable, and therefore the Cis-effect would appear to override the disadvantage of the eclipsing conformation.

The change of halogen orientation seen in this series is found in other literature examples[114-116]. A number of α-haloacetophenones have been characterised, and the torsional angle of the halogen to the carbonyl calculated. The chloro-[114] and bromo-[115] substituted compounds show very small angles (<5°), while iodo-[116] substituted compounds have relatively large angles (>90°)

The almost identical conformations of (a) and (b) may suggest that these two samples will pack in the same manner in the unit cell, but this is not the case. Examination of the crystal packing as shown in Figure 5.5 shows that the two compounds arrange themselves in entirely different fashions in the solid state.

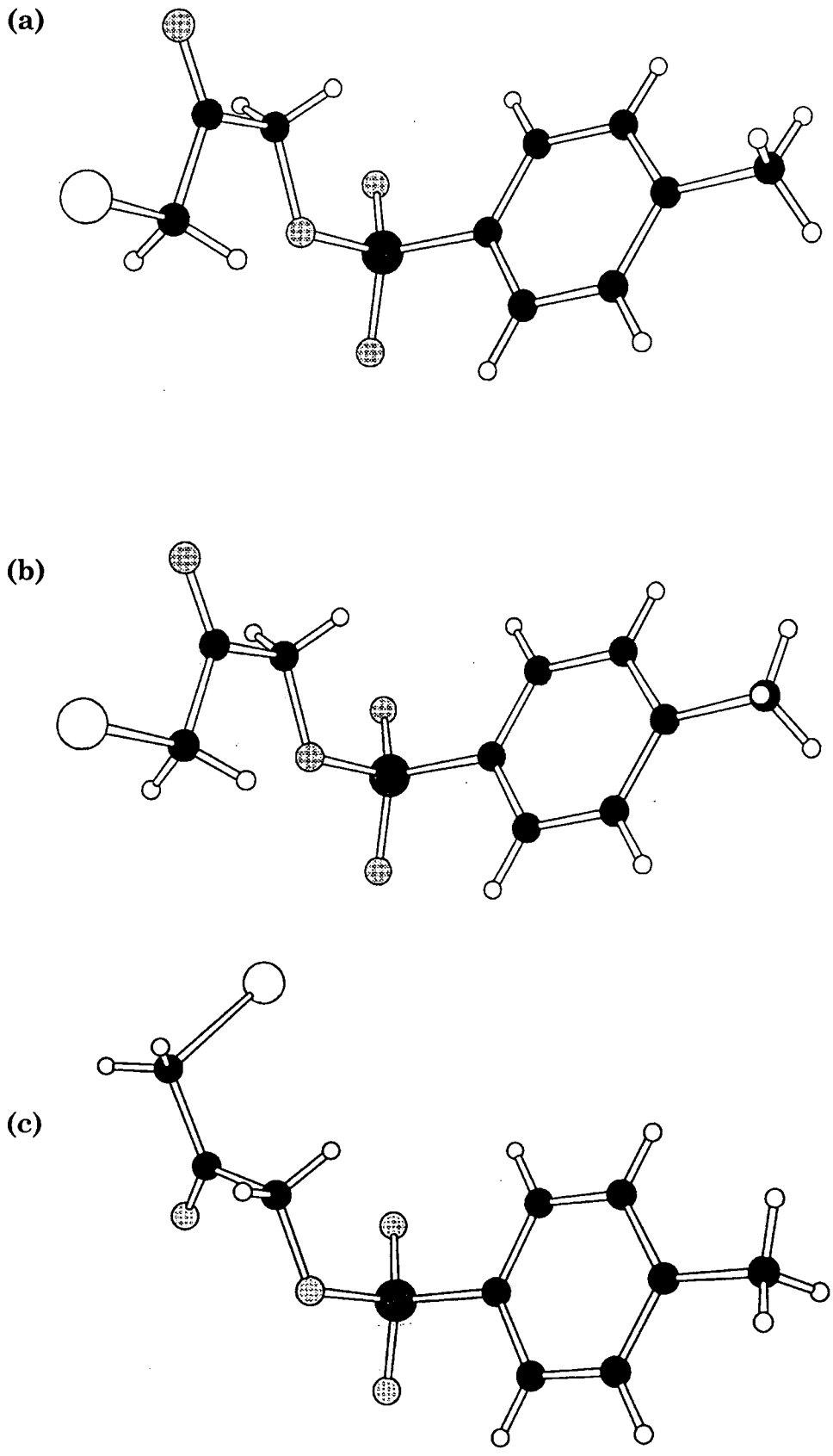


Figure 5.4 *Crystal structures of* ***(a)*** *3-Chloro-* ***(74)*** ***(b)*** *3-Bromo-* ***(85)*** *and* ***(c)*** *3-Iodo-2-oxopropyl p-toluenesulfonate* ***(87)***

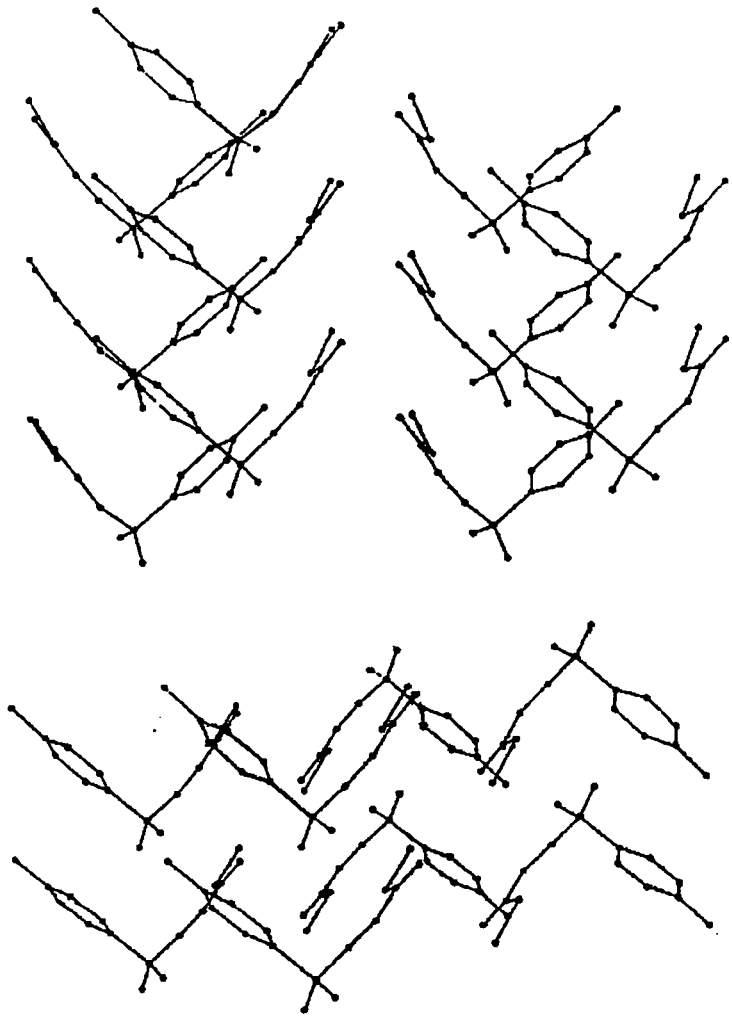


Figure 5.5 *Crystal packing of 3'-chloro-2'-oxopropyl* p-*toluene-sulfonate* ***(74)*** *(top) and 3'-bromo-2'-oxopropyl* p-*toluene-sulfonate* ***(85)*** *(bottom)*

5.2 α-Chloroketones

5.2.1 Introduction

The formation of α-chloroketones by treating diazoketones with anhydrous hydrogen chloride is well established[87,88], and mirrors the formation of the analogous tosylate derivatives by treatment with *p*-toluenesulfonic acid. However, unlike the tosylate reaction, the absence of water from the ethereal HCl solution allows the products to form in much higher yields. This fact renders this methodology ideal as a part of a route to making epoxides from acid chlorides, as shown in Figure 5.6. The large number of commercially available acid chlorides opens up access to a similarly large number of epoxides.

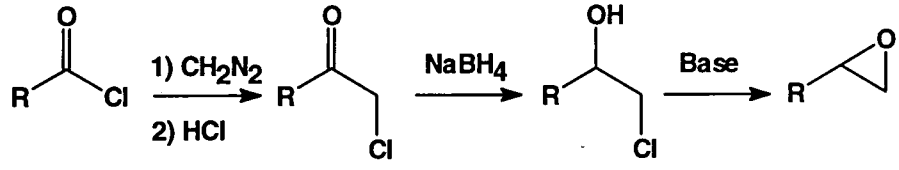


Figure 5.6 *Synthetic route from acid chlorides to epoxides*

There is a great deal of interest in additives for high performance epoxy resin systems that improve the properties of the cured resin. The addition of a small amount of a compound to the resin may increase the glass transition temperature (Tg) of a resin, or reduce the amount of water absorbed, resisting weakening and deformation of the matrix. Potential additives have to conform to certain constraints, the most important of which is that they should produce no volatile materials as they react, a fact which makes epoxides excellent candidates.

In order to explore the potential of such epoxides as resin additives, and to use our established diazoketone methodology, it was

proposed to prepare and test the two compounds shown in Figure 5.7.

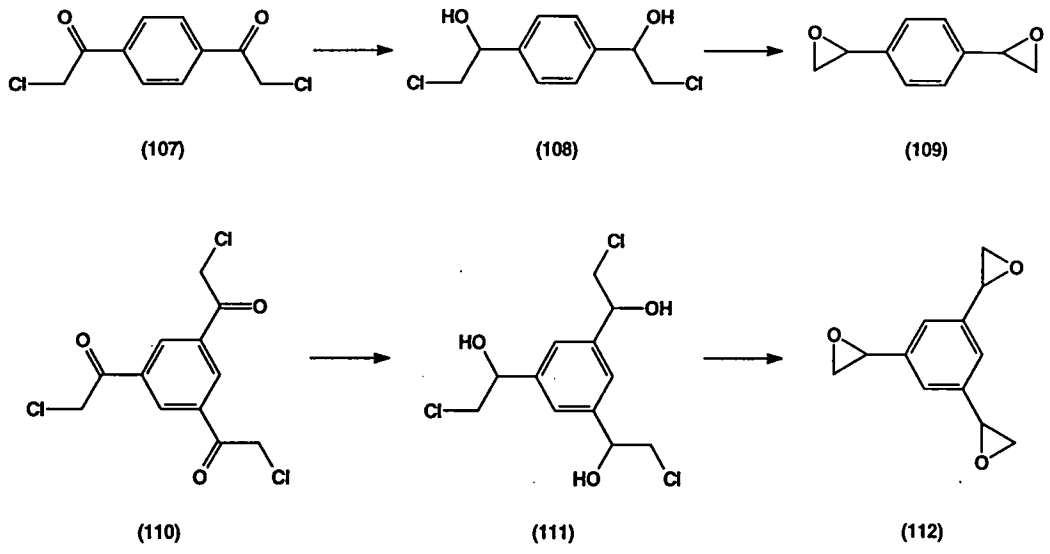


Figure 5.7 *Routes to two potential resin additives*

Both compounds have been synthesised previously[88,117]. This was accomplished by direct chlorination with chlorine gas of the acetyl moieties of 1,4-diacetylbenzene **(113)** and 1,3,5-triacetylbenzene **(114)**. Treatment with lithium aluminium hydride and then potassium hydroxide produced the desired di- and triepoxides.

On the other hand the required acid chlorides **(96)** and **(98)** are readily available and cheap. It was proposed to prepare the target compounds via their diazoketones to give the α-chloroketones **(107)** and **(110)**, which could then be reduced to the secondary alcohols **(108)** and **(111)**, and treated with base to give the epoxides **(109)** and **(112)**.

5.2.2 Experimental Results

The synthesis of the two target compounds proceeded exactly as expected, to give an overall yield of 75% for the diepoxide **(109)** and 51% for the triepoxide **(112)**. The diepoxide had a low melting point and was a mixed solid/liquid at room temperature, while the triepoxide

was a white crystalline solid. Both were produced in gram quantities with a minimum of purification.

The two compounds were then tested as additives for the TGDDM/DDS resin system. The epoxides were added to the curing mixture, and after curing the resins were tested to assess their glass transition temperatures. The water uptake after 24 days was also monitored for each sample.

The table in Figure 5.8 summarises the data for the two compounds, and compares them to controls without any additives. The diepoxide **(109)** does not exhibit any significant deviation, with the Tg and water absorption figures largely unchanged when 10% is added to the cure mixture. The triepoxide **(112)**, however, has a rather significant effect on the resin properties, affecting both the Tg and water absorption. The results show a rise in the Tg accompanied by an undesirable increase in water absorption. The relatively large increase in the Tg was unexpected, and is interesting. While the most striking effect is noticed at high additive concentrations, probably the most important result is for the 10% concentration case. At this low level of addition, the triepoxide produces a significant increase in Tg without affecting the water absorption to any significant degree.

In conclusion, the triepoxide species shows promise as an additive for high performance epoxy resins. It remains to be seen however if this promise is fulfilled once it has been fully tested and evaluated.

5.2.3 Enzymatic Reduction with Bakers' Yeast

The use of bakers' yeast (*Saccharomyces cerevisiae*) for the stereoselective reduction of ketone groups to secondary alcohols is well known[118-120], and many examples exist. The methodology is relatively easy to apply and use on a small or large scale, and in most cases gives

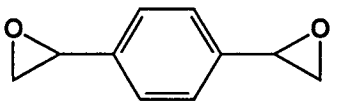
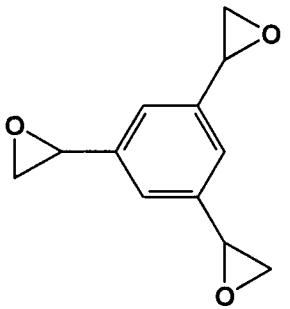
Additive	Concentration (parts per 100 parts TGDDM by weight)	Postcure temperature (°C)	Glass Transition Temperature (°C)	Water uptake after 24 Days (%)
None		200	267	3.63
 **(109)**	10	200	267	
	10	220	268	3.67
 **(112)**	10	200	281	
	10	220	281	3.78
	20	200	286	3.90
	20	220	287	4.44
	30	200	292	4.09
	30	220	293	4.57

Figure 5.8 *Properties of TGDDM / DDS / Additive blends (TGDDM cured with 65% stoichiometric amount of DDS for 5hr at 150°C; Postcure* in vacuo *for 3hr at 180°C, 3hr at 200°C and (where indicated) 1hr at 220°C)*

predictable results in good yield. The relative cheapness of the bakers yeast also makes this enzyme system ideal for performing large scale transformations.

Bakers' yeast contains a number of different dehydrogenase enzymes with contradictory stereoselectivities[119], and the outcome of any reduction is dependant on the relative activities of these enzymes towards the substrate. As a result of this, the stereoselectivity of many reductions is moderate, with enantiomeric excesses of typically 80-90%[118]. Some success has been achieved in improving the selectivity of the system by adding a dehydrogenase inhibitor, such as allyl alcohol, to the fermentation[121], and thereby blocking one or several of the enzymes to different extents. This can often increase (or decrease) the enantioselectivity of the reduction.

In the case of a symmetric compound with two ketone moieties, such as **(107)**, it should be possible to obtain two stereoselective reductions in one molecule. This would lead to a profile like the one shown in Figure 5.9.

The scheme shows the products of the double reduction, and assumes that both reductions occur with the same selectivity (80%ee in this example). After the first step, the substrate exists in two chiral forms in a ratio of 9:1 as expected. After the second reduction there are three products, the (R,R) and (S,S) enantiomers in a 81:1 ratio (98.78%ee), plus 18% of the *meso* compound, which should be amenable to removal by chromatography or recrystallisation. By performing sequential enzymatic reductions, the enantiomeric purity of the product is amplified. If the same principles could be applied to symmetric systems with three or more carbonyl groups, a similar pattern of amplification of enantiomeric purity should be seen.[122]

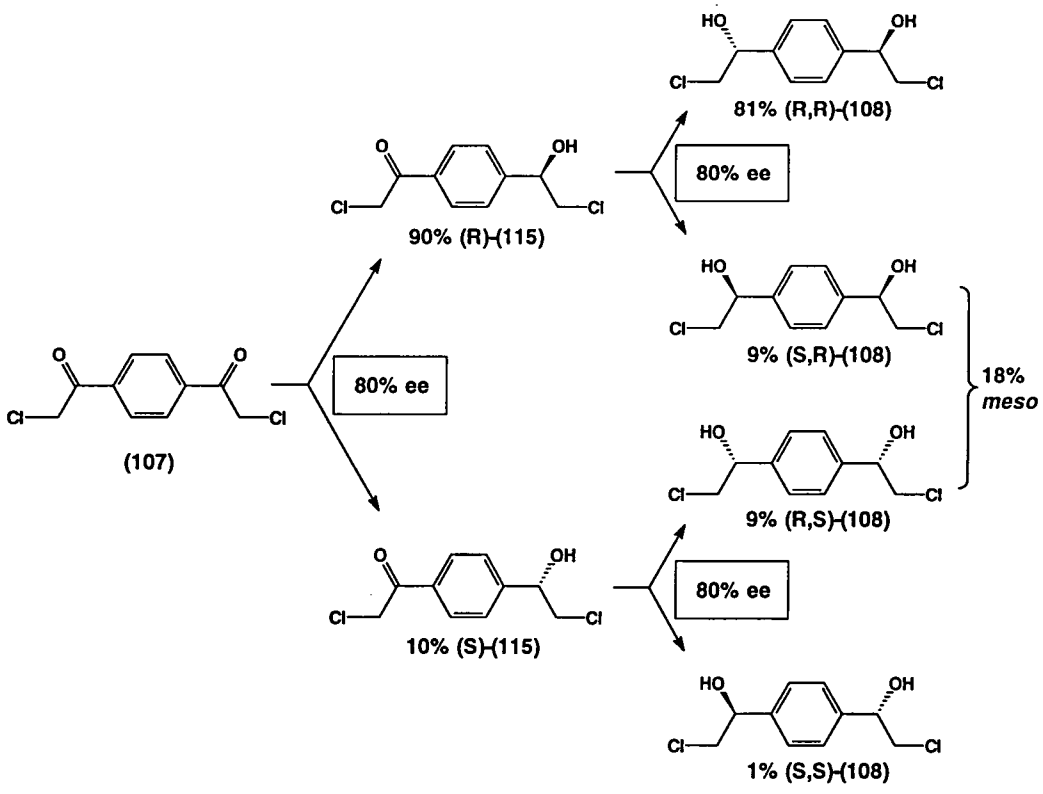
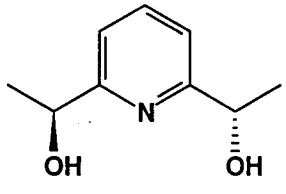


Figure 5.9 *Stereochemical profile of the double reduction of a symmetric dicarbonyl compound by bakers' yeast*

A previous study[121] has exploited this methodology successfully to reduce 2,6-diacetylpyridine **(116)**. It was found that both reductions, performed by the bakers' yeast on the starting material, proceeded with a stereoselectivity of 85%. The *meso* component was easily removed by recrystallisation, which gave the pyridylethanol **(117)** shown in Figure 5.10 with >98.7%ee. Addition of allyl alcohol to the fermentation increased this to >99.92%ee.



(S,S)-(117)

Figure 5.10 *(S,S)-(-)-2,5-di(1'-hydroxyethyl)pyridine (product of double reduction by bakers' yeast)*

In order to explore the possibility of producing the two epoxide compounds **(109)** and **(112)** in a highly enantiopure form, the α-chloro-ketone precursors **(107)** and **(110)** of the epoxides were used as substrates for bakers' yeast fermentation. If the triple reduction of the triketone were success it would be possible to test it as a resin modifier for comparison with the racemate.

The dichloroketone **(107)** was fermented for a total of nine days, after which monitoring by thin layer chromatography (tlc) suggested that the vast majority of the starting material had disappeared. Work up gave the crude diol **(R,R)-(108)**, and esterification to the diacetate **(R,R)-(118)** allowed the *DL:meso* ratio to be calculated by solution state ^{1}H-NMR. The result of approximately 90:10 *DL:meso* suggested that, if the stereochemical profile previously outlined in Figure 5.9 was accurate, the enantiomeric excess of the *DL* mixture should be >99.3%, provided the *meso* component could be removed.

It is interesting to note that while a small amount of unreacted starting material **(107)** was recovered from the fermentation mixture, none of the mono-reduced species **(115)** was recovered. It seems likely that the first reduction is the rate limiting reaction of the two, due to the poor solubility of the diketone **(107)** compared to the mono-reduced species **(115)**.

In order to try to improve the enantiomeric and diastereomeric purity of the isomer mixture, the recovered diol was recrystallised once to remove the impurities, and was then treated with base to generate the epoxide. Chiral high performance liquid chromatography (hplc) of this epoxide **(R,R)-(109)** (Chiracel OJ column) gave the trace shown in Figure 5.11, and shows that the sample has an enantiomeric excess of >95%. The trace produced by a racemic sample **(±)-(109)**, generated after $NaBH_4$ mediated reduction of **(107)** followed by treatment with base, is also shown, for purposes of comparison. The peaks highlighted by the two diamonds (◆) show the possible presence of the two

unwanted stereoisomers as minor impurities.

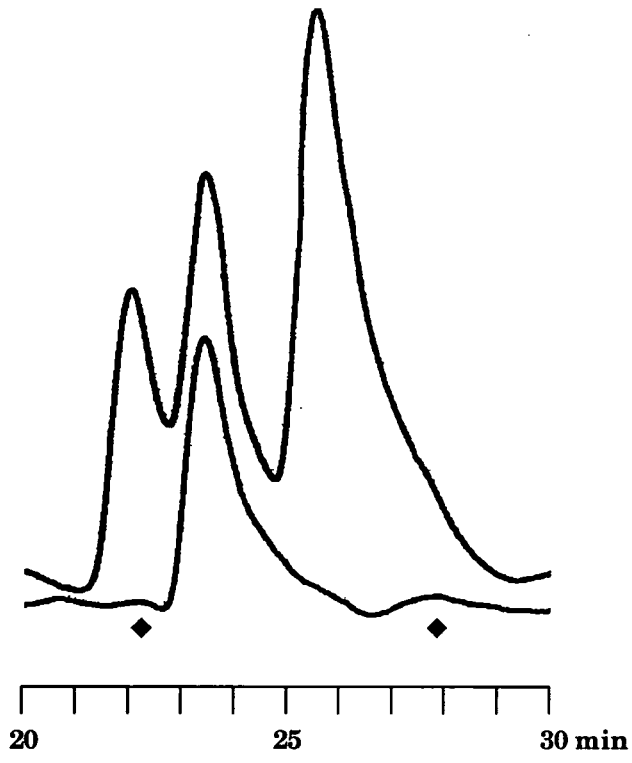


Figure 5.11 *Chiral hplc trace for (top) racemic 1,4-diepoxyethyl-benzene*(±)-**(109)** *and (bottom) chiral 1,4-diepoxyethyl-benzene* **(R,R)-(109)** *(Chiracel OJ column, 2% isopropyl alcohol/98% heptane, 1.0ml min^{-1}, Temp 30°C, λ=240nm)*

The recrystallisation used to improve the enantiomeric and diastereomeric purity of the diol **(R,R)-(108)** also furnished a number of crystals suitable for X-ray analysis. The structure and absolute stereochemistry of the compound was confirmed from these crystals as the (R,R) enantiomer. The crystal structure is shown in Figure 5.12.

The reduction of the triketone **(110)** was attempted in a similar manner, but it proved impossible to recover any identifiable material from the fermentation mixture. It may be that the triol **(111)** is too soluble in the aqueous media of the reaction to be extracted into organic solvents, or that the compound breaks down under the reaction conditions in some manner.

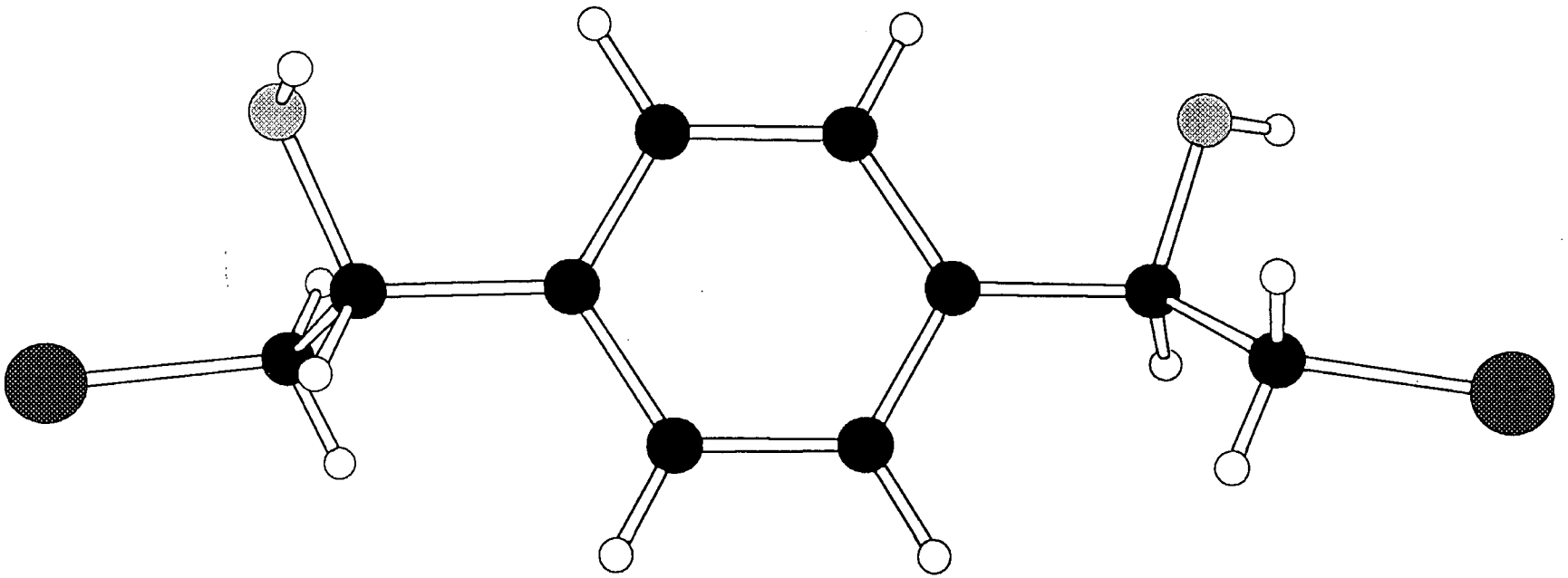


Figure 5.12 Crystal structure of (R,R)-(+)-1,4-di(2'-chloro-1'-hydroxyethyl)benzene ***(R,R)-(108)***

CHAPTER 6

Experimental

6.1 Introduction

6.2 Chapter 2

6.2.1 Synthetic Route 1

6.2.2 Synthetic Route 2

6.2.3 Synthetic Route 3

6.3 Chapter 3

6.4 Chapter 5

Experimental

6.1 Introduction

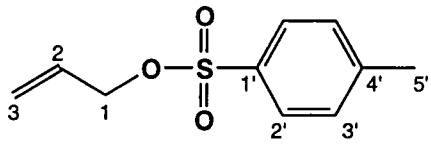
IR spectra were recorded on a Perkin-Elmer F.T. 1720X or 1600 spectrometer. Low resolution mass spectra were recorded on a VG Analytical 7070E Organic mass spectrometer, while gas chromatography-mass spectra (GC-MS) were recorded using a Hewlett Packard 5890 Series II gas chromatograph connected to a VG Mass Lab Trio 1000. Solution state NMR spectra were recorded on Varian Gemini 200MHz (^{1}H at 199.975MHz, ^{13}C at 50.289MHz), Varian XL-200 (^{1}H at 200.057MHz), Varian VXR 400(S) (^{1}H at 399.952MHz, ^{13}C at 100.577MHz, ^{15}N at 40.543MHz, ^{19}F at 376.25MHz) and Bruker AMX-500 (^{1}H at 500.139MHz, ^{13}C at 125.771MHz, ^{15}N at 50.682MHz) spectrometers. Solid state NMR spectra were recorded on a Gemini VXR300 (^{13}C at 75.4MHz, ^{15}N at 30.4MHz) using a Doty probe with a 7mm diameter rotor. Chemical shifts are quoted relative to Me_4Si (δ=0) for ^{1}H and ^{13}C, and to NH_3 (liquid) (δ=0) for ^{15}N, in either chloroform-*d* ($CDCl_3$) or DMSO-*d6* ($(CD_3)_2SO$). Flash chromatography was carried out using Fluka silica gel-60 (35-70μm) or Sorbsil-C60-H (40-60μm).

Compounds prepared for the first time during this project are characterised in full, and their names are underlined. Known compounds were compared to either commercially available material, or spectral data cited in the literature. Where literature spectral data differs significantly from experimental values, or where spectroscopic data is unavailablbe for known compounds, full characterisation is reported.

6.2 Chapter 2

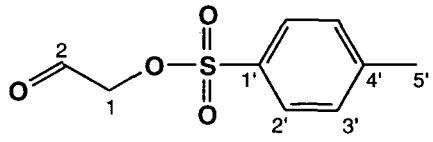
6.2.1 Synthetic Route 1

Preparation of 2-propenyl *p*-toluenesulfonate (60a)



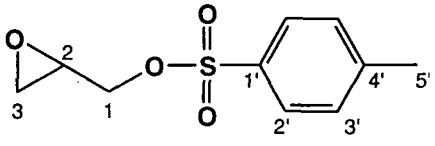
Allyl alcohol **(13a)** (12.8g, 220.4mmol) was treated with tosyl chloride (38.0g, 199.4mmol) and enough 30% NaOH solution to keep the mixture alkaline. The reaction was then shaken for 2h in a sealed vessel. The pH was monitored with litmus paper, and further portions of NaOH solution added as necessary to maintain an alkaline solution. A clear oil formed as the reaction proceeded. After 2h, CH_2Cl_2 (50ml) was added, and the reaction mixture was washed with H_2O (5x30ml). The organic extracts were dried ($MgSO_4$) and the solvent removed under reduced pressure to give a crude product. Chromatography over silica gel with CH_2Cl_2/petroleum ether (1:9) as the eluent gave **(60a)** as a clear oil (21.11g, 50%); δ_H(200MHz; $CDCl_3$) 2.45(3H, s, H-5'), 4.52(2H, ddd, J 1.2, 1.2 and 5.9Hz, H-1), 5.24(1H, ddt, J 1.1, 10.2 and 1.1, H-3(trans)), 5.31(1H, ddt, J 1.4, 17.0 and 1.4Hz, H-3(cis)), 5.82(1H, ddt, J 10.3, 17.1 and 5.9Hz, H-2), 7.35(2H, m, H-3'), 7.79(2H, m, H-2').[123]

Preparation of 2-oxoethyl *p*-toluenesulfonate (61)



Ozone was bubbled through a solution of **(60a)** (3.47g, 18.0mmol) in CH_2Cl_2 (100ml) at -78°C, until a faint blue colour developed. Nitrogen gas was then bubbled through the solution until the colour disappeared. Methyl sulfide (10.0g, 161.0mmol) was added, and the mixture left to stand for 3h. The volatile solvents were removed under reduced pressure, to give **(61)** as a viscous pale green liquid (3.47g, 99%); ν_{max}/cm^{-1} 3092, 3067, 3033, 2959, 2926, 1740, 1598, 1495, 1362, 1191, 1178, 1097, 667; δ_H (200MHz; $CDCl_3$) 2.46(3H, s, H-5'), 4.26(2H, d, J 1Hz, H-1), 7.38(2H, m, H-3'), 7.82(2H, m, H-2'), 9.61(1H, t, J 1Hz, H-2); δ_C (50MHz; $CDCl_3$) 22.2(C-5'), 72.5(C-1), 128.6(C-2'), 130.6(C-3'), 132.5(C-4'), 146.3(C-1'), 195.5(C-2); *m/z* 214 (M^+, 18%).

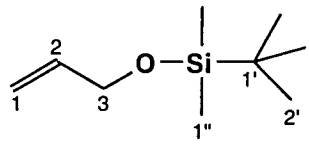
Preparation of 2,3-epoxypropyl *p*-toluenesulfonate (62a)



A solution of glycidol **(14)** (13.0g, 175.5mmol), tosyl chloride (35.0g, 183.6mmol) and triethylamine (22.0g, 217.4mmol) in CH_2Cl_2 (200ml) was placed in a sealed container in a freezer for 15h. The reaction mixture was filtered to remove solid (Et_3NHCl), and the resultant solution washed with 10% tartaric acid solution (3x100ml) and saturated brine (1x100ml), dried ($MgSO_4$), filtered and the solvent removed under reduced pressure to leave a yellow oil. Crystallisation

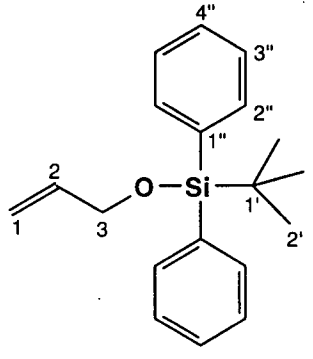
was seeded with previously obtained solid, to give **(62a)** as a colourless crystalline solid (30.13g, 75%) m.p. 38 - 39°C (lit 37.5 - 39°C).[124]

Preparation of 3-(t-butyldimethyl)silyloxy-1-propene (63a)



Allyl alcohol **(13a)** (2.04g, 35.1mmol), t-butyldimethylsilyl chloride (6.17g, 40.9mmol) and imidazole (6.03g, 88.6mmol) were dissolved in DMF (50ml), and heated at 35°C for 15h. The mixture was then quenched with H_2O (50ml), and extracted into Et_2O (3x50ml). The organic fractions were washed with H_2O, dried ($MgSO_4$), filtered, and the solvent removed under reduced pressure to give **(63a)** as a clear oil (6.00g, 99%); δ_H(200MHz; $CDCl_3$) 0.08(6H, s, H-1"), 0.92(9H, s, H-2'), 4.18(2H, ddd, J 1.8, 1.8 and 4.6Hz, H-3), 5.08(1H, ddd, J 1.8, 10.4 and 1.8Hz, H-1(*trans*)), 5.26(1H, ddt, J 1.8, 1.8 and 17.1Hz, H-1(*cis*)), 5.92(1H, ddt, J 10.3, 17.1 and 4.6Hz, H-2).[125]

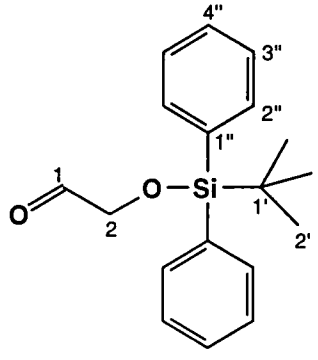
Preparation of 3-(t-butyldiphenyl)silyloxy-1-propene (65)



Allyl alcohol **(13a)** (0.88g, 15.2mmol), t-butyldiphenylsilyl chloride (5.00g, 18.2mmol) and imidazole (2.58g, 37.9mmol) were dissolved in

DMF (50ml) and heated at 60°C for 15h. The mixture was then quenched with H_2O (50ml) and extracted into Et_2O (3x50ml). The organic extracts were washed with H_2O (3x50ml), dried ($MgSO_4$), filtered and the solvent removed under reduced pressure to give **(65)** as a clear oil (4.47g, 99%); ν_{max}/cm^{-1} 3071, 3050, 2960, 2931, 2892, 2858, 1646, 1473, 1428, 1113, 918, 701; δ_H(200MHz; $CDCl_3$) 1.07(9H, s, H-2'), 4.21(2H, ddd, J 1.8, 2.0 and 4.2Hz, H-3), 5.11(1H, ddt, J 1.8, 10.4 and 1.9Hz, H-1(*trans*)), 5.38(1H, ddt, J 2.0, 17.1 and 2.0Hz, H-1(*cis*)), 5.93(1H, ddt, J 10.4, 17.1 and 4.3Hz, H-2), 7.36(4H, m, H-4"), 7.40(2H, m, H-2"), 7.68(4H, m, H-3"); δ_C(50MHz; $CDCl_3$) 19.3(C-1'), 26.8(C-2'), 64.6(C-3), 113.9(C-1), 127.6(C-2"), 129.6(C-4"), 133.7(C-1"), 135.5(C-3"), 137.0(C-2); *m/z* 296 (M^+, 6%).

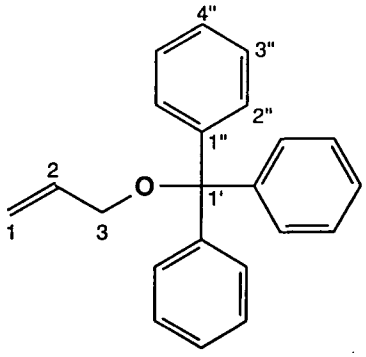
Preparation of 2-(t-butyldiphenyl)silyloxyethanal (66)



Ozone was bubbled through a solution of **(65)** (1.68g, 5.7mmol) in CH_2Cl_2 (50ml) at -78°C until a faint blue colour developed. Nitrogen gas was then bubbled through the solution until the colour had disappeared, and the solution was then allowed to warm to room temperature. Methyl sulfide (5ml, 68.1mmol) was added, and the mixture left to stand for 4h. The volatiles were removed under reduced pressure, and chromatography over silica gel with CH_2Cl_2 as the eluent, gave **(66)**, a viscous oil (0.85g, 50%); δ_H(200MHz; $CDCl_3$)

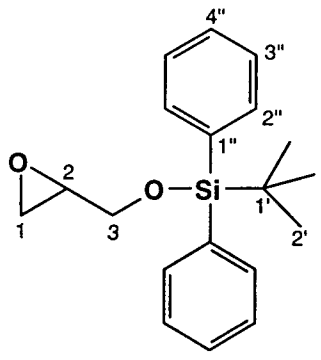
1.11(9H, s, H-2'), 4.21(2H, d, J 0.8Hz, H-2), 7.38(4H, m, H-2"), 7.41(2H, m, H-4"), 7.65(4H, m, H-3"), 9.71(1H, t, J 0.8Hz, H-1).[126]

Preparation of 3-triphenylmethoxy-1-propene (67)



A solution of allyl alcohol **(13a)** (1.05g, 18.1mmol), triphenylmethyl chloride (5.28g, 18.9mmol), triethylamine (2.6g, 25.7mmol) and dimethylaminopyridine (0.084g, 0.7mmol) in DMF (40ml) was stirred at room temperature for 85h. The reaction mixture was then poured onto ice (50ml), extracted into CH_2Cl_2 (3x50ml) and the organic extracts washed with saturated NH_4Cl solution (50ml) and H_2O (100ml). The organic extracts were then dried ($MgSO_4$) and the solvent removed under reduced pressure. The resultant oil crystallised on cooling. The crude solid was recovered by filtration, recrystallised from EtOH and was dried under vacuum to afford **(67)** as a white crystalline solid (4.87g, 90%) m.p. 77°C (lit 77°C).[127]

Preparation of 3-(t-butyldiphenyl)silyloxy-1,2-epoxy-propane (69)



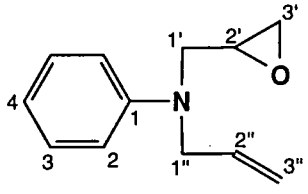
m-Chloroperoxybenzoic acid (moist) (5.20g) was dissolved in CH_2Cl_2 (20ml), dried ($MgSO_4$) and filtered. To this was added a solution of **(65)** (2.0g, 6.7mmol) in CH_2Cl_2 (20ml) and $NaHCO_3$ (5.0g, 59.5mmol), and the mixture was stirred at room temperature for 4 days. The reaction mixture was washed with 10% Na_2SO_3 solution (2x50ml), 10% $NaHCO_3$ solution (2x50ml), H_2O (1x50ml) and saturated brine (1x50ml), dried ($MgSO_4$), filtered and the solvents removed under reduced pressure to give **(69)** as a clear oil (1.43g, 68%); δ_H(200MHz; $CDCl_3$) 1.06(9H, s, H-2'), 2.59(1H, dd, J 2.6 and 5.2Hz, H-1), 2.72(1H, dd, J 4.1 and 5.2Hz, H-1), 3.11((1H, m, H-2), 3.69(1H, dd, J 4.7 and 11.8Hz, H-3), 3.86(1H, dd, J 3.1 and 11.8Hz, H-3), 7.37(4H, m, H-2"), 7.40(2H, m, H-4"), 7.69(4H, m, H-3").[128]

Reaction of Diisopropylamine with 2,3-epoxypropyl *p*-toluene-sulfonate

A mixture of diisopropylamine (2.0g, 19.8mmol), 2,3-epoxypropyl *p*-toluenesulfonate (6.85g, 30.0mmol) and glacial acetic acid (2.25g, 37.5mmol) in DMF (50ml) were heated for 3h for at 95°C. After cooling, the mixture was diluted with H_2O (100ml), and then extracted with CH_2Cl_2 (3x50ml). The organic fractions were dried ($MgSO_4$) and

the solvent removed under reduced pressure to give a semi-solid material. A sample was dissolved in $CDCl_3$ and studied by ^1H-NMR, and in addition to the resonances of unreacted 2,3-epoxypropyl *p*-toluenesulfonate, another set of peaks was clearly visible, showing the presence of a second glycidyl species, assigned to N-(2,3-epoxypropyl)-N,N-diisopropylamine.

Preparation of N-(2,3-epoxypropyl)-N-(2-propenyl)aniline (71)



A solution of N-allylaniline **(70)** (1.00g, 7.5mmol) in THF (25ml) at -78°C was treated with 1.6M n-butyllithium solution (5.2ml, 8.3mmol) and stirred for 30min. The reaction mixture was then added dropwise *via* canula to a solution of **(62a)** (2.04g, 8.9mmol) in THF (25ml) at -78°C. The reaction was stirred for 2h, allowed to warm to room temperature, quenched with H_2O (100ml) and extracted into Et_2O (3x50ml). The organic washings were dried ($MgSO_4$), and the solvents removed under reduced pressure. Column chromatography over silica gel with CH_2Cl_2/petroleum ether (7:1) as the eluent gave **(71)** as a brown oil (0.75g, 53%); ν_{max}/cm^{-1} 3059, 3042, 3025, 2981, 2919, 1600, 1506, 1386, 1234, 1190, 989, 919, 749, 693; δ_H (200MHz; $CDCl_3$) 2.56(1H, dd, J 4.9 and 2.7Hz, H-3'), 2.77(1H, dd, J 4.9 and 3.9Hz, H-3'), 3.15(1H, m, H-2'), 3.41(1H, dd, J 15.9 and 4.6Hz, H-1'), 3.62(1H, dd, J 15.9 and 3.3Hz, H-1'), 3.98(2H, ddd, J 4.9, 1.8 and 1.8Hz, H-1"), 5.15(2H, m, H-3"), 5.84(1H, ddt, J 17.6, 9.9 and 4.9Hz, H-2"), 6.71(1H, m, H-4), 6.73(2H, m, H-2), 7.21(2H, m, H-3); δ_C (50MHz; $CDCl_3$) 45.4

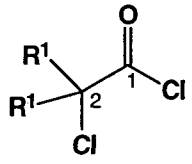
(C-1'), 50.6(C-1"), 51.9(C-2'), 53.6(C-3'), 112.3(C-3), 116.2(C-3"), 116.7 (C-1), 129.2(C-2), 133.6(C-2"), 148.5(C-4); *m/z* 189 (M^+, 100%).

Reaction of N-(2,3-epoxypropyl)-N-(2-propenyl)aniline (71) with *m*CPBA

A solution of N-(2,3-epoxypropyl)-N-(2-propenyl)aniline **(71)** (0.1g, 0.5mmol) in CH_2Cl_2 (20ml) was treated with *m*CPBA (0.18g, 1.0mmol) and $NaHCO_3$ (1.0g, 12.0mmol), and stirred at room temperature for 4 days. The reaction mixture was diluted with a further portion of CH_2Cl_2 (20ml), washed with 10% Na_2SO_3 (2x20ml), 10% $NaHCO_3$ (2x20ml) and saturated brine (1x20ml), and the organic fraction dried ($MgSO_4$). The solvent was removed under reduced pressure to leave a brown oil (0.05g), identified as predominantly the N-oxide of the starting material; (δ_H(200MHz; $CDCl_3$) 2.60(1H, m), 2.83(1H, m), 3.32(1H, m), 3.39(2H, m), 4.33(2H, m), 5.22(1H, m), 5.32(1H, m), 6.02(1H, m), 6.9 - 7.4(5H, m); *m/z* 205 (M^+, 100%).

6.2.2 Synthetic Route 2

Preparation of 2-chloroacetyl chloride (R^1=H) (72a)



A mixture of thionyl chloride (47.70g, 400.9mmol) and glacial acetic acid (6.0g, 99.9mmol) was heated at 70°C for 30min. To this was added N-chlorosuccinimide (26.7g, 199.9mmol), thionyl chloride (33.0g, 277.4mmol) and conc HCl (6 drops), and the mixture heated at 85°C for a further 90min. The volatile components were removed from the reaction mixture under reduced pressure, and collected in a liquid nitrogen trap. The collected mixture was allowed to warm to room temperature, and the excess thionyl chloride removed by distillation. The residual liquid was flash distilled to give **(72a)** as a clear fuming liquid (6.55g, 58%) b.p. 79-80°C (lit 79-81°C)[36].

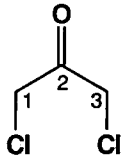
Preparation of [1-^{13}C]-2-chloroacetyl chloride at 99 atom% ^{13}C (R^1=H, C-1=^{13}C) (72b)

As for **(72a)**, with the exception that $CH_3{}^{13}CO_2H$ **(24b)** (5.06g, 82.9mmol, 99 atom% ^{13}C) was used in place of CH_3CO_2H to give **(72b)** (4.14g, 44%); δ_H(200MHz; $CDCl_3$) 4.54(2H, d, J 5.7Hz, H-2); δ_C(50MHz; $CDCl_3$) 49.2(d, J 60.2Hz, C-2), 167.9(C-1).

Preparation of [2-$^2H_2$]-2-chloroacetyl chloride at 99 atom% ^2H (R^1=D) (72c)

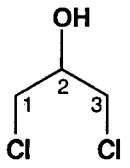
As for **(72a)**, with the exception that CD_3CO_2H **(24c)** (5.00g, 79.3mmol, 99 atom% ^2H) was used in place of CH_3CO_2H to give **(72c)** (5.75g, 63%); δ_C(50MHz; $CDCl_3$) 48.7(d, J 23.6Hz, C-2), 168.1(C-1); *m/z* 51 (CH_2Cl, 64%), 79 (M-Cl, 100%).

Preparation of 1,3-dichloro-2-propanone (48)



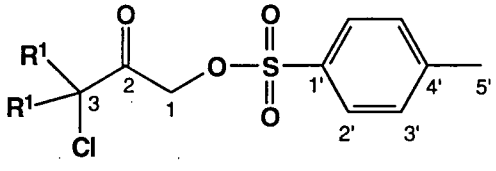
A mixture of 2-(2-ethoxyethoxy)-ethanol (12ml), potassium hydroxide (2.00g, 35.6mmol) in H_2O (4ml), and Et_2O (4ml) was heated at 70°C. As soon as the ether began to evaporate, a solution of N-methyl-N-nitroso-p-toluenesulfonamide (7.20g, 33.6mmol) in Et_2O (50ml) was added dropwise, followed by a further portion of Et_2O (50ml). The vapours from the reaction were collected by bubbling them through two Et_2O traps maintained at 0°C. When the reaction mixture had become colourless, the diazomethane solutions in the two traps were combined, and a solution of chloroacetyl chloride **(72a)** (1.44g, 12.7mmol) in Et_2O (5ml) was added, and stirred at room temperature for 60min to generate the diazoketone **(75)** ($ClCH_2COCHN_2$); δ_H(200MHz; $CDCl_3$) 4.03(2H, s, H-3), 5.88(1H, s, H-1); *m/z* 119 (M^+, 58%). To this mixture was added 1M HCl in Et_2O (25ml, 25mmol), and the reaction refluxed for 4h. The solution was dried ($MgSO_4$), and the volatiles removed under reduced pressure to give **(48)** as a white crystalline solid (1.49g, 92%) m.p. 44°C (lit 45°C).[129]

Preparation of 1,3-dichloro-2-propanol (16)



To a solution of **(48)** (2.0g, 15.8mmol) in 1:1 MeOH: CH_2Cl_2 (40ml) was added sodium borohydride (0.30g, 8.0mmol). The mixture was stirred at room temperature for 60min, washed once with H_2O (20ml), and the aqueous portion extracted into CH_2Cl_2 (20ml). The organic solutions were combined, dried ($MgSO_4$), and the solvent removed under reduced pressure to give **(16)** as a clear colourless oil (1.59g, 78%); (product was spectrally identical to commercial material).

Preparation of 3-chloro-2-oxopropyl p-toluenesulfonate (R^1=H) (74a)



A mixture of 2-(2-ethoxyethoxy)-ethanol (20ml), potassium hydroxide (8.0g, 142.6mmol) in H_2O (16ml), and Et_2O (16ml) was heated at 70°C. As soon as the Et_2O began to evaporate, a solution of N-methyl-N-nitroso-*p*-toluenesulfonamide (28.80g, 134.4mmol) in Et_2O (250ml) was added dropwise, followed by a further portion of Et_2O (20ml). The vapours from the reaction were collected by bubbling them through two Et_2O traps maintained at 0°C. When the reaction mixture had become colourless, the diazomethane solutions in the two traps were combined, and **(72a)** (6.20g, 54.9mmol) was added dropwise, and stirred at room

temperature for 10min to generate the diazoketone ($ClCH_2COCHN_2$) **(75)**. To this mixture was then added wet p-toluenesulfonic acid (25.00g, 145.2mmol), and the reaction was stirred at reflux until the colour had disappeared. The solution was washed once with H_2O (100ml), the aqueous portion was extracted once with Et_2O (100ml), and the two organic solutions combined and dried ($MgSO_4$). The volatiles were removed under reduced pressure to give a crude solid. Recrystallisation from Et_2O gave **(74a)** as white crystals (7.76g, 54%) m.p. 75°C; (Found: C, 45.5; H, 4.1. $C_{10}H_{11}ClO_4S$ requires C, 45.7; H, 4.2%) ν_{max}/cm^{-1} 3093, 3057, 2990, 2941, 1753, 1597, 1494, 1452, 1420, 1364, 1191, 1173, 1011, 850, 820, 772, 671, 601, 567, 549; δ_H (200MHz; $CDCl_3$) 2.46(3H, s, H-5'), 4.27(2H, s, H-3), 4.74 (2H, s, H-1), 7.38(2H, m, H-3'), 7.80(2H, m, H-2'); δ_C(50MHz; $CDCl_3$) 22.2(C-5'), 46.6(C-3), 71.0(C-1), 128.6(C-2'), 130.7(C-3'), 132.3(C-4'), 146.4(C-1'), 195.6(C-2); *m/z* 281 ($M+NH_4^+$, 100%).

Preparation of [2-^{13}C]-3-chloro-2-oxopropyl *p*-toluenesulfonate at 99 atom% ^{13}C (R^1=H, C-2=^{13}C) (74b)

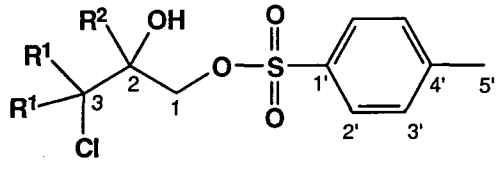
As for **(74a)**, with the exception that **(72b)** (4.14g, 36.3mmol, 99 atom% ^{13}C) was used in place of **(72a)** to give **(74b)** (4.98g, 52%); δ_H(200MHz; $CDCl_3$) 2.47(3H, s, H-5'), 4.28(2H, d, J 4.5Hz, H-3), 4.74(2H, d, J 4.2Hz, H-1), 7.39(2H, m, H-3'), 7.83(2H, m, H-2'); δ_C(50MHz; $CDCl_3$) 21.7(C-5'), 46.0(d, J 43.8, C-3), 70.4(d, J 46.4, C-1), 128.1(C-2'), 130.2(C-3'), 131.8(C-4'), 145.9(C-1'), 195.1(C-2); *m/z* 281 ($M+NH_4^+$, 100%).

Preparation of [2-$^2H_2$]-3-chloro-2-oxopropyl *p*-toluenesulfonate at 99 atom% ^{2}H (R^1=D) (74c)

As for **(74a)**, with the exception that **(72c)** (5.38g, 46.8mmol, 99 atom% ^{2}H) was used in place of **(72a)** to give **(74c)** (6.43g, 52%); δ_H(200MHz;

$CDCl_3$) 2.47(3H, s, H-5'), 4.75(2H, s, H-1), 7.38(2H, m, H-3'), 7.81(2H, m, H-2'); δ_C(50MHz; $CDCl_3$) 21.7(C-5'), 45.5(p, J 23.2Hz, C-3), 70.5 (C-1), 128.1(C-2'), 130.2(C-3'), 131.8(C-4'), 145.9(C-1'), 195.2(C-2); *m/z* 282 ($M+NH_4^+$, 100%).

Preparation of 3-chloro-2-hydroxypropyl *p*-toluenesulfonate (R^1=H, R^2=H) (21a)



To a solution of **(74a)** (5.0g, 19.0mmol) in 1:1 MeOH: CH_2Cl_2 (50ml) was added sodium borohydride (0.36g, 9.5mmol). The mixture was stirred at room temperature for 15min, diluted with CH_2Cl_2 (50ml), washed once with H_2O (50ml), and the aqueous portion extracted once into CH_2Cl_2 (50ml). The organic solutions were combined, dried ($MgSO_4$), and the solvent removed under reduced pressure to give **(21a)** as a clear colourless oil (4.47g, 89%); δ_H(200MHz; $CDCl_3$) 2.44(3H, s, H-5'), 2.80(1H, d, J 6.0Hz, OH), 3.57(2H, d, J 5.1Hz, H-3), 4.08(1H, m, H-2), 4.09(2H, m, H-1), 7.36(2H, m, H-3'), 7.79(2H, m, H-2').[130]

Preparation of [2-^{13}C]-3-chloro-2-hydroxypropyl *p*-toluene-sulfonate at 99 atom% ^{13}C (R^1=H, R^2=H, C-2=^{13}C) (21b)

As for **(21a)**, with the exception that **(74b)** (4.98g, 18.9mmol, 99 atom% ^{13}C) was used in place of **(74a)** to give **(21b)** (4.00g, 80%); δ_H(200MHz; $CDCl_3$) 2.45(3H, s, H-5'), 2.96(1H, m, OH), 3.59(2H, m, H-3), 4.10(1H, m, H-2), 4.12(2H, m, H-1), 7.37(2H, m, H-3'), 7.80(2H, m, H-2');

δ_C(50MHz; $CDCl_3$) 21.7(C-5'), 44.9(d, J 40.1Hz, C-3), 69.0(C-2), 70.5 (d, J 33.0Hz, C-1), 128.0(C-2'), 130.1(C-3'), 132.2(C-4'), 145.4(C-1').

Preparation of [3-$^2H_2$]-3-chloro-2-hydroxypropyl *p*-toluene-sulfonate at 99 atom% ^2H (R^1=D, R^2=H) (21d)

As for **(21a)**, with the exception that **(74c)** (3.09g, 11.7mmol, 99 atom% ^2H) was used in place of **(74a)** to give **(21d)** (2.81g, 90%); δ_H(200MHz; $CDCl_3$) 2.44(3H, s, H-5'), 3.25(1H, d, J 5.4Hz, OH), 4.09(2H, m, H-2), 4.10(2H, m, H-1), 7.36(2H, m, H-3'), 7.79(2H, m, H-2'); δ_C(50MHz; $CDCl_3$) 22.1(C-5'), 44.3(p, 23.2Hz, C-3), 69.2(C-2), 70.7(C-1), 128.5 (C-2'), 130.6(C-3'), 132.5(C-4'), 145.9(C-1'); *m/z* 284 ($M+NH_4^+$, 100%).

Preparation of [2-^2H]-3-chloro-2-hydroxypropyl *p*-toluene-sulfonate at 99 atom% ^2H (R^1=H, R^2=D) (21e)

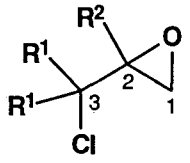
As for **(21a)**, using **(74a)** (2.0g, 7.6mmol), with the exception that sodium borodeuteride (0.16g, 3.8mmol, 99 atom% ^2H) was used in place of sodium borohydride to give **(21e)** (1.86g, 92%); δ_H(200MHz; $CDCl_3$) 2.45(3H, s, H-5'), 3.03(1H, s, OH), 3.58(2H, s, H-3), 4.11(2H, s, H-1), 7.37(2H, m, H-3'), 7.80(2H, m, H-2'); δ_C(50MHz; $CDCl_3$) 22.2(C-5'), 45.3(C-3), 69.1(t, J 22.5Hz, C-2), 70.5(C-1), 128.5(C-2'), 130.6(C-3'), 132.6(C-4'), 145.9(C-1'); *m/z* 283 ($M+NH_4^+$, 100%).

Preparation of [1-^2H, 2-$^2H_2$]-3-chloro-2-hydroxypropyl *p*-toluene-sulfonate at 99 atom% ^2H (R^1=D, R^2=D) (21f)

As for **(21a)**, with the exception that **(74c)** (3.20g, 12.1mmol, 99 atom% ^2H) was used in place of **(74a)**, and sodium borodeuteride (0.25g, 6.0mmol, 99 atom% ^2H) was used in place of sodium borohydride to give **(21f)** (2.92g, 91%); δ_H(200MHz; $CDCl_3$) 2.43(3H, s, H-5'), 3.46(1H, s, OH), 4.10(2H, s, H-1), 7.36(2H, m, H-3'), 7.79(2H, m, H-2');

δ_C(50MHz; $CDCl_3$) 21.6(C-5'), 44.2(p, J 22.8, C-3), 68.3(t, J 22.1Hz, C-2), 70.1(C-1), 127.9(C-2'), 130.1(C-3'), 132.0(C-4'), 145.4(C-1'); *m/z* 285 ($M+NH_4^+$, 100%).

Preparation of epichlorohydrin (R^1=H, R^2=H) (2a)



Sodium metal (0.78g, 33.9mmol) was added to ethylene glycol (30ml), and the mixture was allowed to stir at 20°C for 5h to produce a solution of sodium ethylene glycolate in ethylene glycol. **(21a)** (4.47g, 16.9mmol) was added as a solution in ethylene glycol (10ml), and the mixture was stirred at 20°C for 15min. The product **(2a)** was then removed from the mixture by distillation under reduced pressure and collected in a liquid nitrogen cold finger as a clear liquid (1.23g, 79%); (product spectrally identical to commercial material).

Preparation of [2-^{13}C]-epichlorohydrin at 99 atom% ^{13}C (R^1=H, R^2=H, C-2=^{13}C) (2b)

As for **(2a)**, with the exception that **(21b)** (4.00g, 15.1mmol, 99 atom% ^{13}C) was used in place of **(21a)** to give **(2b)** (1.00g, 71%); δ_H(200MHz; $CDCl_3$) 2.69(1H, m, H-1), 2.90(1H, m, H-1), 3.24(1H, m, H-2), 3.68(2H, m, H-3); δ_C(50MHz; $CDCl_3$) 45.5(d, J 48.1Hz, C-3), 47.4(d, J 28.6Hz, C-1), 51.7(C-2); *m/z* 49 (CH_2Cl, 54%), 58 (M-Cl, 100%), 63 (CH_2ClCH, 32%), 93 (M^+, 1%).

Preparation of [2-^{2}H]-epichlorohydrin at 99 atom% ^{2}H (R^1=H, R^2=D) (2h)

As for **(2a)**, with the exception that **(21e)** (1.86g, 7.0mmol, 99 atom% ^{2}H) was used in place of **(21a)** to give **(2h)** (0.30g, 46%); δ_H(200MHz; $CDCl_3$) 2.69(1H, d, J 4.8Hz, H-1), 2.89(1H, d, J 4.8Hz, H-1), 3.58(2H, m, H-3); δ_C(50MHz; $CDCl_3$) 44.8(C-3), 46.1(C-1), 50.4(t, J 27.6Hz, C-2); *m/z* 49 (CH_2Cl, 24%), 58 (M-Cl, 100%), 63 (CH_2ClCD, 17%).

Preparation of [3-$^2H_2$]-epichlorohydrin at 99 atom% ^{13}C (R^1=D, R^2=H) (2i)

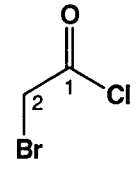
As for **(2a)**, with the exception that **(21d)** (2.00g, 7.5mmol, 99 atom% ^{2}H) was used in place of **(21a)** to give **(2i)** (0.49g, 69%); δ_H(200MHz; $CDCl_3$) 2.67(1H, dd, J 4.8 and 2.5Hz, H-1), 2.87(1H, dd, J 4.8 and 3.9Hz, H-1), 3.21(1H, m, H-2); δ_C(50MHz; $CDCl_3$) 45.2(p, J 23.2Hz, C-3), 47.2(C-1), 51.5(C-2); *m/z* 51 (CD_2Cl, 21%), 59 (M-Cl, 100%), 64 (CD_2ClCH, 17%).

Preparation of [2-^{2}H, 3-$^2H_2$]-epichlorohydrin at 99 atom% ^{2}H (R^1=D, R^2=D) (2l)

As for **(2a)**, with the exception that **(21f)** (2.0g, 7.5mmol, 99 atom% ^{2}H) was used in place of **(21a)** to give **(2l)** (0.40g, 55%); δ_H(200MHz; $CDCl_3$) 2.68(1H, d, J 4.8Hz, H-1), 2.87(1H, d, J 4.8Hz, H-1); δ_C(50MHz; $CDCl_3$) 44.3(p, J 23.4Hz, C-3), 46.1(C-1), 50.3(t, J 27.6Hz, C-2); *m/z* 51 (CD_2Cl, 25%), 60 (M-Cl, 100%), 65 (CD_2ClCD, 22%).

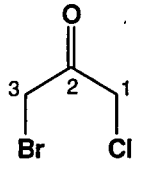
6.2.3 Synthetic Route 3

Preparation of 2-bromoacetyl chloride (76)



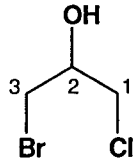
A mixture of thionyl chloride (20.5g, 172.3mmol) and bromoacetic acid **(25a)** (6.0g, 43.2mmol) was stirred at 70°C for 30min. The excess thionyl chloride was removed by distillation, and the residual liquid was flash distilled to give **(76)** as a brown fuming liquid (6.64g, 98%) b.p. 133°C (lit 133 - 135°C).[131]

Preparation of 3-bromo-1-chloro-2-propanone (77)



Following the procedure for **(48)**, **(76)** (6.64g, 42.2mmol) was treated accordingly to give a brown liquid **(77)** (6.41g, 89%); *m/z* 188 ($M+NH_4^+$, 23%).[132]

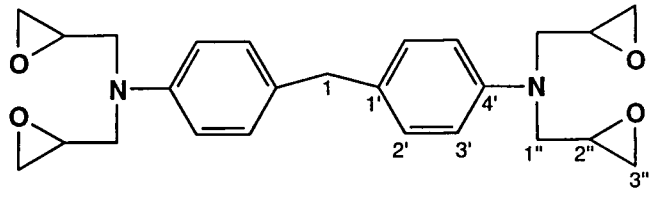
Preparation of 3-bromo-1-chloro-2-propanol (78)



Sodium borohydride (0.58g, 15.3mmol) was added to a solution of **(77)** (5.26g, 30.7mmol) in 1:1 MeOH:CH_2Cl_2 (50ml). The mixture was stirred at room temperature for 15min, diluted with CH_2Cl_2 (50ml), washed once with H_2O (50ml), and the aqueous portion extracted once into CH_2Cl_2 (50ml). The organic extracts were combined, dried ($MgSO_4$), and the solvent removed under reduced pressure to give **(78)** as a clear pale brown oil (3.87g, 73%); δ_H(200MHz; $CDCl_3$) 2.89(1H, d, J 6.6Hz, OH), 3.58(2H, d, J 5.5Hz, H-3), 3.71(2H, d, J 5.6Hz, H-1), 4.06(1H, m, H-2).[133]

6.3 Chapter 3

Preparation of N,N,N',N'-tetraglycidyl-4,4'-diaminodiphenyl-methane (7a)



Aniline **(9a)** (4.98g, 53.5mmol), glacial acetic acid (6.0, 99.7mmol) and epichlorohydrin (39.97g, 432.0mmol) were heated at 95°C for 3h. Unreacted starting materials were removed under reduced pressure at 70°C to leave a viscous brown oil **(11)**, which was then treated with H_2O (11ml), 36% HCl (5.08g, 50.2mmol) and CH_2O (37% solution in H_2O, 2.53g, 31.2mmol). The mixture was heated at 70°C for 12h to give a pale brown solution of **(12)**. The solution was then treated with $PhEt_3NCl$ (0.16g, 0.7mmol), 30% NaOH solution (44ml, 330.0mmol) and C_6H_6 (55ml), and stirred at 50°C for 10min. The reaction was quenched with CH_2Cl_2 (100ml), and the organic layer separated. The aqueous layer was back extracted into CH_2Cl_2 (100ml), and the organic layers combined and dried ($MgSO_4$). The solution was then concentrated under reduced pressure to give the title compound **(7a)** as a viscous brown liquid (6.27g, 56%); (product was spectrally identical to commercially available material).

Preparation of [$^{15}N_2$]-N,N,N',N'-tetraglycidyl-4,4'-diaminodiphenylmethane at 26 atom% ^{15}N (7b)

As for **(7a)**, with the exception that enriched [^{15}N]-aniline **(9b)** (4.98g, 53.5mmol, 26 atom% ^{15}N) was used in place of unenriched aniline **(9a)** to give **(7b)** (9.30g, 82%); δ_N (40MHz; $CDCl_3$) 54.2(s).

Preparation of [2"-$^{13}C_4$]-N,N,N',N'-tetraglycidyl-4,4'-diaminodiphenylmethane at 20 atom% ^{13}C (7d)

Aniline **(9a)** (2.16g, 23.2mmol), [2-^{13}C] epichlorohydrin **(2b)** (1.0g, 10.8mmol, 99 atom% ^{13}C), unenriched epichlorohydrin **(2a)** (4.0g, 43.2mmol), H_2O (0.7ml) and C_6H_6 (3.75ml) were refluxed together for 22h, and the excess reactants removed at reduced pressure to give a viscous pale brown liquid. To this was added 36% HCl (2.30g, 22.7mmol), H_2O (3.5ml), CH_2Cl_2 (1.2ml) and CH_2O (37% solution in H_2O) (1.04g, 12.8mmol), and the resultant mixture stirred at 70°C for 6h. The volatiles were removed under reduced pressure to leave a white powder, to which was added powdered NaOH (4.70g, 117.5mmol) and 2-butanone (100ml). This was stirred vigorously at 50°C for 30min, diluted with a further portion of 2-butanone (100ml), and washed with H_2O (100ml). The aqueous phase was washed with 2-butanone (1x50ml), and the organic fractions combined and dried ($MgSO_4$). The volatiles were removed at reduced pressure, to leave a viscous liquid (6.0g). To this was added CH_2Cl_2 (6ml), and Et_2O was added dropwise to precipitate the product as a thick brown liquid. Once precipitation had ceased, Et_2O addition was stopped, the solvent decanted off, and any remaining solvents were removed under reduced pressure to give **(7d)** (2.90g, 59%); δ_H(200MHz; $CDCl_3$) 2.54(4H, dd, J 2.6 and 4.9Hz, H-3"), 2.74 and 2.75(4H, dd and dd, J 4.9 and 4.0Hz, H-3"), 3.13(4H, m, H-2"), 3.37 and 3.41(4H, dd and dd, J 5.0 and

15.7Hz, H-1"), 3.66 and 3.69(4H, dd and dd, J 3.1 and 15.7Hz, H-1"), 3.78(2H, s, H-1), 6.72(4H, m, H-3'), 7.05(4H, m, H-2'); δ_C(50MHz; $CDCl_3$) 40.3(C-1), 45.9 and 46.0(C-3"), 51.1 and 51.2(C-2"), 53.6(C-1"), 113.1 and 113.2 (C-3'), 130.2(C-2'), 131.1 and 131.2(C-1'), 147.1 (C-4'); *m/z* 422 (M^+ ($4x^{12}C$), 75%), 423 (M^+ ($3x^{12}C$, $1x^{13}C$), 100%), 424 (M^+ ($2x^{12}C$, $2x^{13}C$), 59%), 425 (M^+ ($1x^{12}C$, $3x^{13}C$), 20%), 426 (M^+ ($4x^{13}C$), 5%).

Preparation of [2"-$^2H_4$]-N,N,N',N'-tetraglycidyl-4,4'-diaminodiphenylmethane at 99 atom% ^2H (7f)

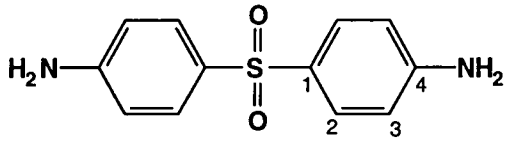
As for **(7d)**, with the exception that enriched [2-^{2}H]-epichlorohydrin **(2h)** (4.07g, 43.5mmol, 99% atom% ^2H) was used in place of unlabelled material to give **(7f)** (2.36g, 51%); δ_H(200MHz; $CDCl_3$) 2.58(4H, d, J 4.9Hz, H-3"), 2.78 and 2.79(4H, d and d, J 4.9Hz, H-3"), 3.40 and 3.45(4H, d and d, J 15.8Hz, H-1"), 3.70 and 3.73(4H, d and d, J 15.8Hz, H-1"), 3.81(2H, s, H-1), 6.74(4H, m, H-3'), 7.07(4H, m, H-2'); δ_C(50MHz; $CDCl_3$) 39.7(C-1), 45.2 and 45.3(C-3"), 50.1 and 50.2(t, J 26.8Hz, C-2"), 52.9(C-1"), 112.5 and 112.6(C-3'), 129.6(C-2'), 130.5 and 130.6(C-1'), 146.5 (C-4');

Preparation of [2"-$^2H_4$, 3"-$^2H_8$]-N,N,N',N'-tetraglycidyl-4,4'-diaminodiphenylmethane at 99 atom% ^2H (7g)

As for **(7d)**, with the exception that enriched [2-^{2}H, 3-$^2H_2$]-epichlorohydrin **(2i)** (3.20g, 33.5mmol, 99% atom% ^2H) was used in place of unlabelled material to give **(7g)** (1.78g, 49%); δ_H(200MHz; $CDCl_3$) 3.41 and 3.45(4H, d and d, J 15.8Hz, H-1"), 3.70 and 3.73(4H, d and d, J 15.8Hz, H-1"), 3.81(2H, s, H-1), 6.75(4H, m, H-3'), 7.08(4H, m, H-2'); δ_C(50MHz; $CDCl_3$) 39.6(C-1), 44.5 and 44.6(p, J 26.4Hz, C-3"),

49.9 and 50.0(t, J 26.8Hz, C-2"), 52.8(C-1"), 112.4 and 112.5(C-3'), 129.5(C-2'), 130.4 and 130.5(C-1'), 146.5 (C-4');

Preparation of 4,4'-Diaminodiphenylsulfone (8a)



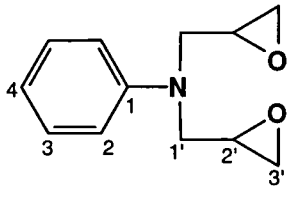
A solution of $SO_2(C_6H_4F)_2$ **(79)** (2.50g, 9.8mmol) and potassium phthalimide **(81a)** (15.0g, 81.0mmol) in DMF (50ml) was heated under reflux for 24h. The reaction mixture was then poured onto H_2O (100ml), and the precipitate filtered off and washed with more H_2O. The solid was added to CH_2Cl_2 (100ml), and the mixture dried ($MgSO_4$). After vigorous stirring, the solid was filtered off, and the organics washed with H_2O (1x50ml), dried ($MgSO_4$), and the solvent removed under reduced pressure, to give the crude diphthalimide **(80a)** (2.44g) (ν_{max}/cm^{-1} 3108, 1715, 1592, 1499, 1374, 1296, 1156, 1073, 883, 747, 714, 679; δ_H(200MHz; $CDCl_3$) 7.73(4H, m, H-3), 7.83(4H, m, H-7 or H-8), 7.98(4H, m, H-7 or H-8), 8.12(4H, m, H-2); δC(50MHz; $CDCl_3$) 124.1(C-3'), 126.6(C-3), 128.7(C-2), 131.4(C-2'), 134.9(C-4'), 136.4(C-1), 140.0(C-4), 166.5(C-1'); *m/z* 508 (M^+, 100%)). This was added to a solution of hydrazine (3.20g, 99.8mmol) in MeOH (50ml), and the mixture heated under reflux for 3h. The MeOH was removed under reduced pressure, and to the remaining solid was added 6M HCl (50ml, 50.0mmol). The mixture was heated under reflux for 3h, suction-filtered while hot, and the H_2O and acid removed under reduced pressure. The resulting solid was taken up in H_2O, brought to neutrality with 3% $NaHCO_3$ solution, and the precipitate that formed was filtered off. The precipitate was washed with more H_2O, taken up in acetone, dried ($MgSO_4$) and filtered. The solvent was then removed

under reduced pressure and the resultant solid dried in an oven to give the title compound **(8a)** (0.84g, 34%); (product was spectrally identical to commercially available material).

Preparation of [$^{15}N_2$]-4,4'-diaminodiphenylsulfone at 30.5 atom% ^{15}N (8b)

As for **(8a)**, with the exception that enriched [^{15}N]-potassium phthalimide **(81b)** (12.99g, 70.0mmol, 30.5% atom% ^{15}N) was used in place of unlabelled material to give **(8b)** (0.62g, 28%); δ_H(200MHz; DMSO) 6.01(4H, s, $^{14}NH_2$), 6.01(4H, d, J 87.1Hz, $^{15}NH_2$), 6.60(4H, m, H-3), 7.46(4H, m, H-2); δ_C(50MHz; DMSO) 112.8(C-3), 128.1(C-1), 128.5(2), 152.7(C-4(^{14}N)), 157.2(d, J 14.3Hz, C-4(^{15}N)); δ_N(50MHz; DMSO) 69.4(s); *m/z* 248 (M^+(2x^{14}N), 33%), 249 (M^+(^{14}N and ^{15}N), 27%), 250 (M^+(2x^{15}N), 8%).

Preparation of N,N-diglycidylaniline (10)

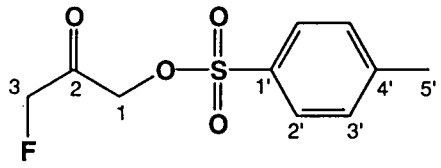


Aniline **(9a)** (1.0g, 10.7mmol), glacial acetic acid (1.20g, 20.0mmol) and epichlorohydrin (8.00g, 86.5mmol) were heated with stirring at 95°C for 3h. The excess reactants were removed under reduced pressure and at 70°C to leave a viscous brown liquid. This was then treated with C_6H_6 (11ml), 30% NaOH solution (8.8ml, 66.0mmol) and $PhEt_3NCl$ (0.03g, 0.1mmol), and heated for 10min at 50°C. The aqueous layer was discarded, and the procedure repeated. The organic extract was separated and the aqueous layer back extracted with CH_2Cl_2 (2x30ml). The organic extracts were combined, dried ($MgSO_4$), and the solvents

removed under reduced pressure, to give **(10)**. The NMR data shows a mixture of two stereoisomers; (product was spectrally identical to commercially available material).

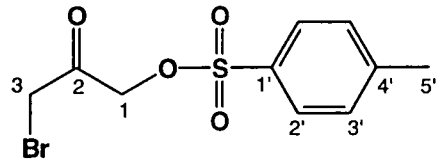
6.4 Chapter 5

Preparation of 3-fluoro-2-oxopropyl *p*-toluenesulfonate (84)



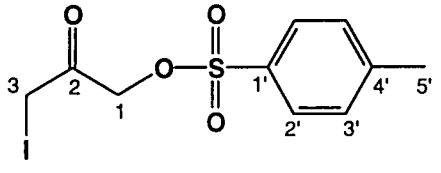
A solution of sodium fluoroacetate **(82)** (5.0g, 50.0mmol) and phosphorus pentachloride (11.73g, 56.3mmol) in nitrobenzene (50ml) was heated at 70°C for 4 hours. The reaction mixture was then cooled in an ice bath to 0°C, and flash distilled at low pressure into a liquid nitrogen cold-finger to yield crude fluoroacetyl chloride **(83)** (3.41g) (δ_H(200MHz; $CDCl_3$) 5.07(2H, d, J 46.7Hz, H-2); δ_C(50MHz; $CDCl_3$) 82.07(d, J 197.6Hz, C-2), 168.68(d, J 22.8Hz, C-1); δ_F(376MHz; $CDCl_3$) -209.77(t, 46.7Hz, F-2)). The impure fluoroacetyl chloride was then processed using the same procedure as for compound **(74a)**, to give **(84)** as a white crystalline solid (1.06g, 8.9%) m.p. 45°C (Found: C, 48.9; H, 4.7. $C_{10}H_{11}FO_4S$ requires C, 48.8; H, 4.5%); ν_{max}/cm^{-1} 2966, 2934, 1752, 1362, 1192, 1179, 985, 553; δ_H(200MHz; $CDCl_3$) 2.47(3H, s, H-5'), 4.81(2H, d, J 1.7Hz, H-1), 5.04(2H, d, J 47.0Hz, H-3), 7.39(2H, m, H-3'), 7.83(2H, m, H-2'); δ_C(50MHz; $CDCl_3$) 21.72(C-5'), 70.25(d, 2.3Hz, C-1), 84.15(d, 183.1Hz, C-3), 128.10(C-2'), 130.10(C-3'), 131.97(C-4'), 145.76(C-1'), 197.85(d, 19.8Hz,C-2); δ_F(376MHz; $CDCl_3$) -223.77(tt, J 47.0 and 1.9Hz, F-3); *m/z* 264 ($M+NH_4^+$, 100%).

Preparation of 3-bromo-2-oxopropyl *p*-toluenesulfonate (85)



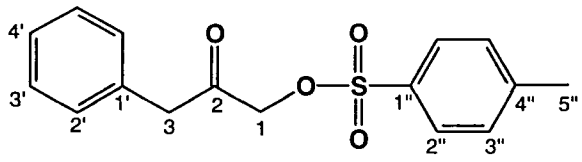
Following the procedure for **(74a)**, bromoacetyl chloride **(76)** (4.30g, 27.3mmol) was processed accordingly to afford **(85)** as a white crystalline solid (3.89g, 49%) m.p. 67°C (Found: C, 39.3; H, 3.6. $C_{10}H_{12}BrO_4S$ requires C, 39.1; H, 3.6%); ν_{max}/cm^{-1} 2997, 2941, 1744, 1361, 1171, 1009, 846, 669, 547; δ_H(200MHz; $CDCl_3$) 2.47(3H, s, H-5'), 4.05(2H, s, H-3), 4.75(2H, s, H-1), 7.39(2H, m, H-3'), 7.83(2H, m, H-2'); δ_C(50MHz; $CDCl_3$) 21.64(C-5'), 30.71(C-3), 69.79(C-1), 128.03(C-2'), 130.06(C-3'), 131.72(C-4'), 145.76(C-1'), 194.57(C-2); *m/z* 324 ($M+NH_4^+$, 100%).

Preparation of 3-iodo-2-oxopropyl *p*-toluenesulfonate (87)



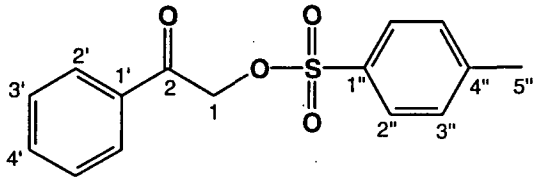
Following the procedure for **(74a)**, iodoacetyl chloride **(86)** (5.43g, 26.6mmol) was processed accordingly to afford **(87)** as a white crystalline solid (3.90g, 41.5%) m.p. 69°C (Found: C, 34.0; H, 3.1. $C_{10}H_{11}IO_4S$ requires C, 33.9; H, 3.1%); ν_{max}/cm^{-1} 3030, 2966, 2949, 1725, 1369, 1173, 1015, 767; δ_H(200MHz; $CDCl_3$) 2.47(3H, s, H-5'), 3.94(2H, s, H-3), 4.75(2H, s, H-1), 7.39(2H, m, H-3'), 7.83(2H, m, H-2'); δ_C(50MHz; $CDCl_3$) 0.67(C-3), 21.67(C-5'), 68.63(C-1), 128.10(C-2'), 130.07(C-3'), 131.76(C-4'), 145.73(C-1'), 195.96(C-2); *m/z* 372 ($M+NH_4^+$, 100%).

Preparation of 3-phenyl-2-oxopropyl *p*-toluenesulfonate (89)



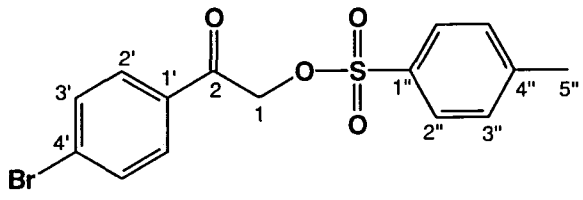
Following the procedure for **(74a)**, 2-phenylacetyl chloride **(88)** (4.11g, 26.6mmol) was processed accordingly to afford **(89)** as a white crystalline solid (4.43g, 54.7%) m.p. 63°C (lit 63°C).[134]

Preparation of 2-phenyl-2-oxoethyl *p*-toluenesulfonate (91)



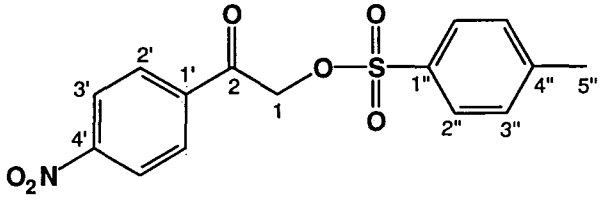
Following the procedure for **(74a)**, benzoyl chloride **(90)** (4.03g, 28.7mmol) was processed accordingly to afford **(91)** as a white crystalline solid (4.02g, 48.3%) m.p. 98 - 99°C (lit 99 - 100°C).[90]

Preparation of 2-(*p*-bromophenyl)-2-oxoethyl *p*-toluene-sulfonate (93)



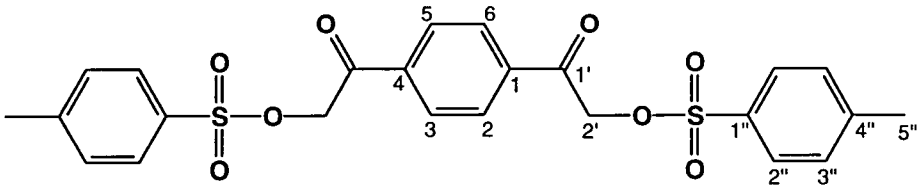
Following the procedure for **(74a)**, p-bromobenzoyl chloride **(92)** (6.19g, 28.2mmol) was processed accordingly to afford **(93)** as a white crystalline solid (4.85g, 46.6%) m.p. 134°C (lit 132 - 133°C).[135]

Preparation of 2-(*p*-nitrophenyl)-2-oxoethyl *p*-toluenesulfonate (95)



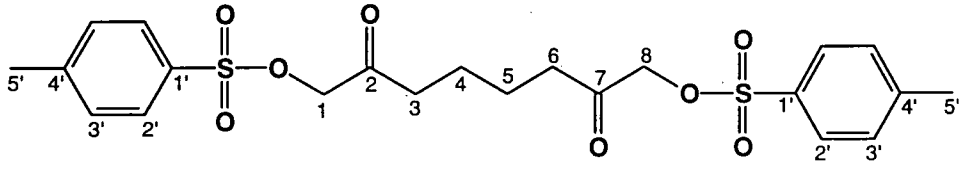
Following the procedure for **(74a)**, p-nitrobenzoyl chloride **(94)** (4.93g, 26.6mmol) was processed accordingly to afford **(95)** as a pale yellow crystalline solid (5.43g, 60.9%) m.p. 142°C (lit 142°C).[90]

Preparation of 1,4-di(1'-oxo-2'-tosyloxyethyl)benzene (97)



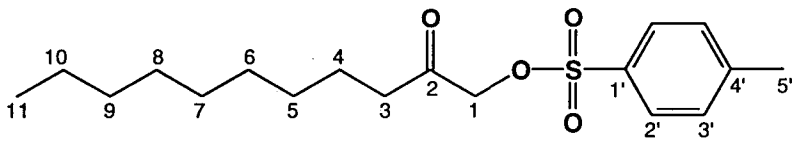
Following the procedure for **(74a)**, 1,4-benzenedicarbonyl dichloride **(96)** (2.70g, 13.3mmol) was processed accordingly to afford **(97)** as a white crystalline solid (0.73g, 10.9%) m.p. 178 - 179°C (Found: C, 57.35; H, 4.4. $C_{24}H_{22}O_8S_2$ requires C, 57.4; H, 4.4%); ν_{max}/cm^{-1} 2926, 1704, 1363, 1175, 1059, 957, 809, 753; δ_H(200MHz; $CDCl_3$) 2.41(6H, s, H-5"), 5.63(4H, s, H-2'), 7.47(4H, m, H-3"), 7.85(4H, m, H-2"), 8.00(4H, s, H-2,3); δ_C(50MHz; $CDCl_3$) 21.10(C-5"), 71.48(C-2'), 127.73(C-2,3), 128.28(C-2"), 130.11(C-3"), 132.51(C-4"), 137.20(C-1,4), 145.15(C-1"), 191.02(C-1); *m/z* 520 ($M+NH_4^+$, 1.5%).

Preparation of 1,8-(2,7-dioxo)octyl di(*p*-toluenesulfonate) (103)



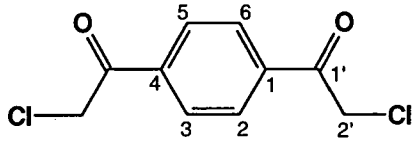
Following the procedure for **(74a)**, adipoyl chloride **(102)** (2.43g, 13.3mmol) was processed accordingly to afford **(103)** as a white crystalline solid (2.62g, 40.9%) m.p. 123°C (lit 121 - 122°C).[90]

Preparation of 2-oxoundecanyl *p*-toluenesulfonate (105)



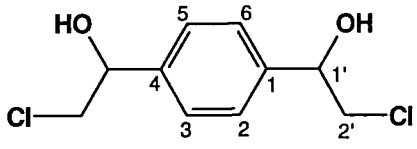
Following the procedure for **(74a)**, decanoyl chloride **(104)** (5.07g, 26.6mmol) was processed accordingly to afford **(105)** as a white crystalline solid (5.36g, 59.2%) m.p. 53°C (lit 51 - 52°C).[136]

Preparation of 1,4-di(2'-chloroacetyl)benzene (107)



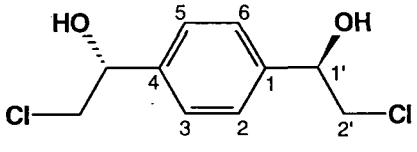
Following the procedure for **(48)**, 1,4-benzenedicarbonyl dichloride **(96)** (11.15g, 54.9mmol) was processed accordingly to afford **(107)** as a pale yellow powder (10.90g, 86%) m.p. 176 - 178°C (lit 184°C)[117] (Found: C, 52.0; H, 3.3. $C_{10}H_8Cl_2O_2$ requires C, 52.0; H, 3.5%); ν_{max}/cm^{-1} 2986, 2947, 1703, 1405, 1213, 995, 817, 786, 747; δ_H(200MHz; DMSO) 5.27(4H, s, H-2'), 8.10(4H, s, H-2,3); δ_C(50MHz; DMSO) 47.99(C-2'), 128.65(C-2,3), 137.91(C-1,4), 191.49(C-1'); *m/z* 104 (-C_6H_4CO-, 30%), 118 (-C_6H_4-$COCH_2$-, 21%), 132 (-COC_6H_4CO-, 10%), 181 ($CH_2ClCOC_6H_4CO$-, 100%).

Preparation of (±)-1,4-di(2'-chloro-1'-hydroxyethyl)benzene (±)-(108)



Sodium borohydride was added (0.65g, 17.2mmol) to a stirred solution of **(107)** (2.0g, 8.7mmol) in $MeOH/CH_2Cl_2$ (1:1) (50ml). The mixture was stirred at room temperature for 1h, quenched with H_2O (50ml), and extracted into EtOAc (3x50ml). The combined organic fractions were dried ($MgSO_4$) and the solvent removed under reduced pressure to give a residue. Purification by column chromatography over silica gel with CH_2Cl_2 as the eluent afforded **(108)** as a white solid (1.98g, 97%) m.p. 158 - 161°C (lit 163 - 164°C)[117]; (Found: C, 51.3; H, 5.2. $C_{10}H_{12}Cl_2O_2$ requires C, 51.1; H, 5.1%) ν_{max}/cm^{-1} 3211, 2957, 2897, 1427, 1076, 715; δ_H(200MHz; $CDCl_3$) 3.64(2H, dd, J 10.9 and 6.7Hz, H-2'), 3.73(2H, dd, J 10.9 and 4.7Hz, H-2'), 4.74(2H, ddd, 6.7, 4.7 and 4.7Hz, H-1'), 5.77(2H, d, J 4.7Hz, OH), 7.35(4H, s, H-2,3); δ_C(50MHz; $CDCl_3$) 50.28(C-1'), 72.25(C-2'), 126.14(C-2,3), 141.48(C-1,4); *m/z* 216 ($M-Cl+NH_4^+$, 50%).

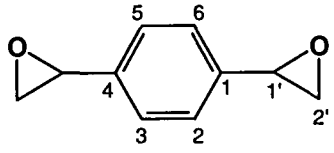
Preparation of (R,R)-(+)-1,4-di(2'-chloro-1'-hydroxyethyl) benzene (R,R)-(108)



Bakers' yeast (100g) was added to solution of glucose (600g, 3.3mol) in H_2O (7.5l) in a sealed reaction vessel venting through a bubbler. As soon as the evolution of CO_2 began, **(107)** (4.0g, 17.3mmol) was added,

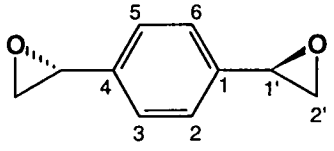
and stirring continued for 9 days. Once the reaction had reached completion, the mixture was extracted into EtOAc (2x2.5l), and the organic portions combined, dried ($MgSO_4$), and the solvent removed under reduced pressure. The crude product was purified by column chromatography over silica gel, with CH_2Cl_2 as the eluent, to give **(R,R)-(108)** as a white amorphous solid (2.20g, 54%); $[\alpha]_D^{22}$ +48.8 (*c* 10.0 in acetone);

Preparation of (±)-1,4-di(epoxyethyl)benzene (±)-(109)



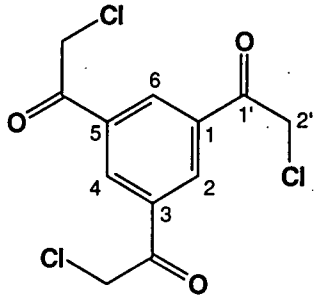
EtOH (10ml) and NaOH (2.02g, 50.5mmol) were added to a solution of **(±)-(108)** (1.98g, 8.4mmol) in CH_2Cl_2 (100ml). The mixture was stirred at room temperature for 90min, then quenched with H_2O (100ml) and extracted with CH_2Cl_2 (3x100ml). The combined organic extracts were dried ($MgSO_4$), and the solvent removed under reduced pressure to afford **(±)-(109)** as a white semi-solid (1.21g, 89%) (lit m.p. 79°C)[117]; ν_{max}/cm^{-1} 3052, 2988, 2919, 1713, 987, 877, 835, 799; δ_H(200MHz; $CDCl_3$) 2.78(2H, dd, J 5.7 and 2.6Hz, H-2'), 3.14(2H, dd, J 5.7 and 4.3Hz, H-2'), 3.85(2H, dd, J 4.3 and 2.6Hz, H-1'), 7.26(4H, s, H-2,3); δ_C(50MHz; $CDCl_3$) 51.13(C-2'), 52.02(C-1'), 125.58(C-1,4), 137.60(C-2,3); *m/z* 180 ($M+NH_4^+$, 100%).

Preparation of (R,R)-(+)-1,4-diepoxyethyl benzene (R,R)-(109)



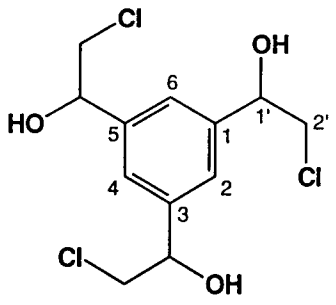
As for **(±)-(109)**, with the exception that **(R,R)-(108)** (0.30g, 1.3mmol) was used in place of **(±)-(108)** to give **(R,R)-(109)** as a white crystalline solid (0.20g, 95%) (decomp above 200°C); $[\alpha]_D^{22}$ +40.3 (*c* 10.0 in $CHCl_3$);

Preparation of 1,3,5-tri(2'-chloroacetyl)benzene (110)



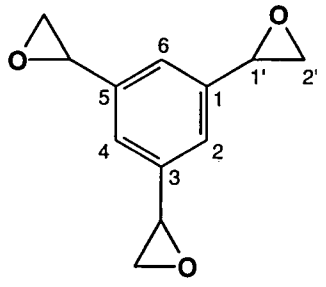
Following the procedure for **(48)**, 1,3,5-benzenetricarbonyl trichloride **(98)** (4.70g, 17.7mmol) was processed accordingly to afford **(110)** as an amorphous yellow solid (3.00g, 55%) m.p. 150 - 151°C (lit 153°C)[117]

Preparation of 1,3,5-tri(2'-chloro-1'-hydroxyethyl)benzene (111)



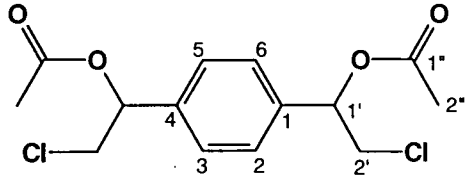
Sodium borohydride (0.74g, 19.6mmol) was added to a stirred solution of **(110)** (2.0g, 6.5mmol) in MeOH/CH_2Cl_2 (1:1) (50ml). The mixture was stirred at room temperature for 1h, and was then quenched with H_2O (50ml) and extracted into EtOAc (3x50ml). The combined organic extracts were dried ($MgSO_4$) and the solvent removed under reduced pressure to afford a residue. Purification over silica gel, with CH_2Cl_2 as the eluent, afforded **(111)** as a white amorphous solid (2.03g, 99%) m.p. 72 - 74°C (lit 80°C)[117]; ν_{max}/cm^{-1} 3388, 2955, 2902, 1713, 1081, 756; δ_H(200MHz; DMSO) 3.62(3H, dd, J 10.9 and 7.0Hz, H-2'), 3.73(3H, dd, J 10.9 and 4.5Hz, H-2'), 4.75(3H, m, H-1), 5.82(3H, d, J 4.7, OH), 7.33(3H, s, H-2,4,6); δ_C(50MHz; DMSO) 50.36(C-1'), 72.53(C-2'), 123.66(C-2,4,6), 141.94(C-1,3,5); *m/z* 330 ($M+NH_4^+$, 100%).

Preparation of 1,3,5-tri(epoxyethyl)benzene (112)



EtOH (10ml) and NaOH (2.33g, 58.3mmol) were added to a solution of **(111)** (2.03g, 6.5mmol) in CH_2Cl_2 (100ml). The mixture was stirred at room temperature for 90min, and was then quenched with H_2O (100ml) and extracted into CH_2Cl_2 (3x100ml). The combined organic extracts were dried ($MgSO_4$), and the solvent removed under reduced pressure to afford **(112)** as a white solid (1.23g, 93%) m.p. 48 - 53°C (lit 64°C)[117]; ν_{max}/cm^{-1} 3053, 2992, 2913, 1717, 1687, 1609, 1481, 1361, 1253, 929, 835; δ_H(200MHz; $CDCl_3$) 2.76(3H, m, H-2'), 3.13(3H, m, H-2'), 3.85(3H, m, H-1'), 7.13(3H, m, H-2,4,6); δ_C(50MHz; $CDCl_3$) 51.02, 51.07 and 51.12(C-1'), 51.93(C-2'), 121.84, 122.24 and 122.55(C-2,4,6), 138.40, 138.50 and 138.60(C-1,3,5); *m/z* 222 ($M+NH_4^+$, 100%).

Preparation of (±)-1,4-di(1'-acetoxy-2'-chloroethyl)benzene (±)-(118)



Triethylamine (0.69g, 6.8mmol) and acetyl chloride (0.53g, 6.8mmol) were added to a solution of dimethylaminopyridine (0.04g, 0.3mmol) in CH_2Cl_2 (10ml). After 5min a solution of **(±)-(108)** (0.20g, 0.9mmol) in

CH_2Cl_2 (10ml) was added at room temperature. The reaction was left for 22 hours, diluted with CH_2Cl_2 (50ml), and the reaction mixture was washed with 1M HCl (50ml), sat. $NaHCO_3$ (50ml) and sat. NaCl (50ml), dried ($MgSO_4$), and the solvent removed under reduced pressure. The crude product was purified over silica gel with CH_2Cl_2 as the eluent to give **(±)-(118)** as a clear oil (0.10g, 37%); ν_{max}/cm^{-1} 2960, 1745, 1372, 1228, 1112, 1030; δ_H(200MHz; $CDCl_3$) 2.14(D and L enantiomers) and 2.28(*meso*)(6H, s, H-2"), 3.71(2H, dd, J 11.6 and 5.0Hz, H-2'), 3.78(2H, dd, J 11.6 and 7.5Hz, H-2'), 5.93(2H, dd, J 7.5 and 5.0Hz, H-1'), 7.37(4H, s, H-2,3); δ_C(50MHz; $CDCl_3$) 20.92(C-2"), 46.26(C-1'), 74.60(C-2'), 127.05(C-2,3), 137.79(C-1,4), 169.81(C-1"); *m/z* 336 ($M+NH_4^+$, 78%).

APPENDIX A

Crystal Structure Data

A.1 3-Chloro-oxopropyl *p*-toluenesulfonate

A.2 3-Bromo-oxopropyl *p*-toluenesulfonate

A.3 3-Iodo-oxopropyl *p*-toluenesulfonate

A.4 (R,R)-(+)-1,4-di(2'-chloro-1'-hydroxyethyl)benzene

Crystal Structure Data

A.1 3-Chloro-2-oxopropyl *p*-toluenesulfonate (74)

Crystal Data

Empirical Formula	$C_{10}H_{11}ClO_4S$
Colour; Habit	Colourless Prism
Crystal Size (mm)	0.11 x 0.12 x 0.48
Crystal System	Monoclinic
Space Group	$P2_1$
Unit Cell Dimensions	$\underline{a}$ = 10.888(8) Å
	$\underline{b}$ = 5.095(3) Å
	$\underline{c}$ = 10.923(8) Å
	$\underline{\beta}$ = 111.16(5)°
Volume	565.1(7) Å^3
Z	2
Formula Weight	262.7
Density (calc.)	1.544 Mg/m^3
Absorption Coefficient	0.517mm^{-1}
F(100)	272

Data Collection

Diffractometer used	Rigaku AFC6S
Radiation	MoKα (λ = 0.71073 Å)
Temperature (K)	150
Monochromator	Highly oriented graphite crystal
2θ Range	5.0 to 50.0°
Scan Type	2θ-θ
Scan Speed	Variable; 1.60 to 8.00°/min. in ω

Scan Range (ω)	1.20° plus Kα-separation
Background Measurement	Stationary crystal and stationary counter at beginning and at end of scan, each for 25.0% of total scan time
Standard Reflections	3 Measured every 150 reflections
Index Ranges	$0 \leq h \leq 12, 0 \leq k \leq 6, -13 \leq l \leq 13$
Reflections Collected	1185
Independent Reflections	1118 (R_{int} = 2.64%)
Observed Reflections	1021 ($F \geq 4.0\sigma(F)$)
Absorption Correction	N/A

Solution and Refinement

System Used	Siemens SHELXTL PLUS (VMS)
Solution	Direct Methods
Refinement Method	Full-Matrix Least-Squares
Quantity Minimized	$\Sigma w(F_o-F_c)^2$
Absolute Structure	N/A
Extinction Correction	N/A
Hydrogen Atoms	Riding model, fixed isotropic U
Weighting Scheme	$w^{-1} = \sigma^2(F) + 0.0002F^2$
Number of Parameters Refined	148
Final R Indices (obs. data)	R = 3.44%, wR = 4.39%
R Indices (all data)	R = 4.12%, wR = 5.36%
Goodness-of-fit	1.71
Largest and Mean Δ/σ	0.001, 0.000
Data-to-Parameter Ratio	6.9:1
Largest Difference Peak	0.47 eÅ^{-3}
Largest Difference Hole	-0.47 eÅ^{-3}

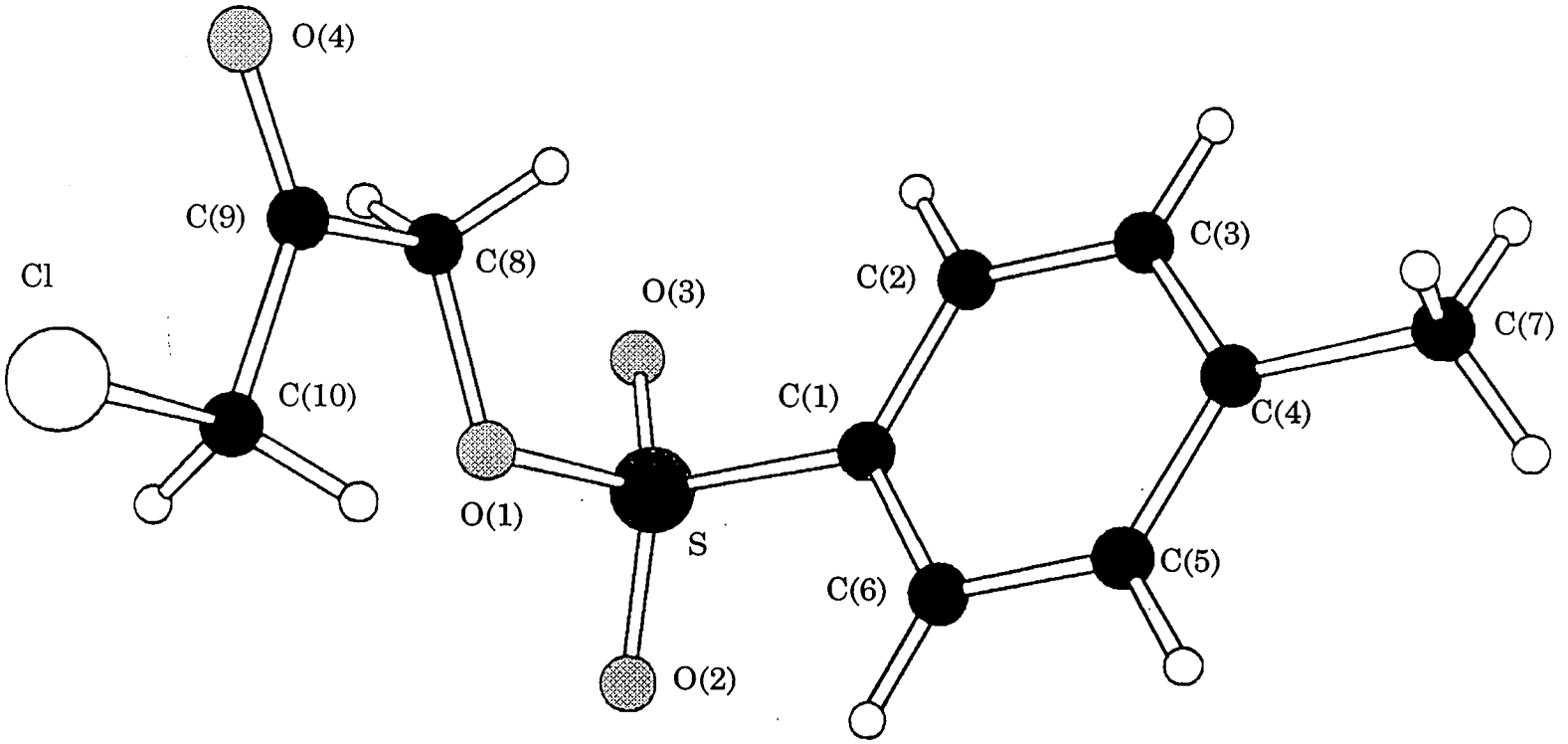


Figure A.1 *Crystal structure of 3-chloro-2-oxopropyl* p-*toluenesulfonate* ***(74)***

Atomic co-ordinates ($x10^4$) and equivalent isotropic displacement coefficients ($Å^2 x10^3$)

	x	y	z	U(eq)
Cl	1719 (1)	2011 (4)	410 (1)	30 (1)
S	2119 (1)	9788	4650 (1)	17 (1)
O(1)	1747 (3)	8040 (7)	3370 (3)	19 (1)
O(2)	2973 (3)	11729 (8)	4446 (3)	22 (1)
O(3)	926 (3)	10572 (8)	4826 (3)	23 (1)
O(4)	-182 (3)	2579 (8)	1743 (3)	27 (1)
C(1)	3005 (4)	7653 (11)	5911 (4)	19 (2)
C(2)	2401 (4)	6539 (11)	6718 (4)	22 (2)
C(3)	3097 (4)	4788 (14)	7672 (4)	26 (2)
C(4)	4374 (5)	4059 (11)	7844 (4)	22 (2)
C(5)	4965 (4)	5214 (10)	7031 (4)	19 (2)
C(6)	4301 (4)	7004 (12)	6076 (4)	21 (2)
C(7)	5105 (5)	2049 (13)	8854 (4)	32 (2)
C(8)	626 (4)	6267 (11)	3076 (4)	23 (2)
C(9)	648 (5)	4271 (11)	2068 (4)	19 (2)
C(10)	1729 (4)	4602 (13)	1503 (4)	24 (2)

Equivalent isotropic U defined as one third of the trace of the orthogonolized U_{ij} tensor

Bond Lengths (Å)

Cl - C(10)	1.777 (6)	S - O(1)	1.582 (3)
S - O(2)	1.429 (4)	S - O(3)	1.437 (4)
S - C(1)	1.747 (5)	O(1) - C(8)	1.458 (6)
O(4) - C(9)	1.206 (6)	C(1) - C(2)	1.396 (7)

C(1) - C(6)	1.395 (6)	C(6) - C(5)	1.377 (6)
C(5) - C(4)	1.401 (8)	C(4) - C(3)	1.385 (7)
C(4) - C(7)	1.505 (7)	C(3) - C(2)	1.373 (7)
C(8) - C(9)	1.506 (8)	C(9) - C(10)	1.523 (8)

Bond Angles (°)

O(1) - S - O(2)	103.0 (2)	O(1) - S - O(3)	108.6 (2)
O(2) - S - O(3)	119.9 (2)	O(1) - S - C(1)	103.8 (2)
O(2) - S - C(1)	110.4 (2)	O(3) - S - C(1)	109.7 (2)
S - O(1) - C(8)	118.0 (3)	S - C(1) - C(6)	119.6 (4)
S - C(1) - C(2)	119.9 (3)	C(6) - C(1) - C(2)	120.4 (4)
C(1) - C(6) - C(5)	119.0 (5)	C(6) - C(5) - C(4)	121.5 (4)
C(5) - C(4) - C(3)	118.0 (4)	C(5) - C(4) - C(7)	120.6 (5)
C(3) - C(4) - C(7)	121.4 (5)	C(4) - C(3) - C(2)	122.0 (5)
C(1) - C(2) - C(3)	119.1 (4)	O(1) - C(8) - C(9)	110.3 (4)
O(4) - C(9) - C(8)	119.3 (5)	O(4) - C(9) - C(10)	124.5 (5)
C(8) - C(9) - C(10)	116.1 (4)	Cl - C(10) - C(9)	111.8 (4)

Anisotropic displacement coefficients ($Å^2x10^3$)

	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
Cl	37 (1)	34 (1)	22 (1)	-1 (1)	12 (1)	-6 (1)
S	16 (1)	21 (1)	16 (1)	0 (1)	7 (1)	0 (1)
O(1)	18 (2)	24 (2)	15 (1)	-3 (2)	7 (1)	0 (1)
O(2)	23 (2)	20 (2)	24 (2)	-4 (2)	11 (1)	-1 (2)
O(3)	19 (2)	31 (2)	24 (2)	7 (2)	12 (1)	3 (2)
O(4)	26 (2)	28 (2)	25 (2)	-7 (2)	9 (1)	0 (2)
C(1)	16 (2)	29 (3)	11 (2)	-5 (2)	4 (2)	-2 (2)
C(2)	15 (2)	29 (3)	22 (2)	-8 (2)	9 (2)	-1 (2)

C(3)	24 (2)	41 (3)	16 (2)	-4 (3)	10 (2)	2 (3)
C(4)	23 (2)	25 (2)	15 (2)	-1 (2)	5 (2)	-4 (2)
C(5)	19 (2)	17 (3)	21 (2)	-2 (2)	7 (2)	-3 (2)
C(6)	17 (2)	30 (3)	18 (2)	-3 (2)	10 (2)	0 (2)
C(7)	40 (3)	36 (3)	22 (2)	-2 (3)	12 (2)	-1 (3)
C(8)	18 (2)	28 (3)	24 (2)	-3 (2)	7 (2)	3 (2)
C(9)	18 (2)	20 (3)	17 (2)	0 (2)	4 (2)	2 (2)
C(10)	26 (2)	29 (3)	19 (2)	-2 (3)	11 (2)	-4 (2)

The anisotropic displacement factor exponent takes the form:

$-2\pi^2(h^2a^{*2}U_{11} + ... + 2hka^*b^*U_{12})$

H-Atom co-ordinates ($x10^4$) and isotropic displacement coefficients ($Å^2x10^3$)

	x	y	z	U
H(2)	1509	6983	6601	25
H(3)	2689	4090	8247	30
H(5)	5855	4764	7143	25
H(6)	4720	7791	5531	25
H(7A)	6018	2491	9272	46 (10)
H(7B)	5027	401	8407	46 (10)
H(7C)	4706	1912	9506	46 (10)
H(8A)	673	5370	3865	30
H(8B)	-175	7261	2748	30
H(10A)	1603	6240	1039	30
H(10B)	2566	4613	2211	30

A.2 3-Bromo-2-oxopropyl *p*-toluenesulfonate (85)

Crystal Data

Empirical Formula	$C_{10}H_{11}BrO_4S$
Colour; Habit	Colourless Plate
Crystal Size (mm)	0.10 x 0.22 x 0.51
Crystal System	Monoclinic
Space Group	$P2_1/n$
Unit Cell Dimensions	$\underline{a}$ = 11.002(2) Å
	$\underline{b}$ = 5.160(2) Å
	$\underline{c}$ = 22.490(3) Å
	$\underline{\beta}$ = 110.48(2)°
Volume	1196.3(3) $Å^3$
Z	4
Formula Weight	307.2
Density (calc.)	1.705 Mg/m^3
Absorption Coefficient	3.606mm^{-1}
F(100)	616

Data Collection

Diffractometer used	Rigaku AFC6S
Radiation	MoKα (λ = 0.71073 Å)
Temperature (K)	293
Monochromator	Highly oriented graphite crystal
2θ Range	5.0 to 50.0°
Scan Type	2θ-θ
Scan Speed	Variable; 2.29 to 16.00°/min. in ω
Scan Range (ω)	1.21° plus Kα-separation

Background Measurement	Stationary crystal and stationary counter at beginning and at end of scan, each for 25.0% of total scan time
Standard Reflections	3 Measured every 150 reflections
Index Ranges	$-14 \leq h \leq 0$, $-6 \leq k \leq 0$, $-27 \leq l \leq 28$
Reflections Collected	2893 (without syst. absences)
Independent Reflections	2752 (R_{int} = 1.77%)
Observed Reflections	1537 ($F \geq 4.0\sigma(F)$)
Absorption Correction	Face-indexed analytical

Solution and Refinement

System Used	Siemens SHELXTL PLUS (VMS)
Solution	Direct Methods
Refinement Method	Full-Matrix Least-Squares
Quantity Minimized	$\Sigma w(F_o-F_c)^2$
Absolute Structure	N/A
Extinction Correction	N/A
Hydrogen Atoms	Riding model, fixed isotropic U
Weighting Scheme	$w^{-1} = \sigma^2(F) + 0.0002F^2$
Number of Parameters Refined	149
Final R Indices (obs. data)	R = 4.00%, wR = 4.34%
R Indices (all data)	R = 10.21%, wR = 4.80%
Goodness-of-fit	1.38
Largest and Mean Δ/σ	0.002, 0.000
Data-to-Parameter Ratio	10.5:1
Largest Difference Peak	0.34 eÅ^{-3}
Largest Difference Hole	-0.36 eÅ^{-3}

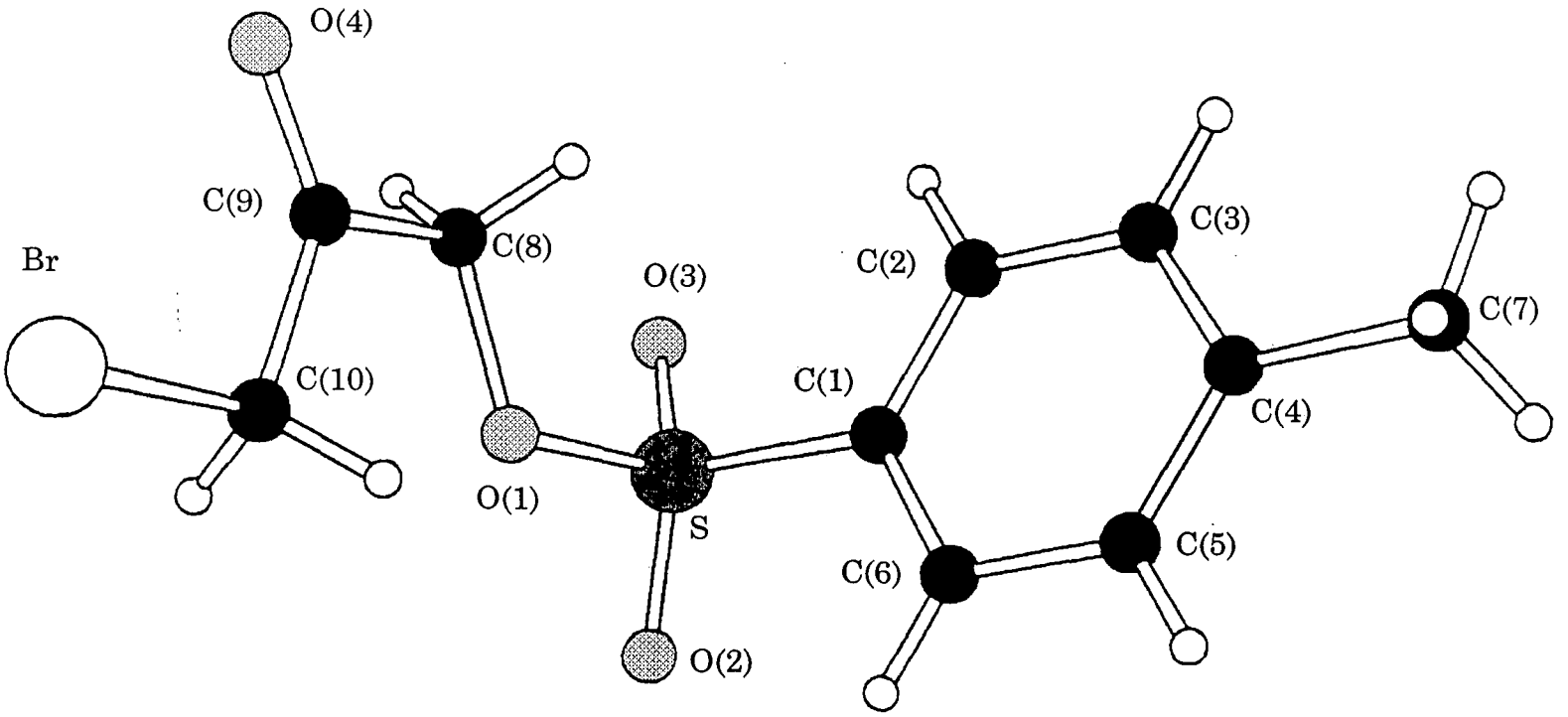


Figure A.2 *Crystal structure of 3-bromo-2-oxopropyl* p-*toluenesulfonate* ***(85)***

Atomic co-ordinates ($x10^4$) and equivalent isotropic displacement coefficients ($Å^2 x10^3$)

	x	y	z	U(eq)
Br	1641 (6)	1985 (1)	196.5 (3)	61.6 (3)
S	2139 (1)	9837 (2)	2327.8 (5)	32.2 (4)
O(1)	1777 (3)	8061 (6)	1712 (1)	34 (1)
O(2)	2996 (3)	11710 (6)	2224 (1)	42 (1)
O(3)	972 (3)	10661 (6)	2413 (1)	41 (1)
O(4)	-188 (3)	2801 (7)	914 (2)	55 (1)
C(1)	2985 (4)	7723 (8)	2941 (2)	30 (2)
C(2)	2356 (5)	6665 (10)	3324 (2)	44 (2)
C(3)	3026 (5)	4939 (11)	3796 (2)	51 (2)
C(4)	4293 (5)	4246 (10)	3892 (2)	41 (2)
C(5)	4904 (4)	5347 (10)	3502 (2)	40 (2)
C(6)	4258 (4)	7083 (9)	3033 (2)	37 (2)
C(7)	4984 (5)	2284 (11)	4389 (3)	63 (2)
C(8)	665 (4)	6367 (9)	1574 (2)	40 (2)
C(9)	656 (4)	4416 (9)	1072 (2)	37 (2)
C(10)	1736 (4)	4634 (9)	810 (2)	43 (2)

Equivalent isotropic U defined as one third of the trace of the orthogonolized U_{ij} tensor

Bond Lengths (Å)

Br - C(10)	1.919 (5)	S - O(1)	1.591 (3)
S - O(2)	1.425 (4)	S - O(3)	1.427 (4)
S - C(1)	1.749 (4)	O(1) - C(8)	1.447 (5)
O(4) - C(9)	1.204 (6)	C(1) - C(2)	1.391 (7)

C(1) - C(6)	1.382 (6)	C(2) - C(3)	1.385 (7)
C(3) - C(4)	1.382 (7)	C(4) - C(5)	1.389 (8)
C(4) - C(7)	1.503 (7)	C(5) - C(6)	1.377 (6)
C(8) - C(9)	1.509 (7)	C(9) - C(10)	1.504 (8)

Bond Angles (°)

O(1) - S - O(2)	103.1 (2)	O(1) - S - O(3)	109.0 (2)
O(2) - S - O(3)	119.8 (2)	O(1) - S - C(1)	103.2 (2)
O(2) - S - C(1)	110.6 (2)	O(3) - S - C(1)	109.6 (2)
S - O(1) - C(8)	118.1 (3)	S - C(1) - C(2)	119.3 (3)
S - C(1) - C(6)	119.9 (4)	C(2) - C(1) - C(6)	120.7 (4)
C(1) - C(2) - C(3)	118.8 (5)	C(2) - C(3) - C(4)	121.5 (5)
C(3) - C(4) - C(5)	118.6 (4)	C(3) - C(4) - C(7)	120.6 (5)
C(5) - C(4) - C(7)	120.8 (5)	C(4) - C(5) - C(6)	120.8 (4)
C(1) - C(6) - C(5)	119.7 (5)	O(1) - C(8) - C(9)	110.3 (4)
O(4) - C(9) - C(8)	119.0 (5)	O(4) - C(9) - C(10)	124.7 (5)
C(8) - C(9) - C(10)	116.3 (4)	Br - C(10) - C(9)	112.1 (3)

Anisotropic displacement coefficients ($Å^2 x 10^3$)

	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
Br	86.6 (5)	56.5 (4)	44.3 (3)	7.9 (3)	26.1 (3)	-6.1 (3)
S	34.8 (6)	30.1 (6)	33.6 (6)	1.1 (5)	14.5 (5)	-0.3 (5)
O(1)	37 (2)	38 (2)	29 (2)	-7 (1)	13 (1)	-5 (1)
O(2)	49 (2)	33 (2)	48 (2)	-7 (2)	20 (2)	1 (2)
O(3)	42 (2)	41 (2)	43 (2)	11 (2)	16 (2)	2 (2)
O(4)	58 (2)	54 (2)	56 (2)	-19 (2)	22 (2)	-12 (2)
C(1)	32 (2)	32 (3)	26 (2)	0 (2)	10 (2)	-3 (2)
C(2)	35 (3)	60 (3)	41 (3)	4 (3)	19 (2)	6 (3)

C(3)	55 (3)	64 (4)	38 (3)	-1 (3)	22 (2)	12 (3)
C(4)	48 (3)	38 (3)	31 (3)	3 (2)	8 (2)	0 (2)
C(5)	32 (2)	47 (3)	40 (3)	7 (2)	9 (2)	2 (2)
C(6)	35 (2)	40 (3)	38 (2)	-1 (2)	17 (2)	-1 (2)
C(7)	72 (4)	62 (4)	51 (3)	17 (3)	18 (3)	17 (3)
C(8)	38 (3)	39 (3)	42 (3)	0 (2)	13 (2)	-5 (2)
C(9)	41 (3)	36 (3)	30 (2)	2 (2)	9 (2)	4 (2)
C(10)	56 (3)	35 (3)	40 (3)	-3 (2)	20 (2)	-5 (2)

The anisotropic displacement factor exponent takes the form:
$-2\pi^2(h^2a^{*2}U_{11} + ... + 2hka^*b^*U_{12})$

H-Atom co-ordinates ($x10^4$) and isotropic displacement coefficients ($Å^2x10^3$)

	x	y	z	U
H(2)	1474	7133	3259	45
H(3)	2600	4189	4062	50
H(5)	5786	4893	3564	62
H(6)	4684	7856	2771	55
H(7A)	4423	1732	4609	109 (14)
H(7B)	5751	3059	4685	109 (14)
H(7C)	5222	815	4191	109 (14)
H(8A)	709	5461	1954	50
H(8B)	-121	7365	1432	50
H(10A)	2551	4493	1154	56
H(10B)	1702	6304	617	56

A.3 3-Iodo-2-oxopropyl *p*-toluenesulfonate (87)

Crystal Data

Empirical Formula	$C_{10}H_{11}IO_4S$
Colour; Habit	Colourless prism
Crystal Size (mm)	0.50 x 0.20 x 0.10mm
Unit Cell Dimensions	$\underline{a}$ = 4.9740 (10) Å
	$\underline{b}$ = 8.344 (2) Å
	$\underline{c}$ = 14.630 (3) Å
	$\underline{\alpha}$ = 96.18 (3)°
	$\underline{\beta}$ = 94.85 (3)°
	$\underline{\gamma}$ = 90.54 (3)°
Volume	601.4 (2) $Å^3$
Z	2
Formula Weight	354.15
Density (calc.)	1.956 Mg/m^3
Absorption Coefficient	2.831 mm^{-1}
F(100)	344

Data Collection

Diffractometer used	Rigaku AFC6S
Radiation	MoKα (λ = 0.71073 Å)
Temperature (K)	150
Monochromator	Highly oriented graphite crystal
2θ Range	2.69 to 27.49°
Scan Type	2θ-θ

Background Measurement	Stationary crystal and stationary counter at beginning and at end of scan, each for 25.0% of total scan time
Standard Reflections	3 Measured every 150 reflections
Index Ranges	$-6 \leq h \leq 6, 0 \leq k \leq 10, -18 \leq l \leq 18$
Reflections Collected	2963
Independant Reflections	2773 (R_{int} = 0.0056%)
Absorption Correction	N/A

Solution and Refinement

System Used	Siemens SHELXTL PLUS (VMS)
Solution	Direct Methods
Refinement Method	Full-Matrix Least-Squares
Quantity Minimized	$\Sigma w(F_o-F_c)^2$
Absolute Structure	N/A
Extinction Correction	N/A
Hydrogen Atoms	Riding model, fixed isotropic U
Weighting Scheme	$w^{-1} = \sigma^2(F) + 0.0002F^2$
Number of Parameters Refined	146
Final R Indices (obs. data)	R1 = 0.0156, wR2 = 0.0376
R Indices (all data)	R1 = 0.0176, wR2 = 0.0381%
Goodness-of-fit	1.089
Largest Difference Peak	0.367 eÅ^{-3}
Largest Difference Hole	-0.520 eÅ^{-3}

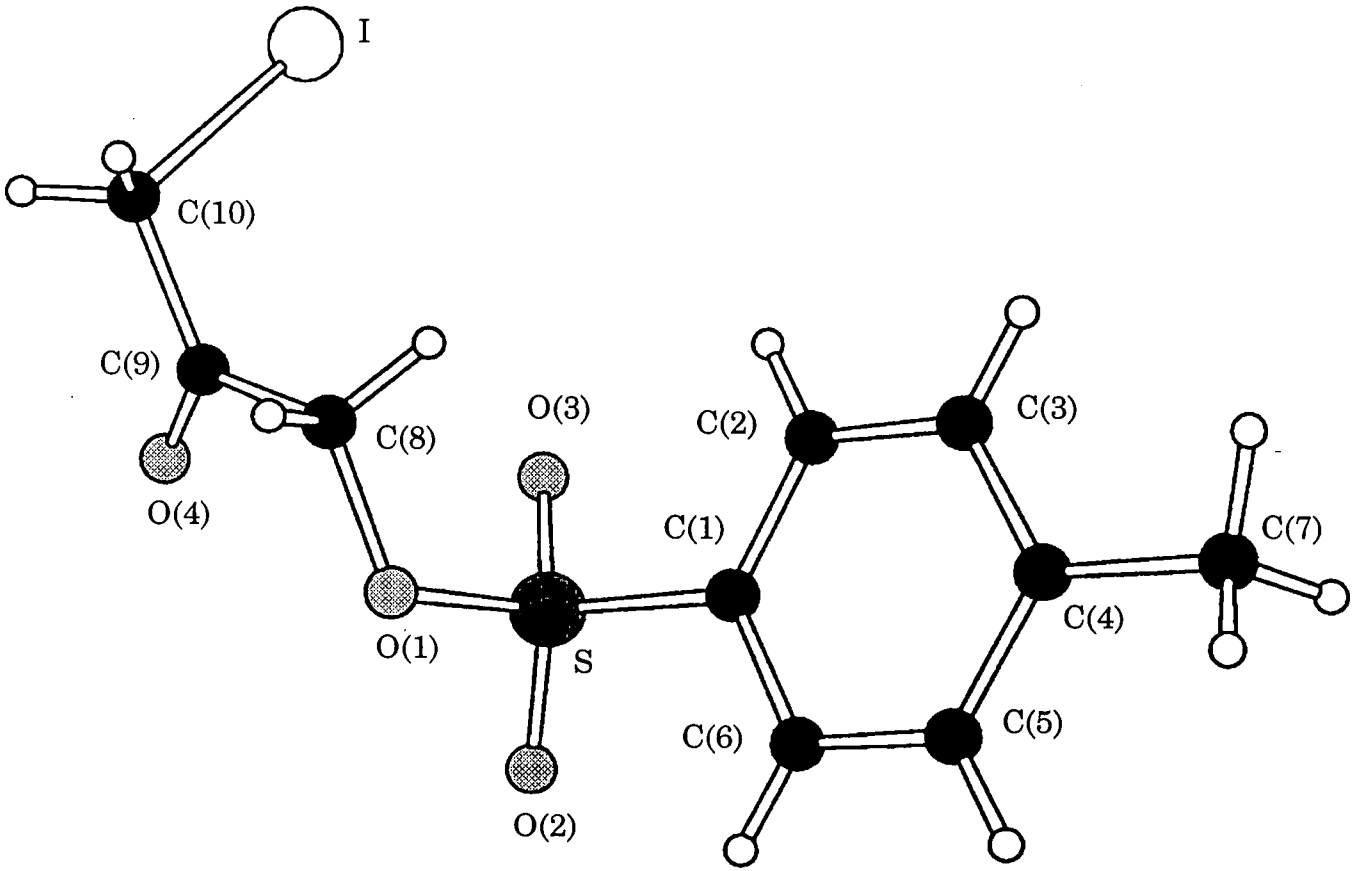


Figure A.3 *Crystal structure of 3-iodo-2-oxopropyl* p-*toluenesulfonate* ***(87)***

Atomic co-ordinates ($x10^4$) and equivalent isotropic displacement coefficients ($Å^2x10^3$)

	x	y	z	U(eq)
I	2250 (1)	7130 (1)	4733 (1)	27 (1)
S	59 (1)	5730 (1)	7924 (1)	17 (1)
O(1)	1978 (2)	7291 (1)	8052 (1)	21 (1)
O(2)	-1786 (3)	6062 (2)	8613 (1)	25 (1)
O(3)	-901 (3)	5425 (2)	6969 (1)	23 (1)
O(4)	-461 (3)	9111 (2)	6795 (1)	26 (1)
C(1)	2223 (3)	4181 (2)	8223 (1)	17 (1)
C(2)	3518 (4)	3264 (2)	7544 (1)	20 (1)
C(3)	5351 (4)	2117 (2)	7809 (1)	22 (1)
C(4)	5885 (3)	1864 (2)	8734 (1)	21 (1)
C(5)	4535 (4)	2793 (2)	9397 (1)	22 (1)
C(6)	2724 (4)	3956 (2)	9149 (1)	21 (1)
C(7)	7881 (4)	628 (2)	9029 (2)	31 (1)
C(8)	3429 (3)	7638 (2)	7285 (1)	21 (1)
C(9)	1776 (3)	8646 (2)	6647 (1)	19 (1)
C(10)	3157 (4)	9054 (2)	5826 (1)	23 (1)

Equivalent isotropic U defined as one third of the trace of the orthogonolized U_{ij} tensor

Bond Lengths (Å)

I - C(10)	2.156 (2)	S - O(1)	1.5926 (14)
S - O(2)	1.4265 (13)	S - O(3)	1.4341 (13)
S - C(1)	1.757 (2)	O(1) - C(8)	1.438 (2)
O(4) - C(9)	1.211 (2)	C(1) - C(2)	1.392 (2)

C(1) - C(6)	1.390 (2)	C(2) - C(3)	1.390 (2)
C(3) - C(4)	1.396 (2)	C(4) - C(5)	1.397 (3)
C(4) - C(7)	1.509 (2)	C(5) - C(6)	1.386 (2)
C(8) - C(9)	1.519 (2)	C(9) - C(10)	1.502 (2)

Bond Angles (°)

O(1) - S - O(2)	103.53 (8)	O(1) - S - O(3)	108.34 (8)
O(2) - S - O(3)	120.57 (8)	O(1) - S - C(1)	103.74 (7)
O(2) - S - C(1)	109.85 (8)	O(3) - S - C(1)	109.38 (8)
S - O(1) - C(8)	118.01 (11)	S - C(1) - C(2)	120.16 (13)
S - C(1) - C(6)	118.68 (13)	C(2) - C(1) - C(6)	121.1 (2)
C(1) - C(2) - C(3)	118.8 (2)	C(2) - C(3) - C(4)	121.3 (2)
C(3) - C(4) - C(5)	118.5 (2)	C(3) - C(4) - C(7)	121.7 (2)
C(5) - C(4) - C(7)	119.8 (2)	C(4) - C(5) - C(6)	121.1 (2)
C(1) - C(6) - C(5)	119.2 (2)	O(1) - C(8) - C(9)	111.57 (14)
O(4) - C(9) - C(8)	122.8 (2)	O(4) - C(9) - C(10)	122.4 (2)
C(8) - C(9) - C(10)	114.7 (2)	Cl - C(10) - C(9)	107.50 (11)

Anisotropic displacement coefficients ($Å^2 x 10^3$)

	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
I	33 (1)	26 (1)	23 (1)	1 (1)	3 (1)	-1 (1)
S	17 (1)	18 (1)	18 (1)	3 (1)	2 (1)	2 (1)
O(1)	24 (1)	19 (1)	19 (1)	2 (1)	2 (1)	-2 (1)
O(2)	23 (1)	29 (1)	26 (1)	5 (1)	9 (1)	6 (1)
O(3)	24 (1)	24 (1)	20 (1)	2 (1)	-3 (1)	1 (1)
O(4)	21 (1)	26 (1)	32 (1)	6 (1)	4 (1)	6 (1)
C(1)	16 (1)	17 (1)	19 (1)	3 (1)	2 (1)	0 (1)
C(2)	24 (1)	21 (1)	16 (1)	1 (1)	1 (1)	1 (1)

C(3)	24 (1)	19 (1)	21 (1)	-2 (1)	3 (1)	2 (1)
C(4)	19 (1)	18 (1)	26 (1)	4 (1)	-1 (1)	0 (1)
C(5)	26 (1)	24 (1)	18 (1)	6 (1)	1 (1)	-1 (1)
C(6)	23 (1)	23 (1)	19 (1)	3 (1)	5 (1)	2 (1)
C(7)	34 (1)	24 (1)	34 (1)	6 (1)	-3 (1)	7 (1)
C(8)	18 (1)	23 (1)	24 (1)	7 (1)	3 (1)	1 (1)
C(9)	20 (1)	16 (1)	22 (1)	2 (1)	0 (1)	-2 (1)
C(10)	24 (1)	23 (1)	22 (1)	4 (1)	2 (1)	-3 (1)

The anisotropic displacement factor exponent takes the form:
$-2\pi^2(h^2a^{*2}U_{11} + ... + 2hka^*b^*U_{12})$

H-Atom co-ordinates ($x10^4$) and isotropic displacement coefficients ($Å^2x10^3$)

	x	y	z	U(eq)
H(2)	3155 (4)	3418 (2)	6912 (1)	30
H(3)	6257 (4)	1494 (2)	7351 (1)	32
H(5)	4862 (4)	2624 (2)	10028 (1)	34
H(6)	1836 (4)	4591 (2)	9606 (1)	32
H(7A)	6914 (5)	-371 (7)	9106 (11)	46
H(7B)	8871 (23)	1043 (8)	9616 (6)	46
H(7C)	9154 (20)	410 (14)	8557 (5)	46
H(8A)	3900 (3)	6613 (1)	6933 (1)	31
H(8B)	5130 (3)	8224 (2)	7519 (1)	31
H(10A)	5131 (4)	9158 (2)	5982 (1)	35
H(10B)	2495 (4)	10089 (2)	5629 (1)	35

A.4 (R,R)-(+)-1,4-di(2'-chloro-1'-hydroxyethyl)benzene (R,R)-(108)

Crystal Data

Empirical Formula	$C_{10}H_{12}Cl_2O_2$
Colour; Habit	Colourless prism
Unit Cell Dimensions	$\underline{a}$ = 4.8100 (10) Å
	$\underline{b}$ = 9.212 (2) Å
	$\underline{c}$ = 24.028 (5) Å
	$\underline{\alpha}$ = 90.0°
	$\underline{\beta}$ = 90.0°
	$\underline{\gamma}$ = 90.0°
Volume	1064.7 (4) $Å^3$
Z	4
Formula Weight	235.10
Density (calc.)	1.467 Mg/m^3
Absorption Coefficient	0.580 mm^{-1}
F(100)	488

Data Collection

Diffractometer used	Rigaku AFC6S
Radiation	MoKα (λ = 0.71073 Å)
Temperature (K)	293(2)
Monochromator	Highly oriented graphite crystal
2θ Range	2.79 to 52.00°
Scan Type	2θ-θ

Background Measurement	Stationary crystal and stationary counter at beginning and at end of scan, each for 25.0% of total scan time
Standard Reflections	3 Measured every 150 reflections
Index Ranges	$-6 \leq h \leq 0$, $-12 \leq k \leq 0$, $0 \leq l \leq 31$
Reflections Collected	3148
Independant Reflections	1576 (R_{int} = 0.0331)
Absorption Correction	N/A

Solution and Refinement

System Used	Siemens SHELXTL PLUS (VMS)
Solution	Direct Methods
Refinement Method	Full-Matrix Least-Squares
Quantity Minimized	$\Sigma w(F_o-F_c)^2$
Absolute Structure	N/A
Extinction Correction	N/A
Hydrogen Atoms	Riding model, fixed isotropic U
Weighting Scheme	$w^{-1} = \sigma^2(F) + 0.0002F^2$
Number of Parameters Refined	137
Final R Indices (obs. data)	R1 = 0.0351, wR2 = 0.0793
R Indices (all data)	R1 = 0.0687, wR2 = 0.1123%
Goodness-of-fit	1.074
Largest Difference Peak	0.212 eÅ^{-3}
Largest Difference Hole	-0.227 eÅ^{-3}

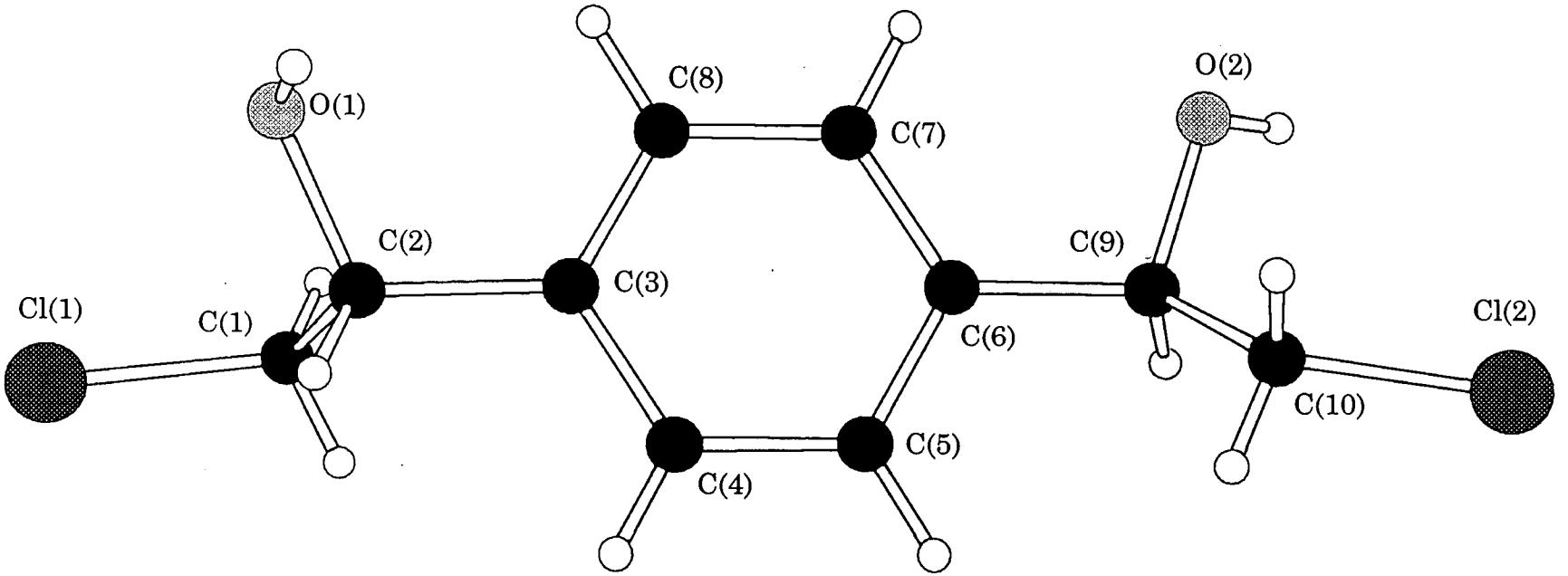


Figure A.4 *Crystal structure of (R,R)-(+)-1,4-di(2'-chloro-1'-hydroxyethyl)benzene* ***(R,R)-(108)***

Atomic co-ordinates ($x10^4$) and equivalent isotropic displacement coefficients ($Å^2x10^3$)

	x	y	z	U(eq)
Cl(1)	14998 (2)	-878 (1)	-3471 (1)	57 (1)
Cl(2)	4963 (2)	702 (1)	444 (1)	50 (1)
O(1)	16220 (5)	-2100 (3)	-2333 (1)	52 (1)
O(2)	6350 (5)	-2057 (2)	-261 (1)	41 (1)
C(1)	12854 (7)	-959 (4)	-2875 (1)	46 (1)
C(2)	14472 (6)	-876 (3)	-2342 (1)	36 (1)
C(3)	12506 (6)	-832 (3)	-1850 (1)	34 (1)
C(4)	11301 (7)	459 (3)	-1694 (1)	40 (1)
C(5)	9399 (7)	505 (3)	-1265 (1)	40 (1)
C(6)	8692 (6)	-735 (3)	-975 (1)	32 (1)
C(7)	9916 (7)	-2028 (3)	-1130 (1)	35 (1)
C(8)	11799 (7)	-2077 (3)	-1565 (1)	38 (1)
C(9)	6605 (6)	-670 (3)	-503 (1)	32 (1)
C(10)	7560 (8)	411 (4)	-74 (1)	48 (1)

Equivalent isotropic U defined as one third of the trace of the orthogonolized U_{ij} tensor

Bond Lengths (Å)

Cl(1) - C(1)	1.767 (3)	Cl(2) - C(10)	1.783 (3)
O(1) - C(2)	1.406 (4)	O(1) - H(1)	0.82
O(2) - C(9)	1.409 (3)	O(2) - H(2)	0.82
C(1) - C(2)	1.500 (4)	C(1) - H(11)	0.91 (2)
C(1) - H(12)	0.91 (2)	C(2) - C(3)	1.515 (4)
C(2) - H(21)	0.97 (3)	C(3) - C(4)	1.375 (4)

C(3) - C(8)	1.378 (4)	C(4) - C(5)	1.379 (4)
C(4) - H(41)	0.91 (3)	C(5) - C(6)	1.382 (4)
C(5) - H(51)	0.94 (3)	C(6) - C(7)	1.380 (4)
C(6) - C(9)	1.516 (4)	C(7) - C(8)	1.384 (4)
C(7) - H(71)	0.95 (3)	C(8) - H(81)	0.95 (3)
C(9) - C(10)	1.504 (4)	C(9) - H(91)	0.93 (3)
C(10) - H(101)	0.88 (2)	C(10) - H(102)	0.88 (2)

Bond Angles (°)

C(2) - O(1) - H(1)	109.5 (2)	C(9) - O(2) - H(2)	109.47 (14)
C(2) - C(1) - Cl(1)	112.8 (2)	C(2) - C(1) - H(11)	109.0 (2)
Cl(1) - C(1) - H(11)	109.04 (12)	C(2) - C(1) - H(12)	109.0 (2)
Cl(1) - C(1) - H(12)	109.04 (12)	H(11) - C(1) - H(12)	107.8
O(1) - C(2) - C(1)	0.6.4 (2)	O(1) - C(2) - C(3)	112.5 (2)
C(1) - C(2) - C(3)	110.1 (2)	O(1) - C(2) - H(21)	109.3 (2)
C(1) - C(2) - H(21)	109.3 (2)	C(3) - C(2) - H(21)	109.2 (2)
C(4) - C(3) - C(8)	118.7 (3)	C(4) - C(3) - C(2)	119.9 (3)
C(8) - C(3) - C(2)	121.3 (3)	C(3) - C(4) - C(5)	120.6 (3)
C(3) - C(4) - H(41)	119.7 (2)	C(5) - C(4) - H(41)	119.7 (2)
C(4) - C(5) - C(6)	121.1 (3)	C(4) - C(5) - H(51)	119.5 (2)
C(6) - C(5) - H(51)	119.5 (2)	C(7) - C(6) - C(5)	118.1 (2)
C(7) - C(6) - C(9)	121.3 (2)	C(5) - C(6) - C(9)	120.6 (2)
C(6) - C(7) - C(8)	120.8 (2)	C(6) - C(7) - H(71)	119.6 (2)
C(8) - C(7) - H(71)	119.6 (2)	C(3) - C(8) - C(7)	120.7 (3)
C(3) - C(8) - H(81)	119.7 (2)	C(7) - C(8) - H(81)	119.7 (2)
O(2) - C(9) - C(10)	110.2 (2)	O(2) - C(9) - C(6)	109.3 (2)
C(10) - C(9) - C(6)	109.6 (2)	O(2) - C(9) - H(91)	109.2 (2)
C(10) - C(9) - H(91)	109.2 (2)	C(6) - C(9) - H(91)	109.24 (14)
C(9) - C(10) - Cl(2)	111.3 (2)	C(9) - C(10) - H(101)	109.4 (2)
Cl(2) - C(10) - H(101)	109.37 (11)	C(9) - C(10) - H(102)	109.4 (2)

Cl(2) - C(10) - H(102) 109.37 (12) H(101) - C(10) - H(102) 108.0

Anisotropic displacement coefficients ($Å^2x10^3$)

	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
Cl(1)	67 (1)	71 (1)	33 (1)	1 (1)	5 (1)	-8 (1)
Cl(2)	61 (1)	48 (1)	42 (1)	-5 (1)	11 (1)	4 (1)
O(1)	47 (1)	71 (1)	39 (1)	-5 (1)	0 (1)	20 (1)
O(2)	37 (1)	39 (1)	46 (1)	11 (1)	10 (1)	-1 (1)
C(1)	39 (2)	61 (2)	38 (2)	0 (2)	1 (1)	-1 (2)
C(2)	32 (2)	42 (1)	33 (1)	-3 (1)	0 (1)	-2 (2)
C(3)	30 (1)	40 (2)	31 (1)	0 (1)	-2 (1)	2 (2)
C(4)	46 (2)	32 (1)	41 (2)	8 (1)	8 (2)	-1 (2)
C(5)	48 (2)	29 (1)	42 (2)	5 (1)	7 (1)	8 (1)
C(6)	31 (1)	33 (1)	31 (1)	2 (1)	-3 (1)	1 (1)
C(7)	44 (2)	29 (1)	33 (1)	3 (1)	2 (2)	1 (2)
C(8)	42 (2)	32 (1)	40 (2)	-1 (1)	1 (1)	5 (2)
C(9)	29 (1)	34 (1)	33 (1)	2 (1)	-1 (1)	1 (1)
C(10)	47 (2)	51 (2)	45 (2)	-8 (2)	10 (2)	-13 (2)

The anisotropic displacement factor exponent takes the form:
$-2\pi^2(h^2a^{*2}U_{11} + ... + 2hka^*b^*U_{12})$

H-Atom co-ordinates ($x10^4$) and isotropic displacement coefficients ($Å^2x10^3$)

	x	y	z	U(eq)
H(1)	17354 (19)	-2016 (18)	-2081 (10)	50
H(2)	4765 (21)	-2164 (14)	-142 (12)	50

H(11)	11618	(31)	-214	(18)	-2886	(1)	50
H(12)	11873	(25)	-1802	(20)	-2881	(1)	50
H(21)	15603	(40)	-2	(31)	-2344	(1)	50
H(41)	11766	(18)	1295	(30)	-1877	(7)	50
H(51)	8566	(30)	1398	(32)	-1169	(4)	50
H(71)	9461	(16)	-2894	(28)	-937	(6)	50
H(81)	12616	(29)	-2981	(31)	-1669	(4)	50
H(91)	4895	(64)	-384	(11)	-642	(5)	50
H(101)	7951	(14)	1243	(21)	-239	(4)	50
H(102)	9095	(40)	89	(8)	86	(4)	50

APPENDIX B

Conferences, Presentations and Publications

Conferences, Presentations and Publications

B.1 Colloquia, Lectures and Seminars from Invited Speakers

1991

October 17 Dr. J.A. Salthouse, University of Manchester
Son et Lumiere - a demonstration lecture.

October 31 Dr. R. Keely, Metropolitan Police Forensic Science
Modern Forensic Science.

November 7 Dr. A.R. Butler, St. Andrews University
Traditional Chinese Herbal Drugs.

November 13 Prof. D. Gani, St. Andrews University
The Chemistry of PLP Dependant Enzymes.

November 20 Dr. R. More O'Ferrall, Dublin
Some Acid-Catalysed Rearrangements in Organic Chemistry.

December 4 Prof. R. Grigg, Leeds University
Palladium Catalysed Cyclisation and Ion Capture Processes.

1992

January 29 Dr. A. Holmes, University of Cambridge
Cycloaddition Reactions in the Service of the Synthesis of Piperidine and indolizidine Natural Products.

January 30	Dr. M. Anderson, Sittingbourne Research Centre, Shell Research *Recent Advances in the Safe and Selective Chemical Control of Insect Pests.*
February 13	Dr. J. Saunders, Glaxo Group Research Limited *Molecular Modelling in Drug Discovery.*
February 19	Prof. E.J. Thomas, University of Manchester *Application of Organo-Stannanes to Organic Synthesis.*
February 20	Prof. E. Vogel, University of Cologne *The Musgrave Lecture: Porrphyrins, Molecules of Interdisciplinary Interest.*
February 25	Prof J.F. Nixon, University of Sussex *Phosphoalkylenes, New Building Blocks in Inorganic and Organometallic Chemistry.*
March 11	Dr. S.E. Thomas, Imperial College London *Recent Advances in Organoiron Chemistry.*
March 12	Dr. R.A. Hann, ICI Image Data *Electronic Photography - An Image of the Future.*
March 18	Dr. H. Maskill, University of Newcastle *Concerted or Stepwise Fragmentation in a Deamination-type Reaction.*
October 20	Dr. H.E. Bryndza, Du Pont Central Research *Synthesis, Reactions and Thermochemistry of Metal (Alkyl) Cyanide Complexes and Their Impact on Olefin Hydrocyanation Catalysis*
October 22	Prof. A. Davies, University College London *The Ingold-Albert Lecture: The Behaviour of Hydrogen as a Pseudometal*
November 5	Dr C.J. Ludman, University of Durham *Explosions, A Demonstration Lecture.*

November 11 Prof. D. Robins, Glasgow University
Pyrrolizidine Alkaloids: Biological Activity, Biosynthesis and Benefits.

November 25 Prof Y. Vallee, University of Caen
Reactive Thiocarbonyl Compounds.

November 26 Dr D. Humber, Glaxo, Greenford
AIDS - The Development of a Novel Series of Inhibitors of HIV

1993

January 21 Prof L. Hall, Cambridge
NMR - Window to the Human Body.

February 3 Prof. S.M. Roberts, University of Exeter
Enzymes in Organic Synthesis.

February 11 Prof. S. Knox, Bristol University
The Tilden Lecture: Organic Chemistry at Polynuclear Metal Centres.

March 17 Dr. R.J.K. Taylor, University of East Anglia
Adventures in Natural Product Synthesis.

March 24 Prof. I.O. Sutherland, University of Liverpool
Chromogenic Reagents for Cations.

June 1 Prof. J.P. Konopelski, University of California, Santa Cruz
Synthetic Adventures with Enantiomerically Pure Acetals.

October 20 Dr. P. Quayle, University of Manchester
Aspects of Aqueous ROMP Chemistry.

December 1 Prof. M.A. McKervey, Queens University, Belfast
Functionalised Calixarenes.

1994

February 9	Prof. D. Young, University of Sussex, *Chemical and Biological Studies on the Coenzyme Tetrahydrofolic Acid.*
February 16	Prof. K.H. Theopold, University of Delaware, U.S.A. *Paramagnetic Chromium Alkyls: Synthesis and Reactivity.*
March 10	Prof. S.V. Ley, University of Cambridge *New Methods for Organic Synthesis.*
April 28	Prof. R.J. Gillespie, McMaster University, Canada *The Molecular Structure of some Metal Fluorides and Oxofluorides: Apparent Exceptions to the VSEPR Model.*

B.2 Research Conferences Attended

December 1991	Stereochemistry in Sheffield, University of Sheffield
April 1992	North East Universities Postgraduate Chemistry Symposium, University of Newcastle
December 1992	Stereochemistry in Sheffield, University of Sheffield
April 1993	North East Universities Postgraduate Chemistry Symposium, University of Newcastle
May-June 1993	Postgraduate Chemistry Seminars, University of Durham
December 1993	Stereochemistry in Sheffield, University of Sheffield
March 1994	Postgraduate Chemistry Symposium, Herriot-Watt University
April 1994	North East Universities Postgraduate Chemistry Symposium, University of Northumbria
May-June 1994	Postgraduate Chemistry Seminars, University of Durham
December 1994	Postgraduate Bio-organic Chemistry Symposium, University of Durham

B.3 Seminars, Colloquia and Poster Presentations Given

December 1993	ICI/Zeneca Postgraduate Chemistry Poster Competition, University of Durham
March 1994	Postgraduate Chemistry Symposium, Herriot-Watt University
May 1994	Postgraduate Chemistry Seminar, University of Durham

B.4 Papers published

'Efficient Routes To Isotopically Labelled Epichlorohydrins' - David O'Hagan, Jeffrey White and David Jones, *J. Labelled Compd. Radiopharm.*, 1994, **34,** 871

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APPENDIX C

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