SYNTHESIS OF NOVEL CYCLIC MONOMERS FOR HYDROGEL POLYMERS.

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SUMMARY.

The aim of the project was to synthesise hydrophilic derivatives of 1,2-dihydroxy-3,5-cyclohexadiene (DHCD) and to copolymerise these derivatives with 2-hydroxyethyl methacrylate (HEMA), to give a completely new range of hydrogel materials. It was thought that hydrogels incorporating hydrophilic derivatives of DHCD could have good mechanical properties and good water binding ability.

A model compound for *cis*-DHCD was sought, as *cis*-DHCD was expensive and stable under only a narrow range of conditions. Catechol was found to be an excellent model for *cis*-DHCD, as ^{1}H NMR spectroscopy indicated that both compounds contained eclipsed hydroxy groups and flat rings. A number of catechol derivatives were prepared in good yield, under non-acidic conditions at room temperature.

The limited availabilty of *cis*-DHCD led to an investigation into synthesising hydrophilic derivatives of both *cis* and *trans*-DHCD indirectly. Hydrophobic derivatives were easily prepared by indirect routes, but it was found that hydrophilic derivatives were considerably more difficult to synthesise. A number of novel routes to both *cis* and *trans*-DHCD were also explored.

Copolymerisation of diacetate, dimethylcarbonate and dipivalate derivatives of *cis*-DHCD with HEMA, to form a hitherto unknown group of hydrogels, is reported. Hydrogels containing these monomers showed significant improvements in both tensile strength and Youngs modulus, at both equivalent composition and water content, over the corresponding HEMA / styrene and HEMA / methyl methacrylate analogues. It was observed that derivatives of *trans*-DHCD polymerise with difficulty. ^{1}H NMR studies indicated that both faces of the ring were shielded by the pendant groups thereby preventing efficient polymerisation of the *trans* monomers.

Keywords: **Cyclic Monomer, 1,2-Dihydroxy-3,5-cyclohexadiene, HEMA Copolymers, Hydrogel, Mechanical Properties**

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CONTENTS.

LIST OF FIGURES.

LIST OF SCHEMES.

LIST OF TABLES.

LIST OF ABBREVIATIONS.

AC	Adiabatic Calorimetry
Ac	Acetyl Group
AIBN	Azobisisobutyronitrile
Ar	Aromatic
ax	Axial
br	Broad
9-BBN	9-Borabicyclo[3.3.1]nonane
BSA	Bis(trimethylsilyl)acetamide
BSTFA	Bis(trimethylsilyl)trifluoroacetamide
CM	Cyclic Monomer
d (NMR)	Doublet
DBU	1,8-Diazabicyclo[5.4.0.]undec-7-ene
dd (NMR)	Double Doublet
DEGDMA	Diethylene Glycol Dimethacrylate
DHCD	1,2-Dihydroxy-3,5-cyclohexadiene
dm (NMR)	Double Multiplet
DMAP	4-Dimethylaminopyridine
DSC	Differential Scanning Calorimetry
dt	Double Triplet
DTA	Differential Thermal Analysis
δ	Chemical Shift / ppm
E	Youngs Modulus
eq	Equatorial
ε_b	Elongation To Break
EDMA	Ethylene Glycol Dimethacrylate
EWC	Equilibrium Water Content

FGI	Functional Group Interconversion
HEMA	2-Hydroxyethyl Methacrylate
HMPA	Hexamethylphosphoramide
IPN	Interpenetrating Polymer Network
J (NMR)	Coupling Constant
m (IR)	Medium
m (NMR)	Multiplet
m-CPBA	*m*-Chloroperoxybenzoic Acid
NADH	Nicotinamide Adenine Dinucleotide
NBS	*N*-Bromosuccinamide
NVP	N-Vinyl Pyrrolidone
PTC	Phase Transfer Catalysis
q (NMR)	Quartet
s (IR)	Strong
s (NMR)	Singlet
σ_b	Tensile Strength
TBDMS	*tert*-Butyldimethylsilyl Group
TEGDMA	Tetraethylene Glycol Dimethacrylate
TLC	Thin Layer Chromatography
TMS	Trimethylsilyl Group
UV	Ultra Violet
-ve (NMR)	Negative Peak
+ve (NMR)	Positive Peak
v/v	Volume / Volume
w (IR)	Weak
w/v	Weight / Volume
w/w	Weight / Weight

Chapter 1: Introduction.

1. INTRODUCTION.

1.1 GENERAL INTRODUCTION.

The use of hydrogels, based on poly (2-hydroxyethyl methacrylate) (poly HEMA), as biomaterials, was first suggested by Wichterle[1-3] in 1961. Much research has been done into the modification of existing hydrogel materials but one of the problems originally associated with them, that of obtaining gels which have a high water content and also exhibit good mechanical properties, remains largely unsolved. A variety of monomers have been used in the preparation of hydrogels but the vast majority of these are simply modifications of acrylic and methacrylic esters and amides. This leaves ample scope for the development of entirely new hydrogel systems based on hydrophilic monomers with completely different structures.[4-17] 2-Hydroxyethyl methacrylate (HEMA) is still the principal hydrophilic monomer used in the majority of hydrogels; poly HEMA is almost the sole hydrogel material employed in many biomedical applications,[8,10] e.g. prostheses, ocular surgery, suture coatings, artificial organs, and drug delivery systems.

Experimentation with the widest variety of monomers, for the development of new hydrogel systems, has been most intensive in the contact lens field, due to the ease of clinical investigation in the eye compared with those in other biomedical applications. Another factor which has made the contact lens system a useful exploratory one is that the problems of biocompatibility encountered in the eye are slight in comparison with those applications which involve blood contact.[13-16] The compound 1,2-dihydroxy-3,5-cyclohexadiene (DHCD) has the potential to be the basis for a whole new area of hydrogel materials, as it contains a polymerisable 1,3-diene group in addition to the two hydroxy groups. These hydroxy groups can be converted, by a number of well established processes, to a wide variety of derivatives.[18-20]

The copolymerisation of hydrophilic derivatives of DHCD into poly HEMA hydrogel networks would be expected to decrease the rotational mobility of the polymer chains, compared with poly HEMA itself, due to the larger steric interaction between pendant groups. These hydrogels could have good mechanical properties and a high to moderate water content. Hydrogels exhibiting these charateristics have been sought since the emergence of hydrogels as important biomaterials.

1.2 HYDROGELS.

Hydrogels can be most usefully described as water swollen polymer networks of either natural or synthetic origin. They are characterised by their hydrophilicity and insolubility in water. The hydrophilicity results from the presence of such groups as OH, $CONH_2$, CONHR, $CONR_2$, COOH and SO_3H, whereas the insolubility of the polymers and their retention of shape, when swollen in water to their equilibrium volume, can be accounted for by the presence of a three dimensional network.

A balance between cohesive forces, which allow water to penetrate the network (usually covalent crosslinking but which can also be electrostatic, dipole-dipole or hydrophobic), and the dispersing forces, which act on the hydrated parts of the polymer chains, produces a stable swollen state.

1.2.1 Preparation of Hydrogels.

Polymerisation of the constituent monomers of a hydrogel polymer may be initiated by chemical means (using radical or anionic initiators), UV irradiation in the presence of a photosensitive chemical, or by ionising radiation (usually γ-rays).[21]

The three dimensional network present in hydrogels may be formed by either simultaneous crosslinking / copolymerisation (usually copolymerisation of a divinyl monomer with the constituent monomers), or by the crosslinking of the linear polymer in solution. The latter

method involves either condensing the hydrophilic groups in the polymer (usually OH) with a suitable crosslinking agent, such as dicarboxylic acids or aldehydes,[21,22] or by irradiating the solution with ionising radiation (usually γ-rays) thereby generating radicals which then combine to form a crosslinked network.[21]

1.2.2 Network Structure.[21]

An ideal non crystalline network is considered to be a collection of random chains between multifunctional cross links. In the non-swollen state the chains may be:

i) in a natural, unstrained state
ii) supercoiled
iii) expanded, due to swelling in a mixture of residual monomers.

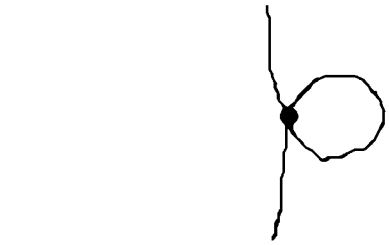
Real networks contain a number of defects resulting in non-random networks. Among the defects are:

i) Pre-existing order: such as crystallites, association of similar groups, artificially oriented chains (resulting in micellar and globular ordering), and segments oriented in a non-random manner. These are all fixed when crosslinking occurs.

ii) Network defects: are caused by the presence of loops, entanglements and unreacted functional groups, see Figure 1.1.

iii) Phase separation: this occurs when the quantity of solvent in the gel exceeds the maximum swelling capacity and manifests itself as either macrosyneresis or microsyneresis. Microsyneresis occurs more readily in lightly crosslinked networks, due to the slowness of the relaxation of the whole network in comparison to the rate of phase separation in local regions within the gel and depends on the chains being mobile.

Macrosyneresis is expected to occur more readily in more heavily crosslinked networks, due to the reduction in the mobility of the polymer chains.[23]



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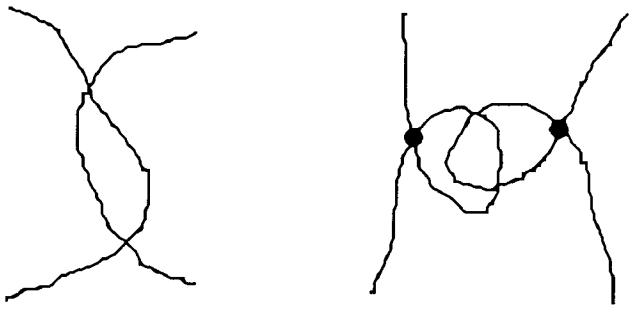

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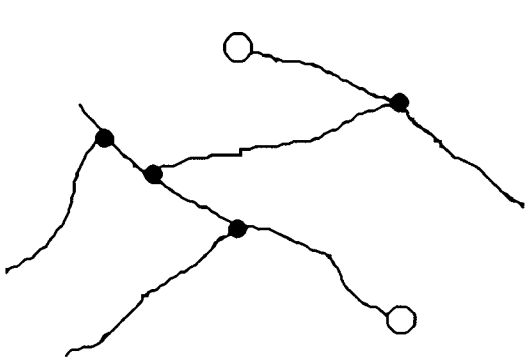


UNREACTED FUNCTIONAL GROUPS

Figure 1.1: Network Defects (redrawn from reference 21).

1.2.3 Water and Hydrogels.

Water plays a number of roles in hydrogels. It acts as a plasticiser, a transport medium for dissolved species, and as a link between the body fluids and the synthetic polymer. It is the presence of water within hydrogels which makes them unique among biomaterials.

1.2.3.1 Equilibrium Water Content.

The equilibrium water content (EWC) is defined as:

$$EWC = \frac{\text{Mass of Water in the Gel}}{\text{Mass of the Swollen Gel}} \times 100$$

Given the various functions which water performs in hydrogels, it is not surprising that EWC is one of the most important properties possessed by these materials. The EWC affects such characteristics as mechanical and surface properties, permeability, and biocompatibility. Unfortunately no simple relationship exists between EWC and these properties.

The nature of the monomer(s) used in the preparation of hydrogels is one of the major factors determining the magnitude of the EWC; the more hydrophilic the constituent monomers the higher the EWC, e.g. the EWC's of poly HEMA and poly(2,3-dihydroxypropyl methacrylate) are reported as 40% and 50% respectively whilst copolymers of the two monomers lie between these two values.[24] Similarly, the introduction of hydrophobic monomers such as methyl methacrylate or styrene into hydrogel systems reduces the EWC.[5,25]

An increase in the crosslink density has the effect of reducing the EWC of a hydrogel; this is due to a reduction in the chain length between crosslinks, which results in a less elastic structure less able to imbibe water.[5]

Temperature also has an effect on EWC. The factors responsible for the temperature dependence are the hydrogen bonding between the water and the polar groups of the polymer, which increases with increasing temperature, and the association of hydrophobic portions of the polymer to form hydrophobic bonds, which effectively increase the crosslink density. These hydrophobic interactions are expected to decrease with increasing temperature. It is the competition between these two processes which determines the temperature dependence of a particular hydrogel.[25]

The presence of dissolved species in the hydrating medium is another factor which may affect EWC. The EWC of a hydrogel swollen in pure water may increase or decrease if swollen in an aqueous solution, depending on the solute present.[26,27]

1.2.3.2 The Nature of Water in Hydrogels.

There is considerable evidence that the water in hydrogels can exist in more than one state and that the properties of the hydrogel are dependent upon the nature of the water imbibed by the gel.[28-39]

Currently, the favoured theory is that water is present in the polymer network in a continuum of states between two extremes. At one extreme there is the water strongly associated with the polymer through hydrogen bonding; this is sometimes called bound, non-freezing or primary water. At the other extreme is the water which is completely unaffected by the polymeric environment; this is sometimes known as unbound, freezing or secondary water. The water which exists between these two states will naturally show a wide variation in the nature of its interactions with the polymer and in some models this water is regarded as a single state which is often referred to as intermediate or interfacial water. The ratio of freezing to non-freezing water is dependent on the technique used to study the water binding in the hydrogel. This ratio together with the EWC has a considerable effect on the properties of the hydrogel.[29]

The techniques which have been used to study the nature of water in hydrogels include differential scanning calorimetry (DSC),[29,33,34] specific conductivity,[28,33] dilatometry,[28,33] dielectric relaxation,[28] reverse osmosis,[30,31] ^{1}H and ^{13}C NMR,[32,38,39] and diffusion techniques.[37]

Despite all the evidence amassed for the water existing in different thermodynamic states in hydrogels, a recent study by Roorda and co-workers, which makes use of differential thermal analysis (DTA) and adiabatic calorimetry (AC), suggests that the previous observations were kinetic rather than thermodynamic in origin.[35,36]

1.2.4 Mechanical Properties of Hydrogels.

The mechanical properties of most hydrogel systems are poor and this has limited their use in many applications. This is not surprising when one considers that hydrogels often contain more than 50% water. A comparison of the mechanical properties of poly HEMA with some common materials[40,41] is presented in Table 1.1.

Table 1.1: Comparison of Mechanical Properties.

	Tensile Strength /MPa	Youngs Modulus /GPa	Elongation To Break /%
Mild Steel	370	200	0.30
Titanium Alloy	690	120	0.15
Wrought Iron	310	190	-
Nylon (polyamide)	90	2	1.0
Polystyrene	60	3.5	0.03
Polyethylene	12	0.2	5.0
Carbon Fibre Composite	1400	170	-
Poly HEMA	0.5	0.25×10^{-3}	198

The mechanical properties above are defined as:

$$\text{Tensile Strength } (\sigma_b) = \frac{\text{Load At Break}}{\text{Cross Sectional Area}}$$

$$\text{Youngs Modulus (E)} = \frac{\text{Stress}}{\text{Strain}}$$

$$\text{Elongation To Break } (\varepsilon_b) = \frac{\text{Extension Of Gauge Length}}{\text{Original Gauge Length}} \times 100\ \%$$

$$\text{Stress} = \frac{\text{Load}}{\text{Cross Sectional Area}}$$

$$\text{Strain} = \frac{\text{Extension Of Gauge Length}}{\text{Original Gauge Length}}$$

The factors which influence the mechanical properties of hydrogels in the hydrated state, are the polymer composition and, to a lesser extent, the EWC.[41]

1.2.4.1 Effect of Hydrogel Composition on Mechanical Properties.

Increasing the proportion of crosslinking in hydrogels has the effect of increasing the tensile strength (σ_b) and Youngs modulus (E) and reducing the elongation to break (ε_b). These effects have been accounted for by a decrease in chain length between crosslinks, which leads to an increased retractive force in the hydrogel.[41-45]

The incorporation of hydrophobic monomers, such as styrene and methyl methacrylate, into poly HEMA hydrogels produces steady increases in σ_b and E with an accompanying decrease in ε_b. These changes have been attributed to the steady decrease in the unbound (and hence plasticising) water content of the gel. At approximately 40% w/w of hydrophobic monomer there is a dramatic increase in σ_b and E and a corresponding decrease in ε_b, producing the change from a flexible to a rigid material.[41,45] Lauryl methacrylate has a long flexible side chain, which acts as an internal plasticiser in poly HEMA hydrogels. This causes significant increases in σ_b, E and ε_b in these copolymers relative to those of poly HEMA itself.[41,46] As expected the introduction of more hydrophilic monomers into a hydrogel system causes a lowering of σ_b, E and ε_b.[45]

1.2.4.2 Effect of EWC on Mechanical Properties.

The major factor governing the mechanical properties of hydrogels is the polymer composition, whilst the EWC is a minor factor. In general, hydrogels with higher values of EWC tend to have lower values of tensile strength and Youngs modulus than those with lower values of EWC. The elongation to break appears to be independent of EWC.[41]

1.2.5 Poly HEMA Hydrogels.

The preparation of crosslinked poly HEMA hydrogel and its use in biomedical applications was first described by Wichterle and Lim;[1-3] the majority of hydrogels are still based on this material.

The dominance of poly HEMA in the hydrogel field is due to several factors:

i) Mechanical integrity: is high when compared with other hydrogel materials. e.g. poly (N-vinylpyrrolidone).

ii) Ease of modification: comonomers may be incorporated easily into the network to alter chemical or mechanical properties.

iii) Chemical stability: it resists acid hydrolysis and reaction with amines,[47] alkaline hydrolysis occurs only at high pH and high temperature.[48]

iv) Thermal stability: is high allowing steam sterilisation.[3]

v) EWC: is relatively insensitive to the nature and degree of crosslinking,[24,49] temperature[3] and the pH and tonicity of the hydrating medium,[8] in comparison with other hydrogel materials.

The major problem encountered in the preparation of poly HEMA based hydrogels is that of obtaining the pure HEMA monomer. The impure monomer may contain methacrylic acid, ethylene glycol, ethylene glycol dimethacrylate and diethylene glycol dimethacrylate.[50] These impurities, even in very small quantities, can have a marked effect on the properties of the hydrogels, causing higher crosslink densities[51] and anomalous swelling.[52,53]

Purification of the HEMA monomer is a lengthy process involving many extractions and distillation at reduced pressure, in the presence of inhibitor, under a nitrogen atmosphere. Great care must be taken when distilling as disproportionation can occur, thus introducing impurities which have already been removed.[52,54] An alternative method involves the use of TLC.[50]

Despite the difficulties encountered in the purification of HEMA monomer, the biocompatibility,[4] stability under a range of conditions and the other useful properties of the hydrogels based on poly HEMA far outweigh this problem, making these the most widely studied hydrogel systems.

1.2.5.1 Preparation of Poly HEMA Hydrogels.

The preparation of poly HEMA hydrogels may be accomplished by the simultaneous polymerisation of the monomer(s) with a crosslinking agent, either in the presence of water or other solvent, or in its absence.[47] A second, but less frequently used, method involves the crosslinking of a solution of the linear polymer.[17]

Initiation of polymerisation is normally brought about by radicals, which may be generated by chemical initiators (such as azobisisobutyronitrile (AIBN) or its ester derivatives,[54] ammonium persulphate,[27] and benzoyl peroxide[24]), UV initiation in the presence of a photosensitive chemical, or by ionizing radiation. The use of anionic initiators in the indirect preparation of poly HEMA can produce stereoregular hydrogels.[5,55]

The most widely used crosslinking agents in poly HEMA systems are the dimethacrylate esters, ethylene glycol dimethacrylate (EDMA), diethylene glycol dimethacrylate (DEGDMA), and tetraethylene glycol dimethacrylate (TEGDMA).[5,56]

1.2.5.2 Swelling of Poly HEMA Hydrogels.

The EWC of pure lightly crosslinked poly HEMA is thermodynamically limited to about 40%.[57] The time required to reach EWC has been reported as 24 hours, although the presence of impurities, such as residual initiator can cause this to be as long as two weeks.[27] When equilibrated at a number of temperatures EWC changes of 3-4% are observed, a swelling minimum occurring between 60-70°C.[24,25] The absence of non-linear swelling, when only small quantities of water are present in the gel, has been attributed to the presence of voids in the network which fill with water before linear expansion begins.[54]

The EWC of poly HEMA hydrogels is relatively insensitive to temperature and the nature and degree of crosslinking; this has been attributed to several factors. It has been suggested that the poor solubility of HEMA in water dominates the other parameters which affect swelling.[24,58] An alternative suggestion is that there is a secondary structure superimposed on the covalent network and that this secondary structure controls the swelling of the gels. It has been proposed that this secondary structure is due either to hydrophobic interactions between the pendant methyl groups on the chain,[26] or to hydrogen bonding between OH-HO groups in hydrophobic regions.[49] Others have criticised this explanation and have suggested that methacrylic acid impurities are responsible for the observed effects.[52,53]

1.3 DHCD (1,2-DIHYDROXY-3,5-CYCLOHEXADIENE).

1,2-Dihydroxy-3,5-cyclohexadiene (DHCD) may exist as either the *cis* **1** or the *trans* **2** isomer, see Figure 1.2.

1
cis -DHCD

2
trans -DHCD

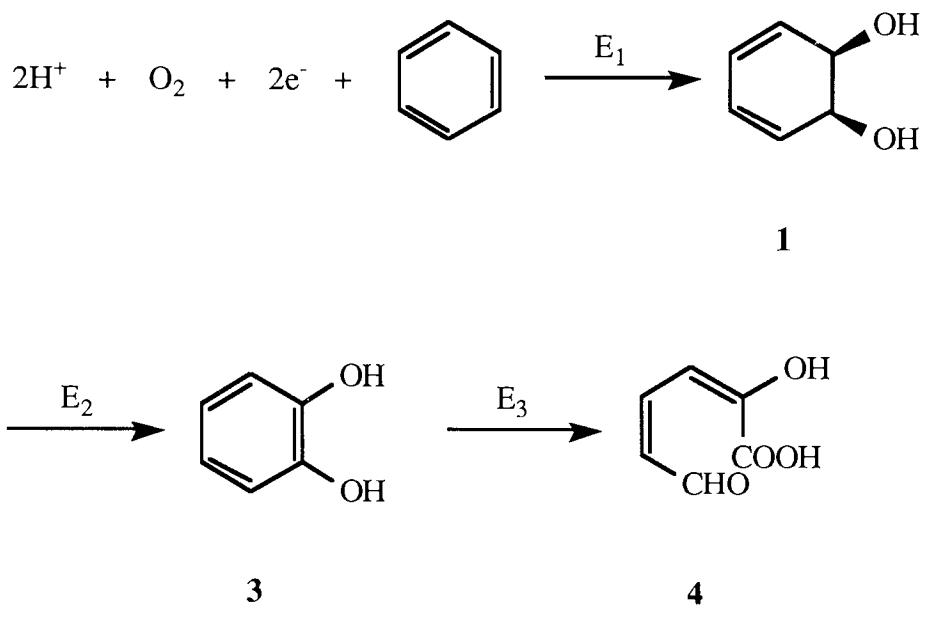
Figure 1.2: Isomers of DHCD.

1.3.1 *cis*-DHCD.

cis-DHCD is a white crystalline solid with a melting point[59] of 60°C. The only practical route to the product so far available is via the microbial oxidation of benzene by the mesophilic bacteria *Pseudomonas putida.* A synthetic route, using conventional chemical techniques, was reported by Nakajima and co-workers in 1959 but gives such a low yield of product that it would be prohibitively expensive to use it for further syntheses.[59]

The microorganisms capable of oxidising benzene to *cis*-DHCD have been known for many years and much research into the biochemistry of the process has been done. Since these organisms had poor oxidation rates and high sensitivity to reaction conditions they lacked the robustness necessary for the large scale preparation of *cis*-DHCD.[60-74]

ICI New Sciences Group were able to isolate a new organism, *Pseudomonas putida* 11767, from a manufacturing site which had been contaminated over many decades with hydrocarbons. This organism was more tolerant to benzene than its predecessors and exhibited a high rate of benzene oxidation. The oxidation within the bacterial cell occurs as shown in Scheme 1.1.



Scheme 1.1: Microbial Oxidation of Benzene.

The enzyme E_1 dioxygenase, together with the protonated form of the cocatalyst, nicotinamide adenine dinucleotide (NADH), reacts with a complete oxygen molecule to form *cis*-DHCD **1**. Enzyme E_2 and NAD^+ cause *cis*-DHCD to aromatise producing catechol **3**, thereby regenerating NADH. The third enzyme, dioxygenase E_3, converts the catechol to a muconic acid **4**.

Genetic manipulation made it possible to produce a variant of *Pseudomonas putida* 11767 from which enzyme E_2 was absent, thereby preventing oxidation of *cis*-DHCD. The *cis*-DHCD diffuses out of the cell into the aqueous media surrounding it, due to its solubility in water, and accumulates therein.

The current generation of organisms give a practically quantitative conversion of benzene to *cis*-DHCD. These organisms are able to tolerate up to 0.5% liquid benzene in water and *cis*-DHCD can accumulate to the extent of 40-50 gl^{-1} without inhibiting oxidation. In practice the organism is added to an aerated, well mixed aqueous solution to which ethanol

and benzene are added. The oxidation of ethanol to carbon dioxide, by other enzymes in the organism, provides the energy required by enzyme E_1 for the oxidation of benzene. The *cis*-DHCD is extracted from the mixture with dichloromethane after oxidation is complete.[19]

1.3.1.1 Properties of *cis*-DHCD.

Pure samples of *cis*-DHCD are relatively stable to heat, dehydrating to phenol and water above 60°C. This reaction is catalysed in acidic media.[19]

The effect of acid on the stability of *cis*-DHCD has been investigated previously at Aston, using NMR spectroscopy. This technique indicated that the *cis*-DHCD, supplied by ICI, contained negligible amounts of phenol. ^1H and ^{13}C NMR studies indicated that, in three hours at room temperature, no decomposition of *cis*-DHCD occurred, but in the presence of traces of acid and water almost 50% conversion was observed over this time.[75]

Pure *cis*-DHCD, when sealed in a vial, was shown to be stable below 4°C for over ten months; impure samples decomposed in two to four weeks. A solution of *cis*-DHCD in acetate buffer, pH 7.6, stored over Resin Dowex 1x4 below 10°C did not decompose in over six months. In contrast a solution of *cis*-DHCD in $3x10^{-4}$% ammonia, pH 7.5, stored under the same conditions decomposed within two to four weeks.[75]

The potential use of *cis*-DHCD as a monomer for the synthesis of 1,4-polyphenylene was the original incentive for its development. Its ready availability led to a number of different applications, which include natural product synthesis and Diels-Alder reactions.[18-20,76-102]

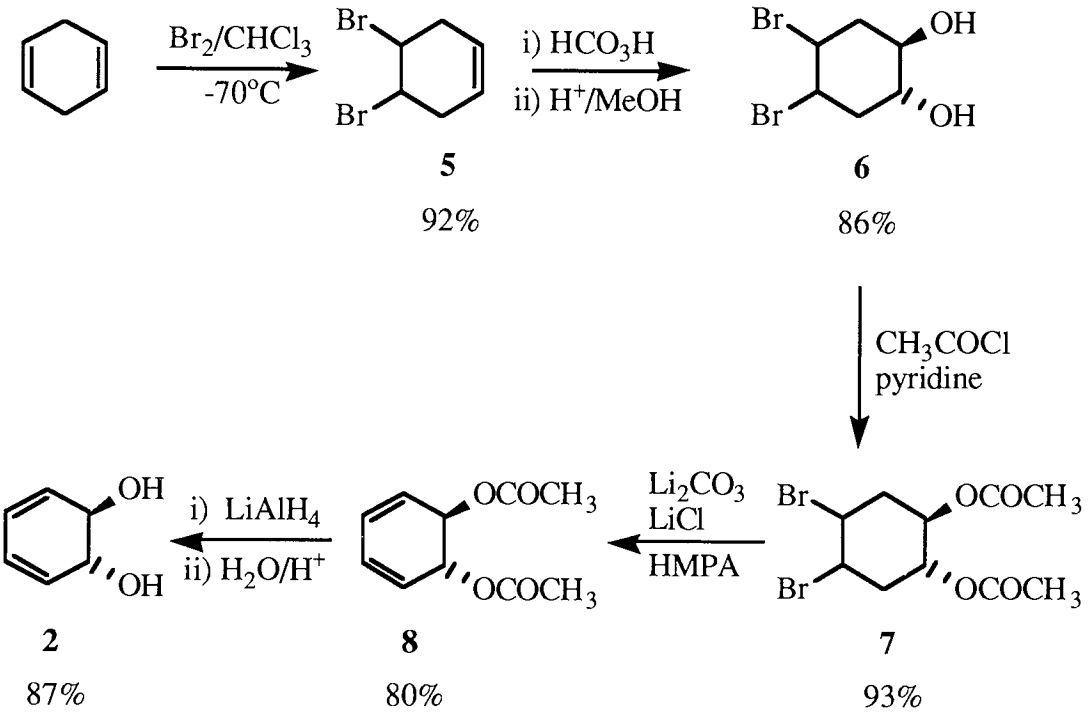
1.3.2 *trans*-DHCD.

Racemic *trans*-DHCD is a white crystalline solid[103] with a melting point of 77°C. It has been synthesised by a number of synthetic routes, which in general give poor yields;[104-106] even the best route, which requires a five step synthesis from 1,4-cyclohexadiene, gave a yield of 51%,[103] see Scheme 1.2. Resolution of the (+) and (-) isomers has also been reported.[107]

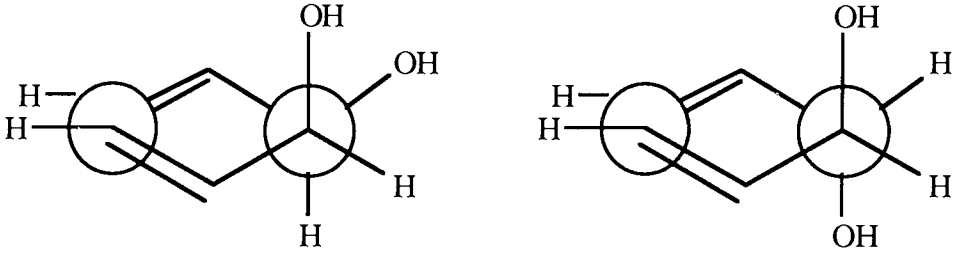
trans-DHCD, like *cis*-DHCD, undergoes aromatisation but much more slowly. In *cis*-DHCD the leaving H and OH groups have the anti periplanar geometry required for efficient E2 elimination, whereas in *trans*-DHCD the H and OH are gauche to one another, see Figure 1.3.

Since no good syntheses of *trans*-DHCD are available it has not had wide use as a useful synthetic reagent. However, it has been employed in the syntheses of muconaldehydes and several polyhydroxylated compounds such as inositols and conduritols.[78,98,104,108]

trans-DHCD, like *cis*-DHCD, has also been found to be a benzene metabolite, but produced by mammalian species rather than bacteria. Both isomers are metabolised further to catechol.[109,110]



Scheme 1.2: Synthesis Of *trans*-DHCD.



cis -DHCD *trans* -DHCD

Figure 1.3: Dehydration of DHCD.

1.3.3 Polymerisation of DHCD and its Derivatives.

Apart from their use as precursors to 1,4-polyphenylene, little use has been made of DHCD and its derivatives as monomers. *cis*-DHCD cannot be radically polymerised directly under the usual conditions, as aromatisation occurs;[19] low temperature initiation, using UV light and uranyl nitrate as initiator, has been shown to be successful.[75] A number of derivatives of *cis*-DHCD can be radically polymerised to produce either homopolymers or copolymers; among the derivatives which have been polymerised are the diacetate, dipivalate, dibenzoate, bis(*p*-nitrobenzoate), bis(*p*-bromobenzoate), dimethylcarbonate, diethylcarbonate, and dimethyl ether.[19,20]

The diacetate derivative of *trans*-DHCD has been polymerised previously, to form a homopolymer.[20] The molecular mass of the homopolymer was reported to be a rather low 6300, and the extent of monomer conversion to be 47%.

Ballard and co-workers found that 85% of the dimethylcarbonate derivative polymerised by a 1,4 addition process (see Scheme 1.3), and suggested that the boat conformation, shown in Figure 1.4, was adopted by the cyclohexene rings of the polymer.[19] McKean and Stille used NMR to estimate the proportion of rings, in several systems, which polymerised by 1,4 and 1,2 addition. They found that the proportion of 1,4 addition could be as high as 91% for the dibenzoate derivative.

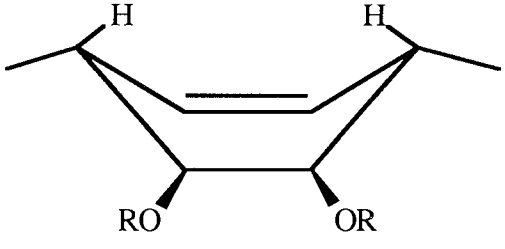
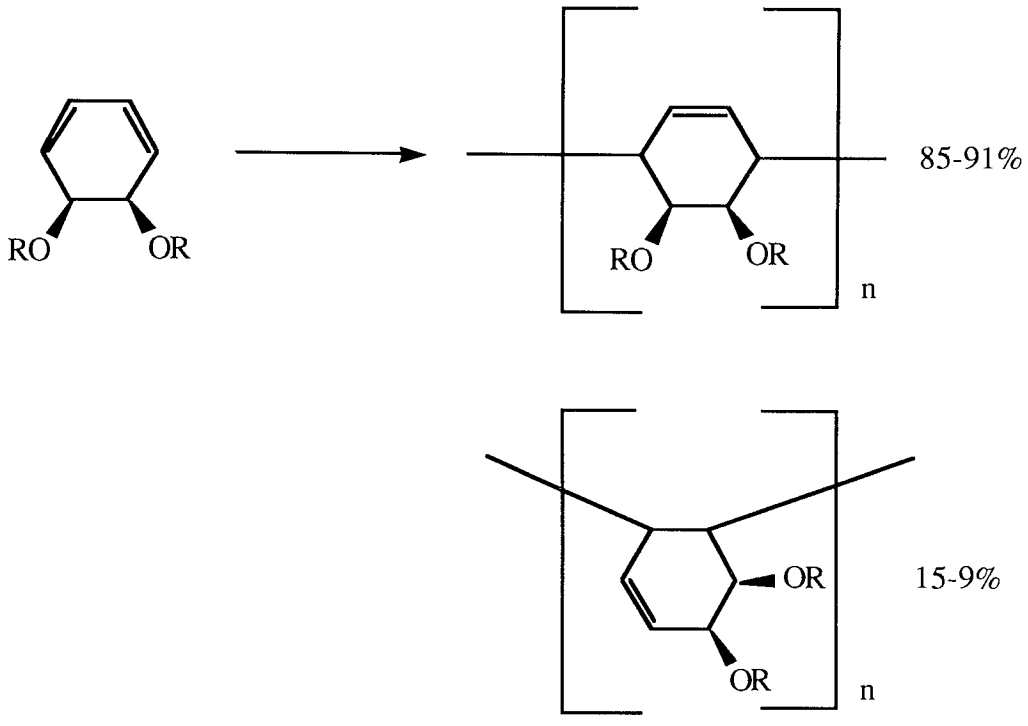


Figure 1.4: Conformation of *cis*-DHCD Derivatives after Polymerisation.



Scheme 1.3: Polymerisation of *cis*-DHCD Derivatives.

1.4 DHCD DERIVATIVES IN HYDROGEL NETWORKS.

Various attempts have been made to improve the mechanical properties of hydrogels, whilst maintaining the hydrophilicity of the materials. Amongst these are the grafting of the hydrogel onto a polymer with superior mechanical properties so that the surface of the support exhibits greatly improved biocompatibility whilst the composite as a whole has good mechanical strength. Naturally these materials are of little use in many biomedical applications, such as membranes, where permeability is the overriding factor.[5,10]

Another approach which has been used is the manufacture of interpenetrating polymer networks (IPN). An IPN is defined as a combination of two polymers each in a network form, at least one of which has been synthesised and / or crosslinked in the presence of the other.[111-116] The opacity of hydrogels made in this way is a disadvantage in optical applications;[116] also, to date, little work has been been done to investigate the permeability

of IPN's.

The introduction of hydrophobic monomers, such as styrene or methyl methacrylate, into a hydrogel network, whilst improving the mechanical properties of the hydrogel, causes a decrease in the EWC, which in turn affects such properties as biocompatibility and permeability. Such materials only exhibit significant improvements in mechanical properties when the plasticising, freezing water, is absent.[41]

Despite these previous efforts no satisfactory method has yet been found whereby good mechanical strength and moderate to high EWC can be combined in simple hydrogel materials.

Up to now only a very limited range of monomers has been used in hydrogel systems so there is ample scope for the introduction of new monomer systems to combat some of these problems. DHCD and its derivatives appear to be suitable candidates for this purpose. The introduction of cyclohexene rings into the polymer backbone would be expected to increase the rotational mobility of the chains, since they would act as spacers between the pendant groups in the polymer chain. By attaching two pendant groups onto the cyclohexene ring the steric interactions between pendant groups in the polymer would be much increased. Incorporation of the DHCD ring, with two hydrophilic pendant chains per monomer unit rather than the one present in most hydrogel systems, should increase the ability of the polymer to bind water and improve its mechanical properties.

1.4.1 Applications of Hydrogels with Improved Mechanical Properties.

The two main areas where moderate to high water content hydrogels, with improved mechanical properties, would be of use are the development of artificial corneas, where good optical properties are also required, and synthetic articular cartilage, where good mechanical properties would be of great importance. It can be seen from Table 1.2 that there are similarities in the composition of the cornea[117] and articular cartilage.[118]

Table 1.2: Compositions of the Cornea and Cartilage.

	Cornea	Cartilage
Water	78.0%	70-75%
Collagen	15.0%	15-20%
Other proteins	5.0%	2-10%
Salts	1.0%	-
Keratin sulphates	0.7%	-
Chondriotin sulphates	0.3%	-

In these composite materials the major constituents are water and collagen; the collagen acts as a reinforcement for the matrix. A comparison of the physical properties of the cornea, articular cartilage and poly HEMA can be found in Table 1.3.

Table 1.3: Comparison of Physical Properties.

(Figures in parentheses indicate the reference number)

	Poly HEMA	Cartilage	Cornea
Tensile Strength / MPa	0.5 (42)	~30 (119)	-
Youngs Modulus / MPa	0.25 (42)	~150 (119)	-
Elongation to break / %	198 (42)	~80 (120)	-
Water content / %	37.6 (42)	75 (118)	78 (117)
Refractive index	1.431(7)	-	1.37(16)

1.4.2 Synthetic Cellulose.

Cellulose is an inexpensive, widely available material, which has been used in a number of important membrane applications.[8,13-15] Unfortunately there is no simple way in which polyhydroxylated cyclic monomer units, such as the glucose unit in cellulose, can be incorporated simply into copolymers and more particularly into hydrogel systems. A DHCD repeat unit in a polymer chain provides a potential precursor to such materials. Hydration of the residual double bond would yield a trihydroxy cyclic repeat unit which resembles the glucose repeat unit in cellulose, see Figure 1.5.

It is possible that the beneficial transport properties exhibited by cellulose are due to the highly hydroxylated, cyclic nature of the repeat unit. Hydrogels containing synthetic cellulose type units could possess unique transport properties, with the added advantage that the proportion of these units in a polymer system could be easily controlled. As DHCD itself can only be polymerised directly, by a radical process, under special conditions, the incorporation of DHCD into hydrogels has to be achieved indirectly, via a protected DHCD monomer.

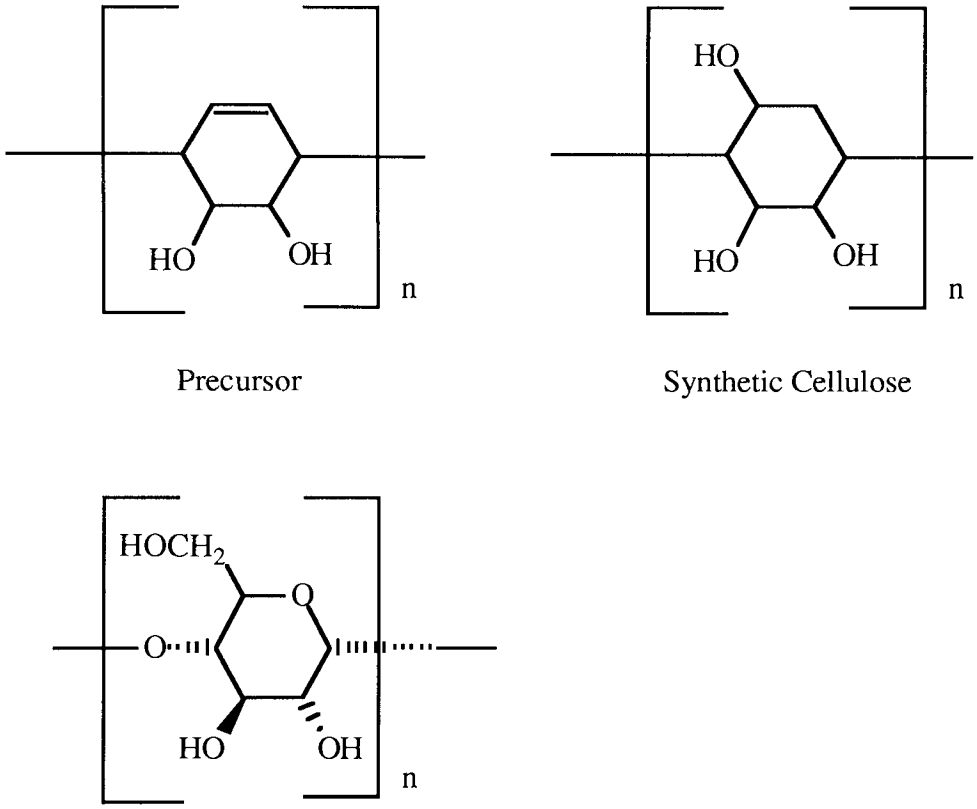


Figure 1.5: Synthetic Cellulose.

1.4.3 Factors Affecting Monomer Design.

In the design of hydrophilic monomers based on DHCD for hydrogel polymers, there are only two factors which need to be considered. These are the choice of hydrophilic group and the length of the pendant chain.

By far the most common hydrophilic group in hydrogels is the hydroxyl group; among the other groups which have also been used are morpholine,[2,3] amide,[5] and carboxylic acid[5] groups. Carboxylic acid and other charged groups, often cause problems in hydrogels, due to their sensitivity to pH and the detrimental effect such groups have on biocompatibility.[8,10] Long pendant chains can also cause problems due to their plasticising effect;[41] it was felt that this effect could mask those caused by the introduction of the cyclic

monomers.

The indirect incorporation of DHCD into hydrogels would have to be accomplished via a derivative which can be prepared simply, polymerised, and deprotected under mild, preferably aqueous, conditions. The hydration of the cyclic double bond to form the synthetic cellulose structure would have to be performed by a method which gives final products which are easily removed when the gel is swollen in water.

1.5 *cis* And *trans*-DHCD AS IMPORTANT SYNTHETIC REAGENTS.

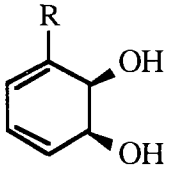
Although *cis*-DHCD had been used as a synthetic material prior to 1983 to prepare inositols, conduritols and muconaldehydes,[59,98] it was not until the pioneering work by ICI, which made *cis*-DHCD available in multigramme quantities, that the exploitation of this material as a unique synthon and monomer began in earnest. This material has been used in the syntheses of inositols and related analogues,[77,78,90-92,95] conduritols,[79,88,93] muconaldehydes,[85] cyclohexadiene dication equivalents,[87] pinitols,[94,96] modified hexoses,[89] chiral synthons,[82] poly(phenylene),[18-20] *o-o'* dibenzenes[102] and in Diels-Alder and carbene reactions.[81-84,97,101] In addition, it has been utilised as a model compound in investigations of osmylation reactions[100] and the ceric oxidation of poly(vinyl alcohol).[99]

trans-DHCD was first synthesised in 1956 but it was not until 1977 that a practical route to the product became available. *trans*-DHCD, like *cis*-DHCD, has great synthetic potential, but even the best available route to *trans*-DHCD is laborious and this has limited its use a synthetic reagent. *trans*-DHCD has been used in the preparation of muconaldehydes,[104] conduritols,[78,98] and inositols.[78,98]

1.5.1 DHCD and Substituted DHCD Analogues in Synthesis.

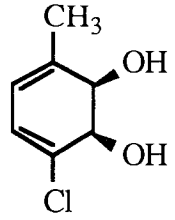
The simple microbial oxidation of benzene, by genetically manipulated *Pseudomonas putida* bacteria, has resulted in the recognition and exploitation of *cis*-DHCD as an important synthetic material. The microbial oxidation is remarkably tolerant to various functional groups, allowing an evergrowing number of *cis*-DHCD analogues to be isolated from microbial oxidation of the appropriate arene. In excess of 120 *cis*-diols, resulting from bacterial oxidation, have been reported in the literature, although fewer than 10% are of known absolute stereochemistry or optical purity.[121] Both monocyclic and polycyclic arenes have been oxidised by this method.[63,64,66,69,122-138] The substituted *cis*-diols have greater synthetic potential than *cis*-DHCD itself due to the presence of more functional groups in the molecules which could allow the synthesis of multifunctional chiral materials. Some of the *cis*-diols which have been reported are shown in Figure 1.6. Compounds **9-12** and **15** have been used in synthetic applications.

The *cis*-diols have been utilised as starting materials for the syntheses of terpene and prostanoid synthons,[129] (-)-lamintol,[125] methyl-muconaldehydes,[85] (-)-zeylena,[134] trihydroxyheliotridanes,[131] conduritols,[124,133] sugars and amino acids,[128] D- and L-erythrose,[130] L-ribonic-γ-lactone,[132] and Diels-Alder products.[63,64,69,83,97,121,127,135] Numerous other synthetic targets have also been proposed.[121-138]



R

9 CH_3
10 CH_2CH_3
11 F
12 Cl
13 CF_3
14 CH_2OAc
15 $CH{=}CH_2$
16 CCH
17 Ph
18 7-norborna-2,5-dienyl



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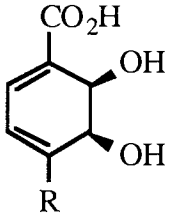
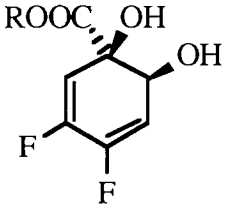


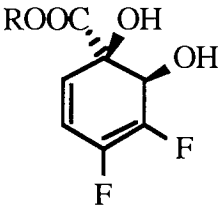
R

20 CH_3
21 CF_3
22 Br



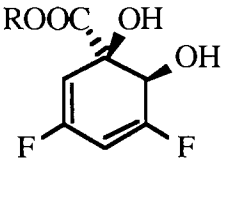
R

23 H
24 CH_3



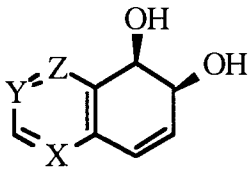
R

25 H
26 CH_3



R

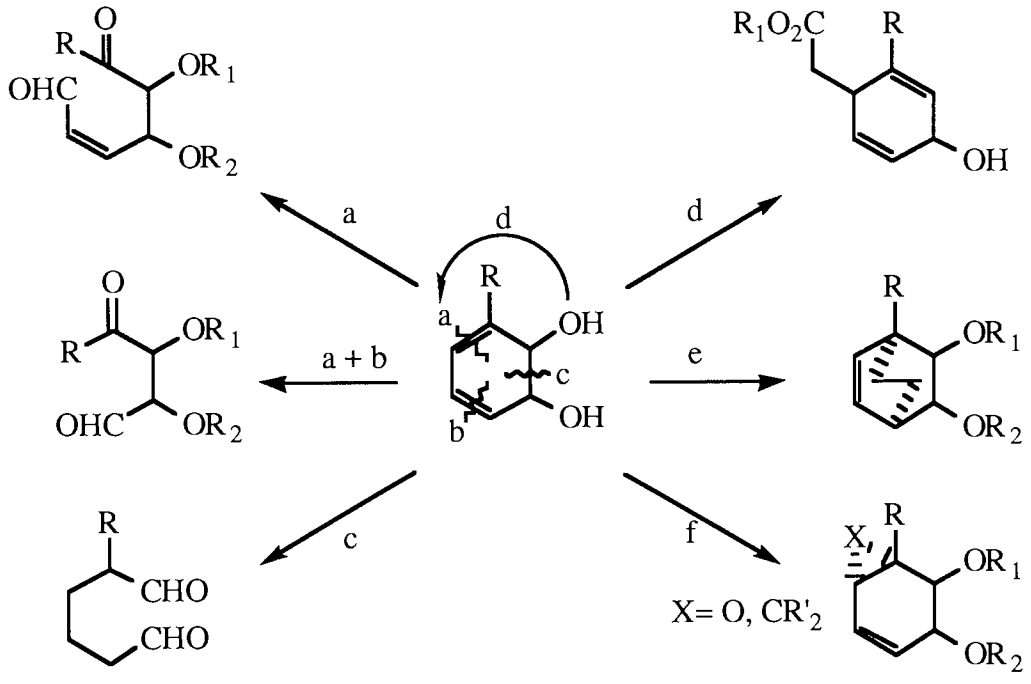
27 H
28 CH_3



29 X=Y=Z=CH
30 X=N, Y=Z=CH
31 Y=N, X=Z=CH,
32 X=Y=N, Z=CH
33 X=Z=N, Y=CH

Figure 1.6: *cis*-Diols.

The synthetic potential of these materials has been discussed by Hudlicky and co-workers.[129] Possible synthetic strategies are represented in Scheme 1.4. Although the synthetic strategies were designed for substituted *cis*-DHCD compounds they are equally applicable to the *trans* analogues.



Scheme 1.4: Synthetic Strategies for DHCD and its Analogues (redrawn from reference 129).

It can be seen that both isomers of DHCD and their substituted analogues have the potential to be used in a wide variety of syntheses. The ability of such materials to produce highly functionalised, chiral compounds could be of great importance in synthesis. The majority of work being carried out in this area is being performed by just two groups of workers: the Hudlicky group at Virginia Polytechnic Institute and State University,[126,128-134] and the Ley group at Imperial College.[90-96] The main reason for this concentration of effort is that *cis*-DHCD and 3-methyl-*cis*-DHCD can only be obtained in reasonable yield by the rather specialised microbial oxidation technique. This means users must either have the

facility to synthesise the material or have sufficient funds to purchase the very expensive commercial product..

1.6 AIMS AND SCOPE.

With regard to the above statement one aim of this project was to develop efficient routes to these compounds.

A second was to develop synthetic routes to derivatives, of both *cis* and *trans*-DHCD, containing hydrophilic groups. The copolymerisation of these monomers with 2-hydroxyethyl methacrylate to form hydrogels could produce a hitherto unknown group of hydrogel materials which could have both improved mechanical properties and a moderate to high equilibrium water content; no simple hydrogel system at present exhibits both of these properties.

Difficulties are encountered in the direct, radical polymerisation of *cis*-DHCD, so attempts to prepare a masked DHCD monomer, which could be polymerised under the usual conditions, were made. Removal of the masking groups could yield a polymer which contained DHCD units in the backbone. The residual double bond in such materials would allow the introduction of a further hydroxyl group to give a synthetic cellulose type of structure. Although cellulose is a cheap and widely available material there is at present no simple way of introducing cellulose type repeat units into a copolymer.

The hydrophilicity and mechanical strength of HEMA copolymers containing DHCD derivatives were determined by measuring the EWC, tensile strength and Youngs modulus.

Chapter 2: Monomer Synthesis.

2. MONOMER SYNTHESIS.

2.1 INTRODUCTION.

Hydrogel systems derived from hydrophilic derivatives of DHCD would be predicted to exhibit both good water binding ability and improved mechanical strength, in comparison with existing hydrogel materials, because of the large steric interactions between pendant groups.

The original aim of the work was to prepare hydrophilic derivatives of *cis*-DHCD directly. *cis*-DHCD was to be provided by ICI but because of its great expense a model compound was sought.

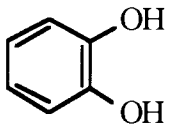
2.2 MODEL COMPOUNDS.

A model compound for *cis*-DHCD was required so that the problems one might encounter in preparing derivatives directly in good yield, under mild non-acidic conditions, could be investigated. The model compounds which were evaluated are shown Figure 2.1. Three factors were considered in the selection of the model compound:

i) the steric environment of the hydroxyl groups

ii) the reactivity of the hydroxyl groups

iii) the cost and commercial availability of the model compound.



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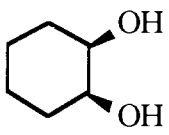

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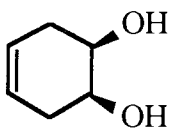

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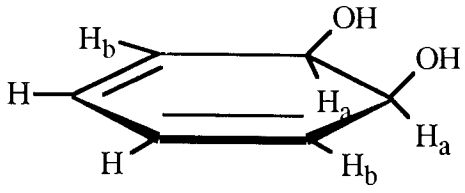
Figure 2.1: Model Compounds.

2.2.1 Conformations of DHCD and its Derivatives.

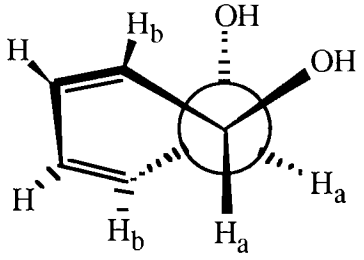
The limiting conformations of *cis* and *trans*-DHCD are shown in Figure 2.2. For *cis*-DHCD in conformation **I**, the ring possesses angle strain, due to the distorted bond angles of the sp^3 carbons. The hydroxyl groups are eclipsed causing steric strain. Electrostatic effects must also be taken into account and the partial charges on the oxygen atoms are closest together in this conformation, corresponding to a maximum coulombic interaction. In conformation **II** the ring deviates from planarity to overcome the angle strain and steric strain but this is at the expense of the electron delocalisation within the 1,3-diene group. The partial charges on the oxygen atoms are furthest apart in this conformation, corresponding to a minimum coulombic interaction.

For *trans*-DHCD the conformation **IV** possesses angle strain due to the distorted bond angles of the sp^3 carbons and steric strain caused by the eclipsing of hydroxyl groups and hydrogen atoms. An intermediate coulombic effect is present in this conformation. The hydroxyl groups are anti to one another in conformation **V**, corresponding to a minimum amount of steric strain within the molecule. Angle strain is also overcome in this conformation but at the expense of the electron delocalisation within the 1,3-diene group. The coulombic effect is at a minimum in this conformation. Conformation **III** is the least favoured as it represents a situation where angle strain is relieved but the electrostatic interaction between oxygen atoms is at a maximum and electron delocalisation within the 1,3-diene group is reduced due to the loss of planarity. In addition, the pendant groups are

gauche to one another, corresponding to maximum steric strain.

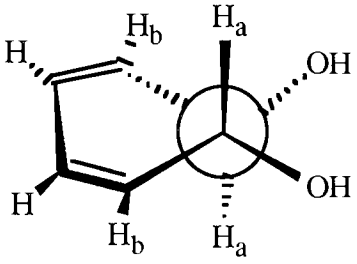


I

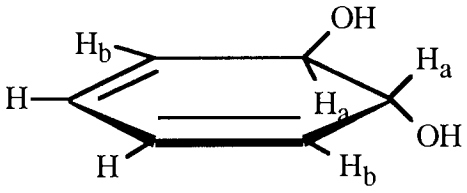


II

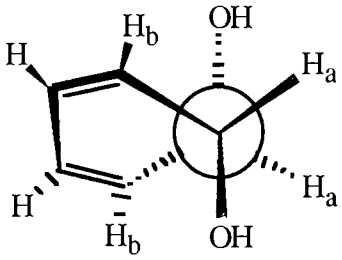
***cis* -DHCD**



III



IV



V

***trans* -DHCD**

Figure 2.2: Limiting Conformations of DHCD.

^{1}H NMR spectroscopy allows the conformations adopted by *cis* and *trans*-DHCD and their derivatives to be determined. By measuring the coupling constant between hydrogens **a** and **b** and applying the Karplus equation[139] the dihedral angle between the hydrogens

can be estimated and hence the conformation of the ring determined:

$$J_{ab} = J^{o} \cos^2 \theta - 0.28$$

J_{ab} is the observed coupling constant between hydrogens **a** and **b**

$J^{o} = 8.5$ the standard value for a dihedral angle (θ); $0^{o} > \theta > 90^{o}$

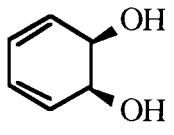
θ is the dihedral angle between hydrogens **a** and **b**

The coupling constants, obtained from the ^{1}H NMR spectra of *cis* and *trans*-DHCD and some of their derivatives (see Figure 2.3), and the dihedral angles calculated by application of the Karplus equation are shown in Table 2.1.

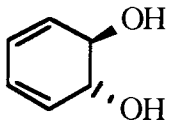
Table 2.1: Conformational Data for *cis* and *trans*-DHCD and their Derivatives.

Compound	Multiplicity	J_{ab} / Hz	Dihedral Angle
cis-DHCD (**1**)	Triplet	1.6	62°
cis-DHCD diacetate (**36**)	Triplet	1.3	64°
cis-DHCD dimethylcarbonate (**37**)	Quartet	1.2	65°
trans-DHCD (**2**)	Singlet	0	90°
trans-DHCD* (**2**)	Triplet	1.0	67°
trans-DHCD diacetate (**8**)	Triplet	1.2	65°
trans-DHCD dimorpholinecarbamate (**38**)	Singlet	0	90°

All NMR spectra were recorded for samples in $CDCl_3$ except * D_2O.



1



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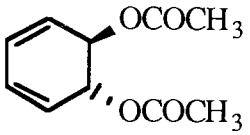

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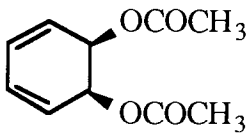

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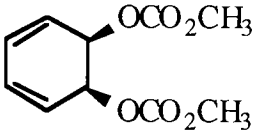

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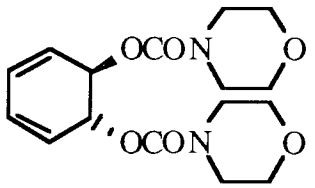

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Figure 2.3: Compounds for Conformational Analysis.

It is clear from Table 2.1 that the conformation adopted by *cis*-DHCD, in deuteriochoroform, is close to the limiting conformation **I** in which the dihedral angle is 60°. The delocalisation of electrons within the 1,3-diene group appears to be the governing factor in determining the conformation, overcoming as it does the unfavourable eclipsing of the pendant groups, the ring strain and the electrostatic interactions between the hydroxyl groups. The steric and electrostatic factors seem to play little part in determining conformation, as both the diacetate and dimethylcarbonate derivatives of *cis*-DHCD (which contain considerably larger pendant groups) also adopt conformations close to the limiting conformation **I**.

The ^1H NMR spectrum of *trans*-DHCD in deuteriochloroform, unexpectedly showed no splitting of the signal corresponding to hydrogen H_a, whilst a coupling constant of 1.0Hz was observed for the compound in D_2O. It would appear that in D_2O the compound adopts a conformation close to conformation **IV**, but with a slight puckering of the ring to reduce steric strain, whereas in deuteriochloroform the hydroxyl groups adopt a diequatorial arrangement corresponding to conformation **III**. The electrostatic interactions and steric strain are at a maximum in this latter conformation and the loss of planarity in the 1,3-diene group must cause a decrease in electron delocalisation within this group. Some other factor must therefore be responsible for the adoption of such an apparently unfavourable conformation. One possible explanation is that the solvation of the hydroxyl groups, by hydrogen bonding to the extremely large deuteriochloroform molecules, produces pendant groups which are so large that there is a significant interaction between them and the 1,3-diene portion of the ring. It is only by adopting conformation **III** that such interactions are reduced to a minimum. In contrast, when the much smaller D_2O molecules hydrogen bond with the hydroxyl groups the effective size of the pendant groups is much smaller and their interaction with the 1,3-diene group is much smaller. Support for this hypothesis comes from a comparison with the calculated dihedral angles for the diacetate and dimorpholinecarbamate derivatives of *trans*-DHCD, which contain medium and large pendant groups respectively. In the former the conformation adopted is very similar to that of *trans*-DHCD itself in D_2O, whilst in the latter the conformation adopted is the same as *trans*-DHCD in deuteriochloroform. It is interesting to note that none of the *trans* compounds favoured conformations approaching conformation **V**. This can only be accounted for if the molecules are relieving the steric interaction between the pendant groups and the 1,3-diene group.

These observations suggest that in *cis*-DHCD and its derivatives the retention of ring planarity, which allows maximum delocalisation of the electrons within the 1,3-diene group, is the predominant factor in determining which conformation is adopted. There is

little opportunity to reduce steric strain within these isomers as even in the most favourable conformation the pendant groups will be gauche to one another. In *trans*-DHCD and its derivatives steric factors play a significant role in determining the conformation adopted by the molecule. When very large pendant groups are present steric interactions between the ring and the pendant groups predominate over both the steric interactions between the two pendant groups and the delocalisation of electrons in the 1,3-diene group.

2.2.2 Reactivity of *cis*-DHCD.

Aliphatic alcohols are generally more nucleophilic than aromatic alcohols. The lone pair electrons on the phenolic oxygen are delocalised over the aromatic ring, making the oxygen atom less nucleophilic. It would be expected that compounds **34** and **35** would have similar reactivities to DHCD, whilst catechol would be expected to be less nucleophilic because of this resonance effect. However, it would appear from examination of the resonance structures for catechol that a partial negative charge resides on the carbon atom to which the hydroxyl group is attached, see Figure 2.4. The inductive effect between this carbon and the oxygen causes an increase in the magnitude of the partial negative charge residing on the oxygen atom, making the hydroxy groups in catechol more nucleophilic than those of a monohydroxy phenol. Considering these two opposing effects, it might be expected that the OH groups of catechol would have comparable nucleophilicity to an aliphatic OH. During this work catechol was found to be more reactive than *cis*-DHCD.

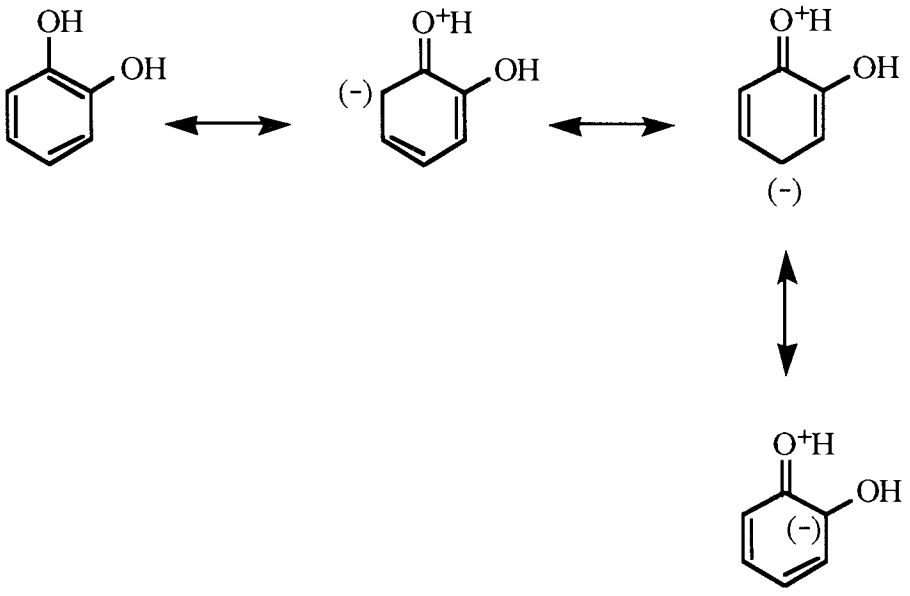


Figure 2.4: Resonance Structures for Catechol.

2.2.3 Choice of Model Compound.

The conformational studies of *cis*-DHCD and its derivatives showed that the ring is virtually flat in these compounds and that the pendant groups are eclipsed. Compounds **34** and **35** should be puckered, with the hydroxyl groups gauche to one another, whilst catechol, like *cis*-DHCD, is flat with eclipsed hydroxyl groups. The reactivity of *cis*-DHCD is predicted to be similar to compounds **34** and **35** but somewhat less than that of catechol. Compound **35** is not commercially available but can be obtained in two steps from 1,4-cyclohexadiene.[20] Compound **34** is commercially available but is almost as expensive as *cis*-DHCD itself, whilst catechol is cheap and readily available.

The geometry of the six membered ring and the steric environment of the hydroxyl groups in catechol and *cis*-DHCD are very similar. This, together with the ready availability and cheapness of catechol, led to it being selected as a model compound for *cis*-DHCD.

2.3 SYNTHESIS OF MODEL COMPOUNDS.

cis-DHCD aromatises readily under acidic conditions or at temperatures over 60°C so the intention was to use catechol for the development of methods which would give a good yield under non-acidic conditions and low temperatures.

Perhaps the two most common reactions which hydroxyl groups undergo are esterification and etherification.

2.3.1 Ester Synthesis

Esterification can most easily be performed by the reaction of acid chlorides or anhydrides with alcohols. Acid chlorides are more readily available and can be prepared more easily than anhydrides. Both systems produce acids which would aromatise *cis*-DHCD. However, reactions carried out in the presence of an organic base, which removes acid, maintain neutrality so this problem is overcome. Since one of the main aims was to produce hydrophilic derivatives this posed a problem as very few compounds are commercially available which possess both hydrophilic groups and acyl chloride or anhydride functions.

There are two obvious solutions to this problem. The first is to prepare acyl chlorides with protected hydrophilic groups. Since a large number of hydroxy acids are commercially available it was envisaged that a large variety of derivatives could be synthesised in this way.

An alternative approach would be to introduce hydroxyl groups via the hydroboration of ester derivatives containing double bonds. This too seemed feasible as a number of unsaturated acyl halides are commercially available.

2.3.2 Ether Synthesis.

Although many new methods of synthesis have been developed for preparing ethers the Williamson synthesis remains one of the best methods for the synthesis of unsymmetrical alkyl ethers. Few compounds are commercially available which possess both hydrophilc groups and an alkyl halide so hydrophilic groups would have to be introduced after formation of the desired ether.

The Williamson synthesis is an excellent and versatile method for the synthesis of ethers but it is not, in its simple form, directly applicable to the synthesis of ethers from diols such as catechol or DHCD. The first step in the Williamson synthesis is the conversion of the alcohol into an alkoxide with excess parent alcohol acting as a solvent. The alkoxide ion is then reacted with an organic halide, to give the desired ether. If the alkoxide ion is to be formed from a solid alcohol it is not possible to use excess parent alcohol as a solvent. It is possible to overcome this problem by using a suitable polar solvent, such as THF. However, this method is not applicable to solid diols as a dialkoxide ion is formed which precipitates from THF and is only soluble in more polar solvents; alcohols and aqueous solvents obviously cannot be used and dipolar aprotic solvents, such as DMSO, HMPA and DMF are difficult to purify, dry, and remove. The heterogeneous system, consisting of solid alkoxide and a solution of organic halide, would be expected to react with difficulty due to the poor solubility of the alkoxide ion in the solvent.

Various approaches have been used to overcome these problems, among them are phase transfer catalysis (PTC),[140-142] ultrasound[143] and micellar catalysis.[144] PTC was chosen as the desired method for the synthesis of the ethers as it is of general applicability and has the advantage that the alkoxide ion does not have to be preformed.

The PTC system consists of two phases, an aqueous solution of sodium hydroxide containing a quaternary ammonium halide (Q^+X^-) (which is converted into the corresponding quaternary ammonium hydroxide (Q^+OH^-), and an immiscible organic phase, which contains the alkyl halide (R'X). The alcohol (ROH) is partitioned between the two phases. In the aqueous phase the alcohol is converted into the quaternary ammonium alkoxide ion (Q^+RO^-) which is readily soluble in the organic phase. Once in the organic phase the alkoxide ion is free to react with the alkyl halide forming the desired ether (ROR'), which is insoluble in the aqueous phase. The quaternary ammonium halide, also formed, redissolves in the aqueous phase where it is again converted into the corresponding quaternary ammonium hydroxide. This process is represented in Figure 2.5.

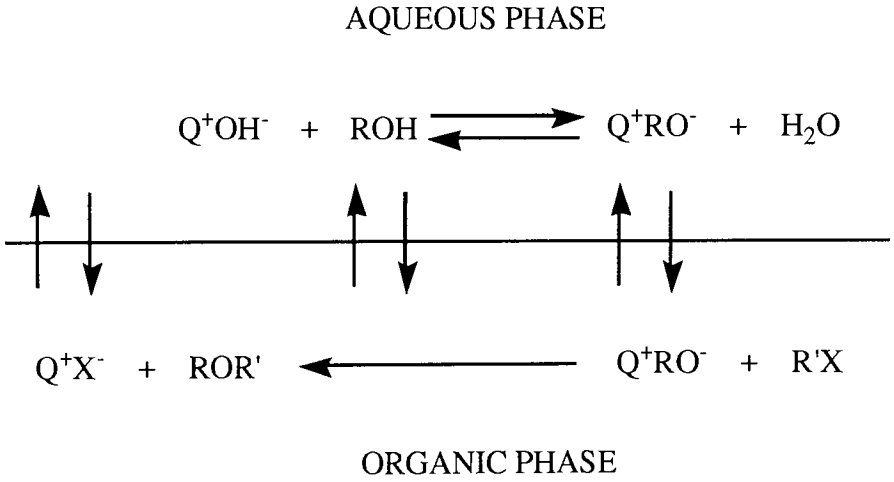
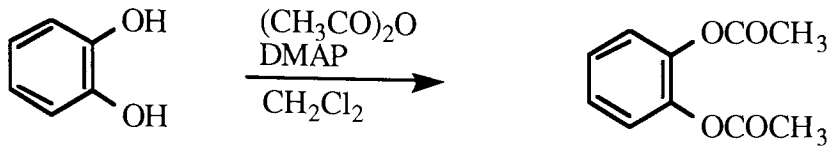


Figure 2.5: Phase Transfer Catalysis.

2.3.3 Synthesis of 1,2-Diacetoxybenzene.

The synthesis of 1,2-diacetoxybenzene **39** in 58% yield was achieved in one step by acetylation of catechol with acetic anhydride in the presence of 4-dimethylaminopyridine (DMAP) and triethylamine at room temperature, see Scheme 2.1. Since the reaction occurs in good yield at a moderate temperature this method would obviously be suitable for the synthesis of the *cis*-DHCD derivative.



3 **39**

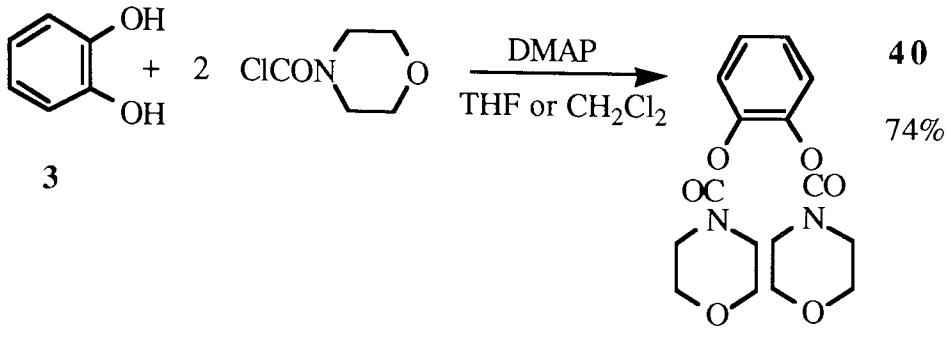
58%

Scheme 2.1: Synthesis of 1,2-Diacetoxybenzene.

2.3.4 Synthesis of 1,2-Bis(4-morpholinecarboxy)benzene.

The reaction of catechol with 4-morpholinecarbonyl chloride, in the presence of DMAP and triethylamine at room temperature, produced the novel catechol derivative 1,2-bis(4-morpholinecarboxy)benzene **40** in good yield (74%), see Scheme 2.2. The compound 4-morpholinecarbonyl chloride was observed to be relatively unreactive, in comparison with other acyl halides. Little reaction occured during the addition of this compound to a mixture of catechol, DMAP and triethylamine in dichloromethane. It was necessary to stir this mixture for several hours at room temperature before a significant amount of triethylamine hydrochloride precipitate was formed. The reaction could be speeded up by substituting THF for dichloromethane as the solvent and refluxing. In this case reaction appeared to be complete in two hours. The yields in both cases were identical. The relative inertness of 4-morpholine carbonyl chloride can be accounted for using the resonance structures shown in Figure 2.6. There is delocalisation of the partial positive charge on the carbonyl carbon making it less electrophilic than other systems for which such delocalisation is not possible.

This method is potentially suitable for synthesising the *cis*-DHCD analogue but the reaction would have to be carried out at room temperature to prevent aromatisation. The synthesis of the *cis*-DHCD derivative would be expected to require a longer reaction time than that for the preparation of **40** because of the higher reactivity of catechol in comparison with *cis*-DHCD.



Scheme 2.2: Synthesis of 1,2-Bis(4-morpholinecarboxy)benzene.

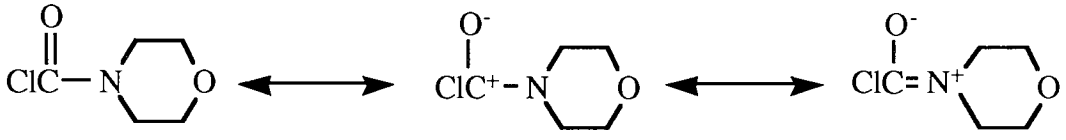
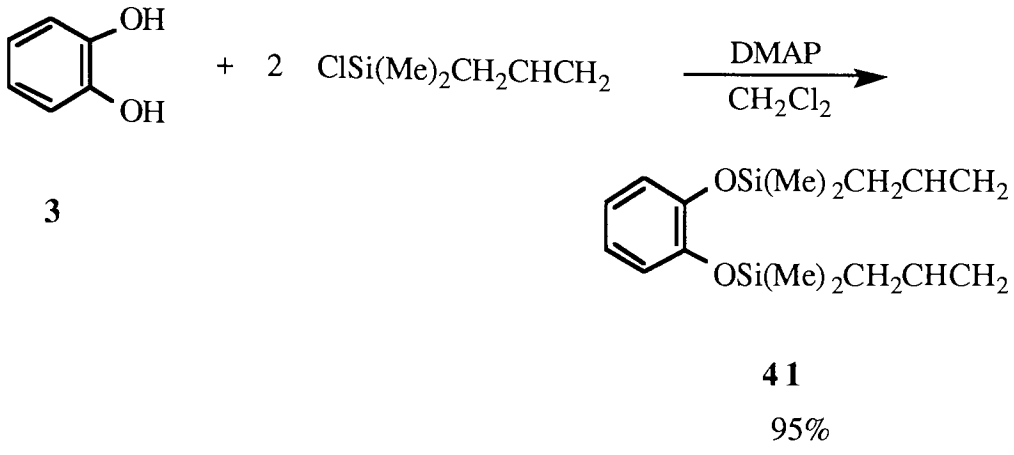


Figure 2.6: Resonance Structures of 4-Morpholinecarbonyl Chloride.

2.3.5 Synthesis of 1,2-Bis(allyldimethylsiloxy)benzene.

A number of derivatives of catechol, which contained double bonds in their pendant chains, were prepared to which hydroxyl groups could be introduced subsequently by hydroboration.

The catechol derivative 1,2-bis(allylsiloxy)benzene **41** was obtained in an excellent yield of 95% by reaction of catechol with allylchlorodimethylsilane, in the presence of DMAP as a catalyst at room temperature, see Scheme 2.3. It would be expected that the analogous reaction with *cis*-DHCD would also occur readily under these conditions.



3

41

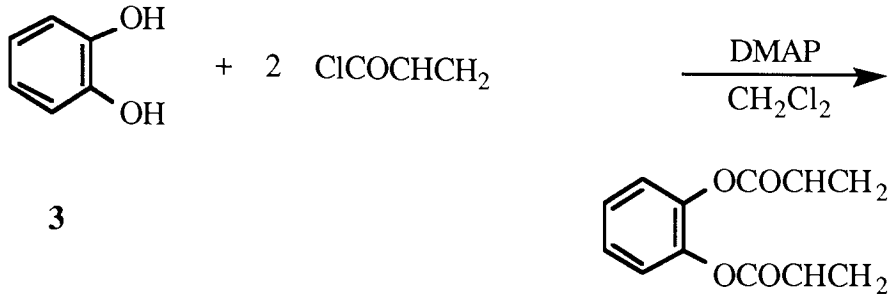
95%

Scheme 2.3: Synthesis of 1,2-Bis(allyldimethylsiloxy)benzene.

2.3.6 Synthesis of 1,2-Bis(acryloxy)benzene.

Reaction of catechol with acryloyl chloride, in the presence of DMAP and triethylamine at room temperature, gave 1,2-bis-(acryloxy)benzene **42** in a very good yield of 85%, see Scheme 2.4. If pyridine, instead of triethylamine, was used as the acid trap, a viscous bright orange precipitate was formed. This material could not be dissolved by adding more dichloromethane, and it did not react further causing the failure of this reaction.

If triethylamine was used, as an acid trap, and DMAP, as a catalyst, this could be an effective method for synthesising the *cis*-DHCD analogue.



3

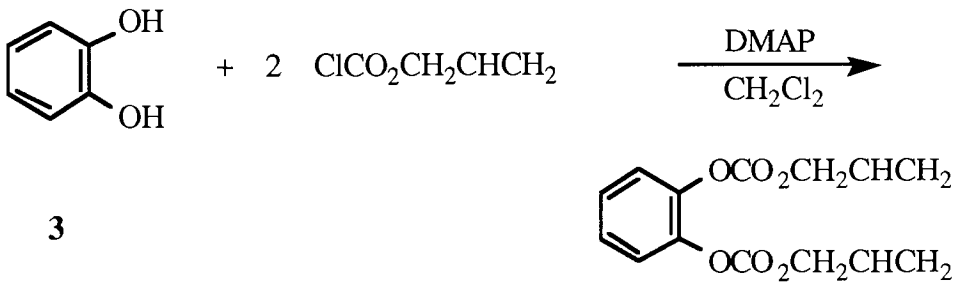
42

85%

Scheme 2.4: Synthesis of 1,2-Bis(acryloxy)benzene.

2.3.7 Synthesis of 1,2-Bis(allyloxyformoxy)benzene.

1,2-Bis(allyloxyformoxy)benzene **43** was prepared in a good yield of 72% by reaction of catechol with allylchloroformate in the presence of DMAP and triethylamine at room temperature.



3

43

85%

Scheme 2.5: Synthesis of 1,2-Bis(allyloxyformoxy)benzene.

In contrast to the compound 1,2-bis-(acryloxy)benzene **42**, the compound 1,2-bis(allyloxyformoxy)benzene **43** could also be prepared using pyridine as the acid trap, in a better yield of 85%, see Scheme 2.5. If the reaction was carried out using pyridine as a

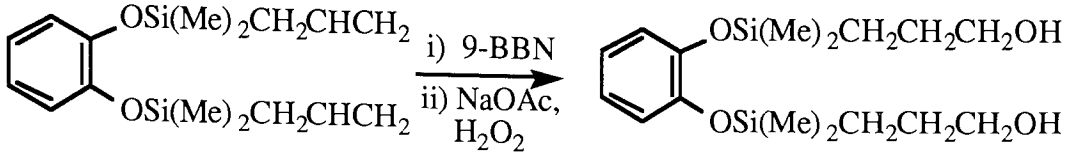
solvent and no catalyst a reduced yield of 22% was obtained.

These observations would suggest that the best method for the synthesis of the corresponding *cis*-DHCD derivative would be with pyridine as the acid trap, dichloromethane as solvent and DMAP as a catalyst.

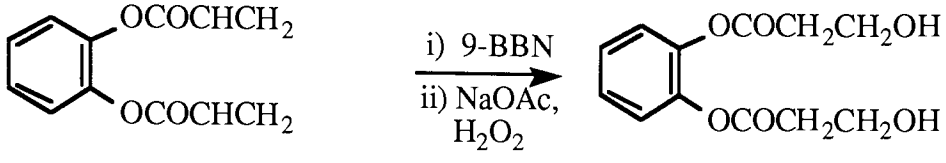
2.3.8 Hydroboration of Unsaturated Model Compounds.

It was hoped that the terminal double bonds in the *cis*-DHCD analogues of compounds **41-43** (Scheme 2.6) could be hydroborated selectively to give the *cis*-DHCD analogues of compounds **44-46**. It has been observed previously that exocyclic double bonds may be hydroborated preferentially in the presence of endocyclic double bonds[145] and that conjugated dienes react more slowly than non conjugated dienes.[146,147] The hydroboration of the model compounds **41-43** was therefore investigated, see Scheme 2.6.

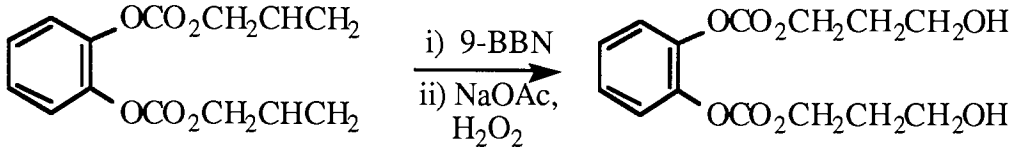
It was observed that the organosilicon compound **41** hydrolysed so readily that it would not survive the reaction conditions required for hydroboration. Attempts to hydroborate compound **43** with 9-BBN were unsuccessful; even after a reaction time of 24 hours there was no indication, from the ^{1}H and ^{13}C NMR spectra, that any reaction had occurred. This lack of reactivity was unexpected and so it was decided to look at the analogous reaction of the phenol analogue **47** which was prepared in an excellent yield 94%. It was discovered that approximately a third of the compound had reacted after four hours; two muliplet signals, of equal intensity, were detected at 3.7δ and 4.3δ, in the ^{1}H NMR of the products, corresponding to hydrogens **a** and **b** respectively, see Scheme 2.6. These observations would suggest that the hydroboration is inhibited by steric hindrance, caused by interaction of the second pendant chain with the incoming 9-BBN molecule. The hydroboration of **42** was not studied since it would be expected that the steric hindrance would be greater in this compound, than in compound **43**, as the pendant chains are shorter and less flexible.



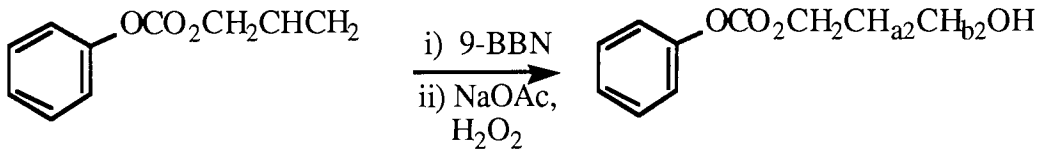
41 **44**



42 **45**



43 **46**



47 **48**

94%

Scheme 2.6: Hydroboration Reactions.

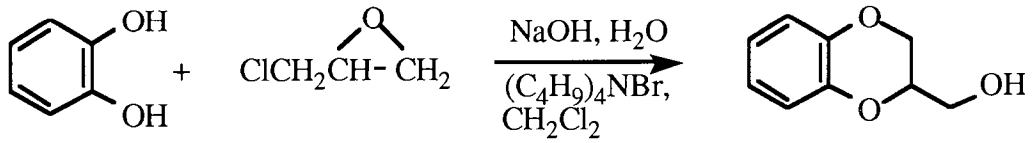
Originally it was hoped that derivatives of *cis*-DHCD, which contained double bonds in their pendant chains, could be selectively hydroborated with 9-BBN. Studies of the model compounds showed that this was not possible because of the steric hindrance caused by the neighbouring pendant group. It might be expected that diborane, which is a much smaller reagent than 9-BBN, might achieve this hydroboration but it is not possible to selectively

hydroborate exocyclic double bonds, in the presence of endocyclic double bonds with this reagent.

2.3.9 Synthesis of 2-Hydroxymethylbenzodioxen.

Catechol was reacted with epichlorohydrin with the hope that opening of the pendant epoxide rings would give a very hydrophilic, tetrahydroxy compound.

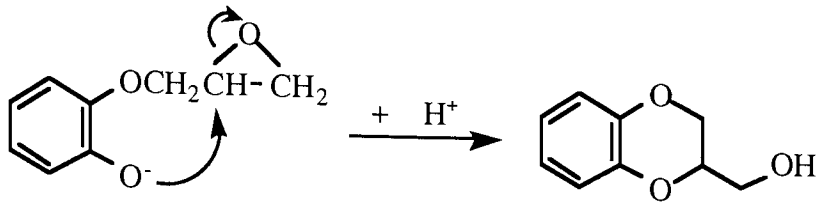
The reaction of phenol with epichlorohydrin under PTC conditions has been described previously by McKillop and co-workers,[141] who obtained the epoxy ether in 77% yield. This procedure was followed for the reaction of catechol with epichlorohydrin but with a reaction time of five days instead of the 2-12 hours used previously for the phenol analogue. The product obtained was not the expected diglycidyl ether but 2-hydroxymethylbenzodioxen **49**, which was isolated in 36% yield, see Scheme 2.7



3 **49** 36%

Scheme 2.7: Synthesis of 2-Hydroxymethylbenzodioxen.

The compound **49** is a common product from the reaction of catechol with epichlorohydrin.[148] It was probably formed in the aqueous phase by an intramolecular ring opening of the epoxide ring by the phenoxide oxygen, see Figure 2.7.



49

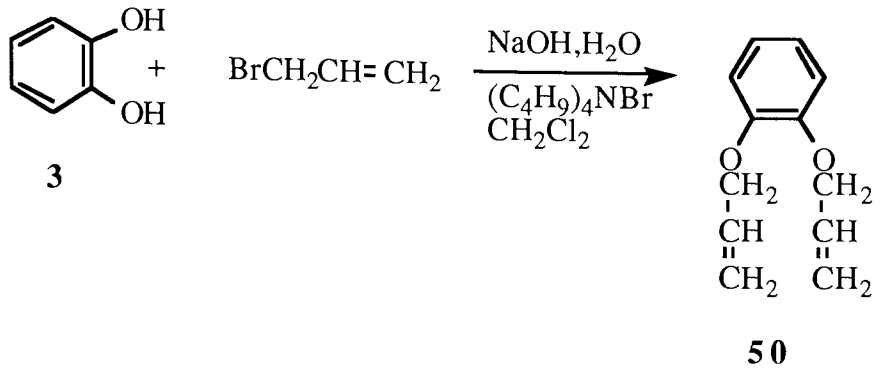
Figure 2.7: Formation of 2-Hydroxymethylbenzodioxen.

It would appear from these observations that the reaction of *cis*-DHCD with epichlorohydrin under PTC conditions could lead to either the diglycidyl derivative or the analogue of compound **49**. Either product would be useful since the diglycidyl compound could be converted to the tetrahydroxy compound, by base catalysed ring opening of the epoxide rings, to give a highly hydrophilic monomer. The *cis*-DHCD analogue of **49** would itself be a useful hydrophilic monomer.

2.3.10 Synthesis of 1,2-Bis(allyloxy)benzene.

The difficulty in preparing the diglycidyl ether derivative of catechol, from epichlorohydrin, led to a search for an alternative route so that a study of the conditions necessary for the opening of the epoxide rings could be undertaken. It was thought that epoxidation of the diallyl ether analogue might lead to the desired compound.

Catechol was reacted with allyl bromide using the method of McKillop and co-workers[141] but with a longer reaction time of five days since the introduction of the second group might be slow due to steric hindrance, see Scheme 2.8.



3 **50**

Scheme 2.8: Synthesis of 1,2-Bis(allyloxy)benzene.

The ^{1}H and ^{13}C and COSY NMR spectra of the products of the reaction are shown in Figure 2.8. Examination of the spectra shows that two different allyl systems are present. The COSY spectrum indicates that the peak between 3-3.5δ is coupled to the peak at 4.5δ. This is consistent with the spectrum of allyl alcohol. The second allyl system could be due to either the desired product or allyl ether.

It appeared from these model compound studies that attempts to synthesise the analogous *cis*-DHCD derivatives would not be profitable.

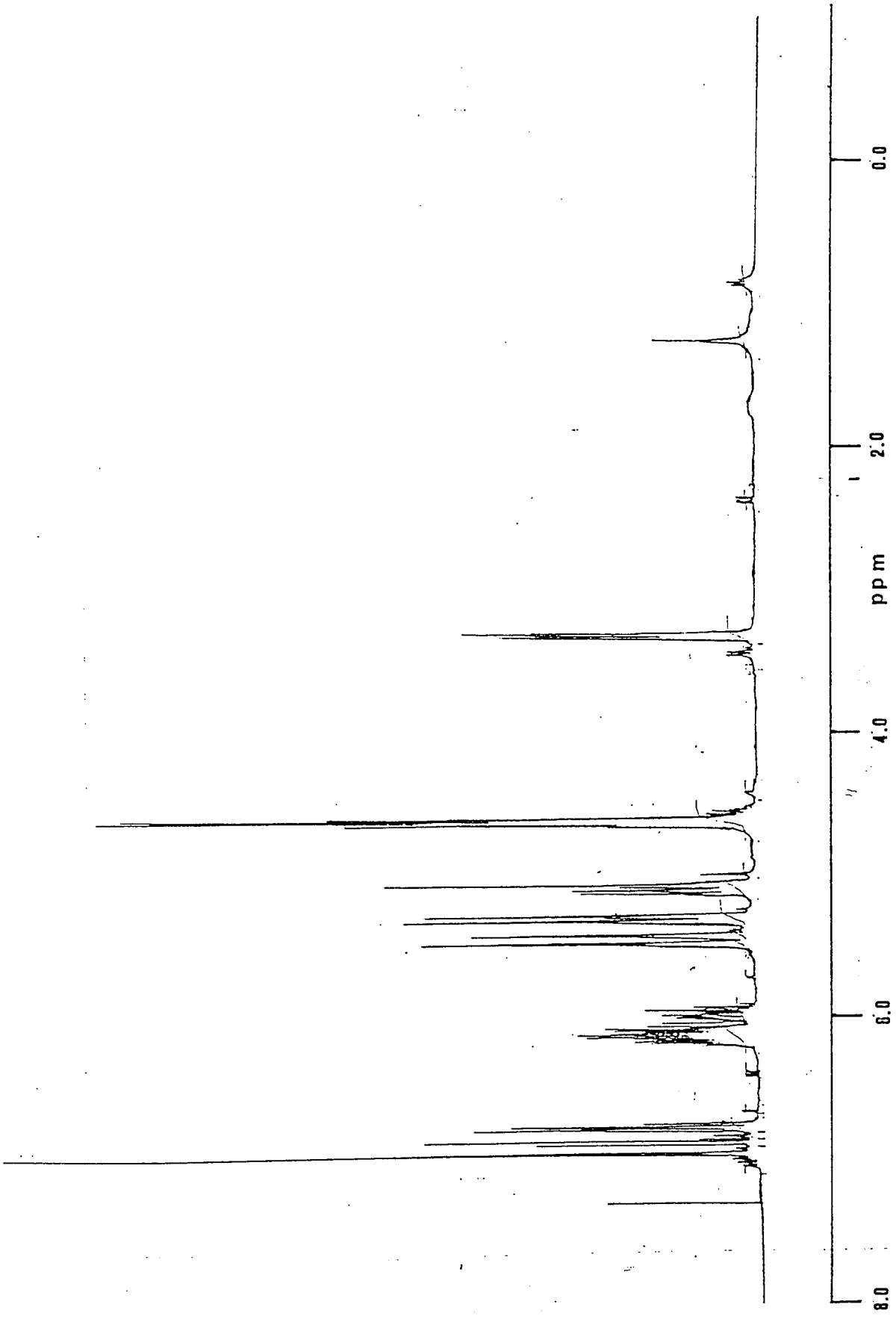


Figure 2.8a: ^{1}H NMR Spectrum. Etherification Products from the Reaction of Catechol with Allylbromide

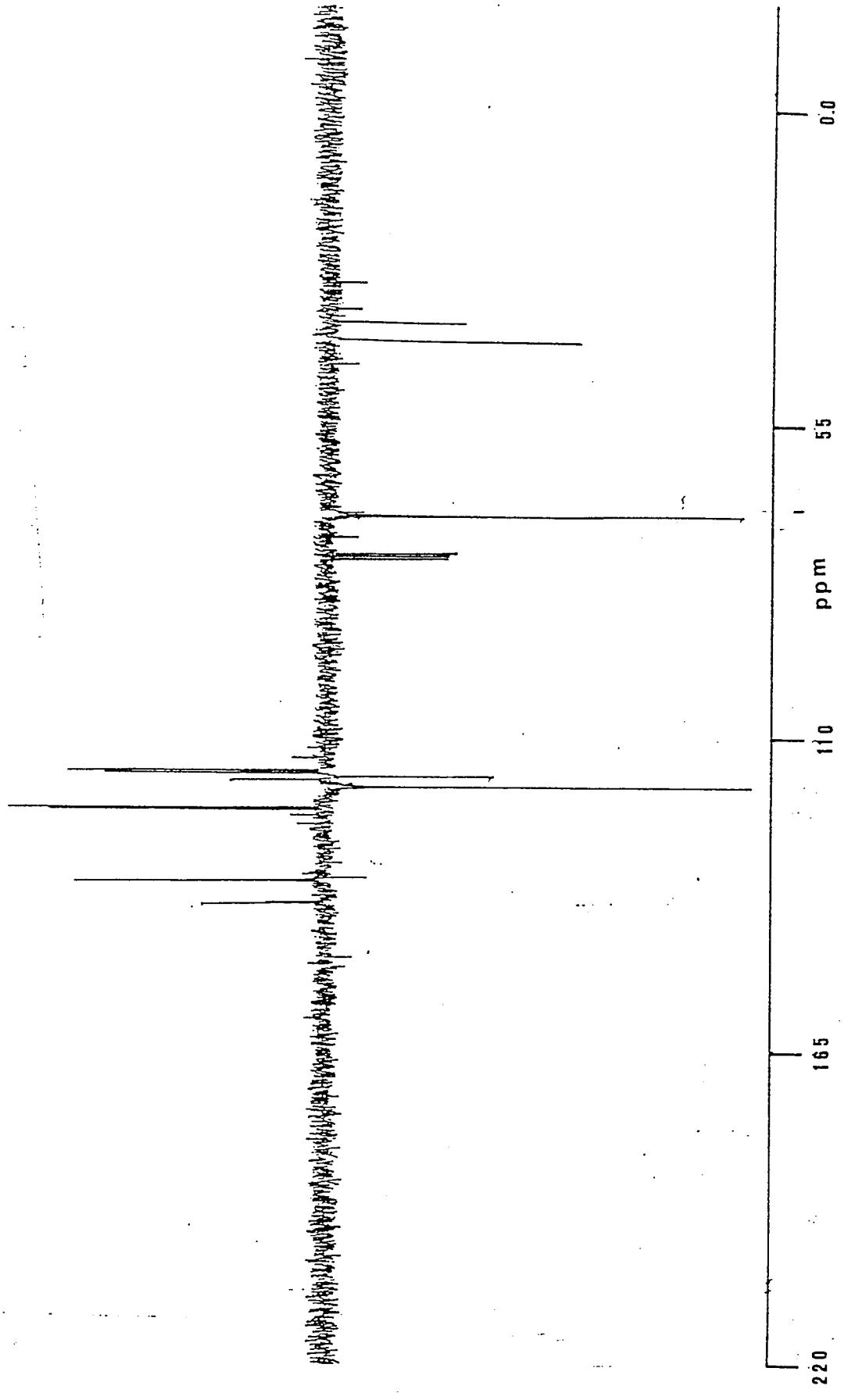


Figure 2.8b: ^{13}C NMR Spectrum, Etherification Products from the Reaction of Catechol with Allylbromide

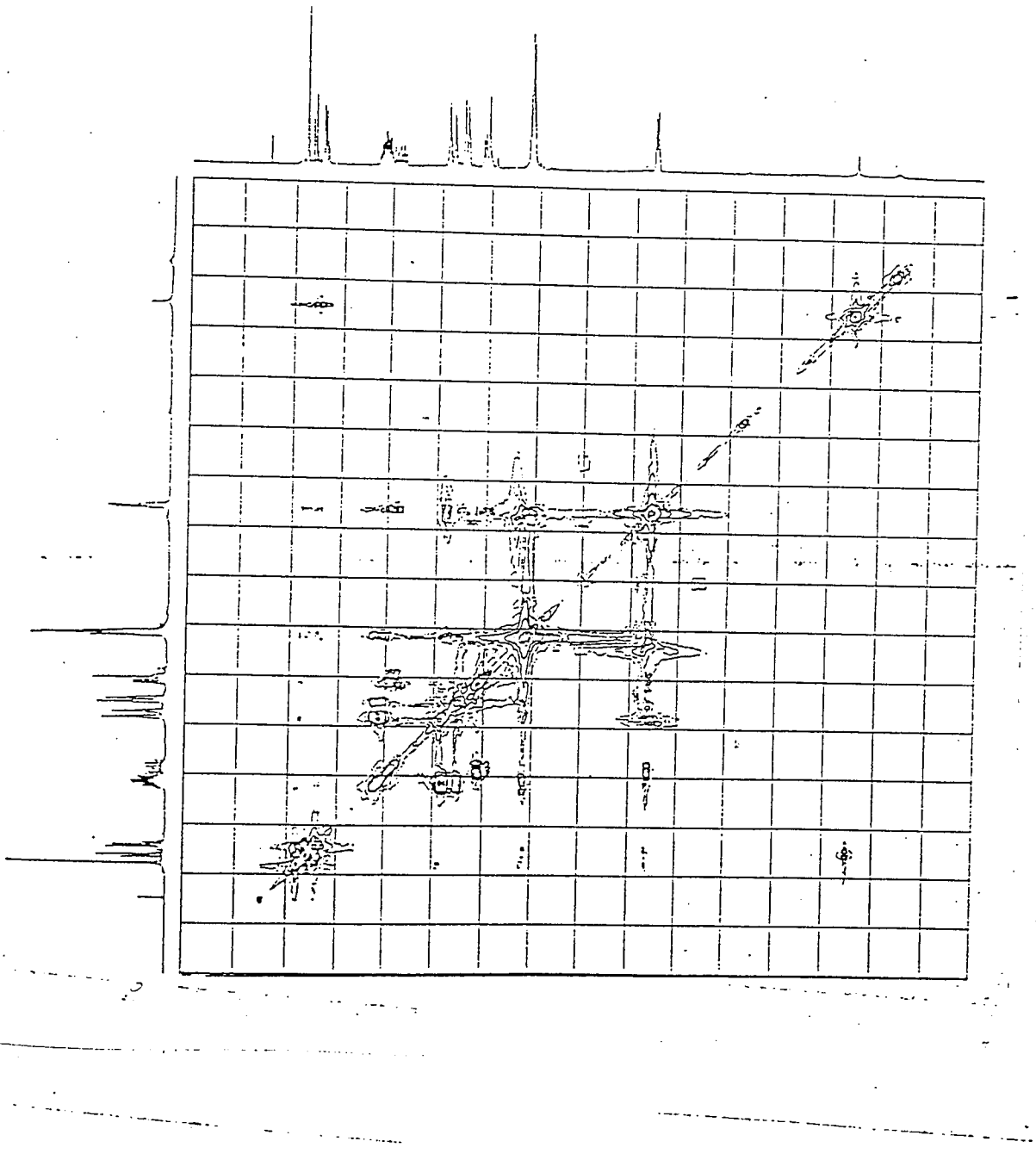


Figure 2.8c: COSY NMR Spectrum, Etherification Products from the Reaction of Catechol with Allylbromide

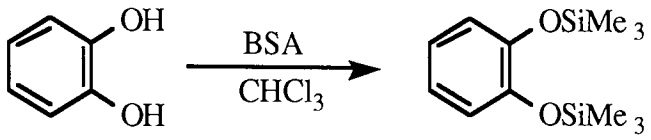
2.3.11 Synthesis of 1,2-Bis(trimethylsiloxy)benzene.

One part of the work was concerned with the synthesis of hydrophilic derivatives of *cis*-DHCD and an assessment of the effects which such monomers would have on the properties of poly HEMA hydrogels. A second approach to the monomer synthesis was the preparation of a masked DHCD monomer which, when polymerised and deprotected, would provide a simple indirect route for the incorporation of *cis*-DHCD itself into hydrogel systems. *cis*-DHCD can not be polymerised directly, under the usual polymerisation conditions, as aromatisation occurs.

The principal factor to be investigated, in the latter approach, was the ease with which the protecting groups could be removed from a hydrogel system, under mild conditions. Although hydrogels may imbibe organic solvents and reagents readily, to facilitate the removal of the protecting groups, the hydrogel must then be reswollen in water for some time in order to remove the products of the reaction. Since a mild, aqueous removal system is far more preferable trimethylsilyl ethers appeared to be suitable protecting groups.

The compound 1,2-bis(trimethylsiloxy)benzene **51** was prepared in 77% yield by reaction of catechol with bis(trimethylsilyl)acetamide (BSA).[149] The removal of the remaining *N*-(trimethylsilyl)acetamide was complicated by the similarity in the boiling points of this compound and 1,2-bis(trimethylsiloxy)benzene **51**; this problem was overcome by the addition of 1M HCl followed by immediate washing with water and drying of the organic phase. Solvent removal and distillation provided the desired product in a good yield of 77%. Trimethylsilyl ethers are known to hydrolyse rapidly but it was observed that if the extractive procedure was performed quickly that this hydrolysis could be kept to a minimum.

This method proved successful for the synthesis of the catechol derivative but the problems encountered in the removal of *N*-(trimethlsilyl)acetamide indicated that it would be preferable to use a silylating agent with more volatile by-products for the synthesis of the *cis*-DHCD analogue.



3 **51**

77%

Scheme 2.9: Synthesis of 1,2-Bis(trimethylsiloxy)benzene.

2.4 SYNTHESIS OF MONOMERS.

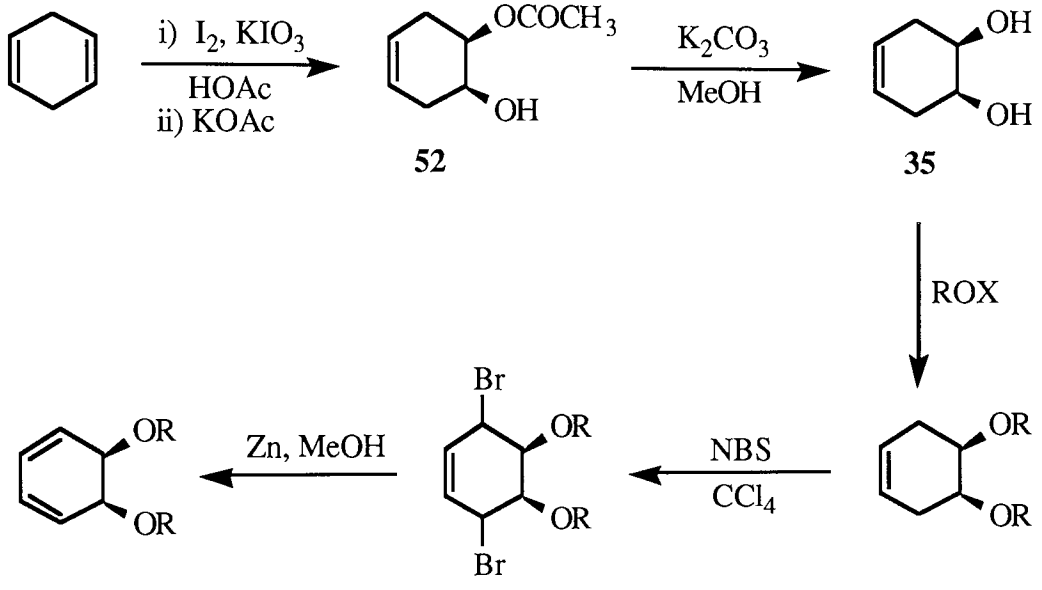
It was originally intended to synthesise hydrophilic derivatives directly from *cis*-DHCD, using the successful methods described above for the syntheses of the model compounds. However, by the time the model syntheses had been completed it became apparent that ICI, due to other commitments, would be unable to supply *cis*-DHCD. At that time the compound was commercially available as a 20% w/v solution in ethyl acetate with triethylamine as a stabiliser. The commercial sample proved to be of poor quality, only 50% of the material, stated to be present, could be isolated after recrystallisation and a further problem was that it was prohibitively expensive. The lack of availabilty of *cis*-DHCD led us to investigate the possibilty of synthesising hydrophilic derivatives of this compound, indirectly.

The use of *trans*-DHCD as a possible material for preparing hydrophilic monomers was also considered as it could be obtained by the five step procedure developed by Platt and Oesch.[103] This somewhat lengthy synthesis of *trans*-DHCD led us to investigate possible indirect syntheses of hydrophilic derivatives of *trans*-DHCD.

2.4.1 Design of Synthetic Routes.

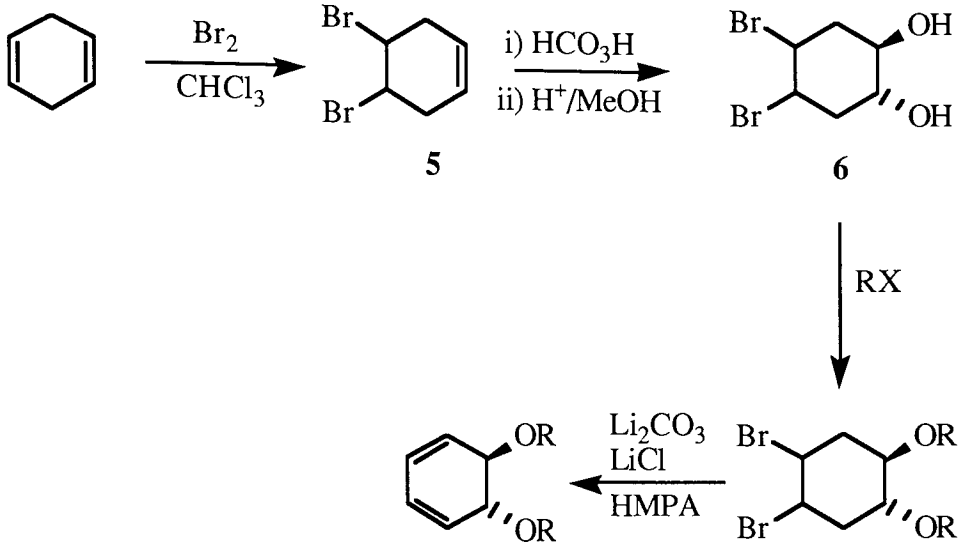
2.4.1.1 Methods for Preparing DHCD Derivatives Indirectly.

The hydrophilic derivatives of *cis*-DHCD were prepared using the method described previously by McKean and Stille for the syntheses of hydrophobic derivatives of *cis*-DHCD, see Scheme 2.10.



Scheme 2.10: Indirect Route to *cis*-DHCD Derivatives.

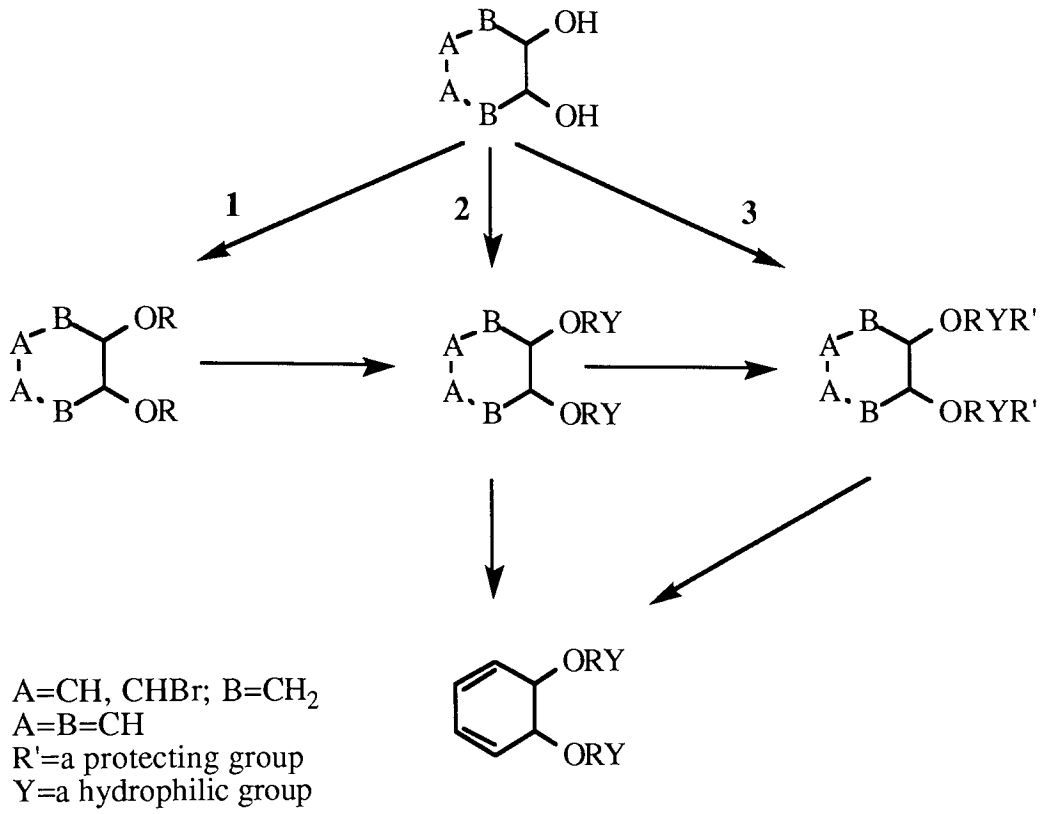
Hydrophilic derivatives of *trans*-DHCD were synthesised using a modification of the Platt and Oesch method for the synthesis of *trans*-DHCD,[103] see Scheme 2.11.



Scheme 2.11: Indirect Route to *trans*-DHCD Derivatives.

2.4.1.2 Methods for Introducing Hydrophilic Groups.

The introduction of hydrophilic groups into DHCD derivatives is complicated by the presence of the diol group, which would be in competition with many hydrophilic groups during derivatisation, causing side reactions, e.g. OH. Most hydrophilic groups would either have to be protected (**Route 3**), or introduced in a separate step (**Route 1**); (**Route 2**) represents the direct introduction of hydrophilic groups if protection is not required, see Scheme 2.12. All three of these methods were employed in the design and synthesis of DHCD derivatives.



Scheme 2.12: Methods for Introducing Hydrophilic Groups.

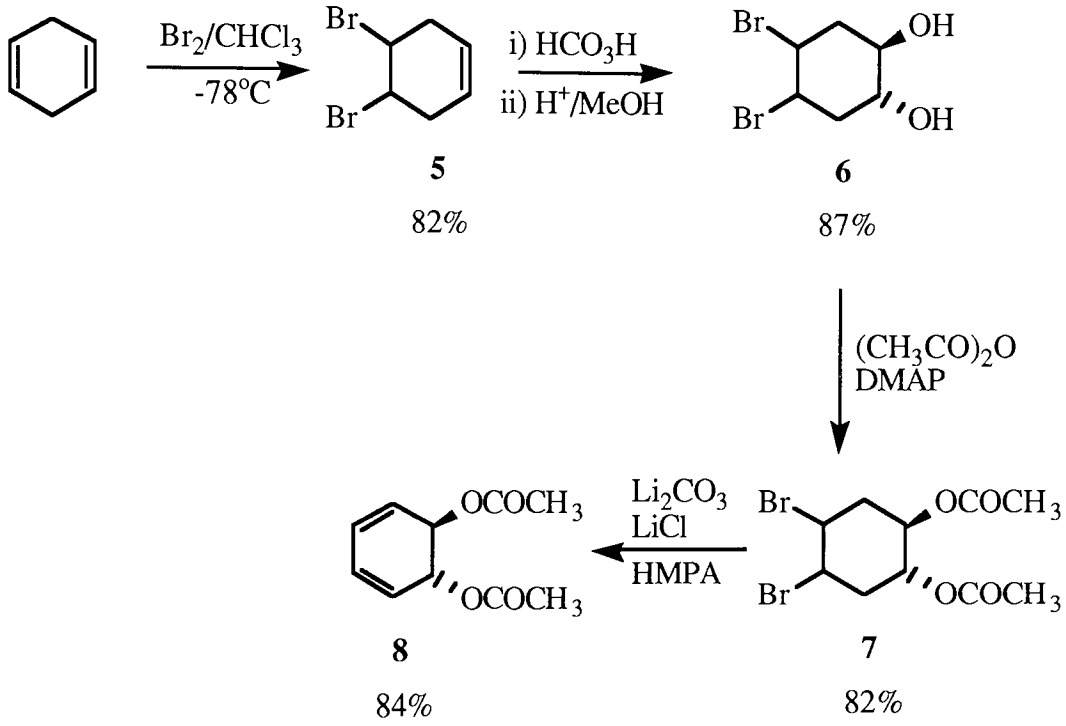
A further complication in the synthesis of hydrophilic monomers is their solubility in water. In order to avoid the need for a lengthy continuous extraction process it was desirable to devise methods whereby the unprotected monomer would not be in contact with an aqueous medium.

The selection of hydrophilic groups to be introduced into the monomers was governed by the ease of introduction and / or protection-deprotection, and their occurrence in current hydrogel systems. The hydroxy group is by far the most common group in such materials. It has the advantage that it may be protected-deprotected under a variety of conditions and can be introduced, in a separate step, via a number of common functional groups.

2.4.2 Synthesis of Monomers.

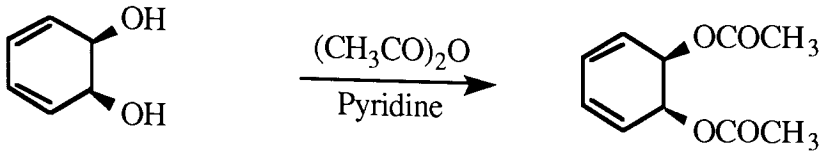
2.4.2.1 Synthesis of 1,2-Diacetoxy-3,5-cyclohexadiene.

The compound *trans*-1,2-diacetoxy-3,5-cyclohexadiene **8** was prepared by the procedure of Platt and Oesch,[103] see Scheme 2.13. All of the steps in this synthesis gave good yields of the desired products.[105,150-153]



Scheme 2.13: Synthesis of *trans*-1,2-Diacetoxy-3,5-cyclohexadiene.

The compound *cis* 1,2-diacetoxy-3,5-cyclohexadiene **36** was prepared by both direct and indirect syntheses. Following the procedure of Ballard and co-workers[19] acetylation of *cis*-DHCD **1** with acetic anhydride in pyridine produced a 40% yield of **36**, see Scheme 2.14. The relatively low yield of **36** was probably due to the high temperatures required to remove the pyridine which caused aromatisation of the product in a basic medium.

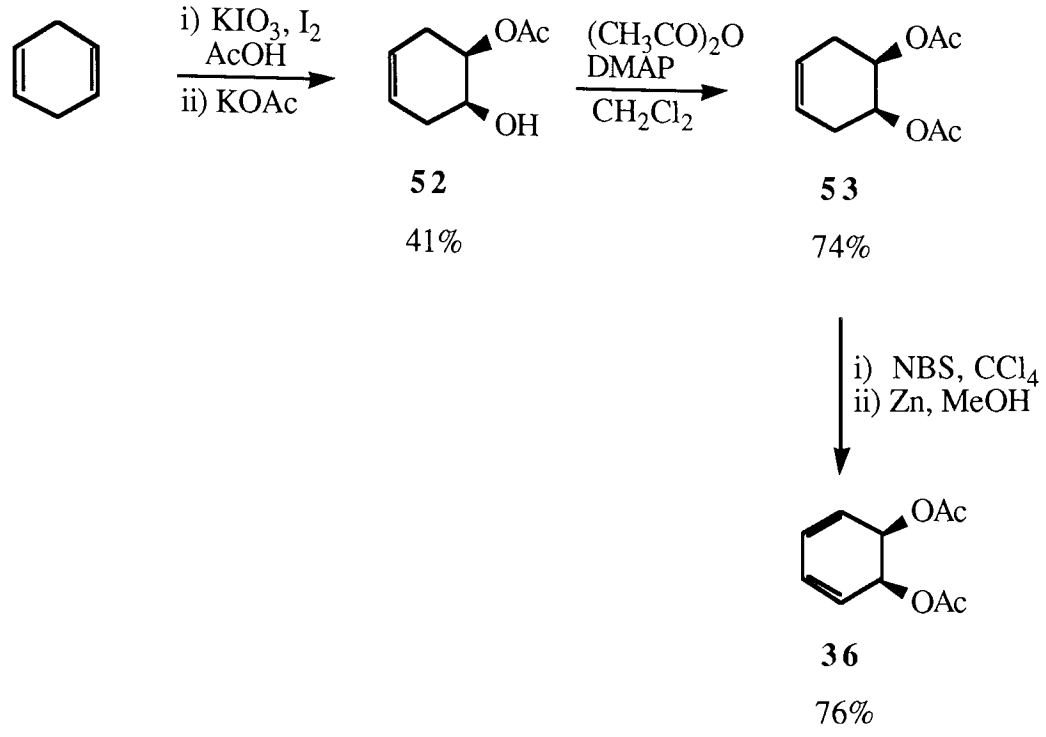


1 **36**

40%

Scheme 2.14: Direct Synthesis of *cis*-1,2-Diacetoxy-3,5-cyclohexadiene.

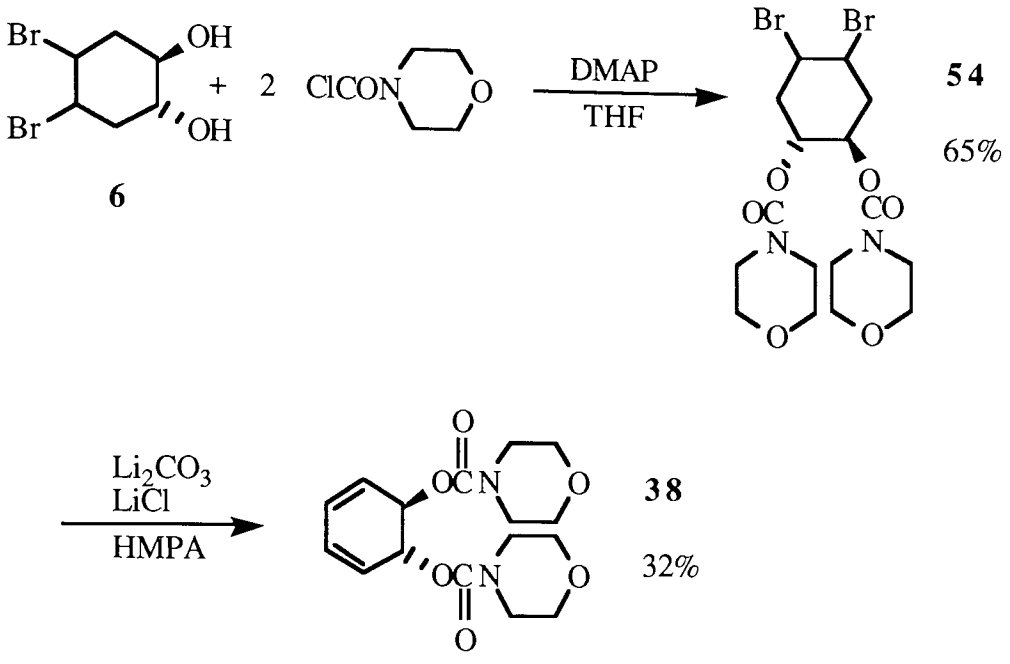
Indirect synthesis of the compound *cis*-1,2-diacetoxy-3,5-cyclohexadiene **36** was achieved by the literature procedure of McKean and Stille,[20] see Scheme 2.15. Compound **52** was prepared in a yield of 41%. The distilled product from this reaction contained 25% of the diacetate **53**. The products from this reaction were acetylated with acetic anhydride in dichloromethane in the presence of triethylamine and DMAP giving **53** in a good yield of 74%. Refluxing compound **53** with NBS in carbon tetrachloride followed by treatment of the crude dibromide with zinc dust in dry methanol under an argon atmosphere gave the *cis* monomer **36**, as a pale orange oil, in a good yield of 76%. It should be noted that the use of anhydrous methanol is essential in the final step if aromatisation is to be avoided,[20] despite this precaution the NMR spectra of the final product indicated that approximately 8% of aromatic material was present.



Scheme 2.15: Indirect Synthesis of *cis*-1,2-Diacetoxy-3,5-cyclohexadiene.

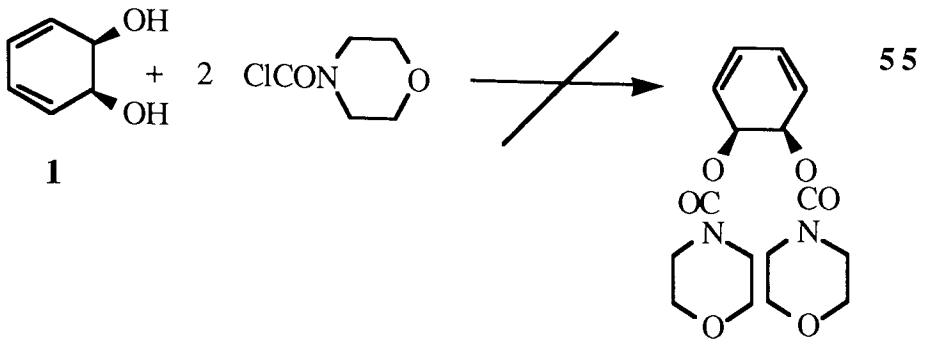
2.4.2.2 Synthesis of 1,2-Bis(4-morpholinecarboxy)-3,5-cyclohexadiene.

The compound *trans*-1,2-bis(4-morpholinecarboxy)-4,5-dibromocyclohexane **54** was obtained in a yield of 65%, when compound **6** was refluxed in dry THF for three days with 4-morpholinecarbonyl chloride, DMAP and triethylamine, see Scheme 2.16. The long reaction time was necessary because of the relative inertness of 4-morpholinecarbonyl chloride compared with other acyl chlorides. Heating compound **54** with Li_2CO_3 and LiCl in HMPA at 90°C for two hours under nitrogen resulted in the formation of *trans*-1,2-bis(4-morpholinecarboxy)-3,5-cyclohexadiene **38** in 32% yield. The main problem encountered was the separation of **38** from the HMPA. The usual procedure of acidifying the solution, followed by extraction with a suitable solvent, gave a product still contaminated with a large amount of HMPA. A pure product was finally isolated by dry flash chromatography (silica gel; ethyl acetate).



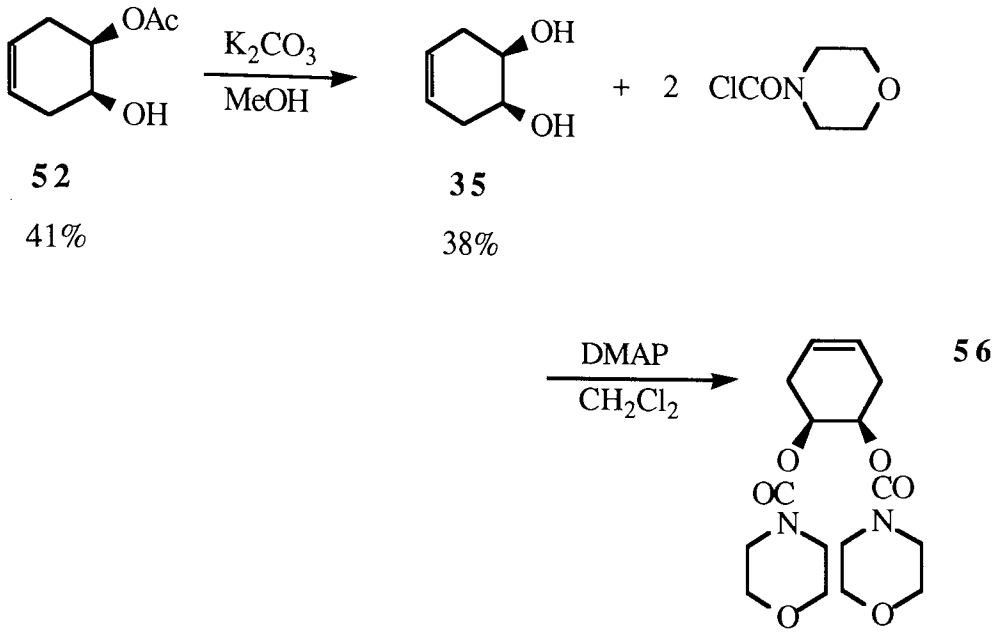
Scheme 2.16: Synthesis of *trans*-1,2-Bis(4-morpholinecarboxy)-3,5-cyclohexadiene.

Routes to the direct and indirect syntheses of *cis*-1,2-bis(4-morpholinecarboxy)-3,5-cyclohexadiene **55** were investigated. The direct synthesis, shown in Scheme 2.17, involved reaction of 4-morpholinecarbonyl chloride with *cis*-DHCD **1** in the presence of DMAP, at room temperature. The only product isolated from this reaction was a minute quantity of the anhydride of 4-morpholinecarbonyl chloride. The failure to isolate any *cis*-1,2-bis(4-morpholinecarboxy)-3,5-cyclohexadiene **55**, by this method, can be accounted for by the relative inertness of 4-morpholinecarbonyl chloride. An obvious method to improve the yield of product would be to carry out the reaction at a higher temperature but this would cause aromatisation of both *cis*-DHCD and any derivatives formed.



Scheme 2.17: Direct Synthesis of *cis*-1,2-Bis(4-morpholinecarboxy)-3,5-cyclohexadiene.

The indirect route to compound **55** which appeared most likely to succeed was based on the procedure of McKean and Stille,[20] see Scheme 2.18. Compound **35** was prepared in a moderate yield of 38%, from the monoacetate **52** by reaction with powdered potassium carbonate in methanol solvent. Reaction of diol **35** with 4-morpholinecarbonyl chloride in refluxing dichloromethane in the presence of DMAP and triethylamine produced an orange oil. This was decolourised with charcoal but TLC analysis of the product (silica gel; ethyl acetate) showed that three compounds were present. Examination of the ^{1}H and ^{13}C NMR spectra showed that both di and monosubstituted compounds were probably present in addition to a significant quantity of the anhydride of 4-morpholinecarbonyl chloride, see Figure 2.9.



Scheme 2.18: Indirect Synthesis of *cis*-1,2-Bis(4-morpholinecarboxy)-3,5-cyclohexadiene.

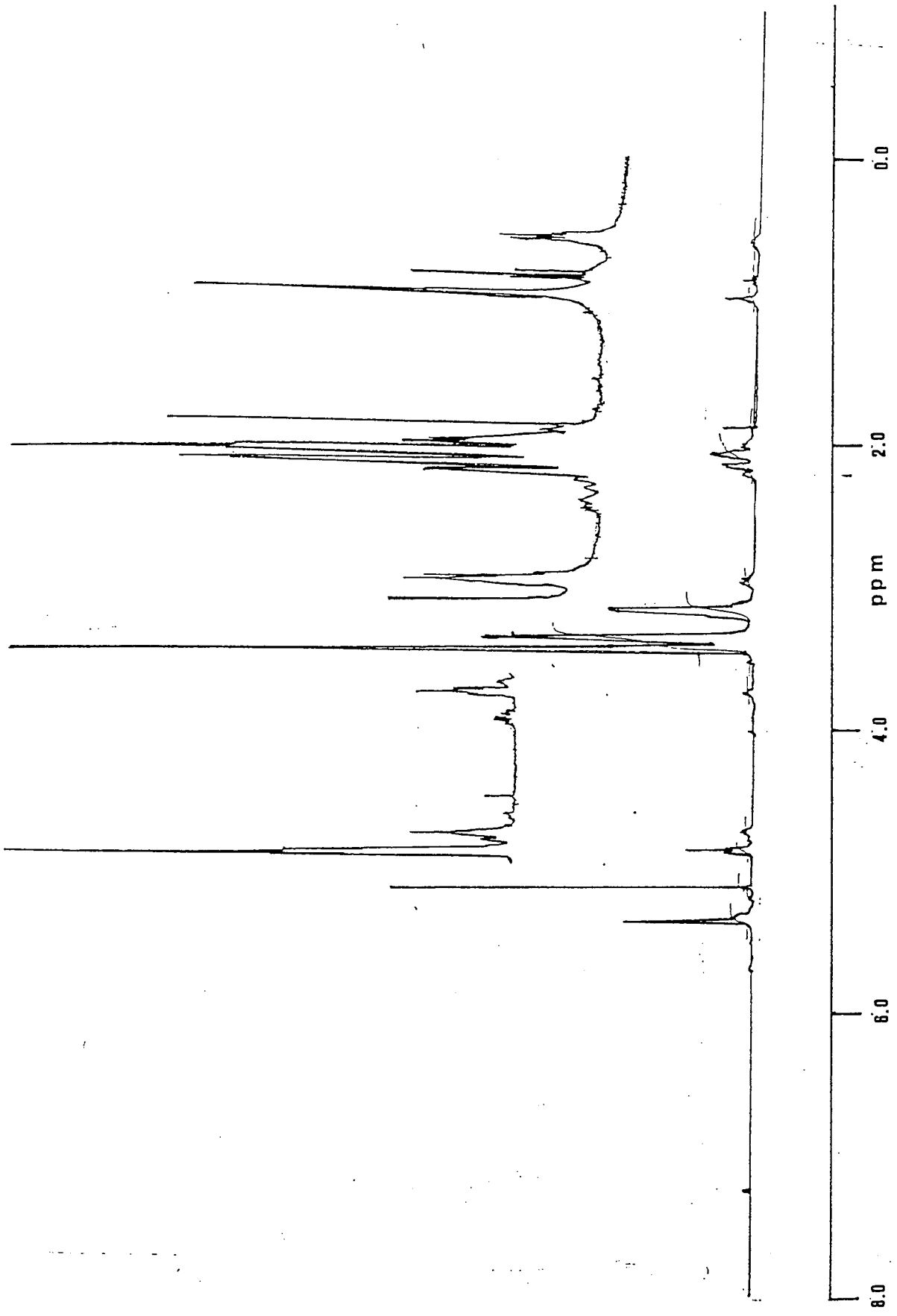


Figure 2.9a: ^{1}H NMR Spectrum, Indirect Synthesis of *cis*-(4-morpholinecarboxy)-3,5-cyclohexadiene.

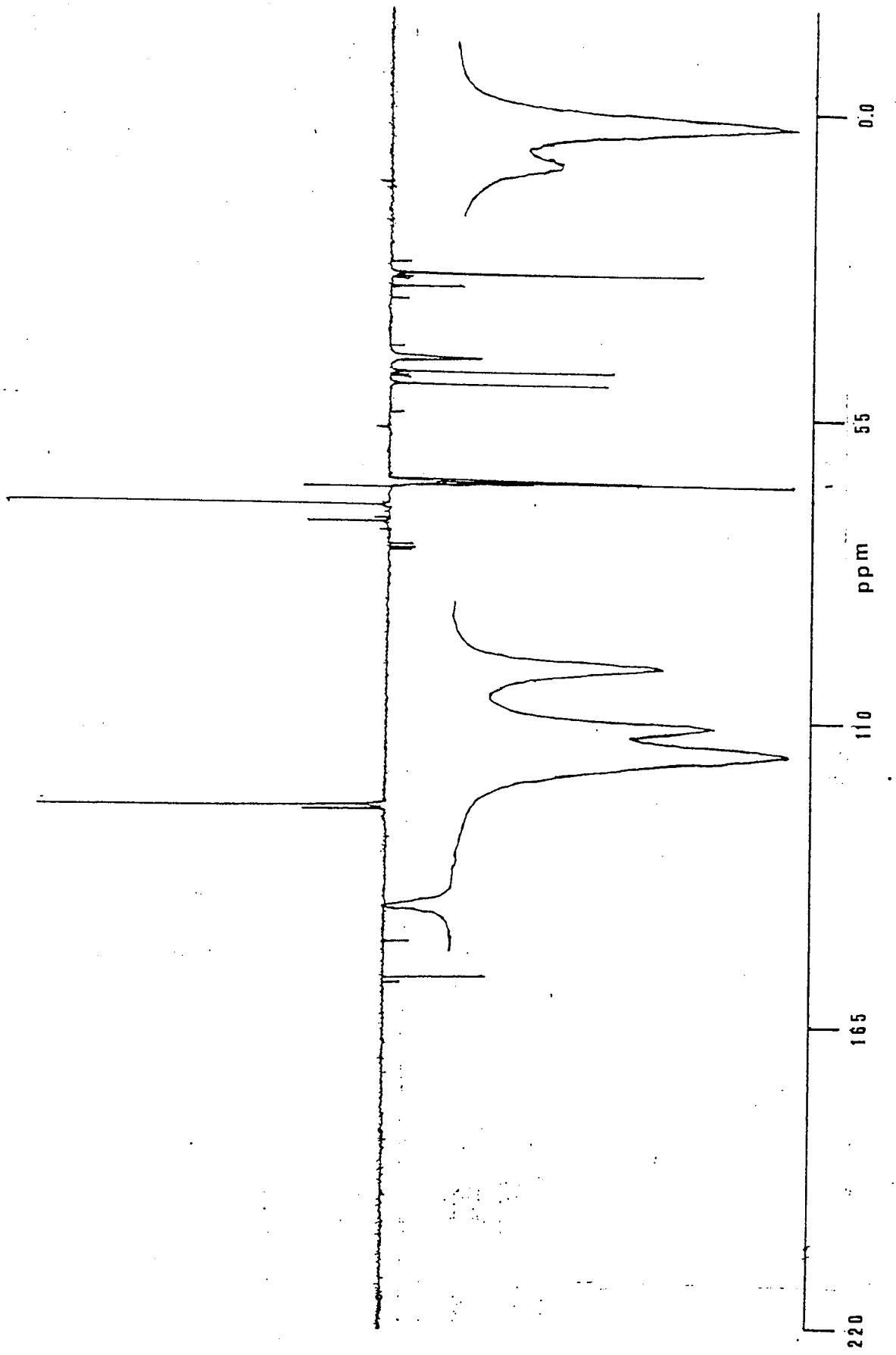
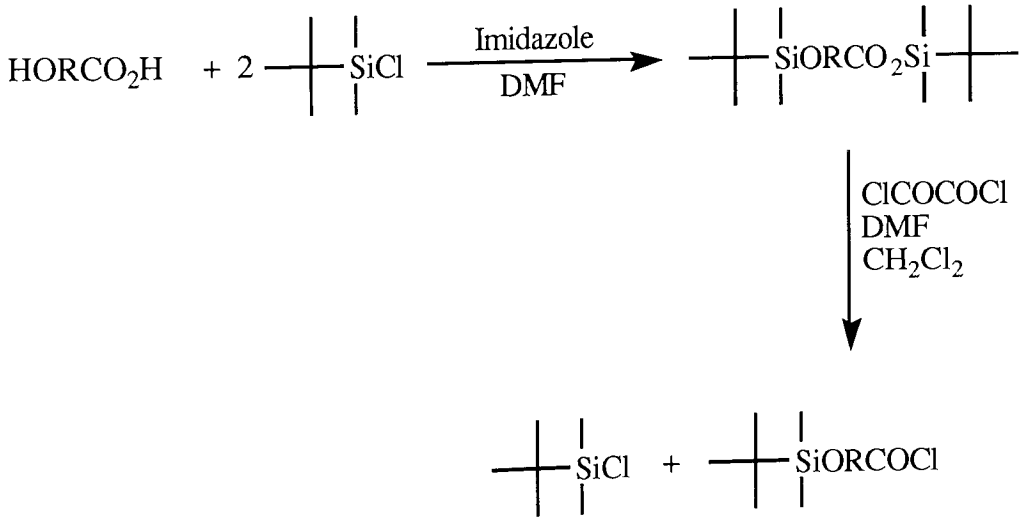


Figure 2.9b: ^{13}C NMR Spectrum. Indirect Synthesis of *cis*-(4-morpholinecarboxy)-3,5-cyclohexadiene.

2.4.2.3 Synthesis of 1,2-Bis(hydroxyacetoxy)-3,5-cyclohexadiene.

A large number of hydroxy carboxylic acids are commercially available and it was envisaged that a variety of hydrophilic derivatives of DHCD might be prepared from these compounds.

The most common methods for preparing acid chlorides are the reactions of carboxylic acids with reagents such as thionyl chloride, phosphorous pentachloride, oxalyl chloride or phosgene.[154] Milder methods are available for synthesising acid chlorides of more sensitive acids,[155,156] but hydroxy acids require the protection of the alcohol groups prior to the formation of the acyl chloride function. The method of Wissner and Grudzinskas[157] has the advantage that the activation of the carboxylic acid group and the protection of the alcohol group is brought about in a single step, under neutral conditions. In addition the ester, produced after reaction of this protected acid chloride with an alcohol, has the alcohol groups already protected for any subsequent steps in the synthesis. The Wissner Grudzinkas route for preparing these protected hydroxy acid chlorides is illustrated in Scheme 2.19.

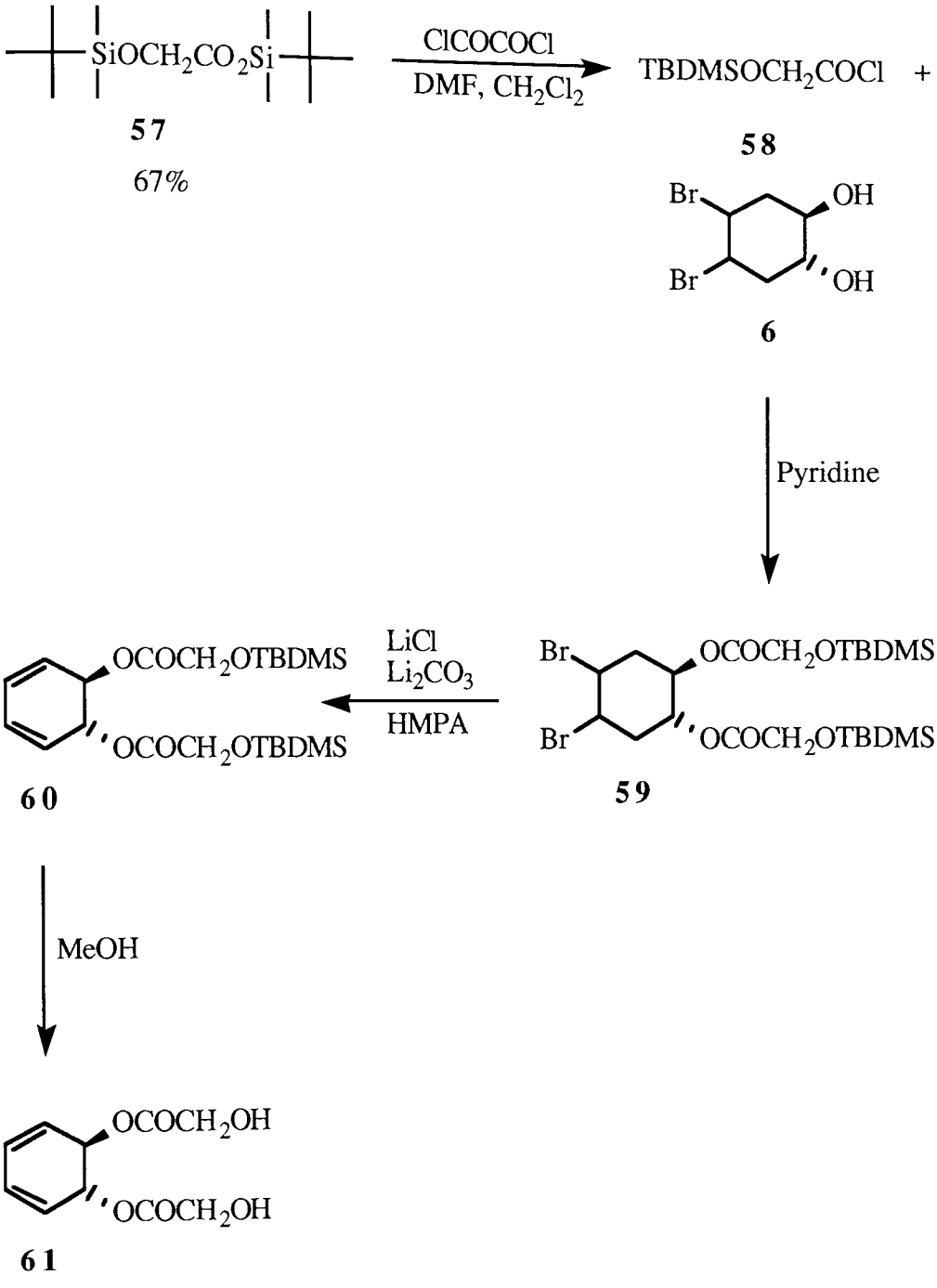


Scheme 2.19: Synthesis of Protected Hydroxy Acid Chlorides.

The reaction of hydroxy groups with *tert*-butyldimethylsilyl chloride is usually perfomed with imidazole in DMF but a more convenient method uses DMAP as a catalyst, and triethylamine as an acid trap, in dichloromethane.[158]

The compound *tert*-butyldimethylsilyl *tert*-butyldimethylsiloxyacetate **57** was prepared, by reaction of glycolic acid with *tert*-butyldimethylsilyl chloride, DMAP and triethylamine in dichloromethane, in a good yield of 67%. The crude product contained *tert*-butyldimethylsilanol and its removal proved difficult. Reduced pressure distillation was the most effective method for the separation of the products. Silyl esters hydrolyse readily on standing[159] but the esters containing the large *tert*-butyldimethylsilyl group do so only slowly, due to their increased stability. Reaction of **57** with oxalyl chloride, followed by removal of the solvent, gave a mixture of the protected acid chloride **58** and *tert*-butyldimethylsilyl chloride.

The synthetic route devised for the synthesis of *trans*-1,2-bis(hydroxyacetoxy)-3,5-cyclohexadiene **61** is shown in Scheme 2.20. Reaction of *tert*-butyldimethylsilyl *tert*-butyldimethylsiloxyacetate **57** with oxalyl chloride, followed by addition of *trans*-1,2-dihydroxy-4,5-dibromocyclohexane **6** in pyridine gave a product which contained a mixture of compounds. Unsubstituted, mono and di substituted compounds are probably present, the ^{1}H and ^{13}C NMR spectra are shown in Figure 2.10. The steric hindrance, due to the large *tert*-butyldimethylsilyl protecting groups, is probably the major cause of the failure of this reaction. It is not possible to promote the reaction with DMAP as a catalyst[160,161] as it would also catalyse the silylation of *trans*-1,2-dihydroxy-4,5-dibromocyclohexane **6** by *tert*-butyldimethylsilyl chloride,[158] nor to increase the temperature at which the reaction is carried out as this would promote cleavage of the silyl ether by the pyridine. The remaining steps in the reaction scheme could not be performed as **59** could not be isolated.



Scheme 2.20: Synthesis of *trans*-1,2-Bis(hydroxyacetoxy)-3,5-cyclohexadiene.

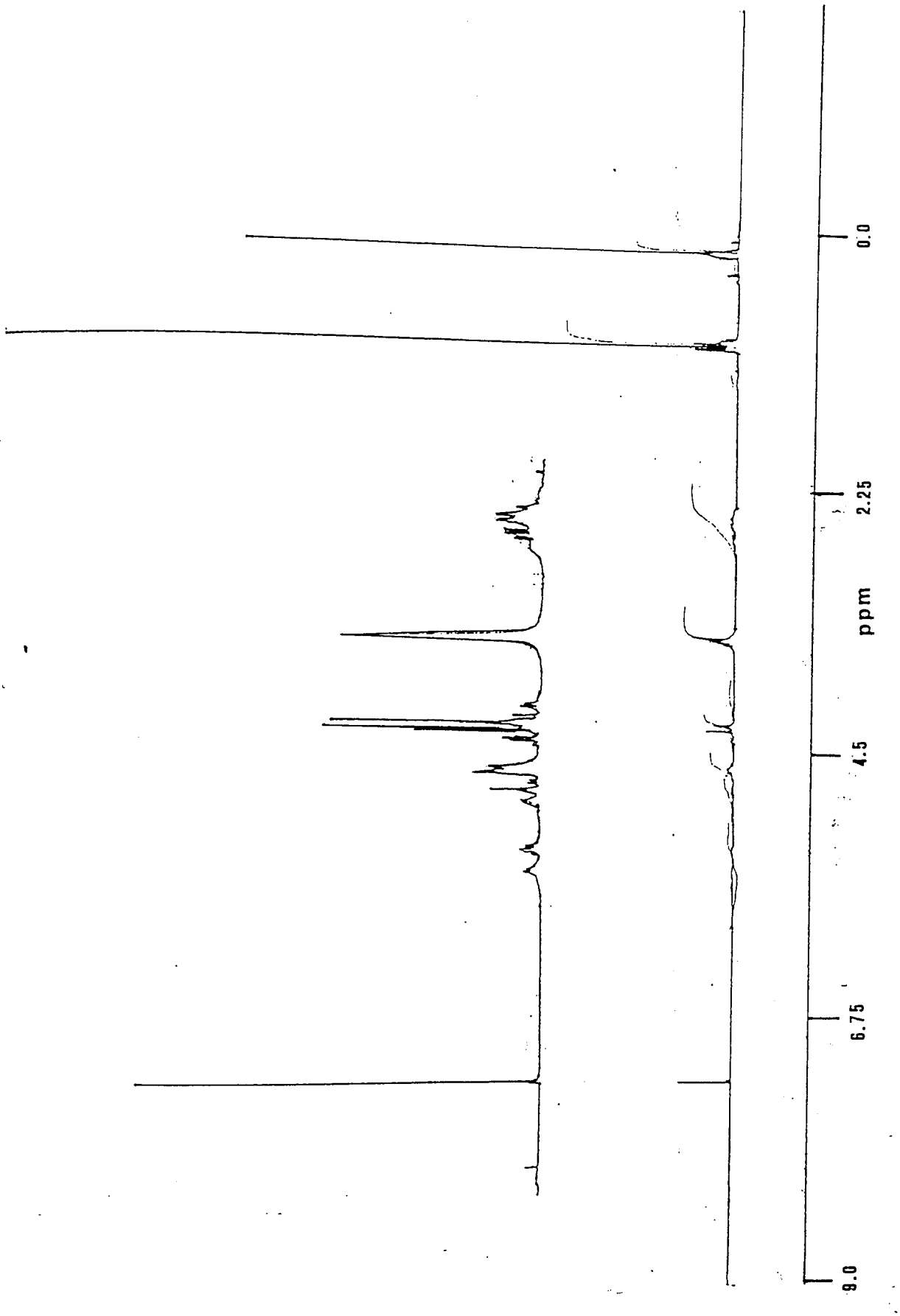


Figure 2.10a: ^{1}H NMR Spectrum, Esterification Products from the Attempted Synthesis of *trans*-1,2-Bis(hydroxyacetoxy)-3,5-cyclohexadiene.

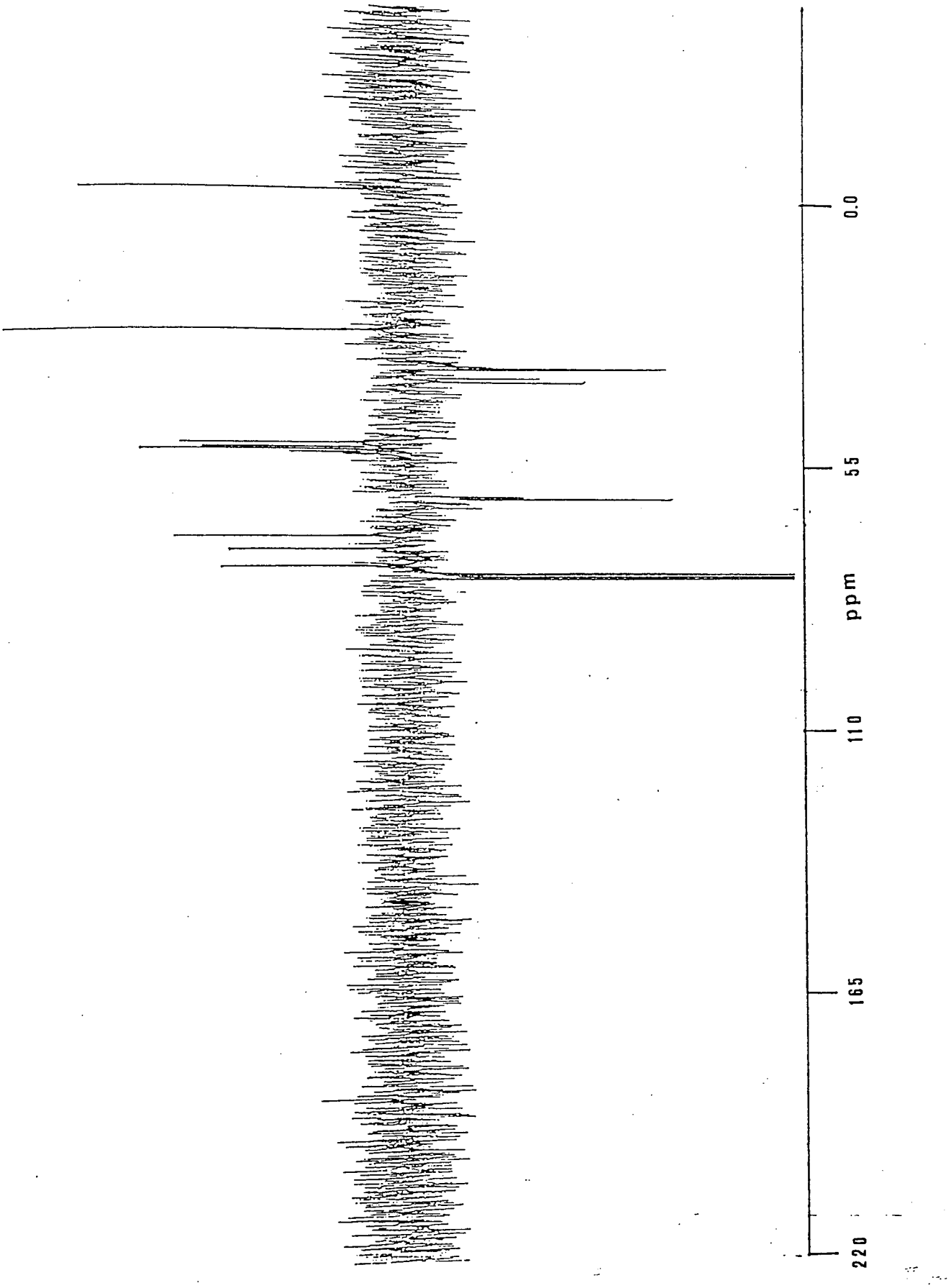
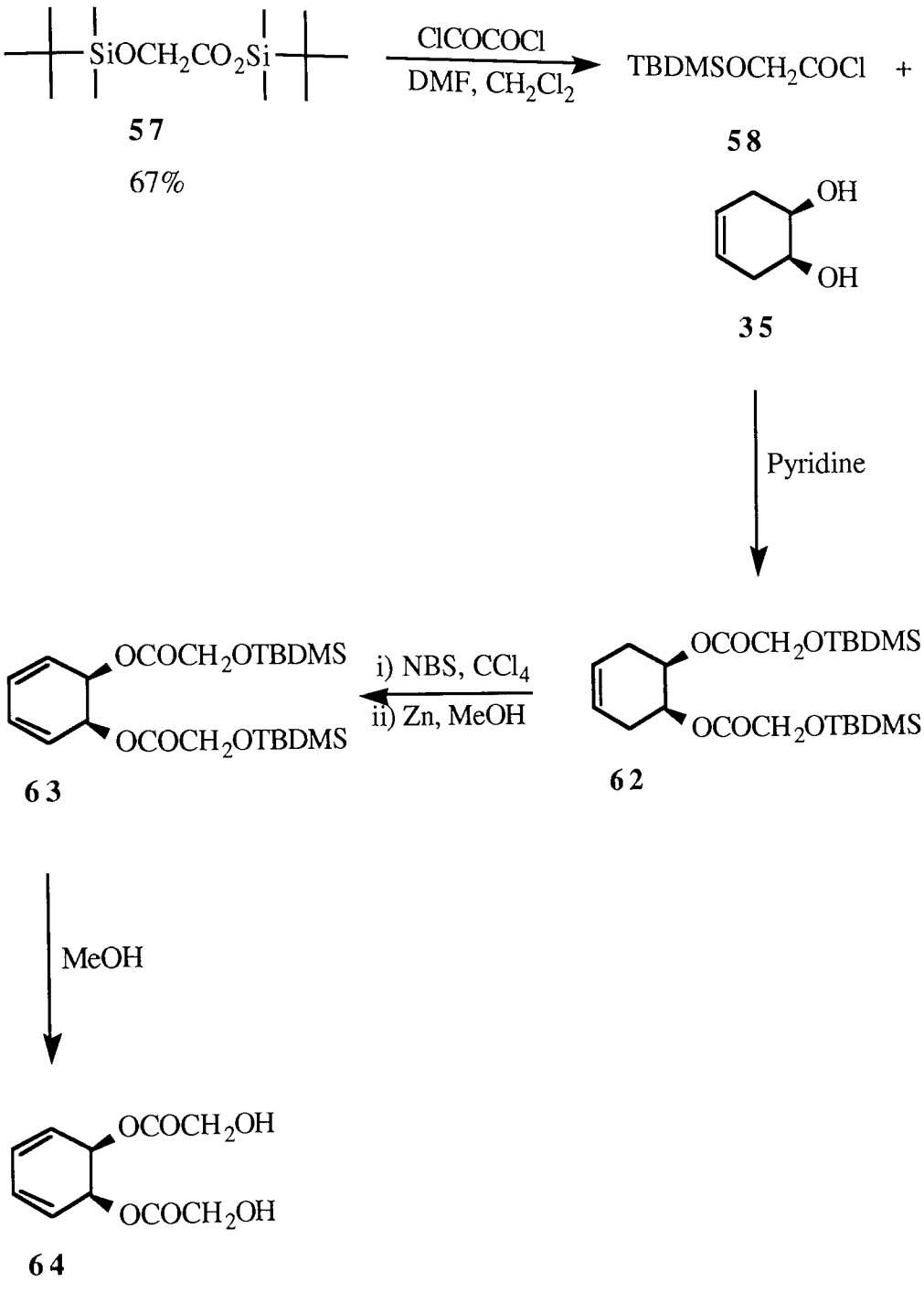


Figure 2.10b: ^{13}C NMR Spectrum, Esterification Products from the Attempted Synthesis of *trans*-1,2-Bis(hydroxyacetoxy)-3,5-cyclohexadiene.

The route devised for the synthesis of *cis*-1,2-bis(hydroxyacetoxy)-3,5-cyclohexadiene **64** is shown in Scheme 2.21. The esterification of compound **35** with the acid chloride **58** gave a mixture of compounds, see Figure 2.11. The remaining steps in the intended synthetic route could not be carried out as it was not possible to prepare compound **62**.



Scheme 2.21: Synthesis of *cis*-1,2-Bis(hydroxyacetoxy)-3,5-cyclohexadiene.

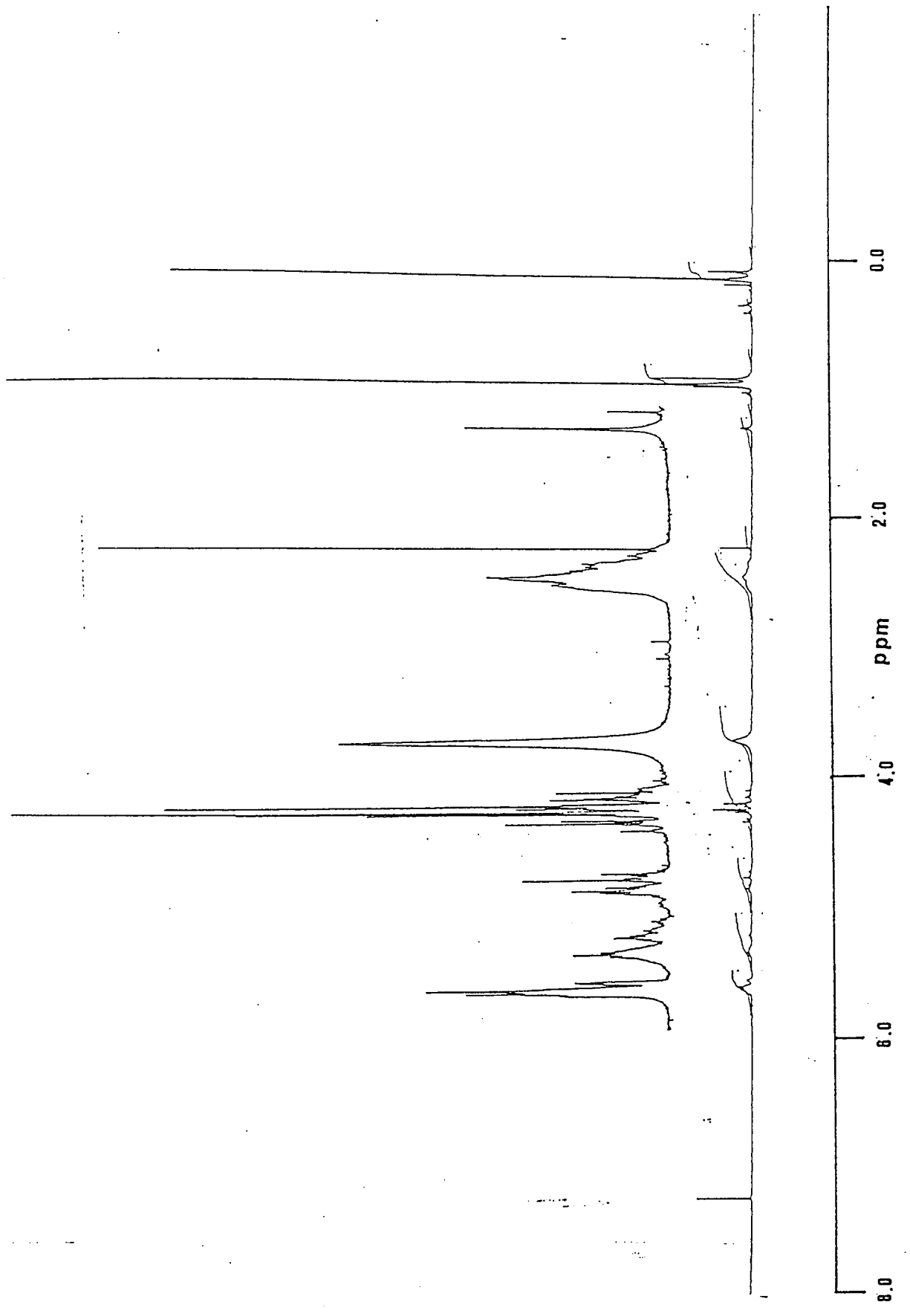


Figure 2.11a: ^{1}H NMR Spectrum, Esterification Products from the Attempted Synthesis of *cis*-1,2-Bis(hydroxyacetoxy)-3,5-cyclohexadiene.

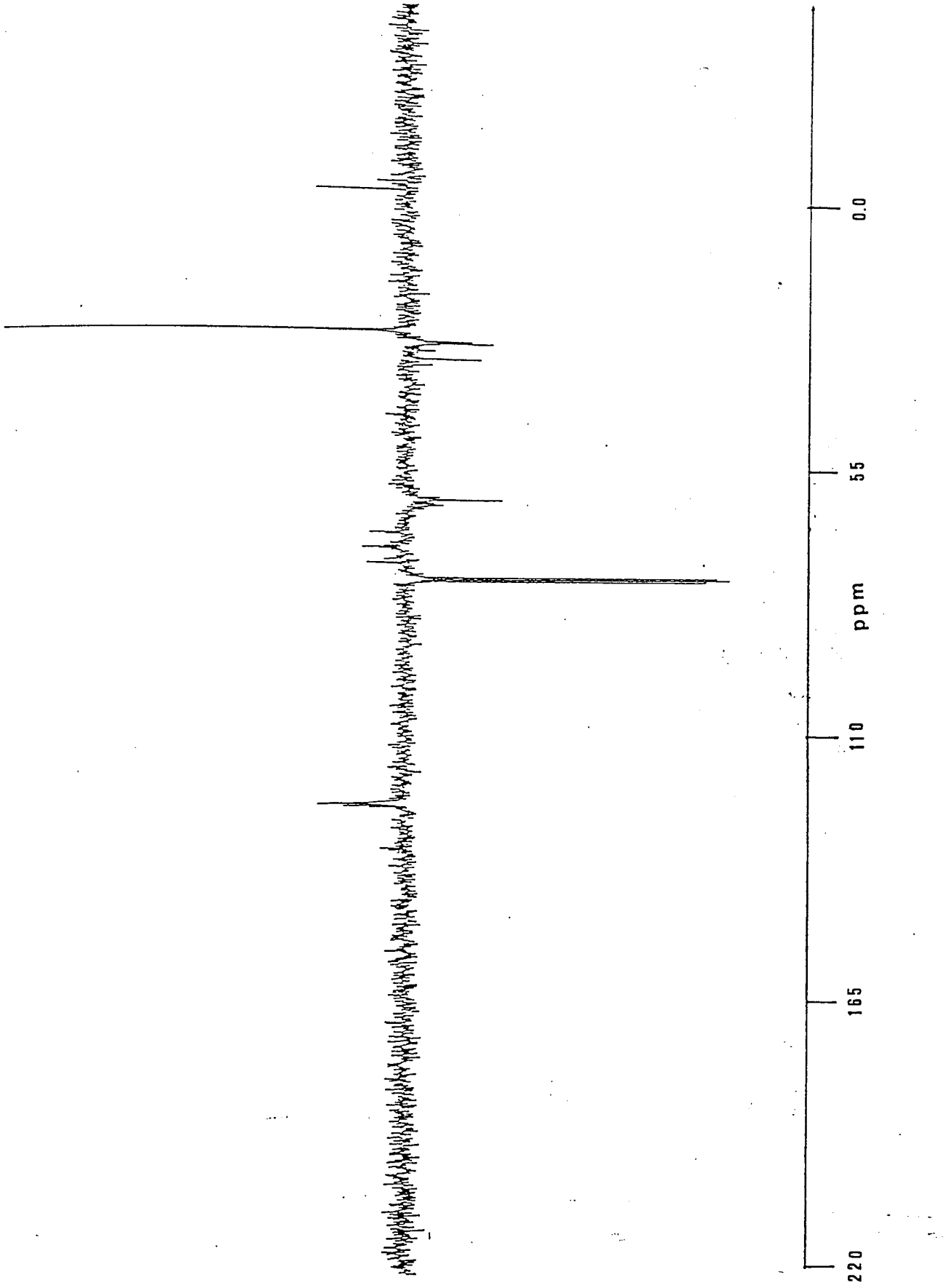
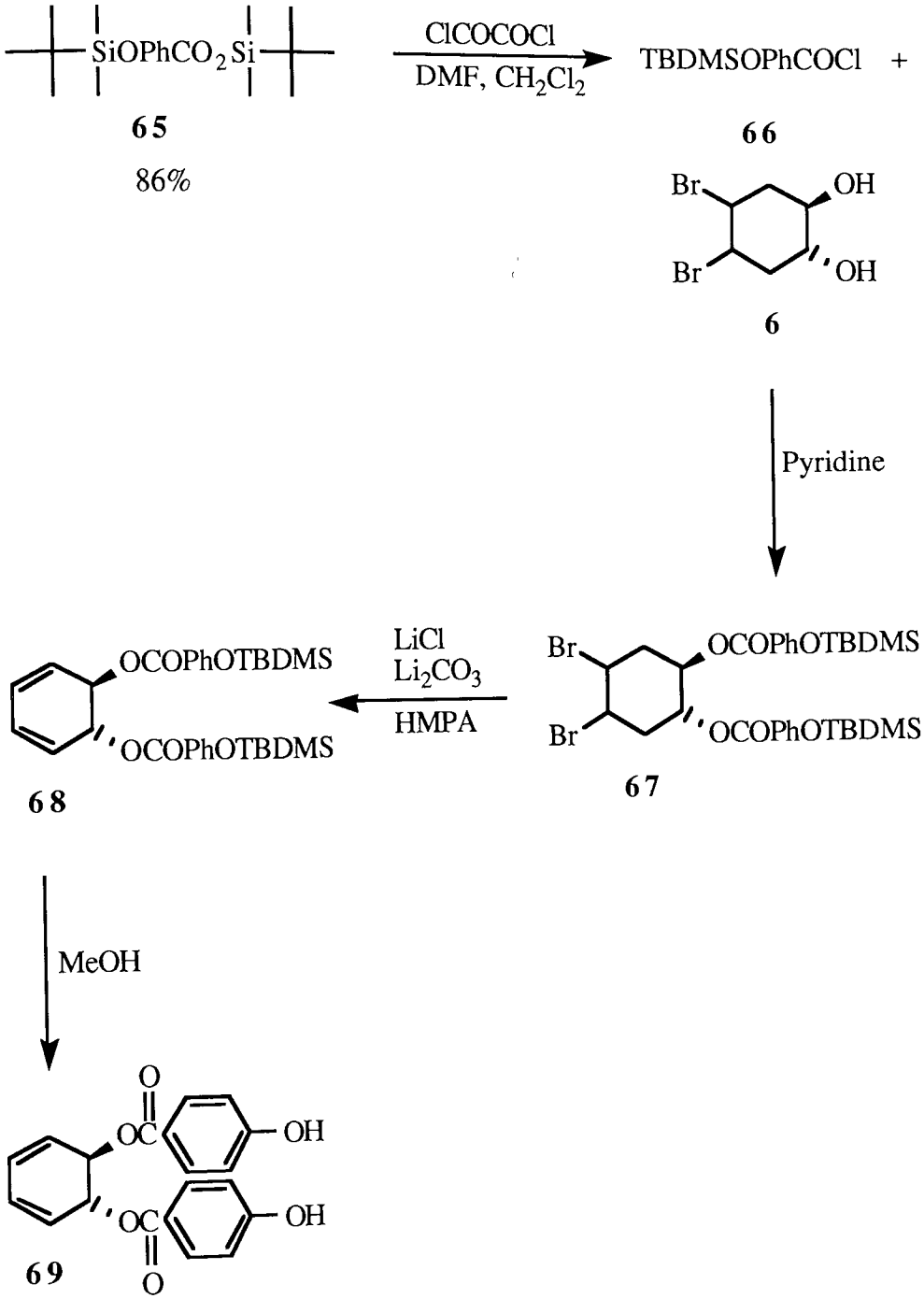


Figure 2.11b: ^{13}C NMR Spectrum, Esterification Products from the Attempted Synthesis of *cis*-1,2-Bis(hydroxyacetoxy)-3,5-cyclohexadiene.

2.4.2.4 Synthesis of 1,2-Bis(*p*-hydroxybenzoxy)-3,5-cyclohexadiene.

The synthetic routes devised for the syntheses of *cis* and *trans*-1,2-bis(*p*-hydroxybenzoxy)-3,5-cyclohexadiene (**69** and **72** respectively) were analogous to those routes described above in Section 2.4.2.3.

The route devised for the synthesis of *trans*-1,2-bis(*p*-hydroxybenzoxy)-3,5-cyclohexadiene **69** is shown in Scheme 2.22. *tert*-Butyldimethylsilyl *p-tert*-butyldimethylsilyoxybenzoate **65** was prepared in a very good yield of 86% by reaction of *p*-hydroxybenzoic acid with *tert*-butyldimethylsilyl chloride in dichloromethane, in the presence of triethylamine and DMAP. Treatment of this compound with oxalyl chloride and DMF followed by addition of *trans*-1,2-dihydroxy-4,5-dibromocyclohexane **6** in pyridine again gave a mixture of products, see Figure 2.12. The probable reason for the reaction not reaching completion is that due to the large size of the *tert*-butyldimethylsilyl group. Both mono and di substitution are retarded and one gets a mixture of starting material and the substituted products. The remaining steps in this route could not be carried out as **67** could not be isolated.



Scheme 2.22: Synthesis of *trans*-1,2-Bis(*p*-hydroxybenzoxy)-3,5-cyclohexadiene

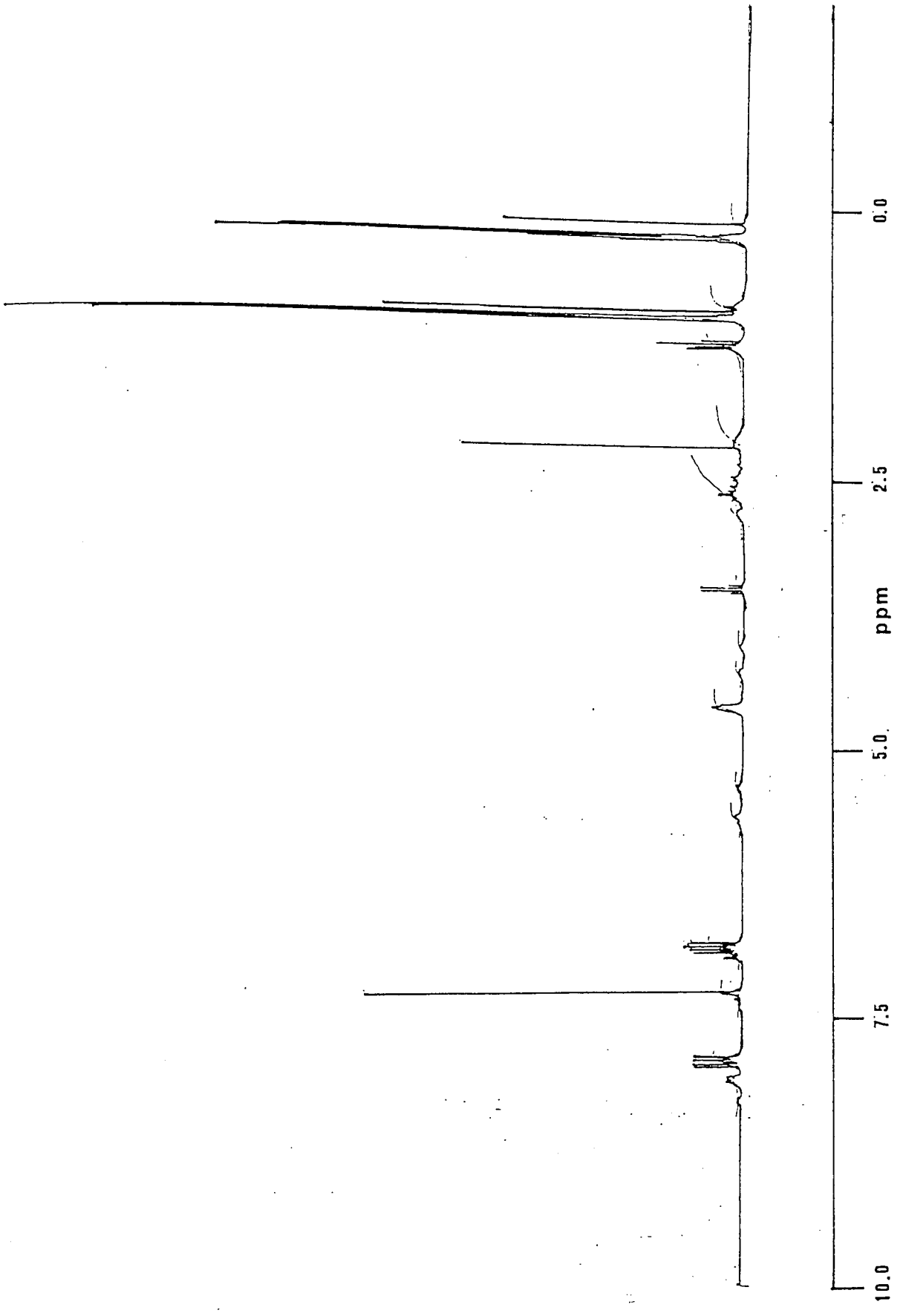


Figure 2.12a: ^{1}H NMR Spectrum, Esterification Products from the Attempted Synthesis of *trans*-1,2-Bis(*p*-hydroxybenzoxy)-3,5-cyclohexadiene.

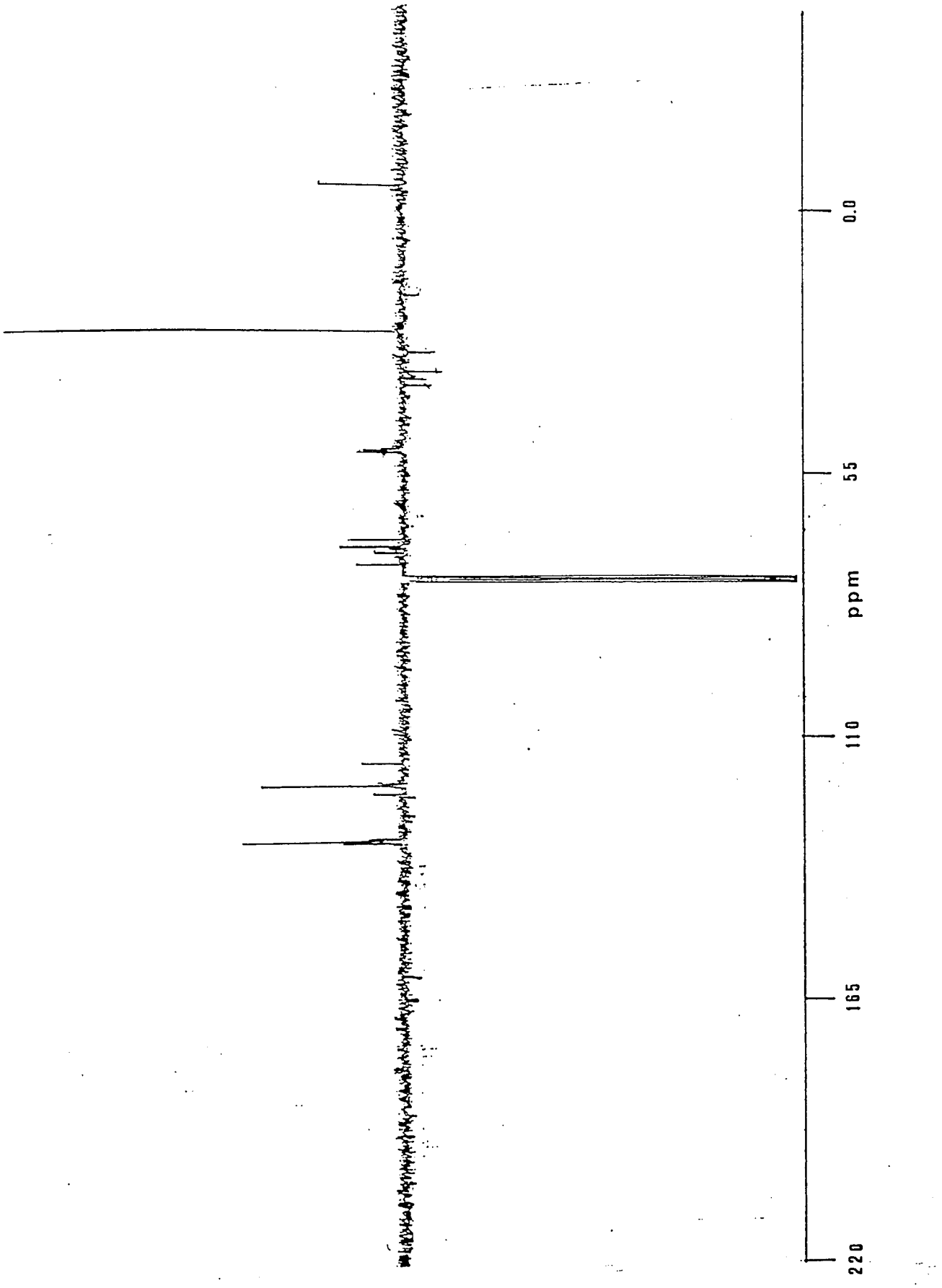
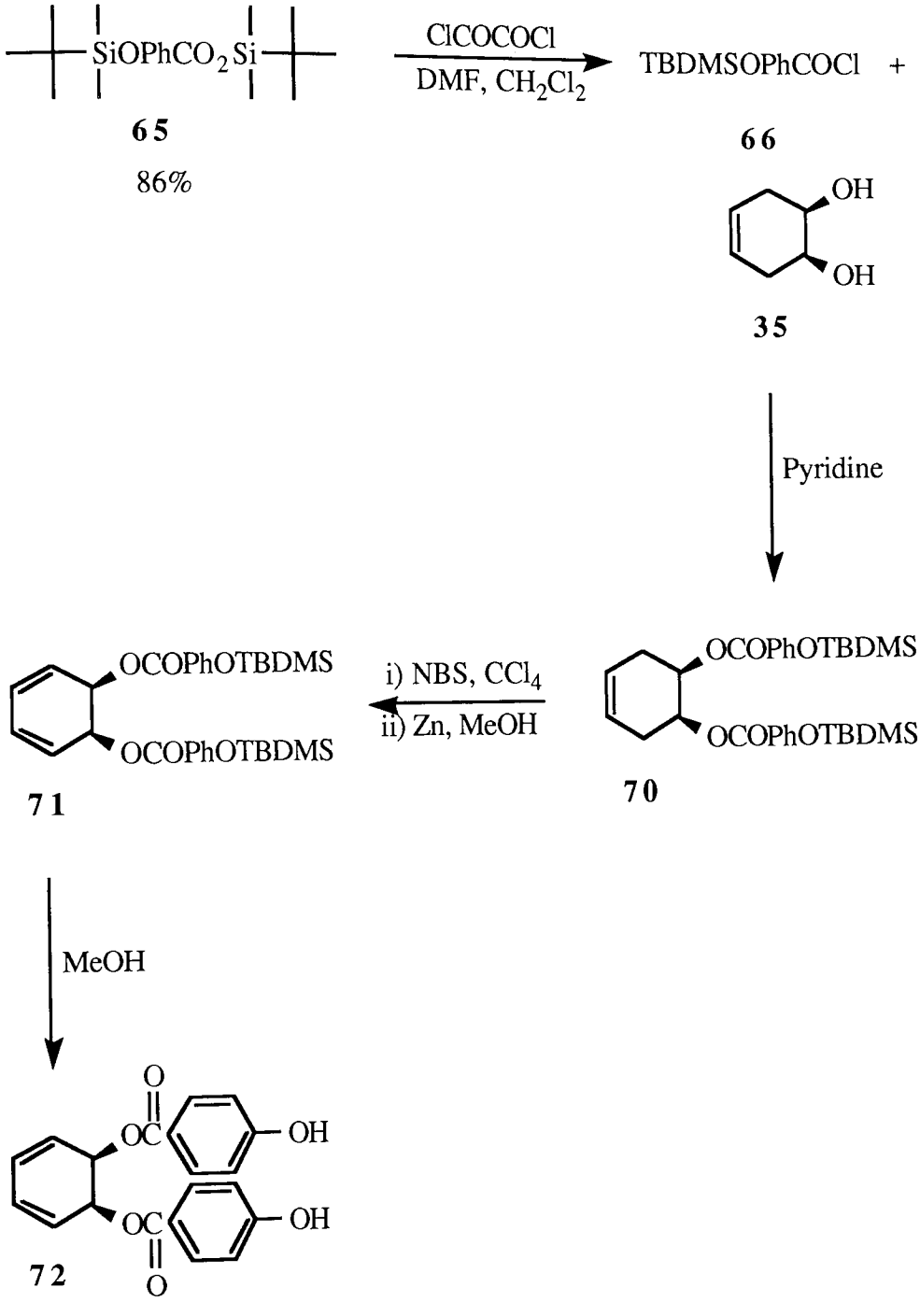


Figure 2.12b: ^{13}C NMR Spectrum, Esterification Products from the Attempted Synthesis of *trans*-1,2-Bis(*p*-hydroxybenzoxy)-3,5-cyclohexadiene.

The route devised for the *cis*-1,2-bis(*p*-hydroxybenzoxy)-3,5-cyclohexadiene **72** is shown in Scheme 2.23.

Esterification of **35** with *p-tert*-butyldimethylsiloxybenzoyl chloride gave a mixture of products, see Figure 2.13. The subsequent steps in this route could not be carried out because **70** could not be isolated.



Scheme 2.23: Synthesis of *cis*-1,2-Bis(*p*-hydroxybenzoxy)-3,5-cyclohexadiene

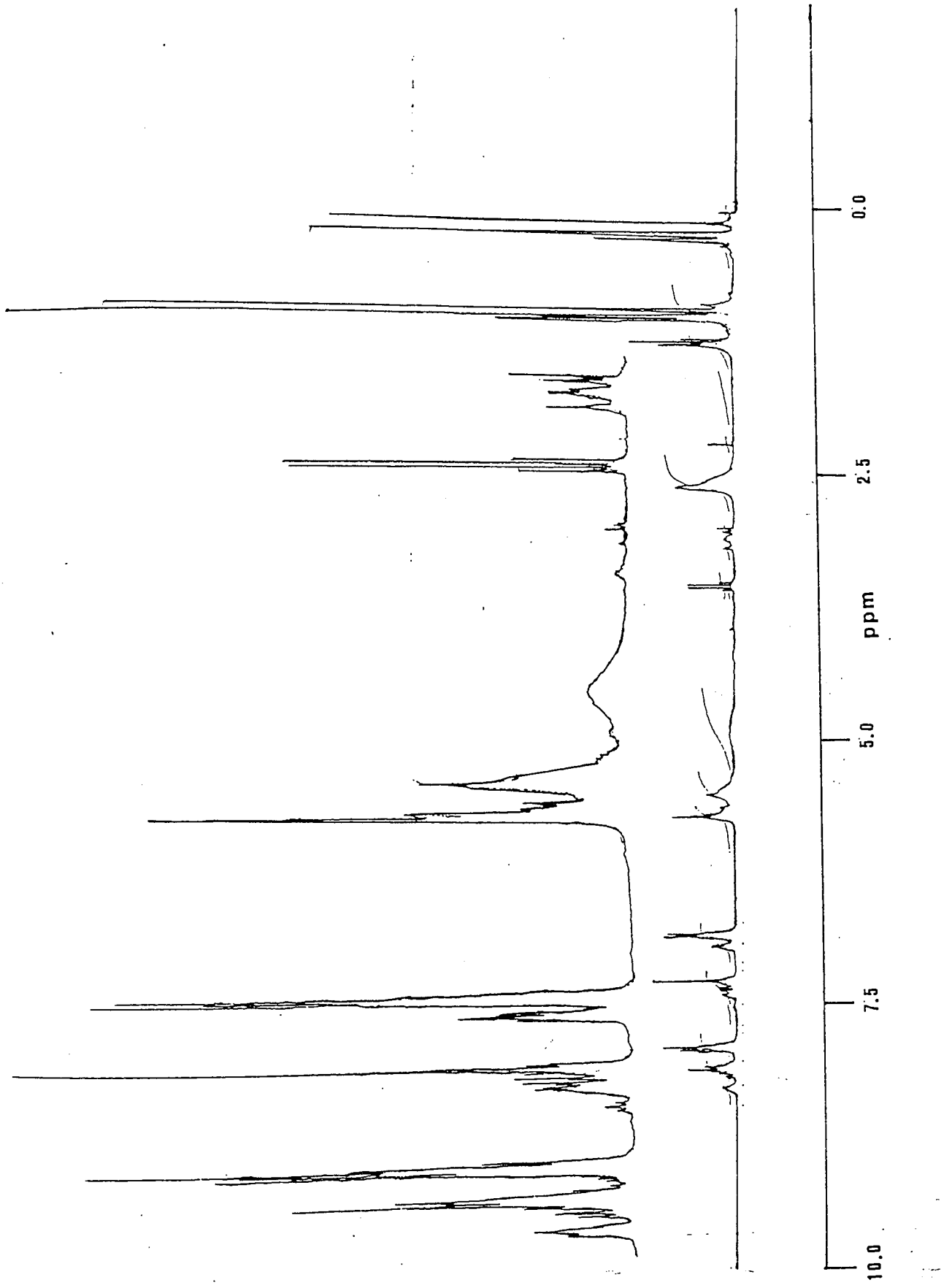


Figure 2.13a: ^{1}H NMR Spectrum. Esterification Products from the Attempted Synthesis of *cis*-1,2-Bis(*p*-hydroxybenzoxy)-3,5-cyclohexadiene.

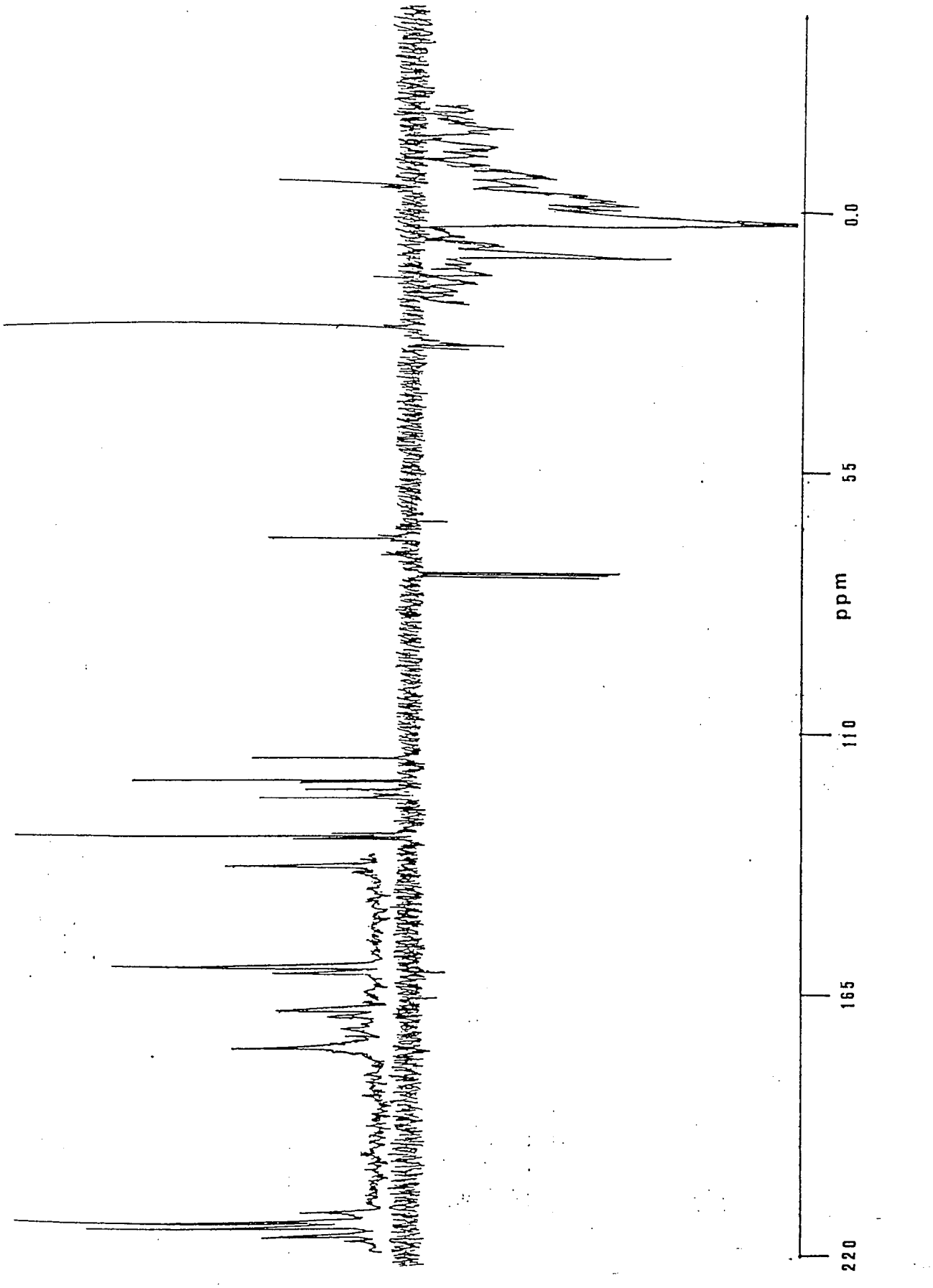
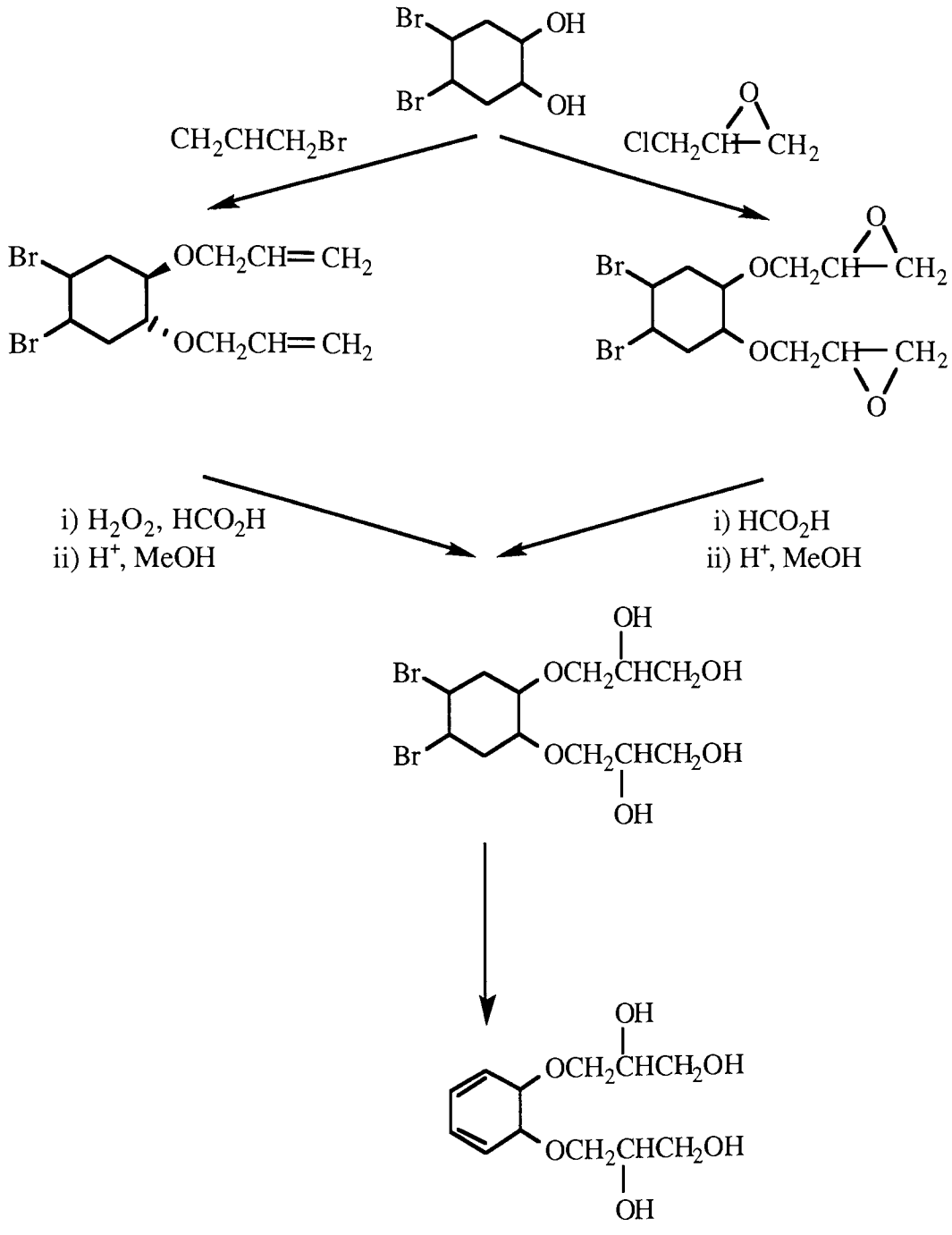


Figure 2.13b: ^{13}C NMR Spectrum, Esterification Products from the Attempted Synthesis of *cis*-1,2-Bis(*p*-hydroxybenzoxy)-3,5-cyclohexadiene.

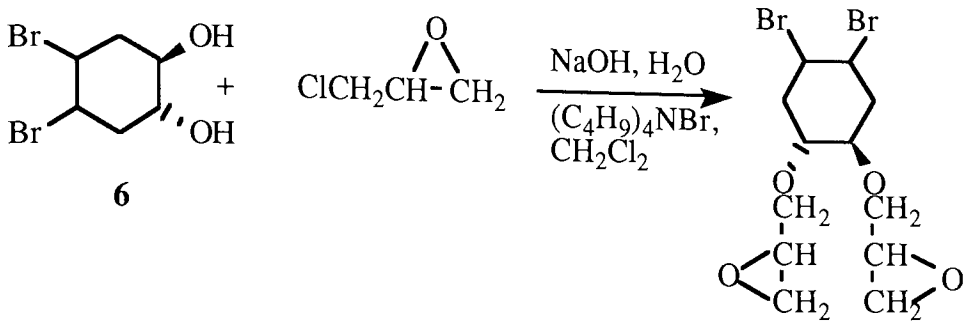
2.4.2.5 Synthesis of 1,2-Bis(2,3-dihydroxypropoxy)-3,5-cyclohexadiene.

Two methods were investigated for preparing this tetrahydroxy monomer. The first involved the use of epichlorohydrin for the synthesis of a diglycidyl ether which could then be be converted into the tetrahydroxy compound, via ring opening of the epoxides with formic acid, followed by acidic hydrolysis in methanol. The second method involved the use of allyl bromide to form an ether which could be epoxidised and then converted into the tetrahydroxy compound in the same way, see Scheme 2.24.

It was found that the etherification of *trans*-1,2-dihydroxy-4,5-dibromocyclohexane **6** under PTC conditions required much more vigorous conditions than for the catechol derivatives. The general method of Freedman and Dubois was followed.[142] The aqueous phase consisted of a 50% w/v solution of NaOH, the organic phase was a four fold molar excess of neat alkyl halide (sufficient THF being added to dissolve the alcohol). The catalyst was 5mol% of tetra-*n*-butylammonium bromide.



Scheme 2.24: Synthetic Routes to 1,2-Bis(2,3-dihydroxypropoxy)-3,5-cyclohexadiene.



6 **7 3**

Scheme 2.25: Synthesis of *trans*-1,2-Bis(2,3-epoxypropoxy)-4,5-dibromocyclohexane.

Reaction of **6** with epichlorohydrin under PTC conditions (see Scheme 2.25.) gave a low yield of a dark brown liquid. The ^{1}H and ^{13}C NMR spectra, shown in Figure 2.14, indicate that a mixture of products were formed in this reaction. It seems likely that the products were derived from reactions of the epoxide ring under these strongly basic conditions.

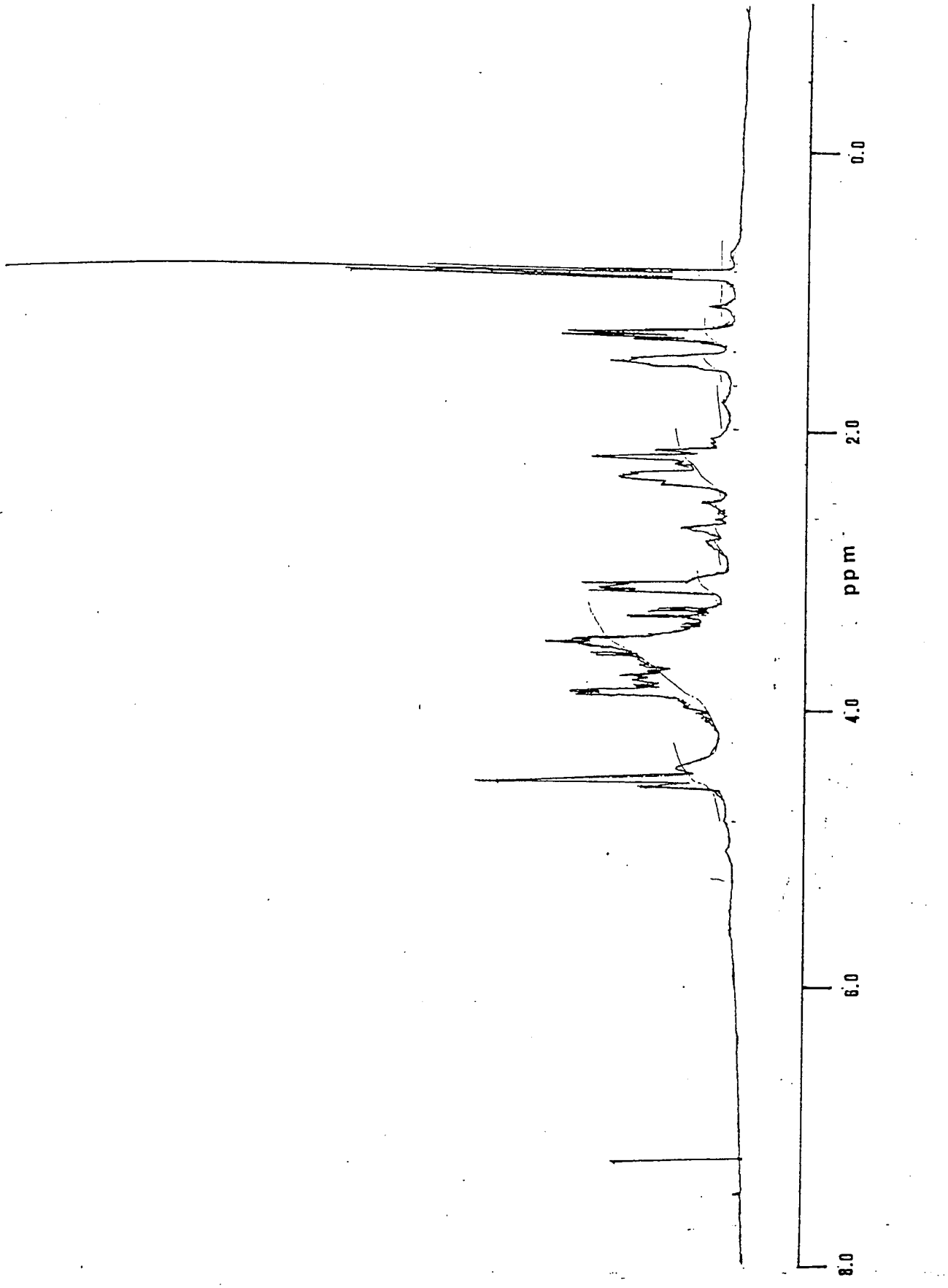


Figure 2.14a: ^{1}H NMR Spectrum. Etherification Products from the Reaction of *trans*-1,2-Dihydroxy-4,5-dibromocyclohexane with Epichlorohydrin.

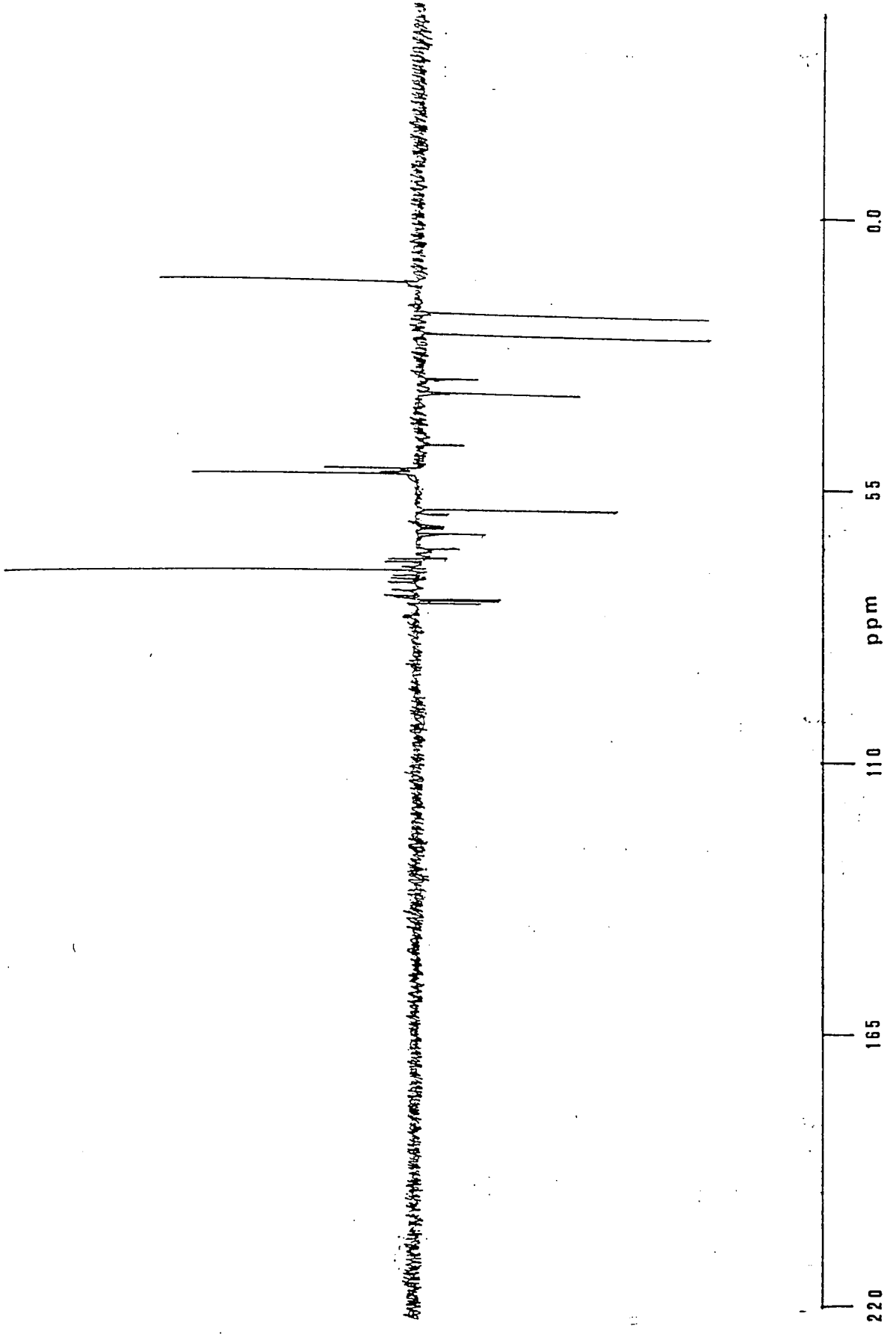
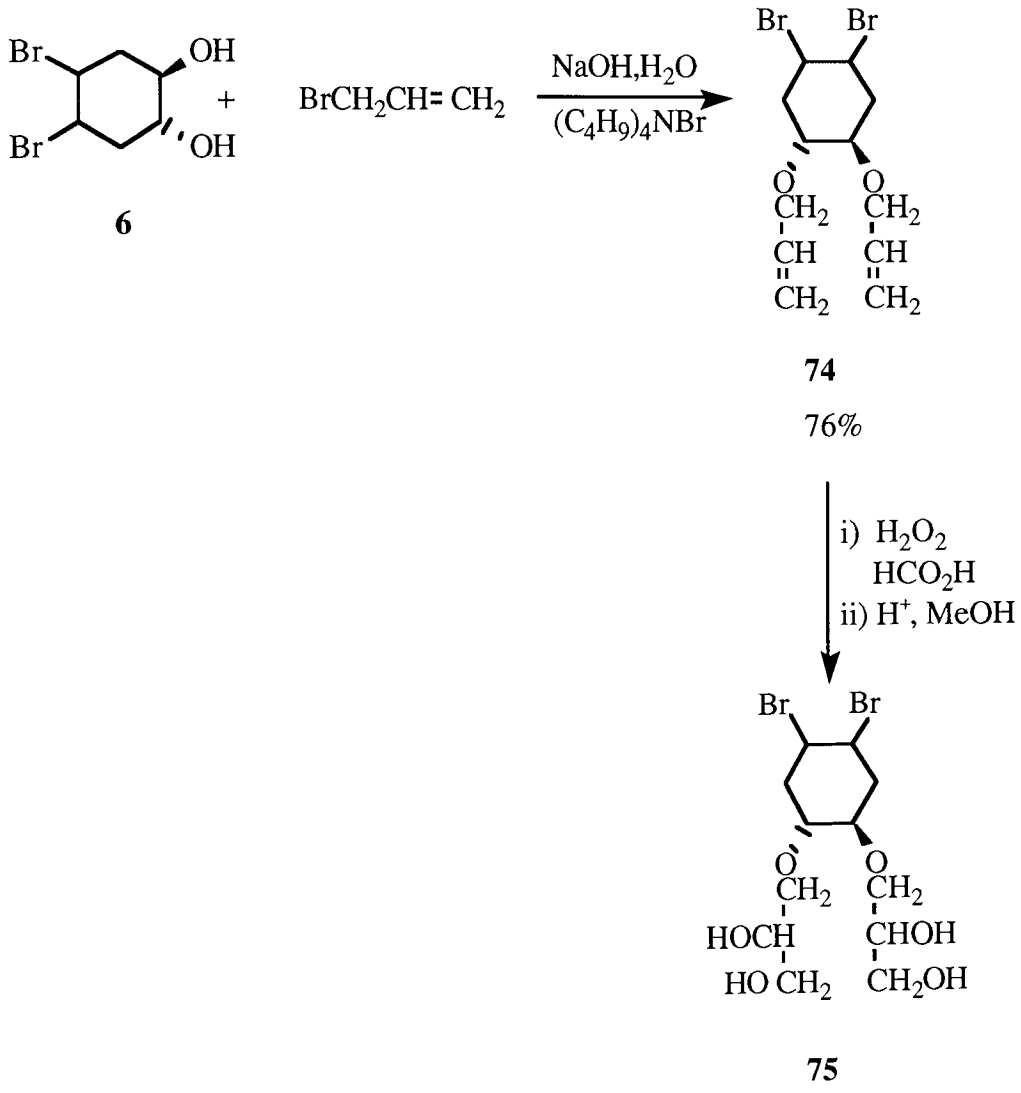


Figure 2.14b: ^{13}C NMR Spectrum Of Etherification Products from the Reaction of *trans*-1,2-Dihydroxy-4,5-dibromocyclohexane with Epichlorohydrin.

The diallyl ether of *trans*-1,2-dihydroxy-4,5-dibromocyclohexane **6** was obtained in a good yield of 76% under PTC conditions, see Scheme 2.26. This compound was then epoxidised and the epoxide ring opened with hydrogen peroxide in formic acid, followed by acidic hydrolysis in methanol. Examination of the ^{1}H and ^{13}C NMR spectra (Figure 2.15) shows that several hydration products are formed in this reaction. It appears that the majority of the diallyl ether had been epoxidised and hydrated, but not cleanly. A mixture of double bond, epoxide and diol groups were probably present.



6

74

76%

75

Scheme 2.26: Synthesis of *trans*-1,2-Bis(2,3-hydroxypropoxy)-4,5-dibromocyclohexane.

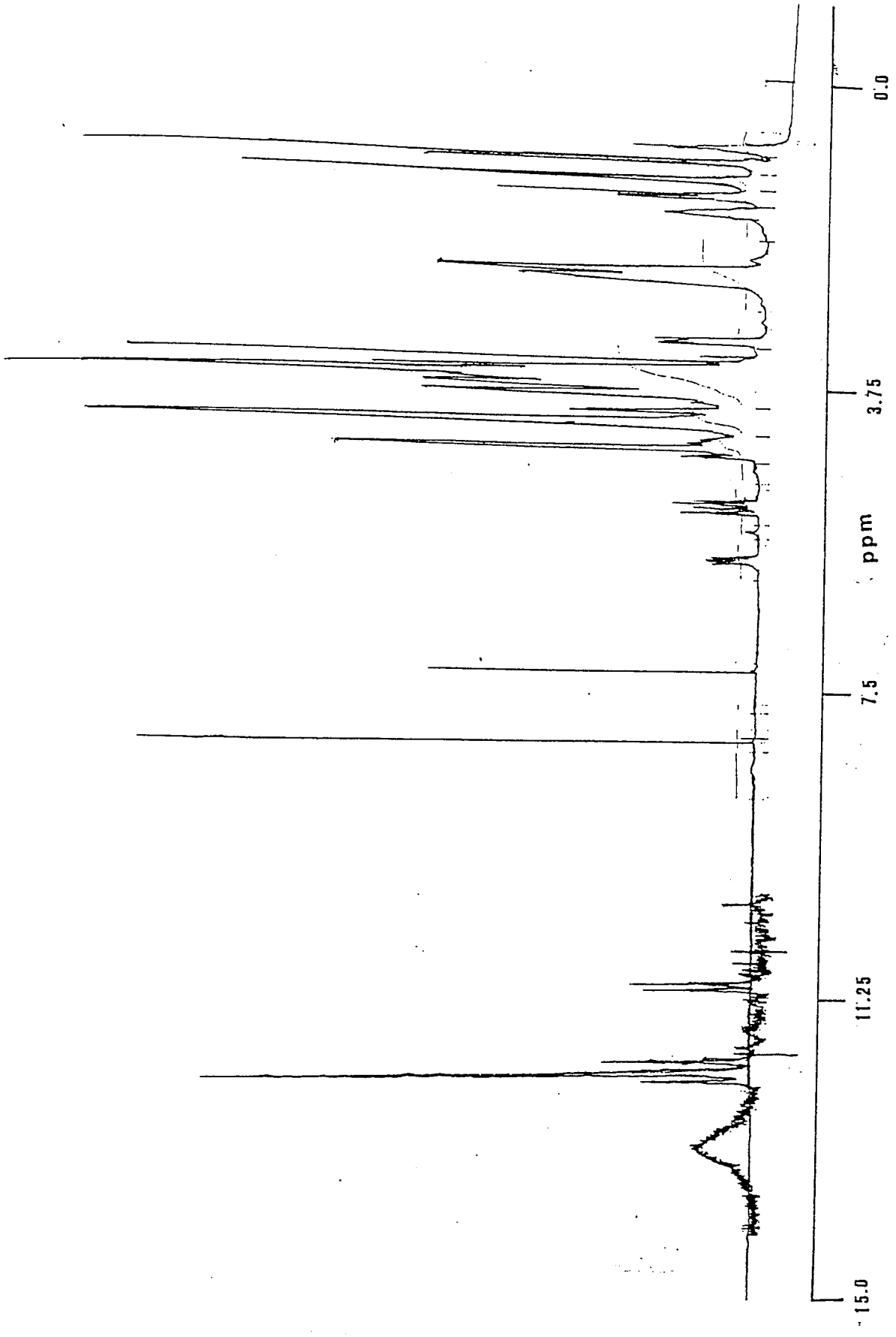


Figure 2.15a: ^{1}H NMR Spectrum of Products from the Hydroxylation of *trans*-1,2-Bis(allyloxy)-4,5-dibromocyclohexane.

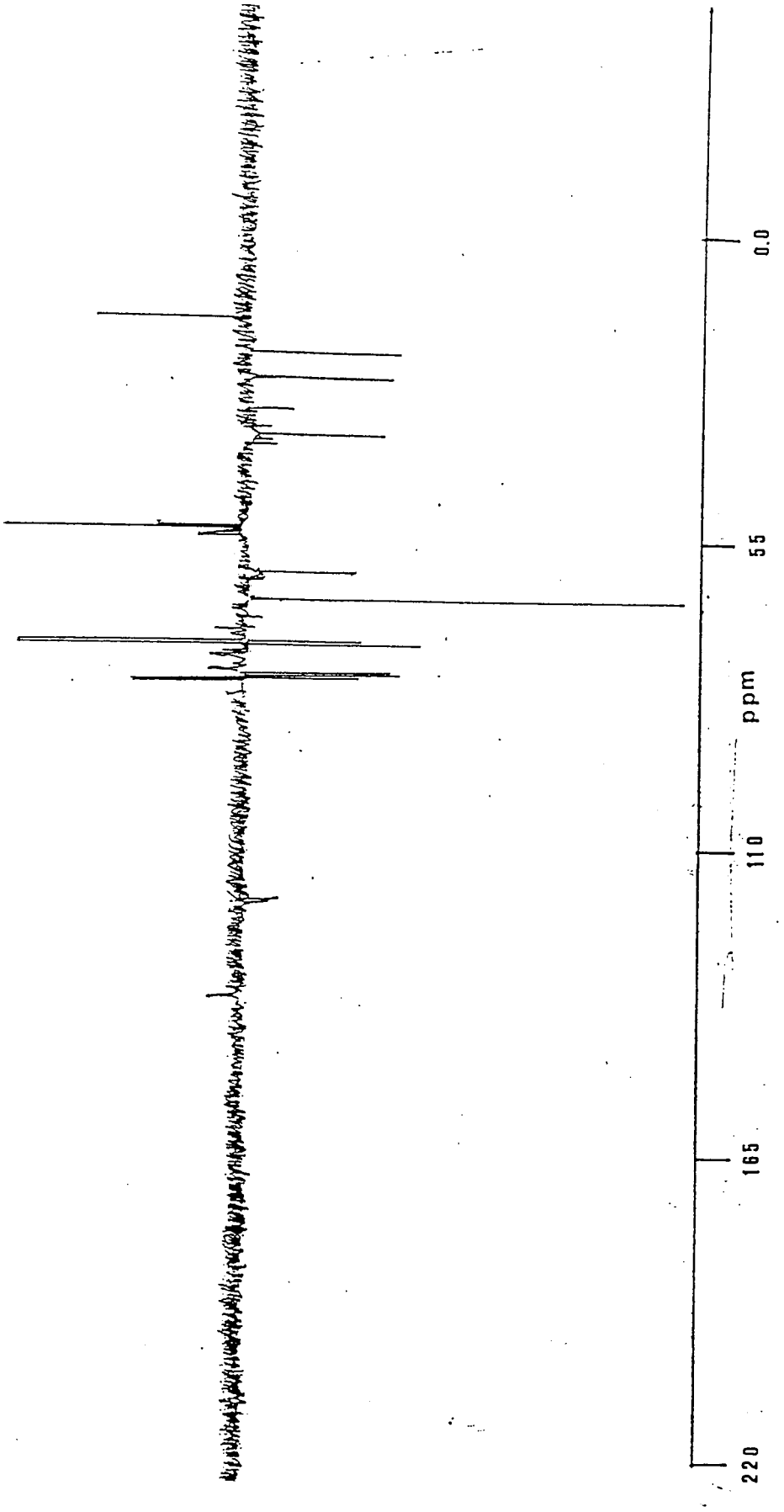
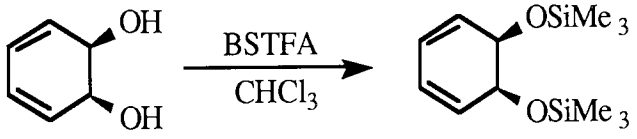


Figure 2.15b: ^{13}C NMR Spectrum Of Products from the Hydroxylation of *trans*-1,2-Bis(allyloxy)-4,5-dibromocyclohexane.

2.4.2.6 Synthesis of *cis*-1,2-Bis(trimethylsiloxy)-3,5-cyclohexadiene.

A simple way of introducing *cis*-DHCD itself into hydrogel networks could be via *cis*-1,2-bis(trimethylsiloxy)-3,5-cyclohexadiene **76**. It would be anticipated that hydrolysis, by the water imbibed by the polymer, would remove the protecting silyl groups.

The silylation of *cis*-DHCD with bis(trimethylsilyl)trifluoroacetamide (BSTFA), see Scheme 2.27, was unsuccessful as it produced considerable quantities of aromatic products. The main reason for the aromatisation was that a relatively high temperature was required to remove *N*-(trimethylsilyl)trifluoroacetamide from the reaction mixture.

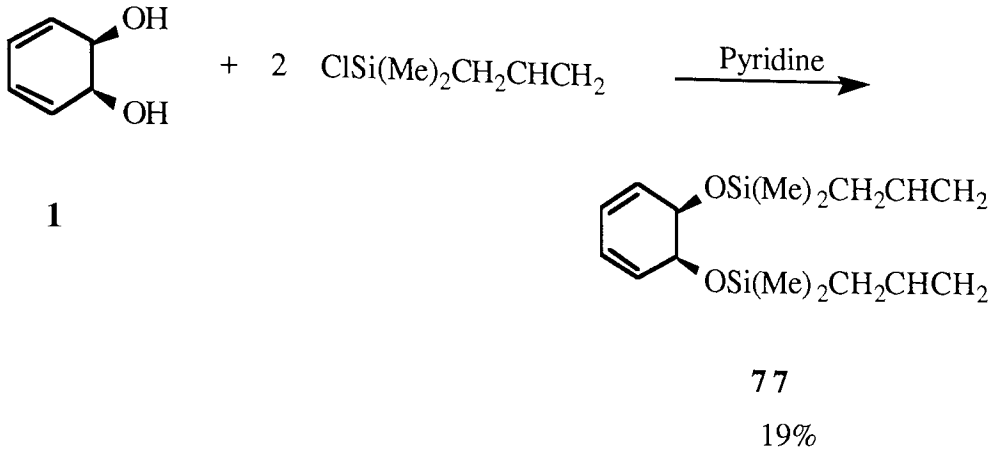


1 **76**

Scheme 2.27: Synthesis of *cis*-1,2-Bis(trimethylsiloxy)-3,5-cyclohexadiene.

2.4.2.7 Synthesis of *cis*-1,2-Bis(allyldimethylsiloxy)-3,5-cyclohexadiene.

The reaction of allyldimethylsilylchloride with *cis*-DHCD **1** in pyridine solvent produced *cis*-1,2-bis(allyldimethylsiloxy)-3,5-cyclohexadiene **77** in a yield of 19%, see Scheme 2.28. Some siloxane was also detected in the NMR spectra. This synthesis was carried out at an early stage of the work before it was observed that a DMAP catalyst significantly improves yields in such reactions. Due to the lack of availability of *cis*-DHCD this synthesis could not be repeated.



1

77

19%

Scheme 2.28: Synthesis of *cis*-1,2-Bis(allyldimethylsiloxy)-3,5-cyclohexadiene.

2.5. CONCLUSIONS.

The conformations adopted by *cis*-DHCD and some of its derivatives were deduced from the ^1H NMR spectra of these compounds. The need for the 1,3-diene group to be planar is the main factor determining their conformation. Comparison of the conformation adopted by *cis*-DHCD with that of catechol shows that there is a great similarity in the steric environment of the hydroxyl groups in these two compounds.

trans-DHCD and its derivatives have greater flexibility, than *cis*-DHCD, in the conformations which they may adopt. There is a tendency for these molecules to adopt conformations in which the pendant groups are in a diequatorial arrangement, to reduce the steric interaction between the pendant groups and the 1,3-diene group.

A number of catechol derivatives were prepared in good to excellent yield. It was found that 1,2-bis(allyloxyformoxy)benzene could not be hydroborated with 9-BBN probably due to steric hindrance.

The synthesis of two derivatives of *cis*-DHCD and two derivatives of *trans*-DHCD was achieved. Attempts to prepare derivatives of *cis* and *trans*-DHCD from hydroxy carboxylic acids were unsuccessful probably because the reaction was hindered by the large *tert*-butyldimethylsilyl group which was used to protect the OH function. Indirect synthesis of ether derivatives proved to be even more difficult than ester derivatives.

Chapter 3: Synthesis of DHCD.

3. SYNTHESIS OF DHCD.

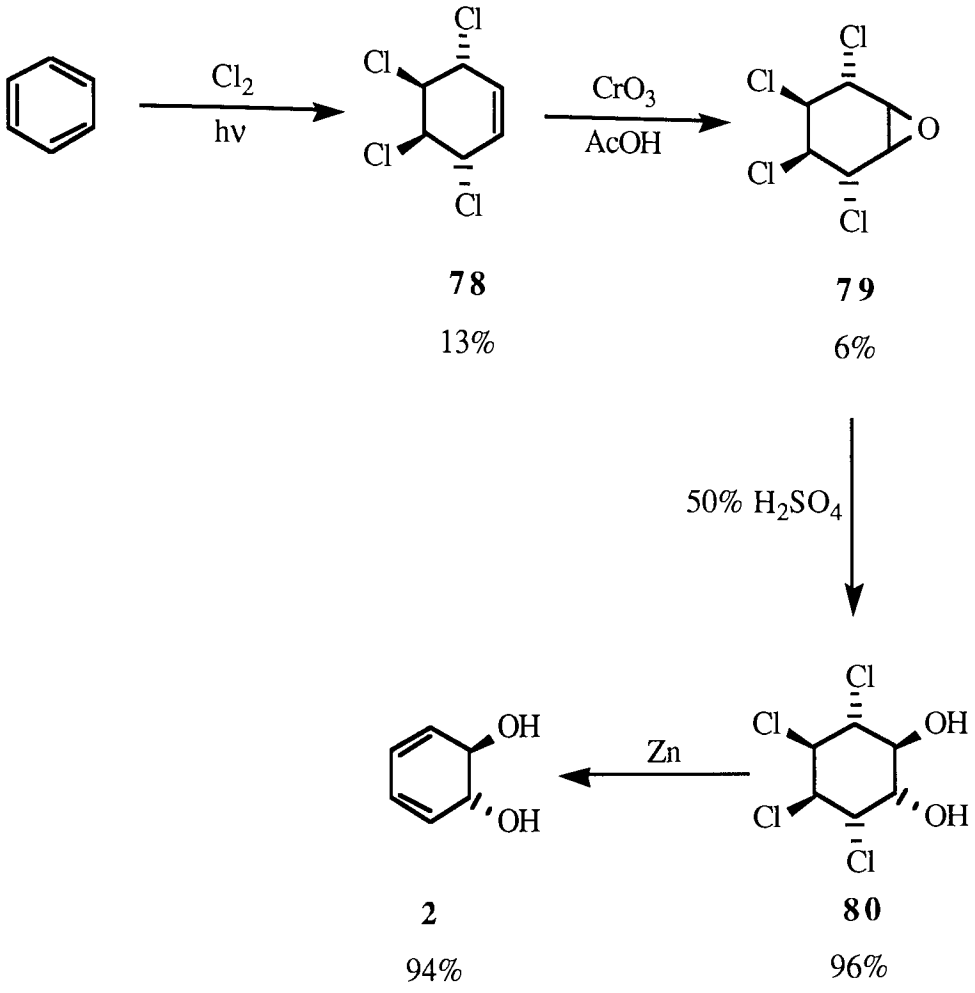
3.1 INTRODUCTION.

Once it became obvious that ICI would not be able to provide *cis*-DHCD it was decided to try to synthesise the material ourselves. It soon became apparent from a literature search that although routes to the synthesis of both *cis* and *trans* isomers were known, these were generally laborious and not very efficient. In the main the syntheses had been carried out some twenty to thirty years ago and it was hoped, somewhat optimistically, that with the development of new methods and reagents it might now be possible to modify and improve the reported techniques and even to develop new routes to the synthesis of *cis* and *trans*-DHCD.

3.1.1 Synthesis of *trans*-DHCD

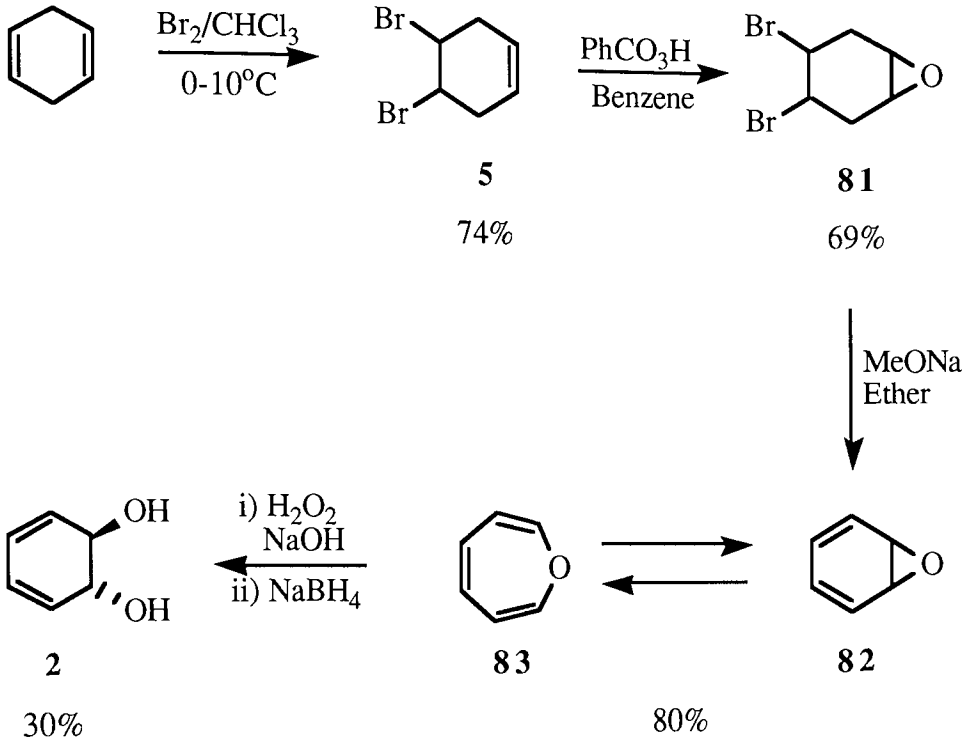
An early route to *trans*-DHCD, which proved to be unsuccessful, involved the reduction of *o*-benzoquinone by lithium aluminium hydride in boiling ether, giving catechol as the product.[162]

The first successful preparation of *trans*-DHCD was reported in 1956 by Nakajima and co-workers.[104] Starting with the partial chlorination of benzene, α-3,4,5,6-tetrachlorocyclohexene **78** was prepared;[163-165] this material was epoxidised with CrO_3 in acetic acid and the epoxide ring opened with sulphuric acid to give *trans*-1,2-dihydroxy-3,4,5,6-tetrachlorocyclohexane **80**. The chlorine was eliminated with zinc dust to produce *trans*-DHCD **2** in an overall yield of less than 1%, see Scheme 3.1.



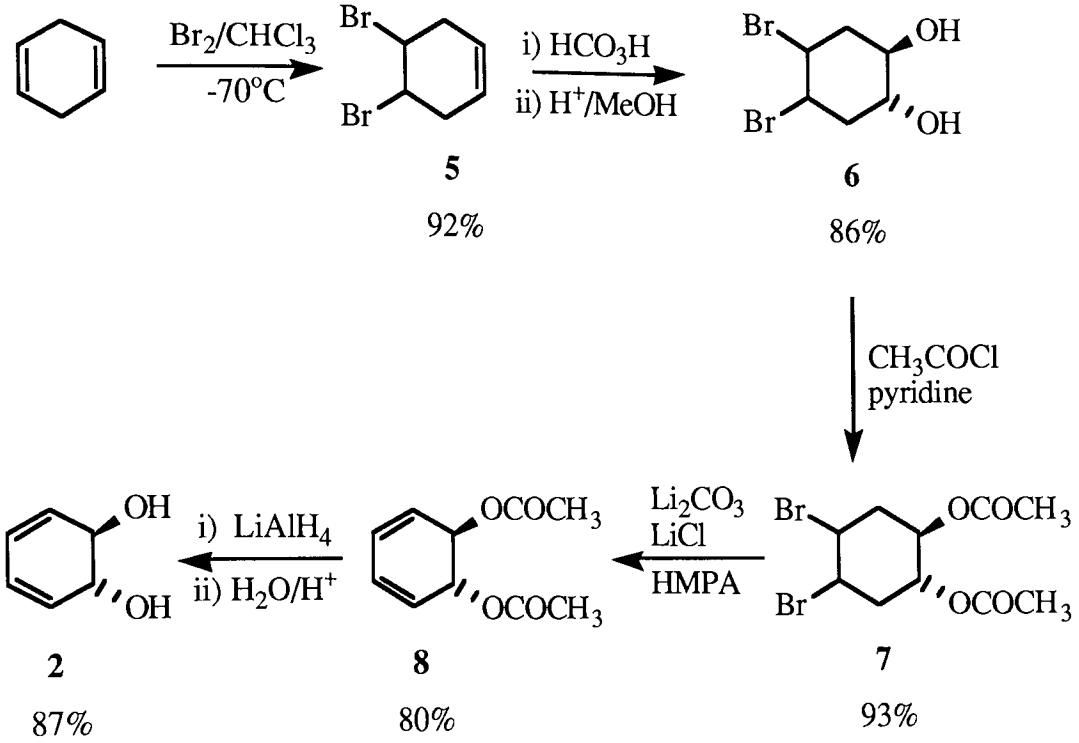
Scheme 3.1: Nakajima Synthesis of *trans*-DHCD.

In 1974 Jeffrey and co-workers reported a rather higher yielding synthesis of *trans*-DHCD.[105] The route involved the formation of benzene oxide **82**, which is in a valence-tautomeric equilibrium with oxepin **83**, from 4,5-dibromocyclohexene oxide **81**. The epoxide ring in benzene oxide was opened with alkaline hydrogen peroxide and the resulting organic peroxide reduced with sodium borohydride, giving *trans*-DHCD in an overall yield of 12%. A slightly improved method reported by Jerina and co-workers gave the 4,5-dibromocyclohexene oxide **81** in 86% yield, thereby improving the overall yield to 15%,[110] see Scheme 3.2.



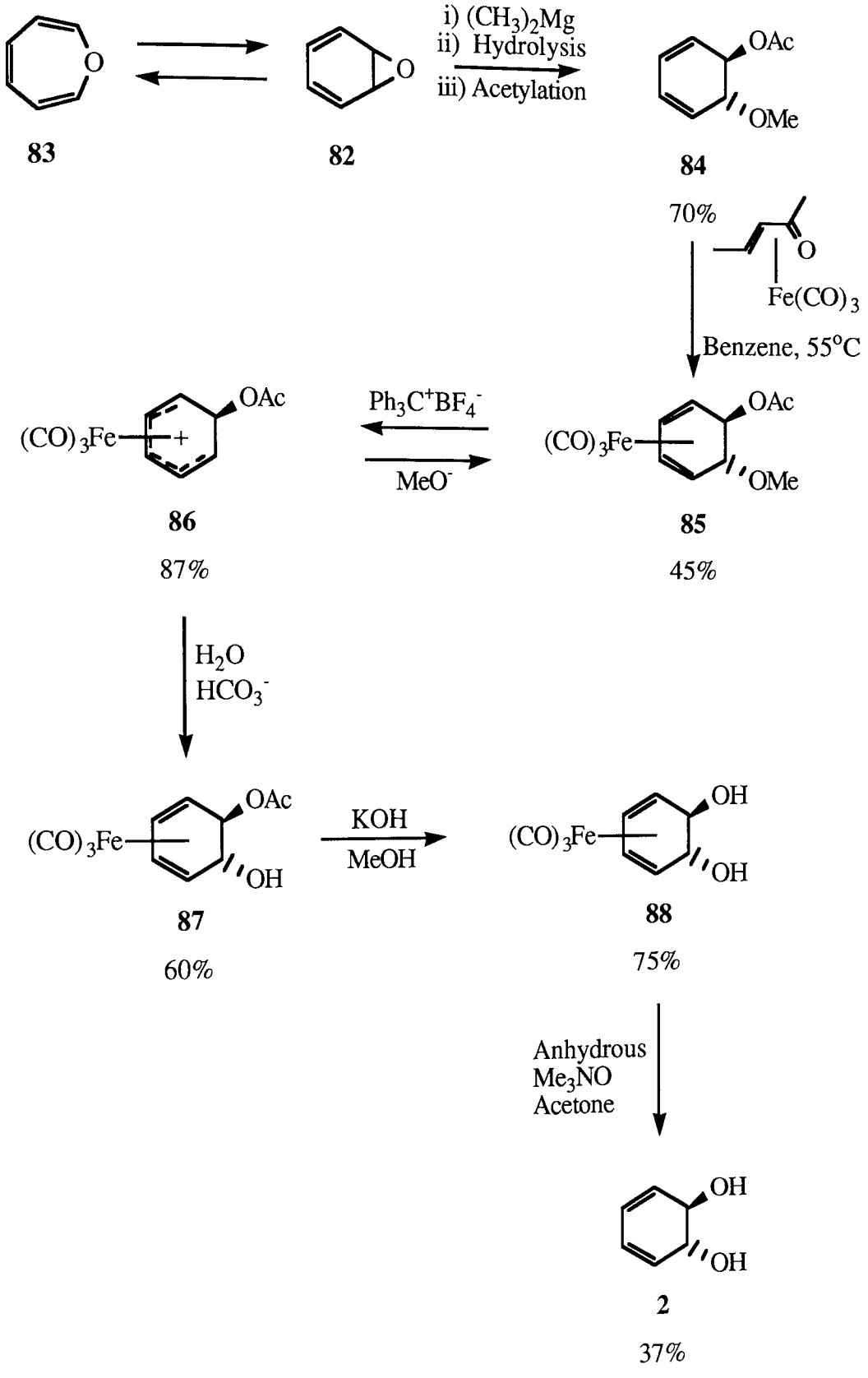
Scheme 3.2: *trans*-DHCD from Benzene Oxide-Oxepin.

It was 1977 before a synthetically useful route to *trans*-DHCD appeared, when Platt and Oesch reported its synthesis from 1,4-cyclohexadiene in a 51% overall yield,[103] see Scheme 3.3.



Scheme 3.3: Platt and Oesch Synthesis of *trans*-DHCD.

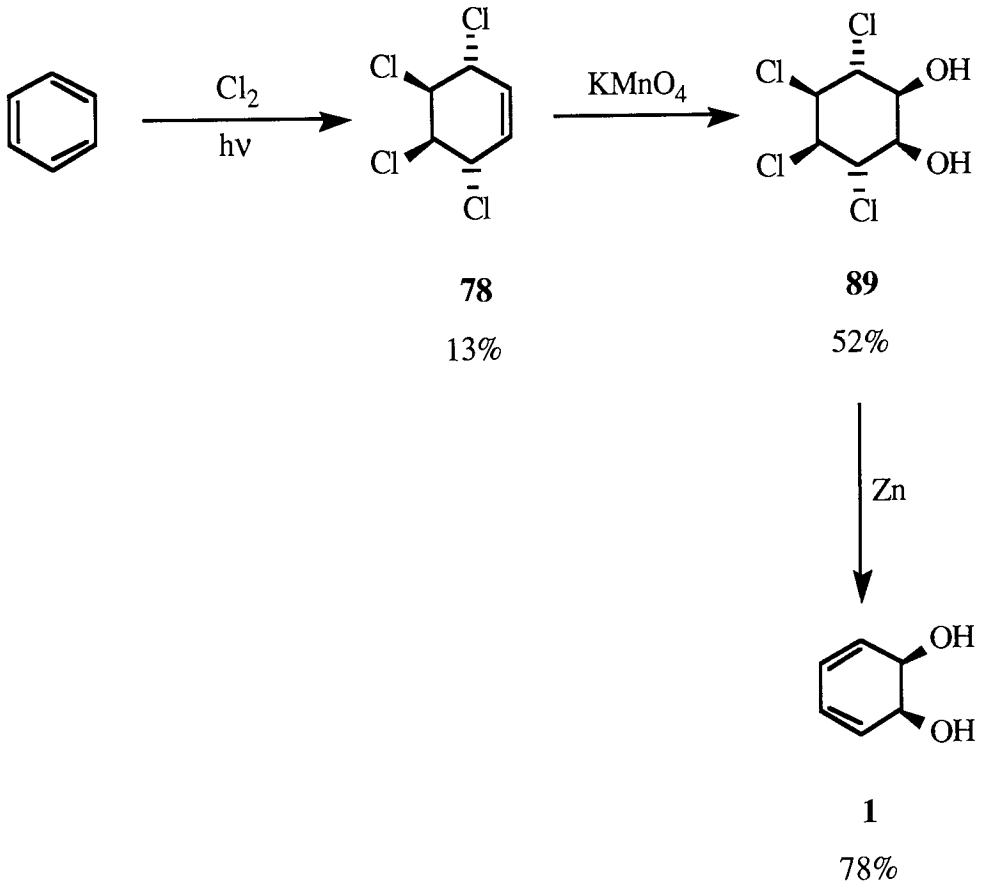
A second route to *trans*-DHCD was also reported in 1977; this involved the use of iron tricarbonyl complexes **85-88** and the methoxy acetate derivative of *trans*-DHCD **84**, which was obtained from benzene oxide-oxepin.[105] The overall yield was a very poor 2%,[106] see Scheme 3.4.



Scheme 3.4: *trans*-DHCD via Iron-Tricarbonyl Complexes.

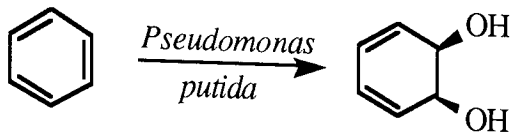
3.1.2 Synthesis of *cis*-DHCD.

An unsuccessful attempt to prepare *cis*-DHCD was reported in 1937. This reaction involved the catalytic oxidation of benzene with osmium tetroxide,[166] giving phenol as the product. It was 1959 before Nakajima and co-workers reported a successful synthesis of *cis*-DHCD.[59] The route employed was similar to that which had been used previously in their synthesis of *trans*-DHCD.[104] Polychlorination of benzene yielded α-3,4,5,6-tetrachlorocyclohexene **78**, which was treated with potassium permanganate to produce *cis*-1,2-dihydroxy-3,4,5,6-tetrachlorocyclohexane **89**. Chlorine was eliminated, by reaction with zinc dust, to give *cis*-DHCD **1** in an overall yield of 5%, see Scheme 3.5. Due to the low overall yield this strategy was of limited practical use.[59]



Scheme 3.5: Nakajima Synthesis of *cis*-DHCD.

It was only in the early 1980's that a simple synthesis of *cis*-DHCD, from benzene, was developed by ICI New Sciences Group.[18,19] Unfortunately this involved the rather specialised microbial oxidation of benzene by the mesophilic organism *Pseudomonas putida*, see Scheme 3.6.



1

Scheme 3.6: Microbial Synthesis of *cis*-DHCD.

3.2 SYNTHETIC STRATEGIES.

DHCD is a simple molecule which is deceptively difficult to synthesise in either isomeric form. All the syntheses of *cis* and *trans*-DHCD published so far have used functional group interconversions (FGI). In such strategies a suitably functionalised six membered ring is manipulated via several functional groups to produce the desired product. An alternative strategy would be to synthesise the ring from suitably functionalised straight chain precursors.

A number of possible FGI's can be envisaged for the synthesis of DHCD. 1,2-Diols may be prepared by the ring opening of epoxides and epoxy alcohols, hydroxylation of alkenes, and reduction of α-hydroxy carbonyls.[167] Ring opening of epoxides and hydroxylation of alkenes have been used to introduce vicinal hydroxy groups, stereospecifically, in the synthesis of DHCD.[59,103-105] The stereospecific conversion of α-hydroxy carbonyls and epoxy alcohols into 1,2-dihydroxy groups is extremely difficult and so little use has been made of these reactions. The simplest way of introducing double bonds is via the elimination of halogens or hydrogen halides from alkyl halides and in all the successful syntheses of DHCD one or other of these methods has been used.[59,103-105] Consideration

of DHCD as a molecule which contains two allylic alcohol functions, rather than separate 1,2-dihydroxy and 1,3-diene functions, allows other synthetic possibilities to emerge. Allylic alcohols can be readily prepared by reduction of α,β-unsaturated carbonyl derivatives, allylic oxidation, cleavage of 1,3-diene monoepoxides, from endoperoxides, isomerisation of epoxides, oxidation of allylsilanes, reduction of propargyl alcohols, reductive cyclisation of ynones, 2,3-sigmatropic rearrangements, the Wharton reaction, and the Wittig reaction.[168] Despite the apparent variety of methods, the constraint of stereochemistry allows only the cleavage of 1,3-diene monoepoxides, (which has been used in the synthesis of *trans*-DHCD[103-105]), and isomerisation of epoxides[169] to be considered as plausible routes for our purposes.

It appeared from a literature survey that the use of straight chain precursors in DHCD synthesis had not been investigated. The simplest disconnections are presented in Figure 3.1.

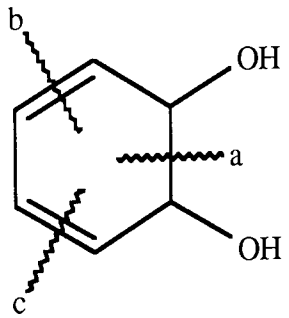


Figure 3.1: Disconnection of DHCD.

The most obvious, and potentially the simplest, route to DHCD would be via disconnection **a**. Although methods are available for the synthesis of 1,2-diols by reductive coupling,[170] the coupling route is complicated by the necessity for the 1,3-diene group to be in a *cis*, *cis* configuration in the precursor. It seemed likely that the synthesis of such a grouping would be difficult, due to the formation of *cis*, *trans* and *trans*, *trans* isomers in addition

to the desired configuration. An alternative method of introducing the diene function would be by elimination of halogen or hydrogen halide from a suitable alkyl halide after the formation of the 1,2-diol by a coupling reaction. The synthetic routes which could be devised using this approach are lengthy since the appropriate intermediates are not commercially available. An entirely different approach via disconnection **a** is the electrocyclic ring closure of a suitably functionalised hexatriene. The preparation of *cis* and *trans*-1,2-dimethyl-3,5-cyclohexadienes by thermal and photolytic ring closure of octatriene respectively, are well documented reactions.[171-178] The substituted hexatriene system, which appeared to be the most suitable precursor for DHCD synthesis via an electrocyclic ring closure, is shown in Figure 3.2.

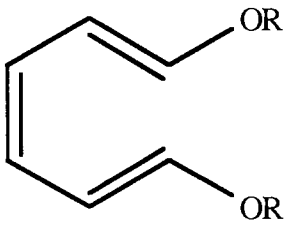
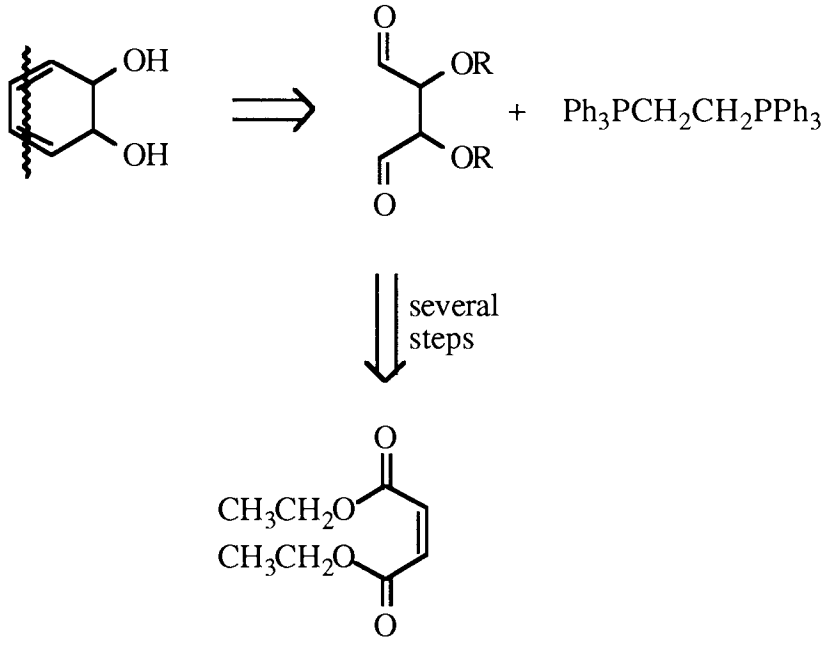


Figure 3.2: Precursor to DHCD.

Alternative routes to DHCD via disconnections **b** or **c** were also considered but require highly functionalised precursors which would be difficult to synthesise. One such route could be via a di-Wittig reagent which could form both double bond functions in the same step. At first sight this approach seems promising but on reflection seems less hopeful as the necessary dialdehyde precursor would take several steps to synthesise, probably from a maleic ester, which would be a lengthy process, see Scheme 3.7. In addition, even if it were possible to prepare the di-Wittig reagent, it is likely to be prone to elimination, forming ethene. Routes involving disconnections **b** and **c** do not appear to be potentially useful.



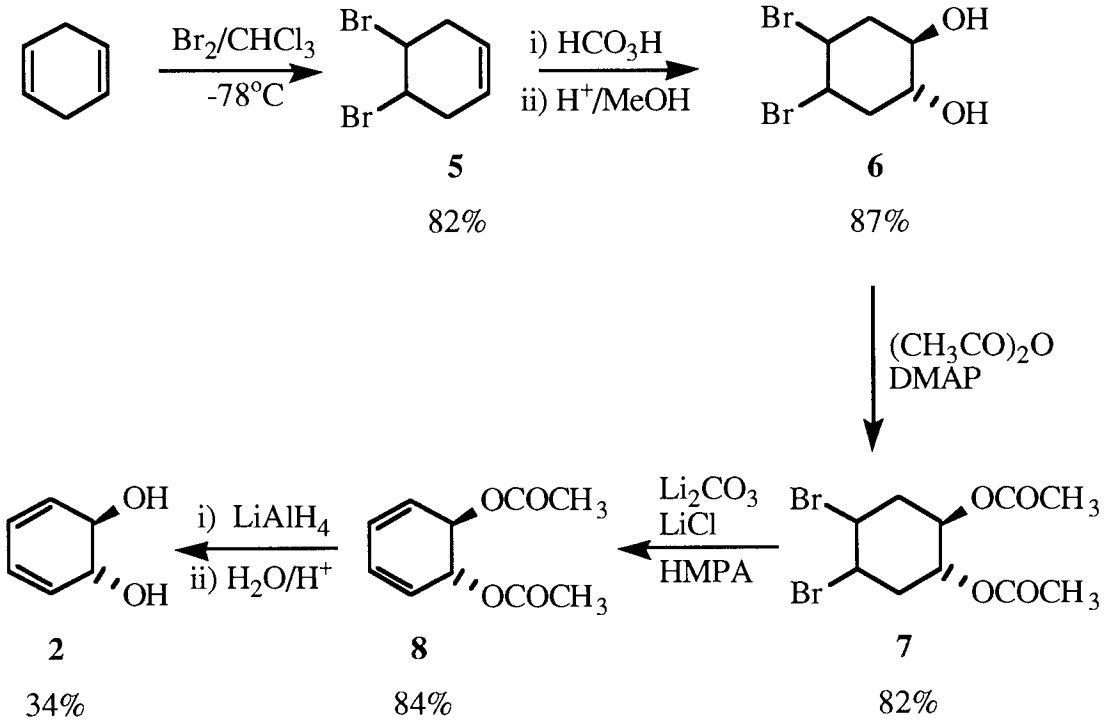
Scheme 3.7: Wittig Synthesis of DHCD.

3.2.1 *trans*-DHCD

3.2.1.1 *trans*-DHCD by Modification of the Platt and Oesch Synthesis.

The successful Platt and Oesch method was the logical starting point in the development of syntheses of *trans*-DHCD,[103] see Scheme 3.8. Good yields were obtained for the first four steps.[105,156-159] The main problem encountered was the procedure described by Platt and Oesch for the reduction of **8** with a suspension of lithium aluminium hydride in ether at 0°C for 1 hour; this gave negligible conversion to *trans*-DHCD. It was observed that even after 5 hours at 0°C the diacetate remained largly unreacted. It was thought that the lithium aluminium hydride might have become deactivated and so it was replaced with a commercially available 1.0M solution of lithium aluminium hydride in ether. Using this latter material the reduction of **8** was complete after 2 hours at 0°C. Despite this, the best yield of *trans*-DHCD which could be obtained was only 34%. In the final reductive step excess lithium aluminium hydride was hydrolysed with dilute acid to obtain the highly water soluble *trans*-DHCD. It was therefore necessary to carry out a three day continuous extraction to isolate this compound. The low yield was probably due to aromatisation of

trans-DHCD whilst dissolved in the acidic aqueous phase during this continuous extraction procedure. Evidence for this comes from the detection of phenol in the IR and NMR spectra of the product. This process gave a relatively low yield of an impure product.



Scheme 3.8: *trans*-DHCD via the Platt and Oesch Route.

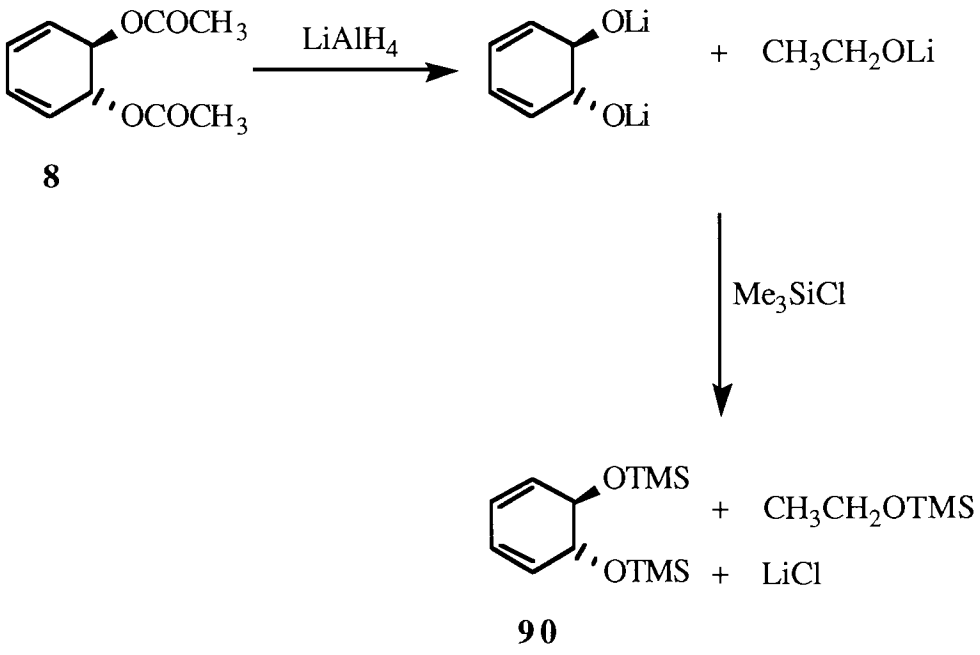
The problems encountered in the final steps of the Platt and Oesch synthesis prompted an investigation into the modification of this synthetic route.

Consideration of the Platt and Oesch method reveals a number of undesirable elements. The first of these is the reluctance of *trans*-1,2-dihydroxy-4,5-dibromocyclohexane **6** to form *trans*-DHCD directly, by the elimination of two molecules of HBr. Investigation of this elimination reaction, using a variety of bases and solvents, was reported by Platt and Oesch but all attempts were unsuccessful.[103] The principal reason for the failure of the elimination is the lability of the hydroxyl hydrogens in comparison to the alkyl hydrogens; any base will react preferentially with the hydroxyl groups giving the dianion. The problem was

overcome by protecting the hydroxyl functions as esters, performing the elimination step and then reducing the ester groups with lithium aluminium hydride. As pointed out previously this leaves the crude *trans*-DHCD in the aqueous, acidic phase, in which it aromatises and from which it can be removed only by a lengthy continuous extraction with ether. Yields were good for all the steps except the final one so this was the stage which had to be improved.

One obvious improvement would be to modify the final step so that *trans*-DHCD was formed in an organic medium. Two different approaches were explored. The first involved reduction of the ester groups with lithium aluminium hydride as before, but the residual reducing agent was destroyed by adding an excess of chlorotrimethylsilane rather than water and sulphuric acid. Lithium aluminium hydride is known to reduce halogenated silanes[179,180] $R_{4-n}SiX_n$ to the corresponding silane $R_{4-n}SiH_n$, whilst reaction of silyl halides with sodium alkoxides readily produces organosilicon alkoxides.[181-183] It was anticipated that the products would be lithium chloride, aluminium chloride, trimethylsilane, trimethylsilyl protected *trans*-DHCD **90** and trimethyl silyl protected ethanol. The reaction is represented in Scheme 3.9.

After the reaction was complete the mixture was filtered, followed by removal of the volatile materials by rotary evaporation; no product could be detected. The products of the reaction were obviously removed, rather surprisingly during the filtration step. Alkoxides react rapidly with silyl chlorides so it is unlikely that the lithium salt of *trans*-DHCD would remain unreacted in the presence of a large excess of chlorotrimethylsilane, and be removed by filtration. It is more probable that the products, whatever they were, became absorbed by the solid material and were subsequently removed by filtration. However, washing the solid residue with small quantities of ether still did not extract any products.

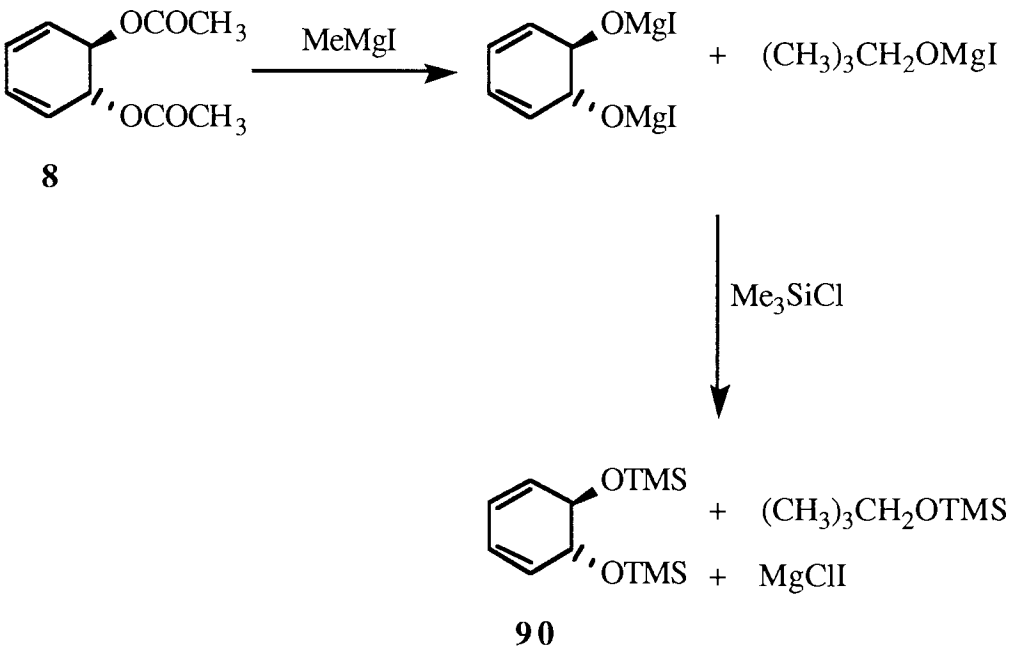


8 **90**

Scheme 3.9: Non-Aqueous Reduction.

A second approach was to use of the Grignard reagent, methylmagnesium iodide, which was expected to react with the diacetate **8** to form the products in Scheme 3.10. Again it was anticipated that addition of an excess of chlorotrimethylsilane, after completion of the Grignard reaction, would give the trimethylsilyl derivative of *trans*-DHCD **90**.

Examination of the ^{1}H and ^{13}C NMR spectra of the material isolated showed that phenol was the major product of this reaction. Normally the addition reaction of Grignard reagents to esters produces a mixture of two alcohols (Scheme 3.10), but allyl esters can behave somewhat abnormally.[184-187] The usual products from the cleavage of allyl esters are carboxylic acids and coupled products,[188] see Figure 3.3. No coupled products were observed in the NMR spectra of the material isolated from this reaction. It can be concluded that in this case the reaction does not take place by the usual mechanism for allyl esters, see Figure 3.3.



Scheme 3.10: Non-Aqueous Grignard Reaction.

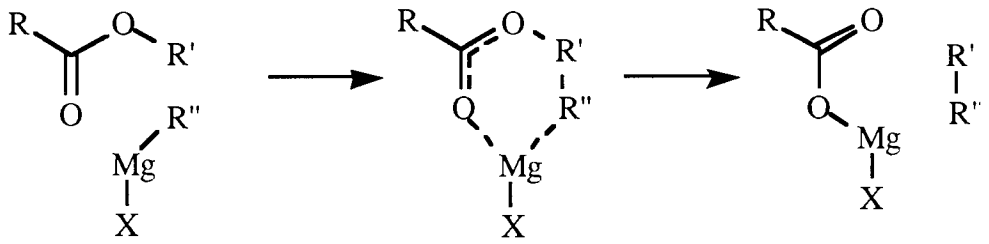
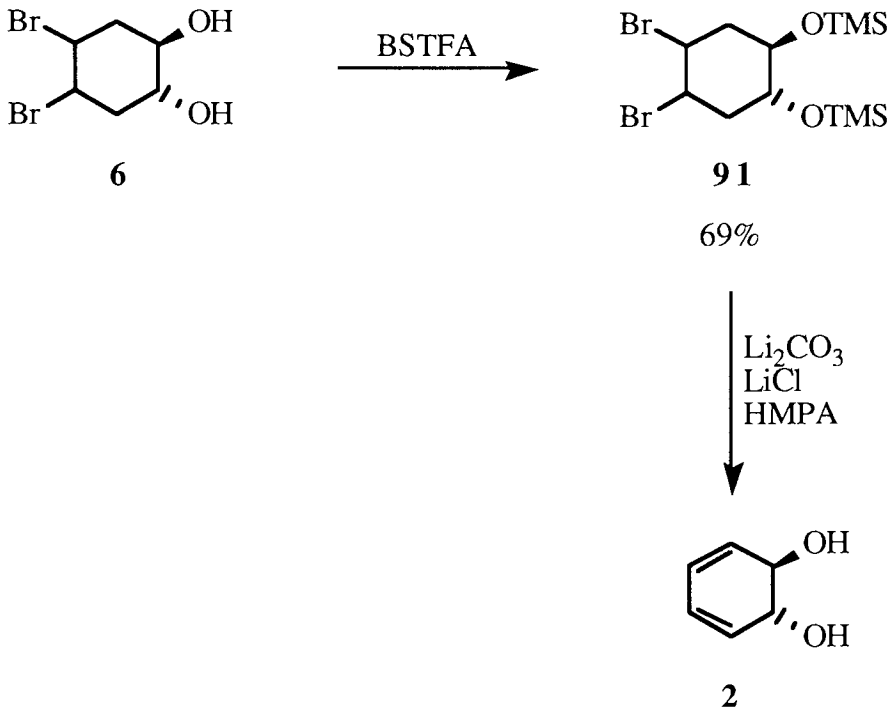


Figure 3.3: Mechanism of Allyl Ester Cleavage.

An alternative modification to the Platt and Oesch synthesis which was considered, was to replace the ester function with silyl functions, since it is possible to remove these latter functions in organic solvents. Protection of hydroxyl groups via alkylsilyl ethers is a well established procedure and, providing the alkyl groups are sufficiently bulky, they will fulfil all the criteria for a protecting group.[189] Trimethylsilyl groups were initially tried as suitable protecting groups, see Scheme 3.11.



6 **91** 69% **2**

Scheme 3.11: Protection via Trimethylsilyl Groups.

Protection of **6** with trimethylsilyl groups was accomplished by reaction of **6** with bis(trimethylsilyl)trifluoroacetamide (BSTFA) to give **91** in a good yield of 69%.[149] The protected compound **91** was then subjected to the elimination conditions used for the diacetate derivative **7**. The usual work-up procedure resulted in the isolation of no product. Continuous extraction of the combined aqueous phase with ether, followed by purification by dry flash chromatography gave a mixture of products, see Figure 3.4. Examination of the ^{1}H NMR spectrum of the products indicated that it contained some residual HMPA, despite extensive efforts to remove it by dry flash chromatography; this is indicative of the tenacity of this solvent. Comparison of the ^{1}H and ^{13}C NMR spectra for *trans*-DHCD **2** and *trans*-1,2-dihydroxy-4,5-dibromocyclohexane **6** with those obtained for the product indicated that both of these compounds were probably present. This suggested that the silyl groups had been removed during the course of the reaction and that success might be achieved with less labile protecting groups.

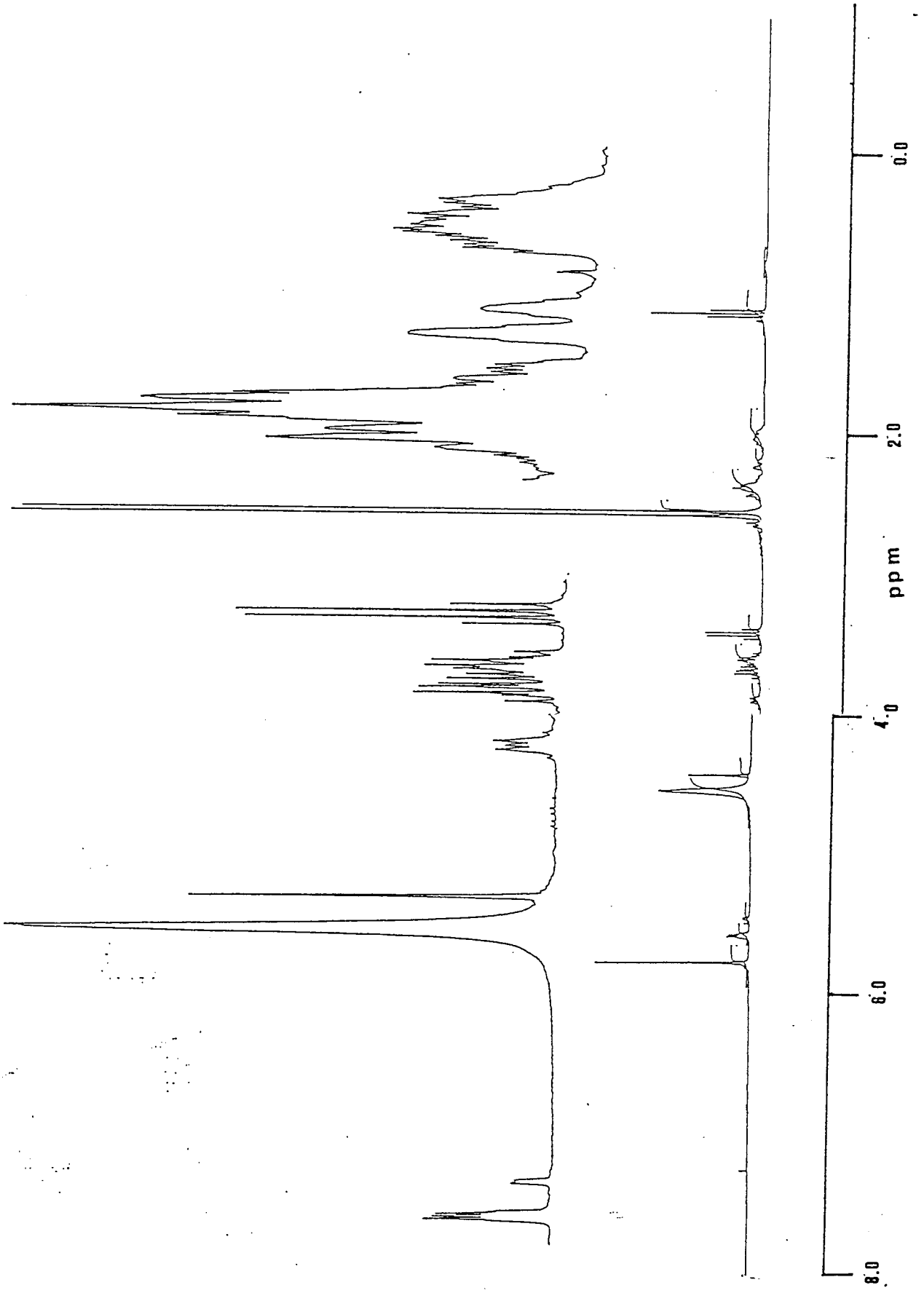


Figure 3.4a: ^{1}H NMR Spectrum. Protection via Trimethylsilyl Groups.

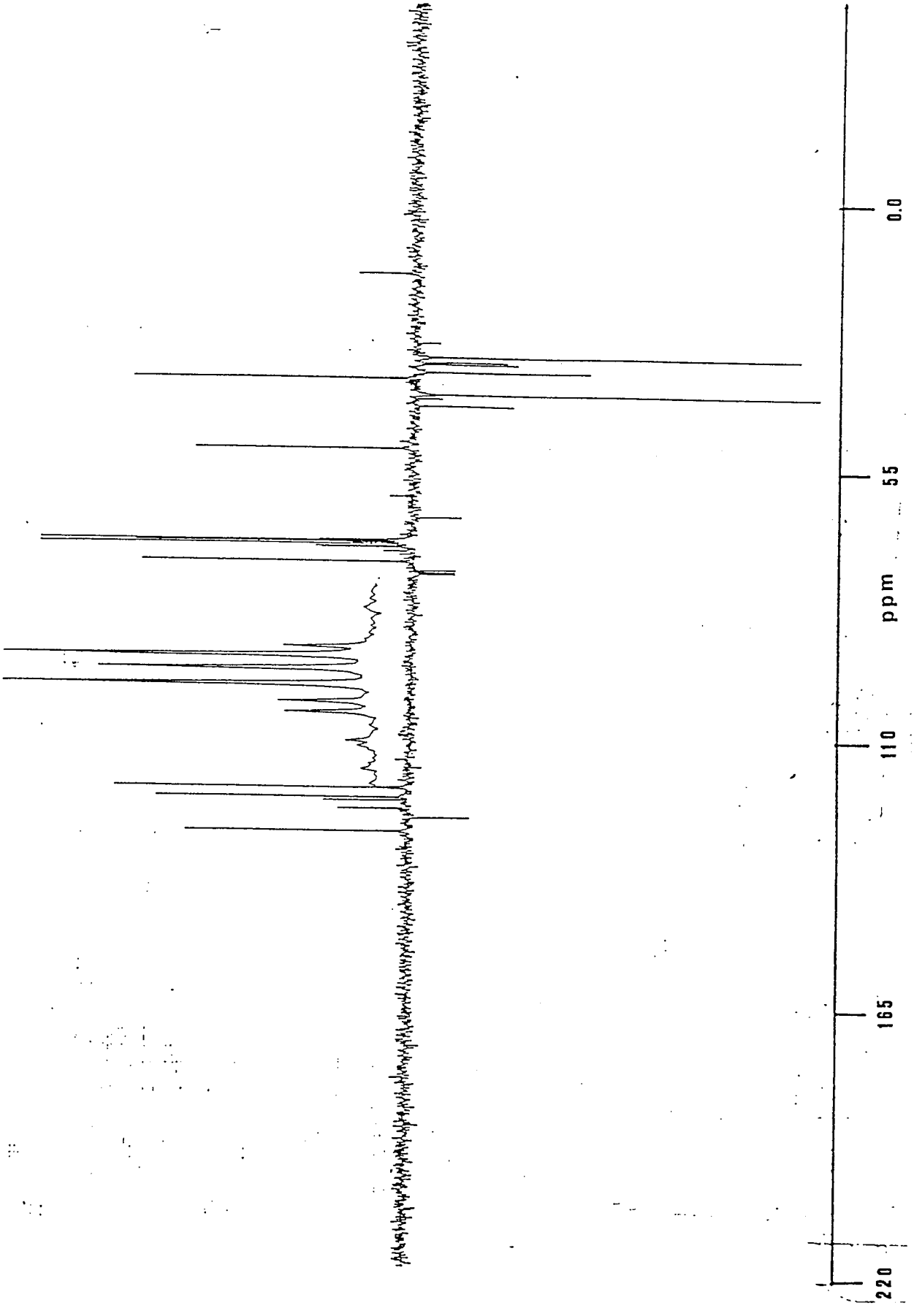
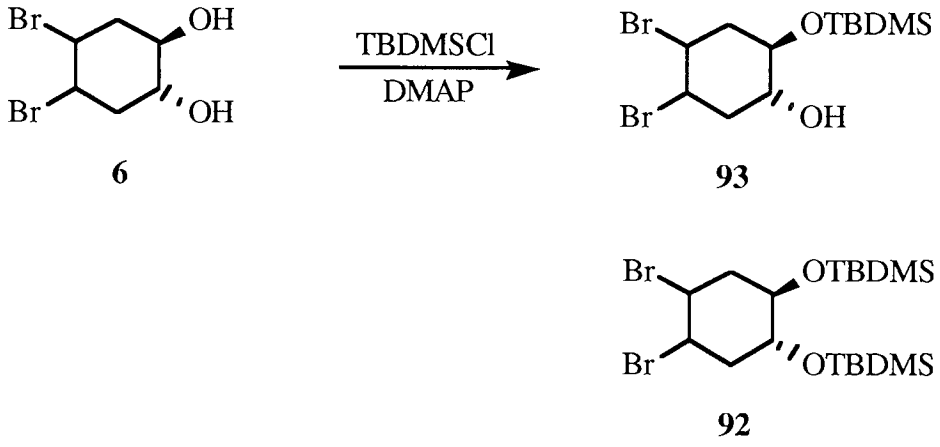


Figure 3.4b: ^{13}C NMR Spectrum. Protection via Trimethylsilyl Groups.

It was decided to use the bulkier and more hydrolytically stable *tert*-butyldimethylsilyl group[189] to protect the diol **6**. Silylation with *tert*-butyldimethylsilyl chloride is normally accomplished in DMF in the presence of imidazole. A more convenient method using DMAP as a catalyst has been reported[158] and this method was used in the attempted synthesis of **92**, see Scheme 3.12.



6 **93** **92**

Scheme 3.12: Protection via *tert*-Butyldimethylsilyl Groups.

Examination of the ^{1}H and ^{13}C NMR spectra (Figure 3.5) showed that a mixture of products were produced. The major products of this reaction appeared to be the di and mono substituted compounds **92** and **93** respectively. It would seem that substitution by the large *tert*-butyldimethylsilyl group substantially retards the introduction of a second *tert*-butyldimethylsilyl group. This approach was not investigated further because of this problem.

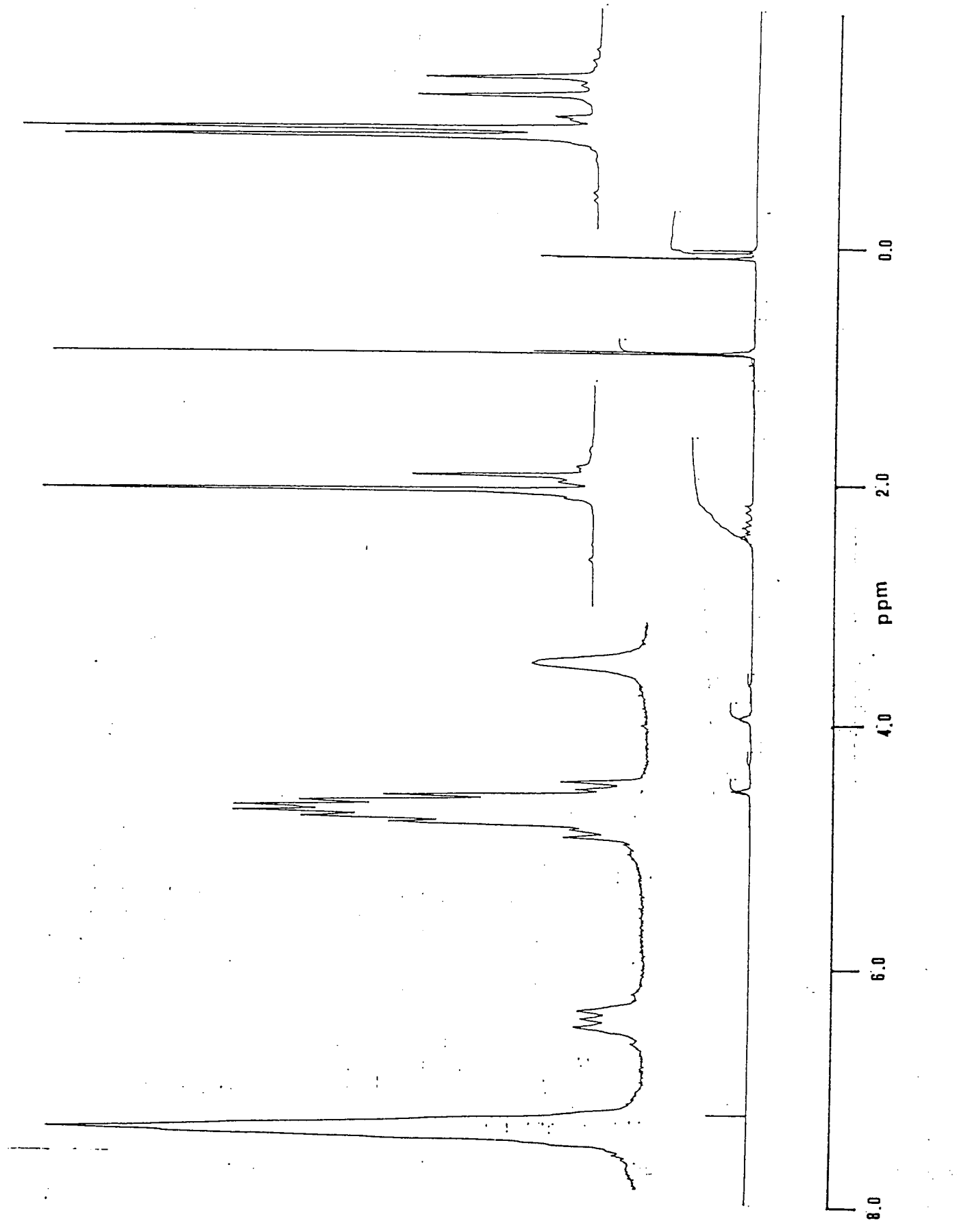


Figure 3.5a: ^{1}H NMR Spectrum, Protection via *tert*-Butyldimethylsilyl Groups.

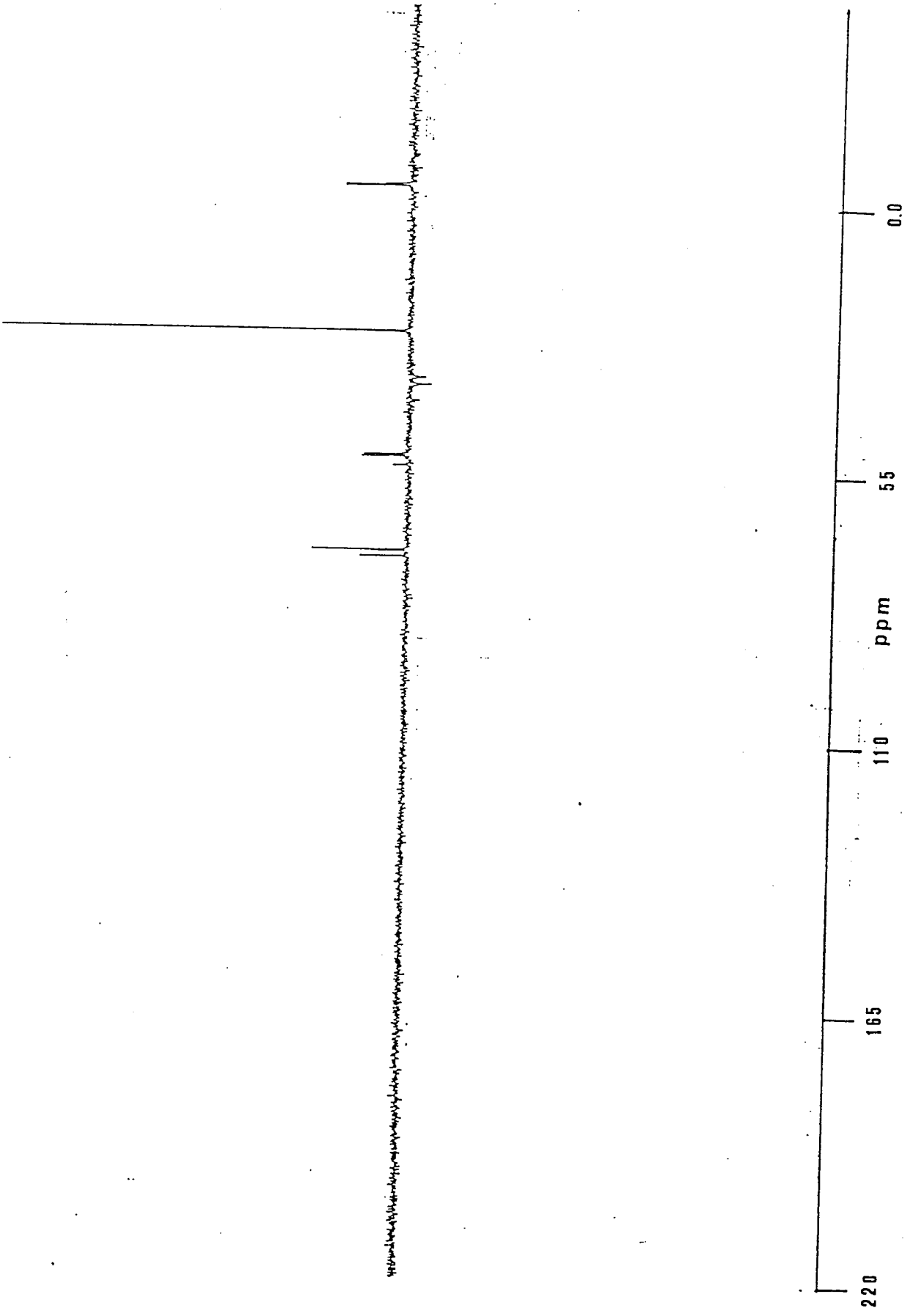
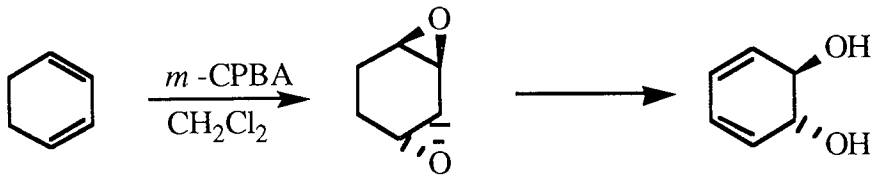


Figure 3.5b: ^{13}C NMR Spectrum. Protection via *tert*-Butyldimethylsilyl Groups.

3.2.1.2 *trans*-DHCD from 1,3-Cyclohexadiene.

The usual strategies for the synthesis of isomers of DHCD treat the diene and diol moeities separately and in the methods used each function is introduced independently. However, if DHCD is considered as a molecule consisting of two allylic alcohols this leads to the possibility of introducing both of these groups simultaneously. Although a number of methods for preparing allylic alcohols are available many are unsuitable for DHCD synthesis for mechanistic or stereochemical reasons; of the remaining procedures perhaps the most promising would appear to be via the rearrangement of epoxides.[168] This reaction has the potential to be used for the synthesis of both *cis* and *trans*-DHCD. Since the method used for the synthesis of the *cis* analogue of the diepoxide **94** occurs in low yield[190-194] this was not investigated further, see Scheme 3.13.

Numerous reagents are available for the isomerisation of allylic alcohols to epoxides.[168,169] Most are unsuitable for the preparation of *trans*-DHCD, since the synthesis of *trans*-DHCD must be carried out at moderate temperatures and under non-acidic conditions. In addition it seemed worthwhile to consider only those methods for which starting materials were commercially available. This approach is shown in Scheme 3.13.



94 **2**

50%

Scheme 3.13: *trans*-DHCD from 1,3-Cyclohexadiene.

3,8-Dioxatricyclo(1α,2β,4β,7α)[5.1.0.0.^{2,4}]octane, *trans*-1,3-cyclohexadiene diepoxide **94**, was prepared by epoxidation of 1,3-cyclohexadiene with *m*-chloroperoxybenzoic acid

(*m*-CPBA) in 50% yield, which is comparable with the literature yields.[192,193] It had been observed by previous workers that a large pot residue remained after distillation and the conversion to the desired product was therefore not great.[192] We observed a similar effect in the synthesis of **94**. Analysis of the distilled product, by GLC and ^{1}H and ^{13}C NMR spectroscopy, indicated that the product contained approximately 10% of *cis* diepoxide. This too had been observed by the other workers.[192]

Lithium diethylamide had been used previously for rearrangement of epoxides to allylic alcohols[196-198] and more particularly, cyclohexene oxide had been converted into 2-cyclohexenol in 67% yield by this process.[180] Lithium diethylamide appeared to be a promising reagent for the initial attempt to rearrange *trans*-1,3-cyclohexadiene diepoxide **94** into *trans*-DHCD **2**. Although the rearrangement of cyclohexene oxide in boiling ether is complete within two days, rearrangement *trans*-1,3-cyclohexadiene dioxide **94** with lithium diethylamide required four days in boiling hexane before the reaction was complete. Even after that time no product was obtained using the procedure described by Crandall and Chang for the rearrangement of cyclohexene oxide.[196] However, combining the initial aqueous phase and the acid washings followed by continuous extraction for three days with ether, gave a crude, dark brown liquid. The ^{1}H and ^{13}C NMR spectra of this crude material indicated that a complex mixture of products had been formed, the structures of which could not be determined, see Figure 3.6. The spectra showed that no diepoxide remained and no *trans*-DHCD had been formed. Both aromatic and aliphatic materials were present, the mixture probably consisted of various hydroxy and diethylamino substituted aromatic and cyclohexane ring derivatives. The aromatisation of 1,3-cyclohexadiene monoepoxide, when reacted with lithium diethylamide, via a benzene hydrate has been reported.[198] A similar mechanism could account for the formation of the aromatic products in this reaction, whilst the usual epoxide ring opening mechanism could account for the formation of the aliphatic compounds.

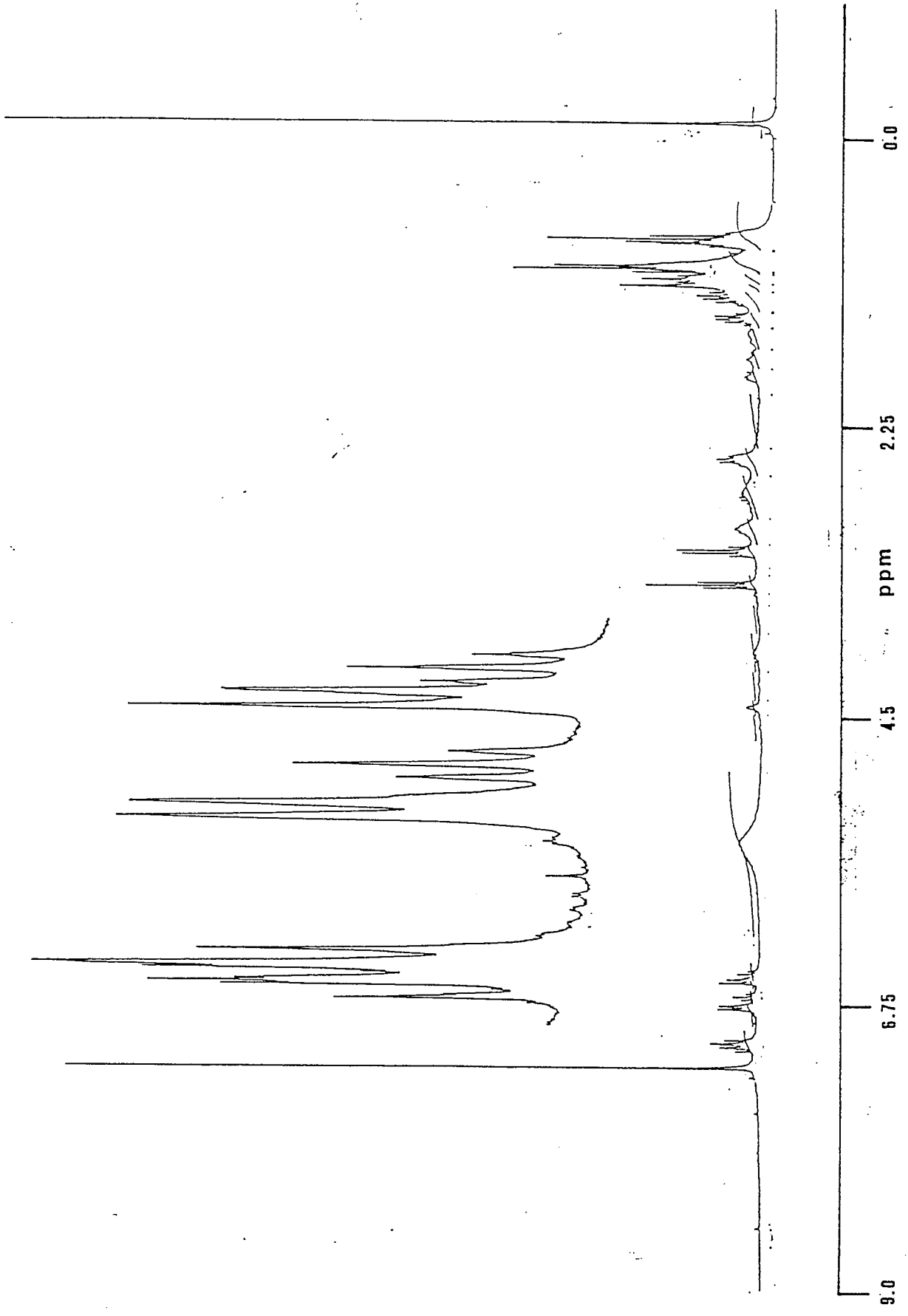


Figure 3.6a: ^{1}H NMR Spectrum. Diepoxide Rearrangement by Lithium Diethylamide.

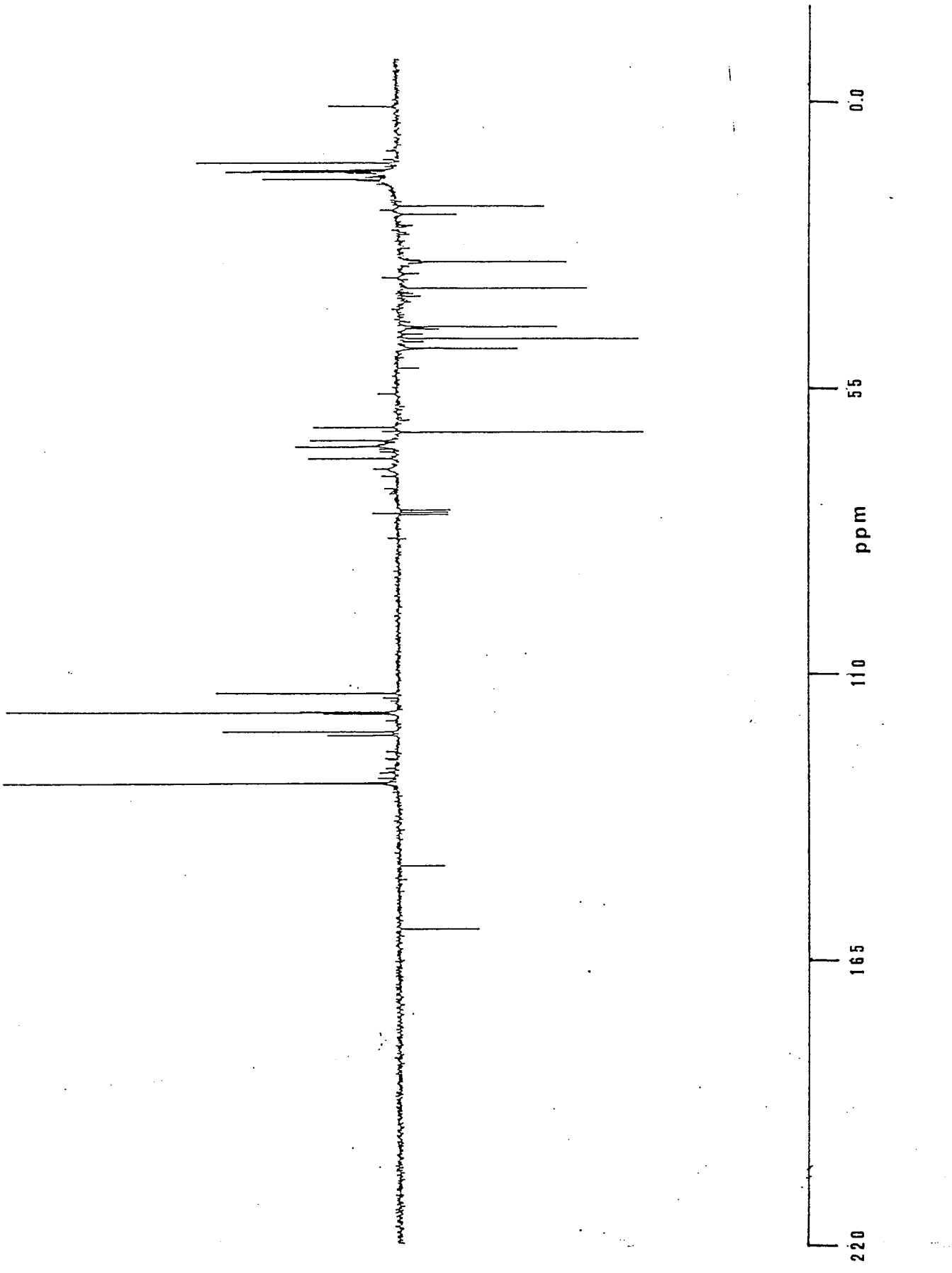
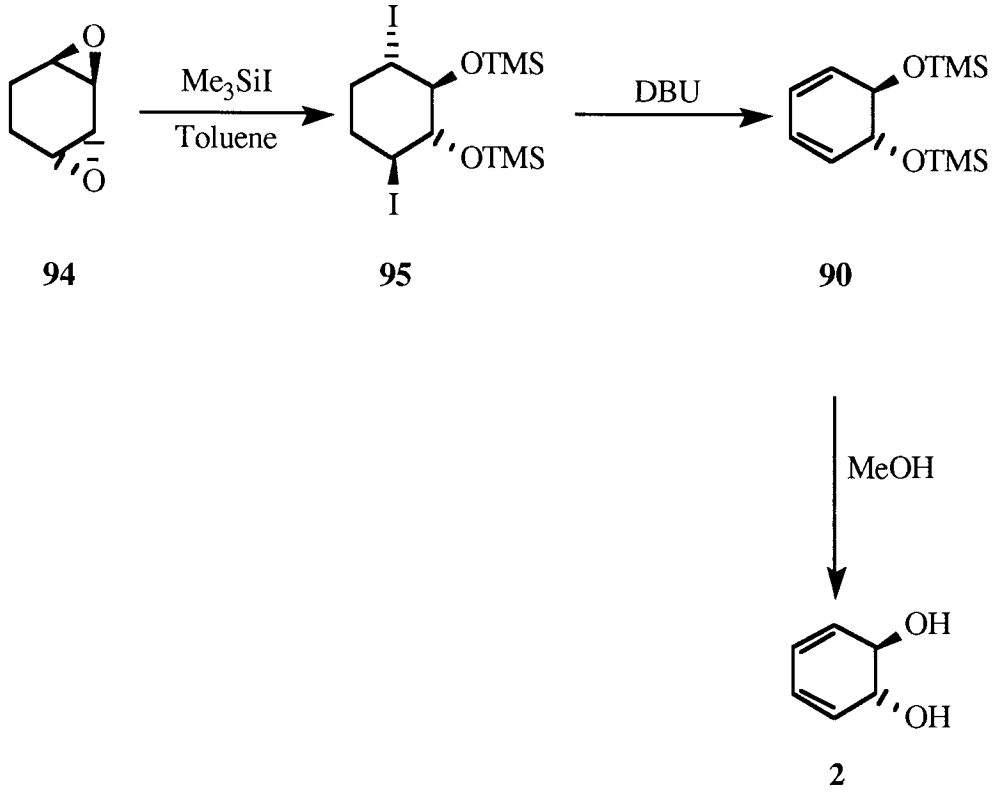


Figure 3.6b: ^{13}C NMR Spectrum. Diepoxide Rearrangement by Lithium Diethylamide.

A second approach was that developed by Sakurai and co-workers.[199] The advantage of this method is that the cyclohexene oxide was converted to the corresponding trimethylsilyl protected allylic alcohol, in 81% yield, under milder conditions than those described above.[199] This route involved the reaction of the diepoxide with trimethylsilyl iodide to give **95**, followed by treatment with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and removal of the silyl groups by methanol, see Scheme 3.14.



94 **95** **90** **2**

Scheme 3.14: Mild Rearrangement of 1,3-Cyclohexadiene Diepoxide.

Again the ^{1}H and ^{13}C NMR spectra indicated that a complex mixture of products had been formed, see Figure 3.7. The mixture contained a significant quantity of aromatic material, together with significant quantities of non-aromatic material, which contained double bonds, and a complex mixture of alicyclic products.

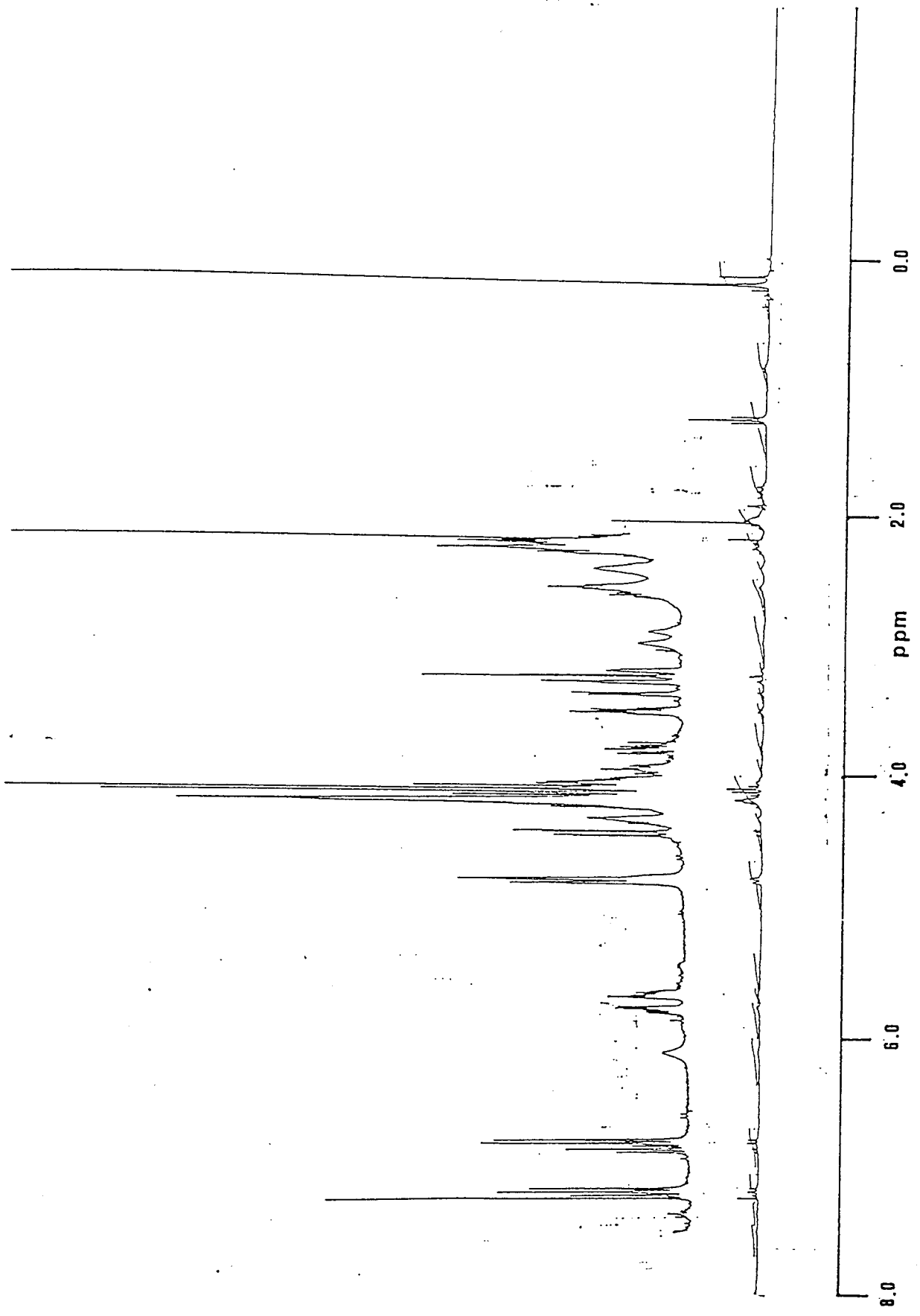


Figure 3.7a: ^{1}H NMR Spectrum, Diepoxide Rearrangement by Iodotrimethylsilane.

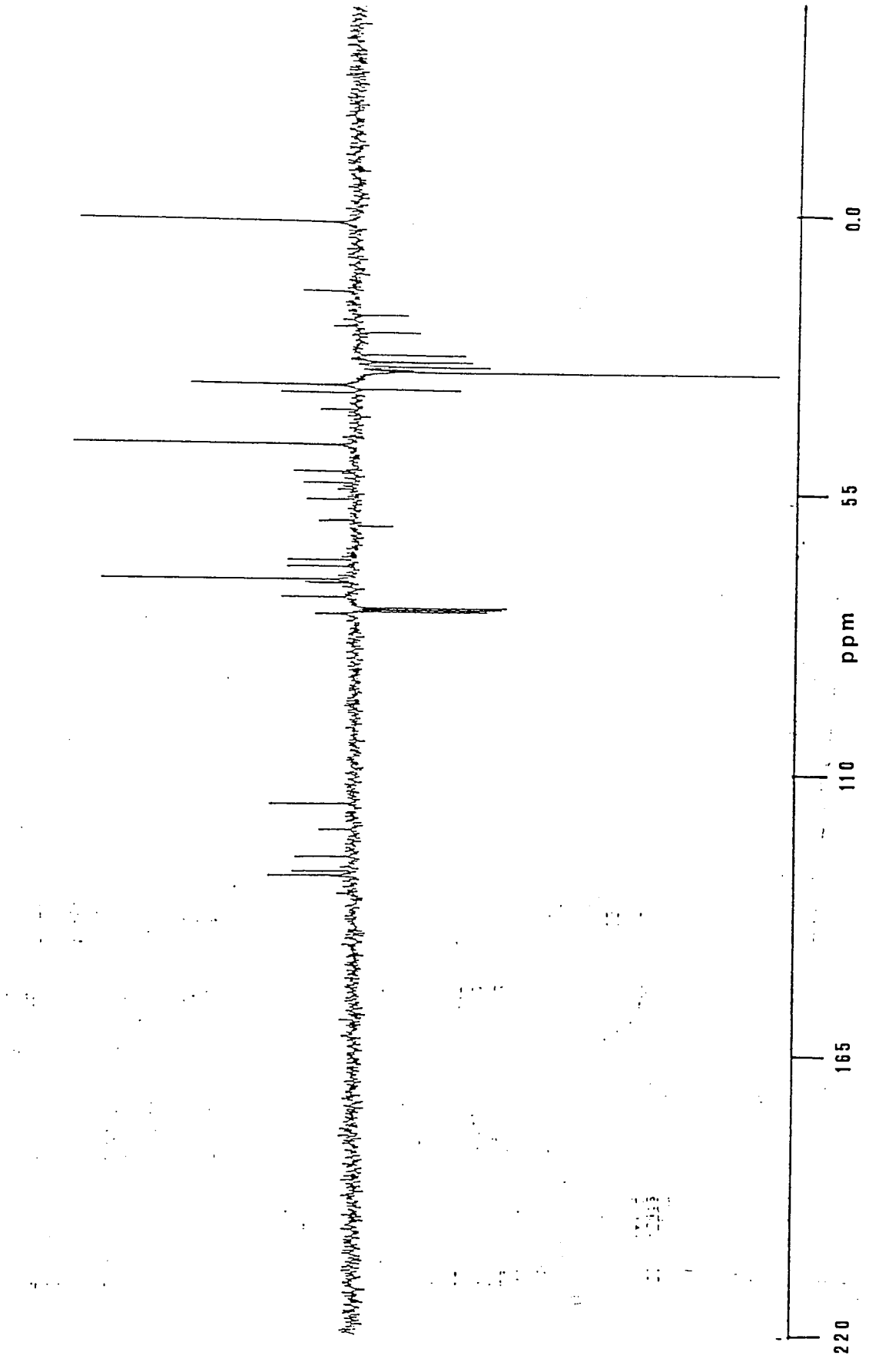


Figure 3.7b: ^{13}C NMR Spectrum. Diepoxide Rearrangement by Iodotrimethylsilane.

The formation of the aromatic material was almost certainly due to the moderately high temperature required for the basic elimination step. Although some compounds containing double bonds were certainly present in the product there was also a large quantity of alicyclic material, which indicated that the intermediate **95** had either not reacted or had undergone side reactions forming compounds in which double bonds are absent.

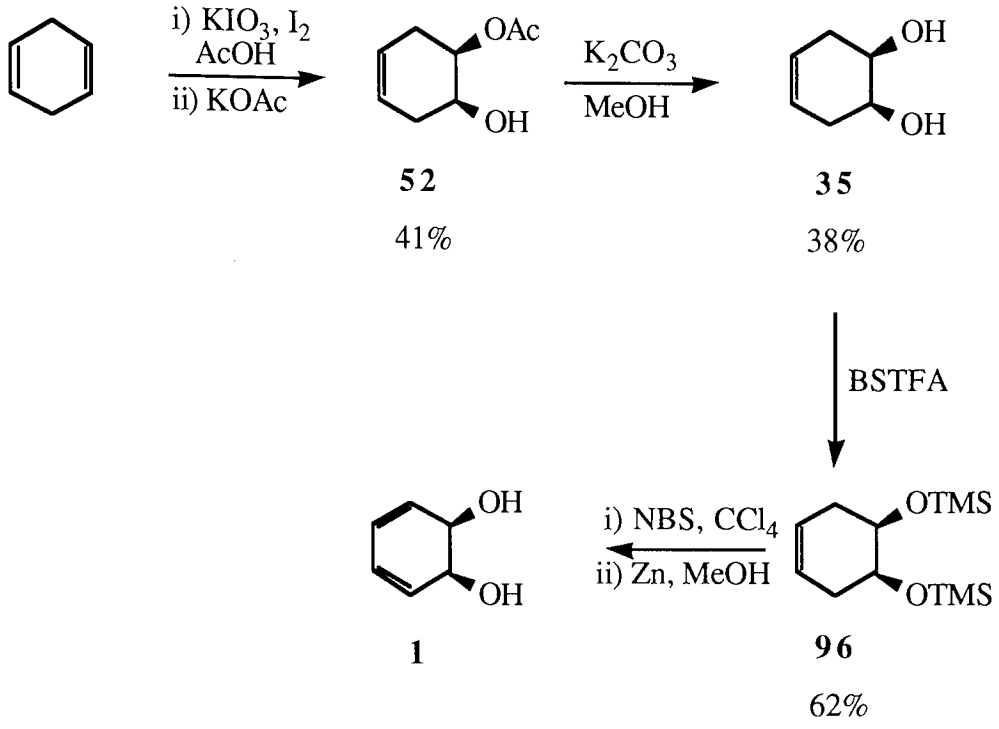
It was apparent that a method of elimination was required which could convert the diiodide precusor **95** efficiently to the diene **76** at a lower temperature, thereby reducing the possibility of the diene aromatising and of the diiodide **95** undergoing side reactions. No suitable method could be found in the literature so this approach was not investigated further.

3.2.2 *cis*-DHCD.

3.2.2.1 *cis*-DHCD from 1,4-Cyclohexadiene.

In 1987 McKean and Stille published the only route to *cis*-DHCD derivatives which uses conventional chemical techniques.[20] To synthesise *cis*-DHCD itself this approach was modified, see Scheme 3.15.

The syntheses of the monoacetate **52** and the diol **35** have been discussed previously in Sections 2.4.2.1 and 2.4.2.2 respectively. Silylation of **35** with BSA produced an azeotropic mixture which hydrolysed readily in aqueous work up. However, silylation of the diol **35** with BSTFA, which produces more volatile by-products, resulted in the isolation of **96** in a yield of 62%. Treatment of **96** with NBS in CCl_4 followed by elimination of the bromine with powdered zinc, in dry methanol, gave phenol as the major product. The trimethylsilyl protecting groups are probably removed in the last step allowing aromatisation to occur.



Scheme 3.15: *cis*-DHCD from 1,4-Cyclohexadiene.

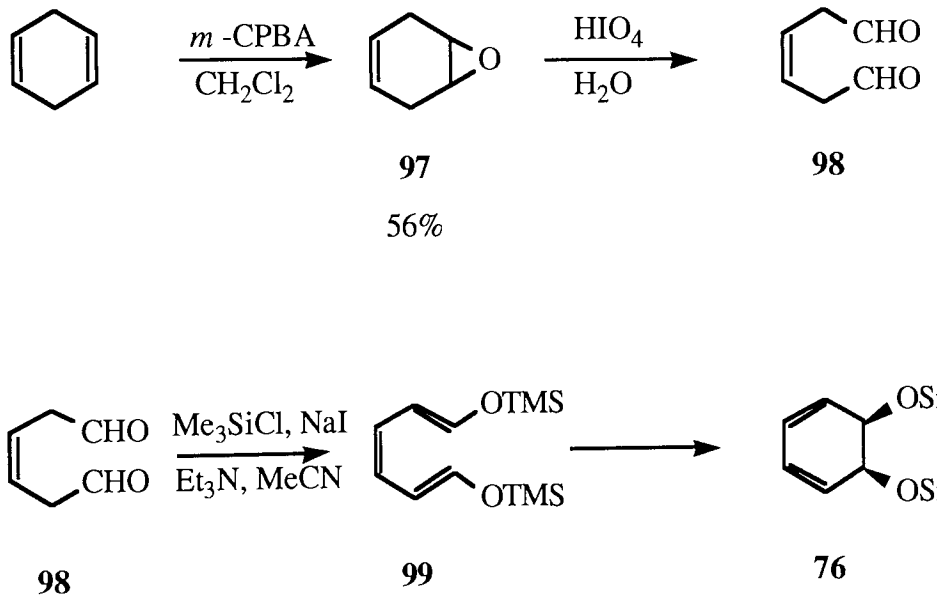
The more hydrolytically stable *tert*-butyldimethylsilyl group could be a better protecting group, but because of the problems of protecting 1,2-diols with this group discussed in Section 3.2.1.1, this approach was not investigated further.

3.2.2.2 *cis*-DHCD via an Electrocyclic Ring Closure.

The formation of *cis*-1,2-dimethyl-3,5-cyclohexadiene from octatriene, via thermal electrocyclic ring closure, is a well documented reaction[171-178] and so it was decided to investigate whether *cis*-DHCD could be prepared by a similar procedure. It was also anticipated that it would be possible to prepare *trans*-DHCD by photochemical electrocyclic ring closure. The hexatriene required for such a reaction would need to possess two enol functions as shown in Figure 3.2.

A number of different enols can be prepared from aldehydes[200] (e.g. silyl enol ethers, boron enol ethers, and lithium enols) but silyl enol ethers are relatively simple to prepare and the silyl protecting group can be easily removed in an organic medium. Several methods are available for the preparation of silyl enol ethers from aldehydes,[201] but one of the simplest was developed by Cazeau and co-workers.[202] The method involves the generation of iodotrimethylsilane *in situ* and its subsequent reaction with the desired aldehyde to give the corresponding trimethylsilyl enol ether.

The dialdehyde **98** had been prepared previously, in two steps from 1,4-cyclohexadiene, by Uchida and co-workers. They observed that the dialdehyde **98** was unstable and used the crude product for their further syntheses.[203] The route devised for the synthesis of *cis*-DHCD via a thermal electrocyclic ring closure is shown in Scheme 3.16



Scheme 3.16: *cis*-DHCD via an Electrocyclic Ring Closure.

The procedure of Uchida[203] was followed and 1,2-epoxy-4-cyclohexene **97** was prepared in a comparable yield of 56%. The boiling point and IR spectrum agree closely with those reported by Uchida, but it was found that the sample had decomposed to a complex mixture of products by the time the NMR was recorded. The conversion of the freshly prepared material to the crude dialdehyde **98** was accomplished by reaction with periodic acid at 0°C. The IR spectrum of the crude product agreed closely with that reported by Uchida, the only exception being the presence of a peak corresponding to a hydroxyl group.[203] The method of Cazeau and co-workers was followed for the attempted conversion of the crude dialdehyde **98** to the dienol **99**. The dialdehyde **98** was reacted with iodotrimethylsilane and triethylamine in acetonitrile, followed by heating at 70°C for two hours. Water was then added and the mixture extracted with hexane. The product isolated from the organic phase showed no absorptions for either enol or carbonyl groups in its IR spectrum. Examination of the products showed that a complex mixture of compounds was present, see Figure 3.8.

The NMR spectra indicated that some residual hexane was probably present, in addition to compounds containing double bonds and aromatic products. The presence of aromatic compounds suggested that the thermal electrocyclisation reaction had occurred but that the products had aromatised. The dienol **99** could not be isolated, so a study of the conditions required for the thermal electrocylic ring closure of this compound could not be investigated further.

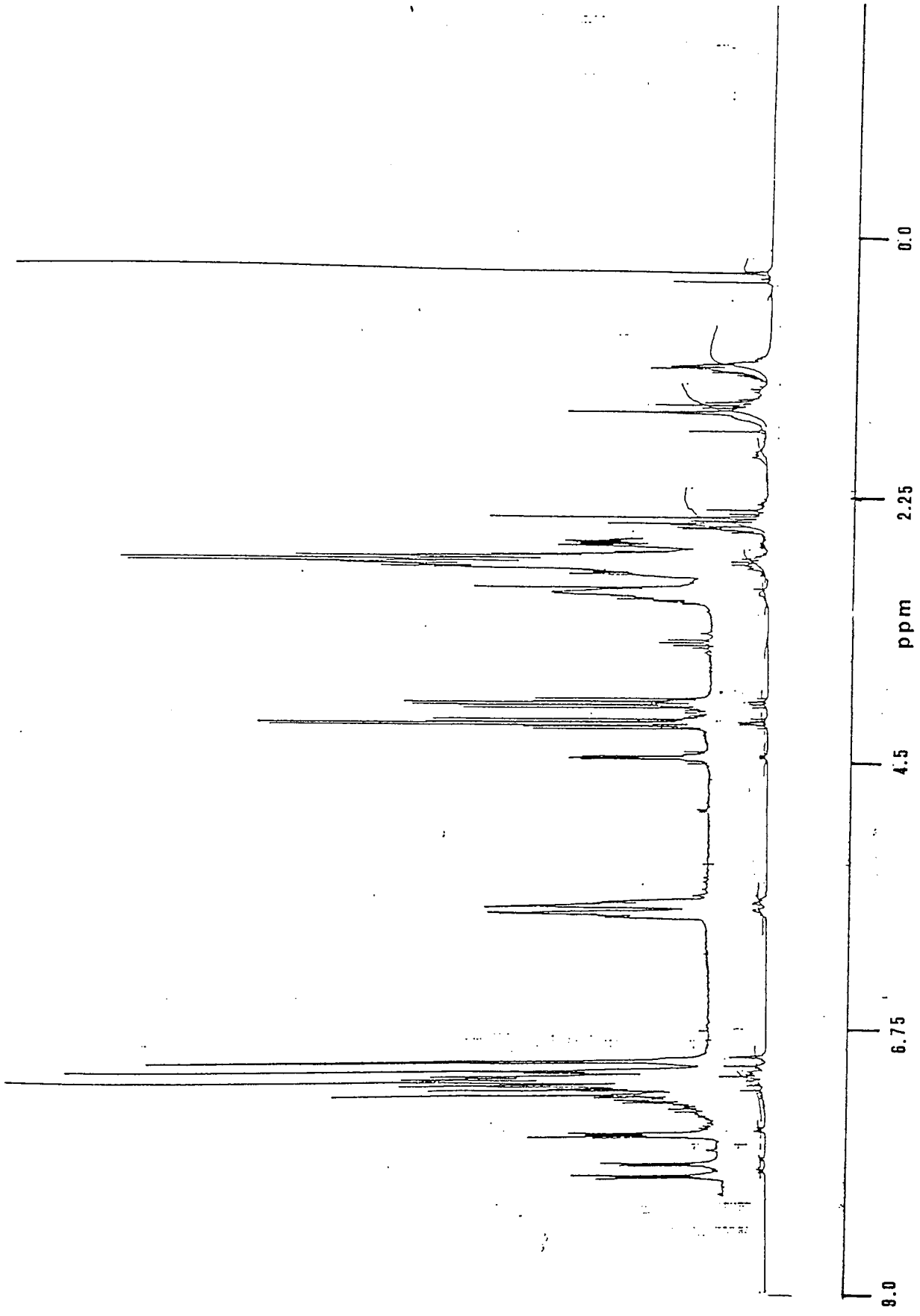


Figure 3.8a: ^{1}H NMR Spectrum. Thermal Electrocyclic Ring Closure.

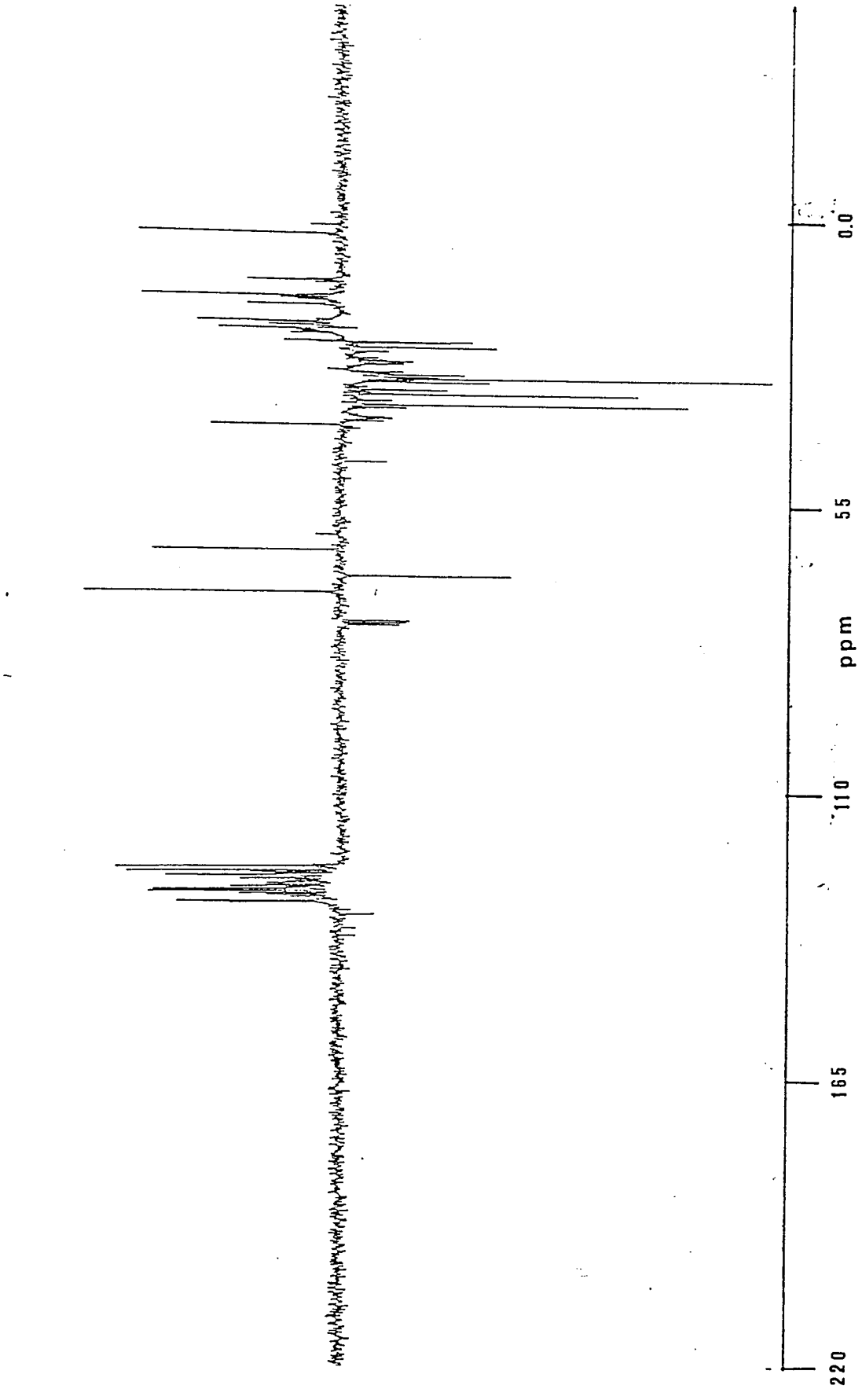


Figure 3.8b: ^{13}C NMR Spectrum, Thermal Electrocyclic Ring Closure.

3.3. CONCLUSIONS.

DHCD remains a singularly elusive molecule, in either isomeric form. There are two main reasons for this. The first is the constraint of stereochemistry, which limits the number of suitable synthetic routes and the second is the ease with which DHCD aromatises, so even if suitable synthetic routes can be devised these are prone to failure because of the ease with which the desired DHCD isomers aromatise.

Two approaches were investigated for the synthesis of *trans*-DHCD by modification of the Platt and Oesch synthesis of this compound. In the first of these, attempts were made to remove the acyl protecting groups in an organic medium, rather than the aqueous medium used by Platt and Oesch. It was found that reduction of the diester with lithium aluminium hydride, followed by quenching with chlorotrimethylsilane, surprisingly gave no detectable product and reaction of the diester with methylmagnesium iodide, followed by quenching with chlorotrimethylsilane, gave phenol as the major product.

In the second approach alkylsilyl groups, rather than the acyl function, were used as protecting groups. The labile trimethylsilyl groups hydrolysed under the conditions used in the elimination step. The OH groups lost their protective function and in consequence a complex mixture of products were formed. The use of the more hydrolytically stable *tert*-butyldimethylsilyl groups was not successful as the protected diol could not be prepared, due to steric factors.

An alternative route which was investigated, involved the rearrangement of the *trans*-diepoxide **94** to *trans*-DHCD. It was found that lithium diethylamide was too harsh a reagent for this rearrangement giving a complex mixture of products. Even the milder system of iodotrimethylsilane and DBU still gave a variety of products.

Two routes to *cis*-DHCD were explored. The synthesis of *cis*-DHCD by modification of the McKean and Stille procedure, which involved the use of trimethylsilyl protecting groups instead of acyl groups, gave phenol as the major product, due to the removal of the trimethylsilyl protecting groups during the final elimination step thereby allowing aromatisation to occur.

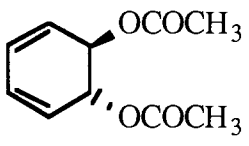
A final synthesis of *cis*-DHCD was via a thermal electrocylic closure which resulted in a complex mixture of products. It appeared that cyclisation did occur but that a significant quantity of the products aromatised.

Chapter 4: Properties Of Hydrogels.

4. PROPERTIES OF HYDROGELS.

4.1 INTRODUCTION.

A new range of hydrogels were prepared by the copolymerisation of HEMA with a variety of cyclic monomers (CM), see Figure 4.1. The EWC, tensile strength and Youngs modulus of these poly HEMA-CM hydrogels were measured and the effects of the cyclic monomer on these various properties discussed. The data in this Chapter is presented graphically so that trends can be easily seen. It is also presented in a tabulated form in Appendices 1-3.



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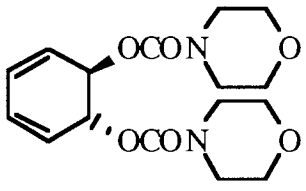

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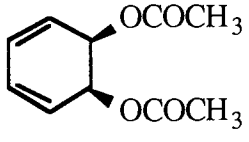

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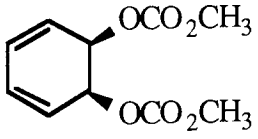

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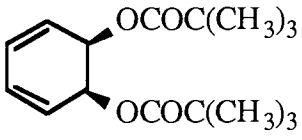

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Figure 4.1: Cyclic Monomers.

It was also of interest to assess the effects that the cyclohexene ring itself would have on the EWC and mechanical properties of the resultant gels, and for this reason HEMA / 1,3-cyclohexadiene copolymers were prepared.

4.2 EQUILIBRIUM WATER CONTENT.

The effect of 1,3-cyclohexadiene incorporation on the EWC of poly HEMA hydrogels is clearly erratic, see Figure 4.2. The polymerisation was carried out at 60°C and at this temperature it was likely that much of the 1,3-cyclohexadiene (b.p. 80°C) evaporated before it polymerised.

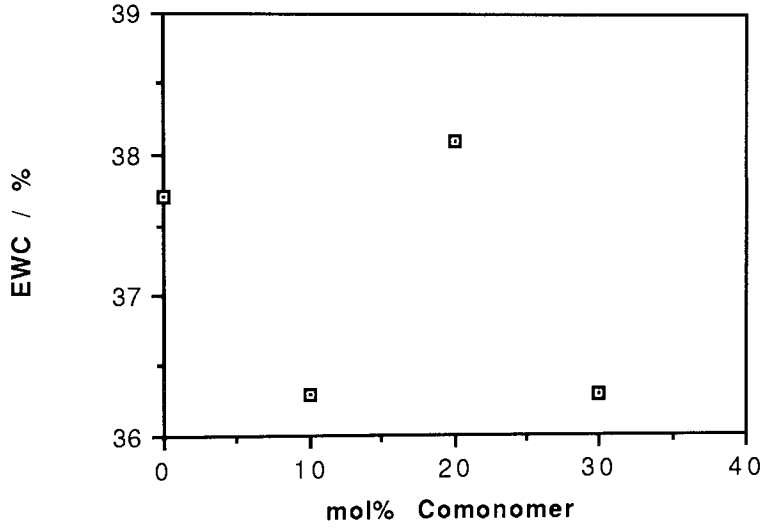

Figure 4.2: Effect of 1,3-Cyclohexadiene Concentration on EWC.

It would be anticipated that incorporation of 1,3-cyclohexadiene into poly HEMA hydrogels would cause a decrease in EWC, due to the hydrophobicity of this monomer. The increase in the EWC for 20% monomer incorporation, compared with poly HEMA, is probably due to voids being formed in the polymerising network as the 1,3-cyclohexadiene evaporates. These voids fill with water during equilibration of the gel, producing an

increase in EWC.

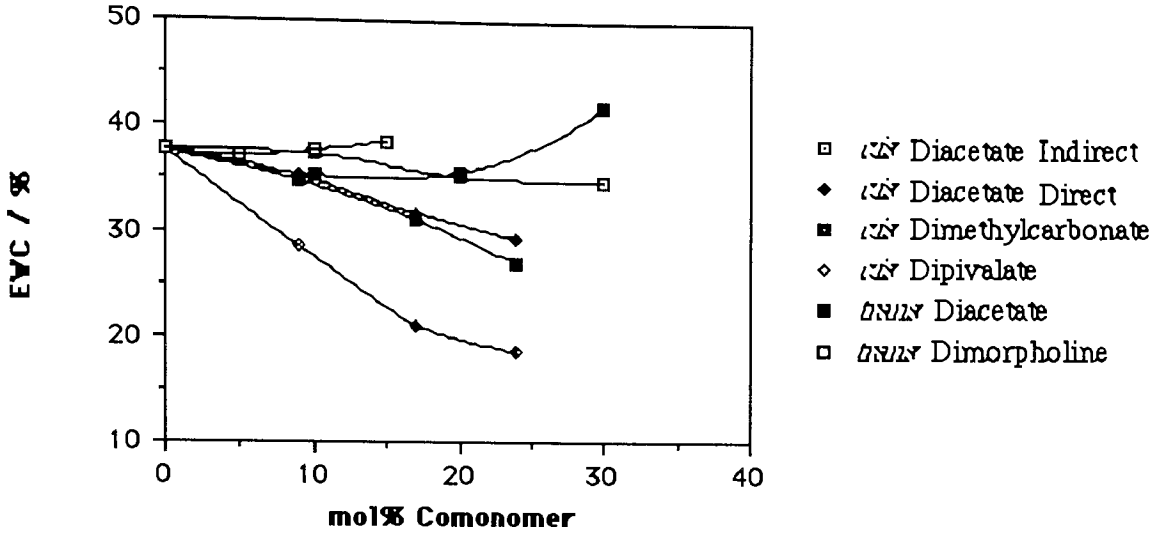

Figure 4.3: Effect of CM Concentration on EWC.

The effects of CM concentration on the EWC's of poly HEMA hydrogels is shown in Figure 4.3. The hydrogels which containing the pure *cis* derivatives showed the expected decrease in EWC with decrease in HEMA content. The pure *cis*-diacetate derivative, prepared by a direct synthetic route, and the *cis*-dimethylcarbonate derivative have very similar structures and showed very similar behaviour. The decrease in EWC with decreasing HEMA content is substantially less for the *cis*-diacetate and dimethylcarbonate derivatives than for the bulky dipivalate. The HEMA copolymers of the *cis*-diacetate and dimethylcarbonate monomers produced clear hydrogels, when hydrated, in all proportions studied, whereas the dipivalate gels were heterogeneous due to the limited miscibility of this monomer with HEMA.

In contrast the hydrogels incorporating the impure *cis*-diacetate derivative, prepared by an indirect synthetic route and contained about 8% of aromatic impurities, showed a less marked drop in EWC than the gels incorporating the pure *cis*-diacetate derivative. This difference in behaviour is probably due to inhibition of polymerisation by the aromatic

impurities. This results in the production of shorter polymer chains and increased yields of low molecular weight oligomers. In water these low molecular weight materials leach out producing voids in the gel which fill with water, resulting in a higher EWC for these materials than the hydrogels incorporating the pure monomer. The observed heterogeneity of the hydrogels polymerised from the impure monomer supports this theory. It is clear that monomer purity is important in determining the behaviour of these materials.

Hydrogels which contained the *trans*-diacetate or the *trans*-dimorpholinecarbamate derivatives showed an increase in EWC with decrease in HEMA content. Whilst this behaviour might be expected for the hydrogels containing the hydrophilic *trans*-dimorpholinecarbamate derivative, the reverse was expected for the hydrophobic *trans*-diacetate derivative. All of the HEMA / CM hydrogels which contained derivatives of *trans*-DHCD were heterogeneous and increased in fragility with decrease in HEMA content. These observations are consistent with a poor network stucture, due to incomplete polymerisation, which results in short polymer chains and increased oligomer formation. In water these low molecular weight materials leach from the gel leaving voids within the network which fill with water, resulting in a higher EWC for the hydrogel.

It has been observed previously that the *trans*-diacetate derivative homopolymerises poorly, giving low conversion of monomer to polymer and low molecular weight polymer.[20] No explanation has yet been advanced to explain the difference in the polymerisation behaviour of *cis* and *trans*-DHCD derivatives.

In the ^{1}H NMR spectra of DHCD derivatives the allylic hydrogens H_a are split by the neighbouring hydrogens H_b, see Figure 4.4. It is possible, by application of the Karplus equation (see Section 2.2.1), to calculate the dihedral angle between H_a and H_b and hence determine the conformation adopted by the molecule and the factors which favour the possible conformations. Both the *cis* and *trans*-diacetate derivatives were found to have a

virtually flat ring whilst the *trans*-dimorpholinecarbamate derivative was found to adopt a highly unfavourable puckered conformation, in which the pendant groups were in a diequatorial arrangement. The governing factor in determining conformation in *trans* derivatives appeared to be the magnitude of the interaction between the pendant groups and the 1,3-diene group. This interaction takes place on both faces of the ring and would be expected to provide effective shielding of the 1,3-diene group from attack by radicals, thereby making polymerisation of *trans*-DHCD derivatives unfavourable. Whilst such an interaction probably also occurs in *cis*-DHCD derivatives, only one face of the ring is shielded. This leaves the other open to attack by radicals, resulting in a more efficient polymerisation of these compounds.

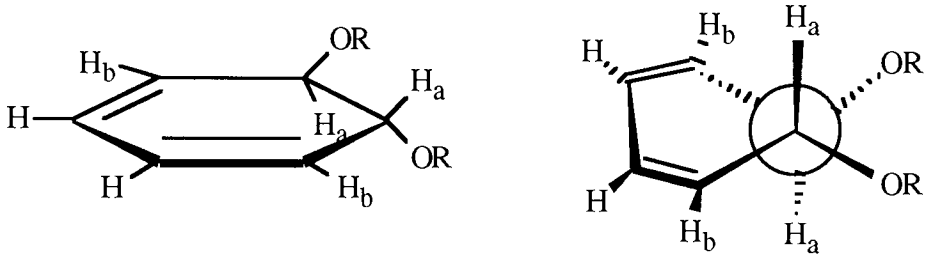

Figure 4.4: Conformations of *trans*-DHCD Derivatives.

4.3 MECHANICAL PROPERTIES.

For hydrogels incorporating 1,3-cyclohexadiene the tensile strength and Youngs modulus are clearly dependent on the EWC rather than the monomer content (see Figure 4.5). This is not suprising, as the concentration of monomers is unknown due to evaporation. The greater the EWC of the gels the higher the tensile strength and Youngs modulus The gels with high water contents probably contained less polymerised 1,3-cyclohexadiene, as hydrophobic cyclohexene rings in the polymer backbone would be expected to act as spacers between the pendant groups, thereby decreasing the steric ineractions between pendant groups and producing more flexible polymer chains than those in poly HEMA itself. The presence of hydrophobic cyclohexene rings would be expected to decrease the

EWC in comparison with poly HEMA.

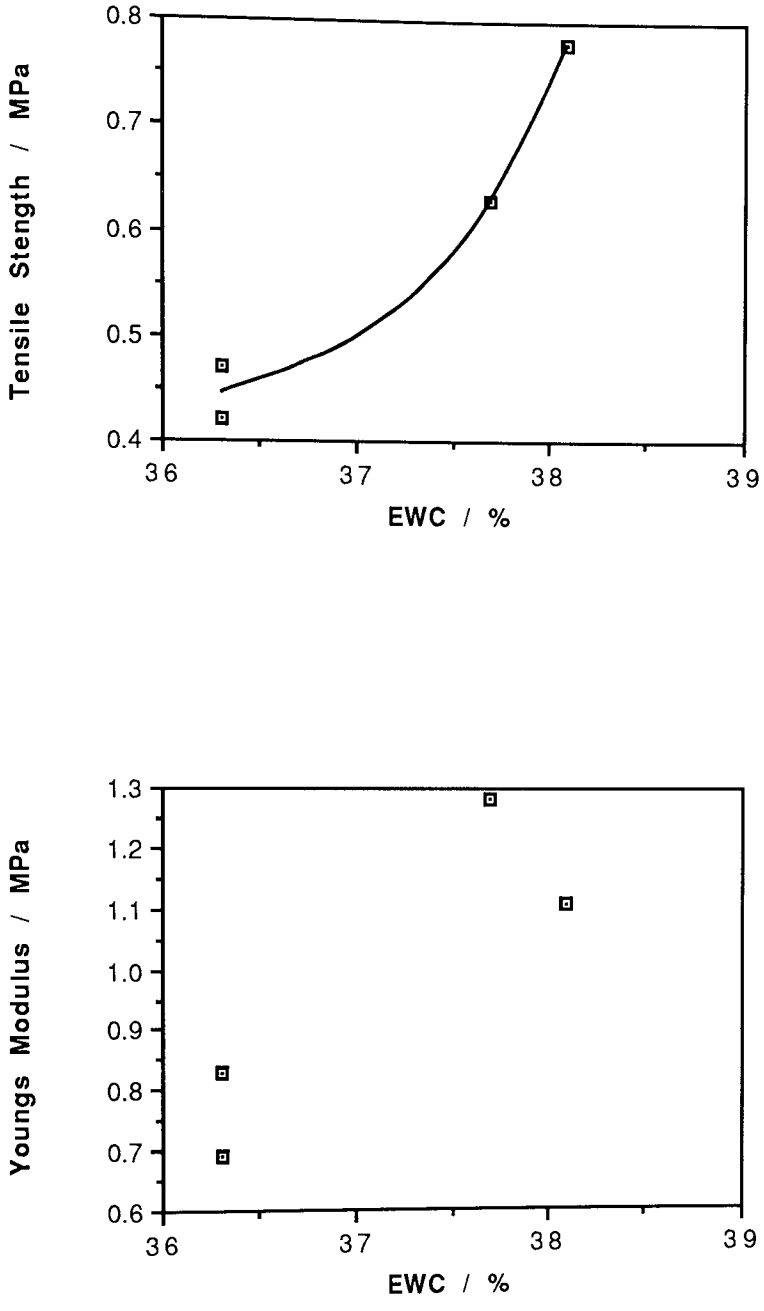

Figure 4.5: Effect of 1,3-Cyclohexadiene on Mechanical Properties.

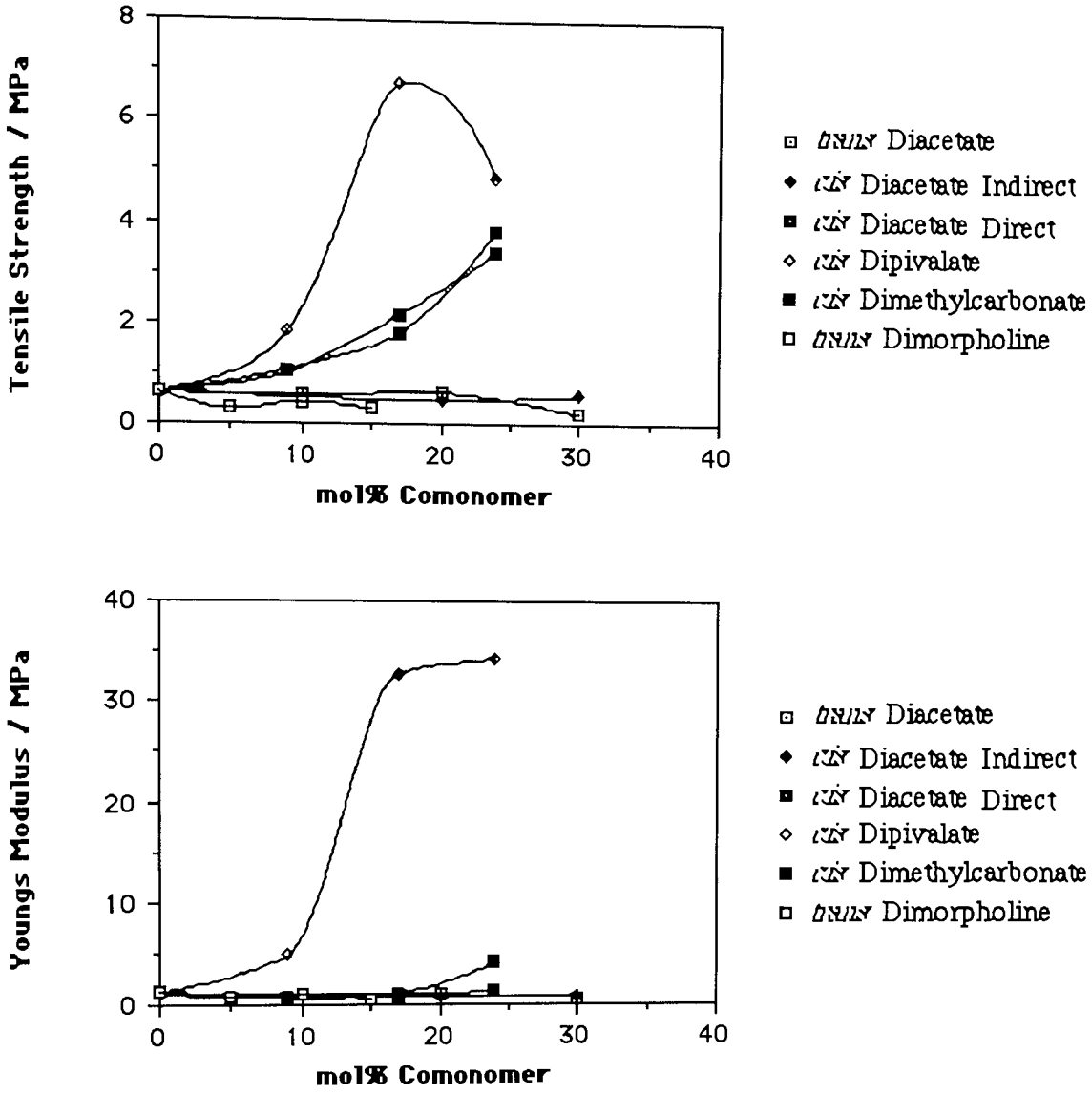

Figure 4.6: Effect of CM Concentration on Mechanical Properties.

The tensile strengths and Youngs moduli of the poly HEMA hydrogels containing the cyclic monomers with pendant groups are shown in Figure 4.6. The observed value of tensile strength for poly HEMA, of 0.63MPa, was consistent with the literature values for this material (0.495MPa,[41] 0.402MPa,[44] 0.318MPa,[46] 1.19MPa,[45] and 1.09MPa[45]). The measured value of 1.28MPa for the Youngs modulus of poly HEMA was somewhat higher than the literature value of 0.25MPa.[41] Those hydrogels mentioned previously as having polymerised with difficulty all exhibited comparable or lower values of tensile strength than poly HEMA itself, due to poor network stucture. Hydrogels containing the *cis* cyclic

monomers all had significantly higher tensile strengths than poly HEMA. The relatively low tensile strength of the gel containing the highest concentration of dipivalate derivative was probably due to its high rigidity, which made samples of this gel difficult to cut out for testing without causing fractures within the sample. With the exception of the hydrogels containing the dipivalate derivative (which showed a large increase in Youngs modulus) the values of Youngs modulus measured for these hydrogels were comparable with those of poly HEMA, although the gels containing the dimethylcarbonate derivative began to show a significant increase in the Youngs modulus at higher proportions of cyclic monomer.

A comparison of the tensile strengths and Youngs moduli of the hydrogels which contained *cis* cyclic monomers, with HEMA / styrene and HEMA / methyl methacrylate hydrogels (data for the latter two materials was recalculated from reference 41), is shown in Figure 4.7. The diacetate and dimethylcarbonate derivatives produced gels with higher tensile strength than the methyl methacrylate analogues and slightly lower than the styrene analogues, whereas the gels which contained the dipivalate derivative exhibited greater tensile strength than the comparable styrene containing hydrogels. The Youngs modulus followed the same pattern for the hydrogels which contained the dipivalate derivative in that the values were higher than those of either styrene or methyl methacrylate derivatives, at similar compositions.

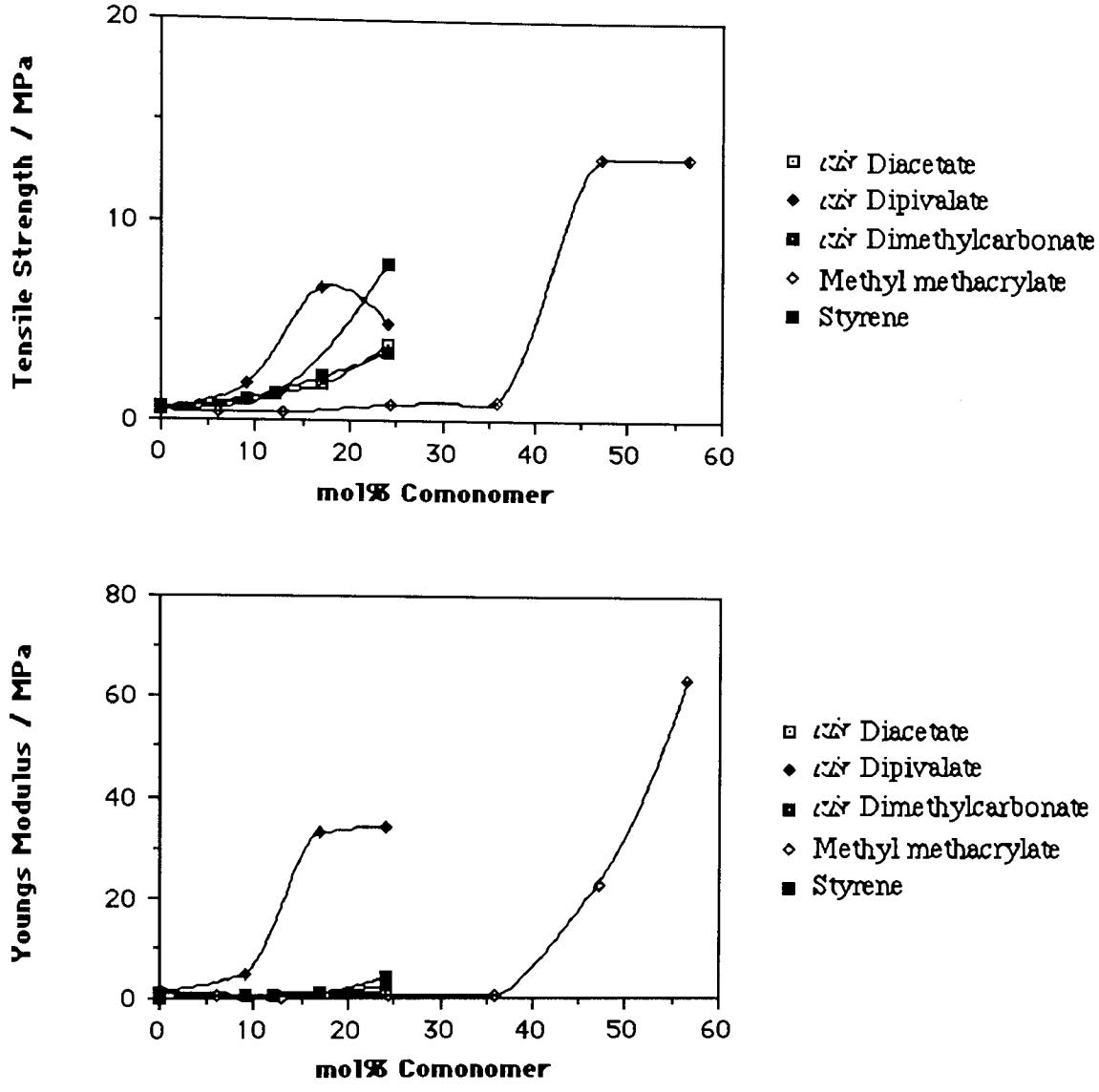

Figure 4.7: Comparison of Mechanical Properties.

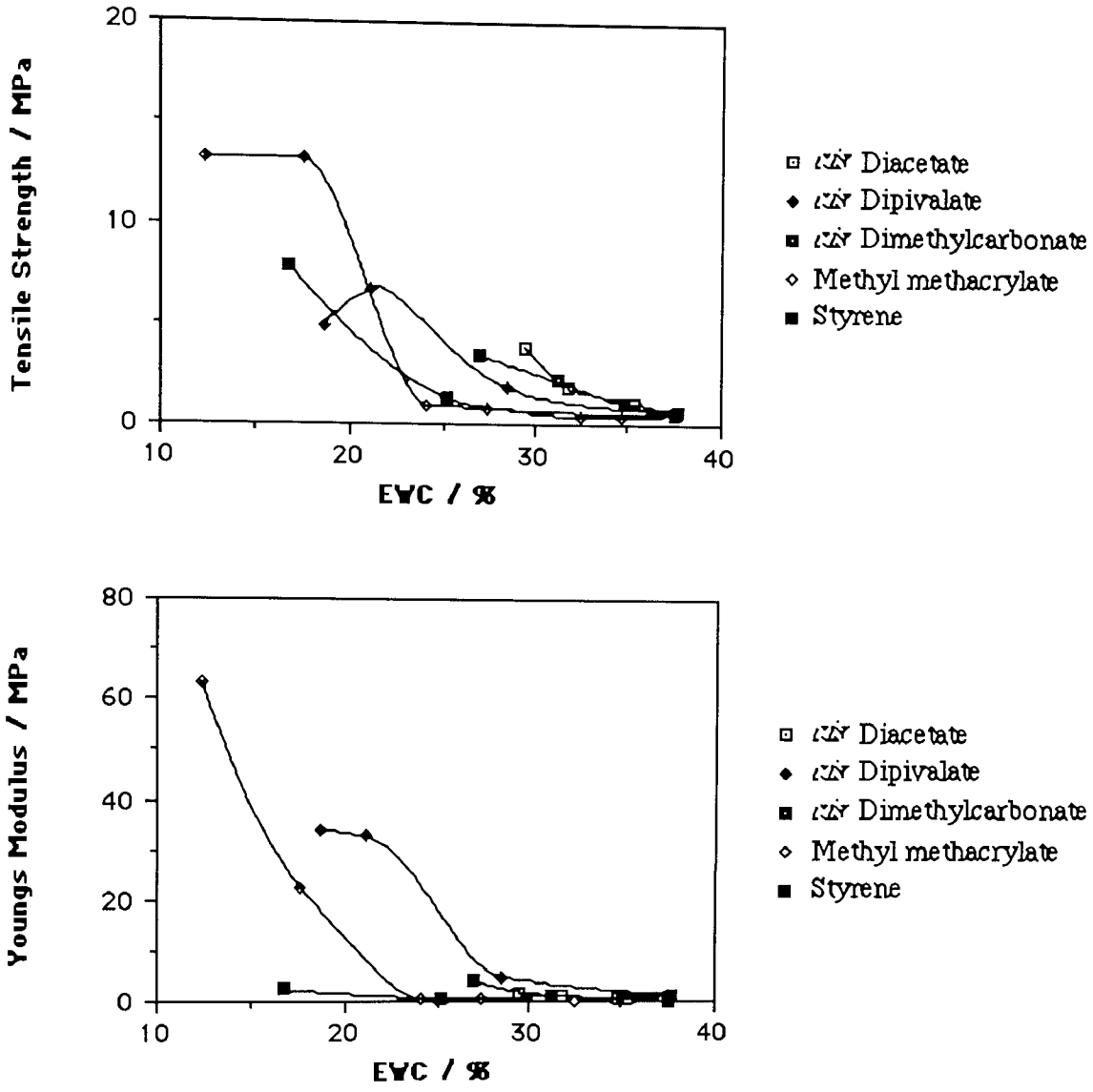

Figure 4.8: Comparison of Dependence of Mechanical Properties on EWC.

It is apparent from Figure 4.8 that the hydrogels which contained *cis* hydrophobic monomers all exhibited greater tensile strengths and Youngs moduli than the styrene and methyl methacrylate analogues of similar EWC. Two factors affect the mechanical properties exhibited by hydrogels. The first is the quantity of plasticising, freezing water within the gel. It has been observed that the sharp rise in the tensile strengths of HEMA / styrene and HEMA / methyl methacrylate hydrogels corresponded to the disappearance of this water.[41] The second factor is the mobility of the polymer chains. Pendant groups which reduce the mobility of these chains will cause tensile strength and Youngs modulus

to increase. The derivatives of *cis*-DHCD have two pendant groups per monomer unit and would be expected to cause large steric interactions between pendant groups in the polymer. This decrease in the mobility of the polymer chains is probably responsible for the greater tensile strengths and Youngs moduli exhibited by these HEMA / CM hydrogels in comparison with the HEMA / methyl methacrylate and HEMA / styrene analogues.

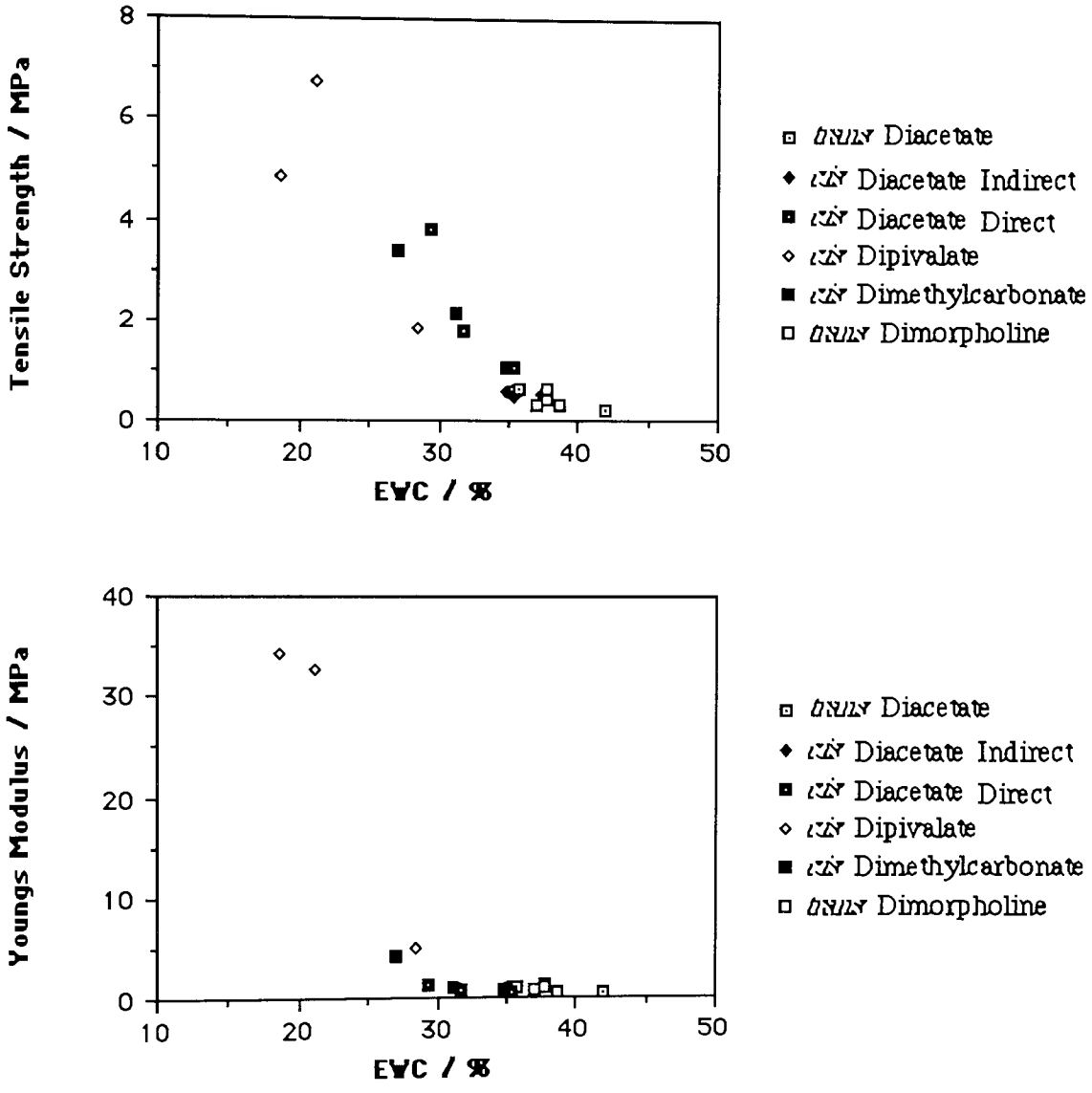

Figure 4.9: Dependence of The Mechanical Properties of CM Hydrogels on EWC.

Figure 4.9 appears to show that the tensile strengths and Youngs moduli of HEMA / CM hydrogels were dependent on EWC. However, this observation may be misleading. The gels which had low EWC contained hydrophobic monomers and would be expected to exhibit good mechanical properties, whereas the gels which had higher EWC's had poor network structure and would therefore be predicted to show poor mechanical properties. Poly HEMA hydrogels containing hydrophilic *cis*-DHCD derivatives would not be expected to show this dependence of mechanical properties on EWC.

4.4 CONCLUSIONS.

Poly HEMA hydrogels which contained pure derivatives of *cis*-DHCD showed improved tensile strengths and Youngs moduli over the more common styrene and methyl methacrylate analogues, both at similar composition and EWC, due to the reduction in the mobility in the polymer chains caused by the pendant groups on the cyclohexene ring.

The *trans* derivatives of DHCD polymerised with difficulty, giving gels with a poor network structure and hence lower values of tensile strength and Youngs modulus than those of pure poly HEMA systems.

Chapter 5: Conclusions.

5. CONCLUSIONS.

The original aim of the project was to synthesise hydrophilic derivatives of *cis*-DHCD, but because of its great cost and its stability under only a narrow range of conditions, catechol was used as a model compound in developing suitable synthetic routes. Catechol was an excellent model compound, as analysis of *cis*-DHCD, by ^{1}H NMR spectroscopy, indicated that both catechol and *cis*-DHCD contained flat rings and eclipsed hydroxy groups.

A variety of catechol derivatives were prepared in good yield, under non-acidic conditions at room temperature. However, by the time the synthesis of the model compounds was complete, it became apparent that ICI would be unable to supply *cis*-DHCD as promised, due to other commitments.

It became necssary to change the emphasis of the project and so indirect syntheses of hydrophilic derivatives of both *cis* and *trans*-DHCD were investigated. Hydrophobic derivatives of *cis* and *trans*-DHCD were synthesised easily by indirect routes, but the indirect syntheses of hydrophilic derivatives proved to be considerably more difficult. Despite this, the interesting hydrophilic dimorpholinecarbamate derivative of *trans*-DHCD was synthesised.

A number of new and interesting routes to both *cis* and *trans*-DHCD were devised but good yields of the desired products could not be obtained.

A variety of derivatives of *cis* and *trans*-DHCD were copolymerised with HEMA to give a completely new range of hydrogel materials. Hydrogels incorporating hydrophobic derivatives of *cis*-DHCD showed significant improvements of both tensile strength and Youngs modulus, compared with the more common HEMA / methyl methacrylate and

HEMA / styrene analogues, both at equivalent compositions and EWC.

Interestingly it was found that derivatives of *trans*-DHCD polymerised with difficulty. A detailed analysis of *cis* and *trans*-DHCD derivatives allowed the conformations adopted by these compounds to be determined. This indicated that shielding of both faces of the ring by the pendant groups prevented efficient polymerisation of *trans*-DHCD derivatives.

Chapter 6: Materials and Methods.

6. MATERIALS AND METHODS.

6.1 REAGENTS.

All reagents were used as supplied unless otherwise stated. Dry ether and THF were obtained by drying over sodium wire, and dry triethylamine and pyridine by drying over KOH. HPLC grade methanol and acetonitrile were used where the dry solvent was required. Acetic anhydride was distilled prior to use. The 50-60% pure *m*-chloroperoxybenzoic acid supplied by Aldrich was purified by dissolving it in dichloromethane to form a 10% w/v solution which was then washed with 1.5 times the volume of phosphate buffer, pH 7.2, in three equal portions and dried over magnesium sulphate. Solvent removal yielded pure *m*-chloroperoxybenzoic acid. m.p. 90-92°C; Lit. m.p. 92°C.[204]

Due to the difficulties encountered in purifying HEMA monomer, a supply of optically pure monomer was used as supplied by Kelvin Lenses.

6.1.1 Monomer Synthesis.

Table 6.1: Materials for Monomer Synthesis.

COMPOUND	R.M.M.	SUPPLIER
Acetic acid	60.05	Fisons
Acetic anhydride	102.09	Fisons
Acryloyl chloride	90.51	Aldrich
Allyl bromide	120.98	Aldrich
Allylchlorodimethylsilane	134.68	Aldrich
Allyl chloroformate	120.54	Aldrich

Argon	39.95	BOC
Azobisisobutyronitrile	136.20	Fluka
Bis(trimethylsilyl)acetamide	203.43	Aldrich
Bis(trimethylsilyl)trifluoroacetamide	257.40	Aldrich
9-Borabicyclo[3.3.1.]nonane 0.5M in THF	122.02	Aldrich
Bromine	159.82	Aldrich, BDH
N-Bromosuccinamide	177.99	BDH
tert-Butyldimethylsilyl chloride	150.73	Aldrich
Carbon tetrachloride	153.82	Fisons
Catechol	110.11	Aldrich
Chloroform	119.38	Fisons
1,4-Cyclohexadiene	80.13	Aldrich, Janssen Chimica
Dichloromethane	84.93	Fisons
Diethyl ether (Ether)	74.12	Fisons
cis-1,2-Dihydroxy-3,5-cyclohexadiene	112.13	ICI
4-Dimethylaminopyridine	122.17	Aldrich
Dimethylformamide	73.10	Fisons
Epichlorohydrin	92.53	Aldrich
Ethanol	46.07	BDH
Ethyl acetate	88.11	Fisons
Formic acid	46.03	Aldrich
Glycolic acid	76.05	Aldrich
Hexamethylphosphoramide	179.20	Aldrich
Hexane	86.18	Fisons
Hydrochloric acid	36.46	Fisons
Hydrogen peroxide 27.5% in water	34.02	Aldrich

p-Hydroxybenzoic acid	138.12	BDH
Iodine	253.81	Hopkin and Williams
Lithium carbonate	73.89	Aldrich
Lithium chloride	42.39	Aldrich
Magnesium sulphate, anhydrous	120.37	Aldrich, BDH, Fisons
Methanol	32.04	Shell
Methanol HPLC Grade	32.04	Fisons
4-Morpholinecarbonyl chloride	149.58	Aldrich
Nitrogen	28.02	BOC
Oxalyl chloride	126.93	Aldrich
Petroleum ether 40-60	-	Fisons
Phenol	94.11	Hopkin and Williams
Potassium acetate	98.15	BDH
Potassium carbonate anhydrous	138.21	Aldrich
Potassium hydroxide	56.11	Fisons
Potassium iodate	214.00	Fisons
2-Propanol	60.10	Fisons
Pyridine	79.10	Fisons
Silica gel, TLC Keiselgel 60H	-	BDH
Sodium	22.99	BDH
Sodium acetate	82.03	Aldrich
Sodium carbonate	105.99	Hopkin and Williams
Sodium chloride	58.44	Aldrich
Sodium hydrogen carbonate	84.01	Aldrich

Sodium hydroxide	40.00	Fisons
Sodium sulphite	126.04	Hopkin and Williams
Sulphuric acid	98.08	Fisons
Tetra-*n*-butylammonium bromide	322.38	Aldrich
Tetrahydrofuran	72.11	Fisons
p-Toluenesulphonic acid monohydrate	190.22	Hopkin and Williams
Triethylamine	101.19	Aldrich, BDH
Zinc powder	65.37	BDH

6.1.2. Synthesis of DHCD.

Table 6.2: Additional Materials for the Synthesis of DHCD.

COMPOUND	R.M.M.	SUPPLIER
Acetonitrile HPLC grade	41.05	Fisons
Butyllithium 1.6M in hexanes	64.06	Aldrich
m-Chloroperoxybenzoic acid	172.57	Aldrich
Chlorotrimethylsilane	108.64	Kodak
1,3-Cyclohexadiene	80.13	Aldrich, Janssen Chimica
1,8-Diazabicyclo[5.4.0]undec-7-ene	152.24	Aldrich
Diethylamine	73.14	BDH
Iodotrimethylsilane	200.10	Aldrich
Lithium aluminium hydride	37.95	Aldrich
Lithium aluminium hydride 1.0M in ether	37.95	Aldrich

Magnesium	24.31	Aldrich
Methyl iodide	141.94	Aldrich
Periodic acid	227.94	Aldrich
Phosphate buffer pH 7.2	-	Aldrich
Sodium iodide	149.89	Aldrich
Toluene	92.14	Fisons

6.1.3 Hydrogel Synthesis.

Table 6.3: Additional Materials for Hydrogel Synthesis.

COMPOUND	R.M.M.	SUPPLIER
cis-1,2-Dimethoxycarboxy -3,5-cyclohexadiene	228.21	ICI
cis-1,2-Pivaloxy-3,5-cyclohexadiene	280.37	ICI
Ethylene glycol dimethacrylate	198.22	BDH
2-Hydroxyethyl methacrylate	130.14	Kelvin Lenses

6.2 EXPERIMENTAL METHODS.

6.2.1 Monomer Synthesis.

6.2.1.1 Synthesis of Model Compounds.

1,2-Diacetoxybenzene (39).

A mixture of 1.1g (10mmol) of catechol (**3**), 0.38g (3.1mmol) of DMAP, and 4.7ml (34mmol) of triethylamine in 30ml of dichloromethane was cooled to -78°C and 2.9ml (31mmol) of acetic anhydride added dropwise. The solution was allowed to warm up to

room temperature and stirring continued for 18 hours. 60ml of ether was added and the solution washed with 15ml of water, 2x15ml of a 10% v/v aqueous solution of HCl, 15ml of water, 2x15ml of a 5% w/v aqueous solution of NaOH, 15ml of water and 15ml of a saturated aqueous solution of sodium chloride. The organic phase was dried over magnesium sulphate, the solvent removed and the solid residue washed with ethanol to give 1.1g (5.8mmol) 58% of **(39)** as white crystals. m.p. 63-64°C; Lit. m.p. 64-65°C[205]

I.R.(cm^{-1}; KBr): 3079(w); 3052(w); 3025(w); 2926(w); 2854(w); 1762(s); 1599(m); 1496(s); 1373(s); 1207(s); 1014(s); 833(s); 768(s)

^1H N.M.R. (δ; $CDCl_3$): 2.27 (s; 6H; C**H**$_3$); 7.15-7.25 (m; 4H; ArC**H**)

^{13}C N.M.R. (δ; $CDCl_3$): 20.59 (+ve; **C**H$_3$); 123.41 (=ve; Ar**C**H); 126.57 (=ve; Ar**C**H); 142.11 (-ve; **C**OAc); 168.22 (-ve; **C**=O)

$C_{10}H_{10}O_4$ (194.2):

	C	**H**	**N**
Calc.	61.84	5.19	-
Found	60.70	5.11	-

1,2-Bis(4-morpholinecarboxy)benzene (40).

1.1g (10mmol) of catechol **(3)**, 0.02g (0.2mmol) of DMAP and 3.5ml (25mmol) of triethylamine were dissolved in 30ml of dichloromethane. To this solution was added 2.9ml (25mmol) of 4-morpholinecarbonyl chloride and the resulting solution stirred for 6 hours. The solution was filtered and the filtrate washed with 10ml of water, 3x15ml of a saturated aqueous solution of sodium hydrogen carbonate, 2x10ml of water and dried over magnesium sulphate. The residue obtained after solvent removal was washed with diethyl ether yielding 2.5g (7.4 mmol) 74% yield of **(40)** as a white crystalline product. m.p.

145-146°C.

I.R.(cm^{-1}; KBr): 3425(m); 3074(w); 3051(w); 3010(w); 2981(s); 2927(s); 2842(s); 1721(s); 1602(m); 1497(s); 1426(s); 1243(s); 1065(s); 1050(s); 847(s)

^1H N.M.R. (δ; $CDCl_3$): 3.50 (s br; 4H; NCH_2); 3.59 (s br; 4H; NCH_2); 3.66 (s br; 4H; CH_2O); 3.67 (s br; 4H; CH_2O); 7.17 (s; 4H; ArCH)

^{13}C N.M.R. (δ; $CDCl_3$): 44.01 (-ve; NCH_2); 44.72 (-ve; NCH_2); 66.29 (-ve; CH_2O); 123.19 (+ve; ArCH); 126.00 (+ve; ArCH); 142.64 (-ve; ArC); 152.42 (-ve; C=O)

$C_{16}H_{20}N_2O_6$ (336.3):

	C	H	N
Calc.	57.14	5.99	8.33
Found	56.46	6.12	7.94

When the reaction was repeated using dry THF as the solvent and refluxing the mixture for 2 hours, followed by filtering, removal of the THF, adding 40ml of dichloromethane and following the same work up procedure as before 2.5g (7.4 mol) 74% of a white amorphous solid was obtained. m.p. 145-146°C. The IR spectrum was identical to that obtained previously for (**40**).

1,2-Bis(allyldimethylsiloxy)benzene (41).

7.7g (70mmol) of catechol (**3**), 0.17g (1.4mmol) of DMAP and 23.7ml (0.17mol) of triethylamine were dissolved in 125ml of dichloromethane and the solution cooled to -78°C. 25.3ml (0.17mol) of allylchlorodimethylsilane were then added dropwise. The solution was allowed to warm up to 0°C and stirred for 2 hours. Stirring was continued at room temperature for a further 2.5 hours; the mixture was then filtered. The filtrate was

washed with 120ml of water and dried over magnesium sulphate. The solvent was removed giving a red / brown liquid. The crude product was taken up in 150ml of ether and stirred with 2% w/w of charcoal for 2 hours. After filtration and solvent removal 20.4g (67mmol) 95% of (**41**) was obtained as an orange oil.

I.R.(cm^{-1}; Neat): 3079(w); 2963(w); 2917(w); 1631(m); 1593(m); 1504(s); 1256(s); 1162(s); 936(s); 909(s); 829(s); 736(s)

^1H N.M.R. (δ; $CDCl_3$): 0.37(s ; 12H; $Si(CH_3)_2$); 1.89 (dt; 4H; J=8.1Hz, J=1.0Hz; $SiCH_2$); 4.99-5.11 (m; 4H; $=CH_2$); 5.85-5.99 (m; 2H; CH=); 6.90-7.04 (m; 4H; ArCH)

^{13}C N.M.R. (δ; $CDCl_3$): -1.96 (+ve; $Si(CH_3)_2$); 24.55 (-ve; $SiCH_2$); 114.10 (-ve; $=CH_2$); 121.12 (+ve; ArCH); 121.93 (+ve; ArCH); 133.18 (+ve; CH=); 146.22 (-ve; ArC)

$C_{16}H_{26}O_2Si_2$ (306.6)

1,2-Bis(acryloxy)benzene (42).

11.0g (0.10mol) of catechol (**3**), 0.2g (2mmol) of DMAP and 33.5ml (0.25mol) of triethylamine were dissolved in 350ml of dichloromethane. After cooling to -78°C 20.3ml (0.25mol) of acryloyl chloride were added dropwise. The mixture was then stirred at 0°C for 2 hours and 2.5 hours at room temperature. The mixture was filtered and the filtrate washed with 100ml of water, 3x120ml of a 10% w/v aqueous solution of sodium hydrogen carbonate, 3x120ml of water, and dried over magnesium sulphate. After solvent removal the crude product was taken up in 150ml of ether and the solution stirred with 2% w/w of charcoal for 2 hours. Removal of the solvent gave 18.6g (85mmol) 85% of (**42**) as an orange oil.

^{1}H N.M.R. (δ; D_2O): 6.39-6.55 (m; 4H; =C**H**$_2$); 7.55-7.64 (m; 4H; ArC**H**); 8.04-8.19 (m; 2H; C**H**=)

$C_{12}H_{10}O_4$ (218.2)

16.5g (0.15mol) of catechol (**3**), 3.7g (30mmol) of DMAP and 30.2ml (0.375mol) of pyridine were added to 400ml of dichloromethane. The mixture was cooled to -78°C and 33.9ml (0.375mol) of acryloyl chloride were added dropwise over 20 minutes. The mixture was stirred at 0°C for 2 hours during which time a viscous orange precipitate had formed, preventing further stirring. This precipitate did not react further, even at room temperature, and could not be dissolved by adding more dichloromethane.

1,2-Bis(allyloxyformoxy)benzene (43).

To a solution of 11.0g (0.10mol) of catechol, 0.4g (3.2mmol) of DMAP and 33.5ml (0.241) of triethylamine in 350ml of dichloromethane at -78°C, was added 26.5ml (0.25mol) of allylchloroformate. The solution was then allowed to warm up to 0°C for 2 hours and stirring was then continuing at room temperature for a further 2.5 hours. After this time the mixture was filtered and the solution washed with 100ml of water, 3x120ml of a 10% w/v aqueous solution of sodium hydrogen carbonate and 3x120ml of water, and dried over magnesium sulphate. The solvent was then removed and 150ml of ether and 2% w/w of decolourising charcoal added. The mixture was stirred for 2 hours at room temperature, after which the solution was filtered and the solvent removed to give 20.1g (72mmol) 72% of (**43**) as an yellow oil.

^{1}H N.M.R. (δ; $CDCl_3$): 4.64 (d; 4H; J=5.7Hz; OC**H**$_2$); 5.19-5.23 (dd; 2H; J=1.2Hz, J=10.5Hz; =C**H**$_2$); 5.29-5.36 (dd; 2H; J=1.4Hz, J=17.2Hz; =C**H**$_2$); 5.81-5.95 (m; 2H; C**H**=); 7.15-7.25 (m; 4H; ArC**H**)

^{13}C N.M.R. (δ; $CDCl_3$): 69.28 (-ve; OCH_2); 119.03 (-ve; $=CH_2$); 123.06 (+ve; ArCH); 126.87 (+ve ArCH); 131.09 (+ve; CH); 142.48 (-ve; ArC), 152.43 (-ve; C=O)

$C_{14}H_{14}O_6$ (278.3):

	C	H	N
Calc.	60.42	5.07	-
Found	59.83	5.62	-

Repeating this reaction with 16.5g (0.15mol) of catechol (**3**), 3.7g (30mmol) of DMAP, 30.2ml (0.375mol) of pyridine and 400ml of dichloromethane and 45.2ml (0.375mol) of allyl chloroformate, gave 36.0g (0.13mol) of compound (**43**) in a yield of 85%. The ^1H and ^{13}C NMR spectra were identical to those of the sample desribed previously.

Allylphenylformate (47).

This was prepared, using the same conditions as for the synthesis of 1,2-bis(allyloxyformoxy)benzene (**43**), from 9.4g (0.10mol) of phenol, 0.2g (1.6mmol) of DMAP and 16.7ml (0.12mol) of triethylamine in 350ml of dichloromethane, and 13.3ml (0.125mmol) of allylchloroformate. This resulted in the isolation of 16.7g (94mmol) 94% of (**47**) as an orange oil.

^1H N.M.R. (δ; $CDCl_3$): 4.68 (dt; 2H; J=1.3Hz, J=4.3Hz; OCH_2); 5.26 (dq; 1H; J=1.2Hz, J=10.4Hz; $=CH_2$); 5.38 (dq; 1H; J=1.5Hz, J=17.2Hz; $=CH_2$); 5.87-6.02 (m; 1H; CH=); 7.15-7.37 (m; 5H; ArCH)

^{13}C N.M.R. (δ; $CDCl_3$): 68.95 (-ve; OCH_2); 119.09 (-ve; $=CH_2$); 121.07 (+ve; ArCH); 125.97 (+ve ArCH); 129.47 (+ve; ArCH); 131.36 (+ve; CH); 151.28 (-ve; ArC), 153.44 (-ve; C=O)

$C_9H_{10}O_3$ (178.2):		C	H	N
	Calc.	67.41	5.66	-
	Found	67.63	5.93	-

Hydroboration Of Allylphenylformate (47).

To 3.65g (20mmol) of allylphenylformate (**47**) was added to 40ml (20mmol) of a 0.5M solution of 9-BBN over 30 minutes under a static nitrogen atmosphere. Stirring was continued for 4 hours, after which time 6.7ml of a 3M aqueous solution of sodium acetate were added, followed by the dropwise addition of 6.7ml of a 27.5% solution of hydrogen peroxide at 0°C. The mixture was then allowed to warm up to room temperature for 24 hours whilst being stirred. The aqueous phase was saturated with sodium chloride and extracted with 2x30ml of THF. The organic phase was combined and dried over magnesium sulphate. Solvent removal produced a viscous yellow liquid.

Hydroboration Of 1,2-Bis(allyloxyformoxy)benzene (43).

5.57g (20mmol) of 1,2-bis(allyloxyformoxy)benzene (**43**) was hydroborated with 80ml (40mmol) of 0.5M 9-BBN under the same conditions as for the phenol derivative, with the exception that stirring was continued for 24 hours before addition of 13.4ml (40mmol) of sodium acetate solution and 13.4ml (40mmol) of 27.5% hydrogen peroxide solution. This resulted in the isolation of a brown liquid.

2-Hydroxymethylbenzodioxen (49) .

1.1g (10mmol) of catechol (**3**), 6.3ml (80mmol) of epichlorohydrin, 0.16g (0.5mmol) of tetra-*n*-butylammonium bromide, 50ml of dichloromethane, 1.2g (30mmol) of sodium hydroxide and 50ml of water were shaken together for 5 days at room temperature. The aqueous layer was extracted with 2x20ml of dichloromethane and the solvent removed from the combined organic phases. 50ml of water was added and the mixture extracted with 2x25ml of ether The combined ethereal phase was extracted with 2x25ml of a 2M aqueous solution of sodium hydroxide and 2x25ml of a saturated aqueous solution of

sodium chloride and dried over magnesium sulphate. Recrystallisation of the residue, obtained after final solvent removal, from a 1:1 toluene 40/60 petroleum ether mixture, yielded 0.6g (3.6mmol) 36% of 2-hydroxymethylbenzodioxen (**49**) as pale yellow crystals. m.p. 83-84°C; Lit. m.p. 90-92°C.[148]

I.R. (cm^{-1}; KBr): 3225(s); 3068(w); 3041(w); 3015(w); 2991(w); 2940(m); 2876(m); 2044(m); 1882(m); 1846(m); 1766(m); 1590(s); 1271(s); 1205(s); 1076(s); 1040(s); 895(s); 843(s); 751(s)

^{1}H N.M.R. (δ; $CDCl_3$): 2.26 (s,br.; 1H; O**H**); 3.79-3.91 (2xdd; 2H; J=4.2Hz, J=12Hz, J=5.2Hz, J=12.0Hz; O**C**$\mathbf{H_2}$CH); 4.05-4.12 (m; 1H; **C**H**C**$\mathbf{H_2}$OH); 4.21-4.30 (m; 2H; **C**$\mathbf{H_2}$OH); 6.61-6.99 (m; 4H; Ar**C**H)

^{13}C N.M.R. (δ; $CDCl_3$): 61.71 (-ve; O**C**$\mathbf{H_2}$CH); 65.08 (-ve; **C**$\mathbf{H_2}$OH); 73.37 (+ve; **C**HCH$_2$OH); 117.16 (+ve; Ar**C**H); 117.24 (+ve; Ar**C**H); 121.52 (+ve; Ar**C**H); 121.60 (+ve; Ar**C**H); 142.95 (-ve; Ar**C**-O); 143.06 (-ve; Ar**C**-O)

$C_9H_{10}O_3$ (166.2):

	C	**H**	**N**
Calc.	65.04	6.06	
Found	65.45	5.99	

1,2-Bis(allyloxy)benzene (50).

1.1g (10mmol) of catechol (**3**), 6.9ml (80mmol) of allyl bromide, 0.16g (0.5mmol) of tetra-*n*-butylammonium bromide, 50ml of dichloromethane, 1.2g (30mmol) of sodium hydroxide and 50ml of water were shaken together for 5 days at room temperature. The aqueous phase was then washed with 2x20ml of dichloromethane and the organic extracts

combined. The solvent was removed from the organic phase and 50ml of water added. This mixture was extracted with 2x25ml of ether, the combined ethereal phase then being extracted with 2x25ml of a 2M aqueous solution of NaOH and 2x25ml of a saturated aqueous solution of sodium chloride The organic phase was then dried over magnesium sulphate. The ether was removed to yield 1.7g of a dark red liquid.

1,2-Bis(trimethylsiloxy)benzene (51).

To 5.5g (50mmol) of catechol (**3**) in 50ml of chloroform was added 24.7ml (0.10mmol) of bis(trimethylsilyl)acetamide and the solution stirred at room temperature for 1 hour. 50ml of a 1M aqueous solution of HCl was added and the mixture shaken. The organic phase was washed with 50ml of water, dried over magnesium sulphate and the solvent removed. The residue was distilled under reduced pressure to give 9.8g (39mmol) 77% of a clear colourless oil (**51**). b.p. 68°C/1mm Hg.

I.R. (cm^{-1}; Neat): 3065(w); 3036(w); 2960(s); 2901(w); 1593(m); 1583(w); 1501(s); 1451(m); 1283(s); 1253(s); 1037(m); 844(s); 751(s)

^1H N.M.R. (δ; $CDCl_3$): 0.36 (s; 18H; $Si(CH_3)_3$); 6.89-6.96 (m; 4H; CH)

^{13}C N.M.R. (δ; $CDCl_3$): 0.33 (+ve; Si(CH3)3); 121.22 (+ve; CH); 121.92 (+ve; CH); 146.0; (-ve; C-O)

$C_{12}H_{22}O_2Si_2$ (254.5):

	C	H	N
Calc.	56.63	8.72	-
Found	56.56	8.73	-

6.2.1.2. Synthesis of *trans*-DHCD Derivatives.

4,5-Dibromocyclohexene (5).

To a stirred solution of 33.0g (0.41mol) of 1,4-cyclohexadiene in 175ml of chloroform at -78°C, was added a solution of 21.6ml (0.42mol) of bromine in 40ml of chloroform dropwise. The mixture was allowed to warm up to room temperature after the addition was complete and 600ml of methanol were added to precipitate any 1,2,4,5-tetrabromocyclohexane. The solution was filtered and the solvents removed to give a solid which, when washed with methanol, gave 80.5g (0.34mol) 82% yield of (**5**) as white crystals. m.p. 35°C; Lit. m.p. 35.1-35.2°C.[150]

I.R. (cm^{-1}; KBr): 3035(m); 2955(m); 2929(m); 2899(m); 2837(w); 1656(m); 1428(s); 1338(s); 1171(s); 841(s); 673(s); 659(s); 620(s)

^1H N.M.R. (δ; $CDCl_3$): 2.53-2.62 (dm; 2H; J=19Hz **CH_2** ax.) and 3.12-3.20 (dm; 2H; J=19Hz **CH_2** eq.); 4.50 (m; 2H; **CH**Br); 5.64 (m; 2H; **CH**=)

^{13}C N.M.R. (δ; $CDCl_3$): 30.91 (-ve; **CH_2**); 48.39 (+ve; **CH**Br); 121.97 (+ve; **CH**=)

$C_6H_8Br_2$ (240.0):

	C	H	N
Calc.	30.03	3.36	-
Found	28.95	3.20	-

***trans*-1,2-Dihydroxy-4,5-dibromocyclohexane (6).**

56.5g (0.24mol) of 4,5-dibromocyclohexene (**5**) in 50ml of chloroform were added over 1 hour at room temperature to a stirred solution of 35ml of 27.5% hydrogen peroxide in 150ml of formic acid. Stirring was continued for 16 hours and the volatile compounds removed by rotary evaporation. 450ml of methanol and 120mg (0.6mmol) of *p*-

toluenesulphonic acid were added and the solution refluxed for 2 hours. The methanol was removed and the residue recrystallised from chloroform, yielding 57.3g (0.21mol) 87% of **(6)** as white crystals. m.p. 123°C; Lit. m.p. 124°C.[103]

I.R. (cm^{-1}; KBr): 3330(m); 2964(w); 2912(w); 2134(w); 1439(m); 1179(m); 1081(s); 1059(s); 936(s); 656(s); 625(s); 552(s)

^1H N.M.R. (δ; $CDCl_3$): 2.25-2.33 (m; 2H; CH_2); 2.41-2.53 (m; 2H; CH_2); 2.64 (s br.; 2H; OH); 3.96-4.05 (m; 2H; CHBr); 4.59 (dd; 2H; J=2.4Hz, J=3.8Hz; CHO)

^{13}C N.M.R. (δ; $CDCl_3$): 35.22 (-ve; CH_2); 50.72 (+ve; CHBr); 71.05 (+ve; CHOH)

$C_6H_{10}Br_2O_2$ (274.0):

	C	H	N
Calc.	26.30	3.68	-
Found	26.55	3.66	-

***trans*-1,2-Diacetoxy-4,5-dibromocyclohexane (7).**

To a stirred solution of 13.7g (50mmol) of *trans*-1,2-dihydroxy-4,5-dibromocyclohexane **(6)**, 2.0g (16mmol) of DMAP, and 23.7ml (0.17mol) of triethylamine in 140ml of dichloromethane were added 15.1ml (0.16mol) of acetic anhydride over 20 minutes, at a temperature of -78°C. After the addition, the mixture was allowed to warm up to ~0°C and stirred for 2 hours, followed by a further 18 hours at room temperature. 290ml of ether were added and the resulting solution washed with 2x75ml of a 10% v/v aqueous solution of HCl, 75ml of water, 2x75ml of a 5% w/v aqueous solution of NaOH, 75ml of water, 75ml of a saturated aqueous solution of sodium chloride. The organic phase was then dried over magnesium sulphate. Removal of the solvent produced beige crystals which on

washing with ethanol gave 14.6g (41mmol) 82% of pale beige crystals (**7**). m.p. 110°C; Lit. m.p. 110°C.[103]

I.R. (cm^{-1}; KBr): 3025(w); 2995(w); 2968(m); 2954(m); 1744(s); 1432(s); 1235(s); 1036(s); 832(s); 691(s); 633(s).

^1H N.M.R. (δ; $CDCl_3$): 1.98 (s; 6H; CH_3); 2.25-2.33 (m; 4H; CH_2); 2.48-2.56 (m; 4H; CH_2); 4.41 (t; 2H; J=2.1 CHBr); 5.15 (t; 2H; J=3.6 CHO)

^{13}C N.M.R. (δ; $CDCl_3$): 20.78 (+ve; CH_3); 34.13 (-ve; CH_2); 49.86 (+ve; CHBr); 69.33 (+ve; CHO); 169.50 (-ve; C=O)

$C_{10}H_{14}Br_2O_4$ (358.0):

	C	H	N
Calc.	33.55	3.94	-
Found	33.62	3.95	-

***trans*-1,2-Diacetoxy-3,5-cyclohexadiene (8).**

23.5g (66mmol) of *trans*-1,2-diacetoxy-4,5-dibromocyclohexane (**7**), 7.9g (0.19mol) of lithium chloride, and 12.4g (0.17mol) of lithium carbonate in 210ml of hexamethylphosphoramide were stirred under nitrogen for 3 hours at 85-90°C. 275ml of ether were then added, followed by the slow addition of 210ml of a 7% v/v aqueous solution of hydrochloric acid. The aqueous phase was extracted with 3x140ml of ether and the combined organic phases washed with 275ml of water and 220ml of a saturated aqueous solution of sodium hydrogen carbonate, followed by drying over magnesium sulphate. After solvent removal the residue was distilled giving 10.9g (56mmol) 84% of a clear colourless oil (**8**). b.p. 98°C/3mm Hg; Lit. b.p. 74°C/0.7mm Hg[103] and 112°C/5mm Hg.[104]

I.R. (cm^{-1}; Neat): 3056(m); 2943(m); 2910(w); 1737(s); 1659(w); 1434(m); 1372(s); 1229(s);1023(s); 695(m); 666(m); 650(m)

^1H N.M.R. (δ; $CDCl_3$): 1.94 (s; 6H; CH_3); 5.44 (t; 2H; J=1.2Hz; CHO); 5.68-5.74 (m; 2H; CH=CHCHO); 5.92-5.97 (m; 2H; CH=CHCHO)

^{13}C N.M.R. (δ; $CDCl_3$): 20.70 (+ve; CH_3); 70.87 (+ve; CHO); 124.53 (+ve; CH=CHCHO); 125.35 (+ve; CH=CHCHO); 169.76 (-ve; C=O)

$C_{10}H_{12}O_4$ (196.2):

	C	H	N
Calc.	61.21	6.17	-
Found	59.54	5.99	-

***trans*-1,2-Bis(4-morpholinecarboxy)-4,5-dibromocyclohexane (54).**

13.7g (50 mmol) of *trans*-1,2-dihydroxy-4,5-dibromocyclohexane (**6**), 17.4ml (0.125mol) of triethylamine, 14.6ml (0.125 mol) of 4-morpholinecarbonyl chloride and 0.09g (0.74mmol) of DMAP were refluxed for three days in 150ml of dry THF. After allowing to cool the THF was removed and 150ml of dichloromethane added. The solution was washed with 100ml of water, 3x50ml of a saturated aqueous solution of sodium hydrogen carbonate, 2x50ml of water and dried over magnesium sulphate. Solvent removal yielded a crude solid product. Washing with ether resulted in 16.2g (32mmol) 65% of the desired material as a pale beige amorphous solid (**54**). m.p. 129-130°C.

I.R. (cm^{-1}; KBr): 3385(w); 2977(m); 2959(m); 2919(m); 2897(m); 2856(m); 1697(s); 1432(s); 1253(s); 1232(s); 1205(m); 1116(s); 1072(m); 978(m); 941(m); 854(m); 764(m)

^{1}H N.M.R. (δ; $CDCl_3$): 2.35 (d br; 2H; J=13.1Hz; CH_2CHBr); 2.57 (s br; 2H; CH_2CHBr); 3.40 (s br; 8H; OCH_2); 3.59 (s br; 8H; NCH_2) 4.47 (s br; 2H; CHO) 5.18 (s br; 2H; CHBr)

^{13}C N.M.R. (δ; $CDCl_3$): 34.42 (-ve; CH_2O) 44.00 (-ve; CH_2N) 44.31 (-ve; CH_2N) 50.04 (+ve; CHBr) 66.53 (-ve; CH_2) 71.24 (+ve; CHO) 154.16 (-ve; C=O)

$C_{16}H_{24}Br_2N_2O_6$ (500.2):

	C	H	N
Calc.	38.42	4.84	5.60
Found	38.25	5.03	5.42

trans-1,2-Bis(4-morpholinecarboxy)-3,5-cyclohexadiene (38).

15.0g (30mmol) of *trans*-1,2-bis(morpholinecarboxy)-4,5-dibromocyclohexane (**54**), 3.6g (85mmol) of LiCl, and 5.6g (76mmol) of Li_2CO_3 in 100ml of HMPA were heated, under nitrogen, for 2.5 hours at 90-100°C. After cooling to room temperature 120ml of dichloromethane was added followed by the dropwise addition of 100ml of a 7% v/v aqueous solution of HCl. The aqueous layer was then extracted with 3x60ml of dichloromethane. The combined organic extracts were washed with 120ml of water and 100ml of a saturated aqueous solution of sodium hydrogen carbonate. The organic phase was dried over magnesium sulphate and the solvent removed. The crude material was purified by dry flash chromatography (silica gel; ethyl acetate). Resulting in 3.2g (9.5mmol) 32% of the monomer (**38**) as a viscous yellow liquid.

I.R. (cm^{-1}; Neat): 3460(w); 3052(w); 2966(m); 2922(m); 2900(m); 2858(m); 1708(s); 1459(m); 1429(s); 1372(w); 1301(w); 1278(s); 1247(s); 1117(s); 1093(w); 1074(w); 1046(w); 1022(w); 989(w); 855(m); 764(m); 695(w)

^{1}H N.M.R. (δ; $CDCl_3$): 3.27 (m br; 8H; CH_2); 3.45 (s br; 8H; NCH_2); 5.44 (s; 2H; CHO); 5.67-5.69 (m; 2H; =CHCHO); 5.81-5.85 (m; 2H; CH=)

^{13}C N.M.R. (δ; $CDCl_3$): 43.74 (-ve; CH_2N); 66.04 (-ve; CH_2O); 73.17 (+ve; CHO); 124.65 (+ve; CH=); 125.76 (+ve; =CH-CHO); 154.09 (-ve; C=O)

$C_{16}H_{22}N_2O_6$ (338.4):

	C	H	N
Calc.	56.78	6.55	8.28
Found	56.40	6.63	7.94

tert-Butyldimethylsilyl _tert_-butyldimethylsiloxyacetate (57).

To a solution of 12.3g (0.16mol) of glycolic acid, 4.3g (35mmol) of DMAP, and 53ml (0.38mol) of triethylamine, in 200ml of dichloromethane at -78°C, was added a solution of 52.8g (0.35mol) of *tert*-butyldimethylsilyl chloride in 100ml of dichloromethane. Stirring was continued at this temperature for 0.5 hours and the solution allowed to warm up to room temperature, stirring being continued for an additional 18 hours. The solution was filtered and the filtrate washed with 50ml of water followed by 50ml of a saturated aqueous solution of sodium carbonate. After drying over magnesium sulphate the solvent was removed to give a residue, from which *tert*-butyldimethylsilanol was removed by distillation at reduced pressure, b.p. 28°C/3mm Hg. 32.8g (0.11mol) 67% of the protected acid (**57**) was obtained as an off white-solid. m.p. 68-70°C.

I.R.(cm^{-1}; KBr): 3231(m); 2956(s); 2931(s); 2898(s); 2859(s); 1751(s); 1474(m); 1257(s); 1217(s); 1153(s); 1006(m); 841(s); 826(s); 790(s)

^{1}H N.M.R. (δ; $CDCl_3$): 0.07 (s; 6H; $(CH_3)_2SiOCH_2$); 0.25 (s; 6H; $(CH_3)_2SiO_2C$); 0.88 (s; 9H; $(CH_3)_3CSiOCH_2$); 0.89 (s; 9H; $(CH_3)_3CSiO_2C$); 4.16 (s; 2H; CH_2)

^{13}C N.M.R. (δ; $CDCl_3$): -5.49 (+ve; $(CH_3)_2SiOCH_2$); -4.81 (+ve; $(CH_3)_2SiO_2C$); 25.5 (+ve; $(CH_3)_3CSiOCH_2$); 25.76 (+ve; $(CH_3)_3CSiO_2C$); 62.33 (-ve; CH_2)

$C_{14}H_{32}O_3Si_2$ (304.6)

trans-1,2-Bis(_tert_-butyldimethylsiloxyacetoxy)-4,5-dibromocyclohexane (59).

16.8g (55mmol) of *tert*-butyldimethylsilyl *tert*-butyldimethylsiloxyacetate (**57**) and 20 drops of DMF were added to 70ml of dichloromethane and the mixture cooled to 0°C. 7.7ml (88mmol) of oxalyl chloride were added dropwise with stirring for 0.5 hours at 0°C and 3 hours at room temperature. The solution was then cooled to -78°C and a solution of 6.9g (25mmol) of *trans*-1,2-dihydroxy-4,5-dibromocyclohexane (**6**) in 70ml of dry pyridine was added dropwise. The solution was allowed to warm up to room temperature, stirring being continued for 16 hours. The solution was filtered and the volatile material removed by rotary evaporation. 200ml of dichloromethane was added and the solution extracted with 100ml of water, 3x50ml of a 10% v/v aqueous solution of HCl, 50ml of water before drying over magnesium sulphate. The solvent was removed to yield 13.8g of a dark red / orange oil.

I.R.(cm^{-1}; Neat): 3490(m); 2937(s); 2916(s); 2877(w); 2840(s); 1747(s); 1246(m); 1139(s); 1006(m); 830(s); 771(m); 729(m)

***tert*-Butyldimethylsilyl *p-tert*-butyldimethylsiloxybenzoate (65).**

To a solution of 22.1g (0.16mol) of *p*-hydroxybenzoic acid, 4.3g (35mmol) of DMAP, and 53ml (0.38mol) of triethylamine, in 200ml of dichloromethane, at -78°C, was added a solution of 52.8g (0.35mol) of *tert*-butyldimethylsilyl chloride in 100ml of dichloromethane. The mixture was stirred at this temperature for 0.5 hours and then the solution was allowed to warm up to room temperature, stirring being continued for an additional 18 hours. The solution was filtered and the filtrate washed with 50ml of water followed by 50ml of a saturated aqueous solution of sodium carbonate. After drying over magnesium sulphate the solvent was removed to give a residue, from which *tert*-butyldimethylsilanol was removed by distillation at reduced pressure, b.p. 28°C/3mmHg. 50.5g (0.14mol) 86% of the protected acid (**65**) was obtained as an off-white solid. m.p. 63-65°C.

I.R.(cm^{-1}; KBr): 3070(w); 2958(s); 2928(s); 2885(s); 2858(s); 1699(s); 1640(w); 1605(s); 1558(w); 1511(s); 1471(s); 1281(s); 1098(s); 1008(m); 910(s); 860(s); 839(s); 790(s)

^{1}H N.M.R. (δ; $CDCl_3$): 0.08 (s; 6H; $(CH_3)_2SiOAr$); 0.22 (s; 6H; $(CH_3)_2SiO_2C$); 0.89 (s; 9H; $(CH_3)_3CSiOAr$); 0.97 (s; 9H; $(CH_3)_3CSiO_2C$); 6.82-6.89 (m; 2H; ArCH); 7.90-8.01 (m; 2H; ArCH)

^{13}C N.M.R. (δ; $CDCl_3$): -4.42 (+ve; $(CH_3)_2SiOAr$); -3.64 (+ve; $(CH_3)_2SiO_2C$); 25.56 (+ve; $(CH_3)_3CSiOAr$); 25.65 (+ve; $(CH_3)_3CSiO_2C$); 119.83 (+ve; ArCH); 132.16 (+ve; ArCH)

$C_{19}H_{34}O_3Si_2$ (366.6)

trans-1,2-Bis(_p-tert_-butyldimethylsiloxybenzoxy)-4,5-dibromocyclohexane (67).

To 45ml of dichloromethane and 20 drops of DMF were added 20.2g (55mmol) of *tert*-butyldimethylsilyl *p-tert*-butyldimethylsiloxybenzoate (**65**) and the solution cooled to 0°C. 7.7ml (88mmol) of oxalyl chloride were added dropwise. The mixture was stirred for 1 hour at this temperature and 3 days at room temperature. The mixture was then cooled to -78°C and a solution of 6.9g (25mmol) of *trans*-1,2-dihydroxy-4,5-dibromocycloxane (**6**) in 50ml of dry pyridine was added dropwise. Stirring was continued for 0.5 hours at this temperature and for 24 hours at room temperature. Next the solution was filtered and the volatile materials removed by rotary evaporation. 300ml of dichloromethane were added and the solution washed with 50ml of water, 2x50ml of a 10% v/v aqueous solution of HCl, 50ml of a 5% w/v aqueous solution of sodium hydroxide, 50ml of water and 50ml of a saturated aqueous solution of sodium chloride and dried over magnesium sulphate. Removal of the solvent produced a residue still contaminated with pyridine. 100ml of ether were added and the solution washed with 2x50ml of a 10% v/v aqueous solution of HCl. After drying over magnesium sulphate the solvent was removed yielding 6.6g of an orange oil.

I.R.(cm^{-1}; Neat): 3057(w); 2956(m); 2931(m); 2859(m); 1719(s); 1603(s); 1510(s); 1265(s); 1162(s); 1098(m); 911(s); 841(m); 785(m)

trans-1,2-Bis(2,3-epoxypropoxy)-4,5-dibromocyclohexane (73).

2.74g (10mmol) of *trans*-1,2-dihydroxy-4,5-dibromocyclohexane (**6**) and 0.1g of tetra-*n*-butylammonium bromide were added to 6.3ml (80mmol) of epichlorohydrin and sufficient THF added to dissolve all the solid material. The solution was cooled to 0°C and 12ml of a 50% w/v aqueous solution of sodium hydroxide were added dropwise at such a rate that the temperature did not exceed 25°C. The mixture was stirred for 0.5 hours after

the addition was complete and then shaken for 18 hours at room temperature; after this time 50ml of water and 25ml of chloroform were added and the organic phase dried over magnesium sulphate. Removal of the solvent followed by decolourisation in 50ml of methanol produced 1.1g of a viscous, dark brown liquid.

I.R.(cm^{-1}; Neat): 3387(s); 2961(s); 2932(s); 2876(s); 1435(m); 1255(m); 1180(m); 1094(s); 1052(s); 933(m); 853(m); 751(m)

trans-1,2-Bis(allyloxy)-4,5-dibromocyclohexane (74).

2.74g (10mmol) of *trans*-1,2-dihydroxy-4,5-dibromocyclohexane (**6**) and 0.3g (9.3mmol) of tetra-*n*-butylammonium bromide were added to 6.9ml (80mmol) of allyl bromide and THF added until all the solid material had dissolved. The solution was cooled to 0°C and 12ml of a 25M aqueous solution of sodium hydroxide were added dropwise at such a rate that the temperature was kept between 20-25°C. The solution was stirred for 30 minutes at room temperature and then shaken for 18 hours. 50ml of water followed by 25ml of chloroform were added and the organic phase dried over magnesium sulphate. The solvent was removed, the residue taken up in 50ml of ethanol and the resulting solution decolourised with charcoal. Removal of the solvent yielded 2.73g (7.6mmol) 76% of (**74**) as an orange oil.

I.R.(cm^{-1}; Neat): 3079(w); 2960(m); 2920(m); 2860(m); 1646(w); 1434(m); 1290(m); 1088(s); 996(m); 927(s)

^{1}H N.M.R. (δ; $CDCl_3$): 2.23-2.34 (m; 2H; CH_2 ax.); 2.42-2.50 (m; 2H; CH_2 eq.); 3.63 (t; 2H; J=2.7Hz; CHBr); 4.04 (d; 4H; J=5.5Hz; $=CH_2$); 4.39 (t; 2H; J=3.5Hz; CH_2CHO); 5.15 (dd; 2H; J=1.1Hz, J=10.4Hz; $=CH_2$); 5.25 (dd; 2H; J=1.1Hz, J=16.4Hz; $=CH_2$); 5.79-5.93 (m; 2H; CH=)

^{13}C N.M.R. (δ; $CDCl_3$): 35.96 (+ve; OCH_2); 52.35 (+ve; CHBr); 70.78 (-ve; $BrCHCH_2$); 75.98 (+ve; CHO); 116.97 (-ve; $=CH_2$); 134.84 (+ve; =CH)

$C_{12}H_{18}Br_2O_2$ (354.1)

Hydroxylation Of *trans*-1,2-Bis(alloxy)-4,5-dibromocyclohexane (74).

2.7g (7.7mmol) of *trans*-1,2-bis(alloxy)-4,5-dibromocyclohexane (**74**) was taken up in 1.5ml of $CHCl_3$ and added dropwise to a solution of 2.5ml of 27.5% hydrogen peroxide and 5ml of formic acid at room temperature. The resulting solution was stirred for 18 hours and the volatile materials removed by rotary evaporation. 15ml of methanol and 4mg (0.02mmol) of *p*-toluene sulphonic acid were added and the mixture heated to reflux for 18 hours. Removal of the solvent produces a viscous cloudy liquid. The addition of hexane did not cause precipitation.

I.R.(cm^{-1}; Neat): 3377(s); 2928(s); 2877(s); 1724(m); 1599(w); 1435(m); 1181(m); 1115(s); 933(m)

6.2.1.3 Synthesis of *cis*-DHCD Derivatives.

cis-1,2-Diacetoxy-3,5-cyclohexadiene (36) Direct Synthesis.

16.0g (0.14mol) of *cis*-DHCD were dissolved in 35ml of pyridine and 33.7ml (0.35mol) of acetic anhydride added dropwise whilst the temperature was maintained at 0°C. The mixture was stirred for 16 hours as the solution warmed up to room temperature. The volatile materials were removed by rotary evaporation at 60°C, the residue then being taken up in 30ml of ether, extracted with 3x10ml of a 10% w/v aqueous solution of sodium hydrogen carbonate and 3x10ml of water, and dried over magnesium sulphate. The solution was then decolourised by stirring with 2% w/w of charcoal for one hour after which time the solution was filtered and the ether removed. Recrystallistion from 2-propanol produced 10.9g (50mmol) 40% of (**36**) as pale beige crystals. m.p. 30°C; Lit.

m.p. 40°C.[19]

I.R. (cm^{-1}; KBr): 3053(w); 2987(w); 2941(w); 2889(w); 1737(s); 1372(s); 1245(s); 1060(s); 728(s)

^1H N.M.R. (δ; $CDCl_3$): 2.03 (s; 6H; CH_3); 5.50 (t; 2H; J=1.3Hz; CHOAc); 5.82-5.88 (m; 2H; =CHCHOAc); 6.07-6.12 (m; 2H; =CH)

^{13}C N.M.R. (δ; $CDCl_3$): 20.81 (+ve; CH_3); 66.90 (+ve; CHOAc); 125.25 (+ve; =CHCHOAc); 126.21 (+ve; =CH); 170.25 (-ve; C=O)

$C_{10}H_{12}O_4$ (196.2):

	C	H	N
Calc.	61.22	6.16	-
Found	61.08	6.18	-

cis-1-Acetoxy-2-hydroxy-4-cyclohexene (52).

33.6g (0.13mol) of iodine was added to a mixture of 21.0g (0.26mol) of 1,4-cyclohexadiene and 14.7g (69mmol) potassium iodate in 400ml of acetic acid at room temperature. The resulting mixture was then heated at 60°C for 3 hours. After cooling to room temperature 26.3g (0.27mol) of potassium acetate was added and the mixture heated to reflux for 3 hours. The volatile material was removed by rotary evaporation and 350ml of ether added. This solution was washed with 50ml of a saturated aqueous solution of sodium sulphite and dried over magnesium sulphate. Distillation of the residue resulted in the isolation of an orange oil and a residue heavily contaminated with iodine. Addition of 200ml of ether to the distillate, followed by washing with 2x50ml of a saturated aqueous solution of sodium sulphite, drying over magnesium sulphate and solvent removal, produced an orange oil which was distilled to give 22.3g of a pale yellow oil. b.p. 104°C/7mm Hg; Lit. b.p. 87-96°C/1.4mm Hg.[20]

I.R. (cm^{-1}; Neat): 3457(m); 3032(m); 2925(m); 2851(w); 1737(s); 1655(w); 1432(m); 1376(s); 1250(s); 1044(m); 672(m)

^1H N.M.R. (δ; $CDCl_3$): 2.05 (s; 3H; $\mathbf{CH_3}$); 2.23-2.40 (m; 4H; $\mathbf{CH_2}$); 3.99-4.03 (m; 1H; **CH**OH); 4.99-5.04 (m; 1H; **CH**OAc); 5.51-5.58 (m; 2H; =**CH**)

^{13}C N.M.R. (δ; $CDCl_3$): 21.10 (+ve; $\mathbf{CH_3}$); 27.77 (-ve; $\mathbf{CH_2}$CHOH); 31.44 (-ve; $\mathbf{CH_2}$CHOAc); 67.12 (+ve; **CH**OH); 72.06 (+ve; **CH**OAc); 123.38 (+ve; =**CH**CH_2CHOH); 123.66 (+ve; =**CH**CH_2CHOAc); 171.05 (-ve; **C**=O)

$C_8H_{12}O_3$ (156.2)

cis-1,2-Diacetoxy-4-cyclohexene (53).

3.9g (25mmol) of *cis*-1-acetoxy-2-hydroxy-4-cyclohexene (**52**), 4.2ml (30mmol) of triethylamine and 0.4g (3mmol) of DMAP were dissolved in 75ml of dichloromethane and cooled to -78°C. 2.8ml (30mmol) of acetic anhydride were added dropwise and the solution allowed to warm up to room temperature. The mixture was stirred for 24 hours, after which time 200ml of ether were added and the solution washed with 2x30ml of a 10% v/v aqueous solution of HCl, 30ml of water, 2x30ml of a 5% w/v aqueous solution of NaOH, 30ml of water and 30ml of a saturated aqueous solution of sodium chloride. It was then dried over magnesium sulphate. The solvent was removed and the residue distilled to give 3.7g (19mmol) 74% of the desired diacetate (**53**) as a pale yellow oil. b.p. 93-95°C/4mmHg.

I.R. (cm^{-1}; Neat): 3035(m); 2935(m); 2856(w); 1741(s); 1655(w); 1433(m); 1367(s); 1251(s); 1045(s); 703(m); 648(m)

^{1}H N.M.R. (δ; $CDCl_3$): 2.04 (s; 6H; CH_3); 2.25-2.42 (m; 4H; CH_2); 5.13-5.17 (m; 2H; CHOAc); 5.57 (s; 2H; =CH)

^{13}C N.M.R. (δ; $CDCl_3$): 21.14 (+ve; CH_3); 28.45 (-ve; CH_2); 68.94 (+ve; CHOAc); 123.52 (+ve; =CH); 170.58 (-ve; C=O)

$C_{10}H_{14}O_4$ (198.2)

cis-1,2-Diacetoxy-3,5-cyclohexadiene (36).

3.7g (19mmol) of *cis*-1,2-diacetoxy-4-cyclohexene (**53**) were dissolved in 125ml of carbon tetrachloride and 6.9g (39mmol) of NBS added. The mixture was degassed with argon, heated to reflux and 0.05g (0.4mmol) of AIBN added. After two hours all the solid material was floating on the surface. The mixture was filtered and the solvent removed from the filtrate. To the residue was added 60ml of dry methanol and the mixture cooled to 0°C. 6.4g (98mmol) of powdered zinc were added and the mixture stirred for 1 hour at 0°C and 4 hours at room temperature. The mixture was filtered and the solvent removed to give 2.8g (14mmol) 76% of the desired monomer (**36**) as a pale orange oil. This partially solidified in the freezer and was not purified further.

I.R. (cm^{-1}; Neat): 3056(w); 2935(m); 2855(w); 1741(s); 1371(m); 1244(s); 1064(m); 737(s)

^{1}H N.M.R. (δ; $CDCl_3$): 2.02 (s; 6H; CH_3); 5.49-5.50 (m; 2H; CHOAc); 5.78-5.92 (m; 2H; =CHCHOAc); 6.06-6.10 (m; 2H; =CH)

^{13}C N.M.R. (δ; $CDCl_3$): 20.81 (+ve; CH_3); 66.92 (+ve; CHOAc); 125.26 (+ve; =CHCHOAc); 126.23 (+ve; =CH)

$C_{10}H_{12}O_4$ (196.2)

cis-1,2-Bis(4-morpholinecarboxy)-3,5-cyclohexadiene (55).

0.9g (8.0mmol) of _cis_-DHCD (**1**), 0.2g (0.2mmol) of DMAP and 2.8ml (20mmol) of triethylamine were dissolved in 30ml of dichloromethane and the solution cooled to -78°C. 2.3ml (20mmol) of 4-morpholinecarbonyl chloride were added dropwise and the mixture allowed to warm up to room temperature. Stirring was continued for 4 days after which the solution was filtered. The filtrate was washed with 10ml of water, 3x10ml of a 10% w/v aqueous solution of sodium hydrogen carbonate, 3x10ml of water and dried over magnesium sulphate. Removal of the solvent and washing the residue with ether resulted in the isolation of 0.09g of white crystals. m.p. 109-111°C.

I.R. (cm^{-1}; KBr): 3415(w); 3010(w); 2975(w); 2896(w); 2860(w); 2842(w); 1715(s); 1416(m); 1238(s); 884(s)

^1H N.M.R. (δ; $CDCl_3$): 3.25 (t; 8H; J=4.7Hz; CH_2N); 3.66 (t; 8H; J=4.7Hz; CH_2O)

^{13}C N.M.R. (δ; $CDCl_3$): 47.23 (-ve; CH_2N); 66.61 (-ve; CH_2O); 146.34 (-ve; C=O)

$C_{10}H_{16}N_2O_5$ (244.3)

cis-1,2-Dihydroxy-4-cyclohexene (35).

To a solution of 22.3g (0.14mol) of _cis_-1-acetoxy-2-hydroxy-4-cyclohexene (**52**) in 150ml of dry methanol, at -5°C under a nitrogen atmosphere, were added 37.3g (0.27mol) of potassium carbonate. The mixture was then stirred at 0°C for 1 hour and at room temperature for 18 hours. The mixture was filtered and the methanol removed by rotary evaporation. 75ml of water was added and the solution neutralised with sulphuric acid. The solution was then continuously extracted with ether for 3 days. The ethereal phase was

dried over magnesium sulphate and the solvent removed. Washing the solid residue with ether resulted in the isolation of 6.0g (53mmol) 38% of (**35**) as slightly off white crystals. m.p. 82-84°C; Lit. m.p. 83-84°C.[20]

I.R. (cm^{-1}; KBr): 3294(s); 3021(w); 2964(w); 2907(w); 1650(m); 1433(s); 1079(s); 1058(s); 897(s); 756(s); 671(s); 664(s)

^1H N.M.R. (δ; $CDCl_3$): 2.15-2.35 (m; 4H; CH_2); 3.11 (s; 2H; OH); 3.87-3.91 (m; 2H; CHOH); 5.53 (t; 2H; J=1.5Hz; =CH)

^{13}C N.M.R. (δ; $CDCl_3$): 30.89 (-ve; CH_2); 68.87 (+ve; CHOH); 123.69 (+ve; =CH)

$C_6H_{10}O_2$ (114.1):

	C	H	N
Calc.	63.16	8.83	-
Found	62.69	8.90	-

cis-1,2-Bis(4-morpholinecarboxy)-4-cyclohexene (56).

To a solution of 4.0g (35mmol) of *cis*-1,2-dihydroxy-4-cyclohexene (**35**), 1.3g (11mmol) of DMAP and 17.0ml (0.12mol) of triethylamine in 50ml of dichloromethane at -5°C were added 12.8ml (0.11mol) of 4-morpholinecarbonyl chloride, dropwise. The solution was allowed to warm up to room temperature and then heated to reflux for 3 days. The solution was cooled and 200ml of dichloromethane was added and the resulting solution washed with 50ml of water, 2x50ml of a 5% w/v aqueous solution of sodium hydroxide, 50ml of water, 50ml of a saturated aqueous solution of sodium chloride, and dried over magnesium sulphate. The crude product contained an absorption in its IR spectrum consistent with an OH group and two carbonyl absorptions. Despite repeated washing with a 5% w/v aqueous solution of NaOH the OH absorption and two carbonyl

absorptions were still present in the spectrum of the 9.7g of orange oil which was isolated.

I.R. (cm^{-1}; Neat): 3468(w); 3033(w); 2968(m); 2924(m); 2858(s); 1742(s); 1703(s); 1429(s); 1251(s); 1205(s); 1117(s0; 1019(s); 831(m); 736(m); 673(m); 660(m)

cis-1,2-Bis(_p-tert_-butyldimethylsiloxyacetoxy)-4-cyclohexene (62).

To 45ml of dichloromethane and 12 drops of DMF were added 10.1g (33mmol) of *tert*-butyldimethylsilyl *p-tert*-butyldimethylsiloxyacetate (**57**). The solution was cooled to 0°C. 3.3ml (38mmol) of oxalyl chloride were added dropwise with stirring for 1 hour at this temperature and 3 days at room temperature. The mixture was then cooled to -78°C and a solution of 1.7g (15mmol) of *cis*-1,2-dihydroxy-4-cyclohexene (**35**) in 50ml of dry pyridine was added dropwise. Stirring was continued for 0.5 hours at this temperature and for 24 hours at room temperature. Next the solution was filtered and the volatile materials removed by rotary evaporation. 250ml of water was added and the solution extracted with 3x100ml of dichloromethane. The combined organic phase was dried over magnesium sulphate and the solvent removed to yield a product still contaminated with pyridine. 100ml of ether were added and the solution was washed with 2x50ml of a 10% v/v aqueous solution of HCl and then dried over magnesium sulphate. Solvent removal yielded a viscous yellow liquid.

I.R.(cm^{-1}; Neat): 3498(w); 3035 (w); 2954(m); 2930(m); 2858(m); 1757(s); 1256(m); 1152(s); 839(m); 781(m); 667(w)

cis-1,2-Bis(_p-tert_-butyldimethylsiloxybenzoxy)-4-cyclohexene (70).

To 45ml of dichloromethane and 20 drops of DMF were added 20.2g (55mmol) of *tert*-butyldimethylsilyl *p-tert*-butyldimethylsiloxybenzoate (**65**). The solution was cooled to 0°C and 7.7ml (88mmol) of oxalyl chloride were added dropwise with stirring for 1 hour

at this temperature and 3 days at room temperature. The mixture was then cooled to -78°C and a solution of 2.9g (25mmol) of *cis*-1,2-dihydroxy-4-cyclohexene (**35**) in 50ml of dry pyridine was added dropwise. Stirring was continued for 0.5 hours at this temperature and for 24 hours at room temperature. Next the solution was filtered and the volatile materials removed by rotary evaporation. 250ml of water was added and the solution extracted with 3x100ml of dichloromethane. The combined organic phase was dried over magnesium sulphate and the solvent removed to yield a product still contaminated with pyridine. 100ml of ether were added and the solution washed with 2x50ml of a 10% v/v aqueous solution of HCl and dried over magnesium sulphate. Solvent removal yielded 6.2g of a viscous yellow liquid.

I.R.(cm^{-1}; Neat): 3037(w); 2955(m); 2931(m); 2858(m); 1718(s); 1671(w); 1603(s); 1510(s); 1264(s); 1162(m); 1098(m); 1055(m); 841(m)

cis-1,2-Bis(trimethylsiloxy)-3,5-cyclohexadiene (76).

To 0.9g (8.0mmol) of *cis*-DHCD (**1**) in 8ml of chloroform were added 4.2ml (16mmol) of BSTFA at room temperature. After stirring for 2 hours at room temperature the chloroform was removed and an attempt made to distil the residue. This resulted in the aromatisation of the product in the residue, even at moderate temperatures.

I.R.(cm^{-1}; Neat): 3375(s); 3047(w); 2959(w); 2926(w); 2855(w); 1740(m); 1705(s); 1607(m); 1596(s); 1502(m); 1475(s); 1367(s); 1230(s); 757(m); 694(m)

cis-1,2-Bis(allyldimethylsiloxy)-3,5-cyclohexadiene (77).

3.0g (27mmol) of *cis*-DHCD (**1**) were dissolved in 15ml of dry pyridine, cooled to below -10°C and 8.8ml (60mmol)of allylchlorodimethylsilane added dropwise over 1 hour. The mixture was stirred for 3 hours at room temperature after which time the solvents were

removed by rotary evaporation. The crude product was taken up in ether , washed with 50ml of water and dried over magnesium sulphate. The solution was then decolourised with charcoal. Removal of the solvent gave 1.6g (5.2mol) 19% of (**77**) as a pale yellow oil.

I.R. (cm^{-1}; KBr): 3030(w); 2980(w); 2950(w); 1630(m); 1400(m); 1250(s); 1100(m)

^1H N.M.R. (δ; $CDCl_3$): -0.49 (s; 12H; $SiCH_3$); 1.56-1.58 (m; 4H; $SiCH_2$); 4.03-4.09 (m; 2H; CHOSi); 4.75-4.84 (m; 2H; $=CH_2$); 5.64-5.85 (m; 6H; =CH)

^{13}C N.M.R. (δ; $CDCl_3$): 1.79 (+ve; $SiCH_3$); 24.97 (-ve; $SiCH_2$); 69.03 (+ve; CHOSi); 113.61 (-ve; $=CH_2$); 123.56 (+ve; =CH); 129.24 (+ve; =CH); 133.48 (+ve; =CH)

$C_{16}H_{28}O_2Si_2$ (308.6)

6.2.2 Synthesis of *trans*-DHCD.

6.2.2.1 *trans*-DHCD by Modification of the Platt and Oesch Synthesis.

***trans*-1,2-Dihydroxy-3,5-cyclohexadiene (2).**

Over 45 minutes a solution of 3.8g (19mmol) of *trans*-1,2-diacetoxy-3,5-cyclohexadiene (**8**) in 40ml of dry ether was added dropwise to a stirred suspension of 1.0g (26mmol) of lithium aluminium hydride in 70ml of dry ether at -5°C. Stirring was continued for 5 hours at 0°C followed by the dropwise addition of water, at 0°C, until effervescence ceased, and 60ml of a 10% v/v aqueous solution of sulphuric acid. The aqueous phase was then continuously extracted with ether for 3 days. The organic phase was dried over magnesium sulphate and the solvent removed. The IR spectrum of the crude product showed a large

carbonyl absorption at 1742cm^{-1}.

0.95g (5.0mmol) of (**8**) in 10ml of dry ether were added dropwise to 6.0ml (6.0mmol) of a well stirred 1.0M solution of lithium aluminium hydride in ether, at -3°C over 45 minutes. The resulting mixture was stirred for an additional 2 hours at 0°C, after which time water was added dropwise until effervesence ceased; this was followed by 15ml of a 10% v/v aqueous solution of sulphuric acid and the aqueous phase was continuously extracted with ether for 3 days. The ethereal phase was then dried over magnesium sulphate and the solvent removed. Washing the solid residue with a small quantity of dry ether resulted in a yield of 0.19g (1.7mmol) 34% of (**2**) as pale yellow crystals. m.p. 65°C; Lit. m.p. 77°C.[103]

I.R. (cm^{-1}; KBr):	3274(s); 3050(w); 2954(w); 2922(w); 2854(w); 1658(m); 1595(m); 1501(m); 1393(s); 1353(s); 1263(s); 1071(s); 1017(s); 840(m); 757(m); 692(s)
^{1}H N.M.R. (δ; $CDCl_3$):	3.88 (s br; 2H; O**H**); 4.47 (s; 2H; C**H**OH); 5.83 (s; 4H; =C**H**)
^{1}H N.M.R. (δ; D_2O):	4.11 (t; 2H; J=1.0Hz; C**H**OH); 5.66-5.71 (m; 2H; C**H**CHOH); 5.80-5.86 (m; 2H; =C**H**)
^{13}C N.M.R. (δ; $CDCl_3$):	74.69 (+ve; **C**HOH); 124.23 (+ve; **C**HCHOH); 130.51 (+ve; **C**H)
^{13}C N.M.R. (δ; D_2O):	73.92 (+ve; **C**HOH); 127.54 (+ve; **C**HCHOH); 130.86 (+ve; **C**H)

$C_6H_8O_2$ (112.1)

Non-Aqueous Reduction.

An alternative method of reducing *trans*-1,2-diacetoxy-3,5-cyclohexadiene (**8**) involved the dropwise addition of a solution of 0.95g (5.0mmol) of *trans*-1,2-diacetoxy-3,5-cyclohexadiene (**8**) in 10ml of dry ether to 6.0ml (6.0mmol) of a well stirred 1.0M solution of lithium aluminium hydride at -3°C. Stirring was continued at 0°C for 2 hours, the excess hydride was then destroyed by the dropwise addition of a solution of 8.3ml (65mmol) of chlorotrimethylsilane in 10ml of dry ether at 0°C. The mixture was then stirred for 24 hours at room temperature, filtered and the volatile materials removed by rotary evaporation. The residue consisted of a minute amount of white solid material. Washing the solid, which had been filtered off, with small quantities of ether gave no detectable product.

Non-Aqueous Grignard Reaction.

To 0.97g (40mmol) of magnesium in 2ml of dry ether were added a few drops of a solution of 2.5ml (40mmol) of methyl iodide in 6ml of dry ether, at room temperature. The reaction mixture was subjected to ultrasound for 15 seconds to initiate the reaction and the remainder of the solution was then added dropwise at such a rate that gentle reflux was maintained. After the addition was complete the mixture was refluxed for 10 minutes. This solution was cooled and added dropwise to a well stirred solution of 1.9g (10mmol) of *trans*-1,2-diacetoxy-3,5-cyclohexadiene (**8**) in 6ml of dry ether, the temperature being kept below 25°C; mild effervescence was observed during the addition. 16.5ml (0.13mol) of chlorotrimethylsilane in 20ml of dry ether were added dropwise and the resulting mixture stirred for 5 hours; the mixture was then filtered. It was necessary to wash the sticky red/brown precipitate with dry ether and filter the resulting solution. The organic phases were combined and the volatile materials removed by rotary evaporation. 50ml of methanol were added and the mixture stirred with 2% w/w of charcoal. Filtration, followed by solvent removal and purification by dry flash chromatography (silica gel; ethyl acetate) resulted in the isolation of 0.11g of a viscous yellow material.

I.R. (cm^{-1}; Neat): 3391(m); 3045(w); 2955(s); 2926(s); 2855(m); 1708(m); 1596(m); 1500(m); 1471(m); 1263(m); 1235(m); 754(m); 692(m)

^1H N.M.R. (δ; $CDCl_3$): 5.96 (s br; 1H; ArO**H**); 6.70-7.23 (m; 5H; Ar-**H**)

^{13}C N.M.R. (δ; $CDCl_3$): 115.36 (+ve; Ar **C**H); 120.65 (+ve; Ar **C**H); 129.63 (+ve; Ar **C**H); 155.60 (-ve; Ar **C**)

***trans*-1,2-Bis(trimethylsiloxy)-4,5-dibromocyclohexane (91).**

To a mixture of 2.74g (10mmol) of *trans*-1,2-dihydroxy-4,5-dibromocyclohexane (**6**) and 10ml of chloroform were added 5.3ml (20mmol) of BSTFA dropwise. Stirring was continued for 2 hours after which the solvent was removed and 2.9g (6.9mmol) 69% (**91**) were isolated by distillation at 133°C/1mm Hg as a clear colourless oil.

I.R. (cm^{-1}; Neat): 2958(s); 2896(m); 1435(m); 1252(s); 1118(s); 843(s)

^1H N.M.R. (δ; $CDCl_3$): 0.04 (s; 18H; $(CH_3)_3Si$); 2.15-2.34 (m; 4H; CH_2); 3.74 (s br; 2H; CHBr); 4.42 (s br; 2H; CHOSi)

^{13}C N.M.R. (δ; $CDCl_3$): 0.03 (+ve; $(CH_3)_3Si$); 38.75 (-ve; CH_2); 51.52 (+ve; CHBr); 71.12 (+ve; CHOSi)

$C_{12}H_{26}Br_2O_2Si_2$ (418.3)

trans-1,2-Bis(trimethylsiloxy)-4,5-dibromocyclohexane-dehydrobromination.

18.1g (43mmol) of _trans_-1,2-bis(trimethylsiloxy)-4,5-dibromocyclohexane (**91**), 5.2g (0.12mol) of LiCl and 8.2g (0.11mol) of Li_2CO_3 in 135ml of HMPA were stirred at 90°C under nitrogen for 2.5 hours. After allowing the solution to cool, 180ml of ether was added followed by the dropwise addition of 135ml of a 7% v/v aqueous solution of HCl. The aqueous phase was extracted with 3x90ml of ether and the organic phases combined. The ethereal phase was then washed with 180ml of water and 150ml of a saturated aqueous solution of sodium hydrogen carbonate and dried over magnesium sulphate. Removal of the solvent yielded no product. The aqueous layers were combined and continuously extracted with ether for 3 days. The organic phase was dried over magnesium sulphate and the solvent removed. The residue was purified by dry flash chromatography (silica gel; ethyl acetate) to give 1.1g of a viscous yellow material which could not be recrystallised from ether.

I.R. (cm^{-1}; Neat): 3382(s); 2976(m); 2904(s); 2810(w); 1658(m); 1438(m); 1299(s); 1064(s); 988(s); 839(m); 751(s); 696(w)

trans-1,2-Bis(_tert_-butyldimethylsiloxy)-4,5-dibromocyclohexane (92).

To a solution of 13.7g (50mmol) of _trans_-1,2-dihydroxy-4,5-dibromocyclohexane (**6**), 15.3ml (0.11mol) of triethylamine and 1.3g (11mmol) of DMAP in 200ml of dichloromethane at -78°C was added a solution of 16.6g (0.11mol) of _tert_-butyldimethylsilyl chloride in 100ml of dichloromethane, dropwise. The solution was then allowed to warm up gradually to room temperature and stirred for 18 hours. The solution was filtered and washed with 100ml of water, 2x50ml of a 10% v/v aqueous solution of HCl, 2x50ml of a saturated aqueous solution of sodium carbonate 50ml of water and dried over magnesium sulphate. Solvent removal followed by removal of _tert_-butyldimethylsilanol by reduced pressure distillation yielded 14.5g of a deep red, viscous

oil.

6.2.2.2 *trans*-DHCD from 1,3-Cyclohexadiene.

3,8-Dioxatricyclo(1α,2β,4β,7α)[5.1.0.0.^{2,4}]octane (94).

20.2g (0.12mol) of *m*-chloroperoxybenzoic acid in 200ml of dichloromethane were added dropwise to a stirred solution of 4.8ml (50mmol) of 1,3-cyclohexadiene in 30ml of dichloromethane at 0°C. The solution was allowed to warm up to room temperature, with stirring, over 16 hours. The solution was filtered, and the filtrate washed with 3x100ml of a saturated aqueous solution of sodium hydrogen carbonate followed by 2x150ml of a saturated aqueous solution of sodium chloride and the organic phase dried over magnesium sulphate. The solvent was removed and the crude product distilled under reduced pressure, leaving a large pot residue, to give 2.8g (25mmol) 50% of the product (**94**) as a clear, colourless oil. b.p. 58°C/2.5mm Hg; Lit. b.p. 60°C/4mm Hg[192] and119°C/12mm Hg.[195]

I.R. (cm^{-1}; Neat): 3005(s); 2932(s); 2849(m); 1429(s); 1247(s); 1198(s); 1067(s); 971(s); 934(s); 888(s); 840(s); 789(s); 743(s)

^{1}H N.M.R. (δ; $CDCl_3$): 1.71 (s; 4H; CH_2); 2.96-2.98 (dd; 2H; J=1.6Hz, J=3.5Hz $OCHCH_2$); 3.15-3.16 (dd; 2H; J=1.6Hz, J=3.6Hz; OCH)

^{13}C N.M.R. (δ; $CDCl_3$): 18.89 (-ve; CH_2); 49.87 (+ve; $OCHCH_2$); 52.87 (+ve; OCH)

$C_6H_8O_2$ (112.1):

	C	H	N
Calc.	64.28	7.19	-
Found	63.95	7.29	-

Reaction of 3,8-Dioxatricyclo(1α,2β,4β,7α)[5.1.0.0.^{2,4}]octane (94) with Lithium Diethylamide.

31.0ml (50mmol) of a 1.6M solution of butyllithium in hexanes were added dropwise to a solution of 5.2ml (50mmol) of diethylamine in 90ml of hexane at 0°C, under a nitrogen atmosphere, and the resulting suspension stirred for 10 minutes at 0°C. 1.1g (10mmol) of 3,8-dioxatricyclo(1α,2β,4β,7α)[5.1.0.0.^{2,4}]octane (**94**) in 10ml of hexane were added and the mixture refluxed for 4 days. The mixture was then cooled and 50ml of water was added dropwise to destroy residual lithium diethylamide. The aqueous phase was then extracted with 3x50ml of ether and the organic layers combined. The organic phase was washed with 200ml of a 1M aqueous solution of HCl, 2x100ml of a saturated aqueous solution of sodium hydrogen carbonate, 100ml of water and dried over magnesium sulphate. No material could be isolated after removal of the solvent. The original aqueous phase and the acid phase were combined and continuously extracted with ether for 3 days. The ether layer was dried over magnesium sulphate and the solvent removed yielding a brown liquid which was analysed by ^{1}H and ^{13}C NMR.

Rearrangement of 3,8-Dioxatricyclo(1α,2β,4β,7α)[5.1.0.0.^{2,4}]octane (94).

1.7g (15mmol) of 3,8-Dioxatricyclo(1α,2β,4β,7α)[5.1.0.0.^{2,4}]octane (**94**) were added to a solution of 4.3ml (30mmol) of iodotrimethylsilane and 30ml of toluene and the mixture stirred for 1 hour at room temperature. 4.9ml (33mmol) of DBU were added and the mixture stirred for 25 hours at 75°C. The solvent was removed and 50ml of methanol added, together with 2 wt % of decolourising charcoal, and the solution stirred at room temperature for 18 hours. Filtration followed by solvent removal produced a residue which was purified by dry flash chromatography (silica gel; ethyl acetate). 0.5g of a viscous yellow material were obtained.

I.R. (cm^{-1}; Neat): 3387(s); 2950(s); 2865(w); 1656(w); 1595(m); 1500(m); 1423(m); 1252(s); 1083(s); 914(s); 844(s); 754(s)

6.2.3 Synthesis of *cis*-DHCD.

6.2.3.1 *cis*-DHCD from 1,4-Cyclohexadiene.

cis-1,2-Bis(trimethylsiloxy)-4-cyclohexene (96).

2.9g (25mmol) of *cis*-1,2-dihydroxy-4-cyclohexene (**35**) were added to 30ml of chloroform; 12.4ml (50mmol) of bis(trimethylsilyl)acetamide (BSA) were added and the mixture stirred for 1 hour. The solvent was removed and the residue distilled at 58°C/2.5mm Hg as a clear oil. This was an azeotrope of the desired product and trimethylsilylacetamide. 25ml of water was shaken with the distillate and the organic residue taken up in ether, dried over magnesium sulphate and the solvent removed. The residue was then distilled to give 1.6g (6.2mmol) 25% of (**96**) as a clear colourless oil. b.p. 69-70°C/3mm Hg.

1.7g (15mmol) of *cis*-1,2-dihydroxy-4-cyclohexene (**35**) were added to 15ml of chloroform and 8.0ml (30mmol) of BSTFA added dropwise. The mixture was then stirred continued for 2 hours. Removal of the solvent yielded a residue which was purified by distillation at reduced pressure, twice, to yield 2.4g (9.3mmol) 62% of (**96**) as a clear, colourless oil, b.p. 69-70°C/3mm Hg.

I.R. (cm^{-1}; Neat): 3029(w); 2957(s); 2923(w); 2898(m); 1655(w); 1251(s); 1122(s); 1076(s); 1007(s); 893(s); 840(s); 749(m)

^{1}H N.M.R. (δ; $CDCl_3$): 0.10 (s; 18H; $(\mathbf{CH_3})_3Si$); 1.54 (s; 4H; $\mathbf{CH_2}$) 3.80-3.83 (m; 2H; **CH**OSi); 5.53-5.54 (m; 2H; =**CH**)

^{13}C N.M.R. (δ; $CDCl_3$): 0.35 (+ve; $(CH_3)_3Si$); 32.23 (-ve; $\mathbf{CH_2}$); 70.19 (+ve; **C**HOSi); 124.24 (+ve; =**C**H)

$C_{12}H_{26}O_2Si_2$ (258.5):

	C	H	N
Calc.	55.75	10.14	-
Found	55.90	10.19	-

cis-1,2-Dihydroxy-3,5-cyclohexadiene (1).

1.5g (5.8mmol) of *cis*-1,2-bis(trimethylsiloxy)-4-cyclohexene (**96**) were dissolved in 100ml of carbon tetrachloride together with 2.1g (12mmol) of NBS and the solution degassed with argon. The mixture was heated to reflux and 14mg (0.1mmol) of AIBN were added; the reflux was continued for 2 hours, under an argon atmosphere, after which time all the solid material was floating on the surface. The solution was filtered and the solvent removed to give the crude dibromide. 20ml of dry methanol were added and the solution cooled to 0°C. 1.9g (29mmol) of powdered zinc were added and the mixture stirred for 1 hour at 0°C and 3 hours at room temperature. The mixture was then allowed to stand in a fridge for 18 hours. The solution was filtered and the solvent removed; ether was added until precipitation ceased, and the mixture filtered through a porosity 3 sintered glass funnel. Removal of the solvent from the filtrate yielded 0.38g of a dark green liquid.

I.R. (cm^{-1}; Neat): 3490(s); 2980(w); 2951(w); 2844(w); 1698(m); 1631(m); 1370(w); 1237(w); 1097(w); 1016(s)

^1H N.M.R. (δ; $CDCl_3$): 5.85 (s br; 1H; ArO**H**); 6.69-7.24 (m; 5H; ArC**H**)

^{13}C N.M.R. (δ; $CDCl_3$): 115.33 (+ve; Ar **C**H); 119.47 (+ve; Ar **C**H); 129.30 (+ve; Ar **C**H)

6.2.3.2 *cis*-DHCD via an Electrocyclic Ring Closure.

1,2-Epoxy-4-cyclohexene (97).

A solution of 10.1g (59mmol) of *m*-chloroperoxybenzoic acid in 100ml of dichloromethane was added dropwise to a stirred solution of 4.7ml (50mmol) of 1,4-cyclohexadiene in 30ml of dichloromethane at 0°C. The mixture was stirred for a further 1 hour at 0°C, after which the solution was filtered and washed with 2x50ml of a 20% w/v aqueous solution of sodium carbonate, 2x50ml of a saturated aqueous solution of sodium chloride and the organic phase dried over magnesium sulphate. Solvent removal followed by distillation gave 2.7g (28mmol) 56% of a clear colourless oil (**97**). b.p. 138-144°C; Lit. b.p. 135-143°C.[203]

I.R. (cm^{-1}; Neat): 3031(s); 2994(s); 2893(s); 2824(m); 1665(w); 1635(w); 1424(s); 1011(m); 896(m); 867(s); 794(s); 661(s)

C_6H_8O (96.12)

Z-3-Hexenedial (98).

2.1g (22mmol) of 1,2-epoxy-4-cyclohexene (**97**) were added dropwise to a stirred solution of 4.7g (21mmol) of periodic acid in 40ml of water at 0°C and the mixture stirred for 15 minutes after the addition was complete. The solution was then saturated with sodium chloride, filtered and extracted with 3x25ml of ether. The ether phase was dried over magnesium sulphate and the solvent removed to give 1.5g of crude dial (**98**) as a yellow oil.[203]

I.R. (cm^{-1}; Neat): 3416(s); 3033(m); 2925(m); 2850(w); 2730(w); 1723(s); 1657(w); 1439(m); 1093(s); 1066(s); 1026(s); 869(m); 698(s)

Enolisation of Z-3-hexenedial (98).

1.3g of crude Z-3-hexenedial (**98**), 3.3ml (24mmol) of triethylamine and 3.6g (24mmol) of sodium iodide in 30ml dry acetonitrile were added to 3.1ml (24mmol) of chlorotrimethylsilane at room temperature. Stirring was continued for 15 minutes and then the mixture was heated to 70°C for two hours. After cooling, 40ml of iced water were added and the aqueous phase extracted with 3x25ml of hexane. Drying of the organic phase over magnesium sulphate followed by solvent removal yielded 1.5g of an orange oil.

I.R. (cm^{-1}; Neat): 2957(s); 2927(s); 2872(w); 2857(w); 1457(s); 1378(m); 1254(s); 1059(s); 846(s); 757(m); 697(w); 667(w)

6.2.4 Hydrogel Synthesis.

A mixture of HEMA, the comonomer, and 1% w/w EDMA were degassed by bubbling nitrogen through the solution for 15 minutes. 0.5% w/w of AIBN was added and the solution injected into the mould shown in Figure 6.1, the needle was then removed. The mould was placed in an oven at 60°C for three days followed by 2 hours postcure at 90°C. The mould was then separated and the xerogel placed in 175ml of distilled water to equilibrate for at least two weeks, the water being changed daily. The mould consisted of two polyethylene gaskets (10cm x 6cm external; 6cm x 2.5cm internal) sandwiched between two melinex (polyethylene terephthalate) sheets which had been attached to two glass plates by spray mount adhesive.

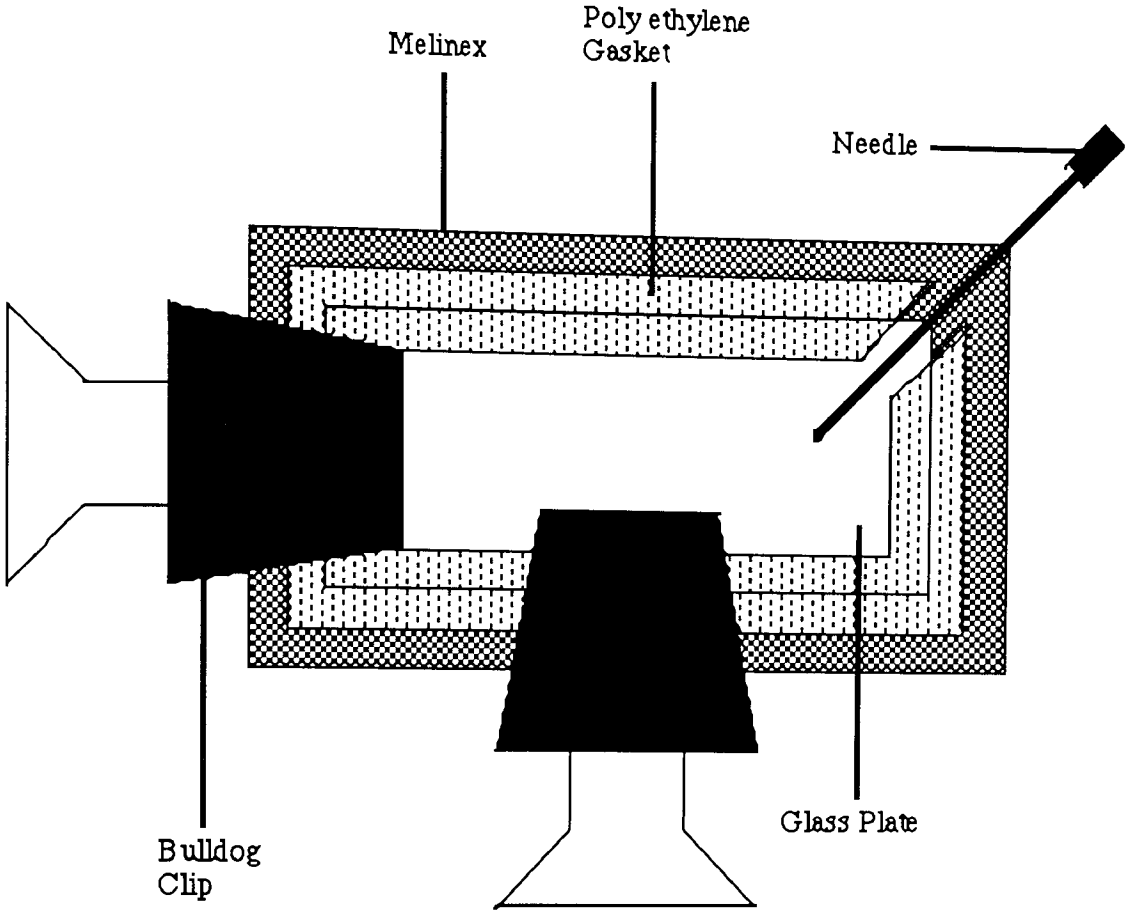

Figure 6.1: Membrane Mould.

6.2.5 Methods of Analysis.

6.2.5.1. Infra-Red Spectroscopy.

All Infra-Red spectra were recorded on either a Nicolet 510 Fourier Transform Infrared Spectrometer or a Perkin Elmer 1710 Fourier Transform Infrared Spectrometer. Solid samples were prepared as KBr discs and liquids as thin films between sodium chloride plates.

6.2.5.2. Nuclear Magnetic Resonance Spectroscopy.

All Nuclear Magnetic Resonance spectra were recorded on a Bruker AC 300 spectrometer. ^{13}C spectra were recorded as either APT (Attached Proton Test) or DEPT (Distortionless Enhanced Polarisation Transfer) spectra.

6.2.5.3. Elemental Analysis.

Elemental microanalyses were performed by Medac Ltd, Department of Chemistry, Brunel University, Uxbridge, Middlesex.

6.2.6.4. Melting Point Determination.

Melting points were determined in capillary tubes with a Gallencamp Melting Point Apparatus, Model No. ME-370, and are uncorrected.

6.2.6. Measurement of the Physical Properties of Hydrogels.

6.2.6.1. Determination of Equilibrium Water Content.

EWC determinations were carried out on five separate pieces of gel and the average value calculated. A No.4 cork borer was used to cut out small discs of gel, which were then placed in a sample bottle of distilled water. For each determination the disc was blotted lightly with filter paper, to remove surface water, and weighed. Dehydration of the gel was achieved by placing it in a microwave oven for twelve minutes, after which the gel was reweighed. The EWC was then calculated using the equation in Section 1.2.3.1.

6.2.6.2. Measurement of Mechanical Properties.

All mechanical tests were performed on a Hounsfield Tensometer with a test speed of 8mm / minute. Five samples were tested for each gel and a minimum of three consistent values used for further calculations. Dumbell shaped samples were used for *cis*-diacetate, dimethylcarbonate and dipivalate containing hydrogels. The samples for the other gels were parallel sided. A gauge length of 10mm and a width of 3mm were used for both sets of samples.

Appendices.

APPENDIX 1: EQUILIBRIUM WATER CONTENTS OF HYDROGELS.

1,3-Cyclohexadiene (100).

mol% Monomer	1 /%	2 /%	3 /%	4 /%	5 /%	Av. EWC /%
0	38.4	37.6	37.7	36.9	38.0	37.7
10	33.9	38.1	36.6	36.6	36.1	36.3
20	37.2	38.8	37.9	37.9	38.5	38.1
30	37.8	35.0	36.0	36.0	36.5	36.3

trans-1,2-Diacetoxy-3,5-cyclohexadiene (8).

mol% Monomer	1 /%	2 /%	3 /%	4 /%	5 /%	Av. EWC /%
10	35.5	35.8	35.7	34.8	34.8	35.3
20	36.0	35.3	35.8	35.8	35.6	35.7
30	43.2	43.8	41.2	40.5	41.0	41.9

cis-1,2-Diacetoxy-3,5-cyclohexadiene (36) Indirect.

mol% Monomer	1 /%	2 /%	3 /%	4 /%	5 /%	Av. EWC /%
10	37.7	38.3	36.7	37.1	37.0	37.4
20	34.5	35.7	35.5	35.6	35.2	35.3
30	33.8	35.1	34.9	35.2	34.9	34.8

***cis*-1,2-Diacetoxy-3,5-cyclohexadiene (36) Direct.**

mol% Monomer	1 /%	2 /%	3 /%	4 /%	5 /%	Av. EWC /%
9	35.1	35.2	35.2	35.6	35.2	35.3
17	31.7	31.6	31.7	32.0	32.1	31.8
24	29.4	29.6	29.0	29.5	29.6	29.4

***cis*-1,2-Dimethoxycarboxy-3,5-cyclohexadiene (37).**

mol% Monomer	1 /%	2 /%	3 /%	4 /%	5 /%	Av. EWC /%
9	34.6	34.7	35.0	34.7	34.8	34.8
17	31.0	30.9	31.2	31.4	31.3	31.2
24	27.3	27.4	26.1	28.1	26.3	27.0

***cis*-1,2-Dipivaloxy-3,5-cyclohexadiene (101).**

mol% Monomer	1 /%	2 /%	3 /%	4 /%	5 /%	Av. EWC /%
9	28.9	27.6	28.0	28.3	29.9	28.5
17	21.4	21.1	20.5	21.0	21.3	21.1
24	17.7	18.4	19.4	19.1	18.5	18.6

***trans*-1,2-Bis(4-morpholinecarboxy)-3,5-cyclohexadiene (38).**

mol% Monomer	1 /%	2 /%	3 /%	4 /%	5 /%	Av. EWC /%
5	36.7	37.6	37.7	37.0	36.6	37.1
10	37.9	37.5	37.3	37.4	38.4	37.7
15	39.0	37.7	40.0	38.2	38.3	38.6

APPENDIX 2: TENSILE STRENGTH OF HYDROGELS.

1,3-Cyclohexadiene (100).

mol% Monomer	1 /MPa	2 /MPa	3 /MPa	4 /MPa	5 /MPa	Av. σ_b /MPa
0	0.66	0.45	0.78	0.62	-	0.63
10	0.55	0.39	0.33	-	-	0.42
20	0.81	0.56	0.70	1.04	-	0.78
30	0.47	0.42	0.41	0.53	0.54	0.47

trans-1,2-Diacetoxy-3,5-cyclohexadiene (8).

mol% Monomer	1 /MPa	2 /MPa	3 /MPa	4 /MPa	5 /MPa	Av. σ_b /MPa
10	0.73	0.72	0.44	0.41	-	0.58
20	0.61	0.60	0.58	0.66	0.63	0.62
30	0.12	0.14	0.26	0.24	-	0.19

cis-1,2-Diacetoxy-3,5-cyclohexadiene (36) Indirect.

mol% Monomer	1 /MPa	2 /MPa	3 /MPa	4 /MPa	5 /MPa	Av. σ_b /MPa
10	0.42	0.46	0.54	0.70	0.48	0.52
20	0.59	0.52	0.43	0.39	0.44	0.47
30	0.68	0.56	0.50	0.47	0.56	0.55

***cis*-1,2-Diacetoxy-3,5-cyclohexadiene (36) Direct.**

mol% Monomer	1 /MPa	2 /MPa	3 /MPa	4 /MPa	5 /MPa	Av. σ_b /MPa
9	1.11	0.85	1.30	1.03	-	1.07
17	1.89	1.67	2.20	1.88	1.35	1.79
24	4.21	3.18	4.10	-	-	3.83

***cis*-1,2-Dimethoxycarboxy-3,5-cyclohexadiene (37).**

mol% Monomer	1 /MPa	2 /MPa	3 /MPa	4 /MPa	5 /MPa	Av. σ_b /MPa
9	1.00	1.05	1.17	1.03	0.85	1.02
17	2.20	2.64	1.55	2.25	-	2.16
24	3.69	3.47	3.02	-	-	3.39

***cis*-1,2-Dipivaloxy-3,5-cyclohexadiene (101).**

mol% Monomer	1 /MPa	2 /MPa	3 /MPa	4 /MPa	5 /MPa	Av. σ_b /MPa
9	1.86	1.81	2.12	1.31	1.96	1.81
17	4.65	8.06	7.13	6.91	6.84	6.72
24	4.57	7.09	2.96	-	-	4.87

***trans*-1,2-Bis(4-morpholinecarboxy)-3,5-cyclohexadiene (38).**

mol% Monomer	1 /MPa	2 /MPa	3 /MPa	4 /MPa	5 /MPa	Av. σ_b /MPa
5	0.26	0.36	0.32	0.22	-	0.29
10	0.50	0.38	0.37	0.51	0.40	0.43
15	0.29	0.28	0.26	0.28	0.37	0.30

APPENDIX 3: YOUNGS MODULUS OF HYDROGELS.

1,3-Cyclohexadiene (100).

mol% Monomer	1 /MPa	2 /MPa	3 /MPa	4 /MPa	5 /MPa	Av. E /MPa
0	1.37	1.28	1.09	1.38	-	1.28
10	0.86	0.74	0.90	-	-	0.83
20	1.13	1.15	0.98	1.17	1.11	1.11
30	0.73	0.67	0.77	0.55	0.74	0.69

trans-1,2-Diacetoxy-3,5-cyclohexadiene (8).

mol% Monomer	1 /MPa	2 /MPa	3 /MPa	4 /MPa	5 /MPa	Av. E /MPa
10	0.88	0.85	0.93	1.01	-	0.93
20	0.87	0.92	1.02	1.00	0.89	0.94
30	0.64	0.90	0.42	-	-	0.65

cis-1,2-Diacetoxy-3,5-cyclohexadiene (36) Indirect.

mol% Monomer	1 /MPa	2 /MPa	3 /MPa	4 /MPa	5 /MPa	Av. E /MPa
10	0.86	0.71	0.66	0.73	0.87	0.77
20	0.81	0.92	0.77	0.89	0.76	0.83
30	0.655	1.01	0.87	0.93	0.84	0.86

***cis*-1,2-Diacetoxy-3,5-cyclohexadiene (36) Direct.**

mol% Monomer	1 /MPa	2 /MPa	3 /MPa	4 /MPa	5 /MPa	Av. E /MPa
9	0.57	0.79	0.71	0.57	0.58	0.64
17	0.81	0.73	0.83	0.81	0.88	0.81
24	1.31	1.45	1.41	-	-	1.39

***cis*-1,2-Dimethoxycarboxy-3,5-cyclohexadiene (37).**

mol% Monomer	1 /MPa	2 /MPa	3 /MPa	4 /MPa	5 /MPa	Av. E /MPa
9	0.73	0.70	0.68	0.64	0.74	0.70
17	1.19	1.11	1.19	0.98	-	1.12
24	3.88	4.06	4.32	-	-	4.09

***cis*-1,2-Dipivaloxy-3,5-cyclohexadiene (101).**

mol% Monomer	1 /MPa	2 /MPa	3 /MPa	4 /MPa	5 /MPa	Av. E /MPa
9	4.7	4.5	5.1	5.1	5.2	4.9
17	32.9	29.9	30.1	37.9	33.4	32.8
24	27.6	51.8	23.1	-	-	34.2

***trans*-1,2-Bis(4-morpholinecarboxy)-3,5-cyclohexadiene (38).**

mol% Monomer	1 /MPa	2 /MPa	3 /MPa	4 /MPa	5 /MPa	Av. E /MPa
5	0.68	0.66	0.62	0.74	-	0.67
10	1.12	1.20	0.98	1.01	0.83	1.03
15	0.41	0.47	0.43	0.49	0.42	0.45

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