SYNTHETIC ROUTES TOWARDS CHIRAL CALIX[4]RESORCINARENES

by

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Abbreviations used in this thesis

Å	Ångstrøm
AcCl	acetyl chloride
Ar	aromatic
aq	aqueous
Bn	benzyl
*i*Bu	*i*-butyl
*n*Bu	*n*-butyl
n-BuLi	*n*-butyl lithium
*t*Bu	*t*-butyl
°C	degrees Celsius
Cbz	benzyloxycarbonyl
cm^{-1}	infrared wave number
conc.	concentrated
d	days
d	^{1}H NMR doublet
DCM	dichloromethane
DCE	1,2-dichloroethane
Δ	application of heat
δ_C	^{13}C NMR chemical shift
δ_H	^{1}H NMR chemical shift
DMF	dimethylformamide
DMSO	dimethylsulphoxide
DIBAL	diisobutylaluminium hydride
DIPEA	diisopropylethylamine, Hünig's base
e.e.	enantiomeric excess
EI	electron impact mass spectrometry
eq	equivalents
Et	ethyl
EtOAc	ethyl acetate

FAB	fast atom bombardment mass spectrometry
g	grams
GC	gas chromatography
h	^{1}H NMR heptet
h	hours
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
Hz	Hertz
ir	infrared
J	^{1}H NMR coupling constant
LRMS	low resolution mass spectrometry
m	^{1}H NMR multiplet
M	molarity
M^+	molecular ion
Me	methyl
MeOAc	methyl acetate
MeOTf	methyl trifluoromethanesulphonate
mg	milligrams
MHz	megahertz
min	minute(s)
mL	milliliters
mmol	millimoles
mol	moles
m.p.	melting point
MS	mass spectrometry
NBS	*N*-bromosuccinimide
NIS	*N*-iodosuccinimide
NMR	nuclear magnetic resonance
o/n	overnight
pet-ether	light petroleum, boiling point 40-60 °C
Ph	phenyl

ppm	parts per million
*i*Pr	*i*-propyl
*n*Pr	*n*-propyl
psi	pounds per square inch
q	^{1}H NMR quartet
r/t	room temperature
t	^{1}H NMR triplet
TBAF	tetrabutylammonium fluoride
TBDMSOTf	*t*-butyldimethylsilyltrifluoromethanesulphonate
temp.	temperature
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TMSCl	trimethylsilylchloride
TMSOTf	trimethylsilyltrifluoromethanesulphonate
triflate	trifluoromethanesulphonate
Ts	tosyl (para-toluenesulphonyl)
p-TSA	para-toluenesulphonic acid
U.V.	ultraviolet
w/w	weight/weight

Abstract

This thesis is divided into three chapters.

Chapter 1 contains a brief overview of the literature reports in the area of calix[4]resorcinarene chemistry. The many methods available for the preparation and use of these macrocycles, their functionalisation on both the upper and lower rims and the use of Mannich reaction protocols for the introduction of chirality into these symmetrical molecules are discussed.

Chapter 2 describes new methodology for the formation of a range of chiral calix[4]resorcinarenes, most notably the formation of tetra alkyloxy calix[4]resorcinarenes as racemic mixtures, which can then be separated as diastereoisomers following the use of new Mannich reaction methodology for the formation of tetra benzoxazine derivatives.
One of these enantiomerically pure resorcinarenes has been used as a catalyst in the addition of diethylzinc to benzaldehyde.
The attempts made at deepening the cavity of these macrocycles, by utilising Sonogashira coupling reactions, are also discussed.

Chapter 3 contains the experimental details and analytical data for the successful reactions discussed in **Chapter 2**.

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Chapter 1

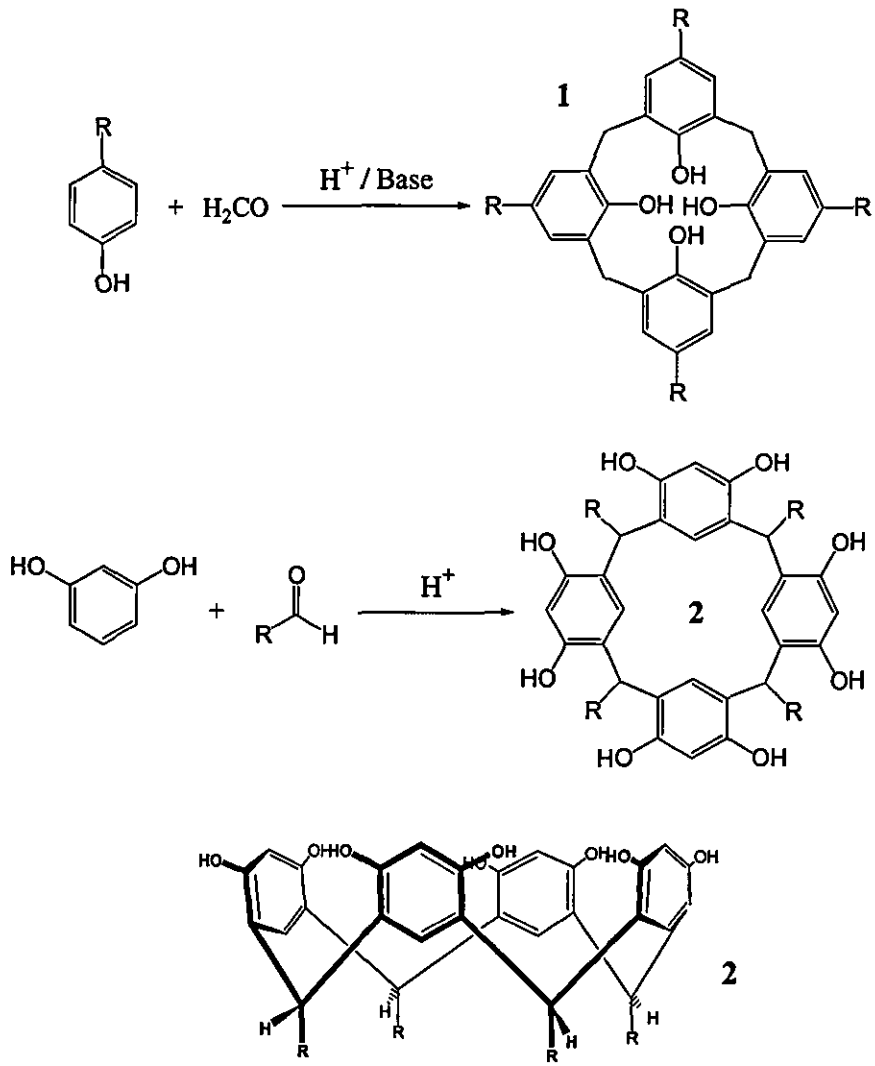
Introduction

1.1 Calix[n]arenes and Calix[4]resorcinarenes

Calixarenes are a family of macrocycles formed in acid catalysed condensation reactions between various phenols and aldehydes. Their name derives from the shapes of these cyclic oligomers as they resemble a Greek vase known as a *calix crater*. The two major classes of calixarene are calix[n]arenes **1** derived from the condensation of a phenol and formaldehyde (where n = 4,6,8 etc.) and calix[4]resorcinarenes **2** derived from the condensation of resorcinol and various aldehydes, **Scheme 1.**

The work discussed here involves calix[4]resorcinarenes unless stated otherwise. The chemistry of calix[n]arenes has been reviewed in depth.[1]

Throughout the majority of this thesis calix[4]resorcinarenes are called resorcinarenes, which is widely accepted as a suitable nomenclature.



Scheme 1

1.2 Resorcinarene synthesis

The established standard procedure for resorcinarene formation follows that shown in **Scheme 1** between resorcinol and one of a large range of aldehydes, other than formaldehyde (which produces an array of polymeric products), in a mixture of ethanol and water with concentrated hydrochloric acid added as catalyst. Weinelt has suggested that the use of any mineral acid should be successful.[2] The reaction mixture is generally heated under reflux for an extended length of time, after which cooling causes precipitation of the desired product. The only product isolated in most cases is the crown

isomer shown in **Scheme 1**; see **Section 1.2.4** for other ring sizes. When considering all of the possible polymers that could be formed, each with many possible conformations, the isolation of **2** as a single product, without the need for high dilution conditions, is remarkable.

The groups of Högberg[3] and Cram,[4] using many aliphatic and aromatic aldehydes, have extensively investigated these conditions. Each aldehyde used requires slight modifications to the reaction conditions to ensure the optimum yield. Some limitations on the aldehyde used have become apparent. Very bulky aldehydes do not readily form resorcinarenes; nor do those bearing functionality close to the reactive centers. Reinhoudt[5] has written a review of resorcinarene chemistry in which are listed a large number of the aldehydes used in resorcinarene formation.

1.2.1 Stereochemical factors

A combination of factors means that in theory resorcinarenes can exist in many stereoisomeric forms. Högberg and others have established three areas to assign the stereochemistry.

(i) The conformation of the macrocyclic ring. Five extreme, symmetrical arrangements can be adopted, **Figure 1**.

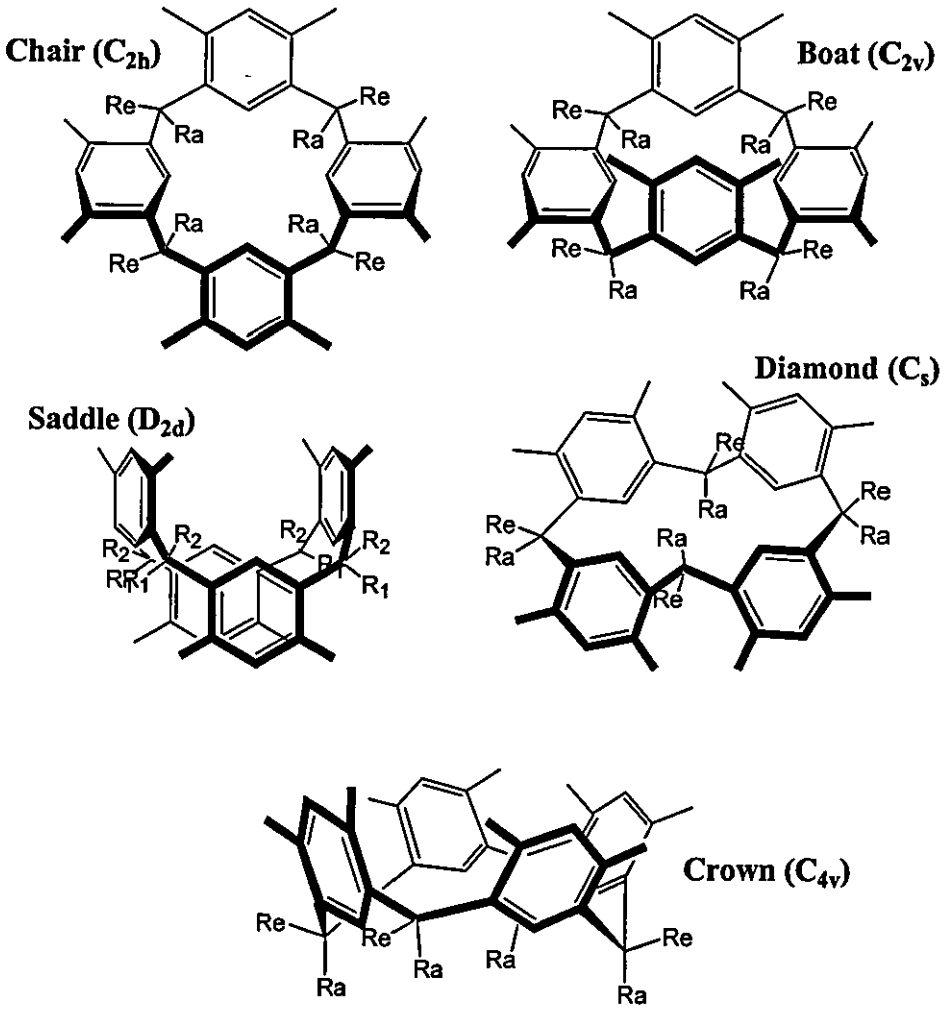


Figure 1

(ii) The relative configuration of the substituents (R group from the aldehyde) at the methine bridges. The four possible arrangements are, all-cis (rccc), cis-cis-trans (rcct, same as rtcc), cis-trans-trans (rctt, same as rttc) or trans-cis-trans (rtct), **Figure 2.** Starting from any of the R substituents (represented by r in the nomenclature) and moving in either direction around the macrocycle, each of the other substituents are in a cis (c) or trans orientation (t) relative to r.

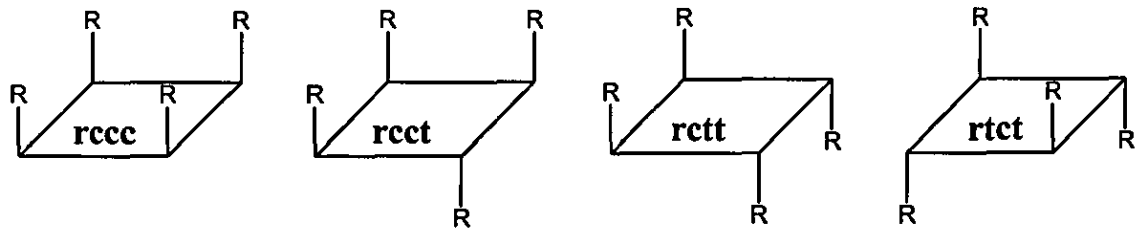


Figure 2

(iii) The individual configuration of the substituents at the methine bridges, which may be either axial or equatorial, when the macrocycle has a C symmetry.

The precipitated product **2**, isolated at the end of a standard resorcinarene forming reaction, has the crown conformation, with an rccc configuration at the methine linkers and all substituents in axial positions. The crown conformer possesses a distinctive cavity giving it possibilities as a host molecule. Its shape also imparts two distinct rims to the molecule, the upper and lower. The upper rim consists of eight phenolic hydroxyl groups and four activated aromatic positions, all available for a number of substitution reactions. The lower rim also has a potential for different substituents to be introduced, with the use of various aldehydes. The research carried out in these areas is discussed later in this chapter.

Högberg[3] and co-workers studied the acid catalysed reaction between resorcinol and benzaldehyde. They isolated two stereoisomers of the expected cyclic tetramer product. The relative amounts of these two isomers varied with time. The initial product formed was the chair isomer, with an rctt configuration, that reached a concentration peak after one hour before decreasing. This isomer rearranged through a proton-dealkylation process with a number of scissions of the methane-aryl carbon-carbon bonds, facilitated by the ortho and para-hydroxy groups. The final product of this process was the crown conformer, with an all axial, rccc configuration. This product was less soluble in the reaction mixture and precipitated, preventing any further rearrangements.
The chair isomer was successfully isolated from the early-stage reaction mixture and when re-subjected to the acidic reaction conditions gradually rearranged to the crown

isomer. This confirmed that the resorcinarene forming reaction was reversible. No chair isomer was formed from a pure sample of the crown isomer. Two carbon-carbon bonds need to be broken to convert between these two isomers. A simple rotation of either a phenyl group or a resorcinol unit (due to steric reasons and the disruption of intramolecular hydrogen bonds) cannot occur by what is known as 'through the annulus rotation'[6] (i.e. passing through the central cavity of the macrocycle). This has been reported with calix[n]arenes but, to the best of our knowledge, not with resorcinarenes.

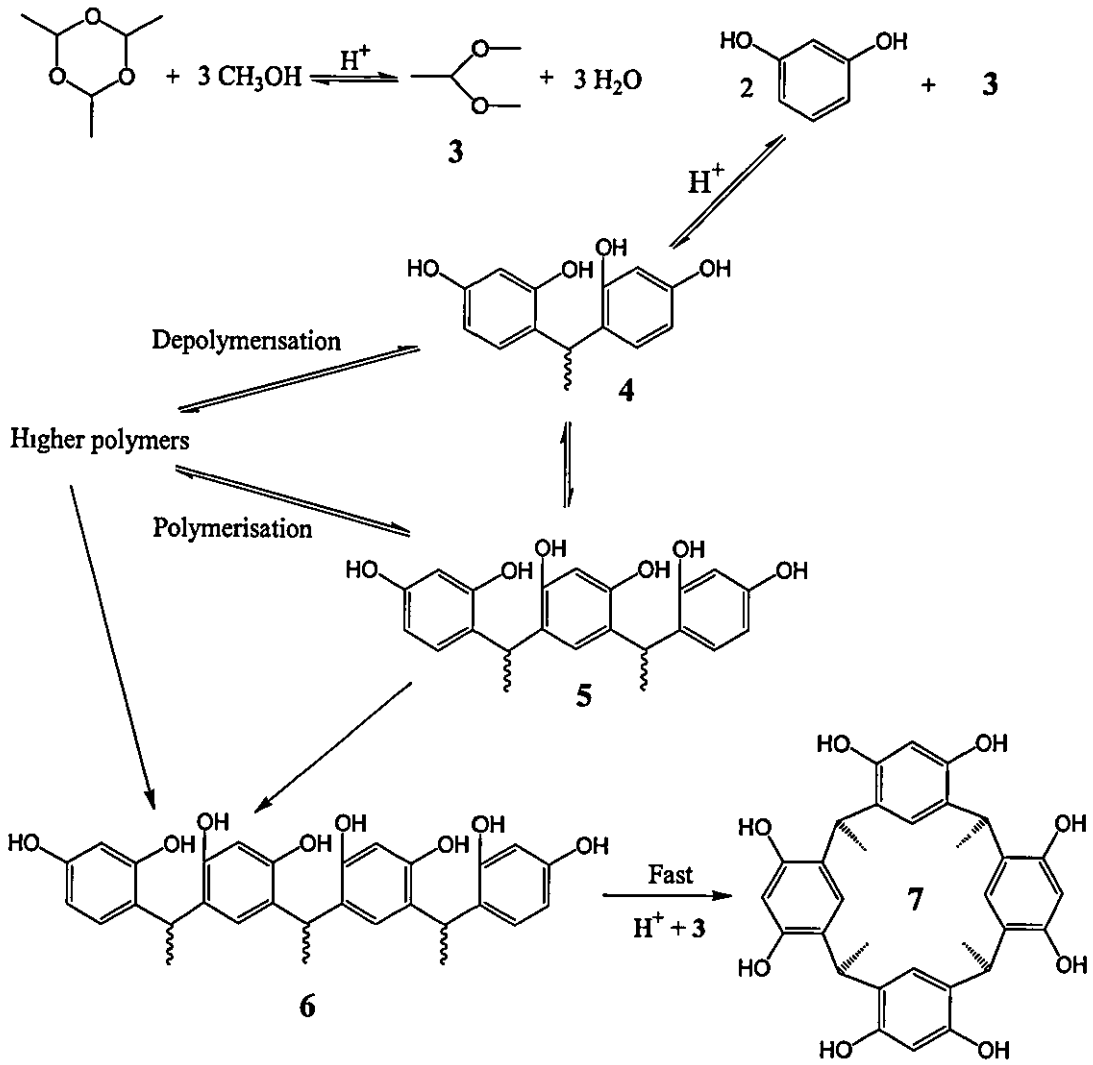
The crown isomer, with an all-cis arrangement of the axially positioned substituents, seems to be the most favoured arrangement for several reasons.
(i) Its lower solubility and hence precipitation from the reaction mixture acts as a thermodynamic sink for the reaction.
(ii) There is maximum intramolecular hydrogen bonding potential for the eight phenolic hydroxyl groups.
(iii) With all of the substituents in an axial position no disruption to the intramolecular hydrogen bonding occurs, which could potentially happen with equatorial substitution.

Högberg[3] repeated these investigations with acetaldehyde, seeing similar results. There was initial formation of the chair isomer, which eventually rearranged to the crown conformer, which precipitated from the reaction mixture.

Abis[7] and co-workers carried out resorcinarene forming reactions using heptanal and dodecanal, two long chain aliphatic aldehydes, at room temperature. The precipitate of the reaction contained three isomers, the chair, boat and previously unseen diamond. These isomers were acetylated to their octa-acetates and could be separated by column chromatography to be fully characterised. These non-crown conformers appear to have also precipitated from the reaction mixture due to a lack of solubility at room temperature. At this temperature rearrangement to the favoured crown product may have been hindered. The heptanal reaction was repeated with heating at reflux for eight hours producing only the crown conformer as the precipitate.

1.2.2 Mechanism of the macrocycle formation

Weinelt and Schneider[2] have studied the mechanism of the formation of resorcinarenes in some depth. By following the reaction with ^1H NMR spectroscopy they were able to identify the formation and degradation of a number of oligomers, as shown in **Scheme 2.** They deduced that the reactive form of the aldehyde was the dimethyl acetal **3**, that is formed rapidly in the reaction in methanol.



Scheme 2

The reaction of **3** with two resorcinol units gave the first observed intermediate **4** which can then react further to produce oligomers **5**, **6** and higher polymers. These higher

polymers could be present in up to 45% concentration. The higher oligomers break down under the reversible reaction conditions to give **4**, **5** and presumably **6**. Linear tetramer **6** can then cyclise, following reaction with another acetal, to give **7**. The importance of the solubility of these higher oligomers was noted. If the water concentration was too high, precipitation of these oligomers occurred, preventing depolymerisation and hence resorcinarene formation.

The rate of cyclisation is rapid, being as fast as chain propagation, so much so that **6** was not seen in the reaction mixture. The linear tetramer is thought to cyclise so rapidly because of its spatial arrangement, being folded in such a way as to give the maximum hydrogen bonding interaction.

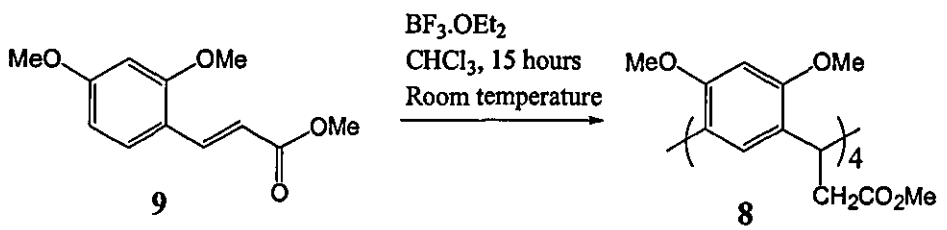
The observation that each linear oligomer has resorcinol terminal units and not methoxy methyl units was also made.

1.2.3 Other methods for resorcinarene formation

A range of alternative methods for resorcinarene formation has been investigated by a number of groups, reflecting the current interest in this family of macrocycles.

1.2.3.1 Lewis acid methodology

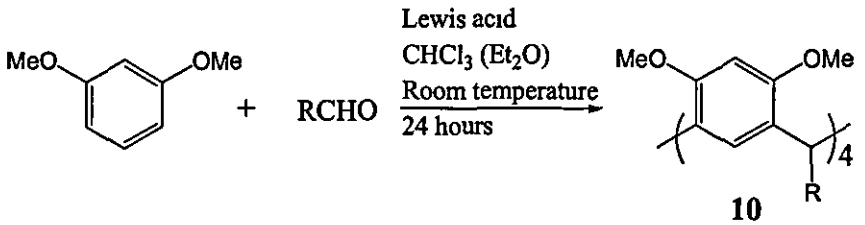
Botta[8] reported the formation of a range of octa methoxy resorcinarenes, such as **8**, from E-2,4-dimethoxycinnamate **9** using the Lewis acid $BF_3.OEt_2$, **Scheme 3**. In each case a mixture of stereoisomers was formed, usually as a mixture of the boat (rccc configuration), diamond (rcct) and saddle (rccc) conformations.



Scheme 3

The resorcinarene is thought to form by a stepwise growth to the tetramer or by the combination of two dimers.

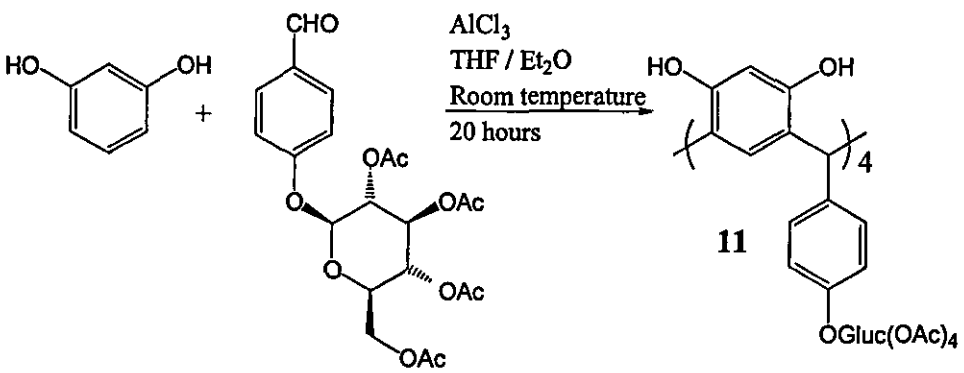
Iwanek[9] has also reported the production of octa methoxy resorcinarenes using 1,3-dimethoxybenzene with a range of aliphatic aldehydes, catalysed by a number of Lewis acids in average to excellent yields, **Scheme 4.** The Lewis acids were initially screened using isovaleraldehyde, producing in each case a mixture of predominantly crown and diamond conformations with rccc and rcct configurations respectively, except with $SnCl_4$ where only the crown conformation (rccc) was formed in 85% yield. ^1H NMR measurements could easily distinguish between each isomer of **10.** Other aldehydes were investigated using $SnCl_4$ producing varying yields of the crown conformer with an rccc configuration, along with traces of other conformers whose configurations were not reported.



10

Scheme 4

Curtis[10] has used the Lewis acid $AlCl_3$ to perform the reaction between resorcinol and acid sensitive glycosidic aldehydes to give the desired resorcinarene, **Scheme 5.**

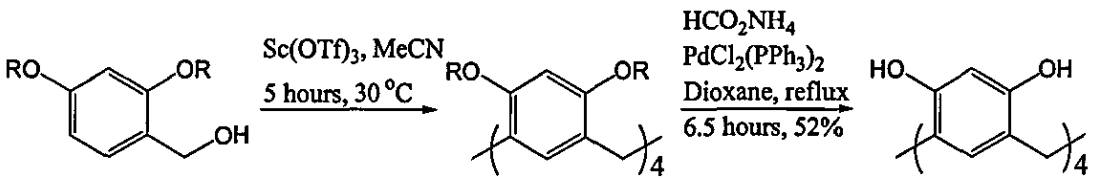


11

Scheme 5

Resorcinarene **11** was formed as a mixture of two isomers (rctt chair (49%) and rccc boat (17%)) in good yield. One notable advantage of these protected carbohydrate resorcinarenes was their increased solubility in common organic solvents. The two isomers could be separated by chromatography.

The treatment of 2,4-bis(alkyloxy)benzyl alcohols with $Sc(OTf)_3$ produced resorcinarenes in reasonable yields,[11] **Scheme 6**.



R=Me **12**
R=allyl **13**

R=Me **14**
R=allyl **15**

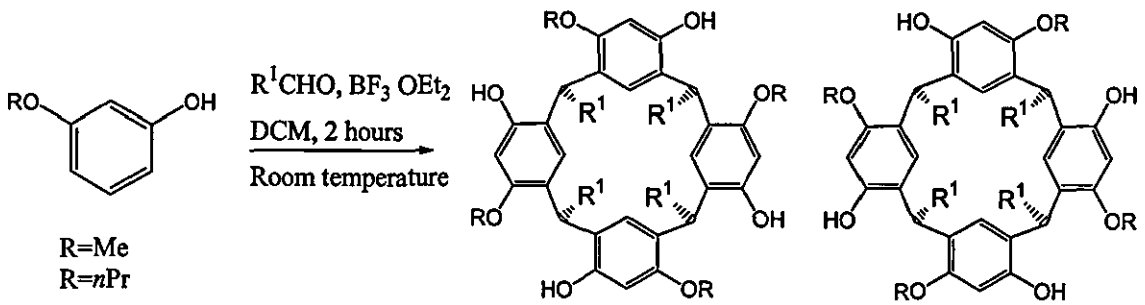
16

Scheme 6

The aim of this work was to produce the previously non-isolated parent resorcinarene **16**, which cannot be formed by a condensation reaction between resorcinol and formaldehyde. This was successfully achieved from the octa allyloxy resorcinarene **15**. The conformations of **14**, **15** and **16** (despite hydrogen bonding) show an average by ^1H NMR spectroscopy. They appear to be conformationaly flexible due to the lack of any substituents on the methylene bridges.

Mocerino *et al.*[12] have developed conditions for resorcinarene formation from 3-methoxyphenol and 3-*n*-propyloxyphenol with aliphatic aldehydes using $BF_3.OEt_2$ in excellent yields. The cyclic tetramers produced in each case possessed the crown conformation with an all cis configuration, confirmed by ^1H NMR spectroscopy and X-ray crystallography. As can be seen from **Scheme 7**, these resorcinarenes have inherent axial chirality (see **Section 1.4.1.2**), with no mirror planes and a C_4 rotational symmetry. They are formed as a racemic mixture of the two enantiomers.

This is the only example of an inherent chirality being introduced into a resorcinarene during its formation. Other examples discussed later involve substitution reactions on the upper or lower rims of standard octa hydroxy resorcinarenes.

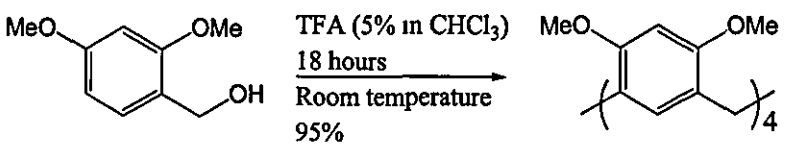


R=Me, $R^1=C_7H_{15}$ **17**
R=Me, $R^1=C_{11}H_{23}$ **18**
R=*n*Pr, $R^1=C_{11}H_{23}$ **19**

Scheme 7

1.2.3.2 Protic acid methodology

The unsubstituted resorcinarene **14** (seen above) was produced in high yield by treatment of the same benzylic alcohol **12** using a catalytic amount of TFA,[14] **Scheme 8**. The same conformational mobility was reported.



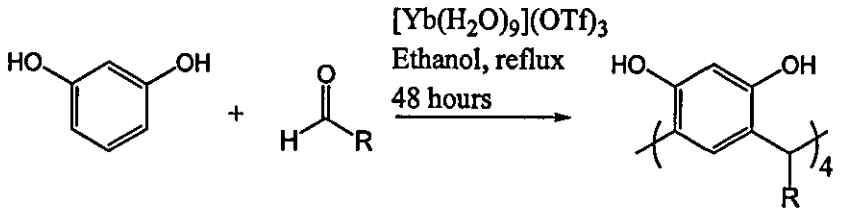
12 **14**

Scheme 8

The parent octa hydroxy resorcinarene was assumed to have been formed following de-methylation with BBr_3, but was not characterised before acetylation.

Ytterbium (III) triflate nonahydrate catalysed the processes shown in **Scheme 9** in excellent yields.[15] Despite this reagent being a Lewis acid, the active species in these reactions is thought to be triflic acid, which is produced in small amounts. With the

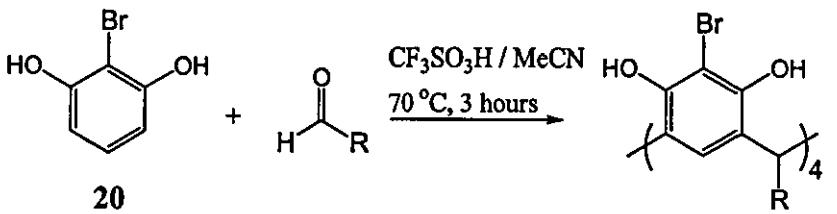
aliphatic aldehydes used, the crown rccc isomers were exclusively isolated. However with benzaldehyde a mixture of the chair and crown conformations was formed.



Scheme 9

R=Ph
R=Et
R=C_5H_{11}
R=C_9H_{19}
R=$C_{11}H_{23}$

Konishi[16] has used trifluoromethanesulphonic acid to synthesise a range of resorcinarenes from 2-bromoresorcinol **20, Scheme 10.**



20

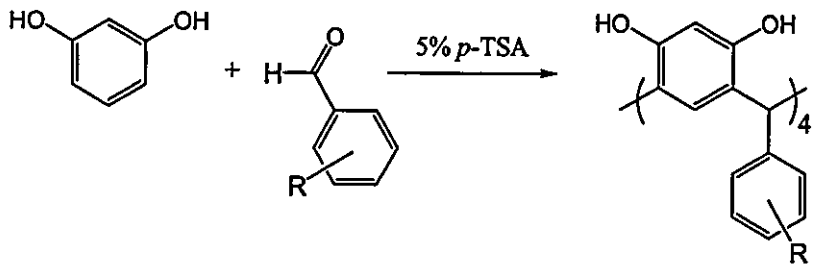
Scheme 10

R=*p*-XPh	**21**
R=Me	**22**
R=$PhCH_2CH_2$	**23**
R=H (from $(CH_2O)_3$)	**24**

The benzaldehyde derivatives (**21**) formed as the chair conformers with rctt configurations. Resorcinarenes **22** and **23** both formed in the crown conformation with rccc configurations. The tetra bromo equivalent of the parent, unsubstituted resorcinarene **24** was made using 1,3,5-trioxane. This macrocycle was thought to be in the chair conformation.

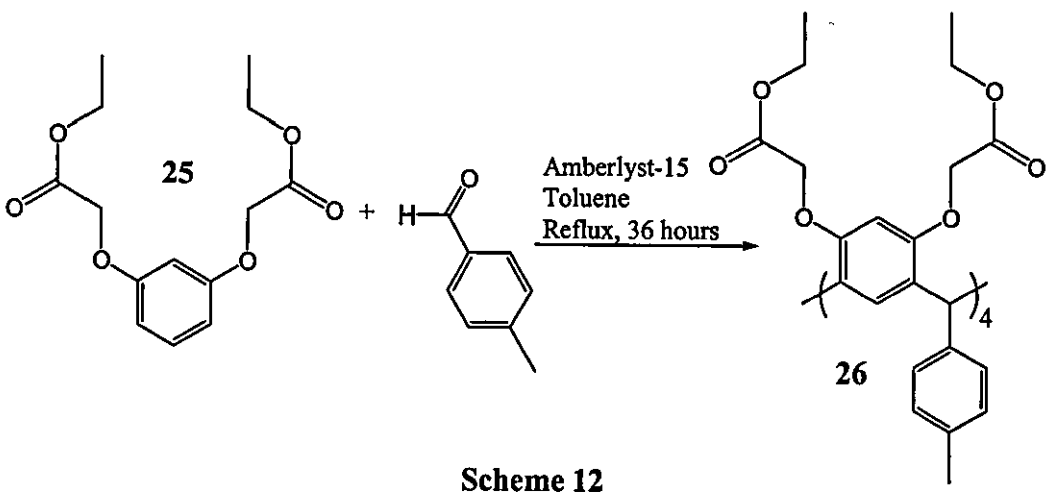
Solvent free, resorcinarene forming reaction conditions have been developed by Scott[17] in which resorcinol, an aldehyde and a catalytic amount of *p*-TSA are ground together,

forming the equivalent resorcinarene in high yield as a mixture of the crown (rccc) and chair (rctt) isomers, **Scheme 11.**



Scheme 11

Use of Amberlyst-15 ion exchange resin as a heterogeneous catalyst was employed to give resorcinarene **26,** from the reaction between resorcinol derivative **25** and *p*-methylbenzaldehyde, as the chair (rctt) conformer in low yield,[18] **Scheme 12.**



Scheme 12

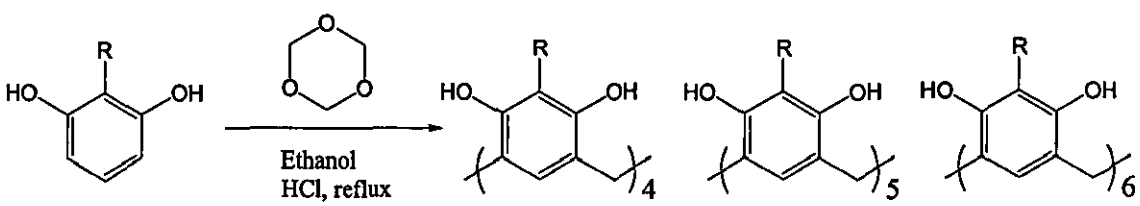
A notable advantage of this method is ease of removal of the catalyst by simple filtration, leaving an acid free solution.

As discussed previously, Högberg suggested that the folding of the intermediate linear tetramer **6 (Scheme 2),** due to hydrogen bonding, under classical resorcinarene forming conditions, promotes formation of the tetrameric macrocycle. Also the precipitation of the product acts as a thermodynamic sink for the reaction. In some of the examples

discussed above no intramolecular hydrogen bonding is present, due to the use of bis-alkylated resorcinol derivatives, and of these only with Iwanek's methodology does a precipitate form. No reasoning has been reported for the sole observation of the cyclic tetramer without any other ring sizes.

1.2.4 Synthesis of calix[5]resorcinarenes and calix[6]resorcinarenes

Calix[n]arenes, were n = 4,6,8 etc, can each be formed preferentially by varying the reaction conditions, while resorcinarenes are almost invariably formed as the cyclic tetramer. Konishi,[19] however, has successfully isolated both calix[5]resorcinarenes and calix[6]resorcinarenes from the reaction between 2-alkylresorcinols and 1,3,5-trioxane, **Scheme 13.**



R=Me
R=C_3H_7
R=C_6H_{13}

Scheme 13

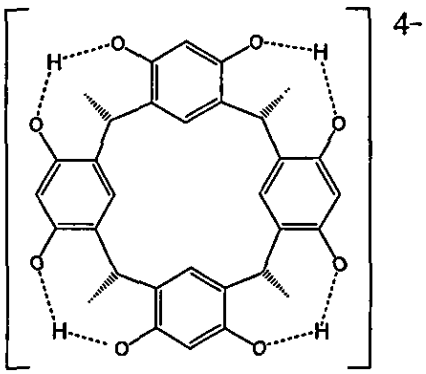
The reaction was heated at reflux for several hours and monitored. After thirty minutes the reaction mixture contained mostly the three different sized macrocycles shown. Calix[6]resorcinarene was the major component, then the calix[5]resorcinarene and in lowest concentration the calix[4]resorcinarene. After two hours the ratios had changed so that the tetramer was the major component over the hexamer, with only a small amount of the pentamer remaining. After six hours only the tetramer could be identified.
An isolated sample of the calix[6]resorcinarene was re-subjected to the reaction conditions, and this resulted in formation of the tetramer. An isolated sample of the calix[5]resorcinarene formed both the hexamer and tetramer and eventually just the tetramer. The proton-dealkylation reversible pathway, suggested by Högberg, appears to

be confirmed here, with the calix[4]resorcinarene being the final product seen in each case.

Rebek *et al.*[20] have recently reported the formation of a calix[6]resorcinarene derived from resorcinol and propanal, using standard hydrochloric acid-catalysed conditions. The calix[6]resorcinarene was isolated by filtration as it precipitated from the reaction mixture with the major, calix[4]resorcinarene product. The hexamer was isolated in 5% yield from the major tetrameric product by differing solubilities. The stability of this calix[6]resorcinarene was confirmed by re-subjecting a sample to the reaction conditions for 24 hours with no observation of the calix[4]resorcinarene having been formed. Why this calix[6]resorcinarene did not dissolve under these reaction conditions and rearrange to the calix[4]resorcinarene, through the proton-dealkylation pathway discussed previously, is unclear.

1.3 Resorcinarene acidity

Resorcinarenes are insoluble in aqueous solutions, with water sometimes added to a resorcinarene-forming reaction to promote precipitation. However they are highly soluble in aqueous basic solutions due to the deprotonation of the phenolic hydroxyl groups. The tetra anion **27** of resorcinarene **7**, **Figure 3**, is easily formed and remains stable as a 'result of the ideal geometric disposition of the O-H-O arrangement'[5] of remaining hydrogen bonds, and potential for charge delocalisation around the macrocycle.[21,22]



27

Figure 3

The first four phenolic hydrogens are much more acidic than the last four. Schneider reported that the pKa values of the first four protons are two units lower than that of resorcinol (7; pKa 11.4, resorcinol; pKa 13.5 in 4:1, DMF : water).[22b]

1.4 Functionalisation of resorcinarenes

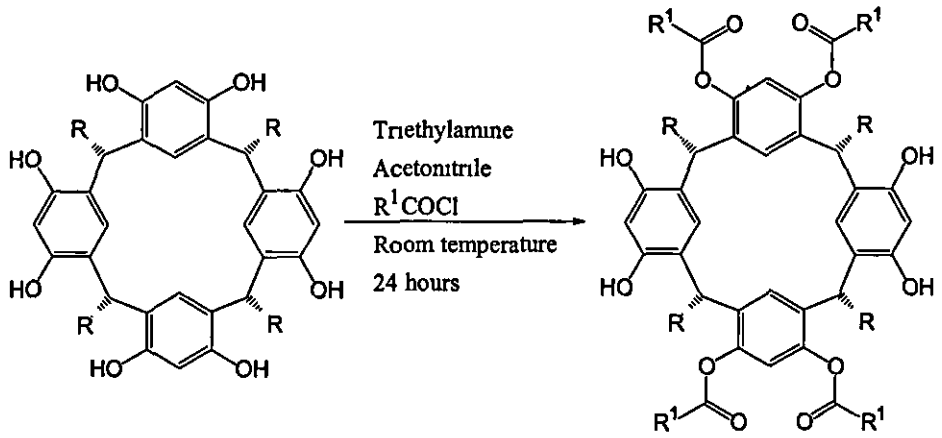
From this point onwards in **Chapter 1** all discussions involve calix[4]resorcinarenes possessing the crown conformation and an all axial, rccc configuration. These resorcinarenes as a result possess two distinctive sites for functionalisation, the upper and lower rims.

1.4.1 Upper rim functionalisation

The upper rim is made up of eight phenolic hydroxyl groups and four aromatic 2-positions. The aromatic 2-positions are highly activated towards substitution because of the two ortho-hydroxy groups and the phenols themselves can be readily protected by many different groups.

A number of researchers have investigated various regioselective functionalisation reactions to give resorcinarenes with C_{2v} rotational symmetry. Shivanyuk[23] and Böhmer[24] have both developed conditions for the selective tetra acylation of a range of

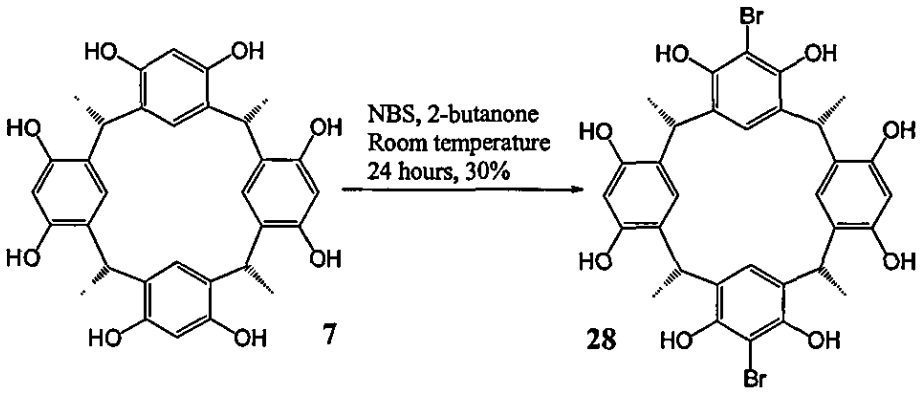
resorcinarenes. The distally, tetra acylated resorcinarenes were the major product in each case, being isolated in poor to moderate yields, **Scheme 14.** A large range of acylating agents was used.



Scheme 14

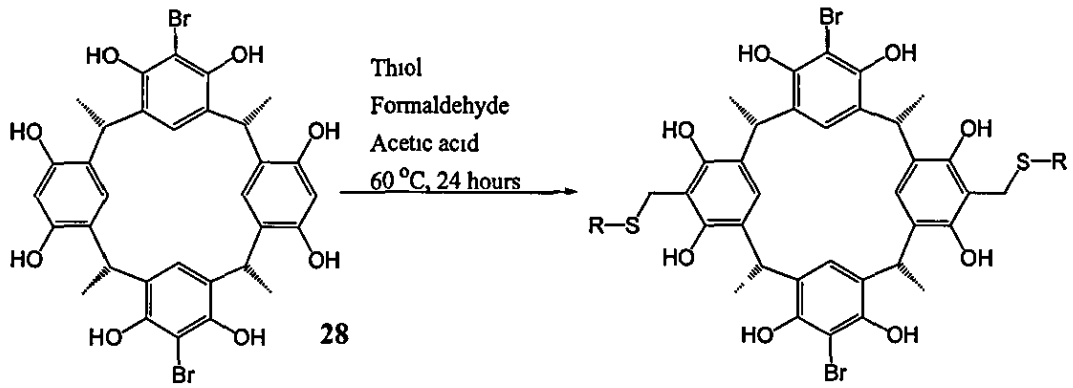
The selectivity seen is dependent on the solvent used, the acylating agent used and the complexation of the triethylamine with the resorcinarene before addition of the acylating agent. The two remaining unprotected resorcinol units can then be derivatised further by, for example, other acylating agents or by bromination of the aromatic positions with NBS.

Konishi *et al.*[25] used two equivalents of NBS with resorcinarene **7** to form the distally dibrominated compound **28** in reasonable yield, **Scheme 15.** They reported the observed selectivity to be due to an electronic effect. When the first unit is brominated, an electron-withdrawing effect is passed through an intramolecular hydrogen bond to the adjacent resorcinol unit, deactivating it towards bromination. Hence the distally positioned resorcinol unit is preferentially brominated next when just two equivalents of NBS are used.



Scheme 15

They then went on to functionalise the remaining free aromatic 2-positions as various thioethers using thiols and formaldehyde, as shown in **Scheme 16**. Some of these involved α,ω-dithiols to produce distally bridged, basket type molecules.



Scheme 16

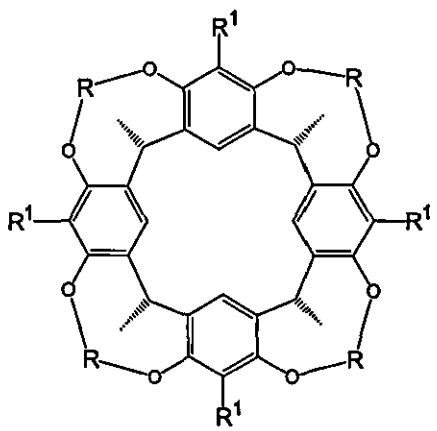
1.4.1.1 Cavitands

The name cavitand was first proposed by Cram[26] to describe synthetic organic compounds containing a cavity within their structure, of a size suitable to accommodate guest molecules. A large number of literature publications has been made concerning resorcinarene-based cavitands.[27] The eight phenolic hydrogen atoms can easily be covalently linked together as shown in **Figure 4**. The products, in comparison with the

parent resorcinarene, are very rigid molecules. The ethylene and propylene bridged cavitands possess more flexibility than the methylene equivalents.

Figure 4 shows some of the large range of functionalities that have been introduced into the upper rims of these cavitands. Those shown are from ethanal-derived resorcinarene **7**, but a range of parent resorcinarenes have been investigated.

These macrocycles, having deep cavities, are generally associated with complexed solvent molecules, in some cases with great stability. In the case of [**29**.EtOAc] the incarcerated ethyl acetate molecule was not removed by heating at 180 °C under high vacuum for 24 hours.



$R=CH_2$, $R^1=H$
$R=CH_2$, $R^1=Me$
$R=CH_2$, $R^1=Br$ **29**
$R=CH_2$, $R^1=CH_2Br$ **30**
$R=CH_2$, $R^1=I$
$R=CH_2$, $R^1=CH_2OH$
$R=CH_2$, $R^1=CH_2Cl$
$R=CH_2$, $R^1=CH_2SH$
$R=(CH_2)_2$, $R^1=Br$
$R=(CH_2)_3$, $R^1=Br$
$R=SiR^2_2$, $R^1=H$ **31**
$R=PR^2$, $R^1=H$ **32**

Figure 4

Silicon[28] and phosphorus[29] have also received investigation as linkers between adjacent resorcinol units, **31** and **32**.

Some resorcinarene-based cavitands can form dimers known as carcerands and hemicarcerands, joined *via* their upper rims through covalent linkers; an example of these is **30**.[5]

Carcerands and hemicarcerands possess a rugby ball type shape. They differ from each other in how they interact with guest molecules. An example of a carcerand is shown in **Figure 5**, which has been shown to incorporate a Cs^+ ion.[30]

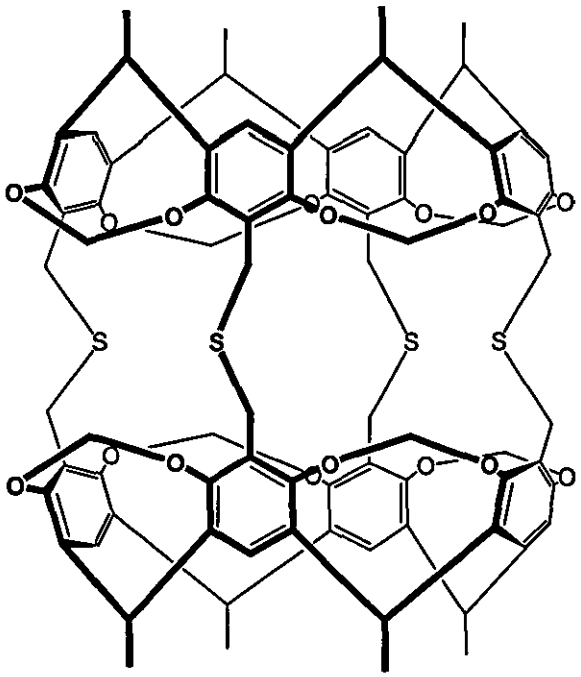


Figure 5

During their synthesis carcerands capture solvent molecules from the reaction mixture, which cannot be released without the breaking of covalent bonds. It is believed that the carcerand formation is in some way templated by the solvent, with no 'empty' carcerands being evident. They can also be selective in the presence of more than one solvent. Hemicarcerands differ because they permit exchange of the guest molecule by either larger gaps between spacers or the absence of a number of the spacers.
The size of the cavity with two resorcinarenes linked together is limited, so even larger, extended, multi-resorcinarene cavities have been developed.[31]

1.4.1.2 Introduction of chirality into a resorcinarene

Some of the recent interest in resorcinarene chemistry has involved the introduction of a chiral element. Two different approaches have been made for the formation of chiral resorcinarenes.

The first is by substitution reactions on the upper rim with chiral groups. If the substituent is enantiomerically pure and remains so following the reaction, the resulting resorcinarene is chiral and enantiomerically pure.[32]

The second method concerns the formation of what have become known as 'inherently chiral' derivatives. This type of chirality is not due to a number of substituted chiral auxiliary groups but the actual shape of the molecule as a whole, having a chiral axis. Cram[33] has achieved this with a range of partial substitutions, shown in **Figure 6**. The obvious problem with this approach is the inevitable formation of a racemic mixture of products. Low yields are also realised because these partial protections result in statistical distributions of a number of compounds.

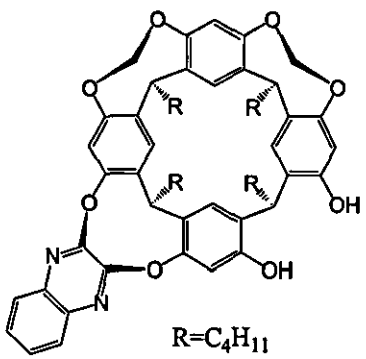


Figure 6

One result of note was the observation of the racemic tetra lactone shown in **Figure 7**.[34] This was formed as an isolable side product from another process. This molecule possesses inherent chirality with no symmetry planes remaining, but also a C_4 rotational symmetry. This type of chirality has been the basis of a great deal of recent interest in resorcinarene chemistry involving the amino methylation reactions discussed below.

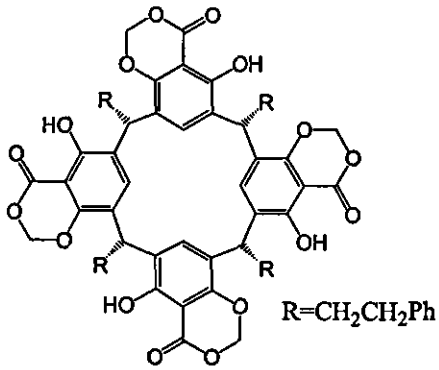
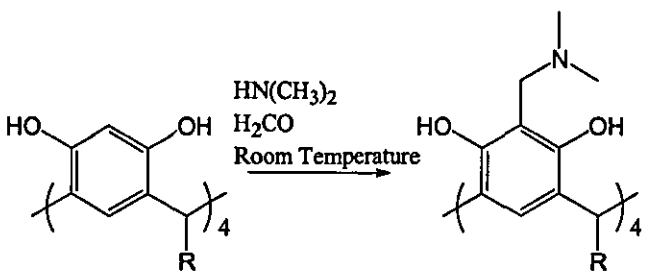


Figure 7

1.4.1.3 Amino methylations of resorcinarenes

Matsushita's[32b] group reported the first examples of the use of Mannich reaction protocols with resorcinarenes in upper-rim functionalisation reactions. Initially using dimethylamine with 37% aqueous formaldehyde in solvent mixtures of either ethanol / benzene or ethanol / DCM, the tetra dimethylaminomethyl derivatives were formed in good to high yields with a range of resorcinarenes, **Scheme 17.**

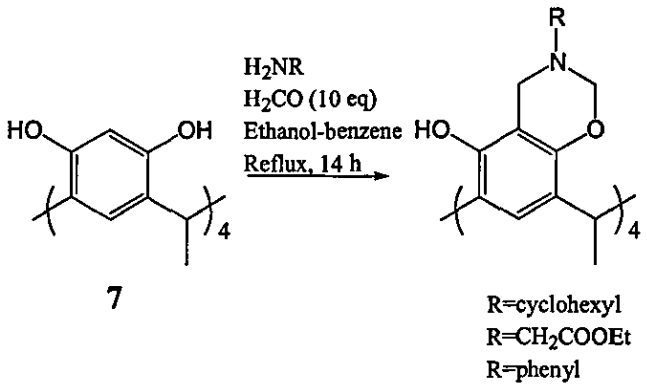


R=CH_3	**7**	R=CH_3	**36**
R=$(CH_2)_8CH_3$	**33**	R=$(CH_2)_8CH_3$	**37**
R=CH_2CH_2Ph	**34**	R=CH_2CH_2Ph	**38**
R=Ph	**35**	R=Ph	**39**

Scheme 17

The group then extended their study to other secondary amines containing a range of functionalities. The amines used included morpholine, piperidine, 1-methylpiperizine, *N*-methylethanolamine and L and D proline. The use of chiral amines L and D proline introduced a chiral element to the macrocycles, although the authors did not discuss this.

They then proceeded to investigate the use of primary amines with more than two equivalents of formaldehyde, using resorcinarene **7**. The tetrakis-(3,4-dihydro-2*H*-1,3-benzoxazine) compounds were formed in good yields, **Scheme 18.**



7

R=cyclohexyl
R=CH_2COOEt
R=phenyl

Scheme 18

The tetra benzoxazine compounds formed are chiral molecules, but inevitably racemic mixtures. They possess an inherent chirality, with all mirror planes having been broken, and C_4 rotational symmetry. This observation was again not noted by the authors. The group of Böhmer[35] carried out further investigations into the formation of these chiral tetra benzoxazine derivatives. The question of interest was why had such a selective reaction taken place when considering all possible outcomes from the reaction. They proposed the possibility of four different regioisomers being formed, shown in **Figure 8.**

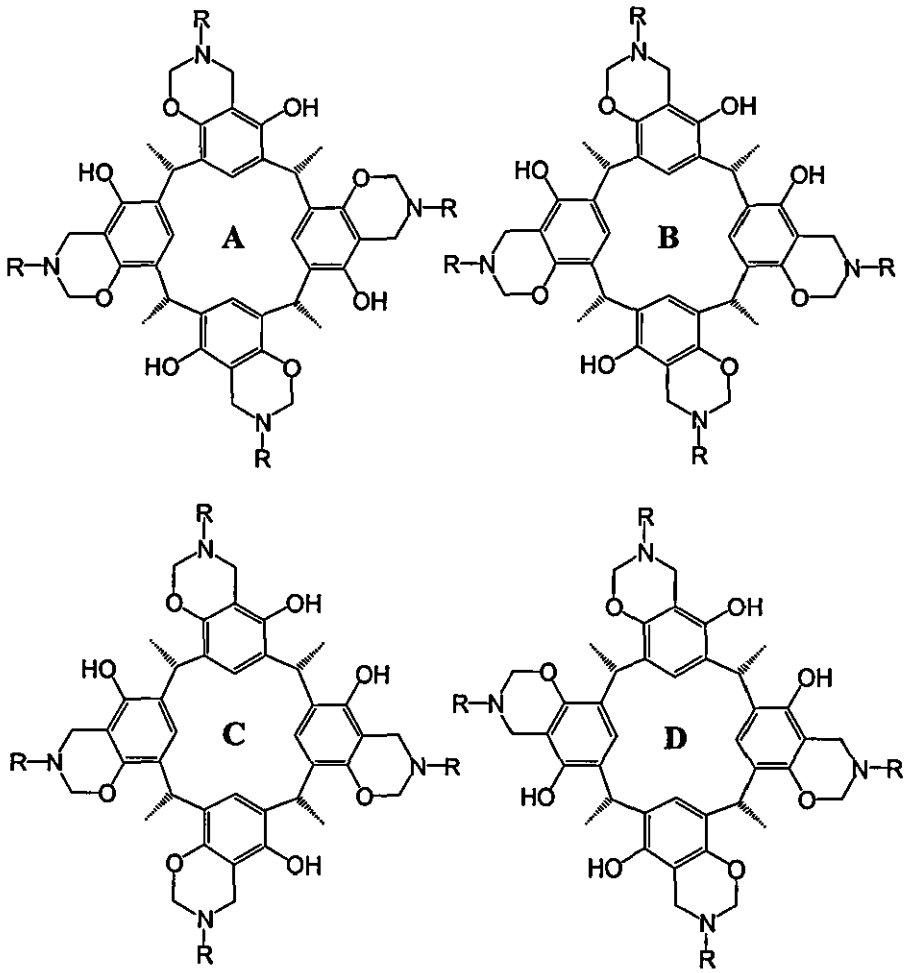


Figure 8

The analytical data they obtained from their results confirmed what Matsushita had reported. Only the C_4 symmetric product **A** was formed as a racemate.

The ^1H NMR spectra showed four distinct doublets, from two AB systems, for the CH_2 groups of the benzoxazine rings. Due to the protons of each methylene group being diastereotopic and all starting materials in the reaction being achiral, it followed that the tetra benzoxazines produced must be chiral as a result of their physical shape.

Only two of the proposed possible products are chiral, **A** and **B**. The ^1H NMR spectra showed only one set of signals for the OH protons, the ring aromatic protons and the bridging methine protons, in accordance with the C_4 structure **A**. Structure **B** would have multiple sets of signals for these protons.

In the achiral regioisomers **C** and **D**, three and two methine signals respectively would have been seen.
The formation of **A** was confirmed by X-ray crystallography.

The production of **A** can be explained by its intramolecular hydrogen bonding potential. In the C_4 symmetric arrangement **A**, four intramolecular hydrogen bonds exist, more than in any of the other stereoisomers. For this to be the case, the benzoxazine ring-closing step must be reversible under the reaction conditions used. A stepwise tetra benzoxazine formation (mono, bis, tri then finally tetra benzoxazine) would not necessarily occur sequentially around the ring, with four reactive sites available.

Böhmer attempted, unsuccessfully, to separate the two enantiomers formed using chiral chromatography.

1.4.1.4 Use of enantiomerically pure chiral amines

The selectivity seen with achiral amines led the groups of Heaney,[36] Böhmer[37] and Iwanek[38] to investigate the use of enantiomerically pure, chiral amines. The three groups all arrived at similar results and conclusions.
Heaney[36] used a range of octa hydroxy resorcinarenes with R-(+)-α-methylbenzylamine, para formaldehyde and a catalytic amount of sodium hydroxide in ethanol or an ethanol / toluene mixture. Heating the reaction mixture at reflux overnight formed the tetra benzoxazine products in high yields. Assuming that the C_4 symmetry seen above would also occur here, two possible diastereoisomeric products were the possible outcome, **Figure 9**.

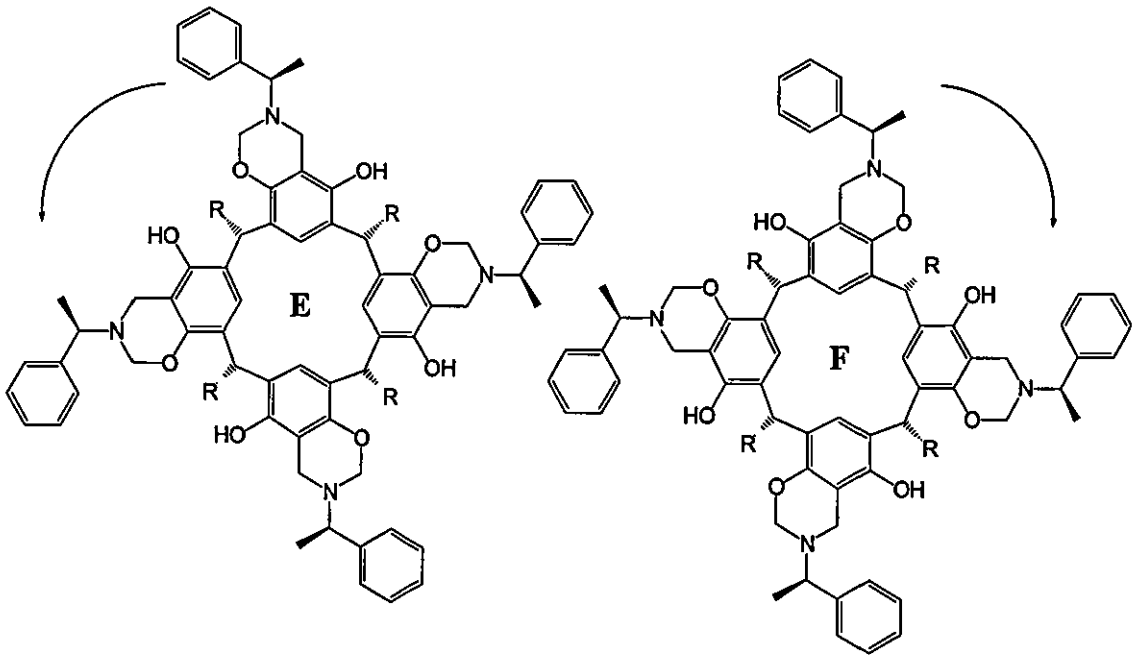
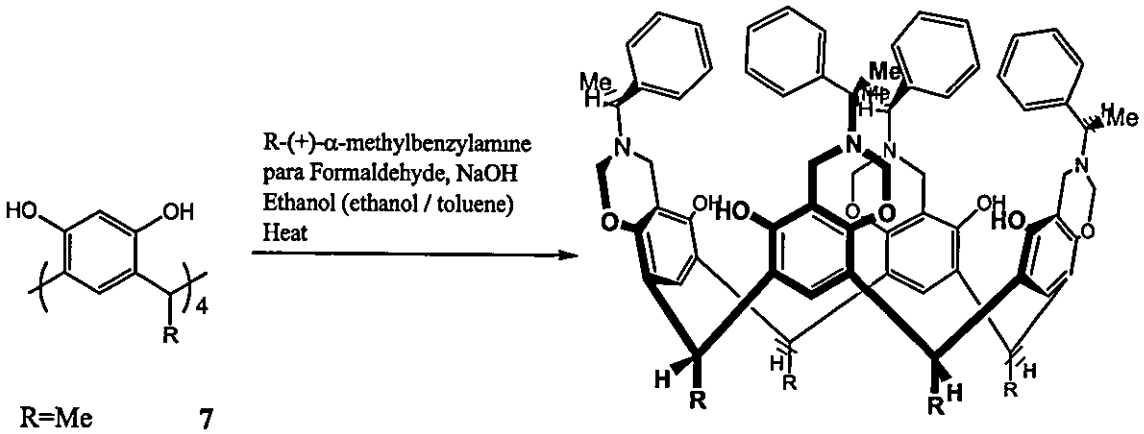


Figure 9

The ^{1}H NMR spectrum showed the tetra benzoxazine to have formed with high diastereoselectivity, with only diastereoisomer **E** evident, **Scheme 19.**



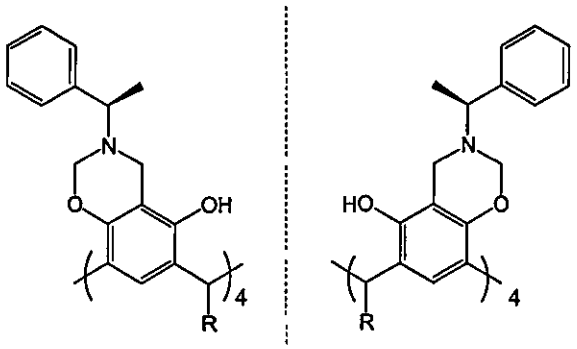
R=Me	**7**
R=C_5H_{11}	**40**
R=$C_{11}H_{23}$	**41**
R=CH_2CH_2Ph	**34**

R=Me	**42**
R=C_5H_{11}	**43**
R=$C_{11}H_{23}$	**44**
R=CH_2CH_2Ph	**45**

Scheme 19

The diastereoisomer observed (**43**) was confirmed by X-ray crystallography, establishing its axial chirality.[36]

The enantiomers of these resorcinarenes were obtained when using S-(-)-α-methylbenzylamine, in similar yields, with the same ^{1}H and ^{13}C NMR spectra and with an equal but opposite optical rotation. From these results, and with the knowledge that the chirality of the amines used is fixed, it can be said that the two products are clearly enantiomers of each other with opposite axial chirality, **Figure 10**.



R=Me **42b**
R=C_5H_{11} **43b**
R=$C_{11}H_{23}$ **44b**
R=CH_2CH_2Ph **45b**

Figure 10

Böhmer[37] and Iwanek[38] used very similar methodology to produce diastereoisomerically and enantiomerically pure resorcinarenes.

Iwanek performed the reactions at –50 °C, gradually warming to room temperature to obtain a diastereoisomeric ratio of 95:5 of the configuration seen above. Three recrystallisations gave material with >99% purity. He cooled the reaction following the observation of a 4:1 ratio at room temperature. Böhmer produced the pure diastereoisomer in excellent yield after one recrystallisation.

Both groups also investigated the use of other enantiomerically pure amines, 1-cyclohexylethylamine and 1-(1-napthyl)ethylamine. Böhmer reported a high diastereoselectivity with these amines, as with α-methylbenzylamine, but later retracted these claims,[39] reporting that 1-cyclohexylethylamine gave an almost 1:1 ratio of diastereoisomers and a 60:40 ratio with 1-(1-napthyl)ethylamine. Iwanek's results confirmed the corrected observations of Böhmer.

A simple method for assigning the chirality of these resorcinarenes has been suggested by Böhmer (unpublished). From the perspective of inside the macrocycle looking out, if the higher priority groups of the upper rim (in this case the benzoxazine moieties over the hydroxyl groups, following the Cahn-Ingold-Prelog rules) are on the right hand side of each resorcinol unit the resorcinarene is assigned as being S. If they are on the left hand side it is assigned R, **Figure 11.**

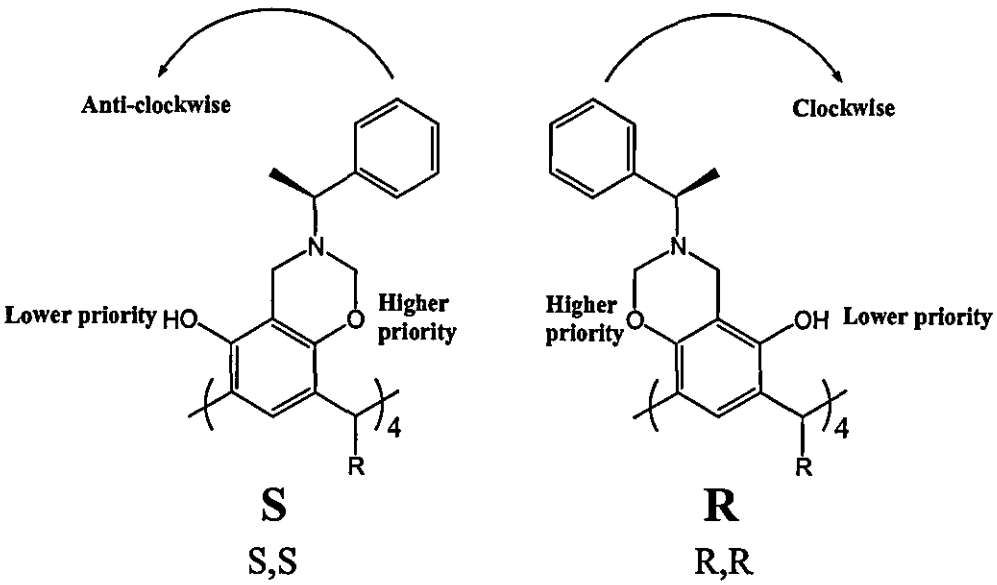
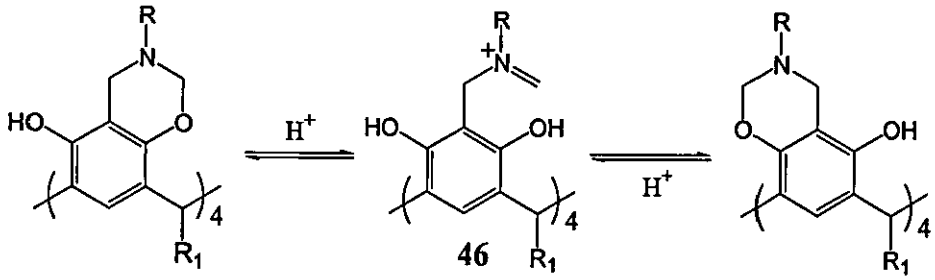


Figure 11

The second element of chirality comes from the α-methylbenzyl groups, either R or S. Therefore the products seen in **Figure 11** are assigned as S,S and R,R. The chirality of the axis is defined first followed by any chiral auxiliary groups. The diastereoisomer of each compound in **Figure 11** would thus have an R,S or S,R configuration.

1.4.1.5 Acid catalysed diastereoisomerisation

Böhmer,[37] Heaney[36] and Iwanek[38] investigated the effects of protic acids on tetra benzoxazine resorcinarenes. The results were formation of the other C_4 symmetric diastereoisomer *via* iminium ion intermediates **46, Scheme 20.**



R=S or R α-methylbenzyl

Scheme 20

The ^{1}H NMR spectra of the products of these investigations clearly show the formation of the other diastereoisomer by the appearance of another set of distinctive doublets, in an AB system, for the NCH_2O diastereotopic methylene protons, **Figure 12.**

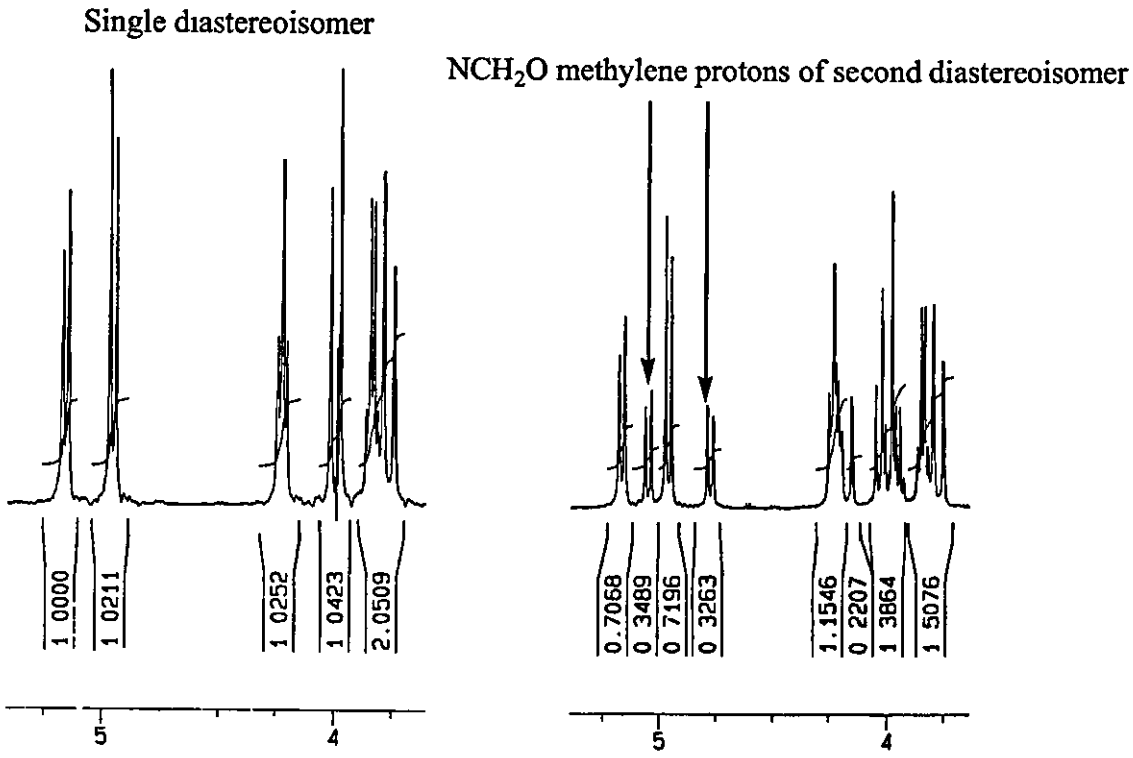


Figure 12

The mixture of the two diastereoisomers reached an equilibrium ratio of approximately 2:1 in $CDCl_3$ after 48 hours, with the starting compound remaining as the major component. No further changes were seen, even after several days.
Böhmer suggested that the stepwise formation of each diastereoisomer is controlled by hydrogen bonding. When one individual benzoxazine unit isomerises it promotes the others to do so in order to maintain the maximum intramolecular hydrogen bonding potential. He believes the intermediate structures to be present in the reaction mixture, but in small unidentifiable concentrations, short lived due to their higher energy.
A 1:1 mixture of the two diastereoisomers was not seen at any time. The two diastereoisomers are thought to be of different energies. They are both formed because of the intramolecular hydrogen bonds, but the minor diastereoisomer is less favoured due to greater steric interactions between the bulky α-methylbenzyl groups.

This diastereoisomerisation was also seen in NMR experiments, just in the presence of carefully purified $CDCl_3$ (passed through a $NaHCO_3$ pad prior to use), with no added acid. This observation suggests that the diastereoisomerisation could be auto catalysed due to the intramolecular hydrogen bonds. Iwanek[38] reported the differing ratios seen by varying the solvent. The amounts of the minor C_4 diastereoisomer formed were less in THF and benzene than those seen in chloroform after prolonged periods. No explanation was offered for these observations and the minor diastereoisomer was never isolated.

1.4.1.6 Reasons for the observed diastereoselectivity

The reason for the formation of the C_4 symmetric product has been discussed above. The reasons for the observation of only one diastereoisomer in the reaction are less clear, but a number of proposals have been made.

Since the initial investigations into these reactions were made, a more simple reaction protocol has been developed by the Loughborough group.[40,41] This involves the simple use of aqueous formaldehyde, in place of para formaldehyde, in ethanol under reflux, without the addition of any hydroxide catalyst. From these conditions (like those

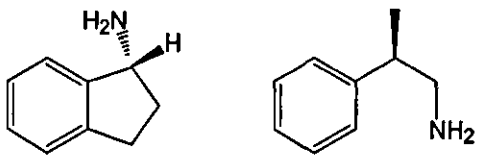
developed by Böhmer[37] and Iwanek[38]), the product precipitates from the reaction mixture and is simply filtered off. One recrystallisation, which appears not to be always necessary, gave the desired pure product in high yield. This precipitation occurred with all of the parent resorcinarenes used.
It seems that the major factor responsible for the diastereoselectivity is simply a fortunate solubility effect. Once the product is formed it precipitates from the reaction, preventing further diastereoisomerisation occurring. The group of Böhmer has investigated this in some detail.[39]

Using α-methylbenzylamine they investigated variation of the reaction solvent and temperature. Methanol, ethanol, acetone and acetonitrile were each tried, in some cases at both room temperature and 80 °C. These changes gave no significant differences to the ratio of the diastereoisomers. It should be noted that the product has to be insoluble in the solvent used: Sampler[41] performed a similar reaction in toluene; no precipitate was formed and an approximately 1:1 mixture of the C_4 diastereoisomers was isolated after removal of the solvent. This residue was then heated under reflux in ethanol, which resulted in the precipitation of a single diastereoisomer. This result suggests that both diastereoisomers are present in the reaction mixture, but in a suitable solvent one may have a lower solubility and precipitates. The precipitation therefore allows sole formation of one diastereoisomer as the reaction proceeds.

Böhmer also noted the production of one diastereoisomer even when an acid catalyst was added, despite the acid catalysed diastereoisomerisation discussed above. Once precipitated clearly the product can no longer diastereoisomerise.
The progress of a reaction was monitored by ^{1}H NMR spectroscopy. A reaction was split into two parts at different stages. After one hour (about the time at which the precipitate begins to form) a sample was taken and poured into water, to end the reaction, and the precipitate collected. This showed both diastereoisomers to be present, along with other partially reacted resorcinarenes. The remainder of the reaction mixture was heated under reflux for three hours. The precipitate that had formed after this time was isolated as normal. This showed essentially only one diastereoisomer, which had been isolated

previously as the product. The liquors of the reaction were poured into water and the precipitate collected. The precipitate contained both diastereoisomers and a small amount of partially reacted resorcinarene.
These results confirm the major factor to be solubility.

The chiral amine used is also important. As discussed above Böhmer and Iwanek both investigated the use of 1-cyclohexylethylamine and 1-(1-napthyl)ethylamine without observing the same diastereoselectivity as with α-methylbenzylamine. Böhmer extended this to para-substituted amines, *p*-methyl-α-methylbenzyl and *p*-bromo-α-methylbenzyl. These both gave the same diastereoselecivity as α-methylbenzylamine. The more rigid 1-aminoindane was also used, which gave a 60:40 mixture of diastereoisomers, and 1-amino-2-phenylpropane, where the stereocentre is one carbon further away, which gave a 60:40 mixture, **Figure 13**. The amine used clearly has an influence on the solubility difference between the two observed diastereoisomers.

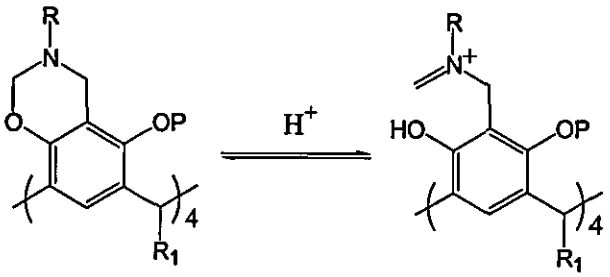


R-1-Aminoindane R-1-Amino-2-phenylpropane

Figure 13

1.4.1.7 Prevention of diastereoisomerisation

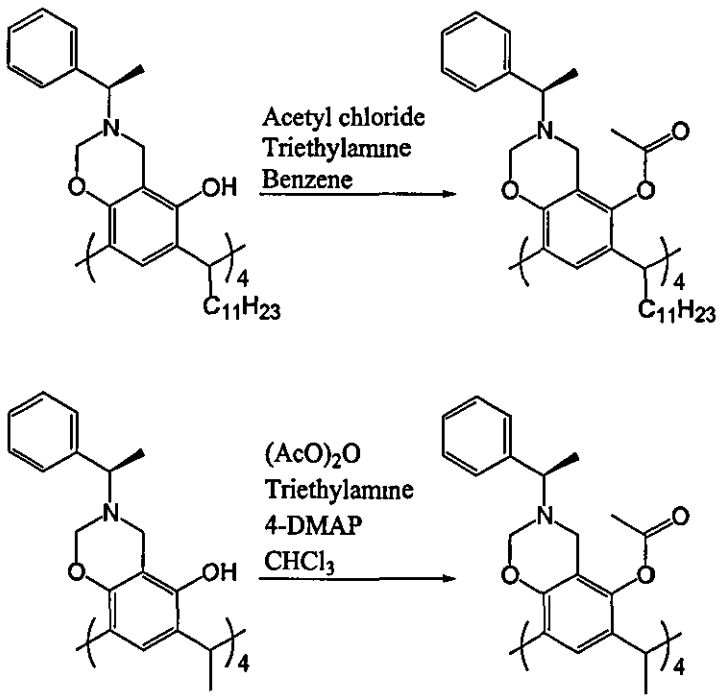
The observations made above of the acid catalysed diastereoisomerisation of tetra benzoxazine resorcinarenes, even in solvents with no added acid, would substantially hinder any further use of these compounds in synthesis. To preclude any diastereoisomerisation, attempts have been made at protection of the four remaining phenolic hydroxyl groups. Although the iminium ion intermediate can still form, ring closure is able to occur in only one direction, hence maintaining the chirality, **Scheme 21.**



R=S or R α-methylbenzyl

Scheme 21

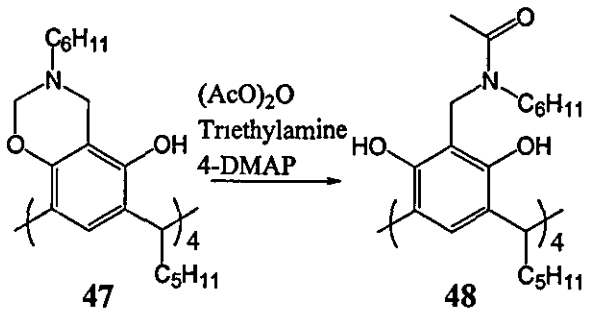
Böhmer[37] and Iwanek[38] have both reported the acetylation of these phenols following the methodology shown in **Scheme 22.**



Scheme 22

Members of the Loughborough group failed in their attempts to repeat these results. Böhmer and co-workers reported that no diastereoisomerisation occurred in the reaction and that the product was stable to acid. No experimental details were provided in the publication and the result was later retracted.[42] They did however isolate amide **48** in low yield from the reaction with resorcinarene **47, Scheme 23.**[42] This is comparable with the

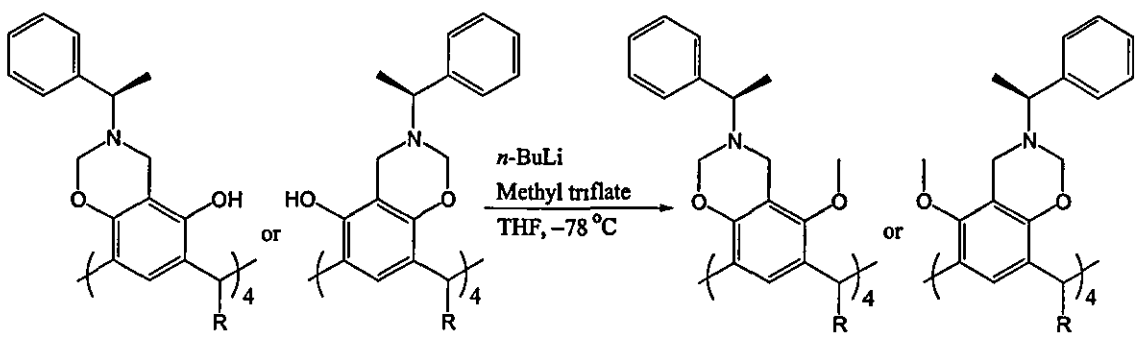
results seen for simple benzoxazines,[43] in which the more nucleophilic nitrogen atom (compared with oxygen) is acylated, with hydrolytic elimination of formaldehyde from the N/O acetal.



47 **48**

Scheme 23

The Loughborough group[40,41] focused on methylation of the free phenols with all other alkylations and acylations having failed, presumably because of high steric demands. All classical methodology that was tried had failed to give the tetra methyl ether, including diazomethane. Strong bases and very reactive methylating agents were tried. NaH and *n*-butyl lithium with methyl iodide both failed, with either resorcinarene starting material recovered or decomposition being observed. *n*-Butyl lithium with dimethyl sulphate as the methylating agent, at –78 °C gave 36% of the tetra methyl ether **49**. High yielding conditions were eventually established using *n*-butyl lithium and methyl trifluoromethanesulphonate in THF at –78 °C, **Scheme 24.**



R= $C_{11}H_{23}$ **44** R= $C_{11}H_{23}$ **44b** R= $C_{11}H_{23}$ **49** R= $C_{11}H_{23}$ **49b**

R=$Ph(CH_2)_2$ **45b** R=$Ph(CH_2)_2$ **50b**

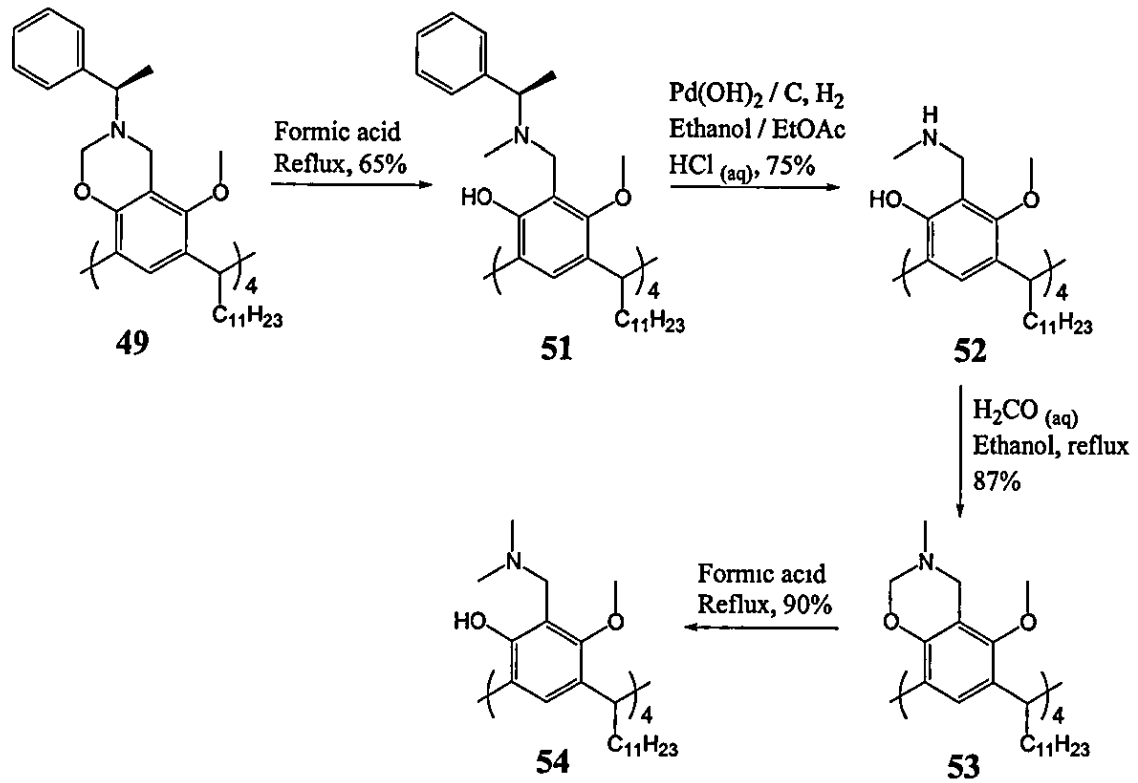
Scheme 24

Addition of the *n*-butyl lithium rapidly formed a tetra anion as a gelatinous precipitate that required vigorous stirring with a mechanical overhead stirrer to ensure thorough mixing. Addition of methyl triflate caused dissolution of this precipitate, furnishing the tetra ethers in yields between 75 and 87%. The importance of the low temperature was noted for the stability of the intermediate tetra anion. Decomposition and as a result a loss in yield was reported when the mixture was warmed to room temperature. The reaction was successfully scaled up to around 20 g of starting resorcinarene, while maintaining the high yield. NMR spectroscopy and chiral HPLC showed no diastereoisomerisation to have occurred under these reaction conditions. The chirality of each resorcinarene had successfully been 'locked,' so preventing any acid catalysed diastereoisomerisation.

1.4.1.8 Removal of the four chiral auxiliary groups

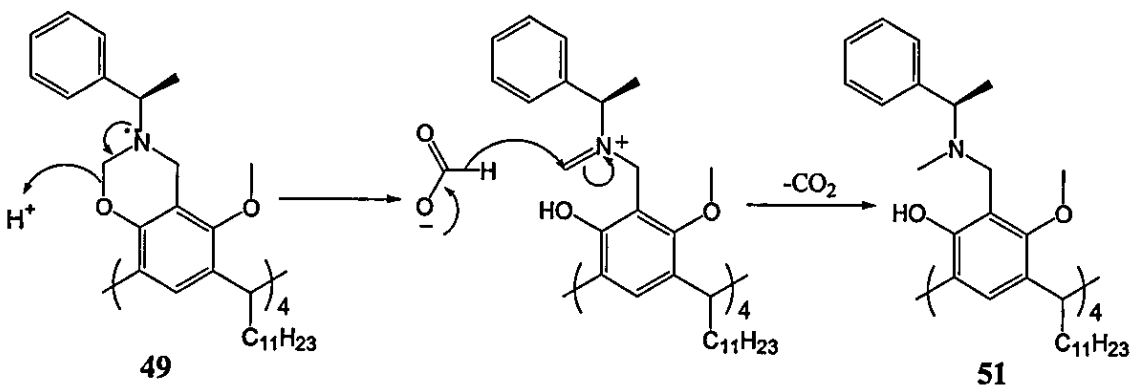
The success seen above in methylation of the four free phenol groups in **Scheme 24** installed a fixed axial chirality on the macrocycles. With this in place, focus turned towards removal of the four α-methylbenzyl chiral auxiliary groups.[40,41] With these removed the only chiral element in the macrocycle would be as a result of its shape, and can be regarded as inherent, axial chirality, and not due, in part at least, to asymmetric substituents. (The introduction of this type of chirality into a resorcinarene makes the carbons of the methine bridges into asymmetric centres, but this is not discussed in any publications.)

The methodology developed for the removal of the four α-methylbenzyl groups is shown in **Scheme 25.**



Scheme 25

The first step of **Scheme 25** is a modified Eschweiler-Clarke reaction. The method uses formic acid as reagent and solvent to perform a reductive ring opening reaction giving the *N*-methyl compound **51**, through the mechanism shown in **Scheme 26.**



Scheme 26

DIBAL or $LiAlH_4$ can also be used to carry out the same transformation in high yield.[41]

The specific configuration of these resorcinarenes changes on ring opening of the four benzoxazines. In compound **51**, and its enantiomer, the methoxy groups now take precedence over the phenolic groups and hence a change in the absolute configuration, following the rules established in **Section 1.4.1.4.** Compound **49** is defined as having absolute configuration R,R compared with S,R for **51**.

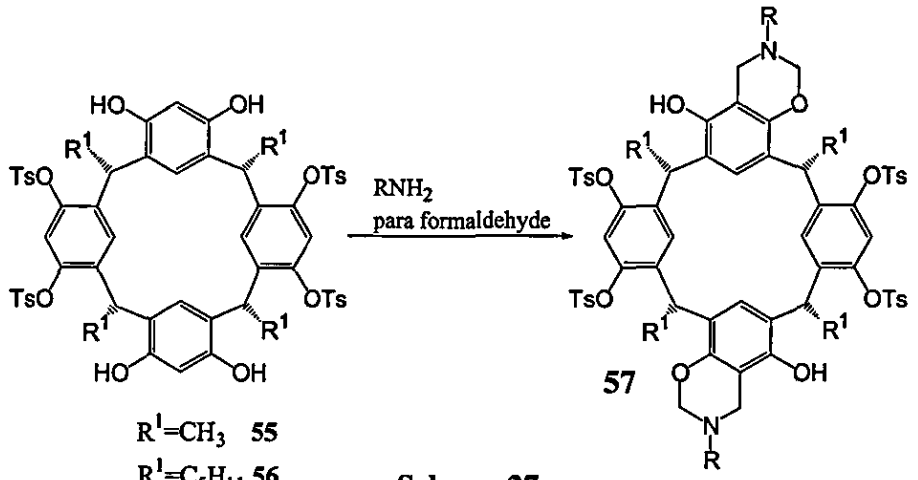
Removal of the *N*-benzyl groups was achieved using a $Pd(OH)_2$ / carbon catalyst in an hydrogenolysis reaction. Literature evidence suggests this is the best available catalyst for the removal of a benzyl group from a nitrogen atom.[44] Cleavage was seen exclusively at the N-$CH(CH_3)$ bonds, no cleavage of the N-CH_2 bonds was observed. The secondary amine **52** was not purified but reacted on with formaldehyde to form the tetra *N*-methyl benzoxazine compound **53**. Another reductive ring opening with formic acid furnished the tetra *N,N*-dimethylamino compound **54** in high yield. Analytical data showed this compound to be an enantiomerically pure resorcinarene.

Repeating the reaction scheme with the enantiomer of **49** gave the enantiomer of **54** in similar yields.

Compound **54** and its enantiomer were the synthetic targets of this research as they are examples of functionalised resorcinarenes that possess an inherent axial chirality. They also have the potential to be used as chiral ligands in asymmetric synthesis. The four *N,N*-dimethylamino groups and four free phenols could perform as ligating centres, thus making this kind of resorcinarene a potentially very effective multi-dentate ligand. The Loughborough group has performed some reactions using resorcinarenes, including **54**, as catalytic ligands in the asymmetric addition of diethylzinc to benzaldehyde.[41] Some promising enantiomeric excesses were obtained in the secondary alcohol product and are discussed in more detail in **Section 2.5.**

1.4.1.9 Introduction of chirality into distally protected resorcinarenes

Böhmer[45] and co-workers have combined two areas of the research discussed above, using tetra tosylates **55** and **56** in combination with various amines in Mannich reactions, **Scheme 27.**



R^1=CH_3 **55**
R^1=C_5H_{11} **56**

Scheme 27

There are two possible regioisomers for the bis benzoxazine products **57.** Chiral structure **A** consisting of two enantiomers, with a trans orientation of the two benzoxazine rings and a C_2 symmetry, or regioisomer **B**, with a cis orientation, possessing a mirror plane and C_S symmetry, **Figure 14.**

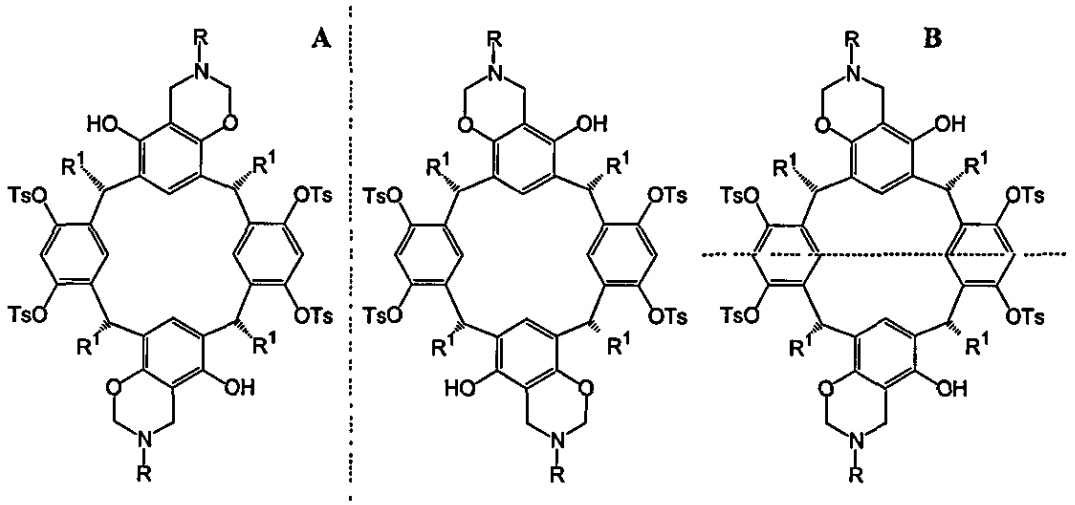


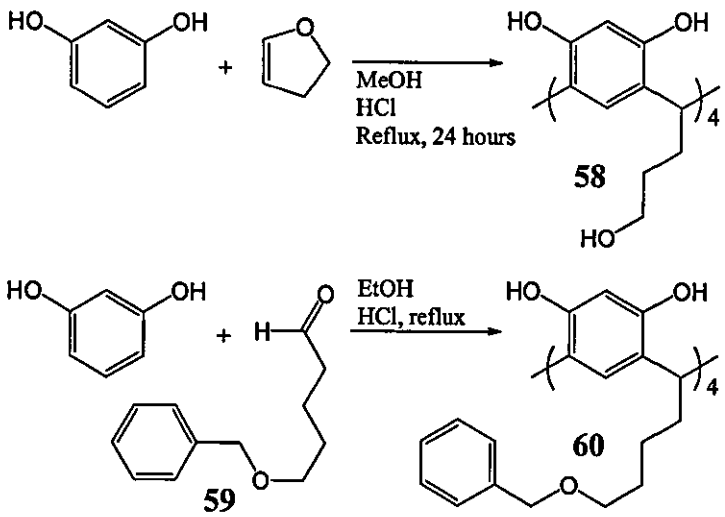
Figure 14

With achiral primary amines structure **A** was produced as a racemic mixture. ^{1}H NMR spectroscopy showed no evidence of structure **B**. When enantiomerically pure 1-cyclohexylethylamine was used, a 60:40 mixture of diastereoisomers with structure **A** was the outcome. No investigations with α-methylbenzylamine or attempts at separation of the two diastereoisomers were reported.

1.4.2 Lower rim functionalisation

A number of different functionalities have been incorporated into the lower rim of resorcinarenes by the use of different aldehydes, followed in some cases by further functional group manipulations.

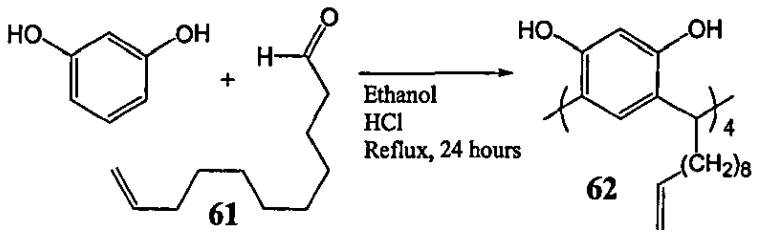
Resorcinarene **58** was formed in excellent yield by reacting resorcinol and 2,3-dihydrofuran, with a hydrochloric acid catalyst, **Scheme 28.**[4,46,47]



Scheme 28

Rebek *et al.*[47] formed resorcinarene **60**, using standard conditions, from 5-benzyloxypentanal **59** in reasonable yield, **Scheme 28.** They made use of resorcinarenes **58** and **60** to impart a large range of functionalities onto the lower rims of resorcinarene-based cavitands.

Resorcinarene **62** was formed in low yield from resorcinol and undec-10-enal **61**, **Scheme 29**.[48] The presence of the carbon-carbon double bond moieties on the lower rim allowed further manipulation,[49] including some selective derivatisation, where one of the alkyl chains has a different functionality from the other three.[50]



Scheme 29

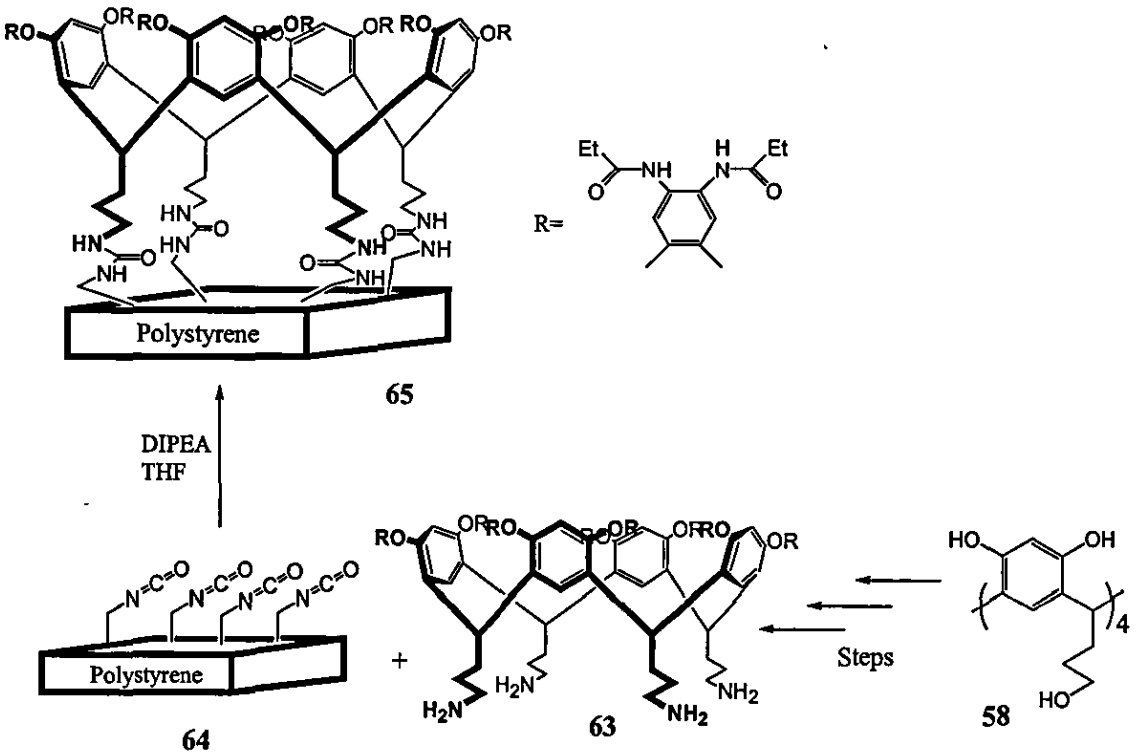
1.4.2.1 The use of lower rim functionality to immobilise resorcinarenes on polymer supports.

The immobilisation of organic molecules onto solid polymer supports is currently of interest to synthetic organic chemists. This is because of the potential for simple, safe and automated processes to be developed, improving the efficiency of a reaction compared with the equivalent solution phase conditions.[51] This research has included various host molecules involved in molecular recognition, namely cyclodextrins,[52] crown ethers,[53] porphyrins[54] and calix[n]arenes.[55] These host molecules have the potential to be used in both chromatographic separations and catalysis.

Only a small number of literature reports exist involving the isolation of resorcinarenes onto solid polymer supports.

Schurig[56] functionalised the upper rim of resorcinarene **62** with chiral amide groups by protection of each of the eight phenols. The resulting resorcinarene was then immobilised on a polymer support, through the ω-unsaturated alkyl chains of the lower rim, and incorporated into the stationary phase of a column for gas chromatography. Fifteen amino acids were successfully separated into their enantiomers. The column exhibited an excellent efficiency over 100 °C and thermal stability up to 200 °C.

Pietraszkiewicz[57] has also used resorcinarenes in chromatographic separations. The lipophilic, lower rim, alkyl chains of undecanal derived, octa hydroxy resorcinarene **41** are strongly adsorbed on the modified silica gel RP-18. This HPLC stationary phase efficiently separated uracil, thyamine, and cytosine.



Scheme 30

Rudkevich and Rebek[58] have attached a range of resorcinarene-based cavitands to various polymer supports, one example of which is **65**, shown in **Scheme 30**. Following a sequence of functional group transformation reactions on both the upper and lower rims of resorcinarene **58**[4,46,47] they formed the amine 'footed' cavitand **63**. The tetra amine was then treated with polymer bound isocyanate **64**[59] in a mixture of THF and Hünig's base. All four 'legs' of the resorcinarene molecules bonded to the polymer.

1.5 Resorcinarene complexes

Resorcinarenes, as with macrocyclic molecules in general, possess a distinct void within their structure, and a large range of functionalities on both the upper and lower rims. This gives them the potential to form complexes with ions and small molecules.

Most reports of complex formation involving resorcinarenes are of cavitands with extended cavities.[27a,58a,60] For example, Gibb[27b] has recently formed a range of such cavitands and investigated their hydrophobic binding properties with small molecules, as well as larger and more elaborate guests such as 1-iodoadamantane and bromocamphor.

Standard octa hydroxy resorcinarenes can be envisaged as tetradentate hosts. The eight phenolic hydroxyl groups form four independent hydrogen bonded binding sites, **Figure 15.**

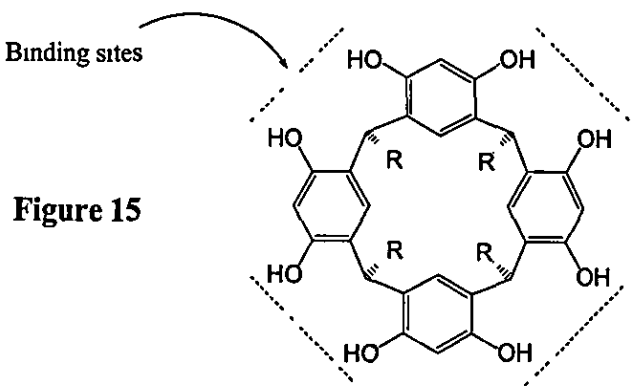
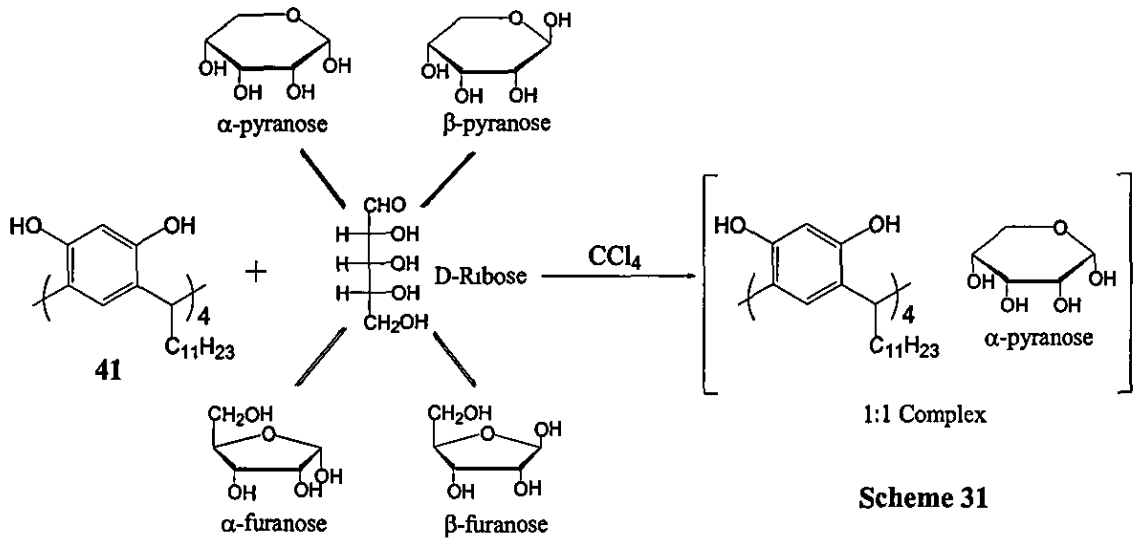


Figure 15

A number of polar organic molecules have been shown to bind to octa hydroxy resorcinarenes. Aoyama *et al.*[61] have investigated their interactions with polyols such as chiral glycols, steroidal polyols, amino acids and sugars. In some cases selectivity between guests was demonstrated.

D-ribose is an aldopentose that exists in two pyranose and two furanose forms and is insoluble in carbon tetrachloride. When an aqueous solution of D-ribose and a carbon tetrachloride solution of undecyl-resorcinarene **41** were stirred together, a 1:1 host : guest complexation between **41** and exclusively the α-pyranose form of D-ribose occurred, and the complex was extracted into the organic phase, **Scheme 31.**[62]



Scheme 31

Tetra aminomethylated resorcinarene **66** encapsulated a DCM molecule when crystallised from a DCM / acetone mixture, **Figure 16**.[63] This is a common feature of resorcinarene X-ray crystal structures, a number of different solvent molecules having been accommodated within the cavity.[4,9,36a]

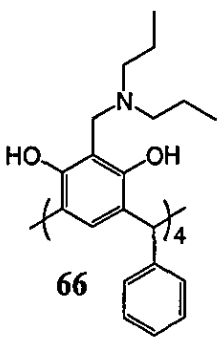


Figure 16

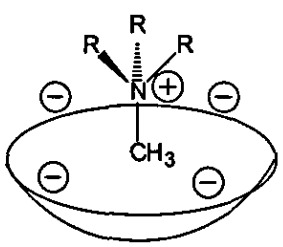


Figure 17

In the crystal structure, macrocycle **66** adopts a cavitand type structure because of the involvement of the upper rim amine groups in intramolecular hydrogen bonding.

The tetra anion of methyl resorcinarene **7 (page 16)** is readily formed in aqueous basic solutions and has been shown to bind methyl trialkylammonium cations with high

binding constants, surpassing those seen in biological systems, **Figure 17**.[22,64] Neutral resorcinarenes can also form complexes with alkylammonium cations.[65]

Chapter 2

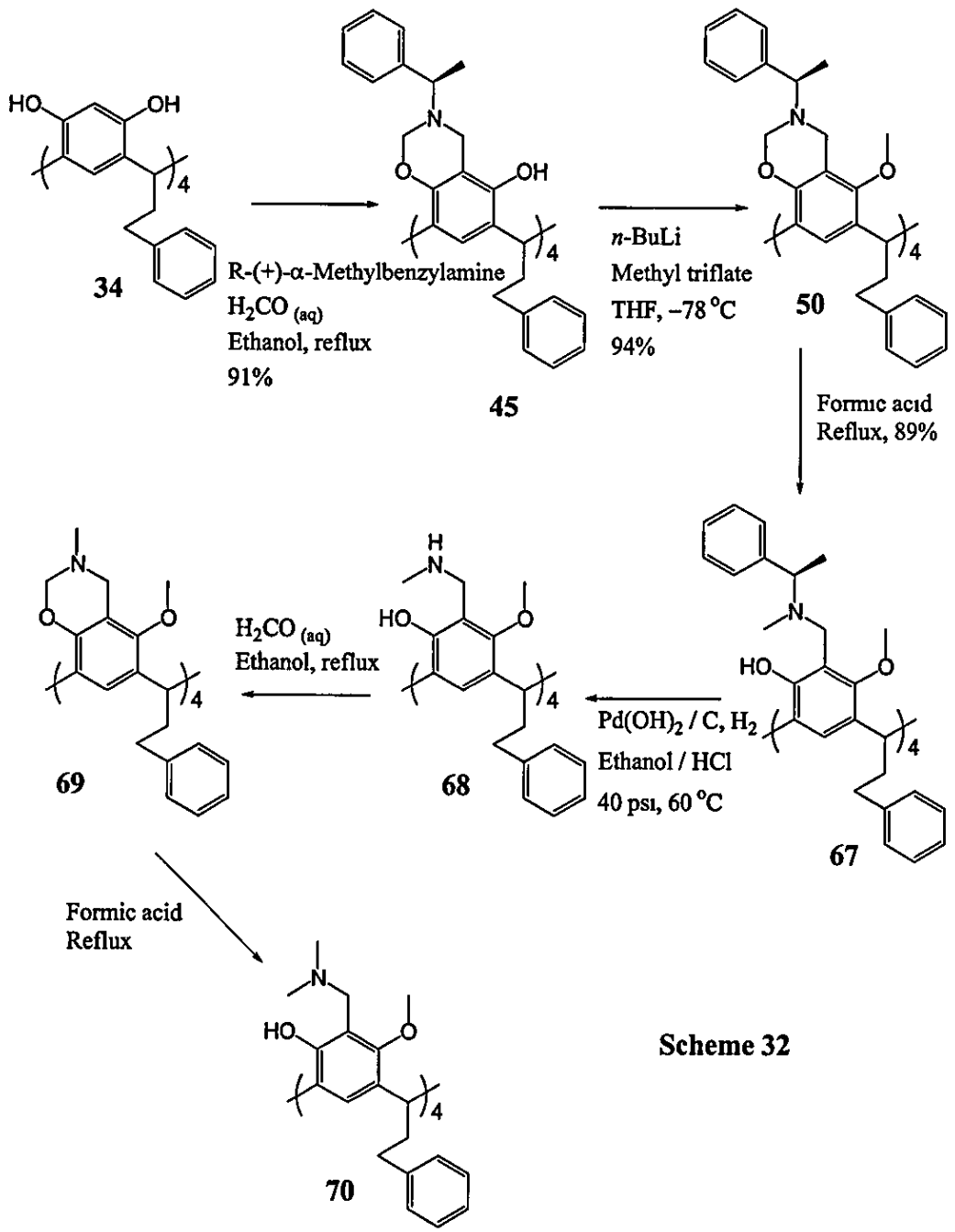
Results and discussion

Research objectives

In recent years the Loughborough group's main research focus has been the development of diastereomerically and enantiomerically pure resorcinarenes. The use of benzoxazine-forming Mannich reactions, using a chiral primary amine to introduce the chirality, followed by prevention of diastereoisomerisation and subsequent removal of the chiral auxiliary groups, is discussed in detail in **Chapter 1**. It was the aim of this project to further these investigations in order to produce a range of functionalised resorcinarenes that could potentially be used as ligands in asymmetric, catalytic reactions.

All resorcinarenes discussed in this chapter are believed to possess, initially at least, the crown conformation with an rccc configuration. Some references to all-cis boat isomers of newly functionalised resorcinarenes have been specifically identified.

2.1 Synthetic routes to inherently chiral, enantiomerically pure resorcinarenes of type 70.



Scheme 32

The methodology shown in **Scheme 32** was developed by previous members of our group.[36,40,41] It includes the introduction and maintenance of chirality into the

macrocycle as discussed above, **Section 1.4.1.2.** The same sequence can be repeated using S-(-)-α-methylbenzylamine giving the enantiomer of all of the compounds in the series.

Resorcinarenes of type **70** are synthetic targets because of their potential as chiral, multi-dentate ligands in asymmetric synthesis, utilising their axial chirality, four tertiary amine moieties and four free phenolic groups.

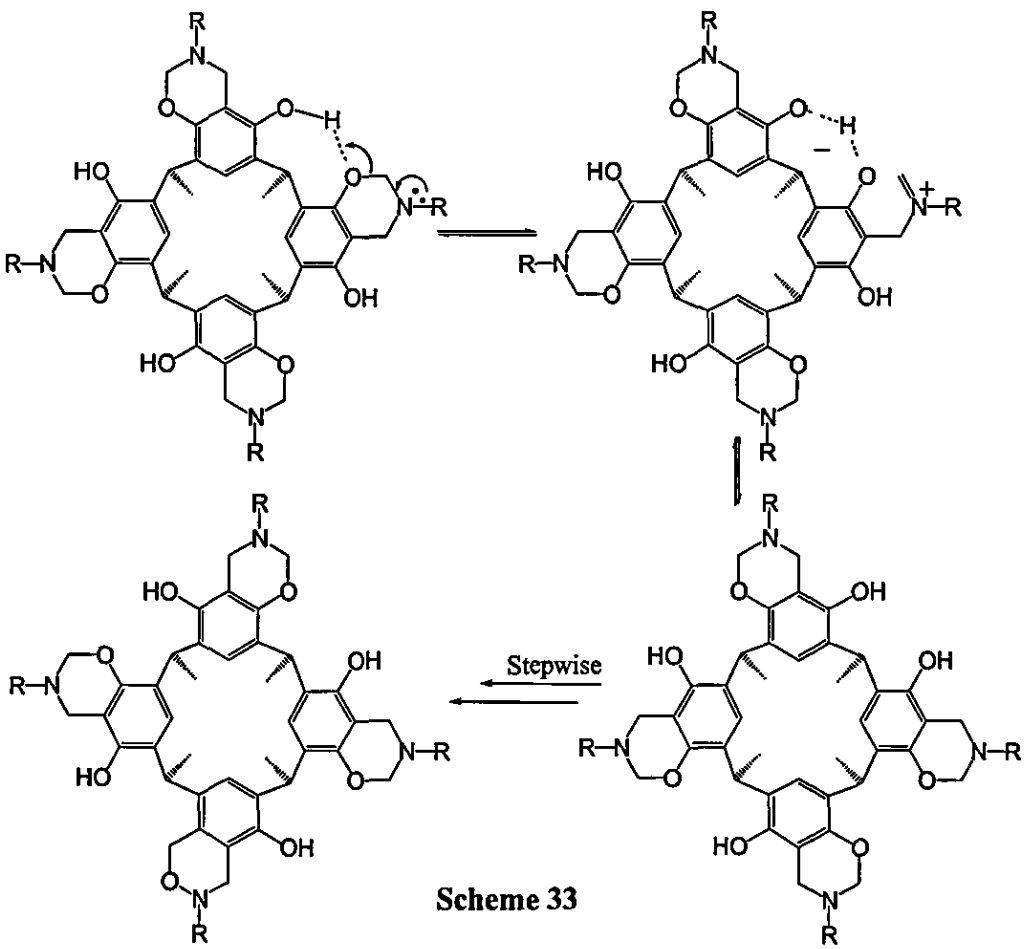
The chemistry shown in **Scheme 32** was established using resorcinarene **41** derived from dodecanal.[4] The chemistry was successfully developed using this resorcinarene but the macrocycles produced in most cases were in the form of a very viscous oil, which made handling difficult. By changing the parent resorcinarene it was hoped that more manageable, crystalline products would be obtained.

The resorcinarene chosen was **34**, formed from dihydrocinnamaldehyde. This had been used before within our group to produce the tetra benzoxazine derivative **45**[4,36,40,41] and by Matsushita in Mannich reactions.[32b] With long, bulky chains making up the lower rim it would also prevent any thermal isomerisation caused by through the annulus rotation, so maintaining the chirality, **Section 1.2.1.** Resorcinarene **34** was formed at best in around 50% yield after recrystallisation. In order to obtain this yield, purification of the aldehyde by Kügelrohr distillation was required before use. The literature precedent for this reaction suggests that higher yields are attainable.[4]

Formation of tetra benzoxazine **45** using aqueous formaldehyde and α-methylbenzylamine occurred in every case in high yield with excellent diastereoselectivity. Of all the slight variations in methodology discussed in **Section 1.4.1.2,** the most simple was chosen: five equivalents of amine and ten equivalents of aqueous formaldehyde were heated at reflux in ethanol. The precipitate formed in the reaction was shown to be the desired compound and at no time was evidence for the other C_4 symmetric diastereoisomer seen in the initial ^{1}H NMR spectrum (**Section 1.4.1.4**).

There was no need for recrystallisation, with the product remaining stable as a solid at room temperature for long periods.[40,41]

The other C_4 symmetric diastereoisomer of **45** was seen by NMR spectroscopy after standing in $CDCl_3$ for prolonged periods, even when the chloroform was passed through a pad of $NaHCO_3$ beforehand, to minimise any trace acids in the chloroform.[36] This may suggest that in solution the stepwise diastereoisomerisation can occur through the intramolecular hydrogen bonds, being promoted by the steric hindrance between adjacent benzoxazine groups, and the re-formation of a maximum hydrogen bonding arrangement, **Scheme 33**. A ratio of approximately 2:1 was observed, in accordance with the results reported previously in **Section 1.4.1.5.**

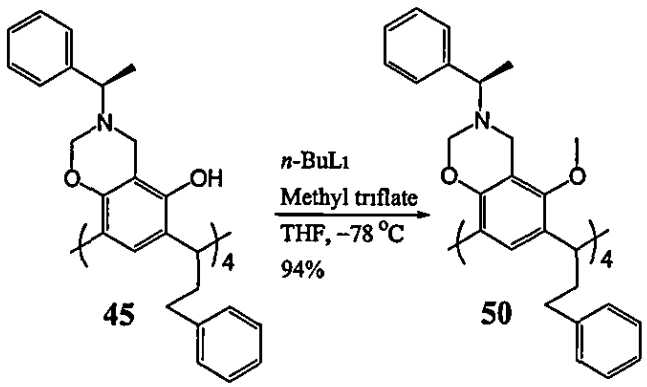


Scheme 33

The methylation of the four remaining free phenolic hydroxyl groups to give **50** (to prevent any acid catalysed diastereoisomerisation through an iminium ion intermediate,

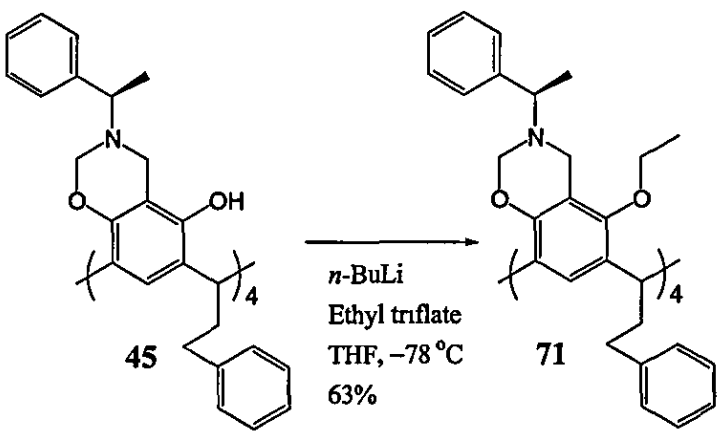
page 34) was carried out in yields of up to 94%, using *n*-BuLi and methyl triflate, on multi-gram scales, **Scheme 32a.**

Scheme 32a



Achieving a high yield is dependent on the dryness of the substrate, the dryness of the solvent and efficient vigorous stirring throughout the reaction, particularly as the proposed tetra anion intermediate is forming.

The same reaction protocol was applied to **45** using ethyl triflate **(Scheme 34)**, forming tetra ethyloxy derivative **71** in a reduced but reasonable yield.

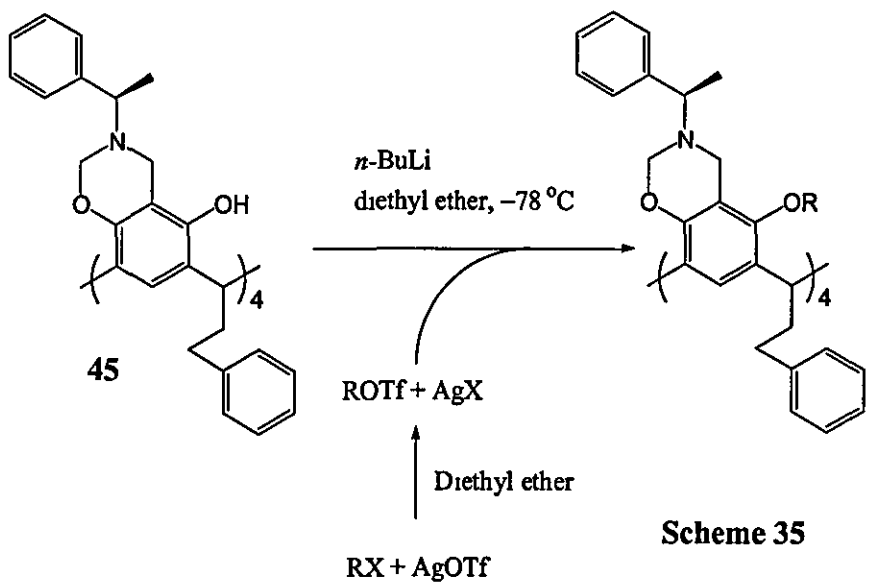


Scheme 34

The lower yield could perhaps be attributed to the increased steric bulk of the ethyl groups, over methyl, but no optimisation was attempted with this reaction. Methylation

until this point had been the only possibility for protection of the four remaining hydroxyl groups. All other standard methods failed.

The success achieved with the established procedure above led to some attempts at synthesising alkyl triflates,[66] notably allyl and *i*-propyl, **Scheme 35**. Allyl was chosen because of a low steric bulk and the inclusion of a carbon-carbon double bond functionality, available for further transformations. Isopropyl was chosen to investigate if a bulkier, more sterically demanding group could be accommodated.
In a reaction with silver triflate and an alkyl halide, the precipitation of a stable silver halide salt, in anhydrous diethyl ether, would promote formation of the desired alkyl triflate. The addition of this ethereal solution to the tetra anion of **45** failed to produce the desired tetra ether, giving a mixture of compounds that defied characterisation. It was unclear if any partial reactions had taken place or if degradation was the only result.



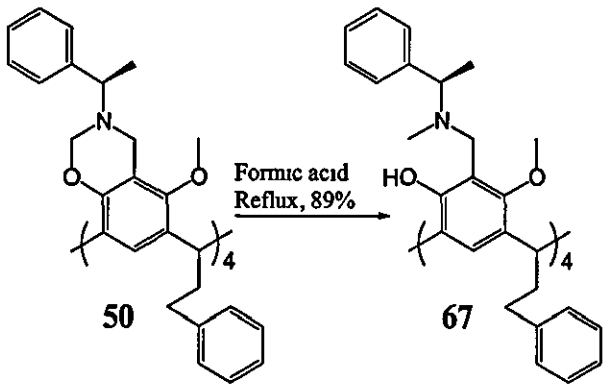
Scheme 35

These reactions were also attempted in THF with consideration of solubilities at –78 °C in mind. This resulted in the polymerisation of the THF, presumably by traces of triflic acid being formed. Forming methyl triflate by this method may show whether or not the alkyl triflate actually formed, or if a higher reaction temperature is needed with a bulkier

alkyl group. Sampler reported the importance of low temperature with the tetra methylation reaction in order to obtain a high yield.[41]

With the chirality of the resorcinarene now 'locked,' the remainder of the chemistry shown in **Scheme 32** was aimed towards removal of the α-methylbenzyl chiral auxiliary groups. After removal of these groups, the only chiral element remaining in these molecules is not due, in part at least, to the presence of asymmetric substituents containing differentially substituted sp^3 centres, but because of their 'inherent' axial chirality.

Scheme 32b

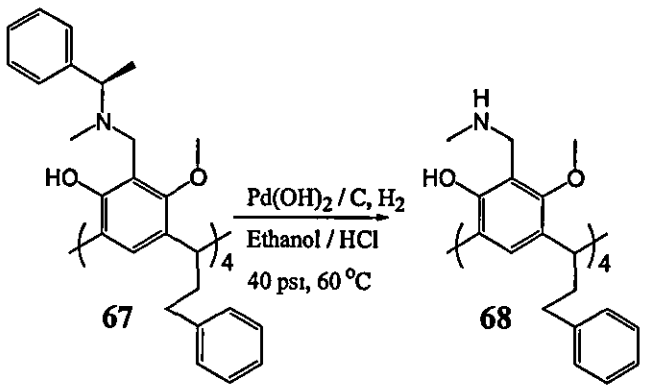


50 **67**

The formic acid reductive ring opening protocol (**page 36**) to give **67** proved very reliable and high yielding on multi-gram scales, **Scheme 32b.**

The hydrogenolysis step to remove the four α-methylbenzyl groups of **67** to give **68** proved very difficult to repeat following the conditions previously reported.[40]
This reaction, even on milligram scales, either failed or was at best very slow, taking a number of weeks to complete under a hydrogen balloon. Other members of the group have since developed new conditions using the same $Pd(OH)_2$ / carbon catalyst under a pressure of 40 psi and temperature of 60 °C in ethanol, with HCl present to aid solubility, **Scheme 32c.**

Scheme 32c



The best yields obtained were in the region of 75%, but they proved to be variable. An important factor seemed to be the quality of the catalyst used. $Pd(OH)_2$ / carbon was always the catalyst of choice, following literature precedent,[40,44] but different bottles from different manufacturers gave different yields. Further work is needed on this step to make an otherwise high yielding, highly repeatable reaction scheme a simple route to chiral resorcinarenes of type **70**.

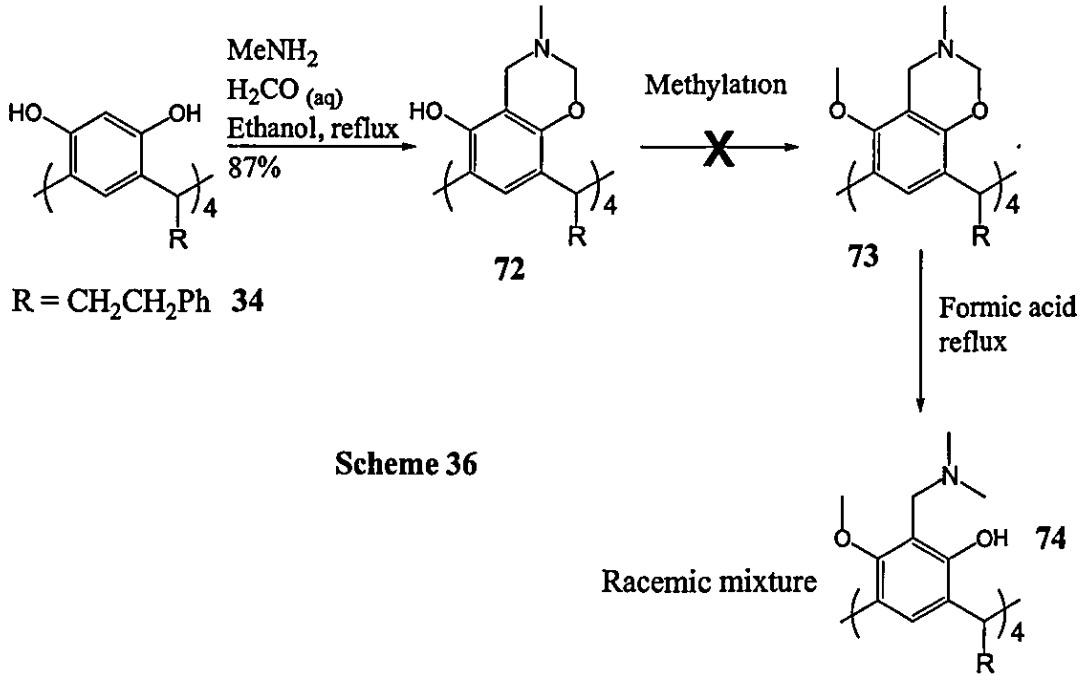
2.1.1 Further manipulation of resorcinarene 70

Although a tertiary amine group is potentially a very effective ligating center in complexation reactions, further functional group transformations may be difficult to carry out. Two main approaches to the replacement of the four *N,N*-dimethylamino groups of **70** were made. Each was aimed at substitution by a different functional group that could be more easily manipulated, notably a halogen atom or a cyano group. The envisaged first step of each method was the conversion of each tertiary amine into a better leaving group by quaternisation of the nitrogen atoms followed by reaction with a nucleophile.

2.1.2 Production of a racemic model version of 70

Following the problems encountered above with the hydrogenolysis step, to remove the α-methylbenzyl groups of **67**, the production of a racemic model version of **70** seemed important and straightforward. The proposed route to this compound is shown in **Scheme 36.**

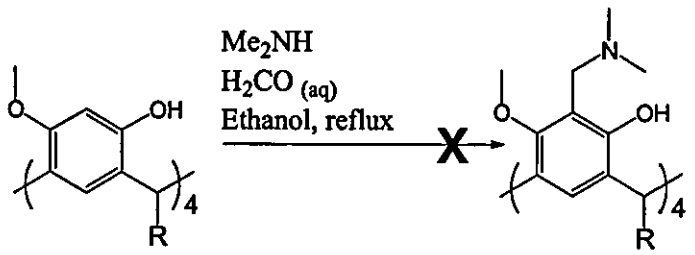
The tetra benzoxazine forming step worked well, giving **72** as expected, with this type of reaction now well documented. The methylation step to give **73** however failed. All manner of conditions were attempted, including the *n*-BuLi methyl triflate method, as well as many more standard procedures. In each case a complex mixture of compounds formed as a gum that was insoluble in common organic solvents, and defied characterisation.



Scheme 36

Seemingly, despite deprotonation of the phenols, methylation was occurring on the more nucleophilic nitrogen atoms (consistent with benzoxazines[43]) followed by a number of secondary reactions resulting in degradation. The methylation of the nitrogen atoms was seen here and not in the enantiomerically pure, chiral series (**Scheme 32**) presumably because of the steric hindrance of the bulky α-methylbenzyl groups.

Mocerino[12] has recently used the Lewis acid $BF_3.OEt_2$ to develop a route towards axially chiral, tetra alkyloxy resorcinarenes (**Scheme 7, page 11**) as racemic mixtures. Using these compounds in a Mannich reaction with dimethylamine and formaldehyde, a route of just two steps towards **74** could be envisaged, **Scheme 37.**



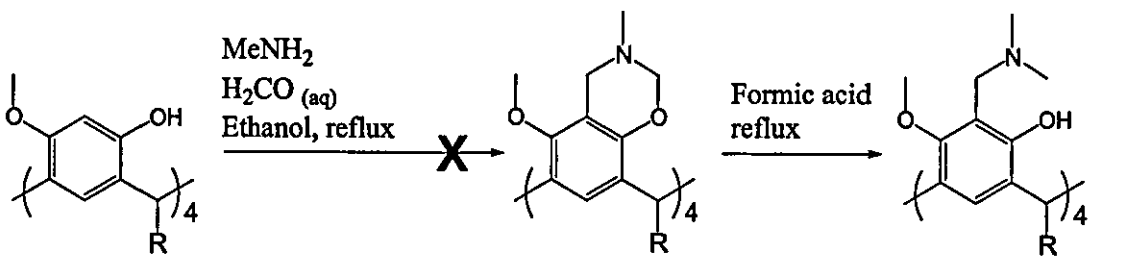
R = CH_2CH_2Ph **75**
R = C_5H_{11} **76**

R = CH_2CH_2Ph **74**
R = C_5H_{11} **77**

Scheme 37

Mocerino's reaction conditions were used to form new tetra methoxy resorcinarenes **75** and **76** from 3-methoxyphenol with dihydrocinnamaldehyde and hexanal. These reactions are discussed in more detail in **Section 2.3.**

All the classical Mannich reaction conditions employed failed to give the desired product. A three-step route through the tetra benzoxazine, followed by a reductive ring opening reaction also failed, **Scheme 38.**



R = CH_2CH_2Ph **75**
R = C_5H_{11} **76**

R = CH_2CH_2Ph **73**
R = C_5H_{11} **78**

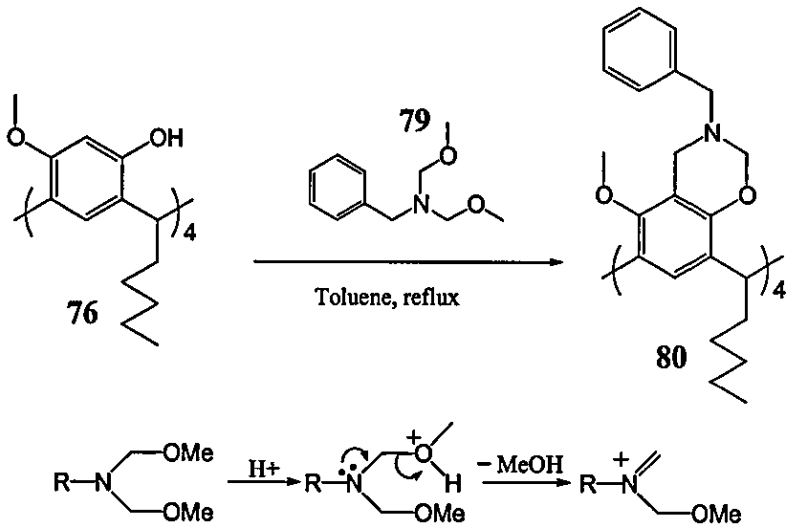
R = CH_2CH_2Ph **74**
R = C_5H_{11} **77**

Scheme 38

Eventually reaction conditions were developed using the route shown in **Scheme 39,** which utilised a preformed bis(aminol ether) **79** as an iminium ion precursor.[67] The reactive, electrophilic species in these Mannich reactions is thought to contain an

iminium ion. The iminium ion is formed following protonation of one of the two oxygen atoms of the bis(aminol ether), **Scheme 39**.

Bis(aminol ethers) are formed from a primary amine, formaldehyde and an alcohol, in this case methanol.



Scheme 39

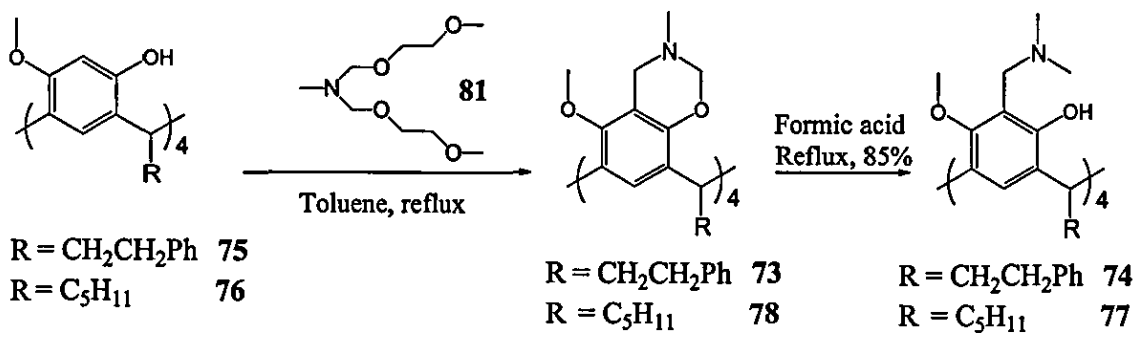
The chemistry of bis(aminol ethers) in Mannich reactions has been investigated within our group, including their use with resorcinarenes, and is discussed in detail in **Section 2.4.1**.[40,41]

With an octa hydroxy resorcinarene, these reactions proceed in ethanol at room temperature.[41] Using the same reaction conditions with tetra methoxy resorcinarene **76** failed to produce the desired tetra benzoxazine product **80**, and unreacted resorcinarene was recovered. Heating the reaction at reflux in ethanol also failed. The conditions required to achieve reaction were heating at reflux in toluene, giving **80** in around 75% yield, although the reaction was slow, requiring several days for multi-gram reactions.

The most acidic proton source present in this reaction, required to form the iminium ion from the bis(aminol ether), is the phenolic hydroxyl groups. It remained unclear at this stage as to whether the required temperature increase and long reaction time was due to the lower acidity of the tetra methoxy resorcinarene and / or to a reduction in reactivity

towards electrophiles of the aromatic 2-positions, compared with octa hydroxy resorcinarenes.

The reaction was developed using the bis(aminol ether) **79** derived from benzylamine. In order to form a racemic version of **70**, a bis(aminol ether) from methylamine was produced. A longer chain alcohol was required due to the volatility of the products when either methanol or ethanol was used. 2-Methoxyethanol was chosen simply because of a ready supply, but other similar length chain alcohols would no doubt produce equivalent results. The Mannich reaction was repeated with this new bis(aminol ether) **81**, giving **73** and **78**, both in around 75% yield in a similar time to that required for the benzyl version, **Scheme 40**.



R = CH_2CH_2Ph **75**
R = C_5H_{11} **76**

R = CH_2CH_2Ph **73**
R = C_5H_{11} **78**

R = CH_2CH_2Ph **74**
R = C_5H_{11} **77**

Scheme 40

A route to **74** and **77** was now available in just three steps. The formic acid reductive ring opening of the four benzoxazine rings of **78** gave **77** in high yield, on a multi-gram scale.

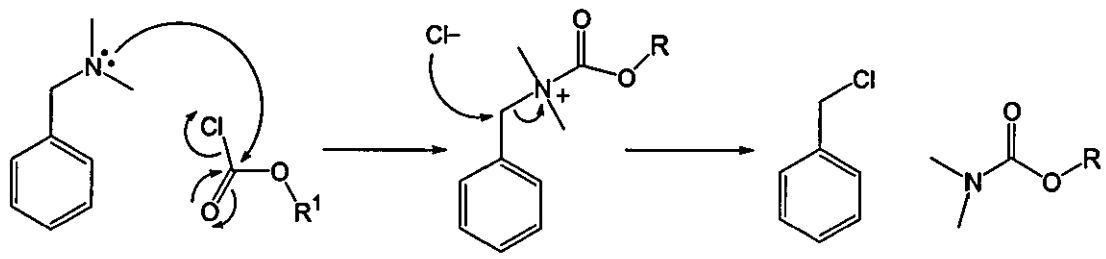
It should be noted that, despite the long reaction times, these Mannich reactions can be carried out open to the air and without any prior need for careful purification of the solvent or the bis(aminol ether), with no apparent reduction in yield.

Further investigations into the formation and use of bis(aminol ethers) with tetra alkyloxy resorcinarenes and the development of the reaction conditions are discussed in more detail later in this chapter **(Section 2.4)**.

2.1.3 Substitution of the NMe_2 groups of 77

2.1.3.1 Use of chloroformates

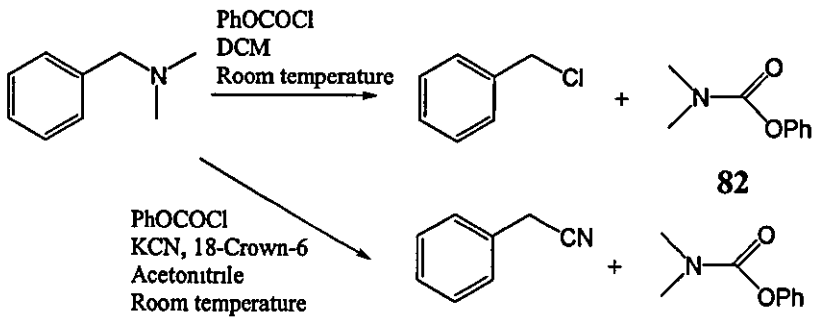
The use of alkyl and aryl chloroformates to functionalise a benzyl group of a tertiary amine has been employed by a number of scientists.[68] The reaction involves the formation of an intermediate carbamate salt followed by nucleophilic substitution as shown in **Scheme 41.**



Scheme 41

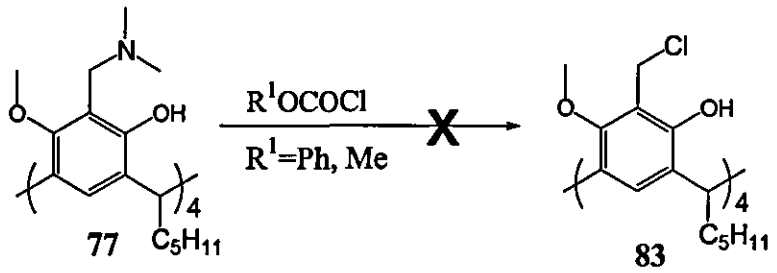
This reaction is generally envisaged as following an S_N2 reaction pathway. (Malpass[68a] suggested that some S_N1 character is evident when the benzylic group has a para-methoxy substituent, which increases the stability of the benzyl carbocation formed.)

A model study using *N,N*-dimethylbenzylamine with phenylchloroformate in DCM at room temperature produced benzyl chloride overnight in good yield, **Scheme 42.** Addition of potassium cyanide and 10 mol% of the phase transfer catalyst 18-crown-6[69] in acetonitrile produced benzyl cyanide in good yield, **Scheme 42.**



Scheme 42

This methodology was applied to resorcinarene **77** using both phenyl and methyl chloroformates, **Scheme 43.**



Scheme 43

The methodology recorded in **Table 1** failed to give the desired tetra chloro resorcinarene product **83.** A mixture of compounds was formed that defied characterisation. The formation of *N,N*-dimethylcarbamate **82** was, however, evident (also the equivalent carbamate when methyl chloroformate was used), with the two distinctive *N*-methyl peaks clearly evident in the ^{1}H NMR spectrum. The nature of the secondary reactions that were taking place to cause degradation remains unclear.

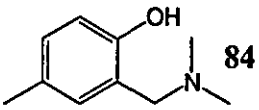
Use of resorcinarenes **50** and **67 (entries 4** and **5),** with the α-methylbenzyl groups still present, also failed to give the desired tetra chloro resorcinarene products.

Use of potassium cyanide with 18-crown-6 present, as a more nucleophilic reagent, failed to give the equivalent tetra cyano product, **entry 6.**

Table 1

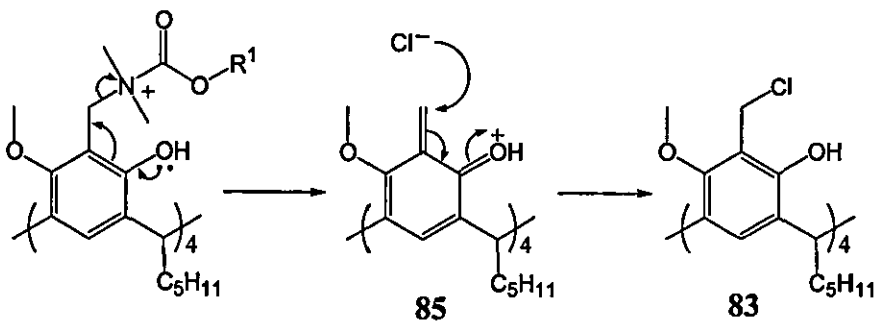
	Resorcinarene	Chloroformate	Solvent	Temp.	KCN /18-crown-6	Yield
1	**77**	phenyl	DCM	r/t	-	mixture
2	**77**	methyl	DCM	r/t	-	mixture
3	**77**	phenyl	DCM	–78°C to r/t	-	mixture
4	**67**	phenyl	DCM	r/t	-	mixture
5	**50**	phenyl	DCM	r/t	-	mixture
6	**77**	phenyl	acetonitrile	r/t	excess KCN, 10 mol% 18-crown-6	mixture

Some investigations into the 'Retro-Mannich' reaction, to replace the NMe_2 group of **84** (made from *p*-cresol, dimethylamine and formaldehyde) with another tertiary amine, have been carried out within the group.[41] The conclusion was that, due to the presence of the ortho-hydroxy group, these kinds of reactions may pass through an intermediate ortho-quinone methide **85**, and hence an S_N1, Michael type addition mechanism, **Scheme 44.**



84

Scheme 44



85 **83**

This would explain the formation of carbamate **82**, seen in the ^1H NMR spectrum, with the resulting intermediate ortho-quinone methide perhaps too unstable and degrading. Performing the reaction at low temperature **(Table 1, entry 3)**, to help stabilise any intermediate formed, gave the same outcome.

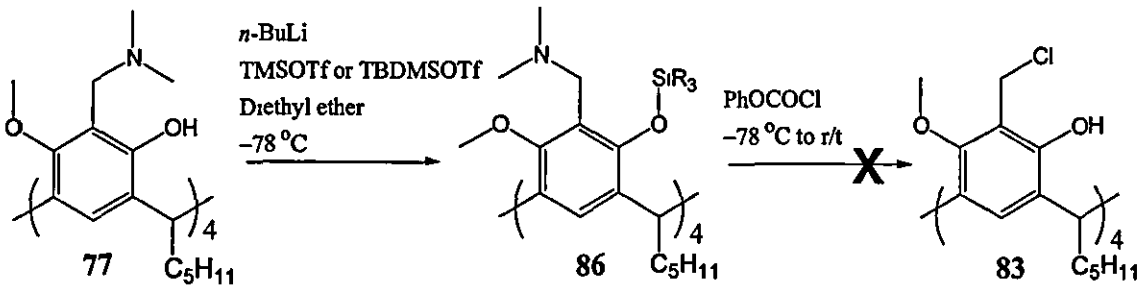
We envisaged the reaction as a stepwise process. Each of the four resorcinol-based units of the resorcinarene would react individually, as opposed to the formation of a tetra ortho-quinone methide intermediate.

It was reasoned that the success seen with *N,N*-dimethylbenzylamine would be repeated here following the protection of the free phenolic hydroxyl groups of **77**, to reduce the potential formation of an ortho-quinone methide intermediate and promote an S_N2 type reaction pathway.

All attempts at alkylation and acetylation of the phenols of resorcinarene **77** failed using a number of standard procedures. This was presumably due to alkylation or acetylation of the nitrogen atoms followed by degradation reactions, as seen previously (**Scheme 36**). Other members of the group have successfully protected the four free phenol groups of tetra methoxy resorcinarene **76** as benzyl and allyl ethers in high yields, using classical conditions (K_2CO_3, alkyl halide, acetonitrile, heated at reflux overnight). This supports the argument that the presence of the tertiary nitrogen groups of **77** interfere with these protection reactions.

Silylation, because of the oxophilicity of silicon, was tried several times using standard procedures as well as the formation of a tetra anion intermediate with *n*-butyl lithium (**Scheme 45**). Addition of either TMS or TBDMS triflate to the tetra anion intermediate caused dissolution of the anion, as observed with the methylation of **45** (**Scheme 32**). Isolation of **86** was never achieved, with starting material recovered in each case. If the tetra silylated product **27** had formed it seemed to be readily hydrolysed on work up, but at least no degradation had been observed.

A one-pot reaction was tried, in which the tetra silylated compound **86** was not isolated before the addition of phenylchloroformate, **Scheme 45**.



Scheme 45

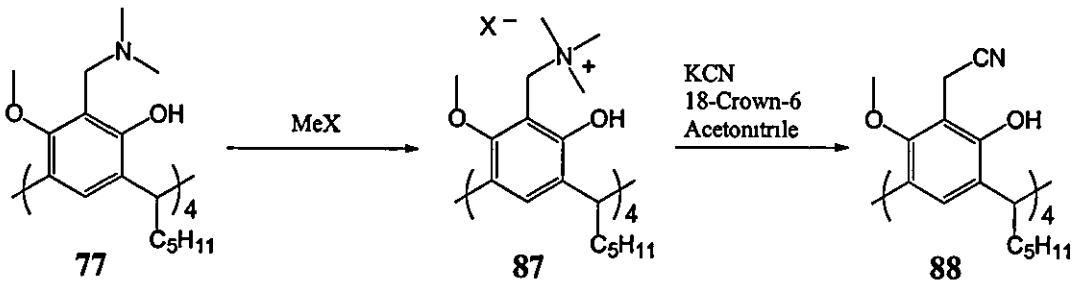
No evidence was seen for the tetra chloro resorcinarene product **83**, only a mixture of products that defied characterisation.

It would appear that substitution of the NMe_2 groups in **77** was being prevented by the presence of the free ortho-phenolic hydroxyl groups. Unfortunately, protection of these phenols appeared to be hindered by the presence of the same nitrogen moieties.

All attempts made at alkyl and acetyl protection of the four phenols in **67**, with the α-methylbenzyl groups still present, also failed, leaving starting material or producing an unidentifiable mixture of compounds. This was presumably due to steric hindrance. If protection of **67** could be achieved and the chloroformate reaction made to work it would serve as a variation to **Scheme 32**, and avoid the difficult hydrogenolysis step.

2.1.3.2 *N*-Methylation

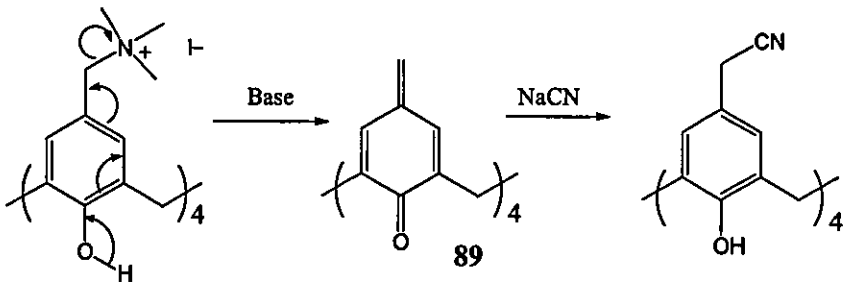
This approach also focused on quaternisation of the nitrogen groups in **77** but by *N*-methylation, **Scheme 46**.



77 **87** **88**

Scheme 46

The mechanistic explanation of this reaction sequence is probably the same as that seen with a chloroformate mediated substitution. There is also literature evidence that these kind of resorcinarene tetra cations, once formed, are stable and can be isolated.[70] It can again be envisaged that this reaction could pass through an ortho-quinone methide, and this is supported by the evidence of Gutsche,[71] who suggested that the reaction shown in **Scheme 47**, involving a calix[4]arene, occurs *via* para-quinone methide **89** in good to excellent yield.



Scheme 47

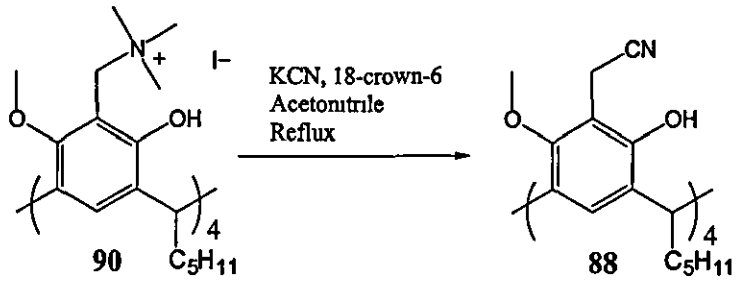
Formation of tetra quaternary ammonium salt **87** was attempted under the various conditions shown in **Table 2.**

Table 2

	Methylating agent	Solvent	Temp.	Yield
1	MeI	acetonitrile	r/t	mixture
2	$(MeO)_2SO_2$	acetonitrile	r/t	mixture
3	MeI	ethanol	reflux	mixture
4	MeI	-	r/t	unclear

For **entries 1-3**, ^{1}H NMR spectroscopy showed that a complicated mixture of products had formed which defied characterisation.

Entry 4 was carried out with methyl iodide as both a reagent and solvent. A white precipitate was formed which, following isolation, gave a ^{1}H NMR spectrum in d_6-DMSO (due to its insolubility in chloroform). Formation of **90** was never established, but the spectrum suggested a reaction had occurred without degradation. Perhaps the resorcinarene had been partly methylated. The reaction was repeated and, following removal of the excess methyl iodide, the residue was dissolved in acetonitrile and potassium cyanide added along with a catalytic amount of 18-crown-6, **Scheme 48.** The assumption was made that the tetra quaternary ammonium species **90** had been formed.



Scheme 48

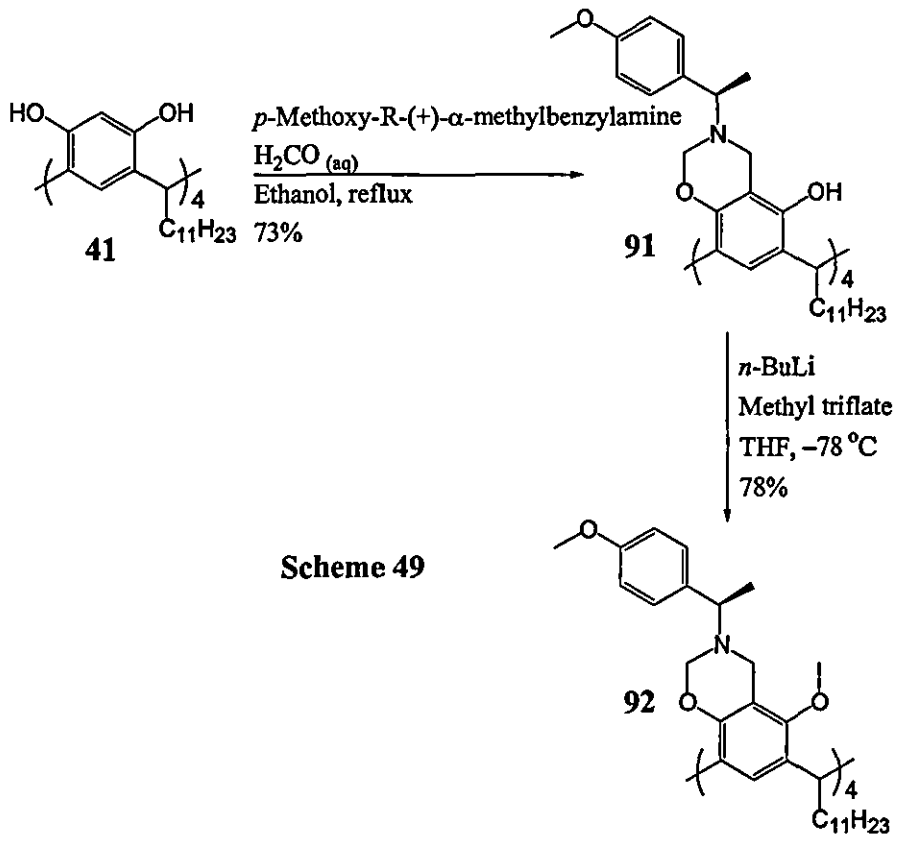
The result of the reaction with cyanide was, however, unclear. The ^{1}H NMR spectrum of the crude reaction mixture suggested that perhaps a partial reaction had taken place with a significant decrease in size of the *N*-methyl peak of **77**, a downfield shift of what appeared to be the *O*-methyl peak and a downfield shift of the four aromatic protons. The infrared spectrum also showed a significant peak at 2252 cm^{-1} that could be evidence for the presence of a nitrile group. Compound **88** was never isolated.
This methodology merits further investigation. Some slight changes in reaction conditions may give the desired tetra cation species **90** followed by substitution with cyanide.

2.1.4 Use of *p*-methoxy-α-methylbenzylamine in the formation of enantiomerically pure resorcinarenes

The use of enantiomerically pure α-methylbenzylamines to form axially chiral diastereomerically and enantiomerically pure resorcinarenes has been discussed in detail. Böhmer[39] extended his studies to include the use of *p*-methyl-α-methylbenzylamine and *p*-bromo-α-methylbenzylamine. Both of these amines gave the same high diastereoselectivities that were seen in the products when using α-methylbenzylamine. Our use of commercially available, enantiomerically pure *p*-methoxy-R-(+)-α-methylbenzylamine with aqueous formaldehyde and undecyl-resorcinarene **41** gave the diastereomerically pure product **91** in good yield, **Scheme 49**. Product **91** was isolated by filtration following its precipitation from the reaction mixture. This *p*-methoxy equivalent is thought to have formed with high diastereoisomeric purity because of its

lower solubility in the reaction mixture, compared with the other possible C_4 symmetric diastereoisomer, as discussed above in **Section 1.4.1.6.**

The chirality of the macrocycle was then subsequently locked by formation of the tetra methyl ether **92** in good yield following the established methodology.



Scheme 49

2.1.5 Conclusions and future work

A previously established synthetic route towards enantiomerically pure resorcinarenes has been extended to include a new parent resorcinarene, making the handling more simple. The sound methodology has been easily followed except for the hydrogenolysis of **67** that requires further optimisation.

A new method for carrying out Mannich reactions on tetra methoxy resorcinarenes has been established using preformed bis(aminol ethers) as iminium ion precursors.

Substitution of the tertiary amine groups of **77** was not achieved but further investigations, in light of the research already carried out, should see success for this desirable transformation.

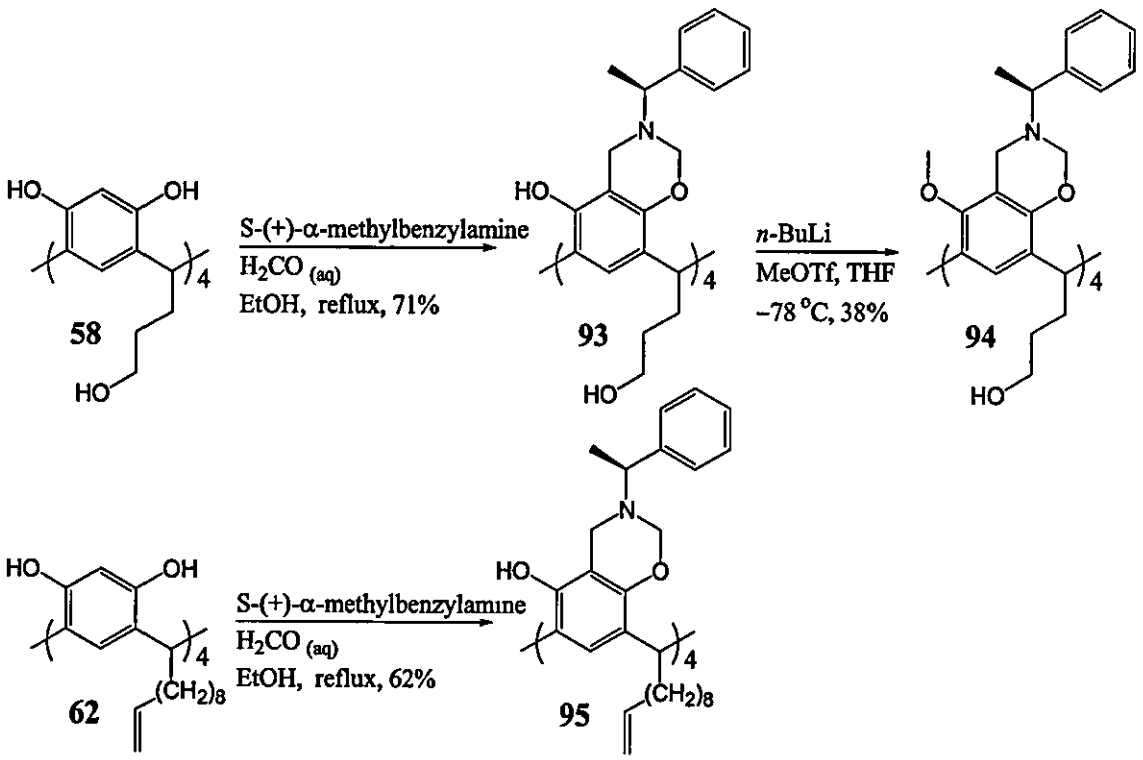
A tetra benzoxazine product **92** from *p*-methoxy-α-methylbenzylamine has been made with excellent diastereoselectivity. Despite the increased cost of this amine over that of α-methylbenzylamine, the presence of the *p*-methoxy groups may facilitate the easier removal of the four chiral auxiliary groups, due to their electron donating effect, increasing the stability of any intermediate benzylic carbocation formed.

2.2 Formation of a new resorcinarene with lower rim functionality, suitable for attachment to a polymer support

A number of literature publications exist that report the formation of resorcinarenes incorporating functionality within the lower rim and these are discussed above, **page 39**.[46-50] This has led to the immobilisation of a range of resorcinarenes onto polymer supports, **page 40**.[56-58]

One of the research goals for the Loughborough group remains the attachment of a chiral, enantiomerically pure resorcinarene onto a polymer support. The reasons for this are their potential use in asymmetric catalysis and as a part of the stationary phase in chiral chromatography.[56,57] The potential benefits of solid phase chemistry over standard solution phase reactions are well documented.[51]

Sampler[41] used resorcinarenes **58** and **62** (made following literature procedures[4,46-48]) in combination with the now well-established use of enantiomerically pure α-methylbenzylamines and aqueous formaldehyde in ethanol, **Scheme 50.**



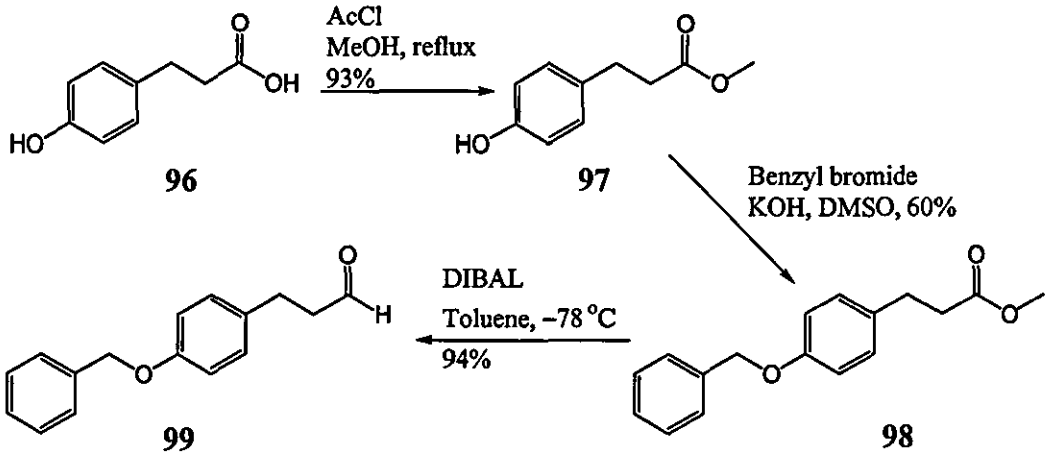
Scheme 50

Both enantiomers of **93** were formed in good yields and excellent diastereoselectivities. The chirality of the S,S enantiomer shown was successfully 'locked' by methylation of the remaining phenols, giving **94** in low yield.

Some efforts were made to protect the four lower rim alcohols prior to the tetra methylation reaction. Attempts at their acetylation caused the decomposition of the tetra benzoxazine **93**, in accordance with previous observations. Silylation with TBDMSCl formed the tetra silylated derivative of **93** in good yield, with some diastereoisomerisation being observed. The minor diastereoisomer was removed by recrystallisation. Problems arose in the methylation step, with the tetra silylated products being insoluble in both THF and diethyl ether below room temperature.

We have further extended these studies by forming another enantiomerically and diastereomerically pure resorcinarene with lower rim functionality. 3-(4-benzyloxyphenyl)propanal **99** was synthesised as shown in **Scheme 51.** This aldehyde was chosen because of the insolubility of the solid product in any common organic solvents, when 4-benzyloxybenzaldehyde was used in a resorcinarene forming reaction.[41] It was postulated that the resorcinarene product from **99** would have an improved solubility due to the additional alkyl portion of the lower rim, while maintaining the phenol functionality.

A literature report exists for the formation of the equivalent resorcinarene from the unprotected 4-hydroxybenzaldehyde[2] but it was thought necessary to use the benzyl protected form of the aldehyde to prevent any interference from the phenol in the following tetra benzoxazine forming step. A protecting group was required that would survive the strongly acidic conditions of the resorcinarene forming reaction.



Scheme 51

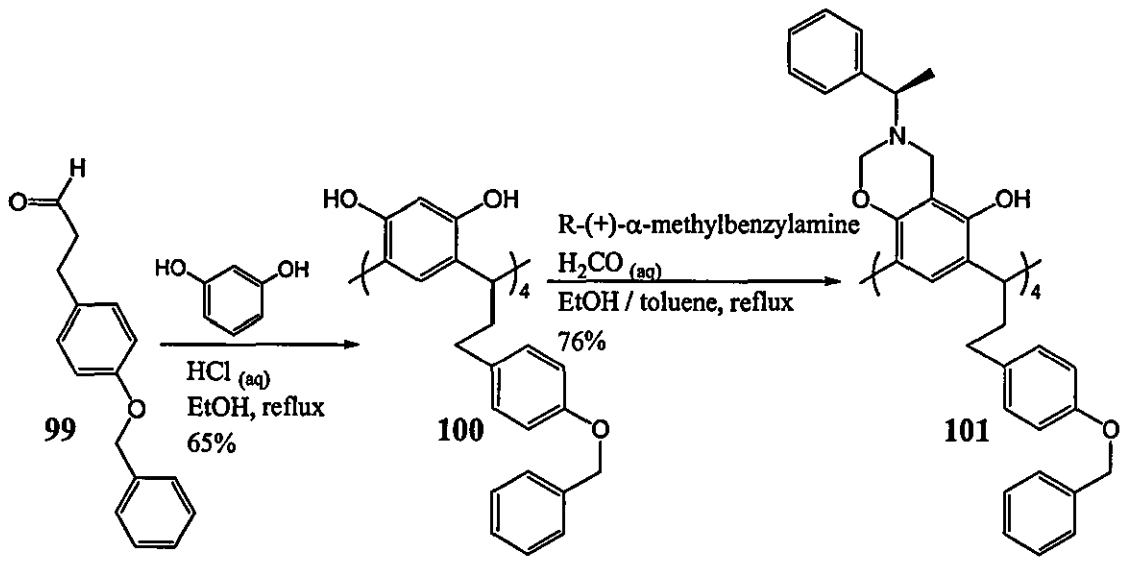
Methyl-3-(4-hydroxyphenyl)propanoate **97**[72] is commercially available but it was more economically viable to form the methyl ester from the much cheaper 3-(4-hydroxyphenyl)propionic acid **96**. This transformation was successfully carried out, in high yield, using acetyl chloride as a source of HCl and heating at reflux in anhydrous methanol.

Ground pearls of KOH in DMSO with benzyl bromide were used to form benzyl ether **98**[73] in reasonable yield. Some hydrolysis of the ester occurred under these conditions, accounting for the reduced yield. No optimisation was attempted with this reaction. The DIBAL reduction of **98**, at low temperature, furnished the desired aldehyde **99**[74] in excellent yield following a recrystallisation.

Resorcinarene **100** was formed in good yield from resorcinol and aldehyde **99** using standard, acid catalysed conditions, **Scheme 52**. The macrocyclic product proved to have an increased solubility over the 4-benzyloxybenzaldehyde derived resorcinarene, in common organic solvents, allowing it to be fully characterised.

Formation of the tetra benzoxazine **101** required a slight modification to the standard conditions. Octa hydroxy resorcinarenes are generally insoluble in ethanol, but dissolve readily on addition of the amine and formaldehyde to the tetra benzoxazine forming

reaction mixture. This was not the case with resorcinarene **100**. Toluene was added to the reaction mixture to increase the solubility of the resorcinarene. As a result, product **101** did not precipitate from the reaction mixture, preventing its isolation by simple filtration. The reaction mixture was allowed to cool to room temperature and the solvent removed under vacuum. The gummy residue recovered was mixed with ethanol and heated under reflux for one hour. The solid precipitate that formed was filtered and analysed by ^{1}H NMR spectroscopy. It showed the product to be mainly the expected, single diastereoisomer shown below. The trace of the minor diastereoisomer was removed by a single recrystallisation.



Scheme 52

Regrettably, the gummy residue formed following removal of the ethanol / toluene mixture was not analysed to assess the diastereoisomeric ratio it contained. Following the observations by Sampler[41] **(page 31)** it would be expected that the gummy residue contained both of the C_4 diastereoisomers of the product **101**. Presumably one predominant diastereoisomer was seen following heating at reflux in ethanol because of the solubility difference between the two inter-converting diastereoisomers, as discussed above **(page 30)**.

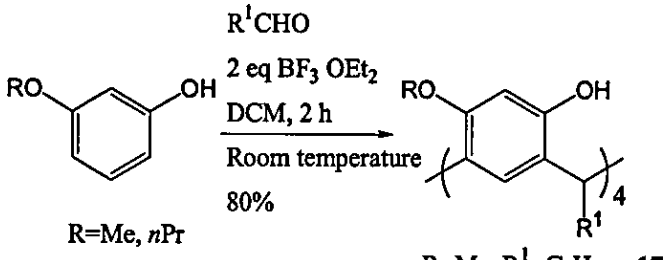
2.2.1 Conclusions and future work

The Loughborough group has now formed a range of axially chiral, enantiomerically pure resorcinarenes with lower rim functionality. Future work could focus on the attachment of these resorcinarenes to solid polymer supports.

2.3 Formation of tetra alkyloxy, chiral resorcinarenes

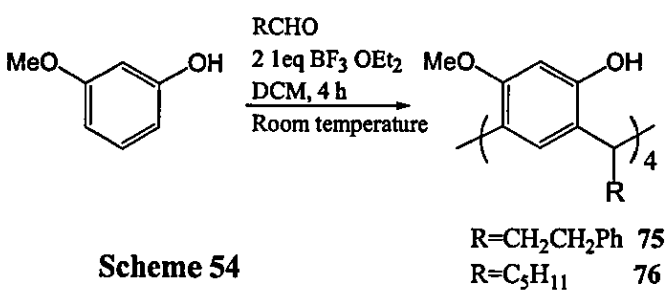
Standard octa hydroxy resorcinarenes of the type shown in **Scheme 1, page 2** are formed using resorcinol, an aldehyde and a hydrochloric acid catalyst. A number of reports have been made using other protic acids[14-18] and Lewis acids[8-12] to catalyse the formation of these tetrameric macrocycles, which are discussed above **(Section 1.2.3).**

Mocerino and co-workers[12] have developed methodology for the formation of inherently chiral resorcinarenes, possessing a C_4 rotational symmetry, as racemic mixtures. They used two equivalents of the Lewis acid, boron trifluoride diethyl etherate, in combination with resorcinol mono-methyl or mono-*n*-propyl ethers and an aldehyde, **Scheme 53.** (Use of 3-methoxyphenol instead of resorcinol with the standard hydrochloric acid conditions gave a mixture of unidentified products.)



Scheme 53

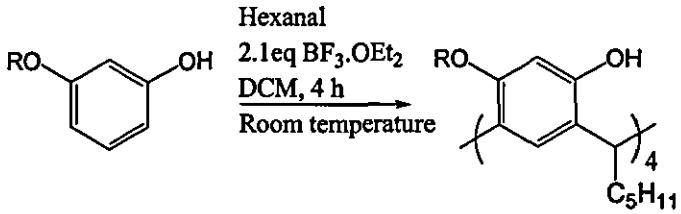
We followed these reaction conditions using commercially available 3-methoxyphenol with hexanal and dihydrocinnamaldehyde, **Scheme 54.** These aldehydes were chosen to help establish generality and to produce new molecules.



Scheme 54

The yields of these reactions were invariably around 65%. Compound **76** was isolated in high purity, following work up, by triturating the impure product with methanol and filtering off the white solid formed. Column chromatography provided **75** in 65% yield. Mass spectrometry and ^{1}H NMR spectroscopy confirmed formation of the tetrameric macrocycles.

As Mocerino had prepared the tetra *n*-propyloxy resorcinarene **19**, we extended this reaction to other resorcinol mono-alkyl ethers, **Scheme 55.**



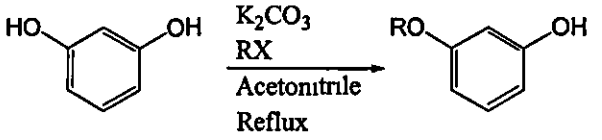
R=Bn **102**
R=*n*Bu **103**
R=*i*Pr **104**

R=Bn **105**
R=*n*Bu **106**
R=*i*Pr **107**

Scheme 55

Except for the tetra benzyloxy case **105** the resorcinarenes were formed in around 65% yield. Compound **106** was purified by trituration with methanol, as with **76**. Compound **107** was purified by column chromatography. Mass spectrometry and ^{1}H NMR spectroscopy confirmed formation of the tetrameric macrocycles.

The resorcinol mono-alkyl ethers were produced using a ten-fold excess of resorcinol to minimise any formation of the bis-alkyl ether derivatives,[75] **Scheme 56**. Unreacted resorcinol was removed with an acid work up, and chromatography gave the pure mono protected compounds in around 75% yield, with respect to the alkyl halide used.



R=Bn	**102**
R=*n*Bu	**103**
R=*i*Pr	**104**
R=*p*-NO_2Bn	**108**

Scheme 56

Formation of the tetra isopropyloxy derivative **107** illustrates that these reaction conditions can accommodate a more bulky, secondary alkyl group. An X-ray crystal structure of **107** was acquired from crystals produced by the slow evaporation of DCM, **Appendix 1.** The classic 'cup' shaped, crown conformation with an rccc configuration can be clearly seen, held in place by intramolecular hydrogen bonding, despite the presence of the large isopropyl groups.

Tetra benzyloxy resorcinarene **105** was chosen as a synthetic target because of the potential ease of removal of the benzyl groups at a later stage following further functionalisation reactions. The ^{1}H NMR spectrum of the crude reaction product from this reaction showed no starting material remaining and peaks in the right areas for the macrocycle, but they were broad and unclear at best. Attempts at column chromatography failed to significantly improve the purity. It may be that the desired cyclic tetramer **105** had formed but only in low yield. The reaction was repeated at 0 °C and –78 °C with no improvement. Why this had failed, when the methoxy, *n*-butyloxy and isopropyloxy phenols successfully formed the C_4 symmetric resorcinarene, remains unclear. It is conceivable that debenzylation reactions may be occurring, caused by the $BF_3.OEt_2$ Lewis acid. We thought that a para-nitrobenzyl group might be stable under the reaction conditions, and so 3-(4-nitrobenzyloxy)phenol **108** was produced, using the same method as shown in **Scheme 56.** The presence of the para-nitro group, as an electron-withdrawing group, would reduce the tendency for any formation of a benzylic cation in a Lewis acid promoted debenzylation because of its electron-withdrawing effect. Subjecting **108** to the $BF_3.OEt_2$ reaction conditions, however, gave a mixture of

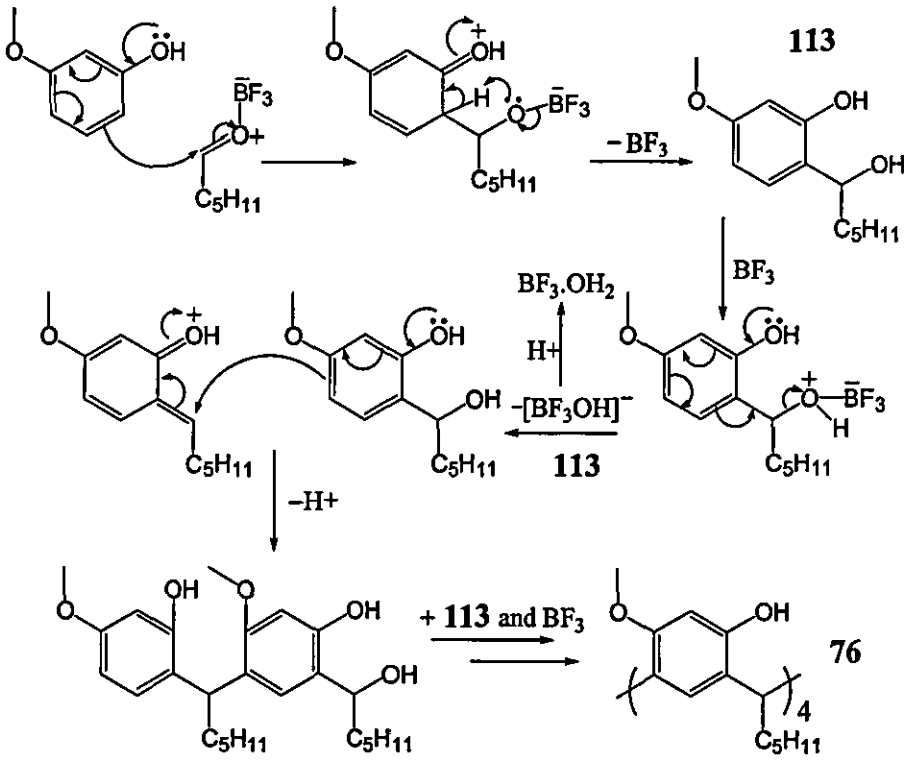
products that defied characterisation. The reaction was repeated at –20 °C with a similar outcome.

2.3.1 Use of preformed reaction intermediates as precursors to tetra alkyloxy resorcinarenes

Mocerino[12] suggested that the C_4 symmetric resorcinarene products obtained in the reactions shown in **Scheme 53** do not result from a reversible process involving the other statistically possible stereoisomers, driven by the formation of four intramolecular hydrogen bonds. This was based on an observation reported by Botta[13] that the Lewis acid catalysed isomerisation of resorcinarenes requires heating at reflux for several hours. If the Lewis acid promoted alkylation reaction is non-reversible, under the reaction conditions used, it does not allow for the formation of higher oligomers than the tetramer. Unless cyclisation of the linear tetramer occurs much more rapidly than chain propogation the calix[4]resorcinarene would only be formed in a reduced yield and not the 80% reported.

Mocerino proposed that the C_4 symmetric product is produced because of the *in situ* formation of intermediate benzylic alcohols of type **113**, shown in **Scheme 57**. These then react with other like molecules until the tetramer is formed, at which point cyclisation occurs. The alkylation of the 3-alkyloxyphenols would also have to occur exclusively at either the 4 or 6 position and not a mixture of the two in order to form the C_4 symmetric product, unless the polymerisation process is reversible.

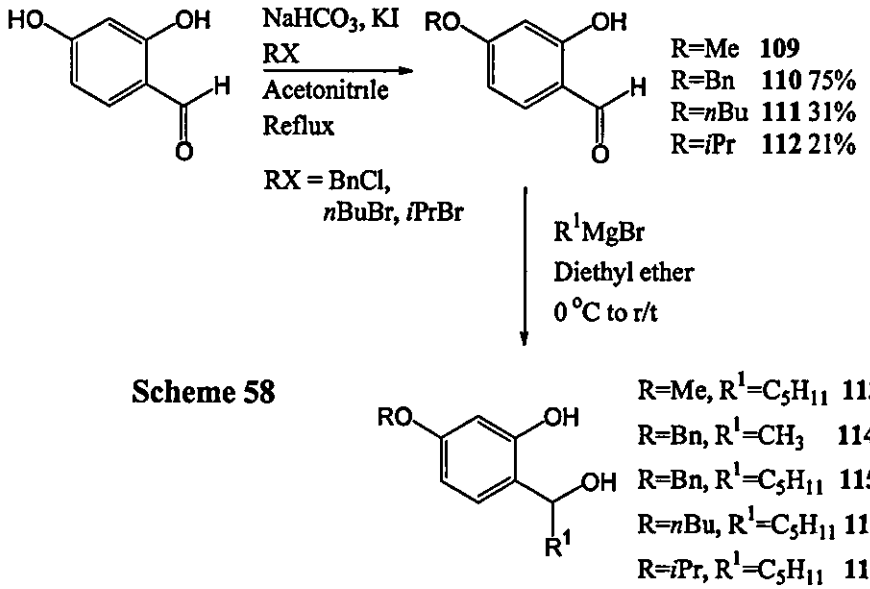
The mechanism also suggests that only one equivalent of Lewis acid is required for the reaction to occur in high yield. Compound **76** was formed in a reaction with only one equivalent of $BF_3.OEt_2$ added, but this result proved difficult to repeat and the reaction was less clean.



Scheme 57

This proposed mechanism explains the formation of a resorcinarene with upper rim C_n symmetry and the axial substituent selectivity at the bridging methine carbons. It is assumed that the crown confomation, with an rccc configuration, is formed in each case, which appears to be confirmed by the crystal structure of compound **17**[12] and the crystal structure we obtained of tetra isopropyloxy resorcinarene **107.** The selectivity seen presumably occurs for the same reasons proposed for the axial orientation of the substituents, on the bridging methine groups, in octa hydroxy resorcinarenes, **page 6.** In an axial position no disruption of intramolecular hydrogen bonding can occur which could be foreseeable with equatorial substitution.

A range of benzylic alcohols of type **113** was produced, as shown in **Scheme 58.** We also thought that these preformed intermediates might offer another route to the desirable tetra benzyloxy resorcinarene **105,** perhaps not requiring a Lewis acid, following reports in the literature of the use of protic acids to form resorcinarenes from benzylic alcohols, discussed above in **Section 1.2.3.2.**

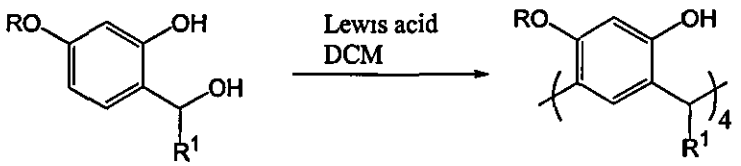


Scheme 58

Benzaldehydes **110**,[76a] **111**[76b] and **112**[76c] were preformed, following a literature procedure,[76a] from 2,4-dihydroxybenzaldehyde with varying yields, although no optimisation was attempted. The 4-mono-alkyloxy products were predominantly formed. Very little 2-alkyloxy or bis-alkyloxy products were seen under these conditions, perhaps due to intramolecular hydrogen bonding and an increased steric hindrance around the 2-hydroxy group. Methoxy version **109** is commercially available.

Use of Grignard reagents gave the desired alcohols in each case in good to excellent yields. The purification of isopropyloxy alcohol **117** proved difficult, and a sample suitable for elemental analysis was never achieved.

These precursor alcohols were converted into the corresponding resorcinarene as shown in **Scheme 59** and **Table 3.**



R=Me, $R^1=C_5H_{11}$ **113**
R=Bn, $R^1=CH_3$ **114**
R=Bn, $R^1=C_5H_{11}$ **115**
R=*n*Bu, $R^1=C_5H_{11}$ **116**
R=*i*Pr, $R^1=C_5H_{11}$ **117**

Scheme 59

R=Me, $R^1=C_5H_{11}$ **76**
R=Bn, $R^1=CH_3$ **118**
R=Bn, $R^1=C_5H_{11}$ **105**
R=*n*Bu, $R^1=C_5H_{11}$ **106**
R=*i*Pr, $R^1=C_5H_{11}$ **107**

Table 3

	Benzylic alcohol	Lewis acid	Equivalents of Lewis acid	Temp.	Yield (product)
1	**113**	$BF_3.OEt_2$	1.1	r/t	85% (**76**)
2	**113**	$BF_3.OEt_2$	0.5	r/t	mixture
3	**113**	$AlCl_3$	1	r/t	82% (**76**)
4	**114**	$BF_3.OEt_2$	1.1	r/t	mixture
5	**114**	$AlCl_3$	1	r/t	mixture
6	**115**	$BF_3.OEt_2$	1.1	r/t	mixture
7	**115**	$BF_3.OEt_2$	1.1	0 °C	mixture
8	**115**	$BF_3.OEt_2$	1.1	–78 °C	mixture
9	**116**	$BF_3.OEt_2$	1.1	r/t	85% (**106**)
10	**117**	$BF_3.OEt_2$	1.1	r/t	82% (**107**)
11	**113**	$Sc(OTf)_3$	0.2	r/t	mixture

Except for benzyloxy derivatives **114** and **115**, the benzylic alcohol precursors all successfully gave the equivalent resorcinarenes in higher yields than were seen when using 3-alkyloxyphenol and aldehyde starting materials, and only 1.1 equivalents of $BF_3.OEt_2$ were used. This accords with the proposed mechanism in which one equivalent of Lewis acid is used to form the intermediate when a separate aldehyde is used.

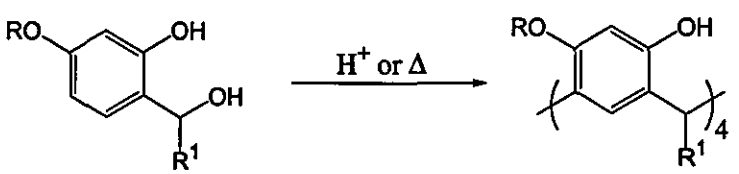
^{1}H NMR spectra of the crude reaction mixtures suggested formation of the tetrameric products **118** and **105**, but again in low yields, along with a number of other products (**entries 4-6**). The same results were achieved when the reaction mixtures were cooled (**entries 7-8**).

The use of half an equivalent of $BF_3.OEt_2$ (**entry 2**) gave the resorcinarene **76** in reasonable yield, as determined from the ^{1}H NMR spectrum, but it was a less clean reaction.

$AlCl_3$ also successfully induced the reaction to form resorcinarene **76** from benzylic alcohol **113** (**entry 3**), following its use by Biali[77] in the formation of a calix[4]arene from a benzylic alcohol. A mixture of compounds was again formed from the benzyloxy compound **114** (**entry 5**).

Scandium (III) triflate (**entry 11**) was tried, following the work of Konishi[11] who formed the parent, unsubstituted reorcinarene **16** from a benzylic alcohol, discussed on **page 9**. The solvent for this reaction was acetonitrile, but again a mixture of compounds was formed from precursor **113**, that defied characterisation.

2.3.1.1 Resorcinarene formation from preformed reaction intermediates using non-Lewis acid methodology



R=Me, R^1=C_5H_{11} **113**
R=Bn, R^1=CH_3 **114**
R=Bn, R^1=C_5H_{11} **115**
R=*n*Bu, R^1=C_5H_{11} **116**

Scheme 60

R=Me, R^1=C_5H_{11} **76**
R=Bn, R^1=CH_3 **118**
R=Bn, R^1=C_5H_{11} **105**
R=*n*Bu, R^1=C_5H_{11} **106**

A number of publications have been made involving the use of protic acids to catalyse the formation of resorcinarenes from benzylic alcohols, which have been discussed above, **Section 1.2.3.2.**

The results, following **Scheme 60**, are shown in **Table 4.**

Table 4

	Benzylic alcohol	Acid source	Solvent	Temp.	Yield (product)
1	**115**	5 mol% TFA	chloroform	r/t	mixture
2	**114**	5 mol% TFA	chloroform	r/t	mixture
3	**113**	5 mol% TFA	chloroform	r/t	mixture
4	**113**	-	toluene	reflux	mixture
5	**115**	-	toluene	reflux	mixture
6	**116**	-	xylene	reflux	mixture
7	**113**	1 eq' 1M HCl in diethyl ether	diethyl ether	0 °C to r/t	mixture
8	**116**	1 eq' 1M HCl in diethyl ether	diethyl ether	–78 °C to r/t	mixture
9	**116**	1 eq' 54% HBF_4 in diethyl ether	diethyl ether	–78 °C to r/t	< 10% (**106**)
10	**116**	5 mol% 54% HBF_4 in diethyl ether	diethyl ether	–78 °C to r/t	mixture
11	**115**	1 eq' 54% HBF_4 in diethyl ether	diethyl ether	–78 °C to r/t	< 10% (**105**)

In each case the reaction was stirred overnight at the temperature shown, then analysed by ^1H NMR spectroscopy. They were each then repeated for longer periods of time, up to 4 days in some cases, with no obvious changes. Shorter reaction times were not investigated, as these resorcinarenes are stable molecules once formed, so degradation was not thought to be an issue.

Each reaction was partially successful in that the ^{1}H NMR spectra of the crude reaction mixtures again showed peaks in the right areas but were at best unclear. This suggests that some of the macrocyclic tetramer was formed but in low yield. It would appear that only mildly acidic conditions are needed to form polymers of the benzylic alcohol precursors or even just heating.

The use of TFA by Keehn[14] to produce the octa methoxy resorcinarene **14** from 2,4-dimethoxybenzyl alcohol discussed above (**page 12**) was applied to our alcohols (**entries 1-3**). No[78] made use of preformed benzylic alcohol dimers to produce calixarenes by heating in toluene or xylene, without the addition of any kind of acid (**entries 4-6**). Use of HCl in diethyl ether to catalyse the reaction gave mixed results, even when cooled to –78 °C (**entries 7-8**).

In **entry 9** of **Table 4** an approximate reaction yield is given. Using HBF_4 in diethyl ether at –78 °C gave a cleaner sample of a cyclic tetramer (**106**) than had formed before. The reaction was investigated using *n*-butyloxy alcohol **116**, and then repeated with benzyloxy alcohol **115**, **entry 11**. In **Chapter 3** the exact experimental details used to form tetra benzyloxy resorcinarene **105** are reported. The analytical data produced is limited because of residual impurities even after column chromatography. The formation of the cyclic tetramer has, however, been confirmed by accurate mass measurement. Why the use of HBF_4 was apparently the most successful is unclear. Perhaps the possibility of small amounts of $BF_3.OEt_2$ being present in the reaction mixture promoted cyclisation, along with a reduction in the amount of any debenzylation reactions taking place.

The high yielding formation of tetra alkyloxy resorcinarenes seemingly requires the presence of certain Lewis acids. Högberg[3] suggested that in a standard, hydrochloric acid catalysed, octa hydroxy calix[4]resorcinarene formation the spatial orientation of the linear tetramer, due to hydrogen bonding, promotes cyclisation and that precipitation of the crown isomer, with an rccc configuration, acts as a thermodynamic sink for the reaction, promoting its formation (**page 5**).

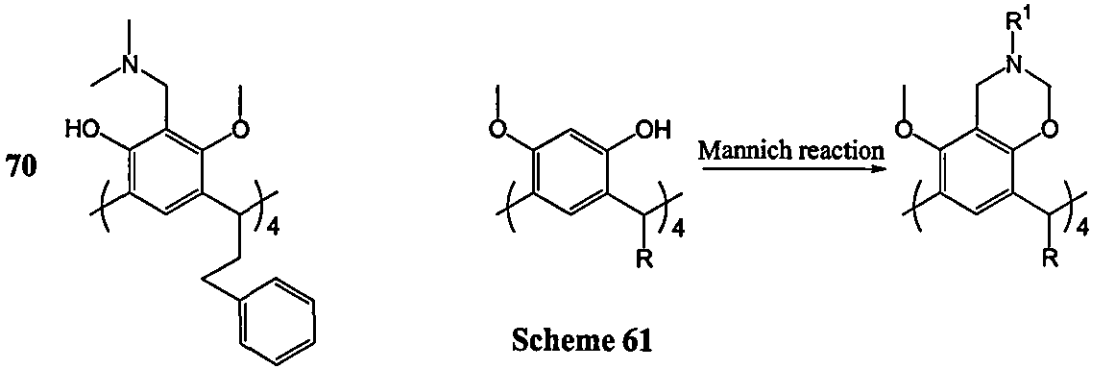
How the Lewis acids, that perform the tetra alkyloxy resorcinarene forming reactions, interact with the linear oligomers to promote cyclisation of the tetramer to give the calix[4]resorcinarene, and seemingly no other ring sizes, is unclear. Hydrogen bonding should play a role here, but the failed reactions discussed above with protic acid methodology suggest other factors are involved. There is also no precipitation of any isomer of the calix[4]resorcinarene product from the reaction mixture to act as a thermodynamic sink.

2.3.2 Conclusions and future work

A range of inherently chiral, C_4 symmetric, tetra alkyloxy resorcinarenes has been prepared, as racemic mixtures, in good yields. Some problems with benzylic functionality were encountered, but the production of a wider range of *O*-alkylated versions seems possible.

2.4 Mannich reactions with tetra alkyloxy resorcinarenes

Development of these reactions was first investigated in the hope of devising a simple route towards a racemic model version of resorcinarene **70, Section 2.1.2.** The first step of this synthesis seemed straightforward using a racemic tetra methoxy resorcinarene,[12] in a Mannich reaction, to give the equivalent tetrakis (1,3-dihydrobenzoxazine) compound, **Scheme 61.**



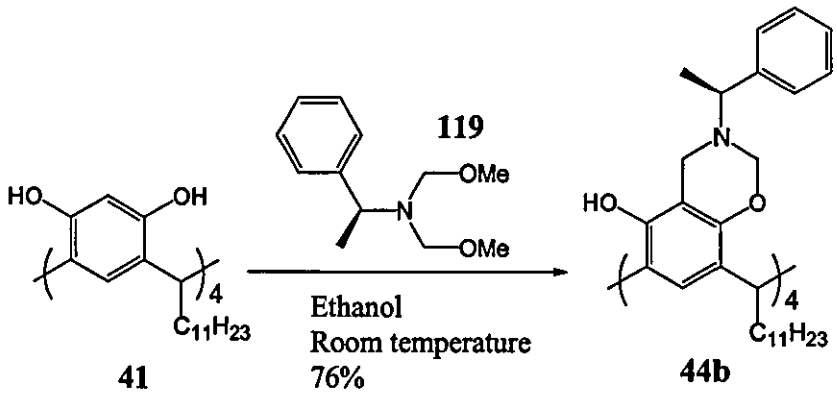
Scheme 61

Classical Mannich reaction conditions failed to give the desired product. Classical reaction conditions involve a primary amine and aqueous formaldehyde in ethanol under reflux. With a standard octa hydroxy resorcinarene, these reactions proceed in high yields.[35-41] The reasons for the observed reduction in reactivity of the tetra alkyloxy resorcinarenes are unclear. Several modifications to the classical conditions were made, including addition of an acid catalyst and the addition of toluene to the ethanolic solution to give a higher reflux temperature. The outcome was invariably unchanged starting material or a mixture of products, even after heating for several days under reflux. The use of dimethylamine with formaldehyde to give an acyclic Mannich product was also unsuccessful.

2.4.1 Use of bis(aminol ethers)

The use of bis(aminol ethers) as iminium ion precursors has been reported in the literature for the formation of benzoxazines.[67] An iminium ion was proposed to be the

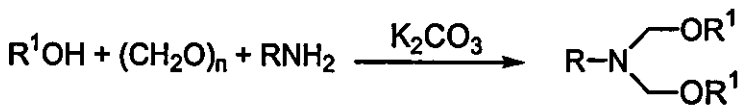
active species in this reaction. The Loughborough group has studied the use of bis(aminol ethers) in resorcinarene chemistry. Stirring an octa hydroxy resorcinarene with a bis(aminol ether) in ethanol at room temperature gives the tetra benzoxazine compound in high yield, **Scheme 62.**[40,41]



41 44b

Scheme 62

Bis(aminol ethers) were formed as shown in **Scheme 63** from a primary amine, para formaldehyde and an alcohol in the presence of K_2CO_3 in around 50-65% yield.[67a] The reactions were allowed to stir at room temperature for 4 days and the products purified by distillation. No optimisation of these conditions was attempted.

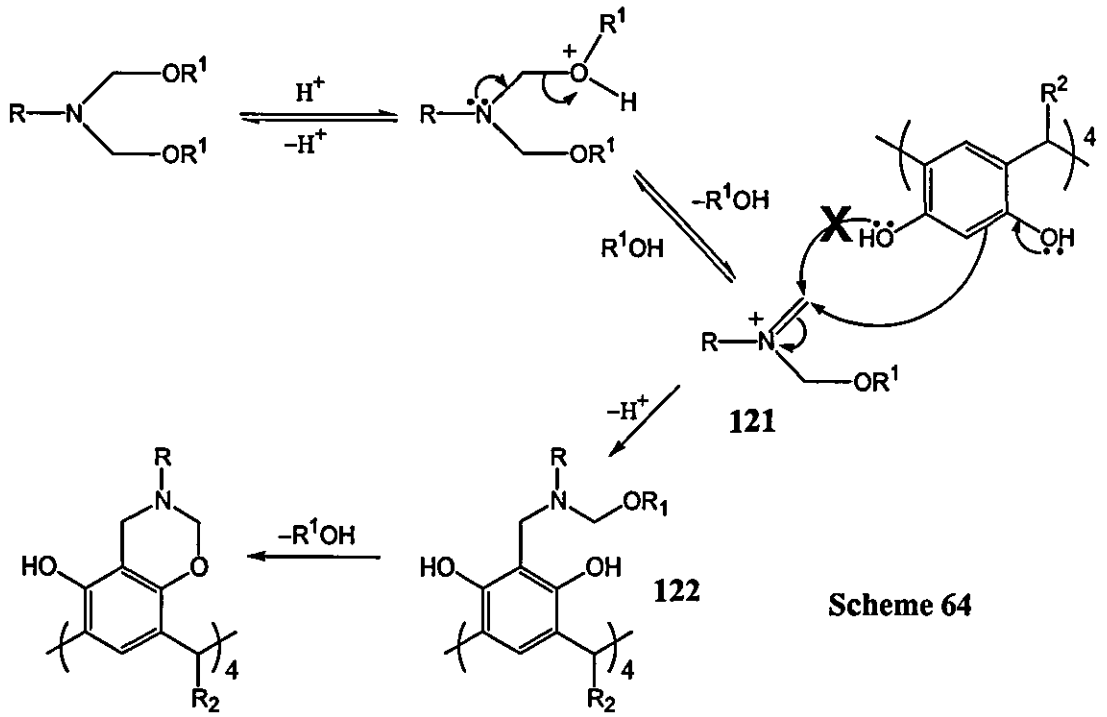


Scheme 63

R=Bn, R^1=Me **79**
R=S-(–)-α-methylbenzyl, R^1=Me **119**
R=R-(+)-α-methylbenzyl, R^1=Me **120**
R=Me, R^1=$(CH_2)_2OMe$ **81**

Compound **81** was made using 2-methoxyethanol because of the high volatility of the product when either methanol or ethanol were used, though any medium length chain alcohol should suffice.

In these Mannich reactions the resorcinarene phenols are the most acidic proton source, and they cause iminium ion **121** formation as shown in **Scheme 64.** An equilibrium exists between the protonation of nitrogen or oxygen. The more nucleophilic nitrogen should be favoured but starting material is eventually regenerated from this. Protonation of either oxygen atom can give the desired, reactive intermediate **121.**

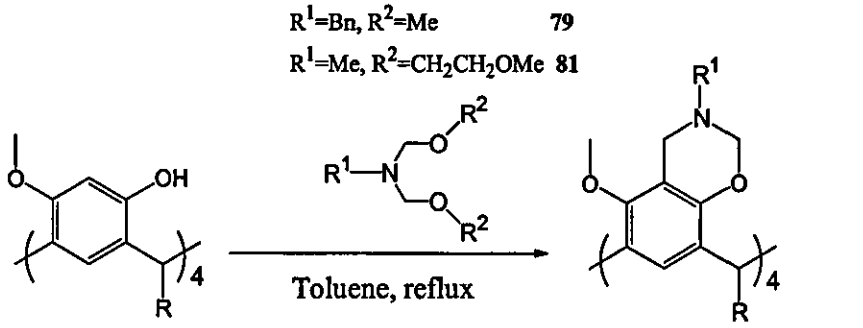


Scheme 64

The first step of the reaction of **121** with a resorcinarene is thought to be an aromatic substitution, rather than an alkylation of one of the phenol groups. The mechanism of the benzoxazine forming, ring closing step from **122** is unclear.

This methodology was applied to the tetra methoxy resorcinarenes **75** and **76.** At room temperature in ethanol, unreacted resorcinarene was recovered. Repeating the reaction at reflux gave a mixture of compounds even after prolonged heating. A similar result was observed with acetonitrile as the solvent. Using toluene as the solvent increased the reflux temperature further and a successful result was achieved, **Scheme 65.** The reaction yields were always around 75%, whichever bis(aminol ether) was being used. On a hundred milligrams of resorcinarene scale, the reaction was complete after heating

at reflux overnight. When scaled up to a few grams a longer time was required, up to 4 days in some cases. Despite the elevated temperatures the reaction was still slow.

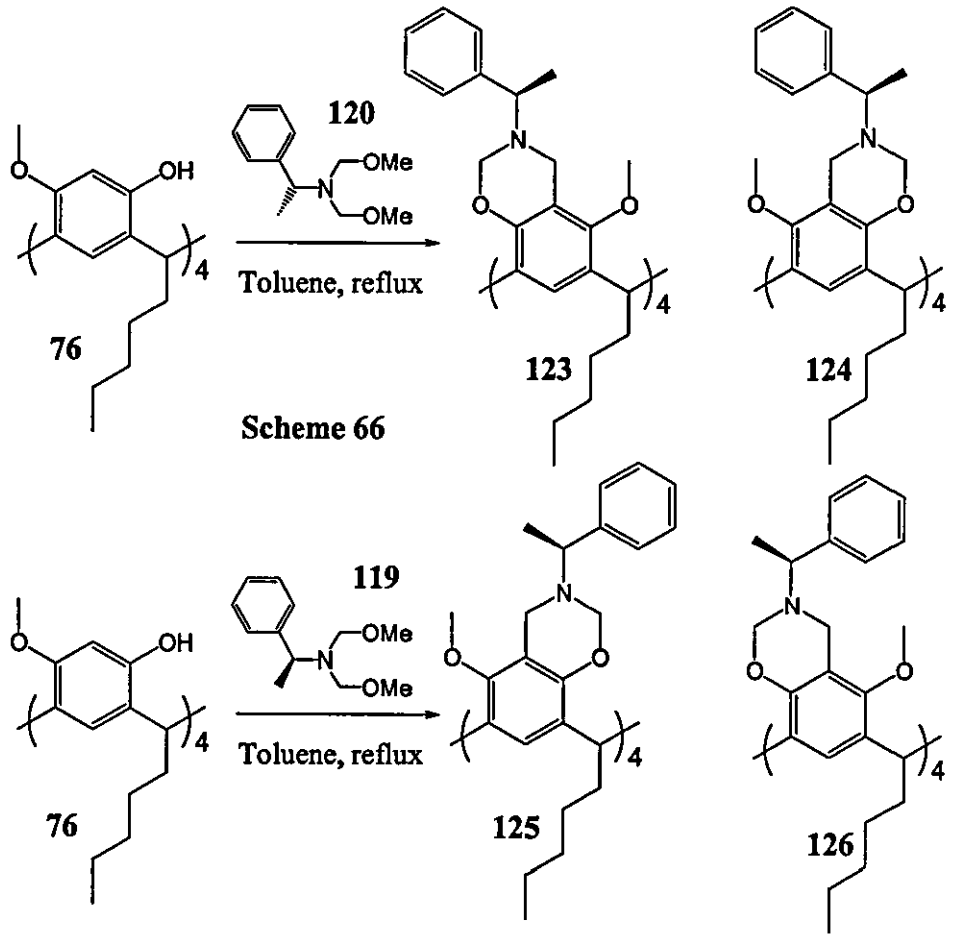


Scheme 65

2.4.2 Use of chiral bis(aminol ethers) with a range of tetra alkyloxy resorcinarenes

Following the success discussed above the reaction was carried out with the enantiomerically pure, chiral bis(aminol ethers) **119** and **120**. The two enantiomers of **76** were expected to give two diastereoisomers as the product in a 1 to 1 ratio. This proved to be the case in a yield of about 75%, **Scheme 66.**

The 1 to 1 mixture of diastereoisomers could be clearly seen in the ^{1}H NMR spectra of the reaction mixtures. The NCH_2O methylene protons of the benzoxazine rings are diastereotopic, appearing as two doublets. These doublets are distinctly different in each diastereoisomer appearing at different chemical shifts. The two diastereoisomers in each case were separated by column chromatography, being isolated in around 35% each, with a small amount recovered as a mixture. The ^{1}H NMR spectra and optical rotations of the first diastereoisomers eluted off the column (**123** and **125**) compare well with **49** and **49b** seen in **Scheme 24, page 34.** From this the absolute configurations of **123** and **125** can be assigned as R,R (**123**) and S,S (**125**) following the guidelines set out on **page 28.** The two diastereoisomers eluted next, **124** and **126**, that are also enantiomers of each other, have absolute configurations S,R (**124**) and R,S (**126**).

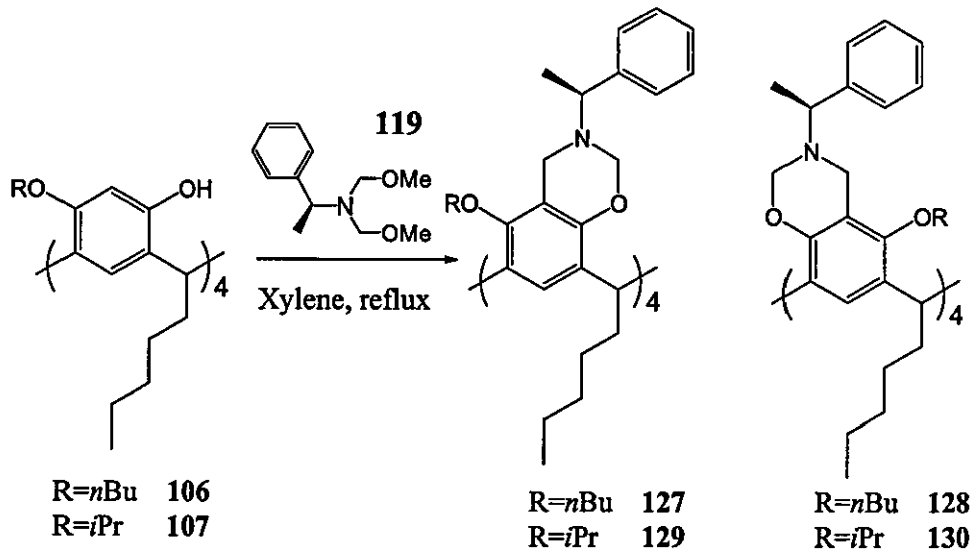


Scheme 66

These chromatographic separations suggested a number of possibilities for this new bis(aminol ether) methodology. If the chiral auxiliary groups of these resorcinarenes were removed they would become enantiomers of each other. Both enantiomers of the resorcinarene are therefore potentially available from the application of just one enantiomerically pure chiral amine.

In **Section 2.3** the production of a range of new tetra alkyloxy resorcinarenes is reported. If this chiral bis(aminol ether) methodology could be applied to them and the resulting diastereoisomers separated on silica gel, a potentially large range of enantiomerically pure resorcinarenes with different alkyloxy groups could be formed. These alkyloxy groups had so far been limited to just methoxy and ethyloxy because of the commercial availability of the corresponding alkyl triflates.

Tetra *n*-butyloxy resorcinarene **106** and tetra isopropyloxy resorcinarene **107** were subjected to the reaction conditions shown in **Scheme 66**. The outcome was recovered resorcinarene starting material in each case. We reasoned that the increased steric bulk of butyl and isopropyl over methyl was causing the reaction to fail. A change in solvent to xylene (with a boiling point of ca. 140 °C) produced the desired result as shown in **Scheme 67**. The yields were similar to those seen previously and the reaction was still slow, needing several days for the completion of a multi-gram scale reaction. A 1 to 1 mixture of diastereoisomers was again formed.



R=*n*Bu **106**
R=*i*Pr **107**

R=*n*Bu **127**
R=*i*Pr **129**

R=*n*Bu **128**
R=*i*Pr **130**

Scheme 67

The two diastereoisomers produced in each reaction were separated on silica gel in similar yields to the methoxy versions. The orders of elution are believed to be the same as with the methoxy equivalents by comparison of the optical rotations and ^{1}H NMR spectra of each resorcinarene. Therefore resorcinarenes **127** and **129** possess an S,S absolute configuration and **128** and **130** an R,S absolute configuration.

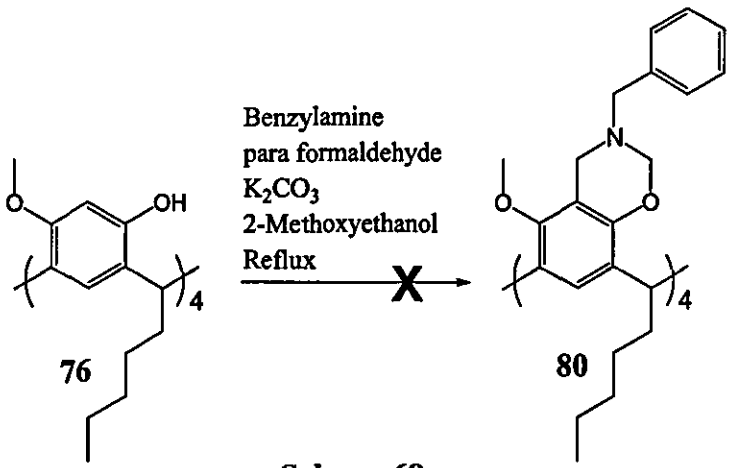
Crystals of **129**, suitable for X-ray analysis, were obtained from toluene / ethanol and then solvent equilibration between toluene and petroleum ether (see **Chapter 3** for details). The crystal structure produced, **Appendix 1**, confirmed the resorcinarene structure. The resorcinarene no longer possesses the characteristic crown shape of the

upper rim. Two of the distal ring phenyl units are laid flat and slightly twisted. The other pair of distal phenyl units are upright and slightly twisted, in what is described as a boat conformation. The resorcinarene still has the rccc configuration as expected.
This boat conformation is presumed to be favoured because no intramolecular hydrogen bonding is possible in this molecule to hold it in the crown orientation. Release of steric strain is probably the major reason for this deviation from the crown conformation, in the absence of any intramolecular hydrogen bonding. The upper rim of the resorcinarene, in the crystal state at least, no longer possesses a C_4 symmetry but is now C_2 symmetric. The lower rim pentyl chains appear in a seemingly random arrangement, showing no real symmetry.

The ^{1}H NMR spectra of all these tetra alkyloxy tetra benzoxazine resorcinarenes show some degree of line broadening, suggesting flexibility within the molecule in solution on the NMR time scale. This could be attributed to the lack of hydrogen bonding and steric influences. This effect is especially evident in the tetra *n*-butyloxy and tetra isopropyloxy versions. ^{1}H NMR experiments at 50 °C in $CDCl_3$ greatly improved the clarity of the spectra. The ^{1}H NMR spectra of **129** at both 25 °C and 50 °C in $CDCl_3$ at 400 MHz are shown in **Appendix 2** for comparison.

2.4.3 Further investigations into the use of iminium ion precursors in Mannich reactions with tetra alkyloxy resorcinarenes

The results described above with heating at reflux in toluene or xylene suggested that perhaps the reason for the failure of the classical Mannich reaction conditions tried was use of a solvent with to low a boiling point. It remains unclear as to what the exact structure of the reactive iminium species is in classical benzoxazine forming Mannich reactions. It is possible that bis(aminol ethers) are formed *in situ*, which then form iminium ions as seen above. This prompted the reaction shown in **Scheme 68** to be attempted, using the high boiling alcohol 2-methoxyethanol, para formaldehyde and K_2CO_3, as in a bis(aminol ether) forming reaction.



Scheme 68

Following 2 days of heating at reflux though there was no evidence of product **80** being formed, just a mixture of unidentified compounds.

Although they are simple reactions to perform, with no need for anhydrous conditions or even high purity bis(aminol ethers), the long reaction times needed for large scale reactions were investigated. Three reasons for the slow reaction rate and high temperatures required were considered: **(i)** The possibility of the bis(aminol ether) reforming by reaction between the alcohol product and the iminium ion formed; **(ii)** the lower acidity of tetra alkyloxy resorcinarenes, compared to octa hydroxy resorcinarenes, hindering iminium ion formation; **(iii)** the lower reactivity of the aromatic 2-positions towards electrophilic substitution, compared with octa hydroxy resorcinarenes.

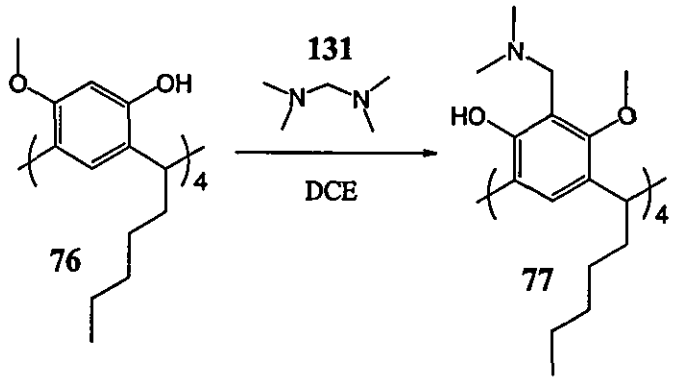
2.4.3.1 Removal of the alcohol side product

The side product following iminium ion formation is an alcohol. Removal of the alcohol formed would prevent any reaction back to the bis(aminol ether), so pushing the equilibrium in **Scheme 64** towards the iminium ion and hence providing a reduction in reaction time. An anhydrous reaction using tetra methoxy resorcinarene **76** and purified bis(aminol ether) **119** was tried at reflux in xylene. A Dean-Stark apparatus was fitted and filled with pre-dried 4Å molecular sieves to remove the methanol produced. A successful reaction occurred but with no obvious rate increase.

2.4.3.2 Importance of the phenol acidity and the reactivity of the aromatic 2-positions

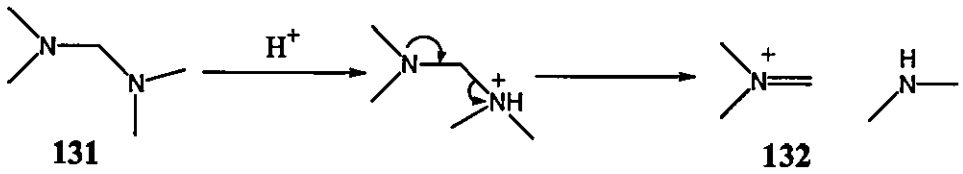
A range of reactions was performed to establish reasons for the reduced reactivity of the tetra alkyloxy resorcinarenes towards the Mannich reaction with iminium ion precursors, including the use of aminal *N,N,N,N*-tetramethylmethylenediamine **131**, to give the acyclic Mannich product **77**, **Scheme 69** and **Table 5.**

All of the reactions discussed below used tetra methoxy resorcinarene **76** because of its ease of preparation and isolation in large quantities. Iminium ion precursors and other reagents were used in excess, normally 8-10 equivalents, with the resorcinarene being 4 equivalents. DCE (1,2-dichloroethane) was chosen for these reactions because of its reasonably high boiling point and polarity. It was envisaged that any reactive intermediate formed would be more stable in this solvent compared with other solvents of similar boiling points, such as ethanol and acetonitrile.



Scheme 69

The iminium ion **132** is thought to form from **131** as shown in **Scheme 70.** The proton sources in the reaction are the phenols of resorcinarene **76.** The reaction with aminal **131** produces an equivalent of dimethylamine. It is unclear if this dimethylamine has any influence on the reaction.



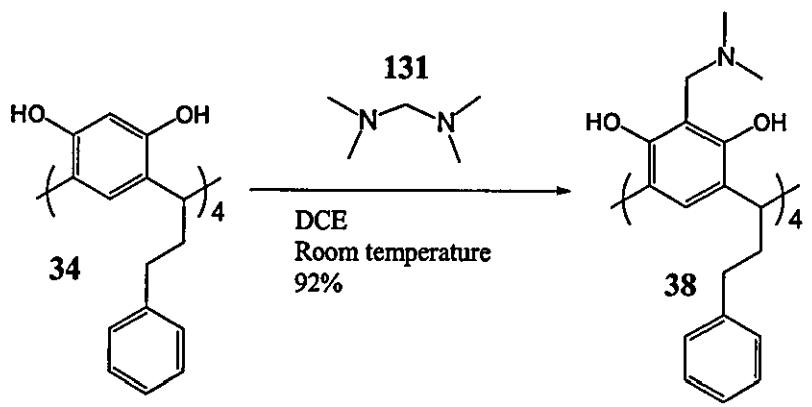
Scheme 70

Table 5

	Iminium ion precursor	Solvent	Temp.	Time	Yield (product)
1	**131**	DCE	r/t	o/n	s/m
2	**131**	DCE	reflux	o/n	93% (77)
3	**119**	DCE	reflux	2 d	mixture

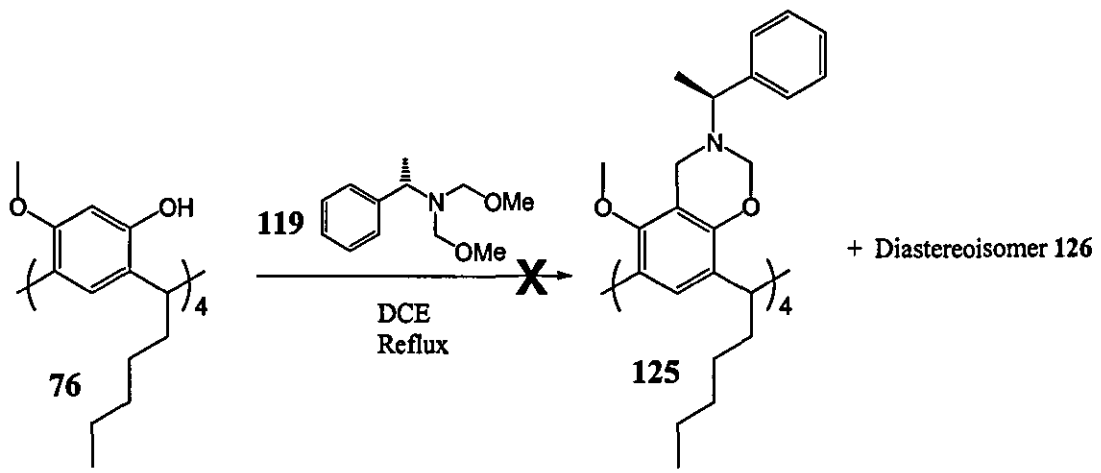
Tetra aminomethylated resorcinarene **77** was formed from **76** in high yield when heated at reflux with aminal **131** in DCE, **entry 2.** The reaction was complete after stirring overnight. As can been seen from **Table 5,** when the reaction was performed at room temperature, **entry 1,** only unreacted resorcinarene **76** was recovered.

Octa hydroxy resorcinarene **34** was reacted with aminal **131** at room temperature in DCE, **Scheme 71.** The reaction was successful, forming **38** in excellent yield after stirring overnight.



Scheme 71

Following the success indicated above with aminal **131**, bis(aminol ether) **119** was heated at reflux in DCE with tetra methoxy resorcinarene **76, Scheme 72.** After 2 days of heating at reflux there was no evidence, by ^{1}H NMR spectroscopy, for the diastereoisomeric mixture of **125** and **126** being formed, only a mixture of unidentified compounds, **Table 5, entry 3.**



Scheme 72

From these results the reduced reactivity of the tetra methoxy resorcinarene, compared with octa hydroxy resorcinarenes, is clearly evident. It was reasoned that the difference in reactivities was due to the lower acidity of the tetra methoxy resorcinarene hindering any iminium ion formation.

Octa hydroxy resorcinarenes are more acidic than tetra alkyloxy resorcinarenes because of the reported ease of removal of the first four phenolic protons from an octa hydroxy resorcinarene,[21,22] discussed above on **page 15.** In the tetra methoxy resorcinarenes, like **76**, all of the phenolic protons are involved in intramolecular hydrogen bonding.

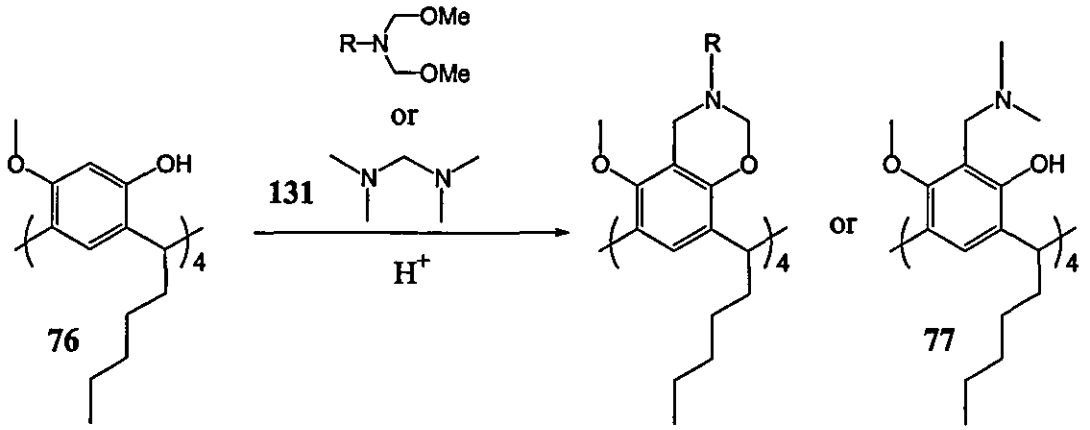
To investigate the acidity of the phenols in question, some pKa measurements were made by co-workers. They were measured in acetone in comparison with 2,6-lutidine ^{1}H NMR shifts.[79a] The results they achieved gave octa hydroxy undecyl-resorcinarene **41** a pKa value of 7 and tetra methoxy resorcinarene **76** a value of 10, some three units higher.

The results obtained confirm the substantially greater acidity of the octa hydroxy resorcinarenes. Shields[79b] also established the pKa values of resorcinol (ca. 9.5) and 3-methoxyphenol (ca. 9.8) to be similar. Schneider[22] reported the pKa values of the first four phenolic protons of an octa hydroxy resorcinarene as two units lower than that of resorcinol. Clearly the intramolecular hydrogen bonding within these macrocycles has a large influence on their acidities.

The successful reaction with aminal **131** could be explained by this argument, in that at these elevated temperatures the tetra methoxy resorcinarene **76** is acidic enough to liberate the iminium ion **132**. It does not, however, fully explain the failure of the bis(aminol ether) reaction shown in **Scheme 72.** Even at elevated temperatures a mixture of unknown compounds was formed with no evidence of the Mannich product. An equilibrium exists upon protonation of a bis(aminol ether) between intermediates protonated at the nitrogen atom and intermediates protonated on either of the two oxygen atoms. It is thought that the more nucleophilic nitrogen is more readily protonated but starting material is regenerated from this, whereas protonation of either oxygen atom gives the iminium ion by loss of an alcohol molecule. Papageorgiou[80] has reported the greater reactivity of a bis(aminol ether)-derived iminium ion over that from an aminal. This suggested that, even when heated under reflux in DCE, the tetra methoxy resorcinarene was not acidic enough to protonate an oxygen atom of a bis(aminol ether). In an aminal reaction it is always a more nucleophilic nitrogen atom that is protonated. Following these observations, a range of reactions was performed with the addition of an acid catalyst, to promote iminium ion formation, **Table 6** and **Scheme 73.**

Table 6

	Iminium ion precursor	Acid	Solvent	Temp.	Yield
1	**119**	10 mol% *p*-TSA	xylene	reflux	s/m
2	**79**	20 mol% HBF_4 in diethyl ether	DCE	reflux	mixture
3	**119**	HCl in diethyl ether	DCE	r/t	mixture
4	**131**	HCl in diethyl ether	DCM	r/t	mixture



R=Bn or α-methylbenzyl

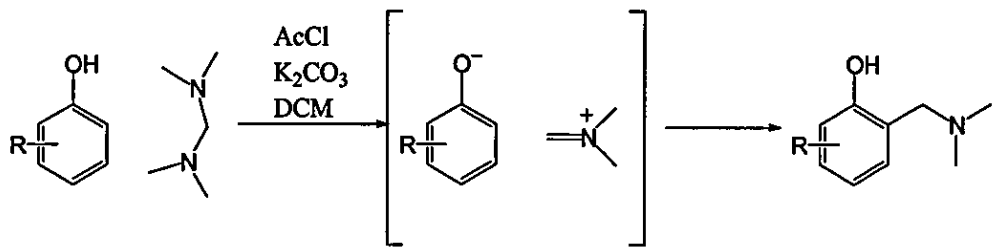
Scheme 73

p-Toluenesulphonic acid was added to the previously successful reaction conditions of heating at reflux in xylene, **entry 1.** After 24 hours only unreacted resorcinarene **76** was evident by ^{1}H NMR analysis. There was no indication of the tetra benzoxazine product being formed. A similar result was observed with HBF_4 and the benzylamine-derived bis(aminol ether) **79, entry 2.** Use of HCl gave a mixture of unidentified products with both the bis(aminol ether) and the aminal, **entries 3-4.**

The addition of a protic acid to a previously slow, but successful procedure **(entry 1)** had thus hindered the reaction. From this we reasoned that the reactive form of each of the 3-methoxyphenol-derived sub-units of the resorcinarene is the phenolate, the formation of which would be severely hindered by addition of an acid.

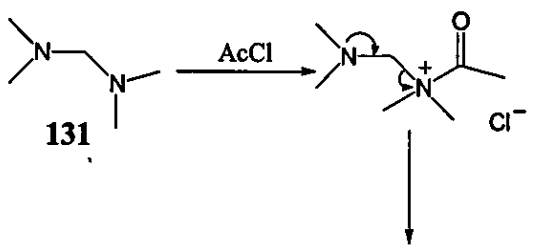
Ungaro and co-workers[81] used the heterogeneous base K_2CO_3 to generate the phenolate in the aminomethylation of various phenols in aprotic solvents, with a preformed iminium salt. They reached the conclusion that the phenolate was the reactive form of the phenol, forming an ion pair with the iminium ion, which reacted together to give the desired product. Ungaro also noted the importance of the heterogeneous base, having observed a big decrease in yield without a base present or with a soluble base such a tri-*n*-butylamine. This may explain the failure of the reaction, at room temperature, when

just *N,N,N,N*-tetramethylmethylenediamine **131** was present. We saw no reason why an *in situ* iminium salt formation would not work as effectively, **Scheme 74.**

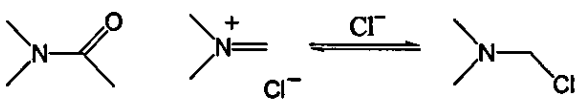


Scheme 74

This required the use of an aprotic reagent to form the iminium ion because of the basic conditions. Acetyl chloride was used, as shown in **Scheme 75.**



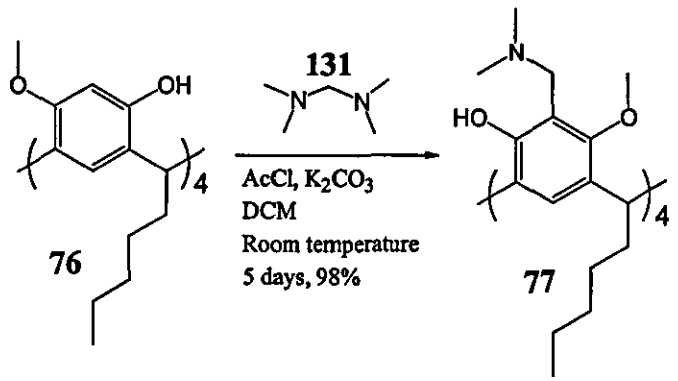
Scheme 75



133 **134** **135**

It is unclear whether the iminium ion exists mainly as part of the salt **134** or as the equivalent chloride **135** when in solution. The other product of this reaction is amide **133.** This prevents any reformation of aminal **131,** as is possible with protic conditions.

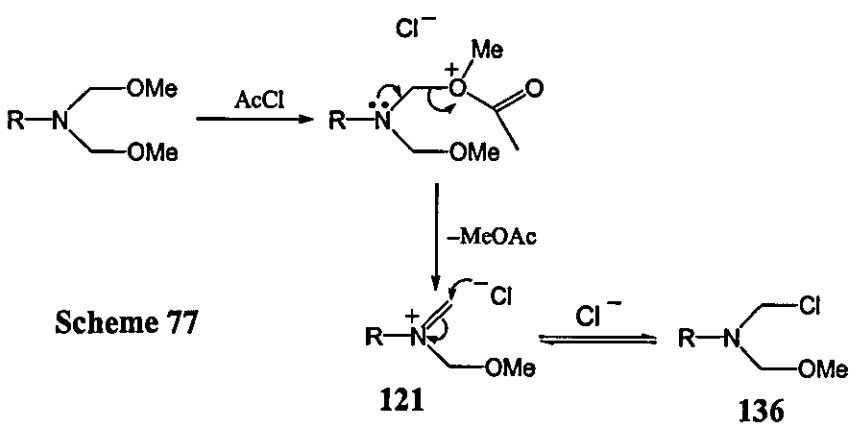
This methodology was applied to tetra methoxy resorcinarene **76, Scheme 76.** K_2CO_3 was used in large excess, some 30 equivalents.



Scheme 76

Although still a slow reaction, requiring 5 days for completion on a multi-gram scale, an excellent yield of very high purity product was obtained at room temperature. This supports the importance of the phenolate in which the aromatic 2-position is more reactive towards aromatic substitution. It seems likely that one phenol at a time is deprotonated. Unfortunately when bis(aminol ether) **79** was used in place of aminal **131** in the reaction a mixture of unidentified products was formed.

With bis(aminol ethers), in reactions with acetyl chloride, as with acids, there is an equilibrium between reaction with the more nucleophilic nitrogen atom and either of the oxygen atoms, **Scheme 77**. It was assumed that any quaternisation of the nitrogen atom would be reversible, reforming the bis(aminol ether) following nucleophilic attack by the chloride ion formed. It is not known whether the iminium ion exists as part of the salt **(121)** or as the equivalent chloride **(136)** when in solution.



Scheme 77

The intermediate shown in **Figure 18**, formed from quaternisation of the nitrogen atom, may behave as an acetylating agent. Any benzoxazines successfully formed in the reaction could be acetylated on the nitrogen atom followed by degradation as observed previously.

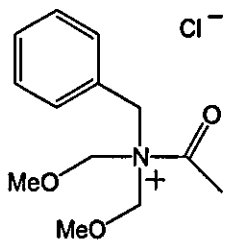
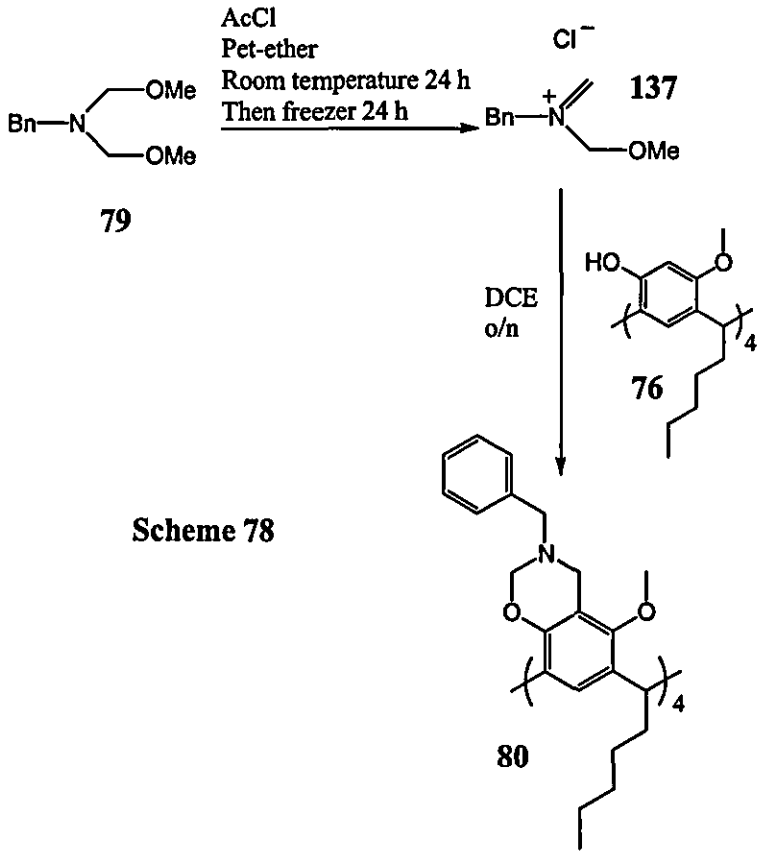


Figure 18

In order to preclude any of these side reactions from *in situ* iminium ion formation a preformed iminium salt was used. Previous members of the Loughborough group have reported the isolation and characterisation of iminium salts of type **121**.[80] This was attempted, but in the authors hands, these species proved too reactive to be practically viable. A different approach was made, using bis(aminol ether) **79** to give iminium salt **137**, shown in **Table 7** and **Scheme 78.**

Table 7

	Added base	Temperature	Yield (product)
1	-	r/t	mixture
2	-	reflux	80% (**80**)
3	K_2CO_3	r/t	mixture



Scheme 78

The iminium salt was formed by reaction with acetyl chloride in dry petroleum ether. The reaction was stirred for 24 hours at room temperature and then placed in the freezer for 24 hours. This caused precipitation of the iminium salt as a white solid. While still cold, so as to prevent the iminium salt dissolving, the petroleum ether was removed using a syringe. A solution of resorcinarene **76** in DCE was added and the mixture stirred at room temperature overnight. An unidentified mixture of products was formed, **entry 1.** Repeating the same procedure but with heating at reflux in DCE overnight gave the desired tetra benzoxazine product **80** in good yield, **entry 2.**

The reaction shown in **entry 3** used the K_2CO_3 methodology with this preformed iminium ion, but again a mixture of unidentified compounds was formed despite the prolonged reaction times. The reasons for this failure are unclear, when considering Papageorgiou's[80] report of bis(aminol ether)-derived iminium ions being more reactive species than aminal-derived iminium ions.

Some interesting observations were made while developing this reaction. When acetyl chloride and the bis(aminol ether) were stirred together in petroleum ether an initial white precipitate formed which dissolved after only a few minutes. This was thought to have been a result of quaternisation of the nitrogen atom, followed by subsequent reactions to form a soluble compound. If this mixture was only stirred for one hour at room temperature then placed in the freezer for 24 hours, only a small amount of iminium salt precipitated. Even when stirred for 24 hours it appeared that the amount precipitated in the freezer was less than 100% conversion, although an exact yield was never established. A high yield of **80** was obtained because of the use of an excess of both the bis(aminol ether) and acetyl chloride. This suggests that iminium salt formation is actually quite slow. This would help to explain the long reaction times seen for successful reactions, but not the mixtures of compounds so often observed.

A part of this reaction scheme is of course the benzoxazine-forming cyclisation step. This was always assumed to occur following aromatic substitution, and occur rapidly. No investigations into how this is affected by use of a tetra alkyloxy resorcinarene and changing of the reaction conditions have been made.

A crystal of **77**, suitable for X-ray analysis, was attained by slow evaporation of a solution in diethyl ether, **Appendix 1**. The observed structure has, like **129**, a boat conformation with two distal resorcinol units lying flat and the other two upright. The difference here is the presence of intramolecular hydrogen bonding in this molecule. We thought this would hold the molecule in the crown conformation. However, the phenolic hydrogens formed hydrogen bonds with the nitrogen atoms of the same resorcinol-derived unit and not the adjacent methoxy oxygen atoms. In the crystal structure of tetra benzoxazine **43**[36], **Figure 19**, intramolecular hydrogen bonding exists between adjacent resorcinol units, despite the presence of the benzoxazine rings and sterically demanding α-methylbenzyl groups, so maintaining a crown conformation.

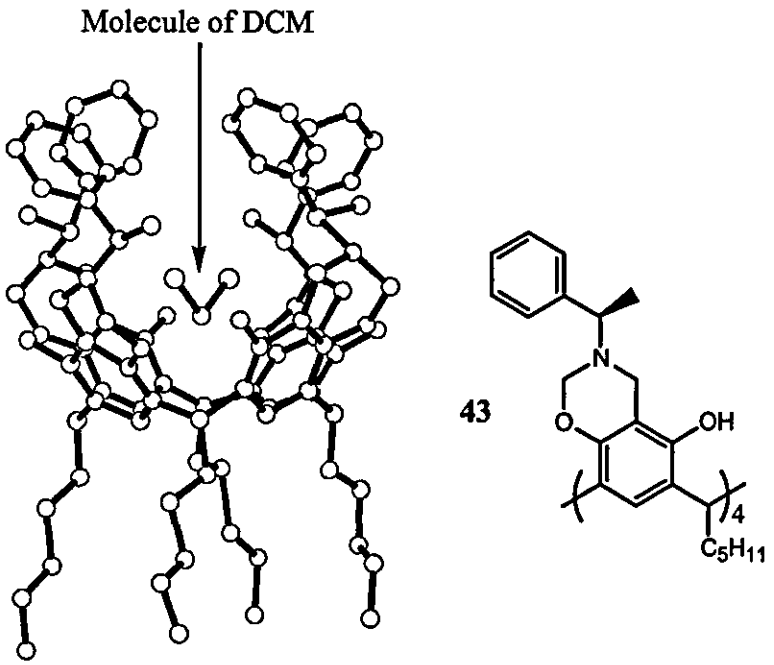


Figure 19

The boat conformation is adopted by **77** maybe because there is a combination of factors. There is another, perhaps more favourable, hydrogen bonding option other than with the adjacent methoxy oxygen, i.e. with the nitrogen atom. Placing this in combination with a release of steric strain, the boat becomes the lowest energy orientation. This O-H-N hydrogen bonding is prevented in **43** because of the fixed benzoxazine rings. So, when present, intramolecular hydrogen bonding appears to be the major influence on the conformation of the macrocycle, with steric influences playing a minor role.

2.4.4 Conclusions and future work

A range of new reaction conditions has been developed for Mannich reactions with tetra alkyloxy resorcinarenes, using iminium ion precursors. This has allowed formation of a range of new, axially chiral resorcinarenes as 1:1 diastereoisomeric mixtures that can be easily separated by column chromatography.

Some investigations have been made into the reasons for the reduced reactivity of these tetra alkyloxy resorcinarenes in Mannich reactions and a number of ideas presented. There are however some unexplained results that require further investigation.

2.5 Use of resorcinarenes as chiral ligands in enantioselective diethylzinc additions to benzaldehyde

One of the main objectives for organic synthetic research is the development of asymmetric reaction protocols that give products with high enantiomeric purity One such transformation that has received a great deal of attention is the addition of dialkylzinc species to various aldehydes [82] Many different chiral, catalytic ligands have been used to produce high yields and high enantiomeric excesses in the alcohol products of these reactions. They include the use of β-amino alcohols The addition of diethylzinc to benzaldehyde was chosen as a starting point, to investigate the use of chiral resorcinarenes as ligands in asymmetric synthesis, because many of the resorcinarenes prepared by the Loughborough group possess this type of functionality [40,41]

Until this point, to the best of our knowledge, there had been no literature reports of the use of any resorcinarene as a ligand in any catalytic reaction.

The methodology used and resorcinarenes investigated by the Loughborough group are shown in **Figure 20** and **Table 8**.

Table 8

	Resorcinarene	Yield of **138**	e.e. of **138**	Configuration of major product
1	**51**	80%	56	(S)-(-)
2	**51b**	75%	55	(R)-(+)
3	**54**	71%	42	(R)-(+)
4	**139**	-	27	(R)-(+)

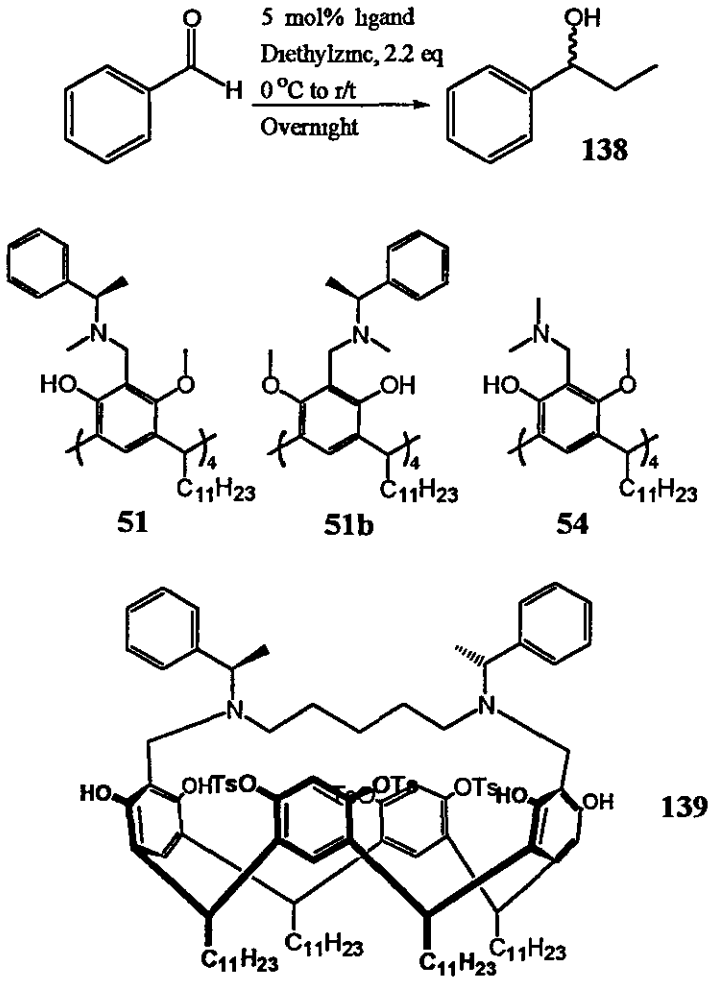


Figure 20

The reactions were performed in toluene at 0 °C and allowed to warm slowly to room temperature overnight 5 mol% of the resorcinarene was used in each case. Enantiomeric excesses of 1-phenyl-1-propanol **138** were determined by chiral HPLC.

Table 8 shows that the alcohol product **138** was formed in good yields in each case. The two enantiomers **51** and **51b**, containing the four α-methylbenzyl groups, gave moderate e.e s in the product, **entries 1-2**. As expected, the configurations of the major enantiomers of **138** formed in each case were opposite Perhaps the most significant result of all was the moderate e e. seen in the alcohol **138** when using resorcinarene **54, entry 3** The asymmetry of this compound is due solely to its inherent axial chirality

This result goes some way towards justifying the efforts made in developing these kinds of resorcinarenes, as they clearly show potential as asymmetric ligands.
The opposite enantiomer of the alcohol was the major product compared with that formed with resorcinarene **51**. They are both the S enantiomer (axial chirality) of the resorcinarene but **51** has the R-α-methylbenzyl groups still present. Clearly the α-methylbenzyl groups are highly influential because of the different magnitudes of e e. and the opposite configuration seen in the secondary alcohol products

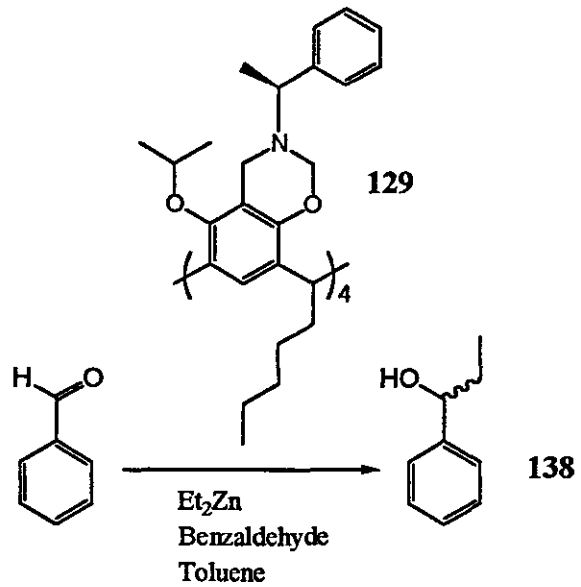
How the resorcinarene is actually involved in the catalytic cycle of these reactions is unknown. Catalytic cycles for the addition of diethylzinc to aldehydes involving amino alcohols such as ephedrine have been proposed [83] These compounds are however small and possess only one amino alcohol 'reactive site.' The C_4 symmetric resorcinarenes used are much larger molecules and have four β-amino alcohol moieties.

The final ligand investigated was the tetra tosylated, distally bridged, C_{2v} symmetric, resorcinarene **139**, developed by Hunter.[84] This is the first example of an enantiomerically pure, chiral, 'basket' type resorcinarene. The asymmetry derives from the two α-methylbenzyl groups and the orientation of the alkyl chain over the cavity This ligand gave a promising 27% e e. but no reaction yield was reported

These investigations were continued using our newly developed, enantiomerically pure tetra isopropyloxy resorcinarene **129**. This ligand was chosen because of the presence of four sterically demanding isopropyloxy groups, which might have a positive effect on any enantiomeric excesses in the alcohol product The reaction shown in **Scheme 79** was performed at 0 °C and –78 °C using only 1 mol% of **129**. The results are shown in **Table 9**.

Table 9

	Temperature	Crude yield of **138**	Optical rotation of **138**	e e. of **138**
1	0 °C to r/t	> 95%	26°	ca 55%
2	–78 °C to r/t	> 95%	43°	82%



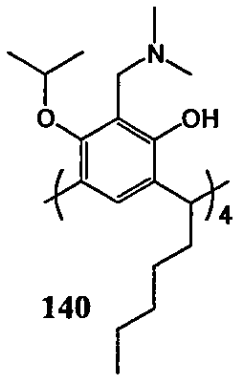
Scheme 79

Each reaction was stirred overnight, gradually reaching room temperature No attempt at purification of the product was made in either case. ^{1}H NMR spectroscopy confirmed the formation of 1-phenyl-1-propanol **138**. The ^{1}H NMR spectra of the crude reaction mixtures showed no benzaldehyde remaining. Yields were calculated from the mass of product and considerations of purity from the ^{1}H NMR spectra, as no major impurities were present Optical rotations were measured in hexane so that comparisons could be made with the values reported for enantiomerically pure **138** from Aldrich Chemical Co [72] Enantiomeric excesses were estimated from these values and accurately calculated by co-workers using chiral GC in the case of **entry 2**

The result in **entry 1** is very similar to the best e.e.s seen previously, but in this case only 1 mol% of the resorcinarene was used. By cooling the reaction further to –78 °C an

increase in e e. to 82% was produced, **entry 2**. The major enantiomer of alcohol **138** in both cases had the R-(+) configuration by comparison with literature optical rotation data [72] The enantiomer of **129** has not been made, so preventing any comparisons. Comparisons of any benefits of the presence of the bulky isopropyloxy groups over the smaller methoxy groups are difficult because of the benzoxazine rings being intact with resorcinarene **129**, compared to those used previously. Clearly further manipulation of **129** should be investigated Following the methodology developed to prepare resorcinarene **54** and its enantiomer **(Scheme 25, page 36)** it should be possible to generate resorcinarene **140, Figure 21**.

The axial chirality of **54** is solely due to the presence of both methoxy and phenolic hydroxyl groups on each aromatic ring. With the four methoxy groups being replaced by much more sterically demanding isopropyloxy groups, in combination with the new colder reaction conditions, an increase in the e e of the alcohol product can be envisaged



140

Figure 21

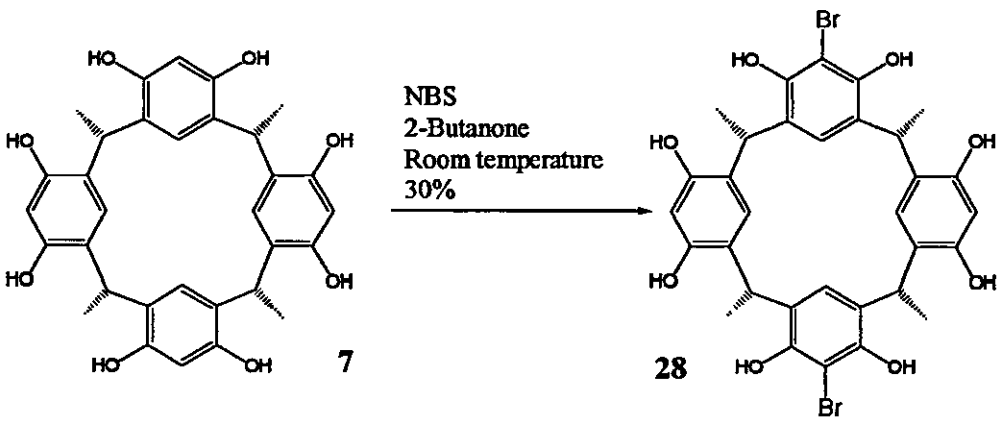
2.5.1 Conclusions and future work

The enantiomeric excess of 82% in alcohol **138** produced when using our new resorcinarene falls short of the very high levels of enantiomeric purity in the alcohol products formed with some established methodology.[82] The results reported here do, however, go some way towards demonstrating the potential usefulness of chiral resorcinarenes as ligands in asymmetric catalysis.

2.6 Synthetic routes to resorcinarenes possessing C_2 symmetry and new upper rim functionalities.

Most of the above discussions have focused on chiral resorcinarenes with a C_4 rotational symmetry. A number of scientists have investigated the use of various protection strategies to give C_2 symmetric resorcinarenes of the type shown in **Section 1.4.1, page 16** [23-25,45] Bohmer has investigated regioselective substitutions with resorcinarenes derived from various aldehydes, but most investigations have focused on **7**, derived from ethanal.[24]

2.6.1 Selective substitution and protection of octa hydroxy resorcinarene 7



Scheme 80

Some of the interest in the chemistry of calix[n]arenes and resorcinarenes derives from the possibility of increasing the size and shape of the cavity within the macrocycle, giving it greater potential as a host molecule, by various substitution and protection reactions Two publications by the group of Konishi,[25] in which distally dibrominated resorcinarene **28** was formed (using NBS in 2-butanone, **Scheme 80**), suggested the potential to build up two opposing sides of the cavity, on the upper rim, utilising a range of terminal alkynes in palladium catalysed Sonogashira[85] coupling reaction protocols, **Figure 22**. The groups of Santoyo-González,[86a] Fukazawa,[86b] and Bohmer[86c] have used this technology with calix[n]arenes.

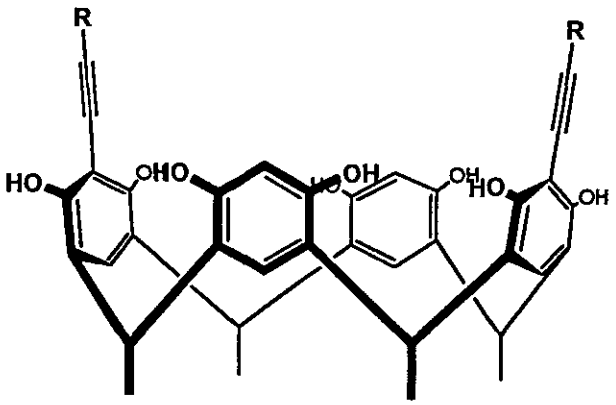


Figure 22

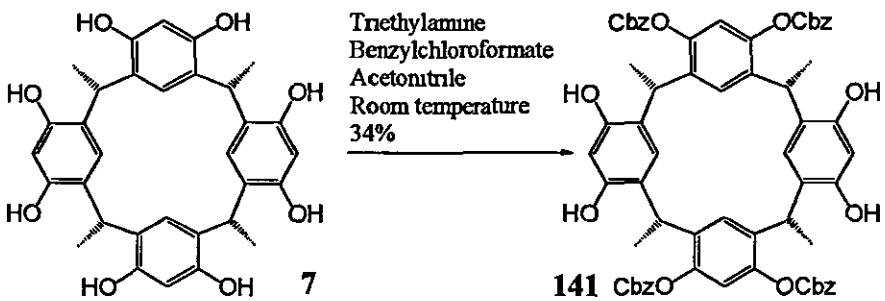
These substitutions would leave the aromatic 2-positions of the other pair of distal resorcinol units available for further and different functionalisation.

We were, however, unable to satisfactorily repeat the work of Konishi ^{1}H NMR spectroscopy data was produced confirming the production of the distally dibrominated species but the yields were invariably very low The reasons for this failure were unclear. Konishi reported the precipitation of **28** as a white solid, which was then recrystallised from methanol following isolation by filtration The yield of precipitate we recovered was around 30% each time but the material was very impure and the recrystallisation gave only a small amount of desired compound. Konishi produced **28** in 30% yield, but the yields we achieved, less than 5% of pure material, made this an unworkable option.

A different approach was decided upon starting with the tetra Cbz protection of **7**, using benzylchloroformate, to give **141** following protocol established by Bohmer,[24] **Scheme 81**. This was chosen because of the potential ease of removal of Cbz at a later stage (compared with tosyl, which had seen successful use within our group[84]) and the ease of isolation of the product by simple filtration A yield of around 34% was regularly achieved on a multi-gram scale. Additions of triethylamine and, 30 minutes later, benzylchloroformate were both done in one portion, very quickly and with vigorous stirring, as is highlighted in the literature procedure The positive effect on the reaction outcome by adding the reagents very quickly as opposed to drop wise is not fully

understood, but a mixture was reported following drop wise additions. The product precipitates from the reaction mixture over 24 hours along with a number of equivalents of triethylamine hydrochloride, which can be clearly seen in the ^{1}H NMR spectrum. This was easily removed though with a simple aqueous work up using DCM as the organic phase.

Some attempts were made at applying these reaction conditions to resorcinarenes with longer alkyl chains on the lower rim, but no precipitation of product was observed, leaving what was thought to be a complex mixture of regioisomers that could not be separated by column chromatography.

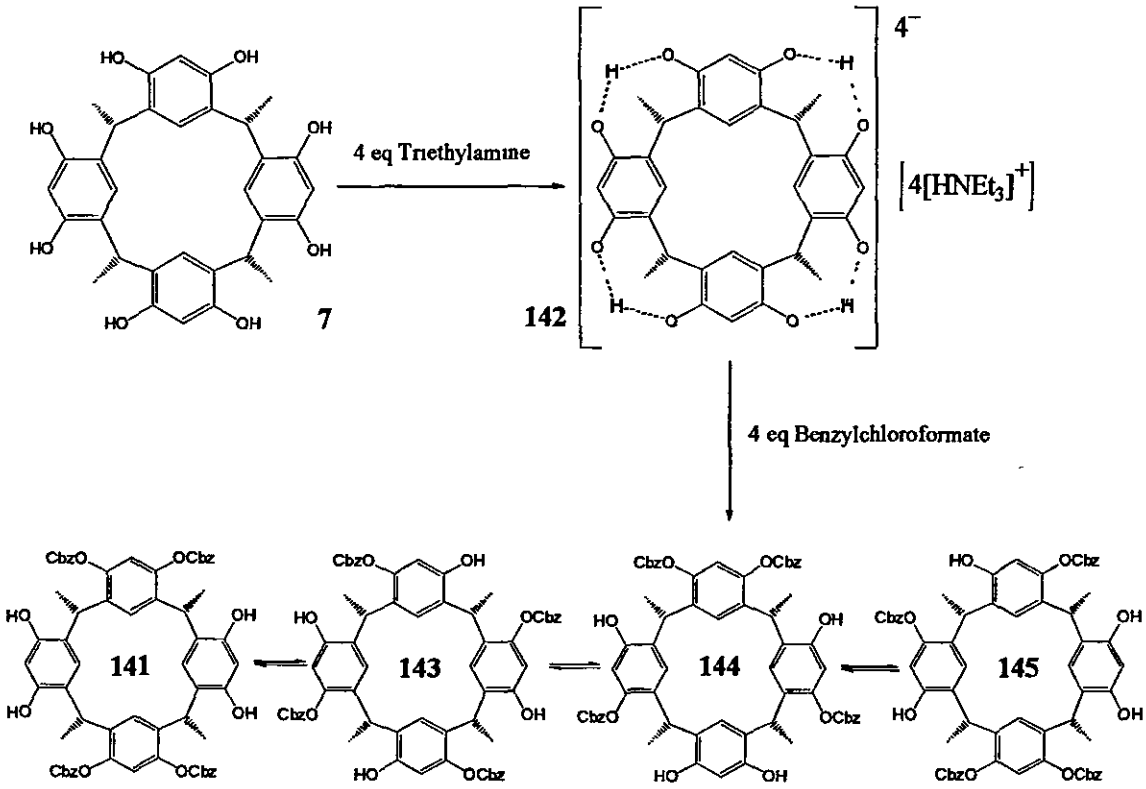


Scheme 81

Why only product **141** precipitates, and in a higher than statistically calculated yield, when considering all other possibilities, is unclear Bohmer[24] believes that regioselectivity greatly depends on the solvent used (a view supported by Shivanyuk[23]), complexation of the product with the hydrochloride salt of the base used (no selectivity was seen with pyridine or *i*-Bu_3N, but the reaction was successfully carried out with triethylamine and Hunig's base), and the acylating agent. The precipitate that forms following addition of the triethylamine, the structure of which was not identified, appears to react very quickly with the benzylchloroformate, forming a solution from which the product slowly precipitates This suggests that the product is not highly insoluble in acetonitrile, a fact that is emphasised by some of the filtered product re-dissolving when washed with excess acetonitrile.

Perhaps all of the possible regioisomers of the tetra Cbz protected macrocycle are in equilibrium in solution, **Scheme 82**. The removal of the first four phenolic hydrogen atoms of **7**, as seen in **Figure 3, page 16,** is relatively easy, as four hydrogen bonds remain. They are much more acidic than the last four phenolic protons. It is possible that the tetra phenolate, tetra triethylammonium ion complex **142** is the precipitated intermediate, which should be stable under the anhydrous reaction conditions. There are literature publications that report the tetra phenolate of **7** binds trialkylammonium cations with high binding constants.[22,64] Bohmer[24] suggested that the intermediate precipitate was 'most probably the complex of **7** with triethylamine,' though no proposal as to the exact structure was made.

Addition of benzylchloroformate to **142** would not necessarily initially produce compound **141**, but, if base catalysed intramolecular rearrangements can occur, as suggested by Hunter,[84] then **141** will eventually be formed, at which point precipitation occurs due simply to a fortunate solubility effect.



Scheme 82

Isomers **141** and **143-145** contain the maximum hydrogen bonding potential, of the possible structures formed from **142**.

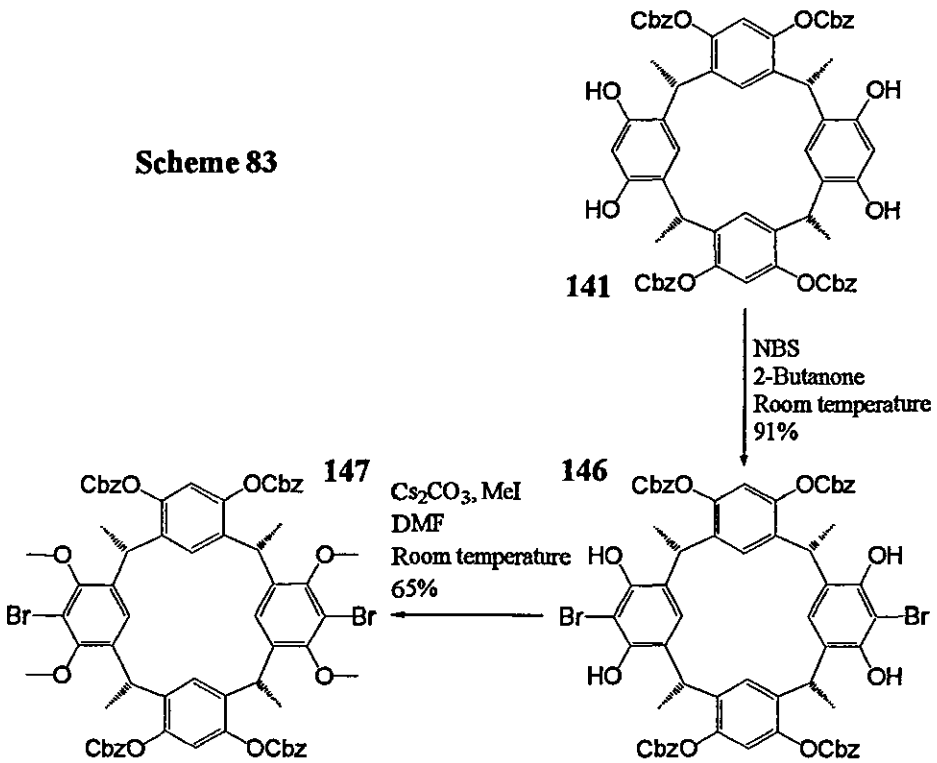
No investigations were made or have been reported as to the contents of the mother liquors of the reaction The mother liquors may contain the other tetra-protected isomers (no doubt along with some mono, di and tri-protected resorcinarenes from incomplete reactions) with product **141** having the lowest solubility and the one to at least partly precipitate, along with triethylamine hydrochloride.

If the suggestion of the intermediate tetra anion forming is not what actually occurs a whole range of mono to octa-protected resorcinarenes may be present in the liquors of the reaction. Clearly some analysis of the mother liquors is needed to shed more light on the reasons for the product that is obtained.

2.6.1.1 Distal dibromination of 141

We envisaged that bromination would predominantly occur on the two more reactive, unprotected resorcinol units using the conditions developed by Konishi,[24,25] namely NBS in 2-butanone at room temperature, **Scheme 83**. This proved to be the case, and even when more than four equivalents of brominating agent were used, the distally dibrominated compound **146** was isolated in high yield

Scheme 83



2.6.1.2 Methylation of the remaining phenolic hydroxyl groups

We decided to protect the four remaining phenolic hydroxyl groups to preclude any benzofuran formation[87] in the alkyne coupling reaction step. This would not really serve to deepen the cavity in the way envisaged and would also introduce the possibility of three stereoisomers being formed, **Figure 23**. **A** and **B** are chiral molecules and are enantiomers of each other, with a trans orientation of the benzofuran rings **C** has a cis orientation of the benzofuran rings [45] Benzofuran formation could potentially be used to introduce a chiral element into these kinds of resorcinarenes. However, without an

enantiomerically pure chiral alkyne giving two diastereoisomers, a racemic mixture would always be formed.

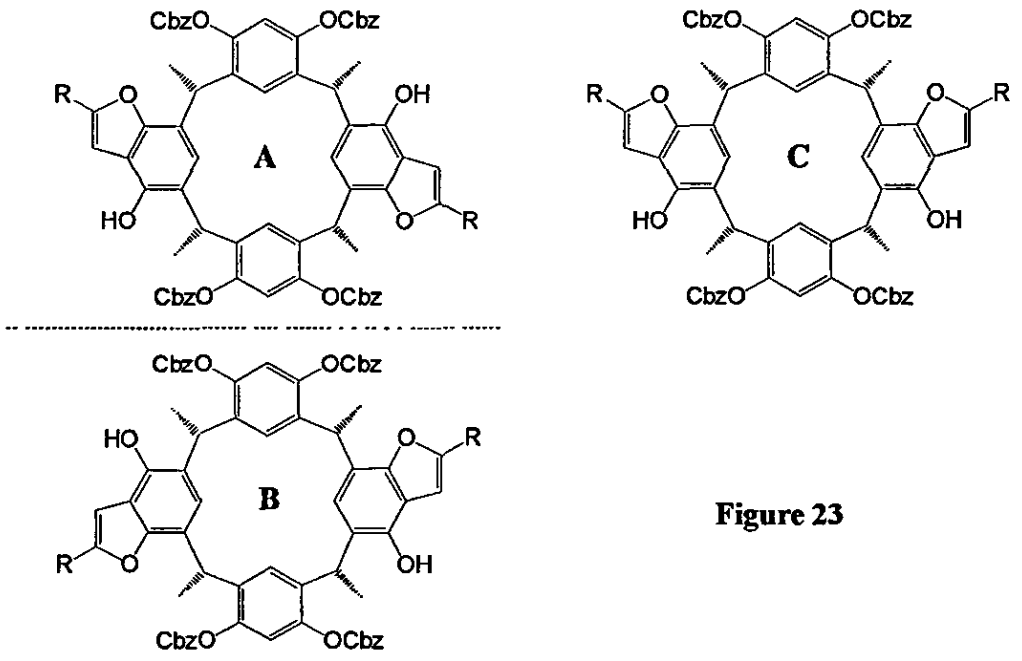


Figure 23

Methylation of the phenolic hydroxyl groups of **146** to give **147** was achieved in around 65% yield using Cs_2CO_3 and MeI in DMF at room temperature, **Scheme 83.**[88] This was the first method tried and no further optimisation was attempted. We thought that a low temperature method would be best in order to reduce the possibility of any thermal and / or base catalysed isomerisation of the Cbz groups as had been observed previously by Hunter [84]

Crystals of **147** suitable for X-ray analysis were obtained by the slow evaporation of DCM. The crystal structure obtained confirmed that the desired product had indeed been formed, **Appendix 1**. It can be clearly seen how the two brominated, resorcinol-derived units lay flat while the Cbz protected units are upright. This arrangement has been described as the boat conformation, **page 4**. A suggested reason for this is the absence of any intramolecular hydrogen bonding to hold the macrocycle in the crown conformation. This probably remains the key factor but steric effects should also be taken into account as observed previously.

The ^{1}H NMR spectrum of **147** was recorded in $CDCl_3$ at 50 °C to reduce the line broadening seen at ambient temperature This line broadening suggests a degree of flexibility within this macrocycle in the solution phase The two spectra are shown in **Appendix 2** for comparison.

2.6.1.3 Formation of a di-iodo version 150

While a number of research papers containing examples of Sonogashira coupling reactions have been published using aryl bromides, we forecast that harsh conditions would potentially be needed, especially with a hindered aryl bromide like **147**. While the development of **147** was ongoing attempts were made at formation of a more reactive di-iodo equivalent

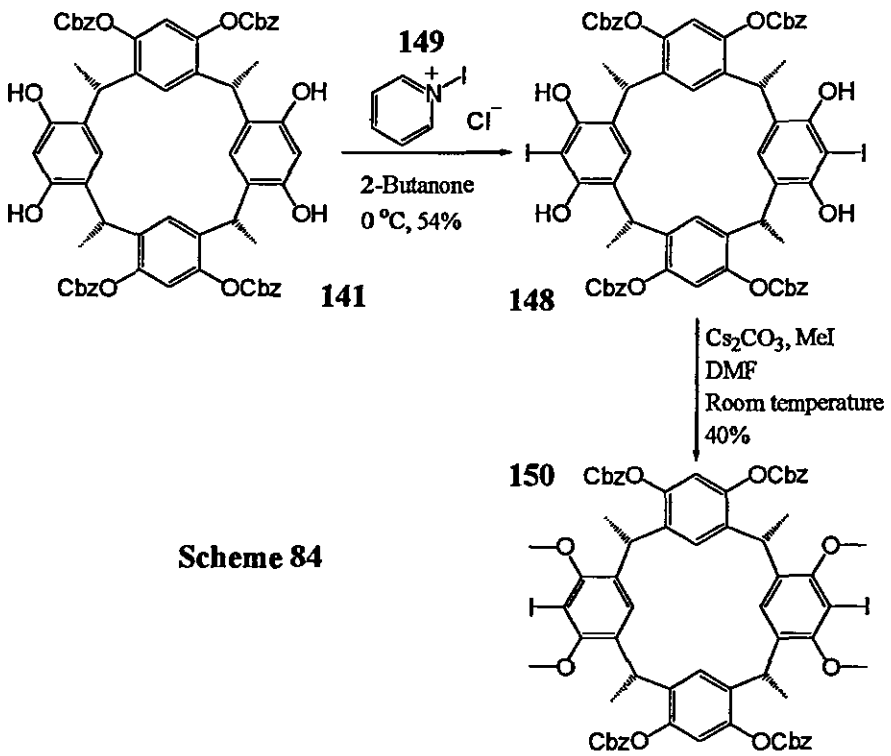
Iodination of **141** proved less straightforward than bromination. A number of iodinating agents were tried and are listed in **Table 10**.

Table 10

	Iodinating agent	Temperature	Solvent	Yield (product)
1	NIS	r/t	2-butanone	mixture
2	NIS	–78 °C to r/t	2-butanone	mixture
3	ICl	r/t	$CHCl_3$	mixture
4	ICl	–78 °C to r/t	DCM	mixture
5	pyridine-ICl	r/t	diethyl ether	mixture
6	pyridine-ICl	0 °C to r/t	2-butanone	54% (**148**)

Using the methodology shown in entries 1 to 5, complex mixtures of compounds were formed Statistically there are only two possible products if iodination occurs as expected, mono and bis, in addition to recovered starting material The ^{1}H NMR spectra of the crude reaction mixtures suggested that other side reactions were taking place forming a range of unidentified compounds. Conditions were eventually established

using a pyridine-iodine monochloride complex **149**,[89] **Scheme 84**. This has been described as a milder iodinating alternative to iodine monochloride.[44a]



Scheme 84

The iodination was carried out at 0 °C with some significant impurities present on completion. The purity of **148** was improved by column chromatography but a sample suitable for elemental analysis was never obtained and the methylation step was carried out on slightly impure material

Methylation to give **150** was achieved using the same conditions as with the bromide equivalent but only in around 40% isolated yield, as further problems with purification presented themselves. ^{1}H NMR spectra of the crude reaction mixture suggested a higher conversion No optimisation of these conditions was attempted Compound **150** also showed a degree of line broadening in the ^{1}H NMR spectrum.

2.6.2 Sonogashira coupling reactions to deepen the cavity

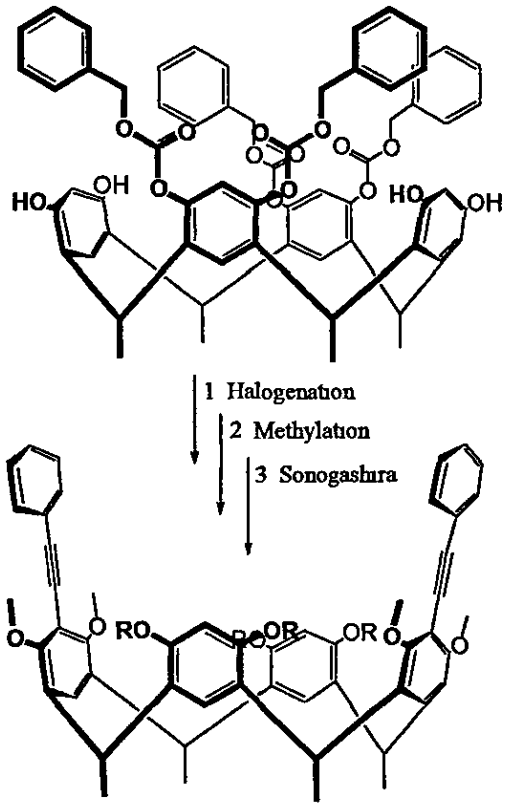


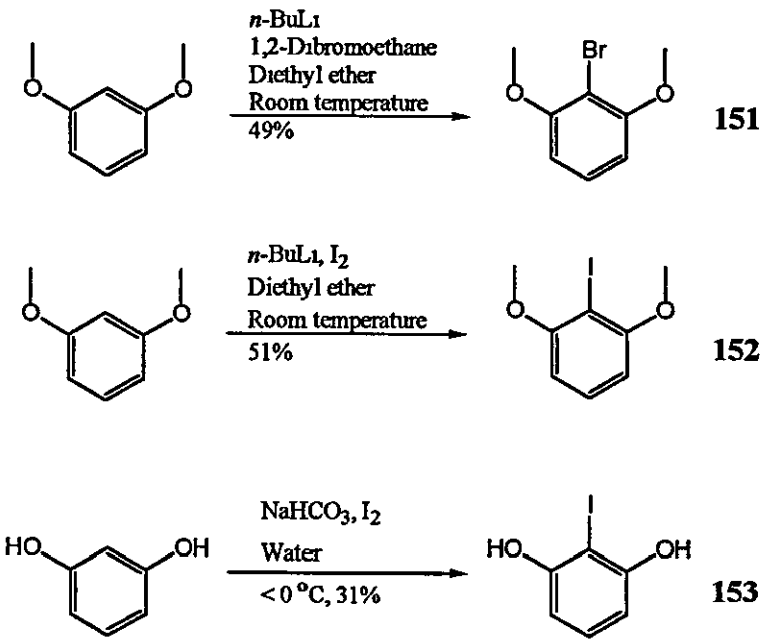
Figure 24

With protocol for the first two steps of **Figure 24** established, our attention was turned towards the Sonogashira coupling reaction between the aryl bromides and iodides produced and a terminal acetylene, initially using phenylacetylene

2.6.2.1 Development of reaction conditions

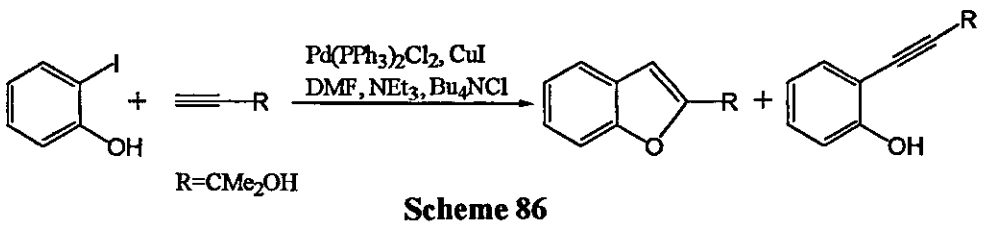
Sonogashira methodology was chosen because of a large number of well established procedures giving high yields of products,[85] including a recent publication involving mild reaction conditions with the less reactive aryl bromides.[90] These reactions would also impart a new alkyne functionality, which to the best of our knowledge, has not been seen before with a resorcinarene A range of model compounds was developed from substituted benzene derivatives in order to establish reaction conditions, **Scheme 85** Compounds **151**[91] and **152**[92] were produced from 1,3-dimethoxybenzene by lithiation

with *n*-BuLi at the aromatic 2-position, followed by a lithium-halogen exchange reaction, in reasonable yields. The multi-gram scales on which the reactions were carried out ensured they needed only to be carried out once to obtain sufficient quantities of the model compounds. 2-Iodoresorcinol **153**[93] was formed in only low yields, with conditions being required to minimise the amounts of para-iodinated and poly-iodinated resorcinol derivatives being formed. Recrystallisation afforded the pure material.



Scheme 85

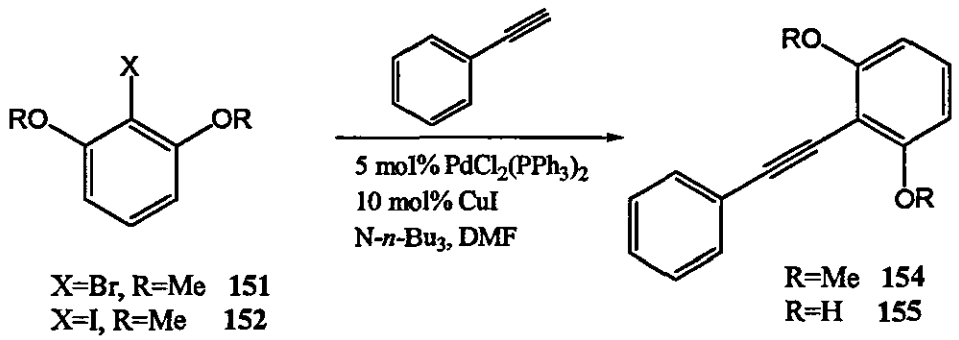
2-Iodoresorcinol **153** was produced to determine if coupling reactions would be possible without any conversion to the corresponding benzofuran. Kundu[87a,e] has reported the successful isolation of a significant amount of the alkyne 3-(*o*-hydroxyphenyl)-1,1-dimethylprop-2-yn-1-ol in a reaction between 2-iodophenol and 2-methyl-3-butyn-2-ol, along with some of the expected benzofuran, **Scheme 86**.



Scheme 86

Making use of the model compounds developed, compounds **154** and **155** were the first synthetic targets, **Scheme 87**. To our knowledge no literature evidence exists for these transformations using any alkyne. Three different reaction protocols were developed and are discussed below.

Method 1



X=Br, R=Me **151**
X=I, R=Me **152**
X=I, R=H **153**

R=Me **154**
R=H **155**

Scheme 87

Table 11

	Model compound	Alkyne equivalents	Temp /°C time	Time	Yield (product)
1	**152**	1 3	r/t	2 d	40% (**154**)
2	**152**	3	r/t	3 d	55% (**154**)
3	**152**	3	70	o/n	60% (**154**)
4	**152**	3	110	o/n	mixture
5	**151**	3	70	o/n	s/m
6	**153**	3	r/t	o/n	mixture

In each case the solvent was deoxygenated by bubbling nitrogen through the reaction mixture for 30 minutes prior to addition of the palladium and copper catalysts to minimise any oxidation Reactions were anhydrous and usually carried out with around 200 mg of aryl halide in 10 mL of DMF. Each reaction was analysed by ^{1}H NMR spectroscopy.

Alkyne **154** was formed in 40% yield from 2,6-dimethoxyiodobenzene **152** using 5 mol% of $PdCl_2(PPh_3)_2$ and 10 mol% of CuI as catalysts at room temperature The reaction was slow under these conditions but no obvious degradative side reactions had taken place, **entry 1** By increasing the amount of phenylacetylene added and lengthening the allowed reaction time, the yield improved to 55%, **entry 2** The yield and reaction time were both further improved by heating the reaction mixture to 70 °C, **entry 3**. High temperatures (**entry 4**) showed **154** to have formed in good yield but in a less clean reaction.

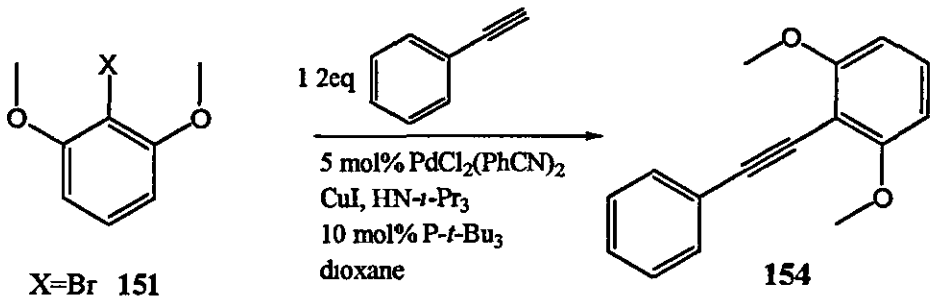
Unreacted starting material was recovered with the bromide equivalent **151, entry 5**. Bromides are known to be less reactive than the equivalent iodides in Sonogashira coupling reactions [90] These halide species are sterically hindered because of the presence of the two ortho-methoxy groups, further reducing their reactivity

A mixture of unidentified products was produced when 2-iodoresorcinol **153** was subjected to the reaction conditions. Neither product **155** nor any of the equivalent benzofuran was isolated.

Method 2

Buchwald and Fu[90] have recently reported the use of $Pd(PhCN)_2Cl_2$ in the presence of P-*t*-Bu_3 as an excellent catalyst system for Sonogashira reactions with aryl bromides at ambient temperatures. They reported success with *p*-methoxybromobenzene and also with the hindered 2,6-dimethylbromobenzene. In our hands this protocol failed to give any of the desired product **154**, even with heating, **entries 1-2, Table 12, Scheme 88.**

The catalyst system did give a reasonable yield of **154** from iodo material **152**, though heating was required and the reaction was slow, **entries 3-5**



X=Br **151**
X=I **152**

154

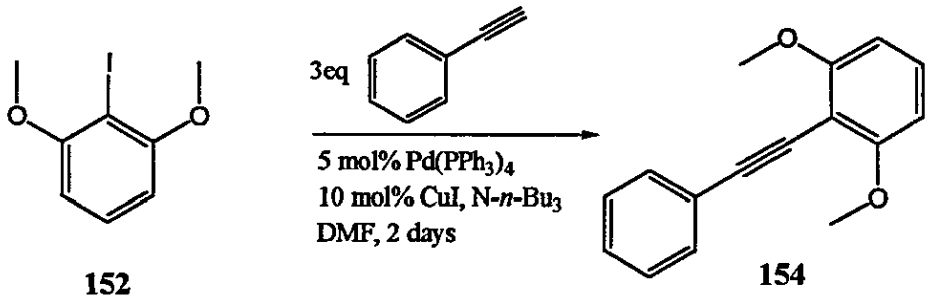
Scheme 88

Table 12

	Model compound	Mol% CuI	Temp / °C	Time	Yield
1	**151**	5	r/t	o/n	s/m
2	**151**	10	75	o/n	s/m
3	**152**	10	r/t	o/n	s/m
4	**152**	10	75	o/n	30% (**154**)
5	**152**	10	75	2 d	55% (**154**)

Method 3

The highest yield of **154** was achieved by using the conditions developed in **Method 1** but with a change in the palladium catalyst to $Pd(PPh_3)_4$ and a temperature increase to 85 °C, **Scheme 89**. A yield of 80% was produced following heating for 2 days



152 **154**

Scheme 89

2.6.2.2 Use of different alkynes possessing added functionality

Two other alkynes were investigated, namely 2-ethynylpyridine and 2-methyl-3-butyn-2-ol. They both possess an additional functionality The nitrogen lone pair of electrons in 2-ethynylpyridine could potentially act as a ligand for various metals if successfully coupled onto a resorcinarene 2-Methyl-3-butyn-2-ol has the potential for further functional group transformations, for example in a base catalysed retro-Favorskii, retro-aldol type reaction giving the terminal acetylene.[94]

The reaction conditions that were successful with 2,6-dimethoxyiodobenzene **152** and phenylacetylene were tested with 2-ethynylpyridine and 2-methyl-3-butyn-2-ol Unfortunately none of the previously established reaction conditions were successful. Invariably only unreacted aryl-iodide **152** was recovered The ^{1}H NMR spectrum of the crude reaction product using 2-methyl-3-butyn-2-ol in **Method 1** protocol showed evidence of another methoxy singlet as well as that of the starting material. Attempts at column chromatography succeeded only in isolating starting aryl-iodide.

The reasons for the failure of these reactions are unclear. Perhaps with the 2-ethynylpyridine reactions the copper was ligated by the nitrogen atoms of the pyridine rings, making it unreactive, although this is not generally reported in the literature [95] It has also been suggested that such legation may be a problem in deactivation of the palladium catalyst [96]

2.6.2.3 Use of newly established methods with resorcinarene 150

All of the reaction conditions which had proved successful with 2,6-dimethoxyiodobenzene **152** and phenylacetylene were applied to the equivalent resorcinarene **150**. In each case the resorcinarene was considered equivalent to two units of aryl iodide and the quantities of the other reagents adjusted accordingly.

The desired bis-alkyne product was never isolated In each case either unreacted starting material was recovered or a mixture of products was produced that defied characterisation. The reason for the failure of these reactions is unclear. It is possible that the slow reaction rates observed with 2,6-dimethoxyiodobenzene **152** are due to steric hindrance effects. Perhaps steric hindrance is further increased in the resorcinarene, due to the proximity of the Cbz groups

2.6.3 Conclusions and future work

A range of new, distally halogenated resorcinarenes has been prepared.

Reaction conditions for the successful and high yielding coupling of hindered 2,6-dimethoxyiodobenzene **154** with phenylacetylene have been established using Sonogashira methodology

Future investigations could focus on a more versatile coupling reaction for these hindered aryl halides to introduce new alkyne functionality onto the upper rim of a resorcinarene

Chapter 3

Experimental section

3.0 General experimental procedures

3.0.1 Purification of reagents, compounds and solvents

Commercially available reagents were used as supplied, without any further purification, unless stated otherwise, and were stored according to the manufacturers recommendations.

Flash chromatography was carried out using glass columns packed with Merck 9385 Kieselgel 60-45 (230-400 mesh) or Fluka Kieselgel 60 using a hand bellows to apply pressure to the column. Thin layer chromatography was carried out on aluminium or glass backed plates coated with Merck Kieselgel 60 GF_{254}. The plates were visualised using U.V. light or developed by staining using aqueous potassium permanganate solution, followed by heating with a hot air blower.

The refrigerator temperature used was 5 °C and the freezer temperature was –25 °C.

All compounds once made and / or purified were dried under vacuum at room temperature unless stated otherwise.

Pet-ether refers to the fraction of petroleum ether boiling between 40 and 60 °C in all cases, and was distilled over $CaCl_2$ before use. Petroleum ether was dried at reflux over phosphorus pentoxide, under nitrogen. Ethyl acetate was also distilled over $CaCl_2$ before use. DCM was distilled over phosphorus pentoxide before use and over phosphorus pentoxide under an atmosphere of nitrogen for anhydrous reactions. THF and diethyl ether were dried at reflux over sodium and benzophenone, under nitrogen. Methanol was dried at reflux over magnesium turnings and iodine, under nitrogen.
All other anhydrous solvents were bought from Aldrich Chemicals.

3.0.2 Reaction conditions

All reactions were carried out using Pyrex or equivalent glass round bottomed flasks fitted with a Teflon coated magnetic follower over a stirrer hot plate, unless otherwise stated. Anhydrous reactions were carried out using pre-dried glassware (oven at 150 °C and cooled in a desiccator over self-indicating silica pellets) under a constant positive pressure of nitrogen, provided by either a steady flow through a bubbler or by a nitrogen filled balloon. Liquid reagents sensitive to air and moisture were added using syringe and cannula techniques through Suba-seal septum caps.
Cold water baths contained water from the cold tap at around 15 °C.

3.0.3 Mass spectrometry

All low resolution mass spectra (LRMS) were Low Resolution Fast Atom Bombardment spectra carried out by the EPSRC National Mass Spectrometry Service Centre. All high resolution mass spectra (HRMS) were recorded on a Jeol (JMX)SX102 instrument using electron impact [(EI) for small molecules] and fast atom bombardment [(FAB) for resorcinarenes] ionisation techniques.

3.0.4 Elemental analyses

Microanalyses were performed on a Perkin Elmer Elemental Analyser 2400 CHN.

3.0.5 Melting points

Melting points were measured on an Electrothermal-IA 9100 apparatus or a Stuart Scientific SMP3.

3.0.6 Optical rotations

Optical rotations were carried out using an Optical Activity Polaar 2001 instrument at room temperature using the solvent stated, usually chloroform. Concentrations (c) are measured in g / 100 cm^3.

3.0.7 Nuclear Magnetic Resonance (NMR)

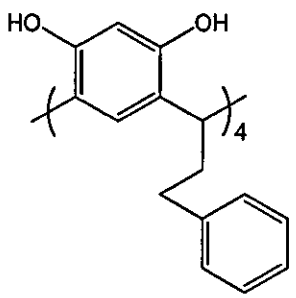
Proton NMR spectra (δ_H) were recorded using Bruker AC-250 and Bruker DPX-400 instruments operating at 250.13 and 400.13 MHz, respectively. The experiments were carried out in deuterated solvents, with tetramethylsilane as the internal standard, at 25 °C unless otherwise stated. Carbon-13 NMR spectra (δ_C) were recorded on a Bruker DPX-400 machine operating at 100 62 MHz using the same solvent and internal standard as the corresponding proton spectra. DEPT spectra were recorded on the same instrument.

3.0.8 Infrared spectra

Infrared spectra were recorded on a Perkin Elmer Paragon 2001 instrument in the range 600-4000 cm^{-1}. Solid compounds were run as thin films of their solution in the solvent stated, usually DCM, on sodium chloride discs. Liquid compounds were run neat on sodium chloride discs.

3.1 Experimental details for Section 2.1

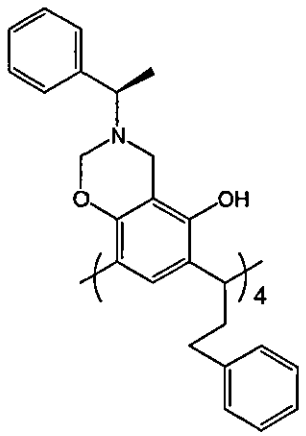
Octa hydroxy phenylethyl resorcinarene 34[4]



Resorcinol (36.1 g, 330 mmol) was dissolved in ethanol (95%, 260 mL) and concentrated HCl (66 mL) and cooled to 0 °C. Pre-distilled dihydrocinnamaldehyde (44 g, 330 mmol) was added drop wise over 1 h. The reaction was then allowed to warm to room temperature and stirred for 24 h. After this time the mixture was heated at reflux for 3 d. After this time the reaction was allowed to cool to room temperature then cooled further to 0 °C. The precipitate was removed by filtration and washed with large amounts of ice cold 10% water / ethanol. The solid was recrystallised from methanol and dried under vacuum at 80 °C, furnishing the title compound (37.2 g, 50%) as a pale brown powder.

LRMS found: M^+, 904, $C_{60}H_{56}O_8$, requires 905; δ_H (d_6-DMSO, 400 MHz) 2.47 (16 H, m, CH_2CH_2), 4.27 (4 H, bt, CH), 6.20 (4 H, s, ArH), 7.11-7.21 (20 H, m, ArH), 7.43 (4 H, s, ArH), 9.06 (8 H, s, OH); δ_C (d_6-DMSO, 100 MHz) 33.56 (CH), 34.71 (CH_2), 36.23 (CH_2), 102 83 (CH), 123.84 (C), 125.25 (CH), 125.93 (CH), 128.51 (CH), 128.79 (CH), 142.61 (C), 152.02 (C).

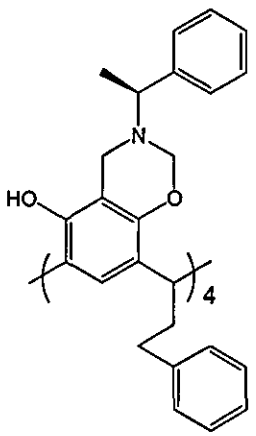
Tetra-[*N*-(R-(+)-α-methylbenzyl)-3,4-dihydro-2*H*-1,3-benzoxazine] resorcinarene 45[36,41]



Octa hydroxy phenylethyl resorcinarene **34** (15 g, 16.6 mmol) was stirred in ethanol (100%, 700 mL) under a nitrogen atmosphere. R-(+)-α-methylbenzylamine (10.1 g, 83 mmol) was added in one portion. Formaldehyde (37% solution in water, 13.5 g, 166 mmol) was added in one portion and the mixture heated at reflux overnight. After this time the reaction was allowed to cool to room temperature and the precipitate filtered and washed with large amounts of ethanol (95%), giving the title compound (20.5 g, 83%) as a pale pink solid.

m.p. 188-189 °C; δ_H ($CDCl_3$, 250 MHz) 1.30 (12 H, d, J = 6.5 Hz, CH_3), 2.50-2.61 (16 H, m, CH_2CH_2), 3 75 (4 H, d, J = 17.6 Hz, NCH_2), 3.81 (4H, q, J = 6.2 Hz, $C\underline{H}CH_3$), 3.99 (4 H, d, J = 17.6 Hz, NCH_2), 4.28 (4 H, t, J = 7.5 Hz, $C\underline{H}CH_2$), 4.94 (4 H, d, J = 10.2 Hz, NCH_2O), 5.14 (4 H, d, J = 10.3 Hz, NCH_2O), 6 92-7.24 (44 H, m, ArH), 7.67 (4 H, s, OH).

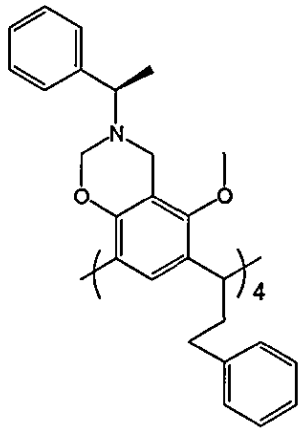
Tetra-[*N*-(S-(-)-α-methylbenzyl)-3,4-dihydro-2*H*-1,3-benzoxazine] resorcinarene 45b[36,41]



Octa hydroxy phenylethyl resorcinarene **34** (9 g, 10 mmol) was stirred in ethanol (100%, 600 mL) under a nitrogen atmosphere. S-(-)-α-methylbenzylamine (6 g, 50 mmol) was added in one portion. Formaldehyde (37% solution in water, 8.1 g, 100 mmol) was added in one portion and the mixture heated at reflux overnight. After this time the reaction was allowed to cool to room temperature and the precipitate filtered and washed with large amounts of ethanol (95%), giving the title compound (13.5 g, 91%) as a pale pink solid.

m.p. 187-190 °C; δ_H ($CDCl_3$, 250 MHz) 1.30 (12 H, d, J = 6.6 Hz, CH_3), 2.52-2.61 (16 H, m, CH_2CH_2), 3.75 (4 H, d, J = 17.5 Hz, NCH_2), 3.81 (4H, q, J = 6.2 Hz, $C\underline{H}CH_3$), 3.99 (4 H, d, J = 17.5 Hz, NCH_2), 4.28 (4 H, t, J = 6.7 Hz, $C\underline{H}CH_2$), 4.94 (4 H, d, J = 10.2 Hz, NCH_2O), 5.14 (4 H, d, J = 10.1 Hz, NCH_2O), 6.92-7.23 (44 H, m, ArH), 7.68 (4 H, s, OH).

Tetra methoxy, tetra-[*N*-(R-(+)-α-methylbenzyl)benzoxazine] resorcinarene 50

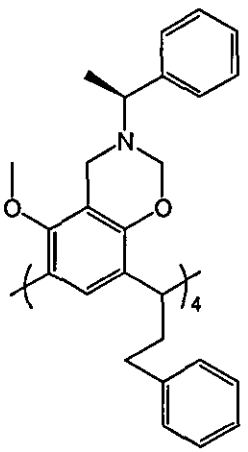


Tetra benzoxazine resorcinarene **45** (18 g, 12.1 mmol) was dissolved in dry THF (500 mL) under an atmosphere of nitrogen and cooled to –78 °C. *n*-Butyl lithium (2.5 M solution in hexanes, 24.2 mL, 60.5 mmol) was added drop wise with vigorous stirring, using an overhead stirrer, and stirred for 30 min. Methyl trifluoromethanesulphonate (10 g, 60.5 mmol) was added drop wise and stirred for 40 min. After this time the reaction was quenched with methanol (20 mL). The mixture was then allowed to warm to room temperature and concentrated. The residue produced was partitioned between DCM (200 mL) and water (200 mL). The organic layer was washed twice with water (250 mL), dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography on silica gel (5% methanol / DCM) to afford the *title compound* (17.6 g, 94%) as a pale yellow foam.

LRMS found: M^+, 1541, $C_{104}H_{108}N_4O_8$, requires, 1542; elemental analysis, found, C, 80.86; H, 6.90; N, 3.56; requires C, 80.80; H, 7.30; N, 3.62%; $[\alpha]_D^{25}$ 135 °, c = 0.46, $CHCl_3$; δ_H ($CDCl_3$, 400 MHz) 1.39 (12 H, d, J = 6.4 Hz, CH_3), 2.11-2.31 (8 H, m, $C\underline{H}_2CH$), 2.69 (8 H, t, J = 7.6 Hz, CH_2Ar), 3.21 (12 H, s, OCH_3), 3.81 (4 H, q, J = 6.4 Hz, $C\underline{H}CH_3$), 3 87 (4 H, d, J = 16 8 Hz, NCH_2), 4.19 (4 H, d, J = 16.8 Hz, NCH_2), 4.53 (4 H, t, J = 7.6 Hz, $C\underline{H}CH_2$), 4.57 (4 H, d, J = 10 Hz, NCH_2O), 4.64 (4 H, d, J = 10 Hz, NCH_2O), 6.84 (4 H, s, ArH), 7.12-7.22 (40 H, m, ArH); δ_C ($CDCl_3$, 100 MHz) 21.33 (CH_3), 34.55 (CH_2), 35.27 (CH), 37.64 (CH_2), 44.50 (NCH_2), 57.12 (CH), 59.94 (OCH_3), 79.57 (NCH_2O), 112.38 (C), 124.35 (CH), 125.50 (CH), 127.32 (CH), 127.50 (CH),

128.21 (CH), 128.40 (CH), 128.45 (CH), 128 53 (C), 142.67 (C), 143.97 (C), 150.27 (C), 153.78 (C), remaining aromatic (C) obscured; ν_{max} (DCM, cm^{-1}) 3054, 2986, 1421, 1265, 896, 740.

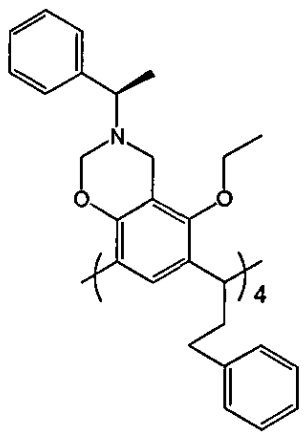
Tetra methoxy, tetra-[*N*-(S-(-)-α-methylbenzyl)benzoxazine] resorcinarene 50b[41]



Tetra benzoxazine resorcinarene **45b** (15 g, 10.1 mmol) was dissolved in dry THF (400 mL) under an atmosphere of nitrogen and cooled to –78 °C. *n*-Butyl lithium (2.5 M solution in hexanes, 20.2 mL, 50.4 mmol) was added drop wise with vigorous stirring, using an overhead stirrer, and stirred for 30 min. Methyl trifluoromethanesulphonate (8.3 g, 50.4 mmol) was added drop wise and stirred for 40 min. After this time the reaction was quenched with methanol (20 mL). The mixture was then allowed to warm to room temperature and concentrated. The residue produced was partitioned between DCM (200 mL) and water (250 mL). The organic layer was washed twice with water (200 mL), dried over $MgSO_4$ and concentrated. The residue was purified on silica gel (5% methanol / DCM) to afford the title compound (14.2 g, 91%) as a pale yellow foam. LRMS found: $(M+H)^+$, 1542, $C_{104}H_{108}N_4O_8$, requires, 1543; δ_H ($CDCl_3$, 400 MHz) 1.39 (12 H, d, J = 8 Hz, CH_3), 2.17-2.24 (8 H, m, $C\underline{H}_2CH$), 2.69 (8 H, t, J = 8 Hz, CH_2Ar), 3.21 (12 H, s, OCH_3), 3.81 (4 H, q, J = 6.4 Hz, $C\underline{H}CH_3$), 3.88 (4 H, d, J = 17 Hz, NCH_2), 4.19 (4 H, d, J = 17 Hz, NCH_2), 4.53 (4 H, t, J = 8 Hz, $C\underline{H}CH_2$), 4.58 (4 H, d, J = 10 Hz, NCH_2O), 4.64 (4 H, d, J = 10 Hz, NCH_2O), 6.84 (4 H, s, ArH), 7.12-7.22 (40 H, m,

ArH); δ_C ($CDCl_3$, 100 MHz) 21.32 (CH_3), 34.55 (CH_2), 35.27 (CH), 37.64 (CH_2), 44.50 (NCH_2), 57.13 (CH), 59.95 (OCH_3), 79.57 (NCH_2O), 112.39 (C), 124.36 (CH), 125.50 (CH), 127.32 (CH), 127.51 (CH), 128.21 (CH), 128.40 (CH), 128.45 (CH), 128.53 (C), 142 67 (C), 143.96 (C), 150.27 (C), 153.78 (C), remaining aromatic (C) obscured.

Tetra ethyloxy, tetra-[*N*-(R-(+)-α-methylbenzyl)benzoxazine] resorcinarene 71

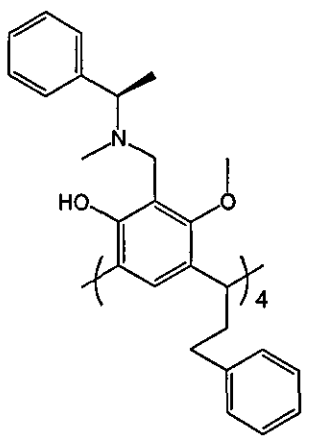


Tetra benzoxazine resorcinarene **45** (8.3 g, 5.6 mmol) was dissolved in dry THF (300 mL) under an atmosphere of nitrogen and cooled to –78 °C. *n*-Butyl lithium (2.5 M solution in hexanes, 11.2 mL, 28 mmol) was added drop wise with vigorous stirring, using an overhead stirrer, and stirred for 30 min. Ethyl trifluoromethanesulphonate (5 g, 28 mmol) was added drop wise and stirred for 1 h. After this time the reaction was quenched with methanol (20 mL). The mixture was then allowed to warm to room temperature and concentrated. The residue produced was partitioned between DCM (150 mL) and water (200 mL). The organic layer was washed twice with water (200 mL), once with saturated brine solution (100 mL), dried over $MgSO_4$ and concentrated. The residue was purified on silica gel (30% EtOAc / pet-ether) to afford the *title compound* (5.6 g, 63%) as a white foam.

LRMS found: M^+, 1597, $C_{108}H_{116}N_4O_8$, requires 1598; elemental analysis, found C, 81.08; H, 7.13; N, 3.39; requires C, 81.17; H, 7.32; N, 3.51%; $[\alpha]_D^{25}$ 110 °, c = 0.79, $CHCl_3$; δ_H ($CDCl_3$, 400 MHz) 1.03 (12 H, t, J = 6.8 Hz, $CH_2C\underline{H}_3$), 1.39 (12 H, d, J = 6.8 Hz, $CHC\underline{H}_3$), 2.15 (4 H, m, $C\underline{H}_2CH$), 2.25 (4 H, m, $C\underline{H}_2CH$), 2 69 (8 H, t, J = 7.6 Hz,

CH_2Ar), 3.30 (8 H, bq, OCH_2), 3.83 (4 H, q, J = 6 Hz, C<u>H</u>CH_3), 3.85 (4 H, d, J = 16.8 Hz, NCH_2), 4.22 (4 H, d, J = 16.8 Hz, NCH_2), 4.50-4.58 (12 H, m, C<u>H</u>CH_2, NCH_2O and NCH_2O), 6.83 (4 H, s, ArH), 7.12-7.30 (40 H, m, ArH); δ_C ($CDCl_3$, 100 MHz) 15.52 (CH_3), 21.48 (CH_3), 34.67 (CH_2), 35 66 (CH), 37.58 (CH_2), 44.54 (NCH_2), 56.85 (CH), 68.09 (OCH_2), 79.49 (NCH_2O), 112.36 (C), 124.56 (CH), 125.46 (CH), 127.26 (CH), 127.50 (CH), 128.18 (CH), 128.41 (CH), 128.48 (CH), 128.69 (C), 142.74 (C), 144.10 (C), 150.06 (C), 153.11 (C), remaining aromatic (C) obscured; ν_{max} (DCM, cm^{-1}) 3054, 2982, 2305, 1602, 1468, 1266, 896, 742.

Tetra methoxy, tetra-[*N*-(R-(+)-α-methylbenzyl)-*N*-methyl] resorcinarene 67

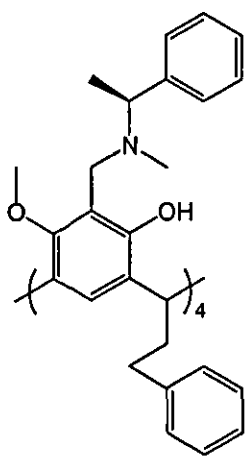


Tetra methoxy, tetra benzoxazine resorcinarene **50** (16 g, 10.3 mmol) was dissolved in formic acid (96%, 120 mL) and heated at reflux for 6 h. After this time the reaction was allowed to cool to room temperature and carefully neutralised with aqueous ammonium hydroxide solution. The mixture was extracted into EtOAc (300 mL). The organic phase was washed twice with water (150 mL), dried over $MgSO_4$ and concentrated leaving a brown foam. Purification on silica gel (5% methanol / DCM) gave the *title compound* (13.2 g, 83%) as a yellow foam.

LRMS found: $(M+H)^+$, 1550, $C_{104}H_{116}N_4O_8$, requires 1551; elemental analysis, found C, 80.51; H, 7.38; N, 3.48; requires C, 80.38; H, 7.78; N, 3.61%; $[\alpha]_D^{25}$ –15 °, c = 0.92, $CHCl_3$; δ_H ($CDCl_3$, 400 MHz) 1.43 (12 H, d, J = 8 Hz, CH_3), 2.09 (16 H, m and s, C<u>H</u>$_2$CH and NCH_3), 2.18-2.23 (4 H, m, C<u>H</u>$_2$CH), 2.67 (8 H, t, J = 8 Hz, CH_2Ar), 3 29 (12

H, bs, OCH_3), 3.59 (4 H, d, J = 12 Hz, NCH_2), 3.71-3.76 (8 H, d and q, NCH_2 and $C\underline{H}CH_3$), 4.61 (4 H, t, J = 8 Hz, $C\underline{H}CH_2$), 6.81 (4 H, s, ArH), 7.07-7.13 (20 H, m, ArH), 7 22-7.32 (20 H, m, ArH); δ_C ($CDCl_3$, 100 MHz) 15.99 (CH_3), 34.63 (CH_2), 35.79 (NCH_3), 37.06 (CH), 37.96 (CH_2), 51.16 (NCH_2), 60.99 (OCH_3), 62 23 (CH), 113.82 (C), 125.28 (CH), 125.38 (CH), 127.31 (C), 127.44 (CH), 128.01 (CH), 128.12 (CH), 128.38 (CH), 128.46 (CH), 141.22 (C), 143.07 (C), 154.42 (C), 154.58 (C), remaining aromatic (C) obscured; ν_{max} (DCM, cm^{-1}) 2979, 2938, 2304, 1732, 1593, 1453, 1265, 1091, 989, 895, 737, 702.

Tetra methoxy, tetra-[*N*-(S-(-)-α-methylbenzyl)-*N*-methyl] resorcinarene 67b

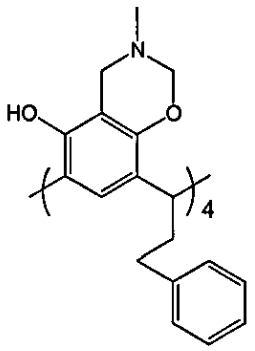


Tetra methoxy, tetra benzoxazine resorcinarene **50b** (8.1 g, 5.3 mmol) was dissolved in formic acid (96%, 60 mL) and heated at reflux for 6 h. After this time the reaction was allowed to cool to room temperature and carefully neutralised with aqueous ammonium hydroxide solution. The mixture was extracted into EtOAc (250 mL). The organic phase was washed twice with water (150 mL), dried over $MgSO_4$ and concentrated leaving a brown foam. Purification on silica gel (5% methanol / DCM) gave the *title compound* (7.2 g, 89%) as a yellow foam.

LRMS found: $(M+H)^+$, 1550, $C_{104}H_{116}N_4O_8$, requires 1551; elemental analysis, found C, 80 40; H, 7.39; N, 3.45; requires C, 80.38; H, 7.78; N, 3 61%; $[\alpha]_D^{25}$ 20 °, c = 0.48, $CHCl_3$; δ_H ($CDCl_3$, 400 MHz) 1.43 (12 H, d, J = 8 Hz, CH_3), 2 08 (16 H, m and s,

$C\underline{H}_2CH$ and NCH_3), 2.16-2.25 (4 H, m, $C\underline{H}_2CH$), 2 66 (8 H, t, J = 8 Hz, CH_2Ar), 3.29 (12 H, bs, OCH_3), 3.59 (4 H, d, J = 12 Hz, NCH_2), 3.70-3.77 (8 H, d and q, NCH_2 and $C\underline{H}CH_3$), 4.61 (4 H, t, J = 8 Hz, $C\underline{H}CH_2$), 6.81 (4 H, s, ArH), 7.06-7.11 (20 H, m, ArH), 7.25-7.31 (20 H, m, ArH); δ_C ($CDCl_3$, 100 MHz) 15.93 (CH_3), 34 60 (CH_2), 35.73 (NCH_3), 37.03 (CH), 37.97 (CH_2), 51.07 (NCH_2), 60.98 (OCH_3), 62.18 (CH), 113.66 (C), 125.27 (CH), 125.50 (CH), 127.27 (C), 127.43 (CH), 127.99 (CH), 128.11 (CH), 128.36 (CH), 128.44 (CH), 141.13 (C), 143.03 (C), 154.36 (C), 154.50 (C), remaining aromatic (C) obscured; ν_{max} (DCM, cm^{-1}) 3054, 2986, 2305, 1595, 1453, 1265, 1092, 896, 739.

Tetra-[*N*-methyl-(3,4-dihydro-2*H*-1,3-benzoxazine)] resorcinarene 72

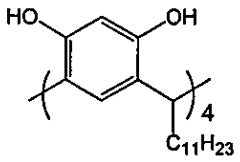


Octa hydroxy phenylethyl resorcinarene **34** (9 g, 10 mmol) was dissolved in ethanol (100%, 300 mL) and toluene (300 mL). Methylamine (40% solution in water, 3.9 g, 50 mmol) was added in one lot. Formaldehyde (37% solution in water, 8.1 g, 100 mmol) was added in one lot and the reaction heated at reflux overnight. After this time the reaction was allowed to cool and the solvent removed under vacuum. The residue was mixed with ethanol (100%, 300 mL) and heated at reflux for 1 h. The mixture was then allowed to cool. The solid product was filtered and washed several times with large amounts of ethanol (95%), furnishing the *title compound* (9.7 g, 87%) as a pale yellow solid.

LRMS found: M^+, 1125, $C_{72}H_{76}N_4O_8$, requires 1125; elemental analysis, found C, 76.56; H, 6.76; N, 4.80; requires C, 76.84; H, 6.81; N, 4.98%; m.p. > 250 °C, degrades; δ_H ($CDCl_3$, 400 MHz) 2.42-2.67 (16 H, m, CH_2CH_2), 2.53 (12 H, s, NCH_3), 3.76 (4 H, d, J =

17.2 Hz, NCH_2), 3.93 (4 H, d, J = 17.2 Hz, NCH_2), 4.30 (4 H, t, J = 7.2 Hz, CH), 4.80 (4 H, d, J = 9.6 Hz, NCH_2O), 4.86 (4 H, d, J = 9.2 Hz, NCH_2O), 7.10-7.23 (24 H, m, ArH), 7.75 (4 H, s, OH); δ_C ($CDCl_3$, 100 MHz) 32.60 (CH), 34.57 (CH_2), 35.98 (CH_2), 40.00 (CH_3), 48.21 (NCH_2), 84.49 (NCH_2O), 108.50 (C), 120.89 (CH), 123.16 (C), 124.15 (C), 125.87 (CH), 128.42 (CH), 128.55 (CH), 141.83 (C), 147.81 (C), 149.93 (C); ν_{max} (DCM, cm^{-1}) 3363, 3053, 2305, 1601, 1473, 1265, 1096, 895, 735.

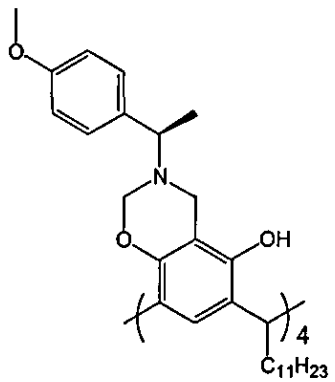
Octa hydroxy undecyl resorcinarene 41[4]



Resorcinol (39.6 g, 360 mmol) was dissolved in ethanol (95%, 200 mL) and concentrated HCl (50 mL) and cooled to 0 °C. Dodecanal (66.4 g, 360 mmol), dissolved in ethanol (95%, 100 mL), was added drop wise over 1 h. The reaction was then allowed to warm to room temperature and heated at reflux for 2 d. After this time the reaction was allowed to cool, then cooled further to 0 °C. The precipitate was removed by filtration and washed with large amounts of ice-cold methanol. The solid was recrystallised from methanol and dried under vacuum at 80 °C, furnishing the title compound (53 g, 53%) as a pale brown powder.

HRMS found: M^+, 1105.8409, $C_{72}H_{112}O_8$, requires 1105.8435; δ_H (CD_3COCD_3, 400 MHz) 0.89 (12 H, t, J = 7.2 Hz, CH_3), 1.30-1.37 (64 H, m, CH_2's), 2.04-2.07 (8 H, m, $C\underline{H}_2CH_2CH$), 2.26-2.30 (8 H, m, $C\underline{H}_2CH$), 4.30 (4 H, t, J = 7.6 Hz, CH), 6.24 (4 H, s, ArH), 7.54 (4 H, s, ArH).

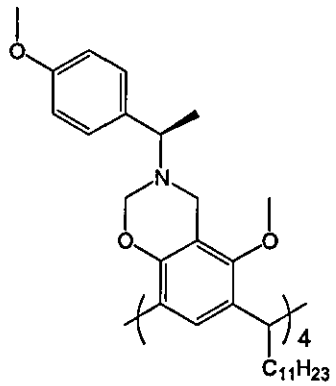
Tetra-[*N*-(*p*-methoxy-R-(+)-α-methylbenzyl)-3,4-dihydro-2*H*-1,3-benzoxazine] resorcinarene 91



Octa hydroxy undecyl resorcinarene **41** (6.1 g, 5.5 mmol) was mixed in ethanol (100%, 350 mL) under a nitrogen atmosphere. *p*-Methoxy-R-(+)-α-methylbenzylamine (5 g, 33 mmol) was added in one portion. Formaldehyde (37% solution in water, 5 mL, 62 mmol) was added in one portion and the mixture heated at reflux overnight. After this time the reaction was allowed to cool to room temperature and the precipitate filtered and washed with large amounts of ethanol (95%) giving the *title compound* (7.2 g, 73%) as a pale pink solid.

Elemental analysis, found C, 77 02; H, 9.08; N, 3.00; $C_{116}H_{164}N_4O_{12}$, requires C, 77.12; H, 9.15; N, 3.10%; m.p. 80 °C, degrades; $[\alpha]_D^{25}$ 110 °, c = 0.75, $CHCl_3$; δ_H ($CDCl_3$, 400 MHz) 0.88 (12 H, t, J = 7.2 Hz, CH_3), 1.27-1.37 (72 H, m, CH_2's), 2.15 (4 H, m, C<u>H</u>$_2$CH), 2.23 (4 H, m, C<u>H</u>$_2$CH), 3 66 (12 H, s, OCH_3), 3.72 (4 H, d, J = 17.2 Hz, NCH_2), 3.77 (4 H, q, J = 6.4 Hz, C<u>H</u>CH_3), 3.94 (4 H, d, J = 17.6 Hz, NCH_3), 4.21 (4 H, t, J = 7.6 Hz, C<u>H</u>CH_2), 4.86 (4 H, d, J = 10 Hz, NCH_2O), 5.08 (4 H, d, J = 10 Hz, NCH_2O), 6.74-6.76 (8 H, m, ArH), 7.15 (4 H, s, ArH), 7.19-7.21 (8 H, m, ArH), 7.66 (4 H, s, OH); δ_C ($CDCl_3$, 100 MHz) 14.14 (CH_3), 21.42 (CH_3), 22.71 (CH_2), 28.16 (CH_2), 29.45 (CH_2), 29.78 (CH_2), 29.82 (CH_2), 29.85 (CH_2), 31.99 (CH_2), 32.65 (CH), 33.71 (CH_2), 44 60 (NCH_2), 55.12 (OCH_3), 57.01 (CH), 80.66 (NCH_2O), 108.92 (C), 113.73 (CH), 121.03 (CH), 123.47 (C), 124.37 (C), 128.21 (CH), 136.74 (C), 148.73 (C), 149.60 (C), 158.58 (C), remaining two (CH_2) signals obscured; ν_{max} (DCM, cm^{-1}) 3356, 3053, 2967, 2845, 2305, 1611, 1512, 1469, 1263, 1035, 896, 750.

Tetra methoxy, tetra-[*N*-(*p*-methoxy-R-(+)-α-methylbenzyl)benzoxazine] resorcinarene 92



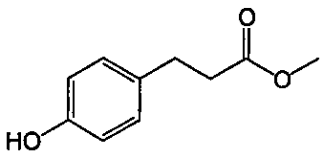
Tetra benzoxazine resorcinarene **91** (7 g, 3.9 mmol) was dissolved in dry THF (300 mL) under an atmosphere of nitrogen and cooled to –78 °C. *n*-Butyl lithium (2.5 M solution in hexanes, 7.8 mL, 19.4 mmol) was added drop wise with vigorous stirring, using an overhead stirrer, and stirred for 30 min. Methyl trifluoromethanesulphonate (2.2 g, 19.4 mmol) was added drop wise and stirred for 45 min. After this time the reaction was quenched with methanol (10 mL). The mixture was then allowed to warm to room temperature and concentrated. The residue produced was separated between EtOAc (200 mL) and water (200 mL). The organic layer was washed twice with water (150 mL), once with saturated brine solution (100 mL), dried over $MgSO_4$ and concentrated. The residue was purified on silica gel (45% EtOAc / pet-ether) to afford the *title compound* (5.6 g, 78%) as a pale yellow oil.

LRMS found: $(M+H)^+$, 1862, $C_{120}H_{172}N_4O_{12}$, requires 1862; $[\alpha]_D^{25}$ 116 °, c = 0 80, $CHCl_3$; δ_H ($CDCl_3$, 400 MHz) 0.87 (12 H, t, J = 8 Hz, CH_3), 1.25-1.34 (72 H, m, CH_2's), 1.36 (12 H, d, J = 6.4 Hz, $C\underline{H}_3CH$), 1.80 (4 H, m, $C\underline{H}_2CH$), 1.89 (4 H, m, $C\underline{H}_2CH$), 3.27 (12 H, s, OCH_3), 3.76 (4 H, q, J = 6.4 Hz, $C\underline{H}CH_3$), 3.79 (12 H, s, p-OCH_3), 3 85 (4 H, d, J = 16.8 Hz, NCH_2), 4.14 (4 H, d, J = 16.8 Hz, NCH_2), 4.42 (4 H, t, J = 7.6 Hz, $C\underline{H}CH_2$), 4.57 (4 H, d, J = 10 Hz, NCH_2O), 4.60 (4 H, d, J = 10 Hz, NCH_2O), 6.71 (4 H, s, ArH), 6.81-6.83 (8 H, m, ArH), 7.18-7.20 (8 H, m, ArH); δ_C ($CDCl_3$, 100 MHz) 14.13 (CH_3), 21.25 (CH_3), 22.70 (CH_2), 28.32 (CH_2), 29.42 (CH_2), 29.76 (CH_2), 29.83 (CH_2), 29.98 (CH_2), 30.11 (CH_2), 31.95 (CH_2), 35.41 (CH), 35.79 (CH_2), 44.52 (NCH_2), 55.22 (OCH_3), 56.53 (CH), 60.08 (OCH_3), 79.51 (NCH_2O), 112.23 (C), 113.67 (CH), 124.50

(CH), 127.76 (C), 128.56 (CH), 128.75 (C), 136.04 (C), 150.08 (C), 153.52 (C), 158.75 (C), remaining (CH_2) obscured; ν_{max} (DCM, cm^{-1}) 3052, 2925, 2852, 2304, 1610, 1512, 1465, 1265, 1174, 1035, 943, 835, 741.

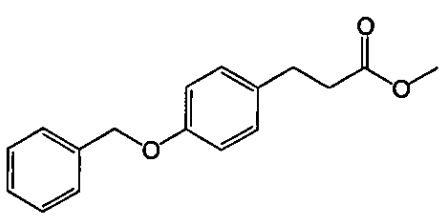
3.2 Experimental details for Section 2.2

Methyl-3-(4-hydroxyphenyl)propanoate 97[72]



Acetyl chloride (12.9 ml, 180 mmol) was added to dry methanol (150 mL) under a nitrogen atmosphere and stirred for 20 min. 3-(4-Hydroxyphenyl)propionic acid (30 g, 180 mmol) was added in one lot and the reaction brought to reflux for 4 h. After this time the reaction mixture was cooled to room temperature and concentrated. The residue was taken up in ethyl acetate (350 mL), washed twice with water (200 mL), once with saturated brine solution (150 mL), dried over $MgSO_4$ and concentrated to give the title compound (30.2 g, 93%) as a pale brown oil, which crystallised with scratching. HRMS found: M^+, 180.0787, $C_{10}H_{12}O_3$, requires 180.0787; elemental analysis, found C, 66 54; H, 6.62; requires C, 66.65; H, 6.71%; δ_H ($CDCl_3$, 250 MHz) 2.61 (2 H, t, $J = 6.5$ Hz, CH_2), 2.88 (2 H, t, $J = 7.4$ Hz, CH_2), 3.67 (3 H, s, CH_3), 6.73-6.76 (2 H, m, ArH), 7.03-7.07 (2 H, m, ArH); ν_{max} (DCM, cm^{-1}) 3399, 3023, 2953, 1884, 1715, 1614, 1516, 1440, 1365, 1266, 1222, 1103.

Methyl-3-(4-benzyloxyphenyl)propanoate 98[73]

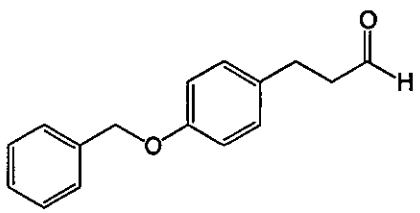


Methyl-3-(4-hydroxyphenyl)propanoate **97** (30 g, 167 mmol) was dissolved in dry DMSO (200 mL) under an atmosphere of nitrogen. Ground pearls of KOH (12.3 g, 220 mmol) were added in one lot and the mixture stirred for 15 min. Benzyl bromide (29.8

ml, 250 mmol) was added drop wise and the reaction stirred for 1 h at room temperature. After this time the reaction mixture was poured into water (500 mL) and extracted twice with diethyl ether (300 mL). The diethyl ether phase was washed twice with water (200 mL), once with saturated brine solution (100 mL), dried over $MgSO_4$ and concentrated. The residue was washed several times with pet-ether to furnish the title compound (27 g, 60%) as a yellow solid.

HRMS found: M^+, 270.1250, $C_{17}H_{18}O_3$, requires 270.1256; elemental analysis, found C, 75.30; H, 6.58; requires C, 75.53; H, 6.71%; δ_H ($CDCl_3$, 250 MHz) 2.59 (2 H, t, J = 8.1 Hz, CH_2), 2.89 (2 H, t, J = 8.1 Hz, CH_2), 3.66 (3 H, s, CH_3), 5.03 (2 H, s, OCH_2), 6.88-6.93 (2 H, m, ArH), 7.09-7.13 (2 H, m, ArH), 7.31-7.35 (5 H, m, ArH); ν_{max} (DCM, cm^{-1}) 3054, 2952, 1732, 1513, 1025.

3-(4-Benzyloxyphenyl)propanal 99[74]

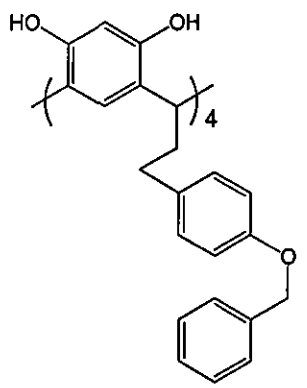


Methyl-3-(4-benzyloxyphenyl)propanoate **98** (8 g, 29.6 mmol) was dissolved in dry toluene (200 mL) under a nitrogen atmosphere and cooled to –78 °C. Diisobutylaluminium hydride (1.0 M solution in toluene, 38.5 mL, 38.5 mmol) was added drop wise, running down the side of the flask and stirred for 2.5 h. After this time the reaction mixture was quenched with 5 M aqueous HCl (10 mL) and allowed to warm to room temperature. The reaction mixture was then washed twice with water (200 mL), dried over $MgSO_4$ and concentrated. Recrystallisation of the residue from pet-ether furnished the title compound (6.7 g, 94%) as a white solid.

HRMS found: M^+, 240.1151, $C_{16}H_{16}O_2$, requires 240.1150; elemental analysis, found C, 79.27; H, 6.60, requires C, 79.97; H, 6.71%; δ_H ($CDCl_3$, 250 MHz) 2.74 (2 H, t, J = 8.8 Hz, CH_2), 2 90 (2 H, t, J = 7 6 Hz, CH_2), 5.04 (2 H, s, CH_2), 6.89-6.91 (2 H, m, ArH),

7.09-7.11 (2 H, m, ArH), 7.31-7.43 (5 H, m, ArH), 9.81 (1 H, s, CHO); ν_{max} (DCM, cm^{-1}) 2927, 1722, 1511, 1240, 1025.

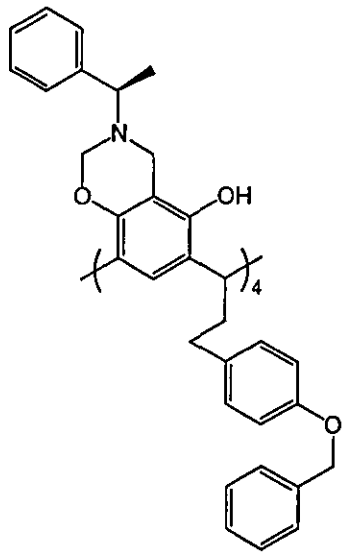
Octa hydroxy *p*-benzyloxyphenylethyl resorcinarene 100



3-(4-Benzyloxyphenyl)propanal **99** (7 g, 29 mmol) and resorcinol (3.2 g, 29 mmol) were dissolved in ethanol (100%, 70 mL) and concentrated HCl (3.5 mL) under a nitrogen atmosphere and heated at reflux overnight. The reaction was then allowed to cool to room temperature. The solid precipitate was filtered, washed three times with large amounts of ethanol (95%) and dried at 80 °C under vacuum, furnishing the *title compound* (6.3 g, 65%) as an off white powder.

HRMS found: M^+, 1329.5738, $C_{88}H_{80}O_{12}$, requires 1329.5728; m.p. > 310 °C, degrades; δ_H (d_6-DMSO, 400 MHz) 2.40 (16 H, m, CH_2CH_2), 4.23 (4 H, bt, CH), 5.08 (8 H, s, OCH_2), 6 20 (4 H, s, ArH), 6.86-6.88 (8 H, m, ArH), 7.03-7.05 (8 H, m, ArH), 7.24-7.32 (12 H, m, ArH), 7.38-7.43 (12 H, m, ArH), 9.09 (8 H, s, OH); δ_C (d_6-DMSO, 100 MHz) 33.69 (CH), 33.89 (CH_2), 36.32 (CH_2), 69.50 (OCH_2), 102.80 (CH), 114.95 (CH), 124.03 (C), 125.26 (CH), 127.83 (CH), 128.02 (CH), 128.69 (CH), 129.72 (CH), 134.87 (C), 137.58 (C), 151.92 (C), 156.70 (C); ν_{max} (Nujol, cm^{-1}) 2919, 2726, 2360, 1614, 1458, 1377, 1158, 1084, 836, 731.

Tetra-[*N*-(R-(+)-α-methylbenzyl)-3,4-dihydro-2*H*-1,3-benzoxazine] resorcinarene 101



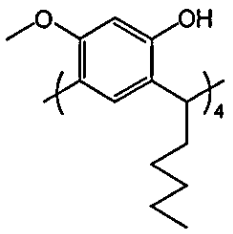
Octa hydroxy *p*-benzyloxyphenylethyl resorcinarene **100** (5 g, 3.8 mmol) was dissolved in ethanol (100%, 150 mL) and toluene (150 mL) under an atmosphere of nitrogen. R-(+)-α-methylbenzylamine (2.43 mL, 18.8 mmol) was added in one portion. Formaldehyde (37% solution in water, 3.1 mL, 37.7 mmol) was added in one portion and the reaction heated at reflux overnight. After this time the reaction was allowed to cool and concentrated. The residue was mixed with ethanol (95%, 100 mL) and heated at reflux for 1 h. The mixture was then cooled, the solid precipitate filtered and washed with large amounts of ethanol (95%). Recrystallisation from DCM / methanol furnished the *title compound* (5.5 g, 76%) as a white solid.

LRMS found: $(M+H)^+$, 1910, $C_{128}H_{124}N_4O_{12}$, requires 1910; elemental analysis, found C, 80.21; H, 6.49; N, 2.83; requires C, 80.48; H, 6.54; N, 2.93%; m.p. > 130 °C, degrades; $[\alpha]_D^{25}$ 67 °, c = 0.40, $CHCl_3$; δ_H ($CDCl_3$, 250 MHz) 1.30 (12 H, d, J = 6.3 Hz, CH_3), 2.44-2.58 (16 H, m, CH_2CH_2), 3.75 (4 H, d, J = 17.8 Hz, NCH_2), 3.80 (4 H, bq, $C\underline{H}CH_3$), 3.99 (4 H, d, J = 17.4 Hz, NCH_2), 4.26 (4 H, bt, $C\underline{H}CH_2$), 4.93 (4 H, d, J = 10.1 Hz, NCH_2O), 5.00 (8 H, s, OCH_2), 5.13 (4 H, d, J = 9.9 Hz, NCH_2O), 6.85-7.37 (60 H, m, ArH), 7.68 (4 H, s, OH); δ_C ($CDCl_3$, 100 MHz) 21.87 (CH_3), 32.99 (CH), 34.11 (CH_2), 36.79 (CH_2), 44.97 (NCH_2), 58.47 (CH), 70.45 (OCH_2), 81.41 (NCH_2O), 109.65 (C),

115.21 (CH), 121.35 (CH), 123.70 (C), 124.51 (C), 127.45 (CH), 127.52 (CH), 127.96 (CH), 128.30 (CH), 128.69 (CH), 128.97 (CH), 129.97 (CH), 134.72 (C), 137.50 (C), 144.87 (C), 149.35 (C), 150.22 (C), 157.54 (C); ν_{max} ($CHCl_3$, cm^{-1}) 3380, 2253, 1610, 1510, 1239, 912, 742, 651.

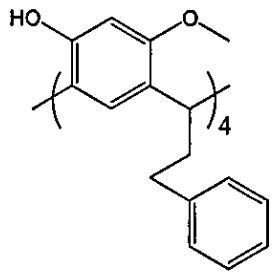
3.3 Expeimental details for Section 2.3

Tetra methoxy pentyl resorcinarene 76



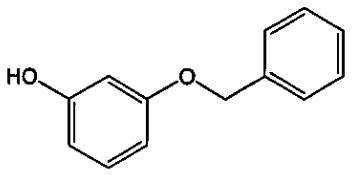
3-Methoxyphenol (2.19 mL, 20 mmol) and hexanal (2 4 mL, 20 mmol) were stirred together in anhydrous DCM (100 mL), under an atmosphere of nitrogen and cooled in a cold water bath. $BF_3.OEt_2$ (5.09 mL, 40.5 mmol) was added drop wise and the reaction allowed to warm to room temperature over 4 h. After this time the reaction was quenched with water (100 mL). The DCM solution was washed twice further with water (100 mL), once with saturated brine solution (100 mL) and dried over $MgSO_4$. Removal of the solvent gave a pink foam which was stirred in hot methanol (150 mL) and allowed to cool. The solid produced was filtered and washed with large amounts of cold methanol, furnishing the *title compound* (2.68 g, 65%) as a white solid.
LRMS found: M^+, 824, $C_{52}H_{72}O_8$, requires 825; elemental analysis, found C, 75.68; H, 8.83; requires C, 75 69; H, 8.79%; m.p. 234-236 °C; δ_H ($CDCl_3$, 400 MHz) 0 89 (12H, t, J = 8 Hz, CH_3), 1.34 (24 H, m, $CH_2CH_2CH_2$), 2.18 (8 H, m, CH_2), 3.82 (12 H, s, OCH_3), 4.26 (4 H, t, J = 8 Hz, CH), 6.34 (4 H, s, ArH), 7.21 (4 H, s, ArH), 7.50 (4 H, s, OH), δ_C ($CDCl_3$, 100 MHz) 14.14 (CH_3), 22.71 (CH_2), 27.79 (CH_2), 31.98 (CH_2), 33.14 (CH), 33.96 (CH_2), 55.88 (OCH_3), 100.01 (CH), 123.67 (C), 124.65 (CH), 124.74 (C), 152.96 (C), 153.62 (C); ν_{max} (DCM, cm^{-1}) 3402, 2931, 2363, 1621, 1497, 1265, 1091, 1017, 739.

Tetra methoxy phenylethyl resorcinarene 75



3-Methoxyphenol (2.19 mL, 20 mmol) and dihydrocinnamaldehyde (2 63 mL, 20 mmol) were stirred together in anhydrous DCM (100 mL), under an atmosphere of nitrogen and cooled in a cold water bath. $BF_3.OEt_2$ (5.09 mL, 40.5 mmol) was added drop wise and the reaction allowed to warm to room temperature over 4 h. After this time the reaction was quenched with water (100 mL). The DCM solution was washed twice further with water (100 mL), once with saturated brine solution (100 mL) and dried over $MgSO_4$. Removal of the solvent gave a pink foam which was purified on silica gel (50% EtOAc / pet-ether) furnishing the *title compound* (3 g, 65%) as a white solid. LRMS found: M^+, 961, $C_{64}H_{64}O_8$, requires 961; elemental analysis, found C, 79.67; H, 6.62; requires C, 79 97; H, 6.71%; m.p. 124-127 °C; δ_H ($CDCl_3$, 400 MHz) 2.50-2.62 (16 H, m, CH_2CH_2), 3.82 (12 H, s, OCH_3), 4.34 (4 H, t, J = 7.2 Hz, CH), 6.38 (4 H, s, ArH), 7.09-7.11 (8 H, m, ArH), 7.18-7.26 (16 H, m, ArH), 7.47 (4 H, s, OH); δ_C ($CDCl_3$, 100 MHz) 32.99 (CH), 34.55 (CH_2), 36.32 (CH_2), 55.93 (OCH_3), 100.30 (CH), 123.52 (C), 124.37 (C), 124.47 (CH), 125 91 (CH), 128.46 (CH), 128.56 (CH), 141.78 (C), 153.27 (C), 153.86 (C); ν_{max} (DCM, cm^{-1}) 3388, 3054, 2985, 2945, 2304, 1619, 1589, 1496, 1265, 1096, 896, 740.

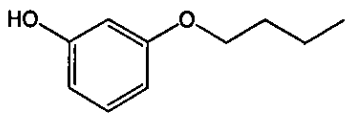
3-Benzyloxyphenol 102[75a]



Resorcinol (50 g, 450 mmol) and K_2CO_3 (6.21 g, 45 mmol) were stirred together in anhydrous acetonitrile (200 mL) under an atmosphere of nitrogen. The mixture was heated at reflux for 1 h. After this time benzyl chloride (5.18 mL, 45 mmol) was added drop wise and the reaction heated at reflux for 3 d. The reaction was then allowed to cool to room temperature and the solvent removed under vacuum. The residue was taken up in DCM (300 mL), washed twice with dilute aqueous HCl (200 mL), once with saturated brine solution (100 mL) and dried over $MgSO_4$. Removal of the solvent gave the crude product. Purification on silica gel (2% methanol / DCM) furnished the title compound (5.2 g, 58%) as an off white solid.

HRMS found: M^+, 200 0836, $C_{13}H_{12}O_2$, requires 200.0837; m.p. 51-53 °C; δ_H ($CDCl_3$, 400 MHz) 5.02 (2 H, s, CH_2), 5.10 (1 H, bs, OH), 6.42-6.48 (2 H, m, ArH), 6.55-6.57 (1 H, m, ArH), 7.10-7.14 (1 H, m, ArH), 7.31-7.42 (5 H, m, ArH); δ_C ($CDCl_3$, 100 MHz) 70.05 (CH_2), 102.51 (CH), 107.34 (CH), 108.10 (CH), 127.50 (CH), 127.99 (CH), 128.59 (CH), 130.18 (CH), 136.88 (C), 156.72 (C), 160.15 (C).

3-*n*-Butyloxyphenol 103[75b]

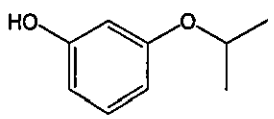


Resorcinol (50 g, 450 mmol) and K_2CO_3 (6.21 g, 45 mmol) were stirred together in anhydrous acetonitrile (200 mL) under an atmosphere of nitrogen. The mixture was heated at reflux for 1 h. After this time 1-bromobutane (4.83 mL, 45 mmol) was added drop wise and the reaction heated at reflux for 3 d. The reaction was then allowed to cool

to room temperature and the solvent removed under vacuum. The residue was taken up in DCM (300 mL), washed twice with dilute aqueous HCl (200 mL), once with saturated brine solution (100 mL) and dried over $MgSO_4$. Removal of the solvent gave the crude product. Purification on silica gel (25% EtOAc / pet-ether) furnished the title compound (6.35 g, 85%) as a pale yellow oil.

HRMS found: M^+, 166.0995, $C_{10}H_{14}O_2$, requires 166.0994; δ_H ($CDCl_3$, 400 MHz) 0.96 (3 H, t, J = 8 Hz, CH_3), 1.43-1.52 (2 H, m, CH_2), 1.71-1.78 (2 H, m, CH_2), 3.92 (2 H, t, J = 8 Hz, OCH_2), 5.14 (1 H, s, OH), 6.40-6.42 (2 H, m, ArH), 6.47-6.50 (1 H, m, ArH), 7.08-7.13 (1 H, m, ArH); δ_C ($CDCl_3$, 100 MHz) 13.83 (CH_3), 19.23 (CH_2), 31.27 (CH_2), 67.79 (OCH_2), 102.11 (CH), 107.12 (CH), 107.62 (CH), 130.10 (CH), 156 69 (C), 160.52 (C); ν_{max} (Neat, cm^{-1}) 3385, 2958, 1909, 1595, 1491, 1284, 1148, 1029, 852, 764, 685.

3-*i*-Propyloxyphenol 104[75c]

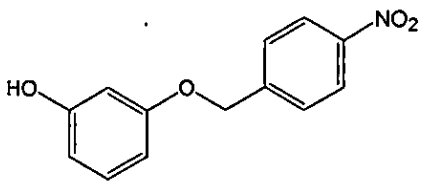


Resorcinol (50 g, 450 mmol) and K_2CO_3 (6.21 g, 45 mmol) were stirred together in anhydrous acetonitrile (200 mL) under an atmosphere of nitrogen. The mixture was heated at reflux for 1 h. After this time 2-bromopropane (4.27 mL, 45 mmol) was added drop wise and the reaction heated at reflux for 3 d. The reaction was then allowed to cool to room temperature and the solvent removed under vacuum. The residue was taken up in DCM (300 mL), washed twice with dilute aqueous HCl (200 mL), once with saturated brine solution (100 mL) and dried over $MgSO_4$. Removal of the solvent gave the crude product. Purification on silica gel (30% EtOAc / pet-ether) furnished the title compound (5.3 g, 77%) as a pale orange oil.

HRMS found: M^+, 152.0838, $C_9H_{12}O_2$, requires 152.0837; δ_H ($CDCl_3$, 400 MHz) 1.31 (6 H, d, J = 8 Hz, CH_3), 4.49 (1 H, h, J = 8 Hz, CH), 5.31 (1 H, s, OH), 6.39-6.42 (2 H, m, ArH), 6.46-6.49 (1 H, m, ArH), 7.08-7.12 (1 H, m, ArH); δ_C ($CDCl_3$, 100 MHz) 22.04 (CH_3), 70 11 (CH), 103.42 (CH), 107.70 (CH), 108.36 (CH), 130.13 (CH), 156.77 (C),

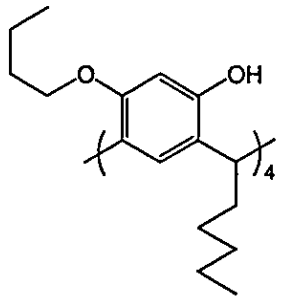
159 21 (C); ν_{max} (Neat, cm^{-1}) 3385, 2977, 1917, 1616, 1490, 1374, 1283, 1144, 986, 844, 767, 687.

3-(4-Nitrobenzyloxy)phenol 108



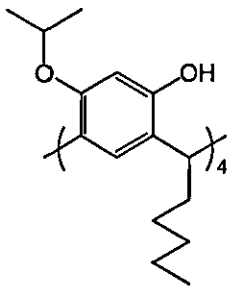
Resorcinol (50 g, 450 mmol) and K_2CO_3 (6.21 g, 45 mmol) were stirred together in anhydrous acetonitrile (200 mL) under an atmosphere of nitrogen. 4-Nitrobenzyl bromide (9.82 g, 45 mmol) was added in one portion and the reaction heated at reflux overnight. The reaction was then allowed to cool to room temperature and the solvent removed under vacuum. The residue was taken up in DCM (300 mL), washed three times with dilute aqueous HCl (200 mL), once with water (200 mL) and dried over $MgSO_4$. Removal of the solvent gave the crude product. Recrystallisation from chloroform / hexane gave the *title compound* (7.5 g, 67%) as an off white solid. HRMS found: M^+, 245.0684, $C_{13}H_{11}NO_4$, requires 245.0688; m.p. 117-119 °C; δ_H ($CDCl_3$, 400 MHz) 5.14 (2 H, s, CH_2), 5.33 (1 H, s, OH), 6.46-6.49 (2 H, m, ArH), 6.52-6.55 (1 H, m, ArH), 7.15 (1 H, m, ArH), 7.58-7.60 (2 H, m, ArH), 8.22-8.25 (2 H, m, ArH); δ_C ($CDCl_3$, 100 MHz) 69.02 (CH_2), 102.87 (CH), 107.49 (CH), 109 06 (CH), 124.24 (CH), 127.98 (CH), 130.76 (CH), 144.86 (C), 147.89 (C), 157.27 (C), 159.83 (C); ν_{max} (DCM, cm^{-1}) 3409, 1644, 1494, 1347, 1169, 974, 734, 666.

Tetra *n*-butyloxy pentyl resorcinarene 106



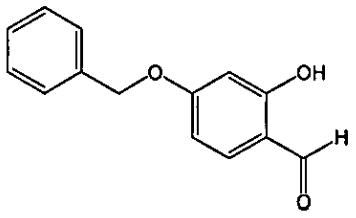
3-Butyloxyphenol **103** (5 g, 30 mmol) and hexanal (3.6 ml, 30 mmol) were stirred together in anhydrous DCM (120 mL), under an atmosphere of nitrogen and cooled in a cold water bath. $BF_3.OEt_2$ (7.98 mL, 63 mmol) was added drop wise and the reaction allowed to warm to room temperature over 4 h. After this time the reaction was quenched with water (120 mL). The DCM solution was washed twice further with water (100 mL), once with saturated brine solution (100 mL) and dried over $MgSO_4$. Removal of the solvent gave a pink foam which was stirred in hot methanol (100 mL) and allowed to cool. The solid produced was filtered and washed with large amounts of cold methanol, furnishing the *title compound* (4.5 g, 61%) as a white solid.
LRMS found: M^+, 993, $C_{64}H_{96}O_8$, requires 993; elemental analysis, found C, 77.41; H, 9.75; requires C, 77.38; H, 9.74%; m.p. 109-111 °C; δ_H ($CDCl_3$, 400 MHz) 0.92 (12 H, t, J = 6.8 Hz, CH_3), 1.02 (12 H, t, J = 7.2 Hz, CH_3), 1.36 (24 H, m, CH_2's), 1.55 (8 H, m, CH_2), 1.87 (8 H, m, CH_2), 2.21 (8 H, m, CH_2), 3.94 (4 H, m, OCH_2), 4.06 (4 H, m, OCH_2), 4.32 (4 H, t, J = 8 Hz, CH), 6.37 (4 H, s, ArH), 7.25 (4 H, s, ArH), 7.56 (4 H, s, OH); δ_C ($CDCl_3$, 100 MHz) 14.17 (CH_3), 14.52 (CH_3), 19.58 (CH_2), 23.06 (CH_2), 28.11 (CH_2), 31.27 (CH_2), 32.27 (CH_2), 33.49 (CH), 34.38 (CH_2), 69.37 (OCH_2), 101.41 (CH), 124.03 (C), 125.15 (CH), 125.28 (C), 153.26 (C), 153.52 (C); ν_{max} (DCM, cm^{-1}) 3417, 2932, 2089, 1621, 1497, 1265, 1176, 1088, 739.

Tetra *i*-propyloxy pentyl resorcinarene 107



3-*i*-Propyloxyphenol **104** (4 g, 26.3 mmol) and hexanal (3.16 mL, 26.3 mmol) were stirred together in anhydrous DCM (120 mL), under an atmosphere of nitrogen and cooled in a cold water bath. $BF_3.OEt_2$ (7 mL, 55.3 mmol) was added drop wise and the reaction allowed to warm to room temperature over 4 h. After this time the reaction was quenched with water (120 mL). The DCM solution was washed twice further with water (100 mL), once with saturated brine solution (100 mL) and dried over $MgSO_4$. Removal of the solvent gave a brown foam which was purified on silica gel (40% EtOAc / pet-ether), furnishing the *title compound* (3.9 g, 63%) as an off white solid. Crystals suitable for X-ray analysis were obtained by slow evaporation of DCM.
LRMS found: M^+, 936, $C_{60}H_{88}O_8$, requires 937; elemental analysis, found C, 76.91; H, 9.41; requires C, 76.88; H, 9.46%; m.p. 196-202 °C; δ_H ($CDCl_3$, 400 MHz) 0.89 (12 H, t, J = 7.2 Hz, CH_3), 1.26-1.40 (48 H, m, $CH_2CH_2CH_2$ and $(C\underline{H}_3)_2CH$), 2.14-2.23 (8 H, m, $C\underline{H}_2CH$), 4.27 (4 H, t, J = 7.6 Hz, $C\underline{H}CH_2$), 4.55 (4 H, h, J = 6.4 Hz, $C\underline{H}(CH_3)_2$), 6.34 (4 H, s, ArH), 7.23 (4 H, s, ArH), 7.69 (4 H, s, OH); δ_C ($CDCl_3$, 100 MHz) 14.15 (CH_3), 21.84 (CH_3), 22.70 (CH_2), 27.79 (CH_2), 31.94 (CH_2), 33.38 (CH), 34 03 (CH_2), 71.79 (OCH), 102.59 (CH), 123.75 (CH), 125.41 (C), 125.65 (C), 151.75 (C), 152.86 (C); ν_{max} (DCM, cm^{-1}) 3418, 2931, 2089, 1626, 1494, 1265, 1108, 738.

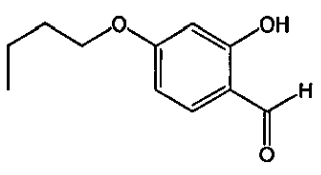
2-Hydroxy-4-benzyloxybenzene-1-carbaldehyde 110[76a]



2,4-Dihydroxybenzaldehyde (30 g, 217 mmol), $NaHCO_3$ (20.8 g, 247 mmol) and potassium iodide (3.65 g, 22 mmol) were stirred together in anhydrous acetonitrile (200 mL) under an atmosphere of nitrogen. The mixture was heated to 60 °C and benzyl chloride (32.5 mL, 282 mmol) added drop wise over 30 min. The reaction was then heated at reflux for 2 d. After this time the reaction was allowed to cool to room temperature and the solvent removed. The residue was taken up in EtOAc (300 mL). The organic solution was washed with water (250 mL) containing concentrated HCl (6 mL). It was then washed a further three times with water (200 mL) and dried over $MgSO_4$. Removal of the solvent gave a gummy solid. This was stirred in ice-cold pet-ether, filtered and washed with ice-cold pet-ether, furnishing the title compound (37 g, 75%) as a pale brown solid.

HRMS found: M^+, 228.0786, $C_{14}H_{12}O_3$, requires, 228.0787; elemental analysis, found, C, 73.66; H, 5.18; requires, C, 73.67; H, 5.30%; δ_H ($CDCl_3$, 250 MHz) 5.10 (2 H, s, CH_2), 6.50-6.51 (1 H, m, ArH), 6.58-6.63 (1 H, m, ArH), 7.34-7.82 (6 H, m, ArH), 9.71 (1 H, s, OH), 11.47 (1 H, s, CHO).

4-*n*-Butyloxy-2-hydroxybenzene-1-carbaldehyde 111[76b]

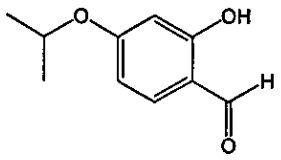


2,4-Dihydroxybenzaldehyde (15 g, 109 mmol), $NaHCO_3$ (10.4 g, 124 mmol) and potassium iodide (1.83 g, 11 mmol) were stirred together in anhydrous acetonitrile (200

mL) under an atmosphere of nitrogen. The mixture was heated at reflux for 30 min then 1-bromobutane (15.2 mL, 142 mmol) was added portion wise over 10 min. The reaction was then heated at reflux for 2 d. After this time the reaction was allowed to cool to room temperature and the solvent removed. The residue was taken up in diethyl ether (200 mL). The organic solution was washed with water (200 mL) containing concentrated HCl (10 mL). It was then washed twice more with water (200 mL), once with saturated brine solution (100 mL) and dried over $MgSO_4$. Removal of the solvent gave a cream solid. The crude product was purified on silica gel (30 % EtOAc / pet-ether) furnishing the title compound (6.5 g, 31%) as a colourless oil which crystallised in the refrigerator.

HRMS found: M^+, 194.0943, $C_{11}H_{14}O_3$, requires 194.0943; elemental analysis, found C, 68.11; H, 7.30; requires C, 68 02; H, 7.26; m.p. 28-30 °C; δ_H ($CDCl_3$, 400 MHz) 0.98 (3H, t, J = 8 Hz, CH_3), 1.46-1.52 (2 H, m, CH_2), 1.74-1.81 (2 H, m, CH_2), 4.02 (2 H, t, J = 8 Hz, OCH_2), 6.41 (1 H, m, ArH), 6.50-6.53 (1 H, m, ArH), 7.38-7.40 (1 H, m, ArH), 9.70 (1 H, s, OH), 11.42 (1 H, s, CHO); δ_C ($CDCl_3$, 100 MHz) 13.99 (CH_3), 19.46 (CH_2), 31.34 (CH_2), 68.68 (OCH_2), 101.59 (CH), 109.06 (CH), 115.52 (C), 135.48 (CH), 164.94 (C), 166.88 (C) 194.49 (CHO).

2-Hydroxy-4-*i*-propyloxybenzene-1-carbaldehyde 112[76c]

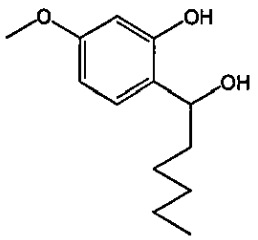


2,4-Dihydroxybenzaldehyde (20 g, 145 mmol), $NaHCO_3$ (13.9 g, 165 mmol) and potassium iodide (2.41 g, 14.5 mmol) were stirred together in anhydrous acetonitrile (200 mL) under an atmosphere of nitrogen. The mixture was heated to 60 °C and 2-bromopropane (17.7 mL, 189 mmol) added portion wise over 30 min. The reaction was then heated at reflux for 4 d. After this time the reaction was allowed to cool to room temperature and the solvent removed. The residue was taken up in DCM (250 mL). The organic solution was washed with water (200 mL) containing concentrated HCl (6

mL). It was then washed a further three times with water (200 mL) and dried over $MgSO_4$. Removal of the solvent gave a yellow solid. The crude product was purified on silica gel (30 % EtOAc / pet-ether) furnishing the title compound (6 g, 21%) as a colourless oil which crystallised in the refrigerator.

HRMS found: M^+, 180.0787, $C_{10}H_{12}O_3$, requires 180.0787; elemental analysis, found C, 66.60; H, 6.77; requires C, 66.65; H, 6.71%; m p. 38-40 °C; δ_H ($CDCl_3$, 400 MHz) 1.37 (6 H, d, J = 8 Hz, CH_3), 4.62 (1 H, h, J = 8 Hz, CH), 6.40 (1 H, m, ArH), 6.48-6.51 (1 H, m, ArH), 7.39-7.42 (1 H, m, ArH), 9.69 (1 H, s, OH), 11.47 (1 H, s, CHO); δ_C ($CDCl_3$, 100 MHz) 21.85 (CH_3), 70.67 (CH), 101.78 (CH), 109.45 (CH), 114.89 (C), 135.31 (CH), 164.54 (C), 165.43 (C), 194.21 (CHO); ν_{max} (DCM, cm^{-1}) 3388, 2981, 1635, 1505, 1286, 1223, 1106, 985, 748.

1-[4-(Methoxy)-2-hydroxyphenyl]hexan-1-ol 113

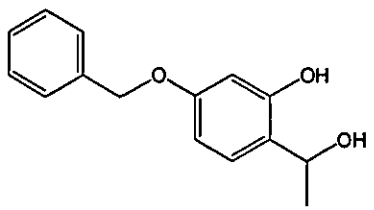


2-Hydroxy-4-methoxybenzaldehyde **109** (5 g, 33 mmol) was dissolved in anhydrous diethyl ether (100 mL) under an atmosphere of nitrogen, and cooled to 0 °C. Pentyl magnesium bromide (2 M solution in diethyl ether, 41.5 mL, 83 mmol) was added drop wise and stirred for 1 h at 0 °C. The reaction temperature was then allowed to rise to room temperature and stirred for 6 h. After this time the reaction was quenched slowly with saturated aqueous ammonium chloride solution. The organic phase was washed twice with water (200 mL) and dried over $MgSO_4$. The residue after removal of the solvent was purified on silica gel (30% EtOAc / pet-ether) furnishing the *title compound* (5.3 g, 65%) as a colourless oil which crystallised in the freezer.

HRMS found: M^+, 224.1417, $C_{13}H_{20}O_3$, 224.1413; elemental analysis, found C, 69.82; H, 9.05; requires C, 69.61; H, 8 99%, m.p. 60-62 °C; δ_H ($CDCl_3$, 400 MHz) 0.88 (3 H, bt,

CH_3), 1.23-1.32 (5 H, m, $CH_2CH_2CH_2$), 1.42-1.48 (1 H, m, $C\underline{H}_2CH_2CH$), 1.70-1.94 (2 H, m, $C\underline{H}_2CH$), 2.46 (1 H, bd, $CHO\underline{H}$), 3.75 (3 H, s, OCH_3), 4.77 (1 H, m, CH), 6.36-6.38 (1 H, m, ArH), 6.43 (1 H, m, ArH), 6.81-6.83 (1 H, m, ArH), 7.91 (1 H, s, ArOH); δ_C ($CDCl_3$, 100 MHz) 13.95 (CH_3), 22 57 (CH_2), 25.47 (CH_2), 31.64 (CH_2), 37.36 (CH_2), 55.32 (OCH_3), 75.95 (CH), 102.82 (CH), 105.76 (CH), 120.12 (C), 127.83 (CH), 156.92 (C), 160.55 (C); ν_{max} (DCM, cm^{-1}) 3409, 2931, 2305, 1626, 1506, 1465, 1266, 1198, 1155, 1035, 748.

2-(1-Hydroxyethyl)-5-benzyloxybenzen-1-ol 114

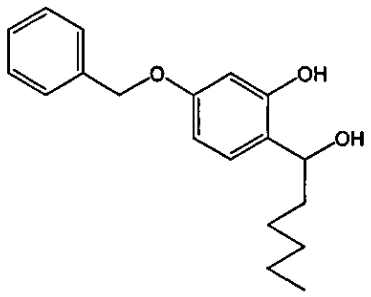


2-Hydroxy-4-(benzyloxy)benzene-1-carbaldehyde **110** (2.5 g, 11 mmol) was dissolved in anhydrous diethyl ether (100 mL) under an atmosphere of nitrogen, and cooled to 0 °C. Methyl magnesium bromide (3 M solution in diethyl ether, 9.2 mL, 27.4 mmol) was added drop wise and stirred for 1 h at 0 °C. The reaction temperature was then allowed to rise to room temperature and stirred for 5 h. After this time the reaction was quenched slowly with saturated aqueous ammonium chloride solution. The organic phase was washed twice with water (200 mL) and dried over $MgSO_4$. The solid produced after removal of the solvent was dissolved in the minimum amount of hot diethyl ether, allowed to cool, filtered and washed with hexane, furnishing the *title compound* (4.3 g, 65%) as a white solid.

HRMS found: M^+, 244.1104, $C_{15}H_{16}O_3$, requires 244.1100; elemental analysis, found C, 73.95; H, 6.58; requires C, 73.75; H, 6.60%; m.p. 100-101 °C; δ_H ($CDCl_3$, 400 MHz) 1.55 (3 H, d, $J = 6.4$ Hz, CH_3), 4.99 (1 H, m, CH), 5.00 (2 H, s, CH_2), 6.44-6.47 (1 H, m, ArH), 6.51-6.52 (1 H, m, ArH), 6.85-6.87 (1 H, m, ArH), 7.29-7.42 (5 H, m, ArH); δ_C ($CDCl_3$, 100 MHz) 23.91 (CH_3), 70.40 (CH_2), 71.57 (CH), 103.96 (CH), 106.99 (CH),

121.55 (C), 127.48 (CH), 127.87 (CH), 128.35 (CH), 128.97 (CH), 137.33 (C), 157 07 (C), 159.97 (C); ν_{max} (DCM, cm^{-1}) 3372, 2983, 2304, 1621, 1505, 1265, 1170, 1007, 896, 740.

1-[2-Hydroxy-4-(benzyloxy)phenyl]hexan-1-ol 115

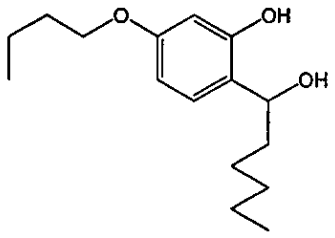


2-Hydroxy-4-(benzyloxy)benzene-1-carbaldehyde **110** (5 g, 22 mmol) was dissolved in anhydrous diethyl ether (250 mL) under an atmosphere of nitrogen, and cooled to 0 °C. Pentyl magnesium bromide (2 M solution in diethyl ether, 30 mL, 60 mmol) was added drop wise and stirred for 1 h at 0 °C. The reaction temperature was then allowed to rise to room temperature and the solution was stirred for 5 h. After this time the reaction was quenched slowly with saturated aqueous ammonium chloride solution. The organic phase was washed twice with water (200 mL) and dried over $MgSO_4$. The residue, after removal of the solvent, was purified on silica gel (20% EtOAc / pet-ether) furnishing the *title compound* (4.3 g, 65%) as a colourless crystalline solid.

HRMS found: M^+, 300.1723, $C_{19}H_{24}O_3$, requires 300.1726; elemental analysis, found C, 75.95; H, 7.91; requires C, 75.97; H, 8.05%; m.p. 79-84 °C; δ_H ($CDCl_3$, 400 MHz) 0.97 (3 H, t, J = 11.6 Hz, CH_3), 1.41 (5 H, m, $CH_2CH_2CH_2$), 1.53 (1 H, m, $C\underline{H}_2CH_2CH$), 1.85 (1 H, m, $C\underline{H}_2CH$), 1.94 (1 H, m, $C\underline{H}_2CH$), 2.82 (1 H, d, J = 3.6 Hz, $CHO\underline{H}$), 4 83 (1 H, m, CH), 5.10 (2 H, s, OCH_2), 6.55-6.57 (1 H, m, ArH), 6.61-6.62 (1 H, m, ArH), 6.90-6.92 (1 H, m, ArH), 7.42-7.53 (5 H, m, ArH), 8.19 (1 H, s, ArOH); δ_C ($CDCl_3$, 100 MHz) 14.45 (CH_3), 22.99 (CH_2), 25.87 (CH_2), 32.01 (CH_2), 37.66 (CH_2), 70.42 (OCH_2), 76.22 (CH), 103.95 (CH), 106.89 (CH), 120.73 (C), 127.93 (CH), 128.27 (CH), 128.37 (CH),

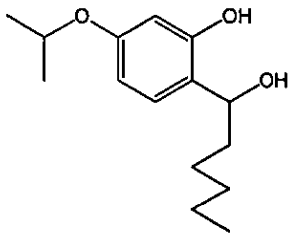
128.98 (CH), 137.30 (C), 157.11 (C) 159.90 (C); ν_{max} (DCM, cm^{-1}) 3364, 2933, 1627, 1508, 1169, 1024, 739.

1-[4-(*n*-Butyloxy)-2-hydroxyphenyl]hexan-1-ol 116



4-(*n*-Butyloxy)-2-hydroxybenzene-1-carbaldehyde **111** (2 g, 10.3 mmol) was dissolved in anhydrous diethyl ether (100 mL) under an atmosphere of nitrogen, and cooled to 0 °C. Pentyl magnesium bromide (2 M solution in diethyl ether, 12.9 mL, 25.8 mmol) was added drop wise and stirred for 1 h at 0 °C. The reaction temperature was then allowed to rise to room temperature and stirred for 5 h. After this time the reaction was quenched slowly with saturated aqueous ammonium chloride solution. The organic phase was washed twice with water (100 mL) and dried over $MgSO_4$. The residue, after removal of the solvent, was purified on silica gel (20% EtOAc / pet-ether) furnishing the *title compound* (2.2 g, 80%) as a colourless oil which crystallised in the freezer. HRMS found: M^+, 266.1884, $C_{16}H_{26}O_3$, requires 266.1882; elemental analysis, found C, 72.21; H, 9.79; requires C, 72.14; H, 9 84%; m.p. 47-49 °C; δ_H ($CDCl_3$, 400 MHz) 0.87 (3 H, t, J = 8 Hz, CH_3), 0.96 (3 H, t, J = 8 Hz, CH_3), 1.29-1.31 (5 H, m, CH_2's), 1.42-1.52 (3 H, m, CH_2's), 1.66-1.79 (3 H, m, CH_2's), 1.83-1.87 (1 H, m, CH_2), 2.57 (1 H, d, J = 3.2 Hz, CHOH), 3.91 (2 H, t, J = 6.4 Hz, OCH_2), 4.75 (1 H, m, CH), 6.35-6.38 (1 H, m, ArH), 6.42 (1 H, m, ArH), 6.79-6.81 (1 H, m, ArH), 7.99 (1 H, s, ArOH); δ_C ($CDCl_3$, 100 MHz) 13.84 (CH_3), 14.02 (CH_3), 19.25 (CH_2), 22.57 (CH_2), 25.47 (CH_2), 31.29 (CH_2), 31.59 (CH_2), 37.24 (CH_2), 67.73 (OCH_2), 75.94 (CH), 103.11 (CH), 106 23 (CH), 119.73 (C), 127.77 (CH), 156.69 (C), 159.91 (C); ν_{max} (DCM, cm^{-1}) 3358, 2952, 1627, 1507, 1265, 1174, 988, 736.

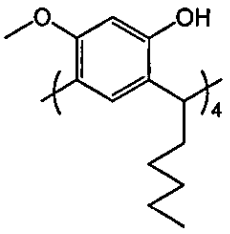
1-(2-Hydroxy-4-[*i*-propyloxy]phenyl)hexan-1-ol 117



1,2-Hydroxy-4-*i*-propyloxybenzene-1-carbaldehyde **112** (5 g, 27.8 mmol) was dissolved in anhydrous diethyl ether (200 mL) under an atmosphere of nitrogen, and cooled to 0 °C. Pentyl magnesium bromide (2 M solution in diethyl ether, 34.7 mL, 69.5 mmol) was added drop wise and stirred for 1 h at 0 °C. The reaction temperature was then allowed to rise to room temperature and stirred for 5 h. After this time the reaction was quenched slowly with saturated aqueous ammonium chloride solution. The organic phase was washed twice with water (200 mL) and dried over $MgSO_4$. Removal of the solvent gave the impure *title compound* (5.7 g, 82%) as a colourless oil which was reacted on without further purification.

δ_H ($CDCl_3$, 400 MHz) 0.88 (3 H, bt, CH_3), 1.25-1.32 (11 H, m, $CH_2CH_2CH_2$ and $(C\underline{H}_3)_2CH$), 1.43 (1 H, m, $C\underline{H}_2CH_2CH$), 1.72-1.83 (1 H, m, $C\underline{H}_2CH$), 1.85-1.93 (1 H, m, $C\underline{H}_2CH$), 4 48 (1 H, h, $J = 6$ Hz, $C\underline{H}(CH_3)_2$), 4.75 (1 H, m, $C\underline{H}CH_2$), 6.34-6.37 (1 H, m, ArH), 6.41 (1 H, m, ArH), 6.79-6.81 (1 H, m, ArH); δ_C ($CDCl_3$, 100 MHz) 14.01 (CH_3), 22.06 (CH_3), 22.50 (CH_2), 25.48 (CH_2), 31.52 (CH_2), 37.22 (CH_2), 69.84 (OCH), 75.94 (CH), 104.32 (CH), 107.48 (CH), 119.75 (C), 127.80 (CH), 156.74 (C), 158.86 (C).

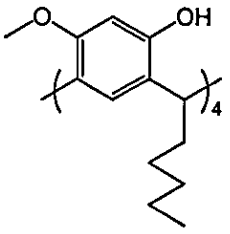
Tetra methoxy pentyl resorcinarene 76, method 2



1-[4-(Methoxy)-2-hydroxyphenyl]hexan-1-ol **113** (200 mg, 0.9 mmol) was dissolved in dry DCM (20 mL) under an atmosphere of nitrogen and cooled in a cold water bath. $BF_3.OEt_2$ (0.12 mL, 0 98 mmol) was added drop wise and stirred to room temperature for 3 h. After this time the reaction mixture was washed twice with water (50 mL), once with saturated brine solution (50 mL) and dried over $MgSO_4$. Removal of the solvent gave the crude product as a pink foam, which furnished the *title compound* (0.16 g, 85%) following trituration in methanol.

HRMS found: M^+, 825.5290, $C_{52}H_{72}O_8$, requires 825.5306; δ_H ($CDCl_3$, 400 MHz) 0.89 (12 H, t, $J = 8$ Hz, CH_3), 1.27-1.39 (24 H, m, $CH_2CH_2CH_2$), 2.15-2.21 (8 H, m, $C\underline{H}_2CH$), 3.82 (12 H, s, OCH_3), 4.26 (4 H, t, $J = 8$ Hz, CH), 6.34 (4 H, s, ArH), 7.21 (4 H, s, ArH), 7.53 (4 H, s, OH); δ_C ($CDCl_3$, 100 MHz) 14.16 (CH_3), 22.71 (CH_2), 27.79 (CH_2), 31.98 (CH_2), 33.11 (CH), 33.93 (CH_2), 55.85 (OCH_3), 99.97 (CH), 123.63 (C), 124.61 (CH), 124.70 (C), 152.92 (C), 153.58 (C).

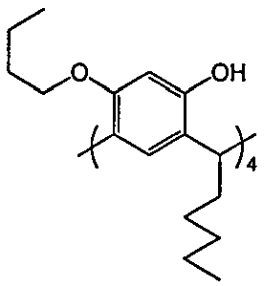
Tetra methoxy pentyl resorcinarene 76, method 3



1-[4-(Methoxy)-2-hydroxyphenyl]hexan-1-ol **113** (100 mg, 0.45 mmol) was dissolved in dry DCM (10 mL) under an atmosphere of nitrogen. $AlCl_3$ (60 mg, 0.45 mmol) was

added in two portions over 10 mın and the reaction stirred at room temperature for 2 h. After this time water (20 mL) was added and the reaction stirred for a further 20 min. The organic phase was washed with aqueous $NaHCO_3$ solution (20 mL), twice wıth water (20 mL) and dried over $MgSO_4$. Removal of the solvent and trituration in methanol gave the *tıtle compound* (92 mg, 82%) as a white powder.
HRMS found: M^+, 825.5290, $C_{52}H_{72}O_8$, requires 825.5306; δ_H ($CDCl_3$, 400 MHz) 0 89 (12 H, t, J = 8 Hz, CH_3), 1.28-1.38 (24 H, m, $CH_2CH_2CH_2$), 2.15-2 21 (8 H, m, $C\underline{H}_2CH$), 3.82 (12 H, s, OCH_3), 4.27 (4 H, t, J = 8 Hz, CH), 6.34 (4 H, s, ArH), 7.22 (4 H, s, ArH), 7.53 (4 H, s, OH); δ_C ($CDCl_3$, 100 MHz) 14.16 (CH_3), 22.71 (CH_2), 27.79 (CH_2), 31.98 (CH_2), 33.11 (CH), 33.93 (CH_2), 55.85 (OCH_3), 99.97 (CH), 123.63 (C), 124.61 (CH), 124.69 (C), 152.92 (C), 153.58 (C).

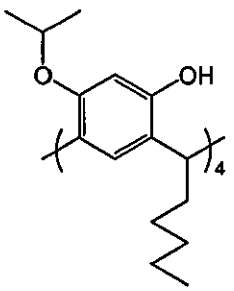
Tetra *n*-butyloxy pentyl resorcinarene 106, method 2



1-[4-(*n*-Butyloxy)-2-hydroxyphenyl]hexan-1-ol **116** (200 mg, 0.75 mmol) was dissolved in dry DCM (20 mL) under an atmosphere of nitrogen and cooled in a cold water bath. $BF_3.OEt_2$ (0.1 mL, 0.83 mmol) was added drop wise and stirred to room temperature for 5 h. After this time the reaction mixture was washed twice with water (30 mL), once with saturated brine solution (30 mL) and dried over $MgSO_4$. Removal of the solvent gave the crude product as a pink foam. Trituration in methanol furnished the *tıtle compound* (0.16 g, 85%) as a white powder.
HRMS found: M^+, 993.7196, $C_{64}H_{96}O_8$, requires 993.7183; δ_H ($CDCl_3$, 400 MHz) 0.89 (12 H, t, J = 7.2 Hz, CH_3), 0.98 (12 H, t, J = 7 6 Hz, CH_3), 1.25-1.37 (24 H, m, CH_2's), 1.43-1.54 (8 H, m, CH_2), 1.80-1.89 (8 H, m, CH_2), 2.15-2.22 (8 H, m, CH_2), 3.88-3.94 (4

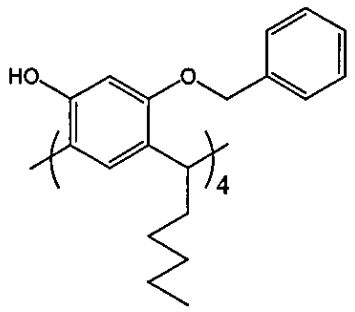
H, m, OCH_2), 4.00-4.06 (4 H, m, OCH_2), 4.29 (4 H, t, J = 8 Hz, CH), 6.34 (4 H, s, ArH), 7.22 (4 H, s, ArH), 7.57 (4 H, s, OH); δ_C ($CDCl_3$, 100 MHz) 14.23 (CH_3), 14.59 (CH_3), 19.61 (CH_2), 23.11 (CH_2), 28.15 (CH_2), 31.29 (CH_2), 32.31 (CH_2), 33.49 (CH), 34.37 (CH_2), 69.36 (OCH_2), 101.40 (CH), 124.04 (CH), 125.16 (C), 125.27 (C), 153.26 (C), 153.53 (C).

Tetra *i*-propyloxy pentyl resorcinarene 107, method 2



1-(2-Hydroxy-4-[*i*-propyloxy]phenyl)hexan-1-ol **117** (1 g, 4 mmol) was dissolved in dry DCM (50 mL) under an atmosphere of nitrogen and cooled in a cold water bath. $BF_3.OEt_2$ (0.55 mL, 4.4 mmol) was added drop wise and stirred to room temperature for 5 h. After this time the reaction mixture was washed twice with water (60 mL), once with saturated brine solution (60 mL) and dried over $MgSO_4$. Removal of the solvent gave the crude product as a brown foam. Purification on silica gel (40% EtOAc / pet-ether) furnished the *title compound* (0.76 g, 82%) as a white powder.
LRMS found: M^+, 936, $C_{60}H_{88}O_8$, requires 937; δ_H ($CDCl_3$, 250 MHz) 0.89 (12 H, bt, J = 6.7 Hz, CH_3), 1.27-1.41 (48 H, m, $CH_2CH_2CH_2$ and $(C\underline{H}_3)_2CH$), 2.14-2.24 (8 H, m, $C\underline{H}_2CH$), 4.27 (4 H, t, J = 7.8 Hz, $C\underline{H}CH_2$), 4.55 (4 H, h, J = 6 2 Hz, $C\underline{H}(CH_3)_2$), 6.34 (4 H, s, ArH), 7.23 (4 H, s, ArH), 7.69 (4 H, s ,OH).

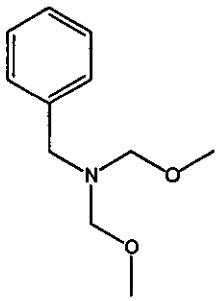
Tetra benzyloxy pentyl resorcinarene 105



1-[2-Hydroxy-4-(benzyloxy)phenyl]hexan-1-ol (4.6 g, 15.3 mmol) **115** was dissolved in dry diethyl ether (150 mL) under an atmosphere of nitrogen and cooled to –78 °C. HBF_4 (54% solution in diethyl ether, 15.3 mmol, 2.11 mL) was added slowly down the side of the flask. The reaction was then allowed to warm slowly to room temperature overnight. After this time EtOAc (100 mL) was added. The reaction mixture was washed with dilute aqueous ammonium hydroxide solution (200 mL). The organic phase was then washed twice with water (250 mL) and dried over $MgSO_4$. Removal of the solvent gave the crude product as an off white foam. Purification on silica gel (2% methanol / DCM) furnished the still crude *title compound* (< 10%) as a white foam. HRMS found: M^+, 1129.6531, $C_{76}H_{88}O_8$, requires 1129.6557; δ_H ($CDCl_3$, 400 MHz) 0.86 (12 H, bt, CH_3), 1.21-1.31 (24 H, m, $CH_2CH_2CH_2$), 2.10-2.16 (8 H, m, $C\underline{H}_2CH$), 4.25 (4 H, bt, $J = 8$ Hz, CH), 4.97 (4 H, d, CH_2O), 5.01 (4 H, d, CH_2O), 6.38 (4 H, s, ArH), 7.14-7.39 (24 H, m, ArH).

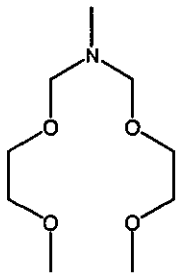
3.4 Experimental details for Section 2.4

N,N-Di[(methoxy)methyl]-*N*-benzylamine 79[41]



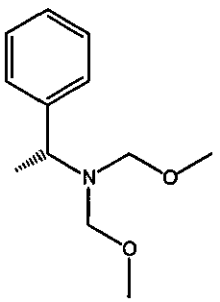
Benzylamine (10 g, 93 mmol) was dissolved in methanol (100 mL) and cooled to 0 °C. K_2CO_3 (32.2 g, 233 mmol) and para formaldehyde (7 g, 233 mmol) were added each in one portion. The reaction mixture was allowed to warm to room temperature and stirred for 3 d. After this time the reaction was filtered to remove any solid material and the filtrate concentrated under vacuum. The residue was taken up in DCM (200 mL), washed twice with water (200 mL), once with saturated brine solution (100 mL) and dried over $MgSO_4$. Removal of the solvent gave the crude product which was purified by Kügelrohr distillation to furnish the title compound (11.7 g, 65%) as a colourless oil. δ_H ($CDCl_3$, 400 MHz) 3.26 (6 H, s, CH_3), 4.00 (2 H, s, CH_2Ar), 4.23 (4 H, s, NCH_2O), 7.25-7.33 (5 H, m, ArH); δ_C ($CDCl_3$, 100 MHz) 52.61 (CH_2), 55.24 (OCH_3), 85.82 (NCH_2O), 127.04 (CH), 128.28 (CH), 128.88 (CH), 138.82 (C); ν_{max} (Neat, cm^{-1}) 3473, 2902, 1602, 1495, 1452, 1383, 1175, 1068, 921, 742, 699.

_N_-Methyl-_N_,_N_-di({[(methoxy)ethyl]oxy}methyl)amine 81



Methylamine (40% solution in water, 10 g, 129 mmol) and 2-methoxyethanol (30.5 mL, 387 mmol) were mixed in DCM (150 mL) and cooled in a cold water bath. K_2CO_3 (53.5 g, 387 mmol) and para formaldehyde (11.6 g, 387 mmol) were added, each in one portion. The mixture was allowed to come to room temperature and stirred for 5 d. After this time the reaction was filtered and the filtrate dried over $MgSO_4$. Removal of the DCM under vacuum gave the crude product which was purified by Kugelrohr distillation, giving the *title compound* (14.7 g, 55%) as a colourless oil.
HRMS found: $(M-1)^+$, 206.1391, $C_9H_{21}NO_4$, requires 206.1392; δ_H ($CDCl_3$, 400 MHz) 2.57 (3 H, s, NCH_3), 3.38 (6 H, s, OCH_3), 3.52-3.55 (4 H, m, CH_2O), 3.56-3.59 (4 H, m, CH_2O), 4.31 (4 H, s, NCH_2O); δ_C ($CDCl_3$, 100 MHz) 36.88 (NCH_3), 58.99 (OCH_3), 66.88 (OCH_2), 72.21 (OCH_2), 86.63 (NCH_2O); ν_{max} (Neat, cm^{-1}) 3482, 2875, 1448, 1358, 1250, 1092, 854.

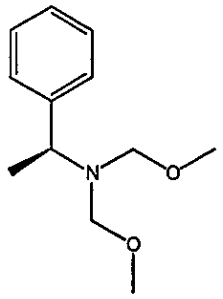
***N*,*N*-Di[(methoxy)methyl]-*N*-[(1R)-1-phenylethyl]amine 120[41]**



R-(+)-α-methylbenzylamine (10 g, 83 mmol) was dissolved in methanol (100 mL) and cooled to 0 °C. K_2CO_3 (28.7 g, 208 mmol) and para formaldehyde (6.2 g, 208 mmol) were each added in one portion. The reaction mixture was allowed to warm to room temperature and stirred for 3 d. After this time the reaction was filtered to remove any solid material and the filtrate concentrated under vacuum. The residue was taken up in DCM (200 mL), washed twice with water (200 mL), once with saturated brine solution (100 mL) and dried over $MgSO_4$. Removal of the solvent gave the crude product which was purified by Kügelrohr distillation to furnish the title compound (10.7 g, 62%) as a colourless oil.

Elemental analysis, found C, 68 81; H, 9.13; N, 6.99; $C_{12}H_{19}NO_2$, requires C, 68.87; H, 9.15; N, 6.69%; δ_H ($CDCl_3$, 250 MHz) 1.47 (3 H, d, J = 7 Hz, CH_3), 3.20 (6 H, s, OCH_3), 4.20 (2 H, d, J = 9.7 Hz, CH_2), 4.28 (2 H, d, J = 9.7 Hz, CH_2), 4.29 (1 H, q, J = 7 Hz, CH), 7.23-7.35 (5 H, m, ArH); δ_C ($CDCl_3$, 100 MHz) 20.40 (CH_3), 54.75 (OCH_3), 56.75 (CH), 84.64 (CH_2), 126.93 (CH), 127.50 (CH), 128.22 (CH), 144.27 (C).

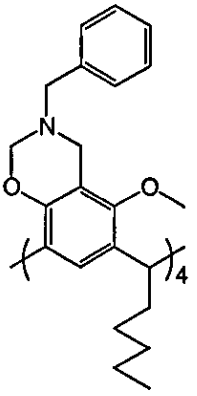
***N,N*-Di[(methoxy)methyl]-*N*-[(1S)-1-phenylethyl]amine 119[41]**



S-(-)-α-methylbenzylamine (10 g, 83 mmol) was dissolved in methanol (100 mL) and cooled to 0 °C. K_2CO_3 (28.7 g, 208 mmol) and para formaldehyde (6.2 g, 208 mmol) were each added in one portion. The reaction mixture was allowed to warm to room temperature and stirred for 3 d. After this time the reaction was filtered to remove any solid material and the filtrate concentrated under vacuum. The residue was taken up in DCM (200 mL), washed twice with water (200 mL), once with saturated brine solution (100 mL) and dried over $MgSO_4$. Removal of the solvent gave the crude product which was purified by Kügelrohr distillation to furnish the title compound (10 g, 58%) as a colourless oil.

δ_H ($CDCl_3$, 400 MHz) 1.47 (3 H, d, J = 6.8 Hz, CH_3), 3.20 (6 H, s, OCH_3), 4.20 (2 H, d, J = 9.6 Hz, CH_2), 4.28 (2 H, d, J = 9.6 Hz, CH_2), 4.29 (1 H, q, J = 6.8 Hz, CH), 7.23-7.35 (5 H, m, ArH); δ_C ($CDCl_3$, 100 MHz) 20.79 (CH_3), 55.13 (OCH_3), 57.26 (CH), 85.04 (CH_2), 127.33 (CH), 127.73 (CH), 128.50 (CH), 144.70 (C); ν_{max} (Neat, cm^{-1}) 3484, 2924, 1602, 1492, 1452, 1382, 1180, 1068, 913, 762, 700.

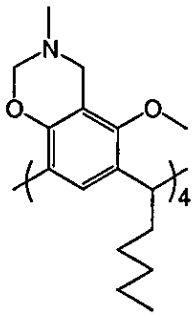
Tetra methoxy, tetra-(*N*-benzylbenzoxazine) resorcinarene 80



Tetra methoxy resorcinarene **76** (1 g, 1 2 mmol) was dissolved in toluene (90 mL). *N,N*-Di[(methoxy)methyl]-*N*-benzylamine **79** (1.18 g, 6.1 mmol) in toluene (10 mL) was added in one lot and the reaction mixture heated at reflux for 2 d. After this time the reaction was allowed to cool to room temperature and the solvent removed under reduced pressure. The residue was slurried in hexane and left overnight in the refrigerator. The solid produced was filtered and washed with cold hexane to furnish the *title compound* (1.2 g, 74%) as a pale brown powder.

LRMS found: M^+, 1348, $C_{88}H_{108}N_4O_8$, requires 1349; elemental analysis, found C, 78.13; H, 7.95; N, 4.06; requires C, 78.30; H, 8.06; N, 4.15%; m.p. 152-153 °C, degrades; δ_H ($CDCl_3$, 400 MHz) 0.87 (12 H, bt, CH_3), 1.31-1.40 (24 H, m, $CH_2CH_2CH_2$), 1.79-1.84 (4 H, m, $C\underline{H}_2CH$), 1.92-1.97 (4 H, m, $C\underline{H}_2CH$), 3.40 (12 H, s, OCH_3), 3.62 (4 H, d, J = 12.8 Hz, NCH_2), 3.74 (4 H, d, J = 12 4 Hz, NCH_2), 3.93 (4 H, d, J = 16.8 Hz, NCH_2), 4.04 (4 H, d, J = 16.4 Hz, NCH_2), 4.46 (4 H, t, J = 7.2 Hz, CH), 4.56 (4 H, d, J = 9.6 Hz, NCH_2O), 4.69 (4 H, d, J = 9.6 Hz, NCH_2O), 6.76 (4 H, s, ArH), 7.22-7.34 (20 H, m, ArH); δ_C ($CDCl_3$, 100 MHz) 14.21 (CH_3), 22.71 (CH_2), 27.93 (CH_2), 32.21 (CH_2), 35 55 (CH), 35.69 (CH_2), 47.33 (NCH_2), 55.32 (NCH_2), 60.02 (OCH_3), 80.17 (NCH_2O), 112 09 (C), 124.48 (CH), 127.32 (CH), 127.99 (C), 128.26 (CH), 128.79 (C), 129 43 (CH), 137.99 (C), 149.59 (C), 153.81 (C); ν_{max} (DCM, cm^{-1}) 2930, 2856, 2304, 1589, 1475, 1264, 1082, 947, 740.

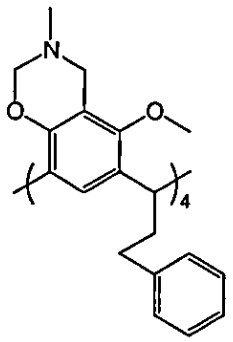
Tetra methoxy, tetra-(*N*-methylbenzoxazine) resorcinarene 78



Tetra methoxy resorcinarene **76** (10 g, 12 mmol) was dissolved in toluene (450 mL). *N*-Methyl-*N*,*N*-di({[(methoxy)ethyl]oxy}methyl)amine **81** (12.6 g, 61 mmol) in toluene (50 mL) was added in one lot and the reaction mixture heated at reflux for 4 d. After this time the reaction was allowed to cool to room temperature and the solvent removed under reduced pressure. The residue was slurried in hexane and left overnight in the refrigerator. The solid produced was filtered and washed with cold hexane to furnish the *title compound* (9.3 g, 73%) as a yellow powder.

LRMS found: $(M+H)^+$, 1045, $C_{64}H_{92}N_4O_8$, requires 1045; elemental analysis, found C, 73.71; H, 8.85; N, 5.25; requires C, 73.53; H, 8.87; N, 5.36; m.p. 179-181 °C, degrades; δ_H ($CDCl_3$, 400 MHz) 0.85 (12 H, bt, CH_3), 1.29 (24 H, m, $CH_2CH_2CH_2$), 1.75-1.87 (8 H, m, $C\underline{H}_2CH$), 2.46 (12 H, s, NCH_3), 3.42 (12 H, s, OCH_3), 3.83 (4 H, d, J = 16 Hz, NCH_2), 3.93 (4 H, d, J = 16 Hz, NCH_2), 4.44 (4 H, t, J = 8 Hz, CH), 4.50 (4 H, d, J = 8 Hz, NCH_2O), 4.67 (4 H, d, J = 8 Hz, NCH_2O), 6.67 (4 H, s, ArH); δ_C ($CDCl_3$, 100 MHz) 14.16 (CH_3), 22.67 (CH_2), 27.82 (CH_2), 32.12 (CH_2), 35.40 (CH), 35.56 (CH_2), 39.63 (NCH_3), 48.75 (NCH_2), 60.11 (OCH_3), 83.03 (NCH_2O), 112.02 (C), 124.58 (CH), 127.80 (C), 129.03 (C), 149.21 (C), 153.67 (C); ν_{max} (DCM, cm^{-1}) 2931, 2304, 1589, 1473, 1265, 1088, 895, 748.

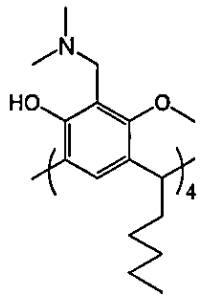
Tetra methoxy, tetra-(*N*-methylbenzoxazine) resorcinarene 73



Tetra methoxy resorcinarene **75** (1 g, 1 mmol) was dissolved in toluene (40 mL). *N*-Methyl-*N*,*N*-di({[methoxy)ethyl]oxy}methyl)amine **81** (1.3 g, 6.2 mmol) in toluene (5 mL) was added in one lot and the reaction mixture heated at reflux for 3 d. After this time the reaction was allowed to cool to room temperature and the solvent removed under reduced pressure. The residue was purified on silica gel (30% EtOAc / pet-ether) to furnish the *title compound* (0.84 g, 71%) as an off white powder.

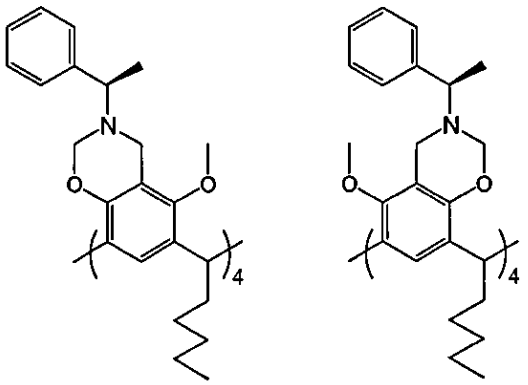
LRMS found: $(M+H)^+$, 1181, $C_{76}H_{84}N_4O_8$, requires 1182; m.p. 178-182 °C, degrades; δ_H ($CDCl_3$, 400 MHz) 2.12-2.20 (8 H, m, $CH_2C\underline{H}_2CH$), 2.47 (12 H, s, NCH_3), 2.64 (8 H, t, J = 8 Hz, $ArC\underline{H}_2CH_2$), 3.37 (12 H, s, OCH_3), 3.86 (4 H, d, J = 16 Hz, NCH_2), 3.94 (4 H, d, J = 16 Hz, NCH_2), 4.53-4.57 (8 H, d and t, NCH_2O and CH), 4.68 (4 H, d, J = 8 Hz, NCH_2O), 6.79 (4 H, s, ArH), 7.07-7.17 (20 H, m, ArH); δ_C ($CDCl_3$, 100 MHz) 34.41 (CH_2), 35.13 (CH), 37.62 (CH_2), 39.59 (NCH_3), 48.61 (NCH_2), 60.02 (OCH_3), 83.06 (NCH_2O), 112.20 (C), 124.38 (CH), 125.47 (CH), 127.37 (C), 128.17 (CH), 128.42 (CH), 128.84 (C), 142.64 (C), 149.40 (C), 153.85 (C).

Tetra methoxy, tetra-(*N*,*N*-dimethyl) resorcinarene 77



Tetra methoxy tetra-(*N*-methylbenzoxazine) resorcinarene **78** (6.1 g, 5.8 mmol) was dissolved in formic acid (96%, 100 mL) and heated at reflux for 7 h. After this time the reaction was allowed to cool to room temperature and carefully neutralised with aqueous ammonium hydroxide solution. The product was extracted into EtOAc (200 mL), washed twice with water (200 mL) and dried over $MgSO_4$. Removal of the solvent under reduced pressure gave the crude product as a yellow foam. The crude product was slurried in boiling methanol, then allowed to cool to room temperature, filtered and washed with methanol, giving the *title compound* (5.2 g, 85%) as a white powder. LRMS found: $(M+H)^+$, 1053, $C_{64}H_{100}N_4O_8$, requires 1054; elemental analysis, found C, 72 68; H, 9.60; N, 5.14; requires C, 72.97; H, 9.57; N, 5.32%; m p. 187-189 °C; δ_H ($CDCl_3$, 400 MHz) 0.84 (12 H, bt, CH_3), 1.25-1.34 (24 H, m, $CH_2CH_2CH_2$), 1.80 (4 H, m, $C\underline{H}_2CH$), 1.90 (4 H, m, $C\underline{H}_2CH$), 2.22 (24 H, s, NCH_3), 3.44 (12 H, s, OCH_3), 3.55 (4 H, d, J = 12 Hz, NCH_2), 3.67 (4 H, d, J = 16 Hz, NCH_2), 4.51 (4 H, t, J = 8 Hz, CH), 6.75 (4 H, s, ArH); δ_C ($CDCl_3$, 100 MHz) 14.13 (CH_3), 22.77 (CH_2), 28 10 (CH_2), 32.31 (CH_2), 35.99 (CH), 36.10 (CH_2), 44.36 (NCH_3), 56.41 (NCH_2), 61.09 (OCH_3), 113.73 (C), 125.85 (CH), 127.66 (C), 128.07 (C), 154.40 (C), 154.47 (C); ν_{max} (DCM, cm^{-1}) 3424, 2954, 1641, 1602, 1462 1265, 1089, 896, 739.

Tetra methoxy, tetra-[*N*-(R-(+)-α-methylbenzyl)benzoxazine] resorcinarenes 123 and 124

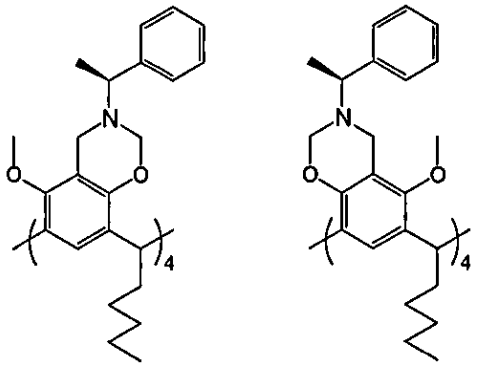


Tetra methoxy resorcinarene **76** (4 g, 4.9 mmol) was dissolved in toluene (100 mL). *N,N*-Di[(methoxy)methyl]-*N*-[(1R)-1-phenylethyl]amine **120** (5.1 g, 24.3 mmol) in toluene (10 mL) was added in one lot and the reaction mixture heated at reflux for 4 d. After this time the reaction was allowed to cool to room temperature and the solvent removed under reduced pressure. The residue was purified on silica gel (30% EtOAc / pet-ether) to furnish the *title compounds* (2.4 g, 35% each) as pale yellow foams.

First diastereoisomer 123: LRMS found: M^+, 1405, $C_{92}H_{116}N_4O_8$, requires 1405; elemental analysis, found C, 78.34; H, 8.26; N, 4.11; requires C, 78.60; H, 8.32; N, 3.99%; $[\alpha]_D^{25}$ 125 °, c = 0.55, $CHCl_3$; δ_H ($CDCl_3$, 400 MHz) 0.88 (12 H, bt, J = 6.8 Hz, CH_3), 1.33 (24 H, m, $CH_2CH_2CH_2$), 1.38 (12 H, d, J = 6.4 Hz, $C\underline{H}_3CH$), 1.79-1.82 (4 H, m, $C\underline{H}_2CH$), 1.88-1.91 (4 H, m, $C\underline{H}_2CH$), 3.25 (12 H, s, OCH_3), 3.80 (4 H, q, J = 6.8 Hz, $C\underline{H}CH_3$), 3.84 (4 H, d, J = 16.4 Hz, NCH_2), 4.16 (4 H, d, J = 17.2 Hz, NCH_2), 4.20 (4 H, t, J = 7.2 Hz, $C\underline{H}CH_2$), 4 58 (4 H, d, J = 10 Hz, NCH_2O), 4.63 (4 H, d, J = 10.4 Hz, NCH_2O), 6.73 (4 H, s, ArH), 7.25 (20 H, m, ArH); δ_C ($CDCl_3$, 100 MHz) 14.25 (CH_3), 21.26 (CH_3), 22.69 (CH_2), 27.90 (CH_2), 32.20 (CH_2), 35.37 (CH), 35.74 (CH_2), 44.60 (NCH_2), 57.20 (CH), 60.03 (OCH_3), 79 50 (NCH_2O), 112.16 (C), 124.49 (CH), 127.30 (CH), 127.51 (CH), 127.81 (C), 128.38 (CH), 128.78 (C), 144.05 (C), 150.05 (C), 153.52 (C); ν_{max} (DCM, cm^{-1}) 3054, 2985, 2305, 1421, 1265, 896, 747.

Second diastereoisomer 124: LRMS found: M^+, 1405, $C_{92}H_{116}N_4O_8$, requires 1405; elemental analysis, found C, 78.40; H, 8.16; N, 4.00; requires C, 78.60; H, 8.32; N, 3 99%; $[\alpha]_D^{25}$ –5 °, c = 0.53, $CHCl_3$; δ_H ($CDCl_3$, 400 MHz) 0.87 (12 H, bt, CH_3), 1.30 (24 H, m, $CH_2CH_2CH_2$), 1.38 (12 H, d, J = 6.4 Hz, CH_3CH), 1.75-1.80 (4 H, m, CH_2CH), 1.90-1.95 (4 H, m, CH_2CH), 3.33 (12 H, s, OCH_3), 3.70 (4 H, q, J = 6.4 Hz, $CHCH_3$), 3.88 (4 H, d, J = 16.8 Hz, NCH_2), 3.97 (4 H, d, J = 17.2 Hz, NCH_2), 4.44 (4 H, t, J = 7.2 Hz, $CHCH_2$), 4.55 (4 H, d, J = 10 Hz, NCH_2O), 4.98 (4 H, d, J = 10 Hz, NCH_2O), 6.80 (4 H, s, ArH), 7.16-7.30 (20 H, m, ArH); δ_C ($CDCl_3$, 100 MHz) 14.17 (CH_3), 21.41 (CH_3), 22 69 (CH_2), 27.75 (CH_2), 32.16 (CH_2), 35.38 (CH), 36.09 (CH_2), 45.36 (NCH_2), 57.44 (CH), 60.20 (OCH_3), 79.22 (NCH_2O), 112.28 (C), 124.49 (CH), 127.14 (CH), 127.39 (CH), 127.87 (C), 128.37 (CH), 128.51 (C), 144.41 (C), 150.31 (C), 153 96 (C); ν_{max} (DCM, cm^{-1}) 3054, 2985, 2305, 1421, 1265, 896, 749.

Tetra methoxy, tetra-[*N*-(S-(-)-α-methylbenzyl)benzoxazine] resorcinarenes 125 and 126

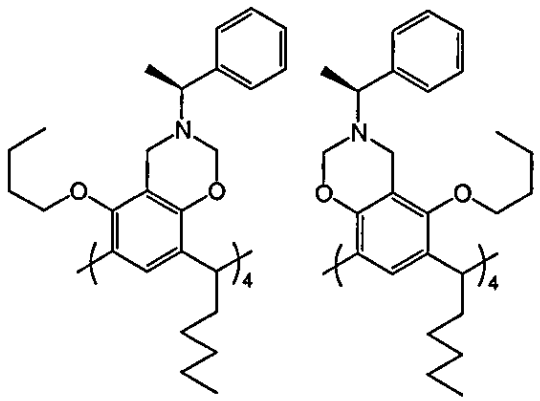


Tetra methoxy resorcinarene **76** (5 g, 6.1 mmol) was dissolved in toluene (100 mL). *N,N*-Di[(methoxy)methyl]-*N*-[(1S)-1-phenylethyl]amine **119** (6.4 g, 30 mmol) in toluene (10 mL) was added in one lot and the reaction mixture heated at reflux for 4 d. After this time the reaction was allowed to cool to room temperature and the solvent removed under reduced pressure. The residue was purified on silica gel (30% EtOAc / pet-ether) to furnish the *title compounds* [(3 g, 35%) of the first diastereoisomer and (2.7 g, 32%) of the second diastereoisomer)] as pale yellow foams.

First diastereoisomer 125: LRMS found: M^+, 1405, $C_{92}H_{116}N_4O_8$, requires 1405; $[\alpha]_D^{25}$ –107 °, c = 0.50, $CHCl_3$; δ_H ($CDCl_3$, 400 MHz) 0.88 (12 H, bt, *J* = 6.8 Hz, CH_3), 1.33 (24 H, m, $CH_2CH_2CH_2$), 1.38 (12 H, d, *J* = 6.8 Hz, $C\underline{H}_3CH$), 1.79-1.82 (4 H, m, $C\underline{H}_2CH$), 1.89-1.91 (4 H, m, $C\underline{H}_2CH$), 3.25 (12 H, s, OCH_3), 3.80 (4 H, q, *J* = 6.4 Hz, $C\underline{H}CH_3$), 3.84 (4 H, d, *J* = 16 8 Hz, NCH_2), 4.15 (4 H, d, *J* = 17.2 Hz, NCH_2), 4.24 (4 H, t, *J* = 7.6 Hz, $C\underline{H}CH_2$), 4.58 (4 H, d, *J* = 10 Hz, NCH_2O), 4.63 (4 H, d, *J* = 10 4 Hz, NCH_2O), 6 73 (4 H, s, ArH), 7.26 (20 H, m, ArH); δ_C ($CDCl_3$, 100 MHz) 14.25 (CH_3), 21.25 (CH_3), 22.69 (CH_2), 27.90 (CH_2), 32.20 (CH_2), 35.37 (CH), 35.74 (CH_2), 44.60 (NCH_2), 57.20 (CH), 60 03 (OCH_3), 79.50 (NCH_2O), 112.16 (C), 124.49 (CH), 127.30 (CH), 127.53 (CH), 127.81 (C), 128.38 (CH), 128.78 (C), 144.05 (C), 150.05 (C), 153.52 (C).

Second diastereoisomer 126: LRMS found: M^+, 1405, $C_{92}H_{116}N_4O_8$, requires 1405; $[\alpha]_D^{25}$ 7 °, c = 0.70, $CHCl_3$; δ_H ($CDCl_3$, 400 MHz) 0.87 (12 H, bt, CH_3), 1.30 (24 H, m, $CH_2CH_2CH_2$), 1.38 (12 H, d, *J* = 6.4 Hz, $C\underline{H}_3CH$), 1.75-1.80 (4 H, m, $C\underline{H}_2CH$), 1.90-1.95 (4 H, m, $C\underline{H}_2CH$), 3.33 (12 H, s, OCH_3), 3.70 (4 H, q, *J* = 6.4 Hz, $C\underline{H}CH_3$), 3.88 (4 H, d, *J* = 16 8 Hz, NCH_2), 3.97 (4 H, d, *J* = 17.2 Hz, NCH_2), 4.44 (4 H, t, *J* = 7.6 Hz, $C\underline{H}CH_2$), 4.55 (4 H, d, *J* = 10 Hz, NCH_2O), 4.98 (4 H, d, *J* = 10 Hz, NCH_2O), 6.80 (4 H, s, ArH), 7.18-7.30 (20 H, m, ArH); δ_C ($CDCl_3$, 100 MHz) 14.19 (CH_3), 21.41 (CH_3), 22.68 (CH_2), 27.76 (CH_2), 32.15 (CH_2), 35.36 (CH), 36.08 (CH_2), 45.33 (NCH_2), 57.36 (CH), 60.20 (OCH_3), 79.17 (NCH_2O), 112.22 (C), 124.49 (CH), 127.14 (CH), 127.39 (CH), 127.87 (C), 128.37 (CH), 128.51 (C), 144.41 (C), 150.31 (C), 153.97 (C).

Tetra *n*-butyloxy, tetra-[*N*-(S-(-)-α-methylbenzyl)benzoxazine] resorcinarenes 127 and 128



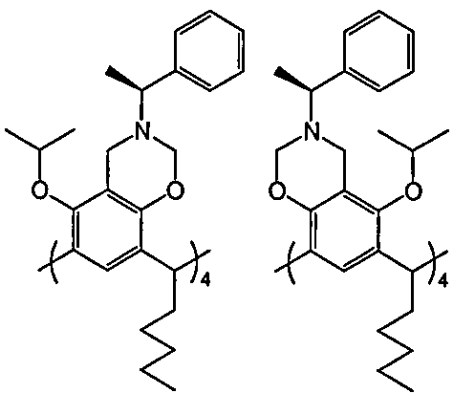
Tetra *n*-butyloxy resorcinarene **106** (1 g, 1 mmol) was dissolved in xylene (80 mL). *N,N*-Di[(methoxy)methyl]-*N*-[(1S)-1-phenylethyl]amine **119** (1.7 g, 8 mmol) in xylene (20 mL) was added in one lot and the reaction mixture heated at reflux for 4 d. After this time the reaction was allowed to cool to room temperature and the solvent removed under reduced pressure. The residue was purified on silica gel (15% EtOAc / pet-ether) to furnish the *title compounds* (0.5 g, 31% of each diastereoisomer) as pale yellow foams.

First diastereoisomer 127: HRMS found: M^+, 1573.0708, $C_{104}H_{140}N_4O_8$, requires 1573.0671; elemental analysis, found C, 79.27; H, 9.03; N, 3.62; requires C, 79.35; H, 8.96; N, 3.56%; $[\alpha]_D^{25}$ –105 °, c = 0.23, $CHCl_3$; δ_H ($CDCl_3$, 400 MHz, 50 °C) 0.93 (12 H, t, J = 7.2 Hz, CH_3), 0.97 (12 H, t, J = 6.4 Hz, CH_3), 1.41 (32 H, m, CH_2's), 1.46 (12 H, d, J = 6.8 Hz, $C\underline{H}_3CH$), 1.56-1.65 (8 H, m, CH_2), 1.86-1.92 (4 H, m, $C\underline{H}_2CH$), 1.97-2.02 (4 H, m, $C\underline{H}_2CH$), 3 50-3.41 (4 H, m, OCH_2), 3.47-3.52 (4 H, m, OCH_2), 3.89-3.95 (8 H, d and q, NCH_2 and $C\underline{H}CH_3$), 4.26 (4 H, d, J = 16.8 Hz, NCH_2), 4.54 (4 H, t, J = 7.2 Hz, CH), 4.69 (4 H, d, J = 10 Hz, NCH_2O), 4.73 (4 H, d, J = 10 Hz, NCH_2O), 6.85 (4 H, s, ArH), 7.31-7.39 (20 H, m, ArH); δ_C ($CDCl_3$, 100 MHz, 50 °C) 14.29 (CH_3), 14.37 (CH_3), 19.63 (CH_2), 21.59 (CH_3), 22.98 (CH_2), 28.24 (CH_2), 32.53 (CH_2), 32.87 (CH_2), 36.15 (CH), 36.25 (CH_2), 45.22 (NCH_2), 57.91 (CH), 72.70 (OCH_2), 80.08 (NCH_2O), 112.92 (C), 125.28 (CH), 127.47 (CH), 127.86 (CH), 127.94 (C), 128.69 (CH), 129.03 (C),

144.80 (C), 150.54 (C), 153.27 (C); ν_{max} (DCM, cm^{-1}) 3053, 2958, 2305, 1466, 1421, 1265, 896, 747.

Second diastereoisomer 128: LRMS found: $(M+H)^+$, 1573, $C_{104}H_{140}N_4O_8$, requires 1574; elemental analysis, found C, 79.45; H, 9.02; N, 3.53; requires C, 79.35; H, 8.96; N, 3 56%; $[\alpha]_D^{25}$ 21 °, c = 0.51, $CHCl_3$; δ_H ($CDCl_3$, 400 MHz, 50 °C) 0.77 (12 H, t, J = 7.2 Hz, CH_3), 0.86 (12 H, bt, CH_3), 1.15-1.24 (8 H, m, CH_2's), 1.30 (24 H, m, CH_2's), 1.39 (12 H, d, J = 6.4 Hz, CHC$\underline{H}_3$), 1.41-1.48 (8 H, m, CH_2's), 1.74-1.79 (4 H, m, C$\underline{H}_2$CH), 1.88-1.93 (4 H, m, C$\underline{H}_2$CH), 3.32-3.43 (8 H, m, OCH_2), 3.70 (4 H, q, J = 6.8 Hz, C$\underline{H}$CH$_3$), 3.88 (8 H, 2 bd's, NCH_2), 4.43 (4 H, t, J = 7.2 Hz, C$\underline{H}$CH$_2$), 4.53 (4 H, d, J = 10 Hz, NCH_2O), 4.90 (4 H, d, J = 10 Hz, NCH_2O), 6.77 (4 H, s, ArH), 7.12-7.27 (20 H, m, ArH); δ_C ($CDCl_3$, 100 MHz, 50 °C) 14.16 (CH_3), 14.35 (CH_3), 19.51 (CH_2), 21.40 (CH_3), 22.96 (CH_2), 28.08 (CH_2), 32.51 (CH_2), 32.74 (CH_2), 36.08 (CH), 36.36 (CH_2), 46.13 (NCH_2), 58.12 (CH), 72.60 (OCH_2), 79.58 (NCH_2O), 112.98 (C), 125.10 (CH), 127.33 (CH), 127.86 (CH), 128.07 (C), 128.60 (CH), 128.91 (C), 144.78 (C), 150.60 (C), 153.55 (C), ν_{max} (DCM, cm^{-1}) 3053, 2959, 2305, 1590, 1465, 1421, 1265, 896, 748.

Tetra *i*-propyloxy, tetra-[*N*-(S-(-)-α-methylbenzyl)benzoxazine] resorcinarenes 129 and 130



Tetra *i*-propyloxy resorcinarene **107** (2 g, 2.1 mmol) was dissolved in xylene (80 mL). *N*,*N*-Di[(methoxy)methyl]-*N*-[(1S)-1-phenylethyl]amine **119** (3 6 g, 17.1 mmol) in xylene (20 mL) was added in one lot and the reaction mixture heated at reflux for 4 d.

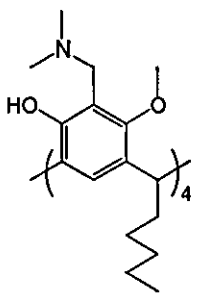
After this time the reaction was allowed to cool to room temperature and the solvent removed under reduced pressure. The residue was purified on silica gel (20% EtOAc / pet-ether) to furnish the *title compounds* [(1.2 g, 35%) of the first diastereoisomer and (1.1 g, 32%) of the second diastereoisomer)] as yellow foams. Crystals of the **first diastereoisomer 129**, suitable for X-ray analysis, were obtained from toluene / ethanol then solvent equilibration between toluene and pet-ether. The crystals obtained from the ethanol / toluene mixture were dissolved in the minimum amount of toluene in a small sample vial. This was then placed in a larger sample tube containing pet-ether and the large tube sealed. This was then left to stand at room temperature for several days until crystal formation occurred.

First diastereoisomer 129. LRMS found: M^+, 1518, $C_{100}H_{132}N_4O_8$, requires 1518; elemental analysis, found C, 79.19; H, 8.78; N, 3.61; requires C, 79.12; H, 8.76; N, 3.69%; $[\alpha]_D^{25}$ –116 °, c = 0.32, $CHCl_3$; m.p. 169-172 °C; δ_H ($CDCl_3$, 400 MHz, 50 °C) 0.81 (12 H, d, J = 6 Hz, $CH(C\underline{H}_3)_2$), 0.85 (12 H, bt, J = 6.4 Hz, CH_3), 1.02 (12 H, d, J = 6 Hz, $CH(C\underline{H}_3)_2$), 1.28 (24 H, m, $CH_2CH_2CH_2$), 1.38 (12 H, d, J = 6.4 Hz, $CHC\underline{H}_3$), 1.73-1.78 (4 H, m, $C\underline{H}_2CH$), 1.94-1.97 (4 H, m, $C\underline{H}_2CH$), 3.82 (4 H, q, J = 6.4 Hz, $C\underline{H}CH_3$), 3.85 (4 H, d, J = 16.8 Hz, NCH_2), 4.10 (4 H, bh, $C\underline{H}(CH_3)_2$), 4.15 (4 H, d, J = 16.8 Hz, NCH_2), 4.37 (4 H, t, J = 7.2 Hz, $C\underline{H}CH_2$), 4.53 (4 H, d, J = 10 Hz, NCH_2O), 4.59 (4 H, d, J = 9.6 Hz, NCH_2O), 6.85 (4 H, s, ArH), 7.19-7.30 (20 H, m, ArH); δ_C ($CDCl_3$, 100 MHz, 50 °C) 14.21 (CH_3), 21.61 (CH_3), 21.94 (CH_3), 22 60 (CH_3), 22.72 (CH_2), 28.06 (CH_2), 32.11 (CH_2), 36 05 (CH_2), 36.60 (CH), 45.50 (NCH_2), 57.05 (CH), 73.72 (OCH), 79.48 (NCH_2O), 113.05 (C), 125.31 (C), 127.17 (CH), 127.54 (CH), 128.23 (CH), 128.36 (CH), 129.04 (C), 144.26 (C), 149.92 (C), 151.28 (C); ν_{max} (DCM, cm^{-1}) 3054, 2986, 2305, 1421, 1265, 896, 749, 705.

Second diastereoisomer 130: LRMS found: M^+, 1518, $C_{100}H_{132}N_4O_8$, requires 1518; elemental analysis, found C, 78.27; H, 8.45; N, 3.54; requires C, 79.12; H, 8.76; N, 3.69%; $[\alpha]_D^{25}$ 3 °, c = 0.36, $CHCl_3$; δ_H ($CDCl_3$, 400 MHz, 50 °C) 0.85 (12 H, bt, CH_3), 0.88 (12 H, d, J = 5.6 Hz, $CH(C\underline{H}_3)_2$), 1.03 (12 H, d, J = 6 Hz, $CH(C\underline{H}_3)_2$), 1.33 (24 H, m, $CH_2CH_2CH_2$), 1.40 (12 H, d, J = 6.8 Hz, $CHC\underline{H}_3$), 1.70-1.78 (4 H, m, $C\underline{H}_2CH$), 1.94-2.00

(4 H, m, C<u>H</u>$_2$CH), 3.75-3.90 (12 H, q, d and d, C<u>H</u>CH$_3$, NCH$_2$ and NCH$_2$), 4.09 (4 H, bh, J = 6 Hz, C<u>H</u>(CH$_3$)$_2$), 4.37 (4 H, t, J = 7.3 Hz, C<u>H</u>CH$_2$), 4.53 (4 H, d, J = 10 Hz, NCH$_2$O), 4.92 (4 H, d, J = 10 Hz, NCH$_2$O), 6.86 (4 H, s, ArH), 7.17-7.27 (20 H, m, ArH); δ_C ($CDCl_3$, 100 MHz, 50 °C) 14.36 (CH_3), 21.39 (CH_3), 22 65 (CH_3), 22.88 (CH_3), 22.95 (CH_2), 28.15 (CH_2), 32.41 (CH_2), 36.66 (CH_2), 36 91 (CH), 47.12 (NCH_2), 58.47 (CH), 74.16 (OCH), 79.38 (NCH_2O), 113.89 (C), 125.71 (CH), 127.31 (CH), 127.78 (CH), 128 63 (CH), 145.01 (C), 150.67 (C), 152.09 (C).

Tetra methoxy, tetra-(*N*,*N*-dimethyl) resorcinarene 77, method 2

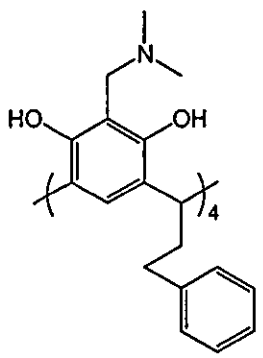


Tetra methoxy resorcinarene **76** (1 g, 1.2 mmol) was dissolved in dry dichloroethane (100 mL) under an atmosphere of nitrogen. *N*,*N*,*N*,*N*-Tetramethylmethylenediamine **131** (1.65 mL, 12.2 mmol) was added in one portion. The reaction mixture was then heated at reflux overnight. After this time the reaction was allowed to cool to room temperature and the solvent removed under reduced pressure. The residue was taken up in DCM (100 mL), washed twice with water (100 mL), once with saturated brine solution (60 mL) and dried over $MgSO_4$. Removal of the solvent gave a yellow foam which was slurried in hot methanol. The solid produced was filtered and washed with methanol furnishing the *title compound* (1.2 g, 93%) as a white solid.

δ_H ($CDCl_3$, 400 MHz) 0.84 (12 H, bt, CH_3), 1.27-1.34 (24 H, m, $CH_2CH_2CH_2$), 1.79 (4 H, m, C<u>H</u>$_2$CH), 1.90 (4 H, m, C<u>H</u>$_2$CH), 2.22 (24 H, s, NCH_3), 3.44 (12 H, s, OCH_3), 3.54 (4 H, d, J = 16 Hz, NCH_2), 3.67 (4 H, d, J = 16 Hz, NCH_2), 4.51 (4 H, t, J = 8 Hz, CH), 6.75 (4 H, s, ArH); δ_C ($CDCl_3$, 100 MHz) 14.41 (CH_3), 23.05 (CH_2), 28.38 (CH_2), 32.59

(CH_2), 36.27 (CH), 36.38 (CH_2), 44.64 (NCH_3), 56.69 (NCH_2), 61.37 (OCH_3), 114.00 (C), 126.14 (CH), 127.94 (C), 128.34 (C), 154.69 (C), 154.75 (C).

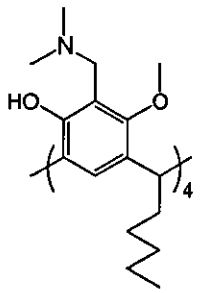
Octa hydroxy, tetra-(*N*,*N*-dimethyl) resorcinarene 38[32b]



Octa hydroxy resorcinarene **34** (2 g, 2.2 mmol) and dry dichloroethane (70 mL) were mixed together under an atmosphere of nitrogen and cooled in a cold water bath. *N*,*N*,*N*,*N*-Tetramethylmethylenediamine **131** (2 4 mL, 17.7 mmol) was added drop wise and the reaction stirred to room temperature overnight. After this time the solvent was removed under vacuum leaving a solid residue. The residue was filtered and washed with large amounts of diethyl ether giving the title compound (2.3 g, 92%) as a pink solid.

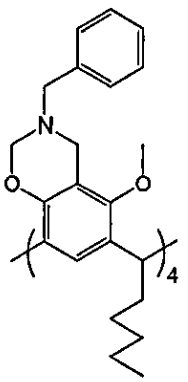
HRMS found: $(M+H)^+$, 1133.6357, $C_{72}H_{84}N_4O_8$, requires 1133.6367; δ_H (d_6-DMSO, 400 MHz, 50 °C) 2.44 (24 H, s, CH_3), 2.58 (16 H, m, CH_2CH_2), 3.86 (8 H, s, NCH_2), 4.32 (4 H, bt, CH), 5.84 (8 H, bs, OH), 7.16-7.25 (20 H, m, ArH), 7.48 (4 H, s, ArH); δ_C (d_6-DMSO, 100 MHz, 50 °C) 33.25 (CH), 34.11 (CH_2), 34.49 (CH_2), 42.75 (CH_3), 55.11 (NCH_2), 106.47 (C), 123 02 (CH), 123.45 (C), 125.22 (CH), 127.80 (CH), 128.18 (CH), 141.89 (C), 151.84 (C).

Tetra methoxy, tetra-(*N,N*-dimethyl) resorcinarene 77, method 3



K_2CO_3 (2.5 g, 18 mmol), and dry DCM (50 mL) were mixed together under an atmosphere of nitrogen. *N,N,N,N*-Tetramethylmethylenediamine **131** (0.85 mL, 6 mmol) was added in one lot. Acetyl chloride (0.45 mL, 6 mmol) was added drop wise and the reaction mixture stirred for 30 min. Tetra methoxy resorcinarene **76** (0.5 g, 0.6 mmol), dissolved in dry DCM (10 mL), was added drop wise to the reaction and stirred for 5 d at room temperature. After this time the reaction was filtered to remove any solid material. The filtrate was then washed twice with water (100 mL) and dried over $MgSO_4$. The DCM was removed under reduced pressure. The residue was taken up in diethyl ether (50 mL) and allowed to slowly evaporate, furnishing the *title compound* (0 63 g, 98%) as a colourless crystalline solid suitable for X-ray analysis.
δ_H ($CDCl_3$, 400 MHz) 0.84 (12 H, bt, J = 6.4 Hz, CH_3), 1 24-1.35 (24 H, m, $CH_2CH_2CH_2$), 1.78 (4 H, m, $C\underline{H}_2CH$), 1.90 (4 H, m, $C\underline{H}_2CH$), 2.23 (24 H, s, NCH_3), 3.44 (12 H, s, OCH_3), 3.55 (4 H, d, J = 14 Hz, NCH_2), 3.67 (4 H, d, J = 14.4 Hz, NCH_2), 4.48 (4 H, t, J = 7.6 Hz, CH), 6.72 (4 H, s, ArH); δ_C ($CDCl_3$, 100 MHz) 14.21 (CH_3), 22.76 (CH_2), 28.17 (CH_2), 32.29 (CH_2), 35.87 (CH), 35.98 (CH_2), 44.33 (NCH_3), 56.22 (NCH_2), 61.09 (OCH_3), 113.65 (C), 125.57 (CH), 127.50 (C), 127.95 (C), 154.07 (C), 154.32 (C).

Tetra methoxy, tetra-(*N*-benzylbenzoxazine) resorcinarene 80, method 2

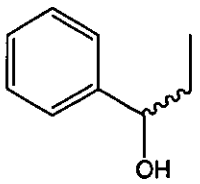


N,N-Di[(methoxy)methyl]-*N*-benzylamine **79** (2 g, 10.3 mmol) was dissolved in dry pet-ether (50 mL) under an atmosphere of nitrogen. Acetyl chloride (0.73 mL, 10.3 mmol) was added drop wise and the reaction mixture stirred for 24 h at room temperature. After this time the reaction was placed in the freezer for 24 h. After this time, while still cold, the solvent was removed using a cannula. To the residue, under a nitrogen atmosphere, was added tetra methoxy resorcinarene **76** (0.85 g, 1 mmol) dissolved in dry 1,2-dichloroethane (50 mL) in one lot. The mixture was then heated at reflux overnight. After this time the reaction was allowed to cool and the solvent removed under vacuum. The residue was slurried in hexane and put in the refrigerator for 24 h. The solid produced was filtered and washed with cold hexane to furnish the *title compound* (1.1 g, 80%) as a pale brown powder.

Elemental analysis, found C, 78.00; H, 8.00; N, 4.04; $C_{88}H_{108}N_4O_8$, requires C, 78.30; H, 8.06; N, 4.15%; δ_H ($CDCl_3$, 400 MHz) 0.87 (12 H, bt, CH_3), 1.33 (24 H, m, $CH_2CH_2CH_2$), 1.77-1.83 (4 H, m, C<u>H</u>$_2$CH), 1.93-1.94 (4 H, m, C<u>H</u>$_2$CH), 3.40 (12 H, s, OCH_3), 3.62 (4 H, d, J = 12.4 Hz, NCH_2), 3.75 (4 H, d, J = 12.8 Hz, NCH_2), 3.94 (4 H, d, J = 16.4 Hz, NCH_2), 4.05 (4 H, d, J = 16.8 Hz, NCH_2), 4 46 (4 H, t, J = 7.6 Hz, CH), 4.57 (4 H, d, J = 9.6 Hz, NCH_2O), 4.70 (4 H, d, J = 9.6 Hz, NCH_2O), 6.76 (4 H, s, ArH), 7.18-7.33 (20 H, m, ArH); δ_C ($CDCl_3$, 100 MHz) 14.22 (CH_3), 22.70 (CH_2), 27.94 (CH_2), 32.20 (CH_2), 35.53 (CH), 35.66 (CH_2), 47.29 (NCH_2), 55.26 (NCH_2), 60.01 (OCH_3), 80.10 (NCH_2O), 112.05 (C), 124.44 (CH), 127.32 (CH), 127.95 (C), 128.25 (CH), 128.76 (C), 129.43 (CH), 137.93 (C), 149.54 (C), 153.76 (C).

3.5 Experimental details for Section 2.5

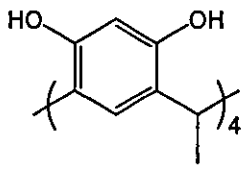
1-Phenyl-1-propanol 138[72]



Resorcinarene **129** (13 mg, 8.6 μmol, 1 mol%) was dissolved in dry toluene (1 mL) under a nitrogen atmosphere and cooled in a cold water bath. Diethylzinc (1.0 M in hexanes, 2.2 mL, 2.2 mmol) was added slowly and the mixture stirred for 30 min. After this time the reaction was cooled to –78 °C. Benzaldehyde (0.1 mL, 1 mmol) was added drop wise. The reaction was allowed to gradually warm to room temperature overnight. The reaction mixture was then partitioned between diethyl ether (60 mL) and aqueous 2 N HCl (60 mL). The organic phase was dried over $MgSO_4$ and concentrated, furnishing the crude title compound (135 mg, > 95%) as a colourless oil. The residue produced was not purified, with analysis taking place on the crude product. Specific rotations were in comparison to those reported by the Aldrich Chemicals sales catalogue. Enantioselectivity was determined by comparison of optical rotations and by chiral GC (125 °C isothermal on a β-cyclodextrin 30 cm column at 10 psi flow pressure).
$[\alpha]_D^{25}$ 43 °, c = 0.27, hexane; δ_H ($CDCl_3$, 250 MHz) 0.89 (3 H, t, J = 7.4 Hz, CH_3), 1.63-1.87 (2 H, m, CH_2), 3.27 (1 H, bs, OH), 4.56 (1 H, t, J = 6.7 Hz, CH), 7.25-7.34 (5 H, m, ArH).

3.6 Experimental details for Section 2.6

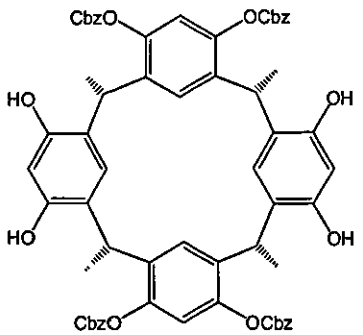
Octa hydroxy methyl resorcinarene 7[4]



Resorcinol (55 g, 0.5 mol) was dissolved in ethanol (95%, 100 mL), water (100 mL) and concentrated HCl (50 mL) and cooled to 0 °C. Acetaldehyde (28 mL, 0.5 mol) was added drop wise over 30 min. The reaction was heated at 50 °C for 1 h. It was then allowed to cool to room temperature and stirred for 4 d. After this time the yellow precipitate was filtered and washed with large amounts of 1 : 1, ethanol : water. The solid was recrystallised from ethanol / water and dried overnight under high vacuum at 80 °C, furnishing the title compound (35 g, 51%) as an off white powder.

LRMS found: M^+, 544, $C_{32}H_{32}O_8$, requires 544; δ_H (d_6-DMSO, 400 MHz) 1.31 (12 H, d, J = 8 Hz, CH_3), 4.46 (4 H, q, J = 8 Hz, CH), 6.15 (4 H, s, ArH), 6.78 (4 H, s, ArH), 8.53 (8 H, s, OH); δ_C (d_6-DMSO, 100 MHz) 21.49 (CH_3), 28.46 (CH), 102.02 (CH), 123.03 (C), 125.18 (CH), 151.77 (C).

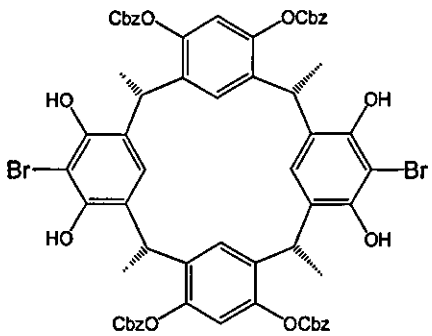
Tetra Cbz resorcinarene 141[24]



Octa hydroxy methyl resorcinarene 7 (10 g, 18.4 mmol) was mixed with dry acetonitrile (200 mL) under an atmosphere of nitrogen. Triethylamine (10.3 mL, 73.6 mmol) was added quickly, in one portion, with fast stirring and stirred for 30 min. Benzylchloroformate (95% purity, 10.5 mL, 73.6 mmol) was added quickly in one portion. The reaction was stirred for 24 h at room temperature. The solid product was filtered and washed with the minimum necessary amount of acetonitrile. The solid was taken up in DCM (200 mL), washed three times with water (200 mL), once with saturated brine solution (100 mL) and dried over $MgSO_4$. Removal of the solvent furnished the title compound (6.5 g, 33%) as a white foam.

LRMS found: M^+, 1080, $C_{64}H_{56}O_{16}$, requires 1080; δ_H ($CDCl_3$, 400 MHz) 1.40 (12 H, d, J = 7.2 Hz, CH_3), 4.18 (4 H, q, J = 6.8 Hz, CH), 5.24 (4 H, d, J = 12 Hz, CH_2), 5.28 (4 H, d, J = 12 Hz, CH_2), 6.03 (2 H, s, ArH), 6.26 (2 H, s, ArH), 6.74 (4 H, s, OH), 6.99 (2 H, s, ArH), 7.02 (2 H, s, ArH), 7.30-7.39 (20 H, m, ArH); δ_C ($CDCl_3$, 100 MHz) 20.48 (CH_3), 32.25 (CH), 71.37 (CH_2), 103.40 (CH), 115.35 (CH), 120.08 (C), 125.17 (CH), 127.26 (CH), 128.95 (CH), 129.11 (CH), 129.21 (CH), 134.88 (C), 138.21 (C), 147.08 (C), 153.61 (C), 154.72 (C).

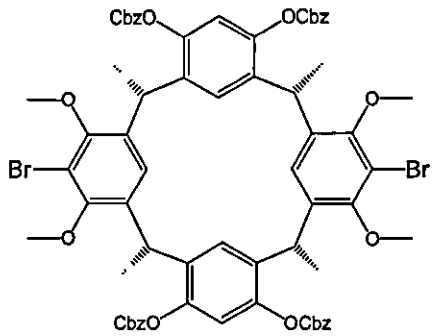
Tetra Cbz dibromo resorcinarene 146



Tetra Cbz resorcinarene **141** (4 g, 3.7 mmol) was dissolved in 2-butanone (300 mL). *N*-Bromosuccinimide (3.96 g, 22 mmol) was added in one lot and the reaction mixture stirred at room temperature for 4 d. After this time the reaction was concentrated. The residue was taken up in DCM (100 mL), washed twice with water (100 mL), once with saturated brine solution (100 mL), dried over $MgSO_4$ and concentrated. The resulting foam was solidified from acetonitrile / water and recovered by filtration, giving the *title compound* (4.2 g, 91%) as an off white solid.

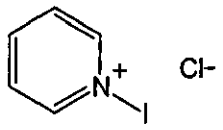
LRMS found: M^+, 1238, $C_{64}H_{54}Br_2O_{16}$, requires 1238; elemental analysis, found C, 62.05; H, 4.29; requires C, 62.05; H, 4.39%, m.p. 200 °C; δ_H ($CDCl_3$, 400 MHz) 1.44 (12 H, d, J = 7.2 Hz, CH_3), 4.32 (4 H, q, J = 7.2 Hz, CH), 5.28 (4 H, d, J = 12 Hz, CH_2), 5.33 (4 H, d, J = 12 Hz, CH_2), 5.66 (4 H, s, OH), 6 24 (2 H, s, ArH), 7.047 and 7.053 (4 H, 2s, 2ArH), 7.35-7.45 (20 H, m, ArH); δ_C ($CDCl_3$, 100 MHz) 20.28 (CH_3), 32.18 (CH), 70.86 (CH_2), 100.68 (C), 115.38 (CH), 120.92 (C), 123.41 (CH), 126 01 (CH), 128.58 (CH), 128.72 (CH), 128.87 (CH), 134.60 (C), 137.13 (C), 146.68 (C), 149.39 (C), 154.02 (C); ν_{max} (DCM, cm^{-1}) 3427, 2122, 1761, 1641, 1265, 747.

Tetra Cbz, tetra methoxy dibromo resorcinarene 147



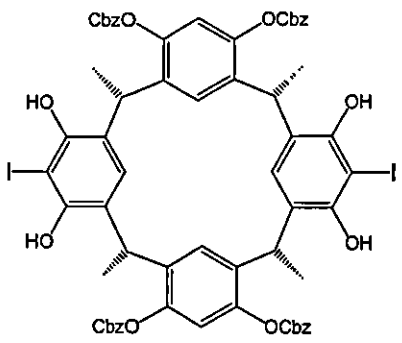
Tetra Cbz dibromo resorcinarene **146** (8.6 g, 7 mmol) was dissolved in dry DMF (250 mL) under a nitrogen atmosphere. Cesium carbonate (13.7 g, 42 mmol) was added in one lot. Methyl iodide (2.61 mL, 42 mmol) was added drop wise and the reaction mixture stirred for 3 d at room temperature. After this time the reaction was separated between diethyl ether / EtOAc (250 mL) and water (250 mL). The organic phase was washed twice with water (200 mL), once with saturated brine solution (100 mL) and dried over $MgSO_4$. The residue, following removal of the solvent, was purified on silica gel (30% EtOAc / pet-ether) to produce the *title compound* (5.9 g, 65%) as an off white foam. Crystals suitable for X-ray analysis were obtained by slow evaporation of DCM. LRMS found: $(M+H)^+$, 1295, $C_{68}H_{62}Br_2O_{16}$, requires 1296; elemental analysis, found C, 62.81; H, 4.75; requires C, 63.06; H, 4.83; m.p. 204-206 °C; δ_H ($CDCl_3$, 400 MHz, 50 °C) 1.47 (12 H, d, J = 7.2 Hz, CH_3), 3.50 (12 H, s, OCH_3), 4.55 (4 H, q, J = 7.2 Hz, CH), 5.13 (4 H, d, J = 12.4 Hz, CH_2), 5.22 (4 H, d, J = 12 Hz, CH_2), 6.64 (4 H, bs, ArH), 7.14 (2 H, s, ArH), 7.32 (20 H, m, ArH); δ_C ($CDCl_3$, 100 MHz, 50 °C) 20.74 (CH_3), 32.94 (CH), 60.94 (OCH_3), 70.74 (CH_2), 113.52 (C), 116.56 (CH), 124.70 (CH), 126.23 (CH), 128.82 (CH), 128.97 (CH), 135.29 (C), 135.37 (C), 135.57 (C), 147.28 (C), 153.35 (C), 154.93 (C), remaining (CH) unseen; ν_{max} (DCM, cm^{-1}) 3055, 2973, 2305, 1764, 1458, 1421, 1380, 1266, 1118, 962, 738.

Pyridine-iodine monochloride 149[89]



Pyridine (10 mL, 124 mmol) was dissolved in DCM (200 mL) and cooled in a cold water bath. Iodine monochloride (7.1 mL, 136 mmol), dissolved in DCM (200 mL), was added portion wise and the reaction stirred at room temperature for 24 h. After this time the solvent was removed under vacuum and the residue recrystallised from ethanol (100%), furnishing the title compound (17.7 g, 59%) as a yellow solid.
m.p. 130-134 °C; δ_H ($CDCl_3$, 400 MHz) 7.50-7.53 (2 H, m, ArH), 8.03-8.08 (1 H, m, ArH), 8.68-8.70 (2 H, m, ArH); δ_C ($CDCl_3$, 100 MHz) 127.00 (CH), 140.10 (CH), 148 38 (CH).

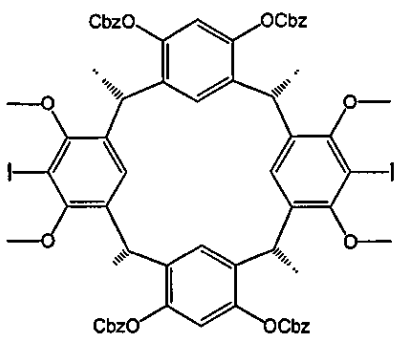
Tetra Cbz diiodo resorcinarene 148



Tetra Cbz resorcinarene **141** (3.8 g, 3.5 mmol) was dissolved in 2-butanone (200 mL) and cooled to 0 °C. Pyridine-iodine monochloride **149** (5.1 g, 21.1 mmol) in 2-butanone (20 mL) (pre-cooled to 0 °C) was added in one lot and the reaction allowed to warm to room temperature and stirred for 3 d. After this time the reaction was concentrated. The residue was taken up in DCM (150 mL), washed three times with water (150 mL), dried over $MgSO_4$, and concentrated. The crude product was subjected

to chromatography on silica gel (2% methanol / DCM) furnishing the *title compound* (2.5 g, 54%) as a pale brown foam which was reacted on without further purification. LRMS found: $(M+Na)^+$, 1355, $C_{64}H_{54}I_2O_{16}$, requires 1355; δ_H ($CDCl_3$, 400 MHz) 1.43 (12 H, d, J = 8 Hz, CH_3), 4.28 (4 H, q, J = 8 Hz, CH), 5.30 (4 H, d, J = 12 Hz, CH_2), 5.35 (4 H, d, J = 12 Hz, CH_2), 5.78 (4 H, s, OH), 6.23 (2 H, s, ArH), 7 05 (2 H, s, ArH), 7.09 (2 H, s, ArH), 7.36-7.46 (20 H, m, ArH); δ_C ($CDCl_3$, 100 MHz) 20.52 (CH_3), 32.54 (CH), 70.98 (CH_2), 115.34 (CH), 119.80 (C), 123.43 (C), 124.90 (CH), 126.05 (CH), 128.60 (CH), 128.74 (CH), 128.91 (CH), 134.46 (C), 137.35 (C), 146.75 (C), 152.17 (C), 154.12 (C); ν_{max} (DCM, cm^{-1}) 3464, 3054, 2985, 2305, 1763, 1421, 1266, 896, 739.

Tetra Cbz, tetra methoxy diiodo resorcinarene 150

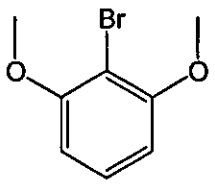


Tetra Cbz diiodo resorcinarene **148** (2 g, 1.5 mmol) was dissolved in dry DMF (100 mL) under a nitrogen atmosphere and cooled to 0 °C. Cesium carbonate (3.9 g, 12 mmol) was added in one lot. Methyl iodide (0 75 mL, 12 mmol) was added drop wise and the reaction mixture stirred for 2 d at room temperature. After this time the reaction was separated between diethyl ether / EtOAc (100 mL) and water (100 mL). The organic phase was washed twice with water (100 mL), once with saturated brine solution (100 mL), dried over $MgSO_4$ and concentrated. The residue was taken up in diethyl ether and placed in the freezer overnight. This caused a brown solid to form which was filtered and washed with cold diethyl ether (60 mL), giving the *title compound* (0.8 g, 40%) as a brown powder.

HRMS found· $(M-H)^+$, 1335.1717, $C_{64}H_{58}I_2O_{16}$, requires 1335.1736; elemental analysis, found C, 58.88; H, 4.32; requires C, 58.80; H, 4.50%; m.p. 199-202 °C; δ_H ($CDCl_3$, 400

MHz, 50 °C) 1.49 (12 H, d, J = 7.2 Hz, CH_3), 3.52 (12 H, bs, OCH_3), 4.58 (4 H, q, J = 7.2 Hz, CH), 5.16 (4 H, d, J = 12 Hz, CH_2), 5.25 (4 H, d, J = 12 Hz, CH_2), 6.66 (2 H, bs, ArH), 6.74 (2 H, bs, ArH), 7.17 (2 H, s, ArH), 7.36 (20 H, m, ArH); δ_C ($CDCl_3$, 100 MHz, 50 °C) 20.80 (CH_3), 33.21 (CH), 61.18 (OCH_3), 70.73 (CH_2), 91.01 (C), 116.53 (CH), 126 20 (CH), 126.50 (CH), 128.79 (CH), 128.96 (CH), 135.02 (C), 135.29 (C), 135.52 (C), 147.31 (C), 153 32 (C), 157.76 (C), remaining (CH) obscured; ν_{max} ($CDCl_3$, cm^{-1}) 3418, 2253, 1761, 1468, 1381, 1223, 1100, 912, 743, 651.

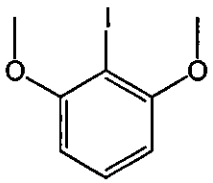
2,6-Dimethoxybromobenzene 151[91]



m-Dimethoxybenzene (13.1 mL, 100 mmol) was dissolved in dry diethyl ether (300 mL) under an atmosphere of nitrogen. *n*-Butyl lithium (2.5 M in hexanes, 46 mL, 115 mmol) was added drop wise and the mixture stirred for 30 min. The reaction was then left to stand at room temperature for 2 d. 1,2-Dibromoethane (11.5 mL, 133 mmol) was added drop wise and the reaction stirred for 3 d at room temperature. After this time the reaction mixture was washed twice with water (200 mL) and dried over $MgSO_4$. The filtrates, following removal of the $MgSO_4$, were placed in the freezer overnight. The title compound (10 6 g, 49%) precipitated as colourless needle crystals which were filtered and washed with large amounts of cold diethyl ether.

HRMS found: M^+, 215.9786, $C_8H_9BrO_2$, requires 215.9786; m.p. 94-96 °C; δ_H ($CDCl_3$, 400 MHz) 3.89 (6 H, s, CH_3), 6.57 (2 H, d, J = 8 4 Hz, ArH), 7.23 (1 H, t, J = 8.4 Hz, ArH); δ_C ($CDCl_3$, 100 MHz) 56.43 (CH_3), 100.84 (C), 104.64 (CH), 128.31 (CH), 157.14 (C).

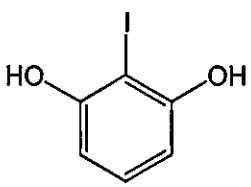
2,6-Dimethoxyiodobenzene 152[92]



m-Dimethoxybenzene (10 mL, 76.4 mmol) was dissolved in dry diethyl ether (400 mL) under a nitrogen atmosphere. *n*-Butyl lithium (2.5 M in hexanes, 34 mL, 84 mmol) was added drop wise and the mixture stirred for 30 min. The reaction was then left to stand at room temperature for 2 d. Iodine (21.3 g, 84 mmol) dissolved in dry diethyl ether (200 mL) was added portion wise and the mixture stirred for 2 d at room temperature. After this time the reaction was washed with aqueous ammonium chloride solution (300 mL), twice with aqueous sodium thiosulphate solution (200 mL), saturated brine solution (100 mL), dried over $MgSO_4$ and concentrated. The residue was slurried in hexane. The resulting solid was filtered and washed with hexane furnishing the title compound (10.3 g, 51%) as a brown solid.

HRMS found: M^+, 263.9650, $C_8H_9IO_2$, requires 263.9647; m p. 102-105 °C; δ_H ($CDCl_3$, 400 MHz) 3.88 (6 H, s, CH_3), 6.50 (2 H, d, $J = 8$ Hz, ArH), 7.26 (1 H, t, $J = 8$ Hz, ArH); δ_C ($CDCl_3$, 100 MHz) 55.56 (CH_3), 104.07 (CH), 123.42 (C), 129.83 (CH), 159.49 (C).

2-Iodoresorcinol 153[93]

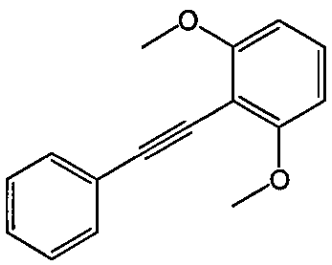


Resorcinol (2.75 g, 25 mmol) and $NaHCO_3$ (3 g, 36 mmol) were mixed in water (20 mL) and cooled in an ice / salt water bath. Iodine (6.7 g, 26 mmol, pre-cooled, in a sample vial, as a solid in the ice / salt water bath) was added in one lot with fast stirring. The mixture was stirred for 30 min with any precipitate being washed down the sides of

the flask with ice cold water. After this time the solid was filtered and washed with ice cold water. The aqueous solution was extracted twice with diethyl ether (100 mL). The combined organic layers were dried over $MgSO_4$ and concentrated. The residue was recrystallised from chloroform giving the title compound (1.8 g, 31%) as a pale brown powder.

HRMS found: M^+, 235.9335, $C_6H_5IO_2$, requires 235.9334; m.p. 97-101 °C; δ_H ($CDCl_3$ + CD_3OD, 400 MHz) 6.48 (2 H, d, J = 8 Hz, ArH), 7.04 (1 H, t, J = 8 Hz, ArH); δ_C ($CDCl_3$ + CD_3OD, 100 MHz) 106.77 (CH), 129.92 (CH), 156.44 (C), remaining (C) unclear.

1,3-Di(methoxy)-2-(2-phenyleth-1-ynyl)benzene 154



2,6-Dimethoxyiodobenzene **152** (200 mg, 0.76 mmol) was dissolved dry DMF (10 mL) under an atmosphere of nitrogen. Phenylacetylene (0.25 mL, 2.3 mmol) was added in one lot and nitrogen bubbled through the mixture for 30 min. Tri-*n*-butylamine (0.2 mL, 8.3 mmol), $Pd(PPh_3)_4$ (5 mol%, 44 mg) and CuI (10 mol%, 15 mg) were each added in one lot. The reaction mixture was then heated at 85 °C for 2 d. After this time the mixture was allowed to cool and partitioned between diethyl ether (100 mL) and water (100 mL). The organic phase was washed twice with water (100 mL), dried over $MgSO_4$ and concentrated. The residue was purified on silica gel (10% EtOAc / hexane) to give the *title compound* (144 mg, 80%) as a brown oil.

HRMS found: M^+, 238.0993, $C_{16}H_{14}O_2$, requires 238.0994; δ_H ($CDCl_3$, 400 MHz) 3.91 (6 H, s, CH_3), 6.56 (2 H, d, J = 8.4 Hz, ArH), 7.24 (1 H, t, J = 8.4 Hz, ArH), 7.29-7.33 (3 H, m, ArH), 7.58-7.60 (2 H, m, ArH); δ_C ($CDCl_3$, 100 MHz) 56.14 (CH_3), 81.81 (C), 97.85 (C), 101.53 (C), 103.50 (CH), 123.92 (C), 127.89 (CH), 128.11 (CH), 129.75 (CH),

131.72 (CH), 161.37 (C); ν_{max} (DCM, cm^{-1}) 3054, 2966, 2839, 2304, 2214, 1583, 1476, 1432, 1256, 1113, 1032, 896, 735.

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Appendix 1

Crystal structures

X-ray crystal structures were produced using a Bruker AXS SMART 1000 CCD diffractometer instrument at Loughborough University Chemistry Department.

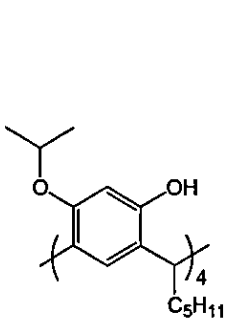
The methods used for obtaining each crystal, of a quality suitable for analysis, are explained in the experimental section.

1. Tetra *i*-propyloxy pentyl resorcinarene **107**.

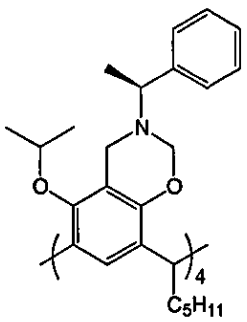
2. Tetra *i*-propyloxy, tetra *N*-(S-(-)-α-methylbenzyl)benzoxazine resorcinarene, **129**.

3. Tetra methoxy, tetra *N,N*-dimethylamino resorcinarene **77**, **method 3**.

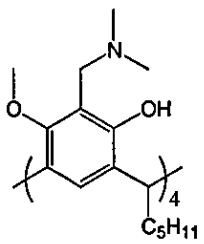
4. Tetra CBz, tetra methoxy dibromo resorcinarene **147**.



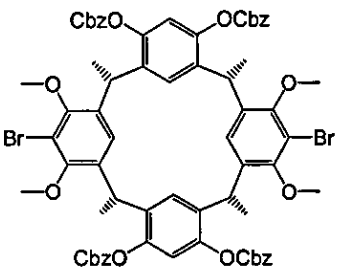
107



129



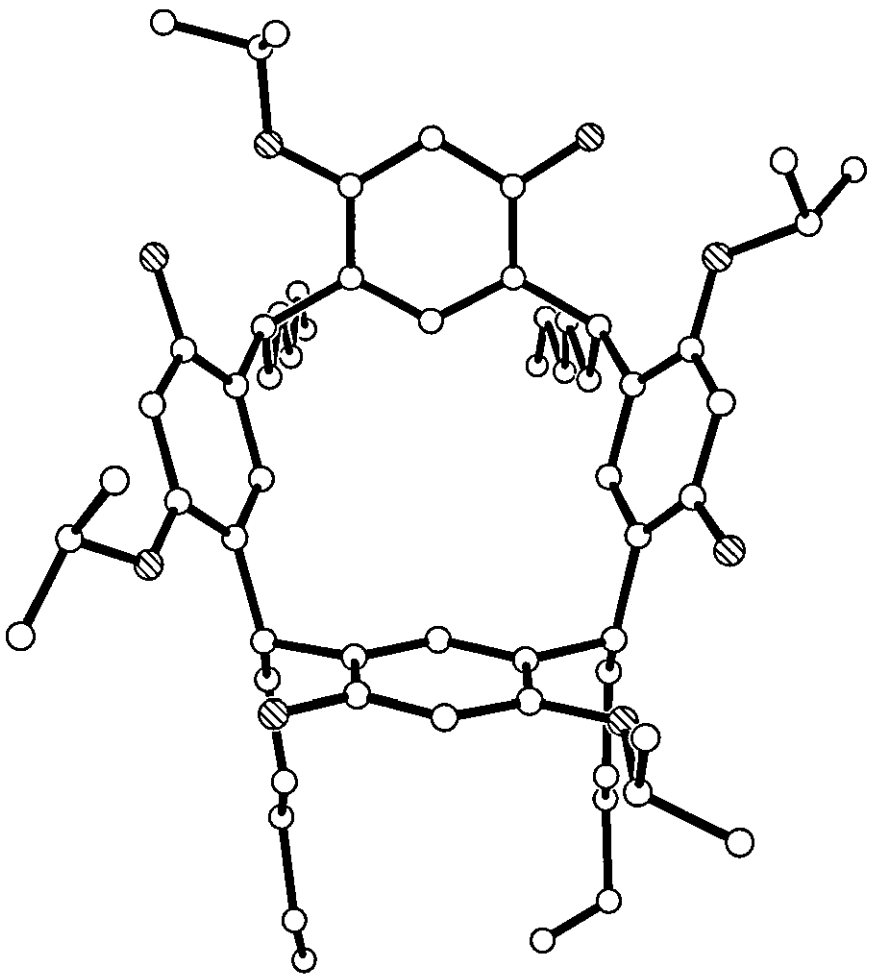
77



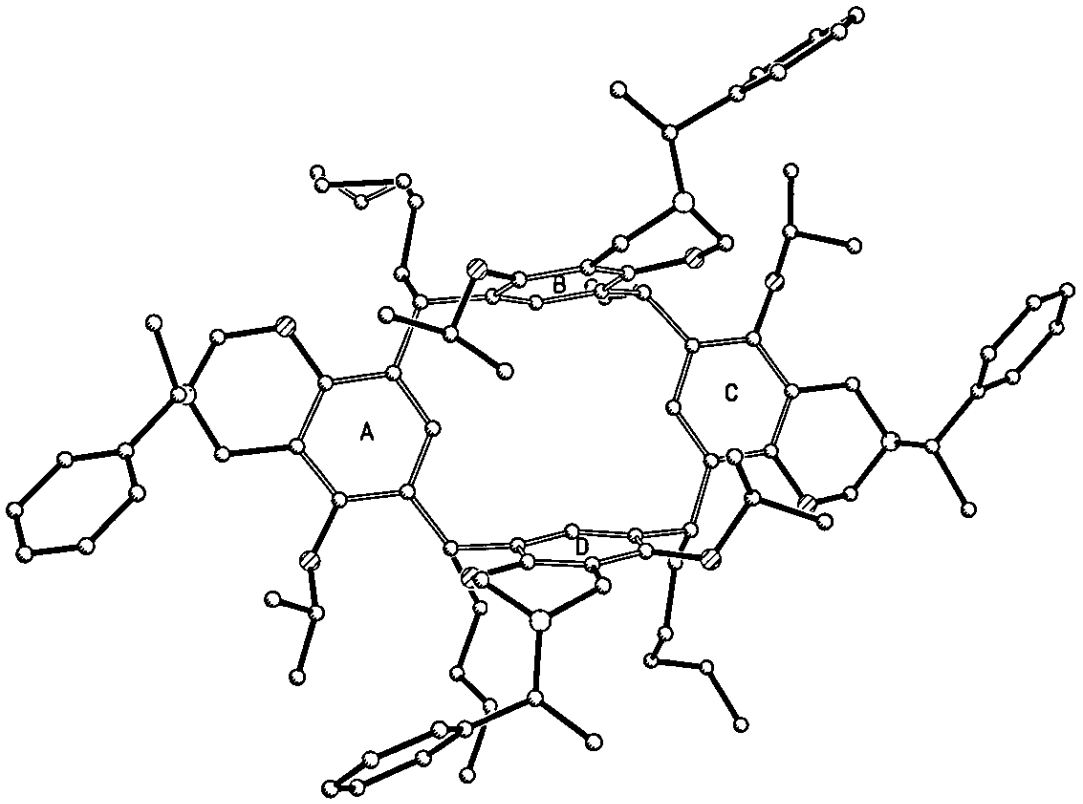
147

Crystal structure data is available for **77**, **107** and **129** from H.Heaney@lboro.ac.uk.

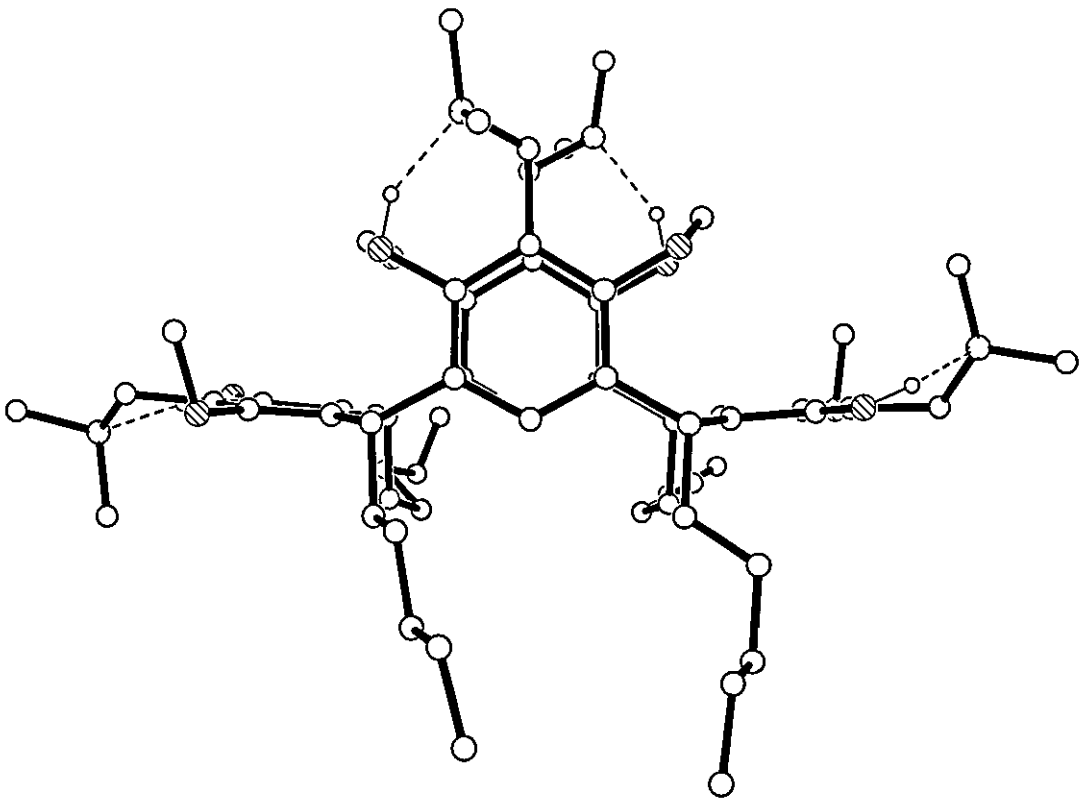
1. 107



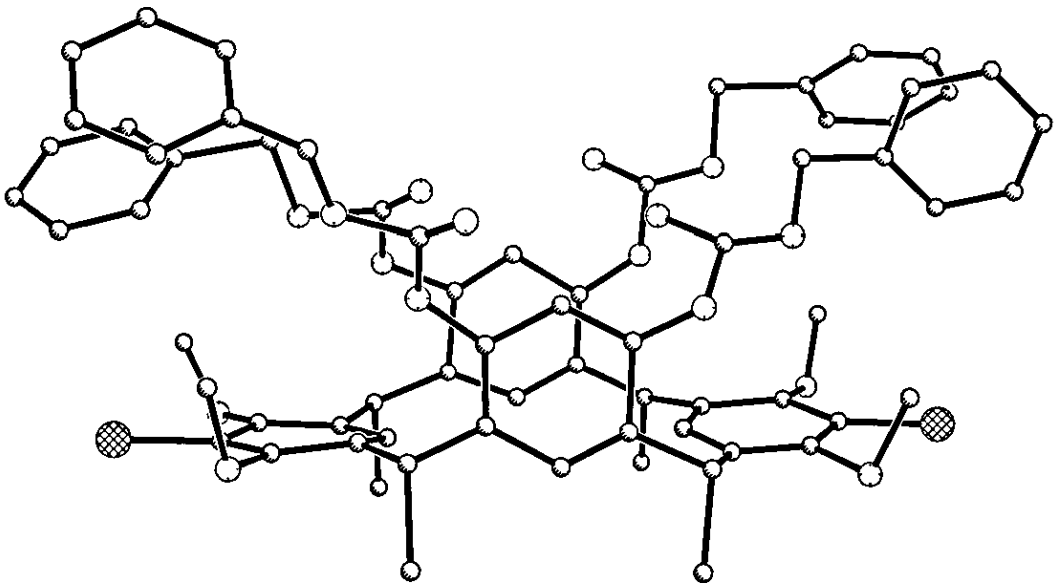
2. 129



3. 77



4 147



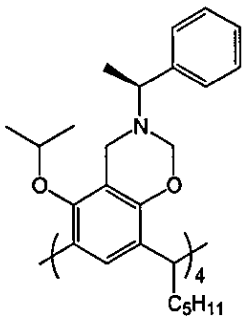
Appendix 2

^{1}H NMR Spectra

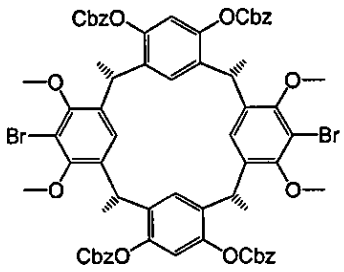
Spectra recorded at 25 °C and 50 °C in $CDCl_3$ at 400 MHz.

1. Tetra *i*-propyloxy, tetra *N*-(S-(-)-α-methylbenzyl)benzoxazine resorcinarene, **129**.

2. Tetra CBz, tetra methoxy dibromo resorcinarene **147**.

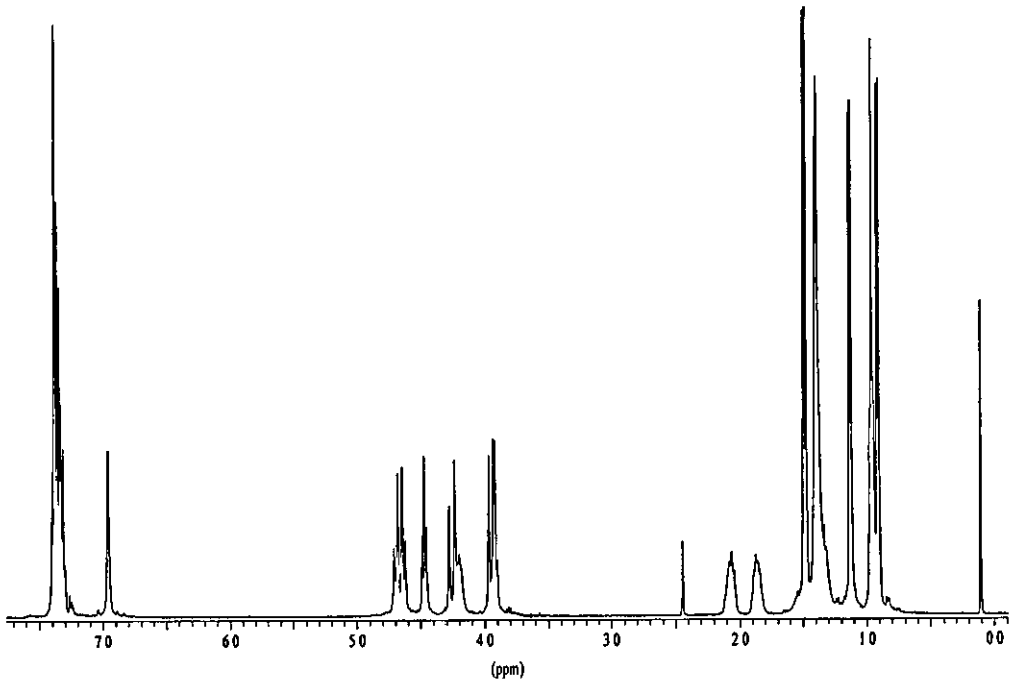


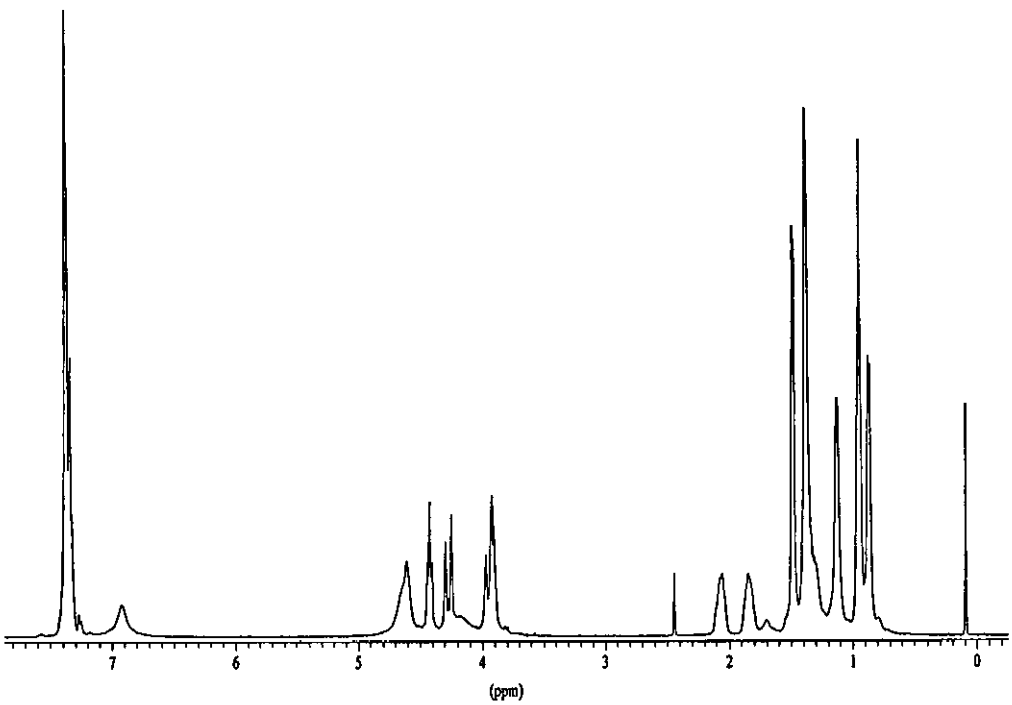
129



147

1. 129 Top spectrum recorded at 50 °C, bottom spectrum recorded at 25 °C.





2. 147 Top spectrum recorded at 50 °C, bottom spectrum recorded at 25 °C.