Department of Applied Chemistry

The Synthesis and Structure of C_4 Symmetric Resorcinarenes

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Declaration

To the best of my knowledge and belief this thesis contains no material previously published by any other person except where due acknowledgment has been made.

This thesis contains no material which has been accepted for the award of any other degree or diploma in any university.

Signature: …….

Date: ……...

Contents

Abstract

This study investigates methods for the synthesis and resolution of chiral resorcinarenes.

The first direct synthesis of C_4 dissymmetric resorcinarenes by the Lewis acid catalysed condensation of 3-alkoxyphenols and alkyl aldehydes was developed.The chirality of these novel resorcinarenes was demonstrated by nuclear magnetic resonance spectroscopy (n.m.r.) and enantioselective HPLC. The structure and physical properties of the new materials were characterised by several methods including X-ray crystallography.

Resolution of the chiral resorcinarenes was achieved on a multi-gram scale by either formation of their diastereomeric camphorsulfonate esters or diastereomeric "amide" derivatives followed by flash chromatographic separation. The absolute configuration of one resorcinarene camphorsulfonate diastereomer was determined by X-ray crystallography and the stereochemistry of the related diastereomers assigned based on spectroscopic and chromatographic properties. Hydrolysis of the resolved resorcinarene camphorsulfonate diastereomers afforded the C_4 symmetric resorcinarenes of known absolute stereochemistry. The absolute configuration of one resorcinarene "amide" diastereomer was also determined by X-ray crystallography.

Functionalisation of the resorcinarene racemates with 2- and 3-picolyl ethers afforded a number of resorcinarene based pyridine ligands. The complexation behaviour of the ligands was examined and X-ray crystallographic data obtained for complexes with silver(I) and copper(II) salts.

A significant proportion of the work described in this thesis has been published in four separate peer reviewed papers which have been attached as **appendicies 12–15**.

Acknowledgments

I would like to make use of this opportunity to express my deepest gratitude to those who have helped me make this thesis possible. First of all, I would like to thank my family for their encouragement and regular enquiries on the progress of my thesis which in turn motivated me to complete it.

My sincerest thanks to Associate Professors Mauro Mocerino and Mark Ogden, for their generosity and wisdom. Their knowledge and continuous optimism has been vital to the completion of this document. I greatly appreciate their patience during the proof reading of this thesis, which could be rather daunting at times.

My gratitude also goes to Prof. Harry Heaney, Prof. Allan White, Dr Brian Skelton, Joyce Wong and Allan Oliveira, for their assistance and contribution to this project.

Finally, special thanks to my patient and loving partner, Lihui, who has been a great pillar of strength throughout. Without her support and encouragement, I would not have kept my sanity and this thesis would not have existed.

Preface – structural representation of resorcinarenes and their chirality

Many forms of resorcinarene representation have developed over the relatively brief period which they have been studied. To avoid confusion the particular depictions of resorcinarenes that will be used throughout this document are outlined here.

The most unambiguous representations of the resorcinarenes and their chirality are the three-dimensional depictions shown in **figure 1**. In this case the crown, chair and diamond conformations are shown. These are closely related to the calixarene cone, partial cone and 1,2-alternate conformations respectively.

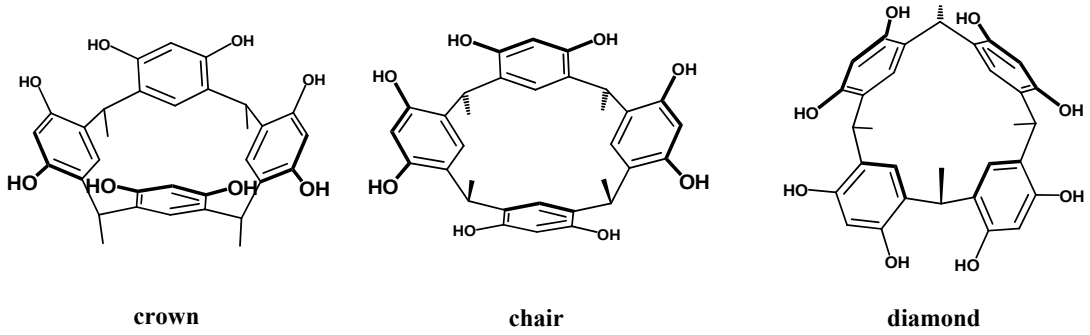

Figure 1 – Three dimensional depictions of the crown, chair and diamond conformations of resorcinarenes.

However, due to the cumbersome nature of these pictures (particularly with additional functionality present) and the exceptional effort required to construct them in a clear manner, they are generally not used. Accordingly, the reader will note that where a molecule of significant complexity is being described it shall be as the "flat" type diagram shown in **figure 2**.

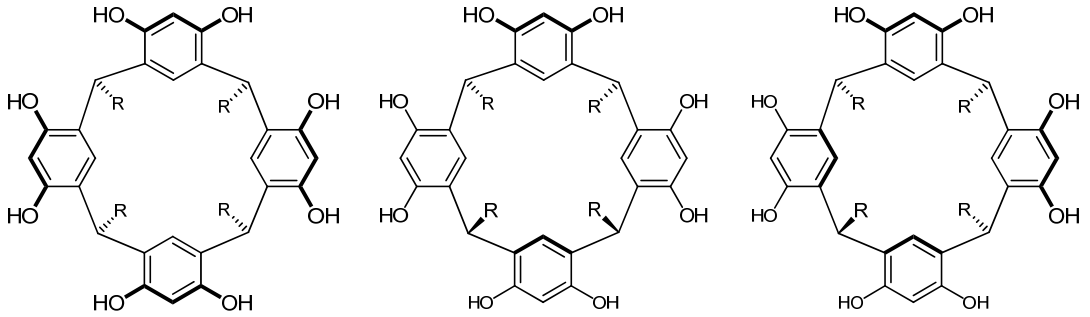

Figure 2 – "Flat" style depictions of the crown, chair and diamond conformations of resorcinarenes.

In these cases the diagram will represent the resorcinarene molecule viewed from above the cavity with the orientation of the alkyl chains indicated using wedged bonds in the usual manner.

The focus of resorcinarene research predominantly revolves around the crown isomer, as this is generally the most readily obtainable. For convenience, and for the sake of efficient usage of space, the crown isomer shall also be represented in the bracketed form shown below.

Figure 3 - "Simplified" depictions of the resorcinarene crown conformation shown with "all axial" alkyl groups and the calixarene cone conformation.

This is very similar to the commonly used depiction of the calixarene cone (also shown). However, unlike the calixarenes, the resorcinarenes possess a carbon centre with the potential for chirality. This added complication may be overcome by applying the conventions shown in **figure 4**.

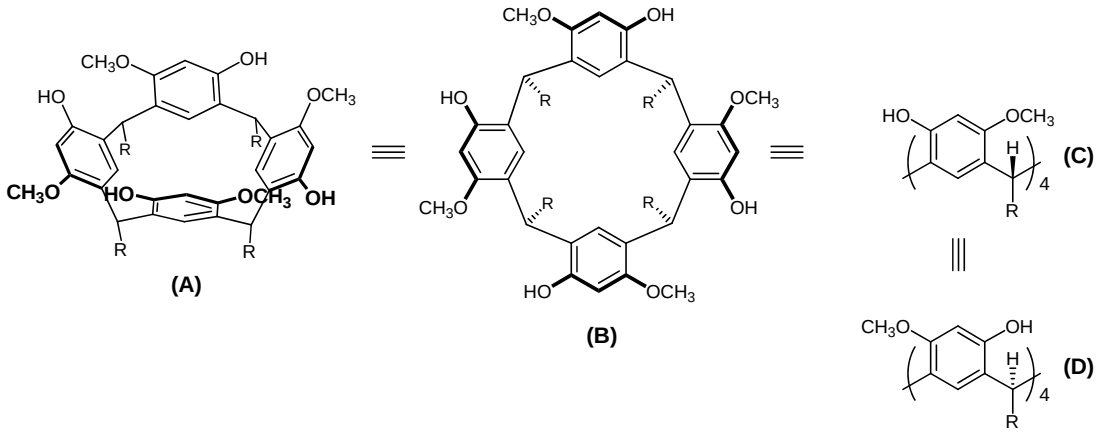

Figure 4 – Four depictions describing the absolute stereochemistry of a single chiral resorcinarene enantiomer.

The third diagram **(C)** is shown with the alkyl groups (R) in the all pseudo axial position and the methine proton projecting "out of the page" to indicate that the resorcinarene is being viewed from a position "outside" of the resorcinarene annulus. This depiction has the advantage that the absolute stereochemistry of the resorcinarene is described with a relatively efficient diagram. The resorcinarene enantiomer **(C)** is described equally well by the corresponding structure **(D)** viewed from "inside the annulus".

The racemate of a chiral resorcinarene is perhaps best represented (when using the simplified drawing convention) with the two individual enantiomers drawn separately in the fashion shown in **figure 5 (A)** where both are viewed from the same perspective (from outside the annulus in this case).

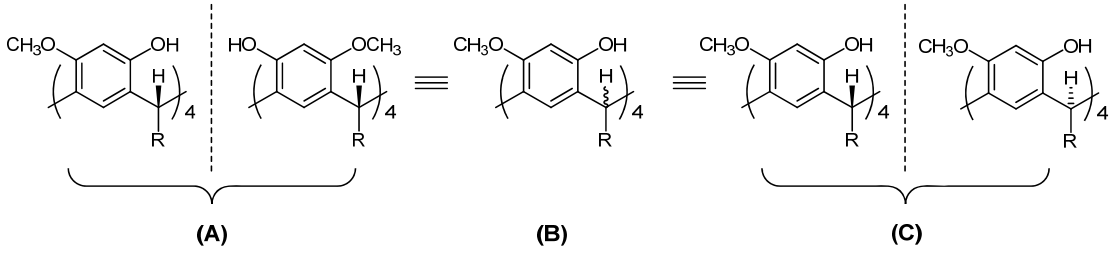

Figure 5 – Simplified depictions of the resorcinarene racemate.

However, this also can become cumbersome in schematics. Where convenient, the racemate shall be drawn with a wavy bond to the methine proton **(B)**, to distinguish it

as such. This is intended to represent the two enantiomers, one being viewed from within the annulus and the other from without **(C)**.

In 2002, IUPAC published new recommendations for the nomenclature of phanes with specific reference to the calixarene ring system[1]. This new system completely replaced the previous long-winded alkene cyclic alkene based nomenclature, obviating the need for a shortened independant nomenclature system for the calixarenes. It also brings calixarene numbering in to line with already well established alkane and ring system nomenclature. Thus the new IUPAC name for the calixarene (A) and the resorcinarene (B) below would be designated 1,3,5,7(1,3)-tetrabenzenacyclooctaphane-1^2,3^2,5^2,7^2-tetrol and 1,3,5,7(1,3)-tetrabenzenacyclooctaphane-1^4,1^6,3^4,3^6,5^4,5^6,7^4,7^6-octol. Although this name is of a adequate length to be applied in text it may be conveniently shortened by replacement of the common "1,3,5,7(1,3)-tetrabenzenacyclooctaphane" component with "calix[4]arene" to yield more familiar nomenclature shown in **Figure 6**.
The "correct" and "incorrect" numbering assignments of (C) are shown to exemplify the rules for phane nomenclature. The list of structural features, for which priority assignment of the lowest locant is given, is shown below:

1. numbering of phane parent hydride
2. heteroatoms introduced by skeletal replacement
3. indicated hydrogen
4. nondetachable 'hydro-'/'dehydro-' prefixes
5. principal characteristic group (named as suffix)
6. unsaturation ('-ene'/'-yne' endings and 'hydro-'/'dehydro-' prefixes)
7. substituents named as prefixes (alphabetized substituents)

Thus the hydroxyl groups of calixarene (C), which are given the characteristic group suffix "-ol" (rule 5), precede the bromine atom (rule 7) with regard to assignment of the lowest locant.

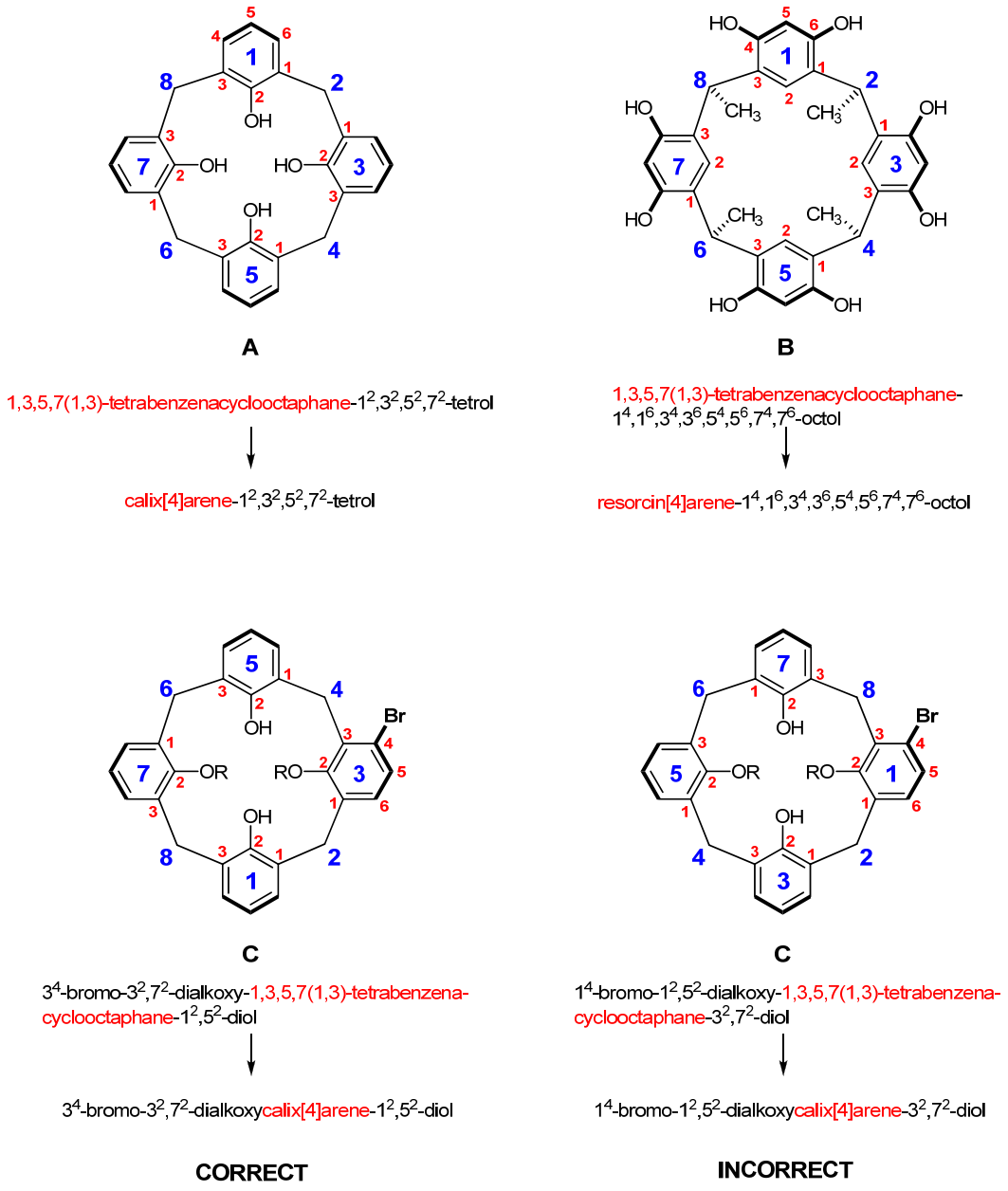

Figure 6 – Application of the "phane" numbering to the calixarene ring system and its adaptation to the calixarene "common" name usage.

1.0 A brief review of C_n Symmetric calixarenes and resorcinarenes.

Chiral calixarenes can be categorised into two distinct subtypes, each with their own distinct methods of preparation. The categories are commonly described as chiral by attachment and chiral by asymmetric functionalisation. The factor separating these two groups is unmistakably the method by which the chirality of the calixarene is generated.

Chirality by attachment, as the name suggests, is simply the generation of a chiral calixarene or resorcinarene species by appending an already chiral functionality to the macrocyclic skeleton. This is by far the easiest method for preparing an enantiomerically pure calixarene species by virtue of the fact that no resolution procedure is required and there are an abundance of chiral materials available as single enantiomers. Many of these materials also have some useful functionality that may be used to attach them to the calixarene skeleton. Consequently, when combined with the various positions on the macrocyclic framework available for attachment, there are numerous possible combinations for the calixarene chemist to explore. Two admirable examples are the upper rim amino-acid functionalised compound **(A)** (**Figure 1.1 (A)**) produced by Ungaro[2] and lower rim sugar functionalised compound **(B)** (**Figure 1.1 (B)**) produced by Lhoták.[3]

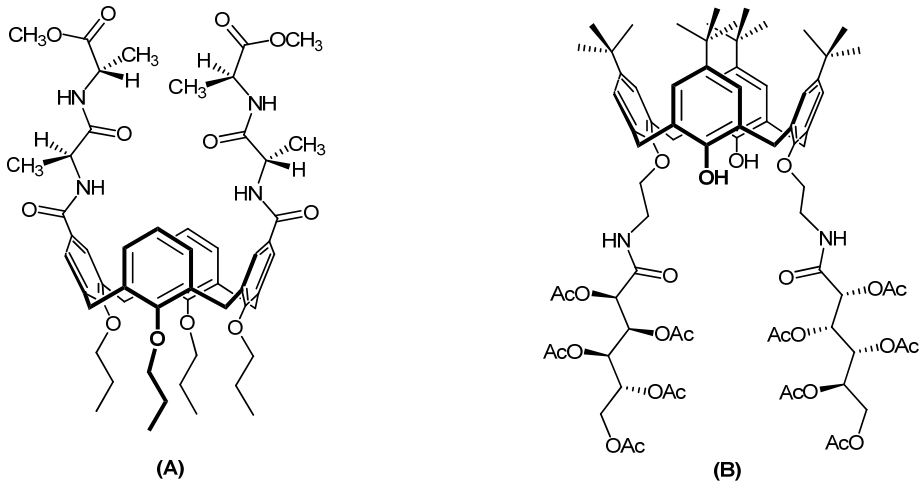

Figure 1.1 – Two examples of chiral calixarenes formed by the attachment of a chiral moiety.

Chirality by asymmetric functionalisation essentially encompasses the remainder of the chiral calixarenes. A broad definition for this class would simply be generation of chirality by functionalisation of the non-planar calixarene framework with achiral moieties. This is achieved by attachment of functionality at particular positions so as to destroy the C_{4v} symmetry of the calixarenes and resorcinarenes and thus afford the lower symmetry C_2 or C_1 symmetric entities. This subcategory can be divided into two further groups which are separated predominantly by symmetry concerns. The first group encompasses macrocycles which have been made chiral by the introduction of achiral substituents at the phenols or the X^{5*} positions in a manner so as to render the molecule asymmetric. These molecules have no mirror planes or symmetry axes (greater than C_1) and can be described as "planar chiral" or "conformationally chiral".[4] For example a calixarene such as that shown in **figure 1.2** below having four differently substituted aromatic units must necessarily be an asymmetric molecule. In fact it can be stated that in general in order to produce this type of asymmetry a minimum of two functionalisations on the calixarene is required to produce three adjacent aromatic units which are different. The remaining aromatic unit in this case may be anything except B (A, C or D). Thus the aromatic units in a chiral calixarene of this type may be of the pattern ABCD or AABC.

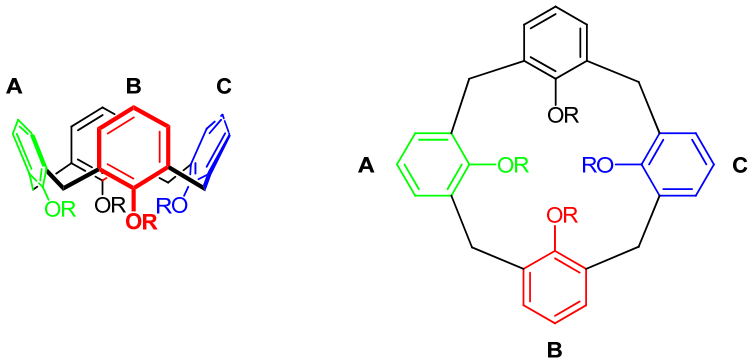

Figure 1.2 – Side and top views of a chiral calixarene having three sequential different aromatic units.

The second form of asymmetric functionalisation is comprised of those molecules for which asymmetry has be generated by the inclusion of a group at the X^4 or X^6

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* Please refer to the new IUPAC nomenclature for phane ring systems (2002) including specific reference to calixarenes[1].

positions (or both) which also destroys the vertical mirror planes of the C_{4v} macrocycles. This is shown in **figure 1.3** where the position of R^2 (in the case of the calixarene **A**) and the kind of functionality at R^2 (in the case of the resorcinarene **B**) renders the desired asymmetry.

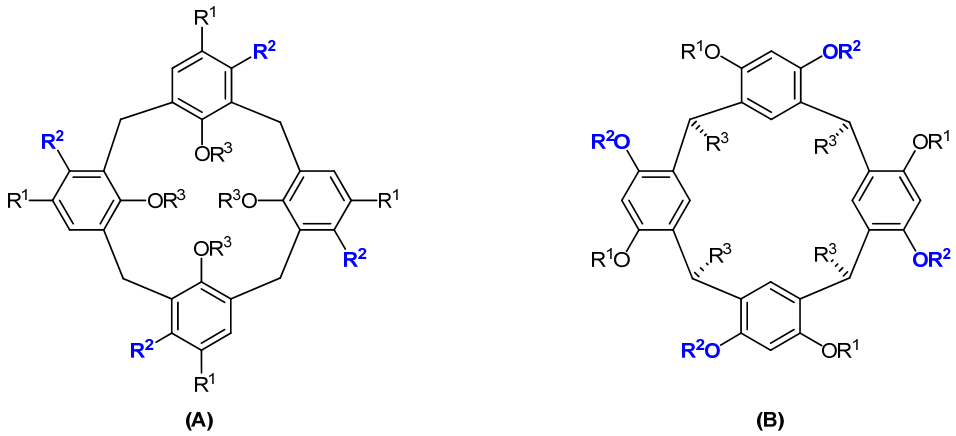


Figure 1.3 – Examples of a chiral dissymmetric calixarene (**(A),** where R ≠ H) and chiral dissymmetric resorcinarene **(B)**.

In these cases only a single different functionality at the X^4 or X^6 positions generates the desired asymmetry, unlike the AABC type (see **Figure 1.2**) where at least two different functionalisations are required.**

Elements of conformational, axial or helical chirality may potentially be ascribed to calixarene **(A)** (**figure 1.3)**. The "chirality axis" (co-incident with the C_n symmetry axis) has generally been favoured in the calixarene literature, although, a proposal for modification of the Cahn, Ingold and Prelog classification of chirality recommended the usage of the "helical axis"[5] The term "inherent chirality"[6] is often applied but has no stereochemical significance[7] and has more suitable replacements in the stereochemical literature[8]. Application of these chirality descriptors to calix[4]arenes is commonplace, however, despite the abundance of completely asymmetric calix[4]arenes (for examples see references 9-11) with an AABC type pattern, no formal method for describing their absolute stereogenicity appears to have been applied. In 2004, Mandolini proposed a method for describing the chirality sense of the AABC type calixarene derivatives[7] (**figure 1.4**). By assigning a priority order (a,

** While a single functionalisation of a calixarene in concert with a conformational change is sufficient to generate a chiral entity, the facile interconversion of the conformation is generally considered by calixarene chemists to result in an achiral species, unless otherwise restricted.

b, c and d) to the calixarene methylenes, an observer standing within the calixarene cavity could then demonstrate a clockwise (c*R*) or counterclockwise (c*S*) array.

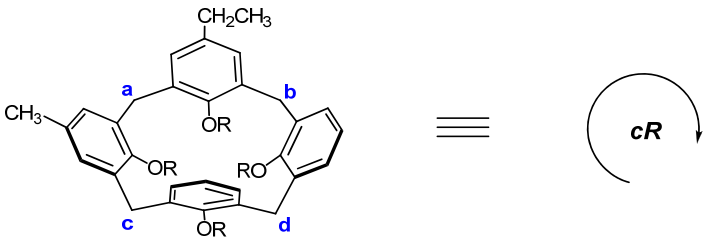


Figure 1.4 – Application of Mandolini's priority method for assignment of chirality sense.

However, this method does not appear to have been applied in any calixarene publications since it was introduced.[12-15]

Similarly untested are the rules delineated by Prelog and Helmchen for describing the chirality sense of those molecules not containing any stereogenic centres[16-17] i.e. those having a "chirality plane" or a "chirality axis". This method was exemplified in 1984 by Schlögl for smaller phanes[18] such as the benzoic acid **(A)** given in **figure 1.5**

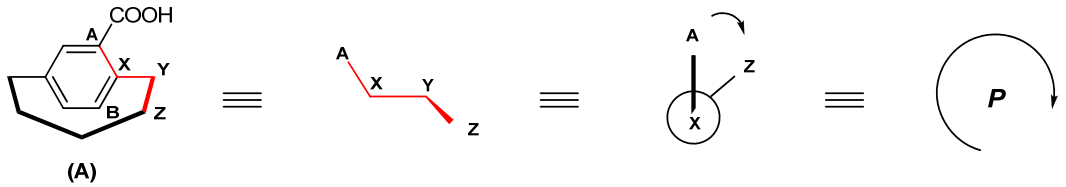


Figure 1.5 – Application of the helical chirality descriptor to phane molecules.

Description of resorcinarene chirality on the other hand has no such complications as the presence of four stereogenic centres makes application of the IUPAC prescribed[19] Cahn-Ingold-Prelog rules[4] a simple task. Thus the structures A and B in **figure 1.6** below can be described as the 2*R*,4*R*,6*R*,8*R*- and 2*S*,4*S*,6*S*,8*S*- respectively.

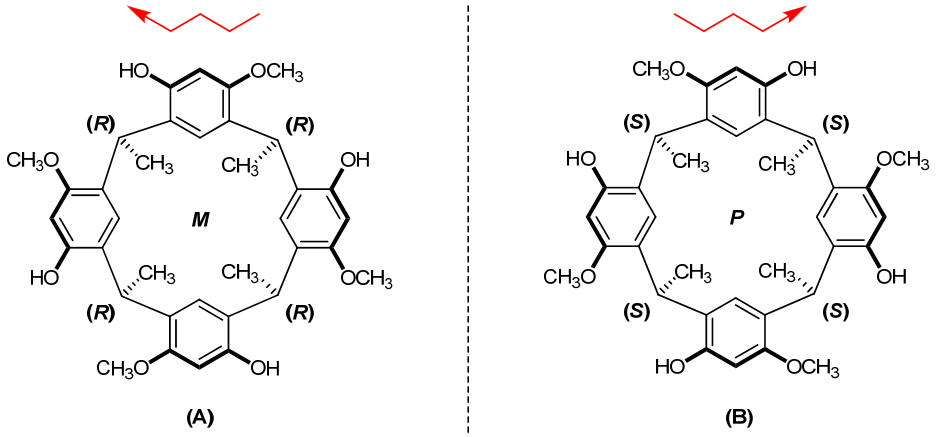
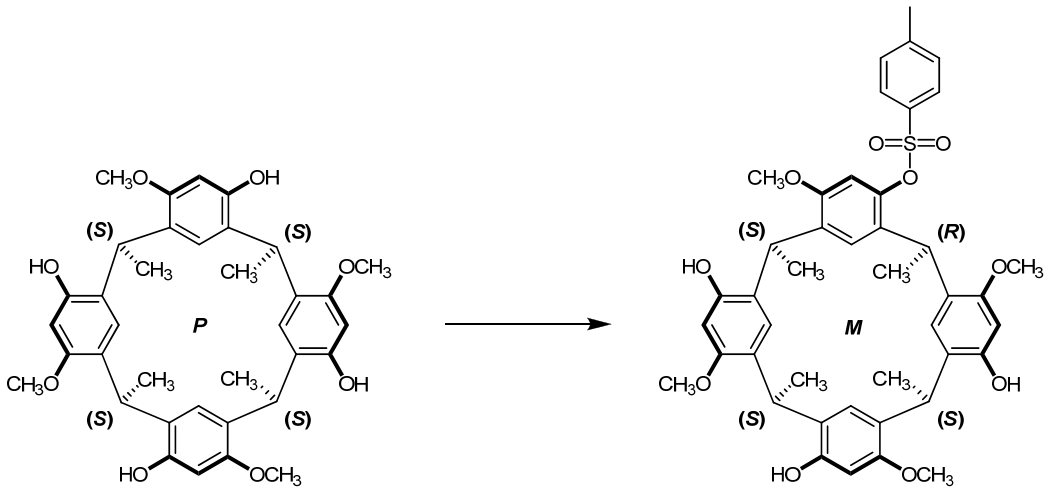


Figure 1.6 – C_4 dissymmetric resorcinarene enantiomers with assigned stereochemistry using the CIP *R*/*S* and the recently applied *M*/*P* notation.

Recently,[20] we have applied the *M* and *P* notation to describe the absolute stereogenicity of C_4 dissymmetric resorcinarenes. This notation is clearly the simplest to apply "in text" as it obviates the need for individually identifying the four necessarily identical stereogenic centres i.e. *R*,*R*,*R*,*R*- or *S*,*S*,*S*,*S*-. However, this notation was intended purely as an abbreviated method for description of C_4 dissymmetric resorcinarenes and can only be applied (without complication) to C_4 dissymmetric resorcinarenes (as opposed to the C_1 or C_2 symmetric). In the event of a minor functionalisation such as that shown in **scheme 1.1** below, the resulting C_1 symmetric derivative is better described with the usual *R*/*S* notation for stereogenic centres.



Scheme 1.1 – Changes to the chirality sense of a resorcinarene in the event of a minor functionalisation.

We believe that in most instances preservation of the Cahn, Ingold and Prelog classification of chirality, and the methods described therein, describes the chirality of resorcinarenes very adequately. This is also true of the chiral calixarenes with special reference to the modifications recommended by Dodziuk and Mirowicz[5] and the examples of Schlögl.[18]

Reviews on chiral calixarenes are currently available in the literature.[6, 21-22] However, due to the many recent advances in the field, a further summation of the current work is justified.

The current review is limited to the calixarenes and resorcinarenes with helical dissymmetry of the type described in **figure 1.3** and on which the bulk of chiral research has been focused. However, it is acknowledged that good work has also been reported on the minor members of the calixarene family such as the oxa-calixarenes.[23]

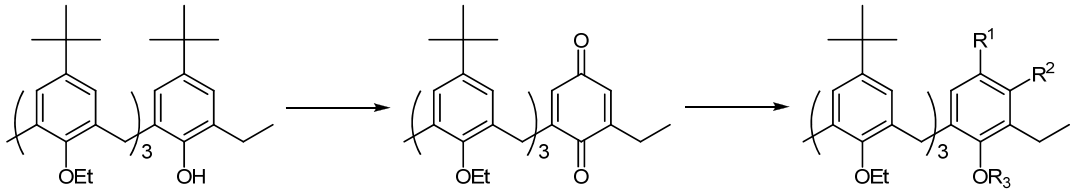
The dissymmetric calixarenes and resorcinarenes with C_n symmetry do not by any means comprise the largest portion of the chiral calixarene family. However, their high symmetry[24] and simplicity makes them by far the most aesthetically pleasing. The following sections are arranged in order of increasing symmetry (i.e. C_1 to C_4). Although all completely asymmetric molecules must necessarily have a C_1 axis of symmetry, since the axis about which the calix defines is preserved in all examples described herein, it is deemed logical to begin by examining those molecules which have one moiety positioned about that axis affording a "direction" in the spirit of helix-like dissymmetry. This should then sensibly be followed by two groups (C_2 symmetric) and finally four groups (C_4 symmetric).

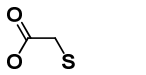
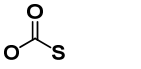
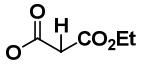
1.1 The C_1 dissymmetric

The chiral calixarenes and resorcinarenes having C_1 symmetry are perhaps the least "attractive" of the family in terms of aesthetics. However, they are significantly appealing with regards to the simplicity of their preparation from the parent macrocycles.

1.1.1 Calixarene based

Of the methods used to prepare chiral derivatives from the parent macrocycles the most flexible approach appears to be via the calix[4]quinones. The monoquinone **2** is prepared by direct oxidation of the triether **1** with thallium(III) triflate in good yield (51 %[25]). Compound **2** can then be readily converted into a variety of racemic dissymmetric derivatives by 1,4-addition with generally greater than 60 % conversion (**scheme 1.2**).

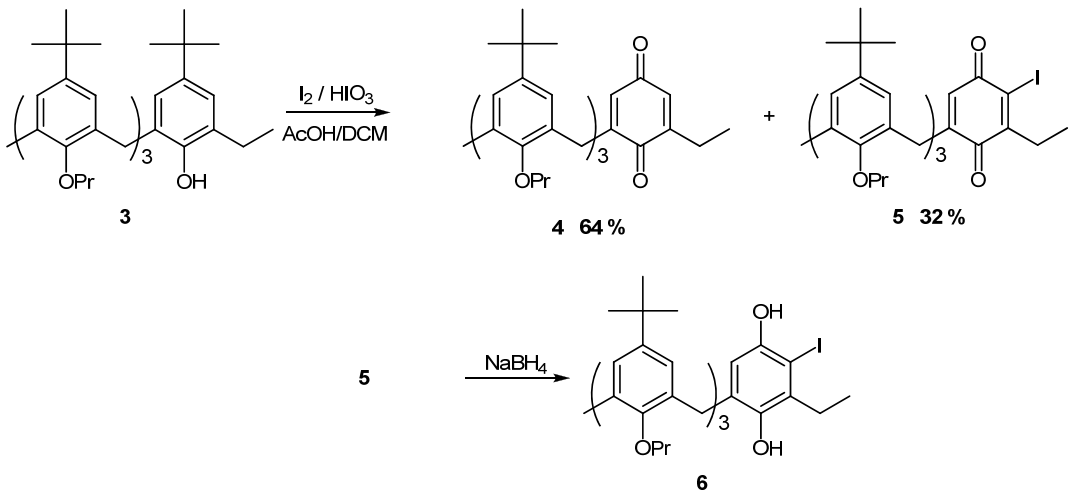


R^1	R^2	R^3	%Yield
OAc	OAc	Ac	62
OH	$SArCH_3$	OH	80
		OH	31
		OH	80
		OH	67

Scheme 1.2 – The preparation of chiral calixarenes from mono-quinone **2**.

Gutsche demonstrated the chirality of the prepared materials by n.m.r. spectroscopy in the presence of Pirkle's reagent ((*S*)-(+)-2,2,2-trifluoro-1-(9-anthryl)ethanol).[25] All of the compounds showed doubling of peaks however no efforts appear to have been made to resolve the racemic mixtures.

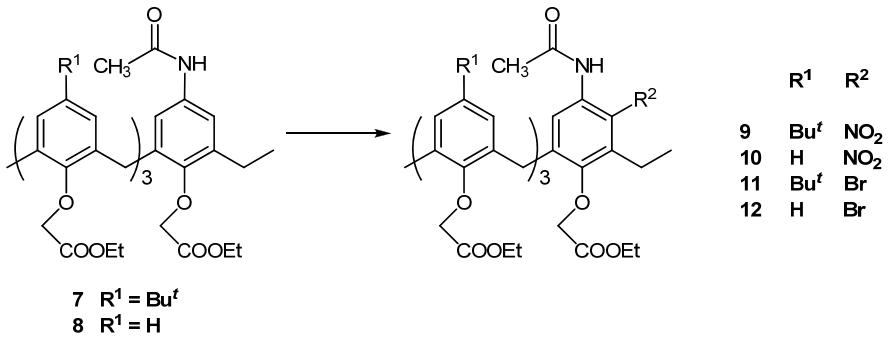
Similar materials have been prepared during the oxidation of the tripropyl ether **3** to the monoquinone **4**.[26] The *meta* substituted iodide **5** was obtained in 32 % yield in addition to the monoquinone which was obtained in 63 % yield. The iodide **5** was then reduced to the hydroquinone **6** with sodium borohydride.



Scheme 1.3 – Iodination of the calixarene triether **3** to afford the asymmetric monoiodide **5** and its subsequent reduction to **6**.

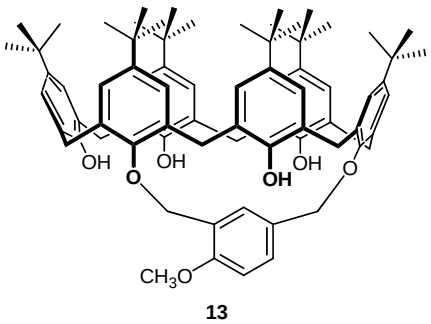
The n.m.r. spectroscopic analysis of **5** and **6** appear indicative of mono-meta substituted species but no further proof of chirality was offered.

Verboom and coworkers have also introduced a *meta* group via the slightly more flexible approach of electrophilic substitution adjacent to the acetamide functionality of compounds **7** and **8**[27] **scheme 1.4**. This method allowed the preparation of **9** and **10** by direct nitration in 91 and 98 % yield respectively. Bromination of **7** and **8** afforded their respective monobromides (**11** and **12**) in 64 and 58 %. Compounds **9** – **12** were demonstrated to be racemic by ^{1}H n.m.r. spectroscopy in the presence of Pirkle's reagent, however, none of the racemates were resolved.



Scheme 1.4 – Bromination or nitration of calixarenes **7** and **8** to afford the corresponding chiral monobromides and nitrates.

Perhaps a simpler example is the restricted calix[6]arene derivative **13** (**Figure 1.7**) produced by Shinkai.[28] The 4-methoxy-*m*-xylenyl moiety bridges the 1,3-phenyl units and is restrictive enough to prevent ring inversion and therefore racemisation. The chirality of **13** was proven by n.m.r. spectroscopy with Pirkle's reagent, and subsequent resolution by enantioselective HPLC (Daicel Chiralpak AD, *n*-hexane/2-propanol 98:2)



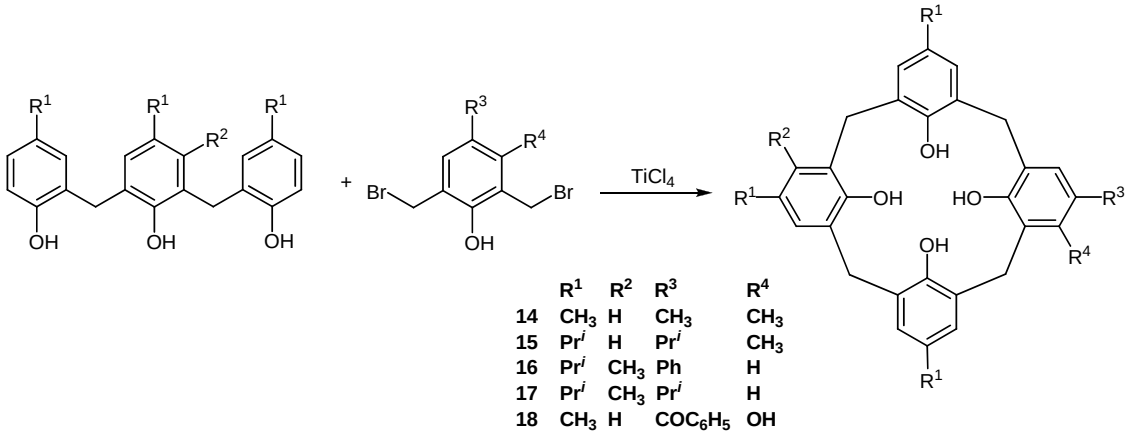
13

Figure 1.7 - A chiral 1,5- linked hexamer produced by Shinkai.[28]

Fragment condensation for the preparation of *C* dissymmetric calixarenes is generally a much more cumbersome and low yielding approach. However, stepwise synthesis is a proven method for the preparation of the achiral calixarenes[29-30] and planar chiral calixarenes.[31-32] Consequently, it has also found its place in the generation of chiral species.

Casabianca and coworkers[33] performed several 3+1 condensations using the bisbromomethyl phenols with $TiCl_4$ in dioxane to produce the chiral calixarenes **14** –

17 given in **scheme 1.5**. These were afforded in yields of 10-35 %. A single crystal X-ray structural determination of **17** was reported later.[34]

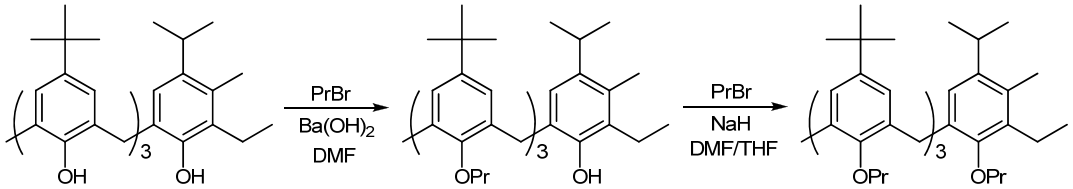


	R^1	R^2	R^3	R^4
14	CH_3	H	CH_3	CH_3
15	Pr^i	H	Pr^i	CH_3
16	Pr^i	CH_3	Ph	H
17	Pr^i	CH_3	Pr^i	H
18	CH_3	H	COC_6H_5	OH

Scheme 1.5 – Some 3 + 1 fragment condensation reactions to produce dissymmetric calixarenes having C_1 symmetry.

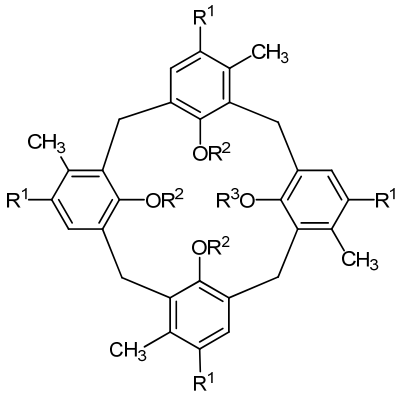
In a similar 3+1 condensation Böhmer has incorporated a resorcinol unit linked via its 2,6- positions[35] to give compound **18** (**scheme 1.5**). In this case the chirality was demonstrated at low temperatures (-40 ºC) by n.m.r. spectroscopy with Pirkle's reagent. At such low temperatures the ring inversion is slow on the n.m.r. time scale and interaction of the enantiomers with the reagent may be observed.

Shinkai went one step further and locked the chiral calixarene into the cone conformation via a selective propylation.[36] The calixarene **19** (**scheme 1.6**), prepared using the standard 3+1 fragment condensation method in 9 % yield, was initially propylated with barium hydroxide as the base to give the tri-ether **20** and then converted to the tetra-ether **21** using standard conditions (PrBr, NaH, DMF/THF). This stepwise alkylation procedure avoided the complication of multiple confomational isomers produced by direct per-alkylation of calixarene **19**. The chirality of **20** was demonstrated by n.m.r. spectroscopy at low temperatures (-40 ºC) in the presence of Pirkle's reagent. More significantly, the tetra-ether **21** was resolved to its enantiomers using enantioselective HPLC (Daicel ChiralPak OP(+), hexane/2-propanol/methanol 1:3:16).



Scheme 1.6 – Sequential alkylation at the lower rim of calixarene **19** to prevent racemisation.

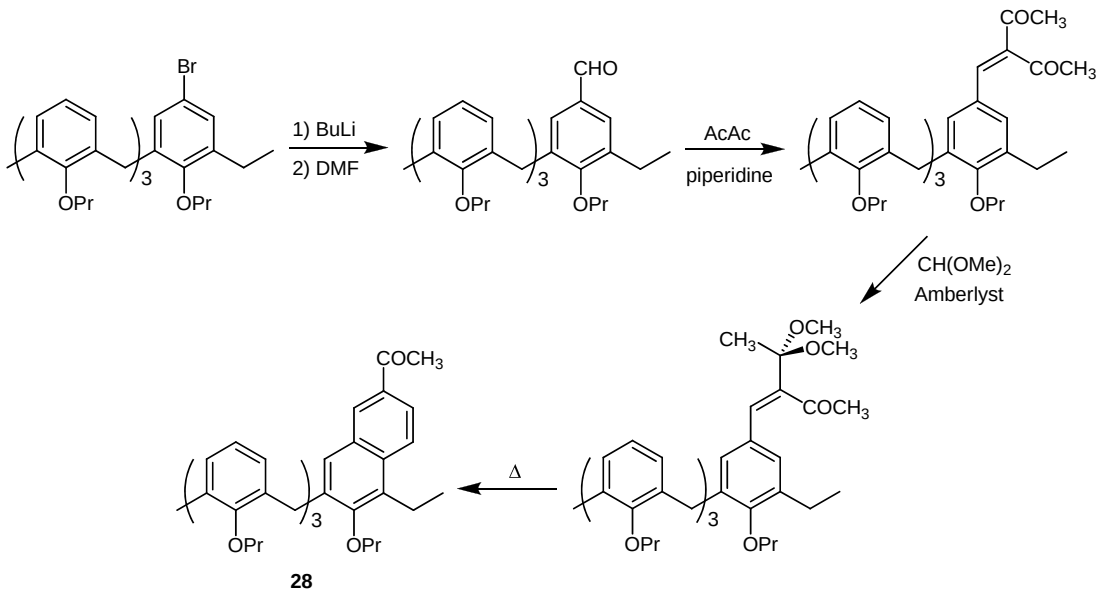
The reverse approach was also adopted by Böhmer.[37] By preparing the mono or tri-ether derivatives of the C_4 dissymmetric calixarene **22** (**Figure 1.8**) the 'lower' symmetry materials **23** - **27** were obtained.



	R^1	R^2	R^3
22	CH_3	H	H
23	CH_3	H	*n*Bu
24	CH_3	H	$CH_2C_6H_4NO_2$
25	CH_3	H	CH_3
26	CH_3	H	Pr^i
27	Pr^i	CH_2COOEt	H

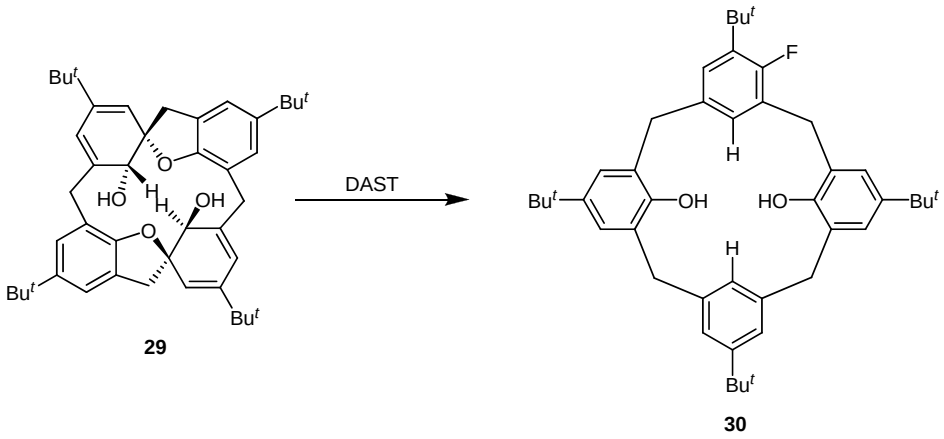
Figure 1.8 – Desymmetrisation of C_4 dissymmetric calixarene **22** by alkylation at the lower rim.

Shinkai[38] developed a stepwise process to construct a naphthalene unit on the calixarene (**scheme 1.7**). The product (**28**) is locked in the cone conformation and so cannot racemise. The chirality was established by n.m.r. spectroscopy in the presence of Pirkle's reagent, however, it was not resolved.



Scheme 1.7 – Scheme for the preparation of the C_1 symmetric naphthalene derivative **28** (note: AcAc = 2,4-pentanedione).

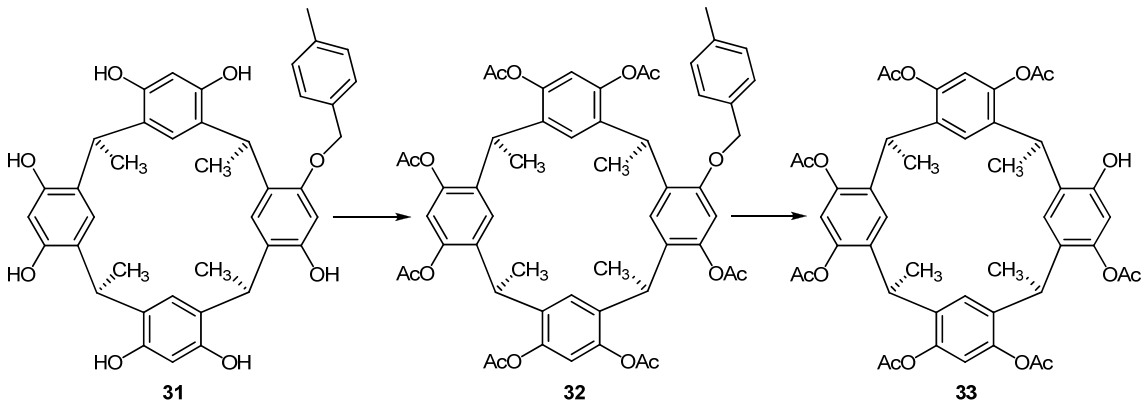
More recently a novel approach was adopted by Biali.[39] Treatment of the bis(spirodienol) **29** with diethylamino sulfur trifluoride (DAST) afforded the mono-fluoro compound **30** in 8 % yield. However, this compound is not locked into a particular conformation and can therefore readily racemise.



Scheme 1.8 – Fluorination of compound **29** affords the asymmetric monofluoride **30**.

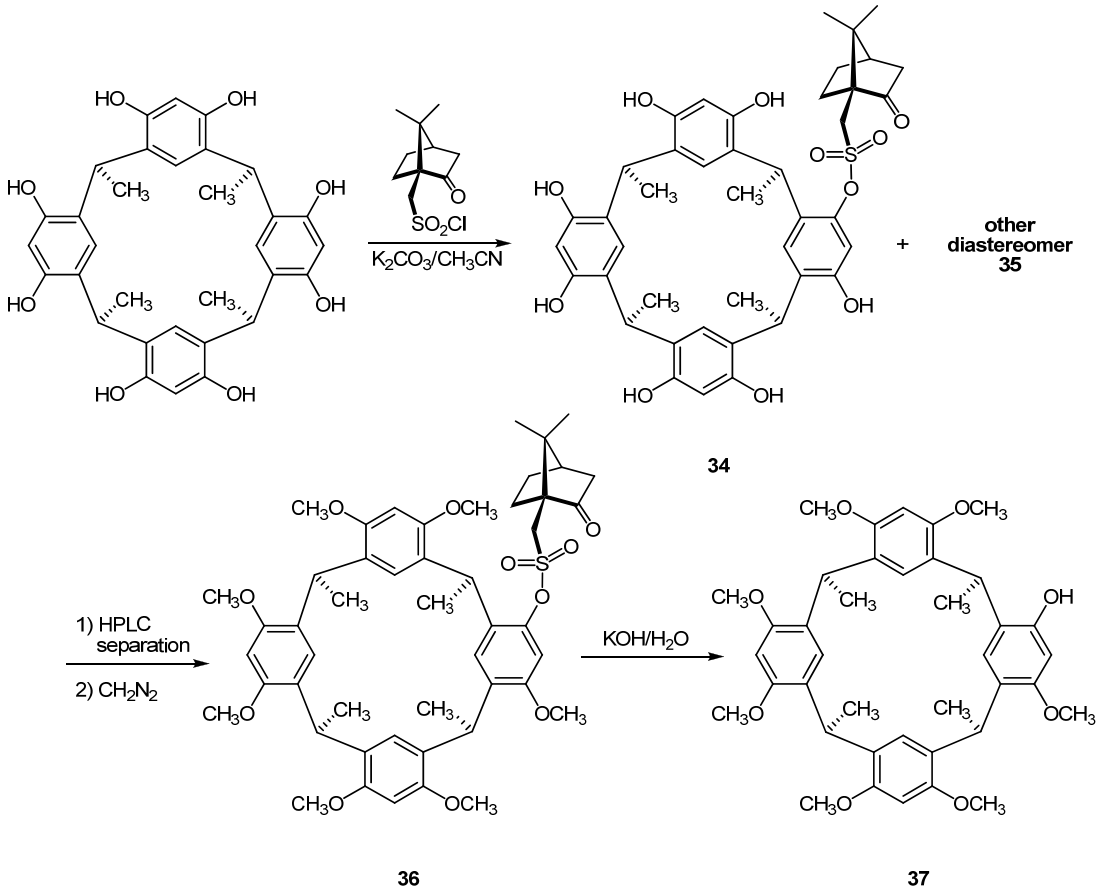
1.1.2 Resorcinarene based

The preparation of resorcinarene derivatives having C_1 dissymmetry is significantly simpler than the oxidation and fragment condensations of the calixarenes. Yet surprisingly there are fewer examples. Asymmetry may be introduced simply by alkylation of one of the parent resorcinarene phenols[40] (**scheme 1.9**) as is the case for the *p*-methylbenzyl ether **31** (32 %). Per-acetylation to give **32** in 64 % yield and subsequent cleavage of the benzylic ether yielded the heptaacetate **33** (23 %). The resorcinarene derivatives were not resolved, however, n.m.r. spectroscopic studies of **31** in the presence of (*R*)-*N,N,N*-trimethyl-α-methylbenzylammonium iodide showed doubling of the resorcinarene signals.



Scheme 1.9 – Introduction of asymmetry to *C*-methylcalix[4]resorcinarene by mono-benzylation (to afford **31**) and subsequent transformations.

Mattay and coworkers[41] took the more efficient approach of generating dissymmetry with the introduction of a single chiral moiety. The reaction of camphorsulfonyl chloride with the parent resorcinarene (**scheme 1.10**) produces the diastereomers **34** and **35**, making the resolution of enantiomers unnecessary. The diastereomers were separated by normal phase HPLC and methylated to give **36** the chiral auxiliary was then removed to afford the heptamethyl ether enantiomer **37**.

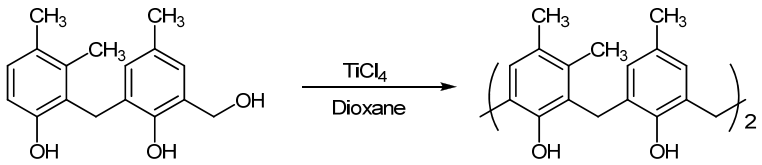


Scheme 1.10 – Preparation of the enantiomers of the heptamethylether of *C*-methylcalix[4]resorcinarene (**37**).

1.2 The C_2 dissymmetric

1.2.1 Calixarene based

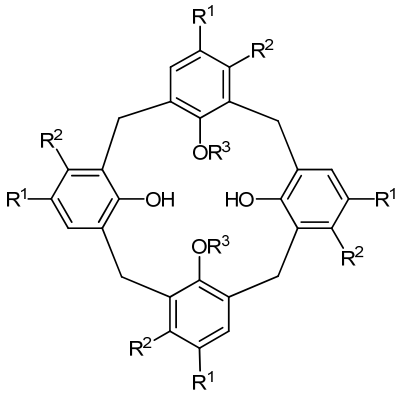
Few examples of fragment condensations to produce *meta* substituted C_2 dissymmetric materials exist. The only example of note is that described by Böhmer[42] (**scheme 1.11**). Condensation of the hydroxymethylated bisphenol **38** with titanium tetrachloride gave the calixarene **39** in 18 % yield. Böhmer attributes the lack of interest in compounds of this type to the substantial efforts required to prepare the bisphenol **38** which requires five separate reaction steps. The desired cyclised material **39** is obtained in an overall yield of only 3 % as a result.



38 **39**

Scheme 1.11 – The 2 + 2 fragment condensation of benzylic alcohol **38** to give the corresponding C_2 dissymmetric calixarene **39**.

Alternatively, dialkylation of the more readily obtained C_4 dissymmetric calixarenes[43] produces the lower symmetry diethers **40** – **47** shown in **figure 1.9**.



	R^1	R^2	R^3
40	CH_3	CH_3	CH_3
41	CH_3	CH_3	nBu
42	CH_3	CH_3	Pr^i
43	CH_3	CH_3	CH_2COOEt
44	CH_3	CH_3	$CH_2C_6H_4NO_2$
45	Pr^i	CH_3	CH_2COOEt
46	Pr^i	CH_3	*n*Bu
47	$CH_2CH_2CH_2$		CH_2COOEt

Figure 1.9 - C_2 dissymmetric calixarenes produced by 1,3-distal dialkylation of C_4 dissymmetric calixarenes.

Compounds **40**, **43**, **45**, and **47** were later resolved by Böhmer[44-45] by HPLC on a ChiralPak AD column. The decamethyl derivative **40** is not fixed in the cone conformation and the energy barrier for interconversion of the enantiomers was determined by examining their CD spectra as a function of time.

Another route to the *meta*-substituted C_2 dissymmetric calixarenes is via the quinone route developed by Gutsche.[46] The calixarene-1,3-diquinones undergo 1,4-nucleophilic additions in a similar manner to the monoquinones. However, the reaction is complicated by the concomitant formation of the C_{2v} isomer (**49**). Consequently the desired isomer **48** is recovered in only 14 % yield.

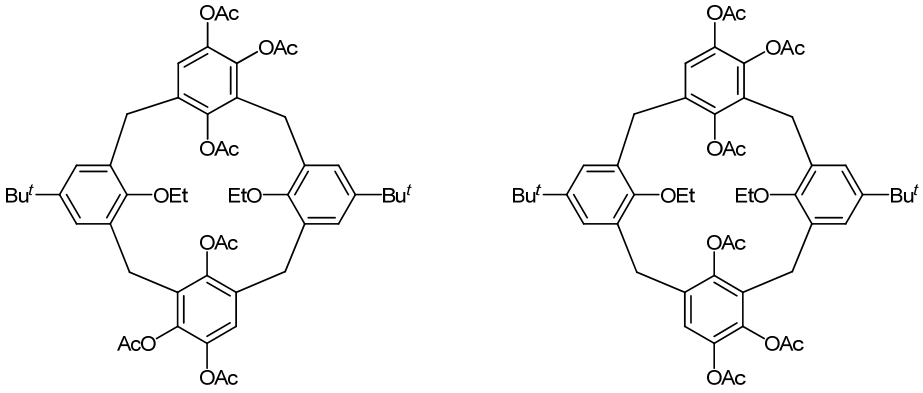


Figure 1.10 – Regio-isomers **48** and **49** produced by 1,4-addition to a calixarene-1,3-diquinone.

A regioisomeric mixture was also obtained[27] by bromination of the bisacetamide **50** to give a 10 % recovery of the dibromide **51**. Nitration was substantially more selective yielding 53 % of the desired isomer **52**. Significantly these calixarenes were prepared as the tetrapropyl ethers and thus are conformationally fixed and so can not racemise by ring inversion. The structure of **51** (as the racemate) was proven by single crystal X-ray determination, however the racemates were not resolved.

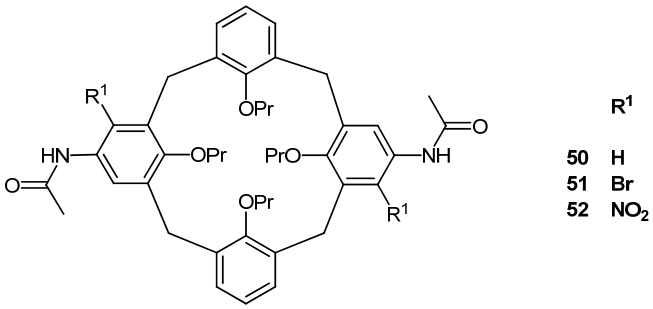


Figure 1.11 – Chiral dibromo- and dinitro- derivatives produced by bromination and nitration of the bis-acetamide **50** respectively.

The propensity of the calixarenes for 1,3- distal functionalisation on both the upper and lower rims[47] lends them to the preparation of a variety of C_2 dissymmetric materials. The calixarene 1,3-diester **53** was effectively exploited by Bitter[48] for the preparation of proximal doubly bridged calix[4]arenes such as **54** shown in **figure 1.12**.

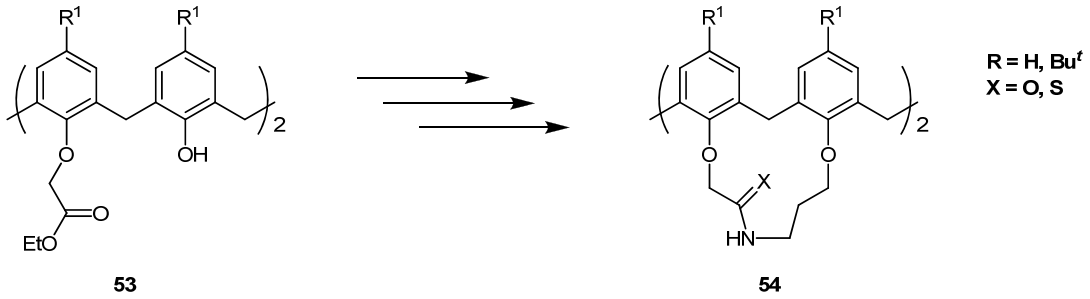
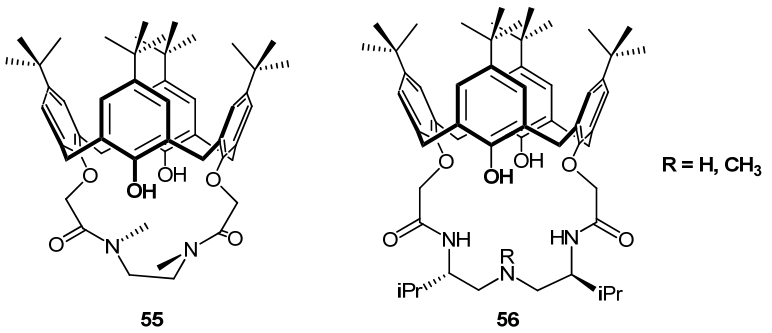


Figure 1.12 - Linking of adjacent phenolic groups to generate dissymmetric calixarene **54**.

The chirality of the amides and their sulfur analogues was investigated by n.m.r. spectroscopy with Pirkle's reagent to give characteristic doubling of signals. However, resolution by enantioselective HPLC had been unsuccessful up to the point of publication.

Also of interest in this regard are the 1,3-bridged compounds produced by Böhmer **55**[49] and also Wu **56**.[50] While the latter example may be considered chirality by attachment, the product does have fixed C_2 symmetry. The former example is chiral

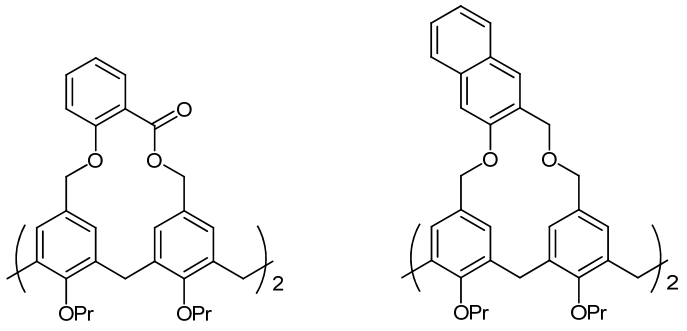
by virtue of the conformational rigidity of the amide bridge. This was clearly demonstrated by the doubling of the n.m.r. signals in the presence of Pirkle's reagent.



55 56

Figure 1.13 – Chiral C_2 dissymmetric derivatives produced by linking distal phenolic groups.

Of the upper rim examples the compounds prepared by Shinkai[51-52] from the tetrachloromethylated calixarenes are a noteworthy example. The proximally bridged salicylic acid derivative **57** was produced in 36 % yield directly from tetrachloromethylcalix[4]arene. Similarly the hydroxymethyl-2-naphthol bridged compound **58** was prepared in low yield. The latter was resolved by enantioselective HPLC (Daicel Chiralpak AD).



57 58

Figure 1.14 – Proximal bridging at the upper rim to produce dissymmetry.

1.2.2 Resorcinarene based

The largest contribution to the C_2 dissymmetric family are the 1,3-bisbenzoxazines prepared by Böhmer.[53] A number of derivatives were prepared from the distal tetratosylates including several bridged bisbenzoxazines (**Figure 1.15**).

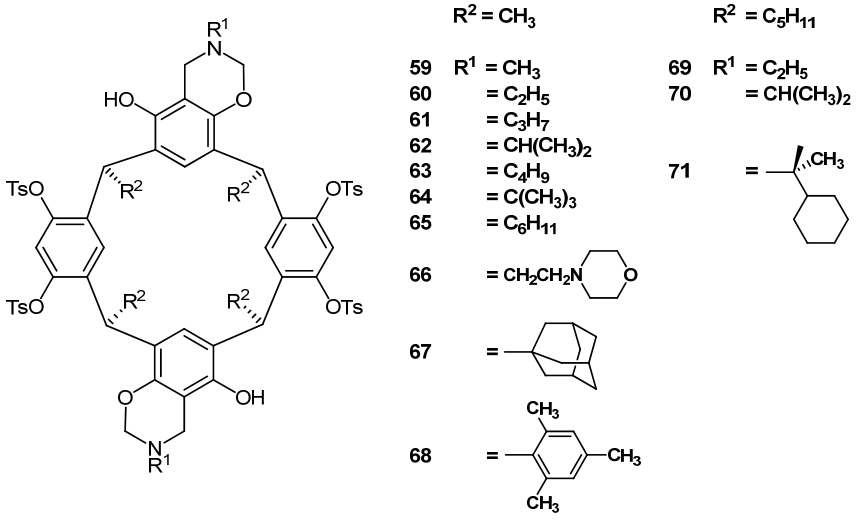
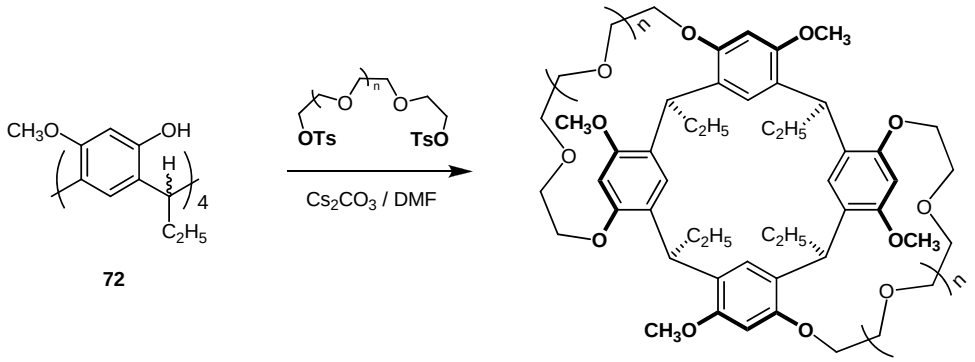


Figure 1.15 – C_2 dissymmetric resorcinarene bisbenzoxazine derivatives produced from two distal tetra-tosylates.

More recently, the racemic bis-crowns **73** and **74** have been produced by Salorinne and Nissinen.[54] Desymmetrisation of the tetramethoxyresorcinarene **72** with tri- and tetraethylene glycol afforded the C_2 symmetric derivatives in 18 and 22 % yields respectively.



72

73 n = 1
74 n = 2

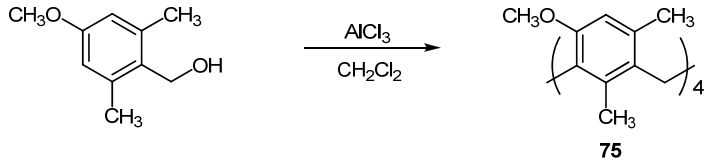
Scheme 1.12 – Formation of the racemic resorcinarene bis-crowns from the tetramethoxy resorcinarene **72**

1.3 The C_4 dissymmetric

1.3.1 Calixarene based

No example of a C_4 dissymmetric calixarene appears to have been generated from the parent calixarenes. This is no doubt due to the fact that introduction of a *meta* substituent would be significantly complicated by the formation of regioisomers. An extenuating factor in this regard would likely be that the preparation of C_4 dissymmetric calix[4]arenes by fragment condensation is substantially easier and higher yielding than the corresponding C_1 or C_2 dissymmetric derivatives. This is a direct result of the ease of preparation of the starting benzylic alcohol. Consequently, many excellent examples of condensations of benzyl alcohols to give C_4 dissymmetric calixarenes have been published.

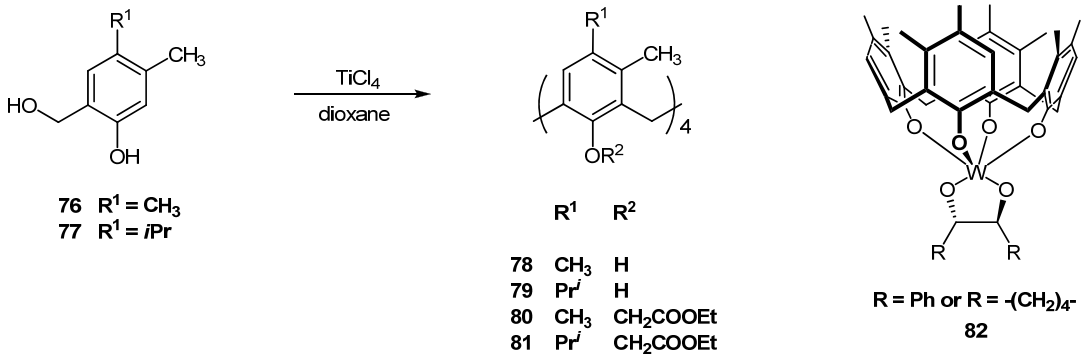
The earliest preparation of this kind was provided by Wu.[55] The condensation of 2,6-dimethyl-4-methoxybenzyl alcohol in the presence of aluminium chloride afforded the cyclic tetramer **75** with four 'exo' methoxy groups in 80 % yield.



75

Scheme 1.13 – Condensation of 2,6-dimethyl-4-methoxybenzyl alcohol to afford the chiral calixarene **75**.

The first of the standard calix[4]arene examples was produced by Böhmer.[56-57] Benzyl alcohols **76** and **77** were treated with titanium tetrachloride in dioxane to give their respective tetramers (**78** and **79**). Alkylation of the phenols gave the tetra-ester cone conformers **80** and **81** in 62 and 34 % respectively. Swager *et al*.[58] resolved the octamethyl compound (**78**) as the diastereomeric tungsten(VI) adducts (**82**), prepared with two different chiral diols, by HPLC. The hydrobenzoin derivative (**82**) was also separable by flash chromatography.



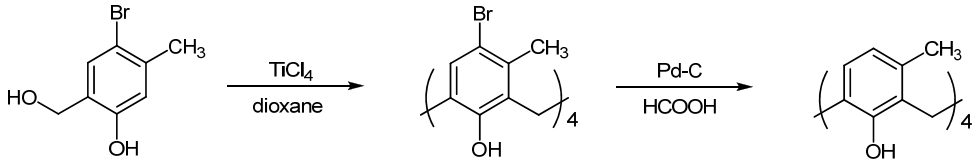
76 $R^1 = CH_3$
77 $R^1 = i$Pr

	R^1	R^2
78	CH_3	H
79	Pr^i	H
80	CH_3	CH_2COOEt
81	Pr^i	CH_2COOEt

82

Scheme 1.14 – Condensation of benzylic alcohols **76** and **77** and their further functionalisation as esters (**80** and **81**) and diastereomeric derivatives **82**.

The more synthetically useful X^4-methylcalix[4]arene **85**[59] was prepared by condensation of 4-bromo-2-(hydroxymethyl)-5-methylphenol (**83**) and subsequent debromination of the calixarene **84** with Pd/C/formic acid. The authors demonstrated the potential application of this calixarene by conversion to the azo (45 % yield), tetrachloromethyl (88 %) and tetra(dimethylamino)methyl (75 %) derivatives, which have all been applied to the standard calixarenes previously.[60-62] Addition of an adamantyl group to the upper rim failed and was attributed to the greater steric hinderance of the X^4-methyl unlike the adamantyl derivative of the parent calixarene prepared by Khomich *et al.*.[63]

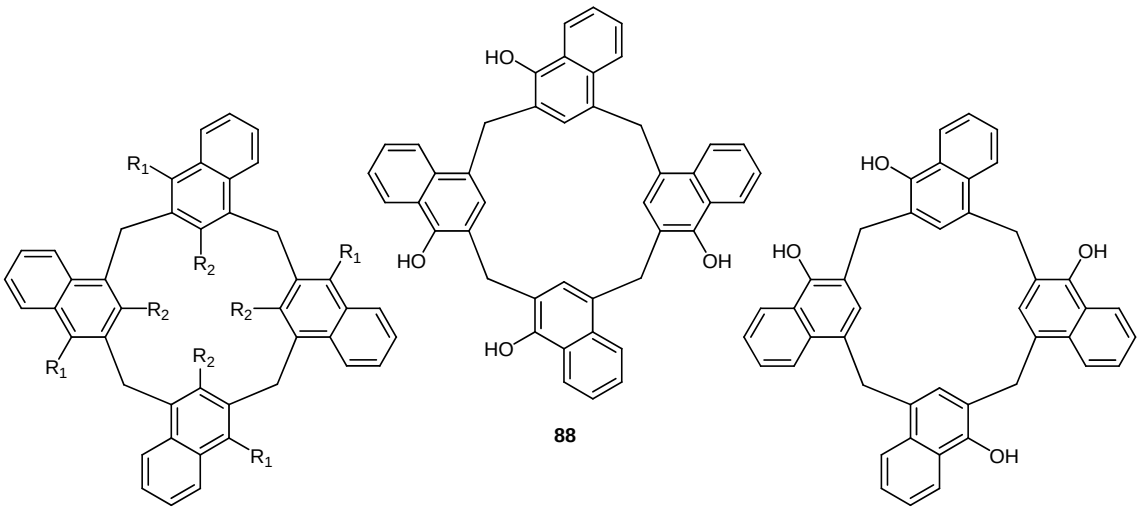


83 **84** **85**

Scheme 1.15 – Condensation of benzylic alcohol **83** followed by de-bromination affords chiral calixarene **85** with a free reactive position for further functionalisation.

A very important member of the C_4 dissymmetric calixarenes is the calix[4]naphthalenes. The calix[4]naphthalene with 'endo' OH groups (see **86**, **Figure 1.16**) was first prepared by Böhmer in 5 % yield by the condensation of 1-hydroxymethyl-2-naphthol with titanium tetrachloride in dioxane.[42] The synthesis of the calix[4]naphthalene with 'exo' OH groups (**87**) was first reported by

Georghiou.[64-65] Condensation of 1-naphthol with formaldehyde in the presence of potassium carbonate as a catalyst yields the calix[4]naphthalene in 9.6 % yield along with the corresponding isomers **88** and **89** in 16 and 5% respectively. The most notable application of the calix[4]naphthalenes has been the complexation of [60]fullerene.[66] Georghiou and coworkers have investigated these complexes in some detail.[67-68]



86 R_1 = H, R_2 = OH
87 R_1 = OH, R_2 = H

88

89

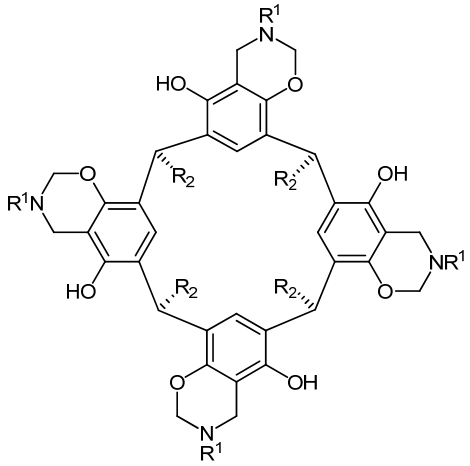
Figure 1.16 – Calix[4]naphthalene regioisomers

1.3.2 Resorcinarene based

Of all of the helically chiral calixarene and resorcinarene compounds it is the C_4 dissymmetric resorcinarenes that are the most well studied of the series. The preparation of these can be divided into two categories, (i) the generation of chirality by the regioselective placement of groups about the resorcinarene upper rim, (ii) by the regioselective formation of the resorcinarene skeleton using resorcinol mono-ethers.

The tetra-benzoxazine derivatives make up a substantial portion of the first category (**Figure 1.17**). The first examples of this (**90** – **92**) were prepared by Matsushita and Matsui.[69] Using achiral amines and aqueous formaldehyde solution they produced the corresponding racemic mixtures of benzoxazine functionalised resorcinarenes.

However, no analytical details were reported and no mention of the chirality was made.



	R_1	R_2		R_1	R_2
90	cyclohexyl	CH_3	**106**	*p*-$C_6H_4OC_6H_5$	C_5H_{11}
91	CH_2COOEt	CH_3	**107**	3,4-$C_6H_3(OMe)_2$	C_5H_{11}
92	Ph	CH_3	**108**	2-(N-morpholino)ethyl	C_5H_{11}
93	CH_2Ph	CH_3	**109**	2-methoxyethyl	C_5H_{11}
94	mesityl	CH_3	**110**	CH_2CH_2Ph	C_5H_{11}
95	CH_3	C_5H_{11}	**111**	mesityl	C_5H_{11}
96	C_2H_5	C_5H_{11}	**112**	*n*Bu	$C_{11}H_{23}$
97	C_3H_7	C_5H_{11}	**113**	CH_2Ph	$C_{11}H_{23}$
98	*i*Pr	C_5H_{11}	**114**	1-adamantyl	$C_{11}H_{23}$
99	*n*Bu	C_5H_{11}	**115**	*p*-$C_6H_4NO_2$	$C_{11}H_{23}$
100	*t*Bu	C_5H_{11}	**116**	*p*-$C_6H_4OC_6H_5$	$C_{11}H_{23}$
101	$C_{10}H_{21}$	C_5H_{11}	**117**	$(CH_2)_2OH$	C_2H_5
102	allyl	C_5H_{11}	**118**	$(CH_2)_2OH$	C_5H_{11}
103	CH_2Ph	C_5H_{11}	**119**	$(CH_2)_2OH$	$C_{11}H_{23}$
104	1-adamantyl	C_5H_{11}	**120**	$(CH_2)_4OH$	C_5H_{11}
105	*p*-$C_6H_4NO_2$	C_5H_{11}	**121**	$(CH_2)_6OH$	$C_{11}H_{23}$

Figure 1.17 – The formation of tetrabenzoxazine derivatives from achiral amines.

Further work by Böhmer[70] with achiral amines (compounds **99**, **103-106**, **112** – **116**) made full recognition of the chirality of the C_4 dissymmetric species and the potential for regioisomers. However ^{1}H n.m.r. spectroscopy with Pirkle's reagent produced no doubling of peaks and attempts at resolution failed until some years later.[71] This was ascribed to the epimerisation of the benzoxazine ring via the iminium species (**Figure 1.18**). Resolution of several benzoxazine derivatives was achieved by HPLC[71] on a Whelk O-1 chiral stationary phase, however, baseline separation was only achieved for **93** at low temperatures (T = -3 ºC) to minimise the epimerisation (Daicel ChiralPak AD). The compounds produced by Bohmer and collaborators (**93** – **116**) and their syntheses have been reviewed.[72] The energy barrier for interconversion of the enantiomers was calculated later by Trapp *et al*. to be $\Delta G^{\#}$(298 K) = 92 ± 2 kJ mol^{-1}.[73]

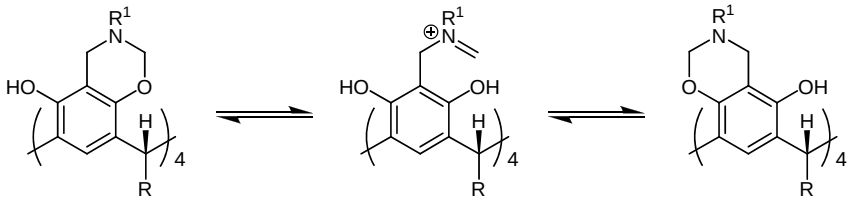


Figure 1.18 – Proposed mechanism for the epimerisation of the benzoxazine rings.

Similar preparations of benzoxazine derivatives using aminoalcohols (**Figure 1.17**, **117** – **121**) provide an extended cavity with potentially useful functionality about the upper rim.[74]

The preparation of the benzoxazine derivatives using a variety of chiral amines was reported independently by Böhmer *et al*.[75] (**122 - 124, 128**), Heaney *et al*.[76] (**122, 125 – 131**) and Iwanek *et al*.[77-78] (**126** and **130**). When chiral amines were employed they acted as a chiral auxilliary and directed the ring closure reaction thereby enhancing the production of one diastereomer relative to the other. Thus, application of the appropriate (*R*)- amines afforded the dextro-rotary tetrakisbenzoxazines **122** – **127** while the (*S*)- amines afford the laevo-rotary enantiomers (**128** – **131**). This method of chiral resorcinarene preparation is particularly efficient as it requires no enantioselective separations. However, as the benzoxazine ring is labile, epimerisation still occurs. The three groups investigated the diastereomeric mixtures produced by acid catalysed epimerisation of the benzoxazine ring by n.m.r. spectroscopy. They also all produced compounds of good diastereomeric purity using *R*-(+)- and *S*-(-)-α-methylbenzylamine using differing resorcinarene substrates.

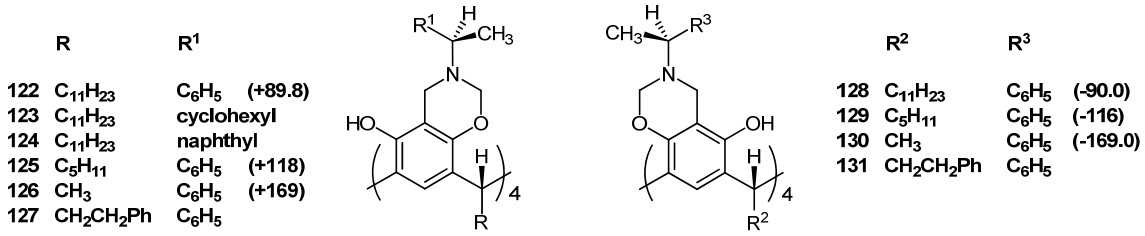
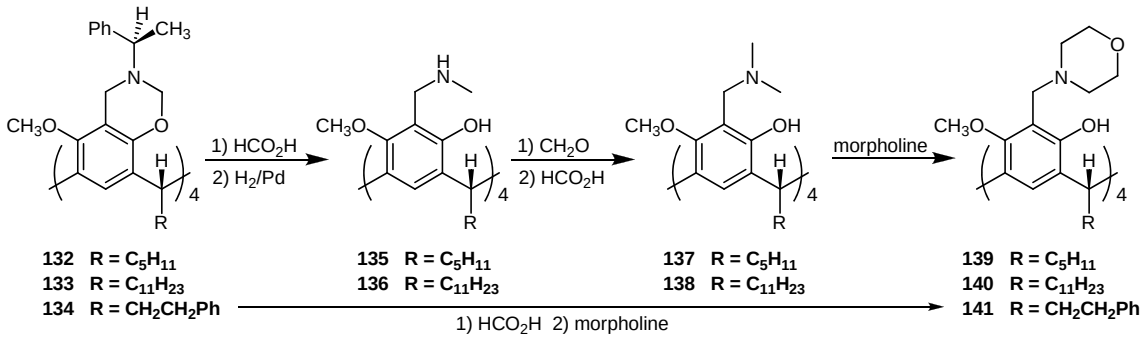


Figure 1.19 – Resorcinarene tetrabenzoxazine derivatives produced using chiral amines.

The absolute stereochemistry of compounds **125** and **126** were determined using X-ray methods by Heaney *et al*. and Iwanek *et al*. respectively.
Compound **130** was applied by Smith *et al*.[79] as a chiral n.m.r. spectroscopy additive however, no significant interaction with a variety of guest molecules, was observed Preparation of the first stable, enantiomerically pure helically chiral resorcinarene was achieved by Heaney *et al*..[80-81] By methylation of the diastereomerically pure benzoxazine derivatives (**122, 125 and 127** and respective enantiomers) using

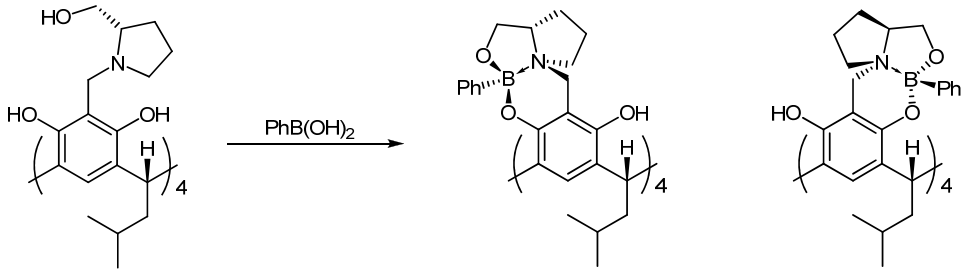
butyllithium and dimethylsulfate (or methyl triflate), racemisation can no longer occur (**132** – **134**, only (+) enantiomers shown). The chiral auxiliary may then be removed and useful transformations realised (**scheme 1.16**).



132 R = C_5H_{11}
133 R = $C_{11}H_{23}$
134 R = CH_2CH_2Ph
135 R = C_5H_{11}
136 R = $C_{11}H_{23}$
137 R = C_5H_{11}
138 R = $C_{11}H_{23}$
139 R = C_5H_{11}
140 R = $C_{11}H_{23}$
141 R = CH_2CH_2Ph

Scheme 1.16 – Further transformations applied to single enantiomers of the resorcinarene tetrabenzoxazine derivatives.

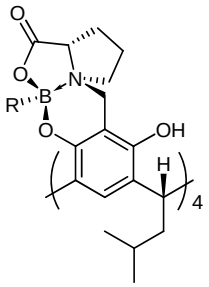
The Mannich base theme was continued in 2002 by Iwanek[82] who combined the L-prolinol derived **142** and phenylboronic acid to obtain a mixture of the boron-heterocycle diastereomers **143** and **144**.



142 **143** **144**

Scheme 1.17 – Preparation of chiral derivatives **143** and **144** from the L-prolinol derived mannich base **142**.

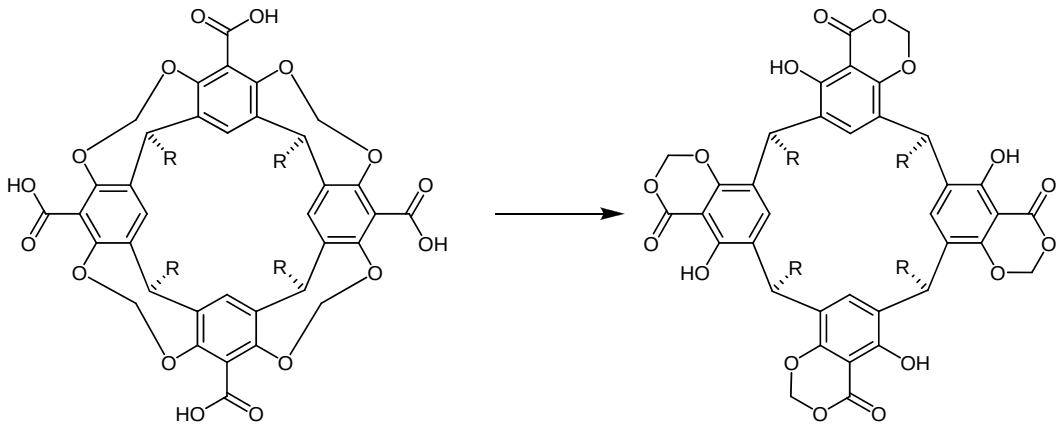
These structurally rigid derivatives were formed as a mixture (80:20, **143**/**144**) which could be separated by multiple fractional crystallisations. Both diastereomers were characterised by x-ray crystallography.
The methodology was expanded later[83] to the L-proline derivatives described in figure **1.20**. All of the compounds were prepared in good yield and >98 % de



145 R = Ph
146 R = Et
147 R = OCH_3
148 R = OH

Figure 1.20 – Chiral derivatives **145 - 148** prepared from the corresponding L-proline derived mannich base.

Somewhat related to the resorcinarene benzoxazines is the phenolic lactone acetal **150** produced by Cram.[84] **150** and its enantiomer were prepared in 18 % yield by the acid catalysed rearrangement of the cavitand **149**.

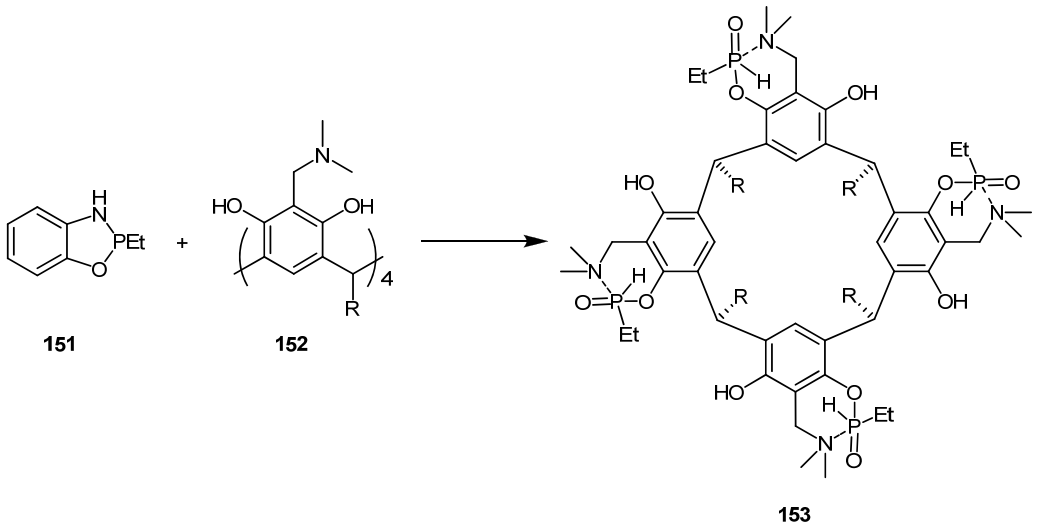


149 **150**

Scheme 1.18 – Acid catalysed rearrangement of cavitand **149** to afford the C_4 dissymmetric derivative **150**.

A very interesting example of regioselective placement of groups about the resorcinarene cavity to generate C_4 dissymmetry is that given in **Scheme 1.19**. Terent'eva and coworkers[85] produced the C_4 isomer **153** by reaction of 2-ethyl-1,3,2-benzoxaphospholine **151** with the tetra(dimethylaminomethyl)calix[4]-resorcinarene **152**. This reaction is especially curious since alkylation with the majority of alkylating agents produce a complex mixture of regioisomers (see **section 2.2**) or in the case of reagents such as toluenesulfonyl chloride, produces the distal

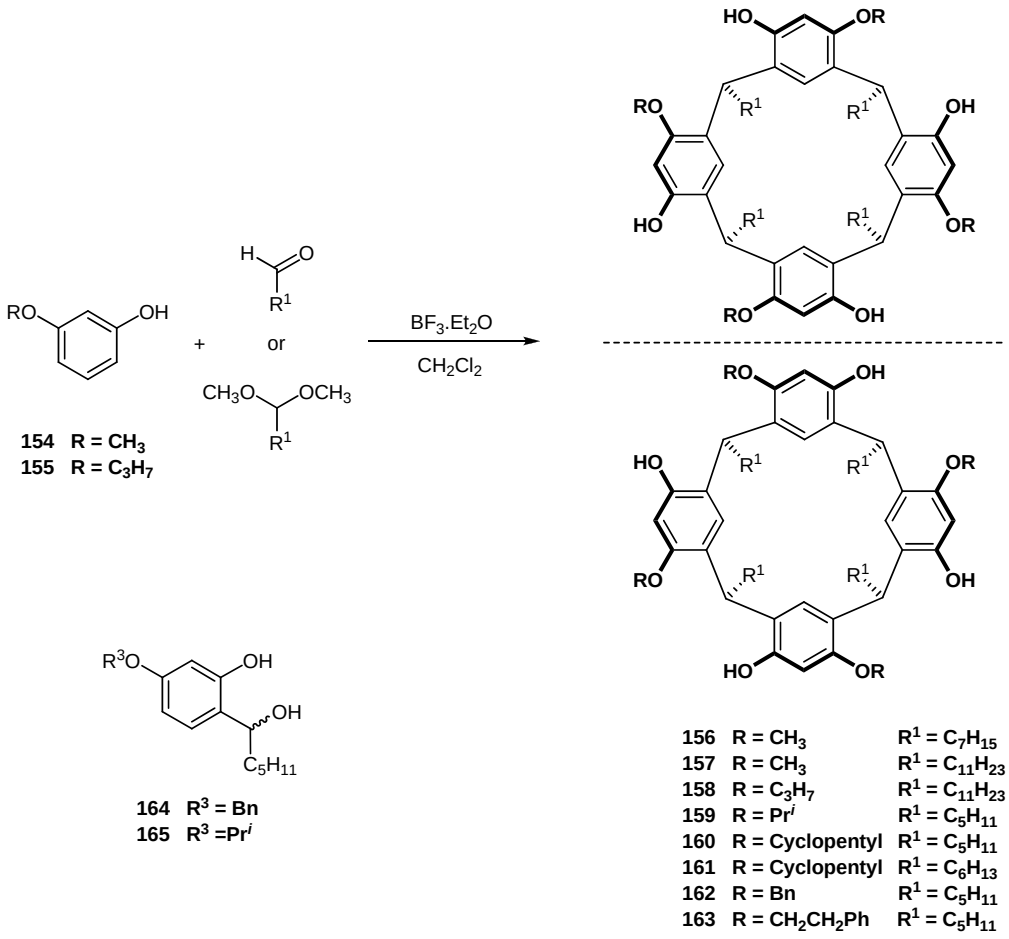
tetratosylate.[86] No ^{13}C n.m.r data was provided for **153** and the ^{1}H n.m.r. spectroscopic data provided is insufficient for a conclusive assignment.



151 **152** **153**

Scheme 1.19 – Synthesis and proposed structure of the phosphorus based resorcinarene derivative **153**.

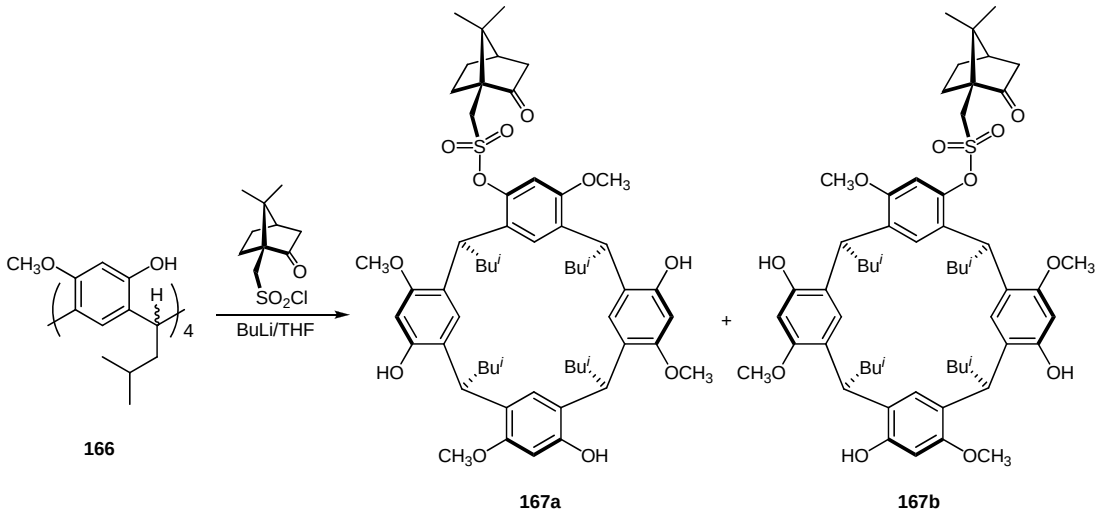
We reported the first example of a regioselective formation of the resorcinarene skeleton from resorcinol mono-ethers.[87] The condensation of the mono-ethers **154** and **155** with alkyl aldehydes in the presence of boron trifluoride etherate gave the respective C_4 dissymmetric resorcinarenes **156** – **158** as their racemates in high yields (**scheme 1.20**, see **chapter 2 for details**).



Scheme 1.20 – The synthesis of C_4 dissymmetric resorcinarenes by condensation of resorcinol mono-ethers and alkyl aldehydes.

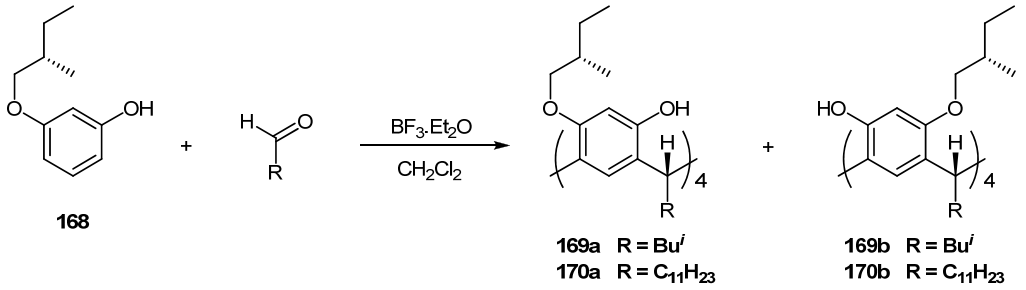
Heaney *et al*. further expanded the series with the preparation of **159** - **163**.[88] He found that the tetracyclopentyloxy and tetrabenzyloxy resorcinarenes **160 – 162** could not be prepared by the standard boron trifluoride / aldehyde protocol presumably due to instability of the reaction intermediate. By application of the aldehyde dimethyl acetals rather than the aldehydes the resorcinarenes were afforded in moderate to excellent yields. In the same publication the presumed reaction intermediates (**164** and **165**) were prepared and studied as useful precursors to the resorcinarenes. In particular the proposed intermediate **165** in the presence of boron trifluoride etherate did indeed give the desired resorcinarene (**159**) in 82 % yield. The facile preparation of the C_4 dissymmetric resorcinarenes was made all the more potent by Heaney with the publication of a simple synthesis for resorcinol mono-ethers.[89]

The first resolution of a C_4 dissymmetric resorcinarene prepared by this method was achieved by Mattay and coworkers.[90] By monofunctionalisation of the resorcinarene **166** with a camphorsulfonyl moiety, the resulting diastereomers could be resolved by HPLC. Hydrolysis of the sulfonate esters **167a** and **167b** yielded the pure resorcinarene enantiomers. Unfortunately the absolute stereochemistry of the resorcinarenes was not determined.



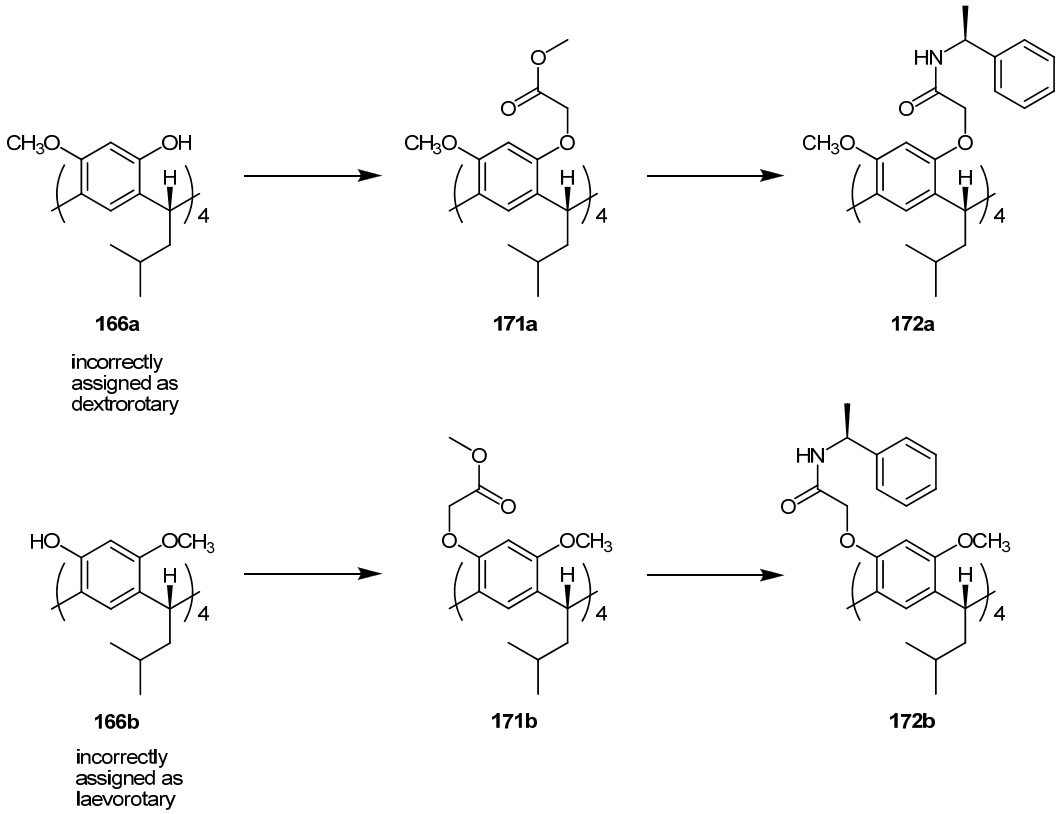
Scheme 1.21 – Resolution of chiral tetramethoxyresorcinarene by formation of the diastereomeric mono-camphorsulfonate esters.

They also applied the boron trifluoride protocol (in the same publication) to the chiral resorcinol mono-ether **168** so as to recover the resorcinarenes as diastereomeric mixtures (see **Scheme 1.22**) which could be separated by HPLC. Resorcinarene formation with **168** and 3-methyl butanal appeared to favour the formation of the laevorotary diastereomer while dodecanal produced a 1:1 mixture of diastereomers (**170a** and **170b**). Again, no X-ray data was provided for any of the diastereomers and the absolute stereochemistry was not elucidated at the time.



Scheme 1.22 – Preparation of diastereomeric resorcinarenes by condensation of a chiral resorcinol mono-ether (**168**) with alkyl aldehydes.

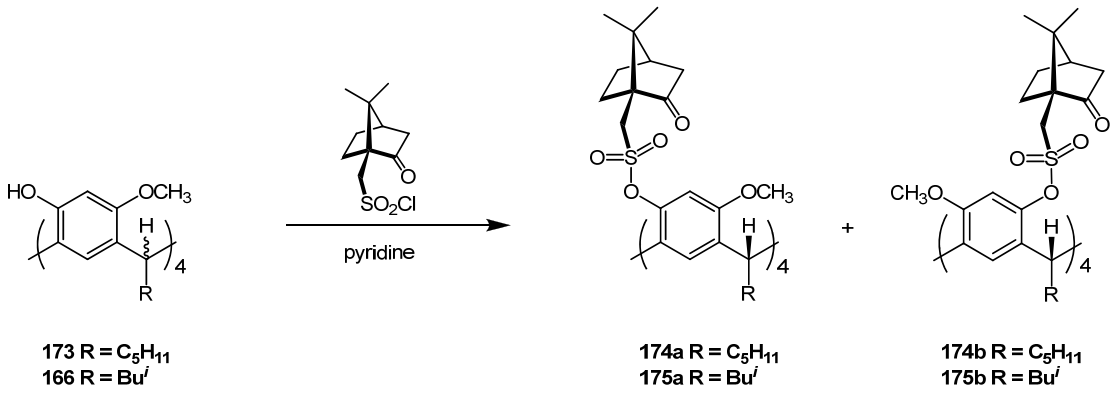
The issue of the absolute stereochemistry was addressed by Mattay *et al.* in 2005.[91] However, due to their earlier incorrect designation of the optical rotations for the enantiomers **166a** and **166b** (prepared by hydrolysis of **167a** and **167b**), the resulting assignment of the all (*S*) configuration (**166b**) to the laevorotary enantiomer of **166** by correlation to the single crystal x-ray structure of **172a** was indeed wrong.



Scheme 1.23 – Synthesis of the diastereomeric amide derivatives **172** by amidation of the tetraester.

Likewise, the assignment of the absolute stereochemistry of **169a** and **169b** was incorrect due to the same error.

The correct absolute stereochemistry for several resorcinarene enantiomers, including **166**, was elucidated by X-ray crystallography in 2006[92] by the synthesis and resolution of the tetracamphorsulfonates (**Scheme 1.24**, see **Chapter 3 for details**).



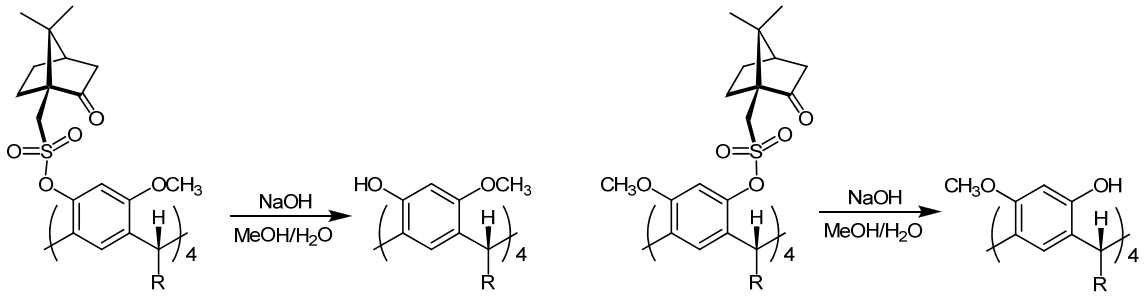
173 R = C_5H_{11}
166 R = Bu^i

174a R = C_5H_{11}
175a R = Bu^i

174b R = C_5H_{11}
175b R = Bu^i

Scheme 1.24 – Synthesis of the resorcinarene tetracamphorsulfonate esters with the absolute stereochemistry for the first eluting (series a) and second eluting (series b) diastereomers.

Having determined the absolute stereochemistry of the tetracamphorsulfonate esters the ester functionality was removed by alkaline hydrolysis to obtain the pure enantiomers for characterisation. Thus it was proven that the absolute stereochemistry of the dextrorotary resorcinarenes **173a** and **166a** were of the all (*S*)-configuration as shown in scheme **1.25**.



174a R = C_5H_{11}
175a R = Bu^i

(+)-173a R = C_5H_{11}
(+)-166a R = Bu^i

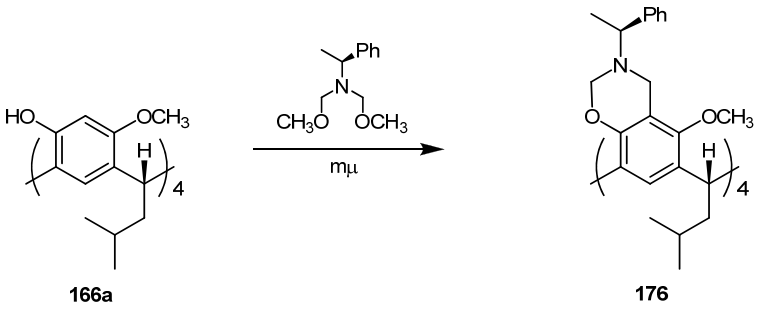
174b R = C_5H_{11}
175b R = Bu^i

(-)-173b R = C_5H_{11}
(-)-166b R = Bu^i

Scheme 1.25 – Hydrolysis of the camphorsulfonate esters to afford enantio-pure chiral resorcinarenes.

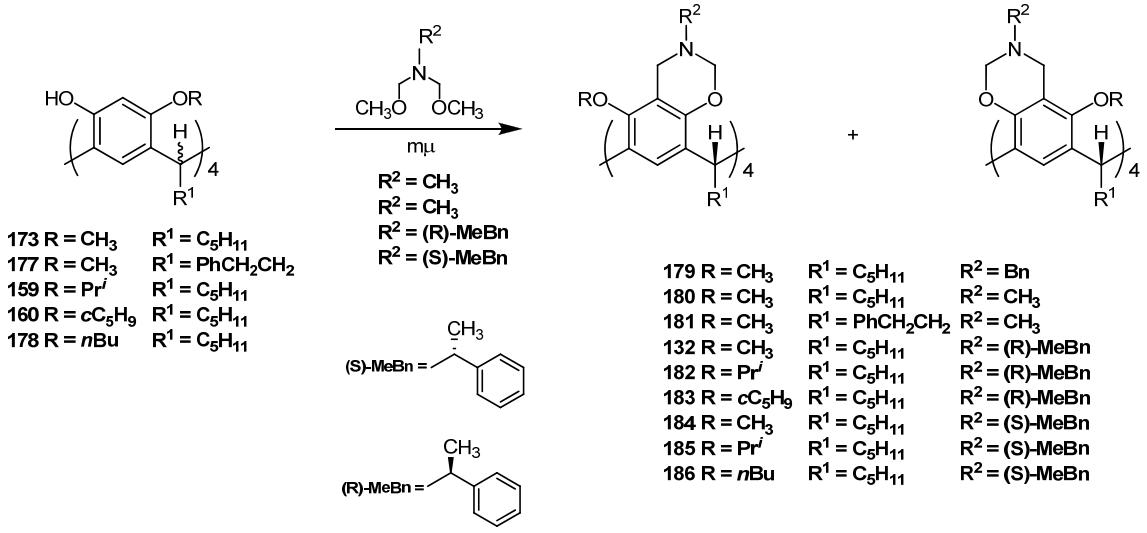
During the course of the camphorsulfonylation studies a number of di- and tri-camphorsulfonates were also observed. In particular when resorcinarenes with larger ether groups at the upper rim such as **159** and **160** were combined with camphorsulfonyl chloride, the mono- or di-esters could be obtained depending on the base and conditions applied.

The absolute stereochemistry of the resorcinarenes was corroborated[92] by conversion into their tetrabenzoxazine derivatives (such as **176**, **scheme 1.26**).



Scheme 1.26 – Synthesis of the diastereomerically pure tetrabenzoxazine derivative **176**.

The absolute stereochemistry of **176** had been determined by x-ray crystallography in a previous study regarding the functionalisation and resolution of the resorcinarenes described in **scheme 1.27** as their tetrabenzoxazine derivatives **132**, **179 - 186**.[20]



Scheme 1.27 – Preparation of several tetrabenzoxazine derivatives from the chiral C_4 dissymmetric resorcinarenes (note: cC$_5$H$_9$ = cyclopentyl).

During the course of those studies[92] it was determined that the C_4 dissymmetric resorcinarenes could not be functionalised as the tetrabenzoxazines in the usual manner (cat. NaOH, amine and paraformaldehyde). The failure was ascribed to the

relatively weakly acidic phenols of the C_4 resorcinarenes which were determined to be approximately 2 pKa units less acidic than the achiral octahydroxyresorcinarenes. However, by application of more forcing conditions or microwave irradiation, the tetrabenzoxazine derivatives could be obtained in good yield.
The chiral tetrabenzoxazines were examined as ligands for the addition of diethylzinc to benzaldehyde. In general only moderate % ee's were obtained the best being a conversion of 95 % with an ee of 83 % with compound **182** (in favour of (*S*)-(-)-1-phenylpropanol).

1.4 Outlook

This review provides a summary of current work regarding the syntheses and application of calixarenes and resorcinarenes having C_n dissymmetry. It is not intended to be comprehensive but merely a guide to some of the major themes. However, there are a vast array of modifications and application yet still available to the aspiring macrocycle chemist. Chiral ligands for catalysis, enzyme mimicry and chiral separation science have barely been explored and offer much promise.

2.0 Synthesis and characterisation of C_4 dissymmetric resorcinarenes

The majority of C_4 dissymmetric calixarenes have been synthesised by fragment condensation to generate the calixarene skeleton (see **section 1.3.1**). The C_4 dissymmetric resorcinarenes however, have in the main, been produced by attachment of functionality to the upper-rim in a regioselective fashion e.g. the resorcinarene benzoxazines (see **section 1.3.2**). No direct synthesis of a C_4 dissymmetric resorcinarene appears to have been achieved prior to 2000.
We considered that it would be feasible to produce a C_4 dissymmetric resorcinarene such as **188** by condensation of a 3-alkoxyphenol of the general structure **187** with an aldehyde using the appropriate solvent and catalyst. It has been reported by Weinelt that resorcinol derivatives in which the hydroxyl groups are (partially) alkylated do not give cyclomeric products on condensation with aldehydes in the presence of mineral acids in alcoholic solvents.[93-94]

187 **188**

Scheme 2.1 – proposed scheme for the formation of chiral resorcinarenes

However, octamethyl resorcinarenes have been prepared by employing a Lewis acid catalyst.[95-98] Considering the limited combination of catalyst and solvent conditions applied by Weinelt, we thought it prudent to make a thorough investigation of this synthetic methodology.
The reaction of a 3-alkoxyphenol with an aldehyde can potentially produce up to four different regio-isomers as shown in **figure 2.1**.

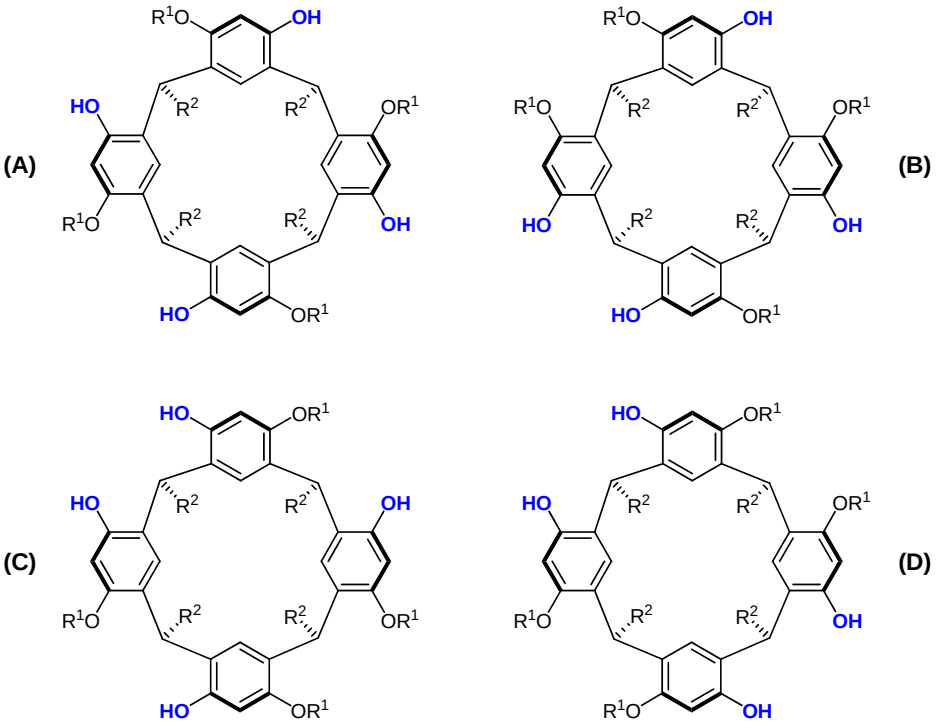
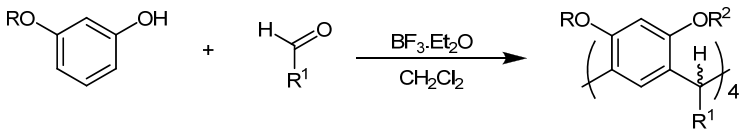


Figure 2.1 – Four regioisomers that may be formed by the condensation of aldehydes with resorcinol mono-ethers.

The first of these (**Figure 2.1 (A)**) is the C_4 symmetric isomer, the second is completely asymmetric (**(B)**, C_1 symmetry) and the last two have C_{2v} symmetry (**(C) and (D)**). When these are combined with the potential for stereoisomerism at any one of the resulting methine carbons the possibilities are numerous. The assembly of eight separate molecules into a single isomer is by no means a simple task.
Initial attempts to synthesise the resorcinarenes having C_4 dissymmetry (**Figure 2.1 (A)**) with a variety of mineral acid/alcoholic solvent conditions failed to produce significant quantities of the desired material (generally less than 5 %). These results corroborate Weinelt's findings.[93] However, the fact that any of this material was produced at all despite the statistical possibilities indicated to us that some selectivity in the reaction may be obtained with an alternate reaction system. Application of Lewis acids such as tin tetrachloride, titanium tetrachloride, boron trichloride and aluminium chloride in dichloromethane and zinc chloride in ether failed to produce anything but complex mixtures or promoted reactions other than the desired pathway.

Catalytic or mole quantities of protic acids such as camphorsulfonic acid, trifluoroacetic acid, trifluoromethanesulfonic acid or toluenesulfonic acid in anhydrous protic or aprotic solvents failed to produce any desired reaction.
It was discovered that the desired C_4 dissymmetric product could be prepared simply by adding an excess (2 – 3 mol equivalents w.r.t. the phenol) of boron trifluoride etherate to a 1:1 mixture of the 3-alkoxyphenol and an alkyl aldehyde in anhydrous dichloromethane (or chloroform). Initially the reaction of 3-methoxyphenol with one equivalent of octanal in the presence of two equivalents of boron trifluoride etherate in anhydrous dichloromethane afforded **156** in high yield (80 %).
The procedure was readily applied to a range of alkyl aldehydes and two 3-alkoxyphenols to produce the suite of compounds described in **scheme 2.2**.



	R	R^1	R^2	%		R	R^1	R^2	%
189	CH_3	CH_3	Ac	20	192	CH_3	C_9H_{19}	H	48
190	CH_3	C_3H_7	H	68	157	CH_3	$C_{11}H_{23}$	H	74
191	CH_3	C_6H_{13}	H	28	193	Pr	C_7H_{15}	H	52
156	CH_3	C_7H_{15}	H	80	158	Pr	$C_{11}H_{23}$	H	44

Scheme 2.2 – Synthesis of the C_4 dissymmetric resorcinarenes and their yields.

The yields indicated in **scheme 2.2** were generally obtained by reacting 3-methoxyphenol and aldehydes obtained commercially without further purification. However, the reaction to produce **190** with commercially obtained butanal, containing approximately 6 % butyric acid impurity (by ^{1}H n.m.r.), initially produced a yield of only 23 %. When the butanal was purified by basic extraction and distillation the yield was increased markedly (68 %) indicating the substantial deleterious effect of carboxylic acid contaminant. Purification of commercially obtained heptanal and decanal by the same method for the preparation of **191** and **192** failed to afford any improvement in isolated yield. The materials derived from 3-propoxyphenol (**193** and **158**) were produced in lower yields due to the poorer purity of the phenol (see **section 2.8.19**) and some difficulties with crystallisation due to their wax like properties.

In the case of the *C*-methyl-tetramethoxyresorcin[4]arene the product was not isolable from the product mixture by crystallization like the longer chain resorcinarenes and purification by chromatography was problematic. It was, however, isolable by per-acetylation of the product mixture and then recovery of the tetraacetate (**189**) by crystallization from methanol.

The optimal quantity of boron trifluoride etherate was determined by an n.m.r. study of reactions containing varying quantities of the catalyst. **figure 2.2** shows spectra for reactions performed under identical conditions but with 0.5, 1.0, 1.5, 2.0 and 3.0 mol equivalents of boron trifluoride. Quite clearly an improvement is evident with increasing catalyst quantities, however only marginal gains are achieved by increasing from two to three mole equivalents of catalyst. No further improvement was achieved by increasing to beyond three equivalents.

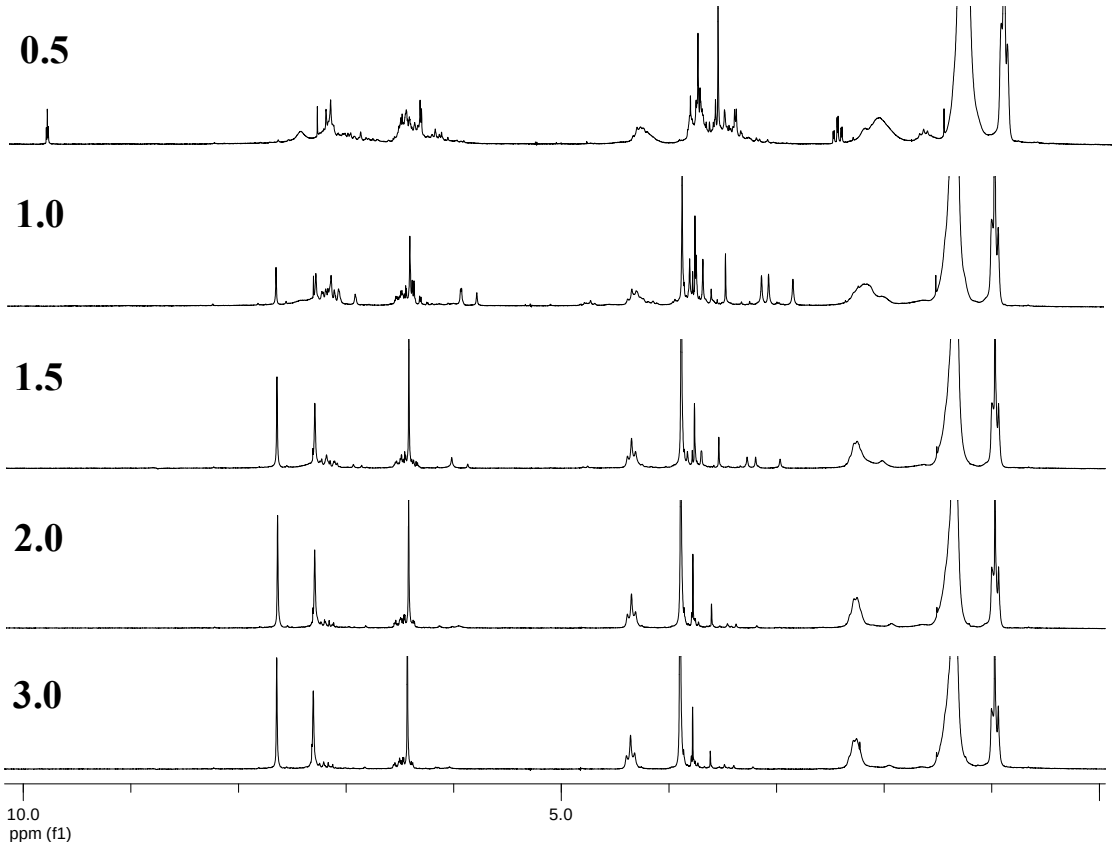
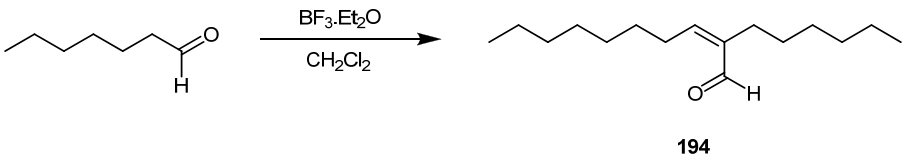


Figure 2.2 – The reaction of 3-methoxyphenol with dodecanal in the presence of 0.5, 1.0, 1.5, 2.0 and 3.0 mole equivalents of boron trifluoride.

During the course of the resorcinarene preparations, particularly when the reaction was inhibited by the presence of carboxylic acid impurities, a second UV absorbing compound was observed (by t.l.c.). Isolation of the significantly more lipophilic byproduct by chromatography from a synthesis of **156** and analysis of its ^{1}H and ^{13}C n.m.r. spectra revealed it to be 2-hexyldec-2-enal (**194**). Aldehyde **194** is clearly derived from the well known aldol condensation.[99]



194

Scheme 2.3 – Self aldol condensation of octanal to give 2-hexyldec-2-enal (**194**).

Aldol condensations are frequently performed in the presence of Lewis acids and are generally rapid.[100-101] The 2-hexyldec-2-enal is known in the literature and has been prepared by the self-condensation of octanal in the presence of Lewis and protic acids[102] and as a by-product of palladium catalysed coupling reactions.[103] To investigate the nature of the potentially competing aldol reaction, a small scale reaction containing only octanal and boron trifluoride etherate in dichloromethane was performed (**Scheme 2.3,** see **section 2.8.14**). The aldol product **194** was obtained pure in essentially quantitative yield after standard workup. The condensation was monitored by t.l.c. and appeared to be complete within thirty minutes indicating that the reaction is quite fast at room temperature. Quite clearly, any slowing of the aldehyde – arene condensation, due to contaminants or otherwise, will allow the undesired aldol to compete significantly.

This could logically be countered by using an aldehyde that does not enolise such as benzaldehyde. However, despite the fact that resorcinarenes have been prepared with aryl aldehydes in the past,[104-105] they failed with the current protocol.

2.1 Mechanism of resorcinarene formation

The calix[4]resorcinarenes are predominantly prepared by the condensation of an alkyl or aryl aldehyde with resorcinol in an alcoholic solvent and catalysed by a mineral acid.[105-108] The generally accepted mechanism for this reaction is the rapid formation of the corresponding acetal (**195**) and subsequent condensation of the acetal with resorcinol. This affords a number of intermediate oligomers which then cyclise to the tetrameric resorcinarenes as described by Weinelt and Schneider[93] (**Figure 2.3**).

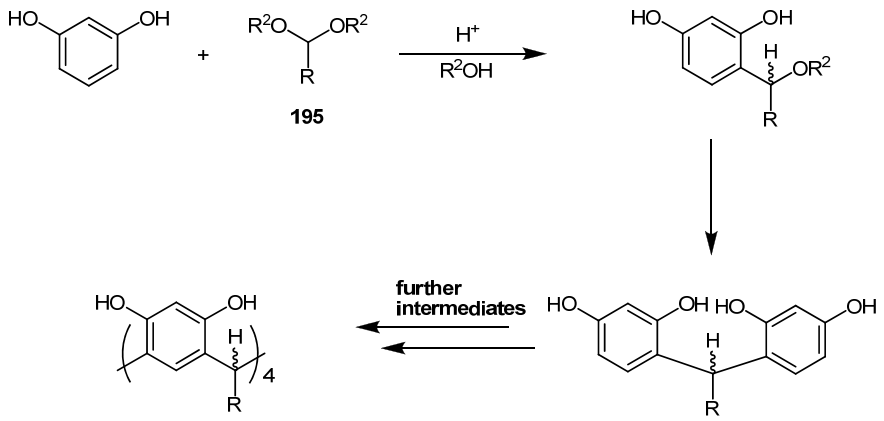
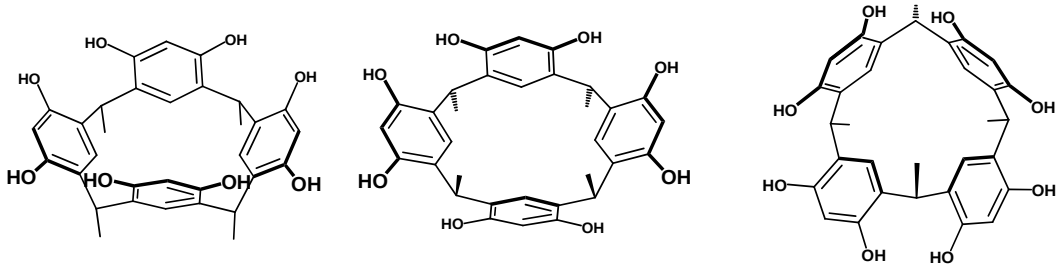


Figure 2.3 – Partial mechanism for the formation of achiral resorcinarenes proposed by Weinelt and Schneider.[93]

The stereochemical outcome of the reaction appears to be a case of kinetic vs thermodynamic control.[104, 107] The initial cyclomeric products resulting from the reaction of heptanal with resorcinol are reported to be the crown (**Figure 2.4 (A)**) and the chair stereoisomers (**Figure 2.4 (B)**).[104] A third isomer, in the diamond conformation (**Figure 2.4 (C)**) was reported later by Abis.[107] The chair stereoisomer (**B**) which is the result of kinetic control is gradually converted to the all cis stereoisomer with extended reaction times. The production of the kinetic product was determined to be driven by solubility, the chair stereoisomer being the least soluble in the alcoholic reaction medium.



(A) (B) (C)

Figure 2.4 – Stereoisomers formed in the preparation of achiral resorcinarenes.

There are however rather characteristic differences between the standard achiral resorcinarene syntheses and the formation of the chiral C_4 dissymmetric resorcinarenes. These differences have significant mechanistic consequences which directly affect both the regio- and stereochemical outcome of the chiral resorcinarene formation.

The standard resorcinarenes have an inherent symmetry as a direct result of using symmetric resorcinol derivatives (such as 1,3-dimethoxybenzene) or resorcinol itself. This is obviously not the case for the C_4 dissymmetric resorcinarenes which are derived from 3-alkoxyphenols and do not have the same symmetry. The consequence of this lack of symmetry is simple yet makes the reaction outcome all the more significant. As indicated earlier (**section 2.0**), analogous to the standard resorcinarenes, there is the potential to produce a variety of stereoisomers from the condensation of a 3-alkoxyphenol with an aldehyde. However, unlike the standard resorcinarenes, the resorcinarenes prepared from a 3-alkoxyphenol could also exist as four different regioisomers (**Figure 2.1**). The actual outcome of the reaction, which is effectively a single isomer is surprising considering the multitude of possibilities. The rate at which the reaction occurs is also quite significant. By performing a small scale reaction of 3-methoxyphenol with dodecanal catalysed by boron trifluoride etherate in deuterated chloroform and observing the reaction progress by ^{1}H n.m.r. spectroscopy it became apparent that the reaction was approximately >90 % complete within 20 minutes. The “clean” nature of the reaction and its rapid completion begs investigation of the intermediates and the accompanying reasoning for their selective formation.

One must presume that because the overall reaction is quite fast it is likely that the final resorcinarene and its intermediates are produced as a consequence of kinetic control (as opposed to thermodynamic control which generally requires more vigorous reaction conditions[109]). This assumption however, does not exclude the possibility that it is also the thermodynamic product. One must also presume that in order to produce the exceptionally high regioselectivity of the C_4 dissymmetric resorcinarenes, the first condensation of phenol and aldehyde must also occur in an exceptionally regioselective manner. The logical manifestation of this principle is described in **figure 2.5** where the alkoxyphenol rapidly condenses with the alkyl aldehyde to give solely the intermediate **196** with the newly formed α-hydroxyalkyl group adjacent to the phenolic hydroxyl. This intermediate then being the sole reactive species in solution must then condense in one (or several) of the previously described stepwise methods for tetrameric resorcinarene formation.[93] This has been tested recently by the Heaney group.[88] They found that condensation of **196**-like intermediates in the presence of boron trifluoride did afford the desired cyclomeric products in good yields.

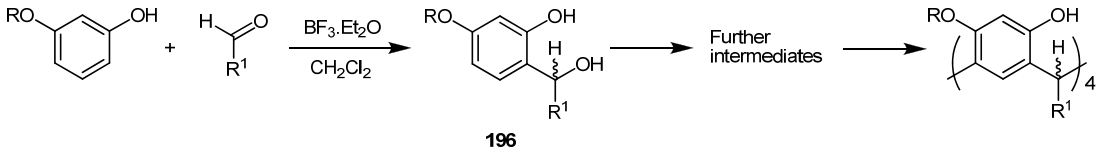


Figure 2.5 – Proposed pathway for the formation of C_4 dissymmetric resorcinarenes.

The intermediate is assumed to be the isomer with the α-hydroxyalkyl group adjacent to the phenolic hydroxyl[110] but could very reasonably be the alternative isomer with the α-hydroxyalkyl group adjacent to the alkoxyl. Unfortunately the reaction intermediate can not be observed by n.m.r. due to the rapid nature of the reaction. In order to test the hypothesis the reaction of an alkyl aldehyde with a large excess of 3-methoxyphenol was examined. The product of the reaction, which could potentially be any of the three dimeric compounds given in **figure 2.6**, would allow elucidation of the intermediate isomer that is most rapidly formed.

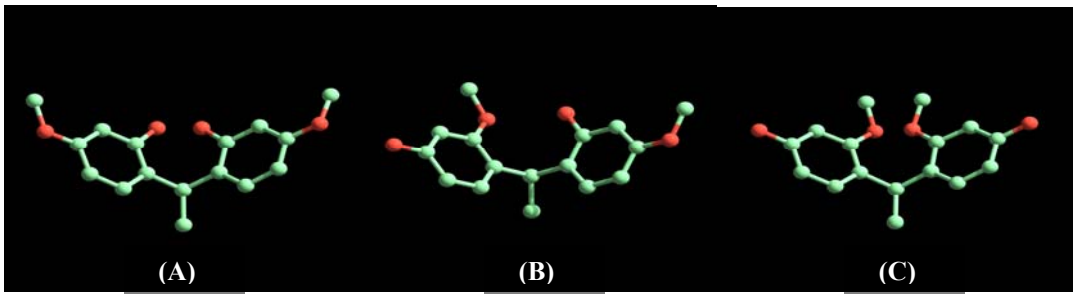


Figure 2.6 – Three possible dimers from the condensation of an alkyl aldehyde (acetaldehyde in this case) and an excess of 3-methoxyphenol.

The identity of the dimeric compound formed reveals a substantial quantity of information regarding the reactive pathway of the resorcinarene formation. In particular the reactivity of the alkoxyphenol would be clarified. For example, if the dimer **(A)** (**Figure 2.6**) is formed it indicates the first step of α-hydroxyalkylation occurs regioselectively at the position adjacent to the phenolic hydroxyl. It also reveals that the position adjacent to the phenol is the most reactive (in this system) and therefore the intermediate **196** must completely form very fast before any further condensations (to form dimers) can occur.
The second dimer (**Figure 2.6 (B)**) offers no concrete information about the initial intermediate but does indicate that the second condensation to form a dimer is a regioselective process. **Figure 2.7** shows that the initial condensation can be adjacent to either the phenol (**197**) or the methoxyl (**198**) as long as the subsequent condensation is also selective to produce the appropriate dimer compound.

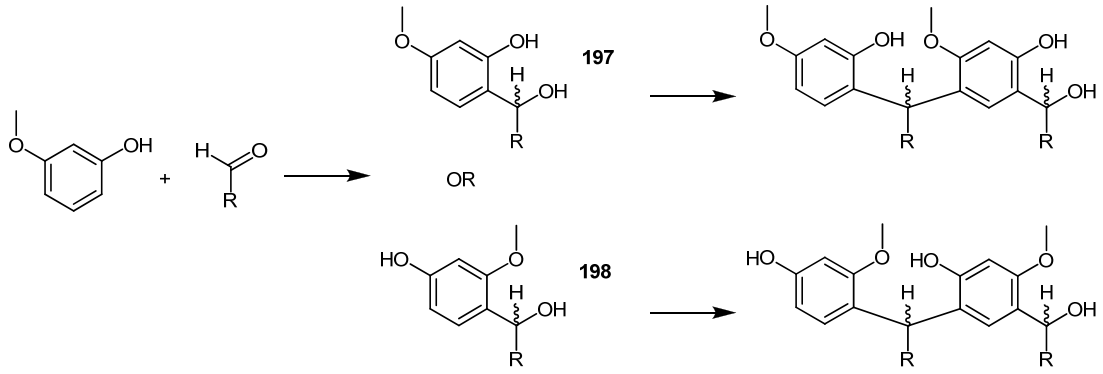


Figure 2.7 – Two possible pathways for the formation of C_4 dissymmetric resorcinarenes.

This process also assumes that the initial condensation of phenol and aldehyde occurs rapidly and completely before any subsequent condensations.
The last dimeric species (**Figure 2.6 (C)**) is identical to the first case but with the most reactive position being adjacent to the methoxyl group.
Reaction of dodecyl aldehyde (1 equiv.) with 3-methoxyphenol (10 equiv.) in dichloromethane and boron trifluoride etherate (2 equiv.) afforded a mixture containing two major products (see **Section 2.8.15**). The two compounds, which were formed in approximately equal quantities, had alkyl signals in the proton n.m.r. commensurate with the expected condensation reaction. The aryl region of the most polar material appeared to contain four doublets, two doublet of doublets and two phenolic singlets indicative of the dimer with no plane of symmetry (**199**, **Figure 2.8**). As expected, the spectrum also contained two methoxyl signals of equal intensity and a single methine triplet. The second dimeric material clearly contained a plane of symmetry having only two aryl doublets, one doublet of doublets, one phenolic singlet and a single methoxyl signal. Confirmation of the symmetry was obtained from the ^{13}C n.m.r. which contained only six aryl signals. This would indicate the compound to be either dimer **200** or **201** (**Figure 2.8**). The NOESY spectrum of the product (**Figure 2.9**) shows cross peaks for the OH – CH interaction as would be expected for **200** as opposed to the OMe – CH interaction that would be expected for dimer **201**. There are also substantial NOE interactions between the methoxyl and two of the aryl protons indicating that the site of condensation must be adjacent to the phenol.

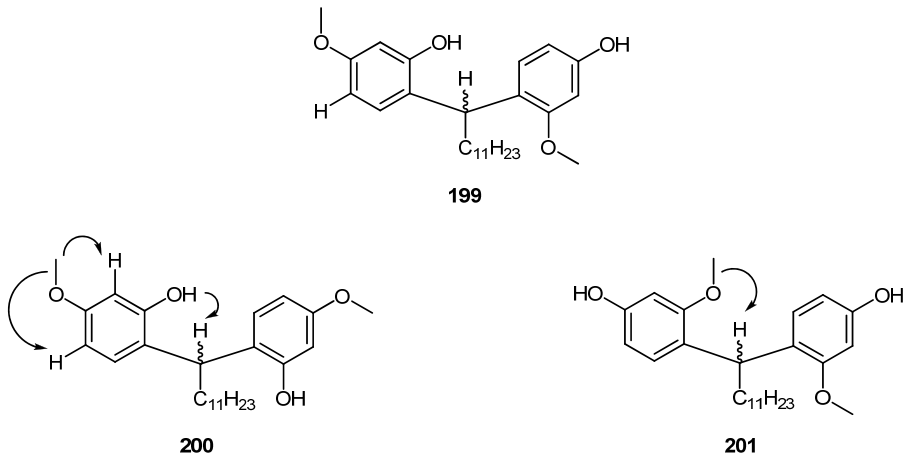


Figure 2.8 – Products for the condensation of dodecyl aldehyde with ten mole equiv. of 3-methoxyphenol and some important NOE interactions.

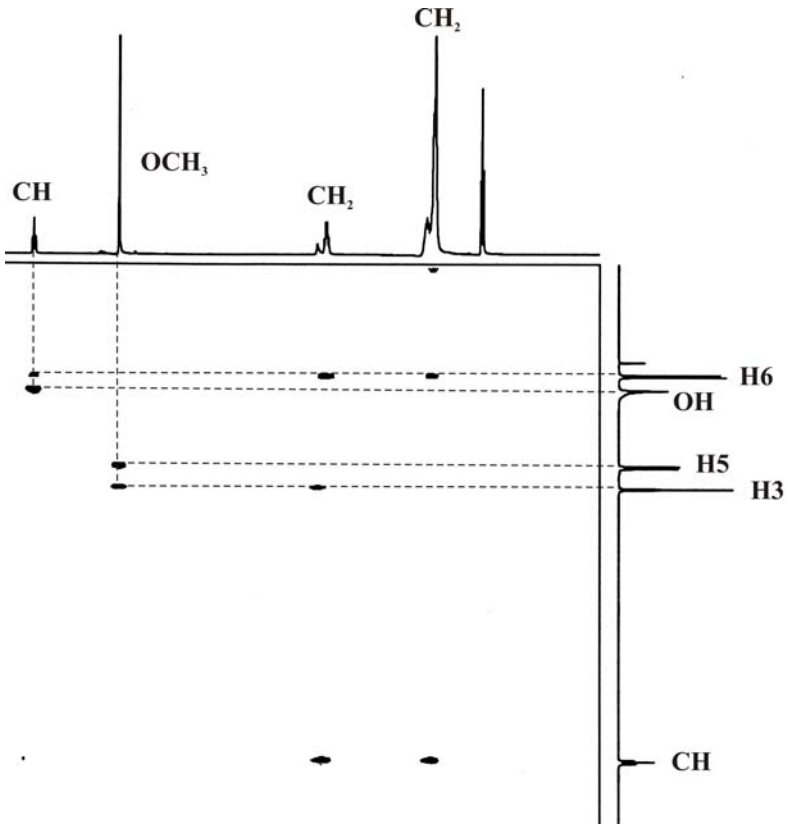


Figure 2.9 – Partial NOESY spectrum of dimer **200**

The formation of both dimers in the presence of excess 3-methoxyphenol in almost equal amounts clearly indicates that the condensation of the intermediate **197** with 3-methoxyphenol is not particular to either the four or six position. Thus the mechanism of regioselective resorcinarene formation must necessarily rely on the rapid and regioselective formation of intermediate **197** followed by subsequent condensations.

The preparation of the C_4 dissymmetric resorcinarenes is not only regioselective but also appears to be completely stereoselective. Unlike the preparation of the achiral resorcinarenes, no stereoisomers were observed either in the reaction mixture or the recovered product. The rapidity of the reaction must indicate that the product is the result of kinetic control, however, it is likely that the kinetic and thermodynamic products are identical in this case. One possible reason for this may lie in the structure of the intermediate and the solvent in which the reaction is performed. In previous syntheses of achiral resorcinarenes the primary and secondary intermediates have been determined to be of the form **202** and **203** by n.m.r spectroscopy.[93]

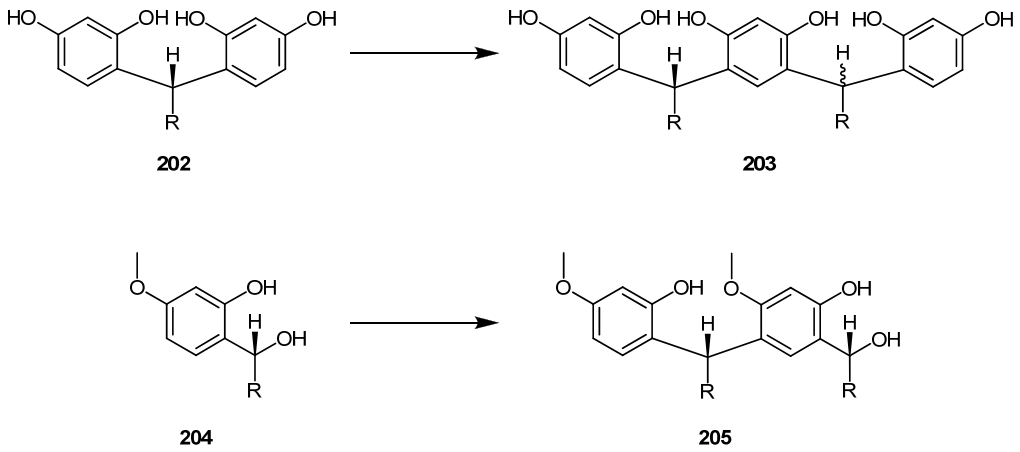


Figure 2.10 – Intermediates in the preparation of achiral and chiral resorcinarenes.

The condensation of the intermediate **202** with one mole of additional aldehyde and resorcinol may occur to give two distinct diastereoisomers of **203** depending on the approach of the incoming resorcinol to the reactive centre. This and subsequent condensations have been argued as the origin of the resorcinarene stereoisomers. One might presume this would be the case for the C_4 dissymmetric resorcinarenes, however no stereoisomers are observed. The most likely conclusion is that the condensation of **204** to give the corresponding dimer **205** must occur in either a highly diastereoselective manner, or through rapid epimerisation of the intermediate secondary benzylic alcohol **206** (in the presence of $BF_3.Et_2O$) so as to afford a single diastereomer (**205**) as shown below (**Figure 2.11**).

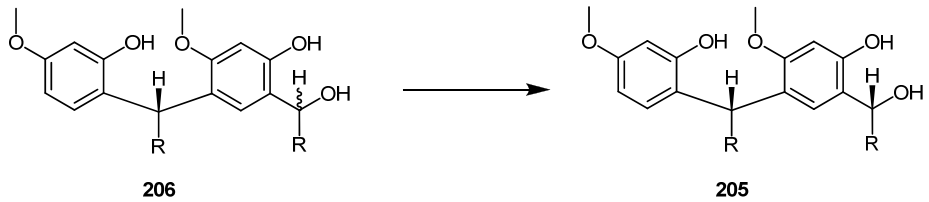
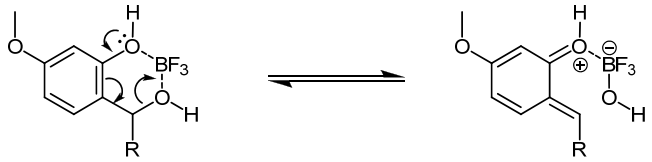


Figure 2.11 – Epimerisation of reaction intermediate **206** to give the single diastereomer **205**.

In either case, it is reasonable to assume that the boron trifluoride is, in some manner, templating the formation of a particular diastereomer. This templating effect would

also be relevant to the diastereoselective reaction of quinone methide intermediates which have been implicated in the formation of the calix[n]arenes.[111] The equilibrium interconversion of the boron trifluoride complex of compound **204** (complex **207**) and the quinone methide **208** may also account for the presumed large difference in reaction rate between the initial formation of the hydroxyalkyl intermediate **204** and its subsequent reaction to form the oligomer **206**. Reversion to the complex **207** is likely to be favoured on average due to the relative proximity (and bulk presumably) of the $[BF_3OH]^-$ anion.



207 **208**

Figure 2.12 – Formation of a potential quinone methide intermediate (**208**)

A distinct deep red colour, which may be associated with the quinone methide intermediate, is formed immediately on combining the reactants.
Initially, the reaction to form C_4 dissymmetric resorcinarenes was performed in chloroform solution. However, it was discovered that when a source of chloroform containing a small percentage of ethanol as stabiliser was used, the reaction no longer produced a single product. A series of test reactions using dodecanal and 3-methoxy phenol in the presence of three equivalents of boron trifluoride and varying quantities of ethanol in the reaction medium (DCM), were conducted. The results are summarised in **figure 2.13** where it is evident that the increasing quantity of ethanol results in a relative increase in signals not associated with the desired cylcomeric product. It was postulated that the deleterious effect of the alcoholic contaminant may be a direct result of the coordination to the boron trifluoride catalyst in direct competition with the other reactants thereby reducing the effective quantity of boron trifluoride available for the primary reaction pathway. This hypothesis was tested by performing the identical reaction, this time in the presence of a soluble anion with which boron trifluoride may associate in the dichloromethane solution. Thus the reaction of 3-methoxyphenol and dodecanal with boron trifluoride etherate was performed with the addition of one mole equivalent of anhydrous

tetraethylammonium chloride. The resulting n.m.r. spectral data is shown in **figure 2.14,** the features of which bear a striking resemblance to the spectra of **figure 2.13**.

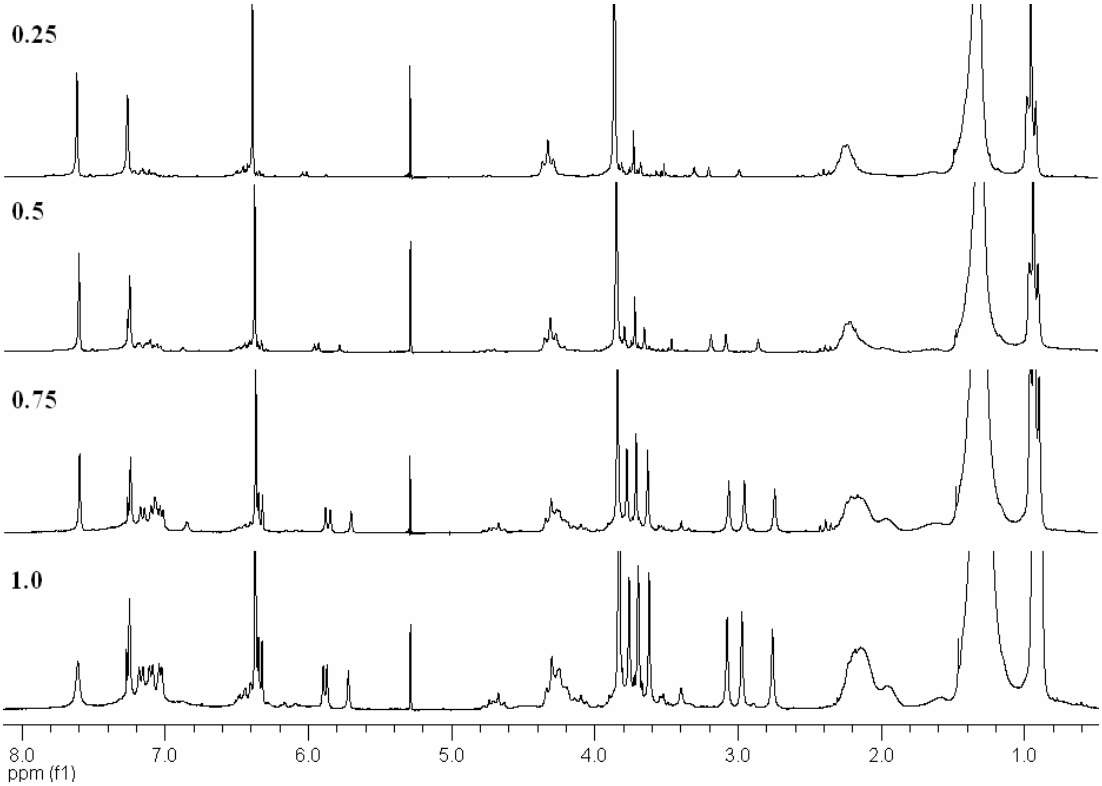


Figure 2.13 – The effect of 0.25, 0.5, 0.75 and 1.0 mole equivalents of ethanol on the condensation of dodecanal with 3-methoxyphenol in the presence of boron trifluoride etherate.

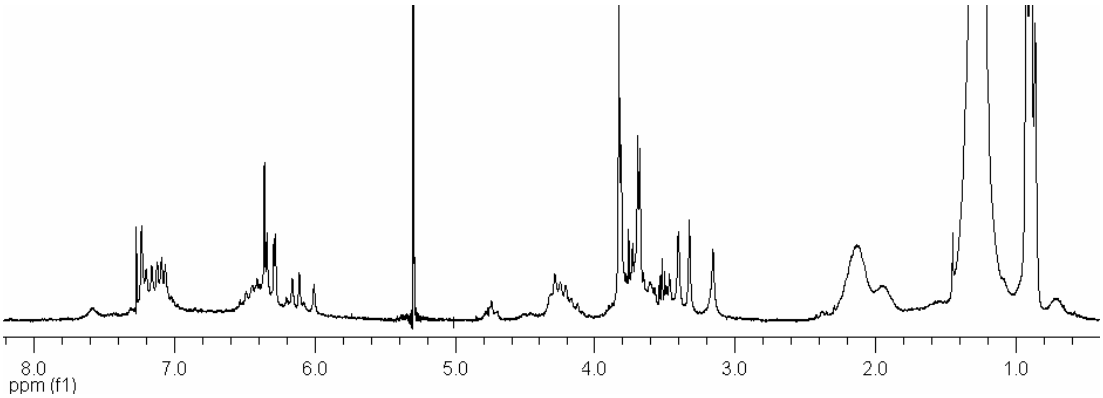
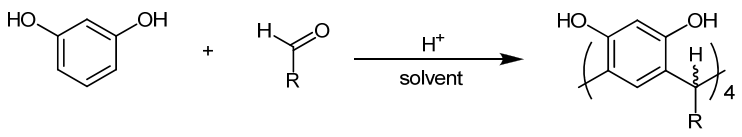


Figure 2.14 – The effect of 1.0 mole equivalents of tetraethylammonium chloride on the condensation of dodecanal with 3-methoxyphenol in the presence of boron trifluoride etherate.

The identity of the resulting materials formed in the presence of either contaminant was not determined, however it is presumed several acyclic oligomers are the likely constituents.

2.2 Alkylation of the octahydroxy resorcinarenes

The preparation of the C_4 dissymmetric resorcinarenes has only proven to be effective with alkyl aldehydes (see **section 2.0**). However, the preparation of the achiral octahydroxy- resorcinarenes with a variety of alkyl and aryl aldehydes (see **Scheme 2.4**, **209** – **216** for examples) is well established and requires relatively inexpensive reagents.[105, 112-115] A method for regio-selective alkylation of four of the hydroxyl groups would provide a useful alternate route to the C_4 dissymmetric resorcinarenes with greater potential for functionality at the methine. Previous studies on Williamson alkylation[116] of the phenolic hydroxyls have generally attempted per-alkylation.[117-120] However, Konishi *et. al*. have mono-alkylated with *p*-methylbenzyl bromide to give a mixture of enantiomers[40] (see **section 1.1.2**). Regioselective tosylation to give the C_{2v} tetra-tosylate was also obtained by Shivanyuk.[86]



	R		R
209	CH_3	**213**	C_6H_{13}
210	C_2H_5	**214**	$C_{11}H_{23}$
211	Pr^i	**215**	Ph
212	Bu^i	**216**	*p*-BrPh

Scheme 2.4 – Selected literature examples of the achiral resorcinarenes.

Alkylation of the *C*-undecylcalix[4]resorcinarene **214** with potassium carbonate and four equivalents of methyl iodide or methyl tosylate produced intractable mixtures. Conceivably this was comprised of all the possible methylated resorcinarenes from the mono- to the octa-methyl ether and all regioisomers therein. Similar results were obtained with sodium hydride as the base in dimethylformamide. It was thought that application of a more hindered alkylating agent may produce a more selective reaction. However, the significantly more sterically hindered 2-bromopropane produced a mixture of over ten compounds (by t.l.c.) which appeared to be a combination of di- and tri-ethers from proton n.m.r. integration values.

Although these preliminary results are not very promising, reaction of the octahydroxy resorcinarenes with an even larger group such as *t*-butyldimethylsilyl chloride,[86] *t*-butyldiphenylsilyl chloride[121] or trityl chloride under standard conditions[122] may produce the desired selectivity.

2.3 Physical and spectroscopic properties of the C_4 resorcinarenes

All of the racemic C_4 dissymmetric tetramethoxyresorcinarenes prepared are crystalline solids with melting points greater than 120 ˚C. The melting points decrease roughly linearly with respect to increasing chain length at the methine carbon. The tetrapropoxyresorcinarenes have significantly lower melting points compared with their tetramethoxy analogues. This is unsurprising as the longer chain materials appear more wax-like with increasing chain length. The mass spectra of the *C*-heptyl-tetramethoxyresorcinarene (**156**) and the *C*-undecyl-tetramethoxyresorcinarene (**157**) contain parent ions of $M^+ = 936.6$ and $M^+ = 1161.0$ respectively, corresponding to the molecular weight of the expected tetramers. The spectra for the two compounds are exceptionally similar with very few significant fragments. The base peak in each spectrum corresponds to the loss of a single alkyl chain, presumably resulting in an ion of the type shown in **Figure 2.15** (**A**). The two remaining major mass fragments appear to be a result of at least two carbon-carbon bond cleavages to give ion (**B**) (m/z 457, n = 11; m/z 345.3, n = 7) which is likely present as the stabilised tropylium ion (**C**). Further fragmentation then gives the third major fragment (**D**) (m/z 303, n = 11; m/z 247.2, n = 7).

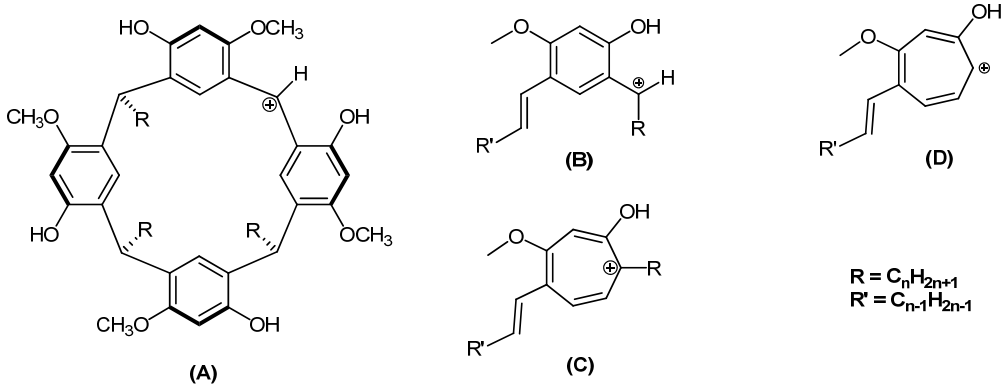


Figure 2.15 – Postulated structures for observed ions in the mass spectra of C_4 dissymmetric resorcinarenes.

The ^{1}H n.m.r. characteristics of the tetramethoxy compounds are substantially similar. The 8 – 3 ppm region is identical in all cases, the only variation in the spectra being in the up-field alkyl region. The aromatic region contains 2 signals at ~7.23 and ~6.35 corresponding to the lower and upper rim aromatic protons respectively and one phenolic signal at ~7.54 (determined by the addition of D_2O). Based on the n.m.r. spectral pattern, the structures that we initially had to consider, were either the C_4 dissymmetric isomers (**217, Figure 2.16**) or the S_4 stereoisomers (**218**) since all the other possible isomers have lower symmetry.

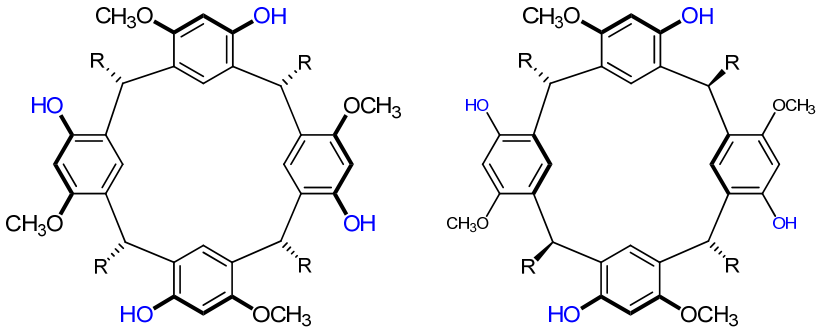


Figure 2.16 – Two structures which would fit the obtained n.m.r. spectroscopic data.

The differences in the chemical shifts for the majority of signals for each of these isomers are not likely to be very significant. The methine signals may vary somewhat due to their positions with respect to the adjacent aromatic rings. The C_4 isomer methine hydrogens are in a pseudo-equatorial position with respect to the resorcinarene annulus, whereas the S_4 isomer methine hydrogens are apparently midway between a pseudo-axial and pseudo-equatorial position. This bears resemblance to the difference of the calix[4]arene methylene hydrogens in the cone and 1,3-alternate conformations.[111] Thus the methine signal for the stereoisomer **218** should appear somewhat downfield from the C_4 isomer (**217**) methine. The structures of the resorcinarenes have been proven conclusively by X-ray crystallography to be of the type **217** and are described in **section 2.5**.

2.4 Chirality of the resorcinarenes

The crown stereoisomers of the parent octahydroxy resorcinarenes such as *C*-methylresorcin[4]arene, ideally have C_{4v} symmetry. Indeed, in solution they appear to have an average C_{4v} symmetry, while in the solid phase they are generally significantly distorted from the ideal. In the case of the resorcinarene tetramethyl ethers the vertical mirror planes have been destroyed and the methoxyl (or hydroxyls) all point in the same direction about the axis of symmetry. Thus, these compounds (again, in solution), have an average C_4 dissymmetry. The nature of the enantiomeric mixture was demonstrated first by ^{1}H n.m.r spectroscopy in the presence of the chiral shift reagent tris[3-(heptafluoropropyl hydroxymethylene)-(+)-camphorate. As shown in **figure 2.17** the phenolic and aromatic signals clearly split into two peaks of equal area in the presence of the shift reagent signifying the compound is racemic. Addition of the chiral quaternary ammonium salt (*R*)-(α-methylbenzyl)trimethylammonium iodide (see **section 2.8.28**) to an n.m.r. sample of **156** failed to show any interaction.

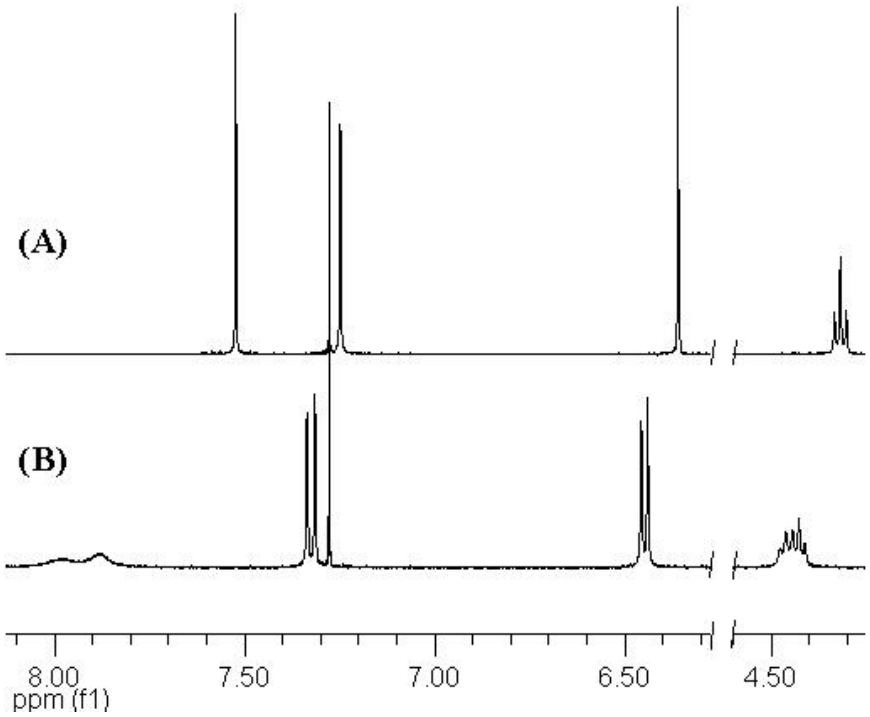


Figure 2.17 – ^{1}H n.m.r. spectra of **(A) 156** and **(B) 156** with tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorate

Enantioselective HPLC of the *C*-heptylresorcinarene (**156**) on a Daicel ChiralPak AD column (**Figure 2.18**) afforded only partial separation of the enantiomers. However, this did also confirm that the mixture was racemic.

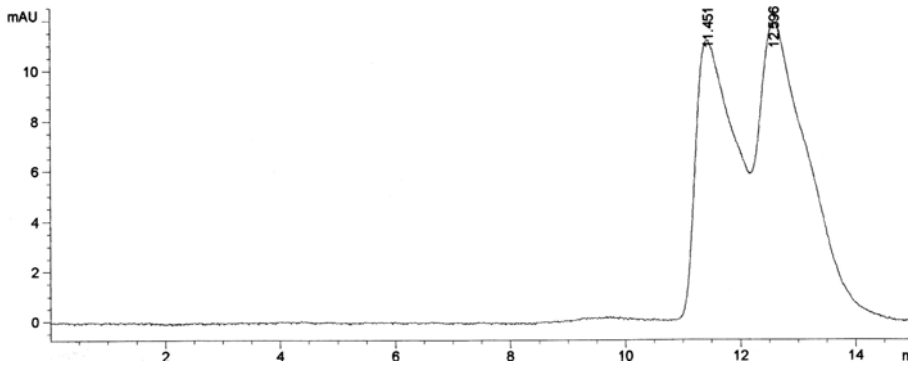


Figure 2.18 – HPLC of the *C*-heptylresorcinarene (**156**) on a Daicel ChiralPak AD column.

2.5 Structure of the resorcinarenes

The first structural determination of a resorcinarene was supplied by Erdtman and co-workers.[105] Gutsche, indicated in 1989 that for all of the symmetric parent resorcinarenes no crystal structures had been obtained without first preparing a derivative of some kind[114] (i.e. the octaacetate). However, many examples[123–126] of the parent structures have since been obtained. The C_4 dissymmetric resorcinarenes are effectively tetra-functionalised versions of the octahydroxy resorcinarenes and as such did not suffer the difficulties initially associated with structural characterisation of those molecules. Conversely, while obtaining single crystals suitable for X-ray crystallographic determination was not problematical, the structures were generally obtained as solvates and the inclusion of solvent in the lattice frequently complicated microanalysis results.

A single crystal of x-ray quality was obtained for **156** (**figure 2.19**) by diffusion of methanol into a solution of **156** in tetrahydrofuran. The unit cell contains two molecules of **156** each with an accompanying molecule of tetrahydrofuran which is engaged in hydrogen bonding with one phenolic hydroxyl. The remaining hydroxyls are hydrogen bound intramolecularly with adjacent methoxyls. A single molecule of

156 and associated THF comprise the asymmetric unit consistent with its crystallisation in the centrosymmetric triclinic space group $P\bar{1}$. The crystal packing is of interest with the alkane "tails" associated in a somewhat interlocking fashion. The macrocycles are also aligned with alternating rows of either enantiomer facing opposite directions creating a bilayer-like structure.

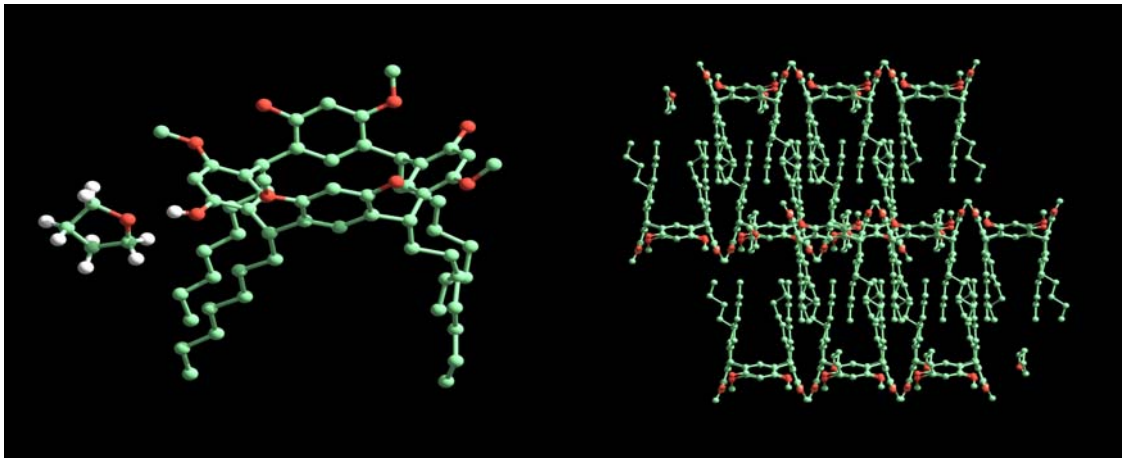


Figure 2.19 – Single crystal X-ray structure of *C*-heptyl-tetramethoxy calix[4]resorcinarene (**156**) shown with associated THF molecule (note: a larger version of the packing diagram is given in **Appendix 1**).

These bilayer structures appear to be typical of the octahydroxyresorcinarenes and are also associated with sometimes heavy interdigitation of the alkyl tails. The structure of the *C*-undecyloctahydroxy resorcinarene (**214**) is well known as both the ethanol[123] and dimethylformamide[126] solvates. In both of those structures the maximum number of intramolecular hydrogen bonds (4) are observed, leaving the remaining four hydroxyls to form intermolecular hydrogen bonds. Surprisingly, these available hydrogen bond donors are not engaged directly with any other resorcinarene bowl but are bridged by the solvates contained between the layers. This is also the case for resorcinarene **156**, for which all of the hydroxyl groups participate in an intramolecular fashion (O...H contact lengths; 2.134 Å, 2.341 Å, 2.224 Å) or intermolecularly with the associated tetrahydrofuran (O...H contact length 1.958 Å). The resorcinarene “bowl” deviates from the ideal “crown” conformation. The inclination of the plane of the aromatic rings measured with respect to the plane defined by the four methines of the resorcinarene skeleton are 106.6 º, 151.5 º, 103.9

º and 147.2 º. Thus the oppositely facing aromatic rings have inclinations of similar but not identical magnitude. Similarly calculated angles for the parent octahydroxy resorcinarenes described by Hibbs *et al*.[123] and Pietraszkiewicz *et al*.[126] are within the range of 107-140º indicating a somewhat less "pinched" crown conformation. The slightly pinched structure of **156** is likely due to the decrease in hydrogen bond interactions and the larger steric bulk of the methoxyl groups (relative to a hydroxyl group). In particular, the oppositely facing arenes with the steepest inclination (147.20 º and 151.50 º) differ in that one is engaged in two intramolecular $ArO(CH_3)$...HO hydrogen bonding interactions and the latter in only one intramolecular $ArO(CH_3)$...HO interaction and one intermolecular R(R)O...HO hydrogen bond with tetrahydrofuran solvate. Because the inclination of the latter arene is not maintained by participation in hydrogen bonding intramolecularly the ring is able to "flatten" with respect to methine plane.

A single crystal of **192** of x-ray quality was obtained (**figure 2.20**) by slow evaporation of solvent from an *n*-propanol - dichloromethane solution of **192**. The unit cell contains two molecules of **192** each with an associated *n*-propanol engaged in hydrogen bonding with a methyl ether in this case. While **156** and **192** are dissimilar only in the length of the alkyl chains (by two carbons) and both crystallise in the $P\bar{1}$ space group, the packing arrangement differs significantly. Again a bilayer type structure is manifest, however a head to head interaction with methoxyls impinging on the cavity of opposing enantiomers in a mutual fashion is evident.

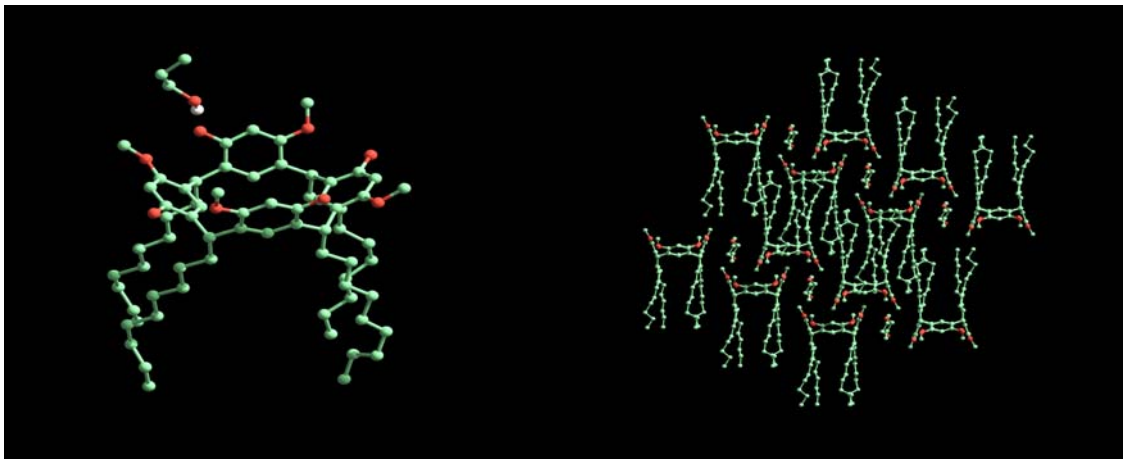


Figure 2.20 – Single crystal X-ray structure of *C*-nonyl-tetramethoxy calix[4]resorcinarene (**192**) shown with associated *n*-propanol molecule (note: a larger version of the packing diagram is given in **Appendix 2**).

The hydrogen bonding interactions for **192** are rather different to that of the previous structures. Two phenols on oppositely facing aromatic rings are engaged in intramolecular hydrogen bonds to an adjacent methoxyl group (H...O contact lengths 1.937, 2.060 Å) in a similar manner to that found in the solid state for **156**. However, one of the remaining two hydroxyl groups forms an intermolecular hydrogen bond with the oxygen atom of the associated propanol solvate (H...O contact length of 1.919 Å) and the second hydroxyl group does not appear to engage in any significant interaction at all. The resorcinarene-propanol-resorcinarene interactions form a hydrogen bonded cluster. Curiously, the conformation of the resorcinarene is closer to the ideal "crown" than **156**, despite the fact that there is one fewer favourable intramolecular hydrogen bond. The inclinations of the aromatic rings with respect to the plane defined by the four methines are 106.2 º, 150.9 º, 106.5 º and 145.5 º.

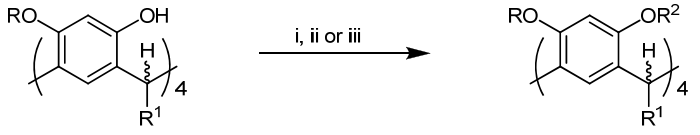
2.6 Functionalisation of the resorcinarene phenols

Unfunctionalised resorcinarenes such as the *C*-undecylcalix[4]resorcinarene **214** have found application for the selective complexation of certain polyhydroxy compounds[127] or the stereochemical assignment of chiral guests.[128] However, in general, the octahydroxyresorcinarenes require further functionalisation to achieve their potential as molecular scaffolds. To that end, the general reactivity of the

phenolic functionality requires some assessment.

2.6.1 Formation and structure of the resorcinarene esters

The preparation of the *C*-methyl-tetramethoxyresorcin[4]arene tetraacetate (**189**) was necessitated by the problems encountered purifying the parent *C*-methyl-tetramethoxyresorcin[4]arene as described in **section 2.0**. The acetylation was achieved by applying standard acetic anhydride/pyridine conditions[129] (**Scheme 2.5**) (see **section 2.8.8**).



	R	R^1	R^2
189	CH_3	CH_3	Ac
219	CH_3	C_3H_7	Ac
220	CH_3	C_7H_{15}	Ac
221	CH_3	$C_{11}H_{23}$	Ac
222	CH_3	C_7H_{15}	Bz
223	CH_3	C_7H_{15}	Ts

Scheme 2.5 - C_4 dissymmetric resorcinarene derivatives, i) Ac_2O, pyridine, ii) BzCl, TEA, DCM, iii) NaH, TsCl, THF.

These conditions were also applied smoothly to **190**, **156** and **157** to afford the corresponding *C*-propyl- (**219**), *C*-heptyl- (**220**) and *C*-undecyltetramethoxyresorcin[4]arene tetraacetates (**221**). Initial attempts to esterify **156** using acetyl chloride and triethylamine in dichloromethane strangely only provided complex mixtures.

Conversly, benzoylation of **156** with benzoyl chloride and triethylamine in refluxing dichloromethane[130] easily afforded the tetrabenzoate (**222**), while **156** was unreactive to benzoyl chloride in pyridine.[131]

Preparation of the tetra-toluenesulfonyl ester of **156** (**223**) was best effected with NaH as base in tetrahydrofuran solvent.[132] The use of toluenesulfonyl chloride in dichloromethane with pyridine[133] or dimethylaminopyridine as base required long reaction times and gave complex mixtures.

A single crystal of the acetate **189** (**figure 2.21**) was obtained by slow evaporation of solvent from a methanol - dichloromethane solution of **189**. Like resorcinarenes **156** and **192**, the tetraacetate **189** has crystallised in the $P\bar{1}$ space group, however without any associated solvent molecules. The interaction between the calix rims

occur to a less significant extent than previous structures. Presumably this is due to the lack of capacity for hydrogen bonding interactions and the additional steric bulk of the acetates. However, the packing is still organised in an interlocking manner producing a bilayer arrangement with resorcinarenes of opposing chirality. The crown conformation is significantly "pinched" with respect to the unprotected resorcinarenes. The structure is so distorted from the ideal crown conformation that the arenes more perpendicular to the methine plane are in fact past the perpendicular with angles of 88.71 º and 88.76 º. The remaining two benzene rings are so "flattened" as to be close to parallel with the methine plane with angles of 172.53 º and 171.21 º. This is a common feature of the protected resorcinarenes and is no doubt due to the steric bulk of the adjacent groups on the phenolic oxygens coupled with loss of hydrogen bonding interactions about the upper rim.

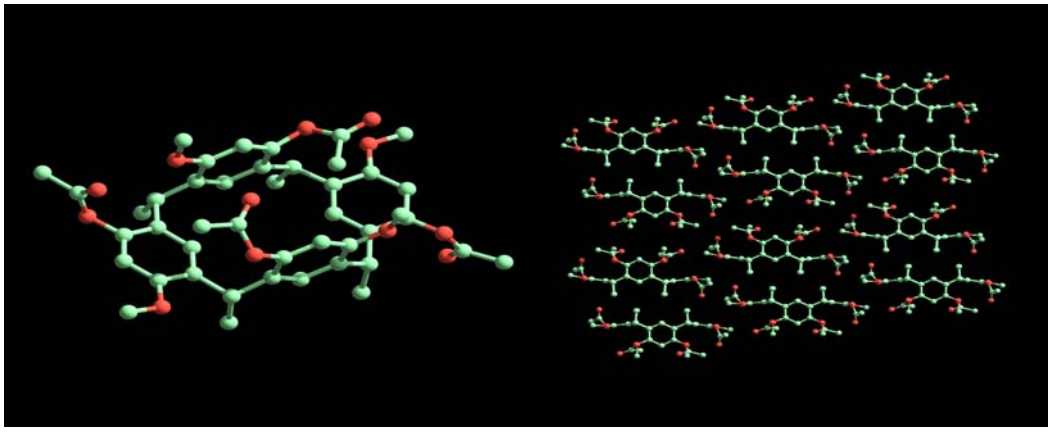


Figure 2.21 – Single crystal X-ray structure of *C*-methyl-tetramethoxycalix[4] resorcinarene tetraacetate (**189**) (note: a larger version of the packing diagram is given in **Appendix 3**).

A single crystal of x-ray quality was obtained for **219** (**figure 2.22**) by slow evaporation of solvent from a methanol - dichloromethane solution of **219**. Unlike the previous structures **219** crystallised in the $P2_1/c$ space group with four resorcinarene molecules in the unit cell. The asymmetric unit comprises of a single molecule of **219** with an associated dichloromethane molecule partially included within the calix, a common feature for the calixarenes.[134] Interestingly, while the alkyl chains are once again intermingled with resorcinarenes of opposite stereochemistry, the packing in this case is strikingly different from the previous

bilayer arrangements. Instead, an interlocking framework is evident with molecules essentially at right angles with a methoxyl of one protruding into the cavity of the adjacent calix.

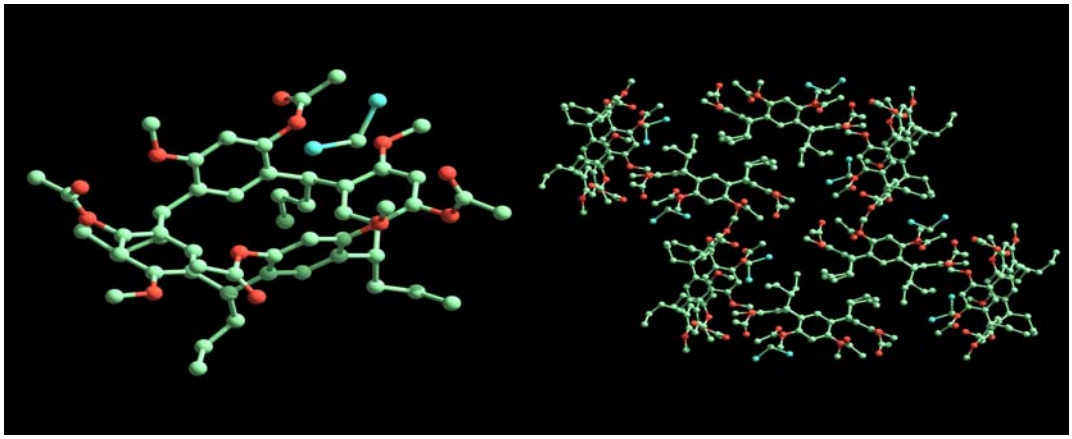
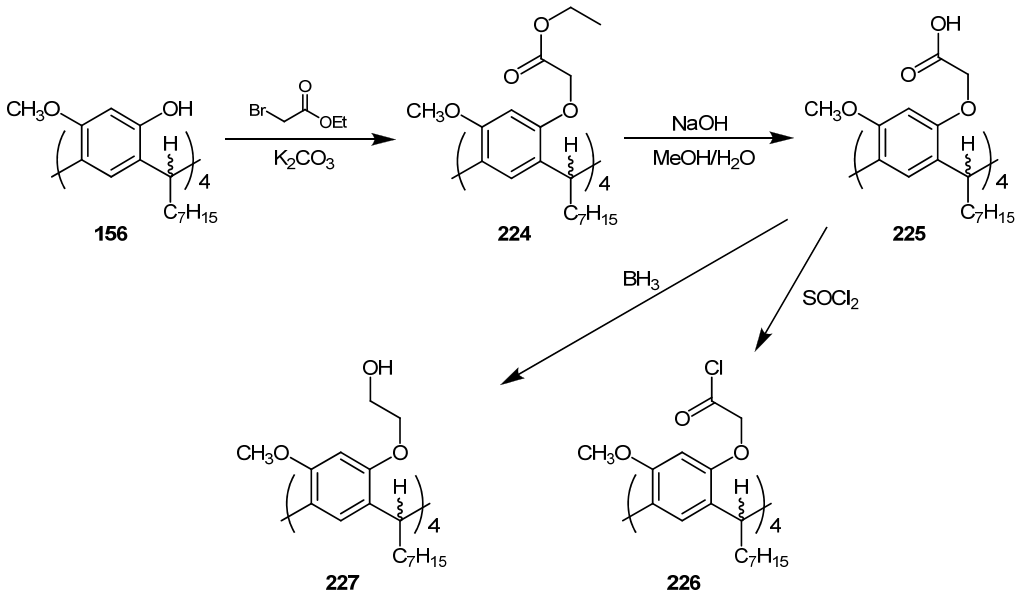


Figure 2.22 – Single crystal X-ray structure of *C*-propyl-tetramethoxy calix[4]resorcinarene tetraacetate (**219**) shown with associated dichloromethane molecule (note: a larger version of the packing diagram is given in **Appendix 4**).

Once again the conformation is somewhat pinched due to the steric bulk of the acetates. However, the acetates are directed outwardly from the bowl and as such the effect is minimised, resulting in benzene ring inclinations of 107.73 º, 159.89 º, 101.54 º and 161.95 º.

2.6.2 Alkylation of the C_4 dissymmetric resorcinarenes

The reaction of an α-haloester such as ethyl bromoacetate with resorcinarenes[135-136] and calixarenes[137-138] is a frequently applied methodology for incorporation of a "flexible" functional group. The ester-ether moiety is readily attached via a simple Williamson ether synthesis and the facile hydrolysis of the ester to the acid has been applied in some instances to enhance water solubility.[139] The acid is a particularly useful intermediate from which compounds such as the glycol monoether and the acid chloride may be obtained. The acid chloride is a very useful functionality indeed, upon which a number of divergent transformations may be effected.[140] Reaction of **156** (**scheme 2.6**) with ethyl bromoacetate and anhydrous potassium carbonate in acetone solvent afforded **224** as a colourless solid.



Scheme 2.6 – Synthesis and transformations of the resorcinarene tetraester **224**.

The proton n.m.r. spectrum of the tetraester was as expected. Addition of the chiral shift reagent tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorate, did not result in splitting of the signals. As **224** failed to rotate the plain of polarised light it was assumed that the particular shift reagent used was ineffective in this case and the product was indeed racemic.

A single crystal suitable for x-ray analysis was obtained by slow evaporation of solvent from a methanol – dichloromethane solution of **224**. Surprisingly, the x-ray data revealed that the structure was in fact that of the tetra-methyl ester (**Figure 2.23**), rather than the expected tetra-ethyl ester.

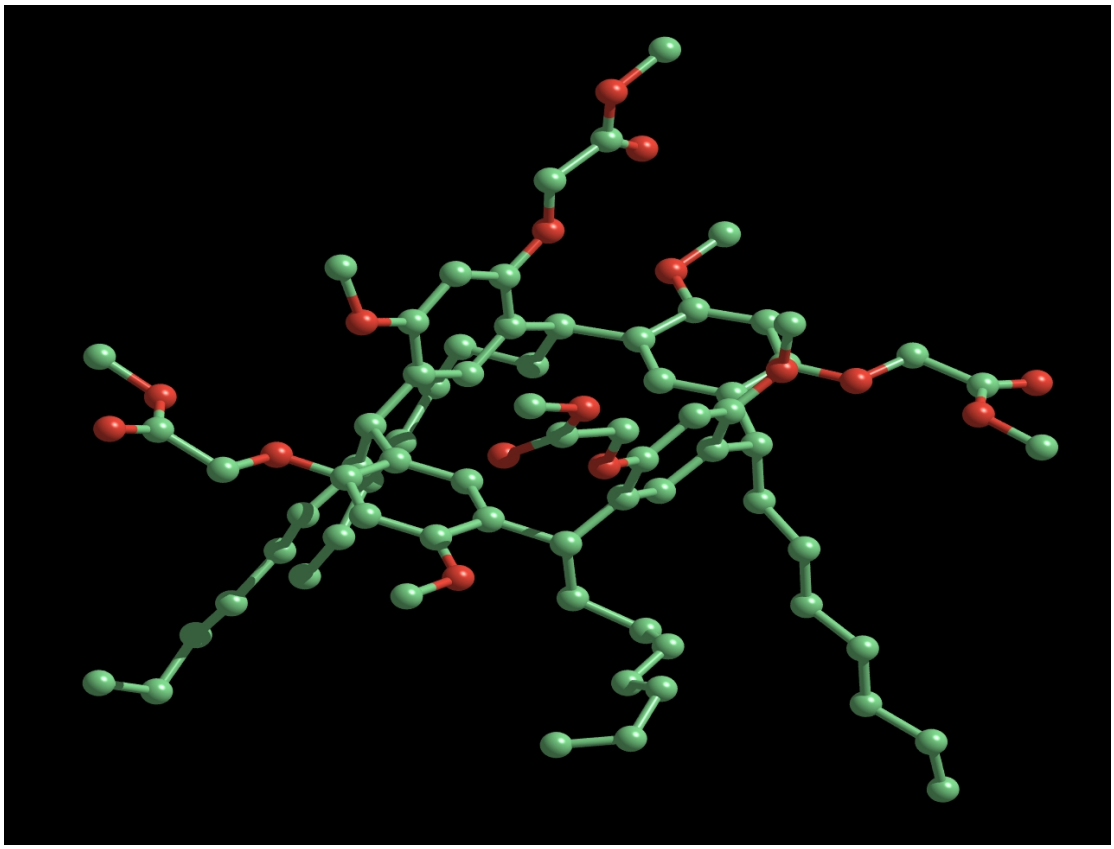


Figure 2.23 – Single crystal X-ray structure of *C*-heptyl-tetramethoxy calix[4]resorcinarene tetramethyl-ester (note: The packing diagram is given in **Appendix 5**).

Presumably, the formation of the tetra-methyl ester is due to a trace of acid in the methanolic crystallisation medium, causing a gradual transesterification to occur. The equilibrium may have been driven by the tetra-methyl ester being less soluble in that solvent mixture. The methanol solution of **224** was stable for approximately one week before crystallisation occurred. The structure of **224** proper could not be obtained as it would not crystallise favourably from any other solvent (including ethanol-based) mixture in our hands.

Hydrolysis of the ester to the tetra-acid **225** (**scheme 2.6**) proceeded smoothly in the presence of sodium hydroxide/methanol/water. Hydrolysis with sodium hydroxide/water alone was very slow due to the lipophilicity of **224**.

The tetra-glycolether **227** is also a very interesting intermediate. It has the potential for further functionalisation in the form of crown ethers. Chiral crown ethers have been used for the enantioselective transport of amines[141] amino acids[142] and in chiral

chromatography.[143] Reduction of the tetra-acid **225** with borane-dimethylsulfide afforded the tetrol in good yield. This could equally well have been achieved using lithium aluminium hydride on either the acid **225** or the ester **224.**

The tetra-acid was significantly soluble in alkaline solution and demonstrated a potential for application as a surfactant. Calixarene and resorcinarene surfactants have already been investigated.[144 - 151] Chiral surfactants have been applied to a variety of systems including enantio-discriminating n.m.r. solvent additives,[152-153] enantioselective reduction of prochiral ketones with sodium borohydride[154] and chiral capillary electrophoresis.[155-156]

To that end it was deemed prudent to evaluate the critical micelle concentration (CMC) of the model racemic surfactant with a view to future use of the enantiopure acid.

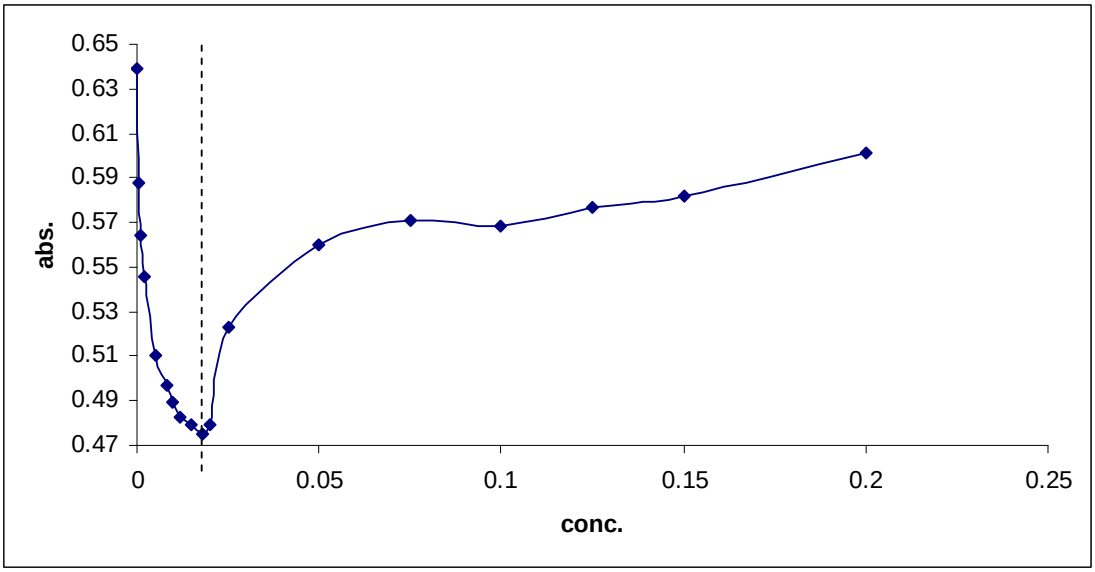


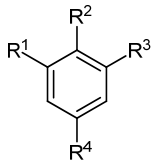
Figure 2.24 – Plot of concentration of **225** (acid form) vs absorbance of methylene blue indicator.

Determination of the UV-Vis absorbance for methylene blue indicator[157-158] at a range of concentrations of **225** revealed a critical micelle concentration of approximately 1.8 x 10^{-2} mol L^{-1}. This value is reasonable considering the resorcinarene alkyl chains are comparatively short when compared to typical anionic surfactants such as sodium dodecyl sulfate (CMC ~ 5 x 10^{-3} mol L^{-1}). Also, the CMC has been shown to increase with decreasing chain length.[159] It is well known that

cationic dyes such as methylene blue form ion-association complexes with anionic dyes below the CMC.[160-161] The steep decrease in the apparent absorbance of methylene blue below the CMC is likely due to association of the dye with the increasing concentration of anionic resorcinarene surfactant. Potentially this may involve incorporation of the dye in the calix of the resorcinarene, however, no substantial evidence for this is available.

2.7 Synthesis of C_4 dissymmetric resorcinarenes using other aromatics

In order to determine how generally applicable the boron trifluoride / dichloromethane system is for the preparation of resorcinarene like molecules, the reaction of a number of arenes in the presence of an alkyl aldehyde, was investigated. The aromatic species chosen are shown in Figure **2.25** below. These have been chosen on the basis of relative activation of the arene, substitution pattern and availability.



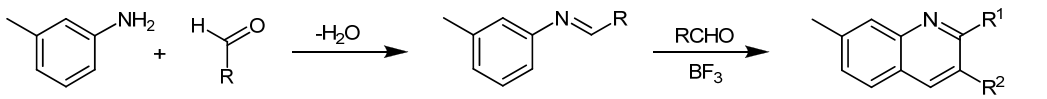
	R^1	R^2	R^3	R^4		R^1	R^2	R^3	R^4
228	CH_3	H	OH	H	**237**	OH	H	NH_2	H
229	CH_3	H	OCH_3	H	**238**	OCH_3	H	NH_2	H
230	Ph	H	OH	H	**239**	CH_3	H	NH_2	H
231	Br	H	OH	H	**240**	OH	H	NHAc	H
232	H	H	OCH_3	H	**241**	OCH_3	H	NHAc	H
233	H	H	OH	H	**242**	CH_3	H	NHAc	H
234	H	Bz	OH	OH	**243**	OH	H	NHPiv	H
235	H	Br	OH	OH	**244**	NHAc	H	NHAc	H
236	H	CH_3	OH	OH	**245**	NHCOPr	H	NHCOPr	H

Figure 2.25 – Arenes subjected to the boron trifluoride protocol for C_4 dissymmetric resorcinarene formation.

Initially, the condensation reaction was attempted with a suite of *meta* substituted phenols or phenol ethers (**228** – **231**) and monosubstituted arenes (**232** – **233**). It quickly became evident that the *meta* substituted arenes, although possessing the same activation pattern and not any particularly deactivating functionality, were simply not activated enough for the reaction to proceed effectively. The arenes were returned intact and the octanal had been completely consumed by the aldol condensation process catalysed by the Lewis acid to afford **194** (see **section 2.0**). The only exception to this was *m*-cresol (**228**) which gave a complicated mixture, no

doubt a result of poor reaction selectivity and some aldol condensation material. The monosubstituted arenes (**232** – **233**), while reactive, completely lacked any selectivity and only afforded complex mixtures. Attempts to prepare more calixarene like macrocycles with hydroxyls at the lower rim with phenols **234** – **236** were unsuccessful. It is perhaps surprising that despite the fact bromoresorcinol **235** is quite electron rich, it gave no reaction at all.

On discovering that resorcinarene formation using the current method requires more electron rich arenes than one oxygen group can provide, a further suite of nitrogen functionalised arenes (**237** – **245**) were examined. The *m*-aminophenol (**237**) appeared to be unreactive due to poor solubility in the dichloromethane solvent. An improvement in solubility was obtained with *m*-anisidine (**238**) however on addition of boron trifluoride a precipitate, which is presumably the amine-BF_3 adduct, formed and no further reaction was observed even after one week. *m*-Toluidine proved to be adequately soluble and remained so even after the addition of boron trifluoride etherate. However, this is likely due to the rapid formation of the imine **246**. The t.l.c. and proton n.m.r spectrum revealed the reaction had produced a very complicated mixture although one fluorescent product of substance was observed on the t.l.c. plate. The same reaction performed with butyraldehyde (see **section 2.8.27**) rather than octanal afforded a marginally cleaner reaction with an apparent slight increase in the fluorescent material. Isolation of the basic materials from the crude reaction mixture by extraction into acid solution and purification by chromatography yielded the quinoline **249**. The quinoline must necessarily be the result of condensation of imine **247** (**Scheme 2.7**) with a second mol equivalent of aldehyde akin to the reactions investigated by Tanaka *et. al.*.[162]

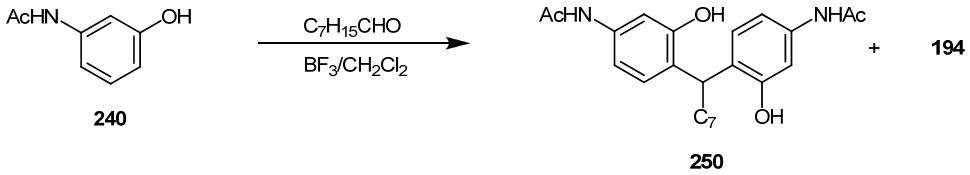


246 R = C_7H_{15}
247 R = C_3H_7
248 $R^1 = C_7H_{15}$ $R^2 = C_6H_{13}$
249 $R^1 = C_3H_7$ $R^2 = C_2H_5$

Scheme 2.7 – Substituted quinoline by-product formation in the reaction of *m*-toluidine with aldehydes.

To retard the reactivity of the amines and generally improve solubility, the amines **237** – **239** were acetylated at the nitrogen to afford the anilides **240** – **242**,

respectively. *m*-Hydroxyacetanilide (**240**) was only slightly soluble under the reaction conditions and failed to react in the desired manner. The products (**scheme 2.8**) instead comprised of starting material, aldol condensation product **194** and a small quantity of the dimer **250**. The appearance of **250** indicates that, while the reactivity of the arene is good, it is still not rapid enough to compete effectively with the aldol condensation of the aldehyde. As **240** was only partially soluble in dichloromethane, the pivaloyl amide **243** was also tested, however it too produced a similar result.



Scheme 2.8 – Condensation of *m*-hydroxyacetanilide with octanal to give the symmetric dimer **250**.

Finally the two 1,3-diamidobenzenes **244** and **245** were prepared in order to test whether an amine based resorcinarene macrocycle could be obtained by applying the boron trifluoride/dichloromethane protocol. While the products would not be chiral, the symmetry of the diamides avoids the necessity for selectivity in the aldehyde-arene condensation. Compound **244** did not react with the aldehyde however it failed to dissolve fully under the reaction conditions. The more lipophilic **245** also failed to condense favourably. Presumably, two amide moieties are not sufficiently activating to allow the condensation to occur.

2.8 Experimental

Melting points were determined on a Reichert hot stage apparatus or an Electrothermal 9100 apparatus. Nuclear magnetic resonance spectra were acquired on a Varian Gemini 2000 instrument at 200 MHz for proton and 50.3 MHz for carbon or a Bruker ARX-500 spectrometer at 500 MHz for proton and 125.8 MHz for carbon. COSY and NOESY experiments were conducted on a Bruker AV600 (600 MHz for proton and 150.9 MHz for carbon) spectrometer. Carbon assignments (where given) were made with the assistance of DEPT 135 and DEPT 90 experiments. Spectra are calibrated to their respective solvent signals: deuteriochloroform ($CDCl_3$, ^1H, δ7.27 ppm; ^{13}C, δ77.7); d_6-acetone (CD_3COCD_3, ^1H, δ2.20; ^{13}C, δ29.8 or δ206.2); d_6-dimethylsulfoxide (CD_3SOCD_3, ^1H, δ2.50; ^{13}C, δ39.5).

Infrared spectra were recorded on a Bruker Vector 22 or a Perkin-Elmer SpectrumOne FTIR spectrometer. Samples were prepared as a thin film on sodium chloride plates or by the potassium bromide disc method.

Mass spectra were recorded with a VG-Autospec spectrometer or a Jeol-SX102 using fast atom bombardment (FAB), unless specified otherwise.

Elemental microanalyses were carried out by the Central Science Laboratory, University of Tasmania, Australia.

All solvents were purified by distillation, and solvents dried according to the methods of Burfield.[163-166]

Chromatography was performed on short columns (10 - 15 cm) of Fluka silica gel 60 (230 mesh) under a positive pressure unless otherwise stated. Thin layer chromatography was on Merck silica gel 60 F_{254} aluminium backed plates. Compounds were visualised on t.l.c. by UV light (aromatics) or by spraying and heating with one or more of the following: 10 % sulfuric acid in ethanol, 10 % ammonium molybdate in 2 M sulfuric acid (general), aqueous 0.3 % ninhydrin solution (amines) or a dinitrophenylhydrazine/sulfuric acid in ethanol solution (aldehydes and ketones).

Chiral shift n.m.r. experiments were performed by stepwise addition of 0.25 mol equivalents of tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorate to an n.m.r. sample containing 20 mg of the relevant calixarene in 0.8 mL deuterated

chloroform.

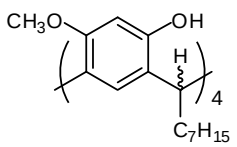
Optical rotations were determined using a Perkin-Elmer 141 polarimeter at room temperature.

UV-Vis experiments were performed on a Shimadzu Mini 1240 instrument.

HPLC was conducted using Hewlett Packard 1090 HPLC system equipped with a photodiode array detector.

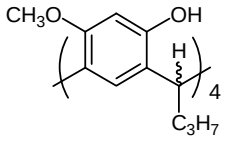
X-ray crystallography data was obtained on a Bruker SMART diffractometer or an Oxford Diffraction Xcalibur-S diffractometer.

2.8.1 2,4,6,8-Tetraheptyl-1^6,3^4,5^4,7^4-tetramethoxyresorcin[4]arene-1^4,3^6,5^6,7^6-tetrol (156)



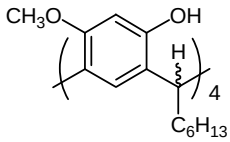
Boron trifluoride etherate (1.14 g, 8.1 mmol) was added to a stirred solution of 3-methoxyphenol (0.5 g, 4.0 mmol) and octanal (0.52 g, 4.0 mmol) in anhydrous dichloromethane (20 mL) and left to stir at room temperature (2 h). The reaction mixture was then washed with water (2 x 20 mL) and brine (1 x 20 mL), dried ($MgSO_4$) and the solvent removed at reduced pressure to give a dark red oil. The oil was crystallised from a minimum amount of hot ethanol affording pale pink plates. Recrystallisation from methanol then gave pure **156** (0.75 g, 80 %) as colourless plates, m.p. 160 °C. ^{1}H n.m.r. ($CDCl_3$) δ 0.90 (br t, 12 H, CH_2CH_3), 1.20-1.42 (m, 40 H, 5 x CH_2), 2.20 (m, 8 H, CH_2CH), 3.84 (s, 12 H, OCH_3), 4.28 (t, 4 H, J = 7.8 Hz, $CHCH_2$), 6.36, 7.23 (s, 2 x 4 H, ArH), 7.52, (s, 4 H, OH). ^{13}C n.m.r. ($CDCl_3$) δ 14.7 (CH_3), 23.2, 28.7, 30.0, 30.3, 32.5, 34.6 (CH_2), 33.7 (CH), 56.5 (OCH_3), 100.7, 124.4, 125.3, 125.4, 153.7, and 154.4 (Ar). Found: C, 76.8; H, 9.4; $C_{60}H_{88}O_8$ requires C, 76.9; H, 9.5 %. MS *m/z* 936.6 (M^+).

2.8.2 2,4,6,8-Tetrapropyl-1^6,3^4,5^4,7^4-tetramethoxyresorcin[4]arene-1^4,3^6,5^6,7^6-tetrol (190)



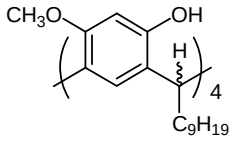
The procedure for **156** was repeated using 3-methoxyphenol (0.50 g, 4.0 mmol), butanal (0.29 g, 4.0 mmol) and boron trifluoride etherate (1.71 g, 12.1 mmol) to afford after normal workup and crystallisation **190** (0.49 g, 68 %) as off white plates, m.p. 257-258 °C (MeOH). ^{1}H n.m.r. (500 MHz, $CDCl_3$) δ 0.99 (t, 12 H, J = 7.4 Hz, CH_2CH_3), 1.32 (apparent sex, 8 H, CH_2CH_3), 2.20 (q, 8 H, J = 7.4 Hz, CH_2CH), 3.84 (s, 12 H, OCH_3), 4.31 (t, 4 H, J = 7.8 Hz, $CHCH_2$), 6.35, 7.24 (s, 2 x 4 H, ArH), 7.51, (s, 4 H, OH). ^{13}C n.m.r. ($CDCl_3$) δ 14.6 (CH_3), 21.7, 33.3, 36.6 (CH_2 and CH), 56.5 (OCH_3), 100.7, 124.5, 125.3, 125.4, 153.8, and 154.4 (Ar). Found: C, 74.1; H, 7.9; $C_{44}H_{56}O_8$ requires C, 74.1; H, 7.9 %.

2.8.3 2,4,6,8-Tetrahexyl-1^6,3^4,5^4,7^4-tetramethoxyresorcin[4]arene-1^4,3^6,5^6,7^6-tetrol (191)



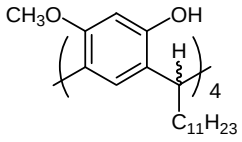
The procedure for **156** was repeated using 3-methoxyphenol (0.5 g, 4.0 mmol), heptanal (0.46 g, 4.0 mmol) and boron trifluoride etherate (1.71 g, 12.1 mmol) to afford after normal workup and crystallisation **191** (0.25 g, 28 %), m.p. 182-183 °C (MeOH). ^{1}H n.m.r. ($CDCl_3$) δ 0.90 (br t, 12 H, CH_2CH_3), 1.2-1.5 (m, 32 H, CH_2), 2.20 (m, 8 H, CH_2CH), 3.84 (s, 12 H, OCH_3), 4.28 (t, 4 H, J = 8.0 Hz, $CHCH_2$), 6.36, 7.23 (s, 2 x 4 H, ArH), 7.52, (s, 4 H, OH). ^{13}C n.m.r. ($CDCl_3$) δ 14.6 (CH_3), 23.3, 28.7, 30.0, 32.5, 33.7, 34.6 (CH_2 and CH), 56.5 (OCH_3), 100.7, 124.4, 125.4, 125.5, 153.7, and 154.4 (Ar). Found: C, 76.3; H, 9.0; $C_{56}H_{80}O_8$ requires C, 76.3; H, 9.1 %.

2.8.4 2,4,6,8-Tetranonyl-1^6,3^4,5^4,7^4-tetramethoxyresorcin[4]arene-1^4,3^6,5^6,7^6-tetrol (192)



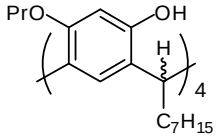
The procedure for **156** was repeated using 3-methoxyphenol (0.5 g, 4.0 mmol), decanal (0.63 g, 4.0 mmol) and boron trifluoride etherate (1.71 g, 12.1 mmol) to afford after normal workup and crystallisation **192** (0.50 g, 48 %), m.p. 150 °C (MeOH). ^{1}H n.m.r. ($CDCl_3$) δ 0.90 (br t, 12 H, CH_2CH_3), 1.20-1.4 (m, 56 H, CH_2), 2.20 (m, 8 H, CH_2CH), 3.84 (s, 12 H, OCH_3), 4.28 (t, 4 H, J = 7.6 Hz, $CHCH_2$), 6.53, 7.23 (s, 2 x 4 H, ArH), 7.52, (s, 4 H, OH). ^{13}C n.m.r. ($CDCl_3$) δ 14.7 (CH_3), 23.3, 28.7, 30.0, 30.3, 30.4, 32.6, 33.7, 34.6 (CH_2 and CH), 56.5 (OCH_3), 100.7, 124.4, 125.4, 125.5, 153.7, and 154.4 (Ar). Found: C, 77.8; H, 9.9; $C_{68}H_{104}O_8$ requires C, 77.8; H, 10.0 %.

2.8.5 2,4,6,8-Tetraundecyl-1^6,3^4,5^4,7^4-tetramethoxyresorcin[4]arene-1^4,3^6,5^6,7^6-tetrol (157)



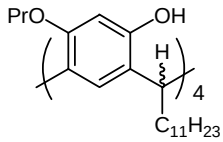
The procedure for **156** was repeated using 3-methoxyphenol (0.5 g, 4.0 mmol), dodecanal (0.74 g, 4.0 mmol) and boron trifluoride etherate (1.14 g, 8.1 mmol) to afford after normal workup and crystallisation **157** (0.86 g, 74 %), m.p. 128 - 130 °C (MeOH). ^{1}H n.m.r. ($CDCl_3$) δ 0.88 (br t, 12 H, CH_2CH_3), 1.10-1.5 (m, 72 H, CH_2), 2.1-2.3 (m, 8 H, CH_2CH), 3.82 (s, 12 H, OCH_3), 4.26 (t, 4 H, J = 7.8 Hz, $CHCH_2$), 6.34, 7.21 (s, 2 x 4 H, ArH), 7.52, (s, 4 H, OH). ^{13}C n.m.r. ($CDCl_3$) δ 14.7 (CH_3), 23.3, 28.7, 30.0, 30.3, 30.4, 32.6, 33.7, 34.6 (CH_2 and CH), 56.5 (OCH_3), 100.7, 124.4, 125.3, 125.5, 153.7, and 154.4 (Ar) (NOTE: coincident signals at 30.4). Found: C, 78.5; H, 10.4; $C_{76}H_{120}O_8$ requires C, 78.6; H, 10.4 %. MS *m/z* 1161 (M^+)

2.8.6 2,4,6,8-Tetraheptyl-1^6,3^4,5^4,7^4-tetrapropoxyresorcin[4]arene-1^4,3^6,5^6,7^6-tetrol (193)



The procedure for **156** was repeated using 3-propoxyphenol (0.5 g, 3.3 mmol), octanal (0.42 g, 3.3 mmol) and boron trifluoride etherate (1.40 g, 9.9 mmol) to afford after normal workup and crystallisation **193** (0.45 g, 52 %), m.p. 107 - 108 °C (EtOH). ^{1}H n.m.r. ($CDCl_3$) δ 0.90 (br t, 12 H, CH_2CH_3), 1.07 (t, 12 H, J = 7.4 Hz, $CH_3(CH_2)_2O$), 1.20-1.46 (m, 40 H, CH_2), 1.76 - 2.20 (m, 8 H, CH_2CH_2O), 2.10 – 2.28 (m, 8 H, CH_2CH), 3.81 – 4.08 (m, 8 H, OCH_2), 4.31 (t, 4 H, J = 7.6 Hz, $CHCH_2$), 6.34, 7.24 (s, 2 x 4 H, ArH), 7.57, (s, 4 H, OH). ^{13}C n.m.r. ($CDCl_3$) δ 11.1, 14.8 (CH_3), 22.9, 23.3, 28.7, 30.0, 30.3, 32.6, 33.7 (CH_2), 34.7 (CH), 71.4 (OCH_2), 100.7, 124.4, 125.4, 125.5, 153.5, and 153.8 (Ar). Found: C, 77.8; H, 9.9; $C_{68}H_{104}O_8$ requires C, 77.8; H, 10.0 %.

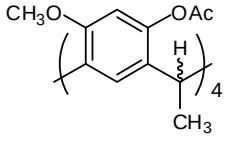
2.8.7 2,4,6,8-Tetraundecyl-1^6,3^4,5^4,7^4-tetrapropoxyresorcin[4]arene-1^4,3^6,5^6,7^6-tetrol (158)



The procedure for **156** was repeated using 3-propoxyphenol (0.5 g, 3.3 mmol), dodecanal (0.61 g, 3.3 mmol) and boron trifluoride etherate (1.40 g, 9.9 mmol) to afford after normal workup and crystallisation **158** (0.46 g, 44 %), m.p. 78.5-79.0 °C (EtOH). ^{1}H n.m.r. ($CDCl_3$) δ 0.89 (t, 12 H, J = 6.0 Hz, $(CH_2)_{10}CH_3$), 1.07 (t, 12 H, J = 7.3 Hz, $(CH_2)_2CH_3$), 1.16-1.48 (m, 72 H, CH_2), 1.8-2.0 (m, 8 H, CH_2CH_2O), 2.1-2.3 (br m, 8 H, CH_2CH), 3.8-4.08 (m, 8 H, OCH_2), 4.30 (t, 4 H, J = 7.8 Hz, $CHCH_2$), 6.34, 7.24 (s, 2 x 4 H, ArH), 7.56, (s, 4 H, OH). ^{13}C n.m.r. ($CDCl_3$) δ 11.0, 14.7 (CH_3), 22.8, 23.3, 28.7, 30.0, 30.3, 30.4, 32.6, 33.7, 34.7 (CH_2 and CH), 74.1 (OCH_2), 101.7, 124.4, 125.5, 125.6, 153.7, and 153.9 (Ar) note: co-incident signals. Found: C, 79.1; H, 10.7; $C_{84}H_{132}O_8$ requires C, 79.2; H, 10.8 %.

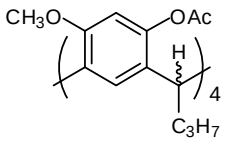
Resorcinarene Acetates and benzoates and tosylates

2.8.8 $1^4,3^6,5^6,7^6$-tetraacetyloxy-$1^6,3^4,5^4,7^4$-tetramethoxy-2,4,6,8-tetramethylresorcin[4]arene (189)



Boron trifluoride etherate (2.56 g, 18.0 mmol) was added dropwise to a stirred solution of 3-methoxyphenol (1.12 g, 9.0 mmol) and acetaldehyde (0.40 g, 9.0 mmol) in anhydrous dichloromethane (20 mL) and left to stir at 0 ºC for 1 h followed by a further 2 h at room temperature. The reaction mixture was then washed with water (2 x 20 mL) and brine (1 x 20 mL), dried ($MgSO_4$) and the solvent removed at reduced pressure to give a tarry residue. To the residue was added pyridine (10 mL) and acetic anhydride (9.21 g, 90.2 mmol) and the mixture heated at reflux overnight. The cooled solution was then poured into dilute hydrochloric acid (100 mL) and extracted with ether (3 x 30 mL). The extracts were washed with dilute hydrochloric acid (3 x 50 mL), water (1 x 50 mL), brine (1 x 40 mL) and dried ($MgSO_4$). The solvents were removed at reduced pressure and the resulting material crystallised from dichloromethane - methanol to afford an off-white powder (0.35 g, 20 %), m.p. >300 °C. ^{1}H n.m.r. ($CDCl_3$) δ 1.46 (d, 12 H, J = 7.2 Hz, CHC*H*$_3$), 2.14 (s, 12 H, CH_3CO), 3.63 (s, 12 H, OCH_3), 4.39 (q, 4 H, C*H*CH_2), 6.43, 6.65 (s, 2 x 4 H, ArH). ^{13}C n.m.r. ($CDCl_3$) δ 20.6, 21.3, 31.6 (CH and CH_3), 56.1 (OCH_3), 105.7, 125.9, 130.0, 132.4, 147.6, 155.6 (Ar) and 170.0 (C=0). Found: C, 66.0; H, 6.3; $C_{44}H_{48}O_{12}.0.5CH_2Cl_2$ requires C, 65.9; H, 6.1 %.

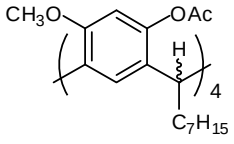
2.8.9 $1^4,3^6,5^6,7^6$-tetraacetyloxy-$1^6,3^4,5^4,7^4$-tetramethoxy-2,4,6,8-tetrapropylresorcin[4]arene (219)



The crystallisation liquor from a large scale synthesis (10 g) of **190** was evaporated to dryness and the residue (~1.8 g) dissolved in pyridine (20 mL). Acetic anhydride (5 mL) was added slowly and the solution heated to reflux overnight. The reaction mixture was then cooled to room temperature and diluted with vigorous stirring in water (100 mL). The resulting oily suspension was extracted with ether and the extract washed thoroughly with dilute hydrochloric acid (3 x 30 mL), water (2 x 30 mL) brine (1 x 30 mL) and dried

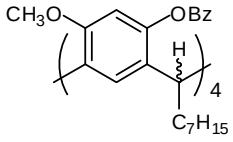
($MgSO_4$). Concentration of the organic layer at reduced pressure produced a viscous oil which was dissolved in methanol. Slow evaporation of the solution produced a small quantity of crystals of **219** suitable for x-ray structural analysis (see **section 2.6.1**, **Figure 2.17**). ^{1}H n.m.r. ($CDCl_3$) δ 0.93 (br t, J = 7.0 Hz, 12 H, CH_3), 1.20 – 1.49 (m, 8 H, C*H*$_2$CH$_3$), 1.74 – 1.93 (m, 8 H, C*H*$_2$CH), 2.16 (s, 12 H, CH_3CO), 3.62 (s, 12 H, OCH_3), 4.36 (t, 4 H, J = 7.4 Hz, CH_2C*H*), 6.41 (s, 1 H, ArH), 6.83 (s, 1 H, ArH). HRMS m/z 880.4448 $[M+1]^+$

2.8.10 $1^4,3^6,5^6,7^6$-tetraacetyloxy-$1^6,3^4,5^4,7^4$-tetramethoxy-2,4,6,8-tetraheptylresorcin[4]arene (220)



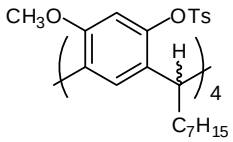
Acetic anhydride (2.5 mL) was added to a solution of **156** (200 mg, 0.2 mmol) in pyridine (20 mL) and the solution heated to reflux overnight. The reaction mixture was then cooled to room temperature and diluted with vigorous stirring in water (100 mL). The resulting oily suspension was extracted with ether and the extract washed thoroughly with dilute hydrochloric acid (3 x 30 mL), water (2 x 30 mL) brine (1 x 30 mL) and dried ($MgSO_4$). Concentration of the organic layer at reduced pressure produced a viscous oil which was crystallised from methanol. The off white solid was recovered by filtration and then recrystallised from methanol - chloroform to afford **220** as colourless crystals (187 mg, 79 %). ^{1}H n.m.r. ($CDCl_3$) δ 0.87 (br t, 12 H, J = 6.8 Hz, CH_2C*H*$_3$), 1.15-1.40 (m, 40 H, 5 x CH_2), 1.75-1.95 (m, 8 H, C*H*$_2$CH), 2.14 (s, 12 H, CH_3CO), 3.62 (s, 12 H, OCH_3), 4.32 (t, 4 H, J = 7.4 Hz, C*H*CH_2), 6.42, 6.79 (s, 2 x 4 H, ArH). ^{13}C n.m.r. ($CDCl_3$) δ 14.8 (CH_2*C*H_3), 21.4, 23.4, 28.4, 30.0, 30.5, 32.7, 35.9, 56.0 (OCH_3), 105.7, 126.5, 128.6, 131.1, 147.9, 155.6 (Ar) and 170.0 (C=O). MS *m/z* 1104.3 (M^+).

2.8.11 $1^4,3^6,5^6,7^6$-tetrabenzoyloxy-$1^6,3^4,5^4,7^4$-tetramethoxy-2,4,6,8-tetraheptylresorcin[4]arene (222)



Benzoyl chloride (600 mg, 4.3 mmol) was added to a solution of **156** (200 mg, 0.2 mmol) and triethylamine (647 mg, 6.4 mmol) in dichloromethane (20 mL) and the solution heated at reflux overnight. The reaction mixture was then concentrated at reduced pressure to yield a viscous oil. The oil was dissolved in ether (30 mL) and washed successively with sodium carbonate solution (1 M, 30 mL), dilute hydrochloric acid (1 x 30 mL), water (2 x 30 mL) and brine (1 x 30 mL) and then dried ($MgSO_4$). The ether solution was concentrated at reduced pressure affording a glassy solid which was crystallised from methanol to yield an off-white solid. The crude solid was recrystallised from methanol - chloroform to afford **222** as colourless crystals (218 mg, 76 %), m.p. 183 - 184 °C. ^{1}H n.m.r. ($CDCl_3$) δ 0.86 (br t, 12 H, CH_2CH_3), 1.10-1.50 (m, 40 H, 5 x CH_2), 1.95-2.05 (m, 8 H, CH_2CH), 3.26 (s, 12 H, OCH_3), 4.37 (t, 4 H, J = 7.2 Hz, $CHCH_2$), 6.42, 6.79 (s, 2 x 4 H, ArH), 7.49-7.62 (m, 12 H, ArH), 8.00-8.08 (m, 8 H, ArH). ^{13}C n.m.r. ($CDCl_3$) δ 14.8, 23.3, 28.6, 30.0, 30.7, 32.6, 35.2, 37.0, 55.4, 105.5, 126.6, 129.2, 130.7, 130.9, 131.3, 133.9, 148.2, 155.9 and 165.4 (NOTE: coincident arom signals). Found: C, 78.0; H, 8.0; $C_{88}H_{104}O_{12}$; requires C, 78.1; H, 7.7 %.

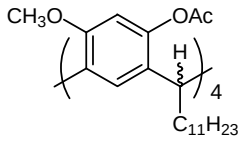
2.8.12 $1^4,3^6,5^6,7^6$-tetratoluenesulfonyloxy-$1^6,3^4,5^4,7^4$-tetramethoxy-2,4,6,8-tetraheptylresorcin[4]arene (223)



A mixture of resorcinarene **156** (0.50 g, 0.53 mmol) and sodium hydride (0.128 g, 60 % in oil, 3.20 mmol) in dry tetrahydrofuran was stirred for 30 mins under nitrogen atmosphere. Toluenesulfonyl chloride (0.49, 2.56 mmol) was added in one portion with stirring and the reaction mixture was stirred at room temperature overnight. The reaction was quenched with methanol (10 mL) and a few drops of water and stirred for a further 30 mins. The tetrahydrofuran was then removed at reduced pressure and ether (30 mL) and water (30 mL) added to the mixture. The layers were separated and the aqueous layer extracted with a second volume of ether. The combined extracts were washed with water (1 x 30 mL), brine (1 x 30 mL) and dried ($MgSO_4$). The solvent

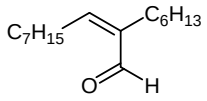
was removed at reduced pressure. The glassy solid residue was recrystallised from ethanol to afford pale yellow needles (0.57 g, 69 %), m.p. 127.0-127.5 °C. ^{1}H n.m.r. ($CDCl_3$) δ 0.86 (br t, 12 H, CH_2CH_3), 0.96 – 1.37 (m, 40 H, 5 x CH_2), 1.49 – 1.81 (m, 8 H, CH_2CH), 2.46 (s, 12 H, $ArCH_3$), 3.52 (s, 12 H, OCH_3), 4.18 (t, 4 H, J = 7.2 Hz, $CHCH_2$), 6.52 (s, 4 H, ArH), 6.61 (s, 4 H, ArH), 7.29 – 7.39 (m, 8 H, ArH), 7.74 – 7.80 (m, 8 H, ArH). ^{13}C n.m.r. ($CDCl_3$) δ 14.8, 22.4, 23.4, 28.6, 30.1, 30.5, 32.6, 35.0, 36.8, 56.1, 105.1, 126.8, 128.6, 128.9, 130.3, 131.4, 134.6, 145.6, 147.1, 156.1. Found: C, 67.7; H, 7.8; $C_{88}H_{112}O_{16}S_4.CH_3CH_2OH$; requires C, 67.6; H, 7.4 %.

2.8.13 $1^4,3^6,5^6,7^6$-tetraacetyloxy-$1^6,3^4,5^4,7^4$-tetramethoxy-2,4,6,8-tetraundecylresorcin[4]arene (221)



Acetic anhydride (2 mL) was added to a solution of **157** (200 mg, 0.17 mmol) in pyridine (20 mL) and the solution heated at reflux overnight. The reaction mixture was cooled to room temperature and diluted with water with vigorous stirring. The resulting solid was collected by vacuum filtration and washed thoroughly with dilute hydrochloric acid and then water. The off white solid was air dried and then recrystallised from methanol - chloroform to afford **221** as colourless crystals (180 mg, 79 %), m.p. 181 - 182 °C. ^{1}H n.m.r. ($CDCl_3$) δ 0.87 (br t, 12 H, CH_2CH_3), 1.17-1.38 (m, 72 H, CH_2), 1.78-1.92 (m, 8 H, CH_2CH), 2.14 (s, 12 H, CH_3CO), 3.62 (s, 12 H, OCH_3), 4.32 (t, 4 H, J = 7.4 Hz, $CHCH_2$), 6.42, 6.79 (s, 2 x 4 H, ArH). ^{13}C n.m.r. ($CDCl_3$) δ 14.7 (CH_3), 21.3, 23.3, 28.4, 29.8, 30.0, 30.3, 30.37, 30.45, 30.5, 32.6, 35.8, 35.9, 56.0 (OCH_3), 105.7, 126.6, 128.6, 131.2, 148.0, 155.7 (Ar) and 170.0 (C=O). Found: C, 75.9; H, 9.7; $C_{84}H_{128}O_{12}$; requires C, 75.9; H, 9.7 %.

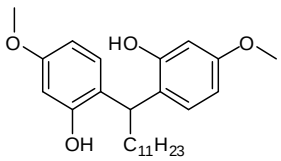
2.8.14 2-hexyl-dec-2-enal (194)



A solution of octanal (0.37 g, 2.9 mmol) and boron trifluoride etherate (1.23 g, 8.7 mmol) in anhydrous dichloromethane (10 mL) was left to stand at room temperature for 2 h. Standard workup produced a quantitative yield of colourless **194** which was found to be pure by n.m.r. ^{1}H n.m.r. ($CDCl_3$) δ 0.80-0.98 (m, 6 H, 2 x CH_3), 1.20-1.60 (m, 18 H, 9 x CH_2), 2.16-2.28 (m,

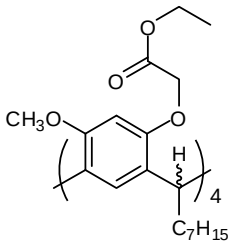
2 H, CH_2CCHO), 2.35 (apparent q, 2 H, J = 8.0 Hz, CH_2CH=), 6.49 (t, 1 H, J = 7.5 Hz, =CH), 9.36 (s, 1 H, CHO). I.R. 1688 cm^{-1} (C=O).

2.8.15 2-(1-(2-hydroxy-4-methoxyphenyl)dodecyl)-5-methoxyphenol (200) and 2-(1-(4-hydroxy-2-methoxyphenyl)dodecyl)-5-methoxyphenol (199)



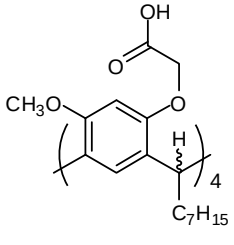
Boron trifluoride etherate (4.57 g, 32.2 mmol) was added to a solution of dodecanal (0.297 g, 1.6 mmol) and 3-methoxyphenol (2.01 g, 16.2 mmol) in dichloromethane (50 mL) at room temperature. The reaction was stirred for 3 hours and then quenched with water. The mixture was washed several times with water and then concentrated at reduced pressure. The resulting residue was dissolved in sodium hydroxide solution (1 M, 100 mL) and the solution washed once with hexanes. The aqueous layer was then acidified with conc. hydrochloric acid and extracted with hexanes (2 x 50 mL). The combined extracts were dried ($MgSO_4$) and concentrated at reduced pressure. The residue was purified by chromatography (silica gel, 10 % ethyl acetate / hexanes) to afford **200** (0.199 g, 30 %) and **199** (0.163 g, 24 %) as colourless viscous oils. Data for **200** ^{1}H n.m.r. ($CDCl_3$, 500 MHz) δ 0.90 (br t, 3 H, J = 7.1 Hz, CH_2CH_3), 1.22 – 1.36 (m, 18 H, 9 x CH_2), 2.05 – 2.10 (m, 2 H, CH_2CH), 3.64 (s, 6 H, OCH_3), 4.32 (t, 1 H, J = 7.7 Hz, $CHCH_2$), 6.32 (d, 2 H, J = 2.6 Hz, ArH), 6.48 (dd, 2 H, J = 2.6, J = 8.6 Hz, ArH), 7.10 (bs, 2 H, OH), 7.17 (d, 2 H, J = 8.6, ArH). ^{13}C n.m.r. ($CDCl_3$, 126.0 MHz) δ 14.8, 23.4, 28.5, 30.0, 30.2, 30.29, 30.31, 30.33, 32.6, 34.3, 34.8, 55.8, 102.2, 108.0, 124.1, 128.2, 154.0, 159.4 (note: coincident signal at 30.3). Data for **199** ^{1}H n.m.r. ($CDCl_3$, 500 MHz) δ 0.90 (br t, 3 H, J = 7.0 Hz, CH_3), 1.14 – 1.40 (m, 18 H, 9 x CH_2), 1.94 – 2.10 (m, 2 H, CH_2CH), 3.74 (s, 3 H, OCH_3), 3.80 (s, 3 H, OCH_3), 4.27 (t, 1 H, J = 7.7 Hz, $CHCH_2$), 5.46 (br s, 1 H, OH), 6.34 (d, 1 H, J = 2.3 Hz, ArH), 6.38 (dd, 1 H, J = 2.3 Hz, J = 8.1 Hz, ArH), 6.44 (d, 1 H, J = 2.5 Hz), 6.49 (dd, 1 H, J = 2.6 Hz, 8.4 Hz, ArH), 6.87 (s, 1 H, OH), 7.05 (d, 1 H, J = 8.1 Hz, ArH), 7.19 (d, 1 H, J = 8.4 Hz, ArH).

2.8.16 $1^4,3^6,5^6,7^6$-tetraethoxycarbonylmethyleneoxy-$1^6,3^4,5^4,7^4$-tetramethoxy-2,4,6,8-tetraheptylresorcin[4]arene tetraethyl ester (224)



To a solution of **156** (1.52 g, 1.6 mmol) and ethyl bromoacetate (2.17 g, 13.0 mmol) in dry acetone (250 mL) was added anhydrous potassium carbonate (4.48 g, 32.4 mmol) and the resulting mixture heated to reflux for 40 h. The reaction mixture was cooled to room temperature and filtered. The liquor was concentrated at reduced pressure to yield a mobile oil. The oil was dissolved in ether (80 mL) and washed successively with water (2 x 50 mL) and brine (1 x 50 mL) and dried ($MgSO_4$). The solvent was then removed at reduced pressure to afford a colourless oil which crystallised from a minimum amount of methanol upon cooling to 4°C for 24 h to yield **224** (1.77 g, 85 %), m.p. 63.5 – 64.0 °C. IR 2927, 1760, 1500, 1302, 1192 cm^{-1}. ^1H n.m.r. ($CDCl_3$, 500 MHz) δ 0.86 (br t, J = 6.7 Hz, 12 H, CH_2CH_3), 1.16-1.42 (m, 52 H, $(CH_2)_5$ and CH_3CH_2O), 1.76-1.90 (m, 8 H, CH_2CH), 3.62 (s, 12 H, OCH_3), 4.24 (q, J = 7.2 Hz, 8 H, OCH_2CH_3), 4.03, 4.19 (AB quartet, 8 H, 15.9 Hz, OCH_2COO), 4.52 (t, 4 H, J = 7.4 Hz, $CHCH_2$), 6.31 (s, 4 H, ArH), 6.62 (s, 4 H, ArH). ^{13}C n.m.r. ($CDCl_3$, 126 MHz) δ 14.8, 14.9 (CH_3), 23.4, 28.7, 30.0, 30.6, 32.7, 35.3, 36.2 (6 x CH_2 and CH), 56.2, 61.6, 69.1 (OCH_3, OCH_2CH_3, and OCH_2COO), 100.2, 127.0, 128.1, 128.8, 155.6, 156.2 (6 x Ar) and 170.3 (C=O). FAB-MS m/z 1281.8331 $[M+H]^+$

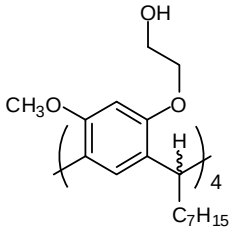
2.8.17 $1^4,3^6,5^6,7^6$-tetramethylenecarboxy-$1^6,3^4,5^4,7^4$-tetramethoxy-2,4,6,8-tetraheptylresorcin[4]arene (225)



To a solution of **224** (0.51 g, 0.40 mmol) in methanol (200 mL) and water (2 mL) was added sodium hydroxide (3.18 g, 79.6 mmol) and the mixture heated at reflux for 5 h. The solvents were then removed at reduced pressure to give a white solid to which was added hydrochloric acid (5M, 50 mL). The precipitate was collected by suction filtration and dried in a vacuum desiccator over phosphorus pentoxide for 72 h (0.43 g, 92 %). Recrystallisation from methanol afforded an analytical sample as colourless needles m.p. 84.0 – 85.0 °C. ^1H n.m.r. ($CDCl_3$ + d_6-DMSO) δ 0.80 (br t, 12 H, CH_2CH_3), 1.10-1.35 (m, 40 H, $(CH_2)_5$), 1.70-1.90 (m, 8

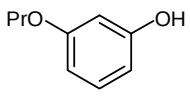
H, C*H*$_2$CH), 3.60 (s, 12 H, OCH$_3$), 4.11, 4.27 (AB quartet, 8H, J = 15.9 Hz, OC*H*$_2$COO), 4.50 (t, 4 H, J = 7.4 Hz, C*H*CH$_2$), 5.98 (br s, 4 H, COOH), 6.24 (s, 4 H, ArH), 6.67 (s, 4 H, ArH). ^{13}C n.m.r. (CDCl$_3$) δ 14.7 (CH$_3$), 23.2, 28.4, 30.0, 30.4, 32.6, 35.2, 35.7 (6 x CH$_2$ and CH), 56.4, 67.7 (OCH$_3$ and O*C*H$_2$COO), 99.0, 126.7, 127.5, 128.0, 154.7, 155.8 (6 x Ar) and 171.4 (C=O). FAB-MS m/z 1125.6844 [M+H-CO$_2$]$^+$.

2.8.18 1^4,3^6,5^6,7^6-tetra-(2-hydroxyethoxy)-1^6,3^4,5^4,7^4-tetramethoxy-2,4,6,8-tetraheptylresorcin[4]arene (227)



To a solution of **225** (0.50 g, 1.71mmol) in dry tetrahydrofuran (10 mL) was added borane dimethylsulfide complex (1.71 mL, 10 M, 17.1 mmol). The mixture was stirred at room temperature for 2 h and then heated to reflux overnight. The remaining borane was quenched with methanol and the solvents removed at reduced pressure. The resulting mixture was treated with an excess of hydrochloric acid (3 M) and the resulting white solid recovered by filtration (463 mg, 97 %) which was pure by n.m.r. spectroscopy m.p. 186 – 187 °C. ^{1}H n.m.r. (CDCl$_3$) δ 0.87 (br t, 12 H, CH$_2$C*H*$_3$), 1.15-1.39 (m, 40 H, (CH$_2$)$_5$), 1.74-1.92 (m, 8 H, C*H*$_2$CH), 2.50 (bs, 4 H, OH), 3.56 (s, 12 H, OCH$_3$), 3.62 – 4.00 (m, 16 H, OC*H*$_2$C*H*$_2$O), 4.51 (t, 4 H, J = 7.4 Hz, C*H*CH$_2$), 6.22 (s, 4 H, ArH), 6.78 (s, 4 H, ArH). ^{13}C n.m.r. (CDCl$_3$) δ 14.8 (CH$_3$), 23.4, 28.6, 30.0, 30.6, 32.7, 35.4, 35.9 (6 x CH$_2$ and CH), 56.9 (OCH$_3$), 62.1, 70.6 (2 x OCH$_2$), 97.8, 126.7, 127.2, 127.6, 155.0, 156.0 (6 x Ar). Found: C, 73.4; H, 9.5; C$_{68}$H$_{104}$O$_{12}$; requires C, 73.3; H, 9.4 %.

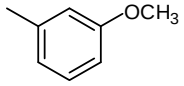
2.8.19 3-Propoxyphenol



A solution of resorcinol (5.00 g, 45.4 mmol), propyl bromide (5.58 g, 45.4 mmol) and potassium carbonate (12.5 g, 90.8 nmmol) in dry acetone (100 mL) was heated at reflux overnight. The reaction mixture was then concentrated at reduced pressure and potassium hydroxide solution added (5 g in 80 mL) and the mixture stirred for 30 mins. The solution was washed with chloroform (2 x 30 mL) and then acidified to litmus with hydrochloric acid (conc.). The resulting mixture was then extracted with chloroform (3 x 50 mL) and the combined extracts washed with water (2 x 50 mL), brine (1 x 50 mL) and dried (MgSO$_4$). The solvent

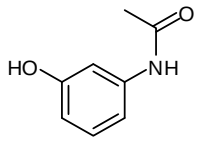
was removed at reduced pressure to afford a red/brown oil (3.08 g, 45 %, ~95 % purity) which was used without further purification. ^{1}H n.m.r. ($CDCl_3$) δ 1.03 (t, 3 H, J = 7.2 Hz, CH_3), 1.80 (apparent hex, 2 H, C*H*$_2$CH$_3$), 3.90 (t, 2 H, J = 6.6 Hz, OCH_2), 4.60 (v br s, 1 H, OH), 6.39-6.46 (m, 2 H, ArH), 6.50 (apparent ddd, 1 H, ArH), 7.13 (t, 1 H, J = 8.6 Hz, ArH). ^{13}C n.m.r. ($CDCl_3$) δ 11.2, 23.2, 70.2, 102.8, 107.8, 108.3, 130.8, 157.4 and 161.2.

2.8.20 3-methoxytoluene (229)



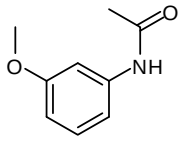
A mixture of *m*-cresol (5.00 g, 46.2 mmol), anhydrous potassium carbonate (31.9 g, 0.23 mol) and iodomethane (32.8 g, 0.23 mol) in dry acetonitrile was stirred at room temperature for 3 days. The solvents were then removed at reduced pressure and the residue stirred with dichloromethane (50 mL). The suspension was filtered and the solid washed thoroughly with more dichloromethane. The solvent was removed at reduced pressure to afford an orange oil (4.59 g, 81 %) which was pure by n.m.r. and used without further purification. ^{1}H n.m.r. ($CDCl_3$) δ 2.37 (s, 3 H, $ArCH_3$), 3.82 (s, 3 H, CH_3O), 6.72 – 6.83 (m, 3 H, ArH), 7.17 – 7.26 (m, 1 H, ArH). ^{13}C n.m.r. ($CDCl_3$) δ 22.2, 55.8, 111.5, 115.4, 122.2, 129.8, 140.1, 160.3.

2.8.21 *m*-Hydroxyacetanilide (240)



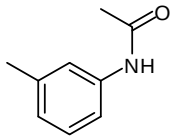
To a solution of *m*-aminophenol (10 g, 91.6 mmol) in sodium carbonate solution (55 g in 200 mL) was added dropwise acetic anhydride (18.71 g, 183.3 mmol) with vigorous stirring. The mixture was stirred for a further 2 hours at room temperature and then extracted with ethyl acetate (4 x 50 mL). The combined extracts were washed once with brine and then dried (Na_2SO_4). The solvent was removed at reduced pressure and the dark solid residue crystallized from a minimum of methanol to afford a purple solid (5.54 g, 40 %). ^{1}H n.m.r. (d_6-DMSO, 500 MHz) δ 2.01 (s, 3 H, CH_3), 6.40 – 6.42 (m, 1 H, ArH), 6.90 – 6.92 (m, 1 H, ArH), 7.04 (t, 1 H, J = 8.0 Hz, ArH), 7.18 (apparent br t, 1 H, ArH), 9.31, 9.77 (2 s, 2 H, NH and OH). ^{13}C n.m.r. (d_6-DMSO) δ 24.1, 106.1, 109.7, 110.1, 129.3, 140.4, 157.6, and 168.1 (C=O).

2.8.22 *m*-Methoxyacetanilide (241)



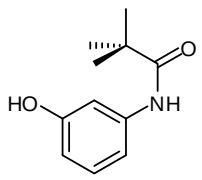
A mixture of *m*-anisidine (0.5 g, 4.1 mmol), acetic anhydride (0.415 g, 4.1 mmol) a few grains of zinc powder and glacial acetic acid (0.42 g) were heated at reflux for 2 hours. The reaction mixture was then poured into water (20 mL) and stirred at room temperature overnight by which time the product had crystallised. The solid was recovered by vacuum filtration and air dried affording **241** (0.42 g, 62 %) as a pale pink powder, m.p. 82 – 83 °C (lit.[167] 81 – 82 °C). ^{1}H n.m.r. ($CDCl_3$) δ 2.17 (s, 3 H, CH_3CO), 3.79 (s, 3 H, CH_3O), 6.66 (dd, 1 H, J = 2.0, J = 8.2, ArH), 6.97 – 6.99 (m, 1 H, ArH), 7.20 (t, 1 H, J = 8.1 Hz, ArH), 7.28 (apparent br t, 1 H, ArH), 7.47 (br s, 1 H, NH). ^{13}C n.m.r. ($CDCl_3$) δ 25.3, 56.0, 106.4, 110.7, 112.7, 130.3, 139.8, 160.8, 169.2.

2.8.23 *N*-Acetyl-*m*-toluidine (242)



m-Toluidine (10.5 g, 98.0 mmol) was added slowly drop-wise to acetic anhydride (50.0 g, 0.49 mol) maintained at 0°C with vigorous stirring. The resulting mixture was then heated for 30 mins at reflux. The excess acetic anhydride was then removed at reduced pressure and the resulting oil purified by passage through an alumina plug (CH_2Cl_2). The pale brown oil (12.4 g , 90 %) was essentially pure by n.m.r. and was used without further purification. ^{1}H n.m.r. ($CDCl_3$) δ 2.16 (s, 3 H, $ArCH_3$), 2.31 (s, 3 H, $COCH_3$), 6.92 (br d, 1H, ArH), 7.18 (t, 1 H, J = 7.6 Hz, ArH), 7.24-7.38 (m, 2 H, ArH), 7.77 (br s, 1 H, NH). ^{13}C n.m.r. ($CDCl_3$) δ 22.1, 25.1, 117.8, 121.4, 125.8, 129.4, 138.5, 139.5 and 169.4 (C=O)

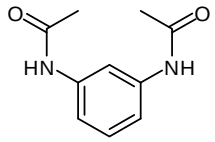
2.8.24 3-(1,1,1-Trimethylacetamido)phenol (243)



Trimethylacetyl chloride (5.93 g, 48.2 mmol) was added dropwise to vigorously stirred mixture of *m*-aminophenol (5.0 g, 45.8 mmol), sodium bicarbonate (11.5 g, 137.5 mmol), ethyl acetate (125 mL) and water (150 mL). The mixture was stirred for a further 2 h at which point the organic layer was separated and washed with dilute hydrochloric

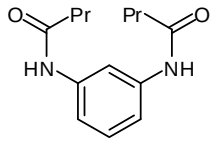
acid (2 x 50 mL), water (1 x 50 mL), brine (1 x 50 mL) and dried (Na_2SO_4). The solvent was removed at reduced pressure and the residue crystallised from chloroform/hexane to afford off-white plates. m.p. 142 - 144 °C (lit.[168], 144 – 145 °C). ^{1}H n.m.r. ($CDCl_3$) δ 1.34 (s, 9 H, CH_3), 6.65-6.55 (m, 1 H, ArH), 6.65-6.70 (m, 1 H, ArH), 7.16 (t, 1 H, J = 8.0 Hz, ArH), 7.46 (br s, 1 H, NH), 7.94 (apparent t, 1 H, J = 2.2 Hz, ArH). ^{13}C n.m.r. ($CDCl_3$) δ 28.2, 40.5, 108.2, 111.2, 112.8, 130.3, 139.2, 158.4 and 178.5.

2.8.25 1,3-Diacetamidobenzene (244)



To *m*-diaminobenzene (4.50 g, 41.6 mmol) in pyridine (50 mL) at 0°C was added acetic anhydride (25.4 g, 249.7 mmol) slowly with vigorous stirring at 0 °C. The mixture was then warmed to 60 °C for 30 mins and the cooled reaction mixture then poured into dilute hydrochloric acid (250 mL, 1M). The slurry was stirred for a further 1 h and the crude dark solid collected by suction filtration. Purification by column chromatography (silica, 80 % EtOAc/hexanes) afforded an off-white solid (6.96 g, 87 %) m.p. 194-195 °C (lit.[169] 196 – 198 °C), IR (cm^{-1}) 3293, 1645. ^{1}H n.m.r. (d_6-DMSO, 500 MHz) δ 2.10 (s, 6 H, CH_3), 7.22 - 7.19 (m, 1 H, ArH), 7.28 - 7.25 (m, 2 H, ArH), 7.83 - 7.82 (m, 1 H, ArH). ^{13}C n.m.r. (d_6-DMSO) δ 23.9, 112.9, 116.7, 129.7, 140.0, 171.3.

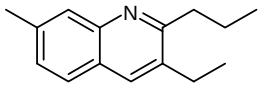
2.8.26 1,3-Dibutanamidobenzene (245)



Butanoyl chloride (15.1 g, 141.9 mmol) was added slowly dropwise with vigorous stirring to a solution of *m*-diaminobenzene (5.12 g, 47.3 mmol) in pyridine (50 mL) at 0°C. After complete addition the solution was allowed to warm to room temperature and stirred for a further 2 hours. The reaction mixture was then poured into ice water with rapid stirring. To the mixture was added excess solid sodium carbonate and the solution stirred for a further hour at room temperature. The mixture was then extracted with ethyl acetate (3 x 30 mL) and the combined extracts washed successively with saturated sodium carbonate solution (1 x 30 mL), water (1 x 30 mL), dilute hydrochloric acid (5 x 30 mL), water (1 x 30 mL) and brine (1 x 30 mL). The ethyl acetate solution was dried ($MgSO_4$) and the solvent removed at reduce pressure to

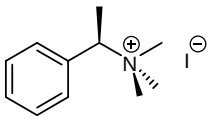
afford a tan powder (8.7 g, 74 %) m.p. 142-143 °C. ^{1}H n.m.r. (d_6-acetone) δ 1.09 (t, 6 H, J = 7.4 Hz, CH_3), 1.83 (apparent hex, 4 H, J = 7.4 Hz, C*H*$_2$CH$_3$), 2.48 (t, 4 H, J = 7.0 Hz, $COCH_2$), 7.31 (t, 1 H, J = 7.4 Hz, ArH), 7.46-7.56 (m, 2 H, ArH), 8.13 (br t, 1 H, ArH), 9.27 (br s, 2 H, NH). ^{13}C n.m.r. (d_6-acetone) 14.4, 20.0, 39.9, 111.2, 115.2, 129.9, 141.1 and 172.2.

2.8.27 quinoline byproduct (249)



To a solution of *m*-toluidine (0.50 g, 4.67 mmol) and butanal (0.34 g, 4.67 mmol) in dicloromethane was added boron trifluoride etherate (1.99 g, 14.0 mmol) with stirring at room temperature. The reaction was stirred for 5 h followed by dilution with dichlormethane and careful basification with dilute sodium bicarbonate solution. The organic layer was washed with water (2 x 20 mL) followed by dilute hydrochloric acid (2 x 20 mL). The acid washes were then rendered alkaline with sodium hydroxide solution and washed with ether (3 x 20 mL). The combined ether extracts were washed with water (1 x 20 mL), brine (1 x 20 mL) and dried ($MgSO_4$). The solvent was removed at reduced pressure to afford **249** as a pale yellow oil (0.22 g, 22 %). ^{1}H n.m.r. ($CDCl_3$) δ 1.07 (t, 3 H, J = 7.4 Hz, CH_3), 1.34 (t, 3 H, J = 7.4 Hz, CH_3), 1.74 – 1.93 (m 2 H, CH_2C*H*$_2$CH$_3$), 2.54 (s, 3 H, $ArCH_3$), 2.83 (q, 2 H, J = 7.4 Hz, $ArCH_2$), 2.89 – 3.20 (m, 2 H, $ArCH_2$), 7.29 (dd, 1 H, J = 1.6 Hz, J = 8.4 Hz, ArH), 7.63 (d, 1 H, J = 8.4 Hz, ArH), 7.83 (br s, 2 H, 2 x ArH). ^{13}C n.m.r. ($CDCl_3$) δ 15.0, 15.2, 22.5, 23.6, 25.8, 38.4, 126.0, 127.2, 128.1, 128.5, 134.4, 135.1, 139.2, 147.2, 162.5.

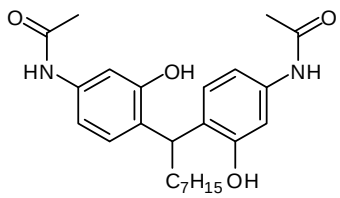
2.8.28 (α-Methylbenzyl)trimethylammonium iodide from R(+)



A mixture of α-methylbenzylamine (2.00 g, 16.5 mmol), formic acid (4.2 g, 99 %, 90.3 mmol) and formaldehyde (2.75 g, 40 %, 36.6 mmol) was heated on a steam bath for 4 h. The mixture was acidified with concentrated hydrochloric acid and then concentrated at reduced pressure. The cold reaction mixture was then made alkaline with concentrated sodium hydroxide solution and extracted with ether (2 x 20 mL). The combined organic layers were washed with water (1 x 20 mL), brine (1 x 20 mL) and dried ($MgSO_4$). The solvent was removed at reduced pressure and the resulting oil passed

through a small alumina plug. The oil was then dissolved in dry ether (5 mL) and an excess of methyl iodide (11.7 g, 82.5 mmol) added. The mixture was left to stand overnight and the resulting yellow solid recovered by suction filtration to yield a pale yellow solid (2.59 g, 54 %), m.p. 155 – 156.5 (lit.[170] 155 – 156 °C). ^{1}H n.m.r. ($CDCl_3$) δ 1.84 (d, 3 H, J = 6.9 Hz, CHC*H*$_3$), 3.53 (s, 9 H, NCH_3), 5.37 (q, 1 H, J = 6.9 Hz), 7.40-7.50 (m, 3 H, ArH), 7.60-7.66 (m, 2 H, ArH). ^{13}C n.m.r. ($CDCl_3$) δ 16.1, 52.1, 74.0, 129.9, 131.2, 131.5 and 132.9. $[\alpha]_D$ +23.0 [(c = 2.1, EtOH), lit. +23.3 (EtOH)[170]].

2.8.29 Attempted procedure for the reaction of hydroxyacetanilide and octanal with BF_3



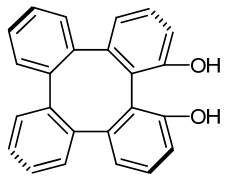
Boron trifluoride etherate (1.41 g, 9.9 mmol) was added to a stirred solution of 3-hydroxyacetanilide (0.5 g, 3.3 mmol) and octanal (0.42 g, 3.3 mmol) in anhydrous dichloromethane (15 mL) and left to stir at room temperature (5 h). The reaction mixture was then quenched with water (10 mL) and the entire mixture (water and dichloromethane) filtered to yield a white powder (130 mg, 19 %) which appeared to be a dimer by n.m.r. ^{1}H n.m.r. (d_6-DMSO, 500 MHz) δ 0.83 (t, 3 H, J = 6.9 Hz, CH_2CH_3), 1.15 – 1.25 (m, 10 H, 5 x CH_2), 1.80 (apparent br q, 2 H, C*H*$_2$CH), 1.98 (s, 6 H, 2 x CH_3CO), 4.43 (t, 1 H, J = 7.8 Hz, CH), 6.78 (dd, 2 H, J = 2.1 Hz, J = 8.3 Hz, ArH), 6.91 (d, 2 H, J = 8.3 Hz, ArH), 7.21 (d, 2 H, J = 2.1, ArH), 9.12 (br s, 2 H, 2 x OH), 9.68 (s, 2 H, 2 x NH). ^{13}C n.m.r. (d_6-DMSO) δ 13.9 (CH_2CH_3), 22.1 (CH_2CH_3), 23.9 (CH_3CO), 27.7, 28.6, 29.0, 31.3, 33.8 (5 x CH_2), 35.2 (CH), 106.2, 109.5, 126.0, 127.8, 137.5, 154.8, 167.8. HRMS *m/z* (M^+) 412.2366

3.0 Resolution of C_4 dissymmetric resorcinarenes by formation of their diastereomeric camphorsulfonates.

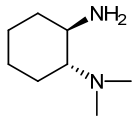
The resolution of chiral calixarenes has been achieved by direct separation on enantioselective chromatographic phases and by the formation of diastereomers (discussed in detail in **section 1.0** and references therein). Large scale separations (>1 g) necessitate the application of the latter method in the majority of cases due to the limited capacity of chiral preparative HPLC columns. It is for this reason primarily that we have chosen to investigate resolution by the formation of diastereomers and not focus on HPLC separation. We have, however, achieved partial separation of the parent *C*-heptylcalix[4]resorcinarene on a Daicel ChiralPak AD column (see **section 2.4**) with the intention of proving the prepared compound was a racemic mixture.

There are several possible reagents for the formation of diastereomeric species from the resorcinarene enantiomers. The requirements for such a reagent are simple, they must be easy to introduce while producing diastereomers dissimilar enough to be separated by chromatography or fractional crystallization and be easily removed. While the requirements are simple it is not often easy to discover a reagent with such substrate specific properties. Where the substrate is phenolic, the obvious choice of reagent is one which will form a diastereomeric ester derivative. The ester is of course easily cleaved and perhaps the acid may be recovered for re-use. Of all of the chiral derivatising reagents available that fit within this category, the cheapest is (+)-camphor-10-sulfonyl chloride. Other reagents which may be as effective, such as (*S*)-(+)-2-(6-methoxy-2-naphthyl)propionic acid (naproxen), *N*-protected amino-acids and (*R*)-(+)-α-methoxy-α-trifluoromethylphenylacetic acid (Mosher's acid) are generally more expensive.
(+)-Camphor-10-sulfonyl chloride of good enantiomeric purity is a crystalline sulfonylchloride (m.p. 65-67 ºC[171]) and like toluenesulfonyl chloride relatively stable and can be stored under argon for long periods. This makes it an extremely convenient reagent for gram scale resolutions. The ease with which it may be attached to amines and phenols makes it an ideal chiral auxiliary for resolutions. Two fairly recent examples are the resolutions of 1,16-dihydroxytetraphenylene (**251**,

Figure 3.1[172]) and *trans*-1-amino-2-dimethylaminocyclohexane (**252**, **Figure 3.1**[173]). In the case of the tetraphenylene the camphorsulfonyl group was removed via a simple hydrolysis with potassium hydroxide in methanol/water.



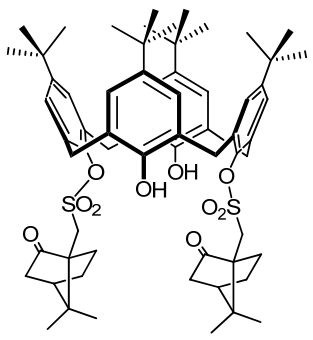
251



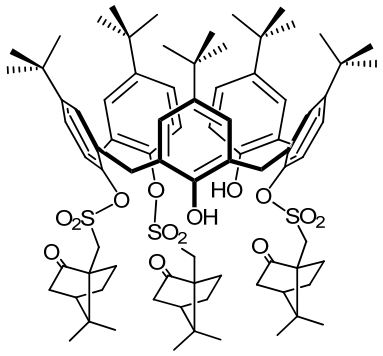
252

Figure 3.1 - 1,16-dihydroxytetraphenylene (**251**) and *trans*-1-amino-2-dimethylaminocyclohexane (**252**).

Considering the relatively low cost and ease of use, the camphorsulfonyl functionality has not been well explored in the context of calixarene chemistry. Camphorsulfonyl chloride has, in a few cases, been used to prepare chiral derivatives from the achiral parent calixarenes. Examples such as the tetramer (**253**) and pentamer (**254**) were produced by Motta and coworkers.[174-175] Gutsche *et al*. also produced an octamer.[176] However the application has been very limited.



253

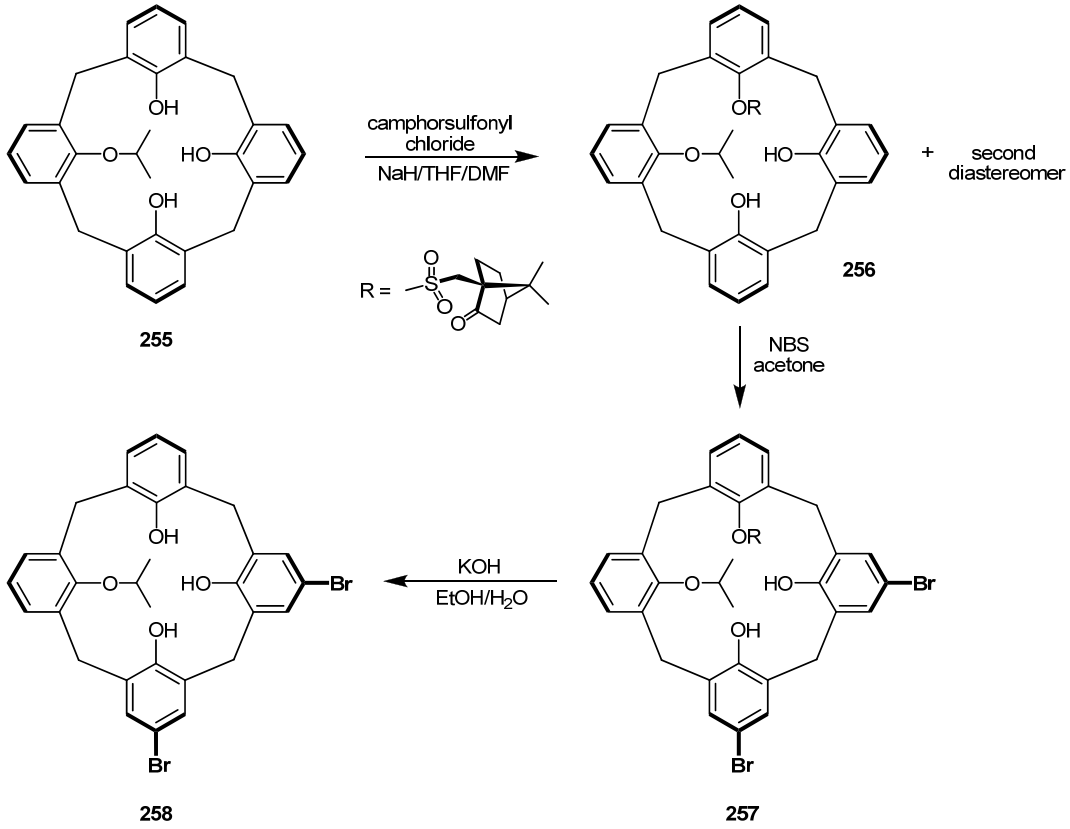


254

Figure 3.2 – Motta's calixarene di- and tri-camphorsulfonyl esters, **253** and **254** respectively.

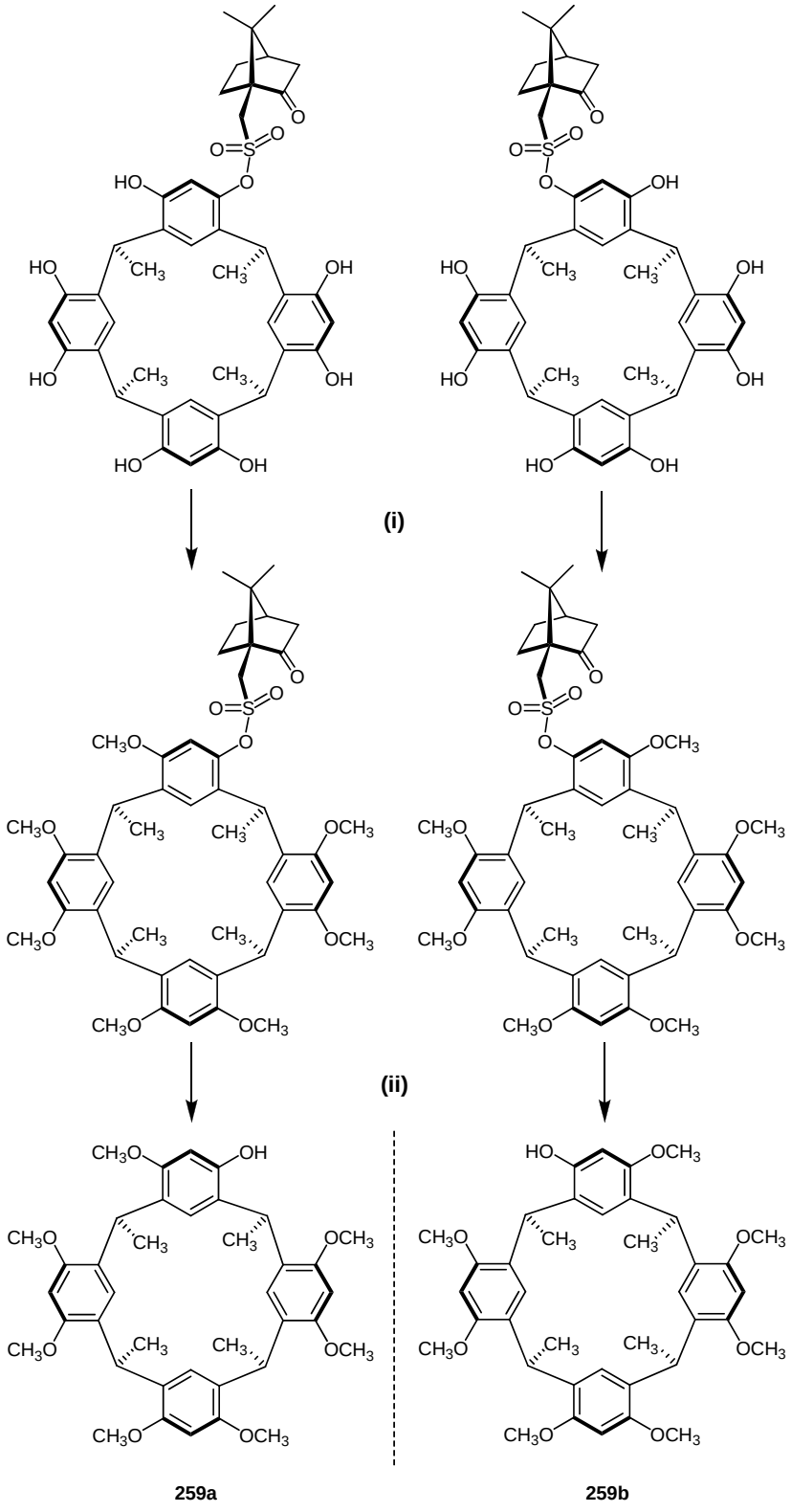
Similarly, despite the favourable reactivity and convenience, camphorsulphonyl chloride has scarcely been used for the resolution of chiral calixarenes and resorcinarenes. This may be due to the fact that sulfonyl esters of alkyl alcohols are

generally prohibitively reactive to be used as resolving reagents. However, this is clearly not the case for phenols. Even in Shinkai's rather large work on planar chiral AABC type calix[4]arenes.[177] the reagent of choice was the substantially more expensive (-)-menthoxyacetyl chloride.[178] Only three significant resolution applications of the camphorsulfonyl functionality to the calixarene family appear to exist. The first example, and most recent, is from Kalchenko and co-workers.[12] Kalchenko's synthesis is not technically a resolution but the production of two diastereomers (**256**) from the achiral monoisopropoxycalix[4]arene **255** which were separated and converted into the enantiomeric products via a bromination step (see **Scheme 3.1**).



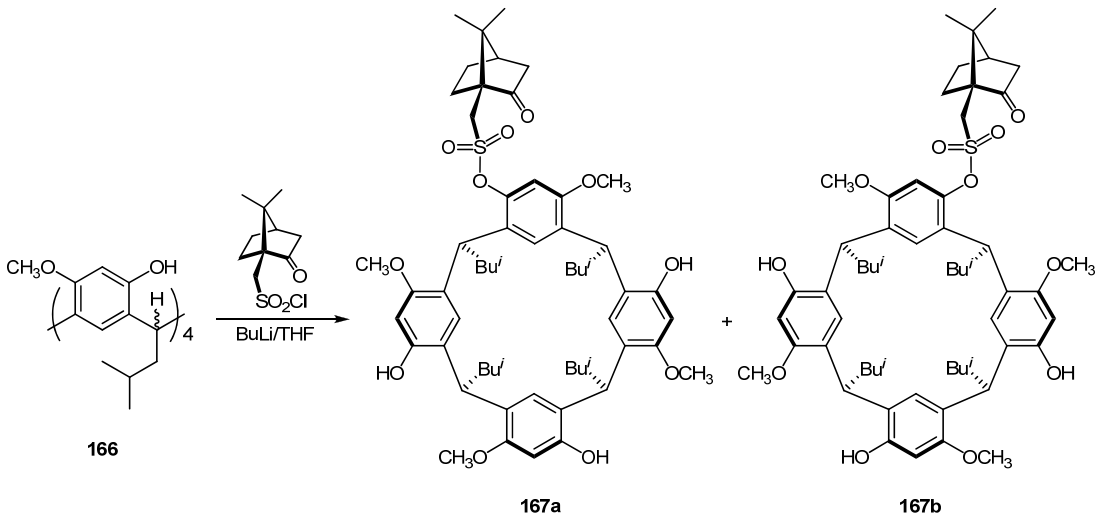
Scheme 3.1 – Kalchenko's preparation of chiral calix[4]arenes via camphorsulfonate diastereomers.

Mattay and co-workers[41] had previously applied the same kind of methodology to the achiral octahydroxyresorcinarenes to produce diastereomers which were then separated and converted into the enantiomeric products **259a** and **259b** (**Scheme 3.2**).



Scheme 3.2 – Preparation of **259a** and **259b, (i)** CH_2N_2/silica gel, **(ii)** KOH/water.

The third example, from Mattay *et al*.[90] applied a monocamphorsulfonylation procedure to the resolution of the 2,4,6,8-tetraisobutyl-1^6,3^4,5^4,7^4-tetramethoxyresorcin[4]arene-1^4,3^6,5^6,7^6-tetrol (**166**), prepared using our protocol[87] (see **section 2.0**). The monocamphorsulfonate esters were resolved on a small scale by preparative HPLC to afford the pure diastereomers **167a** and **167b**.



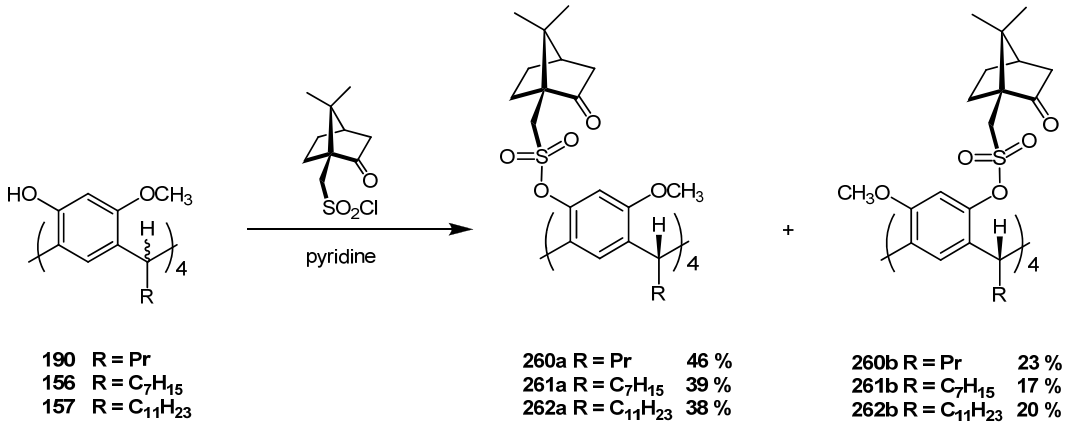
Scheme 3.3 – Resolution of chiral *C*-isobutyl-tetramethoxyresorcinarenes by monocamphorsulfonylation.

Mattay's resolution was a significant step in the chemistry of the C_4 symmetric chiral resorcinarenes and should be duly recognised. However, the method of preparation and the resolution scale leave room for improvement. The synthesis of the camphorsulfonates in Mattay's case applied one equivalent of butyllithium and five equivalents of camphorsulfonyl chloride. This ratio was applied apparently with the intention of producing only the monocamphorsulfonate. The resulting mixture however contained a significant quantity of the starting material and a portion of dicamphorsulfonates with the total yield of monocamphorsulfonates being only 29 %. The other noteworthy factor associated with the resolution is the scale. The mixture of diastereomers was resolved by preparative HPLC, consequently less than 200 mg of each diastereomer was isolated. Mattay noted that the monocamphorsulfonyl esters **167a** and **167b** were formed in equal quantities as judged from the proton n.m.r spectra of the crude reaction mixture, thus suggesting that the production of one diastereomer in preference to the other does not occur. No

X-ray crystallographic data nor indication of the absolute stereochemistry were provided.

3.1 Synthesis of the camphorsulfonyl derivatives

The procedure used here for camphorsulfonylation of the resorcinarenes was adapted from Gutsche's paper on the preparation of 2,4-dinitrophenyl and camphorsulfonyl derivatives of the calix[8]arene.[177] In order to prevent the possibility of complex mixtures obtained by Mattay[90] the camphorsulfonyl chloride was added in significant excess (100 % excess per phenol) and the mixture heated to force the reaction to completion (see **section 3.6.1**). Under these conditions the majority of the resorcinarene material appeared to react. However a small quantity of what is likely to be the tricamphorsulfonate is also present (by n.m.r. spectroscopy).



Scheme 3.4 – Preparation of the chiral resorcinarene tetracamphorsulfonates.

3.2 Resolution of the tetracamphorsulfonate diastereomers

The only resorcinarene camphorsulfonate that is reliably crystalline is the first diastereomer of the shorter *C*-propylresorcin[4]arene derivative (**260a**). Thus, a fractional crystallisation methodology was not applicable to the separation of the diastereomers and consequently the derivatives had to be resolved by flash chromatography. A fairly specific mixture of between 5 – 7 % ethyl acetate in dichloromethane produced a separation that was effective on a multi-gram scale.

This is clearly superior to the relatively small scale separations achievable with preparative HPLC.
The second diastereomer (b series) was isolated in somewhat lower yield in all cases. This is predominantly due to the chromatographic separation, which was not ideal. Frequently the first eluting diastereomer would "streak" and contaminate the second eluting diastereomer and thus a secondary separation would be required.
N.m.r. spectra of the isolated diastereomeric mixtures indicated that the diastereomers were formed in approximately equal quantities, which is consistent with Mattay's monocamphorsulfonylations.[90]

3.3 Physical and spectroscopic properties of the tetracamphorsulfonates

3.3.1 Crystallinity and solubility

Among the pure diastereomers prepared, only diastereomer A of the *C*-propylresorcin[4]arene (**260a**) has been obtained in a substantially crystalline form. The remaining derivatives are produced as glassy solids. Curiously enough the *C*-heptylresorcin[4]arene diastereomers (**261a** and **261b**), when diastereomerically pure, are glasses, while a 1:1 mixture of the diastereomers will readily crystallize from a methanolic liquor. The *C*-propyl derivatives (**260a** and **260b**) also crystallise as a 1:1 mixture from alcoholic solvents. As is often the case with the resorcinarene series, the shorter the alkyl chain the more crystalline the material (see **section 2.3**). The series of camphorsulfonates appear to conform to this model. Also, at least in the case of the *C*-propylresorcin[4]arene the first diastereomer appears to be more crystalline than the second.

3.3.2 N.m.r. spectroscopic and optical rotation properties

The n.m.r. spectra of the mixture of **261a** and **261b** (**figure 3.3 (a)**), diastereomer A (**261a**, **figure 3.3 (b)**) and diastereomer B (**261b**, **figure 3.3 (c)**) are given for comparison. There is little difference between the resorcinarenes of different chain

length, merely an appropriate change in the alkyl region corresponding to the length of the chain.

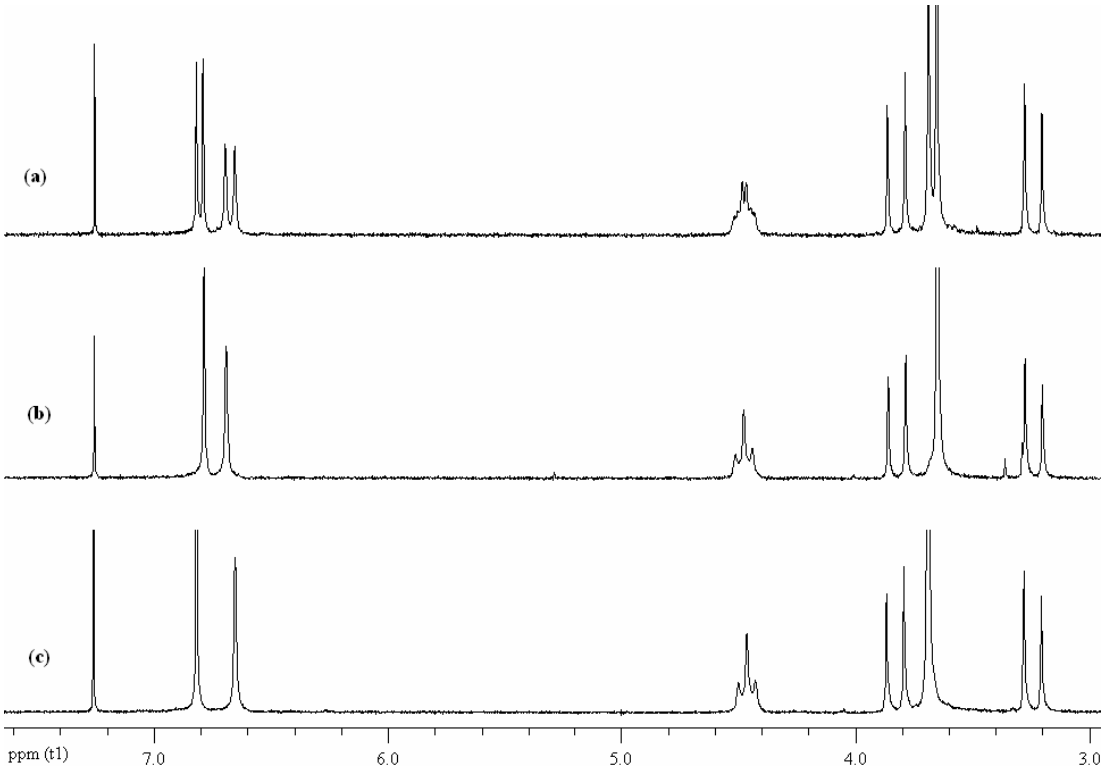


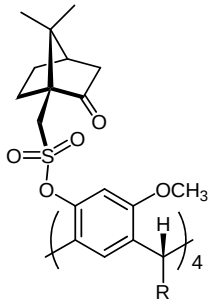
Figure 3.3 – Proton n.m.r. spectra showing the region 3.0 – 7.5 ppm for **(a)** crystallised diastereomeric mixture of **261a** and **261b**, **(b) 261a**, **(c) 261b**.

The spectrum **(a)** (**figure 3.3 (a)**) shows the mixture of diastereomers of **261** which has been recrystallised from ethanol. It is evident that the mixture crystallises very effectively in a 1:1 ratio as indicated in **section 3.3.1** (the crude mixture also contains a 1:1 mixture of diastereomers). A trend is evident on inspection of the proton n.m.r. spectral data for each of the diastereomers and is summarised in **table 3.1**.

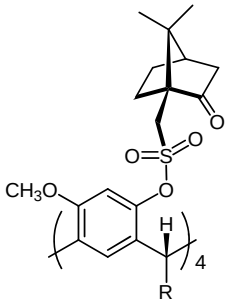
Table 3.1 – Selected proton n.m.r. signals for the tetracamphorsulfonates **260**, **261** and **262**.

	lower rim ArH		upper rim ArH		OMe	
	a	**b**	**a**	**b**	**a**	**b**
11	6.80	6.83	6.73	6.68	3.67	3.70
12	6.80	6.83	6.71	6.66	3.67	3.70
13	6.79	6.82	6.70	6.65	3.66	3.70

Quite clearly, all of the first eluting diastereomers have similar chemical shifts for the lower (~6.83) and upper rim (~6.71) aromatic protons and also the methoxyl groups (~3.67). A similar relationship is also present for the second eluting diastereomers for each of the mixtures. One may reasonably assume that all of the first eluting diastereomers are of the same stereochemistry based on the similarity of the spectral features. This assumption is substantiated by the optical rotation data given in **figure 3.4** below.



260a R = Pr +61.3
174a R = C_5H_{11} +41.8
261a R = C_7H_{15} +46.7
262a R = $C_{11}H_{23}$ +51.4



260b R = Pr +2.6
174b R = C_5H_{11} +12.3
261b R = C_7H_{15} +5.6
262b R = $C_{11}H_{23}$ +0.1

Figure 3.4 – Specific rotation values for the resorcinarene tetracamphorsulfonate diastereomers.

Clearly, the magnitude of the rotations for the first eluting diastereomers is significantly greater than that of the second eluting diastereomers, which is in agreement with the result for compounds **174a** and **174b**[92] produced by Heaney *et al.*. Also, the magnitude of the rotations are similar within each series which is logical for a group of very closely related diastereomers (e.g. (*R*,*R*)-diethyl-, (*R*,*R*)-diisopropyl- and (*R*,*R*)-di-t-butyltartrates are +7.5 ($CHCl_3$), +16.1 (neat), +11 (c = 1 acetone)[179]).

3.4 Structure and absolute stereochemistry

In comparison to the parent resorcinarene solid state structures (see **section 2.5**), the addition of four bulky camphorsulfonyl substituents to the upper rim causes significant flattening of the crown conformation. Remarkably, unlike the majority of resorcinarene structures, the bowl is symmetrical with identical benzene ring – methine plane angles for oppositely facing arenes (angles of 79.53 º and 165.78 º).

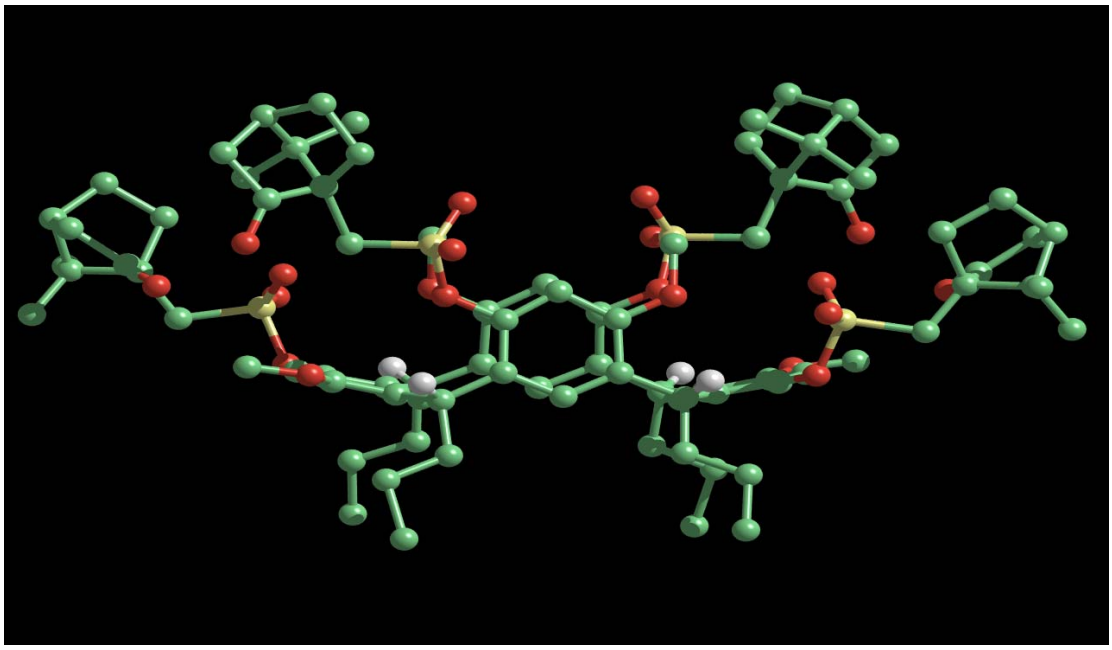


Figure 3.5 – Side view of the 2(*R*),*4*(*R*),*6*(*R*),*8*(*R*)-1^4,3^6,5^6,7^6-tetracamphorsulfonyl-oxy-1^6,3^4,5^4,7^4-tetramethoxy-2,4,6,8-tetrapropylresorcin[4]arene (**260a**, solvent and hydrogen atoms have been omitted for clarity).

This pinched cone conformation is typical of resorcinarenes functionalised at all eight phenols and may simply be a consequence of the steric bulk not present in the parent molecules (see **sections 2.6.1** and **2.6.2**). The exceptional degree to which **260a** is pinched is simply a consequence of the significant size of the camphorsulfonyl moieties.

The packing of **260a** (see **figure 3.6**) is dramatically different to the typical bilayer patterns seen in previous X-ray structures of unfunctionalised resorcinarenes (see **section 2.5**). This is presumably due to the polar functionality of the resorcinarene being essentially buried by the large camphor moieties thus retarding the impetus for

the usual head to head interactions. The molecules of **260a** are interlocked in a repeating V-shaped arrangement with camphorsulfonyl group of the more "flattened" arenes projected towards the cavity of the adjacent resorcinarenes.

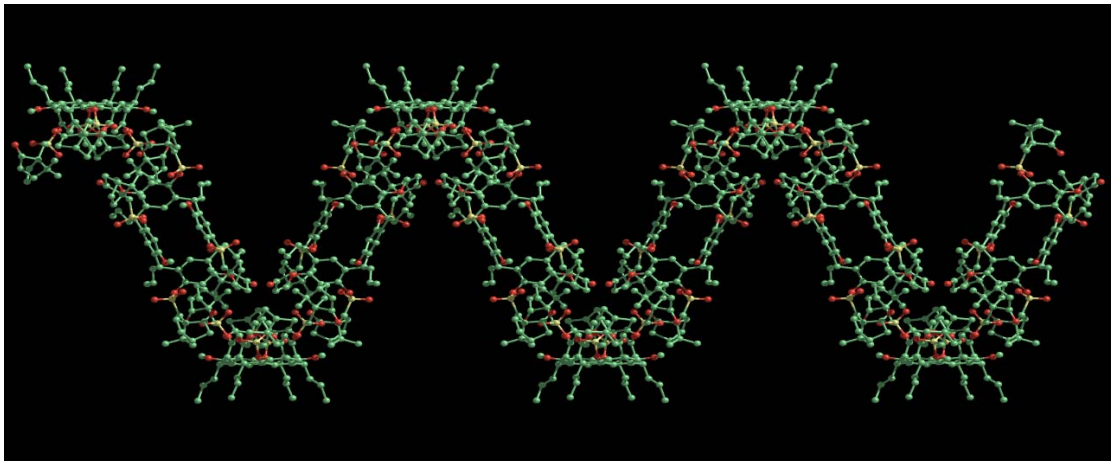


Figure 3.6 – Packing view of the derivative **260a**, solvent and hydrogen atoms have been omitted for clarity (note: a larger version of the packing diagram is given in **Appendix 6**).

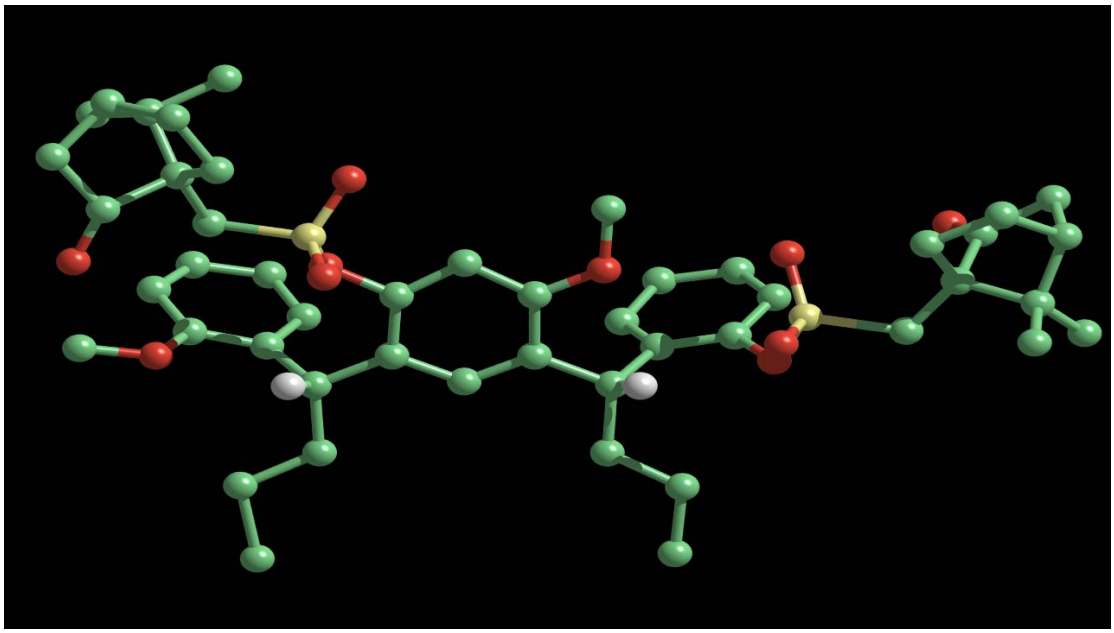
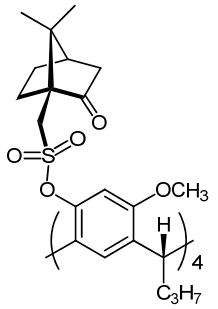


Figure 3.7 – Fragment of derivative **260a** clearly showing the stereochemistry.

The fragment view of the resorcinarene (**figure 3.7**) clearly shows that stereo-centers of **260a** are all *R*. Consequently the 2(*R*),*4*(*R*),*6*(*R*),*8*(*R*)-1^4,3^6,5^6,7^6-tetracamphorsulfonyloxy-1^6,3^4,5^4,7^4-tetramethoxy-2,4,6,8-tetrapropylresorcin[4]arene may be adequately represented in the fashion described in **figure 3.8**.



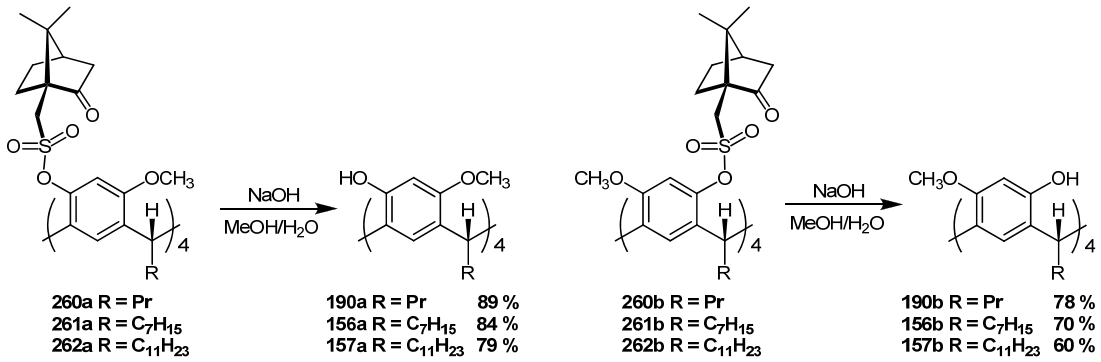
260a

Figure 3.8 – Structural representation of **260a** showing appropriate stereochemistry.

On the basis of the spectroscopic evidence (see **section 3.3.2**) it is reasonable to assume that all of the first eluting diastereomers are of the same absolute stereochemistry as **260a**.

3.5 Hydrolysis of the camphorsulfonates

Sulfonate esters are traditionally removed by basic hydrolysis.[180] For the hydrolysis of resorcinarene monocamphorsulfonates **167a** and **167b** Mattay *et al*. applied a simple aqueous KOH solution. However, this method was no doubt only effective due to the presence of acidic phenolic groups and relatively short pendant isobutyl chains. For the tetracamphorsulfonates, which are substantially more lipophilic (particularly in the case of the heptyl and undecyl versions) it was deemed prudent to apply a system reminiscent of that used for hydrolysis of the bis camphorsulfonate ester of 1,16-dihydroxytetraphenylene (**251**,[173] **section 3.0**). Thus, the resorcinarene tetrasulfonates were hydrolysed smoothly with a mixture of sodium hydroxide in water/methanol solution to afford the enantiomerically pure C_4-dissymmetric resorcinarenes with the yields summarised in **scheme 3.5**.



260a R = Pr
261a R = C_7H_{15}
262a R = $C_{11}H_{23}$

190a R = Pr 89 %
156a R = C_7H_{15} 84 %
157a R = $C_{11}H_{23}$ 79 %

260b R = Pr
261b R = C_7H_{15}
262b R = $C_{11}H_{23}$

190b R = Pr 78 %
156b R = C_7H_{15} 70 %
157b R = $C_{11}H_{23}$ 60 %

scheme 3.5 – Hydrolysis of the resorcinarene tetracamphorsulfonates to the corresponding single enantiomers.

The approximate reaction periods (deduced by t.l.c.) were different for the diastereomers. Although unconfirmed, the propensity for loss of the first camphorsulfonyl ester moiety appeared greater for the diastereomer B series. Confirmation may be obtained in the future by competitive hydrolysis experiments of the diastereomers within the same reaction mixture and potentially a kinetic resolution method developed.

3.5.1 Physical and spectroscopic properties of the enantiomerically pure resorcinarenes

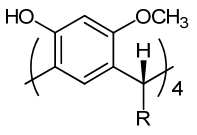
3.5.1.1 M.p., crystallinity, solubility

All of the single enantiomer resorcinarenes resolved via the camphorsulfonyl esters were produced as crystalline solids. This is not surprising as the corresponding racemates are also substantially crystalline (see **section 2.3**). However, there are large differences between the melting points of the single enantiomers and the racemate i.e. differences of 45, 18 and 19 °C for resorcinarenes **190a**, **156a** and **157a** vs their respective racemates. A difference in melting point between single enantiomers and the racemate is a fairly common occurrence (c.f. (+/-)-naproxen 150-151 °C,[181] (*S*)-naproxen 156 °C,[182] (*R*)-naproxen 155-157 °C[183]). However, the racemate is typically lower in melting point due to freezing point depression.

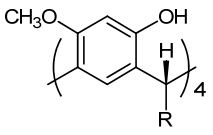
Racemates **190** and **156** both have melting points higher than their corresponding single enantiomers. The racemic C_4 dissymmetric resorcinarenes appear to crystallise in a head to head fashion in general, which is demonstrated in their x-ray crystal structures (see **section 2.5**). In this way the two enantiomers can interlock in ordered bilayer structures. Presumably, this mode of crystallisation is disfavoured for the single enantiomers and an alternate packing must be adopted. This may explain the odd behaviour of the melting point data to some extent. Solvates of the resorcinarenes are also a frequent occurrence (see **section 2.5**)

3.5.1.2 N.m.r. spectroscopic and optical rotation properties

Comparison of the spectra for the single enantiomers and the racemates expectedly revealed no differences. Application of the chiral shift reagent tris[3-(heptafluoro propylhydroxymethylene)-(+)-camphorate at a variety of concentrations to an n.m.r. sample of **156a** produced no splitting of the signals, indicating that the sample was a single enantiomer.



190a R = Pr +88.5
156a R = C_7H_{15} +65.4
157a R = $C_{11}H_{23}$ +51.0



190b R = Pr -89.2
156b R = C_7H_{15} -66.1
157b R = $C_{11}H_{23}$ -46.9

Figure 3.9 – Specific rotation values for the enantiomerically pure resorcinarenes.

Measurement of the optical rotations (**figure 3.9**) demonstrated that the two isolated hydrolysis products for each resorcinarene pair are of equal magnitude but in opposite directions, indeed confirming that they are enantiomers. The rotation of **157b** was somewhat depressed due to a slight contamination with **157a**. All of the resorcinarenes obtained from the hydrolysis of the first eluting camphorsulfonate diastereomers had a positive rotation. Thus, the resorcinarene enantiomers with a positive optical rotation value are the 2(*S*),*4*(*S*),*6*(*S*),*8*(*S*)-2,4,6,8-tetraalkyl-1^6,3^4,5^4,7^4-tetramethoxyresorcin[4]arene-1^4,3^6,5^6,7^6-tetrols.The magnitude of the

rotations decreased with increasing chain length in both cases, presumably due to effective "dilution" of the stereocentres.[184]

Interestingly, the magnitude of the optical rotations for the enantiomers of the tetramethoxyresorcinarenes, are significantly higher than the enantiomers of the heptamethylresorcinarene enantiomers produced by Mattay (see **section 1.1.2**). His *C*-methylheptamethoxyresorcinarenes were found to have rotations of +15.0 and -15.1.

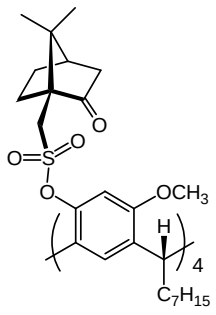
3.6 Experimental

A single crystal of x-ray quality was obtained for **260a** by slow evaporation of solvent from a methanol - dichloromethane (~5 mL each) solution containing approximately 40 mg of **260a**. Chiral shift n.m.r. experiments were performed by stepwise addition of 0.25 mol equivalents of tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorate to an n.m.r. sample containing 20 mg of **156a** in 0.8 mL deuterated chloroform.

General procedure for the preparation of the camphorsulfonyl derivatives

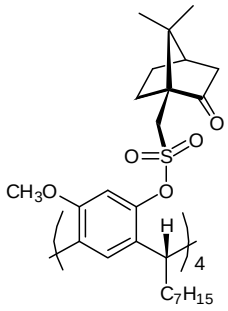
3.6.1 $1^4,3^6,5^6,7^6$-tetracamphorsulfonyloxy-$1^6,3^4,5^4,7^4$-tetramethoxy-2,4,6,8-tetraheptylresorcin[4]arene (261)

To solution of **156** (0.50 g, 0.53 mmol) in dry pyridine (10 mL) was added camphorsulfonyl chloride (1.07 g, 4.3 mmol) in several portions at room temperature. The mixture was then heated at reflux overnight. The bulk of the pyridine was then removed at reduced pressure and the residue stirred with dilute hydrochloric acid (30 mL) for 30 minutes. The mixture was then extracted with ether (2 x 30 mL) and the combined extracts washed with dilute hydrochloric acid (2 x 30 mL), water (1 x 30 mL), brine (1 x 30 mL) and dried ($MgSO_4$). The ether was removed at reduced pressure to give the tetrasulfonates as a glassy solid. The solid was purified by chromatography (silica, CH_2Cl_2/EtOAc 95:5) to give:



Diastereomer A (**261a**) 0.38 g (39 %) as a colourless glass. ^{1}H n.m.r. ($CDCl_3$, 400 MHz) δ 0.86 (t, 12 H, J = 6.8 Hz, CH_2CH_3), 0.90 (s, 12 H, CCH_3), 1.13 (s, 12 H, CCH_3), 1.18-1.39 (m, 40 H, CH_2 x 20), 1.41-1.48 (m, 4 H, camph), 1.66-1.75 (m, 4 H, camph), 1.79-1.89 (m, 8 H, $CH_2CH_2CH_3$), 1.97 (d, 4 H, J = 18.4 Hz, camph), 2.02-2.16 (m, 8 H, 2 x camph 4H), 2.38-2.57 (m, 8 H, 2 x camph 4H), 3.26 (d, 4 H, J = 14.8 Hz, CH_2S), 3.67 (s, 12 H, OCH_3), 3.84 (d, 4 H, CH_2S), 4.49 (t, 4 H, J = 7.2 Hz, CH_2CHAr), 6.71 (s, 4 H, Ar), 6.80 (s, 4 H, Ar). ^{13}C n.m.r. ($CDCl_3$) δ14.8, 20.4, 20.6, 23.4, 25.8, 27.6, 28.7, 30.0, 30.6, 32.7, 35.5, 36.8,

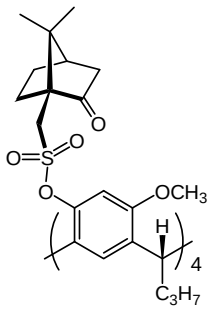
43.2, 43.6, 48.5, 49.1, 56.6, 58.8, 105.4, 126.9, 129.0, 131.8, 146.4, 156.1, 214.7. $[\alpha]_D$ +46.7 (c = 4.1), MS *m/z* 1793.9 (M^+), IR υ_{max} = 2928, 2856, 1749, 1498, 1358 cm^{-1}.



Diastereomer B (**261b**) 0.16 g (17 %) as a colourless glass. ^{1}H n.m.r. ($CDCl_3$, 400 MHz) δ 0.86 (t, 12 H, J = 6.7 Hz, CH_2CH_3), 0.94 (s, 12 H, CCH_3), 1.167 (s, 12 H, CCH_3), 1.173-1.38 (m, 40 H, CH_2 x 20), 1.40-1.56 (m, 4 H, camph), 1.60-1.70 (m, 4 H, camph), 1.77-1.88 (m, 8 H, $CH_2CH_2CH_3$), 1.97 (d, 4 H, J = 18.4 Hz, camph), 2.01-2.15 (m, 8 H, 2 x camph 4H), 2.36-2.55 (m, 8 H, 2 x camph 4H), 3.25 (d, 4 H, J = 15.0 Hz, CH_2S), 3.70 (s, 12 H, OCH_3), 3.84 (d, 4 H, CH_2S), 4.47 (t, 4 H, J = 7.3 Hz, CH_2CHAr), 6.66 (s, 4 H, Ar), 6.83 (s, 4 H, Ar). ^{13}C n.m.r. ($CDCl_3$) δ 14.8, 20.4, 20.7, 23.4, 25.8, 27.6, 28.7, 30.0, 30.5, 32.7, 35.3, 36.9, 43.1, 43.6, 48.5, 49.3, 56.5, 58.8, 105.5, 126.9, 128.8, 131.6, 146.4, 156.1, 214.6. $[\alpha]_D$ +5.6 (c = 5.7), MS *m/z* 1793.9 (M^+), IR υ_{max} = 2928, 2856, 1749, 1498, 1358 cm^{-1}.

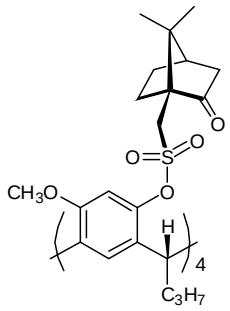
3.6.2 $1^4,3^6,5^6,7^6$-tetracamphorsulfonyloxy-$1^6,3^4,5^4,7^4$-tetramethoxy-2,4,6,8-tetrapropylresorcin[4]arene (260)

The above procedure followed using **190** (2.00 g, 2.8 mmol) and camphorsulfonyl chloride (5.63 g, 22.5 mmol) to give a glassy solid which was purified by chromatography (silica, CH_2Cl_2/EtOAc 93:7). The resulting glassy solids were crystallised from methanol to give:



Diastereomer A (**260a**) as off white crystals (2.02 g, 46 %). m.p. 189-191 °C (Softens 165 °C). ^{1}H n.m.r. ($CDCl_3$, 400 MHz) δ 0.90 (s, 12 H, CCH_3), 0.95 (t, 12 H, J = 7.4 Hz, CH_2CH_3), 1.14 (s, 12 H, CCH_3), 1.30-1.50 (m, 12 H, CH_2CH_3 and camph 1H), 1.65-1.75 (m, 4 H, camph), 1.79-1.90 (m, 8 H, $CH_2CH_2CH_3$), 1.97 (d, 4 H, J = 18.8 Hz, camph), 2.01-2.16 (m, 8 H, 2 x camph 4H), 2.38-2.57 (m, 8 H, 2 x camph 4H), 3.26 (d, 4 H, J = 14.8 Hz, CH_2S), 3.67 (s, 12 H, OCH_3), 3.84 (d, 4 H, CH_2S), 4.52 (t, 4 H, J = 7.4 Hz, CH_2CHAr), 6.73 (s, 4 H, Ar), 6.80 (s, 4 H, Ar). ^{13}C n.m.r. ($CDCl_3$) δ 14.9 (CH_3CH_2), 20.4, 20.6 ($C(CH_3)_2$), 21.7 (CH_3CH_2),

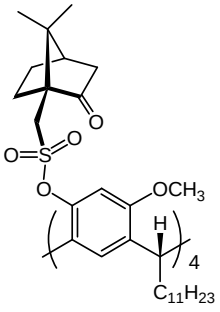
25.8 (camph C6), 27.6 (camph C5), 36.4 (*C*HAr), 37.7 ($CH_3CH_2CH_2$), 43.2 (camph C3), 43.6 (camph C4), 48.5 (camph C7), 49.1 (camph C10), 56.6 (OCH_3), 58.8 (camph C1), 105.4 (ArH), 126.9 (ArH), 129.0 (Ar), 131.7 (Ar), 146.4 (Ar), 156.1 (Ar), 214.7 (C=O). $[\alpha]_D$ +61.3 (c = 6.2), IR υ_{max} = 2958, 2873, 1748, 1498, 1357 cm^{-1}.



Diastereomer B (**260b**) as a glassy solid (1.02 g, 23 %). ^1H n.m.r. ($CDCl_3$, 400 MHz) δ 0.92-0.96 (m, 24 H, CCH_3 and CH_2CH_3), 1.17 (s, 12 H, CCH_3), 1.30-1.51 (m, 12 H, CH_2CH_3 and camph 1H), 1.61-1.71 (m, 4 H, camph), 1.79-1.88 (m, 8 H, $CH_2CH_2CH_3$), 1.97 (d, 4 H, J = 18.4 Hz, camph), 2.00-2.16 (m, 8 H, 2 x camph 4H), 2.37-2.56 (m, 8 H, 2 x camph 4H), 3.26 (d, 4 H, J = 15.0 Hz, CH_2S), 3.70 (s, 12 H, OCH_3), 3.85 (d, 4 H, CH_2S), 4.50 (t, 4 H, J = 7.3 Hz, CH_2CHAr), 6.68 (s, 4 H, Ar), 6.83 (s, 4 H, Ar). ^{13}C n.m.r. ($CDCl_3$) δ 14.9 (CH_3CH_2), 20.4, 20.7 ($C(CH_3)_2$), 21.7 (CH_3CH_2), 25.8 (camph C6), 27.6 (camph C5), 36.6 (*C*HAr), 37.5 ($CH_3CH_2CH_2$), 43.1 (camph C3), 43.7 (camph C4), 48.5 (camph C7), 49.3 (camph C10), 56.6 (OCH_3), 58.8 (camph C1), 105.5 (ArH), 126.9 (ArH), 128.8 (Ar), 131.5 (Ar), 146.5 (Ar), 156.1 (Ar), 214.6 (C=O). $[\alpha]_D$ +2.6 (c = 4.2), MS *m/z* 1568.6 (M^+), IR υ_{max} = 2957, 2872, 1749, 1498, 1357 cm^{-1}.

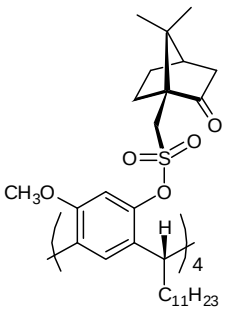
3.6.3 $1^4,3^6,5^6,7^6$-tetracamphorsulfonyloxy-$1^6,3^4,5^4,7^4$-tetramethoxy-2,4,6,8-tetraundecylresorcin[4]arene (262)

The above procedure followed using **157** (0.50 g, 0.43 mmol) and camphorsulfonyl chloride (0.86 g, 3.4 mmol) to give 0.76 g of the diastereomeric mixture which was purified by chromatography (silica, CH_2Cl_2/EtOAc 93:7) to give:



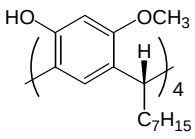
Diastereomer A (**262a**) 0.33 g (38 %) as a glassy solid. ^1H n.m.r. ($CDCl_3$, 400 MHz) δ 0.83-0.92 (m, 24 H, CCH_3 and CH_2CH_3), 1.15 (s, 12 H, CCH_3), 1.17-1.37 (m, 72 H, CH_2 x 36), 1.40-1.50 (m, 4 H, camph), 1.65-1.75 (m, 4 H, camph), 1.78-1.90 (m, 8 H, $CH_2CH_2CH_3$), 1.97 (d, 4 H, J = 18.5 Hz, camph), 2.01-2.16 (m, 8 H, 2 x camph 4H), 2.37-2.56 (m, 8 H, 2 x camph 4H), 3.25 (d, 4 H, J =

15.0 Hz, CH_2S), 3.66 (s, 12 H, OCH_3), 3.83 (d, 4 H, CH_2S), 4.48 (t, 4 H, J = 7.2 Hz, CH_2CHAr), 6.70 (s, 4 H, Ar), 6.79 (s, 4 H, Ar). ^{13}C n.m.r. ($CDCl_3$) δ14.8, 20.4, 20.6, 23.4, 25.8, 27.6, 28.7, 30.1, 30.4, 30.5, 30.6, 30.7, 32.6, 35.5, 36.8, 43.2, 43.6, 48.5, 49.1, 56.6, 58.8, 105.4, 126.9, 129.0, 131.8, 146.4, 156.1, 214.6. $[\alpha]_D$ +51.4 (c = 3.6), MS *m/z* 2018.0 (M^+), IR υ_{max} = 2925, 2854, 1749, 1498, 1358 cm^{-1}.



Diastereomer B (**262b**) 0.17 g (20 %) as a glassy solid. ^1H n.m.r. ($CDCl_3$, 400 MHz) δ 0.87 (t, 12 H, J = 6.5 Hz, CH_2CH_3), 0.94 (s, 12 H, CCH_3), 1.167 (s, 12 H, CCH_3), 1.17-1.37 (m, 72 H, CH_2 x 36), 1.38-1.50 (m, 4 H, camph), 1.60-1.71 (m, 4 H, camph), 1.76-1.87 (m, 8 H, $CH_2CH_2CH_3$), 1.97 (d, 4 H, J = 18.5 Hz, camph), 2.00-2.15 (m, 8 H, 2 x camph 4H), 2.35-2.54 (m, 8 H, 2 x camph 4H), 3.25 (d, 4 H, J = 15.0 Hz, CH_2S), 3.70 (s, 12 H, OCH_3), 3.84 (d, 4 H, CH_2S), 4.47 (t, 4 H, J = 7.2 Hz, CH_2CHAr), 6.65 (s, 4 H, Ar), 6.82 (s, 4 H, Ar). ^{13}C n.m.r. ($CDCl_3$) δ 14.8, 20.4, 20.7, 23.4, 25.8, 27.6, 28.8, 30.1, 30.4, 30.5, 30.57, 30.64, 32.6, 35.3, 36.9, 43.1, 43.6, 48.5, 49.3, 56.5, 58.8, 105.5, 126.9, 128.8, 131.6, 146.4, 156.1, 214.6. $[\alpha]_D$ +0.14 (c = 7.02), MS *m/z* 2018.3 (M^+), IR υ_{max} = 2928, 2856, 1749, 1498, 1358 cm^{-1}.

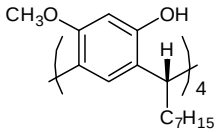
3.6.4 2(*S*),4(*S*),6(*S*),8(*S*)-2,4,6,8-tetraheptyl-1^6,3^4,5^4,7^4-tetramethoxy resorcin[4]arene-1^4,3^6,5^6,7^6-tetrol (156a)



To a solution of **261a** (0.37 g, 0.2 mmol) in methanol (30 mL) and water (1 mL) was added sodium hydroxide (1.6 g, 40 mmol) and the mixture heated at reflux overnight. The solvent was removed at reduced pressure and to the residue was added water (approx. 10 mL). The pH of the mixture was then adjusted to pH 2 with hydrochloric acid (conc.) and the acidified mixture extracted with dichloromethane (2 x 10 mL). The extracts were dried ($MgSO_4$) and the solvent removed under reduced pressure. Crystallisation of the residue from methanol yielded off-white plates (0.16 g, 84 %), m.p. 141.7 – 142.5 °C. ^1H n.m.r. ($CDCl_3$) δ 0.90 (br t, 12 H, CH_2CH_3), 1.20-1.42 (m, 40 H, CH_2), 2.10-

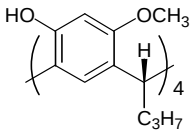
2.28 (m, 8 H, C*H*$_2$CH), 3.84 (s, 12 H, OCH$_3$), 4.27 (t, 4 H, J = 8.0Hz, C*H*CH$_2$), 6.35, 7.23 (s, 2 x 4 H, ArH), 7.52, (s, 4 H, OH). ^{13}C n.m.r. ($CDCl_3$) δ 14.8 (CH_3), 23.3, 28.8, 30.0, 30.3, 32.6, 34.7 (CH_2), 33.8 (CH), 56.6 (OCH_3), 100.7, 124.4, 125.3, 125.4, 153.7, and 154.3 (Ar). $[\alpha]_D$ +65.4 (c = 1.3). Found: C, 76.9; H, 9.6; $C_{60}H_{88}O_8$; requires C, 76.9; H, 9.5 %.

3.6.5 2(*R*),4(*R*),6(*R*),8(*R*)-2,4,6,8-tetraheptyl-1^6,3^4,5^4,7^4-tetramethoxy resorcin[4]arene-1^4,3^6,5^6,7^6-tetrol (156b)



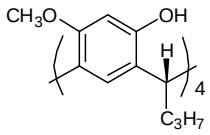
Hydrolysis of **261b** (0.32 g, 0.18 mmol) with sodium hydroxide (0.71 g, 17.8 mmol) as described for the preparation of **156a** and crystallisation of the residue from methanol yielded colourless plates (0.12 g, 70 %), m.p. 140.6 – 141.8 °C. ^{1}H n.m.r. ($CDCl_3$) δ 0.90 (br t, 12 H, CH_2CH_3), 1.17-1.46 (m, 40 H, CH_2), 2.10-2.28 (m, 8 H, C*H*$_2$CH), 3.84 (s, 12 H, OCH_3), 4.27 (t, 4 H, J = 7.8Hz, C*H*CH$_2$), 6.35, 7.22 (s, 2 x 4 H, ArH), 7.54, (s, 4 H, OH). ^{13}C n.m.r. ($CDCl_3$) δ 14.8 (CH_3), 23.3, 28.8, 30.0, 30.4, 32.6, 34.7 (CH_2), 33.8 (CH), 56.6 (OCH_3), 100.7, 124.4, 125.3, 125.4, 153.7, and 154.3 (Ar). $[\alpha]_D$ -66.1 (c = 1.9). MS (FAB): calcd. for $[C_{60}H_{88}O_8]^+$ 936.6479; found 936.6469.

3.6.6 2(*S*),4(*S*),6(*S*),8(*S*)-2,4,6,8-tetrapropyl-1^6,3^4,5^4,7^4-tetramethoxy resorcin[4]arene-1^4,3^6,5^6,7^6-tetrol (190a)



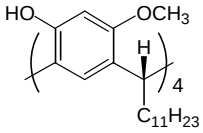
Hydrolysis of **260a** (0.52 g, 0.33 mmol) with sodium hydroxide (1.32 g, 33.1 mmol) as described for the preparation of **156a** and crystallisation of the residue from methanol yielded pale orange plates (0.21 g, 89 %), m.p. 212-213 °C**.** ^{1}H n.m.r. ($CDCl_3$) δ 0.99 (t, 12 H, J = 7.4 Hz, CH_2CH_3), 1.32 (hex, 8 H, J = 7.4 Hz, CH_2), 2.20 (q, 8 H, J = 7.4 Hz, C*H*$_2$CH), 3.84 (s, 12 H, OCH_3), 4.31 (t, 4 H, J = 8.0 Hz, C*H*CH$_2$), 6.35 (s, 4 H, ArH), 7.24 (s, 4 H, ArH), 7.51, (s, 4 H, OH). ^{13}C n.m.r. ($CDCl_3$) δ 14.7 (CH_3), 21.7, 33.4, 36.7 (CH_2 and CH), 56.6 (OCH_3), 100.7, 124.5, 125.3, 125.4, 153.7, and 154.4 (Ar). $[\alpha]_D$ +88.5 (c = 2.6). Found: C, 73.8; H, 7.8; $C_{44}H_{56}O_8$; requires C, 74.1; H, 7.9 %.

3.6.7 2(*R*),4(*R*),6(*R*),8(*R*)-2,4,6,8-tetrapropyl-1^6,3^4,5^4,7^4-tetramethoxy resorcin[4]arene-1^4,3^6,5^6,7^6-tetrol (190b)



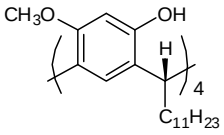
Hydrolysis of **260b** (0.16 g, 0.10 mmol) with sodium hydroxide (0.41 g, 10.2 mmol) as described for the preparation of **156a** and crystallisation of the residue from methanol yielded pale orange plates (0.057 g, 78 %), m.p. 212-213 °C**.** ^{1}H n.m.r. ($CDCl_3$) δ 0.99 (t, 12 H, J = 7.4 Hz, CH_2CH_3), 1.32 (hex, 8 H, J = 7.2 Hz, CH_2), 2.20 (q, 8 H, J = 7.2 Hz, CH_2CH), 3.84 (s, 12 H, OCH_3), 4.31 (t, 4 H, J = 8.0 Hz, $CHCH_2$), 6.35 (s, 4 H, ArH), 7.24 (s, 4 H, ArH), 7.50, (s, 4 H, OH). ^{13}C n.m.r. ($CDCl_3$) δ 14.7 (CH_3), 21.7, 33.4, 36.7 (CH_2 and CH), 56.6 (OCH_3), 100.7, 124.5, 125.3, 125.4, 153.7, and 154.4 (Ar). $[\alpha]_D$ -89.2 (c = 1.2). Found: C, 72.7; H, 8.0; $C_{44}H_{56}O_8.CH_3OH$; requires C, 72.6; H, 8.1 %.

3.6.8 2(*S*),4(*S*),6(*S*),8(*S*)-2,4,6,8-tetraundecyl-1^6,3^4,5^4,7^4-tetramethoxy resorcin[4]arene-1^4,3^6,5^6,7^6-tetrol (157a)



Hydrolysis of **262a** (0.11 g, 0.05 mmol) with sodium hydroxide (0.22 g, 5.5 mmol) as described for the preparation of **156a** and crystallisation of the residue from ethanol yielded tan coloured micro-crystals (0.05 g, 79 %), m.p. 148.5-149.5 °C. ^{1}H n.m.r. ($CDCl_3$) δ 0.89 (br t, 12 H, CH_2CH_3), 1.12-1.48 (m, 72 H, CH_2), 2.07-2.29 (m, 8 H, CH_2CH), 3.84 (s, 12 H, OCH_3), 4.27 (t, 4 H, J = 7.4 Hz, $CHCH_2$), 6.35 (s, 4 H, ArH), 7.22 (s, 4 H, ArH), 7.53 (s, 4 H, OH). ^{13}C n.m.r. ($CDCl_3$, 125 MHz) δ 14.8 (CH_3), 23.4, 28.8, 30.1, 30.42, 30.44, 30.5, 32.6, 33.8, 34.7 (CH_2 and CH), 56.6 (OCH_3), 100.7, 124.4, 125.3, 125.4, 153.6, and 154.3 (Ar). $[\alpha]_D$ + 51.0 (c = 1.3). Found: C, 77.9; H, 10.7; $C_{44}H_{56}O_8.CH_3CH_2OH$; requires C, 77.6; H, 10.5 %.

3.6.9 2(*R*),*4*(*R*),*6*(*R*),*8*(*R*)-2,4,6,8-tetraundecyl-1^6,3^4,5^4,7^4-tetramethoxy resorcin[4]arene-1^4,3^6,5^6,7^6-tetrol (157b)



Hydrolysis of **262b** (0.064 g, 0.03 mmol) with sodium hydroxide (0.15 g, 3.8 mmol) as described for the preparation of **156a** and crystallisation of the residue from ethanol yielded pale orange waxy micro-crystals (0.022 g, 60 %), m.p. 146.5-147.5 °C (softens 141-143). ^{1}H n.m.r. ($CDCl_3$, 500 MHz) δ 0.90 (br t, 12 H, CH_2CH_3), 1.22-1.42 (m, 72 H, CH_2), 2.16-2.23 (m, 8 H, CH_2CH), 3.84 (s, 12 H, OCH_3), 4.28 (t, 4 H, J = 7.8 Hz, $CHCH_2$), 6.35 (s, 4 H, ArH), 7.22 (s, 4 H, ArH), 7.52, (s, 4 H, OH). ^{13}C n.m.r. ($CDCl_3$) δ 14.8 (CH_3), 23.4, 28.8, 30.10, 30.41, 30.44, 30.5, 32.64, 33.7 (CH), 34.7 (CH_2), 56.5 (OCH_3), 100.7, 124.4, 125.3, 125.4, 153.6, and 154.3 (Ar). $[\alpha]_D$ – 46.9 (c = 1.0).

4.0 Resolution of C_4 dissymmetric resorcinarenes by formation of their diastereomeric amides

Enantiomeric resolution of the C_4 dissymmetric resorcinarenes can be achieved effectively by formation of their (+)-camphorsulfonate esters and subsequent hydrolysis of the separated diastereomers (see **section 3.0**). Application of the resulting enantiomers as ligands for chiral catalysis where a metal centre is involved[185-186] or as lanthanide based chiral shift reagents[79] seems logical. However, the resorcinarene enantiomers, as the free phenols, are unlikely to prove very effective as chiral ligands. Phenolic oxygens alone are generally not a good coordinating functionality, except in the case of a pre-organised multidentate ligand.[187] In the case of the resorcinarenes the oxygen donors are spaced somewhat far apart to participate as donors in a concerted fashion. Consequently, the free phenolic enantiomers are unlikely to form a strong association with the majority of metal cations.

There are many published examples where researchers have functionalised the phenols so as to increase the usefulness of resorcinarenes as chiral[188] and achiral[189] species. The unfortunate consequence is that in order to get to the desired functionalised material the parent racemic resorcinarenes must suffer a minimum of three reactions. These reactions are of course the formation of the diastereomers with camphorsulfonyl chloride, hydrolysis of the sulfonate ester and then functionalisation. While three steps is not a large reaction sequence, each of the steps has associated losses. In an attempt to minimise those losses and produce an alternative method for resolution of the racemic resorcinarenes a derivative of the type given in **Figure 4.1** was considered. A group of this kind when attached to the resorcinarene could be expected to provide a means of simultaneous diastereomer formation and useful functionalisation. This would of course limit the need for further transformations post resolution and thus avoid the loss of precious enantiopure material.

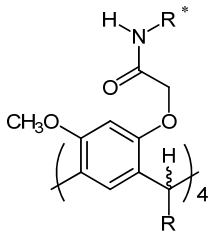
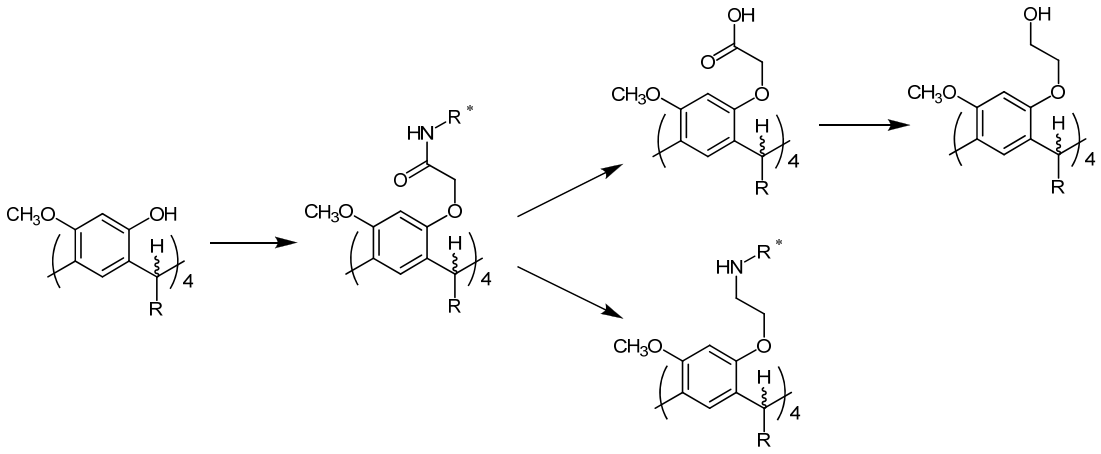


Figure 4.1 – Proposed derivative for the formation of resorcinarene diastereomers.

The amido-ether function is not one generally used simply for the resolution of chiral alcohol species. This is primarily because of the difficulty associated in removing what is quite a robust group. Likely candidates for the removal of such a group would be standard ether cleaving reagents such as boron tribromide[190-191] or perhaps strong oxidants such as RuO_4.[192] Each of these reagents, in the case of the resorcinarene, is fraught with danger. The ether cleaving reagents not only have the potential to cleave the carboxymethyl ethers but also the adjacent methyl ethers. Similarly the oxidising reagents have the potential to oxidise other reactive portions of the molecule.

The robustness of the group in this case is of benefit rather than a hindrance as it is intended that the group (or part thereof) should remain to serve some useful purpose. The intended useful purpose may be something as simple as co-ordination of a metal cation in order to act as a chiral catalyst. In this case it is a necessity that the ligand be sturdy enough to survive the conditions required for the catalysed reaction.

The amide portion of the functionality is amply stable for the majority of applications as has been proven on many previous occasions and its ligating ability is well documented.[193] Unsurprisingly, calixarene and resorcinarene chemists have recognised its value and applied it with vigour.[194-196] In the current synthesis, however, the amide is not just intended as useful functionality in its own right but also as a potential means to other functionality as described in **Scheme 4.1**.



Scheme 4.1 – Proposed scheme for transformation of the resorcinarene amide derivatives.

The chiral amido-ether group must necessarily be prepared from a chiral amine. A range of chiral amines (**Figure 4.2**) are commercially available such as (*S*)-(+)-2-amino-3-methylbutane (**263**), the cyclohexylethylamines (**264**), (-)-isopinocampheylamine (**265**), (*S*)-(-)-2-methyl-1-butylamine (**266**), the 1-(1-naphthyl)ethylamines (**267**), (-)-bis[(*S*)-1-phenylethyl]amine (**268**), (*R*)-(+)-N-methyl-1-phenylethylamine (**269**) and the α-methylbenzylamines (**270**). However the α-methylbenzylamines are particularly cost effective (approx one tenth the price of the amines listed) and are readily available with excellent enantiomeric purity. Conveniently, both enantiomers can be bought at a reasonable price and quantity for comparison. The amines have also been applied on many previous occasions for the resolution of a variety of substrates.[197-200]

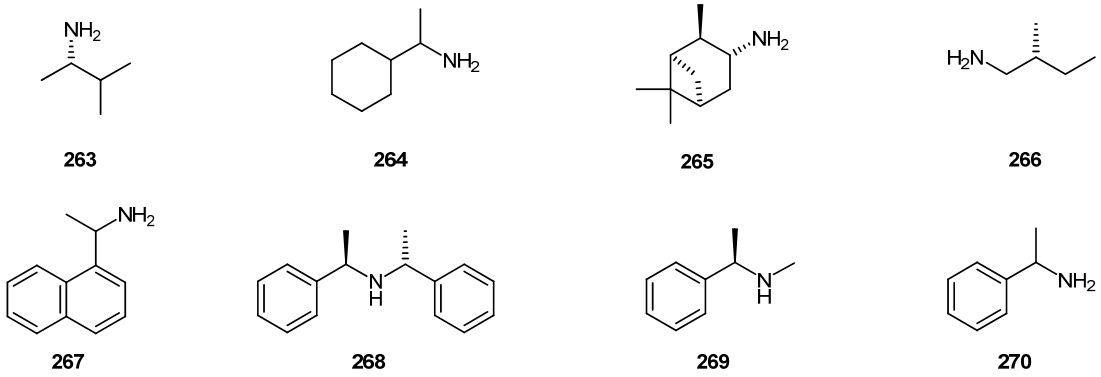


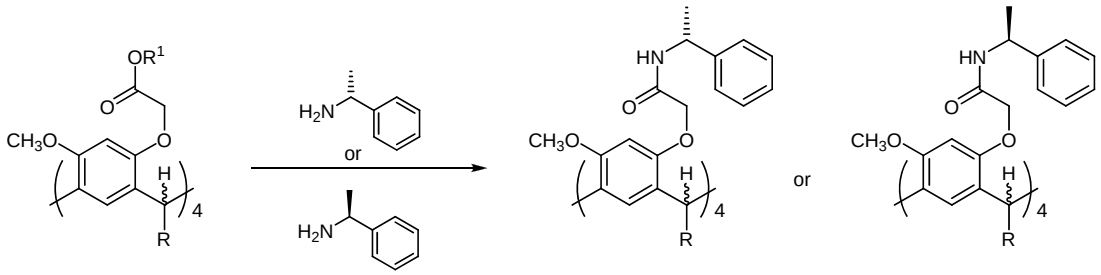
Figure 4.2 – possible amines that may be used for the formation of diastereomeric resorcinarene amide derivatives

4.1 Synthesis of the diastereomeric amide derivatives

The beauty of this amido-ether group is not just in that it is cheap and efficient in terms of functionalisation but also that it is a convenient group to synthesise. Several methods may be used to attach (or construct) the group to the resorcinarene skeleton. The first two (**section 4.1.1 and 4.1.2**) form the amide bond in the presence of the resorcinarene. The third (**section 4.1.3**) makes use of a preformed amide containing alkylating reagent.

4.1.1 Synthesis by direct aminolysis

It was envisaged that the amides of the general structure **271**(**a and b**) (**Figure 4.3**) may be prepared using an adapted procedure described by Toda *et al*.[201] for the conversion of diethyltartrate to its bis(dimethylamide). This seemed convenient as the procedures for attachment of the ester functionality are very well documented for a large variety of calixarene and resorcinarene substrates.[202, 91] The method has more recently been applied to a calixarene tetraester[203] although the authors specifically state that benzylamine, as opposed to the *n*-alkylamines, failed to produce an amide product. This result was ascribed to the additional steric interaction of the larger amine. A similar poor result was also obtained for other sterically crowded amines such as cyclohexylamine, aniline, *t*-butylamine and diethylamine.



272

224 R = C_7H_{15}, R^1 = Et
274 R = Bu^i, R^1 = Me

271a

273 R = C_7H_{15}

271b

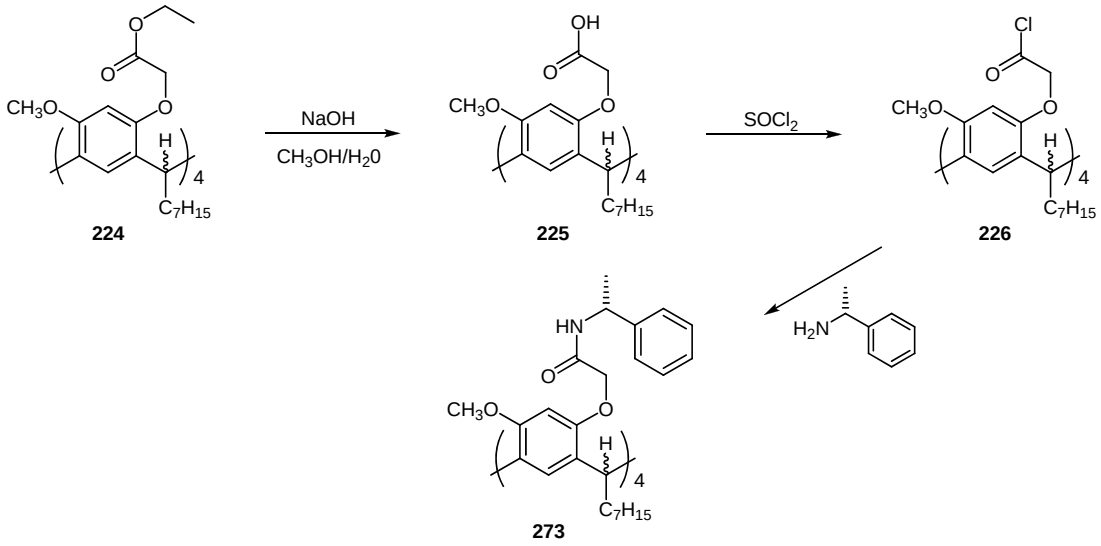
275 R = Bu^i

Figure 4.3 – Synthesis of diastereomeric resorcinarene amide derivatives by aminolysis

The calixarene and resorcinarene esters are substantially different substrates and so it was deemed prudent to test the methodology despite the poor result obtained for the calixarene tetraester with sterically crowded amines. Thus the conversion of resorcinarene tetraester **224** was attempted by the addition of the amine to the resorcinarene firstly in an alcohol solvent (**section 4.6.5**) and then in the neat amine with strong heating (**section 4.6.6**). Neither of these procedures proved fruitful. It is known that the simple esters (Me, Et etc.) are generally difficult to convert to amides by direct aminolysis[204] and in some cases strongly basic catalysis or high pressure[205] have been used. However the addition of sodium hydride to the mixture proved only to yield a complicated mixture of apparent resorcinarene containing materials.
After this part of the study had been concluded, the successful aminolysis of the related compound **274** to afford **275** was reported.[91] In that work Mattay found that heating the mixture of **274** and (S)-(-)-α-methylbenzylamine to 160 °C was required to effect the desired transformation. At lower temperatures up to only three ester moieties could be converted to the amide.

4.1.2 Synthesis by the acid chloride route

The next attempted route to the amide functionality was via the tetra-acid chloride **226** (**Scheme 4.2**). This method has been successfully applied to calix[4]arenes of various kinds and is very well established in the literature.[206] The racemic tetraester **224** was smoothly converted to the tetra acid **225** by hydrolysis at reflux with sodium hydroxide in methanol (**section 2.6.2**). Conversion of **225** to **226** was affected with a vast excess of thionyl chloride at reflux (**section 4.6.7**).



Scheme 4.2 – Synthesis of diastereomeric resorcinarene amide derivatives via the resorcinarene tetra-acid chloride (**226**)

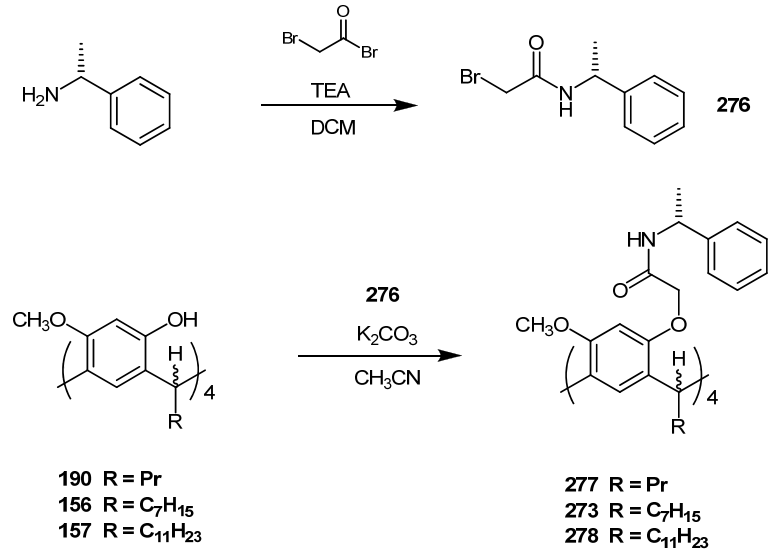
The resulting (not isolated) acid chloride product was then treated with the chiral amine in the presence of a tertiary amine base (triethylamine) or an excess of the chiral amine. However, both methods failed to produce the desired product, instead only affording complex mixtures. The reason for this is not yet known but may be due to inter- or intramolecular anhydride (or imide) formation resulting in a substantial drop in reactivity. A model reaction with diethylamine was performed to eliminate the possibility of imide formation and simplify the potential products. The recovered material was again a mixture of apparently partially substituted resorcinarene materials which were not easily purified. This result could indicate that the reaction may be complicated by some form of anhydride formation prior to the addition of the amine.

Reagents such as dicyclohexylcarbodiimide[207-208] and *N*-hydroxybenzotriazole[209-210] could also be applied to effect the transformation of the acid to the amide. However, these were not investigated as the alternative approach described below was preferred.

4.1.3 Synthesis by attachment of a preformed amide moiety

Alkylation of the resorcinarene hydroxyls appears to be a proven method for a substantial number of alkylating reagents.[117-120, 135-136] A preformed alkylating agent containing the chiral amide fragment in advance would provide a simple path to the desired material without the complications of the former syntheses.[211]

The (*R*)-2-bromo-*N*-(1-phenylethyl)acetamide **276** (**Scheme 4.3**) is known in the literature and is prepared from the (*R*)-(+)-α-methylbenzylamine and bromoacetyl bromide in dichloromethane. The procedure affords the white crystalline amide in approximately 75 % yield with an optical rotation of +19.6.[212] The amide (**276**) has been used as an intermediate in the preparation of chiral ligands for asymmetric palladium catalysed allylic substitution reactions.[212]



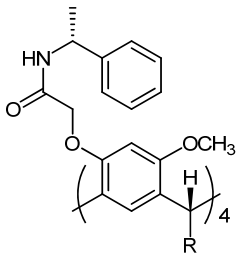
Scheme 4.3 - Synthesis of diastereomeric resorcinarene amide derivatives via the attachment of a chiral amide alkylating agent

The resorcinarenes **156-157** and **190,** were treated with 4.8 equivalents of the alkylating agent **276** with potassium carbonate as the base at reflux in acetone as shown in **Scheme 4.3**. However, even after an overnight reflux no alkylation was observed. However, the reaction was essentially quantitative when acetonitrile was used as the solvent. This rather large solvent effect is presumably due to the more effective solvation of the potassium ion of the potassium phenoxide ion pair by acetonitrile and more significantly due to weaker solvation of the carbonate anions

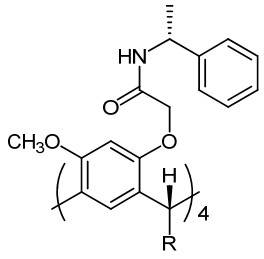
by acetonitrile.[213] The effective increase in basicity is necessary, as the tetramethoxyresorcinarenes are known to be substantially less acidic than the octahydroxy resorcinarenes.[20]

4.2 Resolution of the resorcinarene amide diasteromers

Initially it was discovered that partial enrichment of one diastereomer could be effected by fractional crystallisation from an ether solution. However, this crystallisation was somewhat unpredictable and therefore could not be used reliably as a means of resolution. Ultimately the simplest and most effective route proved to be flash chromatography of the diastereomers with a very specific solvent mixture. The solvent mixture that was used (1:1 EtOAc/CH_2Cl_2) appeared to make use of the significant difference in solubility (in general) of the diastereomeric pairs. To obtain a good separation a relatively low loading on the silica gel column was required and the diastereomers could be separated on a multi-gram scale by this method. The yields obtained for separation of the diastereomers are shown in **figure 4.4**.



277a R = Pr 35 %
273a R = C_7H_{15} 35 %
278a R = $C_{11}H_{23}$ 37 %



277b R = Pr 12 %
273b R = C_7H_{15} 25 %
278b R = $C_{11}H_{23}$ 23 %

Figure 4.4 – The resolved diastereomers of mixtures **273**, **277** and **278** and their respective yields after recrystallisation.

The yields of the second eluting diastereomers (**273b**, **277b** and **278b**) are generally lower than the corresponding diastereomer. This is, in part, due to some minor losses on chromatography as a consequence of the first diastereomer tailing into the second. However majority of losses were encountered on recrystallisation (see **section 4.3.1**)

4.3 Physical and spectroscopic properties of the resorcinarene amides

4.3.1 M.p., crystallinity and solubility

All of the amide derivatives produced are substantially crystalline however much like the camphorsulfonates it is those resorcinarenes prepared from shorter alkyl aldehydes that produced crystalline material suitable for X-ray structural analysis. The longer alkyl chain resorcinarenes, while clearly microcrystalline, did not produce anything more substantial than hair like solids or microcrystalline powders. The difference in crystallinity between the varying length of alkyl chain may be effectively illustrated by the decrease in melting point of the first diastereomers with increasing chain length. The *C*-propylresorcinarene (**277a**) has a melting point of 180-181 °C, *C*-heptyl resorcinarene (**273a**) 170-171 °C and *C*-undecylresorcinarene (**278a**) 164-165 °C. The difference between the diastereomers within each pair is even more marked. In each of the diastereomeric pairs the second diastereomer (**277b**, **273b** and **278b**) has a significantly lower melting point than the first diastereomer (**277a**, **273a** and **278a**). These results appear to concur with the solubility of the different diastereomers. In particular this is demonstrated by the diastereomers **277a** and **277b** both of which are recrystallised from methanol, however the first diastereomer requires approximately five times the quantity of solvent to dissolve. While this represents significant potential for a resolution by fractional crystallisation the diastereomers in this solvent system appear to co-crystallise and crystallise unpredictably in other systems (see **section 4.2**).

4.3.2 N.m.r. spectroscopic and optical rotation properties

The n.m.r. spectrum of the first eluting diastereomer from the mixture **273** (**273a**, **figure 4.5 (a)**) and the second eluting diastereomer (**273b**, **figure 4.5 (b)**) are given for comparison. There is little difference between the spectral features of the resorcinarene component in the up-field region. In **figure 4.5** the signal corresponding to the methoxyl at approximately 3.4 ppm is shifted slightly between the two diastereomers, however the resorcinarene alkyl chains and the methyl

adjacent to the amide are generally in similar positions.

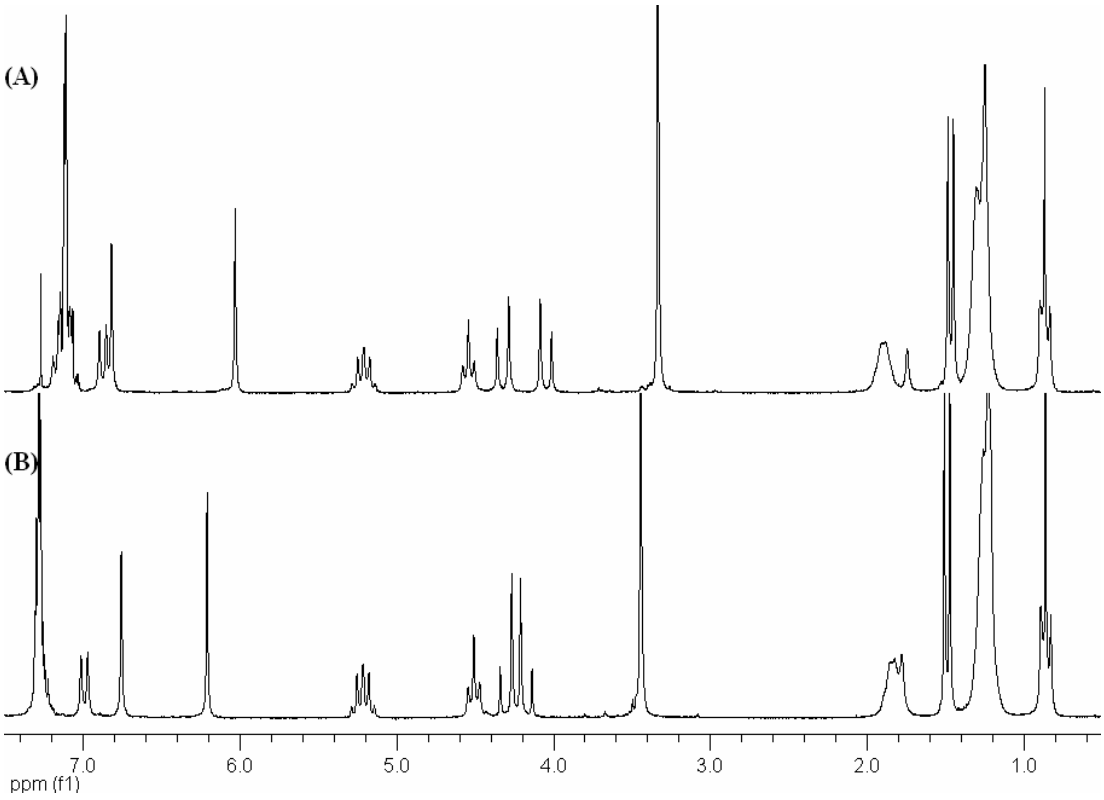


Figure 4.5 – comparison of the proton n.m.r spectra for (**A**) **273a** and (**B**) **273b**

The AB quartet corresponding to the OCH_2CON methylene is somewhat compressed in the spectrum of the second diastereomer. The aromatic region of the spectra clearly demonstrate the differences between the diastereomers. Both aromatic proton signals for the resorcinarene are distinctly different between **273a** and **273b**. Similarly the shift of the phenyl group of the amide functionality is different between **273a** and **273b**. The amide N-H signal which appears as an apparent doublet is also at a substantially different shift between the diastereomers. The doublet signal for the amide N-H appears to be more downfield than is usual for an amide. This is probably due to hydrogen bonding rigidification which is clearly evident in the solid state (see **section 4.4**). The nature of the hydrogen-bonding is shown in **figure 4.6** where the amide N-H is interacting with the ethereal oxygen of the same moiety.

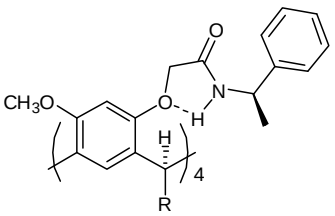
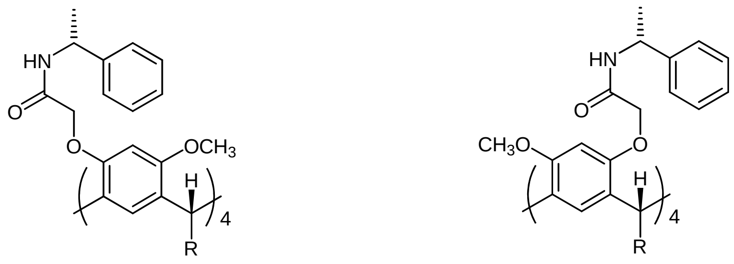


Figure 4.6 – H-bonding features of the amide resorcinarenes.



277a	**R = Pr**	**-7.8**	**277b**	**R = Pr**	**-13.8**
273a	**R = C_7H_{15}**	**-12.6**	**273b**	**R = C_7H_{15}**	**-14.3**
278a	**R = $C_{11}H_{23}$**	**-12.9**	**278b**	**R = $C_{11}H_{23}$**	**-13.0**

Figure 4.7 – Specific rotation values for the resorcinarene amide diastereomers

The optical rotations of the amide functionalised resorcinarenes have surprisingly small differences between diastereomers. Unlike the resorcinarene camphorsulfonates described in section **3.3.2** which typically have a difference in optical rotation values of greater than 40˚ between diastereomers, the amides have a maximum difference of 6˚. However, much like the camphorsulfonates the first eluting diastereomer for each of the amides also has the most positive rotation. The optical rotations of some similarly functionalised calixarene amide derivatives produced by Stibor *et al.*[214-215] are shown in **figure 4.8**.

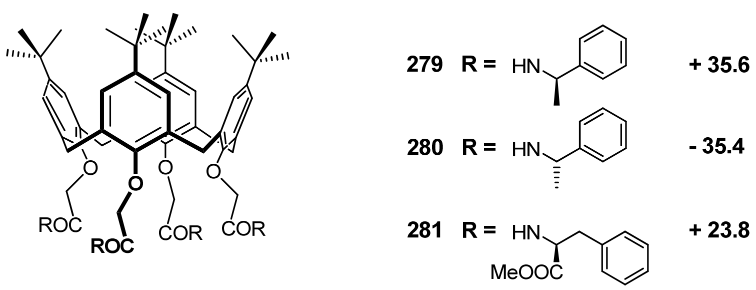


Figure 4.8 – Chiral calixarene amide derivatives produced by Stibor *et al.*

The optical rotations for the calixarenes, like the resorcinarene amides, are fairly low. However, the rotations of the resorcinarene amide derivatives derived from (*R*)-(+)-α-methylbenzylamine have a negative rotation whereas the calixarene derivative prepared with the same amine has a positive rotation. This difference is presumably due to the contribution of the resorcinarene chirality.

4.4 Structure and absolute stereochemistry

The partial x-ray crystal structure of the amide derivative **277a** is depicted in **Figure 4.9**. It is evident from the structure that the first diastereomer eluting from the chromatographic separation has the *R,R,R,R* configuration at the calix methine carbons and can thus be described as 2(*R*),4(*R*),6(*R*),8(*R*)-1^4,3^6,5^6,7^6-tetra-2-oxo-2-{[(1*R*)-1-phenylethyl]amino)ethoxy-1^6,3^4,5^4,7^4-tetramethoxy-2,4,6,8-tetrapropylresorcin[4]arene, the structure is also described by the representation for **277a** in **Figure 4.7**.

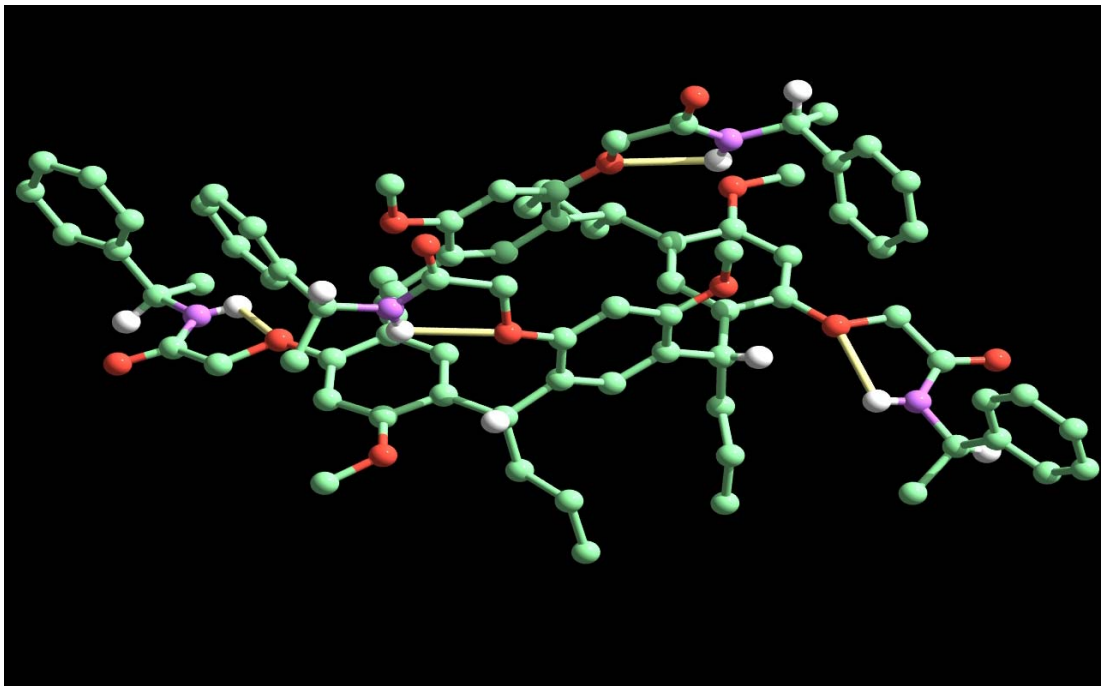


Figure 4.9 – Partial x-ray structure of 2(*R*),4(*R*),6(*R*),8(*R*)-1^4,3^6,5^6,7^6-tetra-2-oxo-2-{[(1*R*)-1-phenylethyl]amino}ethoxy-1^6,3^4,5^4,7^4-tetramethoxy-2,4,6,8-tetrapropylresorcin[4]arene (**277a**, solvent and hydrogen atoms have been omitted for clarity) showing the stereochemistry and hydrogen bonding (gold bonds).

The conformation of **277a** is significantly "pinched" with respect to the unprotected resorcinarenes. In fact, like the *C*-methyl-tetramethoxycalix[4] resorcinarene tetraacetate described in section **2.6.1**, the benzene rings are so pinched that they have passed the point of perpendicular with the methine plane (angles of 85.74 º and 185.07 º)

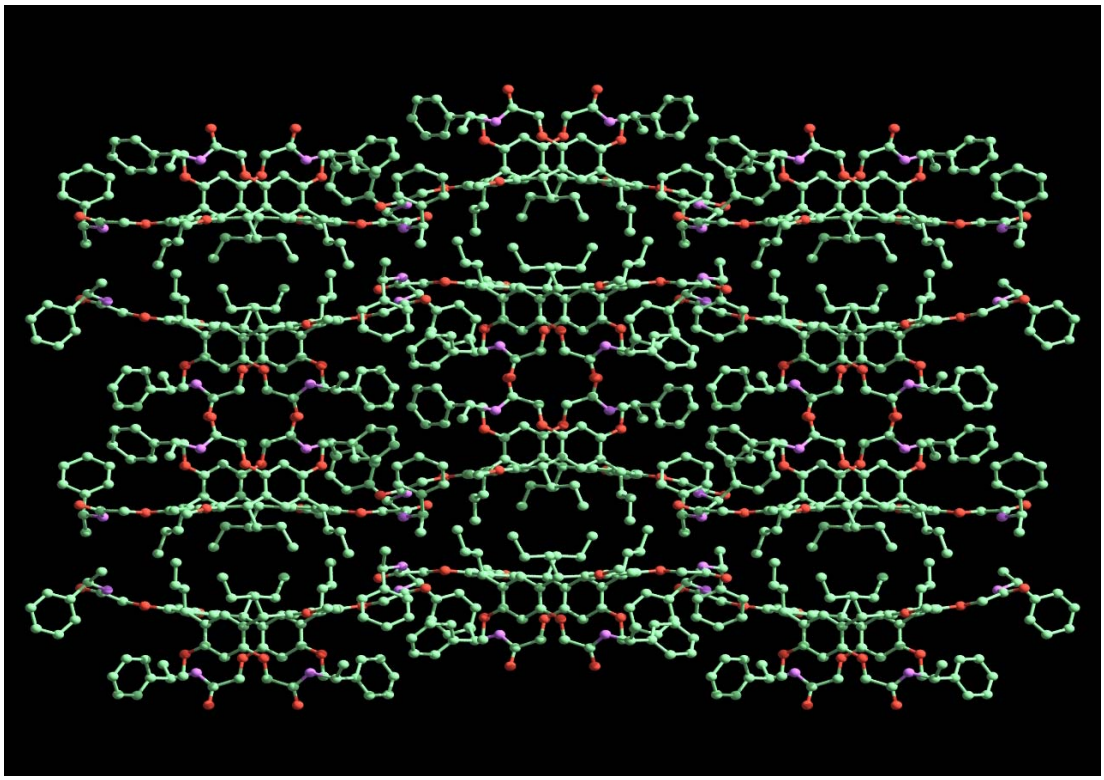


Figure 4.10 – x-ray structure of **277a** showing the packing features (note: a larger version of the packing diagram is given in **Appendix 7**).

The packing diagram above (**Figure 4.10**) clearly shows the typical interlocking bilayer type structure. However, in this instance interdigitation of the alkane tails does not occur in the usual manner but instead couple at right angles to define a cavity between the interlocking resorcinarenes. The hydrogen atoms of the amide NH are engaged in hydrogen bonding with the adjacent ethereal oxygen atoms of the same resorcinarene "arm" with NH...O bond distances of 2.043 Å and 2.246 Å for the two "arms" not related by symmetry. Despite the potential for head to head hydrogen bonding interactions, no intermolecular hydrogen bonds are observed.

The first eluting diastereomer of each resorcinarene pair (**273a**, **277a**, **278a**) appear to have similar n.m.r. spectral features (see **section 4.3.2**). Such a pattern is also evident in the second eluting diastereomer series (**273b**, **277b**, **278b**). It is reasonable to assume that each series therefore has a similar stereochemistry at the resorcinarene methines i.e. all of the first eluting diastereomers are of the *R,R,R,R* configuration. Coincidentally, this is also the case for the resorcinarene camporsulfonates (section

3.4).

The first eluting diastereomeric amide derivative of **275** prepared from (S)-(-)-α-methylbenzylamine was reported by Mattay to have the *S*,*S*,*S*,*S* configuration.[205] However, he incorrectly related this structure to the parent tetramethoxyresorcinarene having a positive optical rotation. This was indeed an error which was retracted and the correct stereochemical assignment was subsequently reported by us.[92]

4.5 Attempted hydrolysis of the amide groups

In general, amides can be cleaved by acidic or basic hydrolysis.[216-218] The latter method is the more common and is usually applied with hydroxide solutions of varying strength.[219] More lipophilic amides may be hydrolysed with sodium alkoxide solutions.[220] In the case of the current amides, the usual methods of hydrolysis were ineffective. Dilute hydrochloric or sulfuric acids, concentrated sulfuric or 100% phosphoric acids, dilute and concentrated sodium and potassium hydroxide solutions and a variety of sodium alkoxides in their respective alcohols (methanol, ethanol and *t*BuOH), all failed. In the majority of cases the result was purely recovery of the starting amide material, however in the case of the concentrated sulphuric acid, 100 % phosphoric acid[221] and 48 % hydrobromic acid the reactions resulted in significant decomposition. Several additional systems for the hydrolysis of amides have been reported, such as the hydrolysis via BOC[222] or nitroso[223] adducts or milder methods such as catalytic copper salts.[224] However, these were not investigated in this study.

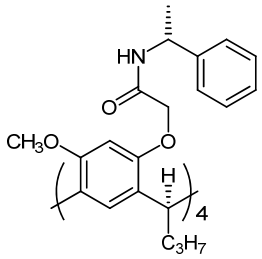
4.6 Experimental

A single crystal of x-ray quality was obtained for **277a** by slow evaporation of solvent from a methanol - dichloromethane (~5 mL each) solution containing approximately 20 mg of **277a**.

4.6.1 - General procedure for amides

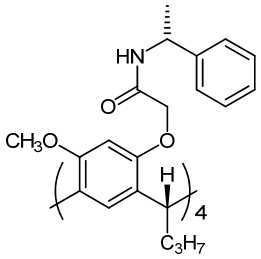
The following general procedure was used to prepare the diastereomeric amide derivatives from the corresponding racemic resorcinarenes.

A mixture of the resorcinarene (3.0 g), alkylating agent (4.8 equiv.) and potassium carbonate (8.0 equiv) in dry acetonitrile (80 mL) were heated to reflux overnight. The reaction mixture was then cooled and to it was added water (80 mL). The resulting precipitate was collected by vacuum filtration and dried under vacuum to give the corresponding diastereomeric mixtures in essentially quantitative yield.



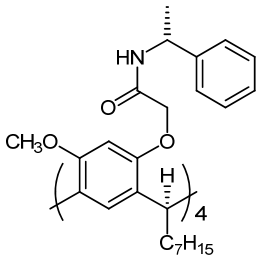
4.6.2 – *C*-Propylresorcinarene amides – The diastereomers were separated by flash chromatography (silica gel, 1:1 EtOAc/CH_2Cl_2).

The first eluting diastereomer (**277a**) was recrystallised from methanol (2.01 g, 35 %) m.p. 180-181 °C, $[\alpha]_D$ -7.8 (c = 2.0). ^{1}H n.m.r. ($CDCl_3$) δ 0.95 (t, J = 7.2 Hz, 12 H, CH_2CH_3), 1.23-1.41 (m, 8H, CH_2CH_3), 1.46 (d, J = 6.6 Hz, 12 H, $CHCH_3$), 1.82-1.98 (m, 8 H, CH_2CH), 3.34 (s, 12H, OCH_3), 4.06, 4.33 (AB quartet, J = 14.5 Hz, 8H, OCH_2), 4.57 (t, J = 8.0 Hz, 4 H, $CHCH_2$), 5.11-5.31 (m, 4 H, $CHCH_3$), 6.03 (s, 4 H, ArH), 6.80-6.92 (m, 8 H, ArH and NH), 7.02-7.22 (m, 20 H, ArH). ^{13}C n.m.r. ($CDCl_3$) δ 14.9, 22.0, 22.5, 35.6, 38.0, 48.6, 56.7, 68.3, 98.0, 126.1, 126.5, 126.9, 127.0, 127.9, 129.2, 143.4, 154.1, 156.3, 168.1. IR 3422, 2955, 2930, 2870, 1684, 1501, 1299, 1199 cm^{-1}. HRMS (FAB): calcd. for $C_{84}H_{100}N_4O_{12}$ $[M]^+$ 1356.7338; found 1356.7129.

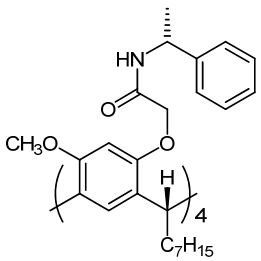


The second eluting diastereomer (**277b**) was recrystallised from methanol (0.67 g, 12 %) m.p. 168-169 °C, $[\alpha]_D$ –13.8 (c = 1.3). ^{1}H n.m.r. ($CDCl_3$) δ 0.89 (t, J = 7.4 Hz, 12 H, CH_2CH_3), 1.16-1.37 (m, 8H, CH_2CH_3), 1.49 (d, J = 6.6 Hz, 12 H, $CHCH_3$), 1.75-1.90 (m, 8 H, CH_2CH), 3.44 (s, 12H, OCH_3), 4.20, 4.30 (AB quartet, J = 14.8 Hz, 8H, OCH_2), 4.58 (t, J = 7.2 Hz, 4 H, $CHCH_2$), 5.16-5.35 (m, 4 H, $CHCH_3$), 6.25 (s, 4 H, ArH), 6.81 (s, 4 H, ArH), 7.03 (d, 4 H, NH), 7.26-7.40 (m, 20 H, ArH). ^{13}C n.m.r. ($CDCl_3$) δ 14.9, 22.0, 22.4, 35.6, 38.1, 48.7, 57.0, 69.1, 98.8, 126.7, 126.9, 127.0, 127.8, 128.0, 129.3, 143.5, 154.3, 156.3, 168.3. IR 3419, 2955, 2931, 2870, 1682, 1499, 1298, 1197 cm^{-1}. Found: C, 73.9; H, 7.3; N, 4.1 %. $C_{84}H_{100}N_4O_{12}$ requires C, 74.3; H, 7.4; N, 4.1 %.

4.6.3 - *C*-heptylresorcinarene amides - The diastereomers were separated by flash chromatography (silica gel, 1:1 EtOAc/CH_2Cl_2.

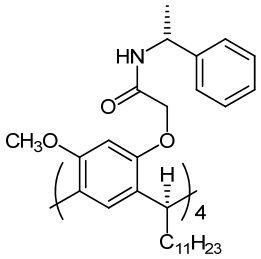


The first eluting diastereomer (**273a**) was recrystallised from ethanol (1.78 g, 35 %) m.p. 170-171 °C. $[\alpha]_D$ -12.6 (c = 4.2). ^{1}H n.m.r. ($CDCl_3$) δ 0.87 (br t, 12 H, CH_2CH_3), 1.14-1.39 (m, 40H, CH_2CH_3 x 20), 1.47 (d, J = 6.6 Hz, 12 H, $CHCH_3$), 1.80-1.99 (m, 8 H, CH_2CH), 3.33 (s, 12H, OCH_3), 4.06, 4.32 (AB quartet, J = 14.6 Hz, 8H, OCH_2), 4.55 (t, J = 7.2 Hz, 4 H, $CHCH_2$), 5.11-5.31 (m, 4 H, $CHCH_3$), 6.03 (s, 4 H, ArH), 6.80-6.92 (m, 8 H, ArH and NH), 7.01-7.22 (m, 20 H, ArH). ^{13}C n.m.r. ($CDCl_3$) δ 14.8, 22.5, 23.3, 29.0, 30.0, 30.6, 32.7, 35.8, 36.0, 48.6, 56.8, 68.5, 98.1, 126.3, 126.6, 127.0, 127.2, 127.9, 129.2, 143.5, 154.1, 156.3, 168.1. IR 3421, 2926, 2854, 1684, 1499, 1298, 1198 cm^{-1}. Found: C, 75.6; H, 8.4; N, 3.5 %. $C_{100}H_{132}N_4O_{12}$ requires C, 75.9; H, 8.4; N, 3.5 %.



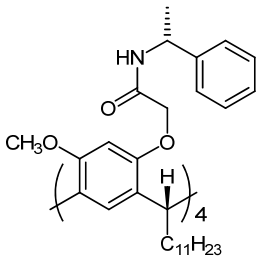
The second eluting diastereomer (**273b**) was recrystallised from methanol (1.28 g, 25 %) m.p. 137-138 °C. $[\alpha]_D$ -14.2 (c = 3.7). ^{1}H n.m.r. ($CDCl_3$) δ 0.87 (br t, 12 H, CH_2CH_3), 1.13-1.36 (m, 40H, CH_2CH_3 x 20), 1.49 (d, J = 7.4 Hz, 12 H, $CHCH_3$), 1.72-1.93 (m, 8 H, CH_2CH), 3.44 (s, 12H, OCH_3), 4.19, 4.30 (AB quartet, J = 14.8 Hz, 8H, OCH_2), 4.51 (t, J = 7.2 Hz, 4 H, $CHCH_2$), 5.14-5.32 (m, 4 H, $CHCH_3$), 6.21 (s, 4 H, ArH), 6.76 (s, 4 H, ArH), 6.99 (d, J = 8.8 Hz, 4 H,

NH), 7.22-7.35 (m, 20 H, ArH). ^{13}C n.m.r. ($CDCl_3$) δ 14.8, 22.5, 23.3, 28.9, 30.0, 30.6, 32.6, 35.9, 36.0, 48.7, 57.0, 69.1, 98.9, 126.6, 126.9 (two coincident signals), 127.9, 128.0, 129.3, 143.5, 154.3, 156.3, 168.3. IR 3418, 2926, 2854, 1685, 1500, 1297, 1198 cm^{-1}. Found: C, 75.6; H, 8.3; N, 3.5 %. $C_{100}H_{132}N_4O_{12}$ requires C, 75.9; H, 8.4; N, 3.5 %.



4.6.4 - *C*-undecylresorcinarene amides - The diastereomers were separated by flash chromatography (silica gel, 1:1 EtOAc/CH_2Cl_2.

The first eluting diastereomer (**278a**) was recrystallised from ethanol (1.74 g, 37 %) m.p. 164-165 °C. $[\alpha]_D$ -12.9 (c = 3.7). ^{1}H n.m.r. ($CDCl_3$) δ 0.88 (br t, 12 H, CH_2CH_3), 1.17-1.38 (m, 72H, CH_2CH_3 x 36), 1.47 (d, J = 7.4 Hz, 12 H, $CHCH_3$), 1.80-1.98 (m, 8 H, CH_2CH), 3.33 (s, 12H, OCH_3), 4.05, 4.32 (AB quartet, J = 14.5 Hz, 8H, OCH_2), 4.54 (t, J = 7.4 Hz, 4 H, $CHCH_2$), 5.11-5.31 (m, 4 H, $CHCH_3$), 6.04 (s, 4 H, ArH), 6.81 (s, 4 H, ArH), 6.87 (d, J = 8.2 Hz, 4 H, NH), 7.03-7.21 (m, 20 H, ArH). ^{13}C n.m.r. ($CDCl_3$) δ 14.8, 22.6, 23.4, 29.1, 30.1, 30.4, 30.45, 30.5, 30.7, 32.6, 35.8, 36.1, 48.6, 56.7, 68.4, 98.1, 126.2, 126.6, 127.0, 127.1, 128.0, 129.2, 143.5, 154.1, 156.3, 168.1 (coincident signals at 30.4). IR 3422, 2924, 2853, 1684, 1509, 1298, 1198 cm^{-1}. Found: C, 77.2; H, 9.1; N, 3.1 %. $C_{116}H_{164}N_4O_{12}$ requires C, 77.1; H, 9.2; N, 3.1 %.



The second eluting diastereomer (**278b**) was recrystallised from ethanol (1.09 g, 23 %) m.p. 108.5-110.0 °C. $[\alpha]_D$ -13.0 (c = 2.8). ^{1}H n.m.r. ($CDCl_3$) δ 0.88 (br t, 12 H, CH_2CH_3), 1.13-1.37 (m, 72H, CH_2CH_3 x 36), 1.49 (d, J = 6.6 Hz, 12 H, $CHCH_3$), 1.76-1.95 (m, 8 H, CH_2CH), 3.44 (s, 12H, OCH_3), 4.19, 4.29 (AB quartet, J = 14.7 Hz, 8H, OCH_2), 4.50 (t, J = 7.4 Hz, 4 H, $CHCH_2$), 5.12-5.31 (m, 4 H, $CHCH_3$), 6.21 (s, 4 H, ArH), 6.75 (s, 4 H, ArH), 6.98 (d, J = 8.0 Hz, 4 H, NH), 7.22-7.36 (m, 20 H, ArH). ^{13}C n.m.r. ($CDCl_3$) δ 14.8, 22.5, 23.4, 29.0, 30.1, 30.39, 30.4, 30.47, 30.5, 30.7, 32.6, 35.9, 36.0, 48.7, 57.0, 69.2, 98.9, 126.6, 126.9, 127.0, 127.9, 128.0, 129.3, 143.5, 154.3, 156.3, 168.3. IR 3418, 2924, 2853, 1685, 1500, 1297, 1198 cm^{-1}. Found: C, 77.0; H, 9.0; N, 3.0 %. $C_{116}H_{164}N_4O_{12}$ requires C, 77.1; H, 9.2; N, 3.1 %.

4.6.5 - Attempted procedure for prep of amide via amine - alcohol exchange

A solution of **224** (0.5 g, 0.4 mmol) and *R*-(+)-α-methylbenzylamine (0.38 g, 3.1 mmol) in anhydrous methanol was heated to reflux for 24 h. The solvent was removed at reduced pressure to afford a colourless oil which was dissolved in ether (30 mL). The ether was then washed with hydrochloric acid (1 M, 2 x 30 mL), water (1 x 30 mL) and dried ($MgSO_4$). The solvent was then removed at reduced pressure and the resulting oil crystallised from methanol to give essentially quantitative recovery of pure starting material **224** (by ^1H n.m.r. spectroscopy)

4.6.6 - Attempted procedure for prep of amide via amine – neat amine

A mixture of **224** (0.50 g, 0.39 mmol) and *R*-(+)-α-methylbenzylamine (0.94 g, 7.8 mmol) was heated at 100 ºC for 3 h. The resulting residue was cooled and diluted with dichloromethane (20 mL) and washed with dilute hydrochloric acid (1 M, 3 x 20 mL), water (1 x 20 mL), brine (1 x 10 mL) and dried ($MgSO_4$). the solvents were removed at reduced pressure to afford only starting material by ^1H n.m.r. spectroscopy.

4.6.7 - Attempted procedure for prep of amide via acid chloride

A mixture of **225** (0.20 g, 0.17 mmol), thionyl chloride (10 mL) and a catalytic quantity of dimethylformamide were heated at reflux for 3 h. The reaction mixture was then cooled and the excess thionyl chloride removed under vaccuum. To the residue was added dry toluene and the solvent again removed at vaccuum. A solution of *R*-(+)-α-methylbenzylamine (0.41 g, 3.42 mmol) or dimethylamine (0.45 mL, 6.84 mmol) in dry diethyl ether (10 mL) was added and the mixture stirred overnight under nitrogen atmosphere. The mixture was washed with dilute hydrochloric acid (1 M, 3 x 10 mL), water (1 x 10 mL), brine (1 x 10 mL) and dried ($MgSO_4$). The solvent was removed at reduced pressure to afford light brown glassy solids which were complex mixtures by ^1H n.m.r spectroscopy.

5.0 Pyridine functionalised C_4 symmetric resorcinarenes

The 2-picolyl ethers of calix[4]arenes, such as **282**, were first reported by Pappalardo[225-226] and shortly thereafter, the syntheses of calix[6]arene derivatives such as **283**[227-228] were published. These were prepared in order to apply them as pre-organised ligands much like the calixarene tetraester,[202] tetraketone[229] and tetraamides[211] that had demonstrated ligating ability earlier. However, derivative **282** was less efficient for the extraction of alkali metal cations than the analogous tetraester.[225] The hexamer **284** was successfully applied for the complexation of copper(II) by Reinaud[230] but this ligand failed to coordinate to zinc(II).[231]

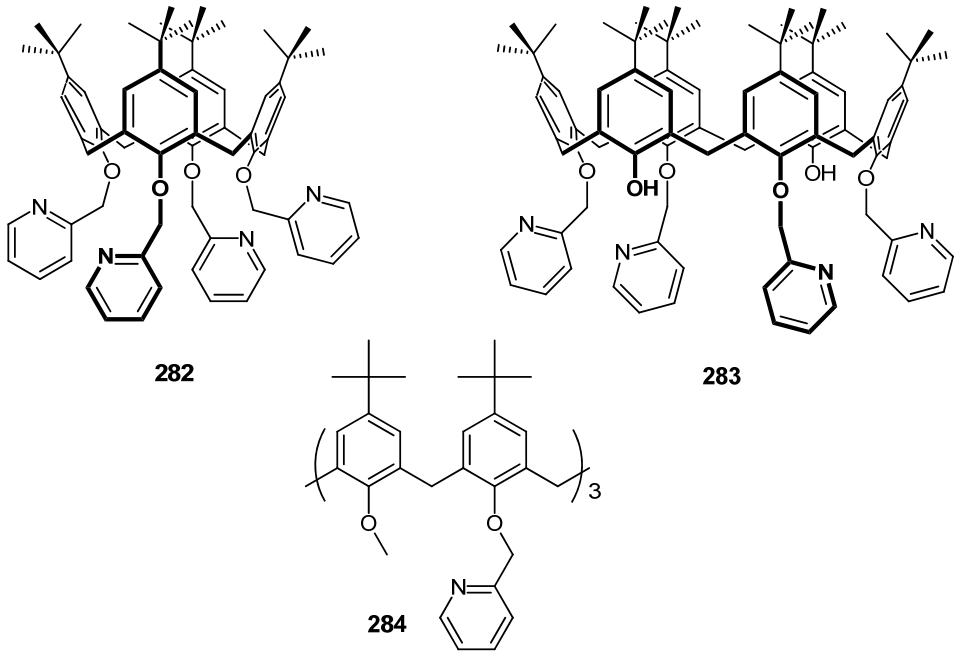


Figure 5.1 – Examples of previously synthesised calixarene picolyl ethers.

Shinkai produced several derivatives with pyridine moieties directly coupled to the upper rim of calix[4]- and calix[5]arenes[232-233] and an oxacalixarene[234] all of which were applied to palladium coordination. A number of lower rim picolyl ethers of the dihomooxacalixarene were described by Marcos.[235] The only resorcinarene analogues (**285** and **286**) functionalised with picolyl moieties appear to have been the cavitands prepared by Reinhoudt.[236] These compounds were mixed with the tetra-acid (**287**) to prepare capsular structures, however no X-ray structural determinations

of the adducts were presented.

Of the chiral pyridine substituted derivatives, the most significant contribution appears to have been made by Pappalardo *et al*. with the picolyl substituted chiral calixarenes of the general structure **288** (where R ≠ H[11, 237-240]).

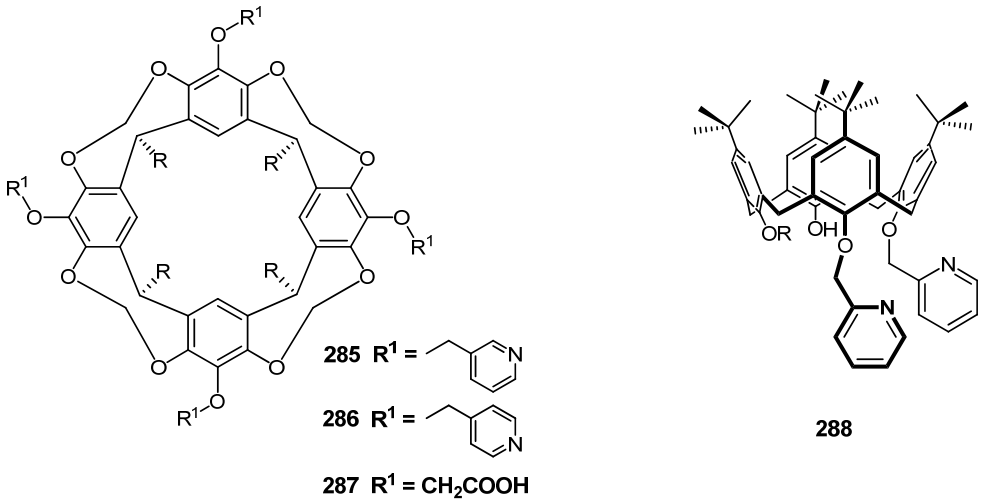


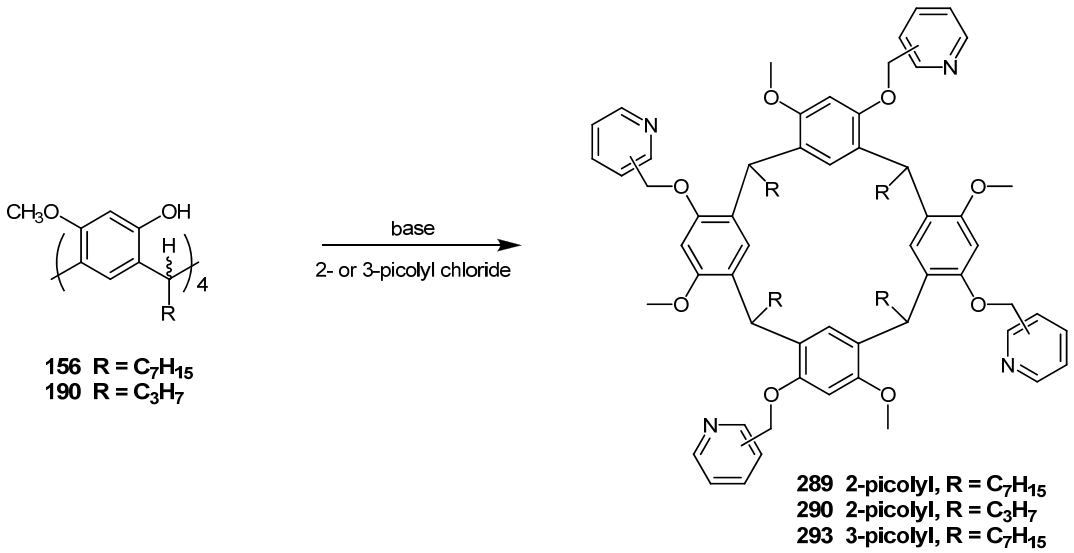
Figure 5.2 – Some cavitand based derivatives (**285-287**) and a the general structure of Pappalardo's chiral picolyl derivatives (**288**).

5.1 Preparation of the pyridine functionalised resorcinarenes

The alkylation of calixarene and resorcinarenes with the chloromethylpyridines appears to have been investigated fairly thoroughly for the 2-picolyl ethers but significantly less so for the 3- and 4-picolyl ethers. The derivatives are prepared by a standard Williamson ether synthesis[241] involving a base, a solvent and the appropriate alkylating agent. The choice of base and solvent for the preparation of the 2-picolyl ethers appears to be substrate dependant. Combinations such as sodium hydride,[11, 225, 227-228, 235] cesium carbonate,[226] sodium carbonate[226] and potassium carbonate[226, 235, 240] in dimethylformamide and potassium carbonate in acetonitrile[228] have afforded good yields of alkylated products.

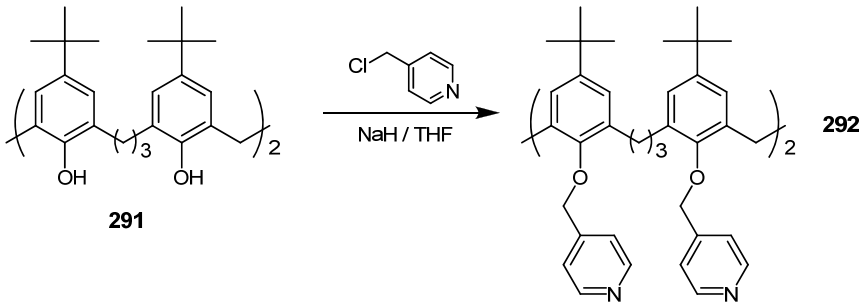
In our hands the alkylation of the racemic *C*-heptylresorcinarene (**156**, **Scheme 5.1**) and *C*-propylresorcinarene (**190**) with 2-chloromethylpyridine hydrochloride and

potassium carbonate in acetonitrile at reflux afforded the tetra-picolyl ethers **289** and **290** in 84 % and 80 % yield respectively. The corresponding preparation of **289** using sodium hydride in dimethylformamide at room temperature yielded 81 % of the desired product with identical physical and spectroscopic properties. Quite clearly the method of choice in this case is to use the more convenient and less hazardous base.



Scheme 5.1 – Syntheses of the pyridine functionalised C_4 dissymmetric resorcinarenes.

Reinhoudt has appended both 3- and 4-picolyl groups to cavitands derived from pyrogallol using a cesium carbonate in acetonitrile protocol[236] (**285** and **286 section 5.0**). This method, however, produced the per-ethers in only 37 and 25 % yield respectively. Reinhoudt indicated that the low yields could be attributed to competing alkylation of the pyridine ring either in the chloromethylpyridines or the alkylated resorcinarene products. Yamato obtained significantly a higher yield with his tetrahydroxy[3.1.3.1]metacyclophane (**291**) using sodium hydride and 4-chloromethylpyridine hydrochloride in THF, recovering 80 % of the peralkylated material[242] (**292**, **scheme 5.2**). Using cesium carbonate as the base he obtained a 65 % recovery and with potassium carbonate only an intractable mixture was obtained.



Scheme 5.2 – Yamato's synthesis of pyridine functionalised metacyclophane **292**.

The increased yields obtained utilising sodium hydride as the base are presumably due to more effective deprotonation of the macrocyclic components, and subsequently a more rapid overall reaction. This would have the beneficial effect of quickly reducing the concentration of alkylating agent available to participate in detrimental side reactions. With this in mind we applied the sodium hydride/dimethylformamide system to alkylate **156** with 3-picolyl chloride obtaining 72 % yield for **293**. No reduction in yield when **156** was alkylated with 2-chloromethylpyridine hydrochloride and potassium carbonate (rather than NaH/DMF) to give **289** was observed. This is presumably due to the more sterically hindered, and therefore less reactive, 2-picolyl nitrogen.[243] Attempts at alkylation of **156** with 3-chloromethylpyridine using potassium carbonate were lower yielding (15 %) in accordance with the previous findings.

5.2 Structure of the pyridine functionalised resorcinarenes

A single crystal of x-ray quality was obtained for **289** by slow evaporation of solvent from a methanol/dichloromethane solution. The space group was found to be $P\bar{1}$; the unit cell contains two molecules of **289** and two molecules of methanol each disordered over two sites. The significantly flattened cone conformation and the orientation of the pendant picolyl ethers is shown in the side and top views given in **figure 5.3**.

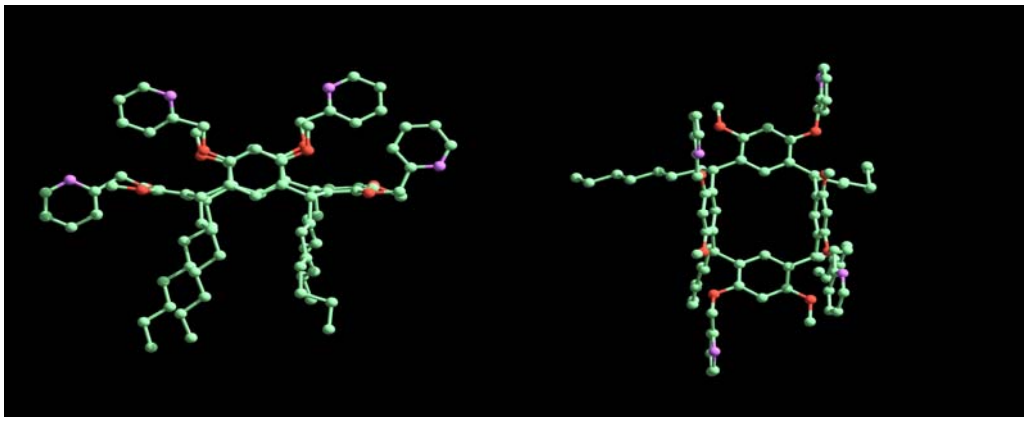


Figure 5.3 - Side and top views of **289** showing orientation of the picolyl moieties (hydrogen atoms and methanol solvent omitted for clarity).

Inspection of packing diagrams of **289** (**Figure 5.4**) reveals extended heavily interlocking arrays stabilised by the presence of significant π-π stacking interactions.

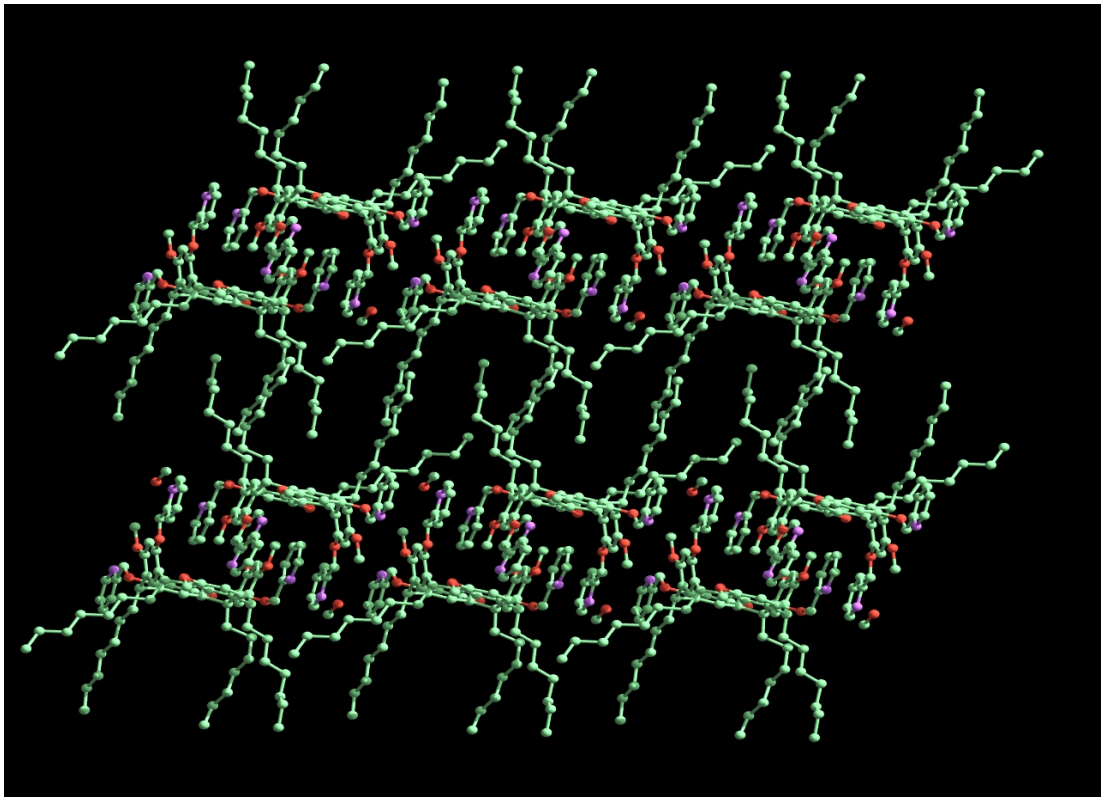


Figure 5.4 - Packing view of **289** (hydrogen atoms omitted for clarity, a larger version of this picture is given in **Appendix 8**).

The orientation of aromatic systems and the typical distances/offset encountered in π-π stacking interactions have been evaluated by Hunter and Sanders.[244-246] They generated a general model relating the orientation and distance of π-π contacts and is described using **figure 5.5**. The figure shows three idealised geometries of π-π interactions and their relative attractive/repulsive nature.

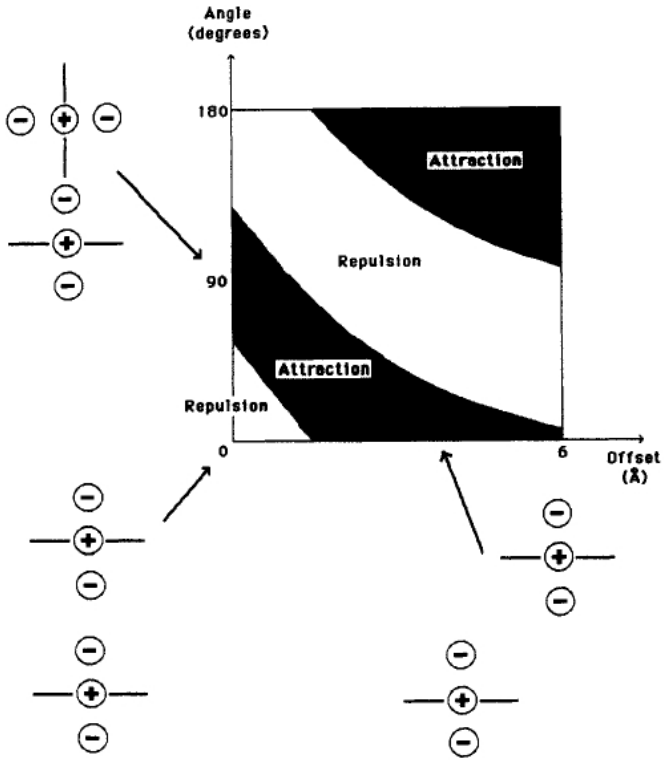


Figure 5.5 – Interaction of two idealised π-atoms as a function of orientation, from Hunter and Sanders.[245]

Typical interplanar separations for face-face interactions are generally observed in the 3.3-3.8 Å range while so called T-π-π contacts (edge to face) appear to occur at an average centroid-centroid distance of 5 Å. These distances were corroborated by Tsuzuki,[247] who calculated ideal separations of approximately 3.5 – 4 Å for face-face interactions and 4.75 – 5.25 Å (centroid-centroid) for T-π-π interactions for the benzene dimer.

Analysis of the short intermolecular ring-ring interactions reveals no less than four separate instances of close contacts consistent with π-π stacking interactions, three of which are repeated within the dimeric unit shown (with two different views) in

figure 5.6(A) and **5.6(B)** due to the inversion centre.

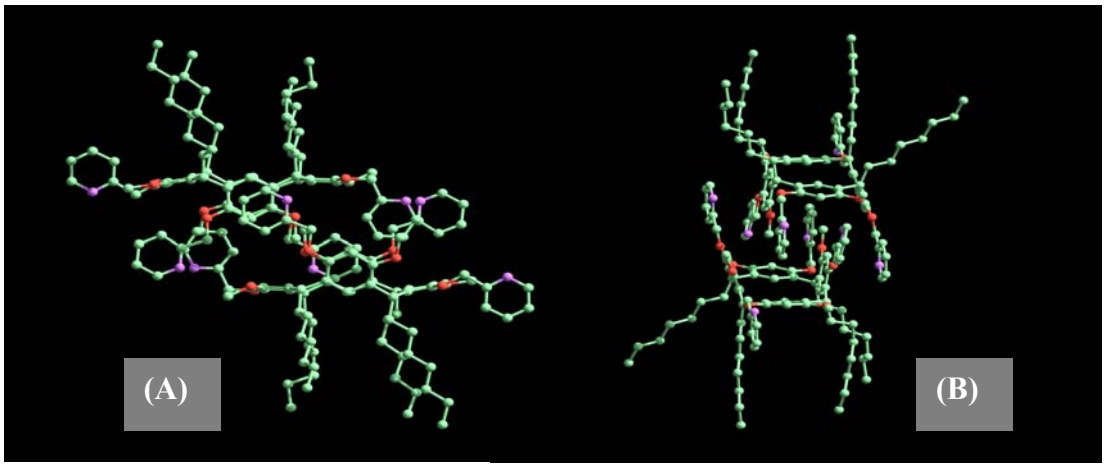


Figure 5.6 – Dimeric unit of **289** showing overlapping aromatic systems (hydrogen atoms omitted for clarity).

The intramolecular overlap of one pyridine moiety and one arene of the resorcinarene skeleton from each enantiomer comprising the dimeric unit is clearly visible in the central region of **figure 5.6(A)** and is of the typical offset π-π type (ring centre to ring centre offset distance of approx. 0.7 Å). The interplanar separation is approximately 3.601 Å which is consistent with this mode of interaction and the additional electrostatic repulsion incurred with significant overlap of the π systems. A second close contact of the offset π-π type is evident between pyridine rings in the left hand and right hand regions of **figure 5.6(A)** (centroid-centroid offset distance of approx. 2.29 Å). The closest carbon-carbon distance in this case is approximately 3.381 Å, again typical of this mode of interaction. The third intermolecular close contact alluded to earlier incorporated in the "dimeric unit" is of the T-π-π type and is again between one pyridine moiety and one arene of the resorcinarene skeleton from each of the molecules comprising the dimeric unit. This is evident in the central portion of **figure 5.6(B)** and has a closest hydrogen-centroid distance of approximately 2.589 Å (centroid-centroid distance 4.872 Å).
The last π-π interaction is observed linking between dimeric units and is of the T-π-π type. This is shown in the central region of **figure 5.7** and is again between one pyridine moiety and one arene of the resorcinarene skeleton (hydrogen-centroid distance 3.189 Å, centroid-centroid distance 5.449 Å).

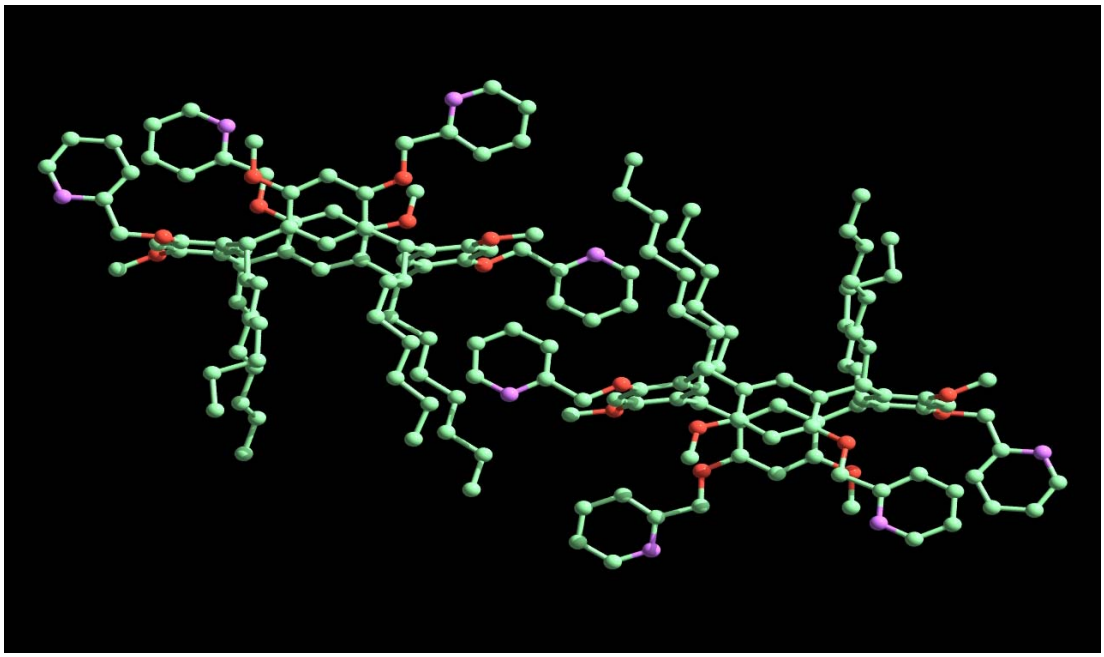


Figure 5.7 - T-π-π stacking interaction observed between one pyridine moiety and one arene of the resorcinarene skeleton of **289** (hydrogen-centroid distance of approximately 3.189 Å)(hydrogen atoms and methanol solvent omitted for clarity).

Resorcinarene **293** was crystallised by slow evaporation of solvent from a methanol/dichloromethane solution of **293** and a resulting crystal characterised by structure determination. The molecular structures and conformations of **293** and **289** are almost identical, and as such, the crystal packing of **293** (**Figure 5.8**) has some similar features to the x-ray crystallographic data of **289**. However, the differing position of the nitrogen atom does have a significant impact on the nature of the intermolecular interactions. Again crystallising in $P\bar{1}$, each molecule of **293** is associated with a molecule of methanol and of water. The macrocycle forms a centrosymmetric hydrogen-bonded cluster through a pyridine nitrogen atom with the solvent water and methanol molecules (N...HOH 1.96(8)Å; H_2O...HOR 1.886(6)Å) as can be seen in **figure 5.9(A)**. Unlike **289**, **293** packs in the distinctive head to head, tail to tail bilayer structure that is typical of other resorcinarenes. Like the structure of **289**, the packing of **293** revolves around a "dimeric unit" composed of the two resorcinarene enantiomers which are interlocked (see **Figure 5.9(B)**).

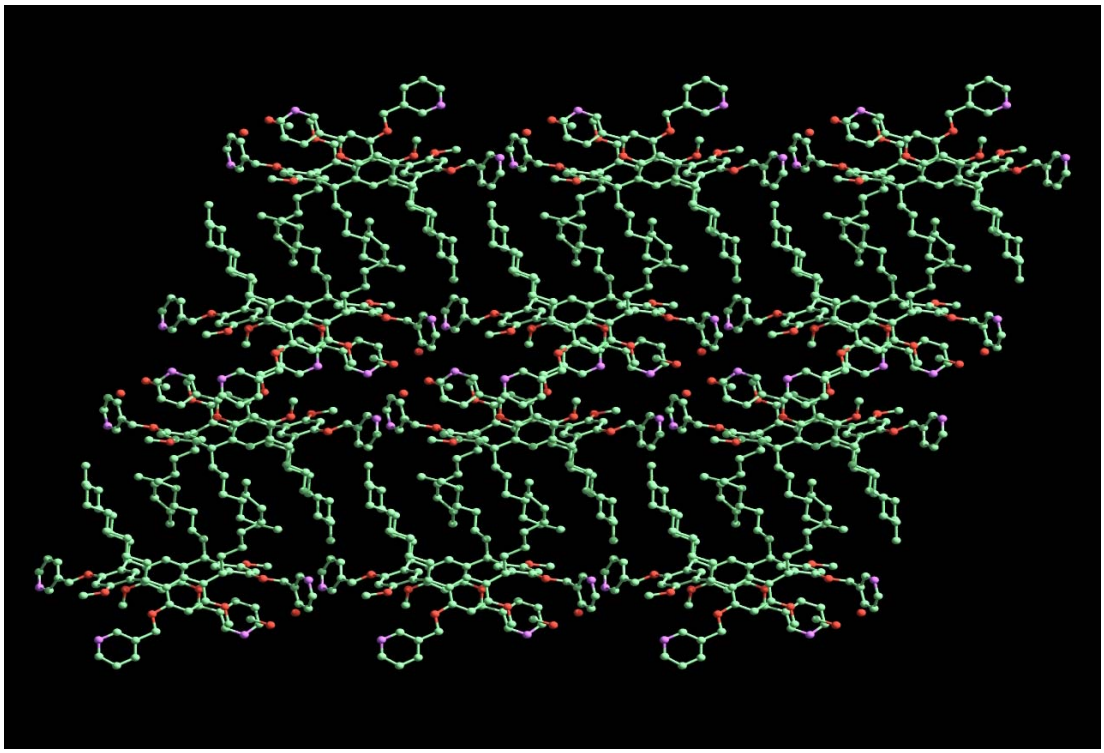


Figure 5.8 – Packing view for **293** (hydrogen atoms omitted for clarity, a larger version of this picture is given in **appendix 9**).

The extent of π-π interactions observed for **293** is also significant. One can see in **figure 5.9(A)** that a similar offset type π-π overlap is evident about the central core of the dimeric unit. Though in this case, the extent of overlap is minimal and the picolyl moiety which is engaged in the π-π stacking is located within the resorcinarene cavity, rather than adjacent to the outer side of the cavity, as in **289**. As such, the picolyl group is approximately equidistant from either internal side of the resorcinarene cavity (3.126 and 3.217 Å plane to plane) and appears to be interacting with both π systems (see left image of **figure 5.10**). The close contact distances are consistent with the larger offset (approximately 2.76 Å centroid to ring centroid) and are presumably due to the lesser electrostatic repulsion between π systems.

The remaining picolyl moieties are occupied in a T-π-π stacking interaction with adjacent resorcinarene molecules (see right image of **figure 5.10**) with an ideal centroid to centroid separation of approximately 5.03 Å (closest hydrogen to centroid distance of 2.825 Å).

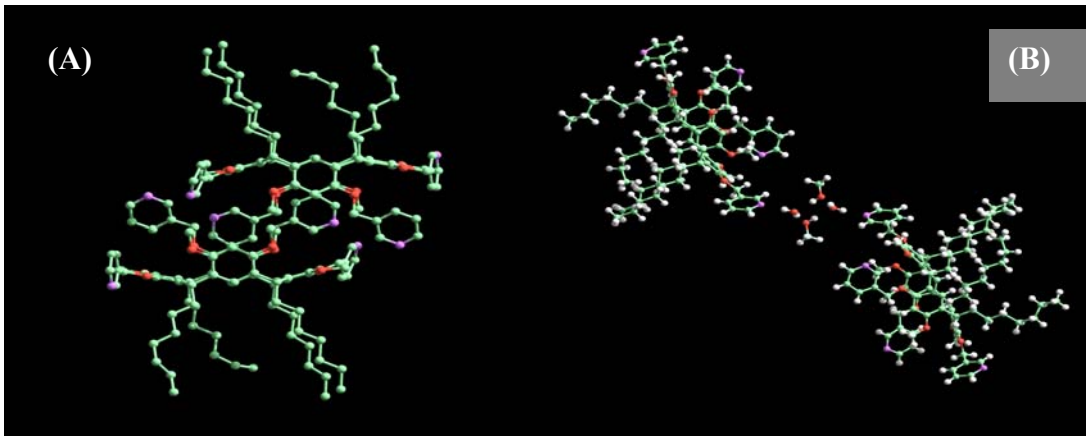


Figure 5.9 - Dimeric unit of **293** showing overlapping aromatic systems (hydrogen atoms omitted for clarity).

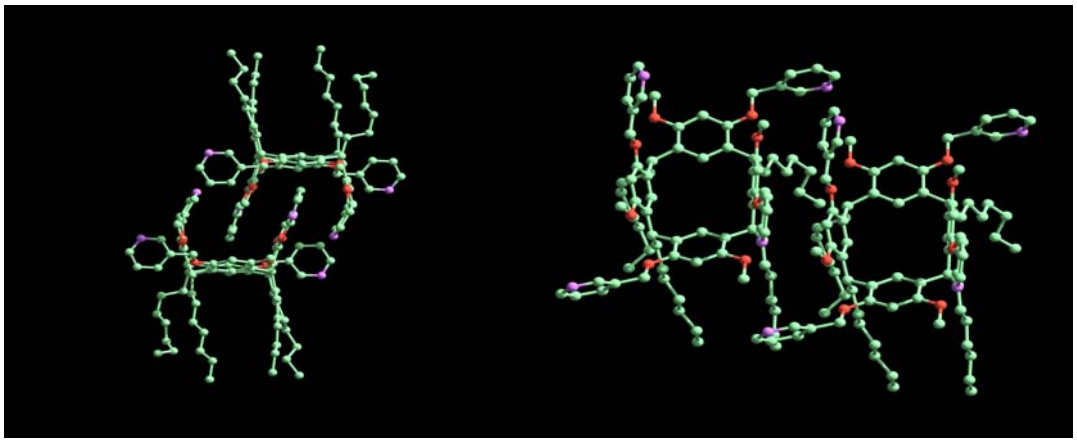


Figure 5.10 – Left: Alternate view of dimeric unit of **293** showing overlapping aromatic systems. Right: Adjacent molecules of **293** showing T-π-π close contact (hydrogen atoms omitted for clarity).

Unsurprisingly, the intermolecular interactions observed between the enantiomers in the interlocking "dimeric unit" of **289** are also evident in the crystal structure of the similarly functionalised **290** (2-picolyl). The packing arrangement of the dimeric units can bee seen below in **figure 5.11**.

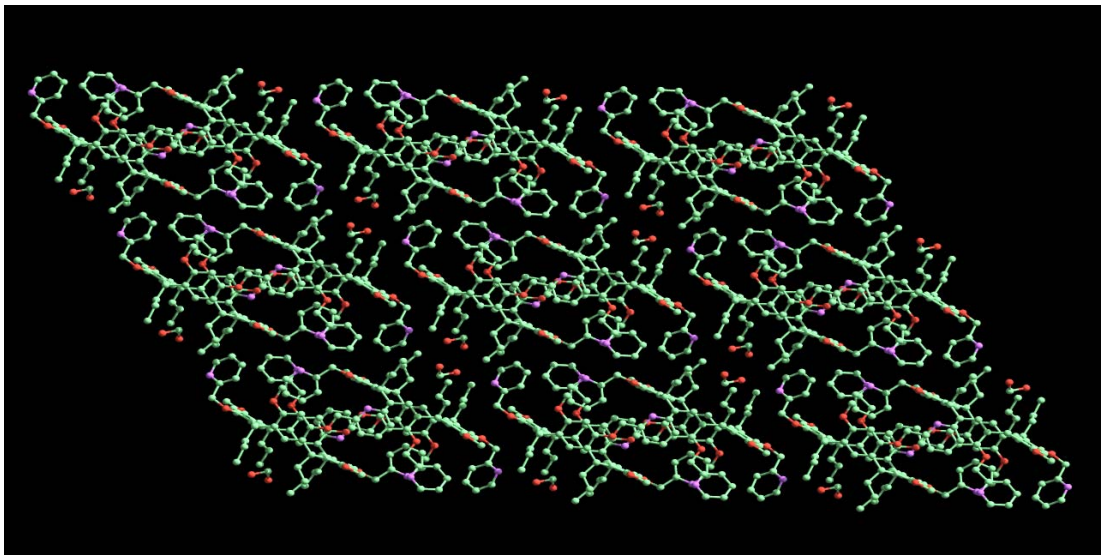


Figure 5.11 – Packing view for **290** (hydrogen atoms omitted for clarity, a larger version of this picture is given in **appendix 10**)

An offset parallel π-π interaction (which can be seen in the central region of **figure 5.12** and is repeated within the dimer by virtue of the inversion centre), occurs between a pyridine moiety of one enantiomer to the outer side of an arene of the resorcinarene skeleton (of the corresponding enantiomer) in identical fashion to resorcinarene **289**. The closest carbon-nitrogen distance being approximately 3.388 Å with a centroid-centroid offset distance of 1.52 Å. Similarly, a T-π-π stacking interaction, also common to **289**, is evident in **figure 5.12**. The closest hydrogen-centroid distance in that case being approximately 2.668 Å (centroid to centroid of 4.985 Å), somewhat shorter than for **289**. The last significant interaction occurs between adjacent molecules of **293** and is again of the T-π-π type (hydrogen-centroid = 2.631 Å, centroid-centroid = 4.815 Å). Unlike **289**, the interaction does not occur about a centre of symmetry and so is not repeated. The protrusion of the picolyl moiety towards the adjacent resorcinarene is unmistakable in **figure 5.13**.

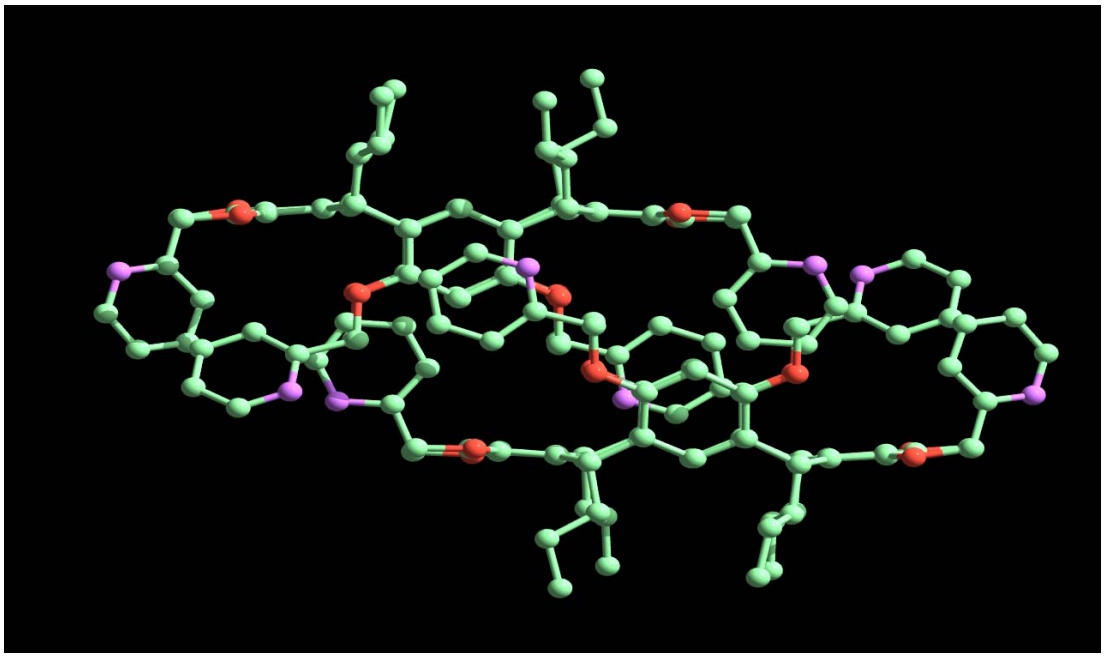


Figure 5.12 – Dimeric unit of **290** showing overlapping aromatic systems (hydrogen atoms omitted for clarity).

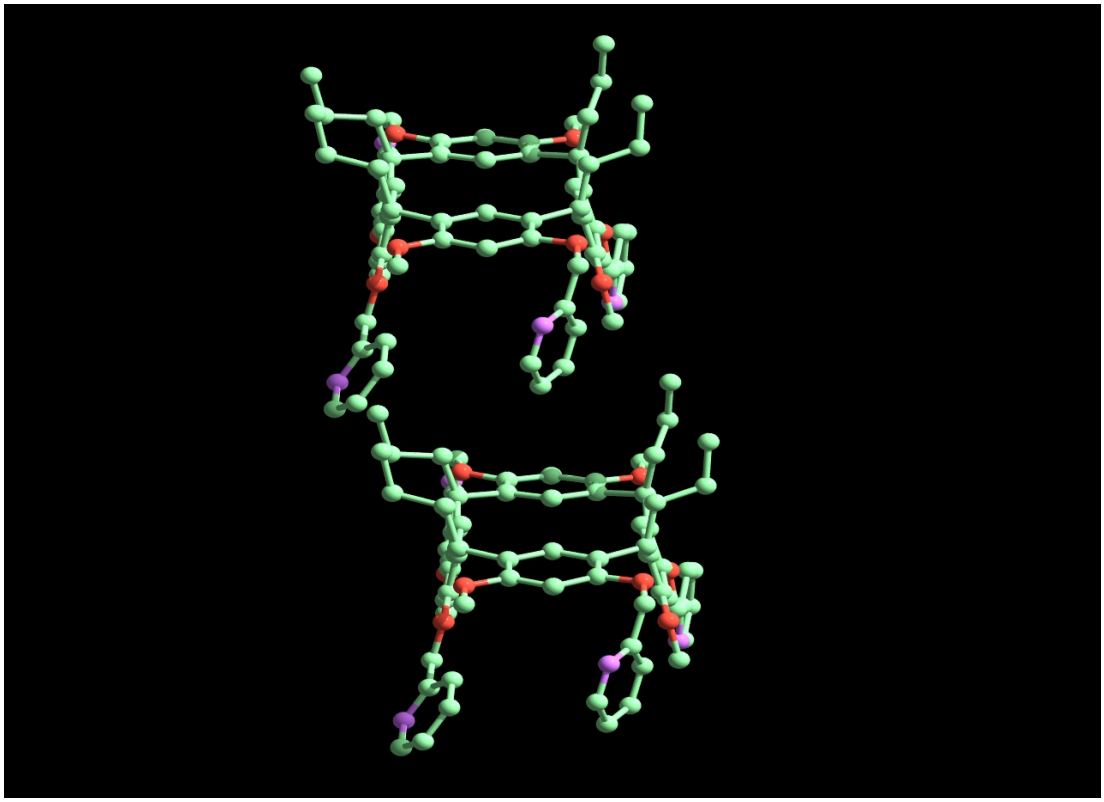


Figure 5.13 – T-π-π stacking interaction observed between adjacent molecules of **290** (hydrogen atoms and methanol solvent omitted for clarity).

5.3 Chirality and resolution

The attachment of an acidic[248-249] or basic[250] moiety to an otherwise neutral racemic compound and subsequent diastereomeric salt formation is a rational scheme for the separation of chiral species with no direct means of resolution . The picolyl ether does not appear to have been applied as a functionality for the resolution of chiral alcohols or phenols. However, it has a moderately basic nitrogen[251] that may form diastereomeric salts with enantiopure acids. It can also potentially be removed from substrates that are not degraded under hydrogenation conditions.[252]
In the case of the racemic resorcinarenes, the attachment of one or more picolyl moieties presents a possible basic route for resolution. Development of a methodology for formation of diastereomeric salts could facilitate the separation of the enantiomers on a multi-gram scale. In addition the commercially available 2-, 3- and 4-chloromethylpyridine hydrochlorides are cheap enough to allow large scale preparation and resolution of the resorcinarene enantiomers. This is especially true if the salt formation for resolution is with something like the very cheap (+)-10-camphorsulfonic or tartaric acids.

5.3.1 N.m.r. spectroscopy and interaction with chiral acids

Interaction of **289** with chiral acids was demonstrated initially with ^{1}H and ^{13}C n.m.r. experiments. On addition of one mole equivalent of (+)-10-camphorsulfonic acid to a sample of **289** in deuterated chloroform, a significant downfield shift (and broadening) of the pyridine proton signals was observed. In addition, the methylene protons of the picolyl ether which appear as an AB quartet (see **Figure 5.14 (A)**) were split into two AB signals of equal intensity (**Figure 5.14 (B)**). The splitting of the AB signal in such a manner is indicative of formation of diastereomeric species. However, the mechanism by which the diastereomeric species are generated is not obvious. The splitting effect in the proton n.m.r. may be a result of inclusion of the CSA within the cavity of the resorcinarene rather than an acid-base interaction.

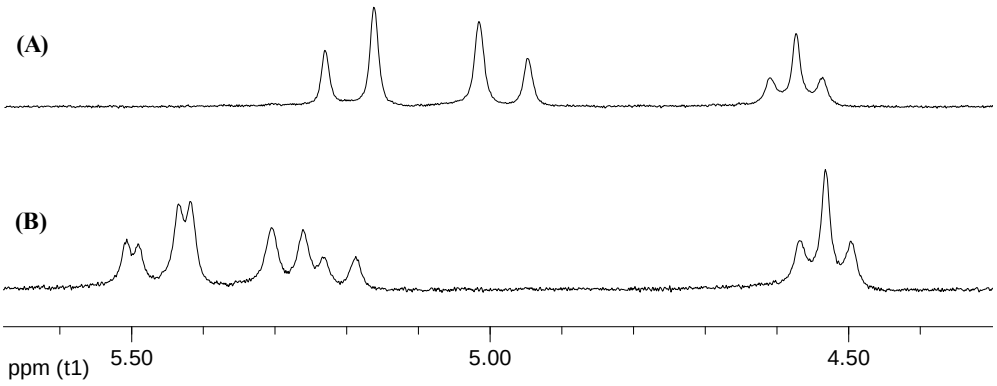


Figure 5.14 – ^{1}H n.m.r. spectra (4.3-5.7 ppm) of **(A) 289**, **(B) 289** with one equivalent of (+)-10-camphorsulfonic acid.

The ^{13}C n.m.r. spectrum of **289** (**Figure 5.15 (A)**) on addition of the (+)-10-camphorsulfonic acid (**Figure 5.15 (B)**) clearly shows significant shifting of the 2, 4 and 6 carbons of the pyridine ring. The upfield shift of the 2 and 6 carbon signals and the downfield shift of the 4 carbon are typical of protonation at the pyridine nitrogen.

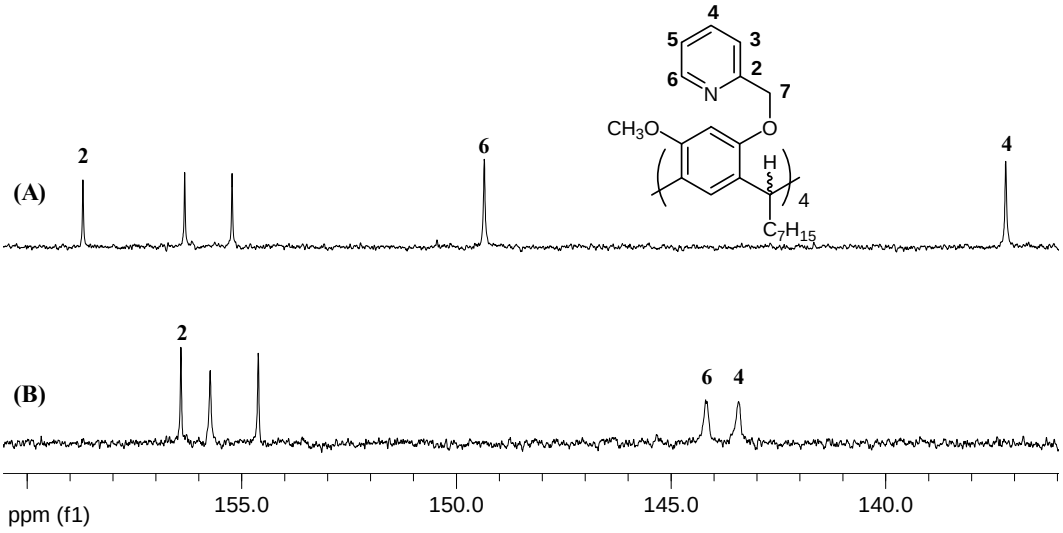
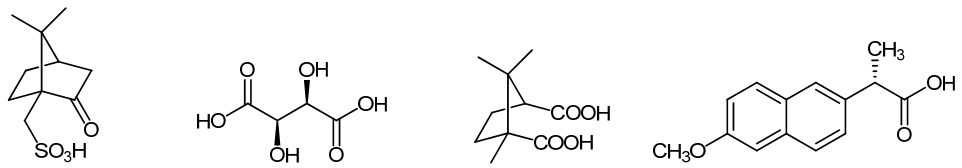


Figure 5.15 – ^{13}C n.m.r. spectra (136.0-165 ppm) of **(A) 289** and **(B) 289** with one equivalent of (+)-10-camphorsulfonic acid.

5.3.2 Resolution by fractional crystallisation

The resolution of racemic **289** by fractional crystallisation of diastereomeric salts was attempted with a variety of enantio-pure acids. Mixtures of (+)-10-camphorsulfonic acid (**294**), (+)-tartaric acid (**295**), (+)-camphoric acid (**296**) and (S)-(+)-2-(6-methoxy-2-naphthyl)propionic acid (**297**) were crystallised from alcoholic solvents (see **section 5.5**). Despite the diversity of crystallisation conditions, no material enriched in either enantiomer was obtained, as determined by optical rotation experiments. In the majority of cases only free **289** was obtained (by ^{1}H n.m.r. spectroscopy). In some cases no crystallisation was observed at all, particularly from 2-propanol.



294 **295** **296** **297**

Figure 5.16 – Chiral acids screened for the resolution of racemic **289**.

While it is clear from section **5.3.1** that protonation of the pyridine nitrogen does appear to occur to some extent, it is not significant enough to prevent crystallisation of the free macrocycle. Even with excess of the chiral acids in solution, crystallisation of **289** alone is favoured.

5.4 Interaction with transition and soft metal cations

The picolyl functionalised resorcinarene may also serve as a multidentate ligand for the coordination of some transition metals such as palladium, zinc, nickel and copper. The use of calixarenes as ligands for transition metals is of significant interest and has been reviewed by Weiser *et al*.[196] The catalytic application of transition metals and their complexes is also well known.[253]

Preliminary ^{1}H n.m.r. spectroscopy experiments clearly show that on addition of one equivalent of $Zn(ClO_4)_2.6H_20$ to a solution of **289** in d_6-acetone (**Figure 5.17 (B)**), significant changes in chemical shift and broadening occurs. The addition of excess $Zn(ClO_4)_2.6H_20$ (**Figure 5.17 (C)**) does not appear to cause any significant change from that already cause by the addition of one equivalent. These signal changes are very similar to the n.m.r. spectral data obtained by Pappalardo[238] on addition of $Zn(CF_3SO_3)_2$ to a $CDCl_3$ solution of his picolyl functionalised calix[4]crowns. Pappalardo described these changes as being a direct result of complex formation with the zinc species.

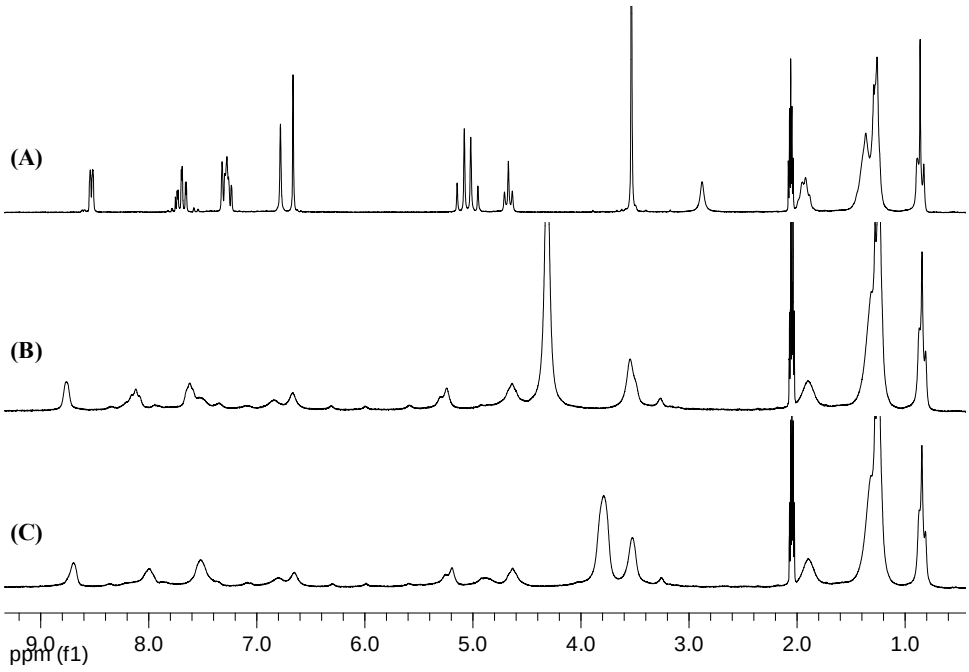


Figure 5.17 – ^{1}H n.m.r. spectra of **(A) 289**, **(B) 289** with one equivalent of $Zn(ClO_4)_2.6H_20$, **(C) 289** with excess of $Zn(ClO_4)_2.6H_20$.

Solubilisation experiments with copper (II) and nickel (II) salts also demonstrated the significant ligating ability of **289** and **293**. When solid copper (II) acetate hydrate was added to a dichloromethane solution of **289** or **293** substantial dissolution of salt was observed. An example of the strongly aquamarine coloured solutions is given in **figure 5.18**.

Figure 5.18 – A solution of the copper(II) complex of **293** in DCM

A similar effect was observed for nickel (II) acetate tetrahydrate with **289** and **293** affording pale blue-green solutions in dichloromethane.
When this experiment was performed with known quantities of ligand (**289**) and copper (II) acetate hydrate, two mole equivalents of the salt (per mole of calix ligand) were taken into solution. The stoichiometry of the **293** complexes could not be determined in this manner due to partial insolubility of the complexes.

Despite significant efforts, the majority of ligand/cation/solvent combinations failed to produce crystals of x-ray quality. In almost all cases only fine micro-crystals or powder materials were recovered from crystallisation attempts. However, a single crystal of x-ray quality was obtained for **290** by slow evaporation of solvent from a methanol/dichloromethane solution.
It was anticipated that the ligand would, at the very least, act as a bidentate ligand for a single copper atom with the two remaining picolyl “arms” available for further bonding. However, the complex of **290** with copper(II) acetate appears to be a linear polymer of the form $2(L4)Cu_3(OAc)_6$ with associated dichloromethane and methanol as shown in **figure 5.19**.

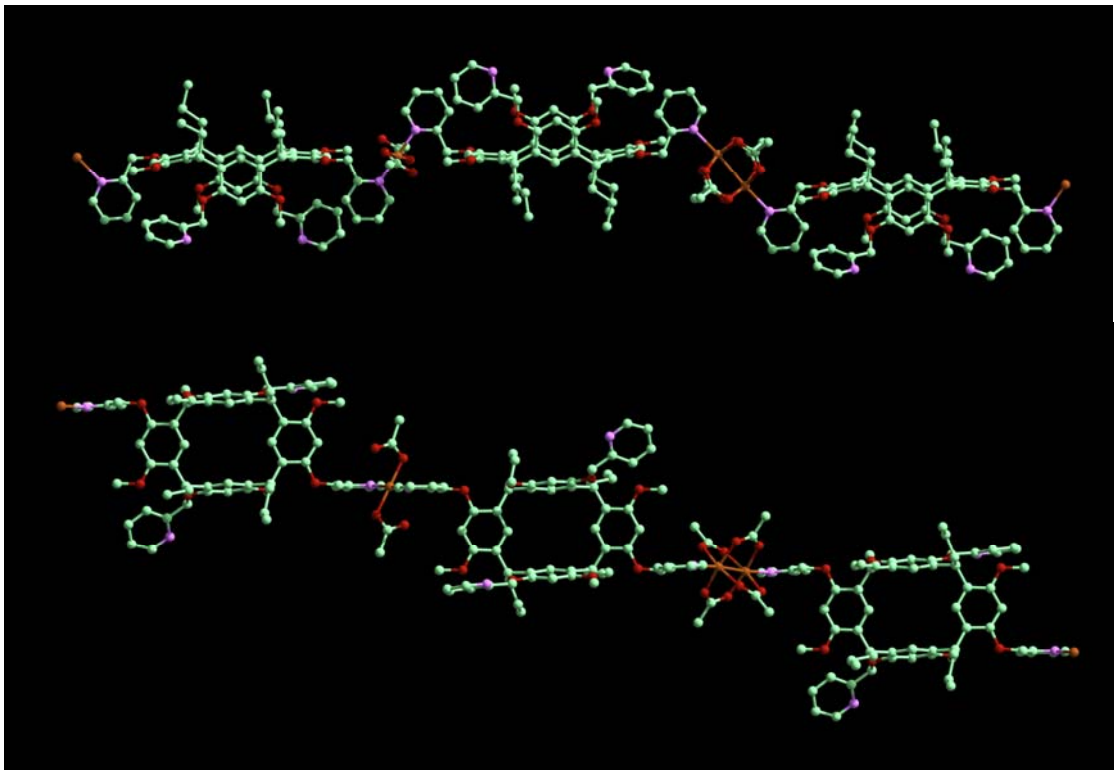


Figure 5.19 – Two projections of the **290**- copper(II) acetate complex.

The pyridine groups on opposite sites of the ligand containing the 'horizontal' phenyl rings bind to two Cu atoms. One pyridine ring is coordinated to a Cu atom of a $Cu(OAc)_2$ group situated on a crystallographic inversion centre. The N atom on the opposite pyridine group is bound to a Cu atom of a $Cu_2(OAc)_4$ 'paddlewheel' group, which is also situated on a crystallographic inversion centre thus forming the polymeric chain, which is parallel to the 111 direction. The coordination around Cu1 is therefore square planar, Cu1–N1, OAc 2.003(3), 1.971(3) Å, O101–Cu1–N2 89.6(1)º (the acetate anion is considered to be unidentate, the other Cu/O distance being 2.611(3) Å). The coordination around Cu2 is a slightly distorted octahedral arrangement with the Cu2–OAc bonds being 1.967(3), 1.969(3), 1.980(3) Å and the Cu2–N 2.200(3) Å. The angles around the Cu2 atom range from 92.0(1)–95.8(1) with the Cu2/Cu2 distance in the $Cu_2(OAc)_4$ group being 2.643(1) Å.
The metal-ligand polymer chains are connected via two typical π-π stacking modes. Firstly, adjacent polymer chains are interlocked through the offset π-π interactions clearly shown in the upper portion of **figure 5.20**, between pyridine moieties and electron rich arenes of the resorcinarene skeleton (interplanar separation for both of

the π-π contacts are approximately 3.420 Å, centroid-centroid offset: ~1.40 Å). The second close contact is a T π-π stacking interaction that is evident in **figure 5.21** and occurs perpendicular to the polymer chains between the picolyl "arms" of adjacent resorcinarene-metal polymer chains. The hydrogen-centroid distance for this contact is 2.669 Å (centroid-centroid distance 4.819 Å). This interlocking pattern is identical to that of the free ligand **290** described in **figure 5.12**. Remarkably, the arrangement of the "arms" of the ligand is similar in both structures. The crystal packing "spreads out" to accommodate the copper coordination as can be seen by comparing the structures of the ligand with (upper, **Figure 5.20**), and without copper (lower, **Figure 5.20**), below.

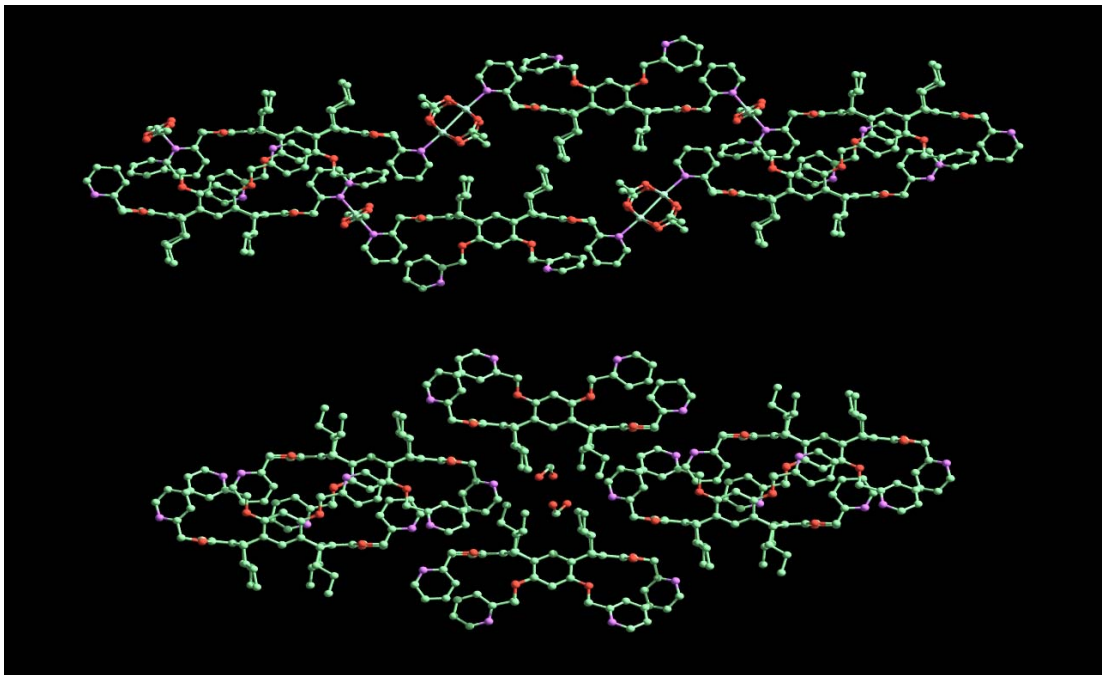


Figure 5.20 – Upper: interlocking pattern of the **290**-copper complex and Lower: the interlocking pattern of the free ligand **290**.

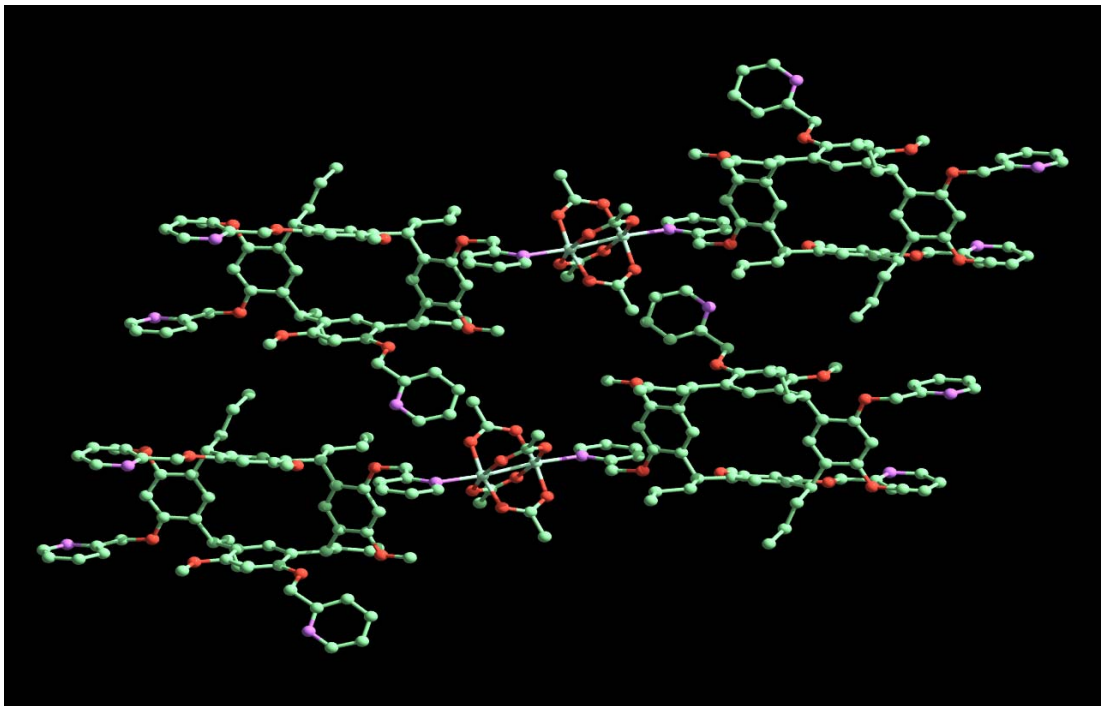


Figure 5.21 – T π-π contacts with close hydrogen-centroid distance of 2.669 Å present in the copper(II)-**290** complex.

Addition of soft metal cations such as silver(I) and palladium(II) to solutions of **289**, **290** and **293** generally resulted in the rapid formation of precipitates. The solids were too fine for single crystal x-ray analysis in all cases and too insoluble for further manipulation. However, the combination of silver(I) trifluoroacetate and resorcinarene **290** in tetrahydrofuran – ethanol solution afforded suitable crystals for x-ray analysis.

The complex crystallised as colourless prisms in the triclinic spacegroup $P\bar{1}$ with a unit cell containing two ligands, six silver atoms and associated trifluoroacetates and four molecules of tetrahydrofuran resulting in a polymeric structure of the form (L4) $Ag_3(OCOCF_3)_3.2THF$.

The three silver atoms are present as a carboxylate-bridged conglomerate, each being differently coordinated (**Figure 5.22 (A)**) A *syn-syn O,O'*-carboxylate bridges Ag1, and Ag3 (Ag1-O101, 2.216(7); Ag3-O102, 2.336(7) Å). The other two carboxylates are unidentate, forming a μ-O bridge between Ag1 and Ag2 (Ag1-O301, 2.510(5); Ag2-O301, 2.447(5) Å), and a somewhat asymmetric μ_3-O bridge between all three silver atoms (O201-Ag1,2,3; 2.624(5), 2.302(4), 2.495(5) Å respectively). A silver-carboxylate structure of this nature has been observed previously, but only as a

component of a 1D silver tetrafluorosuccinate network.[254] The remainder of the coordination sphere comprises N atoms from the resorcinarene ligands (Ag1-N3, 2.219(7); Ag2-N1, 2.192(5); Ag3-N2, 2.262(5); Ag3-N4, 2.224(5) Å).

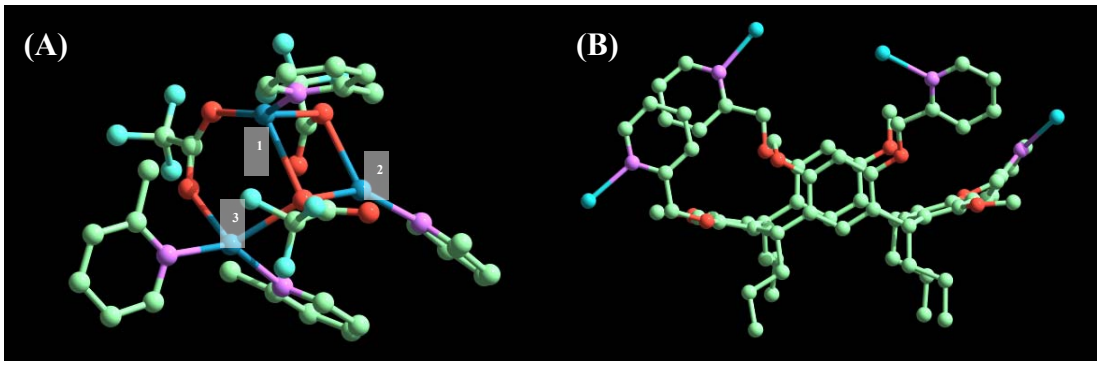


Figure 5.22 – Silver-ligand interactions for the silver(I)-**290** complex.

The interactions of an individual macrocycle with silver atoms is straightforward (**Figure 5.22 (B)**) with each N atom bound to a different silver atom. No close interatomic contacts indicative Ag-π complexes are evident. The bridging between silver conglomerates leads to a complex layered structure (**Figure 5.23**) revealed a layered structure consisting of metal-ligand polymeric arrays extending two dimensionally to form "sheets", which are bridged by interaction of the *n*-propyl "tails" of resorcinarene ligands in adjacent layers. The resulting structure is porous with channels running parallel to *b* within which are collected the associated tetrahydrofuran molecules. **Figure 5.23** shows the packing diagram of the silver(I)-**290** complex viewed along *a* showing the layered structure. Please note that the associated tetrahydrofuran solvates are not shown in the lower channels for clarity.

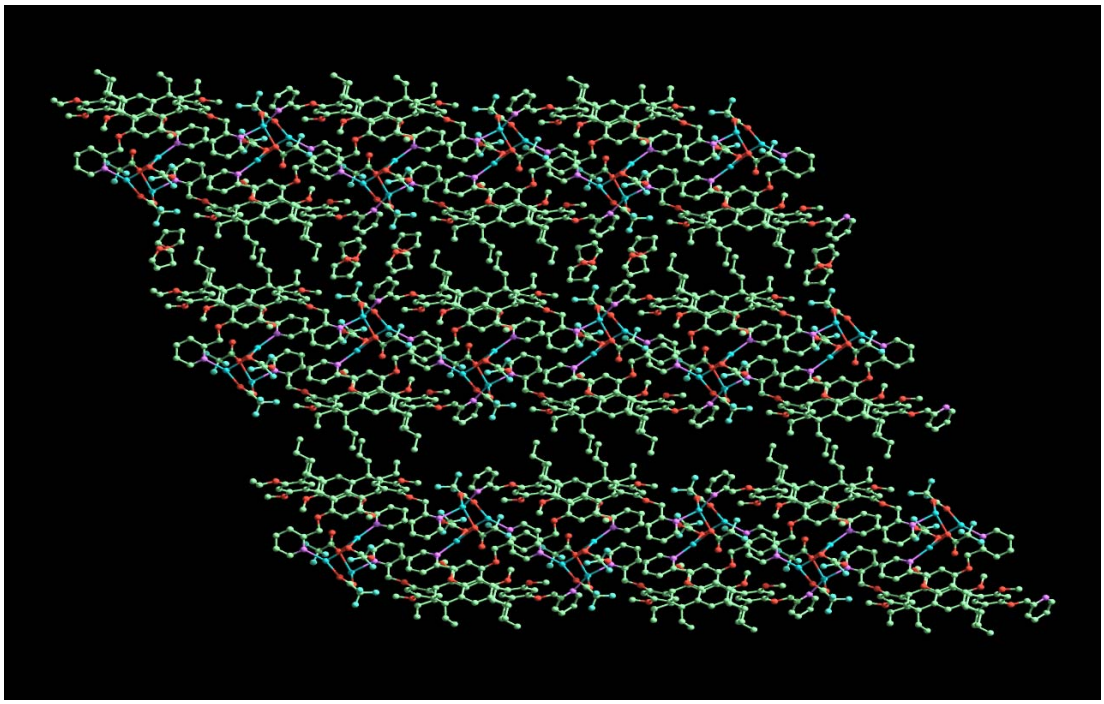


Figure 5.23 – Packing diagram of the silver(I)-**290** complex viewed along *a* showing the layered structure. Note: associated tetrahydrofuran molecules have been removed from the lower channels for clarity and a larger version of this picture is given in **appendix 11**.

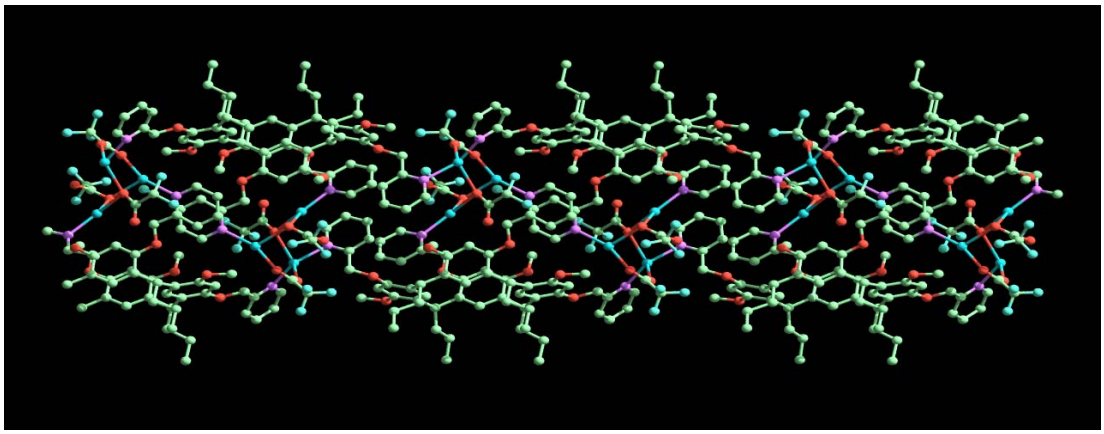


Figure 5.24 – A single "sheet" of the silver(I)-**290** complex viewed along *a* showing the ligand-ligand and ligand-metal interactions.

The "sheets", as shown in **Figure 5.24** above, consist of resorcinarene ligands with a significantly flattened crown conformation packed in an alternating head to head fashion, presumably as a consequence of ligand-ligand and ligand-metal interactions

associated with the pyridine moieties. These sheet structures are not found in the ligand crystal structure.

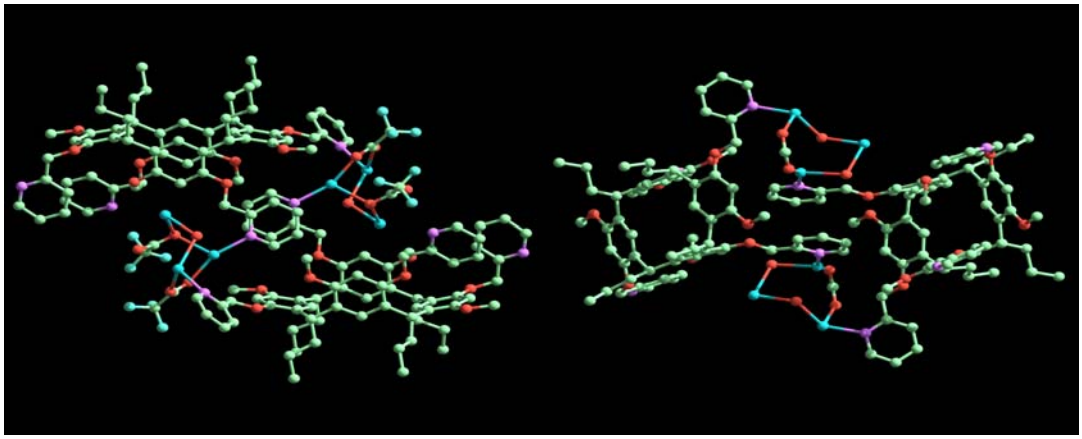


Figure 5.25 – central dimer core viewed along x axis and alternate view of central core dimer showing the short pyridine-pyridine ring interactions (closest atom-atom distance of 3.405 Å, trifluoroacetates partially removed for clarity)

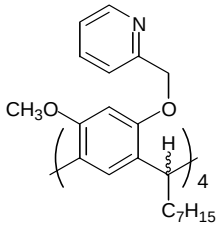
Figure **5.25** shows two views of what is essentially the repeating unit consisting of two resorcinarene ligands (which are enantiomers) related by an inversion (note that trifluoroactetate anions have been cropped for clarity in both views). Typical π-π stacking of the offset type is clearly evident in the "core unit" with a closest interatomic distance of approximately 3.405 Å and a centroid-centroid offset of 1.38 Å.

5.5 Experimental

Colourless prisms of **289**, **290** and **293** suitable for single crystal x-ray analysis were obtained by slow evaporation of a filtered solution of the appropriate resorcinarene (20 - 40 mg) in methanol (~ 5mL) and dichloromethane (~ 5 mL). Blue prisms of the copper complex of **290** suitable for single crystal x-ray analysis were obtained by slow evaporation of a filtered solution of **290** (~20 mg) and excess copper (II) acetate in methanol (~ 5mL) and dichloromethane (~ 5 mL).

Fractional crystallisations were typically performed using **289** (50 mg) and either one or five mole equivalents of chiral acid. The acids used were (+)-10-camphorsulfonic acid (**294**), (+)-tartaric acid (**295**), (+)-camphoric acid (**296**) or (S)-(+)-2-(6-methoxy-2-naphthyl)propionic acid (**297**). The mixtures were dissolved in 10 mL of methanol, ethanol or isopropanol with heating if required and filtered. If no crystallisation occurred within one week the solutions were opened to the atmosphere and allowed to slowly reduce in volume until crystallisation was evident. Crystalline samples were recovered by filtration and dried at reduced pressure for a minimum of two hours. The identity of the solids was determined by proton n.m.r. spectroscopy experiments and enantiomeric enrichment determined by polarimetry (minimum c=1).

5.5.1 $1^4,3^6,5^6,7^6$-Tetra-(pyridin-2-ylmethoxy)-$1^6,3^4,5^4,7^4$-tetramethoxy-2,4,6,8-tetraheptylresorcin[4]arene (289)

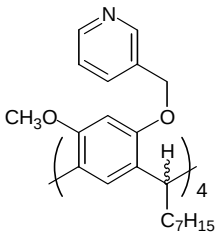


(a) A mixture of resorcinarene **156** (0.5 g, 0.53 mmol) potassium carbonate (1.47 g, 10.6 mmol) and 2-chloromethylpyridine hydrochloride (1.05 g, 6.40 mmol) in acetonitrile (20 mL) was heated at reflux overnight. The reaction mixture was then cooled and the solvent removed at reduced pressure. To the residue was added sodium hydroxide solution (3 M, 50 mL) and the mixture stirred for 30 minutes. The mixture was extracted with dichloromethane (3 x 30 mL) and the combined organic layers washed with water (2 x 30 mL) and then dried (Na_2SO_4). The solvent was removed at reduced pressure and the residual solid recrystallised from methanol to give **289** as off-white needles (0.58 g, 84 %) m.p. 99.5 – 100.0 °C.

^{1}H n.m.r. ($CDCl_3$) δ 0.84 (br t, 12 H, CH_2CH_3), 1.13-1.48 (m, 40 H, CH_2), 1.83-1.99 (m, 8 H, CH_2CH), 3.42 (s, 12 H, OCH_3), 4.59 (t, 4 H, J = 7.4 Hz, $CHCH_2$), 4.90, 5.09 (AB quartet, J = 33.5 Hz, 8 H, CH_2O), 6.42, 6.71 (s, 2 x 4 H, ArH), 7.27-7.39 (m, 8 H, pyr ArH), 7.69 (apparent d of t, 4H, pyr ArH), 8.56 (br d, 4 H, J = 4.8 Hz, pyr ArH). ^{13}C n.m.r. ($CDCl_3$) δ 14.8 (CH_3), 23.4, 29.1, 30.1, 30.7, 32.7, 35.2 36.6 (CH and CH_2), 56.4 (OCH_3), 70.1 (OCH_2), 97.9, 123.3, 124.0, 126.5, 127.11, 127.18, 140.2, 146.6, 154.9, 156.4 and 157.2 (Ar). Found: C, 77.5; H, 8.4; N, 4.2 %. $C_{84}H_{108}N_4O_8$ requires C, 77.5; H, 8.4; N, 4.3 %.

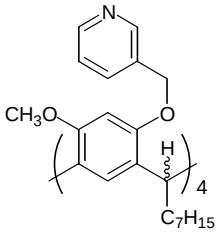
(b) A mixture of resorcinarene **156** (0.52 g, 0.55 mmol) sodium hydride (1.12 g, 60 % in oil, 28.0 mmol) and imidazole (1 crystal) in dry dimethylformamide (20 mL) was stirred at room temperature for 30 minutes. 2-Chloromethylpyridine hydrochloride (0.459g, 2.80 mmol) was then added in portions and the mixture stirred at room temperature overnight. The majority of the solvent was then removed at reduced pressure and the resulting residue dissolved in dichloromethane (50 mL). The solution was washed with water (5 x 50 mL) and dried (Na_2SO_4). The solution was concentrated at reduced pressure and the residue crystallised from methanol to afford colourless needles (0.58 g, 81 %). The n.m.r. and physical data were identical to that given above.

5.5.3 $1^4,3^6,5^6,7^6$-Tetra-(pyridin-3-ylmethoxy)-$1^6,3^4,5^4,7^4$-tetramethoxy-2,4,6,8-tetraheptylresorcin[4]arene (293) (NaH/DMF method)



A mixture of resorcinarene **156** (0.50 g, 0.53 mmol) sodium hydride (1.07 g, 60 % in oil, 26.7 mmol) and imidazole (1 crystal) in dry dimethylformamide (20 mL) was stirred at room temperature for 30 minutes. 3-Chloromethylpyridine hydrochloride (0.70g, 4.24 mmol) was then added in portions and the mixture stirred at room temperature overnight. The majority of the solvent was then removed at reduced pressure and the resulting residue dissolved in dichloromethane (50 mL). The solution was washed with water (5 x 50 mL) and dried (Na_2SO_4). The solvent was removed at reduced pressure and the residue crystallised from dichloromethane-methanol to afford **293** as off-white needles (0.50 g, 72 %) m.p. 133 - 134 °C. ^{1}H n.m.r. (d_6-acetone) δ 0.85 (br t, 12 H, CH_2CH_3), 1.14-1.46 (m, 40 H, CH_2), 1.80-1.97 (m, 8 H, CH_2CH), 3.51 (s, 12 H, OCH_3), 4.60 (t, 4 H, J = 7.4 Hz, $CHCH_2$), 4.89, 5.15 (AB quartet, J = 29.2 Hz, 8 H, CH_2O), 6.68, 6.76 (s, 2 x 4 H, ArH), 7.31 (d of d, 4 H, J = 4.8 Hz, J = 7.8 Hz, pyr ArH), 7.56-7.66 (m, 4H, pyr ArH), 8.48-8.61 (m, 4 H, pyr ArH). ^{13}C n.m.r. (d_6-acetone) δ 14.8 (CH_3), 23.7, 29.6, 30.6, 31.0, 33.1, 35.6 (CH_2), 37.0 (CH), 56.2 (OCH_3), 69.7 (OCH_2), 99.2, 124.4, 126.8, 127.1, 134.7, 136.4, 150.2, 150.3, 156.5 and 157.1 (Ar) note - one coincident Ar signal. Found: C, 74.9; H, 8.3; N, 4.0 %. $C_{84}H_{108}N_4O_8.½CH_3OH.½CH_2Cl_2$ requires C, 75.0; H, 8.2; N, 4.1 %.

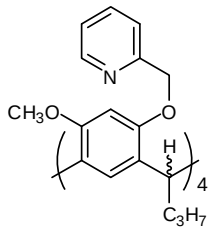
5.5.4 $1^4,3^6,5^6,7^6$-Tetra-(pyridin-3-ylmethoxy)-$1^6,3^4,5^4,7^4$-tetramethoxy-2,4,6,8-tetraheptylresorcin[4]arene (293) (potassium carbonate/acetonitrile method)



A mixture of resorcinarene **156** (0.25 g, 0.27 mmol) potassium carbonate (0.74 g, 5.3 mmol) and 3-chloromethylpyridine hydrochloride (0.52 g, 3.20 mmol) in acetonitrile (10 mL) was heated at reflux overnight. The reaction mixture was then cooled and the solvent removed at reduced pressure. To the residue was added sodium hydroxide solution (3 M, 20 mL) and the mixture stirred for 30 minutes. The mixture was extracted with dichloromethane (3 x 20 mL) and the combined organic layers washed with water (2 x 30 mL) and then dried (Na_2SO_4). The solvent was removed

at reduced pressure and the residual solid recrystallised from dichloromethane-methanol to give **293** as off-white needles (0.05 g, 15 %). The n.m.r. and physical data were identical to that given in **5.5.3**.

5.5.5 $1^4,3^6,5^6,7^6$-Tetra-(pyridin-2-ylmethoxy)-$1^6,3^4,5^4,7^4$-tetramethoxy-2,4,6,8-tetrapropylresorcin[4]arene (290)



A mixture of resorcinarene **190** (0.5 g, 0.70 mmol) potassium carbonate (1.94 g, 14.0 mmol) and 2-chloromethylpyridine hydrochloride (1.38 g, 8.40 mmol) in acetonitrile (20 mL) was heated at reflux overnight. The reaction mixture was then cooled and the solvent removed at reduced pressure. To the residue was added sodium hydroxide solution (3 M, 50 mL) and the mixture stirred for 30 minutes. The mixture was extracted with dichloromethane (3 x 30 mL) and the combined organic layers washed with water (2 x 30 mL) and then dried (K_2CO_3). The solvent was removed at reduced pressure and the residue passed through a silica plug (dichloromethane/ethyl acetate 4:1 followed by dichloromethane/ethylacetate 4:1 with 5 % triethylamine). The crude solid was recrystallised from methanol to give **289** as colourless plates (0.60 g, 80 %) m.p. 184 – 185 °C. ^{1}H n.m.r. ($CDCl_3$, 500 MHz) δ 0.94 (t, 12 H, J = 7.4 Hz, CH_2CH_3), 1.41 (apparent sextet, 8 H, CH_2), 1.85-1.96 (m, 8 H, CH_2CH), 3.43 (s, 12 H, OCH_3), 4.61 (t, 4 H, J = 7.5 Hz, $CHCH_2$), 4.90, 5.08 (AB quartet, J = 13.2 Hz, 8 H, CH_2O), 6.40, 6.71 (s, 2 x 4 H, ArH), 7.15-7.19 (m, 4 H, pyr ArH), 7.27 (br d, 4H, pyr ArH), 7.53 (apparent d of t, 4H, pyr ArH), 8.53-8.55 (m, 4 H, pyr ArH). ^{13}C n.m.r. ($CDCl_3$) δ 15.04 (CH_3), 22.17 (CH_2CH_3), 36.48 (CH), 37.45 ($CHCH_2$), 56.14 (OCH_3), 71.79 (OCH_2), 97.58, 121.83, 122.95, 126.35, 126.77, 127.01, 137.26, 149.35, 155.22, 156.32 and 158.67 (Ar). MS m/z 1125.2 $[M+1]^+$

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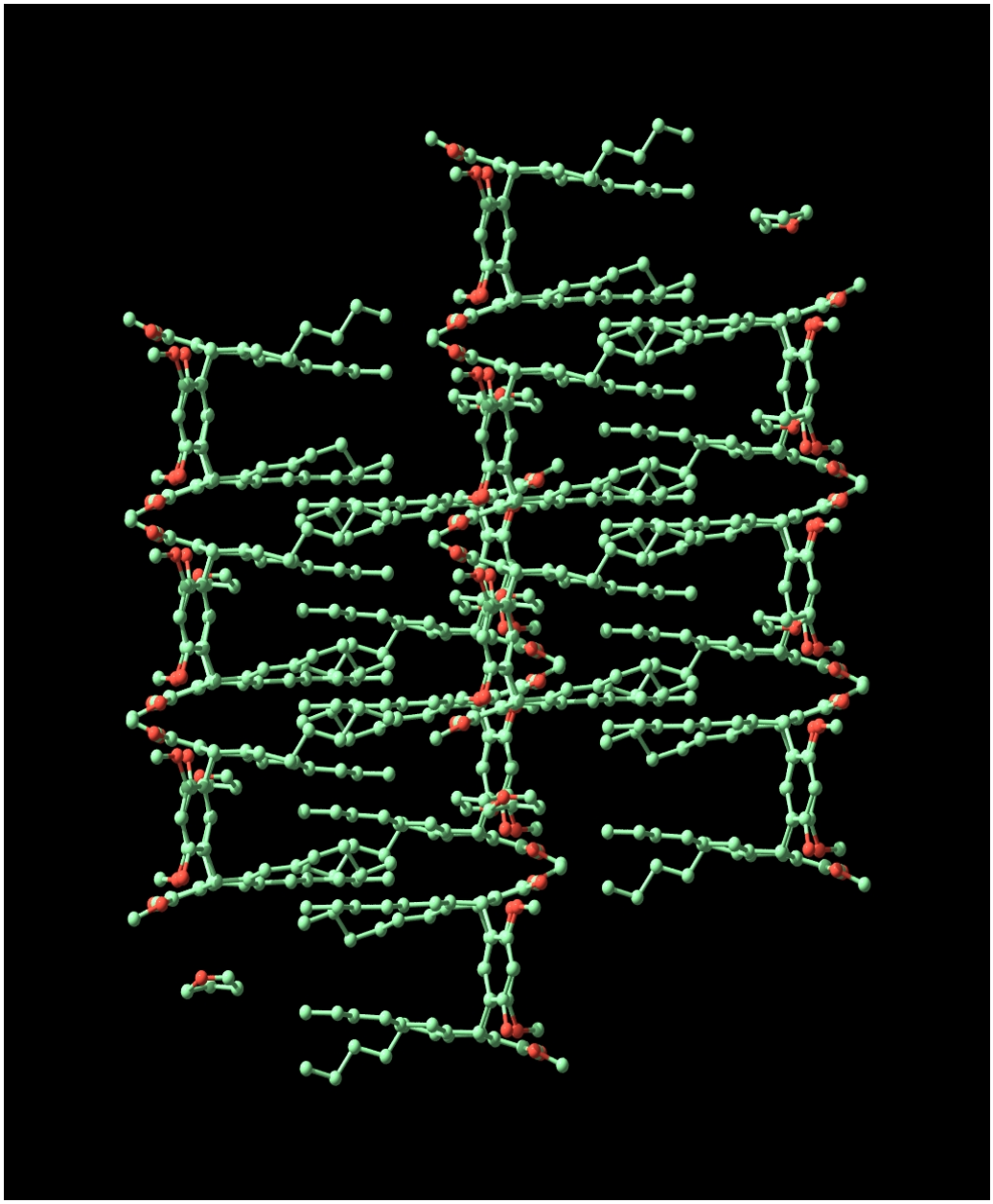
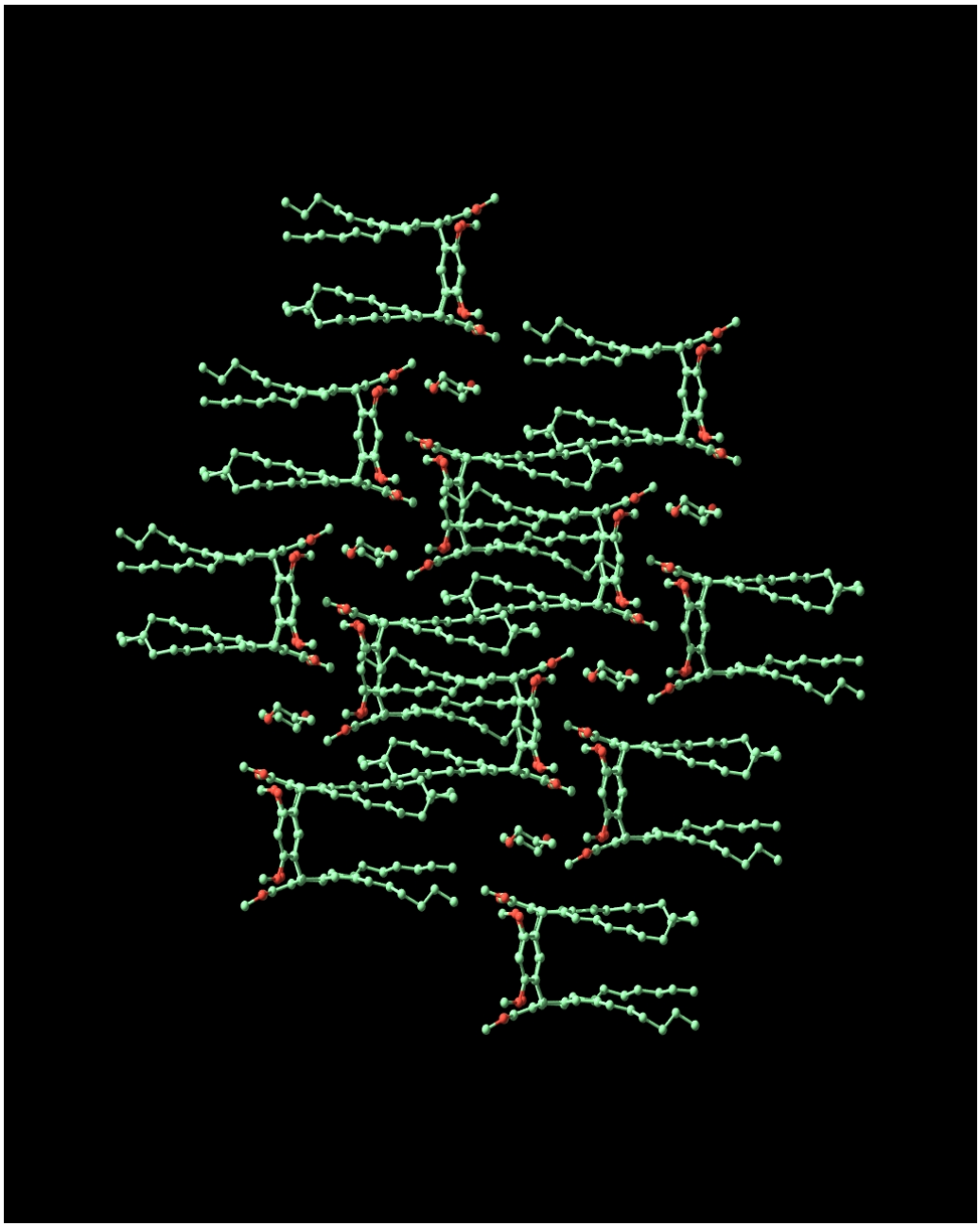
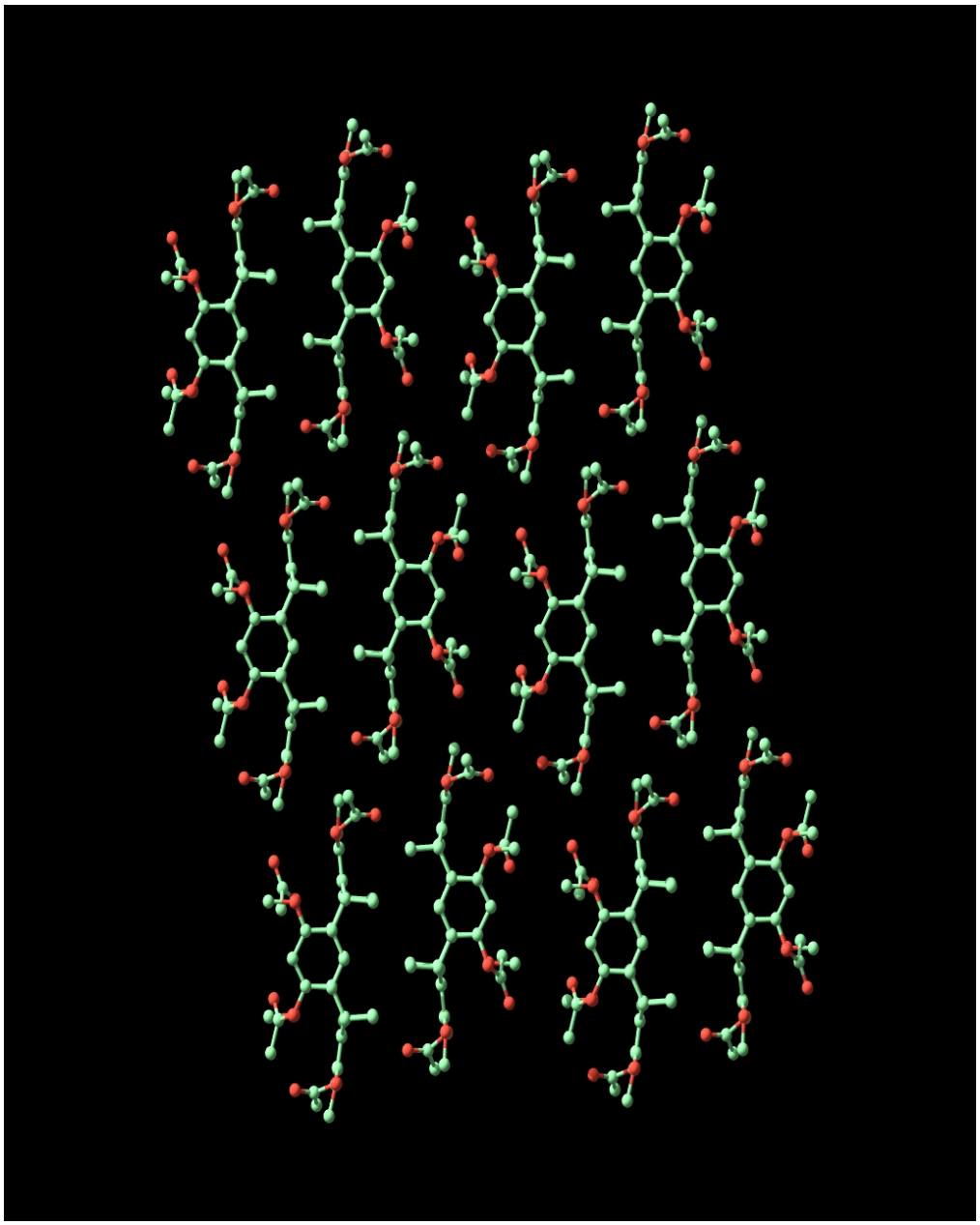
7.0 Appendices



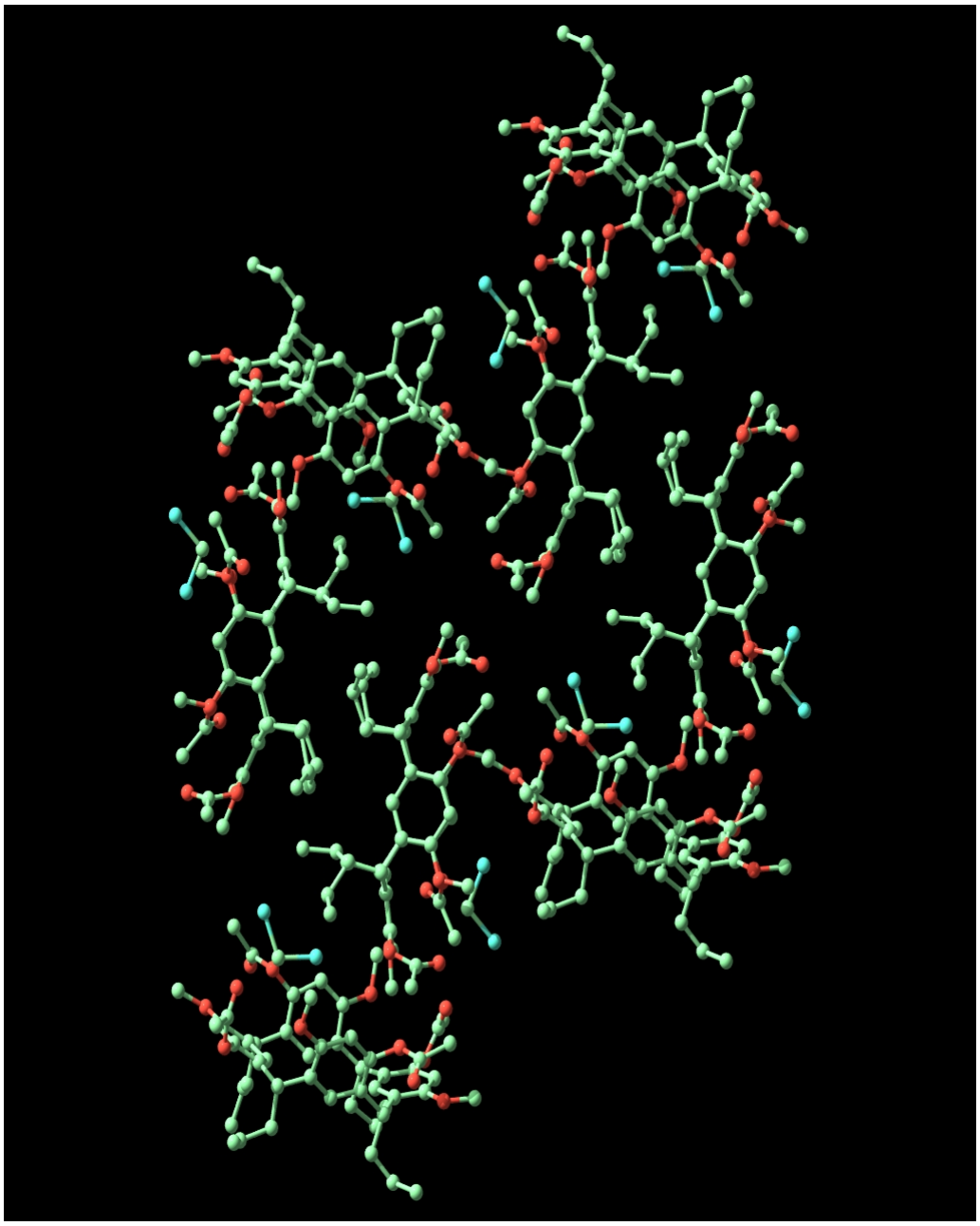
Appendix 1 – Single crystal X-ray structure of *C*-heptyl-tetramethoxy calix[4]resorcinare (**156**)



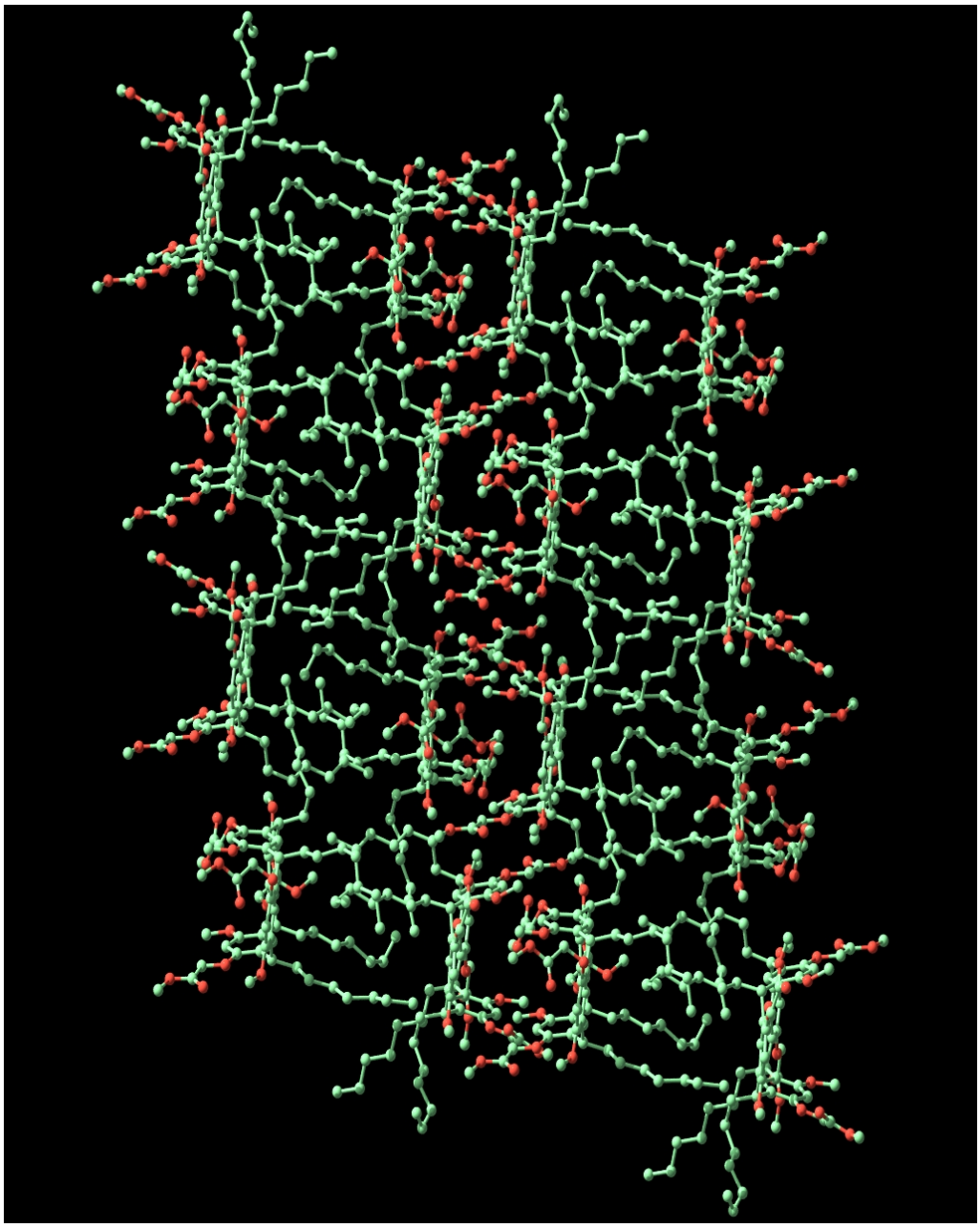
Appendix 2 – Single crystal X-ray structure of *C*-nonyl-tetramethoxy calix[4]resorcinare (**192**)



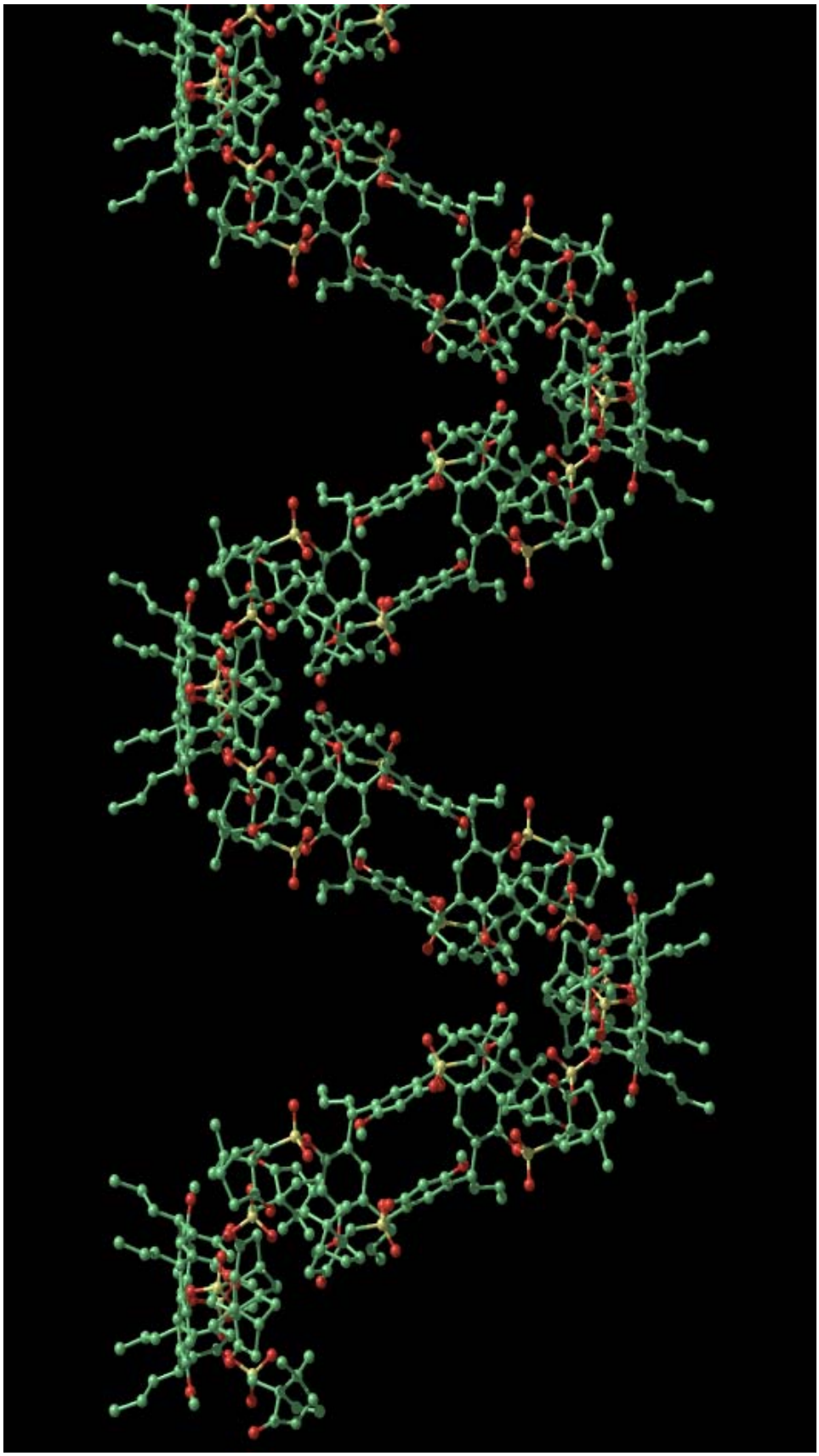
Appendix 3 – Single crystal X-ray structure of *C*-methyl-tetramethoxycalix[4] resorcinare tetraacetate (**189**)



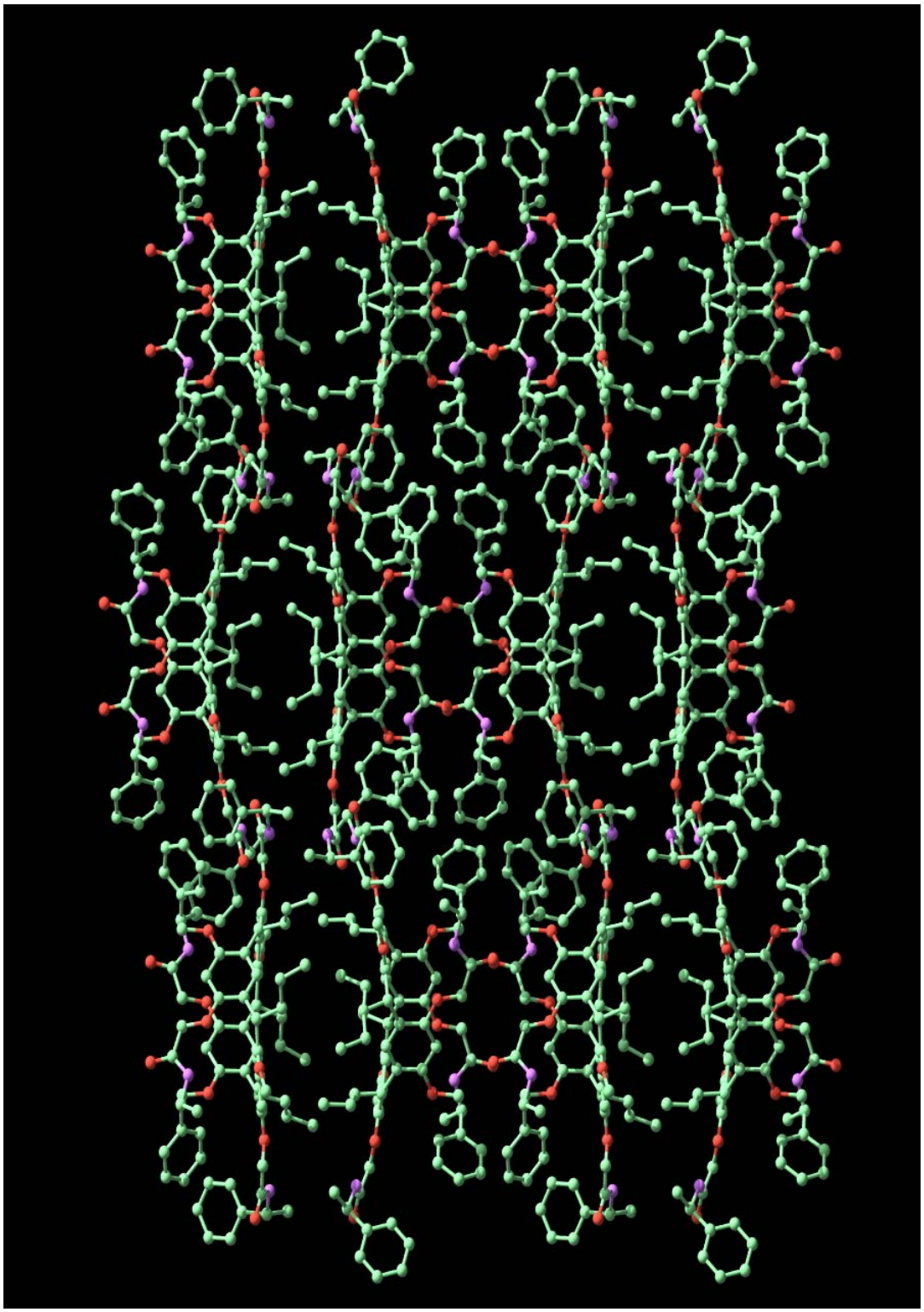
Appendix 4 – Single crystal X-ray structure of *C*-propyl-tetramethoxy calix[4]resorcinare tetraacetate (**219**)



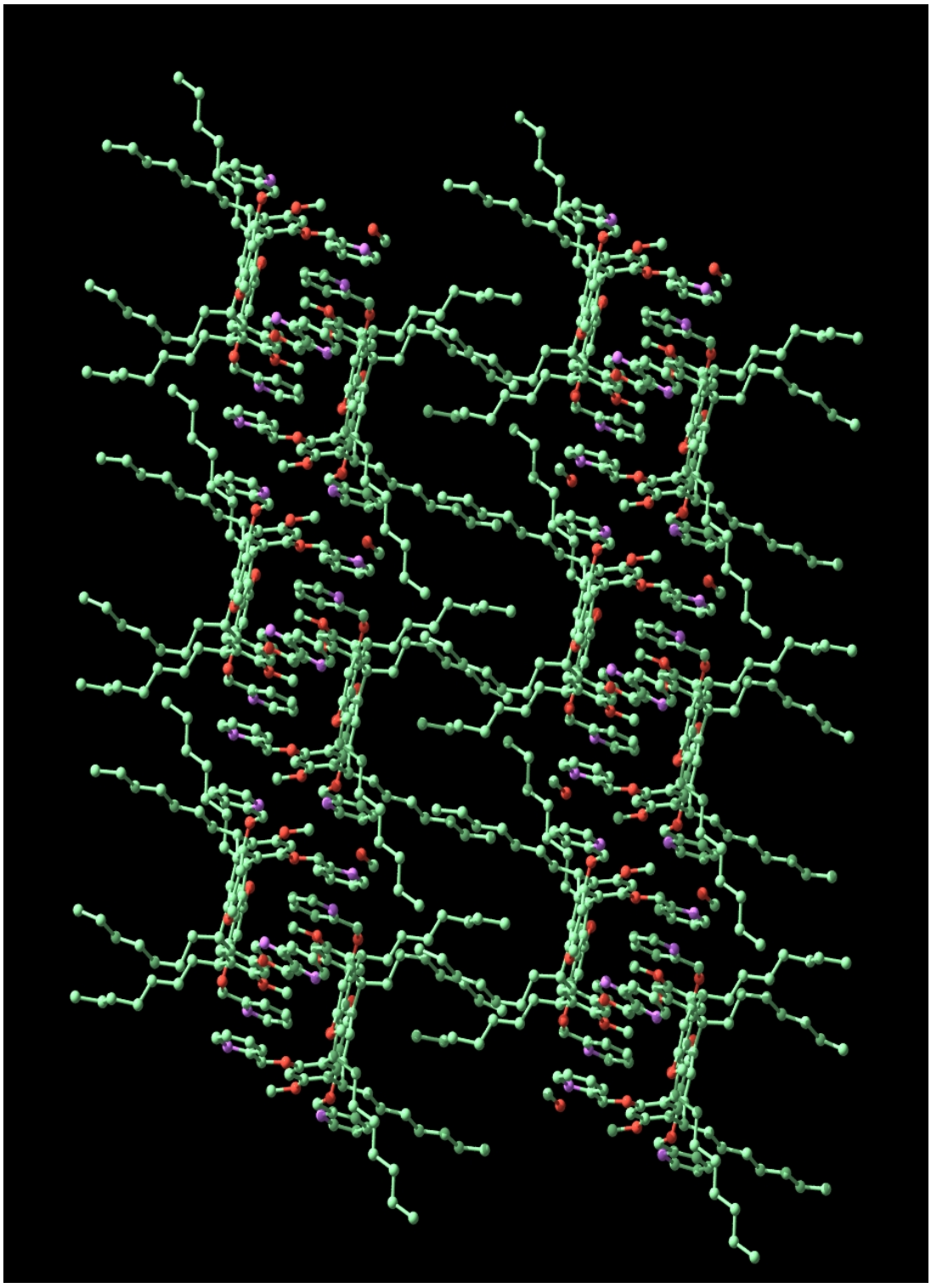
Appendix 5 – Single crystal X-ray structure of *C*-heptyl-tetramethoxy calix[4]resorcinare tetramethyl-ester.



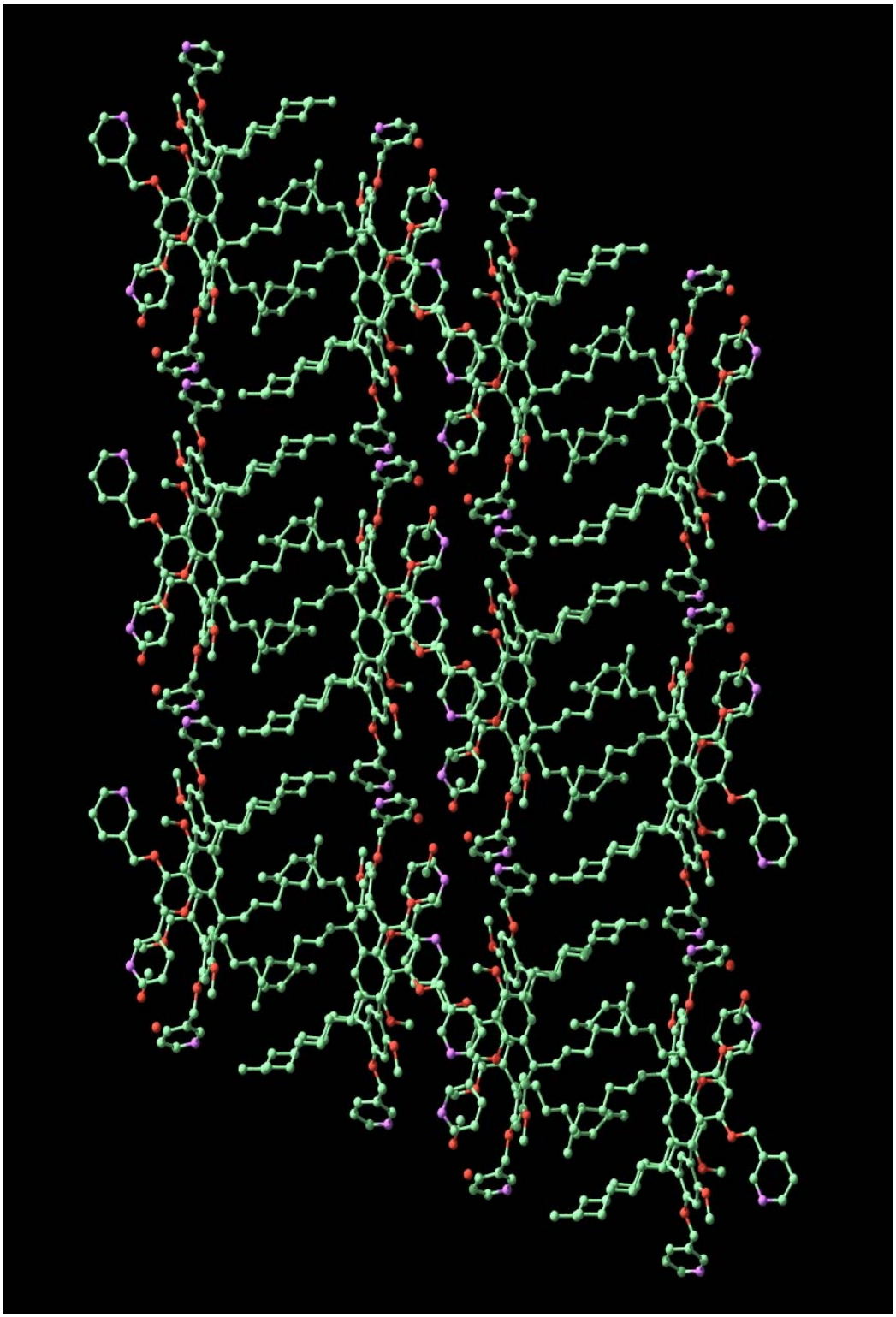
Appendix 6 – Packing view of the derivative **260a**, solvent and hydrogen atoms have been omitted for clarity).



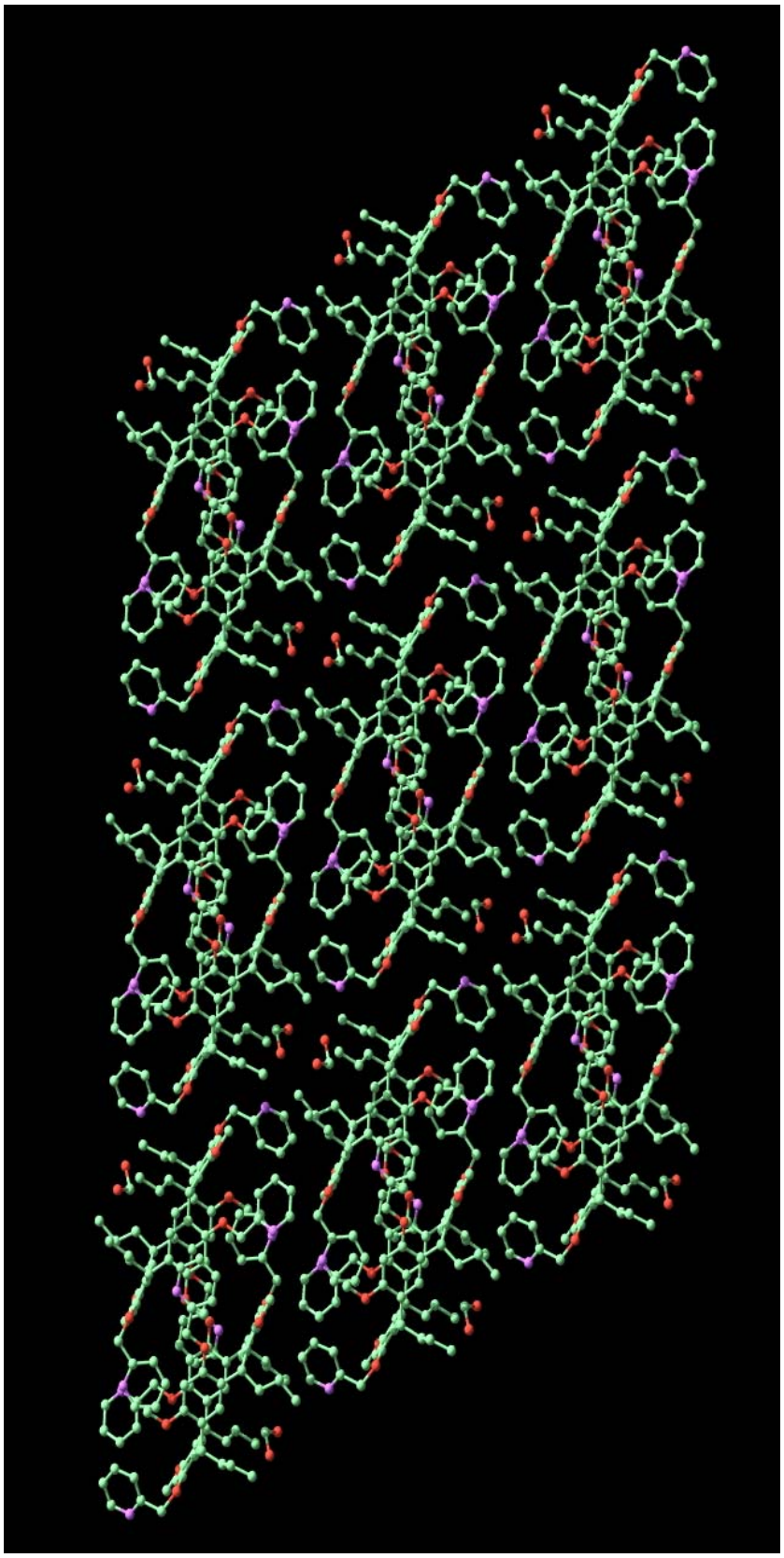
Appendix 7 - x-ray structure of **277a** showing the packing features.



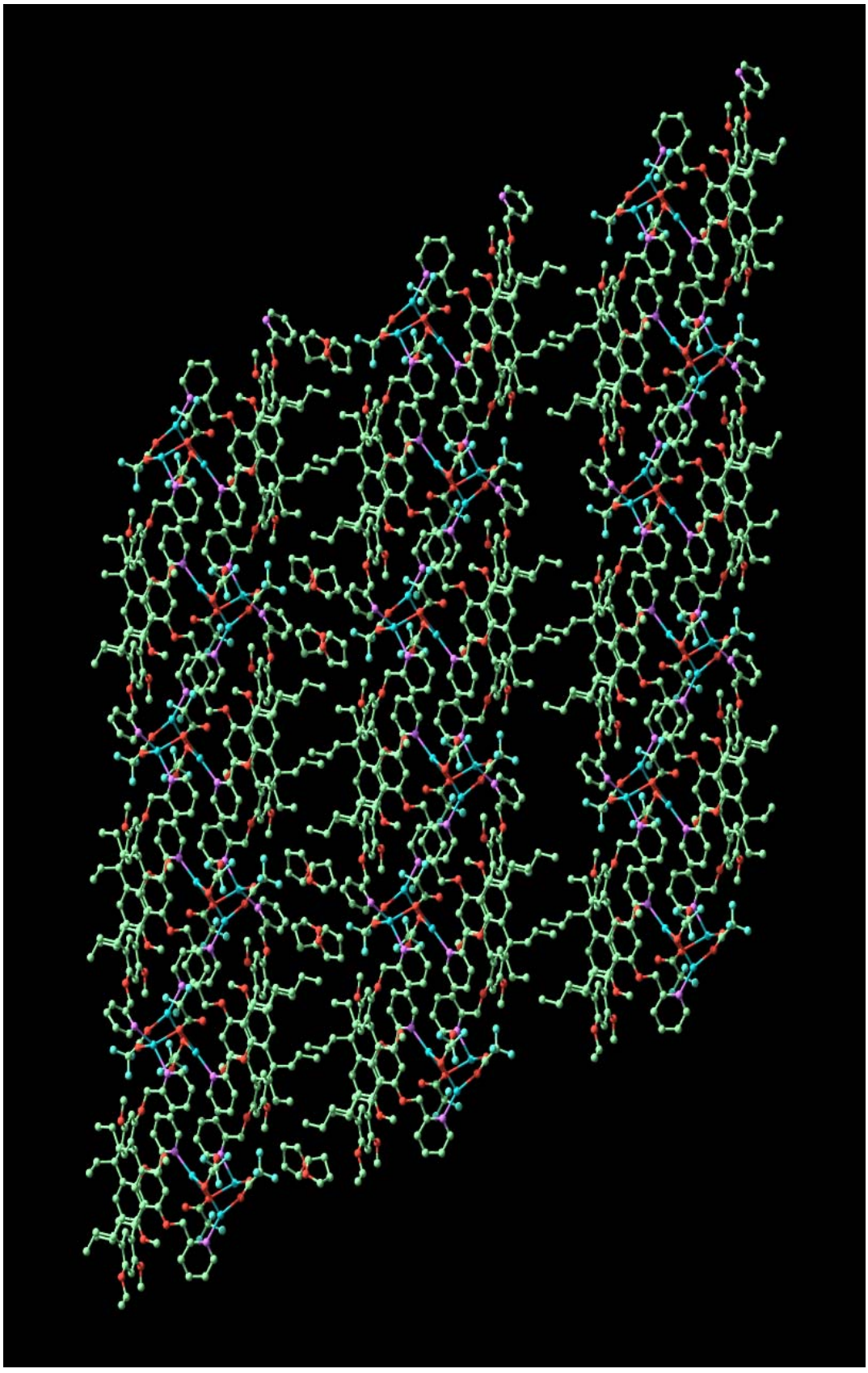
Appendix 8 - Packing view of **289** (hydrogen atoms omitted for clarity).



Appendix 9 - Packing view for **293** (hydrogen atoms omitted for clarity).



Appendix 10 - Packing view for **290** (hydrogen atoms omitted for clarity).



Appendix 11 - Packing diagram of the silver(I)-**290** complex viewed along *a* showing the layered structure. Note: associated tetrahydrofuran molecules have been removed from the upper and lower channels for clarity.

Appendix 12

“Facile Lewis Acid Catalyzed Synthesis of *C*$_4$ Symmetric Resorcinarenes”

Appendix 13

"Mannich and *O*-Alkylation Reactions of Tetraalkoxyresorcin[4]arenes – The Use of Some Products in Ligand-Assisted Reactions"

Appendix 14

"The Preparation and Absolute Configurations of Enantiomerically Pure C_4-Symmetric Tetraalkoxyresorcin[4]arenes Obtained from Camphorsulfonate Derivatives"

Appendix 15

“Pyridine-functionalised C_4 symmetric resorcinarenes”