A brief review of C_n-symmetric calixarenes and resorcinarenes

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Calixarene and resorcinarene macrocycles are renowned for their ability to form inclusion complexes or act as molecular scaffolds. The addition of chirality to these non-planar molecules is an exciting enhancement of their already robust potential, offering much promise as ligands for chiral catalysis and enantioselective separations. Chiral calixarenes can be produced by the attachment of a chiral moiety or by the placement of an achiral functionality on the macrocyclic structure so as to render it asymmetric. The latter method is particularly intriguing, often resulting in molecules which have C_n dissymmetry. This review describes examples of the C_n-dissymmetric calixarenes and resorcinarenes prepared to date and discusses aspects of their chirality, including their pictorial and written descriptors.

Keywords: calixarene; resorcinarene; chirality; dissymmetry

Introduction

Calixarenes and resorcinarenes have been successfully applied in a variety of roles such as catalysis (*1*), as selective ionophores (*2*) and chromatographic stationary phases (*3*). The addition of chirality to these non-planar molecules offers a great potential not only for the enhancement of these applications but also for the development of exciting new functionality.

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 many 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(A)) produced by Ungaro (*4*) and lower rim sugar-functionalised compound (**B**; Figure 1(B)) produced by Lhoták (*5*).

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 the 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 at the X^5 positions[1] 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' (*7*). For example, a calixarene such as that shown in Figure 2 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 that 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.

The second form of asymmetric functionalisation is comprised of those molecules for which asymmetry has been generated by the inclusion of a group at the X^4 or X^6 positions (or both), which also destroys the vertical mirror planes of the C_{4v} macrocycles. This is shown in Figure 3,

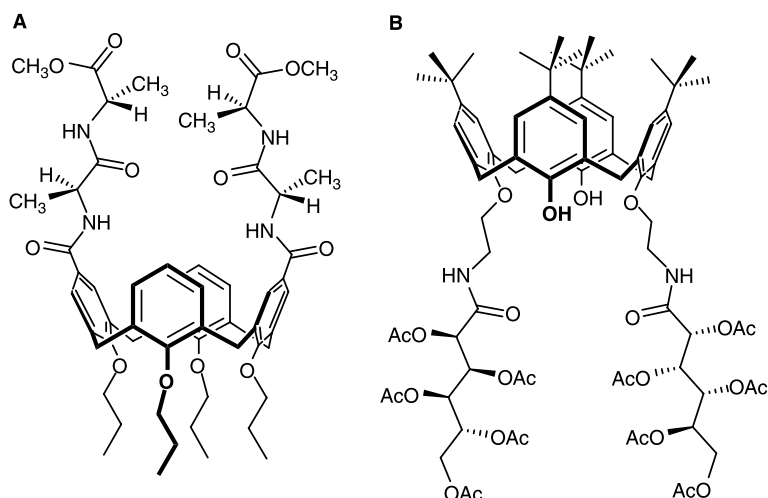*Corresponding author. Email: m.mcildowie@curtin.edu.au

Figure 1.   Two examples of chiral calixarenes formed by the attachment of a chiral moiety.
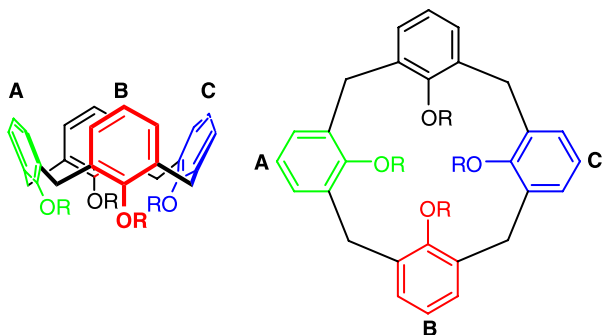

Figure 2.   The side and top views of a chiral calixarene having three sequential different aromatic units.

where the position of R^1 (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.

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 2), where at least two different functionalisations are required.[2]

Elements of conformational, axial or helical chirality may potentially be ascribed to the calixarene (**A**; Figure 3). The 'chirality axis' (coincident 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' (*8*). The term 'inherent chirality' (*9*) is often applied but has no stereochemical significance (*10*) and has more suitable replacements in the stereochemical literature (*11*). An application of these chirality descriptors to calix[4]arenes is commonplace, however, despite the abundance of the completely asymmetric calix[4]arenes [for examples, see Refs (*12, 13*)] with an AABC-type pattern, no formal method for describing their absolute stereogenicity appears to have been applied. In 2004, Mandolini (*10*) proposed a method for describing the chirality sense of the AABC-type
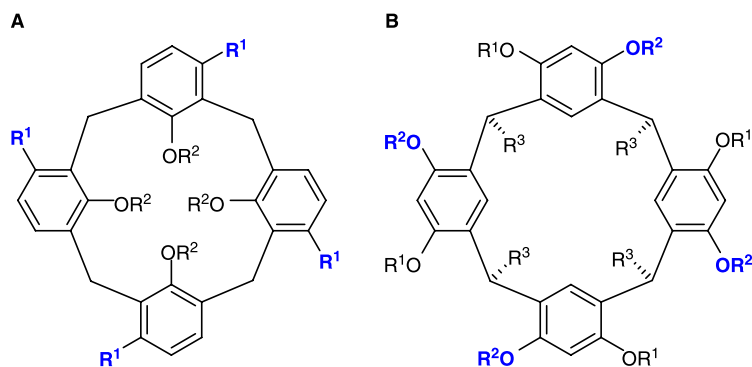

Figure 3.   Examples of a chiral dissymmetric calixarene (**A**; where $R^1 \neq$ H) and a chiral dissymmetric resorcinarene (**B**; where $R^1 \neq R^2$).
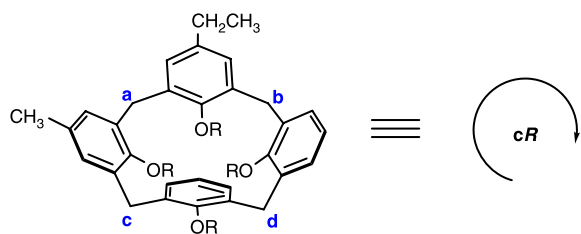
Figure 4. Application of Mandolini's priority method for assignment of chirality sense.

calixarene derivatives (Figure 4). By assigning a priority order (a, 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.

However, the majority of calixarene publications (for example (*14*)) have not adopted this notation since it was introduced, with a few exceptions (*15–17*).

Similarly untested are the rules delineated by Prelog and Helmchen (*18*) for describing the chirality sense of those molecules not containing any stereogenic centres, i.e. those having a 'chirality plane' or a 'chirality axis'. This method was exemplified in 1984 by Schlögl (*19*) for smaller phanes such as the benzoic acid derivative (**A**) shown in Figure 5.

Description of resorcinarene chirality, on the other hand, has no such complications as the presence of four stereogenic centres makes the application of the IUPAC-prescribed (*20*) Cahn–Ingold–Prelog (CIP) rules (*7*) a simple task. Thus, the structures A and B in Figure 6 can be described as the 2*R*,4*R*,6*R*,8*R*- and 2*S*,4*S*,6*S*,8*S*-, respectively.

Recently (*21*), 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 the 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, the resulting C_1-symmetric derivative is better described with the usual *R/S* notation for stereogenic centres.

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
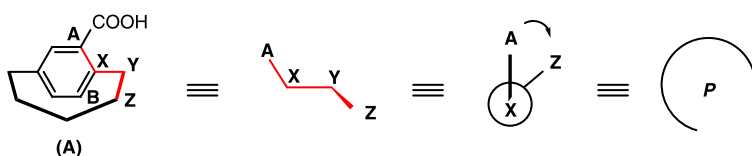

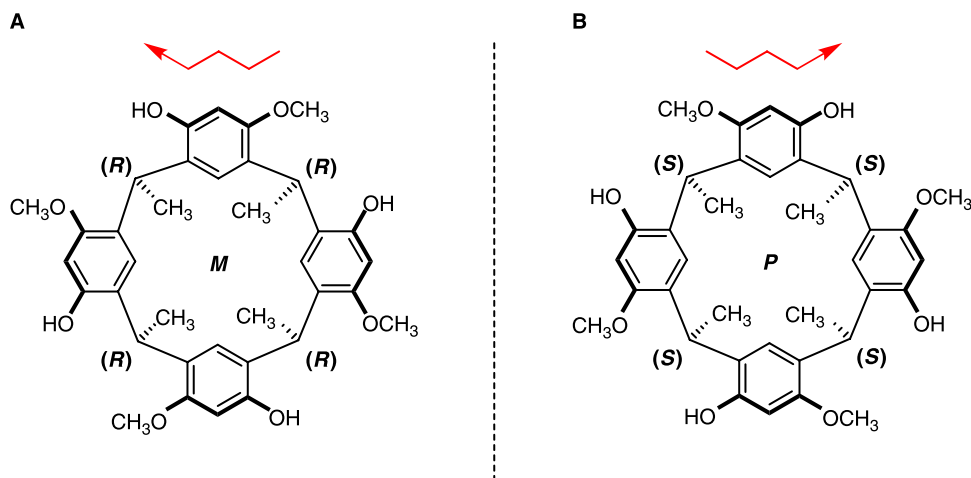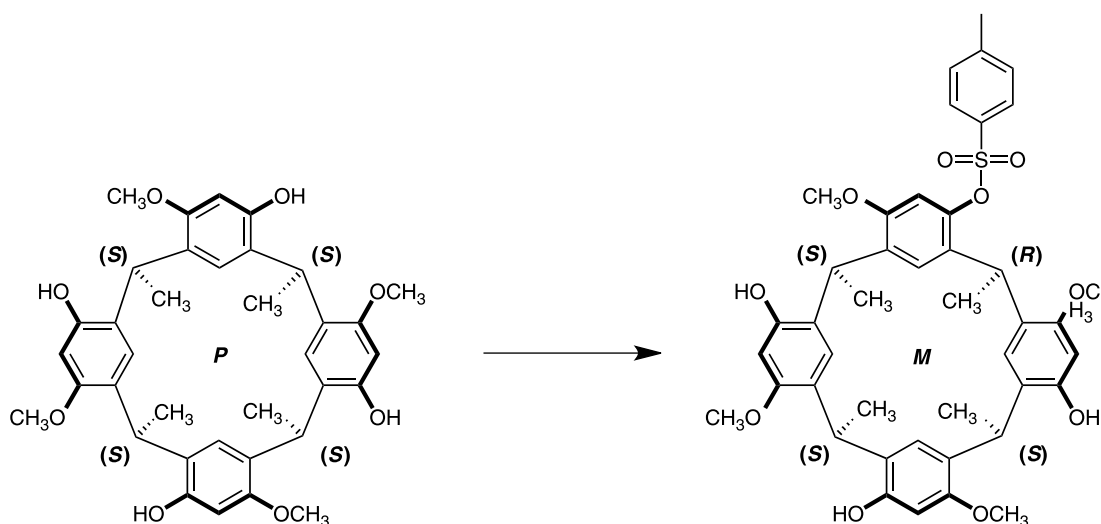Figure 5. Application of the helical chirality descriptor to phane molecules.

Figure 6. C_4-dissymmetric resorcinarene enantiomers with assigned stereochemistry using the CIP *R/S* and the recently applied *M/P* notation.

Scheme 1.   Changes to the chirality sense of a resorcinarene in the event of a minor functionalisation.

modifications recommended by Dodziuk and Mirowicz (*8*) and the examples of Schlögl (*19*).

Structural representation of resorcinarenes and their chirality

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

The most unambiguous representations of the resorcinarenes and their chirality are the three-dimensional depictions shown in Figure 7. 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.

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 8.

In these cases, the diagram will represent the resorcinarene molecule viewed from above the cavity with the orientation of the alkyl chains indicated using the 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 in Figure 9.

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 10.

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
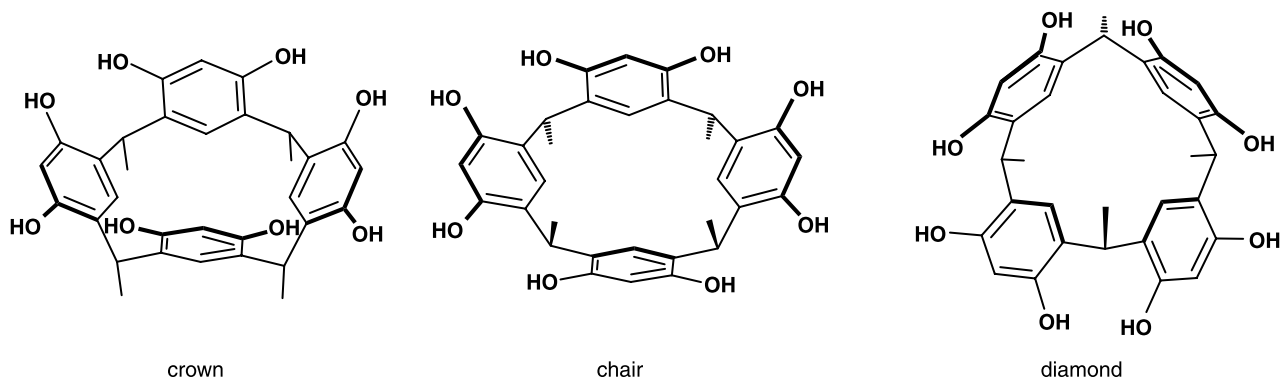

Figure 7.   Three-dimensional depictions of the crown, chair and diamond conformations of resorcinarenes.
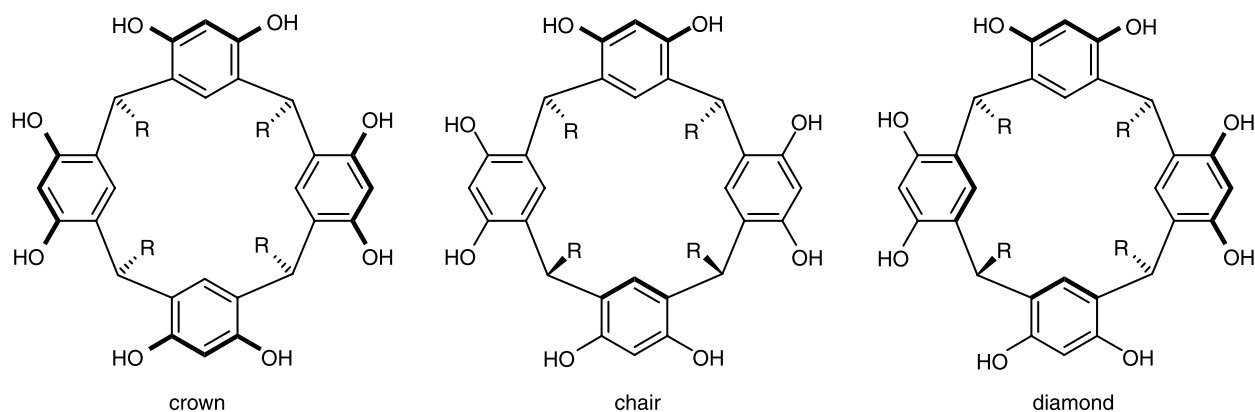
Figure 8. 'Flat' style depictions of the crown, chair and diamond conformations of resorcinarenes.

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 11(A), where both are viewed from the same perspective (from outside the annulus in this case).

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, the IUPAC published new recommendations for the nomenclature of phanes with specific reference to the calixarene ring system (*6*). This new system completely replaced the previous long-winded alkene cyclic alkene-based nomenclature, obviating the need for a shortened independent nomenclature system for the calixarenes. It also brings calixarene numbering in to line with the already well-established alkane and ring system nomenclature. The IUPAC list of the 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 (alphabetised substituents)

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 an 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 the more familiar nomenclature shown in Figure 12.

The 'correct' and 'incorrect' numbering assignments of (**C**) are shown to exemplify the IUPAC priority rules for phane nomenclature. Specifically, 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.

Reviews on chiral calixarenes are currently available in the literature (*9*, *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 3 and on which the bulk of the 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
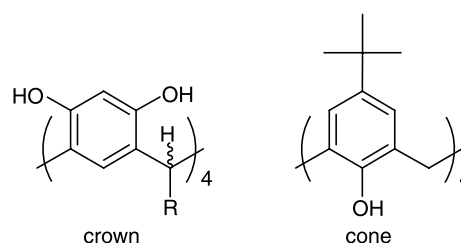

Figure 9. 'Simplified' depictions of the resorcinarene crown conformation shown with 'all axial' alkyl groups and the calixarene cone conformation.
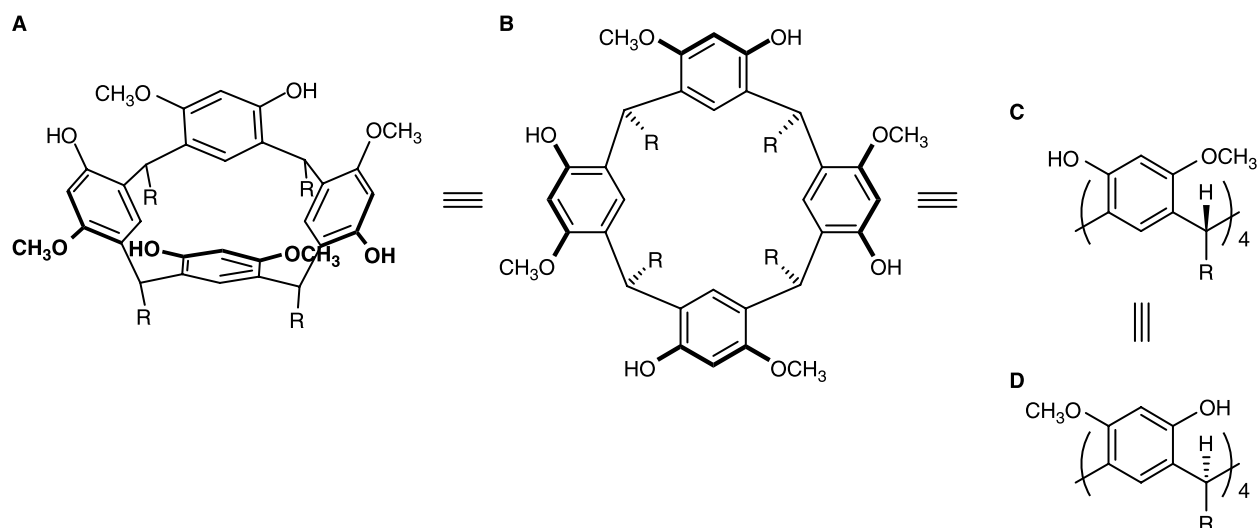
Figure 10.   Four depictions describing the absolute stereochemistry of a single chiral resorcinarene enantiomer.

symmetry (*24*) and simplicity makes them by far the most aesthetically pleasing. The following sections are arranged in the 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). The consequence of such a structural arrangement is the necessary repetition of references to publications containing molecules from more than one symmetry group, i.e. a publication containing a calixarene with C_2 symmetry and another having C_4 symmetry must necessarily be referenced in both the sections.

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 regard to the simplicity of their preparation from the parent macrocycles.

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 the 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 >60% conversion (Scheme 2).

Gutsche (*25*) demonstrated the chirality of the prepared materials by NMR spectroscopy in the presence of Pirkle's reagent [(*S*)-(+)-2,2,2-trifluoro-1-(9-anthryl)ethanol]. 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 3).

The NMR spectroscopic analysis of **5** and **6** appears to be indicative of the mono-*meta*-substituted species but no further proof of chirality was offered.
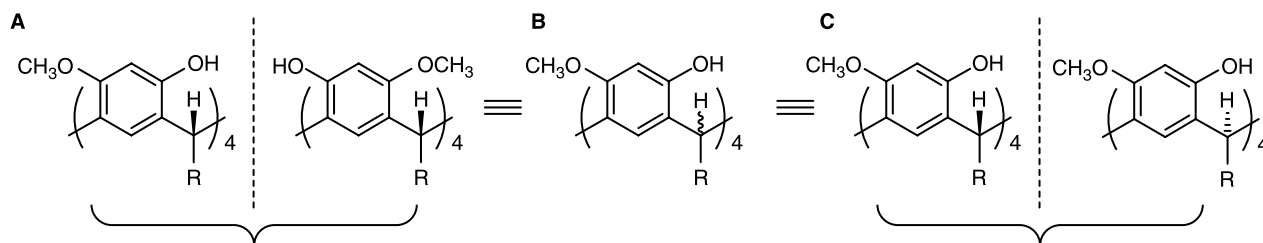

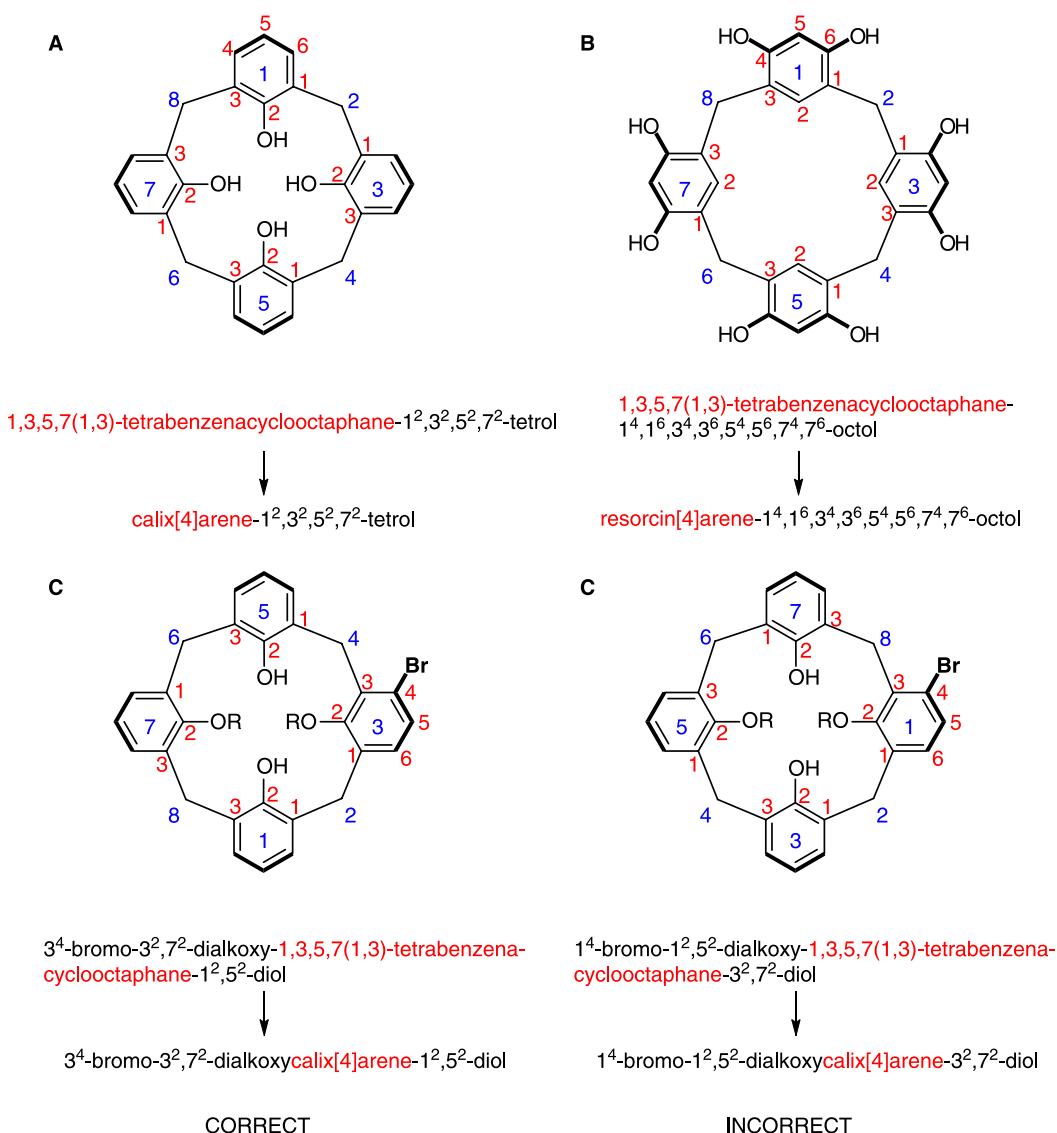Figure 11.   Simplified depictions of the resorcinarene racemate.

Figure 12. Application of the 'phane' numbering to the calixarene ring system and its adaptation to the calixarene 'common' name usage.

Verboom and co-workers (*27*) 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** (Scheme 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% yield. Compounds **9**–**12** were demonstrated to be racemic by the ^{1}H NMR spectroscopy in the presence of Pirkle's reagent; however, none of the racemates were resolved.

Huang et al. (*17*) made the logical advancement to Verboom's method with the introduction of an *N*-Boc-L-proline amide to afford calixarene **13**. Bromination or nitration of the ring positions adjacent to the amide resulted in the direct formation of diastereomers of **14** and **15** in good yields (Scheme 5).

The diastereomers were resolved by preparative TLC or column chromatography. Removal of the *N*-Boc-L-proline auxiliary was achieved by hydrolysis with $Ba(OH)_2 \cdot 8H_2O$ in a butanol–dimethyl sulphoxide mixture affording the enantio-pure primary amines of **18** and **19**. The laevorotary enantiomer **18b** ($[\alpha]_D^{25}$ − 15.9, $c = 1$ (dichloromethane, DCM)) was determined by X-ray crystallography to have the *P* configuration, as shown in Scheme 5. The methodology was extended further (*15*) by reduction of the nitro diastereomers **15** with hydrazine to give the anilines **16** which were methylated to yield the diastereomeric tertiary amines **17**. Removal of the Boc-protecting groups with trifluoroacetic acid in DCM gave the diamines

R^1	R^2	R^3	%Yield
OAc	OAc	Ac	62
OH	SArCH$_3$	OH	80
		OH	31
		OH	80
	CO$_2$Et	OH	67
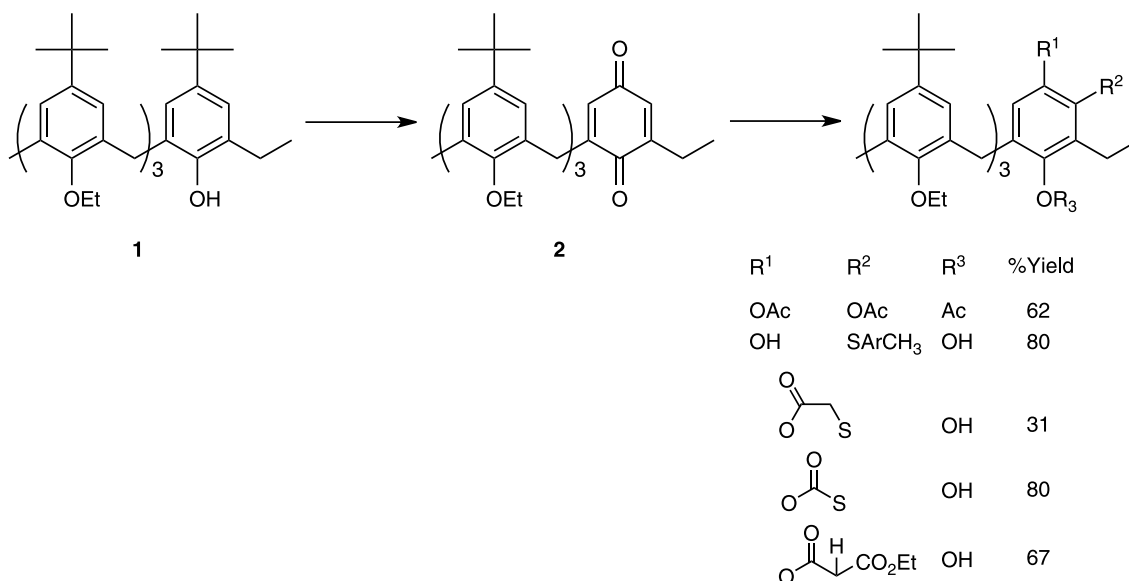
Scheme 2.   The preparation of chiral calixarenes from monoquinone **2**.
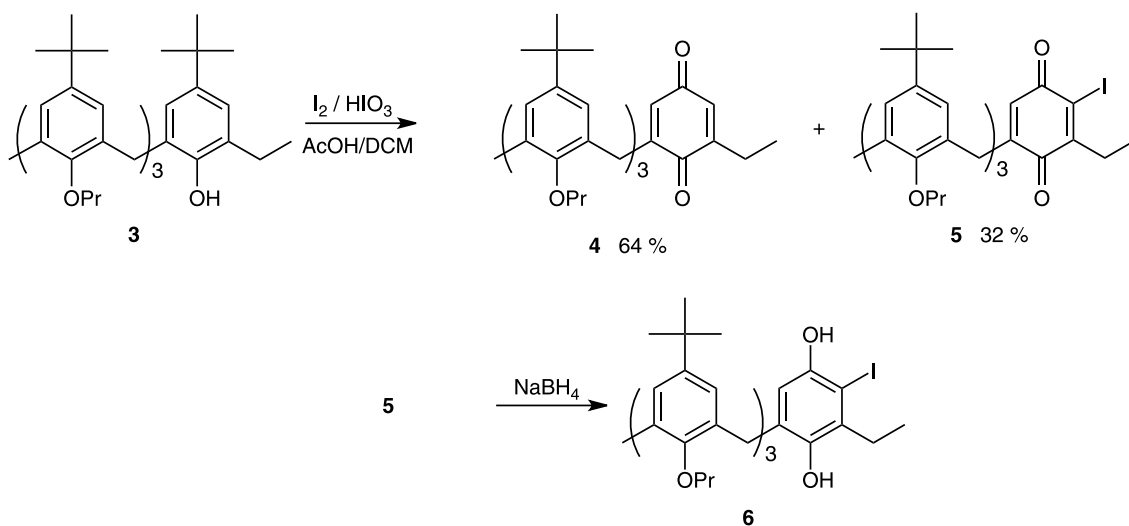
Scheme 3.   Iodination of the calixarene triether **3** to afford the asymmetric monoiodide **5** and its subsequent reduction to **6**.

	R^1	R^2
9	Bu^t	NO$_2$
10	H	NO$_2$
11	Bu^t	Br
12	H	Br

7 R^1 = Bu^t
8 R^1 = H
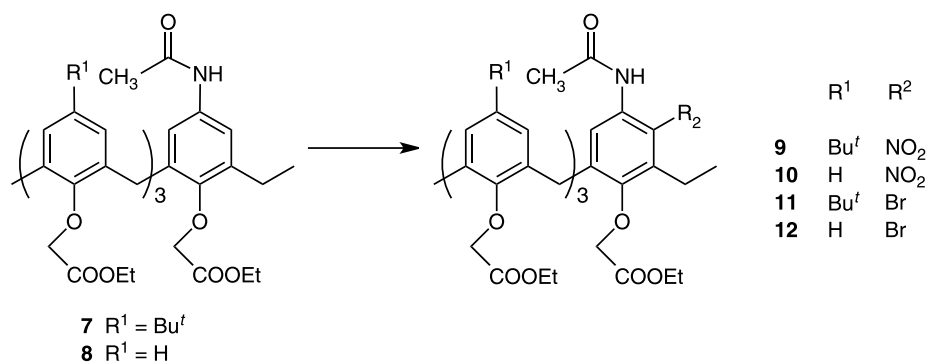
Scheme 4.   Bromination or nitration of calixarenes **7** and **8** to afford the corresponding chiral monobromides and nitrates.

13

a   b

	R^1	R^2
14	Br	*N*-Boc-L-Pro
15	NO$_2$	*N*-Boc-L-Pro
16	NH$_2$	*N*-Boc-L-Pro
17	N(CH$_3$)$_2$	*N*-Boc-L-Pro
18	Br	H
19	NO$_2$	H
20	N(CH$_3$)$_2$	L-Pro
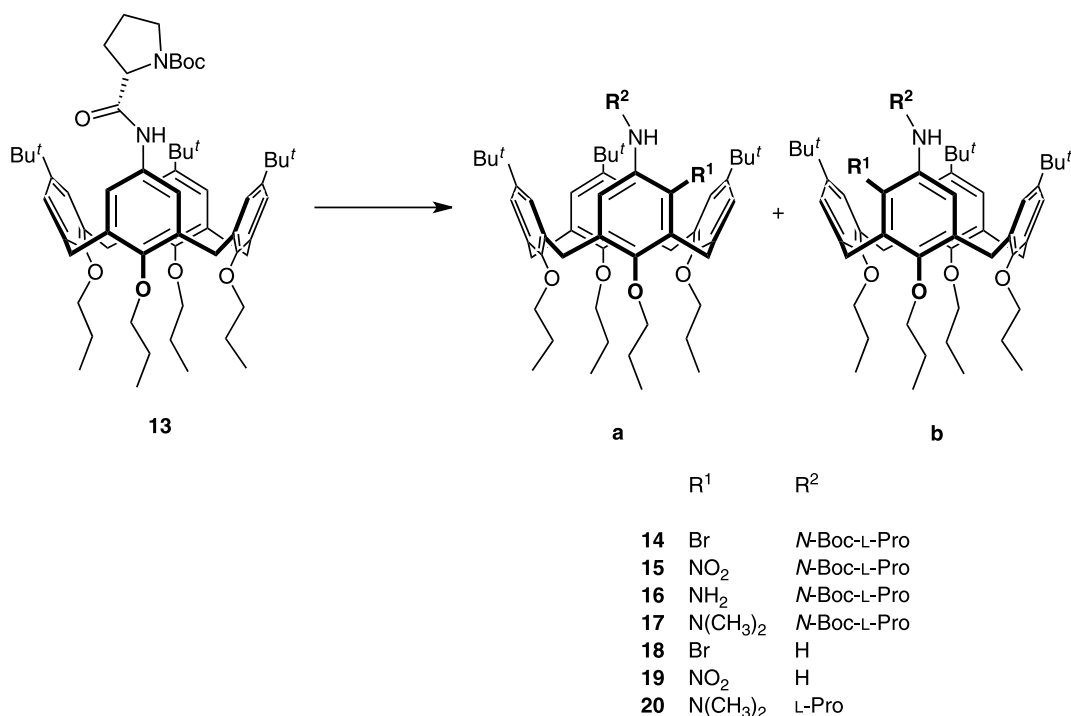
Scheme 5.   Functionalisation of the chiral amide **13** to afford diastereomeric species.

20a and **20b**, which were examined as organocatalysts for the enantioselective aldol reaction (*15*).

Perhaps a simpler example is the restricted calix[6]-arene derivative **21** (Figure 13) produced by Shinkai (*28*). The 4-methoxy-*m*-xylenyl moiety bridges the 1,5-aryl units and is restrictive enough to prevent ring inversion and therefore racemisation. The chirality of **21** was proven by NMR spectroscopy with Pirkle's reagent, and subsequent resolution by enantioselective HPLC (Daicel Chiralpak AD, Tokyo, Japan; *n*-hexane–2-propanol 98:2), though the absolute stereochemistry was not determined.

Fragment condensation for the preparation of *C*-dissymmetric calixarenes is generally a much more cumbersome and a low-yielding approach. However, stepwise synthesis is a proven method for the preparation
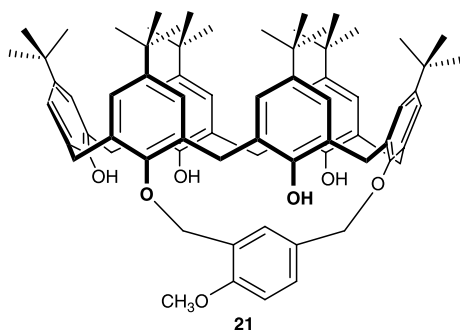

21

Figure 13.   One enantiomer of a chiral 1,5-linked hexamer produced by Shinkai (*28*).

of the achiral calixarenes (*29*) and planar-chiral calixarenes (*12*, *30*). Consequently, it has also found its place in the generation of chiral species.

Casabianca and co-workers (*31*) performed several 3+1 condensations using the bisbromomethyl phenols with TiCl$_4$ in dioxane to produce the chiral calixarenes **22**–**25** given in Scheme 6. These were afforded in yields of 10–35%. A single-crystal X-ray structural determination of **25** was reported later (*32*).

In a similar 3+1 condensation, Böhmer (*33*) has incorporated a resorcinol unit linked via its 2,6-positions to give compound **26** (Scheme 6). In this case, the chirality was demonstrated at low temperatures (-40°C) by NMR spectroscopy with Pirkle's reagent. At such low temperatures, the ring inversion is slow on the NMR time scale and interaction of the enantiomers with the reagent may be observed.

Shinkai (*34*) went one step further and locked the chiral calixarene into the cone conformation via a selective propylation. The calixarene **27** (Scheme 7), 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 **28** and then converted to the tetra-ether **29** using standard conditions (PrBr, NaH, DMF/THF). This stepwise alkylation procedure avoided the complication of multiple conformational isomers produced by direct per-alkylation of calixarene **27**. The chirality of **28** was demonstrated by NMR spectroscopy at low temperatures (-40°C) in the presence

	R^1	R^2	R^3	R^4
22	CH$_3$	H	CH$_3$	CH$_3$
23	Pr^i	H	Pr^i	CH$_3$
24	Pr^i	CH$_3$	Ph	H
25	Pr^i	CH$_3$	Pr^i	H
26	CH$_3$	H	COC$_6$H$_5$	OH
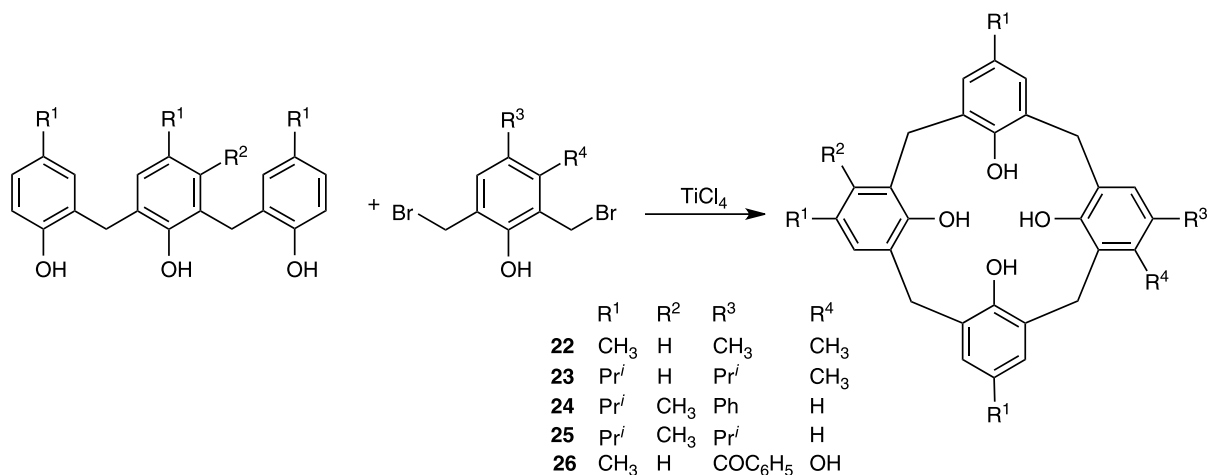
Scheme 6. Some 3+1 fragment condensation reactions to produce dissymmetric calixarenes having C_1 symmetry.
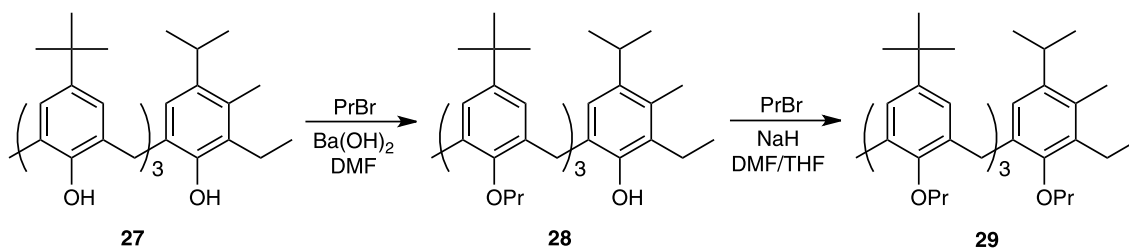
Scheme 7. Sequential alkylation at the lower rim of calixarene **27** to prevent racemisation.

of Pirkle's reagent. More significantly, the tetra-ether **29** was resolved to its enantiomers using enantioselective HPLC [Daicel ChiralPak OP(+), hexane–2-propanol–methanol 1:3:16].

The reverse approach was also adopted by Böhmer (*35*). By preparing the mono- or tri-ether derivatives of the C_4-dissymmetric calixarene **30** (Figure 14), the 'lower' symmetry materials **31–35** were obtained.

Shinkai (*36*) developed a stepwise process to construct a naphthalene unit on the calixarene (Scheme 8).

The product (**36**) is locked in the cone conformation and so cannot racemise. The chirality was established by NMR spectroscopy in the presence of Pirkle's reagent; however, it was not resolved.

More recently, a novel approach was adopted by Biali (*37*). Treatment of the bis(spirodienol) **37** with diethyla-mino sulphur trifluoride afforded the mono-fluoro compound **38** in 8% yield (Scheme 9). However, this compound is not locked into a particular conformation and can therefore readily racemise.

	R^1	R^2	R^3
30	CH$_3$	H	H
31	CH$_3$	H	*n*Bu
32	CH$_3$	H	CH$_2$C$_6$H$_4$NO$_2$
33	CH$_3$	H	CH$_3$
34	CH$_3$	H	Pr^i
35	Pr^i	CH$_2$COOEt	H
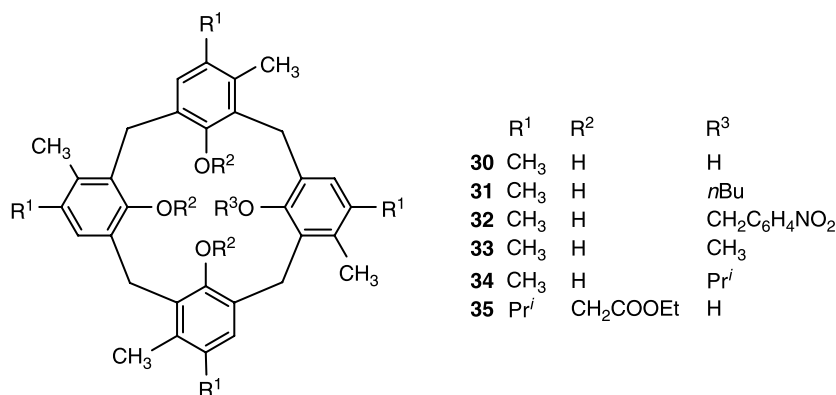
Figure 14. Desymmetrisation of C_4-dissymmetric calixarene **30** by alkylation at the lower rim.
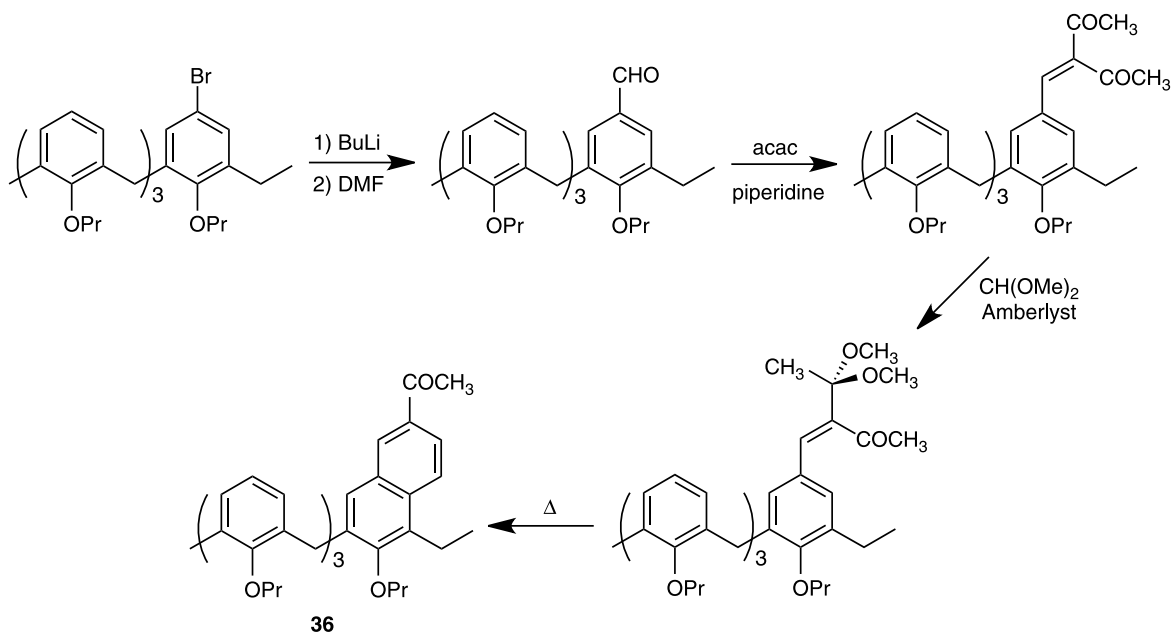
Scheme 8. A scheme for the preparation of the C_1-symmetric naphthalene derivative **36** (acac=2,4-pentanedione).

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 (*38*) (Scheme 10) as is the case for the *p*-methylbenzyl ether **39** (32%). Per-acetylation to give **40** in 64% yield and subsequent cleavage of the benzylic ether yielded the heptaacetate **41** (23%). The resorcinarene derivatives were not resolved; however,

NMR spectroscopic studies of **39** in the presence of (*R*)-*N*,*N*,*N*-trimethyl-α-methylbenzylammonium iodide showed doubling of the resorcinarene signals.

Mattay and co-workers (*39*) took the more efficient approach of generating dissymmetry with the introduction of a single chiral moiety. The reaction of camphorsulphonyl chloride with the parent resorcinarene (Scheme 11) produces the diastereomers **42** and **43**, making the resolution of enantiomers unnecessary. The diastereomers were separated by normal-phase HPLC and methylated to give **44**. The chiral auxiliary was then removed to afford the heptamethyl ether enantiomer **45**.
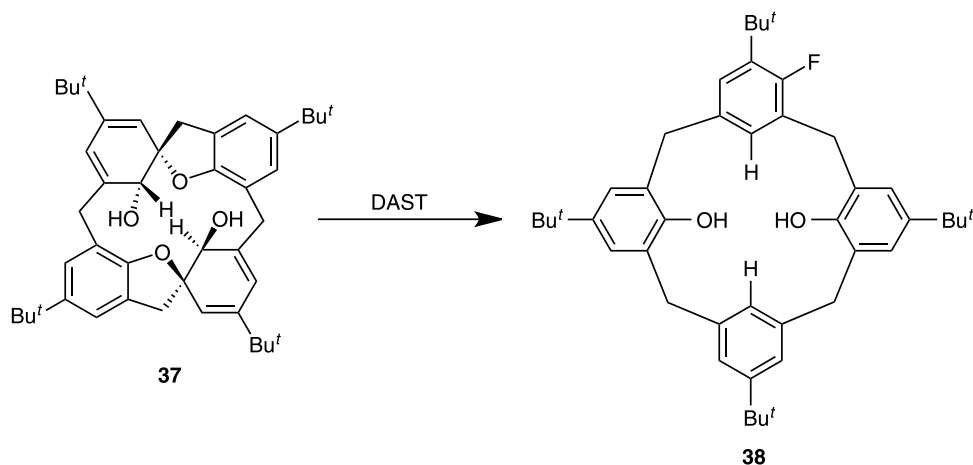
Scheme 9. Fluorination of compound **37** affords the asymmetric monofluoride **38**.
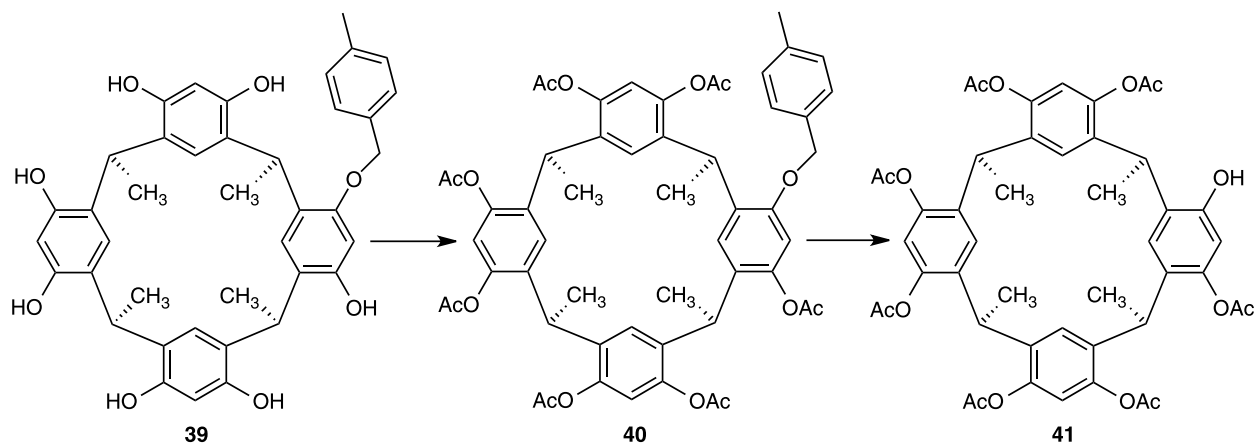
Scheme 10. Introduction of asymmetry to *C*-methylcalix[4]resorcinarene by mono-benzylation (to afford **39**) and subsequent transformations.

The *C₂*-dissymmetric

Calixarene based

Few examples of fragment condensations to produce *meta*-substituted *C₂*-dissymmetric materials exist. The only example of note is that described by Böhmer (*40*) (Scheme 12). Condensation of the hydroxymethylated bisphenol **46** with titanium tetrachloride gave the calixarene **47** in 18% yield. Böhmer attributes the
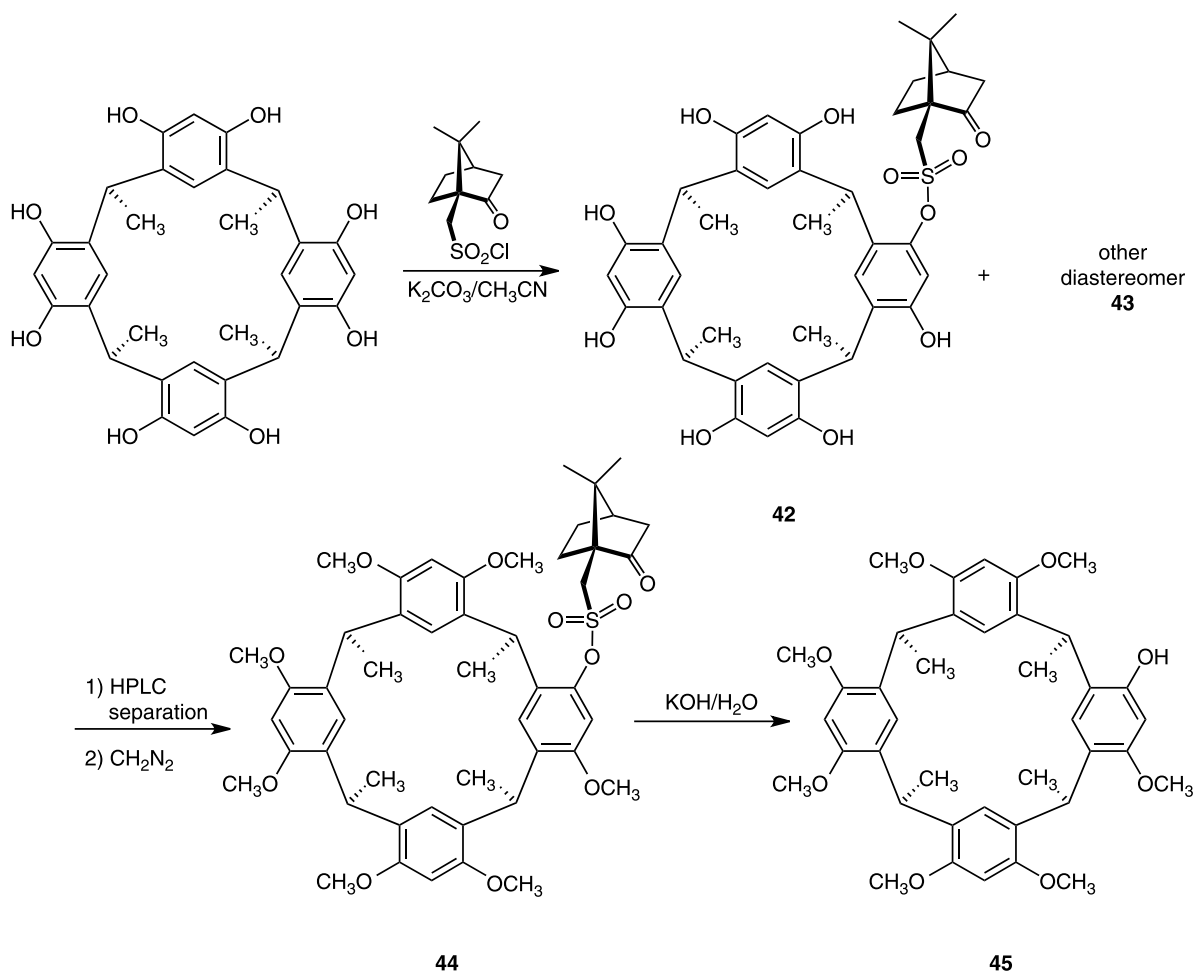
Scheme 11. Preparation of the enantiomers of the heptamethylether of *C*-methylcalix[4]resorcinarene (**45**).
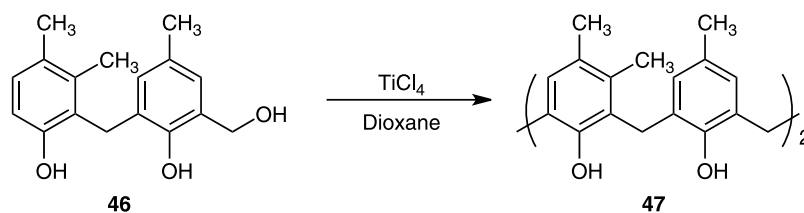
Scheme 12. The 2+2 fragment condensation of benzylic alcohol **46** to give the corresponding C_2-dissymmetric calixarene **47**.

	R¹	R²	R³
48	CH₃	CH₃	CH₃
49	CH₃	CH₃	*n*Bu
50	CH₃	CH₃	Pr^i
51	CH₃	CH₃	CH₂COOEt
52	CH₃	CH₃	CH₂C₆H₄NO₂
53	Pr^i	CH₃	CH₂COOEt
54	Pr^i	CH₃	*n*Bu
55	CH₂CH₂CH₂	CH₂COOEt	
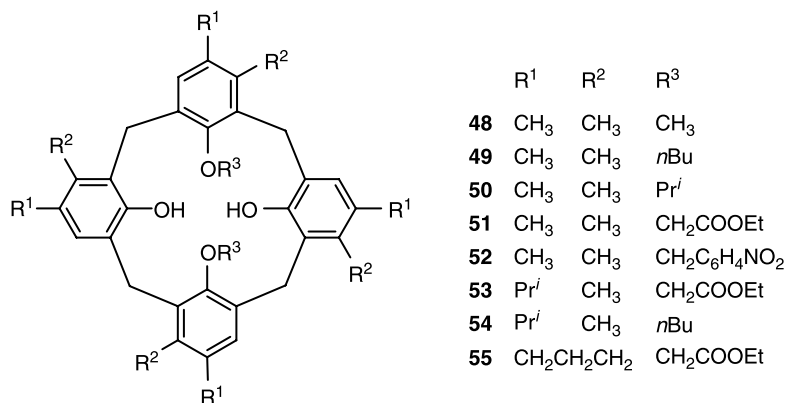
Figure 15. C_2-dissymmetric calixarenes produced by 1,5-distal dialkylation of C_4-dissymmetric calixarenes.

lack of interest in compounds of this type to the substantial efforts required to prepare the bisphenol **46** which requires five separate reaction steps. The desired cyclised material **47** is obtained in an overall yield of only 3% as a result.

Alternatively, dialkylation of the more readily obtained C_4-dissymmetric calixarenes (*35*) produces the lower symmetry diethers **48**–**55** shown in Figure 15.

Compounds **48**, **51**, **53** and **55** were later resolved by Böhmer (*41*) by HPLC on a ChiralPak AD column. The decamethyl derivative **48** is not fixed in the cone conformation and the energy barrier for the 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 (*25*). The calixarene-1,5-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 (**57**). Consequently, the desired isomer **56** is recovered in only 14% yield (Figure 16).

Figure 16. Regioisomers **56** and **57** produced by 1,4-addition to a calixarene-1,5-diquinone.

A regioisomeric mixture was also obtained (*27*) by bromination of the bisacetamide **58** to give a 10% recovery of the dibromide **59**. Nitration was substantially more selective yielding 53% of the desired isomer **60**. Significantly, these calixarenes were prepared as the tetrapropyl ethers and thus are conformationally fixed and so cannot racemise by ring inversion. T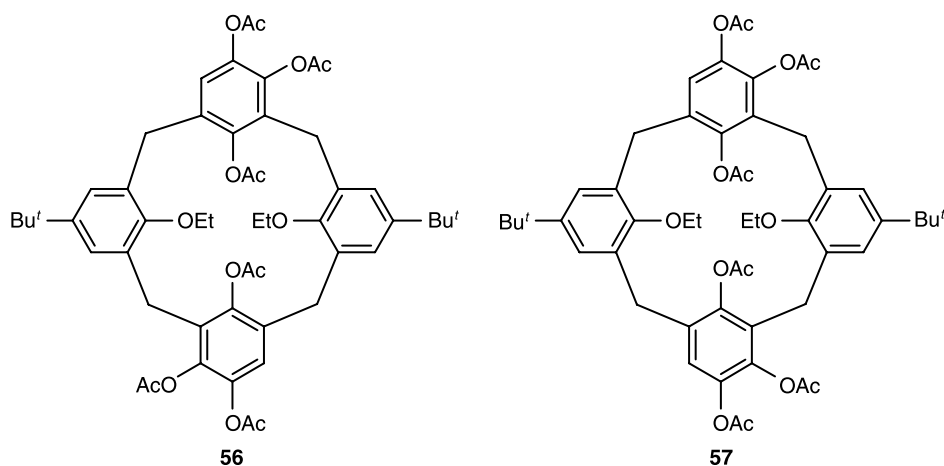he structure of **59** (as the racemate) was proven by the single-crystal X-ray determination, however the racemates were not resolved (Figure 17).

The propensity of the calixarenes for 1,5-distal functionalisation on both the upper and lower rims (*42*) lends them to the preparation of a variety of C_2-dissymmetric materials. The calixarene 1,5-diester **61** was effectively exploited by Bitter (*43*) for the preparation

of the proximal doubly bridged calix[4]arenes such as **62** shown in Figure 18.

The chirality of the amides and their sulphur analogues was investigated by NMR 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 1,5-bridged compounds produced by Böhmer **63** (*35*) and also by Wu **64** (*44*) (Figure 19). While the latter example may be considered chirality by attachment, the product does have a 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 NMR signals in the presence of Pirkle's reagent.

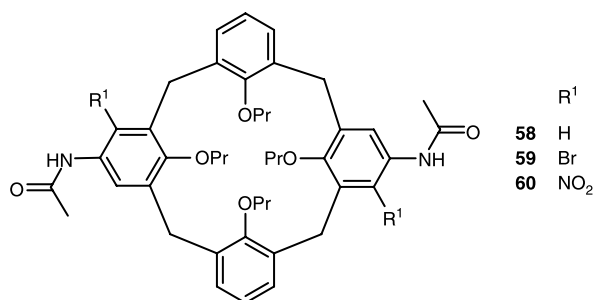|	R^1
58	H
59	Br
60	NO$_2$

Figure 17.   Chiral dibromo- and dinitro-derivatives produced by bromination and nitration of the bis-acetamide **58**, respectively.
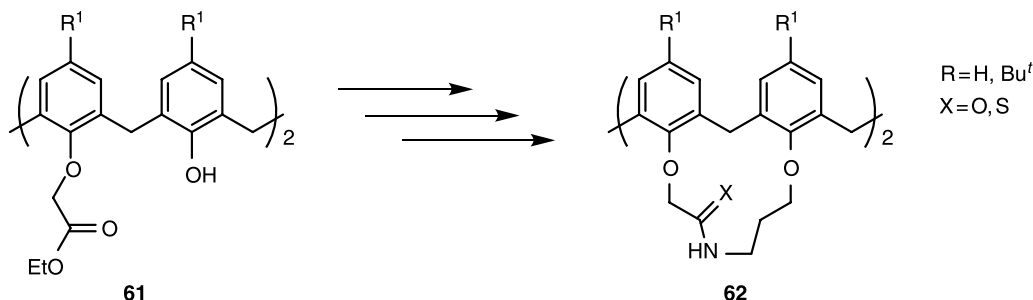

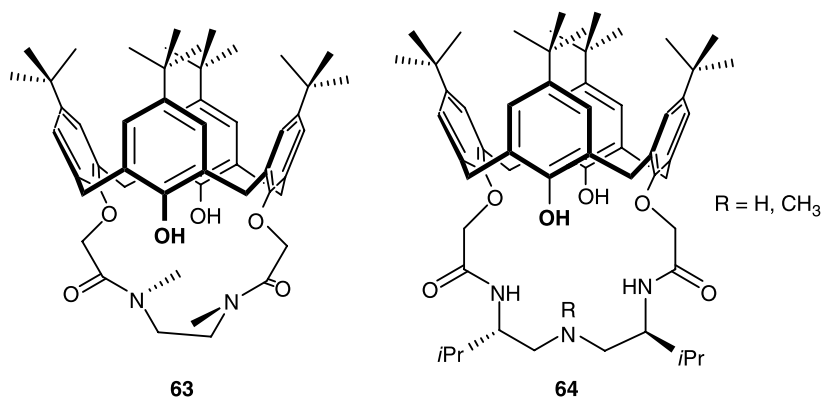Figure 18.   Linking of adjacent phenolic groups to generate dissymmetric calixarene **62**.

Figure 19.   Chiral C_2-dissymmetric derivatives produced by linking distal phenolic groups.
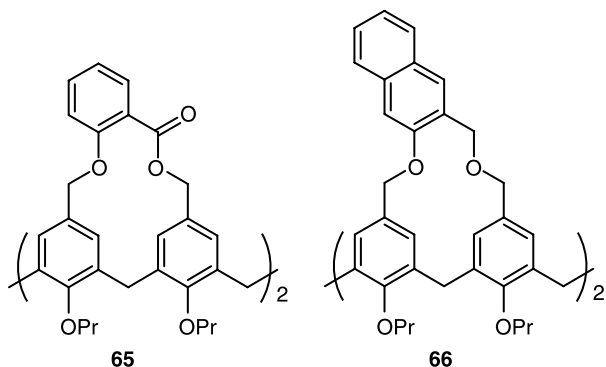
Figure 20. Proximal bridging at the upper rim to produce dissymmetry.

Of the upper rim examples, the compounds prepared by Shinkai (*36*, *45*) from the tetrachloromethylated calixarenes are a noteworthy example. The proximally bridged salicylic acid derivative **65** was produced in 36% yield directly from tetrachloromethylcalix[4]arene. Similarly, the hydroxymethyl-2-naphthol-bridged compound **66** was prepared in low yield (Figure 20). The latter was resolved by enantioselective HPLC (Daicel Chiralpak AD).

Resorcinarene based

The largest contribution to the C_2-dissymmetric family is the 1,5-bisbenzoxazines prepared by Böhmer (*46*). A number of derivatives were prepared from the distal tetratosylates including several bridged bisbenzoxazines (Figure 21).

More recently, the racemic bis-crowns **81** and **82** have been produced by Salorinne and Nissinen (*47*). Desymmetrisation of the tetramethoxyresorcinarene **80** with tri- and tetraethylene glycol afforded the C_2-symmetric derivatives in 18 and 22% yield, respectively (Scheme 13).

The C_4-dissymmetric

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 (*48*). The condensation of 2,6-dimethyl-4-methoxybenzyl alcohol in the presence of aluminium chloride afforded the cyclic tetramer **83** with four 'exo' methoxy groups in 80% yield (Scheme 14).

The first of the standard calix[4]arene examples was produced by Böhmer (*35*, *40*). Benzyl alcohols **84** and **85** were treated with titanium tetrachloride in dioxane to give their respective tetramers (**86** and **87**). Alkylation of the phenols gave the tetra-ester cone conformers **88** and **89** in 62 and 34% yield, respectively. Swager et al. (*49*) resolved the octamethyl compound (**86**) as the diastereomeric tungsten(VI) adducts (**90**), prepared with two different
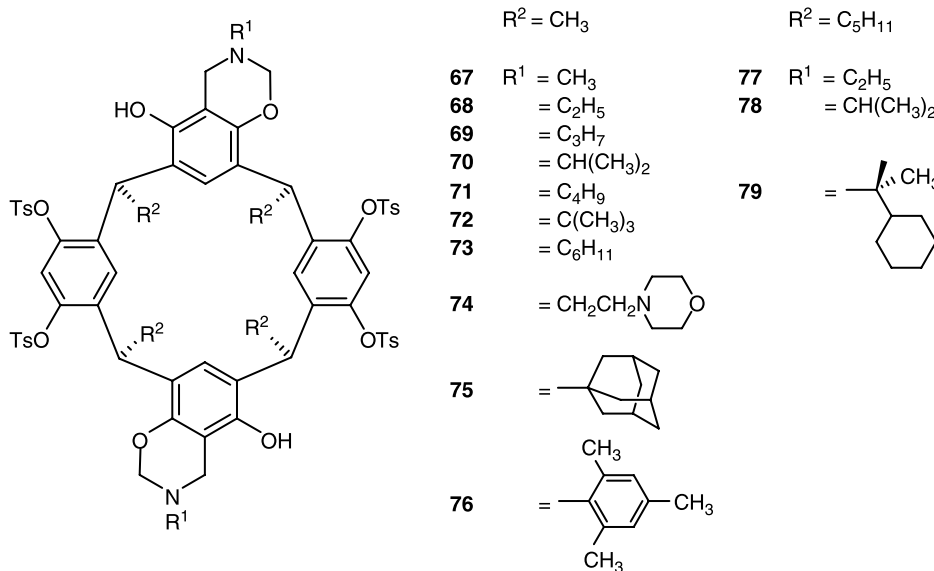
Figure 21. C_2-dissymmetric resorcinarene bisbenzoxazine derivatives produced from two distal tetratosylates.
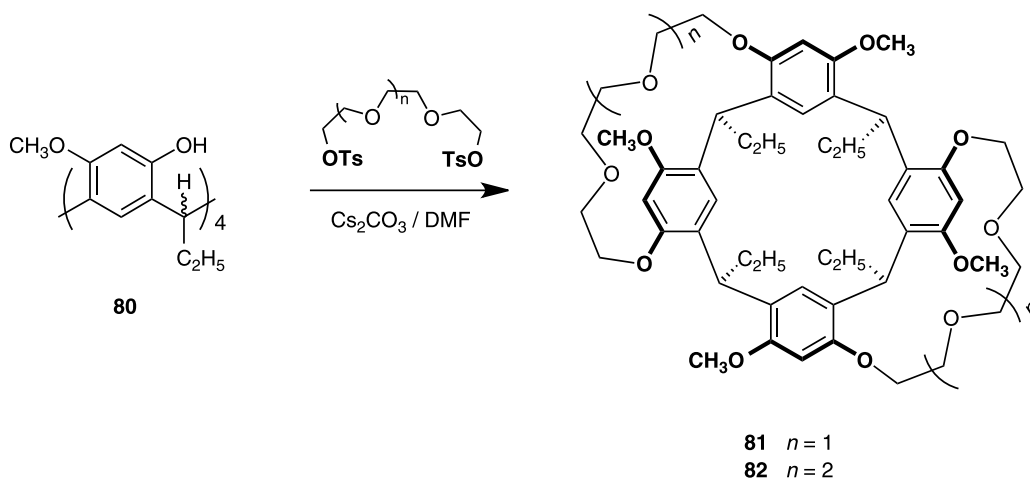
Scheme 13. Formation of the racemic resorcinarene bis-crowns from the tetramethoxy resorcinarene **80**.
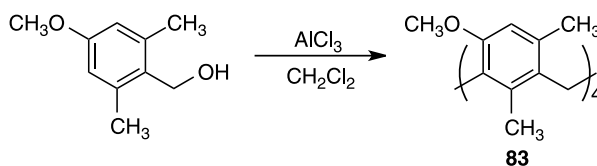
Scheme 14. Condensation of 2,6-dimethyl-4-methoxybenzyl alcohol to afford the chiral calixarene **83**.

chiral diols, by HPLC. The hydrobenzoin derivative (**90**) was also separable by flash chromatography (Scheme 15).

The more synthetically useful X^4-methylcalix[4]arene **93** (*49*) was prepared by condensation of 4-bromo-2-(hydroxymethyl)-5-methylphenol (**91**) and the subsequent debromination of the calixarene **92** with Pd/C/formic acid (Scheme 16). The authors demonstrated the potential application of this calixarene by conversion to the azo (45% yield), tetrachloromethyl (88%) and tetra(dimethyl-amino)methyl (75%) derivatives, which have all been applied to the standard calixarenes previously (*50*). 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. (*51*).

A very important member of the C_4-dissymmetric calixarenes is the calix[4]naphthalenes. The calix[4]-naphthalene with 'endo' OH groups (see **94**, Figure 22) was first prepared by Böhmer in 5% yield by the condensation of 1-hydroxymethyl-2-naphthol with tita-nium tetrachloride in dioxane (*40*). The synthesis of the calix[4]naphthalene with 'exo' OH groups (**95**) was first reported by Georghiou (*52*). Condensation of 1-naphthol with formaldehyde in the presence of potassium carbonate
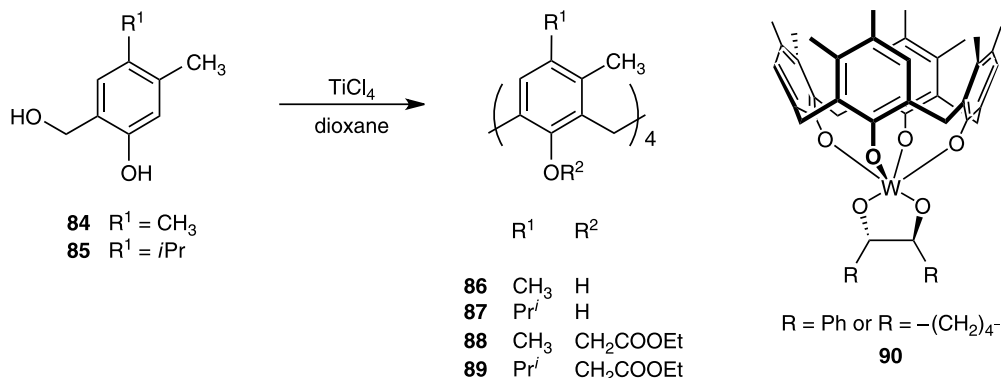
Scheme 15. Condensation of benzylic alcohols **84** and **85** and their further functionalisation as esters (**88** and **89**) and diastereomeric derivatives **90**.
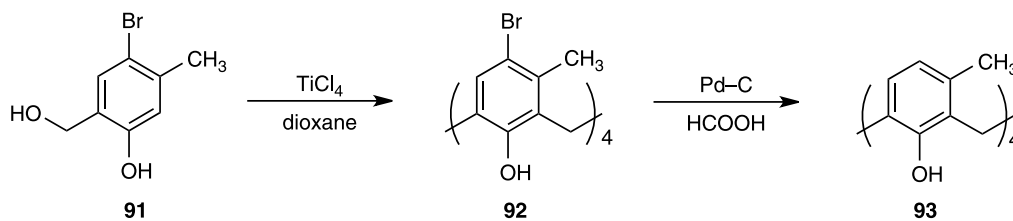
Scheme 16.   Condensation of benzylic alcohol **91** followed by debromination affords chiral calixarene **93** with a free reactive position for further functionalisation.

94 R^1 = H, R^2 = OH
95 R^1 = OH, R^2 = H
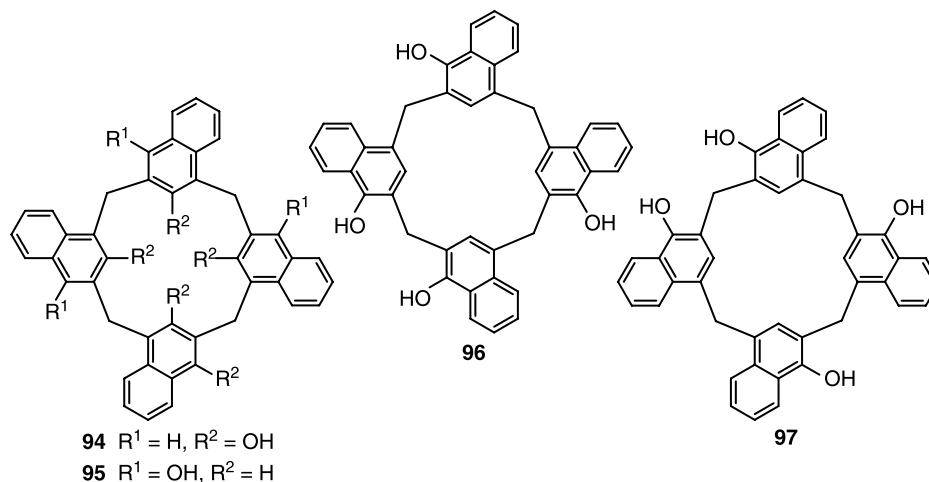
Figure 22.   Calix[4]naphthalene regioisomers.

as a catalyst yields the calix[4]naphthalene in 9.6% yield along with the corresponding isomers **96** and **97** in 16 and 5% yield, respectively. The most notable application of the calix[4]naphthalenes has been the complexation of [60]fullerene (*53*). Georghiou and co-workers (*23*, *54*) have investigated these complexes in some detail.

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 and (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 23). The first examples of this (**98**–**100**) were prepared by Matsushita and Matsui (*55*). 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.

Further, work by Böhmer (*56*) with achiral amines (compounds **107**, **111**–**114**, **120**–**124**) made full recognition of the chirality of the C_4-dissymmetric species and the potential for regioisomers. However, ^{1}H NMR spectroscopy with Pirkle's reagent produced no doubling of peaks and attempts at resolution failed until some years later (*57*). This was ascribed to the epimerisation of the benzoxazine ring via the iminium species (Figure 24). Resolution of several benzoxazine derivatives was achieved by HPLC (*57*) on a Whelk O-1 chiral stationary phase; however, baseline separation was only achieved for **101** at low temperatures ($T = -3°$C) to minimise the epimerisation (Daicel ChiralPak AD). The compounds produced by Böhmer and collaborators (**101**–**124**) and their syntheses have been reviewed (*58*). The energy barrier for the interconversion of the enantiomers was calculated later by Trapp et al. (*59*) to be $\Delta G^{\#}$ (298 K) = 92 ± 2 kJ mol^{-1}.

Similar preparations of benzoxazine derivatives using aminoalcohols (Figure 23, **125**–**129**) provide an extended

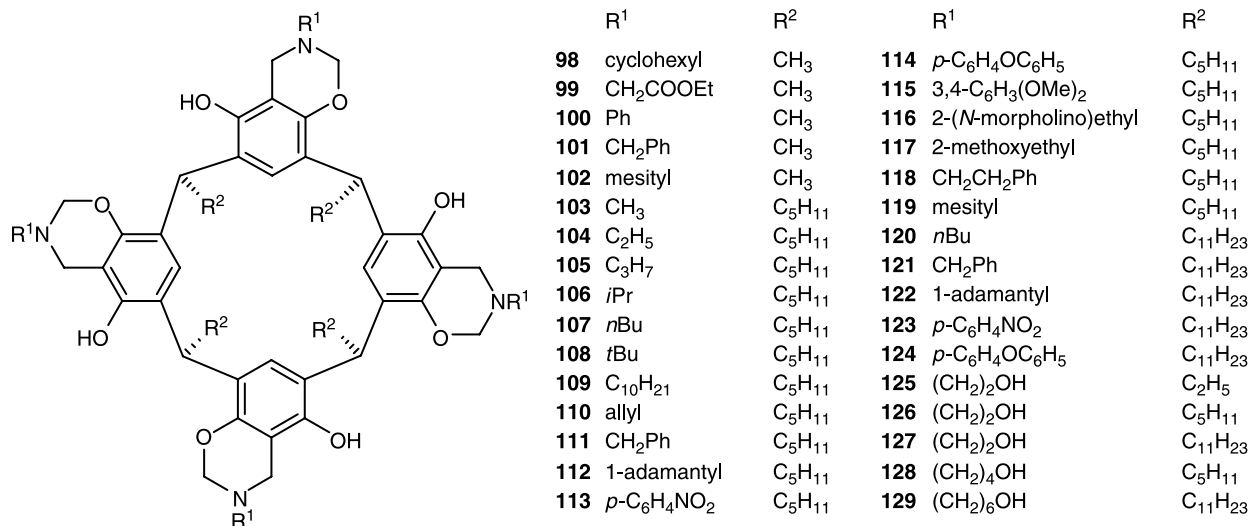|	R^1	R^2		R^1	R^2
98	cyclohexyl	CH$_3$	114	*p*-C$_6$H$_4$OC$_6$H$_5$	C$_5$H$_{11}$
99	CH$_2$COOEt	CH$_3$	115	3,4-C$_6$H$_3$(OMe)$_2$	C$_5$H$_{11}$
100	Ph	CH$_3$	116	2-(*N*-morpholino)ethyl	C$_5$H$_{11}$
101	CH$_2$Ph	CH$_3$	117	2-methoxyethyl	C$_5$H$_{11}$
102	mesityl	CH$_3$	118	CH$_2$CH$_2$Ph	C$_5$H$_{11}$
103	CH$_3$	C$_5$H$_{11}$	119	mesityl	C$_5$H$_{11}$
104	C$_2$H$_5$	C$_5$H$_{11}$	120	*n*Bu	C$_{11}$H$_{23}$
105	C$_3$H$_7$	C$_5$H$_{11}$	121	CH$_2$Ph	C$_{11}$H$_{23}$
106	*i*Pr	C$_5$H$_{11}$	122	1-adamantyl	C$_{11}$H$_{23}$
107	*n*Bu	C$_5$H$_{11}$	123	*p*-C$_6$H$_4$NO$_2$	C$_{11}$H$_{23}$
108	*t*Bu	C$_5$H$_{11}$	124	*p*-C$_6$H$_4$OC$_6$H$_5$	C$_{11}$H$_{23}$
109	C$_{10}$H$_{21}$	C$_5$H$_{11}$	125	(CH$_2$)$_2$OH	C$_2$H$_5$
110	allyl	C$_5$H$_{11}$	126	(CH$_2$)$_2$OH	C$_5$H$_{11}$
111	CH$_2$Ph	C$_5$H$_{11}$	127	(CH$_2$)$_2$OH	C$_{11}$H$_{23}$
112	1-adamantyl	C$_5$H$_{11}$	128	(CH$_2$)$_4$OH	C$_5$H$_{11}$
113	*p*-C$_6$H$_4$NO$_2$	C$_5$H$_{11}$	129	(CH$_2$)$_6$OH	C$_{11}$H$_{23}$

Figure 23.   The formation of tetrabenzoxazine derivatives from achiral amines.
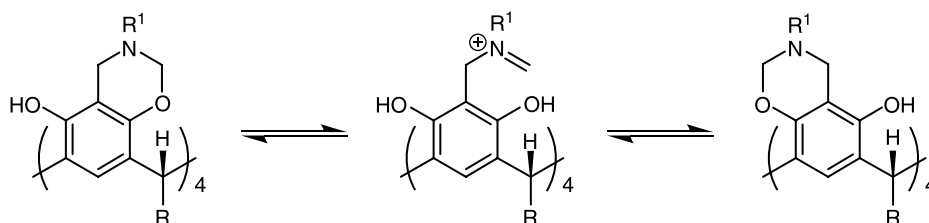

Figure 24.   The proposed mechanism for the epimerisation of the benzoxazine rings.

cavity with potentially useful functionality about the upper rim (*60*).

The preparation of the benzoxazine derivatives using a variety of chiral amines was reported independently by Böhmer et al. (*56*) (**130–132**, **136**), Heaney et al. (*61*) (**130**, **133–139**) and Iwanek et al. (*62*) (**134** and **138**). When chiral amines were employed, they acted as a chiral auxiliary and directed the ring-closure reaction, thereby enhancing the production of one diastereomer relative to the other. Thus, the application of the appropriate (*R*)-amines afforded the dextrorotary tetrakisbenzoxazines

130–135 while the (*S*)-amines afforded the laevorotary enantiomers (**136–139**). 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 NMR spectroscopy. They also all produced compounds of good diastereomeric purity using *R*-(+)- and *S*-(−)-α-methylbenzylamine using differing resorcinarene substrates (Figure 25).

	R	R^1	
130	C$_{11}$H$_{23}$	C$_6$H$_5$	(+89.8)
131	C$_{11}$H$_{23}$	cyclohexyl	
132	C$_{11}$H$_{23}$	naphthyl	
133	C$_5$H$_{11}$	C$_6$H$_5$	(+118)
134	CH$_3$	C$_6$H$_5$	(+169)
135	CH$_2$CH$_2$Ph	C$_6$H$_5$	

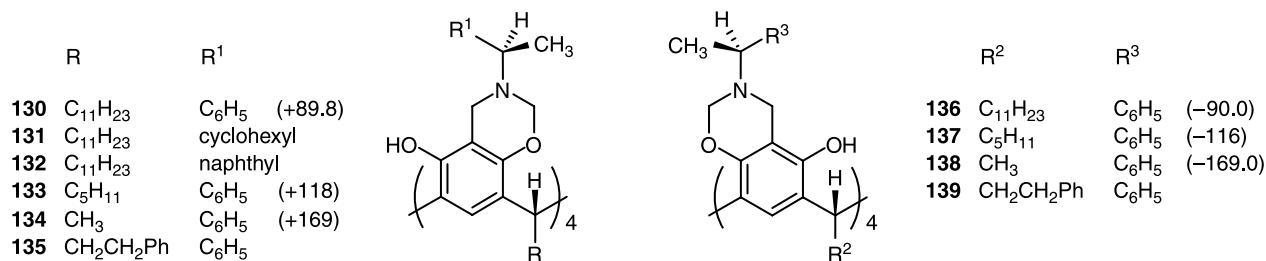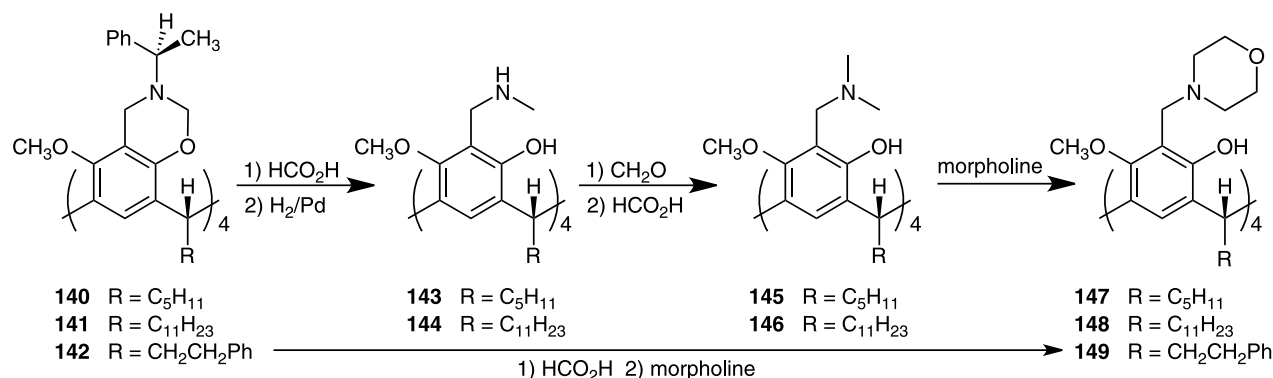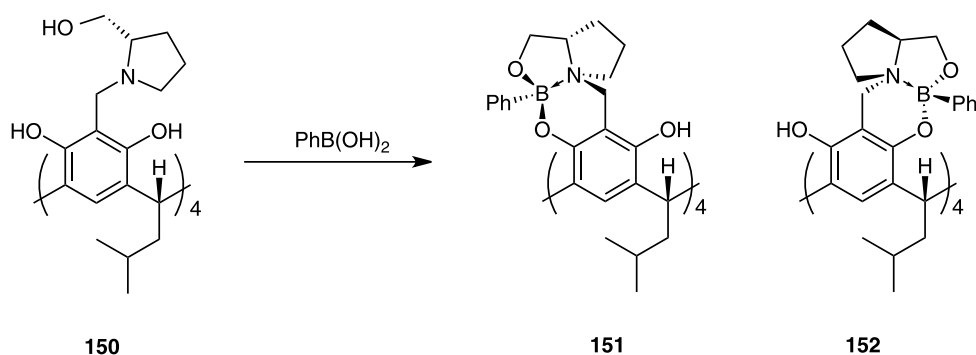|	R^2	R^3	
136	C$_{11}$H$_{23}$	C$_6$H$_5$	(−90.0)
137	C$_5$H$_{11}$	C$_6$H$_5$	(−116)
138	CH$_3$	C$_6$H$_5$	(−169.0)
139	CH$_2$CH$_2$Ph	C$_6$H$_5$	

Figure 25.   Resorcinarene tetrabenzoxazine derivatives produced using chiral amines.

Scheme 17. The further transformations applied to single enantiomers of the resorcinarene tetrabenzoxazine derivatives.

Scheme 18. The preparation of chiral derivatives **151** and **152** from the L-prolinol-derived mannich base **150**.

The absolute stereochemistry of compounds **133** and **134** was determined using X-ray methods by Heaney et al. and Iwanek et al., respectively.

Compound **138** was applied by Smith et al. (*63*) as a chiral NMR 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. (*64, 65*). By methylation of the diastereomerically pure benzoxazine derivatives (**130**, **133** and **135** and the respective enantiomers) using butyllithium and dimethyl-sulphate (or methyl triflate), racemisation can no longer occur (**140–142**, only (+) enantiomers shown). The chiral auxiliary may then be removed and useful transformations realised (Scheme 17).

The Mannich base theme was continued in 2002 by Iwanek (*66*) who combined the L-prolinol-derived **150** and phenylboronic acid to obtain a mixture of the boron-heterocycle diastereomers **151** and **152** (Scheme 18).

These structurally rigid derivatives were formed as a mixture (80:20, **151/152**) which could be separated by multiple fractional crystallisations. Both diastereomers were characterised by X-ray crystallography.

The methodology was expanded later (*67*) to the L-proline derivatives described in Figure 26. All of the compounds were prepared in good yield and > 98% diastereomeric excess.

Somewhat related to the resorcinarene benzoxazines is the phenolic lactone acetal **158** produced by Cram (*68*). Compound **158** and its enantiomer were prepared in 18% yield by the acid-catalysed rearrangement of the cavitand **157** (Scheme 19).

A very interesting example of regioselective placement of groups about the resorcinarene cavity to generate C_4 dissymmetry is that given in Scheme 20. Terent'eva and co-workers (*69*) produced the C_4 isomer **161** by the reaction

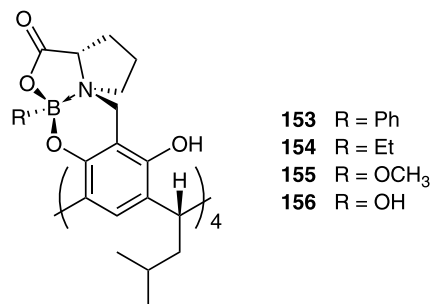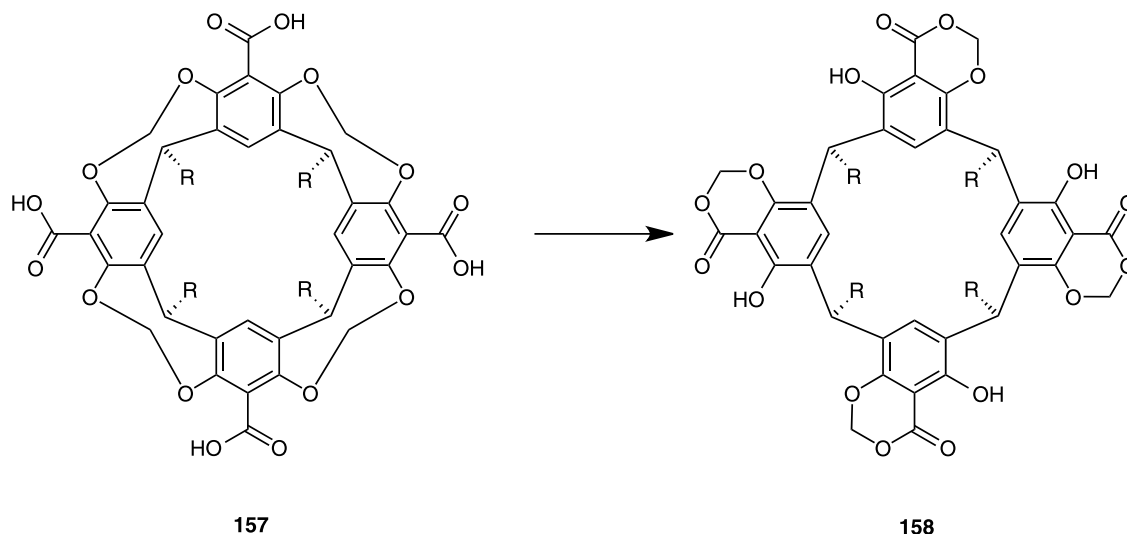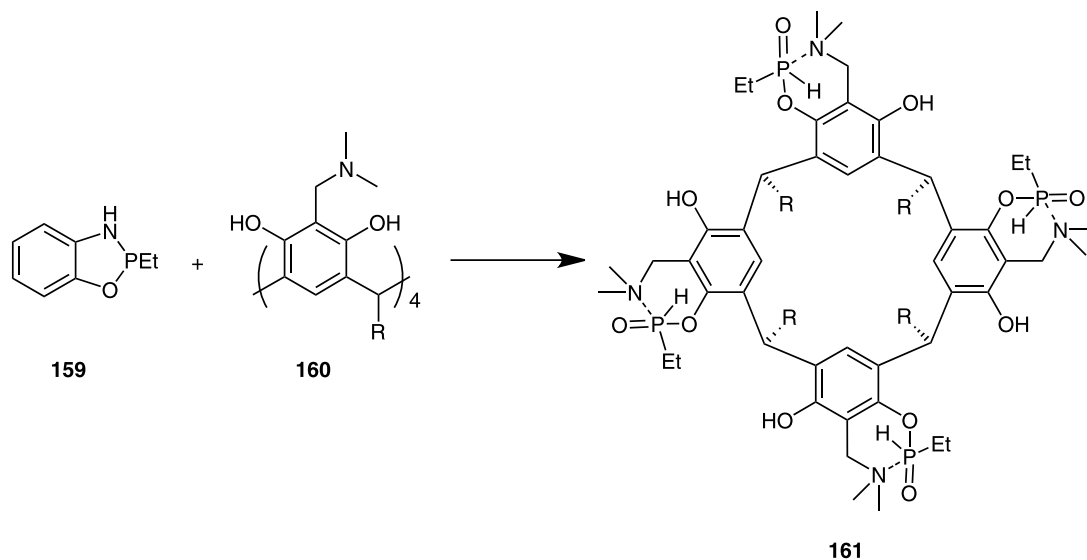|	
153	R = Ph
154	R = Et
155	R = OCH₃
156	R = OH

Figure 26. Chiral derivatives **153–156** prepared from the corresponding L-proline-derived mannich base.

Scheme 19. The acid-catalysed rearrangement of cavitand **157** to afford the C_4-dissymmetric derivative **158**.


Scheme 20. Synthesis and proposed structure of the phosphorus-based resorcinarene derivative **161**.

of 2-ethyl-1,3,2-benzoxaphospholine **159** with the tetra(di-methylaminomethyl)calix[4]-resorcinarene **160**. This reaction is especially curious since alkylation with the majority of alkylating agents produce a complex mixture of regioisomers or in the case of reagents such as toluenesul-phonyl chloride produce the distal tetratosylate (*70*). No ^{13}C NMR data were provided for **161** and the ^{1}H NMR spectroscopic data provided are insufficient for a conclusive assignment.

We reported the first example of a regioselective formation of the resorcinarene skeleton from resorcinol mono-ethers (*71*). The condensation of the mono-ethers **162** and **164** with alkyl aldehydes in the presence of boron trifluoride etherate gave the respective C_4-dissymmetric

resorcinarenes **164–166** as their racemates in high yields (Scheme 21). This synthesis is rather remarkable as it involves the condensation of eight individual molecules that combine in a completely regioselective manner despite the possibilities. The chirality was demonstrated by the ^{1}H NMR spectroscopy with the chiral shift reagent tris[3-(heptafluoropropylhydroxy-methylene)-(+)-cam-phorate], which caused doubling of the aromatic, phenolic and methine signals. The partial separation of resorcinar-ene **164** was also achieved by enantioselective HPLC (Daicel Chiralpak AD hexane–2-propanol 98:2). An X-ray crystal structure for **164** was obtained, which confirmed the dissymmetric arrangement of the resorci-narene upper rim.
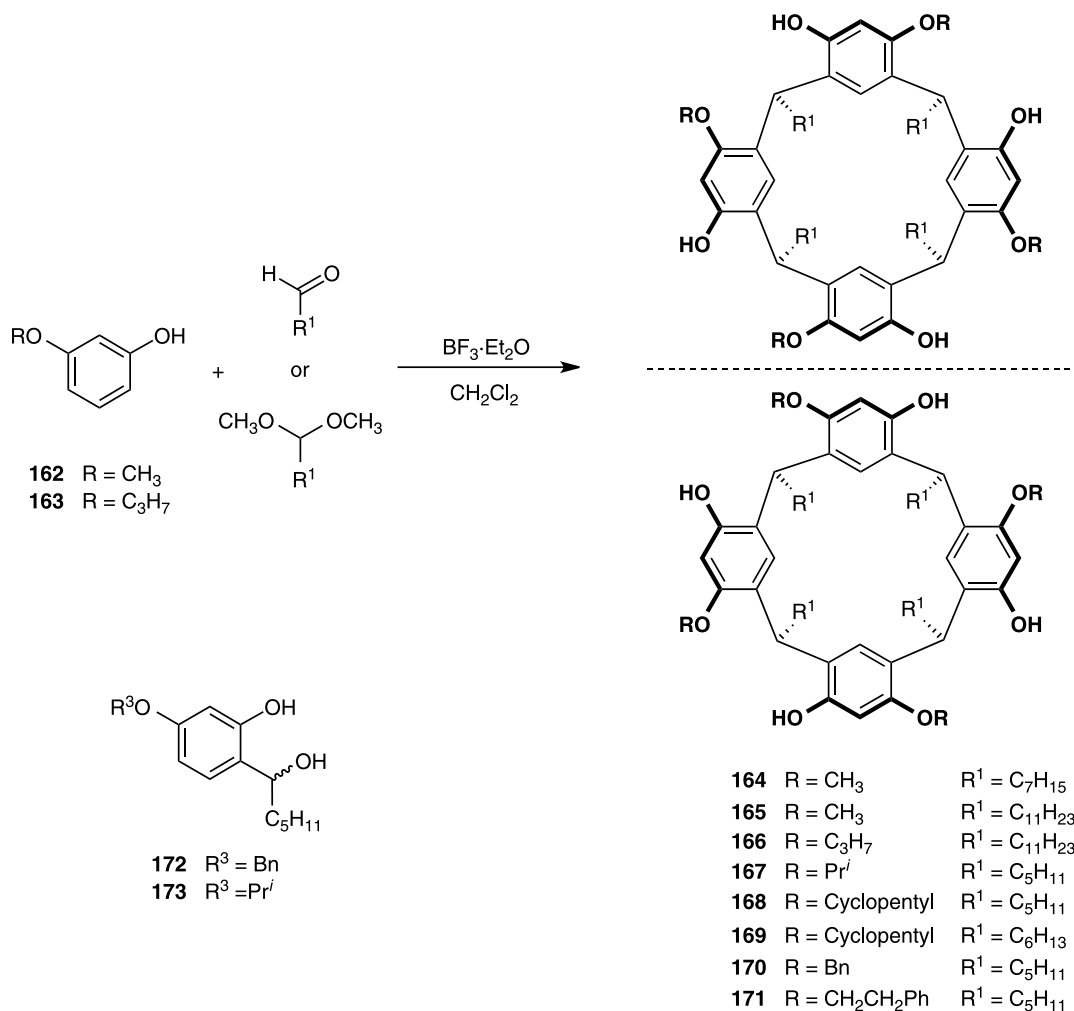
Scheme 21. The synthesis of C_4-dissymmetric resorcinarenes by condensation of resorcinol mono-ethers and alkyl aldehydes.

Heaney et al. (*65*) further expanded the series with the preparation of **167–171**. They found that the tetracyclopentyloxy and tetrabenzyloxy resorcinarenes **168–170** could not be prepared by the standard boron trifluoride/aldehyde protocol presumably due to instability of the reaction intermediate. By the 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 (**172** and **173**) were prepared and studied as useful precursors to the resorcinarenes. In particular, the proposed intermediate **173** in the presence of boron trifluoride etherate did indeed give the desired resorcinarene (**167**) in 82% yield.

The facile preparation of the C_4-dissymmetric resorcinarenes was made all the more potent by Heaney (*65*) with the publication of a simple synthesis for resorcinol mono-ethers.

The first resolution of a C_4-dissymmetric resorcinarene prepared by this method was achieved by Mattay and

co-workers (*72*). By monofunctionalisation of the resorcinarene **174** with a camphorsulphonyl moiety, the resulting diastereomers could be resolved by HPLC. Hydrolysis of the sulphonate esters **175a** and **175b** yielded the pure resorcinarene enantiomers (Scheme 22). Unfortunately, the absolute stereochemistry of the resorcinarenes was not determined.

They also applied the boron trifluoride protocol (in the same publication) to the chiral resorcinol mono-ether **176** so as to recover the resorcinarenes as diastereomeric mixtures (see Scheme 23) which could be separated by HPLC. Resorcinarene formation with **176** and 3-methyl butanal appeared to favour the formation of the laevorotary diastereomer while dodecanal produced a 1:1 mixture of diastereomers (**178a** and **178b**). Again, no X-ray data were provided for any of the diastereomers and the absolute stereochemistry was not elucidated at the time.

The issue of the absolute stereochemistry was addressed by Mattay et al. in 2005 (*73*). They converted
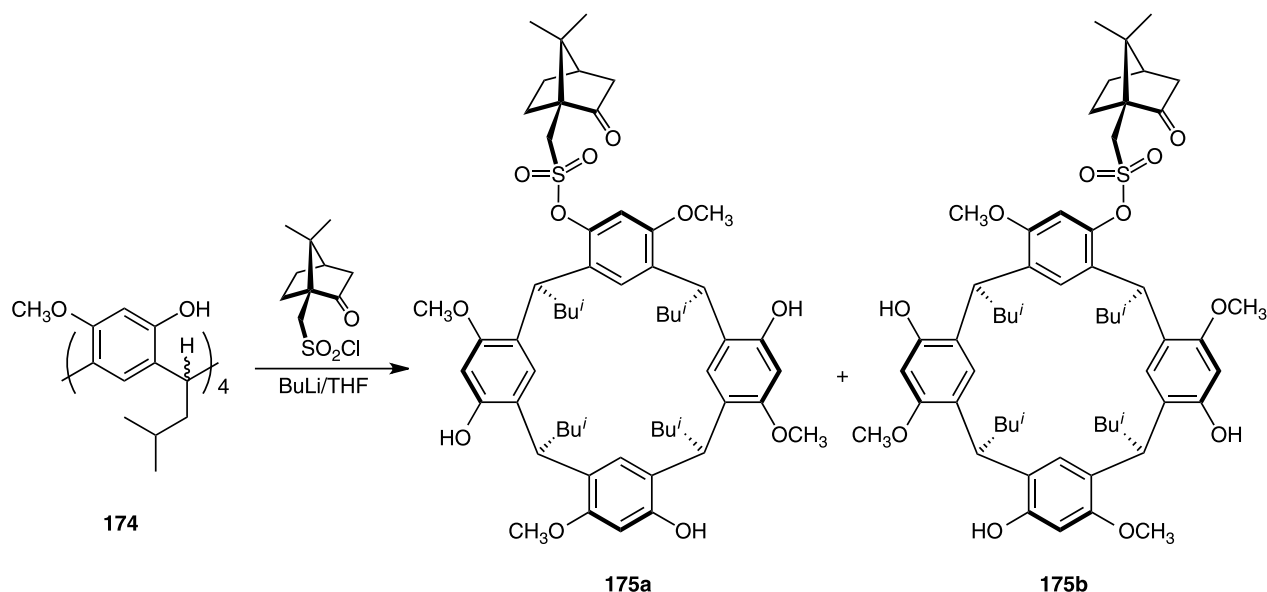
Scheme 22.   Resolution of chiral tetramethoxyresorcinarene by formation of the diastereomeric mono-camphorsulphonate esters.
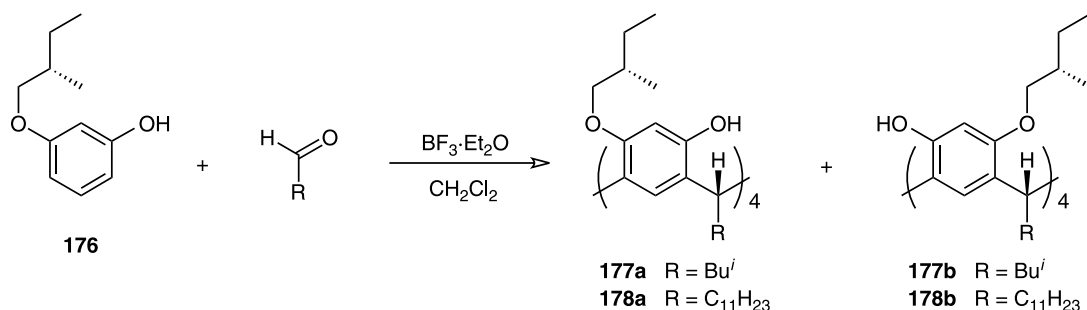
Scheme 23.   Preparation of diastereomeric resorcinarenes by condensation of a chiral resorcinol mono-ether (**176**) with alkyl aldehydes.

the resolved enantiomers **174a** and **174b** into the (*S*)-(−)-(α)-methylbenzylamine-derived diastereomeric amide derivatives **180a** and **180b**. A single-crystal X-ray structure of **180a** was obtained and the absolute stereochemistry of the laevorotary enantiomer of **174** assigned the all (*S*)-configuration by relation to **180a** (Scheme 24).
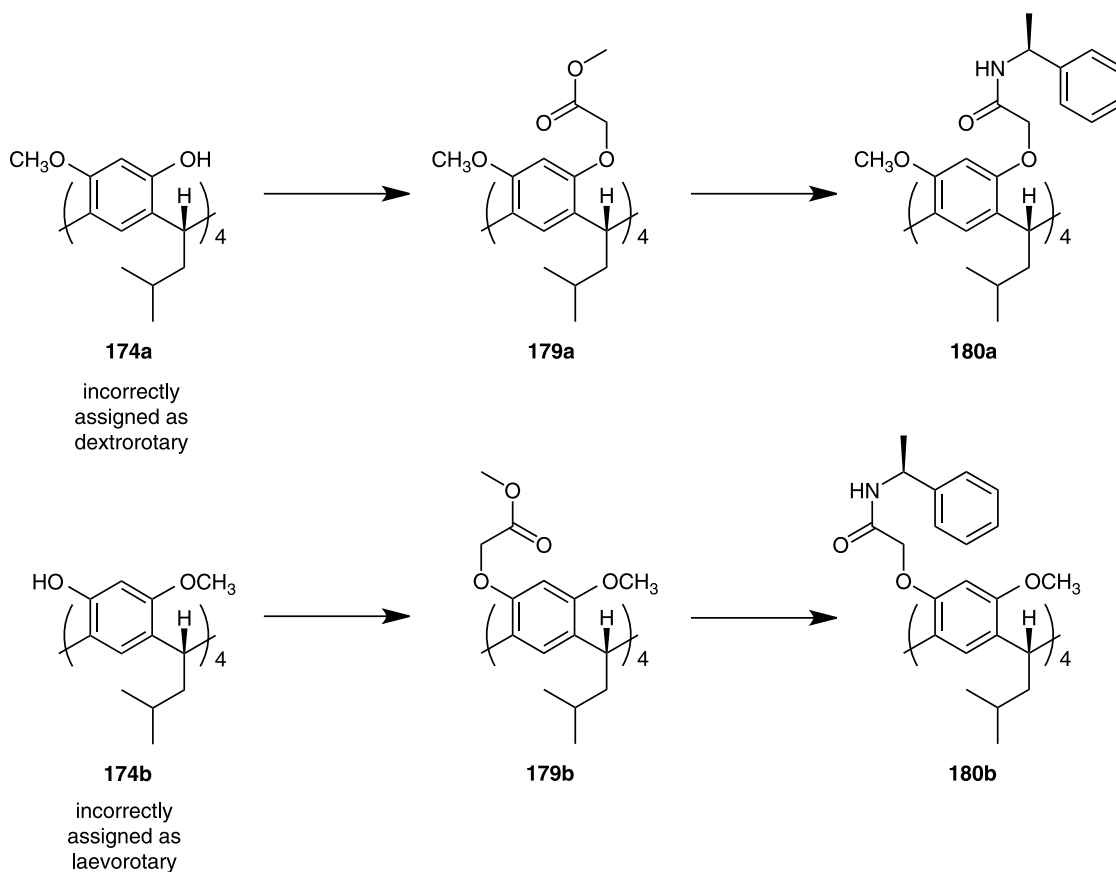
We reported (*21*) the gram scale syntheses of the amides **182**–**184** by an alternate route using the enantiopure alkylating agent derived from (*R*)-(+)-(α)-methylbenzylamine (Scheme 25). These amide-functionalised resorcinarenes were readily resolved to their respective diastereomers in good yields, demonstrating the generality of the resolution process. A single-crystal X-ray structure of **182a** was obtained and the absolute stereochemistry of the first eluting diastereomer was found to be the all (*R*)-configuration at the resorcinarene stereocentres, in good accord with Mattay's findings.

The absolute stereochemistry for several resorcinarene enantiomers, including **174**, was elucidated

by X-ray crystallography in 2006 (*74*) by the synthesis and resolution of the tetracamphorsulphonates (Scheme 26).

Having determined the absolute stereochemistry of the tetracamphorsulphonate esters, the ester functionality was removed by alkaline hydrolysis to obtain the pure enantiomers for which the absolute stereochemistry of the dextrorotary resorcinarenes **185a** and **174a** was of the all (*S*)-configuration as shown in Scheme 27. This result contradicted Mattay's previous assignment; however, the evidence is strongly in favour of our conclusion and has been corroborated by Mattay (*74*).

During the course of the camphorsulphonylation studies, a number of di- and tri-camphorsulphonates were also observed. In particular, when resorcinarenes with larger ether groups at the upper rim such as **167** and **168** were combined with camphorsulphonyl chloride, the mono- or di-esters could be obtained depending on the base and conditions applied.

174a
incorrectly
assigned as
dextrorotary

179a

180a

174b
incorrectly
assigned as
laevorotary

179b

180b

Scheme 24. The synthesis of the diastereomeric amide derivatives **180** by amidation of the tetraesters **179** with (*S*)-(−)-(α)-methylbenzylamine.

The absolute stereochemistry of the resorcinarenes was corroborated (*21*) by conversion into their tetra-benzoxazine derivatives (such as **188**, Scheme 28).

The absolute stereochemistry of **188** had been determined by X-ray crystallography in a previous study regarding the functionalisation and resolution of the resorcinarenes described in Scheme 29 as their tetra-benzoxazine derivatives **140**, **191–198** (*21*).

During the course of those studies (*21*), 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 pK_a units less acidic than the achiral octahydroxyresorcinarenes.

181 R = C_3H_7
164 R = C_7H_{15}
165 R = $C_{11}H_{23}$

182a R = C_3H_7
183a R = C_7H_{15}
184a R = $C_{11}H_{23}$

182b R = C_3H_7
183b R = C_7H_{15}
184b R = $C_{11}H_{23}$
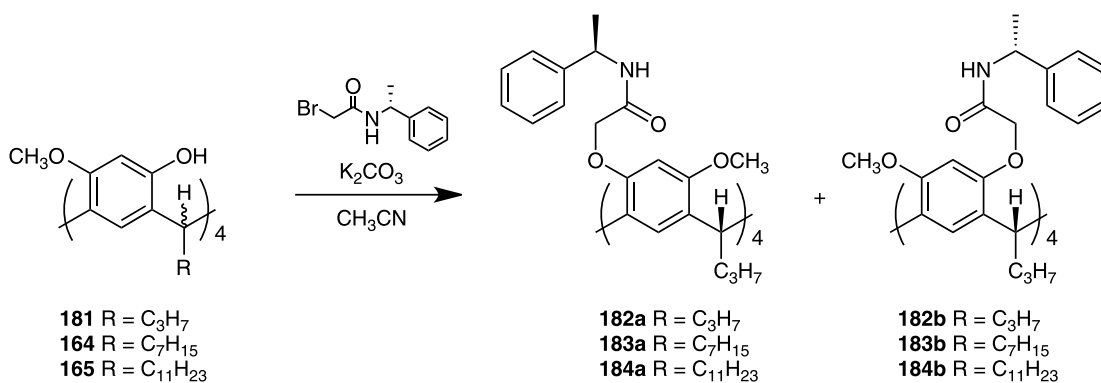
Scheme 25.   The synthesis of diastereomeric amide derivatives by attachment of a chiral alkylating agent.
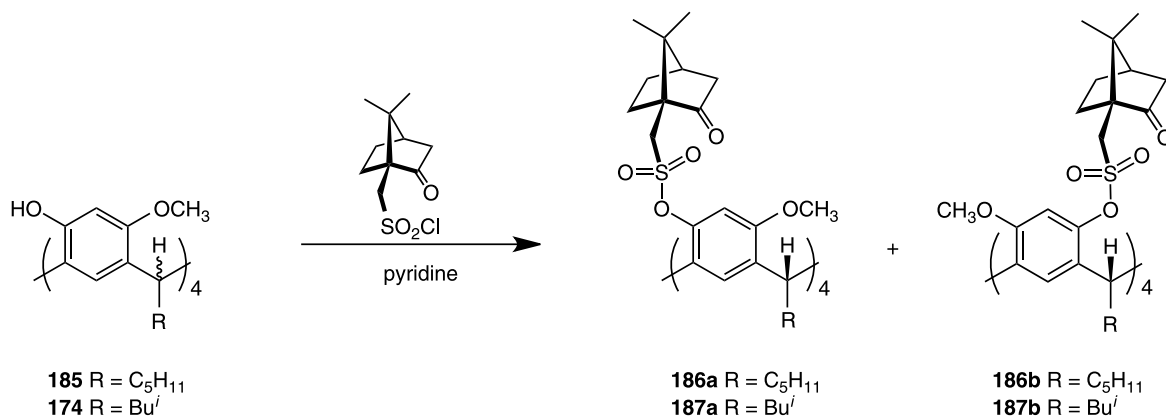
Scheme 26.   Synthesis of the resorcinarene tetracamphorsulphonate esters with the absolute stereochemistry for the first-eluting (series a) and second-eluting (series b) diastereomers.
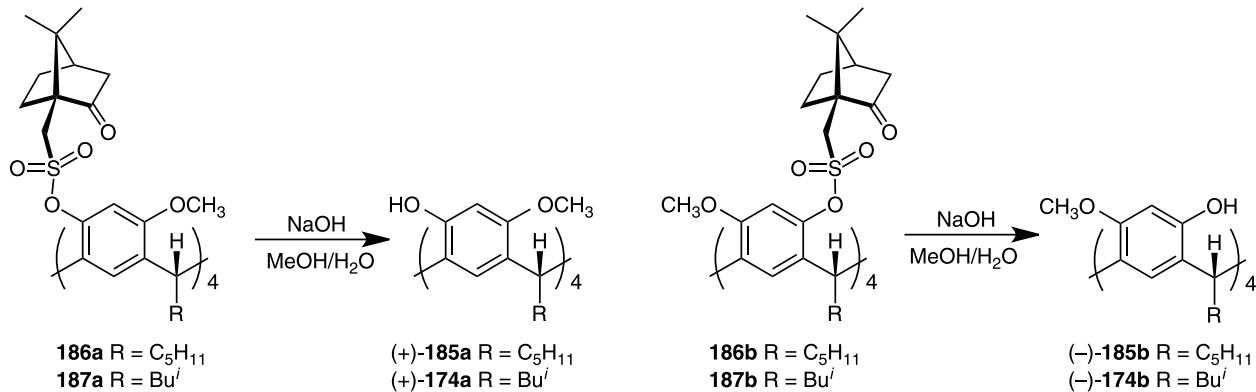
Scheme 27.   Hydrolysis of the camphorsulphonate esters to afford enantio-pure chiral resorcinarenes.
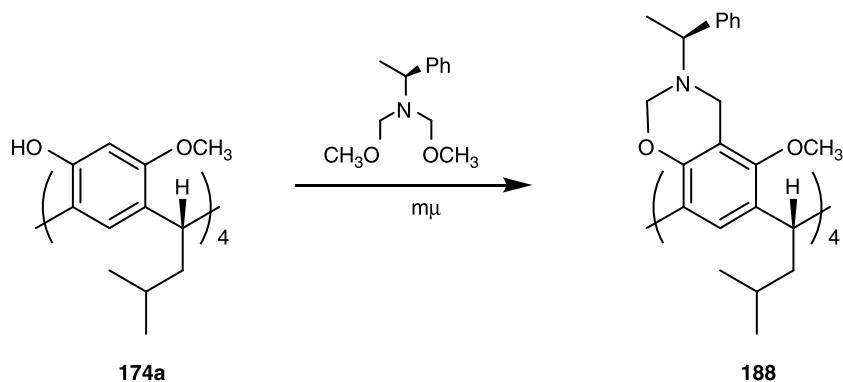
Scheme 28.   Synthesis of the diastereomerically pure tetrabenzoxazine derivative **188**.

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 (*21*). In general, only moderate per cent enantiomeric excesses

185 R = CH$_3$ R^1 = C$_5$H$_{11}$
189 R = CH$_3$ R^1 = PhCH$_2$CH$_2$
167 R = Pr^i R^1 = C$_5$H$_{11}$
168 R = cC$_5$H$_9$ R^1 = C$_5$H$_{11}$
190 R = nBu   R^1 = C$_5$H$_{11}$

R^2 = CH$_3$
R^2 = CH$_3$
R^2 = (*R*)-MeBn
R^2 = (*S*)-MeBn

(*S*)-MeBn =

(*R*)-MeBn =

191 R = CH$_3$ R^1 = C$_5$H$_{11}$ R^2 = Bn
192 R = CH$_3$ R^1 = C$_5$H$_{11}$ R^2 = CH$_3$
193 R = CH$_3$ R^1 = PhCH$_2$CH$_2$ R^2 = CH$_3$
140 R = CH$_3$ R^1 = C$_5$H$_{11}$ R^2 = (*R*)-MeBn
194 R = Pr^i R^1 = C$_5$H$_{11}$ R^2 = (*R*)-MeBn
195 R = cC$_5$H$_9$ R^1 = C$_5$H$_{11}$ R^2 = (*R*)-MeBn
196 R = CH$_3$ R^1 = C$_5$H$_{11}$ R^2 = (*S*)-MeBn
197 R = Pr^i R^1 = C$_5$H$_{11}$ R^2 = (*S*)-MeBn
198 R = nBu   R^1 = C$_5$H$_{11}$ R^2 = (*S*)-MeBn
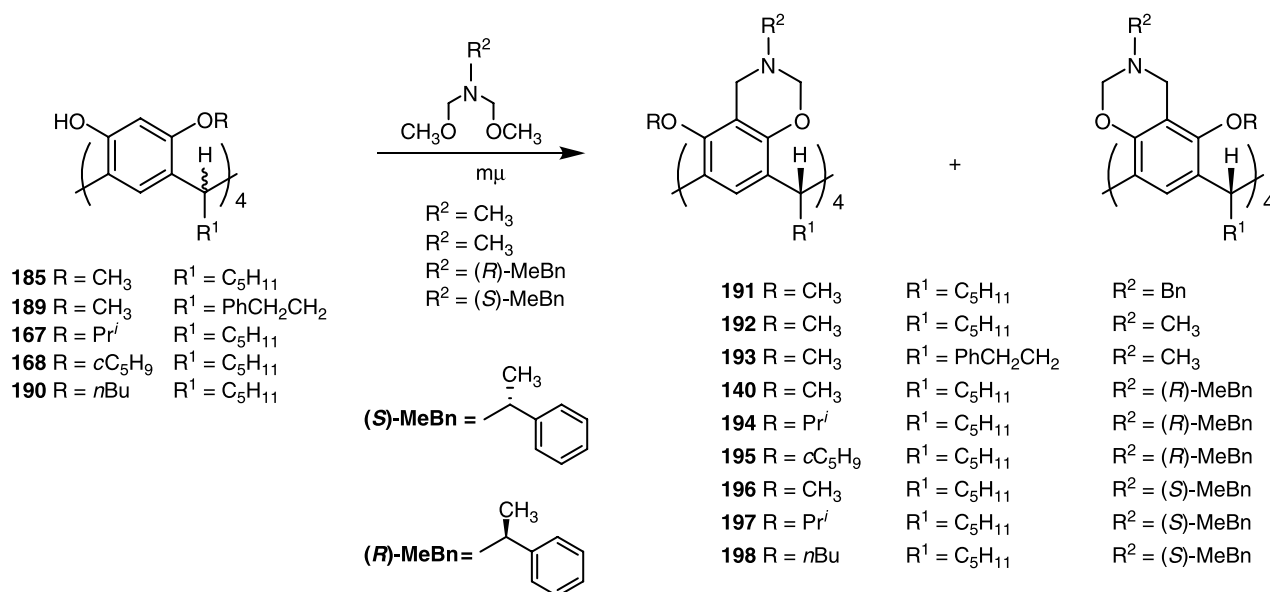
Scheme 29. The preparation of several tetrabenzoxazine derivatives from the chiral C_4-dissymmetric resorcinarenes (cC$_5$H$_9$ = cyclopentyl).

(ee) were obtained, the best being a conversion of 95% with an ee of 83% with compound **194** (in favour of (*S*)-(−)-1-phenylpropanol).

Outlook

This review provides a summary of the 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 is a vast array of modifications and applications yet still available to the aspiring macrocycle chemist. The chiral ligands for catalysis, enzyme mimicry and chiral separation science have barely been explored and offer much promise.

Notes

1. Please refer to the new IUPAC nomenclature for phane ring systems (2002) including specific reference to calixarenes (6).
2. 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.

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