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REVIEW ARTICLE

O-alkyl resorcarenes: where are we now?

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Abstract This review describes the current position in the emerging field of direct synthesis of *O*-alkyl resorcarenes through the use of *O*-protected precursors. The use of this approach for the selective synthesis of the diastereoisomers of resorc[4]arenes, the synthesis of parent resorcarenes and pyrogalloranes and the preparation of chiral partially alkylated resorc[4]arenes are highlighted. The applications of such molecules, with regard to their role as ligand platforms, for binding of cations, organic electron acceptors and in chiral discrimination are discussed.

Keywords Resorcarenes · Resorcinarenes · Calixarenes, *O*-alkyl resorcarenes

Introduction

Resorc[4]arenes, alternatively known as resorcin[4]arenes, calix[4]resorcinarenes and Högberg compounds, have proved to be highly useful structural building blocks and ligand platforms (Fig. 1) [1–3]. Unlike the structurally related calixarenes, resorcarenes, prepared by the cyclisation of resorcinol or pyrogallol with aldehydes, are almost invariably formed as the tetrameric macrocycles as a consequence of hydrogen bonding interactions. They feature up to twelve *exo*-hydroxyl groups, offering a large number of points of functionalisation, and through the presence of substituents at the methylene bridge positions can be prepared in a number of diastereoisomers. These latter properties have been widely exploited in determining the role of steric arrangements of ligands in selective binding interactions.

Much research has concentrated on the unsubstituted resorc[4]arenes and on the cavitands and carcerands formed from them and this work has been comprehensively reviewed by both Timmerman [1] and Botta [2, 3]. In contrast, less attention has been turned to the synthesis and applications of *O*-alkyl resorc[4]arenes. This growing field, which focuses on the use of *O*-protected precursors, allows the ready synthesis of orthogonally functionalised macrocycles in a single step, the controlled synthesis of less readily available diastereoisomers, the isolation of higher oligomers, the one step preparation of chiral derivatives and the synthesis of parent resorc[4]arenes not easily accessible through the cyclisation of resorcinols and formaldehyde. This review brings together the range of synthetic techniques that have been developed for the preparation of *O*-alkyl derivatives and highlights some of the applications of these molecules in binding and in enantioselective interactions.

Conformers and diastereoisomers

The three dimensional shapes adopted by resorc[4]arenes and octa-*O*-alkyl resorc[4]arenes are crucial to their further applications both as structural motifs and host molecules. The shape can be affected both by the orientation of the aromatic residues relative to each other and the configuration of the substituents at the methylene bridge positions.

For the parent resorc[4]arenes, those featuring no *C*-alkyl substituents, four extreme conformations can be

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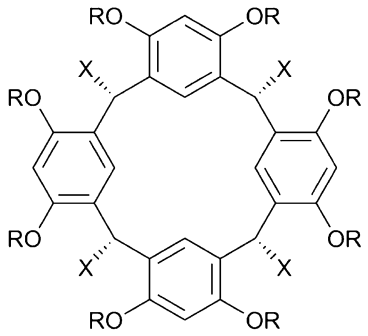

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R = H, X =Alkyl, aryl, Resorc[4]arene
R = Alkyl, X =Alkyl, aryl, Octa-*O*-alkyl resorc[4]arene

Fig. 1 Resorc[4]arenes and Octa-*O*-alkyl resorc[4]arenes

adopted (Fig. 2) which can be simply interchanged through rotation. In contrast, for the majority of derivatives which feature *C*-alkyl substituents, the results are more complex as the arrangement of these residues needs to be taken into account. Thus, the different products are diastereomeric requiring bond cleavage before inter-conversion can take place. A convention has been introduced to allow easy description of each diastereoisomer, in which the side chain orientation is characterised relative to the macrocyclic plane and to the orientation of the first substituent, thus in a *rccc* diastereoisomer, all of the side chains are *cis* and on the same side of the macrocycle plane, whereas in an *rctt* diastereoisomer the second methylene bridge substituent is *cis* to the first and on the same side of the macrocycle plane and the third and fourth are *trans* and on the opposite side of the plane. The structures of the three most commonly isolated diastereoisomers along with a frequently found conformer of the *rccc* cone, the flattened cone, are shown in Fig. 3.

A degree of confusion has arisen from the use in literature of a range of names for the same diastereoisomer or conformer and in this review we will use a single set of definitions, as shown in Fig. 3, to describe each, for example the nomenclature 1,2-alternate will be used throughout in preference to diamond.

With larger ring sizes, such as pentamers and hexamers, the available number of diastereoisomers increases and, due to the increased ring size, conformational inversion can occur easily thus leading to a larger number of potential products.

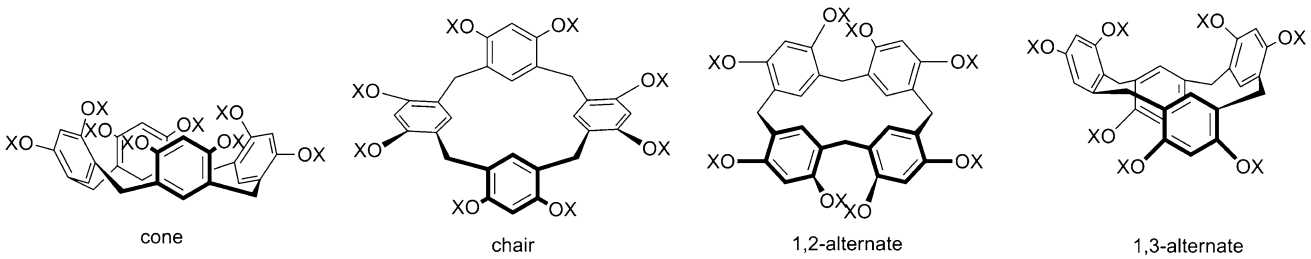
O-alkyl resorcarenes

Synthesis of *C*-alkyl resorcarenes

C-alkyl resorc[4]arenes are particularly useful intermediates for a number of applications. In one synthetic step, the preparation of molecules that can adopt a range of three-dimensional shapes and undergo synthetic elaboration at both the *C* and *O* positions can be achieved. However, a particular challenge of this synthetic route is to determine conditions which allow for the formation and isolation of discrete diastereoisomers.

Functionalised resorcinol precursors

Lewis acid catalysed reactions Iwanek and co-workers [4, 5] investigated a range of Lewis acids as catalysts for the condensation of 1,3-dimethoxybenzene **2** with isovaleraldeyde **3** in chloroform (Scheme 1). In all cases, except for $SnCl_4$, three diastereoisomers were isolated with the *rccc* cone, and *rctc* 1,2-alternate predominating over the *rctt* chair isomer. With $SnCl_4$ the *rccc* cone is exclusively formed in 85% yield (Scheme 1). Unfortunately, transferring these synthetic conditions to other aldehydes showed that these were not universal and do not always lead to a clean stereochemical outcome. Only branched aldehydes undergo cyclisation in $CHCl_3$, whilst changing the solvent to Et_2O allows the formation of resorc[4]arenes from straight chain aldehydes. These reactions are lower yielding overall (30–55%) and other diastereoisomers are also formed in low quantities.



X = H, Reorc[4]arene
X = Alkyl, *O*-alkyl resorc[4]arene

Fig. 2 Conformers of the parent resorc[4]arenes

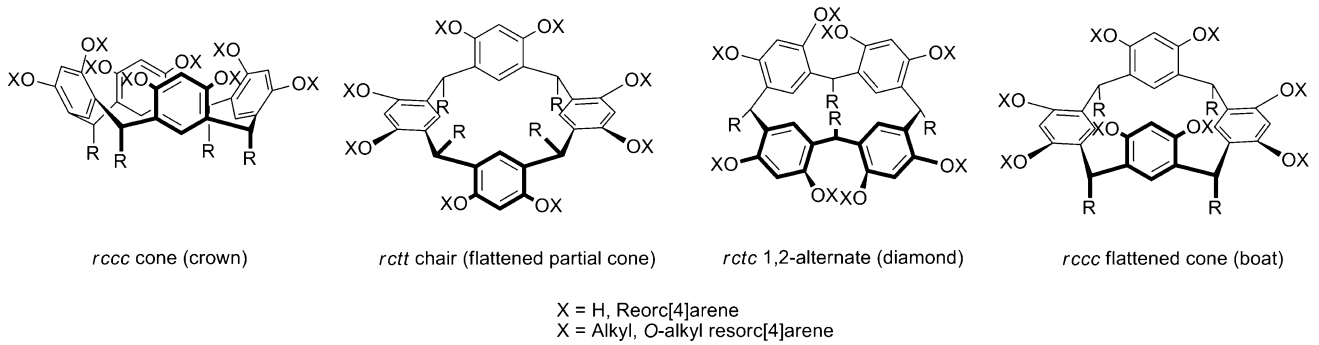
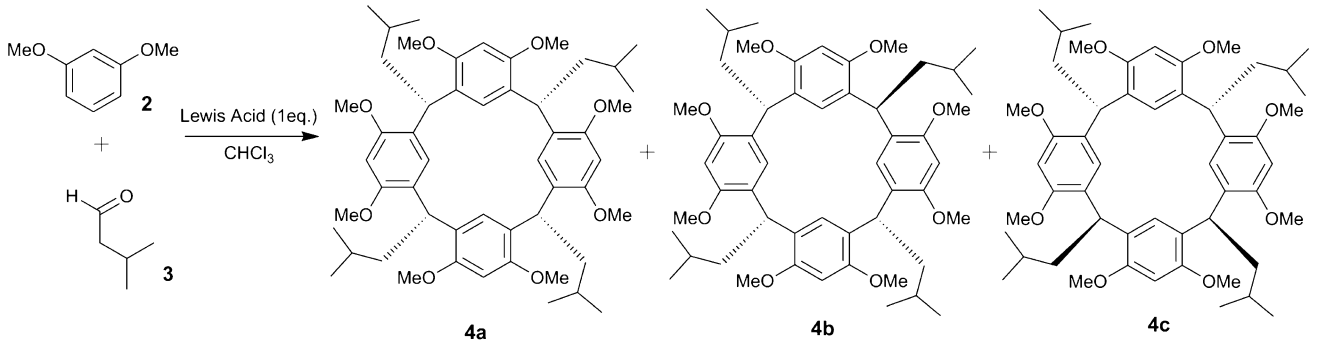


Fig. 3 The common diastereoisomers of resorc[4]arenes



	4a	4b	4c
$SnCl_4$	100%		
$SOCl_2$	40%	55%	5%
$POCl_3$	35%	62%	3%
$AlCl_3$	30%	60%	10%
$SiCl_2Me_2$	50%	43%	7%
SiClMe	50%	45%	5%

Scheme 1 Lewis acid synthesis of octa-*O*-methyl resorc[4]arenes

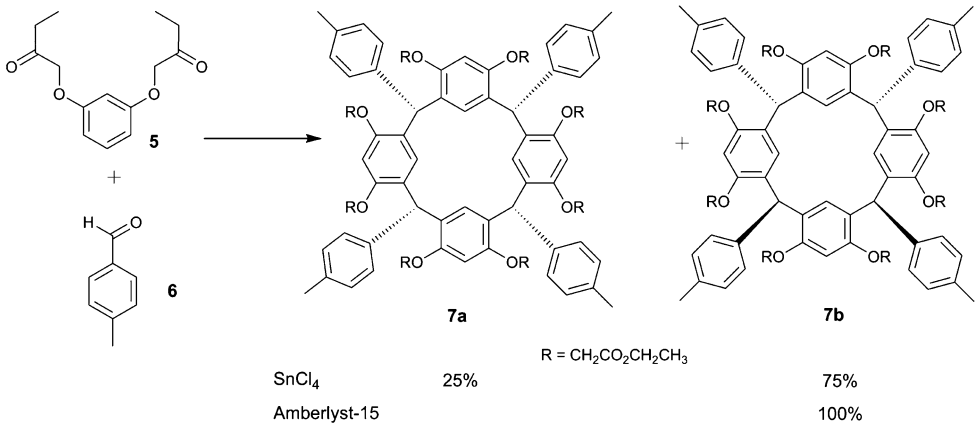
The group of Pieroni [6–8] have also investigated $AlCl_3$ for the synthesis of *C*-alkyl resorc[4]arenes using diethyl benzene-1,3-diyldioxydiacetate **5** and compared the stereochemical outcome of this reaction with the product formed using a cation exchange resin. By this choice of resorcinol derivative, functionality is built in at the oxygen positions prior to macrocyclisation. In this case, whilst the Lewis acid catalysed reaction is high yielding it gives a mixture of two diastereoisomers in a 3:1 ratio in favour of the *rctt* chair isomer at low catalyst concentrations (0.05 mol L^{-1}). On increasing the concentration of the catalyst (5 mol L^{-1}) the *rccc* flattened cone isomer predominates indicating that, under these conditions, this is the thermodynamic product. In contrast, the use of Amberlyst-15 in toluene, resulted in much lower yield but exclusive formation of the *rctt* chair isomer (Scheme 2).

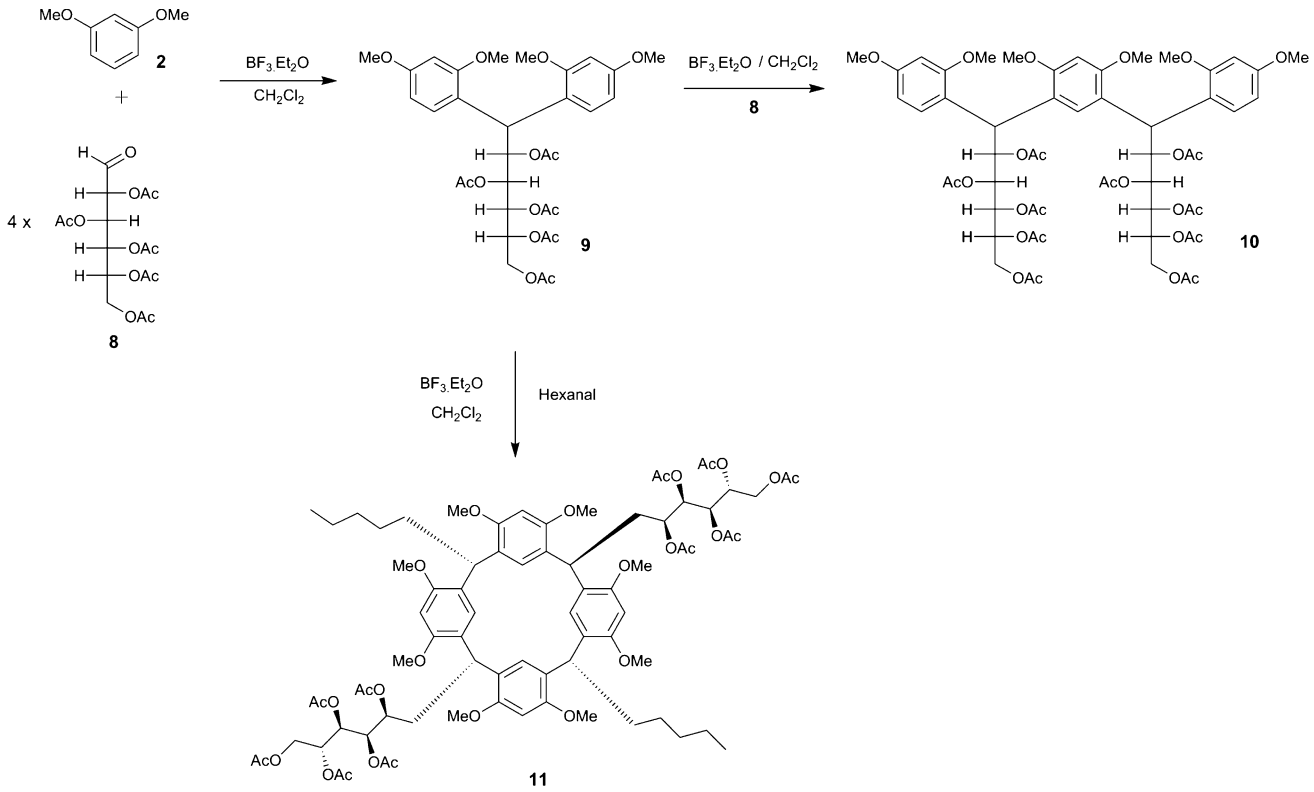
Lewis acid catalysis has also been investigated for the preparation of open-chain sugar containing resorc[4]arenes from the reaction of 1,3-dimethoxybenzene and protected aldoses (Scheme 3) [9]. Whilst taking an equimolar ratio of **2** and **8**, led to a complex product distribution, using an excess of **2** resulted in a dimer **9** which could be further reacted to yield a trimer **10** but further reaction to the tetramer and macrocyclic ring closure could not be achieved. However, as this was thought to be a steric issue, the mixed condensation with hexanal in the presence of $BF_3.Et_2O$ was investigated and successfully yielded a single diastereoisomer **11**, identified through ^1H NMR and NOEs as the *rctc* 1,2-alternate, in 44% yield.

Thus, Lewis acid catalysis has proved to be a useful method of preparing octa-*O*-alkyl resorc[4]arenes, with most acids promoting cyclisation, although as both the nature of the aldehyde and the Lewis acid seem to direct the stereochemical outcomes, the ideal conditions for obtaining a single diastereoisomer have yet to be determined.

Brønsted acid catalysed reactions Initial reports on the synthesis of *O*-alkyl resorc[4]arenes indicated that both

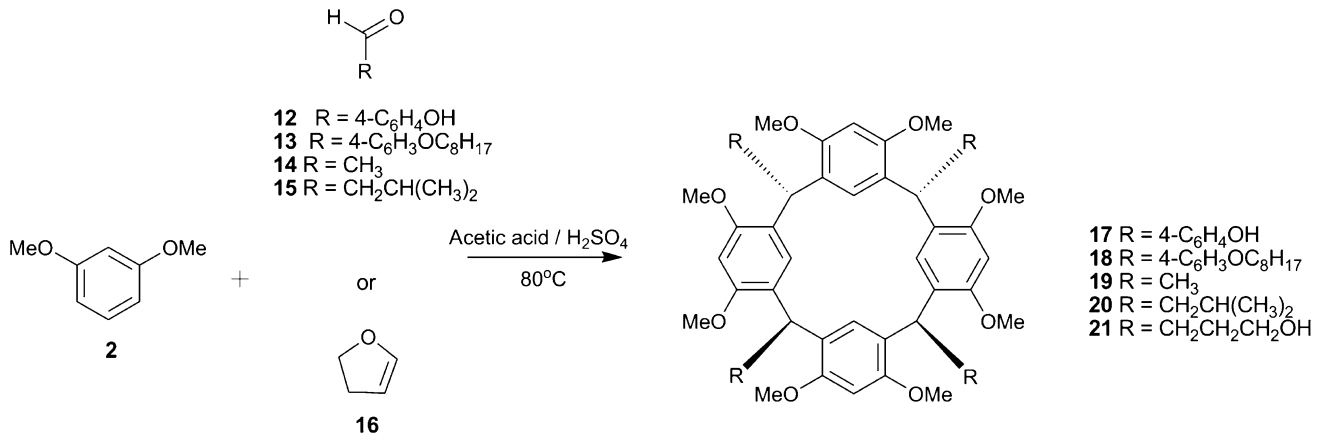
Scheme 2 Comparison of diastereomeric outcomes between ion exchange and Lewis acid catalysis





Scheme 3 Synthesis of a sugar functionalised octa-*O*-methyl resorc[4]arene

fully and partially alkylated derivatives could not be formed under Brønsted acid catalysis [10]. However, a preliminary report on the successful synthesis of the parent resorc[4]arene using acid catalysis in acetic acid [11, 12] led us to investigate these conditions for the formation of *C*-alkyl derivatives [13]. The reaction between *p*-hydroxybenzaldehyde **12** and 1,3-dimethoxybenzene **2** was first investigated under the Lewis acid conditions developed by Iwanek [4, 5] and using HCl catalysis in ethanol and in both cases a mixture of the *rccc* cone and the *rctt* chair diastereoisomers was formed in high yield. This mixture could be separated following butyrylation, column chromatography and subsequent ester hydrolysis to give the single products. In contrast, when acetic acid was used as the solvent at 80 °C, in the presence of either HCl or H_2SO_4 as the catalyst, the *rctt* chair was exclusively formed whereas at 25 °C a mixture of the two diastereoisomers was formed This reaction proved to be remarkably adaptable with exclusive formation of the *rctt* chair for a range of aromatic and aliphatic aldehydes including masked aldehydes, however, the analogous reaction with 1,2,3-trimethoxybenzene to form an *O*-alkyl pyrogallol[4]arene failed to yield any macrocyclic product, as did reactions with bulky aromatic aldehydes (Scheme 4).



Scheme 4 Brønsted acid catalysis for formation of octa-*O*-methyl resorc[4]arenes

Not all Brønsted acids were successful in promoting the catalysis and the failure of trifluoroacetic acid to act as a catalyst in these conditions is particularly interesting when compared with the results of Iwanek [14]. As noted earlier, the all *cis* diastereoisomer of **4** can be exclusively formed by Lewis acid catalysis. On taking this isomer in the presence of a large excess of trifluoroacetic acid in $CHCl_3$ an isomerisation process is observed which after 24 h gives a diastereoisomer profile of 5:4:1 *rctc* 1,2-alternate: *rccc* cone: *rctt* chair indicating that higher trifluoroacetic acid concentrations may indeed allow cyclisation to occur.

In a similar approach, Konovalov et al. have revisited the traditional resorc[4]arene synthesis conditions of HCl catalysis in ethanol for the cyclisation of 1,3-di(2-hydroxyethoxy)benzene **22** with aliphatic aldehydes (Scheme 5) [15]. Using a large excess of the acid, and heating at reflux for 48 h, allowed isolation of **27–30** in relatively low yields of 20–55%. The simplicity of the ^{1}H NMR, featuring two singlets in the aromatic region, indicates that under these conditions, with aliphatic aldehydes, the *rccc* cone isomer is exclusively formed.

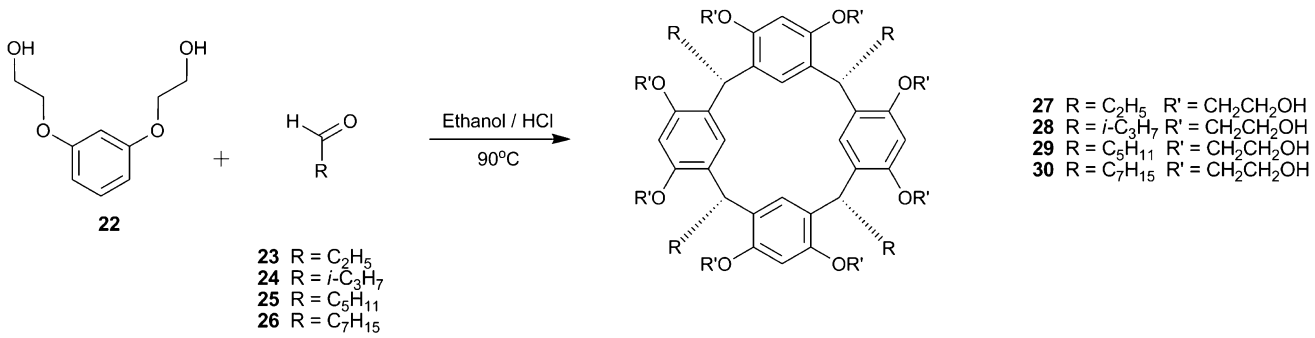
These contrasting results with Brønsted acids, open up the possibility of control of the reaction outcomes and thus the directed synthesis of either the *rccc* cone or *rctt* chair diastereoisomers.

Cinnamic acid precursors

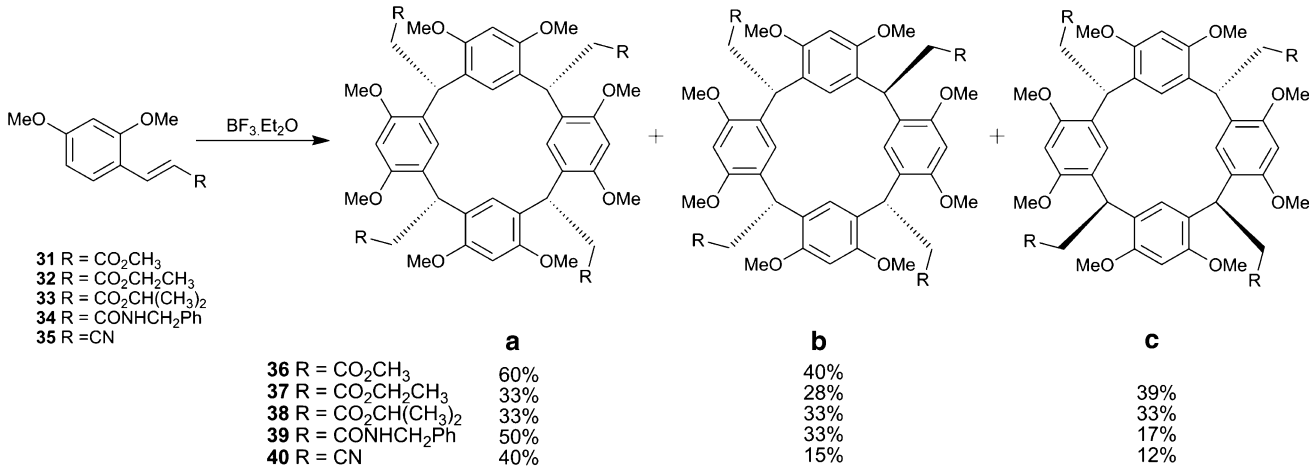
Following the successful synthesis of aryltetralin lignans by $BF_3.Et_2O$ catalysed dimerisation of (*E*)-3,4-dimethoxycinnamic acid methyl ester [16] the group of Botta applied these conditions to the 2,4 isomer and unexpectedly isolated, rather than a dimer, macrocyclic derivatives which proved to be octa-*O*-methyl resorc[4]arenes featuring ester functionalised *C*-alkyl side-chains [17, 18]. The reaction yielded two diastereomeric products, with the major product assigned as the *rccc* flattened cone **36a** and the minor product the *rctc* 1,2-alternate **36b** (Scheme 6). With larger ester precursors [19], such as ethyl and isopropyl, an additional product was isolated **37c, 38c** which was initially assigned as the *rccc* 1,3-alternate conformer of **37a, 38a**, based on ^{1}H NMR and molecular modelling studies, however these could not be converted to **37a** or **38a** by simply heating as would be expected of such a conformer. The ^{1}H NMR is also, however, consistent with the macrocycle adopting an *rctt* chair arrangement and much later, in 2007 [20], the structure of the third isomer was unambiguously determined as this chair by X-ray analysis (Fig. 4).

The isomer mix obtained in the reaction was related to Lewis acid concentration; an increase leading to an enhanced yield of the flattened cone and a reduced yield of 1,2-alternate with little effect on the chair, length of reaction; the flattened cone predominating with longer reaction times, and reaction temperature; higher temperatures favouring the flattened cone which suggests that formation of the 1,2-alternate product is kinetically controlled and the flattened cone thermodynamically controlled. This proposal was reinforced by isomerisation experiments on **37** where treatment of **37b** with an excess of $BF_3.Et_2O$ resulted in the isolation of **37a** whilst no effect was seen in the isomer distribution with **37a**. Treatment of **37c** under isomerisation conditions, led to the isolation of both **37a** and **37b** which led to the suggestion that the isomerisation process involved two bond scissions each followed by a re-macrocyclisation which could account for **37b** being formed as an intermediate. This inter-conversion can also be achieved under the conditions for reduction of the esters to alcohols with $LiAlH_4$.

This synthetic method has proved to be the major development in the synthesis of octa-*O*-alkyl resorc[4]arenes enabling the preparation of derivatives with a wide range of *C*-alkyl substituents and larger ring analogues. From a simple amide precursor **34**, the same three isomeric materials **39** were isolated as for the esters [21]. However



Scheme 5 Synthesis of octa-*O*-alkyl resorc[4]arenes using HCl in ethanol



Scheme 6 Cyclisation of 2,4-dimethoxycinnamic acid derivatives

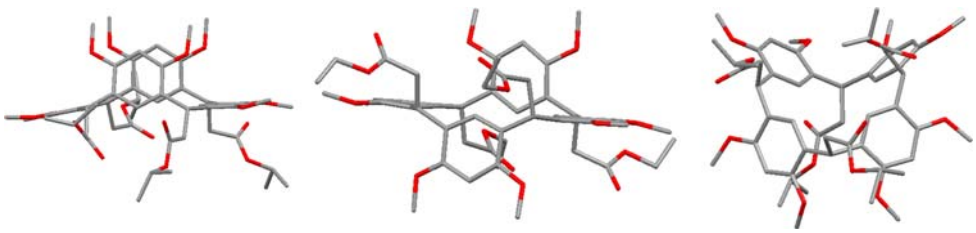


Fig. 4 X-ray crystal structures of **37a, 37b**[19] and **37c**[20]

where more complex chiral amides were used four products were isolated, as expected the *rccc* flattened cone and *rctc* 1,2-alternate isomers were formed but in addition both the majority product, an *rccc* flattened partial cone arrangement, and traces of a *rctt* chair product were identified. Isomerisation studies indicated that, as with the ester derivatives, the flattened cone isomer is the thermodynamically stable product. HPLC monitoring of the reaction of cyano precursor **35** with $BF_3.Et_2O$ allowed the isolation of the three expected isomers of the resorc[4]arene **40** but also three isomeric cyclic pentamers, which through an extensive study of reaction progress and isomerisation experiments, were identified as the kinetic products which converted to the thermodynamically more stable tetramers [22]. Interestingly, it is not possible to form a macrocycle featuring both intra- and extra-annular *O*-alkyl groups by extending this methodology to the 2,6-dimethoxycinnamic acid ethyl ester [23]. In this reaction, the precursor first undergoes an acid catalysed rearrangement to the 2,4 isomer which then cyclises to form **37** as a mixture of three isomers in 67% yield.

Synthesis of the parent resorcarene

The synthesis of the parent resorcarene in which the resorcinol units are joined by methylene bridges has been a major challenge as when resorcinol is treated with formaldehyde a polymeric material is isolated due to the high reactivity of the aldehyde. This has been overcome by using 2-substituted resorcinols under a range of reaction

conditions, thus 2-alkyl resorcinols yield both tetramers and hexamers [24, 25] in an HCl-catalysed reaction with 1,3,5-trioxane, and additionally pentamers when the aldehyde source is formaldehyde diethyl acetal [26], whereas base catalysis is also possible with 2-butyryl [27], and 2-nitro resorcinols [28]. However an alternative approach, which also enables the preparation of 2-unsubstituted derivatives, is to initially prepare an *O*-alkyl derivative which can subsequently be deprotected to yield the parent resorcarene.

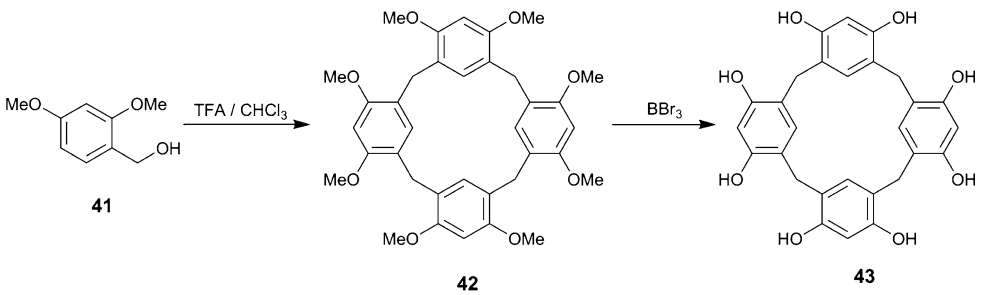
Keehn and Stevenson [29] were the first to exploit this approach for the synthesis of resorc[4]arene (Scheme 7). Treatment of 2,4-dimethoxybenzyl alcohol **41**, a proposed intermediate in the formation of resorc[4]arenes from 1,3-dimethoxybenzene and formaldehyde, with trifluoroacetic acid in chloroform yielded a single material in 95% yield which was identified as the tetramer **42** by mass spectrometry. This gave a remarkably simple, temperature independent, ^{1}H NMR spectrum featuring four singlets suggesting that either the molecule is highly conformationally flexible or is fixed in a rigid 1,3-alternate conformation (see Fig. 2). **42** could be deprotected by treatment with BBr_3 and the crude material further functionalised as the octa-*O*-acetate which retains the same conformational specificity.

Using an analogous approach, Konishi et al. used both **41** and 2,4-diallyoxybenzyl alcohol in a $Sc(OTf)_3$ catalysed cyclisation in acetonitrile to prepare the respective octa-*O*-alkyl resorc[4]arenes in reasonable yields [30]. Further investigations of the reaction conditions indicated that higher oligomers were also formed when in cooled high dilution conditions. Thus at 50 °C the octa-*O*-ethylresorc[4]arene was formed in 89% yield with a 3% yield of the pentamer and 1% of the hexamer, however on cooling the reaction to 0 °C the product distribution extended to include low yields of the septamer, octamer and nonamer with a concomitant reduction in the yield of the tetramer to 61% and an overall reduction in the yield of cyclic products relative to linear oligomers. The importance of the solubility of the products in the reaction conditions in dictating product distribution was shown in the reaction of 2,4-dimethoxybenzyl alcohol as, at 0 °C, the predominant product was the octamer which precipitated out of the reaction mixture and was isolated in 54% yield [31]. Variable temperature ^{1}H NMR of the tetramers was again indicative of the molecule adopting a 1,3-alternate conformation.

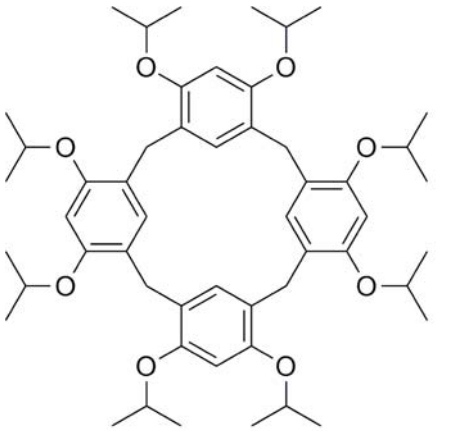
Moravcová and co-workers [32], investigated a range of Brønsted and Lewis acids for the cyclisation of 2,4-diisopropoxy benzyl alcohol and identified chlorotrimethylsilane in acetonitrile as the ideal reaction conditions for the formation of the tetramer. Following deprotection with BCl_3 the parent resorc[4]arene was isolated in the highest yield to date of 76%. ^{1}H NMR analysis of **44** was consistent with the molecule adopting a 1,3-alternate conformation over a wide temperature range of −100 to 35 °C and, in the first example for this type of molecule, X-ray crystallography indicated that this conformer is also seen in the solid state (Fig. 5).

Interestingly, when 1,3-dimethoxybenzene **2** is condensed with paraformaldehyde in 2-ethoxyethanol at 100 °C in the presence of HCl as a catalyst two different conformers of the resulting resorc[4]arene **42** are isolated [33, 34]. The two conformers were identified by ^{1}H NMR, one adopts a C_2 symmetrical arrangement which was proposed to be the chair conformation and the second showing C_4 symmetry was proposed to be a flattened cone. However, comparison of the data for the second conformer shows it to be identical to that reported by Konishi and co-workers [30] and identified as the 1,3-alternate conformation. In the absence of solid state data this NMR is indeed more consistent with the 1,3-alternate conformation as the methylene bridge protons appear as an equivalent singlet. The conformer distribution was affected by the concentration of HCl in the reaction with the chair conformer being isolated in higher yield at higher concentrations. The conformers could also be inter-converted by heating of the solid material, ^{1}H NMR studies of the heated material in $CDCl_3$ showed that whilst the chair is stable at 230 °C heating to 240 °C results in a change to an intermediate conformation, whilst at 250 °C full conversion to the highly symmetric C_4 conformer is achieved.

The first examples of confused resorc[4]arenes e.g. **47** were isolated, as minor products, along with the expected parent resorcarenes, in 2006 by Konishi and co-workers, when 1,3-dimethoxy or diethoxy benzene were reacted



Scheme 7 Synthesis of the parent resorc[4]arene



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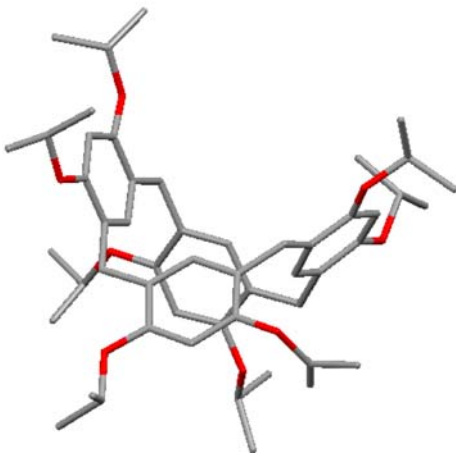


Fig. 5 X-ray crystal structure of **44**

with trioxane in a $Sc(OTf)_3$ catalysed condensation (Scheme 8) [35]. In this reaction, one aromatic ring reacts at the 2,4 rather than the 4,6 positions leading to a resorc[4]arene featuring one interannular alkoxy group. The product was identified by ^{1}H NMR studies, where a significant upfield shift of one *O*-alkyl peak is observed compared to the regular resorc[4]arene, e.g. from 3.78 to 3.04 ppm for the methyl derivative. No changes are seen in the spectrum on heating, indicating that no inter-conversion occurs between the isomers and thus the confused ring is unable to rotate through the annulus. As with, the standard parent resorcarenes, this molecule adopts the 1,3-alternate conformation in the solid state (Fig. 6).

Using similar approaches the parent pyrogallol[4]arene can also be prepared. Hybrid pyrogallol[4]arene and mesitylene based metacyclophanes e.g. **49** were isolated from the reaction of 3,4,5-trimethoxytoluene **48** and paraformaldehyde (Scheme 9) [36]. Whilst higher oligomers, featuring between 5 and 13 aromatic units were favoured by using Brønsted acid catalysis (H_2SO_4) in tetrahydrofuran the tetrameric product could only be formed, in a relatively low yield of 9.4%, by using sulphuric acid as both catalyst and solvent. As with the structurally related mesitylene based metacyclophanes [37], this pyrogallol[4]arene adopts a rigid 1,3-alternate structure both in solution, as shown by a single residue at 4 ppm for the bridge protons in the ^{1}H NMR, and in the solid state.

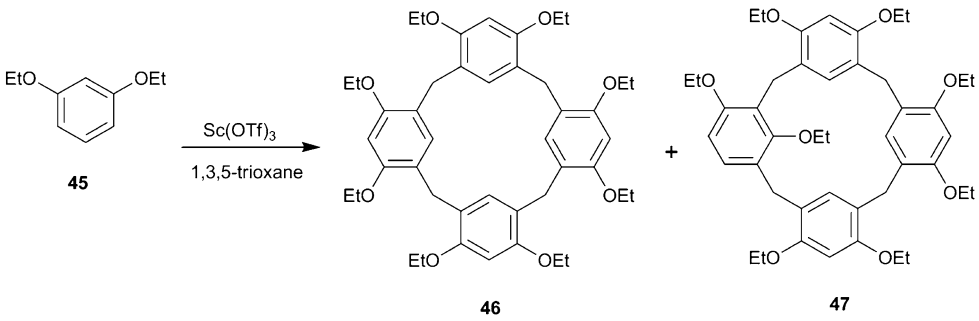
More recently a Lewis acid approach has been exploited for the exclusive synthesis of a pyrogallol[4]arene in 75% yield [38]. Pre-treatment of 1,2,3-trimethoxybenzene with $SnCl_4$ in chloroform led to the precipitation of a charge-transfer complex which on reaction with trioxane yielded the macrocycle. This molecule was identified as adopting the crown conformation from the ^{1}H NMR spectrum which features a broad singlet for the methylene bridge protons. Unfortunately this conformational assignment was not confirmed through solid state data and it cannot be ruled out that, as with the other parent molecules, a 1,3-alternate conformation is in fact adopted.

Partial *O*-alkyl resorcarenes

The preparation of partial *O*-alkyl derivatives of resorcarenes is of particular interest as it offers the potential for the preparation of enantiomerically pure chiral derivatives. Whilst, such derivatives are also accessible by sequential removal of the ethers of a fully *O*-alkylated resorcarene two direct synthetic routes have been described for the synthesis of tetra-*O*-alkylated resorcarenes.

Mocerino [39] first identified a synthetic route for the synthesis of C_4 symmetric resorcarenes from monoalkylated resorcinol units using a $BF_3.Et_2O$ catalysed condensation (Scheme 10). Surprisingly, despite the many different configurations and regioisomers of the resorc[4]arene that potentially could be formed, only the C_4 *rccc* isomer **64** was isolated as a racemic mixture. X-ray crystallography studies demonstrated that the molecule adopts a flattened cone conformation in the solid state (Fig. 7) and ^{1}H NMR showed that, due to the simplicity of the aromatic region, the molecule exists in a time averaged cone in solution at room temperature. The presence of the racemate was proven by the doubling of the signals in the presence of a chiral shift reagent. The authors proposed that this exclusivity in the reaction was not a result of isomerisation of different species to enable the formation of the maximum OH-OMe hydrogen bonds but instead due to the initial formation of a single benzyl alcohol intermediate, where the OMe group is in the 5-rather than the 2-position, prior to condensation. The formation of these synthetic intermediates seems likely, as in an extension of this work by Heaney [40], it was shown that whilst the condensation fails between monobenzyl resorcinol **54** and hexanal, pre-formation of the alcohol intermediate allows isolation of the C_4 tetra-*O*-benzyl resorcarene from a

Scheme 8 Synthesis of a confused resorc[4]arene



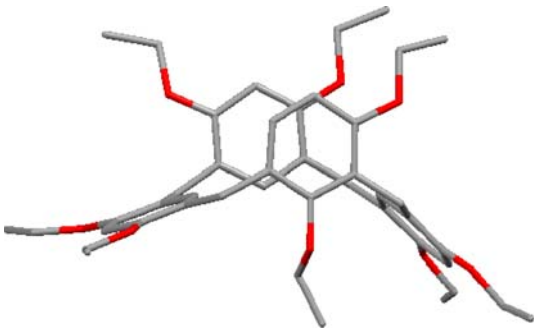


Fig. 6 X-ray crystal structure of **47**

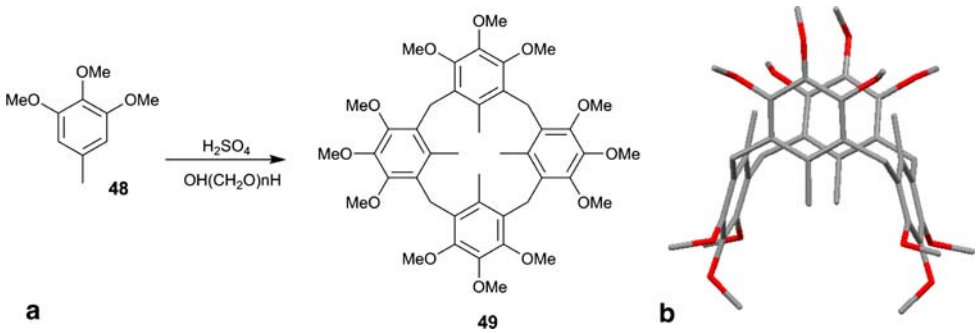
condensation using tetrafluoroboric acid in diethyl ether. These workers also extended the synthesis to include tetracyclopentyl derivatives and demonstrated higher yields by replacing the aldehyde with a dimethyl acetal. Determination of the absolute configuration of the enantiomerically pure materials has proved difficult and initial reports [41–43] have been superseded by a collaborative study from the three key research groups [44] in this area. Using a chiral auxiliary method, camphorsulfonate derivatives were prepared that could be separated by column chromatography and their absolute configuration assigned through X-ray crystallography. Whilst with the *O*-methyl derivatives, this functionalisation proved straight forward, with larger *O*-alkyl substituents exhaustive functionalisation was more difficult to achieve and, by using a variety of conditions, it was only possible to isolate diastereomeric pairs of mono- and di-camphorsulfonate derivatives.

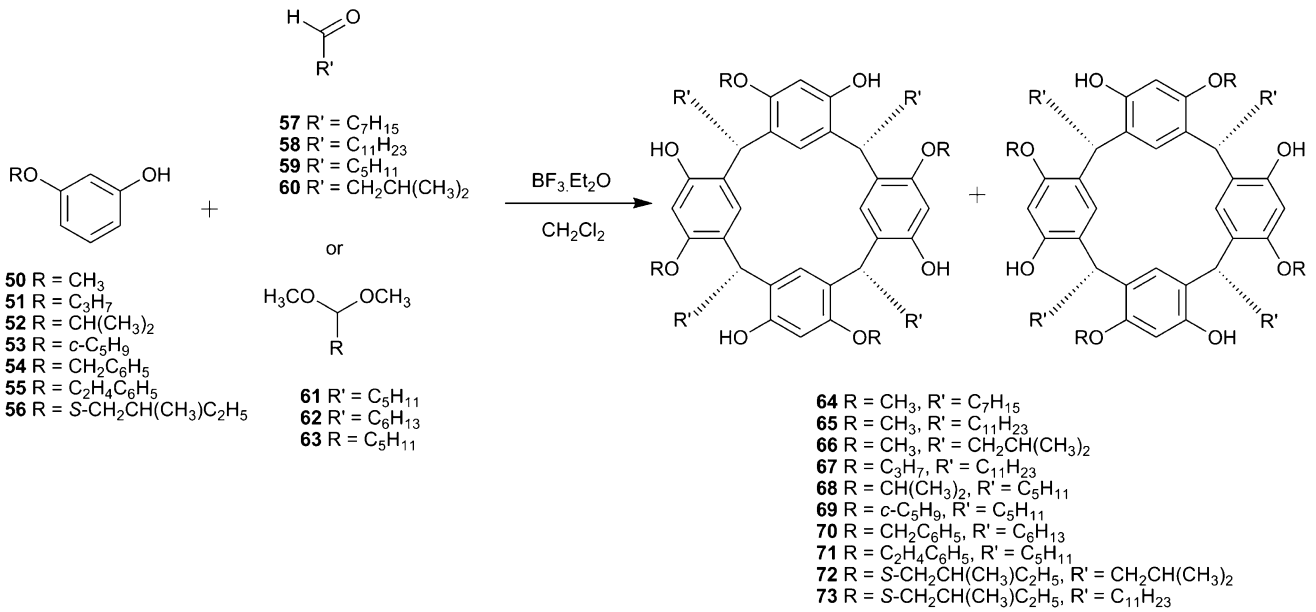
Taking a different tack, Mattay and co-workers [41] were able to directly prepare chiral and enantiomerically pure derivatives by using a chiral alkylphenol, (−)-3-[(2*S*)-2-methylbutoxy]phenol **56**, in the cyclisation reaction with either 3-methylbutanal **60** or *n*-dodecanal **58** followed by HPLC separation of the (+) and (−) diastereoisomers.

In the second approach for preparing partially alkylated derivatives, Konishi and co-workers [45] described a stepwise synthesis of a C_{2v} symmetrical derivative **76** of the parent resorcarene, with an ABAB ring arrangement, through the condensation of alternating fully alkylated and unalkylated resorcinol units (Scheme 11).

Whilst, this 2 + 2 fragment condensation approach using $Sc(OTf)_3$, is relatively low yielding with the most successful reactions giving only 15% yield in the final condensation step, it proves a flexible approach, allowing the incorporation of a range of alkyl groups. Conformational analysis, using ^{1}H NMR, indicates that the molecules adopt a cone or flattened cone conformation, stabilised by four hydrogen bonds, as on reduction of temperature an AB system is observed for the methylene bridge protons whilst on heating the signals coalesce due to a rapid cone–cone inter-conversion. These results are in line with those reported for the analogous tetra-*O*-isopropyl derivative [46] prepared through sequential deprotection of the octa-*O*-isopropyl resorc[4]arene where the activation free energy $\Delta G^{\ddagger}$ for the inter-conversion at the coalescence temperature (−50 °C) was measured as 42 kJ mol^{-1}. The stability of the cone conformation was confirmed by molecular modelling studies using density functional theory on the

Scheme 9 **a** Synthesis of parent pyrogallorene, **b** X-ray crystal structure of **49**





Scheme 10 Synthesis of C_4 symmetric tetra-*O*-alkyl resorc[4]arenes

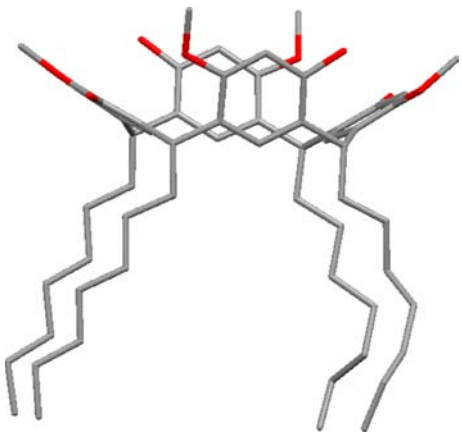


Fig. 7 X-ray crystal structure of **64**

tetra *O*-methyl derivative where it was identified as the global minimum with the closest energy conformers proving to be the two partial cone arrangements which can be stabilised by only two hydrogen bonds.

Applications

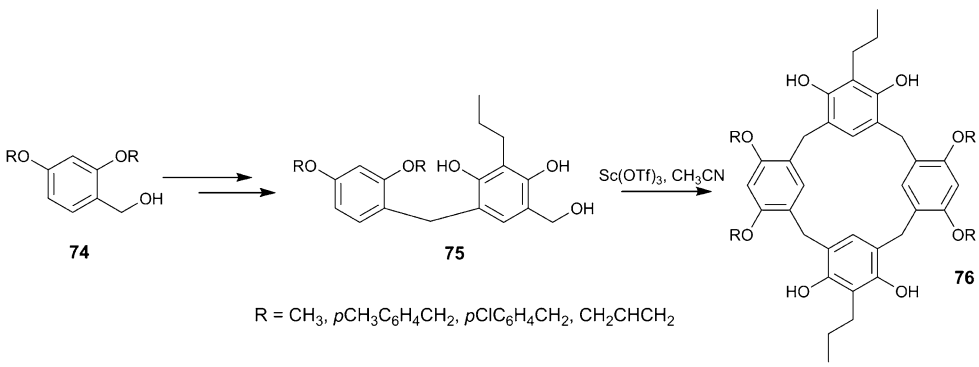
Applications of fully *O*-alkylated derivatives

Cation binding

The discovery of the potential of cinnamic acid derivatives for the formation of *O*-alkylated resorc[4]arenes has allowed the preparation of a number of resorc[4]arenes suitably functionalised for interaction with cations.

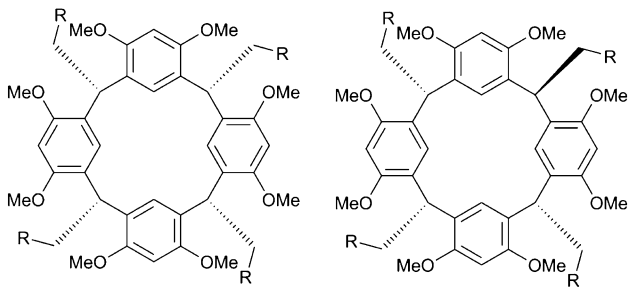
In the first report of this type [47], Botta and co-workers examined the ability of a range of resorc[4]arene derivatives to bind iron(III). With the *rccc* cone resorc[4]arene **38a**, featuring ester side chains, on initial complexation three new UV bands at 330, 568 and 628 nm are seen and over time the band at 628 nm increases in size with a concomitant reduction in the band at 568 nm. In contrast with **77a** (Fig. 8) where there is no side chain functionality bands are only seen at 568 and 628 nm which again over time change to a single band at 628 nm. These results

Scheme 11 Synthesis of C_{2v} symmetric tetra-*O*-alkyl resorc[4]arenes



suggest that in **38a** the ester can be involved in binding and there are likely to be two binding sites. This was confirmed by the complex results seen in ^{1}H NMR studies using gallium(III) as a substitute probe for iron(III) for **38a**. In contrast for **77a** ^{1}H NMR studies indicate that there is a single binding site at the upper-rim of the resorc[4]arene as the aromatic and methoxy protons are most affected by binding. The importance of the macrocycle in the binding was confirmed by comparison with two molecules representing monomers which show no spectral changes on binding. The results found with bridged receptors [48, 49] also attested to the involvement of the ester moieties in the metal binding and from ^{1}H and ^{13}C NMR shifts it was proposed that the binding occurs not in the cavity but between two resorc[4]arenes. An interesting side isomerisation reaction was observed in these studies with the methyl derivative **77**. On treatment with either iron or gallium two species were isolated after complexation the first being the *rccc* cone **77a**, the second being a *rctc* 1,2 alternate **77b** complex which could also be prepared by synthesis of the methyl derivative from the corresponding ester **38b** and complexation with the cations. The binding of gallium by both cone and 1,2-alternate water soluble amino derivatives **78** has also been investigated by ^{1}H NMR [50]. Unfortunately the stoichiometry of binding could not be established but the relatively large shifts experienced by protons in the macrocycle suggest binding at the lower rim close to the macrocycle and that the charged nitrogens are not involved in binding (Fig. 8).

As discussed earlier, cyano groups can also be introduced to the lower rim by using the appropriate cinnamic derivative in the cyclisation reaction [51]. Reduction to the corresponding amines was not simple using a range of standard reductions, and thus amines were prepared through a multi-step synthetic pathway from the bromo derivative (Scheme 12). Comparison of the copper binding properties of the three cyano diastereoisomers **40a, b, c**



77a R = H
78a R = $CH_2N^+C_5H_5$
79a R = $CH_2NHCH_2C_6H_5$
80a R = $CH_2NHCH_2C_5H_4N$

77b R = H
78b R = $CH_2N^+C_5H_5$

Fig. 8 Octa-*O*-methyl resorc[4]arenes developed for cation binding

using ^{1}H NMR and mass spectrometry indicated that in the case of the *rccc* cone **40a** binding of a single copper occurs exclusively at the lower-rim cyano groups and that preorganisation of the cyano groups is crucial to binding as no binding is seen with the precursor dimer, or with the *rctc* 1,2-alternate isomer **40b**. The corresponding *rccc* cone amino derivative **86** showed limited solubility in CD_3CN and therefore binding was assessed by EPR studies and molecular modelling studies which suggested that rather than forming a 1:1 complex the metal ion is held between the lower rims of two resorc[4]arenes in a distorted octahedral arrangement involving three amines on each resorc[4]arene. Due to the low solubility of the amines, substituted amino derivatives such as **79a** and **80a** have also been developed and their binding ability with both cobalt and mercury investigated by UV spectroscopy [49]. Both molecules formed 1:1 complexes with the metal cations, unlike the ester precursor which showed no binding, which indicated that the interaction was occurring at the lower-rim. In particular **80a** showed more affinity for cobalt than for mercury and formed a more stable cobalt complex than **79a**.

The straightforward post synthetic alteration of the lower-rim esters of octa-*O*-methyl resorc[4]arenes into alcohols, acids and bromo derivatives has been exploited for the formation of lower-rim bridged resorc[4]arenes [48] and capped porphyrins (Fig. 9) featuring a range of intra cavity distances [51]. Introduction of such caps can affect the oxidation state of metal ions on binding into the porphyrin core and thus the binding of cobalt(II) was investigated by UV-spectroscopy. In the case of **87**, the cobalt on binding showed similar Soret bands to those seen for uncapped porphyrin derivatives were observed upon binding of cobalt, indicating that the porphyrin binding site featured an oxidised cobalt(III) ion. With **88**, the bound cobalt remained in the cobalt(II) oxidation state, a result confirmed by application of the reducing agent $Na_2S_2O_5$ which resulted in no change in the spectrum, and EPR spectra that showed the cobalt(II) to be high-spin. In contrast to this, a complex UV spectrum with two Soret bands was obtained for **89,** suggesting a mixture of cobalt(II) and cobalt(III) species and in fact full oxidation could be achieved by treating the mixture with O_2.

More recently, the interaction of octa-*O*-methyl resorc[4]arene hosts with the nitrosonium cation has been investigated with the intended application of absorption of this cation from tobacco smoke [20, 52]. Initial studies on *rccc* cone **83** incorporating a halogen in the side chain resulted in the formation of highly coloured solutions either when bubbling NO_2 through a chloroform solution or when treating a solution with an excess of $NOBF_4$. UV analysis of this process showed the formation of charge transfer bands between the cation and the aromatic rings but

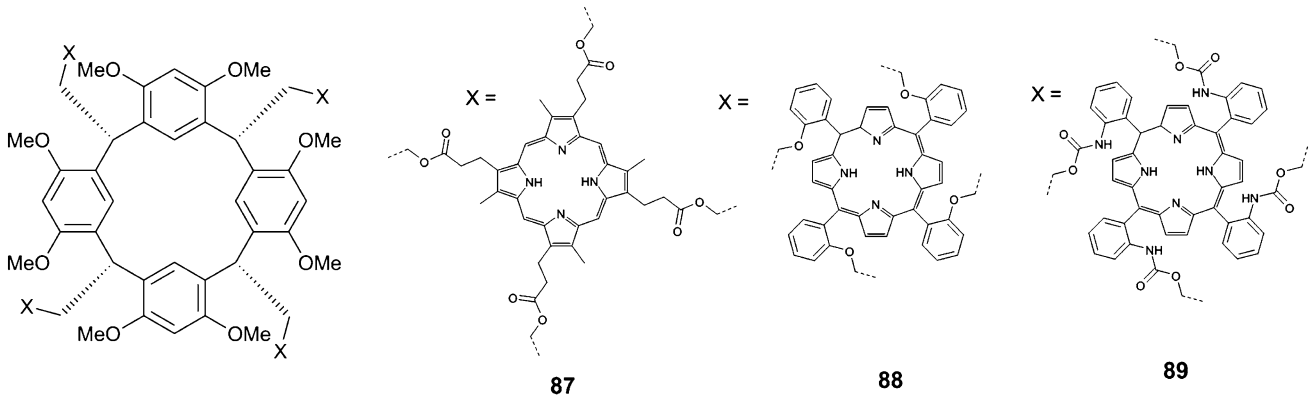
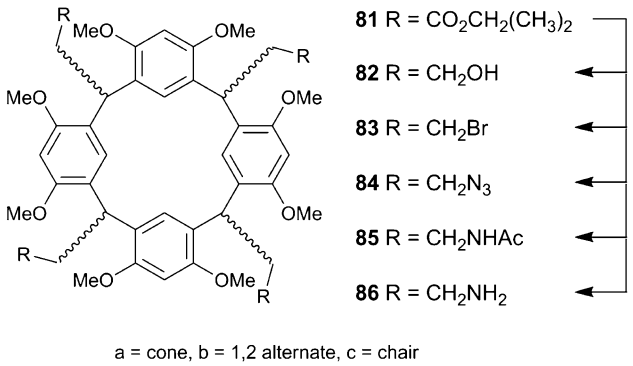


Fig. 9 Resorc[4]arene capped porphyrins



Scheme 12 Synthesis of amino derivatives

indicated that the binding was complex involving the formation of a number of unstable complexes prior to the final stable arrangement. Molecular modelling studies suggested that whilst it was possible for the cation to be bound at the lower-rim the most stable arrangements were those which adopted a flattened cone arrangement with the cation held between two aromatic rings. In contrast, with the *rccc* resorc[4]arene **37a** featuring esters in the side chain, the more stable arrangements by modelling involved exo-cavity binding with the cation being held by the ester groups and this is consistent with the UV spectra where no changes were seen above 400 nm. With the *rctt* resorc[4]arene **37b**, again complicated binding is observed involving formation of unstable complexes prior to stable complexes. This diastereoisomer does not form an obvious cavity with opposite aromatic residues but rather one featuring a combination of aromatic and ester binding sites at each face. The lowest energy structures from modelling show the cation binding above the plane of the two horizontal aromatic rings and between the vertical aromatic rings and the two ester groups. Such a binding mode is consistent with the UV results which show the formation of a charge transfer band between the cation and the aromatic ring. The crucial role of the macrocycle in enabling binding of the cation was proved by the lack of spectral changes on treatment of the cinnamic acid precursor with nitrosonium cations.

The alkali metal binding properties of *O*-alkyl pyrogallorene **90** [38] (Fig. 10) have been investigated through competitive ESI mass spectrometry. The ligand was caesium selective, showing 70 fold higher binding than for lithium. Molecular modelling studies predict that this binding is through a combination of interactions at the OMe groups and π–cation interactions with the aromatic rings. When incorporated into an ion selective electrode, binding selectivity is less clear, however, and whilst caesium is indeed bound better than the other alkali metals, the best binding is seen with the guanidinium cation which may be a result of additional hydrogen bond interactions with the methyl ethers.

Binding of strong electron acceptors

The ability of both *C*-alkylated resorc[4]arenes **4a**, **b** and parent pyrogallorenes **90** to bind strong electron acceptors, such as tetracyanoethylene, tetrachlorobenzoquinone and tetracyanoquinodimethane, has been studied using UV

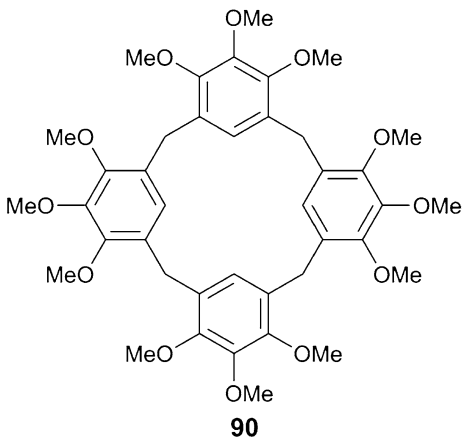


Fig. 10 *O*-alkyl pyrogallorene

spectroscopy. Charge transfer band formation is apparent in the 1:1 complex of tetracyanoethylene with both the *rccc* cone ($K = 4.00\ M^{-1}$, 25 °C) and *rctc* 1,2-alternate ($K = 2.92\ M^{-1}$, 25 °C) diastereoisomers of **4**, and the different wavelengths, 705 and 738 nm respectively indicate that the shape of the macrocycle can have an effect on how the molecules are bound [53]. Whilst these charge transfer bands are considerably different for the macrocycle compared to 1,3-dimethoxybenzene, this is less apparent when tetrachlorobenzoquinone is used and the complex formation constants are much lower ($K = 0.68\ M^{-1}$, 25 °C *rccc* cone, $K = 0.49\ M^{-1}$, 25 °C *rctc* 1,2-alternate). With tetracyanoquinodimethane no complex is formed with the 1,2-alternate diastereoisomer **4b** and only weak charge transfer bands are seen with the cone **4a**. As ^{1}H NMR shows no significant changes on binding of the electron acceptors, no prediction of binding mode could be made, however, molecular modelling studies on an *O*-alkyl resorc[4]arene with no *C*-alkyl substituents suggested that the charge transfer complex occurs externally to the cavity. With **53** [38], again only addition of tetracyanoethylene resulted in distinct changes to the UV spectrum and these could be fitted to the formation of a 1:1 complex ($K = 6.49\ M^{-1}$, 25 °C) which was also proposed to be through an external binding mode.

Synthesis of chiral ligands

The *rctc* 1,2-alternate diastereoisomer of **82** is particularly interesting as whilst two of the side chain alcohols can be considered equivalent the other two are in distinct regioisomeric positions. Botta and co-workers [54] exploited the selectivity of the lipase enzyme to selectively introduce an ester group at one of the alcohols, at the C2 position, in a range of organic solvents, and were able to show that even on prolonged treatment of the mono-acylated derivatives only 10% of a racemic diacylated material, in which the second acylation occurs at one of the equivalent C8 or C20 positions, could be isolated. These results are consistent with molecular modelling docking studies where three of the four side-chains are resident in the enzyme active site, with the C2 chain closest to the catalytic triad, and the fourth C14 side chain points out of the binding site.

The ready synthesis of valine appended resorc[4]arenes (Fig. 11), as different diastereoisomers, in a one-step reaction from the cinnamic acid precursor, has resulted in these chiral derivatives being extensively investigated for their enantioselective binding [55–61]. These studies have focused on the use of gas phase ligand displacement reactions between protonated complexes of the host and guest and a suitable base, either (*S*)-(+)-but-2-ylamine or (*R*)-(−)-but-2-ylamine, using ion cyclotron resonance mass spectrometry. This technique offers the opportunity, in

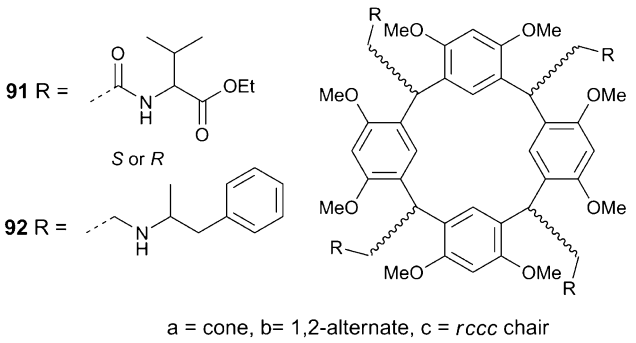


Fig. 11 Enantioselective hosts

particular, to observe binding interactions for poorly soluble hosts and guests where ^{1}H NMR studies are not possible. A wide range of amino acids and neurotransmitters have been studied with the *rccc* cone derivative **91a** and can be classified into three distinct types. The first type is those amino acids which feature no additional functionality, such as alanine, where the guest molecule is held on the external surface of the receptor and any enantioselectivity is dependent on the attack of the amine. In the second type, where the amino acids feature additional hydroxyl functionality, such as in serine, the enantioselectivity is a result of the greater stability of the heterochiral complex in which the guest is held within the cavity compared to the homochiral complexes where the guest is held externally. In the final class the amino acids or neurotransmitters feature additional aromatic and hydrogen bonding functionality, such as tyrosine, and their enantioselectivities are more complex as a consequence of two different structures of the complex where the guest is held in either the upper-rim cavity or in the lower-rim cavity. A particularly interesting example of this is the binding of tryptophan, where an enantioselective allosteric effect is observed on binding of the amine [57]. Tryptophan can bind both at the lower-rim where it is stabilized by H-bonding interactions or at the upper-rim where π–π interactions and an H-bonding interaction between the side-chain NH and the methoxy groups at the resorc[4]arene upper-rim create a binding site. In the upper-rim case, such binding does not affect the hydrogen-bond array between the valines at the lower-rim and the guest can only be expelled by the base disrupting this binding, which surprisingly shows a pronounced enantioselectivity, and thus exerting a conformational change on the upper-rim.

Broadening these studies to the other two readily available valine appended resorc[4]arenes, the *rctc* 1,2-alternate **91b** and the *rccc* flattened partial cone **91c** some differences in binding were observed indicating that both the spatial arrangement of the side chains and the cavities available affect binding [57]. Unlike the *rccc* cone which features two binding sites, complexes with the *rctc*

1,2-alternate show only one regioisomer, suggesting only one possible binding site, and displacement from this exhibits little enantioselectivity whereas the *rccc* chair again shows some discrimination and two potential binding sites. The importance of the carbonyl groups in binding has been demonstrated by the preparation of chiral amine derivatives **92** [49] which showed no ability to bind a selection of amino acids in ESI mass spectrometry experiments.

These enantioselective binding studies have been extended to dipeptides through the preparation of a series of *rccc* cone hosts featuring complimentary N-linked dipeptide units at the lower rim **93**, **94** (Fig. 12) [62]. It is interesting to note that the ability of these molecules to act as effective hosts can be seen during their synthesis where on treatment of the acid chloride with an excess of dipeptide, the resulting product, even after column chromatography, includes complexed dipeptide which can only be removed by heating at reflux in methanol. These hosts exhibit, through a broadening of the OMe ^{1}H NMR signals, a slower exchange, between the two flattened cone conformations than for the ester functionalised derivatives **32**. ^{1}H NMR solution binding studies demonstrated a high degree of enantioselectivity with the association constant for the homochiral **93a**:**96a** complex being 10 fold higher than for the heterochiral **93a**:**96b**. ROSY NMR studies for the homochiral complex showed that the interaction occurs through hydrogen bonding and at the external surface of the host as irradiation of the leucine CH of the guest not only affects the CH of the leucine and valine of the host but also of the upper-rim aromatic proton. In contrast, in the gas phase no selectivity could be observed in ESI-MS experiments and whilst there is evidence for both 1:1 and 1:2 host:guest complexes the host preferentially binds sodium cations.

Chiral bridged receptors could also be expected to offer a degree of enantioselectivity in their binding with chiral guests [63]. Four *rccc* flattened cone chiral amide bridged receptor **97**, **98** (Fig. 13) have been prepared and their

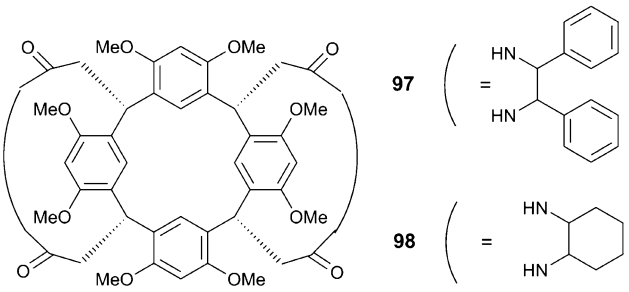


Fig. 13 Lower-rim bridged hosts

solution structure investigated by both ^{1}H NMR and molecular modelling studies. These studies indicate that whilst the conformation of the resorc[4]arene is unchanged, the bridges can be orientated in low energy open wing, mixed wing and folded wing conformations and that the structure most likely to be taken up in solution differs with receptor **97** being more flexible and adopting the more convergent folded wing and receptor **98** the open wing conformation. Collision-induced decomposition spectra in ESI were used to investigate gas phase binding on preformed host:guest complexes with tryptophan, tyrosine methylester and amphetamine. Whilst no difference was seen between the diastereoisomers of tryptophan, the homochiral complex of tyrosine methylester was considerably more stable than the heterochiral complex whereas the reverse is seen for the amphetamine complex with the heterochiral complex proving more stable.

This interesting result obtained with amphetamine, and the complex biological roles of its two diastereoisomers, led to a further binding study with the previously prepared mono **91** and dipeptide derivatives **93**, **94** [64]. Using ligand displacement FT-ICR experiments, two of the hosts were shown to be highly enantioselective, **91*S*** and **93b** with the homochiral complexes being destroyed more slowly than the heterochiral complexes. Molecular

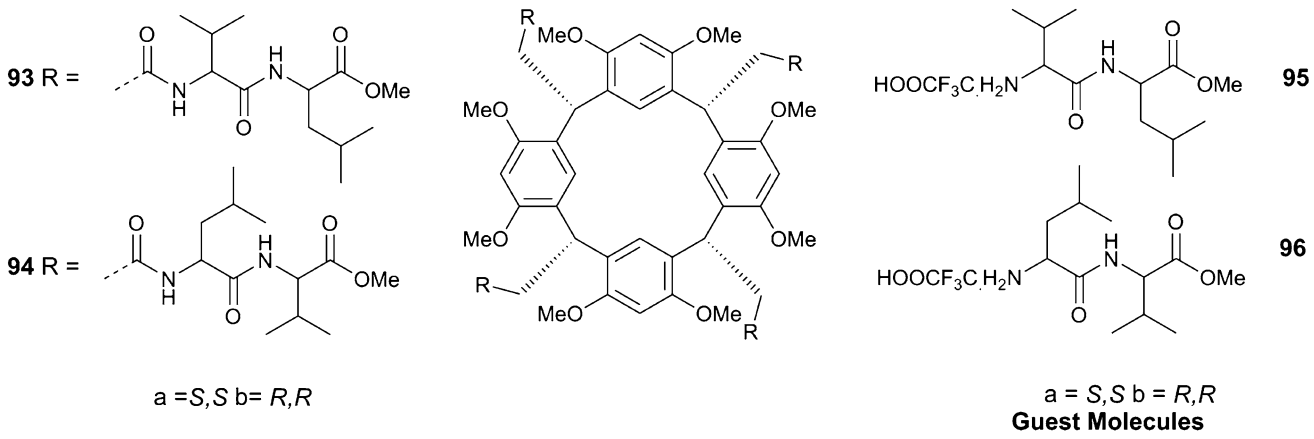


Fig. 12 Dipeptide hosts

modelling studies on the **91*S*** complexes indicated that whilst in the heterocomplex the binding occurs externally to the resorc[4]arene, in the case of the homochiral complex two different structures are possible, both an external binding mode and also a second structure in which the aromatic ring is located within the lower cavity formed by the four peptide residues. In the case of both selective hosts the first residue in the chain is valine and it is proposed that the selectivity is a result of the amino acid binding to the carbonyl of the first residue and thus that the displacement by but-2-ylamine is affected by the environment around the carbonyl. The same panel of receptors has been recently evaluated for binding of the two subunits of the vinca alkaloids. which are powerful cytotoxic agents used in chemotherapy, in an effort to elucidate further the dimerisation of the subunits in vivo [65]. Whilst, slight enantioselectivities were observed in the binding of the catharanthine and vindoline subunits by the majority of the host molecules, one result was particularly striking, the interaction between **97** and catharanthine showed a 17 fold selectivity with the heterochiral complex decaying more slowly than the homochiral complex. Docking studies, *in silico*, led to the identification of global minima for both the hetero- and homo-chiral complexes, in which the catharanthine is bound in the lower-rim cavity provided by the chiral ligands and the protonated nitrogen of the guest forming a hydrogen bond to a carbonyl residue. Whilst, the two complexes show these commonalities, the orientation of the guest is very different within this site and it is proposed that this can alter the ease in which the but-2-ylamine can enter the cavity and displace the guest.

Despite these extensive studies on chiral recognition by octa-*O*-alkyl resorc[4]arenes, to date, this has not a reached a predictive level and thus each potential guest provides significant insights into how the receptor can bind guest molecules and on the relative stabilities of the resulting complexes.

Applications of partial *O*-alkylated derivatives

The identification of a rapid synthetic route for the formation of tetra-*O*-alkyl *rccc* cone resorc[4]arenes has led to their use in a variety of applications. As a consequence of their defined stereochemistry they offer interesting platforms for further selective functionalisation of the free hydroxyl groups and the preparation of receptors.

Cation binding

Nissinen and co-workers [66, 67] have used tetra-*O*-methyl derivatives in the preparation of bis crown molecules suitable for investigating the synergistic role of the crown either and resorcarene cavity in cation binding (Fig. 14). The synthesis of the bis crowns was achieved by alkylation with the ditosylates of the relevant ethylene glycols and resulted in a conformational change in the resorc[4]arene forcing the skeleton to adopt a flattened cone conformation as shown by X-ray crystallography and ^{1}H NMR studies. From ^{1}H NMR titration studies with PF_6 salts, **100** was shown to be able to bind potassium, rubidium and caesium at high ion concentrations and picrate extraction studies indicated a four-fold selectivity for the larger two cations, whereas **99**, with a smaller crown unit, was unable to bind any of the alkali metals. Changes in the resorc[4]arene NMR peaks suggested that the cavity was involved alongside the crown ether oxygens in binding these cations a conclusion that was strengthened by the identification of cation-aromatic and cation-methoxy oxygen interactions in a crystal structure of the di-potassium complex.

No binding of sodium was observed by ^{1}H NMR and a crystal structures showed the sodium to be bound outside of the cavity. By incorporating an additional aromatic ring [67], capable of cation–π interactions, into the crown unit, further selectivity towards larger cations could be achieved with **101** showing no extraction of potassium, and a 16-fold selectivity for caesium over rubidium.

Tetra functionalisation with either 2- or 3-picoyl groups, for binding of transition metals, was achieved in high yields using standard Williamson ether conditions (Fig. 15) [68]. Again, removal of the hydrogen-bond array results in the resorc[4]arene adopting a flattened cone conformation in the solid state. Whilst, interactions between the picoyl groups and zinc, palladium and silver occur, their exact nature is not apparent, in contrast both the 2- and 3-picoyl

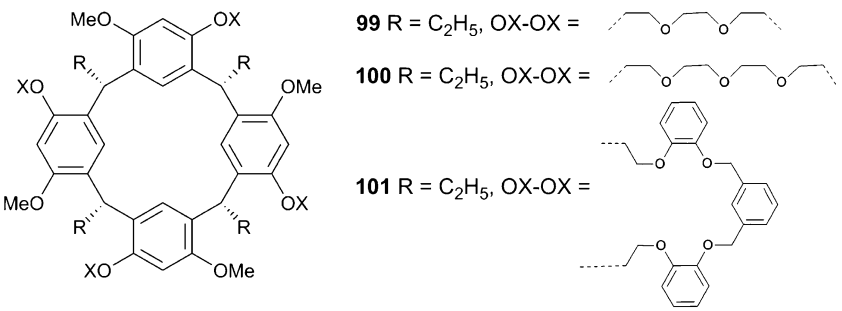


Fig. 14 Crown bridged resorc[4]arenes

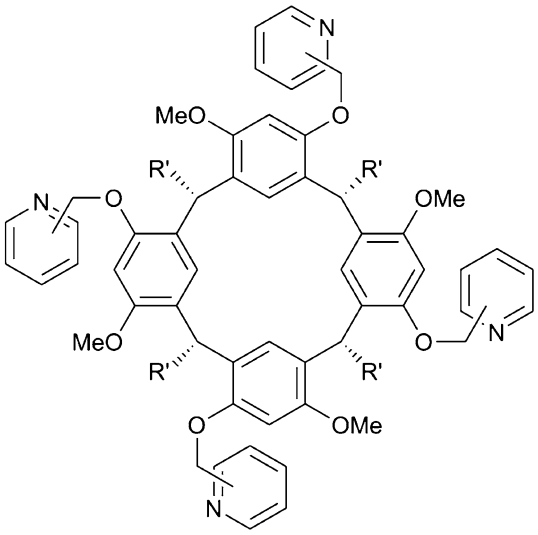


Fig. 15 Picoyl appended resorc[4]arenes

functionalized resorcarenes are able to extract copper(II)acetate from a dichloromethane solution and a crystal structure was obtained for **104** which indicated that a linear polymer of resorcarenes is formed through picoyl-copper bridges.

Synthesis of chiral ligands

The establishment of the absolute configuration of the C_4 tetra-*O*-alkyl resorcarenes has led to the synthesis of a range of other chiral derivatives which have potential to act as ligands.

Heaney and co-workers have explored Mannich reactions for the formation of optically pure resorc[4]arene derivatives, and in an initial approach [69], first formed tetrabenzoaxazines at the 2-position with chiral (α-methylbenzyl)amines and formaldehyde, before methylation of the free hydroxyl groups to prevent diastereomerisation after ring opening. However, this approach did not prove reliable for a number of amines and did not allow the introduction of alkyl groups larger than ethyl. Thus an approach starting from the tetra-*O*-alkyl resorc[4]arene [70] should allow access into a wider range of derivatives e.g. **105** (Fig. 16). Whilst standard Mannich reactions failed with these derivatives, possibly as a result of the OH being considerably less acidic than in octahydroxy resorc[4]arenes, when the conditions are changed, to involve heating for a prolonged time period with a large excess of bis-(aminol) ethers, the benzoxazines can be formed. These derivatives, once separated into their single diastereoisomers by chromatography, were assessed as ligands in the

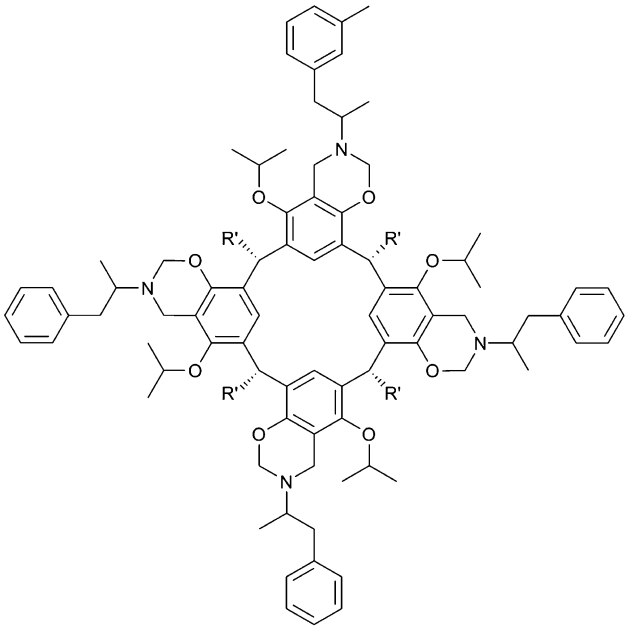


Fig. 16 An example of a benzoxazine

ligand-assisted addition of diethylzinc to aromatic aldehydes and it was evident that the enantioselectivity of the reactions was affected by the *O*-alkyl substituent with isopropyl groups giving the highest enantiomeric excesses and methyl the lowest and by the resorc[4]arene cavity as a low enantiomeric excess and lower yield were achieved with a single benzoxazine ligand.

Both the groups of Mattay [42] and Heaney [70] have introduced amides to the free hydroxyl positions of tetra-*O*-

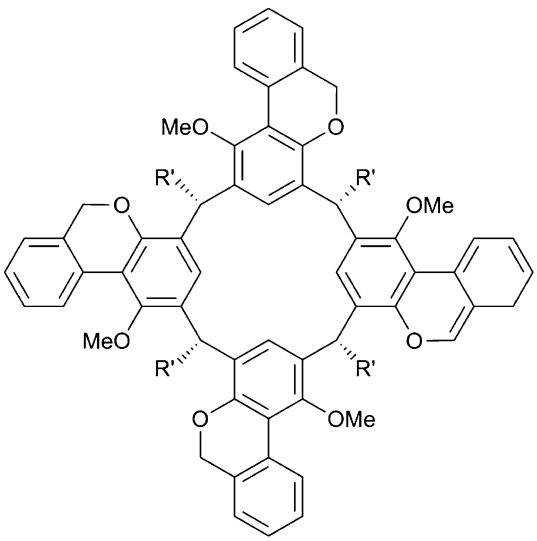


Fig. 17 Extended cavity resorc[4]arenes

methyl resorc[4]arene, either through initial introduction of a methyl ester using 2-bromoethylacetate followed by aminolysis with enantiomerically pure phenylethylamine or by direct treatment with 2-bromo-N-[(R)-(+)-(α-methylbenzyl)acetamide]. The preparation of stable, extended cavity, chiral resorc[4]arenes e.g. **106** (Fig. 17) through the synthesis of benzoxazines by palladium C–C cross coupling reactions has also proved possible by using tetra-*O*-methyl derivatives [71]. Additionally, the potential of such chiral molecules to act as chiral dendrimer cores has been investigated through the introduction of Fréchet-type dendron repeating units to the free phenolic groups via an [18] crown-6 catalysed alkylation reaction [72].

Conclusion

This emerging field of direct synthesis of *O*-alkyl functionalised resorc[4]arenes offers considerable potential in the preparation of ligand platforms for selective binding of a range of guest molecules. Two recent significant synthetic advances stand out. Firstly, the development of selective conditions for the preparation of single diastereoisomers of *O*-alkyl resorc[4]arenes has opened up the possibility of preparing a diverse series of ligands in which orthogonal addressable functionality can be built into the macrocycle simply at the cyclisation step. Secondly, the straightforward synthesis of C_4 symmetric tetra-*O*-alkyl resorc[4]arenes, and their subsequent separation, resulting in chiral host molecules offers the prospect of ligand platforms ideal for probing biological interactions.

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