Introduction to the Chirality of Resorcinarenes

Waldemar Iwanek* and Alicja Wzorek

Institute of Chemistry, Jan Kochanowski University in Kielce, Świętokrzyska 15G, 25-148 Kielce, Poland

Abstract: Resorcinarenes constitute a very attractive class of macrocycles possessing a cavity capable of complexing small molecules. They can be simply transformed into chiral derivatives by functionalisation of their hydroxy groups as well as the "*ortho*" position at the resorcinol ring. The appropriate modifications lead to various chiral resorcinarene derivatives. The chirality of these compounds results from their structure (the axial chirality) or from the presence of chiral auxiliaries. Moreover, the synthesis of chiral resorcinarene derivatives from chiral substrates is also possible. In this short review, we wish to present the strategies and methodology of the synthesis of chiral resorcinarenes, treating this article as an introduction to the chirality of resorcinarenes.

Keywords: Calixarene, Resorcinarene, Chirality, Symmetry.

1. INTRODUCTION

Resorcinarenes **1** belong to the class of macrocycles called calixarenes [1-4] which are formed in the reaction of resorcinol or its derivatives with an aliphatic or aromatic aldehyde [5]. The methods of synthesis of resorcinarenes, potential possibilities to use these compounds as synthetic receptors as well as selected examples of their applications in chromatography were described in the literature [6, 7]. A general molecular structure as well as the cavity pattern of these compounds is shown in Fig. (**1**).

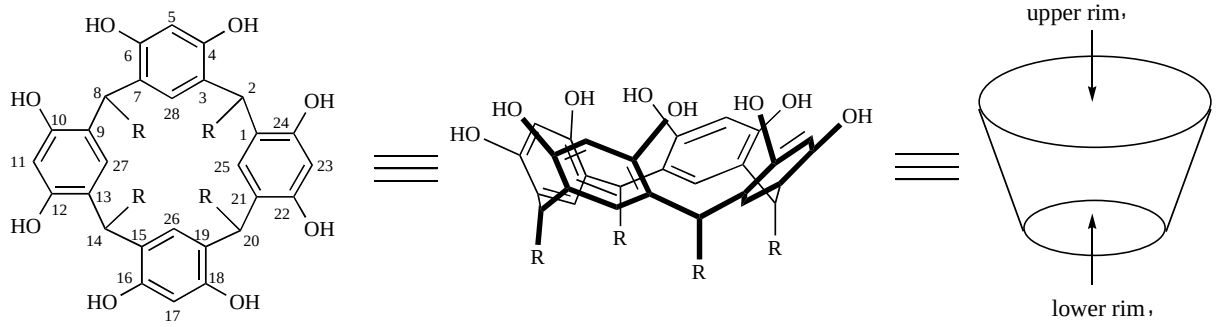

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Fig. (1).

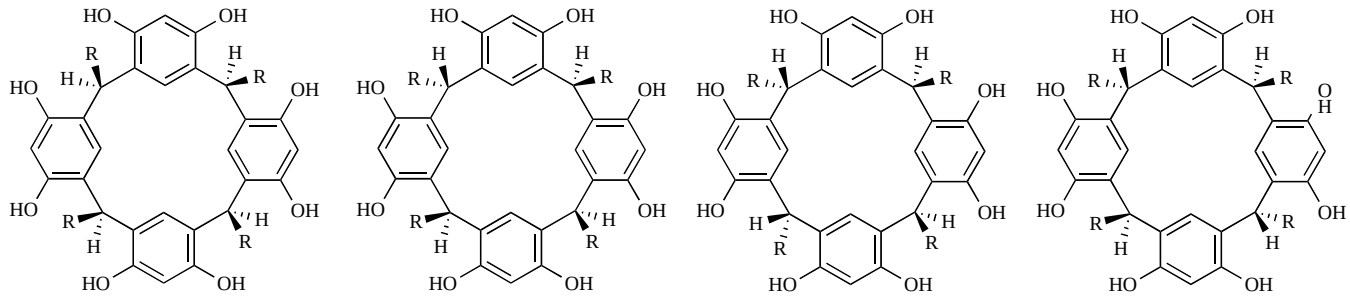

Fig. (2).

Resorcinarenes possess four prochiral centres at the bridging carbon atoms and, consequently, can exist in four different diastereomeric forms, as shown in Fig. (**2**). For the purpose of analysing the stereochemical relationships between the prochiral centres, the macrocyclic ring may be considered to be planar with the residues R of the CHR-bridges pointing to the same or the other direction. Having assigned one of these residues at a prochiral centre as the reference group (*r*) and then proceeding clockwise around the ring, one can designate the residues R of the consecutive groups as being *cis* (c) or *trans* (t) with relation to the reference group (*r*). The reference group (*r*) is chosen so as to maximise the number of *cis* (c) designations [8].

Actually, resorcinarenes are not planar and can exist in a variety of conformations, as illustrated in Fig. (**3**). In practice, the *r*ccc isomers have always been found to have either the C_4 symmetrical "*crown*" conformation or the C_{2v} symmetrical "*boat*" conformation; the *r*ctt isomers have been found only of the C_{2h} symmetry "*chair*" conformation; the *r*cct isomer adopts the C_s symmetrical "*diamond*" conformation, while the *r*tct isomer is predicted to adopt the S_4 symmetrical "*saddle*" conformation.

*Address correspondence to this author at the Institute of Chemistry, Jan Kochanowski University in Kielce, Świętokrzyska 15G, 25-148 Kielce, Poland;
E-mail: Waldemar.Iwanek@pu.kielce.pl

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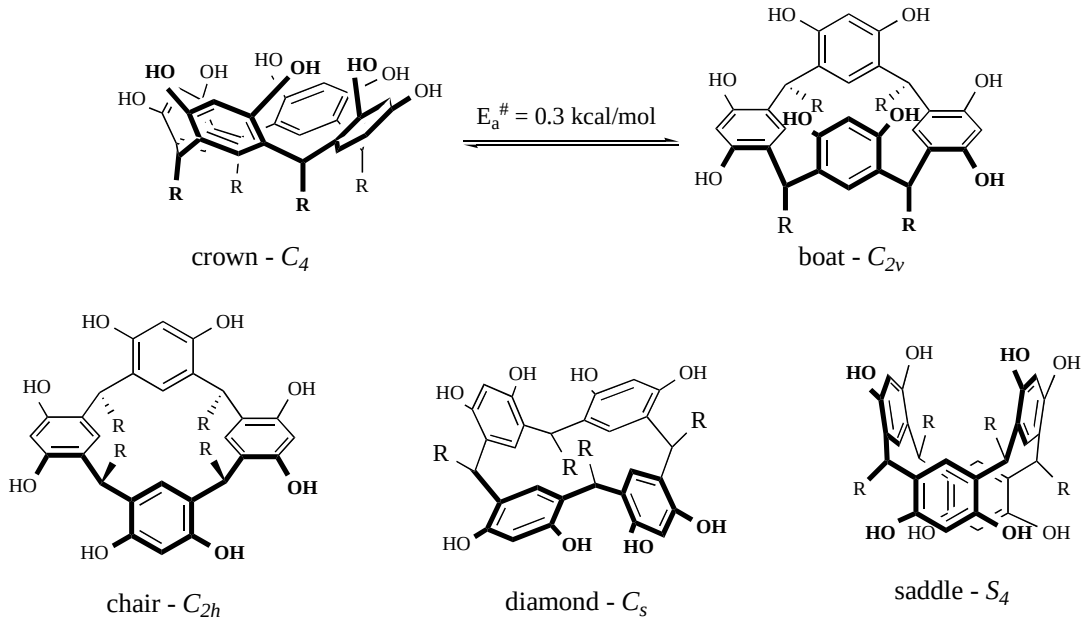


Fig. (3).

The conformations and conformational interconversions of the resorcinarene **1** have been studied by the molecular mechanics calculations (MM3) [9]. The lowest calculated energy corresponds to the boat conformer having the C_{2v} symmetry stabilised by intramolecular hydrogen bonds of two "*parallel*" resorcinol units as donors. The C_4 symmetrical structure represents the transition state of the $C_2 \leftrightarrow C_2$ pseudo-rotation for which a barrier of only 0.3 kcal/mol is calculated.

The presence of so many active sites makes such molecules a convenient platform for the synthesis of new types of macrocycles. Their relatively simple chemical modifications can provide a great number of derivatives having predetermined stereochemical properties. The structure of these molecules creates many options for the synthesis of new chiral derivatives by functionalisation of the hydroxy groups and the "*ortho*" position of the molecule. The chirality of the chiral resorcinarenes can result from their spatial structure (axial chirality) or from the presence of chiral auxiliaries.

The resorcinarenes, along with their plenty of non-covalent interactions, including hydrogen bonds, hydrophobic interactions, charge-transfer interactions, arene-cation interactions, ion-dipole interactions, and so on, can be excellent models of chiral receptors for biological mimicry.

The search for new effective supramolecular systems exhibiting selective differentiation plays currently, and certainly will play in the future, the more and more important role because of increasing demands for pharmaceutical compounds, pesticides, as well as foodstuffs. Besides, these compounds can be used for the synthesis of receptors interacting selectively with tumour markers. Simple and diverse modifications of these compounds allow us to believe that we will see the further progress in their synthetic methodology (including chiral derivatives) as well as many novel applications of these compounds.

In this short review, we try to systematise the knowledge about chiral resorcinarenes, focusing our attention on the possible types of chiral resorcinarenes.

2. THE GENERAL METHOD OF SYNTHESIS OF CHIRAL RESORCINARENES

From among the several possible conformations of resorcinarenes, the crown conformer is the most attractive one for functionalisation due to the possibilities of forming various chiral derivatives having a cavity which could hold small molecules.

The chiral resorcinarene derivatives can be obtained by two methods.

1. The first one consists in transformation of resorcinarenes into the derivatives having no stereogenic centre at all, where their optical activity is a consequence of their spatial structure associated with the C_1 symmetry ("inherently chiral"), C_2 or C_4 symmetry;
2. The second one consists in the synthesis of chiral resorcinarene derivatives from chiral substrates: a) chiral derivatives of resorcinol; b) chiral aldehydes, or c) modification of an achiral form of the resorcinarene by introduction of chiral auxiliaries.

Because of the presence of active sites suitable for further modification, it is possible to introduce the chiral auxiliaries into the upper rim of the resorcinarene platform. As a result, the macrocycle cavity can be increased. Such a functionalisation can be performed by modification of a definite number of hydroxy groups or the "*ortho*" positions in the resorcinarene molecule. The appropriate choice of reagents and reaction conditions enables also the asymmetric synthesis, leading to chiral resorcinarene derivatives.

3. THE STEREOCHEMICAL NOMENCLATURE FOR THE COMPOUNDS OF AXIAL SYMMETRY

There are several possible types of functionalisation of the resorcinarene structure due to the presence of hydroxy groups as well as the "*ortho*" position what leads to a broad range of chiral resorcinarene derivatives, including also the axially chiral (structurally chiral) derivatives. The nomenclature and the stereochemical designation for this class of compounds were not consistent. Due to a different viewing of the resorcinarene structure - from a position inside, outside or above the cavity - many authors differently described the axial chirality or the direction of closing new heterocyclic rings in the resorcinarene derivatives obtained by modifications of the hydroxy groups and/or the "*ortho*" positions. In 2006, Heaney and co-workers [10, 11] proposed a standardisation of stereochemical designation for the resorcinarene derivatives. The most important rules of the stereochemical designation for the resorcinarene derivatives are explained using, as an example, a resor-

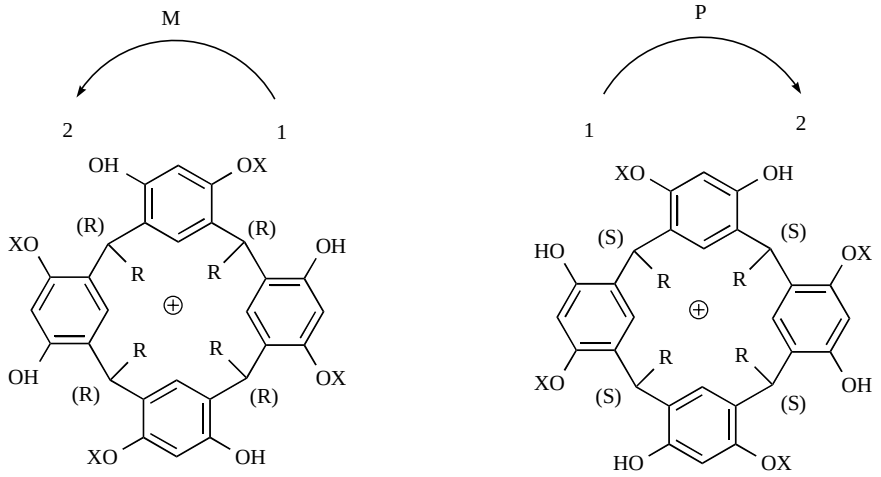


Fig. (4).

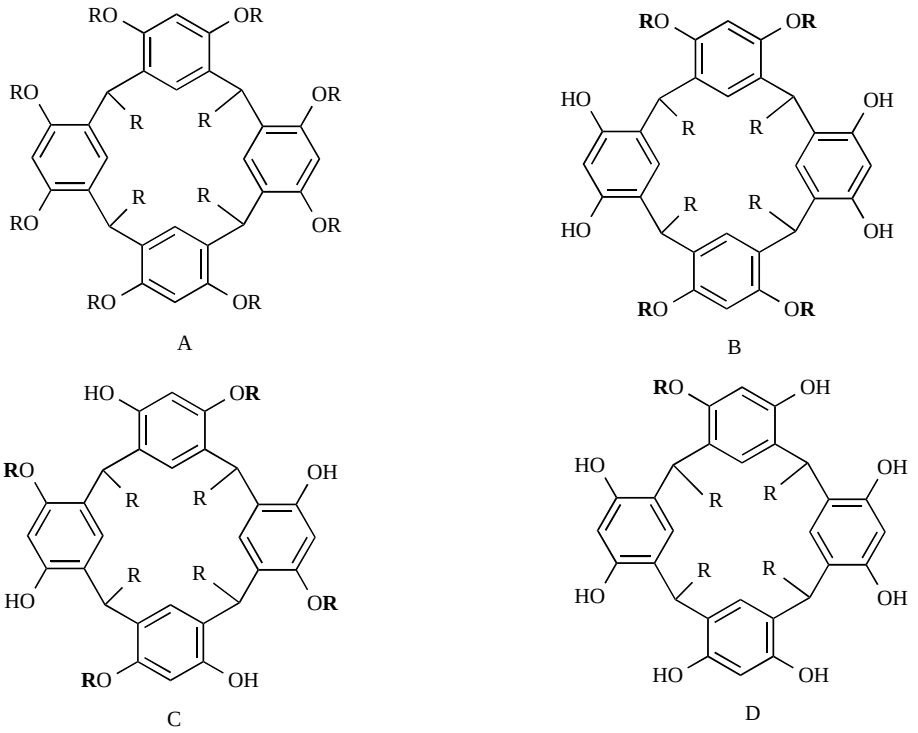


Fig. (5).

cinarene molecule bearing four functionalised hydroxy groups, one per each resorcinol unit, what makes such a compound axially chiral with the C_4 symmetry, as illustrated in Fig. (**4**).

As shown in Fig. (**4**), in order to make the stereochemical designation of the C_4 symmetric resorcinarenes, we determine consequently: 1) the priority of the substituent groups at the upper rim around the axis of symmetry viewed from a position above the cavity (axial chirality) - either *M* or *P*; 2) the configuration of the chiral auxiliary; 3) the configuration of the carbon atoms at the bridge connecting the resorcinol units in the lower rim. The *P* and *M* notation is used to define the axis of chirality of C_n symmetric resorcinarenes. By definition, a clockwise priority of the sequence of groups, that are attached to the phenolic groups, is named the *P* axial chirality. Correspondingly, when the priority of substituents is counter-clockwise, we use the notation *M*. In the case of derivatives, in which the formed ring can be oriented outside or inside the resorcinarene cavity, we use the prefixes "*out*" for outside and "*in*" for inside the cavity, respectively.

In the next part of this review, we will use the stereochemical nomenclature of C_4 symmetric compounds as described above.

4. FUNCTIONALISATION OF THE HYDROXY GROUPS IN THE RESORCINARENE MOLECULE

Resorcinarenes are the macrocycles characterised by a significant reactivity. One of the reasons for that is the presence of the hydroxy groups in resorcinarene structure which, in combination with the suitably selected reagents, yields various new derivatives having new physicochemical properties. The hydroxy groups play also a crucial role in the stabilisation of the crown conformation. A modification of the hydroxy groups can be achieved by transformation of all eight hydroxy groups (A); four hydroxy groups (B, C) or only one hydroxy group (D).

The general possibilities of the modification of the hydroxy groups are shown in Fig. (**5**).

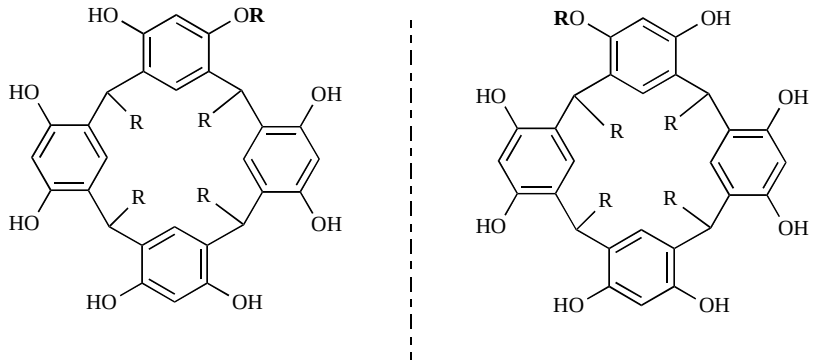
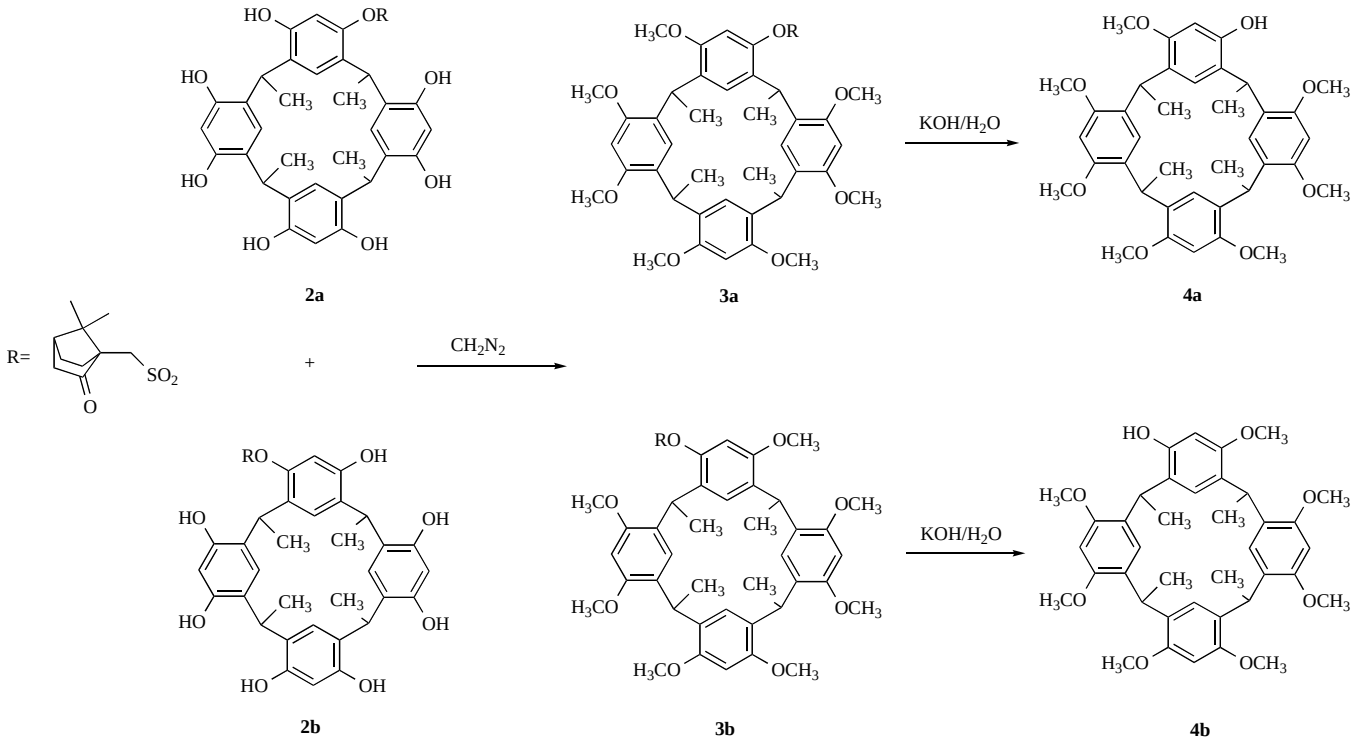


Fig. (6).



Scheme 1.

4.1. Functionalisation of one Hydroxy Group in the Resorcinarene Molecule

Modification of one resorcinol unit in the achiral form of the resorcinarene **1** makes that molecule chiral and having the C_1 symmetry (Fig. **6**) [12], often being called "*inherently chiral*". The optical activity of such compounds is not a result of the presence of groups having stereogenic centres; it results from their spatial structure. The molecule as a whole has neither a plane of symmetry, an inversion centre, nor an alternating axis of symmetry.

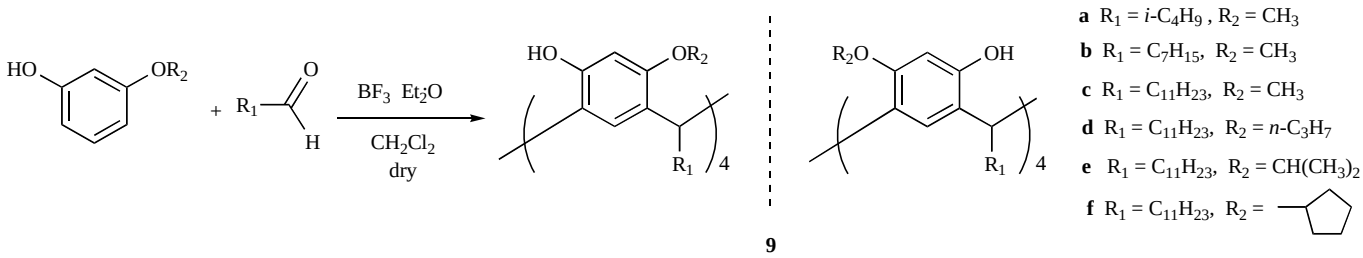
Many examples of functionalisation of only one out of eight available OH groups are known in the literature [13]. Monofunctionalisation of the crown conformer of resorcinarene **1** was carried out using the optically active (*S*)-(+)-camphorosulphonyl chloride and gave a mixture of two diastereoisomers **2a** and **2b**, which was separated by HPLC [14]. The separated diastereoisomers **2a** and **2b** were reacted with diazomethane, what resulted in the hepta-*O*-methyl substituted derivatives **3a** and **3b**. The enantiomerically pure „inherently chiral" resorcinarenes **3a** and **3b** were synthesised by subjecting the hepta-*O*-methyl resorcinarene derivatives **4a** and **4b** to alkaline hydrolysis (Scheme **1**).

4.2. Functionalisation of Four Hydroxy Groups in the Resorcinarene Molecule

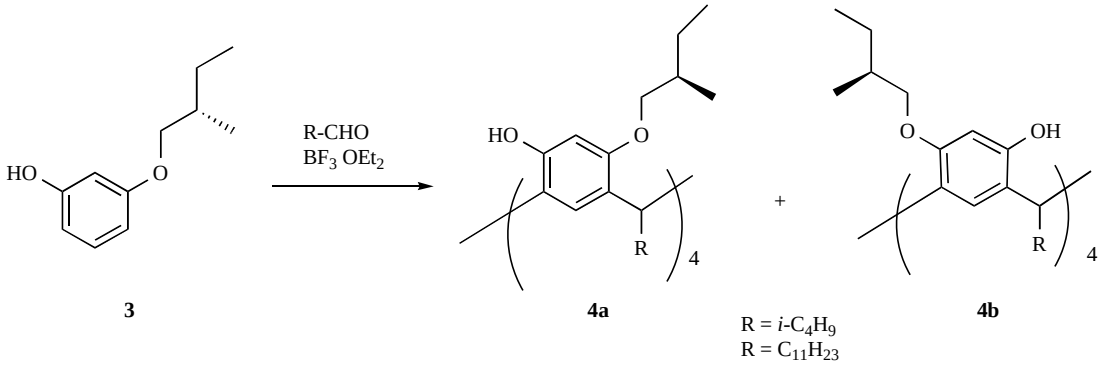
The possible routes for functionalisation of four hydroxy groups are shown in Fig. (**4**). Two approaches are possible to obtain resorcinarenes having four modified hydroxy groups:

1. The first method converts the starting resorcinarene **1** into a resorcinarene derivative having the C_{2v} symmetry, in which the hydroxy groups at two opposite resorcinol units are modified (Fig. **5B**);
2. The second method consists in condensation between the mono-substituted resorcinol derivatives and the aldehydes. The product having the C_4 symmetry (Fig. **5C**) is obtained as a racemic mixture, in crown conformation which is stabilised by hydrogen bonds (Scheme **2**). Such compounds are characterised by only one modified hydroxy group at each resorcinol unit. Typically, the condensation is catalysed by Lewis acids [15].

This method of synthesis is useful for preparing the structurally chiral tetra-*O*-substituted resorcinarene derivatives [16]. In the case, when the condensation reaction employs the chiral 3-[(2*S*)-2-



Scheme 2.



Scheme 3.

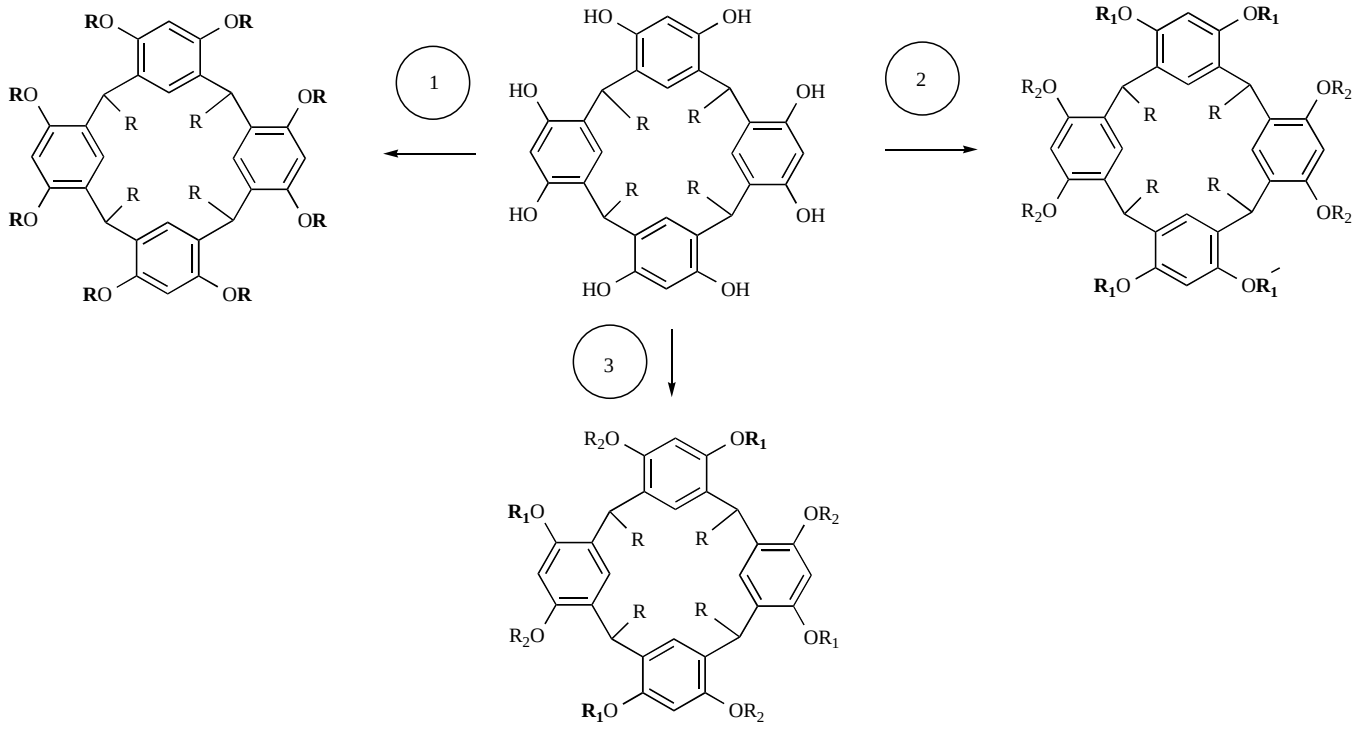


Fig. (7).

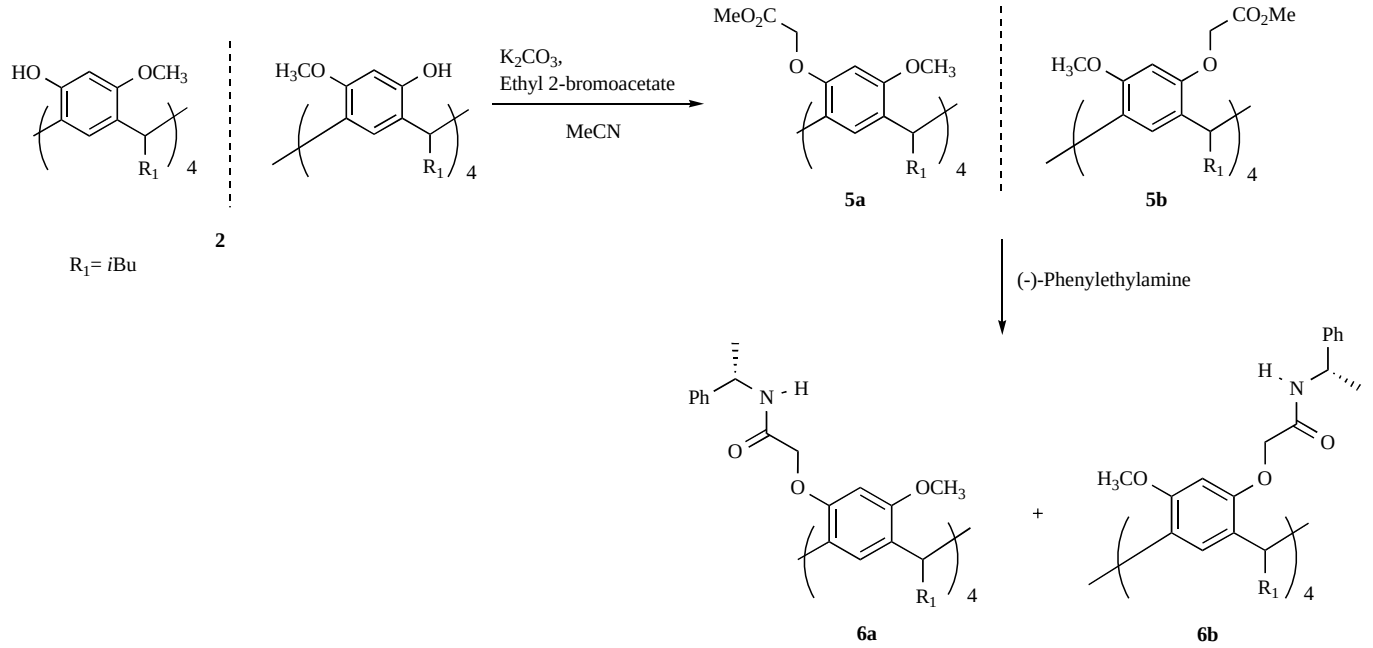
methylbutoxy] phenol **3**, one step yields a mixture of two diastereoisomeric tetra-*O*-(2-methylbutyl)resorcinarenes **4a** and **4b**, which can be easily separated by HPLC (Scheme **3**) [17].

4.3. Functionalisation of Eight Hydroxy Groups in the Resorcinarene Molecule

There are several possible routes of transformation of resorcinarenes involving all eight hydroxy groups in the resorcinarene structure, as shown in Fig. (**7**).

1. The first method of functionalisation consists in transformation of the hydroxy groups by introduction of chiral auxiliaries, either directly or indirectly - by initial transformation of hydroxy groups into, *e.g.*, ester derivatives followed by modification of these groups with chiral auxiliaries.

2. The second method consists in initial transformation of four hydroxy groups of the resorcinarene platform, and further modification of four other in the opposite resorcinol units. Similarly to the variant 1 above, this functionalisation may be carried out also di-



Scheme 4.

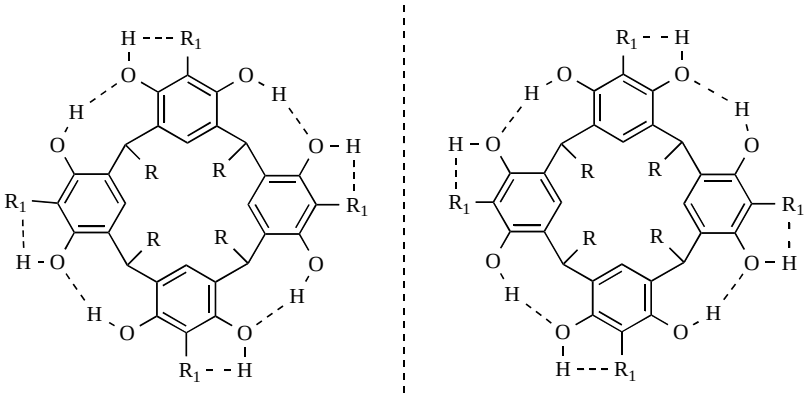


Fig. (8).

rectly or indirectly. Chiral derivatives of resorcinarene are obtained by introduction of chiral auxiliaries into four or eight positions.

3. The third method consists in the synthesis of the axially chiral resorcinarenes having the C_4 symmetry from the suitable substrates (see Fig. **5C**). Subsequent separation of the obtained racemic mixture provides the enantiomers having one free hydroxy group at each resorcinol unit. Further modification of these remaining hydroxy groups may be chiral or achiral. Chiral modification leads to diastereoisomers while achiral modification leads to chiral derivatives of resorcinarenes having the C_4 axial symmetry. This type of chirality is often called a "*cyclochirality*".

Examples of the synthesis of the resorcinarene derivatives having functionalised all hydroxy groups are also described in the literature [18-23].

Alkylation of a racemic mixture of tetramethoxyresorcinarene **2** with ethyl 2-bromo-acetate results in formation of a racemic mixture of octa-derivatives **5a** and **5b**. The subsequent aminolysis of this racemic mixture with chiral (-)-phenylethylamine yields two inherently chiral diastereoisomers, **6a** and **6b**, that can be separated by column chromatography (Scheme **4**) [24].

5. FUNCTIONALISATION OF RESORCINARENES AT THE "*ORTHO*" POSITION

The presence of two electron-donating hydroxy groups in the aromatic rings of resorcinarene renders the "*ortho*" position very susceptible to electrophilic aromatic substitution. Many electrophiles can be easily introduced at this position [25, 26]. The "*ortho*" substituent capable of forming intramolecular hydrogen bonds with the neighbouring hydroxy groups of the resorcinarene units enables formation of the chiral derivative, which has the C_4 symmetry. This is caused by formation of a cyclic structure giving rise to a racemic mixture of enantiomers classified as (*P*,..,*S*)- and (*M*,..,*R*)- *via* intramolecular hydrogen bonds – see Fig. (**8**).

The creation of the axially chiral resorcinarene derivatives by introduction of substituents into the "*ortho*" position capable of forming intramolecular hydrogen bonds with the neighbouring hydroxy groups of the resorcinarene units is not limited to the tetra-substituted resorcinarene only. It is theoretically possible also in the case of tri-substituted (A), di-substituted (B, C) and mono-substituted (D) resorcinarenes, as shown in Fig. (**9**).

In addition to the synthesis of the axially chiral resorcinarene derivatives ("inherently chiral"), the functionalisation of the "*ortho*" position by direct or indirect introduction of the chiral auxilia-

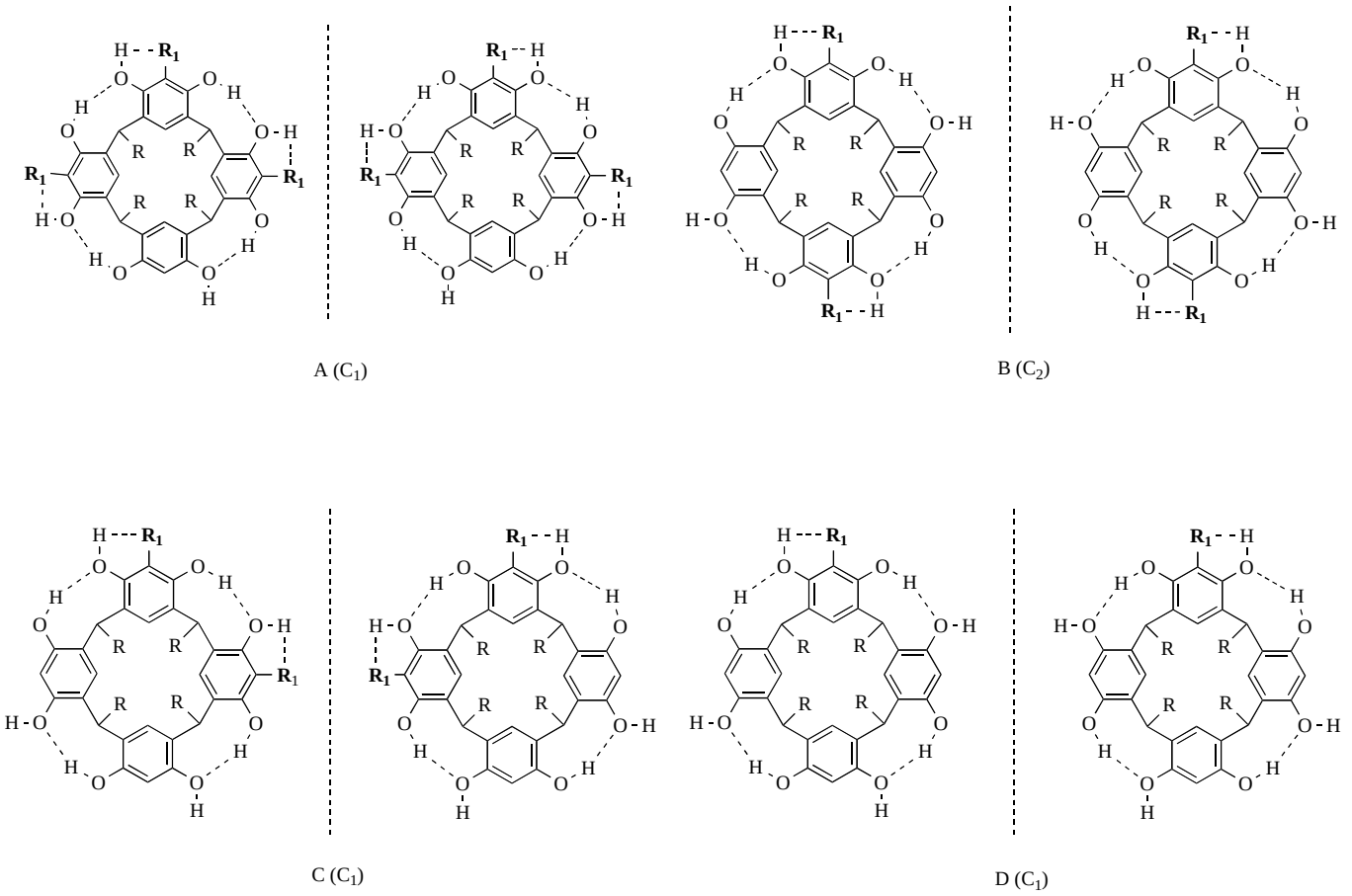


Fig. (9).

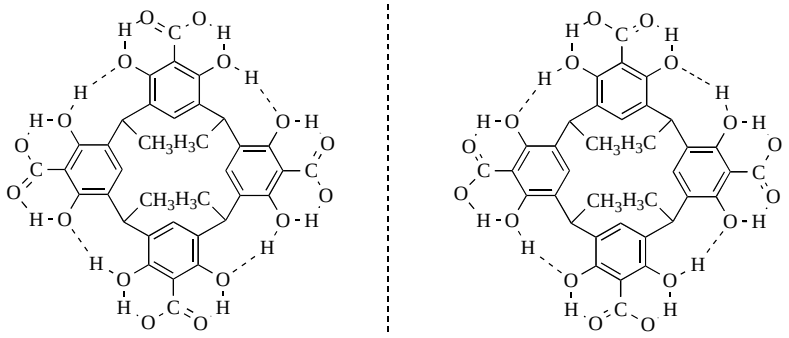


Fig. (10).

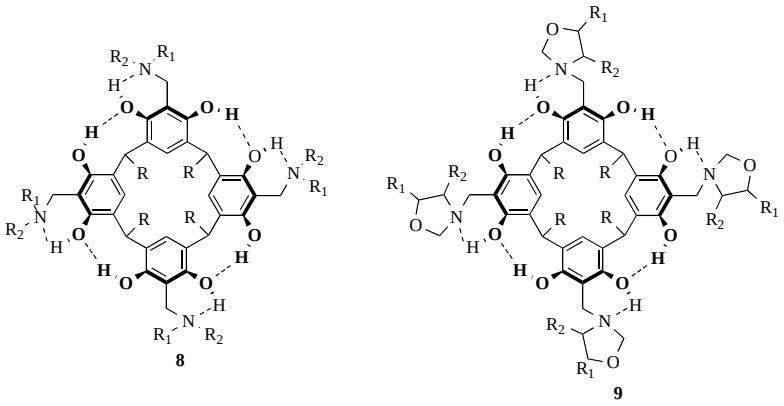
ries is also possible. The examples of resorcinarene derivatives having the modified "*ortho*" position are presented below.

An example of a chiral derivative with the C_4 symmetry is tetracarboxyresorcinarene **7**, obtained from 2-carboxyresorcinol and acetaldehyde [27]. The carboxy group of this derivative can participate in two types of intramolecular hydrogen bonds, as shown in Fig. (**10**).

The most frequently employed reaction of electrophilic substitution for resorcinarenes is the Mannich reaction. Depending on the type and amount of reagents used, various derivatives can be obtained. In the case of an achiral secondary amine, the aminomethyl derivative **8** having the C_4 symmetry is obtained (Fig. **10**). This conformation exists not only in the crystalline state but also in the solution, as confirmed by the ^{1}H NMR spectra. Two doublets of doublets resulting from diastereotopic protons of the Ar-CH_2-N group and two singlets of protons from phenolic hydroxy groups are observed [28].

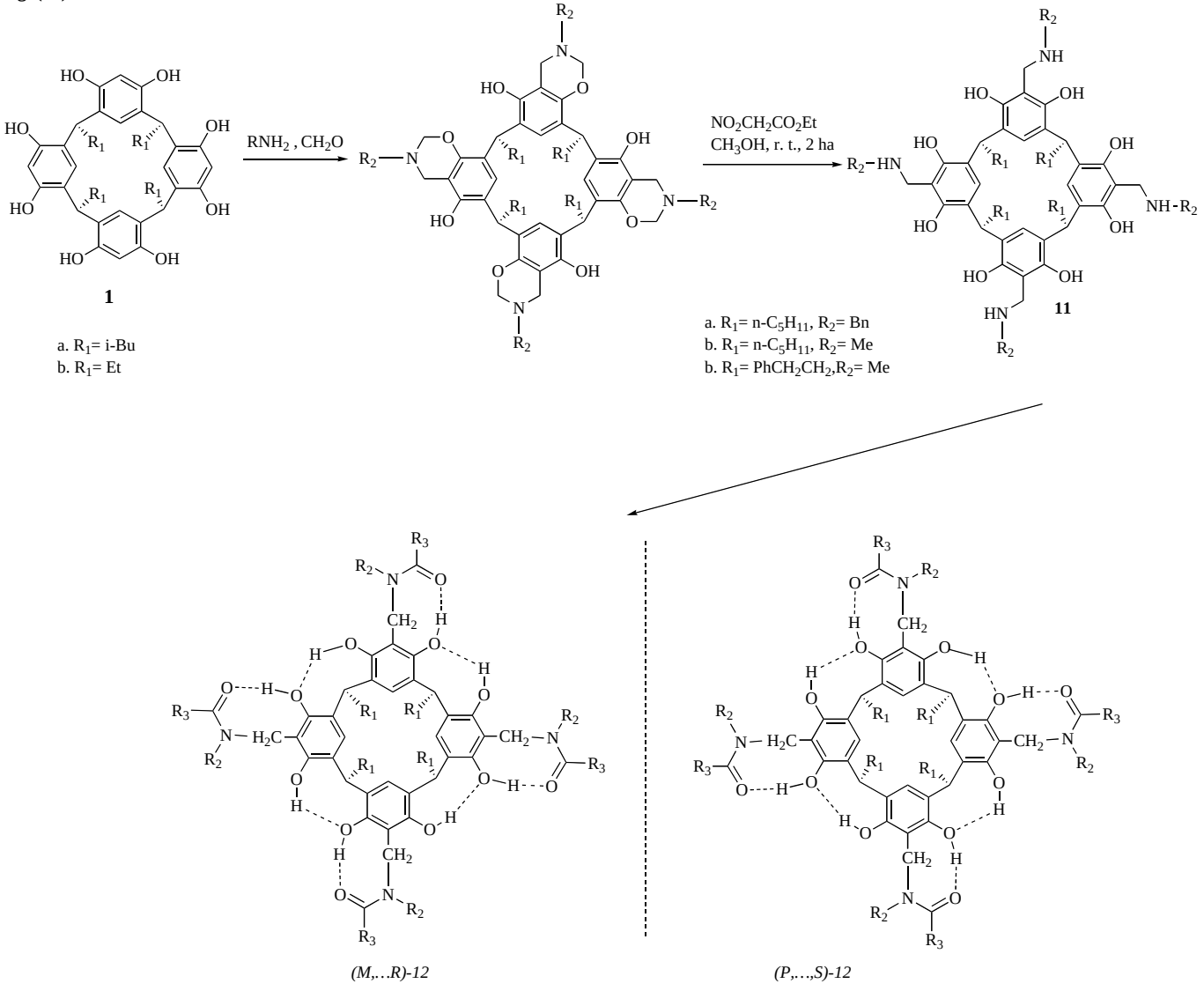
Aminomethylation of resorcinarenes using chiral secondary amines should lead to two diastereoisomers having the C_4 symmetry. In fact, this is observed also for the tetraoxazolidine derivatives **9** obtained from amino alcohols [29] (see Fig. **11**).

Scheme **5** illustrates the possible routes of synthesis of the tetraamide derivatives of the resorcinarene **12**. The resulting resorcinarenes **12** exist in two cyclochiral conformations (cycloconformers) stabilised by belts of hydrogen bonds. The cycloisomerisation process is characterised by the relatively high racemisation barrier (14.6–18.5 kcal mol^{-1}), as determined by the 2D EXSY measurements. One can explain that the transformation of one cyclocon-



8 **9**

Fig. (11).



Scheme 5.

former into the other requires simultaneous rupture of all eight hydrogen bonds. In the case of the amide-substituted resorcinarene with additional stereocentres, two cyclodiastereoisomeric conformations were detected experimentally [30].

6. MIXED FUNCTIONALISATION OF RESORCINARENES

Many examples of the resorcinarene derivatives having the functionalised hydroxy groups as well as the "*ortho*" positions in their structure are known in the literature. These compounds will be

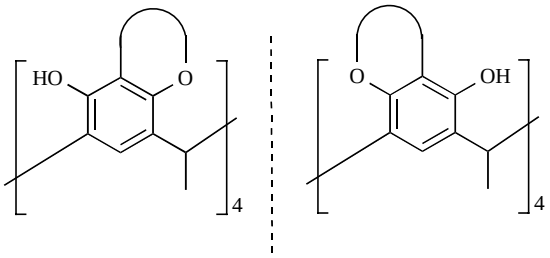


Fig. (12).

described in this chapter. In spite of a broad range of these well-known resorcinarene derivatives, we can make some generalisations concerning the following types of experimentally observed resorcinarene derivatives:

1. Resorcinarenes comprising a new heterocyclic ring formed by the hydroxy groups and the "*ortho*" position (Fig. **12**). These derivatives are structurally chiral, having the C_4 symmetry.

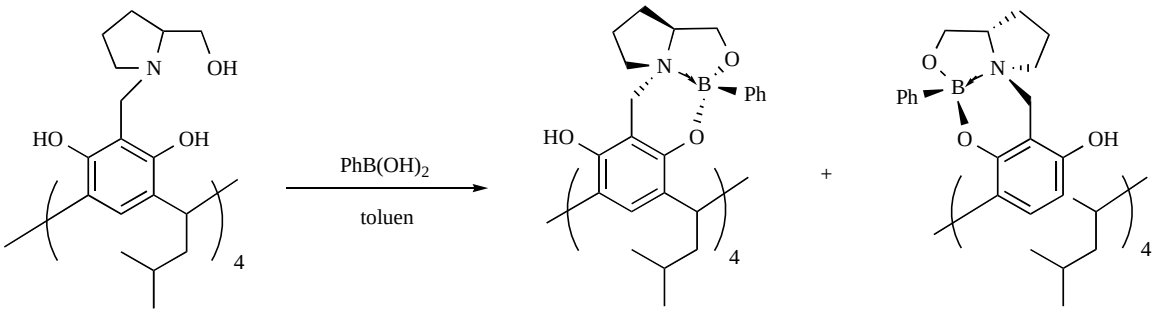
The most often used reaction for preparing the derivatives of such type is the Mannich reaction, in which a primary amine or its methoxy-derivative react with resorcinarene in the presence of an excess of formaldehyde to form the oxazine derivatives [31-33]. When an achiral amine is used then a racemic mixture of axially chiral oxazine derivatives is obtained. The racemic mixture is separable into enantiomers by chiral HPLC [34]. When a chiral amine is used, then a mixture of diastereoisomers is formed. In many cases, the reactions are highly diastereoselective.

Another example of compound having this type of chirality is resorcinarene **14** synthesised as shown in Scheme **6**. In the first step, the chiral L-prolinol derivative **13** is prepared by the Mannich reaction with L-prolinol and formaldehyde. The resorcinarene **13** has an electron lone pair at the nitrogen atom and free hydroxy groups which can be "clipped" together by the reaction with phenylboronic acid. The resulting novel resorcinarenes **14**, having the bora-oxazine-oxazolidine rings in their structure, are obtained in 65% yield as a mixture of two diastereoisomers: *out-(M,S,R,*S_N*,*R_B*)*-**14** and *in-(P,S,S,*S_N*,*R_B*,)*-**14** in a ratio of 80:20. The resorcinarenes **14** contain two new stereogenic centers: at the boron atom and at the nitrogen atom. This information complements the stereochemical designation of these compounds. In both isomers, the nitrogen atom has the *S* configuration, whereas the boron atom has the *R* configuration [35].

2. The next type of resorcinarene derivatives comprises the molecules having four modified hydroxy groups at the opposite resorcinol units, and the heterocyclic rings, formed as described above, at the other resorcinol units. These derivatives are axially chiral, having the C_2 symmetry, so the reactions with achiral reagents lead to racemic mixtures. In the case, when a chiral auxiliary is used for modification of the hydroxy groups or forming the heterocyclic ring, the diastereoisomeric mixture is formed (see Fig. **13**).

The most frequently used synthetic method for obtaining such derivatives proceeds *via* the tetrasulpho-*O*-resorcinarenes and modification of two hydroxy groups from the opposite resorcinol units to obtain the oxazine derivatives [36].

The tetratosyl derivative of resorcinarene undergoes the Mannich reaction with formaldehyde and N-methylamide derivatives of amino acids in the presence of catalytic amounts of acetic acid to afford the cyclochiral dibenzooxazine derivatives **15** [37] (see Fig.



13 ***out-(M,S,R,*S_N*,*R_B*)*-**14** ***in-(P,S,S,*S_N*,*R_B*)*-**14**

Scheme 6.

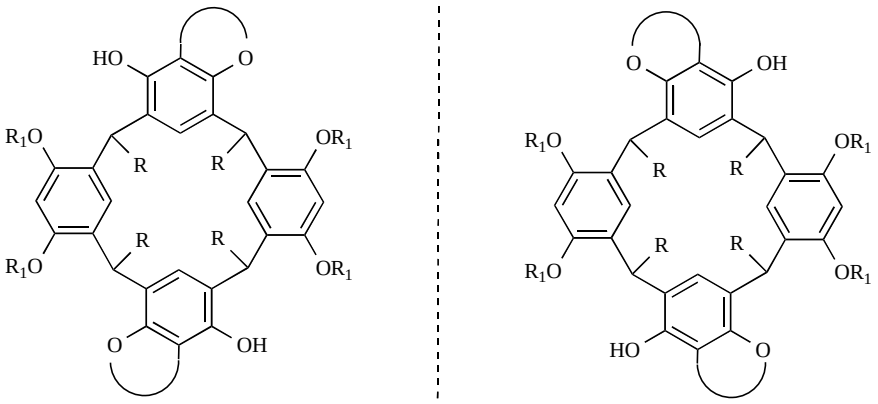


Fig. (13).

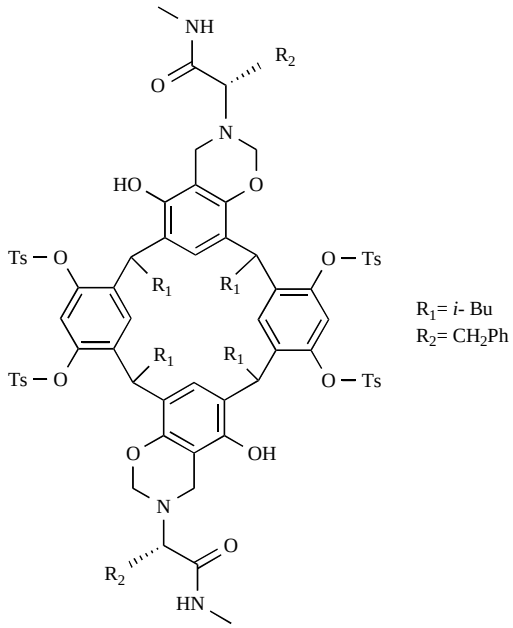


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Fig. (14).

14). The X-ray structures indicate that these compounds are the boat conformers, and can be classified as the (*M*,*S*,*R*)-isomers.

3. Another type of compounds with mixed functionalisation comprises the axially chiral derivatives having four modified hydroxy groups, only one in each of resorcinol units (according to Fig. **5C**) and the substituents at the "*ortho*" position (A) or heterocyclic rings formed by the hydroxy groups and the "*ortho*" position (B) (see Fig. **15**).

Examples of this type of chiral resorcinarenes are described in the literature [9] and shown in Scheme **7** below.

4. Another type of derivatives obtained by the mixed functionalisation comprises the resorcinarene derivatives with four modified hydroxy groups at the opposite resorcinol units (OR_1), and substituents at 2-position at one or two of the remaining resorcinol units (R_2) (see Fig. **16**).

The above-presented types of chiral resorcinarene derivatives synthesised by the mixed functionalisation are most often found in the literature, because of the possibility to obtain a broad range of derivatives having various substituents with potential receptors ability. An example of the chiral tetratosyl derivatives of resorcinarene obtained *via* the Mannich reaction is shown in Scheme **8**. The estimated racemisation barrier for this derivative is 13 kcal/mol and the coalescence temperature (T_c) is 280.5K [38].

7. FUNCTIONALISATION OF THE LOWER RIM OF RESORCINARENES

Three approaches to modify the lower rim are described in the literature - see Fig. (**17**).

1) The most frequently used and the simplest method is to use a chiral aldehyde in the condensation reaction. There are known examples of reaction with chiral derivatives of carbohydrates [39] as well as with trimethylcholanal [40].

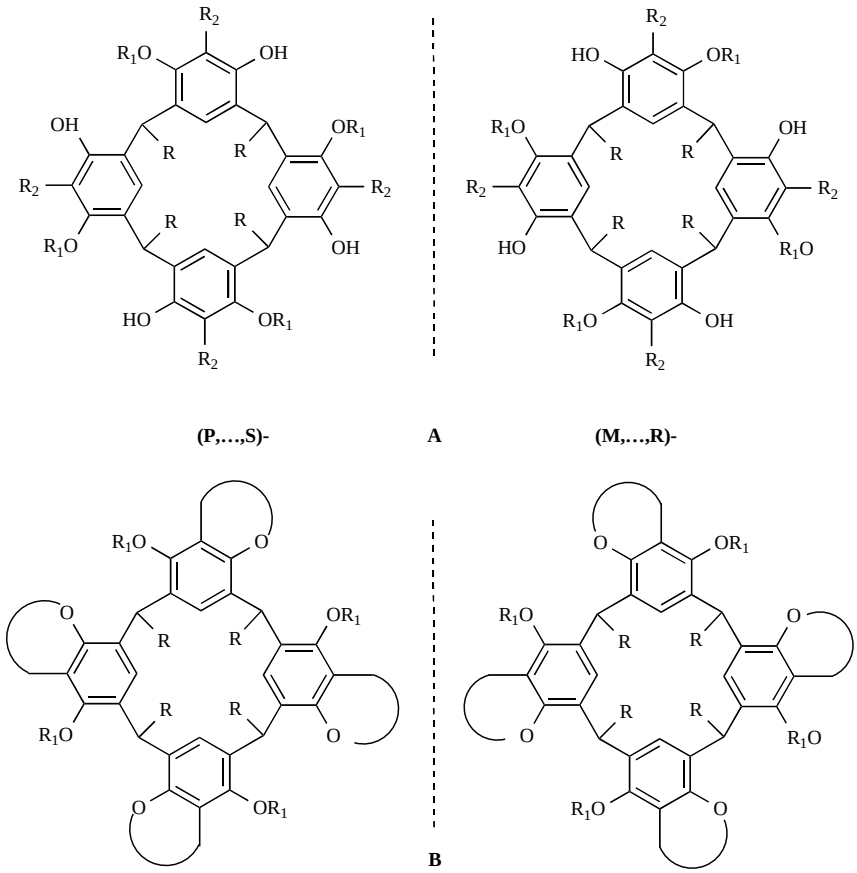


Fig. (15).

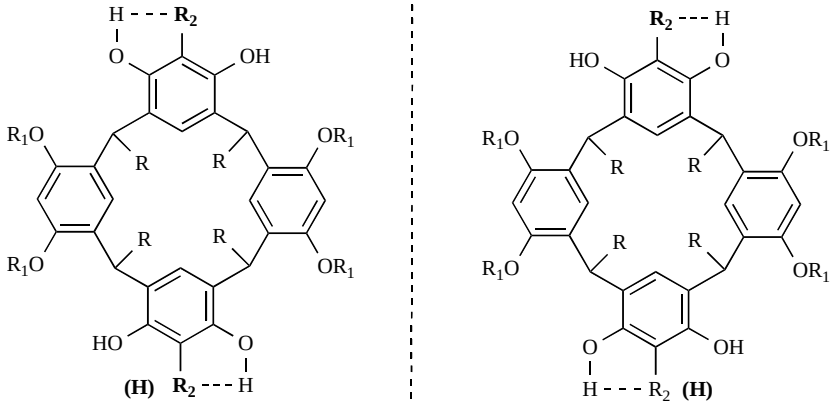
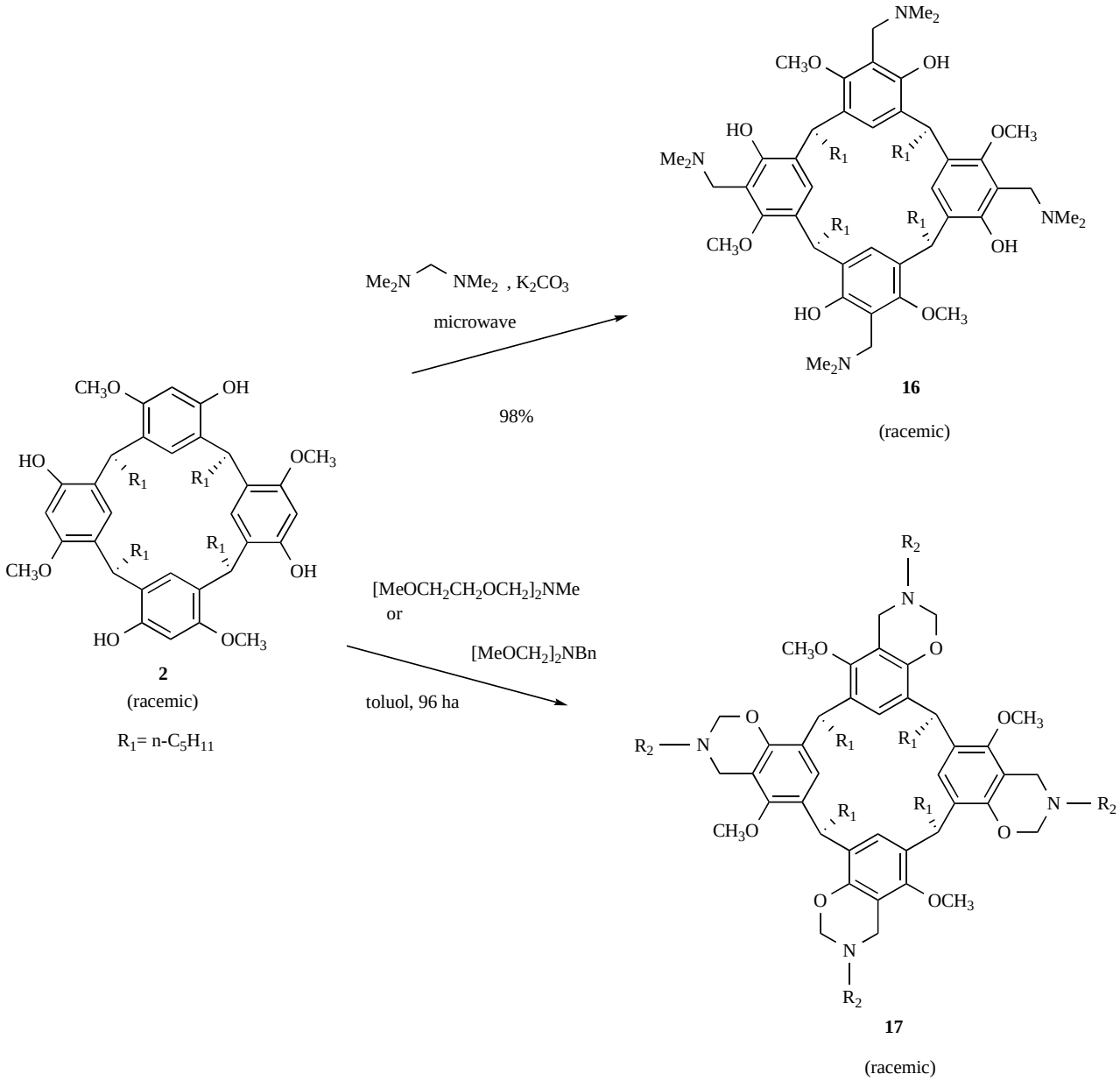
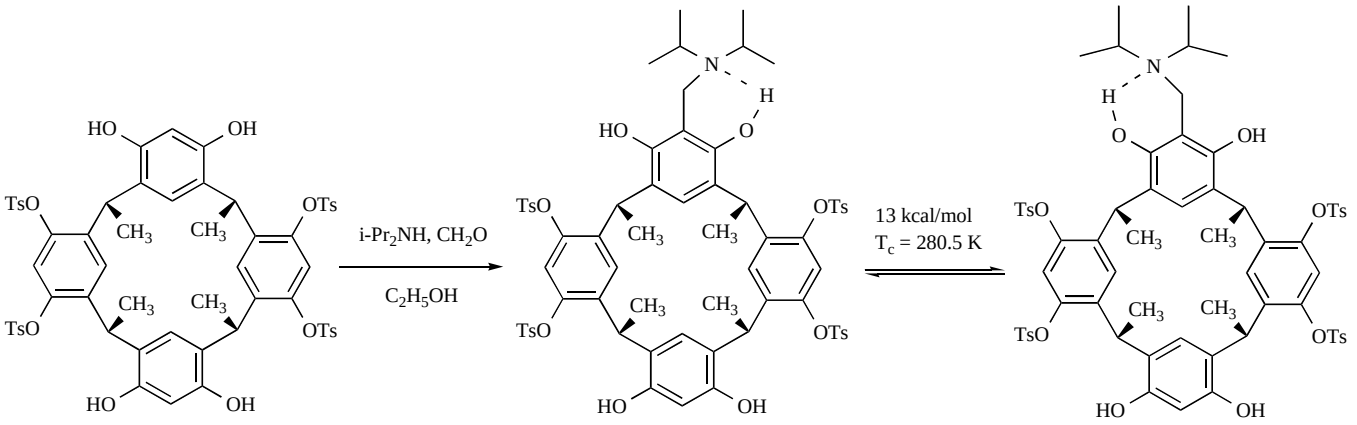


Fig. (16).



Scheme 7.



Scheme 8.

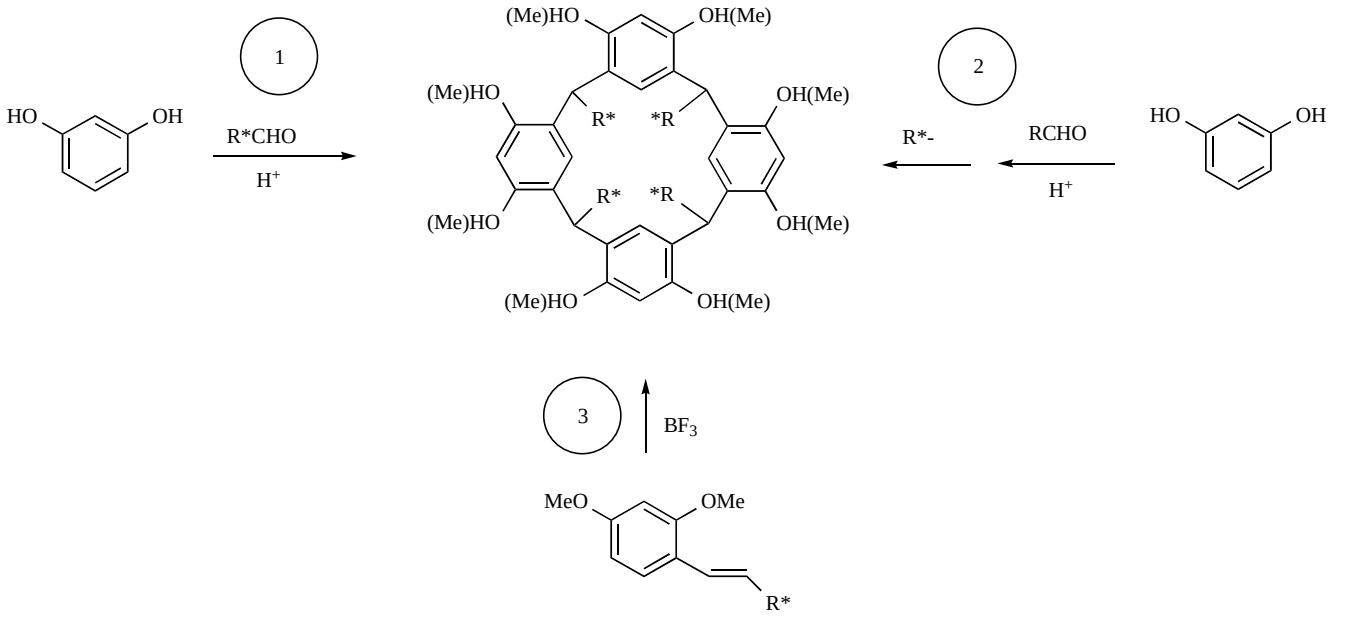


Fig. (17).

2) The stereogenic centre at the lower rim of the resorcinarene can be created by modification of the functional groups introduced with an aldehyde. Condensation of resorcinol with 4-formylphenylboronic acid in the presence of an acidic catalyst yields a mixture of two resorcinarenes composed of the crown and chair conformers, which contain four phenylboronic acid units at carbon bridges. Esterification using (-)-pinanediol affords a chiral boronic ester [41].

3) An example of the synthesis of a chiral resorcinarene from the derivative of resorcinol is also known. Chiral octamethoxy-resorcinarenes were synthesised from chiral monomers of D- and L-valinamides of (E)-2,4-dimethoxycinnamic acid in the presence of catalytic amounts of $BF_3 \cdot Et_2O$ [42].

8. CONCLUSIONS

Resorcinarenes constitute a very attractive class of macrocyclic compounds because of the presence of a cavity capable of complexing small molecules. They can be easily converted into chiral derivatives by functionalisation of their hydroxy groups as well as the "*ortho*" position at the resorcinol ring. Moreover, the synthesis of chiral resorcinarene derivatives from chiral substrates is also possible.

A broad range of obtainable chiral resorcinarene derivatives creates many opportunities for using these compounds in many fields of chemistry, industry and medicine. For example, these compounds can be used as chiral stationary phases [43-45], chiral catalysts [46-49], receptors and sensors for biologically-active compounds [50-53], tumour markers [54], chiral NMR solvating agents [55], and also for investigation of enantioselective recognition processes [56, 57].

Currently, a rapid development of methods of synthesis of these compounds is observed, accompanied by a growing number of papers devoted to practical applications of the resorcinarene derivatives.

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