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Inherently chiral heterocyclic resorcinarenes using a Diels–Alder reaction†

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This paper presents a novel approach to highly diastereoselective synthesis of resorcinarenes having enlarged cavities. Inherently chiral heterocyclic resorcinarenes have been obtained with unusually high diastereoselecivity by a "one pot" sequence involving thermal generation of *o*-quinomethide resorcinarene derivatives and the subsequent Diels–Alder reaction with dienophiles (exemplified by α-methylstyrene). The diastereoselectivity of this reaction is explained based on the thermodynamic stability of the products. The enantiomers of rac-**4** have been separated by HPLC and their absolute configuration was assigned by comparison of their experimental and theoretical CD spectra.

Resorcinarenes and their derivatives are found among key macrocyclic compounds that have contributed to main developments and applications of supramolecular chemistry. In comparison to many other macrocycles, resorcinarene derivatives emerge as particularly convenient building blocks for formation of chiral structures, owing to their unique structural and conformational features.[1,2] Chiral resorcinarenes have been widely employed, namely: for monitoring the formation of host–guest type complexes,[3] preparing catalysts with catalytic stages occurring within the cavity,[4] forming large molecular containers for transporting molecules and ions,[5] as chiral agents for discrimination of enantiomers,[6] as enzyme models,[7] and also as chiral stationary phases in chromatography.[8] Chiral resorcinarene derivatives can be obtained in several ways including classical modifications with chiral auxiliaries or by, utilized to a much less extent thus far, generation of inherent chirality (also called cyclochirality).[2,9] The latter approach has been implemented by simultaneous modification of one of the hydroxyl groups and the central *ortho* position of resorcinol units leading to heterocyclic resorcinarenes that exhibit inherent chirality due to introduced directionality of the concave skeleton. At present, only few classes of inherently chiral resorcinarenes are known including oxazines,[10] boronooxazino-oxazolidines,[11] iminoresorcinarenes,[12] mono-[13] and tetra-substituted[14] derivatives of resorcinarenes. The possibility of employing the Diels–Alder reaction for formation of a heterocyclic ring and building inherently chiral resorcinarenes has not been described in the literature yet.

Here we report the use of Diels–Alder reaction for highly regio- and diastereoselective preparation of a new class of heterocyclic resorcinarene derivatives – benzopyrane resorcinarenes rac-**4** – using *in situ* generated resorcinarene diene **2** (Scheme 1). We analyse the possible reasons for such selectivity, separate inherently chiral enantiomers and assign their absolute configurations. The vast potential present in this approach allows not only for the synthesis of macrocycles with a broad array of various substituents, but also for a significant extension of the resorcinarene skeleton.

The presence of highly reactive *o*-quinomethine intermediates has been postulated in many chemical reactions leading to the synthesis of natural products.[15] The methods that has been used to generate *o*-quinomethines include thermolysis, oxidation, photolysis, or β-elimination reactions assisted with acids or bases.[16] The major pathways of consecutive reactions of *o*-quinomethines are: (1) cycloaddition leading to benzopyrane derivatives; (2) 1,4-Michael nucleophilic addition leading to *o*-substituted phenols; (3) 1,5-sigmatropic shift leading to styrenes.[17] Here, we have assumed that resorcinarene derivatives **1a–1d** may potentially form transition intermediates having the *o*-quinomethide structure **2** that can further participate in cycloaddition reactions, for example with α-methylstyrene **3**.

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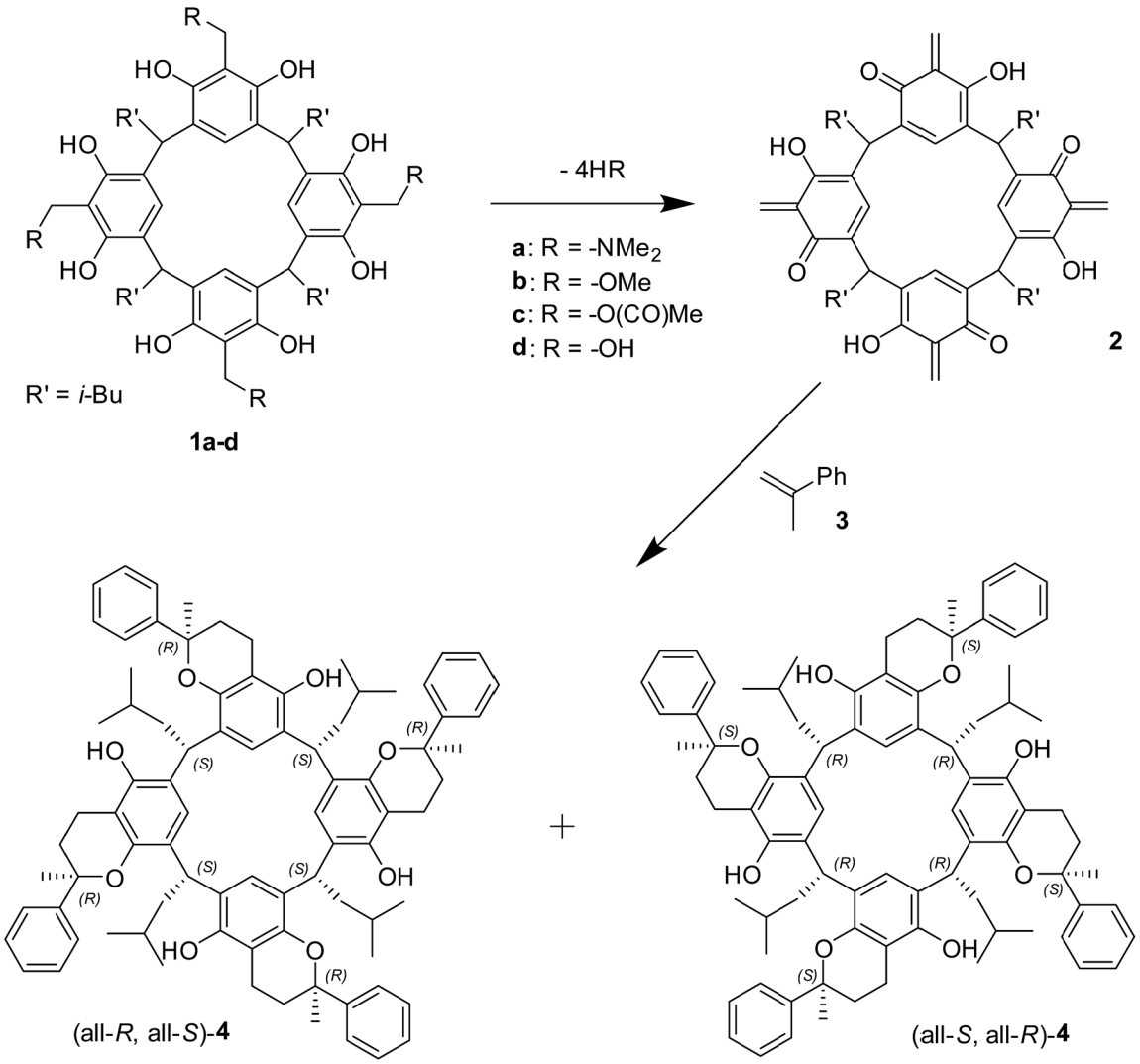

Scheme 1 Cycloaddition reaction of resorcinarene derivatives.

We have found that reaction of **1a** with **3** under thermal conditions proceeds smoothly and gives the main product in a high yield (Table 1, entry 1), that can be isolated by simple precipitation/crystallization procedure. It is important to note that the Diels–Alder reaction of resorcinarene derivatives **1a** with **3** can lead to formation of numerous isomers due to simultaneous generation of eight new stereogenic centres (absolute configuration marked in Scheme 1).

Table 1 Synthesis of rac-**4** *via* Diels–Alder reaction of resorcinarene derivatives with α-methylstyrene **3**

Substrate	Solvent	*T*, °C	Reaction time, h	Yield of rac-**4**, %
1a	**3**	140	7	88
1a	Chlorobenzene	130	7	4
1b	**3**	120	3	70
1c	**3**	120	3	13
1d	**3**	120	3	8

The statistical abundance of all C_4-symmetric isomers (four isomers) is $4/2^8$ (statistical yield 1.6%). In the current reaction only a single diastereoisomer, rac-**4**, was isolated in yields up to 88%, meaning that the amplification of formation of rac-**4** is *ca.* 110 times (88% *vs.* statistical yield 0.8%). The X-ray structure of rac-**4** (Fig. 1) shows that the relative configuration of the amplified diastereoisomer is (all-*R*, all-*S*). Rac-**4** exhibits a crown conformation stabilised by four intramolecular hydrogen bonds. Interestingly, bulky phenyl groups originating from α-methylstyrene point towards the interior of the resorcinarene cavity. The phenyl groups are involved in C–H$\cdots\pi$ interactions (Fig. 1b) that can be considered a favourable stabilizing force. They also enclose a small space inside the cavity which seems not accessible for any kind of guest molecules (Fig. 1c).

The best yield of rac-**4** was obtained by subjecting the *N*,*N*-dimethylamino derivative **1a** to a prolonged heating (7 h) at high temperature in α-methylstyrene solution. Analogous reactions of **1a** with α-methylstyrene **3** in chlorobenzene lead to a lower yield of about 4%. In the case of derivatives **1b–1d**,

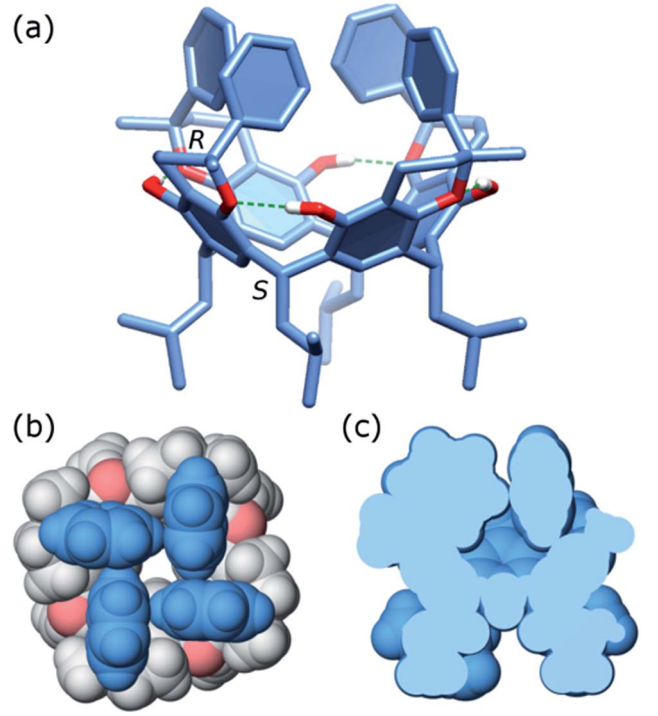

Fig. 1 X-ray structure of rac-**4**: (a) side view in a stick representation showing relative configuration (all-*R*, all-*S*); (b) top view in a van der Waals representation, blue-phenyl rings forming C–H···π interactions; (c) slice through a van der Waals representation of the structure.

heating above 120 °C leads to partial formation of insoluble precipitates. This may result from the polymerisation of the resorcinarene derivatives used for these reactions, which would lower the yield of rac-**4**. Indeed, a test reaction has shown that **1b** alone upon heating above 120 °C, forms an insoluble yellow precipitate.

In order to rationalize the fact that only one diastereoisomer is preferred, we considered the possibility, that under high temperature conditions the most thermodynamically stable products are amplified. For resorcinarene derivatives, presence of four intramolecular hydrogen bonds usually leads to stabilization of C_4 symmetric structures. Therefore, we calculated the heat of formation (ΔH) only for the two possible C_4-symmetric diastereoisomers (all-*R*, all-*S*) and (all-*S*, all-*S*) using the semi-empirical PM7 method implemented in MOPAC2012 software.[18] The results confirmed that indeed (all-*R*, all-*S*) diastereoisomer is thermodynamically more stable ($\Delta H = -378.80$ kcal mol^{-1}) than (all-*S*, all-*S*) diastereoisomer ($\Delta H = -356.30$ kcal mol^{-1}, see Fig. S8† for full computational details).

Rac-**4**, the amplified product of the reaction, is formed as a mixture of two enantiomers (all-*R*, all-*S*)-**4** and (all-*S*, all-*R*)-**4**. This was confirmed by separation of enantiomers using chiral HPLC (Fig. 2a). The CD spectra, that have been recorded for both fractions, exhibit mirror-image relationship (Fig. 2b) confirming the enantiomeric relationship between compounds. To assign the absolute configuration of enantiomers of **4** we have used quantum mechanical calculations (TD-DFT method at B3LYP/6-31G* level) for the model compound (*S*)-2,6,8-trimethyl-2-phenylchroman-5-ol (Fig. 2c).[19] We have compared the theoretical ECD spectrum to the experimental spectra for both enantiomers. A good agreement of the theoretical ECD spectrum with the experimental spectrum of first eluting enantiomer allows us to assume that it has a (all-*S*, all-*R*) configuration (Fig. 2d).

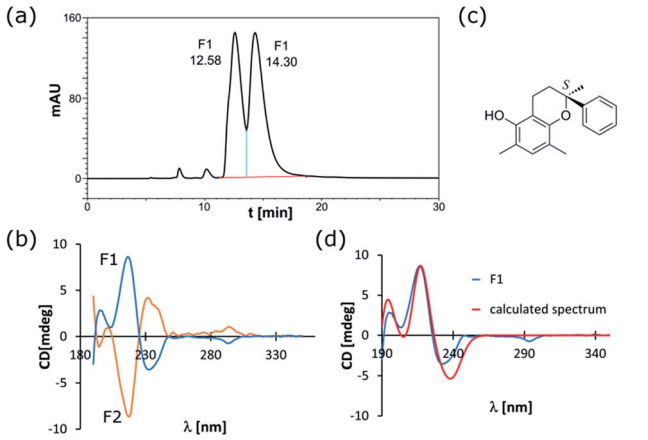

Fig. 2 (a) HPLC separation of enantiomers of rac-**4** (Nucleocel Delta S column from Macherey&Nagel); (b) CD spectra of enantiomers (blue – enantiomer having the shorter retention time, F1); (c) structure of (*S*)-2,6,8-trimethyl-2-phenylchroman-5-ol; (d) assignment of the absolute configurations using comparison of experimental and theoretical results (TD DFT B3LYP/6-31G*).

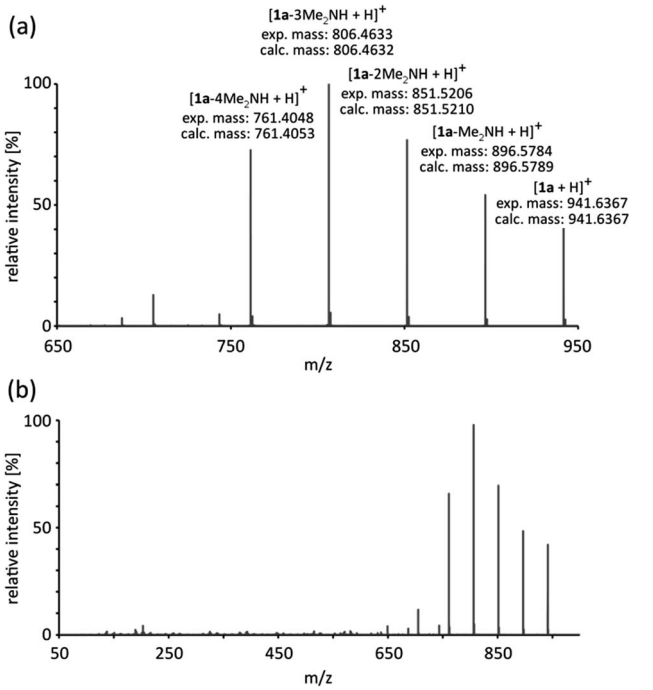

Fig. 3 (a) ESI-MS spectrum of **1a** demonstrating the sequential formation of *o*-quinomethide derivatives through gradual release of dimethylamine fragments (calculated and experimental high resolution *m*/*z* values are given); (b) the full measured range of the spectrum.

Although the existence of reactive *o*-quinomethide intermediate **2** seems to be a plausible explanation of participation of **1a–1d** in the Diels–Alder reaction, we undertook an additional effort to prove their existence. The ESI-MS/MS spectra for both, the substrate **1a** (Fig. 3) and the product rac-**4**, show the sequential appearance of the intermediates containing various number of *o*-quinomethide units in their structure. This observation supports the presence of *o*-quinomethide intermediates during the course of reaction.

Conclusions

In conclusion, the paper presents a novel approach which allows for highly diastereoselective synthesis of chiral heterocyclic derivatives of resorcinarenes. Making use of the possibility of generating the *o*-quinomethide intermediates and their subsequent reactions with dienophiles opens new opportunities for obtaining resorcinarenes with various functionalities and new stereochemical features. The Diels–Alder reaction is one of the most widely studied and useful reactions for generation of carbon–carbon bonds as well as new stereogenic centres. Furthermore, a great number of substrates and chiral catalysts for this reaction are already known. Considering these facts we expect that our findings may open up new possibilities in the chemistry of resorcinarenes.

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