DOI: 10.1002/ejoc.200700802

Cavity-Extended Inherently Chiral Resorcin[4]arenes: Synthesis and Chiroptical Properties of the Cycloenantiomers

Marlene Paletta,[a] Michael Klaes,[a] Beate Neumann,[b] Hans-Georg Stammler,[b] Stefan Grimme,[c] and Jochen Mattay*[a]

Keywords: Atropisomerism / Calixarenes / Chirality / Circular dichroism / Cross-coupling

Inherently chiral resorcin[4]arenes **2** and **3** were prepared from enantiomerically pure C_4-symmetric *rccc*-2,8,14,20-tetraisobutyl-4,10,16,22-tetra-*O*-methylresorcin[4]arene (**1**). The four 2-bromobenzyl ether residues in precursor **2** were introduced as halide moieties to partake in an intramolecular Pd-catalysed C–C cross-coupling reaction to give tetrabiaryl ether compound **3**. The absolute configurations could be derived from the starting compounds and were assigned as (*M*,*R*)-(–)-**2** and (*P*,*S*)-(+)-**2** for the tetrakis(2′-bromobenzyl) ether compounds as well as (*M*,*R*)-(–)-**3** and (*P*,*S*)-(+)-**3** for the cavity-extended resorcinarenes. The carbon scaffold of **3** contains four new stereogenic axes whose configurations were assigned by single-crystal X-ray analysis. The simulation of the CD spectra by time-dependent Pariser–Parr–Pople calculations (TDPPP) based on the X-ray data gave very good images of the experimental spectra.

Introduction

Resorcinarenes are three-dimensional macrocycles that are used in various aspects of supramolecular chemistry, for example, as building blocks and in molecular recognition[1] as well as in chiral assemblies.[2] The chirality of inherently chiral resorcinarenes originates from the topology of the nonplanar structure. Host–guest complexation experiments with chiral ammonium ions have shown some effect of chiral discrimination.[3] For the purpose of complex formation with a larger variety of guest molecules, the synthetic approach to cavity-extended resorcinarenes is of interest.

Inherently chiral resorcinarenes can be obtained directly as racemates from the Lewis acid catalysed reaction of 3-alkoxyphenols with aldehydes[4] or from the cyclisation of the corresponding benzylic alcohols.[5] The C_4-symmetric enantiomers of the starting material, *rccc*-2,8,14,20-tetraisobutyl-4,10,16,22-tetra-*O*-methylresorcin[4]arene, are already characterised with regard to the absolute configuration.[6]

A very convenient one-step procedure to synthesise cavity-enlarged chiral 1,3-oxazine derivatives was reported by us more than one decade ago.[7] However, although enantiomerically pure, these compounds were not stable under protic conditions. Therefore, we decided to enlarge the cavity of simple resorcinarenes by using Pd-catalysed intramolecular C–C cross-coupling reactions to obtain more stable macrocycles of this type. The four phenolic hydroxy groups of tetramethoxy resorcin[4]arene **1** provide the advantage of introducing an aryl halide component as an ether or ester functionality for a subsequent intramolecular C–C cross-coupling reaction.[8,9] The direct arylation leading to a biaryl compound requires no further activation of the *upper rim* aryl position of the resorcinarene, which is otherwise necessary for intermolecular cross-coupling reactions. Intramolecular arylation reactions generating four carbon–carbon bonds have not been reported in the literature so far.

Herein, we report the synthesis and optical resolution of inherently chiral resorcin[4]arenes with known absolute configuration and an extended cavity following a synthetic pathway for intramolecular biaryl formation. The circular dichroism spectra of the enantiomers are compared to those of time-dependent Pariser–Parr–Pople (TDPPP) calculations.

Results and Discussion

Synthesis of Tetrakis(2′-bromobenzyl) Ether 2 and Tetrabiaryl Ether 3

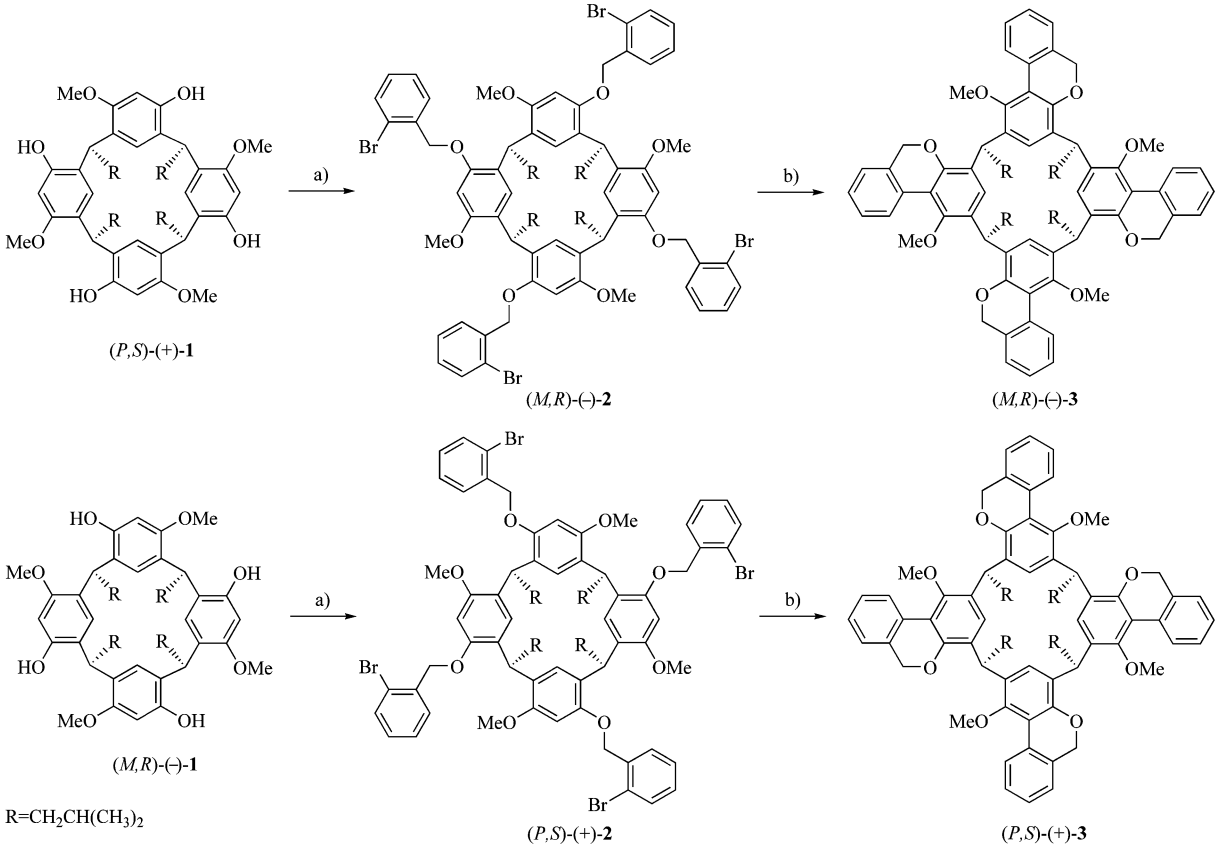
C_4-symmetric inherently chiral resorcin[4]arene *rac*-**1** was synthesised according to literature procedures.[4] The racemate was monofunctionalised with freshly prepared (*S*)-(+)-10-camphorsulfonyl chloride in acetonitrile by using K_2CO_3 as the base to convert the enantiomers into diastereomers that were separable by silica gel HPLC.[7,10] The resorcinarenes were characterised by NMR spectroscopy,

[a] Organische Chemie I, Fakultät für Chemie, Universität Bielefeld, Postfach 100131, 33501 Bielefeld, Germany
Fax: +-49-521-1066417
E-mail: oc1jm@uni-bielefeld.de
[b] Anorganische Chemie III, Fakultät für Chemie, Universität Bielefeld,
Postfach 100131, 33501 Bielefeld, Germany
[c] Organisch-Chemisches Institut (Abt. Theoretische Chemie), Westfälische Wilhelms-Universität,
48149 Münster, Germany

and the diastereomeric excess was determined to be 100%. The esters were hydrolysed under strong alkaline conditions to afford (*P*,*S*)-(+)-**1** and (*M*,*R*)-(–)-**1** in overall moderate yields. The $[\alpha]_D$ values correspond to the optical properties of the resorcin[4]arenes with known absolute configurations.[5] The compounds subsequently synthesised from (*P*,*S*)-(+)-**1** and (*M*,*R*)-(–)-**1** were therefore enantiomerically pure. The reactions were carried out first with the racemates and then with the enantiomerically pure compounds (Scheme 1).

Tetrakis(2′-bromobenzyl) ether **2** was first prepared from *rac*-**1** and 2-bromobenzyl bromide (1.4–1.8 equiv. per functionality) in dry DMF in the presence of K_2CO_3 (8 equiv.) and were separated from the tris(bromobenzyl) ether by column chromatography. To improve the procedure, racemate *rac*-**1** was deprotonated with NaH (5 equiv. per functionality) in dry DMF to yield the phenolate salt, which was then treated with 2-bromobenzyl bromide (1.07 equiv. per hydroxy group) to give tetrakis(bromobenzyl) ether *rac*-**2**. Recrystallisation from chloroform and methanol yielded 84% of pure *rac*-**2**. The enantiomerically pure products were obtained following the described protocol and purified by column chromatography on silica gel to remove the excess amount of 2-bromobenzyl bromide. Compounds (*M*,*R*)-(–)-**2** and (*P*,*S*)-(+)-**2** were received in 92 and 72% yield, respectively, and show specific rotations of $[\alpha]_D^{25}$ = –4.2 (*c* = 0.69, $CHCl_3$) and $[\alpha]_D^{25}$ = +5.6 (*c* = 1.00, $CHCl_3$), respectively.

The synthetic challenge was to generate four new carbon–carbon bonds on the sterically demanding *upper rim* of the resorcinarene. The biaryl scaffold was built up through an intramolecular coupling reaction following the procedures for direct arylation of simple arenes.[8a,8b,11–13] As the catalytic system, $Pd(OAc)_2$ and PCy_3 (2 equiv.) were chosen; an amount of 30 mol-% per functionality was necessary to complete the reaction and K_2CO_3 (2 equiv. per functionality) was added as the base. The extent of conversion was followed by MALDI-ToF spectrometry. The gradual formation of the product was observed as a mixture of the mono, di, tri and tetrabiaryl compounds. After 20 h of heating at 130 °C in DMA, the only indicated *m*/*z* signals were 1122 $[M + H]^+$ and 1144 $[M + Na]^+$, which could be ascribed to tetrabiaryl ether *rac*-**3**. Resorcinarene *rac*-**3** was purified by column chromatography on silica gel to remove inorganic salts and catalyst residues. After recrystallisation from chloroform and methanol the yield was 18%. The enantiomerically pure resorcinarenes were obtained in 12% [(*M*,*R*)-(–)-**3**] and 17% [(*P*,*S*)-(+)-**3**] yield starting from the enantiomers of **2**. The low yield of the arylation reaction cannot be justified yet. After workup and purification, there was no difference in the yield due to the addition of the ligand as a free phosphane or as an HBF_4 salt that could



Scheme 1. Synthesis of tetrakis(2′-bromobenzyl) ether **2** and cyclic tetrabiaryl ether **3**. Reagents and conditions: (a) (i) NaH, DMF, (ii) 2-bromobenzyl bromide, 92%; (b) $Pd(OAc)_2$, $PCy_3{\cdot}HBF_4$, K_2CO_3, DMA, 130 °C, 20 h, 18%.

have led to decomposition of the resorcinarene by a Lewis acid catalysed reaction.

Recently, the absolute configuration of a C_4-symmetric tetramethyl resorcinarene (**1**) with pendant isobutyl groups was determined by X-ray crystallographic analysis of the separated diastereomers containing four (*S*)-(+)-10-camphorsulfonyl esters as auxiliaries.[6] The internal chirality reference revealed the configuration of the methine bridges. After hydrolysis, the (–)-enantiomer of tetramethoxyresorcin[4]arene was shown to be of (*M*,*R*)-chirality and the (+)-enantiomers of (*P*,*S*)-chirality. These results were confirmed by analysis and alkaline hydrolysis of the tetra-(*R*)-(–)-10-camphorsulfonyl ester diastereomers. Starting from compounds (*M*,*R*)-(–)-**1** and (*P*,*S*)-(+)-**1**, the absolute configurations of the scaffolds of (+)-**2** and (–)-**2** had changed owing to the introduction of the 2-bromobenzyl residues, which have a higher priority according to the Cahn–Ingold–Prelog rules. Thus, the configurations of (+)-**2** and (–)-**2** were determined as (*P*,*S*) and (*M*,*R*), respectively, and in analogy, those of (+)-**3** and (–)-**3** were determined as (*P*,*S*) and (*M*,*R*).

Crystal Structures and NMR Studies in Solution

Tetrakis(2′-bromobenzyl) ether resorcin[4]arene **2** was recrystallised from chloroform and methanol to give transparent crystals suitable for single-crystal X-ray analysis. The racemic crystal with a $P2_1/c$ space group shows a boat conformation of the resorcinol scaffold. The 2′-bromobenzyl ether residues are not oriented regularly (Figure 1). The crystal structure of **3** shows the extended resorcin[4]arene in the boat conformation as well (Figure 2). The crystals of the racemic $P\bar{1}$ space group comprise the two cycloenantiomers. This differs from the enantiomerically pure compounds precipitating each as an amorphous solid. The biaryl ether scaffold builds up four new atropisomeric units, which leads to the potential diastereomeric nature of **3**. In the solid state, the dibenzopyran units are twisted between 19.6 and 22.3° owing to the nonplanar ether bridges that have dihedral angles between 54.5° and 58.4°. On the basis of the configuration of the methine bridges of **1**, the relative configuration can be derived as (*M*,*M*,*M*,*P*) for (*M*,*R*)-(–)-**3** and as (*P*,*P*,*P*,*M*) for (*P*,*S*)-(+)-**3**. The biaryl ethers with opposite axial chirality are located in the parallel arranged resorcinol residues. Each methoxy group points in the same direction as the methylene ether bridges of the dibenzopyran units. Compound **3** containing four stereogenic bridging carbon atoms and four atropisomeric biaryl units was hence found to be of enantiomeric character.

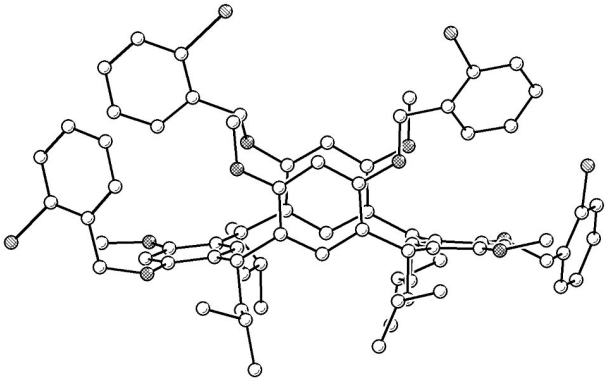


Figure 1. Crystal structure of tetrakis(2′-bromobenzyl) ether resorcin[4]arene **2**. Carbon atoms are shown as colourless circles, bromine atoms as striped circles and the oxygen atoms as hatched circles. Hydrogen atoms are omitted for clarity.

The boat conformation should give rise to two sets of resonance signals for the aromatic protons in the ^{1}H NMR spectrum; however, the cavity of **3** is not fixed in this conformation in solution. Instead, the C_4 symmetry of **3** can only be assumed on the basis of an averaged data set on the NMR timescale (Figure 4). The ^{1}H and ^{13}C NMR resonance peaks were assigned by means of 1D and 2D NMR experiments (COSY, HMBC) (Figure 3). At room temperature, the peaks are slightly broadened and the multiplets are not resolved properly. With increasing temperature up to 330 K, the resonances convert into definite singlets or multiplets, as can be seen for the methoxy groups at δ = 3.26 ppm, the ether bridge protons at δ = 4.63 and 4.84 ppm, the aryl protons at δ = 6.73 ppm and 8.13 ppm and the diastereotopic protons of the methylene unit of the alkyl chain at δ = 1.78 and 1.84 ppm (Figure 4). The ether bridges show two doublets for each proton at δ = 4.85 and 4.64 ppm, respectively, which was already observed for the diastereotopic protons of **2** at δ = 5.03 and 4.82 ppm.

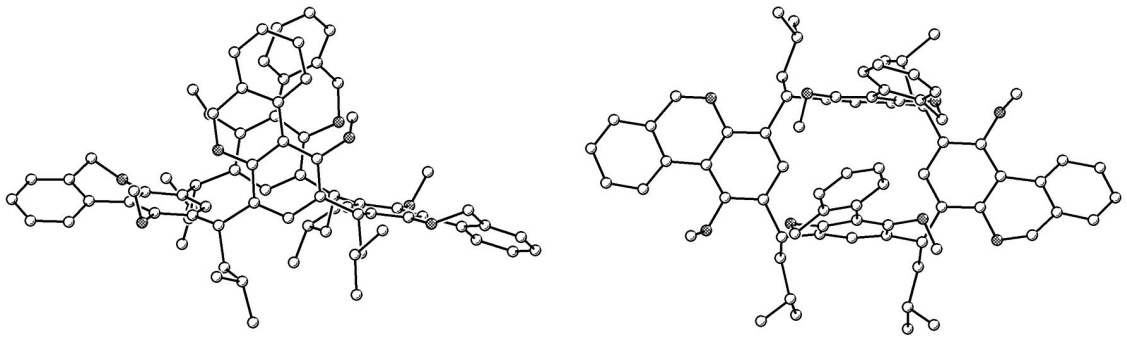


Figure 2. Crystal structure of tetrabiaryl ether resorcin[4]arene **3**. View along the chiral axis of the inherently chiral scaffold. Carbon atoms are shown as colourless circles and oxygen atoms as hatched circles. Hydrogen atoms are omitted for clarity.

Hence, for the observed doublets of **3**, there are two possible effects on the benzylic protons resulting in that motif. Either the anisotropic effect of the inherently chiral cavity is very strong and helimerisation of the biaryl units is too weak for monitoring by NMR spectroscopic techniques or the ether bridge is configurationally stable and consequently no interconversion occurs. The methoxy group is sterically demanding and the high grade of substitution prohibits free rotation around the C_{Ar}–O-bond. The stability of the chiral axes in cyclic ether atropisomers is known for several benzonaphthopyran compounds.[14] At higher temperature, the doublets are resolved sharply, which supports the assumption of a strong anisotropic effect. Fast helimerisation should lead to a broadened signal for each proton.

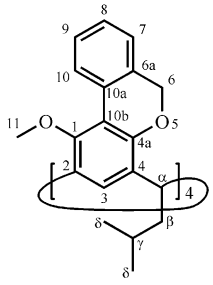


Figure 3. The designation of the carbon and hydrogen atoms of **3** for NMR spectroscopic studies.

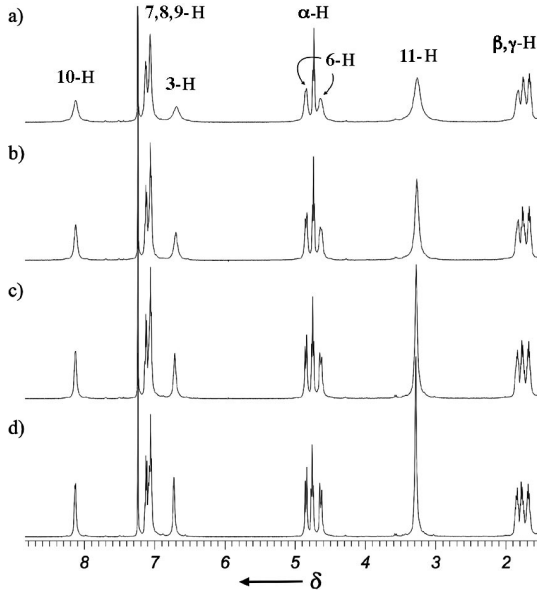


Figure 4. Partial ^{1}H NMR spectra (500 MHz) of biaryl ether resorcinarene **3** at (a) 300 K; (b) 310 K; (c) 320 K; and (d) 330 K in $CDCl_3$.

Low-temperature NMR spectroscopic studies were carried out in 1:1.5 mixtures of $CDCl_3$ and CD_2Cl_2 due to solubility of the sample. The NMR spectrum shown in Figure 5 was measured in deuterated chloroform.

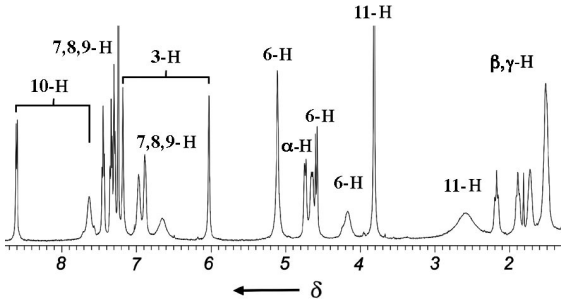


Figure 5. Partial ^{1}H NMR spectrum (500 MHz) of biaryl ether resorcinarene **3** at 213 K in $CDCl_3$.

The interconversion of the two boat conformers becomes slow and a coalescence point is observed at T_c = 263 K. Below this temperature, peaks separate into two sets that can be ascribed to the fixed boat conformation. The resonance peaks were assigned by NOESY experiments at 203 K. The free enthalpy $\Delta G_c^{\ddagger}$ for this interconversion was calculated by Equation (1), where $\Delta\nu$ is the resonance shift difference in Hz.[15]

$$\Delta G^{\ddagger} = 19.1 T_c\,(9.97 + \log T_c - \log \Delta\nu) \quad (1)$$

The complete freezing of the dynamics may not have been reached, and therefore, the shift difference maxima of the aromatic 3-H and 10-H protons and of the methoxy groups were used. The energy barrier $\Delta G_c^{\ddagger}$ was calculated to be 48.4 kJ mol^{-1}. A very slow interconversion of the boat conformations at low temperature minimises the anisotropy for the coplanar arene units; however, the NMR spectroscopic experiments did not allow unambiguous interpretation of the resonance peaks for the protons of the ether bridge between 5.2 and 4.1 ppm and for those of the *ortho* aryl position, which is referred to as diastereoisomerism of the nonplanar pyran units. In conclusion the anisotropic effect of the inherently chiral scaffold is adopted as the main cause for the different resonance peaks, whereas a stable configuration of the atropisomers cannot be excluded.

Chiroptical Properties

The UV and CD spectra of the enantiomeric pairs of **2** and **3** were measured in the nonpolar solvent cyclohexane and show almost perfect mirror images (Figure 6 a and b).

The absolute configuration of the macrocyclic scaffold can be deduced from the starting material, but the introduced chiral axes may change their configuration in solution depending on the temperature. Only little is known about rotational barriers of cyclic biaryl ethers of the pyran type.[14] The racemisation of the atropisomers can take place within hours at room temperature depending on the *ortho* substituents, or it can be completely suppressed. The configurations of the biaryl units in solution are not known and the simulation of the CD spectra was performed on the basis of the X-ray data. The CD spectra of (*M*,*R*)-(–)-**3** with the (*M*,*M*,*M*,*P*)-configuration were generated by means of

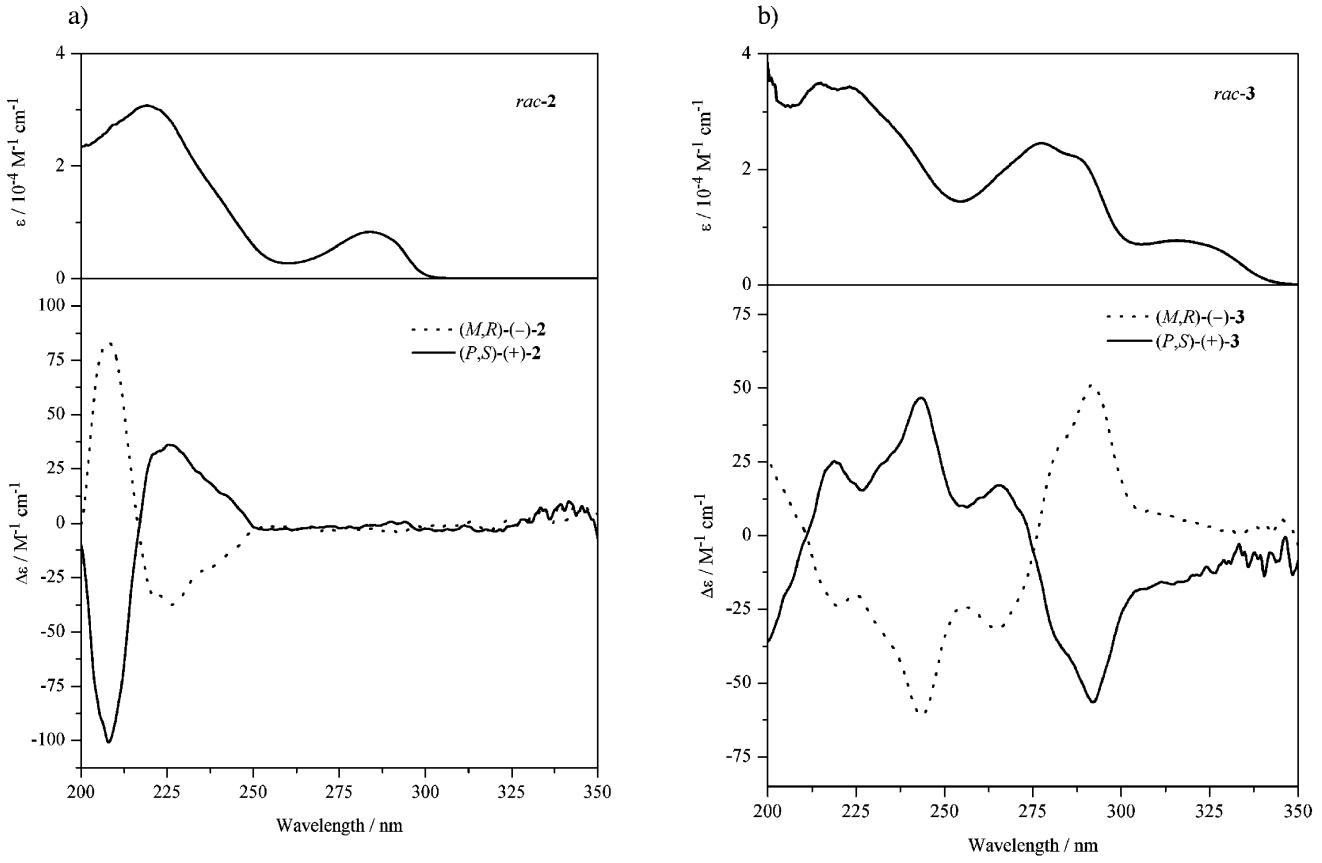


Figure 6. UV/Vis (top) and CD spectra (bottom) of (a) *rac*-**2** and enantiomerically pure tetrakis(bromobenzyl) ether resorcin[4]arenes (*M*,*R*)-(–)-**2** and (*P*,*S*)-(+)-**2**, respectively and of (b) *rac*-**3** and enantiomerically pure tetrabiaryl ether resorcin[4]arenes (*M*,*R*)-(–)-**3** and (*P*,*S*)-(+)-**3**, respectively. The measurements were carried out in cyclohexane at ambient temperature.

time-dependent Pariser–Parr–Pople (TDPPP) calculations,[16] which included only the π-electrons of the basic biaryl ethers (Figure 7).

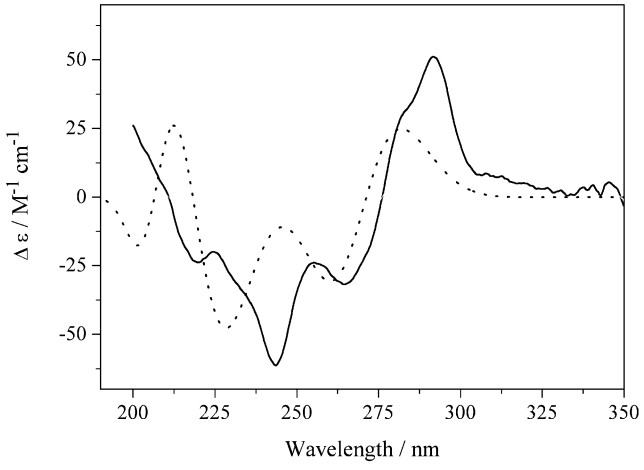


Figure 7. CD spectrum of (*M*,*M*,*M*,*P*)-(*M*,*R*)-(–)-**3** generated by TDPPP calculations (dotted line) and the experimentally obtained spectrum (solid line).

TDPPP calculations gave very good reproduction of the experimental data. Compared to the experimental spectrum, the theoretical excitation energies merely seem to be slightly shifted to shorter wavelengths. Analogous simulations of the CD signal with different dibenzopyran and methoxy configurations resulted in significantly differing spectra.

Conclusions

Cavity-extended inherently chiral resorcin[4]arenes (*M*,*R*)-(–)-**3** and (*P*,*S*)-(+)-**3** were prepared from enantiomerically pure tetramethoxy resorcinarenes (*P*,*S*)-(+)-**1** and (*M*,*R*)-(–)-**1** with known absolute configurations by reaction with 2-bromobenzyl bromide and a subsequent intramolecular Pd-catalysed C–C cross-coupling reaction. Racemic compounds **2** and **3** were characterised by X-ray data analysis, and the relative configurations of the dibenzopyran units of **3** in the solid state were determined as (*M*,*M*,*M*,*P*) for (*M*,*R*)-(–)-**3** and as (*P*,*P*,*P*,*M*) for (*P*,*S*)-(+)-**3**. The conformational studies in solution show a magnetic equivalence of all aromatic protons and of the benzylic protons at temperatures between 300 and 330 K. The interconversion process of the two boat conformations requires 48 kJ mol^{-1}.

The CD spectra of (*M*,*R*)-(–)-**3** and (*P*,*S*)-(+)-**3** are mirror images, which shows their enantiomeric nature. On the basis of the X-ray data, the spectra were simulated by

TDPPP calculations and reproduced the experimental data in a very good manner. As compounds (*M*,*R*)-(–)-**3** and (*P*,*S*)-(+)-**3** are enantiomers in the crystal structure and show mirror images in their CD spectra, they are denoted as cycloenantiomers.

Experimental Section

General Remarks: All solvents used were of an analytically pure quality or purified by distillation. Melting points were determined with a Büchi B-540 apparatus and are uncorrected. NMR spectra were recorded with a Bruker DRX 500 (^{1}H NMR: 500.13 MHz, ^{13}C NMR: 125.77 MHz) instrument in $CDCl_3$ with $CHCl_3$ as reference (^{1}H: 7.24 ppm, ^{13}C: 77.0 ppm). Single-crystal X-ray analyses were carried out at 100(2) K with a Nonius KappaCCD diffractometer by using Mo-K_α radiation of the wavelength 0.71073 Å. The structures were solved and refined with SHELXS-97 with refinements on F^2. The hydrogen atoms were normally calculated to idealised temperature factors and refined as riding atoms. Disordered solvent molecules and pendant alkyl chains were treated isotropically. IR spectra were recorded with a Perkin–Elmer 841 infrared spectrophotometer. HRMS were recorded with a Bruker APEX III with ESI in positive ion mode, and spectra were internally calibrated with HP TuneMix (*m*/*z* = 622/922/1522). Specific rotations were recorded with a Perkin–Elmer 341 polarimeter. $[a]_D$ values are given in units of 10^{-1}° $cm^2 g^{-1}$. CD spectra were recorded in cyclohexane at room temperature with a JASCO J-810 spectropolarimeter.

CCDC-644932 and -644933 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(±)-*rccc*-4,10,16,22-Tetrakis-*O*-(2′-bromobenzyl)-2,8,14,20-tetraisobutyl-6,12,18,24-tetra-*O*-methylresorcin[4]arene (*rac*-2): NaH (60% in paraffin oil, 2.20 g, 55.0 mmol) was washed with cyclohexane and suspended in dry DMF (50 mL). A solution of (±)-*rccc*-2,8,14,20-tetraisobutyl-4,10,16,22-tetra-*O*-methylresorcin[4]arene (*rac*-**1**; 2.00 g, 2.60 mmol) in dry DMF (30 mL) was added dropwise, and the suspension was stirred for 0.5 h at ambient temperature. 2-Bromobenzyl ether (2.78 g, 11.1 mmol, 4.3 equiv.) was dissolved in DMF (10 mL) and added dropwise. After the mixture was stirred for 12 h, methanol (5 mL) was added to remove the excess amount of NaH. The solvent was removed in vacuo, and the residue was dissolved in water and $CHCl_3$. The layers were separated, and the aqueous phase was extracted with $CHCl_3$ (2 × 40 mL). The combined organic phase was washed with brine, dried with anhydrous $MgSO_4$ and evaporated under reduced pressure. The colourless solid was recrystallised from $CHCl_3$/MeOH to give *rac*-**2** as colourless crystals (3.15 g, 84%). M.p. 210–212 °C. ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 7.530 (dd, ^3J = 8.2 Hz, ^4J = 1.3 Hz, 4 H, 3′-H), 7.305 (d, ^3J = 7.6 Hz, 4 H, 6′-H), 7.159 (td, ^3J = 6.6 Hz, ^4J = 1.3 Hz, 4 H, 5′-H), 7.118 (td, ^3J = 7.5 Hz, ^4J = 1.3 Hz, 4 H, 4′-H), 6.697 (s, 4 H, ArH *meta* $ArOCH_3$), 6.384 (s, 4 H, ArH *ortho* $ArOCH_3$), 5.030 (d, ^2J = 12.6 Hz, 4 H, OCH_2), 4.819 (d, ^2J = 13.2 Hz, 4 H, OCH_2), 4.715 (t, ^3J = 7.6 Hz, 4 H, ArCHAr), 3.424 (s, 12 H, OCH_3), 1.758 (m, 8 H, $CHCH_2CH$), 1.598 [m, 4 H, $(CH_3)_2CH$], 0.897 [d, ^3J = 6.3 Hz, 12 H, $(CH_3)_2CH$], 0.863 [d, ^3J = 6.3 Hz, 12 H, $(CH_3)_2CH$] ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 155.64 ($ArOCH_3$), 154.55 ($ArOCH_2$), 136.97 (C-1′), 132.10 (C-3′), 129.25 (C-6′), 128.81 (C-4′), 127.36 (C-5′), 126.45 (Ar_q), 126.39 (Ar_q), 125.97 (Ar_q), 121.94 (ArBr), 97.51 (ArH *ortho* CO), 69.98 (OCH_2), 55.59 (OCH_3), 43.81 ($CHCH_2CH$), 33.46 (ArCHAr), 25.94 [$(CH_3)_2CH$], 22.89 [$(CH_3)_2CH$], 22.79 [$(CH_3)_2CH$] ppm. IR (KBr): $\tilde{\nu}$ = 2951, 2864, 2831, 1610, 1582, 1498, 1464, 1444, 1405, 1381, 1364, 1297, 1192, 1130, 1098, 1042, 1026, 944, 912, 813, 781, 750, 664, 613 cm^{-1}. UV/Vis (cyclohexane): λ (ε, $mol^{-1}dm^3cm^{-1}$) = 224 (64000), 286 (17000) nm. HRMS (ESI): calcd. for $C_{76}H_{88}Br_4NO_8^+$ $[M + NH_4]^+$ 1458.3238; found 1458.3246. $C_{76}H_{84}O_8Br_4$ (1445.1): calcd. C 63.17, H 5.86; found C 63.07, H 5.98.

***rac*-2:** Crystal size 0.30 × 0.30 × 0.26 mm, monoclinic, $P2_1/c$, a = 19.1950(2) Å, b = 23.9900(3) Å, c = 15.98900(10) Å, β = 111.2580(5)°, Z = 4, V = 6861.76(10) Å^3, $\rho_{calcd.}$ = 1.399 mg m^{-3}, $2\Theta_{max}$ = 54.96°, μ = 2.401 mm^{-1}, F(000) = 2976, 817 parameters, R_1 = 0.0500, wR_2 = 0.1299 {for 12184 reflections [$I > 2\sigma(I)$]}, R = 0.0682, $wR(F_2)$ = 0.1425 (for 15680 unique reflections), R_{int} = 0.057, S = 1.035, $\Delta\rho$(min/max) = –1.59/2.81 e Å^{-3}.

(*M*,*R*)-(–)-*rccc*-4,10,16,22-Tetrakis-*O*-(2′-bromobenzyl)-2,8,14,20-tetraisobutyl-6,12,18,24-tetra-*O*-methylresorcin[4]arene [(*M*,*R*)-(–)-2]: NaH (60% in paraffin oil, 130 mg, 3.25 μmol) was washed twice with cyclohexane and suspended in dry DMF (6 mL). A solution of (*P*,*S*)-(+)-**1** (143 mg, 186 μmol) in dry DMF (12 mL) was added dropwise, and the suspension was stirred for 0.5 h at room temperature. 2-Bromobenzyl ether (398 mg, 1.59 mmol) was dissolved in DMF (3 mL) and added dropwise. After the mixture was stirred for 12 h, methanol (5 mL) was added to remove the excess amount of NaH. The solvent was removed in vacuo, and the residue was dissolved in water and $CHCl_3$. The phases were separated, and the aqueous phase was extracted with $CHCl_3$ (3 × 15 mL). The combined organic phase was washed with brine, dried with anhydrous $MgSO_4$ and evaporated under reduced pressure. The colourless residue was purified by column chromatography (SiO_2; cyclohexane → cyclohexane/ethyl acetate, 9:1) to yield 247 mg of (*M*,*R*)-(–)-**2** (92%). $[a]_D^{25}$ = –4.2 (c = 0.69, $CHCl_3$). HRMS (ESI): calcd. for $C_{76}H_{88}Br_4NO_8^+$ $[M + NH_4]^+$ 1458.3238; found 1458.3217.

(*P*,*S*)-(+)-*rccc*-6,12,18,24-Tetrakis-*O*-(2′-bromobenzyl)-2,8,14,20-tetraisobutyl-4,10,16,22-tetra-*O*-methylresorcin[4]arene [(*P*,*S*)-(+)-2]: NaH (60% in paraffin oil, 30.0 mg, 750 μmol) was washed twice with cyclohexane and suspended in dry DMF (6 mL). A solution of (*M*,*R*)-(–)-**1** (72.0 mg, 93.6 μmol) in dry DMF (5 mL) was added dropwise, and the suspension was stirred for 0.5 h at room temperature. 2-Bromobenzyl ether (103 mg, 412 μmol) was dissolved in DMF (8 mL) and added. After the mixture was stirred for 12 h, methanol (5 mL) was added to remove the excess amount of NaH. The solvent was removed in vacuo, and the residue was taken up with water (40 mL) and $CHCl_3$ (30 mL). The phases were separated, and the aqueous phase was extracted with $CHCl_3$ (3 × 15 mL). The combined organic phase was washed with brine, dried with anhydrous $MgSO_4$ and evaporated under reduced pressure and purified by column chromatography (cyclohexane/ethyl acetate, 4:1) to yield the colourless solid of (*P*,*S*)-(+)-**2** (98.0 mg, 72%). $[a]_D^{25}$ = +5.6 (c = 1.00, $CHCl_3$). HRMS (ESI): calcd. for $C_{76}H_{88}Br_4NO_8^+$ $[M + NH_4]^+$ 1458.3238; found 1458.3244.

Biaryl Ether *rac*-3: *rac*-**2** (500 mg, 346 μmol), dried K_2CO_3 (383 mg, 2.77 mmol) and DMA (10 mL) were placed and in a two-necked round-bottom flask. The suspension was degassed by three freeze–pump–thaw cycles. $Pd(OAc)_2$ (67.0 mg, 298 μmol) and $PCy_3{\cdot}HBF_4$ (206 mg, 559 μmol) were added under an argon atmosphere. The yellow mixture was heated to 130 °C for 20 h. The suspension turned black and was filtered through silica gel. The solvent was removed under reduced pressure, and the residue was purified by column chromatography (SiO_2; cyclohexane/ethyl acetate, 95:5). The colourless solid was recrystallised from $CHCl_3$/

MeOH to yield *rac*-**3** (60.2 mg, 16%). M.p. 207 °C (decomp.). ^{1}H NMR (500 MHz, $CDCl_3$, 57 °C): δ = 8.121 (d, ^3J = 6.9 Hz, 4 H, 10-H), 7.029–7.160 (m, 12 H, 7-H, 8-H, 9-H), 6.728 (s, 4 H, 3-H), 4.848 (d, ^2J = 11.9 Hz, 4 H, OCH_2), 4.759 (t, ^3J = 7.5 Hz, 4 H, ArCHAr), 4.637 (d, ^2J = 12.6 Hz, 4 H, OCH_2), 3.285 (s, 12 H, OCH_3), 1.811 (m, 8 H, $CHCH_2CH$), 1.682 [m, 4 H, $(CH_3)_2CH$], 1.027 [d, ^3J = 6.9 Hz, 12 H, $(CH_3)_2CH$], 1.010 [d, ^3J = 6.9 Hz, 12 H, $(CH_3)_2CH$] ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 154.31 (C-1), 151.91 (C-4a), 131.97 (Ar_q), 129.67 (Ar_q), 128.21 (C-7 or C-8 or C-9), 126.66 (C-7 or C-8 or C-9), 126.27 (C-3), 125.67 (C-10), 124.11 (C-7 or C-8 or C-9), 115.52 (C-10b), 68.38 (C-6), 59.74 (OCH_3), 44.05 ($CHCH_2CH$), 34.34 (ArCHAr), 25.97 [$(CH_3)_2CH$], 22.88 [$(CH_3)_2CH$] ppm. UV/Vis (cyclohexane): λ (ε, $mol^{-1}dm^3cm^{-1}$) = 224 (68000), 278 (50000), 316 (16000) nm. HRMS (ESI): calcd. for $C_{76}H_{84}NO_8^+$ $[M + NH_4]^+$ 1138.6192; found 1138.6200. $C_{76}H_{80}O_8 \cdot CHCl_3$ (1240.8): calcd. C 74.53, H 6.58; found C 74.52, H 6.33.

***rac*-3·1.5CHCl$_3$:** Crystal size 0.30 × 0.22 × 0.08 mm, triclinic, $P\bar{1}$, a = 12.4810(2) Å, b = 15.5000(3) Å, c = 18.5860(4) Å, α = 98.1190(9)°, β = 108.1580(10)°, γ = 95.1430(10)°, Z = 2, V = 3347.95(11) Å^3, $\rho_{calcd.}$ = 1.290 mg m^{-3}, $2\Theta_{max}$ = 54.96°, μ = 0.254 mm^{-1}, $F(000)$ = 1374, 841 parameters, R_1 = 0.0610, wR_2 = 0.1585 {for 11846 reflections [$I > 2\sigma(I)$]}, R = 0.0799, $wR(F_2)$ = 0.1745 (for 15260 unique reflections), R_{int} = 0.042, S = 1.023, $\Delta\rho$(min/max) = –0.75/0.61 e Å^{-3}.

(*M*,*R*)-(–)-Biaryl Ether (*M*,*R*)-(–)-3: (*M*,*R*)-(–)-**2** (200 mg, 138 μmol), dried K_2CO_3 (174 mg, 1.26 mmol) and DMA (10 mL) were placed and in a two-necked round-bottom flask. The suspension was degassed by two freeze–pump–thaw cycles. $Pd(OAc)_2$ (50.1 mg, 223 μmol) and $PCy_3 \cdot HBF_4$ (162 mg, 440 μmol) were added under an argon atmosphere. The yellow mixture was heated to 130 °C for 20 h. The suspension turned black and was filtered through silica gel. The solvent was removed under reduced pressure, and the residue was purified by column chromatography (SiO_2; cyclohexane/ethyl acetate, 95:5) to yield (*M*,*R*)-(–)-**3** as a colourless solid (18.1 mg, 12%). $[\alpha]_D^{25}$ = –7.1 (c = 1.00, $CHCl_3$). HRMS (ESI): calcd. for $C_{76}H_{88}NO_8^+$ $[M + NH_4]^+$ 1138.6192; found 1138.6199.

(*P*,*S*)-(+)-Biaryl Ether (*P*,*S*)-(+)-3: (*P*,*S*)-(+)-**2** (80.0 mg, 55.3 μmol), dried K_2CO_3 (86.1 mg, 623 mmol) and DMA (10 mL) were placed and in a two-necked round-bottom flask. The suspension was degassed by three freeze–pump–thaw cycles. $Pd(OAc)_2$ (18.0 mg, 80.0 μmol) and $PCy_3 \cdot HBF_4$ (24.7 mg, 162 μmol) were added under an argon atmosphere. The yellow mixture was heated to 130 °C for 20 h. The suspension turned black and was filtered through silica gel. The solvent was removed under reduced pressure, and the residue was purified by column chromatography (SiO_2; cyclohexane/ethyl acetate, 95:5) to yield (*P*,*S*)-(+)-**3** as a colourless solid (10.3 mg, 17%). $[\alpha]_D^{25}$ = +7.2 (c = 1.00, $CHCl_3$). HRMS (ESI): calcd. for $C_{76}H_{88}NO_8^+$ $[M + NH_4]^+$ 1138.6192; found 1138.6199.

Acknowledgments

We gratefully acknowledge financial support of the Deutsche Forschungsgemeinschaft and the Innovationsfonds der University of Bielefeld. M. P. thanks the Gleichstellungskommission der Fakultät für Chemie for a fellowship.

[1] a) C. D. Gutsche, *Calixarenes Revisited*, Royal Society of Chemistry, Cambridge, **1998**; b) B. Botta, M. Cassani, I. D'Acquatica, D. Misiti, D. Subissati, G. Delle Monache, *Curr. Org. Chem.* **2005**, *9*, 337–355.

[2] M. O. Vysotsky, C. Schmidt, V. Böhmer, *Advances in Supramolecular Chemistry* (Ed.: G. Gokel), JAI Press, Stamford, **2000**, vol. 7, pp. 139–233.

[3] A. Medizadeh, M. C. Letzel, M. Klaes, C. Agena, J. Mattay, *J. Mass Spectrometry* **2004**, *10*, 649–655.

[4] M. J. McIldowie, M. Mocerino, B. W. Skeleton, H. A. White, *Org. Lett.* **2000**, *2*, 3869–3871.

[5] J. Y. Boxhall, P. C. B. Page, M. R. J. Elsegood, Y. Chan, H. Heaney, K. E. Holmes, M. J. McGrath, *Synlett* **2003**, 1002–1006.

[6] B. R. Buckley, P. C. Bulman Page, Y. Chan, H. Heaney, M. Klaes, M. J. McIldowie, V. McKee, J. Mattay, M. Mocerino, E. Moreno, B. W. Skelton, A. H. White, *Eur. J. Org. Chem.* **2006**, 5135–5151.

[7] W. Iwanek, J. Mattay, *Liebigs Ann.* **1995**, 1463–1466.

[8] a) L.-C. Campeau, M. Parisien, A. Jean, K. Fagnou, *J. Am. Chem. Soc.* **2006**, *128*, 581–590; b) L.-C. Campeau, M. Parisien, M. Leblanc, K. Fagnou, *J. Am. Chem. Soc.* **2004**, *126*, 9186–9187; c) L.-C. Campeau, K. Fagnou, *Chem. Commun.* **2006**, 1253–1264.

[9] a) G. Bringmann, M. Breuning, S. Tasler, *Synthesis* **1999**, *4*, 525–558; b) For a review, see: G. Bringmann, A. J. Price Mortimer, P. A. Keller, M. J. Gresser, J. Garner, M. Breuning, *Angew. Chem.* **2005**, *117*, 5518–5563.

[10] M. Klaes, C. Agena, M. Köhler, M. Inoue, T. Wada, Y. Inoue, J. Mattay, *Eur. J. Org. Chem.* **2003**, 1404–1409.

[11] For a review, see: D. Alberico, M. E. Scott, M. Lautens, *Chem. Rev.* **2007**, *107*, 174.

[12] According to the Bringmann-lactone concept (see ref.[9]), tetrakis(2′-bromobenzoyl) ester resorcin[4]arene was synthesised in 82% yield (see ref.[13]), and it was estimated to be transformed into the tetralactone. Preliminary studies of the lactone formation of 3-methoxyphenol-based esters were carried out successfully. The lactone was formed in 78% overall yield as a 4:1 mixture of isomers with the bond formed in the 6- and 2-positions, respectively. Investigations on intramolecular coupling reactions of the resorcin[4]arene to yield the lactone with $Pd(OAc)_2$ and 2 equiv. of PPh_3 and $Pd(PPh_3)_2Cl_2$ with 2 equiv. per functionality of NaOAc in DMA at 120 °C led to decomposition of the resorcinarene and to ester hydrolysis. Therefore, we chose the ether functionality for further experiments, as it is less sensitive to cleavage.

[13] (±)-*rccc*-4,10,16,22-Tetrakis-*O*-(2′-bromobenzoyl)-2,8,14,20-tetraisobutyl-6,12,18,24-tetra-*O*-methylresorcin[4]arene: 2-bromobenzoic acid (2.64 g, 13.1 mmol) was treated with thionyl chloride (16.0 mL, 220 mmol) and heated to reflux for 10 min. The excess amount of thionyl chloride was removed in vacuo. The residue was dissolved in dry THF (15 mL). Pyridine (3.0 mL, 36.6 mmol) was added under an argon atmosphere and a colourless solid precipitated. A solution of (±)-*rccc*-2,8,14,20-tetraisobutyl-4,10,16,22-tetra-*O*-methylresorcin[4]-arene (*rac*-**1**; 1.00 g, 1.30 mmol) in THF (6 mL) was added slowly to the stirred suspension. After the mixture was stirred for 17 h, the solvent was removed in vacuo. The residue was dissolved in ethyl acetate (30 mL) and hydrochloric acid (20 mL). The layers were separated, and the organic phase was washed with $NaHCO_3$ solution (3 × 25 mL) and dried with $MgSO_4$. The solvent was removed in vacuo and the colourless solid was recrystallised from $CHCl_3$/EtOH (1:4) to give 1.59 g (82%) of the product. M.p. 256 °C (decomp.). ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 7.736 (dd, ^3J = 7.6 Hz, ^4J = 1.3 Hz, 4 H, 6′-H), 7.701 (d, ^3J = 8.2 Hz, 4 H, 3′-H), 7.496 (td, ^3J = 7.5 Hz, ^4J = 1.3 Hz, 4 H, 5′-H), 7.358 (td, ^3J = 8.2 Hz, ^4J = 1.9 Hz, 4 H, 4′-H), 6.751 (s, 4 H, ArH *meta* Ar-OCH_3), 6.478 (s, 4 H, ArH *ortho* Ar-OCH_3), 4.484 (t, ^3J = 7.6 Hz, 4 H, ArCHAr), 3.358 (s, 12 H, OCH_3), 1.762 (t, ^3J = 6.9 Hz, 8 H, $CHCH_2CH$), 1.615 [m, 4 H, $(CH_3)_2CH$], 0.879 [d, ^3J = 6.3 Hz, 12 H, $(CH_3)_2CH$], 0.796 [d, ^3J = 6.3 Hz, 12 H, $(CH_3)_2CH$] ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 163.76 (C=O), 155.20 (Ar-COH_3), 147.23 (*C*-OC=O), 134.47 (C-3′), 132.94 (C-4′),

132.27 (C-6′), 131.16 (C-1′), 130.55 (Ar_q *ortho* Ar-O), 128.10 (Ar_q *ortho* Ar-O), 127.39 (C-5′), 126.10 (ArH *meta* Ar-O), 122.28 (Ar-Br), 104.81 (ArH *ortho* Ar-O), 54.95 (OCH_3), 43.74 ($CHCH_2CH$), 33.97 (ArCHAr), 25.67 [$(CH_3)_2CH$], 22.86 [$(CH_3)_2CH$], 22.71 [$(CH_3)_2CH$] ppm. HRMS (ESI): calcd. for $C_{76}H_{80}Br_4NO_{12}^+$ [M + NH_4]$^+$ 1514.2409; found 1514.2425. $C_{76}H_{76}O_{12}Br_4$ (1500.2): calcd. C 60.81, H 5.10; found C 60.62, H 5.08.

[14] a) G. Bringmann, T. Hartung, L. Göbel, O. Schupp, C. L. J. Ewers, B. Schöner, R. Zagst, K. Peters, H. G. von Schnering, C. Burschka, *Liebigs Ann. Chem.* **1992**, 225–232; b) G. Bringmann, J. R. Jansen, *Heterocycles* **1989**, *28*, 137–142.

[15] R. J. Abraham, J. Fisher, *NMR Spectroscopy*, Wiley, New York, **1988**.

[16] a) F. Vögtle, A. Hünten, E. Vogel, S. Bischbeck, O. Safarowsky, J. Recker, A. Parham, M. Knott, W. Müller, U. Müller, Y. Okamoto, T. Kubota, W. Lindner, E. Francotte, S. Grimme, *Angew. Chem. Int. Ed.* **2001**, *40*, 2468–2471; b) N. Harada in *Circular Dichroism: Principles and Applications* (Eds.: N. Berova, K. Nakanishi, R. W. Woody), VCH, New York, **2000**, pp. 431–457.

Received: August 29, 2007
Published Online: November 12, 2007

