First Synthesis, Isolation and Complete Characterization of Both Enantiomers of Inherently Chiral Resorc[4]arenes by Monofunctionalization

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The monofunctionalization of *rccc*-2,8,14,20-tetramethylresorc[4]arene **(1)** with (*S*)-(+)-10-camphorsulfonyl chloride led to a diastereomeric mixture of **(+)-2a** and **(–)-2b**, which were separated by HPLC. Permethylation of these compounds was achieved with diazomethane. The inherently chiral, enantiomerically pure resorc[4]arenes **(+)-4** and **(–)-4** were obtained by alkaline hydrolysis of **(+)-3a** or **(+)-3b**, respectively.

Introduction

Resorc[4]arenes are cavity-shaped macrocycles which can be easily synthesized from resorcinol and aldehydes.[1,2] They have attracted much interest in the field of supramolecular chemistry as artificial receptors and starting materials for the preparation of more sophisticated molecules. Due to their structural features they play an important rule as host molecules for a variety of neutral and charged guest compounds.

The synthesis of chiral resorc[4]arenes is still a challenge, especially in supramolecular chemistry. Enantiomerically pure resorc[4]arenes have been prepared by Mannich reactions of resorc[4]arenes with an excess of formaldehyde and chiral amines or α-amino alcohols, yielding 1,3-oxazine-[3−5] or 1,3-oxazolidine derivatives[6] of the resorc[4]arenes. Chiral resorc[4]arenes can also be obtained from this type of reaction with amino acids such as L-proline.[5,7] One chiral resorc[4]arene with four methylene L-proline ethyl ester substituents is known in the literature. This compound was synthesized from the corresponding tetrabromomethyl resorc[4]arene.[8] All these compounds possess middle C_4 symmetry due to fast equilibration between various conformers, such as *crown* and *boat* forms, but only the 1,3-oxazine derivatives are inherently chiral at room temperature in solution. The methylation of the four residual phenolic groups of the 1,3-oxazine derivatives can be achieved without epimerization. After the removal of the chiral auxiliary, enantiomerically pure resorc[4]arenes were obtained.[9] Chiral C_2 symmetrical resorc[4]arenes based on 1,3-oxazine rings have been described by Böhmer et al.[10]

Another approach to synthesize inherently chiral resorc[4]arenes is the modification of only one of the eight phenolic groups, which leads to a racemic mixture of monofunctionalized asymmetric resorc[4]arenes. In 1996 Konishi et al.[11] reported the mono-*O*-benzylation of resorc[4]arene **1** in 32% yield. Furthermore, the per-*O*-acetylated mono-*O*-benzylated- and hepta-*O*-acetylated resorc[4]arenes were described, but none of these racemic mixtures were separated into the enantiomerically pure compounds. The authors only produced evidence that the mono-*O*-benzylation of the resorc[4]arene **1** leads to a racemic mixture by means of ^{1}H NMR measurements with chiral shift reagents.

In this paper we report the first synthesis of inherently chiral, enantiomerically pure resorc[4]arenes by mono-*O*-functionalization. The key-step in our approach is the mono-*O*-functionalization of the resorc[4]arene **1** with a chiral auxiliary, yielding two diastereomers that can easily be separated. These compounds have to be stable against epimerization by a shift of the chiral residue from one OH-group to another.

Results and Discussion

The *rccc*-2,8,14,20-tetramethylresorc[4]arene **(1)** was treated with (*S*)-(+)-10-camphorsulfonyl chloride (1 equivalent) in dry acetonitrile in the presence of an excess of potassium carbonate (Figure 1). This reaction leads to a mixture which contains the mono-*O*-esterified diastereomers **(+)-2a** and **(−)-2b**, higher esterified resorc[4]arenes and the starting material **1**.

Separation of the two diastereomeric compounds **(+)-2a** and **(−)-2b** was achieved by RP-18 HPLC in overall yield of 21%. As expected both mono-*O*-esterified diastereomers were formed in equal amounts and showed specific rotations of $[\alpha]^{25}_{589} = +34.9$ ($c = 1.28$ in acetonitrile) and $[\alpha]^{25}_{577} = -9.6$ ($c = 1.02$ in acetonitrile), respectively. The ^{1}H NMR spectra of both compounds recorded at 25 °C

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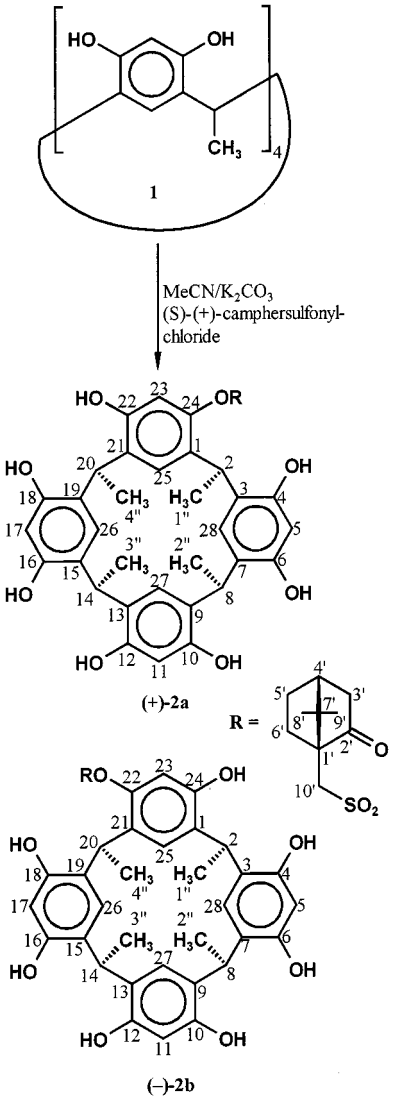

Figure 1. Monofunctionalization of *rccc*-resorc[4]arene **1** to the diastereomers **(+)-2a** and **(−)-2b**

showed eight sharp singlets of the aromatic protons, indicating either fixed conformations or a fast interconversion of the two *boat*-conformers on the NMR time scale. Almost all ^{1}H and ^{13}C NMR resonance peaks could be assigned by means of COSY, HSQC and HMBC experiments. Since phenolic sulfonic acid esters are stable under acid conditions but unstable towards strong nucleophiles it was necessary to carry out the permethylation in the absence of base. This problem was solved by using an excess of ethereal diazomethane solution in the presence of silica gel as the Lewis acid (Figure 2), leading to the permethylated pure resorc[4]arenes **(+)-3a** and **(+)-3b** without epimerization in 48% and 44% yield, respectively. Both compounds showed specific rotations of $[\alpha]_{589}^{24} = +21.2$ ($c = 0.75$ in $CHCl_3$) and $[\alpha]_{589}^{24} = +2.6$ ($c = 0.60$ in $CHCl_3$), respectively.

Whereas the NMR signals of the aromatic protons of both diastereomers were broad, the peaks of the camphorsulfonic acid residue were sharp pointing to a slow interconversion of two different *boat*-conformers on the ^{1}H NMR time scale. The spectra were therefore measured in $CDCl_2CDCl_2$ at 65 °C, leading to sharper signals. An almost complete assignment of all NMR resonances for **(+)-3a** was possible by the use of 2D NMR experiments. However, the NMR signals for **(+)-3b** were less well resolved, and an exact assignment could not be made. The chiral aux-

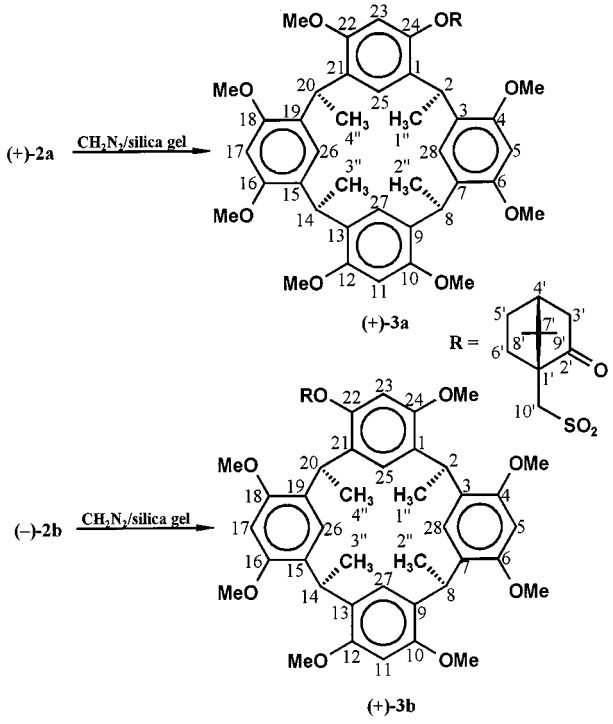

Figure 2. Permethylation of compound **(+)-2a** and **(−)-2b**

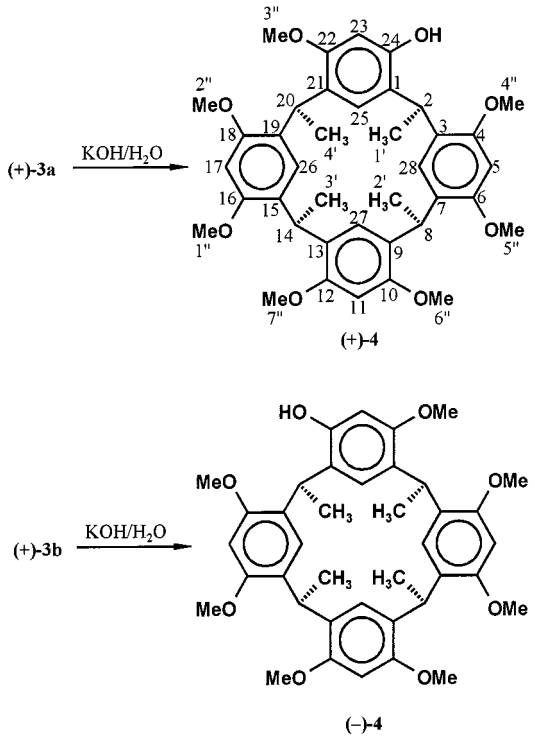

Figure 3. Alkaline hydrolysis to the resorc[4]arenes **(+)-4** and **(−)-4**

iliary was removed by treating the resorc[4]arenes **(+)-3a** and **(+)-3b** with aqueous potassium hydroxide solution (Figure 3), leading to the enantiomeric compounds **(+)-4** and **(−)-4** in 93% and 85% yield, respectively. They showed specific rotations of $[\alpha]_{546}^{26} = +15.0$ ($c = 0.88$ in CH_2Cl_2) and $[\alpha]_{546}^{26} = -15.1$ ($c = 0.75$ in CH_2Cl_2).

Identical IR and NMR spectra, melting points and HRMS spectra clearly showed that both compounds are enantiomers. Nearly all ^1H and ^{13}C NMR resonance peaks could be assigned exactly with the help of COSY, HSQC and HMBC experiments.

Conclusion

In summary, we have synthesized a new type of inherently chiral, enantiomerically pure resorc[4]arene by mono-*O*-functionalization of **1** with (*S*)-(+)-10-camphorsulfonyl chloride, leading to the diastereomers **(+)-2a** and **(−)-2b**. After permethylation and removal of the chiral auxiliary both enantiomeric resorc[4]arenes **(+)-4** and **(−)-4** were obtained. These inherently chiral resorc[4]arenes have the advantage that they are stable towards moderate acid and basic conditions. Our ongoing investigations aim at the preparation of other chiral resorc[4]arenes by this new reaction sequence and the applications of these compounds in chiral discrimination processes.

Experimental Section

General: All solvents used were of p.a. quality or were purified by distillation. Acetonitrile was dried with molecular sieves 3 Å. *rccc*-2,8,14,20-Tetramethylresorc[4]arene (**1**) was prepared as described in the literature.[1] Melting points were determined on a Büchi B-540 apparatus and are uncorrected. NMR spectra were measured on a Bruker DRX 500 instrument (^1H NMR: 500.13 MHz; ^{13}C NMR: 125.77 MHz) with tetramethylsilane (TMS) as reference ($\delta = 0$). IR spectra were recorded on a Perkin- Elmer 841 infrared Spectrophotometer. HRMS were measured on a Bruker APEX II 7T with ESI in positive ion mode and spectra were externally calibrated with a CSD spectrum of LHRH free acid ($m/z = 500-1200$). HPLC separations were performed with a PREP 2025 (250 × 20 mm) LICHROSORB RP 18 (7.0 μm) column from Bischoff Chromatography or a SP 250/21 Nucleosil 100−7 column from Macherey−Nagel and UV detection at 280 nm. Specific rotations were measured on a Jasco DIP-360 digital polarimeter.

Synthesis of (+)-*rccc*-24-*O*-[(*S*)-10′-camphorsulfonyl]-2,8,14,20-tetramethylresorc[4]arene (+)-2a and (−)-*rccc*-22-*O*-[(*S*)-10′-camphorsulfonyl]-2,8,14,20-tetramethylresorc[4]arene (−)-2b: *rccc*-2,8,14,20-Tetramethylresorc[4]arene (**1**; 4.00 g, 7.34 mmol) was dissolved in dry acetonitrile (3000 mL), and potassium carbonate (4.06 g, 29.3 mmol) was added under an argon atmosphere. At ambient temperature, a solution of (*S*)-(+)-10-camphorsufonyl chloride (1.84 g, 7.34 mmol) in dry acetonitrile (600 mL) was added drop by drop over a period of 6 h. The reaction mixture was stirred for an additional four days and the solvent was then removed under reduced pressure. The resulting residue was suspended in water, acidified with conc. hydrochloric acid and extracted three times with ethyl acetate. The combined organic layers were washed twice with dilute hydrochloric acid and dried with $MgSO_4$. The crude product was purified by HPLC (RP-18, MeCN/H_2O, 60:40) to afford the starting material **1** (900 mg, 1.65 mmol, 23%), **(+)-2a** (590 mg, 0.78 mmol, 11%) and **(−)-2b** (596 mg, 0.79 mmol, 11%) as red brown solids.

(+)-2a: M.p. 210 °C (dec.). − IR (KBr): $\tilde{\nu}$ = 3411, 2971, 1739, 1618, 1502, 1431, 1352, 1281, 1170, 1099, 1023, 895, 840, 807, 761 cm^{-1}. − $[\alpha]_{589}^{25} = +34.9$ ($c = 1.28$ in MeCN). − HRMS [M + H^+: $C_{42}H_{44}O_{11}S$]: calcd. 759.2833; found 759.2829; declination 0.4 mmu/0.5 ppm. − ^1H NMR (500 MHz, CD_3OD, 25 °C): δ = 0.87 and 1.02 (s, 6 H, 8′-H and 9′-H), 1.41 (ddd, ^2J = 12.2, ^3J = 9.3 Hz, ^3J = 4.1 Hz, 1 H, 5′$_{endo}$-H), 1.52 (d, ^3J = 7.2 Hz, 6 H, 1′′-H and 2′′-H), 1.53 (d, ^3J = 7.2 Hz, 3 H, 3′′-H), 1.56 (d, ^3J = 7.2 Hz, 3 H, 4′′-H), 1.68 (ddd, ^2J = 14.0, ^3J = 9.4 Hz, ^3J = 4.7 Hz, 1 H, 6′$_{endo}$-H), 1.92 (d, ^2J = 18.5 Hz, 1 H, 3′$_{endo}$-H), 2.01 (m, 1 H, 5′$_{exo}$-H), 2.04 (dt, ^3J = 4.5, ^3J = 4.2 Hz, 1 H, 4′-H), 2.32 (ddd, ^2J = 14.4, ^3J = 10.9, ^3J = 3.8 Hz, 1 H, 6′$_{exo}$-H), 2.38 (ddd, ^2J = 18.4, ^3J = 5.0 Hz, ^4J = 3.4 Hz, 1 H, 3′$_{exo}$-H), 3.31 (d, ^2J = 15.0 Hz, 1 H, 10$_b$′-H), 3.73 (d, ^2J = 15.0 Hz, 1 H, 10$_a$′-H), 4.52 (q, ^3J = 7.0 Hz, 1 H, 8-H), 4.53 (q, ^3J = 7.0 Hz, 1 H, 14-H), 4.63 (q, ^3J = 7.2 Hz, 1 H, 20-H), 4.68 (q, ^3J = 7.1 Hz, 1 H, 2-H), 6.21, 6.26 and 6.28 (s, 3 H, 5-H, 11-H and 17-H), 6.67 (s, 1 H, 28-H), 6.97 (s, 1 H, 27-H), 6.73 (s, 1 H, 23-H), 6.74 (s, 1 H, 26-H), 7.15 (s, 4 H, 25-H). − ^{13}C NMR (125 MHz, CD_3OD, 25 °C): δ = 19.9 (C-8′ and C-9′), 20.6 (C-4′′), 20.8 (C-3′′), 20.9 (C-2′′), 21.5 (C-1′′), 26.5 (C-6′), 27.6 (C-5′), 30.6 (C-14), 30.9 (C-8), 31.2 (C-20), 31.5 (C-2), 43.3 (C-3′), 44.2 (C-4′), 49.1 (C-7′), 49.3 (C-10′), 59.3 (C-1′), 103.6, 103.7 and 103.8 (C-5, C-11 and C-17), 109.8 (C-23), 124.9 and 124.96 (C-9 and C-13), 125.007 (C-19), 125.013 (C-3), 125.5 (C-7), 125.8 (C-15), 126.1 (C-26), 126.2 (C-27), 126.4 (C-28), 127.1 (C-25), 130.6 (C-1), 132.9 (C-21), 146.1 (C-24), 153.4 and 153.47 (C-12 and C-16), 153.48 and 153.5 (C-6 and C-10), 153.5 (C-4), 153.6 (C-22), 153.7 (C-18), 216.4 (C-2′).

(−)-2b: M.p. 210 °C (dec.). − IR (KBr): $\tilde{\nu}$ = 3379, 2970, 1738, 1618, 1502, 1431, 1356, 1280, 1171, 1098, 1023, 981, 896, 841, 806, 762 cm^{-1}. − $[\alpha]_{577}^{25} = -9.6$ ($c = 1.02$ in MeCN). − HRMS [M + H^+: $C_{42}H_{44}O_{11}S$]: calcd. 759.2833; found 759.2827; declination 0.6 mmu/0.8 ppm. − ^1H NMR (500 MHz, CD_3OD, 25 °C): δ = 0.91 and 1.11 (s, 6 H, 8′-H and 9′-H), 1.42 (ddd, ^2J = 12.1, ^3J = 9.4 Hz, ^3J = 4.0 Hz, 1 H, 5$_{endo}$′-H), 1.517 (d, ^3J = 7.2 Hz, 3 H, 4′′-H), 1.523 (d, ^3J = 7.2 Hz, 3 H, 3′′-H), 1.53 (d, ^3J = 7.2 Hz, 3 H, 2′′-H), 1.56 (d, ^3J = 7.2 Hz, 3 H, 1′′-H), 1.67 (ddd, ^2J = 14.0, ^3J = 9.4 Hz, ^3J = 4.7 Hz, 1 H, 6′$_{endo}$-H), 1.93 (d, ^2J = 18.6 Hz, 1 H, 3′$_{endo}$-H), 2.03 (m, 1 H, 5′$_{exo}$-H), 2.06 (m, 1 H, 4′-H), 2.39 (dddd, ^2J = 18.9, ^3J = 4.8 Hz, ^4J = 3.2, ^4J = 0.8 Hz, 1 H, 3′$_{exo}$-H), 2.40 (m, 1 H, 6′$_{exo}$-H), 3.46 (d, ^2J = 15.0 Hz, 1 H, 10′$_b$-H), 3.69 (d, ^2J = 15.0 Hz, 1 H, 10′$_b$-H), 4.52 (q, ^3J = 7.1 Hz, 1 H, 14-H), 4.53 (q, ^3J = 7.1 Hz, 1 H, 8-H), 4.63 (q, ^3J = 7.1 Hz, 1 H, 2-H), 4.66 (q, ^3J = 7.1 Hz, 1 H, 20-H), 6.24 (s, 1 H, 11-H), 6.26 (s, 1 H, 17-H), 6.27 (s, 1 H, 5-H), 6.70 (s, 1 H, 26-H), 6.75 (s, 1 H, 23-H), 6.76 (s, 1 H, 28-H), 6.95 (s, 1 H, 27-H), 7.13 (s, 1 H, 25-H). − ^{13}C NMR (125 MHz, CD_3OD, 25 °C): δ = 19.97 and 20.00 (C-8′ and C-9′), 20.6 (C-1′′), 20.79 (C-2′′), 20.83 (C-3′′), 21.5 (C-4′′), 26.7 (C-6′), 27.6 (C-5′), 30.7 (C-8), 30.9 (C-14), 31.2 (C-2), 31.6 (C-20), 43.3 (C-3′), 44.2 (C-4′), 49.1 (C-7′), 49.3 (C-10′), 59.3 (C-1′), 103.6 (C-17), 103.7 (C-5), 103.9 (C-11), 109.8 (C-23), 124.86, 124.88, 125.06 and 125.09 (C-3, C-7, C-13 and C-19), 126.11 (C-28), 126.2 (C-27), 126.3 (C-26), 127.1 (C-25), 130.7 (C-21) 133.0 (C-1), 146.1 (C-22), 153.3 and 153.49 (C-10 and C-12), 153.4 and 153.51 (C-4 and C-6), 153.56 (C-16), 153.58 (C-18), 153.7 (C-24), 216.4 (C-2′).

Synthesis of (+)-*rccc*-24-*O*-[(*S*)-10′-camphorsulfonyl]-2,8,14,20-tetramethyl-4,6,10,12,16,18,22-hepta-*O*-methylresorc[4]arene (+)-3a. Procedure 1: The monosulfonated resorc[4]arene **(+)-2a** (229 mg, 302 μmol) was dissolved in acetone. Silica gel (4.2 g)[12] was added and the suspension was stirred for 30 min. at ambient temperature. The solvent was removed under reduced pressure and the solid residue was dried in vacuo. At 0 °C, an ethereal diazomethane solution (120 mL, 84.6 mmol) was added in small portions within two days. The reaction was monitored by MALDI-TOF (matrix DHB) and was stopped after almost no partially methylated products could be detected. The reaction mixture was then filtered through silica gel (cyclohexane/ethyl acetate, 60:40). The residue was purified by HPLC (Si-100, cyclohexane/ethyl acetate, 60:40) to yield 123 mg (144 μmol, 48%) of **(+)-3a** as a colourless solid. − M.p. 256−257 °C (dec.). − IR (KBr): $\tilde{\nu}$ = 2968, 2837, 1751, 1702, 1613, 1584, 1561, 1546, 1502, 1466, 1400, 1365, 1300, 1244, 1200, 1121, 1087, 1035, 980, 961, 897, 863, 839, 817, 780, 751, 720, 683 cm^{-1}. − $[\alpha]_{589}^{24}$ = +21.2 (*c* = 0.75 in $CHCl_3$). − HRMS [M + Na^+: $C_{49}H_{60}O_{11}SNa^+$]: calcd. 879.3749; found 879.3750; declination 0.1 mmu/0.1 ppm. − ^{1}H NMR (500 MHz, $CDCl_2CDCl_2$, 338 K): δ = 0.92 and 1.16 (s, 6 H, 8′-H and 9′-H), 1.444 and 1.445 (d, ^3J = 7.2 Hz, 6 H, 2′′-H and 3′′-H), 1.459 (d, ^3J = 7.2 Hz, 3 H, 4′′-H), 1.461 (m, 1 H, 5′$_{endo}$-H), 1.50 (d, ^3J = 7.2 Hz, 3 H, 1′′-H), 1.73 (ddd, ^2J = 14.1, ^3J = 9.3 Hz, ^3J = 4.7 Hz, 1 H, 6′$_{endo}$-H), 1.97 (d, ^2J = 18.4 Hz, 1 H, 3′$_{endo}$-H), 2.08 (m, 1 H, 5′$_{exo}$-H), 2.14 (dd, ^3J = 4.5, ^3J = 4.5 Hz, 1 H, 4′-H), 2.43 (ddd, ^2J = 18.4, ^3J = 4.5 Hz, ^4J = 3.0 Hz, 1 H, 3′$_{exo}$-H), 2.49 (ddd, ^2J = 14.1, ^3J = 11.6, ^3J = 4.0 Hz, 1 H, 6′$_{exo}$-H), 3.25 (d, ^2J = 15.0 Hz, 1 H, 10′$_a$-H), 3.579 (s, 3 H, OMe at C-16), 3.585 and 3.652 (s, 6 H, OMe at C-12 and C-18), 3.590 and 3.594 (s, 6 H, OMe at C-4 and C-6), 3.69 (s, 3 H, OMe at C-10), 3.70 (s, 3 H, OMe at C-22), 3.82 (d, ^2J = 15.0 Hz, 1 H, 10′$_b$-H), 4.586 (q, ^3J = 7.2 Hz, 1 H, 2-H), 4.590 (q, ^3J = 7.2 Hz, 1 H, 14-H), 4.601 (q, ^3J = 7.2 Hz, 1 H, 8-H), 4.64 (q, ^3J = 7.2 Hz, 1 H, 20-H), 6.308 (s, 1 H, 11-H), 6.311 (s, 1 H, 17-H), 6.38 (s, 1 H, 5-H), 6.50 (s, 1 H, 27-H), 6.65 (s, 2 H, 26-H and 28-H), 6.68 (s, 1 H, 25-H), 6.83 (s, 1 H, 23-H). − ^{13}C NMR (125 MHz, $CDCl_2CDCl_2$, 338 K): δ = 19.5 and 19.71 (C-8′ and C-9′), 19.69 (C-4′′), 19.88 (C-2′′), 19.93 (C-3′′), 20.1 (C-1′′), 25.3 (C-6′), 26.8 (C-5′), 30.2 (C-8), 30.4 (C-14), 30.5 (C-20), 31.1 (C-2), 42.4 (C-3′), 43.0 (C-4′), 47.6 (C-7′), 48.6 (C-10′), 55.8 (OMe at C-12), 56.07 (OMe at C-22), 56.09 (OMe at C-4), 56.15 (OMe at C-6), 56.18 (OMe at C-16), 56.3 (OMe at C-18), 56.4 (OMe at C-10), 58.1 (C-1′), 97.2 (C-11), 97.7 (C-17), 97.9 (C-5), 104.8 (C-23), 125.0 (C-26), 125.1 (C-27), 125.3 (C-28), 125.96 (C-25), 126.01 (C-9), 126.8 (C-19), 127.8 (C-7, C-13 and C-15), 128.1 (C-3), 130.6 (C-1), 134.5 (C-21), 145.0 (C-24), 155.2 (C-22), 155.3 (C-4), 155.5 (C-12 and C-18), 155.6 (C-10), 155.8 (C-16), 156.0 (C-6), 213.5 (C-2′).

Synthesis of (+)-*rccc*-22-*O*-[(*S*)-10′-camphorsulfonyl]-2,8,14,20-tetramethyl-4,6,10,12,16,18,24-hepta-*O*-methylresorc[4]arene (+)-3b: Prepared following procedure 1 above: **(−)-2b** (200 mg, 264 μmol), silica gel (3.7 g), ethereal diazomethane solution (105 mL, 73.9 mmol). The residue was purified by HPLC (Si-60, cyclohexane/ethyl acetate, 60:40) to yield 100 mg (117 μmol, 44%) of **(+)-3b** as a colourless solid. − M.p. 232 °C. − IR (KBr): $\tilde{\nu}$ = 2964, 2836, 1749, 1613, 1584, 1501, 1400, 1367, 1299, 1201, 1123, 1108, 1036, 980, 962, 896, 841, 817 cm^{-1}. − $[\alpha]_{589}^{24}$ = +2.6 (*c* = 0.60 in $CHCl_3$). − HRMS [M + Na^+: $C_{49}H_{60}O_{11}SNa^+$]: calcd. 879.3749; found 879.3753; declination 0.4 mmu/0.5 ppm. − ^{1}H NMR (500 MHz, $CDCl_2CDCl_2$, 338 K): δ = 0.95 and 1.19 (s, 6 H, 8′-H and 9′-H), 1.45 (d, ^3J = 7.1 Hz, 6 H, 2′′-H and 3′′-H), 1.460 (m, 1 H, 5′$_{endo}$-H), 1.461 (d, ^3J = 7.1 Hz, 3 H, 1′′-H), 1.50 (d, ^3J = 7.1 Hz, 3 H, 4′′-H), 1.72 (ddd, ^2J = 14.0, ^3J = 9.3 Hz, ^3J = 4.7 Hz, 1 H, 6′$_{endo}$-H), 1.98 (d, ^2J = 18.4 Hz, 1 H, 3′$_{endo}$-H), 2.10 (dddd, ^2J = 16.1, ^3J = 12.1, ^3J = 4.7 Hz, ^3J = 4.0 Hz, 1 H, 5′$_{exo}$-H), 2.15 (dd, ^3J = 4.0, ^3J = 4.0 Hz, 1 H, 4′-H), 2.43 (ddd, ^2J = 18.4, ^3J = 4.0 Hz, ^4J = 4.0 Hz, 1 H, 3′$_{exo}$-H), 2.54 (ddd, ^2J = 14.0, ^3J = 12.1, ^3J = 4.0 Hz, 1 H, 6′$_{exo}$-H), 3.28 (d, ^2J = 15.0 Hz, 1 H, 10′$_a$-H), 3.57 (s, 3 H, OMe), 3.58 (s, 3 H, OMe), 3.59 (s, 6 H, 2 × OMe), 3.67 (s, 3 H, OMe), 3.71 (s, 6 H, 2 × OMe), 3.80 (d, ^2J = 15.0 Hz, 1 H, 10′$_b$-H), 4.56 (q, ^3J = 7.1 Hz, 1 H, 20-H), 4.59 and 4.61 (q, ^3J = 7.1 Hz, 2 H, 8-H and 14-H), 4.64 (q, ^3J = 7.1 Hz, 1 H, 2-H), 6.308, 6.311 and 6.40 (s, 3 H, H-5, 11-H and 17-H), 6.47, 6.65, 6.66 and 6.67 (s, 4 H, 25-H, 26-H, 27-H and 28-H), 6.85 (s, 1 H, 23-H). − ^{13}C NMR (125 MHz, $CDCl_2CDCl_2$, 338 K): δ = 19.5 (C-2), 19.6 and 19.75 (C-8′ and C-9′), 19.86 and 19.88 (C-2′′ and C-3′′), 20.5 (C-4′′), 25.2 (C-6′), 26.8 (C-5′), 30.39 and 30.40 (C-8 and C-14), 30.6 (C-2), 31.2 (C-20), 42.4 (C-3′), 43.0 (C-4′), 47.7 (C-7′), 48.4 (C-10′), 55.8, 56.05, 56.06, 56.15, 56.18, 56.23 and 56.4 (7× OMe), 97.3, 97.7 and 97.8 (C-5, C-11 and C-17), 104.9 (C-23), 125.03, 125.04, 125.3 and 125.8 (C-25, C-26, C-27 and C-28), 125.7, 126.7, 127.7, 127.8, 127.9 and 128.1 (C-3, C-7, C-9, C-13, C-15 and C-19), 130.5 (C-21), 134.6 (C-1), 145.0 (C-22), 155.2 (C-24), 155.3, 155.5, 155.59, 155.60, 155.9 and 156.1 (C-4, C-6, C-10, C-12, C-16 and C-18), 213.6 (C-2′).

Synthesis of (+)-*rccc*-2,8,14,20-tetramethyl-4,6,10,12,16,18,22-hepta-*O*-methyl-resorc[4]arene (+)-4. Procedure 2: Resorc[4]arene **(+)-3a** (64 mg, 74.7 μmol) was suspended in ethanol (10 mL) and aqueous potassium hydroxide solution (8 mL, 20% by weight) was added under argon. The reaction mixture was stirred for 4 h at 120 °C until a clear solution was obtained, and was then allowed to warm to room temp. The mixture was acidified with conc. hydrochloric acid and diluted with water (130 mL). The resulting suspension was extracted with CH_2Cl_2 (2 × 75 mL) and the combined organic layers were washed with dilute hydrochloric acid (3 × 30 mL) and dried with $MgSO_4$. After removing the solvent under reduced pressure and drying the residue in vacuo the monohydroxy resorc[4]aren **(+)-4** (44 mg, 69 μmol, 93%) was obtained as a colourless solid. − M.p. 279 °C (dec.). − IR (KBr): $\tilde{\nu}$= 3543, 2965, 2878, 2836, 1585, 1500, 1466, 1400, 1365, 1299, 1201, 1165, 1121, 1106, 1036, 958, 893, 816 cm^{-1}. − $[\alpha]_{546}^{26}$ = +15.0 (*c* = 0.88 in CH_2Cl_2). − HRMS [M + Na^+, $C_{39}H_{46}O_8Na^+$]: calcd. 665.3085; found 665.3098; declination 1.3 mmu/2.0 ppm.

Synthesis of (−)-*rccc*-2,8,14,20-tetramethyl-4,6,10,12,16,18,24-hepta-*O*-methylresorc[4]arene (−)-4: Prepared analogously to procedure 2 above with **(+)-3b** (33 mg, 38.5 μmol) as starting material. From this reaction the hepta-*O*-methylresorc[4]arene **(−)-4** (21 mg, 33 μmol, 85%) was obtained as a colourless solid. − m.p: 279 °C (dec.). − IR (KBr): $\tilde{\nu}$ = 3543, 2965, 2877, 2835, 1583, 1503, 1466, 1400, 1364, 1299, 1200, 1164, 1121, 1106, 1035, 959, 893, 817 cm^{-1}. − $[\alpha]_{546}^{26}$ = −15.1 (*c* = 0.75 in CH_2Cl_2). − HRMS [M + Na^+, $C_{39}H_{46}O_8Na^+$]: calcd. 665.3085; found 665.3087; declination 0.2 mmu/0.3 ppm. − ^{1}H NMR (500 MHz, CD_2Cl_2, 25 °C): δ = 1.305 (d, ^3J = 7.2 Hz, 3 H, 1′-H), 1.313 (d, ^3J = 7.2 Hz, 3 H, 4′-H), 1.317 (d, ^3J = 7.2 Hz, 3 H, 3′-H), 1.38 (d, ^3J = 7.0 Hz, 3 H, 2′-H), 3.35 (s, 3 H, 7′′-H), 3.38 (s, 3 H, 3′′-H), 3.43 (s, 3 H, 6′′-H),3.754 and 3.755 (s, 6 H, 1′′-H and 2′′-H), 3.780 (s, 3 H, 5′′-H), 3.784 (s, 3 H, 4′′-H), 4.28 (q, ^3J = 7.0 Hz, 1 H, 2-H), 4.42 (q, ^3J = 7.2 Hz, 1 H, 20-H), 4.446 (q, ^3J = 7.2 Hz, 1 H, 14-H), 4.454 (q, ^3J = 7.2 Hz, 1 H, 8-H), 5.98 (s, 1 H, 26-H), 6.07 (s, 1 H, 23-H), 6.15 (s, 1 H, 11-H), 6.20 (s, 1 H, 28-H), 6.39 (s, 1 H, 17-H), 6.41 (s, 1 H, 5-H), 6.92 (s, 1 H, 25-H), 6.95 (s, 1 H, 27-H). − ^{13}C NMR (125 MHz, CD_2Cl_2, 25 °C): δ = 19.83 (C-3′), 19.87 (C-4′), 19.95 (C-2′), 20.05 (C-1′), 30.40 (C-2), 30.43 (C-8), 30.46 (C-14), 30.7 (C-20), 55.7 (C-3′′), 55.8 (C-4′′), 55.99 (C-7′′), 56.03 (C-5′′), 56.05,

56.07, 56.09 (C-6′′, C-1′′, C-2′′), 95.4 (C-5), 95.9 (C-17), 97.3 (C-11), 99.8 (C-23), 122.2 (C-1), 124.4 (C-3), 125.0 (C-26), 125.43 (C-9), 125.45 (C-27), 125.46 (C-25), 125.6 (C-21), 125.8 (C-13), 126.1 (C-28), 128.3 (C-15), 128.6 (C-19), 129.3 (C-7), 152.4 (C-24), 155.2 (C-4), 155.35 (C-16), 155.37 (C-18), 156.2 (C-10), 156.31 (C-22), 156.33 (C-12), 156.38 (C-6).

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