First Synthesis, Isolation and Characterization of Enantiomerically Pure and Inherently Chiral Resorc[4]arenes by Lewis Acid Cyclization of a Resorcinol Monoalkyl Ether

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Keywords: Resorc[4]arenes / Monofunctionalization / Circular dichroism / Asymmetric synthesis / Chirality

Cyclization of resorcinol monoalkyl ethers with aliphatic aldehydes leads to the corresponding racemic mixtures of C_4-symmetric *rccc*-resorc[4]arenes. Separation of these isomers was achieved by mono-*O*-functionalization of the *rccc*-2,8,14,20-tetramethylresorc[4]arene (**2**) with (*S*)-(+)-10-camphorsulfonyl chloride leading to a diastereomeric mixture of **(+)-5a** and **(–)-5b**. After removal of the chiral auxiliary the inherently chiral pure enantiomers **(+)-2** and **(–)-2** were obtained. Further enantiomerically pure *rccc*-resorc[4]arenes were obtained by cyclization of (+)-3-[(2*S*)-2-methylbutoxy]-phenol (**6**) followed by chromatographic separation. The resulting diastereomeric resorc[4]arenes **(+)-7a** and **(–)-7b** were examined by CD spectroscopy, showing a perfect mirror image in all solvents examined. This indicates that the resorcarene cavities of **(+)-7a** and **(–)-7b** are essentially enantiomers of each other.

Introduction

Resorcarenes are unique three-dimensional cyclic aromatic tetramers which are easily available by well-established one-pot procedures.[1,2] They have attracted much interest in the field of supramolecular chemistry as artificial receptors and as starting materials for the preparation of more sophisticated molecules. Due to their structural features they play an important role as host molecules for a variety of neutral and charged guest compounds.[3–5]

The synthesis of inherently chiral resorc[4]arenes is still a challenge in synthetic organic chemistry.

An early example of the preparation of such molecules is the Mannich reaction of resorc[4]arenes with a sufficient excess of formaldehyde and chiral amines or amino alcohols, leading either to 1,3-oxazine[6–8] or 1,3-oxazolidine derivatives.[9] Instead of chiral amines amino acids like L-proline can be used as well.[8,10] The inherently chiral 1,3-oxazine derivatives are very sensitive to acidic and basic conditions due to their *N*,*O*-acetal functions. The epimerization can be prevented by methylation of the four residual phenolic groups as described in the literature.[11] After removal of the chiral auxiliary enantiomerically pure, inherently chiral resorcarenes are obtained.

Last year we published the first example of our synthetic strategy towards inherently chiral, enantiomerically pure *rccc*-hepta-*O*-methylresorc[4]arenes with monofunctionalization with a chiral auxiliary as the key step. These C_1-symmetric compounds are stable towards moderately acidic and basic conditions.[12]

In 2000 Mocerino and co-workers published the cyclization of 3-alkoxyphenols with aliphatic aldehydes leading to the corresponding C_4-symmetric *rccc*-resorc[4]arenes, which are obtained as racemic mixtures. This cyclization method with $BF_3{\cdot}OEt_2$ can be considered as a breakthrough in this area (Figure 1).[13] However, the separation of these enantiomers has not been reported in the literature.

In this paper we report the first synthesis of inherently chiral and enantiomerically pure resorc[4]arenes following this cyclization method. The first key step in our approach is the mono-*O*-functionalization of the resorc[4]arenes **2** with a chiral auxiliary yielding two diastereomers **(+)-5a** and **(–)-5b** which can easily be separated. The second approach is the use of an enantiomerically pure 3-alkoxyphenol as chiral building block for the cyclization reaction to obtain readily separable diastereomers.

Results and Discussion

Synthesis and Structure

The cyclization involves the dropwise addition of $BF_3{\cdot}OEt_2$ to a mixture of 3-methoxyphenol (**1**) and the cor-

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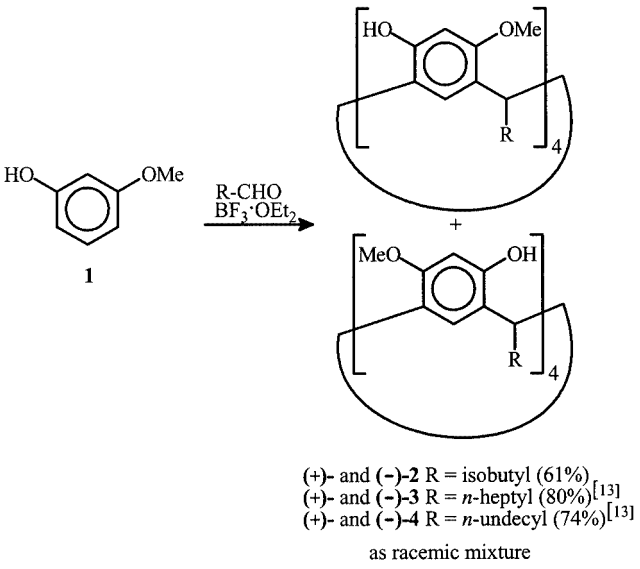

Figure 1. Synthesis of *rccc*-tetra-*O*-methylresorc[4]arenes

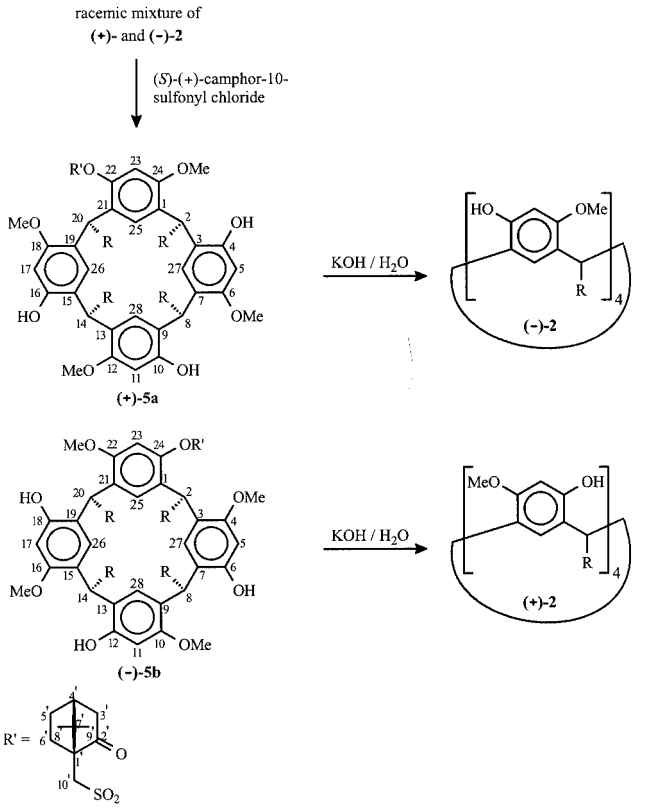

Figure 2. Monofunctionalization of the racemic mixture of **2** and removal of the chiral auxiliary leads to the pure enantiomers

responding aldehyde at room temperature. After recrystallization the corresponding C_4-symmetric *rccc*-tetra-*O*-methylresorc[4]arenes **2** were obtained in high yields as racemic mixtures (Figure 1).[14] This method was unsuccessful with aldehydes containing shorter alkyl chains such as propanal.

The *rccc*-tetra-*O*-methylresorc[4]arenes **2** were treated with (*S*)-(+)-10-camphorsulfonyl chloride (five equivalents) in dry THF with *n*-butyllithium (one equivalent) as base at −78 °C. This reaction leads to a mixture of two mono-*O*-esterified diastereomers **(+)-5a** and **(−)-5b**, higher esterified resorc[4]arenes and the starting material **2** (Figure 2).

Separation of the two diastereomeric compounds **(+)-5a** and **(−)-5b** was achieved using silica gel HPLC, with an overall yield of 29%. As expected, both mono-*O*-esterified diastereomers were formed in equal amounts[15] and showed specific rotations of $[\alpha]_D^{25} = +63.8$ ($c = 0.92$, $CHCl_3$) and $[\alpha]_D^{25} = -44.2$ ($c = 2.98$, $CHCl_3$), respectively. The ^1H NMR spectra of both compounds recorded at 25 °C show eight sharp singlets for the aromatic protons, pointing either to fixed conformations or fast interconversions of the two boat conformers on the NMR time scale. All important ^1H and ^{13}C NMR resonance peaks could be assigned exactly by means of COSY, HSQC and HMBC experiments. Without X-ray analysis it is only possible to determine the relative structure for all enantiomerically pure compounds presented in this publication. The chiral auxiliary was removed by treating the resorc[4]arenes **(+)-5a** and **(−)-5b** with an aqueous potassium hydroxide solution, leading to the enantiomeric compounds **(−)-2** and **(+)-2** in 72% and 70% yield, respectively. They show specific rotations of $[\alpha]_D^{25} = -66.0$ ($c = 0.75$, $CHCl_3$) and $[\alpha]_D^{25} = +65.4$ ($c = 0.75$, $CHCl_3$). Together with their identical IR and NMR spectra, melting points and HRMS spectra there is no doubt that these two compounds are enantiomers.

Another approach to obtain separable diastereomers is the use of (+)-3-[(2*S*)-2-methylbutoxy]phenol (**6**) for the BF_3-induced reaction. This chiral alkoxyphenol **6** was synthesized from resorcinol and (2*S*)-(−)-2-methylbutyl tosylate as described in the literature.[16] The cyclization was done with 3-methylbutanal and *n*-dodecanal leading to the corresponding C_4-symmetric, enantiomerically pure *rccc*-resorc[4]arenes **7** and **8** (Figure 3).

In the case of 3-methylbutanal the corresponding (+)-*rccc*-2,8,14,20-tetraisobutyl-4,10,16,22-tetra-*O*-[(2*S*)-2-methylbutyl]resorc[4]arene **[(+)-7a]** and (−)-*rccc*-2,8,14,20-tetraisobutyl-6,12,18,24-tetra-*O*-[(2*S*)-2-methylbutyl]resorc[4]arene **[(−)-7b]** were separated by HPLC, yielding the two diastereomers (9% and 18%). The ^1H NMR spectrum of the reaction mixture before purification shows that **(−)-7b** is preferred, with a *de* of 20%. They have specific rotations of $[\alpha]_D^{25} = +62.0$ ($c = 1.00$, $CHCl_3$) and $[\alpha]_D^{25} = -16.6$ ($c = 1.00$, $CHCl_3$), respectively. On the other hand the reaction with *n*-dodecanal leads to a 1:1 ratio of the diastereomers (+)-*rccc*-2,8,14,20-tetra-*n*-undecyl-4,10,16,22-tetra-*O*-[(2*S*)-2-methylbutyl]resorc[4]arene **[(+)-8a]** and (−)-*rccc*-2,8,14,20-tetra-*n*-undecyl-6,12,18,24-tetra-*O*-[(2*S*)-2-methylbutyl]resorc[4]arene **[(−)-8b]**, which were easier to separate and were isolated in higher yields (25% and 29%). To the best of our knowledge, these C_4-symmetric compounds are currently the most easily accessible inherently chiral and enantiomerically pure *rccc*-resorc[4]arenes, with the advantage

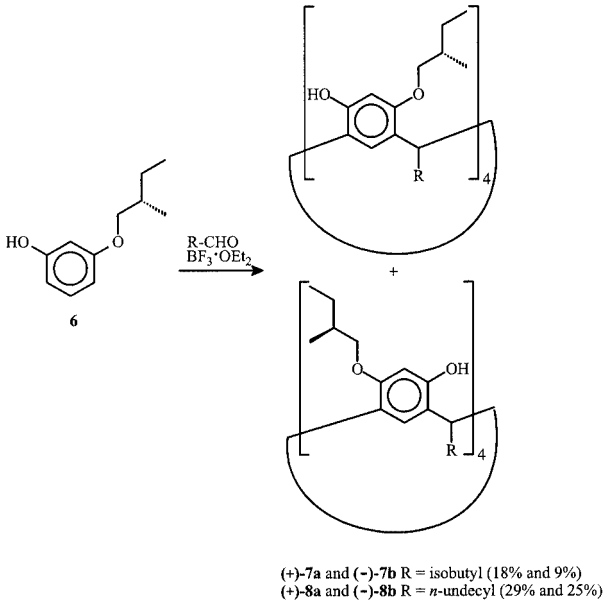

Figure 3. Synthesis of enantiomerically pure *rccc*-tetra-*O*-alkylresorc[4]arenes based on (+)-3-[(2*S*)-2-methylbutoxy]phenol (**6**)

of higher physical and chemical stability than the well-known chiral resorc[4]arenes based on Mannich reactions.[6]

Circular Dichroism Spectra

The UV and CD spectra of diastereomeric resorc[4]arenes **(+)-7a** and **(−)-7b** were measured in three representative solvents of different polarity and proton availability, namely, nonpolar methylcyclohexane, polar aprotic acetonitrile and polar protic methanol as illustrated in Figure 4.

As can be seen from Figure 4 (a−c, top traces), the UV spectra of diastereomeric resorcarenes **(+)-7a** and **(−)-7b** resemble each other in all solvents employed, exhibiting the ^1L_a and ^1L_b bands of appreciably different molar extinction coefficients at practically the same wavelengths of 225 and 285 nm, respectively. The CD spectrum of the diastereomeric pair is an almost perfect mirror image in all the solvents examined (Figure 4, a−c, bottom traces). This indicates that the resorcarene cavities of **(+)-7a** and **(−)-7b** are essentially enantiomeric to each other, although due to the chiral centers at the alkyl chains they are diastereomeric compounds. These remote chiral centers do not contribute appreciably to the electronic transition leading to the CD spectrum. However, the most intriguing feature of the present CD spectra is the dramatic switching of the spectral pattern caused by a change in the solvent from a polar protic to less-polar aprotic solvent. Thus, in methanol, each band of the CD spectrum of **(+)-7a** and **(−)-7b** displays a normal Cotton effect peak for both the ^1L_a and ^1L_b bands (Figure 4, c). In contrast, the CD spectrum in acetonitrile or methylcyclohexane exhibits a split Cotton effect peak with enhanced amplitude (Figure 4, a and b). This spectral pattern is best interpreted by exciton coupling between two adjacent resorcinol chromophores. The reason for this striking behavior is still unknown. We are currently studying the possible influence of the conformation such as crown, boat and others, the complex formation with solvent molecules, H-bonding effects, etc. Although the details remain vague these results clearly show that the CD spectral study is particularly useful in elucidating special features of chiral resorcarene derivatives, since the NMR spectral examination cannot discriminate, for example, the crown from the rapidly equilibrating boat conformation in the present case.

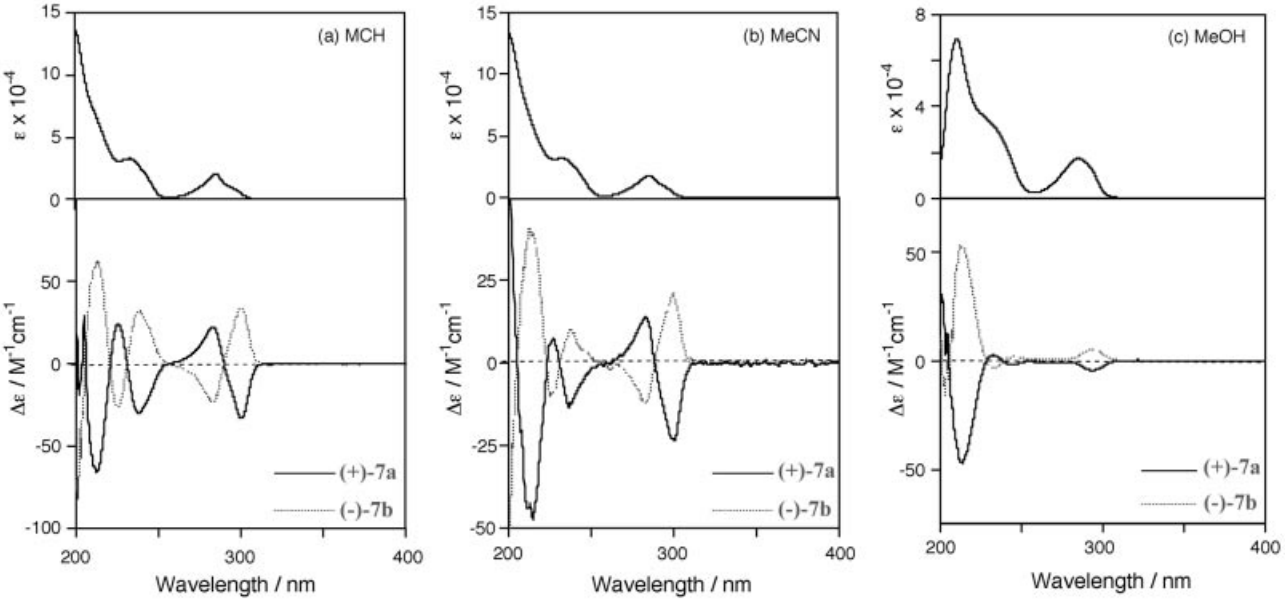

Figure 4. UV (top) and CD (bottom) spectra of diastereomeric resorc[4]arenes **(+)-7a** and **(−)-7b** in: (a) methylcyclohexane (MCH), (b) acetonitrile and (c) methanol

Further studies to elucidate the origin and mechanism of the drastic CD spectral changes are currently in progress.

Conclusion

In summary, we have synthesized a new type of inherently chiral and enantiomerically pure C_4-symmetric resorc[4]arenes. The first method is the separation of the enantiomers by mono-*O*-functionalization of **2** with (*S*)-(+)-10-camphorsulfonyl chloride leading to the diastereomers **(+)-5a** and **(−)-5b**. After removal of the chiral auxiliary both enantiomeric resorc[4]arenes **(−)-2** and **(+)-2** were obtained.

The second strategy uses (+)-3-[(2*S*)-2-methylbutoxy]-phenol (**6**) for the cyclization reaction to obtain diastereomers **(+)-7a**, **(−)-7b**, **(+)-8a** and **(−)-8b** in moderate yields, which are easily separable by HPLC.

These inherently chiral resorc[4]arenes have the advantage of being stable towards acidic and basic conditions. Our ongoing investigations aim at the preparation of other chiral resorc[4]arenes using this new reaction sequence and applications of these compounds in chiral discrimination processes.

Experimental Section

General Remarks: The (+)-3-[(2*S*)-2-methylbutoxy]phenol (**6**) was prepared as described in the literature.[16] All solvents used were of an analytically pure quality or purified by distillation. Melting points were determined on a Büchi B-540 apparatus and are uncorrected. NMR spectra were measured either on a Bruker 600 (^{1}H NMR: δ = 600.14 MHz. ^{13}C NMR: δ = 150.90 MHz) or a Bruker DRX 500 (^{1}H NMR: δ = 500.13 MHz. ^{13}C NMR: δ = 125.77 MHz) instrument in $CDCl_3$ with $CHCl_3$ as reference (for, ^{1}H: δ = 7.26 ppm; for ^{13}C: 77.0 ppm). IR spectra were recorded on a Perkin−Elmer 841 Infrared Spectrophotometer. HRMS were measured on a Bruker APEX III with ESI in positive ion mode and spectra were internally calibrated with HP TuneMix (*m*/*z* = 622/922/1522). HPLC separations were performed with a SP 250/21 Nucleosil 100−7 column from Macherey−Nagel and UV detection at 290 nm. Specific rotations were measured on a Perkin−Elmer 341 polarimeter. CD spectra of **7** (1.25×10^{-5} M) were recorded in various solvents at room temperature on a JASCO J-720W spectropolarimeter equipped with a temperature controller.

Synthesis of (+)-*rccc*-2,8,14,20-Tetraisobutyl-4,10,16,22-tetra-*O*-methylresorc[4]arene [(+)-2] and (−)-*rccc*-2,8,14,20-Tetraisobutyl-4,10,16,22-tetra-*O*-methylresorc[4]arene [(−)-2]: Boron trifluoride−diethyl ether (22.7 g, 160 mmol) was added to a solution of 3-methoxyphenol (9.93 g, 80.0 mmol) and 3-methylbutanal (6.89 g, 80.0 mmol) in 250 mL dichloromethane. The mixture was stirred at room temp. for 2 h, washed with distd. water (2×200 mL) and brine (1×200 mL) and dried over $MgSO_4$. After removal of the solvent the product was recrystallized from ethanol to yield **2** (9.40 g, 12.2 mmol, 61%) as a colorless solid. M.p. 320 °C (dec.). IR (KBr): $\tilde{\nu}$ = 3427, 2958, 2872, 1618, 1588, 1495, 1468, 1425, 1384, 1367, 1330, 1293, 1226, 1194, 1155, 1125, 1107, 1089, 1038, 999, 955, 920, 906, 883, 841 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 0.972 (d, ^3J = 6.7 Hz, 12 H, CH_3CH), 0.982 (d, ^3J = 6.7 Hz, 12 H, CH_3CH), 1.453 (m, 4 H, Me_2CH), 2.084 (dd, ^3J = 7.8, ^3J = 6.9 Hz, 8 H, CH_2), 3.844 (s, 12 H, OCH_3), 4.418 [t, ^3J = 7.9 Hz, 4 H, ArCH(R)Ar], 6.356 (s, 4 H, CH *ortho* to C−OH), 7.216 (s, 4 H, CH *meta* to C−OH), 7.544 (s, 4 H, OH) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 22.77 (CH_3CH), 22.81 (CH_3CH), 25.99 (CH_3CH), 30.53 ($CHCH_2$), 42.87 (CH_2), 55.85 (OCH_3), 99.93 (CH *ortho* to C−OH), 123.95 (CH *meta* to C−OH), 124.49 and 124.60 ($2 \times C_{quat.,arom.}$), 152.88 and 153.52 ($2 \times$ C−O) ppm.

Synthesis of (+)-*rccc*-24-*O*-[(*S*)-10′-Camphorsulfonyl]-2,8,14,20-tetraisobutyl-4,10,16,22-tetra-*O*-methylresorc[4]arene [(+)-5a] and (−)-*rccc*-22-*O*-[(*S*)-10′-Camphorsulfonyl]-2,8,14,20-tetraisobutyl-6,12,18,24-tetra-*O*-methylresorc[4]arene [(−)-5b]: A 1.6 M solution of *n*-butyllithium in hexane (0.63 mL, 1.00 mmol) was added to a solution of **2** (0.77 g, 1.00 mmol) in THF (20 mL) at −78 °C. The mixture was stirred for 30 min and (*S*)-(+)-10-camphorsulfonyl chloride (1.25 g, 5 mmol) in THF (20 mL) was added. The solution was warmed up and stirred at room temp. overnight. The reaction mixture was acidified with diluted hydrochloric acid and extracted with diethyl ether (3×100 mL). The combined organic layers were dried with $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by HPLC (Si-100, cyclohexane/ethyl acetate, 66:34) to afford the starting material **2** (168 mg, 218 μmol, 22%), **(+)-5a** (125 mg, 127 μmol, 13%) and **(−)-5b** (162 mg, 163 μmol, 16%) as colorless solids.

(+)-5a: M.p. 129 °C (dec.). IR (KBr): $\tilde{\nu}$ = 3438, 2958, 2871, 1749, 1714, 1617, 1588, 1497, 1466, 1417, 1367, 1289, 1195, 1127, 1086, 1036, 1003, 921, 835 cm^{-1}. $[\alpha]_D^{25}$ = +63.8 (c = 0.92, $CHCl_3$). HRMS ESI [M + Na$^+$: $C_{58}H_{78}O_{11}SNa^+$]: calcd. 1005.5156; found 1005.5156; declination 0.02 mmu/0.02 ppm. ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 0.915 (d, ^3J = 6.6 Hz, 3 H, CHCH_3), 0.927 (s, 3 H, 8′-H), 0.950 (d, ^3J = 6.6 Hz, 3 H, CHCH_3), 0.958 (d, ^3J = 6.6 Hz, 3 H, CHCH_3), 0.961 (d, ^3J = 6.5 Hz, 3 H, CHCH_3), 0.967 (d, ^3J = 6.7 Hz, 3 H, CHCH_3), 0.973 (d, ^3J = 6.4 Hz, 3 H, CHCH_3), 0.976 (d, ^3J = 6.9 Hz, 3 H, CHCH_3), 0.982 (d, ^3J = 6.7 Hz, 3 H, CHCH_3), 1.163 (s, 3 H, 9′-H), 1.340−1.480 (m, 4 H, 2"-H, 6"-H, 10"-H, 14"-H), 1.674 (ddd, ^2J = 14.1, ^3J = 9.4, ^3J = 4.6 Hz, 1 H, 5′$_{endo}$-H), 1.715 (ddd, ^2J = 13.8, ^3J = 8.4, ^3J = 5.8 Hz, 1 H, 6′$_{endo}$-H), 1.930−2.200 (m, 10 H, 4′-H, 5′$_{exo}$-H, 1"-H, 5"-H, 9"-H, 13"-H), 1.959 (d, 1 H, 18.5 Hz, 3′$_{endo}$-H), 2.425 (ddd, ^2J = 18.8, ^3J = 3.9, ^3J = 3.9 Hz, 1 H, 3′$_{exo}$-H), 2.560 (ddd, ^2J = 13.8, ^3J = 11.8, ^3J = 3.8 Hz, 1 H, 6′$_{exo}$-H), 3.347 (d, ^2J = 15.0 Hz, 1 H, 10′$_a$-H), 3.749 (s, 3 H, OMe at C-4), 3.825 (s, 3 H, OMe), 3.839 (s, 3 H, OMe), 3.869 (d, ^2J = 15.0 Hz, 1 H, 10′$_b$-H), 3.919 (s, 3 H, OMe at C-22), 4.372 (dd, ^3J = 7.8, ^3J = 7.8 Hz, 1 H, 8-H), 4.417 (dd, ^3J = 7.9, ^3J = 7.9 Hz, 1 H, 14-H), 4.437 (dd, ^3J = 7.8, ^3J = 7.8 Hz, 1 H, 20-H), 4.874 (dd, ^3J = 10.6, ^3J = 5.6 Hz, 1 H, 2-H), 6.317 (s, 1 H, 5-H), 6.356 (s, 1 H, 11-H), 6.362 (s, 1 H, 17-H), 6.919 (s, 1 H, 23-H), 7.101 (s, 1 H, 28-H), 7.176 (s, 1 H, OH), 7.200 (s, 1 H, 27-H), 7.241 (s, 1 H, 26-H), 7.249 (s, 1 H, OH), 7.308 (s, 1 H, OH at C-6), 7.358 (s, 1 H, 25-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 19.74 (C-8′), 19.90 (C-9′), 21.98, 22.58, 22.73, 22.74, 22.83, 22.93, 23.00, 23.71 (C-3′′, C-4′′, C-6′′, C-8′′, C-11′′, C-12′′, C-15′′, C-16"), 25.47 (C-6′), 25.84, 25.88, 25.89, 25.99 (C-2′′, C-6′′, C-10′′, C-14"), 26.79 (C-5′), 30.49 (C-14), 30.74 (C-8), 30.92 (C-2), 31.05 (C-20), 42.48 (C-3′), 43.02 (C-4′), 43.27, 43.29, (C-5′′, C-9′′, C-13"), 44.75 (C-1"), 47.65 (C-10′), 47.76 (C-7′), 55.68 (OMe at C-4), 56.80, 56.84 ($2 \times$ OMe), 56.34 (OMe at C-22), 58.19 (C-1′), 99.81, 99.81 (C-11, C-17), 99.94 (C-5), 104.64 (C-23), 122.73 (C-7), 122.83, 124.39, 124.68, 124.84 (C-9, C-13, C-15, C-19), 123.94 (C-3), 124.04 (C-28), 124.10, 124.10 (C-26, C-27), 126.31 (C-25), 131.30 (C-21), 132.19 (C-1), 145.14 (C-24), 152.54 (C-12), 153.00 (C-6), 153.07 (C-22), 153.12 (C-18), 153.65 (C-10), 153.96 (C-16), 156.12 (C-4), 214.22 (C-2′) ppm.

(−)-5b: M.p. 136 °C (dec.). IR (KBr): $\tilde{\nu}$ = 3430, 2958, 2872, 1753, 1729, 1618, 1587, 1497, 1466, 1419, 1367, 1293, 1195, 1171, 1124, 1087, 1067, 1038, 1002, 956, 921, 836 cm^{-1}. $[\alpha]_D^{24}$ = −44.2 (*c* = 2.98, $CHCl_3$). HRMS ESI [M + Na$^+$: $C_{58}H_{78}O_{11}SNa^+$]: calcd. 1005.5156; found 1005.5156; declination 0.1 mmu/0.1 ppm. ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 0.890 (s, 3 H, 8′-H), 0.899 (d, ^3J = 6.5 Hz, 3 H, CHC*H*$_3$), 0.935 (d, ^3J = 6.1 Hz, 3 H, CHC*H*$_3$), 0.962 (m, 9 H, 3 × CHC*H*$_3$), 1.165 (s, 3 H, 9′-H), 1.330−1.490 (m, 5 H, 5′$_{endo}$-H, 2"-H, 6"-H, 10"-H, 14"-H), 1.732 (ddd, ^2J = 14.0, ^3J = 9.3, ^3J = 4.7 Hz, 1 H, 6′$_{endo}$-H), 1.972 (d, ^2J = 18.5 Hz, 1 H, 3′$_{endo}$-H), 1.970−2.180 (m, 10 H, 4′-H, 5′$_{exo}$-H, 1"-H, 5"-H, 9"-H, 13"-H), 2.397 (ddd, ^2J = 18.5, ^3J = 4.6, ^3J = 3.5 Hz, 1 H, 3′$_{exo}$-H), 2.558 (ddd, ^2J = 14.3, ^3J = 11.4, ^3J = 3.9 Hz, 6′$_{exo}$-H), 3.293 (d, ^2J = 14.7 Hz, 1 H, 10′$_a$-H), 3.762 (s, 3 H, OMe at C-18), 3.840 (s, 6 H, 2 × OMe), 3.929 (s, 3 H, OMe at C-24), 3.951 (d, ^2J = 14.7 Hz, 1 H, 10′$_b$-H), 4.371 (dd, ^3J = 7.9, ^3J = 7.9 Hz, 1 H), 4.407 (dd, ^3J = 7.9, ^3J = 7.9 Hz, 1 H), 4.431 (dd, ^3J = 7.9, ^3J = 7.9 Hz, 1 H), 4.842 (dd, ^3J = 10.4, ^3J = 6.0 Hz, 1 H, 20-H), 6.325 (s, 1 H, 17-H), 6.364, 6.369 (s, 2 H, 5-H, 11-H), 6.953 (s, 1 H, 23-H), 7.136 (s, 1 H, 26-H), 7.200 (s, 1 H, OH), 7.202 (s, 1 H, 27-H), 7.256 (s, 1 H, OH), 7.270 (s, 1 H, 28-H), 7.352 (s, 1 H, 25-H), 7.380 (s, 1 H, OH at C-16) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 19.63 (C-8′), 19.84 (C-9′), 22.09, 22.65, 22.76, 22.78, 22.79, 22.89, 22.90, 23.60 (C-3′′, C-4′′, C-6′′, C-8′′, C-11′′, C-12′′, C-15′′, C-16"), 25.04 (C-6′), 25.80, 25.85, 25.88, 25.97 (C-2′′, C-5′′, C-10′′, C-14"), 26.83 (C-5′), 30.45, 30.66, 30.72, 30.92 (C-2, C-8, C-14, C-20), 42.40 (C-3′), 42.91 (C-4′), 43.08, 43.18, 43.30 (C-5′′, C-9′′, C13′′), 44.74 (C-1′′), 47.67 (C-10′), 47.81 (C-7′), 55.64 (OMe at C-18), 55.80, 55.81 (2 × OMe), 56.28 (OMe at C-24), 57.94 (C-1′), 99.72, 99.86, 99.89 (C-5, C-11, C17), 104.41 (C-23), 122.72, 122.74, 123.85, 124.42, 124.61, 124.79 (C-3, C-7, C-9, C-13, C-15, C-19), 123.92 (C-26), 123.95 (C-28), 124.12 (C-27), 126.36 (C-25), 131.10 (C-1), 131.87 (C-21), 144.72 (C-22), 152.50, 153.01, 153.04, 153.14, 153.55, 153.95 (C-4, C-6, C-10, C-12, C-16, C-24), 156.03 (C-18), 214.13 (C-2′) ppm.

Synthesis of (−)-*rccc*-2,8,14,20-Tetraisobutyl-4,10,16,22-tetra-*O*-methylresorc[4]arene [(−)-2]. − Procedure 1: An aqueous potassium hydroxide solution (7 mL, 20% by weight) was added to a solution of resorc[4]arene **(+)-5a** (32 mg, 32.5 μmol) in ethanol (6 mL) under argon. The reaction mixture was refluxed for 1 h and stirred at room temp. for 1 h. The clear solution was acidified with concd. hydrochloric acid and diluted with distd. water (50 mL). The resulting suspension was extracted with dichloromethane (4 × 50 mL) and the combined organic layers were washed with dilute hydrochloric acid (2 × 30 mL) and dried with $MgSO_4$. After removing the solvent under reduced pressure and drying the residue in vacuo the resorc[4]arene **(−)-2** (18 mg, 23.4 μmol, 72%) was obtained as a colorless solid. M.p. 279 °C (dec.). IR (KBr): $\tilde{\nu}$= 3422, 2958, 2872, 1618, 1588, 1495, 1468, 1426, 1384, 1367, 1330, 1292, 1228, 1194, 1155, 1124, 1106, 1089, 1038, 999, 956, 920, 906, 883, 842 cm^{-1}. $[\alpha]_D^{25}$ = −66.0 (*c* = 0.75, $CHCl_3$). HRMS ESI [M + Na$^+$, $C_{48}H_{64}O_8Na^+$]: calcd. 791.4493; found 791.4498; declination 0.4 mmu/0.5 ppm. ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 0.963 (d, ^3J = 5.0 Hz, 12 H, C*H*$_3$CH), 0.976 (d, ^3J = 5.0 Hz, 12 H, C*H*$_3$CH), 1.445 (m, 4 H, Me$_2$C*H*), 2.075 (dd, ^3J = 7.7, ^3J = 7.7 Hz, 8 H, CH_2), 3.837 (s, 12 H, OCH_3), 4.410 [dd, ^3J = 7.9, ^3J = 7.9 Hz, 4 H, ArC*H*(R)Ar], 6.348 (s, 4 H, H *ortho* to C−OH), 7.209 (s, 4 H, CH *meta* to C−OH), 7.534 (s, 4 H, OH) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 22.78 (*C*H$_3$CH), 22.81 (*C*H$_3$CH), 26.00 (Me$_2$*C*H), 30.55 [Ar*C*H(R)Ar], 42.88 (CH_2), 55.86 (CH_3O), 99.94 (CH *ortho* to C−OH), 123.97 (CH *meta* to C−OH), 124.50 and 124.61 (2 × $C_{quat.,arom.}$ *ortho* to C−O), 152.90 and 153.54 (2 × C−O) ppm.

Synthesis of (+)-*rccc*-2,8,14,20-Tetraisobutyl-6,12,18,24-tetra-*O*-methylresorc[4]arene [(+)-2]: Analogous to **Procedure 1: (−)-5b** (64 mg, 65.1 μmol) as starting material. From this reaction the tetra-*O*-methylresorc[4]arene **(+)-2** (35 mg, 45.5 μmol, 70%) was obtained as a colorless solid. M.p. 280 °C (dec.). IR (KBr): $\tilde{\nu}$ = 3420, 2958, 2873, 1618, 1588, 1494, 1467, 1426, 1384, 1367, 1329, 1292, 1228, 1193, 1155, 1124, 1106, 1089, 1037, 999, 955, 920, 906, 883, 841 cm^{-1}. $[\alpha]_D^{25}$ = +65.4 (*c* = 0.75, $CHCl_3$). HRMS ESI [M + Na$^+$, $C_{48}H_{64}O_8Na^+$]: calcd. 791.4493; found 791.4497; declination 0.3 mmu/0.4 ppm. ^{1}H NMR (600 MHz, $CDCl_3$, 25 °C, ref.: TMS): δ = 0.961 (d, ^3J = 6.1 Hz, 12 H, C*H*$_3$CH), 0.972 (d, ^3J = 6.3 Hz, 12 H, C*H*$_3$CH), 1.449 (m, 4 H, Me$_2$C*H*), 2.075 (dd, ^3J = 7.7, ^3J = 7.7 Hz, 8 H, CH_2), 3.836 (s, 12 H, OCH_3), 4.409 [dd, ^3J = 7.9, ^3J = 7.9 Hz, 4 H, ArC*H*(R)Ar], 6.346 (s, 4 H, H *ortho* to C−OH), 7.208 (s, 4 H, CH *meta* to C−OH), 7.506 (s, 4 H, OH) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 22.78 (*C*H$_3$CH), 22.81 (*C*H$_3$CH), 26.00 (Me$_2$*C*H), 30.55 [Ar*C*H(R)Ar], 42.89 (CH_2), 55.87 (CH_3O), 99.94 (CH *ortho* to C−OH), 123.97 (CH *meta* to C−OH), 124.50 and 124.61 (2 × $C_{quat.,arom.}$ *ortho* to C−O), 152.91 and 153.54 (2 × C−O) ppm.

Synthesis of (+)-*rccc*-2,8,14,20-Tetraisobutyl-4,10,16,22-tetra-*O*-[(2*S*)-2-methylbutyl]resorc[4]arene [(+)-7a] and (−)-*rccc*-2,8,14,20-Tetraisobutyl-6,12,18,24-tetra-*O*-[(2*S*)-2-methylbutyl]resorc[4]arene [(−)-7b]: Boron trifluoride−diethyl ether (6.30 g, 44.4 mmol) was added to a solution of (+)-3-[(2*S*)-2-methylbutoxy]phenol (4.00 g, 22.2 mmol) and 3-methylbutanal (1.91 g, 22.2 mmol) in 60 mL dichloromethane. The mixture was stirred at room temp. for 2 h, washed with distd. water (2 × 30 mL) and brine (1 × 30 mL) and dried over $MgSO_4$. After removal of the solvent the crude product was purified by HPLC (Si-60, cyclohexane/ethyl acetate, 90:10) to afford **(+)-7a** (0.59 g, 0.60 mmol, 18%) and **(−)-7b** (0.31 g, 0.32 mmol, 9%) as colorless solids.

(+)-7a: M.p. 128−129 °C. IR (KBr): $\tilde{\nu}$ = 3408, 2962, 2874, 1620, 1588, 1494, 1468, 1384, 1367, 1328, 1292, 1233, 1179, 1125, 1086, 1034, 921, 859, 837 cm^{-1}. $[\alpha]_D^{25}$ = +62.0 (*c* = 1.00, $CHCl_3$). HRMS ESI [M + Na$^+$: $C_{64}H_{96}O_8Na^+$]: calcd. 1015.6997; found 1015.7009; declination 1.2 mmu/1.2 ppm. ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 0.947 (dd, ^3J = 7.5, ^3J = 7.5 Hz, 12 H, C*H*$_3$CH$_2$), 0.970 [d, ^3J = 6.9 Hz, 12 H, C*H*$_3$CH(R)CH$_3$], 0.976 [d, ^3J = 6.3 Hz, 12 H, CH$_3$CH(R)C*H*$_3$], 1.103 [d, ^3J = 6.9 Hz, 12 H, C*H*$_3$CH(CH$_2$)$_2$], 1.269 (ddq, ^2J = 13.6, ^3J = 7.6, ^3J = 7.4 Hz, 4 H, CH$_3$C*H*$_2$), 1.525−1.400 (m, 8 H, Me$_2$C*H* and CH$_3$C*H*$_2$), 1.957 [m, 4 H, CH$_3$C*H*(CH$_2$)$_2$], 2.073 (ddd, ^2J = 13.1, ^3J = 7.8, ^3J = 6.9 Hz, 4 H, CHC*H*$_2$CH), 2.096 (ddd, ^2J = 13.1, ^3J = 7.8, ^3J = 6.9 Hz, 4 H, CHC*H*$_2$CH), 3.591 (dd, ^2J = 9.1, ^3J = 8.9 Hz, 4 H, CH_2O), 3.986 (dd, ^2J = 9.1, ^3J = 4.7 Hz, 4 H, CH_2O), 4.474 [dd, ^3J = 7.8, ^3J = 7.8 Hz, 4 H, ArC*H*(R)Ar], 6.340 (s, 4 H, H *ortho* to C−OH), 7.236 (s, 4 H, CH *meta* to C−OH), 7.565 (s, 4 H, OH) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 11.19 (*C*H$_3$CH$_2$), 16.88 [*C*H$_3$CH(CH$_2$)$_2$], 22.72 [*C*H$_3$CH(R)CH$_3$], 22.79 [CH$_3$CH(R)*C*H$_3$], 25.96 (Me$_2$*C*H), 26.15 (CH$_3$*C*H$_2$), 30.61 [Ar*C*H(R)Ar], 34.41 [CH$_3$*C*H(CH$_2$)$_2$], 43.09 (CH*C*H$_2$CH), 74.33 (*C*H$_2$O), 101.00 (CH *ortho* to C−OH), 123.92 (CH *meta* to C−OH), 124.70 and 124.78 (2 × $C_{quat.,arom.}$), 152.84 and 153.20 (2 × C−O) ppm.

(−)-7b: M.p. 225−226 °C. IR (KBr): $\tilde{\nu}$ = 3392, 2963, 2874, 1619, 1587, 1494, 1467, 1384, 1367, 1328, 1293, 1229, 1155, 1126, 1086, 1036, 955, 921, 858, 837 cm^{-1}. $[\alpha]_D^{25}$ = −16.6 (*c* = 1.00, $CHCl_3$). HRMS ESI [M + Na$^+$: $C_{64}H_{96}O_8Na^+$]: calcd. 1015.6997; found 1015.7012; declination 1.5 mmu/1.4 ppm. ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 0.956 (dd, ^3J = 7.4, ^3J = 7.4 Hz, 12 H, C*H*$_3$CH$_2$), 0.962 [d, ^3J = 6.2 Hz, 12 H, C*H*$_3$CH(R)CH$_3$], 0.970 [d, ^3J = 6.7 Hz, 12 H, C*H*$_3$CH(R)CH$_3$], 0.995 [d, ^3J = 6.8 Hz, 12 H,

$CH_3CH(CH_2)_2$], 1.314 (ddq, ^2J = 13.6, ^3J = 7.6, ^3J = 7.6 Hz, 8 H, CH_3CH_2), 1.453 [m, 4 H, $CH_3CH(R)CH_3$], 1.675 (ddq, ^2J = 13.7, ^3J = 7.5, ^3J = 4.6 Hz, 4 H, CH_3CH_2), 1.975 [m, 4 H, $CH_3CH(CH_2)_2$], 2.057 (ddd, ^2J = 13.5, ^3J = 7.9, ^3J = 6.7 Hz, 4 H, $CHCH_2CH$), 2.094 (ddd, ^2J = 13.5, ^3J = 7.9, ^3J = 7.1 Hz, 4 H, $CHCH_2CH$), 3.717 (dd, ^2J = 9.4, ^3J = 8.0 Hz, 4 H, CH_2O), 3.874 (dd, ^2J = 9.4, ^3J = 5.5 Hz, 4 H, CH_2O), 4.454 [dd, ^3J = 7.9, ^3J = 7.9 Hz, 4 H, ArCH(R)Ar], 6.342 (s, 4 H, H *ortho* to C−OH), 7.221 (s, 4 H, CH *meta* to C−OH), 7.530 (s, 4 H, OH) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 10.87 (CH_3CH_2). 16.04 [$CH_3CH(CH_2)_2$], 22.70 [$CH_3CH(R)CH_3$], 22.82 [$CH_3CH(R)CH_3$], 25.96 [$CH_3CH(R)CH_3$], 26.15 (CH_3CH_2), 30.64 [ArCH(R)Ar], 34.20 [$CH_3CH(CH_2)_2$], 43.10 ($CHCH_2CH$), 74.22 (CH_2O), 101.17 (CH *ortho* to C−OH), 123.92 (CH *meta* to C−OH), 124.70 and 124.83 (2 × $C_{quat.,arom.}$), 152.82 and 153.17 (2 × C−O) ppm.

Synthesis of (+)-*rccc*-2,8,14,20-Tetra-*n*-undecyl-4,10,16,22-tetra-*O*-[(2*S*)-2-methylbutyl]resorc[4]arene [(+)-8a] and (−)-*rccc*-2,8,14,20-Tetra-*n*-undecyl-6,12,18,24-tetra-*O*-[(2*S*)-2-methylbutyl]resorc[4]-arene [(−)-8b]: Boron trifluoride−diethyl ether (1.26 g, 8.88 mmol) was added to a solution of (+)-3-[(2*S*)-2-methylbutoxy]phenol (0.840 g, 4.44 mmol) and *n*-dodecanal (0.860 g, 4.44 mmol) in 60 mL dichloromethane. The mixture was stirred for 2 h at room temp., washed with distd. water (2 × 100 mL) and brine (1 × 100 mL) and dried over $MgSO_4$. After removal of the solvent the crude product was purified by HPLC (Si-60, cyclohexane/ethyl acetate, 90:10) to afford **(+)-8a** (0.44 g, 0.32 mmol, 29%) and **(−)-8b** (0.38 g, 0.28 mmol, 25%) as pale yellow oils.

(+)-8a: IR (KBr): ṽ = 3404, 2928, 2857, 1620, 1588, 1494, 1467, 1378, 1330, 1293, 1232, 1179, 1093, 1006, 902, 836 cm^{-1}. $[\alpha]_D^{25}$ = +13.9 (*c* = 1.10, $CHCl_3$). HRMS ESI [M + Na^+: $C_{92}H_{152}O_8Na^+$]: calcd. 1408.1379; found 1408.1365; declination 1.5 mmu/1.0 ppm. ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 0.862 (t, ^3J = 7.0 Hz, 12 H, $CH_3CH_2CH_2$), 0.925 (dd, ^3J = 7.5 Hz ^3J = 7.5 Hz, 12 H, CH_3CH_2CH), 1.092 (d, ^3J = 6.8 Hz, 12 H, CH_3CH), 1.150−1.390 (m, 76 H, CH_3CH_2CH and 9 × CH_2), 1.478 (ddq, ^2J = 13.4, ^3J = 7.5, ^3J = 5.6 Hz, 4 H, CH_3CH_2CH), 1.926 (m, 4 H, $CHCH_3$), 2.139 (m, 4 H, $CHCH_2CH_2$), 2.197 (m, 4 H, $CHCH_2CH_2$), 3.608 (dd, ^2J = 9.0, ^3J = 8.9 Hz, 4 H, CH_2O), 3.972 (dd, ^3J = 9.2, ^3J = 4.9 Hz, CH_2O), 4.309 [dd, ^3J = 7.9, ^3J = 7.9 Hz, 4 H, ArCH(R)Ar], 6.336 (s, 4 H, CH *ortho* to C−OH), 7.227 (s, 4 H, CH *meta* to C−OH), 7.513 (s, 4 H, OH) ppm. ^{13}C NMR (125 MHz, CDCl3, 25 °C): δ = 11.20 (CH_3CH_2CH), 14.12 ($CH_3CH_2CH_2$), 16.86 (CH_3CH), 22.69 (CH_2), 26.16 (CH_2), 27.98 (CH_2), 29.40 (CH_2), 29.58 (CH_2), 29.72 (CH_2), 29.74 (CH_2), 29.77 (CH_2), 31.94 (CH_2), 32.95 [ArCH(R)Ar], 33.97 (CH_2), 34.41 (CH_3CH), 74.48 (CH_2O), 101.13 (CH *ortho* to C−OH), 123.65 (CH *meta* to C−OH), 124.70 and 124.91 (2 × $C_{quat.,arom.}$), 152.81 and 153.31 (2 × C−O) ppm.

(−)-8b: Yellow oil. IR (KBr): ṽ = 3398, 2928, 2858, 1618, 1589, 1495, 1466, 1379, 1333, 1298, 1233, 1181, 1092, 1026, 902, 836 cm^{-1}. $[\alpha]_D^{25}$ = −2.1 (*c* = 1.10, $CHCl_3$). HRMS ESI [M + Na^+: $C_{92}H_{152}O_8Na^+$]: calcd. 1408.1379; found 1408.1370; declination 0.9 mmu/0.7 ppm. ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 0.881 (t, 12 H, ^3J = 7.0 Hz, $CH_3CH_2CH_2$), 0.963 (t, ^3J = 7.5 Hz, 12 H, CH_3CH_2CH), 0.994 (d, ^3J = 6.8 Hz, CH_3CH), 1.170−1.420 (m, 76 H, CH_3CH_2CH and 9 × CH_2), 1.664 (ddq, ^2J = 13.6, ^3J = 7.6, ^3J = 4.7 Hz, 4 H, CH_3CH_2CH), 1.964 (m, 4 H, $CHCH_3$), 2.142 (m, 4 H, $CHCH_2CH_2$), 2.216 (m, 4 H, $CHCH_2CH_2$), 3.726 (dd, ^2J = 9.5, ^3J = 7.7 Hz, 4 H, CH_2O), 3.863 (dd, ^2J = 9.5, ^3J = 5.6 Hz, 4 H, CH_2O), 4.296 [dd, ^3J = 7.9, ^3J = 7.9 Hz, 4 H, ArCH(R)Ar], 6.342 (s, 4 H, CH *ortho* to C−OH), 7.219 (s, 4 H, CH *meta* to C−OH), 7.485 (s, 4 H, OH) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 10.99 (CH_3CH_2CH), 14.11 ($CH_3CH_2CH_2$), 16.10 (CH_3CH), 22.69 (CH_2), 26.24 (CH_2), 27.96 (CH_2), 29.40 (CH_2), 29.59 (CH_2), 29.72 (CH_2), 29.75 (CH_2), 29.78 (CH_2), 31.94 (CH_2), 32.96 [ArCH(R)Ar], 33.98 (CH_2), 34.23 (CH_3CH), 74.43 (CH_2O), 101.27 (CH *ortho* to C−OH), 123.65 (CH *meta* to C−OH), 124.68 and 124.96 (2 × $C_{quat.,arom.}$), 152.79 and 153.27 (2 × C−OH) ppm.

Acknowledgments

We gratefully acknowledge financial support by the Department of Science and Research NRW (MSWF), the Fonds der Chemischen Industrie (FCI) and the Forschungs- und Innovationsfonds der Universität Bielefeld.

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Received October 15, 2002
[O02573]