DOI: 10.1002/ejoc.201100733

The Diastereoselective Formation of Tetraalkoxy[4]resorcinarenes Derived from (–)-(2*R*)-2-Methoxy-2-phenylethanol and Proof of Absolute Configurations

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Keywords: Calixarenes / Configuration determineation / Chirality / Diastereoselectivity / Macrocycles

The preparation of optically pure (–)-3-[(2*R*)-2-methoxy-2-phenylethoxy]phenol from resorcinol monobenzoate and its conversion into diastereoisomeric tetraalkoxyresorcin[4]-arenes together with proof of the absolute configurations of the products is reported. The results of the study indicate that diastereoselective ring closure of linear tetrameric intermediates is controlled by the steric demand of the alkyl group in the precursor 3-alkoxyphenol.

Introduction

A large number of studies of calixarenes have concentrated on inherently chiral C_1-symmetric systems where the dissymmetry generated by unsymmetrical substitution[1] is recognized as being related to the nonplanar structures of the parent compounds as a result of blocked curvature.[2] Considerable effort has been devoted to the synthesis of inherently chiral calixarenes, but, in the majority of published examples, the products have been obtained as racemates that could not be resolved except by using chiral HPLC techniques; this has inevitably meant that only very small amounts of optically pure material has been available for use in other investigations. The ready availability of resorcin[4]arenes as the *rccc* (all-*cis*) C_{4v}-symmetric cyclic tetramers, which are prepared in high yields by the acid-catalyzed interaction of a number of aldehydes with resorcinol, has made the study of those compounds particularly attractive.[3] Derivatives of the parent tetramers have been used for a wide variety of purposes.[4] The use of aldehydes, other than formaldehyde and acetaldehyde, in the preparation of resorcin[4]arenes, prevents racemization by processes involving "through-the-annulus rotation".[5] The observation of axial chirality (sometimes referred to as cyclochirality) was first noted by Prelog in connection with cyclopeptides,[6] and has subsequently been studied in a number of other areas, including rotaxanes.[7] Cyclochirality, as applied to resorcinarenes, has been discussed in several recent reviews.[8] Our studies have concentrated on axially chiral C_4-symmetric resorcin[4]arenes; for example, studies carried out by us[9a] and others[9b–9d] using optically pure α-methylbenzylamines resulted in the highly diastereoselective formation of tetrakis(benzoxazines), derived from a number of resorcin[4]arenes. Methylation of the residual phenolic hydroxy groups was performed to preclude diastereoisomerization and loss of axial chirality after ring opening of the 1,3-oxazine ring and removal of the chiral auxiliary.[10] The formation of a racemic tetramethoxyresorcinarene by the boron trifluoride catalyzed reaction of octanal with resorcinol monomethyl ether, reported by Mocerino and co-workers,[11] provided an important advance in the chemistry of axially chiral C_4-symmetric resorcin[4]-arenes. We showed, subsequently, that the desymmetrization of resorcinol could be achieved in high yields[12] to give a wide range of 3-alkoxyphenol derivatives starting from 3-iodophenol, using alkanols and copper(I) iodide/9,10-phenanthroline catalysis,[13] or from resorcinol monobenzoate using alcohols in Mitsunobu reactions,[14] followed by base-catalyzed alcoholysis. We were thus able to access a range of other racemic tetraalkoxyresorcinarene derivatives in good to excellent yields by the interaction of boron trifluoride with 1,1-dimethoxyalkanes and, for example, the 3-alkoxyphenol derivatives.[15] We also recently reported the conversion of a number of racemic tetraalkoxyresorcinarenes into diastereoisomeric mixtures of tetrakis(1,3-benzoxazine) derivatives, together with the separation of the diastereoisomers and proof of their absolute configurations.[16]

Results and Discussion

The method developed by Mocerino[11] provided, in principle, a route to diastereoisomeric resorcinarene derivatives by using suitable optically pure 3-alkoxyphenols. During the course of our investigation, the Mocerino protocol was used to prepare diastereoisomeric tetrakis(2-methylbutyloxy)resorcin[4]arenes in a 3:2 ratio using 3-methylbutanal, and in a 1:1 ratio using dodecanal.[17] However, as far as

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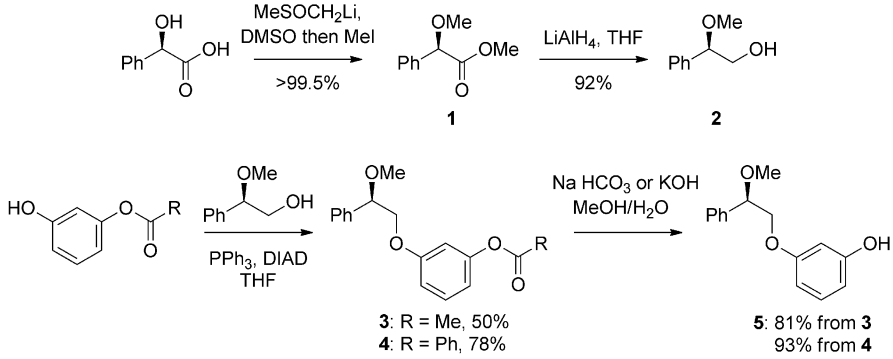
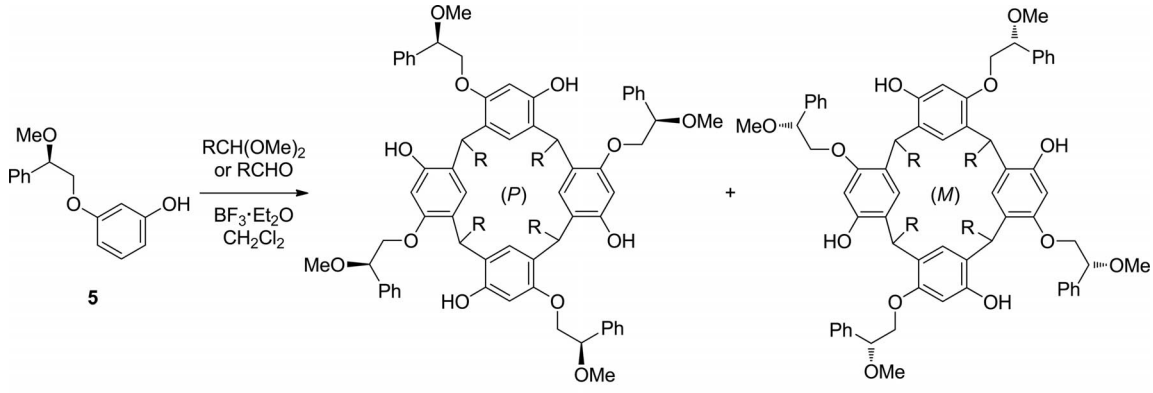


Scheme 1. Preparation of (–)-3-[(2*R*)-2-methoxy-2-phenylethoxy]phenol (**5**).

we are aware, the absolute configurations of the products have not been confirmed. Our investigation required a viable route to quantities of (–)-3-[(2*R*)-2-methoxy-2-phenylethoxy]phenol. We showed that hydroxycarboxylic acids could be converted in excellent yields into the related ether–esters using dimsyllithium in dimethyl sulfoxide (DMSO) and methyl iodide; we prepared (–)-methyl (2*R*)-2-methoxy-2-phenylacetate (**1**) in an essentially quantitative yield by using that method with no loss of optical purity.[18] Reduction of the ester using lithium aluminium hydride in tetrahydrofuran (THF) gave (–)-(2*R*)-2-methoxy-2-phenylethanol (**2**) in 92% yield. Although the Mitsunobu reaction using (–)-(2*R*)-2-methoxy-2-phenylethanol proceeded efficiently using commercial resorcinol monoacetate, the liquid resorcinol monoacetate used, which is known to be a mixture of monoacetate, diacetate and resorcinol, resulted in the isolation of (–)-3-[(2*R*)-2-methoxy-2-phenylethoxy]-phenyl acetate (**3**) in only 50% yield. However, using the commercially available pure crystalline resorcinol monobenzoate gave (–)-3-[(2*R*)-2-methoxy-2-phenylethoxy]-phenyl benzoate (**4**) in 78% yield. Hydrolysis of the esters gave (–)-3-[(2*R*)-2-methoxy-2-phenylethoxy]phenol (**5**) in excellent yields. The sequence of reactions is shown in Scheme 1.

Reactions using (–)-3-[(2*R*)-2-methoxy-2-phenylethoxy]-phenol (**5**) were carried out using hexanal (or 1,1-dimethoxyhexane) and 2-phenylpropanal (or 1,1-dimethoxy-3-phenylpropane), together with boron trifluoride–diethyl ether (Scheme 2). Unfortunately, reactions carried out under apparently identical reaction conditions at ambient temperature, using the aldehydes or the related dimethyl acetals, behaved capriciously. The yields of a mixture of the diastereoisomers **6a** and **6b** varied from 20–70%, typically 60%. The yields of the boron trifluoride catalyzed reactions using (–)-3-[(2*R*)-2-methoxy-2-phenylethoxy]phenol and 3-phenylpropanal, or the related dimethyl acetal, resulted in the formation of a mixture of diastereoisomers **7a** and **7b**, but in only 20–25% yield.

We prefer to reserve the use of the term "inherent chirality" to calixarenes that are not C_n-symmetric. We also pre-

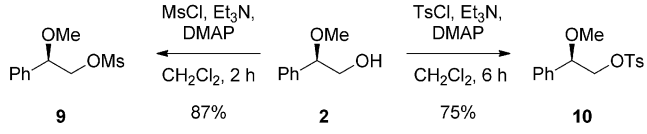


Entry	Aldehyde/Acetal	*dr* (**a**/**b**)	Yield [%]
1	*n*-$C_5H_{11}CHO$	1:2	60
2	*n*-$C_5H_{11}CH(OMe)_2$	1:3	66
3	$PhCH_2CH_2CHO$	1:2	25
4	$PhCH_2CH_2CH(OMe)_2$	1:2	20

Scheme 2. Diastereoselective formation of C_4-symmetric (*P*)- and (*M*)-tetraalkoxyresorcin[4]arenes from (–)-3-[(2*R*)-2-methoxy-2-phenylethoxy]phenol.

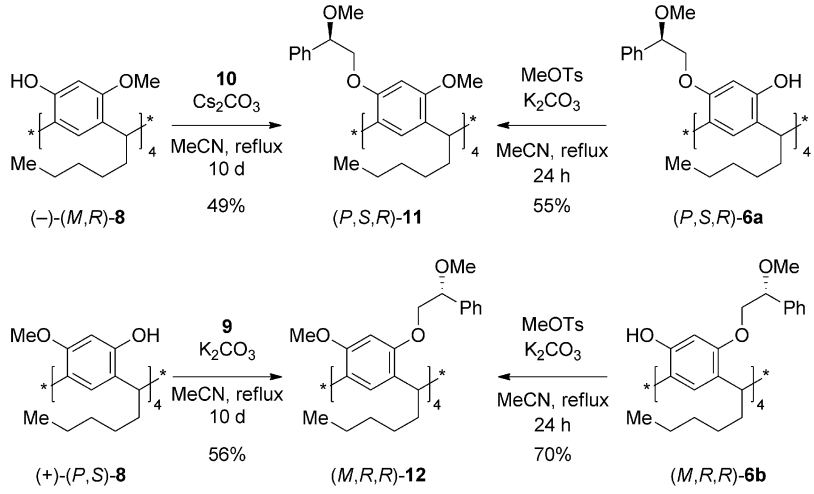
fer to use the term "axial chirality" rather than "cyclochirality" and the configurational symbols (*M*) and (*P*) for axially chiral C_4-symmetric resorcinarenes,[16] as recommended by the Cahn–Ingold–Prelog system.[19] The configurational symbol (*M*) refers to an anticlockwise sequence of groups around the chiral axis as defined by the Cahn–Ingold–Prelog system and the configurational symbol (*P*) to a clockwise sequence; in each case, the sequence is determined either by viewing the groups from inside the cavity of the resorcin[4]arene or from above the upper polar rim; both operations give the same configurational symbol. When determining the correct sequence it is also important to note that the pendant groups (R) occupy pseudo-axial orientations.

Inspection of the ^{1}H NMR spectra of the crude reaction mixtures showed that the diastereoisomer ratio for **6a** and **6b** was typically 1:3 for reactions using 1,1-dimethoxyhexane, and 1:2 for reactions using hexanal. The diastereoisomer ratios for reactions using 3-phenylpropanal were typically 1:2. The formation of tetraalkoxyresorcin[4]arenes is thought to involve the reversible formation of a series of linear dimeric and tetrameric intermediates,[12] and the final cyclization of linear tetrameric diastereoisomers, with differing steric demands, accounts for the observed diastereoselectivities in the reactions recorded here. When the reactions leading to the formation of compounds **6a** and **6b** were carried out at –78 °C, no improvement in yields or diastereoisomer ratios was observed. Separation of the mixtures was achieved by using flash chromatography on silica gel, with the slower eluting diastereoisomer being obtained in larger amounts in each case (Scheme 3). Despite numerous attempts, we were unable to obtain crystalline derivatives of the pure diastereoisomers in order to establish their absolute configurations by X-ray crystallographic analysis. Our unambiguous proof of structures of the (+) and (–) enantiomers for a range of tetraalkoxyresorcin[4]arenes provided a method for establishing the configurations of the diastereoisomers **6a/b** and **7a/b** that did not rely on X-ray crystallography.[20] Attempted methylation of a mixture of **6a/b** using a variety of Mitsunobu protocols or using diazomethane failed. Finally, when either of the diastereoisomers **6a** or **6b** was heated to reflux in acetonitrile using methyl *p*-toluenesulfonate and potassium carbonate, the corresponding methyl ethers were obtained in 70% yield from the major diastereoisomer **6b**, and in 55% yield from the minor diastereoisomer **6a**, respectively. We have noted previously that diastereoisomeric tetraalkoxyresorcin[4]arenes frequently show different reactivities, especially when sterically demanding alkoxy groups are present.[16,21] To establish the absolute configurations of the diastereoisomers **6a** and **6b** it was necessary to prepare compounds **11** and **12**, with known absolute configurations, by alkylating the enantiomerically pure tetramethoxyresorcin[4]arenes (–)-(*M*,*R*)-**8** and (+)-(*P*,*S*)-**8**, derived from 3-methoxyphenol and hexanal, which we had prepared and fully characterized previously, and to compare these compounds with those prepared by the methylation of **6a** and **6b**.[22] We chose to optimize the alkylation of the racemic tetramethoxyresorcin[4]-arene (±)-**8** using the mesylate **9** and tosylate **10** (the enantiomer of which has been reported previously)[23] prepared in 87 and 75% yields, respectively, from (–)-(2*R*)-2-methoxy-2-phenylethanol (**2**), as shown in Scheme 3.



Scheme 3. Preparation of methane- and *p*-toluenesulfonates from (–)-(*R*)-2-methoxy-2-phenylethanol.

A series of experiments showed that alkylation of the racemic tetramethoxyresorcin[4]arene (±)-**8** using tosylate **10** gave slightly higher yields of the diastereoisomers **11** and **12** than when mesylate **9** was used. The reactions proceeded very slowly when heated to reflux in acetonitrile in the presence of either potassium or cesium carbonate. The results of the alkylation experiments are shown in Scheme 4.



Scheme 4. Proof of absolute configurations of diastereoisomers **6a** and **6b** using alkylation reactions.

Alkylation of (+)-(*P*,*S*)-**8** using the mesylate **9** gave the derivative (*M*,*R*,*R*)-**12**, which was shown to be identical to the product obtained by methylation of the major diastereoisomer **6b**. As anticipated, we found that alkylation of (–)-(*M*,*R*)-**8**, even using tosylate **10**, proceeded more slowly to form the derivative (*P*,*S*,*R*)-**11**, and in lower yield than the similar reaction using (+)-**8**. In this way we were able to establish and confirm unambiguously the absolute configurations of the tetraalkoxyresorcin[4]arenes (*P*,*S*,*R*)-**6a** and (*M*,*R*,*R*)-**6b**. The results obtained from the methylation of the diastereoisomers **6a** and **6b** and the differential ease of formation and yields of diastereoisomeric camphorsulfonates,[22] and trifluoromethanesulfonates,[21] obtained from sterically demanding racemic tetraalkoxyresorcin[4]arenes [prepared, for example, from 3-(isopropyloxy)phenol and 3-(cyclopentyloxy)phenol], allows us to draw general conclusions concerning diastereoisomer formation when tetraalkoxyresorcin[4]arenes are prepared from optically pure 3-alkoxyphenol derivatives. Although we have not carried out experiments to establish the absolute configurations of compounds **7a** and **7b** using tetramethoxyresorcin[4]arene derivatives of known absolute configurations, it is not unreasonable to conclude that the major diastereoisomer is (*M*,*R*,*R*)-**7b**.

Conclusions

The results of the investigation of tetraalkoxyresorcin[4]arene formation from optically pure (–)-3-[(2*R*)-2-methoxy-2-phenylethoxy]phenol (**5**) using boron trifluoride catalysis, indicate that diastereoselective ring closure of linear tetrameric intermediates is controlled by the steric demand of the alkyl group in the precursor 3-alkoxyphenol.

Experimental Section

General: Commercially available reagents were used as supplied, unless stated otherwise, and stored according to the manufacturer's recommendations. Flash chromatography was carried out using glass columns packed with Merck Kieselgel 60–45. Thin layer chromatography was carried out on aluminium-backed plates coated with Merck Kieselgel 60 GF_{254}. Plates were viewed under UV light and developed by staining using aqueous potassium permanganate or ethanolic phosphomolybdic acid, followed by heating. All infrared spectra were obtained with a Perkin–Elmer Paragon 2000 FTIR spectrophotometer; thin-film spectra were acquired using sodium chloride plates. All ^{1}H and ^{13}C NMR spectra were measured at 400 and 100 MHz with a Bruker DPX 400 spectrometer; samples were dissolved in deuteriochloroform solution unless otherwise stated, using TMS (tetramethylsilane) as the internal reference. Mass spectra were recorded by the EPSRC national mass spectrometry service at the University of Wales, Swansea; measurements were performed utilising electrospray (ES) and MALDI-TOF and using a Jeol-SX102 instrument with electron-impact (EI) and fast atom bombardment (FAB). Optical rotations were measured with a B&S ADP-440 spectrometer.

(2*R*)-2-Methoxy-2-phenylethanol (2):[24] Methyl (2*R*)-2-methoxy-2-phenylacetate (8.4 g, 46.7 mmol, 1 equiv.) was dissolved in anhydrous diethyl ether (150 mL) in an oven-dried 500 mL round-bottomed flask under a flux of nitrogen from an inverted funnel. $LiAlH_4$ (2.3 g, 60.7 mmol, 1.3 equiv.) was then added in small portions to the solution under the flux of nitrogen. The grey reaction mixture was stirred at room temperature for 2 h, after which time anhydrous sodium sulfate (10 g) was added. Water (10 mL) was cautiously added, and the mixture was stirred for a further 30 min, after which time the suspension became white. The mixture was filtered through a pad of Celite, and the filtrate was concentrated under reduced pressure to give **2** as a pale-yellow liquid (6.5 g, 91%). $[\alpha]_D$ = –15.4 (c = 2.0, $CHCl_3$). HRMS: calcd. for $C_9H_{12}O_2$ $[M]^+$ 152.0837; found 152.0835. IR (CH_2Cl_2): $\tilde{\nu}_{max}$ = 3427, 2978, 2932, 2871, 2834, 1453, 1112, 759 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.52 (br. s, 1 H, OH), 3.33 (s, 3 H, OCH_3), 3.69 (m, 2 H, CH_2OH), 4.33 (dd, J = 8.6, 4.0 Hz, 1 H, CHOMe), 7.28–7.42 (m, 5 H, PhH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 56.9 (CH_3), 67.4 (CH_2OH), 84.6 (CHOMe), 126.9 (C_{Ar}H), 128.2 (C_{Ar}H), 128.6 (C_{Ar}H), 138.2 (C_{Ar}) ppm.

3-[(2*R*)-2-Methoxy-2-phenylethoxy]phenyl Acetate (3): (*R*)-2-Methoxy-2-phenylethanol (**2**; 11.3 g, 85.5 mmol, 1.0 equiv.), resorcinol monoacetate (16.9 g, 111 mmol, 1.3 equiv.) and triphenylphosphane (31.6 g, 138 mmol, 1.6 equiv.) were dissolved in anhydrous THF (150 mL) in a 500 mL oven-dried round-bottomed flask under nitrogen, and the mixture was cooled to 0 °C. Diisopropyl azodicarboxylate (23 mL, 117 mmol, 1.4 equiv.) was then added dropwise over 30 min. The solution was warmed to room temperature and stirred at room temperature for 12 h. The solvent was then removed under reduced pressure, and the residue was triturated in cold diethyl ether to give a white solid. The suspension was filtered, and the filtrate was concentrated under reduced pressure. The residue was placed on a column of silica gel and eluted with ethyl acetate/hexane (5:95) to give **3** as a colourless oil (12.0 g, 50%). $[\alpha]_D$ = –34.9 (c = 0.93, $CHCl_3$). HRMS: calcd. for $C_9H_{13}O_2^+$ $[M + H]^+$ 287.1283; found 287.1281. IR (CH_2Cl_2): $\tilde{\nu}_{max}$ = 2933, 1764, 1605, 1591, 1487, 1208, 1140, 1111 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.27 (s, 3 H, CH_3), 3.35 (s, 3 H, OCH_3), 3.97 (dd, J = 10.4, 3.6 Hz, 1 H, CH_2OAr), 4.14 (dd, J = 10.4, 7.8 Hz, 1 H, CH_2OAr), 4.57 (dd, J = 7.8, 3.6 Hz, 1 H, CHOMe), 6.64 (s, 1 H, ArH), 6.66 (m, 1 H, ArH), 6.78 (m, 1 H, ArH), 7.24 (m, 1 H, ArH), 7.26–7.37 (m, 5 H, PhH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.1 (CH_3), 57.2 (OCH_3), 72.5 (CH_2OAr), 81.9 (CHOMe), 108.5 (C_{Ar}H), 112.4 (C_{Ar}H), 114.0 (C_{Ar}H), 127.0 (C_{Ar}H), 128.3 (C_{Ar}H), 128.5 (C_{Ar}H), 129.8 (C_{Ar}H), 138.4 (C_{Ar}), 151.6 (C_{Ar}), 159.9 (C_{Ar}), 169.3 (C=O) ppm.

3-[(2*R*)-2-Methoxy-2-phenylethoxy]phenyl Benzoate (4): (2*R*)-2-Methoxy-2-phenylethanol (**2**; 8.0 g, 52.6 mmol, 1.0 equiv.), resorcinol monobenzoate (13.5 g, 63.1 mmol, 1.2 equiv.) and triphenylphosphane (20.7 g, 78.8 mmol, 1.5 equiv.) were dissolved in anhydrous THF (150 mL) in a 500 mL oven-dried round-bottomed flask under nitrogen, and the mixture was cooled to 0 °C. Diisopropyl azodicarboxylate (13.4 mL, 68.3 mmol, 1.3 equiv.) was then added dropwise over 30 min, after which time the mixture was warmed to room temperature and stirred for 12 h. The solvent was then removed under reduced pressure, and the residue was triturated with cold diethyl ether to give a white solid. The suspension was filtered, and the filtrate was concentrated under reduced pressure. The residue was placed on a column of silica gel and eluted with ethyl acetate/hexane (3:97) to give **4** as a colourless oil (14.3 g, 78%). $[\alpha]_D$ = –30.0 (c = 0.85, $CHCl_3$). HRMS: Calcd. for $C_{22}H_{20}O_4^+$ $[M]^+$ 348.1362; found 348.1360. IR (CH_2Cl_2): $\tilde{\nu}_{max}$ = 3062, 3030, 2982, 2931, 2874, 2824, 1733, 1606, 1488, 1450, 1259, 936 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.27 (s, 3 H, OCH_3), 3.92 (dd, J = 10.4, 3.6 Hz, 1 H, CH_2OAr), 4.07 (dd, J = 10.4, 8.0 Hz, 1 H, CH_2OAr), 4.65 (dd, J = 8.0, 3.6 Hz, 1 H, CHOMe),

6.69–6.74 (m, 3 H, ArH), 7.15–7.31 (m, 6 H, ArH), 7.39–7.43 (m, 2 H, ArH), 7.49–7.53 (m, 1 H, ArH), 8.08–8.11 (m, 2 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 57.6 (O*C*H$_3$), 72.9 (*C*H$_2$OAr), 82.5 (*C*HOMe), 108.9 (*C*$_{Ar}$H), 113.0 (*C*$_{Ar}$H), 114.6 (*C*$_{Ar}$H), 127.4 (*C*$_{Ar}$H), 128.7 (*C*$_{Ar}$H), 129.0 (*C*$_{Ar}$H), 129.1 (*C*$_{Ar}$H), 130.3 (*C*$_{Ar}$H), 130.58 (*C*$_{Ar}$H), 130.60 (*C*$_{Ar}$), 134.0 (*C*$_{Ar}$H), 138.7 (*C*$_{Ar}$), 152.2 (*C*$_{Ar}$), 160.0 (*C*$_{Ar}$), 165.5 (*C*=O) ppm.

3-[(2*R*)-2-Methoxy-2-phenylethoxy]phenol (5)

First Method: 3-[(2*R*)-2-Methoxy-2-phenylethoxy]phenyl acetate (**3**; 11.3 g, 36 mmol, 1 equiv.) was dissolved in methanol (200 mL) and water (2 mL) in a 500 mL round-bottomed flask. A solution of saturated sodium hydrogen carbonate (15 mL) was then added, and the mixture was stirred at room temperature for 1 d. Water (200 mL) and CH_2Cl_2 (200 mL) were added, and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 50 mL) and the combined organic phases were washed with brine, dried with anhydrous sodium sulfate and concentrated under reduced pressure. The residue was placed on a column of silica gel and eluted with ethyl acetate/hexane (1:9) to give **5** as a yellow oil (7.1 g, 81%).

Second Method: 3-[(2*R*)-2-Methoxy-2-phenylethoxy]phenyl benzoate (**4**; 14.0 g, 40.2 mmol, 1 equiv.) was added to a solution of potassium hydroxide (1 M) in ethanol (50 mL) in a 250 mL round-bottomed flask. The mixture was stirred at room temperature for 15 h, then hydrochloric acid (3.5 M) was added to bring the pH below 3. The aqueous phase was extracted with diethyl ether (3 × 50 mL), and the combined organic phases were washed with brine, dried with anhydrous sodium sulfate and concentrated under reduced pressure. The residue was placed on a column of silica gel and eluted with ethyl acetate/hexane (1:9) to give **5** as a colourless oil (9.6 g, 93%). $[\alpha]_D$ = –35.4 (*c* = 1.89, $CHCl_3$). HRMS: Calcd. for $C_{15}H_{16}O_3^+$ $[M]^+$ 244.1100; found 244.1102. IR (CH_2Cl_2): $\tilde{\nu}_{max}$ = 3354, 2931, 2874, 1597, 1492, 1454, 1287, 1175, 1117, 1086, 1064, 841 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.39 (s, 3 H, OC*H*$_3$), 4.00 (dd, *J* = 10.6, 3.2 Hz, 1 H, C*H*$_2$OAr), 4.16 (dd, *J* = 10.6, 8.2 Hz, 1 H, C*H*$_2$OAr), 4.65 (dd, *J* = 8.2, 3.2 Hz, 1 H, C*H*OMe), 6.19 (s, 1 H, ArO*H*), 6.46 (m, 2 H, ArH), 6.52 (m, 1 H, ArH), 7.09 (m, 1 H, ArH), 7.27–7.38 (m, 5 H, PhH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 57.5 (O*C*H$_3$), 72.6 (*C*H$_2$OAr), 82.6 (*C*HOMe), 103.7 (*C*$_{Ar}$H), 106.8 (*C*$_{Ar}$H), 108.7 (*C*$_{Ar}$H), 127.4 (*C*$_{Ar}$H), 128.8 (*C*$_{Ar}$H), 129.0 (*C*$_{Ar}$H), 130.4 (*C*$_{Ar}$H), 138.6 (*C*$_{Ar}$), 157.5 (*C*$_{Ar}$), 160.3 (*C*$_{Ar}$) ppm.

General Procedure for the Preparation of the Tetraalkoxyresorcinarenes: 3-[(2*R*)-2-Methoxy-2-phenylethoxy]phenol (**5**; 1 equiv.) and the dimethoxyalkane (1 equiv.) or the aldehyde (1 equiv.) were dissolved in anhydrous CH_2Cl_2 under nitrogen. The reaction mixture was cooled to 0 °C, and boron trifluoride–diethyl ether (2 equiv.) was added dropwise. The reaction mixture was then warmed to room temperature and stirred for 6 h. Water was then added to the reaction mixture, and the phases were separated. The aqueous layer was extracted with CH_2Cl_2, and the combined organic phases were washed with brine, dried with anhydrous sodium sulfate and concentrated under reduced pressure. The residue was placed on a column of silica gel and eluted with ethyl acetate/hexane to give the pure product.

Resorcinarenes 6a and 6b

Using 1,1-Dimethoxyhexane: 3-[(2*R*)-2-Methoxy-2-phenylethoxy]-phenol (**5**; 500 mg, 2.05 mmol, 1 equiv.), 1,1-dimethoxyhexane (250 μL, 2.05 mmol, 1 equiv.) and boron trifluoride–diethyl ether (500 μL, 4.1 mmol, 2 equiv.) were used to give diastereoisomer **6a** (first eluting; 107 mg, 16%) and **6b** (second eluting; 334 mg, 50%) as brown foams after chromatography on silica gel with hexane/ethyl acetate (85:15) as eluent.

Using Hexanal: 3-[(2*R*)-2-Methoxy-2-phenylethoxy]phenol (**5**; 2.0 g, 8.2 mmol, 1 equiv.), hexanal (1.0 mL, 8.2 mmol, 1 equiv.) and boron trifluoride–diethyl ether (2.0 mL, 16.4 mmol, 2 equiv.) were used to give diastereoisomer **6a** (first eluting; 0.55 g, 21%) and **6b** (second eluting; 1.05 g, 39%) as brown foams after chromatography on silica gel with hexane/ethyl acetate (85:15) as eluent.

First Eluting Diastereoisomer 6a: $[\alpha]_D$ = +3.2 (*c* = 1.1, $CHCl_3$). HRMS: Calcd. for $C_{84}H_{105}O_{12}^+$ $[M + H]^+$ 1305.7610; found 1305.7606. IR (CH_2Cl_2): $\tilde{\nu}_{max}$ = 3447, 2927, 2858, 1623, 1617, 1587, 1506, 1496, 1462, 1330, 1291, 1174, 1115, 1026, 908, 838, 761, 701 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.84 [t, *J* = 6.8 Hz, 12 H, (CH$_2$)$_3$C*H*$_3$], 1.19–1.30 [m, 24 H, (C*H*$_2$)$_3$CH$_3$], 2.05 (m, 8 H, Ar$_2$CHC*H*$_2$), 3.28 (s, 12 H, OC*H*$_3$), 3.92 (dd, *J* = 10.1, 8.8 Hz, 4 H, C*H*$_2$OAr), 3.99 (dd, *J* = 10.1, 2.9 Hz, 4 H, C*H*$_2$OAr), 4.25 (t, *J* = 7.0 Hz, 4 H, Ar$_2$C*H*CH$_2$), 4.52 (dd, *J* = 8.8, 2.9 Hz, 4 H, C*H*OMe), 6.23 (s, 4 H, ArH), 7.13 (s, 4 H, ArH), 7.21–7.30 (m, 24 H, ArH and ArOH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.2 [(CH$_2$)$_3$*C*H$_3$], 22.8 (*C*H$_2$CH$_3$), 27.7 (CHCH$_2$*C*H$_2$), 32.0 (*C*H$_2$CH$_2$CH$_3$), 33.2 (Ar$_2$*C*HCH$_2$), 34.5 (Ar$_2$CH*C*H$_2$), 57.0 (O*C*H$_3$), 73.2 (*C*H$_2$OAr), 82.0 (*C*HOMe), 101.5 (*C*$_{Ar}$H), 124.1 (*C*$_{Ar}$H), 125.0 (*C*$_{Ar}$), 125.2 (*C*$_{Ar}$), 127.0 (*C*$_{Ar}$H), 128.2 (*C*$_{Ar}$H), 128.5 (*C*$_{Ar}$H), 137.7 (*C*$_{Ar}$), 153.0 (*C*$_{Ar}$), 153.4 (*C*$_{Ar}$) ppm.

Second Eluting Diastereoisomer 6b: $[\alpha]_D$ = –44.3 (*c* = 4.5, $CHCl_3$). HRMS: Calcd. for $C_{84}H_{104}O_{12}^+$ $[M]^+$ 1304.7528; found 1304.7509. IR (CH_2Cl_2): $\tilde{\nu}_{max}$ = 3441, 2927, 2857, 1615, 1586, 1494, 1454, 1292, 1233, 1174, 1116, 1026, 761, 701 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.88 [t, *J* = 6.8 Hz, 12 H, (CH$_2$)$_3$C*H*$_3$], 1.24–1.33 [m, 24 H, (C*H*$_2$)$_3$CH$_3$], 2.01–2.22 (m, 8 H, Ar$_2$CHC*H*$_2$), 3.33 (s, 12 H, OC*H*$_3$), 3.97 (dd, *J* = 10.1, 4.2 Hz, 4 H, C*H*$_2$OAr), 4.10 (dd, *J* = 10.1, 8.6 Hz, 4 H, C*H*$_2$OAr), 4.23 (t, *J* = 7.0 Hz, 4 H, Ar$_2$C*H*CH$_2$), 4.57 (dd, *J* = 8.6, 4.2 Hz, 4 H, C*H*OMe), 6.35 (s, 4 H, ArH), 7.21 (s, 4 H, ArH), 7.21–7.34 (m, 24 H, ArH and ArOH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.2 [(CH$_2$)$_3$*C*H$_3$], 22.8 (*C*H$_2$CH$_3$), 27.7 (CHCH$_2$*C*H$_2$), 32.0 (*C*H$_2$CH$_2$CH$_3$), 33.2 (Ar$_2$*C*HCH$_2$), 34.6 (Ar$_2$CH*C*H$_2$), 56.9 (O*C*H$_3$), 72.8 (*C*H$_2$OAr), 82.0 (*C*HOMe), 101.8 (*C*$_{Ar}$H), 124.0 (*C*$_{Ar}$H), 125.0 (*C*$_{Ar}$), 125.3 (*C*$_{Ar}$), 127.2 (*C*$_{Ar}$H), 128.5 (*C*$_{Ar}$H), 128.7 (*C*$_{Ar}$H), 137.7 (*C*$_{Ar}$), 153.0 (*C*$_{Ar}$) ppm.

Resorcinarenes 7a and 7b

Using 1,1-Dimethoxy-3-phenylpropane: 3-[(2*R*)-2-Methoxy-2-phenylethoxy]phenol (**5**; 700 mg, 2.88 mmol, 1 equiv.), 1,1-dimethoxy-3-phenylpropane (520 mg, 2.88 mmol, 1 equiv.) and boron trifluoride–diethyl ether (700 μL, 5.76 mmol, 2 equiv.) were used to give diastereoisomer **7a** (first eluting; 134 mg, 13%) and **7b** (second eluting; 134 mg, 13%) as pale-red foams after chromatography on silica gel with hexane/ethyl acetate (4:1) as eluent.

Using 3-Phenylpropanal: 3-[(2*R*)-2-Methoxy-2-phenylethoxy]phenol (**5**; 700 mg, 2.88 mmol, 1 equiv.), 3-phenylpropanal (380 μL, 2.88 mmol, 1 equiv.) and boron trifluoride–diethyl ether (700 μL, 5.76 mmol, 2 equiv.) were used to give diastereoisomer **7a** (first eluting; 83 mg, 8%) and **7b** (second eluting; 176 mg, 17%) as pale-red foams after chromatography on silica gel with hexane/ethyl acetate (4:1) as eluent.

First Eluting Diastereoisomer 7a: $[\alpha]_D$ = –20.3 (*c* = 0.9, $CHCl_3$). HRMS: Calcd. for $C_{96}H_{97}O_{12}^+$ $[M + H]^+$ 1441.6980; found 1441.7 (the isotopic distribution of the observed data matched the theoretical $[M]^+$ and $[M + Na]^+$ isotopic distributions). IR (CH_2Cl_2): $\tilde{\nu}_{max}$ = 3442, 3112, 2923, 2859, 1631, 1624, 1583, 1539, 1506, 1496, 1461, 1334, 1285, 1049, 1026, 907, 841, 759, 701 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.33–2.47 (m, 16 H, C*H*$_2$C*H*$_2$Ph), 3.27 (s,

12 H, OCH_3), 3.93 (dd, J = 8.5, 10.2 Hz, 4 H, CH_2OAr), 4.02 (dd, J = 10.2, 3.0 Hz, 4 H, CH_2OAr), 4.33 (t, J = 7.5 Hz, 4 H, CH_2CHAr$_2$), 4.53 (dd, J = 8.5, 3.0 Hz, 4 H, CHOMe), 6.28 (s, 4 H, ArH), 7.02–7.04 (m, 8 H, ArH), 7.11–7.18 (m, 24 H, ArH), 7.25–7.38 (m, 16 H, ArH and ArOH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 33.3 (CH_2CHAr$_2$), 34.5 (CH_2Ph), 36.9 (CH_2CH$_2$Ph), 56.9 (OCH_3), 73.1 (CH_2OAr), 81.6 (CHOMe), 101.6 (C_{Ar}H), 123.9 (C_{Ar}H), 124.6 (C_{Ar}), 124.9 (C_{Ar}), 125.8 (C_{Ar}H), 127.0 (C_{Ar}H), 128.5 (C_{Ar}H), 128.6 (C_{Ar}H), 128.7 (C_{Ar}H), 137.7 (C_{Ar}), 142.1 (C_{Ar}), 153.2 (C_{Ar}), 153.4 (C_{Ar}) ppm.

Second Eluting Diastereoisomer 7b: $[\alpha]_D$ = –26.7 (c = 1.2, $CHCl_3$). HRMS: Calcd. for $C_{96}H_{100}O_{12}N^+$ [M + NH_4]$^+$ 1458.7245; found 1458.7 (the isotopic distribution of the observed data matched the theoretical [M]$^+$ isotopic distributions). IR (CH_2Cl_2): $\tilde{\nu}_{max}$ = 3445, 2927, 2852, 1619, 1588, 1495, 1450, 1291, 1229, 1176, 1033, 755. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.39–2.46 (m, 16 H, CH_2CH_2Ph), 3.11 (s, 12 H, OCH_3), 3.72 (dd, J = 9.5, 3.6 Hz, 4 H, CH_2OAr), 3.95 (t, J = 9.5 Hz, 4 H, CH_2OAr), 4.22 (t, J = 7 Hz, 4 H, CH_2CHAr$_2$), 4.28 (dd, J = 9.5, 3.6 Hz, 4 H, CHOMe), 6.18 (s, 4 H, ArH), 6.75–7.20 (m, 48 H, ArH and ArOH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 32.7 (CH_2CHAr$_2$), 34.4 (CH_2Ph), 36.7 (CH_2CH$_2$Ph), 56.9 (OCH_3), 72.8 (CH_2OAr), 81.9 (CHOMe), 102.0 (C_{Ar}H), 123.8 (C_{Ar}H), 124.5 (C_{Ar}), 125.0 (C_{Ar}), 125.9 (C_{Ar}H), 127.1 (C_{Ar}H), 128.5 (C_{Ar}H), 128.6 (C_{Ar}H), 128.7 (C_{Ar}H), 128.8 (C_{Ar}H), 137.7 (C_{Ar}), 142.0 (C_{Ar}), 153.3 (C_{Ar}) ppm.

(2*R*)-2-Methoxy-2-phenylethyl Methanesulfonate (9): (2*R*)-2-Methoxy-2-phenylethanol (**2**; 1.0 g, 6.6 mmol, 1 equiv.), triethylamine (1.3 g, 13.2 mmol, 2 equiv.) and a catalytic amount of DMAP were dissolved in CH_2Cl_2 (40 mL) in a 100 mL round-bottomed flask. Methanesulfonyl chloride (764 μL, 9.1 mmol, 1.4 equiv.) was then added, and the reaction mixture was stirred at room temperature for 2 h. Brine (20 mL) was added to the mixture, and the two phases were separated. The organic phase was dried with anhydrous sodium sulfate and concentrated under reduced pressure. The residue was placed on a column of silica gel and eluted with ethyl acetate/hexane (3:7) to give **9** as a yellow oil (1.3 g, 87%). $[\alpha]_D$ = –71.1 (c = 1.8, $CHCl_3$). HRMS: Calcd. for $C_{10}H_{15}O_4S^+$ [M + H]$^+$ 231.0691; found 231.0694. IR (CH_2Cl_2): $\tilde{\nu}_{max}$ = 3404, 3086, 3016, 2938, 2891, 2831, 1450, 1336, 1172, 1121, 970, 763, 701 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.00 (s, 3 H, SO_2CH_3), 3.31 (s, 3 H, OCH_3), 4.21–4.25 (m, 1 H, CH_2OSO$_2$), 4.29–4.34 (m, 1 H, CH_2OSO$_2$), 4.50 (dd, J = 8.0, 3.6 Hz, 1 H, CHOMe), 7.32–7.35 (m, 5 H, PhH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 37.7 (SO_2CH_3), 57.0 (OCH_3), 72.8 (CH_2OSO$_2$), 81.5 (CHOMe), 126.0 (C_{Ar}H), 128.9 (C_{Ar}H), 135.5 (C_{Ar}) ppm.

(2*R*)-2-Methoxy-2-phenylethyl *p*-Toluenesulfonate (10):[23] (2*R*)-2-Methoxy-2-phenylethanol (**45**; 1 g, 6.6 mmol, 1 equiv.), triethylamine (1.3 g, 13.2 mmol, 2 equiv.) and a catalytic amount of DMAP were dissolved in CH_2Cl_2 (40 mL) in a 100 mL round-bottomed flask. Toluenesulfonyl chloride (1.5 g, 7.8 mmol, 1.2 equiv.) was then added, and the reaction mixture was stirred at room temperature for 6 h. Brine (20 mL) was added, the phases were separated, and the organic phase was dried with anhydrous sodium sulfate and concentrated under reduced pressure. The residue was placed on a column of silica gel and eluted with ethyl acetate/hexane (1:4) to give **10** as a yellow oil (1.5 g, 75%). $[\alpha]_D$ = –93.8 (c = 1.6, $CHCl_3$) {ref.[23] (for enantiomer): $[\alpha]_D$ = +92.6 (c = 3.0, C_6H_6)}. HRMS: Calcd. for $C_{16}H_{19}O_4S^+$ [M + H]$^+$ 307.1004; found 307.1002. IR (CH_2Cl_2): $\tilde{\nu}_{max}$ = 3378, 2935, 2826, 1358, 1189, 1176, 1121, 975, 666 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.44 (s, 3 H, C_6H_4CH_3), 3.23 (s, 3 H, OCH_3), 4.02–4.11 (m, 2 H, CH_2OSO$_2$), 4.41 (dd, J = 7.6, 4.4 Hz, 1 H, CHOMe), 7.23–7.34 (m, 7 H, ArH). 7.73 (d, J = 6.4 Hz, 2 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.6 (C_6H_4CH_3), 57.1 (OCH_3), 72.9 (CH_2OSO$_2$), 81.3 (CHOMe), 127.0 (C_{Ar}H), 127.9 (C_{Ar}H), 128.6 (C_{Ar}H), 128.7 (C_{Ar}H), 129.8 (C_{Ar}H), 133.1 (C_{Ar}), 136.9 (C_{Ar}), 144.7 (C_{Ar}) ppm.

4,10,16,22-Tetramethoxy-6,12,18,24-tetrakis[(2*R*)-2-methoxy-2-phenylethoxy]-2,8,14,20-tetrapentylresorcinarene (11)

First Method: Tetramethoxyresorcinarene (–)-**8** (100 mg, 0.1 mmol, 1 equiv.), (2*R*)-2-methoxy-2-phenylethyl toluenesulfonate (**10**; 310 mg, 1.0 mmol, 10 equiv.) and cesium carbonate (500 mg, 1.5 mmol, 15 equiv.) were dissolved in anhydrous acetonitrile (10 mL) in a 50 mL oven-dried round-bottomed flask under nitrogen. The reaction mixture was heated to reflux for 10 d, then water (10 mL) was added, and the phases were separated. The aqueous layer was extracted with diethyl ether (3 × 10 mL), and the organic phases were combined, washed with brine, dried with anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was placed on a column of silica gel and eluted with ethyl acetate/hexane (1:9) to give **11** (81 mg, 49%) as a yellow oil.

Second Method: Resorcinarene (**6a**; 200 mg, 0.15 mmol, 1 equiv.) was dissolved in acetonitrile (30 mL) in a 50 mL round-bottomed flask under nitrogen, and potassium carbonate (348 mg, 1.84 mmol, 12 equiv.) and methyl tosylate (342 mg, 1.84 mmol, 12 equiv.) were slowly added to the solution at room temp. The solution was heated to reflux overnight, then brine (100 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 × 20 mL). The organic phases were combined, dried with anhydrous sodium sulfate and concentrated under reduced pressure. The residue was placed on a column of silica gel and eluted with hexane/ethyl acetate (85:15) to give **11** (113 mg, 55%) as a yellow oil.

$[\alpha]_D$ = –32.7 (c = 1.2, $CHCl_3$). HRMS: Calcd. for $C_{88}H_{112}O_{12}Na^+$ [M + Na]$^+$ 1383.8051; found 1383.8 (the isotopic distribution of the observed data matched the theoretical [M + Na]$^+$ isotopic distributions). IR (CH_2Cl_2): $\tilde{\nu}_{max}$ = 3027, 2926, 2856, 1731, 1609, 1582, 1497, 1452, 1296, 1194, 1117, 1039, 913 cm^{-1}. ^{1}H NMR (400 MHz, [D$_6$]DMSO, 100 °C): δ = 0.75 [m, 12 H, $(CH_2)_3$CH_3], 1.09–1.24 [m, 24 H, $(CH_2)_3CH_3$], 1.56–1.71 (m, 8 H, Ar$_2$CHCH_2), 3.28 (s, 12 H, OCH_3), 3.38 (s, 12 H, ArOCH_3), 3.86 (dd, J = 10.1, 3.9 Hz, 4 H, CH_2OAr), 3.97 (dd, J = 10.1, 7.0 Hz, 4 H, CH_2OAr), 4.35 (dd, J = 7.0, 3.9 Hz, 4 H, CHOMe), 4.70 (t, J = 7.2 Hz, 4 H, Ar$_2$CHCH$_2$), 6.37 (s, 4 H, ArH), 6.51 (s, 4 H, ArH), 7.26–7.34 (m, 20 H, C_6H_5) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO, 100 °C): δ = 13.0 [$(CH_2)_3$CH_3], 21.3 (CH_2CH$_3$), 26.6 (CHCH$_2$CH_2), 30.9 (CH_2CH$_2$CH$_3$), 34.0 (Ar$_2$CHCH$_2$), 34.3 (Ar$_2$CHCH_2), 55.0 (ArOCH_3), 56.0 (OCH_3), 72.8 (CH_2OAr), 81.7 (CHOMe), 98.5 (C_{Ar}H), 125.13 (C_{Ar}H), 125.32 (C_{Ar}), 125.88 (C_{Ar}), 126.26 (C_{Ar}H), 126.97 (C_{Ar}H), 127.51 (C_{Ar}H), 138.68 (C_{Ar}), 154.37 (C_{Ar}), 155.09 (C_{Ar}) ppm.

4,10,16,22-Tetramethoxy-6,12,18,24-tetrakis[(2*R*)-2-methoxy-2-phenylethoxy]-2,8,14,20-tetrapentylresorcinarene (12)

First Method: Tetramethoxyresorcinarene (+)-**8** (70 mg, 0.1 mmol, 1 equiv.), (2*R*)-2-methoxy-2-phenylethyl methanesulfonate (**9**; 230 mg, 1.0 mmol, 10 equiv.) and potassium carbonate (140 mg, 1.0 mmol, 10 equiv.) were dissolved in anhydrous acetonitrile (10 mL) in a 50 mL oven-dried round-bottomed flask under nitrogen. The reaction mixture was heated to reflux for 10 d, then water (10 mL) was added, and the two phases were separated. The aqueous layer was extracted with diethyl ether (3 × 10 mL), and the organic phases were combined, washed with brine, dried with anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was placed on a column of silica gel and eluted with ethyl acetate/hexane (15:85) to give **12** (92 mg, 56%) as a yellow oil.

Second Method: Resorcinarene **6b** (200 mg, 0.15 mmol, 1 equiv.) was dissolved in acetonitrile (30 mL) in a 50 mL round-bottomed flask under nitrogen. Potassium carbonate (1.84 mmol, 12 equiv.) and methyl tosylate (1.84 mmol, 12 equiv.) were slowly added to the solution at room temp., then the solution was heated to reflux overnight. Brine (100 mL) was added to the solution, and the mixture was extracted with CH_2Cl_2 (3 × 200 mL). The organic phases were combined, dried with anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was placed on a column of silica gel and eluted with hexane/ethyl acetate (85:15) to give **12** (144 mg, 70%) as a yellow oil.

$[a]_D$ = –1.4 (c = 1.4, $CHCl_3$). HRMS: Calcd. for $C_{88}H_{112}O_{12}Na^+$ $[M + Na]^+$ 1383.8051; found 1383.8 (the isotopic distribution of the observed data matched the theoretical $[M + Na]^+$ isotopic distributions). IR (CH_2Cl_2): $\tilde{\nu}_{max}$ = 3027, 2926, 2856, 1731, 1609, 1582, 1497, 1452, 1296, 1194, 1117, 1039, 913 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.84 [m, 12 H, $(CH_2)_3CH_3$], 1.19–1.31 [m, 24 H, $(CH_2)_3CH_3$], 1.71–1.80 (m, 8 H, Ar_2CHCH_2), 3.26 (s, 12 H, OCH_3), 3.48 (s, 12 H, $ArOCH_3$), 3.86 (d, J = 6 Hz, 8 H, CH_2OAr), 4.34 (t, J = 6 Hz, 4 H, CHOMe), 4.46 (t, J = 7.4 Hz, 4 H, Ar_2CHCH_2), 6.22 (s, 4 H, ArH), 6.56 (s, 4 H, ArH), 7.27–7.41 (m, 20 H, PhH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.2 [$(CH_2)_3CH_3$], 22.7 (CH_2CH_3), 28.1 ($CHCH_2CH_2$), 32.3 ($CH_2CH_2CH_3$), 34.50 (Ar_2CHCH_2), 35.8 (Ar_2CHCH_2), 55.7 (OCH_3), 57.3 (OCH_3), 73.6 (CH_2OAr), 82.3 (CHOMe), 98.15 ($C_{Ar}H$), 126.29 ($C_{Ar}H$), 126.97 ($C_{Ar}H$), 127.85 ($C_{Ar}H$), 128.36 ($C_{Ar}H$), 139.7 (C_{Ar}), 154.9 (C_{Ar}), 155.7 (C_{Ar}) ppm.

Acknowledgment

This work has enjoyed the support of EPSRC, Loughborough University and a Royal Society Industrial Fellowship. We are also indebted to the EPSRC Mass Spectrometry Unit, Swansea and the Secretaria de Estado de Educacion y Universidades y Fondo Social Europeo.

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Received: May 25, 2011
Published Online: August 8, 2011

