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Synthesis of Enantiopure (*S*,*R*,*S*)- and (*R*,*S*,*R*)-1,4,5,8,9,16-Hexahydroxytetraphenylenes

An-Hui Wu,[a] Chun-Kit Hau,[a] and Henry N. C. Wong[a,*]

[a] Department of Chemistry, Center of Novel Functional Molecules, and Central Laboratory of the Institute of Molecular Technology for Drug Discovery and Synthesis [An Area of Excellence of the University Grants Committee (Hong Kong)], The Chinese University of Hong Kong, Shatin, New Territories, Hong Kong SAR, People's Republic of China
Fax: (+852)-2603-5057; e-mail: hncwong@cuhk.edu.hk

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Dedicated to Professor Masakatsu Shibasaki on the occasion of his 60th birthday.

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Abstract: 1,4,5,8,9,16-Hexahydroxytetraphenylene (**5**) was synthesized by an iodobenzene diacetate-mediated phenolic oxidation. Enantiopure forms of 1,4,5,8,9,16-hexahydroxytetraphenylenes [(*S*,*R*,*S*)-**5** and (*R*,*S*,*R*)] were successfully synthesized either by using (*S*,*S*)-and (*R*,*R*)-1,8,9,16-tetramethoxytetraphenylenes [(*S*,*S*)-**7** and (*R*,*R*)-**7**] as starting materials or by direct resolution of 1,4,5,8,9,16-hexahydroxytetraphenylene (**5**).

Keywords: demethylation; hypervalent compounds; iodobenzene diacetate; phenolic oxidation; quinone; resolution

Introduction

Tetraphenylene (**1**)[1] is a structurally highly interesting molecule with a ground state D_{2d} geometry and with a distinct saddle-shaped structure[2,3] in which all the benzene rings are orientated above and below the average plane of the molecule (Figure 1).

Our group has been very active in the synthesis of tetraphenylene derivatives.[4] With the unique structural property, it was envisioned that the formation of super-molecules through interconnection of appropriate derivatives of tetraphenylene would lead to many interesting complex structures. For this reason, a project was initiated in our group on the construction of three-dimensional molecular scaffolds using polyhydroxytetraphenylenes (tetraphenyl-enols) as building blocks. In this project, five polyhydroxylated tetraphenylenes, namely, tetraphenylenediol **2**,[5a] tetraphenylenetetraol **3**,[5b] tetraphenylenetetraol **4**,[5c] tetraphenylenehexaol **5** and tetraphenyleneoctaol **6**[5d] were chosen as the target compounds (Figure 2). Herein we report the synthesis of racemic hexahydroxytetraphenylene **5** as well as its enantiopure forms.

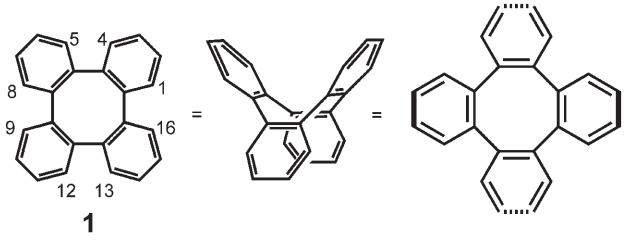


Figure 1. Different representations of tetraphenylene (**1**).

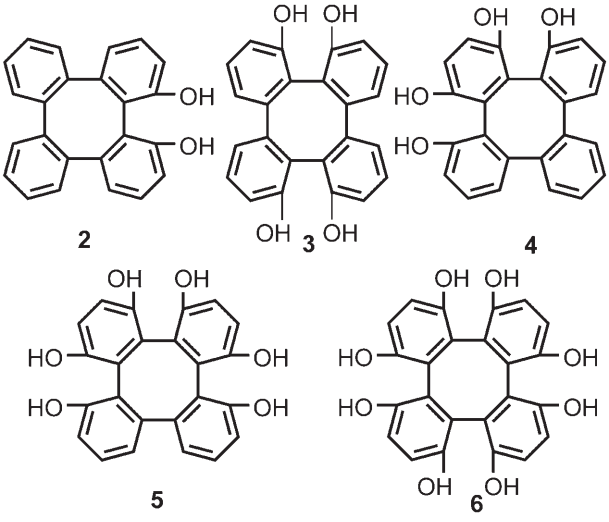
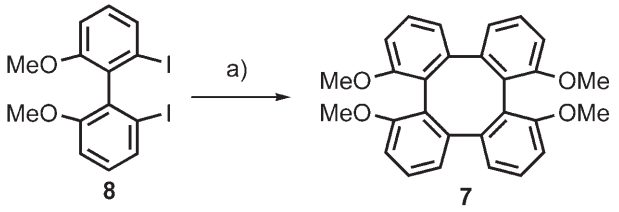
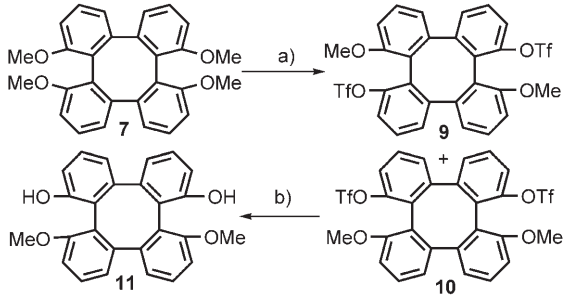


Figure 2. Tetraphenylenols as targeted building blocks for supramolecular scaffolds.



Scheme 1. Synthesis of **7** from **8**. a) i) *n*-BuLi, Et_2O, −78 °C, 2 h; ii) $ZnCl_2$, −50 °C, 2 h; iii) $CuCl_2$, −78 °C, 2 h, 38 %.



Scheme 2. Sythesis of intermediate **11** from **7**. a) i) 2.2 equivs. BBr_3, CH_2Cl_2, 0 °C, 15 min; ii) 2.2 equivs. Tf_2O, pyridine, CH_2Cl_2, 10 h, 31 % for **9**, 30 % for **10**; b) NaOH, dioxane, methanol, 60 °C, 12 h, 97 %.

Results and Discussion

In the synthesis of the racemic **5**, 1,8,9,16-tetramethoxytetraphenylene (**7**) was employed as starting material, which can be prepared from the oxidative coupling of 2,2′-diiodo-6,6′-dimethoxybiphenyl (**8**)[5b] employing Wittig's protocol.[6] In our previous work, tetraphenylene **7** had been prepared in a modest yield of 23 %, and now we improved the yield to 38 % by using a copper-catalyzed coupling of the arylzinic intermediate[7] (Scheme 1).

Partial demethylation of 1,8,9,16-tetramethoxytetraphenylene **7** by BBr_3 and subsequent formation of a triflate utilizing triflic anhydride led to two isolable bis-triflates **9** and **10** (Scheme 2), whose structures were established by X-ray crystallographic studies (Figure 3 and Figure 4). Hydrolysis of bis-triflate **10** furnished the intermediate 1,8-dihydroxy-9,16-dimethoxytetraphenylene **11** (Scheme 2).

With the intermediate **11** in hand, we then tested the oxidation of **11** to bis-quinone **12**. However, most popular oxidizing reagents for oxidizing phenols to *p*-quinones such as Fremy's salt[8] and Salcomine[9] with molecular oxygen, all failed to oxidize **11**. Fortunately, an efficient phenolic oxidation of **11** was achieved by a hypervalent iodine reagent, iodobenzene diacetate[10] in CH_3CN-H_2O. This environmental friendly oxidation of **11** furnished the desirable bis-quinone **12**[11] in a yield of 48 % with amide **13**[11] as a by-product. The formation of **13** is presumably due to acetonitrile incorporation at the *para* position.[12] Regeneration of the benzene rings by reduction of **12** with zinc[13] in acetic acid afforded bis-hydroquinone **14** which was demethylated to form racemic **5** (Scheme 3).

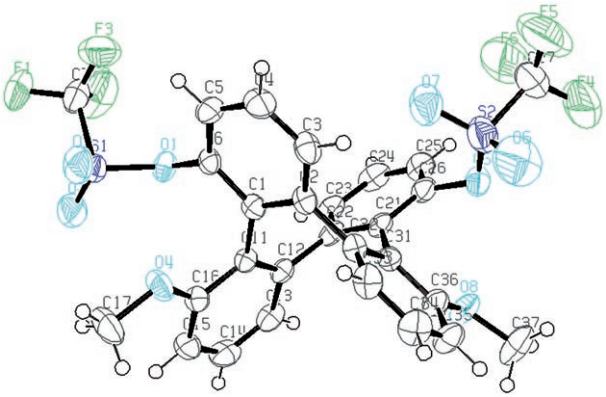


Figure 3. X-ray structure of bis-triflates **9**.

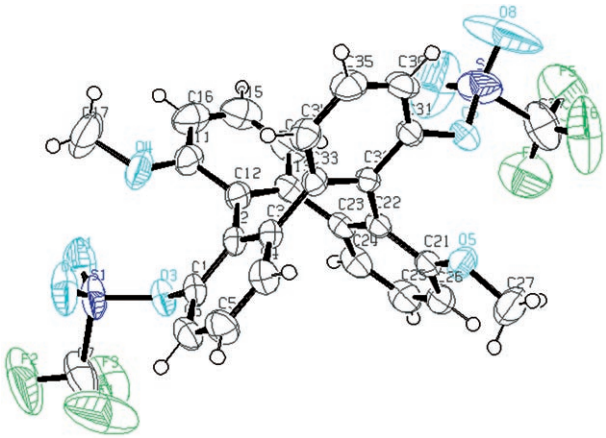
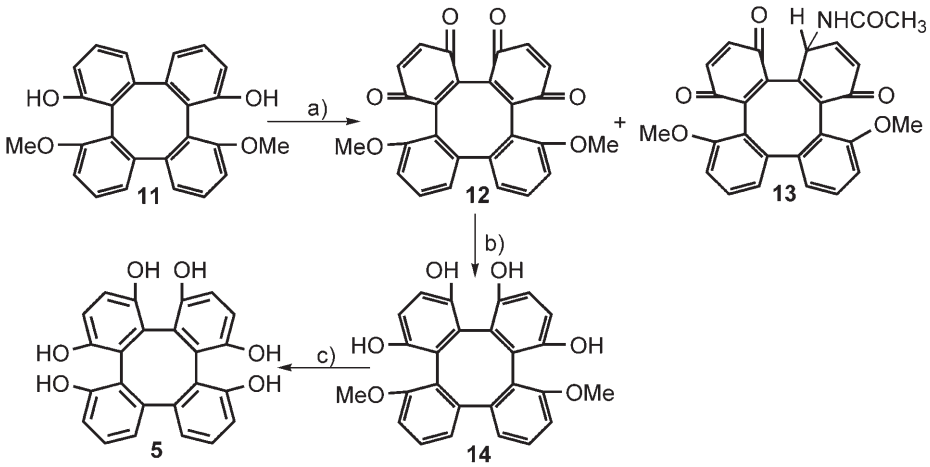


Figure 4. X-ray structure of bis-triflates **10**.

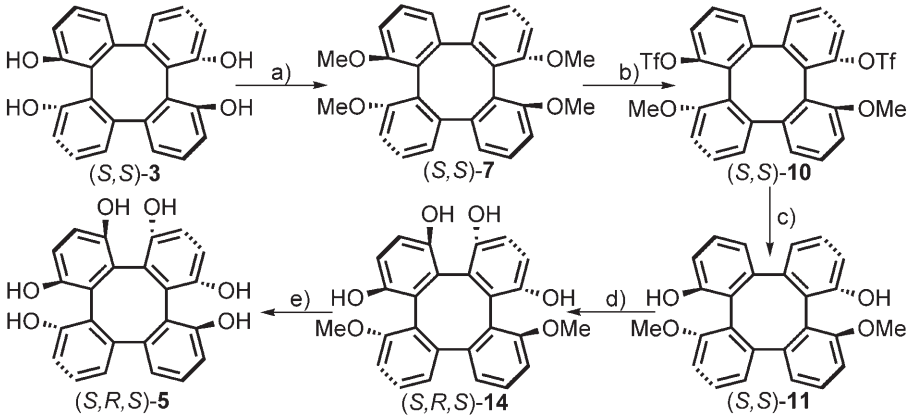
In the synthesis of the enantiopure forms of **5**, (*S*,*S*)- and (*R*,*R*)-tetrahydroxytetraphenylenes [(*S*,*S*)-**3** and (*R*,*R*)-**3**], which could be obtained by resolution of racemic **3**,[5b] were initially protected to give (*S*,*S*)- and (*R*,*R*)-1,8,9,16-tetramethoxytetraphenylenes [(*S*,*S*)-**7** and (*R*,*R*)-**7**]. Following the aforementioned procedure for the synthesis of racemic **5**, (*S*,*S*)-**7** and (*R*,*R*)-**7** were employed as starting materials to realize enantiopure (*S*,*R*,*S*)-and (*R*,*S*,*R*)-1,4,5,8,9,16-hexahydroxytetraphenylenes [(*S*,*R*,*S*)-**7** and (*R*,*S*,*R*)-**7**] [(Scheme 4) and (Scheme 5)].

These two enantiomers of **5** were fully characterized by NMR, MS and CD spectroscopic methods (for CD spectra, see Figure 5).

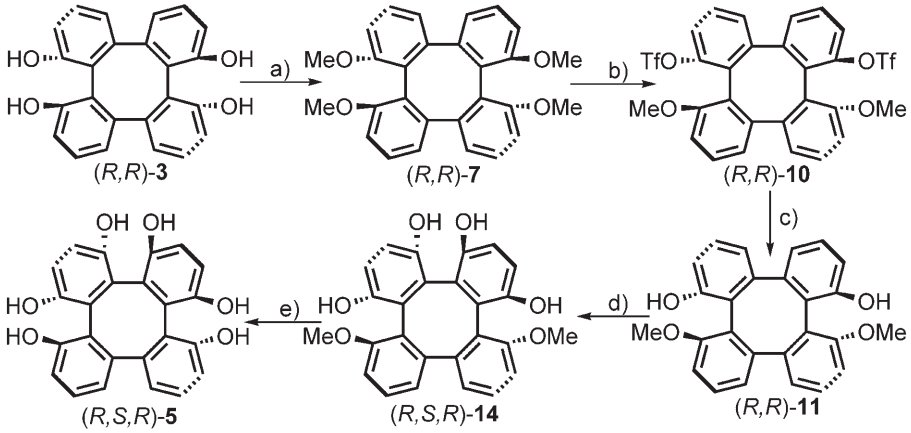
Another way to synthesize enantiopure forms of **5** is by a direct resolution of racemic **9** *via* generation of its two diastereomeric hexakis-(*S*)-camphorsulfonates **15** and **16** (Scheme 6). After hydrolysis, optically pure



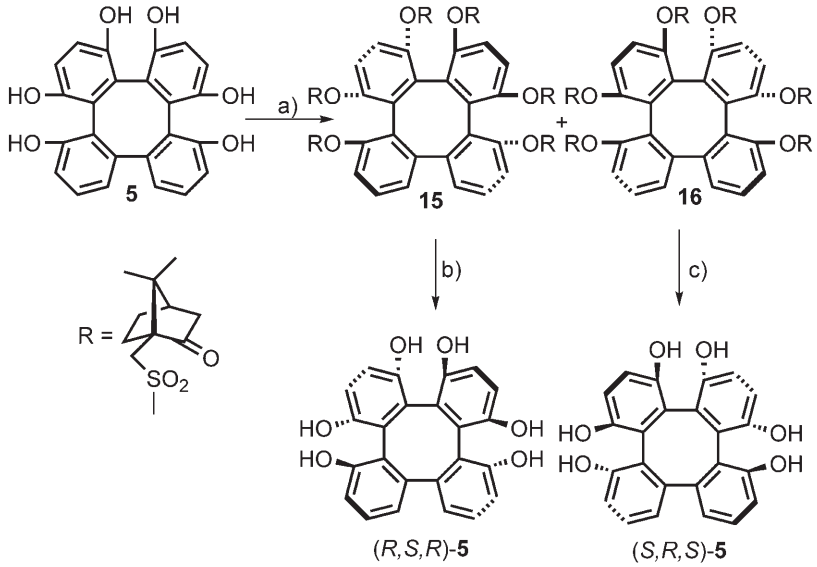
Scheme 3. Synthesis of racemic **5** from **11**. a) $PhI(OAc)_2$, CH_3CN, H_2O, 0 °C, 2 h, 48 % for **12**, 22 % for **13**; b) Zn, AcOH, room temperature, 7 h, 74 %; c) BBr_3, CH_2Cl_2, 0 °C to room temperature, 12 h, 90 %.



Scheme 4. Synthesis of (*S*,*R*,*S*)-**5**. a) CH_3I, K_2CO_3, acetone, reflux, 3 h, 100 %; b) i) 2.2 equivs. BBr_3, CH_2Cl_2, 0 °C, 15 min; ii) 2.2 equivs. Tf_2O, pyridine, CH_2Cl_2, 10 h, 27 %; c) NaOH, dioxane, methanol, 60 °C, 12 h, 98 %; d) i) $PhI(OAc)_2$, CH_3CN, H_2O, 0 °C, 2 h; ii) Zn, AcOH, room temperature, 7 h, 36 %; e) BBr_3, CH_2Cl_2, 0 °C to room temperature, 12 h, 90 %



Scheme 5. Synthesis of (*R*,*S*,*R*)-**5**. a) CH_3I, K_2CO_3, acetone, reflux, 3 h, 100 %; b) i) 2.2 equivs. BBr_3, CH_2Cl_2, 0 °C, 15 min; ii) 2.2 equivs. Tf_2O, pyridine, CH_2Cl_2, 10 h, 27 %; c) NaOH, dioxane, methanol, 60 °C, 12 h, 97 %; d) i) $PhI(OAc)_2$, CH_3CN, H_2O, 0 °C, 2 h; ii) Zn, AcOH, room temperature, 7 h, 34 %; e) BBr_3, CH_2Cl_2, 0 °C to room temperature, 12 h, 92 %.



Scheme 6. Resolution of racemic **5**. a) (*S*)-camphorsulfonyl chloride, THF, Et_3N, 0 °C to room temperature, 36 h, 24 % for **15**, 22 % for **16**; b) KOH, CH_3OH, H_2O, 60 °C, 12 h, 34 % for (*S,R,S*)-**5**, 32 % for (*R,S,R*)-**5**.

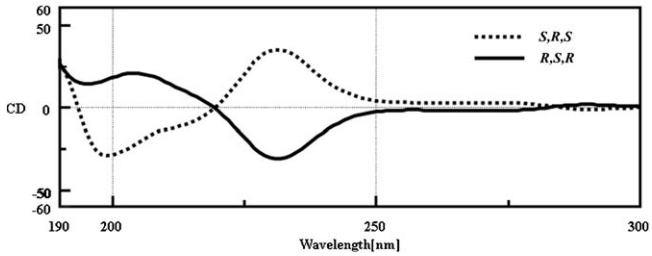


Figure 5. CD spectra of (*S,R,S*)-**5** and (*R,S,R*)-**5**.

(*S,R,S*)-**5** and (*R,S,R*)-**5** were obtained from **15** and **16**, respectively (Scheme 6).

Conclusions

In summary, we report herein an efficient approach for the synthesis of 1,4,5,8,9,16-hexahydroxytetraphenylene (**5**) by an iodobenzene diacetate-mediated phenolic oxidation, as well as the synthesis of its enantiopure (*S,R,S*) and (*R,S,R*) forms. Studies on the applications of the optically pure (*S,R,S*)-**5** or (*R,S,R*)-**5** as three-dimensional building blocks and the potential use of derivatives of these two enantiomers as asymmetric catalysts are in progress in our laboratories.

Experimental Section

General Remarks

All reagents and solvents were reagent grade. Further purification and drying by standard methods were used when necessary. Melting points were measured on a Reichert Microscope apparatus and are reported uncorrected. Optical rotations were measured on a Perkin–Elmer model 241 polarimeter, operating at 589 nm, and at 20 °C. CD spectra were recorded on a JASCO model J-500 A spectropolarimeter. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker DPX-300 spectrometer (300.13 MHz for ^{1}H and 75.45 MHz for ^{13}C). Mass spectra were obtained with an HP 5989B spectrometer and determined at an ionizing voltage of 70 eV unless otherwise stated; Infrared spectra were obtained from KBr pellets on a Perkin–Elmer 1600 Fourier transform spectrometer. Elemental analyses were performed at Shanghai Institute of Organic Chemistry, The Chinese Academy of Sciences, China or at MEDAC Ltd., Department of Chemistry, Brunel University, Uxbridge, United Kingdom. X-ray analyses were obtained using SHELXTL PLUS (PC Version) with a P4 X-ray four circle diffractometer unless otherwise stated.

1,8,9,16-Tetramethoxytetraphenylene (7)

To a suspension of 2,2′-diiodo-6,6′-dimethoxybiphenyl (**8**; 1 g, 2.1 mmol) in Et_2O (60 mL) was added dropwise *n*-BuLi (3.0 mL, 1.6 M in hexane, 4.8 mmol) at −78 °C over 30 min. After stirring for 2 h at −78 °C, a solution of pre-dried $ZnCl_2$ (630 mg, 4.62 mmol) in THF (10 mL) was added dropwise to the mixture at −50 °C over 15 min. The mixture was stirred for another 2 h at −50 °C, and $CuCl_2$ (850 mg, 6.3 mmol) was then added. After further stirring for 2 h at −78 °C, the reaction mixture was allowed to warm to ambient temperature overnight. The resulting solution was quenched with 6 M hydrochloric acid (10 mL). The organic layer was then separated and the aqueous layer was extracted with dichloromethane (3 × 30 mL). The combined organic extracts were washed with saturated sodium bicarbonate (2 × 20 mL), and dried over anhydrous sodium sulfate. Chromatography on silica gel (10 g, dichloromethane-hexanes, 1:2) gave 1,8,9,16-tetramethoxytetraphenylene (**7**) as a white solid; yield: 338 mg (38 %), mp 283–284 °C. ^{1}H NMR

(300.13 MHz, $CDCl_3$): $\delta = 7.19$ (t, 4H, $J = 7.9$ Hz), 6.88 (d, 4H, $J = 7.8$ Hz), 6.78 (d, 4H, $J = 8.1$ Hz), 3.67 (s, 12H); ^{13}C NMR (75.45 MHz, $CDCl_3$): $\delta = 156.6$, 143.3, 127.9, 125.9, 120.9, 110.0, 56.2; EI-MS: *m/z* (relative intensity) = 424 (71), 153 (53), 136 (33), 84 (100), 77 (46); IR: $\nu_{max} = 2927$, 2828, 2349, 1566, 1422, 1254, 1140, 1034, 798, 730 cm^{-1}; HR-MS: $m/z = 424.1671$, calcd. for $C_{28}H_{24}O_4$: 424.1669; anal. calcd for $C_{28}H_{24}O_4$: C 79.22, H 5.70; found: C 78.96, H 5.64.

1,9-Bis(trifluoromethanesulfonyloxy)-8,16-dimethoxytetraphenylene (9) and 1,8-Bis(trifluoromethanesulfonyloxy)-9,16-dimethoxytetraphenylene (10)

To a suspension of 1,8,9,16-tetramethoxytetraphenylene (**7**; 400 mg, 0.94 mmol) in dichloromethane (150 mL) was added a 0.4 M solution of boron tribromide in dichloromethane (5 mL, 2 mmol). The mixture was stirred for 15 min at 0 °C and a clear, brownish red solution was obtained. The reaction mixture was hydrolyzed by careful addition of cold water (10 mL), and the white solid that precipitated was dissolved by the addition of ethyl acetate (20 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 × 50 mL). The combined extracts were washed with saturated sodium bicarbonate solution (2 × 50 mL) and dried over anhydrous sodium sulfate. Chromatography on silica gel (5 g, ethyl acetate-hexanes, 1:2) provided a di-demethylation mixture as a white solid (yield: 323 mg, 87 %) which was used directly in the next step without further characterization.

The mixture mentioned above was dissolved in dry dichloromethane (150 mL) containing pyridine (1 mL, 12.3 mmol), and the resulting solution was cooled to 0 °C in an ice-water bath. To the stirred solution was added dropwise trifluoromethanesulfonic anhydride (1.0 mL, 1.7 g, 5.8 mmol) over a period of 10 min. After stirring at 0 °C for 10 h, the reaction mixture was quenched by slow addition of cold water (5 mL). Removal of organic solvent by evaporation under reduced pressure gave an aqueous brown mixture that was taken up in ethyl acetate (2 × 50 mL). Washing of the ethyl acetate-water mixture with saturated sodium bicarbonate (2 × 50 mL), drying of the organic layer over anhydrous sodium sulfate, and evaporation of the solvent under reduced pressure gave a brownish solid. Chromatography of the crude material on silica gel (10 g, ethyl acetate-hexanes, 1:20) furnished the following two triflates.

The less polar triflate 1,9-bis(trifluoromethanesulfonyloxy)-8,16-dimethoxytetraphenylene (**9**) was obtained as a white solid; yield: 204 mg (33 %), mp 235–237 °C. ^{1}H NMR (300.13 MHz, acetone-d_6): $\delta = 7.48$ (t, 2H, $J = 7.8$ Hz), 7.29–7.36(m, 4H), 7.01 (d, 2H, $J = 8.1$ Hz), 6.86 (d, 2H, $J = 7.5$ Hz), 3.70 (s, 6H); ^{13}C NMR (75.45 MHz, acetone-d_6): $\delta = 156.8$, 147.6, 144.7, 142.9, 130.7, 130.6, 130.1, 129.6, 125.2, 122.9, 121.7, 121.0, 120.4, 116.8, 111.2, 55.8. IR: $\nu_{max} = 2358$, 1581, 1416, 1318, 1251, 1210, 1185, 1045, 942, 860, 757, 599, 509 cm^{-1}; HR-MS: $m/z = 660.0346$, calcd. for $C_{28}H_{18}F_6O_8S_2$: 660.0342; anal. calcd. for $C_{28}H_{18}F_6S_2O_8$: C 50.91, H 2.75; found: C 50.90, H 2.79.

The more polar triflate 1,8-bis(trifluoro-methanesulfonyloxy)-9,16-dimethoxytetraphenylene (**10**) was obtained also as a white solid; yield: 198 mg (32 %), mp 226–227 °C. ^{1}H NMR (300.13 MHz, acetone-d_6): $\delta = 7.45$ (t, 2H, $J = 7.8$ Hz), 7.30–7.35 (m, 4H), 6.94 (d, 2H, $J = 8.1$ Hz), 6.87 (d, 2H, $J = 7.8$ Hz), 3.68 (s, 6H); ^{13}C NMR (75.45 MHz, acetone-d_6): $\delta = 156.9$, 148.2, 144.6, 143.7, 131.6, 130.7, 130.2, 129.5, 125.6, 122.9, 122.9, 121.2, 117.1, 112.9, 111.0, 56.1. IR: $\nu_{max} = 2921$, 2852, 2358, 1732, 1574, 1416, 1224, 1141, 1032, 894, 798, 750, 599, 503 cm^{-1}; HR-MS: $m/z = 660.0348$, calcd. for $C_{28}H_{18}F_6O_8S_2$: 660.0342; anal. calcd for $C_{28}H_{18}F_6S_2O_8$: C 50.91, H 2.75; found: C 50.74, H 2.56.

1,8-Dihydroxy-9,16-dimethoxytetraphenylene (11)

Triflate **10** (198 mg, 0.3 mmol) was dissolved in 1,4-dioxane (80 mL) and methanol (40 mL). To the resulting solution was added 3 M aqueous sodium hydroxide solution (5 mL) at room temperature and the reaction mixture was stirred at 60 °C for 12 h after which it was acidified to pH 1 by the addition of a small amount of concentrated hydrochloric acid. The mixture was extracted with dichloromethane (2 × 100 mL) and the combined extracts were dried over magnesium sulfate, filtered, and concentrated under reduced pressure, 1,8-dihydroxy-9,16-dimethoxytetraphenylene (**11**) was obtained as a white solid; yield: 115.2 mg (97 %), mp 197–198 °C. ^{1}H NMR (300.13 MHz, acetone-d_6): $\delta = 7.40$, (s, 2H), 7.14 (t, 2H, $J = 8.4$ Hz), 7.01 (t, 2H, $J = 7.8$ Hz), 6.76–6.83 (m, 4H), 6.63–6.67 (m, 4H), 3.62 (s, 6H); ^{13}C NMR (75.45 MHz, acetone-d_6): $\delta = 157.7$, 155.0, 145.0, 129.0, 128.6, 126.4, 125.1, 121,6, 120.3, 114.7, 111.0, 56.2. IR: $\nu_{max} = 3400$, 2957, 2350, 1720, 1570, 1457, 1420, 1255, 1022, 932, 790, 722 cm^{-1}; HR-MS: $m/z = 396.1859$, calcd. for $C_{26}H_{20}O_4$: 396.1856; anal. calcd. for $C_{26}H_{20}O_8$: C 78.77, H 5.09; found: C 78.86, H 5.24.

1,4,5,8-Tetrahydroxy-9,16-dimethoxytetraphenylene (14)

To a suspension of dihydroxydimethoxytetraphenylene **11** (50 mg, 0.13 mmol) in acetonitrile-water (2/1, v/v; 30 mL) at 0 °C under nitrogen was added dropwise a solution of $PhI(OAc)_2$ (81 mg, 0.26 mmol) in acetonitrile (20 mL) over 30 min. The resulting solution was stirred at 0 °C under nitrogen for 2 h. The organic solvent was removed under vacuum and the resulting aqueous residue was extracted with ethyl acetate (3 × 20 mL). The combined organic extracts were dried over sodium sulfate and evaporated to dryness. The crude product (presumably the bis-quinone **12**) was immediately used in the subsequent reaction without further purification.

Zinc powder (65 mg, 1 mmol) was added to a stirred solution of the above crude product in AcOH (80 mL), and the mixture was stirred for 7 h at room temperature. Excess zinc powder was removed by gravity filtration, and the filtrate was concentrated to near dryness before water (20 mL) was added. The aqueous mixture was extracted with ethyl acetate (3 × 50 mL). The combined organic extracts were washed with brine (10 mL), dried over sodium sulfate and evaporated. Chromatography on silica gel (5 g, ethyl acetate-hexanes 2:1) gave 1,4,5,8-tetrahydroxy-9,16-dimethoxytetraphenylene (**14**) as an air and moisture sensitive white solid; yield: 25 mg (32 %), mp > 300 °C. ^{1}H NMR (300.13 MHz, acetone-d_6): $\delta = 7.15$ (t, 2H, $J = 7.8$ Hz), 6.79 (2d, 4H, $J = 7.8$, 7.5 Hz), 6.57 (dd, 4H, $J = 8.7$, 6.0 Hz), 3.62 (s, 6H); ^{13}C NMR (75.45 MHz, CD_3OD): $\delta = 157.9$, 148.4, 148.0, 145.1, 129.2, 127.4, 126.7, 122.3, 116.3, 111.9, 57.0; DEPT (135) 128.9, 122.0, 116.0, 111.6, 56.7. IR: $\nu_{max} = 3415$,

2912, 2837, 2350, 1690, 1562, 1255, 1015, 790, 745, 692 cm^{-1}; HR-MS: $m/z = 428.1253$, calcd. for $C_{26}H_{20}O_6$: 428.1254.

1,4,5,8,9,16-Hexahydroxytetraphenylene (5)

To a suspension of tetrahydroxydimethoxytetraphenylene **13** (16 mg, 0.04 mmol) in dichloromethane (20 mL) was added 0.4 M solution of boron tribromide in dichloromethane (1 mL, 0.4 mmol). The mixture was stirred overnight at room temperature and a clear, brownish red solution was obtained. The reaction mixture was hydrolyzed by careful addition of cold water (5 mL), and the white solid precipitated was dissolved by addition of ethyl acetate (10 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2×20 mL). The combined extracts were washed with saturated sodium bicarbonate solution (2×20 mL) and dried over anhydrous sodium sulfate. Chromatography on silica gel (2 g, ethyl acetate-hexanes, 4:1) gave 1,4,5,8,9,16-hexahydroxytetraphenylene (**5**) as an air and moisture sensitive white solid (samples of this compound should be kept in evacuated sealed tubes); yield: 13.4 mg (90%), mp >300 °C. ^{1}H NMR (300.13 MHz, acetone-d_6): $\delta = 7.05$ (t, 2H, $J = 7.8$ Hz), 6.59–6.73 (m, 8H); ^{13}C NMR (75.45 MHz, acetone-d_6): $\delta = 154.6$, 148.4, 148.0, 144.9, 128.8, 125.9, 125.4, 124.4, 120.7, 117.0, 116.9, 115.2; IR: $\nu_{max} = 3407$, 2920, 2350, 1637, 1442, 1262, 820, 730, 535 cm^{-1}; HR-MS: $m/z = 400.0938$, calcd. for $C_{24}H_{16}O_6$: 400.0941.

(*S,S*)- and (*R,R*)-1,8,9,16-Tetramethoxytetraphenylenes [(*S,S*)-7 and (*R,R*)-7]

To a solution of individual (*S,S*)- or (*R,R*)- tetrahydroxytetraphenylene (**3**; 390 mg, 1.03 mmol) in acetone (100 mL) was added potassium carbonate (1.0 g, 7.24 mmol) in one portion and iodomethane (0.5 mL, 8.04 mmol) dropwise. The reaction mixture was refluxed for 3 h, cooled to room temperature, filtered through a Celite pad, and the solid was washed with diethyl ether. The filtrate was concentrated under reduced pressure to give (*S,S*)-**7** or (*R,R*)- **7** each as a white solid; yields: 436 mg, 100% for both (*S,S*)- **7** and (*R,R*)-**7**), mp 281–282 °C for (*S,S*)-**7** and 282–283 °C for (*R,R*)-**7**. ^{1}H NMR of each sample (300.13 MHz, $CDCl_3$): $\delta = 7.17$ (t, 4H, $J = 7.9$ Hz), 6.87 (d, 4H, $J = 7.8$ Hz), 6.76 (d, 4H, $J = 8.1$ Hz), 3.66 (s, 12H); ^{13}C NMR (75.45 MHz, $CDCl_3$): $\delta = 156.0$, 142.7, 127.4, 125.5, 120.3, 109, 55.7; IR: $\nu_{max} =$ 2920, 2822, 2343, 1560, 1416, 1250, 1137, 1030, 792, 726 cm^{-1}; HR-MS: $m/z = 424.1670$ for (*S,S*)-**7** and 424.1668 for (*R,R*)-**7**, calcd. for $C_{28}H_{24}O_4$ 424.1669. These two optically pure antipodes **7** had the identical spectral data as depicted above but exhibited the following optical rotations: (*S,S*)-**7** $[\alpha]_D^{20}$: −45.2 ($CHCl_3$, *c* 0.47); (*R,R*)-**7** $[\alpha]_D^{20}$: +44.8 ($CHCl_3$, *c* 0.50)

(*S,S*)- and (*R,R*)- 1,8-Bis(trifluoromethane-sulfonyloxy)-9,16-dimethoxytetraphenylenes [(*S,S*)-10 and (*R,R*)-10]

To a suspension of (*S,S*)- or (*R,R*)-1,8,9,16-tetramethoxytetraphenylene (**7**) (400 mg, 0.94 mmol) in dichloromethane (150 mL) was added a 0.4 M solution of boron tribromide in dichloromethane (5 mL, 2 mmol). The mixture was stirred for 15 min at 0 °C and a clear, brownish red solution was obtained. The reaction mixture was hydrolyzed by careful addition of cold water (10 mL), and the white solid that precipitated was dissolved by the addition of ethyl acetate (20 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2×50 mL). The combined extracts were washed with saturated sodium bicarbonate solution (2×50 mL) and dried over anhydrous sodium sulfate. Chromatography on silica gel (5 g, ethyl acetate-hexanes, 1:2) provided a di-demethylation mixture as a white solid (yield: 324 mg, 87%) which was used directly in the next step without further purification.

The mixture mentioned above was dissolved in dry dichloromethane (150 mL) containing pyridine (1 mL, 12.3 mmol) and the resulting solution was cooled to 0 °C in an ice-water bath. To the stirred solution was added dropwise trifluoromethanesulfonic anhydride (1.0 mL, 1.7 g, 5.8 mmol) over a period of 10 min. After stirring at 0 °C for 10 h, the reaction mixture was quenched by slow addition of cold water (5 mL). Removal of organic solvent by evaporation under reduced pressure gave an aqueous brown mixture, which was taken up in ethyl acetate (2×50 mL). Washing of the ethyl acetate-water mixture with saturated sodium bicarbonate (2×50 mL), drying of the organic layer over anhydrous sodium sulfate, and evaporation of the solvent under reduced pressure gave a brownish solid. Chromatography of the crude material on silica gel (10 g, ethyl acetate-hexanes, 1:20) gave (*S,S*)- or (*R,R*)-1,8-bis-(trifluoromethanesulfonyloxy)-9,16-dimethoxy-tetraphenylene (**10**) as a white solid; yield: 186 mg (30%) for (*S,S*)-**10** and 192 mg (31%) for (*R,R*)-**10**], mp 225–226 °C for (*S,S*)-**10** and 227–228 °C for (*R,R*)-**10**. ^{1}H NMR of each sample (300.13 MHz, acetone-d_6): $\delta = 7.46$ (t, 2H, $J = 7.8$ Hz), 7.32–7.37 (m, 4H), 6.96 (d, 2H, $J = 8.1$ Hz), 6.89 (d, 2H, $J = 7.8$ Hz), 3.71 (s, 6H); ^{13}C NMR (75.45 MHz, acetone-d_6): $\delta = 157.1$, 148.6, 144.9, 144.1, 131.9, 131.1, 130.8, 129.9, 125.9, 123.2, 123.0, 121.9, 117.6, 121.4, 111.6, 56.7. IR: $\nu_{max} = 2920$, 2846, 2352, 1730, 1573, 1410, 1221, 1140, 1035, 899, 804, 757, 602, 505 cm^{-1}; HR-MS: $m/z = 660.0346$ for (*S,S*)-**10** and 660.0343 for (*R,R*)-**10**, calcd. for $C_{28}H_{18}F_6O_8S_2$: 660.0342. These two optically pure **10** antipodes had the identical spectral data as depicted above but exhibited the following optical rotations: (*S,S*)-**10** $[\alpha]_D^{20}$: +72.3 ($CHCl_3$, *c* 0.46); (*R,R*)-**10** $[\alpha]_D^{20}$: −69.6 ($CHCl_3$, *c* 0.42).

(*S,S*)- and (*R,R*)-1,8-Dihydroxydimethoxytetraphenylenes [(*S,S*)-11 and (*R,R*)-11]

The triflate (*S,S*)- or (*R,R*)-**10** (198 mg, 0.3 mmol) was dissolved in 1,4-dioxane (80 mL) and methanol (40 mL). To the resulting solution was added 3 M aqueous sodium hydroxide solution (5 mL) at room temperature and the reaction mixture was stirred at 60 °C for 12 h after which it was acidified to pH 1 by the addition of a small amount of concentrated hydrochloric acid. The mixture was extracted with dichloromethane (2×100 mL) and the combined extracts were dried over magnesium sulfate, filtered, and concentrated under reduced pressure to afford (*S,S*)- or (*R,R*)-**11** as a white solid; yield: 115 mg (97%) for (*S,S*)-**11** and 114 mg (95%) for (*R,R*)-**11**, mp 196–197 °C for (*S,S*)-**11** and 198–199 °C for (*R,R*)-**11**. ^{1}H NMR of each sample (300.13 MHz, acetone-d_6): $\delta = 7.42$, (s, 2H), 7.16 (t, 2H, $J = 8.4$ Hz), 7.04 (t, 2H, $J =$ 7.8 Hz), 6.78–6.85 (m, 4H), 6.65–6.69 (m, 4H), 3.65 (s, 6H);

^{13}C NMR (75.45 MHz, acetone-d_6): $\delta = 158.2$, 155.5, 145.6, 129.7, 129.2, 126.9, 125.7, 122.2, 120.8, 115.3, 111.5, 56.7; IR: $\nu_{max} = 3404$, 2959, 2346, 1728, 1576, 1460, 1426, 1262, 1029, 937, 794, 726 cm^{-1}; HRMS: $m/z = 396.1858$ for (*S*,*S*)-**11** and 396.1854 for (*R*,*R*)-**11**, calcd. for $C_{26}H_{20}O_4$: 396.1856. These two optically pure antipodes had the identical spectral data as depicted above but exhibited the following optical rotations: (*S*,*S*)-**11** $[\alpha]_D^{20}$: +58.4 (MeOH, *c* 0.10); (*R*,*R*)-**11** $[\alpha]_D^{20}$: −54.0 (MeOH, *c* 0.10).

(*S*,*R*,*S*)- and (*R*,*S*,*R*)-1,4,5,8-Tetrahydroxy-9,16-dimethoxytetraphenylenes [(*S*,*R*,*S*)-14 and (*R*,*S*,*R*)-14]

To a suspension of (*S*,*S*)- or (*R*,*R*)-1,8-dihydroxy-9,16-dimethoxytetraphenylene (**11**; 50 mg, 0.13 mmol) in acetonitrile-water (2/1, v/v; 30 mL) at 0 °C under nitrogen was added dropwise a solution of $PhI(OAc)_2$ (81 mg, 0.26 mmol) in acetonitrile (20 mL) over 30 min. The resulting solution was stirred at 0 °C under nitrogen for 2 h. The organic solvent was removed under vacuum and the resulting aqueous residue was extracted with ethyl acetate (3 × 20 mL). The combined organic extracts were dried over sodium sulfate and evaporated to dryness. Because the crude product (presumably the bis-quinone) was found to be unstable at room temperature, it was immediately used in the subsequent reaction without further purification.

In each experiment, zinc powder (65 mg, 1 mmol) was added to a stirred solution of the above crude product from (*S*,*S*)-**11** or (*R*,*R*)-**11** in AcOH (80 mL), and the mixture was stirred for 7 h at room temperature. Excess of zinc powder was removed by gravity filtration, and the filtrate was concentrated to near dryness before water (20 mL) was added. The aqueous mixture was extracted with ethyl acetate (3 × 50 mL). The combined organic extracts were washed with brine (10 mL), dried over sodium sulfate and evaporated. Chromatography on silica gel (5 g, ethyl acetate-hexanes 2:1) gave (*S*,*R*,*S*)- or (*R*,*S*,*R*)-1,4,5,8-tetrahydroxy-9,16-dimethoxy-tetraphenylene (**14**) each as an air- and moisture-sensitive white solid; yields: 23 mg (29 %) for (*S*,*R*,*S*)-**14** and 26 mg (33 %) for (*R*,*S*,*R*)-**14**), mp > 300 °C for both samples. ^{1}H NMR of each sample (300.13 MHz, acetone-d_6): $\delta = 7.12$ (t, 2H, $J = 7.8$ Hz), 6.76 (2d, 4H, $J = 7.8$, 7.5 Hz), 6.54 (dd, 4H, $J = 8.7$, 6.0 Hz), 3.58 (s, 6H); ^{13}C NMR (75.45 MHz, CD_3OD): $\delta = 157.0$, 147.7, 147.3, 144.4, 128.4, 126.8, 126.0, 121.5, 115.7, 111.2, 56.3; DEPT (135) 128.7, 122.0, 115.8, 111.3, 56.0; IR: $\nu_{max} = 3410$, 2911, 2834, 2345, 1689, 1554, 1250, 1012, 789, 742, 690 cm^{-1}; HR-MS: $m/z = 428.1250$ for (*S*,*R*,*S*)-**14** and 428.1248 for (*R*,*S*,*R*)-**14**, calcd. for $C_{26}H_{20}O_6$: 428.1254. These two optically pure antipodes had the identical data as depicted above but exhibited the following optical rotations: (*S*,*R*,*S*)-**14** $[\alpha]_D^{20}$: −42.5 (MeOH, *c* 0.48); (*R*,*S*,*R*)-**14** $[\alpha]_D^{20}$: +38.7(MeOH, *c* 0.50).

(*S*,*R*,*S*)- and (*R*,*S*,*R*)-1,4,5,8,9,16-Hexahydroxytetraphenylenes [(*S*,*R*,*S*)-5 and (*R*,*S*,*R*)-5]

To a suspension of (*S*,*R*,*S*)- or (*R*,*S*,*R*)-1,4,5,8-tetrahydroxy-9,16-dimethoxytetraphenylene (**14**; 16 mg, 0.04 mmol) in dichloromethane (20 mL) was added 0.4 M solution of boron tribromide in dichloromethane (1 mL, 0.4 mmol). The mixture was stirred overnight at room temperature and a clear, brownish red solution was obtained. The reaction mixture was hydrolyzed by careful addition of cold water (5 mL), and the white solid precipitated was dissolved by addition of ethyl acetate (10 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 × 20 mL). The combined extracts were washed with saturated sodium bicarbonate solution (2 × 20 mL) and dried over anhydrous sodium sulfate. Chromatography on silica gel (2 g, ethyl acetate-hexanes, 4:1) gave (*S*,*R*,*S*)- or (*R*,*S*,*R*)-1,4,5,8,9,16-hexahydroxytetraphenylene (**5**) each as an air- and moisture-sensitive white solid (samples of these compounds had to be kept in evacuated sealed tubes); yield: 12.7 mg (85 %) for (*S*,*R*,*S*)-**5** and 13.1 mg (88 %) for (*R*,*S*,*R*)-**5**, mp > 300 °C for both samples. ^{1}H NMR of each sample (300.13 MHz, acetone-d_6): $\delta = 7.01$ (t, 2H, $J = 7.8$ Hz), 6.55–6.69 (m, 8H); ^{13}C NMR (75.45 MHz, acetone-d_6): $\delta = 154.0$, 147.8, 147.4, 144.3, 128.2, 125.3, 124.9, 124.0, 120.3, 116.6, 116.3, 114.8; IR: $\nu_{max} = 3400$, 2925, 2344, 1634, 1430, 1250, 813, 726, 530 cm^{-1}; HR-MS: $m/z = 400.0940$ for (*S*,*R*,*S*)-**5** and 400.0935 for (*R*,*S*,*R*)-**5**, calcd. for $C_{24}H_{16}O_6$ 400.0941. These two optically pure antipodes had virtually identical spectral data as depicted above but exhibited the following optical rotations: (*S*,*R*,*S*)-**5** $[\alpha]_D^{20}$: −20.3 (MeOH, *c* 0.48); (*R*,*S*,*R*)-**5** $[\alpha]_D^{20}$: +23.5 (MeOH, *c* 0.48).

Resolution of 1,4,5,8,9,16-Hexahydroxytetraphenylene (5)

To a solution of 1,4,5,8,9,16-hexahydroxy-tetraphenylene (**5**; 50 mg, 0.12 mmol) in dry dichloromethane (50 mL) and triethylamine (0.1 mL, 0.7 mmol) was added (1*S*)-camphor-10-sulfonyl chloride (0.47 g, 1.68 mmol). The mixture was stirred at room temperature until TLC indicated completion of reaction (about 40 h). Water (10 mL) was added and the mixture was extracted with dichloromethane (3 × 20 mL). The combined extracts were washed with dilute hydrochloric acid (2 × 20 mL), saturated sodium bicarbonate (2 × 20 mL), and dried over anhydrous sodium sulfate. Chromatography on silica gel (5 g, ethyl acetate-hexanes, 1.5:1) gave two diastereomers.

The less polar fraction provided hexakis-(*S*)-camphorsulfonate **15** as a white solid; yield: 50 mg (24 %), mp 158–160 °C. ^{1}H NMR(300.13 MHz, $CDCl_3$): $\delta = 7.68$ (q, 2H), 7.59 (d, 2H, $J = 9.0$ Hz), 7.34–7.44 (m, 6H), 3.68 (q, 4H, $J = 15$, 14.9 Hz), 3.40 (d, 2H, $J = 15$ Hz), 3.24 (d, 2H, $J = 15$ Hz), 3.09 (d, 2H, $J = 15$ Hz), 2.80 (d, 2H, $J = 15$ Hz), 2.28–2.33 (m, 10H), 1.86–2.11 (m, 24H), 1.40–1.59 (m, 12H), 0.76–1.10 (m, 36H); ^{13}C NMR (75.45 MHz, $CDCl_3$): $\delta = 218.9$, 218.6, 218.5, 147.0, 145.0, 143.7, 142.7, 182.3, 129.8, 129.7, 128.2, 125.0, 123.8, 121.5, 118.6, 57.9, 57.8, 50.0, 49.5, 48.4,48.3, 48.2, 42.9, 42.7, 42.6, 42.4, 42.2, 27.0, 26.9, 26.7, 24.8, 24.4, 19.6, 19.5; ESI-MS: $m/z = 1686$ (M^+); IR: $\nu_{max} =$ 3430, 2965, 2357, 2327, 1742, 1645, 1480, 1450, 1225, 1165, 1112, 1045, 872, 790, 752, 557 cm^{-1}; anal. calcd for $C_{94}H_{116}O_{26}S_6$: C 59.84, H 5.98; found: C 60.11, H 5.82; $[\alpha]_D^{20}$: +10.2 ($CHCl_3$, *c* 0.50).

The more polar fraction from column chromatography on solvent removal afforded hexakis-(*S*)-camphorsulfonate **16** also as a white solid; yield: 46 mg (22 %), mp 170–172 °C. ^{1}H NMR (300.13 MHz, $CDCl_3$): $\delta = 7.67$ (d, 2H, $J = 9.3$ Hz), 7.56 (d, 2H, $J = 8.4$ Hz), 7.48 (d, 2H, $J = 9.0$ Hz), 7.36 (t, 2H, $J = 8.1$ Hz,), 7.11 (d, 2H, $J = 7.8$ Hz), 3.71 (d, 2H, $J = 15$ Hz),

3.60 (t, 4H, $J=14.1$ Hz), 3.38 (d, 2H, $J=15$ Hz), 3.18 (d, 2H, $J=15$ Hz), 2.86 (d, 2H, $J=15$ Hz), 2.25–2.30 (m, 12H), 1.85–2.07 (m, 24H), 1.00–1.59 (m, 24H), 0.76–0.92 (m, 36H); ^{13}C NMR (75.45 MHz, $CDCl_3$): $\delta=213.8$, 213.5, 146.7, 145.5, 143.2, 142.8, 131.7, 129.7, 129.4, 127.5, 125.6, 123.3, 120.6, 119.0, 58.0, 57.8, 49.7, 49.1, 48.4, 48.0, 43.2, 42.7, 42.4, 29.6, 29.3, 28.9, 27.0, 26.9, 26.7, 25.7, 25.0, 24.7, 19.8, 19.6, 19.5; ESI-MS: $m/z=1686$ (M^+); IR: $\nu_{max}=3430$, 2965, 2912, 2350, 2327, 1742, 1637, 1540, 1360, 1262, 1217, 1157, 1120, 1045, 830, 790, 745, 557 cm^{-1}; anal. calcd. for $C_{94}H_{116}O_{26}S_6$: C 59.84, H 5.98; found: C 60.02, H 6.13; $[\alpha]_D^{20}$: +26.0 ($CHCl_3$, *c* 0.37).

To a suspension of the hexakis-(1*S*)-camphor-10-sulfonate **15** or **16** (40 mg, 0.02 mmol) in methanol (20 mL) was added an aqueous solution of 2M sodium hydroxide (1 mL). The resulting mixture was warmed to 60 °C with stirring until a clear yellow solution was obtained. The progress of hydrolysis was monitored by TLC and complete reaction required about 12 h. After the solution was cooled to room temperature, it was acidified with 2M hydrochloric acid (5 mL), and methanol was evaporated under reduced pressure. The aqueous residue was extracted with ethyl acetate (3×20 mL) and the combined extract was washed successively with saturated sodium bicarbonate (2×20 mL) and saturated brine solution (2×20 mL). The organic solution was dried with anhydrous sodium sulfate, filtered and evaporated to give the individually optically pure (*S*,*R*,*S*)- or (*R*,*S*,*R*)-1,4,5,8,9,16-hexahydroxytetraphenylene (**5**) as an air- and moisture-sensitive white solid. (*S*,*R*,*S*)-**5**: yield: 34% from **15**, $[\alpha]_D^{20}$: +26.4 (MeOH, *c* 0.12). (*R*,*S*,*R*)-**5**: yield: 32% from **15**, $[\alpha]_D^{20}$: +26.4 (MeOH, *c* 0.12). By comparing with the specific rotation values of the two enantiomeric **5** obtained from chiral non-racemic starting materials, (*S*,*S*)- and (*R*,*R*)-**7**, hexakis-(*S*)-camphorsulfonate **15** was assigned the (*S*,*R*,*S*) configuration, and hexakis-(*S*)-camphorsulfonate **16** was assigned the (*S*,*R*,*S*) configuration.

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[11] Both of the compounds **12** and **13** turned out to be relatively unstable and decomposed with relative ease at room temperature. However, quick sample handling allowed the measurements of HR-MS and ^{13}C NMR of compound **12**. HR-MS: $m/z=424.1254$, calcd. for $C_{26}H_{16}O_6$: 424.1248; the two carbonyl carbon peaks appeared at $\delta=184.5$ and 184.0. As for compound **13**, it showed in MS a molecular ion peak ($m/z=467$) and in ^{13}C NMR carbonyl peaks at $\delta=184.8$, 183.9 and 182.8.
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