The Preparation of Rigid Linear Di- (and Tri-)catechol Derivatives

Markus Albrecht,* Matthias Schneider

Institut für Organische Chemie, Universität Karlsruhe, Richard-Willstätter-Allee, D-76131 Karlsruhe, Germany
Fax +49(721)698529; E-mail: albrecht@ochhades.chemie.uni-karlsruhe.de
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Abstract: The aryl-bridged rigid rod-like di- and tricatechol ligands **1**–**5** were prepared by aryl–aryl coupling reactions. Hereby either Suzuki coupling strategies [starting with 2,3-dimethoxyphenylboronic acid (**6**) as an important building block] or oxidative coupling with methyltributylammonium permanganate were used to obtain the desired compounds.

Key words: catechol, chelating ligands, Suzuki coupling, oxidative coupling, ether cleavage

During the last 15 years the chemistry of double- and triple-stranded helicates has become an important field of supramolecular research.[1] Many different ligand systems were tested for their ability to form linear oligonuclear coordination compounds in metal-directed self-assembly processes. However, most of the ligands possess either flexible spacers which connect the ligand moieties or the helicity of the oligonuclear complex already is embodied in a rigid ligand.[2] There are few examples described, where rigid linear ligands were used in the formation of helicates.[3]

Recently we communicated the synthesis of the rigid *p*-phenylene-bridged dicatechol ligand **2** which forms a triple-stranded helicate with titanium(IV) ions in the presence of an appropriate base.[4,5] Herein we describe the synthetic details for the preparation of **2** as well as of the derivatives **1** and **3**–**5**. In the compounds **1**–**3** the size of the rigid system is systematically varied. The dicatechol **1** possesses a length of approximately 9.2 Å.[6] The *p*-phenylene-bridged compound **2** is 13.5 Å and the 4,4'-substituted 1,1'-biphenylene derivative **3** is 17.8 Å long (Figure 1). In 1,1':4',1"-terphenyl-2,2',2",3,3',3"-hexol (**4**) three catechol units are linearly connected. The compounds **1**–**4** are all synthesized by Suzuki-coupling strategies, while the ligand **5**, which bears two additional methyl groups, was prepared by symmetric oxidative coupling of two aromatic moieties.

The dicatechol ligands **1**–**3** were prepared by Suzuki coupling[7] using the boronic acid derivative **6**, which was prepared according to a procedure described by Weiss et al.[8] Refluxing a mixture of **6**, 2,3-dimethoxybromobenzene (**7**) (prepared from veratrole as described earlier),[9] tetrakis(triphenylphosphane)palladium(0) (0.033 equiv) and sodium carbonate in toluene leads to the formation of 2,2',3,3'-tetramethoxy-1,1'-biphenyl (**8**). After chromatographic workup (silica gel, CH_2Cl_2), compound **8** is obtained in 61% yield. The methyl ethers of **8** are cleaved by reaction with BBr_3 and the ligand 1,1'-biphenyl-2,2',3,3'-tetrol (**1**) is obtained in quantitative yield as a yellow, slightly hygroscopic solid (Scheme 1).

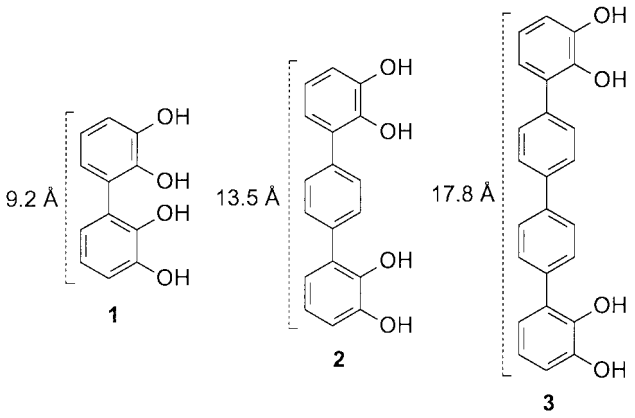
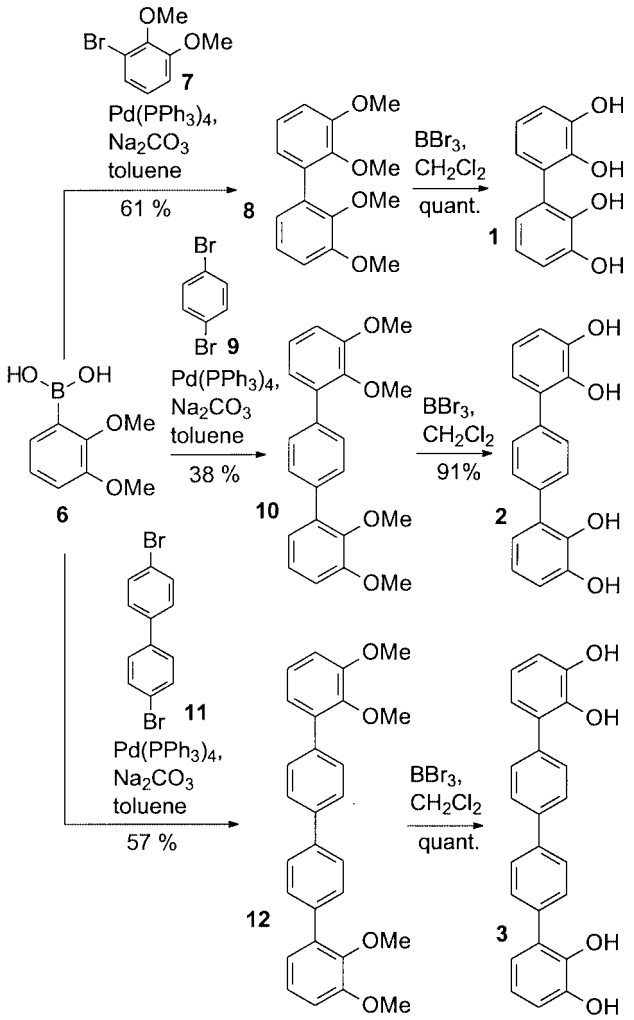


Figure 1 Structures of catechol ligands **1**–**3**

The introduction of a *p*-phenylene spacer is achieved by Suzuki coupling of the boronic acid **6** with 1,4-dibromobenzene (**9**) [$Pd(PPh_3)_4$, Na_2CO_3]. The ligand precursor **10** is obtained in 38% yield and by reaction with BBr_3 in 91% is transformed into 1,1':4',1"-terphenyl-2,2",3,3"-tetrol (**2**).[4] 4,4'-Dibromo-1,1'-biphenyl (**11**) is coupled with two equivalents of **6** to obtain the linear derivative **12** in 57% yield. Reaction of **12** with BBr_3 leads to 1,1':4',1":4",1'"-quaterphenyl-2,2"',3,3'"-tetrol (**3**) in quantitative yield.

The tricatechol derivative **4** is obtained by reaction of boronic acid **6** with 1,4-dibromo-2,3-dimethoxybenzene (**13**) (prepared from veratrole)[9] in the presence of $Pd(PPh_3)_4$ and sodium carbonate (Scheme 2). The double Suzuki coupling yields **14** in 28%. The low yield of coupling product **14** might be due to the close proximity of the two coupling positions which are located at the same aromatic nucleus. Similar yields were observed for the preparation of the analogous **10**, while in the preparation of the larger compound **12** a better yield of 57% is achieved. However, much better yields were described in the literature for Suzuki coupling reaction in related systems.[5] The ligand precursor **14** is deprotected quantitatively by reaction with BBr_3 to afford 1,1':4',1"-terphenyl-2,2',2",3,3',3"-hexol (**4**).

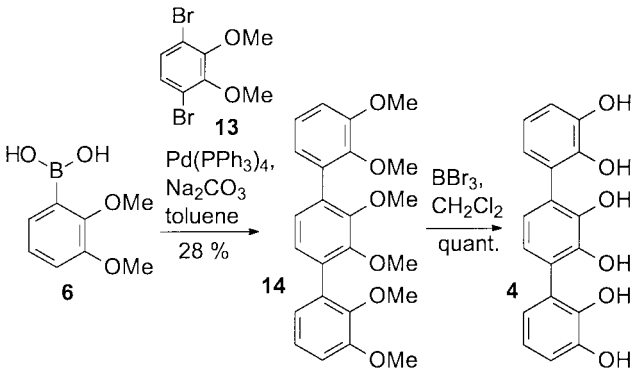
As an alternative for the preparation of tetrahydroxybiphenyl derivatives, an oxidative coupling reaction can be applied. Hereby 2-methoxy-4-methylphenol (**15**) is oxidatively coupled, using methyltributylammonium permanganate (MTBAP)[10] as the oxidizing reagent. The



Preparation of the dicatechol derivatives **1**–**3** by Suzuki coupling

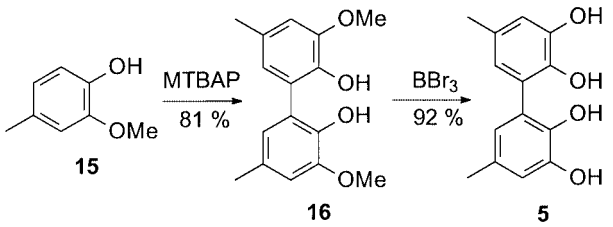
Scheme 1

obtained ligand precursor **16** is used without purification and 5,5'-dimethyl-1,1'-biphenyl-2,2',3,3'-tetrol (**5**) is obtained in 92% yield after ether cleavage with BBr_3 (Scheme 3).



Preparation of the tricatechol derivative **4** by Suzuki coupling

Scheme 2



Oxidative approach to the dicatechol derivative **5** (MTBAP = methyltributylammonium permanganate)

Scheme 3

The dicatechol derivatives **1** and **5** possess a structural moiety which also is found in the natural occurring mastigophorenes A and B (Figure 2). However, it is not known, if the binding of the mastigophorenes to metal ions might be important for their biological activity.[11]

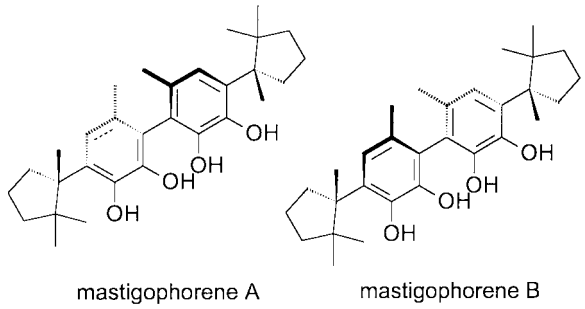


Figure 2

In summary we have presented the synthesis of four rigid rod-like dicatechol ligands **1**–**3** and **5** and of the linear tricatechol derivative **4**. In the key step of the reaction sequences Suzuki coupling procedures were used to obtain the linear di-, tri,- or tetraaryl systems or as an alternative two building blocks were coupled oxidatively by use of MTBAP. The reaction sequences which lead to the desired oligocatechol ligands are short and allow the preparation of large amounts of the derivatives. The behavior of **1**–**5** in metal-directed self-assembly processes is currently investigated in our laboratories.

^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker DRX 500 spectrometer using DEPT techniques for the assignment of the multiplicity of carbon atoms. FT-IR spectra were recorded by diffuse reflection (KBr) on a Bruker IFS spectrometer. UV-vis spectra were recorded on a Perkin Elmer Lambda 2 spectrometer. Mass spectra (EI, 70 eV) were taken on a Finnigan MAT 90 mass spectrometer. Elemental analyses were obtained with a Heraeus CHN-O-Rapid analyzer. Solvents were purified by standard methods. Melting points: Büchi 535 (uncorrected). Air sensitive compounds were prepared and handled under Ar using Schlenk techniques. 2,3-Dimethoxyphenylboronic acid (**6**),[8] 3-bromoveratrole (**7**),[9] and 3,6-dibromoveratrole (**13**)[9] were prepared by published procedures.

2,2',3,3'-Tetramethoxy-1,1'-biphenyl (8)
3-Bromoveratrole (**7**;[9] 650 mg, 3.0 mmol) and $Pd(PPh_3)_4$ (120 mg, 0.01 mmol) were dissolved in toluene (20 mL) and successively 2 M aq Na_2CO_3 solution (3.5 mL) and 2,3-dimethoxyphenylboronic acid (**6**; 560 mg, 3.07 mmol) in EtOH (5 mL) were added. After refluxing overnight the mixture was washed with aq Na_2CO_3 solution, dried ($MgSO_4$) and solvent was removed under vacuum. The crude product of **8** was purified by column chromatography (silica gel, CH_2Cl_2); yield: 508 mg (61%); yellow solid; mp 98 °C (CH_2Cl_2).

^{1}H NMR ($CDCl_3$): δ = 7.09 (t, *J* = 7.9 Hz, 2 H), 6.95 (dd, *J* = 7.9, 1.5 Hz, 2 H), 6.89 (dd, *J* = 7.9, 1.5 Hz, 2 H), 3.92 (s, 6 H), 3.68 (s, 6 H).

^{13}C NMR ($CDCl_3$): δ = 152.8 (C), 146.8 (C), 132.9 (C), 123.3 (CH), 123.2 (CH), 111.7 (CH), 60.6 (CH_3), 55.8 (CH_3).

IR (KBr): ν = 2999, 2958, 1591, 1578, 1465, 1420, 1294, 1141, 1006, 764, 664 cm^{-1}.

UV/vis (MeOH): λ (ε) = 204 (46000), 277 nm (3500).

MS: *m*/*z* (%) = 274 (14) $[M]^+$, 138 (100).

HRMS (EI, 70 eV): $C_{16}H_{18}O_4$ (274.3): *m*/*z* calcd: M 274.1205; found M^+ 274.1215.

$C_{16}H_{18}O_4$ (274.3)	calcd	C 70.06	H 6.61
	found	69.96	6.70

1,1'-Biphenyl-2,2',3,3'-tetrol (1)
The tetramethoxy derivative **8** (198 mg, 0.72 mmol) was dissolved in CH_2Cl_2 (20 mL) and BBr_3 (3.5 mL, 1 M in CH_2Cl_2) was added at 0 °C. The mixture was stirred overnight at r.t. and after addition of MeOH (5 mL) the solvent was removed under vacuum. The residue was dissolved in Et_2O (30 mL), washed with H_2O (3 × 30 mL), dried ($MgSO_4$) and the solvent was removed in vacuum; yield: 172 mg (quant); light brown solid; mp 214 °C (dec., Et_2O).

^{1}H NMR (CD_3OD): δ = 6.81 (dd, *J* = 7.5, 2.5 Hz, 2 H), 6.79 (t, *J* = 7.5 Hz, 2 H), 6.76 (dd, *J* = 7.5, 2.5 Hz, 2 H).

^{13}C NMR (CD_3OD): δ = 147.4 (C), 142.9 (C), 128.3 (C), 123.1 (CH), 121.6 (CH), 115.2 (CH).

IR (KBr): ν = 3454, 3328, 1622, 1595, 1465, 1374, 1217, 1072, 965, 746, 724 cm^{-1}.

UV/vis (MeOH): λ (ε) = 213 (37500), 249 (10800), 286 nm (4500).

MS: *m*/*z* (%) = 218 (100) $[M]^+$.

HRMS (EI, 70 eV): $C_{12}H_{10}O_4$ (218.2): *m*/*z* calcd: M 218.0579; found M^+ 218.0570.

$C_{12}H_{10}O_4 \bullet 1/3\ H_2O$ (224.2)	calcd	C 64.28	H 4.80
	found	64.29	4.76

Suzuki Coupling of Dibromides 9, 11, and 13 with 2,3-Dimethoxyphenylboronic Acid (6); General Procedure
The aryl dibromide (**9**, **11**, or **13**[8]; 3.5 mmol) and $Pd(PPh_3)_4$ (0.17 mmol) were dissolved in toluene and 2 M aq Na_2CO_3 solution (3.5 mL) was added. Boronic acid **6** (2 equiv, 7 mmol dissolved in a small amount of EtOH) was added and the mixture was heated to reflux overnight. After cooling to r.t. the solution was washed with H_2O, dried ($MgSO_4$) and the solvent was removed in vacuum. The crude product was purified by column chromatography (silica gel, CH_2Cl_2).

2,2",3,3"-Tetramethoxy-1,1':4',1"-terphenyl (10)
Yield: 38%; yellow solid; mp 181−182 °C (CH_2Cl_2).

^{1}H NMR ($CDCl_3$): δ = 7.62 (s, 4 H), 7.13 (t, *J* = 7.9 Hz, 2 H), 7.03 (dd, *J* = 7.9, 1.5 Hz, 2 H), 6.94 (dd, *J* = 7.9, 1.5 Hz, 2 H), 3.93 (s, 6 H), 3.64 (s, 6 H).

^{13}C NMR ($CDCl_3$): δ = 153.2 (C), 146.7 (C), 137.0 (C), 135.7 (C), 129.0 (CH), 124.1 (CH), 122.7 (CH), 111.5 (CH), 60.7 (CH_3), 56.0 (CH_3).

IR (KBr): ν = 3447, 3104, 3007, 2841, 1597, 1579, 1480, 1427, 1398, 1268, 1228, 1017, 1005, 838, 754, 652 cm^{-1}.

UV/vis (MeOH): λ (ε) = 204 (53800), 266 nm (25600).

MS: *m*/*z* (%) = 350 (100) $[M]^+$.

HRMS (EI, 70 eV): $C_{22}H_{22}O_4$ (350.4): *m*/*z* calcd: M 350.1518; found M^+ 350.1530.

$C_{22}H_{22}O_4$ (350.4)	calcd	C 75.41	H 6.33
	found	75.83	6.44

2,2"',3,3'"-Tetramethoxy-1,1':4',1":4",1'"-quaterphenyl (12)
Yield: 57%; yellow solid; mp 156 °C (CH_2Cl_2).

^{1}H NMR ($CDCl_3$): δ = 7.72 (d, *J* = 8.1 Hz, 4 H), 7.66 (d, *J* = 8.1 Hz, 4 H), 7.14 (dd, *J* = 8.1, 7.8 Hz, 2 H), 7.02 (dd, *J* = 7.8, 1.6 Hz, 2 H), 6.95 (dd, *J* = 8.1, 1.6 Hz, 2 H), 3.93 (s, 6 H), 3.64 (s, 6 H).

^{13}C NMR ($CDCl_3$): δ = 153.2 (C), 146.7 (C), 139.5 (C), 137.2 (C), 135.5 (C), 129.7 (CH), 126.7 (CH), 124.1 (CH), 122.6 (CH), 111.6 (CH), 60.7 (CH_3), 56.0 (CH_3).

IR (KBr): ν = 2946, 2834, 1598, 1423, 1315, 1259, 1229, 1171, 854, 788, 750, 641 cm^{-1}.

UV/vis (MeOH/qualitative): λ = 209, 287 nm.

MS: *m*/*z* (%) = 426 (100) $[M]^+$.

HRMS (EI, 70 eV): $C_{28}H_{26}O_4$ (426.5): m/z calcd: M 426.1831; found M^+ 426.1810.

$C_{28}H_{26}O_4$ (426.5)	calcd	C 78.85	H 6.14
	found	78.28	6.18

2,2',2",3,3',3"-Hexamethoxy-1,1':4',1"-terphenyl (14)
Yield: 28%; white solid; mp 126 °C (CH_2Cl_2).

^{1}H NMR ($CDCl_3$): δ = 7.11 (t, *J* = 7.9 Hz, 2 H), 7.03 (s, 2 H), 6.95 (m, 4 H), 3.92 (s, 6 H), 3.72 (s, 6 H), 3.68 (s, 6 H).

^{13}C NMR ($CDCl_3$): δ = 152.8 (C), 150.8 (C), 146.9 (C), 132.9 (C), 132.4 (C), 125.4 (CH), 123.5 (CH), 123.3 (CH), 111.7 (CH), 60.7 (CH_3), 60.6 (CH_3), 55.9 (CH_3).

IR (KBr): ν = 3444, 2962, 2837, 1601, 1476, 1399, 1269, 1225, 1140, 1010, 833, 785 cm^{-1}.

UV/vis (MeOH): λ (ε) = 217 (62300), 249 nm (17100).

MS: *m*/*z* (%) = 410 (100) $[M]^+$.

HRMS (EI, 70 eV): $C_{24}H_{26}O_6$ (410.5): *m*/*z* calcd: M 410.1729; found M^+ 410.1749.

$C_{24}H_{26}O_6$ (410.5)	calcd	C 70.23	H 6.38
	found	70.01	6.45

1,1':4',1"-Terphenyl-2,2",3,3"-tetrol (2)
Ether cleavage was performed as described for the preparation of **1**.

Yield: 91%; yellow solid; mp 163 °C (Et_2O).

^{1}H NMR (CD_3OD): δ = 7.59 (s, 4 H), 6.82 (dd, *J* = 7.6, 2.0 Hz, 2 H), 6.79 (dd, *J* = 7.6, 2.0 Hz, 2 H), 6.76 (t, *J* = 7.6 Hz, 2 H).

^{13}C NMR (CD_3OD): δ = 146.7 (C), 143.7 (C), 138.0 (C), 130.1 (C), 129.9 (CH) 122.3 (CH), 120.7 (CH), 115.0 (CH).

IR (KBr): ν = 3491, 3328, 1616, 1470, 1357, 1301, 1262, 845, 779, 715 cm^{-1}.

UV/vis (MeOH): λ (ε) = 203 (57900), 269 nm (24500).

MS: *m*/*z* (%) = 294 (100) $[M]^+$.

HRMS (EI, 70 eV): $C_{18}H_{14}O_4$ (294.3): *m*/*z* calcd: M 294.0892; found M^+ 294.0879.

$C_{18}H_{14}O_4$ (294.3)	calcd	C 73.46	H 4.79
	found	73.02	4.76

1,1':4',1":4",1'"-Quaterphenyl-2,2"',3,3'"-tetrol (3)
Ether cleavage was performed as described for the preparation of **1**.

Yield: quantitative; yellow solid; mp 264 °C (dec., Et_2O).

^{1}H NMR (CD_3OD): δ = 7.70 (d, *J* = 8.6 Hz, 4 H), 7.67 (d, *J* = 8.6 Hz, 4 H), 6.83 (dd, *J* = 7.5, 2.0 Hz, 2 H), 6.80 (dd, *J* = 7.5, 2.0 Hz, 2 H), 6.76 (t, *J* = 7.5 Hz, 2 H).

^{13}C NMR (CD_3OD): δ = 146.7 (C), 143.8 (C), 140.4 (C), 139.2 (C), 130.8 (CH), 129.8 (C), 127.4 (CH), 122.2 (CH), 120.7 (CH), 115.1 (CH).

IR (KBr): ν = 3535, 3481, 3034, 1622, 1498, 1470, 1344, 1268, 1244, 1003, 758, 736 cm^{-1}.

UV/vis (MeOH): λ (ε) = 209 (79800), 289 nm (39600).

MS: *m*/*z* (%) = 370 (100) $[M]^+$.

HRMS (EI, 70 eV): $C_{24}H_{18}O_4$ (370.4): m/z calcd: M 370.1205; found M^+ 370.1192.

$C_{24}H_{18}O_4$.1/4 H_2O (374.9)	calcd	C 76.89	H 4.79
	found	76.83	4.87

1,1':4',1"-Terphenyl-2,2',2",3,3',3"-hexol (4)
Ether cleavage was performed as described for the preparation of **1**.

Yield: quantitative; beige solid; mp 273 °C (dec., Et_2O).

^{1}H NMR (CD_3OD): δ = 6.92 (s, 2 H), 6.83 (s, 6 H).

^{13}C NMR (CD_3OD): δ = 142.2 (C), 143.8 (C), 143.0 (C), 128.0 (C), 127.1 (C), 123.7 (CH), 123.1 (CH), 121.6 (CH), 115.3 (CH).

IR (KBr): ν = 3892, 3310, 2925, 1624, 1500, 1447, 1445, 1377, 1361, 994, 801, 725 cm^{-1}.

UV/vis (MeOH): λ (ε) = 219 (47300), 267 nm (24400).

MS: *m*/*z* (%) = 326 (100) $[M]^+$.

HRMS (EI, 70 eV): $C_{18}H_{14}O_6$ (326.31): *m*/*z* calcd: M 326.0790; found M^+ 326.0773.

$C_{18}H_{14}O_6$.1/4 H_2O (330.81):	calcd	C 65.35	H 4.42
	found	65.51	4.65

3,3'-Dimethoxy-5,5'-dimethyl-1,1'-biphenyl-2,2'-diol (16)
2-Methoxy-4-methylphenol (**15**; 414 mg, 3.00 mmol) was dissolved in CH_2Cl_2 (10 mL) and a CH_2Cl_2 solution of freshly prepared methyltributylammonium permanganate (MTBAP)[10] (480 mg, 1.50 mmol) was added at 0 °C. H_2O (10 mL) was added after 15 min and the mixture was stirred for further 10 min. The organic phase was separated, dried ($MgSO_4$) and solvent was removed in vacuum to obtain crude **16** which was used without further purification; yield: 334 mg (81%); beige solid.

^{1}H NMR ($CDCl_3$): δ = 6.82 (d, *J* = 1.8 Hz, 2 H), 6.71 (d, *J* = 1.8 Hz, 2 H), 3.98 (s, 6 H), 2.31 (s, 6 H).

5,5'-Dimethyl-1,1'-biphenyl-2,2',3,3'-tetrol (5)
Ether cleavage was performed as described for the preparation of **1**.

Yield: 92%; beige solid; mp 209 °C (dec., Et_2O).

^{1}H NMR (CD_3OD): δ = 6.65 (d, *J* = 1.6 Hz, 2 H), 6.58 (d, *J* = 1.6 Hz, 2 H), 2.24 (s, 6 H).

^{13}C NMR (CD_3OD): δ = 147.0 (C), 140.4 (C), 131.1 (C), 128.1 (C), 123.3 (CH), 116.0 (CH), 21.0 (CH_3).

IR (KBr): ν = 3371, 2916, 1602, 1420, 1345, 1279, 1251,, 836, 734 cm^{-1}.

UV-vis (MeOH): λ (ε) = 216 (35700), 252 (10100), 292 nm (4200).

MS: *m*/*z* (%) = 246 (100) $[M]^+$.

HRMS (EI, 70 eV): $C_{14}H_{14}O_4$ (246.3): *m*/*z* calcd: M 246.0892; found M^+ 246.0887.

$C_{14}H_{14}O_4$.1/3 H_2O (252.26):	calcd	C 66.66	H 5.86
	found	66.71	5.68

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