The *O*-substitution Pattern of the $MoCl_5$-Mediated Oxidative Aryl-Aryl Coupling Reaction

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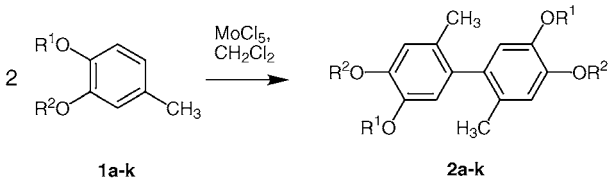
Received 12 August 2002; revised 11 October 2002

Abstract: Different protective groups for the phenolic oxygen were investigated in the molybdenum pentachloride-mediated dehydrodimerization reaction. Cyclic acetals and ketals, triisopropylsilyl and alkoxycarbonylmethyl moieties are compatible with the strong acidic reaction conditions.

Key words: biaryls, coupling, dimerizations, protective groups, molybdenum



1a-k 2a-k

Scheme 1

The oxidative coupling reaction of electron rich aromatics by molybdenum pentachloride gives access to novel structures which are particular useful in supramolecular chemistry.[1] The molybdenum pentachloride mediated dehydrodimerization can be exploited for the installation of the tetramethoxybiaryl moiety resulting in the selective formation of eight-membered lignans.[2] Furthermore, multiple iodinated substrates are tolerated and can be subjected to coupling without loss of the iodo-substituents.[3] In order to use these particularly interesting structures for pharmaceutical purposes it is necessary to make them less lipophilic. This means cleavage or replacement of the methyl protective group.

Molybdenum pentachloride exhibits a substrate selectivity for 1,2-disubstituted benzenes.[4] Due to the strong Lewis acid character and the oxophilic behaviour of molybdenum pentachloride, the phenolic oxygen is usually protected by simple alkyl groups or sterically demanding ketals. When longer reaction times or additives like sulfuric acid are applied, a partial loss of the alkyl moieties is observed.[5] Complete removal of the methyl groups however requires harsh conditions and selective deprotection of one oxygen is almost impossible.[6] To overcome this severe limitation in the molybdenum pentachloride mediated dehydrodimerization reaction, we were prompted to investigate a variety of different protective groups for the phenolic substrates. Subsequent removal or modification of the O-protective groups should allow an easy tuning of the physical properties. Differently blocked 4-methylcatechols **1a**–**k** were subjected to the molybdenum pentachloride-mediated dehydrodimerization reaction (Table 1). The presence of a methyl group in one *para*-position leads normally to exclusive formation of the desired biaryls, avoiding multiple oxidative coupling (Scheme 1).

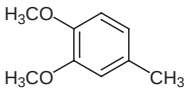
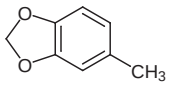
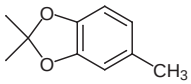
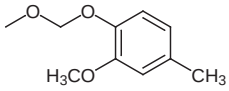
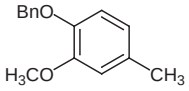
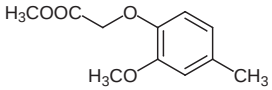
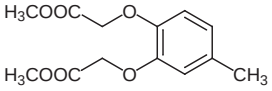
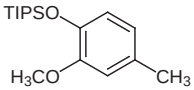
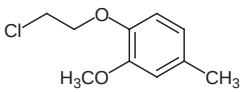
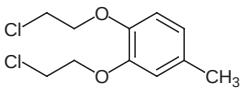
The starting materials were synthesized according to known or standard procedures.[8–10] Recently, we reported on the oxidative coupling reaction of **1a** by molybdenum pentachloride forming the parent tetramethoxy biphenyl compound **2a**.[4] The reaction proceeded to completion within several minutes at room temperature while the evolution of hydrogen chloride was observed. In a first set of experiments we focused on common protective groups based on ketals or acetal moieties. The 1,3-benzodioxole is of particular interest since it is a widely occurring structural feature in natural products. The conversion of 5-methyl-1,3-benzodioxole (**1b**) resulted in the known biaryl **2b**.[7] In order to avoid partial oxidation of the methylene moiety, performing the reaction at lower temperature is advantageous. The increased stability of the acetone-derived benzodioxole **1c** leads to higher yields. The reaction can be conducted at ambient temperature without significant loss of product. Unfortunately, open-chain acetals like the methoxymethyl group are not suitable for the molybdenum pentachloride-mediated transformation. Even low temperature conditions do not result in any of the desired biaryl system. The starting material **1d** undergoes almost immediate cleavage and the liberated formaldehyde equivalent does an electrophilic attack onto the electron rich aromatic systems (Scheme 2). Beside the known methylene-bridged dimer **3**,[11] we isolated a significant amount of the trimeric compound **4**. No other isomers of **4** were detected. Higher aggregates were only present in traces and identified by mass spectrometry. The structure of **4** was assigned by the X-ray analysis of a single crystal (Figure 1).[17] Remarkably, all phenolic protons form distinct hydrogen bonds to the adjacent methoxy groups.

Based on the practical significance of benzyl protective groups, we subjected **1e** to the $MoCl_5$-mediated coupling reaction. The conversion is very sluggish even at low temperature and the only detectable component is the newly formed benzyl chloride. We investigated the 4-nitro and 4-methoxy benzyl groups as well, leading to the same sluggish result. Obviously, the oxophilic character of

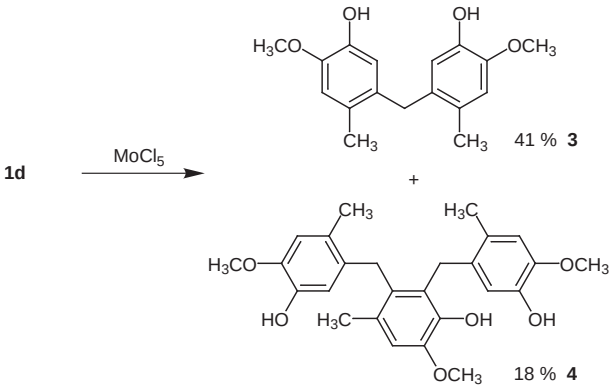
Synthesis 2003, No. 1, Print: 30 12 2002.
Art Id.1437-210X,E;2003,0,01,0091,0096,ftx,en;T09302SS.pdf.

ISSN 0039-7881

Table 1 Oxidative Coupling Reaction of **1** using $MoCl_5$

Entry	Substrate		Reaction Conditions	Yield (%)[a]
1		**1a**	25 °C, 40 min	69 (**2a**) [4]
2		**1b**	0 °C, 40 min	64 (**2b**) [7]
3		**1c**[8]	25 °C, 40 min	73 (**2c**)
4		**1d**[9]	–10 °C, 15 min	–
5		**1e**[10]	–10 °C, 15 min	–
6		**1f**	0 °C, 40 min	91 (**2f**)
7		**1g**	–10 °C, 15 min argon stream	64 (**2g**)
8		**1h**	–35 °C, 8 min argon stream	62 (**2h**)
9		**1i**	0 °C, 50 min	>99 (**2i**)
10		**1k**	0 °C, 50 min	96 (**2k**)

[a] Yields refer to isolated biaryls **2**.



Scheme 2 *Reagents and conditions:* 1.8 equiv $MoCl_5$, CH_2Cl_2, 0 °C, 20 min.

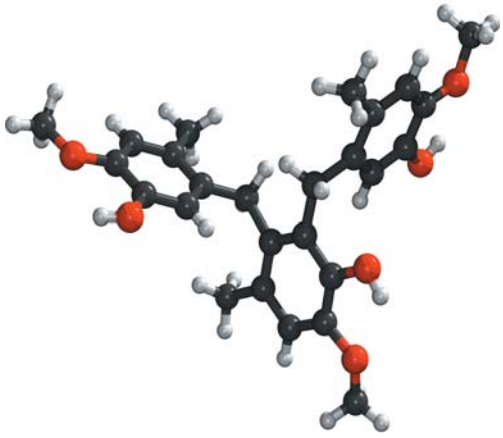


Figure 1 Solid state structure of **4**.

molybdenum pentachloride can be employed to liberate the benzyl moiety as benzyl chloride, while the electron rich phenol undergoes degradation processes. Similar results are obtained when the corresponding allyl derivative is used.[12]

Surprisingly, the methoxycarbonylmethyl group, which is readily installed,[13] turned out to be very stable under the strong acidic reaction conditions. The conversion of **1f** to **2f** proceeds very quickly in excellent yield. After a few seconds the transformation is accomplished. Possibly the ester group assists in the recognition of the molybdenum reagent, similar to the anticipated reaction mechanism for 1,2-dialkoxy-substituted benzenes. When employing two methoxycarbonylmethyl groups the biaryl **2g** is also readily formed from **1g**. A small amount of monochlorinated by-product turned out to be almost inseparable. Alkoxycarbonylmethyl systems are not considered as protective groups but the ester moiety offers a variety of transformations, e.g. the conversion to a substituted amide, and is therefore especially suitable for a tuning of the physical properties. If the phenolic oxygen is protected as the acetate or 2-methoxyacetate, no oxidative coupling reaction with molybdenum pentachloride is observed.

Silyl protective groups usually show a limited stability in a strongly acidic environment.[14] We found that the triisopropylsilyl system is a reliable protective group for the oxidative coupling reaction (entry 8). Other silyl moieties, like *tert*-butyldimethyl and *tert*-butyldiphenyl lead to sluggish results. In order to avoid traces of protolytic removal by hydrogen chloride, the dehydrodimerization reaction is performed at low temperatures and with a gentle stream of inert gas extracting the hydrogen chloride.

Best results were obtained using 2-chloroethyl as the protecting group[15] for the oxidative coupling reaction with molybdenum pentachloride. The biaryl **2i** was easily isolated in almost quantitative yield, analytically pure without further purification. The removal of the 2-chloroethyl moiety can be done by the known elimination-hydrolysis sequence.[16] Furthermore, the 2-chloroethyl moieties in **2i** and **2k** give access to a variety of modifications by simple nucleophilic displacement of the chlorine and therefore another possibility for tuning the physical properties of the biaryls. Even if two 2-chloroethyl moieties are involved in the starting material **1k**, a clean conversion was found without any chlorinated by-products. Since the dehydrodimerization process is slow, an active role of the protective group during the oxidative coupling process can be excluded.

In conclusion, several protective groups for the phenolic oxygen were found to be compatible with the $MoCl_5$-mediated oxidative coupling reaction. Clean transformations are obtained with cyclic acetals or ketals, triisopropylsilyl, alkoxycarbonylmethyl and 2-chloroethyl systems. Therefore, the enlarged scope of the molybdenum pentachloride-mediated transformations is no longer limited to methyl protected phenols. The application to the synthesis of more complex natural products will be reported in due course.

Melting points were determined on a MFB 595 Gallenkamp apparatus (UK) and were uncorrected. Microanalysis was performed using a Vario EL III (Elementar-Analysensysteme, Hanau, D). NMR spectra were recorded on a Bruker 300 ARX or on a Varian 600 Unity Plus using TMS as an internal standard. The abbreviation sp denotes a septet. Mass spectra were obtained on a MAT8200 system (Finnigan-MAT, Bremen, D). Exact mass was determined with a GC-TOF (Micromass, Manchester, UK).

(2-Methoxy-4-methylphenoxy)acetic Acid Methyl Ester (1f)[19]

4-Methylguaiacol (8.00 g, 0.058 mol) was treated with K_2CO_3 (8.78 g, 0.064 mol), 2-bromomethylacetate (8.86 g, 0.058 mol) in acetone (150 mL) and the reaction mixture was heated to reflux over a period of 4 h. The white inorganic solid was filtered off and washed with EtOAc (100 mL). Removal of the solvents and subsequent distillation in vacuo (93 °C; 1.3×10^2 mbar) provided pure **1f** (11.1 g, 91%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.23 (s, 3 H, Ar-CH_3), 3.71 (s, 3 H, OCH_3), 3.79 (s, 3 H, $ArOCH_3$), 4.59 (s, 2 H, OCH_2), 6.58–6.71 (m, 3 H, Ar-H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.7 (Ar-CH_3), 51.8 (OCH_3), 55.6 ($ArOCH_3$), 66.7 (OCH_2), 113.1 (C-6), 114.8 (C-3), 120.7 (C-5), 132.3 (C-4), 145.0 (C-1), 149.3 (C-2), 169.4 (CO).

MS (EI, 70 eV): *m*/*z* = 210.0 (100) [M^+], 137.0 (90), [$M^+ - CH_2CO_2CH_3$], 91.0 (36) [$M^+ - CH_2CO_2CH_3 - CH_3 - OCH_3$].

Anal. Calcd for $C_{11}H_{14}O_4$ (210.35): C, 62.85; H, 6.71. Found: C, 62.72; H.6.67.

(2-Methoxycarbonylmethoxy-4-methylphenoxy)acetic Acid Methyl Ester (1g)

4-Methylcatechol (8 g,0.064 mol) was treated with K_2CO_3 (26.64, 0.193 mol), 2-bromomethylacetate (29.57 g, 0.193 mol) in acetone (150 mL) and the reaction mixture was heated to reflux over a period of 5 h. Standard work-up (see **1f**) and fractional distillation in high vacuum (120 °C; 1.3×10^2 mbar) gave **1g** (14.78 g; 87%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.22 (s, 3 H, $ArCH_3$), 3.72 (s, 3 H, OCH_3), 3.74 (s, 3 H, OCH_3), 4.62 (s, 2 H, OCH_2), 4.66 (s, 2 H, OCH_2), 6.67–6.77 (m, 3 H, Ar.-H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.6 ($ArCH_3$), 51.8 (OCH_3), 66.5 (OCH_2), 66.8 (OCH_2), 115.8 (C-6), 116.4 (C-3), 122.7 (C-5), 132.4 (C-4), 145.7 (C-1), 147.9 (C-2), 169.3 (CO).

MS (EI, 70 eV): *m*/*z* (%) = 268.1 (73) [M^+], 209.1 (6) [$M^+ - CO_2CH_3$], 195.1 (12) [$M^+ - CH_2CO_2CH_3$], 137.0 (47) [$H_3CC_6H_3O_2CH_3^+$], 45.0 (100) [HCO_2^+].

HRMS: *m*/*z* calcd for $C_{13}H_{16}O_6$, 268.0947; found, 268.0944.

Triisopropyl-(2-methoxy-4-methylphenoxy)silane (1h)

4-Methylguaiacol (5.1 g, 0.036 mol) was deprotonated with NaH (60% in oil, 1.71 g , 0.042 mol) in anhyd THF at ambient temperature. The suspension was treated with chloro-tris(isopropyl)silane (7 g, 0.036 mol) and stirred for 16 h. Standard work-up (see **1f**) and fractional distillation in high vacuum (105 °C; 4×10^3 mbar) gave **1h** (6.1 g; 58%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.11 (d, 18 H, ^3J = 6.9 Hz, CH_3), 1.24 (sp, 3 H, ^3J = 6.9 Hz, CH), 2.27 (s, 3 H, 7-H), 3.79 (s, 3 H, 8-H), 6.58–6.67 (m, 2 H, ArH), 6.76–6.78 (s, 1 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.9 (CH), 17.9 (CH_3), 21.0 ($ArCH_3$), 55.4 (OCH_3), 113.4 (C-3), 120.1; 121.0 (C-5, C-6), 130.8 (C-4), 143.3 (C-1), 150.5 (C-2).

MS (EI, 70 eV): *m*/*z* (%) = 294.2 (9) [M^+], 251.1 (100) [M^+ – isopropyl], 236.0 (85) [M^+ – isopropyl – CH_3].

Anal. Calcd for $C_{17}H_{30}O_2Si$ (294.50): C, 69.33; H, 10.27. Found: C, 69.52; H.10.60.

1-(2-Chloroethoxy)-2-methoxy-4-methylbenzene (1i)
1f (7 g, 0.033 mol) was reduced with $NaBH_4$ (2.52 g , 0.066 mol) in MeOH (120 mL) at 0 °C providing the alcohol (5.7 g, 95%) which was then converted into the chloro derivative using Appel's procedure. For the conversion, PPh_3 (9.86 g , 0.038 mol) was dissolved in CCl_4 (25 mL), stirred for 15 min at 0 °C, treated with alcohol (5.7 g , 0.031 mol), dissolved in CCl_4 (15 mL) and toluene (35 mL). After the reaction mixture was heated 7 h to reflux, all volatile components were removed. The residue was fractionated between Et_2O (3 × 150 mL) and $NaHCO_3$ soln (100 mL). Afterwards the combined organic phases were washed with brine (50 mL), dried and concentrated. The pure **1i** (4.17 g; 67%) was obtained after sublimation in vacuo (60 °C; 5×10^2 mbar).

Mp 45–46 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.30 (s, 3 H, $ArCH_3$), 3.79 (t, 2 H, ^3J = 6.3 Hz, CH_2Cl), 3.84 (s, 3 H, OCH_3), 4.23 (t, 2 H, ^3J = 6.3 Hz, OCH_2), 6.67–6.83 (m, 3 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.0 ($ArCH_3$), 41.8 (CH_2Cl), 56.0 (OCH_3), 70.0 (OCH_2), 113.5 (C-3), 115.7 (C-6), 121.1 (C-5), 132.4 (C-4), 145.5 (C-1), 149.9 (C-2).

MS (EI, 70 eV): *m*/*z* (%) = 200.0 (100) [M^+], 137.0 (89) [M^+ CH_2CH_2Cl].

Anal. Calcd for $C_{10}H_{13}ClO_2$ (200.66): C, 59.86; H, 6.53. Found: C, 59.80; H, 6.35.

1,2-Bis-(2-chloroethoxy)-4-methylbenzene (1k)
It was prepared in an analogous manner to **1i**, using **1g** as starting material and reagents (2.5 equiv). The pure **1k** (60%) was obtained after sublimation in vacuo (85 °C; 5×10^2 mbar).

Mp 56–57 °C (from MeOH).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.26 (s, 3 H, $ArCH_3$), 3.73 (t, 2 H, ^3J = 6.0 Hz, CH_2Cl), 3.77 (t, 2 H, ^3J = 6.0 Hz, CH_2Cl), 4.17 (t, 2 H, ^3J = 6.0 Hz, CH_2O), 4.24 (t, 2 H, ^3J = 6.0 Hz, CH_2O), 6.72–6.84 (m, 3 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.8 ($ArCH_3$), 42.1 (CH_2Cl), 42.1 (CH_2Cl), 69.9 (OCH_2), 70.4 (OCH_2), 116.9; 117.2 (C-3, C-6), 122.9 (C-5), 132.7 (C-4), 146.4 (C-1), 148.6 (C-2).

MS (EI, 70 eV): *m*/*z* (%) = 248.0, 250.0 (71) [M^+], 213.1 (5) [M^+ Cl], 186.0 (35) [M^+ – $CHCH_2Cl$], 123.0 (100) [M^+ – 2($CHCH_2Cl$)].

Anal. Calcd for $C_{11}H_{14}Cl_2O_2$ (249.13): C, 53.03; H, 5.66. Found: C, 53.00; H, 5.41.

Oxidative Coupling Reaction; General Procedure
The substrate (9–10 mmol) in anhyd CH_2Cl_2 (30 mL) was placed in a well dried flask and after the temperature was adjusted, $MoCl_5$ (2.73 g, 10 mmol) was added. The reaction mixture was quenched after the time given in Table 1 with $NaHCO_3$ soln (50 mL). The aq phase was partitioned with EtOAc (3 × 100 mL). Subsequent washings of the combined organic fractions with H_2O (100 mL) as well as brine (100 mL) and concentration provided crude product that was purified either by column chromatography on silica (cyclohexane–ethyl acetate) or recrystallization.

2,2,6,2′,2′,6′-Hexamethyl-[5,5′]bi(benzo[1,3]dioxolyl) (2c)
Mp 121 °C (from MeOH).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.81 (s, 6 H, CH_3), 1.89 (s, 6 H, CH_3), 2.01 (s, 6 H,), 6.56, 6.79 (s, 4 H, ArH) .

^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.0 ($ArCH_3$), 30.1 (CH_3), 30.3 (CH_3), 97.1 (C-2), 113.8 (C-4), 116.2 (C-7), 130.0 (C-5), 142.1 (C-3a), 144.7 (C-7).

MS (EI, 70 eV): *m*/*z* (%) = 326.15 (100) [M^+], 311.1 (8) [M^+ – CH_3].

Anal. Calcd for $C_{20}H_{22}O_4$ (326.38): C, 73.60; H, 6.79. Found: C, 73.42; H, 6.66.

(4,4′-Dimethoxy-3′-methoxycarbonylmethoxy-6,6′-dimethyl-biphenyl-3-yloxy)-acetic Acid Methyl Ester (2f)
Mp 132 °C (from MeOH).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.99 (s, 6 H, $ArCH_3$), 3.76 (s, 6 H, OCH_3), 3.90 (s, 6 H, $ArOCH_3$), 4.65 (s, 4 H, OCH_2), 6.58 (s, 2 H, ArH), 6.78 (s, 2 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.3 ($ArCH_3$), 52.0 (OCH_3), 55.9 ($ArOCH_3$), 66.7 (OCH_2), 113.8 (C-2), 116.3 (C-5), 130.2 (C-6), 133.0 (C-1), 144.8 (C-3), 148.5 (C-4), 169.4 (CO).

MS (EI, 70 eV): *m*/*z* (%) = 418.0 (100) [M^+], 359.1 (4) [M^+ – CO_2CH_3].

Anal. Calcd for $C_{22}H_{26}O_8$ (418.44): C, 63.15; H, 6.26. Found: C, 63.01; H, 6.00.

4,4′-Dimethoxy-2,2′-dimethyl-5,5′-bis-triisopropylsilanyloxy-biphenyl (2h)
Mp 100–101 °C (from MeOH).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.06 (d, 36 H, ^3J = 6.9 Hz, CH_3), 1.19 (sp, 6 H, ^3J = 6.9 Hz, CH), 1.95 (s, 6 H, $ArCH_3$), 3.80 (s, 6 H, OCH_3), 6.58 (s, 2 H, ArH), 6.68 (s, 2 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.9 (CH), 17.9 (CH_3), 19.3 ($ArCH_3$), 55.7 (OCH_3), 113.8 (C-3), 121.9 (C-6), 128.8 (C-2), 133.8 (C-1), 142.9 (C-5), 149.6 (C-4).

MS (EI, 70 eV): *m*/*z* (%) = 586.3 (47) [M^+], 543.3 (100) [M^+ – isopropyl], 470.1 (61) [M^+ – 2 isopropyl – 2 CH_3].

Anal. Calcd for $C_{34}H_{58}O_4Si_2$ (586.99): C, 69.57; H, 9.96. Found: C, 69.27; H, 9.94.

(4,3′,4′-Tris-(methoxycarbonylmethoxy)-6,6′-dimethylbiphenyl-3-yloxy)-acetic Acid Methyl Ester (2g)
^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.94 (s, 6 H, $ArCH_3$), 3.76 (s, 6 H, OCH_3), 3.81 (s, 6 H, OCH_3), 4.67 (s, 4 H, OCH_2), 4.74 (s, 4 H, OCH_2), 6.60 (s, 2 H, ArH), 6.75 (s, 2 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.3 ($ArCH_3$), 52.1 (OCH_3), 52.1 (OCH_3), 66.8 (OCH_2), 66.9 (OCH_2), 117.1 (C-2), 117.2 (C-5), 130.4 (C-6), 134.8 (C-1), 145.6 (C-3), 147.0 (C-4), 169.4 (CO), 169.6 (CO).

MS (EI, 70 eV): *m*/*z* (%) = 534.3 (100) [M^+], 475.2 (2) [M^+ – CO_2CH_3].

HRMS: *m*/*z* calcd mass for $C_{26}H_{30}O_{12}$, 534.1737; found, 534.1739.

5,5′-Bis-(2-chloro-ethoxy)-4,4′-dimethoxy-2,2′-dimethylbiphenyl (2i)
Mp 132–134 °C (from EtOAc).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.01 (s, 6 H, $ArCH_3$), 3.80 (t, 4 H, ^3J = 6.3 Hz, CH_2Cl), 3.90 (s, 6 H, OCH_3), 4.24 (dt, 4 H, ^2J = 1.8 Hz, ^3J = 6.3 Hz, OCH_2), 6.68 (s, 2 H, 3-H), 6.79 (s, 2 H, 6-H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.4 ($ArCH_3$), 41.8 (CH_2Cl), 56.1 (OCH_3), 69.8 (OCH_2), 114.0 (C-6), 116.9 (C-3), 130.0 (C-2), 133.4 (C-1), 145.2 (C-5), 148.8 (C-4).

MS (EI, 70 eV): *m*/*z* (%) = 397.9, 399.3 (100, 68) [M^+], 335.0 (6) [M^+ – CH_2CH_2Cl].

Anal. Calcd for $C_{20}H_{24}Cl_2O_4$ (399.31): C, 60.16; H, 6.06. Found: C, 59.93; H, 6.35.

4,5,4′,5′-Tetrakis-(2-chloroethoxy)-2,2′-dimethylbiphenyl (2k)
Mp 93–94 °C (from MeOH).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.91 (s, 6 H, $ArCH_3$), 3.71–3.79 (m, 8 H, CH_2Cl), 4.15 (m, 8 H, CH_2O), 6.63 (s, 2 H, 3-H), 6.76 (s, 2 H, 6-H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.2 ($ArCH_3$), 41.9 (CH_2Cl), 42.2 (CH_2Cl), 70.1 (CH_2O), 70.3 (CH_2O), 117.8; 117.9 (C-3, C-6), 130.4 (C-2), 135.0 (C-1), 146.2 (C-5), 147.6 (C-4).

MS (EI, 70 eV): *m*/*z* (%) = 494.0; 496.0; 498.0 (76, 100, 50) [M^+], 63.0 (31) [$CHCH_2Cl^+$].

Anal. Calcd for $C_{22}H_{26}Cl_4O_4$ (496.25): C, 53.25; H, 5.28. Found: C, 52.79; H, 5.16 (Calcd for $C_{22}H_{26}Cl_4O_4 \cdot 0.25\ CH_3OH$ (504.25.): C, 53.00; H, 5.40).

2,3-Bis-(5-hydroxy-4-methoxy-2-methylbenzyl)-6-methoxy-4-methylphenol Hemihydrate (4)[18]
Mp 200–202 °C (from hexane).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.64 (s, 1 H, 0.5 H_2O), 2.11 (s, 3 H, 7-H), 2.16 (s, 3 H, 8′-H), 2.17 (s, 3 H, 8″-H), 3.54 (s, 2 H, 1′-H), 3.67 (s, 2 H, 1″-H), 3.82 (s, 3 H, 9″-H), 3.83 (s, 3 H, 9′-H), 3.89 (s, 3 H, 8-H), 5.31 (s, 2 H, 4′-OH; 4″-OH), 5.54 (s, 1 H, 1-OH), 6.18 (s, 1 H, 3′-H), 6.33 (s, 1 H, 3″-H), 6.63 (s, 1 H, 6″-H), 6.65 (s, 1 H, 6′-H), 6.66 (s, 1 H, 3-H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 19.2 (C-8′), 19.3 (C-8″), 19.8 (C-7), 28.5 (C-1″), 31.3 (C-1′), 55.9 (C-8; C-9′; C-9″), 111.2 (C-3), 112.5 (C-6'), 112.6 (C-6″), 113.4 (C-3′), 113.6 (C-3″), 125.2 (C-6), 127.2 (C-7′), 127.3 (C-7″), 128.2 (C-4), 130.1 (C-5), 131.4 (C-2′), 131.6 (C-2″), 142.3 (C-1), 143.3 (C-4″), 143.4 (C-4′), 144.1 (C-5′; C-5″), 144.6 (C-2).

GCOSY (600 MHz / 600 MHz, $CDCl_3$): δ (^{13}C) / δ (^{1}H) = 2.11 (7-H) / 6.66 (3-H), 2.16 (8′-H) / 3.54 (1′-H) / 6.65 (6′-H), 2.17 (8″-H) / 3.67 (1″-H) / 6.63 (6″-H), 2.16 (8′-H) / 3.54 (1′-H) / 6.18 (3′-H), 2.17 (8″-H) / 3.67 (1″-H) / 6.33 (3″-H).

GHSQC (150 MHz / 600 MHz, $CDCl_3$): δ (^{13}C) / δ (^{1}H) = 19.2 / 2.16 (C-8′ / 8′-H), 19.3 / 2.17 (C-8″ / 8″-H), 19.8 / 2.11 (C-7 / 7-H), 28.5 / 3.67 (C-1″ / 1″-H), 31.3 / 3.54 (C-1′ / 1′-H), 55.9 / 3.82 (C-8, C-9′, C-9″ / 9″-H), 55.9 / 3.83 (C-8, C-9′, C-9″ / 9′-H), 55.9 (C-8, C-9′, C-9″ / 8-H), 111.2 / 6.66 (C-3 / 3-H), 112.5 / 6.65 (C-6′ / 6′-H), 112.57 / 6.61 (C-6″ / 6″-H), 113.4 / 6.18 (C-3′ / 3′-H), 113.61 / 6.33 (C-3″ / 3″-H).

GHMBC (50 MHz / 600 MHz, $CDCl_3$): δ (^{13}C) / δ (^{1}H) = 28.5 (C-1″); 127.3 (C-7″); 143.3 (C-4″); 144.1 (C-5′; C-5″) / 6.33 (3″-H), 31.3 (C-1′); 127.2 (C-7′); 143.4 (C-4′); 144.1 (C-5′; C-5″) / 6.18 (3′-H), 125.2 (C-6); 127.2 (C-7′); 128.2 (C-4); 130.1 (C-5); 131.4 (C-2′) / 3.54 (1′-H), 125.2 (C-6); 127.3 (C-7″), 130.1 (C-5), 131.6 (C-2″) / 3.67 (1″-H), 125.2 (C-6) / 5.54 (1-OH), 127.2 (C-7′) / 6.18 (3′-H), 127.3 (C-7″) / 6.33 (3″-H), 128.2 (C-4); 130.1.(C-5) / 2.11 (7-H), 143.3 (C-4″); 144.1 (C-5′ C-5″) / 6,33 (3″-H), 143.4 (C-4′); 144.1 (C-5′; C-5″) / 6.18 (3′-H).

1D-NOE (600 MHz, $CDCl_3$): Irradiation at δ = 2.11 (7-H), NOE-signal at 3.54 (1′-H), 6.18 (3′-H), 6.66 (3-H); irradiation at δ = 3.53 (1′-H), NOE-signal at 2.11 (7-H), 2.16 (8′-H), 3.67 (1″-H), 6.18 (3′-H), 6.33 (3″-H); irradiation at δ = 3.66 (1″-H), NOE-signal at 2.17 (8″-H), 3.54 (1′-H), 6.18 (3′-H), 6.33 (3″-H); irradiation at δ = 3.89 (8-H), NOE-signal at 6.66 (3-H).

MS (EI, 70 eV): *m*/*z* (%) = 438.2 (100) [M^+], 285.1 (86) [$M^+ - C_9H_{13}O_2$], 151.1 (37) [$C_9H_{12}O_2^+$].

Anal. Calcd for $C_{26}H_{30}O_6 \cdot 0.5\ H_2O$ (447.52): C, 69.78; H, 6.98. Found: C, 70.02; H, 6.74.

Acknowledgement

This work was supported by the Deutsche Forschungsgemeinschaft (DFG) and the European Graduate College 'Template Directed Chemical Synthesis'. The gift of $MoCl_5$ by H.C. Starck (Goslar, Germany) was very helpful.

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(17) X-ray crystal structure analysis of **4**: formula $C_{26}H_{30}O_6$ M = 438.50 colorless crystal 0.35 × 0.30 × 0.10 mm a = 11.923(2) b = 12.352(2) c = 16.974(2) Å α = 96.80(1) β = 92.64(2) γ = 112.76(1)° V = 2277.4(6) Å3 ρcalc = 1.279 gcm^{-3} μ = 7.34 cm^{-1} empirical absorption correction via ψ scan data (0.783 ≤ T ≤ 0.930) Z = 4 triclinic space group P1bar (No. 2) λ = 1.54178 Å T = 223 K ω/2θ scans 9478 reflections collected (+h ±k ±l) [(sinθ)/λ] = 0.62 Å-1 9040 independent (Rint = 0.026) and 7595 observed reflections [I ≥ 2 σ(I)] 595 refined parameters R = 0.047 $wR2$ = 0.134 max. residual electron density 0.30 (–0.24) e Å^{-3} two independent molecules in the asymmetric unit hydrogens calculated and refined as riding atoms.
Data set was collected with an Enraf Nonius CAD4 diffractometer. Programs used: data collection Express (Nonius B.V. 1994) data reduction MolEN (K. Fair 1990) structure soln SHELXS-97 (Sheldrick, G. M. *Acta Cryst.* **1990**, *A46*, 467) structure refinement SHELXL-97 (Sheldrick, G. M. Universität Göttingen, **1997**) graphics POV-Ray 3.2.
Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication CCDC 191456. Copies of the data can be obtained free of charge on application to The Director CCDC 12 Union Road CambridgeCB2 1EZ UK [fax: +44(1223)336033 e-mail: deposit@ccdc.cam.ac.uk].

(18) Structure of **4**: The chemical shifts for the structure were assigned by long range coupling experiments and refer to the following numbering (Figure 2).
(19) For a multi-step synthesis of **1f**, see: Freudenberg, K.; Müller, H. G. *Liebigs Ann. Chem.* **1953**, *584*, 40.

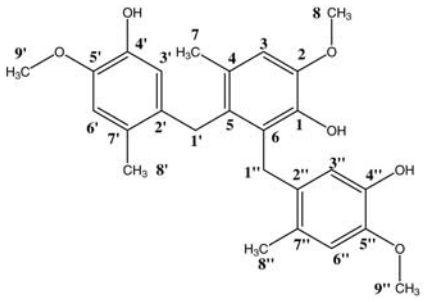

Figure 2