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Synthesis of novel 3-oxa-chromanol type antioxidants

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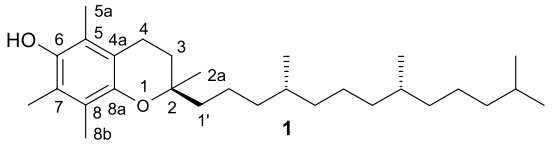
Abstract—Condensation of trimethylhydroquinone with aldehydes provides 2,4-disubstituted 5,7,8-trimethyl-4*H*-benzo[1,3]dioxin-6-ols in a straightforward one-pot reaction. These compounds are 3-oxa-derivatives of α-tocopherol (vitamin E) and represent an interesting novel class of phenolic antioxidants. The formation reaction proceeds according to a two-step mechanism consisting of electrophilic substitution and acetalization, and provides the product as a *cis*/*trans*-mixture of diastereomers.

1. Introduction

α-Tocopherol (**1**), the component of vitamin E with the highest biologically activity, is known to be one of the most effective chain breaking phenolic antioxidants.[1] It reacts rapidly with a variety of radicals to form the relatively stable α-tocopheroxyl radical, which is either reduced back to α-tocopherol, or further oxidized to quinoid structures. The exceptional high efficiency of vitamin E as phenolic antioxidant has been attributed to substituent effects,[2] and to stereoelectronic influences[3] as well: the three methyl groups activate the aromatic system, and the fused 6-membered heterocyclic ring adopts a geometry that allows optimum overlapping of the lone-pair electrons of the chroman oxygen and the aromatic π-electrons, which brings about additional stabilization of the phenoxyl radical. The synthesis of antioxidants with tocopherol structure is aimed at both developing novel antioxidants and at providing model compounds for studies of the physiologically important tocopherol system.

In recent studies, we used the condensation of trimethylhydroquinone (TMHQ, **2**) with aldehydes for the synthesis of antioxidants with α-tocopherol-type structures. The products, a 'twin chromanol'[4] from the reaction with malondialdehyde tetramethyl acetal, and the 3-oxa-chromanol model compound 2,4,5,7,8-pentamethyl-4*H*-benzo[1,3]dioxin-6-ol (**4**, PBD)[5] obtained by condensation with acetaldehyde, formed relatively stable phenoxyl radicals and exhibited an intriguing redox behavior. Due to these properties, 3-oxa-tocopherol derivatives appeared to be valuable candidates for further studies of their antioxidative properties, both in lipid membranes[6] and in isolated perfused rat hearts during ischemia/reperfusion events.[7] These investigations required synthesizing 3-oxa-tocopherol type compounds with varying lipophilicity, which gave the impetus to the present work.



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2. Results and discussion

The formation of benzodioxinol analogues of α-tocopherol by condensation of **2** with aldehydes proceeds according to a two-step mechanism. In the first step, TMHQ undergoes electrophilic substitution at the only available aromatic ring position by the aldehyde, forming an *o*-(hydroxymethyl)-phenol intermediate **3**, which requires activation of the aldehyde by protonation beforehand. In the second step, intermediate **3** immediately traps another aldehyde molecule in a cyclic acetal structure (Scheme 1). Formation of the latter is evidently quite favored, as in no case free **3** was detected. Even when applying a large excess of TMHQ the reaction always resulted in a mixture of unchanged **2** besides benzodioxinol product, without free intermediate **3** being formed. Also very short reaction times do not allow the isolation of **3**.

Under optimized reaction conditions, the condensation of **2** with aldehydes proceeded at 4°C in as little glacial acetic acid as required to keep the hydroquinone in solution, catalyzed by concentrated aqueous HCl. Raising the reaction temperature to rt caused a significant reduction in yield, e.g. from 78 to 35% in the synthesis of **4**. The use of other catalysts, e.g. ethereal HCl or Lewis acids (BF_3

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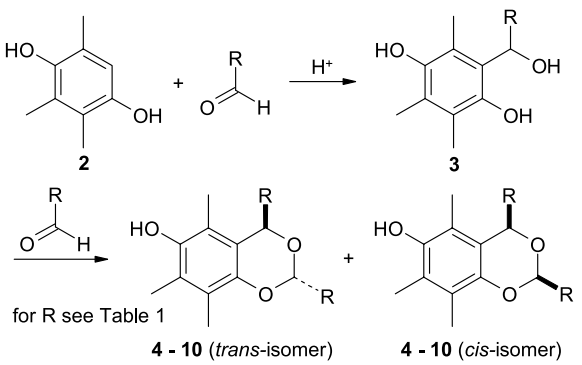

Scheme 1. Reaction of TMHQ with aldehydes.

etherate, $ZnCl_2$) proved to be completely ineffective. Concentrated sulfuric acid is an efficient catalyst, but promotes the reaction of the phenolic hydroxyl groups with the solvent at the same time, so that formation of TMHQ diacetate becomes a major competing process. Diluted sulfuric acid, which would avoid catalyzing this esterification, was found to be inferior as condensation catalyst. Acetic acid was the most convenient solvent applied, as in most cases the products could be readily precipitated from this medium simply by addition of water. Other solvents tested required either a lengthy separation by evaporation and column chromatography ($CHCl_3$, dichloroethane) or gave lower yields upon precipitation with water (ethanol, dioxane, formic acid, trifluoroacetic acid). Thus, for the condensation with aldehydes, the system glacial acetic acid/concentrated aqueous HCl was optimal, whereas condensation with protected aldehydes (acetals) worked best in a 2:1-mixture of chloroform and trifluoroacetic acid without catalyst.[4]

Addition of more than 2 equiv. of coreacting aldehyde did not improve the yields, neither did prolonged reaction times beyond 2 h. Condensation of TMHQ with ketones instead of aldehydes did not succeed in our hands so far.

According to the optimized procedure, several 3-oxa-chromanol derivatives (**4**–**10**) were synthesized (Table 1), the lipophilicity of which varied according to the substituents in position 2 and 4 of the heterocycle.[8] According to the above mechanism, all benzodioxinols were obtained as a mixture of two diastereomers, which are distinguished by the two substituents in position 2 and 4 having either *cis*- or *trans*-arrangements. The *cis*/*trans*-ratio is determined by the steric conditions in the second reaction step: the *trans*-configuration is generally favored for sterically crowded

Table 1. Synthesis of benzodioxinols **4**–**10**: yields and diastereomer ratios

Compound	R[a]	Exp. ratio *cis*/*trans*[b]	Yield (%)[c]
4	Me	1:1	78
5	Et	1:1.4	78
6	Prop	1:3.2	59
7	*i*-Prop	1:26	64
8	Cyclohexyl	Only *trans*	64
9	Phenyl	Only *trans*	81
10	4-Nitrophenyl	1:2	52

[a] See Scheme 1.
[b] Determined from the integrals in the ^{1}H NMR spectra.
[c] Isolated yields (mixture of diastereomers).

Table 2. Benzodioxinols **4**–**10**: diastereomer ratios at 273 K from computations

Compound	R[a]	Theor. ratio *cis*/*trans*[b]	$\Delta(\Delta_B H)$ (kJ mol^{-1})[b]
4	Me	1:2.37	−1.96
5	Et	1:4.00	−3.15
6	Prop	1:13.32	−5.88
7	*i*-Prop	1:16.02	−6.30
8	Cyclohexyl	1:49.47	−8.86
9	Phenyl	1:35.87	−8.13
10	4-Nitrophenyl	1:122.55	−10.92

[a] See Scheme 1.
[b] cf. Ref. 9.

substituents, whereas small substituents, such as methyl, cause no discernible *cis*/*trans* discrimination.

The two isomers can readily be separated by column chromatography (see Section 3), but also in the genuine product mixture the *cis*/*trans* ratio can easily determined by NMR: only the *cis*-isomers exhibit a long-range W-coupling of the two protons in the heterocyclic ring (H-2 and H-4), the ^4J coupling constant being 0.4 Hz independent of the substituent R.

If the formation of the product benzodioxinols was under thermodynamic control, an equilibrium between intermediate **3** and the respective product would exist, with the product ratio being determined by the thermodynamic stability of the diastereomers. Table 2 lists the theoretical values for the diastereomeric ratios.[9] Comparison with the experimental values demonstrated clearly that the formation reaction proceeded under kinetic control: while computations predicted that the *trans*-isomer should be formed in large excess (if not exclusively) also in the case of **4**–**6** and **10**, considerable amounts of *cis*-isomer were obtained experimentally (*cf.* Table 1). Thus, under the reaction conditions used, the 3-oxa-chromanols, once formed, are stable and do not react back to intermediate **3**, so that an equilibrium between **3** and the products can be ruled out.

EPR measurements of 3-oxa-tocopherol derivatives produce well-resolved multi-line spectra, resulting from five different groups of 3,3,3,1, and 1 equiv. protons. The

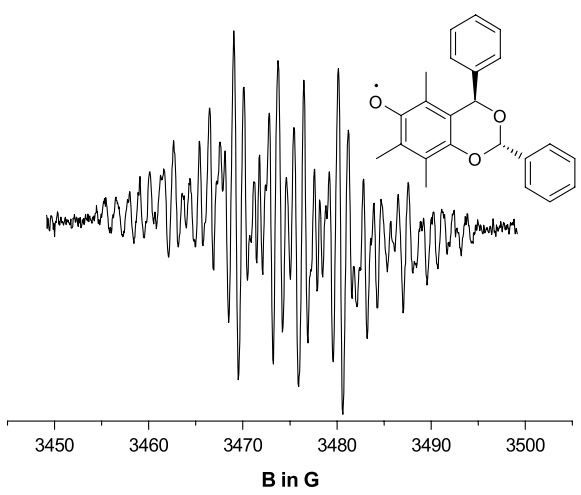

Figure 1. EPR spectrum of the phenoxyl radical derived from **9** in benzene/acetonitrile (v/v=10:1).

hyperfine couplings depend only weakly on the nature of the substituents R. Aromatic substituents, such as in **9** or **10**, increase the spin density at H-4 and H-2 and thus the splitting values for these protons. The hyperfine coupling constants of a(5a-CH_3)=6.0–6.5 G, a(7a-CH_3)=4.5–5.0 G, a(8b-CH_3)=0.9–1.2 G, and a(4-CH)=1.3–1.7 G, respectively, are quite similar to those measured for the α-tocopheroxyl radical.[10] Interestingly, also the proton at position 2 exhibits a comparatively large coupling of a(4-CH)=0.8–1.7 G, which illustrates spin delocalization also onto this rather 'remote' position, and consequently indicates increased stability of the radicals.[11] Figure 1 gives a representative spectrum of diphenyl derivative **9**.[12]

3. Experimental

Chemicals were purchased from commercial suppliers and used without further purification. Thin layer chromatography (TLC) was performed on silica gel 60 plates (5×10 cm, 0.25 mm) with fluorescence detection under UV light at 254 nm. Flash column chromatography was performed on silica gel G60 (40–63 μm). Melting points, determined on a Kofler-type micro hot stage with Reichert-Biovar microscope, are uncorrected. ^{1}H NMR spectra were recorded at 300 MHz, ^{13}C NMR spectra at 75.47 MHz with $CDCl_3$ as the solvent and TMS as the internal standard, if not stated otherwise. Data are given in ppm. ^{13}C peaks were assigned by means of APT, HMQC and HMBC spectra. FT-IR spectra were recorded on a Bruker Equinox-55 spectrometer using the KBr technique, data are given in cm^{-1}. EPR measurements were carried out on a Bruker ESP 300 and a TM cavity with the following instrument settings: 9.76 GHz microwave frequency, 20 mW microwave power, 3474 G center field, 50 G sweep, 0.5 G modulation amplitude, 1×10^6 receiver gain, 17.9 G/min scan rate, 0.167 s time constant, six scans, at a temperature of 298 K.

3.1. EPR measurement of phenoxyl radicals

The 3-oxa-chromanol derivatives (50 mM) were dissolved in benzene or benzene/acetonitrile (v/v=10:1). Oxygen was carefully removed by flushing with nitrogen. The samples were transferred into a quartz flat cell and were irradiated inside the EPR cavity by a high-pressure mercury UV lamp.

3.2. General preparation procedure for 3-oxa-chromanols

To a solution of the 2,3,5-trimethylhydroquinone (**2**) in glacial acetic acid and conc. HCl 2 equiv. of aldehyde were added via a syringe or a dropping funnel while stirring at 3–5°C. After stirring for 2 h at 4°C, the reaction mixture was poured into ice-water. The precipitated products were thoroughly washed with water and dried in vacuo. If no product was precipitated, the aqueous phase was repeatedly extracted with Et_2O. The combined organic phases were washed sequentially with water, saturated $NaHCO_3$ solution and water, dried over $MgSO_4$, and the solvent was removed in vacuo. The crude product was purified by column chromatography (EtOAc/toluene, v/v=1:10) and were obtained as a mixture of *cis*- and *trans*-isomers. Separation of the isomers was carried out on neutral aluminum oxide (Brockmann grade 1) with toluene as the eluent, or on silica gel with EtOAc/toluene (v/v=15:1) as the eluent.

3.2.1. 2,4,5,7,8-Pentamethyl-4*H*-1,3-benzodioxin-6-ol (4). 1,3-Benzo-dioxin-6-ol **4** was prepared as a white solid (0.59 g, 78%, *cis*/*trans*=1:1) according to the general procedure employing TMHQ (0.50 g, 3.29 mmol) and acetaldehyde (0.29 g, 6.60 mmol).

trans-Isomer. ^{1}H NMR: δ 1.48 (d, 3H, ^3J=6.2 Hz, $^{2a}CH_3$), 1.55 (d, 3H, ^3J=5.1 Hz, $^{4b}CH_3$), 2.12; 2.15; 2.18 (3×s, 3×3H, C^{Ar}–CH_3), 4.36 (s, 1H, OH), 4.95 (q, 1H, ^3J=5.1 Hz, ^{4}CH), 5.23 (q, 1H, ^3J=6.2 Hz, ^{2}CH). ^{13}C NMR: δ 11.7; 12.2; 12.7 ($^{5a}CH_3$, $^{7a}CH_3$ $^{8b}CH_3$), 20.8 ($^{4b}CH_3$); 21.1 ($^{2a}CH_3$); 71.2 (^{4}CH), 95.6 (^{2}CH), 116.4; 121.3; 122.2; 122.9; 145.8; 146.2 (^{Ar}C). IR: 3430, 2987, 1415, 1255, 1097. Mp=124–125°C. Anal. calcd for $C_{13}H_{18}O_3$ (222.29): C, 70.25; H, 8.16. Found: C, 70.31; H, 8.08.

cis-Isomer. ^{1}H NMR: δ 1.55 (d, 3H, ^3J=6.6 Hz, $^{2a}CH_3$), 1.56 (d, 3H, ^3J=5.1 Hz, $^{4b}CH_3$), 2.08; 2.14; 2.18 (3×s, 3×3H, C^{Ar}–CH_3), 4.32 (s, 1H, OH), 5.02 (dq, 1H, ^3J=6.6 Hz, ^4J=0.4 Hz, ^{2a}CH), 5.33 (dq, 1H, ^3J=5.1 Hz, ^4J=0.4 Hz, ^{4a}CH). ^{13}C NMR: δ 11.5; 11.6; 12.3 ($^{5a}CH_3$, $^{7a}CH_3$ $^{8b}CH_3$), 21.3 ($^{4b}CH_3$); 22.4 ($^{2a}CH_3$); 69.1 (^{4}CH); 89.6 (^{2}CH), 116.7; 121.8; 122.6; 123.2; 144.0; 146.6 (^{Ar}C). IR: 3432, 2991, 1398, 1257, 1095. Mp=129–132°C. Anal. calcd for $C_{13}H_{18}O_3$ (222.29): C, 70.25; H, 8.16. Found: C, 70.35; H, 8.05.

3.2.2. 2,4-Diethyl-5,7,8-trimethyl-4*H*-1,3-benzodioxin-6-ol (5). 1,3-Benzodioxin-6-ol **5** was prepared as a white solid (0.19 g, 78%, *cis*/*trans*=1:1.4) according to the general procedure employing TMHQ (0.15 g, 1.00 mmol) and propanal (0.15 g, 2.10 mmol).

trans-Isomer. ^{1}H NMR: δ 0.94 (t, 3H, CH_2–CH_3, ^3J=7.5 Hz), 1.01 (t, 3H, CH_2–CH_3, ^3J=7.4 Hz), 1.47 (m, 1H, CH_2–CH_3), 1.70 (m, 1H, CH_2–CH_3), 1.91 (m, 2H, CH_2–CH_3), 2.08; 2.11; 2.12 (3×s, 3×3H, C^{Ar}–CH_3), 4.18 (s, 1H, OH), 4.92 (t, 1H, ^{4}CH, ^3J=5.5 Hz), 5.21 (dd, 1H, ^{2}CH, ^3J=6.0 Hz). ^{13}C NMR: δ 7.4; 10.2 (2×CH_3 in Et), 11.8; 12.4; 12.5 ($^{5a}CH_3$, $^{7a}CH_3$ $^{8b}CH_3$), 28.5 (^{4}CH–CH_2–CH_3); 29.3 (^{2}CH–CH_2–CH_3); 70.4 (^{4}CH), 93.9 (^{2}CH), 116.2; 121.6; 122.0; 122.4; 145.4; 146.6 (^{Ar}C). Mp=95–96°C. IR: 3410, 2989, 1412, 1202. Anal. calcd for $C_{15}H_{22}O_3$ (250.34): C, 71.97; H, 8.86. Found: C, 71.85; H, 8.89.

cis-Isomer. ^{1}H NMR: δ 0.98 (t, 3H, CH_2–CH_3, ^3J=7.4 Hz), 1.03 (t, 3H, CH_2–CH_3, ^3J=7.4 Hz), 1.48 (m, 1H, CH_2–CH_3), 1.71 (m, 1H, CH_2–CH_3), 1.94 (m, 2H, CH_2–CH_3), 2.06; 2.12; 2.14 (3×s, 3×3H, C^{Ar}–CH_3), 4.55 (s, 1H, OH), 4.95 (ddd, 1H, ^{4}CH, ^3J=6.3 Hz, ^4J=0.6 Hz), 5.28 (ddd, 1H, ^{2}CH, ^3J=5.0 Hz, ^4J=0.6 Hz). ^{13}C NMR: δ 7.6; 10.0 (2×CH_3 in Et), 12.0; 12.3; 12.8 ($^{5a}CH_3$, $^{7a}CH_3$ $^{8b}CH_3$), 28.1 (^{4}CH–CH_2–CH_3); 29.4 (^{2}CH–CH_2–CH_3); 69.8 (^{4}CH); 90.1 (^{2}CH), 116.8; 121.8; 122.4; 123.6; 144.2; 146.7 (^{Ar}C). Mp=101°C. IR: 3415, 2993, 1410, 1246, 1054. Anal. calcd for $C_{15}H_{22}O_3$ (250.34): C, 71.97; H, 8.86. Found: C, 71.86; H, 9.05.

3.2.3. 2,4-Dipropyl-5,7,8-trimethyl-4*H*-benzo[1,3]dioxine-6-ol (6). 1,3-Benzodioxin-6-ol **6** was prepared as a

white solid (0.52 g, 59%, *cis*/*trans*=1:3.2) according to the general procedure from TMHQ 2 (0.50 g, 3.29 mmol) and butanal (0.47 g, 6.60 mmol). ^{1}H NMR: δ 0.89 (t, 3H, ^3J=7.5 Hz, $CH_2CH_2CH_3$), 1.00 (t, 3H, ^3J=7.5 Hz, CH_3), 1.45–1.98 (m, 8H, CH_2CH_2), 2.10 and 2.09 (2×s, 3H, C^{Ar}–CH_3), 2.12 and 2.11 (2×s, 3H, C^{Ar}–CH_3), 2.18 and 2.16 (2×s, 3H, C^{Ar}–CH_3), 4.74 (dd, 1H, ^3J=5.2 Hz, ^{4}CH), 4.71 and 4.78 (2×s, 1H, OH), 5.10 (dd, 1H, ^3J=5.2 Hz, ^{2}CH). ^{13}C NMR: δ 11.7 and 11.6 (^{5a}C), 12.3 and 12.2 (^{8b}C), 14.1 and 13.9 (^{7a}C), 18.9, 18.2, 17.6, and 17.5 ($CH_2CH_2CH_3$), 38.32, 36.9, 36.6, 36.5 (CH_2CH_2), 74.3 and 72.9 (^{4}CH), 98.6 and 92.3 (^{2}CH), 116.6 and 116.3 (^{7}C), 121.5 and 121.0 (^{5}C), 122.5 and 122.0 (^{8}C), 122.9 and 122.6 (^{4a}C), 145.7 and 144.2 (^{6}C), 147.1 and 146.5 (^{8a}C). Mp=76–78°C. IR: 3330, 2958, 2927, 2871, 1456, 1400, 1265, 1235, 1168, 1146, 1087, 1049, 995, 910. Anal. calcd for $C_{17}H_{26}O_3$ (278.39): C, 73.35; H, 9.41. Found: C 73.35; H 9.61.

3.2.4. 2,4-Diisopropyl-5,7,8-trimethyl-4*H*-benzo[1,3]-dioxin-6-ol (7). *trans-Isomer*. 1,3-Benzodioxin-6-ol **7** was prepared as a white solid (0.59 g (64%, *cis*/*trans*=1:26) according to the general procedure from **2** (0.50 g, 3.29 mmol) and 2-methyl-propanal (0.47 g, 6.60 mmol). ^{1}H NMR: δ 0.55 (d, 3H, CH(CH_3), ^3J=6.9 Hz), 1.00 (d, 3H, CH(CH_3), ^3J=6.9 Hz), 1.03 (d, 3H, CH(CH_3), ^3J=6.9 Hz), 1.10 (d, 3H, CH(CH_3)$_2$, ^3J=6.9 Hz), 1.96 (m, 2×1H, C*H*–(CH_3)$_2$), 2.03 (s, 3H, C^{Ar}–CH_3), 2.08 (s, 3H, C^{Ar}–CH_3), 2.12 (s, 3H, C^{Ar}–CH_3), 4.26 (s, 1H, OH), 4.40 (d, 1H, ^3J=4.8 Hz, ^{4}CH), 4.95 (d, 1H, ^3J=1.7 Hz, ^{2}CH). ^{13}C NMR: δ 11.7; 12.4; 12.5 (^{Ar}C–CH_3), 15.2; 17.1; 17.6; 20.3 (CH–(CH_3)$_2$), 33.0; 33.2 (2×CH(CH_3)$_2$), 78.2 (^{4}C), 102.0 (^{2}C), 116.8; 121.6; 122.5; 123.0; 146.8; 148.2 (C^{Ar}). Mp=61–63°C. IR: 3499, 2962, 2928, 2870, 1458, 1390, 1259, 1084, 1038, 981, 901, 843. Anal. calcd for $C_{17}H_{26}O_3$ (278.39): C, 73.35; H, 9.41. Found: 73.19; H, 9.41.

3.2.5. 2,4-Dicyclohexyl-5,7,8-trimethyl-4*H*-1,3-benzodioxin-6-ol (8). *trans-Isomer*. 1,3-Benzodioxin-6-ol **8** was prepared as a white solid, (0.142 g, 64%, only *trans*) according to the general procedure from **2** (0.15 g, 1.00 mmol) and cyclohexanecarbaldehyde (0.24 g, 2.10 mmol). ^{1}H NMR: δ 1.42 (m, 10H), 2.08; 2.12; 2.14 (3×s, 3×3H, C^{Ar}–CH_3), 2.22 (m, 1H), 2.26 (m, 1H), 4.36 (s, 1H, OH), 4.58 (d, 1H, ^3J=4.8 Hz, ^{4}CH), 5.05 (d, 1H, ^3J=2.2 Hz, ^{2}CH). ^{13}C NMR: δ 11.7; 12.1; 12.6 (3×s, 3×3H, $C^{Ar}CH_3$), 22.3 (d.i.), 22.8 (d.i.), 24.8 (d.i.), 24.9 (d.i.), 26.9, 27.3, 33.4 (^{2}CH–*C*H), 36.5 (^{4}CH–*C*H); 75.9 (^{4}CH), 101.3 (^{2}CH), 116.3; 121.5; 122.5; 122.8; 145.4; 146.5 (^{Ar}C). Mp=61–63°C. IR: 3460, 2958, 2928, 1390, 1255, 1132, 1018, 980, 831. Anal. calcd for $C_{23}H_{34}O_3$ (358.53): C, 77.05; H, 9.56. Found: C, 76.93; H, 9.68.

3.2.6. 5,7,8-Trimethyl-2,4-diphenyl-4*H*-1,3-benzodioxin-6-ol (9). *trans-Isomer*. 1,3-Benzodioxin-6-ol **9** was prepared as a white solid (2.80 g, 81%, only *trans*) according to the general procedure using **2** (10 mmol, 1.52 g) and benzaldehyde (2.33 g, 22 mmol). ^{1}H NMR: δ 1.54 (s, 3H, CH_3), 2.18 (s, 6H, 2×CH_3), 4.32 (s, b, OH), 5.71 (s, 1H, ^{4}CH), 5.96 (s, 1H, ^{2}CH), 7.28 (m, 8H, ^{Ar}CH), 7.42 (m, 2H, ^{Ar}CH). ^{13}C NMR: δ 11.8; 11.9; 12.4 (q, C^{Ar}–CH_3); 75.6 (^{4}CH), 92.3 (^{2}CH), 117.1 (^{5}C), 117.5 (^{4a}C), 123.0 (^{7}C), 123.2 (^{8}C), 126.3 (d.i.); 128.3 (d.i.); 128.5; 128.6 (d.i.); 129.0; 129.4 (d.i., ^{Ar}CH in Ph); 138.0 (^{2a}C in Ph), 140.4 (^{4b}C in Ph), 145.2 (^{8a}C), 145.9 (^{6}C). Mp=165–167°C. IR: 3470, 1452, 1382, 1274, 1248, 10012, 700. Anal. calcd for $C_{23}H_{22}O_3$ (346.6): C, 79.74; H, 6.40. Found: C, 79.51; H, 6.27.

3.2.7. 2,4-Bis(4-nitrophenyl)-5,7,8-trimethyl-4*H*-benzo[1,3]-dioxin-6-ol (10). *trans-Isomer*. 1,3-Benzodioxin-6-ol **10** was prepared as yellow crystals (2.27 g, 52%) according to the general procedure using **2** (10 mmol, 1.52 g) and 4-nitro-benzaldehyde (3.32 g, 22 mmol). ^{1}H NMR (DMSO-d_6): δ 1.69 (s, 3H, CH_3), 2.13 (s, 3H, CH_3); 2.16 (s, 3H, CH_3), 3.65 (s, b, OH), 5.77 (s, 1H, ^{4}CH), 6.27 (s, 1H, ^{2}CH), 7.55 (d, 1H, ^{Ar}CH), 7.70 (d, 2H, ^{Ar}CH), 8.00 (s, 1H, ^{Ar}CH), 8.20 (m, 4H, ^{Ar}CH). ^{13}C NMR: δ 11.8; 12.6; 13.1 (C^{Ar}–CH_3); 73.9 (^{4}CH), 91.2 (^{2}CH), 116.0 (^{5}C), 119.4 (^{4a}C), 122.2 (^{7}C), 124.0 (d.i., ^{Ar}CH in Ph), 125.7 (^{8}C), 128.1 (q.i., ^{Ar}CH in Ph), 130.6 (d.i., ^{Ar}CH in Ph), 143.8 (^{2a}C in Ph), 144.0 (^{4b}C in Ph), 147.2 (^{8a}C), 147.3 (C–NO_2), 147.7 (^{6}C), 148.2 (C–NO_2). Mp=157–160°C. IR: 3533, 2912, 2852, 1609, 1516, 1456, 1348, 1257, 1092, 1045, 856, 837 (isomer mixture). Anal. calcd for $C_{23}H_{20}N_2O_7$ (436.43): C, 63.30; H, 4.62; N, 6.42. Found: C, 63.32; H, 4.83; N, 6.16.

cis-Isomer. ^{1}H NMR (DMSO-d_6): δ 1.63 (s, 3H, CH_3), 2.11 (s, 3H, CH_3); 2.13 (s, 3H, CH_3), 3.88 (s, b, OH), 6.17 (s, 1H, ^{4}CH), 6.47 (s, 1H, ^{2}CH), 7.52 (d, 1H, ^{Ar}CH), 7.80 (d, 2H, ^{Ar}CH), 7.93 (s, 1H, ^{Ar}CH), 8.22 (m, 4H, ^{Ar}CH). ^{13}C NMR: δ 11.7; 13.0; 13.2 (C^{Ar}–CH_3); 77.1 (^{4}CH), 96.3 (^{2}CH), 119.4; (^{5}C), 119.9 (^{4a}C), 122.5 (^{7}C), 123.9 (q.i., ^{Ar}CH in Ph), 125.3 (^{8}C), 127.89 (d.i., ^{Ar}CH in Ph); 130.1 (d.i., ^{Ar}CH in Ph); 143.8 (^{2a}C in Ph), 145.6 (^{4b}C in Ph), 147.5 (^{8a}C), 147.9 (^{6}C), 148.2 (C–NO_2), 148.3 (C–NO_2). Mp=143–145°C. Anal. calcd for $C_{23}H_{20}N_2O_7$ (436.43): C, 63.30; H, 4.62; N, 6.42. Found: C, 63.54; H, 4.81; N, 6.22.

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8. Preparation and properties of the basis compound without substituents in the dioxinol moiety will be reported elsewhere. This compound is not accessible by condensation with formaldehyde (formaline) according to the general procedure, which in this case leads to complex mixtures containing 1,3,4, 5,6,8-hexamethyl-9*H*-xanthene-2,7-diol as the only identifiyable compound.
9. The energies of formation were calculated by DFT methods (B3LYP/6-31G*), based on PM3 starting geometries. Under the assumption of fast equilibria, the calculated difference in formation energies $\Delta(\Delta E)$ gives the equilibrium ratio of *trans*- and *cis*-isomer: $N_{cis}/N_{trans}=\exp(-\Delta(\Delta E)/RT)$.
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11. DFT computations on the B3LYP/6-311+G* level corroborate this result; the ratio of the computed spin densities (ρ(5a)/ρ(2)=3.85) agrees with the ratio of the hyperfine splitting constants (a(5a-CH_3)/a(2-CH)=3.89), as follows from the McConnell equation.
12. The spectrum can be best reconstructed with following couplings: a(5a-CH_3)=6.11 G, a(7a-CH_3)=4.70 G, a(8b-CH_3)=0.97 G, a(4-CH)=2.46 G, a(2-CH)=1.57 G (g=2.008218).