Synthesis and Oxidation Behavior of 2,4,5,7,8-Pentamethyl-4*H*-1,3-benzodioxin-6-ol, a Multifunctional Oxatocopherol-Type Antioxidant

Thomas Rosenau,*[,†] Antje Potthast,[†] Thomas Elder,[‡] Thomas Lange,[†] Herbert Sixta,[§] and Paul Kosma[†]

Institute of Chemistry, Christian-Doppler Laboratory, University of Agricultural Sciences, Muthgasse 18, A-1190 Vienna, Austria, School of Forestry and Wildlife Sciences, Auburn University, Auburn, Alabama 46849, and Lenzing AG, R & D Dept., A-4860 Lenzing, Austria

trosenau@edv2.boku.ac.at

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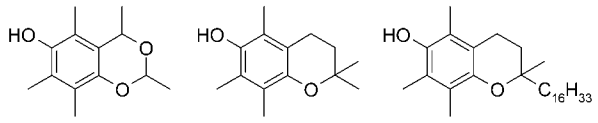
2,4,5,7,8-Pentamethyl-4*H*-1,3-benzodioxin-6-ol (PBD, **1**) is a novel 3-oxa-tocopherol-type stabilizer, which is obtained as a mixture of two diastereomers by condensation of trimethylhydroquinone with acetaldehyde in an acid-catalyzed reaction. The oxidation behavior of **1** is governed by the amount of water available. In aqueous media, **1** is oxidized by one oxidation equivalent to 2,5-dihydroxy-3,4,6-trimethylacetophenone (**3**) via 2-(1-hydroxyethyl)-3,5,6-trimethylbenzo-1,4-quinone (**2**). The acid-catalyzed conversion of **2** into **3** proceeds in solution with first-order kinetics with regard to **2** but works also in solid phase. Oxidation in the presence of just 1 equiv of water produces acetophenone **3** as well, but according to a different mechanism involving *o*-quinone methide **5** and styrene derivative **6**, from which finally acetaldehyde is released. A [1,5]-sigmatropic proton shift from the C-4a methyl group to the exocyclic methylene group in **5** causes formation of **6**, as demonstrated by labeling experiments. In addition, the presence of both intermediates was proven by hetero-Diels−Alder trapping reactions. In the absence of water, oxidation of **1** produces chromenone **10** via the intermediates **5** and **6** and chromanone **9**, and oxidation of **9** to **10** is preferred to oxidation of starting material **1**. When the formation of an exocyclic methylene group at C-4 is impossible as a result of structural prerequisites, as in the diphenyl derivative **12**, the initially generated *o*-quinone methide **5** cannot form **6** but undergoes dimerization to spiro-compounds. The transformation of *p*-quinone **2** into acetophenone **3** might contribute to the chemistry of tocopherols oxidized at C-4, i.e., 4-hydroxy-α-tocopherol and 4-oxo-α-tocopherol, which have been proposed as precursors of natural vitamin E metabolites.

Introduction

2,4,5,7,8-Pentamethyl-4*H*-1,3-benzodioxin-6-ol (PBD, **1**) is a novel 3-oxa-tocopherol-type stabilizer. It shows high antioxidative effectiveness and is distinguished by a higher hydrophilicity as compared to that of 2,2,5,7,8-pentamethyl-6-chromanol (PMC), the most commonly applied model compound for α-tocopherol (vitamin E, **3**).[1] PBD is currently being tested as stabilizer in the Lyocell process, which is a modern, environmentally benign industrial route toward production of cellulosic fibers. To obtain Lyocell fibers, native cellulose pulp is dissolved in *N*-methylmorpholine-*N*-oxide monohydrate (NMMO) to produce a dope, which is simply spun into water. Addition of stabilizers to the dope is crucial to minimize homolytic and heterolytic side reactions of NMMO and cellulose, which might cause cellulose degradation, discoloration of the resulting fibers, and decreased fiber performance. An optimum stabilizer would be hydrophilic and thus readily miscible with the dope, and it should act both as a traditional phenolic antioxidant, which scavenges radicals and minimizes homolytic reactions, and as a formaldehyde trap, which limits the heterolytic decomposition processes.[2] The observation of PBD being both an efficient radical trap and a source of acetaldehyde, which is an efficient HCHO scavenger under Lyocell conditions, made it a promising candidate for further testing,[3] and gave impetus to study its oxidation behavior in more detail.



PBD, **1** PMC α-tocopherol

The oxidation behavior of PBD turned out to be much more complex than assumed at a first glance, providing some new insight into the chemistry of substituted trimethylhydroquinones and the closely related tocopherol family. Especially intriguing are the parallels in the chemical behavior of PBD derivatives and tocopherols oxygenated at C-4, possibly indicating that PBD and its oxidation products are well-suited as model

[†] University of Agricultural Sciences.
[‡] Auburn University.
[§] Lenzing AG.

(1) For a general review on chromans and tocopherols, see: Parkhurst, R. M.; Skinner, W. A. *Chromans and Tocopherols* in *Chemistry of Heterocyclic Compounds*; Ellis, G. P., Lockhardt, I. M., Eds.; Wiley: New York, 1981; Vol. 36.

(2) For the chemistry of side reactions in the Lyocell systems, see: Rosenau, T.; Potthast, A.; Sixta, H.; Kosma, P. *Prog. Polym. Sci.* **2001**, *26*(9), 1763−1837.

(3) Results on the stabilizing efficiency will be reported elsewhere.

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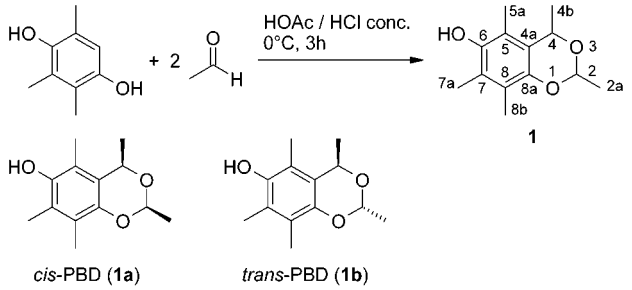
Scheme 1



compounds for the very labile and redox-sensitive vitamin E derivatives 4-hydroxy-α-tocopherol and 4-oxo-α-tocopherol. These two compounds have recently been proposed to be involved as precursors of natural vitamin E metabolites,[4] and they are of current interest due to possible mutagenicity.

Results and Discussion

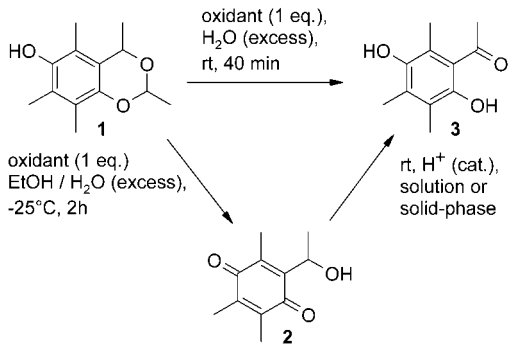
Synthesis. PBD was synthesized by treating trimethylhydroquinone with a double molar amount of acetaldehyde, in an acid-catalyzed reaction. The product was obtained as a mixture of two diastereomeres, *cis*- and *trans*-PBD, in an approximate ratio of 3:1 (Scheme 1). The two isomers can be separated by traditional column chromatography but can also be distinguished in a mixture by proton NMR spectroscopy, since only the *cis*-isomer shows a long-range W-coupling of the two protons in the heterocyclic ring. Both isomers behave identically in oxidation reactions, so that in nearly all experiments a mixture of both isomers was employed.

The formation of the 5,7,8-trimethyl-4*H*-1,3-benzodioxin-6-ols from trimethylhydroquinone and aldehydes is evidently governed by steric factors. Only the *trans*-isomers are obtained in the case of sterically more demanding substituents, for instance, when benzaldehyde or isobutyric aldehyde was used in the condensation reaction instead of acetaldehyde.

Oxidation in Aqueous Media. In aqueous media, i.e., either in water or in organic solvents containing water as the cosolvent, benzodioxinol **1** is oxidized by 1 equiv of a two-electron oxidant to 2,5-dihydroxy-3,4,6-trimethylacetophenone (**3**). This outcome is largely independent of the oxidant used. Ferric chloride, potassium permanganate, *N*-methylmorpholine-*N*-oxide, silver oxide, hydrogen peroxide, bromine and chromium(VI) salts all gave the same results.[5] Interestingly, it was observed that bromine acts similarly to the other oxidants, with no formation of 5a-bromo derivatives, in contrast to vitamin E chemistry.[6] The yields of the acetophenone in the oxidation reactions were generally in the 40% range.

Addition of an aldehyde scavenger, used to trap the acetaldehyde released upon oxidation, increased the isolated yields up to 85%. Although the oxidation appeared to be a clean and unambiguous conversion, its mechanism seemed puzzling at first glance, because the benzylic hydroxyl group was apparently more prone to oxidation than the hydroquinone structure. Later it was demonstrated that the initial reaction product is 2-(1-hydroxyethyl)-3,5,6-trimethylbenzo-1,4-quinone (**2**), as expected (Scheme 2). However, isolation of the dark red *p*-quinone in high yields requires working at lower temperature in aqueous ethanol followed by very quick workup under careful exclusion of acids. Under the usual conditions at room temperature, the conversion into **3** is too fast for the intermediate *p*-quinone **2** to be isolated. Nevertheless, its intermediacy must be assumed also in this case, since addition of oxidant always causes a very short-lived red coloration of the reaction mixture, which almost immediately gives way to the faint yellow color of acetophenone **3**.

Scheme 2



p-Quinone **2** is very readily converted into acetophenone **3**, a quite unusual reaction. Other structurally similar hydroquinone-derived acetophenones, especially 2,5-dihydroxyacetophenone, 2,5-dihydroxy-3,4-dimethylacetophenone, and 2,5-dihydroxy-4-nitro-acetophenone, cannot be obtained by rearrangement of the corresponding (1-hydroxyethyl)-quinones. The rearrangement seems to be a peculiarity of the 2-(1-hydroxyethyl)-3,5,6-trimethylbenzo-1,4-quinone (**2**)/2,5-dihydroxy-3,4,6-trimethylacetophenone (**3**) redox couple, since quinones with similar structure do not undergo the rearrangement.[7] The conversion proceeds rather slowly in organic solution and is largely independent of the solvent used, as long as acids and bases are carefully excluded. In a 5 M ethanolic solution, for instance, the reaction was completed within about 7 h. Acids have a very strong catalytic effect, with the addition of trifluoroacetic acid to the above solution (0.1% relative to **2**) increasing the reaction rate drastically so that full conversion is achieved in less than 13 min, as monitored by UV spectrometry. Correspondingly, bases retard the reaction, and *p*-quinone **2** can only be stored for longer periods of time if a small amount of base, preferably gaseous ammonia or triethylamine, has been added for stabilization.

Surprisingly, the reaction of the quinone **2** to acetophenone **3** does also proceed in solid phase. Under neutral conditions, the oily red *p*-quinone slowly starts to "crystallize" and is transformed overnight into a pale yellow, crystalline mass. Acids seem to be efficient catalysts also for the solid-phase reaction. This can be demonstrated very nicely by "inoculating" the *p*-quinone with a needle previously dipped into an acid, thereby initiating the spontaneous transformation, which spreads out from the

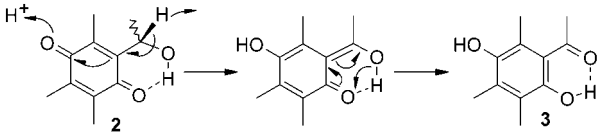
(4) a) Packer, L.; Fuchs, J. *Vitamin E in Health and Disease*; Marcel Dekker Inc.: New York, 1993. (b) Isler, O.; Brubacher, G. *Vitamins I*; Georg Thieme Verlag: Stuttgart, 1982; p 126.

(5) Besides the standard oxidants $KMnO_4$ and $K_2Cr_2O_7$, two classical oxidizing agents in tocopherol chemistry, $FeCl_3 \cdot 6H_2O$ and $AgNO_3$, were selected, along with NMMO and H_2O_2 as they play a crucial role in the Lyocell process.

(6) Rosenau, T.; Chen, C. L.; Habicher, W. D. *J. Org. Chem.* **1995**, *60*, 8120−8121.

(7) Compare also: (a) Novak, L.; Kovacs, P.; Szantay, C. *Synthesis* **1995**, *6*, 693−698. (b) Mizuguchi, E.; Suzuki, T.; Achiwa, K. *Synlett* **1996**, *8*, 743−744.

Scheme 3



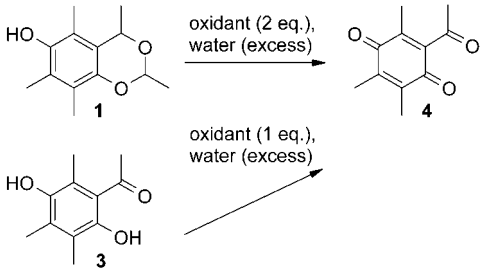
contact point and will be finished within a few minutes.[8] Both in solution and in solid phase, the conversion is a quantitative process. If pure starting material **2** is employed, acetophenone **3** will be obtained free of any byproducts.

The rate-determining step in the conversion of **2** into **3** is an intramolecular reaction, with intermolecular mechanisms being excluded since the reaction strictly follows a first-order kinetics with regard to **2**.[9] However, regarding the conversion merely as an intramolecular redox reaction seems problematic, as the oxidative power of a donor-substituted benzoquinone would not be sufficient to oxidize a benzylic hydroxyl group. Even though the strong hydrogen bond of the benzylic hydroxyl to the quinone carbonyl facilitates the reaction by preorganizing the transition state geometry, this contribution should be of minor influence only. Moreover, assuming a simple intramolecular redox process cannot explain why the reaction occurs exclusively with the trimethyl-substituted 1-hydroxyethyl-benzoquinone.

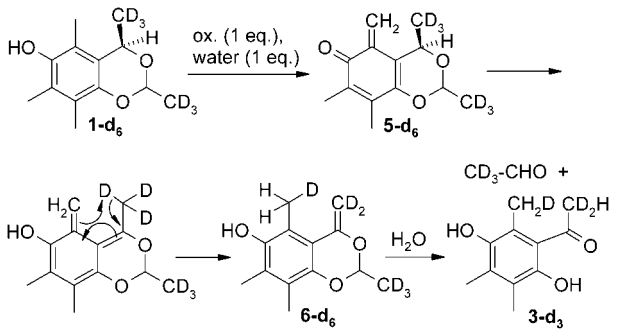
A second possible explanation for the reaction mechanism is a [1,5]-sigmatropic proton shift in which the benzylic proton is transferred to the 4-oxygen of the quinone to form the phenolic OH group (Scheme 3). Conceivably, protonation at the position 4 carbonyl oxygen, the most nucleophilic position, favors formation of an intermediate *o*-quinone methide involving C-2. This *o*-quinone methide would immediately rearrange to acetophenone **3**, whose spatial structure is already preformed by the strong hydrogen bond (Scheme 3). This process, driven by rearomatization, is apparently very fast, so that all attempts to trap the *o*-quinone methide in a hetero-Diels−Alder reaction failed. Unfortunately, deuteration experiments combined with NMR spectroscopy are also unsuitable as a means of monitoring. Since the oxidative pathway described requires the presence of water, there is immediate H−D exchange for phenolic hydroxyls so that the actual rearrangement cannot be followed. In summary, oxidation of PBD **1** in aqueous media with 1 equiv of oxidant always produces acetophenone **3**, formed via the *p*-quinone **2**.

Results for heats of formation and reaction from PM3 calculations on the mechanism proposed in Schemes 2 and 3 indicate considerable exothermicity in the overall reaction. The initial oxidation ($\Delta H = -62.6$ kcal/mol) and final rearrangement step ($\Delta H = -18.6$ kcal/mol) contribute significantly to the stability.

Scheme 4



Scheme 5



The application of 2 equiv of a two-electron oxidant in an aqueous medium causes direct formation of 2-acetyl-3,5,6-trimethylbenzo-1,4-quinone (**4**). The same product was obtained when **3** was further oxidized by one oxidation equivalent under identical reaction conditions (Scheme 4). It can therefore be assumed that the direct oxidation of **1** to **4** proceeds via acetophenone **3**.

Oxidation in the Presence of 1 Equiv of Water. Working in the presence of a limited amount of water—1 or up to 2 equiv of H_2O relative to **1**—caused the reaction mechanism to change, no matter if polar or less polar solvents were used. The *p*-quinone **2** is no longer obtained as a reaction intermediate, but the oxidation still generates acetophenone **3** as the final product. The reaction proceeds now via *o*-quinone methide **5** as the initial intermediate, and styrene derivative **6** as a second intermediate, as shown in Scheme 5.

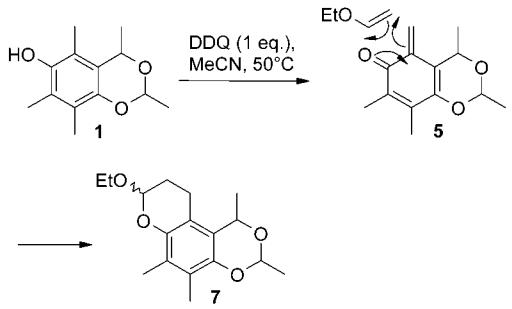
The occurrence of **5** and **6** was indirectly demonstrated by experiments with selectively deuterated PBD (**1**-d_6), which was synthesized from deuterated acetaldehyde, CD_3−CHO. Upon oxidation of this material in the presence of 1 equiv of water, one deuterium was selectively transferred to the 5a-methyl group at the aromatic ring. At the same time, a hydrogen was introduced into the methyl group at C-4b. This outcome is indicative of the occurrence of both *o*-quinone methide **5** and styrene derivative **6**. The deuterium atoms of the dideuterioacetyl group in **3**-d_3 exhibit, in aqueous solution, only a very slow H−D exchange. This, apart from the NMR shift data, is another indication of a strong intramolecular hydrogen bridge in **3**, which largely prevents keto−enol tautomerism by "anchoring" the keto form. The CH_2D group at the ring is of course completely stable toward hydrolysis.

This mechanism has also been followed by PM3 calculations, with the initial oxidative step being less exothermic ($\Delta H = -48.9$ kcal/mol) than for the *p*-quinone mechanism ($\Delta H = -62.6$ kcal/mol) in Scheme 2. Although the rearrangement from the *o*-quinone methide **5** to the styrene **6** is quite exothermic ($\Delta H = -11.3$ kcal/mol), the

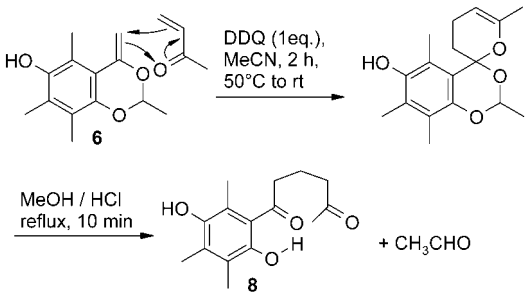
(8) As the diffusion of the acid is very limited in the highly viscous oil **2**, a transport similar to the Grotthus mechanism for the charge transfer in water must be assumed. On the basis of the assumption that, especially in solid state, strong intermolecular H-bonds exist, the protons would make intensive use of this intermolecular H-bridge network to achieve an effective transport over longer distances without undergoing considerable movement themselves. The proton released from the benzylic position of one molecule of **2** upon conversion into **3** would be used to protonate the next molecule of **2**.

(9) The conversion of **2** into **3** follows a second-order rate law: $d[\mathbf{3}]/dt = k[\mathbf{2}][H^+]$. At a pH of 0 and 1 (1 and 0.1 M HCl) k' was determined to be 1.8×10^{-5} and 1.8×10^{-6} M^{-1} s^{-1}, respectively, giving a kinetic rate konstant of $k = 1.83 \times 10^{-5}$ s^{-1}. It appears reasonable to assume that the reaction is composed of a reversible protonation of **2**, followed by unimolecular decomposition of **2**-H^+: **2** + H^+ ⇄ **2**-H^+ → **3** + H^+.

Scheme 6



Scheme 7



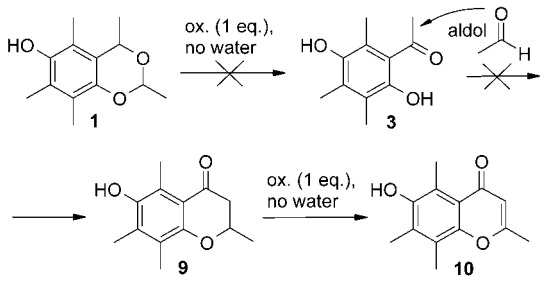
heat of reaction from **1** to **6** is still less than that of the conversion of **1** to **2**, as previously indicated.

The occurrence of **5** was also demonstrated by trapping **5** in a hetero-Diels−Alder reaction, which afforded pyranobenzodioxin **7** as the product (Scheme 6). Ethyl vinyl ether was used both as the cosolvent and as the electron-rich dienophilic trapping agent, according to a procedure established for the trapping of the structurally similar *o*-quinone methide of α-tocopherol.[10]

Trapping by means of a hetero-Diels−Alder reaction was also applied to verify the involvement of intermediate **6** in the oxidation mechanism. Methyl vinyl ketone, acting as diene and cosolvent, produced a primary tricyclic addition product[11] that was not isolated but hydrolyzed to hexanedione derivative **8** (Scheme 7). The styrene derivative **6**, which can also be regarded as an enol ether, is energetically favored by rearomatization and appeared to be a relatively stable compound, which under normal oxidation conditions adds water to produce acetophenone **3** with simultaneous release of acetaldehyde.

According to the mechanism in Scheme 5, 1 equiv of water is needed to release acetaldehyde from the enol ether **6**. The final oxidation product, namely, acetophenone **3**, is the same as the one observed under aqueous condition, but its formation mechanism is different. The formation of **5** as a primary intermediate in oxidation reactions finds its analogue in the formation of the *o*-quinone methide of α-tocopherol, a very frequently observed intermediate in vitamin E chemistry.[12] However, while the vitamin E derived intermediate readily undergoes dimerization to form the spiro-dimer of α-tocopherol, the corresponding process was not observed for the structurally similar *o*-quinone methide **5**. For **5**, hydrogen abstraction from C-4b and formation of **6** is apparently more favored than dimerization under formation of a spiro-product.[13]

Scheme 8



Oxidation in the Absence of Water. Oxidation of PBD in carefully dried solvents with 1 equiv of a two-electron oxidant consistently gave conversions approaching 50%. Obviously, a four-electron oxidation was taking place, with half of the starting material being left unchanged. The use of the double amount of oxidant increased the isolated yield to 85%. One main product was obtained, which still retained the phenolic character as seen by IR spectroscopy. The oxidation product was identified as chromenone **10** by NMR spectroscopy; its formation mechanism remained initially unclear, however. Our first proposal involved an initial two-electron oxidation step to acetophenone **3**, which would subsequently undergo an aldol addition with the released acetaldehyde to form chromanone **9**. Chromanone **9** would thereafter be further oxidized to the chromenone product **10** in a second two-electron oxidation (Scheme 8).

However, the suggested pathway had to be ruled out for two reasons. First, acetaldehyde cannot be liberated without water being present, rendering participation of free CH_3CHO in a "regular" aldol reaction impossible as the cause for the formation of **9** and **10**. Second, isolated acetophenone **3** does not react with acetaldehyde, even if it were present, to give the chromanone **9** under the prevailing reaction conditions, no matter if oxidants are present or not. Thus, this step also cannot be involved in the formation of **10** from PDB. Obviously, generation of the chromanone **9** is the reaction path that is always taken when the absence of water prevents the release of acetaldehyde. This again proved the crucial role of water in governing the oxidation behavior of PBD.

For the actual reaction mechanism it seems plausible to assume that again the intermediates **5** and **6** are formed, analogous to the mechanism shown in Scheme 5. For this step, 1 equiv of a two-electron oxidant is required. As the absence of water prevents the formation of acetaldehyde, an alternative reaction path is needed. Ring opening by heterolytic cleavage of the weak acetal bond produces a zwitterionic intermediate **11**. Rotation

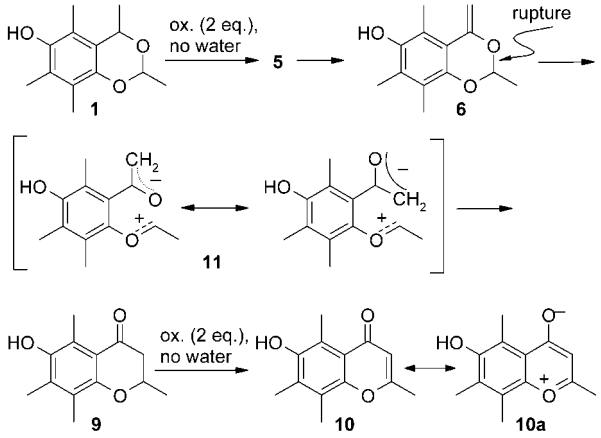
(10) Rosenau, T.; Habicher, W. D. *Tetrahedron* **1995**, *51*, 7919−7926.

(11) NMR of the crude product shows characteristic resonances of the spiro-carbon at 102.4 ppm and of the enol carbons, so that a possible formation of **8** simply by addition of methyl vinyl ketone to **3** can be excluded.

(12) Compare ref 1 and Machlin, L. J. *Vitamin E: A Comprehensive Treatise*; Marcel Dekker Inc.: New York, 1980. For trapping of the *o*-quinone methide of α-tocopherol, see: (a) Bolon, D. A. *J. Org. Chem.* **1970**, *35*, 3666−3671. (b) Rosenau, T.; Potthast, A.; Habicher, W. D.; Kosma, P. *Synlett* **1999**, *3*, 291−294.

(13) DFT calculations (pBP/DN**) show that the HOMO−LUMO gap in the *o*-quinone methide derived from the vitamin E model 2,2,5,7,8-pentamethylchroman-6-ol (ΔE_{QME}) is significantly smaller than that in *o*-quinone methide **5** (ΔE_{PBD}): $\Delta E_{PBD} - \Delta E_{QME} = 0.306$ eV for **5** derived from *cis*-PBD (**1a**) and 0.309 eV for **5** derived from *trans*-PBD (**1b**). This explains why the dimerization to spiro-compounds, which is a hetero-Diels−Alder reaction with inverse electron demand and thus requires HOMO−LUMO interaction according to the classical frontier orbital theory, is preferred for the former intermediate, whereas it is less favored for the latter.

Scheme 9



of the enolate group and recombination of the charges generates chromanone **9**, which is immediately further oxidized to the product chromenone **10**, consuming the second equivalent of oxidant (Scheme 9). By means of independently prepared **9** [14] it was demonstrated that the last reaction step, dehydrogenation of chromanone **9** to chromenone **10**, does indeed readily proceed under the reaction conditions used. As mentioned above, use of only 1 equiv of a two-electron oxidant gives only a 50% conversion to chromenone **10**, with half of the starting material remaining unchanged. The dehydrogenation of the chromanone must consequently be preferred over the oxidation of PBD under the strictly nonaqueous conditions used. Oxidation of **1**-d_6 produces the pentadeuterated chromenone **10**-d_5 with a 2a-trideuteriomethyl group and a deuterium at each C-3 and C-5a. The latter deuteration position is again an indication of the involvement of the unsaturated intermediates **5** and **6**; cf. Schemes 5 and 9.

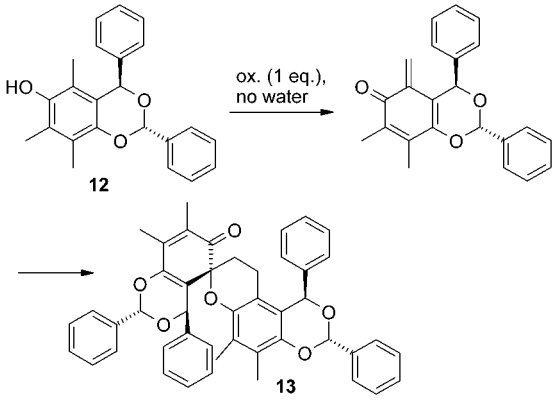
At a first glance, intermediate **11** would be regarded as rather labile, especially in less polar solvents that are unable to stabilize the charges. However, the negative charge is stabilized by a carbanion-enolate resonance, the positive charge by the neighboring electron pairs of the phenolic oxygen. The stabilization gained is obviously large enough to achieve a sufficiently long lifetime to allow rotation of the enolate group followed by bond formation.

Derivatization of the carbonyl group in **10**, e.g., as phenylhydrazone, fails, and precipitation as pyrylium salt, for instance, by tetrafluoroborate or perchlorate, occurs very readily. This indicates that the γ-pyrone ring in **10** is additionally stabilized by resonance, namely, participation of the pyrylium form **10a** (Scheme 9).

PM3 energetic results for the mechanisms proposed in Scheme 9 show that the rupture of the acetal bond in **6** is, as was expected, quite facile. The rotation of the resulting enolate group and subsequent reformation of the carbon−carbon bond, however, provides considerable stabilization ($\Delta H = -21.0$ kcal/mol). It can also be seen that the final reaction with the second oxidizing equivalent is quite exothermic ($\Delta H = -72.1$ kcal/mol).

5,7,8-Trimethyl-4*H*-1,3-benzodioxin-6-ol derivatives that are unable to form an exocyclic double bond extending from C-4 are initially oxidized to an *o*-quinone methide similar to **5**. Since formation of a styrene derivative analogous to **6** is impossible, dimerization in a hetero-Diels−Alder reaction becomes the only viable reaction

Scheme 10



path, so that the resulting spiro-dimers are obtained in quantitative yields. This was shown for 5,7,8-trimethyl-2,4-diphenyl-4*H*-1,3-benzodioxin-6-ol (**12**), which was neatly oxidized in nonaqueous media to spiro-dimer **13**, with both acetal structures remaining intact during the whole process; cf. Scheme 10.

Since similar dimerizations were not observed with material able to form derivatives such as **6**, it must again be concluded that proton transfer, leading from *o*-quinone methide **5** to styrene derivative **6**, is largely preferred over dimerization of **5** to the spiro-product. Only if the proton-transfer pathway is blocked, as it is in **12**, an alternative reaction path is entered.

Experimental Section

General. ^{1}H NMR spectra were recorded at 300 MH and ^{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 units. ^{13}C peaks were assigned by means of DEPT, HMQC, and HMBC spectra. Nomenclature and numbering of the carbon atoms in chromans and tocopherols as proposed by the IUPAC[15,16] have been used throughout. The abbreviation "d.i." denotes peaks from two equivalent carbons. IR spectra were recorded in KBr technique, and data are given in wavenumbers (cm^{-1}). Elemental analyses were performed at the microanalytical laboratory of the Institute of Physical Chemistry at the University of Vienna. All chemicals used were of reagent grade, and all solvents were of HPLC grade. Solvents were dried according to standard procedures, and *n*-hexane was dried over sodium metal.

Computational results reported throughout this paper were done on a Silicon Graphics-Indy workstation at Auburn University using PM3 semiempirical calculations[17] and DFT calculations as implemented through Spartan (Wavefunction Inc.), with full geometry optimization of each structure.

Synthesis of PBD (1). A suspension of trimethylhydroquinone (100 mmol, 15.22 g) in glacial acetic acid (200 mL) was cooled to 0 °C in a nitrogen atmosphere. Acetaldehyde (200 mmol, 8.81 g) and 20 mL of concentrated HCl were added, and the mixture was stirred for 3 h. The starting material dissolved, and a white solid started to precipitate. The reaction mixture was poured into ice water (1500 mL), stirred for 1 h, and filtered. The precipitate was washed with cold, aqueous acetic acid (50 mL) and water (250 mL) and was recrystallized from aqueous EtOH (1:1 v/v) to afford the product **1** as fine, colorless needles (17.34 g, 78%). Separation of the diastereomers was carried out by column chromatography on neutral

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aluminum oxide (Brockmann grade 1) with toluene as the eluent or on silica gel with toluene/EtOAc (15:1 v/v) as the eluent.

2,4,5,7,8-Pentamethyl-4*H*-1,3-benzodioxin-6-ol (3-Oxa-2,4,5,7,8-pentamethyl-4*H*-1,3-benzodioxin-6-ol), *trans*-Isomer (1a). ^{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). 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.

2,4,5,7,8-Pentamethyl-4*H*-1,3-benzodioxin-6-ol, (3-Oxa-2,4,5,7,8-pentamethyl-4*H*-1,3-benzodioxin-6-ol), *cis*-Isomer (1b). ^{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). Mp: 129−132 °C. IR: 3430, 2991, 1402, 1257, 1097. Anal. Calcd for $C_{13}H_{18}O_3$ (222.29): C, 70.25; H, 8.16. Found: C, 70.35; H, 8.05.

2,4-Bis(trideuteriomethyl)-5,7,8-trimethyl-4*H*-1,3-benzodioxin-6-ol (1-d_6). The labeled compound **1** was obtained (1.71 g, 75%) according to the above procedure with trimethylhydroquinone (10 mmol, 1.52 g) and 1,1,1-trideuterioacetaldehyde (20 mmol, 0.862 g) as the starting materials. ***trans*-Isomer (1a-d_6).** ^{1}H NMR: δ 2.12; 2.15; 2.18 (3 × s, 3 × 3H, ^{Ar}C−CH_3), 4.82 (s, 1H, OH), 4.92 (s, 1H, ^{4}CH), 5.27 (s, 1H, ^{2}CH). ^{13}C NMR: δ 11.7; 12.2; 12.7 ($^{5a}CH_3$, $^{7a}CH_3$ $^{8b}CH_3$); 20.4 (sept., $^{4b}CD_3$: $^1J_{CD}$ = 21.3 Hz); 20.6 (sept., $^{2a}CD_3$: $^1J_{CD}$ = 20.8 Hz); 71.0 (^{4}CH); 95.3 (^{2}CH); 116.3; 121.3; 122.1; 123.0; 145.6; 146.3 (^{Ar}C). Mp: 124 °C.

***cis*-Isomer (1b-d_6).** ^{1}H NMR: δ 2.08; 2.14; 2.18 (3 × s, 3 × 3H, C^{Ar}-CH_3), 4.98 (s, 1H, ^{4}CH), 5.00 (s, 1H, ^{2}CH), 5.19 (s, 1H, OH). ^{13}C NMR: δ 11.5; 11.6; 12.3 ($^{5a}CH_3$, $^{7a}CH_3$ $^{8b}CH_3$); 21.0 (sept., $^{4b}CD_3$: $^1J_{CD}$ = 21.3 Hz); 22.0 (sept., $^{2a}CD_3$: $^1J_{CD}$ = 20.6 Hz); 68.7 (^{4}CH); 89.3 (^{2}CH); 116.7; 121.7; 122.8; 123.3; 144.3; 146.6 (^{Ar}C). Mp: 130−132 °C. Anal. Calcd for $C_{13}H_{12}D_6O_3$ (228.22): C, 68.41; H (D), 7.95. Found: C, 68.24; H (D), 7.86.

General Procedure 1. Oxidation of PBD in Aqueous Media. Method A: Without Aldehyde Trapping. A solution of **1** (1 mmol, 0.222 g) in EtOH (2 mL) was diluted with water (10 mL). The oxidant (1 molar equiv of a two-electron oxidant in 10 mL of water) was added dropwise over a period of 10 min. The solution was stirred at room temperature for 30 min and extracted three times with CH_2Cl_2 (10 mL). The combined organic extracts were washed with 1 M H_2SO_4 (10 mL) and twice with water. Drying over $MgSO_4$, evaporation of the solvent, and chromatographic purification of the residue (silica gel, EtOAc) afforded acetophenone **3** as yellow powder. For yields and oxidants used see Table 1.

Method B: With Aldehyde Trapping. A solution of **1** (1 mmol, 0.222 g) and dimedone (3 mmol, 0.396 g) in EtOH (10 mL) was diluted with water (10 mL) and heated to 40 °C. The oxidant (1 molar equiv of a two-electron oxidant in 10 mL of water) was added dropwise over a period of 1 h. The solution was stirred for another hour, heated to 80 °C for 10 min, and cooled to room temperature. After addition of water (50 mL) and extraction with $CHCl_3$ (three times with 20 mL) the combined organic extracts were thoroughly washed with 1 M H_2SO_4 (10 mL) and three times with water. Drying over $MgSO_4$ and evaporation of the solvent provided a crude crystalline material, which was recrystallized from water/EtOH (5:1 v/v) to give pure **3** in yields of approximately 85% (Table 1).

1-(2,5-Dihydroxy-3,4,6-trimethylphenyl)-1-ethanone (2,5-dihydroxy-3,4,6-trimethyl-acetophenone, 3). ^{1}H NMR: δ 2.18 (s, 3H, ^{3}C−CH_3), 2.23 (s, 3H, ^{4}C−CH_3), 2.42 (s, 3H, ^{6}C−CH_3), 2.61 (s, 3H, CH_3−CO), 4.60 (s, b, 1H, OH), 11.65 (s, 1H, H-bonded OH). ^{13}C NMR: δ 12.0 (^{4}C−*C*H_3); 13.5 (^{3}C−*C*H_3); 15.9 (^{6}C−*C*H_3), 33.0 (*C*H_3−CO), 119.8 (^{6}C), 120.4 (^{1}C), 123.9 (^{3}C), 132.0 (^{4}C), 144.9 (^{5}C), 153.9 (^{2}C), 206.2 (CO). Mp: 110−113 °C. IR: 3444, 1608, 1360, 1311, 1186. Anal. Calcd for $C_{11}H_{14}O_3$ (194.22): C, 68.02; H, 7.26. Found: C, 68.24; H, 7.07.

Table 1. Oxidation of PBD in Aqueous Media, with (A) and without (B) Aldehyde Trapping

oxidant	method used	product [yield in %][a]
$FeCl_3 \cdot 6H_2O$	A	**3** [38]
$FeCl_3 \cdot 6H_2O$	B	**3** [85]
$FeCl_3 \cdot 6H_2O$	B[b]	**4** [86]
$KMnO_4$	A	**3** [32]
$KMnO_4$	B	**3** [68]
$KMnO_4$	B[b]	**4** [67]
$AgNO_3$	A	**3** [44]
$AgNO_3$	B	**3** [83]
$AgNO_3$	B[b]	**4** [81]
H_2O_2 *c*	A	**3** [44]
H_2O_2 *c*	B	**3** [82]
H_2O_2 *c*	B[b]	**4** [75]
$K_2Cr_2O_7$	A	**3** [38]
$K_2Cr_2O_7$	B	**3** [86]
NMMO[d]	B	**3** [81]
NMMO[d]	B[b]	**4** [81]

[a] Isolated yields (before chromatography [method A] or after recrystallization [method B]), averaged value in case of repeated syntheses. [b] 2 equiv of oxidant was used. [c] Washing with H_2SO_4 was omitted. [d] *N*-Methylmorpholine-*N*-oxide, reaction at 80 °C for 12 h.

2-Acetyl-3,5,6-trimethylbenzo-1,4-quinone (4). Applying general procedure 1 (method B), starting from 10 mmol of **1**, provided benzoquinone **4** as a red oil in 78% yield (1.50 g, averaged value). Two molar equivalents of oxidant was used, and heating to 80 °C for 10 min was omitted. ^{1}H NMR: δ 1.92; 1.94; 1.97; 2.15 (4 × s, 4 × 3H, CH_3).^{13}C NMR: δ 11.1; 11.8; 12.1 (CH_3), 28.0 (*C*H_3−CO), 139.4; 140.7; 140.8; 142.9 (C); 182.8; 184.5; 198.6 (C═O). Anal. Calcd for $C_{11}H_{12}O_3$ (192.21): C, 68.74; H, 6.29. Found: C, 68.92; H, 6.41.

2-(1-Hydroxyethyl)-3,5,6-trimethylbenzo-1,4-quinone (2). Benzodioxinol **1** (10 mmol, 2.222 g) was dissolved in a solvent mixture of EtOH (10 mL), H_2O (2 mL), and ethylene glycol (5 mL). The solution was cooled to −25 °C, and a solution of $FeCl_3$ hexahydrate (20 mmol, 5.400 g) in 10 mL of EtOH/H_2O (5:1 v/v) was added dropwise over a period of 10 min. The solution, which slowly turned red upon addition of the oxidant, was stirred at −25 °C for 2 h. Brine (20 mL) and $CHCl_3$ were added, and the mixture was intensively stirred for 2 min. After phase separation the organic layer was removed, washed with brine (10 mL) and twice with 1 M $NaHCO_3$ solution, and dried over anhydrous Na_2CO_3. After evaporation of the solvent, the residue was chromatographed on basic aluminum oxide with *n*-hexane as the eluent (CAUTION! The solvent is known to have neurotoxic effects!), giving *p*-benzoquinone **2** in a 87% yield (averaged value, 1.69 g). The synthesis was repeated several times, and the product was stored in an atmosphere containing gaseous ammonia. ^{1}H NMR: δ 1.38 (d, 3H, ^3J = 6.4 Hz, C*H*$_3$−CH), 1.92 (s, 3H, CH_3), 1.93 (s, 3H, CH_3), 1.96 (s, 3H, CH_3), 2.60 (s, b, 1H, OH), 4.47 (q, 1H, ^3J = 6.4 Hz, *H*C−CH_3).^{13}C NMR: δ 11.1; 12.0; 12.5 (CH_3), 23.1 (*C*H_3−CH), 66.8 (*C*H−CH_3), 139.5; 140.9; 141.0; 143.1, 187.2 (C═O), 189.0 (C═O). IR: 2976, 1643, 1375, 1259, 1099. Anal. Calcd for $C_{11}H_{14}O_3$ (194.22): C, 68.02; H, 7.26. Found: C, 68.24; H, 7.07.

General Procedure 2. Oxidation of PBD in the Presence of 1 Equiv of Water. Compound **1** (1 mmol, 0.222 g) was dissolved in acetonitrile (5 mL) containing exactly 1 mmol of water. One equivalent of a two-electron oxidant dissolved in acetonitrile (5 mL) was added dropwise over a period of 10 min at 50 °C. The solution was stirred for another 30 min, cooled to room temperature, and evaporated in vacuo. The solid residue was dissolved in EtOAc (2 mL) and chromatographed on neutral aluminum oxide with ethyl acetate as the eluent. Product **3** was obtained as yellow powder in yields between 68% and 82%, depending on the oxidant used (Table 2). Acetonitrile as the solvent can generally be substituted for THF. General procedure 2 was also applied for the oxidation of labeled PBD (**1**-d_6, 1 mmol, 0.23 g) with DDQ, producing 78% (0.15 g) of **3**-d_3.

Table 2. Oxidation of PBD to 3 with 1 Equiv of Water Present

oxidant	yield (%)[a]	remarks
chloranil[b]	72	
chloranil[b]	71	oxidation of **1**-d_6 to **3**-d_3
DDQ[c]	82	
DDQ[c]	78	oxidation of **1**-d_6 to **3**-d_3
Br_2	68	reaction at 0 °C for 30 min
H_2O_2·urea	73	in dry MeCN, no water added
$K_2Cr_2O_7$	68	
NMMO[d]	75	reaction in toluene at 110 °C for 4 h

[a] Isolated yields, averaged value in case of repeated syntheses. [b] Tetrachloro-1,4-benzoquinone. [c] 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone. [d] *N*-Methylmorpholine-*N*-oxide.

2-Dideutero-1-(2,5-dihydroxy-3,4-dimethylphenyl-6-deuteriomethyl)-1-ethanone (3-d_3). ^{1}H NMR: δ 2.18 (s, 3H, ^{3}C−CH_3), 2.23 (s, 3H, ^{4}C−CH_3), 2.42 (s, 2H, ^{6}C−CH_2D), 2.61 (s, 1H, CHD_2−CO), 4.60 (s, b, 1H, OH), 11.65 (s, 1H, H-bonded OH). ^{13}C NMR: δ 12.0 (^{4}C−*C*H$_3$); 13.5 (^{3}C−*C*H$_3$); 15.4 (t, ^{6}C−*C*H$_2$D, $^1J_{CD}$ = 16.5 Hz), 32.5 (quint, *C*HD_2−CO, $^1J_{CD}$ = 20.0 Hz), 119.6 (^{6}C), 120.5 (^{1}C), 123.9 (^{3}C), 132.1 (^{4}C), 145.0 (^{5}C), 153.7 (^{2}C), 206.0 (CO). Mp: 110−111 °C. Anal. Calcd for $C_{11}H_{11}D_3O_3$ (197.12): C, 67.02; H, 7.16. Found: C, 66.89; H, 7.12.

Trapping of *o*-Quinone Methide 5 with Ethyl Vinyl Ether. Compound **1a** (1 mmol, 0.222 g) was dissolved acetonitrile (2 mL) containing exactly 1 mmol of water. Freshly distilled ethyl vinyl ether (10 mL) was added, and the mixture was heated to 50 °C. A solution of DDQ (1 mmol, 0.227 g) in acetonitrile (5 mL) was added during 1 min. The solution was heated to 80 °C for 10 min and evaporated in vacuo. The residue was extracted with *n*-hexane (10 mL), and the solid remainder was discarded. The extract was filtered through a layer of basic aluminum oxide and evaporated to dryness, providing pyrano-benzodioxin **7** as colorless solid (23% relative to **1a**, 0.067 g).

7-Ethoxy-2,4,9,10-tetramethyl-4,5,6,7-tetrahydro-1,3,8-trioxa-phenanthrene (7). ^{1}H NMR: δ 1.15 (t, 3H, CH_3 in Et), 1.48 (d, 3H, J = 6.2 Hz, ^{2a}CH_3), 1.55 (d, 3H, J = 5.1 Hz, ^{4b}CH_3), 1.58 (m, 2H, ^{6}CH_2), 2.16 (s, 3H, ^{Ar}C−CH_3); 2.24 (s, 3H, ^{Ar}C−CH_3), 2.66 (m, 2H, ^{5}CH_2), 3.64 (m, 2H, CH_2 in Et), 4.95 (q, 1H, J = 5.1 Hz, ^{4}CH), 5.18 (t, 1H, ^{7}CH), 5.23 (q, 1H, J = 6.2 Hz, ^{2}CH). ^{13}C NMR: δ 12.0; 12.2 (^{Ar}C−*C*H$_3$), 15.6 (CH_3 in Et), 20.6 (^{4b}CH_3); 21.3 (^{2a}CH_3); 26.6 (^{6}CH_2), 34.7 (^{5}CH_2), 62.5 (CH_2 in Et), 71.8 (^{4}CH), 95.4 (^{2}CH), 96.2 (^{7}CH), 116.8; 121.1; 122.8; 122.9; 142.8; 145.2 (^{Ar}C). Mp: 32 °C. Anal. Calcd for $C_{17}H_{24}O_4$ (292.36): C, 68.16; H, 7.63. Found: C, 68.34; H, 7.70.

Trapping of Styrene 6 with Methyl Vinyl Ketone. PBD (1 mmol, 0.222 g) was dissolved in acetonitrile (2 mL) containing exactly 1 mmol of water. Methyl vinyl ketone (10 mL), which had been freshly distilled and kept over anhydrous Na_2CO_3, was added, and the mixture was heated to 50 °C. A solution of DDQ (1 mmol, 0.227 g) in acetonitrile (5 mL) was added at once. The solution was stirred for 2 h at 50 °C and cooled to room temperature. The solvents were removed in vacuo, and the waxy remainder was dissolved in MeOH (5 mL). Diluted HCl (2 M, 2 mL) was added, and the mixture was refluxed for 15 min. After neutralization with 1 M aqueous NaOH and addition of 10 mL of brine, the mixture was extracted with ethyl acetate (three times 15 mL). The extracts were combined, dried over $MgSO_4$, concentrated to a volume of about 3 mL, and chromatographed on silica gel with EtOAc/toluene (1:1 v/v), affording trapping product **8** as a colorless, viscous oil (64% relative to **1a**, 0.169 g).

1-(2,5-Dihydroxy-3,4,6-trimethylphenyl)-1,5-hexanedione (8). ^{1}H NMR: δ 1.99 (m, 2H, ^{3}CH_2), 2.15 (s, 3H, ^{Ar}C−C*H*$_3$), 2.25 (s, 3H, ^{Ar}C−C*H*$_3$), 2.33 (s, 3H, ^{Ar}C−C*H*$_3$), 2.42 (t, 2H, ^{4}CH_2), 2.60 (s, 3H, ^{6}CH_3), 2.99 (t, 2H, ^{2}CH_2), 4.36 (s, 1H, OH), 11.36 (s, 1H, H-bonded OH). ^{13}C NMR: δ 12.0; 13.2; 15.5 (^{Ar}C−*C*H$_3$), 18.7 (^{3}CH_2), 29.4 (^{6}CH_3), 34.8 (^{4}CH_2), 42.3 (^{2}CH_2), 119.5; 120.6; 123.6; 132.1; 145.1; 152.4 (^{Ar}C), 205.3 (^{5}CO), 206.2 (^{1}CO). Anal. Calcd for $C_{15}H_{20}O_4$ (264.31): C, 68.16; H, 7.63. Found: C, 68.39; H, 7.54.

Table 3. Oxidation of PBD to 10 in Nonaqueous Media

oxidant	yield (%)[a]	remarks
chloranil[b]	84	
chloranil[b]	81	oxidation of **1**-d_6 to **10**-d_5
DDQ[c]	93	
DDQ[c]	92	oxidation of **1**-d_6 to **10**-d_5
Br_2	68	reaction at 0 °C for 30 min
Py·CrO_3[d]	73	
NMMO[e]	75	reaction in refluxing toluene for 4 h

[a] Isolated yields, averaged value in case of repeated syntheses. [b] Tetrachloro-1,4-benzoquinone. [c] 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone. [d] Pyridinium chromium oxide complex. [e] *N*-Methylmorpholine-*N*-oxide.

General Procedure 3. Oxidation of PBD in Nonaqueous Media. 3-Oxa-chromanol **1** (1 mmol, 0.222 g) was dissolved in dry acetonitrile (5 mL). Two molar equivalents of a two-electron oxidant, dissolved in 5 mL of acetonitrile, was added at once at 50 °C. The solution was stirred for 30 min and cooled to room temperature, and the solvent was removed in vacuo. The solid residue was dissolved in EtOAc (2 mL) and chromatographed on neutral aluminum oxide. Chromenone **10** eluted first with ethyl acetate as the eluent. For oxidants used and yields obtained, see Table 3.

6-Hydroxy-2,5,7,8-tetramethyl-4*H*-4-chromenone (10). Compound **10** has been previously described as byproduct of Fries rearrangements,[18] with analytical data slightly differing from our results. ^{1}H NMR: δ 1.66 (s, 3H, ^{7a}CH_3), 1.69 (s, 3H, ^{8b}CH_3), 1.71 (s, 3H, ^{2a}CH_3), 2.13 (s, 3H, ^{5a}CH_3), 5.39 (s, 1H, ^{3}CH), 7.33 (s, 1H, OH). ^{13}C NMR: δ 11.0 (^{8b}C); 12.4 (^{7a}C); 12.6 (^{5a}C), 18.8 (*C*H$_3$-^{2}C), 109.5 (^{3}CH), 118.5 (^{4a}C), 119.8 (^{5}C), 121.9 (^{8}C), 130.6 (^{7}C), 148.6 (^{8a}C), 149.3 (^{6}C), 162.4 (^{2a}CH_3), 179.9 (^{4}CO). Mp: 225 °C. IR: 3458, 1647, 1604, 1400, 1282, 1199. Anal. Calcd for $C_{13}H_{14}O_3$ (218.24): C, 71.54; H, 6.47. Found: C, 71.83; H, 6.21.

3-Deutero-6-hydroxy-2-trideuteriomethyl-5-monodeuteriomethyl-7,8-dimethyl-4*H*-4-chromenone (10-d_5). General procedure 3 was also applied for the oxidation of labeled PBD (**1**-d_6, 1 mmol, 0.23 g) with DDQ, giving 92% (0.20 g) of **10-d_5**. ^{1}H NMR: δ 1.72 (s, 3H, ^{7a}CH_3), 1.74 (s, 3H, ^{8b}CH_3), 2.08 (s, 2H, ^{5a}CH_2D), 4.20 (s, b, 1H, OH). ^{13}C NMR: δ 11.2 (^{8b}C); 12.4 (^{7a}C); 12.4 (t, ^{5a}CH_2D, $^1J_{CD}$ = 18.5 Hz), 18.4 (sept., ^{4b}CD_3, $^1J_{CD}$ = 22.3 Hz), 108.9 (t, ^{3}CD, $^1J_{CD}$ = 16.5 Hz), 118.3 (^{4a}C), 119.9 (^{5}C), 122.0 (^{8}C), 130.4 (^{7}C), 148.6 (^{8a}C), 149.4 (^{6}C), 162.3 (^{2}*C*), 179.6 (^{4}CO). Mp: 222−224 °C. Anal. Calcd for $C_{13}H_9D_5O_3$ (218.20): C, 71.55; H, 6.47. Found: C, 71.83; H, 6.21.

6-Hydroxy-2,5,7,8-tetramethyl-4-chromanone (9). Compound **9** was prepared by condensation of acetophenone **3** with acetaldehyde in the presence of equivalent amounts of pyrrolidine in refluxing toluene according to a general literature procedure.[14] ^{1}H NMR: δ 1.46 (d, 3H, J = 6.3 Hz, ^{2a}CH_3), 1.95 (s, 3H, ^{7a}CH_3), 2.08 (s, 3H, ^{8b}CH_3), 2.21 (s, 3H, ^{5a}CH_3), 2.73 (m, 2H, ^{3}CH_2), 4.25 (s, 1H, OH), 4.68 (m, 1H, ^{2}CH). ^{13}C NMR: δ 12.0; 12.1; 12.5 (^{5a}CH_3, ^{7a}CH_3, ^{8b}CH_3), 21.2 (^{2a}CH_3), 43.8 (^{3}CH_2), 75.0 (^{2}CH), 112.9; 122.6; 123.4; 128.2; 147.5; 149.5 (^{Ar}C), 198.9 (CO). Mp: 109 °C. Anal. Calcd for $C_{13}H_{16}O_3$ (220.26): C, 70.89; H, 7.32. Found: C, 70.98; H, 7.54. Compound **9** was dehydrogenated by 1 equiv of DDQ according to general procedure 3, providing chromenone **10** in 82% yield. Chloranil gave a slightly higher yield (85%).

5,7,8-Trimethyl-2,4-diphenyl-4*H*-1,3-benzodioxin-6-ol, *trans*-Isomer (12). Benzodioxinol **12** was prepared according to the procedure described for the synthesis of **1** with trimethylhydroquinone (10 mmol, 1.52 g) and benzaldehyde (22 mmol, 2.33 g) as the starting materials, in 81% yield (2.80 g). ^{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 (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

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(^{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.

1,3′,4′,8,9,10-Hexahydro-5,6,7′,8′-tetramethyl-3′,9-dioxa-2′,4′,8,10-tetraphenyl-spiro-(benzo[1,2-*b*′4,3-*b*′]dipyran)-3(2*H*),5′-[5*H*-1]-benzopyran-6′(2′*H*)-one (13). General procedure 3 was applied for the oxidation of 5,7,8-trimethyl-2,4-diphenyl-4*H*-1,3-benzodioxin-6-ol (**12**) in nonaqueous media. The solid product obtained by evaporation of the acetonitrile was extracted with *n*-hexane, and the extract was filtered through a layer of basic aluminum oxide, affording spiro-dimer **13** in quantitative yield (0.34 g) after evaporation of the solvent. ^{1}H ($CDCl_3$, 300 MHz): δ 1.84; 1.90; 2.12; 2.19 (4 × s, 4 × 3H, CH_3); 2.14 (m, 2H, CH_2), 2.72 (m, 2H, CH_2), 5.35; 5.42; 5.51; 5.58 (4 × s, 4 × 1H, CH), 7.40 (m, 20H, ^{Ar}CH). Mp: 73−75 °C. Anal. Calcd for $C_{46}H_{40}O_6$ (688.77): C, 80.21; H, 5.85. Found: C, 79.96; H, 5.89.

Conclusions

PBD (**1**) is a novel oxa-tocol-type antioxidant. The supply of water apparently dominates its oxidation behavior, while the polarity of the medium is of minor influence. Three different reaction pathways have been elucidated, which can be distinguished according to the amount of water present during the oxidation.

Both in an excess of water and with 1 equiv of water present, acetophenone **3** is the final oxidation product. However, the formation mechanism is different, involving a *p*-quinone (**2**) in aqueous media or a styrene intermediate (**6**) in the case of equimolar amounts of H_2O present. The release of acetaldehyde, which requires water to proceed, cannot occur upon oxidation in nonaqueous media, so that the mechanism changes once more, and a chromenone (**10**) becomes the final product.

The oxidation of PBD to the *p*-quinone **2** in aqueous media finds its parallel in vitamin E chemistry, where under similar conditions *p*-tocopherylquinone is obtained.[19] Also the formation of the *o*-quinone methide at C-5a is very well-known in vitamin E chemistry. However, while the tocopherol-derived *o*-quinone methide dimerizes to the spiro-dimer of α-tocopherol,[20] the *o*-quinone methide **5** forms a quinone dimethide at C-5a and C-4, which is subsequently stabilized by rearomatization to **6**. Involvement of C-4 in quinone methide structures has not been observed in the tocopherol family,[21] its ready formation in the PBD system can certainly be linked to the electronegative oxygen substituent at C-4. Therefore, also tocopherols oxidized at C-4 might reasonably be suspected to form quinone methide structures involving C-4 and to undergo transformations that are not observed for vitamin E derivatives without the strongly electronegative substituent at C-4.

Also the newly found transformation of *p*-quinone **2** into acetophenone **3** might have a bearing on the chemistry of tocopherols oxidized at C-4, i.e., 4-hydroxy-α-tocopherol or 4-oxo-α-tocopherol. Conceivably, 4-hydroxy-*p*-tocopheryl quinone shows a similar behavior, being converted into 4-oxo-α-tocopherol. Tocopherols oxidized at C-4 have recently been proposed as precursors of natural vitamin E metabolites,[22] the so-called Simon compounds.[4] Possibly, a reaction similar to the conversion of **2** into **3** can be expected for the corresponding vitamin E compounds and would be involved in metabolite formation. This hypothesis is currently being tested in our lab. Also the use of the chromanone and chromenone formation reaction by oxidation of benzodioxin-6-ol derivatives to obtain tocopherol derivatives oxygenated in 4-position is under investigation.

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