Oxidation with a "Stopover" – Stable Zwitterions as Intermediates in the Oxidation of α-Tocopherol (Vitamin E) Model Compounds to their Corresponding *ortho*-Quinone Methides

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As a prominent member of the vitamin E group, α-tocopherol is an important lipophilic antioxidant. It has a special oxidation chemistry that involves phenoxyl radicals, quinones and quinone methides. During the oxidation to the *ortho*-quinone methide, an intermediary zwitterion is formed. This aromatic intermediate turns into the quinone methide by simply rotating the initially oxidized, exocyclic methyl group into the molecule's plane. This initial zwitterionic intermediate and the quinone methide are not resonance structures but individual species, whose distinct electronic structures are separated by a mere 90° bond rotation. In this work, we hindered this crucial rotation, by substituting the affected methyl group with alkyl or phenyl groups. The alkyl groups slowed down the conversion to the quinone methide by 18-times, while the phenyl substituents, which additionally stabilize the zwitterion electronically, completely halted the conversion to the quinone methide at −78 °C, allowing for the first time the direct observation of a tocopherol-derived zwitterion. Employing a ^{13}C-labeled model, the individual steps of the oxidation sequence could be observed directly by NMR, and the activation energy for the rotation could be estimated to be approximately 2.8 kcal/mol. Reaction rates were solvent dependent, with polar solvents exerting a stabilizing effect on the zwitterion.

The observed effects confirmed the central relevance of the rotation step in the change from the aromatic to the quinoid state and allowed a more detailed examination of the oxidation behavior of tocopherol. The concept that a simple bond rotation can be used to switch between an aromatic and an anti-aromatic structure could find its use in molecular switches or molecular engines, driven by the specific absorption of external energy.

1. Introduction

The vitamin E group plays an important role in protecting the cell membranes of the body from oxidation. It is the biologically most important fat-soluble antioxidant, which has become a commodity product and bulk chemical since its first report about 100 years ago. Besides its antioxidant function, several non-antioxidant actions of the compound have been identified recently, and new ones are still being discovered.[1–5] The vitamin E group is divided into α-, β-, γ- and δ-tocopherol according to the number and position of methyl substituents on the aromatic ring. Of these substances, α-tocopherol (**1**) is the most important and effective (Scheme 1). As a lipophilic antioxidant, it prevents the radical breakdown of lipids in the cell membrane by capturing free radicals. While the isoprenoid side chain anchors the molecule in the cell membrane, the phenolic OH group is the basis of the antioxidative effect, which is remarkably high due to the special chemical properties of the substituted chroman rings.

The model substance PMC (2,2,5,7,8-pentamethylchromanol, **1a**),[6] permethylated at the aromatic ring, was used as model compound of α-tocopherol in our studies. This compound has already been used almost ubiquitously as model compound in studies of tocopherol chemistry, for example on the formation of the corresponding *ortho*-quinone methide. Although the activity of the vitamin depends on the length and stereochemistry of the side chain *in vivo*, *in vitro* studies of the chemical behavior of tocopherols usually use model compounds that contains a methyl group instead of tocopherol's long C_{16} chain. This simplifies synthesis, workup and analysis of vitamin E derivatives without changing the antioxidant behavior of the chromanol system.

The general oxidation behavior of vitamin E is well established.[7] Upon oxidation of α-tocopherol, three different intermediates are formed depending on the reaction medium: a tocopheroxyl radical (**2**)[8–11] is obtained by one-electron oxidation, i.e. by abstracting a hydrogen atom (= one electron plus a proton) from the phenolic OH group. A second one-electron oxidation of the tocopheroxyl radical leads to the

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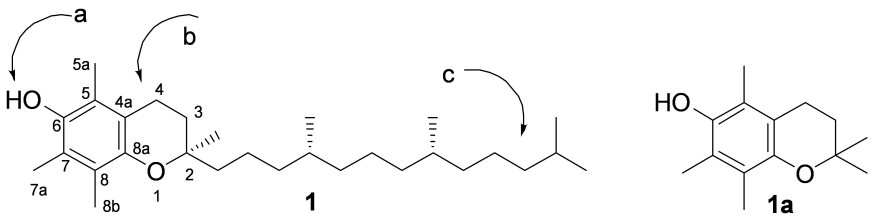
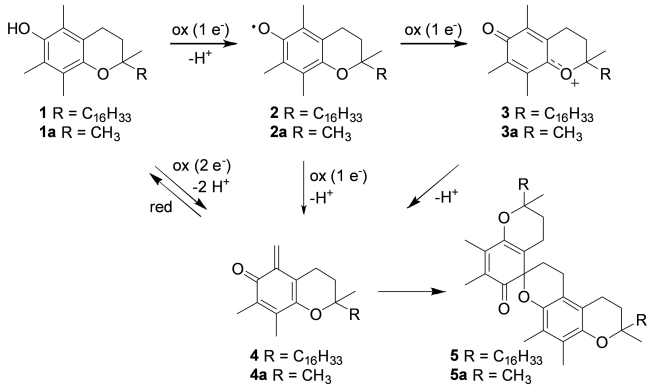
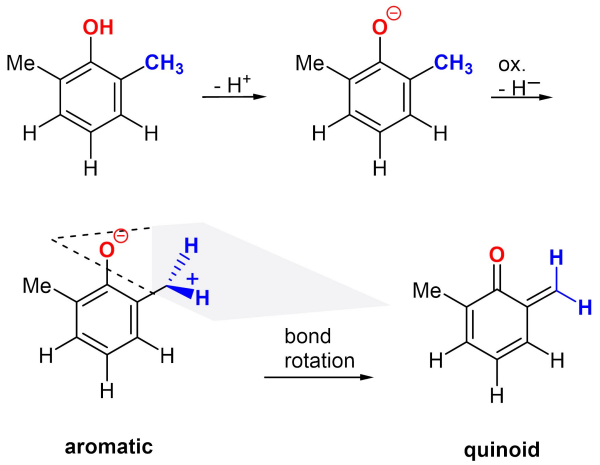


Scheme 1. Important structural features of α-tocopherol (**1**) and its model compounds PMC (**1 a**). a: phenolic OH group, b: chroman skeleton, c: isoprenoid C_{16} side chain.

formation of a resonance-stabilized chromanoxylium cation (**3**).[12] Else, if α-tocopherol is directly subjected to two-electron oxidation, or if a proton is abstracted from the chromanoxylium cation (**3**), the *ortho*-quinone methide (oQM, **4**)[13] is formed, which in previous work was directly spectroscopically observed (NMR) for the first time.[14] Characteristic subsequent reactions of *ortho*-quinone methide that convert it into stable products are the 1,4-addition of nucleophiles to 5a-substituted α-tocopherol and the hetero-Diels-Alder reaction with olefins. A special case of this reaction is the reaction of two *ortho*-quinone



Scheme 2. Typical oxidation reactions of α-tocopherol (**1**) or its model compound PMC (**1 a**).



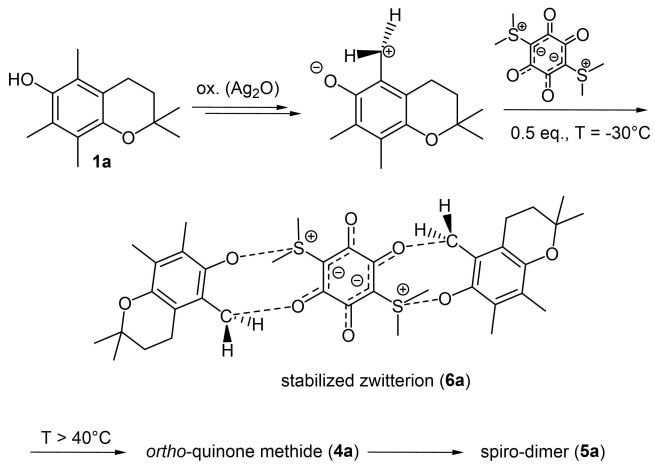
Scheme 3. Oxidation of *ortho*-methylphenols to oQMs involves a zwitterionic, aromatic intermediate. In-plane rotation of the methylene group goes hand in hand with the transition from an aromatic to a quinoid system.

methide molecules to the α-tocopherol spirodimer (**5**),[15–18] a very frequent end product of vitamin E oxidation chemistry. In this spiro-dimerization, one oQM reacts as the diene and the other as the dienophile.

The detailed steps in the formation of the *ortho*-quinone methide of α-tocopherol (**4**) was the subject of our present investigations because of its crucial importance as a central intermediate in vitamin E chemistry. The starting point for the study was the consideration that oQM generation from *ortho*-methylphenols is not an elementary reaction, i.e., it can be divided into different steps. Altogether, the system loses two protons and two electrons, mostly as a proton and a hydride, but also other combinations are possible (single-electron steps, cf. Scheme 2). A zwitterionic, still aromatic, intermediate with an out-of-plane benzylic methylene group is formed (Scheme 3). A simple bond rotation, which brings the exocyclic methylene group in plane with the aromatic ring system, would cause the change from an aromatic to a quinoid system. This intermediate can be stabilized electronically, by Coulomb interactions with another zwitterion.[13,14] But also hindering this rotation "mechanically", e.g. by steric properties, or electronically, e.g. by conjugation effects, should stabilize the zwitterion and delay the formation of the oQM.

If indeed provable, such a mechanically or electronically restrained oQM structure would be the first chemical system where such a fundamental property change as the aromatic-to-quinone transition (and back) is coupled to and governed by a very simple molecular process, namely the rotation around a single bond. Studies of such a system could not only shed new light on the tocopherol system in particular, but contribute to our understanding of aromaticity/antiaromaticity as one of the basic concepts in organic chemistry. To find out more about this system, special derivatives of tocopherol were synthesized and their oxidation to oQMs studied.

The detailed mechanism of oQM formation from α-tocopherol with silver oxide as oxidant has already been established: in two steps – abstraction of a proton from the phenolic OH group and a hydride ion from the 5-methyl group – elemental silver, water and an α-tocopherol zwitterion are formed (Scheme 4).[7,13,14] This zwitterion carries a negative charge on the phenolic oxygen and a positive charge on a benzylic carbon, which is always the 5a-carbon, not the seemingly equivalent 7a-carbon. The reason for this nearly complete regioselectivity has been explained previously based on the theory of strain-induced bond localization (SIBL)[19–21] which has been reviewed later.[22,23] Due to the spatial arrange-



Scheme 4. Zwitterionic intermediate **6a** stabilized by electrostatic interaction with another zwitterion, before bond rotation leads on to oQM **4a** and further dimerization to spiro-dimer **5a**.

ment necessary for hydride abstraction, the two hydrogens remaining on the benzylic 5a-carbocation are initially placed perpendicular to the ring plane of the chroman, and the benzene ring still retains its aromaticity. The conjugated quinoid double bond system of the *ortho*-quinone methide can only form when this methylene group rotates into the ring plane by spinning around the bond between C–5 and C–5a, so that the two 5a-hydrogens now lie in the ring plane (cf. Schemes 3 and 4). The pronounced resonance stabilization of the oQM favors it over the aromatic zwitterion. This is why the reverse reaction – which would require further C–5/C–5a bond rotation for an out-of-plane movement of the two hydrogens – is not observed. At low temperatures, the initial zwitterionic state can be stabilized by complexation with the likewise zwitterionic *N*-methylmorpholine *N*-oxide or the zwitterionic bis (dimethylsulfonium)ylide from 2,5-dihydroxy[1,4]benzoquinone (cf. Scheme 4).[24] The strong electrostatic zwitterion-zwitterion interactions play a major role in this stabilization, which allowed to observe the α-tocopherol derived oQM, or more correctly, its zwitterionic precursor, directly by spectroscopic (NMR, UV) means.[14] It should be noted once more, that the initial zwitterionic intermediate and the actual oQM are not resonance structures, but individual species, "separated" by the molecular movement of the C5–C5a bond rotation.

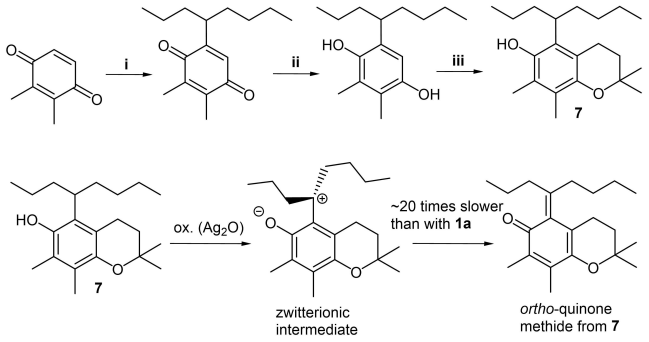
Since this C5–C5a bond rotation occurs very easily – given the two hydrogens as the smallest possible substituents at C–5a – it was logical to assume that larger substituents would restrict the rotatability, in this way making the zwitterionic intermediate more stable by impeding transition into the oQM. Also the stabilization of the cationic charge at C–5a by resonance effects should render the zwitterionic intermediate more permanent. Therefore, the aim of this study was the preparation of α-tocopheryl derivatives of which the zwitterions, as first oxidation intermediates, are significantly more stable, in order to make these intermediates more accessible and perhaps observable without stabilization by interaction with other zwitterions.

2. Results and Discussion

As a first approach, a vitamin E model compound carrying a 4-octyl residue in 5-position instead of the "usual" methyl group was synthesized. 2,2,7,8-Tetramethyl-5-(4-octyl)-chroman-6-ol (**7**) represents an α-tocopherol, in which two of the three protons at the C–5a methyl group are replaced by alkyl groups, a propyl and a butyl moiety, so that C–5a is being placed in the middle of an octyl chain. These substituents are evidently much larger than a hydrogen atom and have a much higher angular momentum when rotation around the C5–C5a bond is to occur.

The synthesis (Scheme 5) did not follow the obvious path, alkylation of the γ-tocopherol model 2,2,7,8-tetramethyl-chroman-6-ol (**8**) at the free aromatic 5-position, because the yields of the attempted variants were rather inferior, no matter whether olefin or alkyl halides were employed as the alkylating agents or whether the phenol was temporarily OH-protected. Instead, 2,3-dimethylbenzoquinone was equipped with the 4-octyl moiety by hydroboration with 3-octene and the product was then reduced to the corresponding hydroquinone and further converted to the target chromanol **7** by reaction with 2-methyl-3-butene-2-ol (Scheme 5, upper row). This last step, an alkylation/cyclization process, resembles the conversion of trimethylhydroquinone to α-tocopherol in today's standard industrial synthesis of α-tocopherol.[1,2] Although this three-step sequence might seem rather lengthy and indirect at a first glance, it provided a much better yield than all direct alkylation approaches and was thus clearly superior.

When the 5-octyl tocopherol model was oxidized with silver oxide at −78 °C, the corresponding *ortho*-quinone methide was formed 18 times slower than in the case of α-tocopherol (Scheme 5, lower row). The complex of the oxidized 5-(3-octyl)-tocopherol model with the bis(dimethylsulfonium)ylide of 2,5-dihydroxy-[1,4]benzoquinone decomposed about 10 times slower than the corresponding complex with α-tocopherol. This was clear evidence of the involvement of C5–C5a bond rotation in the process and pointed to its importance in the transition from the zwitterion to the oQM. Two separate properties of the alkyl substituents at C–5a are responsible for the observed stabilization of the zwitterionic transition state: first, the larger



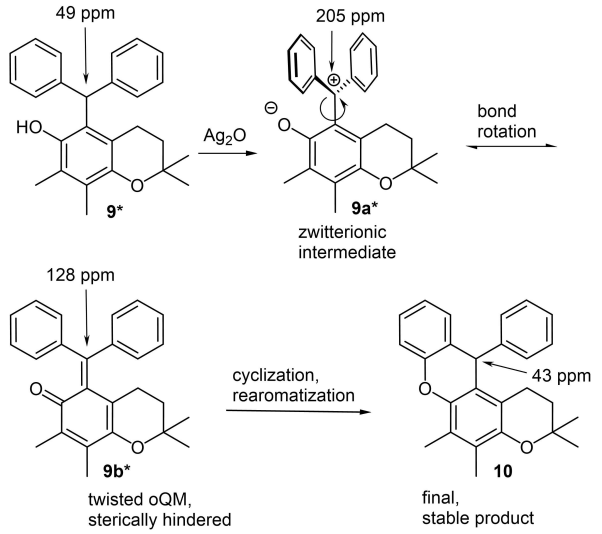
Scheme 5. Synthesis of 2,2,7,8-tetramethyl-5-(4-octyl)-chroman-6-ol (**7**) (upper row) and its oxidation to the corresponding *ortho*-quinone methide (lower row). **i** = 4-octene, 1,3,2-benzodioxaborol, DCM, reflux, 5 h; then *N,N'*-dimethylpropylene urea, air, r.t., 2 h, **ii** = $NaBH_4$, THF, r.t., 140 min, **iii** = 2-methyl-3-buten-2-ol, HCOOH, 110 °C, 4 h.

alkyl chains make the rotation about the C–5/C–5a axis more difficult due to steric requirements for the movement, and second their significantly higher angular momentum increases the energy required for bond rotation. The rotation of the chains into the ring plane requires a higher rotational torque, which translates into to a slower rotation. This effect can be easily imagined by means of a figure skater, whose pirouette is much faster with arms on than with arms off.

As a second approach, a 5a,5a-diphenyl-α-tocopherol model (5-benzhydryl-2,2,7,8-tetramethyl-chroman-6-ol, **9**) was synthesized, which bears two phenyl rings at the C–5a methyl group. The synthetic path and the X-ray structure of this compound are presented in Scheme 6. The γ-tocopherol model compound 2,2,7,8-tetramethyl-chroman-6-ol (**8**) was alkylated with diphenylmethanol, and the same general approach was used to introduce a ^{13}C-label at C–5a position (**9***), the required diphenyl-^{13}C-methanol being synthesized from ethyl ^{13}C-formiate and phenylmagnesium bromide.

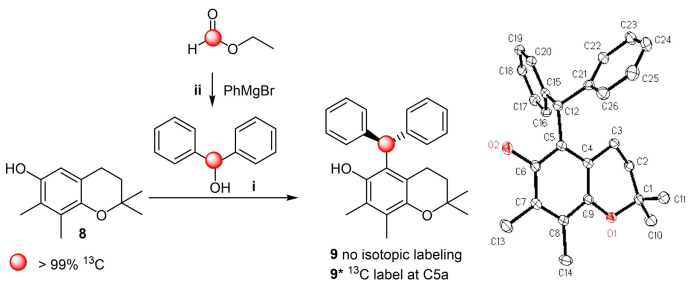
Replacing the two C5a-hydrogens of α-tocopherol model **1 a** by the two aromatic substituents had a significant effect on the oxidation behavior, in particular on the rate of conversion of the corresponding zwitterionic intermediate into the corresponding oQM. First, the phenyl groups are significantly larger than even the alkyl groups of the above octyl-substituted model compound (**7**). The in-plane arrangement – as the prerequisite of oQM-formation – is sterically additionally disadvantaged, and the perpendicular alignment of the C5a-substituents in the zwitterion is favoured. In other words, the bulky C5a-phenyl substituents effectively impede the rotation around the C5–C5a bond that is necessary for the formation of *ortho*-quinone methide from the initial zwitterionic oxidation intermediate.

In addition to these steric effects, also electronic effects become active. The aromatic substituents electronically strongly stabilize the positive charge at C5a, the cation being actually embedded in a triphenylmethyl (trityl) structure. Quantum chemical calculations indicate that the HOMO of the zwitterion of the biphenyl-α-tocopherol model (**9**) is distributed across all three aromatic rings. Therefore, the zwitterionic intermediate from model compound **9** is stabilized by both steric effects and electronic stabilization. After the C5–C5a bond rotation has eventually taken place and the *ortho*-quinone methide has been formed, the phenyl substituents, for steric reasons, cannot lie in the chroman plane and must protrude from it. Oriented in this way, however, the electrons of the aromatic systems in the phenyl substituents cannot participate in conjugation with the planar double bond system of the *ortho*-quinone methide. This is why the *ortho*-quinone methide from **9** is not additionally favored over the aromatic state of the intermediate zwitterion, this missing preference being different from the case of α-tocopherol (**1**) and its truncated model compound **1 a**.



Scheme 7. Oxidation of 5a-^{13}C–5a,5a-diphenyl-2,2,7,8-tetramethyl-chroman-6-ol (**9***), monitored by changes of the ^{13}C5a-resonance (^{13}C NMR, $CDCl_3$, 4 scans). The starting compound (δ_{5a} 49 ppm) treated with Ag_2O initially yields the zwitterionic compound with perpendicularly oriented phenyl substituents (δ_{5a} 205 ppm), which is transformed into the oQM (δ_{5a} 129 ppm) upon C5–C5a bond rotation. The final stable product is a xanthene derivative (δ_{5a} 33 ppm) formed by ring closure and rearomatization.

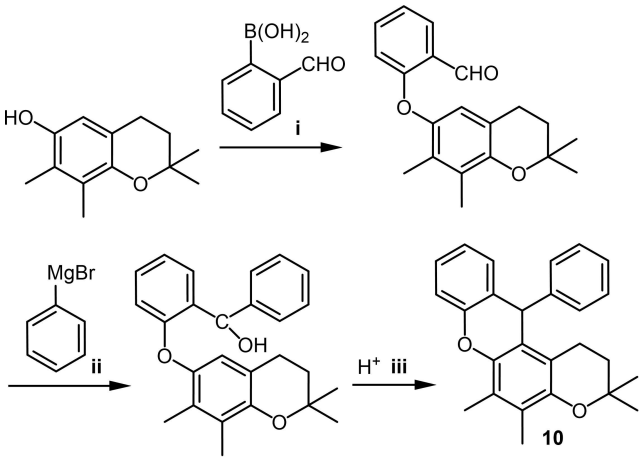
Using the ^{13}C-isotopically labeled model compound **9*** with a ^{13}C-label at C5a (see Scheme 6), the individual steps of the oxidation – formation of the primary zwitterionic intermediate (**9 a***), rotation to give the *ortho*-quinone methide (**9 b***), and subsequent generation of a stable end product (**10**) – became directly observable by ^{13}C NMR spectroscopy by following the peak of C5a, which was now about 100 times enhanced by the increased isotopic abundance compared to the natural ^{13}C isotopic abundance of approx. 1 % (Scheme 7). Accumulation of only 4 scans was (more than) sufficient to report the state of the isotopic label, while all other carbons of natural isotopic abundance are blinded out.



Scheme 6. Synthesis and X-ray structure of 5a,5a-diphenyl-2,2,5,7,8-pentamethyl-chroman-6-ol (**9**). The same approach was used for the ^{13}C-isotopically labeled compound 5a-^{13}C–5a,5a-diphenyl-2,2,5,7,8-pentamethyl-chroman-6-ol (**9***). **i** = $AlCl_3$, THF, r.t., 42 h, **ii** = THF, 0 °C, 2 h.

The chemical environment of C5a is heavily affected by the oxidation process: being aliphatic (benzylic) in the starting material **9***, C5a first becomes the cationic center of the zwitterionic intermediate (**9a***) and after that a part of the oQM's double bond system (**9b***), see Scheme 7. In each of these states, C5a has a significantly different ^{13}C NMR shift, which enabled us to determine the concentration of each intermediate directly. Model compound **9*** was dissolved in chloroform at −78 °C, and the C5-resonance appeared at 49 ppm. Upon addition of silver oxide as the oxidant at −78 °C, the resonance changed fast (within seconds) to 205 ppm. This chemical shift agrees with the structure of a carbocation with three phenyl substituents – the zwitterionic intermediate – and corresponds excellently with the chemical shift of triphenylmethylium (tritylium) cations.[25] At −78 °C, this zwitterion was obviously stable, since no decrease in its concentration was observed and no other signals indicative of decomposition products appeared (Figure 1). Notably, an inherently stable tocopherol-type zwitterion has never been observed before, previous stabilization attempts had to resort to chemical stabilization by interaction with other zwitterions.[14] When the sample was warmed to room temperature within 20 s and kept at this temperature for 10 min, the signal intensity of the peak at 205 ppm decreased, and a new signal at 128 ppm appeared within 60 s, which was assigned to the now "olefinic" C5a in the *ortho*-quinone methide (**9b***). The intensity of this signal decreased slowly during the next 9 min at room temperature and then also after the temperature had been quickly lowered again to −78 °C. The temperature profile and the concentration profiles of starting material **9*** and intermediates (**9a*** and **9b**) are shown in Figure 1.

During the 10 min room temperature interval, a new signal at 33 ppm appeared and increased at the same rate as the 128 ppm-resonance decreased. The new signal constantly increased and then kept constant, but never decreased, so it obviously originated from a final, stable product (Figure 1). It was the only resonance detectable when the reaction mixture was left standing at room temperature for several hours. This end product was, at first, preliminarily identified by NMR and UV/Vis as 3,3,5,6-tetramethyl-12-phenyl-1,2,3,12-tetrahydro-pyrano[*3,2-a*]xanthene (**10**). Subsequently the structure was confirmed by independent synthesis of an authentic sample (see Scheme 8).



Scheme 8. Three-step synthesis of xanthene **10** for independent structure confirmation. **i** = $Cu(OAc)_2$, NEt_3, DCM, r.t., 17 h, **ii** = THF, r.t. 30 min, **iii** = cat. H_2SO_4 conc., 0 °C, 5 min.

When the sample was cooled down again to −78 °C after the intermission of 10 min at room temperature, no new *ortho*-quinone methide (**9b***) was formed from the zwitterion (**9a***), because the zwitterion concentration did not change even over hours. However, oQM still present in the reaction mixture slowly continued to react to the xanthene (**10**), easily recognizable by the decreasing peak at 128 ppm and the corresponding increase of the resonance at 33 ppm (Figure 1, Scheme 7). Evidently, the underlying ring closure reaction proceeded even at this low temperature. It was intriguing to see that this reaction apparently proceeded even faster at −78 °C than at room temperature, as was evident in Figure 1 from the faster consumption of the oQM after decreasing the temperature from r.t. to −78 °C. This result was counterintuitive at a first glance and seemed to collide with basic kinetic laws. However,

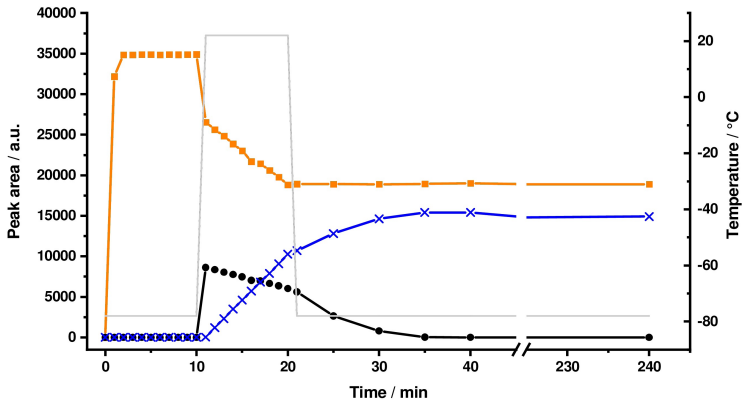


Figure 1. Oxidation of 5a-^{13}C-5a,5a-diphenyl-2,2,7,8-tetramethyl-chroman-6-ol (**9***) by Ag_2O in CDCl. ^{13}C-peak intensities (4 scans per data point) of the C–5a resonances of zwitterion intermediate **9a*** (squares), the oQM **9b*** (circles) und final xanthene product **10** (crosses) in dependence of the temperature (temperature profile: solid line without symbols, right y-axis).

it became understandable when the geometric conditions were taken into account: formation of the xanthene requires chroman and phenyl ring to be arranged in the same plane. Even with the oQM's C5–C5a double bond properly in place, the phenyl rings would easily remain in rotational motion. At room temperature, both the rotation around the C5–C5a bond and the rotation of the phenyl rings would be much faster than at −78 °C, so that the rings align only fleetingly in a geometry optimal for xanthene formation. The lower the temperature, the more frequent become the "opportunities" for the rings to "meet" in an in-plane arrangement suitable for ring closure, which explains the faster reaction at −78 °C.

Since NMR-signal intensities correspond directly to concentrations, we were able to determine the concentrations of all four substances at any time of measurement. This data was used to approximate the difference in activation energies for the reaction of the zwitterion to the oQM, according to a simple Arrhenius-type equation. At 295 K, the ratio of zwitterion to oQM was constantly 3.1 : 1. Assuming both compounds to be in equilibrium is justified since the "reaction" consists only in the rotation of the phenyl groups in and out of the plane of the chroman. This yields an approximated activation energy (rotational barrier) of 2.8 kJ/mol.

The influence of the solvent on the reaction rate of the formation of the oQM was investigated as well. Apolar solvents favoured oQM formation, and the ratio of the reaction rates in d6-DMSO, $CDCl_3$ and C_6D_6 was 1 : 8 : 13, respectively. This corresponds to observations from the chemistry of α-tocopherol, for which apolar-aprotic media favour oxidation to the oQM, while polar media promote formation of the chromanoxylium intermediate (Scheme 7). Since the formation of the *ortho*-quinone methide is slower in polar solvents and can even be stopped temporarily by zwitterionic stabilizers, it was expected that ionic liquids – due to their permanently present cations and anions – might also delay the formation of the oQM by stabilization of the zwitterion. This effect was indeed observed, but was not particularly pronounced. In 1-butyl-3-methylimidazolium ionic liquids with different anions, the conversion to the oQM was only 22 times slower than in C_6D_6, i.e. about 1.5 times slower than in DMSO-d6. It was speculated that the two opposite charges in the stabilizing agent must be arranged in quite close proximity and must be quite localized to exert a large stabilizing effect. While this is the case in amine *N*-oxides and in the sulfonium ylide, bulky ions and additionally delocalized charges, as in the case of ions with solvent shells and ionic liquids, are probably too scattered to exert a strong effect.

3. Conclusion

The zwitterionic intermediate in the formation of *ortho*-quinone methides from the parent *ortho*-alkylphenols was observed directly by spectroscopy for vitamin E-related compounds, without the addition of stabilizing zwitterionic molecules. The transition from the primary aromatic, zwitterionic oxidation intermediate to the *ortho*-quinone methide is effected by a mere rotation around a single bond. Substitution of two hydrogens of the crucial exocyclic methyl group with alkyl chains increased both the angular momentum and the steric demand of this rotation, which was sufficiently hindered to result in an 18 times slower oQM-formation compared to the methylene structure. When aromatic substituents were attached to the *ortho*-methyl group, the additional steric and electronic effects stabilized the intermediate zwitterion at −78 °C completely so that it became stable at this temperature. By means of ^{13}C-labeling, all stages of the oxidation reaction – starting material, zwitterion, oQM, final oxidation product – were observed in the order of their appearance and recording kinetics became possible. At room temperature, the conversion of zwitterion **9a** to oQM **9b** was still slow enough to determine its activation energy to be 2.8 kcal/mol, which corresponds to the rotational barrier of the C5–C5a bond. Reaction rates were found to be solvent dependent, with polar solvent having a stabilizing effect on the zwitterion. The oxidation product, a xanthene derivative, was fully analytically characterized and its identity additionally confirmed by independent synthesis.

The fact that a simple rotation around a single bond can act as a switch between aromaticity and antiaromaticity, such as between **9a** and **9b**, might in future allow to construct molecular switches, to assemble uniformly moving molecular arrays or to drive molecular machines by the absorption energy of aromatic/antiaromatic structures. While these applications lie in the future, the findings certainly give more detailed insights into *ortho*-quinone methide chemistry already now, and they complement conventional teaching about oQM formation and oQM chemistry.

Experimental Section

Materials and Methods

Commercial chemicals were of the highest grade available and were used without further purification. 2,2,7,8-Tetramethylchroman-6-ol was available from previous projects. Reagent-grade solvents were used for all extractions and workup procedures. Dichloromethane (DCM) was dried over P_2O_5, while dry THF and ethyl ether (EE) were obtained by refluxing over from sodium. Distilled water was used for all aqueous extractions and for all aqueous solutions. All reactions involving non-aqueous conditions were conducted in oven-dried (140 °C, overnight) or flame-dried glassware under argon or nitrogen. TLC was performed with Merck silica gel 60 F254 pre-coated plates. Flash chromatography was performed with Baker silica gel (40 μm particle size). All products were purified to homogeneity as checked by TLC/GC-MS analysis. The use of brine refers to saturated NaCl (aq.). All given yields refer to isolated, pure products.

^1H NMR spectra were recorded at 300.13 MHz (400.13 MHz, respectively) for ^1H and at 75.47 MHz (100.41 MHz, respectively) for ^{13}C NMR with $CDCl_3$ as the solvent if not otherwise stated. Chemical shifts, relative to TMS as internal standard, are given as δ values, coupling constants in Hz. ^{13}C peaks were assigned with the aid of APT, HMQC, and HMBC spectra.

GC-MS was performed on a GC 6890N/MSD 5973B instrument with a fused silica HP-5 ms (30 m, 0.25 mm, 25 μm) column and helium as carrier gas. Total flow was 27.5 mL min^{-1} at 46.9 kPa carrier gas

pressure and the resulting column flow was 0.9 mL min^{-1}. The temperature programs were as follows: 100 °C (5 min), 10 °C min^{-1} to 280 °C (20 min). Aliquots (0.2 μL) of the dissolved samples were injected at 230 °C inlet temperature in split mode (25:1). Ionization was performed in EI mode at 70 eV.

X-ray Crystallographic Study: X-ray data collection was performed with a Bruker AXS Smart APEX CCD diffractometer and graphite-monochromatized Mo-*Kα* radiation, $\lambda = 0.71073$ Å; corrections for absorption with the program SADABS, structure solution with direct methods, structure refinement on *F*2 (Bruker AXS, 2001: programs SMART, version 5.626; SAINT, version 6.36 A; SADABS version 2.05; XPREP, version 6.12; SHELXTL, version 6.10. Bruker AXS Inc., Madison, WI, USA).

2,2,7,8-Tetramethyl-5-(4-octyl)-chroman-6-ol (7)

The alkylated model compounds were prepared in two steps *via* 2,3-dimethyl-5-(1-propyl-pentyl)-[1,4]benzoquinone.

2,3-Dimethyl-5-(4-octyl)-[1,4]-benzoquinone. (*Z*)-4-Octene (659 mg, 5.88 mmol, 2.0 eq.) and *N,N*-dimethylacetamide (DMAc, 51 mg, 0.588 mmol, 0.2 eq.) were dissolved in dry DCM (6 mL) under an atmosphere of argon. The solution was cooled to 0 °C and 1,3,2-benzodioxaborole (880 mg, 7.34 mmol, 2.5 eq.) was added slowly. The solution was heated to reflux for 5 h, water (317 mg, 6.0 eq.) was added slowly, and the mixture was stirred for another 20 min. *N,N′*-Dimethylpropylene urea (753 mg, 5.88 mmol, 2.0 eq.) and 2,3-dimethyl-[1,4]-benzoquinone (400 mg, 2.94 mmol, 1.0 eq., dissolved in 5 ml of DCM) were added. Air (3 mL) was bubbled into the solutions with a syringe to increase radical formation. After two hours, the reaction was quenched with saturated NH_4Cl-solution and extracted two times with diethyl ether. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and evaporated *in vacuo*. Column chromatography (silica gel, hexane:EE, v/v = 50:1) yielded 245 mg of 2,3-dimethyl-5-(4-octyl)-[1,4]-benzoquinone (34 %) as a yellow oil.

^{1}H NMR: δ = 0.78-0.99 (m, 6H, alkyl CH_3), 1.07–1.61 (m, 12H, 10H alkyl CH_2), 2.00–2.03 (m, 6H, H-2a, H-3a), 2.86 (m, 1H, H-5a), 6.44 (s, 1H, 6-H). ^{13}C NMR: δ = 12.0 (C2a/C3a), 12.5 (C3a/C2a), 13.9 (Cε), 14.1 (Cγ′), 20.4 (Cβ′), 22.7 (Cδ), 29.5 (Cγ), 34.2 (Cβ), 36.8 (Cα′), 37.1 (Cα), 131.5 (C6), 140.1 (C2/C3), 141.2 (C3/C2), 152.7 (C5), 187.9 (C1, C4).

EI-MS (70 eV): 151 (100 %), 150 (93 %), 122 (82 %), 248 (55 %), 137 (37 %), 91 (31 %), 205 (28 %), 177 (28 %), 178 (27 %), 152 (27 %), 135 (26 %), 138 (25 %), 163 (25 %), 41 (25 %), 179 (24 %), 191 (23 %), 192 (22 %), 77 (20 %), 164 (20 %), 53 (19 %), 79 (%), 165 (19 %), 219(18 %), 107 (18 %), 55 (18 %), 123 (17 %), 136 (16 %), 43 (16 %), 159 (15 %), 121 (15 %), 149 (15 %), 105 (15 %), 206 (14 %), 193 (14 %), 39 (13 %), 93 (13 %), 67 (13 %), 161 (10 %), 81 (10 %), 249 (10 %), 54 (10 %).

R_f (*n*-hexane/ethyl acetate, v/v = 5:1) = 0.51.

2,2,7,8-Tetramethyl-5-(4-octyl)-chroman-6-ol (7). The above benzoquinone (195 mg, 785 μmol, 1.0 eq.) was dissolved in THF (2 mL) under an argon-atmosphere and cooled to 0 °C. Sodium borohydride (45 mg, 1.18 mmol, 1.5 eq.) was added to reduce the benzoquinone to the hydroquinone, and the reaction mixture was stirred at 0 °C for five minutes and for 130 minutes at room temperature. Formic acid (8 mL) was added, the flask equipped with a condenser, and the mixture heated to 110 °C. 2-Methyl-3-buten-2-ol (135 mg, 1.57 mmol, 2.0 eq.) was added slowly. After 4 hours, the reaction was quenched with ice water and extracted three times with diethyl ether (~40 ml in total). *n*-Hexane (40 mL) was added to the organic extract, which was washed with distilled water, dried over $MgSO_4$, filtered, and evaporated *in vacuo*.

The obtained residue was dissolved in methanol (25 mL) and concentrated hydrochloric acid (1 mL), and the solution was heated to 65 °C to cleave the formic acid ester formed in the previous step. After 70 minutes, the solvent was evaporated, and diethyl ether was added. The organic solution was washed two times with distilled water and once with saturated $NaHCO_3$-solution, dried over $MgSO_4$, filtered, and evaporated *in vacuo*. Column chromatography (silica gel, hexane:EE, v/v = 100:1) yielded 104 mg of 2,2,7,8-tetramethyl-5-(4-octyl)-chroman-6-ol as a yellow oil (42 % yield).

^{1}H NMR: δ = 0.80–0.89 (m, 6H, H-ε, H-γ′), 1.07–1.32 (m, 6H, H-δ, H-γ, H-β′), 1.26 (s, 6H, H-2a), 1.60–1.90 (m, 4H, H-β, H-α′), 1.76 (t, $^3J_{HH}$ = 6.9 Hz, H-3), 2.10 (s, 3H, H-7a), 2.11 (s, 3H, H-8b), 2.66 (t, $^3J_{H,H}$ = 6.9 Hz, H-4), 2.87 (m, 1H, H-α), 4.21 (s, 1H, OH). ^{13}C NMR: δ = 12.0 (C-8b/C-7a), 12.1 (C-7a/C-8b), 14.1 (C-ε), 14.8 (C-γ′), 21.7 (C-4/ C-β′), 21.8 (C-β′/C-4), 23.1 (C-δ), 26.5 (C-2a), 26.6 (C-2a), 30.8 (C-γ), 33.5 (C-3), 34.1 (C-β/C-α′), 36.6 (C-α′/C-β), 38.5 (C-α), 72.1 (C-2), 117.5 (C-8), 121.7 (C-7), 122.9 (C-4a), 126.3(C-5), 127.1 (C-6), 145.5 (C-8a).

EI-MS (70 eV): 318 (100 %), 219 (62 %), 319 (22 %), 165 (21 %), 164 (13 %), 220 (10 %).

R_f (*n*-hexane/ethyl acetate, v/v = 5:1) = 0.53.

5 a,5 a-Diphenyl-2,2,5,7,8-pentamethylchroman-6-ol (9)

Aluminum chloride (262 mg, 1.96 mmol, 4.0 eq.) and 2,2,7,8-tetramethylchroman-6-ol (101 mg, 490 μmol, 1.0 eq.) were placed in a dry 2-necked round bottom flask equipped with a drying tube and were dissolved in dry THF (3 mL). Diphenylcarbinol (90 mg, 490 μmol, 1.0 eq.) was dissolved in dry THF (1 mL) and added to the reaction mixture. The reaction was stirred at room temperature for 42 h, and then distilled water was added. The aqueous mixture was extracted three times with EE. The organic layers were combined and washed three times with saturated $NaHCO_3$-solution and two times with brine. The organic phase was dried over Na_2SO_4, filtered, and evaporated *in vacuo*. The crude product (172 mg of a yellow oil) was purified by column chromatography (hexane:ethyl acetate, v/v = 50:1, 6 g of silica gel), yield: 151 mg of colorless crystals (83 %).

^{1}H NMR: δ = 1.27 (s, 6H, H-2a), 1.72 (t, 2H, $^3J_{H,H}$ = 6.4 Hz, H-3), 2.08 (s, 3H, H-8b), 2.13 (s, 3H, H-7a), 2.69 (t, 2H, $^3J_{H,H}$ = 6.4 Hz, H-4), 4.36 (s, 1H, OH), 5.77 (s, 1H, H-5a), 7.17–7.34 (m, 10 H, Ar–H). ^{13}C NMR: δ = 12.1 (C-7a), 12.2 (C-8b), 21.3 (C-4), 26.6 (C-2a), 33.2 (C-3), 49.1 (C-5a), 72.3 (C-2), 116.7 (C-8), 124.2 (C-5), 124.3 (C-4a), 125.2 (C-7), 126.9 (C-4′), 128.9 (C-2′, C-6′), 129.0 (C-3′, C-5′), 141.6 (C-1′) 145.7 (C-8a), 145.9 (C-6).

EI-MS (70 eV): 372 (100 %), 239 (39 %), 238 (31 %), 373 (28 %), 225 (19 %), 315 (15 %), 301 (14 %), 165 (12 %), 224 (12 %), 316 (10 %).

R_f (*n*-hexane/ethyl acetate, v/v = 5:1) = 0.56.

5 a-^{13}C-5 a,5 a-Diphenyl-2,2,5,7,8-pentamethylchroman-6-ol (9*)

The ^{13}C-labeled biphenyl model compound was prepared in two steps. Ethyl ^{13}C-formate (75 mg, 999 μmol, 1.0 eq.) was dissolved in dry THF (2 mL) under argon and cooled to 0 °C. Phenylmagnesium bromide (666 μL, 3 M in diethyl ether, 1.99 mmol, 2.0 eq.) was diluted with dry THF (3 mL) and added dropwise. The solution was stirred at 0 °C for two hours, and then quenched with distilled water (5 mL). The obtained mixture was extracted three times with EE. The combined organic extracts were washed with water, dried over Na_2SO_4, filtered, and evaporated *in vacuo* to obtain crude diphenyl-^{13}C-carbinol, which was used further without purification.

2,2,7,8-Tetramethylchroman-6-ol (207 mg, 1.00 mmol, 1.0 eq.) and aluminum chloride (268 mg, 2.01 mmol, 2.0 eq.) were placed into an oven-dried three-necked round bottom flask with reflux condenser under argon and dissolved in dry THF (2.5 mL). The crude diphenyl-^{13}C-carbinol (prepared according to the above protocol) was dissolved in dry THF (1 mL) and added dropwise to the reaction mixture. After 15 h at room temperature, another 5 ml of dry THF and some aluminum chloride (67 mg, 0.5 mmol, 0.50 eq.) were added to the suspension. The reaction was quenched after 70 h at room temperature by adding distilled water (5 mL). The mixture was extracted three times with EE. The combined organic extracts were washed with saturated $NaHCO_3$-solution and water, dried over Na_2SO_4, filtered, and evaporated *in vacuo*. Column chromatography (16 g of silica gel, hexane:EE, v/v = 50:1) yielded 252 mg of 5a-^{13}C-5a,5a-diphenyl-2,2,5,7,8-pentamethylchroman-6-ol (**9***) as colorless crystals (68% overall yield).

^{1}H NMR: δ = 1.27 (s, 6H, H-2a), 1.72 (t, 2H, $^3J_{H,H}$ = 6.8 Hz, H-3), 2.08 (s, 3H, H-8b), 2.13 (s, 3H, H-7a), 2.69 (t, 2H, $^3J_{H,H}$ = 6.8 Hz, H-4), 4.36 (s, 1H, OH), 5.77 (d, 1H, $^1J_{C,H}$ = 125 Hz), 7.17–7.36 (m, 10H, Ar–H) ^{13}C NMR: δ = 12.1 (C-7a), 12.2 (C-8b), 21.3 (C-4), 26.6 (C-2a), 33.2 (C-3), 49.1 (C-5a), 72.3 (C-2), 116.7 (C-8), 124.2 (C-5), 124.3 (C-4a), 125.2 (C-7), 126.9 (C-4′), 128.9 (C-2′, C-6′), 129.0 (C-3′, C-5′), 141.6 (C-1′), 145.7 (C-8a), 145.9 (C-6).

EI-MS (70 eV): 373 (100%), 240 (44%), 239 (36%), 374 (27%), 225 (21%), 226 (18%), 316 (17%), 302 (15%), 166 (14%), 317 (10%), 179 (10%). R_f (*n*-hexane/ethyl acetate, v/v = 5:1) = 0.58.

3,3,5,6-Tetramethyl-12-phenyl-1,2,3,12-tetrahydropyrano [3,2-*a*]xanthene (10)

The reference compound for the final oxidation product of the biphenyl model compound was prepared in three steps.

2-(2,2,7,8-tetramethyl-chroman-6-yl-oxy)-benzaldehyde

2,2,7,8-Tetramethylchroman-6-ol (241 mg, 1.17 mmol, 1.0 eq.), 2-formylphenylboronic acid (350 mg, 2.33 mmol, 2.0 eq.), copper(II) acetate (350 mg, 1.75 mmol, 1.50 eq.), triethylamine (354 mg, 3.50 mmol, 3.0 eq.) and 4 Å molecular sieve (0.50 g) were mixed with DCM (10 mL) under argon and stirred at room temperature. After 17 hours, distilled water was added and the mixture was extracted three times with DCM. The combined organic extracts were washed with saturated $NaHCO_3$-solution, dried over Na_2SO_4, filtered, and evaporated *in vacuo*. The crude product was used further without purification.

^{1}H NMR: δ = 1.36 (s, 6H, 2a), 1.80 (t, 2H, $^3J_{H,H}$ = 6.7 Hz, H-3), 2.09 (s, 3H, N-7a), 2.17 (s, 3H, H-8b), 2.74 (t, 2H, $^3J_{H,H}$ = 6.7 Hz, H-4), 6.62 (s, 1H, H-5), 6.65 (ddd, 1H, J_1 = 8.43 Hz, J_2 = 1.00 Hz, J_3 = 0.46 Hz, H-6′), 7.06 (dddd, 1H, J_1 = 7.75 Hz, J_2 = 7.25 Hz, J_3 = 0.96 Hz, J_4 = 0.84 Hz, H-4′), 7.42 (ddd, 1H, J_1 = 8.46 Hz, J_2 = 7.25 Hz, J_3 = 1.85 Hz, H-5′), 7.91 (ddd, 1H, J_1 = 7.74 Hz, J_2 = 1.84 Hz, J_3 = 0.45 Hz, H-3′), 10.67 (d, 1H, J_1 = 0.87 Hz, CHO).^{13}C NMR: δ = 12.0 (C-7a), 12.6 (C-8b), 23.0 (C4), 27.0 (C-2a), 33.2 (C-3), 74.4 (C2), 115.6 (C-6′), 118.4 (C-5), 119.3 (C-4a), 121.5 (C-4′), 125.4 (C-8), 126.9 (C-7), 128.1 (C-2′), 128.1 (C-3′), 135.7 (C-5′), 145.6 (C-6), 149.5 (C-8a), 161.7 (C-1′), 189.8 (CHO). EI-MS (70 eV): 310 (100%), 121 (30%), 255 (27%), 135 (23%), 311 (22%), 211 (16%), 239 (13%), 91 (12%), 134 (11%), 77 (10%). R_f (*n*-hexane/ethyl acetate, v/v = 5:1) = 0.48.

Phenyl-[2-(2,2,7,8-tetramethylchroman-6-yloxy)-phenyl]-methanol

The crude residue was dissolved in dry THF (10 mL) and phenylmagnesium bromide (930 μL, 2.5 M in THF, 2.33 mmol, 2.0 eq.) was added dropwise. After 30 minutes, the reaction was quenched with saturated NH_4Cl-solution (5 mL). The mixture was extracted three times with EE. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and evaporated *in vacuo*. Column chromatography yielded 103 mg (23%) of phenyl-[2-(2,2,7,8-tetramethylchroman-6-yloxy)-phenyl]-methanol as a colorless solid.

^{1}H NMR: δ = 1.24 (s, 6H, H-2a), 1.67 (t, 2H, $^3J_{H,H}$ = 6.9 Hz, H-3), 1.78 (s, 3H, H-7a), 2.03 (s, 3H, H-8b), 2.57 (t, 2H, $^3J_{H,H}$ = 6.9 Hz, H-4), 2.88 (br, 1H, OH), 6.11 (s, 1H, CHOH), 6.30 (s, 1H, H-6′), 6.41 (d, 1H, *J* = 8.2 Hz, H-2′), 6.91 (t, 1H, *J* = 7.6 Hz, H-4′), 7.03 (t, 1H, *J* = 7.6 Hz, H-5′), 7.13–7.28 (m, 3H, H-3″, H-4″, H-5″), 7.33–7.40 (m, 3H, H-3′, H-2″, H-6″).

^{13}C NMR: δ = 12.0 (C-7a), 12.3 (C-8b), 22.5 (C-4), 27.0 (C-2a), 32.7 (C-3), 72.5 (CHOH), 73.9 (C-2), 114.6 (C-6′), 118.2 (C-5), 118.7 (C-4a), 121.5 (C-4′), 126.1 (C-8), 126.6 (C-2″, C-6″), 127.2 (C-4″), 127.7 (C-3′), 127.9 (C-7), 128.2 (H-3″, H-5″), 128.5 (C-5′), 132.2 (C-2′), 143.5 (C-1″), 145.5 (C-6), 148.7 (C-8a), 156.2 (C-1′).

EI-MS (70 eV): 135 (100%), 388 (73%), 190 (65%), 207 (26%), 197 (25%), 293 (22%), 370 (21%), 181 (21%), 77 (20%), 389 (19%), 105 (19%), 91 (18%), 372 (16%), 165 (16%), 121 (16%), 191 (15%), 313 (15%), 175 (14%), 69 (13%), 136 (11%), 301 (11%), 79 (11%), 152 (10%), 314 (10%), 134 (10%).

R_f (*n*-hexane/ethyl acetate, v/v = 5:1) = 0.33.

3,3,5,6-Tetramethyl-12-phenyl-1,2,3,12-tetrahydropyrano [3,2-a]xanthene (10)

The intermediate carbinol obtained according to the above protocol (10 mg) was dissolved in dry THF (2 mL) under argon and cooled to 0 °C. Concentrated sulfuric acid (5 μl) was added. The solution was diluted with EE (10 mL), neutralized with saturated $NaHCO_3$-solution, dried over $MgSO_4$, filtered, and evaporated *in vacuo*. 9 mg of 3,3,5,6-tetramethyl-12-phenyl-1,2,3,12-tetrahydropyrano[3,2-a]xanthene (**10**) were obtained as colorless solid (95% yield).

^{1}H NMR: δ = 1.08 (s, 3H, H-3a), 1.19 (s, 3H, H-3a), 1.52-1.70 (m, 1H, H-2), 2.09 (s, 3H, H-5a/H-6b), 2.21-2.32 (m, 1H, H-1), 2.30 (s, 3H, H-6b/H-5a), 2.60-2.70 (m, 1H, H-1), 5.09 (s, 1H, H-12), 6.87 (t, 1H, *J* = 7.2 Hz, H-4′), 6.98-7.14 (m, 6H, H-8, H-9, H-10, H-11, H-2′, H-6′), 7.19 (2 H, d, *J* = 7.8 Hz, H-3′, H-5′). ^{13}C NMR: δ = 11.9 (C-5a/C-6b), 12.1 (C-6b/C-5a), 19.8 (C-1), 26.6 (C-3a), 26.7 (C-3a), 32.6 (C-2), 42.8 (C-12), 72.8 (C-3), 115.5 (c-12b), 116.7 (C-8), 119.3 (C-11a), 122.7 (C-4′), 123.1 (C-5), 124.9 (C-6), 125.7 (C-12a), 126.3 (C-10), 127.3 (C-9, C-2′, C-6′), 128.6 (C-3′, C-5′), 128.7 (C-11), 143.6 (C-6a), 145.7 (C-1′), 147.5 (C-4a), 151.5 (C-7a). EI-MS (70 eV): 370 (100%), 293 (88%), 313 (68%), 314 (41%), 237 (29%), 371 (28%), 315 (25%), 294 (19%), 299 (17%), 209 (25%), 194 (11%), 298 (10%), 195 (10%), 249 (10%). R_f (*n*-hexane/ethyl acetate, v/v = 5:1) = 0.61.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: α-tocopherol · aromaticity · *ortho*-quinone methides · oxidation reactions · vitamin E · zwitterions

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