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Bromination of Tocopherols: Oxidative Halogenations and Rearrangements

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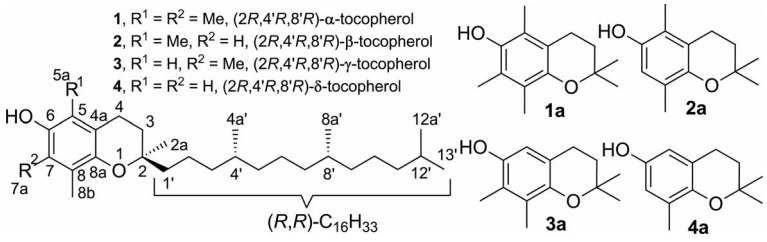
The bromination behaviour of all four tocopherols and the corresponding model compounds in acidic and basic aqueous media was studied. Acidic conditions resulted in quinones and brominated quinones, with the bromination of the tocopherol preceeding the oxidation to the quinone. Buffer type and concentration did not influence the reaction results, whereas pH and the ratio of buffer and ethanol used as a co-solvent strongly affected the reaction rates. In alkaline media, two or three major products and a multitude of minor byproducts were obtained, because the combination of oxidizing hypobromite and alkaline conditions allowed for more complex reaction pathways (oxidation, substitution, condensation, elimination) than the acidic conditions did. The *para*-quinones were major reaction products observed for all four tocopherols. Interestingly, if the quinone was substituted at C-5, it rearranged in a Michael-type addition process followed by substitution with a bromonium ion. The absence of a substituent at C-5, the presence of a bromine atom at C-7, or the absence of bromine in the reaction medium were all able to prevent this reaction. The rearrangement products could react further by substitution of the newly acquired bromine group for a hydroxy group. In the cases of γ- and δ-tocopherol, further rearrangement led to the formation of trioxo compounds.

Introduction

The term "vitamin E" is usually used synonymously with the chemical compound α-tocopherol. Strictly speaking, this is not correct, because "vitamin E" actually denotes a mixture of four different tocopherols (**1**–**4**, Scheme 1) – denoted α through δ – in varying ratios together with minor amounts of four tocotrienols that are distinguished from their tocopherol counterparts by their unsaturated side chains.[1] The Greek letters refer to certain methyl substituent patterns at the aromatic ring, the α-form being the permethylated form without free aromatic ring positions.[2]

The antioxidant effects of the tocopherols have been well documented[3] – especially for the α-isomer – so the term "vitamin E" is commonly linked with terms such as antioxidants, radical scavenger and "health". This "healthy touch" is also reflected in its usage in all kinds of cosmetics, nutrition additives, and "green" stabilizers for polymers.

The antioxidant action and chemistry of α-tocopherol (**1**) has been established for almost a century and vitamin E research seemed to offer few surprises any longer. Still, in the past decade vitamin E chemistry has experienced a revival, mainly for two reasons. Firstly, it was recognized that the prominent antioxidant effect of α-tocopherol was one of its functions, but by no means the only one. The influence of the substance on cell signaling, gene regulation, and other physiological functions is currently being actively studied.[4] The second reason for renewed interest in tocopherols was the growing opinion that the chemistry of the non-α-tocopherols had been severely neglected at the ex-



Scheme 1. Formulae of the four tocopherols **1**–**4** and their truncated model compounds **1a**–**4a** with methyl groups in place of their isoprenoid side chains.

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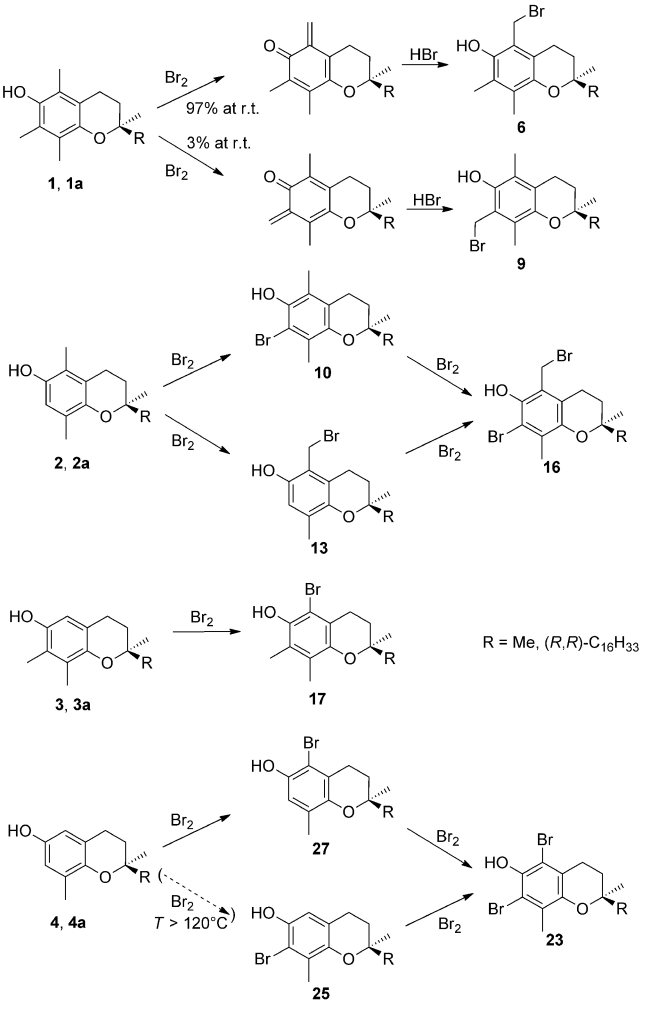
pense of the now well-studied α-form. A possible reason for this is that the antioxidant effect was for long regarded as the most important – if not only – significant characteristic of the tocopherols, and the antioxidant efficiency of the α-form was the highest out of the four tocopherols.[1,2] The non-α-tocopherols were thus simply regarded as "not as good" as α-tocopherol; a remnant of this view is still found in industrial processes in which non-α-tocopherols are permethylated to afford the α-isomer.

Non-α-tocopherols are, of course, potent antioxidants and in this respect resemble α-tocopherol in one chemical facet. However, because of their free aromatic positions they also show a rich chemistry of electrophilic substitution that α-tocopherol is unable to provide. γ-Tocopherol – in contrast with the α-form[5,6] – has been established to be a potent scavenger of reactive ionic and radical electrophiles, especially nitrogen-derived ones such as nitroxide, peroxynitrite, nitronium, and nitroso species, and the corresponding trapping products have been detected in human plasma and tissue samples.[7–9] So far, this research has centered mainly on γ-tocopherol, because it is more abundant. Similar reactivity would also be expected for the β- and δ-congeners, but no analogous studies for these compounds exist.

In our studies we are focusing on two strategies. One goal is to study the basic chemistry of non-α-tocopherols – in particular in relation to the α-form – while trying to introduce a certain systematization. Another is to provide standard compounds and reliable analytical data for non-α-tocopherol derivatives, the literature being rather ambiguous with regard to those compounds. Five sets of different analytical data (UV and ^{1}H NMR) existed for 5-nitro-γ-tocopherol,[10–16] for example, which left the actual identities of the analyzed compounds unclear. This was, of course, unacceptable, especially with regard to medical studies. In recent work we have focused on interactions of the tocopherols with nitrosating[17] and nitrating[18] species and have provided complete sets of analytical data, including crystal structures of the corresponding truncated model compounds in which the isoprenoid tocopherol side chains were replaced with methyl groups (cf. **1a**–**4a** in Scheme 1). This was followed by studies on the bromination of tocopherols, with the in vivo interactions of non-α-tocopherols with oxidatively halogenating enzymes, such as myeloperoxidases, generating hypohalite species, as background.[19]

At the very start of the bromination study it became clear that the system was more complicated than we had assumed, due to the strong dependence of products and kinetics both on the reaction medium and on the actual reactive bromine species. Generally, the halogenation based on bromonium species Br^+ and the oxidation, based on formation of $HOBr/BrO^-$ and dependent on the pH value, are superimposed on one another, which causes complex product mixtures and hard-to-follow kinetics. The previous study focused on reactions between tocopherols and elemental bromine in apolar media (*n*-hexane).[23] This specific reaction setup admittedly appears quite remote from physiological conditions, but in tocopherol chemistry the *n*-hexane medium is commonly used to simulate the strongly lipophilic membranes in which tocopherols are mainly situated in mammalian cells. Reference literature support in this field was rather limited: apart from data on 5-bromo-γ-tocopherol[20] and rearrangement products from the action of hypochlorite on α- and γ-tocopherol[21,22] there was no pertinent information. This previous study provided the bromination products of all four tocopherols in neat form without byproducts (Scheme 2), allowing unambiguous analytical characterization.[23]



Scheme 2. Bromination of all four tocopherols with elemental bromine under apolar aprotic conditions and structures of the products. Note that the process of electrophilic aromatic substitution leading to 5-bromo and 7-bromo derivatives competes with the formation of bromomethyl derivatives that are formed by a two-step oxidation/addition mechanism involving *ortho*-quinone methide intermediates.

For this work we were focusing on the structures of the bromination products of tocopherols in aqueous (aqueous/organic) media, on one hand to understand this physiologically relevant chemistry, and the other to provide standard compounds and reliable sets of analytical data for reference and comparison with compounds from in vivo studies. In aqueous systems, the pH becomes of primary importance, because it has an influence on the nature of the reactive species present, their oxidation potentials, and the types

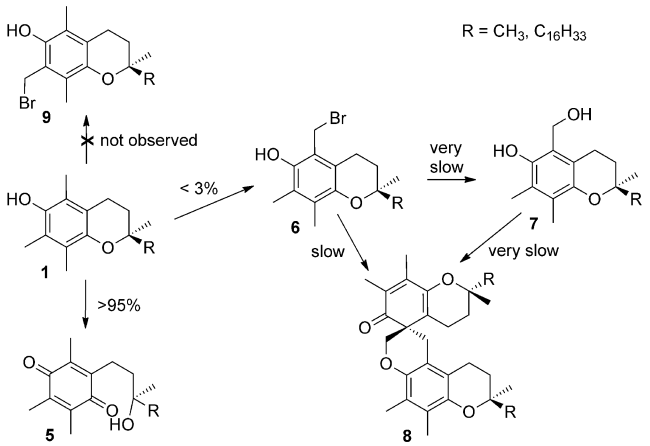
and ratios of parallel reactions taking place. We therefore kept the pH constant during the reactions to avoid scrambling of pH-dependent pathways, working throughout either under slightly acidic conditions (pH = 6) or under alkaline conditions (pH = 11). At first we focused on bromine as the halogen, mainly for practical reasons, such as to avoid the difficult-to-handle and difficult-to-dose gaseous chlorine. As in the previous studies, the reactions were in all cases carried out in parallel both for the tocopherols **1**–**4** themselves and for the corresponding truncated model compounds **1a**–**4a** (cf. Scheme 1).

Results and Discussion

Reaction in Acidic to Neutral Media

In aprotic media, α-tocopherol is brominated to the 5a-bromo derivative **6** and to small amounts of the 7a-bromo derivative **9** (Scheme 2).[23] The product ratio is determined by the relative stabilities of the intermediate *ortho*-quinone methides (oQMs), which are formed in a constant ratio of approximately 97:3 at room temp., as has been explained by the theory of strain-induced bond localization (SIBL).[24] In acidic or neutral aqueous media, the main product of bromination was the *para*-tocopherylquinone **5** (Scheme 3). Yields were above 95% independently of the reaction conditions, such as temperature, rate of oxidant addition, and also solvent composition, as long as water was the main component (>50%) in a binary mixture with ethanol, methanol, or dioxane. Small amounts (<3%) of the 5a-bromo derivative **6** were detected as well. The 7a-bromo derivative was not found at all. At room temperature, the starting material was completely consumed in less than 15 min. Upon prolonged standing of the reaction mixture for between 2 and 14 d, the *para*-quinone proved to be completely stable, but 5a-bromo-α-tocopherol (**6**) was converted into a mixture of 5a-hydroxy-α-tocopherol (**7**) and the α-tocopherol spiro dimer **8**. It was shown in a separate experiment that the 5a-hydroxy derivative also forms the spiro dimer under the pertinent conditions. This conversion happened much more slowly than in the original reaction mixture upon standing. It was thus reasonable to assume that the small amount of 5a-bromo derivative **6** present reacted slowly to form the dimer **8** and in an even slower parallel reaction to afford the 5a-hydroxy derivative **7**, this being further converted to dimer **8** in an equally slow reaction (Scheme 3). Because the reaction rates were strongly dependent on the solvent composition (H_2O/ethanol ratio) and the pH, we refrained from determining absolute kinetic values. The relative reaction rates of the three reactions **6** → **8**, **6** → **7**, and **7** → **8** in aqueous ethanol (50%) at pH = 6.0 and 22 °C were 11.4:1.8:1 (three independent runs).

It was evident in the case of α-tocopherol that the halogenating effect was minor and that the oxidative action, resulting in the *para*-quinone **5**, was the principal path. α-Tocopherol is the dominant species in cells and cell compartments, so this result might also be relevant for consideration of the fate of this tocopherol congener in its interaction with oxidative and halogenating enzymes in vivo, and of the physiological effects of its *para*-quinone metabolites that have only recently come into closer focus in research.[25,26]



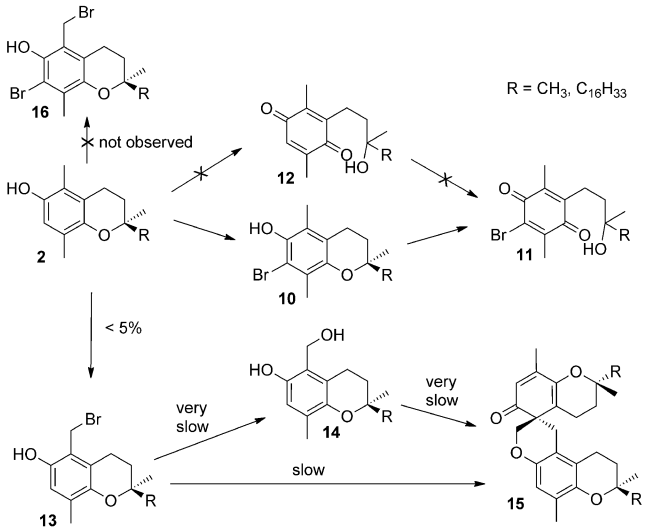
Scheme 3. Bromination of α-tocopherol (and α-tocopherol model compound) with bromine under neutral protic conditions.

The bromination of β-tocopherol in aprotic media offered quite complex chemistry, with two competing pathways leading to two monobromination products (compounds **10** and **13**, Scheme 2): a reaction at C-5a by a two-step oxidation/addition mechanism via the corresponding *o*QM, and a reaction at C-7 representing a classical electrophilic substitution on the aromatic core.[24] Both monobromination products can react further, at greatly different rates, at their "remaining" bromination sites to afford the dibromo derivative **16**.

The situation is somewhat less complicated in aqueous systems (acidic to neutral medium) insofar as no dibromination product **16** was found, regardless of the conditions, and the 5a-bromination product (**13**) was only formed above 50 °C, and even then in amounts below 5%. At temperatures below that limit, the only product was the 2-bromo-*para*-β-tocopherylquinone **11** (Scheme 4), the yields being nearly quantitative (>95% after isolation and purification). Conversion was as fast as in the case of α-tocopherol, with the starting material being completely consumed and converted into **11** at room temp. in approx. 15 min.

There are two conceivable pathways for the formation of this product: either 7-bromination to 7-bromo-β-tocopherol (**10**) and subsequent oxidation to the quinone **11**, or formation of β-tocopherylquinone (**12**) first, followed by bromination in a second step. It was easy to decide in favor of the first pathway, because β-tocopherylquinone is largely inert under the reaction conditions (although it forms a mixture of different ring bromination products upon prolonged reaction times of up to 14 d), whereas 7-bromo-β-tocopherol (**10**) – introduced as neat starting material – is readily converted into the observed brominated *para*-quinone **11** under the employed bromination conditions (Scheme 4).

When the bromination was conducted with only 1 equiv. of bromine (note that the reaction to the final product **11**

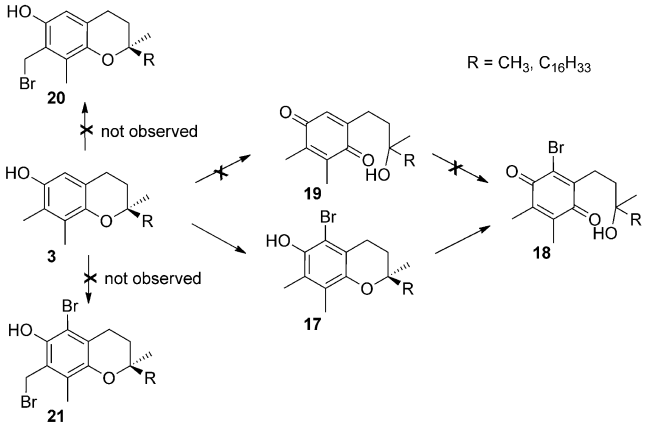


Scheme 4. Bromination of β-tocopherol (and β-tocopherol model compound) with bromine under neutral protic conditions.

requires 2 equiv.: one for bromination and one for oxidation to the quinone), nearly 90% of 7-bromo-β-tocopherol (**10**) along with about 5% bromoquinone **11** and 5% of unreacted starting materials was found. Direct comparison of the bromination of β-tocopherol to 7-bromo-β-tocopherol (**10**) and the oxidation of 7-bromo-β-tocopherol (**10**) to the *para*-quinone **11** at 20 °C showed that the former reaction proceeded 8.3 times faster than the latter, with application of first-order kinetics for the consumption both of β-tocopherol and of 7-bromo-β-tocopherol (**10**). The reaction rates were strongly dependent on the reaction medium and the pH value, in this case 50% ethanol and 50% phosphate buffer (2 M, pH = 6), as given in the Experimental Section.[27]

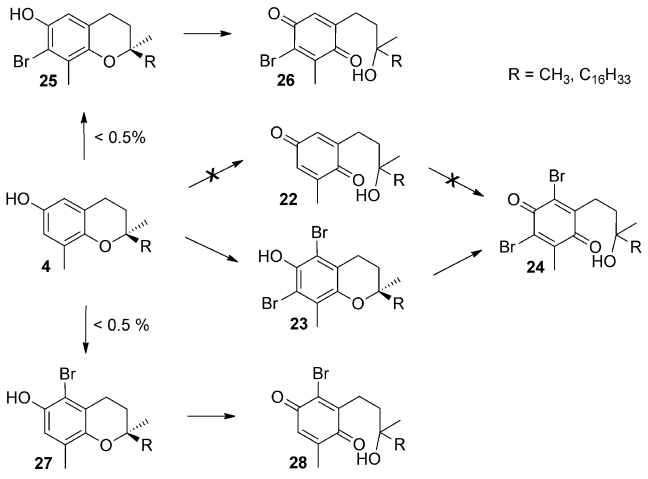
Similarly to the α-tocopherol case, the small amount of the 5a-bromo derivative **13** formed in the bromination reaction was slowly transformed upon standing into a mixture of 5a-hydroxy-β-tocopherol (**14**) and the β-tocopherol spiro dimer **15**. Compound **14** also afforded the spiro dimer **15** upon standing, but more slowly than the bromo derivative **13**. The relative reaction rates of the three reactions **13** → **15**, **13** → **14**, and **14** → **15** in aqueous ethanol (50%) at pH = 6.0 and 22 °C were 8.8:2.4:1 (three independent runs), and thus largely comparable to the α-tocopherol case.

In the case of γ-tocopherol, bromination in apolar media exclusively afforded the 5a-bromo product **17** (Scheme 2).[24] Just one product was also found in acidic to neutral protic medium. This was the bromo-*para*-quinone **18** (Scheme 5); no direct or indirect products of 7a-bromination [7a-bromo-γ-tocopherol (**20**) or 5,7a-dibromo-γ-tocopherol (**21**)] were observed. Analogously to the β-tocopherol case, the formation of **18** could either be via γ-tocopherylquinone (**19**), which is later further brominated, or via 5-bromo-γ-tocopherol (**17**), subsequently oxidized to the *para*-quinone. Again, the latter pathway was confirmed by additional experiments: whereas γ-tocopheryl quinone produced only very small amounts of **18** in complex mixtures after prolonged times, 5-bromo-γ-tocopherol (**17**) was readily converted into the bromoquinone **18** under the corresponding reaction conditions. Application of first-order kinetics (20 °C) showed the bromination of γ-tocopherol (**3**) to 5-bromo-γ-tocopherol (**17**) to proceed 12.4 times faster than the oxidation of 5-bromo-γ-tocopherol (**17**) to the bromoquinone **18**. The overall reaction from γ-tocopherol (**3**) to **18** was faster than the corresponding reactions of α- and β-tocopherol: the starting material was fully consumed in less than 3 min.



Scheme 5. Bromination of γ-tocopherol (and γ-tocopherol model compound) with bromine under neutral protic conditions.

In the case of δ-tocopherol one would expect complex behavior due to two aromatic positions being susceptible to electrophilic aromatic substitution and thus at least three bromination products: two monobrominated ones (**25**, **27**) and a dibrominated (**23**) one, along with their corresponding quinones (Scheme 6). However, the situation in acidic/neutral protic medium proved to be quite simple, with only one major product, the dibrominated *para*-quinone 2,6-dibromo-δ-tocopherylquinone (**24**), being found. The accumulated concentration of all other byproducts was below 0.5%. Whereas δ-tocopherylquinone (**22**) could not be bro-



Scheme 6. Bromination of δ-tocopherol (and δ-tocopherol model compound) with bromine under neutral protic conditions.

minated to **24** under these conditions, 5,7-dibromo-δ-tocopherol (**23**) reacted smoothly and quantitatively to afford **24** when treated with Br_2 in aqueous buffered ethanol (pH = 6). For δ-tocopherol the formation pathway of the brominated quinone is thus also via a brominated tocopherol, which is further oxidized, and not via a subsequently brominated quinone.

The formation of **24** from δ-tocopherol (**4**) consumes 3 equiv. of bromine: two for electrophilic substitutions at C-5 and C-7 and one to oxidize the quinone. Use of 3 equiv. or even an excess of bromine gave quantitative yields of **24**. Application of 2 equiv. of bromine resulted in a mixture of the dibromo-δ-tocopherol **23** with rather minor amounts (<0.5% each) of monobrominated δ-tocopherols (compounds **25** and **27**), unreacted starting material, and some dibromoquinone **24**. Going from 2 to 3 equiv. of bromine shifted the ratio of **23/24** increasingly towards the latter compound. Application of 1 equiv. of Br_2 only produced the dibromide **23** and monobromides (compounds **25** and **27**) in a 72:28 ratio, along with unconverted starting material and less than a 1% yield of **24**. These reactions indicated that the second bromination reaction proceeded quite rapidly (even more rapidly than the initial monobromination!), immediately consuming any intermediate monobromination product formed. Furthermore, both brominations are fast relative to the subsequent oxidation to the quinone. The apparent ease of the bromination of the monobromo derivative to afford the dibromide **23** is somewhat surprising, but as we had already seen in the case of bromination in apolar media, monobromination at C-5 has a minor activating effect rather than a deactivating one on the second bromination.[24] This effect was apparently even increased in polar protic media.

The formation of 5,7-dibromo-δ-tocopherol (**23**) from δ-tocopherol was 15.1 times faster than oxidation of **23** to the dibromoquinone **24** according to first-order kinetics (20 °C). The overall reaction from δ-tocopherol (**4**) to **24** was comparable to that of γ-tocopherol, again being much faster than the corresponding reactions of α- and β-tocopherol, so that conversion was complete in less than 3 min.

Reliable characterization of the δ-tocopherol monobromination products and their quinones were not possible with the small amounts obtainable on use of substoichiometric amounts of bromine. We thus prepared the bromoquinones **26** and **28** independently by bromination of δ-tocopherol under apolar conditions, which provided sufficient amounts of the monobromination products **25** and **27**,[24] and subsequent oxidation with $FeCl_3$ in methanol, a common protocol for the generation of tocopherylquinones. Comparison with these authentic samples confirmed the trace formation of **26** and **28** in the originally used bromination system.

It should be mentioned that down to pH = 3, the reaction outcome of the bromination did not change. For δ-tocopherol, for which at pH = 6 rather small amounts of byproducts apart from the main product **24** were found, the reaction at pH = 3 was quantitative, without any traces of byproducts. The trend of the overall reaction rate, however, was to slow down with decreasing pH. It could be speculated that the higher concentration of H^+ disfavors the formation of equally charged bromonium ions Br^+ and also disfavors deprotonation of the phenolic species into the phenolate forms, which are much more easily oxidized than the phenols themselves, resulting in an overall impeded reaction.

Reaction in Alkaline Media

When the bromination reactions were carried out in increasingly alkaline media, the product distributions changed gradually but profoundly. At pH = 7 the outcomes were insignificantly different from those of the above reactions at pH = 6, the only differences being some byproducts from the final bromoquinones in total amounts of less than 4%. Although these byproducts were not further studied in detail, mass spectra indicate the formal addition of HOBr and OH to these bromoquinones. At pH = 8 the formation of byproducts was already becoming more prominent, and at pH = 9 the amounts of the final products that had been observed at pH = 6 were reduced to no more than 15%. At pH = 11, which was thus chosen as the standard condition for bromination in protic, alkaline media, none of the products formed at pH = 6 were found at all. It is reasonable to assume that the fundamental change in the product distributions is due to the different oxidizing species present: whereas in protic media bromonium ions and elemental bromine are the main "active" species, under alkaline conditions hypobromite ($HOBr/OBr^-$) is mainly involved. This shows less brominating action but is rather strongly oxidizing.

Generally, the bromination reactions in alkaline media were much less "pleasant" than their counterparts at pH = 6, with the product mixtures being far more complex and structure elucidation of the final products also being more demanding. At pH = 6, for all four tocopherols, there was one major product formed quantitatively or near-quantitatively by a readily identifiable pathway. At pH = 11, the maximum yields of the main products were 50–55%, together with one or two products in the concentration range of 15–20%. Additionally, there were generally several minor products that still could amount up to 20%, although the concentration of each individual minor byproduct was less than 3%.

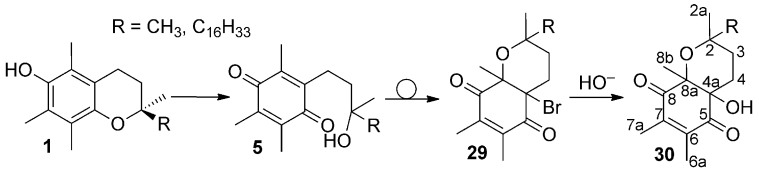
It was evident that increasing amounts of oxidant led to increasingly complex reaction mixtures, which is plausible because any phenolic or quinoid structures would be unstable in the presence of excess hypobromite and would undergo subsequent reactions. Moreover, all kinds of nucleophilic substitutions, condensations, and eliminations would also be favored in alkaline media. To reduce this complexity and to allow identification of pathways in the system, we used different stoichiometric amounts of bromine relative to the tocopherol, starting with 0.5 equiv., which would – in the hypothetical neat reaction to afford the *para*-quinone – correspond to 50% tocopherol conversion, followed by 1 equiv., corresponding to theoretically 100% conversion.

Because the reactions in acidic/neutral media had shown that up to 3 equiv. of oxidant could be consumed, we further increased the stoichiometric ratio in steps of 1 and also worked with 2, 3, 4 and 5 equiv. of oxidant relative to tocopherol. It should be noted that these stoichiometries were based on the assumption that the bromine added would be quantitatively converted into hypobromite. The pH value during the reactions was constant at 11, so that effects from changing alkalinity could be excluded.

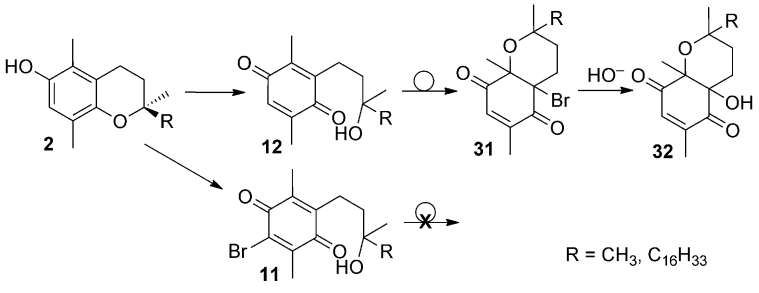
The three main products of the hypobromite treatment of α-tocopherol (see Scheme 7) were *para*-α-tocopherylquinone (**5**), 4a-bromo-2,6,7,8a-tetramethyl-2-(4,8,12-trimethyltridecyl)-3,4,4a,8a-tetrahydro-2*H*-chromene-5,8-dione (**29**) as a product of an oxidative and halogenative rearrangement reaction, and the derived 4a-hydroxychromenedione (**30**). The maximum product yield (**5**: 10.5%; **29**: 46%; **30**: 25.5%; sum 82%; ratio 1:4.3:2.4) was obtained with 2 equiv. of hypobromite. Use of any larger excess of hypobromite decreased the yield and increased the number and yields of minor byproducts that were not further studied (see above). With regard to the reaction mechanism, it was a noteworthy result that *para*-α-tocopherylquinone (**5**) was evidently an intermediate in the formation of the chromenedione **29**, which was readily confirmed: treatment of **5** in place of α-tocopherol (**1**) under otherwise identical conditions produced **29**, whereas in an alkaline medium without oxidant no transformation of **5** occurred (for a detailed discussion of the mechanism see below). Employment of increasing amounts of oxidant increased the amounts of **29** and **30** formed at the expense of **5**. Compound **29** was also clearly an intermediate in the formation of **30**, because introduction of **29** into the alkaline bromination reaction produced **30** in good yields. However, this reaction did not require hypobromite in order to take place, but just an alkaline medium, because quantitative yields of **30** were obtained when **29** was treated only with NaOH at pH = 11 (i.e., without added hypobromite), so its mechanism of formation is a simple nucleophilic substitution.

It should be noted that a chlorinated rearrangement product with a structure similar to **29** and **30** has been described by Southwell-Keely et al.[22,28] for the hypochlorite treatment of α- and γ-tocopherol, and structure elucidation of the rearrangement products in our work was greatly supported by their superb account. In this previous work, HOCl treatment was performed without a constant pH and without identification of intermediates and subsequent products, and so the earlier mechanistic proposal for the formation of the rearrangement products had to be adjusted in agreement with the new data, as discussed below.

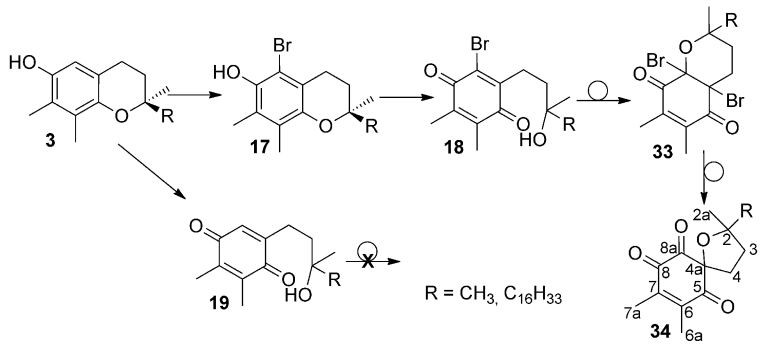
Very similar behavior was observed for the oxidation of β-tocopherol under alkaline conditions. Three main products were found (Scheme 8): the rearranged compound 4a-bromo-2,6,8a-trimethyl-2-(4,8,12-trimethyl-tridecyl)-3,4,4a,8a-tetrahydro-2*H*-chromene-5,8-dione (**31**), the derived 4a-hydroxychromenedione **32**, and the brominated compound 2-bromo-β-tocopherylquinone (**11**). *para*-β-Tocopherylquinone (**12**) was present only in small amounts (<5%) when substoichiometric amounts of hypobromite were used. The maximum yield of rearrangement products (sum 76%; **11**: 34%; **31**: 23%; **32**: 19%; ratio 1.8:1.2:1) was reached at 2 equiv. of hypobromite. Analogously to the α-case, the corresponding *para*-tocopherylquinone **12** was confirmed as an intermediate in the formation of **31**, and **32** was also shown to be formed from **31** by simple alkali treatment. Unlike the behavior of the α-congener, the yields of the (non-brominated) *para*-tocopherylquinone **12** were small (less than 2 equiv. of hypobromite) or even zero (2 equiv. of hypobromite or more), whereas appreciable amounts of the brominated *para*-quinone **11** were formed. Unlike the non-brominated *para*-quinone **12**, which reacted with hypobromite to afford **31**, the brominated *para*-quinone was stable under the reaction conditions. Only very



Scheme 7. Bromination of α-tocopherol (and α-tocopherol model compounds) with bromine under alkaline protic conditions.



Scheme 8. Bromination of β-tocopherol (and β-tocopherol model compounds) with bromine under alkaline protic conditions.



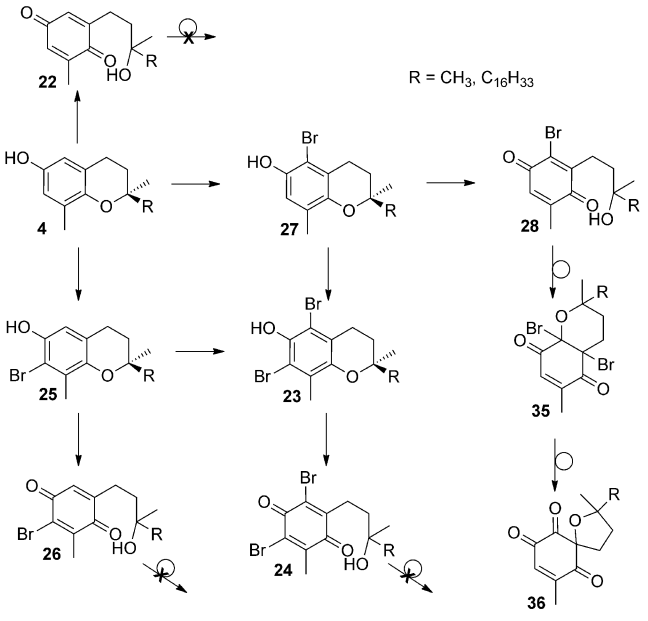
Scheme 9. Bromination of γ-tocopherol (and γ-tocopherol model compounds) with bromine under alkaline protic conditions.

large amounts of hypobromite (more than 5 equiv.) caused slow consumption of **11** with conversion into a complex mixture of fragments and multiple brominated products. Because the only structural difference between **11** and **12** is the 2-Br substituent in the former case, this seemingly insignificant modification must have had a pronounced influence, with the reactivity and reaction path being fundamentally changed.

The alkaline oxidation behavior of γ-tocopherol (Scheme 9) was quite different from that of the α- and β-forms. The three main products were γ-tocopherylquinone (**19**), the rearrangement product **33**, analogous to the rearrangement products of α- and β-tocopherol, and a hydrolysis product of this with spiro structure (compound **34**). The maximum yield of rearrangement products (sum 88%; **19**: 39%; **33**: 36%; **34**: 13%; ratio 3:2.8:1) was reached at 3 equiv. of hypobromite (2 equiv. in the α- and β-cases). In the path from **3** to **33**, the first equivalent is consumed in the bromination to afford **17**, another in the oxidation to afford the brominated *para*-quinone **18**, and the third in the rearrangement to **33** (for the detailed mechanism see Scheme 11, below).

An interesting aspect was the dissimilar natures of the involvements of the *para*-quinoid compounds *para*-tocopherylquinone (**19**) and 2-bromo-*para*-tocopherylquinone (**18**) in the reaction, despite their quite similar structures. Both were formed as primary intermediates, the former directly from **3**, the latter analogously to the reaction behavior in neutral media via the brominated phenol **17** (cf. Scheme 5). However, whereas the brominated quinone **18** underwent rearrangement into **33**, *para*-tocopherylquinone (**19**) was not further changed. The bromination of γ-tocopherol at C-5 (to afford **17** and then **18**) was thus a prerequisite for the rearrangement to occur: without that substituent at this position the reaction stopped at the quinone stage. This finding seemed somewhat contradictory, because one would assume that the cyclization reaction should proceed more easily at a sterically less hindered, unsubstituted site than at the Br-substituted (brominated γ-tocopherol) or Me-substituted (α-tocopherol, β-tocopherol) position. Evidently, the steric hindrance was completely overruled by much stronger effects, with rearrangement occurring *only if* C-5 was substituted, but at present we are unable to provide a conclusive explanation as to what this effect could be based on. The conversion from **33** into the spiro compound **34** is easier to understand. It is formed by formal substitution of the 8a-bromine by a hydroxide anion, followed by substitution of the second bromine atom at C-4a with ring contraction. More detailed mechanistic considerations are discussed below (see Scheme 12).

The chemical behavior of δ-tocopherol under alkaline oxidative conditions proved somewhat like a "superposition" of the chemistries of β- and γ-tocopherol. Bromination at C-7 prevented the occurrence of cyclization of the corresponding *para*-quinones, as had also been observed in the β-case: neither 6-bromo-δ-tocopherylquinone (**26**), formed via 7-bromo-δ-tocopherol (**25**), nor 2,6-dibromo-δ-tocopherylquinone (**24**), formed via 5,7-dibromo-δ-tocopherol (**23**), reacted further under the pertinent conditions (Scheme 10). Also here, the reason for this peculiar "blocking effect" remains unclear.



Scheme 10. Bromination of δ-tocopherol (and δ-tocopherol model compounds) with bromine under alkaline protic conditions.

δ-Tocopherylquinone (**22**) – formed as one major product – was stable in the presence of hypobromite and did not rearrange. Of all quinones formed, only 2-bromo-δ-toc-

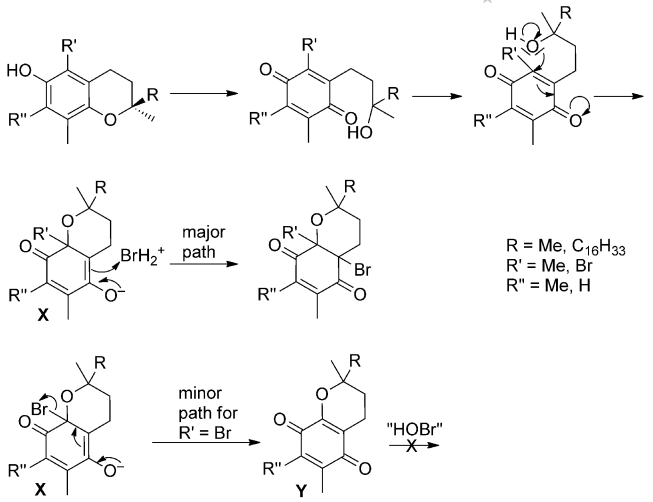
opherylquinone (**28**), the oxidation product of 5-bromo-δ-tocopherol (**27**), produced a rearrangement product (compound **35**) with a structure similar to those observed for the three other tocopherols. Analogously to the γ-tocopherol system, this rearrangement product formed the spiro compound **36** by alkaline hydrolysis (Scheme 10; for a detailed mechanism see Scheme 12, below).

With 3 equiv. of hypobromite, δ-tocopheryl quinone (**22**), the rearrangement product **35**, and the spiro compound **36** were the three main products, obtained in 36%, 34%, and 10% yields, respectively (sum of the three compounds: 80%, molar ratio 3.6:3.4:1). The brominated quinones **24** and **26** were present only in 3% and 7% yields, respectively.

The mechanism of the rearrangement reactions is basically the same for all four tocopherols. In a first step a *para*-tocopherylquinone is formed by two-electron oxidation of the parent phenol (Scheme 11). In the α- and β-cases this parent phenol is the tocopherol, in the γ- and δ-case the corresponding 5-bromo derivative. The subsequent key step is a cyclization involving nucleophilic attack of the former O-1 at C-5 with formation of an enolate intermediate **X** that immediately adds a bromonium ion at the former C-4a (Scheme 11). Apparently, the overall cyclization process is not a simple Michael-type addition, which would restore the *para*-quinoid system: in the absence of bromine compounds (i.e., when the quinones are treated just in alkali at pH = 11), no cyclization takes place, so the second step, the Br addition, seems to be crucial for the overall reaction to proceed (Scheme 11). Elimination of bromide from C-8a in **X** (i.e., the classical Michael path) was evidently disfavored, because the corresponding elimination product **Y** was not observed. Its formation would theoretically anyway be possible only for γ and δ derivatives that have a 8a-bromine substituent, but not for α and β compounds with an 8a-methyl group that cannot be eliminated. Compounds such as the rearrangement products **33**–**36** could, in theory, also be formed by addition of bromine or hypobromite to the hypothetical intermediate **Y**. However, *para*-quinoid systems, such as those in the 2-unsubstituted tocopherylquinones or the rearrangement products, were quite stable towards 1,2-dihalide or bromohydrin formation, so a similarly low reactivity also had to be assumed for intermediate **Y**. In addition, an independently synthesized material with a structure similar to **Y**, available from previous work,[29] was inert under the conditions of the oxidative rearrangement, so the involvement of **X** and **Y** in the overall rearrangement process could safely be ruled out.

The cyclization/Br addition sequence can also be conceived as an oxidation of the former C-4a and C-5 from the formal oxidation state ±0 to +1. It appears that the entropic gain through the cyclization must be quite large, because it is able to compensate for the energetically unfavorable destruction of a quinoid (i.e., cross-conjugated) system.

There are two interesting structural aspects with regard to the rearrangement. At first, the presence of a substituent at C-5 of the phenolic starting material [i.e., α-tocopherol (**1**), β-tocopherol (**2**), 5-bromo-γ-tocopherol (**17**), and 5-bromo-δ-tocopherol (**27**)] is an essential condition for the

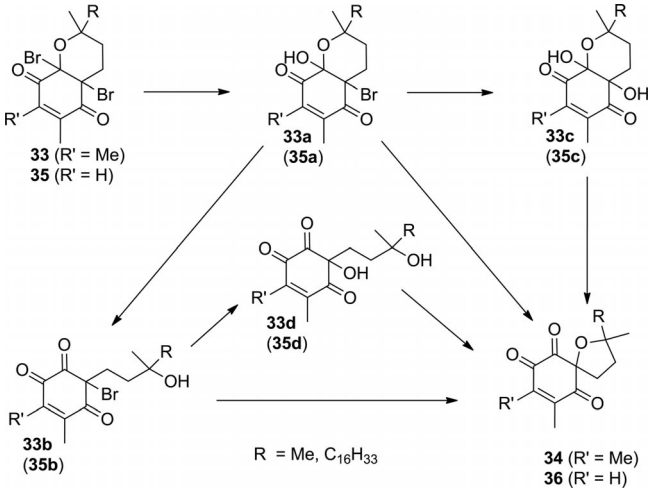


Scheme 11. Detailed rearrangement mechanism (cf. Schemes 7, 8, 9, and 10).

rearrangement to proceed. This substituent then becomes the substituent at C-2 in the corresponding *para*-quinones [i.e., α-tocopherylquinone (**5**), β-tocopherylquinone (**12**), 2-bromo-γ-tocopherylquinone (**18**), and 2-bromo-γ-tocopherylquinone (**28**)], and after rearrangement the angular group at the 8a-position in the rearrangement products (**29**, **31**, **33**, **35**). The quinones without 2-substituents, namely γ-tocopheryl quinone (**19**) and δ-tocopheryl quinone (**22**), are stable under the reaction conditions and do not rearrange. Secondly, 7-brominated compounds, such as 7-bromo-β-tocopherol (**11**), 7-bromo-δ-tocopherol (**25**), and 5,7-dibromo-δ-tocopherol (**23**), are only oxidized to the corresponding *para*-quinones, but these are stable and give no rearrangement products. This blocking effect at C-7 is also effective when C-5 is substituted, such as in 5,7-dibromo-δ-tocopherol (**23**).

The nucleophilic exchange of the bromine atom at C-4a leading to the 4-hydroxy compounds (see Schemes 7, 8, 9, 10, and 12) is a separate, subsequent reaction that does not directly belong to the actual rearrangement sequence. For α- and β-tocopherol, these hydroxy compounds (**30** and **32**, respectively) are stable and the final products, whereas in the cases of the γ- and δ-tocopherol compounds, there are subsequent reactions that eventually lead to trioxo compounds (**34** and **36**, respectively). The mechanism is discussed for the γ-tocopherol-type compounds **33** and **34** below, but it applies equally for **35** and **36** of the δ-tocopherol type.

The bromine atom in the 8a-position of **33** is quite readily nucleophilically substituted. An S_N1 mechanism is likely, because the intermediately occurring positive charge is resonance-stabilized by the adjacent oxygen atom. The resulting bicyclic 8a-hydroxy compound **33a**, a lactal, is equivalent to its monocyclic chain form, the trione **33b**. From both compounds, the "second" bromine atom can also be substituted by a hydroxy anion, which would result in compounds **33c** and **33d**, respectively (see Scheme 12). Formation of **34** would be conceivable either directly from **33a** and **33b** by



Scheme 12. Proposed mechanism of the transformation of brominated quinones **33** and **36** into the triones **34** and **36**, respectively.

nucleophilic substitution of the 4a-bromine atom or from **33c** and **33d** by nucleophilic substitution of the 4a-hydroxy group. Which of the compounds **33a**–**d** was the actual precursor of **34** was not determined. It was evident, however, that formation of the five-membered spiro compound **34** was greatly favored, because all four of the hypothetical intermediates **33a**–**d** were detected in the reaction mixture only in trace amounts as evidenced by GC–MS analysis of the crude mixture and might possibly be artifacts of the GC analysis. Chromatographic separation and attempted purification, however, resulted in the formation of trione **34** in all cases.

Conclusions

The bromination behavior of the tocopherols under protic conditions at pH = 6 provided quite consistent results. Independently of the actual tocopherol (or tocopherol model compound) used as starting material, *para*-tocopherylquinones were obtained; in the cases of the non-α compounds these were additionally brominated. In all cases it was confirmed that the bromoquinones were formed by bromination of the parent phenols and subsequent oxidation to the bromoquinones, rather than by oxidation to non-brominated quinones that would undergo bromination. The electrophilic bromination reactions proceeded in all cases about 10 times faster than the subsequent oxidations to the bromoquinons (8.3 times for β-, 12.4 times for γ-, and 15.1 times for δ-tocopherol). The overall reactions from the tocopherol to the (brominated) *para*-tocopherylquinone were similar between the two pairs of α- and β-tocopherol and of γ- and δ-tocopherol, with the reactions being about five times faster for the γ/δ pair. A similar pairing of the reactivities has also been found for bromination under apolar conditions[24] and for the nitration of tocopherols.[30] In general, reaction rates were strongly dependent on the reaction medium (i.e., the ratio between aqueous buffer and ethanol used and the set pH value). The concentration of the buffer and the type of buffer system – which, of course, had to be inert towards bromine and bromine-derived oxidizing species – were of little influence, by contrast.

Bromination of tocopherols under alkaline conditions resulted in complex reaction mixtures, each consisting of two or three main components and a multitude of minor products. With increasing pH value, the numbers and amounts of byproducts increased as well. Because the dominant species under alkaline conditions is the strong oxidant hypobromite ($HOBr/OBr^-$) and because alkaline conditions favor all kinds of nucleophilic substitutions, condensations, and eliminations, the obtained mixtures reflected the instability of tocopherylquinones under these conditions. Contributions of radical pathways to the formation of the bromination products are rather unlikely, because all typical homolytic products of tocopherols, such as dimers, were absent. Increasing the equivalents of brominating agent influenced product distribution as well. Usually, the highest yields of major components were obtained with 3 equiv.

One common reaction pathway was the oxidation to tocopherylquinones. Quinones without substituent at C-5 were stable and could be isolated from the reaction mixtures. Quinones bearing methyl groups (α- and β-tocopherol) or already brominated at C-5 (γ- and δ-tocopherol) underwent additional rearrangement reactions. Most likely, the former O-1 atom attacks C-5 in a Michael-type reaction, forming a new annulated ring and forcing a negative excess charge on the aromatic ring. This charge is then neutralized by the addition of a bromonium ion. If no free bromine was available, or if the quinone was not substituted at C-5, or if the quinone was brominated at C-7, the reaction did not take place. The newly introduced bromine atom in the obtained rearrangement products was readily substituted by hydroxide anions. For the γ- and δ-tocopherol-derived substances a final rearrangement step led to trioxo compounds.

Experimental Section

General: Commercial chemicals were of the highest grade available and were used without further purification. (2*R*,4′*R*,8′*R*)-Tocopherols were used throughout all reactions. Reagent-grade solvents were used for all extractions and workup procedures. Distilled water was used for all aqueous extractions and for all aqueous solutions. *n*-Hexane, diethyl ether, ethyl acetate, and chloroform used in chromatography were distilled before use. 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 precoated 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. Melting points, determined with a Kofler-type micro hot stage and a Reichert-Biovar microscope, are uncorrected. Elemental analyses were performed at the Microanalytical Laboratory of the Institute of Physical Chemistry at the University of Vienna. NMR spectra were recorded with a Bruker AV II 400 spectrometer with BBFO

probehead operating at 400.13 MHz (^{1}H) or 100.61 MHz (^{13}C) and a Bruker DPX 300 spectrometer with QNP probehead operating at 300.13 MHz (^{1}H) or 75.47 MHz (^{13}C) using standard Bruker software 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 by means of APT, HMQC and HMBC spectra. The abbreviation "d.i." denotes ^{13}C NMR resonances originating from two magnetically equivalent carbon atoms. GC–MS was performed with a GC 6890N/MSD 5973B instrument with a fused silica HP-5ms (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.

Synthesis of Brominated *p*-Tocopherylquinones

(1) From β-Tocopherol: 2-Bromo-β-tocopherylquinone [2-bromo-5-(3-hydroxy-3,7,11,15-tetramethylhexadecyl)-3,6-dimethyl-[1,4]benzoquinone, **11**]. A solution (0.1 M) of Br_2 (1.60 g, 0.51 mL) in ethanol (50 mL) and phosphate buffer (pH = 6, 2 M, 50 mL) was prepared. Part of this solution (2.5 mL, corresponding to 0.25 mmol Br_2) was added in one portion at 0 °C to a stirred solution of β-tocopherol (**2**, 41.7 mg, 0.10 mmol) in the same solvent (20 mL). The solution was stirred for 1 h, allowed to warm to room temp., stirred for another 10 min, and then concentrated in vacuo at room temp. to about two thirds of its volume. The remaining solution was extracted with *n*-hexane (3 times 10 mL), and the combined extracts were dried with $MgSO_4$. After removal of the solids, the solvent was evaporated and the residue was purified by flash chromatography on silica gel (*n*-hexane/diethyl ether, 20:1, v/v) to afford **11** as a colorless oil (47.1 mg, 91%). R_f = 0.27 (*n*-hexane/diethyl ether 5:1, v/v). $C_{28}H_{47}BrO_3$ (511.59): calcd. C 65.74, H 9.26; found C 65.84, H 9.52.

2-Bromo-β-tocopherylquinone Model [2-Bromo-5-(3-hydroxy-3-methylbutyl)-3,6-dimethyl-[1,4]benzoquinone, 11a]: A solution (0.1 M) of Br_2 (1.60 g, 0.51 mL) in aqueous ethanol (1:1, v/v, total volume 100 mL) was prepared. Part of this solution (5.0 mL, corresponding to 0.50 mmol Br_2) was added in one portion at 0 °C to a stirred solution of the 6-hydroxy-2,2,5,8-tetramethylchroman β-tocopherol model **2a** (41.2 mg, 0.20 mmol) in the same solvent (20 mL). The solution was stirred for 1 h, allowed to warm to room temp., stirred for another 10 min, and then concentrated in vacuo at room temp. to about one third of its volume. The remaining solution was extracted with dichloromethane (3 times 10 mL), and the combined extracts were dried with $MgSO_4$. After removal of the solids, the solvent was evaporated, and the residue was purified by flash chromatography on silica gel (*n*-hexane/diethyl ether, 5:1, v/v) to afford **11a** as a white, waxy solid. M.p. 27–29 °C (48.2 mg, 80%). R_f = 0.32 (*n*-hexane/diethyl ether, 1:1, v/v). $C_{13}H_{17}BrO_3$ (301.18): calcd. C 51.84, H 5.69; found C 52.00, H 5.62.

(2) From γ-Tocopherol: 2-Bromo-γ-tocopherylquinone [2-bromo-3-(3-hydroxy-3,7,11,15-tetramethylhexadecyl)-5,6-dimethyl-[1,4]-benzoquinone, **18**]. The same procedure as described above for the preparation of **11** was used with γ-tocopherol (**3**, 41.7 mg, 0.10 mmol) as the starting material, affording **18** as a colorless oil (45.0 mg, 88%). R_f = 0.24 (*n*-hexane/diethyl ether, 5:1, v/v). $C_{28}H_{47}BrO_3$ (511.59): calcd. C 65.74, H 9.26; found C 65.72, H 9.29.

2-Bromo-γ-tocopherylquinone Model [2-Bromo-3-(3-hydroxy-3-methylbutyl)-5,6-dimethyl-[1,4]benzoquinone, 18a]: The same procedure as described above for the preparation of **11a** was used with the γ-tocopherol model (**3a**, 41.2 mg, 0.20 mmol) as the starting material, affording **18a** as a slightly yellow solid. M.p. 41–42 °C (46.9 mg, 78%). R_f = 0.23 (*n*-hexane/diethyl ether, 5:1, v/v). $C_{13}H_{17}BrO_3$ (301.18): calcd. C 51.84, H 5.69; found C 51.78, H 5.89.

(3) From δ-Tocopherol: 2,6-Dibromo-δ-tocopherylquinone [2,6-dibromo-3-(3-hydroxy-3,7,11,15-tetramethylhexadecyl)-5-methyl-[1,4]benzoquinone, **24**]. The same procedure as described above for the preparation of **11** was used, with δ-tocopherol (**4**, 40.3 mg, 0.10 mmol) and the Br_2 solution (0.1 M, 3.5 mL, corresponding to 0.35 mmol Br_2) as the starting materials, affording **24** as a yellow wax. M.p. 27–28 °C (53.6 mg, 93%). R_f = 0.33 (*n*-hexane/diethyl ether, 5:1, v/v). $C_{27}H_{44}Br_2O_3$ (576.46): calcd. C 56.26, H 7.69; found C 56.37, H 8.01.

2,6-Dibromo-δ-tocopherylquinone Model [2,6-Dibromo-3-(3-hydroxy-3-methylbutyl)-5-methyl-[1,4]benzoquinone, 24a]: The same procedure as described above for the preparation of **11a** was used, with the δ-tocopherol model (**4a**, 38.4 mg, 0.20 mmol) and the Br_2 solution (0.1 M, 6.5 mL, corresponding to 0.65 mmol Br_2) as the starting materials, affording **24a** as a yellow solid. M.p. 55–56 °C (54.0 mg, 74%). R_f = 0.29 (*n*-hexane/diethyl ether, 5:1, v/v). $C_{12}H_{14}Br_2O_3$ (366.05): calcd. C 39.38, H 3.86; found C 39.28, H 4.14.

2-Bromo-δ-tocopherylquinone [2-Bromo-3-(3-hydroxy-3,7,11,15-tetramethylhexadecyl)-5-methyl-[1,4]benzoquinone, 28]: $FeCl_3 \cdot 6H_2O$ (3 equiv.) was added in one portion at 0 °C to a solution of 5-bromo-δ-tocopherol (**27**, 24.1 mg, 0.05 mmol) in the ternary solvent system methanol/water/diethyl ether (19:1:20, v/v/v, 40 mL). The mixture was stirred at this temperature for 1.5 h. A gradual color change to yellow indicated progressing formation of the *para*-quinone. Water (50 mL) was added, and the mixture was extracted with diethyl ether (30 mL). The organic phase was washed with brine and water, dried with $MgSO_4$, and concentrated in vacuo. The oily residue was purified by flash chromatography on silica gel (*n*-hexane/diethyl ether, 20:1, v/v) to afford **28** as a colorless oil (23.4 mg, 94%). R_f = 0.27 (*n*-hexane/diethyl ether, 5:1, v/v). $C_{27}H_{45}BrO_3$ (497.56): calcd. C 65.18, H 9.12; found C 65.22, H 9.03.

2-Bromo-δ-tocopherylquinone Model [2-Bromo-3-(3-hydroxy-3-methylbutyl)-5-methyl-[1,4]benzoquinone, 28a]: $FeCl_3 \cdot 6H_2O$ (3 equiv.) was added in one portion at 0 °C to a solution of 5-bromo-δ-tocopherol model (**27a**, 27.1 mg, 0.10 mmol) in the ternary solvent system methanol/water/diethyl ether (19:1:20, v/v/v, 40 mL). The mixture was stirred at this temperature for 1.5 h. A gradual color change to yellow indicated progressing formation of the *para*-quinone. Water (50 mL) was added, and the mixture was extracted with diethyl ether (3 times 20 mL). The combined organic phases were washed with water, dried with $MgSO_4$, and concentrated in vacuo. The waxy residue was purified by flash chromatography on silica gel (*n*-hexane/diethyl ether, 5:1, v/v) to afford **28a** as a colorless solid (19.5 mg, 68%). R_f = 0.39 (*n*-hexane/diethyl ether, 1:1, v/v). $C_{12}H_{15}BrO_3$ (287.16): calcd. C 50.19, H 5.27; found C 50.42, H 28.12.

2-Bromo-5-(3-hydroxy-3,7,11,15-tetramethylhexadecyl)-3-methyl-[1,4]benzoquinone (26): The same procedure as above was used for the preparation of **28**. The starting material was 7-bromo-δ-tocopherol (**25**, 24.1 mg, 0.05 mmol); the product was obtained as a yellowish oil (21.9 mg, 88%). $C_{27}H_{45}BrO_3$ (497.56): calcd. C 65.18, H 9.12; found C 65.32, H 9.11.

2-Bromo-5-(3-hydroxy-3-methylbutyl)-3-methyl-[1,4]benzoquinone (26a): The same procedure as above was used for the preparation of

28a. The starting material was 7-bromo-δ-tocopherol model (**25a**, 27.1 mg, 0.10 mmol); the product was obtained as an off-white solid (17.8 mg, 62%). $C_{12}H_{15}BrO_3$ (287.16): calcd. C 50.19, H 5.27, Br 27.83; found C 50.21, H 5.31.

(4) α-Tocopherol (Comparison): α-Tocopherylquinone [2-(3-hydroxy-3,7,11,15-tetramethylhexadecyl)-3,5,6-trimethyl-[1,4]-benzoquinone, **5**]. The same procedure as described above for the preparation of **11** was used with α-tocopherol (**1**, 43.1 mg, 0.10 mmol) as the starting material, affording **5** as a yellow oil (41.1 mg, 92%). R_f = 0.35 (*n*-hexane/diethyl ether, 5:1, v/v). The product was identical to the product obtained from α-tocopherol by oxidation with $FeCl_3$.[31] $C_{29}H_{50}O_3$ (446.72): calcd. C 77.97, H 11.28; found C 77.86, H 11.46.

α-Tocopherylquinone Model [2-(3-Hydroxy-3-methylbutyl)-3,5,6-trimethyl-[1,4]benzoquinone, 5a]: The same procedure as described above for the preparation of **11a** was used with α-tocopherol model (**1a**, 44.0 mg, 0.20 mmol) as the starting material, affording **5a** as a slightly yellow solid. M.p. 30 °C (46.9 mg, 78%). R_f = 0.39 (*n*-hexane/diethyl ether, 5:1, v/v). $C_{14}H_{20}O_3$ (236.31): calcd. C 71.16, H 8.53; found C 71.23, H 8.86.

General Procedure for the Preparation of the Products of the Oxidative Halogenation Rearrangement: A solution of the tocopherol (0.1 mmol) or tocopherol model compound (0.2 mmol) of interest in *n*-hexane (10 mL) was cooled to 0 °C. A buffer solution (pH = 11) was prepared by dissolving sodium tetraborate in aqueous NaOH (1 M). The solution was cooled to 0 °C and bromine (as a 0.1 M solution in THF, 0.5 to 5 mL, 1 mL corresponds to 0.1 mmol) and NaOH (as a 1 M solution in THF, 0.05 to 0.5 mL, 0.1 mL corresponds to 0.1 mmol) was added in one portion to the buffer solution, corresponding to 0.5 to 5 equiv. of hypobromite relative to the tocopherol. As soon as the solution had become colorless, the tocopherol solution was added, and the two-phase mixture was stirred vigorously for 15 min so that intimate mixing was guaranteed. Care should be taken that the contact between the aqueous alkaline hypobromite solution and the organic phase is not extended much beyond 15 min and that the pH does not deviate from 11 by more than 1 unit – otherwise the yield of the desired rearrangement products decreases rapidly, and a multitude of degradation products is obtained. After phase separation, the organic phase was washed with cold water (twice with 10 mL) and dried with $MgSO_4$. After separation of the solvents and removal of the solvents in vacuo, the remainder was purified by flash chromatography (silica gel, *n*-hexane/diethyl ether, 50:1, v/v), TLC was performed with an *n*-hexane/diethyl ether eluent (10:1, v/v).

(1) From α-Tocopherol: 4a-Bromo-2,6,7,8a-tetramethyl-2-(4,8,12-trimethyltridecyl)-3,4,4a,8a-tetrahydro-2*H*-chromene-5,8-dione (**29**). The above General Procedure was used, starting from α-tocopherol (**1**, 43.1 mg, 0.10 mmol) and affording **29** as reddish oil (27.3 mg, 52%). R_f = 0.33. $C_{29}H_{49}BrO_3$ (525.62): calcd. C 66.27, H 9.40; found C 66.21, H 9.62.

4a-Bromo-2,2,6,7,8a-pentamethyl-3,4,4a,8a-tetrahydro-2*H*-chromene-5,8-dione (29a): The above General Procedure was used, starting from 6-hydroxy-2,2,5,7,8-pentamethylchroman (**1a**, 44.1 mg, 0.20 mmol) and affording **29a** as a reddish oil (37.8 mg, 60%). R_f = 0.50. $C_{14}H_{19}BrO_3$ (315.21): calcd. C 53.35, H 6.08; found C 53.32, H 6.12.

(2) From β-Tocopherol: 4a-Bromo-2,6,8a-trimethyl-2-(4,8,12-trimethyltridecyl)-3,4,4a,8a-tetrahydro-2*H*-chromene-5,8-dione (**31**). The above General Procedure was used, starting from β-tocopherol (**2**, 41.7 mg, 0.10 mmol) and affording **31** as a reddish oil (18.4 mg, 36%). R_f = 0.37. $C_{28}H_{47}BrO_3$ (511.59): calcd. C 65.74, H 9.26; found C 66.01, H 9.13.

4a-Bromo-2,2,6,8a-tetramethyl-3,4,4a,8a-tetrahydro-2*H*-chromene-5,8-dione (31a): The above General Procedure was used, starting from 6-hydroxy-2,2,5,8-tetramethylchroman (**2a**, 41.2 mg, 0.20 mmol) and affording **31a** as a yellow oil (256.5 mg, 44%). R_f = 0.51. $C_{13}H_{17}BrO_3$ (301.18): calcd. C 51.84, H 5.69; found C 51.68, H 6.00.

(3) From γ-Tocopherol

4a,8a-Dibromo-2,6,7-trimethyl-2-(4,8,12-trimethyltridecyl)-3,4,4a,8a-tetrahydro-2*H*-chromene-5,8-dione (33): The above General Procedure was used, starting from γ-tocopherol (**4**, 43.1 mg, 0.10 mmol) and affording **33** as a yellowish oil (33.6 mg, 57%). R_f = 0.35. $C_{28}H_{46}Br_2O_3$ (590.49): calcd. C 56.96, H 7.85; found C 57.01, H 7.84.

4a,8a-Dibromo-2,2,6,7-tetramethyl-3,4,4a,8a-tetrahydro-2*H*-chromene-5,8-dione (33a): The above General Procedure was used, starting from 6-hydroxy-2,2,7,8-tetramethylchroman (**3a**, 41.2 mg,

Table 1. NMR spectroscopic data for the brominated *para*-tocopherylquinones.

Nucleus	α-Form, *p*-quinone **5**	β-Form, Br-*p*-quinone **11**	γ-Form, Br-*p*-quinone **18**	δ-Form, Br-*p*-quinone **28**	δ-Form, Br-*p*-quinone **26**	δ-Form, Br_2-*p*-quinone **24**
3-H	1.54 (m, 2 H)	1.52 (m, 2 H)	1.57 (m, 2 H)	1.56 (m, 2 H)	1.56 (m, 2 H)	1.55 (m, 2 H)
4-H	2.58 (m, 2 H)	2.58 (m, 2 H)	2.45 (m, 2 H)	2.46 (t, 2 H)	2.45 (t, 2 H)	2.47 (t, 2 H)
5a-H, 7a-H, 8b-H	2.01 (s, 6 H), 2.04 (s, 3 H)	2.03 (s, 6 H)	1.94 (s, 3 H), 1.96 (s, 3 H)	1.98 (s, 3 H)	1.99 (s, 3 H)	1.98 (s, 3 H)
5-H					6.45 (s, 1 H)	
7-H				6.49 (s, 1 H)		
OH	2.34 (s, 1 H)	1.65 (br. s, 1 H)	5.10 (br. s, 1 H)	4.85 (br. s, 1 H)	2.23 (br. s, 1 H)	4.13 (br. s, 1 H)
C-2	71.12	71.48	71.38	71.28	71.34	71.89
C-2a	26.66	26.99	27.12	27.17	27.15	27.21
C-3	39.90	39.92	39.64	39.68	39.65	39.64
C-4	21.84	21.88	24.52	24.63	24.60	24.66
C-5a, C-7a, C-8b	11.74, 12.08, 12.17	10.32 (C-8b),	11.66, 12.35	16.02	15.58	16.00
non-keto quinoid ring C	140.06, 140.23, 140.36, 144.23	124.66 (CBr), 140.55, 144.34, 144.55	124.34 (CBr), 141.23, 142.00, 147.88	124.66 (CBr), 133.34 (CH), 144.66, 148.52	124.90 (CBr), 132.32 (CH), 144.76, 149.50	123.67 (CBr), 124.13 (CBr), 145.02, 149.12
C-6, C-8a	186.06, 187.44	187.12, 187.19	186.88, 187.89	187.12, 188.01	187.03, 187.33	187.34, 188.00

0.20 mmol) and affording **33a** as a reddish oil (42.6 mg, 56%). R_f = 0.48. $C_{13}H_{16}Br_2O_3$ (380.08): calcd. C 41.08, H 4.24; found C 40.96, H 4.37.

(4) From δ-Tocopherol

4a,8a-Dibromo-2,6-dimethyl-2-(4,8,12-trimethyltridecyl)-3,4,4a,8a-tetrahydro-2*H*-chromene-5,8-dione (35): The above General Procedure was used, starting from δ-tocopherol (**4**, 40.5 mg, 0.10 mmol) and affording **35** as a reddish oil (21.9 mg, 38%). R_f = 0.35. $C_{27}H_{44}Br_2O_3$ (576.46): calcd. C 56.26, H 7.69; found C 56.11, H 7.86.

4a,8a-Dibromo-2,2,6-trimethyl-3,4,4a,8a-tetrahydro-2*H*-chromene-5,8-dione (35a): The above General Procedure was used, starting from 6-hydroxy-2,2,8-trimethylchroman (**4a**, 38.4 mg, 0.20 mmol) and affording **35a** as a red oil (28.5 mg, 39%). R_f = 0.39. $C_{12}H_{14}Br_2O_3$ (366.05): calcd. C 39.38, H 3.86; found C 39.52, H 4.04.

Table 2. NMR spectroscopic data for the truncated brominated *para*-tocopherylquinones.

Nucleus	α-Form, *p*-quinone **5a**	β-Form, Br-*p*-quinone **11a**	γ-Form, Br-*p*-quinone **18a**	δ-Form, *p*-quinone **28a**	δ-Form, *p*-quinone **26a**	δ-Form, *p*-quinone **24a**
2a-H	1.29 (s, 6 H)	1.30 (s, 6 H)	1.22 (s, 6 H)	1.24 (s, 6 H)	1.22 (s, 6 H)	1.22 (s, 6 H)
3-H	1.54 (m, 2 H)	1.52 (m, 2 H)	1.57 (m, 2 H)	1.56 (m, 2 H)	1.56 (m, 2 H)	1.55 (m, 2 H)
4-H	2.58 (m, 2 H)	2.58 (m, 2 H)	2.45 (m, 2 H)	2.46 (t, 2 H)	2.45 (t, 2 H)	2.46 (t, 2 H)
5a-H, 7a-H, 8b-H	2.01 (s, 6 H) 2.06 (s, 3 H)	2.04 (s, 6 H)	1.94 (s, 3 H) 1.95 (s, 3 H)	1.98 (s, 3 H)	1.99 (s, 3 H)	1.98 (s, 3 H)
5-H					6.45 (s, 1 H)	
7-H				6.49 (s, 1 H)		
OH	2.34 (s, 1 H)	1.65 (br. s, 1 H)	5.10 (br. s, 1 H)	4.85 (br. s, 1 H)	2.23 (br. s, 1 H)	4.13 (br. s, 1 H)
C-2	70.54	70.72	70.66	70.88	70.70	70.88
C-2a	28.84	28.92	29.00	29.02	28.92	29.01
C-3	42.02	41.95	41.73	41.75	41.77	41.75
C-4	21.52	21.54	24.22	24.26	24.24	24.24
C-5a, C-7a, C-8b	11.74, 12.07, 12.13	10.30 (C-8b)	11.66, 12.35	16.02	15.58	16.00
non-keto quinoid ring C	140.09, 140.25, 140.35, 144.24	124.70 (CBr), 140.60, 144.38, 144.58	124.40 (CBr), 141.12, 141.88, 148.02	124.66 (CBr), 133.34, (CH), 144.76, 148.34	125.03 (CBr), 132.38 (CH), 144.92, 149.71	123.24 (CBr), 124.08 (CBr), 144.45, 149.13
C-6, C-8a	186.03, 187.42	187.18, 187.31	186.82, 187.95	186.99, 187.92	187.23, 187.26	187.30, 188.23

Table 3. NMR spectroscopic data for the oxidative halogenation rearrangement products of tocopherols and tocopherol model compounds (**29**, **29a**, **31**, **31a**, **33**, **33a**, **35**, **35a**; atom labelling according to Scheme 7).

Nucleus	α-Toc	α-Toc model	β-Toc	β-Toc model	γ-Toc	γ-Toc model	δ-Toc	δ-Toc model
2a-H	1.30 (s, 3 H)	1.11 (s, 3 H), 1.35 (s, 3 H)	1.30 (s, 3 H)	1.12 (s, 3 H), 1.35 (s, 3 H)	1.30 (s, 3 H)	1.12 (s, 3 H), 1.30 (s, 3 H)	1.28 (s, 3 H)	1.13 (s, 3 H), 1.33 (s, 3 H)
3-H	1.76–1.90 (m, 1 H), 2.02–2.08 (m, 1 H)	1.76–1.92 (m, 1 H), 2.02–2.10 (m, 1 H)	1.72–1.90 (m, 1 H), 2.00–2.06 (m, 1 H)	1.72–1.92 (m, 1 H), 2.01–2.09 (m, 1 H)	1.90–1.96 (m, 1 H), 2.01–2.09 (m, 1 H)	1.89–1.96 (m, 1 H), 2.01–2.12 (m, 1 H)	1.94–2.00 (m, 1 H), 2.06–2.11 (m, 1 H)	1.94–1.98 (m, 1 H), 2.06–2.12 (m, 1 H)
4-H	2.15–2.22 (m, 1 H), 2.83–2.95 (m, 1 H)	2.16–2.24 (m, 1 H), 2.82–2.96 (m, 1 H)	2.28–2.34 (m, 1 H), 2.94–2.97 (m, 1 H)	2.26–2.34 (m, 1 H), 2.92–2.96 (m, 1 H)	2.31–2.37 (m, 1 H), 2.90 (br., 1 H)	2.31–2.40 (m, 1 H), 2.91 (br., 1 H)	2.34–2.44 (m, 1 H), 2.97 (br., 1 H)	2.38–2.46 (m, 1 H), 2.97 (br., 1 H)
CH_3-6a	2.12[a] (s, 3 H)	2.12[a]	2.12 (s, 3 H)	2.12	2.08[a] (s, 3 H)	2.07[a] (s, 3 H)	2.11 (s, 3 H)	2.11 (s, 3 H)
7-H			6.62 (2, 1 H)	6.62 (2, 1 H)			6.66 (s, 1 H)	6.66 (s, 1 H)
CH_3-7a	2.14[a] S, 3 H)	2.15[a]			2.10[a] S, 3 H)	2.10[a] S, 3 H)		
CH_3-8b	1.74 (s, 3 H)	1.72 (s, 3 H)	1.71 (s, 3 H)	1.72 (s, 3 H)				
C-2	77.90	77.22	77.96	77.96	77.94	77.25	77.20	77.20
C-2a	23.92	27.68, 27.80	23.85	27.88, 28.03	23.92	27.93, 28.26	23.94	28.03, 28.27
C-3	36.65	38.78	36.70	38.82	36.62	38.60	36.37	38.59
C-4	27.68	27.40	28.04	27.87	28.82	28.77	27.91	28.25
C-4a	86.21	86.06	86.22	86.25	87.70	87.53	87.94	87.80
C-5	191.29	191.46	192.10	192.12	191.79	192.03	191.99	192.06
C-6	141.45	141.43	138.42	138.72	140.84	140.44	151.01	150.37
CH_3-6a	13.52[a]	13.49[a]	15.18	15.24	13.82[a]	13.76[a]	16.23	16.97
C-7	144.20	144.17	132.01	132.23	145.12	145.08	131.80	131.85
CH_3-7a	13.54[a]	13.52[a]			14.02[a]	14.03[a]		
C-8	185.70	185.62	186.19	186.37	182.11	183.81	182.73	182.94
C-8a	90.89	90.87	92.88	92.84	89.01	89.05	89.92	90.09
CH_3-8b	20.44	20.09	20.32	20.21				

[a] These assignments can be exchanged.

Table 4. NMR spectroscopic data for the hydrolyzed products of the oxidative halogenation rearrangements of tocopherols and tocopherol model compounds (**30**, **30a**, **32**, **32a**, **34**, **34a**, **36**, **36a**; atom labelling according to Schemes 7 and 9).

Nucleus	α-Toc	α-Toc model	β-Toc	β-Toc model	γ-Toc	γ-Toc model	δ-Toc	δ-Toc model
2a-H	1.30 (s, 3 H)	1.12 (s, 3 H), 1.35 (s, 3 H)	1.30 (s, 3 H)	1.13 (s, 3 H), 1.35 (s, 3 H)	1.29 (s, 3 H)	1.12 (s, 3 H), 1.31 (s, 3 H)	1.28 (s, 3 H)	1.11 (s, 3 H), 1.35 (s, 3 H)
3-H	1.78–1.92 (m, 1 H), 2.02–2.06 (m, 1 H)	1.78–1.92 (m, 1 H), 2.02–2.08 (m, 1 H)	1.74–1.90 (m, 1 H), 2.01–2.06 (m, 1 H)	1.73–1.92 (m, 1 H), 2.01–2.07 (m, 1 H)	1.82–1.89 (m, 2 H)	1.82–1.89 (m, 2 H)	1.82–1.89 (m, 2 H)	1.82–1.89 (m, 2 H)
4-H	1.92–2.02 (m, 1 H), 2.83–2.95 (m, 1 H)	1.92–2.03 (m, 1 H), 2.82–2.96 (m, 1 H)	1.95–2.03 (m, 1 H), 2.94–2.97 (m, 1 H)	1.94–2.03 (m, 1 H), 2.92–2.96 (m, 1 H)	2.08–2.22 (m, 1 H), 3.04–3.08 (td, 1 H)	2.08–2.20 (m, 1 H), 3.04–3.10 (m, 1 H)	2.12–2.22 (m, 1 H), 3.00–3.10, (td, 1 H)	2.12–2.21 (m, 1 H), 3.00–3.10, (m, 1 H)
CH_3-6a	2.15[a] (s, 3 H)	2.14[a]	2.15 (s, 3 H)	2.15	2.10[a] (s, 3 H)	2.10[a] (s, 3 H)	2.12 (s, 3 H)	2.12 (s, 3 H)
7-H			6.56 (s, 1 H)	6.56 (s, 1 H)			6.64 (s, 1 H)	6.64 (s, 1 H)
CH_3-7a	2.15[a] (s, 3 H)	2.15[a]			2.11[a] (s, 3 H)	2.11[a] (s, 3 H)		
CH_3-8b	1.72 (s, 3 H)	1.70 (s, 3 H)	1.70 (s, 3 H)	1.71 (s, 3 H)				
C-2	78.62	78.26	78.84	78.80	80.30	80.01	79.55	79.57
C-2a	23.92	27.80, 27.88	23.60	27.88, 28.96	23.68	27.84, 28.20	23.68	27.90, 28.20
C-3	34.35	36.98	34.39	37.06	38.84	40.02	38.76	40.04
C-4	27.24	26.90	27.66	27.33	28.60	28.58	28.07	28.38
C-4a	89.80	89.82	89.92	89.89	96.12	95.94	96.42	96.28
C-5	190.88	190.90	191.77	191.78	188.08	188.38	188.12	188.30
C-6	141.42	141.40	138.32	138.68	146.55[a]	146.20[a]	152.78	153.12
CH_3-6a	14.18[a]	14.24[a]	16.24	16.22	14.55[b]	14.50[b]	16.23	16.97
C-7	144.12	144.12	132.33	132.39	146.24[a]	146.32[a]	133.24	133.28
CH_3-7a	13.92[a]	13.90[a]			14.52[b]	14.52[b]		
C-8	186.13	185.08	186.60	186.73	181.04	181.39	181.12	181.18
C-8a	90.23	90.19	92.24	92.22	191.34	191.52	191.18	191.24
CH_3-8b	18.22	18.02	18.16	18.12				

[a] These assignments can be exchanged. [b] These assignments can be exchanged.

NMR: The ^1H and ^{13}C NMR spectroscopic data for the isoprenoid side are given only once because there are only insignificant differences between the derivatives. ^1H NMR: δ = 0.83–0.88 (m, 12 H, 4 CH_3), 1.30 (s, 3 H, 2a-H), 1.00–1.67 (m, 23 H, 10 CH_2, 3 CH) ppm. ^{13}C NMR: δ = 19.66 (C-4a′), 19.75 (C-8a′), 20.8 (C-2′), 22.61 (C-13′), 22.72 (C-12a′), 24.47 (C-6′), 24.77 (C-10′), 27.90 (C-12′), 32.62 (C-8′), 32.69 (C-4′), 37.25 (C-7′), 37.38 (C-9′), 37.50 (C-5′), 37.52 (C-3′), 39.31 (C-11′), 40.8 (C-1′) ppm. Other NMR data are listed in Tables 1, 2, 3, and 4.

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