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Bromination of Non-α-Tocopherols: A Comparative Synthetic, Kinetic and Computational Study

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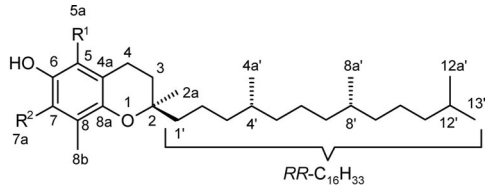
The bromination chemistry of the three non-α-tocopherols and of their truncated model compounds in apolar solvents was extensively studied and compared to that of the α-congener. Bromination occurs at free aromatic positions for all non-α-tocopherols. In the case of δ-tocopherol, there is a preference for C-5 over C-7. In the presence of a 5-methyl substituent, as in β-tocopherol, formation of the 5a-bromo derivative by an oxidation/addition mechanism via the corresponding *o*-quinone methide becomes a competitive process. By measurement of product ratios at different temperatures, the relative and absolute activation energies of the reaction systems with parallel reactions going on (β- and δ-tocopherol) were established. The kinetic data were in very good agreement with DFT results that showed the product ratio for δ-tocopherol bromination to correlate with the stabilities of the cationic bromination intermediates. All products were comprehensively characterized, providing reliable analytical standards and reference compounds.

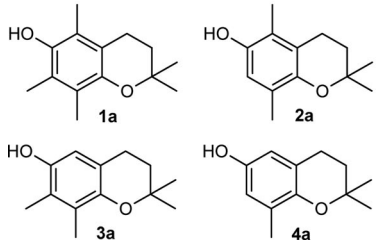
Introduction

The term "vitamin E" is usually (and incorrectly) used as a synonym for α-tocopherol, although it actually denotes a mixture of four tocopherols (**1**–**4**, Scheme 1) and four tocotrienols.[1–3] All four tocopherols are superb antioxidants, with the α-form having the highest vitamin E activity,[4,5] and have the (2*R*,4′*R*,8′*R*) stereochemistry. They differ in the number and positions of methyl groups on their aromatic rings and are distinguished by the Greek prefixes α to δ. In the case of α-tocopherol (**1**), comprehensive data have been accumulated on oxidation behavior, general chemistry, and different facets of medical and physiological effects and applications. The non-α-tocopherols **2**–**4**, in contrast, have been somewhat neglected, which might be due variously to the prominence of α-tocopherol in all kinds of formulations, the fact that non-α-tocopherols are industrially permethylated to give the α-congener, and the still high costs for the pure non-α forms as opposed to the cheap and readily available α-tocopherol.

α-Tocopherol (**1**), which is substituted at all aromatic positions, offers rich oxidation chemistry, but little possibility for derivatization at the aromatic ring. The non-α-tocopherols **2**–**4** possess free aromatic positions, and so they are readily susceptible to electrophilic aromatic substitution. It is known today that the γ-homologue – in contrast with the α-form[6,7] – is a good trap of electrophiles under physiological conditions, and such trapping products have been detected in human plasma and tissue samples.[8–10] No analogous studies for the β- and δ-homologues exist.



1, R¹ = R² = Me, (2*R*,4′*R*,8′*R*)-α-tocopherol
2, R¹ = Me, R² = H, (2*R*,4′*R*,8′*R*)-β-tocopherol
3, R¹ = H, R² = Me, (2*R*,4′*R*,8′*R*)-γ-tocopherol
4, R¹ = R² = H, (2*R*,4′*R*,8′*R*)-δ-tocopherol



Scheme 1. Formulae of the four tocopherols **1**–**4** and their truncated model compounds **1a**–**4a**, each bearing a methyl group instead of the isoprenoid side chain.

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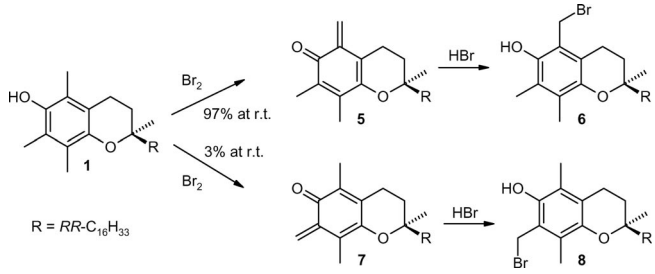
trite, cyanate, or thiocyanate. Non-α-tocopherols seem to be ideal candidates as molecular probes of the reaction modes of such enzymes. In previous studies we addressed the nitrosation[11] and nitration[12] chemistry of non-α-tocopherols, both to provide the different nitroso- and nitrotocopherols as standard compounds and to establish their analytical data reliably. This was necessary because a review of the pertinent literature had revealed largely contradictory analytical data (UV, NMR) for the reaction products of γ-tocopherol with nitrating/nitrosating species,[13–19] as well as a nearly complete lack of data for the reaction products of β- and δ-tocopherol. When we started to work on the interplay of non-α-tocopherols with hypohalites and halogenating enzyme systems we faced a similar problem. Apart from data on 5-bromo-γ-tocopherol[20] and rearrangement products from the action of hypochlorite on α- and γ-tocopherol,[21,22] the pertinent literature did not provide relevant information. For practical reasons we focused first on bromine as the halogen (to avoid the difficult-to-handle and difficult-to-dose gaseous chlorine), and this lack of data left us with the task either of establishing (for β- and δ-tocopherol) or reinvestigating (for γ-tocopherol) the structures of the corresponding bromination products, so that standard compounds and a reliable reference set of analytical data would then be available. This was done in all cases both for the tocopherols **1**–**4** themselves and for the corresponding truncated model compounds **1a**–**4a**, each bearing a methyl group instead of the tocopherols' isoprenoid side chain. Replacement of this chain is known to have no effect on the UV data and the aromatic NMR resonances.[23,24] The α-form has been included in the following report for reasons of comparability and completeness.

Here we would like to present our synthetic work on the bromination chemistry of non-α-tocopherols in apolar media (also in comparison with that of the α-congener), together with the products' analytical data as references for further work. The more complex reaction systems of β-tocopherol and δ-tocopherol (reaction at C-5/C-5a vs. reaction at C-7) were studied kinetically and computationally as well. Although purely brominating conditions (elemental bromine in *n*-hexane) were chosen for this work, forthcoming studies will focus on protic or aqueous solvents and thus will also cover oxidatively halogenating conditions (hypobromite). The presence of such solvents would be expected to change both the types of products formed and the product distributions. The isolation, purification, and unambiguous identification of the in vitro reaction products and intermediates provides a firm basis on which studies on the in vivo reactions with electrophiles can build.

Results and Discussion

Bromination of α-tocopherol (**1**) in aprotic media has been shown to proceed by a non-radical, two-step oxidation/addition mechanism via the intermediate *o*-quinone methide (*o*QM) **5**, which combines with the hydrogen bromide produced in the first step (Scheme 2).[25] The involvement of **5** has been comprehensively confirmed by trapping reactions, addition of competing nucleophiles, and spirodimerization in the absence of co-reactants.



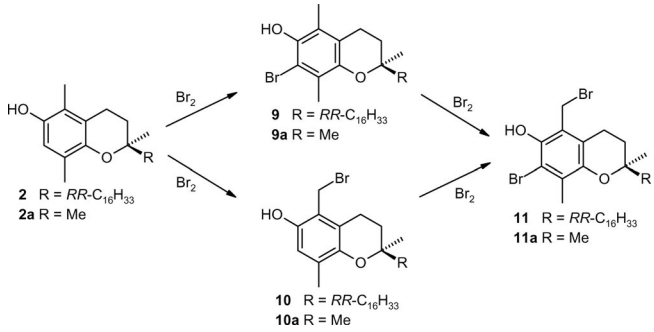
Scheme 2. Bromination of α-tocopherol leading to 5a-bromo-α-tocopherol (**6**) as the main product, by a two-step oxidation/addition mechanism involving *o*QM (**5**).

The bromination product 5a-bromo-α-tocopherol (**6**) is a key starting material in tocopherol chemistry, being used, for instance, to introduce the Toc (5a-α-tocopherol) protecting group[26] or to produce a variety of 5a-substituted tocopherols. The bromination reaction provides 5a-*o*QM (**5**) and 7a-*o*QM (**7**) in an approximate 97:3 ratio at room temp. – and thus also the subsequent bromination products 5a-bromo-α-tocopherol (**6**) and 7a-bromo-α-tocopherol (**8**), respectively. The unusual regioselectivity has been explained by the theory of strain-induced bond localization (SIBL),[27] which predicts the ratio of the two *o*QM intermediates as a function of the annulation angle sum of the heterocyclic ring adjacent to the trimethylaromatic core. By and large, the bromination chemistry of α-tocopherol and its mechanistic facets can be regarded as reasonably well established, and so shall not be discussed further here. A brief mechanistic summary is given in Scheme 2.

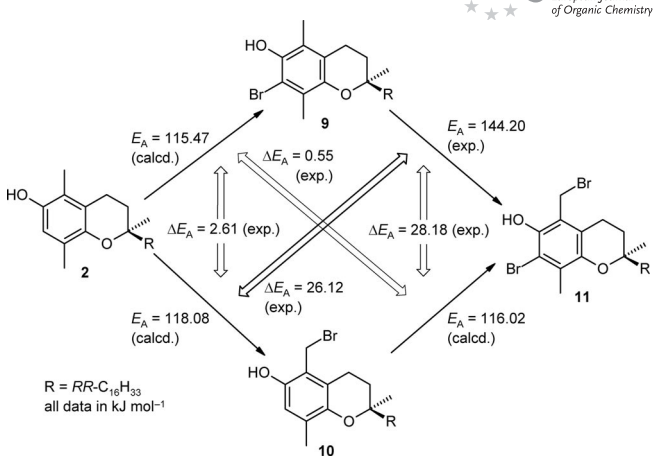
Unlike that of the α-congener, bromination of the non-α-tocopherols had remained largely unstudied with regard both to mechanisms and to products, as mentioned above. In the case of β-tocopherol (**2**), bromination is more complex than one would think at first glance. β-Tocopherol (**2**) and its truncated model compound **2a** are each characterized by an unsubstituted aromatic carbon (C-7), which is also the position at which bromination predominantly occurs. The aromatic proton in **2** and **2a** resonates at δ = 6.47 ppm in the ^{1}H NMR ($CDCl_3$).[12,28]

Two competitive initial reactions took place: bromination at the only available aromatic ring position C-7 to afford 7-bromo-β-tocopherol (**9**), together with bromination at C-5a analogously to the reaction of α-tocopherol, providing 5a-bromo-β-tocopherol (**10**). At –78 °C, the former reaction dominated over the latter, with the product ratio of **9** and **10** being 85:15. At 333 K, the ratio had decreased to 72:28. However, as soon as the two primary oxidation products have formed and excess bromine is still present, two subsequent reactions set in: bromination of 7-bromo-β-tocopherol at C-5a, and bromination of 5a-bromo-β-tocopherol at C-7. Both reactions lead to the same dibromide product (Scheme 3): 5a,7-dibromo-β-tocopherol (**11**). There

are therefore four parallel bromination reactions going on, which renders the product formation kinetics rather complex.



Scheme 3. Bromination of β-tocopherol (**2**), leading to 5a-bromo-β-tocopherol (**10**) and 7-bromo-β-tocopherol (**9**) and further to 5a,7-dibromo-β-tocopherol (**11**). The reactions proceed analogously with the truncated model compound **2a**.



Scheme 4. Bromination system of β-tocopherol (**2**): activation energy differences (ΔE_A) taken from kinetic measurements [temperature dependence of the product ratio, according to Equation (1)]. Activation energies (E_A) have either been determined kinetically (bromination of **9** to **11**) or have been calculated from the ΔE_A values.

The two mechanisms leading to either monobromination product are quite different: bromination at C-7 is an electrophilic aromatic substitution, whereas the reaction at C-5a proceeds by a two-step oxidation/addition mechanism, analogously to the bromination of α-tocopherol. The ratio (*r*) between the two bromination products is determined by the activation energy difference (ΔE_A) between the two rate-determining steps of the corresponding pathways, according to Equation (1). For the bromination at C-5a this is the formation of the intermediate *o*-quinone methide – or more precisely the hydride abstraction from C-5a leading to that *o*-quinone methide.[27] For bromination at C-7, the rate-determining step is the formation of the intermediate σ complex with a cyclohexadienol structure. Although the activation energy difference between the two reactions is readily but rather approximately provided by the product ratio (*r*) of the two possible products N_1 and N_2 at a certain temperature as in Equation (1), it can more reliably be obtained by regression analysis of temperature dependence versus product ratio: that is, from the slope ($-\Delta E_A/R$) in a plot of ratio *r* against $1/T$. With a ΔE_A value of 2.61 kJ mol^{-1} (Scheme 4) it was evident that the electrophilic substitution to form 7-bromo-β-tocopherol (**9**) was the preferred process over the competitive formation of monobromide **10**.

$$r = N_1/N_2 = \exp(-\Delta E_A/RT) \quad (1)$$

Equation (1) and the regression plot can be analogously applied to calculate the activation energy difference between the two bromination reactions leading to dibromide **11**, by subjecting an equimolar mixture of the two monobromides **9** and **10** to bromination treatment. No product ratio can be determined, of course, because both processes form the same final product **11**, but it can be derived from the ratio of remaining starting materials, because both bromination reactions proceeded quantitatively and without formation of byproducts. In this way, the activation energy difference between the brominations of **9** and **10** to form the dibromide **11** was determined to be 28.18 kJ mol^{-1} (Scheme 4). The activation energy difference this time was significantly larger, indicating either that the presence of the Br substituent at C-7 retarded further bromination at C-5a or that the presence of the bromine substituent at C-5a facilitated further bromination at C-7 (or both effects at the same time). It seemed reasonable to assume the first case: bromination directly on the aromatic ring could easily influence the electron density and thus the oxidation potential of the phenolic system in a way that oxidation to the corresponding *o*-quinone methide – the intermediate en route to the 5a-bromide – would be more difficult, whereas bromination at C-5a should have only a small influence on the electron density of the aromatic system and thus the bromination rate at C-7. However, acquiring a definitive answer was only possible by experiment.

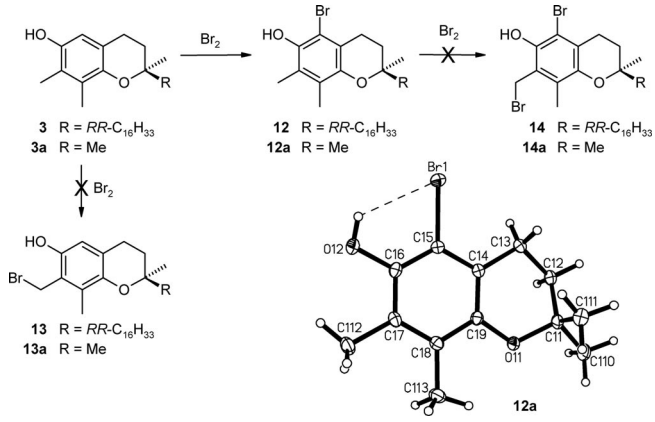
We thus used an equimolar mixture of β-tocopherol (**2**) and 7-bromo-β-tocopherol (**9**), which both undergo bromination at their respective C-5a atoms, in the bromination reaction, and the overall conversion was kept below 5%. At those low degrees of conversion, the two starting compounds are always present in large excess over the reaction products so that it can be approximated that bromine is only reacting with starting **2** and **9**, but not with the newly formed monobromides to afford the dibromide. At higher degrees of conversion the consumption of bromine by the just generated monobromides can no longer be neglected without introducing significant errors. The amounts of consumed β-tocopherol (**2**) and consumed 7-bromo-β-tocopherol (**9**), again determined at different temperatures, correspond to the amounts of the bromination products 5a-bromo-β-tocopherol (**10**) and 5a,7-dibromo-β-tocopherol (**11**) – if it is kept in mind that the 7-bromo derivative **9** is not only consumed by bromination, but is also newly generated from **2**. The ratio of the formation of **9** or **10** from **2** as determined above can readily be used to correct the consumption value of β-tocopherol for the part that is converted into the 7-bromo derivative. From the large activation energy difference obtained – 26.12 kJ mol^{-1}

(Scheme 4) – it was evident that bromination of β-tocopherol to afford the 5a-bromo compound **10** proceeds much more readily than the analogous 5a-bromination of **9** to give **11**. The introduction of the bromo substituent at C-7 of the aromatic ring thus evidently altered the electron density and oxidation potential of the phenol in such a way that the formation of the corresponding *o*QM and further reaction to provide the 5a-bromo compound **11** was disfavored, verifying the first of the two alternative assumptions above.

In a similar way, bromination of an equimolar mixture of β-tocopherol (**2**) and 5a-bromo-β-tocopherol (**10**) at different temperatures was used to determine the activation energy difference for the electrophilic substitution at C-7. Calculation of the formation of **9** (from **2**) and **11** from **10** from the consumption of **2** and **10** provided the activation energy difference (0.55 kJ mol^{-1}; see Scheme 4), which was rather small in relation to the values obtained above. Again, the consumption value for β-tocopherol was corrected for the competitive parallel reaction to afford the 5a-bromo derivative. This outcome demonstrated that the introduction of a 5a-bromo substituent as in **10** had only a negligible effect on the electron density and bromination rate of the aromatic core. The four activation energy differences (ΔE_A) as obtained from the kinetics are summarized in Scheme 4. From the experimentally determined activation energy of 144.20 kJ mol^{-1} for the bromination of **9** to **11**,[29] simple arithmetic allowed the actual activation energies (E_A) to be calculated from those differences. These values are also given in Scheme 4, and provide an interesting overview of the kinetics of this system of bromination reactions.

Bromination of γ-tocopherol (**3**) is a straightforward reaction that affords the 5-bromide **12** quantitatively (Scheme 5).[20] γ-Tocopherol (**3**) and its model compound **3a** each possess one free aromatic ring position, like the β-isomer, but this time it is located at C-5. The NMR resonance of the aromatic proton is found at δ = 6.37 ppm ($CDCl_3$).[12,28] In the case of the truncated model compound **3a**, bromination provided product **12a** as colorless crystals suitable for X-ray structure determination (Scheme 5). In crystalline **12a**, four chemically equivalent but crystallographically different molecules are contained per monoclinic unit cell (space group $P2_1/c$). All OH hydrogens form intramolecular H-bonds to the bromine, and two OH hydrogens exhibit bifurcated H-bonds to neighboring hydroxy groups.

It was interesting to see that the bromination product **12** was completely inert towards further bromination at C-7a. Whereas in the case of α-tocopherol C-7a showed some minor reactivity (cf. Scheme 2), in the case of γ-tocopherol this position was completely inert, giving no sign of the hypothetical 7a-bromo-γ-tocopherol (**13**) or 5,7a-dibromo-γ-tocopherol (**14**). The absence of 5,7a-dibromo-γ-tocopherol can be explained by the electronic effects of the bromo substituents directly on the aromatic ring on *o*QM formation, as seen already in the case of the bromination of 7-bromo-β-tocopherol (**9**) to afford 5a,7-dibromo-β-tocopherol (**11**, cf. Scheme 4). Although in the β-tocopherol case



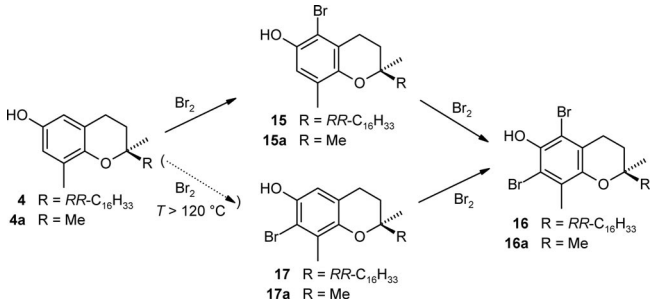
Scheme 5. Bromination of γ-tocopherol (**3**), affording 5-bromo-γ-tocopherol (**12**) as the only product. The hypothetical species 7a-bromo-γ-tocopherol (**13**) or 5,7a-dibromo-γ-tocopherol (**14**), formation of which could be imagined by analogy to the bromination chemistry of α-tocopherol (Scheme 2) and β-tocopherol (Scheme 3), are not observed. The reactions proceed analogously with the truncated model compound **3a**, giving the bromination product **12a**, a crystal structure of which (thermal ellipsoid plot, 40% ellipsoids) and crystallographic atom labeling are given.

the 7-bromo substituent was not completely deactivating with regard to *o*QM formation and subsequent bromination at C-5a, the 5-bromo substituent in the γ-tocopherol case had an even more rigorous effect and apparently caused complete inertness of C-7a.

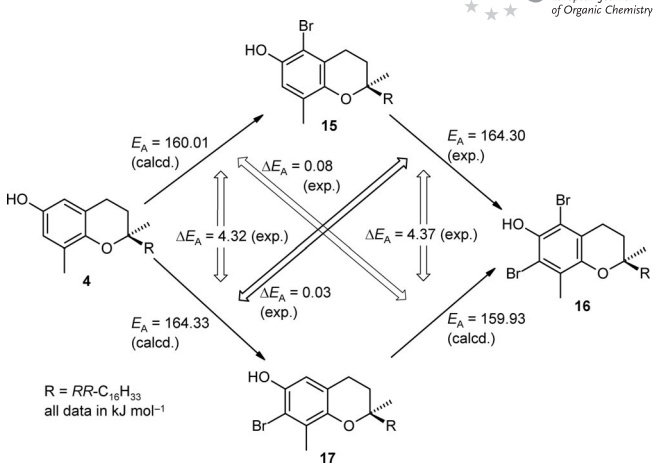
The deactivating effects of aromatic bromine substituents cannot, however, explain why no 7a-bromo-γ-tocopherol (**13**) was observed, because in **3** no deactivating Br is present. The only structural difference between γ-tocopherol (**3**) and α-tocopherol (**1**) is the "missing" methyl group at the C-5 position in the former compound. One can therefore hardly evoke strong electronic effects to explain why the latter compound is (at least moderately) reactive at C-7a whereas the former is not reactive at all at this position. Furthermore, because *o*-quinone methide formation in tocopherol-type antioxidants is dependent on the annulation angle of the heterocyclic ring,[28] it was logical also to assume that reason for the differing oxidation/bromination behavior. However, the annulation angles of **3** and **1** are identical to the second decimal according to computations on the DFT level (B3LYP/6–31G*; see Experimental), so different strains imposed by the substituents and annulated heterocycle also had to be excluded as a rationale. Moreover, no differences in the zwitterionic transition states that lead from **3** or **1** to the corresponding C-7a-*o*-quinone methides could be found. At present, no satisfactory explanatory statement for the difference in the reactivities at C-7a of α-tocopherol (**1**) and γ-tocopherol (**3**) can be given.

Bromination of δ-tocopherol (**4**) – carried out as for the other tocopherols under aprotic apolar conditions – was somewhat more complex than that of the γ-congener, and thus comparable with the non-trivial β-tocopherol case (Scheme 6). δ-Tocopherol (**4**) is the only tocopherol with more than one free aromatic position: both positions *ortho*

to the phenolic hydroxy group, C-5 and C-7, are unsubstituted.[30] The aromatic protons resonate at δ = 6.30 and 6.38 ppm in the ^{1}H NMR ($CDCl_3$) with a coupling constant of 2.9 Hz.[12]



Scheme 6. Bromination of δ-tocopherol (**4**), leading to 5-bromo-δ-tocopherol (**15**) and 5,7-dibromo-δ-tocopherol (**16**). 7-Bromo-δ-tocopherol (**17**) can only be obtained in small amounts at elevated temperatures. With the truncated model compound **4a** the reactions proceed analogously.



Scheme 7. δ-Tocopherol (**4**) bromination system: activation energy differences (ΔE_A) taken from kinetic measurements [temperature dependence of the product ratio, according to Equation (1)]. Activation energies (E_A) were either determined kinetically (bromination of **15** to afford **16**) or calculated from the ΔE_A values.

At –78 °C, bromination of δ-tocopherol provided quantitative yields of 5-bromo-δ-tocopherol (**15**, Scheme 6). This outcome was independent of the amount of bromination agent used: even with a large excess of bromine only this monobromination product was obtained. At room temperature and with one equivalent of bromine, yields of **15** were still well above 80%, but in addition the dibromination product 5,7-dibromo-δ-tocopherol (**16**) was formed along with some 7-bromo-δ-tocopherol (**17**). With two or more equivalents of bromine, quantitative formation of **16** was achieved either after prolonged reaction times (12 h) or within 2 hours at elevated temperatures (60 °C and above). Independently of the amount of bromine present, the yields of **17** – if found at all – were always very low (<3%), indicating that its further bromination to dibromide **16** was preferred over the bromination reaction leading to it. As soon as it was formed it would be immediately consumed again in the second bromination process.

Apparently, C-5-monosubstitution had not a deactivating, but rather a weak activating effect on the second substitution at C-7, although the difference was not very large. With equimolar mixtures of 5-bromo-δ-tocopherol (**15**) and δ-tocopherol (**4**), the former was consumed with slight preference. With 1 equiv. of bromine at room temp., for instance, 53% of **15** and 47% of **4** were converted into the corresponding bromides.

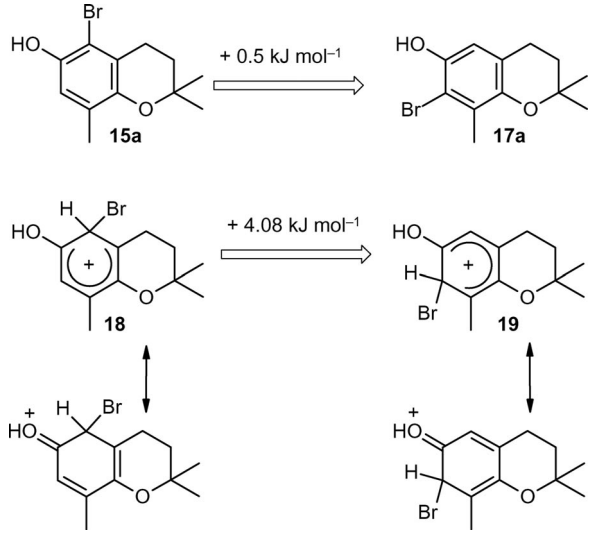
Kinetic measurements for the δ-tocopherol bromination system were carried out similarly to the β-tocopherol scenario, by measuring the product ratios or the corresponding consumption of starting materials as functions of the reaction temperature. The resulting activation energy differences (ΔE_A) are shown in Scheme 7. From those values and from the experimentally determined activation energy for the bromination of **15** to afford **16** (E_A = 164.3 kJ mol^{-1}), the activation energies for the other bromination steps in the system were derived.

It was intriguing to see that below temperatures of about –20 °C there was a clear preference with regard to bromination at C-5 versus at C-7: monobromination of δ-tocopherol occurred predominantly at C-5 and much less so at C-7, with only a 7% yield of **17** being formed at –40 °C and a 13% yield at –20 °C. Formation of the C-7 bromination product **17** could only be enforced by applying rather drastic reaction conditions (120 °C), but yields were still as low as 22% and compounds **15** and **16** dominated (Scheme 6).

At a first glance, there was no obvious reason for such regioselectivity: the two *o*-positions in **4** have no obvious differences with regard to electronic effects, spatial conditions, or steric hindrance. The C-7 position, with a neighboring rotating methyl group (C-8b), would even appear slightly more easily accessible than the C-5 position, with its inflexible heterocyclic methylene neighbor (C-4). Neither can thermodynamic reasons be evoked to explain the selectivity: the ZPE-corrected total energies of the 5-bromo derivative **15a** and the 7-bromo derivative **17a**, computed at the MP-2/6–31G(d,p)//B3LYP/6–31G(d,p) level of theory, differ only by 0.5 kJ mol^{-1}, which is almost within the computational error limit and would not translate into any experimentally noticeable preference of one position [cf. Equation (1)].

However, the observed preference for the C-5 position can be explained in terms of the stabilities of the primary bromination intermediates: the bromocyclohexadienyl cations or σ complexes (**18**, **19**, Scheme 8). The 5-bromo intermediate **18** was calculated to be 4.1 kJ mol^{-1} more stable than the corresponding 7-bromo counterpart (**19**), a result that agreed well with the observed dominance of the 5-bromo product and the experimentally determined value of ΔE_A = 4.32 kJ mol^{-1}.[31] The theory of strain-induced bond localization (SIBL) can readily clarify the preference for **18** over **19**. Recently applied to the case of the frequently observed preference for the α-tocopherol-derived 5-*o*-quinone methide (the "up"-*o*QM) over the isomeric 7-*o*-quinone

methide (the "down"-*o*QM),[28,32] the theory can be analogously applied to the bromination intermediates. Both **18** and **19** can be regarded as quinoid systems, so the same argument as used for those *o*-quinone methides can be applied to these bromocyclohexadienyl cations. In short, the stabilities of the intermediates (no matter whether they are *o*QMs or the bromination intermediates **18** and **19**) are governed by the sums of the annulation angles of the heterocyclic rings. For tocopherols and other 2,2-dialkyl-substituted chroman-6-ol derivatives, these annulation angle sums are approx. 242°. This translates into a theoretical ratio of 97:3 between the two possible *o*QMs of α-tocopherol (at C-5a and C-7a) at room temperature, and exactly this ratio was found experimentally. For the bromination of δ-tocopherol (**4**), the computationally predicted ratios of the two isomeric bromination intermediates **18** and **19** were 92.6:7.4 in favor of the 5-bromo compound at –78 °C and 77.8:22.2 at 120 °C. Experimentally, the yields of 7-bromo compound were <3% at –78 °C and 20% at 120 °C, which seem to represent a satisfying overall agreement between computation and experiment.



Scheme 8. Calculated ZPE-corrected energy differences between 5-bromo-δ-tocopherol model **15a** and 7-bromo-δ-tocopherol model **17a**, and between the two σ complexes (**18, 19**) leading to them.

Conclusions

The bromination chemistry of the three non-α-tocopherols in polar media has been established and compared to that of α-tocopherol. β-Tocopherol and δ-tocopherol each afforded three different bromination products depending on the conditions, whereas γ-tocopherol formed only a single bromination product. All products were fully purified and comprehensively characterized, not only for the tocopherols themselves, but also for the truncated model compounds carrying a methyl group instead of the isoprenoid side chain. A complete set of reference compounds and analytical standards for the bromination products of the tocopherols is now available.

Further studies will now focus on the bromination products formed in aqueous (protic) media. Preliminary experiments have shown that a superposition of oxidizing and halogenating effects is apparently active in such media, affording halogenated *p*-quinones as one main product class as well as rearrangement products, none of these products having been observed when working in aprotic media as in the present study.

Experimental Section

General: Commercial chemicals were of the highest grade available and were used without further purification. Tocopherols were provided by DSM Nutritional Products. 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 F_{254} 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.

Melting points, determined on a Kofler-type micro hot stage with 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.

^{1}H NMR spectra were recorded at 300.13 MHz (400.13 MHz, respectively) for ^{1}H 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. The abbreviation "d.i." denotes ^{13}C NMR resonances originating from two magnetically equivalent carbon atoms.

GC/MS was performed on 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.

Computations, as implemented with the Spartan Pro 04 program package, were carried out on geometries pre-optimized by the semi-empirical PM3 method. For full geometry optimization the widely employed B3LYP hybrid method, which includes a mixture of HF and DFT exchange terms and the gradient-corrected correlation functional of Lee, Yang, and Parr,[33,34] parametrized by Becke,[35,36] was used, along with the double-zeta split valence basis sets 6–31+G(d,p)[37,38] which includes diffuse functions, or the higher 6-311G(2df,2p) analogue. Vibrational frequencies were calculated at the corresponding level of theory to characterize local minima (equilibrium structures) or first-order saddle points (transition states) on the potential energy surface and to determine zero-point vibrational energies. All equilibrium geometries were characterized by real frequencies only, all transition states by one imaginary frequency.

X-ray Crystallographic Study: X-ray data collection was performed with a Bruker AXS Smart APEX CCD diffractometer and graphite-monochromatized Mo-K_α radiation, λ = 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 6.36A; SADABS version 2.05; XPREP, version 6.12; SHELXTL, version 6.10. Bruker AXS Inc., Madison, WI, USA).

CCDC-270830 contains the supplementary crystallographic data for compound **12a**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

7-Bromo-β-tocopherol (9): A solution of Br_2 in *n*-hexane [1 M, equiv. to 0.0028 mL (0.056 mmol) of Br_2] was added dropwise at 0 °C to a stirred solution of β-tocopherol (23.3 mg, 0.056 mmol) in *n*-hexane (10 mL). The solution was stirred for 1 h and allowed to warm to room temp., and the solvent was evaporated in vacuo. The residue was purified by flash chromatography on silica gel with an *n*-hexane/diethyl ether gradient (50:1 → 20:1 v/v) to afford **9** as a colorless oil (22.7 mg, 82%). R_f = 0.62 (*n*-hexane/diethyl ether 9:1 v/v). ^{1}H NMR: δ = 1.72–1.85 (m, 2 H, 3-H), 2.17 (s, 3 H, 8b-H), 2.25 (s, 3 H, 5a-H), 2.59 (t, J = 6.9 Hz, 2 H, 4-H), 5.22 (br. s, 1 H, –OH) ppm. ^{13}C NMR: δ = 12.1 (C-5a), 15.8 (C-8b), 20.7 (C-4), 23.8 (C-2a), 31.3 (C-3), 75.3 (C-2), 111.7 (C-7), 120.04; 120.08 (C-4a; C-5), 122.9 (C-8), 142.9 (C-8a), 145.7 (C-6), isoprenoid side chain: 19.7 (C-4a′), 19.8 (C-8a′), 21.0 (C-2′), 22.7 (C-13′), 22.7 (C-12a′), 24.4 (C-6′), 24.8 (C-10′), 28.0 (C-12′), 32.6 (C-8′), 32.8 (C-4′), 37.3 (C-7′), 37.39; 37.40; 37.44 (C-5′; C-9′; C-3′), 39.4 (C-11′), 39.6 (C-1′) ppm. $C_{28}H_{47}BrO_2$ (495.58): calcd. C 67.86, H 9.56; found C 67.70, H 9.50.

7-Bromo-6-hydroxy-2,2,5,8-tetramethylchroman (9a): A solution of Br_2 in *n*-hexane [equiv. to 0.012 mL (0.24 mmol) of Br_2] was added dropwise at 0 °C to a stirred solution of 6-hydroxy-2,2,5,8-tetramethylchroman (50 mg, 0.24 mmol) in *n*-hexane (10 mL). The solution was stirred for 1 h and allowed to warm to room temp., and the solvent was evaporated in vacuo. The residue was purified by flash chromatography on silica gel with *n*-hexane/diethyl ether (9:1 v/v) to afford **9a** as a waxy solid (56.1 mg, 82%). R_f = 0.53 (*n*-hexane/ethyl acetate 8:2 v/v). ^{1}H NMR: δ = 1.29 (s, 6 H, 2a-H), 1.79 (t, J = 6.9 Hz, 2 H, 3-H), 2.17 (s, 3 H, 8b-H), 2.25 (s, 3 H, 5a-H), 2.60 (t, J = 6.9 Hz, 2 H, 4-H), 5.23 (s, 1 H, –OH) ppm. ^{13}C NMR: δ = 12.0 (C-5a), 15.9 (C-8b), 21.0 (C-4), 26.6 (C-2a), 32.8 (C-3), 73.2 (C-2), 111.8 (C-7), 119.8; 120.0 (C-4a; C-5), 123.0 (C-8), 143.0 (C-8a), 145.8 (C-6) ppm. $C_{13}H_{17}BrO_2$ (285.18): calcd. C 54.75, H 6.01; found C 54.60, H 5.99.

5-Bromomethyl-β-tocopherol (10): A solution of β-tocopherol quinone[39] (0.1 mmol, 43.3 mg) and Me_3SiBr (1.0 mmol, 0.125 g) in dry *n*-hexane (10 mL) was stirred under nitrogen at 40 °C for 2 h. Solvent and excess silylating agent were removed under reduced pressure, and the residue was co-evaporated with toluene (10 mL). The residue was dissolved in diethyl ether (20 mL), and water (10 mL) and tetrabutylammonium fluoride (100 mg) were added. After vigorous stirring for 10 min at room temp., water (10 mL) was added and the phases were separated. The organic phase was dried with $MgSO_4$, and the solvent was removed in vacuo. The residue was purified by flash chromatography on silica gel with *n*-hexane/diethyl ether (20:1 v/v) to afford **10** as a greenish oil (37.2 mg, 75%). R_f = 0.52 (*n*-hexane/diethyl ether 9:1 v/v). ^{1}H NMR: δ = 1.70–1.78 (m, 2 H, 3-H), 2.14 (s, 3 H, 8b-H), 2.60 (t, J = 6.8 Hz, 2 H, 4-H), 4.58 (s, 2 H, 5a-H), 5.10 (s, 1 H, –OH) ppm. ^{13}C NMR: δ = 15.6 (C-8b), 19.8 (C-4), 23.8 (C-2a), 27.2 (C-5a), 31.2 (C-3), 75.2 (C-2), 116.0 (C-5), 119.4 (C-4a), 121.4 (C-7), 124.9 (C-8), 143.9 (C-8a), 146.6 (C-6), isoprenoid side chain: 19.7 (C-4a′), 19.8 (C-8a′), 20.9 (C-2′), 22.6 (C-13′), 22.7 (C-12a′), 24.4 (C-6′), 24.8 (C-10′), 27.8 (C-12′), 32.6 (C-8′), 32.8 (C-4′), 37.35 (C-7′), 37.36 (C-5′), 37.40; 37.44 (C-9′; C-3′), 39.2 (C-11′), 39.5 (C-1′) ppm. $C_{28}H_{47}BrO_2$ (495.58): calcd. C 67.86, H 9.56; found C 67.80, H 9.71.

5-Bromomethyl-6-hydroxy-2,2,8-trimethylchroman (10a): A solution of 3-(3-hydroxy-3-methylbutyl)-2,5-dimethyl-1,4-benzoquinone[38] (truncated β-tocopherol quinone, 0.2 mmol, 44.4 mg) and Me_3SiBr (1.0 mmol, 0.125 g) in chloroform (10 mL) was stirred under nitrogen at 40 °C for 2 h. Solvent and excess silylating agent were removed under reduced pressure, and the residue was co-evaporated with toluene (10 mL). The residue was dissolved in diethyl ether (20 mL), and water (10 mL) and tetrabutylammonium fluoride (100 mg) were added. After vigorous stirring for 10 min at room temp., water (10 mL) was added and the phases were separated. The organic phase was dried with $MgSO_4$, and the solvent was removed in vacuo. The residue was purified by flash chromatography on silica gel with *n*-hexane/diethyl ether (8:2 v/v) to afford **10a** as a greenish, waxy solid (35.9 mg, 63%). R_f = 0.40 (*n*-hexane/ethyl acetate 8:2 v/v). ^{1}H NMR: δ = 1.28 (s, 6 H, 2a-H), 1.79 (t, J = 6.8 Hz, 2 H, 3-H), 2.14 (s, 3 H, 8b-H), 2.61 (t, ^3J = 6.8 Hz, 2 H, 4-H), 4.16 (s, 1 H, –OH), 4.52 (s, 2 H, 5a-H), 6.47 (s, 1 H, 7-H) ppm. ^{13}C NMR: δ = 15.8 (C-8b), 19.9 (C-4), 26.5 (C-2a.), 32.4 (C-3), 73.2 (C-2), 116.0 (C-5), 119.7 (C-4a), 121.4 (C-7), 124.6 (C-8), 144.0 (C-8a), 146.4 (C-6) ppm. $C_{13}H_{17}BrO_2$ (285.18): calcd. C 54.75, H 6.01; found C 54.86, H 6.00.

7-Bromo-5-bromomethyl-β-tocopherol (11): A solution of Br_2 in *n*-hexane (equiv. to 0.0087 mL, 0.174 mmol of Br_2) was added in one portion at 40 °C to a stirred solution of β-tocopherol (24.1 mg, 0.058 mmol) in *n*-hexane (10 mL). The solution was stirred for 1 h and allowed to cool to room temp. The solution was purged with nitrogen to remove excess bromine until the color had changed to light yellow, and the solvent was evaporated in vacuo. The residue was purified by flash chromatography on silica gel with *n*-hexane/diethyl ether (20:1 v/v) to afford **11** as a green-yellow oil (30.6 mg, 92%). R_f = 0.54 (*n*-hexane/diethyl ether 9:1 v/v). ^{1}H NMR: δ = 1.72–1.79 (m, 2 H, 3-H), 2.15 (s, 3 H, 8b-H), 2.58 (t, J = 6.8 Hz, 2 H, 4-H), 4.60 (s, 2 H, 5a-H), 5.42 (s, 1 H, –OH) ppm. ^{13}C NMR: δ = 15.8 (C-8b), 19.9 (C-4), 23.8 (C-2a), 26.5 (C-5a), 31.3 (C-3), 75.2 (C-2), 112.0 (C-5), 119.4; 120.0 (C-4a; C-7), 127.9 (C-8), 143.6 (C-8a), 146.6 (C-6), isoprenoid side chain: 19.7 (C-4a′), 19.8 (C-8a′), 21.0 (C-2′), 22.7 (C-13′), 22.7 (C-12a′), 24.4 (C-6′), 24.8 (C-10′), 27.9 (C-12′), 32.6 (C-8′), 32.8 (C-4′), 37.32 (C-7′), 37.36 (C-5′), 37.42; 37.45 (C-9′; C-3′), 39.3 (C-11′), 39.6 (C-1′) ppm. $C_{28}H_{46}Br_2O_2$ (574.48): calcd. C 58.54, H 8.07; found C 58.48, H 8.11.

7-Bromo-5-bromomethyl-6-hydroxy-2,2,8-trimethylchroman (11a): A solution of Br_2 (0.037 mL, 0.72 mmol) in *n*-hexane (5 mL) was added in one portion at 40 °C to a stirred solution of 6-hydroxy-2,2,5,8-tetramethylchroman (50 mg, 0.24 mmol) in *n*-hexane (10 mL). The solution was stirred for 1 h, allowed to cool to room temp., and purged with nitrogen to remove excess bromine until the color had changed to light yellow. The solvent was evaporated in vacuo. The residue was purified by flash chromatography on silica gel with *n*-hexane/diethyl ether (9:1 v/v) to afford **11a** as a greenish, waxy solid (77.8 mg, 89%). R_f = 0.42 (*n*-hexane/ethyl acetate 8:2 v/v). ^{1}H NMR: δ = 1.28 (s, 6 H, 2a-H) 1.75 (m, J = 6.9 Hz, 2 H, 3-H), 2.10 (s, 3 H, 8b-H), 2.74 (t, J = 6.9 Hz, 2 H, 4-H), 4.59 (s, 2 H, 5a-H), 5.43 (s, 1 H, –OH) ppm. ^{13}C NMR: δ = 16.3 (C-8b), 19.4 (C-4), 26.4 (C-2a), 27.1 (C-5a), 32.3 (C-3), 73.6 (C-2), 112.1 (C-5), 119.4; 119.9 (C-4a; C-7), 127.5 (C-8), 143.6 (C-8a),

146.3 (C-6) ppm. $C_{13}H_{16}Br_2O_2$ (364.08): calcd. C 42.89, H 4.43; found C 42.94, H 4.21.

5-Bromo-γ-tocopherol (12): A solution of Br_2 in *n*-hexane (equiv. to 0.0036 mL, 0.072 mmol of Br_2) was added dropwise at 0 °C to a stirred solution of γ-tocopherol (30 mg, 0.072 mmol) in *n*-hexane (10 mL). The solution was stirred for 1 h and allowed to warm to room temp., and the solvent was evaporated in vacuo. The residue was chromatographed on silica gel with an *n*-hexane/diethyl gradient (50:1 → 20:1 v/v) to give **12** as a colorless oil (25.7 mg, 72%). R_f = 0.60 (*n*-hexane/diethyl ether 9:1 v/v). ^{1}H NMR: δ = 1.72–1.88 (m, 2 H, 3-H), 2.11 (s, 3 H, 7a/8b-H), 2.23 (s, 3 H, 7a/8b-H), 2.68 (t, J = 6.8 Hz, 2 H, 4-H), 5.21 (br. s, 1 H, –OH) ppm. ^{13}C NMR: δ = 11.8 (C-7a), 12.9 (C-8b), 21.0 (C-4), 23.7 (C-2a), 31.4 (C-3), 75.4 (C-2), 109.2 (C-5), 117.3 (C-4a), 122.3 (C-7), 125.4 (C-8), 143.4 (C-6), 145.9 (C-8a), isoprenoid side chain: 19.6 (C-4a′), 19.6 (C-8a′), 19.7 (C-2′), 22.6 (C-13′), 22.7 (C-12a′), 24.5 (C-6′), 24.6 (C-10′), 28.0 (C-12′), 32.6 (C-8′), 32.8 (C-4′), 37.50; 37.55; 37.56 (C-5′; C-7′; (C-9′), 37.5 (C-3′), 39.55 (C-11′), 39.6 (C-1′) ppm. $C_{28}H_{47}BrO_2$ (495.58): calcd. C 67.86, H 9.56; found C 67.70, H 9.50.

5-Bromo-6-hydroxy-2,2,7,8-tetramethylchroman (12a): A solution of Br_2 (0.012 mL, 0.24 mmol) in *n*-hexane (10 mL) was added dropwise at 0 °C to a stirred solution of 6-hydroxy-2,2,5,8-tetramethylchroman (50 mg, 0.24 mmol) in *n*-hexane (10 mL). The solution was stirred for 1 h and allowed to warm to room temp., and the solvent was evaporated in vacuo. The residue was purified by flash chromatography on silica gel with *n*-hexane/diethyl ether (9:1 v/v) to afford **12a** as a waxy solid (47.9 mg, 70%). R_f = 0.55 (*n*-hexane/ethyl acetate 8:2 v/v). ^{1}H NMR: δ = 1.29 (s, 6 H, 2a-H), 1.78 (t, J = 7.2 Hz, 2 H, 3-H), 2.08 (s, 3 H, 7a-H), 2.21 (s, 3 H, 8b-H), 2.68 (t, J = 7.2 Hz, 2 H, 4-H), 5.19 (s, 1 H, OH) ppm. ^{13}C NMR: δ = 11.8 (C-7a), 12.9 (C-8b), 24.3 (C-4), 26.5 (C-2a and C-2b), 33.0 (C-3), 73.3 (C-2), 109.3 (C-5), 117.1 (C-4a), 122.4 (C-7), 125.4 (C-8), 143.4 (C-6), 146.0 (C-8a) ppm. $C_{13}H_{17}BrO_2$ (285.18): calcd. C 54.75, H 6.01; found C 54.72, H 6.28. For X-ray crystallographic data see above.

5-Bromo-δ-tocopherol (15) and 7-Bromo-δ-tocopherol (17): A solution of Br_2 in *o*-dichlorobenzene (equiv. to 0.003 mL, 0.06 mmol of Br_2) was added dropwise at 80 °C to a stirred solution of δ-tocopherol (48.3 mg, 0.12 mmol) in *o*-dichlorobenzene (10 mL). The solution was stirred for 30 min and allowed to cool to room temp., and the solvent was evaporated in vacuo. The residue was purified by flash chromatography on silica gel (*n*-hexane/diethyl ether 50:1 v/v) to give **15** as a colorless oil (19.1 mg, 33%), **17** as a colorless oil (6.9 mg, 12%), and unreacted δ-tocopherol (22.7 mg, 47%) in the order of elution.

5-Bromo-δ-tocopherol (15): TLC: R_f = 0.34 (*n*-hexane/diethyl ether 9:1 v/v). ^{1}H NMR: δ = 1.73–1.86 (m, 2 H, 3-H), 2.11 (s, 3 H, 8b-H), 2.68 (t, J = 6.8 Hz, 2 H, 4-H), 5.05 (s, 1 H, OH), 6.73 (s, 1 H, Ar-H) ppm. ^{13}C NMR: δ = 15.9 (C-8b), 21.2 (C-4), 22.6 (C-2a), 31.3 (C-3), 75.4 (C-2), 109.0 (C-5), 115.1 (CH, C-4a), 120.1 (C-7), 127.0 (C-8), 144.8 (C-8a), 146.3 (C-6), isoprenoid side chain: 19.6 (C-4a′), 19.7 (C-8a′), 20.9 (C-2′), 22.7 (C-13′), 23.7 (C-12a′), 24.1 (C-6′), 24.4 (C-10′), 28.0 (C-12′), 32.7 (C-8′), 32.8 (C-4′), 37.28; 37.39; 37.43; 37.44 (C-3′; C-5′; C-7′; C-9′), 39.3 (C-11′), 39.4 (C-1′) ppm. $C_{27}H_{45}BrO_2$ (481.56): calcd. C 67.34, H 9.42; found C 67.24, H 9.39.

7-Bromo-δ-tocopherol (17): TLC: R_f = 0.27 (*n*-hexane/ethyl acetate 9:1 v/v), 0.31 (*n*-hexane/diethyl ether 9:1 v/v). ^{1}H NMR: δ = 1.69–1.84 (m, 2 H, 3-H), 2.26 (s, 3 H, 8b-H), 2.68 (m, 2 H, 4-H), 5.11 (s, 1 H, –OH), 6.63 (s, 1 H, Ar-H) ppm. ^{13}C NMR: δ = 15.9 (C-8b), 22.3 (C-4), 22.6 (C-2a), 31.2 (C-3), 75.4 (C-2), 111.5 (C-7), 112.4 (C-5), 121.1 (C-4a), 126.0 (C-8), 144.8 (C-8a), 146.0 (C-6), isoprenoid side chain: 19.6 (C-4a′), 19.8 (C-8a′), 20.9 (C-2′), 22.7 (C-13′), 23.7 (C-12a′), 24.0 (C-6′), 24.4 (C-10′), 28.0 (C-12′), 32.6 (C-8′), 32.8 (C-4′), 37.2 (C-7′), 37.28; 37.39; 37.40; 37.44 (C-3′; C-5′; C-7′; C-9′), 39.4 (C-11′), 39.9 (C-1′) ppm. $C_{27}H_{45}BrO_2$ (481.56): calcd. C 67.34, H 9.42; found C 67.2, H 9.35.

5-Bromo-6-hydroxy-2,2,8-trimethylchroman (15a) and 7-Bromo-6-hydroxy-2,2,8-trimethylchroman (17a): A solution of Br_2 in *o*-dichlorobenzene (equiv. to 0.007 mL, 0.14 mmol of Br_2) was added dropwise at 40 °C to a stirred solution of 6-hydroxy-2,2,8-trimethylchroman[12] (50 mg, 0.26 mmol) in *o*-dichlorobenzene (10 mL). The solution was stirred for 30 min and allowed to cool to room temp., and the solvent was evaporated in vacuo. The residue was purified by flash chromatography on silica gel (*n*-hexane/diethyl ether 9:1 v/v) to give **15a** as a yellow wax (21.9 mg, 31%), **17a** as a yellow wax (11.2 mg, 16%), and unreacted starting material (21 mg, 42%) in the order of elution.

5-Bromo-6-hydroxy-2,2,8-trimethylchroman (15a): TLC: R_f = 0.34 (*n*-hexane/diethyl ether 8:2 v/v). ^{1}H NMR: δ = 1.29 (s, 6 H, 2a-H), 1.81 (t, J = 6.8 Hz, 2 H, 3-H), 2.11 (s, 3 H, 8b-H), 2.70 (t, J = 6.8 Hz, 2 H, 4-H), 5.00 (s, 1 H, –OH), 6.73 (s, 1 H, Ar-H) ppm. ^{13}C NMR: δ = 16.0 (C-8b), 24.4 (C-4), 26.5 (C-2a), 32.7 (C-3), 73.4 (C-2), 109.0 (C-5), 115.1 (CH, C-4a), 119.9 (C-7), 126.9 (C-8), 144.8 (C-8a), 146.4 (C-6) ppm. $C_{12}H_{15}BrO_2$ (271.15): calcd. C 53.16, H 5.58; found C 53.34, H 5.37.

7-Bromo-6-hydroxy-2,2,8-trimethylchroman (17a): TLC: R_f = 0.28 (*n*-hexane/diethyl ether 8:2 v/v). ^{1}H NMR: δ = 1.29 (s, 6 H, 2a-H), 1.80 (t, J = 6.8 Hz, 2 H, 3-H), 2.19 (s, 3 H, 8b-H), 2.68 (t, J = 6.8 Hz, 2 H, 4-H), 5.35 (s, 1 H, –OH), 6.75 (s, 1 H, Ar-H) ppm. ^{13}C NMR: δ = 15.8 (C-8b), 24.8 (C-4), 26.3 (C-2a), 32.7 (C-3), 73.2 (C-2), 111.5 (C-7), 112.4 (CH, C-5), 121.1 (C-4a), 127.0 (C-8), 144.8 (C-8a), 145.7 (C-6) ppm. $C_{12}H_{15}BrO_2$ (271.15): calcd. C 53.16, H 5.58; found C 53.24, H 5.26.

5,7-Dibromo-δ-tocopherol (16): A solution of Br_2 (0.015 mL, 0.30 mmol) in *n*-hexane (5 mL) was added in one portion at 40 °C to a stirred solution of δ-tocopherol (48.3 mg, 0.12 mmol) in *n*-hexane (10 mL). The solution was stirred for 30 min and allowed to cool to room temp., and excess bromine was removed by purging with nitrogen. The solvent was evaporated in vacuo and the residue was purified by flash chromatography on silica gel (*n*-hexane/diethyl ether 50:1 v/v) to give **16** as a colorless oil (53.8 mg, 80%). TLC: R_f = 0.46 (*n*-hexane/diethyl ether 9:1 v/v). ^{1}H NMR: δ = 1.74–1.87 (m, 2 H, 3-H), 2.25 (s, 3 H, 8b-H), 2.68 (t, J = 6.8 Hz, 2 H, 4-H), 5.55 (br. s, 1 H, –OH) ppm. ^{13}C NMR: δ = 15.0 (C-8b), 20.2 (C-4), 21.7 (C-2a), 31.6 (C-3), 75.1 (C-2), 107.5 (C-7), 109.8 (C-5), 119.4 (C-4a), 125.2 (C-8), 141.3 (C-8a), 145.8 (C-6), isoprenoid side chain: 18.6 (C-4a′), 19.7 (C-8a′), 19.9 (C-2′), 22.6 (C-13′), 22.6 (C-12a′), 23.0 (C-6′), 23.4 (C-10′), 27.0 (C-12′), 31.6 (C-8′), 31.7 (C-4′), 36.2 (C-7′), 36.33; 36.35 (C-5′; C-9′), 36.4 (C-3′), 38.3 (C-11′), 38.4 (C-1′) ppm. $C_{27}H_{44}Br_2O_2$ (560.45): calcd. C 57.86, H 7.91; found C 57.72, H 7.89.

5,7-Dibromo-6-hydroxy-2,2,8-trimethylchroman (16a): A solution of Br_2 (0.033 mL, 0.65 mmol) in *n*-hexane (8 mL) was added in one portion at 40 °C to a stirred solution of 6-hydroxy-2,2,8-trimethylchroman[12] (50 mg, 0.26 mmol) in *n*-hexane (10 mL). The solution was stirred for 30 min and allowed to cool to room temp., and excess bromine was removed by flushing with nitrogen. The solvent was evaporated in vacuo and the residue was purified by flash chromatography on silica gel (*n*-hexane/diethyl ether, 50:1 v/v) to give **16a** as a brownish wax (83.7 mg, 92%). TLC: R_f = 0.33 (*n*-hexane/ethyl acetate, 9:1 v/v). ^{1}H NMR: δ = 1.30 (s, 6 H, 2a-H), 1.80 (t, J = 6.8 Hz, 2 H, 3-H), 2.25 (s, 3 H, 8b-H), 2.69 (t, J =

6.8 Hz, 2 H, 4-H), 5.55 (s, 1 H, –OH) ppm. ^{13}C NMR: δ = 16.0 (C-8b), 24.5 (C-4), 26.4 (C-2a), 32.6 (C-3), 74.1 (C-2), 108.5 (C-7), 110.8 (C-5), 120.0 (C-4a), 126.2 (C-8), 142.4 (C-8a), 146.4 (C-6) ppm. $C_{12}H_{14}Br_2O_2$ (350.05): calcd. C 41.17, H 4.03; found C 41.36, H 3.94.

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