The "Tocopherol–Acetaminophen Reaction" – A New [1,4]-Rearrangement Discovered in Vitamin E Chemistry[‡]

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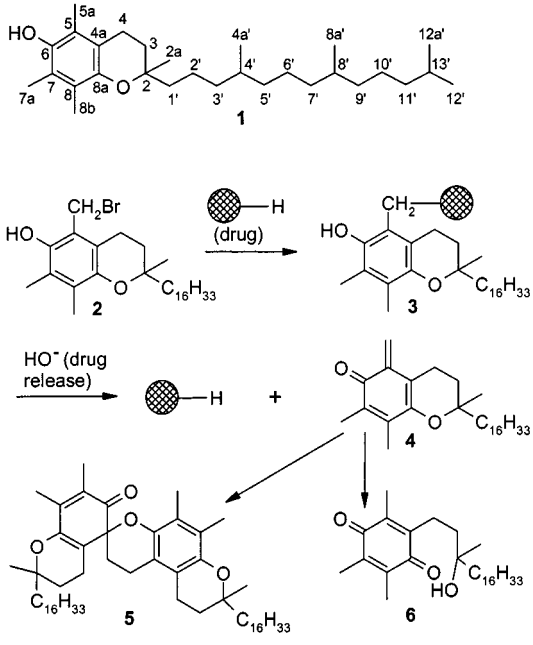
Treatment of *N*-{4-[3,4-dihydro-6-hydroxy-2,7,8-trimethyl-2-(4,8,12-trimethyltridecyl)-2*H*-1-benzopyran-5-ylmethoxy]-phenyl}acetamide (**8a**) – the Toc prodrug of acetaminophen (**7**) – with aqueous base yields 4-hydroxy-3-(6-*O*-α-tocopheryl)acetanilide (**10a**) as the main product. This hitherto unknown reaction type can formally be regarded either as a rearrangement involving [1,4]-sigmatropic and [1,3]-sigmatropic shifts, or as an intramolecular redox process. Alternative pathways, such as an intermolecular reaction or a free radical process, have been ruled out. The formation of **10a** by a multi-step sequence consisting of elimination, redox reaction, 1,4-addition to a quinone intermediate, and re-aromatization has also been ruled out, by trapping reactions. During the reaction, a proton from the acetaminophen structure is selectively transferred to C-5a in the tocopheryl moiety as proven by deuteration experiments. The 4′-*N*-acyl structure is crucial for the reaction to proceed, with the *N*-acetyl group giving the highest yield of rearrangement product. As 5a-substituted tocopherols are also intermediates in many homolytic reactions of tocopherols in biological model systems, this type of rearrangement might well contribute to the "prooxidative effect" of α-tocopherol, with acetaminophen being replaced by other 5a-substituents that exhibit similar chemical behavior in the reaction.

Introduction

In vitamin E chemistry over the past decade, α-tocopherol (**1**, vitamin E) has found valuable applications beyond its traditional utilization as a "healthy antioxidant". In particular, 5a-substituted tocopherols[1] have attracted much attention since the 5a-α-tocopheryl structure can be applied as a selectively cleavable amino protecting group (Toc) in organic synthesis,[2] as a precursor for *ortho*-quinone methide structures, and also as a lipophilic drug carrier.[3] In the last-mentioned case, the substituent at C-5a of the tocopherol moiety is itself an active substance. Attachment to the tocopheryl group renders the drug more lipophilic, and the resulting Toc-prodrug **3** acquires significantly altered solubility and transportability properties.

Toc-prodrugs are generally synthesized by simple procedures, mostly starting from 5a-bromo-α-tocopherol (**2**, Toc-Br, tocopheryl bromide)[4] as the Toc donor. The resulting prodrugs **3** are completely stable in acidic media, such as in the stomach, for instance, but are neatly cleaved under the basic conditions prevailing in the lower intestinal tract, thereby giving an illustrative example of pH-dependent drug release from prodrugs. The action of aqueous base usually leads to quantitative release of the drug in a clean and unambiguous reaction. Simultaneously, the carrier structure is released in the form of an *ortho*-quinone methide **4**; cf. Scheme 1. This intermediate undergoes subsequent reactions to give a mixture of two naturally occurring vitamin E metabolites, namely the spiro dimer of α-tocopherol (**5**)[5] and *para*-tocopheryl quinone (**6**),[6] both of which are nontoxic and physiologically harmless. In the presence of a reductant, **4** can also be reduced to α-tocopherol (**1**).[7] The ratio of **1**, **5**, and **6** usually varies depending on the reaction conditions. The formation of other vitamin E-derived compounds upon cleavage of the Toc carrier has not so far been observed.



Scheme 1

[‡] Novel Tocopherol Derivatives, XII. – Part XI: T. Rosenau, W. D. Habicher, A. Potthast, P. Kosma, *Synlett* **1999**, *3*, 291–294.

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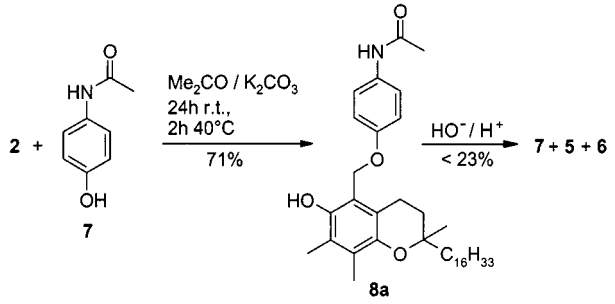
Results and Discussion

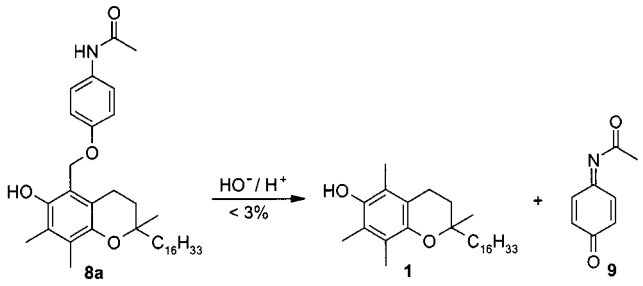
Treatment of tocopheryl bromide (**2**) with the analgesic and antipyretic acetaminophen (INN: paracetamol, 4-acetamidophenol, **7**)[8] according to Claisen etherification methodology afforded the corresponding Toc prodrug (Toc-acetaminophen, 4-(5a-α-tocopheroxy)acetanilide, **8a**) in fair yields. Drug release from **8a**, induced by treatment with a 3:1 (v/v) mixture of ethanol and 0.1 M aqueous sodium hydroxide, followed by neutralization by the standard technique for the cleavage of Toc prodrugs, did not quantitatively regenerate acetaminophen (**7**) as expected, but did so only in 23% yield; cf. Scheme 2.



Scheme 2

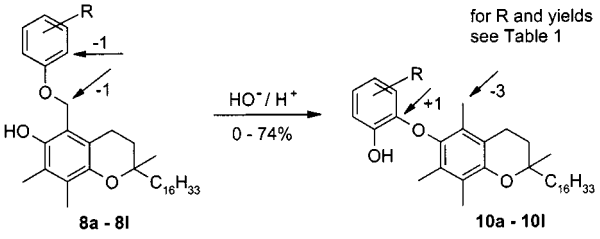
In view of the fact that 4-hydroxyacetanilide is a substance readily susceptible to oxidation, the initially assumed reaction mechanism was one that had already been established for drug release from Toc prodrugs of readily oxidizable substances, such as thiols, cysteine, or ascorbic acid. In this mechanism, the intermediate *ortho*-quinone methide generated upon drug release acts as an oxidant towards the released drug, and is reduced to α-tocopherol (**1**), while the drug undergoes oxidation (see Scheme 3). According to this hypothesis, the *para*-quinoid oxidation product of 4-hydroxyacetanilide (**7**), namely *N*-acetyl-benzoquinone monoimine (**9**), should be produced in addition to α-tocopherol (**1**). However, only small amounts of **1** and **9** (less than 3%) were found in the reaction mixture. Hence, the oxidation of acetaminophen by the presumed *ortho*-quinone methide intermediate, as shown in Scheme 3, does not contribute to overall product formation to any significant extent.

In contrast, 4-hydroxy-3-(6-*O*-α-tocopheryl)acetanilide (**10a**), a compound still containing both the acetaminophen and the tocopheryl moieties, was obtained as the major reaction product from the treatment of **8a** with aqueous base. The yield of 61% for the standard procedure (aqueous NaOH/ethanol) can be increased to 74% by working with a 0.1 M solution of NaOH in pure ethanol. Obviously, the Toc prodrug of acetaminophen is a singular case that deviates from the usual behavior of 5a-substituted tocopherols.



Scheme 3

The formation of **10a** is by no means a minor side reaction, but must rather be regarded as the main pathway in the reaction system, as this compound represents the major product. The conversion of Toc-acetaminophen (**8a**) into **10a** proceeds according to a hitherto unknown reaction type, which can formally be seen either as a rearrangement or as an intramolecular redox process. The rearrangement consists of a [1,4]-sigmatropic shift with regard to the tocopheryl moiety − and a [1,3]-sigmatropic shift with regard to acetaminophen − effecting the transfer of the 5a-substituent from the 5a-benzyl position to the phenolic oxygen of the tocopherol unit. If interpreted as a redox reaction, the formation of **10a** comprises the reduction of a benzyl ether structure to the corresponding methylbenzene and the concomitant oxidation ("aroxylation") of a substituted benzene to an aryl ether, as indicated in Scheme 4.



Scheme 4

To test whether the reaction is indeed a unique feature of Toc-acetaminophen, or whether it can be extended to structurally similar compounds, the acetaminophen moiety in **8a** was replaced by other, structurally related, groups. To reduce the number of possible candidates, the monosubstituted phenol structure was kept constant, but the type and position of the substituent at the phenolic ring was altered. Hydroquinone monomethyl ether, hydroquinone monoacetate, 4-chlorophenol, 4-aminophenol, and 4-(dimethylamino)phenol were treated with tocopheryl bromide to give the corresponding 5a-substituted tocopherols **8b**−**8f** in satisfactory to excellent yields, see Table 1. In all cases, etherification with the aid of powdered, dry K_2CO_3 in an organic solvent mixture (modified Claisen procedure) proved superior to Williamson-type variants that employed preformed phenolates, or the generation of the phenolates in situ with the aid of sodium hydride in THF. In analogous procedures, 2-acetamidophenol and 3-acetamidophenol were converted into the Toc-protected derivatives **8g**−**8h** to determine whether the *N*-acetyl group might be the cause of the observed special reactivity, regardless of its position in the 5a-substituent.

However, treatment of the compounds **8b**−**8h** with aqueous alkali merely resulted in the expected, "conventional" reaction behavior of 5a-substituted tocopherols: i.e., a neat release of the 5a-substituent with simultaneous formation of **5** and **6** from the tocopherol moiety, in agreement with the mechanism in Scheme 1. The fact that neither different

Table 1. Synthesis and rearrangement of 5a-substituted tocopherols

Compound	Substituent (position)[a]	Yield [%][b]	Rearr. product	Rearr. yield [%][c]
8a	−NH−Ac (4′)	71	**10a**	74
8b	$-OCH_3$ (4′)	74	**10b**	0
8c	−O−Ac (4′)	75	**10c**	0
8d	−Cl (4′)	88	**10d**	0
8e	$-NH_2$ (4′)	82	**10e**	0
8f	$-N(CH_3)_2$ (4′)	76	**10f**	0
8g	−NH−Ac (2′)	63	**10g**	0
8h	−NH−Ac (3′)	61	**10h**	0
8i	−NH−CHO (4′)	43	**10i**	18
8j	$-NH-COC_2H_5$ (4′)	70	**10j**	33
8k	$-NH-COC(CH_3)_3$ (4′)	58	**10k**	12
8l	$-NH-COC_6H_5$ (4′)	62	**10l**	5

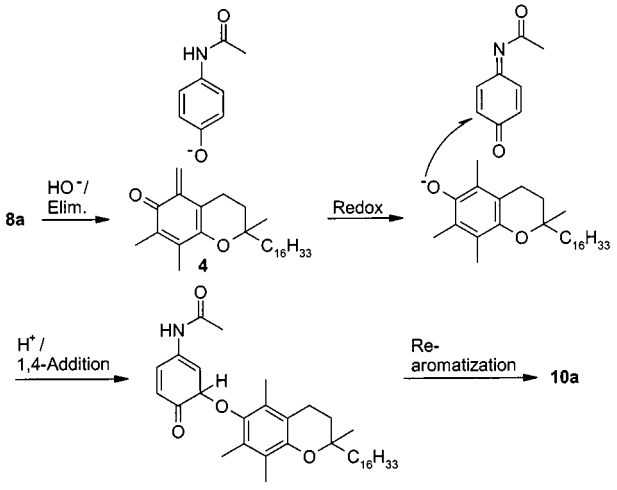
[a] See Scheme 4 for formulae. − [b] Synthesis according to Scheme 2. − [c] Synthesis according to Scheme 4.

substitution at the 4′-position nor an *N*-acetyl group in the 2′or 3′-position produced any rearrangement products similar to **10a** indicated that the 4′-*N*-acetyl group, or at least a 4′-*N*-acyl structure, is required for the observed rearrangement to proceed.

To confirm this hypothesis, the same etherification procedure as described above was employed to synthesize several tocopherol derivatives in which the 4′-*N*-acetyl group was replaced by different 4′-*N*-acyl groups. The product compounds **8i**−**8l** (cf. Table 1) were treated analogously with aqueous alkali to induce decomposition or possible rearrangement. Although the yields of the respective rearrangement products **10i**−**10l** were lower than in the case of acetaminophen, replacement of the 4-acetamido function by other 4-(*N*-acyl) substituents did not totally block the rearrangement (Table 1). The outcome of the experiments thus showed that a 4′-*N*-acyl group in a 5a-α-tocopheroxyphenyl structure does indeed appear to be a structural prerequisite for the process shown in Scheme 4. Good yields in this reaction have so far been observed only for acetaminophen. Therefore, the term "tocopherol−acetaminophen rearrangement" might serve as a temporary description for the reaction, until a more appropriate or general name is found.

The first reaction pathway proposed for the formation of **10a** from **8a** was a multi-step mechanism based on reactions well known in vitamin E chemistry (Scheme 5). The sequence is initiated by the elimination of the 5a-substituent with concomitant formation of the *ortho*-quinone methide **4**. The released phenolate is oxidized by this *ortho*-quinone methide to the quinone imine **9**.[9] This is followed by 1,4-addition of α-tocopherol (**1**) to **9**, and rearomatization, the latter step possibly being the driving force. The whole sequence thus consists of four steps: elimination − redox reaction − 1,4-addition to benzoquinone imines − rearomatization.

The mechanism appeared quite plausible, since every individual step finds some parallel evidence in traditional vitamin E chemistry, but raised several questions. Why would only tocopherol add to the benzoquinone imine **9**, and not the solvent − ethanol or water − which is present in a large excess? Why is the 1,4-addition exclusively directed by the imino group, and not by the carbonyl group?



Scheme 5

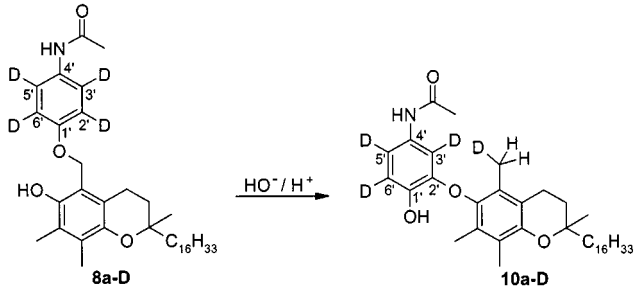
And finally, is the oxidative power of the *ortho*-quinone methide really sufficiently high to oxidize the comparatively stable acetaminophen? To answer these questions, several trapping reaction were carried out to prove or disprove the proposed mechanism. Firstly, trapping of the intermediate *ortho*-quinone methide **4** by vinyl ethers according to well established procedures[10] was tried. Secondly, addition of α-tocopherol (**1**) to benzoquinone imine **9** was attempted, and thirdly, oxidation of acetaminophen by an excess of **4** − the latter generated in situ by treatment of tocopheryl bromide (**8**) with solid Ag_2O − was investigated. However, all of these reactions produced negative results, thereby disproving the postulated mechanism shown in Scheme 5.

Kinetic experiments revealed that both Toc-acetaminophen (**8a**) and hydroxyl ions are consumed according to first-order kinetics: $d[\mathbf{8a}]/dt = -k[\mathbf{8a}][HO^-]$. The HO^- concentration may be considered constant if it is much higher than the concentration of **8a**. In this case, a rather simple kinetic rate law of pseudo-first order results for the rearrangement: $d[\mathbf{8a}]/dt = -k[\mathbf{8a}]$, with k being the kinetic rate constant. In 1 M alkali at 20 °C, a rate constant of approx. $5.5 \cdot 10^{-4} s^{-1}$ was obtained by the method of initial reaction rates. This first order rate law with respect to the tocopherol derivative ruled out a possible bimolecular mechanism, which would have been expected for an inter-

molecular process involving two molecules of **8a** in the rate-determining step. Kinetics first order with regard to both HO^- and **8a** fit with the deprotonation of the phenolic hydroxyl group as the rate-determining step of the rearrangement. An intermolecular mechanism for the tocopherol−acetaminophen rearrangement could thus be dismissed, in addition to the multi-step sequence of Scheme 5.

The formation of **10a** by a free radical process was ruled out because no dimeric coupling products, which are indicative of homolytic processes involving α-tocopherol (**1**) or its derivatives **3**,[11] were observed. Apart from the absence of species detectable by EPR, the absence of those coupling products, both in the usual reaction mixture and in the presence of additional **1**, allowed the occurrence of homolytic reactions during the rearrangement to be reliably discounted.

To examine possible participation of solvents in later steps of the reaction, the conversion of **8a** to **10a** was carried out in deuterated solvents, employing D_2O, CD_3OD, and NaOD. However, the expected incorporation of deuterium at C-5a was not observed. This outcome also did not change after several modifications of reaction conditions with respect to solvent composition, reaction temperature, and concentration of **8a**. This indicated that the newly introduced hydrogen at position 5a had originated from the acetaminophen moiety as the only available proton source in the reaction system. To verify this hypothesis conclusively, we used deuterated acetaminophen (**7-D**)[12] for the preparation of the corresponding labeled Toc prodrug (**8a-D**). Base-induced "drug release" from **8a-D** provided the labeled compound **10a-D** without formation of non-deuterated **10a**. Indeed, one deuterium had been incorporated into the tocopherol moiety at position 5a (Scheme 6). Thus, the hydrogen at the 2′-position of the acetaminophen moiety, which is replaced by the tocopheroxyl group during the reaction, is not released into the solvent, but selectively transferred to the 5a-position of tocopherol − formally a 1,4-sigmatropic proton shift − resulting in the observed formation of the CH_2D group.



Scheme 6

To gain additional insight as to how the reaction might proceed, and of the role of *N*-acyl groups in this process, molecular mechanical and quantum chemical calculations were carried out. As the spatial arrangement of the 5a-substituent relative to the tocopheryl moiety is characterized by the two dihedrals C-6−C-5−C-5a−O and C-5−C-5a−O−C-1′, conformational energies were calculated dependent on these angles. For the computations, deprotonated **8a** in the ground state was used as the starting structure, with the isoprenoid side chain in the tocopheryl moiety replaced by a methyl group.

When molecular mechanics using Allinger's MM2 force field were applied, no distinguished conformations were found among the stable geometries (as expected),[13] and no significant differences between compounds with 4′-*N*-acyl substituents (**8a**, **8i**−**8l**) and other substituents (**8b**−**8h**) could be detected. For consideration of electronic effects, the semiempirical PM3 method was used. Studies of the complete conformational space of the two dihedrals at 10° increments, giving a 36×36 energy matrix, provided an interesting result. For the substituted tocopherols with 4′-acetamido (**8a**), 4′-formamido (**8i**), and 4′-propionamido groups (**8j**), energy minima were found around 45° for C-6−C-5−C-5a−O and −100° for C-5−C-5a−O−C-1′.[14] The minima were less pronounced for the compounds **8k** and **8l**, while compounds without 4′-*N*-acyl substituents (**8b**−**8h**) exhibited no minima at all. Tested for deprotonated Toc-acetaminophen (**8a**), energy optimization produced the same minimum energy conformation independently of the starting dihedrals, which supports the assumption that this conformation represents the global energy minimum for the molecule.

The minimum geometry is characterized by an arrangement of the atoms O, C-6, C-5, C-5a, O, H-2′ in a twisted chair conformation. The hydrogen at the C-2′ position is situated above the two oxygens at C-6 and C-5a, at distances of 1.9 Å and 2.8 Å, respectively, and thus brought close to C-5a (2.7 Å). C-2′ is positioned at a distance of 2.4 Å from the tocopheryl oxygen. C-5a and the adjacent O are located on one side of a plane which is defined by the planar acetaminophen substituent, with C-6 and the adjacent O on the opposite side, and C-5 and the hydrogen at C-2′ lying within this plane.

The results of the computations, however, could not account for the especially high yields of rearrangement product in the case of Toc-acetaminophen **8a** as compared to **8i** and **8j**. While the different behavior of 4′-*N*-benzoyl (**8l**) and 4′-*N*-pivaloyl groups (**8k**) agreed with the computations, the calculated minor differences between 4′-*N*-acetyl (**8a**) and 4′-*N*-formyl (**8i**) or 4′-*N*-propionyl (**8j**) substituents must be regarded as too small to be a likely cause for the observed preference of **8a**.

However, there is an intriguing parallel between the yield of rearrangement product and the standard redox potentials of 4′-*N*-acyl-phenols.[15] The corresponding values for U° range around +0.75 V ±0.04 V for 4′-*N*-acylphenols (including *N*-formyl, *N*-propionyl, and *N*-benzoyl), with the exception of acetaminophen which exhibits an maximum at +0.90 V. The standard potentials of other substituents tested in the rearrangement are either significantly − more than 0.20 V − higher (**8b**−**8d**), or lower (**8e**, **8f**). If the existence of an "optimum" redox potential around the value for acetaminophen is assumed, rendering the occurrence of the tocopherol−acetaminophen rearrangement especially fav-

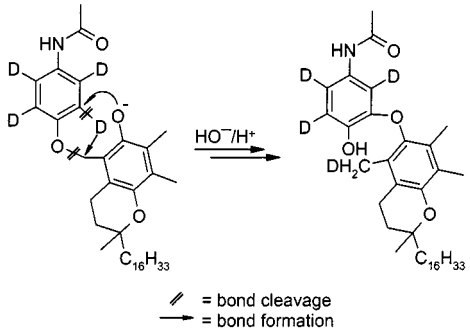
orable, it would become clear why 5a-substituents with a slightly diverging redox potential give only minor amounts of rearrangement product, whereas 5a-substituents with a value far removed from that of acetaminophen produce no rearrangement product at all.

Summarizing these theoretical results, 4′-*N*-acyl substituents promote a certain set of atomic coordinates for the respective 5a-substituted tocopherol. In the case of other 5a-substituents this special geometry is not adopted, so that "conventional" decomposition of 5a-substituted tocopherols (cf. Scheme 1) by elimination of the 5a-substituent occurs. The conformational minimum, in turn, is obviously a prerequisite for the rearrangement to proceed since starting materials that do not adopt this geometry do not produce any rearrangement products. An effective stabilization of this geometry is only possible after deprotonation of the phenolic OH group, which fits with conclusions drawn from the kinetic data. The stabilization might be explained by polarization effects: the hydrogen at C-3′ interacts with the oxygen in the amide group, and the hydrogen at C-2′ is influenced by the oxygens at C-6 and C-5a. Both polarizing effects are required to effect a measurable geometry stabilization. In the favored conformation, the reaction centers for the rearrangement are brought into close proximity, and arranged in a twisted chair conformation. Because of such preorganization of the rearrangement's reaction centers, only minimal further conformational changes and structural reorganization are required to obtain the transition state and product geometries. The prearrangement is likely to be the driving force of the rearrangement.

Theoretical and experimental evidence for the assumption of a concerted mechanism for the course of the tocopherol−acetaminophen rearrangement appears compelling: the O−C-5a bond is broken, a proton and two electrons are transferred from the acetaminophen to the tocopheryl moiety, and the C-2′−O bond is subsequently formed. The three steps proceed without large spatial separation of the tocopherol and acetaminophen moieties, unlike in the mechanism in Scheme 5. A mechanism initiated by attack of the tocopheryl oxygen at C-2′, followed by proton transfer to C-5a would involve attack of the tocopherolate anion at a highly electron-rich ring position and the intermediacy of a highly unstable benzyl anion at C-5a. This process can be ruled out as energetically highly unfavorable. A simultaneous transfer of the proton and two electrons, corresponding to a hydride transfer from C-2′ to C-5a, appears similarly unlikely. Therefore, the rearrangement must be regarded as a redox process (two-electron transfer) between the tocopherol and the acetaminophen moieties, with concomitant proton transfer in a highly organized structure, which is entirely compatible with the experimental and theoretical data.

Conclusion

The tocopherol−acetaminophen rearrangement − the formation of **10a** from **8a** − can be divided into three steps, which are shown in Scheme 7:



Scheme 7

1. cleavage of the bond between the acetaminophen oxygen and C-5a,

2. formation of a bond between the phenolic oxygen of the tocopherol and C-2′, and

3. selective transfer of the hydrogen from the 2′-position of acetaminophen to the 5a-position of tocopherol, in a formal [1,4]-sigmatropic shift.

The reaction is a non-radical, intramolecular process that is induced by deprotonation of the phenolic OH group. As demonstrated by computation, 4′-*N*-acyl substituents cause the 5a-substituted tocopherols to adopt a minimum energy conformation that places the reaction centers for the rearrangement in close proximity in a twisted chair conformation. This prearrangement explains why the molecules with 4′-*N*-acyl substituents undergo the rearrangement reaction, whereas in all other cases only elimination of the 5a-substituent occurs.

Apart from being a novel reaction type, the tocopherol−acetaminophen rearrangement might also help to elucidate some effects in vitamin E chemistry that have previously been ascribed to the rather vaguely defined term "pro-oxidative action" of α-tocopherol.[16] Various radical processes that take place in the presence of comparatively large amounts of vitamin E generate 5a-substituted tocopherols in biological model systems and in experiments in vitro. The 5a-substituent is assumed to originate in the components of the reaction mixture: solvent components, different amino acids, or purine bases. The 5a-substituted tocopherols decompose to form mixtures of **5** and **6**, together with small amounts of stable products which still contain the tocopheryl moiety as well as other groups.[17] Provided that certain compounds in the respective reaction mixtures behave similarly to acetaminophen, the rearrangement reaction might be one pathway for the formation of those compounds. The structure of the rearrangement product of Toc-acetaminophen now having been established, the search for similar compounds in other samples should be strongly facilitated.

Experimental Section

General Remarks: ^{1}H NMR spectra were recorded at 300 MHz, ^{13}C NMR spectra at 75.47 MHz, with $CDCl_3$ as the solvent and TMS as the internal standard unless stated otherwise. ^{13}C peaks were assigned by means of DEPT, GD, HMQC and HMBC spectra.

Nomenclature and numbering of the carbon atoms in tocopherols are used throughout as proposed by IUPAC.[18] The carbon δ values for the isoprenoid side chain of tocopherol derivatives (C-1′ to C-13′) are not listed, since they are only slightly affected by modifications of the chroman structure and are well established.[19] Resonances of the tocopherol and the 5a-substituent moieties are listed separately; the abbreviations "d.i." and "t.i." denote peaks from two and three equivalent carbons, respectively. The aliphatic region below δ = 1.5 in the ^{1}H NMR spectra is crowded with aliphatic tocopherol side chain resonances. Signals of aliphatic moieties attached to the tocopherol component are mostly covered by these resonances; the δ values in this region of proton NMR spectra are therefore not given.

MALDI-MS experiments were carried out on a time-of-flight instrument with linear geometry (pulsed N_2 laser, 337 nm, pulse duration 3 ns, acceleration voltage 20 kV) with gentisic acid as the matrix. GCMS analyses were performed in EI mode (70 eV, ITD), HPLC analyses used UV detection (RP-C_{18} column, 5 μm, 200 × 4.6 mm). − Elemental analyses were performed at the Institute of Organic Chemistry at Dresden University of Technology and the microanalytical laboratory of the Institute of Physical Chemistry at the University of Vienna. − All chemicals used were of reagent grade, all solvents were of HPLC grade. *n*-Hexane was dried with sodium metal.

General Procedure for the Preparation of Compounds 8a−8l: The phenolic coreactant (quantities, see below) was dissolved in 50 mL of dry acetone. Powdered, anhydrous potassium carbonate (0.420 g, 3.000 mmol) was added under an inert atmosphere, with stirring, and the mixture was refluxed for 10 min. After cooling to −10 °C by means of an ice/NaCl bath, a precooled solution of 5a-bromo-α-tocopherol (**2**, 1.529 g, 3.000 mmol) in 20 mL of chloroform was added dropwise with efficient stirring. The reaction mixture was stirred for 30 min at −10 °C, then allowed to warm slowly to room temperature, stirred for 24 h, and finally stirred for an additional 2 h at 40 °C. The solvents were evaporated in vacuo, and the residue was extracted three times with 100 mL of *n*-hexane (**caution!** The substance is known to have neurotoxic effects!). The solid remainder was discarded, the combined extracts were washed three times with 20 mL of water and dried with Na_2SO_4. The solvent was evaporated to a volume of 10 mL and chromatographed on acidic aluminum oxide (Brockmann, grade I). By-products **5** and **6** were eluted first with *n*-hexane, and the product was eluted with chloroform, unless stated otherwise below. Yields are listed for purified products, average values are given in the case of repeated syntheses.

General Procedure for the Preparation of Rearranged Compounds 10a−10l: A solution of a 5a-substituted tocopherol (**8a−8l**, quantities: see below) was dissolved in 30 mL of ethanol and stirred for 10 min at room temperature under an N_2 atmosphere. Aqueous NaOH (0.1 M, 10 mL) was added slowly over 30 min. If a cloudy mixture was obtained, ethanol was added dropwise until the solution turned clear again. The resulting solution was stirred for 24 h at room temperature, neutralized by addition of 1 mL of 1 M HCl, and extracted twice with 50 mL of chloroform. The organic phase was washed with water and dried with Na_2SO_4. The solvent was evaporated in vacuo, the residue was dissolved in dry *n*-hexane and chromatographed on acidic aluminum oxide. Tocopherol-derived by-products (**1**, **5**, and **6**) were eluted first with *n*-hexane and *n*-hexane/chloroform (v/v = 9:1); the product was then eluted with chloroform, unless stated otherwise below. Evaporation of the solvent yielded the pure products (yields below). The course of the reaction could be followed by HPLC: a 0.5 mL aliquot of the reaction mixture was taken after certain reaction times, chloroform (0.5 mL) added, and the sample analyzed by HPLC. A ternary solvent system (A/B/C, A: distilled water + H_3PO_4 (pH 3); B: CH_3CN/MeOH (v/v = 1:1); C: 2-propanol) with a gradient program was used: 1) 70:30:0 to 0:100:0 over 25 min, hold for 10 min; 2) 0:100:0 to 0:40:60 over 15 min, hold for 15 min; 0:40:60 to 0:100:0 over 1 min, hold.

***N*-{4-[3,4-Dihydro-6-hydroxy-2,7,8-trimethyl-2-(4,8,12-trimethyltridecyl)-2*H*-1-benzopyran-5-ylmethoxy]phenyl}acetamide (8a):** [Toc-acetaminophen, 4-(5a-α-tocopheroxy)acetanilide]. Starting material: 4-hydroxy-acetanilide (**7**) (1.516 g, 10.0 mmol), yield: 1.235 g (71%). The synthesis was repeated several times to obtain sufficiently large amounts of **8a**. − ^{1}H NMR: δ = 1.78 (m, 2 H, $^3CH_2$), 2.05 (s, 3 H, CH_3−CO), 2.08; 2.11 [s (2×), 3 H (2×), $^{7a}CH_3$, $^{8b}CH_3$], 2.68 (t, 2 H, $^4CH_2$) 5.32 (s, 2 H, $^{5a}CH_2$), 5.80 (s, b, 1 H, OH), 6.72 (d, 2 H, ^{Ar}H), 7.44 (d, 2 H, ^{Ar}H), 8.22 (s, 1 H, NH). − ^{13}C NMR: δ(tocopherol) = 11.9 (^{8b}C), 12.3 (^{7a}C), 20.4 (^{4}C), 23.6 (^{2a}C), 31.6 (^{3}C), 58.3 (^{5a}C), 74.9 (^{2}C), 116.5 (^{4a}C), 119.8 (^{5}C), 121.4 (^{7}C), 123.0 (^{8}C), 145.7 (^{6}C), 147.2 (^{8a}C); substituent: 23.4, 116.2 (d.i.), 122.0 (d.i.), 130.8, 152.2, 168.4. − MALDI-MS (*m*/*z*): 581 (MH^+); without matrix: 581 (MH^+), 429 (**4**-H^+). − $C_{37}H_{57}NO_4$ (579.86): calcd. C 76.64, H 9.91, N 2.42; found C 76.73, H 10.01, N 2.56.

***N*-{4-[3,4-Dihydro-6-hydroxy-2,7,8-trimethyl-2-(4,8,12-trimethyltridecyl)-2*H*-1-benzopyran-5-ylmethoxy]-2,3,5,6-tetradeuteriophenyl}acetamide (8a-D):** [2′,3′,4′,5′-Tetradeuterio-Toc-acetaminophen, 4-(5a-α-tocopheroxy)-2′,3′,4′,5′-tetradeuterioacetanilide]. Starting material: 4-hydroxy-2,3,5,6-tetradeuterioacetanilide (**7-D**) (0.466 g, 3.000 mmol), yield: 1.340 g (76%). The synthesis was repeated twice. − ^{1}H NMR: δ = 1.78 (m, 2 H, $^3CH_2$), 2.04 (s, 3 H, CH_3−CO), 2.08, 2.11 [s (2×), 3 H (2×), $^{7a}CH_3$, $^{8b}CH_3$], 2.67 (t, 2 H, $^4CH_2$) 5.31 (s, 2 H, $^{5a}CH_2$), 5.55 (s, b, 1 H, OH), 7.56 (s, 1 H, NH). − ^{13}C NMR: δ(tocopherol) = 11.8 (^{8b}C), 12.3 (^{7a}C), 20.4 (^{4}C), 23.7 (^{2a}C), 31.7 (^{3}C), 58.2 (^{5a}C), 75.3 (^{2}C), 116.5 (^{4a}C), 119.9 (^{5}C), 121.3 (^{7}C), 123.0 (^{8}C), 145.5 (^{6}C), 146.9 (^{8a}C); substituent: 23.0, 116.5 (d.i., t, *J* = 24.0 Hz), 121.7 (2×, t, *J* = 24.0 Hz), 132.8 (t (p), *J* = 6.2 Hz), 149.1, 168.4. − MALDI MS (*m*/*z*): 585 (MH^+); without matrix: 585 (MH^+), 429 (**4**-H^+). − $C_{37}H_{53}D_4NO_4$ (583.87): calcd. C 76.64; H(D), 9.91, N 2.42; found C 76.61, H 10.04, N 2.53.

5-[(4-Methoxyphenoxy)methyl]-2,7,8-trimethyl-2-(4,8,12-trimethyltridecyl)-6-chromanol (8b): (*O*-Toc-hydroquinone methyl ether). Starting material: hydroquinone monomethyl ether (0.700 g, 5.640 mmol), yield: 1.227 g (74%). − ^{1}H NMR: δ = 1.80 (m, 2 H, $^3CH_2$), 2.09, 2.10 [s (2×), 3 H (2×), $^{7a}CH_3$, $^{8b}CH_3$], 2.64 (t, 2 H, $^4CH_2$), 3.42 (s, 3 H, O−CH_3), 5.21 (s, 2 H, $^{5a}CH_2$), 5.03 (s, 1 H, OH), 6.75 (m, 4 H, ^{Ar}H). − ^{13}C NMR: δ(tocopherol) = 11.8 (^{8b}C), 12.1 (^{7a}C), 20.2 (^{4}C), 23.7 (^{2a}C), 31.7 (^{3}C), 61.3 (^{5a}C), 75.1 (^{2}C), 117.0, 119.8, 121.4, 122.1 (^{Ar}C), 143.4 (^{6}C), 147.5 (^{8a}C); substituent: 55.6, 115.1 (d.i.), 116.0 (d.i.), 151.2, 153.8. − $C_{36}H_{56}O_4$ (552.83): calcd. C 78.21, H 10.21; found C 78.35, H 10.34.

4-[6-Hydroxy-2,7,8-trimethyl-2-(4,8,12-trimethyltridecyl)-3,4-dihydro-2*H*-1-benzopyran-5-yl]methoxyphenyl acetate (8c): (*O*-Toc-*O*-Ac-hydroquinone). Starting material: hydroquinone monoacetate (1.217 g, 8.000 mmol), yield: 1.308 g (75%). − ^{1}H NMR: δ = 1.72 (m, 2 H, $^3CH_2$), 2.11, 2.16 [s (2×), 3 H (2×), $^{7a}CH_3$, $^{8b}CH_3$], 2.61 (t, 2 H, $^4CH_2$), 2.13 (s, 3 H, OOC−CH_3), 5.08 (s, 2 H, $^{5a}CH_2$), 6.00 (s, 1 H, OH, b), 6.92 (d (m), 4 H, ^{Ar}H). − ^{13}C NMR: δ(tocopherol) = 11.8 (^{8b}C), 12.1 (^{7a}C), 20.4 (^{4}C), 23.5 (^{2a}C), 31.5 (^{3}C), 62.2 (^{5a}C), 75.0 (^{2}C), 117.2, 119.5, 121.4, 123.0 (^{Ar}C), 143.2 (^{6}C), 147.4 (^{8a}C); substituent: 21.0, 114.2 (d.i.), 122.3 (d.i.), 146.3, 151.8, 168.9. − $C_{37}H_{56}O_5$ (580.84): calcd. C 76.51, H 9.72; found C 76.75, H 10.01.

5-[(4-Chlorophenoxy)methyl]-2,7,8-trimethyl-2-(4,8,12-trimethyltridecyl)-6-chromanol (8d): (*O*-Toc-*para*-chlorophenol). Starting material: *p*-chlorophenol (1.286 g, 10.000 mmol), yield: 1.471 g (88%). The product was eluted with chloroform/diethyl ether (v/v=1:1). − ^{1}H NMR: δ = 1.81 (m, 2 H, ^{3}CH$_2$), 2.11, 2.14 [s (2×), 3 H (2×), ^{7a}CH$_3$, ^{8b}CH$_3$], 2.68 (t, 2 H, ^{4}CH$_2$), 5.08 (s, 2 H, ^{5a}CH$_2$), 5.83 (s, 1 H, OH), 6.96 (s (m), 4 H, ^{Ar}H). − ^{13}C NMR: δ(tocopherol) = 11.9 (^{8b}C), 12.0 (^{7a}C), 20.4 (^{4}C), 23.5 (^{2a}C), 31.5 (^{3}C), 62.2 (^{5a}C), 75.5 (^{2}C), 117.3, 119.3, 122.5, 123.6 (^{Ar}C), 144.3 (^{6}C), 149.0 (^{8a}C); substituent: 115.4 (d.i.), 127.4 (d.i.), 128.3, 158.2. − $C_{35}H_{53}ClO_3$ (557.25): calcd. C 75.44, H 9.59. Cl, 6.36; found C 75.23, H 9.67; Cl, 6.59.

5-[(4-Aminophenoxy)methyl]-2,7,8-trimethyl-2-(4,8,12-trimethyltridecyl)-6-chromanol (8e): (*O*-Toc-*para*-aminophenol). Starting material: *p*-aminophenol (0.871 g, 8.000 mmol), yield: 1.322 g (82%). − ^{1}H NMR: δ = 1.83 (m, 2 H, ^{3}CH$_2$), 2.11, 2.14 [s (2×), 3 H (2×), ^{7a}CH$_3$, ^{8b}CH$_3$], 2.64 (t, 2 H, ^{4}CH$_2$), 5.22 (s, 2 H, ^{5a}CH$_2$), 6.78 (s, 4 H, ^{Ar}H), 7.30 (s, b, 3 H, OH, NH$_2$). − ^{13}C NMR: δ(tocopherol) = 11.9 (^{8b}C), 12.1 (^{7a}C), 20.4 (^{4}C), 23.6 (^{2a}C), 31.6 (^{3}C), 60.3 (^{5a}C), 74.9 (^{2}C), 117.2, 119.6, 121.3, 122.8 (^{Ar}C), 143.2 (^{6}C), 147.8 (^{8a}C); substituent: 113.2 (d.i.), 115.9 (d.i.), 140.3, 153.4. − $C_{35}H_{55}NO_3$ (537.82): calcd. C 78.16, H 10.31, N 2.60; found C 76.23, H 10.50, N 2.52.

5-[4-(Dimethylamino)phenoxy]methyl-2,7,8-trimethyl-2-(4,8,12-trimethyltridecyl)-6-chromanol (8f): (*O*-Toc-*para*-dimethylaminophenol). Starting material: *p*-(dimethylamino)phenol (1.372 g, 10.000 mmol), yield: 1.290 g (76%). − ^{1}H NMR: δ = 1.82 (m, 2 H, ^{3}CH$_2$), 2.12, 2.15 [s (2×), 3 H (2×), ^{7a}CH$_3$, ^{8b}CH$_3$], 2.82 (s, 6 H, N-(CH$_3$)$_2$), 5.13 (s, 2 H, ^{5a}CH$_2$), 6.18 (d (m), 2 H, ^{Ar}H), 6.70 (d (m), 2 H, ^{Ar}H), 8.12 (s, 1 H, OH). − ^{13}C NMR: δ(tocopherol) = 11.2 (^{8b}C), 12.4 (^{7a}C), 20.5 (^{4}C), 23.5 (^{2a}C), 31.5 (^{3}C), 62.0 (^{5a}C), 75.2 (^{2}C), 117.2, 119.1, 120.8, 123.4 (^{Ar}C), 148.2 (^{6}C), 151.9 (^{8a}C); substituent: 39.3 (d.i.), 114.2 (d.i.), 121.8 (d.i.), 142.4, 150.9. − $C_{37}H_{59}NO_3$ (565.88): calcd. C 78.53, H 10.51, N, 2.48; found C 78.72, H 10.31, N, 2.28.

***N*-{2-[3,4-Dihydro-6-hydroxy-2,7,8-trimethyl-2-(4,8,12-trimethyltridecyl)-2*H*-1-benzopyran-5-ylmethoxy]phenyl}acetamide (8g):** [*O*-Toc-2-hydroxyacetanilide, 2-(5a-α-tocopheroxy)acetanilide]. Starting material: 2-hydroxyacetanilide (0.758 g, 5.000 mmol), yield: 1.096 g (63%). − ^{1}H NMR: δ = 1.80 (m, 2 H, ^{3}CH$_2$), 2.08, 2.11 [s (2×), 3 H (2×), ^{7a}CH$_3$, ^{8b}CH$_3$], 2.10 (s, 3 H, CH$_3$−CO), 2.66 (t, 2 H, ^{4}CH$_2$), 3.83 (s, b, 1 H, OH), 4.58 (s, 2 H, ^{5a}CH$_2$), 6.84 (t, 1 H, $^{5'}$CH), 7.11 (t, 1 H, $^{4'}$CH), 7.22 (d, 1 H, $^{3'}$CH), 7.48 (d, 1 H, $^{6'}$CH). − ^{13}C NMR: δ(tocopherol) = 11.8 (^{8b}C), 12.0 (^{7a}C), 20.7 (^{4}C), 23.7 (^{2a}C), 31.6 (^{3}C), 57.0 (^{5a}C), 75.1 (^{2}C), 117.1 (^{4a}C), 119.4 (^{5}C), 121.4 (^{7}C), 123.2 (^{8}C), 144.2 (^{6}C), 149.2 (^{8a}C); substituent: 23.2, 114.1, 119.3, 122.0, 123.7, 123.8, 149.4. − $C_{37}H_{57}NO_4$ (579.86): calcd. C 76.64, H 9.91, N 2.42; found C 76.48, H 10.08, N 2.24.

***N*-{3-[3,4-Dihydro-6-hydroxy-2,7,8-trimethyl-2-(4,8,12-trimethyltridecyl)-2*H*-1-benzopyran-5-ylmethoxy]phenyl}acetamide (8h):** [*O*-Toc-3-hydroxyacetanilide, 3-(5a-α-tocopheroxy)acetanilide]. Starting material: 3-hydroxyacetanilide (0.758 g, 5.000 mmol), yield: 1.025 g (59%). The product was eluted with chloroform/methanol (v/v = 9:1). − ^{1}H NMR: δ = 1.80 (m, 2 H, ^{3}CH$_2$), 2.09, 2.10 [s (2×), 3 H (2×), ^{7a}CH$_3$, ^{8b}CH$_3$], 2.12 (s, 3 H, CH$_3$−CO), 2.64 (t, 2 H, ^{4}CH$_2$), 5.06 (s, 2 H, ^{5a}CH$_2$), 5.30 (s, b, 1 H, OH), 6.52 (m, 1 H, $^{4'}$CH), 6.92 (m, 1 H, $^{6'}$CH), 7.02 (t, 1 H, $^{5'}$CH), 7.18 (s (m), 1 H, $^{2'}$CH). − ^{13}C NMR: δ(tocopherol) = 11.7 (^{8b}C), 11.9 (^{7a}C), 20.5 (^{4}C), 23.2 (^{2a}C), 31.7 (^{3}C), 59.2 (^{5a}C), 75.2 (^{2}C), 117.4 (^{4a}C), 119.1 (^{5}C), 121.1 (^{7}C), 122.9 (^{8}C), 144.4 (^{6}C), 149.0 (^{8a}C); substituent: 23.6, 108.9, 113.4, 116.4, 129.2, 133.6, 159.2. − $C_{37}H_{57}NO_4$ (579.86): calcd. C 76.64, H 9.91, N 2.42; found C 76.72, H 9.77, N 2.27.

***N*-{4-[3,4-Dihydro-6-hydroxy-2,7,8-trimethyl-2-(4,8,12-trimethyltridecyl)-2*H*-1-benzopyran-5-ylmethoxy]phenyl}formamide (8i):** [*O*-Toc-4-hydroxyformanilide, 4-(5a-α-tocopheroxy)formanilide]. Starting material: 4-hydroxyformanilide (1.371 g, 10.000 mmol), yield: 0.730 g (63%). The synthesis was repeated twice. ^{1}H NMR: δ = 1.78 (m, 2 H, ^{3}CH$_2$), 2.07; 2.11 [s (2×), 3 H (2×), ^{7a}CH$_3$, ^{8b}CH$_3$], 2.65 (t, 2 H, ^{4}CH$_2$), 5.12 (s, 2 H, ^{5a}CH$_2$), 6.82 (d, 2 H, ^{Ar}H), 7.35 (d, 2 H, ^{Ar}H), 7.92 (s, 1 H, −CHO), 9.12 (s, b, 2 H, OH, NH). − ^{13}C NMR: δ(tocopherol) = 11.8 (^{8b}C), 12.3 (^{7a}C), 20.4 (^{4}C), 23.7 (^{2a}C), 31.5 (^{3}C), 60.9 (^{5a}C), 75.4 (^{2}C), 116.8 (^{4a}C), 119.9 (^{5}C), 121.3 (^{7}C), 123.4 (^{8}C), 144.9 (^{6}C), 148.0 (^{8a}C); substituent: 118.2 (d.i.), 120.5 (d.i.), 129.4, 153.0, 164.8. − $C_{36}H_{55}NO_4$ (565.83): calcd. C 76.42, H 9.80, N 2.48; found C 76.69, H 10.04, N, 2.66.

***N*-{4-[3,4-Dihydro-6-hydroxy-2,7,8-trimethyl-2-(4,8,12-trimethyltridecyl)-2*H*-1-benzopyran-5-ylmethoxy]phenyl}propanamide (8j):** (*O*-Toc-4-propionamidophenol). Starting material: *N*-(4-hydroxyphenyl)propanamide (1.652 g, 10.000 mmol), yield: 1.247 g (70%). − ^{1}H NMR: δ = 1.84 (m, 2 H, ^{3}CH$_2$), 2.10, 2.12 [s (2×), 3 H (2×), ^{7a}CH$_3$, ^{8b}CH$_3$], 2.22 (q, 2 H, CO−CH$_2$), 2.62 (t, 2 H, ^{4}CH$_2$), 5.19 (s, 2 H, ^{5a}CH$_2$), 6.24 (s, b, 2 H, OH, NH), 6.80 (d, 2 H, ^{Ar}H), 7.42 (d, 2 H, ^{Ar}H). − ^{13}C NMR: δ(tocopherol) = 11.9 (^{8b}C), 12.0 (^{7a}C), 20.6 (^{4}C), 23.5 (^{2a}C), 31.6 (^{3}C), 62.1 (^{5a}C), 75.1 (^{2}C), 117.0 (^{4a}C), 119.5 (^{5}C), 121.0 (^{7}C), 123.2 (^{8}C), 141.8 (^{6}C), 148.4 (^{8a}C); substituent: 10.2, 30.8, 116.2 (d.i.), 120.1 (d.i.), 133.1, 150.9, 170.2. − $C_{38}H_{59}NO_4$ (593.88): calcd. C 76.85, H 10.01, N 2.36; found C 76.92, H 10.23, N, 2.56.

***N*-{4-[3,4-Dihydro-6-hydroxy-2,7,8-trimethyl-2-(4,8,12-trimethyltridecyl)-2*H*-1-benzopyran-5-ylmethoxy]phenyl}-2,2-dimethylpropanamide (8k):** (*O*-Toc-4-pivaloylamidophenol). Starting material: *N*-(4-hydroxyphenyl)-2,2-dimethylpropanamide, (0.966 g, 5.000 mmol), yield: 1.082 g (58%). − ^{1}H NMR: δ = 1.85 (m, 2 H, ^{3}CH$_2$), 2.09; 2.11 [s (2×), 3 H (2×), ^{7a}CH$_3$, ^{8b}CH$_3$], 2.62 (t, 2 H, ^{4}CH$_2$), 5.05 (s, 2 H, ^{5a}CH$_2$), 6.86 (d, 2 H, ^{Ar}H), 7.36 (d, 2 H, ^{Ar}H), 8.08 (s, b, 2 H, OH, NH). −^{13}C NMR: δ(tocopherol) = 11.9 (^{8b}C), 12.4 (^{7a}C), 21.0 (^{4}C), 23.2 (^{2a}C), 31.5 (^{3}C), 61.4 (^{5a}C), 75.3 (^{2}C), 117.4 (^{4a}C), 119.1 (^{5}C), 121.5 (^{7}C), 123.8 (^{8}C), 142.9 (^{6}C), 146.8 (^{8a}C); substituent: 27.4, 36.1, 117.2 (d.i.), 119.4 (d.i.), 133.9, 145.4, 172.8. − $C_{40}H_{63}NO_4$ (621.94): calcd. C 77.25, H 10.21, N 2.25; found C 77.08, H 10.44, N, 2.42.

***N*-{4-[3,4-Dihydro-6-hydroxy-2,7,8-trimethyl-2-(4,8,12-trimethyltridecyl)-2*H*-1-benzopyran-5-ylmethoxy]phenyl}benzamide** (*O*-Toc-4-benzamidophenol, **8l**): Starting material: *N*-(4-hydroxyphenyl)-benzamide, (1.066 g, 5.000 mmol), yield: 1.194 g (62%). The synthesis was repeated twice. − ^{1}H NMR: δ = 1.78 (m, 2 H, ^{3}CH$_2$), 2.09, 2.12 [s (2×), 3 H (2×), ^{7a}CH$_3$, ^{8b}CH$_3$], 2.64 (t, 2 H, ^{4}CH$_2$), 4.23 (s, b, 2 H, OH, NH), 5.15 (s, 2 H, ^{5a}CH$_2$), 6.90 (d, 2 H, ^{Ar}H), 7.32 (m, 1 H, ^{Ar}H), 7.52 (m, 2 H, ^{Ar}H), 7.58 (d, 2 H, ^{Ar}H), 7.64 (m, 2 H, ^{Ar}H). − ^{13}C NMR: δ(tocopherol) = 11.9 (^{8b}C), 12.2 (^{7a}C), 21.4 (^{4}C), 23.5 (^{2a}C), 31.5 (^{3}C), 59.8 (^{5a}C), 75.0 (^{2}C), 116.9 (^{4a}C), 119.3 (^{5}C), 121.0 (^{7}C), 123.4 (^{8}C), 145.1 (^{6}C), 148.0 (^{8a}C); substituent: 27.4, 36.1, 115.8 (d.i.), 120.1 (d.i.), 127.2 (d.i.), 128.6 (d.i.), 131.8, 132.8, 133.9, 149.6, 164.3. − $C_{42}H_{59}NO_4$ (641.93): calcd. C 78.59, H 9.26, N 2.18; found C 78.38, H 8.99, N, 2.20.

***N*-{4-Hydroxy-3-[3,4-dihydro-2,5,7,8-tetramethyl-2-(4,8,12-trimethyltridecyl)-2*H*-1-benzopyran-6-yloxy]phenyl}acetamide (10a):** Starting material: *O*-Toc-acetaminophen (**8a**, 1.000 g, 1.724 mmol), yield: 0.610 g (61%). The use of 0.1 M ethanolic NaOH instead of 0.1 M aqueous solution increased the yield to 0.740 g (74%). − ^{1}H NMR: δ = 1.83 (m, 2 H, ^{3}CH$_2$), 2.06 (s, 3 H, CH$_3$−CO), 2.10,

2.14, 2.23 (s (3×), 3 H (3×), $^{7a}CH_3$, $^{8b}CH_3$, $^{5a}CH_3$), 2.68 (t, 2 H, $^{4}CH_2$), 4.56 (s, b, 1 H, OH), 6.70 (dd, 1 H, J = 8.8 Hz, J = 1.7 Hz, ^{Ar}H), 7.08 (dd, 1 H, J = 2.5 Hz, J = 1.7 Hz, ^{Ar}H), 7.38 (dd, 1 H, J = 8.8 Hz, J 2.7 Hz, ^{Ar}H), 7.55 (s, 1 H, NH). − ^{13}C NMR: δ(tocopherol) = 11.9 (^{8b}C), 12.1 (^{7a}C), 13.8 (^{5a}C), 20.8 (^{4}C), 23.7 (^{2a}C), 31.6 (^{3}C), 74.5 (^{2}C), 118.3 (^{4a}C), 123.8 (^{8}C), 124.6 (^{5}C), 125.1 (^{7}C), 142.3 (^{6}C), 149.4 (^{8a}C); substituent: 22.6, 108.8, 114.7, 117.2, 133.0, 142.2, 143.0, 168.2. − MALDI MS (*m*/*z*): 581 (MH^+); without matrix: 581 (MH^+), no signal at 429 (**4**-H^+). − $C_{37}H_{57}NO_4$ (579.86): calcd. C 76.64, H 9.91, N 2.42; found C 76.59, H 9.97, N, 2.38.

***N*-{4-Hydroxy-3-[5-deuteriomethyl-3,4-dihydro-2,7,8-trimethyl-2-(4,8,12-trimethyltri-decyl)-2*H*-1-benzopyran-6-yloxy]-2,5,6-trideuteriophenyl}acetamide (10a-D):** Starting material: **8a-D** (1.000 g, 1.722 mmol), yield: 0.573 g (57%). − ^1H NMR: δ = 1.84 (m, 2 H, $^{3}CH_2$), 2.08 (s, 3 H, CH_3-CO), 2.11, 2.15, 2.20 [s (3×), 3 H (3×), $^{7a}CH_3$, $^{8b}CH_3$, $^{5a}CH_2D$], 2.68 (t, 2 H, $^{4}CH_2$), 5.80 (s, b, H, OH), 9.03 (s, 1 H, NH). − ^{13}C NMR: δ(tocopherol) = 11.9 (^{8b}C), 12.1 (^{7a}C), 13.9 (t, J = 22.5 Hz, ^{5a}C), 20.7 (^{4}C), 23.7 (^{2a}C), 31.6 (^{3}C), 74.5 (^{2}C), 118.1 (^{4a}C), 123.6 (^{8}C), 124.7 (^{5}C), 125.3 (^{7}C), 142.3 (^{6}C), 149.5 (^{8a}C); substituent: 22.6, 108.7 (t, J = 25.5 Hz), 114.8 (t, J = 24 Hz), 117.2 (t, J = 24 Hz), 133.0, 142.2, 143.0, 168.2. − MALDI MS (*m*/*z*): 585 (MH^+); without matrix: 585 (MH^+), no signal at 429 (**4**-H^+). − $C_{37}H_{53}D_4O_4N$ (583.87): calcd. C 76.64; H(D), 9.91, N 2.42; found C 76.75; H(D), 10.12, N, 2.58.

***N*-{4-Hydroxy-3-[3,4-dihydro-2,5,7,8-tetramethyl-2-(4,8,12-trimethyltridecyl)-2*H*-1-benzopyran-6-yloxy]phenyl}formamide (10i):** Starting material: **8i** (0.566 g, 1.000 mmol), yield: 0.102 g (18%). − ^1H NMR: δ = 1.81 (m, 2 H, $^{3}CH_2$), 2.08, 2.11, 2.21 [s (3×), 3 H (3×), $^{7a}CH_3$, $^{8b}CH_3$, $^{5a}CH_3$], 2.64 (t, 2 H, $^{4}CH_2$), 3.80 (s, b, H, OH), 6.74 (dd, 1 H, J = 8.7 Hz, J = 1.3 Hz, ^{Ar}H), 7.06 (dd, 1 H, J = 2.2 Hz, J = 1.3 Hz, ^{Ar}H), 7.18 (dd, 1 H, J = 8.7 Hz, J = 2.2 Hz, ^{Ar}H). − ^{13}C NMR: δ(tocopherol) = 11.8 (^{8b}C), 12.2 (^{7a}C), 13.8 (^{5a}C), 20.4 (^{4}C), 23.5 (^{2a}C), 31.5 (^{3}C), 74.7 (^{2}C), 119.7 (^{4a}C), 124.2 (^{8}C), 125.5 (^{5}C), 127.4 (^{7}C), 141.1 (^{6}C), 149.3 (^{8a}C); substituent: 109.0, 116.0, 117.1, 134.6, 141.2, 142.2, 162.0. − $C_{36}H_{55}NO_4$ (565.83): calcd. C 76.42, H 9.80, N 2.48; found C 76.23, H 10.02, N, 2.33.

***N*-{4-Hydroxy-3-[3,4-dihydro-2,5,7,8-tetramethyl-2-(4,8,12-trimethyltridecyl)-2*H*-1-benzopyran-6-yloxy]phenyl}propanamide (10j):** Starting material: **8j** (0.594 g, 1.000 mmol), yield: 0.196 g (33%). − ^1H NMR: δ = 1.83 (m, 2 H, $^{3}CH_2$), 2.09 (t, 2 H, $CO-CH_2$), 2.11; 2.15; 2.22 [s (3×), 3 H (3×), $^{7a}CH_3$, $^{8b}CH_3$, $^{5a}CH_3$], 2.65 (t, 2 H, $^{4}CH_2$), 4.56 (s, b, 2 H, 2 × OH), 6.64 (dd, 1 H, J = 8.7 Hz, J = 1.2 Hz, ^{Ar}H), 6.98 (dd, 1 H, J = 2.3 Hz, J = 1.2 Hz, ^{Ar}H), 7.20 (dd, 1 H, J = 8.7 Hz, J = 2.3 Hz, ^{Ar}H), 7.55 (s, 1 H, NH). − ^{13}C NMR: δ(tocopherol) = 11.9 (^{8b}C), 12.1 (^{7a}C), 13.9 (^{5a}C), 20.5 (^{4}C), 23.6 (^{2a}C), 31.5 (^{3}C), 74.5 (^{2}C), 118.3 (^{4a}C), 124.2 (^{8}C), 125.1 (^{5}C), 125.4 (^{7}C), 140.9 (^{6}C), 148.3 (^{8a}C); substituent: 10.4, 31.5, 108.4, 116.4, 119.0, 133.9, 143.2, 143.4, 169.6. − $C_{38}H_{59}NO_4$ (593.89): calcd. C 76.85, H 10.01, N 2.36; found C 76.98, H 9.87, N, 2.43.

***N*-{4-Hydroxy-3-[3,4-dihydro-2,5,7,8-tetramethyl-2-(4,8,12-trimethyltridecyl)-2*H*-1-benzopyran-6-yloxy]phenyl}-2,2-dimethylpropanamide (10k):** Starting material: **8k** (0.933 g, 1.500 mmol), yield: 0.112 g (12%). ^1H NMR: δ = 1.81 (m, 2 H, $^{3}CH_2$), 2.11, 2.14, 2.22 [s (3×), 3 H (3×), $^{7a}CH_3$, $^{8b}CH_3$, $^{5a}CH_3$], 2.68 (t, 2 H, $^{4}CH_2$), 6.66 (s, b, 1 H, OH), 6.69 (dd, 1 H, J = 8.8 Hz, J = 1.3 Hz, ^{Ar}H), 6.90 (dd, 1 H, J = 2.2 Hz, J = 1.3 Hz, ^{Ar}H), 7.19 (dd, 1 H, J = 8.8 Hz, J = 2.2 Hz, ^{Ar}H), 9.52 (s, 1 H, NH). ^{13}C NMR: δ(tocopherol) = 11.8 (^{8b}C), 12.4 (^{7a}C), 13.7 (^{5a}C), 20.6 (^{4}C), 23.7 (^{2a}C), 31.4 (^{3}C), 74.5 (^{2}C), 119.2 (^{4a}C), 124.7 (^{8}C), 124.9 (^{5}C), 125.6 (^{7}C), 140.3 (^{6}C), 147.1 (^{8a}C); substituent: 27.5, 37.1, 107.9, 115.2, 118.3, 134.4, 143.4, 144.1, 172.4. − $C_{40}H_{63}NO_4$ (621.94): calcd. C 77.25, H 10.21, N 2.25; found C 77.46, H 10.13, N, 2.33.

***N*-{4-Hydroxy-3-[3,4-dihydro-2,5,7,8-tetramethyl-2-(4,8,12-trimethyltridecyl)-2*H*-1-benzopyran-6-yloxy]phenyl}benzamide (10l):** Starting material: **8l** (1.882 g, 2.000 mmol), yield: 0.094 g (5%). − ^1H NMR: δ = 1.84 (m, 2 H, $^{3}CH_2$), 2.09; 2.13; 2.21 (s (3×), 3 H (3×), $^{7a}CH_3$, $^{8b}CH_3$, $^{5a}CH_3$), 2.65 (t, 2 H, $^{4}CH_2$), 3.08 (s, b, 1 H, OH), 6.78 (dd, 1 H, J = 8.7 Hz, J = 1.5 Hz, ^{Ar}H), 7.12 (dd, 1 H, J = 2.2 Hz, J = 1.5 Hz, ^{Ar}H), 7.34 (dd, 1 H, J = 8.7 Hz, J = 2.5 Hz, ^{Ar}H), 8.92 (s, 1 H, NH). − ^{13}C NMR: δ(tocopherol) = 11.8 (^{8b}C), 12.2 (^{7a}C), 13.7 (^{5a}C), 20.5 (^{4}C), 23.8 (^{2a}C), 31.7 (^{3}C), 74.8 (^{2}C), 119.2 (^{4a}C), 123.9 (^{8}C), 125.0 (^{5}C), 125.1 (^{7}C), 143.4 (^{6}C), 147.5 (^{8a}C); substituent: 127.4 (d.i.), 128.2 (d.i.), 129.9, 134.2, 164.5. − $C_{42}H_{59}NO_4$ (641.93): calcd. C 78.59, H 9.26, N 2.18; found C 78.42, H 9.50, N, 2.35.

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[13] By setting the values for the two dihedrals in 10° intervals, a 36 × 36 matrix of optimized energies was obtained for compounds **8a** to **8l**. For many dihedrals, the proximity of substituent atoms and the tocopherol moiety resulted in strong steric

repulsion, and thus in unstable geometries. The additional steric constraint with bulky substituents, such as in **8k** or in **8l**, was clearly evident.

[14] The exact values for the dihedral angles C-6−C-5−C-5a−O and C-5−C-5a−O−C-1′ are 46.2° and −103.5° for Toc-acetaminophen (**8a**), 45.9° and −101.4° for **8i**, and 46.4° and −101.9° for **8j**. The stabilization gained by adopting this geometry can be visualized by considering the rotational barrier for the bond C-5a−O, which corresponds to a change of the dihedral angle C-5−C-5a−O−C-1′. For deprotonated Toc-acetaminophen (**8a**) the rotational barrier was 31 kJ/mol, and the values for **8i** and **8j** were 26 kJ/mol and 29 kJ/mol, respectively. For the bulky 4′-*N*-acyl substituents (**8k** and **8l**) the rotational barrier was lower at 23 kJ/mol. Interestingly, neutral (i.e., not deprotonated) **8a** exhibited only a shallow energy minimum of 19 kJ/mol at slightly altered dihedral angles (C-6−C-5−C-5a−O: 45.4° and C-5−C-5a−O−C-1′: −104.9°).

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