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Novel tocopheryl compounds. Part 16: Nitration of α-tocopheryl acetate—a mechanistic study

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Abstract—The reaction of α-tocopheryl acetate (vitamin E acetate, **3**) with concentrated nitric acid proceeds according to a non-radical, two-step mechanism, producing 5-nitromethyl-γ-tocopheryl acetate (**4**) in good yields. In the first step, oxidation of **3** affords a benzylic cation intermediate (**8**), which in the second step adds nitrite to give **4**. The acetyl group, which stabilizes intermediate **8** intramolecularly, remains bound to the tocopheryl moiety throughout the reaction.

1. Introduction

Reaction of α-tocopherol (**1**), the main component of vitamin E,[1] with diluted HNO_3 or silver nitrate in alcoholic solutions is one of the oldest reactions in vitamin E chemistry, which was discovered by Further and Meyer as early as in 1939.[2] Because of the intensively red color evolving during this process, the reaction is still utilized today in a qualitative assay to indicate the presence of α-tocopherol in biological samples.[3] Smith and Ungnade[4] identified the red reaction product as 5,6-tocopheryldione (**2**, 'α-tocored'), and Rosenau et al. established its formation to proceed via *ortho*-quinone methide and 5-alkoxy intermediates, with the 5a-CH_3 group being released as methanol.[5] In 1996, Witkowski and Markowska[6] showed that also α-tocopheryl acetate (**3**), the main application form of α-tocopherol in all types of formulations, can be nitrated by HNO_3 in acetic acid, affording 5-nitromethyl-γ-tocopheryl acetate (**4**) as the main product in good yields. This conversion thus causes regioselective introduction of a nitro group at the 5a-methyl group under maintenance of the acetate at the phenolic hydroxyl group. This is interesting insofar as nitrations of alkanes are known to proceed as non-selective radical reactions under rather drastic conditions. Moreover, *ortho*-quinone methides, which are intermediates in the nitration of the free phenol, seemed hard to evoke in the case of a protected phenolic OH group.

The nitration product 5-nitromethyl-γ-tocopheryl acetate (**4**) is a very useful starting material for the preparation of novel tocopherol derivatives, which is due to the protected OH group that increases the oxidative stability of such compounds under synthesis and work-up conditions, and ensures increased long-term efficiency of the derived stabilizers as compared to the free phenol. It has the additional advantage of being accessible from the standard vitamin E derivative **3** by a simple one-step procedure. In connection with our recent utilization of **4** as nitrile oxide precursor in [3+2]-cycloadditions,[7] we have reexamined the mechanism of the nitration of α-tocopheryl acetate in this work.

2. Results and discussion

Used mainly in industrial bulk processes, direct nitration of alkanes with nitric acid or NO_x species is a radical reaction that proceeds in the gas phase under drastic conditions (Hass process). On a laboratory scale, nitroalkanes are usually prepared from the corresponding alkyl halides with sodium nitrite in DMF in the presence of urea.[8] Given these facts, it appeared rather surprising that 5-nitromethyl-γ-tocopherol acetate **4** could be readily prepared from α-tocopheryl acetate by reaction with concentrated nitric acid (65–67%) in glacial acetic acid, since the reaction proceeded at ambient temperature in good yields (71–74%). The product can be easily identified by its orange color and the prominent singlet of the 5-nitromethyl group at 5.39 ppm in the ^1H NMR spectrum (67.6 ppm in ^{13}C NMR). The main byproducts of the nitration reaction are 5,6-tocopheryldione (**2**) and 5-formyl-γ-tocopheryl acetate (**5**). The former side-product is evidently generated by deacetylation of α-tocopheryl acetate and reaction of the resulting free tocopherol with nitric acid in the 'classical' way, the latter is formed from the main nitration product **4** in a Nef-type process. The amount of byproducts increases with reaction times and with increasing reagent concentration.

Keywords: vitamin E; tocopheryl acetate; nitration; ortho-quinone methide; reaction mechanism.
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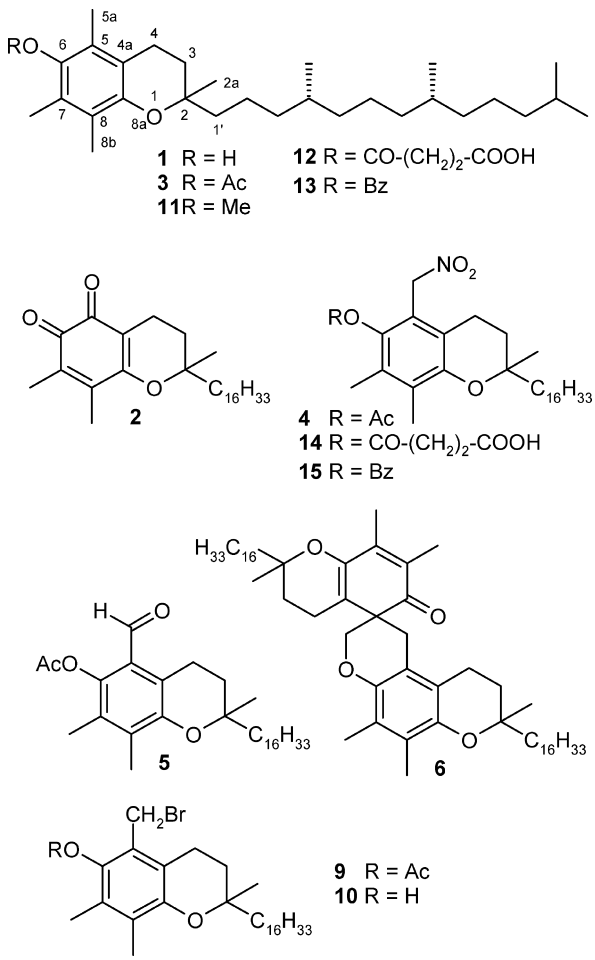
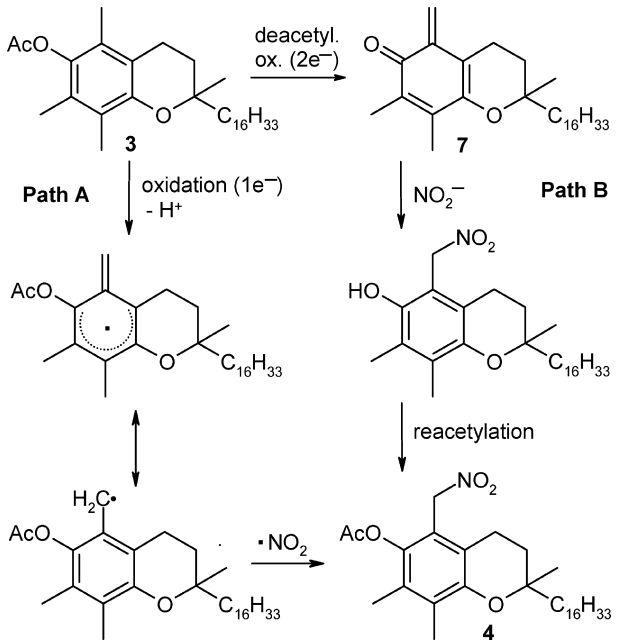


First experiments were aimed at establishing whether the nitration reaction was indeed a radical process or not. EPR experiments gave no indication of *C*-centered radicals, but the absence of radicals in EPR was no conclusive proof of a heterolytic process. Furthermore, the presence of oxygen did not influence yield or product distribution, and radical coupling products, which are a reliable sign of homolytic reactions of tocopherols, were completely absent. Both observations were strongly indicative of a non-radical process. The fact that the reaction proceeded equally well at −70°C in the dark was taken as the final affirmation of the non-radical course of the nitration. A homolytic path—as 'path A' in Scheme 1—was thus ruled out.

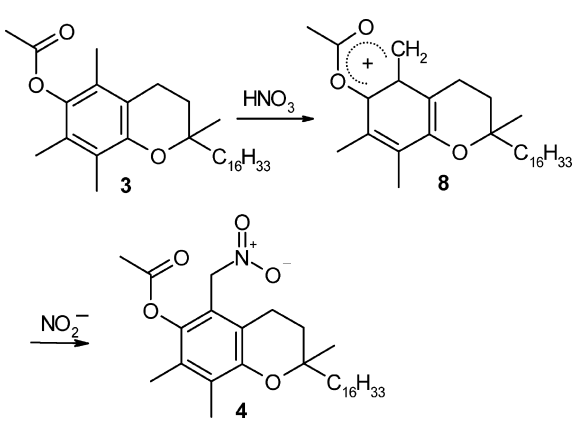
The heterolytic path B as shown in Scheme 1 was the next mechanistic suggestion. A deacetylation of **3** caused by the strong acid seemed plausible, as did reacetylation by the glacial acetic acid present as the solvent. However, the *ortho*-quinone methide intermediate (**7** in Scheme 1), if indeed formed, should dimerize to the spiro-dimer of α-tocopherol (**6**) under the prevailing strongly oxidative conditions, rather than add nitrite to give the corresponding 5a-nitro derivative. Nitration of α-tocopherol (**1**) under the conditions used for nitration of α-tocopheryl acetate (**3**) provided spiro-dimer **6**, which proved that **7**, once formed, underwent dimerization, but not nitrite addition. In a next step, the solvent was changed from acetic acid to neat



Scheme 1. Preliminary mechanistic proposals for nitration of α-tocopheryl acetate. Path A: homolytic reaction; path B: oxidation–addition mechanism involving deacetylation and reacetylation steps.

propionic acid. If the reaction mechanism indeed involved deacetylation and reacylation, the product should now present a propionyl instead of an acetyl group. However, exclusively 5-nitromethyl-γ-tocopheryl acetate was found—exactly as upon nitration in glacial acetic acid. This fact disproved a participation of deacylation/reacylation steps in the mechanism, and furthermore demonstrated that the acetyl group remained bound to the tocopheryl moiety throughout the reaction. Thus, also path B (Scheme 1) had to be rejected.

Resulting from different experiments, the reaction mechanism as shown in Scheme 2 was established for the nitration. Oxidation of **3** affords the cationic intermediate **8**. The positive charge at the benzylic position is stabilized through the *o*-acyloxy function by pronounced charge distribution and thus resonance stabilization. Addition of nitrite to C-5a eventually gives the nitration product **4**. The different experiments used to clarify the nitration mechanism are summarized in Table 1.



Scheme 2. Nitration of α-tocopheryl acetate: reaction mechanism and intermediate.

According to the mechanism in Scheme 2, the nitration reaction should exhibit a pronounced solvent influence, since the positively charged intermediate would be stabilized by polar and protic solvents,[9] while less polar solvents should have a destabilizing effect so that less product is formed in that case. This was experimentally confirmed: in the case of methylene chloride as the solvent (Table 1) no **4** was formed, but only α-tocored (**2**). To support the reaction mechanism further, 5-bromomethyl-γ-tocopheryl acetate (**9**) was reacted with sodium nitrite in the absence of HNO_3 under otherwise identical conditions, which afforded 58% of 5-nitromethyl-γ-tocopherol acetate (**4**). This proved that the second reaction step—addition of nitrite to the benzylic 5a-position—is possible under the prevailing reaction conditions and leads to the expected product **4** in the case of an acyl-protected phenolic OH group. The analogous reaction with 5-bromomethyl-γ-tocopherol (**10**), lacking this acetyl group, led to spiro-dimer **6**, which indicated involvement of the *ortho*-quinone methide intermediate **7**. From these experiments and from the completely different course of the nitration of α-tocopherol and α-tocopheryl acetate the crucial role of the acetyl group became obvious.

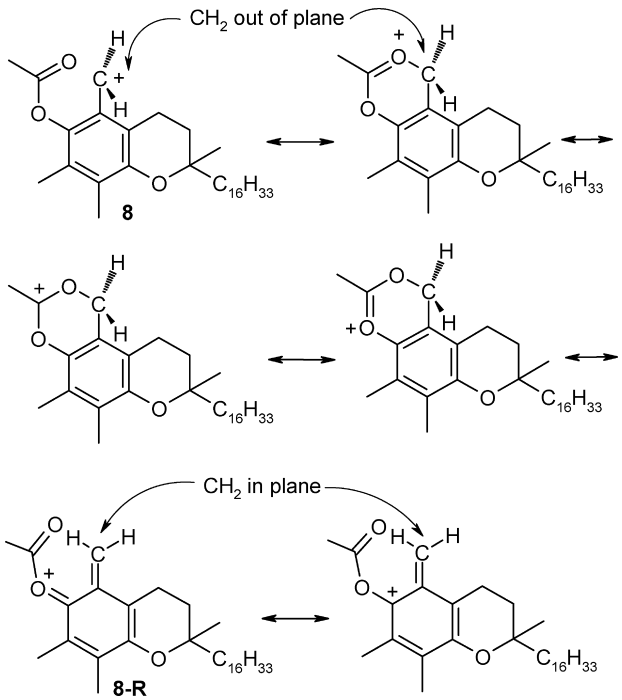
The function of the acetyl (acyl) group at the phenolic OH was further investigated by means of α-tocopheryl ethers and esters. Nitration of α-tocopheryl methyl ether (**11**) led to a dark, complex mixture with α-tocored (**2**) as the main component and no formation of 5-nitromethyl-γ-tocopheryl acetate (**4**), while nitration of α-tocopheryl succinate (**12**), and α-tocopheryl benzoate (**13**) proceeded similarly to the nitration of acetate **3**, giving the corresponding 5-nitromethyl-γ-tocopheryl derivatives (**14**-**15**) in 68 and 62% yield, respectively. Evidently, the *o*-acyloxy function exerts a stabilizing effect on the benzylic cation, which *o*-alkyl functions are unable to provide. Thus, tocopheryl compounds containing an acyl-protected phenolic OH groups give the corresponding 5-nitromethyl derivative upon nitration, whereas in compounds lacking this acyl group the stabilized intermediate **8** cannot be formed so that competitive reaction paths are taken.

Table 1. Nitration of α-tocopheryl acetate under different reaction conditions

Starting material	Conditions	Solvent	Yield[a]	Procedure variant[b]
3	rt, 0.5 h	AcOH	74	A
3a[c]	rt, 0.5 h	AcOH	71	B
3	rt, 0.5 h ($NaNO_2$)	AcOH	78	C
3	rt, 0.5 h	PrA[d]	52	D
3	rt, 0.5 h	CH_2Cl_2	0	E
3	−70°C, 0.5 h	CH_2Cl_2	32	E
9	rt, 8 h ($NaNO_2$)	AcOH	58	F
10	rt, 8 h ($NaNO_2$)	AcOH	0	F
11	rt, 0.5 h	AcOH	0	G
12	rt, 0.5 h	AcOH	68	H
13	rt, 0.5 h	AcOH	62	I
3	rt, 2 h ($NaNO_2$)	NMMO	54	J

[a] Isolated yields (%) after chromatographic purification.
[b] See Section 3.
[c] 2,2,5,7,8-Pentamethylchroman-6-yl acetate (model compound of **3** with the isoprenoid side chain replaced by a methyl group).
[d] Propionic acid.

DFT computations (B3LYP/6-31+G*) on intermediate **8** were carried out by means of a model with truncated isoprenoid side chain, carrying a methyl group instead. Analysis of the conformational space of the acetyl group, considering the rotation around the C(O)–O bond, revealed a deep minimum at a (O)C–O–C^{Ar}–C^{Ar} dihedral angle of 0.4°, so that the acetyl group lies nearly perfectly in the aromatic plane.[10] In minimum geometry, the three atoms of the carboxyl group together with C-6, C-5 and C-5a are positioned into in a six-membered ring structure with twisted chair geometry.[11] The acyl oxygen is placed into a distance of 1.45 Å to C-5a, which comes close to a C–O single bond, with bond lengths of 1.40 and 1.43 Å, in benzyl alcohol and benzyl acetate, respectively. The C=O bond, having typically a length of 1.21 Å in organic acetates, is stretched to 1.31 Å in **8**, indicating a weakened double bond, while the C(O)–O bond obtains partial double bond character, being shortened from 1.36–1.37 to 1.31 Å. The benzylic carbon, which is sp^2 hybridized in benzylium, *o*-hydroxybenzylium and *o*-methoxybenzylium cations, thus having trigonal planar geometry, has a tetragonal environment in **8**. The H–C–H angle (109.27°) comes quite close to the tetrahedral angle in carbon sp^3 hybrids, and the group stands perpendicular to the aromatic ring plane. These structural features can be rationalized by participation of four mesomeric structures of **8**, as shown in Scheme 3. The spatial interaction of the partially negative acyl oxygen with the positive benzylic position causes effective charge delocalization over four atoms, so that the resulting 1,3,8-trioxa-phenanthrylium cation experiences strong resonance stabilization. The occurrence of similar out-of plane benzylic intermediates, obtained from α-tocopherol upon oxidation, has recently been described and directly observed by NMR,[12] even though the stabilization was effected intermolecularly by interaction of the benzylic cation with



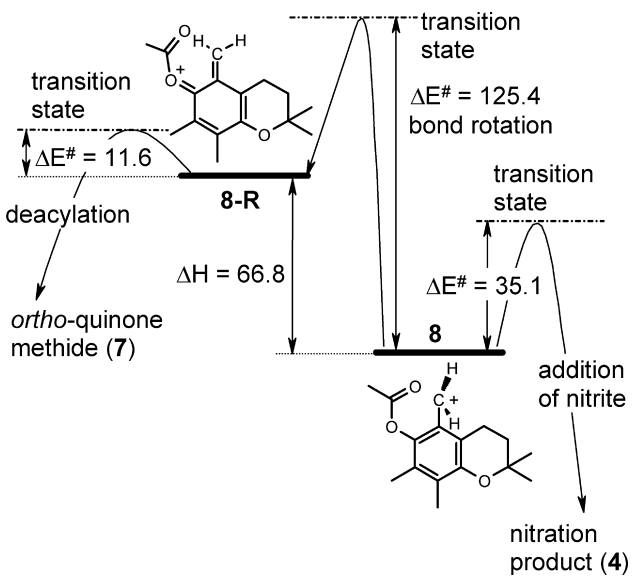
Scheme 3. Resonance stabilization in the cationic intermediate **8** and **8-R**.

the negative charge of an amine *N*-oxide, rather than intramolecularly by an acyl group, as in the present case.

It should be noted that **8**-**R**—with its three ring-centered resonance forms, one of which is shown in Scheme 3—is not a resonance hybrid of **8**. It is formally obtained by rotation of the benzylic CH_2 in **8**, which breaks resonance. In **8**-**R**, which represents the *O*-acetylated *ortho*-quinone methide **7**, the benzylic methylene group is fully planar and lies in the ring plane. The geometry of the tocopheryl moiety in **7** remains nearly unchanged (differences <0.04 Å) in **8**-**R**, and the C(O)–O bond is very long, indicating a rather weak linkage. This agrees with transition state computations for the loss of CH_3CO^+ from **8**-**R**, which afforded a low activation energy of 11.6 kJ/mol only. Comparing the total energies, **8** is favored over **8**-**R** by 66.8 kJ/mol.

The rotational barrier for the benzylic methylene group between the out-of-plane state in **8** and the in-plane geometry in **8**-**R** was calculated to be relatively high at 125.4 kJ/mol.[13] In contrast, to reach the transition state for the addition of nitrite to **8** (which is the same as for the elimination of nitrite from **4**) an activation energy of only 35.1 kJ/mol is required. From these data, intermediate **8**, once formed, will add nitrite to give **4**, rather than undergo methylene group rotation to give **8**-**R**. However, as soon as **8**-**R** is formed—for instance in the case of higher reaction temperatures, insufficient amounts of nitrite present, or destabilizing apolar solvents, it will immediately loose the acyl group to give **7** (which further dimerizes to spiro-dimer **6**). The calculated reaction data are summarized in Scheme 4.

In the mechanism shown in Scheme 2, the stabilized intermediate **8** adds nitrite, which is formed by reduction of HNO_3 upon oxidation of the tocopheryl acetate starting material. If this mechanism is correct, additional nitrite should increase the amount of nitration product formed. Exactly this was experimentally observed: adding sodium nitrite to the nitration mixture[14] clearly increased the yield



Scheme 4. Calculated energetics for the reaction pathways from **8**, all values in kJ/mol.

of **4**. Finally, the double-faced role of nitric acid as both the oxidant and the nitrite source can also be played by another oxidant in combination with nitrite, a fact, which is also strongly supportive of the proposed mechanism. For example, the reagent couple *N*-methylmorpholine-*N*-oxide (NMMO) and $NaNO_2$ converts α-tocopheryl acetate (**3**) into 5-nitromethyl-γ-tocopheryl acetate (**4**) in 54% yield, in the same way as nitric acid alone does. NMMO oxidizes **3** to the intermediate **8**,[15] and nitrite adds onto **8** to give the final product **4**.[16] Summarizing the experimental results in combination with the computational data, there seems to be sufficient evidence in favor of the nitration mechanism shown in Scheme 2.

3. Experimental

All chemicals were commercially available. Thin layer chromatography (TLC) was performed on silica gel 60 plates (5×10 cm, 0.25 mm) with fluorescence detection under UV light at 254 nm. Column chromatography was performed on silica gel G60 (40–63 μm). Melting points, determined on a Kofler-type micro hot stage with Reichert–Biovar microscope, are uncorrected. ^{1}H NMR spectra were recorded at 300 MHz, ^{13}C NMR spectra at 75.47 MHz in $CDCl_3$ as the solvent and TMS as the internal standard. Data are given in ppm. ^{13}C peaks were assigned by means of APT, HMQC and HMBC spectra. Resonances of the isoprenoid side chain of tocopherols are not influenced by modifications of the chroman ring, and are therefore not listed; 'd.i.' denotes peaks with double intensity.

Computations, as implemented through Spartan Pro 02 by Wavefunction, Inc., Irvine, CA, USA, 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[17] parametrized by Becke,[18] was used, along with the double-zeta split valence basis sets 6-31+G*,[19] which includes diffuse functions. Transition states and minima were confirmed by analysis of the calculated vibrational spectrum, and by intrinsic reaction coordinate analysis. For all transition states the number of imaginary frequencies was 1 ($N_{\text{imaginary}}=1$), for all minimum geometries it was 0 ($N_{\text{imaginary}}=0$).

3.1. General experimental procedure for the nitration of α-tocopheryl acetate

To a solution of **3** (or model compound **3a**)[20] in acetic acid (100 mL) concentrated nitric acid (16 mL) was added dropwise at ambient temperature. After half an hour the solution was diluted with water and extracted with *n*-hexane. The combined organic layers were neutralized with saturated $NaHCO_3$-solution, washed with water and brine, and dried over $MgSO_4$. The solution was filtered, and the solvent was removed in vacuo. The crude product was purified by column chromatography (EtOAc/*n*-hexane, v/v=1:20).

Variant A. The nitro-compound **4** was obtained from

α-tocopheryl acetate (**3**) (3.17 g, 6.69 mmol) according to the general procedure as a yellow oil (2.55 g, 74%).

3.1.1. Acetic acid (3,4-dihydro-5-nitromethyl-2,7,8-trimethyl)-2-(4,8,12-trimethyltridecyl)-2*H*-1-(benzopyran-6-yl) ester (4). ^{1}H NMR: δ 5.39 (s, 2H, H-5a), 2.76 (t, 2H, ^3J=6.8 Hz, H-4), 2.34 (s, 3H, Me in acetyl), 2.13 (s, 3H, H-7a), 2.02 (s, 3H, H-8b), 1.82–1.78 (m, 2H, H-3), 1.28 (s, 3H, H-2a). ^{13}C NMR: δ 169.7 (CO), 149.9 (C-8b), 141.6 (C-6), 128.7 (C-7), 128.1 (C-5), 118.6 (C-8), 118.6 (C-4a), 75.7 (C-2), 67.6 (C-5a), 32.8 (C-3), 27.9 (C-2a), 21.0 (Me in acetyl), 20.5 (C-4), 13.1 (C-8b), 12.3 (C-7a). Anal. calcd for $C_{31}H_{51}NO_5$ (517.74): C 71.71, H 9.93, N 2.71. Found: C 72.08, H 9.84, N 2.57.

Variant B. The nitro-compound **4a** was obtained from chromanol acetate (**3a**)[20] (2.20 g, 9.00 mmol) and concentrated nitric acid (27 mL) according to the general procedure as a white solid (1.96 g, 71%) as a white solid, mp=122–124°C.

3.1.2. Acetic acid (3,4-dihydro-5-nitromethyl-2,2,7,8-tetra-methyl)-2*H*-1-(benzopyran-6-yl) ester (4a). ^{1}H NMR: δ 5.38 (s, b, 2H, H-5a), 2.76 (t, 2H, ^3J=6.8 Hz, H-4), 2.34 (s, 3H, Me in acetyl), 2.13 (s, 3H, H-7a), 2.02 (s, 3H, H-8b), 1.82 (t, 2H, ^3J=6.8 Hz, H-3), 1.31 (s, 6H, H-2a, H-2b). ^{13}C NMR: δ 169.3 (CO), 150.1 (C-8b), 141.7 (C-6), 129.0 (C-7), 128.2 (C-5), 118.6 (C-8), 117.9 (C-4a), 73.7 (C-2), 71.5 (C-5a), 32.3 (C-3), 26.8 (d.i., C-2a, C-2b), 20.4 (Me in acetyl), 20.3 (C-4), 13.2 (C-8b), 12.4 (C-7a). Anal. calcd for $C_{16}H_{21}NO_5$ (307.24): C 62.53, H 6.89, N 4.56. Found: C 62.44, H 6.79, N 4.46.

Variant C. Nitration of **3** (3.17 g, 6.69 mmol) was carried out according to the general procedure under addition of pulverized sodium nitrite (10.7 mmol (1.6 equiv.), 0.74 g) to give **4** (2.69 g, 74%).

Variant D. Nitration of **3** (0.50 g, 1.06 mmol) with HNO_3 (3.2 mL) was carried out according to the general procedure with propionic acid (20 mL) instead of acetic acid to give **4** (1.79 g, 52%).

Variant E. Nitration of **3** (3.17 g, 6.69 mmol) was carried out according to the general procedure with methylene chloride as the solvent instead of acetic acid. Yield of **4** was 0% at rt, but 1.10 g (32%) at −70°C.

Variant F. To a solution of 5-bromo-α-tocopheryl acetate (**9**) (0.11 g, 0.20 mmol) in dry DMF (10 mL) $NaNO_2$ (0.02 g, 0.29 mmol) was added and stirred for 8 h. Water (50 mL) was added and the mixture was extracted with *n*-hexane, and further worked up according to the general procedure to give **4** (0.06 g, 58%). Employing the same procedure with 5-bromo-α-tocopherol (**10**) no **4** was obtained.

Variant G. Nitration was carried out according to the general procedure with α-tocopheryl methyl ether (**11**) as the starting material (0.100 g, 0.22 mmol) in acetic acid (4.0 mL) and HNO_3 (0.6 mL) instead of **3**. No nitration product was found.

Variant H. Nitration was carried out according to the general procedure with α-tocopheryl succinate (**12**) as the starting material (2.00 g, 3.77 mmol) instead of **3**. Acidic aluminum oxide was used for column chromatographic separation, which provided 5-nitromethyl-γ-tocopheryl succinate (**14**) as a waxy semi-solid (1.47 g, 68%).

3.1.3. Succinic acid (3,4-dihydro-5-nitromethyl-2,7,8-trimethyl)-2-(4,8,12-trimethyltridecyl)-2*H*-1-(benzopyran-6-yl) monoester (14). ^{1}H NMR: δ 5.39 (s, 2H, H-5a), 2.72 (m, 2H, ^3J=7.0 Hz, H-4), 2.60 (m, 2H, ^3J=7.0 Hz, HOOC–CH_2), 2.41 (t, 2H, ^3J=7.0 Hz, ROOC–CH_2), 2.11 (s, 3H, H-7a), 2.04 (s, 3H, H-8b), 1.80 (m, 2H, H3), 1.27 (s, 3H, H-2a). ^{13}C NMR: δ 173.3 (COOR), 171.9 (COOH), 149.9 (C-8b), 141.5 (C-6), 129.0 (C-7), 128.5 (C-5), 118.6 (C-8), 118.6 (C-4a), 75.7 (C-2), 67.4 (C-5a), 32.8 (C-3), 29.7 (ROOC–*C*H$_2$), 29.3 (HOOC–*C*H$_2$), 27.9 (C-2a), 20.4 (C-4), 13.2 (C-8b), 12.2 (C-7a). Anal. calcd for $C_{33}H_{53}NO_7$ (575.79): C 68.84, H 9.28 N 2.43. Found: C 79.02, H 9.40, N 2.56.

Variant I. Nitration was carried out according to the general procedure with α-tocopheryl benzoate (**13**) as the starting material (2.00 g, 3.74 mmol) instead of **3**, providing 5-nitromethyl-γ-tocopheryl benzoate (**15**) as yellow oil (1.35 g, 62%).

3.1.4. Benzoic acid (3,4-dihydro-5-nitromethyl-2,7,8-trimethyl)-2-(4,8,12-trimethyltridecyl)-2*H*-1-(benzopyran-6-yl) ester (15). ^{1}H NMR: δ 7.70 (m, 5H, Ph), 5.39 (s, 2H, H-5a), 4.10 (s, b, COOH), 2.74 (t, 2H, ^3J=6.9 Hz, H-4), 2.14 (s, 3H, H-7a), 2.05 (s, 3H, H-8b), 1.78 (m, 2H, H-3), 1.28 (s, 3H, H-2a). ^{13}C NMR: δ 166.1 (CO), 149.7 (C-8b), 142.0 (C-6), 133.9 (C-4′ in Ph), 130.3 (C-1′ in Ph), 128.2 (C-7), 128.8 (d.i., C-3′ and C-5′ in Ph), 128.1 (d.i., C-2′ and C-6′ in Ph), 127.7 (C-5), 118.6 (C-8), 118.6 (C-4a), 75.7 (C-2), 66.8 (C-5a), 32.8 (C-3), 27.9 (C-2a), 20.5 (C-4), 13.1 (C-8b), 12.3 (C-7a). Anal. calcd for $C_{36}H_{53}NO_5$ (579.83): C 74.57, H 9.21, N 2.42. Found: C 74.42, H 9.12, N 2.61.

Variant J. A mixture of *N*-methylmorpholine-*N*-oxide (5 g), α-tocopheryl acetate (**3**, 1.00 g, 2.12 mmol) and pulverized sodium nitrite (0.20 g, 2.90 mmol) was heated to 100°C under magnetic stirring for 4 h, while additional $NaNO_2$ (0.2 g in total) was added in portions in 1 h intervals. Water (200 mL) was added and the mixture was extracted with *n*-hexane, and further worked up according to the general procedure to give **4** (0.59 g, 54%).

Acknowledgements

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7. Results will be reported in due course.
8. This reaction gives considerable amounts of the corresponding alkyl nitrite besides the desired products due to the ambifunctionality of nitrite as nucleophile.
9. Formation of **8** from **3** means a formal hydride abstraction from the benzylic position at C-5a. A transfer of two electrons, however, giving a quinoid dicationic intermediate which then releases a proton from C-5a to produce **8**, appears more plausible.
10. Besides this global minimum there is a shallow local minimum at a (O)C–O–C^{Ar}–C^{Ar} dihedral angle of 142.4°.
11. This spatial arrangement is evidently favored by strong resonance stabilization (66.9 kJ/mol as compared to an acetyl group lying in the aromatic plane, but with the acyl oxygen facing opposite direction, i.e. towards C-7a).
12. The occurrence of similar out-of plane benzylic intermediates derived from α-tocopherol has recently been described and directly observed by NMR: Rosenau, T.; Potthast, A.; Elder, T.; Kosma, P. *Org. Lett.* **2002**, *4*(24), 4285–4288.
13. Enforced rotation of the CH_2 group in 5° steps with full geometry optimization in addition to transition state localization. Here, again the crucial role of the acetyl group can be seen. While the value for **8** is high, the rotational barrier shrinks to mere 8.2 kJ/mol in the system without acetyl group.
14. The major part of the nitrite reacted with excess HNO_3 in a symproportionation to NO_2 gas. Nevertheless, the positive effect of nitrite addition on the yield was evident.
15. Under the conditions used, oxidation of nitrite to NO_2 or nitrate by NMMO was negligible, **5** was observed as the major byproduct.
16. **8** Can also be trapped with other nucleophiles, which additionally confirms the proposed mechanism. In such cases oxidants milder than concentrated HNO_3 are advantageously used. See for instance: (a) Rosenau, T.; Habicher, W. D.; Chen, C. L. *Heterocycles* **1996**, *43*, 787–798. Rosenau, T.; Habicher, W. D. *Tetrahedron Lett.* **1997**, *38*, 5959–5960.
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20. Compound **3a** was obtained by acetylation of 2,2,5,7,8-pentamethylchroman-6-ol (0.10 g, 0.45 mmol) by acetyl chloride (0.32 mL, 0.50 mmol) in CH_2Cl_2 in the presence of TEA (55 mg, 0.50 mmol). After addition of water (100 mL) and extraction with EtOAc **3a** was isolated quantitatively. Analytical data are consistent with those given in the literature: Burton, G. W.; Doba, T.; Gabe, E. J.; Hughes, L.; Lee, F. L.; Prasad, L.; Ingold, K. U. *J. Am. Chem. Soc.* **1985**, *107*, 7053.