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Novel tocopheryl compounds XXV: synthesis and comparison of the *para*-quinones of all four homologous tocopherol model compounds and their 3,4-dehydro derivatives

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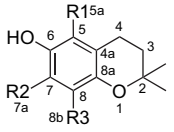
Abstract—Four tocopherol model compounds, the chroman-6-ols (**1**–**4**) having the typical substitution pattern of α-, β-, γ-, and δ-tocopherol (vitamin E), were oxidized to the corresponding *para*-quinones (**5**–**8**), and dehydrogenated to the 2*H*-chromen-6-ols (**17**–**20**) involving initial acetyl protection of the phenolic OH and deprotection as the last step. The chromenols were also converted into the *para*-quinones (**21**–**24**), which existed in the bicyclic hemiketal form, in contrast to the chromanol-derived, monocyclic quinones **5**–**8**, the ketalization behavior agreeing well with computations on the DFT level.

1. Introduction

α-Tocopherol ('vitamin E') and ubiquinone (UQ) are two compounds occurring in mammalian cells, which exert important functions in antioxidative defense and bioenergetics, respectively. Being closely related, bioquinones and biochromanols can be readily interconverted by reductive cyclization and oxidative ring opening. For the major component of vitamin E, α-tocopherol, the chemistry between the reduced (chromanol) state and the oxidized (*para*-quinone) state is well known.[1–3] It is distributed in the lipid membranes of various organs acting as a radical-scavenging antioxidant, thereby forming the corresponding relatively stable chromanoxyl radical upon one-electron oxidation. This radical is either recycled by other antioxidants or further oxidized to the two-electron oxidation product *para*-tocopheryl quinone (α-pTQ).[4–6] Since this quinoid oxidation product has a structure similar to UQ, it has been suggested that the former interferes with certain mitochondrial UQ functions.[7] This was confirmed by the finding that α-pTQ acted as a weak competitive inhibitor at the mitochondrial complexes II and III.[8]

In a current study to determine the suitability and properties of tocopherol-derived oxidation products as substrates for the mitochondrial bc_1 complex in comparison to UQ and α-pTQ, the synthesis of three compound classes was required: the tocopherol-derived *para*-quinones, the 3,4-dehydro-tocopherols, and the *para*-quinones of the latter. For each class, all four homologues α–δ were synthesized, differing in the number and position of methyl substituents at the aromatic ring (Scheme 1). In addition, the truncated model compounds[9] were to be used, which have a methyl group instead of the isoprenoid side chain. This was done to avoid analytical problems by lipophilic substrates during enzyme assays, which render the determination of kinetic constants difficult due to micelle formation.



1 R1 = R2 = R3 = Me, α-tocopherol model
2 R1 = R3 = Me, R2 = H, β-tocopherol model
3 R1 = H, R2 = R3 = Me, γ-tocopherol model
4 R1 = R2 = H, R3 = Me, δ-tocopherol model

Scheme 1. Formulae of truncated tocopherol model compounds (**1**–**4**) used as starting material for the oxidation reactions.

From the comparatively low structural complexity of the target structures we actually expected a large number of references dealing with the compounds, but we had to realize that the situation was quite different. Apart from α-tocopherol

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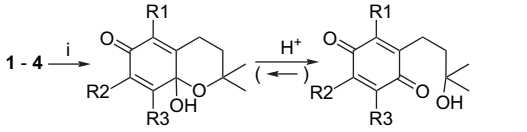
and its model, of which the *para*-quinones[10,11] and the 3,4-dehydro derivatives[12] are mentioned aplenty in the literature, there were two accounts of the 3,4-dehydro-δ-tocopherol model,[13,14] one of the 3,4-dehydro-γ-tocopherol model[15] and one of the *para*-quinone model of δ-tocopherol,[16] listing UV features but none of them giving NMR and MS data. Other target compounds have apparently not been described so far.

In this paper, we would like to present our synthetic studies towards the α-, β-, γ-, and δ-homologues of tocopherol-derived *para*-quinones, 3,4-dehydro derivatives, and 3,4-dehydro-*para*-quinones, including optimization of the reaction conditions for each class of compounds and reports of comprehensive analytical data.

2. Results and discussion

Oxidation of tocopherol-type model compounds with $FeCl_3$ in aqueous medium is still the method of choice to obtain the corresponding *para*-quinones in good yields, and was also used in the present case to provide the quinones **5–8** (Scheme 2). It was imperative that the oxidation was carried out at 0–5 °C. Already at room temperature side reactions became increasingly dominant and accounted for more than one third of the conversion, whereas at the lower temperature the conversion into the desired *para*-quinones was virtually quantitative. Products of those side reactions were elimination products of the aliphatic hydroxyl group and dimers. The oxidant should be applied in about fivefold excess. Both increasing this amount to more than 10 equiv and decreasing it to less than 2 equiv resulted in appreciable yield penalty. This is probably due to an increased acidity in the former case and to extended reaction times required in the latter case. It should be noted that under acidic and protic conditions during workup and flash chromatography minor amounts (less than 10%) of the corresponding 8a-hydroxy-chromanones (**5a–8a**) were formed, which were difficult to separate under those conditions as they were readily interconverted with the *para*-quinones. Working in aprotic media, the neat *para*-quinones (**5–8**) were obtained.



5a R1 = R2 = R3 = Me **5** R1 = R2 = R3 = Me
6a R1 = R3 = Me, R2 = H **6** R1 = R3 = Me, R2 = H
7a R1 = H, R2 = R3 = Me **7** R1 = H, R2 = R3 = Me
8a R1 = R2 = H, R3 = Me **8** R1 = R2 = H, R3 = Me

i $FeCl_3$ (5 eq.), H_2O / MeOH, 0 °C, 2 - 30 min, 42 - 82%

Scheme 2. Synthesis of the *para*-quinones **5–8** derived from the four homologous tocopherol model compounds (**1–4**).

Both the ^1H and ^{13}C NMR spectra confirmed the *para*-quinoid structure, cf. NMR data and assignment in Table 1. The presence of two keto carbons at about 187 ppm indicated the absence of hemiketal structures, such as 8a-hydroxy-chromanones (**5a–8a**). A peculiar feature of the α-form was that three of the four non-keto quinone ring carbons resonated at nearly the same frequency of about 140 ppm. It was interesting to note that a certain 'pairing' of the compounds into an α/β-group and a γ/δ-group, which had also been found in some other aspects of the chemistry of tocopherols, was reflected by the NMR data. The presence of the 5a-methyl group can be assumed to be the decisive factor for this 'pairing' due to its special reactivity.[17] In the ^1H spectra, the signals of H-4 were found at 2.58 ppm for the first pair and at 2.45 ppm for the second one. The proton resonances of the two magnetically equivalent 2a-CH_3 groups were found at 1.28 ppm for the α- and β-forms, but shifted about 0.1 ppm to higher field for γ- and δ-homologues. Similarly, C-4 resonated at 21.5 ppm for α- and β-, but 3 ppm more downfield for γ- and δ-forms. The CH resonated at the highest field of the quinoid carbons at 132–133 ppm.

For the synthesis of 3,4-dehydro derivatives (chromenols) starting from **1–4** the oxidant 2,3-dichloro-5,6-dicyano-benzoquinone (DDQ) was used. Non-protected chromanols afforded mixtures of different dimers, whereas the reaction with appropriately *O*-protected chromanols proceeded smoothly. The chromenol synthesis thus required suitable protection of the phenolic hydroxyl before the actual dehydrogenation step, and deprotection afterwards. Acetyl protection was chosen due to reasons of simplicity and near-quantitative yields of both attachment and removal of the protecting group. Acetylation of the chromanols **1–4** with acetic anhydride in pyridine provided the

Table 1. ^1H and ^{13}C NMR data and assignments of *para*-quinones **5–8** (all shift values in ppm, $CDCl_3$, standard TMS)

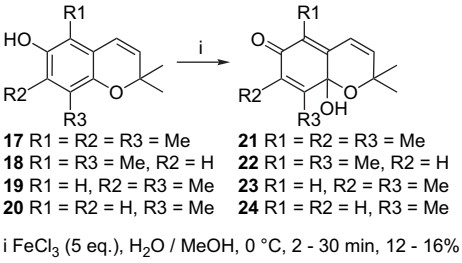
Nucleus	α-Form, *p*-quinone **5**	β-Form, *p*-quinone **6**	γ-Form, *p*-quinone **7**	δ-Form, *p*-quinone **8**
H-2a	1.28 (s, 6H)	1.30 (s, 6H)	1.21 (s, 6H)	1.22 (s, 6H)
H-3	1.54 (m, 2H)	1.52 (m, 2H)	1.57 (m, 2H)	1.56 (m, 2H)
H-4	2.58 (m, 2H)	2.58 (m, 2H)	2.45 (m, 2H)	2.46 (t, 2H)
H-5a, 7a, 8b	2.01 (s, 6H), 2.04 (s, 3H)	2.03 (s, 6H)	1.94 (s, 3H), 1.96 (s, 3H)	1.99 (s, 3H)
H-5			6.46 (t, 1H, ^4J=1.4 Hz)	6.46 (s, 1H)
H-7		6.55 (q, 1H, ^4J=1.3 Hz)		6.49 (s, 1H)
O–H	2.34 (s, 1H)	1.75 (br s, 1H)	1.40 (br s, 1H)	2.05 (br s, 1H)
C-2	70.42	70.68	70.62	70.62
C-2a[a]	28.86	29.04	29.24	29.27
C-3	41.92	41.95	41.78	41.74
C-4	21.52	21.63	24.29	24.40
C-5a, 7a, 8b	11.74, 12.08, 12.17	11.60, 15.77	12.02, 12.35	16.02
Non-keto quinoid ring carbons	140.06, 140.23, 140.36, 144.23	133.13 (CH), 140.55, 144.86, 145.36	132.13 (CH), 140.63, 141.06, 149.25	132.37 (CH), 133.16, 145.98, 149.76
C-6, C-8a	187.06, 187.44	187.72, 187.73	187.56, 187.59	187.75, 187.91

[a] Two magnetically equivalent carbons.

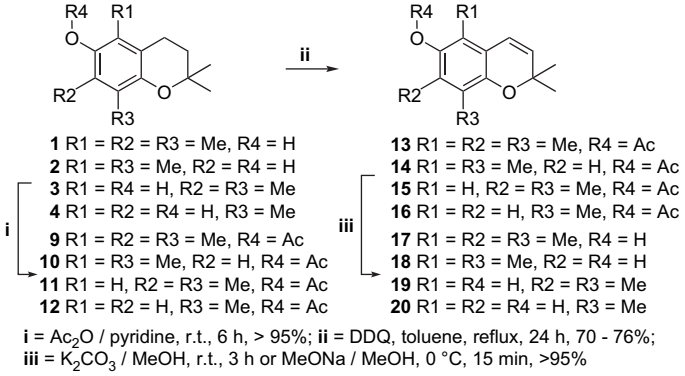
corresponding chromanyl acetates (**9**–**12**), which were dehydrogenated by DDQ in dry toluene to give the corresponding chromenyl acetates (**13**–**16**), see Scheme 3. Both working in an inert atmosphere and using carefully dried solvents were imperative to boost the yields, which ranged about 70% after chromatography. Deprotection afforded the target chromenols (**17**–**20**) in overall good yields. While for α- and β-forms deprotection with potassium carbonate in methanol was successful, the two remaining homologues required NaOMe in MeOH for full conversion. It should be noted that acidic deprotection, e.g., HCl or ion exchange resin, was unsuitable as strong byproduct formation was observed.

The assignment of the ^{1}H and ^{13}C resonances of the 3,4-dehydro-chromanols **17**–**20** is given in Table 2, additional ^{1}H NMR data of the intermediates are listed in Section 3. The ^{1}H NMR spectra showed the typical paired doublet for the olefinic protons (H-3 and H-4) with a coupling constant of 10 Hz. H-3 resonated at about 5.60 ppm for all homologues, while the resonance of H-4 was found at about 6.50 ppm for α- and β-forms and at about 6.20 ppm for γ- and δ-forms—another example of the above-described 'pairing' of α/β versus γ/δ. This was also seen, albeit less prominently, in the case of the C-4 resonances: 120 ppm for the former pair versus 122.5 ppm for the latter. For all homologues, the ^{13}C resonances of the aromatic CH carbons appeared at higher field than the other (substituted) aromatic carbons.

The 3,4-dehydro derivatives **17**–**20** were oxidized to the corresponding *para*-quinoid structures **21**–**24** according to the procedure in Scheme 4, using $FeCl_3$ as for the oxidation of chromanols **1**–**4**. In contrast to the chromanol oxidation, which produced hemiketals only in acidic media to minor extent, oxidation of the chromenols afforded the hemiketals of the *para*-quinones exclusively. Yields were generally rather low; the byproducts formed were not the open-chain *para*-quinones, but rearrangement products and dimers of which the structure is currently studied.



Scheme 4. Synthesis of the *para*-quinone hemiketals **21**–**24** from the four homologous 3,4-dehydro derivatives (**17**–**20**).



Scheme 3. Synthesis of the 3,4-dehydro derivatives (**17**–**20**) derived from the four homologous tocopherol model compounds (**1**–**4**).

Table 2. ^{1}H and ^{13}C NMR data and assignments of 3,4-dehydro-chromanols **17**–**20** (all shift values in ppm, $CDCl_3$, standard TMS)

Nucleus	3,4-Dehydro-α-compound **17**	3,4-Dehydro-β-compound **18**	3,4-Dehydro-γ-compound **19**	3,4-Dehydro-δ-compound **20**
H-2a	1.38 (s, 6H)	1.38 (s, 6H)	1.39 (s, 6H)	1.39 (s, 6H)
H-3	5.63 (d, 1H, ^{3}J=10.0 Hz)	5.66 (d, 1H, ^{3}J=10.0 Hz)	5.57 (d, 1H, ^{3}J=9.7 Hz)	5.61 (d, 1H, ^{3}J=9.7 Hz)
H-4	6.50 (d, 1H, ^{3}J=10.0 Hz)	6.51 (d, 1H, ^{3}J=10.0 Hz)	6.19 (d, 1H, ^{3}J=9.7 Hz)	6.22 (d, 1H, ^{3}J=9.7 Hz)
H-5a, 7a, 8b	2.12 (s, 3H), 2.15 (s, 3H), 2.17 (s, 3H)	2.11 (s, 3H), 2.16 (s, 3H)	2.12 (s, 3H), 2.13 (s, 3H)	2.13 (s, 3H)
H-5			6.30 (s, 1H)	6.32 (d, 1H, ^{4}J=2.9 Hz)
H-7		6.46 (s, 1H)		6.47 (d, 1H, ^{4}J=2.9 Hz)
OH	4.24 (br s, 1H)	4.24 (s, 1H)	4.38 (s, 1H)	4.30 (br s, 1H)
C-2	74.34	74.38	75.43	75.55
C-2a[a]	27.25	27.31	27.56	27.60
C-3	130.57	131.36	130.82	131.68
C-4	119.91	119.85	122.43	122.45
C-5a, C-7a, C-8b	10.86, 11.59, 12.42	10.54 (C-5a), 15.82 (C-8b)	11.68, 11.78 (C-7a, C-8b)	15.47 (C-8b)
C-4a/C-8	116.07, 122.48	120.41, 123.63	118.99, 125.49	121.58, 126.68
C-5	117.88	116.78	109.77 (CH)	110.18 (CH)
C-6/C-8a	145.35, 144.55	144.90, 146.69	144.59, 147.01	144.80, 148.62
C-7	122.89	116.66 (CH)	123.54	116.97 (CH)

[a] Two magnetically equivalent carbons.

At present it cannot be decided whether the hemiketal products were formed by intramolecular ring closure from initially produced *para*-quinones, or whether they were generated directly from the starting chromenols without intermediate ring opening. Preference of **21**–**24** over the corresponding open-chain *para*-quinones might be the result of a certain pre-organization effect: apparently the steric conditions for ring closure—or ring maintenance—were favorable in the case of the more rigid olefinic side chain in **21**–**24** as compared to the fully flexible aliphatic chains in the *para*-quinones **5**–**8**. Computational results on the B3LYP/6-31G(d,p) level of theory agreed with the observed formation of *para*-quinone hemiketals (**21**–**24**) from the chromenes (**17**–**20**), while the chromanes (**1**–**4**) formed the open-chain *para*-quinones (**5**–**8**). The difference of the ZPE-corrected absolute energies between the open-chain *para*-quinones and the corresponding hemiketal *para*-quinones was 10.5 kJ/mol in favor of the former for compounds **5**–**8**, and 6.1 kJ/mol in favor of the latter for the bicycles **21**–**24**. The influence of the methyl substitution pattern was marginal with deviations from those values below 0.6 kJ/mol.

The assignment of the ^{1}H and ^{13}C resonances of the *para*-quinone hemiketals **21**–**24** is given in Table 3. In contrast to the *para*-quinones (Table 1) and chromenes (Table 2), the two CH_3 groups at C-2 became magnetically non-equivalent, as they can be either placed cis or trans with regard to the hemiketal hydroxyl group. Conformational ring changes ('puckering') can thus no longer average the shifts as it does in the chromenes **17**–**20**. The positive and negative shift differences relative to the shift of the chromenes (1.38 ppm vs 1.30 and 1.57 ppm) can also be explained by the anisotropy effect of the pyran ring double bond. The vicinal H-3/H-4 coupling constant was slightly larger than for the chromenols **17**–**20**. The resonance of H-3 appeared at 6.20 ppm for all isomers and experienced a downfield shift by about 0.6 ppm as compared to the chromenols. The shifts of 4-H were similar to the chromanol case, with values at 6.55 ppm for the α- and β-isomers and 6.33 ppm for the γ- and δ-isomers. A typical feature of the ^{13}C spectra was the signal of the hemiketal carbon (C-8a) at 89 ppm. This resonance is also the main proof that compounds **21**–**24** have no free *para*-quinone structure as compounds **5**–**7**. While the four non-keto resonances of the quinoid ring were found over a relatively small range between 132 and 149 ppm for those *para*-quinones **5**–**7**, the unsaturated side chain and the hemiketal structure in **21**–**24** brought about a much higher differentiation with shift values, especially noticeable for the α-form. With regard to the parent chromenols the signals of 3-C were shifted about 10 ppm downfield, whereas the 4-C resonances remained largely unchanged.

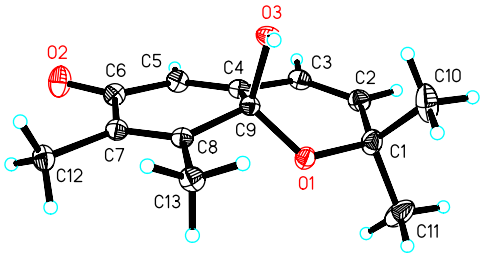


Figure 1. Thermal ellipsoid plot (50% ellipsoids) and crystallographic atom labeling of hemiketal **23** (see CCDC 642188 for details).

From compound **23**, 8a-hydroxy-2,2,7,8-tetramethyl-2*H*, 8a*H*-chromen-6-one, a crystal structure was obtained, which confirmed the hemiketal structure. The quinone ring assumes a very flat half-chair conformation, the pyran ring a twisted chair conformation. The hemiketal hydroxy group is placed nearly perpendicular to the quinone plain with a C5–C4–C9–O3 dihedral angle of 100°, and forms an intermolecular hydrogen bridge to the quinone oxygen with O(H)–O=2.764 Å (Fig. 1).

3. Experimental

3.1. General

All chemicals were commercially available and used without further purification. Reagent-grade solvents were used for all extractions and workup procedures. Distilled water was used for all aqueous extractions and for all aqueous solutions.

Table 3. ^{1}H and ^{13}C NMR data and assignments of *para*-quinone hemiketals **21**–**24** (all shift values in ppm, all coupling constants in Hz, $CDCl_3$, standard TMS)

Nucleus	α-Form, *p*-quinone **21**	β-Form, *p*-quinone **22**	γ-Form, *p*-quinone **23**	δ-Form, *p*-quinone **24**
H-2a	1.29 (s, 3H)	1.30 (s, 3H)	1.31 (s, 3H)	1.31 (s, 3H)
H-2b	1.58 (s, 3H)	1.57 (s, 3H)	1.59 (s, 3H)	1.57 (s, 3H)
H-3	6.20 (d, 1H, ^{3}J=10.4 Hz)	6.21 (d, 1H, ^{3}J=10.8 Hz)	6.21 (d, 1H, ^{3}J=10.1 Hz)	6.21 (d, 1H, ^{3}J=10.1 Hz)
H-4	6.55 (d, 1H, ^{3}J=10.4 Hz)	6.57 (d, 1H, ^{3}J=10.8 Hz)	6.33 (d, 1H, ^{3}J=10.1 Hz)	6.34 (d, 1H, ^{3}J=10.1 Hz)
H-5a/H-7a/H-8b	1.92 (s, 3H), 1.88 (s, 3H), 2.09 (s, 3H)	1.91 (s, 3H), 2.11 (s, 3H)	1.86 (s, 3H), 2.10 (s, 3H)	2.13 (s, 3H)
H-5			5.92 (s, 1H)	5.90 (m, 1H)
H-7		6.01 (q, 1H, ^{4}J=1.5 Hz)		5.96 (m, 1H)
O–H	2.64 (s, 1H)	2.64 (s, 1H)	2.74 (s, 1H)	2.70 (s, 1H)
C-2	74.05	74.33	74.69	74.87
C-2a	29.41	29.64	29.32	29.34
C-2b	30.67	30.72	30.64	30.51
C-3	141.27	141.64	142.55	142.73
C-4	118.54	118.77	120.25[a]	120.39[a]
C-5a, 7a, 8b	10.07, 11.31, 12.92	9.82, 16.19	10.91, 12.93	15.83
C-4a/C-5/C-7/C-8	140.86, 126.11, 130.36, 148.04	141.86, 126.69, 125.54 (CH), 154.95	146.91, 120.32 (CH),[a] 130.68, 148.80	147.83, 120.61 (CH),[a] 125.58 (CH), 155.61
C-8a, C-6	89.01, 185.63	89.30, 185.98	89.11, 185.72	88.96, 185.95

[a] Assignment may be interchanged.

n-Hexane, diethyl ether, ethyl acetate, and petroleum ether 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 an argon or nitrogen atmosphere. TLC was performed using Merck silica gel 60 F_{254} pre-coated plates. Flash chromatography was performed on Baker silica gel (40 μm particle size). All products were purified to homogeneity by TLC/GC analysis; yields refer to isolated, pure products with satisfying elemental analysis data. Melting points, determined on a Kofler-type micro hot stage with Reichert-Biovar microscope, are uncorrected. ^{1}H NMR spectra were recorded at 300.13 MHz for ^{1}H and at 75.47 MHz for ^{13}C NMR in $CDCl_3$. Chemical shifts, relative to TMS as internal standard, are given in δ values, coupling constants in Hz. ^{13}C peaks were assigned by means of APT, HMQC, and HMBC spectra. The nomenclature of tocopherols and chromanols as recommended by IUPAC[18,19] was used throughout. 'd.i.' denotes peaks with double intensity. Elemental analyses were performed at the Microanalytical Laboratory of the Institute of Physical Chemistry at the University of Vienna.

3.2. Computations

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[20,21] parameterized by Becke,[22,23] was used, along with the double-zeta split valence basis sets 6-31+G*,[24,25] which includes diffuse functions, or the higher 6-311-G(2df,2p) analogue. Vibrational frequencies were calculated at the respective level of theory to characterized 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.

3.3. Synthesis of *para*-quinones 5–8

$FeCl_3$ hexahydrate (5 equiv) was added at once into the solution of the respective chromanol in the ternary solvent system methanol/water/diethyl ether (40 mL, v/v/v=19:1:20) at 4 °C. The mixture was stirred at this temperature for 1.5 h. A gradual color change to yellow indicated progressing formation of the *para*-quinone. Water (50 mL) was added and the mixture was extracted with diethyl ether. The organic phase was washed with brine and water, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash chromatography on silica gel to give the *para*-quinone as a yellow viscous oil.

3.3.1. 3-(3-Hydroxy-3-methyl-butyl)-3,5,6-trimethyl-[1,4]benzoquinone (5). 6-Hydroxy-2,2,5,7,8-pentamethylchroman (**1**, 0.1 g, 0.46 mmol) and $FeCl_3$ hexahydrate (2.3 mmol, 0.62 g) were used as the starting materials producing **5** in 63% yield (68 mg) after purification by flash chromatography (*n*-hexane/diethyl ether, v/v=3:7). TLC: R_f=0.24 (*n*-hexane/diethyl ether, v/v=4:6), MS (EI, 70 eV): *m/z* 236.1 ([M$^+$]). Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53; found: C, 70.81; H, 8.33.

3.3.2. 3-(3-Hydroxy-3-methyl-butyl)-2,5-dimethyl-[1,4]benzoquinone (6). 6-Hydroxy-2,2,5,8-tetramethylchroman (**2**, 0.1 g, 0.48 mmol) and $FeCl_3$ (2.4 mmol, 0.65 g) were used as the starting materials producing **6** in 65% yield (69 mg) after purification by flash chromatography (*n*-hexane/diethyl ether, v/v=7:3→*n*-hexane only). TLC: R_f=0.25 (*n*-hexane/diethyl ether, v/v=3:7), MS (ESI Q-TOF): *m/z* 245.1152 ([M+Na]$^+$), calcd 245.1148 ([M+Na]$^+$). Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16; found: C, 69.89; H, 8.26.

3.3.3. 5-(3-Hydroxy-3-methyl-butyl)-2,3-dimethyl-[1,4]benzoquinone (7). 6-Hydroxy-2,2,7,8-tetramethylchroman (**3**, 0.1 g, 0.48 mmol) and $FeCl_3$ (2.4 mmol, 0.65 g) were used as the starting materials producing **7** in 82% yield (88 mg) after purification by flash chromatography (*n*-hexane/diethyl ether, v/v=5:5→5:4). TLC: R_f=0.15 (*n*-hexane/diethyl ether, v/v=5:5), MS (ESI Q-TOF): *m/z* 223.1293 ([M+Na]$^+$), calcd 223.1329 ([M+Na]$^+$). Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16; found: C, 69.92; H, 8.06.

3.3.4. 2-(3-Hydroxy-3-methyl-butyl)-6-methyl-[1,4]-benzoquinone (8). 6-Hydroxy-2,2,8-trimethylchroman (**4**, 0.1 g, 0.52 mmol) and $FeCl_3$ (2.6 mmol, 0.70 g) were used as the starting materials producing **8** in 42% yield (42 mg) after purification by flash chromatography (*n*-hexane/diethyl ether, v/v=5:5→5:4). TLC: R_f=0.16 (*n*-hexane/diethyl ether, v/v=4:8), MS (ESI Q-TOF): *m/z* 209.1339 ([M+Na]$^+$), calcd 209.1172 ([M+Na]$^+$). Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74; found: C, 68.89; H, 7.78.

3.4. Synthesis of 3,4-dehydro derivatives 17–20

3.4.1. General procedure for the acetylation. Acetic anhydride was added into the solution of the respective chromanol (**1**–**4**) in pyridine, and the solution was stirred at rt for 6 h. The solvents were evaporated in vacuo and the residue was purified by flash chromatography to give the acetate as a white wax.

Compound **1** (0.2 g, 0.92 mmol), pyridine (3.78 mL), and Ac_2O (7.03 mL) were employed to afford 6-acetoxy-2,2,5,7,8-pentamethylchroman (**9**, 227 mg, 94%) after flash chromatography (*n*-hexane/diethyl ether, v/v=18:1). TLC: R_f=0.54 (*n*-hexane/diethyl ether, v/v=8:2). ^{1}H NMR: δ 1.29 (s, 6H, CH_3-2a), 1.78 (t, 2H, ^3J=6.8 Hz, H-3), 1.98 (s, 3H, CH_3), 2.02 (s, 3H, CH_3), 2.08 (s, 3H, CH_3), 2.33 (s, 3H, acetyl CH_3), 2.60 (t, 2H, ^3J=6.8 Hz, H-4).

Compound **2** (0.1 g, 0.48 mmol), pyridine (2.00 mL), and Ac_2O (3.72 mL) were employed to afford 6-acetoxy-2,2,5,8-tetramethylchroman (**10**, 117 mg, 98%) after flash chromatography (*n*-hexane/diethyl ether, v/v=18:1). TLC: R_f=0.36 (*n*-hexane/diethyl ether, v/v=8:2). ^{1}H NMR: δ 1.28 (s, 6H, CH_3-2a), 1.79 (t, 2H, ^3J=6.8 Hz, H-3), 2.05 (s, 3H, CH_3-5a), 2.09 (s, 3H, CH_3-8b), 2.33 (s, 3H, acetyl CH_3), 2.61 (t, 2H, ^3J=6.8 Hz, H-4), 6.48 (s, 1H, ^{Ar}H).

Compound **3** (0.1 g, 0.48 mmol), pyridine (2.00 mL), and Ac_2O (3.72 mL) were employed to afford 6-acetoxy-2,2,7,8-tetramethylchroman (**11**, 110 mg, 94%) after flash chromatography (*n*-hexane/diethyl ether, v/v=18:1). TLC: R_f=0.33 (*n*-hexane/diethyl ether, v/v=8:2). ^{1}H NMR: δ 1.30 (s, 6H, CH_3-2a), 1.74 (t, 2H, ^3J=6.7 Hz, H-3), 2.01 (s, 3H, CH_3-7a), 2.10 (s, 3H, CH_3-8b), 2.28 (s, 3H, acetyl CH_3), 2.71 (t, 2H, ^3J=6.7 Hz, H-4), 6.57 (s, 1H, ^{Ar}H).

Compound **4** (0.1 g, 0.52 mmol), pyridine (2.10 mL), and Ac_2O (4.00 mL) were employed to afford 6-acetoxy-2,2,8-trimethylchroman (**12**, 110 mg, 90%) after flash chromatography (*n*-hexane/diethyl ether, v/v=7:2). TLC: R_f=0.34 (*n*-hexane/diethyl ether, v/v=8:2). ^{1}H NMR: δ 1.39 (s, 6H, CH_3-2a), 1.84 (t, 2H, ^3J=6.7 Hz, H-3), 2.21 (s, 3H, CH_3-8b), 2.32 (s, 3H, –$COCH_3$), 2.81 (t, 2H, ^3J=6.74 Hz, H-4), 6.70 (t, 1H, ^{Ar}H), 6.74 (s, 1H, ^{Ar}H).

3.4.2. General procedure for the dehydrogenation of the acetyl-protected tocopherol model compounds with DDQ. The solution of the respective 6-acetoxychroman (**9**–**12**) in anhydrous toluene (6 mL) was heated at 105 °C for 30 min. A solution of DDQ in dry toluene (6 mL) was added dropwise over 3 h, and this mixture was refluxed for 24 h. The solution was cooled to rt and filtered, and the solvent was evaporated in vacuo. The residue was dissolved in diethyl ether, washed with 5% aq $NaHCO_3$ solution and water, dried over $MgSO_4$, and the solution was concentrated in vacuo. The residue was purified by flash chromatography on silica gel to afford 6-acetoxychromene as viscous oil. TLC showed the product nearly at the same position as the starting material, but on spraying with 4% H_2SO_4 in methanol and heating the starting material turned yellow and the product brown, and became thus distinguishable.

Acetoxychroman **9** (0.22 g, 0.84 mmol) and DDQ (0.40 g, 1.76 mmol) were employed to yield 6-acetoxy-2,2,5,7,8-pentamethylchromene (**13**, 166 mg, 76%) after flash chromatography (*n*-hexane/diethyl ether, v/v=18:1). TLC: R_f=0.54 (*n*-hexane/diethyl ether, v/v=8:2). ^{1}H NMR: δ 1.43 (s, 6H, CH_3-2a), 2.02 (s, 3H, CH_3), 2.04 (s, 3H, CH_3), 2.10 (s, 3H, CH_3), 2.33 (s, 3H, acetyl CH_3), 5.63 (d, 1H, ^3J=16.0 Hz, H-3), 6.47 (d, 1H, ^3J=16.0 Hz, H-4).

Acetoxychroman **10** (0.1 g, 0.40 mmol) and DDQ (0.20 g, 0.88 mmol) were employed to yield 6-acetoxy-2,2,5,8-pentamethylchromene (**14**, 75 mg, 76%) after flash chromatography (*n*-hexane/diethyl ether, v/v=18:1). TLC: R_f=0.36 (*n*-hexane/diethyl ether, v/v=8:2). ^{1}H NMR: δ 1.41 (s, 6H, CH_3-2a), 2.03 (s, 6H, CH_3), 2.30 (s, 3H, acetyl CH_3), 5.61 (d, 1H, ^3J=15.2 Hz, H-3), 6.62 (d, 1H, ^3J=15.2 Hz, H-4).

Acetoxychroman **11** (0.1 g, 0.40 mmol) and DDQ (0.20 g, 0.88 mmol) were employed to yield 6-acetoxy-2,2,7,8-pentamethylchromene (**15**, 75 mg, 76%) after flash chromatography (*n*-hexane/diethyl ether, v/v=18:1). TLC: R_f=0.33 (*n*-hexane/diethyl ether, v/v=8:2). ^{1}H NMR: δ 1.40 (s, 6H, CH_3-2a), 2.02 (s, 3H, CH_3-7a), 2.12 (s, 3H, CH_3-8b), 2.28 (s, 3H, acetyl CH_3), 5.57 (d, 1H, ^3J=9.7 Hz, H-3), 6.22 (d, 1H, ^3J=9.7 Hz, H-4), 6.51 (s, 1H, ^{Ar}H).

Acetoxychroman **12** (0.10 g, 0.43 mmol) and DDQ (0.20 g, 0.88 mmol) were employed to yield 6-acetoxy-2,2,8-pentamethylchromene (**16**, 74 mg, 74%) after flash chromatography (*n*-hexane/diethyl ether, v/v=7:1). TLC: R_f=0.34 (*n*-hexane/diethyl ether, v/v=8:2). ^{1}H NMR: δ 1.41 (s, 6H, CH_3-2a), 2.15 (s, 3H, CH_3-8b), 2.25 (s, 3H, acetyl CH_3), 5.61 (d, 1H, ^3J=9.8 Hz, H-3), 6.23 (d, 1H, ^3J=9.8 Hz, H-4), 6.55 (d, 1H, ^4J=2.6 Hz, ^{Ar}H), 6.68 (d, 1H, ^4J=2.6 Hz, ^{Ar}H).

3.4.3. 2,2,5,7,8-Pentamethyl-2*H*-chromen-6-ol (17). Into the solution of **13** (59 mg, 0.23 mmol) in methanol (8 mL), K_2CO_3 (94 mg, 0.68 mmol) was added and the mixture was stirred for 3 h at rt. The solvent was evaporated and the residue was purified by flash chromatography (*n*-hexane/diethyl ether, v/v=9:0.6) to afford chromenol **17** (27.6 mg, 55%) as a white solid. TLC: R_f=0.23 (*n*-hexane/diethyl ether, v/v=8:2). Anal. Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31; found: C, 76.92; H, 8.07.

3.4.4. 2,2,5,8-Tetramethyl-2*H*-chromen-6-ol (18). Into the solution of **14** (39 mg, 0.16 mmol) in methanol (8 mL), K_2CO_3 (66 mg, 0.48 mmol) was added and the mixture was stirred for 3 h at rt. The solvent was evaporated and the residue was purified by flash chromatography (*n*-hexane/diethyl ether, v/v=9:0.6) to afford chromanol **18** (21.2 mg, 65%) as a white solid. TLC: R_f=0.37 (*n*-hexane/diethyl ether, v/v=6:4), MS (EI, 70 eV): 204.1 $[M]^+$. Anal. Calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90; found: C, 76.26; H, 7.60.

3.4.5. 2,2,7,8-Tetramethyl-2*H*-chromen-6-ol (19). Sodium methanolate (0.1 M, 5.52 mL, 0.552 mmol) was added dropwise into solution of **15** (68 mg, 0.28 mmol) in dry methanol (2.8 mL) at 0 °C. The mixture was stirred for 15 min at rt and the reaction was monitored by TLC. After completion, the mixture was diluted with methanol, cation exchange resin (H^+ form) was added until neutral. The solids were filtered off and the filtrate was concentrated in vacuo. The residue was purified by flash chromatography (*n*-hexane/diethyl ether, v/v=9:0.6) to provide chromanol **19** (43 mg, 76%) as a yellowish wax. TLC: R_f=0.37 (*n*-hexane/diethyl ether, v/v=6:4), MS (ESI Q-TOF): *m*/*z* 205.1194 $[MH]^+$, calcd 205.1223 $[MH]^+$. Anal. Calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90; found: C, 76.26; H, 8.28.

3.4.6. 2,2,8-Trimethyl-2*H*-chromen-6-ol (20). Sodium methanolate (0.1 M, 2 equiv, 2.34 mL, 0.234 mmol) was added dropwise into the solution of **16** (27 mg, 0.12 mmol) in dry methanol (1.2 mL) at 0 °C. The mixture was stirred for 15 min at rt and the reaction was monitored by TLC. After completion, the mixture was diluted with methanol, cation exchange resin (H^+ form) was added until neutral. The solids were filtered off and the filtrate was concentrated in vacuo. The residue was purified by flash chromatography (*n*-hexane/diethyl ether, v/v=7:2) to provide chromanol **20** (22 mg, 95%) as a yellowish wax. TLC: R_f=0.22 (*n*-hexane/diethyl ether, v/v=7:3), MS (ESI Q-TOF): *m*/*z* 191.1094 $[MH]^+$, calcd 191.1066 $[MH]^+$. Anal. Calcd for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42; found: C, 75.70; H, 7.51.

3.5. Synthesis of *para*-quinone hemiketals 21–24

$FeCl_3$ (5 equiv) was added at once into the solution of the respective chromenol in the ternary solvent system methanol/water/diethyl ether (40 mL, v/v/v=19:1:20) at 4 °C.

The mixture was stirred at this temperature for 1.5 h. A gradual color change to yellow indicated progressing formation of the *para*-quinone hemiketals. Water (50 mL) was added and the mixture was extracted with diethyl ether. The organic phase was washed with brine and water, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash chromatography on silica gel to give the *para*-quinone hemiketals as waxy solids.

3.5.1. 8a-Hydroxy-2,2,5,7,8-pentamethyl-2*H*,8a*H*-chromen-6-one (21). 6-Hydroxy-2,2,5,7,8-pentamethyl-chroman (**17**, 19.5 mg, 0.089 mmol) and $FeCl_3$ hexahydrate (0.44 mmol, 72 mg) were used as the starting materials producing **21** as a yellow wax in 16% yield (3.3 mg) after purification by flash chromatography (*n*-hexane/diethyl ether, v/v=7:3→8:2). TLC: R_f=0.23 (*n*-hexane/diethyl ether, v/v=6:4).

3.5.2. 8a-Hydroxy-2,2,5,8-tetramethyl-2*H*,8a*H*-chromen-6-one (22). 6-Hydroxy-2,2,5,8-tetramethylchroman (**18**, 24.9 mg, 0.121 mmol) and $FeCl_3$ (0.60 mmol, 98 mg) were used as the starting materials producing **22** as a white waxy solid in 12% yield (3.2 mg) after purification by flash chromatography (*n*-hexane/diethyl ether, v/v=6:5→7:3). TLC: R_f=0.36 (*n*-hexane/diethyl ether, v/v=3:7).

3.5.3. 8a-Hydroxy-2,2,7,8-tetramethyl-2*H*,8a*H*-chromen-6-one (23). 6-Hydroxy-2,2,7,8-tetramethylchroman (**19**, 27.6 mg, 0.135 mmol) and $FeCl_3$ (0.67 mmol, 0.109 g) were used as the starting materials producing **23** as a yellow wax in 16% yield (4.7 mg) after purification by flash chromatography (*n*-hexane/diethyl ether, v/v=5:5→6:4). TLC: R_f=0.23 (*n*-hexane/diethyl ether, v/v=4:6).

3.5.4. 8a-Hydroxy-2,2,8-trimethyl-2*H*,8a*H*-chromen-6-one (24). 6-Hydroxy-2,2,8-trimethylchroman (**20**, 23.9 mg, 0.125 mmol) and $FeCl_3$ (0.62 mmol, 0.101 g) were used as the starting materials producing **24** as a white waxy solid in 15% yield (3.8 mg) after purification by flash chromatography (*n*-hexane/diethyl ether, v/v=5:6→5:5). TLC: R_f=0.21 (*n*-hexane/diethyl ether, v/v=3:7).

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