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On a Novel Chromanone–Naphthalenetrione Rearrangement Related to Vitamin E

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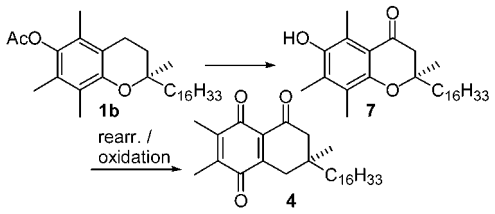
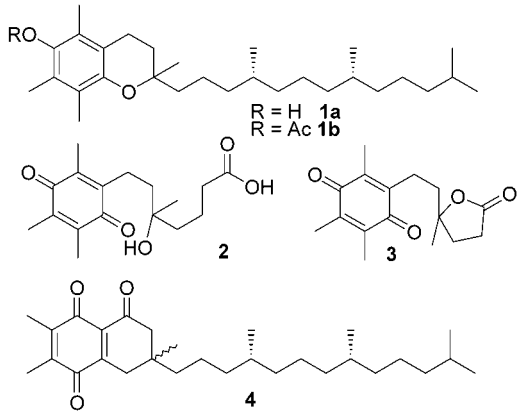
ABSTRACT



4-Oxo-α-tocopherol (7) was synthesized in an efficient three-step procedure starting from α-tocopheryl acetate (1b) and rearranged under physiological conditions into naphthalenetrione 4, a minor vitamin E metabolite. The rearrangement involves a [4 + 2]-cycloaddition as the key step.

α-Tocopherol (**1a**), a component of vitamin E, is the biologically most active lipid-soluble phenolic antioxidant in mammalian tissues. It inhibits the free-radical-chain autoxidation of unsaturated fatty acid esters present in cell membranes and other lipidic tissues[1] with very high antioxidative efficacy.[2] The so-called Simon compounds[3] **2** and **3** are the main in vivo metabolites of vitamin E. Some additional minor in vivo and in vitro metabolites have been identified,[4] among them the recently identified naphthalene-1,4,5-trione **4**, often referred to as the "Simon II metabolite". The formation pathway of the latter was hitherto completely unclear, so it was speculated that **4** might be an impurity in the vitamin E material rather than an actual metabolite.



To prove our hypothesis that **4** was formed from tocopherol derivatives oxidized at C-4 by a far-reaching reorganization of the carbon skeleton, 4-oxo-α-tocopherol had to be synthesized in quantities sufficiently large for rearrangement studies. Known syntheses of chromanones

(1) Machlin, L. J. *Vitamin E: a Comprehensive Treatise*; Marcel Dekker Inc.: New York, 1980.

(2) (a) Burton, G. W.; Hughes, L.; Ingold, K. U. *J. Am. Chem. Soc.* **1983**, *105*, 5950−5951. (b) Burton, G. W.; Doba, T.; Gabe, E. J.; Hughes, L.; Lee, F. L.; Prasad, L.; Ingold, K. U. *J. Am. Chem. Soc.* **1985**, *107*, 7053−7065.

(3) (a) Simon, E. S.; Gross, C. S.; Milhorat, A. T. *J. Biol. Chem.* **1956**, *221*, 797. (b). Simon, E. S.; Eisengart, A.; Sundheim, L.; Milhorat, A. T. *J. Biol. Chem.* **1956**, *221*, 807.

(4) (a) Pope, S. A.; Burtin, G. E.; Clayton, P. T.; Madge, D. J.; Muller, D. P. *Bioorg. Med. Chem.* **2001**, *9*, 1337−1343. (b) Parker, R. S.; Swanson, J. E. *Biochem. Biophys. Res. Commun.* **2000**, *269*, 580.

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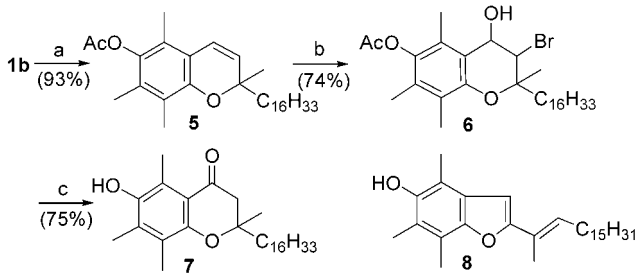
applied either the low-yielding Friedel−Crafts acylation of trimethylhydroquinone with the corresponding 2,2-disubstituted crotonic acid or the base-catalyzed aldol reaction of 2,5-dihydroxy-3,4,6-trimethylacetophenone with ketones,[5] which provided satisfying yields but required a rather tedious multistep protocol to obtain the coreacting ketones. In our approach, we chose to start from the readily available α-tocopheryl acetate, which was converted into 4-oxo-α-tocopherol in a facile three-step sequence.

α-Tocopheryl acetate was readily dehydrogenated to 3,4-dehydro-α-tocopheryl acetate (**5**) by DDQ in toluene,[6] followed by conversion into the corresponding racemic bromohydrin **6** by NBS (Scheme 1).[7] The subsequent direct

Scheme 1[a]



[a] (a) DDQ, toluene, reflux, 24 h; (b) NBS, DME, 4 °C, 24 h; (c) ZnO (10 equiv), rt, 4 h.

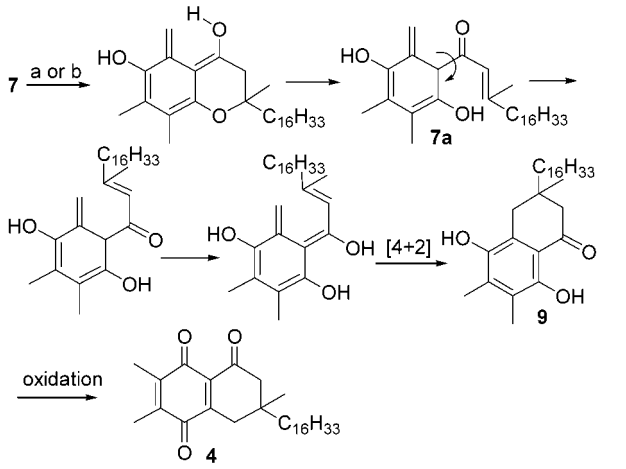
conversion into 4-oxo-α-tocopherol (**7**) by deacetylation along with dehydrobromination and tautomerization of the resulting enol intermediate was rather difficult: treatment with triethylamine, DBU, and other bases gave inseparable, complex product mixtures. Even freshly precipitated Ag_2O yielded only 15% of the desired product. Use of ZnO as the base finally provided **7** in 52% overall yield relative to **1b**. Benzofuran **8** was additionally obtained as a byproduct (8%), formed by ring contraction according to an elimination−addition mechanism in the last reaction step.

Simply stirring a 0.1 M solution of **7** in aqueous buffer (phosphate or citrate, pH 6) containing 1% sodium dodecyl sulfate at room temperature produced 11% of hydroquinone **9** after 72 h, which could be easily further oxidized to naphthalenetrione **4** (Scheme 2). If **7** was treated in a solution which was flushed with air during stirring, or in a solution containing 1 equiv of an oxidant (H_2O_2, $FeCl_3$, CAN), **4** was obtained directly (6%). These results represent unambiguous proof that 4-oxo-α-tocopherol (**7**) can be rearranged under aqueous conditions into naphthalenetrione **4** and is thus a potential precursor of the tocopherol metabolite **4**.

The formation of **4** requires that the C-1−O bond in **7** is broken and that a new bond between the former C-5a and

(5) Kabbe, H. J.; Wittig, A. *Angew. Chem.* **1982**, *94*, 254−262.
(6) Cf. also: Lei, H.; Atkinson, J. *J. Org. Chem.* **2000**, *65*, 2560−2567.
(7) An improved procedure for chlorohydrin formation using NMMO and a chloride source will be reported elsewhere in due course.

Scheme 2



[a] (a) Buffer pH 6, 1% SDS, air, 72 h, rt; (b) buffer pH 6, 1% SDS, H_2O_2 or $FeCl_3$ or CAN (1 equiv), 6 h, rt.

C-1 is formed. Opening of the alicyclic ring occurs, followed by formation of different tautomers including rotation around the C-4a−C-4 bond in tautomer **7a**, before the ring closure as the key step can proceed (Scheme 2). The ready formation of like tautomers and quinoid structures in the redox chemistry of tocopherols has been observed before.[8]

The incorporation of C-5a into the alicyclic ring in **9** was demonstrated by means of material trideuterated at C-5a, which produces **9** bisdeuterated at C-4, the former C-5a. The complete absence of deuterium at other positions, such as C-2a or C-1', and the absence of hydrogen at C-4, allow us to rule out alternative mechanisms, such as sequences of 1,7-sigmatropic hydrogen shifts, and thus favor the [4 + 2]-cycloaddition mechanism.[9]

Even though the formation of **4** from 4-oxo-α-tocopherol (**7**) was demonstrated, the open question remains of whether and how the 4-oxo derivative is generated from genuine vitamin E (**1a**) or its acetate (**1b**) in vivo. This ought to be a topic of further studies, along with mutagenicity tests.

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Supporting Information Available: Experimental procedures and full characterization for compounds **4**−**9** (^{1}H NMR, ^{13}C NMR, and elemental analysis data). This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) See for instance: (a) ref 1. (b) Rosenau, T.; Habicher, W. D. *Tetrahedron* **1995**, *51*, 7919−7926. (c) Rosenau, T., Potthast, A., Kosma, P.; Habicher, W. D. *Synlett* **1999**, *3*, 291−294.
(9) No deuterium was incorporated into **7** or **4** upon working in D_2O. In addition, a radical mechanism was ruled out by EPR spectroscopy and by scavenger experiments. A photochemical course was likewise rejected as the reaction proceeds in the dark and is not accelerated upon irradition.