Novel Tocopherol Compounds VII. γ-Tocopherol-5-carboxylic Acid - a Novel Route to γ-Tocopherol

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Abstract: A novel route for the synthesis of γ-tocopherol starting from the readily available vitamin E (α-tocopherol) has been found. The key step is the photochemical decarboxylation of γ-tocopherol-5- carboxylic acid.

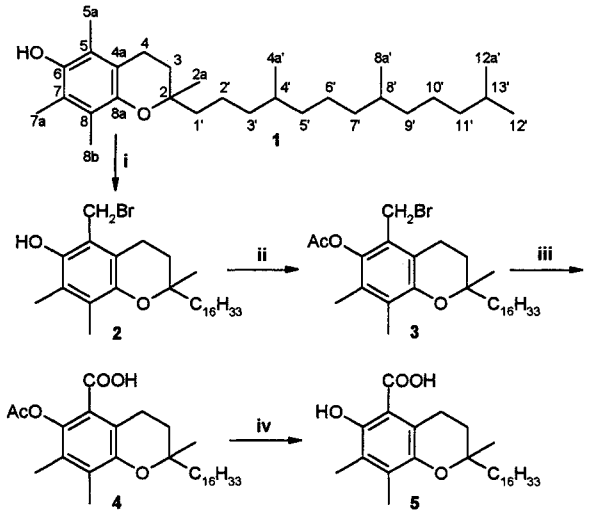
The expression "vitamin E" is commonly used as a generic term for tocopherols and tocotrienols. α-Tocopherol is produced synthetically on an industrial scale and used as food supplement, additive, medication, or as antioxidant in various fields.[1] In contrast, γ-tocopherol as the second main component of natural tocopherol mixtures is still obtained from natural plant oils by extraction and separation processes.[2] The high costs of commercially available γ-tocopherol[3] are even more annoying as the focus of the research on tocopherol and tocopherol derivatives has shifted considerably within the past several years from the well-investigated α-tocopherol to the less prominent components of natural tocopherol mixtures, such as γ-tocopherol. Continuing our investigations on novel tocopherol derivatives as new lipophilic drug carriers and antioxidants,[4] we describe here the preparation of γ-tocopherol-5-carboxylic acid (**5**) and its photochemical decarboxylation to γ-tocopherol (**8**).

Bromination of α-tocopherol (**1**) gives 5a-bromo-α-tocopherol (**2**) in quantitative yields.[5] This compound, a most valuable starting material for the preparation of a variety of novel tocopherol derivatives, is stable at room temperature, but is highly susceptible to oxidation, bases, and temperatures above 50°C.[6] In these cases, immediate elimination of HBr produces an *ortho*-quinone methide intermediate **6** that dimerizes to give the spiro-dimer of α-tocopherol (**7**). Before the benzylic function in **2** was oxidized, the phenolic hydroxyl group was protected by acid-catalyzed acetylation under mild conditions; basic conditions cannot be used for the reason just mentioned. The obtained 6-*O*-acetyl-5a-bromo-α-tocopherol (**3**) can now be oxidized to 6-*O*-acetyl-γ-tocopherol-5-carboxylic acid (**4**) under phase-transfer conditions in the presence of potassium permanganate and tetrabutylammonium chloride. The acetylated tocopheryl bromide **3** was not isolated from the reaction mixture, but was directly subjected to oxidation after addition of solvents, phase-transfer catalyst and oxidant.[7] The protecting group was removed under equally convenient experimental conditions. The organic phase of the phase-transfer oxidation was washed and then simply refluxed with methanol and aqueous HCl to remove the acetyl group. Pure γ-tocopherol-5- carboxylic acid (**5**)[8] was obtained by extraction from the organic phase with aqueous NaOH and reextraction after acidification.

In contrast to our previously reported reactions of vitamin E derivatives, this synthetic approach employs rather conventional transformations and reaction conditions. However, the experimental procedure was deliberately kept as convenient and widely applicable as possible: the product is not only an interesting novel tocopherol derivative, but also a useful starting material for further manipulations as shown in the following, and should therefore be provided in larger amounts.

In addition to traditionally applied analytical techniques, the identity of **5** was also confirmed by MALDI-TOF-MS[9] experiments. This technique allows easy determination of the molecular weight of the analytes, and is preferentially used for labile molecules and biopolymers. When γ-tocopherol-5-carboxylic acid embedded in gentisic acid as the matrix was analyzed by the MALDI technique, the expected peak at MH^+ = 461 was obtained.[10] However, when no matrix was added to the analyte, a second signal at 417 appeared, indicating a decarboxylation process with the loss of 44 resulting in the formation of γ-tocopherol (**8**). The decarboxylation must be a photochemically induced process since it occurs upon direct excitation of **5**, but not in the presence of a matrix when the analyte is not absorbing irradiation energy itself.[11]

The fact that 5-tocopherolcarboxylic acid decarboxylates upon irradiation at 337 nm was somewhat astonishing. Substituted 2,5-dihydroxybenzoic acids or 2,5-dialkoxybenzoic acids having structural features similar to **5** are also strongly absorbing at this wavelength, but do not



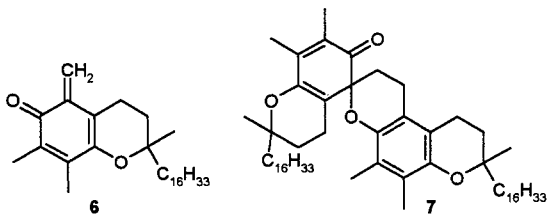
Conditions: i = Br_2, n-hexane, 2h, rt; ii = Ac_2O, AcOH, 12h, rt;
iii = $KMnO_4$, $Bu_4N^+Cl^-$, CH_2Cl_2 / H_2O (PTC), 15min, 0°C;
iv = conc. HCl / MeOH, 1h reflux, 82% overall

Scheme 1

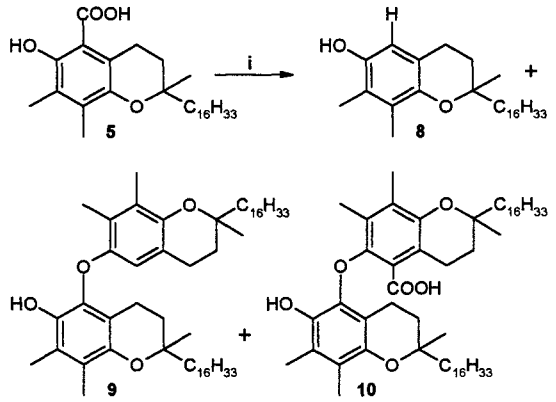
decarboxylate. In fact, some of the best MALDI matrices known belong to this class of compounds. Naturally, these matrices must exhibit the highest possible degree of inertia under the conditions of the MALDI experiment, completely opposite to a photodecarboxylation. The photochemical behavior of γ-tocopherol-5- carboxylic acid might be attributable to structural peculiarities of the tocopherol system, similar to the high reactivity of C-5a as compared to the quite inert 7a- and 8b-positions. However, a conclusive explanation cannot be provided yet.

From theoretical considerations it became clear that the reaction must be a radical process. This has been experimentally confirmed: **5** was completely converted into products upon irradiation at 337 nm for 2h in the presence of iron complexes or activated titanium dioxide.[12] In the absence of these reagents the decarboxylation rate was immeasurably slow. Thus, **5** undergoes photodecarboxylation to γ-tocopherol (**8**) in the presence of substances that are able to transfer electrons, but is stable under irradiation in the absence of those redox mediators.

The first step of the reaction consists in the formation of an unstable excited radical[13] formed by H-atom abstraction from **5**. The radical supposedly exists in two tautomeric forms analogous to similar vitamin E derivatives, with the single electron located either at the carboxyl group or at the phenolic OH group. The second step is the decarboxylation of this radical to form the γ-tocopheroxyl radical[14] which produces γ-tocopherol (**8**) by H abstraction from the solvent. The proposed radical mechanism is also supported by the formation of byproducts that are indicative of one-electron processes. Besides the main product γ-tocopherol, two dimers, namely 5-(γ-tocopheroxy)- γ-tocopherol (γ-tocopherol diphenyl ether dimer **9**), and 6-*O*-(γ-tocopher-5-yl-)-γ-tocopherol-5-carboxylic acid (**10**)[15] were found. These compounds are



formed by coupling reactions of the γ-tocopheroxyl radical with either γ-tocopherol that had been already produced, or with starting material **5** that still was present in the reaction mixture.



Conditions: i = hν (337nm), C_6H_6 / MeOH (v/v=9:1), 1h, rt, **5** (10 mM), iron(III)-phenanthroline (10^{-4} mM), 65-75% **8**, 25-35% dimers, **9** : **10** appr. 3 : 1

Scheme 2

The observation of the ready photodecarboxylation of 5-tocopherol-carboxylic acid gave the impetus to use this reaction on a preparative scale for the production of γ-tocopherol (**8**).[16] The procedure was optimized to increase the yield of **8** relative to the dimeric by-products.[17] Irradiation of 100 mL samples of a 10^{-2} M solution of **5** in benzene / methanol (v/v = 9:1) produced γ-tocopherol in an average yield of 72%, thus providing sufficiently large amounts for other experiments.

In summary, we have prepared γ-tocopherol-5-carboxylic acid (**5**), a less lipophilic, base-soluble tocopherol derivative that appears to be easily applicable as a vitamin E-based carrier for active substances due to its carboxylic function as the point for binding. Moreover, **5** shows an unambiguous redox behavior in contrast to α-tocopherol itself and almost all of its derivatives.[1] This change in the chemical properties is caused by the failure to form *ortho*-quinone methide structures involving the 5a-position of the tocopherol system. Even more interesting is the photochemical decarboxylation of γ-tocopherol-5- carboxylic acid to γ-tocopherol that is otherwise difficult to synthesize. The presented synthetic approach towards γ-tocopherol represents a convenient way to produce this compound in the laboratory on a gram scale.

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(2) Ames, S. R. In *The Vitamins*, Vol.5; Sebrell, W. H., Harris, R. S., Eds.; Academic Press: New York, 1972; p 218. Pratt, D. E. *ACS Symp. Ser.* **1992**, *507*, 54. Synthesis of γ-tocopherol has been described: Jacob, A.; Steiger, M. Todd, A. R.; Work, T.S. *J. Chem. Soc.* **1939**, 542. However, the procedure gives low yields and involves rather lengthy purification steps.

(3) The price per gram of γ-tocopherol is currently approximately 2500 times higher than that of α-tocopherol.

(4) Rosenau, T.; Habicher, W. D. *Book of Abstracts,* 212th ACS National Meeting, Orlando, 1996, Part 2, ORGN 322, and series entitled "Novel Tocopherol Derivatives".

(5) For preparation and reaction conditions see: Rosenau, T.; Habicher, W. D. *Tetrahedron* **1995**, *51*, 7919.

(6) Rosenau, T.; Habicher, W. D. *J. Prakt. Chem.* **1996**, *338*, 647. Rosenau, T.; Habicher, W. D. *Heterocycles* **1996**, *43*, 787.

(7) For a similar approach in the oxidation of 6-*O*-acetyl-5a-chloro- α-tocopherol to 5-formyl-α-tocopherol see: Dallacker, F.; Eisbach, R.; Holschbach, M. *Chem. Ztg.* **1991**, *115*, 113.

(8) Under exclusion of oxygen, a solution of **2** (3 mmol, 1.528 g) in CH_2Cl_2 (10 mL), glacial acetic acid (10 mL), acetic anhydride (2 mL), and concentrated sulfuric acid (0.1 mL) was stirred for 12 h at room temperature. 50 mL of H_2O and 50 mL of CH_2Cl_2 were added, and the mixture was stirred for additional 30 min. After cooling to 0°C, potassium permanganate (2.53 mmol, 0.400 g) dissolved in 10 mL of water, and tetrabutylammonium chloride (0.3 mmol, 0.083 g) was added. The mixture was vigorously stirred for 15 min at 0°C. The organic phase was separated and washed with 10 mL of 1N HCl and repeatedly with water. The solvent was removed and the residue refluxed with 50 mL of methanol and 10 mL of concentrated HCl for 1 h. 100 mL of water was added and the mixture thoroughly extracted with CH_2Cl_2 to give a solution of crude **5** which was purified by extraction into 20 mL of 1N aqueous NaOH, acidification with 1N HCl and reextraction with three 20 mL portions of CH_2Cl_2. After drying over Na_2SO_4 and evaporation of the solvent, γ-tocopherol-5-carboxylic acid (**5**) was obtained as a light-yellow waxy oil. ^{1}H-NMR (300 MHz, $CDCl_3$, CD_3COOD): δ 2.08 (s, 3H, Ar-CH_3), 2.10 (s, 3H, Ar-CH_3), 2.59 (t, 2H, Ar-CH_2-). The strong resonances of the isoprenoid side chain below 2.0 ppm are not listed. ^{13}C-NMR (80 MHz, $CDCl_3$): δ 11.8, 12.1, 19.5, 19.6, 20.8, 21.0, 22.5, 22.6, 23.6, 24.5, 24.8, 27.9, 31.6, 32.6, 32.7, 37.3, 37.4, 37.5, 37.6, 39.4, 39.8, 74.3, 118.2, 120.7, 121.5, 126.2, 143.9, 144.1, 167.6. MALDI-TOF- MS (matrix gentisic acid): 461 (MH^+). MALDI-TOF-MS (without matrix): 461 (MH^+) , 417 ([MH - CO_2]$^+$). Anal. calcd. for $C_{29}H_{48}O_4$: C, 75.61; H, 10.50. Found: C, 75.68; H 10.72.

(9) Hillenkamp, F.; Karas, M.; Beavis, R. C.; Chait, B. T. *Anal. Chem.* **1991**, *63*, 1193A. Bornsen, K. F. *Anal. Methods Instrum.* **1995**, *2*, 202.

(10) Experiments were carried out on a Shimadzu time-of-flight instrument with linear geometry (pulsed N_2-laser, 337 nm, pulse duration 3 ns, acceleration voltage 20 kV).

(11) Since the matrix is present in up to tenthousandfold excess and is absorbing near the irradiation wavelength, the analyte itself is spared from excessive energy and remains in the ground state during and after the desorption process: Karas, M.; Hillenkamp, F. *AIP Conf. Proc.* **1993**, *288*, 447. Vekey, K. *J. Mass Spectrom.* **1996**, *31*, 445. Hillenkamp, F. In *Biological Mass Spectrometry: Present and Future*; Matsuo, T., Ed.; Wiley: Chichester, 1994.

(12) For representative examples see: Gilbert, B. C.; Smith, J. R. L.; MacFaul, P.; Taylor, P. *J. Chem. Soc., Perkin Trans. 2* **1996**, *4*, 511. Park, K. H., Kim, J. H. *Bull. Korean Chem. Soc.* **1991**, *12*, 438. Izumi, I.; Fan, F.; Bard, A. J. *J. Phys. Chem.* **1981**, *85*, 218.

(13) The radical produced upon reaction of **5** with radical starters, such as AIBN, does not decarboxylate, but undergoes coupling reactions with radicals derived from the starter. Hence, only the photochemically excited form of the γ-tocopherol-5-carboxylic acid radical, but not the chemically produced species in the ground state is able to stabilize itself by decarboxylation.

(14) For preparation and ESR/ENDOR experiments see: Boguth, W.; Neimann, H. *Biochim. Biophys. Acta* **1971**, *248*, 121. Mukai, K.; Tsuzuki, N.; Ishizu, K.; Ouchi, S.; Fukuzawa, K. *Chem. Phys. Lipids* **1984**, *35*, 199.

(15) Dimer **9** has been described in the literature as one of the coupling products of γ-tocopheroxyl radicals: Ha, K.-H.; Igarashi, O. *J. Nutr. Sci. Vitaminol.* **1990**, *36*, 411. Yamauchi, R.; Matsui, T.; Kato, K.; Ueno, Y. *Agric. Biol. Chem.* **1990**, *54*, 2703. Dimer **10** has been identified by its NMR and MS data.

(16) In a photochemical reactor equipped with a thermostat and a circulator, 100 mL of a degassed benzene / methanol mixture (v/v=9:1) containing **5** (1 mmol, 0.46 g) and 1,10-phenanthroline iron(III)-complex (10^{-5} mmol, 0.0023g) was irradiated at 20°C for 1h. External irradiation with a N_2 laser (337 nm) or internal irradiation with a high-pressure mercury vapor immersion lamp gave comparable yields. The product mixture can easily by separated

by chromatography on aluminum oxide. γ-Tocopherol **(8)** is eluted first with n-hexane.

(17) Both the presence of sufficient amounts of a hydrogen donor (10% methanol with catalytic amounts of CF_3COOH) and the absence of larger quantities of the redox mediator (1,10-phenanthroline iron(III) complex) were crucial to obtain yields above 70%. The hydrogen donor was necessary to favor proton abstraction leading to γ-tocopherol over the competitive dimerization processes; higher concentrations of the redox mediator resulted in complex product mixtures. A ratio of 10000 : 1 between substrate and phenanthroline complex gave the best results.