Novel Tocopherol Compounds XI. Synthesis, Bromination and Oxidation Reactions of 3-(5-Tocopheryl)propionic Acid

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Abstract: 3-(5-Tocopheryl)propionic acid (γ-tocopherol-5-propionic acid, **13**) has been synthesized by a multi-step sequence involving the hetero-*Diels-Alder* reaction between *O*-methyl-*C*,*O*-bis-(trimethylsilyl)ketene acetal **(10)** and the *ortho*-quinone methide of α-tocopherol **(5)** as the key step. The title compound is the first 5a-substituted tocopherol that shows an oxidation behavior largely similar to α-tocopherol.

Key words: α-tocopherol, 5a-substituted tocopherols, *ortho*-quinone methide, ketene acetal, hetero-*Diels-Alder* reaction

α-Tocopherol (vitamin E, **1**) is a biological radical scavenger and a potent lipophilic antioxidant.[1] Derivatives of α-tocopherol are currently undergoing a surge of interest as they show changed properties, such as an altered redox behavior or increased hydrophilicity as compared to vitamin E. 5a-Substituted tocopherols **2** differ considerably from α-tocopherol in the chemical behavior, even though they possess the two structural features crucial for physiological effectiveness, a free phenolic hydroxyl group and an intact isoprenoid side chain.[2] The altered chemical properties are caused by the electronic influence of the substituent at C-5a. These effects are much larger than one would expect, they are even pronounced enough to determine the reactivity of the whole tocopherol system. The special role of the 5a-position in vitamin E chemistry is often named by the rather vague term "*Mills-Nixon* effect", but it is very far from being comprehensively understood.[3]

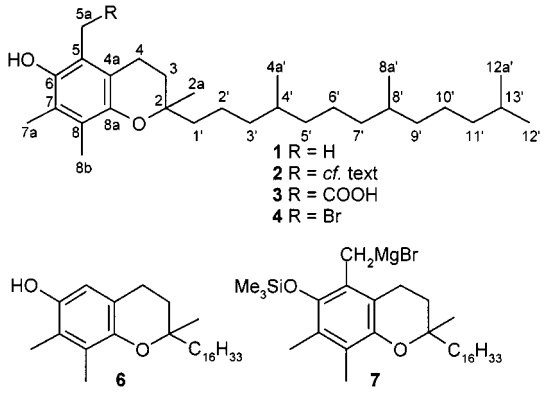
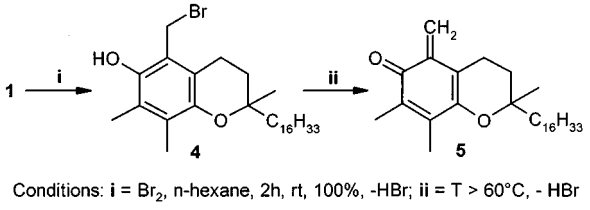


Figure 1

5-Tocopherylacetic acid **(3)**, carrying a carboxylic substituent at C-5a, forms a reversible redox system which makes it different from all vitamin E derivatives known so far.[4] However, in 3-(5-tocopheryl)propionic acid **(13)** which can be regarded as "homo"-tocopherylacetic acid, the direct influence of the substituent on C-5a is interrupted by a methylene group. Hence, the oxidation behavior of this compound should "return to normal", that means, resemble again that of α-tocopherol. For these reasons, 3-(5-tocopheryl)propionic acid **(13)** was expected to be a rewarding synthetic target as the first 5a-substituted tocopherol with possibly largely unchanged oxidation behavior as compared to the parent compound vitamin E.

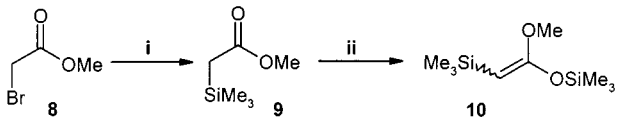
The synthesis of **13** turned out to be unexpectedly difficult. Neither the alkylation of γ-tocopherol **(6)**[5] with β-halopropionic acid derivatives nor the reaction of α-tocopheryl-*Grignard* **(7)**[6] with haloacetic acid derivatives produced the desired compound in exploitable yields. Other attempts to obtain **13** failed similarly. Consequently, we used a multi-step approach which was admittedly less direct, but provided 3-(5-tocopheryl)propionic acid in a satisfying overall yield. The key step of the sequence is the $ZnCl_2$-catalyzed hetero-*Diels-Alder* reaction of *O*-methyl-*C*,*O*-bis-(trimethylsilyl)ketene acetal **(10)** with the *ortho*-quinone methide **5**.[7]

Intermediate **5** is readily formed from 5a-bromo-α-tocopherol **(4)** by elimination of hydrogen bromide at temperatures above 50°C[8] and is conveniently prepared by adding a solution of **4** into the preheated reaction mixture (Scheme 1). The *ortho*-quinone methide normally undergoes dimerization to the spiro-dimer of α-tocopherol **(15)**, unless it is trapped in a faster reaction, as in the present example.



Scheme 1

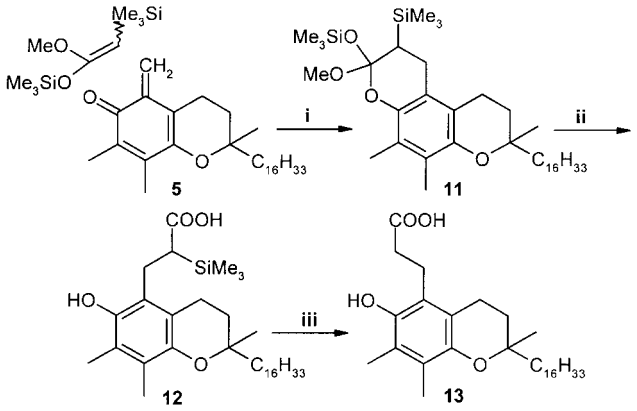
To obtain the trapping reagent **10**, methyl bromoacetate **(8)** was treated with trimethylsilyl chloride and zinc to produce methyl trimethylsilylacetate **(9)**.[9] Treatment with lithium diisopropyl amide and quenching with an excess of trimethylsilyl chloride finally provided *O*-methyl-*C*,*O*-bis-(trimethylsilyl)ketene acetal **(10)** in a good overall yield (Scheme 2).[10]



Conditions: i = Me_3SiCl, toluene, reflux, Zn,))), 64%
ii = 1) LDA, THF, -78ºC, 4h; 2) Me_3SiCl, -78°C to rt, 2h, 78%

Scheme 2

The primary product of the hetero-*Diels-Alder* reaction between **5** and an excess of **10**, the ortho-ester derivative **11**,[11] was not isolated, but immediately hydrolyzed to methyl 3-(5-tocopheryl)-2-trimethylsilyl-propionate **(12)**.[12] Further treatment with tetrabutylammonium fluoride (TBAF) and acidic hydrolysis finally produced 3-(5-tocopheryl)-propionic acid **(13)** in 72% overall yield[13] from 5a-bromo-α-tocopherol **(4)**, (Scheme 3).



Conditions:
i = CH_3CN, $ZnCl_2$, 70ºC, 1h; ii = NH_4Cl (sat.), rt, 30 min;
iii = 1) TBAF, rt, 30 min, 2) HCl conc., reflux, 2h, 72% overall

Scheme 3

It is recommended not to replace *O*-methyl-*C*,*O*-bis-(trimethylsilyl)ketene acetal **(10)** by another dienophile. *O*-methyl-*O*-(trimethylsilyl)ketene acetal, for instance, gave very poor yields when employed instead of **10**. The additional step in the synthesis of **13**, the removal of the trimethylsilyl group, is more than compensated by the gain in yield in the addition step.

Bromination of **13** with elemental bromine is a very interesting reaction providing 3-(5-tocopheryl)-3-bromopropionic acid **(14)** in almost quantitative yield.[14] Thus, this reaction yields a β-bromocarboxylic acid from a propanoic acid derivative, a surprising result since one should expect α-halogenation. However, the mechanism for the formation of 3-(5-tocopheryl)-3-bromopropionic acid **(14)** is completely different, namely a two-step oxidation-addition process analogous to the one which had been established for the bromination of α-tocopherol.[7] The outcome of the reaction is consequently a first indication that **1** and **13** behave chemically quite similarly.

Apart from the bromination reaction, the following experiments clearly demonstrated that 3-(5-tocopheryl)propionic acid **(13)** and vitamin E **(1)** react alike in oxidative processes. Oxidation of **13** with Ag_2O in n-hexane produced the spiro-dimer **16** by dimerization of the intermediate *ortho*-quinone methide in 69% isolated yield.[15] An analogous reaction, the formation of spiro-dimer **15**, is well-known for vitamin E.[16] Oxidation of **13** with $FeCl_3$ in a water/methanol mixture afforded the correspondent *para*-quinone **18**.[17] This reaction too, finds its counterpart in the conversion of vitamin E to *para*-tocopheryl quinone **(17)**.[18]

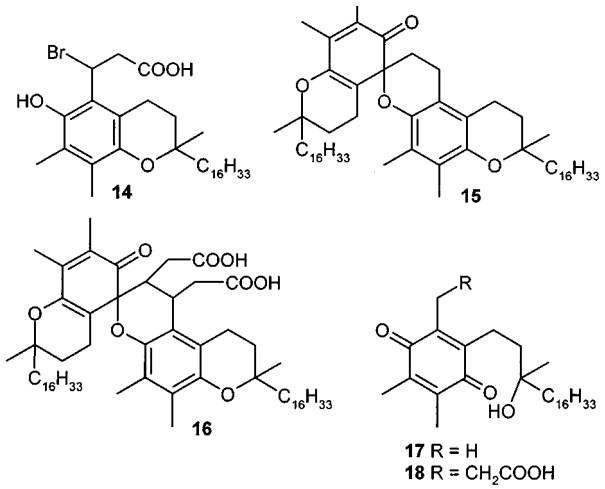


Figure 2

In summary, we have prepared 3-(5-tocopheryl)propionic acid **(13)**, a less lipophilic, base soluble tocopherol derivative. Contrary to all 5a-substituted tocopherols known so far, the compound resembles α-tocopherol in its chemical behavior as demonstrated by bromination and oxidation reactions typical of vitamin E. Moreover, **13** appears to be easily applicable as a starting material for further derivatization due to its carboxylic function as site of attachment. This opens the way to novel tocopherol derivatives that exhibit some modified properties, such as solubility or lipophilicity, but maintain essentially the same chemical behavior as vitamin E itself.

Acknowledgement

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(2) Different examples for 5a-substituted tocopherols, their synthesis and chemical behavior are given in part III - IV and IX of the current series "Novel tocopherol derivatives", for part X see: Rosenau, T.; Habicher, W. D. *Tetrahedron Lett.*, **1997**, *38*, 5959.

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(10) Matsuda, I.; Murata, S.; Izumi, Y. *J. Org. Chem.* **1980**, *45*, 237. Compound **10** was obtained in 72% yield as a mixture of the *E*- and *Z*-isomer. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.03 and 0.05 (s, 9H, O-Si($C\underline{H}_3$)$_3$), 0.20 and 0.25 (s, 9H, CSi($C\underline{H}_3$)$_3$), 2.95 and 3.08 (s, 1H, $H\underline{C}$=C), 3.48 and 3.52 (s, 3H, O-$C\underline{H}_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ -0.4 and -1.0 (O-Si(CH_3)$_3$), -0.15 and -0.4 (C-Si($\underline{C}H_3$)$_3$), 53.7 and 54.8 (O-CH_3), 63.8 and 72.5 (s, 1H, H$\underline{C}$=C), 161.4 and 164.5 (HC=$\underline{C}$).

(11) The ketene acetal **10** is normally employed as a *Michael* donor with exceptionally high reactivity towards α,β-unsaturated carbonyl compounds, see also ref. 9. However, in the present case it reacts as a dienophile in a [4+2]-cycloaddition. Thus, intermediate **11** is an ortholactone formed by a $ZnCl_2$-catalyzed hetero-*Diels-Alder* reaction, but not the respective *Michael* adduct, methyl 3-[2,7,8-trimethyl-6-trimethylsilyloxy-2-(4,8,12-trimethyltridecyl)-chro-man-5-yl]-2-(trimethylsilyl)propionate. This was confirmed by NMR. For instance, the ^{13}C spectrum shows a ortholactone signal at 108.4 ppm, but no indication of an ester carbon atom.

(12) In a 100 mL flask, a mixture of anhydrous zinc chloride (0.028 g, 0.220 mmol), compound **10** (4.400 g, 20.080 mmol), and 10 mL of CH_3CN was heated to 70°C. A solution of 5a-bromo-α-tocopherol (3.058 g; 6.000 mmol) in 10 ml of CH_3CN was slowly added (approx. 15 min) under constant stirring, and the reaction vessel kept for 1 h at 70°C, then 10 min at 85°C, and cooled to rt. Hydrolysis of the primary product was carried out by addition of 5 mL of water and, after 5 min, 10 mL of a saturated NH_4Cl solution. 100 mL of n-hexane were added, the mixture was washed twice with water and dried over Na_2SO_4. The oily residue remaining after evaporation of the solvent was used for further reactions without purification. An analytical sample of **12** was prepared by chromatography on neutral aluminum oxide.

(13) A 2 M solution of tetrabutylammonium fluoride (TBAF) in DMSO (20 mL, 40 mmol) was added to a solution of the crude product **12** in 15 ml of DMF. After stirring for 30 min, 50 mL of n-hexane were added, and the mixture was washed 5 times with 50 mL of water. The organic layer was evaporated to a volume of about 3 mL, diluted with 10 mL of ethanol and 20 mL of 5 N HCl, and refluxed for 2h. To obtain an aqueous solution of **13**, the mixture was extracted with ether (3 x 20 mL) and re-extracted into 50 mL of 5 N NaOH. After 5 min of vigorous stirring, the aqueous layer was washed with ether (3 x 10 mL), which was discarded afterwards. The aqueous phase was acidified by 5 N HCl and extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were washed once with ice-cold water, dried over $MgSO_4$, and brought to a volume of approx. 5mL. Petrol ether was added until the mixture became slightly cloudy. Cooling for several hours afforded 2.11 g (72%, referred to **1**) pure 3-[3,4-dihydro-6-hydroxy-2,7,8-trimethyl-2-(4,8,12- trimethyltridecyl)-*2H*-1-benzopyran-5-yl]propionic acid (**13**) as a yellow, waxy solid. ^{1}H NMR ($CDCl_3$, CD_3COOH): δ 1.83 (m, 2H, $^3C\underline{H}_2$), 2.10 and 2.14 (2s, 6H, $^{7a}C\underline{H}_3$, $^{8b}C\underline{H}_3$), 2.50 (t, 2H, $^{5a}CH_2$-$C\underline{H}_2$), 2.64 (t, 2H, $^4C\underline{H}_2$), 2.90 (t, 2H, $^{5a}C\underline{H}_2$). ^{13}C NMR (300 MHz, $CDCl_3$ / CD_3COOH) δ: 11.8; 12.3 (^{8b}C; ^{7a}C), 20.6 (^{4}C), 21.5 (^{5a}C), 31.6 (^{3}C), 36.4 ($^{5a}CH_2$-$\underline{C}H_2$), 75.3 (^{2}C), 115.5; 121.8; 122.9; 124.6; 145.5; 147.3 (^{Ar}C), 176.2 (COOH). Anal. calcd. for $C_{31}H_{52}O_4$ (488.75): C, 76.18; H, 10.72. Found: C, 76.24; H, 10.88. For the reason of clarity, the resonances of the isoprenoid side chain are not listed here and in the following. The convention of numbering carbon atoms in vitamin E derivatives is explained in (**14b**).

(14) The synthesis of **14** followed the procedure described in (7), **13** was used as the starting material instead of **1**. ^{1}H NMR ($CDCl_3$, CD_3COOH): δ 1.84 (m, 2H, $^3C\underline{H}_2$), 2.11 and 2.18 (2s, 6H, $^{7a}C\underline{H}_3$, $^{8b}C\underline{H}_3$), 2.64 (t, 2H, $^4C\underline{H}_2$), 3.05 and 3.22 (2dd, 2H, ^{5a}CHBr-$C\underline{H}_2$COOH), 5.52 (m, 1H, $^{5a}C\underline{H}$Br-CH_2). ^{13}C NMR: δ 11.9; 12.4 (^{8b}C; ^{7a}C), 20.4 (^{4}C), 21.7 (^{5a}C), 31.7 (^{3}C), 33.9 (^{5a}C), 43.5 (^{5a}CHBr-$\underline{C}H_2$) 75.3 (^{2}C), 116.9; 121.5; 123.2; 124.8; 144.9; 147.0 (^{Ar}C), 177.2 (COOH). Anal. calcd. for $C_{31}H_{51}O_4Br$ (567.64): C, 65.59; H, 9.06; Br, 14.08. Found: C, 65.45; H, 8.99; Br, 14.12.

(15) Freshly prepared, dry (!) silver oxide (1.160 g, 5.050 mmol) was added to a solution of **12** (0.489 g, 1.000 mmol) in 50 mL of dry n-hexane. The mixture was stirred at rt for 10 min, and the solids were separated. The residue was chromatographed on neutral aluminum oxide with n-hexane as the eluent, affording 0.336 g (69%) of **16**. ^{13}C NMR ($CDCl_3$) : δ 11.1 (^{11}C), 11.5 (^{12}C), 11.5 ($^{11'}$C), 14.6 ($^{12'}$C), 15.2 ($^{10'}$C), 18.0 (^{4}C), 19.4 ($^{4'}$C), 23.8 (^{13}C), 25.2 ($^{13'}$C), 31.0 (^{3}C), 33.8 ($^{3'}$C), 33.9 ($^{14'}$C), 34.3 (^{14}C), 74.6 (^{2}C), 74.6 ($^{2'}$C), 80.5 (^{5}C), 115.4 ($^{5'}$C), 115.5 (^{10}C), 121.9 (^{8}C), 123.7 (^{7}C), 127.3 ($^{8'}$C), 142.4 ($^{9'}$C), 144.0 (^{9}C), 145.2 ($^{7'}$C), 145.7 (^{6}C), 201.9 ($^{6'}$C), CH-CH_2-COOH (x 2): 21.5, 25.3, 33.4, 34.6, 175.1, 175.7. MALDI-TOF-MS (sinapic acid, *m/z*): 974 (MH^+). Anal. calcd. for $C_{62}H_{100}O_8$ (973.48): C, 76.50; H, 13.15. Found: C, 76.62; H, 13.23.

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(17) Preparation of 18 was carried out according to the procedure given for compound **17** in (16). ^{1}H NMR ($CDCl_3$): δ 1.71 (2H, t, $ArCH_2C\underline{H}_2$, C-3), 1.94 (3H, s, $C\underline{H}_3$, C-7a), 2.04 (3H, s, $C\underline{H}_3$, C-8b), 2.06 (2H, t, $ArC\underline{H}_2CH_2$, C-4), 2.42 (2H, t, $^{5a}CH_2$-$C\underline{H}_2$), 2.78 (t, 2H, $^{5a}C\underline{H}_2$-CH_2-), 5.23 (2H, b, OH and COOH). ^{13}C

NMR: δ 18.3 (^{4}C), 25.3 (^{5a}C), 26.7 (^{2a}C), 34.9 (-$\underline{C}H_2$-COOH), 40.4 (^{3}C), 72.0 (^{2}C), 146.1 (^{4a}C), 141.3, 141.4, 144.4 (^{5}C, ^{7}C, ^{8}C), 186.7, 186.8 (^{6}C, ^{8a}C). Anal. calcd. for $C_{31}H_{52}O_5$ (504.75): C, 73.76; H, 10.38. Found: C, 73.89; H, 10.39.

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