

NOVEL TOCOPHEROL COMPOUNDS IV. 5-TOCOPHERYLACETIC ACID AND ITS DERIVATIVES

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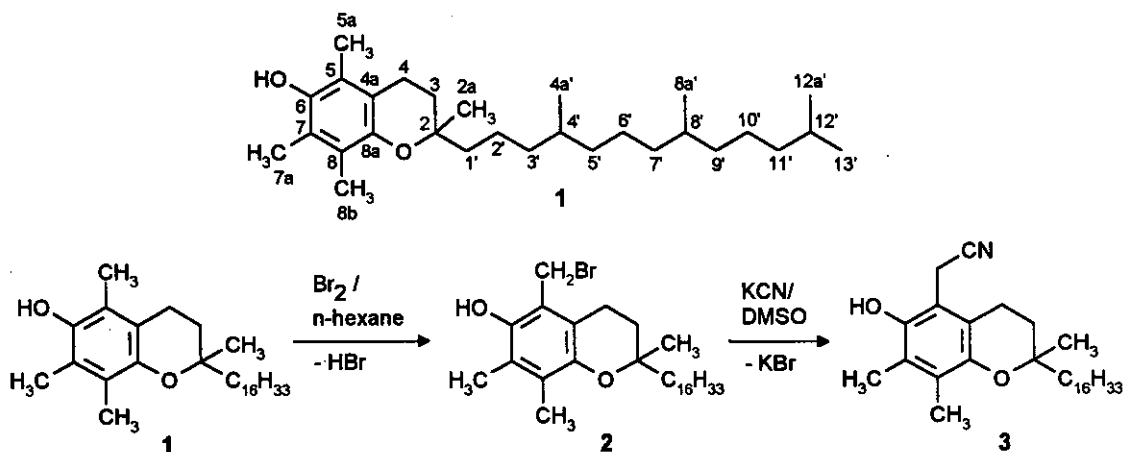
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Abstract - A new class of tocopherol (vitamin E) compounds, 5-tocopherylacetic acid derivatives, is presented. The synthesis and some unexpected properties of these compounds, such as relatively high thermal and chemical stability, are described and discussed in comparison with the labile 5 α -halogeno-, 5 α -alkoxy- or 5 α -amino-substituted tocopherols.

In recent papers we described reactions of α -tocopherol yielding products different from those of the well-investigated oxidation reactions.¹ These products are mainly 5 α -substituted derivatives of α -tocopherol with an electronegative substituent such as halogen, OR, or NR₂. Usually this substituent is readily eliminated at elevated temperature or by treatment with a base. In this paper we will report the preparation and properties of a new class of tocopherol compounds, namely, 5-tocopherylacetic acid and its derivatives. These compounds carry a "substituent" which is very tightly bound to the chroman structure, and which cannot be removed without degradation of the molecule. The present investigation represents a major step in our efforts to transfer the antioxidant effects of tocopherols into aqueous media, and to develop methods to link the tocopherol to carrier molecules without impairing its biological activity. 5-Tocopherylacetic acid is a highly efficient phase transfer catalyst for mild oxidations of molecules with inherent hydroquinone structures.²

First, the synthesis of the novel compounds 5-tocopherylacetonitrile, 5-tocopherylacetic acid and its derivatives will be briefly described. The bromination of α -tocopherol (vitamin E) (**1**) under certain reaction conditions gives quantitative yields of 5a-bromo- α -tocopherol (**2**)¹ which reacts with KCN to produce 5-tocopherylacetonitrile (5a-cyano- α -tocopherol, 5-cyanomethyl- γ -tocopherol) (**3**). Since cyanide represents an ambifunctional nucleophile, the reaction conditions must be chosen in a way that minimizes the formation of the corresponding isonitrile. In addition, the elimination of HBr from the starting material and subsequent formation of by-products must be prevented. The solution of KCN in a 1 : 1 (v/v) mixture of ethanol and water, which is usually applied in *Kolbe* nitrile syntheses, and which has relatively high basicity, favors the elimination of HBr. Therefore, it is not applicable as the solvent. The ternary system of acetone, ethanol and water (3 : 1 : 1, v/v/v) is a solvent giving satisfactory yields. With this solvent system, we initially obtained **3** and small amounts of impurities (9%, determined by GCMS), the latter consisting of the α -tocopherol spiro-dimer³ and α -tocopheryl quinone.⁴ The purification of the nitrile can be easily accomplished by flash chromatography.

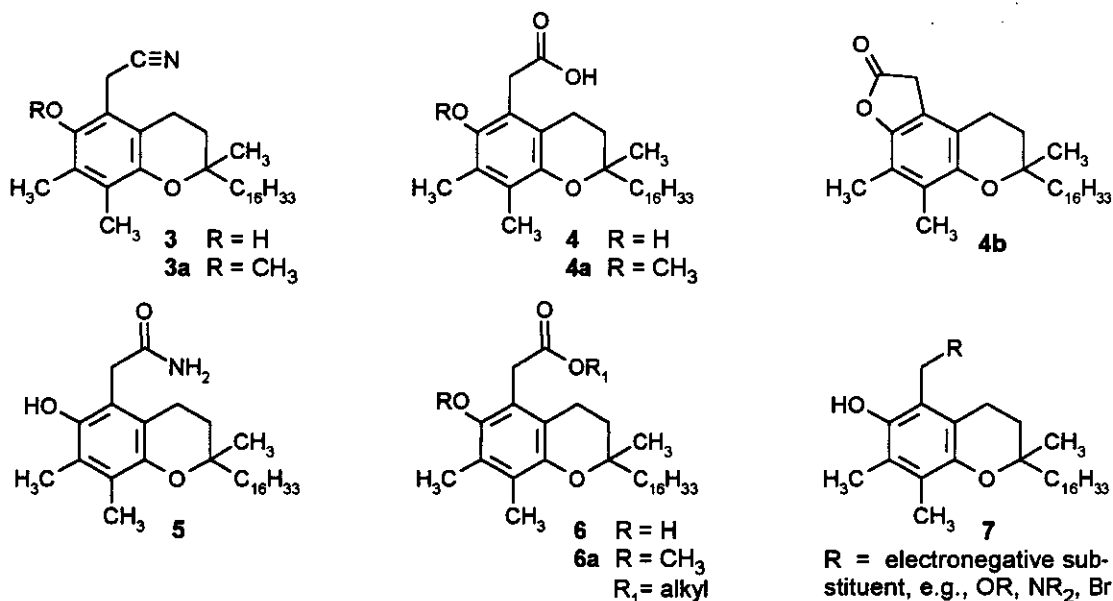
After optimization of the procedure, quantitative yields of **3** were obtained when DMSO was used as the solvent. No further purification of the product was required. The reaction temperature - unlike similar reactions of this type which range between 90 and 130°C - must not exceed 60°C in this case, due to possible decomposition of the starting material (**2**).



On hydrolysis of the nitrile (**3**) in aqueous dioxan with gaseous HCl, the corresponding acid, 5-tocopherylacetic acid (**4**), was obtained. To the best of our knowledge, this compound is the first water-soluble tocopherol derivative with a free phenolic OH group and unchanged isoprenoid side chain.

The antioxidative properties of this compound, especially in biological model systems, are currently under investigation in our laboratory. Although the solubility of **4** in cold water is very low, it is sufficiently soluble in warm water (40°C) and readily soluble in aqueous base solutions. Moreover, **4** shows good solubility in all common polar protic and polar aprotic organic solvents.

Treatment of the nitrile (**3**) in concentrated formic acid with dry hydrogen bromide gives the 5-tocopherylacetamide (**5**), which is also amenable to hydrolysis to give the acid (**4**) as well. In contrast to hydrolysis in basic media, acidic hydrolysis yields the desired products quantitatively.



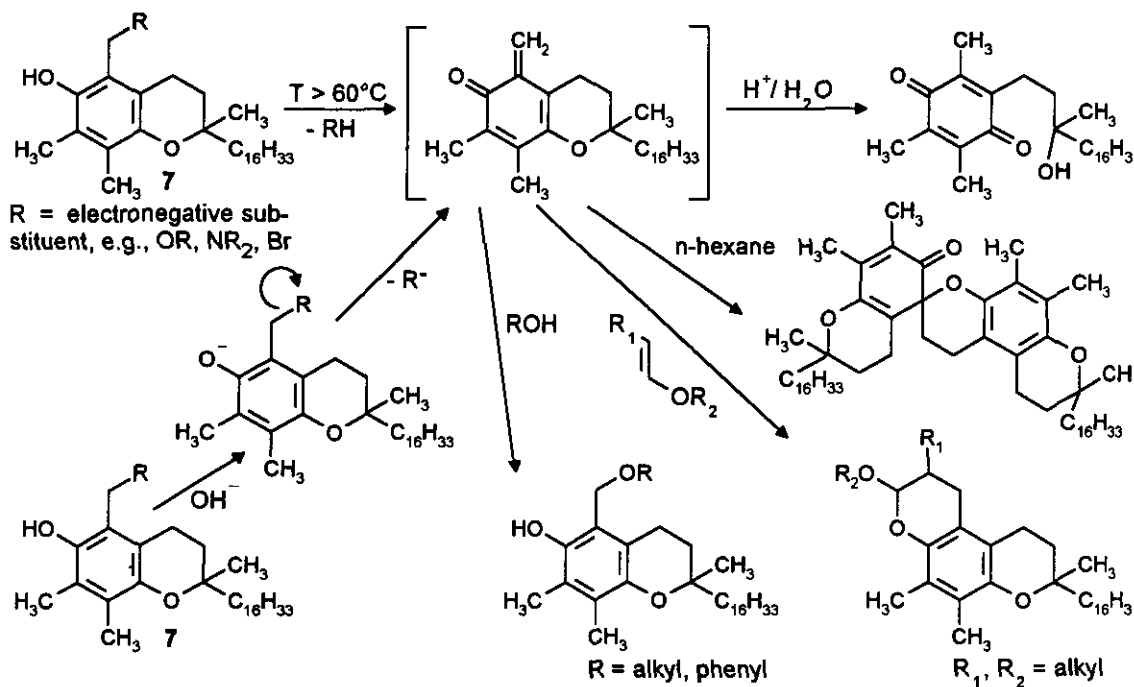
5-Tocopherylacetonitrile methyl ether (**3a**) was prepared by etherification of the phenolic OH group of **3** according to the method of *Claisen*.⁵ Acidic hydrolysis of the nitrile (**3a**) to the amide or acid unfortunately causes some cleavage of the methyl ether bond in **3a**, which leads to a mixture of the 5-tocopherylacetic acid (**4**) and its methyl ether (**4a**). This methyl ether (**4a**) was separated from the reaction mixture by extraction with base after converting the accompanying 5-tocopherylacetic acid to its lactone (**4b**) by polyphosphoric acid. An authentic sample of 5-tocopherylacetic acid lactone (**4b**) was prepared with the corresponding acid (**4**) as the starting material. The direct conversion of the nitrile (**3**) to the lactone of 5-tocopherylacetic acid (**4b**) as a simple one-pot synthesis was not successful.

A convenient method for the preparation of various 5-tocopherylacetic acid alkyl esters (**6**) and their methyl ethers (**6a**) comprises two steps. First, the nitriles (**3**) or (**3a**) are alcoholized in the presence of equimolar amounts of an alkyl alcohol in *n*-hexane or ether into which dry HBr is passed at -10°C.

Second, the crystalline imidate hydrobromide precipitated is hydrolyzed in aqueous acidic media to give the corresponding alkyl esters. The overall yields range from 90% to quantitative. No by-products were observed, indicating the stability of the ether bond in **3a** under the prevailing conditions. This approach can be referred to as a modified *Pinner* procedure.⁶ The choice of the solvent seems to be crucial to obtain crystalline imidate salts. In case of commonly applied solvents for *Pinner* syntheses, such as toluene, benzene and dioxan, a waxy solid was obtained that was not amenable to recrystallization, although it did yield the corresponding ester upon treatment with base or water. Thus, n-hexane or ether are recommended as solvents for the synthesis of **6** or **6a**. Several 5-tocopherylacetic acid alkyl esters were prepared according to this method; examples and a general procedure are given in the Experimental Section. 5-Tocopherylacetic acid esters (**6**) and the corresponding methyl ethers (**6a**) are insoluble in water, but show good solubility in polar aprotic and apolar organic solvents. Those compounds are potential antioxidants, and especially interesting because of their unambiguous behavior in oxidation reactions. According to current investigations, all esters (**6**) are converted into their corresponding substituted *para*-quinones upon oxidation, independent of the oxidant applied. This stands in complete contrast to α -tocopherol itself which can be oxidized to a variety of products dependent on the respective oxidizing agent and solvent.

Thermal stability of 5-tocopherylacetic acid compared to 5a-substituted tocopherols.

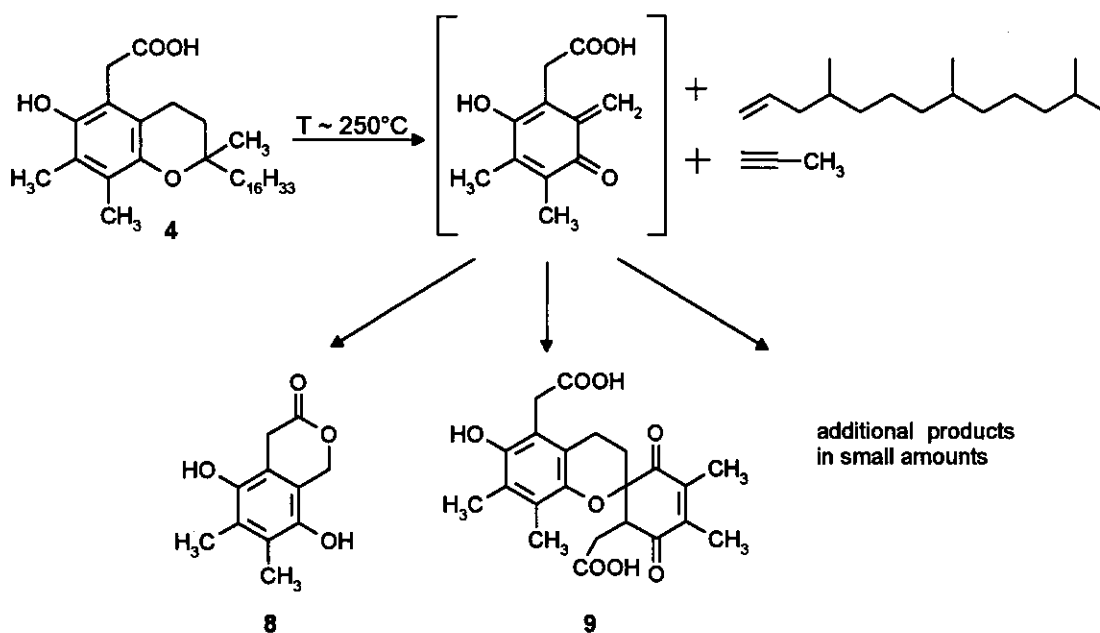
5-Tocopherylacetonitrile shows remarkable thermal stability, as do the 5-tocopherylacetic acid and its derivatives. This is in contrast to the thermolability of 5a-substituted tocopherols (**7**) carrying an electro-negative substituent at position 5a, and thus, having a heteropolar bond between C-5a and that substituent. These compounds, e.g., 5a-tocopheryl esters, ethers, halides or amines, undergo elimination of the substituent at C-5a when heated above 60°C to form an *ortho*-quinonemethide intermediate. Therefore, a direct determination of these compounds by gc or gcms is not feasible. The *ortho*-quinonemethide seems to be a very favorable intermediate that reacts further in consecutive reactions to form stable products.⁷ The products finally obtained are determined by the co-reactants present, e.g., solvents that "trap" the *ortho*-quinonemethide. Among these trapping reactions are hetero-*Diels-Alder* reactions with dienophiles, or additions of nucleophiles.¹ The pathways for the decomposition of 5a-substituted tocopherol derivatives (**7**), induced by heat or by means of a base, in different solvents and under different conditions are shown in Scheme 1.



Scheme 1. Thermal Treatment of 5a-Substituted Tocopherols.

The effects of thermal stress on the tocopherylacetic acid derivatives (3 - 6) has been studied by means of gcms and nmr techniques. These compounds can be heated up to 200°C without noticeable decomposition and can therefore be determined by gc or gcms. The homopolar C-C bond in the C₂-unit at the 5-position of the tocopherol has been shown to be very stable. In contrast to the aforementioned 5a-substituted compounds (7), elimination of the 5a-"substituent", namely heterolytic C-C cleavage, is very unlikely to proceed. Moreover, thermal treatment of the 5-tocopherylacetic acid derivatives at 250 - 280°C leads to an almost complete breakdown of the chroman structure. It was observed that the C-C bond between C-5a and the C of the adjacent non-aromatic carbon in tocopherylacetic acid and its derivatives remains intact, even if the isoprenoid side chain and the pyran ring have already been thermally degraded (see Scheme 2). Surprisingly, decarboxylation during the heat treatment was not observed. The products are formed *via ortho*-quinonemethide intermediates produced by elimination of C-2, C-2a and C-3 as propyne, and elimination of the side chain as 4,8,12-trimethyltridec-1-ene.⁸ These *ortho*-quinonemethides involve C-4 and the O at position 1, unlike the *ortho*-quinonemethide shown in Scheme 1 which involves C-5a and the O of the phenolic OH group. While the intermediacy of the latter *ortho*-quinonemethides has been proposed and thoroughly discussed in the literature,⁷ the present report on the formation of an

ortho-quinonemethide intermediate involving a C other than C-5a is a new finding. It might also contribute to a better understanding of the antioxidant effects in chroman-6-ol and tocopherol systems. To avoid misunderstandings in nomenclature, we would like to introduce the name "C-4-*ortho*-quinonemethide of α -tocopherol" for the newly found intermediate, and "C-5a-*ortho*-quinonemethide of α -tocopherol" for the well-established intermediate.



Scheme 2. Thermal Treatment of 5-Tocopherylacetic Acid.

Apparently, formation of the C-5a-*ortho*-quinonemethide, which would otherwise occur very readily, is strongly impeded or totally prevented as soon as C-5a is connected to another carbon that cannot be eliminated. This results in unusually stable tocopherol derivatives. However, extreme thermal stress leads to a structural breakdown even of these compounds. Again, an *ortho*-quinonemethide is formed, this time involving C-4 and causing destruction of the chroman ring structure as discussed above. The formation of spiro compounds during the heat treatment of tocopherylacetic acid is consequently the result of a hetero-*Diels-Alder* reaction of two C-4-*ortho*-quinonemethide molecules. Scheme 2 shows the constituents of a reaction mixture obtained upon thermal treatment of 5-tocopherylacetic acid in triethylene glycol. Compounds (8) and (9), the main components, are formed *via* the C-4-*ortho*-quinonemethide intermediate by cyclization, or by reaction of two molecules of the C-4-*ortho*-quinonemethide, respectively. Other products derived from the quinonemethide were obtained only in trace amounts.

The product distribution of the thermal decomposition of 5-tocopherylacetic acid derivatives appeared to be independent of solvents applied during the heat treatment. This is again in complete contrast to the behavior of the 5 α -substituted tocopherols (7). To induce thermal decomposition of the corresponding tocopherol derivative, the boiling point of the solvent employed must be sufficiently high, as it is in triethylene glycol.

In summary, we have described the synthesis and selected properties of a novel class of compounds derived from vitamin E, 5-tocopherylacetic acid and its derivatives. These compounds are not only remarkably stable as compared with other tocopherol derivatives, they represent an interesting new group of compounds with a stable bond between the tocopherol part and the added chemical function.

EXPERIMENTAL

¹H Nmr spectra were recorded at 300 MHz, ¹³C nmr spectra at 80 MHz (Bruker AC-300P) in CDCl₃ with TMS as the internal standard. ¹³C peaks were assigned by means of DEPT (Distortionless Enhancement by Polarization Transfer) and GD (Gated Decoupling). Chemical shifts are expressed in δ value. The δ -values of the atoms of the isoprenoid side chain (C-1' to C-13') are well established and will not be listed in the following, since they are only very slightly effected by modifications of the chroman structure and insignificant for the identification of the molecule concerned.⁹ GCms was performed on a Hewlett Packard (5890 Series II, EI, 70 eV, ITD). Analytical tlc was carried out on precoated silica gel plates. Column chromatography was performed using silica gel (Merck, 230 - 400 mesh). The numbering of the carbon atoms and the nomenclature for tocopherol derivatives proposed by the IUPAC¹⁰ have been used throughout. Melting points are uncorrected.

[6-Hydroxy-2,7,8-trimethyl-2-(4,8,12-trimethyltridecyl)chroman-5-yl]acetonitrile (5-Tocopherylacetonitrile) (3). 5 α -Bromo- α -tocopherol (10.000 g, 19.623 mmol) was added slowly, in approximately 1 h, to a rapidly stirred, partially-soluble mixture of potassium cyanide (1.302 g, 20.000 mmol) in 50 ml of dry DMSO at 40°C. The temperature was maintained at 40°C by a temperature controlled oil bath. During the reaction, the yellow solution turned almost colorless, and the solids more crystalline. After 24 h, 250 ml of H₂O was added and the mixture extracted five times with 50 ml of CH₂Cl₂. The organic layer was washed with 50 ml of H₂O, 20 ml of 5N HCl and again 50 ml of H₂O, dried over MgSO₄ and then concentrated to a volume of about 20 ml. 3 ml of petrol ether (bp 40-50°C) was added, and the solution was left in the refrigerator overnight. An additional 2 ml of ice-cold petrol ether was added and the mixture kept at -10°C for 48 h. A waxy solid precipitated, that was filtered off and washed twice with 50 ml of petrol ether. Remaining solvent was removed under vacuum at room temp to yield 8.138 g (91%) of a pure product. Anal. Calcd for C₃₀H₄₉NO₂: C, 79.07; H, 10.84; N, 3.07. Found: C, 79.11; H, 10.92; N, 3.13. ¹H Nmr (CDCl₃): δ 2.10 (3H, s, CH₃, C-7a), 2.15 (3H, s, CH₃, C-8b), 2.70 (2H, t, $J=7$ Hz, ArCH₂CH₂, C-4),

3.68 (2H, s, Ar-CH₂-CN, C-5a), 4.60 (1H, br, OH, exch. with D₂O). ¹³C Nmr (CDCl₃): δ 12.0 (C-8b), 12.1 (C-7a), 20.4 (C-4), 22.3 (CH₂-CN, C-5a), 23.5 (C-2a), 31.1 (C-3), 74.2 (C-2), 118.4 (CN); 118.3; 123.0; 123.4; 129.2; 145.2; 148.7 (C^Δ).

[6-Methoxy-2,7,8-trimethyl-2-(4,8,12-trimethyltridecyl)chroman-5-yl]acetonitrile (5-Tocopherylacetonitrile methyl ether, O-methyl-5-tocopherylacetonitrile) (3a). A mixture of 5-tocopherylacetonitrile (3) (2.000 g, 4.389 mmol) in 20 ml of dry acetone was placed into a 100 ml three-neck flask equipped with dropping funnel, gas inlet and condenser. Anhydrous potassium carbonate (0.829 g, 6.000 mmol) was added. After stirring under N₂ for 15 min at room temp, methyl iodide (0.632 g, 4.450 mmol) in 5 ml of dry acetone was added dropwise. The mixture was stirred for 48 h at room temp. The coarse-grained K₂CO₃ slowly turned into a finely crystalline precipitate consisting of KHCO₃ and KI. An additional 0.100 g (0.723 mmol) of potassium carbonate and 0.030 g (0.211 mmol) of methyl iodide in 2 ml of acetone was added and the mixture stirred for additional 24 h. After addition of n-hexane (100 ml), the mixture was cooled to 0°C and washed twice with 10 ml of distilled water, 10 ml of 5N NaOH and again twice with 10 ml of distilled water. The organic layer was dried over MgSO₄ and the solvent evaporated *in vacuo*. The resulting straw-colored oil consisted of pure 5-tocopherylacetonitrile methyl ether. Yield: 1.980 g (96%). Anal. Calcd for C₃₁H₅₁NO₂: C, 79.26; H, 10.94; N, 2.98. Found: C, 79.21; H, 10.99; N, 2.96. ¹H Nmr (DMSO-d₆): δ 2.10 (3H, s, CH₃, C-7a), 2.15 (3H, s, CH₃, C-8b), 2.70 (2H, t, J=7 Hz, ArCH₂CH₂, C-4), 3.65 (2H, s, Ar-CH₂-CN, C-5a), 3.85 (3H, s, CH₃-O).

[6-Hydroxy-2,7,8-trimethyl-2-(4,8,12-trimethyltridecyl)chroman-5-yl]acetic acid (5-Tocopherylacetic acid) (4). In a 50 ml two-neck flask equipped with reflux condenser, gas inlet and magnetic stirrer, 5-tocopherylacetonitrile (3) (4.557 g, 10.000 mmol) was dissolved in 15 ml of freshly distilled dioxan. Water was added until the solution became slightly cloudy. Hydrogen bromide was passed slowly through the reaction mixture for 1 h. The mixture was heated on a water bath for 3 h and cooled to room temp maintaining the flushing with HBr throughout. 5 ml of dioxan was added and the reaction vessel kept closed overnight under stirring. After addition of 50 ml of n-hexane, the reaction mixture was washed with 5 ml of ice-cold water. The organic layer was poured into 5N NaOH (50 ml) and stirred vigorously for 5 min. The phases were separated and the aqueous phase extracted with an additional 10 ml of n-hexane. The combined organic phases were discarded. The aqueous phase was neutralized and acidified with 5N HCl, then extracted three times with 20 ml of CH₂Cl₂. The combined organic phases were washed with 10 ml of water, dried over MgSO₄ and concentrated to a volume of about 5 ml. Petrol ether (bp 40-50°C) was added until the solution became cloudy. The mixture was kept in the refrigerator for several hours. The precipitate obtained was filtered off and dried under vacuum. Recrystallization (CHCl₃) yielded 4.178 g (88%) 5-tocopherylacetic acid as off-white crystals, mp: 52-55°C. Anal. Calcd for C₃₀H₅₀O₄: C, 75.90; H, 10.62. Found: C, 75.92; H, 10.73. ¹H Nmr (CDCl₃, CH₃COOD added): δ 2.10 (3H, s, CH₃, C-7a), 2.15 (3H, s, CH₃, C-8b), 2.72 (2H, t, J=7 Hz, ArCH₂CH₂, C-4), 3.55 (2H, s, Ar-CH₂-COOH, C-5a). ¹³C Nmr (CDCl₃): δ 12.1 (C-8b), 12.3 (C-7a), 20.4 (C-4), 41.1 (CH₂-COOH, C-5a), 23.5 (C-2a), 31.1 (C-3), 74.2 (C-2), 178.6 (COOH); 119.8; 123.2; 123.9; 129.2; 146.2; 149.7 (C^Δ).

[6-Methoxy-2,7,8-trimethyl-2-(4,8,12-trimethyltridecyl)chroman-5-yl]acetic acid (6-Methoxy-5-tocopherylacetic acid) (4a). The preparation follows the above given procedure. 0.939 g (2.000 mmol) of 5-tocopherylacetonitrile methyl ether (**3a**) was used as starting material instead of 5-tocopherylacetonitrile. The following steps are taken to separate the desired product from 5-tocopherylacetic acid that was formed as the by-product by cleavage of the methyl ether bond. After concentration of the dried organic phase to a volume of 5 ml, toluene (20 ml) and polyphosphoric acid (1 g) were added to the above solution.¹¹ The reaction mixture was stirred for 10 min, and the slightly yellow solids were filtered off and washed with 10 ml of toluene. Again, 1 g of polyphosphoric acid was added to the combined organic phases and the mixture then stirred for 1 h at 50°C. After cooling to room temp, the solids were filtered off and thoroughly washed with 50 ml of toluene. The combined organic phases were washed with 10 ml of water and quickly extracted three times with 20 ml of 5N NaOH. The basic extracts were neutralized and acidified with 5N HCl, and extracted three times with 10 ml of CH₂Cl₂. The combined organic layers were washed with water, dried over MgSO₄ and concentrated to a volume of about 5 ml. Petrol ether (bp 40-50°C) was added until the solution became cloudy. The mixture was kept in the refrigerator for several hours. The crystalline precipitate was filtered off, dried under vacuum and recrystallized twice from chloroform, mp: 38-39°C. Yield: 0.469 g (48%). Anal. Calcd for C₃₁H₅₂O₄: C, 76.18; H, 10.72. Found: C, 76.28; H, 10.78. ¹H Nmr (CDCl₃, CH₃COOD added): δ 2.11 (3H, s, CH₃, C-7a), 2.12 (3H, s, CH₃, C-8b), 2.68 (2H, t, *J*=7 Hz, ArCH₂CH₂, C-4), 3.53 (2H, s, Ar-CH₂-COOH, C-5a), 3.8 (3H, s, CH₃-O).

[6-Hydroxy-2,7,8-trimethyl-2-(4,8,12-trimethyltridecyl)chroman-5-yl]acetamide (5-Tocopherylacetamide) (5). 5-Tocopherylacetonitrile (**3**) (2.279 g, 5.000 mmol) was dissolved in concentrated formic acid (97%, d. 1.22, 2.303 g) and benzene (10 ml). The solution was placed into a 50 ml flask equipped with gas inlet, magnetic stirrer and condenser, then heated to 50°C in an oil bath and flushed with dry hydrogen chloride for 10 min using a diffuser stone. The reaction vessel was kept closed afterwards at 50°C under magnetic stirring. When the reaction mixture became opaque after approximately 3 h, flushing with dry HCl was started again. After additional 1 h, the flushing was stopped, and the mixture was cooled below 0°C in an ice/NaCl mixture. 20 ml of benzene and after 5 min 10 ml of petrol ether (bp 40-50°C) was added. The crystalline precipitate obtained was washed twice with 5 ml ice-cold petrol ether, dried under vacuum and recrystallized from ethyl acetate (addition of small amounts of petrol ether was necessary to obtain crystals upon recrystallization), mp below 40°C. Yield: 1.730 g (73%). Anal. Calcd for C₃₀H₅₁NO₃: C, 76.06; H, 10.85; N, 2.96. Found: C, 76.01; H, 10.85; N, 3.01. ¹H Nmr (CDCl₃, CH₃COOD added): δ 2.11 (3H, s, CH₃, C-7a), 2.13 (3H, s, CH₃, C-8b), 2.70 (2H, t, *J*=7 Hz, ArCH₂CH₂, C-4), 3.47 (2H, s, Ar-CH₂-CONH₂, C-5a). ¹³C Nmr (CDCl₃): δ 12.1 (C-8b), 12.2 (C-7a), 20.2 (C-4), 23.4 (C-2a), 31.1 (C-3), 41.3 (CH₂-CONH₂, C-5a), 74.2 (C-2), 172.5 (CONH₂); 118.8; 122.3; 124.1; 129.1; 145.3; 148.9 (C^{ar}).

[6-Hydroxy-2,7,8-trimethyl-2-(4,8,12-trimethyltridecyl)chroman-5-yl]acetic acid alkyl esters (5-Tocopherylacetic acid alkyl esters) (6). In a 100 ml flask, 5-tocopherylacetonitrile (0.456 g, 1.000 mmol) and 1.100 mmol of alcohol were dissolved in n-hexane (50 ml), and stirred with a magnetic stirrer while flushing the reaction mixture with dry HBr.¹² As soon as the reaction mixture became cloudy (approximately 2 h), the flow of HBr was stopped

and the reaction mixture refluxed for 1 h. A very fine, off-white precipitate formed during this period. The process of flushing for 2 h with subsequent refluxing for 1 h is continued until a filtered sample of the reaction mixture shows no peaks upon gc analysis besides the solvent and the alcohol employed. The precipitate, i.e., the corresponding imidate hydrobromide, is separated in a glass filter under HBr, washed three times with n-hexane and dried under vacuum. The white crystals can be infinitely kept in an desiccator over H_2SO_4 , or in a HBr atmosphere. For the preparation of the 5-tocopherylacetic acid alkyl esters, 0.010 mol of the imidate hydrobromide was added to 50 ml of 1N aqueous $NaHCO_3$ solution. After 30 min of stirring the mixture was extracted three times with 10 ml of benzene. The combined organic phases were washed twice with water, dried carefully over Na_2SO_4 and concentrated to a volume of about 10 ml. In most cases, crystals were obtained upon addition of light petrol ether at temperatures below $0^\circ C$. If no solid was precipitated or if the recrystallization failed, the crude product was subjected to flash chromatography, eluting the by-products with n-hexane and the product with benzene / chloroform (9 : 1, v/v). In the following, data of three representative examples are given. Data on further compounds can be obtained from the authors upon request.

[6-Hydroxy-2,7,8-trimethyl-2-(4,8,12-trimethyltridecyl)chroman-5-yl]acetic acid ethyl ester. Yield: 0.442 g (88 %). Anal. Calcd for $C_{32}H_{54}O_4$: C, 76.45; H, 10.83. Found: C, 76.46; H, 10.86. 1H Nmr ($CDCl_3$): δ 2.10 (3H, s, CH_3 , C-7a), 2.13 (3H, s, CH_3 , C-8b), 2.72 (2H, t, $J=7$ Hz, $ArCH_2CH_2$, C-4), 3.62 (2H, s, $Ar-CH_2-COOEt$, C-5a), 4.16 (2H, q, $J=7$ Hz, $O-CH_2-CH_3$). ^{13}C Nmr ($CDCl_3$): δ 12.1 (C-8b), 12.2 (C-7a), 14.6 ($O-CH_2-CH_3$), 20.2 (C-4), 23.5 (C-2a), 31.3 (C-3), 41.4 ($CH_2-COOEt$, C-5a), 60.9 ($O-CH_2-CH_3$), 74.2 (C-2), 119.5; 123.3; 123.9; 128.9; 145.2; 147.9 (C^A), 171.5 ($COOEt$).

[6-Hydroxy-2,7,8-trimethyl-2-(4,8,12-trimethyltridecyl)chroman-5-yl]acetic acid allyl ester. Yield: 0.422 g (82 %). Anal. Calcd for $C_{33}H_{54}O_4$: C, 76.98; H, 10.58. Found: C, 77.02; H, 10.58. 1H Nmr ($CDCl_3$): δ 2.10 (3H, s, CH_3 , C-7a), 2.12 (3H, s, CH_3 , C-8b), 2.70 (2H, t, $J=7$ Hz, $ArCH_2CH_2$, C-4), 3.68 (2H, s, $Ar-CH_2-COOAll$, C-5a), 4.56 (2H, d, $J=5.5$ Hz, $O-CH_2-CH=CH_2$), 5.21 (2H, m (b), $O-CH_2-CH=CH_2$), 5.92 (1H, m, $O-CH_2-CH=CH_2$). ^{13}C Nmr ($CDCl_3$): δ 12.1 (C-8b), 12.2 (C-7a), 20.3 (C-4), 23.4 (C-2a), 31.3 (C-3), 41.2 ($CH_2-COOAll$, C-5a), 65.4 ($O-CH_2-CH=CH_2$), 74.2 (C-2), 118.3; 128.4 ($O-CH_2-CH=CH_2$), 119.3; 123.3; 123.9; 128.0; 145.3; 147.9 (C^A), 171.8 ($COOAll$).

[6-Hydroxy-2,7,8-trimethyl-2-(4,8,12-trimethyltridecyl)chroman-5-yl]acetic acid hexyl ester. Yield: 0.341 g (61%). Anal. Calcd for $C_{36}H_{62}O_4$: C, 77.35; H, 11.19. Found: C, 77.36; H, 11.23. 1H Nmr ($CDCl_3$): δ 2.11 (3H, s, CH_3 , C-7a), 2.11 (3H, s, CH_3 , C-8b), 2.74 (2H, t, $J=7$ Hz, $ArCH_2CH_2$, C-4), 3.54 (2H, s, $Ar-CH_2-COOHex$, C-5a), 4.22 (2H, q, $J=7$ Hz, $O-CH_2-C_5H_{11}$). The other resonances of the hexyl group are hidden by signals of the isoprenoid tocopheryl side chain. ^{13}C Nmr ($CDCl_3$): δ 12.15 (C-8b), 12.2 (C-7a), 13.9; 22.6; 25.6; 28.7; 31.5; 64.6 ($O-CH_2-C_5H_{11}$), 20.4 (C-4), 23.4 (C-2a), 31.3 (C-3), 41.2 ($CH_2-COOHex$, C-5a), 74.2 (C-2), 119.4; 123.4; 124.1; 128.8; 145.6; 147.8 (C^A), 171.1 ($COOHex$).

Thermal decomposition of 5-tocopherylacetic acid.

In a closed 100 ml vessel, 5-tocopherylacetic acid (2.000 g) was slowly (10°/min) heated to 250°C in a nitrogen atmosphere and kept at this temperature for 2 h. After cooling to room temperature, gaseous products were analyzed by means of headspace gc technique. The dark-yellow, oily remainder was dissolved in 50 ml of chloroform and chromatographed on silica gel. The components were determined by ms and nmr. The heat treatment was also carried out in 20 ml of triethylene glycol as the solvent. After cooling to room temperature, the mixture was poured into 200 ml of water and extracted twice with 50 ml of chloroform. The combined organic extracts were dried over Na₂SO₄ and chromatographed. In the following we describe the data of the compounds (8) and (9) (see Scheme 2), since the other products of the thermal treatment are well-known and comprehensively described in literature.⁸

5,8-Dihydroxy-6,7-dimethylisochroman-3-one (8). Yield: 0.153g (18%). Anal. Calcd for C₁₁H₁₂O₄: C, 63.45; H, 5.81. Found: C, 63.47; H, 5.88. ¹H Nmr (CDCl₃): δ 2.03 (3H, s, CH₃), 2.12 (3H, s, CH₃), 3.35 (2H, s, ArCH₂CO), 4.74 (2H, s, Ar-CH₂-O), 6.20 (2H, br, OH). ¹³C Nmr (CDCl₃): δ 12.2 (C-8b), 12.3 (C-7a), 32.8 (C-4), 66.9 (C-1), 119.0; 124.5; 125.7; 127.0; 150.1; 151.3 (C^Δ), 175.1 (CO).

2',3',3,4-Tetrahydro-5',6',7,8-tetramethyl-2',5-bis(methylcarboxyl)-spiro[2H-benzopyran]-3'-benzoquinone (9)
Yield: 0.290g (34%). Anal. Calcd for C₂₂H₂₄O₈: C, 63.45; H, 5.81. Found: C, 63.44; H, 5.89. ¹³C Nmr (CDCl₃): δ 11.7; 11.8; 12.4; 12.9 (CH₃), 27.5; 33.1 (CH₂-COOH), 24.8; 34.9 (CH₂ in chromane), 46.4 (CH), 92.4 (C-spiro); 119.4; 123.7; 124.1; 125.0; 150.9; 152.3 (C^Δ), 144.2; 144.3 (C=C), 177.3; 178.1 (COOH), 195.5; 196.0 (CO).

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