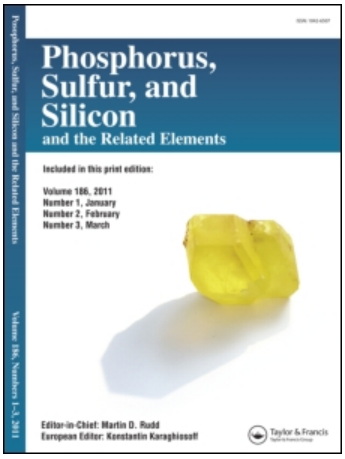


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# NOVEL TOCOPHEROL COMPOUNDS IX. SYNTHESIS OF 5a-FUNCTIONALIZED TOCOPHEROLS WITH ORGANOELEMENT SUBSTITUENTS

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# NOVEL TOCOPHEROL COMPOUNDS IX. SYNTHESIS OF 5A-FUNCTIONALIZED TOCOPHEROLS WITH ORGANOELEMENT SUBSTITUENTS

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5a-Substituted tocopherols bearing silicon, sulfur, or phosphorus moieties at position 5a have been synthesized starting from 5a-bromo-α-tocopherol **(5)**. 5a-Trialkylsilyl-α-tocopherols **(6, 7)** were obtained by a sonochemically catalyzed reaction as the key step. Reaction of 5a-bromo-α-tocopherol with *N*-substituted thioureas provided satisfying yields of the corresponding 5a-α-tocopheryl-thiouronium salts **(8–10)**, whereas the reaction with thiols did not produce the 5a-substituted products, but a complex mixture of products due to the occurrence of uncontrollable redox processes during the reaction. Tocopheryltriphenylphosphonium bromide **(11)** was obtained by a simple quaternization reaction, and has been further exploited as a useful intermediate in the syntheses of novel vitamin E derivatives **(12–18)** with the tocopherol unit being incorporated into a stable furobenzopyran structure.

*Keywords:* vitamin E; 5a-substituted tocopherols; furobenzopyrans; sonochemistry; Wurtz-coupling; intramolecular Wittig reaction

## INTRODUCTION

5a-Substituted tocopherols are produced upon reaction of vitamin E (α-tocopherol, **1**) with radicals either *in vivo* or *in vitro*.[1] In addition, these compounds have been undergoing a surge of interest as auxiliaries in synthesis,[2] enzyme inhibitors[3] and potential lipophilic drug carriers, and they gave impetus to investigations aimed at a better understanding of the chemical behavior of the biologically important vitamin E system.

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Previous results from our lab indicate that 5a-substituted tocopherols exhibit a significantly different chemical behavior depending on the nature of the 5a-substituent. With an electronegative 5a-substituent, such as Br, OR or $NR_2$ [R = H, alkyl, aryl], the compounds tend to eliminate this substituent under formation of an intermediate *ortho*-quinone methide (**2**). This elimination process can be induced by mild oxidation, treatment with base or slightly elevated temperatures. The *ortho*-quinone methide as the primary intermediate forms stable compounds in subsequent reactions, namely the spiro-dimer of $\alpha$-tocopherol (**4**) by dimerization, or *para*-tocopheryl quinone (**3**) by addition of water. In contrast, a carbonyl group adjacent to C-5a alters the reaction behavior of the whole chromanol structure. The resulting tocopherol derivative becomes stable towards bases and thermal treatment up to 150°C, and forms exclusively *para*-quinoid structures upon oxidation.

To gain more thorough knowledge about the influence of the 5a-substituents on the reactivity and the chemical behavior of tocopherols, new derivatives with hitherto unknown substituents had to be synthesized. These functional groups had to meet the following requirements: first, their electronegativity should be smaller than that of halide, oxygen or amino groups. Second, the substituents should be sufficiently stable to ensure that the compounds can be tested for their chemical behavior and vitamin E activity. Resulting from these demands, 5a-substituted tocopherols with silicon-, sulfur- and phosphorus-containing functional groups were synthesized for the first time. The introduction of elemental-organic substituents at position 5a does not only promise to fill the gaps in knowledge concerning the influence of the type of substituent on the reactivity of the tocopherol system. Moreover, the resulting compounds are auspicious candidates for drug testing and new vitamin E-derived antioxidants.



## RESULTS

The silicon-containing compounds 5a-trimethylsilyl-$\alpha$-tocopherol (**6**) and 5a-(*tert*-butyl-dimethylsilyl)-$\alpha$-tocopherol (**7**) were obtained by a sonochemical reaction starting from 5a-bromo-$\alpha$-tocopherol (Toc-Br, **5**). The latter compound can easily be prepared from vitamin E by bromination with elemental bromine.[4] Reaction of 5a-bromo-$\alpha$-tocopherol (**5**) with zinc metal and an excess of trialkylchlorosilan in refluxing toluene provided low yields of **6** and **7**. By applying ultrasound and working at room temperature the yield could be drastically increased.

The sonochemical reaction was strongly dependent on the solvent and the ratio between tocopheryl bromide **5** and silylating agent. A short period of son-

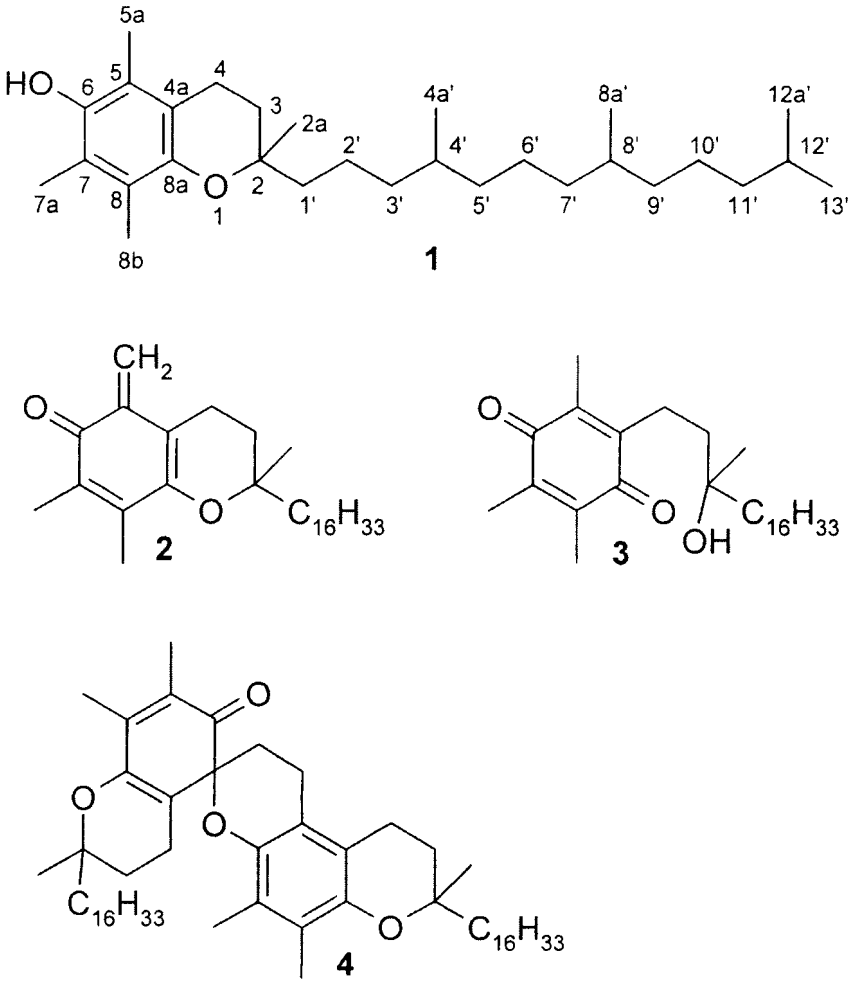


FIGURE 1

ication in a water-bath sonifier (5 to 10 min) was sufficient to achieve complete conversion of the starting material into products. Through optimization of the reaction parameters, the 5a-trialkylsilyl tocopherols 5a-trimethylsilyl-$\alpha$-tocopherol (**6**) and 5a-(*tert*-butyl-dimethylsilyl)-$\alpha$-tocopherol (**7**) were obtained in 71 and 78% yield, respectively, a surprisingly good result regarding the lability of the starting material 5a-bromo-$\alpha$-tocopherol (**5**) and the type of reaction. The influence of different reaction conditions on the yield of **6** is summarized in Table I.

The introduction of sulfur-containing groups into the position 5a of the tocopherol structure proved to be somewhat arduous. Attempts to produce the

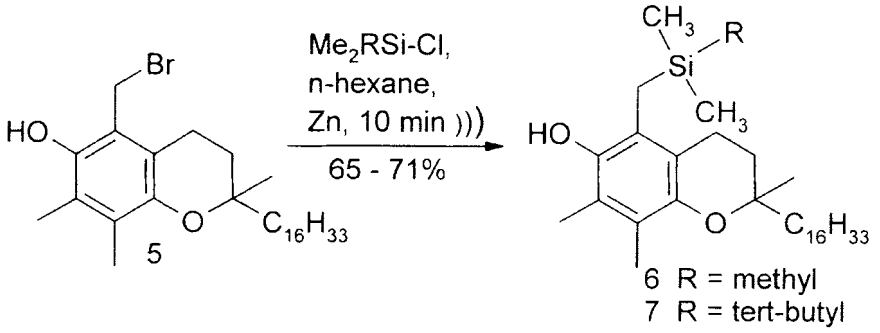


FIGURE 2

*S*-alkylthiouronium bromide by simple *S*-alkylation of thiourea did not succeed: an oily mixture consisting of the spiro-dimer (**3**) and minor amounts of the desired product was obtained. All efforts aiming at separating the product lead to its decomposition. Finally the thiouronium salt could be precipitated as the picrate at lower temperature of about $-10°C$ affording the *S*-(5a-α-tocopheryl)thiouronium picrate (**8**) as a bright yellow, waxy solid. This, at least, demonstrated that the synthesis of thiouronium salts of the 5a-α-tocopheryl moiety was possible. However, the use of the toxic picrate as the counter ion was a serious drawback, and so was the instability of **8**. The compound was only storable under inert atmosphere and rapidly decomposed upon treatment with base and even exposure to atmospheric oxygen. The main tocopherol-derived product of this decomposition was again the spiro-dimer (**3**) which was formed by elimination of the thiourea substituent *via* the *ortho*-quinone methide **2** as described above.

The use of *N*-acyl-thioureas provided a solution: reaction of 5a-bromo-α-tocopherol (**5**) with *N*-acetyl-thiourea and *N*-benzoyl-thiourea[5] produced *N*-ace-

TABLE I Reaction conditions for the sonochemically catalyzed reaction of 5a-bromo-α-tocopherol with trimethylsilyl chloride and zinc.

| *Ratio Toc-Br/ $Me_3Si$-Cl* | *Solvent* | *Product yield [%]* |
|---|---|---|
| 1:1 | methylene chloride | 19 |
| 1:1 | n-hexane | 32 |
| 1:5 | methylene chloride | 41 |
| 1:10 | methylene chloride | 38 |
| 1:10 | diethyl ether | 52 |
| 1:10 | toluene | 39 |
| 1:10 | methanol | 28 |
| 1:10 | n-hexane | 64 |
| >1:50 | n-hexane | 71 |

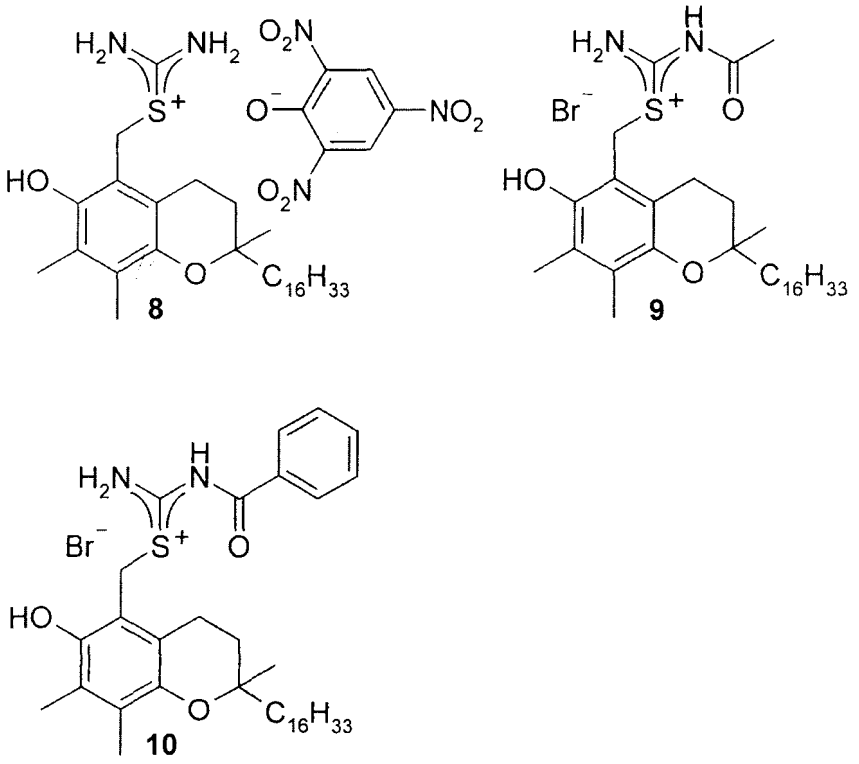


FIGURE 3

tyl-*S*-(5a-$\alpha$-tocopheryl)thiouronium bromide (**9**) and *N*-benzoyl-*S*-(5a-a-tocopheryl)thiouronium bromide (**10**) as off-white crystalline precipitates that could be refined by reprecipitation from acetonitrile/n-hexane. Carbon-13 NMR results showed that alkylation of the thiourea proceeded exclusively at the sulfur atom. Compounds **9** and **10** are stable towards air and can be indefinitely stored in an inert atmosphere. It should be mentioned that these substances are not only the first 5a-thio-substituted derivatives of vitamin E, they belong to the very small group of derivatives that are solids and not oils as $\alpha$-tocopherol itself.

The preparation of 5a-$\alpha$-tocopherylalkyl thioethers by reaction of 5a-bromo-$\alpha$-tocopherol (**5**) with thiols in a nucleophilic displacement did not succeed, not even extensive trials aimed at optimizing the reaction parameters were rewarded with preparatively practicable yields. The main pathway observed was the elimination of HBr from **5** and oxidation of the thiols to dithioethers by the intermediate *ortho*-quinone methide **2** which was in turn reduced to $\alpha$-tocopherol.

Apart from this reaction, more intricate side processes lead to the formation of a complex mixture of by-products. The reason for this erratic reaction be-

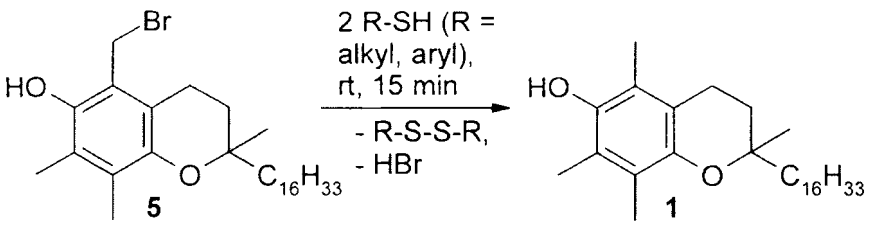


FIGURE 4

havior can certainly be seen in the presence of the highly redox-active tocopherol system in the presence of other easily oxidizable substances. In this case, formation of the *ortho*-quinone methide and its subsequent action as an oxidant are preferred over alternative reaction pathways. A similar behavior was ascertained for the 5a-$\alpha$-tocopheryl moiety and the cystin/cystein system,[2] and in the case of ascorbic acid.

The first tocopherol derivative with a phosphorus group at position 5a was obtained by reaction of 5a-bromo-$\alpha$-tocopherol (**5**) with triphenyl phosphine. The resulting product, 5a-$\alpha$-tocopheryltriphenyl phosphonium bromide **11**, precipitated as a white voluminous solid that is not filtrable and must be separated by centrifugation. The elimination of HBr from 5a-bromo-$\alpha$-tocopherol (**5**) with concomitant formation of the spiro-dimer **3** is a competitive process during the preparation of **11**. However, it can be almost completely suppressed by working at room temperature and quickly adding a solution of triphenyl phosphin to 5a-bromo-$\alpha$-tocopherol, but not *vice versa*.

As a pure substance, the suspension of 5a-$\alpha$-tocopheryltriphenyl phosphonium bromide (**11**) appears in a bright white color, a yellow discoloration indicates that larger amounts of spiro-dimer **3** have been formed. Compound **11** is stable towards acidic hydrolysis and temperatures up to 100°C as demonstrated by $^{31}P$ NMR experiments, but quickly darkens under decomposition when coming into contact with air or other oxidants. Thus, its applicability as a new vitamin E preparation will certainly be limited. Nevertheless, the compound proved to be a valuable intermediate for the preparation of novel tocopherol compounds.

Reaction of the phosphonium salt **11** with carboxylic acid chlorides catalyzed by triethyl amine leads to the furobenzopyrans **12–18** in yields between 53 and 81%.[6] The result in the case of substituted benzoic acids is slightly better than with acetic acid or cinnamic acid. In the case of chloroacetic acid no definite product was obtained. Only one COCl group of phthaloyl dichloride reacted in the expected manner, even with a large excess of the phosphonium salt. This might be attributable to steric repulsion between the two bulky tocopheryl side moieties that prevent the formation of the corresponding 1,4-

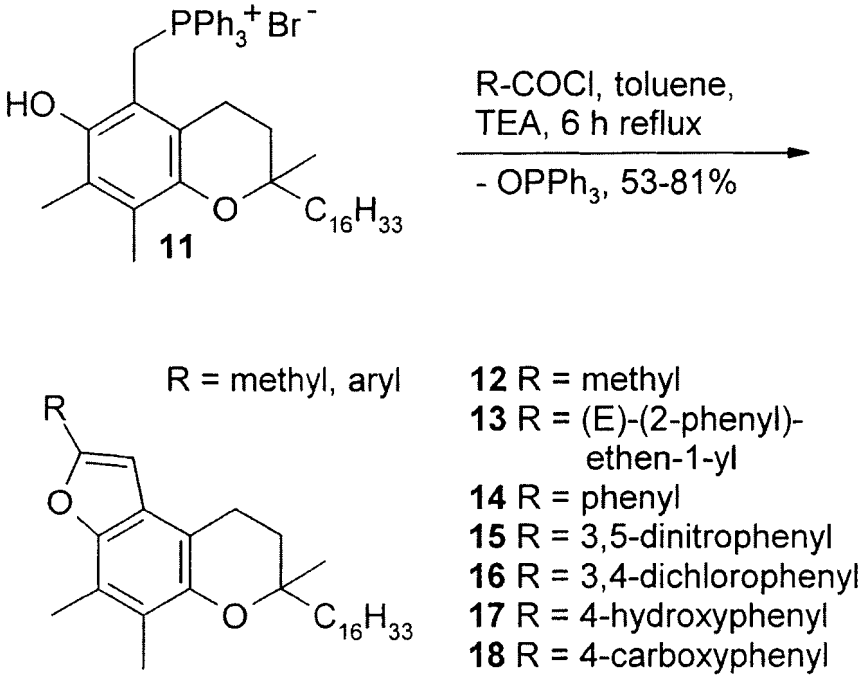


FIGURE 5

bis(pyrobenzofuranyl)benzene. The furobenzopyrans obtained by the reaction are crystalline solids or viscous oils depending on the carboxylic acid moiety used. The different starting materials, products and yields are shown in Table II.

## DISCUSSION

Utilization of ultrasound to accelerate chemical processes, and to improve the yields of heterogeneous reactions has been a subject of intensive studies,[7] especially in the case of metal-mediated reactions, such as the *Barbier* reaction

TABLE II Formation of novel furobenzopyrans 12–18 with tocopherol structure.

| *Carboxylic Acid Chloride* | *Product* | *Yield [%]* |
|---|---|---|
| cinnamoyl chloride | **12** | 54 |
| acetyl chloride | **13** | 51 |
| benzoyl chloride | **14** | 41 |
| 3,4-dinitrobenzoyl chloride | **15** | 81 |
| 4-chloro-benzoyl chloride | **16** | 72 |
| 4-hydroxy-benzoyl chloride | **17** | 57 |
| phthaloyl dichloride | **18** | 68 |

and the *Wurtz* coupling.[8] In our approach to 5a-trialkylsilyl-tocopherols we employed an effect that is usually referred to as "sonochemical switching".[9] This term implies that a reaction which can proceed either heterolytically or homolytically will be forced into a radical way by sonochemical catalysis. Applied to the reaction presented, heterolytic cleavage of the C-5a-Br bond of 5a-bromo-$\alpha$-tocopherol (**5**) is discriminated against the homolytic cleavage required for the *Wurtz* coupling with zinc and trialkylsilyl chloride. Analogous to similar sonochemically catalyzed reactions with metals[8] the formation of **6** and **7** supposedly proceeds mainly at the activated metal surface. Thus, almost no free radicals appear in the reaction mixture, single-electron intermediates are formed only in contact with the solid metal, and are there converted into products. This accounts for the unexpectedly high yields of the presented sonochemical catalyzed process. A large excess of silylating agent is crucial for suppressing the formation of tocopheryl dimers by recombination of two tocopheryl radicals. Also, protic solvents or solvents with hydrogens that can readily be abstracted will react with these radicals under formation of $\alpha$-tocopherol. Inert solvents are thus a prerequisite for the reaction to proceed in high yields. The best results were obtained with n-hexane.

The formation of a relatively stable 5a-$\alpha$-tocopheryl-triphenylphosphonium salt and its conversion to benzofurans, such as **12–18**, is a major step towards general methods to functionalize tocopherols. The TEA-catalyzed reaction of 5a-$\alpha$-tocopheryl-triphenyl phosphonium bromide **11** with carboxylic acid chlorides is a two-step process consisting of the formation of the corresponding tocopheryl ester, followed by an intramolecular *Wittig* reaction. Replacement of triethyl amine ($pK_B$ = 3.25) by pyridine ($pK_B$ = 8.75) allows only the first step to proceed: the tocopheryl carboxylic esters are formed, but pyridine is too weak a base to catalyze the subsequent *Wittig* reaction. The formation of the furobenzopyrans eventually resumes upon addition of triethyl amine.

In almost all of the traditional vitamin E preparations $\alpha$-tocopherol is applied as an ether or ester. After hydrolysis of the C-O-C bond the tocopherol molecule is released as an isolated molecule, being no longer connected to or interacting with the former molecular counterpart. In contrast, after hydrolysis of the C-O-C bond in the novel furobenzopyrans and derived compounds alike, the tocopherol moiety remains linked *via* C-5a to the second chemical structure that might be a biologically active compound itself. This opens the way to a conceivable application of tocopherol as a lipophilic carrier for active substances with slow-release features.

Besides these unexpected advantageous properties, the newly prepared compounds will serve their initially intended purpose: to provide more comprehensive knowledge about the chemical behavior of substituted tocopherols. The

compounds exhibit the crucial requirement, a 5a-substituent that is less electronegative than Br, OR or $NR_2$, and they are sufficiently stable to be able to undergo extensive testing of their redox properties and reaction behavior.

## EXPERIMENTAL

$^1H$ NMR spectra were recorded at 300 MHz, $^{13}C$ NMR spectra at 75 MHz, $^{31}P$ NMR spectra at 121 MHz on a Bruker AC-300P, $^{29}Si$ NMR spectra at 99 MHz on a Bruker DRX-500, in $CDCl_3$ with TMS as the internal standard unless otherwise stated. $^{13}C$ peaks were assigned by means of DEPT (**D**istortionless **E**nhancement by **P**olarization **T**ransfer) and GD (**G**ated **D**ecoupling). The $\delta$-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 affected by modifications of the chroman structure and insignificant for the identification of the molecule concerned.[10] GCMS was performed on a Hewlett Packard (5890 Series II, EI, 70 eV, ITD). Elemental analyses have been carried out at Dresden University of Technology, Institute if Organic Chemistry. For sonication experiments a water-bath sonifier (Elma Transsonic 460, 35 kHz, 60W) was used. The numbering of the carbon atoms and the nomenclature for tocopherol derivatives proposed by the IUPAC[11] have been used throughout.



### *5a-Trimethylsilyl-α-tocopherol (6).*

In an inert atmosphere, a mixture of 5a-bromo-$\alpha$-tocopherol (3.00 mmol, 1.529 g), $Me_3SiCl$ (60.00 mmol, 6.518 g), zinc powder (5 mmol, 0.327 g) and 10 mL of dry n-hexane was sonicated in a tightly closed one-neck flask for 10 min at room temperature. Solids were filtered off, then the solvent and the excess of silating agent were removed under reduced pressure. The oily residue was dissolved in 20 mL of n-hexane and purified by adsorption on anhydrous aluminum oxide to provide pure **6** as a yellowish oil (1.070 g, 71%). Anal. Calcd. for $C_{32}H_{58}O_2Si$ (502.89): C, 76.43; H, 11.62. Found: C, 76.33; H, 11.78. $^1H$ NMR ($CDCl_3$): $\delta$ 0.15 (9H, s, $Si(CH_3)_3$), 1.72 (2H, m, $^3CH_2$), 1.92 (2H, s, $^{5a}CH_2Si$), 2.10; 2.11 (2 × 3H, 2 × s, $^{7a}CH_3$ and $^{8b}CH_3$), 2.65 (2H, t, $^3J$ = 7.0 Hz, $^4CH_2$), 5.80 (1H, br, O*H*). $^{13}C$ NMR: $\delta$ 0.9 ($Si(CH_3)_3$), 12.1 ($^{8b}C$), 12.2 ($^{7a}C$), 13.2 ($^{5a}C$), 19.4 ($^4C$), 23.6 ($^{2a}C$), 31.2 ($^3C$), 75.1 ($^2C$), 118.1; 120.1; 121.9; 127.1; 145.7; 147.2 ($^{Ar}C$). $^{29}Si$ NMR ($CDCl_3$): $\delta$ 3.11.[12]

***5a*-tert-Butyldimethylsilyl-α-tocopherol (7).**

The compound was prepared according to the procedure described for the synthesis of **6** with $^{t}BuMe_2SiCl$ (10 mmol, 1.507 g) instead of $Me_3SiCl$. Yield: 1.275 g (78%), light-brown oil. Anal. Calcd. for $C_{35}H_{64}O_2Si$ (544.97): C, 77.14; H, 11.84. Found: C, 77.32; H, 11.78. $^1H$ NMR ($CDCl_3$): $\delta$ 0.42 (6H, s, $Si(CH_3)_2$), 0.78 (9H, s, $C(CH_3)_3$), 1.72 (2H, m, $^3CH_2$), 1.92 (2H, s, $^{5a}CH_2Si$), 2.11; 2.12 (2 × 3H, 2 × s, $^{7a}CH_3$ and $^{8b}CH_3$), 2.62 (2H, t, $^3J$ = 7.0 Hz, $^4CH_2$), 4.30 (1H, br, O*H*). $^{13}C$ NMR: $\delta$ −1.4 ($Si(CH_3)_2$), 6.4 ($^{5a}C$), 12.1 ($^{8b}C$), 12.2 ($^{7a}C$), 19.6 ($^4C$), 23.5 ($^{2a}C$), 21.1 ($C(CH_3)_3$), 24.8 ($C(CH_3)_3$), 31.1 ($^3C$), 74.9 ($^2C$), 118.1; 120.1; 121.9; 127.1; 145.7; 147.2 ($^{Ar}C$). $^{29}Si$ NMR ($CDCl_3$): $\delta$ 7.52.[12]

**S-(*5a*-α-tocopheryl)thiouronium picrate (8).**

A solution of 5a-bromo-α-tocopherol (3.00 mmol, 1.529 g) and thiourea (3.20 mmol, 0.244 g) in 5 mL of aqueous ethanol (ethanol/water: v/v = 4:1) was warmed to 50°C for 1 h and then cooled to room temperature. Picric acid (3.20 mmol, 0.733 g) in 5 mL of ethanol/water (v/v = 1:1) was added, and the solution was cooled to −10°C. *S*-(5a-α-tocopheryl)thiouronium picrate (0.925 g, 42%), a yellow solid, was separated by filtration, washed with 10 mL of n-hexane and dried under reduced pressure. At room temperature, **8** is a yellow wax that has to be stored under exclusion of oxidants. Anal. Calcd. for $C_{36}H_{55}N_5O_9S$ (733.92): C, 58.92; H, 7.55; N, 9.54; S, 4.37. Found: C, 58.82; H, 7.71; N, 9.48; S, 4.44. $^1H$ NMR (DMSO-$d_6$/$CDCl_3$ = 1:1): $\delta$ 1.73 (2H, m, $^3CH_2$), 1.99; 2.06 (2 × 3H, 2 × s, $^{7a}CH_3$ and $^{8b}CH_3$), 2.65 (2H, t, $^3J$ = 7.0 Hz, $^4CH_2$), 4.36 (2H, d, $^{5a}CH_2$), 8.27; 8.78; 9.07 (4H, b, O*H*), 8.64 (2H, s, $^{Ar}CH$ in picrate). $^{13}C$ NMR: $\delta$ 11.7 ($^{8b}C$), 12.3 ($^{7a}C$), 19.1 ($^4C$), 23.7 ($^{2a}C$), 27.2 ($^{5a}C$), 30.7 ($^3C$), 74.9 ($^2C$), 116.0; 116.7; 123.4; 125.0; 144.7; 145.1 ($^{Ar}C$ in tocopherol), 124.1; 125.3; 141.2; 170.8 ($^{Ar}C$ in picrate), 161.1 (C=S).

**N-*Acetyl*-S-(*5a*-α-tocopheryl)thiouronium bromide (9).**

To a solution of *N*-acetylthiourea (3 mmol, 0.354 g) in 15 mL of dry acetonitrile was added 5a-bromo-α-tocopherol (3.00 mmol, 1.529 g) in 10 mL of n-hexane. The solution was warmed to 50°C for 2 h and cooled. The off-white precipitate that formed was collected to give 1.62 g (86%) of **9**, mp. 64–68°C. An analytical sample (mp. 68–69°C) was obtained by recrystallization from an actonitrile/n-hexane mixture (v/v = 1:1). Anal. Calcd. for $C_{32}H_{55}N_2O_3BrS$ (627.76): C, 61.23; H, 8.83; N, 4.46; S, 5.11; Br, 12.73. Found: C, 61.21; H, 8.72; N, 4.67;

S, 5.24; Br 12.86. $^1$H NMR ($CDCl_3$): $\delta$ 1.75 (2H, m, $^3CH_2$), 2.06; 2.20 (2 × 3H, 2 × s, $^{7a}CH_3$ and $^{8b}CH_3$), 2.32 (3H, s, $CH_3CO$), 2.63 (2H, t, $^3J$ = 7.0 Hz, $^4CH_2$), 4.33 (2H, m, $^{5a}CH_2$), 7.33; 10.41; 10.72; 12.52 (4H, 4 × s, O*H*). $^{13}$C NMR: $\delta$ 12.2 ($^{8b}$C), 13.5 ($^{7a}$C), 20.2 ($^4$C), 23.6 ($^{2a}$C), 24.6 ($CH_3CO$), 28.6 ($^{5a}$C), 31.0 ($^3$C), 75.2 ($^2$C), 116.4; 117.3; 124.5; 127.6; 142.9; 147.3 ($^{Ar}$C), 171.6 (C=S), 173.0 (C=O).

### N-*Benzoyl-S-(5a-α-tocopheryl)thiouronium bromide (10).*

The compound was prepared according to the procedure described for the synthesis of **9** with *N*-benzoylthiourea instead of *N*-acetylthiourea. Yield: 1.696 g (82%), white powder, mp. 76–78°C. Anal. Calcd. for $C_{37}H_{57}N_2O_3BrS$ (689.83): C, 64.42; H, 8.33; N, 4.06; S, 4.65; Br, 11.58. Found: C, 64.38; H, 8.31; N, 4.11; S, 4.76; Br 11.65. $^1$H NMR ($CDCl_3$): $\delta$ 1.80 (2H, m, $^3CH_2$), 2.08; 2.23 (2 × 3H, 2 × s, $^{7a}CH_3$ and $^{8b}CH_3$), 2.73 (2H, t, $^3J$ = 7.0 Hz, $^4CH_2$), 4.36 (2H, m, $^{5a}CH_2$), 7.01; 10.48; 11.10; 12.52 (4H, 4 × s, O*H*), 7.50 (2H, m, $^{Ar}CH$), 7.62 (1H, m, $^{Ar}CH$), 8.30 (2H, m, $^{Ar}CH$). $^{13}$C NMR: $\delta$ 12.2 ($^{8b}$C), 13.4 ($^{7a}$C), 20.3 ($^4$C), 23.7 ($^{2a}$C), 28.7 ($^{5a}$C), 31.1 ($^3$C), 75.1 ($^2$C), 116.1; 117.4; 123.6; 127.5; 142.8; 147.2 ($^{Ar}$C in tocopherol), 129.0; 129.3; 129.6; 134.4 ($^{Ar}$C in benzoyl), 166.0; 175.0 (C=O, C=S).

### *5a-α-Tocopheryltriphenylphosphonium bromide (11).*

A solution of triphenylphosphine (3 mmol, 0.787 g) in 20 mL of n-hexane was quickly added to a solution of 5a-bromo-α-tocopherol (3 mmol, 1.529 g) in 10 mL of n-hexane at room temperature. The mixture was stirred for 2 h. After approximately 10 min a white voluminous precipitate of **11** appeared which was used for subsequent reactions without further working-up, assuming quantitative yields for further transformations. For NMR spectroscopy, a sample of the precipitate was separated by centrifugation, washed with n-hexane and dried quickly under reduced pressure. MALDI-TOF-MS (gentisic acid as the matrix): 691 [5a-α-tocopheryl triphenylphosphonium cation]. $^1$H NMR ($CDCl_3$): $\delta$ 1.52 (2H, m, $^3CH_2$), 1.91 (3H, s, $^{8b}CH_3$), 2.05 (3H, d, $^{7a}CH_3$), 2.32 (2H, t, $^4CH_2$, $^3J$ = 7 Hz), 4.80 (2H, m, $^{5a}CH_2$), 7.32–7.64 (15H, m, $^{Ar}CH$). $^{13}$C NMR: $\delta$ 11.7 ($^{8b}$C), 13.1 ($^{7a}$C), 20.7 ($^4$C), 23.2 ($^{2a}$C), 25.3 ($^{5a}$C, d, $^1J$ = 47 Hz), 31.2 ($^3$C), 74.3 ($^2$C), 112.3 ($^{4a}$C, d, $^3J$ = 9.5 Hz); 116.7 ($^5$C, d, $^2J$ = 5.4 Hz); 125.0 ($^7$C, d, $^4J$ = 4.1 Hz); 126.0 ($^8$C, d, $^5J$ = 4.9 Hz); 145.7 ($^{8a}$C, d, $^4J$ = 3.5 Hz); 146.4 ($^6$C, d, $^3J$ = 6.3 Hz) ($^{Ar}$C in tocopherol), 118.8 (d, $^1J$ = 84.4 Hz); 129.4 (d, $^3J$ = 12.4 Hz); 134.1 (d, $^2J$ = 9.6 Hz) 134.1 (s) ($^{Ar}$C in phenyl). $^{31}$P NMR ($CDCl_3$): $\delta$ 20.99.[13]

*General procedure for the preparation of furobenzopyrans from 5a-α-tocopheryl triphenylphosphonium bromide (11) and carboxylic acid chlorides.* The suspension of 5a-α-tocopheryl triphenylphosphonium bromide **(11)** in 30 mL of n-hexane as obtained according to the above procedure was taken to a volume of approximately 10 mL by evaporation of the solvent under reduced pressure. Toluene (20 mL), 3.0 mmol of the respective carboxylic acid chloride, and 10 mmol of triethyl amine were added. The mixture was stirred for 10 min without heating, refluxed for 6 h, and then cooled to room temperature. n-Hexane (20 mL) was added, the triethylammonium salt was separated by filtration, and remaining solvents were removed *in vacuo*. The resulting product was recrystallized from aqueous ethanol, or chromatographed on aluminum oxide, after eluting byproducts with n-hexane, the product was eluted with n-hexane/diethyl ether (v/v = 5:1).



***2,4,5,7-Tetramethyl-7-(4,8,12-trimethyltridecyl)-8,9-dihydro-7H-furo[3,2-f]chromene (12).***

Anal. Calcd. for $C_{31}H_{50}O_2$ (454.73): C, 81.88; H, 11.08. Found: C, 81.89; H, 10.99. $^1$H NMR ($CDCl_3$): δ 1.78 (2H, m, $^3CH_2$), 2.12; 2.23 (2 × 3H, 2 × s, $^{7a}CH_3$ and $^{8b}CH_3$), 2.35 (1H, d, $^4J$ = 1.0 Hz, $CH_3C=$), 2.72 (2H, t, $^3J$ = 7.0 Hz, $^4CH_2$), 6.89 (1H, q, $^4J$ = 1.0 Hz, $^{5a}CH$). $^{13}$C NMR: δ 12.1; 12.2 ($^{8b}$C; $^{7a}$C), 17.8 ($CH_3C=$), 20.2 ($^4$C), 23.6 ($^{2a}$C), 31.4 ($^3$C), 75.1 ($^2$C), 105.1; 148.3 ($^{Ar}$C in furan), 116.4; 118.2; 123.6; 125.1; 145.5; 146.9 ($^{Ar}$C in tocopherol).

***4,5,7-Trimethyl-2-[(E)-2-phenyl-1-ethenyl]-7-(4,8,12-trimethyltridecyl)-8,9-dihydro-7H-furo-[3,2-f]-chromene (13).***

Anal. Calcd. for $C_{38}H_{54}O_2$ (542.84): C, 84.08; H, 10.03. Found: C, 83.98; H, 10.22. $^1$H NMR ($CDCl_3$): δ 1.78 (2H, m, $^3CH_2$), 2.12; 2.14 (2 × 3H, 2 × s, $^{7a}CH_3$ and $^{8b}CH_3$), 2.68 (2H, t, $^3J$ = 7.0 Hz, $^4CH_2$), 6.96 (1H, dd, $^3J$ = 16.8 Hz, $^5J$ = 3.2 Hz, ϕ-C(*H*) = CH), 7.00 (1H, m, $^{Ar}CH$), 7.05 (1H, d, $^5J$ = 3.3 Hz, $^{5a}CH$), 7.51 (1H, d, $^3J$ = 16.8 Hz, ϕ-C(H) = C*H*), 7.21–7.26 (2H, m, $^{Ar}CH$), 7.38–7.42 (2H, m, $^{Ar}CH$). $^{13}$C NMR: δ 11.9; 12.1 ($^{8b}$C; $^{7a}$C), 20.0 ($^4$C), 23.6 ($^{2a}$C), 31.4 ($^3$C), 75.1 ($^2$C), 104.2; 142.8 ($^{Ar}$C in furan), 116.3; 117.2; 124.1; 125.9; 145.8; 148.7 ($^{Ar}$C in tocopherol), 118.2; 127.4; 128.8; 129.2; 130.4; 138.4 ($^{Ar}$C in cinnamyl).

***4,5,7-Trimethyl-2-phenyl-7-(4,8,12-trimethyltridecyl)-8,9-dihydro-7H-furo[3,2-f]chromene (14).***

Anal. Calcd. for $C_{36}H_{52}O_2$ (454.73): C, 83.67; H, 10.14. Found: C, 83.81; H, 10.29. $^1$H NMR ($CDCl_3$): $\delta$ 1.82 (2H, m, $^3CH_2$), 2.16; 2.28 (2 × 3H, 2 × s, $^{7a}CH_3$ and $^{8b}CH_3$), 2.78 (2H, t, $^3J$ = 7.0 Hz, $^4CH_2$), 6.84 (1H, s, $^{5a}CH$), 7.12–7.28 (4H, m, $^{Ar}CH$), 7.55 (1H, m, $^{Ar}CH$). $^{13}$C NMR: $\delta$ 11.9; 12.1 ($^{8b}$C; $^{7a}$C), 19.9 ($^4$C), 23.7 ($^{2a}$C), 31.1 ($^3$C), 75.5 ($^2$C), 103.9; 148.0 ($^{Ar}$C in furan), 117.5; 118.3; 120.3; 124.9; 146.3; 147.1 ($^{Ar}$C in tocopherol), 128.8; 129.3; 130.1; 130.9 ($^{Ar}$C in phenyl).

***2-(3,5-Dinitrophenyl)-4,5,7-trimethyl-7-(4,8,12-trimethyltridecyl)-8,9-dihydro-7H-furo[3,2-f]-chromene (15).***

Anal. Calcd. for $C_{36}H_{50}N_2O_6$ (606.80): C, 71.26; H, 8.31; N, 4.62. Found: C, 71.33; H, 8.40; N, 4.58. $^1$H NMR ($CDCl_3$): $\delta$ 1.88 (2H, m, $^3CH_2$), 2.22; 2.46 (2 × 3H, 2 × s, $^{7a}CH_3$ and $^{8b}CH_3$), 2.87 (2H, t, $^3J$ = 7.0 Hz, $^4CH_2$), 7.21 (1H, s, $^{5a}CH$), 8.83 (3H, s, $^{Ar}CH$). $^{13}$C NMR: $\delta$ 12.0; 12.1 ($^{8b}$C; $^{7a}$C), 19.7 ($^4$C), 23.8 ($^{2a}$C), 30.6 ($^3$C), 76.0 ($^2$C), 104.6; 149.2 ($^{Ar}$C in furan), 109.3; 118.6; 124.3; 125.6; 148.3; 149.4 ($^{Ar}$C in tocopherol), 116.3; 123.4; 134.4; 148.9 ($^{Ar}$C in phenyl).

***2-(4-Chlorophenyl)-4,5,7-trimethyl-7-(4,8,12-trimethyltridecyl)-8,9-dihydro-7H-furo[3,2-f]-chromene (16).***

Anal. Calcd. for $C_{36}H_{51}ClO_2$ (551.25): C, 78.44; H, 9.32; Cl, 6.43. Found: C, 78.49; H, 9.28; Cl, 6.58. $^1$H NMR ($CDCl_3$): $\delta$ 1.82 (2H, m, $^3CH_2$), 2.18; 2.31 (2 × 3H, 2 × s, $^{7a}CH_3$ and $^{8b}CH_3$), 2.78 (2H, t, $^3J$ = 7 Hz, $^4CH_2$), 4.35 (1H, b, OH), 6.95 (1H, s, $^{5a}CH$), 7.48 (4H, m, $^{Ar}CH$). $^{13}$C NMR: $\delta$ 12.0; 12.1 ($^{8b}$C; $^{7a}$C), 19.9 ($^4$C), 23.7 ($^{2a}$C), 30.8 ($^3$C), 75.7 ($^2$C), 104.3; 147.9 ($^{Ar}$C in furan), 117.5; 118.3; 120.3; 124.9; 146.3; 147.1 ($^{Ar}$C in tocopherol), 126.4; 128.7; 131.2; 133.8 ($^{Ar}$C in phenyl).

***2-(4-Hydroxyphenyl)-4,5,7-trimethyl-7-(4,8,12-trimethyltridecyl)-8,9-dihydro-7H-furo[3,2-f]-chromene (17).***

Anal. Calcd. for $C_{36}H_{52}O_3$ (532.80): C, 81.15; H, 9.84. Found: C, 81.22; H, 10.01. $^1$H NMR ($CDCl_3$): $\delta$ 1.80 (2H, m, $^3CH_2$), 2.13; 2.20 (2 × 3H, 2 × s, $^{7a}CH_3$ and $^{8b}CH_3$), 2.75 (2H, t, $^3J$ = 7.0 Hz, $^4CH_2$), 6.88 (1H, s, $^{5a}CH$), 7.10 (2H, m, $^{Ar}CH$), 7.18 (2H, m, $^{Ar}CH$). $^{13}$C NMR: $\delta$ 12.1; 12.2 ($^{8b}$C; $^{7a}$C), 20.1

($^{4}$C), 23.7 ($^{2a}$C), 31.0 ($^{3}$C), 74.9 ($^{2}$C), 104.5; 147.5 ($^{Ar}$C in furan), 118.1; 118.3; 119.8; 125.1; 145.9; 147.2 ($^{Ar}$C in tocopherol), 118.4; 125.2; 125.6; 152.6 ($^{Ar}$C in phenyl).

### *4-[-4,5,7-trimethyl-7-(4,8,12-trimethyltridecyl)-8,9-dihydro-7*H*-furo[3,2-f]-chromene-2-yl]-benzoic acid (18).*

Anal. Calcd. for $C_{37}H_{52}O_4$ (560.81): C, 79.24; H, 9.35. Found: C, 79.09; H, 9.44. $^{1}$H NMR ($CDCl_3$): $\delta$ 1.82 (2H, m, $^{3}CH_2$), 2.15; 2.17 (2 × 3H, 2 × s, $^{7a}CH_3$ and $^{8b}CH_3$), 2.75 (2H, t, $^{3}J$ = 7.0 Hz, $^{4}CH_2$), 7.04 (1H, s, $^{5a}CH$), 7.12 (2H, m, $^{Ar}CH$), 7.34 (2H, m, $^{Ar}CH$), 10.86 (1H, b, O*H*). $^{13}$C NMR: $\delta$ 12.0; 12.1 ($^{8b}$C; $^{7a}$C), 19.9 ($^{4}$C), 23.7 ($^{2a}$C), 30.8 ($^{3}$C), 75.5 ($^{2}$C), 102.9; 148.4 ($^{Ar}$C in furan), 113.2; 118.3; 121.7; 125.4; 147.2; 147.9 ($^{Ar}$C in tocopherol), 126.8; 128.1; 132.0; 138.1 ($^{Ar}$C in phenyl); 168.3 (COOH).



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