Pergamon

SCIENCE DIRECT®

Tetrahedron 59 (2003) 3231–3235

TETRAHEDRON

Novel tocopheryl compounds. Part 15: One-pot formation of furotocopheryl derivatives☆

Christian Adelwöhrer,[a] Thomas Rosenau,[a,*] Wolfgang H. Binder[b] and Paul Kosma[a]

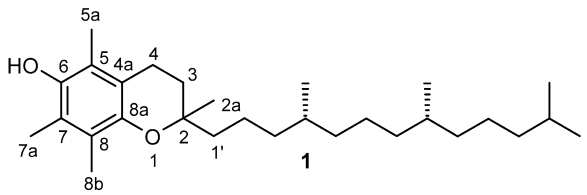
[a]*Institute of Chemistry, University of Agricultural Sciences, Muthgasse 18, A-1190 Vienna, Austria*
[b]*Institute of Applied Synthetic Chemistry, University of Technology Vienna/163/MC, A-1040 Vienna, Austria*

Received 17 December 2002; revised 24 February 2003; accepted 17 March 2003

Abstract—Reaction of tocopheryl bromide **2a** or chromanyl bromide **2b** with triphenyl phosphine produced phosphomium salt intermediates (**3a**–**b**), which further reacted with acyl chlorides to novel furotocopherol compounds **4**–**11** in good yields. The cyclization proceeded according to a two step esterification–Wittig mechanism. Similarly, furotocopheryl dimer **12** was prepared starting from oxalyl chloride. The coupling of tocopheryl phosphonium salt **3a** onto modified polystyrene provided a new, vitamin E-loaded resin.

1. Introduction

α-Tocopherol (**1**), the component of vitamin E with the highest biological activity, is known to be one of the most effective chain breaking phenolic antioxidants.[1] It reacts rapidly with a variety of radicals to form the relatively stable α-tocopheroxyl radical, which is either reduced back to α-tocopherol, or further oxidized to quinoid structures. The exceptional high efficiency of vitamin E as phenolic antioxidant has been attributed to substituent effects,[2] and to stereoelectronic influences[3] as well.



Especially for packaging in the food industry, esters of α-tocopherol are used as stabilizers for plastics and other synthetic polymers. These vitamin E derivatives are advantageous because of their full physiological compatibility, but a wider application is hampered by three major drawbacks. First, some fabrication steps, such as extrusion, pressing or melt processing, cause severe problems with phase-separation of the oily stabilizer and demixing, second, their thermostability is low, and third, the action time is rather short, as the esters are readily cleaved releasing the phenol as the active antioxidant. These difficulties stimulated the search for novel tocopherol-based antioxidants, which are covalently linked to polymeric structures and possess phenolic hydroxyls protected by more stable structures than the labile ester linkages. Such derivatives would remain intimately mixed in the polymer matrix during processing, would be more resistant towards thermal stress, and release the antioxidatively acting free phenol much slower, thus increasing the long-term efficiency of the stabilizer.

In this work, the synthesis and comprehensive analytical characterization of novel functional antioxidants—furotocopherol derivates, a furotocopheryl dimer and furotocopherols linked to a polystyrene matrix—is described, which represent a first step toward this goal.

2. Results and discussion

The well known formation of 5a-bromo-α-tocopherol (**2a**) by reaction of α-tocopherol (**1**) with elemental bromine proceeds quantitatively according to a two-step mechanism: oxidation and subsequent addition of hydrogen bromide to the intermediate *ortho*-quinone methide.[4] The tocopheryl bromide was readily converted into the triphenyl phosphonium salt **3a**, which started to precipitate within 10 min from *n*-hexane, giving complete conversion after about 2 h. Similar to other 5a-substituted tocopherols, the phosphonium salt is rather labile, so that heating above 40°C should be avoided. Best results were obtained if **3** was not isolated, but prepared in situ and immediately employed in further reactions.

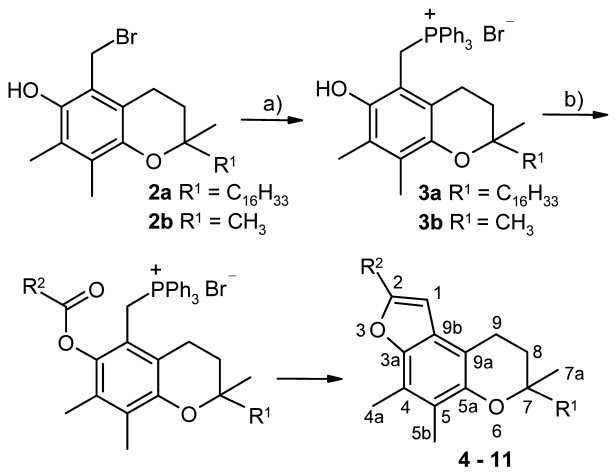
Reaction of the phosphonium salt with acyl chlorides in dry, refluxing toluene[5] containing a threefold excess of auxiliary

☆ See ref. 9.

Keywords: furotocopheryl derivatives; cyclization; vitamin E; tocopherol.

* Corresponding author. Tel.: +43-1-36006-6071; fax: +43-1-36006-6059; e-mail: trosenau@edv2.boku.ac.at

0040–4020/03/$ - see front matter
doi:10.1016/S0040-4020(03)00426-5



a) PPh_3, *n*-hexane, r.t., b) R^2-COCl, PhMe, TEA, reflux
for R^1 and R^2 see Table 1

Scheme 1. Formation reaction of furotocopherols **4**–**11**.

base (TEA or NaH) provided furotocopheryl derivatives **4**–**11** in fair to good yields (Scheme 1). The reaction proceeded according to a two-step process consisting of esterification of the phenolic hydroxyl group followed by an intramolecular *Wittig*-type reaction. The auxiliary base facilitates both the acylation reaction and the intramolecular cyclization. By employing different acyl chlorides, the 2-substituents of the stable 5-membered furan ring can be varied (Scheme 1).[6]

This one-pot conversion is equally feasible with chroman-6-ols—compounds lacking the isoprenoid side chain, which are frequently used as tocopherol model compounds. The yields are generally comparable to those in the tocopherol group; one example, 2-phenyl-furochroman **6**, is given in Table 1. Also the reaction with oxalyl chloride as a bifunctional acid chloride proceeded smoothly providing the furotocopheryl dimer **12**.

To test the furotocopherol formation on a polymeric support, polymer-bound carboxyl groups, in the form of a polystyrene Merrifield resin containing 0.88 mmol/g carboxyl groups, were converted into acid chloride groups by treatment with $SOCl_2$. Further reaction with phosphonium salt **3a** provided a novel tocopherol-loaded resin with possible applications as thermostable, extrudable polymer stabilizer. The presence of tocopheryl moieties on the polymer beads was confirmed by high resolution MAS

Table 1. Synthesis and yields of furotocopherols **4**–**13**

Compound	R1	R2	Yield (%)[a]
4	$C_{16}H_{33}$	Methyl	61
5	$C_{16}H_{33}$	Phenyl	55
6	CH_3	Phenyl	55
7	$C_{16}H_{33}$	2-Nitrophenyl	57
8	$C_{16}H_{33}$	Vinyl	45
9	$C_{16}H_{33}$	1-Phenylethenyl	67
10	$C_{16}H_{33}$	Methoxymethyl	62
11	$C_{16}H_{33}$	*tert*-Butyl	51
12	$C_{16}H_{33}$	Furotocopheryl	46
13	$C_{16}H_{33}$	Polystyrene resin	See text

[a] Isolated yields.

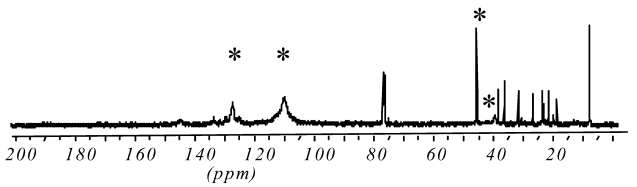
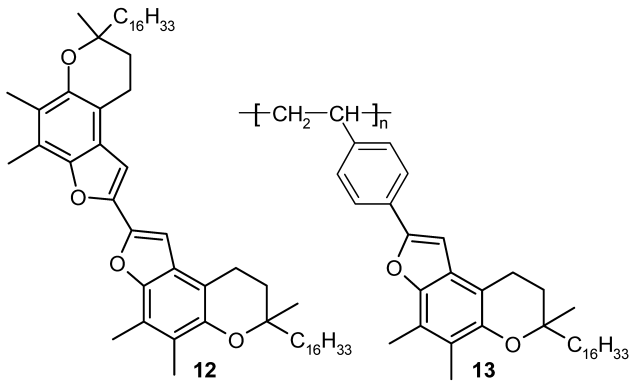


Figure 1. Gel ^{13}C NMR of furotocopherol loaded polystyrene resin **13**. Stars mark resonances of the resin.



NMR, see Figure 1. This method has been found to be useful in monitoring reactions conducted directly on the resin material without cleavage from the resin.[7] Critical is the use of a solvent, which allows a good swelling of the resin material.[8] In this work, $CDCl_3$ as the swelling solvent and spinning rates of 4000 Hz to minimize resonances from the resin material were used. The observed ^{13}C NMR resonances of the isoprenoid side chain in polymer-bound furotocopherol **13** are identical to those of monomeric furotocopherols. Due to signal overlap with the resonances from the Kel-F spacer and reduced mobility an assignment in the aromatic region was not possible. All other relevant resonances in the aliphatic region, however, are in strong accordance with the corresponding solution spectrum of **12**. Even though quantitation of the load cannot be achieved by this method, chemical identity of the vitamin E moiety and the fixation to the resin could be unambiguously proven.

All furotocopheryl derivatives were purified by column chromatography (cf. Section 3) at least two times to obtain analytically pure products. In contrast to tocopheryl esters, which release the free tocopherol quite readily, the furotocopherols represent derivatives with a much more stable form of protection for the hydroxyl group. Future tests must reveal whether this property makes them efficient stabilizers with long-term antioxidative action. Furotocopherol derivatives with conjugated double bonds at 2-position are strongly fluorescent and light sensitive. They are even unstable when stored for prolonged times at −78°C in the dark. It will be tested if vinyl compound **8** and styrene derivative **9** can be co-polymerized, which would provide novel functional polymers with chemically attached, ‘on-line’ stabilizer functions.

In summary, the synthesized furotocopherols represent vitamin E derivatives, in which the tocopherol structure is linked to other moieties by stable, non-hydrolyzable carbon–carbon bonds extending from C-5a. In addition, the protection of the phenolic hydroxyl group in the

tocopherol moiety is much more stable than in conventionally used tocopheryl esters. These properties render the novel furo-derivatives promising as stabilizers with long-term efficiency, possibly applicable either as additives or in co-polymerized form.

3. Experimental

All chemicals were commercially available. The Merryfield resin used was obtained from Rapp-Polymer, Germany (particle size 200–400 mesh, 1% DVB cross-linked, 0.88 mmol/g carboxyl groups). Thin layer chromatography (TLC) was performed on silica gel 60 plates (5×10 cm, 0.25 mm) with fluorescence detection under UV light at 254 nm. Flash column chromatography was performed on silica gel G60 (40–63 μm). Melting points, determined on a Kofler-type micro hot stage with Reichert-Biovar microscope, are uncorrected. ^{1}H NMR spectra were recorded at 300 MHz, ^{13}C NMR spectra at 75.47 MHz with $CDCl_3$ or DMSO-d_6 as the solvents and TMS as the internal standard. Data are given in ppm. ^{13}C peaks were assigned by means of APT, HMQC and HMBC spectra. Resonances of the isoprenoid side chain of tocopherols are not influenced by modifications of the chroman ring, and are therefore not listed; 'd.i.' denotes peaks with double intensity. High resolution MAS NMR measurements were carried out on a Bruker DRX-400 with a 4 mm gel-phase probe-head. Samples were prepared by weighing 100 mg of resin into a small vial and adding approximately 1 mL of $CDCl_3$. After equilibration (about 1 h), excess $CDCl_3$ was removed and the swollen resin was filled into 4 mm zirconia rotors. After adding a small drop of $CDCl_3$ in excess the rotor was closed with a Kel-F screw to avoid liquid leaking out during spinning, and subsequently closed with the rotor cap. The rotors were spun at 4000 Hz and ^{13}C spectra were recorded in the direct mode with $CDCl_3$ as lock and internal standard. FT-IR spectra were recorded on a Bruker Equinox-55 spectrometer; data are given in cm^{-1}. All new compounds exhibited satisfactory elemental analysis data.

3.1. General procedure for the bromination reaction

To a solution of α-tocopherol (**1**) or the model compound 2,2,5,7,8-pentamethylchromanol chromanol in dry *n*-hexane (50 mL) a solution of bromine (1.1 equiv.) in *n*-hexane (20 mL) was added at once at room temperature. The mixture was stirred for 2 h. Solvent, remaining bromine and physically dissolved HBr were removed in vacuo at room temperature with the water bath temperature not exceeding 40°C. The products, **2a** and **2b**, respectively, were obtained in quantitative yield.

3.1.1. 5-Bromomethyl-3,4-dihydro-2,7,8-trimethyl-2-(4,8,12-trimethyltridecyl)-2*H*-chroman-6-ol (2a). 2a was prepared according to the general procedure from α-tocopherol (0.50 g, 1.16 mmol) and bromine (0.19 g, 1.20 mmol) as a dark-brown oil (0.59 g, 100%). Analytical data are consistent with those given in the literature.[4]

3.1.2. 5-Bromomethyl-3,4-dihydro-2,2,7,8-tetramethyl-2*H*-chroman-6-ol (2b). 2b was prepared according to the general procedure from chroman-6-ol (0.20 g, 0.91 mmol) and bromine (0.16 g, 1.10 mmol) as a brown oil (0.27 g, 100%). ^{1}H NMR ($CDCl_3$): δ 4.66 (s, 2H, H-5a), 3.98 (s, b, 1H, OH), 2.78 (t, 2H, H-4, ^3J=6.8 Hz), 2.15 and 2.12 (2×s, 2×3H, H-8b, H-7a), 1.82 (t, 2H, H-3, ^3J=6.8 Hz), 1.29 (2×s, 2×3H, H-2a, H-2b). ^{13}C NMR ($CDCl_3$): δ 146.1 (C-6), 145.5 (C-8a). 127.2 (C-5), 122.2 (C-8), 119.2 (C-7), 117.2 (C-4a), 75.1 (C-2), 32.6 (C-3), 26.6 (d.i., C-2a), 21.2 (C-4), 12.4 and 12.2 (H-7a, H-8b). IR (film): 3402, 2927, 2864, 1442, 1272, 1166, 1122, 1088.

3.2. General procedures for the cyclization reaction

5a-Bromo-α-tocopherol (**2a**) or 5-bromomethyl-2,2,7,8-tetramethyl-chroman-6-ol (**2b**) was stirred with PPh_3 (1 equiv.) in *n*-hexane (20 mL) for 2 h at rt. The solvent was removed in vacuo (water bath temperature lower than 40°C!) and dry toluene (20 mL) was added. The carboxylic acid chloride (1.1 equiv.) and TEA (3.3 equiv.) were added, and the mixture was refluxed for 16 h. The solvent was removed in vacuo, the remainder was dissolved in *n*-hexane (20 mL), and was washed sequentially with water and brine. The organic layer was dried over $MgSO_4$, and the solvent was removed in vacuo. The crude product was purified by flash chromatography (EtOAc/*n*-hexane, v/v=1:50).

3.2.1. 2,4,5,7-Tetramethyl-7-(4,8,12-trimethyltridecyl)-8,9-dihydro-7*H*-furo[3,2-*f*]chromene (4). Methyl-furotocopherol **4** was prepared according to the general procedure from 5-bromomethyl-γ-tocopherol (**2a**) (0.18 g, 0.32 mmol), PPh_3 (0.08 g), TEA (0.13 g) and acetyl chloride (0.03 g). After chromatographic purification **4** (0.09 g, 62%) was obtained as a yellow oil. ^{1}H NMR ($CDCl_3$): δ 6.22 (s, 1H, H-1), 2.77 (t, 2H, H-9, ^3J=6.8 Hz), 2.41 (s, 3H, H-2a), 2.37 and 2.17 (2×s, 2×3H, H-5b, H-4a), 1.92–1.72 (m, 2H, H-8). ^{13}C NMR ($CDCl_3$): δ 154.0 (C-2), 148.0 (C-5a), 147.1 (C-3a), 124.7 (C-9a), 120.6 (C-4), 117.7 (C-5), 108.2 (C-3b), 100.8 (C-1), 75.4 (C-7), 31.0 (C-8), 23.9 (C-7a), 21.1 (C-9), 12.0 (C-4a), 11.6 (C-5b). IR (film): 2916, 2869, 1462, 1397, 1377, 1248, 1164, 1119, 1091. Anal. Calcd for $C_{31}H_{50}O_2$ (454.74): C, 81.88; H, 11.08. Found: C, 81.89; H, 10.99.

3.2.2. 2-Phenyl-4,5,7-trimethyl-7-(4,8,12-trimethyltridecyl)-8,9-dihydro-7*H*-furo[3,2-*f*]chromene (5). Phenyl-furotocopherol **5** was prepared according to the general procedure from **2a** (1.53 g, 3.00 mmol), PPh_3 (0.79 g), TEA (1.01 g) and benzoyl chloride (0.42 g). After chromatographic purification **5** (0.70 g, 45%) was obtained as colorless oil. ^{1}H NMR ($CDCl_3$): δ 7.84 (d, 2H, ^3J=7.7 Hz, ^{Ar}H-2), 7.42 (t, 2H, ^3J=7.7 Hz, ^{Ar}H-3), 7.30 (m, 1H, ^{Ar}H-4), 6.84 (s, 1H, H-1), 2.87 (t, 2H, ^3J=6.6 Hz, H-9), 2.46 and 2.21 (2×s, 2×3H, H-5b, H-4a), 1.92–1.78 (m, 2H, H-8), 1.29 (s, 3H, H-7a). ^{13}C NMR ($CDCl_3$): δ 154.6 (C-2), 148.3 (C-5a), 147.5 (C-3a), 131.2 (Bn, C-1), 128.7 (d.i., Bn, C-2), 127.8 (d.i., Bn, C-3), 125.0 (C-9a), 124.5 (Bn, C-4), 122.4 (C-5), 118.2 (C-4), 108.8 (C-9b), 99.8 (C-1), 75.6 (C-7), 32.8 (C-8), 28.0 (C-7a), 19.7 (C-9), 12.1 (C-5b), 11.8 (C-4a). IR (film): 3039, 2860, 1605, 1460, 1396, 1377, 1203, 1118, 1085, 760, 689. Anal. Calcd for $C_{36}H_{52}O_2$ (516.81): C, 83.67; H, 10.14. Found: C, 83.81; H, 10.29.

3.2.3. 2-Phenyl-4,5,7-trimethyl-8,9-dihydro-7*H*-furo[3,2-*f*]-chromene (6). Phenyl-furochroman **6** was prepared according to the general procedure from **2b** (0.27 g,

0.91 mmol), PPh_3 (0.25 g), TEA (0.27 g) and benzoyl chloride (0.13 g). After chromatographic purification **6** (0.15 g, 55%) was obtained as white crystals, mp=135–137°C. ^{1}H NMR ($CDCl_3$): δ 7.83 (d, 2H, ^3J=8.4 Hz, ^{Ar}H-2), 7.39 (t, 2H, ^3J=7.8 Hz, ^{Ar}H-3), 7.28 (m, 1H, ^{Ar}H-4), 6.84 (s, 1H, H-1), 2.86 (t, 2H, ^3J=6.8 Hz, H-9), 2.46 and 2.21 (2×s, 2×3H, H-4a, H-5b), 1.84 (t, 2H, ^3J=6.8 Hz, H-8). 1.34 (s, 6H, H-7a; H-7b). ^{13}C NMR: δ 154.7 (C-2), 148.4 (C-5a), 147.7 (C-3a), 131.1 (Bn, C-1), 128.6 (d.i., Bn, C-2), 127.8 (d.i., Bn, C-3), 125.0 (C-9a), 124.5 (Bn, C-4), 122.4 (C-5), 118.2 (C-4), 108.2 (C-9b), 99.8 (C-1), 75.6 (C-7), 32.5 (C-8), 26.8 (C-7a, C-7b), 20.1 (C-9), 12.0 (C-5b), 11.8 (C-4a). IR (KBr): 3023, 2882, 1604, 1458, 1400, 1377, 1204, 1120, 760. Anal. Calcd for $C_{21}H_{22}O_2$ (306.41): C, 82.32; H, 7.24. Found: C, 82.38; H, 7.32.

3.2.4. 2-(2-Nitrophenyl)-4,5,7-trimethyl-7-(4,8,12-trimethyltridecyl)-8,9-dihydro-7*H*-furo[3,2-*f*]chromene (7). 2-(2-Nitrophenyl)-furotocopherol **7** was prepared according to the general procedure from **2a** (0.20 g, 0.39 mmol), PPh_3 (0.10 g), TEA (0.13 g) and 2-nitrobenzoyl chloride (0.08 g). After chromatographic purification **7** (0.13 g, 57%) was obtained as a yellow oil. NMR: ^{1}H NMR ($CDCl_3$): δ 7.87 (dd, 1H, ^3J=7.9 Hz, ^4J=1.3 Hz, ^{Ar}H-3), 7.71 (dd, 1H, ^3J=8.1 Hz, ^4J=1.2 Hz, ^{Ar}H-5), 7.60 (dt, 1H, ^3J=7.7 Hz, ^4J=1.3 Hz, ^{Ar}H-4), 7.43 (dt, 1H, ^3J=7.7 Hz, ^4J=1.4 Hz, ^{Ar}H-3), 6.92 (s, 1H, H-3), 2.86 (t, 2H, ^3J=7.0 Hz, H-9), 2.39 and 2.20 (2×s, 2×3H, H-5b, H-4a), 1.89–1.76 (m, 2H, H-8), 1.29 (s, 3H, H-2a). ^{13}C NMR ($CDCl_3$): δ 149.5, 149.3 (C-2, C5a), 148.4, 148.2 (^{Ar}C–NO_2, C-3a), 132.1 (Bn, C-4), 129.6 (Bn, C-3), 128.9 (Bn, C-5), 124.7, 124.4 (C-4, C-3a), 125.0 (Bn, C-1), 118.8 (C-9a), 109.5 (C-3a), 104.9 (C-3), 76.2 (C-7), 31.2 (C-8), 28.4 (C-7a), 21.4 (C-9), 12.1 and 11.8 (C-5b, C-4a). IR (film): 3372, 2937, 2850, 1718, 1600, 1533, 1460, 1396, 1377, 1205, 1089, 748. Anal. Calcd for $C_{36}H_{51}O_4N$ (561.81): C, 76.97; H, 9.15; N, 2.49. Found: C, 77.21; H, 8.97; N, 2.41.

3.2.5. 2-Ethenyl-4,5,7-trimethyl-7-(4,8,12-trimethyltridecyl)-8,9-dihydro-7*H*-furo[3,2-*f*]chromene (8). Vinyl-furotocopherol **8** was prepared according to the general procedure from **2a** (0.20 g, 0.39 mmol), PPh_3 (0.10 g), TEA (0.13 g) and acryloyl chloride (0.03 g). After chromatographic purification **7** (0.08 g, 45%) was obtained as yellow oil. ^{1}H NMR ($CDCl_3$): δ 6.60 (dd, 1H, ^3J=17.4 Hz, ^3J=11.2 Hz, C*H*=CH_2), 6.48 (s, 1H, H-1), 5.87 (dd, 1H, ^2J=0.8 Hz, ^3J=17.4 Hz, CH=CH_2), 5.28 (dd, 1H, ^2J=1.0 Hz, ^3J=11.2 Hz, CH=CH_2), 2.80 (t, 2H, ^3J=6.8 Hz, H-9), 2.40 and 2.19 (2×s, 2×3H, H-4a, H-5b), 1.91–1.77 (m, 2H, H-8), 1.27 (s, 3H, H-7a). ^{13}C NMR ($CDCl_3$): δ 153.8 (C-2), 148.1 (C-5a), 147.3 (C-3a), 125.7 (*C*H=CH_2), 124.5 (C-9a), 122.8 (C-5), 118.8 (C-4), 113.8 (CH=*C*H_2), 108.8 (C-9b), 103.2 (C-1), 75.5 (C-7), 32.8 (C-8), 23.9 (C-7a), 19.7 (C-9), 12.0 and 11.8 (C-4a, C-5b). IR (film): 3037, 2859, 1597, 1460, 1397, 1377, 1315, 1201, 1116, 1087. Anal. Calcd for $C_{32}H_{50}O_2$ (466.75): C, 82.35; H, 10.80. Found: C, 82.50; H, 10.92.

3.2.6. 2-Phenylethenyl-4,5,7-trimethyl-7-(4,8,12-trimethyltridecyl)-8,9-dihydro-7*H*-furo[3,2-*f*]chromene (9). 2-Styryl-furotocopherol **9** was prepared according to the general procedure from **2a** (0.20 g, 0.39 mmol), PPh_3 (0.10 g), TEA (0.13 g) and cinnamoyl chloride (0.07 g). After chromatographic purification **9** (0.14 g, 67%) were obtained as a yellow oil. ^{1}H NMR ($CDCl_3$): δ 7.52 (d, 2H, ^3J=7.4 Hz, ^{Ar}H-2), 7.39 (t, 2H, ^3J=7.3 Hz, ^{Ar}H-3,), 7.39 (d, 2H, ^3J=16.2 Hz, ^{Ar}H-4, C*H*=CHPh), 7.00 (d, 1H, ^3J=16.2 Hz, CH=C*H*Ph), 6.58 (s, 1H, H-1), 2.83 (t, 2H, ^3J=6.7 Hz, H-9), 2.45 (s, 3H, H-4a), 2.21 (s, 3H, H-5b), 1.91–1.75 (m, 2H, H-8), 1.28 (s, 3H, H-7a). ^{13}C NMR ($CDCl_3$): δ 153.9 (C-2), 148.3 (C-5a), 147.5 (C-3a), 136.0 (Ph, C-1), 128.7 (d.i., Ph, C-3), 128.5 (*C*H=CHPh), 127.7 (d.i., Ph, C-2), 126.5 (Ph, C-4), 124.9 (C-9a), 122.9 (C-5), 117.9 (C-4), 117.9 (CH=*C*HPh), 108.7 (C-9b), 103.9 (C-1), 75.5 (C-7), 30.9 (C-8), 23.9 (C-7a), 21.0 (C-9), 12.1 and 11.9 (C-4a, C-5b). IR (film): 3040, 2860, 1597, 1460, 1394, 1377, 1315, 1201, 1116, 1083, 950, 792. Anal. Calcd for $C_{38}H_{54}O_2$ (542.85): C, 84.08; H, 10.03. Found: C, 83.98; H, 10.29.

3.2.7. 2-Methoxymethyl-4,5,7-trimethyl-7-(4,8,12-trimethyltridecyl)-8,9-dihydro-7*H*-furo[3,2-*f*]chromene (10). 2-Methoxymethyl-furotocopherol **10** was prepared according to the general procedure from **2a** (0.20 g, 0.39 mmol), PPh_3 (0.10 g), TEA (0.13 g) and 2-methoxyacetyl chloride (0.05 g). After chromatographic purification **10** (0.12 g, 62%) was obtained as yellow oil. ^{1}H NMR ($CDCl_3$): δ 6.68 (s, 1H, H-1), 4.52 (s, 2H, CH_2OCH_3), 3.41 (s, 3H, CH_2OCH_3), 2.81 (t, 2H, ^3J=6.7 Hz, H-9), 2.40 (s, 3H, H-4a), 2.19 (s, 3H, H-5b), 1.92–1.73 (m, 2H, H-8), 1.28 (s, 3H, H-7a). ^{13}C NMR ($CDCl_3$): δ 153.0 (C-2), 148.0 (s, C-5a), 147.3 (C-3a), 123.8 (C-9a), 122.4 (C-5), 118.8 (C-4), 108.8 (C-9b), 104.3 (C-1), 75.5 (C-7), 67.2 (*C*H_2OCH_3), 58.0 (CH_2O*C*H_3), 32.8 (C-8), 23.9 (C-7a), 21.9 (C-9), 12.1 (C-5b), 11.9 (C-4a). IR (film): 2860, 1460, 1400, 1377, 1170, 1116, 950. Anal. Calcd for $C_{32}H_{52}O_3$ (484.77): C, 79.29; H, 10.81. Found: C, 78.80; H, 10.51.

3.2.8. 2-(2′,2′-Dimethyl-propyl)-4,5,7-trimethyl-7-(4,8,12-trimethyltridecyl)-8,9-dihydro-7*H*-furo[3,2-*f*]chromene (11). *tert*-Butyl-furotocopherol **11** was prepared according to the general procedure from **2a** (0.2 g, 0.39 mmol), PPh_3 (0.10 g), TEA (0.13 g) and pivaloyl chloride (0.03 g). After chromatographic purification **11** (0.10 g, 51%) was obtained as a yellow oil. NMR: ^{1}H NMR ($CDCl_3$): δ 6.22 (s, 1H, H-1), 2.79 (t, 2H, ^3J=6.9 Hz, H-9), 2.34 (s, 3H, H-4a), 2.18 (s, 3H, H-5b), 1.90–1.74 (m, 2H, H-8), 1.36 (s, 9H, C(CH_3)$_3$), 1.27 (s, 3H, H-7a). ^{13}C NMR ($CDCl_3$): δ 166.1 (C-2), 147.8 (C-5a), 147.0 (C-3a), 124.3 (C-9a), 124.3 (C-5), 117.7 (C-4), 108.5 (C-9b), 97.0 (C-1), 75.7 (C-7), 33.2 (C(CH_3)$_2$), 32.8 (*C*(*C*H_3)$_2$), 31.1 (C-8), 24.0 (C-7a), 21.0 (C-9), 12.0 and 11.6 (C-4a, C-5b). IR (film): 2916, 2869, 140, 1400, 1377, 1250, 1164, 1119, 1091. Anal. Calcd for $C_{34}H_{56}O_2$ (496.82): C, 82.20; H, 11.36. Found: C, 82.40; H, 11.12.

3.2.9. 4,5,7,4′,5′,7′-Hexamethyl-7,7′-bis(4,8,12-trimethyltridecyl)-8,9,8′,9′-tetrahydro-7*H*,7′*H*-2,2′-bis{furo[3,2-*f*]-chromene} (12). The furotocopheryl dimer **12** was prepared according to the general procedure from **2a** (0.10 g, 0.20 mmol), PPh_3 (0.05 g), TEA (0.07 g) and oxalyl chloride (0.03 g). After chromatographic purification **12** (0.07 g, 41%) was obtained as a yellow oil. ^{1}H NMR ($CDCl_3$): δ 7.01 (s, 1H, H-1), 2.88 (t, 2H, ^3J=6.7 Hz, H-9), 2.49 (s, 3H, H-4a), 2.22 (s, 3H, H-5b), 1.92–1.80 (m, 2H, H-8), 1.30 (s, 3H, H-7a). ^{13}C NMR ($CDCl_3$): δ 148.5 (C-2),

147.7 (C-3a), 147.4 (C-5a), 124.6 (C-9a), 122.9 (C-5), 118.1 (C-4), 109.0 (C-9b), 101.2 (C-1), 75.6 (C-7), 30.9 (C-8), 23.9 (C-7a), 19.8 (C-9), 12.1 (C-5b), 11.9 (C-4a). IR (film): 3023, 2860, 1598, 1496, 1460, 1396, 1377, 1317, 1166, 1114, 1085, 952, 748, 690. Anal. Calcd for $C_{60}H_{94}O_4$ (879.42): C, 81.95; H, 10.77. Found: C, 82.15; H, 11.01.

3.2.10. 4,5,7-Trimethyl-7-(4,8,12-trimethyltridecyl)-8,9-dihydro-7*H*-furo[3,2-*f*]chromen-2-yl, linked to polystyrene (13). Merryfield resin (polystyrene, crosslinked with 1% divinylbenzene (DVB), containing 0.88 mmol/g carboxyl groups, 200 mg corresponding to 0.176 mmol COOH) was refluxed with 2 mL of $SOCl_2$ for 3 h. The resin was filtered off and was repeatedly washed with EtOAc and *n*-hexane. 5-Bromomethyl-γ-tocopherol (**2a**, 450 mg, 0.88 mmol) was stirred with PPh_3 (0.25 g, 1.1 equiv.) in *n*-hexane (50 mL) for 2 h. The modified Merryfield resin (COCl form, 0.2 equiv.) and TEA (0.29 g, 3.3 equiv.) were added, and the mixture was refluxed for 16 h. The furotocopherol-loaded resin was removed by filtration, and thoroughly washed with ethyl acetate and *n*-hexane. IR (KBr): 3423, 2928, 2675, 1735, 1683, 1600, 1460, 1434, 1394, 1377, 1230, 1169, 1078, 1035, 744, 694. ^{13}C NMR ($CDCl_3$): δ 75.4, 38.9, 36.9, 32.3, 31.1, 27.5, 24.3, 23.9, 22.3, 22.2, 20.5, 19.3, 8.4.

Acknowledgements

The financial support by the Austrian Fonds zur Förderung der wissenschaftlichen Forschung, project P-14687 (T. R.) and project P-14844 CHE (W. B.), is gratefully acknowledged. The authors would like to thank Dr. Andreas Hofinger and Dr Jürgen Röhrling, Institute of Chemistry at the University of Agricultural Sciences Vienna, for recording the NMR spectra, as well as Dr. Barbara Hinterstoisser for providing access to IR instrumentation.

References

1. (a) Packer, L.; Fuchs, J. *Vitamin E in Health and Disease*; Marcel Dekker: New York, 1993. (b) Isler, O.; Brubacher, G. *Vitamins I*; Georg Thieme: Stuttgart, 1982; pp 126. For a general review on chromans and tocopherols see: (c) Parkhurst, R. M.; Skinner, W. A. Chromans and Tocopherols. In *Chemistry of Heterocyclic Compounds*; Ellis, G. P., Lockhardt, I. M., Eds.; Wiley: New York, 1981; Vol. 36.
2. (a) Mukai, K.; Fukuda, K.; Tajima, K.; Ishizu, K. *J. Org. Chem.* **1988**, *53*, 430. (b) Mukai, K.; Yokoyama, S.; Fukuda, K.; Uemoto, Y. *Bull. Chem. Soc. Jpn* **1987**, *60*, 2161. (c) Mukai, K.; Kageyama, Y.; Ishida, T.; Fukuda, K. *J. Org. Chem.* **1989**, *54*, 522.
3. 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.
4. Rosenau, T.; Habicher, W. D. *Tetrahedron* **1995**, *51*, 7919.
5. Both raising and lowering the reaction temperature caused a significant decrease in yield, as did changes of the solvent, e.g. refluxing in DMF or CH_2Cl_2.
6. Hercouet, A.; LeCorre, M. *Tetrahedron Lett.* **1979**, *23*, 2145.
7. Sarkar, S. K.; Garigipati, R. S.; Adams, J. L.; Keifer, P. A. *J. Am. Chem. Soc.* **1996**, *118*, 2305–2306.
8. Meissner, A.; Bloch, P.; Humpfer, E.; Spraul, M.; Sörensen, O. W. *J. Am. Chem. Soc.* **1997**, *119*, 1787–1788.
9. Part 14: Rosenau, T.; Potthast, A.; Elder, T.; Kosma, P. *Org. Lett.* **2002**, *4(24)*, 4285–4288.