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Novel Tocopherol Compounds. III [1]

Reaction of 5a-Bromo-α-tocopherol with Nucleophiles

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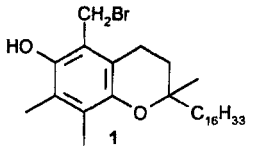
Abstract. The synthesis of different classes of 5a-substituted tocopherols is described. These compounds are potent antioxidants and highly interesting as vitamin E carriers. The reaction of the readily available 5a-bromo-α-tocopherol with alcohols and phenols is shown to produce 5a-alkoxy-α-tocopherols (**3**–**5**, **8**, **9**) and 5a-aryloxy-α-tocopherols (**6**, **7**), respectively, with high yields. 5a-α-Tocopheryl esters (**10**, **11**) are prepared by reaction with metal carboxylates. 5a-Bromo-α-tocopherol is used as well to introduce tocopheryl groups into tertiary amines by quaternization, that renders these compounds (**13**, **14**) soluble in water and in common organic solvents. 5a-Bromo-α-tocopherol also reacts as an alkylating agent with sterically hindered phenols in a Friedel-Crafts reaction. Phenols not highly substituted are exclusively alkylated in the *para* position at room temperature or below, whereas at higher temperature the *para*- as well as the *ortho*-alkylated product is observed.

5a-Substituted tocopherols are of constantly increasing interest because of their antioxidant activity and their use as tocopherol carriers and potential pharmaceuticals. However, there are no elaborated procedures for the syntheses of these compounds thus far. Therefore, it was the aim of this work to develop generally applicable methods for the preparation of a variety of 5a-substituted tocopherols. These vitamin E derivatives retain their antioxidant activity *in vitro* after the modification at the position 5a. The antioxidant performance can even be increased by linking the tocopherol to another antioxidant, as described below. In addition, 5a-substituted compounds are currently being investigated as tocopherol carriers in biological model systems. By substituting the 5a-position of α-tocopherol, the possibility exists, for instance, to render the lipophilic α-tocopherol amphiphilic or even hydrophilic. Furthermore, after linking the tocopherol to another moiety, the latter can act either as a carrier or as an independently effective compound. The main advantage of the 5a-substituted tocopherol compounds can be seen in the fact that its properties, for instance solubility, can be determined in advance by the choice of the 5a-substituent.

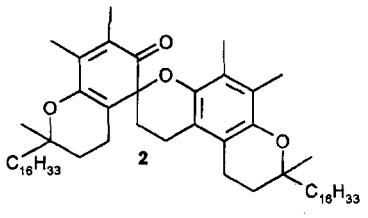
The availability of 5a-bromo-α-tocopherol (**1**) in quantitative yields [2] makes it an attractive starting material for the preparation of 5a-substituted α-tocopherols. Because of its inherent benzyl bromide structure, 5a-bromo-α-tocopherol shows high reactivity and is amenable to facile nucleophilic substitution. However, preparative difficulties arise since this compound readily eliminates hydrogen bromide in basic media or at slightly elevated temperatures (above 40 °C). The elimination of HBr leads to the formation of a strongly favored ortho-quinone methide intermediate which couples in a hetero-Diels–Alder reaction to yield the α-tocopherol spiro-dimer **2** [3], as the most frequently observed by-product when unsuitable reaction conditions were chosen. The spiro-dimer is also produced upon elimination of the 5a-substituent in 5a-substituted tocopherols. The elimination appears to be almost independent of the nature of this substituent.

5a-α-Tocopherylalkyl Ethers and 5a-α-Tocopherylaryl Ethers

The reaction of 5a-bromo-α-tocopherol as a benzyl bromide with sodium alkoxides at 0 °C or at room temperature proceeded quantitatively to afford the 5a-alkoxy-α-tocopherols **3**, **4**, and **5** as very pure products requiring no further purification.



1



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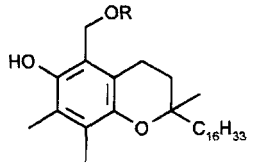
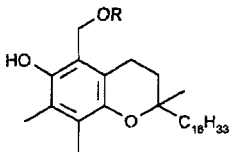


R	
3	Et
4	*i*-Pr
5	*n*-Hex



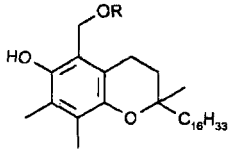
R	
6	Ph
7	*o*-Tolyl
8	Allyl
9	*t*-Bu

This result was somewhat surprising since the reaction of 5a-bromo-α-tocopherol with aqueous NaOH yields the spiro-dimer of α-tocopherol **2**, a product which was supposed to be formed in the reaction with NaOR as well. However, no detectable amounts of the α-tocopherol spiro-dimer were found in the reaction mixture. Even in the presence of small amounts of NaOH in the alcoholic solution of the sodium alkoxide no spiro-dimer was generated. The cause of this chemical behavior is to be seen in the higher nucleophilicity of RO^- as compared with HO^-, making the attack of RO^- by far the favored reaction.

5a-Bromo-α-tocopherol does not react with sodium phenolates in the same manner. At room temperature or below no reaction was observed, whereas at elevated temperatures (above 50 °C) no ethers were formed, but the α-tocopherol spiro-dimer **2** was obtained as the main product, as expected. Although all attempts to convert 5a-bromo-α-tocopherol to 5a-aryloxy-α-tocopherols according to the Williamson procedure have failed, the Claisen ether synthesis [4] provided an easily feasible method to yield these compounds. In this procedure, the bromide reacts with the pure phenol in the presence of anhydrous potassium carbonate in acetone. On the one hand, the potassium carbonate is too weak a base to promote the elimination of HBr from the starting material. On the other hand, it activates the phenol and binds the HBr formed. After refluxing of the reaction mixture, by-products were observed independent of heating time. Hence, milder conditions, such as working at room temperature and applying prolonged reaction time, were preferred to avoid the formation of by-products. Unfortunately, not all the 5a-bromo-α-tocopherol was converted under these milder conditions, even if the coreacting phenol was used in threefold excess and the reaction time was extremely extended (up to 5 d), but no by-products were formed. The 5a-aryloxy-α-tocopherols **6** and **7** were obtained in reasonable yields of 76% and 70%, respectively. The Claisen method was also applied successfully in the etherification of labile alcohols with the tocopheryl bromide **1**. Compounds **8** and **9** were obtained by reaction of **1** with allyl alcohol or *tert*-butyl alcohol. In contrast to the etherification with phenols, the yields were quantitative, not only if the alcohol was used in excess, but also if a stoichiometric ratio of reactants was applied.

5a-α-Tocopheryl Esters

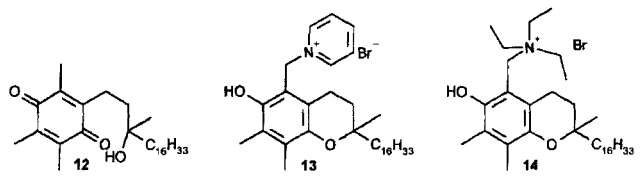
The conversion of 5a-bromo-α-tocopherol (**1**) to the corresponding esters was in so far difficult as no auxiliary bases for the removal of HBr from the ester formation equilibrium could be applied. For instance, working according to commonly known methods, such as the Schotten-Baumann or the Einhorn procedure, or using hindered bases as auxiliaries, e.g., *N*-ethyldiisopropylamine, the spiro-dimer **2**, but not the desired ester, was obtained almost quantitatively. Reaction of the tocopheryl bromide and carboxylic acids without auxiliaries produced only unsatisfactory results. However, if the sodium salts of carboxylic acids were applied, the esters were formed in reasonable yields. The reaction between 5a-bromo-α-tocopherol and sodium benzoate yielded 72% of the corresponding ester **10** after work-up, and reaction with sodium acetate yielded 56% of the product **11**. The presence of NaOH or water affected the yield drastically, even traces lead to the formation of the spiro-dimer **2** in unreasonable amounts. This makes the application of carefully dried and base free carboxylates crucial to minimize the formation of by-products.



10 R = $COCH_3$
11 R = COPh

Treatment of 5a-bromo-α-tocopherol with silver carboxylates [5] represents an improved method for producing 5a-α-tocopheryl esters. Using dry silver acetate instead of sodium acetate, the yield of **10** was quantitative, and so was the yield of the ester **11**. The silver salt was added all at once to the solution of the tocopheryl bromide **1** in *n*-hexane. Immediately after the addition a yellow precipitate of silver bromide was observed which had to be separated from the reaction mixture

shortly after its formation, otherwise the AgBr was further reduced by the tocopherol derivative to elemental silver, identifiable by darkening of the precipitate. Working at –5 to 0 °C was also crucial to avoid this competitive reaction.



Quaternary Ammonium Salts [*N*-(5a-α-Tocopheryl)-ammonium Bromides]

On reaction of tertiary amines with tocopheryl bromide **1** above 40 °C hydrogen bromide is eliminated, and the α-tocopherol spiro-dimer **2** is formed. This reaction proceeds in competition with the alkylation of the amine. In some cases, a small amount of α-tocopheryl quinone **(12)** [6] as the second by-product was observed.

To get the quaternary ammonium salts, the reaction temperature must not exceed –10 °C in order to minimize the amount of by-products which, even at these favorable conditions, could not be entirely suppressed. But, fortunately, the desired products can easily be separated and purified. With pyridine and triethyl amine, compounds **13** and **14** were obtained with yields of 68% and 76%.

Nitromethane or equimolar mixtures of nitromethane and *n*-hexane turned out to be appropriate solvents for the quaternization.

At room temperature (20 °C) the products of both elimination and alkylation were obtained in comparable amounts. At temperatures below –20 °C the elimination of HBr seems to cease completely, but the reaction rate of the quaternization also becomes very low.

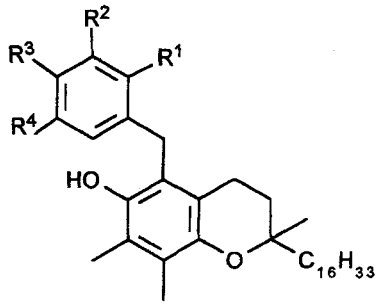
The *N*-(5a-α-tocopheryl)-ammonium salts are almost insoluble in ice-cold water or ice-cold diluted mineral acids, but readily soluble in water at room temperature or above. The solubility in polar aprotic or protic organic solvents is generally good, while the salts are insoluble in non-polar solvents like *n*-hexane or ligroin. The dry compounds seem to be stable at room temperature in the absence of oxygen. At temperatures above 50 °C, elimination of the tocopherol moiety occurs in aqueous solution, in organic solvents, or in substance.

The reaction of **1** with primary amines and the use of 5a-bromo-α-tocopherol as an advantageous amino-protecting group in the synthesis of secondary amines, monoalkylated amino acids, and peptides has been discussed elsewhere [1].

Reaction of 5a-Bromo-α-tocopherol as Alkylating Agent in Friedel-Crafts Reactions

Due to its benzyl bromide structure, 5a-bromo-α-tocopherol **(1)** is a potential Friedel-Crafts alkylating agent. With phenols, no reaction was observed at room temperature, even if common Friedel-Crafts catalysts, such as aluminum chloride, zinc chloride, boron trifluoride, or *p*-toluenesulfonic acid, and prolonged reaction times were applied. At temperatures above 50 °C, the alkylation seems to proceed at reasonable rates. However, the process is once more complicated by concomitant elimination of hydrogen bromide from the alkylating agent 5a-bromo-α-tocopherol. At temperatures between 30 to 40 °C, the elimination of HBr was decelerated, however it remained the dominant reaction. Bubbling gaseous HBr through the mixture provided a solution for this problem: the HBr acts not only as a catalyst for the alkylation, but it also favors the reverse reaction to the elimination, i.e., the addition of HBr to the ortho-quinone methide, thereby suppressing the side reaction and minimizing the formation of **2** as by-product. Using HBr, a temperature of 50 °C could be maintained during the reaction. The alkylated products **15** and **16** were obtained in overall yields of 82% and 76%, respectively. Formation of by-products was observed, but only in small amounts, less than 10%. The addition of anhydrous $ZnCl_2$ to the reaction mixture in the presence of gaseous HBr led to further improvements. The products were obtained in quantitative yields at 30 °C, a surprising result for a Friedel-Crafts alkylation that is expected to proceed under formation of by-products in at least small amounts.

When $HBr/ZnCl_2$ is used as the catalyst at 20–30 °C, phenols are alkylated exclusively in *para*-position, while at 50 °C a mixture of the *para*- and *ortho*-alkylated product was obtained. Freshly distilled phenol yielded upon alkylation at 20 °C the *p*-(5a-α-tocopheryl) phenol **17** quantitatively. At 50 °C, 73% of **17** and 27% of the *ortho*-alkylated product **18** were obtained. With *para*-cresol, the *ortho*-position was alkylated at 20 °C, and **19** was obtained almost quantitatively. In all cases, the phenol applied was alkylated only singly; polyalkyla-



	R^1	R^2	R^3	R^4
15	H	*t*-Bu	OH	*t*-Bu
16	OH	*t*-Bu	H	Me
17	H	H	OH	H
18	OH	H	H	H
19	OH	H	H	Me

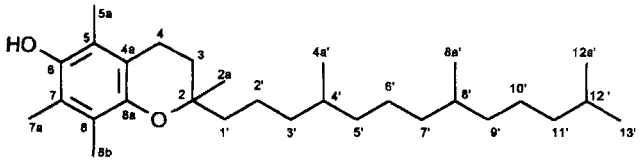
tions seem to be prohibited due to the bulky shape of the alkylating agent **1**.

The products of alkylation are thermally stable up to temperatures of above 200 °C in the absence of oxygen, rendering them well analyzable by GCMS. This stands in contrast to the thermolabile tocopherol derivatives described before, carrying -OR, -OCOR or $-NR_3^+$ substituents at position 5a [7].

We thank Dr. M. Gruner for the NMR measurements, Dr. H. Kroschwitz for the GCMS experiments and Ms. Pinske for carrying out the elemental analyses. The authors are grateful to Dr. C. L. Chen, North Carolina State University, Raleigh, USA, for advice and discussion. We also thank the Studienstiftung des Deutschen Volkes, Bonn, Germany, for a doctoral fellowship to T.R.

Experimental

NMR spectra were recorded at 200 MHz for ^1H nuclei and at 50 MHz for ^{13}C nuclei (Bruker AC-200P) in $CDCl_3$ with TMS as the internal standard. Chemical shifts are expressed in δ values. ^{13}C peaks were assigned by means of DEPT and GD. GCMS was performed on a Hewlett Packard device (5890 Series II, EI, 70 eV, ITD). Elemental analyses were performed at the Institut für Organische Chemie, Technische Universität Dresden. The numbering of the carbon atoms and the nomenclature proposed by the IUPAC [8] have been used, as shown for the starting material α-tocopherol. The δ-values of the atoms of the isoprenoid side chain (C-1' to C-13') are not listed, since they are well established and are not or are only slightly affected by modifications of the chroman structure [9]. The signals of aliphatic moieties attached to the tocopherol part are masked by the resonances of the side chain in the majority of cases. The corresponding δ-values in the ^1H NMR spectra are therefore not given.



Reaction of 5a-bromo-α-tocopherol with sodium alkoxides

In an inert atmosphere, a solution of 0.320 g (4.702 mmol) EtONa in 10 ml EtOH (or 0.400 g (4.873 mmol) of *i*-PrONa in isopropanol, or 0.583 g (4.700 mmol) of sodium *n*-hexoxide in *n*-hexanol) was added dropwise to a solution of 2.366 g (4.644 mmol) 5a-bromo-α-tocopherol in 20 ml of *n*-hexane and 10 ml of absolute EtOH at 0 °C, cooling with an ice bath. The solution was stirred for 1 h and warmed to room temp. 50 ml of *n*-hexane were added and the solution was washed successively with 20 ml H_2O, 10 ml 1N HCl, twice with 10 ml H_2O and dried over $MgSO_4$. The solvent was evaporated at room temp. under reduced pressure affording the pure products.

5a-Ethoxy-α-tocopherol (**3**):
Yield 2.2 g (100%) yellow oil. – $C_{31}H_{54}O_3$ (474.8); calcd. C 78.43; H, 11.46; found C 78.49; H 11.53%. – ^1H NMR ($CDCl_3$): 2.10 (s, 3H, CH_3, C-7a), 2.15 (s, 3H, CH_3, C-8b), 2.65 (t, 2H, $ArC\underline{H}_2CH_2$, C-4), 3.65 (q, 2H, O-CH_2-CH_3), 4.75 (s, 2H, Ar-CH_2-O, C-5a). – ^{13}C NMR ($CDCl_3$): 15.0 (O-CH_2-$\underline{C}H_3$), 19.9 (C-4), 31.5 (C-3), 65.9 (O-$\underline{C}H_2$-CH_3), 67.9 (C-5a), 74.1 (C-2), 114.9; 116.0; 123.0; 125.4 (C-4a; C-5; C-7; C-8), 144.6; 147.5 (C-6; C-8a).

5a-Isopropoxy-α-tocopherol (**4**)
Yield 2.2 g (98%) yellow oil. – $C_{32}H_{56}O_3$ (488.8); calcd.: C 78.63; H, 11.55; found: C 78.63; H 11.60%. – ^1H NMR ($CDCl_3$): 1.10 (d, 6H, O-CH-($C\underline{H}_3$)$_2$), 2.10 (s, 3H, CH_3, C-7a), 2.15 (s, 3H, CH_3, C-8b), 2.60 (t, 2H, $ArC\underline{H}_2CH_2$, C-4), 3.65 (sept, 2H, O-C$\underline{H}$-(CH_3)$_2$), 4.73 (s, 2H, Ar-CH_2-O, C-5a). – ^{13}C NMR ($CDCl_3$): 20.1 (C-4), 22.6 (O-CH($\underline{C}H_3$)$_2$), 31.5 (C-3), 68.4 (O-$\underline{C}H$(CH_3)$_2$), 65.8 (C-5a), 74.1 (C-2), 114.8; 116.5; 123.4; 125.5 (C-4a; C-5; C-7; C-8), 144.6; 147.4 (C-6; C-8a).

5a-n-Hexoxy-α-tocopherol (**5**)
Yield 2.46 g (100%) yellow oil. – $C_{35}H_{62}O_3$ (530.9); calcd.: C 79.18; H 11.77; found: C 79.22; H 11.79%. – ^1H NMR ($CDCl_3$): 0.90 (t, 3H, $C\underline{H}_3$-C_5H_{10}-O-), 2.05 (s, 3H, CH_3, C-7a), 2.15 (s, 3H, CH_3, C-8b), 2.60 (t, 2H, $ArC\underline{H}_2CH_2$, C-4), 3.40 (t, 2H, C_5H_{11}-$C\underline{H}_2$-O-), 4.75 (s, 2H, Ar-CH_2-O, C-5a). – ^{13}C NMR ($CDCl_3$): 20,4 (C-4), 31.5 (C-3), 67.9 (C-5a), 74.1 (C-2), 114.9; 116.0; 123.0; 125.4 (C-4a; C-5; C-7; C-8), 144.6; 147.5 (C-6; C-8a); hexyl group: 15.1, 23.5, 26.9, 30.7, 32.6, 68.9.

Reaction of 5a-bromo-α-tocopherol with phenols (*O*-Alkylation)

2.350 mmol (0.221 g) of freshly distilled (!) phenol (or 0.254 g (2.350 mmol) freshly distilled (!) *o*-cresol) was dissolved in 20 ml of dry acetone. Anhydrous K_2CO_3 (1.000 g, 7.235 mmol) was added, and the solution was refluxed for 10 min in an inert atmosphere. After cooling to room temperature, a solution of 1.183 g (2.322 mmol) 5a-bromo-α-tocopherol in 20 ml acetone was added dropwise, and the solution became cloudy. After stirring for 48 hours at room temperature, the solids were removed by filtration, 100 ml of *n*-hexane was added and the solution was washed twice with 50 ml of 2% aqueous $NaHCO_3$ and twice with 20 ml H_2O. The organic phase was separated, dried over Na_2SO_4 and evaporated at room temperature under reduced pressure. The remaining residue was chromatographed on silica gel, eluting first the impurities with *n*-hexane/ligroin (1:1, v/v) and *n*-hexane/Et_2O (5:1, v/v) and then the product with benzene/*n*-hexane (5:1, v/v).

5a-Phenoxy-α-tocopherol (**6**)
Yield 0.92g (76%) oil. – $C_{35}H_{54}O_3$ (522.8); calcd.: C 80.41; H 10.41; found: C 80.48; H 10.50%. – ^1H NMR ($CDCl_3$); 2.10 (s, 3H, CH_3, C-7a); 2.15 (s, 3H, CH_3, C-8b), 2.63 (t, 2H, $ArCH_2CH_2$, C-4), 4.70 (s, 2H, Ar-C$\underline{H}_2$-O, C-5a), 7.10 (m, 5H, H^{Ar}, phenoxy group). – ^{13}C NMR ($CDCl_3$): 19.7 (C-4), 31.5 (C-3), 59.4 (C-5a), 74.2 (C-2), 113.6; 115.7; 123,0; 125.9

(C-4a; C-5; C-7; C-8), 144.9; 145.6 (C-6; C-8a); phenoxy group: 115.5 (C-2'; C-6'), 121.9 (C-4'), 129.2 (C-3'; C-5'), 156.4 (C-1').

5a-(o-Tolyloxy)-α-tocopherol (**7**)
Yield 0.87 g (70%) oil. – $C_{36}H_{56}O_3$ (536.8); calcd.: C 80.54; H 10.51; found: C 80.50; H 10.58%. – ^{1}H NMR ($CDCl_3$): 2.12 (s, 3H, CH_3 , C-7a); 2.15 (s, 3H, CH_3, C-8b), 2.20 (s, 3H, CH_3 of *o*-tolyloxy group), 2.60 (t, 2H, $ArC\underline{H}_2CH_2$, C-4), 4.68 (s, 2H, Ar-CH_2-O, C-5a), 6.80 (m, 2H, H^{Ar}), 7.10 (m, 2H, H^{Ar}). – ^{13}C NMR ($CDCl_3$): 20.0 (C-4), 31.5 (C-3), 61.4 (C-5a), 74.2 (C-2), 113.7; 115.7; 122.9; 126.1 (C-4a; C-5; C-7; C-8), 144.9; 145.6 (C-6; C-8a); *o*-tolyloxy group: 16.3, (CH_3), 109.1; 120.1; 125.9; 126.1 130.2; 157.0.

Reaction of 5a-bromo-α-tocopherol with alcohols

A mixture of 1.183 g (2.322 mmol) 5a-bromo-α-tocopherol, 1.000 g (7.235 mmol) anhydrous potassium carbonate, 0.135 g (2.325 mmol) allyl alcohol (or 0.172 g (2.325 mmol of *tert*-butanol), and 20 ml of dry acetone was stirred at room temperature for 72 h under N_2. The solids were removed by filtration, 100 ml of *n*-hexane was added and the solution washed successively with 10 ml of 1N HCl and twice with 20 ml H_2O. The organic phase was separated and dried over Na_2SO_4. The solvents were evaporated at room temperature under reduced pressure. The remaining residue consisted of pure product, that did not need to be purified. If the alcohol is used in tenfold molar excess, the time of stirring can be shortened to 24 hours, yielding the same pure product.

5a-Allyloxy-α-tocopherol (**8**)
Yield 1.130 g (100%) oil. – $C_{32}H_{54}O_3$ (486.8); calcd.: C 78.96; H 11.18; found : C 78.93; H 11.51%. – ^{1}H NMR ($CDCl_3$): 2.10 (s, 3H, CH_3, C-7a), 2.15 (s, 3H, CH_3 , C-8b), 2.62 (t, 2H, $ArC\underline{H}_2CH_2$, C-4), 4.10 (d, 2H, O-$C\underline{H}_2$-CH=CH_2), 4.72 (s, 2H, Ar-CH_2-O, C-5a), 5.25 (2d, 1H, O-CH_2-CH=$C\underline{H}_2$ [*trans*]), 5.35 (d, 1H, O-CH_2-CH=$C\underline{H}_2$ [*cis*]), 5.90 (m, 1H, O-CH_2-CH=$C\underline{H}_2$). – ^{13}C NMR ($CDCl_3$): 19.9 (C-4), 31.5 (C-3), 67.1 (C-5a), 115.3; 116.0; 123.1; 125.8 (C-4a; C-5; C-7; C-8), 144.8; 147.5 (C-6; C-8a); allyloxy group: 71.1, 118.0, 133.8.

*5a-*tert*-Butyloxy-α-tocopherol* (**9**)
Yield: 1.167 g (100%) yellow oil. – $C_{33}H_{58}O_3$ (502.9); calcd.: C 78.83; H 11.63; found: C 78.81; H 11.72%. – ^{1}H NMR ($CDCl_3$): 1.20 (s, 9H, $(C\underline{H}_3)_3$C-O-), 2.14 (s, 3H, CH_3 , C-7a), 2.15 (s, 3H, CH_3 , C-8b), 2.65 (t, 2H, $ArC\underline{H}_2CH_2$, C-4). – ^{13}C NMR ($CDCl_3$): 20.0 (C-4), 31.5 (C-3), 68.3 (C-5a), 114.9; 115.7; 123.3; 126.3 (C-4a; C-5; C-7; C-8), 144.6; 148.0 (C-6; C-8a); *tert*-butyloxy group : 27.1, 73.4.

Reaction of 5a-bromo-α-tocopherol with sodium carboxylates

0.357 g (2.500 mmol) of dry and NaOH-free sodium benzoate (or 0.205 g (2.500 mmol) anhydrous sodium acetate) were added to a solution of 1.183 g (2.322 mmol) 5a-bromo-α-tocopherol in 50 ml of carefully dried acetone. The cloudy mixture was stirred at room temperature under N_2 until a white solid precipitated, and further stirred at 40 °C for 2 h. After cooling to room temperature the solid was removed by filtration, 100 ml of CH_2Cl_2 was added and the solution washed in succession twice with 10 ml of 1% NaOH and twice with 20 ml H_2O. The organic phase was separated, carefully dried over $MgSO_4$, and concentrated by evaporation at room temperature to a volume of 50 ml. Petroleum ether (b. p. 40–50 °C) was added dropwise until the solution became slightly cloudy. The mixture was kept in a refrigerator at 0 °C, and an additional 3 ml of petrol ether was added. After 48 h at –10 °C the mixture was cooled to –78 °C for 2 h. The precipitated solids were very quickly separated, dried under vacuum and recrystallized twice from *n*-hexane/petroleum ether (1:1, v/v).

5a-Benzoyloxy-α-tocopherol (**10**)
Yield 0.970 g (76%), *m.p.* 28–32°C. – $C_{36}H_{54}O_4$ (550.8); calcd.: C 78.50; H 9.88; found: C 78.55; H 9.83%. – ^{1}H NMR ($CDCl_3$): 2.10 (s, 3H, CH_3, C-7a), 2.15 (s, 3H, CH_3 , C-8b), 2.60 (t, 2H, $ArCH_2CH_2$, C-4), 5.30 (s, 2H, Ar-CH_2-O, C-5a), 6.90 (m, 5H,H^{Ar}). – ^{13}C NMR ($CDCl_3$): 17.9 (C-4), 31.2 (C-3), 59.4 (C-5a), 74.2 (C-2), 114.8; 115.6; 122.0; 123.4 (C-4a; C-5; C-7; C-8), 144.7; 145.5 (C-6; C-8a); benzoyloxy group: 127.0 (C-4'), 129.6 (C-2'; C-6'), 130.6 (C-1'), 132.6 (C-3'; C-5'), 166.3 (CO).

5a-Acetoxy-α-tocopherol (**11**)
Yield: 0.635 g (56%), *m.p.* 5–8 °C. – $C_{31}H_{52}O_4$ (488.8); calcd.: C 76.18; H 10.72; found: C 76.13; H 10.75%. – ^{1}H NMR ($CDCl_3$): 2.08 (s, 3H, CH_3 , C-7a), 2.18 (s, 3H, CH_3 , C-8b), 2.70 (t, 2H, $ArC\underline{H}_2CH_2$, C-4), 5.20 (s, 2H, Ar-CH_2-O, C-5a). – ^{13}C NMR ($CDCl_3$): 19.5 (C-4), 31.2 (C-3), 60.4 (C-5a), 74.7 (C-2), 115.1; 115.7; 123.5; 125.2 (C-4a; C-5; C-7; C-8), 145.5; 146.8 (C-6; C-8a); acetoxy group: 20.5, 173.7.

Reaction of 5a-bromo-α-tocopherol with silver carboxylates

5a-Bromo-α-tocopherol (2.366 g, 4.644 mmol) was dissolved in 50 ml of *n*-hexane and cooled to –5 °C (ice/NaCl freezing mixture) in an inert gas atmosphere. 9.300 mmol of the appropriate silver carboxylate was added all at once to the vigorously stirred mixture. Immediately after the addition the mixtures turned yellow and cloudy and, after few seconds, a yellow precipitate formed. The solution was stirred for additional 10 min. After removal of the solids the solution was washed with 10 ml of 5N HNO_3 and twice with 10 ml H_2O. The organic phase was separated, carefully dried over $MgSO_4$, and concentrated to a volume of 20 ml. Petroleum ether (*b.p.* 40–70°C) was added dropwise until the solution became slightly cloudy. The mixture was kept in a refrigerator at 0 °C, and an additional 1 ml of petrol ether was added. After 48 h at –10 °C the mixture was cooled to –78 °C for 2 h. The precipitate was very quickly separated, dried under vacuum and recrystallized twice from *n*-hexane : petrol ether = 1:1. Both **10** and **11** are formed in quantitative yield.

Reaction of 5a-bromo-α-tocopherol with tertiary amines

A solution of 1.183 g (2.322 mmol) 5a-bromo-α-tocopherol in a mixture of 20 ml nitromethane and 20 ml *n*-hexane was added dropwise at –10 °C in an inert atmosphere to a stirred solution of 0.220 g (2.781 mmol) pyridine (or 0.283 g (2.800 mmol) triethyl amine) in 10 ml CH_3NO_2. The solution was stirred for additional 30 min and warmed to room

temperature. The slightly yellow precipitate was removed by filtration, washed thoroughly three times with 20 ml of *n*-hexane and held under reduced pressure for 1 hour at room temperature. The color of the precipitate changed to white during the washing. The solid was washed with 100 ml ice-cold 2% HBr and 10 ml ice-cold H_2O. The remaining residue was dried under reduced pressure over $CaCl_2$ and recrystallized from ethyl acetate.

N-*(5a-α-Tocopheryl)-pyridinium bromide* **(13)**
Yield 0.939 g (68%), *m.p.* 58–61°C (dec.). – $C_{34}H_{54}O_2NBr$ (588.7); calcd.: C 69.37; H 9.25; N 2.38; Br, 13.57; found: C 69.41; H 9.26; N 2.44; Br 13.67%. – ^1H NMR ($CDCl_3$): 2.10 (s, 3H, CH_3 , C-7a), 2.15 (s, 3H, CH_3 , C-8b), 2.60 (t, 2H, $ArC\underline{H}_2CH_2$, C-4), 4.95 (s, 2H, CH_2, Ar-CH_2-N, C-5a), 8.20 (m, 2H, H^{Ar}), 8.70 (m, 2H, H^{Ar}), 8.90 (m, 1H, H^{Ar}). – ^{13}C NMR ($CDCl_3$): 19.3 (C-4), 31.2 (C-3), 59.4 (C-5a), 74.2 (C-2), 114.6; 115.9; 122.4; 123.9 (C-4a; C-5; C-7; C-8), 144.9; 146.1 (C-6; C-8a); pyridinium moiety: 128.4; 147.6; 149,3.

N-*(5a-α-Tocopheryl)-triethylammonium bromide* **(14)**
Yield: 1.020 g (72%), *m.p.* 57–59 °C (dec.). – $C_{35}H_{64}O_2NBr$ (610.8); calcd.: C 68.83; H 10.56; N 2.29; Br 13.08; found: C 68.78; H 10.65; N 2.24; Br 12.98%. – ^1H NMR($CDCl_3$): 1.50 (t, 9H, N-CH_2-$C\underline{H}_3$), 2.10 (s, 3H, CH_3, C-7a), 2.15 (s, 3H, CH_3, C-8b), 2.60 (t, 2H, $ArC\underline{H}_2CH_2$, C-4), 3.45 (q, 6H, N-$C\underline{H}_2$-CH_3), 4.85 (s, 2H, Ar-CH_2-N, C-5a). – ^{13}C NMR ($CDCl_3$): 9.8 (N-CH_2-$\underline{C}H_3$), 19.4 (C-4), 31.1 (C-3), 54.1 (N-$\underline{C}H_2$-CH_3), 58.2 (C-5a), 74.5 (C-2), 114.2; 115.7; 124.0; 125.3 (C-4a; C-5; C-7; C-8), 144.5; 145.7 (C-6; C-8a).

Reaction of 5a-bromo-α-tocopherol with phenols (C-Alkylation)

In a 200 ml flask, equipped with a reflux condenser, gas inlet, and dropping funnel, the mixture of 1.183 g (2.322 mmol) 5a-bromo-α-tocopherol and 0.313 g anhydrous $ZnCl_2$ in 50 ml of *n*-hexane was stirred at room temperature for 15 min. The solution was saturated with dry hydrogen bromide and warmed to 50 °C. A solution of 0.478 g (2.322 mmol) 2,6-di-*tert*-butyl-phenol (or 0.381 g (2.322 mmol) 2-*tert*-butyl-4-methyl-phe- nol, or 0.235 g (2.500 mmol) freshly distilled phenol, or 0.270 g (2.500 mmol freshly distilled *p*-cresol) in 10 ml CH_2Cl_2 was added dropwise under stirring, while a moderate stream of HBr was passed through the reaction mixture. After 1 h the HBr stream was stopped and the mixture was stirred at 50 °C for an additional 3 h (in the case of phenol and cresol 24 h) . After cooling to room temperature, the solution was washed thoroughly with 20 ml of 2N HCl and twice with 20 ml H_2O. The organic phase was separated, dried over Na_2SO_4, and the solvent evaporated to yield pure **15**. If by-products were obtained as a result of too high reaction temperature (above 50 °C), the mixture was chromatographed on silica gel, eluting the impurities first with *n*-hexane and *n*-hexane/Et_2O (1:1, v/v), and then the product with benzene/methanol (5:1, v/v).
In the case of (unhindered) phenol at a reaction temperature above 40 °C, apart from the *para*-alkylated phenol **17** the product of *ortho*-alkylation **18** was obtained and identified by GCMS.

*(3,5-Di-*tert*-butyl-4-hydroxy-phenyl)-5a-α-tocopherol* **(15)**
Yield: 1.475 g (100%) yellow oil. – $C_{43}H_{70}O_3$ (635.0); calcd.: C 81.33; H 11.11; found: C 81.27; H 11.17. – ^1H NMR ($CDCl_3$): 2.10 (s, 3H, CH_3, C-7a), 2.15 (s, 3H, CH_3, C-8b), 2.73 (t, 2H, $ArC\underline{H}_2CH_2$, C-4), 3.92 (s, 2H, Ar-CH_2-Ar, C-5a), 7.20 (d, 2H, H^{Ar}). – ^{13}C NMR ($CDCl_3$): 20.7 (C-4), 30.2 (C-5a), 30.3 ($C(\underline{C}H_3)_3$), 31.8 (C-3), 34.3 ($\underline{C}(CH_3)_3$), 74.5 (C-2), 117.2 (C-4a), 122.0; 122.1 (C-5;C-7), 123.8 (C-8), 124.5 (C-2', C-6'), 129.8 (C-1', C^{Ar}-CH_2-), 136.2 (C-3'; C-5'), 145.3; 145.7 (C-6; C-8a), 152.5 (C-4'). – MS *m/z* (%): 634 (M^+, 30), 428 (25), 311 (35), 255 (35), 203 (50), 165 (40), 57 (100), 43 (60).

*(3-*tert*-Butyl-2-hydroxy-5-methyl-phenyl)-5a-α-tocopherol* **(16)**
Yield 1.377 g (100%) red oil. – $C_{40}H_{64}O_3$ (592.9); calcd.: C 81.03; H 10.88; found: C 80.96; H 10.93%. – ^1H NMR ($CDCl_3$): 2.10 (s, 3H, CH_3 , C-7a), 2.15 (s, 3H, CH_3, C-8b), 2.70 (t, 2H, $ArC\underline{H}_2CH_2$, C-4), 3.88 (s, 2H, Ar-CH_2-Ar, C-5a), 6.80 (d, 1H, H^{Ar}), 6.95 (d, 1H, H^{Ar}). – ^{13}C NMR ($CDCl_3$): 20.8 (C-4), 20.9 (CH_3 of phenyl moiety), 27.4, (C-5a), 30.0 ($C(\underline{C}H_3)_3$), 31.5 (C-3), 34.6 ($\underline{C}(CH_3)_3$), 74.7 (C-2), 118.2 (C-4a), 121.1; 121.4 (C-5;C-7), 124.1 (C-8), 125.9 (C-1', $\underline{C}^{Ar}$-CH_2-), 125.95 (C-4'), 128.5 (C-5'), 128.8 (C-6'), 136.5 (C-3'), 144.1; 146.4 (C-6; C-8a), 151.2 (C-2'). – MS *m/z* (%): 592 (M^+, 55), 416 (80), 365 (40), 269 (50), 164 (75), 151 (80), 57 (100), 43 (70).

(4-Hydroxyphenyl)-5a-α-tocopherol **(17)**
Yield 1.190 g (98%) oil. – $C_{35}H_{54}O_3$ (522.8); calcd.: C 80.40; H 10.41; found: C 80.33; H 10.49%. – ^1H NMR ($CDCl_3$): 2.12 (s, 3H, CH_3, C-7a), 2.15 (s, 3H, CH_3, C-8b), 2.65 (t, 2H, $ArC\underline{H}_2CH_2$, C-4), 3.74 (s, 2H, Ar-CH_2-Ar, C-5a), 6.70 (d, 2H, H^{Ar}), 7.05 (d, 2H, H^{Ar}). – ^{13}C NMR ($CDCl_3$): 20.3 (C-4), 31.5 (C-3), 35.5 (C-5a), 74.2 (C-2), 115.3 (C-2'; C-6'), 118.3 (C-4a), 121.6;'121.8 (C-5; C-7), 125.3 (C-8), 128.2 (C-3'; C-5'), 137.2 (C-1', $\underline{C}^{Ar}$-CH_2-), 144.6; 145.8 (C-6; C-8a), 153.1 (C-4'). – MS *m/z* (%): 522 (M^+, 100), 429 (30), 416 (65), 318 (50), 278 (50), 205 (45), 107 (80), 64 (30)

(2-Hydroxyphenyl)-5a-α-tocopherol **(18)**
The compound was obtained as by-product, when phenol was alkylated by **1** at 50 °C. Yield : 27% (GC). – MS *m/z* (%): 522 (M^+, 60), 429 (20), 416 (100), 318 (60), 278 (40), 205 (25), 107 (75), 64 (35).

(2-Hydroxy-5-methyl-phenyl)-5a-α-tocopherol **(19)**
Yield 1.196g (95%) oil. – $C_{36}H_{56}O_3$ (536.8); calcd.: C 80.54; H 10.52; found: C 80.50; H 10.57%. – ^1H NMR ($CDCl_3$): 2.12 (s, 3H, CH_3 , C-7a), 2.16 (s, 3H, CH_3, C-8b), 2.68 (t, 2H, $ArCH_2CH_2$, C-4), 3.80 (s, 2H, Ar-CH_2-Ar, C-5a), 6.65 (m, 1H, H^{Ar}), 6.95 (m, 2H, m, H^{Ar}). – ^{13}C NMR ($CDCl_3$): 20.5 (C-4), 30.4, (C-5a), 31.5 (C-3), 74.2 (C-2), 115.6 (C-3'), 118.0 (C-4a), 120.8; 121.0 (C-5; C-7), 122.5 (C-8), 127.8 (C-4'), 128.5 (C-6'), 130.2 (C-5'), 133.2 (C-1', C^{Ar}-CH_2-), 144.5; 146.0 (C-6; C-8a), 151.1 (C-2'). – MS *m/z* (%): 536 (M^+, 100), 429 (20), 416 (80), 331 (50), 291 (50), 165 (45), 205 (30), 121 (70).

References

[1] For the preceding paper see: T. Rosenau, W. D. Habicher, J. Org. Chem. **60** (1995) 8121

[2] T. Rosenau, W. D. Habicher, Tetrahedron **51** (1995) 7919

[3] For preparation see: D. R. Nelan, C. D. Robeson, J. Am. Chem. Soc. **84** (1962) 2963; P. Schudel, H. Mayer, J. Metzger, R. Rüegg, O. Isler, Helv. Chim. Acta **46** (1963) 636. For NMR data see: H. M. Fales, J. Chem. Soc., Perkin Trans. II **1990** 1005

[4] For an illustrative example see: C. F. H. Allen, J. W. Gates jr., Org. Synth., Coll. Vol.III (1955) 140

[5] The silver salts have to be carefully liberated from water. In addition, satisfactory results were obtained only with finely powdered material.

[6] P. Schudel, H. Mayer, J. Metzger, R. Rüegg, O. Isler, Helv. Chim. Acta **46** (1963) 333; W. John, Z. Physiol. Chem. **252** (1938) 222

[7] Substituents at the position 5a, such as -OR, -OCOR or $-NR_3^+$, are readily eliminated, analogous to the elimination of HBr from 5a-bromo-α-tocopherol (**1**). However, 5a-alkoxy-α-tocopherols or 5a-aryloxy-α-tocopherols and, especially, 5a-α-tocopheryl esters are not as thermolabile as 5a-bromo-α-tocopherol. Elimination of the substituents does not occur below 80 °C.

[8] IUPAC-IUB Commission on Biochemical Nomenclature (CBN), Arch. Biochim. Biophys. **165** (1974) 1; IUPAC-IUB Nomenclature of Tocopherols and Related Compounds, Eur. J. Biochem. **123** (1982) 473

[9] S. Urano, M. Matsuo, Chem. Pharm. Bull. **28** (1980) 1992, and S. Brownstein, K. U. Ingold, J. Org. Chem. **54** (1989) 561

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