Pergamon

Tetrahedron Vol. 51, No. 29, pp. 7919-7926, 1995
Elsevier Science Ltd
Printed in Great Britain
0040-4020/95 $9.50+0.00

0040-4020(95)00421-1

Novel Tocopherol Compounds I. Bromination of α-Tocopherol - Reaction Mechanism and Synthetic Applications

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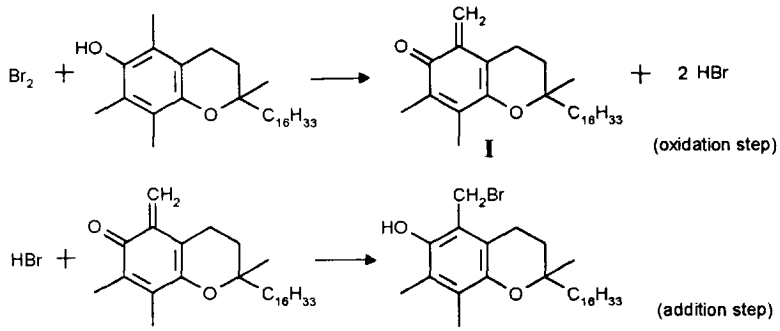
Abstract : Bromination of α-tocopherol is shown to proceed as a two-step process including the occurrence of an ortho-quinone methide, not as a radical-chain reaction, contrary to earlier reports. The ortho-quinone methide intermediate is also produced by oxidation of a-tocopherol with silver oxide and can be trapped in the presence of electron-rich dienophiles in a hetero-Diels-Alder reaction to form novel dichromanes in high yields.

Bromination of α-tocopherol - reaction mechanism

In chemical reactions α-tocopherol (vitamin E) is usually used as a radical trapping agent or as a reductant, corresponding to its biological action. In any case the tocopherol molecule is either modified on the phenolic OH-group or oxidized by destruction of the chromane structure. There are very few reports on reactions of α-tocopherol that are not oxidations or radical trapping reactions. One of these reactions is the bromination of α-tocopherol with elemental bromine leading to 5a-bromo-α-tocopherol (5-bromomethyl-γ-tocopherol) **(1)**. The reaction was postulated to proceed as a radical reaction,[1] since it yields a 5a-substituted product which is also obtained by the reaction of α-tocopherol with various radicals.[2] For example, the reaction between α-tocopherol and benzoyl peroxide leads to the formation of 5-benzoyloxymethyl-γ-tocopherol **(2)**.

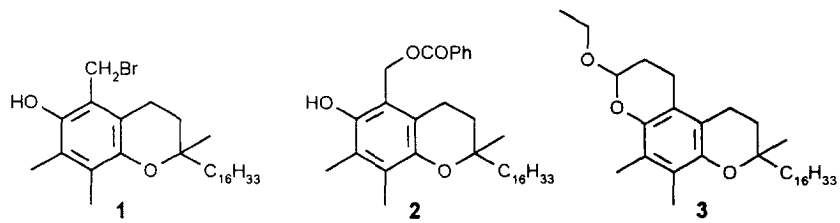
The possibility of obtaining 5a-bromo-α-tocopherol quantitatively by using carefully dried n-hexane as the solvent and moisture-free bromine as the brominating agent gave rise to doubts about the course of the reaction, since a radical-chain mechanism should yield by-products in at least small amounts. The initial step of the radical mechanism, the photolytic cleavage of bromine molecules,[3] cannot proceed in the dark and is not supposed to proceed fast at lower temperature. However, the reaction rate is not noticeably reduced by working a) in the dark and at room temperature, b) at temperatures of about 0 or -20°C, c) at -78° C, d) in the dark and at -20°C, or e) in the dark and at -78° C. For these reasons we postulated a new mechanism for the bromination of α-tocopherol that consists of two steps, an oxidation step followed by an addition step : bromine oxidizes α-tocopherol to the ortho-quinone methide **I**, which adds hydrogen bromide that was formed in the first step. It should be noted that there are not any radical intermediates formed in the reaction according to this mechanism, all steps proceed via two-electron processes. This mechanism matches all of the observations made : the formation exclusively of one product is not surprising, since a sufficient amount of HBr

is always present to react with the ortho-quinone methide. A homolytic cleavage of bromine molecules is not involved. This makes the reaction possible in the dark and at low temperatures.



Scheme 1. Reaction Mechanism of the Bromination of α-tocopherol

The occurrence of the ortho-quinone methide **I** during the reaction was shown by trapping with ethyl-vinyl ether, leading to the Diels-Alder adduct **3** in a yield of about 15%. The reaction of bromine exclusively with ethylvinyl ether instead of α-tocopherol caused some difficulties, which could be avoided by carefully chosen reaction conditions, e.g., dosing of bromine and ethylvinyl ether by peristaltic pumps to minimize the mixing of reagents and to enable the bromine to react with the α-tocopherol as well. The Diels-Alder product **3** was identified using NMR techniques and by comparison with an authentic sample prepared by a method described later in this paper.

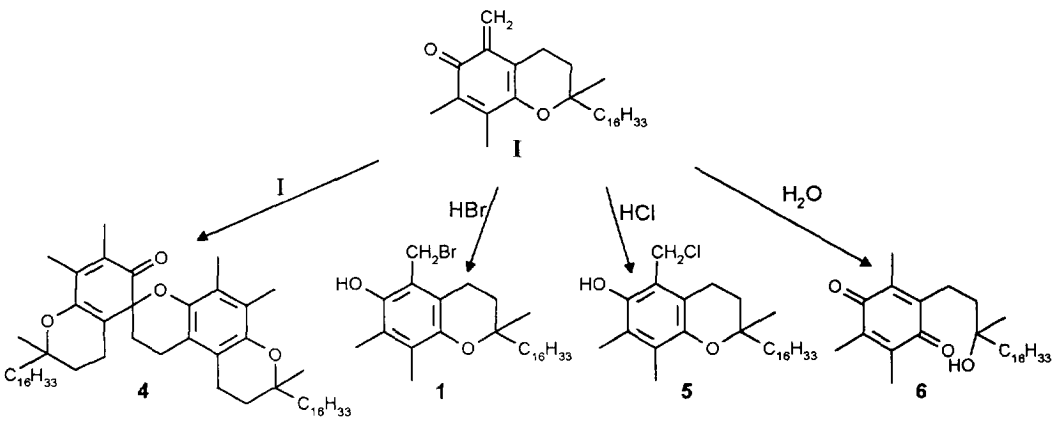


A nearly complete absence of HBr in the reaction mixture during the bromination was achieved by a strong flow of dry nitrogen blown rapidly through the reaction mixture. If an insufficient amount of HBr is present to react with the ortho-quinone methide intermediate, formation of **1** cannot proceed. Instead of this, the α-tocopherol spiro-dimer **4**[4] was observed as the main product. The formation of the spiro-dimer is thought to be a hetero-Diels-Alder reaction of one molecule of ortho-quinone methide **I** with another molecule of **I** regardless of the unfavorable steric conditions for this reaction.[5]

Using dry hydrogen chloride instead of nitrogen to sweep out the forming HBr during the bromination reaction, the addition of HCl to the ortho-quinone methide becomes a competitive reaction to the addition of HBr. The yield of 5a-chloro-α-tocopherol **(5)** was strongly dependent on the intensity of the passing flow of HCl and could be increased up to 82%. 5a-Bromo-α-tocopherol was always formed as the second product. No other by-products were observed.

Presence of water during the bromination reaction leads to a drastic decrease in yield of 5a-bromo-α-tocopherol, with α-tocopheryl quinone **6**[6] becoming the main product. Even small traces of water caused the formation of detectable amounts of **6**. Hence, water has to be carefully excluded, if 5a-bromo-α-tocopherol is to be obtained quantitatively.

The different products resulting from the ortho-quinone methide **I** under the above described conditions are briefly summarized in the following scheme :



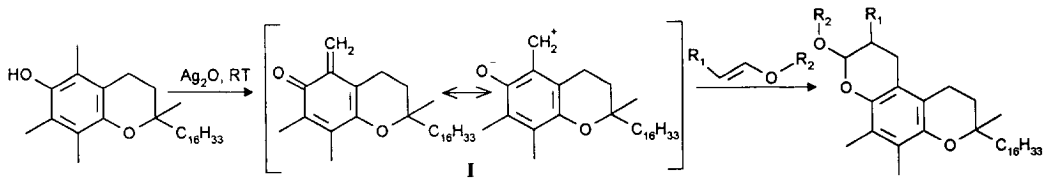
Scheme 2. Reactions of the ortho-quinone methide of α-tocopherol with different coreactants

The ortho-quinone methide intermediate **I** is always formed by the phenolic OH group and the ring-methyl group in the 5-position, never by the 7-methyl group. The higher reactivity of the 5-methyl group in comparison with the 7-methyl group, the so-called "Mills-Nixon-Effect" is frequently observed in the chemistry of chroman-6-ols and tocopherols and can be attributed to the formation of the ortho-quinone methide in many cases, as already discussed by Behan et al.[7]

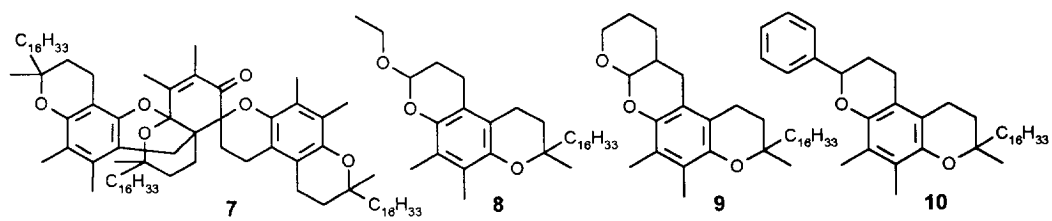
Formation of the ortho-quinone methide I from α-tocopherol by Ag_2O - synthetic applications

Oxidation of a-tocopherol leads to an enormous number of products depending on the oxidant employed.[8] When α-tocopherol was oxidized with freshly prepared silver oxide, in carefully dried n-hexane, without any coreactants, the spiro-dimer **4** and spiro-trimer **7**[9] of α-tocopherol were obtained in a molar ratio of approximately 6 : 4 without formation of any other products. This provided, once again, strong evidence for the intermediacy of **I**. The reaction mechanism, as mentioned above, is accomplished by an hetero-Diels- Alder reaction of a molecule of **I** with another molecule of **I**, or with a molecule of spiro-dimer, respectively. Moreover, Ag_2O had already been used to generate ortho-quinone methide structures starting from substituted ortho-methylphenols.[10] The foregoing lent support to the view that Ag_2O is able to convert α-tocopherol quantitatively to its ortho-quinone methide, opening the way for synthetic application based on trapping reactions of this intermediate. It should be mentioned that the Ag_2O has to be carefully liberated from H_2O, otherwise α-tocopheryl quinone **6** is formed in small amounts, analogous to the bromination of α-tocopherol with bromine. But, in contrast to bromine, the "clean" oxidant Ag_2O is easy to handle, does not interfere with most of the coreactants, and can easily be separated from the reaction mixture.

The ortho-quinone methide intermediate **I**, a hetero-analogous diene with electron deficiency, was trapped in the presence of electron-rich dienophiles, such as enol ethers, in a hetero-Diels-Alder reaction with "inverse electron demand". The resulting Diels-Alder adducts, substituted dichromanes, are formed readily under very mild conditions, since the aromatic system of the chromane is reconverted by the reaction.



The direction of addition of the dienophile to the hetero-analogous diene is clearly determined by the charge distribution in the reacting molecules and can easily be proven by NMR spectroscopy of the products. The use of ethylvinyl ether or dihydropyran, as highly reactive trapping reagents, lead to the formation of the oligocyclic compounds **8** and **9**. The yield was quantitative, if the enol ether was used in excess or applied as solvent and if certain reaction conditions were observed.[11] For instance, vigorous stirring during the reaction and the use of freshly precipitated and powdered Ag_2O as starting material seem to be absolutely crucial to obtain quantitative yields.



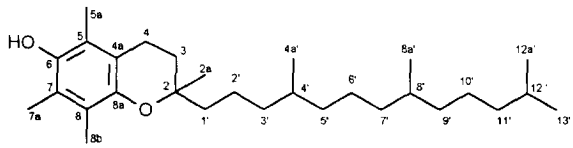
Styrene - a less reactive electron-rich dienophile than enol ethers - formed compound **10** at a 70% yield, and the α-tocopherol spiro-dimer **4** was generated as a by-product. The reaction between one molecule of ortho-quinone methide, as a diene, and another molecule of **I**, reacting as a dienophile, becomes competitive when the applied trapping reagent is not a highly reactive dienophile. In the presence of less reactive compounds, such as styrene or cyclopentene, the formation of the dimer **4** and trimer **7** of α-tocopherol consequently dominate. No reaction was observed between electron-deficient dienophiles, such as maleic anhydride, and the ortho-quinone methide.

In summary, we have described a new, non-radical mechanism for the bromination of α-tocopherol. The intermediacy of an ortho-quinone methide has been proved and synthetic use of this intermediate as a diene in hetero-Diels-Alder reactions involving tocopherols has been described. These reactions represent a novel approach to substituted dichromanes with tocopherol-like substitution patterns. Current investigations in our group are aimed at studying further synthetic applicability of this reaction type employing tocopherol model compounds instead of α-tocopherol itself and using other dienophiles, e.g. hetero-analogous dienes.

EXPERIMENTAL

^{1}H NMR spectra were recorded at 200 MHz, ^{13}C NMR spectra at 50 MHz (Bruker AC-200P) in $CDCl_3$ with TMS as the internal standard. Chemical shifts are expressed in δ value. ^{13}C-peaks were assigned by means of DEPT (**D**istortionless **E**nhancement by **P**olarization **T**ransfer) and GD (**G**ated **D**ecoupling). IR spectra were recorded on a FTIR spectrometer Nicolet 205. GCMS was performed on a Hewlett Packard device (5890 Series II, EI, 70 eV, ion trap detector). Elementary analyses were performed at the Institut für Organische Chemie, Technische Universität Dresden. The chlorine and bromine content in compounds **1** and **5** was established by argentometric titration after combustion of the samples.

The numbering of the carbon atoms in tocopherols and the nomenclature proposed by the IUPAC[12] have been used, as shown in the following figure for the starting material α-tocopherol.



The δ-values for the atoms of the isoprenoid side chain (C-1' to C-13') are not listed, since they are well established[13] and are not or only slightly effected by modifications of the chromane structure.

Bromination of α-tocopherol with bromine - general procedure. All reagents and glassware were carefully liberated from H_2O by common procedures.[14] A solution of α-tocopherol (1.29 g ; 3.00 mmol) in 50 mL n-hexane was placed into a 250 mL flask equipped with a dropping funnel, magnetic stirrer and a drying tube filled with $CaCl_2$. A solution of Br_2 (0.50 g ; 3.13 mmol) in 20 mL n-hexane was quickly added at room temperature. The solution was stirred for 2 h. The solvent and remaining Br_2 were removed *in vacuo* at room temperature. The clear, oily residue obtained consisted of pure 5a-bromo-α-tocopherol requiring no further purification. The same product is also obtained quantitatively in the dark or at lower temperatures under otherwise identical conditions. *3,4-Dihydro-5-bromomethyl-2,7,8-trimethyl-2-(4,8,12- trimethyltridecyl)-2H-1-benzopyran-6-ol, (5a-bromo-α-tocopherol, 5-bromomethyl-γ-tocopherol)* **(1)**. Yield : 1.52 g (99%). Anal. Calcd. for $C_{29}H_{49}O_2Br$: C, 68.35; H, 9.69; Br, 15.68. Found : C, 68.29; H, 9.74; Br : 15.87%. ^{1}H NMR ($CDCl_3$) : δ 1.8 (2H, m, $ArCH_2\underline{CH_2}$, C-3), 2.12 (2 x H, 2 x s, 2 x $\underline{CH_3}$, C-7a and C-8b), 2.65 (2H, t, $Ar\underline{CH_2}CH_2$, C-4), 4.0 (1H, br s, OH), 4.65 (2H, s, $\underline{CH_2}Br$, C-5a). ^{13}C NMR ($CDCl_3$) : δ 12.0 (C-8b), 12,1 (C-7a), 19.1 (C-4), 20.9 (C-2'), 23.5 (C-2a), 27.5 (C-5a), 31.0 (C-3), 74.5 (C-2), 117.2 (C-4a), 119.4 (C-5), 122.4 (C-7), 126.9 (C-8), 145.4 (C-6), 145.8 (C-8a).

Bromination of α-tocopherol with bromine, sweeping out the forming HBr by nitrogen. The reaction was carried out in a 250 mL flask equipped with dropping funnel, reflux condenser and gas inlet. The preparation follows the above procedure. Under otherwise identical conditions, a stream of dry, oxygen-free N_2 was blown rapidly through the mixture during and after the addition of bromine using a sintered bubbler. The nitrogen feed was maintained at a constant flow. The composition of the reaction mixture, containing mainly α-tocopherol spiro-dimer **4** and 5a-bromo-α-tocopherol **(1)** as by-product, was determined by GC and TLC

with hexane/ethyl ether (9 : 1, v/v) as the solvent system. Pure 1,3′,4′,8,9,10-hexahydro-2′,5,6,7′,8,8′-hexamethyl-2′,8-bis(4,8,12-trimethyltridecyl)-spiro-[benzo-[1,2-b:4,3-b′]dipyran]-3(2H),5′-[5H-1]benzopyran-6′(2′H)-one **(4)** was obtained by silica gel column chromatography eluting the product with n-hexane and the impurities with benzene. The NMR data were consistent with the literature.[15]

Bromination of α-tocopherol with bromine, sweeping out the forming HBr by hydrogen chloride. The preparation follows the above directions. Before the addition of Br_2 , the α-tocopherol solution was flushed with dry, water free HCl for 15 min, which was also blown through the reaction mixture during the bromination and for an additional hour thereafter. The reaction mixture containing 3,4-dihydro-5-chloromethyl-2,7,8-trimethyl-2-(4,8,12-trimethyltridecyl)-2H-1-benzopyran-6-ol **(5)** as well as the bromide **1** was determined by elemental analysis (ratio of halogens) and ^{1}H NMR (ratio of the intensities of the clearly distinguishable methylene signals of the -CH_2Br- and the -CH_2Cl group, respectively). The absence of other products in the reaction mixture was determined by TLC. The following data were obtained for a reaction mixture with a comparatively high content of **5**, obtained upon vigorous flushing of the reaction mixture with HCl. Anal. Found : C, 73.29; H, 10.36; Cl, 5.42; Br, 4.60%. This leads to the stoichiometric formula $C_{29}H_{49}Cl_{0.72}Br_{0.28}$ referred to the C-29 unit of tocopherol. Hence, the ratio of **5** to **1** is about 7 / 3. This was verified by ^{1}H NMR : I_{Cl}(δ 4.95, s, $\underline{CH_2}$Cl) / I_{Br} (δ 4.65, s, $\underline{CH_2}$Br) = 3 / 7.

Bromination of α-tocopherol with bromine in the presence of water. The preparation follows the above given general procedure. Excessive amounts of H_2O (1.00 g ; 55.51 mmol) were added to the solution of α-tocopherol before the addition of Br_2. The reaction mixture contained α-tocopheryl quinone **(6)** as the main product (93%) and smaller amounts of 5a-bromo-α-tocopherol **(1)** (7%) as determined by means of GC. If no extra H_2O was added, but n-hexane and bromine were not especially free of water, 5a-bromo-α-tocopherol **(1)** was obtained in yields above 95%. However, α-tocopheryl quinone **(6)** was always present as a by-product. The mass spectrum of the obtained 3,4,5-trimethyl-2-(3-hydroxy-3,7,11,15-tetramethyl-hexadecan-1-yl)-p-benzoquinone **(6)** was identical to that of an authentic sample prepared according to John.[6] The NMR and MS data are given in the following since the literature values are contradictory. ^{13}C NMR ($CDCl_3$) : δ 21.1 (C-4), 26.2 (C-2a), 41.9 (C-3), 72.0 (C-2), 139.8; 140.0; 140.1 (C-5; C-7; C-8), 144.2 (C-4a), 186.7; 187.0 (C-6; C-8a). MS : 447/446 (100%) (M^+), 429/428 (40%) (M^+ - 18 [H_2O]), 221 (90%) (M^+ - 225 [C_{16}-side chain]), 178 (60%), 165 (90%), 150 (20%), 43 (30%).

Oxidation of α-tocopherol with Ag_2O in the absence of trapping reagents. 0.55 g (2.37 mmol) freshly prepared and well-powdered Ag_2O was added to a solution of α-tocopherol (1.00 g; 2.32 mmol) in 100 mL of dry n-hexane. The reaction mixture was stirred until the black colour of the oxide was replaced by the gray of elemental silver. The solids were filtered off and the solvent evaporated *in vacuo*. The resulting oily residue was chromatographed on silica gel. The spiro-dimer **4** was eluted with n-hexane, the trimer **7** with n-hexane / diethyl ether (1:1, v/v). Yield : α-tocopherol spiro-dimer : 0.52 g (52%), α-tocopherol spiro-trimer : 0.34 g (34%). For spectroscopic data of the spiro-dimer and spiro-trimer of α-tocopherol see [15] and.[16]

Oxidation of α-tocopherol with Ag_2O in the presence of trapping reagents to 8-ethoxy-1,2,3,8,9,10-hexahydro-3,5,6-dimethyl-3-(4,8,12-trimethyltridecyl)-pyrano[3,2-f]chroman **(8)**. α-Tocopherol (1.00 g ; 2.32 mmol) was dissolved in 20 mL dry n-hexane and 80 mL freshly distilled ethylvinyl ether. A slurry of Ag_2O (0.65 g ; 2.81 mmol) in 20 mL n-hexane was added to the tocopherol solution in four equal charges at intervals of about 5 min. The reaction mixture was stirred for 1 h at room temperature and the solids were filtered off. The solvents were evaporated, the oily residue was dissolved in 30 mL n-hexane, washed twice with 10 mL of H_2O and dried over Na_2SO_4. The solvent was carefully removed to give 1.06 g (96%) of **8**. Anal. Calcd. for $C_{33}H_{56}O_3$: C, 79.15; H, 11.27. Found : C, 79.11; H, 11.31%. ^{13}C NMR ($CDCl_3$) : δ 15.2 (C^D), 20.5 (C-4), 20.9 (C-5a), 26.65 (C^A), 31.2 (C-3), 60.5 (C^C), 74.4 (C-2), 96.2 (C^B), 115.6; 117.0; 123.0; 123.4; 142.6; 145.3 (C^{Ar}). The capitals A-D mark the C atoms in the former ethylvinyl "moiety" : C^AH_2=C^BH-O-C^CH_2-C^DH_3. MS : 500 (100%) (M^+), 275 (15%) (M^+ - 225 [side chain]), 235 (70%) (M^+ - 225 - 40 [propyne]), 189 (40%) (M^+ - 225 - 40 - 46 [EtOH]), 175 (20%), 43 (45%).

2,3,9,10,11,12-Hexahydro-6,7-dimethyl-3-(4,8,12-trimethyltridecyl)-[2'-3'-f]pyrano-benzo[1,2-b:4,3-b'] dipyran **(9)**. The product is formed by the above procedure at a yield of 1.15g (96%) using 50 mL dihydropyran instead of ethylvinyl ether. Anal. Calcd. for $C_{34}H_{56}O_3$: C, 79.63; H, 11.01. Found : C, 79.65; H, 11.07%. MS : 512 (100%) (M^+), 428 (30%) (M^+ - 84 [pyran unit]), 287 (25%) (M^+-225 [side chain]), 247 (75%) (M^+-225-40 [propyne]), 205 (45%) (M^+-225 -84),165 (M^+-225-84-40 [propyne]), 150 (45%), 43 (65%).

1,2,3,8,9,10-Hexahydro-3,5,6-dimethyl-8-phenyl-3-(4,8,12-trimethyltridecyl)-pyrano[3,2-f]chromene **(10)**. α-Tocopherol (1.00 g; 2.32 mmol) was dissolved in 20 mL dry n-hexane and 80 mL freshly distilled styrene. A slurry of Ag_2O (0.65 g; 2.81 mmol) in 20 mL n-hexane was added to the tocopherol solution in 6 equal charges at intervals of about 5 min. The reaction mixture was stirred for 3 h at room temperature and the solids were removed by filtration thereafter. The solvents were evaporated under vacuum. The oily residue obtained was chromatographed on silica gel. By-products were eluted with n-hexane, the product with n-hexane / benzene (2 :1, v/v). Yield : 0.78 g (63%). Anal. Calcd. for $C_{37}H_{56}O_2$: C, 83.40; H, 10.59. Found : C, 83.39; H : 10.62%. ^{13}C NMR ($CDCl_3$) : δ 20.4 (C-4), 21.2 (C-5a), 24.9 (C^A), 31.1 (C-3), 74.4 (C-2), 67.9 (C^B), 115.5; 117.2; 123.0; 123.6; 143.6; 146.0 (C^{Ar} of chroman), 127.1; 127.4; 128.6; 141.7 (C^{Ar} of phenyl substituent). The capitals A and B mark the C atoms in the former styrene "moiety" : C^AH_2=C^BH-Ph. MS : 532 (70%) (M^+), 267 (60%) (M^+ - 225 [side chain] - 40 [propyne]), 203 (30%) (M^+ - 225-104 [styrene]), 175 (20%), 165 (15%), 91 (100%) (tropylium cation), 43 (60%), 28 (40%), 14 (30%).

ACKNOWLEDGEMENT

We are grateful to Dr. M.R. Gmünder, Hoffmann-La Roche Inc., Basel, for the generous donation of α-tocopherol. We thank Dr. M. Gruner for providing the NMR spectra, Dr. H. Kroschwitz for running the GCMS experiments and Ms. Pinske for carrying out the elemental analyses. We thank the Studienstiftung des Deutschen Volkes for a PhD fellowship to T.R.

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(*Received in Germany* 6 *March* 1995; *accepted* 23 *May* 1995)