Synthesis of \( \alpha \)-Tocopheryl Glycosides

S. Witkowski* and P. Wałejko
Institute of Chemistry, University of Bialystok, Pilsudskiego 11/4, 15-443 Bialystok, Poland
Reprint requests to Dr. St. Witkowski. E-mail: wit@noc.uwb.edu.pl

Z. Naturforsch. 56b, 411–415 (2001); received April 10, 2000

Vitamin E, Glucosylation, \( \alpha \)-Tocopheryl Glycosides

An unusual course of d-\( \alpha \)-tocopherol glucosylation by the Helferich method was observed. The product distribution very depended on acid catalyst and solvent used. The \( \beta \)-glucoside was accompanied by an unsaturated \( \alpha \)-glucoside. Other unsaturated d-\( \alpha \)-tocopheryl glucosides were obtained by reactions with acetylated glucal and 2-acetoxy glucal.

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(rrr-\(+\)-\( \alpha \)-tocopherol (1)

The therapeutic application of vitamin E is seriously limited by its very low solubility in aqueous phases, and tocopherols cannot be used when instant administration of a strong antiradical and antioxidant agent is needed. To increase solubility in water and facilitate permeability through cellular membranes tocopherol can be attached to a carbohydrate moiety [1]. The synthesis of some tocopheryl mono- and disaccharide derivatives has been reported earlier [2,3].

The reaction of \( \alpha \)-tocopherol (1) and 1,2,3,4,6-penta-O-acetyl-\( \beta \)-D-glucose (2) was carried out at 100 °C in the presence of catalytic amounts of p-toluenesulfonic acid (PTSA), according to Helferich [4] with continuous removal of acetic acid (vacuum, 40 Torr) [2]. Two products in the ratio 4:1 (by \( ^1 \)H NMR) were isolated (Scheme 1). The major (more polar) one was identified as d-\( \alpha \)-tocopheryl 2,3,4,6-tetra-O-acetyl-\( \beta \)-D-gluco-pyranoside (3a). The structure was confirmed by comparison of \( ^1 \)H and \( ^{13} \)C NMR data with those recently reported by Lahmann and Thiem [3]. The less abundant product showed in its \( ^1 \)H and \( ^{13} \)C NMR spectra, the presence of only three acetyl groups. Since olefinic signals were also observed [doublet at 5.92 ppm in the proton spectrum and two carbon resonances at 116.8 (tertiary) and 145.6 ppm (quaternary)] the structure was assigned to be d-\( \alpha \)-tocopheryl 2,4,6-tri-O-acetyl-3-deoxy-\( \alpha \)-D-erythro-hex-2-enopyranoside (4) (Scheme 1).

When the glucosylation was carried out in triglyme solution, the product 4 was prevailing (ratio 3a:4 = 1:2 by \( ^1 \)H NMR). The glucosides 3a and 4 were subjected to deacetylation in two ways: MeONa/MEOH [5] and NaCN/MEOH [6]. The glucoside 3a yielded 3b in high yield. Compound 4 appeared unstable under the deacetylation conditions and free \( \alpha \)-tocopherol was isolated. Catalytic hydrogenation of 4 yielded two saturated glycosides 5a and 5b in the ratio 3:5 (Scheme 1). The anomeric carbon signal for 4 at 96.1 ppm disappeared and two resonances of anomeric carbons for d-\( \alpha \)-tocopheryl 2,4,6-tri-O-acetyl-\( \alpha \)-D-erythro-hexopyranoside (5a) and d-\( \alpha \)-tocopheryl 2,4,6-tri-O-acetyl-\( \alpha \)-D-arabinohexopyranoside (5b) at 100.3 and 98.1 ppm, respectively, were observed.

\[ \text{RRR-}(+)\text{-}\alpha\text{-tocopherol (1)} \]

\[ \text{Scheme 1} \]

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After deacetylation (MeOH, KCN) the two free stable glycosides 5c and 5d were obtained. The values of the anomeric carbon-proton coupling constant (172.2 Hz for 4) [7] and the chemical shifts for the anomeric carbon below 100 ppm [8] for 4, 5a and 5b proved the α-configuration of the glucosidic bonds in these compounds.

Reduction of 4 by LiAlH₄ yielded the unsaturated product d-α-tocopheryl 3,4-dideoxy-α-D-erythro-hex-3-enopyranoside (6). The olefinic protons of 6 gave a doublet of doublets in the ¹H NMR ($J_{3,4}=10.5$ Hz) and no coupling with the anomeric proton signal was observed. In order to prove the position of the double bond, the synthesis of the glucoside 8 was carried out according to Scheme 2. 3,4,6-Tri-O-acetyl-1,5-anhydro-2-deoxy-D-arabino-hex-1-enitol (triacetyl glucal, 7) and tocopherol (1) were refluxed in chlorobenzene for 3h, and a mixture of α- and β-glycosides 8 (d-α-tocopheryl 4,6-di-O-acetyl-2,3-dideoxy-α/β-D-erythro-hex-2-enopyranoside) was obtained [9, 10]. After deacetylation (KCN/MeOH) [6], a mixture of chromatographically unseparable α- and β-glycosides 8a in ratio 4:1 (by ¹H NMR) was obtained (overall 49% yield). The olefinic signals in the ¹H and ¹³C NMR spectra of the mixture are different from those recorded for 6. This result confirmed that double bond shift from the 2,3 to the 3,4 position must have occurred during the reaction of 1 with 2.

2,3,4,6-Tetra-O-acetyl-1,5-anhydro-D-arabino-hex-1-enitol (9) [11] as a possible intermediate in the glycosylation was considered. However, when neat 2 was heated with PTSA in diglyme at 120 °C, no reaction was observed. On the other hand, heating of neat 9 and α-tocopherol in the presence of traces of ZnCl₂ at 80–90 °C resulted in the glucoside 4 formation with Ferrier rearrangement [12] as the main product (19% yield). The same reaction was also carried out at higher temperature (130–140 °C) and d-α-tocopheryl 6-O-acetyl-3,4-dideoxy-α-D-hex-3-enopyranosid-2-ulose (10) was isolated in 20% yield. Heating of 4 in the presence of ZnCl₂ at 110–120 °C yielded 10. When 4 in methanol was allowed to stand at room temperature for four days it was also converted to 10. Reduction of 4 and 10 with LiAlH₄ led to the product 6 (Scheme 3).

The role of solvent in the formation of α-glucoside 4 seems to be unclear. The intermediate oxycarbenium ion probably forms with ethereal solvent a complex having β-oriented configuration. For this reason, diethyl ether is known to enhance the formation of α-glycosides [13–15]. The shielding effect of diglyme and triglyme probably tender α-glycoside formation more favourable. The reaction is accompanied by acetyl group elimination from the C-3 position. Further investigations of this problem are under current investigation.

**Experimental**

The numbering of the carbon atoms in tocopherols and the nomenclature proposed by the IU-PAC have been used [16, 17] (Scheme 4).

Natural d-α-tocopherol was purchased from Aldrich. Diglyme and triglyme were used without purification. 2-Acetoxy-D-glucal triacetate (9) was obtained according to Lemieux and Lineback [11]. ¹H, ¹³C NMR, ¹H decoupling and ¹H-¹³C HETCOR NMR spectra were obtained using a Bruker AC 200F spectrometer (200.13 MHz). Chemical shifts (δ) are reported in ppm downfield from TMS. Spectra were taken for CDCl₃ or
DMSO-d_6 solutions. IR spectra were recorded on Nicolet Magna 550 FTIR spectrometer. Mass spectra were performed on an MS AMD-604 spectrometer. Specific rotation was measured on a Perkin-Elmer 141 polarimeter. Melting points were measured in a Boetius apparatus and are uncorrected. The course of the reactions and the purity of products were checked by TLC (DC Fertigplatten 60 F 254 Merck). Preparative thin layer chromatography (PTLC) was performed on DC Fertigplatten 60 F 254 Merck (thickness 0.5 mm). Column chromatography was performed on Merck silica gel (70-230 mesh).

Glucosylation of d-α-tocopherol in diglyme or triglyme. d-α-Tocopheryl 2,3,4,6-tetra-O-acetyl-β-D-gluco-pyranoside (3a) and d-α-tocopheryl 2,4,6-tri-O-acetyl-3-deoxy-α-D-erythro-hex-2-enopyranoside (4)

d-α-Tocopherol (430 mg, 1 mmol), per-O-acetyl-β-D-glucopyranose (2) (585 mg, 1.5 mmol) and PTSA (30 mg) in 5 ml of solvent (diglyme or triglyme) was heated at 100 °C under reduced pressure (40 Torr) for 4 h. The reaction mixture was diluted with ethyl acetate (50 ml) and washed with water (3 x 30 ml). The organic layer was dried over MgSO_4 and evaporated to dryness. The crude oily mixture (680 mg) was purified by column chromatography (hexane-ethyl acetate 15:1, v/v) and two fractions were collected. The reaction performed in diglyme solution lead to 49 mg of 4 (6% yield) and 144 mg of 3a (19% yield). In triglyme solution 110 mg of 4 (14% yield) and 90 mg of 3a (11% yield) were isolated.

d-α-Tocopheryl 2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside (3a)

M.p. 81-2 °C. [α]_D^{20} = +7.2° (CH_2Cl_2, c = 1). - IR (CHCl_3): ν = 2980, 2930, 1745 (C=O), 1455, 1370, 1060, 1030 cm^{-1}. The 1H and 13C NMR spectra were identical with those described earlier [3].

Reaction of d-α-tocopherol with 2,3,4,6-tetra-O-acetyl-1,5-anhydro-D-arabino-hex-1-enitol (9) in the presence ZnCl_2 at 80-90 °C or (130-140 °C). d-α-Tocopheryl 2,4,6-tri-O-acetyl-3-deoxy-α-D-erythro-hex-2-enopyranoside (4) or d-α-Tocopheryl 6-O-acetyl-3,4-dideoxy-α-D-hex-3-enopyranosid-2-ulose (10)

d-α-Tocopherol (430 mg, 1 mmol), 2,3,4,6-tetra-O-acetyl-1,5-anhydro-D-arabino-hex-1-enitol (9) (418 mg, 1.2 mmol) and anhydrous ZnCl_2 (30 mg) was heated in argon atmosphere under reduced pressure (30 Torr) for 30 min. Ethyl acetate (50 ml) was added and the solution was washed with water (3 x 30 ml). The organic layer was dried over MgSO_4, filtered off and the filtrate was evaporated to dryness. The crude mixture was purified by column chromatography (hexane-ethyl acetate 15:1, v/v). When the reaction was performed at 80-90 °C, 140 mg (20%) of 4 was isolated as the
main product. When the reaction was carried out at 130–140 °C, only glucoside 10 was isolated (19% yield) and no 4 was observed.

d-α-Tocopherol 6-O-acetyl-3,4-dideoxy-α-D-hex-3-enopyranosid-2-uloside (10)

\[ [\alpha]_D^0 = +3.5^\circ \] (CH\(_2\)Cl\(_2\), c = 1) 
- IR (CHCl\(_3\)): \( \nu = 2954, 2928, 2868, 1740 \) (C = O), 1700 (C = O), 1462, 1378, 1165, 1078, 983, 1071 cm\(^{-1}\), 
- \( ^1\)H NMR (200.13 MHz, CDCl\(_3\)): \( \delta = 1.80 \) (t, 2H, 4-H, \( ^3J \approx 7.0 \) Hz), 2.05–2.21 (4xs, 12H, H-5a, 7a, 8a and all OAc), 2.57 (t, 2H, 3-H, \( ^3J \approx 7.0 \) Hz), 4.30, 4.40 (ddd, 2H, 6'\( R \) and 6'S-H, \( ^3J_{6'R, 6'S} = 11.6 \), \( ^3J_{6'R, 6'S} = 5.5 \) and \( ^3J_{6'-S} = 4.6 \) Hz), 5.04 (–s, 1H, 1"-H), 5.27–5.22 (m, 1H, 5"-H), 7.05, 6.31 (ddd, 2H, 3" and 4"-H, \( ^3J_{3', 4'} = 10.6 \) and \( ^3J_{3, 4'} = 2.6 \) Hz). 
- \( ^13\)C\(^{1}\)H NMR (50.32 MHz, CDCl\(_3\)): \( \delta = 68.2 \) (\( ^3\)s), 74.9 (2), 98.4 (1"), 137.8 (13'), 127.8 (8), 126.3 (4"), 126.0 (7), 123.1 (5), 117.7 (4a), 100.6 (1"), 74.9 (2), 68.2 (5"), 64.8 (6"), 40.0 (1"'), 39.4 (11"'), 37.4, 37.3 (3"'), 37.2, 38.7 (4"', 8"), 31.3 (3), 29.7 (12''), 24.8 (10''), 24.4 (6''), 23.8 (2a), 22.7, 22.6 (12'a' and 13''), 21.0 (2''), 20.8 (OAc), 20.7 (4), 19.7, 19.6 (4a' and 8a'), 13.7 (7a), 12.7 (8b), 11.9 (5a). 
- MS (LSIMS, NBA, 8 kV): \( m/z \) (% ) = 599 (8) \( [M+H]^+ \). 

Reduction of d-α-tocopherol 6-O-acetyl-3,4-dideoxy-α-D-erythro-hex-3-enopyranoside to d-α-Tocopherol 2,3-dideoxy-α/β-D-erythro-hex-2-enopyranoside (9a)

Compound 4 (34 mg, 0.05 mmol) was reduced in ether (5 ml) and LiAlH\(_4\) (20 mg) was added. After complete disappearance of the substrate (TLC), the excess of LiAlH\(_4\) was decomposed with wet ether (20 ml). The solution was filtered through a pad of Celite, the filtrate was concentrated by column chromatography (hexane-ethyl acetate 20:3, v/v), to give pure product (24 mg, 86% yield, oil, \( [\alpha]^0 \approx +4.5^\circ \) \( \text{CH}_2\text{Cl}_2, \text{c} = 1 \)). 
- IR (CHCl\(_3\)): \( \nu = 2954, 2928, 2868, 1740, 1700, 1606, 1462, 1378, 1165, 1078, 983 \) cm\(^{-1}\). 
- \( ^1\)H NMR (200.13 MHz, CDCl\(_3\)): \( \delta = 1.81 \) (t, 2H, 4-H, \( ^3J \approx 7.0 \) Hz), 2.22, 2.18, 2.09 (3xs, 12H, H-5a, 7a, and 8b), 2.57 (t, 2H, 3-H, \( ^3J \approx 6.6 \) Hz), 3.71, 3.45 (ddd, 2H, 6'\( R \) and 6'S-H, \( ^3J_{6'R, 6'S} = 11.6 \), \( ^3J_{6'R, 6'S} = 6.6 \) and \( ^3J_{6'-S} = 3.5 \) Hz), 4.37–4.10 (m, 1H, 2"-H), 4.54–4.44 (m, 1H, 5"-H), 5.43 (d, 1H, 1"-H, \( ^3J_{1', 2'} = 4.0 \) Hz), 6.03, 5.86 (ddd, 2H, 3" and 4"-H, \( ^3J_{3', 4'} = 10.5 \) Hz). 
- \( ^13\)C\(^{1}\)H NMR (50.32 MHz, CDCl\(_3\)): \( \delta = 11.9 \) (5a), 13.1 (8b), 14.0 (7a), 19.7, 19.6 (4a' and 8a'), 20.7 (4), 21.0 (2''), 22.7, 22.6 (12'a and 13''), 23.9 (2a), 24.4 (6''), 24.8 (10''), 27.9 (12''), 31.2 (3), 32.8, 32.7 (4"' and 8"'), 37.4, 37.3 (3"'), 37.5, 7' and 9').

Reduction of d-α-tocopherol 6-O-acetyl-3,4-dideoxy-α-D-erythro-hex-3-enopyranosid-2-uloside (10) with LiAlH\(_4\)

Compound 10 (30 mg, 0.05 mmol) was reduced with LiAlH\(_4\) as described above. After aqueous work-up and chromatographic purification, pure product was obtained (24 mg, 86%).

Reduction of d-α-tocopherol with 3,4,6-tri-O-acetyl glacial (7) in chlorobenzene and deacetylation.

Catalytic hydrogenation of d-α-tocopherol 2,4,6-tri-O-acetyl-3-deoxy-α/β-D-erythro-hex-2-enopyranoside (9a)

Compound 4 (34 mg, 0.05 mmol) was dissolved in ethyl acetate (10 ml) and the catalyst (Pd/C-10%, 10 mg) was added. The hydrogenation was carried out under atmospheric pressure until completion (TLC, benzene-ethyl acetate 10:3, v/v). The catalyst was filtered off and after evaporation of the filtrate, 27 mg of a mixture 5a and 5b was obtained. The ratio 5a/5b = 3:5 was estimated from the intensity of anomeric carbon signals (98.1 ppm for 5a and 100.3 ppm for 5b).
Deacetylation of d-α-tocopheryl 2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside (3a), d-α-Tocopheryl β-D-glucopyranoside (3b)

To the glycoside 3a (380 mg, 0.5 mmol) dissolved in anhydrous methanol (50 ml), KCN (10 mg) was added. The mixture was stirred at rt overnight. After evaporation to dryness, the solid residue was extracted with ethyl acetate (4 x 30 ml). The combined extracts were concentrated and 286 mg of 3b was obtained. M.p. 159-160 °C. [α]$^2_0 = +7.26$ (MeOH, c = 1). - IR (KBr): ν = 3390, 2927, 2868, 1461, 1378, 1254, 1072, 1035, 1012 cm$^{-1}$. - $^1$H NMR (200.13 MHz, CDCl$_3$): δ = 1.74 (m, 2H, 4-H), 2.14, 2.11, 2.02 (3xs, 9H, H-5a, 7a and 8b), 2.50 (m, 2H, 3-H), 3.19-3.22 (m, 1H, 5''-H), 3.85-3.65 (m, 5H, H-2'', 3'', 4'' and 6''). 4.56 (d, 3 J = 7.0 Hz, 1H, 1''-H). - $^{13}$C{[H] NMR (50.32 MHz, DMSO-d$_6$): δ = 11.7 (5a), 12.6 (8b), 13.5 (7a), 19.6, 19.5 (4'a and 8'a), 20.1 (4), 20.4 (2''), 22.5, 22.4 (12'a and 13''), 23.4 (2a), 23.7 (6''), 24.1 (10''), 27.4 (12''), 30.7 (3), 32.0, 31.9 (4' and 8''), 36.8, 36.7, 36.6 (3', 5', 7' and 9''), 38.7 (11''), 38.9 (1''), 61.2 (6''), 70.0 (4''), 74.1 (2''), 76.5 (5''), 76.6 (3''), 74.3 (2), 104.8 (1''), 116.8 (4a), 121.2 (5), 126.7 (7), 128.3 (8), 145.9 (6), 147.4 (8a). - MS (LSIMS, NBA, 8 kV): m/z (%) = 593 (11) [M+H]$^+$, with NaOAc 615 (31) [M+Na]$^+$. Deacetylation of glycosides mixture 5a and 5b, d-α-Tocopheryl 2,4,6-tri-O-acetyl-α-D-ribo-hexopyranoside (5c) and d-α-tocopheryl 2,4,6-tri-O-acetyl-α-D-arabino-hexopyranoside (5d).

The mixture of 5a and 5b (20 mg) in anhydrous methanol (3 ml) was dissolved and a catalytic amount of KCN was added. After stirring overnight followed by work-up 17 mg of 5c and 5d mixture was obtained.

Attempted deacetylation of d-α-tocopheryl 2,4,6-tri-O-acetyl-3-deoxy-α-D-erythro-hex-2-enopyranoside (4)

a) Deacetylation according to Herzig et al. [6]: Compound 4 (35 mg, 0.05 mmol) was treated as described above for 3a. After work-up 14 mg of free α-tocopherol was isolated.

b) Deacetylation according to Zemplen and Pascu [5]. Compound 4 (35 mg, 0.05 mmol) was dissolved in dry methanol (4 ml) and a 2M solution of MeONa in methanol (2 ml) was added. The mixture was refluxed for 5 min. After aqueous work-up, 11 mg of α-tocopherol was isolated.