Studies in the Acid Catalysed Glycosylation of α-Tocopherol

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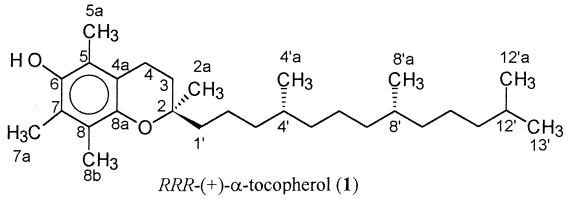
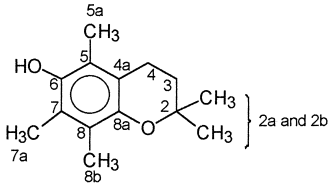
α-Tocopherol, Glycosylation, Acidic Catalysis

Condensation of α-tocopherol and 2,2,5,7,8-pentamethyl-6-hydroxychroman (the model compound) with peracetylated glucose, mannose and galactose was carried out. The influence of various acidic catalysts on the chemical yield and the stereochemical outcome of the glycosylation was investigated.

The water insolubility of α-tocopherol is very likely the predominant factor responsible for its much-diminished absorption following oral administration. Therefore, several attempts have been made to increase the bioavailability of vitamin E. One of the most promising ways is to convert α-tocopherol into an amphiphilic glycoconjugate. The synthesis of some tocopheryl mono- and disaccharides has already been reported [1–4]. The preparations were mostly based on the Helferich method and usually yielded *trans*-1,2-glycosides [5].The described methods revealed some shortcomings: low yields [1], a large excess (6-fold) of tocopherol was needed [2] or long protection-deprotection procedure was used [3]. We have recently reported that heating of a neat peracetylated sugar with α-tocopherol in the presence of $ZnCl_2$, $FeCl_3$ or $SnCl_4$ at 140 °C under diminished pressure (40 mm Hg) yielded the mixture of α- and β-glycosides [6]. The composition of products depended mostly on the catalyst used for the reaction.



RRR-(+)-α-tocopherol (**1**)



2,2,5,7,8-pentamethyl-6-chromanol (**2**)

Scheme 1.

The formation of a glycosidic carbon-oxygen bond employing activated sugar derivatives and phenols has been explored extensively [7, 8]. The stereoselective formation of anomeric centers is a major problem in the synthesis of glycosides. Many combinations of leaving group, promoter, and protecting group have been devised to achieve this. The synthesis of aryl glycosides, in general, is more difficult because of lower nucleophilicity of phenolic hydroxy groups in comparison with that of alcohols. Glycosylation of α-tocopherol encounters some additional problems due to the steric hindrance around the phenolic group from two flanking 5,7-dimethyl groups as well as due to some specific stereoelectronic effects occurring in the 6-hydroxychromanyl system.

In continuation of our project we decided to study the influence of an acidic catalyst on the chemical yield and stereochemical outcome of the glycosylation of α-tocopherol.

Results and Discussion

In preliminary experiments, α-tocopherol (**1**) or its model compound **2**, and 1.5 equiv. of a peracetylated sugar (**3**, **4**, **13**, **18** or **19**) were heated with catalytic amounts of $ZnCl_2$ for 4 h at 130–140 °C with continuous removal of acetic acid (*vacuum* 30–40 mm Hg). After aqueous work-up, the glycosidic fractions were purified by column chromatography and analysed by ^1H and ^{13}C NMR.

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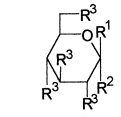
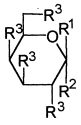


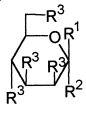
3-12

	R^1	R^2	R^3
3	OAc	H	OAc
4	H	OAc	OAc
5	Ar	H	OAc
6	H	Ar	OAc
7	Ar	H	OH
8	H	Ar	OH
9	Ar*	H	OAc
10	H	Ar*	OAc
11	Ar*	H	OH
12	H	Ar*	OH



13-17

	R^1	R^2	R^3
13	OAc	H	OAc
14	Ar	H	OAc
15	Ar	H	OH
16	Ar*	H	OAc
17	Ar*	H	OH



18-23

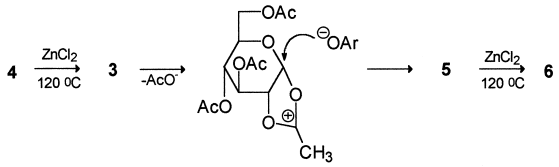
	R^1	R^2	R^3
18	OAc	H	OAc
19	H	OAc	OAc
20	H	Ar	OAc
21	H	Ar	OH
22	H	Ar*	OAc
23	H	Ar*	OH

Ar = tocopheryl
Ar* = 6-hydroxychromanyl

Scheme 2.

The yields and composition of the reaction products (α- and β-glycosides) are summarised in Table 1.

The anomeric pairs of glycosides were unseparable by column chromatography. The composition of the mixtures was determined by integration of the anomeric carbon signals (recorded with gated decoupling [10] or by comparison of the proton 5″-H signal intensity [9]). In all cases the 1,2-*trans*-glycosides (β-glucoside, β-galactoside or α-mannoside) were the prevailing products. According to the commonly accepted mechanism, the *trans* configuration results from the involvement of the neighbouring 2-Ac group with formation of a cyclic oxycarbonium intermediate [11, 12]. The 1,2-*cis*-glycosides are less abundant.



Ar = tocopheryl or 6-hydroxychromanyl

Scheme 3.

There are controversial opinions on the mechanism of formation of α-glucosides in the reaction of peracetylated glucose with phenols. Some authors considered that a prolonged heating of peracetylated β-glucose with phenol initially leads to an anomerization [13]. Nevertheless, it is known that aryl glycosides are stable under acidic conditions of anomerization (opposite to the alkyl glycosides) [14, 15]. The α-isomer can also be created by *trans*-glucosylation with an excess of a phenol [16] or by removal of the β-isomer from the reaction mixture by a selective cleavage [17, 18].

The (+)-α-tocopheryl 2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside (**5**) was subjected to the heating with freshly molten $ZnCl_2$ at 120–130 °C. The progress of the reaction was monitored by ^1H NMR spectroscopy (Table 1). A partial isomerization of β-glucoside (**5**) to the α-isomer was observed. The maximum of conversion was achieved after *ca.* 4 h (see Fig. 1). The α/β ratio was approxi-

Sugar	Aglycon	Catalyst: $ZnCl_2$ yield [%][b] (α + β)	$ZnCl_2$ ratio[c] (α/β)	$BF_3 \cdot Et_2O$ yield [%][b]	$BF_3 \cdot Et_2O$ yield [%][a,b]	$FeCl_3$ yield [%][b]
3	1	48	36:64	47 (β)	65 (β)	45 (β)
	2	44	28:72	49 (β)	66 (β)	47 (β)
13	1	35	38:62	45 (β)	66 (β)	35 (β)
	2	45	21:79	39 (β)	69 (β)	41 (β)
18 + 19 (1:1)	1	45	13:87	47 (α)	64 (α)	51 (α)
	2	40	82:18	47 (α)	67 (α)	53 (α)

Table 1. Chemical yields and α/β ratio of the glycosylation products of **1** and **2**.

[a] In the presence of molecular sieves; [b] Isolated yields by dry-flash chromatography; [c] determined by ^{13}C NMR for C-1″ and ^1H NMR for H′′ [9].

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mately the same as that obtained during glycosylation by melting of α-tocopherol with peracetylated sugar **3** (Table 1). Similarly, (+)-α-tocopheryl 2,3,4,6-tetra-O-acetyl-β-D-galactoside (**15**) at 130 °C isomerised to the mixture of both anomers with the same α/β ratio as that obtained by melting of α-tocopherol with **13** (α/β 38:62). The prolonged time of heating or increasing of temperature above 140 °C led only to decomposition of the mixture with liberation of free α-tocopherol. Under the same conditions, the attempts of isomerization of peracetylated β-glucose (**3**) and phenyl 2,3,4,6-tetra-O-acetyl-β-D-glucoside in the presence of $ZnCl_2$ under atmospheric pressure led to carbonisation with liberation of acetic acid. Thus, one can conclude that isomerization of β- to α-glycosides is possible only when a substrate undergoes melting with $ZnCl_2$ below the temperature of carbonisation.

The similar anomerization was not possible for deacetylated glycosides, which usually have higher melting points. For instance, the (+)-α-tocopheryl β-D-glucoside (**7**) (m.p. 159–160 °C) did not undergo any reaction during heating with $ZnCl_2$ at 130–160 °C. Above 165 °C only decomposition products were observed. Some similar observations were reported for the glycosylation of coumarins [17].

The formation of less abundant 1,2-*cis*-mannosides seems to be unclear. The attempts of isomerization of the model compounds methyl 2,3,4,6-tetra-O-acetyl-α-D-glucopyranoside, phenyl 2,3,4,6-tetra-O-acetyl-α-D-mannopyranoside, and 2,2,5,7,8-pentamethyl-6-chromanyl 2,3,4,6-tetra-O-acetyl-α-D-mannoside (**22**) to the respective 1,2-*trans* derivatives by prolonged heating with anhydrous $ZnCl_2$ failed. The minor 1,2-*cis*-mannosides are probably formed according to the S_N2 mechanism with inversion of configuration at the anomeric centre [19].

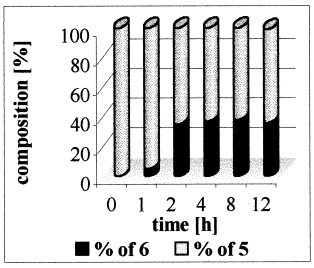

Fig 1. The progress of isomerization of **5** in the presence of $ZnCl_2$ at 120–130 °C.

Glucosylation of (+)-α-tocopherol by peracetylated β-D-glucose (**3**) in the presence of other acidic catalysts was also carried out (Table 2). Melting and heating of the reagents (see Experimental, procedure B) yielded mixtures of products, which after aqueous work-up were analyzed by ^1H and ^{13}C NMR spectroscopy. The chemical yields ranged from 10 to 50% and depended on the catalyst used. The highest contents of the α-anomer were obtained (43%) when $SnCl_4$ was used; however, a higher chemical yield of the glucosides was obtained in case of $ZnCl_2$ or $FeCl_3$. The latter seems to be the most effective catalyst. It gave not only the best chemical yield (50%), but also a relatively high content of the α-glucoside (30%). When peracetylated α-glucose was used instead of the β-isomer, the reaction gave a poor yield of α- and β-glucosides (15%) with the same ratio as that for peracetylated β-D-glucose. The elimination of α-acetoxy group followed by creation of cyclic oxonium intermediate is impossible due to steric requirements. Therefore, the isomerization of α- to β-peracetyl glucose must have occurred, and this step influences the overall yield. In the course of the reaction, the initially formed β-glucoside probably undergoes an anomerization to the α-isomer. The prolonged time of the reaction (up to 8 h) led to an increase of yield (up to 40%) with retention of the α/β ratio (Table 2).

Glycosylation of α-tocopherol according to Lahmann and Thiem [2] gave 1,2-*trans*-glycosides with high yields (up to 67%) on the condition, that a six-fold excess of tocopherol was applied. When equimolar amounts of the substrates are used, the

Table 2. Glucosylation of **1** in the presence of various acidic catalysts.

Sugar	Catalyst[a]	Yield [%][b] (α + β)	Ratio [%][c] (α/β)
3	$ZnCl_2$	48	36/64
3	$FeCl_3$	50	30/70
3	$SnCl_4$	35	43/57
3	PPA	10	100 β
4	$ZnCl_2$	15 (4 h)	37/63
		40 (8 h)	35/65

[a] 50 mg of a catalyst per 1 equiv. of **1** and 1.2 equiv. of sugar; [b] yield of isolated fraction of glucosides; [c] by ^{13}C NMR [10] or ^1H NMR [9].

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yield drops to *ca.* 40%. Therefore, the synthesis using the relatively expensive natural (+)-α-tocopherol by this method seems not economically profitable. We improved the synthesis by addition of activated molecular sieves (4 Å) to the reaction mixture. The mannosylation and galactosylation of tocopherol was also carried out more efficiently (Table 1).

Chatterjee and Nuhn [20] described a stereoselective α-glycosylation of alcohols in the presence of anhydrous $FeCl_3$. The glycosylation of α-tocopherol in the presence of anhydrous $FeCl_3$ according to the procedure A (see Experimental Section) gave the proper glycosides with good yields (45–50%) (Table 1). The final success strictly depended on the anhydrous conditions of the reaction. In the solution containing a trace of water, α-tocopherol is partially oxidised by the system Fe^{+3}/Fe^{+2} to α-tocopherylquinone and the yield of glycosylation is lowered even in the presence of molecular sieves.

The glycosylation of α-tocopherol in the presence of anhydrous $FeCl_3$ yielded selectively only 1,2-*trans*-glycosides (Table 1). The α-stereoselectivity described for alkyl glycosides [20] was not observed when aryl aglycones were used.

Experimental Section

The numbering of the carbon atoms and the nomenclature proposed by the IUPAC in tocopherol (**1**) and its model compound **2** have been used [21, 22] (Scheme 1). In the sugar parts of the tocopheryl glycosides the numbering with double primes (1″, 2″, 3″ *etc.*) was used, and for the respective chromanyl glycosides the numbering with primes (1′, 2′, 3′ *etc.*) was used. Natural (+)-α-tocopherol (**1**) was purchased from Aldrich. 2,2,5,7,8-Pentamethyl-6-chromanol (**2**) was synthesised according to Smith *et al.* [23]. Peracetylated sugars (**3**, **4**, **13**, and a mixture of **18** and **19**) were obtained by acetylation of commercially available glucose, galactose and mannose by acetic anhydride in pyridine. ^1H, ^{13}C, ^1H decoupling and $^1H-^{13}C$ 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 $CDCl_3$ or CD_3OD solutions. IR spectra were recorded on Nicolette 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).

General method for glycosylation of phenols with β-peracetylated sugars in the presence of acidic catalyst (for details see Table 1)

To the stirred mixture of a phenol (1 mmol) and sugar (1.2 mmol) in 5 ml CH_2Cl_2 was added 3 equiv. of $BF_3 \cdot Et_2O$ or 0.25 equiv. of anhydrous $FeCl_3$. The stirred mixture was kept in the dark under nitrogen atmosphere for 12 h. The reaction mixture was diluted with ethyl acetate (50 ml) and washed with water (3 × 30 ml). The organic layer was dried over $MgSO_4$ and evaporated to dryness. The crude reaction mixture was purified by column chromatography (hexane–ethyl acetate 15:1, v/v). The yields of corresponding glycosides are summarized in Table 1.

(+)-α-Tocopheryl 2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside (**5**): M.p. 81–2 °C, $[\alpha]_D^{20} = -10.4°$ ($CHCl_3$, $c = 1$). – IR ($CHCl_3$): ν = 2980, 2930, 1745 (C=O), 1455, 1370, 1060, 1030 cm^{-1}. The ^1H and ^{13}C NMR spectra were identical with those described earlier [2].

(+)-α-Tocopheryl 2,3,4,6-tetra-O-acetyl-β-D-galactopyranoside (**14**): Oil, $[\alpha]_D^{20} = +5.4°$ (CH_2Cl_2, $c = 1$). – IR ($CHCl_3$): ν = 2980, 1745 (C=O), 1455, 1370, 1060, 1030, 900 cm^{-1}. – ^1H NMR (200.13 MHz, $CDCl_3$): δ = 1.85 (t, ^3J = 6.5 Hz, 2H, 3-H), 2.00–2.20 (7×s, 21H, 5a-, 7a-, 8b-H and all OAc), 2.55 (t, ^3J = 6.5 Hz, 2H, 4-H), 3.77–3.74 (m, 1H, 5″-H), 4.07 and 4.11 (ddd, ^2J = 8.7, $^3J_{5'',6''}$ = 6.3 and $^3J_{5'',6''}$ = 6.8 Hz, 2H, 6″-H_2), 4.68 (d, $^3J_{1'',2''}$ = 7.9 Hz, 1H, 1″-H), 5.05–5.12 (m, 1H, 2″-H), 5.54–5.38 (m, 2H, 3″ and 4″-H). – $^{13}C\{^1H\}$ NMR (50.32 MHz, $CDCl_3$): δ = 11.8 (5a), 12.8 (8b), 13.4 (7a), 19.7, 19.6 (4′a, 8′a), 20.5 (4), 20.6, 20.7, 20.6 (all OAc), 21.0 (2′), 22.5, 22.6 (12′a and 13′), 23.8 (2a), 24.3 (6′), 24.9 (10′), 27.8 (12′), 31.1 (3), 32.6, 32.7 (4′ and 8′), 37.2, 37.4 (3′, 5′, 7′ and 9′), 39.3, 39.5 (11′ and 1′), 61.7 (6″), 68.0 (4″), 69.4 (5″), 70.4 (2″), 71.0 (3″), 74.8 (2), 102.6 (1″), 117.7 (4a), 122.8 (5), 126.9 (7), 128.2 (8), 145.3 (6), 148.5 (8a). – MS (LSIMS, NBA, 8 kV): m/z (%) = 761 (10) $[M+H]^+$, with NaOAc 783 (16) $[M+Na]^+$.

(+)-α-Tocopheryl 2,3,4,6-tetra-O-acetyl-α-D-mannopyranoside (**20**): Oil, $[\alpha]_D^{20} = +27.67°$ (CH_2Cl_2, $c = 1$). – IR ($CHCl_3$): ν = 2980, 1747 (C=O), 1461,

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1372, 1246, 1133, 1083, 1052, 1012, 981 cm^{-1}. – ^1H NMR (200.13 MHz, $CDCl_3$): δ = 1.83 (t, ^3J = 6.7 Hz, 2H, 3-H), 2.05–2.22 (7×s, 21H, 5a-, 7a-, 8b-H and all OAc), 2.57 (t, ^3J = 6.7 Hz, 2H, 4-H), 4.39 and 4.13 (ddd, $^2J_{6'',6''}$ = 12.1, $^3J_{5'',6''}$ = 2.4 and $^3J_{5'',6''}$ = 5.4 Hz, 2H, 6″-H_2), 4.48–4.55 (m, 1H, 5″-H), 4.91 (~s, 1H, 1″-H), 5.44–5.39 (m, 1H, 3″-H), 5.68–5.60 (m, 2H, 3″ and 2″-H). – $^{13}C\{^1H\}$ NMR (50.32 MHz, $CDCl_3$): δ = 11.9 (5a), 12.8 (8b), 13.7 (7a), 19.7, 19.6 (4′a, 8′a), 20.5 (4), 20.6, 20.7, 20.8 (all OAc), 21.0 (2′), 22.6, 22.7 (12′a and 13′), 23.8 (2a), 24.4 (6′), 24.7 (10′), 27.9 (12′), 31.2 (3), 32.6, 32.7 (4′ and 8′), 37.2- 37.5 (3′, 5′, 7′ and 9′), 39.3 (11′), 39.8 (1′), 62.7 (6″), 66.1 (4″), 69.0 (2″), 69.9 (3″), 70.0 (5″), 74.8 (2), 101.5 (1″), 117.6 (4a), 123.2 (5), 125.5 (7), 127.4 (8), 148.0 (6), 148.4 (8a). – MS (LSIMS, NBA, 8 kV): *m/z* (%) = 761 (8) $[M+H]^+$, with NaOAc 783 (12) $[M+Na]^+$.

2,2,5,7,8-Pentamethyl-6-hydroxychromanyl 2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside (**9**): M.p. 141–3 °C, $[\alpha]_D^{20}$ = −7.06° ($CHCl_3$, *c* = 1). – IR ($CHCl_3$): ν = 2943, 1754 (C=O), 1457, 1369, 1231, 1168, 1064, 1040 cm^{-1}. – ^1H NMR (200.13 MHz, $CDCl_3$): δ = 1.3 (s, 6H, 2a- and 2b-H), 1.79 (t, ^3J = 6.9 Hz, 2H, 4-H), 2.03–2.33 (7×s, 21H, 5a-, 7a-, 8b-H and all OAc), 2.58 (t, ^3J = 6.9 Hz, 2H, 4-H), 3.51–3.56 (m, 1H, 5′-H), 4.06 and 4.12 (ddd, $^2J_{6',6'}$ = 12.2, $^3J_{5',6'}$ = 2.7 and $^3J_{5',6'R}$ = 4.5 Hz, 2H, 6′-H_2), 4.72 (d, $^3J_{1',2'}$ = 7.6 Hz, 1H, 1′-H), 5.27–5.35 (m, 1H, 2′ , 3′ and 4′-H). – $^{13}C\{^1H\}$ NMR (50.32 MHz, $CDCl_3$): δ = 11.8 (5a), 12.6 (8b), 13.3 (7a), 20.9 (4), 20.5 –20.7 (all OAc), 26.6, 26.8 (2a and 2b), 32.7 (3), 61.7 (6′), 68.5 (4′), 71.4 (5′), 71.8 (2′), 72.8 (2), 73.0 (3′), 101.9 (1′), 117.2 (4a), 122.8 (5), 126.8 (7), 128.2 (8), 145.2 (6), 148.6 (8a). – MS (LSIMS, NBA, 8 kV): *m/z* (%) = 551 (13) $[M+H]^+$, with NaOAc 573 (14) $[M+Na]^+$.

2,2,5,7,8-Pentamethyl-6-hydroxychromanyl 2,3,4,6-tetra-O-acetyl-β-D-galactopyranoside (**16**): M.p. 71–3 °C, $[\alpha]_D^{20}$ = −2.4° ($CHCl_3$, *c* = 0.5). – IR ($CHCl_3$): ν = 2931, 2863, 1748 (C=O), 1459, 1370, 1067, 1125, 1076 cm^{-1}. – ^1H NMR (200.13 MHz, $CDCl_3$): δ = 1.05 (2×s, 6H, 2a- and 2b-H), 1.79 (t, ^3J = 6.8, 2H, H-4), 1.95–2.21 (7×s, 21H, 5a-, 7a-, 8b-H and all OAc), 2.58 (t, ^3J = 6.8 Hz, 2H, 4-H), 3.74–3.77 (m, 1H, 5′-H), 4.06 and 4.09 (ddd, $^2J_{6',6'}$ = 8.8, $^3J_{5',6'}$ = 6.8 and $^3J_{5',6'}$ = 7.3 Hz, 2H, 6′-H_2), 4.68 (d, ^3J = 8.0 Hz, 1H, 1′-H), 5.04–5.11 (m, 1H, 2′-H), 5.37–5.56 (m, 2H, 3′- and 4′-H). – $^{13}C\{^1H\}$ NMR (50.32 MHz, $CDCl_3$): δ = 11.8 (5a), 12.7 (8b), 13.4 (7a), 20.4–20.8 (all OAc), 21.0 (4), 26.8 and 26.6 (2a and 2b), 32.7 (3), 60.7 (6′), 66.9 (4′), 69.4 (2′), 70.4 (3′), 71.0 (5′), 72.8 (2), 102.5 (1′), 117.2 (4a), 122.8 (5), 126.8 (7), 128.3 (8), 145.3 (6), 148.6 (8a). – MS (LSIMS, NBA, 8 kV): *m/z* (%) = 551 (10) $[M+H]^+$, with NaOAc 573 (16) $[M+Na]^+$.

2,2,5,7,8-Pentamethyl-6-hydroxychromanyl 2,3,4,6-tetra-O-acetyl-α-D-mannopyranoside (**22**): M.p. 115- 17 °C, $[\alpha]_D^{20}$ = −21.2° ($CHCl_3$, *c* = 0.5). – IR ($CHCl_3$): ν = 3465, 2968, 1743 (C=O), 1455, 1369, 1252, 1227, 1130, 1086, 1058 cm^{-1}. – ^1H NMR (200.13 MHz, $CDCl_3$): δ = 1.29 (s, 6H, 2a and 2b-H), 1.78 (t, ^3J = 7.8 Hz, 2H, 4-H), 2.04–2.21 (7×s, 21H, 5a-, 7a-, 8b-H and all OAc), 2.59 (t, ^3J = 7.8 Hz, 2H, 4-H), 4.38 and 4.12 (ddd, $^2J_{6',6'}$ = 12.1, $^3J_{5',6'}$ = 2.4 and $^3J_{5',6'}$ = 4.3 Hz, 2H, 6′-H_2), 4.47–4.55 (m, 1H, 5′-H), 4.91 (s, 1H, 1′-H), 5.34–5.44 (m, 1H, 3′-H), 5.60–5.68 (m, 2H, 2′- and 3′-H). – $^{13}C\{^1H\}$ NMR (50.32 MHz, $CDCl_3$): δ = 11.9 (5a), 12.8 (8b), 13.7 (7a), 20.7–20.8 (all OAc), 21.1 (4), 26.7 (2a and 2b), 32.8 (3), 62.7 (6′), 66.1 (4′), 69.0 (2′), 69.9 (3′), 70.0 (5′), 72.8 (2), 101.5 (1′), 117.4 (4a), 123.1 (5), 125.5 (7), 127.5 (8), 148.1 (6), 148.5 (8a). – MS (LSIMS, NBA, 8 kV): *m/z* (%) = 551 (11) $[M+H]^+$, with NaOAc 573 (17) $[M+Na]^+$.

General method for glycosylation of (+)-α-tocopherol and β-peracetylated sugars in the presence of a Lewis acid (for details see Table 2)

(+)-α-Tocopherol (430 mg, 1 mmol), sugar (1.5 mmol) and 0.25 equiv. of a Lewis acid (see Table 2) was heated on an oil bath at 130 °C under diminished pressure (40 Torr) for 4 h. The reaction mixture was diluted with ethyl acetate (50 ml) and washed with water (3 × 30 ml). The organic layer was dried over $MgSO_4$ and evaporated to dryness. The crude reaction mixture was purified by column chromatography (hexane–ethyl acetate 15:1, v/v). The unseparable by column mixture of α- and β-glycosides was obtained. The composition of anomers in the mixture was identified by comparison of the intensity of 1″-H or 5″-H NMR signals or C-1″ signals in the ^{13}C NMR spectrum of the sugar residue.

General method for deacetylation of phenyl glycosides.

The glycosides were deacetylated according to Herzig *et al.* (MeOH, KCN, RT) [24]. After evaporation to dryness, the solid residue was extracted with ethyl acetate (4 × 30 ml). The combined extracts were concentrated and purified by "dry-flash" chromatography. The yield of deprotection ranged from 95 to 98%. After preliminary purification, the chromatographic separation was possible only for the α- and β-tocopheryl or 6-hydroxychromanyl glucosides. For mixtures α and β galactosides or mannosides the separation failed.

(+)-α-Tocopheryl β-D-glucopyranoside (**7**): M.p. 159–60 °C, $[\alpha]_D^{20}$ = +7.26° (MeOH, *c* = 1). – IR

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(KBr): ν = 3390, 2927, 2868, 1461, 1378, 1254, 1072, 1035, 1012 cm^{-1}. The ^{1}H and ^{13}C NMR spectra were identical with those described earlier [2].

(+)-α-Tocopheryl α-D-glucopyranoside (**8**): $[\alpha]_D^{20}$ = +17.4° (MeOH, *c* = 1). – IR (KBr): ν = 3386, 2952, 2868, 1462, 1411, 1378, 1248, 1110, 1076, 1051, 1017 cm^{-1}. – ^{1}H NMR (200.13 MHz, MeOH): δ = 1.71 (m, 2H, 3-H), 1.97, 2.17, 2.18 (3×s, 9H, 5a-, 7a- and 8b-H), 2.50 (m, 2H, 4-H), 3.20–3.67 (m, 5H, 2″-, 3″-, 4″-, 6″-H), 3.80–3.88 (m, 1H, 5″-H), 4.93 (d, ^3J = 4.2 Hz, 1H, 1″-H). – ^{13}C{^{1}H} NMR (50.32 MHz, MeOH): δ = 11.7 (5a), 13.0 (8b), 14.0 (7a), 19.5, 19.6 (4′a, 8′a), 20.2 (4), 20.3 (2′), 22.4, 22.5 (12′a and 13′), 23.4 (2a), 24.7 (6′), 24.1 (10′), 27.4 (12′), 31.0 (3), 31.9, 32.1 (4′ and 8′), 36.6, 36.7, 36,8 (3′, 5′, 7′ and 9′), 38.8, 38.9 (11′ and 1′), 60.8 (6″), 69.9 (4″), 72.3 (5″), 72.6 (2″), 74.6 (3″), 74.2 (2), 102.5 (1″), 117.1 (4a), 121.5 (5), 125.6 (7), 127.4 (8), 146.9 (6), 147.7 (8a). – MS (LSIMS, NBA, 8 kV): *m*/*z* (%) = 761 (12) [M+H]$^+$, with NaOAc 783 (18) [M+Na]$^+$.

(+)-α-Tocopheryl β-D-galactopyranoside (**15**): M.p. 174–77 °C, IR (KBr): ν = 3409, 2953, 2869, 1464, 1377, 1252, 1088, 1044 cm^{-1}. – ^{1}H NMR (200.13 MHz, MeOH): δ = 1.76 (t, ^3J = 6.4 Hz, 2H, 3-H), 1.97, 2.12, 2.14 (3×s, 9H, 5a-, 7a-, and 8b-H), 2.50 (t, ^3J = 6.5 Hz, 2H, 4-H), 3.17–3.60 (m, 6H, 2″-, 3″-, 4″-, 5″- and 6″-H), 4.30 (d, ^3J = 7.6 Hz, 1H, 1″-H). – ^{13}C{^{1}H} NMR (50.32 MHz, MeOH): δ = 11.6 (5a), 12.6 (8b), 13.6 (7a), 19.5, 19.6 (4′a, 8′a), 20.3 (4), 20.4 (2′), 20.5, 20.4 (12′a and 13′), 23.4 (2a), 23.7 (6′), 24.1 (10′), 27.3 (12′), 31.9 (3), 31.9, 32.0 (4′ and 8′), 36.5, 36.6, 36.7 (3′, 5′, 7′ and 9′), 40.3, 40.7 (11′ and 1′), 60.0 (6″), 67.7 (4″), 71.1 (2″), 74.3 (3″), 74.9 (5″), 73.2 (2), 105.4 (1″), 116.9 (4a), 121.2 (5), 126.6 (7), 128.3 (8), 145.9 (6), 147.3 (8a). – MS (LSIMS, NBA, 8 kV): *m*/*z* (%) = 593 (11) [M+H]$^+$, with NaOAc 615 (14) [M+Na]$^+$.

(+)-α-Tocopheryl α-D-mannopyranoside (**21**): M.p. 117–19 °C, $[\alpha]_D^{20}$ = +50.3° (MeOH, *c* = 1). – IR (KBr): ν = 3492, 2972, 2919, 1454, 1421, 1386, 1364, 1263, 1221, 1160, 1010, 958 cm^{-1}. – ^{1}H NMR (200.13 MHz, MeOH): δ = 1.83 (t, ^3J = 5.0 Hz, 2H, 3-H), 2.04, 2.14, 2.17 (3×s, 9H, 5a-, 7a- and 8b-H), 2.55 (t, ^3J = 5.0 Hz, 2H, 4-H), 3.99–3.76 (m, 5H, 2″-, 3″-, 4″- and 6″-H), 4.20–4.23 (m, 1H, 5″-H), 4.83 (d, ^3J = 6.5 Hz, 1H, 1″-H). – ^{13}C{^{1}H} NMR (50.32 MHz, MeOH): δ = 11.7 (5a), 12.8 (8b), 13.7 (7a), 19.5, 19.6 (4′a, 8′a), 20.1 (4), 20.4 (2′), 20.5, 20.6 (12′a and 13′), 22.5 (2a), 23.6 (6′), 24.1 (10′), 27.3 (12′), 31.9 (3), 32.0 (4′ and 8′), 36.6, 36.7 (3′, 5′, 7′ and 9′), 39.3 (11′), 39.8 (1′), 61.3 (6″), 66.6 (4″), 70.5 (2″), 70.9 (3″), 75.9 (5″), 74.2 (2), 105.0 (1″), 117.3 (4a), 121.6 (5), 125.5 (7), 127.2 (8), 147.2 (6), 147.9 (8a). – MS (LSIMS, NBA, 8 kV): *m*/*z* (%) = 593 (15) [M+H]$^+$, with NaOAc 615 (18) [M+Na]$^+$.

2,2,5,7,8-Pentamethyl-6-hydroxychromanyl β-D-glucopyranoside (**11**): M.p. 145–6 °C, $[\alpha]_D^{20}$ = –5.8° (MeOH, *c* = 1). – IR (KBr): ν = 3050–3600, 2972, 2925, 1643, 1412, 1381, 1272, 1225, 1168, 1077, 1039, 926 cm^{-1}. – ^{1}H NMR (200.13 MHz, MeOH): δ = 1.26 (s, 6H, 2a- and 2b-H), 1.77 (t, ^3J= 6.8 Hz, 2H, 3-H), 2.02, 2.18, 2.21 (3×s, 9H, 5a-, 7a- and 8b-H), 2.59 (t, ^3J = 6.8 Hz, 2H, 4-H), 3.08–3.15 (m, 1H, 5′-H), 3.29–3.55 (m, 3H, 2′-, 3′-, 4′-H), 3.78–3.58 (ddd, ^2J = 11.7, $^3J_{5',6'}$ = 2.6 and $^3J_{5',6'}$ = 5.16 Hz, 2H, 6′-H$_2$), 4.55 (d, ^3J = 7.40 Hz, 1H, 1′-H). – ^{13}C{^{1}H} NMR (50.32 MHz, MeOH): δ = 11.6 (5a), 12.8 (8b), 13.7 (7a), 22.6 (4), 26.6 (2a and 2b), 33.6 (3), 62.5 (6′), 71.6 (4′), 73.4 (2), 75.5 (2′), 77.4 (5′), 77.6 (3′), 105.6 (1′), 117.9 (4a), 123.0 (5), 127.6 (7), 129.3 (8), 146.9 (6), 149.0 (8a). – MS (LSIMS, NBA, 8 kV): *m*/*z* (%) = 383 (8) [M+H]$^+$, with NaOAc 405 (13) [M+Na]$^+$.

2,2,5,7,8-Pentamethyl-6-hydroxychromanyl α-D-glucopyranoside (**12**): M.p. = 159–60 °C, $[\alpha]_D^{20}$ = +7.26° (MeOH, *c* = 0.5). – IR (KBr): ν = 3424, 2972, 2930, 1459, 1405, 1367, 1261, 1223, 1170, 1080, 1013, 926 cm^{-1}. – ^{1}H NMR (200.13 MHz, MeOH): δ = 1.27 (s, 6H, 2a- and 2b-H), 1,79 (t, ^3J = 6.8 Hz, 2H, 3-H), 2.09, 2.23, 2.26 (3×s, 9H, 5a-, 7a- and 8b-H), 2.60 (t, ^3J = 6.8 Hz, 2H, 4-H), 3.40–3.92 (m, 5H, 2′-, 3′-, 4′-, 6′-H), 4.03–4.11 (m, 1H, 5′-H), 5.18 (d, ^3J = 4.4 Hz, 1H, 1′-H). – ^{13}C{^{1}H} NMR (50.32 MHz, MeOH): δ = 11.6 (5a), 13.3 (8b), 14.3 (7a), 21.7 (4), 26.6 (2a and 2b), 33.7 (3), 62.2 (6′), 71.1 (4′), 73.4 (2), 73.6 (2′), 74.1 (5′), 75.1 (3′), 103.2 (1′), 117.9 (4a), 123.4 (5), 126.5 (7), 128.3 (8), 148.5 (6), 148.6 (8a). – MS (LSIMS, NBA, 8 kV): *m*/*z* (%) = 551 (9) [M+H]$^+$, with NaOAc 573 (16) [M+Na]$^+$.

2,2,5,7,8-Pentamethyl-6-hydroxychromanyl β-D-galactopyranoside (**17**): M.p. 125–6 °C, $[\alpha]_D^{20}$ = –5.13° (MeOH, *c* = 0.5). – IR (KBr): ν = 3449, 2971, 2928, 1462, 1381, 1263, 1082, 926 cm^{-1} – ^{1}H NMR (200.13 MHz, MeOH): δ = 1.26 (s, 6H, 2a and 2b-H), 1.76 (t, ^3J= 6.7 Hz, 2H, 3-H), 2.02, 2.18, 2.21 (3×s, 9H, 5a-, 7a- and 8b-H), 2.58 (t, ^3J = 6.7 Hz, 2H, 4-H), 3.02–3.30 (m, 1H, 5′-H), 3.51–3.87 (m, 5H, 2′-, 3′-, 4′-, 6′-H), 4.46 (d, ^3J = 7.6 Hz, 1H, 1′-H). – ^{13}C{^{1}H} NMR (50.32 MHz, MeOH): δ = 11.6 (5a), 12.8 (8b), 13.8 (7a), 21.5 (4), 26.5, 26.6 (2a and 2b), 33.6 (3), 61.7 (6′), 69.7 (4′), 73.3 (2), 72.8 (2′), 74.4 (3′), 75.8 (5′), 106.2 (1′), 117.9 (4a), 122.9 (5), 127.6 (7), 129.4 (8), 147.0 (6), 148.9 (8a). – MS (LSIMS, NBA, 8 kV): *m*/*z* (%) = 383 (11) [M+H]$^+$, with NaOAc 405 (15) [M+Na]$^+$.

2,2,5,7,8-Pentamethyl-6-hydroxychromanyl α-D-mannopyranoside (**23**): M.p. 167–70 °C, $[\alpha]_D^{20}$ = +66.26° (MeOH, *c* = 0.5). – IR (KBr): ν = 3396, 2973, 2932, 1459, 1411, 1382, 1367, 1262, 1225, 1168, 1125, 1064, 1004, 978 cm^{-1}. – NMR (200.13 MHz,

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MeOH): δ = 1.23 (s, 6H, 2a- and 2b-H), 1.73 (t, ^3J = 7.0 Hz, 2H, 3-H), 1.99, 2.02, 2.10 (3×s, 9H, 5a-, 7a- and 8b-H), 2.49 (t, ^3J = 7.0 Hz, 2H, 4-H), 3.40–3.72 (m, 5H, 2′-, 3′-, 4′-, 6′-H), 4.01 (m, 1H, 5′-H), 4.83 (d, ^3J = 1.6 Hz, 1H, 1′-H). – $^{13}C\{^1H\}$ NMR (50.32 MHz, MeOH): δ = 11.8 (5a), 12.8 (8b), 13.7 (7a), 20.5 (4), 26.4, 26.5 (2a and 2b), 32.3 (3), 61.3 (6′), 66.6 (4′), 72.5 (2), 70.5 (2′), 70.9 (3′), 72.5 (2), 75.9 (5′), 105.9 (1′), 117.1 (4a), 121.6 (5), 125.6 (7), 127.2 (8), 147.4 (6), 147.9 (8a). – MS (LSIMS, NBA, 8 kV): *m*/*z* (%) = 383 (12) $[M+H]^+$, with NaOAc 405 (17) $[M+Na]^+$.

Acetylation of α-tocopheryl α-D-glucoside (**8**) *and 2,2,5,7,8-pentamethyl-6-hydroxychromanyl α-D-glucoside* (**12**)

To the glucoside **8** or **12** (0.25 mmol) dissolved in 5 ml of anhydrous pyridine, 1.5 mmol of acetic anhydride was added. The mixture was allowed to stand at room temp. for 12 h. After evaporation to dryness *in vacuum*, the resulted acetylated glucosides were purified by PTLC. The yields for both glycosides were 97%.

(+)-α-Tocopheryl 2,3,4,6-tetra-O-acetyl-α-D-glucopyranoside (**6**): Oil, $[\alpha]_D^{20}$ = +33.2° (CH_2Cl_2, *c* = 0.5). – IR ($CHCl_3$): ν = 2980–2930, 1745, 1455, 1370, 1060, 1030, 900 cm^{-1}. – ^1H NMR (200.13 MHz, $CDCl_3$): δ = 1.78 (t, ^3J = 6.5 Hz, 2H, 3-H), 2.30–2.00 (7×s, 21H, 5a-, 7a-, 8b-H and all OAc), 2.55 (t, ^3J = 6.5 Hz, 2H, 4-H), 4.33 and 4.15 (ddd, $^2J_{6'',6''}$ = 12.3, $^3J_{5'',6''}$ = 2.2 and $^3J_{5'',6''}$ = 4.5 Hz, 2H, 6″-H_2), 4.57–4.49 (m, 1H, 5″-H), 5.30–5.06 (m, 3H, 1″-, 2″- and 4″-H), 5.86 and 5.80 (dd, ^3J = 9.4 Hz, 1H, 3″-H). – $^{13}C\{^1H\}$ NMR (50.32 MHz, $CDCl_3$). δ = 13.0 (5a), 13.3 (8b), 13.9 (7a), 19.7, 19.6 (4′a and 8′a), 20.6 (4), 20.8, 20.5 ($OCOCH_3$), 21.0 (2′), 22.7, 22.6 (12′a and 13′), 23.6 (2a), 24.8 (10′), 24.4 (6′), 27.9 (12′), 31.3 (3), 32.8 and 32.7 (4′ and 8′), 37.4, 37.2 (3′, 5′, 7′ and 9′), 39.3 (11′), 40.2 (1′), 62.0 (6″), 69.0 (4″), 70.0 (5″), 71.0 (2″), 74.8 (3″), 74.9 (2), 98.7 (1″), 117.7 (4a), 123.3 (5), 124.8 (7), 126.8 (8), 147.6 (6), 148.0 (8a), 169.5, 169.6, 169.9, 170.2 ($OCOCH_3$). – MS (LSIMS, NBA, 8 kV): *m*/*z* (%) = 761 (12) $[M+H]^+$, with NaOAc 783 (15) $[M+Na]^+$.

2,2,5,7,8-Pentamethyl-6-hydroxychromanyl 2,3,4,6-tetra-O-acetyl-α-D-glucopyranoside (**10**): Oil, $[\alpha]_D^{20}$ = +23.2° (CH_2Cl_2, *c* = 0.5). – IR ($CHCl_3$): ν = 2987–2935, 1746, 1454, 1378, 1060, 1030, 923 cm^{-1}. – ^1H NMR (200.13 MHz, $CDCl_3$): δ = 1.27 and 1.30 (2×s, 6H, 2a- and 2b-CH_3), 1,79 (t, ^3J = 6.9 Hz, 2H, 3-H), 2.30–2.00 (7×s, 21H, 5a-, 7a-, 8b-H and all OAc), 2.58 (t, ^3J = 6.9 Hz, 2H, 4-H), 4.32 and 4.15 (ddd, $^2J_{6',6'}$ = 12.5, $^3J_{5',6'}$ = 2.3 and $^3J_{5',6'}$ = 4.5 Hz, 2H, 6′-H_2), 4.53 (ddd, ^3J = 10.3 Hz, 1H, 5′-H), 5.09–5.26 (m, 3H, 1′-, 2′- and 4′-H), 5.81 (dd, ^3J = 9.4 Hz, 1H, 3′-H). – $^{13}C\{^1H\}$ NMR (50.32 MHz, $CDCl_3$): δ = 20.6 (4), 20.8, 20.5 ($OCOCH_3$), 21.0 (2′), 23.6 (2a and 2b), 31.3 (3), 62.0 (6′), 69.0 (4′), 70.0 (5′), 71.0 (2′), 74.8 (3′), 74.9 (2), 98.7 (1′), 117.7 (4a), 123.3 (5), 124.8 (7), 126.8 (8), 147.6 (6), 148.0 (8a), 169.5, 169.6, 169.9, 170.2 ($OCOCH_3$). – MS (LSIMS, NBA, 8 kV): *m*/*z* (%) = 551 (19) $[M+H]^+$, with NaOAc 573 (22) $[M+Na]^+$.

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