Tetrahedron 67 (2011) 1654–1664

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Transformations of chromanol and tocopherol and synthesis of ascorbate conjugates

Martina Lahmann [†], Joachim Thiem [*]

University of Hamburg, Faculty of Science, Department of Chemistry, Martin-Luther-King-Platz 6, 20146 Hamburg, Germany

ARTICLE INFO

Article history:
Received 7 July 2010
Received in revised form 22 December 2010
Accepted 29 December 2010
Available online 8 January 2011

Keywords:
6-Chromanol
α-Tocopherol
Ascorbate
Glucopyranoside spacer element
Conjugates

ABSTRACT

α-Tocopherol and as a model compound pentamethylchromanol could be transferred into simple and more complex 5a-ether derivatives including galactopyranose as well as ascorbic acid conjugates. Following elaboration of a glucopyranoside spacer element this could be used for tethering the vitamin E and the vitamin C components to give novel conjugates for subsequent biostudies concerning their proposed synergism of antioxidant properties in tissues.

1. Introduction

Degenerative processes, including aging and age-related dysfunctions are believed to be caused by free radical attack on a number of essential and sensitive molecules in biopathways. In healthy organisms free radicals are intercepted by antioxidants at rates faster than these biomolecules.[1–3] One of the most effective lipid-soluble antioxidant in mammalian blood plasma is α-tocopherol,[4,5] a dominant active component of vitamin E.[6] In contrast to α-tocopherol active in unpolar moieties, L-ascorbic acid, vitamin C, is the responsible antioxidant in aqueous regions. Consequently, early on a synergistic system of these two vitamins was postulated.[7,8] More recent papers indicate that in vivo the α-tocopheryl radical is indeed quenched by reaction with vitamin C.[9,10]

Various derivatives of α-tocopherol attracted interest, such as the nicotinic acid ester **A**,[11] the β-D-glucopyranoside **B**,[12] the 6′-functionalized ascorbate ester component **C**,[13] the uridine-5′-phosphate ester **D**,[14] as well as the *C*-glucosylated structure **E**[15] (Fig. 1).

This cooperative system of the two vitamins has inspired researcher to form and study further conjugates of α-tocopherol and L-ascorbic acid,[4,16–18] and also produce some of them on considerable scale for addition in cosmetics,[19–21] including the 6-substituted PEG ether derivatives.[22,23] Since antioxidants are also added to many foodstuff and pharmaceuticals this area is objective of continuous research,[24,25] and further an extension to formation of novel synthetic structures became of interest. Recently, both the synthesis of more lipophilic ascorbates,[26] as well as α-tocopheryl β-D-glucopyranosides,[27,28] analogs therof[29] and *C*-glucopyranosides[15] as more hydrophilic vitamin E analogs were reported and their properties studied.

In this contribution we wish to disclose our efforts to arrive at novel tocopherol–ascorbate conjugates bridged by saccharide-derived tether structures. Of particular interest were directly linked α-tocopherol–ascorbate structures like **22** as well as saccharide-spacered structures, such as **47** and **48**. In addition and as a model structure for α-tocopherol pentamethylchromanol was studied and carried all through to the corresponding derivatives.

2. Results and discussion

In addition to α-tocopherol (all-*rac*-α-tocopherol) the structurally less demanding 2,2′,5,7,8-pentamethyl-chroman-6-ol (**3**) could be employed in these studies since its chemical properties, in particular the sensitivity to oxidation, are largely similar. In a simple acid-catalyzed condensation of trimethylhydroquinone (**1**) with isoprene (**2**) originally developed by Claisen[30] and improved by Smith et al.[31] **3** could be obtained easily. Mild oxidation with silver nitrate led to 2-(3′-hydroxy-3′-methyl-but-1-yl)-3,5,6-trimethyl-quinone (**4**), and

* Corresponding author. Tel.: +49 40 42838 4241; fax: +49 40 42838 4325; e-mail address: joachim.thiem@chemie.uni-hamburg.de (J. Thiem).
† Present address: Bangor University, School of Chemistry, Bangor, GwyneddLL57 2UW, UK.

0040-4020/$ – see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2010.12.066

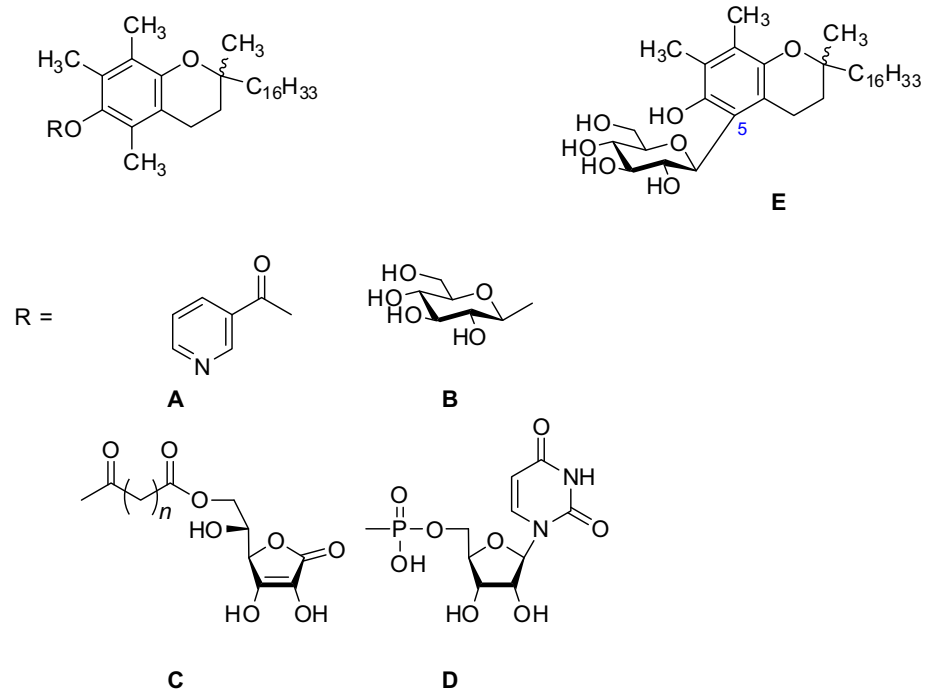
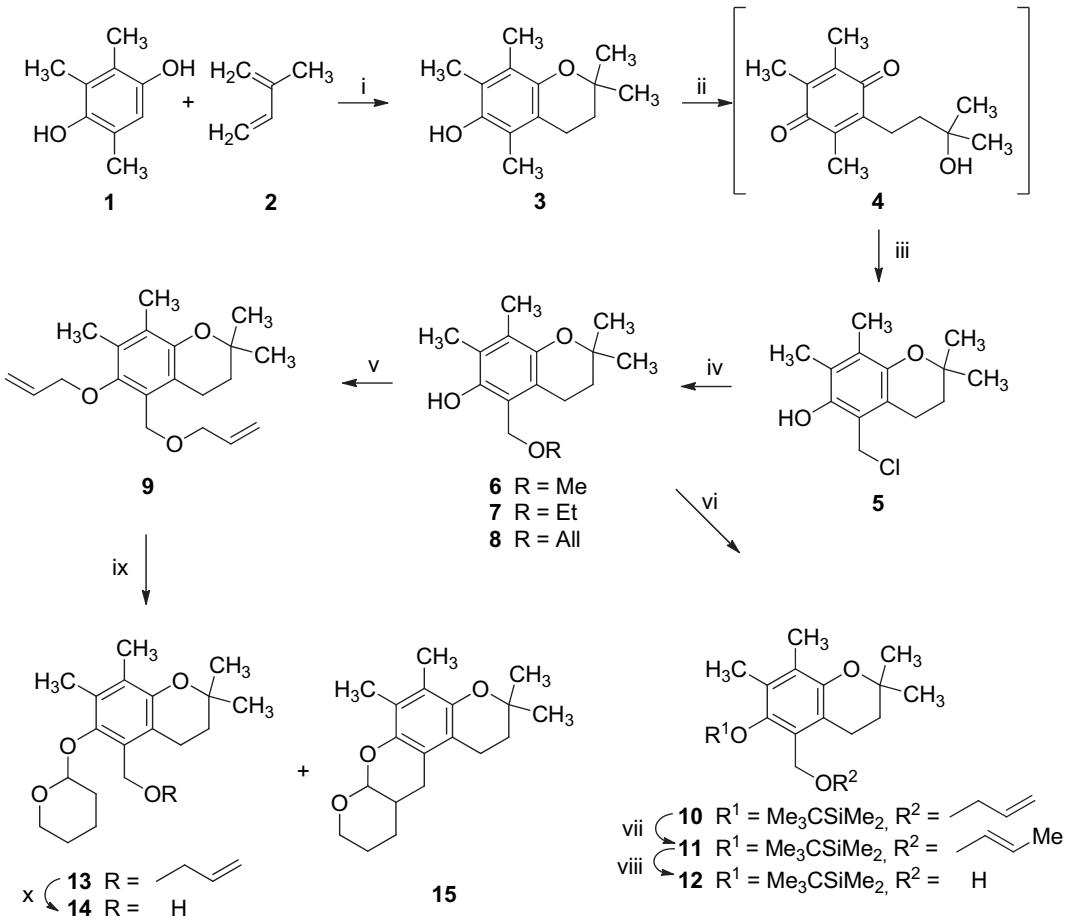


Fig. 1. Previously reported tocopherol conjugates.



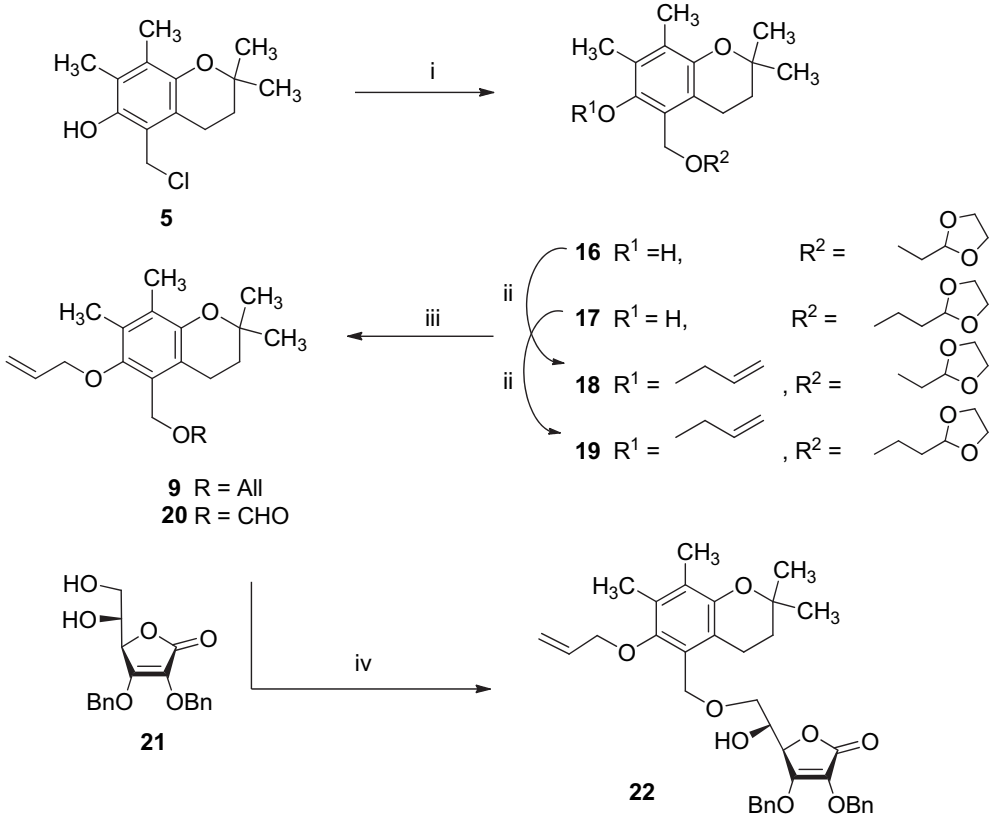
Scheme 1. Reagents and conditions: (i) HOAc, ZnCl, H_2SO_4 (48%) (Ref. 31); (ii) $AgNO_3$ (quant., in situ) (Ref. 33,34); (iii) AcCl (40%) (Ref. 33,34); (iv) ROH, THF, 0–20 °C, NaH, 18 h: R=Me→**6**, R=Et→**7**, R=All→**8** (99%); (v) THF, NaH, AllBr, 0–20 °C (60%); (vi) lutidine, Me_3CSiMe_2OTf, 0–20 °C (quant., in situ); (vii) $(Ph_3P)_3RhCl$, DABCO, 2 h, EtOH/H_2O reflux, (79%); (viii) acetone/H_2O/HgO, $HgCl_2$, 2 h, reflux (79%); (ix) CH_2Cl_2, DHP, TsOH, −10 °C, 3 h (78%); (x) $(Ph_3P)_3RhCl$, DABCO, 2 h, EtOH/H_2O, reflux then acetone/H_2O, HgO/$HgCl_2$, 1.5 h reflux (23%).

further treatment with acetyl chloride readily gave 6-*O*-acetyl-5-chloromethyl-2,2′,7,8-tetramethyl-chromon-6-ol (**5**).[32–34] Thus, this easily accessible and highly reactive 5a-chloro derivative can function as the starting material for attachment of a variety of functionalities to the chromanol system. The 5a-methyl-(**6**), the 5a-ethyl-(**7**) as well as the corresponding 5a-allyl ethers (**8**) could be obtained facily in high yield by reaction of **5** with the corresponding sodium alkoxide (cf. Ref. 33,34). Reaction of **8** with sodium hydride and allylbromide gave the di-allyl ether derivative **9**, and with lutidine as base and *tert*-butyldimethylsilyl triflate compound **10** could be obtained. With 1,4-diazabicyclo[2.2.2.]octane (DABCO) and tris-triphenyl-phosphine-rhodium (I) chloride the sensitive propenyl ether **11** was isolated, which on further treatment with mercury (II) salts gave the labile silylether-protected 5a-hydroxy derivative **12**. Transformation of compound **8** with dihydropyran led to the tetrahydropyranyl derivative **13** in high yield (78%). This was accompanied by some 2,2′,7,8-tetramethyl-5,6-dipyranyl-chromane (**15**) presumably formed via cycloaddition of an intermediate *ortho*-quinomethide structure derived from **8**.[35] De-protection of **13** with Wilkinson catalyst followed by mercury (II) treatment gave the THP-blocked 5a-hydroxychroman **14** in fair yield (Scheme 1).

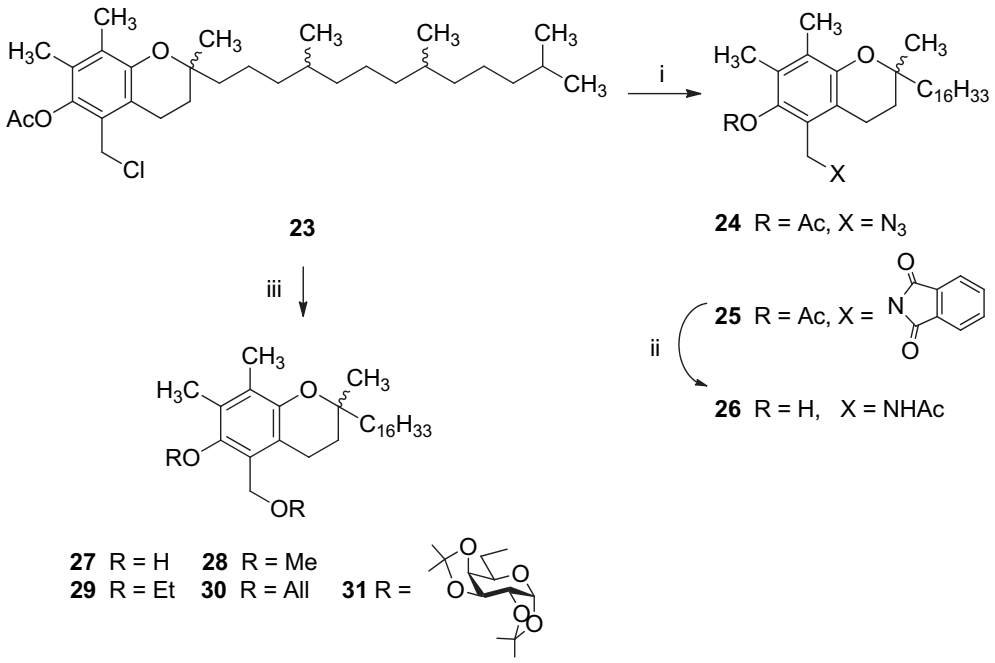
It was of interest to link chromanol via a simple spacer function to ascorbic acid. Thus, the 5a-chloro-chromanol **5** could be transformed as above with sodium hydride and 1,3-dioxolane-2-methanol in THF to give the crystalline derivative **16** in over 60% yield. The corresponding reaction of **5** with 1,3-dioxolane-2-ethanol gave amorphous **17** in 79% yield. For both these compounds the above base-catalyzed allylation led to the allyl ether derivatives **18** and **19**, respectively, in about 70% yield. Surprisingly, both compounds **18** and **19** on short treatment with formic acid at room temperature led to the formation of the 5a-formate **20** in high yield. On further reaction of **20** with 2,3-di-*O*-benzyl-ascorbate (**21**)[36] under acid conditions the ether-linked chromanol-6-*O*-ascorbate structure **22** was obtained in average yield. In another experiment the same compound **22** could be prepared from the di-allyl ether **9** and **21** under similar acid conditions. Apparently, both chromanol 5a-esters or 5a-ethers are facily cleaved under mild acid treatment to give the benzylic 5a-carbenium ion, which will readily accept alcohols to form novel 5a-ether derivatives (Scheme 2).

Subsequent studies were done in order to transfer some of the above findings to the tocopherol system and also possibly extend the functionalization. Following the approach to **5** also the acetylated 5a-chloromethyl tocopherol **23** could be obtained by treatment with acetyl chloride.[32] Its reaction with sodium azide led to the 5a-azido derivative **24**[37] in quantitative yield. Even though 6-methoxy-5a-amino-methyl chromanol was reported to be reduced to the 5-amino component by Staudinger reaction[38] a corresponding or other reductive approaches did not lead to 5a-amino tocopherol. Therefore, **23** was transferred in situ into the more reactive 5a-iodomethyl component, which on treatment with potassium phthalate gave the phthalimido derivative **25** quantitatively. By de-blocking with hydrazine an O→*N*-acetyl migration occurred to give the final derivative **26** in 90% yield. Further attempts to reactivate the amino function for extension from a 5a-aminomethyl group were discontinued at this stage.

In a series of transformation compound **23** could be reacted with sodium hydroxide to give the 5a-hydroxymethyl compound **27** in average yield. Treatment with sodium hydride and various alcohols gave the 5a-alkoxymethyl derivatives in good yield (e.g., **30**: 92% yield). In a corresponding reaction also 1,2,3,4-di-*O*-isopropylidene-α-D-galactopyranose[39] could be attached via its 6-OH-position



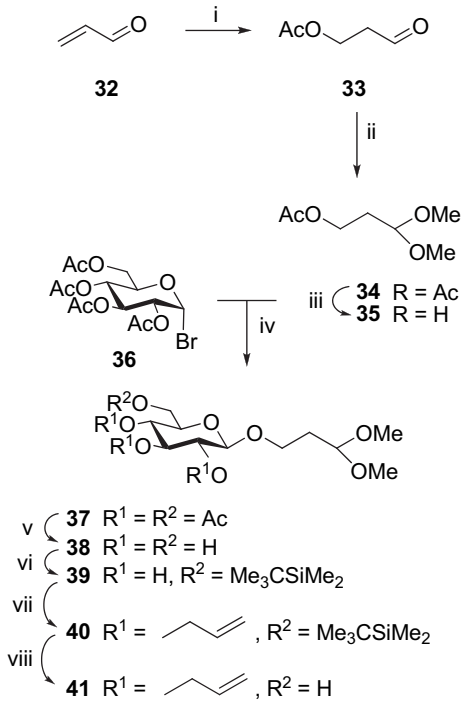
Scheme 2. Reagents and conditions: (i) Et_2O, 1,3-dioxolane-2-methanol, NaH, 0–20 °C, 2.5 h, **16** (62%); Et_2O, 1,3-dioxolane-2-ethanol, NaH, 0–20 °C, 12 h, **17** (79%); (ii) Et_2O, AllBr, NaH, 0–20 °C, 24 h, **18** (62%); 73%); (iii) HCO_2H, 20 °C, 20 min, **19** (93%); (iv) toluene, TsOH, 1.5 h reflux, **22** from **20** (40%); **22** from **9** (24%).



Scheme 3. Reagents and conditions: (i) for **24**: CH_3CN, NaN_3, 5 h, reflux (quant.); for **25**: NaI, K-phthalimide, DMF, 20 °C, 15 h (98%); (ii) THF, N_2H_5OH, 12 h, reflux (90%); (iii) THF/NaH/ROH, Bu_4NI, 3 h, reflux, for **27**: R=H (40%); for **28**: R=Me (quant.); for **29**: R=Et (quant.); for **30**: R=All (92%); for **31**: R=diisopropylidene-galactopyranos-6-yl (32%).

(cf. lit.[40]) to give the first tocopherol sugar ether structure **31** (Scheme 3).

In the next section the spacer-functionalized saccharide unit had to be prepared. Addition of acetic acid to acrolein (**32**) gave the very labile 3-acetoxy-propanal (**33**)[41] in low yield. This in turn was treated with trimethylorthoformate to give 3-acetoxy-1,1-dimethoxy-propane (**34**) (cf. lit.[42]:different reaction, 4% yield, no data).



Scheme 4. Reagents and conditions: (i) HOAc, 20 °C, 48 h (16%); (ii) $CH_3C(OCH_3)_3$, $MeOH/H_2SO_4$ (19:1), 20 °C, 2 h (51%); (iii) MeOH, Na_2CO_3, 20 °C, 18 h (quant.); (iv) CH_2Cl_2, Ag_2CO_3, 20 h, 20 °C (41%); (v) MeOH, NaOMe, 20 °C, 15 h (quant.); (vi) imidazole, DMF, −10 °C, Me_3CSiMe_2Cl, 1 h (quant., in situ); (vii) THF, AllBr, NaH, 0–20 °C, 24 h (55%); (viii) THF, Bu_4NF, 20 °C, 3 h (quant., in situ).

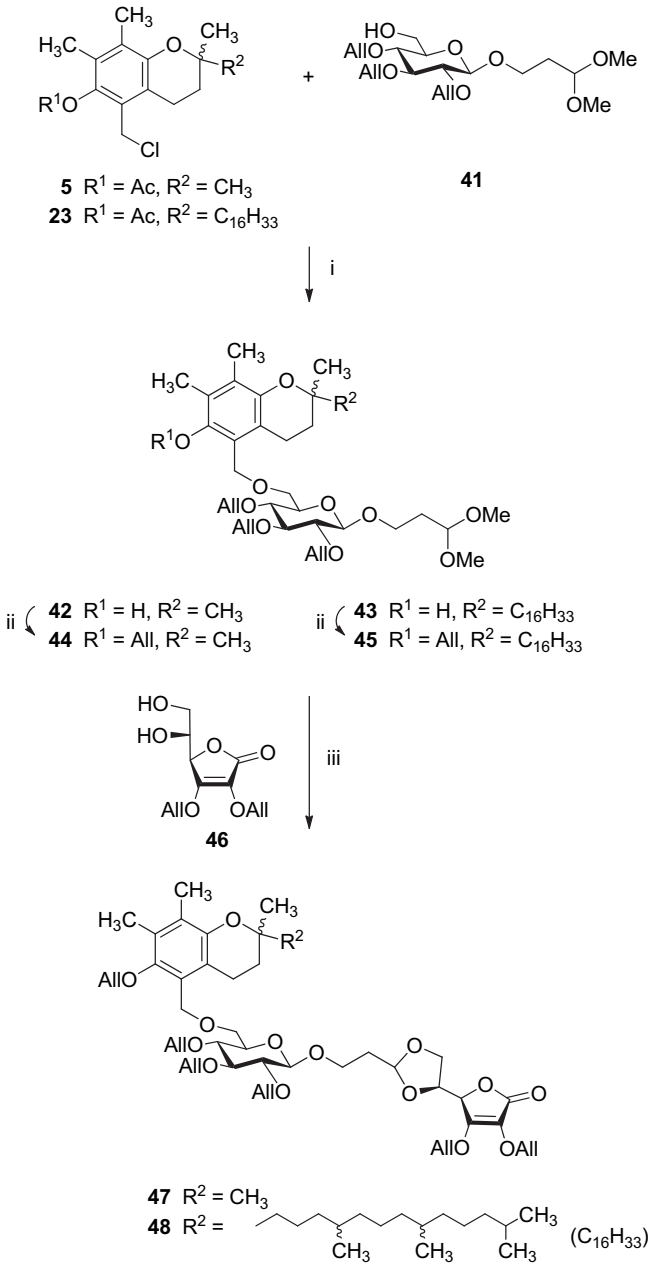
By deacetylation the colourless liquid 3-hydroxy-1,1-dimethoxy-propane (**35**) resulted quantitatively (lit.[43]:different reaction, 23% yield, no data), which could be used for glycosylation employing α-acetobromoglucose **36**[44] under classical Koenigs–Knorr conditions to give the β-glucopyranoside **37** in good yield. Its Zemplén deacetylation gave **38** quantitatively, which was regioselectively silylated at 6-OH-position with TBDMS chloride to give **39** in situ and then further tri-allylated to **40** (55% yield over two steps). Following fluoride-catalyzed cleavage of the silyl-protected spacer-arm glucopyranoside **41** was ready for condensation with the chromanol and tocopherol derivatives, respectively (Scheme 4).

Thus, as described above both the acetylated 5a-chloro-chromanol **5** as well as 5a-chlorotocopherol **23** were condensed under NaH-conditions with **41** to give the syrupy adducts **42** as well as **43**. The isolated yields amount to 64% for **42** and 46% for **43**, respectively, due to oxidative side reactions during workup. For stabilization the phenolic groups at 6-position was readily allylated to give the crystalline chromanol-sugar conjugate **44** in 72% yield. A corresponding reaction with **43** resulted in the syrupy tocopherol sugar conjugate **45** in 76% yield.

For the final conjugation the 2,3-di-*O*-allyl ascorbate **46** was required and formed according to the synthesis of the 2,3-di-*O*-benzyl derivative.[36] The hygroscopic crystalline compound **46** decomposed readily and was thus obtained in just 23% yield. By subsequent transacetalization this compound could be attached to the conjugate **44** via the 5,6-dihydroxy functions to give the target compound **47** in 93% yield. Due to the new stereogenic acetal centre two diastereomers were formed in a ratio of about 1:1, and these could be largely separated and characterized.

The corresponding condensation of the vitamin C derivate **46** with the all-*rac*-α-tocopherol component **45** resulted in formation of the conjugate **48** in 75% yield. Whereas compound **45** as a mixture of eight diastereomers appears homogeneous, the transformation product **48** shows two sets of distereomers in the ratio of about 1:1, which is apparently due to the dominating influence of the new stereogenic acetal centre (Scheme 5).

Further reactions will focus on the simultaneous de-blocking of the six allyl ether functions to generate the polar conjugates, which



Scheme 5. Reagents and conditions: (i) for 42: THF, NaH, 0–20 °C, 12 h (64%); for **43**: (46%); (ii) for **44**: THF, NaH, AllBr, 0–20 °C, 18 h (72%); for **45**: (76%); (iii) *n*-hexane/CH_2Cl_2, TsOH, 1.5 h, reflux; for **47**: (93%); for **48**: (93%).

will be employed for studies concerning the postulated synergism of vitamins E and C (cf. Ref. 7–10).

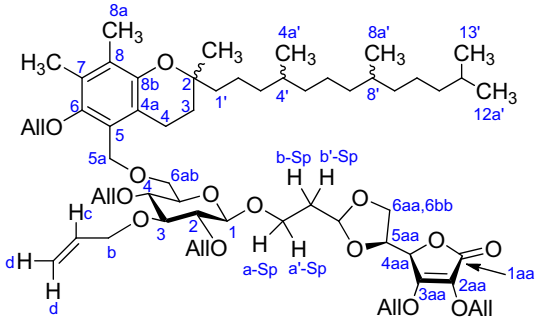
3. Conclusion

In this contribution the chemistry of α-tocopherol and its model compound pentamethylchromanol could be elaborated and a number of novel phenol-alkyl ethers synthesized including sugar-attached species. By extension via the reactive 5a-position both systems could be conjugated to ascorbic acid derivatives directly. Alternatively, after formation of a glucose spacer glycoside α-tocopherol as well as pentamethylchromanol derivatives and ascorbic acid ethers could be condensed to give novel tethered conjugates ready for further studies.

4. Experimental

4.1. General

TLC was carried out on silica gel (60 GF 254, Merck) and on aluminium plates. Detection was by UV-light followed by charring with sulfuric acid (10%) in ethanol. Preparative column chromatography was performed on silica gel (60, 230–400 mesh, particle size 40–63 μm, Merck), using the flash technique. ^{1}H NMR spectra were recorded on a Bruker AMX 400 at 400 MHz or a Bruker AMX 500 at 500 MHz ^{13}C NMR spectra were recorded on a Bruker AMX 400 at 100.67 MHz and on a Bruker AMX 500 at 125.77 MHz. NMR assignments were made using standard ^{1}H–^{1}H- and ^{1}H–^{13}C-COSY experiments. The connectivities of carbon atoms were given by DEPT experiments. For numbering cf. NMR data of Scheme 6. Mass spectra were taken on MAT 311A (70 eV) and FAB-MS on VG-Analytical VG 70-250S (*m*-nitrobenzyl alcohol matrix) in positive mode at the given fragmentor voltage. Melting points were taken on an Olympus BH-polarising microscope with Mettler FP 82 heating plate and are uncorrected. Optical rotations were measured at 20 °C on a Perkin–Elmer model 241 polarimeter using a 1 dm cuvette. Evaporations were carried out at <45 °C under dimished pressure. Elemental analyses were provided by the Microanalytical Section, Department of Chemistry.



Scheme 6. Description for NMR assignment of compounds.

4.2. Syntheses

4.2.1. 5-Methyloxymethyl-2,2′,7,8-tetramethyl-chroman-6-ol ***6***. ^{1}H NMR (400 MHz, $CDCl_3$) δ=7.41 (s, 1H, HO–Ar); 4.66 (s, 2H, CH_2-5a); 3.43 (s, 3H, OMe); 2.62 (m, 2H, CH_2-4); 2.15, 2.10 (s, 6H, CH_3-7a and -8a); 1.77 (m, 2H, CH_2-3); 1.28 (s, 6H, CH_3-2a, -2a'). ^{13}C NMR (100 MHz, $DCDl_3$) δ=147.43, 144.89 (2C, C-6, C-8b); 125.77, 123.09, 115.95, 115.16 (4C, C-8, C-7, C-5, C-4a); 72.41 (1C, C-2); 69.83 (1C, C-5a); 58.10 (3C, OMe); 32.94 (1C, C-3); 26.66 (2C, C-2a, C-2a'); 20.27 (1C, C-4); 11.93, 11.71 (2C, C-7a, -8a).

4.2.2. 5-Ethyloxymethyl-2,2′,7,8-tetramethyl-chroman-6-ol ***7***. ^{1}H NMR (400 MHz, $CDCl_3$) δ=7.72 (s, 1H, HO–Ar); 4.70 (s, 2H, CH_2-5a); 3.60 (q, 2H, OCH_2); 2.60 (m, 2H, CH_2-4); 2.15, 2.10 (s, 6H, CH_3-7a and -8a); 1.76 (m, 2H, CH_2-3); 1.28 (m, 9H, CH_3-2a, -2a' and CH_2CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ=147.01, 144.37 (2C, C-6 and C-8b); 125.13, 122.64, 115.70, 114.51 (4C, C-8, C-7, C-5, C-4a); 71.94 (1C, C-2); 67.57, 69.83 (2C, C-5a, OEt); 32.48 (1C, C-3); 26.21 (2C, C-2a, C-2a'); 19.82 (1C, C-4); 14.69 (1C, OEt); 11.93, 11.71 (2C, C-7a, -8a).

4.2.3. 5-Allyloxymethyl-2,2′,7,8-tetramethyl-chroman-6-ol ***8***. To 6-*O*-acetyl-5-chloromethyl-2,2′,7,8-tetramethyl-choman-6-ol (**5**,[33,34] 1.06 g, 3.6 mmol) and allyl alcohol (0.9 mL, 18 mmol) dissolved in anhydrous tetrahydrofuran (10 mL) were added sodium hydride (3.4 g, 85 mmol, 60%) at 0 °C under stirring. The reaction mixture was stirred for another 18 h gradually warming to room temperature, and then methanol (20 mL) was added at 0 °C to destroy

remaining sodium hydride. The mixture was extracted with diethylether (50 mL), washed three times with saturated sodium chloride (20 mL each), dried over $MgSO_4$ and evaporated. The residue was purified by flash chromatography with ether to give compound **8** as a colourless wax: 980 mg (90%).

^{1}H NMR (400 MHz, $CDCl_3$) δ=7.43 (s, 1H, HO–Ar); 5.94 (m, 1H, H-c); 5.31 (m, 1H, H-d); 5.25 (m, 1H, H-d'); 4.71 (s, 2H, CH_2-5a); 4.07 (m, 2H, H-b); 2.61 (m, 2H, CH_2-4); 2.15, 2.10 (s, 6H, CH_3-7a and -8a); 1.76 (m, 2H, CH_2-3); 1.27 (s, 6H, CH_3-2a, -2a'). ^{13}C NMR (100 MHz, $CDCl_3$) δ=147.47, 144.88 (2C, C-6 and C-8b); 133.77 (1C, =CH, C-all-c); 125.80, 123.13 (2C, C-7, C-8); 118.15 (1C, =CH_2, C-all-d); 116.00, 115.18 (2C, C-5, C-4a); 72.41 (1C, C-2); 71.11, 67.09 (4C, OCH_2, C-all-b and CH_2, C-5a); 32.90, 20.25 (2C, CH_2, C-3, C-4); 26.65 (2C, CH_3, C-2′, C-2a'); 11.94 (2C, CH_3, C-7a, 8a).

4.2.4. 6-O-Allyl-5-allyloxymethyl-2,2′,7,8-tetramethyl-chroman-6-ol ***9***. Under a nitrogen cover compound **8** (980 mg, 3.6 mmol) dissolved in anhydrous THF (10 mL) was cooled to 0 °C, treated with sodium hydride (60%, 3.6 g, 90 mmol) and stirred for 30 min. Then allylbromide (3.0 mL, 36 mmol) were added and the mixture kept at room temperature for 18 h. Workup and purification by flash chromatography (pet. ether/ethyl acetate 7:1) was as for **8** to give compound **11** as a pale yellow syrup: 600 mg (60%).

^{1}H NMR (40 MHz, $CDCl_3$) δ=6.12 (m, 1H, H-c); 5.95 (m, 1H, H-c); 5.45 (m, 1H, H-d); 5.29 (m, 1H, H-d); 5.25 (m, 1H, H-d'); 5.17 (m, 1H, H-d'); 4.53 (s, 1H, CH_2-5a); 4.26 (dt, 2H, H-b); 4.03 (dt, 2H, H-b'); 2.83 (m, 2H, CH_2-4); 2.18, 2.10 (s, 6H, CH_3-7a and -8a); 1.78 (m, 2H, CH_2-3); 1.31 (s, 6H, CH_3-2a, -2a'). ^{13}C NMR (100 MHz, $CDCl_3$) δ=148.85, 147.78 (2C, C-6 and C-8b); 134.71, 133.91 (2C, =CH, C-all-c); 127.69, 125.82, 125.25 (3C, C-5, C-7, C-8); 118.18 (1C, C-4a); 116.46, 116.23 (2C, =CH_2, C-all-d); 75.05, 70.94, 63.74 (3C, C-5a, 2×C-all-b); 72.61 (1C, C-2); 32.32, 19.36 (2C, C-3, C-4); 26.51 (2C, C-2′, C-2a'); 12.36, 11.69 (2C, CH_3, C-7a, -8a). Anal. Calcd for $C_{20}H_{28}O_3$(316.4): C, 75.91; H, 8.92. Found: C, 76.11; H, 8.94. EI-MS: 316(M^+).

4.2.5. 5-Allyloxymethyl-6-O-tert-butyldimethylsilyl-2,2′,7,8-tetramethyl-chroman-6-ol ***10***. A solution of compound **8** (1.28 g, 4.64 mmol) in lutidine (3.3 mL, 27.8 mmol) was cooled to 0 °C and *tert*-butyldimethylsilyl triflate (2.1 mL, 9.27 mmol) added drop wise under stirring. After 3 h at room temperature the silylation reagent was hydrolysed with water (1 mL), then diluted with ethyl acetate (20 mL) and the organic phase washed thoroughly with saturated NaCl, 0.5 N H_2SO_4 and saturated $NaHCO_3$ then dried ($MgSO_4$) and the solvents evaporated to give the raw material **10** as an oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ=5.92 (m, 1H, H-c); 5.25 (m, 1H, H-d); 5.13 (m, 1H, H-d'); 4.50 (s, 2H, CH_2-5a); 3.92 (m, 2H, H-b); 2.81 (m, 2H, CH_2-4); 2.09, 2.08 (s, 6H, CH_3-7a and -8a); 1.77 (m, 2H, CH_2-3); 1.28 (s, 6H, CH_3-2a, -2a'); 1.05 (s, 9H, *t*-Bu–Si); 0.10 (s, 6H, CH_3–Si).

4.2.6. 6-O-tert-butyldimethylsilyl-5-(1-propenyl)-oxymethyl-2,2′,7,8-tetramethyl-chroman-6-ol ***11***. The raw material **10** (1.64 g, 4.2 mmol) was dissolved in ethanol (100 mL) and water (10 mL). Then tris-triphenyl-phosphine-rhodium (I) chloride (260 mg, 0.29 mmol) and 1,4-diazabicyclo [2.2.2] octane (DABCO, 95 mg, 0.94 mmol) were added and the mixture heated under reflux for 2 h. After cooling ethyl acetate (100 mL) was added, the organic phase dried ($MgSO_4$) and evaporated. Purification was by flash chromatography (pet. ether/ethyl acetate 13:1) to give compound **11**: 1.30 g (79%) as a pale yellow wax.

^{1}H NMR (400 MHz, $CDCl_3$) δ=6.30 (m, 1H, H-a); 6.02 (m, 1H, H-A); 4.84 (m, 1H, H-b); 4.79 (s, 2H, CH_2-5a-Z); 4.66 (s, 2H, CH_2-5a-E); 4.35 (m, 1H, H-B); 2.82 (m, 2H, CH_2-4-Z); 2.74 (m, 2H, CH_2-4-E); 2.10, 2.09 (s, 2×6H, CH_3-7a and -8a); 1.78 (m, 2H, CH_2-3); 1.58 (s, 3H, CH_3-Vin); 1.54 (s, 3H, CH_3-Vin); 1.30 (s, 2×6H, CH_3-2a, -2a'); 1.05 (s, 2×9H, *t*-Bu–Si); 0.12 (s, 2×6H, CH_3–Si).

4.2.7. 6-O-tert-butyldimethylsilyl-5-hydroxymethyl-2,2′,7,8-tetramethyl-chroman-6-ol ***12***. Compound **11** (58 mg, 0.149 mmol) was dissolved in a mixture of acetone (18 mL) and water (2 mL) and kept with HgO (60 mg) and $HgCl_2$ (60 mg) under reflux for 2 h. After filtration the residue was taken up in ethyl acetate (10 mL), washed with aqueous KI (50%) and saturated NaCl, dried over $MgSO_4$, evaporated and purified by flash chromatography (pet. ether/ethyl acetate 13:2) to give **12**: 41.5 mg (79%) as a pale yellow syrup.

^{1}H NMR (400 MHz, $CDCl_3$) δ=4.67 (s, 2H, CH_2-5a); 2.84 (m, 2H, CH_2-4); 2.10, 2.09 (s, 6H, CH_3-7a and -8a); 1.79 (m, 2H, CH_2-3); 1.31 (s, 6H, CH_3-2a, -2a'); 1.05 (s, 9H, *t*-Bu–Si); 0.16 (s, 6H, CH_3–Si).

4.2.8. 5-Allyloxymethyl-6-O-tetrahydropyranyl-2,2′,7,8-tetramethyl-chroman-6-ol ***13***. Compound **8** (138 mg, 0.5 mmol) was dissolved in anhydrous dichloromethane (2 mL), cooled to −10 °C and treated with dihydropyran (113 μL, 1.25 mmol) and TsOH (1 mg) for 3 h at −10 °C. Then the mixture was warmed to room temperature, dichloromethane (15 mL) added and the organic phase washed successively with saturated NaCl and $NaHCO_3$ solution, dried ($MgSO_4$), evaporated and purified by flash chromatography (pet. ether/ethyl acetate 9:1) to give **13**: 140 mg (78%) as a pale yellow syrup.

^{1}H NMR (400 MHz, $CDCl_3$) δ=5.97 (m, 1H, H-c); 5.30 (m, 1H, H-d); 5.17 (m, 1H, H-d'); 4.74 (m, 1H, OCH-THP); 4.71 (d, 1H, CH_2-5a); 4.51 (d, 1H, CH_2-5a'); 4.12–3.98 (m, 3H, H-b, -b', OCH_2-THP); 3.38 (m, 1H, OCH_2-THP); 2.86 (m, 2H, CH_2-4); 2.21, 2.12 (s, 6H, CH_3-7a and -8a); 2.06–1.32 (m, 14H, CH_2-3, 3×CH_2-THP, CH_3-2a, -2a').

As side product 2,2′,7,8-tetramethyl-5,6-dipyranyl-chroman **15**[35] was obtained and characterized.

^{1}H NMR (400 MHz, $CDCl_3$) δ=5.18 (s, 1H, H-c); 3.39 (m, 1H, H-b); 3.64 (m, 1H, H-b'); 2.86–2.38 (m, 4H, CH_2-4, 2×CH_2-THP); 2.15–2.04 (m, 1H, CH-e); 2.09, 2.04 (s, 6H, CH_3-7a and -8a); 1.74–1.51 (m, 6H, CH_2-3, 2×CH_2); 1.22 (s, 6H, CH_3-2a, -2a'). ^{13}C NMR (100 MHz, $CDCl_3$) δ=145.83, 143.41 (2C, C-6 and C-8b); 123.97, 123.20 (2C, C-7, C-8); 115.83, 114.72 (2C, C-5, C-4a); 96.31 (1C, C-a); 72.73 (1C, C-2); 31.89 (1C, C-e); 33.08, 20.33 (2C, C-3, C-4); 27.12, 26.87 (2C, C-2′, C-2a'); 26.33, 25.02, 23.65 (3C, CH_2, C-c, C-d, C-f); 11.90 (2C, CH_3, C-7a, -8a). EI-MS: 302 (M^+). Anal. Calcd for $C_{19}H_{26}O_3$(302.4): C, 75.46; H, 8.67. Found: C, 74.77; H, 8.67.

4.2.9. 5-Hydroxymethyl-6-O-tetrahydropyranyl-2,2′,7,8-tetramethyl-chroman-6-ol ***14***. Compound **13** (100 mg, 0.27 mmol) were dissolved in ethanol (10 mL) and water (1 mL) and refluxed for 2 h with $(Ph_3P)_3RhCl$ (18 mg, 0.018 mmol) and DABCO (4 mg, 0.037 mmol). Then the mixture was evaporated, dissolved in acetone (36 mL) and water (4 mL) and refluxed for 90 min with HgO (110 mg) and $HgCl_2$ (110 mg), filtered over Celite and evaporated. The residue was dissolved in dichloromethane (10 mL) washed with aqueous KI (50%), saturated NaCl, dried ($MgSo_4$) and purified by flash chromatography (pet. ether/ethyl acetate 13:2) to give **14**: 20 mg (23%) as a pale yellow syrup.

^{1}H NMR (400 MHz, $CDCl_3$) δ=4.84 (dd, 1H, CH_2-5a); 4.55 (dd, 1H, OCH–THP-1); 4.34 (dd∼t, CH_2-5b); 4.02 (m, 3H, OCH_2–THP-5a); 3.73 (dd, 1H, 5a-OH); 3.42 (m, 1H, OCH_2-THP-5b); 2.98 (m, 2H, CH_2-4a); 2.78 (m, 2H, CH_2-4b); 2.14, 2.10 (s, 6H, CH_3-7a and -8a); 1.98–1.49 (m, 6H, 3×CH_2-THP); 1.80 (m, 2H, CH_2-3); 1.34, 1.27 (s, 6H, CH_3-2a, -2a'). $J_{5a,OH}$=2.5, $J_{a,b}$=11.7, $J_{1THP,5aTHP}$=2.0, $J_{1THP,5bTHP}$=8.6 Hz. ^{13}C NMR (100 MHz, $CDCl_3$) δ=148.19, 146.39 (2C, C-6 and C-8b); 129.80, 126.89, 125.43, 117.02 (4C, C-4a, C-5, C-7, C-8); 102.67 (1C, C-THP-1); 72.69 (1C, C-2); 66.04, 55.54 (2C, OCH_2, C-THP-5 and CH_2, C-5a); 32.28, 30.92, 24.50, 21.54, 19.35 (5C, CH_2, C-3, C-4, C-THP-2, C-THP-3, C-THP-4); 27.36, 25.60 (2C, CH_3, C-2′, C-2a'); 12.97, 11.71 (2C, CH_3 C-7a, -8a).

4.2.10. 5-[1′-(1,3-Dioxolane-2-yl)-methyl-1′-oxy]-methyl-2,2′,7,8-tetramethyl-chroman-6-ol ***16***. Compound **5** (296 mg, 1.0 mmol) and 1,3-dioxolane-2-methanol (hydroxyacetaldehyde ethylene acetal,

150 mg, 1.44 mmol) dissolved in anhydrous diethylether (5 mL) were treated with sodium hydride (60%, 60 mg, 1.5 mmol) under nitrogen at 0 °C. After 2.5 h workup as for **8** followed by flash chromatography (pet. ether/ethyl acetate 5:1) gave **16**: 200 mg (62%) as a yellow solid; mp 63–64 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ=7.18 (s, 1H, Ar–OH); 5.10 (t, 1H, CH-5c); 4.78 (s, 2H, CH_2-5a); 4.05–3.91 (m, 4H, OCH_2–dioxolane); 3.63 (d, 2H, CH_2-5b); 2.65 (m, 2H, CH_2-4); 2.16, 2.10 (s, 6H, CH_3-7a and -8a); 1.76 (m, 2H, CH_2-3); 1.28 (s, 6H, CH_3-2a, -2a'); $J_{5b,c}$=3.6 Hz. EI-MS: 322 (M^+). Anal. Calcd for $C_{18}H_{26}O_5$(322.4): C, 67.06; H, 8.13. Found: C, 67.04; H, 8.32.

*4.2.11. 5-[2′-(1,3-Dioxolane-2-yl)-ethyl-1′-oxy]-methyl-2,2′,7,8-tetramethyl-chroman-6-ol **17**.* Compound **5** (1.8 g, 6.0 mmol) and 1,3-dioxolane-2-ethanol (3-hydroxypropionaldehyde ethylene acetal, 743 mg, 6.3 mmol) dissolved in anhydrous diethylether (10 mL) were treated with sodium hydride (60%, 378 mg, 9.0 mmol) under nitrogen at 0 °C for 12 h. Workup as for **8** followed by flash chromatography purification gave **17**: 670 mg, 79% as a yellow amorphous solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ=7.46 (s, 1H, 6-OH); 4.99 (t, 1H, CH-5d); 4.67 (s, 2H, CH_2-5a); 4.01–3.99, 3.89–3.86 (m, 4H, OCH_2-dioxolane); 3.70 (m ~ t, 2H, CH_2-5b); 2.63 (m, 2H, CH_2-4); 2.15, 2.10 (s, 6H, CH_3-7a and -8a); 2.06–2.01 (m, 2H, CH_2-5c); 1.76 (m, 2H, CH_2-3); 1.27 (s, 6H, CH_3-2a, -2a'); $J_{5c,d}$=4.4 Hz.

*4.2.12. 6-O-Allyl-5-[1′-(1,3-dioxolane-2-yl)-methyl-1′-oxy]-methyl-2,2′,7,8-tetramethyl-chroman-6-ol **18**.* Compound **16** (1.278 g, 3.97 mmol) and allylbromide (3 mL, 35 mmol) dissolved in anhydrous diethylether (30 mL) were treated with sodium hydride (60%, 800 mg, 20 mmol) under nitrogen at 0 °C for 24 h. Workup as for **8** followed by flash chromatography (pet. ether/ethyl acetate 5:1) gave **18**: 200 mg (62%) as yellow syrup.

^{1}H NMR (400 MHz, $CDCl_3$) δ=6.16–6.06 (m, 1H, CH-6c); 5.44 (m, 1H, CH_2-6d); 5.24 (m, 1H, CH_2-6d'); 5.04 (t, 1H, CH-5c); 4.63 (s, 2H, CH_2-5a); 4.24 (m, 2H, CH_2-6b); 3.99–3.85 (m, 4H, OCH_2-dioxolane); 3.54 (d, 2H, CH_2-5b); 2.83 (m, 2H, CH_2-4); 2.16, 2.09 (s, 6H, CH_3-7a and -8a); 1.77 (m, 2H, CH_2-3); 1.30 (s, 6H, CH_3-2a, -2a'); $J_{5c,d}$=4.4 Hz. EI-MS: 362 (M^+).

*4.2.13. 6-O-Allyl-5-[2′-(1,3-dioxolane-2-yl)-ethyl-1′-oxy]-ethyl-2,2′,7,8-chroman-6-ol **19**.* Compound **17** (600 mg, 1.78 mmol) and allylbromide (25 μL, 2.95 mmol) dissolved in anhydrous THF (25 mL) were treated with sodium hydride (60%, 120 mg, 30 mmol) under nitrogen at 0 °C for 24 h. Workup as for **8** followed by flash chromatography gave **19**: 440 mg (73%) as a pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ=6.11 (ddd, 1H, CH-6c); 5.43 (ddd, 1H, CH_2-6d); 5.25 (ddd, 1H, CH_2-6d'); 4.96 (t, 1H, CH-5d); 4.52 (s, 2H, CH_2-5a); 4.25 (ddd ~ dt, 2H, CH_2-6b); 3.96, 3.83 (m, 4H, OCH_2-dioxolane); 3.63 (t, 2H, CH_2-5b); 2.81 (m, 2H, CH_2-4); 2.16, 2.09 (s, 6H, CH_3-7a and -8a); 1.96 (dt, 2H, CH_2-5c); 1.78 (m, 2H, CH_2-3); 1.30 (s, 6H, CH_3-2a, -2a'); $J_{6d,6d'}$=1.5, $J_{6d,b}$=3.1, $J_{6d,c(Z)}$=10.7, $J_{6d,c(E)}$=16.8, $J_{6c,b}$=5.6, $J_{5b,c}$=6.6, $J_{5c,d}$=5.1 Hz. ^{13}C NMR (100 MHz, $CDCl_3$) δ=149.18 (1C, C-6); 148.20 (1C, C-8a); 134.32, (1C, =CH, C-all-6c); 128.15 (1C, C-7); 126.23 (1C, C-8); 124.64 (1C, C-4a); 118.58 (1C, C-5); 116.74 (1C, $=CH_2$, C-all-6d); 102.51 (1C, CH, C-5d); 75.52 (1C, CH_2, C-6b); 73.05 (1C, C2); 65.96 (1C, CH_2, C-5b); 64.90, 64.78 (2C, CH_2, C-5a and OCH_2-dioxolane); 34.37 (1C, CH_2, C-5c); 32.71 (1C, CH_2, C-3); 26.94 (2C, CH_3, C-2′, C-2a'); 19.71 (1C, CH_2, C-4); 12.80 (1C, CH_3, C-7a); 12.13 (1C, CH_3, C-8a). EI-MS: 376 (M^+).

*4.2.14. 6-O-Allyl-5-formyloxymethyl-2,2′,7,8-tetramethyl-chroman-6-ol **20**.* Compound **18** (120 mg, 0.33 mmol) was dissolved in formic acid (3 mL) and stirred at room temperature for 20 min. The deep yellow solution was diluted with diethylether (15 mL), successively washed with aqueous $NaHCO_3$ and NaCl, dried (Na_2SO_4) and evaporated in high vacuum to give **20**: 95 mg (93%) as a yellow syrup.

^{1}H NMR (400 MHz, $CDCl_3$) δ=8.14 (s, 1H, CHO); 6.09 (ddd, 1H, CH-6c); 5.42 (dd, 1H, CH_2-6d); 5.29 (s, 2H, CH_2-5a); 5.27 (dd, 1H, CH_2-6d'); 4.24 (d, 2H, CH_2-b); 2.73 (m, 2H, CH_2-4); 2.19 (s, 6H, CH_3-7a and -8a); 1.79 (m, 2H, CH_2-3); 1.32 (s, 6H, CH_3-2a, -2a'); $J_{6d,6d'}$=1.3, $J_{6c,d(E)}$=17.0, $J_{6c,d(Z)}$=10.7, $J_{6b,c}$=5.7, $J_{3,4}$=6.9 Hz.

*4.2.15. 6-O-Allyl-5-(2,3-di-O-benzyl-L-ascorbate-6-oxy)-methyl-2,2′,7,8-tetramethyl-chroman-6-ol **22**.* (a) Compound **20** (60 mg, 0.2 mmol) and di-*O*-benzyl-ascorbate **21**[36] (127 mg, 0.36 mmol) dissolved in toluene (2 mL) were treated with TsOH (1 mg) and heated under reflux for 1.5 h. The cold reaction mixture was neutralised with basic ion exchanger (Amberlite IRA-420, OH^-), evaporated, and the residue purified by flash chromatography (pet. ether/ethyl acetate 5:1 plus 0.4% triethylamine) to give **22**: 49 mg (40%) as pale yellow oil.

(b) Compound **9** (170 mg, 0.54 mmol) and di-*O*-benzyl-ascorbate **21**[36] (250 mg, 0.7 mmol) dissolved in toluene (10 mL) were treated with TsOH (3 mg) and heated under reflux for 3 h. Workup and purification as in (a) gave **22**: 79 mg (24%). $[\alpha]_D^{20}$ +61.0 (*c* 0.31, CH_2Cl_2).

^{1}H NMR (500 MHz, $CDCl_3$) δ=7.41–7.31, 7.17–7.15 (m, 10H, Aryl); 6.07 (m, 1H, CH-all-c); 5.41 (dd, 1H, CH_2-all-d); 5.22 (dd, 1H, CH_2-aa-d'); 5.18 (d, 1H, CH_2–Bn); 5.09 (s, 2H, CH_2–Bn); 5.09 (d, 1H, CH_2–Bn); 4.70 (d, 1H, H-4-aa); 4.56 (s, 2H, CH_2-5a); 4.21 (d, 1H, CH_2-b-all); 4.04 (~dt, H-5-aa); 3.67 (dd, 1H, H-6b-aa); 3.62 (dd, 1H, H-6b-aa); 2.76 (m, 2H, CH_2-4); 2.16–2.09 (s, 6H, CH_3-7a and -8a); 1.75 (m, 2H, CH_2-3); 1.28 (s, 6H, CH_3-2′, -2a'). $J_{4,5aa}$=2.0, $J_{5,6a\text{-}aa}$=6.1, $J_{5,6b\text{-}aa}$=6.6, $J_{6aa,gem}$=9.7, $J_{c,d(E)}$=18.1, $J_{c,d(Z)}$=10.7, $J_{c,b}$=5.6, $J_{d,gem}$=1.6, J_{Bn}=11.9 Hz. ^{13}C NMR (125 MHz, $CDCl_3$) δ=169.50 (1C, C-1-aa); 157.26 (1C, C-3-aa); 149.17, (1C, C-6); 148.24 (1C, C-8a); 135.97 (1C, C–Bn-2aa); 135.34 (1C, C–Bn-3aa); 133.99 (1C, =CH, C-all-c); 129.06 (1C, C–Bn); 128.58, 128.55 (2C, CH, C–Bn); 128.24 (1C, C-7); 127.74 (1C, CH, C–Bn); 126.70 (1C, C-8); 124.94 (1C, C-4a); 120.91 (1C, C-2-aa); 118.40 (1C, C-5); 116.84 (1C, $=CH_2$, C-all-d); 75.44 (1C, OCH_2, C-all-b); 75.09 (1C, CH, C-4-aa); 73.83 (1C, CH_2, C–Bn); 73.37 (1C, C-2); 73.08 (1C, CH_2, C–Bn); 70.07 (1C, CH_2, C-6-aa); 68.13 (1C, CH, C-5-aa); 65.25 (1C, CH_2, C-5a); 32.57 (1C, CH_2, C-3); 26.87 (CH_3 C-2′, -2a'); 19.76 (1C, CH_2, C-4); 12.80 (1C, CH_3, C-7a); 12.12 (1C, CH_3, C-8a). EI-MS: 614 (M^+).

*4.2.16. 6-O-Acetyl-5-azidomethyl-γ-tocopherol **24**[37].* 6-*O*-Acetyl-5-chloromethyl-γ-tocopherol **23**[33,34] (1.065 g, 2.1 mmol) and sodium azide (270 mg, 4.2 mmol) dissolved in acetonitrile (40 mL) were heated under reflux for 5 h. The mixture was diluted with dichloromethane (100 mL) washed with saturated NaCl solution, dried ($MgSO_4$) and evaporated in vacuum and high vacuum to give the raw material **24**: 1.03 g (99%) as orange syrup. An analytical sample was purified by flash chromatography (pet. ether/ethyl acetate 1:1). IR: 1761 (C=O), 2099 (N_3)cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ=4.19 (s, 2H, CH_2-5a); 2.73 (m, 2H, CH_2-4); 2.35 (s, 3H, OAc); 2.12, 2.03 (s, 6H, CH_3-7a and -8a); 1.89–1.70 (m, 2H, CH_2-3); 1.62–0.99 (m, 24H, CH_3-2a, CH-4′, -8′, -12′, CH_2-⟨1′-11⟩); 0.89–0.80 (m, 12H, CH_3-4a', -8a', -12a', -13′). Anal. Calcd for $C_{31}H_{51}O_3N_3$ (513.8): C, 72.47; H, 10.00; N, 8.18. Found: C, 72.76; H, 10.03; N, 8.09.

*4.2.17. 6-O-Acetyl-5-phthalimidomethyl-γ-tocopherol **25**.* Compound **24** (540 mg, 1.07 mmol), sodium iodide (10 mg, 0.07 mmol) and potassium phthalimide (305 mg, 1.64 mmol) were dissolved in anhydrous dimethylformamide (15 mL) and stirred for 15 h at room temperature. The mixture was diluted with ethyl acetate (50 mL), washed with water (3×20 mL), dried ($MgSO_4$) and evaporated to give **25**: 650 mg (98%) as colourless solid, which turned brown in air; mp 78–80 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ=7.80–7.66 (m, 4H, CH–Ph); 4.69 (m, 2H, CH_2-5a); 2.30 (s, 3H, OAc); 2.08, 1.92 (s, 6H, CH_3-7a

and -8a); 1.92–1.00 (m, 28H, CH_2-4, CH_2-3, CH_3-2a, CH-4′, -8′, -12′, CH_2-⟨1′-11′⟩); 0.88–0.82 (m, 12H, CH_3-4a', -8a', -12a', -13′). EI-MS: 617 (M^+), 575 ($M^+-C_2H_2O$).

4.2.18. 5-Acetamidomethyl-γ-tocopherol ***26***. Compound **25** (116 mg, 0.19 mmol) dissolved in THF (3 mL) was treated with hydrazine hydrate (0.3 mL, 6.17 mmol) and then heated under reflux for 12 h. The mixture was evaporated, then water (2 mL) and dichloromethane (5 mL) added, and the organic phase successively washed with saturated aqueous $NaHCO_3$ and NaCl, dried ($MgSO_4$) and evaporated. Purification was by flash chromatography (pet. ether/ethyl acetate 1:1) gave **26**: 83 mg (90%) as colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ=8.77 (s, 1H, HO–Ar); 6.33 (t, 1H, NH); 4.37 (d, 2H, CH_2-5a); 2.66 (m, 2H, CH_2-4); 2.19 (s, 3H, NHAc); 2.10, 1.99 (s, 6H, CH_3-7a and -8a); 1.88–1.69 (m, 2H, CH_2-3); 1.64–0.99 (m, 24H, CH_3-2a, CH-4′, -8′, -12′, CH_2-⟨1′-11′⟩); 0.93–0.79 (m, 12H, CH_3-4a', -8a', -12a', -13′); $J_{NH,CH2}$=6.1 Hz. ^{13}C NMR (100 MHz, $CDCl_3$) δ=172.50 (1C, C=O, NHAc); 146.64, 145.11 (2C, C-6 and C-8b); 126.43, 124.86, 119.27, 115.81 (4C, C-8, C-7, C-5, C-4a); 74.48 (1C, C-2); 60.41 (1C, CH_2, C-5a); 40.00, 39.40 (2C, CH_2, C-1′, -11′); 37.49, 37.42, 37.31, 36.34 (4C, CH_2, C-3′, -5′, -7′, -9′); 32.80, 32.74 (2C, CH C-4′, -8′); 31.40 (1C, CH_2, C-3); 28.00 (1C, C-12′); 24.82, 24.47 (2C, CH_2, C-6′, -10′); 22.81–22.64 (2C, CH_3, C-12′, -13′); 21.04, 20.39 (2C, CH_2, C-2′, -4′); 19.76, 19.70 (2C, CH_3, C-4a', -8a'); 12.50, 12.04 (2C, CH_3, C-7a,-8b).

4.2.19. 5-Hydroxymethyl-γ-tocopherol ***27***. Compound **23**[33,34] (478 mg, 0.94 mmol) was dissolved in oxygen free THF (15 mL) and added to a degassed mixture of sodium hydroxide solution (0.25 M, 10 mL) and THF (15 mL). Then tetrabutyl ammonium iodide (10 mg) were added and the mixture refluxed for 3 h. Following neutralisation with 2 N H_2SO_4 ethyl acetate (50 mL) was added, the organic phase washed with saturated NaCl solution, dried ($MgSO_4$), evaporated and purified by flash chromatography (pet. ether/ethyl acetate 5:1) to give **27**: 170 mg (40%) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ=7.12 (s, 1H HO–Ar); 4.84 (s, 2H, CH_2-5a); 2.60 (m, 2H, CH_2-4); 2.16, 2.10 (s, 6H, CH_3-7a and -8b); 1.84–1.68 (m, 2H, CH_2-3); 1.66–1.00 (m, 24H, CH_3-2a, CH-4′, -8′, -12′, CH_2-⟨1′-11′⟩); 0.91–0.79 (m, 12H, CH_3-4a', -8a', -12a', -13′). ^{13}C NMR (100 MHz, $CDCl_3$) δ=146.78, 144.47 (2C, C-6 and C-8a); 125.29, 122.55, 118.41 (3C, C-8, C-7, C-5); 114.77 (1C, C-4a); 74.14 (1C, C-2); 59.54 (1C, CH_2, C-5a); 39.43, 38.94 (2C, CH_2, C-1′,-11′); 37 02–36.85 (4C, CH_2, C-3′, -5′, -7′, -9′); 32.34, 32.27 (2C, CH, C-4′, -8′); 30.91 (1C, CH_2, C-3); 27.54 (1C, CH, C-12′); 24.36, 24.00 (2C, CH_2, C-6′, -10′); 22.27, 22.18 (2C, CH_3, C-12a', -13′); 20.60–19.20 (4C, CH_2, C-2′, -4 and CH_3, C-4a', -8a'); 11.49, 11.27 (CH_3, C-7a, -8a). EI-MS: 446 (M^+), 429 (M^+-OH), 428 (M^+-H_2O). Anal. Calcd for $C_{29}H_{50}O_3$ (446.7): C, 77.97; H, 11.28; N, 8.18. Found: C, 77.75; H, 11.28.

4.2.20. 5-Methyloxymethyl-γ-tocopherol ***28***. ^{1}H NMR (400 MHz, $CDCl_3$) δ=7.42 (s, 1H, HO–Ar); 4.65 (s, 2H, CH_2-5a); 3.43 (s, 3H, OCH_3); 2.60 (m, 2H, CH_2-4); 2.15, 2.10 (s, 6H, CH_3-7a and -8a); 1.84–1.68 (m, 2H, CH_2-3); 1.66–1.00 (m, 24H, CH_3-2a, CH-4′, -8′, -12′, CH_2-⟨1′-11′⟩); 0.87–0.83 (m, 12H, CH_3, C-4a', -8a', -12a', -13′). ^{13}C NMR (100 MHz, $CDCl_3$) δ=147.36, 144.74 (2C, C-6 and C-8b); 125.78, 123.06, 115.92, 115.38 (4C, C-8, C-7, C-5, C-4a); 74.45 (1C, C-2); 69.82 (1C, CH_3, OMe); 58.10 (1C, CH_2, C-5a); 39.86–37.30 (6C, CH_2, C-1′, -3′, -5′, -7′, -9′, -11′); 32.80 (2C, CH, C-4′, -8′); 32.70 (1C, CH_2, C-3); 28.00 (1C, CH, C-12′); 24.82, 24.46 (2C, CH_2, C-6′, -10′); 23.75–22.64 (2C, CH_3, C-12a', -13′); 21.03–19.66 (4C, CH_2, C-2′, -4 and CH_3, C-4a', -8a'); 11.93, 11.71 (2C, CH_3, C-7a, -8a).

4.2.21. 5-Ethyloxymethyl-γ-tocopherol ***29***. ^{1}H NMR (400 MHz, $CDCl_3$) δ=7.68 (s, 1H, HO–Ar); 4.69 (s, 2H, CH_2-5a); 3.60 (q, 2H, OCH_2); 2.60 (m, 2H, CH_2-4); 2.17, 2.10 (s, 6H, CH_3-7a and -8a); 1.87–1.69 (m, 2H, CH_2-3); 1.61–1.00 (m, 24H, CH_3-2a, CH-4′, -8′, -12′, CH_2-⟨1′-11′⟩); 1.24 (t, 3H, OEt); 0.91–0.80 (t, 12H, m, CH_3, C-4a', -8a', -12a', -13′). ^{13}C NMR (100 MHz, $CDCl_3$) δ=146.94, 144.23 (2C, C-6 and C-8b); 125.15, 122.61, 117.39, 115.66, (4C, C-8, C-7, C-5, C-4a); 73.97 (1C, C-2); 67.57, 65.74 (2C, CH_2, OEt, C-5a); 39.41–36.85 (6C, CH_2, C-1′, -3′, -5′, -7′, -9′, -11′); 32.34, 32.26 (2C, CH, C-4′, -8′); 30.97 (1C, CH_2, C-3); 27.54 (1C, CH, C-12′); 24.36, 24.00 (2C, CH_2, C-6′, -10′), 23.30–22.18 (2C, CH_3, C-12a',-13′); 20.58–19.24 (4C, CH_2, C-2′, -4 and CH_3, C-4a', -8a'); 14.68 (1C, CH_3, OEt); 11.45, 11.25 (CH_3, C-7a, -8a).

4.2.22. 5-Allyloxymethyl-γ-tocopherol ***30***. Anhydrous allyl alcohol (120 μL, 1.76 mmol) in anhydrous dimethylacetamide (5 mL) was treated under nitrogen at 0 °C with sodium hydride (80%, 280 mg, 9.33 mmol). Drop wise a solution of compound **23**[33,34] (200 mg, 0.33 mmol) in dimethylacetamide (5 mL) was added and the mixture stirred for 1 h at 0 °C. Excess of NaH was destroyed with methanol, the mixture diluted with ethyl acetate (50 mL) and the organic phase washed successively with water, 2 N H_2SO_4 and saturated NaCl solution. After drying ($MgSO_4$) and evaporation the residue was purified by flash chromatography (pet. ether/ethyl acetate 3:1) to give **30**: 150 mg (92%) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ=7.43 (s, 1H, HO–Ar); 5.94 (ddd, 1H, H-c); 5.31 (dd, 1H, H-d); 5.25 (dd, 1H, H-d'); 4.71 (s, 2H, CH_2-5a); 4.07 (d, 2H, H-b); 2.59 (m, 2H, CH_2-4); 2.15, 2.10 (s, 6H, CH_3-7a and -8a); 1.84–1.69 (m, 2H, CH_2-3); 1.63–1.00 (m, 24H, CH_3-2a, CH-4′, -8′, -12′, CH_2-⟨1′-11′⟩); 0.87–0.83 (m, 12H, CH_3-4a', -8a', -12a', -13′). $J_{d,d'}$=1.5, $J_{d,c(Z)}$=17.3, $J_{d',c(E)}$=10.5, $J_{b,c}$=5.6 Hz. ^{13}C NMR (100 MHz, $CDCl_3$) δ=146.96 (2C, C-6 and C-8a); 133.34 (1C, CH, C-all-c); 125.37, 122.65 (3C, C-5, C-7, C-8); 117.66 (1C, CH_2, C-all-d); 114.96 (1C, C-4a); 74.01 (1C, C-2); 70.67, 66.64 (2C, OCH_2, C-all-b and CH_2, C-5a); 38.94 (2C, CH_2, C-1′, -11′); 36.95–36.85 (4C, CH_2, C-3′, -5′, -7′, -9′); 32.34 (2C, CH, C-4′, -8′); 29.25 (1C, CH_2, C-3); 27.54 (1C, CH, C-12′); 24.36, 24.00 (2C, CH_2, C-6′, -10′); 22.27, 22.28 (2C, CH_3, C-12a', -13′); 20.58, 19.49 (2C, CH_2, C-2′, -4); 19.30, 19.24 (2C, CH_3, C-4a', -8a'); 11.47, 11.27 (2C, CH_3, C-7a, -8a).

4.2.23. 5-(1,2,3,4-Di-O-isopropylidene-α-D-galactopyranos-6-oxy)-γ-tocopherol ***31***. 1,2,3,4-Di-*O*-isopropylidene-α-D-galactopyranose[39] (208 mg, 0.8 mmol) dissolved in anhydrous THF (5 mL) under nitrogen was treated with NaH (192 mg, 8 mmol) at room temperature. Then compound **23** (300 mg, 0.5 mmol) dissolved in anhydrous THF (5 mL) was added drop wise and the reaction kept for 2.5 h at room temperature under stirring. Excess NaH was destroyed with methanol, the mixture evaporated, dissolved in dichloromethane (20 mL) washed with water (2×10 mL), dried ($MgSO_4$) and evaporated. Purification was by flash chromatography (pet. ether/ethyl acetate 5:1) gave **31**: 108 mg (32%), pale yellow syrup. $[\alpha]_D^{20}$ –133.3 (*c* 1.0, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ=7.08 (s, 1H, HO–Ar); 3.71 (d, 2H, CH_2-5a); 2.60–2.68 (m, CH_2-4); 2.10, 2.17 (s, 6H, CH_3-7a, -8a); 1.67–1.84 (m, 2H, CH_2-3); 1.68–1.00 (m, 24H, CH_3-2a, CH-4′, -8′, -12′, CH_2-⟨1′-11′⟩); 0.87–0.83 (m, 12H, CH_3-4a', -8a', -12a', -13′); 5.55 (d, 1H, H-1); 4.25 (dd, 1H, H-2); 4.60 (dd, 1H, H-3); 4.32 (t, 1H, H-4); 4.02 (dt, 1H, H-5); 4.75 (dd, 1H, H-6a); 4.68 (dd, 1H, H-6b); $J_{1,2}$=4.6, $J_{2,3}$=7.9, $J_{3,4}$=2.1, $J_{4,5}$=5.1, $J_{5,6a}$=4.1, $J_{5,6b}$=4.1, $J_{6a,6b}$=11.9 Hz.

4.2.24. 3-Acetoxy-propanal ***33***[41]. Acroleine **32** (53 mL, 0.8 mmol) and acetic acid (47 mL, 0.82 mmol) were mixed with ion exchange resin IRA-420 (200 ml, acetate form) and kept at room temperature for 48 h. The ion exchange resin was rinsed with ethyl acetate (300 mL), the organic phase washed with saturated $NaHCO_3$ solution (200 mL), NaCl solution (100 ml), dried (Na_2SO_4) and evaporated. Distillation gave **33**: 15.0 g (16%) as a clear colourless oil, which decomposes within minutes. Bp_{12}:71–72 °C; Ref. 41: 43%, $bp_{0.5}$:35–40 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ=9.74 (s, 1H, CHO); 4.32 (t, 2H, OCH_2); 2.70 (dt, 2H, CH_2); 1.98 (s, 3H, OAc); $J_{1,2}$=1.5, $J_{2,3}$=6.1 Hz.

4.2.25. 3-Acetoxy-1,1-dimethoxy-propane ***34***[42]. Compound **33** (14.06 g, 121 mmol), trimethylorthoformate (14 mL, 127.5 mmol) and methanol (5 mL) were mixed. Drop wise a mixture (1.4 mL) of methanol and concentrated H_2SO_4 (19:1) was added under stirring. After 2 h the mixture was neutralised with triethylamine, evaporated and purified by flash chromatography (pet. ether/ethyl acetate 3:1) to give compound **34**: 10.0 g (51%) as a colourless liquid; Ref. 42: no data.

^{1}H NMR (400 MHz, $CDCl_3$) δ=4.48 (t, 1H, CH-1); 4.11 (t, 2H, CH_2-3); 3.31 (s, 6H, 2×OCH_3); 2.03 (s, 3H OAc); 1.91 (q, 2H, CH_2-2); $J_{1,2}$=5.6, $J_{2,3}$=6.6 Hz. EI-MS: 131 (M−OCH_3), 87 (H_3CO=CH−OCH_3). Anal. Calcd for $C_7H_{14}O_4$ (162.2): C, 51.70; H, 8.70. Found: C, 51.71; H, 8.73.

4.2.26. 3-Hydroxy-1,1-dimethoxy-propane ***35***[43]. Compound **34** (1.05 g, 6.48 mmol) dissolved in anhydrous methanol (5 mL) was stirred with Na_2CO_3 (1.13 g, 9.72 mmol) for 18 h at room temperature. Filtration and evaporation gave the liquid **35**: 775 mg (quant.), which was used without further purification; Ref. 43: no data.

4.2.27. 3,3-Dimethoxypropyl-2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside ***37***. 2,3,4,6-Tetra-*O*-acetyl-α-D-glucopyranosyl bromide **36**[44] (2.7 g, 6.6 mmol) and compound **35** (780 mg, 6.5 mmol) dissolved in anhydrous dichloromethane (10 mL) were treated under nitrogen in the dark with silver carbonate (1.9 g, 6.8 mmol) and stirred for 20 h at room temperature. After filtration over Celite and washing with dichloromethane (50 mL) the solvents were evaporated and the residue purified by flash chromatography (dichloromethane/acetone 15:1) to give **37**: 121 g (41%), colourless syrup; $[\alpha]_D^{20}$ −11.5 (*c* 2.7, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$) δ=5.20 (t, 1H, H-3); 5.09 (t, 1H, H-4); 4.99 (dd, 1H, H-2); 4.50 (d, 1H, H-1); 4.46 (t, 1H, CH-c-Sp); 4.27 (dd, 1H, H-6a); 4.13 (dd, 1H, H-6b); 3.93 (m, 1H, CH_2-a-Sp); 3.70 (ddd, 1H, H-5); 3.58 (m, 1H, CH_2-a'-Sp); 3.33 (s, 3H, OMe); 3.32 (s, 3H, OMe); 2.08, 2.03, 2.01, 1.99 (s, 12H, 4×CH_3, OAc); 1.98−1.84 (m, 2H, CH_2-b-Sp); $J_{1,2}$=8.1, $J_{2,3}$=9.7, $J_{3,4}$=9.7, $J_{4,5}$=9.7, $J_{5,6a}$=4.6, $J_{5,6b}$=5.5, $J_{6a,6b}$=12.2, $J_{b,c}$=5.9 Hz. ^{13}C NMR (100 MHz, $CDCl_3$) δ=170.22, 169.84, 168.96, 168.81 (C, C=O, OAc); 101.45 (1C, C-c-Sp); 100.45 (1C, C-1); 72.39 (1C, C-3); 71.33 (1C, C-5); 70.87 (1C, C-2); 67.96 (1C, C-4); 65.81 (1C, C-a-Sp); 61.51 (1C, C-6); 53.07, 52.47 (2C, 2×OMe); 32.47 (1C, C-b-Sp); 20.27, 20.21, 20.16, 20.15 (4C, 4×CH_3, OAc). EI-MS: 419 (M^+−OCH_3).

4.2.28. 3,3-Dimethoxypropyl-β-D-glucopyranoside ***38***. Compound **37** (4.5 g, 10.0 mmol) dissolved in anhydrous methanol (20 mL) was deacetylated with NaOMe at pH 8 for 3 h at room temperature. After neutralisation with Amberlite IR 120H^+ the solution was evaporated to give **38**: 2.8 g (quant.) as colourless syrup; $[\alpha]_D^{20}$ −11.0 (*c* 1.1, CH_2Cl_2).

4.2.29. 3,3-Dimethoxypropyl-6-O-tert-butyldimethylsilyl-β-D-glucopyranoside ***39***. Imidazol (0.98 g, 14.36 mmol) was dissolved in anhydrous DMF (10 mL) at −10 °C and compound **38** (2.7 g, 9.57 mmol) added under stirring. Then *tert*-butyldimethylsilyl chloride (1.7 g, 11.50 mmol) was added and the reaction kept under stirring at −10 °C for 1 h. Excessive silyl chloride was destroyed with water the mixture evaporated at 50 °C and the residue dissolved in dichloromethane (100 mL). Washing with saturated NaCl solution, drying (Na_2SO_4) and evaporation gave 3.9 g of the raw material **39**, which was directly used for the allylation reaction.

^{1}H NMR (400 MHz, $CDCl_3$) δ=4.53 (t, 1H, CH-c-Sp); 4.25 (d, 1H, H-1b); 3.94 (m, 1H, CH_2-a-Sp); 3.88 (dd, 1H, H-6a); 3.83 (dd, 1H, H-6b); 3.60 (m, 1H, CH_2-a'-Sp); 3.38−3.26 (m, 10H, H-2, H-3, H-4, H-5 and s, 6H, 2×OMe); 1.91 (m, 2H, CH_2-b-Sp); 0.87 (s, 9H, *t*-Bu−Si); 0.07 (s, 6H, Me−Si); $J_{1,2}$=7.6, $J_{5,6a}$=5.1, $J_{5,6b}$=5.1, $J_{6a,6b}$=10.7, $J_{b,c\text{-}Sp}$=5.6 Hz.

4.2.30. 3,3-Dimethoxypropyl 2,3,4-tri-O-allyl-6-O-tert-butyldimethylsilyl-β-D-glucopyranoside ***40***. The raw material **39** (3.8 g, 0.51 mmol) dissolved in anhydrous THF (30 mL) was treated with NaH (60%, 12.0 g, 0.3 mmol), sodium iodide (catalytic amount) and allylbromide (13 mL, 0.15 mmol). After 24 h at room temperature workup was as for compound **8**. The residue was purified by flash chromatography (pet. ether/ethyl acetate 3:1) to give **40**: 2.7 g (55% based on the amount of **38**) as colourless syrup. $[\alpha]_D^{20}$ −1.3 (*c* 0.15, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$) δ=5.94 (m, 3H, CH-all-c); 5.26 (m, 3H, CH_2-all-d); 5.15 (m, 3H, CH_2-d'-all): 4.53 (t, 1H, CH-c-Sp); 4.37–4.10 (m, 7H, CH_2-b-all); 4.24 (d, 1H, H-1b); 3.92 (m, 1H, CH_2-a-Sp); 3.84 (dd, 1H, H-6a); 3.78 (dd, 1H, H-6b); 3.59−3.48 (m, 1H, CH_2-a'-Sp); 3.40−3.31 (m, 8H, H-3, H-4 and 2×OMe); 3.17 (m, 1H, H-5); 3.13 (dd, 1H, H-2); 1.90 (m, 2H, CH_2-b-Sp); 0.89 (s, 9H, *t*-Bu−Si); 0.06, 0.05 (s, 6H, Me−Si); $J_{1,2}$=7.6, $J_{2,3}$=8.6, $J_{5,6a}$=2.0, $J_{5,6b}$=4.1, $J_{6a,6b}$=11.2, $J_{b,c\text{-}Sp}$=5.9 Hz. ^{13}C NMR (100 MHz, $CDCl_3$) δ=134.89, 134.76, 134.61 (3C, =CH, C-al1-c); 116.36, 116.30, 116.16 (3C, =CH_2, C-all-d); 102.81 (1C, C-1); 101.75 (1C, C-c-Sp); 83.80, 75.30 (2C, C-3, C-4); 81.39 (1C, C-2); 74.07 (1C, C-5); 73.27, 73.15 (2C, CH_2, C-all-b); 65.16, (1C, CH_2, C-a-Sp); 61.78 (1C, C-6); 52.85, 52.66 (2C, 2×OMe); 32.84 (1C, CH_2, C-b-Sp); 25.44 (1C, CH_3, C-*t*-Bu−Si); 17.89 (1C, *t*-Bu−Si); −5.90, −6.01 (2C, CH_3, C−Me−Si). EI-MS: 516 (M^+). Anal. Calcd for $C_{26}H_{48}O_8Si$(516.7): C, 60.43; H, 9.36. Found: C, 60.43, H, 9.38.

4.2.31. 3,3-Dimethoxypropyl 2,3,4-tri-O-allyl-β-D-glucopyranoside ***41***. Compound **40** (1.3 g, 2.51 mmol) was dissolved in anhydrous THF (10 mL), a solution of tetrabutyl ammonium fluoride in THF (2.7 mL, 1.1 M) added and stirred for 3 h at room temperature. The raw syrupy material **41** obtained after evaporation was directly used for the next etherification step.

4.2.32. 5-[2,3,4-tri-O-allyl-1-O-(3,3-dimethoxypropyl)-β-D-glucopyranos-6-oxy]-methyl-2,2′,7,8-tetramethyl-chroman-6-ol ***42***. Compound **41** (1.0 g, 2.5 mmol) in anhydrous THF (20 mL) was treated with sodium hydride (60%, 3.0 g, 75 mmol) for 30 min at room temperature. Then compound **5** (900 mg, 3.0 mmol) dissolved in anhydrous THF (5 mL) was added drop wise and kept for 12 h at room temperature. Workup was as for compound **8** and flash chromatographic purification (pet. ether/ethyl acetate 2:1) gave **42**: 1.0 g (64%) as a yellow syrup.

^{1}H NMR (400 MHz, $CDCl_3$) δ=6.02−5.84 (m, 3H, CH-all-c); 5.33−5.15 (m, 6H, CH_2-all-d); 4.78 (d, 1H, CH_2-5a); 4.72 (d, 1H, CH_2-5a); 4.58 (t, 1H, CH-c-Sp); 4.41–4.16 (m, 6H, 5×CH_2-all-b and H-1b); 4.07 (m, 2H, CH_2-all-b, CH_2-a-Sp); 3.83 (dd, 1H, H-6a); 3.70 (dd, 1H, H-6b); 3.61 (m, 1H, CH_2-a'-Sp); 3.42 (m, 1H, H-5); 3.40 (t, 1H, H-4); 3.36 (s, 6H, 2×OCH_3); 3.28 (t, 1H, H-3); 3.21 (dd∼t, 1H, H-2); 2.66 (m, 2H, CH_2-4); 2.16, 2.12 (s, 6H, CH_3-7a and -8a); 1.96 (m, 2H, CH_2-b-Sp); 1.78 (m, 2H, CH_2-3); 1.30 (s, 6H, CH_3-2a, -2a'); $J_{1,2}$=7.6, $J_{2,3}$=9.5, $J_{3,4}$=9.5, $J_{4,5}$=4.5, $J_{5,6a}$=2.5, $J_{5,6b}$=5.7, $J_{6a,6b}$=10.7, $J_{5a,gem}$=12.0, $J_{c,b\text{-}Sp}$=5.7 Hz.

4.2.33. 5-[2,3,4-tri-O-allyl-1-O-(3,3-dimethoxypropyl)-β-D-glucopyranos-6-oxy]-methyl-γ-tocopherol ***43***. Compound **41** (1.0 g, 2.5 mmol) in anhydrous THF (20 mL) was treated with NaH (60%, 3.0 g, 75 mmol) for 30 min at room temperature. Then compound **23** (1.52 g, 3.0 mmol) in anhydrous THF (5 mL) was added drop wise and stirring continued for 12 h. Workup was as for compound **8** and flash chromatographic purification (pet. ether/ethyl acetate 5:1) gave **43**: 950 mg (46%) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ=5.99−5.81 (m, 3H, m, CH-all-c); 5.30−5.12 (m, 6H, CH_2-all-d); 4.75 (m, 1H, CH_2-5a); 4.69 (m, 1H, CH_2-5a); 4.55 (t, 1H, CH-c-Sp); 4.37–4.09 (m, 7H, 5×CH_2-b-all and H-1b, Ar−OH); 4.05 (m, 2H, 1×CH_2-b-all, CH_2-a-Sp); 3.81 (m, 1H, H-6a); 3.67 (m, 1H, H-6b); 3.59 (m, 1H, CH_2-a'-Sp); 3.40 (m, 1H, H-5); 3.37 (dd∼t, 1H, H-4) 3.33 (s, 6H, 2×OMe); 3.25 (dd∼t, 1H, H-3); 3.19 (dd∼t, 1H, H-2); 2.62 (m, 2H, CH_2-4); 2.13, 2.10 (s, 6H, CH_3-7a and -8b); 1.93 (m, 2H, CH_2-b-Sp); 1.74 (m, 2H, CH_2-3); 1.58−1.00 (m, 24H, CH_3-2a, CH-4′, -8′, -12′, CH_2-⟨1′-11′⟩); 0.90−0.81 (m, 12H,

CH_3-4a', -8a', -12a', -13′); $J_{1,2}$=7.0, $J_{2,3}$=9.0, $J_{3,4}$=9.0, $J_{4,5}$=9.0, $J_{5a,gem}$=12.0 Hz.

4.2.34. 6-O-Allyl-5-[2,3,4-tri-O-allyl-1-O-(3,3-dimethoxypropyl)-β-D-glucopyranos-6-oxy]-methyl-2,2′,7,8-tetramethyl-chroman-6-ol ***44***. Compound **42** (900 mg, 1.45 mmol) dissolved in anhydrous THF (10 mL) was treated with NaH (60%, 650 mg, 16.0 mmol) for 30 min, and then allylbromide (1.4 mL, 16.0 mmol) was added and the mixture kept at room temperature for 18 h. Workup as for compound **8** followed by flash chromatographic purification (pet. ether/ethyl acetate 3:1) gave **44**: 690 mg (72%) pale rose crystals; mp 52–53 °C; $[\alpha]_D^{20}$ −2.5 (*c* 0.9, CH_2Cl_2).

^{1}H NMR ($CDCl_3$) δ=6.12 (m, 1H, CH-all-c); 5.96 (m, 2H, CH-all-c); 5.84 (m, 1H, CH-all-c); 5.47 (m_c, 1H, CH_2-all-d); 5.33–5.11 (m, 7H, CH_2-all-d); 4.63 (d, 1H, CH_2-5a); 4.55 (d, 1H, CH_2-5a); 4.53 (t, 1H, CH-c-Sp); 4.38–4.15 (m, 8H, 7×CH_2-all-b, H-1b); 3.96 (m, 2H, CH_2-all-b, CH_2-a-Sp); 3.76 (dd, 1H, H-6a); 3.66 (dd, 1H, H-6b); 3.54 (m, 1H, CH_2-a'-Sp); 3.40–3.32 (m, 8H, H-3, H-5, 2×OCH_3); 3.26 (m, 1H, H-4); 3.17 (dd, 1H, H-2); 2.85 (m, 2H, CH_2-4); 2.19, 2.11 (s, 6H, CH_3-7a and -8a); 1.90 (m, 2H, CH_2-b-Sp); 1.78 (m, 2H, CH_2-3); 1.32 (s, 6H, CH_3-2a, -2a'); $J_{1,2}$=8.2, $J_{2,3}$=9.5, $J_{3,4}$=9.5, $J_{4,5}$=9.5, $J_{5,6a}$=1.9, $J_{5,6b}$=5.0, $J_{6a,6b}$=10.7, $J_{5a,gem}$=10.1, $J_{c,b\text{-}Sp}$=5.7 Hz. ^{13}C NMR (100 MHz, $CDCl_3$) δ=135.66, 135.59, 135.12, 134.73 (4C, =CH, C-all-c); 117.33, 117.17, 117.06 (3C, =CH_2, C-all-d); 103.62 (1C, C-c-Sp); 102.49 (1C, C-1); 81.98 (1C, C-3); 78.21 (1C, C-2); 76.82–75.69 (3C, C-4, C-5, C-all-b); 71.70, 68.11, 67.66 (3C, C-6, C-a-Sp, C-5a); 55.57 (2C, 2×OMe); 35.54, 35.05 (2C, C-b-Sp, CH_2-3); 29.50, 29.14 (1C, C-2a, C-2a'); 22.14 (1C, CH_2-4); 14.50 (2C, C-7a, 8a). EI-MS: 660 (M^+). Anal. Calcd for $C_{37}H_{56}O_{10}$(660.8): C, 67.14; H, 8.54. Found: C, 67.14; H, 8.54.

4.2.35. 6-O-Allyl-5-[2,3,4-tri-O-allyl-1-O-(3,3-dimethoxypropyl)-β-D-glucopyranos-6-oxy]-methyl-γ-tocopherol ***45***. Compound **43** (920 mg, 1.11 mmol) in anhydrous THF (10 mL) was treated with NaH (60%, 650 mg, 16.0 mmol) for 30 min, and then allylbromide (2.0 ml, 23.0 mol) was added and the mixture kept at room temperature for 24 h. Workup as for compound **8** and purification by flash chromatography (pet. ether/ethyl acetate 5:1) gave **45**: 730 mg (76%) as a pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ=6.10 (m, 1H, CH-all-c); 5.92 (m, 2H, CH-all-c); 5.81 (m, 1H, CH-all-c); 5.44 (m, 1H, CH_2-all-d); 5.31–5.08 (m, 7H, CH_2-all-d); 4.62–4.68 (m, 3H, CH_2-5a, CH-c-Sp); 4.37–4.11 (m, 8H, CH_2-b-all, H-1b); 3.99–3.87 (m, 2H, CH_2-b-all, CH_2-a-Sp); 3.74 (m, 1H, H-6a); 3.64 (m, 1H, H-6b); 3.52 (m, 1H, CH_2-a'-Sp); 3.38–3.28 (m, 8H, H-3, H-5, 2×OMe); 3.23 (m, 1H, H-4); 3.15 (t, 1H, H-2); 2.81 (m, 2H, CH_2-4); 2.16, 2.08 (s, 6H, CH_3-7a and -8a); 1.88 (m, 2H, CH_2-b-Sp); 1.74 (m, 2H, CH_2-3); 1.59–0.99 (m, 24H, CH_3-2a, CH-4′, -8′, -12′, CH_2-⟨1′-11′⟩); 0.87–0.83 (m, 12H, CH_3-4a', -8a', -12a', -13′); $J_{1,2}$=8.1 Hz. ^{13}C NMR (100 MHz, $CDCl_3$) δ=148.73 (2C, C-6, C-8a); 134.84, 134.67, 134.30, 133.94 (4C, =CH C-all-c); 127.64, 125.90, 125.09, 118.34 (4C, C-4a, C-5, C-7, C-8); 116.47, 116.32, 116.21 (3C, =CH_2 C-all-d); 102.80, 101.65 (2C, C-1, C-c-Sp); 83.74, 81.16, 77.39, (3C, C-2, C-3, C-4); 74.99–73.14 (4C, C-2, C-5, C-6, C-all-b); 65.30, 64.90 (2C, C-a-Sp, C-5a); 52.70 (2C, CH_3, 2×OMe); 38.93, 37.03, 36.99, 36.86, 32.73 (8C, C-b-Sp, CH_2-3, C-1′, -3′, -5′, -7′, -9′, -11′); 32.36, 27.54 (3C, C-4′, -8′, -12′); 24.38, 24.03 (2C, C-6′, -10′); 23.56–22.2 (3C, CH_3, C-2a,-12a', -13′); 20.57 (1C, CH_2-4); 13.32, 19.24 (2C, CH_3, C-4a', -8a'); 18.99 (1C, C-2′); 12.34, 11.67 (2C, CH_3, C-7a, -8a). EI-MS: 871 (M^+).

4.2.36. 2,3-Di-O-allyl-L-ascorbic acid ***46***. L-Ascorbic acid (3.0 g, 17.0 mmol) and allylbromide (3.03 mL. 36 mmol) dissolved in anhydrous dimethylformamide (10 mL) were treated with sodium hydride (60%, 1.44 g 36.0 mmol) for 3 h at room temperature. Workup as for compound **8** was followed by chromatography (diethylether) to give **46**: 1.0 g (23%) as a pale yellow waxy hygroscopic solid; mp 45–47 °C (decomposition); $[\alpha]_D^{20}$ +31.8 (*c* 1.2, CH_2Cl_2).

^{1}H NMR ($CDCl_3$) δ=5.98 (m, 2H, H-c); 5.35 (m, 2H, H-d); 5.30 (m, 2H, H-d′); 4.95 (m, 2H, H-b); 4.71 (d, 1H, H-4); 4.59 (m, 2H, H-b′); 3.97 (~dt, 1H, H-5); 3.85 (dd, 1H, H-6a); 3.79 (dd, 1H, H-6b); 2.78 (s, 2H, 2×OH); $J_{4,5}$=2.6, $J_{5,6a}$=5.9, $J_{5,6b}$=4.6, $J_{6a,6b}$=11.5 Hz. ^{13}C NMR (100 MHz, $CDCl_3$) δ=169.11 (1C, C=O, C-1); 156.33 (1C, C-3); 132.36, 131.34 (2C, =CH, C-all-c); 120.81 (1C, C-2); 119.04–118.70 (2C, =CH_2, C-all-d); 75.28 (1C, C-4); 72.32–71.55 (2C, OCH_2, C-all-b); 69.51 (1C, C-5); 62.93 (1C, C-6). EI-MS: 256 (M^+). Anal. Calcd for $C_{12}H_{16}O_8$(256.3): C, 56.24; H, 6.29. Found: C, 55.57; H, 6.43.

4.2.37. 6-O-Allyl-5-[2-(5,6-O-metylidene-2,3-di-O-allyl-L-ascorbyl)-ethyl-2,3,4-tri-O-allyl-β-D-glucopyranos-6-oxy]-methyl-2,2′,7,8-tetramethyl-chroman-6-ol ***47***. Compounds **44** (200 mg, 0.3 mmol) and **46** (80 mg, 0.31 mmol) dissolved in a mixture of *n*-hexane (5 mL) and dichloromethane (5 mL) were treated with *p*-TsOH (1 mg) and heated at a water separator for 1.5 h. After cooling dichloromethane (30 mL) was added, neutralised with saturated $NaHCO_3$ solution, washed with NaCl solution, dried (Na_2SO_4), evaporated and purified by flash chromatography (pet. ether/ethyl acetate 5:1) to give **47**: 238 mg (93%) as a pale rose oil consisting of two diastereomers, which could be partly separated. *Upper diastereomer*: 110 mg (43%), *lower diastereomer*: 91 mg (36%), *mixed fraction*: 37 mg (14%).

Upper diastereomer: $[\alpha]_D^{20}$ +4.1 (*c* 0.3, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ=6.08 (m, 1H, CH-all-c); 5.94 (m, 4H, CH-all-c); 5.81 (m, 1H, CH-all-c); 5.48–5.06 (m, 10H, CH_2-d-all); 5.03 (m, 1H, CH-c-Sp); 4.91 (m, 2H, CH_2-d-all); 4.67–4.49 (m, 5H, CH_2-b-all, H-4-aa, CH_2-5a); 4.35–4.09 (m, 10H, H-1b, CH_2-b-all, H-6a-aa, H-5-aa); 3.94 (m, 3H, CH_2-a-Sp, CH_2-b-all, H-6b-aa); 3.72 (m, 1H, H-6a); 3.63 (m, 1H, H-6b); 3.56 (m, 1H, CH_2-a'-Sp); 3.33 (m, 2H, H-3, H-5); 3.22 (t, 1H, H-4); 3.14 (t, 1H, H-2); 2.82 (m, 2H, CH_2-4); 2.15, 2.08 (s, 6H, CH_3-7a and -8a); 1.93 (m, 2H, CH_2-b-Sp); 1.74 (m, 2H, CH_2-3); 1.29, 1.28 (s, 6H, CH_3, 2′, -2a'). ^{13}C NMR (100 MHz, $CDCl_3$) δ=168.15 (1C, C-1-aa); 155.29 (1C, C-3-aa); 148.78 (1C, C-6); 147.77 (1C, C-8a); 134.90, 134.77, 134.36, 133.92, 132.39, 131.36 (6C, =CH, C-c-all); 127.63, 125.86, 125.15 (3C, C-5, C-7, C-8); 120.89 (1C, C-2-aa); 118.86–116.10 (2C, C-4a and =CH_2 C-d-all); 103.37 (1C, C-c-Sp); 102.92 (1C, C-1β); 83.68 (1C, C-3); 81.04 (1C, C-2); 77.35 (1C, C-4); 74.99 (1C, CH_2 C-b-all); 74.43 (1C, C-4-aa); 74.37–73.05 (2C, CH_2 C-b-all and C-5-aa); 72.93 (1C, C-5); 72.60 (1C, C-2); 72.12, 71.96 (2C, CH_2, C-b-all); 68.89 (1C, C-6); 65.80 (1C, C-6-aa); 64.88 (1C, C-5a); 64.59 (1C, CH_2, C-a-Sp); 33.83 (1C, CH_2, C-b-Sp); 32.25 (1C, C-3); 26.66, 26.35 (2C, CH_3, C-2′, -2a'); 19.34 (1C, C-4); 12.34 (1C, CH_3, C-7a); 11.67 (1C, CH_3, C-8b).

Lower diastereomer: $[\alpha]_D^{20}$ +15.3 (*c* 2.5, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ=6.09 (m, 1H, CH-all-c); 5.93 (m, 4H, CH-all-c); 5.80 (m, 1H, CH-all-c); 5.47–5.06 (m, 10H, CH_2-d-all); 5.03 (t, 1H, CH-c-Sp); 4.92 (m, 2H, CH_2-d-all); 4.66–4.50 (m, 5H, H-4-aa, CH_2-b-all ⟨2H⟩, CH_2-5a); 4.34–4.18 (m, 10H, H-1b, H-5-aa, CH_2-b-all ⟨8H⟩); 4.12 (m, 1H, CH_2-b-all); 4.06 (dd, 1H, H-6a-aa); 3.94 (m, 3H, H-6b-aa, CH_2-a-Sp, CH_2-b-all); 3.72 (m, 1H, H-6a); 3.64 (m, 1H, H-6b); 3.57 (m, 1H, CH_2-a'-Sp); 3.33 (m, 2H, H-3, H-5); 3.23 (t, 1H, H-4); 3.13 (t, 1H, H-2); 2.83 (m, 2H, CH_2-4); 2.16, 2.08 (s, 6H, CH_3-7a and -8a); 1.97 (m, 1H, CH_2-b-Sp); 1.88 (m_c, 1H, CH_2-b-Sp); 1.75 (m, 2H, CH_2-3); 1.29, 1.28 (s, 6H, CH_3, 2′, -2a'); $J_{1,2}$=8.2, $J_{2,3}$=8.8, $J_{3,4}$=9.1, $J_{4,5}$=9.5, $J_{5,6b}$=5.1, $J_{6a,6b}$=10.7, $J_{5,6a\text{-}aa}$=4.7, $J_{6a,b\text{-}aa}$=8.5, $J_{b,c\text{-}Sp}$=5.4 Hz. ^{13}C NMR ($CDCl_3$) δ=168.22 (1C, C-1-aa); 155.10 (1C, C-3-aa); 148.78 (1C, C-6); 147.78 (1C, C-8a); 134.89–131.41 (6C, =CH, C-c-al1); 127.62, 125.82, 125.14 (3C, C-5, C-7, C-8); 121.16 (1C, C-2-aa); 118.88–116.11 (12C, =CH_2, C-d-all); 118.20 (1C, C-4a); 102.83 (2H, C-c-Sp and C-1b); 83.69 (1H, C-3); 81.15 (1C, C-2); 77.33 (1C, C-4); 74.99 (1C, CH_2, C-b-all); 74.46 (1C, C-4-aa); 74.37–71.96 (12C, CH_2, C-b-all, C-5-aa and CH, C-5); 72.60 (1C, C-2); 68.78 (1C, C-6); 65.42 (1C, C-6-aa); 64.94 (1C, C-5a); 64.86 (1C, C-a-Sp); 33.65 (1C, C-b-Sp); 32.25 (1C, C-3);

26.68, 26.34 (2C, CH_3, C-2, -2a'); 19.34 (1C, C-4); 12.35 (1C, CH_3, C-7a); 11.67 (1C, CH_3, C-8b).

4.2.38. 6-O-Allyl-5-[2-(5,6-O-methylidene-2,3-di-O-allyl-L-ascorbyl)-ethyl-2,3,4-tri-O-allyl-β-D-glucopyranos-6-oxy]-methyl-γ-tocopherol ***48****.* Compounds **45** (208 mg, 0.24 mmol) and **46** (67 mg, 0.26 mmol) dissolved in a mixture of *n*-hexane (5 mL) and dichloromethane (5 mL) were treated with *p*-TsOH (1 mg) and heated in a water separator for 1 h. Workup as for compound **47** was followed by flash chromatographic purification (pet. ether/ethyl acetate 5:1) to give **48**: 190 mg (75%) as a colourless oil consisting of two diastereomers, which could be partly separated. *Upper set of diastereomers*: 57 mg (22.5%), *lower set of diastereomers*: 55 mg (22%), *mixed fraction*: 78 mg (30.5%).

^{1}H NMR (400 MHz, $CDCl_3$) δ=6.09 (m, 1H, CH-all-c); 5.93 (m, 4H, CH-all-c); 5.79 (m, 1H, CH-all-c); 5.47–5.06 (m, 12H, CH_2-all-d); 5.03 (t, 1H, CH-c-Sp), 4.92 (m, 2H, CH_2-D-all); 4.66–4.47 (m, 5H, H-4-aa, CH_2-b-all, CH_2-5a); 4.35–4.17 (m, 7H, H-1β, H-5-aa, CH_2-b-all); 4.17 (m, 1H, CH_2-b-all); 4.05 (dd, 1H, H-6a-aa); 3.94 (m, 3H, H-6b-aa, CH_2-a-Sp, CH_2-b-all); 3.76 (m, 1H, H-6a); 3.65 (m, 1H, H-6b); 3.66 (m, 1H, CH_2-a'-Sp); 3.33 (m, 2H, H-3, H-5); 3.24 (t, 1H, H-4); 3.13 (t, 1H, H-2); 2.80 (m, 2H, CH_2-4); 2.16, 2.08 (s, 6H, CH_3-7a and -8a); 1.98 (m, 1H, CH_2-b-Sp); 1.88 (m, 1H, CH_2-b-Sp); 1.75 (m, 2H, CH_2-3); 1.63–1.01 (m, 24H, CH_3-2a, CH-4′, -8′, -12′, CH_2-⟨1′-11′⟩); 0.89–0.81 (m, 12H, CH_3-4a', -8a', -12a', -13′). ^{13}C NMR (100 MHz, $CDCl_3$) δ=168.09 (1C, C-1-aa); 155.10 (1C, C-3-aa); 148.86 (1C, C-6); 147.54 (1C, C-8a); 134.89–131.41 (6C, =CH, C-c-al1); 127.61, 125.85, 125.01 (3C, C-5, C-7, C-8); 121.16 (1C, C-2-aa); 118.88–116.09 (6C, =CH_2, C-d-all); 118.20 (1C, C-4a); 102.84 (2C, CH, C-c-Sp and C-1β); 83.69 (1C, C-3); 81.15 (1C, C-2); 77.34 (1C, C-4); 74.99 (1C, C-b-all); 74.62 (1C, C-4-aa); 74.46–71.93 (8C, C-b-all, C-5-aa and C-5, C-2); 68.08 (1C, C-6); 65.41 (1C, C-6-aa); 64.96 (2C, C-5a and C-a-Sp); 38.94 (2C, CH_2 C-1′, -11′); 38.96–36.86 (4C, CH_2, C-3′, -5′, -7′, -9′); 33.64 (1C, CH_2, C-b-Sp); 32.35 (2C, CH, C-4′, -8′); 29.25 (1C, C-3); 27.54 (1C, CH, C-12′); 24.37, 24.02 (2C, CH_2, C-6′, -10′); 23.55, 23.35 (2C, CH_3, C-12a', -13′); 22.28 (1C, C-2a); 19.31, 19.24 (2C, CH_3, C-4a', -8a'); 19.01 (2C, CH_2, C-2′ and C-4); 12.33 (1C, CH_3, C-7a); 11.66 (1C, CH_3, C-8b). FAB-MS: 1062.8 $(M-H)^+$.

Acknowledgements

Support of this work by the Fonds der Chemischen Industrie and Beiersdorf AG is gratefully acknowledged.

Supplementary data

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.tet.2010.12.066.

References and notes

1. part C *Methods Enzymol.*; Packer, L., Ed.; Academic: San Diego, 1994; Vol. 233.
2. part A *Methods Enzymol.*; Packer, L., Ed.; Academic: San Diego, 1999; Vol. 299.
3. part B *Methods Enzymol.*; Packer, L., Ed.; Academic: San Diego, 1999; Vol. 300.
4. Herschberger, L. A.; Tappel, A. L. *Lipids* **1982**, *17*, 686–691.
5. Iwatsuki, M.; Komuro, E.; Niki, E. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 620–624.
6. Gordon, M. H. *Nat. Prod. Rep.* **1996**, *13*, 265–273.
7. Liebler, D. C.; Kaysen, K. L.; Kennedy, T. A. *Biochemistry* **1989**, *28*, 9772–9777.
8. Buettner, G. R. *Arch. Biochem. Biophys.* **1993**, *300*, 535–543.
9. Wright, J. S.; Johnson, E. R.; DiLabio, G. A. *J. Am. Chem. Soc.* **2001**, *123*, 1173–1183.
10. Amorati, R.; Ferroni, F.; Pedulli, G. F.; Valgimigli, L. *J. Org. Chem.* **2003**, *68*, 9654–9658.
11. Nakamura, T.; Kijima, S. *Ger. Offen.* **1974**, 2331058; *Chem. Abstr.* **1974**, *80*, P82664h.
12. Schneider, G.; Thiem, J.; Lahmann, M. (Beiersdorf AG), EP 0726273A1, 1996; *Chem. Abstr.* **1996**, *125*, 196234w.
13. Arakawa, S.; Ogawa, S.; Arakawa, E.; Sato, H. Jpn. Kokai Tokkyo Koho, JP 62,187,470, 1986; *Chem. Abstr.* **1988**, *109*, P73692f.
14. Ogata, K. (Senju Pharmaceutical), Eur. Pat. Appl. EP 226753, 1987; *Chem. Abstr.* **1987**, *107*, P218015h.
15. Praly, J.-P.; He, L.; Quin, B. B.; Tanoh, M.; Chen, G.-R. *Tetrahedron Lett.* **2005**, *46*, 7081–7085.
16. Packer, J. E.; Slater, T. F.; Willson, R. L. *Nature* **1979**, *278*, 737–738.
17. Doba, T.; Burton, G. W.; Ingold, K. U. *Biochim. Biophys. Acta* **1985**, *835*, 298–303.
18. Scarpa, M.; Rigo, A.; Maiorino, M.; Ursini, F.; Gregolin, G. *Biochim. Biophys. Acta* **1984**, *801*, 215–319.
19. Ogata, K.; Yamamoto, K.; Tsuruoka, H. *Iyakuhin Kenkyu* **1990**, *21*, 222–228; *Chem. Abstr.* **1990**, *113*, 78123g.
20. Kuribayashi, Y.; Yoshida, K.; Sakaue, T.; Okumura, A. *Drug Res.* **1992**, *42*, 1072–1074.
21. Morizaki, K.; Fukuota, T.; Sasaki, M.; Jpn. Kokai Tokkyo Koho, JP 05,331,166; *Chem. Abstr.* **1994**, *121*, P109569k.
22. Kim, Y.D.; Kim, C.K.; Lee, C.N.; Ha, J. (Pacific Chemical) DE 4232686 A1, 1993; *Chem. Abstr.* **1994**, *120*, P37812p.
23. Kim, Y. D.; Kim, C. K.; Lee, C. N.; Ha, J. *Cosmet. Toiletries* **1993**, *108*, 63–78.
24. Huassain, H. H.; Babic, G.; Durst, T.; Wright, J. S.; Flueraru, M.; Chichisau, A.; Chepelev, L. L. *J. Org. Chem.* **2003**, *68*, 7023–7032.
25. Adelwöhrer, C.; Rosenau, T.; Kosma, P. *Tetrahedron* **2003**, *59*, 8177–8182.
26. Tai, A.; Goto, S.; Ishiguro, Y.; Suzuki, K.; Nitoda, T.; Yamamoto, I. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 623–627.
27. Lahmann, M.; Thiem, J. *Carbohydr. Res.* **1997**, *299*, 23–31.
28. Uhrig, R. K.; Picard, M. A.; Beyreuther, K.; Wiessler, M. *Carbohydr. Res.* **2000**, *325*, 72–80.
29. Giorgi, G.; Ponticelli, F.; Salvini, L.; Trendafilova, A.; Valoti, M.; Pessina, F. *Eur. J. Org. Chem.* **2003**, 106–115.
30. Claisen, L. *Ber. Dtsch. Chem. Ges.* **1921**, *54*, 200–203.
31. Smith, L. I.; Ungnade, H. E.; Hoehn, H. H.; Wawzonek, S. *J. Org. Chem.* **1939**, *4*, 311–317.
32. Skinner, W. A.; Parkhurst, R. M.; Scholler, J.; Schwarz, K. *J. Med. Chem.* **1969**, *12*, 64–66.
33. Dallacker, F.; Eisbach, R.; Holschbach, M. *Chem. Ztg.* **1991**, *115*, 883–887.
34. Dallacker, F.; Reperich, K. *Chem. Ztg.* **1991**, *115*, 306–309.
35. Rosenau, T.; Habicher, W. D. *Tetrahedron* **1995**, *51*, 7919–7926.
36. Dallacker, F.; Sanders, J. *Chem. Ztg.* **1985**, *109*, 197–202.
37. Adelwöhrer, C.; Rosenau, T.; Kloser, E.; Mereiter, K.; Netscher, T. *Eur. J. Org. Chem.* **2006**, 2081–2086.
38. Koufaki, M.; Detsi, A.; Theodorou, E.; Kiziridi, C.; Calogeropoulou, T.; Vassilopoulos, A.; Kourounakis, A. P.; Rekka, E.; Kourounakis, P. N.; Gaitanaki, C.; Papazafiri, P. *Bioorg. Med. Chem.* **2004**, *12*, 4835–4841.
39. Tipson, R. S. *Methods Carbohydr. Elems.* **1963**, *2*, 246–251.
40. Hombrecher, H. K.; Schell, C.; Thiem, J. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1199–1202.
41. Hofstraat, R. G.; Lange, J.; Scheeren, H. W.; Nivard, R. J. F. *J. Chem. Soc., Perkin Trans. 1* **1988**, 2315–2322.
42. Fernandez, E.; Castillon, S. *Tetrahedron Lett.* **1994**, *35*, 2361–2364.
43. Hosokawa, T.; Aoki, S.; Murahashi, S. *Synthesis* **1992**, 558–561.
44. Lemieux, R. U. *Methods Carbohydr. Chem.* **1963**, *2*, 221–222.