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C-Glycopyranosyl-1,4-benzoquinones and -hydroquinones opening access to *C*-glycosylated analogs of vitamin E

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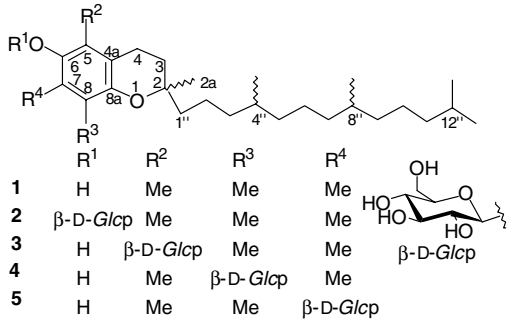
Abstract—2-(Per-*O*-acetyl-β-D-glycopyranosyl)-1,4-dimethoxybenzenes led to *C*-glycosyl-hydroquinones suitable for preparing *C*-glycosylated analogs of vitamin E, having the sugar moiety free or acetylated.

The function of antioxidants is to intercept and react with free radicals at a rate faster than the substrate, and since free radicals are able to attack various biomolecules, it is believed that they are implicated in a number of degenerative processes, including aging and age-related diseases.[1] Normal diet provides a large variety of natural molecules possessing antioxidant properties, flavonoids, vitamin E, vitamin C being the more important.[2] The most effective lipid-soluble chain-breaking antioxidant in human blood plasma is α-tocopherol (**1**), the most active component of vitamin E.[3] In vivo, the α-tocopheryl radical is quenched by reaction with vitamin C, so that detrimental chain reactions are broken while α-tocopherol is regenerated, mainly by H-atom transfer. This cooperative process benefits from favorable values of bond dissociation enthalpy (BDE) in α-tocopherol (~77 kcal/mol) and, depending on the pH, ascorbic acid or ascorbate (68.5 kcal/mol).[3,4] Obviously, thermodynamical data are of extreme importance, but other factors must be considered for understanding what makes an effective antioxidant. They include the bulkiness of the groups near the OH group, the hydrogen bonding properties of the solvent, or, in a biological context, solubility, bioavailability, and transport to specific tissues.[5] Antioxidants, which are added to many foodstuffs, pharmaceuticals, and cosmetics to prevent them from becoming rancid, are the object of intensive research efforts.[6,7] The general opinion is that naturally occurring antioxidants rather than novel synthetic molecules should be used as additives. Extending their applications appeared feasible by resorting to sugars, as shown with novel sugar-containing lipophilic ascorbic acid derivatives with C_8–C_{16} acyl chains.[8] Conversely, α-tocopheryl β-D-glucopyranoside (**2**)[9,10] and analogs[11] are more hydrophilic than vitamin E. The biological applicability of such compounds is, however, dependent on deglycosylation in vivo in particular because the free 6-OH group is essential for the redox properties of tocopherols. Therefore, *C*-glycosylated analogs of vitamin E, as **3**–**5** (Scheme 1) appeared to be promising antioxidants with tunable properties, depending on the sugar moiety present.[12]



	R^1	R^2	R^3	R^4
1	H	Me	Me	Me
2	β-D-*Glcp*	Me	Me	Me
3	H	β-D-*Glcp*	Me	Me
4	H	Me	β-D-*Glcp*	Me
5	H	Me	Me	β-D-*Glcp*

Scheme 1. α-Tocopherol and *O*-/*C*-glucosylated derivatives.

Keywords: *C*-Glucopyranosyl hydroquinones; *C*-Glucopyranosyl benzoquinones; *C*-Glucopyranosyl chromanes; *C*-Glucosylated analogs of vitamin E.

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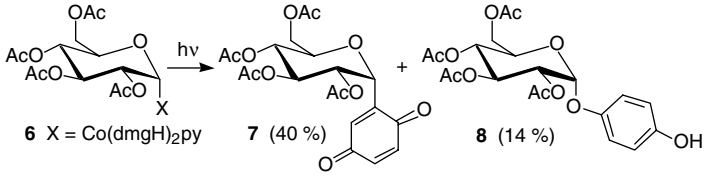
Access to *C*-glycosylated aryls is well documented, involving generally either nucleophilic attack of suitable sugar derivatives (as base-resistant glyconolactones treated by organometallic species, followed by a reductive step), or electrophilic aromatic substitution, a well suited reaction for electron-rich substrates.[13] Our project required *C*-glycosylated hydroquinones that appeared to be poorly known compounds. Only Kalvoda described a multi-step synthesis based on electrophilic substitution of 1,4-dimethoxybenzene by glycofuranosyl oxocarbeniums to afford glycofuranosyl-1,4-dimethoxybenzenes, that can be oxidized to the corresponding benzoquinones, in turn reduced to the hydroquinones.[14]

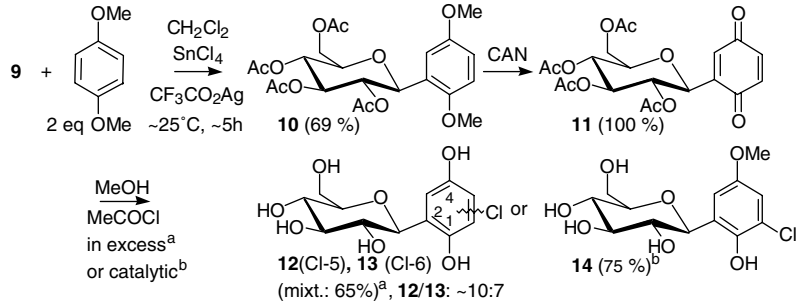
At first, we tested the addition of the tetra-*O*-acetyl-D-glucopyranos-1-yl radical to benzoquinone, a good radical acceptor (Scheme 2). Thus, irradiating a solution of peracetylated α-D-glucopyranosyl cobaloxime **6**[15] in the presence of benzoquinone (20 equiv) led to a dark mixture from which the addition product **7** (found α-configurated, as expected for radical-mediated pathways) could be isolated in 40% yield as well as tetra-acetyl α-arbutin **8** (14%). Meanwhile, the reaction of acetylated β-D-galactopyranosyl tolyl telluride with benzoquinone to afford the D-*galacto* analogs of **7** (39%) and **8** (45%) was reported,[16] showing conclusively the specificity and limits of these radical additions.

As another minimalist strategy, rearrangement of *O*-glycosides to *C*-glycosyl compounds, tried with 4-hydroxyphenyl tetra-*O*-acetyl-β-D-galactopyranoside,[17] was, in our hands, not encouraging. So, we turned our attention to the route developed by Kalvoda as an access, via recently reported glycopyranosyl-1,4-dimethoxybenzenes,[18,19] to the *C*-glycosylated hydroquinones, suitable for preparing the desired *C*-glycosylated antioxidants, and to the corresponding benzoquinones, both being not well known but valuable compounds in terms of synthesis and potential bioactivities. *p*-Dimethoxybenzene was reacted with 1,2,3,4,6-penta-*O*-acetyl-β-D-glucopyranose **9** in the presence of $SnCl_4/F_3CCO_2Ag$ to afford the *C*-glucosyl derivative **10** (Scheme 3) in good yield, provided the reaction was performed at ~25–30 °C, rather than 0 °C, as recommended for a more reactive precursor.[18,19] Mild oxidation of **10** with ceric ammonium nitrate (CAN) in aqueous acetonitrile led to glycosyl-benzoquinone **11**, isolated in high yield as a moderately stable brown solid.[20] Considering the diverse properties reported for natural and synthetic benzoquinone derivatives, we wanted to test **11** after conversion into a water-soluble compound. Attempts to achieve deacetylation under basic conditions (MeO-Na in MeOH or $NEt_3/MeOH/H_2O$) were, in our hands, not encouraging. Acid-catalyzed deacetylation of **11** (MeOH containing acetyl chloride, 25/100 equiv) led by unselective addition of hydrochloric acid, to **12** and **13** (ratio: ~10:7) in 65% yield. Unexpectedly, when deacetylation was carried out with catalytic acetyl chloride in MeOH, **11** was converted within 1 week to a single product **14** (75% yield) having a 1,2,3,5-tetra-substituted phenyl ring with one methoxy group.[21]

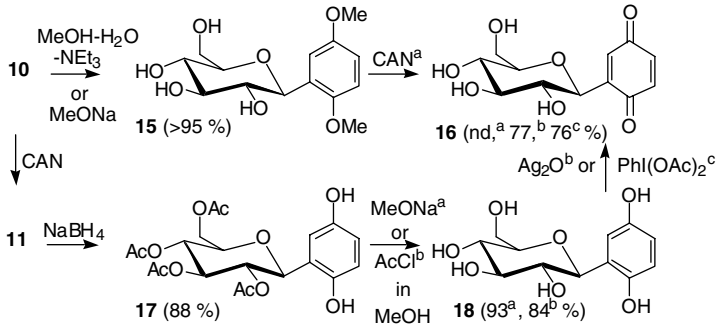
Hence, due to the unexpected outcome of the deacetylation of **11**, appropriate combinations of oxidation, reduction, and deacetylation were developed (Scheme 4), applying deacetylation to *C*-glycosyl-hydroquinone derivatives **10** and **17**, which are not prone to side reactions. Two parallel routes were feasible, to afford readily deprotected *C*-glycosyl-1,4-dimethoxybenzene **15**, *C*-glycosyl-benzoquinone **16**, and -hydroquinone **18**. Although the CAN oxidation of **15** afforded **16** only, its purification by chromatography was troublesome, because of contamination by colored materials (probably derived from CAN). While longer by two steps, the other route via **11** was straightforward, giving pure **16** in good yield.



Scheme 2. Access towards *C*-glucosyl-benzoquinone by radical coupling.



Scheme 3. Access to peracetylated β-D-glucopyranosyl-1,4-dimethoxybenzene, its oxidation, and deacetylation of benzoquinone **11**.



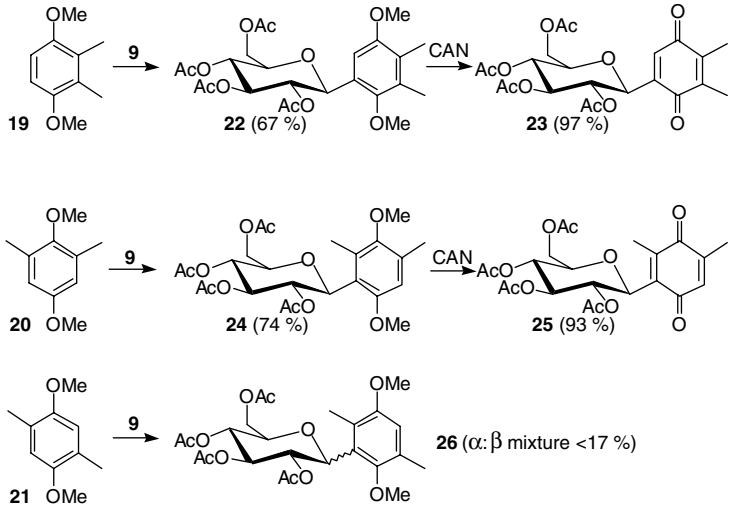
Scheme 4. Synthetic routes to acetylated or deprotected β-D-glucopyranosyl-hydroquinones, and derivatives (dimethyl ether and benzoquinones).

Treatment of **17** with all racemic phytol in the presence of $ZnCl_2$ afforded a mixture of *C*-glucosylated unmethylated analogs of vitamin E, as hardly separable regio- and stereoisomers. Therefore, syntheses were adapted to isomeric *o*-, *m*-, and *p*-dimethyl-1,4-dimethoxybenzenes **19**–**21**, the first one being obtained upon methylation of commercially available *o*-dimethylhydroquinone[22] while the others were prepared from 2,6-dimethylanisole and 2,5-dimethylanisole, respectively, by high-yielding three-step sequences (oxidation with Fremy's salt, reduction with $Na_2S_2O_4$, methylation[22] in ~94%, 90%, and 88% yield, respectively). Electrophilic coupling of **9** with **19** and **20** (2 equiv) proceeded well (Scheme 5), affording the desired isomeric *C*-glucosyl compounds **22** and **24** in 67% and 74% yield, respectively, while substitution in **21** (2 equiv) was less satisfactory, affording **26**, as an anomeric mixture, in ~10% yield increased to 17% (~3/7 α:β ratio) by using 4 equiv of **21**. These differences can be rationalized, considering that substitution in **21** may suffer from steric hindrance (compared to **19**) and from less favorable electronic effects exerted by two *o*-substituents, as compared to **20**, for which synergistic activation by three groups may explain a more efficient coupling reaction. Therefore, only **22** and **24** were subjected to CAN-mediated oxidation to furnish **23** and **25** in 97% and 93% yield, respectively.

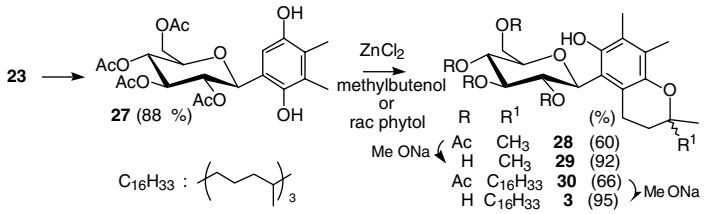
Having in hand **23** and **25**, the rest of the sequence was accomplished first by high-yielding reduction to the corresponding *C*-glucosyl-dimethylhydroquinones, as **27** which, in the presence of $ZnCl_2$, reacted smoothly with 3-methyl-2-buten-1-ol or racemic phytol.[23] This afforded the corresponding 5-(D-glucosyl)-7,8-dimethylchromane **28** (60% yield) as a single product, while the glycosylated γ-tocopherol **30** (66% yield) was a diastereoisomeric mixture (Scheme 6).

Applied to **25**, this sequence (Scheme 7) led in similarly good yields to isomeric products, bearing a β-D-glucopyranosyl moiety at the 8 position of the 5,7-dimethylchromane ring. Based on the known arrangements for the methyl groups in tocopherols (indicated by α, β, γ, and δ),[24] we propose the symbol ε to account for their location at positions 5 and 7 in products **4** and **34**.

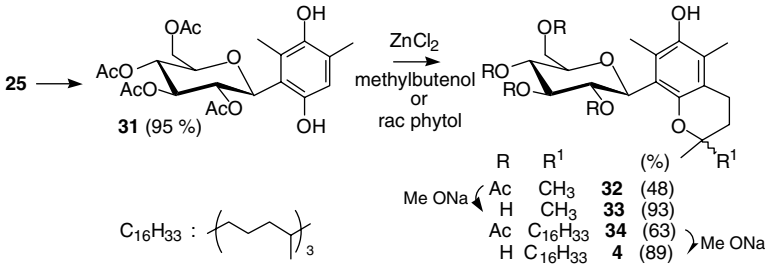
Compounds **30** and **34** were mixtures of eight diastereoisomers, with *R* or *S* configurations at 2, 4″, 8″ which we could not separate by chromatography, although **30** gave two very close spots on TLC plates. Their 200/50 MHz NMR spectra (^1H and ^{13}C) showed most of the expected resonances, some being superimposed. The deacetylated product **3** was partially resolved by



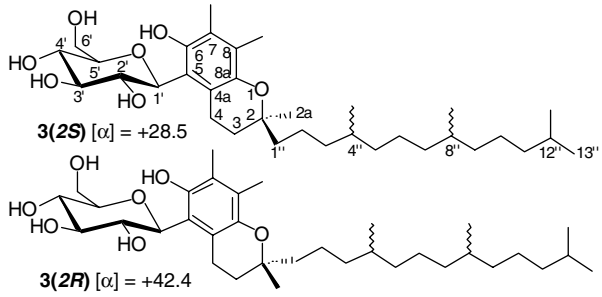
Scheme 5. Access to *C*-glucosyl derivatives of *o*-, *m*-, and *p*-dimethyl-1,4-dimethoxylbenzenes and to *C*-glycosyl-dimethyl-1,4-benzoquinones.



Scheme 6. Access to 5-(β-D-glucopyranosyl)-7,8-dimethylchromanes and glucosylated γ-tocopherols.



Scheme 7. Access to 8-(β-D-glucopyranosyl)-5,7-dimethylchromanes, and glucosylated ε-tocopherols.



Scheme 8. Diastereoisomers **3** (2*R*) and (2*S*) and numbering.

chromatography, as diastereoisomeric mixtures **3** (2*R*) and **3** (2*S*) (Scheme 8). Configurations at C-2 were deduced by comparing the measured optical rotations ([α] +42.4/+28.5, isomers 2*R* and 2*S*, respectively; difference: ~14) with those reported for various α-tocopherol stereoisomers, showing that 2*R*-configurated ones are dextrorotatory, whereas the 2*S* analogs are less dextrorotatory (measurements in EtOH) or generally levorotatory.[25] The specific rotations reported for 2*R*- and 2*S*-α-tocopheryl *p*-phenylazobenzoates for both 4′*R*,8′*R* and 4′*RS*,8′*RS* configurated isomers differ by ~14,[25] as found with **3** (2*R*) and **3** (2*S*). Their 500/125 MHz NMR spectra recorded in acetone-d_6 were very similar, except for the resonances of protons at position 4 which appeared differentiated (δ H4a, H4b: 3.00, 2.65 ppm for **3** (2*S*); 2.96, 2.68 ppm for **3** (2*R*)). Carbons located on the alkyl chain near the asymmetric carbons at 4″ and 8″ (Scheme 8) were differentiated depending on the 4″/8″ configurations, giving smaller signals in certain zones of the spectra that appeared more complex than when recorded at 200/50 MHz. For both compounds, H4a and H4b appeared to be at a close distance of the anomeric proton, as indicated by 2D NMR correlations (NOESY and CROESY). We hypothesized that in **3**, H-bonds existed between the phenolic hydroxy group and the sugar ring oxygen, or the hydroxy groups, with rigidification of the structure, whose chromatographic properties might depend on the chain orientation. In our hands, separation turned out to be not feasible with **4**, possibly because the 2*R* and 2*S* diastereoisomers were structurally less differentiated due to weaker intramolecular bonding.

Deacetylated compounds **3**, **4** and **29**, **33** were soluble (~0.5 mg/0.1 mL) in MeOH, DMSO, pyridine, acetone while they were poorly soluble (~0.5 mg/0.5 mL) (**3** and **4**) or soluble (**29** and **33**) in H_2O.[9] In $CHCl_3$, solubility was modest (~0.5 mg/0.2 mL) (**3** and **4**) or poor (**29** and **33**). Such extended solubility in varied solvents, as compared to water-insoluble tocopherols, appears favorable for exerting biological activities in different environments that might be more accessible. This will be ascertained by a comparative evaluation of the antioxidant properties of the prepared compounds. They were investigated as ligands of glycogen phosphorylase (GP),[26] concluding that **16** and **18** are weak inhibitors (IC_{50} 3.8, 2.6 mM, respectively) that bind at the catalytic site of GP*b* (unphosphorylated isoform) as determined enzymatically and crystallographically.[27] We were also happy to learn from tests carried out at National Center for Drug Screening (Shanghai, PR China) that, while no inhibition was found for benzoquinone itself, compounds **11** and **16** (IC_{50} 4.8, 25.6 μM, respectively) inhibited significantly protein tyrosine phosphatase 1B (PTP 1B), as found for some related naturally occurring molecules (quercetin, bergenin, flavonoids, and anthraquinone or chalcone derivatives).[28,29] PTP 1B is receiving considerable attention, because of its key role in insulin signaling, with the idea that its selective inhibition could remediate insulin resistance in type 2 diabetes.[30,31] It is worth to note that **11** and **16** are simple, as compared to other sugar-derived inhibitors of PTP

1B.[32,33] Complete synthetic results, including extension of the syntheses to D-*galacto* configurated analogs, and comparative biological evaluation will be reported in due course.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.07.125.

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