

In the Search of Glycogen Phosphorylase Inhibitors: Synthesis of C-D-Glycopyranosylbenzo(hydro)quinones – Inhibition of and Binding to Glycogen Phosphorylase in the Crystal^[‡]

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Penta-O-acetyl- β -D-glycopyranoses and 1,4-dimethoxybenzene led selectively by electrophilic substitution to C- β -D-glycopyranosyl-1,4-dimethoxybenzenes which were converted by simple and efficient reactions (oxidation, reduction and deacetylation) to the corresponding C-glycosylhydro- and C-glycosylbenzoquinones, with either an acetylated or deprotected sugar moiety. C- β -D-Glucosylbenzoquinone **19** and C- β -D-Glucosylhydroquinone **23** were found to be competitive inhibitors of rabbit muscle glycogen phosphorylase b (GPb), with respect to the substrate α -D-glucose-1-phosphate, with K_i values of 1.3 and 0.9 mM, respectively,

whereas C- β -D-glucosylhydroquinone **17** was not effective up to a concentration of 8 mM. In order to elucidate the structural basis of inhibition, we determined the crystal structures of **19** and **23** in complex with GPb at a 2.03–2.05 Å resolution. The complex structures reveal that the inhibitors can be accommodated at the catalytic site at approximately the same position as α -D-glucose and stabilise the transition state conformation of the 280s loop by making several favourable contacts to Asp283 and Asn284 of this loop.

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Introduction

Besides common sugars, Nature provides a variety of sugar analogues which can be regarded as molecular tools for diverse applications in glycoscience. These findings have spurred intensive researches in the field of glycomimics.^[1] Among them, C-glycosyl derivatives^[2] have attracted special attention due to the resistance of the glycosidic C–C bond towards acid- or enzyme-catalyzed hydrolysis. Being more

stable than O-glycosides, C-linked analogues^[3] can inhibit sugar-processing enzymes such as glycosidases, glycosyl transferases and phosphorylases.^[3–5] Their synthesis is well developed and uses free radical chemistry,^[6] nucleophilic C-glycosyl donors^[7,8] and other methods.^[9–11] C-Glycosylated flavonoids^[12] and C-glycosylarenes^[13,14] have also attracted much attention.

In studies towards antithrombotic sugar derivatives,^[15] we prepared C-glycosyl derivatives of phloroglucinol, resorcinol and phenol. Analogues derived from hydroquinone appeared, in contrast, quite rare,^[16–19] although hydroquinone O-glycosides are known,^[20] or even commercially available as naturally occurring arbutin (4-hydrobenzene β -D-glucopyranoside). Because benzo(hydro)quinone moieties offer many synthetic opportunities, and because they might favour diverse bioactivities, as shown by the properties of many related molecules,^[21] we developed routes to acetylated C-glycosylhydro-, and C-glycosylbenzoquinones, as well as to C-glycosyl analogues of vitamin E.^[22] Upon deacetylation, such compounds would afford eventually varied water-soluble materials to be tested in particular as inhibitors and ligands of glycogen phosphorylase (GP).^[23]

Recent interest in GP stems from the increasing prevalence of metabolic disorders such as diabetes and obesity and from the need for a better understanding of their etiology, as well as more adequate treatments.^[24] GP has appeared as a possible therapeutic target because: (1) high

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blood glucose concentration in type 2 diabetes is in part due to abnormal hepatic glucose production; (2) inhibition of hepatic GP, which catalyses the first step in glycogen breakdown (glycogenolysis), would reduce hepatic glucose production;^[25] (3) the efficacy of such inhibitors on control of blood glucose and hepatic glycogen balance has been confirmed.^[26] Among the inhibitors of the enzyme,^[27] various glucose-derived motifs were found to bind at the catalytic site of GP, and structural information has provided a better understanding of the mechanism of inhibition of GP.

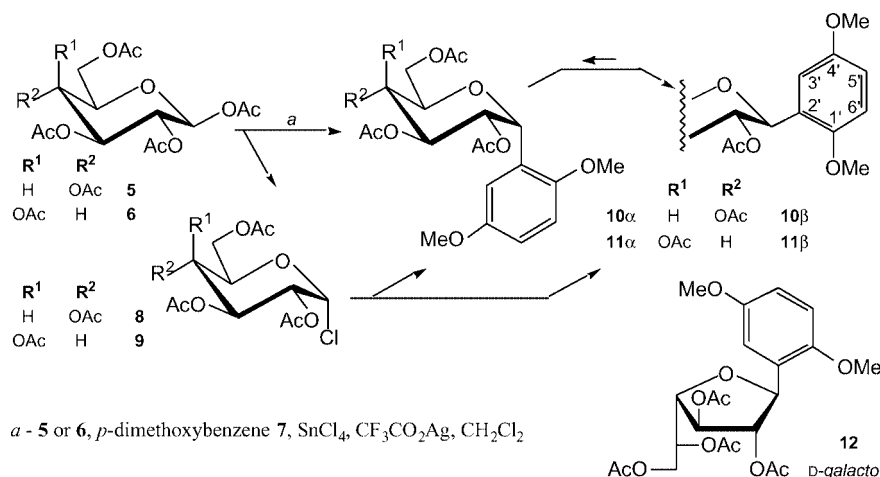
We describe in full detail herein, routes to acetylated or deprotected C-glycosyl derivatives of hydroquinone, 1,4-benzoquinone and dimethylhydroquinone, as well as enzymatic and crystallographic studies carried out with D-*gluco* configured ones when bound to rabbit muscle GPb (unphosphorylated isoform).

Results and Discussion

Among the possible accessible pathways to C-glycosyl compounds, three simple routes were considered for the desired C-glycosylbenzo(hydro)quinones: (1) rearrangement of O-glycosides to the corresponding C-glycosyl compounds;^[13] (2) addition of glycosyl radicals to 1,4-benzoquinone, whereby α -configured products can be expected;^[28] (3) coupling of glycopyranosyl units to electron-rich aryls^[18,19] by electrophilic substitution. Attempted rearrangement of 4-hydroxyphenyl tetra-*O*-acetyl- β -D-galactopyranoside **1**^[20d] failed to produce C-glycosyl compounds. Since, to the best of our knowledge, neither the rearrangement of **1** nor that of analogous O-glycosides has been reported, this route was abandoned. Attempts to react tetra-*O*-acetyl- α -D-glucopyranosyl bromide with tri-*n*-butyltin hydride in view of producing D-glycosyl radicals^[20c] that could add to 1,4-benzoquinone^[29,30] failed and afforded mainly hydroquinone as the product. Therefore, precursors able to produce D-glycosyl radicals by monomolecular homolytic pathways appeared more suitable. Thus, illuminating a solution of peracetylated α -D-glucopyranosyl cobaloxime **2**^[31] in the

presence of 1,4-benzoquinone (20 equiv.) provided α -configured addition product **3** in 40% yield as well as tetraacetyl α -arbutin **4** (14%). Meanwhile, the reaction of acetylated β -D-galactopyranosyl tolyl telluride with 1,4-benzoquinone was reported to afford D-*galacto* analogues of **3** (39%) and **4** (45%).^[20c] Hence, product distribution pointed to a moderate selectivity for both reactions, nevertheless accomplished with high α -stereoselectivity.

Therefore, electrophilic coupling appeared more promising, considering also the early work carried out by Kalvoda in the D-ribofuranosyl series,^[16] and its recent extension to the pyranosyl series.^[18,19] At the outset of our work, we chose penta-*O*-acetyl- β -D-galactopyranose **6** because its coupling to 1,4-dimethoxybenzene (**7**) was found more efficient for producing β -D-glycosyl-1,4-dimethoxybenzenes (D-*galacto*: 82%, D-*gluco*: 52%).^[19] However, experiments carried out at 0 °C according to the reported procedures^[18,19] afforded mixtures difficult to resolve by chromatography. The compounds obtained were identified as α -D-galactopyranosyl chloride **9**, α -D-galactopyranosyl **11a** and β -D-galactopyranosyl **11b**. While doubly substituted compounds^[15b,15c] with an opened sugar residue can result from such reactions,^[11] an experiment allowed to proceed over an extended time afforded unexpectedly low amounts of β -D-galactofuranosyl **12**, probably through pathways controlled by complexation between Sn^{IV} species and oxygen-containing intermediates. Although electrophilic coupling of 1,4-dimethoxybenzene (**7**) with such a reactive glycosyl donor as L-fucose tetraacetate might proceed well at 0 °C as reported,^[18,19] the α -chloride and α -configured C-glycosyl compound isolated were kinetic products formed at the early stage of the reaction (Scheme 1). Therefore, penta-*O*-acetyl- β -D-glycopyranoses **5** and **6** required somehow stronger conditions to shift equilibria towards the thermodynamically more stable β -configured C-glycosyl compounds. By maintaining the reaction temperature at 25–30 °C for 4–5 h, and with the use of anhydrous alcohol-free dichloromethane as the solvent, the desired β -D-*gluco*- and -D-*galacto*-configured compounds were obtained in



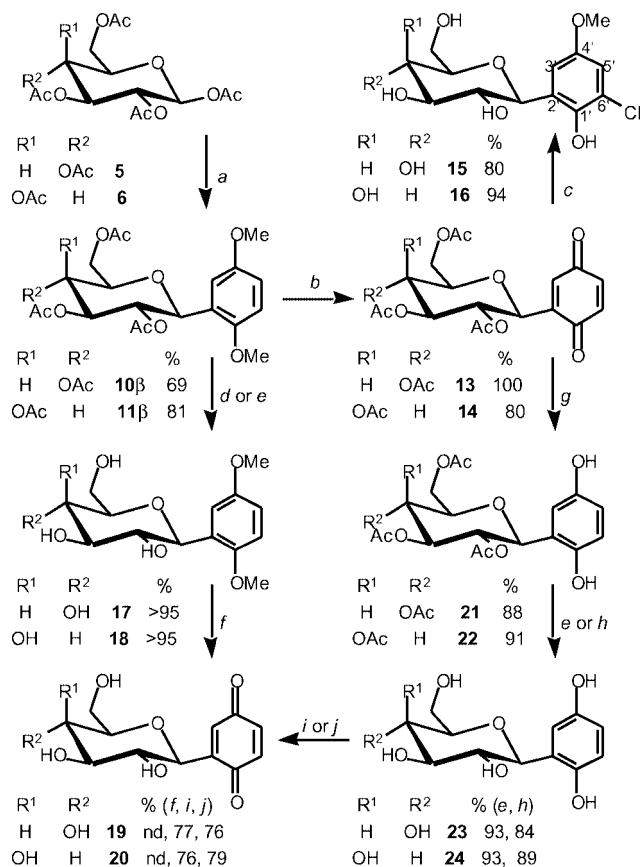
Scheme 1. Products isolated upon electrophilic substitution of dimethylhydroquinone by sugar peracetates, and probable reaction pathways.

good and reproducible yields on the gram scale (caution: the amount of SnCl_4 recommended in a published procedure^[19] appears to be erroneous).

The availability of C-glycosyl compounds in sufficient quantities allowed further developments (Scheme 2). Oxidation of **10** β and **11** β with ceric ammonium nitrate (CAN) in aqueous acetonitrile led to glycosylbenzoquinones **13** and **14** in high isolated yield, as moderately stable brown solids.^[32] Upon deacetylation, water-soluble derivatives suitable for in vitro assays were expected. Attempts to achieve base-catalyzed deacetylation (MeONa in MeOH or $\text{NEt}_3/\text{MeOH}/\text{H}_2\text{O}$) were, in our hands, not encouraging, as reported for a related analogue.^[21] Acid-catalyzed deacetylation of **13** (MeOH containing acetyl chloride in large excess, for example 25/100 equiv.) occurred with simultaneous unselective addition of hydrochloric acid to the 1,4-benzoquinone moiety, to afford a mixture of C-5' and C-6' chlorinated isomers ($\approx 10:7$ ratio, 65% yield).^[22] However, when deacetylation was carried out with catalytic acetyl chloride in MeOH , **13** and **14** were converted within one week to single products **15** (80%) and **16** (94%) having a 1,2,3,5-tetrasubstituted phenyl ring with one chlorine atom and one methoxy group, as indicated by mass spectrometry and NMR studies. Indeed, this unexpected reaction has some precedent,^[33] and may result from an initial protonation of the carbonyl group at C-4' (probably because of better stabilization of the positive charge distributed at C-2' and C-4' by resonance) followed by nucleophilic attack by chloride ions at C-6'. In a next step, the resulting hydroquinone may undergo tautomerization preferentially at the 4'-OH group to give a carbonyl flanked with a methylene, a process energetically less demanding (minimal steric hindrance, least molecular motion), as compared to tautomerization at C-1', which should accommodate the pyranosyl and chloro substituents at C-2' and C-6'. Then, nucleophilic attack of the carbonyl by methanol in large excess would form hemiketals which may lose water to afford **15** or **16**.

To overcome difficulties arising from additions to benzoquinones, routes ending by oxidation of either 1,4-dimethoxybenzene or hydroquinone moieties in deacetylated sugar derivatives were considered. Hence, deacetylation of **10** β and **11** β (conditions d or e) efficiently afforded **17** and **18**, which upon CAN oxidation yielded desired glycosylbenzoquinones **19** and **20** as polar substances contaminated by coloured materials probably derived from CAN and difficult to remove by chromatography. Although less direct, a three step sequence from **13** and **14** [NaBH_4 reduction, deacetylation conditions e or h, oxidation with Ag_2O or $\text{PhI}(\text{OAc})_2$] afforded pure glycosylbenzoquinones **19** and **20** in good overall yield, via corresponding hydroquinones **23** and **24**.

TLC monitoring of the reactions and checking of the fractions collected after column chromatography, sometimes difficult because of similar mobilities of substrates and products, were facilitated by examining the plates under UV light at different wavelength (254, 312 nm). Depending on the UV absorbance of the compounds examined, the observed spots might differ in terms of colour, or intensity.



Scheme 2. a) **5** or **6**, *p*-dimethoxybenzene (2 equiv.), SnCl_4 (3 equiv.), $\text{CF}_3\text{CO}_2\text{Ag}$ (1.5 equiv.), CH_2Cl_2 , 25–30 °C, ≈ 5 h; b) CAN (3 equiv.), $\text{CH}_3\text{CN}/\text{H}_2\text{O}$, 1:1 or 2:3, 25 min; c) MeOH containing 0.5% AcCl , 1 week, room temp.; d) $\text{MeOH}/\text{NEt}_3/\text{H}_2\text{O}$, 8:1:1, room temp., 10–12 h; e) for **10** β /**11** β or **21**/**22**, respectively, 0.1 M or 0.033 M MeONa in MeOH , room temp., ≈ 2 h; f) CAN (3 equiv.), H_2O , room temp., 30 min; g) NaBH_4 (2 equiv.), EtOAc , room temp., 30 min; h) MeOH containing 1% AcCl , 5 d, room temp.; i) Ag_2O (8 equiv. with **23**, oxidation almost complete; 3 equiv. with **24**, $\approx 95\%$ conversion), 2-propanol, room temp., 2 h; j) $\text{PhI}(\text{OAc})_2$ (1.5 equiv.), MeOH , room temp., 40 min; nd: not determined.

Compounds could also be distinguished from the colour that appeared on TLC plates at the first stage of charring, after acidic spray (see Experimental Section). On the basis of the vicinal couplings measured by ^1H NMR, all β -anomers displayed pyranosyl rings in a $^4\text{C}_1$ -D chair conformation, whereas α -D-glucosylbenzoquinone **3** and **11a** exhibited distorted conformations in solution.^[31] Mass spectroscopy proved the presence of a chlorine atom in **15** and **16**, whereas ^1H NMR spectroscopy indicated two *meta* related aromatic protons ($J \approx 3$ Hz). Long range correlations (HMBC) were found between the sugar protons 1-H, 2-H, and the aromatic carbons C-1', C-2' and C-3' by way of 3J couplings. Thus, the C-4' signal, deshielded because of O-substitution, could be assigned and was found to correlate (HMBC) to the OMe group. Accordingly, NOESY correlations recorded for **15** and **16** showed no NOE contact between the anomeric proton and the 4-OMe group. These

data proved the location of the methoxy group and the chlorine atom at the 4'- and 6'-positions, respectively, in **15** and **16**.

Kinetic and Crystallographic Studies with Glycogen Phosphorylase

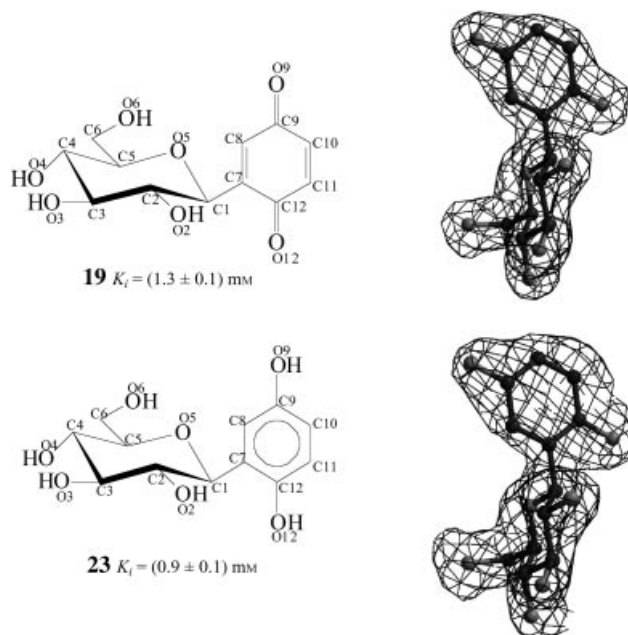
Rabbit muscle unphosphorylated glycogen phosphorylase (GPb) was isolated, purified, recrystallised and assayed as described.^[34] Kinetic experiments were performed in the direction of glycogen synthesis by the release of orthophosphate from Glc-1-P, in the presence of constant concentrations of glycogen (1% w/v), AMP (1 mM) and various concentrations of Glc-1-P (3–20 mM) and inhibitors (0.5–5.0 mM). Native GPb crystals, grown in the tetragonal lattice^[35] space group $P4_32_12$, were soaked with 100 mM of compound **17** (for 5.5 h), 45 mM of compound **19** (for 1 h) or 100 mM of **23** (for 5 h) in a buffered solution (10 mM Bes, 0.1 mM EDTA, 0.02% sodium azide, pH 6.7), prior to data collection. Diffraction data (see Supporting information) were collected from single crystals at EMBL-Hamburg outstation (Beamline X13) to a resolution of 2.03–2.05 Å, respectively for **19** and **23**. The reflections were recorded with an ADSC Q4 CCD detector. Data reduction and integration followed by scaling and merging of the intensities obtained were performed with Denzo and Scalepack, respectively, as implemented in HKL suite.^[36]

Crystallographic refinement of the four complexes was performed with CNS version 1.1^[37] by using positional and individual B-factor refinement with bulk-solvent correction. The starting model employed for the refinement of the complexes was the structure of the GPb- α -D-glucose complex determined at 2.1 Å resolution.^[38] 2Fo-Fc and Fo-Fc electron density maps calculated were visualised by using the program for molecular graphics "O".^[39] Ligand models, constructed and minimized by using the program SYBYL 6.8 (Tripos Associates Inc., St. Louis, MO, USA), were fitted to the electron density maps after adjustment of their torsion angles. Alternate cycles of manual rebuilding with "O" and refinement with CNS improved the quality of the models.

The stereochemistry of the protein residues was validated by PROCHECK.^[40] Hydrogen bonds and van der Waals interactions were calculated with the program CONTACT as implemented in CCP4^[41] by applying a distance cut off of 3.3 Å and 4.0 Å, respectively. The program calculates the hydrogen position for those target nitrogen atoms where the hydrogen position is unambiguous, and the angle O···H···N is calculated and printed. For source···oxygen hydrogen bonds, the angle source···O···bonded carbon is calculated. Limits on both of these angles must be supplied, and bonds with angles less than these limits are rejected. Suitable values are 120° and 90°. A Luzatti plot^[42] suggests an average positional error for all structures of approximately 0.24–0.26 Å. GPb complex structures were superimposed over well-defined residues using LSQKAB.^[41] Comparisons of the water molecules in the complex structures were made

taking into consideration their equivalent positions. The schematic representation of the crystal structures presented in all figures were prepared with the programs MolScript^[43] and BobScript^[44] and rendered with Raster3D.^[45] The coordinates of the new structures have been deposited with the RCSB Protein Data Bank (<http://www.rcsb.org/pdb>) with codes 2FF5 (GPb-**19** complex), and 2FET (GPb-**23** complex).

The kinetic results also showed that glucosylhydroquinone **17** was not an inhibitor when tested at 1–8 mM. However, the kinetic parameters indicated that glucosylhydroquinone **23** was a slightly better competitive inhibitor [$K_i = (0.9 \pm 0.1)$ mM] than glucosylbenzoquinone **19** [$K_i = (1.3 \pm 0.1)$ mM]. In order to elucidate the structural basis of inhibition we have determined the crystal structure of GPb in complex with **19** and **23**. The resulting electron density map for compound **17** showed no binding to the catalytic site, in agreement with the kinetic results. For complexes **19** and **23**, the 2Fo-Fc Fourier electron density maps indicated that compounds **19** and **23** bound tightly at the catalytic site. Electron density maps (Scheme 3) clearly defined the position of each inhibitor within the catalytic site, consistent with the kinetic results.



Scheme 3. Structure of compounds **19** and **23**, with the numbering used for crystallography, and inhibition constants. Diagrams of the 2Fo-Fc electron density maps, contoured at 1 σ , for the bound compounds at the catalytic site of GPb are also shown.

The mode of binding and the hydrogen bonding network to the peripheral hydroxy groups of the glucopyranose moiety of **19** and **23** are analogous to those observed for the α -D-glucose complex.^[46] The benzo(hydro)quinone groups can be accommodated at the β -pocket of the catalytic site, a side channel from the catalytic site with no access to the bulk solvent, lined by both polar and nonpolar groups,^[46] and stabilize the closed conformation of the 280s loop.

Thus, O12 makes direct polar interactions with Leu136 N, and Asp283 OD1, and water-mediated hydrogen interactions with Gly134 N, Gly135 N, Glu88 OE2, Asp283 OD1 and Asp283 OD2. Atom O9 also forms a hydrogen bond with Asp339 OD1 of the β -pocket. In GPb-**19** complex, the latter hydrogen bond requires Asp339 to be protonated. The hydrogen bonds formed between **19** and **23** and the protein are illustrated in Figure 1a.

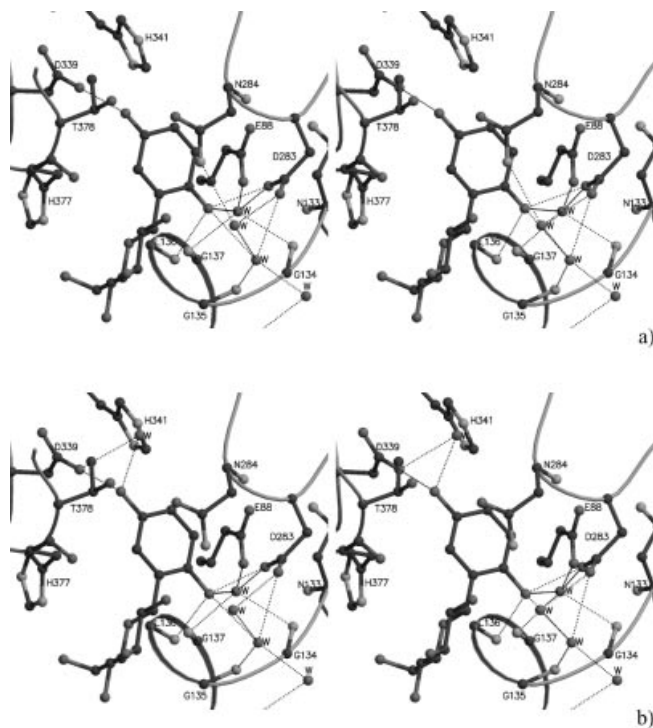


Figure 1. Interactions of compounds **19** (a), and **23** (b) with GPb in the vicinity of the catalytic site, shown in stereo. The hydrogen bond pattern between the inhibitors, protein residues and water molecules (w) is represented by dotted lines. The interactions of the glucopyranose ring are retained throughout the structures analysed and were not incorporated in the figures for clarity reasons.

Both compounds are moderate inhibitors and bind slightly better than α -D-glucose ($K_i = 1.7$ mM),^[46] possibly because of the additional interactions of the 1,4-benzo(hydro)quinone groups with the protein residues. Examination of the van der Waals contacts indicates a number of polar/nonpolar contacts, which may account for moderate inhibition. Atom C7 makes van der Waals interactions with ND2 (3.3 Å), C12 with OD1 Asp283 (3.3 Å), O12 with CG Asp283 (3.3 Å), C11 with OD1 Asp283 (3.2 Å) and N Asn284 (3.4 Å), C10 with N Asn284 (3.4 Å), and O9 with CG2 Thr378 (3.1 Å). Hydrogen bonds and van der Waals interactions of the two compounds with residues lining the catalytic site are given as Supporting Information.

In Figure 2, we compare the binding of **19**, **23** and α -D-glucose within the catalytic site of GPb. The comparison reveals that there were small shifts in the side chain atoms of Leu136, Asp283, Asn284 and Asp339, of between 0.4 and 1.2 Å, in order to optimize interactions with the li-

gands. Furthermore, Wat12 and Wat233 (numbering from the α -D-glucose complex) were displaced, and Wat201, Wat417 and Wat510 (Wat229, Wat302 and Wat124 in the α -D-glucose complex, respectively) shifted ≈ 0.7 – 0.8 Å to create more space for the benzo(hydro)quinone groups to be accommodated without causing steric hindrance. In addition, the glucopyranose ring also moved away from His377 (shifts of O5 and C1 atoms by ≈ 0.4 Å).

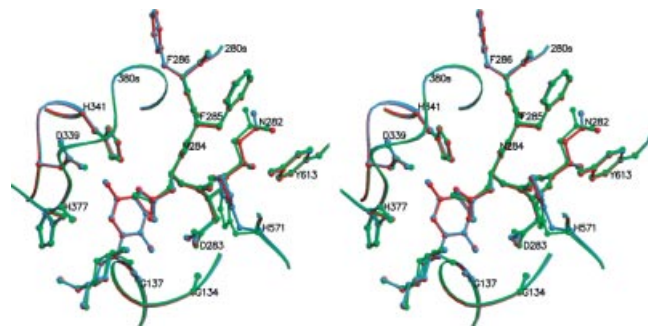


Figure 2. Comparison between GPb-**19** complex (red), GPb-**23** complex (cyan), and GPb- α -D-glucose complex (green) in the vicinity of the catalytic site.

Conclusions

In summary, the kinetic and X-ray crystallographic study of the two enzyme complexes of GPb with ligands of the C-glucosylbenzo(hydro)quinone type showed that these novel analogues are competitive inhibitors of the enzyme albeit with moderate affinity. The two analogues form direct and water-mediated hydrogen bonds and extensive van der Waals interactions with residues of the 280s loop (Asp283 and Asn284), the glycine helix (Gly134 and Gly137), Glu88 and Asp339. These interactions provide a rationale for the potency of glucosylbenzo(hydro)quinones to inhibit GPb activity, and should assist the design of more effective compounds. Despite the appearance of an improved network of interactions compared with α -D-glucose, there is little difference in the free energy of binding between **19**, **23** and α -D-glucose (0.16 and 0.38 kcal/mol, respectively). It is possible that, in complexes **19** and **23**, the energy gain due to the increased van der Waals interactions is outbalanced by the energy loss due to subtle structural changes of protein residues, changes in water structure and accommodation of the benzo(hydro)quinone substituents at a rather unfavourable environment.

Because C- β -D-glucopyranosyl-1,4-hydro- and C- β -D-glucopyranosyl-1,4-benzoquinones represent a new type of glucose-derived competitive inhibitors of GP which bind at the catalytic site,^[27] further work is currently under progress to synthesize and evaluate modified analogues with greater potency for the β -pocket of the catalytic site of the enzyme. This will be reported in forthcoming papers, as well as our efforts for converting C-glycosylhydroquinones into glycosylated analogues of Vitamin E^[22] as amphiphilic antioxidants.

Experimental Section

General Methods: Dichloromethane was washed three times with water, dried (CaCl₂) and distilled from CaH₂ before use. Other organic solvents were distilled. Thin-layer chromatography (TLC) was carried out on aluminium sheets coated with silica gel 60 F₂₅₄ (Merck, Darmstadt, Germany). TLC plates were inspected under UV light (254, 312 nm), and/or developed by treatment with a mixture of 5% H₂SO₄ in EtOH followed by heating. Silica gel column chromatography was performed with Geduran silica gel Si 60 (40–63 μm) purchased from Merck. ¹H- and ¹³C NMR spectra were recorded at 23 °C with Bruker AC200, DRX300 or DRX500 spectrometers with the residual solvent as the internal standard. The following abbreviations are used to indicate the observed multiplicities: s, singlet; d, doublet; dd, doublet of doublet; t, triplet; q, quadruplet; m, multiplet; br., broad. In the description of NMR spectra, atoms in pyranosyl rings and aglycons are numbered, respectively, with simple and primed figures. NMR solvents were purchased from Euriso-Top (Saint Aubin, France). HRMS (LSIMS) mass spectra were recorded in the positive mode (unless stated otherwise) with a Thermo Finnigan Mat 95 XL spectrometer. MS (ESI) mass spectra were recorded in the positive mode with a Thermo Finnigan LCQ spectrometer. Optical rotations were measured with a Perkin–Elmer polarimeter. Elemental analyses were performed at the Service Central d'Analyses du CNRS (Verneuil, France).

2-(2,3,4,6-Tetra-*O*-acetyl- α -D-glucopyranosyl)-1,4-benzoquinone (3) and 4-Hydroxyphenyl 2,3,4,6-Tetra-*O*-acetyl- α -D-glucopyranoside (tetraacetyl α -arbutin 4): A solution of sugar cobaloxime **2** (*D*-gluco) (140 mg, 0.2 mmol) and 1,4-benzoquinone (432 mg, 4 mmol, 20 equiv.) in benzene (6 mL) was introduced in a pyrex two-wall reactor (cooled to $\approx$ 15 °C) receiving the visible light beam emitted by a slide-projector (halogen lamp: 100 W). After the dark brown coloured solution, maintained under an atmosphere of argon, was irradiated for 13 h, TLC showed the almost complete conversion of the starting material (R_f = 0.1, Et₂O/CH₂Cl₂, 1:5) into two more mobile products (major: R_f = 0.85, minor: R_f = 0.75, Et₂O/CH₂Cl₂, 1:5). After concentration of the solution under reduced pressure, the residue was applied to a column of silica gel irrigated with EtOAc/petroleum ether, 4:6 then EtOAc (100 mL), then EtOAc/EtOH, 2:1, to afford **3** (31 mg, 40%, based on the transformed substrate), known tetraacetyl α -arbutin **4** (11 mg, 14%)^[20a] and unreacted starting material **2** (15 mg). Compound **3**: Yellowish oil, decomposed after a time. $[\alpha]_D^{25} = +35$ (c = 0.75, CH₂Cl₂), $[\alpha]_D^{25} = +21$ (c = 1.25, acetone). IR (KBr): $\tilde{\nu}$ = 1740 (C=O, acetyl), 1655 (C=O, quinone) cm⁻¹. ¹H NMR (500.13 MHz, CDCl₃): δ = 6.89 (t, 1 H, $J_{3',1}$ = 2.0 Hz, J = 2 Hz, 3'-H), 6.78 (m, 2 H, 5'-H, 6'-H), 5.21 (t, 1 H, $J_{1,2}$ = 2.0 Hz, 1-H), 5.14 (t, 1 H, $J_{2,3}$ = 2.6 Hz, $J_{3,4}$ = 4.1 Hz, 3-H), 5.12 (t, 1 H, 2-H), 4.96 (t, 1 H, $J_{4,5}$ = 4.4 Hz, 4-H), 4.53 (dd, 1 H, $J_{5,6a}$ = 7.4 Hz, $J_{6a,6b}$ = 11.9 Hz, 6a-H), 4.27 (dt, 1 H, $J_{5,6b}$ = 4.2 Hz, 5-H), 4.22 (dd, 1 H, 6b-H), 2.19, 2.11, 2.09, 1.98 (4s, 3 H each, acetyl) ppm. ¹³C NMR (125.76 MHz, CDCl₃): δ = 187.5, 186.0 (C=O, quinone), 171.0, 170.0, 169.8, 169.3 (C=O), 144.7 (C-2'), 137.1, 136.8 (C-5', C-6'), 133.1 (C-3'), 73.6 (C-5), 69.1, 68.9 (C-2, C-3), 67.0 (C-4), 66.2 (C-1), 61.5 (C-6), 21.3, 21.3, 21.2, 21.0 (acetyl) ppm. MS (CI, isobutane): m/z = 441 [M + H]⁺, benzoquinone reduced to hydroquinone. HRMS: calcd. for C₂₀H₂₅O₁₁ [M + H]⁺ 441.1397; found 441.13995. HRMS (EI): calcd. for C₂₀H₂₂O₁₁ [M]⁺ 438.11621; found 438.11734.

2-(2,3,4,6-Tetra-*O*-acetyl- α -D-galactopyranosyl)-1,4-dimethoxybenzene (11 α), 2-(2,3,4,6-Tetra-*O*-acetyl- β -D-galactopyranosyl)-1,4-dimethoxybenzene (11 β) and 2-(2,3,5,6-Tetra-*O*-acetyl- β -D-galactofuranosyl)-1,4-dimethoxybenzene (12): 1,2,3,4,6-Penta-*O*-acetyl- β -

D-galactopyranose **6** (985 mg, 2.5 mmol), 1,4-dimethoxybenzene (**7**) (692 mg, 5 mmol, 2 equiv.), silver trifluoroacetate (831 mg, 3.75 mmol, 1.5 equiv.) and dry CH₂Cl₂ (12.5 mL) were introduced in a flask equipped with a stirring bar (for removing moisture, the reagents were maintained overnight under vacuum ca. 1 Torr, except for the more volatile **7**, which was dried for 0.5 h only). After the mixture was cooled to 0 °C with an ice bath, a 1 M solution of SnCl₄ in CH₂Cl₂ (7.5 mL, 7.5 mmol, 3 equiv.) was added with stirring. The resulting milky suspension was stirred at 0 °C for 3.5 h, under an atmosphere of argon. TLC indicated completion of the reaction after 2.5 h. The galactose pentaacetate (R_f = 0.42, CH₂Cl₂/Et₂O, 5:0.5) was converted into slightly less polar products (R_f = 0.50 and 0.45), and a trace amount of 2,3,4,6-tetra-*O*-acetyl-D-galactopyranose (R_f = 0.15) due to hydrolysis. The reaction was quenched by the addition of saturated aq. NaHCO₃ (36 mL); then, the solids were filtered off through a bed of Celite and rinsed. The liquid phase, diluted with CH₂Cl₂, was washed with saturated aq. NaCl (3 $\times$ 50 mL), then with water (10 mL) and dried (MgSO₄). The clear oil (1.33 g) obtained upon concentration under reduced pressure was shown by ¹H NMR, on the basis of the comparison of the intensity of the acetyl signals, to contain four products (proportion: **7**, **27**, **23**, **15**%) with estimated weights of 80, 360, 310 and 200 mg, respectively. After chromatography (two successive separations) on silica gel ($\approx$ 150 g) with CH₂Cl₂/Et₂O [5:0.5, then 5:0.35 (more efficient)] as the mobile phases, the mixture led successively to three products identified as 2,3,4,6-tetra-*O*-acetyl- α -D-galactopyranosyl chloride (**9**), (26 mg, 0.14 mmol, $\approx$ 2.5%), **11 α** (290 mg, 0.62 mmol, 25%) and **11 β** (220 mg, 0.47 mmol, 19%). Product **11 β** was an admixture with an unidentified side product (estimated amount: 65 mg) inseparable by chromatography with CH₂Cl₂/Et₂O mixtures. With oxolane/petroleum ether (1:3) TLC mobilities for **9**, **11 α** , **11 β** and side product were as follows: R_f = 0.32, 0.28, 0.25, 0.22, respectively. Note that **11 α** and **11 β** appeared on TLC plates as orange-brown spots during the initial stage of charring, after H₂SO₄ spray. Product **11 α** : Amorphous solid. R_f = 0.50 (CH₂Cl₂/Et₂O, 5:0.5). $[\alpha]_D^{25} = +55$ (c = 1, CH₂Cl₂). ¹H NMR (500.13 MHz, C₆D₆): δ = 7.58 (d, 1 H, $J_{3',5'}$ = 3.1 Hz, 3'-H), 6.72 (dd, 1 H, $J_{5',6'}$ = 8.9 Hz, 5'-H), 6.41 (d, 1 H, 6'-H), 5.91 (d, 1 H, $J_{1,2}$ = 1.9 Hz, 1-H), 5.87 (dd, 1 H, $J_{2,3}$ = 4.2 Hz, 2-H), 5.84 (dd, 1 H, $J_{3,4}$ = 3.2 Hz, $J_{4,5}$ = 6.4 Hz, 4-H), 5.73 (t, 1 H, 3-H), 5.04 (dd, 1 H, $J_{5,6a}$ = 9.3 Hz, 6a-H), 4.62 (ddd, 1 H, $J_{5,6b}$ = 3.0 Hz, 5-H), 4.40 (dd, 1 H, $J_{6a,6b}$ = 12.3 Hz, 6b-H), 3.41 (s, 3 H, 4'-OMe), 3.34 (s, 3 H, 1'-OMe), 1.66, 1.64, 1.55, 1.37 (4s, 3 H each, acetyl) ppm. ¹H NMR (500.13 MHz, CDCl₃): δ = 7.07 (d, 1 H, $J_{3',5'}$ = 3 Hz, 3'-H), 6.78 (dd, 1 H, $J_{5',6'}$ = 9 Hz, 5'-H), 6.73 (d, 1 H, 6'-H), 5.53 (dd, 1 H, $J_{4,5}$ = 6.3 Hz, 4-H), 5.45 (broad s, 1 H, 1-H), 5.33 (m, 2 H, 2-H, 3-H), 4.73 (dd, 1 H, $J_{5,6a}$ = 9 Hz, 6a-H), 4.47 (ddd, 1 H, $J_{5,6b}$ = 3.2 Hz, 5-H), 4.29 (dd, 1 H, $J_{6a,6b}$ = 12.5 Hz, 6b-H), 3.787 (s, 3 H, 4'-OMe), 3.77 (s, 3 H, 1'-OMe), 2.195, 2.096, 2.044, 1.82 (4s, 3 H each, acetyl) ppm. In CDCl₃, CD₃COCD₃, or C₅D₅N as the solvent, the 2-H and 3-H resonances appeared as superimposed signals. ¹³C NMR (50.32 MHz, CDCl₃): δ = 171.0 (6-OAc), 169.7 (4-OAc), 169.3, 169.0 (C=O), 153.4 (C-1'), 150.1 (C-4'), 125.6 (C-2'), 113.9, 113.6, 110.8 (C-3', C-5', C-6'), 72.2 (C-5), 69.1, 68.2 (C-2, C-3), 65.9 (C-4), 64.8 (C-1), 59.9 (C-6), 55.9 (4'-OMe), 55.9 (1'-OMe), 21.0, 20.9, 20.8, 20.5 (acetyl) ppm. A NOESY correlation indicated contacts in C₆D₆ between 1'-OMe and 2-H (weak), and more interestingly for proving the α -configuration, between 1-H (anomer) and 6a-H, but no contact with either 3-H or 5-H. HRMS (CI, isobutane): calcd. for C₂₂H₂₉O₁₁ [M + H]⁺ 469.170986; found 469.17090. C₂₂H₂₈O₁₁ (468.16): calcd. C 56.41, H 6.02, O 37.57; found C 55.73, H 6.05, O 37.38. Product **12**: When the reaction was prolonged for an extended time, **12** was obtained in low amount after

repeated chromatographic purifications. On TLC plates, it gave yellow spots during the initial stage of charring, after H₂SO₄ spray. ¹H NMR (500.13 MHz, CDCl₃): δ = 7.00 (m, 1 H, $J_{1,3'} = <1$ Hz, 3'-H), 6.80 (m, 2 H, 5'-H, 6'-H), 5.48 (dd, 1 H, $J_{2,3} = 3.0$ Hz, 2-H), 5.43 (ddd, 1 H, $J_{5,6a} = 4.3$ Hz, 5-H), 5.31 (br. d, 1 H, $J_{1,2} = 4.4$ Hz, $J_{1,3'} = <1$ Hz, 1-H), 5.20 (dd, 1 H, $J_{3,4} = 4.3$ Hz, 3-H), 4.45 (dd, 1 H, $J_{5,6b} = 6.9$ Hz, 6a-H), 4.39 (t, 1 H, $J_{4,5} = 5.3$ Hz, 4-H), 4.26 (dd, 1 H, $J_{6a,6b} = 12.0$ Hz, 6b-H), 3.80 (s, 3 H, OMe), 3.77 (s, 3 H, OMe), 2.19, 2.15, 2.10, 2.03 (4s, 3 H each, acetyl) ppm. ¹³C NMR (125.76 MHz, CDCl₃): δ = 171.0, 170.7, 170.4, 170.0 (C=O), 154.0, 151.2 (C-1', C-4'), 128.4 (C-2'), 113.5 (C-3'), 113.5, 111.7 (C-5', C-6'), 81.8 (C-2), 81.7 (C-4), 80.8 (C-1), 78.9 (C-3), 70.3 (C-5), 63.2 (C-6), 56.2 (2 C, OMe), 21.43, 21.36, 21.17, 21.17 (acetyl) ppm. The COSY experiment clearly showed a coupling between 3'-H and 1-H. The NOESY spectrum showed correlations between aromatic 3'-H and 2-H, 1-H, and also 4-H.

2-(2,3,4,6-Tetra-*O*-acetyl- β -D-glucopyranosyl)-1,4-benzoquinone (13): 2-(2,3,4,6-Tetra-*O*-acetyl- β -D-glucopyranosyl)-1,4-dimethoxybenzene (**10** β) (280 mg, 0.6 mmol) dissolved in acetonitrile (1.5 mL) was treated with ceric ammonium nitrate (990 mg, 1.8 mmol, 3 equiv.) dissolved in water (1.5 mL) and stirred efficiently for 25 min at room temperature under a normal atmosphere.^[47] Although **10** β and glucosylbenzoquinone **13** have the same mobilities by TLC ($R_f \approx 0.3$, Et₂O/petroleum ether, 3:1), they could be distinguished by examination of the TLC plates under different wavelengths: the substrate was not very visible at 254 nm, but gave dark spot at 312 nm, while the glucosylbenzoquinone appeared very visible at 254 nm, and visible at 312 nm. After dilution with dichloromethane (10 mL), the reaction mixture was washed with aqueous saturated NaHCO₃ (≈ 5 mL), followed by water. It was then dried (MgSO₄) and concentrated under reduced pressure. The residue, obtained in almost quantitative yield (256 mg) was essentially pure **13** (NMR) and crystallized as yellow needles. M.p. 132–133 °C (Et₂O). $[\alpha]_D^{25} = -28$ ($c = 1$, acetone). IR (KBr): $\tilde{\nu} = 1740$ (C=O, acetyl), 1655 (C=O, quinone) cm⁻¹. UV (CH₂Cl₂): λ (ϵ) = 222 (5130), 225.4 (4890), 248.2 (15110) nm. ¹H NMR (200.13 MHz, CDCl₃): δ = 6.91 (d, 1 H, $J = 1$ Hz, 3'-H), 6.77 (d, 2 H, $J = 1.2$ Hz, 5'-H, 6'-H), 5.37 (t, 1 H, $J_{3,4} = 9.4$ Hz, 3-H), 5.15 (t, 1 H, $J_{4,5} = 9.8$ Hz, 4-H), 4.98 (t, 1 H, $J_{2,3} = 9.5$ Hz, 2-H), 4.64 (dd, 1 H, $J_{1,3'} = 0.8$ Hz, $J_{1,2} = 9.7$ Hz, 1-H), 4.26 (dd, 1 H, $J_{5,6a} = 4.6$ Hz, $J_{6a,6b} = 12.4$ Hz, 6a-H), 4.14 (dd, 1 H, $J_{5,6b} = 2.2$ Hz, 6b-H), 3.80 (ddd, 1 H, 5-H), 2.10, 2.06, 2.02, 1.91 (4s, 3 H each, acetyl) ppm. ¹³C NMR (125.8 MHz, CDCl₃): δ = 186.9, 185.5 (C=O, quinone), 170.6, 170.0, 169.7, 169.5 (C=O), 144.1 (C-2'), 136.5, 136.4 (C-5', C-6'), 133.7 (C-3') (C-5'/C-6', C-3' in this order from HSQC), 76.3 (C-5), 73.7 (C-3), 72.5 (C-2), 72.0 (C-1), 68.2 (C-4), 62.0 (C-6), 20.7, 20.6, 20.6, 20.5 (acetyl) ppm. MS (CI, isobutane): m/z (%) = 441.4 (100) [M + 3 H]⁺, 439.3 (17) [M + H]⁺. HRMS: calcd. for C₂₀H₂₃O₁₁ [M + H]⁺ 439.12404; found 439.12392. C₂₀H₂₂O₁₁: calcd. C 54.79, H 5.02, O 40.18; found C 54.37, H 5.00, O 40.68.

2-(2,3,4,6-Tetra-*O*-acetyl- β -D-galactopyranosyl)-1,4-benzoquinone (14): Galactopyranosyl **11** β (280 mg, 0.6 mmol) was oxidized with CAN as described previously for **10** β . After workup, the residue was purified by chromatography with EtOAc/petroleum ether (4:6) as the eluent to afford pure **14** (208 mg, 80%) as a yellow foam, $[\alpha]_D^{25} = -11.2$ ($c = 0.95$, acetone). IR (KBr): $\tilde{\nu} = 1740$ (C=O, acetyl), 1655 (C=O, quinone) cm⁻¹. UV (CH₂Cl₂): λ (ϵ) = 220.4 (4920), 225.6 (4090), 248.2 (15180) nm. ¹H NMR (200.13 MHz, CDCl₃): δ = 6.98 (d, 1 H, $J = 0.8$ Hz, 3'-H), 6.76 (d, 2 H, $J = 1$ Hz, 5'-H, 6'-H), 5.50 (dd, 1 H, $J_{4,5} = 0.7$ Hz, $J_{3,4} = 3.1$ Hz, 4-H), 5.20 (dd, 1 H, $J_{2,3} = 10.0$ Hz, 3-H), 5.11 (t, 1 H, $J_{1,2} = 8.6$ Hz, 2-H), 4.63 (d, 1 H, 1-H), 4.21–3.99 (m, 3 H, 5-H, 6a-H, 6b-H), 2.18, 2.04, 1.99, 1.91 (4s, 3 H each, acetyl) ppm. In the ¹H NMR spectrum recorded

at 500.13 MHz, 6a-H and 6b-H appeared as a multiplet ($\delta = 4.17$ to 4.09 ppm) and 5-H as a triplet ($\delta = 4.04$ ppm, $J_{5,6a} = J_{5,6b} \approx 6.4$ Hz). ¹³C NMR (50.3 MHz, CDCl₃): δ = 187.1, 185.7 (C=O, quinone), 170.4, 170.2, 170.0, 169.9 (C=O), 144.6 (C-2'), 136.5, 136.3 (C-5', C-6'), 133.9 (C-3'), 74.7 (C-5), 72.1 (C-1), 71.7 (C-3), 70.1 (C-2), 67.4 (C-4), 61.7 (C-6), 20.7, 20.7, 20.6, 20.6 (acetyl) ppm. MS (CI, isobutane): m/z (%) = 441.4 (100) [M + 3 H]⁺, 439.3 (13) [M + H]⁺. HRMS: calcd. for C₂₀H₂₃O₁₁ [M + H]⁺ 439.12404; found 439.12405.

1-Chloro-3-(β -D-glucopyranosyl)-2-hydroxy-5-methoxybenzene (15): Glucosylbenzoquinone **13** (200 mg, 0.427 mmol) was dissolved in MeOH (20 mL) containing 0.5% v/v AcCl (3.28 equiv. of AcCl). Upon stirring for 8 d at room temperature, the starting material was converted into a single more polar compound (**6**) ($R_f = 0.55$, MeOH/CH₂Cl₂, 1:4). The volatiles were evaporated under reduced pressure. The residue was subjected to chromatography on silica gel (MeOH/CH₂Cl₂, 1:10) to afford compound **15** (110 mg, 80%) as a pale yellow amorphous solid, amenable to crystallization. M.p. 83–85 °C. $R_f = 0.55$, MeOH/CH₂Cl₂ (1:4). $[\alpha]_D^{25} = +24.8$ ($c = 0.9$, methanol). ¹H NMR (500.13 MHz, D₂O): δ = 7.00 (d, 1 H, $J_{3',5'} = 3.1$ Hz, 5'-H), 6.88 (d, 1 H, 3'-H), 4.64 (d, 1 H, $J_{1,2} = 9.5$ Hz, 1-H), 3.80 (br. d, 1 H, $J_{6a,6b} = 12.0$ Hz, 6a-H), 3.71 (dd, 1 H, $J_{5,6b} = 4.7$ Hz, 6b-H), 3.70 (s, 3 H, OMe), 3.61 (t, 1 H, $J_{2,3} = 9.4$ Hz, 2-H), 3.55 (br. t, 1 H, $J_{3,4} = 9.2$ Hz, 3-H), 3.49 (m, 2 H, 4-H, 5-H) ppm. ¹³C NMR (125.8 MHz, CD₃OD): δ = 153.4 (C-4'), 144.5 (C-1'), 127.9 (C-2'), 123.0 (C-6'), 115.9 (C-5'), 113.3 (C-3'), 80.6 (C-5), 77.7 (C-3), 76.8 (C-1), 73.8 (C-2), 70.0 (C-4), 61.1 (C-6), 56.4 (OMe) ppm. MS (ESI⁻): m/z (%) = 321 (35), 319 (100) [M – H]⁻, 355, 357 [M + Cl]⁻, 639, 641 [2M – H]⁻.

1-Chloro-3-(β -D-galactopyranosyl)-2-hydroxy-5-methoxybenzene (16): Galactosylbenzoquinone **14** (26 mg, 0.059 mmol) was treated with acidic methanol (1.2 mL containing 1.42 equiv. of AcCl) prepared by adding freshly distilled AcCl (25 μ L) to dry methanol (5 mL; 0.5% v/v solution). Upon stirring for 1 week at room temperature, the starting material ($R_f \approx 1$, EtOAc/MeOH, 20:1) was converted into a single compound ($R_f = 0.18$, EtOAc/MeOH, 20:1). Concentration of the solution overnight under reduced pressure afforded a residue (24 mg) which was purified by column chromatography with silica gel and EtOAc/MeOH (20:1) as the eluent. Concentration of homogeneous fractions afforded a yellow gum (15 mg, 94% yield), identified as **16**. $[\alpha]_D^{25} = +41$ ($c = 0.7$, methanol). ¹H NMR (500.13 MHz, D₂O): δ = 7.02 (d, 1 H, $J_{3',5'} = 3.1$ Hz, 5'-H), 6.98 (d, 1 H, 3'-H), 4.62 (d, 1 H, $J_{1,2} = 9.6$ Hz, 1-H), 4.00 (d, 1 H, $J_{3,4} = 3.3$ Hz, $J_{4,5} = 0$ Hz, 4-H), 3.82 (t, 1 H, $J_{2,3} = 9.6$ Hz, 2-H), 3.77 (dd, 1 H, $J_{5,6a} = 6.4$ Hz, $J_{5,6b} = 5.6$ Hz, 5-H), 3.73 (s, 3 H, OMe), 3.72 (dd, 1 H, $J_{6a,6b} = 11.3$ Hz, 6a-H), 3.70 (dd, 1 H, 3-H), 3.68 (dd, 1 H, 6b-H) ppm. ¹H NMR (500.13 MHz, CD₃OD): δ = 6.99 (d, 1 H, $J_{3',5'} = 3.1$ Hz, 3'-H), 6.89 (d, 1 H, 5'-H), 4.50 (d, 1 H, $J_{1,2} = 9.4$ Hz, 1-H), 4.00 (br. d, 1 H, $J_{3,4} = 2.9$ Hz, $J_{4,5} = 0$ Hz, 4-H), 3.85 (t, 1 H, $J_{2,3} = 9.4$ Hz, 2-H), 3.82 (dd, 1 H, $J_{5,6a} = 6.9$ Hz, $J_{6a,6b} = 11.6$ Hz, 6a-H), 3.76 (s, 3 H, OMe), 3.75 (dd, 1 H, $J_{5,6b} = 5.3$ Hz, 6b-H), 3.69 (dd, 1 H, 5-H), 3.64 (dd, 1 H, 3-H) ppm. ¹³C NMR (75.5 MHz, D₂O): δ = 153.5 (C-4'), 144.6 (C-1'), 128.2 (C-2'), 122.9 (C-6'), 116.1 (C-5'), 113.2 (C-3'), 79.7 (C-5), 77.1 (C-1), 74.5 (C-3), 71.4 (C-2), 69.6 (C-4), 61.6 (C-6), 56.5 (OMe) ppm. ¹³C NMR (125.8 MHz, CD₃OD): δ = 153.5 (C-4'), 145.1 (C-1'), 128.9 (C-2'), 121.9 (C-6'), 114.7 (C-5'), 113.1 (C-3'), 79.8 (C-5), 78.8 (C-1), 75.4 (C-3), 72.1 (C-2), 69.8 (C-4), 61.9 (C-6), 55.4 (OMe) ppm. MS (CI, isobutane): m/z = 321 [M + H]⁺. MS (ESI⁻): m/z = 319 [M – H]⁻. HRMS (FAB, nitrobenzyl alcohol): calcd. for C₁₃H₁₆O₇Cl₁ [M – H]⁻ 319.0584; found 319.05876.

2-(β -D-Glucopyranosyl)-1,4-dimethoxybenzene (17): Deacetylation with MeONa in MeOH: Upon stirring, **10** β (94 mg, 0.2 mmol) was

dissolved at room temperature into a 0.1 M solution of MeONa in MeOH (4 mL, prepared from commercial MeONa). After 2 h, the starting material ($R_f = 0.57$, EtOAc/petroleum ether, 2:3, as violet spot under 312 nm) was converted to a polar product ($R_f \approx 0$, as violet spot under 312 nm). Exchange resin IR-120 (H^+) was added to the mixture. After stirring for a few minutes, filtration and concentration led to a residue which was applied to a short column eluted with EtOAc/EtOH, (5:1) to afford **17** (59.2 mg, 98% yield) as a white solid. *Deacetylation with MeOH/Et₃N/H₂O (8:1:1)*: On stirring overnight a MeOH/Et₃N/H₂O (8:1:1) mixture containing **10β**, deacetylation was almost complete by TLC (vide infra preparation of **18** from **11β**) and the product was purified by chromatography to afford **17** (94.5% yield) as a white foam. $[a]_D^{20} = -28.8$ ($c = 0.6$, EtOH). ¹H NMR (500.13 MHz, D₂O): $\delta = 7.02$ (m, 2 H), 6.96 (m, 1 H), 4.75 (d, 1 H, $J_{1,2} = 9.2$ Hz, 1-H), 3.76 (br. s, 6 H, OMe), 3.82–3.50 (m, 6 H) ppm. ¹³C NMR (50.3 MHz, D₂O): $\delta = 153.8$, 152.6 (C-1', C-4'), 127.6 (C-2'), 115.8, 114.5, 114.5 (C-3', C-5', C-6'), 80.7, 78.0, 75.7, 74.0, 70.3 (C-1 to C-5), 61.3 (C-6), 57.4, 56.4 (OMe) ppm. MS (EI): m/z (%) = 300, (75) $[M]^+$, 167 (100), 151 (54).

2-(β-D-Galactopyranosyl)-1,4-dimethoxybenzene (18): *Deacetylation with MeONa in MeOH*: Galactopyranosyl **11β** was treated with MeONa in MeOH (vide supra preparation of **17** from **10β**) to afford **18** (99%), visible on TLC plates after H₂SO₄ spray and upon charring first as brown reddish spots. *Deacetylation with MeOH/Et₃N/H₂O (8:1:1)*: **11β** (702 mg, 1.5 mmol) dissolved in a MeOH/Et₃N/H₂O, (8:1:1, 10 mL) was kept for 5 d at room temperature. TLC showed the complete transformation of the substrate into a single polar product ($R_f = 0.35$, EtOAc/MeOH, 20:3). The volatiles were removed under vacuum and the clear residue (quantitative yield) was crystallized from MeOH with successive addition of EtOAc, Et₂O, and petroleum ether, to afford **18** (372 mg, 83%) as colourless prisms. M.p. 128–129.5 °C (MeOH/EtOAc/petroleum ether). $[a]_D^{20} = -13$ ($c = 0.6$, EtOH). ¹H NMR (500.13 MHz, D₂O): $\delta = 7.11$ (d, 1 H, $J_{3',5'} = 3.1$ Hz, 3'-H), 7.01 (d, 1 H, $J_{5',6'} = 9.0$ Hz, 6'-H), 6.94 (dd, 1 H, 5'-H), 4.65 (d, 1 H, $J_{1,2} = 9.7$ Hz, 1-H), 4.00 (br. d, 1 H, $J_{3,4} = 3.4$ Hz, $J_{4,5} \approx 0$ Hz, 4-H), 3.84 (t, 1 H, $J_{2,3} = 9.7$ Hz, 2-H), ≈ 3.77 (overlapping signal, 5-H), 3.76 (s, 3 H, OMe), 3.75 (s, 3 H, OMe), 3.71 (dd, 1 H, 3-H), 3.68 (d, 2 H, $J = 6.2$ Hz, 6a-H, 6b-H) ppm. ¹³C NMR (50.3 MHz, D₂O): $\delta = 153.8$, 152.6 (C-1', C-4'), 127.9 (C-2'), 115.9, 114.5, 114.2 (C-3', C-5', C-6'), 79.7, 75.6, 74.8, 71.7, 69.7 (C-1 to C-5), 61.5 (C-6), 57.4, 56.4 (OMe) ppm. MS (EI): m/z (%) = 300 (69) $[M]^+$, 167 (100), 151 (76).

2-(β-D-Glucopyranosyl)-1,4-benzoquinone (19): *Prepared from 17 upon oxidation with CAN*: Glucopyranosyl **17** (100 mg, 0.33 mmol) was dissolved in H₂O (2 mL). A solution of CAN (548 mg, 1 mmol, 3 equiv.) in H₂O (2 mL) was added slowly, while stirring at room temperature. After ca. 30 min, TLC showed conversion of the starting material ($R_f = 0.35$, MeOH/EtOAc, 1:8, violet spot/312 nm) into a less polar product ($R_f = 0.38$, violet spot/312 nm, dark violet spot/254 nm). Water was evaporated under reduced pressure and the residue was applied to a column of silica gel (MeOH/EtOAc, 1:8 as mobile phase) to afford **19** as a dark red solid (190 mg) containing inorganic impurities still present after another chromatography. Analytically pure samples were obtained as dark red solids by other methods. *Prepared from 23 upon oxidation with Ag₂O*: Glucosylhydroquinone **23** (136 mg, 0.5 mmol) was dissolved in 2-propanol (1.5 mL) with the flask wrapped in aluminium foil. Freshly prepared Ag₂O (927 mg, 4 mmol, 8 equiv.) was added. After the mixture was stirred at room temperature for 1.5 h, the reaction was over and **23**, well visible at 312 nm ($R_f \approx 0.37$, MeOH/EtOAc, 1:8) was converted into a more mobile product ($R_f = 0.40$, intense and visible spots at 254 and 312 nm, respectively). The sol-

ids were removed by filtration through a bed of Celite and rinsed with 2-propanol (3 × 10 mL). The volatiles were evaporated under reduced pressure and the residue was applied to a short column eluted with 2-propanol/EtOAc (1:5) to afford **19** as a dark red solid (77% yield). *Prepared from 23 upon oxidation with PhI(OAc)₂*: Glucosylhydroquinone **23** (100 mg, 0.367 mmol) was dissolved in MeOH (2 mL). While stirring at room temperature, PhI(OAc)₂ (179 mg, 0.55 mmol, 1.5 equiv.) was added portionwise to the mixture. The reaction was found to be complete within 40 min (TLC). After evaporation of MeOH under reduced pressure, the residue was dissolved in water (4 mL). The aqueous phase was washed with CH₂Cl₂ (2 × 8 mL) and evaporated to afford a residue that was purified by chromatography (EtOAc/MeOH, 8:1) to afford **19** in 76.3% yield. M.p. 104–106 °C, $[a]_D^{25} = -28$ ($c = 0.8$, EtOH). IR (KBr): $\tilde{\nu} = 3397$ (OH), 2894 (w), 1657 (CO), 1601 (m), 1384 (s), 1283 (m), 1083 (s), 1031 (s), 918 (s), 833 (m) cm⁻¹. UV (EtOH): λ (ϵ) = 203.6 (4660), 213.2 (2640), 245.4 (5730) nm. ¹H NMR (500.13 MHz, D₂O): $\delta = 6.98$ (d, 1 H, $J_{3',5'} = 2.5$ Hz, 3'-H), 6.90 (d, 1 H, $J_{5',6'} = 10.4$ Hz, 6'-H), 6.86 (dd, 1 H, 5'-H), 4.48 (d, 1 H, $J_{1,2} = 9.5$ Hz, 1-H), 3.87 (dd, 1 H, $J_{5,6a} = 1.6$ Hz, $J_{6a,6b} = 12.6$ Hz, 6a-H), 3.74 (dd, 1 H, $J_{5,6b} = 5.0$ Hz, 6b-H), 3.59 (t, 1 H, $J_{2,3} = J_{3,4} = 8.8$ Hz, 3-H), 3.52 to 3.46 (m, 3 H, 2-H, 4-H, 5-H) ppm. ¹³C NMR (125.8 MHz, D₂O): $\delta = 189.9$ (C-4'), 187.6 (C-1'), 145.9 (C-2'), 137.6 (C-6'), 136.8 (C-5'), 134.7 (C-3'), 80.6 (C-5), 77.5 (C-3), 74.7 (C-2), 74.0 (C-1), 70.1 (C-4), 61.2 (C-6) ppm. HRMS (ESI): calcd. for C₁₂H₁₄O₇ $[M + H]^+$ 271.0818; found 271.08252.

2-(β-D-Galactopyranosyl)-1,4-benzoquinone (20): *Prepared from 18 upon oxidation with CAN*: CAN-oxidation of **18** (80 mg, 0.266 mmol), as described for **17** led to impure **20** (170 mg). Analytically pure samples were obtained as dark red solids by other methods. *Prepared from 24 upon oxidation with Ag₂O*: Oxidation of **24**, carried out with Ag₂O (360 mg, 1.5 mmol, 3 equiv.) as described for **23**, was found incomplete (5% of unreacted **24**, based on NMR, due to use of a smaller amount of Ag₂O) and yielded **20** in 76% yield. *Prepared from 24 upon oxidation with PhI(OAc)₂*: Galactosylbenzoquinone **20** was obtained from **24** upon oxidation with PhI(OAc)₂, as described for **23**, in 79% yield, as a dark red solid. M.p. 102–104 °C. $[a]_D^{25} = -18$ ($c = 0.85$, EtOH). IR (KBr): $\tilde{\nu} = 3413$ (OH), 2970 (s), 2904 (s), 1660 (CO), 1601 (m), 1432 (m), 1313 (s), 1078 (s), 914 (s) cm⁻¹. UV (EtOH): λ (ϵ) = 204.6 (7240), 212.2 (5020), 245.2 (15630) nm. ¹H NMR (500.13 MHz, D₂O): $\delta = 7.01$ (d, 1 H, $J_{3',5'} = 1.9$ Hz, 3'-H), 6.88 (d, 1 H, $J_{5',6'} = 10.4$ Hz, 6'-H), 6.84 (dd, 1 H, 5'-H), 4.41 (d, 1 H, $J_{1,2} = 9.1$ Hz, 1-H), 4.00 (d, 1 H, $J = 2.8$ Hz, 4-H), 3.76 to 3.69 (m, 4 H, 3-H, 5-H, 6a-H, 6b-H), 3.68 (t, 1 H, $J_{2,3} = 9.5$ Hz, 2-H) ppm. ¹³C NMR (125.8 MHz, D₂O): $\delta = 190.0$ (C-4'), 187.7 (C-1'), 146.2 (C-2'), 137.6 (C-6'), 136.8 (C-5'), 134.7 (C-3'), 79.9 (C-5), 74.2 (C-1), 74.2 (C-3), 72.0 (C-2), 69.5 (C-4), 61.6 (C-6) ppm. This substance contained a minor amount of the corresponding hydroquinone. MS (CI, isobutane): $m/z = 273$ $[M + 3H]^+$. HRMS (ESI): calcd. for C₁₂H₁₄O₇ $[M + H]^+$ 271.0818; found 271.08236.

2-(2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyl)hydroquinone (21): *Prepared from 13 upon reduction with NaBH₄*: Glucosylbenzoquinone **13** (380 mg, 0.87 mmol) was dissolved in EtOAc (2 mL). Na₂SO₄ (about 60 mg) was then added followed by NaBH₄ (66 mg, 1.74 mmol, 2 equiv.) added portionwise. The mixture was stirred at room temperature for 30 min, whereby the starting compound ($R_f = 0.76$, CH₂Cl₂/EtOAc, 4:1, violet spot under UV 312 nm, dark spot under 254 nm) was converted into a polar product as seen on TLC plates ($R_f = 0.32$, CH₂Cl₂/EtOAc, 4:1, violet spot under UV 312 nm). The reaction mixture was filtered, and the solids were rinsed with EtOAc (3 × 15 mL). The combined organic layers were washed with brine and then dried with MgSO₄. After filtration and

concentration, the residue was applied to a silica gel column with $\text{CH}_2\text{Cl}_2/\text{EtOAc}$ (4:1) as the mobile phase to afford **21** (336 mg, 0.76 mmol, 88%). *Prepared from 13 upon reduction with $\text{Na}_2\text{S}_2\text{O}_4$* : Glucosylbenzoquinone **13** (380 mg, 0.87 mmol) dissolved in CHCl_3 (3 mL) was treated with $\text{Na}_2\text{S}_2\text{O}_4$ (906 mg, 5.2 mmol, 6 equiv.) dissolved in water (3 mL). The mixture was stirred vigorously at room temperature for 8 min whereby the yellow colour of the organic layer disappeared while **13** was transformed into a more polar compound (TLC). The reaction mixture was extracted with CHCl_3 (3×15 mL), and processed as before to afford **21** (368.4 mg, 0.84 mmol, 96%), as a white foam. $[\alpha]_D^{25} = -23$ ($c = 0.9$, chloroform). UV (CHCl_3): $\lambda(\epsilon) = 241.6$ (1130), 259.2 (70), 296.8 (3710) nm. ^1H NMR (500.13 MHz, CDCl_3): $\delta = 6.74$ (d, 1 H, $J_{5',6'} = 8.8$ Hz, 6'-H), 6.68 (dd, 1 H, $J_{3',5'} = 2.9$ Hz, 5'-H), 6.57 (d, 1 H, 3'-H), 6.50 (s, 1 H, OH), ≈ 5.8 (br. s, 1 H, OH), 5.36 (t, 1 H, $J_{2,3} = J_{3,4} = 9.3$ Hz, 3-H), 5.31 (t, 1 H, $J_{1,2} = 9.8$ Hz, 2-H), 5.27 (t, 1 H, $J_{4,5} = 9.8$ Hz, 4-H), 4.61 (d, 1 H, 1-H), 4.31 (dd, 1 H, $J_{5,6a} = 4.0$ Hz, $J_{6a,6b} = 12.5$ Hz, 6a-H), 4.16 (dd, 1 H, $J_{5,6b} = 2.0$ Hz, 6b-H), 3.88 (ddd, 1 H, 5-H), 2.10, 2.07, 2.01, 1.86 (4 s, 3 H each, acetyl at positions 6, 4, 3, 2) ppm. ^{13}C NMR (125.8 MHz, CDCl_3): $\delta = 171.3$, 171.0, 170.0, 169.6 (C=O at positions 6, 4, 3, 2), 149.5 (C-4'), 148.9 (C-1'), 121.9 (C-2'), 118.7 (C-6'), 117.6 (C-5'), 115.3 (C-3'), 79.3 (C-1), 76.4 (C-5), 74.2 (C-3), 71.3 (C-2), 68.5 (C-4), 62.2 (C-6), 21.1, 21.1, 21.0, 20.8 (acetyl) ppm. HRMS (ESI): calcd. for $\text{C}_{20}\text{H}_{25}\text{O}_{11}$ $[\text{M} + \text{H}]^+$ 441.1319; found 441.12890. $\text{C}_{20}\text{H}_{24}\text{O}_{11}$: calcd. C 54.55, H 5.49, O 39.96; found C 53.11, H 5.48, O 39.96.

2-(2,3,4,6-Tetra-O-acetyl- β -D-galactopyranosyl)hydroquinone (22): Galactosylbenzoquinone **14** (438 mg, 1 mmol) was dissolved by stirring at room temperature in dry EtOAc (2 mL) containing Na_2SO_4 (76 mg). Upon portionwise addition of NaBH_4 (76 mg, 2 mmol), the substrate ($R_f = 0.74$, $\text{CH}_2\text{Cl}_2/\text{EtOAc}$, 4:1) was transformed within 30 min (TLC) into a new compound ($R_f = 0.30$). Whereas the starting quinone was visible on the TLC plates under UV light as dark violet and violet spots at 254 and 312 nm, respectively, the product was visible as a violet spot at 312 nm. The solids were filtered off and rinsed with Et_2O (20 mL). The organic phase was washed with brine (10 mL) and water. The aqueous phase was re-extracted with CHCl_3 (10 mL). After drying (MgSO_4) the combined organic layers and concentration of the solution, the residue was applied to a column of silica gel with $\text{CH}_2\text{Cl}_2/\text{EtOAc}$ (4:1) as the eluent. Concentration of homogeneous fractions led to **22** as a white foamy solid (400 mg, 91%). $[\alpha]_D^{25} = -0.6$ ($c = 0.7$, CHCl_3). UV (CHCl_3): $\lambda(\epsilon) = 241.4$ (1620), 257.2 (580), 296 (4300) nm. ^1H NMR (500.13 MHz, CDCl_3): $\delta = 6.77$ (d, 1 H, $J_{5',6'} = 8.5$ Hz, 6'-H), 6.69 (dd, 1 H, $J_{3',5'} = 2.8$ Hz, 5'-H), 6.63 (s, 1 H, OH), 6.55 (d, 1 H, 3'-H), ≈ 6.0 (br. s, 1 H, OH), 5.56 (t, 1 H, $J_{2,3} = 10.1$ Hz, 2-H), 5.54 (superimposed br. s, 1 H, 4-H), 5.16 (dd, 1 H, $J_{3,4} = 2.8$ Hz, 3-H), 4.48 (d, 1 H, $J_{1,2} = 9.8$ Hz, 1-H), 4.18 (m, 2 H, 6a-H, 6b-H), 4.08 (t, 1 H, $J_{5,6a} = J_{5,6b} \approx 6.3$ Hz, 5-H), 2.19, 2.04, 1.98, 1.85 (4s, 3 H each, acetyl at positions 6, 4, 3, 2) ppm. ^{13}C NMR (125.8 MHz, CDCl_3): $\delta = 171.0$, 170.8, 170.5, 169.6 (C=O at positions 6, 4, 3, 2), 149.3, 149.1 (C-1', C-4'), 122.1 (C-2'), 118.5 (C-6'), 117.5 (C-5'), 115.5 (C-3'), 80.7 (C-1), 75.1 (C-5), 72.1 (C-3), 68.3, 68.0 (C-2, C-4), 61.9 (C-6), 20.8 (3C), 20.6 (acetyl) ppm. HRMS (ESI): calcd. for $\text{C}_{20}\text{H}_{25}\text{O}_{11}$ $[\text{M} + \text{H}]^+$ 441.1319; found 441.12993. $\text{C}_{20}\text{H}_{24}\text{O}_{11} \cdot 0.5\text{H}_2\text{O}$: calcd. C 53.45, H 5.61, O 40.94; found C 53.35, H 5.42, O 40.97.

2-(β -D-Glucopyranosyl)hydroquinone (23): *Prepared by Zemplén deacetylation*: Glucosylhydroquinone **21** (66 mg, 0.15 mmol), dissolved in MeOH (1 mL), was treated with a solution of NaOMe in MeOH (0.1 M, 0.5 mL) while stirring. After 2 h at room temperature under an argon atmosphere, TLC showed the almost complete conversion of compound **21** into a polar compound. After concen-

tration, the residue was applied to a column with EtOAc/ CH_3OH (8:1) as the eluent to afford compound **23** (38 mg, 0.14 mmol, 93%). *Prepared upon acid-catalyzed deacetylation*: Glucosylhydroquinone **21** (100 mg, 0.23 mmol) was stirred under an argon atmosphere in MeOH (3 mL) acidified with CH_3COCl (1% v/v). After the reaction mixture was kept at room temperature for 5 d, TLC showed the presence of a more polar compound ($R_f = 0.38$, EtOAc/ CH_3OH , 8:1, violet spot under 312 nm). Work up as before led to compound **23** (52 mg, 0.19 mmol, 83%), as a yellowish solid. M.p. 79.5–81.5 °C. $[\alpha]_D^{25} = +19$ ($c = 0.8$, MeOH). UV (MeOH): $\lambda(\epsilon) = 205$ (8930), 242.4 (1400), 291.6 (4760) nm. ^1H NMR (500.13 MHz, D_2O): $\delta = 6.86$ (d, 1 H, $J_{3',5'} = 2.8$ Hz, 3'-H), 6.82 (d, 1 H, $J_{5',6'} = 8.8$ Hz, 6'-H), 6.77 (dd, 1 H, 5'-H), 4.59 (d, 1 H, $J_{1,2} = 9.7$ Hz, 1-H), 3.85 (d, 1 H, $J_{6a,6b} = 12.3$ Hz, 6a-H), 3.74 (dd, 1 H, $J_{5,6b} = 4.4$ Hz, 6b-H), 3.70 (t, 1 H, $J_{2,3} = J_{3,4} = 9.3$ Hz, 2-H), 3.61 to 3.53 (m, 3 H, 3-H, 5-H, 4-H in this order) ppm. ^{13}C NMR (125.8 MHz, D_2O): $\delta = 149.5$ (C-4'), 148.3 (C-1'), 125.5 (C-2'), 117.9 (C-6'), 117.3 (C-5'), 115.5 (C-3'), 80.6 (C-5), 77.9 (C-3), 76.6 (C-1), 73.6 (C-2), 70.1 (C-4), 61.2 (C-6) ppm. MS (CI, isobutane): $m/z = 273$ $[\text{M} + \text{H}]^+$. MS (ESI-): $m/z = 579$ $[\text{2M} + \text{Cl}]^-$, 307 $[\text{M} + \text{Cl}]^-$, 271 $[\text{M} - \text{H}]^-$. HRMS: calcd. for $\text{C}_{12}\text{H}_{17}\text{O}_7$ $[\text{M} + \text{H}]^+$ 273.0974; found 273.09759.

2-(β -D-Galactopyranosyl)hydroquinone (24): *Prepared by Zemplén deacetylation*: To **22** (110 mg, 0.25 mmol) dissolved in MeOH (1 mL) under an argon atmosphere was added 0.1 M NaOMe (0.5 mL) in MeOH. After stirring for 3 h at room temperature under an argon atmosphere, TLC showed complete transformation of the starting material ($R_f = 0.96$) into a more polar product ($R_f = 0.37$, MeOH/EtOAc, 1:8), visible as a violet spot on TLC plates at 312 nm UV light. Resin IR-120 was added to the liquid, whose pH was checked with litmus paper. After filtration and concentration, the residue was applied to a short column of silica gel with $\text{CH}_3\text{OH}/\text{EtOAc}$ (1:8) as the eluent to afford **24** as a white solid (63.4 mg, 93%), which on standing at ca. -10 °C crystallized from MeOH/ AcOEt as a yellowish solid. M.p. 76–78 °C. *Prepared by acid-catalyzed deacetylation*: Galactosylhydroquinone **22** (260 mg, 0.6 mmol) was dissolved in MeOH (5 mL) containing 50 μL AcCl (1% AcCl solution in MeOH). After stirring at room temperature under an argon atmosphere for 7 d, deacetylation was almost over and the starting material ($R_f \approx 0.95$) was converted into a more polar product ($R_f = 0.37$, MeOH/EtOAc, 1:8) visible as a violet spot on TLC at 312 nm UV light. After the volatiles were removed under reduced pressure, chromatography (MeOH/EtOAc, 1:8) afforded **24** (142.5 mg, 89% yield) as a solid which was recrystallized from MeOH/EtOAc. M.p. 76–78 °C. $[\alpha]_D^{25} = +31.5$ ($c = 0.7$, MeOH). UV (MeOH): $\lambda(\epsilon) = 206$ (8140), 248.6 (370), 294.4 (3700) nm. ^1H NMR (500.13 MHz, D_2O): $\delta = 6.92$ (d, 1 H, $J_{3',5'} = 2.8$ Hz, 3'-H), 6.82 (d, 1 H, $J_{5',6'} = 8.8$ Hz, 6'-H), 6.77 (dd, 1 H, 5'-H), 4.56 (d, 1 H, $J_{1,2} = 9.8$ Hz, 1-H), 4.03 (br. s, 1 H, 4-H), 3.91 (t, 1 H, $J_{2,3} = 9.6$ Hz, 2-H), 3.8 to 3.7 (m, 4 H, 5-H, 3-H, 6a-H, 6b-H) ppm. ^{13}C NMR (125.8 MHz, D_2O): $\delta = 149.5$ (C-4'), 148.3 (C-1'), 125.7 (C-2'), 117.9 (C-6'), 117.2 (C-5'), 115.3 (C-3'), 79.7 (C-5), 76.6 (C-1), 74.6 (C-3), 71.1 (C-2), 69.6 (C-4), 61.6 (C-6) ppm. MS (CI, isobutane): $m/z = 273$ $[\text{M} + \text{H}]^+$. HRMS: calcd. for $\text{C}_{12}\text{H}_{17}\text{O}_7$ $[\text{M} + \text{H}]^+$ 273.0974; found 273.09722.

Supporting Information (see footnote on the first page of this article): Synthesis and spectroscopic data for compounds **1**, **4**, **10 β** , **11 β** . Data collection, refinement statistics, hydrogen bonding interactions and Van der Waals interactions for compounds **19** and **23**.

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