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REACTION OF SEVERAL RESVERATROL GLYCOSIDE DERIVATIVES WITH HYPOCHLORITES IN VARIOUS MEDIA

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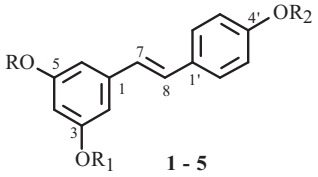
*The reactions of pterostilbenoside (*trans-*3,5-dimethoxystilben-4′*-O-β-*D-glucoside) and Ar*–O–*Tr derivatives of resveratroloside (3,5-dihydroxystilben-4′*-O-β-*D-glucoside) and pinostilbenoside (3-methoxy-5-hydroxystilben-4′*-O-β-*D-glucoside) with NaOCl and* t-*BuOCl in the presence of the stable nitroxyl radical TEMPO were studied in various media. It was found that the principal product of pterostilbenoside transformation was its 2,6-dichloroderivative, a part of which was oxidized to form 2,6-dichloropterostilbene glucuronide. Trityl ethers of resveratroloside and pinostilbenoside reacted with the hypochlorites to form mixtures of products.*

Keywords: resveratrol, stilbene glycosides, oxidation, hypochlorites, triphenylmethyl ethers, TEMPO.

Resveratrol (*trans*-3,5,4′-trihydroxystilbene, **1**) is a natural phytoalexin that occurs in several plants, e.g., grapes, peanuts, cranberries, etc. [1–3]. It was discovered that **1** exhibits a broad spectrum of biological activities such as antitumor, antioxidant, anti-inflammatory, cardioprotective, etc. [4]. Its principal metabolites *in vivo* in humans, mice, and rats are glucuronide or sulfonated derivatives [5–8].



1 - 5

1: R = R_1 = R_2 = H; **2:** R = R_2 = H, R_1 = CH_3
3: R = R_1 = H, R_2 = Glc; **4:** R = H, R_1 = CH_3, R_2 = Glc
5: R = R_1 = CH_3, R_2 = Glc

Glycosides of resveratrol and its derivatives also occur in nature. It was discovered that plants of the family Pinaceae are rich sources of stilbenes [9]. For example, bark of Siberian pine (*Pinus sibirica*) contained resveratrol (**1**), its monomethyl ether pinostilbene (**2**), and their 4′-*O*-*β*-D-glucopyranosides resveratroloside (**3**) and pinostilbenoside (**4**) [10–12].

Despite extensive studies of the biological activities of resveratrol and many other stilbenes, the activities of its glycosylated derivatives are little studied. The reactivities of this class of compounds also have not been studied in detail. However, the syntheses of glycosylated derivatives of resveratrol, in particular, its mono- and diglucosides and 4′-glucuronide have been reported [13–15].

Because one of the metabolic pathways of resveratrol *in vivo* is the formation of its glucuronide, the availability of glucuronide derivatives of resveratrol is important for systematic biological investigations.

One method for synthesizing glucuronides is the addition of a protected glucuronide moiety to the aglycon and subsequent removal of the protecting groups. Another method for synthesizing glucuronides that has been more widely employed is selective oxidation of the carbohydrate primary alcohol of the corresponding glucoside by sodium hypochlorite

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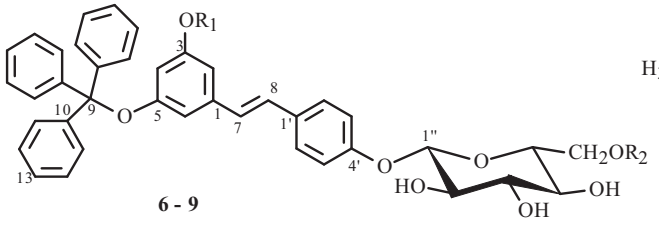
(NaOCl) in the presence of a catalytic amount of a stable nitroxyl radical (TEMPO, etc.). This system was used to synthesize glucuronides from glucosides of various aglycons including those occurring naturally [16–18].

The goal of the present work was to synthesize several derivatives of resveratroloside and pinostilbenoside that were isolated from bark of *P. sibirica* and to study their reactions with NaOCl and *t*-BuOCl in the presence of TEMPO in various media.

Because one of the reagents in the studied reactions was the stable radical TEMPO, which forms H-bonds with phenols or cleaves the H atom from them [19, 20], it became necessary to protect the aromatic hydroxyls of **2** and **3**. Thus, we prepared dimethyl ether **5** (pterostilbenoside) and the Ar–O–Tr ethers of resveratroloside and pinostilbenoside.

The reaction of **3** with CH_3I in refluxing acetone in the presence of K_2CO_3 gave after 4 h according to HPLC an insignificant amount of **4** and only traces of **5**. Apparently the low reactivity of **3** in this instance was due to the low solubilities in acetone of both the starting material and the reaction products. The reaction of **3** or **4** with CH_3I (4 and 2 eq, respectively) in refluxing CH_3CN in the presence of K_2CO_3 formed **5** in 70–80% yield after chromatographic purification. Methylation of the sugar hydroxyls under these conditions was not observed.

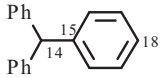
Mixing **3** or **4** with TrCl (2.2 and 1.1 eq, respectively) in CH_3CN and subsequent addition of NEt_3 to the mixture at room temperature gave two reaction products. According to PMR and ^{13}C NMR spectroscopy, not only the aromatic hydroxyls but also the carbohydrate primary OH group were tritylated under these conditions. As a result, **3** produced bis- and tris-trityl derivatives **6** and **7**; **4**, **8** and **9**. Full conversion of the starting materials occurred after 24 h at room temperature. The product ratios from these reactions were ~3:2 for **6** and **7**; ~1:1, for **8** and **9**.

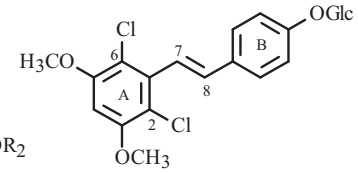


6 - 9

6: R_1 = Tr, R_2 = H; **7:** R_1 = Tr
8: R_1 = CH_3, R_2 = H; **9:** R_1 = CH_3

7, 9: R_2 =





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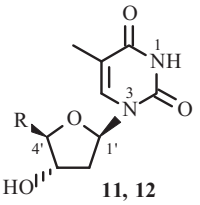
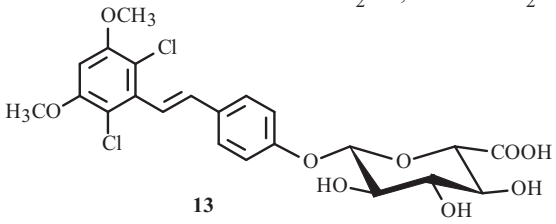


11, 12

11: R = CH_2OH; **12:** R = CO_2H



13

The mole ratio of products **6**:**7** was ~4:1; the yields of **6** and **7** after column chromatography, 75 and 18%, respectively, after treatment of **3** first with NEt_3 (4–6 eq) and then TrCl (2.1 eq). The reaction was stopped after 4.5–5 h at room temperature. The reaction of **4** with TrCl (1.1 eq) under analogous conditions gave **8** and **9** in yields of 73 and 19%, respectively.

The reaction of **5** with NaOCl (3.3 eq) in the presence of TEMPO in *i*-PrOH:H_2O (1:1, v/v) formed only one product according to HPLC. The same product was obtained according to HPLC by treatment of **5** with NaOCl in the presence of *n*-Bu_4NBr (TBAB) and NaBr in EtOAc + sat. aqueous $NaHCO_3$ (1:1) at 0°C. (Use of NaBr should accelerate oxidation of the primary hydroxyl because the hypobromite formed by reaction of NaBr and NaOCl oxidizes TEMPO to the oxonium ion more rapidly than NaOCl [21].) Also, treatment of **5** with NaOCl in the presence of *n*-Bu_4NF in CH_2Cl_2 + sat. aqueous $NaHCO_3$ at room temperature proceeded analogously (Table 1).

Resonances for the sugar C atoms in the ^{13}C NMR spectrum of the resulting product agreed fully with those of the starting material [anomeric C atom with chemical shift (CS) 100.4 ppm; four doublets, 70–80; one triplet, 60.8]. Resonances in the range 170–180 ppm that would indicate a carboxylic acid had formed were missing in the ^{13}C NMR spectrum. The set of resonances for the aglycon changed in the ^{13}C NMR spectrum of this product. Doublets with CS 104.3 ppm corresponding to C-2 and C-6 of the starting material disappeared. The singlet with CS 160.7 corresponding to C-3 and C-5 shifted to stronger field to CS 154.4. The CS of C-4 (97.3) in the reaction product also differed from that in the starting material (99.7). Resonances of the C atoms of the double bond, which were situated between the aromatic rings, also shifted relative to those in the starting material. The resonance with the smaller CS (C-7, 126.8) shifted to stronger field (121.0); with the larger CS (C-8, 128.6), to weaker field (136.1). The CSs of C atoms in ring B were practically unchanged. This indicated that only the structure of ring A changed although its symmetry relative to the axis passing through C-1 and C-4 was not destroyed.

TABLE 1. Reaction Conditions for Oxidation of Substrates (**5**, **6**, **8**, **11**), Reagent Ratios, and Formed Products

Oxidative system and reaction conditions	Product
5	
3.3 eq NaOCl, 0.2 eq TEMPO, *i*-PrOH + H_2O (1:1)	**10**
4 eq NaOCl, 0.01 eq TEMPO, 0.08 eq TBAB, 0.2 eq NaBr; EtOAc + sat. $NaHCO_3$ (1:1), 0°C	**10**
2 eq NaOCl, 0.03 eq TEMPO, 0.15 eq TBAF; CH_2Cl_2 + sat. $NaHCO_3$ (1:1)	**10**
5.5 eq NaOCl, 0.15 eq TEMPO, 0.07 eq TBAB, 0.3 eq NaBr; CH_2Cl_2 + sat. $NaHCO_3$ (1:1), 0°C	**10** + **13** (~1:1.5)
4 eq NaOCl, 0.1 eq TEMPO, 0.07 eq TBAB, 0.2 eq NaBr; CH_2Cl_2 + sat. $NaHCO_3$ (1:1), 0°C	**10** + **13** (~1:1)
6 eq NaOCl, 0.15 eq TEMPO, 1.1 eq $PhCH_2(CH_3)_3NCl$; CH_2Cl_2 + sat. $NaHCO_3$ (1:1)	**10** + **13** (~1:4)
2.2 eq *t*-BuOCl, 0.1 eq TEMPO; CH_2Cl_2 + sat. $NaHCO_3$ (1:1)	**10** + **13** (~20:1)
5 eq *t*-BuOCl, 0.1 eq TEMPO; sat. $NaHCO_3$	**10**
5 eq *t*-BuOCl, 0.05 eq TEMPO, 0.1 eq TBAB, 0.1 eq NaBr; CH_2Cl_2 + sat. $NaHCO_3$ (1:1)	**10** + **13** (~2:1)
6	
2 eq NaOCl, 0.1 eq TEMPO, 0.25 eq TBAF; CH_2Cl_2 + sat. $NaHCO_3$ (1:1)	Sugar resonances in ^{13}C NMR spectra corresponded to glucoside; stilbene moiety was chlorinated.
20 eq NaOCl, 0.1 eq TEMPO, 0.25 eq TBAB, 0.1 eq NaBr; CH_2Cl_2 + sat. $NaHCO_3$ (1:1), 0°C	
8	
2.2 eq NaOCl, 0.06 eq TEMPO, 0.3 eq TBAF; CH_2Cl_2 + sat. $NaHCO_3$ (1:1)	
11	
5.5 eq NaOCl, 0.1 eq TEMPO, 0.07 eq TBAB; CH_2Cl_2 + sat. $NaHCO_3$ (1:1), 0°C	**12**
5 eq NaOCl, 0.1 eq TEMPO, 0.1 eq $PhCH_2(CH_3)_3NCl$; CH_2Cl_2 + sat. $NaHCO_3$ (1:1)	

Analysis of the reaction product by HPLC/MS (electrospray ionization) detected in positive-ion mode an adduct with Na^+ of masses (*m*/*z*) 509.075 and 511.070; in negative-ion mode, an adduct with Cl^- with a base peak at 523.051. The results agreed unambiguously with empirical formula $C_{22}H_{24}Cl_2O_8$ for the product. The calculated masses (*m*/*z*) were for [$C_{22}H_{24}Cl_2O_8$ + Na^+], 509.074 and 511.072; for [$C_{22}H_{24}Cl_2O_8$ + Cl^-], 523.052 taking into account the isotopic distribution of Cl. The relative intensities of the calculated isotopic peaks agreed well with those observed experimentally.

By comparing the empirical formulas of the product ($C_{22}H_{24}Cl_2O_8$) and the starting material ($C_{22}H_{26}O_8$) and taking into account the PMR and ^{13}C NMR spectra, it could be confirmed that electrophilic substitution of two H atoms by Cl atoms had occurred during the course of the reaction. This occurred at the 2- and 6-positions of aromatic ring A (taking into account the ^{13}C NMR spectra) to form **10**.

The fact that oxidation of the glucose primary alcohol that usually occurs under these conditions was not observed in these reactions was surprising. Therefore, we decided to study the oxidizing capacity of the system using oxidation of a sugar bonded to thymidine (**11**) as an example.

Addition of NaOCl (~5.5 eq) to a solution of **11** in CH_2Cl_2 + sat. $NaHCO_3$ in the presence of TEMPO, TBAB, and NaBr at 0°C resulted in practically complete conversion of the substrate to form according to HPLC only one reaction product. Its ^{13}C NMR spectrum contained a singlet with CS 176.6 ppm and lacked the triplet at 62 ppm that corresponded to the CH_2OH group of the deoxyribose moiety. Resonances of the other sugar C atoms were shifted relative to those of the starting material. However, their multiplicity remained the same. The CSs of resonances corresponding to the thymine aglycon were practically unchanged. Their multiplicity remained the same. All this indicated that the primary hydroxyl of deoxyribose was oxidized during the course of the reaction to form carboxylic acid **12**. The ^{13}C NMR spectra of the oxidation product were similar to those published [22–24], for which the synthesis was carried out using oxidation of thymidine by oxygen in the presence of PtO_2.

Product **12** was also prepared by treatment of **11** with NaOCl in CH_2Cl_2 + sat. $NaHCO_3$ in the presence of $PhCH_2(CH_3)_3NCl$ and a catalytic amount of TEMPO. The reaction was carried out without NaBr at room temperature.

Two products with very similar retention times in reversed-phase HPLC were formed by treatment of **5** with NaOCl (5.5 eq) in the presence of TEMPO, NaBr, and TBAB in CH_2Cl_2 + sat. $NaHCO_3$ at 0°C. The CSs and multiplicity of resonances in the ^{13}C NMR spectrum of the reaction mixture indicated that an aromatic ring of the starting material was chlorinated during the reaction. However, a double set of resonances was observed in the range 70–80 ppm that corresponded to the glycoside moiety. In addition to doublets for C-2″–C-5″ of the glucose, doublets with CSs 71.42, 73.01, 75.49, and 75.83 with approximately the same intensities and about 1.5 times as strong as the glucoside resonances were also observed. The spectrum also showed a doublet at 99.78 that was characteristic of an anomeric C atom and a singlet at 170.19.

The PMR spectrum exhibited in the range 4.9–5.2 ppm a doublet at 4.89 (J = 7.3 Hz) that corresponded to a glucose anomeric proton and a doublet at 5.09 (J = 7.3 Hz), the intensity of which was about 1.7 times greater than the first. By comparing the results, we concluded that oxidation of a certain amount of the produced dichloro-derivative **10** had apparently occurred during the course of the reaction to form glucuronide **13**. Their ratio in the mixture was about 1:1.5–1.7. An attempt to separate **10** and **13** by column chromatography over silica gel was unsuccessful because **13** was apparently irreversibly absorbed on the SiO_2.

The amount of the formed glucuronide would be smaller if a smaller amount of oxidant and NaBr were used. However, addition of a larger amount of NaOCl would not increase significantly the amount of **13**.

The largest amount of **13** in the mixture with **10** was observed in an experiment using the phase-transfer catalyst $PhCH_2(CH_3)_3NCl$ and NaOCl (~6 eq). Doublets in the ^{13}C NMR spectrum in the range 70–80 ppm corresponded to C-2″–C-5″ of the glucuronide carbohydrate and were about four times stronger than the resonances of the glucoside. Using a larger amount of oxidant did not increase the amount of **13**.

Chlorination of aromatic substrates during their reaction with NaOCl was reported earlier [25, 26]. Alkylhypochlorites, in particular *t*-BuOCl, were used as the oxidants in several instances in order to avoid such processes. We also studied the reaction of the synthesized resveratroloside derivatives with *t*-BuOCl.

Treatment of **5** (2.2–3 eq) with *t*-BuOCl in CH_2Cl_2 + sat. $NaHCO_3$ in the presence of TEMPO without quaternary ammonium salts gave dichloride **10**. (The ^{13}C NMR spectrum contained resonances with CS 112 ppm.) The ^{13}C NMR spectrum also showed weak resonances with CSs 71.4, 73.0, 75.5, and 75.8 that were consistent with the presence of **13** in the mixture. Only dichloro-derivative **10** was formed if this reaction was carried out without an organic solvent in sat. $NaHCO_3$ solution.

Treatment of **5** with an excess of *t*-BuOCl in CH_2Cl_2 + sat. $NaHCO_3$ in the presence of TEMPO and NaBr formed a mixture of **10** and **13** in a ~2:1 ratio.

Treatment of tritylated derivatives **6** and **8** with NaOCl and with *t*-BuOCl in CH_2Cl_2 + sat. $NaHCO_3$ in the presence of various quaternary ammonium salts also did not lead to complete oxidation of the primary alcohol of the substrate sugar moiety, regardless of whether a quaternary ammonium salt or NaBr was used in the reaction. IR spectra of the reaction products either did not contain in the range 1750–1690 cm^{-1} an absorption band characteristic of a carboxylic acid or the band was very weak. The ^{13}C NMR spectrum exhibited singlets with CS ~112 ppm that indicated the stilbene aromatic ring was chlorinated. In any case, selective and complete oxidation of the sugar could not be achieved in these reactions.

Thus, several derivatives of resveratroloside and pinostilbenoside were synthesized. Their reactions with NaOCl and *t*-BuOCl in the presence of the stable nitroxyl radical TEMPO in various solvents were studied. The principal product from reaction of dimethyl resveratroloside derivative **5** with NaOCl and *t*-BuOCl was 2,6-dichloro-3,5-dimethoxystilben-4′-*O*-β-D-glucopyranoside (**10**). The glucoside moiety was partially oxidized to the glucuronide. However, the amount of formed glucuronide depended on the amount of oxidant. Reactions of Ar–O–Tr derivatives of resveratroloside and pinostilbenoside with NaOCl and *t*-BuOCl formed mixtures of chlorination products of the stilbene substrates.

EXPERIMENTAL

HPLC chromatographic analysis was carried out on a Milikhrom A-02 instrument (ZAO Institute of Chromatography EkoNova, Novosibirsk) using a column (2 × 75 mm) packed with reversed-phase sorbent Prontosil-120-5-C18 AQ (5 μm) thermostatted at 35°C. Gradient elution by trifluoroacetic acid solution (0.1%) and MeOH (100%) at flow rate 150 μL/min was used.

HPLC/MS analysis was performed in an Agilent chromatograph with a micrOTOF-Q hybrid quadrupole time-of-flight mass spectrometer (Bruker) using electrospray ionization at atmospheric pressure (API-ES) in positive-ion and negative-ion modes in the range *m*/*z* 100–1500. The drying gas was N_2 at 4 L/min, 220°C, and 1.0 bar. A solution of the compound in MeOH (~1 mg/mL) was fed into the spray chamber at flow rate 180 μL/h using a syringe pump.

t-Butylhypochlorite was synthesized by the literature method [27]. Household bleach with NaOCl mass concentration 5.0–5.2% was used. Solvents were distilled before use. Glycosides **2** and **3** were isolated from bark of *P. sibirica* using a procedure developed by us that was based on a patent [12]. Melting points were measured on a FP900 instrument (Mettler Toledo).

PMR and ^{13}C NMR spectra were recorded in $CDCl_3$ and DMSO-d_6 on Bruker AV-300 (operating frequencies 300.13 MHz for ^1H and 75.47 MHz for ^{13}C), AM-400 (400.13 MHz, ^1H; 100.61 MHz, ^{13}C), and DRX-500 (500.13 MHz, ^1H; 125.76 MHz, ^{13}C) spectrometers (Bruker). The internal standards were resonances of $CD(H)Cl_3$ (δ_H 7.24 ppm, δ_C 76.90 ppm) and DMSO (δ_H 2.49 ppm, δ_C 39.50 ppm). The structures of the compounds were established using NMR methods based on analysis of PMR spectra, in several instances ^1H–^1H double resonance spectra, and ^{13}C NMR spectra recorded in JMOD mode. Two-dimensional heteronuclear ^{13}C–^1H correlation spectra for direct (C–H COSY, $^1J_{C,H}$ = 160 Hz) and through-space (COLOC, $^1J_{C,H}$ = 10 Hz) spin–spin coupling constants were recorded.

Extraction and Isolation. Ground bark of *P. sibirica* (492.4 g) was extracted with EtOH (95%) in a Soxhlet apparatus for 40 h. The EtOH extract was filtered. The solvent was vacuum distilled to afford an extract (127.4 g) that was worked up with methyl-*t*-butylether (MTBE, 1200 mL) by stirring at room temperature for 5 h and filtering. The filtrate was discarded. The MTBE extraction was repeated twice (280 mL each) to afford an ether-insoluble solid (61.3 g) that was separated by chromatography over SiO_2 (5 g substance per 220 g SiO_2, $CHCl_3$:EtOH eluent, 9:1→0:10) to afford resveratroloside (**3**, 1.2 g) and pinostilbenoside (**4**, 1.7 g). The spectral characteristics of the isolated compounds agreed with those reported [12, 28].

Methylation of 3 and 4. Resveratroloside (**3**, 2.00 g, 5.1 mmol) in CH_3CN (100 mL) was treated with K_2CO_3 (4.22 g, 30.5 mmol) and CH_3I (1.90 mL, 4.35 g, 30.6 mmol). The mixture was refluxed with a $CaCl_2$ trap for 24 h and filtered. The solvent was vacuum distilled. The product was chromatographed over a column of SiO_2 (600 mg substance per 30 g SiO_2, $CHCl_3$:EtOH eluent, 10:0.1→0:0.5) to afford **5** (1.50 g, 3.6 mmol, 70% yield).

The reaction of pinostilbenoside (**4**, 1.50 g, 3.7 mmol) with CH_3I (1.38 mL, 3.16 g, 22.2 mmol) and K_2CO_3 (3.0 g, 21.7 mmol) under analogous conditions formed **5** (1.24 g, 3.0 mmol, 80% yield).

***trans*-3,5-Dimethoxystilben-4′-*O*-β-D-glucopyranoside (5)**, mp 90.7°C.

PMR spectrum (DMSO-d_6, δ, ppm, J/Hz): 3.10–3.52 (5H, m, H-2″, H-3″, H-4″, H-5″, H-6″a); 3.65–3.73 (1H, m, H-6″b); 3.76 (6H, s, 2 × OCH_3); 4.62 (1H, dd, $J_{OH,6''a}$ = 5.9; $J_{OH,6''b}$ = 5.1, $CH_2O\underline{H}$-6″); 4.88 (1H, d, $J_{1'',2''}$ = 7.3, H-1″); 5.04 (1H, d, J = 5.1, CHO<u>H</u>-4″); 5.10 (1H, d, J = 4.1, CHO<u>H</u>-3″); 5.34 (1H, d, J = 4.5, CHO<u>H</u>-2″); 6.38 (1H, br.t, J = 2.0, H-4); 6.73 (2H, d, J = 2.0, H-2, H-6); 7.02 (2H, d, J = 8.7, H-3′, H-5′); 7.04 (1H, d, $J_{7,8}$ = 16.4, H-7); 7.20 (1H, d, $J_{8,7}$ = 16.4, H-8); 7.52 (2H, d, J = 8.7, H-2′, H-6′).

^{13}C NMR spectrum (DMSO-d_6, δ, ppm): 55.27 (q, 2 × OCH_3); 60.79 (t, C-6″); 69.81 (d, C-4″); 73.33 (d, C-2″); 76.68 (d, C-3″); 77.12 (d, C-5″); 99.66 (d, C-4); 100.35 (d, C-1″); 104.33 (d, C-2, C-6); 116.53 (d, C-3′, C-5′); 126.77 (d, C-7); 127.77 (d, C-2′, C-6′); 128.55 (d, C-8); 130.80 (s, C-1′); 139.44 (s, C-1); 157.22 (s, C-4′); 160.74 (s, C-3, C-5).

ESI-MS: found for [$C_{22}H_{26}O_8 + Na^+$], 441.150; calc. 441.152; found for [$C_{22}H_{26}O_8 + Cl^-$], 453.129; calc. 453.132.

Tritylation of Resveratroloside (3). Compound **3** (2 g, 5 mmol) in CH_3CN (150 mL) was treated with NEt_3 (1.4 mL, 1.0 g, 10 mmol), stirred for 20–30 min, treated with TrCl in portions of 0.3–0.4 g (2.78 g, 10 mmol), and stirred for 4.5 h at room temperature. The solvent was vacuum distilled. The solid was chromatographed over SiO_2 (1 g of substance per 20 g SiO_2, $CHCl_3$:EtOH eluent, 10:0→8:2) to afford **6** (3.37 g, 3.85 mmol, 75% yield) and **7** (1.04 g, 0.93 mmol, 18% yield).

***trans*-3,5-Bis(triphenylmethyloxy)stilben-4′-*O*-β-D-glucopyranoside (6)**, mp 97.4°C.

PMR spectrum (DMSO-d_6, δ, ppm, J/Hz): 3.19 (1H, ddd, J = 9.5, 8.5, 5.0, H-4″); 3.26 (1H, ddd, $J_{2'',3''}$ = 9.0, $J_{2'',1''}$ = 7.4, J = 4.8, H-2″); 3.30 (1H, ddd, J = 9.0, 8.5, 4.2, H-3″); 3.32–3.37 (1H, m, H-5″); 3.49 (1H, ddd, J = 11.7, 5.6, 5.6, H-6″a); 3.72 (1H, ddd, J = 11.7, 5.1, 2.0, H-6″b); 4.52 (1H, dd, J = 5.6, 5.1, $CH_2O\underline{H}$-6″); 4.86 (1H, d, J = 7.4, H-1″); 4.96 (1H, d, J = 5.0, CHO<u>H</u>-4″); 5.01 (1H, d, J = 4.2, CHO<u>H</u>-3″); 5.25 (1H, d, J = 4.8, CHO<u>H</u>-2″); 6.08 (1H, t, J = 2.1, H-4); 6.33 (2H, d, J = 2.1, H-2, H-6); 6.62 (1H, d, $J_{7,8}$ = 16.3, H-7), 6.65 (1H, d, $J_{8,7}$ = 16.3, H-8); 6.98 (2H, d, J = 8.8, H-3′, H-5′); 7.12–7.18 (12H, m, H-11); 7.19–7.27 (18H, m, H-12, H-13); 7.36 (2H, d, J_2 = 8.8, H-2′, H-6′).

^{13}C NMR spectrum (DMSO-d_6, δ, ppm): 60.74 (t, C-6″); 69.77 (d, C-4″); 73.21 (d, C-2″); 76.60 (d, C-3″); 77.00 (d, C-5″); 89.89 (s, 2 × C-9); 100.37 (d, C-1″); 113.52 (d, C-4); 113.61 (d, C-2, C-6); 116.43 (d, C-3′, C-5′); 125.91 (d, C-7); 126.98 (d, 6 × C-13); 127.47 (d, C-2′, C-6′); 127.59 (d, 12 × C-12); 127.99 (d, C-8); 128.19 (d, 12 × C-11); 130.48 (s, C-1′); 137.47 (s, C-1); 143.51 (s, 6 × C-10); 155.60 (s, C-3, C-5); 157.06 (s, C-4′).

ESI-MS: found for [$C_{58}H_{50}O_8 + Na^+$], 897.334; calcd 897.340; found for [$C_{58}H_{50}O_8 + Cl^-$], 909.323; calcd 909.320.

***trans*-3,5,6″-Tris(triphenylmethyloxy)stilben-4′-*O*-β-D-glucopyranoside (7)**, mp 133.4°C.

PMR spectrum ($CDCl_3$, δ, ppm J/Hz): 3.27–3.70 (6H, m, H-2″, H-3″, H-4″, H-5″, CH_2-6″); 4.11, 4.47, 4.95 (1H each, all br.s, 3 × OH); 4.87 (1H, d, $J_{1'',2''}$ = 7.5, H-1″); 6.28 (2H, s, H-2, H-6); 6.48 (1H, s, H-4); 7.08 (2H, d, $J_{3',2'} = J_{5',6'}$ = 8.8, H-3′, H-5′); 7.14–7.50 (m, H-8 and other protons).

^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 63.53 (t, C-6″); 70.73 (d, C-4″); 73.21 (d, C-2″); 75.04 (d, C-3″); 76.54 (d, C-5″); 86.68 (s, C-14); 90.63 (s, 2 × C-9); 100.46 (d, C-1″); 114.41 (d, C-2, C-6); 114.80 (d, C-4); 117.01 (d, C-3′, C-5′);

126.88 (d, 6 × C-13); 126.96 (d, 3 × C-18); 127.41 (d, C-7); 127.50 (d, 12 × C-12); 127.63 (d, C-2′, C-6′); 127.75 (d, 6 × C-17); 128.53 (d, C-8); 128.61 (d, 6 × C-16); 128.77 (d, 12 × C-11); 131.80 (s, C-1′); 137.36 (s, C-1); 143.69 (s, 3 × C-15); 143.91 (s, 6 × C-10); 156.11 (s, C-3, C-5); 156.49 (s, C-4′).

ESI-MS: found for $[C_{77}H_{64}O_8 + Cl^-]$, 1151.438; calcd 1151.430.

Tritylation of Pinostilbenoside (4). Compound **4** (2 g, 4.95 mmol) in CH_3CN (250 mL) was treated with NEt_3 (1 mL, 0.7 g, 7 mmol), stirred for 20–30 min, treated with tritylchloride (1.4 g, 4.9 mmol), and stirred for 4.5 h at room temperature. The solvent was vacuum distilled. The product was purified by flash chromatography over SiO_2 (1 g of substance per 20 g SiO_2; eluent $CHCl_3$:EtOH, 10:0→5:5) to afford **8** (2.3 g, 3.61 mmol, 73% yield) and **9** (0.8 g, 0.94 mmol, 19% yield).

***trans*-3-Methoxy-5-triphenylmethyloxystilben-4′-*O*-β-D-glucopyranoside (8)**, mp 112.9°C.

PMR spectrum (DMSO-d_6, δ, ppm, J/Hz): 3.08–3.58 (5H, m, H-2″, H-3″, H-4″, H-5″, H-6″a); 3.70 (1H, br.dd, J = 11.7, 5.2, H-6″b); 3.49 (3H, s, OCH_3); 4.61 (1H, dd, J = 5.6, 5.2, $CH_2O\underline{H}$-6″); 4.86 (1H, d, $J_{1″,2″}$ = 7.3, H-1″); 5.05 (1H, d, J = 4.9, CHO<u>H</u>-4″); 5.12 (1H, d, J = 4.0, CHO<u>H</u>-3″); 5.34 (1H, d, J = 4.8, CHO<u>H</u>-2″); 6.02 (1H, br.dd, J = 2.0, H-4); 6.53 and 6.57 (2H, both br.s, H-2, H-6); 6.84 (1H, d, $J_{7,8}$ = 16.4, H-7); 6.89 (1H, d, $J_{8,7}$ = 16.4, H-8); 7.00 (2H, d, J = 8.6, H-3′, H-5′); 7.16–7.53 (17H, m, other protons).

^{13}C NMR spectrum (DMSO-d_6, δ, ppm): 55.01 (q, OCH_3); 60.77 (t, C-6″); 69.79 (d, C-4″); 73.31 (d, C-2″); 76.66 (d, C-3″); 77.12 (d, C-5″); 89.55 (c, C-9); 100.33 (d, C-1″); 104.64 (d, C-2); 105.62 (d, C-4); 110.66 (d, C-6); 116.50 (d, C-3′, C-5′); 126.50 (d, C-7); 127.40 (d, 3 × C-13); 127.73 (d, C-2′, C-6′); 128.03 (d, 6 × C-12); 128.42 (d, C-8, 6 × C-11); 130.62 (s, C-1′); 138.52 (s, C-1); 143.74 (s, 3 × C-10); 156.92, 157.20 (both s, C-4′, C-5); 159.46 (s, C-3).

ESI-MS: found for $[C_{40}H_{38}O_8 + Na^+]$, 669.245; calcd 669.246; found for $[C_{40}H_{38}O_8 + Cl^-]$, 681.227; calcd 681.226.

***trans*-3-Methoxy-5,6″-bis(triphenylmethyloxy)stilben-4′-*O*-β-D-glucopyranoside (9)**, mp 113°C (dec).

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 3.21–3.73 (6H, m, H-2″, H-3″, H-4″, H-5″, CH_2-6″); 3.54 (3H, s, OCH_3); 4.00, 4.43, 5.16 (1H each, all br.s, 3 × OH); 4.85 (1H, d, $J_{1″,2″}$ = 7.3, H-1″); 6.19 (1H, br.dd, J = 2.0, H-4); 6.50 and 6.53 (1H each, both br.s, H-2, H-6); 6.66 (1H, d, $J_{7,8}$ = 16.4, H-7); 6.72 (1H, d, $J_{8,7}$ = 16.4, H-8); 7.07 (2H, d, J = 8.5, H-3′, H-5′); 7.11–7.56 (m, H-2′, H-6′, other protons).

^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 55.07 (q, OCH_3); 63.53 (t, C-6″); 70.80 (d, C-4″); 73.18 (d, C-2″); 74.93 (d, C-3″); 76.40 (d, C-5″); 86.72 (s, C-14); 90.51 (s, C-9); 100.27 (d, C-1″); 105.35 (d, C-2); 106.20 (d, C-4); 111.68 (d, C-6); 117.14 (d, C-3′, C-5′); 127.02, 127.17, 127.60, 127.68, 127.81, 127.87, 128.10 (all d, C-2′, C-5′, C-7, C-8, 6 × C-12, 3 × C-13, 6 × C-17, 3 × C-18); 128.62 and 128.87 (both d, 6 × C-11, 6 × C-16); 131.81 (s, C-1′); 138.27 (s, C-1); 143.69 and 144.01 (both s, 3 × C-10, 3 × C-15); 156.46 (s, C-4′); 157.50 (s, C-5); 159.65 (s, C-3).

ESI-MS: found for $[C_{59}H_{52}O_8 + Na^+]$, 911.352; calcd 911.355; found for $[C_{59}H_{52}O_8 + Cl^-]$, 932.341; calcd 923.336.

General Method for Oxidation. A solution of substrate (0.01–0.05 M), TEMPO, quaternary ammonium salt, and NaBr (if it was used) in an organic solvent was treated with an equivalent volume of saturated $NaHCO_3$ solution, stirred and cooled if necessary to 0°C, stirred vigorously and treated dropwise with a mixture of NaOCl solution and an equivalent volume of saturated $NaHCO_3$ solution that was cooled beforehand if necessary. If *t*-BuOCl was used as the oxidant, it was added to the substrate to be oxidized as a solution (5–10%) in an organic solvent. After the whole amount of oxidant was added, the mixture was stirred at the given temperature for 1.5–2 h and then analyzed by HPLC.

After the starting material was completely converted, the mixture was treated with EtOH or MeOH (0.5–1 mL) or several milliliters of Na_2SO_3 solution (10%) to remove the excess of oxidant. The aqueous layer was separated and washed with used organic solvent. The organic extracts were combined, washed with H_2O, and dried over $MgSO_4$. The solvent was vacuum distilled.

***trans*-2,6-Dichloro-3,5-dimethoxystilben-4′-*O*-β-D-glucopyranoside (10)**, mp 92°C (dec).

PMR spectrum (DMSO-d_6, δ, ppm, J/Hz): 3.20 (1H, dd, J = 9.5, 8.3, H-4″); 3.27 (1H, dd, J = 9.0, 7.4, H-2″); 3.31 (1H, dd, J = 9.0, 8.3, H-3″); 3.35 (1H, ddd, J = 9.5, 5.7, 2.1, H-5″); 3.50 (1H, dd, J = 11.8, 5.7, H-6″a); 3.71 (1H, dd, J = 11.8, 2.1, H-6″b); 3.92 (6H, s, 2 × OCH_3); 4.90 (1H, d, $J_{1″,2″}$ = 7.4, H-1″); 6.86 (1H, s, H-4); 6.95 (1H, d, $J_{7,8}$ = 16.6, H-7), 6.97 (1H, d, $J_{8,7}$ = 16.6, H-8); 7.06 (2H, d, J = 8.8, H-3′, H-5′); 7.53 (2H, d, J = 8.8, H-2′, H-6′).

^{13}C NMR spectrum (DMSO-d_6, δ, ppm): 56.65 (q, 2 × OCH_3); 60.78 (t, C-6″); 69.82 (d, C-4″); 73.26 (d, C-2″); 76.63 (d, C-3″); 77.05 (d, C-5″); 97.29 (d, C-4); 100.37 (d, C-1″); 112.72 (s, C-2, C-6); 116.63 (d, C-3′, C-5′); 120.96 (d, C-7); 127.83 (d, C-2′, C-6′); 130.03 (s, C-1′); 135.57 (s, C-1); 136.13 (d, C-8); 154.39 (s, C-3, C-5); 157.65 (s, C-4′).

ESI-MS: found for $[C_{22}H_{24}Cl_2O_8 + Na^+]$, 509.075; calcd 509.074; found for $[C_{22}H_{24}Cl_2O_8 + Cl^-]$, 523.051; calcd 523.052.

***trans*-2,6-Dichloro-3,5-dimethoxystilben-4′-*O*-β-D-glucuronide (13)** was characterized as a mixture with **10** (**10**:**13** ratio, ~1:4).

PMR spectrum (DMSO-d_6, δ, ppm, J/Hz) (resonances of the following protons could be identified): 3.92 (6H, s, $2 \times OCH_3$); 5.09 (1H, d, $J_{1'',2''} = 7.3$, H-1′); 6.85 (1H, s, H-4); 7.04 (2H, d, J = 8.8, H-3′, H-5′); 7.55 (2H, d, J = 8.8, H-2′, H-6′). Resonances of other protons overlapped resonances of **10** and appeared in the ranges 3.10–3.85 ppm (H-2″, H-3″, H-4″, H-5″) and 6.78–7.00 ppm (H-7, H-8).

^{13}C NMR spectrum (DMSO-d_6, δ, ppm): 56.73 (q, $2 \times OCH_3$); 71.43, 73.01, 75.49, 75.83 (d, C-2″, C-3″, C-4″, C-5″); 97.09 (d, C-4); 99.78 (d, C-1″); 112.58 (s, C-2, C-6); 116.52 (d, C-3′, C-5′); 121.17 (d, C-7); 128.03 (d, C-2′, C-6′); 130.22 (s, C-1′); 135.66 (s, C-1); 135.92 (d, C-8); 154.45 (s, C-3, C-5); 157.17 (s, C-4′); 170.51 (s, C-6″).

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