Isolation, Synthesis, and Antiplatelet Aggregation Activity of Resveratrol 3-*O*-*β*-D-Glucopyranoside and Related Compounds†

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Resveratrol 3-*O*-*β*-D-glucopyranoside (**1**) has been isolated from the seeds of *Erythrophleum lasianthum* (Caesalpinioidae, Leguminosae), a South African plant used in traditional medicine, and has shown antiplatelet aggregation activity. The synthesis of **1**, related hydroxystilbenes, and their glucosides has been undertaken to provide larger quantities, for further biological evaluation, and has been accomplished via Wittig reactions followed by glucosylation under phase transfer catalysis.

Infusions of different parts of *Erythrophleum lasianthum* Corbishley (Caesalpinioidae, Leguminosae), a South African plant, widely used both as a medicinal plant and a poison, are reported to produce digitalis-like effects on the heart.[1] During the search for the substances responsible for the toxicity of *E. lasianthum*, we isolated two diterpene alkaloids and a phenolic glucoside (**1**) (resveratrol 3-*O*-*β*-D-glucopyranoside).[2] The cassaine type diterpene alkaloids have been found to be active on heart motility with a digitalis-like mechanism;[3,4] resveratrol 3-*O*-*β*-D-glucopyranoside (**1**, Figure 1) showed antiplatelet aggregation activity.[5] The corresponding aglycon resveratrol, isolated from different sources, has also shown antiplatelet aggregation activity[6,7] as well as coronary vasodilator action,[8] antileukemic,[9] antifungal,[10] and protein−tyrosine kinase inhibitory action.[11] Other dihydrostilbene compounds, isolated from natural sources, have been reported as antiplatelet aggregation agents.[12] Since these compounds are available in small amounts from natural sources, the synthesis of **1** and related hydroxystilbenes and their glucosides has been undertaken to provide larger quantities for further biological evaluation. In this paper the results obtained in the evaluation of the antiplatelet aggregation activity of the natural and synthetic compounds are reported.

Results and Discussion

E. lasianthum Corbishley (Caesalpinoideae, Leguminosae) is a large tree widely used by Zulu people in medicine and magic.[1] Detailed chemical investigation of the poisonous seeds yielded two diterpene alkaloids, namely 3-hydroxynorerythrosuamine and its 3-*O*-*β*-D-glucopyranoside, which have been found to possess a positive inotropic effect and inhibit the Na^+,K^+-ATPase.[2−4]

A modified extraction procedure of the seeds yielded **1** which was characterized as resveratrol 3-*O*-*β*-D-glucopyranoside by spectroscopic evidence and by comparison with literature data.[10,13]

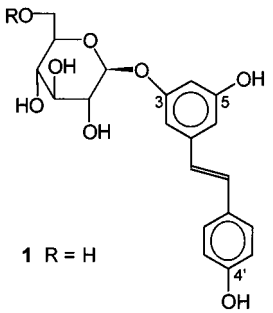

Figure 1. Chemical structure and atom numbering scheme of resveratrol 3-*O*-*β*-D-glucopyranoside.

The stilbene skeleton of (*E*)- and (*Z*)-resveratrol has been efficiently achieved by a Wittig reaction between the phosphonium salt of the commercially available 4-methoxybenzyl chloride and 3,5-bis[(*tert*-butyldimethylsilyl)oxy]benzaldehyde (Scheme 1), followed by desilylation with tetrabutylammonium fluoride.[14,15]

Protection of the hydroxyl group at position 4′ as methyl ether had the advantage that a methoxy group at the 4′-position is present in several natural bioactive compounds with a stilbene skeleton.[16,17] The Wittig product, obtained in 98% yields as a 2.3:1 mixture of the *Z*/*E* isomers **2b** and **2a**, was directly desilylated with tetrabutylammonium fluoride to afford **3a** and **3b**, which were purified by crystallization or flash chromatography.[18]

The glucosylation, which can be troublesome with phenols because of the very low reactivity of the phenolic moiety as a glycosyl acceptor, was tested under a variety of experimental conditions. Aqueous bases under phase transfer catalysis gave the best results in terms of convenience (use of a commercially available sugar) and yield as reported for the synthesis of **4a** (Scheme 2) which was obtained in 32% yield from **3a**, accompanied by a small amount of the corresponding diglucoside (13%) and unreacted aglycon (20%).[15] Treatment of **4a** with a 7.5/1 molar ratio of sodium thioethoxide in dimethylformamide[19,20] afforded resveratrol 3-*O*-*β*-D-glucopyranoside (**1**), identical in all respects to an authentic isolated sample.[21]

The same sequence of reactions described above was applied to the *cis*-aglycon (**3b**) to prepare a series of *cis* derivatives and study the influence of the double bond

† This paper is dedicated to the memory of Prof. G. Jommi.

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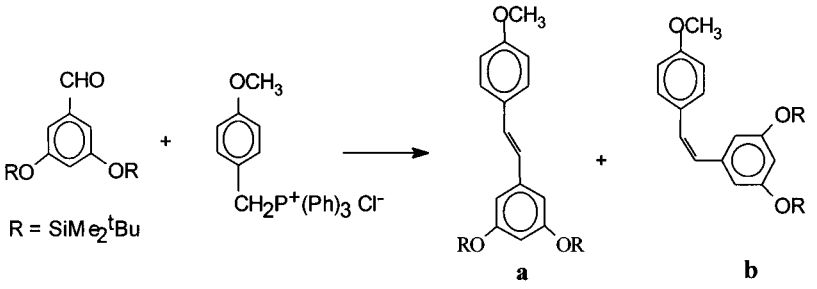
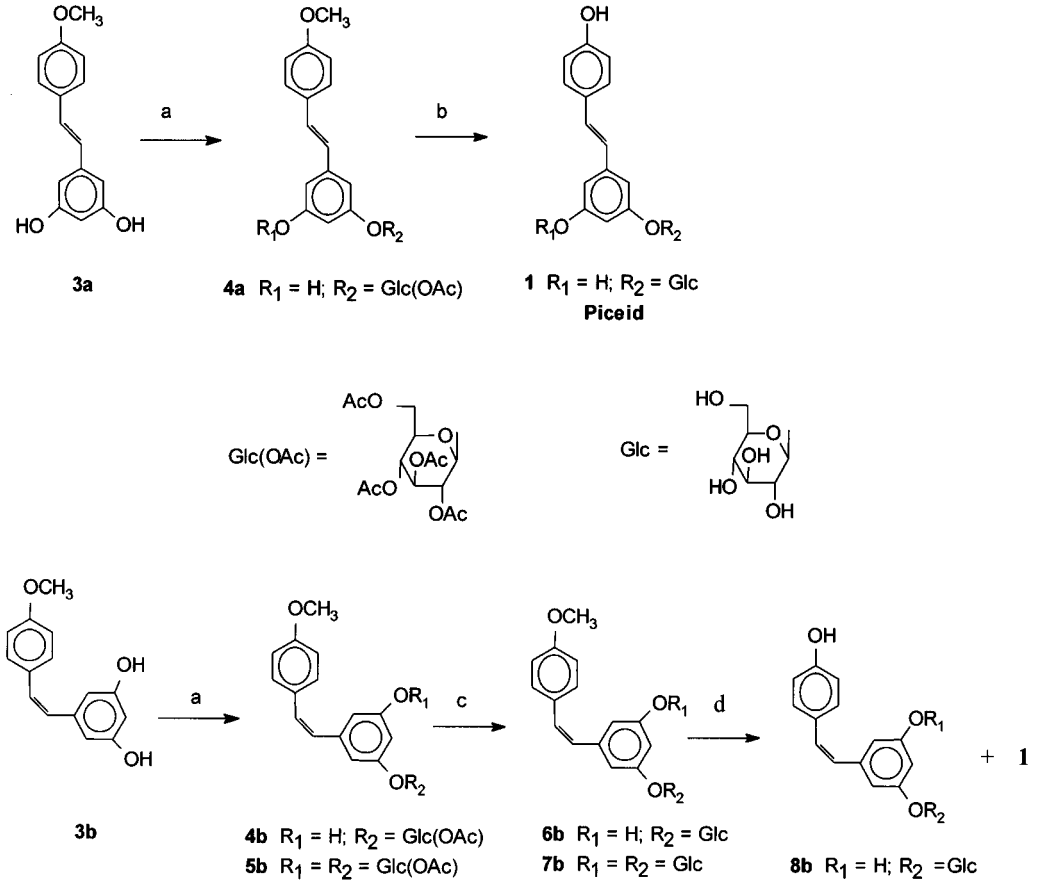
Scheme 1



Scheme 2[a]



[a] (a) $Et_3(PhCH_2)N^+Br^-$, α-bromo-tetra-*O*-acetyl-D-glucose, NaOH, $CHCl_3$, 60 °C; (b) EtSNa (excess), DMF; (c) MeONa, MeOH, 25 °C; (d) EtSNa, DMF.

configuration both on the outcome of the synthetic sequence and on the biologic activity. Glucosylation of **3b** under phase transfer catalysis afforded the monoglucoside **4b** (32%) and a small amount of the diglucoside **5b** (4%). Unreacted aglycon (54%) was recovered and recycled. By treatment with sodium methoxide and methanol, **4b** gave (*Z*)-3,5-dihydroxy-4′-methoxystilbene 3-*O*-β-D-glucopyranoside (**6b**) in quantitative yield. The de-*O*-methylation sequence, when applied to the (*Z*)-glucosides **4b** and **6b**, gave a mixture of (*Z*)- and (*E*)-resveratrol 3-*O*-β-D-glucopyranoside (**8b**) and **1**, due to a sodium thioethoxide-promoted *Z*/*E* isomerization.[22]

(*E*)-Resveratrol 3-*O*-β-D-glucopyranoside (**1**), tested *in vitro* on human platelet-rich plasma (PRP), has shown a significant inhibitory effect on platelet aggregation induced by collagen (IC_{50} value of 69 μM), adrenalin (IC_{50} value of 102 μM) and, to a minor extent, by arachidonic acid (IC_{50} of 149 μM) and by ADP (IC_{50} of 218 μM) (Table 1).[4,5]

Table 1. Effects of (*E*)-Resveratrol 3-*O*-β-D-Glucopyranoside (**1**) on the Platelet Aggregation Induced by Collagen, Adrenalin, Arachidonic Acid (AA), and ADP[a]

inducer	IC_{50} (μg)
collagen	32.55 ± 2.20[b]
adrenaline	49.27 ± 9.26[b]
AA	57.21 ± 5.73[c]
ADP	84.90 ± 6.50[c]

[a] Platelets were preincubated with (*E*)-resveratrol 3-*O*-β-D-glucopyranoside or the solvent (0.25% DMSO, control) at 37 °C for 3 min, and then collagen (2.5 g/mL), adrenalin (2 μM), AA (100 μM), or ADP (6 μM) was added. Results are expressed as means ± SE of five replicate experiments. [b] $p < 0.05$ as compared with control values. [c] $p < 0.01$ as compared with control values.

On the basis of these results, the antiplatelet aggregation activity was then tested on several compounds

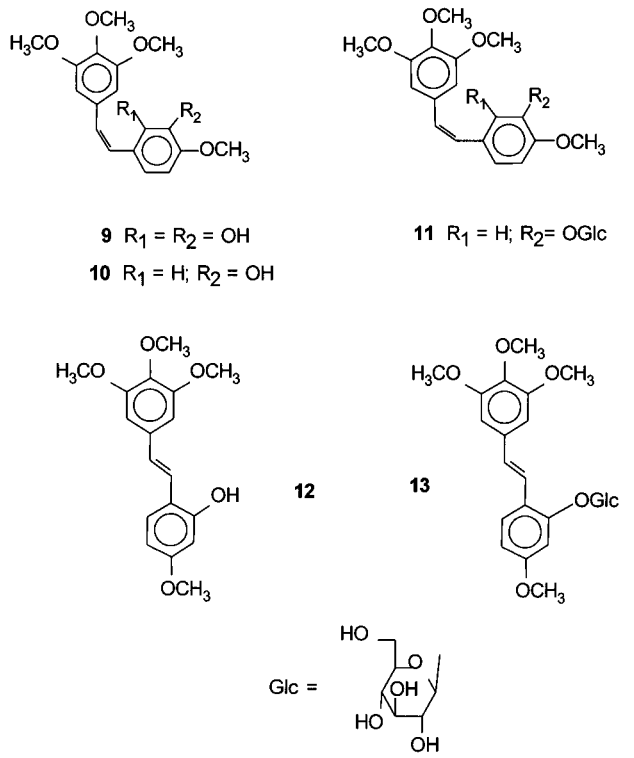


Figure 2. Chemical structure of combretastins derivatives.

derived from 3,4′,5-trihydroxystilbene (resveratrol series). To obtain further insight on the structure−activity relationship, the analysis was extended to some derivatives of the combretastatins series previously synthesized,[15] namely (*Z*)-2′,3′-dihydroxy-3,4,4′,5-tetramethoxystilbene (**9**) (combretastatin A-1);[23] (*Z*)-3′-hydroxy-3,4,4′,5-tetramethoxystilbene (**10**) (combretastatin A-4);[24] (*E*)-2′-hydroxy-3,4,4′,5-tetramethoxystilbene (**12**) ((*E*)-combretastatin iso A-4); combretastatin A-4, 3′-*O*-*β*-D-glucopyranoside (**11**); (*E*)-combretastatin *iso* A-4, 2′-*O*-*β*-D-glucopyranoside (**13**).

As far as the tested compounds are concerned, some parameters responsible for the activity can be suggested: (a) the number and the location of the hydroxyl groups; (b) the derivatization of the hydroxyl groups; and (c) the configuration of the double bond. The effects of these parameters can be further modulated by the different substitution pattern found either within the same series or in the two series.

When platelet aggregation was induced by collagen the most active compounds were found in the resveratrol series, whereas the opposite held true when the platelet aggregation was induced by ADP. Concerning the platelet aggregation induced by collagen, in both series the maximum activity appears to be related to the presence of two free hydroxyl groups as found in (*E*)-3,5-dihydroxy-4′-methoxystilbene (**3a**), (*Z*)-3,5-dihydroxy-4′-methoxystilbene (**3b**), (*E*)-(*β*-D-glucopyranosyloxy)-4′,5-dihydroxystilbene (**1**) [resveratrol series], and 2′,3′-dihydroxy-3,4,4′,5-tetramethoxystilbene (**9**) (combretastatin A-1, Figure 2). Differences in the activity of these compounds could be related to the different substitution pattern as well as to the different location (on the same ring or on different rings) and orientation (meta, ortho) of the hydroxyl groups (Table 2).

Activity appeared to be related to the configuration of the double bond and was lowered by changing the configuration from *E* to *Z*, as observed by comparing **3a** with **3b**. Activity was also depressed by glucosylation as observed by comparing **6a**[15] with **3a**. The combined effects of a *Z*-configuration and glucosylation made (*Z*)-3-(*β*-D-glucopyranosyloxy)-4′,5-dihydroxystilbene (**8b**), (*Z*)-3-(*β*-D-glucopyranosyloxy)-4′-methoxy-5-hydroxystilbene (**6b**), and (*Z*)-3,5-di-(*β*-D-glucopyranosyloxy)-4′-methoxystilbene (**7b**) inactive. Similar observation can be made for platelet aggregation induced by ADP. In particular, glycosylation significantly influences activity.

Table 2. Effects of Compounds **3**−**13** on the Platelet Aggregation Induced by Collagen and ADP[a]

	IC_{50} (μg)	
compound	collagen	ADP
3a	12.9 ± 0.84 (3)[d]	119.14 ± 9.5 (5)[b]
6a	40.40 ± 5.40 (3)[c]	300
7a	112.8 ± 20.5 (3)[d]	300
3b	33.9 ± 6.4 (5)[b]	100.55 ± 5.74 (4)[b]
6b	300	198.0 ± 16.5 (4)[c]
7b	300	300
8b	300	120.15 ± 27.3 (4)[c]
9	68.5 ± 22.1 (4)[d]	60.58 ± 6.87 (6)[a]
10	97.7 ± 19.7 (3)[b]	75.17 ± 26.73 (4)[a]
11	300	300
12	106.2 ± 9.08 (3)[b]	300
13	124.4 ± 16.93 (3)[d]	300

[a] Platelets were preincubated with various agents or DMSO (0.25%, control) at 37 °C for 3 min, then ADP (6 μM) or collagen (2.5 g/mL) was added. Results are presented as means ±SE. Number of replicate experiments is shown in parentheses. [b] $p < 0.05$ as compared with control values. [c] $p < 0.01$ as compared with control values. [d] $p < 0.001$ as compared with control values.

Experimental Section

General Experimental Procedures. Triphenylphosphine, 4-methoxybenzyl chloride, benzyltriethylammonium chloride, and 4-hydroxybenzyl alcohol were purchased from Aldrich and used as received. α-Bromotetra-*O*-acetyl-D-glucose was purchased from Sigma and used as received. Reagents grade tetrahydrofuran, 1,2-dimethoxyethane, and pyridine were refluxed over $LiAlH_4$ and distilled. Reagent grade dichloromethane was refluxed over P_2O_5 and distilled. Reagent grade MeOH was refluxed over CaH_2, distilled, refluxed over Mg, distilled, and kept over 3 Å molecular sieves. Reagent grade dimethylformamide was distilled at low pressure under nitrogen and kept over 4 Å molecular sieves. (*E*)-3,5-Dihydroxy-4′-methoxystilbene 3-*O*-*β*-D-glucopyranoside (**6a**); (*E*)-3,5-dihydroxy-4′-methoxystilbene 3,5-*O*-*β*-D-diglucopyranoside (**7a**); (*Z*)-2′,3′-dihydroxy-3,4,4′,5-tetramethoxystilbene (**9**) (combretastatin A-1); (*Z*)-3′-hydroxy-3,4,4′,5-tetramethoxystilbene (**10**) (combretastatin A-4); (*E*)-2′-hydroxy-3,4,4′,5-tetramethoxystilbene (**11**) ((*E*)-combretastatin *iso* A-4); combretastatin A-4, 3′-*O*-*β*-D-glucopyranoside (**12**); and (*E*)-combretastatin *iso* A-4, 2′-*O*-*β*-D-glucopyranoside (**13**) were synthesized as reported in the literature.[15] NMR spectra were obtained with Varian L-200 and Bruker AC-200 and AC-300 instruments. IR spectra were recorded with a Perkin-Elmer 681 spectrometer and mass spectra with a VG 7070 E 9 spectrometer. Melting points were obtained by using Buchi 535 apparatus, optical rotations were measured on a Perkin-Elmer 241 polarimeter, and the microanalyses for the new compounds were determined on a Perkin-Elmer 240 elemental analyzer. Flash-column chromatography was performed on Si gel Merck Kieselgel 60 (230−400 mesh ASTM). Thin layer chromatography (TLC) was carried out on Si gel plates (60 F_{254}, Merck): spots were detected visually by

ultraviolet absorption (254 nm) or by spraying with MeOH/H_2SO_4, 9:1, followed by heating at 100 °C.

All reactions were carried out at 25 °C in a dry nitrogen atmosphere, using glassware dried by flaming in a stream of dry nitrogen.

Plant Material. Seeds of *E. lasianthum* were collected in False Bay (KwaZulu, Natal, South Africa) in December 1991. A voucher specimen (no. 14122/1) is deposited in the Ward Herbarium in Durban (South Africa).

Extraction and Isolation of Resveratrol 3-*O*-β-D-glucopyranoside. Defatted seeds (800 g) were extracted with H_2O at room temperature (6 × 1.6 L). The dark-brown solution was concentrated and extracted with EtOAc (3 × 400 mL; 1.3 g). This was purified on Fractogel TSK HW 40 (3.5 cm i.d. × 90 cm) eluted with MeOH (flow rate 1.9 mL/min), then on silica gel ($CHCl_3$/MeOH, 4:1), obtaining 180 mg of resveratrol 3-*O*-β-D-glucopyranoside (0.023%).[1] The extraction procedure described in ref 4 did not allow the stilbenic glucoside **1** to be isolated.

Resveratrol 3-*O*-β-D-glucopyranoside (1): mp 220−225 °C (from $CHCl_3$−MeOH, 9:1) [lit.[25] mp 228−230 °C]; $[\alpha]^{25}_D = -56.4$ (*c* 0.22, MeOH) [lit.[26] $[\alpha]^{25}_D$ −65.26]; FAB MS (positive) *m/z* 390 $[M]^+$, 228 $[M - 162]^+$; ^{1}H NMR (200 MHz, DMSO-d_6) δ 9.58 (1H, bs, phenolic OH), 9.43 (1H, bs, phenolic OH), 7.39 (2H, d, J = 8.6 Hz, H-2′ + H-6′), 7.05 (1H, d, J = 17.2 Hz, H-b), 6.85 (1H, J = 17.2 Hz, H-a), 6.72 (2H, d, J = 8.6 Hz, H-3′ + H-5′), 6.70 (1H, dd, J = 1.8, 1.8 Hz, H-2), 6.55 (1H, dd, J = 1.8, 1.8 Hz, H-6), 6.32 (1H, dd, J = 1.8, 1.8 Hz, H-4), 5.29 (1H, d, OH), 5.11 (1H, d, OH), 5.03 (1H, d, OH), 4.80 (1H, d, J = 7.0 Hz, H-1″), 4.62 (1H, t, OH), 3.72 (1H, dd, J = 12.0, 1.8 Hz, H-6″B), 3.6−3.12 (5H, m); ^{13}C NMR (50.3 MHz, DMSO-d_6) δ 158.9 (s, C-3 or C-5), 158.4 (s, C-3 or C-5), 157.3 (s, C-4′), 139.4 (s, C-1), 130.0 (s, C-1′), 128.6 (d, C-β), 128.0 (d, C-2′ + C-6′), 125.2 (d, C-α), 115.6 (d, C-3′ + C-5′), 107.2 (d, C-6), 104.7 (d, C-4), 102.8 (d, C-2), 100.7 (d, C-1″), 77.2 (d, C-5″), 76.7 (d, C-3″), 73.3 (d, C-2″), 69.8 (d, C-4″), 60.7 (t, C-6″).

Platelet Aggregation. The samples were dissolved in DMSO at a final concentration of 0.25%. Platelet-rich plasma (PRP) were obtained from human blood taken from the forearm vein of volunteers. Blood was then collected by free flow along the side of plastic tube containing 3.8% sodium citrate (1:9) and was then centrifuged at room temperature at 1250 rpm for 18 min. Platelets were counted under the microscope, and the platelet count was adjusted to 300 000 platelets/mL with platelet-poor plasma (PPP) obtained by centrifugation of the PRP at 13 000 rpm for 3 min.

Aggregation was measured by the turbidometric method.[27] The aggregometer was calibrated so that the PRP gave 10% of light trasmission while the PPP from the same donor gave 90% of light trasmission. The aggregation was measured by an aggregometer (Elvi Logos 840) connected to dual channel recorders. The platelet suspension was stirred at 1000 rpm. Platelets were preincubated with the test compounds or DMSO for 3 min before the addition of aggregation inducer.

(*E*)- and (*Z*)-3,5-Dihydroxy-4′-methoxystilbene [(*E*)- and (*Z*)-4′-*O*-Methylresveratrol] (3a) and (3b). **3a** and **3b** were synthesized as previously described.[15] Butyllithium (4.5 mL, 1.6 M in hexane, 7.17 mmol) was added dropwise to a suspension of (4-methoxybenzyl)-triphenylphosphonium chloride[15] (3.9 g, 7.17 mmol) in THF (110 mL) at 15 °C. The resulting reddish solution was allowed to warm at room temperature and stirred for additional 30 min. 3,5-Bis[(*tert*-butyldimethylsilyl)-oxy]benzaldehyde (2.64 g, 7.17 mmol) was added, and the reaction mixture was stirred for 1 h, diluted with ice-cold H_2O (2 × 50 mL), and extracted with EtOAc (3 × 60 mL). The combined organic extracts were washed with H_2O (2 × 50 mL), and the solvent was removed under reduced pressure to afford a mixture of *E*- and *Z*-isomers **2a** and **2b** (*E*/*Z*, 2.3/1). Flash chromatography over Si gel (*n*-hexane/EtOAc, 99/1) afforded a small amount of pure *Z* isomer **2b** (0.67 g, 1.43 mmol, 20%) and a mixture of *E* and *Z* isomers (2.64 g, 5.6 mmol, 78.2%). Due to the difficult separation of the isomers **2a** and **2b**, the mixture was directly desilylated to **3a** and **3b**.

To a mixture of **2a** and **2b** (4.6 g, 9.6 mmol) in THF (85 mL) was added tetrabutylammonium fluoride (25 mL of a 1 M solution in THF), and the mixture was stirred at room temperature for 15 min. Et_2O was added (50 mL), the solution was washed with H_2O (2 × 30 mL), and the solvent was removed under reduced pressure. The residue was filtered over silica gel to afford a mixture of **3a** and **3b** (2.34 g, quantitative), which was crystallized from $CHCl_3$ and afforded pure *E* isomer **3a** (0.72 g, 2.98 mmol, 31%). The mother liquors (1.62 g) were flash chromatographed over Si gel (*n*-hexane/EtOAc, 99/1) and afforded **3b** (0.68 g, 2.58 mmol, 29.6%).

3a: colorless prisms: mp 176−178 °C (*n*-hexane/EtOAc); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 3.79 (3H, s, OCH_3), 6.18 (1H, dd, $J_{4,2}$ = 1.5, $J_{4,6}$ = 1.5 Hz, H-4), 6.45 (2H, d, H-2 and H-6), 6.93 (2H, d, $J_{3',2'} = J_{5',6'}$ = 9.6 Hz, H-3′ and H-5′), 6.94 and 6.98 (AB system, 2H, J = 16.4 Hz, CH=CH), 7.51 (2H, d, H-2′ and H-6′), 9.22 (2H, bs exchanges with D_2O, OH); ^{13}C NMR (DMSO-d_6, 300 MHz) δ 55.36 (q), 102.06 (d), 2 × 104.63 (d), 113.90 (s), 2 × 114.40 (d), 126.80 (d), 2 × 127.98 (d), 129.84 (d), 139.35 (s), 2 × 158.53 (s), 159.14 (s); EIMS *m/z* 242 $[M^+]$; *anal.* C 74.44%, H 5.90%, calcd for $C_{15}H_{14}O_3$, C 74.35%, H 5.83%.

3b: colorless syrup; ^{1}H NMR ($CDCl_3$ 300 MHz) δ 3.76 (3H, s, OCH_3), 5.68 (2H, bs, exchanges with D_2O, OH), 6.19 (1H, dd, $J_{4,2}$ = 2.1, $J_{4,6}$ = 2.1 Hz, H-4), 6.31 (2H, d, H-2 and H-6), 6.43 and 6.48 (AB system, 2 H, J = 11.5 Hz, CH=CH), 6.75 (2H, d, $J_{3',2'} = J_{5',6'}$ = 9.5 Hz, H-3′ and H-5′), 7.19 (2H, d, H-2′ and H-6′); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 55.86 (q), 102.52 (d), 2 × 109.0 (d), 2 × 114.40 (d), 129.0 (d), 130.37 (s), 2 × 130.95 (d), 131.0 (d), 140.75 (s), 2 × 157.54 (s), 159.37 (s); EIMS *m/z* 242 $[M^+]$; *anal.* C 74.75%, H 5.98%, calcd for $C_{15}H_{14}O_3$, C 74.35%, H 5.83%.

Typical Glucosylation Procedures. A solution of α-bromotetra-*O*-acetyl-D-glucose (1.06 g, 2.58 mmol) and benzyltriethylammonium bromide (0.287 g, 1.05 mmol) in $CHCl_3$ (5.5 mL) was added to a solution of **3b** (0.5 g, 2.07 mmol) in NaOH (1.25 M, 3.0 mL). The two-phase reaction mixture was vigorously stirred at 60 °C for 5 h. After a second addition of NaOH solution (0.96 mL) and sugar (0.49 g), the mixture was stirred at 60 °C for 5 h. EtOAc was added, and the resulting organic phase was successively washed with H_2O and dried (Na_2SO_4), and the solvent was evaporated under reduced pressure. The residue was purified by flash chromatography (*n*-hexane/EtOAc, 70/30) to afford unreacted aglycon **3b** (0.367 g, 54%), tetra-*O*-acetyl-3-*O*-β-D-glucoside, (*Z*)-3,5-

dihydroxy-4′-methoxystilbene tetra-*O*-acetyl-3-*O*-*β*-D-glucopyranoside (**4b**) (0.472 g, 0.82 mmol, 32%), and a small amount of diglucoside **5b** (0.09 g, 0.103 mmol, 4%).

4b: amorphous solid; $[\alpha]_D = -0.9°$ (*c* 2, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 2.01 (6H, s, 2 × OAc), 2.04 (3H, s, OAc), 2.09 (3H, s, OAc), 3.58 (1H, m, H-5″), 3.80 (3H, s, OCH_3), 3.99 (1H, dd, $J_{6''a,6''b} = 13.4$, $J_{6''a,5''} = 2.4$ Hz, H-6″a), 4.22 (1H, dd, $J_{6''b,5''} = 5.5$ Hz, H-6″b), 4.83 (1H, d, $J_{1'',2''} = 7.9$ Hz, H-1″), 5.12 (1H, dd, $J_{3'',2''} = 9.4$, $J_{3'',4''} = 9.3$ Hz, H-3″), 5.19 (2H, m, H-2″ and H-4″), 5.31 (1H, bs, exchanges with D_2O, OH), 6.33 (1H, dd, $J_{4,2} = 1.5$, $J_{4,6} = 1.5$ Hz, H-4), 6.37 and 6.53 (2H, d, $J = 12.6$ Hz, CH=CH), 6.47 (2H, d, H-2 and H-6), 6.78 (2H, d, $J_{3'2'} = J_{5'6'} = 8.1$ Hz, H-3′ and H-5′), 7.17 (2H, d, H-2′ and H-6′); ^1H NMR (C_6D_6, 300 MHz) δ 1.68 (3H, s, OAc), 1.70 (6H, s, 2 × OAc), 1.73 (3H, s, OAc), 3.13 (1H, ddd, $J_{5'',4''} = 9.0$, $J_{5'',6''b} = 5.2$, $J_{5'',6''a} = 2.5$ Hz, H-5′), 3.33 (3H, s, OCH_3), 3.84 (1H, d, $J_{6''a,6''b} = 14.0$ Hz, H-6′a), 4.19 (1H, dd, H-6″b), 4.79 (1H, d, $J_{1'',2''} = 8.0$ Hz, H-1′), 5.22 (1H, dd, $J_{3'',2''} = 9.0$, $J_{3'',4''} = 9.0$ Hz, H-3″), 5.37 (1H, dd, H-4″), 5.46 (1H, dd, H-2″), 6.34 and 6.45 (AB system, 2H, $J = 12.0$ Hz, CH=CH), 6.42 (2H, s, H-2 and H-6), 6.47 (1H, s, H-4), 6.60 (2H, d, $J_{3',2'} = J_{5',6'} = 8.6$ Hz, H-3′ and H-5′), 6.72 (1H, s, exchanges with D_2O, OH), 7.17 (2H, d, H-2′ and H-6′); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 20.96 (q), 2 × 20.97 (q), 20.98 (q), 55.59 (q), 61.10 (t), 68.76 (d), 71.62 (d), 72.22 (d), 73.98 (d), 99.59 (d), 104.11 (d), 109.02 (d), 111.56 (d), 2 × 114.18 (d), 128.79 (d), 130.02 (s), 2 × 130.03 (d), 130.89 (d), 140.27 (s), 157.95 (s), 158.50 (s), 159.35 (s), 2 × 170.10 (s), 170.90 (s), 171.48 (s); ^{13}C NMR (DMSO-d_6) δ 4 × 20.35 (q), 55.03 (q), 61.50 (t), 68.03 (d), 2 × 70.75 (d), 71.95 (d), 97.69 (d), 103.01 (d), 107.38 (d), 110.26 (d), 2 × 113.71 (d), 128.08 (d), 128.86 (s), 2 × 129.98 (d), 130.0 (d), 139.25 (s), 157.63 (s), 158.39 (s), 158.40 (s), 169.08 (s), 169.1 (s), 169.5 (s), 169.97 (s); FABMS *m/z* 572 [M^+]; *anal.* C 60.94%, H, 5.58%, calcd for $C_{29}H_{32}O_{12}$, C 60.84%, H 5.63%.

5b: colorless solid (*n*-hexane/EtOAc); mp 159−161 °C; $[\alpha]_D$ +2.3° (*c* 5, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 1.98 (6H, s, 2 × OAc), 2.01 (12H, s, 4 × OAc), 2.04 (6H, s, 2 × OAc), 3.58 (2H, ddd, $J_{5'',4''} = J_{5''',4'''} = 9.0$, $J_{5'',6''b} = J_{5''',6'''b} = 5.4$, $J_{5'',6''a} = J_{5''',6'''a} = 2.0$ Hz, H-5″ and H-5‴), 3.82 (3H, s, OCH_3), 3.99 (2H, dd, $J_{6''a,6''b} = J_{6'''a,6'''b} = 12.3$ H-6″a and H-6‴a), 4.21 (2H, dd, H-6″b and H-6‴b), 4.84 (2H, dd, $J_{1'',2''} = J_{1''',2'''} = 7.4$, H-1″ and H-1‴), 5.08 (2H, dd, $J_{3'',2''} = J_{3''',2'''} = 9.0$, $J_{3'',4''} = J_{3''',4'''} = 9.0$ Hz, H-3″ and H-3‴), 5.17 (2H, dd, H-4″ and H-4‴), 5.21 (2H, dd, H-2″ and H-2‴), 6.38 and 6.57 (AB system, 2H, $J = 12.0$ Hz, CH=CH), 6.42 (1H, dd, $J_{4,2} = 1.5$, $J_{4,6} = 1.5$ Hz, H-4), 6.58 (2H, d, H-2 and H-6), 6.82 (2H, d, $J_{3',2'} = J_{5',6'} = 8.5$ Hz, H-3′ and H-5′), 7.18 (2H, d, H-2′ and H-6′); ^1H NMR (C_6D_6) δ 1.67 (6H, s, 2 × OAc), 1.70 (6H, s, 2 × OAc), 1.78 (6H, s, 2 × OAc), 1.82 (6H, s, 2 × OAc), 3.13 (2H, ddd, $J_{5'',4''} = J_{5''',4'''} = 9.0$, $J_{5'',6''b} = J_{5''',6'''b} = 5.0$, $J_{5'',6''a} = J_{5''',6'''a} = 2.0$ Hz, H-5″ and H-5‴), 3.39 (3H, s, OCH_3), 3.85 (2H, dd, $J_{6''a,6''b} = J_{6'''a,6'''b} = 12.0$, $J_{6''a,5''} = J_{6'''b,5'''} = 2.0$ Hz, H-6″a and H-6‴a), 4.18 (2H, dd, H-6″b and H-6‴b), 4.82 (2H, d, $J_{1'',2''} = J_{1''',2'''}$ 8.0 Hz, H-1″ and H-1‴), 5.21 (dd, 2H, $J_{3'',2''} = J_{3''',2'''}$ 9.0, $J_{3'',4''} = J_{3''',4'''} = 9.0$ Hz, H-3″ and H-3‴), 5.37 (2H, dd, Hz, H-4″ and H-4‴), 5.47 (2H, dd, H-2″ and H-2‴), 6.32 and 6.42 (AB system, $J = 12.0$ Hz, CH=CH), 6.61 (2H, d, $J_{3',2'} = J_{5',6'} = 8.2$ Hz, H-3′ and H-5′), 6.77 (1H, dd, $J_{4,2} = 2.0$, $J_{4,6} = 2.0$ Hz, H-4), 6.81 (2H, d, H-2, H-6), 7.12 (2H, d, H-2′ and H-6′); FABMS *m/z* 902 [M^+]; *anal.* C 57.10%, H 5.61%, calcd for $C_{43}H_{50}O_{21}$, C 57.22%, H 5.58%.

(*E*)-3,5-Dihydroxy-4′-methoxystilbene Tetra-*O*-acetyl-3-*O*-*β*-D-glucopyranoside (4a). The title compound **4a** was synthesized from **3a** by treatment with α-bromotetra-*O*-acetyl-D-glucose as described for **3b**.[15]

4a: amorphous powder; ^1H NMR ($CDCl_3$) δ 1.98 (s, 3H, OAc), 2.0 (s, 3H, OAc), 2.01 (s, 3H, OAc), 2.04 (s, 3H, OAc), 3.78 (s, 3H, OCH_3), 4.15 (ddd, 1H, $J_{5'',4''} = 8.0$, $J_{5'',6''a} = 6.0$, $J_{5'',6''b} = 3.0$ Hz, H-5″), 4.12 (dd, 1H, $J_{6''a,6''b} = 12.0$ Hz, H-6″a), 4.22 (dd, 1H, H-6″b), 4.90−5.58 (m, 4H, H-1″, H-2″, H-3″, and H-4″), 6.42 (dd, 1H, $J_{4,2} = 2.6$, $J_{4,6} = 2.6$ Hz, H-4), 6.69 (d, 2H, H-2 and H-6), 6.83 and 7.01 (AB system, 2H, $J = 15.7$ Hz, CH=CH), 6.88 (d, 2H, $J_{3',2'} = J_{5',6'} = 9.4$ Hz, H-3′ and H-5′), 7.42 (d, 2H, H-2′ and H-6′); FABMS *m/z* 572 [M^+]; *anal.* C 60.98%, H 5.73%, calcd for $C_{29}H_{32}O_{12}$, C 60.84%; H, 5.63%.

(*Z*)-3,5-Dihydroxy-4′-methoxystilbene 3-*O*-*β*-D-glucopyranoside ((*Z*)-4′-*O*-methylresveratrol 3-*O*-*β*-D-glucopyranoside, (*Z*)-4′-*O*-methylpiceid) (6b). A 0.2 M solution of sodium methoxide in MeOH (21 mL) was added to a solution of **4b** (0.4 g, 0.7 mmol) in MeOH (27 mL). The solution was stirred at room temperature for 2 h, and then Dowex 50Wx8 (H^+ form) resins were added until neutral pH. The resins were filtered and washed with MeOH, and the solvent was evaporated under reduced pressure to afford **6b** in quantitative yield.

6b: colorless needles; mp 143−145 °C (lit.[12] mp 147−148 °C); $[\alpha]_D$ −33.0° (*c* 8, acetone); ^1H NMR (DMSO-d_6, 300 MHz) δ 3.1−3.5 (6H, H-2″, H-3″, H-4″, H-5″, and H-6″), 3.7 (3H, s, OCH_3), 4.45 (1H, bs, exchanges with D_2O), 4.60 (1H, d, $J_{1'',2''} = 7.8$ Hz, H-1″), 5.15 (1H, bs, exchanges with D_2O), 5.17 (1H, bs, exchanges with D_2O), 5.30 (1H, bs, exchanges with D_2O), 6.32 (2H, dd, $J_{2,4} = J_{6,4} = 2.0$ Hz, H-2 and H-6), 6.38 (1H, dd, H-4), 6.36 and 6.52 (AB system, 2H, $J = 12.0$ Hz, CH=CH), 6.50 (1H, s, exchanges with D_2O), 6.82 (2H, d, $J_{3',2'} = J_{5',6'} = 7.9$ Hz, H-3′ and H-5′), 7.18 (2H, d, H-2′ and H-6′); ^1H NMR (Py-d_5) δ 3.65 (3H, s, OCH_3), 3.88 (1H, ddd, $J_{5'',4''} = 7.0$, $J_{5'',6''a} = 5.0$, $J_{5'',6''b} = 2.0$ Hz, H-5″), 4.15−4.4 (5H, m, H-2″, H-3″, H-6″a, H-6″b, and H-4″), 4.3 (3H, s, exchanges with D_2O), 5.35 (1H, d, $J_{1'',2''} = 6.7$ Hz, H-1″), 6.48 and 6.52 (AB system, 2H, $J = 13.5$ Hz, CH=CH), 6.5 (2H, s, exchanges with D_2O), 6.75 (2H, d, $J_{3',2'} = J_{5',6'} = 8.3$ Hz, H-3′ and H-5′), 6.92 (2H, s, H-2 and H-6), 7.12 (1H, s, H-4), 7.32 (2H, d, H-2′ and H-6′); ^{13}C NMR (Py-d_5, 300 MHz) δ 55.18 (q), 62.23 (t), 71.09 (d), 74.90 (d), 2 × 78.50 (d), 102.45 (d), 104.14 (d), 108.62(d), 110.62 (d), 2 × 114.20 (d), 129.41 (d), 129.85 (s), 130.28 (d), 2 × 130.79 (d), 140.07 (s), 159.37 (s), 2 × 160.07 (s); FABMS *m/z* 404 [M^+]; *anal.* C 62.28%, H 6.03%, calcd for $C_{21}H_{24}O_8$, C 62.37%, H 5.97%.

(*Z*)-3,5-Dihydroxy-4′-methoxystilbene 3, 5-*O*-*β*-D-diglucopyranoside (7b). The diglucoside **5b** treated with sodium methoxide in MeOH as described above for **4b** afforded **7b** in quantitative yield.

7b: amorphous solid; $[\alpha]_D$ −31.0° (*c* 2.7, MeOH); ^1H NMR (Py-d_5, 300 MHz) δ 3.65 (3H, s), 4.08 (2H, m, H-5′, H-5″), 4.2−4.55 (10H, sugar protons), 5.2 (8H, bs, exchanges with D_2O), 5.5 (2H, d, $J_{1'',2''} = J_{1''',2'''} = 7.0$ Hz, H-1″ and H-1‴), 6.5 and 6.52 (AB system, 2H, $J = 12$ Hz, CH=CH), 6.85 (2H, d, $J_{3',2'} = J_{5',6'} = 9.0$ Hz, H-3′ and H-5′), 7.1 (1H, dd, $J_{4,2} = J_{4,6} = 2.1$ Hz, H-4), 7.3

(1H, d, H-2, H-6), 7.32 (2H, d, H-2′ and H-6′); ^{13}C NMR (Py-d_5, 300 MHz) δ 54.75 (q), 2 × 61.92 (t), 2 × 70.81 (d), 2 × 74.40 (d), 2 × 78.07 (d), 2 × 78.10 (d), 2 × 101.85 (d), 104.16 (d), 110.79 (d), 110.80 (d), 113.90 (d), 113.91 (d), 127.5 (d), 2 × 128.0 (d), 129.5 (s), 130.5 (d), 139.20 (s), 159,0 (s), 159.2 (s), 159.5 (s); FABMS *m/z* 589 [M^+ + Na]; *anal.* C 57.00%, H 6.11%, calcd for $C_{27}H_{34}O_{13}$, C 57.24%, H 6.01%.

(*E*)-3,4′,5-Trihydroxystilbene 3-*O*-β-D-glucopyranoside (Resveratrol 3-*O*-β-D-glucopyranoside, Piceid, 1). A 0.5 M solution of sodium ethioethoxide in dimethylformamide was prepared by adding thioethanol (0.93 g, 1.1 mL, 15 mmol) to an ice-cooled and magnetically stirred suspension of sodium hydride (0.4 g of a 60% oil dispersion, 10 mmol) in DMF (20 mL) and stirring at room temperature for 15 min. Then 11 mL (5.5 mmol) of this solution was added to **4a** (0.3 g, 0.74 mmol), and the resulting solution was heated in an oil bath at 140 °C. The reaction was monitored by TLC. After 10 h, the cooled reaction mixture was acidified with 10% HCl and extracted with EtOAc (3 × 10 mL) and with BuOH (2 × 10 mL). The combined organic extracts were washed with H_2O and dried (Na_2SO_4). Removal of the solvent under reduced pressure afforded a residue which was purified by flash chromatography and gave **1** (50%), which was identical in all respects to an authentic isolated sample.

(*Z*)-3,4′,5-Trihydroxystilbene 3-*O*-β-D-glucopyranoside ((*Z*)-Resveratrol 3-*O*-β-D-glucopyranoside, (*Z*)-Piceid, 8b). A 0.5 M solution of sodium thioethoxide in dimethylformamide (2 mL) was added to **6b** (0.25 g, 0.62 mmol), and the solution was heated at 130 °C. The reaction was monitored by TLC. The reaction was cooled, acidified with 1% HCl and extracted with AcOEt (3 × 10 mL) and BuOH (2 × 10 mL). The combined organic extracts were dried, and the solvent removed under reduced pressure to afford a mixture of (*Z*)- and (*E*)-resveratrol (62%) (**8** and **1**) in a 2/1 ratio.

8b (identified in the *Z*/*E* mixture): ^{1}H NMR (DMSO-d_6 + D_2O, 300 MHz) δ 3.2−3.8 (6H, H-2″, H-3″, H-4″, H-5″, H-6″a, and H-6″b), 4.7 (1H, d, $J_{1'',2''}$ = 7.4 Hz, H-1″), 6.36 (2H, d, $J_{2,4} = J_{6,4}$ = 2.0 Hz, H-2 and H-6), 6.39 (1H, dd, H-4), 6.39 and 6.48 (AB system, 2H, J = 12 Hz, CH=CH), 6.68 (2H, d, $J_{3',2'} = J_{5',6'}$ = 8.4 Hz, H-3′ and H-5′), 7.12 (2H, d, H-2′ and H-6′); ^{13}C NMR (DMSO-d_6, 300 MHz) δ 60.38 (t), 69.34 (d), 73.10 (d), 76.43 (d), 76.81 (d), 100.67 (d), 102.49 (d), 107.36 (d), 109.0 (d), 2 × 114.9 (d), 125.22 (d), 127.31 (s), 127.59 (d), 2 × 129.91 (d), 138.97 (s), 156.59 (s), 157.98 (s), 158.56 (s).

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