Polyphenolic Glycosides from African Proteaceae

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The phytochemical investigation of members of the genus *Protea* afforded a series of polyphenolic compounds (**1**−**5**) that were identified by 1D and 2D NMR experiments. Of these, **2**−**5** are new compounds. Chemical syntheses of **1**−**3** were performed in order to confirm the structures and to prepare additional material for biological evaluation.

The Proteaceae or silk-oak family is one of evergreen shrubs, trees, or sometimes subherbaceous perennial plants. The more than 1000 species from approximately 55 genera are found largely in the dry, Mediterranean-type, climatic regions of the southern hemisphere, especially in South Africa and Australia. Proteas were the most prominent woody plants in the Cape Region of South Africa 300 years ago and were used by the early European settlers for a variety of their needs. The bark and leaves of most *Protea* species may be regarded as astringent, and all have probably been used in the Cape Region for tanning. As early as 1720, "Syrupus Protea" was used as a cough syrup. Nectar from *P. nitida* flowers was thickened into a nutritious syrup, described as a tonic and cough syrup in the old Cape Pharmacopoeia and sold as "Bessiestroop" until about 100 years ago. The wood of most species has been used as fuel, and the wood of *P. nitida*, the "Waboom" (Afrikaans for "Wagon Tree"), was used extensively by the early settlers to build wagons.[1]

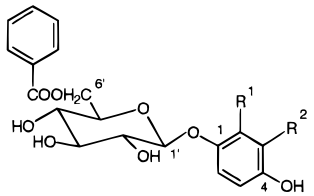
Two classes of glycosides are found in *Protea* sp., the C-glycosides (proteacin or leucodrin) and phenolic glycosides, which have 3,4-dihydroxybenzyl alcohol as a common aglycon. The known sugars involved in the *β*-glycosidic linkage are (+)-D-glucose and (+)-D-allose.[2,3] In this paper we report the phytochemical investigation of 10 *Protea* species. Four new polyphenolic glycosides are described from *P. neriifolia*, together with known polyphenolic glycosides from *P. obtusifolia*, *P. rubropilosa*, and *P. eximia*.

Results and Discussion

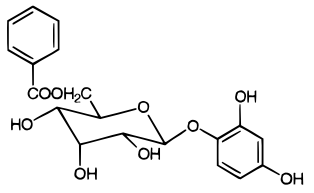
A standardized extraction procedure was carried out on leaves of 10 *Protea* species. The cytotoxicity of the extracts was monitored through the brine shrimp lethality test. Weak cytotoxic activity was found in ethyl acetate extracts of *P. obtusifolia*, *P. eximia*, and *P. neriifolia*.

The dried plant materials were exhaustively extracted with MeOH. The extracts were defatted, then extracted with ethyl acetate to give the yields reported in the Experimental Section. *p*-Hydroxybenzoic acid, protocatheecuic acid, methyl 3,5-dihydroxybenzyl ether, and 3,4-dihydroxybenzyl alcohol were isolated from *P. obtusifolia* and characterized by spectroscopic means and comparison with reference samples or literature data. 2-Hydroxy-4-hydroxymethylphenyl-(6′-*O*-cinnamoyl)-*β*-D-allopyranoside (rubropilosine) and 2-hydroxy-4-hydroxymethylphenyl-(6′-*O*-benzoyl)-*β*-D-allopyranoside (pilorubrosine) were isolated from *P. rubropilosa*.[3] 4-Hydroxyphenyl-(6′-*O*-benzoyl)-*O*-*β*-D-glucopyranoside (**1**) (eximine) was isolated from *P. eximia* and characterized by comparing its spectroscopic data with those in the literature.[4]

P. neriifolia was submitted to a simplified extraction to increase the yield of polyphenolic compounds. Leaves were defatted with petroleum, then extracted with water-saturated ethyl acetate. The ethyl acetate extracts were evaporated, the residue washed with CH_2Cl_2, and then submitted to reversed-phase medium-pressure chromatography, followed by GFC [Sephadex LH20 and Toyopearl HW40(S)] and counter current chromatography (CCC). Four phenolic glycosides (**2**−**5**) were isolated.



1 $R^1 = R^2 = H$
2 $R^1 = H$, $R^2 = OH$
3 $R^1 = OH$, $R^2 = H$



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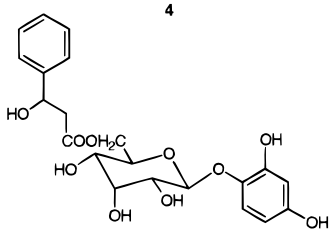

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Compounds **2**−**4** each showed a quasi-molecular peak at *m*/*z* 391 $[M - H]^-$ in FABMS, indicating a molecular formula of $C_{19}H_{20}O_9$. The ^1H and ^{13}C NMR spectra of all three products showed the presence of a benzoyl group

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linked to the hydroxymethylene group. The characteristic deshielding effects on 6′A and B protons and the HMBC spectra confirmed this hypothesis. The sugar is linked to a 1,2,4-trihydroxybenzene nucleus as a phenol glycoside, as shown by the chemical shifts and the splitting pattern in the ^{1}H NMR spectra.

In compounds **2** and **3**, the sugar moiety was identified as β-D-glucopyranose, by self-consistent 2D NMR experiments (HMQC and DQF−COSY) and comparison with reference samples.[5,6] In compounds **4** and **5**, the sugar moiety was identified as β-D-allopyranoside by both 1D and 2D NMR experiments and by methanolysis of **4**, followed by comparison of the resulting methyl alloside with a reference sample of α- and β-D-methyl allopyranoside. The proton and carbon chemical shifts of **3** and **4** show that the same phenolic hydroxyl group is involved in the β-glycosidic linkage, whereas a different hydroxyl group is involved in this linkage in compound **2**.

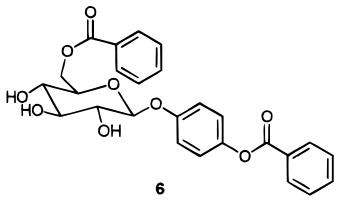
HMBC and 1D NOE experiments confirmed that the four new compounds are 3,4-dihydroxyphenyl-(6′-*O*-benzoyl)-*O*-β-D-glucopyranoside (**2**), 2,4-dihydroxyphenyl-(6′-*O*-benzoyl)-*O*-β-D-glucopyranoside (**3**), 2,4-dihydroxyphenyl-(6′-*O*-benzoyl)-*O*-β-D-allopyranoside (**4**), and 2,4 dihydroxyphenyl-[6′-*O*-(3-hydroxy, 3′-phenyl propanoyl)]-*O*-β-D-allopyranoside (**5**). The trihydroxybenzene moiety and the glycosylated positions were confirmed by permethylation, followed by methanolysis of compounds **2**−**4**. 3,4-Dimethoxyphenol was isolated from **2** and its ^{1}H NMR spectrum compared with literature data; 2,4-dimethoxyphenol was isolated from **3** and **4** and compared with a commercial sample. Compounds **1**−**3** were tested on human fibroblast proliferation showing growth stimulation at concentrations between 1 and 5 μg/mL.[7]

4-Hydroxyphenyl-(6′-*O*-benzoyl)-*O*-β-D-glucopyranoside (eximine) (**1**) was synthesized directly from commercially available arbutin by selective benzoylation of the primary hydroxyl group. The best results were achieved with benzoic acid in dry pyridine in the presence of BOP−Cl [bis-(2-oxo-3-oxazolidinyl)-phosphinic chloride].[8,9] Eximine (**1**) was obtained with 82% regioselectivity with respect to the secondary hydroxyl group, accompanied by a small amount of the dibenzoyl derivative (**6**), easily separated by flash chromatography.

The synthesis of the glucoside **2** was a priori formulated in two key steps from 1,2,4-trihydroxybenzene: (a) regioselective (at position 4) and stereoselective β-glucosidation of the aglycon, and (b) regioselective benzoylation of the primary hydroxyl group in the glucoside. Exclusive glucosidation of position 4 was achieved through protection of the *ortho*-dihydroxy moiety as a methylenedioxy group, which is stable under the basic conditions used for the glucosylation and which may be removed in nonacidic conditions compatible with the glucosyl linkage. A further advantage is that 3,4-methylenedioxyphenol (sesamol) is commercially available.

Glucosylation of sesamol was performed under phase transfer catalysis using α-bromo-2,3,4,6-tetra-*O*-acetyl-D-glucose as the glucosyl donor in $CHCl_3$−NaOH solution in the presence of benzyltriethylammonium hydroxide[6] and afforded **7** in 68.5% yield, accompanied by starting material that was easily separated by flash chromatography and recycled. The reaction was stereoselective and afforded exclusively the β-glucoside. Unsatisfactory results were, however, obtained using phenyl 2,3,4,6-tetra-*O*-acetyl-D-glucosyl sulfoxide as glucosyl donor, a procedure recommended for the glucosylation of low reactive substrates such as phenols.[10] Treatment with sodium thioethoxide in dry DMF, followed by acidic aqueous work up, afforded **8** after simultaneous removal of the acetoxy protective groups.[11]

The synthesis of glucoside **3** required a series of selective protections and deprotections of the phenolic groups to give 2,4-dibenzyloxyphenol, which was transformed in three steps into the glucoside **3**.[12] This approach also afforded the nonnatural glucopyranoside **9**.



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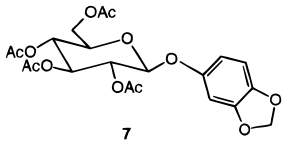

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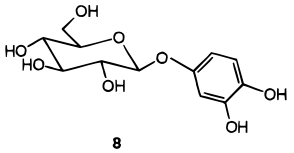

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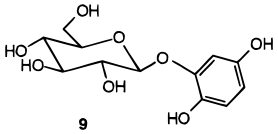

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Experimental Section

General Experimental Procedures. Optical rotations were measured on a Perkin−Elmer 241 polarimeter. Melting points were measured on a Büchi 570 mp apparatus and are uncorrected. Kieselgel 60 F_{254} and RP_{18} (Merck) were used for TLC. Most frequently used solvents were: $CHCl_3$−MeOH−H_2O (5:5:3 or 5:3:2) (organic phase) for Si gel, MeOH−H_2O (45:55 or 1:1) for RP_{18}. Spots were revealed by UV absorption (254 and 366 nm) and by spraying with H_2SO_4−MeOH (1:9), followed by heating, or with $FeCl_3$. Sephadex LH20 (Pharmacia) eluted with MeOH, at a flow rate of 25 mL/min and Toyopearl HW40(S) (Tosohaas), eluted with EtOH at a flow rate of 2 mL/min were used for GFC. Reversed-phase medium-pressure chromatography was carried out using a Büchi 681 pump and Büchi 685 columns, home packed with LiChroprep RP_{18} (40−63 μm, Merck) or LiChroprep RP_8 (25−40 μm, Merck). Counter current chromatography was carried out with a CCC 1000 chromatograph (Pharmatech Research Corp., Baltimore, MD). The equipment consisted of three multilayer coiled columns (1.6 mm i.d. PTFE, total volume capacity 350 mL), rotating at 1032 rpm, a liquid chromatography pump (model 300, Scientific Systems Inc., State College, PA), a speed controller, and an injection valve (Rheodyne). The separations were carried out with the solvent system $CHCl_3$−MeOH−H_2O (4:4:3). ^{1}H and ^{13}C NMR spectra were recorded at 200, 300, and 500 MHz on Bruker spectrometers. 2D experiments (HETCORR, COLOC, HMQC, HMBC) were run using default parameters in the available Bruker software. Samples were dissolved in DMSO-d_6 or $CDCl_3$ and TMS was used as internal standard. Positive and negative FABMS were recorded on a VG7070 EQ spectrometer, using NBA as matrix.

Plant Materials. The locations, month of collection, and the voucher numbers at Ward Herbarium, University of

Durban-Westville follow: *P. wellwitschii* Engl. (Protea Farm Hillcrest, Durban, April 1994, R101), *P. simplex* L. (Durban, April 1994, R102), *P. obtusifolia* Buek ex Meissner (National Botanic Gardens [NGB], Pretoria, April 1994, R103), *P. susannae* Phillips (NBG, Pretoria, April 1994, R104), *P. repens* L. (NBG, Pretoria, April 1994, R105), *P. neriifolia* R. Br. (NBG, Pretoria, April 1994, R106), *P. neriifolia* R. Br. (modified extraction) (Protea Farm Hillcrest, Durban, January 1997 R106A), *P. eximia* (Salisb. ex J. Knight) Fourc. (NBG, Pretoria, April 1994, R107), *P. rubropilosa* Beard (NBG, Pretoria, April 1994, R108), *P. lorifolia* (Salisb. ex J. Knight) Fourc. (NBG, Pretoria, April 1994, R109).

Extraction and Isolation. *P. obtusifolia*: dried leaves (74.3 g) were percolated at room temperature with 3 × 250 mL MeOH. The MeOH extract was concentrated, diluted with H_2O (150 mL), and extracted with petroleum (3 × 400 mL), then with EtOAc (3 × 250 mL). Evaporation of the ethyl acetate gave 7.0 g, 4.0 g of which was purified on Sephadex LH20. Two-hundred fractions (10 mL each) were collected and pooled according to their composition. Fractions 137−150 (372 mg) were submitted to reversed-phase MPLC, eluting with MeOH−H_2O (1:2) (300 mL), then 45:55 (800 mL), and then on Si gel (mixtures of $CHCl_3$−MeOH), obtaining 10 mg of 3,4-dihydroxybenzyl alcohol and 38 mg of methyl 3,5-dihydroxybenzyl ether. Fractions 151−174 (1.075 g) were filtered on SiO_2, then purified by reversed-phase MPLC, eluting with MeOH−H_2O (3:7) (1 L), obtaining 49 mg of 3,4-dihydroxybenzoic acid and 96 mg of *p*-hydroxybenzoic acid. Caffeic acid and quercetin were identified by comparison with reference standards.

P. rubropilosa: dried, minced leaves (229 g) were percolated at room temperature with 5 × 450 mL of MeOH. The MeOH extract was concentrated, diluted with H_2O (450 mL), and extracted with petroleum (1 × 600 mL), then with EtOAc (3 × 200 mL). The ethyl acetate was evaporated to give 18.6 g, 9.12 of which was purified on Sephadex LH20 (5 cm i.d. × 90 cm), 120 fractions (20 mL each). Fractions 96−120 (2 g) were filtered on Si gel, then purified by reversed-phase MPLC (RP_8, MeOH−H_2O 1:1, flow rate 10 mL/min). Fractions 50−80 (306 mg) were partitioned in $CHCl_3$−MeOH−H_2O (5:3:2). The $CHCl_3$ layer afforded 123 mg of rubropilosine.[3] Fractions 30−40 were partitioned in $CHCl_3$−MeOH−H_2O (5:3:2). The $CHCl_3$ layer afforded 29 mg of pilorubrosine.[3]

rubropilosine: white powder, mp 100 °C (lit.[3] 97−100 °C); $[\alpha]^{25}_D$ −68° (*c* 1, MeOH) (lit.[3] −67°, *c* 0.92); ^{1}H NMR (DMSO-d_6+ D_2O, 200 MHz) δ 7.70−7.50 (5H, m, H-2″/6″ + H-3″/5″ + H-4″), 7.66 (1H, d, J = 16 Hz, H-9″), 7.00 (1H, d, J = 8 Hz, H-6) 6.70 (1H, d, J = 1.5 Hz, H-3), 6.65 (1H, d, J = 16 Hz, H-8″), 6.50 (1H, dd, J = 8.0, 1.5 Hz, H-5), 4.97 (1H, d, J = 7.9 Hz, H-1′), 4.42 (1H, dd, J = 11.8, 1.5 Hz, H-6′A), 4.30 (1H, s, H-7), 4.30 (1H, m, H-6′B), 4.00 (1H, m, H-5′), 3.50 (3H, m, H-2′,-3′,-4′); ^{13}C NMR (DMSO-d_6) δ 166.2 (s, C-7″), 146.4 (s, C-1), 144.8 (d, C-9″), 144.1 (s, C-2), 137.3 (s, C-4), 134.0 (s, C-1″), 130.7 (d, C-4″), 2 × 129.1 (d, C-3″ + C-5″), 2 × 128.4 (d, C-2″ + C-6″), 118.0 (d, C-5), 117.4 (d, C-8″), 116.1 (d, C-3), 114.4 (d, C-6), 100.2 (d, C-1′), 71.7 (d, C-5′), 70.9 (d, C-2′), 70.2 (d, C-3′), 67.4 (d, C-4′), 64.7 (t, C-6′), 62.5 (t, C-7); FABMS (negative mode) *m*/*z* 431 $[M - H]^-$; (positive mode) *m*/*z* 455 $[M + Na]^+$.

Pilorubrosine: mp 170 °C (lit.[3] 167−169 °C); $[\alpha]^{25}_D$ −68 ° (*c* 1, MeOH) (lit.[3] −66°, *c* 0.87); ^{1}H NMR (DMSO-d_6 + D_2O) δ 8.00 (2H, dd, J = 7.9, 1.5 Hz, H-2″ + H-6″), 7.68 (2H, d, J = 7.9 Hz H-3″ + H-5″), 7.55 (1H, t, J = 7.9 Hz, H-4″), 7.00 (1H, d, J = 8.5 Hz, H-6), 6.70 (1H, d, J = 2 Hz, H-3), 6.50 (1H, dd, J = 8.5, 2 Hz, H-5), 5.00 (1H, d, J = 8.0 Hz, H-1), 4.60 (1H, dd, J = 11.8, 1.5 Hz, H-6′A), 4.30 (1H, s, H-7), 4.30 (1H, dd, J = 11.8, 7.5 Hz, H-6′B), 4.00 (1H, m, H-5′), 3.50 (3H, m, H-2′,-3′,-4′); ^{13}C NMR (DMSO-d_6) δ 165.7 (s, C-7″), 146.4 (s, C-1), 144.1 (s, C-2), 137.3 (s, C-4), 133.5 (d, C-4″), 129.7 (s, C-1″), 2 × 129.3 (d, C-2″,-6″), 2 × 128.9 (d, C-3″,-5″), 117.2 (d, C-5), 115.9 (d, C-6), 114.3 (d, C-3), 100.2 (d, C-1′), 71.7 (d, C-5′), 70.9 (d, C-2′), 70.2 (d, C-3′), 67.5 (d, C-4′), 64.8 (t, C-6′), 62.5 (t, C-7); FABMS (negative mode) *m*/*z* 405 $[M - H]^-$; (positive mode) *m*/*z* 429 $[M+Na]^+$.

P. eximia: dried, minced leaves (130 g) were percolated at room temperature with MeOH (3 × 300 mL). The MeOH extract was concentrated, diluted with H_2O (500 mL), and extracted with petroleum (3 × 300 mL), then with EtOAc (2 × 250 mL). Evaporation of the ethyl acetate gave 7.4 g that was purified on Sephadex LH20 (5 cm i.d. × 50 cm). In all, 159 fractions (8 mL each) were collected and pooled according to their composition. Fractions 80−89 (1 g) were purified by reversed-phase MPLC (RP_{18}, MeOH−H_2O 2:3, flow rate 5 mL/min), obtaining 134 mg of eximine (**1**).

Compound 1: mp 200− 201 °C ($CHCl_3$−MeOH, lit.[4] 199°−202 °C); $[\alpha]^{20}_D$ −47° (*c* 1,; lit.[4] −48°); R_f 0.56 ($CHCl_3$−MeOH−H_2O 5:5:3, organic phase); ^{1}H NMR (DMSO-d_6) δ 9.00 (1H, br s, OH), 7.98 (2H, dd, J = 7.0, 1.5 Hz, H-2″,-6″), 7.70 (1H, br t, J = 7 Hz, H-4″), 7.55 (2H, br t, J = 7.0 Hz, H-3″,-5″), 6.85 (2H, d, J = 8.7 Hz, H-2,6), 6.56 (2H, d, J = 8.7 Hz, H-3,-5), 5.25 (3H, br s, OH), 4.73 (1H, d, J = 7 Hz, H-1′), 4.60 (1H, dd, J = 11.9, 1.5 Hz, H-6′A), 4.26 (1H, dd, J = 11.9, 7.0 Hz, H-6′B), 3.68 (1H, br t, J = 7.7 Hz, H-5′), 3.29 (3H, m, H-2′,-3′,-4′); ^{13}C NMR (DMSO-d_6) δ 165.6 (s, C-7″), 152.3 (s, C-1), 150.1 (s, C-4), 133.4 (d, C-4″), 129.8 (s, C-1″), 2 × 129.2 (d, C-2″,-6″), 2 × 128.8 (d, C-3″,-5″), 2 × 117.6 (C-3,-5), 2 × 115.4 (d, C-2,-6), 101.4 (d, C-1′), 76.5 (d, C-3′), 73.7 (d, C-5′), 73.3 (d, C-2′), 70.3 (d, C-4′), 64.4 (t, C-6′); FABMS (negative mode) *m*/*z* 375 $[M - H]^-$; (positive mode) *m*/*z* 399 $[M + Na]^+$, 377 $[M + H]^+$.

P. neriifolia: dried, minced leaves (445 g) were defatted by stirring with petroleum (750 mL) at room temperature for 2 h, then filtered. The vegetable material was later extracted at room temperature for 2 h with water-saturated EtOAc (7 × 750 mL). The ethyl acetate extract, on evaporation, gave 73.9 g that was washed with CH_2Cl_2 (2 × 800 mL) to leave 62 g.

From the above extract, 20.4 g was purified by reversed-phase MPLC (RP_8, MeOH−H_2O 45:55, flow rate 15 mL/min); 214 fractions (6 mL each) were collected and pooled according to their composition. Four fractions were obtained: 51−59 (3.446 g), 100−148 (4.561 g), 149−209 (3.597 g), 210−214 (2.168 g). Fractions 100−148 (1 g) were purified first on Toyopearl HW 40(S), then by HSCCC ($CHCl_3$−MeOH−H_2O 4:4:3, aqueous phase as mobile phase), giving 190 mg of **2**. Fractions 149−209 (2.3 g) were purified on Sephadex LH20; 98 fractions (4 mL each) were collected and pooled according to their composition. Fractions 47−50 were purified on Toyopearl HW 40(S), giving 97 mg of **3**. Fractions 51−64 (388 mg) were purified by HSCCC ($CHCl_3$−MeOH−H_2O 4:4:3, aqueous phase as mobile phase), giving 226 mg of **3**, 89 mg of **4**, and 7 mg of **5**.

Compound 2: white powder, mp 91−93 °C (H_2O−MeOH) $[\alpha]^{20}_D$ −50° (*c* 1, MeOH); R_f = 0.36 ($CHCl_3$−MeOH−H_2O 5:5:3 organic phase); ^{1}H NMR (DMSO-d_6, 500 MHz) δ 8.98 and 8.50 (2H, s, phenolic OH), 7.98 (2H, dd, J = 7.5, 1.5 Hz, H-2″,6″), 7.69 (1H, t, J = 7.5 Hz, H-4″), 7.55 (2H, t, J = 7.5 Hz, H-3″,-5″), 6.52 (1H, d, J = 8.1 Hz, H-5), 6.5 (1H, d, J = 2.5 Hz, H-2), 6.33 (1H, dd, J = 8.1, 2.5 Hz, H-6), 5.32 and 5.20 (2H, s, OH), 4.70 (1H, d, J = 7 Hz, H-1′), 4.61 (1H, dd, J = 11.7, 1.5 Hz, H-6′A), 4.24 (1H, dd, J = 11.7, 7.5 Hz, H-6′B), 3.68 (1H, dt, J = 7.5, 1.5 Hz, H-5′), 3.30 (1H, t, J = 7.5 Hz, H-3′), 3.27 (1H, m), 3.25 (1H, m); ^{13}C NMR (DMSO-d_6) δ 165.6 (s, C-7″), 150.0 (s, C-1), 145.5 (s, C-3), 140.2 (s, C-4), 133.5 (d, C-4″), 129.7 (s, C-1″), 2 × 129.3 (d, C-2″,-6″), 2 × 128.9 (d, C-3″,-5″), 115.3 (d, C-5), 106.6 (d, C-6), 105.2 (d, C-2), 101.3 (d, C-1′), 76.3 (d, C-3′), 73.7 (d, C-5′), 73.2 (d, C-2′), 70.1 (d, C-4′), 64.5 (t, C-6′); FABMS (negative mode) *m*/*z* 391 $[M - H]^-$; (positive mode) *m*/*z* 415 $[M + Na]^+$, 392 $[M^+]$.

Compound **2** (30 mg) was added to a suspension of Bu-*t*-ONa (150 mg) and NaOH (30 mg) in 5 mL dry DMSO, under N_2; after 10 min, CH_3I (2 mL) was added. The reaction mixture was stirred, at room temperature, for 3 h. The solution was poured onto ice and extracted with CH_2Cl_2. The organic phase was dried and evaporated to dryness. The crude mixture was purified on Si gel (*n*-hexane−EtOAc 7:3) giving 15 mg of **2a**.

Compound 2a: ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.78 (1H, d, J = 7.8 Hz, H-5), 6.70 (1H, d, J = 3 Hz, H-2), 6.59 (1H, dd, J = 7.8, 3 Hz, H-6), 4.72 (1H,d, J = 7.5 Hz, H-1′), 3.81, 3.79, 3.62, 3.60, 3.50, 3.35 (6 × 3H, s, −OCH_3).

Compound **2a** was refluxed with 10% HCl−MeOH, under N_2, for 2 h. The solution was evaporated under N_2, taken up with H_2O and extracted with CH_2Cl_2. After purification on Si gel (*n*-hexane−EtOAc, 4:1), 11 mg of 3,4 dimethoxyphenol (**2b**) were obtained: ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.74 (1H, d, J = 8.7 Hz, H-5), 6.48 (1H, d, J = 2.7 Hz, H-2), 6.35 (1H, dd, J = 8.7, 2.7 Hz, H-6), 5.03 (1H, s, −OH), 3.83 (6H, s, $-OCH_3$).

Compound 3: white powder, mp 189−190 °C (EtOH−$CHCl_3$) $[\alpha]^{20}_D$ −48° (*c* 1, MeOH), R_f 0.41 ($CHCl_3$−MeOH−H_2O 5:5:3, organic phase); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.94 and 8.40 (2H, s, phenolic OH), 8.00 (2H, dd, J = 7.2, 1.5 Hz, H-2″,-6″), 7.70 (1H, t, J = 7.2 Hz, H-4″), 7.57 (2H, t, J = 7.2 Hz, H-3″,-5″), 6.86 (1H, d, J = 8.7 Hz, H-6), 6.22 (1H, d, J = 2.7 Hz, H-3), 5.90 (1H, dd, J = 8.7, 2.7 Hz, H-5), 5.60 (1H, s, OH), 4.63 (1H, dd, J = 11.9, 1.5 Hz, H-6′A), 4.56 (1H, d, J = 7.9 Hz, H-1′), 4.30 (1H, dd, J = 11.9,7.7 Hz, H-6′B), 3.68 (1H, dt, J = 7.7, 1.5 Hz, H-5′), 3.29 (3H, m, H-2′,-3′,-4′); ^{13}C NMR (DMSO-d_6) δ 165.7 (s, C-7″), 153.4 (s, C-4), 147.7 (s, C-2), 138.3 (s, C-1), 133.6 (d, C-4″), 129.7 (s, C-1″), 2 × 129.3 (d, C-2″,-6″), 2 × 128.9 (d, C-3″,-5″), 118.2 (d, C-6), 105.3 (d, C-5), 2 × 103.3 (d, C-3,-1′), 75.6 (d, C-3′), 73.9 (d, C-5′), 73.3 (d, C-2′), 70.3 (d, C-4′), 64.4 (t, C-6′); FABMS (negative mode) *m*/*z* 391 $[M - H]^-$; (positive mode, NBA) *m*/*z* 415 $[M + Na]^+$, 392 $[M]^+$.

Compound **3** (50 mg) was permethylated under the same conditions used for **2**. After purification, 22 mg of **3a** were obtained: ^{1}H NMR (200 MHz, $CDCl_3$); δ 7.07 (1H, d, J = 8.7 Hz, H-6), 6.50 (1H, d, J = 2.8 Hz, H-3), 6.38 (1H, dd, J = 8.7, 2.8 Hz, H-5), 4.66 (1H, d, J = 7.5 Hz, H-1′), 3.82, 3.70, 3.66, 3.56, 3.41, 3.39 (6 × 3H, s, $-OCH_3$).

Compound 4: white powder, mp 115−116 °C (EtOH−$CHCl_3$) $[\alpha]^{20}_D$ −61.3° (*c* 1, MeOH); R_f 0.45 ($CHCl_3$−MeOH−H_2O 5:5:3 organic phase); ^{1}H NMR (DMSO-d_6, 200 MHz) δ 8.91 and 8.40 (2H, s, phenolic OH), 8.00 (2H, d, J = 7.0 Hz, H-2″,-6″), 7.60 (2H, t, J = 7.8 Hz, H-3″,-5″), 7.55 (1H, t, J = 7.5 Hz, H-4″), 6.90 (1H, d, J = 8.7 Hz, H-6), 6.21 (1H, d, J = 2.7 Hz, H-3), 5.95 (1H, dd, J = 8.7, 2.7 Hz, H-5), 5.43 (1H, d, J = 4.6 Hz, OH), 5.02 (1H, d, J = 3.5 Hz, OH), 4.98 (1H, d, J = 7.5 Hz, OH), 4.80 (1H, d, J = 7.9 Hz, H-1′), 4.60 (1H, dd, J = 11.8, 1.5 Hz, H-6′A), 4.30 (1H, dd, J = 11.8, 7.5 Hz, H-6′B), 4.00 (1H, m, H-5′), 3.50 (3H, m, H-2′,-3′,-4′); ^{13}C NMR (DMSO-d_6) δ 166.2 (s, C-7″), 152.6 (s, C-4), 147.1 (s, C-2), 138.4 (s, C-1), 133.7 (d, C-4″), 129.3 (s, C-1″), 2 × 129.2 (d, C-2″,-6″), 2 × 128.9 (d, C-3″,-5″), 117.6 (d, C-6), 105.6 (d, C-5), 103.4 (d, C-3), 100.4 (d, C-1′), 71.4 (d, C-5′), 70.8 (d, C-2′), 69.9 (d, C-3′), 67.4 (d, C-4′), 64.6 (t, C-6′); FABMS (negative mode) *m*/*z* 391 $[M - H]^-$, (positive mode) *m*/*z* 393 $[M + H]^+$, 267 [M − aromatic ring]$^+$.

Compound **4** (30 mg) was permethylated under the same conditions used for **2**. After purification, 18 mg of **6a** were obtained. **2a**: ^{1}H NMR (200 MHz, $CDCl_3$); δ 7.05 (1H, d, J = 8.7 Hz, H-6), 6.43 (1H, d, J = 2.7 Hz, H-3), 6.32 (1H, dd, J = 8.7, 2.7 Hz, H-5), 5.10 (1H, d, J = 7.5 Hz, H-1′), 3.74, 3.70, 3.62, 3.58, 3.40, 3.34 (6 × 3H, s, $-OCH_3$)

Compound **4a** (18 mg) was hydrolyzed under the same conditions used for **2a**, giving 10 mg of 2,4 dimethoxyphenol (**4b**): ^{1}H NMR ($CDCl_3$, 200 MHz); δ 6.84 (1H, d, J = 8.7 Hz, H-6), 6.50 (1H, d, J = 2.8 Hz, H-3), 6.40 (1H, dd, J = 8.7, 2.8 Hz, H5), 5.22 (1H, s, −OH); 3.87 (3H, s, $-OCH_3$), 3.77 (2 × 3H, s, $-OCH_3$).

Compound 5: $[\alpha]^{25}_D$ −34.2° (*c* 0.53, MeOH); ^{1}H NMR (DMSO-d_6) δ 8.90 (1H, s, OH), 8.42 (1H, s, OH), 7.50−7.30 (5H, m), 6.90 (1H d, J = 8 Hz, H-6), 6.30 (1H, d, J = 2 Hz, H-3), 6.15 (1H, dd, J = 8, 2 Hz, H-5), 5.00 (1H, t, J = 7.0 Hz, H-9″), 4.45 (1H, d, J = 7.9 Hz, H-1′), 4.35 (1H, dd, J = 11.8, 1.5 Hz, H-6′A), 4.05 (1H, dd, J = 11.8, 7.5 Hz, H-6′B), 2.16 (2H, d, J = 7.0 Hz, H-8″); ^{13}C NMR (DMSO-d_6) δ 170.5 (s, C-7″), 153.7 (s, C-4), 147.9 (s, C-2), 144.7 (s, C-1″), 138.3 (s, C-1), 2 × 128.2 (d, C-2″,-6″), 2 × 125.8 (d, C3″,-5″), 118.7 (d, C-6), 105.5 (d, C-1′), 2 × 103.0 (d, C-3,5), 75.7 (d, C-3′), 73.9 (d, C-5′), 73.3 (d, C-2′), 70.1 (d, C-4′), 69.4 (d, C-9″), 63.7 (t, C-6′), 44.5 (t, C-8″); FABMS (positive mode) *m*/*z* 459 [M + Na]$^+$.

Compound **5** was stirred with $Ba(OH)_2$ (10 mg in 1 mL H_2O), under N_2 for 1h. After acidification, the mixture was purified on RP_{18} (MeOH−H_2O 45:55), giving 2 mg of racemic 3-hydroxy,3′-phenyl propanoic acid.

Synthesis. 4-Hydroxyphenyl-(6′-*O*-benzoyl)-O-*β*-D-glucopyranoside (1). A solution of arbutin (4-hydroxyphenyl-*O*-*β*-D-glucopyranoside; 0.5 g, 1.84 mmol) and benzoic acid (0.27 g, 2.22 mmol) in dry pyridine (30 mL) was distilled with azeotropic removal of H_2O to half volume (15 mL) and then cooled. BOP−Cl (1.187 g, 4.67 mmol) was added, and the resulting suspension was stirred at room temperature. The reaction was monitored by TLC (Si gel, using as eluent the organic phase of the biphasic system $CHCl_3$−MeOH−H_2O 5:5:3). After 3 h the solvent was removed under reduced pressure, and the residue was extracted with $CHCl_3$−MeOH−H_2O 5:5:3 (30 mL). The organic phase was dried, the solvent was removed under reduced pressure, and the residue was chromatographed on Si gel eluting with $CHCl_3$−MeOH 9:1 to afford 4-hydroxyphenyl-(6′-*O*-benzoyl)-*O*-*β*-D-glucopyranoside (**1**) (0.137 g). The aqueous phase was extracted with EtOAc (3 × 10 mL) and gave a further 0.390 g of **1**. The total amount of crude **1** (0.527 g, 76%) was crystallized from $CHCl_3$−MeOH and afforded 0.420 g of a colorless compound identical in all respect to the natural compound. As a side product 4-benzoyloxyphenyl-(6′-*O*-benzoyl)-*O*-*β*-D-glucopyranoside (**6**) was obtained in 12.5% yield.

Compound 6: mp 238 °C ($CHCl_3$−MeOH); $[\alpha]^{20}_D$ = −54° (*c* 1, EtOH); R_f 0.58 ($CHCl_3$−MeOH−H_2O 5:5:3, organic phase); ^{1}H NMR (DMSO-d_6) δ 8.12 (2H, dd, J = 7.1, 1.5 Hz, H-2‴+ H-6‴), 7.97 (2H, dd, J = 7.0, 1.5 Hz, H-2″+ H-6″), 7.80−7.70 (2H, m, H-4″+ H-4‴), 7.70−7.50 (4H, m, H-3″ + H-5″ + H-3‴ + H− 5‴), 7.10 (4H, m, H-2, -3, -5, -6), 5.52 (2H, s, OH), 5.38 (1H, s, OH), 4.93 (1H, d, J = 7.1 Hz, H-1′), 4.62 (1H, dd, J = 12.0, 1.5 Hz, H-6′), 4.35 (1H, dd, J = 12.0, 7.0 Hz, H-6), 3.82 (1H, ddd, J = 7.0, 7.0, 1.5 Hz, H-5′), 3.45 (3H, m, H-2′, -3′, -4′); ^{13}C NMR (DMSO-d_6) δ 165.6 (s), 164.8 (s), 154.9 (s), 145.1 (s), 134.1 (d), 133.4 (d), 130.2 (s), 130.1 (s), 2 × 129.8 (d), 2 × 129.2 (d), 2 × 129.0 (d), 2 × 128.8 (d), 2 × 117.7 (d), 2 × 115.5 (d), 101.5 (d), 73.8 (d), 76.4 (d), 73.3 (d), 70.2 (d), 64.2 (t); FABMS (negative mode) *m*/*z* 479 $[M - H]^-$; (positive mode) *m*/*z* 503 $[M + Na]^+$, 481 $[M + H]^+$; *anal*. C 64.7%, H 5.2%, calcd for $C_{26}H_{24}O_9$, C 64.9%, H 5.1%.

3,4-Methylendioxyphenyl-2′,3′,4′,6′- tetraacetyl-*O*-*β*-D-glucopyranoside (7). A solution of tetra-*O*-acetyl-α-bromo-D-glucopyranose (2.97 g, 7.2 mmol) and benzyltriethylammonium bromide (810 mg, 2.9 mmol) in $CHCl_3$ (15.8 mL) was added to a solution of sesamol (3,4-methylenedioxyphenol) (1.04 g, 7.2 mmol) in NaOH (1.25 M, 8.8 mL). The reaction was heated in an oil bath at 60 °C. The progress of the reaction was monitored by TLC (Si gel, eluent *n*-hexane−ethyl acetate 7:3). After 16 h the reaction mixture was diluted with H_2O (50 mL) and extracted with $CHCl_3$ (3 × 30 mL). The combined organic phases were dried (Na_2SO_4) and the solvent removed under reduced pressure. The crude material (4.46 g) was flash chromatographed (Si gel, *n*-hexane−ethyl acetate 7:3) and afforded 0.31 g of unreacted sesamol (29.8%) and 2.31 g of **7** (68.5%), which was crystallized from *n*-hexane−ethyl acetate to afford 1.97 g of colorless crystals.

Compound 7: mp 162 °C (*n*-hexane−ethyl acetate); $[\alpha]^{20}_D$ −68° (*c* 1, $CHCl_3$) R_f 0.24 (*n*-hexane−EtOAc 7:3); ^{1}H NMR ($CDCl_3$) δ 6.71 (1H, d, J = 8.3 Hz, H-5), 6.60 (1H, d, J = 2.3 Hz, H-2), 6.47 (1H, dd, J = 8.3, 2.3 Hz, H-6), 5.30−5.15 (4H, m, H-2′ + H-3′ + H-4′), 4.93 (1H, d, J = 7.6 Hz, H-1′), 4.30 (1H, dd, J = 12.2, 5.4 Hz, H-6′B), 4.18 (1H, dd, J = 12.2, 6.0 Hz, H-6′A), 3.82 (1H, m, H-5′), 2.11 (3H, s), 2.09 (3H, s), 2.06 (3H, s), 2.05 (3H, s); ^{13}C NMR ($CDCl_3$) δ 170.4 (s), 170.1 (s), 169.3 (s), 162.2 (s), 151.9 (s), 148.0 (s), 143.5 (s), 109.5 (d), 107.8 (d), 101.3 (t), 100.4 (d), 100.2 (d), 72.6 (d), 71.8 (d), 70.9 (d), 68.1 (d), 61.8 (t), 4 × 20.5 (q); FABMS (negative mode) *m*/*z* 467 $[M - H]^-$; (positive mode) *m*/*z* 491 $[M + Na]^+$, 469 $[M + H]^+$; *anal*. C 52.9%, H 5.3%, calcd for $C_{21}H_{24}O_{12}$ C 53.8%, H 5.2%.

3,4-Dihydroxyphenyl-*O*-*β*-D-glucopyranoside (8). A 0.5 M solution of NaSEt in DMF was prepared by adding EtSH (0.93 g, 1.1 mL, 15 mmol) to an ice-cooled and magnetically stirred suspension of NaH (0.4 g of a 60% oil dispersion, 10 mmol) in DMF (10 mL) and stirring at room temperature for

15 min. Then the glucoside (**7**) (0.4 g, 0.87 mmol) was added, and the resulting solution was heated in an oil bath at 80 °C. The progress of the reaction was monitored by TLC (Si gel, using as eluent the organic phase of the biphasic system $CHCl_3$−MeOH−H_2O 5:5:3). After 10 h, the cooled reaction mixture was acidified with 10% HCl (10 mL) to achieve a neutral pH and extracted with BuOH (3 × 15 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 (0.37 g) that was purified by chromatography (MPLC, LiChroprep RP8, 25−40 μm, eluting with MeOH−H_2O 45:5). After crystallization (H_2O−MeOH) 0.227 g (90.4%) of 3,4-dihydroxyphenyl-*O*-*β*-D-glucopyranoside (**8**) was obtained.

Compound 8: mp 123 °C; $[\alpha]^{20}_D$ −43° (*c* 1, MeOH); R_f 0.18 ($CHCl_3$−MeOH−H_2O 5:5:3, organic phase); ^{1}H NMR (DMSO-d_6) δ 8.91 (1H, s, OH), 8.49 (1H, s, OH), 6.59 (1H, d, J = 8.5 Hz, H-5), 6.47 (1H, d, J = 2.7 Hz, H-2), 6.32 (1H, dd, J = 8.5, 2.7 Hz, H-6), 5.23 (1H, d, J = 4.4 Hz, OH), 5.02 (1H, d, J = 5.1 Hz, OH), 4.59 (1H, d, J = 7.5 Hz, H-1′), 4.54 (1H, s, OH), 3.65 (1H, dd, J = 11.0, 1.5 Hz, H-6′), 3.45 (1H, m, H-6′), 3.17 (4H, m, H-2′, -3′, -4′, -5′); ^{13}C NMR (DMSO-d_6) δ 150.8 (d), 145.6 (s), 140.3 (s), 115.5 (d), 106.8 (d), 105.4 (d), 101.8 (d), 76.9 (d), 76.7 (d), 73.4 (d), 69.8 (d), 60.8 (t); FABMS (negative mode) m/z 287 $[M - H]^-$; (positive mode) m/z 311 $[M + Na]^+$, 289 $[M + H]^+$; *anal*. C 49.7%, H 5.4%, calcd for $C_{12}H_{16}O_8$, C 50.0%, H 5.6%.

3,4-Dihydroxyphenyl-(6′-*O*-benzoyl)-*O*-*β*-D-glucopyranoside (2). The glucoside **8** was benzoylated according to the protocol given for arbutin. The crude material (0.107 g) was purified by chromatography on Si gel (1:100, eluting with $CHCl_3$−MeOH 8:2) followed by crystallization from H_2O−MeOH) and afforded 0.47 g (69.1%) of **2** identical in all respects to the natural compound.

2,4-Dibenzyloxyphenyl-tetra-*O*-acetyl-*β*-D-glucopyranoside. A solution of tetra-*O*-acetyl α-bromo-D-glucopyranose (0.10 g, 0.24 mmol) and benzyltriethylammonium bromide (0.08 g, 0.27 mmol) in $CHCl_3$ (3 mL) was added to a solution of 2,4-dibenzyloxyphenol[13] (0.073 g, 0.24 mmol) in NaOH (0.5 M, 1.5 mL). The reaction was heated at 60 °C and monitored by TLC (Si gel, eluent *n*-hexane−ethyl acetate 7:3). After 13 h, the reaction mixture was diluted with H_2O (10 mL) and extracted with $CHCl_3$ (3 × 10 mL). The combined organic phases were dried (Na_2SO_4) and the solvent removed under reduced pressure. The crude material was flash chromatographed (Si gel, eluting with *n*-hexane−EtOAc 7:3) and afforded, after crystallization from ethyl acetate−diisopropyl ether, 0.084 g (55%) of pure, colorless 2,4-dibenzyloxyphenyl-tetra-O-acetyl-*β*-D-glucopyranoside: $C_{34}H_{36}O_{12}$; mp 141.5 °C (ethyl acetate−diisopropyl ether); $[\alpha]^{20}_D$ −32.9° (*c* 1.08, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.50−7.35 (10H, m), 7.08 (1H, d, J = 11.0 Hz, H-6), 6.62 (1H, d, J = 3.0 Hz, H-3), 6.45 (1H, dd, J = 10.0, 3.0 Hz, H-5), 5.3−5.1 (3H, m, H-2′,-3′,-4′), 5.05 (2H, s, −CH_2-Ph), 5.00 (2H, s, −CH_2Ph), 4.90 (1H, d, J = 7.6 Hz, H-1′), 4.28 (1H, dd, J = 11.0, 5.6 Hz, H-6′B), 4.11 (1H, dd, J = 11.0, 2.6 Hz, H-6′A), 3.70 (1H, m, H-5′), 2.08, 2.06, 2.05, 2.02 (4 × 3H, s, −CH_3); ^{13}C NMR ($CDCl_3$) δ 170.5 (s), 170.2 (s), 169.4 (s), 169.3 (s), 155.9 (s), 150.5 (s), 140.3 (s), 136.8 (s), 136.5 (s), 129.0 (d), 128.5 (d), 2 × 128.1 (d), 121.8 (d), 105.5 (d), 102.9 (d), 101.0 (d), 72.7 (d), 71.8 (d), 71.1 (d), 70.8 (t), 70.4 (t), 65.4 (d), 61.6 (t), 4 × 20.0 (q); EIMS m/z 636 $[M]^+$, 331 $[C_{14}H_{19}O_9]^+$, 306 $[M - C_{14}H_{18}O_9]^+$, 91 $[CH_2C_6H_5]^+$.

2,4-Dihydroxyphenyl-tetra-*O*-acetyl-*β*-D-glucopyranoside. To a solution of 2,4-dibenzyloxyphenyl-tetra-*O*-acetyl-*β*-D-glucopyranoside (0.045 g, 0.07 mmol) in EtOH (3 mL), cyclohexene (1.5 mL) and palladium hydroxide (0.03 g) were added. The reaction mixture was vigorously stirred at reflux for 3 h, filtered on a Celite pad, and the solvent removed under reduced pressure to afford 2,4-dihydroxyphenyl-tetra-*O*-acetyl-*β*-D-glucopyranoside as an oily compound (0.029 g, 90%): $C_{20}H_{24}O_{12}$, ^{1}H NMR ($CDCl_3$) δ 6.78 (1H, d, J = 9.0 Hz, H-6), 6.45 (1H, d, J = 3.0 Hz, H-3), 6.25 (1H, dd, J = 9.0, 3.0 Hz, H-5), 5.30−5.08 (3H, m, H-2′,-3′,-4′), 4.80 (1H, d, J = 7.2 Hz, H-1′), 4.27 (1H, dd, J = 11.0, 5.6 Hz, H-6′B), 4.15 (1H, dd, J = 11.0, 2.0 Hz, H-6′A), 2.08, 2.06, 2.05, 2.02 (4 × 3H, s, CH_3), 3.78 (1H, m, H-5′); CIMS m/z 457 $[M + H]^+$, 331 $[C_{14}H_{19}O_9]^+$.

2,4-Dihydroxyphenyl-*O*-*β*-D-glucopyranoside (3). A 0.2-M solution of sodium methoxide (1.5 mL) was added to a solution of 2,4-dihydroxyphenyl-tetra-*O*-acetyl-*β*-D-glucopyranoside (0.020 g, 0.05 mmol) in MeOH (2 mL). The reaction was stirred at room temperature and monitored by TLC (Si gel, eluting with $CHCl_3$−MeOH 8:2). After 2 h, DOWEX 50WX was added to achieve a neutral pH. The suspension was filtered, and the solvent was removed under reduced pressure to afford 2,4-dihydroxyphenyl-*O*-*β*-D-glucopyranoside (**3**) in quantitative yields: $C_{12}H_{16}O_8$; ^{1}H NMR (DMSO-d_6 + D_2O) δ 6.90 (1H d, J = 8.0 Hz, H-6), 6.24 (1H d, J = 3 Hz, H-3), 6.12 (1H dd, J = 8.0, 3.0 Hz, H-5), 4.50 (1H d, J = 7.5 Hz, H-1′), 3.70 (1H, m, H-6′B), 3.50 (1H m, H-6′A), 3.20 (4H m, H-2′,3′,4′,5′); ^{13}C NMR (DMSO-d_6) δ 153.7 (s), 148.1 (s), 138.4 (s), 119.1 (d), 105.5 (d), 104.2 (d), 103.3 (d), 77.2 (d), 76 (d), 73.5 (d), 69.9 (d), 60.9 (t); CIMS m/z 288 $[M]^+$.

2-Methoxy-5-benzyloxyphenyl-tetra-*O*-acetyl-*β*-D-glucopyranoside. 2-Methoxy-4-benzyloxyphenol (0.3 g, 1.31 mmol) was treated with tetra-*O*-acetyl α-bromo-D-glucopyranose (0.540 g) under phase-transfer catalysis as described above for the preparation of 2,4-dibenzyloxyphenyl-tetra-*O*-acetyl-*β*-D-glucopyranoside and afforded, after crystallization from *n*-hexane−ethyl acetate, 0.35 g (50% yield) of pure, colorless 2-methoxy-4-benzyloxyphenyl-tetra-*O*-acetyl-*β*-D-glucopyranoside: $C_{28}H_{32}O_{12}$; mp 137.5 °C (*n*-hexane−EtOAc); ^{1}H NMR ($CDCl_3$) δ 7.50−7.35 (5H, m), 6.81 (1H, d, J = 9.0 Hz, H-6), 6.78 (1H, d, J = 2.5 Hz, H-3), 6.61 (1H, dd, J = 9.0, 2.5 Hz, H-4), 5.05−5.30 (3H, m, H-2′,-3′,-4′), 4.98 (2H, s, −CH_2-Ph), 4.95 (1H, d, J = 7.5 Hz, H-1′), 4.93 (1H, m, H-5′), 4.22 (1H, dd, J = 10.0, 6.0 Hz, H-6′B), 4.12 (1H, dd, J = 10.0, 2.8 Hz, H-6′A), 3.75 (3H, s, −CH_3), 2.06, 2.04, 2.03, 2.00 (4 × 3H, s, −CH_3); EIMS m/z: 560 $[M]^+$, 331 $[C_{14}H_{19}O_9]^+$, 230 $[M - C_{14}H_{18}O_9]^+$.

2-Hydroxy-5-benzyloxyphenyl-*O*-*β*-D-glucopyranoside. 2-Methoxy-5-benzyloxyphenyl-tetra-*O*-acetyl-*β*-D-glucopyranoside (0.25 g) was treated with sodium thioethoxide in DMF, as described above for the preparation of 2-methoxy-5-benzyloxyphenol, and afforded, after chromatography (Si gel, eluting with $CHCl_3$−MeOH 9:1), 42% yield of pure 2-methoxy-5-benzyloxyphenyl-*O*-*β*-D-glucopyranoside: $C_{19}H_{22}O_8$, ^{1}H NMR (DMSO-d_6) δ 6.85 (1H, d, J = 2.8 Hz, H-3), 6.69 (1H, d, J = 10.0 Hz, H-6), 6.50 (1H, dd, J = 10.0, 2.8 Hz, H-4), 4.97 (2H, s, −CH_2Ph), 4.63 (1H, d, J = 8.0 Hz, H-1′), 3.70−3.45 (2H, m, H-6′), 3.20 (4H m, H-2′,-3′,-4′,-5′); ^{13}C NMR (DMSO-d_6) δ 151.4 (s), 145.6 (s), 140.7 (s), 137.4 (s), 128.4 (d), 127.7 (d), 115.8 (d), 108.6 (d), 104.6 (d), 102.3 (d), 77.3 (d), 75.9 (d), 75.3 (d), 70.0 (d), 69.7 (t), 60.9 (t), CIMS m/z 378 $[M]^+$

2,5-Dihydroxyphenyl-*O*-*β*-D-glucopyranoside (9). 2-Hydroxy-5-benzyloxyphenyl-*O*-*β*-D-glucopyranoside (0.1 g, 0.262 mmol) in EtOH (4 mL) was treated with cyclohexene (2 mL) and palladium hydroxide (0.04 g) as described above for the preparation of 2,4-dihydroxyphenyl-tetra-*O*-acetyl-*β*-D-glucopyranoside and afforded 2,4-dihydroxy-phenyl-*O*-*β*-D-glucopyranoside (**9**) in quantitative yield: $C_{12}H_{16}O_8$, ^{1}H NMR (DMSO-d_6 + D_2O) δ 6.59 (1H d, J = 8 Hz, H-6), 6.42 (1H d, J = 2.0 Hz, H-3), 6.25 (1H dd, J = 8.0, 2.0 Hz, H-4), 4.55 (1H d, J = 7.0 Hz, H-1′), 3.5−3.7 (2H m, H-6′), 3.25 (4H m, H-2′,-3′,-4′,-5′); ^{13}C NMR (DMSO-d_6) δ 150.1 (s), 145.6 (s), 139.4 (s), 115.8 (d), 109.0 (d), 105.0 (d), 102.6 (d), 77.1 (d), 75.8 (d), 73.3 (d), 69.7 (d), 60.7 (t); CIMS m/z 288 $[M]^+$.

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Supporting Information Available: Synthesis of 2,4-dibenzyloxyphenol and synthetic schemes for compounds **1**, **4**, and **9**. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

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(11) In an alternative approach, characterized by the protection of the *ortho*-dihydroxy moiety in 1,2,4-trihydroxy benzene as a dimethyl ether, the expected glucoside **4** was not obtained. This unexpected outcome of the reaction is due to the failure of sodium thioethoxide to demethylate a phenolic methyl ether in the presence of a free phenolic group on the same aromatic ring. A free phenolic group is, however, tolerated on an other aromatic ring in the same molecule.[6] This approach, however, can be highly convenient for the preparation of less polar monomethyl derivatives, useful for the evaluation of the influence of the free hydroxyl groups on the biological activity.
(12) Direct benzylation of 1,2,4-trihydroxybenzene with benzyl bromide in dimethylformamide afforded 2,4-dibenzyloxyphenol in 5% yield, accompanied by the tribenzyl derivative (5%), by other monobenzyl (35%) and dibenzyl derivatives (7%), with a 52% total recovery.
(13) The synthesis of 2,4-dibenzyloxyphenol is reported in the Supporting Information.

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