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Chemical Synthesis of Hydroxycinnamic Acid Glucosides and Evaluation of Their Ability To Stabilize Natural Colors via Anthocyanin Copigmentation

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This work describes the chemical synthesis of *O*-aryl-β-D-glucosides and 1-*O*-β-D-glucosyl esters of hydroxycinnamic acids. In particular, *O*-aryl-β-D-glucosides were efficiently prepared via a simple diastereoselective glycosylation procedure using phase transfer conditions. Despite the lability of its ester linkage, 1-*O*-β-D-caffeoylglucose could also be obtained using a Lewis acid catalyzed glycosylation step and a set of protective groups that can be removed under neutral conditions. Hydroxycinnamic acid *O*-aryl-β-D-glucosides were then quantitatively investigated for their affinity for the naturally occurring anthocyanin malvin (pigment). Formation of the π-stacking molecular complexes (copigmentation) was characterized in terms of binding constants and enthalpy and entropy changes. The glucosyl moiety did not significantly alter these thermodynamic parameters, in line with a binding process solely involving the polyphenolic nuclei.

KEYWORDS: Hydroxycinnamic acid; glucoside; glucosyl ester; synthesis; copigmentation; anthocyanin

INTRODUCTION

The benefits of a regular consumption of fruits and vegetables in the prevention of cancers, cardiovascular diseases, age-related neurodegeneration, and diabetes could be partially related to the high content in polyphenols displayed by these foods (*1*−*4*). Hydroxycinnamic acids are one of the most abundant classes of dietary polyphenols and are generally found as esters of quinic acid and tartaric acid and also as D-glucose conjugates (*O*-aryl-β-D-glucosides, *O*-β-D-glucosyl esters) (*5*−*10*), especially in berries and tomato.

Interestingly, the glucose moiety of some dietary flavonoids has been shown to allow their uptake by intestinal cells (*1*−*3*) according to two distinct mechanisms (*11*): deglucosylation by the enzyme lactase phlorizin hydrolase and subsequent passive diffusion of the aglycones through the enterocyte layer or active transport via a D-glucose transporter present in the membrane of intestinal cells and subsequent deglucosylation by a cytosolic β-glucosidase. Similarly, the glucosylation of hydroxycinnamic acids could increase their bioavailability.

Derivatives of hydroxycinnamic acids may be difficult to extract in quantities required for biological or chemical studies, especially identification and titration in plants, role in color expression, and investigation of their facilitated intestinal absorption. Hence, their chemical synthesis is an interesting alternative. In this work, we report on novel and simple synthetic routes to prepare hydroxycinnamic acid glucosides and glucosyl esters. In addition, their ability to enhance natural colors by interacting with anthocyanin plant pigments is investigated.

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MATERIALS AND METHODS

All starting materials were obtained from commercial suppliers and were used without purification. Solvents were distilled over $CaCl_2$, CaH_2, KOH, or NaOH. TLC analyses were performed on silica gel 60 F_{254} or C-18 silica gel F_{254s}. Detection was achieved by UV light (254 nm) and by charring after exposure to a 5% H_2SO_4 solution in EtOH. Purifications were performed by column chromatography on silica gel 60 (40−63 μm). Dowex 50Wx4-50 or Amberlite IRC 50 ion-exchange resin was used for acidification. Melting points were measured on a Barnstead Electrothermal 9100 apparatus and are uncorrected.

NMR. ^{1}H and ^{13}C NMR spectra were recorded on an Avance DPX-300 Brucker apparatus at 300.13 MHz (^{1}H) or 75.46 MHz (^{13}C). NMR chemical shifts are in parts per million relative to tetramethylsilane using the deuterium signal of the solvent ($CDCl_3$, CD_3OD) for calibration. ^{1}H−^{1}H coupling constants are in hertz.

HR-MS. High-resolution mass analyses were carried out on Qstar Elite instrument (Applied Biosystems SCIEX, Foster City, CA) equipped with API. Mass detection was performed in the negative or positive electrospray ionization mode.

HPLC-MS. HPLC-MS analyses were performed on a HP1050 apparatus coupled to a UV−visible diode array detector and to a Micromass Platform LCZ 4000 mass spectrometer. Mass detection was performed in the negative electrospray ionization mode with a capillary voltage of 25 V, a desolvation temperature of 80 °C, and a nitrogen flow rate of 300 L/h. A 150 × 4.6 mm Altima C18 column (Alltech, Deerfield, IL) equipped with a 7.5 × 4.6 mm precolumn was used for chromatographic separations at 35 °C. The solvent system was a

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gradient of A (0.05% aqueous HCO_2H) and B (MeCN) with 10% B at 0 min and 100% B at 20 min for *O*-aryl-*β*-D-glucosides and 0% B at 0 min and 90% B at 10 min for 1-*O*-*β*-D-caffeoylglucose (flow rate = 1 mL/min).

UV−Vis Spectroscopy. Copigmentation experiments were performed on a Hewlett-Packard 8452A diode array UV−vis spectrometer equipped with a magnetically stirred quartz cell (optical path length = 1 cm). The temperature in the cell was controlled by means of a water thermostated bath.

Copigmentation. A 2×10^{-3} M solution of malvin was prepared in MeOH acidified by concentrated HCl to a final concentration of 0.2 M. This solution was diluted in a pH 2.5 phosphate buffer (0.1 M H_3PO_4 + 1 M NaOH) to a final malvin concentration of 10^{-4} M. To a portion of the latter solution was added 5×10^{-3} M copigment. The malvin and malvin+copigment solutions were then mixed in various proportions to prepare solutions of intermediate copigment concentrations. The solutions were equilibrated for 20 min before spectroscopic measurements. All calculations were performed at the isosbestic point of malvin and its copigmentation complex, which was determined from strongly acidic malvin and malvin+copigment solutions (copigment/malvin molar ratio = 50). The pH 2.5 malvin and malvin+copigment solutions (copigment/malvin molar ratio = 50) were then used for investigating the temperature dependence of copigmentation in the range of 25−40 °C.

Data Analysis. The curve fittings were carried out on a PC using the Scientist program (MicroMath, Salt Lake City, UT). Curve fittings were achieved through least-squares regression. Standard deviations are reported.

Synthesis. *General Methylation Procedure*. Hydroxycinnamic acid (10.54 mmol) was dissolved in MeOH (30 mL) containing ca. 1 mL of concentrated H_2SO_4. The solution was refluxed for about 24 h. After concentration under reduced pressure, the solution was diluted with EtOAc and washed with 5% aqueous $NaHCO_3$ and water, then dried over anhydrous Na_2SO_4, and concentrated. The raw product was purified by crystallization in hexane/EtOAc.

*Methyl p-coumarate (**1a**):* yield, 90%; white amorphous powder; mp, 138−139 °C; R_f (hexane/EtOAc, 1:1), 0.65; ^{1}H NMR (300 MHz, $CDCl_3$), δ 3.82 (s, 3, CO_2CH_3), 6.30 (d, 1, J = 15.9 Hz, H_α), 6.85 (d, 2, J = 8.7 Hz, H_3, H_5), 7.45 (d, 2, J = 8.7 Hz, H_2, H_6), 7.65 (d, 1, J = 15.9 Hz, H_β); ^{13}C NMR ($CDCl_3$), δ 52.21 ($CO_2\underline{C}H_3$), 115.27 (C_α), 116.34 (C_3, C_5), 128.50 (C_1), 130.5 (C_2, C_6), 145.44 (C_β), 158.52 (C_4), 168.79 ($\underline{C}O_2CH_3$).

*Methyl ferulate (**1b**):* yield, 70%; yellow amorphous powder; mp, 65 °C; R_f (hexane/EtOAc, 1:1), 0.39; ^{1}H NMR ($CDCl_3$), δ 3.82 (s, 3, CO_2CH_3), 3.95 (s, 3, OCH_3), 6.30 (d, 1, J = 15.9 Hz, H_α), 6.94 (d, 1, J = 8.1 Hz, H_5), 7.04 (d, 1, J = 1.8 Hz, H_2), 7.09 (dd, J = 8.1 Hz, 1.8 Hz, H_6), 7.65 (d, 1, J = 15.9 Hz, H_β); ^{13}C NMR ($CDCl_3$), δ 52.02 ($CO_2\underline{C}H_3$), 56.30 (OCH_3), 109.91 (C_2), 115.24 (C_5), 115.42 (C_α), 123.40 (C_6), 127.27 (C_1), 145.46 (C_β), 147.29 (C_4), 148.50 (C_3), 168.25 ($\underline{C}O_2CH_3$).

*Methyl caffeate (**1c**):* yield, 77%; white powder; mp, 158 °C; R_f (hexane/EtOAc, 1:1), 0.65; ^{1}H NMR ($CDCl_3$), δ 3.81 (s, 3, CO_2CH_3), 6.29 (d, 1, J = 15.9 Hz, H_α), 6.90 (d, 1, J = 8.1 Hz, H_5), 7.03 (dd, 1, J = 8.1 Hz, 1.8 Hz, H_6), 7.10 (dd, 1, J = 1.8 Hz, H_2), 7.60 (d, 1, J = 15.9 Hz, H_β); ^{13}C NMR ($CDCl_3$), δ 51.16 ($CO_2\underline{C}H_3$), 114.78 (C_2), 114.87 (C_5), 115.95 (C_α), 122.16 (C_6), 127.15 (C_1), 145.34 (C_β), 148.25 (C_4), 167.58 (C_3), 206.59 ($\underline{C}O_2CH_3$).

General Glycosylation Procedure. A mixture of tetra-*O*-acetyl-α-D-glucopyranosyl bromide (1.5 equiv) in anhydrous CH_2Cl_2 (25 mL) was slowly added to a solution of methyl cinnamate (5.6 mmol) and tris[2-(2-methoxyethoxy)ethyl]amine (1.5 equiv) in 20 mL of 1 M $NaHCO_3$/1 M KCl, 1:1. The mixture was refluxed for 48 h under N_2. After the addition of H_2O (50 mL) and extraction with CH_2Cl_2 (3 × 20 mL), the combined organic phases were successively washed with 1 M HCl (2 × 50 mL) and H_2O (2 × 50 mL), dried over Na_2SO_4, concentrated under reduced pressure, and purified by crystallization or chromatography.

*Methyl 4-(2′,3′,4′,6′-tetra-O-acetyl)-β-D-glucopyranosyl coumarate (**2a**):* crystallization in hexane/EtOAc gave **2a** as a white amorphous powder; yield, 75%; mp, 162 °C; R_f (hexane/EtOAc, 4:6), 0.59; ^{1}H NMR ($CDCl_3$), δ 2.00 (m, 12, $OCOCH_3$), 3.80 (s, 3, OCH_3), 3.90 (ddd, J = 9.9 Hz, 5.4 Hz, 2.4 Hz, $H_{5'}$), 4.17−4.30 (2 dd, 2, J = 12.3, 5.4 Hz, J = 12.3, 2.4 Hz, 2 $H_{6'}$), 5.13−5.33 (m, 4, $H_{2'}$, $H_{3'}$, $H_{4'}$, $H_{1'}$), 6.35 (d, 1, J = 15.9 Hz, H_α), 7.00 (d, 2, J = 8.7 Hz, H_3, H_5), 7.47 (d, 2, J = 8.7 Hz, H_2, H_6), 7.65 (d, 1, J = 15.9 Hz, H_β); ^{13}C NMR ($CDCl_3$), δ 21.01−21.07 (4, $OCO\underline{C}H_3$), 52.10 ($CO_2\underline{C}H_3$), 62.29−70.22−71.47−72.56−73.02 (5, $C_{2'}$, $C_{3'}$, $C_{4'}$, $C_{5'}$,$C_{6'}$), 98.94 ($C_{1'}$), 117.16 (C_α), 117.48 (2, C_3, C_5), 130.00 (3, C_1, C_2, C_6), 144.30 (C_β), 158.61 (C_4), 167.89−170.48 (4, $O\underline{C}OCH_3$), 170.54 ($\underline{C}O_2CH_3$).

*Methyl 4-(2′,3′,4′,6′-tetra-O-acetyl-β-D-glucopyranosyl) ferulate (**2b**):* crystallization in hexane/EtOAc gave **2b** as a white amorphous powder; yield, 65%; mp, 137 °C; R_f (hexane/EtOAc, 4:6), 0.56; ^{1}H NMR ($CDCl_3$), δ 2.10 (m, 12, $OCOCH_3$), 3.86 (s, 3, CO_2CH_3), 3.90 (s, 3, OCH_3), 3.91 (m, 1, $H_{5'}$), 4.24−4.33 (2dd, 2, J = 12.3, 5.1 Hz, J = 12.3, 1.8 Hz, $H_{6'}$), 5.19−5.36 (m, 4, $H_{1'}$, $H_{2'}$, $H_{3'}$, $H_{4'}$), 6.40 (d, 1, J = 15.9 Hz, H_α), 7.10 (m, 3, H_2, H_5, H_6), 7.67 (d, 1, J = 15.9 Hz, H_β); ^{13}C NMR ($CDCl_3$), δ 21.41−21.48 (4, $OCO\underline{C}H_3$), 52.51 ($CO_2\underline{C}H_3$), 56.85 (OCH_3), 62.67−69.10−71.88−72.88−73.27 (5, $C_{2'}$, $C_{3'}$, $C_{4'}$, $C_{6'}$, $C_{5'}$), 101.08 ($C_{1'}$), 112.19 (C_2), 117.92 (C_5), 120.31 (C_α), 122.42 (C_6), 131.70 (C_1), 144.99−148.59−151.52 (3, C_β, C_3, C_4), 168.15−171.05 (4, $O\underline{C}OCH_3$), 171.35 ($\underline{C}O_2CH_3$).

*Methyl 4-(2′,3′,4′,6′-tetra-O-acetyl-β-d-glucopyranosyl) caffeate (**2c**):* column chromatography (SiO_2; hexane/EtOAc, 6:4 to 1:1) gave **2c** as a white amorphous powder; yield, 30%; mp, 50 °C; R_f (hexane/EtOAc, 4:6), 0.52; ^{1}H NMR ($CDCl_3$), δ 2.07 (m, 12, $OCOCH_3$), 3.81 (s, 3, CO_2CH_3), 3.94 (m, 1, $H_{5'}$) 4.15−4.28 (2 dd, 2, J = 12.1, 5.0 Hz, J = 12.1, 1.4 Hz, $H_{6'}$), 5.01 (d, 1, J = 2.0 Hz, $H_{1'}$), 5.19−5.36 (m, 3, $H_{2'}$, $H_{3'}$, $H_{4'}$), 6.35 (d, 1, J = 15.9 Hz, H_α), 6.91−7.16 (m, 3, H_2, H_5,H_6), 7.59 (d, 1, J = 15.9 Hz, H_β); ^{13}C NMR ($CDCl_3$), δ 21.50−21.31 (4, $OCO\underline{C}H_3$), 52.46 ($CO_2\underline{C}H_3$), 62.41−68.86−72.12 72.85−73.13 (5, $C_{2'}$, $C_{3'}$, $C_{4'}$, $C_{5'}$, $C_{6'}$), 101.72 ($C_{1'}$), 115.86−117.83−118.29−121.76 (4, C_α, C_2, C_5, C_6), 132.28 (C_1), 144.71−146.37−148.14 (3, C_3, C_4, C_β), 170.83−171.28 (4, $O\underline{C}OCH_3$), 171.33 ($\underline{C}O_2CH_3$).

*4-β-d-Glucopyranosylcoumaric Acid (**3a**).* Compound **2a** (150 mg, 0.46 mmol) was added to a mixture of 1 M NaOH (8 equiv)/H_2O/MeOH, 1:2:3 v/v/v (22 mL), and stirred for 8 h at room temperature. Then, the mixture was acidified to pH 1−3 (wet pH paper) with Dowex 50 (H^+ form) and concentrated under reduced pressure. Crystallization in hexane/EtOAc afforded **3a** as a white powder: yield, 90%; mp, 193 °C; R_f (C-18 silica, H_2O + 0.05% HCO_2H in MeCN, 1:1), 0.91; ^{1}H NMR (CD_3OD), δ 3.38−3.54 (m, 4, $H_{2'}$, $H_{3'}$, $H_{4'}$, $H_{5'}$), 3.71−3.91 (2dd, 2, J = 12.0, 1.8 Hz, J = 12.0, 5.4 Hz, $H_{6'}$), 4.99 (d, 1, J = 7.5 Hz, $H_{1'}$), 6.37 (d, 1, J = 15.9 Hz, H_α), 7.14 (d, 2, J = 8.7 Hz, H_3, H_5), 7.57 (d, 2, J = 8.7 Hz, H_2, H_6), 7.65 (d, 1, J = 15.9 Hz, H_β); ^{13}C NMR (CD_3OD), δ 61.96 ($C_{6'}$), 70.31−73.84−76.43−76.95−77.23 (5, $C_{1'}$, $C_{2'}$, $C_{3'}$, $C_{4'}$, $C_{5'}$), 116.86 (C_α), 116.97 (2, C_3, C_5), 129.703 (2, C_2, C_6), 130.54 (C_1), 159.80 (C_β), 169.71 (C_4), 178.52 (CO_2H). HRMS-ESI, m/z $[M - H]^-$ calcd for $C_{15}H_{17}O_8$, 325.0929; found, 325.0934.

*Methyl 4-β-d-Glucopyranosylferulate (**3b′**).* Compound **2b** (710 mg, 1.92 mmol) was dissolved in dry MeOH (80 mL) and treated with a catalytic amount of MeONa. After 4 h of stirring, the mixture was acidified with Amberlite IRC 50 (H^+ form) to pH 1−3 (wet pH paper), filtered, and evaporated. Crystallization in Et_2O/MeOH yielded **3b′** as a white solid: yield, 95%; mp, 173 °C; R_f (C-18 silica, 0.05% HCO_2H in MeCN, 1:1), 0.54; ^{1}H NMR (CD_3OD), δ 3.35−3.56 (m, 4, $H_{2'}$, $H_{3'}$, $H_{4'}$, $H_{5'}$), 3.70−3.87 (2 dd, 2, J = 12.3, 1.8 Hz, J = 12.3, 5.1 Hz, $H_{6'}$), 3.79 (s, 3, CO_2CH_3), 3.91 (s, 3, OCH_3), 4.98 (d, 1, J = 7.2 Hz, $H_{1'}$), 6.47 (d, 1, J = 15.9 Hz, H_α), 7.19 (m, 2, H_5, H_6), 7.27 (d, 1, J = 2.1 Hz, H_2), 7.65 (d, 1, J = 15.9 Hz, H_β); ^{13}C NMR (CD_3OD), δ 51.46 ($CO_2\underline{C}H_3$), 56.11 (OCH_3), 61.82 ($C_{6'}$), 70.63−74.16−77.22−77.66 (4, $C_{2'}$, $C_{3'}$, $C_{4'}$, $C_{5'}$), 101.55 ($C_{1'}$), 111.78 (C_2), 116.42−116.73 (2, C_α, C_5), 122.88 (C_6), 130.08 (C_1), 145.45−149.48−150.40 (3, C_3, C_4, C_β), 168.73 ($\underline{C}O_2CH_3$).

*4-β-d-Glucopyranosylferulic Acid (**3b**).* Compound **3b′** (100 mg, 0.27 mmol) was added to a mixture of 1 M NaOH (2 equiv)/H_2O/MeOH, 1:2:3 v/v/v (3.2 mL), and stirred for 8 h at room temperature. Then, the mixture was acidified to pH 1−3 (wet pH paper) with Dowex 50 (H^+ form) and concentrated under reduced pressure. Crystallization in hexane/EtOAc afforded **3b** as a white powder: yield, 85%; mp, 199 °C; R_f (C-18 silica, 0.05% HCO_2H in MeCN, 1:1), 0.88; ^{1}H NMR (CD_3OD), δ 3.36−3.56 (m, 4, $H_{2'}$, $H_{3'}$, $H_{4'}$, $H_{5'}$), 3.71−3.87 (2dd, 2, J = 12.0, 1.5 Hz, J = 12.0, 5.1 Hz, $H_{6'}$), 3.90 (s, 3, OCH_3), 4.99 (d, 1, J =

7.2 Hz, $H_{1'}$), 6.41 (d, 1, J = 15.9 Hz, H_α), 7.16 (dd, 1, J = 9.0, 1.5 Hz, H_6), 7.20 (d, 1, J = 9.0 Hz, H_5), 7.27 (d, 1, J = 1.5 Hz, H_2), 7.63 (d, 1, J = 15.9 Hz, H_β); ^{13}C NMR (CD_3OD), δ 56.10 (OCH_3), 61.82 ($C_{6'}$), 70.63−74.17−77.22−77.65 (4, $C_{2'}$, $C_{3'}$, $C_{4'}$, $C_{5'}$), 101.58 ($C_{1'}$), 111.78 (C_2), 116.76−117.23 (2, C_5, C_α), 122.77 (C_6), 129.99 (C_1), 145.43 (C_β), 149.37−150.39 (2, C_3, C_4), 170.00 (CO_2H). HRMS-ESI, *m*/*z* [M − H]$^-$ calcd for $C_{16}H_{20}O_9$, 355.1035; found, 355.1031.

*Methyl 4-(β-d-Glucopyranosyl)caffeate (**3c′**).* Deacetylation (same procedure as for **2b′**) yielded **3c′** as a white powder after crystallization in Et_2O/MeOH: yield, 80%; mp, 207 °C; R_f (C-18 silica, 0.05% HCO_2H in MeCN, 1:1), 0.67; ^{1}H NMR (CD_3OD), δ 3.47−3.53 (m, 4, $H_{2'}$, $H_{3'}$, $H_{4'}$, $H_{5'}$), 3.73−3.92 (2dd, 2, J = 12.1, 1.8 Hz, J = 12.1, 4.8 Hz, $H_{6'}$), 3.79 (s, 3, CO_2CH_3), 4.86 (d, 1, J = 7.2 Hz, $H_{1'}$), 6.40 (d, 1, J = 15.9 Hz, H_α), 7.06 (dd, 2, J = 8.5, 2.1 Hz, H_6), 7.12 (d, 1, J = 2.1 Hz, H_2), 7.21 (d, 1, J = 8.5 Hz, H_5), 7.59 (d, 1, J = 15.9 Hz, H_β); ^{13}C NMR (CD_3OD), δ 52.87 ($CO_2\underline{C}H_3$), 65.71 ($C_{6'}$), 74.60−78.10−80.87−81.71 (4, $C_{2'}$, $C_{3'}$, $C_{4'}$, $C_{5'}$), 106.20 ($C_{1'}$), 119.23 (C_2), 120.35−121.48−125.47 (3, C_5, C_6, C_α), 134.39 (C_1), 149.40−151.90−152.19 (3, C_3, C_4, C_β), 172.65 ($\underline{C}O_2CH_3$).

*4-β-d-Glucopyranosylcaffeic Acid (**3c**).* **3c** was obtained by saponification of **3c′** in 1 M NaOH (3 equiv)/H_2O/EtOH, 1:2:3 v/v/v: yield, 85%; mp, 135 °C; R_f (C-18 silica, 0.05% HCO_2H in MeCN, 1:1), 0.92; ^{1}H NMR (CD_3OD), δ 3.47−3.59 (m, 4, $H_{2'}$, $H_{3'}$, $H_{4'}$, $H_{5'}$), 3.75−3.94 (dd, 2, J = 12.0, 1.6 Hz, J = 12.0, 4.6 Hz, $H_{6'}$), 4.88 (d, 1, J = 7.2 Hz, $H_{1'}$), 6.34 (d, 1, J = 15.9 Hz, H_α), 7.06 (dd, 1, J = 8.4 Hz, J = 1.9 Hz, H_6), 7.13 (d, 1, J = 1.9 Hz, H_2), 7.22 (d, 1, J = 8.4 Hz, H_5), 7.58 (d, 1, J = 15.9 Hz, H_β); NOE correlation between H_5 and $H_{1'}$; ^{13}C NMR (CD_3OD), δ 61.76 ($C_{6'}$), 70.65 ($C_{4'}$), 74.16−76.91−77.76 (3, $C_{2'}$, $C_{3'}$, $C_{5'}$), 102.91 ($C_{1'}$), 114.61−115.17−117.49 (3, C_α, C_2, C_5), 121.41 (C_6), 130.87 (C_1), 134.25 (C_β), 147.84−148.01 (2, C_3, C_4), 168.59 (CO_2H). HRMS-ESI, *m*/*z* [M − H]$^-$ calcd for $C_{15}H_{18}O_9$, 341.0879; found, 341.0873.

*1,2,3,4,6-Penta-O-chloroacetyl-β-d-glucopyranoside (**4**).* To a suspension of D-glucose (2 g, 11.1 mmol) in CH_2Cl_2/pyridine, 9:1 (50 mL) was added dropwise chloroacetyl chloride (8.8 mL, 111.1 mmol) at room temperature. The mixture was stirred to nearly complete solubilization. Ice water (0 °C) was poured into the solution, and the organic layer was separated and washed, respectively, with 1 M HCl, saturated $NaHCO_3$ and NaCl solution. The mixture was then dried over Na_2SO_4 and concentrated under reduced pressure. The syrupy residue was purified by column chromatography (SiO_2, cyclohexane/EtOAc, 7:3 v/v) to give **4** in 65% yield: ^{1}H NMR ($CDCl_3$), δ 4.03−4.14 (5s, 10, $COCH_2Cl$), 4.08−4.30 (m, 4, H_2, H_4,H_5, H_6), 5.22−5.49 (m, 1, H_3), 5.70 (d, 0.45, J = 8.2 Hz, $H_{1\beta}$), 6.31 (d, 0.55, J = 1.9 Hz, $H_{1\alpha}$).

*2,3,4,6-Tetra-O-chloroacetyl-β-D-glucopyranose (**5**).* A mixture of **4** (2.7 g, 4.8 mmol) and hydrazinium acetate (0.44 g, 4.8 mmol) in THF (50 mL) was stirred for 3 h at room temperature. After concentration to dryness, the resulting oil was purified by column chromatography (SiO_2, cyclohexane/EtOAc, 7:3 v/v) to give **5** in 70% yield: ^{1}H NMR ($CDCl_3$), δ 4.09−4.15 (m, 10, 2 × H_6, 4 × $COCH_2$-Cl), 4.21−4.24 (m, 1, H_5), 4.86−5.53 (m, 4, H_1, H_2, H_3, H_4).

*2,3,4,6-Tetra-O-chloroacetyl-α-D-glucopyranosyltrichloroacetimidate (**6**).* To a solution of **5** (2.7 g, 5.5 mmol) in CH_2Cl_2 (50 mL) were added trichloroacetonitrile (5.57 mL, 55 mmol) and a catalytic amount of 1,8-diazabicyclo[5.4.0]undec-7-ene. The mixture was stirred for 4 h at room temperature. After concentration to dryness, the resulting oil was purified with column chromatography (SiO_2, cyclohexane/EtOAc, 8:2 v/v) to give **6** in 60% yield: ^{1}H NMR ($CDCl_3$), δ 4.03−4.14 (m, 8, 4 × $COCH_2Cl$), 4.32−4.40 (m, 3, H_5, 2 × H_6), 5.25−5.35 (m, 2, H_2, H_4), 5.70 (t, 1, J = 9.8 Hz, H_3), 6.63 (d, 1, J = 3.7 Hz, H_1), 8.79 (s, 1, NH).

*3,4-Di-O-benzylcaffeic Acid Benzyl Ester (**7**).* To a solution of caffeic acid (1.5 g, 8.3 mmol) in acetone (30 mL) were added anhydrous K_2CO_3 (3.45 g, 25 mmol) and benzyl bromide (3.95 mL, 33.3 mmol). The mixture was stirred for 12 h under reflux. Water (200 mL) was poured into the solution, and the mixture was extracted with EtOAc, dried over Na_2SO_4, and concentrated under reduced pressure. The syrupy residue was purified by crystallization in EtOH to afford **7** in 85% yield: mp, 71 °C; ^{1}H NMR ($CDCl_3$), δ 5.18−5.21−5.25 (3s, 6, benzylic CH_2), 6.31 (d, 1, J = 15.9 Hz, H_α), 6.93 (d, 1, J = 8.4 Hz, H_5), 7.08 (dd, 1, J = 1.8, 8.4 Hz, H_6), 7.14 (d, 1, J = 1.8 Hz, H_2), 7.34−7.44 (m, 15, H_{Ar}), 7.63 (d, 1, J = 15.9 Hz, H_β); ^{13}C NMR ($CDCl_3$), δ 70.62−71.33−71.71 (3, benzylic CH_2), 114.12−114.71 (2, C_2, C_5), 116.23 (C_α), 123.44 (C_6), 127.61−129.00 (16, C_1, C_{Bn}−H), 136.65−137.23 (3, $\underline{C}_{Bn}$−C), 145.42 (C_β),149.31−151.52 (2, C_3, C_4), 167.44 (CO).

*3,4-Di-O-benzylcaffeic Acid (**8**).* A mixture of **7** (2 g, 4.44 mmol) in 3 M methanolic KOH (50 mL) was stirred for 12 h under reflux. After cooling, the mixture was acidified with 3 M HCl. The precipitate was collected and purified by crystallization in MeOH to afford **8** in 90% yield: mp, 196 °C; ^{1}H NMR ($CDCl_3$), δ 5.18−5.19 (2s, 4, benzylic CH_2), 6.32 (d, 1, J = 15.9 Hz, H_α), 7.06 (d, 1, J = 8.4 Hz, H_5), 7.16 (dd, 1, J = 1.8, 8.4 Hz, H_6), 7.30 (d, 1, J = 1.8 Hz, H_2), 7.31−7.50 (m, 10, H_{Ar}), 7.57 (d, 1, J = 15.9 Hz, H_β).

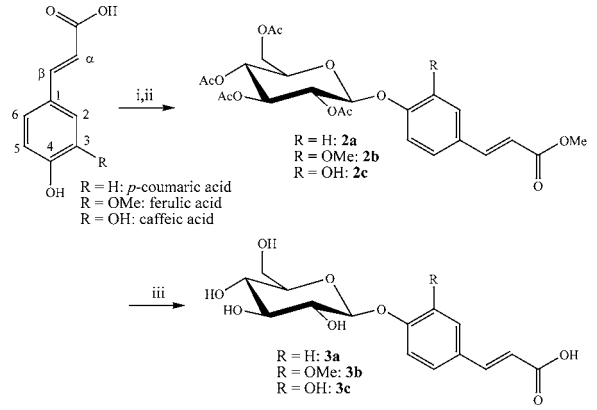
*Compound **9**.* To a solution of **8** (0.33 g, 0.91 mmol) and **6** (0.87 g, 1.37 mmol) in anhydrous CH_2Cl_2 (under N_2, molecular sieves 4A) was added AgOTf (0.23 g, 0.91 mmol). The mixture was stirred for 1 h at room temperature. After filtration on Celite, the solution was washed with saturated $NaHCO_3$ and water, dried over Na_2SO_4, and concentrated under reduced pressure. The syrupy residue was purified with column chromatography (SiO_2, cyclohexane/EtOAc, 3:1 v/v) to give **9** in 50% yield: ^{1}H NMR ($CDCl_3$), δ 3.91 (ddd, 1, J = 2.1, 4.5, 9.9 Hz, $H_{5'}$), 4.04−4.16 (4s, 8, $COCH_2Cl$), 4.15 (dd, 1, J = 12.3, 2.1 Hz, $H_{6'}$), 4.34 (dd, 1, J = 12.3, 4.5 Hz, $H_{6'}$), 5.26−5.31 (m, 7, benzylic CH_2, $H_{2'}$, $H_{3'}$, $H_{4'}$), 5.86 (d, 1, J = 7.8 Hz, $H_{1'}$), 6.23 (d, 1, J = 15.9 Hz, H_α), 6.94 (d, 1, J = 8.4 Hz, H_5), 7.10 (dd, 1, J = 8.4, 1.8 Hz, H_6), 7.15 (d, 1, J = 1.8 Hz, H_2), 7.31−7.50 (m, 10, H_{Ar}), 7.66 (d, 1, J = 15.9 Hz, H_β).

*Compound **10**.* Compound **9** was dissolved in a pyridine/water mixture (1:1 v/v, pH 6.7) and stirred at room temperature for 10 h. After concentration under reduced pressure, the syrupy residue was purified with column chromatography (SiO_2, EtOAc/MeOH, 95:5 v/v) to give **10** in 80% yield: ^{1}H NMR ($CDCl_3$), δ 3.40−3.47 (m, 4, $H_{2'}$, $H_{3'}$, $H_{4'}$, $H_{5'}$), 3.69−3.90 (m, 2, $H_{6'}$), 5.18−5.19 (2s, 4, benzylic CH_2), 5.61 (d, 1, J = 7.1 Hz, $H_{1'}$), 6.42 (d, 1, J = 15.9 Hz, H_α), 7.03−7.49 (m, 13, H_{Ar}, H_2, H_6, H_5), 7.72 (d, 1, J = 15.9 Hz, H_β).

*1-O-β-D-Caffeoylglucose (**11**).* To a solution of **10** (50 mg, 0.095 mmol) in EtOH (10 mL) were added 1,4-cyclohexadiene (153 mg, 1.9 mmol) and 10% palladium on charcoal (20 mg) at room temperature. The reaction was monitored by HPLC analysis. After the reaction was complete, the mixture was filtered on Celite and the solvent was evaporated under reduced pressure. The syrupy residue was purified by flash chromatography (SiO_2, 1% HCO_2H in EtOAc) to give **11** in 40% yield: ^{1}H NMR ($CDCl_3$), δ 3.39−3.83 (m, 6, $2H_{6'}$, $H_{2'}$, $H_{3'}$, $H_{4'}$, $H_{5'}$), 5.58 (d, 1, J = 8.0 Hz, $H_{1'}$), 6.34 (d, 1, J = 16.0 Hz, H_α), 6.87 (d, 1, J = 8.0 Hz, H_6), 7.07 (d, 1, J = 8.0 Hz, H_5), 7.13 (s, 1, H_2), 7.68 (d, 1, J = 16.0 Hz, H_β); ^{13}C NMR ($CDCl_3$), δ 68.82−69.63−72.24−75.49−77.01 (5, $C_{2'}$, $C_{3'}$, $C_{4'}$, $C_{5'}$, $C_{6'}$), 94.14 ($C_{1'}$), 113.45 (C_α), 115.62 (C_2), 115.75 (C_4), 116.49 (C_6), 122.79 (C_3), 123.21 (C_5), 126.30 (C_1), 148.15 (C_β), 167.84 (CO). HRMS-ESI, *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{18}O_9$, 343.1023; found, 343.1024.

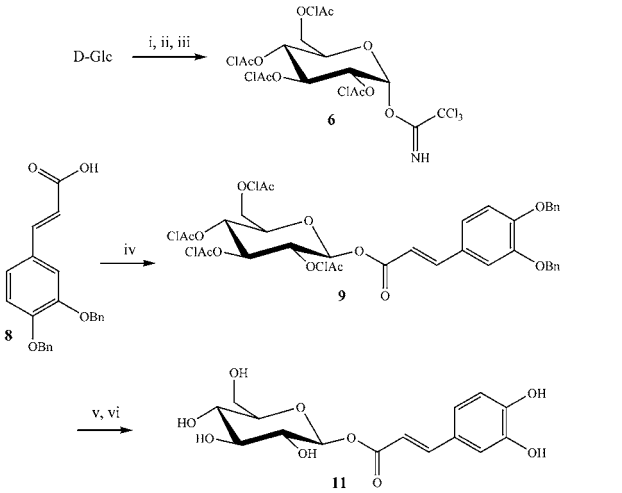
RESULTS AND DISCUSSION

Synthesis of Hydroxycinnamic Acid Glucosides (Figure 1). The key step is the glycosylation of methyl hydroxycinnamates by 1-bromo-2,3,4,6-tetra-*O*-acetyl-α-glucopyranose under phase-transfer conditions according to procedures previously used for the synthesis of flavonoid glucosides (*12*, *13*). The phase-transfer agent tris[2-(2-methoxyethoxy)ethyl]amine (TMEA), which specifically binds K^+, allows the transfer of the phenolate ion from the alkaline aqueous solution to CH_2Cl_2 and its subsequent nucleophilic substitution with the glycosyl bromide. The conditions had to be optimized to allow the deprotonation of methyl hydroxycinnamates while minimizing the hydrolysis of the glycosyl bromide or its conversion into the corresponding glucal (*14*) or orthoester. Using 0.1 M $NaHCO_3$/0.1 M KCl or saturated K_2CO_3 aqueous solutions, we obtained only moderate yields of glucosides (20−30%). The choice of 1 M $NaHCO_3$/1 M KCl led to substantial improvements with yields of 30−75%. In the case of methyl caffeate,



i) MeOH, H_2SO_4 ii) 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosylbromide (1.5 equiv.) TMEA (1.5 equiv.), CH_2Cl_2, 0.1M $NaHCO_3$-0.1M KCl (1:1), 40°C iii) 1M NaOH/H_2O/MeOH (1:2:3) or MeONa cat./MeOH, then 1M NaOH/H_2O/MeOH (1:2:3).

Figure 1. Synthesis route to hydroxycinnamic glucosides.



i) $ClCH_2COCl$ (10 equiv.), CH_2Cl_2/Pyr (9:1) ii) $AcO^-,NH_2NH_3^+$ (1 equiv.), THF, iii) Cl_3CCN (10 equiv.), DBU cat., CH_2Cl_2, iv) **6** (1.5 equiv.), AgOTf (1 equiv.), CH_2Cl_2, 4A sieves v) Pyr/water (1:1), pH 6.7 vi) 1,4-cyclohexadiene (20 equiv.), 10% Pd/C, EtOH.

Figure 2. Synthesis route to 1-*O*-β-D-caffeoylglucose.

mixtures of 3′-*O*-β-D-glucoside, 4′-*O*-β-D-glucoside, and 3′,4′-*O*-β-D-diglucoside were obtained. Only the major 4′-*O*-β-D-glucoside was isolated by chromatography. As expected from the α configuration of glycosyl bromide and the possible orienting effect of the 2-*O*-acetyl group, the glycosidation was stereoselective and led to the exclusive formation of the β anomers [$J(H_1-H_2)$ = 7.5 Hz]. Less expectedly, the final deprotection step (cleavage of the acetyl groups and methyl ester) required rather extensive optimization by HPLC-MS analysis in terms of the selected base and its concentration as well as the temperature and duration of the reaction. For instance, attempts at full deprotection using 1 M KOH in EtOH were generally not satisfying and led to partially deprotected glucosides and substantial degradation. Whereas 4-*O*-β-D-glucopyranosylcoumaric acid (**3a**) could be directly obtained from **2a** using 1 M NaOH/H_2O/EtOH (*15*), **2b** and **2c** had to be deprotected in two steps involving sugar deacetylation by mild catalytic methanolysis followed by methyl ester saponification using 1 M NaOH/H_2O/EtOH. 4-*O*-β-D-Glucopyranosylferulic acid (**3b**) and 4-*O*-β-D-glucopyranosylcaffeic acid (**3c**) were thus obtained in 80−85% overall yield.

All glucosides were characterized by MS and NMR analyses. The characteristics of **3a** and **3b** are in agreement with those reported in the literature with compounds isolated from flaxseed (*7*) or Riesling wine (*16*). Glucosylation at position 4′ of **3c** was confirmed by 1D-NOE experiments.

Synthesis of 1-*O*-β-D-Caffeoylglucose (Figure 2). The main challenges were the development of a route allowing the selective synthesis of the β-anomer and the choice of protecting groups on the sugar and caffeic moieties that can be removed under mild conditions, preserving the vinyl group and glucosyl ester bond. The chloroacetyl group was chosen for the protection of the sugar OH groups because it can be removed under neutral conditions in which the glycosyl ester is expected to be stable and also because it allows a 1,2-trans diastereoselectivity in the glucosylation step (*17*). The preparation of the glucosyl donor (**5**, pure α configuration) was achieved by chloroacetylation of D-glucose with chloroacetyl chloride in CH_2Cl_2/pyridine followed by anomeric deacylation by hydrazinium acetate in THF. Different protecting groups were tested for the phenolic groups of caffeic acid such as the chloroacetyl and acetyl groups (*18*). Both were found to be too labile under the acylation conditions used in the glucosylation step, that is, DCC/DMAP (*19*) or the acyl chloride method in presence of triethylamine, which is known to increase the β stereoselectivity (*20*). In fact, both procedures resulted in the migration (transesterification) of one phenolic acyl group to the anomeric OH group of **5** with retention of the α configuration. Finally, we selected the more stable benzyl group for the protection of the phenolic OH groups of caffeic acid because it has been reported that its cleavage by mild hydrogenolysis using 1,4-cyclohexadiene as a hydrogen donor can be achieved without hydrogenation of a carbon−carbon double bond (*21*). 3,4-Di-*O*-benzylcaffeic acid (**8**) was prepared by perbenzylation of caffeic acid followed by saponification of the benzyl ester in an overall yield of 90%. To ensure a good β diastereoselectivity in the glucosylation step, hemiketal **5** was activated to the corresponding trichloroacetimidate (**6**) and coupled to **8** in the presence of silver triflate in dry CH_2Cl_2 (*22*). Protected caffeoylglucose **9** was obtained in 60% yield as a pure β anomer [$J(H_1-H_2)$ = 7.8 Hz] after purification by chromatography. By contrast, activation of the trichloroacetimidate by BF_3/Et_2O (*23*) or trimethylsilyltriflate and acylation conditions using 3,4-di-*O*-benzylcaffeoyl chloride and **5** all led to anomeric mixtures. Then, the four chloroacetyl groups of **9** were removed selectively in pyridine/H_2O to yield **10** in 80% yield. Finally, the palladium-catalyzed hydrogenolysis of the two benzyl groups by 1,4-cyclohexadiene in EtOH at room temperature was carefully monitored by HPLC-MS over 5 h, that is, until complete consumption of **10**. The major product, 1-*O*-β-D-caffeoylglucose (**11**), was then isolated by flash chromatography in 40% yield. Its structure was confirmed by ^1H and ^{13}C NMR and high-resolution mass spectrometry.

Anthocyanin Copigmentation. Colorless polyphenols play an important role in natural color expression by interacting with anthocyanin pigments in the vacuoles of epidermal plant cells (*24*−*26*). In this process called copigmentation, the colorless polyphenol (copigment) stacks on the colored forms of the anthocyanin, that is, the flavylium cation or the quinonoid bases it forms upon deprotonation of its most acidic OH groups. The visible absorption band of the copigmentation complex is usually shifted to larger wavelengths with respect to the free colored form (bathochromic effect). Moreover, in the mildly acidic conditions of the vacuoles (typical pH in the range of 2.5−7.5), the colored forms are thermodynamically unstable and are converted to colorless forms via a process the key step of which

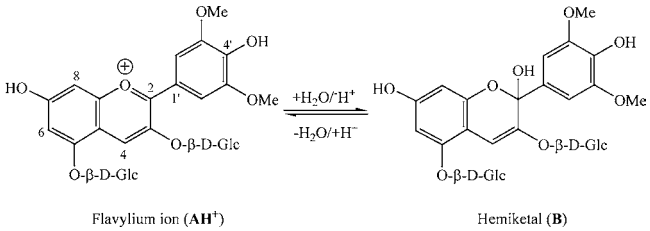


Figure 3. Hydration equilibrium of malvin (3,5-di-*O*-*β*-D-glucopyranosylmalvidin).

is the reversible water addition at C-2 of the flavylium cation (AH^+) and subsequent formation of a colorless hemiketal (B) (thermodynamic constant K_h) (**Figure 3**) (*27*). Unlike B, AH^+ and the quinonoid bases display a flat π-electron-rich aglycone that is prone to developing π-stacking interactions with the copigment molecule, so that copigmentation can be approximatively rationalized as the selective interaction of the copigment with the colored forms of the anthocyanin. Through the copigmentation equilibrium (binding constant *K*), the copigment molecule competes with water for the flavylium ion with the overall effect that a fraction of hemiketal B is dehydrated to AH^+ due to its binding to the copigment (ligand L) to form AHL^+ (*28*−*30*). Thus, the color of the solution is enhanced through a hyperchromic effect.

In this work, malvin (3,5-di-*O*-*β*-D-glucopyranosylmalvidin), a common commercially available anthocyanin, was mixed with various concentrations of the hydroxycinnamic acids and their 4-*O*-*β*-D-glucosides for a quantitative evaluation of the stability of the corresponding copigmentation complexes. The choice of the pH 2.5 phosphate buffer can be justified as follows: (1) at this pH, free malvin is dominantly under the colorless B form [a pH variation in the range of 0.6−3.0 allowed us to re-evaluate the pK_h value of malvin: pK_h = 1.52 (±0.02) at 25 °C (10 points, r = 0.993)], thus providing a strong potential for color regeneration; (2) at this pH, the sole colored form to consider is the flavylium ion [first pK_a ca. 4 (*30*)]. Color enhancement via copigmentation of malvin by one of the chemically synthesized copigments (4-*β*-D-glucopyranosylferulic acid) is represented in **Figure 4**.

Absorbance values for calculations are collected at the wavelength of the isosbestic point of AH^+ and AHL^+ determined in strongly acidic solutions (pH <1) at which malvin is under a pure flavylium form. By definition, at the isosbestic point, AH^+ and AHL^+ display the same molar absorption coefficient, ϵ. Combining the expressions of the thermodynamic constants [$K_h = h[B]/[AH^+]$ with $h = 10^{-pH}$, $K = [AHL^+]/([AH^+][L])$] with the laws of pigment and copigment conservation ($C = [AH^+] + [B] + [AHL^+]$, $L_t = [L] + [AHL^+] \approx [L]$ because $L_t \gg C$) and Beer's law [$A = \epsilon([AH^+] + [AHL^+])$, $A_0 = \epsilon[AH^+]$ in the absence of copigment, $A_0^{ref} = \epsilon C$ = absorbance of a strongly acidic solution of malvin under a pure flavylium form] readily yields eq 1:

$$A = \frac{A_0(1 + K_h/h)(1 + KL_t)}{1 + K_h/h + KL_t} \quad (1)$$

In the absence of copigment, eq 1 simply becomes eq 2:

$$A_0 = \frac{A_0^{ref}}{1 + K_h/h} \quad (2)$$

Equation 2 is used for the determination of pK_h at different temperatures (25−45 °C). From a plot of ln K_h versus 1/T, we deduce ΔH_h° = 5.6 (±0.3) kJ/mol, ΔS_h° = −11 (±1) J/K/mol.

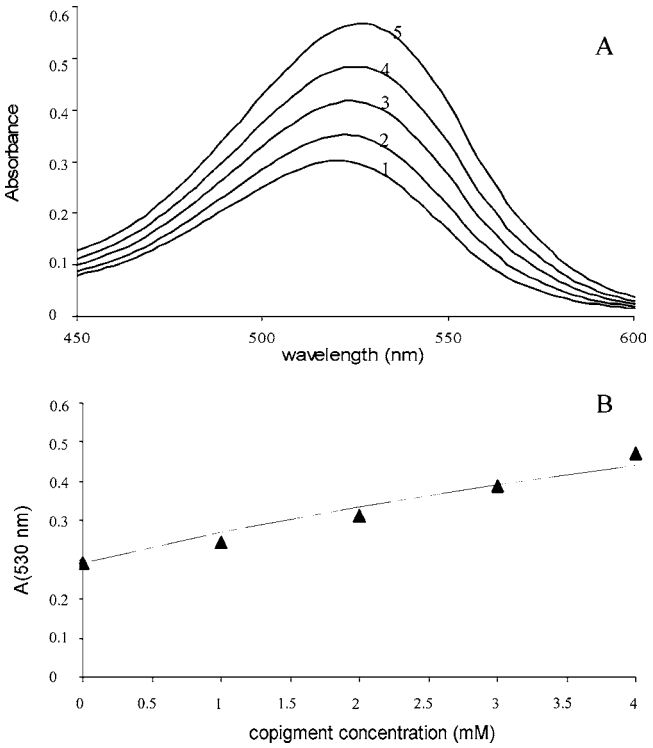


Figure 4. (**A**) Absorption spectra of malvin (0.1 mM) in the presence of 4-*β*-D-glucopyranosylferulic acid in a pH 2.5 phosphate buffer at 25 °C. Copigment/pigment molar ratios: 0 (1), 10 (2), 20 (3), 30 (4), 40 (5). (**B**) Plot of the visible absorbance at 530 nm as a function of copigment concentration; experimental points (▲) and theoretical curve (–) from a curve fitting according to eq 1 (pK_h set at 1.52).

Table 1. Copigmentation Binding Constants for the Different Malvin–Copigment Couples Investigated[a]

copigment	K (M^{-1})	r^2
p-coumaric acid	129 (± 4)	0.998
	120 (± 4)	0.997
4-*β*-D-glucopyranosylcoumaric acid	111 (± 6)	0.996
	121 (± 5)	0.998
caffeic acid	243 (± 8)	0.992
	236 (± 9)	0.999
4-*β*-D-glucopyranosylcaffeic acid	244 (± 12)	0.997
	234 (± 12)	0.998
ferulic acid	331 (± 8)	0.999
4-*β*-D-glucopyranosylferulic acid	277 (± 14)	0.997
	234 (± 12)	0.998

[a] Each experiment is duplicated. Values in parentheses are the standard deviations of the curve-fitting procedure.

Equation 1 is used for the curve fitting of the A versus L_t plots to obtain optimized values for K as the sole adjustable parameter (**Table 1**). Overall, the glucosyl moiety of the copigment has little impact on the stability of the copigmentation complexes. A slight destabilization can be noted, especially for ferulic acid, which can be attributed to the glucosyl moiety hindering the pigment approach on one side of hydroxycinnamic nucleus. The values of copigmentation binding constants are close to the one reported in the literature for the malvin−chlorogenic acid couple (*31*). However, they are ca. 1 order of magnitude higher than those already reported with the copigments caffeic acid and ferulic acid (*32*). However, in the quoted work (*32*), a simplified theoretical treatment was used that assumes the colored forms to be negligible with respect to the colorless forms at the pH investigated. This assumption is actually not valid at pH 2.5 so that a more general treatment

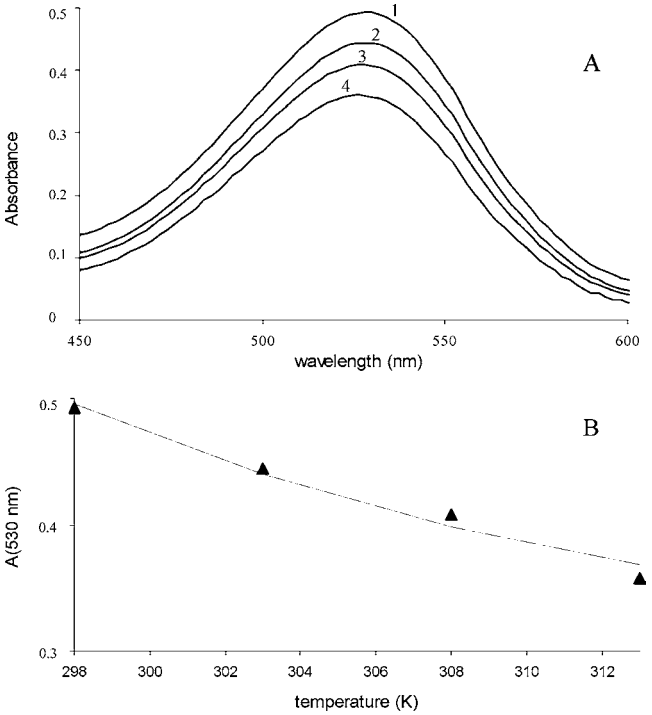


Figure 5. (**A**) Temperature dependence of the absorption spectrum of malvin (0.1 mM) in the presence of 4-β-D-glucopyranosylferulic acid (5 mM) in a pH 2.5 phosphate buffer. T = 298 K (1), 303 K (2), 308 K (3), 313 K (4). (**B**) Plot of the visible absorbance at 530 nm as a function of T; experimental points (▲) and theoretical curve (–) from a curve fitting based on eq 1 and standard relationships expressing the temperature dependence of K and K_h.

Table 2. Copigmentation Enthalpies and Entropies for the Different Malvin–Copigment Couples Investigated

copigment	ΔH^0 (kJ/mol)	ΔS^0 (J/K/mol)	r^2
p-coumaric acid	–32.1 (± 1.9)[a]	–62.8 (± 6.2)[a]	0.998
4-β-D-glucopyranosylcoumaric acid	–26.0 (± 3.4)	–38 (± 11)	0.992
caffeic acid	–25.6 (± 4.7)	–46 (± 15)	0.990
4-β-D-glucopyranosylcaffeic acid	–21.6 (± 4.3)	–31 (± 14)	0.990
ferulic acid	–29.0 (± 2.6)	–50.1 (± 8.7)	0.994
4-β-D-glucopyranosylferulic acid	–33.8 (± 4.2)	–71 (± 14)	0.993

[a] Values in parentheses are the standard deviations of the curve-fitting procedure.

explicitly taking into account the thermodynamics of flavylium hydration becomes necessary (see eq 1).

The partial dissociation of the copigmentation complexes upon heating can be visualized in **Figure 5**. Copigmentation by hydroxycinnamic acids and their glucosides thus appears as an exothermic process. Copigmentation enthalpies (ΔH^0) and entropies (ΔS^0) can be estimated from the curve fittings of the A versus T curves against eq 1 and the additional relationships $K_h = \exp[-\Delta G_h^0/(RT)]$ and $K = \exp[-\Delta G^0/(RT)]$ with $\Delta G_h^0 = \Delta H_h^0 - T\Delta S_h^0$ and $\Delta G^0 = \Delta H^0 - T\Delta S^0$ (**Table 2**). The sole optimizable parameters are ΔH^0 and ΔS^0.

Overall, the copigmentation of malvin by hydroxycinnamic acids and their glucosides appears as an enthalpy-driven process with an unfavorable entropy. Therefore, it can be concluded that the favorable entropic contribution promoted by the rearrangement of the solvation shells of the pigment and copigment molecules when they associate (hydrophobic effect) does not compensate the loss of translational and rotational degrees of freedom. Once more, the influence of the glucosyl moiety is not significant, in agreement with a binding process solely involving the planar polarizable polyphenolic nuclei.

In this work, efficient chemical syntheses of *O*-aryl-β-D-glucosides and 1-*O*-β-D-glucosylesters of hydroxycinnamic acids are described. These naturally occurring polyphenols can be used as standards for the identification and titration purposes in plants and foods and for investigations of their bioavailability and potential health effects. In particular, their glucosyl moiety could allow a better intestinal absorption than the corresponding aglycones. It is also noteworthy that 1-*O*-β-D-caffeoylglucose retains a free catechol moiety that is critical for metal complexation and a strong radical scavenging capacity. Finally, although increasing their water solubility, the glucosyl moiety does not significantly alter the capacity of the hydroxycinnamic acid *O*-aryl-β-D-glucosides to interact with anthocyanins and stabilize natural colors.

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