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Role of caffeic glucoside esters in defense-repair processing of trees II: Synthesis of 2-(3,4-dihydroxyphenyl)-ethyl 3-*O*-(α -L-rhamnopyranosyl)- β -D-glucopyranoside

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Abstract The reference compound (**9**), with a partial structure of acteoside, was synthesized to elucidate the relation between structural features and the precipitation or solubility of the oxidation products of acteoside: 2-(3,4-dihydroxyphenyl)-ethyl 3-*O*-(α -L-rhamnopyranosyl)- β -D-glucopyranoside (**9**). The glycosyl acceptor 2-*O*-benzoyl-3-*O*-(2,3,4-tri-*O*-acetyl- α -L-rhamnopyranosyl)-4,6-*O*-benzylidene- α -D-glucopyranosyl trichloroacetimidate (**7**) was prepared from allyl 2-*O*-benzoyl-3-*O*-(2,3,4-tri-*O*-acetyl- α -L-rhamnopyranosyl)-4,6-*O*-benzylidene- α -D-glucopyranoside (**4**) via isomerization of the allyl group with an iridium complex to the 1-propenyl group and its hydrolysis with HgCl₂/HgO, followed by treatment with CCl₃CN and DBU in a 65.5% overall yield. The glycosyl acceptor 3,4-diacetoxyphenethyl alcohol (**16**) was prepared from homoveratric acid via demethylation with 57% HI and its acetylation with Ac₂O and 85% H₃PO₄, followed by selective reduction of the carboxyl group to the alcohol with a borane–tetrahydrofuran complex in a 61% overall yield. The glycosylation of **7** with **16** in dichloromethane promoted by BF₃·Et₂O gave a 74.3% yield of **8**. Hydrolysis of **8** with 90% CF₃COOH gave the debenzylidenated product, which was treated with NaOMe to afford a 32% overall yield of the desired compound **9**. This compound **9** was identical with the natural specimen.

Key words Synthesis · Acteoside · 2-(3,4-Dihydroxyphenyl)-ethyl 3-*O*-(α -L-rhamnopyranosyl)- β -D-glucopyranoside · 3,4-Diacetoxyphenethyl alcohol · Trichloroacetimidate method

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Introduction

As described in a preceding paper, a physiological role of caffeic glucoside esters in the defense-repair processing of wounded tissue of trees was examined.¹ Their peroxidase-catalyzed oxidation products showed hard solubility in polar solvents. For example, acteoside precipitated as a brown substance in the oxidation medium; but 2-(3,4-dihydroxyphenyl)-ethyl β -D-glucopyranoside, synthesized as one of the partial structures of acteoside, did not. Hence both or one of the caffeoyl and rhamnosyl moieties may be required to cause precipitable substances.

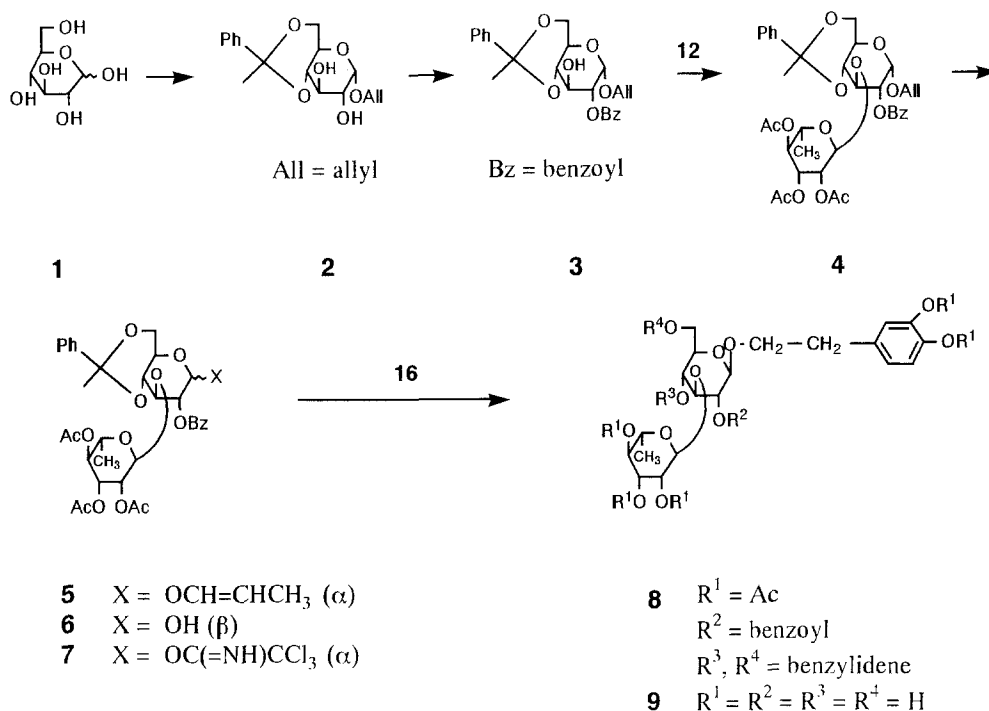
In this report, 2-(3,4-dihydroxyphenyl)-ethyl 3-*O*-(α -L-rhamnopyranosyl)- β -D-glucopyranoside (**9**), the partial structure of acteoside, was prepared to provide a reference compound to elucidate the above acteoside-precipitation behavior (Fig. 1). The fully protected sugar cores of phenylpropanoid glycosides were prepared by the trichloroacetate method, but it appears that full synthesis of acteoside has not yet been realized.² In addition, the related sugar cores were prepared by the Koenigs-Knorr method.^{3,4} Reports on the biological activities of acteoside and another natural phenylpropanoid glycosides are increasing.^{5–7}

Experiment

Instruments and chromatography

Melting points (mp) were uncorrected. The following instruments were used: for specific optical rotations, ATAGO Polarimeter POLAX; for infrared (IR) spectra, JASCO FT/IR-230; for nuclear magnetic resonance (NMR) spectra, BRUKER AM 400 (¹H: 400MHz; for mass spectrometry (MS) spectra, FAB- and EI mass spectra (JEOL JMS-SX102A); for MALDI-TOF mass spectra (Perceptive Biosystems Voyager RP). Chemical shifts (δ) and coupling constants (*J*) are given in as parts per million and Hertz, respectively. Thin-layer chromatography (TLC), reversed

Fig. 1. Construction of decaffeoyl-lacteoside (**9**). All, allyl; Bz, benzoyl



TLC, and column chromatography were performed on silica gel plates (Merck 60G), RP-8F_{254s} (Merck) and on silica gel (Wakogel C-300, 45–75 μm) and Sephadex LH-20 (Pharmacia Fine Chemicals, 25–100 μm), respectively.

Allyl 4,6-*O*-benzylidene- α -D-glucopyranoside (**2**)

A mixture of D-glucose anhydride (24.2 g, 0.134 mol), allyl alcohol (200 ml, dried over active anhydrous calcium sulfate), and dry Dowex 50- \times 8(H⁺) resin (14.2 g) was stirred and refluxed at 114 °C for 2 h.⁸ After cooling, the resin was filtered off and washed with anhydrous ethanol (3 \times 30 ml); the combined filtrate was concentrated. After co-evaporation with a mixture of dry benzene and anhydrous ethanol (2 \times 42 ml), the residue was dried over phosphorus pentoxide at reduced pressure to give the crude syrupy allyl α -D-glucopyranoside (35.9 g). It showed a main spot on TLC with ethyl acetate/isopropyl alcohol/H₂O (9/4/2, v/v), R_f 0.67.

This was directly benzylidened with α , α -dimethoxytoluene (102 ml) in the presence of *p*-toluenesulfonic acid monohydrate (5.14 g, 27 mmol) by shaking for 24 h at room temperature (r.t.). The reaction mixture was diluted with *n*-hexane (120 ml); water (112 ml) and 10% aqueous sodium hydrogen carbonate (56 ml) were added, and the suspension was vigorously shaken for 15 min. The separated crystals were washed with water and then *n*-hexane to give a white crystal (21.2 g), mp 110°–117 °C. It was recrystallized from isopropyl alcohol to give compound **2** (18.8 g, 46%), mp 135°–137 °C; [α]_D³⁰ +106.7° (c 0.89, chloroform) [mp 130°–132 °C; [α]_D²⁵ +100.8° (c 0.79, chloroform)⁸]; TLC (ethyl acetate/*n*-hexane, 1:1, v/v) R_f 0.19; FAB-MS *m/z*: 308 [M]⁺; ¹H NMR (CDCl₃): for a glu-

cose moiety, δ 2.54 (1 H, br. d, *J* = 9.1, OH-2 or OH-3), 3.16 (1 H, br. s, OH-2 or OH-3), 3.48 (1 H, t, *J* = 9.4, H-4), 3.61 (1 H, m, H-5), 3.72 (1 H, t, *J* = 10.2, H_{ax}-6), 3.83 (1 H, dd, *J* = 3.9, 9.8, H-2), 3.93 (1 H, t, *J* = 9.3, H-3), 4.27 (1 H, dd, *J* = 4.8, 10.2, H_{eq}-6), 4.92 (1 H, d, *J* = 3.9, H-1), 5.52 (1 H, s, PhCH), 7.35–7.51 (5 H, m, aromatic); for an aglycone moiety (allyl), 4.04 (1 H, dd, *J* = 5.7, 12.8, -CH₂-CH=CH₂), 4.23 (1 H, dd, *J* = 5.3, 12.8, -CH₂-CH=CH₂), 5.24 (1 H, dd, *J* = 1, 10.4, -CH₂-CH=CH₂), 5.32 (1 H, dd, *J* = 1, 17.2, -CH₂-CH=CH₂), 5.87–5.97 (1 H, m, -CH₂-CH=CH₂).

Allyl 2-*O*-benzoyl-4,6-*O*-benzylidene- α -D-glucopyranoside (**3**)

To a mixture of compound **2** (11.9 g, 38.8 mmol) and 1-(benzoyloxy)benzotriazole (10.0 g, 41.7 mmol, prepared according to the method of Kim et al.⁹) in anhydrous dichloromethane (100 ml), triethylamine (4.25 g, 42 mmol) was added; the reaction mixture was stirred for 16 h at r.t. Dichloromethane (73 ml) was added, and the mixture was washed with 10% aqueous hydrogen carbonate (2 \times 20 ml), water (2 \times 20 ml), and saturated aqueous sodium chloride (20 ml). The combined organic layer was dried over anhydrous sodium sulfate and concentrated to give a syrupy residue (17.5 g). This residue was purified by medium-pressure chromatography with ethyl acetate/*n*-hexane (1:3, v/v) to give a pure compound **3** (14.2 g, 89%); TLC (ethyl acetate/*n*-hexane, 0.8:1.0, v/v) R_f 0.72; FAB-MS *m/z*: 413 [M + 1]⁺; ¹H NMR (CDCl₃): for a glucose moiety, δ 2.35 (1 H, br. s, OH-2), 3.64 (1 H, t, *J* = 9.4, H-4), 3.79 (1 H, t, *J* = 10.3, H_{ax}-6), 3.95–4.03 (1 H, m, H-5), 4.32 (1 H, dd, *J* = 4.9, 10.3, H_{eq}-6), 4.39 (1 H, t, *J* = 9.5, H-3), 5.06 (1 H, dd, *J* = 3.8, 9.7, H-2), 5.22 (1 H, d, *J* = 3.8, H-1), 5.58 (1 H, s, PhCH),

7.36–8.10 (10H, m, aromatic); for an aglycone moiety (allyl), 4.01 (1H, dd, $J = 6.0, 13.0$, $-\text{CH}_2-\text{CH}=\text{CH}_2$), 4.21 (1H, dd, $J = 5.2, 13.2$, $-\text{CH}_2-\text{CH}=\text{CH}_2$), 5.15 (1H, dd, $J = 1.5, 10.4$, $-\text{CH}_2-\text{CH}=\text{CH}_2$), 5.28 (1H, dd, $J = 1.5, 17.2$, $-\text{CH}_2-\text{CH}=\text{CH}_2$), 5.78–5.87 (1H, m, $-\text{CH}_2-\text{CH}=\text{CH}_2$).

Allyl 2-*O*-benzoyl-3-*O*-(2,3,4-tri-*O*-acetyl- α -L-rhamnopyranosyl)-4,6-*O*-benzylidene- α -D-glucopyranoside (**4**)

A mixture of compound **3** (12.0 g, 29.1 mmol), compound **12** (16.4 g, 34.5 mmol), dry molecular sieve 4A (16 g), and anhydrous dichloromethane (65 ml) was stirred at r.t. for 50 min and then at -18°C for 70 min. To the stirred suspension, $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (0.5 g, 3.5 mmol) in anhydrous dichloromethane (18 ml) was added over 10 min. It was further stirred at -18°C for 20 min. The reaction mixture was then removed from the cool bath and further stirred for 160 min. To neutralize it, a powder of sodium hydrogen carbonate (12 g) was added, and the suspension was stirred for 10 min. It was diluted with dichloromethane (400 ml) and filtered through Celite. The filtrate was concentrated to give a white solid (28.4 g). It was recrystallized from a mixture of ethyl acetate and *n*-hexane to give compound **4** (16.8 g, 85% based on compound **3**). mp $183^\circ\text{--}185^\circ\text{C}$; $[\alpha]_{\text{D}}^{30} +65.3^\circ$ (c 1.07, chloroform); TLC (ethyl acetate/*n*-hexane, 0.8:1.0, v/v) Rf 0.67; FAB-MS m/z : 707 $[\text{M} + \text{Na}]^+$ (+NaCl); MALDI-TOF-MS m/z : 707.869 $[\text{M} + \text{Na}]^+$, 723.843 $[\text{M} + \text{K}]^+$; ^1H NMR (CDCl_3): for a glucose moiety, δ 3.73 (1H, t, $J = 9.5$, H-4), 3.81 (1H, t, $J = 10.3$, H_{ax}-6), 3.96–4.04 (1H, m, H-5), 4.33 (1H, dd, $J = 4.8, 10.3$, H_{eq}-6), 4.45 (1H, t, $J = 9.6$, H-3), 5.10 (1H, dd, $J = 3.8, 9.7$, H-2), 5.22 (1H, d, $J = 3.9$, H-1), 5.60 (1H, s, PhCH), 7.32–8.01 (10H, m, aromatic); for a rhamnose moiety, 0.77 (1H, d, $J = 6.5$, H-6), 4.15–4.22 (1H, m, 1H, H-5), 4.90 (1H, t, $J = 10.0$, H-4), 5.00 (1H, d, $J = 1.5$, H-1), 5.05 (1H, dd, $J = 1.5, 3.5$, H-2), 1.89, 1.90, and 1.94 (each 3H, 3s, CH₃CO); for an aglycone moiety, 3.99 (1H, dd, $J = 6.0, 13.2$, $-\text{CH}_2-\text{CH}=\text{CH}_2$), 4.20 (1H, dd, $J = 5.2, 13.2$, $-\text{CH}_2-\text{CH}=\text{CH}_2$), 5.14 (1H, dd, $J = 1.3, 10.3$, $-\text{CH}_2-\text{CH}=\text{CH}_2$), 5.26 (1H, dd, $J = 1.4, 17.1$, $-\text{CH}_2-\text{CH}=\text{CH}_2$), 5.75–5.85 (1H, m, $-\text{CH}_2-\text{CH}=\text{CH}_2$).

1-Propenyl 2-*O*-benzoyl-3-*O*-(2,3,4-tri-*O*-acetyl- α -L-rhamnopyranosyl)-4,6-*O*-benzylidene- α -D-glucopyranoside (**5**)

To a solution of compound **4** [14.2 g, 20.8 mmol; Rf 0.33 (ethyl acetate/*n*-hexane, 0.5:1.0, v/v)] in peroxide-free tetrahydrofuran [50 ml, freshly distilled from benzophenone ketyl and treated with copper (I) chloride] the commercial iridium catalyst [1,5-cyclooctadienebis(methyldiphenylphosphine)-iridium hexafluorophosphate, 300 mg, 0.36 mmol] was added.^{10,11} The stirred solution was degassed, placed under dry and oxygen-free argon, and degassed once more. The catalyst was activated by hydrogen for 7 min. The solution was degassed once more and stirred at r.t. for 150 min under an atmosphere of dry and oxygen-free argon. TLC analysis

showed complete conversion of the allyl glycoside compound (**4**) into the propenyl glycoside compound (**5**) [Rf 0.35 (ethyl acetate/*n*-hexane, 0.5:1.0, v/v)]. The solvent was evaporated, and the residual solid was dissolved in dichloromethane (800 ml). The solution was successively washed with aqueous 10% sodium hydrogen carbonate (100 ml), water (100 ml), and aqueous saturated sodium chloride (100 ml). The organic layer was dried over anhydrous sodium sulfate and concentrated to give a pale yellow solid (16.1 g). This substance was used in the next step without further purification. A small portion of it was purified for ^1H NMR analysis by column chromatography with ethyl acetate/*n*-hexane (0.5:1, v/v) to give the glass (**5**); FAB-MS m/z : 707 $[\text{M} + \text{Na}]^+$ (+NaCl); ^1H NMR (CDCl_3): for a glucose moiety, δ 3.74 (1H, t, $J = 9.5$, H-4), 3.79 (1H, t, $J = 10.3$, H_{ax}-6), 3.94–4.01 (1H, m, H-5), 4.32 (1H, dd, $J = 4.7, 10.2$, H_{eq}-6), 4.47 (1H, t, $J = 9.6$, H-3), 5.24 (1H, dd, $J = 3.5, 10.0$, H-2), 5.40 (1H, d, $J = 3.5$, H-1), 5.60 (1H, s, PhCH), 7.33–8.00 (10H, m, aromatic); for a rhamnose moiety, 0.77 (1H, d, $J = 6.1$, H-6), 4.09–4.21 (1H, m, 1H, H-5), 4.90 (1H, t, $J = 10.0$, H-4), 5.01 (1H, d, $J = 1.7$, H-1), 5.06 (1H, dd, $J = 1.7, 3.4$, H-2), 1.89, 1.91, and 1.94 (each 3H, 3s, CH₃CO); for an aglycone moiety, 1.52 (3H, dd, $J = 1.5, 6.9$, $-\text{CH}=\text{CH}-\text{CH}_3$), 5.18 (1H, m, $-\text{CH}=\text{CH}-\text{CH}_3$), 6.10 (1H, dd, $J = 1.5, 12.3$, $-\text{CH}=\text{CH}-\text{CH}_3$).

2-*O*-Benzoyl-3-*O*-(2,3,4-tri-*O*-acetyl- α -L-rhamnopyranosyl)-4,6-*O*-benzylidene- α -D-glucopyranose (**6**)

A solution of mercuric chloride (5.7 g, 26.9 mmol) in acetone/water (10:1, v/v, 100 ml) was added dropwise to a mixture of compound **5** (15.8 g, 23 mmol), yellow mercuric oxide (5.7 g, 26.9 mmol), and acetone/water (10:1, v/v, 300 ml) during 18 min.¹² After stirring at r.t. for 120 min, the mercuric oxide was removed through Celite, acetone was evaporated, and the residue was extracted twice with a mixture of ether (120 ml) and ethyl acetate (50 ml). The combined organic layer was successively washed with a saturated aqueous potassium iodide (2 \times 100 ml), water (2 \times 50 ml), and a saturated aqueous sodium chloride (100 ml) and dried over anhydrous sodium sulfate to give a solid (12.2 g). Recrystallization from ethanol gave compound **6** (9.2 g, 68%); mp $123^\circ\text{--}125^\circ\text{C}$; $[\alpha]_{\text{D}}^{30} +21.3^\circ$ (c 0.94, chloroform); TLC (ethyl acetate/*n*-hexane, 0.8:1.0, v/v; the detection reagent: aniline hydrogen phthalate) Rf 0.46; FAB-MS m/z : 667 $[\text{M} + \text{Na}]^+$ (+NaCl); MALDI-TOF-MS m/z : 668.270 $[\text{M} + \text{Na}]^+$, 684.259 $[\text{M} + \text{K}]^+$; ^1H NMR (CDCl_3): for a glucose moiety, δ 3.57–3.63 (1H, m, H-5), 3.77 (1H, t, $J = 9.4$, H-4), 3.86 (1H, t, $J = 10.4$, H_{ax}-6), 3.90 (1H, d, $J = 9.2$, OH-1), 4.20 (1H, t, $J = 9.0$, H-3), 4.43 (1H, dd, $J = 4.8, 10.4$, H_{eq}-6), 4.86 (1H, d, $J = 8.9$, H-1), 5.15 (1H, t, $J = 9.2$, H-2), 5.59 (1H, s, PhCH), 7.33–8.01 (10H, m, aromatic); for a rhamnose moiety, 0.75 (3H, d, $J = 6.0$, H-6), 1.89, 1.91, 1.94 (each 3H, each s, CH₃CO), 4.10–4.17 (1H, m, H-5), 4.88 (1H, t, $J = 10.0$, H-4), 4.93 (1H, d, $J = 1.5$, H-1), 5.01 (1H, dd, $J = 1.5, 3.3$, H-2), 5.22 (1H, dd, $J = 3.3, 10.0$, H-3).

2-*O*-Benzoyl-3-*O*-(2,3,4-tri-*O*-acetyl- α -L-rhamnopyranosyl)-4,6-*O*-benzylidene- α -D-glucopyranosyl trichloroacetimidate] (**7**)

A solution of compound **6** (6.7 g, 10.3 mmol) in anhydrous dichloromethane (135 ml) was cooled to -19°C and added with trichloroacetonitrile (7.5 g, 52 mmol) under nitrogen atmosphere. The mixture was added dropwise while stirring with a solution of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (320 mg, 2.0 mmol) in anhydrous dichloromethane (3 ml) for 5 min and stirred for another 4.5 h while the temperature was allowed to become -4°C .^{13,14} The solvent was evaporated to give the solid residue (11 g). It was purified by medium-pressure chromatography with ethyl acetate/*n*-hexane (0.4:1.0, v/v) to give a pure compound **7** (8 g, 96%); mp 202° – 204°C ; TLC (ethyl acetate/*n*-hexane, 0.8:1.0, v/v) Rf 0.47; FAB-MS *m/z*: 812 [M + Na]⁺ (+NaCl); ¹H NMR (CDCl₃): for a glucose moiety, δ 3.84 (1H, t, *J* = 10.2, H_{Ax-6}), 3.86 (1H, t, *J* = 9.35, H-4), 4.10–4.22 (1H, m, H-5), 4.40 (1H, dd, *J* = 4.8, 10.4, H_{eq-6}), 4.49 (1H, t, *J* = 9.6, H-3), 5.37 (1H, dd, *J* = 3.7, 9.6, H-2), 5.64 (1H, s, PhCH), 6.66 (1H, d, *J* = 3.7, H-1), 7.34–7.98 (10H, m, aromatic); for a rhamnose moiety, 0.81 (3H, d, *J* = 6.2, H-6), 1.88, 1.91, and 1.96 (each 3H, each s, CH₃CO), 4.10–4.22 (1H, m, H-5), 4.92 (1H, t, *J* = 10.0, H-4), 5.00 (1H, d, *J* = 1.6, H-1), 5.05 (1H, dd, *J* = 1.6, 3.4, H-2), 5.26 (1H, dd, *J* = 3.4, 10.1, H-3); for an aglycone moiety, 8.59 (1H, s, $-\text{C}(=\text{NH})-\text{CCl}_3$).

2-(3,4-Diacetoxyphenyl)-ethyl 2-*O*-benzoyl-3-*O*-(2,3,4-tri-*O*-acetyl- α -L-rhamnopyranosyl)-4,6-*O*-benzylidene- β -D-glucopyranoside (**8**)

To a mixture of compound **7** (7.0 g, 8.9 mmol), compound **16** (2.0 g, 8.4 mmol) in anhydrous dichloromethane (70 ml), and dry molecular sieve 4A (7.5 g) was added BF₃·Et₂O (126 mg, 0.9 mmol) in anhydrous dichloromethane (5 ml) with stirring at -19°C . The reaction mixture was stirred for 3 h while the temperature was allowed to become -13°C , followed by further stirring at r.t. for 19 h. The solution was diluted with dichloromethane (100 ml), filtered through Celite, and washed with dichloromethane (100 ml). The combined solution was washed with aqueous saturated sodium hydrogen carbonate (30 ml), water (40 ml), and aqueous saturated sodium chloride and then dried over anhydrous sodium sulfate to give a white solid (10.2 g). It was purified by medium-pressure chromatography with ethyl acetate/*n*-hexane (0.4:1.0, v/v) to give compound **8** (6.4 g, 88%); mp 221° – 224°C ; [α]_D³⁰ -35.38° (c 1.13, chloroform); TLC (ethyl acetate/*n*-hexane, 0.8:1.0, v/v) Rf 0.22; FAB-MS *m/z*: 887 [M + Na]⁺ (+NaCl); MALDI-TOF-MS *m/z*: 888.326 [M + Na]⁺, 904.324 [M + K]⁺; ¹H NMR (CDCl₃): for a glucose moiety, δ 3.55 (1H, td, *J* = 4.8, 9.7, H-5), 3.77 (1H, t, *J* = 9.3, H-4), 3.81 (1H, t, *J* = 10.3, H_{ax-6}), 4.09 (1H, t, *J* = 9.0, H-3), 4.38 (1H, dd, *J* = 4.8, 10.5, H_{eq-6}), 4.65 (1H, d, *J* = 8.0, H-1), 5.32 (1H, t, *J* = 8.0, H-2), 5.56 (1H, s, PhCH), 6.83–7.98 (10H, m, aromatic); for a rhamnose moiety, 0.73 (3H, d, *J* = 6.2, H-6), 1.80, 1.90, 1.94 (each 3H, each s,

aliphatic CH₃CO), 4.12 (1H, dq, *J* = 6.2, 10.0, H-5), 4.80 (1H, d, *J* = 1.2, H-1), 4.85 (1H, t, *J* = 10.0, H-4), 5.03 (1H, dd, *J* = 1.3, 3.4, H-2), 5.24 (1H, dd, *J* = 3.6, 10.0, H-3); for an aglycone moiety, 2.24, 2.25 (each 3H, each s, aromatic CH₃CO), 2.81 (t-like, *J* = 7.0, H- β), 3.66 (1H, dt, *J* = 7.0, 9.6, H- α), 4.06 (1H, dt, *J* = 7.0, 9.6, H- α), 6.83–7.98 (3H, m, aromatic).

2-(3,4-Dihydroxyphenyl)-ethyl 3-*O*-(α -L-rhamnopyranosyl)- β -D-glucopyranoside (**9**)

To an ice-cooled solution of compound **8** (0.39 g, 0.451 mmol) in anhydrous dichloromethane (6 ml), 90 wt% trifluoroacetic acid (5.3 ml) was added in one portion, and the reaction mixture was stirred at 0°C for 25 min. The mixture was co-evaporated with anhydrous toluene in vacuo to give a residue (0.42 g). It was purified by medium-pressure chromatography with ethyl acetate/*n*-hexane (1.5:1.0, v/v) to give the product 2-(3,4-diacetoxyphenyl)-ethyl 2-*O*-benzoyl-3-*O*-(2,3,4-tri-*O*-acetyl- α -L-rhamnopyranosyl)- β -D-glucopyranoside (0.18 g, 51%); TLC (ethyl acetate/*n*-hexane (2:1, v/v) Rf 0.24. The starting compound **8** was recovered in a 46% yield; TLC (ethyl acetate/*n*-hexane (2:1, v/v) Rf 0.73. To a solution of the product (180 mg, 0.232 mmol, 1.0 eq.) in anhydrous dichloromethane (5 ml), NaOMe (1.96 mmol, 8.4 eq.) in anhydrous methanol (3 ml) was added at r.t. under nitrogen atmosphere. After stirring for 22 h at r.t., dry Dowex 50- \times 4 (H⁺) resin (1.2 g) was added to the solution and stirred for 15 min. The resin was filtered off and washed with methanol; the combined filtrate was concentrated to give a residue (103 mg). It was chromatographed on Sephadex LH-20 with MeOH/water (1:4, v/v) to give compound **9** (66 mg, 32%); [α]_D³⁰ -47.0°C (c 0.92, CH₃OH); reversed TLC (MeOH/H₂O, 0.5:1.0, v/v) Rf 0.66; FAB-MS *m/z*: 463 [M + 1]⁺, 485 [M + Na]⁺ (+NaCl); MALDI-TOF-MS *m/z*: 485.987 [M + Na]⁺; ¹H NMR (CD₃OD): for a glucose moiety, δ 3.23–3.34 (3H, m, H-2, H-4, H-5), 3.49 (1H, t, *J* = 8.9, H-3), 3.66–3.71 (1H, m, H-6), 3.86 (1H, dd, *J* = 2.0, 11.9, H-6), 4.29 (1H, d, *J* = 7.9, H-1); for a rhamnose moiety, 1.24 (3H, d, *J* = 6.2, H-6), 3.39 (1H, t, *J* = 9.6, H-4), 3.66–3.71 (1H, m, H-3), 3.94 (1H, dd, *J* = 1.5, 3.3, H-2), 3.96–4.05 (1H, m, H-5), 5.15 (1H, d, *J* = 1.5, H-1); for an aglycone moiety, 2.77 (2H, m, H- β), 3.66–3.71 (1H, m, H- α), 3.96–4.05 (1H, m, H- α), 6.55 (1H, dd, *J* = 2.0, 8.1, aromatic H-6), 6.66 (1H, d, *J* = 8.1, aromatic H-5), 6.68 (1H, d, *J* = 2.0, aromatic H-2). ¹³C NMR (CD₃OD): for a glucose moiety, δ 62.6 (C-6), 70.0 (C-4), 75.5 (C-5), 77.8 (C-2), 84.4 (C-3), 104.1 (C-1); for a rhamnose moiety, 17.8 (C-6), 70.1 (C-5), 72.2 (C-2), 72.3 (C-3), 73.9 (C-4), 102.7 (C-1); for an aglycone moiety, 36.5 (C-7), 72.0 (C-8), 116.2 (C-5), 117.0 (C-2), 121.2 (C-6), 131.4 (C-1), 144.6 (C-4), 146.0 (C-3).

1,2,3,4-Tetra-*O*-acetyl- α -L-rhamnopyranose (**10**)

α -L-Rhamnose monohydrate (15.3 g, 84 mmol) was acetylated at r.t. for 40 h with acetic anhydride (61 ml) and pyridine (61 ml). The solution was worked up in the usual

manner to give a paste (27.8 g). The ^1H NMR spectra showed the presence of the α and β anomers; their ratio was 2.2:1.0 ($\text{H}_{\alpha-1}$ δ 6.02; $\text{H}_{\beta-1}$ δ 5.84). This was used in the next step without further purification. TLC (ethyl acetate/*n*-hexane, 0.8:1.0, v/v) Rf 0.49 and 0.44; ^1H NMR (CDCl_3): for an α form, δ 1.24 (d, $J = 6.2$, **H-6**), 2.01, 2.07, 2.16, and 2.17 (each s, CH_3CO), 3.94 (dq, $J = 6.2$, 10.0, **H-5**), 5.12 (t, $J = 10.0$, **H-4**), 5.25 (dd, $J = 1.8$, 3.4, **H-2**), 5.31 (dd, $J = 3.4$, 10.2, **H-3**), 6.02 (d, $J = 1.8$, **H-1**); for a β form, 1.29 (d, $J = 6.2$, **H-6**), 2.00, 2.07, 2.11, and 2.21 (each s, CH_3CO), 3.67 (dq, $J = 6.2$, 10.0, **H-5**), 5.08–5.15 (m, **H-3** and **H-4**), 5.48 (br d-like, **H-2**), 5.84 (d, $J = 0.9$, **H-1**).

2,3,4-Tri-*O*-acetyl- α -*L*-rhamnopyranose (**11**)

A solution of compound **10** (27.7 g, 83.5 mmol) and hydrazine acetate (9.5 g, 103 mmol) in anhydrous dimethylformamide (DMF, 200 ml) was stirred at 50°C for 10 min and then stirred at r.t. for 40 min.¹⁵ It was diluted with ethyl acetate (860 ml) and washed with aqueous saturated sodium chloride (4 \times 370 ml). The organic layer was dried over anhydrous sodium sulfate. After evaporation, a trace of the residual DMF was co-distilled with toluene (13 ml). It was recrystallized from ethyl acetate/*n*-hexane to give compound **11** (22 g, 91.6%). mp 85°–86.5°C; $[\alpha]_D^{30}$ –15.9°C (c 0.94, chloroform); TLC (ethyl acetate/*n*-hexane, 0.8:1.0, v/v; the detection reagent: aniline hydrogen phthalate) Rf 0.34; FAB-MS m/z : 313 $[\text{M} + \text{Na}]^+$ (+NaCl). The ^1H NMR spectra showed the presence of the α and β anomers; their ratio was 4.7:1.0 ($\text{H}_{\alpha-1}$ δ 5.16; $\text{H}_{\beta-1}$ δ 4.95). ^1H NMR (CDCl_3): for an α form, δ 1.22 (d, $J = 6.3$, **H-6**), 2.16, 2.06, 1.99 (each s, CH_3CO $\alpha\beta$), 3.31 (br. s, **OH-1** $\alpha\beta$), 4.13 (dq, $J = 6.3$, 10.0, **H-5**), 5.08 ($J = 10.0$, **H-4** $\alpha\beta$), 5.16 (br s, **H-1**), 5.27 (dd, $J = 2.0$, 3.3, **H-2**), 5.37 (dd, $J = 3.3$, 10.2, **H-3**); for a β form, δ 1.27 (d, $J = 6.1$, **H-6**), 2.16, 2.06, 1.99 (each s, CH_3CO $\alpha\beta$), 3.31 (br. s, **OH-1** $\alpha\beta$), 3.58 (m, **H-5**), 5.08 ($J = 10.0$, **H-4** $\alpha\beta$), 4.95 (br s, **H-1**), 5.38–5.40 (m, **H-2**), 5.02–5.03 (m, 10.2, **H-3**).

2,3,4-Tri-*O*-acetyl- α -*L*-rhamnopyranosyl trichloroacetimidate (**12**)

A solution of compound **11** (20.1 g, 69.4 mmol) in anhydrous dichloromethane (122 ml) was cooled to –19°C, and trichloroacetonitrile (49.9 g, 0.346 mol) was added under nitrogen atmosphere with stirring. DBU (2.1 g, 13.8 mmol) was added dropwise with stirring during 15 min, and the reaction mixture was stirred for 1 h while the temperature was allowed to become –15°C. The reaction mixture was then removed from the cool bath and stirred for an additional 1 h. The solvent was evaporated to give a paste. It was purified by medium-pressure chromatography with ethyl acetate/*n*-hexane (0.2:1.0, v/v) to give a pure compound **12** (30 g, 99.5%); TLC (ethyl acetate/*n*-hexane, 0.8:1.0, v/v) Rf 0.7; FAB-MS m/z : 458 $[\text{M} + \text{Na}]^+$ (+NaCl); ^1H NMR (CDCl_3): δ 1.27 (3H, d, $J = 6.3$, **H-6**), 2.02, 2.07, 2.17 (each 3H, each s, CH_3CO), 4.09 (1H, dq, $J = 6.3$, 10.0, **H-5**), 5.17 (1H, t, $J = 10.0$, **H-4**), 5.37 (1H, dd, $J = 3.4$, 10.2, **H-3**), 5.46

(1H, dd, $J = 1.8$, 3.4, **H-2**), 6.20 (1H, d, $J = 1.8$, **H-1**), 8.74 (1H, s, $-\text{C}(=\text{NH})-\text{CCl}_3$).

3,4-Diacetoxyphenylacetic acid (**15**)

To a solution of compound **14** (13.3 g, 79.2 mmol, prepared as described previously¹) and 85% H_3PO_4 (3.0 g) in anhydrous dichloromethane (210 ml), acetic anhydride (29.1 g, 0.29 mol) was added dropwise with stirring. This solution was refluxed for 3.5 h. After cooling, it was slowly poured into an ice-water mixture (130 ml) and extracted. The water layer was saturated with sodium chloride and extracted with dichloromethane (3 \times 30 ml). The combined organic layer was washed with water (3 \times 30 ml) and aqueous saturated sodium chloride (30 ml) and then dried over anhydrous sodium sulfate. It was concentrated and co-evaporated with toluene (3 \times 14 ml). The residue was dried over phosphorus pentoxide at reduced pressure to give the crude solid (22.2 g). It was recrystallized from ethyl acetate/*n*-hexane (16.8 g, 84.3%); mp 107.5°–109°C; TLC (ethyl acetate/*n*-hexane/formic acid, 0.8:1.0:3.0 drops, v/v/v) Rf 0.28; FAB-MS m/z : 207 $[\text{M}-45]^+$; ^1H NMR (CDCl_3): δ 2.27 (6H, s, CH_3CO), 3.63 (2H, s, $\alpha\text{-CH}_2$), 7.13–7.18 (3H, m, aromatic).

3,4-Diacetoxyphenethyl alcohol (**16**)

Compound **15** (7.1 g, 28 mmol) was placed in a reaction flask, followed by peroxide-free tetrahydrofuran [15 ml, freshly distilled from benzophenone ketyl and treated with copper (I) chloride]. The flask was immersed in an ice-salt bath and cooled to –19°C. Then 0.6M borane solution (51 ml, 30.6 mmol) was added dropwise under nitrogen atmosphere over a period of 20 min.¹⁶ The mixture was stirred and allowed to reach r.t. during a 26.5 h period. It was hydrolyzed with water (20 ml) at 0°C. The mixture was concentrated to dryness and evaporated with methanol (3 \times 6 ml) to give a pale yellow paste (6.9 g). It was purified by medium-pressure chromatography with ethyl acetate/*n*-hexane (0.8:1.0, v/v) to give a pure compound **16** (5.9 g, 89%); TLC (ethyl acetate/*n*-hexane, 0.8:1.0, v/v) Rf 0.25; EI-MS m/z : 238 $[\text{M}]^+$; ^1H NMR (CDCl_3): δ 2.27 (3H, br s, CH_3CO), 2.28 (3H, br.s, CH_3CO), 2.82 (2H, t, $J = 6.5$, $\beta\text{-CH}_2$), 3.80 (2H, t, $J = 6.5$, $\alpha\text{-CH}_2$), 7.04–7.10 (3H, m, aromatic).

Results and discussion

A typical strategy is shown in Fig. 1. Two glycosylation reactions were performed by the imidate method to prepare compounds **4** and **8**, respectively.¹³ The former glycosyl donor (**12**) was prepared as shown in Fig. 2. Treatment of the rhamnose peracetate (**10**) with hydrazine acetate gave a 91.6% yield of the 1-*O*-unprotected rhamnose derivative (**11**), as a white solid.¹⁵ The absence of the 1-*O*-acetyl group was confirmed by the ^1H NMR spectrum of **11** and the TLC experiment (see Experimental study, above). Treatment of

Finally, glycosylation of **16** with the trichloroacetimidate⁷ in the presence of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ and molecular sieve 4A in dichloromethane gave a 71% yield of compound **8**, as a white solid. The anomeric configuration of **8** was assigned to the β -form by ^1H NMR spectroscopy ($J_{\text{H-1,H-2}} = 8.0\text{Hz}$). Hydrolysis of **8** with 90% CF_3COOH resulted in a 51% yield of 4,6-dihydroxyglycoside. Although the TLC experiment showed only a trace of **8** during 4 min of reaction time, the starting compound **8** was recovered in a 46% yield, indicating that some basic reagent to quench the hydrolytic medium should have been required for the workup to avoid the reverse reaction. Treatment of the resulting alcohol with NaOMe in methanol and dichloromethane gave a 32% overall yield of the desired compound **9**. The spectral data of **9** were identical to those reported for the natural decaffeoylacteoside.¹⁷⁻¹⁹

Conclusions

We synthesized the naturally occurring phenylpropanoid glycosides **9** using the trichloroacetimidate⁷ as the key glycosyl donor with the anomeric configurations in full agreement with those of the sugar core of acteoside. Compound **9** may be involved in the formation of acteoside, which can be catalyzed with hydroxycinnanoyltransferases using 1-*O*-acylglucose or hydroxycinnamoyl-CoA esters as an acyl donor.^{20,21} Additionally, compound **8** is a useful intermediate for chemical synthesis of some phenylpropanoid glycosides, as the caffeoyl group can be introduced into the glucose at C-4 or C-6 through the protecting group exchange.

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