Total Synthesis of the Phenylpropanoid Glycoside, Acteoside

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Introduction

2-(3,4-Dihydroxyphenyl)ethyl-*O*-α-L-rhamnopyranosyl-(1→3)-4-*O*-caffeoyl-*β*-D-glucopyranoside (**1**) was first extracted from *Verbascum sinuatum* and named "verbascoside" by M. Scarpati *et al.*[1] in 1963, but they did not provide a complete structural identification. The complete chemical structure of this compound was elucidated by L. Birkofer *et al.*[2] in 1968, who also introduced the new name "acteoside". Between these two common names, we prefer "acteoside". Acteoside has also been found in other plant species such as *Paulownia tomentosa* Steud.,[3,4] *Conandron ramoidioides*,[5] and *Clerodendrum myricoides*.[6]

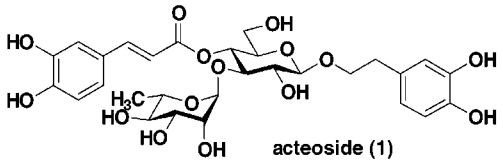
Recently, various bioactivities and pharmaceutical activities of acteoside have been reported. These include antimicrobial activity,[7] hepatoprotective activity,[8] sedative effect,[9] and defense-repair processing in trees.[10] However, the low content of acteoside in each plant species (0.02−0.4%) has limited the further investigation of these activities.

Hence, the chemical synthesis of acteoside has become an important problem. While a total synthesis has not yet been reported, some authors have described the partial synthesis of acteoside[11,12] or osmanthuside B6,[13] a close structural relative of acteoside. We report here the first total synthesis of acteoside.

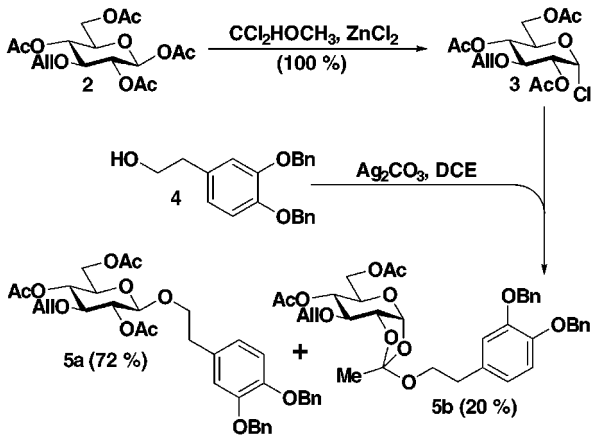
Results and Discussion

Our strategy for the total synthesis of acteoside (**1**, Scheme 1) involved a convergent route from the phenethyl glycoside derivative **5a**, from the glucose derivative **3**, and the phenetyl derivative **4** (Scheme 2). The 2,4,6-tri-*O*-acetyl-3-*O*-allyl-α-D-glucopyranosyl chloride (**3**) was prepared in quantitative yield from acetyl 2,4,6-tetra-*O*-acetyl-3-*O*-allyl-*β*-D-glucopyranoside[14] (**2**) using α,α-dichloromethyl methyl ether and zinc chloride.[15,16] Condensation of chloride **3** and 3,4-di-*O*-benzylphenethyl alcohol (**4**)[17] was achieved by the Koenigs−Knorr method in the presence of silver carbonate. When only 1.2 equiv of silver carbonate was used, a considerable amount of the unexpected ortho ester **5b** was produced. The maximum yield of the desired glycoside **5a** (72%) was obtained by using 15 equiv of silver carbonate. Under these conditions, formation of the ortho ester **5b** was kept at a minimum (20%).

Scheme 1. Structure of Acteoside (1)



Scheme 2. Synthesis of Phenethyl Glucoside 5a



In the next step, the caffeoyl moiety was introduced into the synthesized glycoside **5a**, as shown in Scheme 3. Compound **5a** was first deacetylated using sodium methoxide to afford the triol **6**. To distinguish the 4-OH-group from the 2-OH- and 6-OH groups in compound **6**, the acetyl-migration method was used. Selective tritylation of the 6-OH group of compound **6** gave compound **7** in 82% yield, acetylation of compound **7** gave compound **8** in 92% yield, and treatment of compound **8** with AcOH/dioxane gave compound **9** (79% yield). Esterification of this glycoside **9** with the caffeoyl derivative **10**[18] was achieved using the Steglich reaction[19] (Keck modification)[20,21] to give compound **11** (79% yield).

For rhamnosylation (Scheme 4), the 3-*O*-allyl group of compound **11** was subjected to oxidative cleavage using

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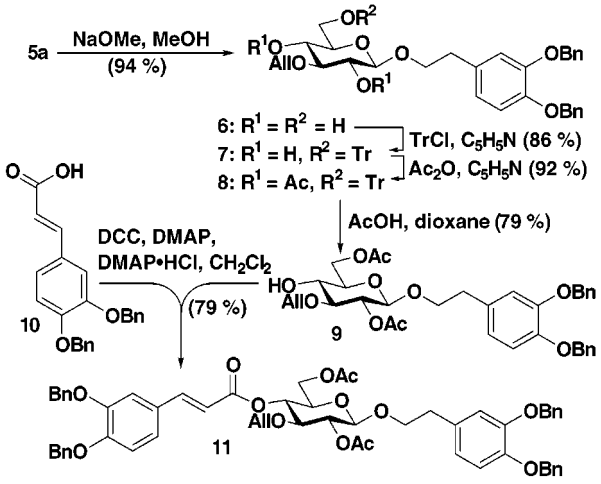
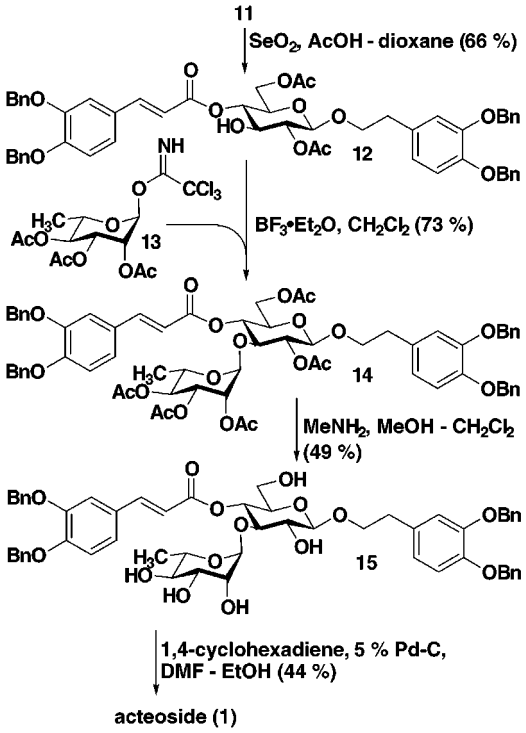
Scheme 3. Synthesis of Caffeoyl Ester 11



Scheme 4. Rhamnosylation and Deprotections



selenium dioxide.[22] Since some cleavage of the caffeoyl ester was observed at a higher reaction temperature (110 °C), the reaction had to be conducted at a lower temperature of around 80 °C to afford compound **12** in acceptable yield (66%). Rhamnosylation of compound **12** was performed with 2,3,4-tri-*O*-acetyl-α-L-rhamnopyranosyl trichloroacetimidate[23] (**13**) in the presence of boron trifluoride diethyl etherate at −20 °C to give the expected α-rhamnoside **14** in 73% yield.

The acetyl groups of compound **14** were then cleaved. Only the acetyl ester needs to be selectively cleaved from caffoeyl ester. In a previous paper on a structurally related phenylpropanoid, osmanthuside B6,[13] it was stated that the 2-*O*-acetyl group in the glucose residue could not be removed selectively from the caffeoyl ester even under treatment with ammonia−methanol at 5−10 °C. Consequently, various alternative reaction conditions were examined. We finally found that a solution of methylamine in methanol ($MeNH_2$−MeOH) was the best reagent for achieving the acetyl cleavage. Using $MeNH_2$−MeOH at −20 °C, all five acetyl groups of compound **14** were successfully removed within 9 h to give compound **15** in 49% yield.

The last step is the debenzylation of compound **15**. Neish[18] reported a catalytic hydrogenolysis of a phenolic benzyl ether of an α,β-unsaturated carboxylic acid in conjugation with an aromatic ring. Using these reaction conditions for compound **15**, TLC ($CHCl_3$/MeOH/H_2O, 30:10:1, v/v/v) analysis indicated that the double bond was stable during the cleavage of three of the four benzyl groups. However, the fourth benzyl group did not undergo hydrogenolysis before the double bond was saturated. Felix *et al.*[24] reported catalytic transfer hydrogenation of benzyl ether using 1,4-cyclohexadiene as a proton source. Knapp and Nandan[25] found that these reactions conditions can be applied to the hydrogenation reaction in the presence of an easily reduced alkene functionality, although they hydrogenated a benzyl ester, not a benzyl ether. Compound **15** was then treated with 1,4-cyclohexadiene/Pd−C in a solvent mixture of DMF/EtOH at 40 °C. The reaction was monitored by TLC ($CHCl_3$/MeOH/H_2O, 30:10:1, v/v/v). At 10 h, the starting compound **15** was completely consumed and the spot corresponding to the desired acteoside (**1**) (R_f = 0.20) had become the major spot, while two additional spots appeared at R_f = 0.40 and 0.25. Since the desired spot at R_f = 0.20 did not increase thereafter, the reaction was stopped. After isolation, we found that acteoside (**1**) had been successfully synthesized in 44% yield. ^1H and ^{13}C NMR spectra of the synthesized acteoside (**1**) were identical to those of the natural compound extracted from *P. tomentosa* Steud.[26] and *R. glutinosa var. hueichingensis*.[27] This result indicates that these catalytic hydrogenolysis reactions under the described conditions are suitable for the desired selective debenzylation in the presence of an olefinic double bond.

The advantage of this synthetic strategy is that several structurally related compounds of the acteoside family (phenylpropanoid glycosides) could also be synthesized if saccharides other than the rhamnosyl residue **13** were used. For example, if a glucose derivative or a xylose derivative was employed, plantamajoside[28] or conandoroside[5] could be obtained, respectively.

Experimental Section

All melting points (mp) are uncorrected. NMR spectra were recorded with TMS as an internal standard. The assignments of the signals were determined using a decoupling and/or a 2D-COSY technique. Coupling constants (*J*) are given in Hz. Anhydrous CH_2Cl_2 and $ClCH_2CH_2Cl$ were obtained by distilling from P_2O_5. Column chromatography was performed on silica gel (Wakogel C-200). Preparative TLC was done on silica gel plates (Kieselgel 60 F_{254}, Merck). Unless otherwise indicated, the usual workup for each reaction mixture consists of extraction with

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EtOAc, washing with brine, drying over Na_2SO_4, and evaporation *in vacuo*.

2,4,6-Tri-*O*-acetyl-3-*O*-allyl-α-D-glucopyranosyl Chloride (3). To a solution of **2**[14] (8.2 g, 21.11 mmol) in CH_2Cl_2 (14 mL) were added α,α-dichloromethyl methyl ether (3.4 mL, 37.59 mmol) and a 2.2 M solution of $ZnCl_2 \cdot Et_2O$ (0.96 mL, 2.11 mmol) in CH_2Cl_2 (0.77 mL) at 0 °C. The solution was stirred in the dark at room temperature for 1 h, diluted with EtOAc, neutralized with saturated aqueous $NaHCO_3$ solution, and worked up to give an oily residue. The residue was purified by column chromatography using a solvent mixture of EtOAc/*n*-hexane (1:2, v/v) to give **3** (7.7 g, 100%) as a colorless oil: $[\alpha]^{20}_D$ +136.10 (*c* 1.01, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$) δ 2.09, 2.10, 2.14 (s, 3 H each), 3.95 (t, *J* = 9.6, 1 H), 4.05−4.30 (m, 2 H), 4.11 (dd, *J* = 2.0, 12.4, 1 H), 4.21 (ddd, *J* = 2.0, 4.2, 9.6, 1 H), 4.25 (dd, *J* = 4.2, 12.4, 1 H), 4.92 (dd, *J* = 4.0, 9.6, 1 H), 5.10 (t, *J* = 9.6, 1 H), 5.17 (ddt, *J* = 1.3, 1.3, 10.6, 1 H), 5.23 (ddt, *J* = 1.3, 1.3, 17.1, 1 H), 5.82 (ddt, *J* = 5.3, 10.6, 17.1, 1 H), 6.29 (d, *J* = 4.0, 1 H).

3,4-Di-*O*-benzylphenethyl 2,4,6-Tri-*O*-acetyl-3-*O*-allyl-β-D-glucopyranoside (5a). To a solution of **3** (8.8 g, 24.12 mmol) in anhydrous $ClCH_2CH_2Cl$ (62 mL) were added 3,4-di-*O*-benzylphenethyl alcohol (**4**)[17] (4.0 g, 11.96 mmol), Ag_2CO_3 (99 g, 359.02 mmol), and powdered molecular sieves (4 Å) at room temperature. The reaction mixture was stirred overnight in the dark at room temperature and filtered, and the filtrate was condensed *in vacuo*. The residue was diluted with EtOAc, washed with water, and worked up to give an oily residue. Crystallization of the residue from EtOH afforded **5a** (5.7 g, 72%) as colorless crystals: mp 68−69 °C; $[\alpha]^{20}_D$ −10.79 (*c* 0.50, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.90, 2.06, 2.07 (s, 3 H each), 2.77 (t, *J* = 6.8, 2 H), 3.50−3.61 (m, 2 H), 3.54 (t, *J* = 9.5, 1 H), 3.99−4.06 (m, 3 H), 4.11 (dd, *J* = 2.7, 12.2, 1 H), 4.21 (dd, *J* = 4.9, 12.2, 1 H), 4.34 (d, *J* = 7.8, 1 H), 4.97 (dd, *J* = 7.8, 9.5, 1 H), 5.04 (t, *J* = 9.5, 1 H), 5.08−5.23 (m, 2 H), 5.11 (s, 2 H), 5.15 (d, *J* = 5.7, 2 H), 5.75 (ddt, *J* = 5.7, 10.3, 17.0, 1 H), 6.69 (dd, *J* = 2.2, 8.4, 1 H), 6.81 (d, *J* = 2.2, 1 H), 6.84 (d, *J* = 8.4, 1 H), 7.24−7.49 (m, 10 H). Anal. Calcd for $C_{37}H_{42}O_{11} \cdot 0.15H_2O$: C, 67.06; H, 6.39. Found: C, 66.81; H, 6.39.

3,4-Di-*O*-benzylphenethyl 3-*O*-Allyl-β-D-glucopyranoside (6). To a solution of **5a** (5 g, 7.55 mmol) in MeOH (35 mL) was added dropwise 28% NaOMe in MeOH (2.3 mL) at 0 °C and the mixture stirred at room temperature for 2 h before neutralization with Dowex AG 50W-X8 (H^+) resin. The resin was filtered off, the filtrate was concentrated *in vacuo*, and the residue was recrystallized from Et_2O to give **6** (3.8 g, 94%) as colorless crystals: mp 99−100 °C; $[\alpha]^{20}_D$ +1.85 (*c* 0.50, MeOH); ^{1}H NMR (270 MHz, CD_3OD) δ 2.74 (t, *J* = 7.3, 2 H), 3.08−3.19 (m, 2 H), 3.19−3.30 (m, 2 H), 3.55 (dd, *J* = 5.4, 11.9, 1 H), 3.60 (m, 1 H), 3.75 (dd, *J* = 1.9, 11.9, 1 H), 3.94 (dt, *J* = 7.3, 9.5, 1 H), 4.81 (d, *J* = 7.3, 1 H), 4.22−4.27 (m, 2 H), 4.96 (s, 2 H), 5.00 (s, 2 H), 5.00 (m, 1 H), 5.20 (ddt, *J* = 1.6, 1.6, 17.3, 1 H), 5.90 (ddt, *J* = 5.9, 10.3, 17.3, 1 H), 6.67 (dd, *J* = 1.9, 8.4, 1 H), 6.81 (d, *J* = 8.4, 1 H), 6.88 (d, *J* = 1.9, 1 H), 7.13−7.36 (m, 10 H). Anal. Calcd for $C_{31}H_{36}O_8 \cdot 0.4H_2O$: C, 69.39; H, 6.76. Found: C, 69.58; H, 6.86.

3,4-Di-*O*-benzylphenethyl 3-*O*-Allyl-6-*O*-trityl-β-D-glucopyranoside (7). To a solution of **6** (3.7 g, 6.9 mmol) in pyridine (41 mL) was added trityl chloride (7.7 g, 27.62 mmol) at 0 °C. The solution was stirred overnight at room temperature in the dark. The reaction mixture was evaporated *in vacuo* and worked up to give an oily residue, which was purified by column chromatography using a solvent mixture of EtOAc/*n*-hexane (1:2 to 1:1, v/v) to give **7** (4.6 g, 86%) as a colorless solid: $[\alpha]^{20}_D$ −22.6 (*c* 0.50, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$) δ 2.19 (d, *J* = 1.9, 1 H), 2.67 (d, *J* = 1.9, 1 H), 2.87 (t, *J* = 7.0, 2 H), 2.37 (t, *J* = 8.9, 1 H), 3.32−3.46 (m, 4 H), 3.59 (dt, *J* = 1.9, 8.9, 1 H), 3.63−3.73 (m, 1 H), 4.07 (dt, *J* = 7.0, 9.7, 1 H), 4.24 (d, *J* = 7.6, 1 H), 4.28 (m, 1 H), 4.39 (m, 1 H), 5.05, 5.11 (s, 2 H each), 5.17 (m, 1 H), 5.29 (m, 1 H), 5.96 (ddt, *J* = 5.7, 10.5, 17.0, 1 H), 6.72 (dd, *J* = 2.2, 8.4, 1 H), 6.81 (d, *J* = 2.2, 1 H), 6.85 (d, *J* = 8.4, 1 H), 7.17−7.46 (m, 25 H). Anal. Calcd for $C_{50}H_{50}O_8 \cdot 0.4H_2O$: C, 77.10; H, 6.47. Found: C, 77.33; H, 6.53.

3,4-Di-*O*-benzylphenethyl 2,4-Di-*O*-acetyl-3-*O*-allyl-6-*O*-trityl-β-D-glucopyranoside (8). To a solution of **7** (4.6 g, 5.91 mmol) in pyridine (33 mL) was added acetic anhydride (28 mL) at 0 °C. This solution was stirred overnight at room temperature and concentrated to give an oily residue. The residue was suspended in EtOAc, neutralized with saturated aqueous $NaHCO_3$ solution, and worked up to give a colorless solid. Recrystallization of the solid from EtOH gave **8** (4.7 g, 92%) as colorless crystals: mp 143−144 °C; $[\alpha]^{20}_D$ +0.98 (*c* 0.51, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.78, 1.94 (s, 3 H each), 2.87 (t, *J* = 7.0, 2 H), 3.10 (dd, *J* = 2.4, 10.3, 1 H), 3.16 (dd, *J* = 4.9, 10.3, 1 H), 3.44−3.51 (m, 1 H), 3.50 (t, *J* = 9.5, 1 H), 3.69 (dt, *J* = 7.0, 9.5, 1 H), 4.01 (m, 2 H), 4.12 (dt, *J* = 6.5, 9.5, 1 H), 4.39 (d, *J* = 7.8, 1 H), 4.97−5.08 (m, 4 H), 5.11 (s, 2 H), 5.03−5.20 (m, 2 H), 5.73 (ddt, *J* = 5.7, 10.5, 17.0, 1 H), 6.72 (dd, *J* = 1.9, 8.1, 1 H), 6.82 (d, *J* = 1.9, 1 H), 6.84 (d, *J* = 8.1, 1 H), 7.15−7.47 (m, 25 H). Anal. Calcd for $C_{54}H_{54}O_8$: C, 75.15; H, 6.31. Found: C, 75.15; H, 6.26.

3,4-Di-*O*-benzylphenethyl 2,6-Di-*O*-acetyl-3-*O*-allyl-β-D-glucopyranoside (9). To a stirred solution of **8** (4.6 g, 5.33 mmol) in 1,4-dioxane (47 mL) was added dropwise AcOH (93 mL). The reaction mixture was heated to 110 °C and stirred at this temperature for 6 h. After being cooled to room temperature, the reaction mixture was diluted with EtOAc, neutralized with a saturated aqueous $NaHCO_3$ solution, and worked up to give an oily residue. The residue was purified by column chromatography with elution first with CH_2Cl_2 and then with EtOAc/*n*-hexane (1:2, v/v) to give **9** (2.6 g, 79%) as a colorless oil: $[\alpha]^{20}_D$ −29.29 (*c* 0.45, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.90, 2.09 (s, 3 H each), 2.76 (t, *J* = 6.8, 2 H), 2.79 (d, *J* = 3.2 1 H), 3.38 (t, *J* = 9.2, 1 H), 3.42 (ddd, *J* = 2.2, 4.3, 9.2, 1 H), 3.48−3.57 (m, 1H), 3.54 (m, 1 H), 4.04 (dt, *J* = 6.8, 9.2, 1 H), 4.17 (m, 2 H), 4.29 (dd, *J* = 2.2, 11.9, 1 H), 4.32 (d, *J* = 7.8, 1 H), 4.45 (dd, *J* = 4.3, 11.9, 1 H), 4.89 (dd, *J* = 7.8, 9.2, 1 H), 5.11 (s, 2 H), 5.15 (d, *J* = 5.7, 2 H), 5.16 (ddt, *J* = 1.6, 1.6, 10.3, 1 H), 5.24 (ddt, *J* = 1.6, 1.6, 17.0, 1 H), 5.85 (ddt, *J* = 5.7, 10.3, 17.0, 1 H), 6.69 (dd, *J* = 1.9, 8.4, 1 H), 6.81 (d, *J* = 1.9, 1 H), 6.84 (d, *J* = 8.4, 1 H), 7.25−7.48 (m, 10 H). Anal. Calcd for $C_{35}H_{40}O_{10}$: C, 67.73; H, 6.50. Found: C, 67.45; H 6.53.

3,4-Di-*O*-benzylphenethyl 2,6-Di-*O*-acetyl-3-*O*-allyl-4-*O*-(3,4-di-*O*-benzylcaffeoyl)-β-D-glucopyranoside (11). A stirred solution of **9** (2.6 g, 4.19 mmol), 3,4-di-*O*-benzylcaffeic acid (**10**)[19] (2.2 g, 6.0 mmol), DCC (1.9 g, 9.21 mmol), DMAP (0.25 g, 2.05 mmol), and DMAP·HCl (0.33 g, 2.05 mmol) in CH_2Cl_2 (410 mL) was refluxed overnight. The reaction mixture was cooled to room temperature and filtered through a plug of silica gel, and the solvent was evaporated *in vacuo*. The residue was purified by column chromatography with elution first with CH_2Cl_2 and then with EtOAc/*n*-hexane (1:2, v/v) to give a colorless oil. Crystallization of the oil from EtOH gave **11** (3.2 g, 79%) as light yellow crystals: mp 139−140 °C; $[\alpha]^{20}_D$ −34.04 (*c* 0.51, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.91, 2.05 (s, 3 H each), 2.78 (t, *J* = 7.1, 2 H), 3.54−3.61 (m, 1 H), 3.61−3.67 (m, 1 H), 3.63 (t, *J* = 9.5, 1 H), 4.01−4.09 (m, 3 H), 4.15 (dd, *J* = 3.2, 12.2, 1 H), 4.19 (dd, *J* = 4.9, 12.2, 1 H), 4.38 (d, *J* = 8.0, 1 H), 5.00 (dd, *J* = 8.0, 9.5, 1 H), 5.12 (s, 2 H), 5.16 (d, *J* = 8.4, 2 H), 5.18, 5.20 (s, 2 H each), 5.12−5.21 (m, 3 H), 5.71 (ddt, *J* = 5.6, 10.4, 17.2, 1 H), 6.20 (d, *J* = 15.9, 1 H), 6.70 (dd, *J* = 2.0, 8.0, 1 H), 6.82 (d, *J* = 2.0, 1 H), 6.85 (d, *J* = 8.0, 1 H), 6.92 (d, *J* = 8.3, 1 H), 7.07 (dd, *J* = 2.0, 8.3, 1 H), 7.11 (d, *J* = 2.0, 1 H), 7.27−7.49 (m, 20 H), 7.59 (d, *J* = 15.9, 1 H). Anal. Calcd for $C_{58}H_{58}O_{13}$: C, 72.33; H, 6.07. Found: C, 72.07; H, 6.09.

3,4-Di-*O*-benzylphenethyl 2,6-Di-*O*-acetyl-4-*O*-(3,4-di-*O*-benzylcaffeoyl)-β-D-glucopyranoside (12). To a solution of **11** (2.7 g, 2.8 mmol) in 1,4-dioxane (92 mL) were added SeO_2 (641 mg, 5.78 mmol) and AcOH (253 μL). The solution was then stirred at 80 °C for 3 h. The reaction mixture was worked up to give an oily residue, which was purified by column chromatography using a solvent mixture of EtOAc/*n*-hexane (1:2 to 1:1, v/v) to give **12** (1.7 g, 66%) as a light yellow solid: $[\alpha]^{20}_D$ −22.30 (*c* 0.52, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.96, 2.05 (s, 3 H each), 2.66 (d, *J* = 5.9, 1 H), 2.79 (t, *J* = 6.6, 2 H), 3.63 (m, 1 H), 3.63−3.74 (m, 1 H), 3.76 (dt, *J* = 5.9, 9.5, 1 H), 4.06 (dt, *J* = 6.5, 9.5, 1 H), 4.16−4.23 (m, 2 H), 4.42 (d, *J* = 7.8, 1 H), 4.88 (dd, *J* = 7.8, 9.5, 1 H), 5.03 (t, *J* = 9.5, 1 H), 5.12 (s, 2 H), 5.15 (d, *J* = 3.5, 2 H), 5.16, 5.19 (s, 2 H each), 6.21 (d, *J* = 15.9, 1 H), 6.71 (dd, *J* = 1.9, 8.1, 1 H), 6.82 (d, *J* = 1.9, 1 H), 6.85 (d, *J* = 8.1, 1 H), 6.91 (d, *J* = 8.4, 1 H), 7.06 (dd, *J* = 1.9, 8.4, 1 H), 7.11 (d, *J* = 1.9, 1 H), 7.25−7.48 (m, 20 H), 7.61 (d, *J* = 15.9, 1 H). Anal. Calcd for $C_{55}H_{54}O_{13} \cdot 0.45H_2O$: C, 71.55; H, 5.90. Found: C, 71.31; H, 5.83.

3,4-Di-*O*-benzylphenethyl 2,6-Di-*O*-acetyl-3-*O*-(2,3,4-tri-*O*-acetyl-α-L-rhamnopyranosyl)-4-*O*-(3,4-di-*O*-benzylcaf-

feoyl)-β-D-glucopyranoside (14). To a stirred solution of **12** (1.7 g, 1.84 mmol) and 2,3,4-tri-*O*-acetyl-α-L-rhamnopyranosyl trichloroacetimidate (**13**)[23] (0.96 g, 2.21 mmol) in anhydrous CH_2Cl_2 (35 mL) was added BF_3·Et_2O (28 μL, 0.22 mmol) at −20 °C. After 5 h, the reaction mixture was diluted with EtOAc, neutralized with saturated aqueous $NaHCO_3$ solution, and worked up to give an oily residue. The residue was purified using gel-permeation chromatography [Sephadex LH-20, $CHCl_3$ / MeOH (1:1, v/v)] to give **14** (1.6 g, 73%) as a colorless solid: $[\alpha]^{20}_D$ −42.91 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.99 (d, *J* = 6.4, 3 H), 1.81, 1.95, 1.96, 2.07, 2.09 (s, 3 H each), 2.78 (t, *J* = 6.8, 2 H), 3.57 (m, 1 H), 3.60−3.66 (m, 1 H), 3.80 (dq, *J* = 6.4, 10.0, 1 H), 3.89 (t, *J* = 9.5, 1 H), 4.04 (dt, *J* = 6.8, 9.2, 1 H), 4.14 (dd, *J* = 3.2, 12.2, 1 H), 4.18 (dd, *J* = 4.6, 12.2, 1 H), 4.37 (d, *J* = 8.0, 1 H), 4.86 (d, *J* = 1.7, 1 H), 4.94 (t, *J* = 10.0, 1 H), 5.01−5.03 (m, 1H), 5.07 (dd, *J* = 8.0, 9.5, 1 H), 5.09−5.11 (m, 1H), 5.12, 5.17, 5.20 (s, 2 H each), 5.17 (d, *J* = 8.8, 2 H), 5.21 (t, *J* = 9.5, 1 H), 6.19 (d, *J* = 15.8, 1 H), 6.70 (dd, *J* = 1.7, 8.0, 1 H), 6.81 (d, *J* = 1.7, 1 H), 6.85 (d, *J* = 8.0, 1 H), 6.91 (d, *J* = 8.4, 1 H), 7.05 (dd, *J* = 1.7, 8.4, 1 H), 7.09 (d, *J* = 1.7, 1 H), 7.28−7.50 (m, 20 H), 7.59 (d, *J* = 15.8, 1 H). Anal. Calcd for $C_{67}H_{70}O_{20}$·0.4H_2O: C, 67.33; H, 5.90. Found: C, 67.14; H, 5.96.

3,4-Di-*O*-benzylphenethyl 3-*O*-(α-L-Rhamnopyranosyl)-4-*O*-(3,4-di-*O*-benzylcaffeoyl)-β-D-glucopyranoside (15). To a solution of **14** (700 mg, 0.59 mmol) in CH_2Cl_2 (9 mL) was added 40% $MeNH_2$ in MeOH (14 mL) at −20 °C. The reaction mixture was stirred at that temperature for 9 h and then concentrated *in vacuo*. The residue was purified by TLC using a solvent mixture of MeOH/CH_2Cl_2 (1:19, v/v) to give **15** (289 mg, 49%) as a colorless solid: $[\alpha]^{20}_D$ −54.74 (*c* 1.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$/CD_3OD) δ 1.12 (d, *J* = 6.3, 3 H), 2.86 (t, *J* = 7.1, 2 H), 3.30 (t, *J* = 9.5, 1 H), 3.40−3.50 (m, 2 H), 3.51−3.68 (m, 3 H), 3.61 (dd, *J* = 3.2, 9.5, 1 H), 3.65−3.76 (m, 1 H), 3.84 (t, *J* = 9.5, 1 H), 3.29 (dd, *J* = 1.7, 3.2, 1 H), 4.00−4.15 (m, 1 H), 4.32 (d, *J* = 8.0, 1 H), 4.96 (t, *J* = 9.5, 1 H), 5.12, 5.14, 5.17 (s, 2H each), 5.19 (br s, 1 H), 5.20 (s, 2 H), 6.26 (d, *J* = 15.9, 1 H), 6.77 (dd, *J* = 2.0, 8.1, 1 H), 6.86−6.92 (m, 2 H), 6.95 (d, *J* = 8.4, 1 H), 7.10 (dd, *J* = 2.0, 8.4, 1 H), 7.16 (br s, 1 H), 7.29−7.47 (m, 20 H), 7.62 (d, *J* = 15.9, 1 H); ^{13}C NMR (400 MHz, $CDCl_3$/CD_3OD) δ 17.9, 35.7, 61.4, 69.0, 69.5, 71.0, 71.1, 71.3, 71.7, 71.8, 71.9, 72.9, 74.8, 74.9, 80.1, 101.5, 103.1, 114.2, 114.5, 114.9, 115.8, 116.5, 122.1, 123.7, 127.5−128.8, 132.2, 136.8, 137.0, 137.5, 146.7, 147.8, 149.1, 151.7, 167.3. Anal. Calcd for $C_{57}H_{60}O_{15}$·0.5H_2O: C, 69.50; H, 6.14. Found: C, 69.26; H, 6.15.

Acteoside (1). A mixture of **15** (110 mg, 0.11 mmol), 5% Pd−C (110 mg), and 1,4-cyclohexadiene (206 μL, 2.2 mmol) in DMF/EtOH (1:1, v/v, 770 μL) was stirred at 40 °C for 10 h. The catalyst was filtered off, and the filtrate was concentrated *in vacuo* to give a yellow oily residue. The residue was purified by preparative TLC using a solvent mixture of $CHCl_3$/MeOH/H_2O (30:8:1, v/v/v) to give acteoside (**1**) (30.2 mg, 44%) as a pale-yellow solid: $[\alpha]^{20}_D$ −77.41 (*c* 0.31, MeOH); ^{1}H NMR (400 MHz, CD_3OD) δ 1.08 (d, *J* = 6.1, 3 H), 2.75−2.81 (m, 2 H), 3.29 (t, *J* = 9.5, 1 H), 3.38 (d, *J* = 7.8, 9.3, 1 H), 3.48−3.64 (m, 4 H), 3.57 (dd, *J* = 3.2, 9.5, 1 H), 3.72 (m, 1 H), 3.81 (t, *J* = 9.3, 1 H), 3.91 (dd, *J* = 1.7, 3.2, 1 H), 4.04 (m, 1 H), 4.37 (d, *J* = 7.8, 1 H), 4.80−5.00 (m, 1 H), 5.18 (d, *J* = 1.7, 1 H), 6.27 (d, *J* = 15.8, 1 H), 6.56 (dd, *J* = 2.0, 8.0, 1 H), 6.67 (d, *J* = 8.0, 1 H), 6.69 (d, *J* = 2.0, 1 H), 6.77 (d, *J* = 8.1, 1 H), 6.95 (dd, *J* = 2.0, 8.1, 1 H), 7.05 (d, *J* = 2.0, 1 H), 7.59 (d, *J* = 15.8, 1 H); ^{13}C NMR (400 MHz, CD_3OD) δ 18.4, 36.5, 62.3, 70.4, 70.6, 72.0, 72.3, 73.8, 76.0, 76.2, 81.3, 103.0, 104.2, 114.7, 115.2, 116.3, 116.5, 117.1, 121.3, 123.2, 127.6, 131.4, 144.7, 146.1, 146.8, 148.0, 149.8, 168.3. Anal. Calcd for $C_{29}H_{36}O_{15}$·2.1H_2O: C, 55.77; H, 5.81. Found: C, 55.37; H, 6.23.

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Supporting Information Available: Reproductions of ^{1}H NMR spectra for compounds **1**, **3**, **5a**,**b**, **6**−**9**, **11**, **12**, **14**, and **15** and ^{13}C NMR spectra for compounds **1** and **15**. This material is available free of charge via the Internet at http://pubs.acs.org.

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