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Syntheses of chlorogenin 6α-*O*-acyl-3-*O*-β-chacotriosides and their antitumor activities

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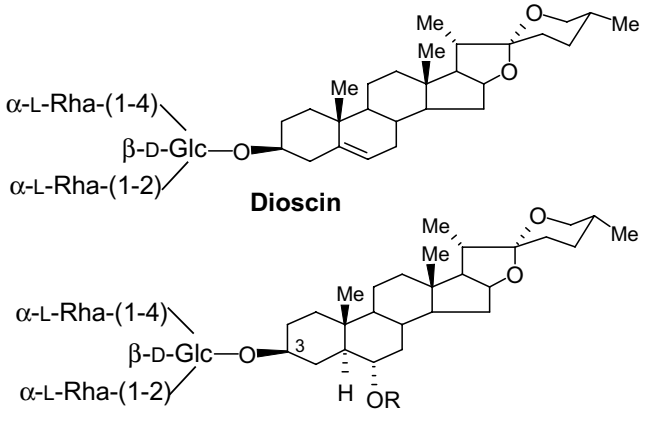
Abstract—Chlorogenin 3-*O*-β-chacotrioside (**1**) and its 6α-*O*-acyl derivatives (**2**–**6**) were concisely synthesized. Introduction of a hydroxyl or acyloxy group onto the C-6 of the steroidal aglycone of dioscin decreased significantly the cytotoxicity of the parent saponin (dioscin).

Keywords: Chlorogenin [3β,5α,6β,25(*R*)-spirostan-3,6-diol]; Chacotrioside; Dioscin; Synthesis; Cytotoxicity

1. Introduction

A quite common feature of spirostan saponins is their inhibitory activities against the growth of tumor cells, with the potency being highly dependent on the 3-*O*-sugar residue. Those bearing a β-chacotriosyl (α-L-rhamnopyranosyl-(1→2)-[α-L-rhamnopyranosyl-(1→4)]-β-D-glucopyranosyl) residue at the 3-OH are among the most active.[1] Dioscin (diosgenin 3-*O*-β-chacotrioside), one of the most abundant spirostan saponins occurring in plants, demonstrates a well-studied example, showing promising anti-tumor activities both in vitro (with IC_{50}s at the μM level) and in vivo.[1,2] Recently, several synthetic approaches toward dioscin have been developed.[3] We have tested a number of its derivatives, such as those with monomethyl or acyl substitution on the sugar hydroxyl groups[4] and those dihydrodiosgenin derivatives with an additional sugar attached at the 26-OH.[5] However, none of these derivatives demonstrated more potent antitumor activities than the parent dioscin. In continuing this research, we prepared dioscin congeners with a hydroxyl or acyloxy group on the C-6 of the aglycone, the chlorogenin derivatives **1**–**6**, and tested their inhibition activities against the growth of HeLa cells.



1: R = H
2-6: R = -(C=O)$(CH_2)_n CH_3$ (n = 0; 4; 8; 10; 14)

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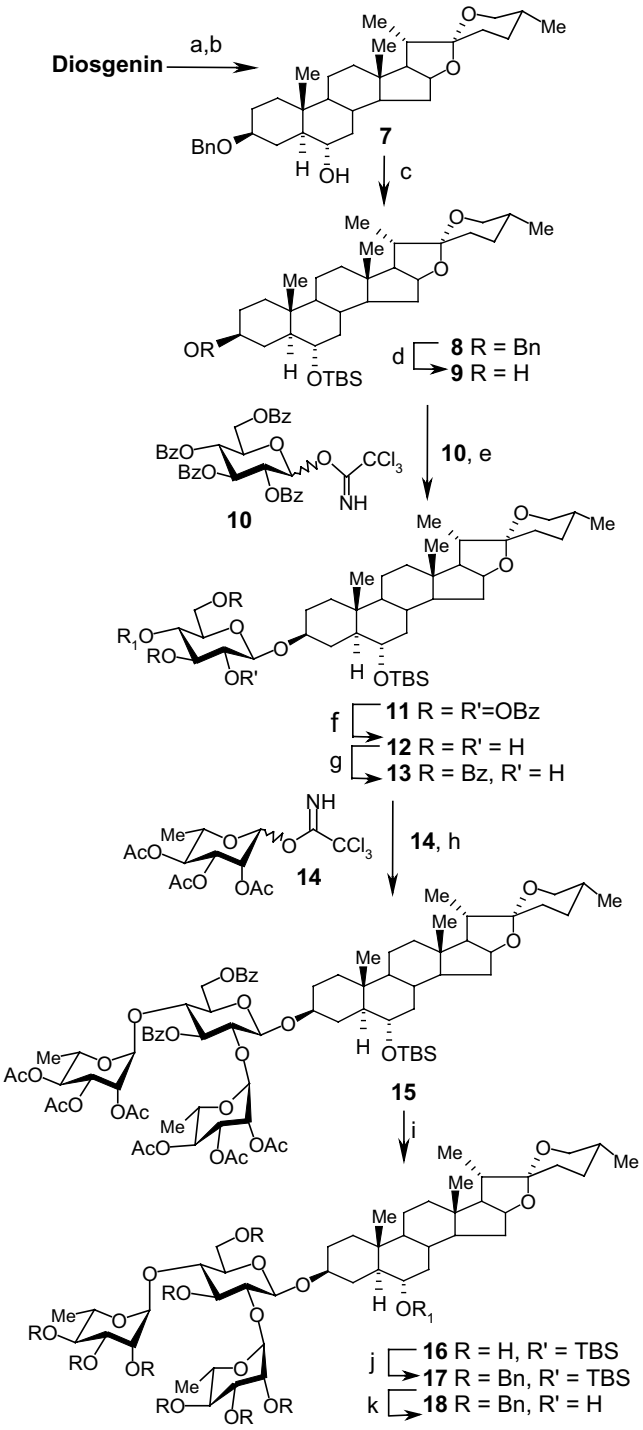
2. Results and discussion

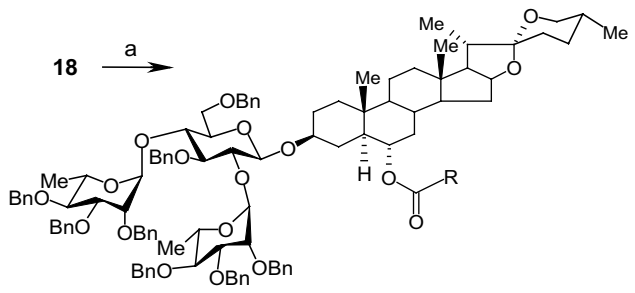
The synthetic route toward chlorogenin 3-*O*-β-chacotriosides **1**–**6** is depicted in Schemes 1 and 2. After protection of the 3-OH of diosgenin with a benzyl group, the 5,6-double bond was subjected to hydroboration–oxidation following a literature procedure to introduce the 6α-OH, providing 3-*O*-benzyl-chlorogenin **7** as the major product (68% yield for three steps).[3c,6] The resulting 6α-OH group was then protected with a TBDMS group, and the 3-*O*-benzyl group was removed by hydrogenolysis, affording **9** (86% yield for two steps). Employing a procedure similar to that used for the previous synthesis of dioscin and its dihydrodiosgenin congeners,[3c,5] the β-chacotriosyl residue was readily introduced onto the 3-OH of **9**. Glycosylation of **9** with 2,3,4,6-tetra-*O*-benzoyl-D-glucopyranosyl trichloroacetimidate (**10**) under the action of a catalytic amount of TMSOTf afforded the 3-*O*-β-glucopyranoside **11** in excellent yield (99%).[7] Removal of the benzoyl groups with NaOMe in MeOH readily gave **12**, which was subjected to 1-BBTZ [1-(benzoyloxy)benzotriazole] in the presence of Et_3N in CH_2Cl_2 to selectively protect the 3,6-OHs of the β-glucopyranosyl residue, leading to 2,4-diol **13** in a satisfactory 70% yield.[5,8] Glycosylation of the 2,4-OHs in **13** with 2,3,4-tri-*O*-acetyl-L-rhamnopyranosyl trichloroacetimidate (**14**) under the 'inverse addition' conditions[9] with $BF_3{\cdot}OEt_2$ as the promoter led to the desired trisaccharide **15** that was contaminated with a small amount of unidentified byproducts after careful column chromatography on silica gel. Fortunately, treatment of the crude **15** with NaOMe in MeOH was able to afford **16** cleanly in a good yield (51% for two steps). The resulting eight hydroxyl groups on the chacotriosyl moiety (in **16**) were then successfully blocked with benzyl groups (BnBr, NaH, $Bu_4N^+I^-$, DMF, rt), affording **17** in 82% yield. Finally, the 6α-OH was quantitatively released via cleavage of the TBDMS protecting group with TBAF to provide **18**, a ready precursor for the preparation of the chlorogenin derivatives **2**–**6**.

Condensation of the 6α-OH group in **18** with fatty acids (i.e., acetic acid, hexylic acid, decylic acid, dodecanoic acid, hexadecanoic acid) was easily achieved in the presence of DCC–DMAP,[10] yielding ester derivatives **19**–**23** in satisfactory yields. Finally, removal of the benzyl groups on the chacotriosyl moiety (in **18**–**13**) via hydrogenolysis over Pd–C readily afforded the target saponins **1**–**6**.

The in vitro inhibitory activities of the chlorogenin 3-*O*-β-chacotriosides **1**–**6** against the growth of HeLa cells were evaluated following the standard MTT assay procedure.[11] While dioscin, as a positive control, showed an IC_{50} of 3.5 μM, the corresponding C-6 derivatized compounds **2**–**6** showed a significantly reduced activities. Compounds **1**–**3** exhibited IC_{50}s of 30, 26, and 21 μM, respectively, while compounds **4**–**6** bearing a long acyloxy chain at the C-6 did not show any inhibitory activity at a concentration of 30 μM.



Scheme 1. Reagents and conditions: (a) BnBr, NaH, 1:1 THF–DMF, reflux, 96%; (b) $B_2H_6{\cdot}Me_2S$, THF, rt, then 30% NaOH, 30% H_2O_2, rt, 71%; (c) TBDMSCl, imidazole, DMAP, CH_2Cl_2, rt, 95%; (d) Pd–C, H_2, Et_3N, CH_2Cl_2–EtOH, rt, 90%; (e) **10**, TMSOTf (0.18 equiv), 4 Å MS, CH_2Cl_2, 0 °C–rt, 99%; (f) NaOMe, MeOH/$CHCl_3$, rt, 93%; (g) 1-BBTZ, Et_3N, rt, 70%; (h) $BF_3{\cdot}OEt_2$, 4 Å MS, CH_2Cl_2; then **14**, −30 °C to rt; (i) NaOMe, MeOH–$CHCl_3$, rt, 51% (for two steps); (j) BnBr, NaH, $Bu_4N^+I^-$, DMF, rt, 82%; (k) TBAF, THF, rt, 100%.



19: R = CH_3; **20**: R = $(CH_2)_4CH_3$; **21**: R = $(CH_2)_8CH_3$;
22: R = $(CH_2)_{10}CH_3$; **23**: R = $(CH_2)_{14}CH_3$

b

2-6 and **1** (from **18**)

Scheme 2. Reagents and conditions: (a) RCOOH, DCC, DMAP, CH_2Cl_2, rt; (b) Pd–C, H_2, AcOH, EtOH–CH_2Cl_2, rt, 52% (two steps for **2**), 84% (two steps for **3**), 65% (two steps for **4**), 91% (two steps for **5**), 76% (two steps for **6**); 90% (for **1**, from **18**).

3. Experimental

3.1. General methods

See Ref. 5.

3.2. 3β-*O*-Benzyl-6α-*O*-*tert*-butyldimethylsilylchlorogenin (8)

To a mixture of **7** (3.39 g, 6.50 mmol), imidazole (1.19 g, 17.5 mmol), and DMAP (73 mg, 0.6 mmol) in CH_2Cl_2 (120 mL), TBDMSCl (1.32 g, 8.74 mmol) was added. After stirring at rt for 20 h, the mixture was concentrated. The residue was subjected to column chromatography on silica gel (1:20 EtOAc–petroleum ether) to give **8** as a white amorphous solid (3.91 g, 95%): R_f 0.35 (1:20 EtOAc–petroleum ether); $[\alpha]_D^{20}$ −33.6 (*c* 0.4, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.34–7.26 (m, 5H, Ar–H), 4.59 (d, 1H, *J* 11.9 Hz, C*H*Ph), 4.53 (d, 1H, *J* 11.9 Hz, C*H*Ph), 4.40 (q, 1H, *J* 7.3 Hz, H-16), 3.48–3.25 (m, 4H, H-26, H-6, H-3), 2.37 (m, 1H), 0.96 (d, 3H, *J* 6.8 Hz, H-21), 0.89 (s, 9H), 0.83 (s, 3H, H-19), 0.79 (d, 3H, *J* 6.4 Hz, H-27), 0.76 (s, 3H, H-18), 0.05 (s, 3H), 0.02 (s, 3H); ESIMS: Calcd *m*/*z* 636.457. Found *m*/*z* 637.287 $[M+H]^+$.

3.3. 6α-*O*-*tert*-Butyldimethylsilylchlorogenin (9)

A suspension of **8** (4.07 g, 6.39 mmol), Et_3N (two drops), and Pd–C (0.6 g, 10%) in CH_2Cl_2–EtOH (1:4, 30 mL) was stirred under H_2 for 12 h and then filtered and concentrated. The residue was purified by recrystallization from MeOH–$CHCl_3$ to give **9** (3.16 g, 90%) as a white amorphous solid: R_f 0.40 (1:3 EtOAc–petroleum ether); $[\alpha]_D^{20}$ −24.5 (*c* 0.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 4.40 (q, 1H, *J* 7.4 Hz, H-16), 3.56 (m, 1H, H-3), 3.47 (ddd, 1H, *J* 2.3, 4.1, 10.5 Hz, H-26), 3.40–3.34 (m, 2H, H-6, H-26), 1.59 (s, 6H, –CH_3 × 2), 0.96 (d, 3H, *J* 6.9 Hz, H-21), 0.88 (s, 9H, –CH_3 × 3), 0.82 (s, 3H, H-19), 0.79 (d, 3H, *J* 6.4 Hz, H-27), 0.76 (s, 3H, H-18), 0.03 (s, 3H), 0.02 (s, 3H); ESIMS: Calcd *m*/*z* 546.410. Found *m*/*z* 547.270 $[M+H]^+$.

3.4. 6α-*O*-*tert*-Butyldimethylsilylchlorogenin 3β-*O*-β-D-glucopyranoside (12)

To a mixture of **9** (2.64 g, 5.0 mmol), imidate **10** (4.87 g, 6.6 mmol), and powdered 4 Å molecular sieves in dried CH_2Cl_2 (70 mL) at 0 °C was added TMSOTf (142 μL, 0.825 mmol). After stirring at 0 °C for 0.5 h and then at rt for 0.5 h, the reaction was quenched with Et_3N. The solid was then filtered off. The filtrate was concentrated and purified by silica gel column chromatography (1:8 EtOAc–petroleum ether) to give **11** as a white amorphous solid (5.40 g, 99%): R_f 0.32 (1:8 EtOAc–petroleum ether); $[\alpha]_D^{20}$ −3.2 (*c* 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 8.03–7.26 (m, 20H, Ar–H), 5.88 (t, 1H, *J* 9.6 Hz, H-3′), 5.62 (t, 1H, *J* 10.1 Hz), 5.51 (dd, 1H, *J* 8.2, 10.1 Hz), 4.92 (d, 1H, *J* 7.8 Hz, H-1′), 4.58 (dd, 1H, *J* 3.7, 12.4 Hz, H-6′), 4.53 (dd, 1H, *J* 5.9, 12.4 Hz, H-6′), 4.39 (q, 1H, *J* 7.3 Hz, H-16), 4.11 (m, 1H, H-5′), 3.54 (m, 1H), 3.46 (ddd, 1H, *J* 1.9, 3.7, 12.6 Hz), 3.36 (t, 1H, *J* 11.0 Hz), 3.28 (td, 1H, *J* 4.6, 10.6 Hz), 0.96 (d, 3H, *J* 7.3 Hz), 0.78 (m, 12H), 0.74 (s, 3H), 0.72 (s, 3H), −0.10 (s, 3H), −0.17 (s, 3H). Compound **11** (5.48 g, 4.87 mmol) was dissolved in 1:1 CH_3OH–$CHCl_3$ (60 mL), and then NaOMe (1 g) was added. After stirring at rt for 2 h, the solution was neutralized with ion-exchange resin (H^+) and then filtered and concentrated. The residue was purified by silica gel column chromatography (10:1 $CHCl_3$–MeOH) to afford **12** as a white amorphous solid (3.22 g, 93.3%): R_f 0.31 (8:1 $CHCl_3$–MeOH); $[\alpha]_D^{20}$ −38.9 (*c* 0.4, MeOH); ^{1}H NMR (Me_2SO-d_6): δ 4.92 (d, 1H, *J* 4.4 Hz, –OH), 4.87–4.86 (m, 2H, –OH × 2), 4.44 (t, 1H, *J* 5.9 Hz, –OH), 4.28 (dd, 1H, *J* 7.3, 13.9 Hz, H-16), 4.20 (d, 1H, *J* 7.7 Hz, H-1′), 3.63 (ddd, 1H, *J* 1.9, 5.9, 11.7 Hz, H-5′), 3.54 (m, 1H, H-3), 3.43–3.40 (m, 3H, H-26, H-6), 3.19 (t, 1H, *J* 11.0 Hz), 3.07–2.88 (m, 4H), 0.90 (d, 3H, *J* 9.0 Hz), 0.86 (s, 9H, –CH_3 × 3), 0.78 (s, 3H), 0.73 (d, 3H, *J* 6.4 Hz), 0.71 (s, 3H), 0.03 (s, 3H), 0.02 (s, 3H); ESIMS: Calcd *m*/*z* 708.463. Found *m*/*z* 731.252 $[M+Na]^+$.

3.5. 6α-*O*-*tert*-Butyldimethylsilyl chlorogenin 3β-*O*-(3,6-di-*O*-benzoyl-β-D-glucopyranoside) (13)

To a solution of **12** (3.95 g, 5.57 mmol) and 1-BBTZ (3.22 g, 13.4 mmol) in CH_2Cl_2 (70 mL) was added Et_3N (2.0 mL, 14.4 mmol). After stirring at rt for 12 h, the mixture was concentrated to afford a residue, which

was subjected to column chromatography on silica gel (1:8:2–1:6:2 EtOAc–petroleum ether–chloroform), providing **13** as a white amorphous solid (2.92 g, 70%): R_f 0.28 (1:3 EtOAc–petroleum ether); $[\alpha]_D^{20}$ −11.5 (*c* 0.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 8.10–7.44 (m, 10H, Ar–H), 5.18 (t, 1H, *J* 9.2 Hz, H-3′), 4.69 (dd, 1H, *J* 5.5, 12.1 Hz, H-6′), 4.62 (dd, 1H, *J* 2.5, 12.1 Hz, H-6′), 4.54 (d, 1H, *J* 7.7 Hz, H-1′), 4.41 (dd, 1H, *J* 7.3, 14.6 Hz, H-16), 3.75 (t, 1H, *J* 9.5 Hz, H-4′), 3.70–3.64 (m, 3H, H-2′, H-5′, H-6), 3.48 (m, 1H, H-26), 3.37 (m, 2H, H-26, H-3), 0.97 (d, 3H, *J* 7.0 Hz), 0.88 (s, 9H, $-CH_3 \times 3$), 0.80 (s, 3H), 0.79 (d, 3H, *J* 6.4 Hz), 0.76 (s, 3H), 0.03 (s, 3H), 0.02 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 167.9, 166.8, 133.5, 133.2, 130.0, 129.9, 129.8, 129.4, 128.4 (2 C), 109.2, 100.9, 80.6, 78.9, 78.7, 74.4, 72.1, 70.1, 69.8, 66.8, 63.8, 62.2, 55.9, 53.7, 51.5, 42.1, 41.6, 40.6, 39.8, 37.2, 36.5, 33.9, 31.8, 31.4, 30.3, 29.2, 28.9, 28.8, 25.9, 20.9, 18.2, 17.1, 16.4, 14.5, 13.5, −4.2, −4.6; ESIMS: Calcd *m*/*z* 916.516. Found *m*/*z* 939.380 $[M+Na]^+$.

3.6. 6α-*O*-*tert*-Butyldimethylsilylchlorogenin 3β-*O*-[2,4-di-*O*-(2,3,4-tri-*O*-acetyl-α-L-rhamnopyranosyl)-3,6-di-*O*-benzoyl-β-D-glucopyranoside] (15)

To a mixture of **13** (1.48 g, 1.61 mmol) and powdered 4 Å molecular sieves in dried CH_2Cl_2 (40 mL) at −30 °C was added $BF_3{\cdot}Et_2O$ (258 μL, 2.0 mmol), followed by a solution of imidate **14** (3.51 g, 8.07 mmol) in CH_2Cl_2 (15 mL). After stirring at −30 °C for 0.5 h and then at 0 °C for 1 h, the reaction was quenched with Et_3N. The solid was filtered off, and the filtrate was concentrated under vacuum to give a yellow oil. The oil was subjected to column chromatography on silica gel (1:5–2:5 EtOAc–petroleum ether) to give crude **15**, which was contaminated with unidentified byproducts difficult to remove. Treatment of a small amount of the crude **15** with TBAF (see the procedure described for the preparation of **18**) provided chlorogenin 3β-*O*-[2,4-di-*O*-(2,3,4-tri-*O*-acetyl-α-L-rhamnopyranosyl)-3,6-di-*O*-benzoyl-β-D-glucopyranoside]: $[\alpha]_D^{20}$ −42.8 (*c* 0.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 8.07–7.42 (m, 10H, Ar–H), 5.60 (t, 1H, *J* 8.7 Hz, H-3′), 5.33 (dd, 1H, *J* 3.7, 10.1 Hz, Rha–H-3), 5.16 (dd, 1H, *J* 3.2, 10.1 Hz, Rha–H-3), 5.12 (m, 1H, Rha–H-2), 4.99 (dd, 1H, *J* 1.9, 3.7 Hz, Rha–H-2), 4.94 (t, 1H, *J* 10.1 Hz, Rha–H-4), 4.87 (t, 1H, *J* 10.1 Hz, Rha–H-4), 4.86 (d, 1H, *J* 1.8 Hz, Rha–H-1), 4.81 (dd, 1H, *J* 2.3, 12.4 Hz, H-6′), 4.79 (d, 1H, *J* 1.4 Hz, Rha–H-1), 4.70 (d, 1H, *J* 7.8 Hz, H-1′), 4.51 (dd, 1H, *J* 5.5, 12.4 Hz, H-6′), 4.46–4.40 (m, 2H, Rha–H-5, H-16), 4.00 (t, 1H, *J* 9.2 Hz, H-4′), 3.86–3.83 (m, 2H, H-5′, H-2′), 3.72 (m, 1H, Rha–H-5), 3.60 (m, 1H, H-3), 3.48 (m, 1H, H-26), 3.41–3.36 (m, 2H, H-26, H-6), 2.00, 1.97, 1.95, 1.93, 1.92, 1.79 (s, $3H \times 6$, $-OAc \times 6$), 1.17 (d, 3H, *J* 6.4 Hz, Rha–CH_3), 0.97 (d, 3H, *J* 6.9 Hz), 0.79 (d, 3H, *J* 5.9 Hz), 0.78 (s, 3H), 0.75 (s, 3H), 0.68 (d, 3H, *J* 5.9 Hz, Rha–CH_3); ESIMS: Calcd *m*/*z* 1346.608. Found *m*/*z* 1369.414 $[M+Na]^+$.

3.7. 6α-*O*-*tert*-Butyldimethylsilylchlorogenin 3β-*O*-[2,4-di-*O*-(α-L-rhamnopyranosyl)-β-D-glucopyranoside] (16)

Crude **15** (1.66 g, 1.14 mmol) was dissolved in 1:1 CH_3OH–$CHCl_3$ (30 mL), and then NaOMe (1.0 g) was added. After stirring at rt for 24 h, the solution was neutralized with ion-exchange resin (H^+) and then filtered and concentrated. The residue was purified by silica gel column chromatography (10:1 $CHCl_3$–MeOH) to afford **16** (0.68 g, 51% for two steps) as a white amorphous solid: R_f 0.16 (5:1 $CHCl_3$–MeOH); $[\alpha]_D^{20}$ −64.8 (*c* 0.2, MeOH); ^{1}H NMR (CD_3OD): δ 5.18 (d, 1H, *J* 1.4 Hz, Rha–H-1), 4.83 (d, 1H, *J* 1.5 Hz, Rha–H-1), 4.49 (d, 1H, *J* 7.7 Hz, H-1′), 4.39 (dd, 1H, *J* 7.3, 14.3 Hz), 4.13 (m, 1H), 3.94–3.89 (m, 2H), 3.83 (dd, 1H, *J* 1.5, 2.9 Hz), 3.79 (dd, 1H, *J* 1.9, 12.1 Hz), 3.74–3.61 (m, 4H), 3.55–3.31 (m, 8H), 3.19 (m, 1H), 1.25 (d, 3H, *J* 6.2 Hz), 1.22 (d, 3H, *J* 6.2 Hz), 0.95 (d, 3H, *J* 7.3 Hz), 0.91 (s, 9H, $-CH_3 \times 3$), 0.86 (s, 3H), 0.79 (m, 6H), 0.10 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (CD_3OD): δ 110.5, 103.0, 102.4, 98.9, 82.1, 79.9, 79.0, 78.2, 77.0, 76.9, 73.6, 73.7, 72.4, 72.2, 71.6, 70.7, 69.8, 67.9, 63.8, 61.9, 57.3, 55.3, 52.9, 43.5, 42.9, 41.0, 38.7, 37.8, 35.2, 32.6, 32.4, 31.4, 30.3, 29.9, 29.2, 26.5, 22.1, 19.1, 18.0, 17.9, 17.5, 16.9, 14.9, 13.9; ESIMS: Calcd *m*/*z* 1023.569. Found *m*/*z* 1000.579 $[M+Na]^+$.

3.8. 6α-*O*-*tert*-Butyldimethylsilylchlorogenin 3β-*O*-[2,4-di-*O*-(2,3,4-tri-*O*-benzyl-α-L-rhamnopyranosyl)-3,6-di-*O*-benzyl-β-D-glucopyranoside] (17)

To a suspension of **16** (460 mg, 0.46 mmol) and NaH (300 mg, 60% dispersion, 7.5 mmol) in DMF (9 mL), which had been stirred at 0 °C for 1 h, $Bu_4N^+I^-$ (137 mg, 0.37 mmol) and then BnBr (0.84 mL, 7.1 mmol) were added. After stirring for additional 1 h at 0 °C, the reaction continued at rt for 24 h. EtOAc (300 mL) was added to dilute the mixture and water (30 mL) was added to decompose the excess NaH. The resulting mixture was washed with 5% HCl (3×30 mL), satd $NaHCO_3$ solution (30 mL), and brine (30 mL), respectively. The organic layer was dried over Na_2SO_4 and then filtered and concentrated. The residue was purified by silica gel column chromatography (1:10 EtOAc–petroleum ether) to afford **17** (595 mg, 76%) as a white amorphous solid: R_f 0.31 (1:5 EtOAc–petroleum ether); $[\alpha]_D^{20}$ −32.8 (*c* 0.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.33–7.03 (m, 40H, Ar–H), 5.20 (d, 1H, *J* 1.4 Hz, Rha–H-1), 5.00 (d, 1H, *J* 1.5 Hz, Rha–H-1), 4.92 (d, 1H, *J* 11.0 Hz, –C*H*Ph), 4.82 (dd, 2H, *J* 2.6, 11.3 Hz), 4.75 (d, 1H, *J* 11.0 Hz), 4.62–4.39 (m, 12H), 4.25 (m, 1H), 4.16 (d, 1H, *J* 12.5 Hz), 4.11 (d, 1H, *J* 12.5 Hz), 3.81–3.64 (m, 8H), 3.56–3.41 (m, 6H), 3.37 (t, 1H, *J*

11.0 Hz), 3.27 (td, 1H, *J* 4.4, 10.3 Hz), 3.22 (m, 1H), 1.29 (d, 3H, *J* 6.2 Hz), 0.97 (d, 3H, *J* 7.0 Hz), 0.93 (d, 3H, *J* 6.5 Hz), 0.87 (s, 9H), 0.79 (d, 3H, *J* 6.6 Hz), 0.77 (s, 3H), 0.61 (s, 3H), 0.02 (s, 3H), −0.02 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 139.2, 138.8, 138.6, 138.5, 138.3, 138.1, 128.3–127.2, 127.1, 126.2, 109.2, 98.5, 98.3, 97.8, 84.1, 80.6, 80.5, 80.4, 79.5, 77.4, 75.7, 75.3, 75.0, 74.9, 73.9, 73.4, 72.5, 72.0, 71.9, 70.3, 68.7, 67.9, 66.8, 62.2, 55.9, 53.6, 51.3, 42.1, 41.7, 40.6, 39.8, 37.4, 36.5, 33.8, 31.8, 31.4, 30.3, 29.5, 28.8, 28.7, 27.5, 26.0, 20.8, 18.2, 17.9, 17.8, 17.1, 16.4, 14.5, 13.1, −4.2, −4.3; ESIMS: Calcd *m*/*z* 1720.955. Found *m*/*z* 1759.652 $[M+Na]^+$.

3.9. Chlorogenin 3β-*O*-[2,4-di-*O*-(2,3,4-tri-*O*-benzyl-α-L-rhamnopyranosyl)-3,6-di-*O*-benzyl-β-D-glucopyranoside] (18)

A solution of **17** (840 mg, 0.487 mmol) in anhyd THF (5 mL) was treated with TBAF (1.0 M in THF, 5 mL). After stirring for 12 h at rt, the solution was concentrated. The residue was purified by silica gel column chromatography (1:8–1:5 EtOAc–petroleum ether) to afford **18** as a white foamy solid (792 mg, 100%): R_f 0.38 (1:3 EtOAc–petroleum ether); $[\alpha]_D^{20}$ −34.2 (*c* 0.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.33–7.03 (m, 40H, Ar–H), 5.25 (d, 1H, *J* 1.5 Hz, Rha–H-1), 4.97 (d, 1H, *J* 1.5 Hz, Rha–H-1), 4.89 (d, 1H, *J* 10.6 Hz, –C*H*Ph), 4.81 (dd, 2H, *J* 4.7, 11.3 Hz), 4.68 (d, 1H, *J* 12.1 Hz), 4.62–4.48 (m, 10H), 4.42–4.31 (m, 3H), 4.19 (d, 1H, *J* 12.4 Hz), 4.12 (d, 1H, *J* 12.1 Hz), 3.81 (dd, 1H, *J* 2.9, 9.2 Hz), 3.78–3.70 (m, 5H), 3.63–3.43 (m, 8H), 3.38 (t, 1H, *J* 11.0 Hz), 3.30 (m, 1H), 2.97 (m, 1H), 1.30 (d, 3H, *J* 6.2 Hz), 0.97 (d, 3H, *J* 7.0 Hz), 0.92 (d, 3H, *J* 5.8 Hz), 0.80 (d, 3H, *J* 6.6 Hz), 0.77 (s, 3H), 0.58 (s, 3H); ESIMS: Calcd *m*/*z* 1606.868. Found *m*/*z* 1629.877 $[M+Na]^+$.

3.10. General procedure for the preparation of 19–23 from 18

A mixture of **18** (0.01 mmol), DCC (0.7 mmol), DMAP (0.7 mmol), and the corresponding fatty acid (0.5 mmol) in CH_2Cl_2 (3 mL) was stirred at rt for 12 h, and was then filtered and concentrated. The residue was purified by silica gel column chromatography.

3.10.1. Chlorogenin 3β-*O*-[2,4-di-*O*-(2,3,4-tri-*O*-benzyl-α-L-rhamnopyranosyl)-3,6-di-*O*-benzyl-β-D-glucopyranoside] 6α-acetate (19).

R_f 0.27 (1:5 EtOAc–petroleum ether); $[\alpha]_D^{20}$ −31.6 (*c* 0.2, $CHCl_3$); ^{1}H NMR (Me_2SO-d_6): δ 7.34–6.98 (m, 40H, Ar–H), 5.10 (s, 1H, Rha–H-1), 4.99 (s, 1H, Rha–H-1), 4.82–4.45 (m, 16H, –CH_2Ph, H-1′, H-16), 4.27 (q, 1H, *J* 6.9 Hz, H-16), 4.20 (m, 1H, Rha–H-5), 4.11 (d, 1H, *J* 11.9 Hz, –C*H*Ph), 3.95 (d, 1H, *J* 11.9 Hz, –C*H*Ph), 3.88 (s, 1H, Rha–H-2), 3.72–3.31 (m, 15H), 1.99 (s, 3H), 1.12 (d, 3H, *J* 5.9 Hz, Rha–CH_3), 0.90 (d, 3H, *J* 6.4 Hz), 0.83 (d, 3H, *J* 5.9 Hz, Rha–CH_3), 0.74 (d, 3H, *J* 6.4 Hz), 0.70 (s, 3H), 0.38 (s, 3H); ^{13}C NMR (Me_2SO-d_6): δ 170.0, 138.8, 138.7, 138.6, 138.5, 138.4, 138.3, 138.2, 128.2–126.0, 108.5, 97.6 (2C), 97.3, 83.3, 80.1, 79.9, 79.7, 79.6, 78.7, 75.9, 75.7, 75.3, 74.8, 74.6, 74.4, 73.7 (2C), 73.3, 72.3, 72.0, 71.7, 71.3, 68.6, 67.8, 67.2, 66.0, 61.6, 55.1, 52.5, 47.4, 41.1, 40.1–39.1 (2C), 37.5, 36.3, 36.1, 33.4, 33.1, 31.3, 30.9, 29.8, 29.0, 28.5, 27.3, 25.3, 24.5, 22.1, 21.1, 20.3, 17.8, 17.7, 16.0, 14.6, 12.3. ESIMS: Calcd *m*/*z* 1648.879. Found *m*/*z* 1671.868 $[M+Na]^+$.

3.10.2. Chlorogenin 3β-*O*-[2,4-di-*O*-(2,3,4-tri-*O*-benzyl-α-L-rhamnopyranosyl)-3,6-di-*O*-benzyl-β-D-glucopyranoside] 6α-hexanoate (20).

R_f 0.31 (1:5 EtOAc–petroleum ether); $[\alpha]_D^{20}$ −24.1 (*c* 0.4, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.33–7.06 (m, 40H, Ar–H), 5.20 (d, 1H, *J* 1.5 Hz, Rha–H-1), 4.97 (d, 1H, *J* 1.4 Hz, Rha–H-1), 4.92 (d, 1H, *J* 11.0 Hz, –C*H*Ph), 4.81 (d, 1H, *J* 11.0 Hz), 4.77 (d, 1H, *J* 11.7 Hz), 4.70 (d, 1H, *J* 11.7 Hz), 4.65–4.36 (m, 13H), 4.23 (s, 2H), 4.19 (m, 1H), 3.77–3.42 (m, 14H), 3.38 (t, 1H, *J* 11.0 Hz), 3.29 (ddd, 1H, *J* 2.2, 4.7, 9.1 Hz), 1.26 (d, 3H, *J* 6.2 Hz), 0.97 (d, 3H, *J* 7.0 Hz), 0.94 (d, 3H, *J* 6.2 Hz), 0.87 (t, 3H, *J* 7.0 Hz), 0.79 (d, 3H, *J* 6.2 Hz), 0.75 (s, 3H), 0.55 (s, 3H); ESIMS: Calcd *m*/*z* 1704.941. Found *m*/*z* 1727.660 $[M+Na]^+$.

3.10.3. Chlorogenin 3β-*O*-[2,4-di-*O*-(2,3,4-tri-*O*-benzyl-α-L-rhamnopyranosyl)-3,6-di-*O*-benzyl-β-D-glucopyranoside] 6α-decanoate (21).

R_f 0.30 (1:5 EtOAc–petroleum ether); $[\alpha]_D^{20}$ −29.0 (*c* 0.2, $CHCl_3$); ^{1}H NMR (Me_2SO-d_6): δ 7.34–6.96 (m, 40H, Ar–H), 5.12 (s, 1H, Rha–H-1), 4.99 (s, 1H, Rha–H-1), 4.83–4.45 (m, 16H, –CH_2Ph, H-1′, H-16), 4.27–4.22 (m, 2H, H-6, Rha–H-5), 4.11 (d, 1H, *J* 11.8 Hz, –C*H*Ph), 3.98 (d, 1H, *J* 11.7 Hz, –C*H*Ph), 3.87 (s, 1H, Rha–H-2), 3.76–3.19 (m, 15H), 1.14 (d, 3H, *J* 6.2 Hz, Rha–CH_3), 0.90 (d, 3H, *J* 7.0 Hz), 0.80 (d, 3H, *J* 5.9 Hz, Rha–CH_3), 0.77 (t, 2H, *J* 6.6 Hz), 0.73 (d, 3H, *J* 6.2 Hz), 0.69 (s, 3H), 0.32 (s, 3H); ^{13}C NMR (Me_2SO-d_6): δ 172.4, 138.6–138.0 (8C), 128.1–126.9, 125.8, 108.3, 97.6, 97.4, 97.0, 83.5, 80.0 (2C), 79.6 (2C), 78.7, 75.6, 75.3, 74.8 (2C), 74.3, 73.8, 73.6, 73.0, 72.2, 71.8, 71.5, 71.3, 70.6, 67.7, 67.1, 65.8, 61.6, 55.0, 52.4, 47.4, 41.0, 39.8, 37.4, 36.2, 36.0, 33.8, 33.0, 31.3, 31.2, 29.7, 28.8 (3C), 28.4, 27.1, 24.6, 22.1, 17.6, 17.5, 17.0, 15.9, 14.5, 13.8, 12.1; ESIMS: Calcd *m*/*z* 1761.004. Found *m*/*z* 1783.974 $[M+Na]^+$.

3.10.4. Chlorogenin β-*O*-[2,4-di-*O*-(2,3,4-tri-*O*-benzyl-α-L-rhamnopyranosyl)-3,6-di-*O*-benzyl-β-D-glucopyranoside] 6α-dodecanoate (22).

R_f 0.34 (1:5 EtOAc–petroleum ether); $[\alpha]_D^{20}$ −27.8 (*c* 0.49, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.33–7.06 (m, 40H, Ar–H), 5.21 (d, 1H, *J* 1.4 Hz, Rha–H-1), 4.97 (d, 1H, *J* 1.9 Hz, Rha–H-1), 4.92 (d, 1H, *J* 10.6 Hz, –C*H*Ph), 4.81 (d, 1H, *J* 11.0 Hz), 4.78 (d, 1H, *J* 11.7 Hz), 4.71 (d, 1H, *J*

11.7 Hz), 4.65–4.50 (m, 10H), 4.41–4.36 (m, 3H), 4.24 (s, 2H), 4.18 (m, 1H), 3.77–3.42 (m, 14H), 3.38 (t, 1H, *J* 11.0 Hz), 3.30 (ddd, 1H, *J* 2.2, 4.7, 9.1 Hz), 2.24 (t, 2H, *J* 7.3 Hz), 1.28 (d, 3H, *J* 6.6 Hz), 1.28–1.23 (m, 18H), 0.97 (d, 3H, *J* 7.0 Hz), 0.94 (d, 3H, *J* 6.2 Hz), 0.85 (t, 3H, *J* 7.0 Hz), 0.79 (d, 3H, *J* 6.6 Hz), 0.75 (s, 3H), 0.55 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 173.2, 138.9, 138.6, 138.4, 138.3, 138.1, 138.0, 128.4–127.4, 126.2, 109.2, 98.9, 98.5 (2C), 84.0, 80.6, 80.5, 80.3, 79.5, 76.4, 75.7, 68.1, 66.9, 62.1, 55.9, 53.6, 48.3, 41.6, 40.6, 39.8, 37.8, 37.0, 36.7, 34.6, 33.5, 31.9, 31.7, 31.4, 30.3, 29.7, 29.5, 29.4, 29.2, 28.8, 27.6, 25.1, 22.7, 20.8, 19.1, 17.9, 17.8, 17.1, 16.4, 14.5, 14.1, 12.8; ESIMS: Calcd *m*/*z* 1789.035. Found *m*/*z* 1811.986 $[M+Na]^+$.

3.10.5. Chlorogenin 3β-*O*-[2,4-di-*O*-(2,3,4-tri-*O*-benzyl-α-L-rhamnopyranosyl)-3,6-di-*O*-benzyl-β-D-glucopyranoside] 6α-hexadecanoate (23). R_f 0.43 (1:5 EtOAc–petroleum ether); $[\alpha]_D^{20}$ −14.2 (*c* 0.18, $CHCl_3$); ^{1}H NMR (Me_2SO-d_6): δ 7.34–6.97 (m, 40H, Ar–H), 5.11 (s, 1H, Rha–H-1), 4.99 (s, 1H, Rha–H-1), 4.83–4.45 (m, 16H, –C*H*$_2$Ph, H-1′, H-16), 4.28–4.21 (m, 2H, H-6, Rha–H-5), 4.12 (d, 1H, *J* 11.8 Hz, –C*H*Ph), 3.98 (d, 1H, *J* 11.7 Hz, –C*H*Ph), 3.87 (s, 1H, Rha–H-2), 3.76–3.20 (m, 15H), 0.90 (d, 3H, *J* 7.0 Hz), 0.81 (t, 3H, *J* 7.3 Hz), 0.79 (d, 3H, *J* 7.3 Hz), 0.74 (d, 3H, *J* 6.2 Hz), 0.69 (s, 3H), 0.32 (s, 3H); ^{13}C NMR (Me_2SO-d_6): δ 172.5, 138.8, 138.7, 138.6, 138.4 (2C), 138.2, 138.0, 128.2–127.0, 125.9, 108.5, 97.7, 97.5, 97.2, 83.7, 80.1 (2C), 79.7, 78.8, 75.7, 75.5, 74.9, 74.4 (2C), 73.9, 73.2, 72.3, 72.0, 71.8, 71.4, 70.7, 67.9, 67.2, 65.9, 61.8, 55.1, 52.5, 47.5, 45.7, 41.1, 36.3, 36.1, 34.0, 33.1, 31.3, 30.9, 29.8, 29.2–28.3, 27.2, 24.8, 22.1 (2C), 17.7, 17.6, 17.0, 16.0, 14.6, 14.0, 12.2; ESIMS: Calcd *m*/*z* 1845.098. Found *m*/*z* 1868.110 $[M+Na]^+$.

3.11. General procedure for the preparation of 1–6

A suspension of **18**–**23**, respectively, AcOH (two drops), and Pd–C (0.2 g, 10%) in 1:1 CH_2Cl_2–EtOH was stirred under H_2 for 12 h and then filtered, and concentrated. The residue was purified by silica gel column chromatography.

3.11.1. Chlorogenin 3β-*O*-[2,4-di-*O*-(α-L-rhamnopyranosyl)-β-D-glucopyranoside] (1). Yield 90%; R_f 0.35 (5:2 $CHCl_3$–MeOH,); $[\alpha]_D^{20}$ −69.3 (*c* 0.2, MeOH); ^{1}H NMR (CD_3OD): δ 5.18 (d, 1H, *J* 1.4 Hz, Rha–H-1), 4.83 (d, 1H, *J* 1.4 Hz, Rha–H-1), 4.52 (d, 1H, *J* 8.2 Hz, H-1′), 4.38 (q, 1H, *J* 7.3 Hz, H-16), 4.15 (m, 1H), 3.93–3.91 (m, 2H), 3.82 (dd, 1H, *J* 1.8, 3.2 Hz), 3.78 (dd, 1H, *J* 1.9, 12.4 Hz), 3.67–3.60 (m, 4H), 3.57 (t, 1H, *J* 9.1 Hz), 3.52 (t, 1H, *J* 9.1 Hz), 3.45–3.28 (m, 7H), 2.38–2.28 (m, 2H), 1.25 (d, 3H, *J* 6.4 Hz), 1.23 (d, 3H, *J* 6.4 Hz), 0.95 (d, 3H, *J* 6.9 Hz), 0.85 (s, 3H), 0.79–0.78 (m, 6H); ^{13}C NMR (CD_3OD): δ 110.5, 103.0, 102.3, 100.2, 82.1, 80.0, 79.4, 78.6, 78.1, 76.6, 74.0, 73.7, 72.5, 72.3, 72.2 (2C), 70.6, 69.9, 69.7, 67.8, 63.8, 61.9, 57.3, 55.3, 52.8, 42.9, 42.7, 41.7, 41.0, 38.7, 37.6, 35.2, 32.7, 32.4, 31.4, 30.4, 29.9, 29.3, 22.1, 18.0, 17.9, 17.5, 16.9, 14.9, 13.8; ESIMS: Calcd *m*/*z* 886.493. Found *m*/*z* 909.626 $[M+Na]^+$.

3.11.2. Chlorogenin 3β-*O*-[2,4-di-*O*-(α-L-rhamnopyranosyl)-β-D-glucopyranoside] 6α-acetate (2). Yield 52% (for two steps); R_f 0.36 (5:1 $CHCl_3$–MeOH,); $[\alpha]_D^{20}$ −43.1 (*c* 0.2, MeOH); ^{1}H NMR (Me_2SO-d_6): δ 4.99 (s, 1H, Rha–H-1), 4.94 (d, 1H, *J* 6.4 Hz, –OH), 4.75–4.73 (m, 2H, –OH × 2), 4.70–4.69 (m, 2H, –OH, Rha–H-1), 4.60 (d, 1H, *J* 4.6 Hz, –OH), 4.60 (d, 1H, *J* 4.1 Hz, –OH), 4.57 (d, 1H, *J* 5.9 Hz, –OH), 4.53 (td, 1H, *J* 4.1, 11.0 Hz), 4.50 (d, 1H, *J* 6.0 Hz, –OH), 4.39 (d, 1H, *J* 7.8 Hz, H-1′), 4.26 (q, 1H, *J* 6.8 Hz), 3.89–3.83 (m, 2H, Rha–H-5), 3.69 (t, 1H, Rha–H-2), 3.60–3.57 (m, 2H, Rha–H-2, H-6′), 3.51 (m, 1H, H-3), 3.42–3.37 (m, 5H), 3.21–3.17 (m, 5H), 2.03 (s, 3H), 1.10 (d, 3H, *J* 6.0 Hz), 1.04 (d, 3H, *J* 6.4 Hz, Rha–CH_3), 0.89 (d, 3H, *J* 6.8 Hz, Rha–CH_3), 0.80 (s, 3H), 0.74 (d, 3H, *J* 6.4 Hz), 0.72 (s, 3H); ^{13}C NMR (Me_2SO-d_6): δ 170.3, 108.4, 100.5 (2C), 98.7, 80.1, 77.6, 76.7, 76.3, 76.0, 75.1, 71.9 (2C), 71.5, 70.7 (2C), 70.6, 70.4, 68.6, 68.0, 65.9, 61.7, 60.1, 55.1, 52.8, 47.5, 41.1, 40.1, 37.5, 36.5, 36.2, 33.2, 31.2, 30.9, 29.8, 28.8, 28.5, 27.7, 21.1, 20.4, 17.8 (2C), 17.1, 16.1, 14.6, 12.8; ESIMS: Calcd *m*/*z* 928.503. Found *m*/*z* 948.517 $[2M+Ca]^{2+}$.

3.11.3. Chlorogenin 3β-*O*-[2,4-di-*O*-(α-L-rhamnopyranosyl)-β-D-glucopyranoside] 6α-hexanoate (3). Yield 84% (for two steps); R_f 0.40 (3:1 $CHCl_3$–MeOH); $[\alpha]_D^{20}$ −53.3 (*c* 0.2, MeOH); ^{1}H NMR (CD_3OD): δ 5.18 (d, 1H, *J* 1.4 Hz, Rha–H-1), 4.83 (d, 1H, *J* 1.8 Hz, Rha–H-1), 4.69 (td, 1H, *J* 4.4, 10.6 Hz, H-16), 4.46 (d, 1H, *J* 7.7 Hz, H-1′), 4.38 (q, 1H, *J* 7.3 Hz, H-6), 4.07 (m, 1H), 3.93–3.89 (m, 2H), 3.82 (dd, 1H, *J* 1.8, 3.2 Hz), 3.79 (dd, 1H, *J* 1.9, 12.1 Hz), 3.68–3.60 (m, 4H), 3.55 (t, 1H, *J* 8.8 Hz), 3.51 (t, 1H, *J* 9.2 Hz), 3.45–3.28 (m, 6H), 2.38–2.28 (m, 2H), 1.25 (d, 3H, *J* 6.2 Hz), 1.20 (d, 3H, *J* 6.2 Hz), 0.95–0.92 (m, 9H), 0.79 (s, 3H), 0.77 (d, 3H, *J* 6.2 Hz); ^{13}C NMR (CD_3OD): δ 175.6, 110.5, 103.0, 102.3, 100.2, 82.0, 80.0, 79.3, 78.1, 76.7, 74.0, 73.7, 72.4 (2C), 72.2, 70.7, 69.8, 67.8, 63.8, 62.0, 57.1, 55.0, 49.8, 42.9, 41.8, 40.9, 39.0, 38.3, 38.0, 35.5, 35.1, 32.6, 32.5, 32.4, 31.4, 30.2, 29.9, 29.4, 26.0, 23.5, 22.0, 18.0, 17.9, 17.5, 16.9, 14.9, 14.4, 13.7; ESIMS: Calcd *m*/*z* 984.566. Found 1007.438 $[M+Na]^+$.

3.11.4. Chlorogenin 3β-*O*-[2,4-di-*O*-(α-L-rhamnopyranosyl)-β-D-glucopyranoside] 6α-decanoate (4). Yield 65% (for two steps); R_f 0.37 (5:1 $CHCl_3$–MeOH); $[\alpha]_D^{20}$ −63.2 (*c* 0.2, MeOH); ^{1}H NMR (Me_2SO-d_6): δ 4.98 (s, 1H, Rha–H-1), 4.90 (d, 1H, *J* 6.4 Hz, –OH), 4.75–4.68 (m, 4H, –OH, Rha–H-1), 4.60 (d, 1H, *J* 4.6 Hz, –OH),

4.59 (d, 1H, *J* 4.1 Hz, –OH), 4.55 (td, 1H, *J* 4.6, 11.0 Hz), 4.50 (d, 1H, *J* 5.9 Hz, –OH), 4.40 (d, 1H, *J* 6.0 Hz, –OH), 4.35 (d, 1H, *J* 7.7 Hz, H-1′), 4.25 (q, 1H, *J* 6.4 Hz), 3.89–3.82 (m, 2H, Rha–H-5 × 2), 3.68 (t, 1H, Rha–H-2), 3.60–3.52 (m, 3H, Rha–H-2, H-6′, H-3), 3.44–3.31 (m, 5H), 3.22–3.13 (m, 5H), 1.10 (d, 3H, *J* 6.0 Hz), 1.05 (d, 3H, *J* 6.4 Hz, Rha–CH_3), 0.89 (d, 3H, *J* 6.8 Hz, Rha–CH_3), 0.86 (t, 2H, *J* 6.8 Hz), 0.81 (s, 3H), 0.73 (d, 3H, *J* 6.4 Hz), 0.72 (s, 3H); ^{13}C NMR (Me_2SO-d_6): δ 172.8, 108.4, 100.6, 100.5, 98.1, 80.1, 77.5, 76.7, 76.1, 75.4, 75.2, 71.9 (2C), 71.4, 70.7, 70.6 (2C), 70.4, 68.7, 68.0, 65.9, 61.7, 60.0, 55.2, 52.8, 47.5, 41.1, 40.1, 37.5, 36.5, 36.3, 33.8, 33.2, 31.3, 31.2, 30.8, 29.8, 28.8, 28.7 (2C), 28.6, 28.5, 28.4, 27.3, 24.7, 22.1, 20.4, 17.8, 17.1, 16.1, 14.6, 14.0, 12.8; ESIMS: Calcd *m*/*z* 1040.628. Found 1063.542 $[M+Na]^+$.

3.11.5. Chlorogenin 3β-*O*-[2,4-di-*O*-(α-L-rhamnopyranosyl)-β-D-glucopyranoside] 6α-dodecanoate (5). Yield 91% (for two steps); R_f 0.51 (3:1 $CHCl_3$–MeOH); $[\alpha]_D^{20}$ −56.7 (*c* 0.2, MeOH); ^{1}H NMR (Me_2SO-d_6): δ 4.99 (s, 1H, Rha–H-1), 4.88 (d, 1H, *J* 6.6 Hz, –OH), 4.71–4.69 (m, 3H, –OH, Rha–H-1), 4.64 (d, 1H, *J* 5.1 Hz, –OH), 4.57–4.54 (m, 3H, –OH, H-16), 4.46 (d, 1H, *J* 5.8 Hz, –OH), 4.37–4.34 (m, 2H, –OH, H-1′), 4.26 (q, 1H, *J* 6.6 Hz, H-6), 3.89–3.82 (m, 2H), 3.68 (m, 1H), 3.60–3.51 (m, 3H), 3.45–3.36 (m, 6H), 3.22–3.15 (m, 5H), 2.35–2.24 (m, 2H), 1.24 (s, 18H), 1.10 (d, 3H, *J* 6.2 Hz), 1.04 (d, 3H, *J* 6.2 Hz), 0.89 (d, 3H, *J* 7.0 Hz), 0.86 (t, 3H, *J* 7.0 Hz), 0.81 (s, 3H), 0.73 (d, 3H, *J* 6.6 Hz), 0.72 (s, 3H); ^{13}C NMR (Me_2SO-d_6): δ 173.3, 109.0, 101.2, 101.1, 98.8, 80.6, 78.0, 77.4, 76.7, 76.1, 75.8, 72.5 (2C), 71.9, 71.3, 71.2 (2C), 70.9, 69.3, 68.5, 66.5, 62.4, 60.6, 55.8, 53.4, 48.1, 41.7, 38.1, 37.1, 36.9, 34.3, 33.7, 31.9, 31.8, 31.4, 30.4, 29.6, 29.5, 29.4, 29.3, 29.2, 29.0, 28.9, 28.0, 25.2, 22.7, 21.0, 18.3, 17.6, 16.7, 15.1, 14.5, 13.4; ESIMS: Calcd *m*/*z* 1068.660. Found *m*/*z* 1091.532 $[M+Na]^+$.

3.11.6. Chlorogenin 3β-*O*-[2,4-di-*O*-(α-L-rhamnopyranosyl)-β-D-glucopyranoside] 6α-hexadecanoate (6). Yield 76% (for two steps); R_f 0.38 (5:1 $CHCl_3$–MeOH); $[\alpha]_D^{20}$ −46.4 (*c* 0.2, MeOH); ^{1}H NMR (Me_2SO-d_6): δ 4.98 (s, 1H, Rha–H-1), 4.92 (d, 1H, *J* 6.8 Hz, –OH), 4.76–4.74 (m, 2H, –OH), 4.70 (d, 1H, *J* 5.0 Hz, –OH), 4.69 (s, 1H, Rha–H-1), 4.62 (d, 1H, *J* 4.6 Hz, –OH), 4.59 (d, 1H, *J* 4.1 Hz, –OH), 4.57–4.53 (m, 2H, –OH, H-16), 4.43 (d, 1H, *J* 6.0 Hz, –OH), 4.35 (d, 1H, *J* 7.7 Hz, H-1′), 4.26 (q, 1H, *J* 6.8 Hz, H-6), 3.89–3.82 (m, 2H), 3.68 (m, 1H), 3.60–3.51 (m, 3H), 3.44–3.36 (m, 6H), 3.21–3.15 (m, 5H), 1.10 (d, 3H, *J* 6.0 Hz), 1.04 (d, 3H, *J* 6.4 Hz), 0.90 (d, 3H, *J* 6.9 Hz), 0.81 (s, 3H), 0.73 (d, 3H, *J* 6.4 Hz), 0.72 (s, 3H); ^{13}C NMR (Me_2SO-d_6): δ 172.8, 108.4, 100.5 (2C), 98.2, 80.1, 77.5, 76.7, 76.1, 75.6, 75.2, 71.9 (2C), 71.4, 70.7 (2C), 70.6, 70.3, 68.7, 68.0, 65.9, 61.8, 60.0, 55.2, 52.9, 47.5, 40.1, 40.1–39.1, 37.5, 36.5, 36.3, 33.7, 33.2, 31.3, 31.2, 30.8, 29.8, 29.1 (2C), 28.9, 28.8, 28.7, 28.6, 28.5, 28.3, 27.4, 24.6, 22.1, 20.4, 17.8, 17.0, 16.1, 14.6, 12.8; ESIMS: Calcd *m*/*z* 1124.722. Found *m*/*z* 582.351 $[M+Ca]^{2+}$.

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Supplementary data

^{1}H NMR spectra for compounds **7**–**9**, **11**–**13**, **15**–**23** and **1**–**6**, and ^{13}C NMR spectra for compounds **1**–**6**, **13**, **16**, **17**, **19**–**22** and **23** are provided. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.carres.2005.03.019.

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