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Synthesis of bidesmosidic dihydrodiosgenin saponins bearing a 3-*O*-β-chacotriosyl moiety

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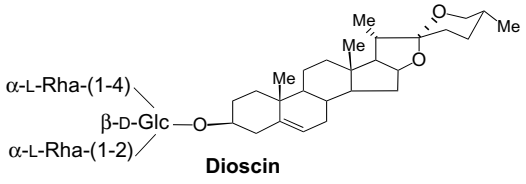
Abstract—3-*O*-β-Chacotriosyl-26-*O*-β-D-glucopyranosyl-(25*R*)-furost-5-en (**1**), a mimic of the antitumor active proto-dioscin, was concisely synthesized from diosgenin in a linear nine steps and in 17% overall yield. Its congeners with a α-L-rhamnopyranosyl, β-lactosyl, or without a substituent at the 26-OH (**13**–**15**) were also prepared. Compound **1**, as well as **13**–**15**, did not show any inhibition against tumor cells, implying that proto-dioscin might be also inactive, but readily converted into the antitumor active dioscin.

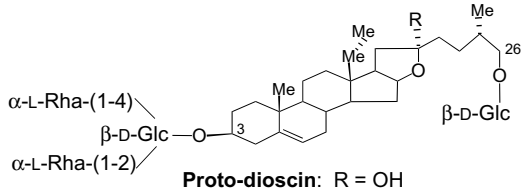
Keywords: 3-*O*-β-Chacotriosyl-26-*O*-β-D-glucopyranosyl-(25*R*)-furost-5-en; Proto-dioscin; Furostan saponin; Synthesis

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 of the 3-*O*-sugar residue. Those bearing a chacotriosyl residue at the 3-OH are among the most active examples.[1] Dioscin (diosgenin 3-*O*-β-chacotrioside), one of the most abundant spirostan saponins occurring in plants, represents a well-studied example, showing promising antitumor activities both in vitro and in vivo.[1,2] The furostan proto-dioscin, 3-*O*-β-chacotriosyl-26-*O*-β-D-glucopyranosyl-22-hydroxyl-(25*R*)-furost-5-en, and its 22-methoxyl derivative are as potent as dioscin in inhibition of the growth of tumor cells (IC_{50}s at the μM level).[1,3] Interestingly, the cytotoxicity pattern of proto-dioscin was found unique against the 60 tumor cell lines in the NCI's anticancer screening.[3a] Furostan saponins are difficult to obtain from natural sources; enzymatic or acidic cleavage of the 26-*O*-glucopyranosyl residue, followed by an intramolecular acetalization, converts furostan saponins readily into the corresponding spirostan saponins. In fact, furostan saponins are regarded as



Dioscin



Proto-dioscin: R = OH
Methyl proto-dioscin: R = OMe
1: R = H

Abbreviations: TBDMS, *tert*-butyldimethylsilyl-; TBDPS, *tert*-butyldiphenylsilyl-; 1-BBTZ, 1-(benzoyloxy)benzotriazole; TBAF, tetrabutylammonium fluoride; DMAP, 4-(dimethylamino)pyridine; SRB, sulforhodamine B

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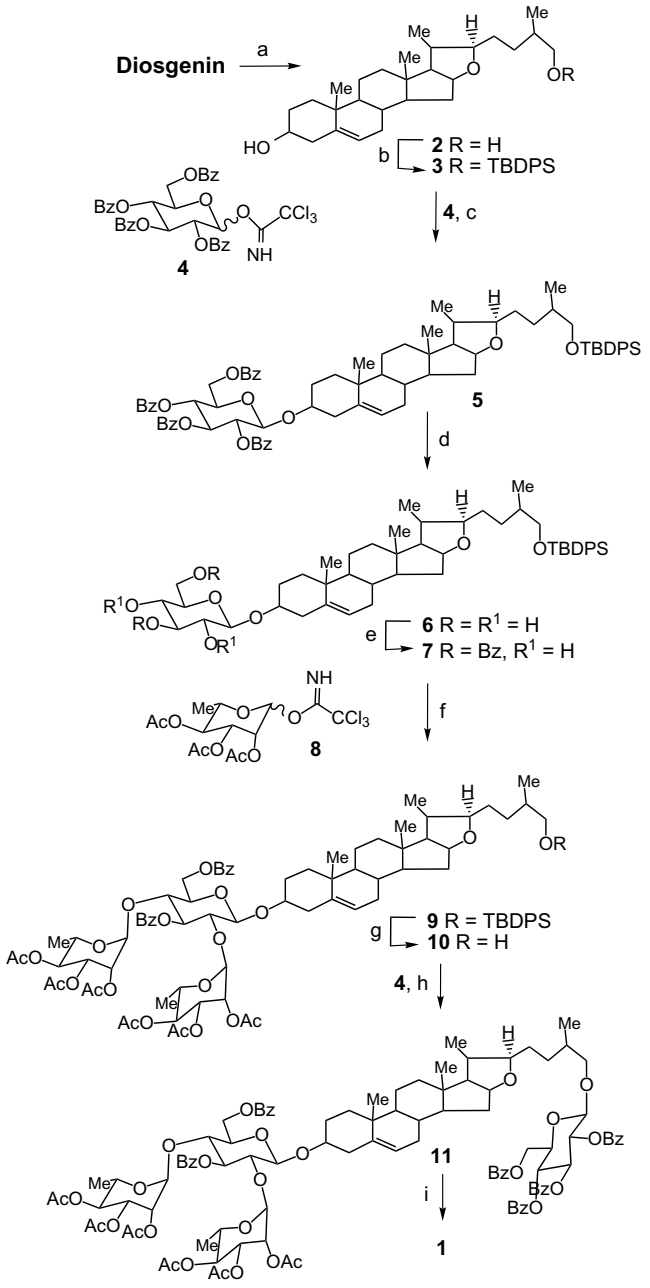
the biosynthetic precursors of the spirostan saponins.[4] Recently, a synthetic approach toward proto-dioscin has been reported,[5] but a practical access still awaits elaboration. Thus, compound **1**, namely 3-*O*-β-chacotriosyl-26-*O*-β-D-glucopyranosyl-(25*R*)-furost-5-en, a synthetically easily accessible mimic of proto-dioscin attracts attention.[6] Here we report a facile synthesis of **1** as well as its congeners with different substituents at the 26-OH (**13**–**15**) for antitumor evaluation.

2. Results and discussion

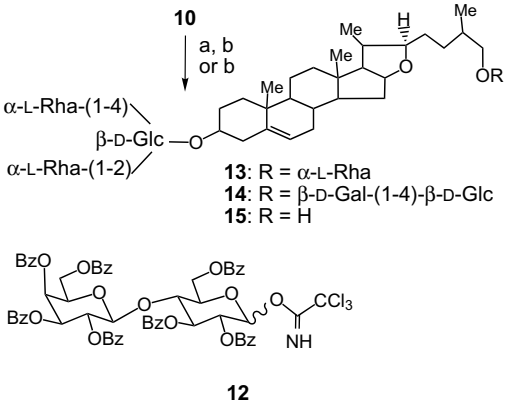
In the recent synthesis of compound **1**,[6] Oscarson and co-workers subjected the 3-*O*-TBDMS protected diosgenin to a mild reductive procedure ($BH_3{\cdot}Me_3N/AlCl_3$) to provide the 3-*O*-TBDMS-dihydrodiosgenin. Subsequent glucosylation of the 26-OH, deprotection of the 3-OTBDMS, assembly of the 3-*O*-chacotriosyl moiety, and final removal of the benzyl protecting groups on the sugar residues afforded the target compound **1**. We intended to assemble the 3-*O*-chacotriosyl linkage before the attachment of the 26-*O*-glucosyl residue; thus the synthetic route would be applicable to the preparation of the 3-*O*-chacotrioside congeners with different sugar residues at the 26-OH. For assembly of the 3-*O*-chacotrioside, we planed to adopt the procedure we developed for the synthesis of dioscin, where acyl-protected glucosyl and rhamnosyl imidates were employed to ensure formation of the 1,2-trans glycosidic bonds and a facile final deprotection.[7]

The synthetic route toward **1** is depicted in Scheme 1. Reductive opening of the spiroketal of diosgenin with $LiAlH_4/AlCl_3$ gave dihydrodiosgenin **2** in 95% yield.[8] Selective protection of the primary 26-OH was achieved with a TBDPS group to provide **3** (82%). Compound **3** was treated with 2,3,4,6-tetra-*O*-benzoyl-D-glucopyranosyl trichloroacetimidate (**4**) in the presence of TMSOTf (0.1 equiv) in CH_2Cl_2, affording the 3-*O*-β-glucopyranoside **5** in an excellent yield (97%).[9] Removal of the benzoyl groups with NaOMe in MeOH readily gave **6**, 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 glucopyranosyl residue, affording 2,4-diol **7** in a satisfactory 61% yield.[7,10] Glycosylation of **7** with 2,3,4-tri-*O*-acetyl-L-rhamnopyranosyl trichloroacetimidate (**8**) under 'inverse addition' conditions[11] provided a crude **9**. After cleavage of the 26-OTBDPS with TBAF in the presence of HOAc in THF, the desired key intermediate **10** was then conveniently purified in 72% yield (two steps). Similar conditions as those used for the glucosylation of the 3-OH of **4** were applied to the coupling of the 26-OH of **10**, but led to only moderate yield of the desired **11** (62%). Finally, ready removal of the acetyl and benzoyl groups (NaOMe, MeOH) furnished the target **1** in 86% yield.



Scheme 1. Reagents and conditions: (a) $LiAlH_4$, $AlCl_3$, Et_2O–CH_2Cl_2, 0 °C → rt, 1 h, 95%; (b) TBDPSCl, imidazole, DMAP, CH_2Cl_2, rt, 1 h, 82%; (c) TMSOTf (0.1 equiv), CH_2Cl_2, 4 Å MS, 0 °C → rt, 97%; (d) NaOMe, MeOH, rt, 2 h, 97%; (e) 1-BBTZ, CH_2Cl_2, Et_3N, rt, 48 h, 61%; (f) TMSOTf (0.2 equiv), CH_2Cl_2, 4 Å MS, −30 °C → rt; (g) TBAF, HOAc, THF, rt, 16 h, 72% (two steps); (h) TMSOTf (0.1 equiv), CH_2Cl_2, 4 Å MS, 0 °C → rt, 62%; (i) NaOMe, MeOH, rt, overnight, 86%.

Starting from the readily available 3-*O*-peracylchacotriosyl-26-OH derivative **10**, the desired congeners with a different substituent at 26-OH were easily prepared (Scheme 2). Glycosylation of the 26-OH of **10** with per-*O*-acetyl-L-rhamnopyranosyl and per-*O*-benzoyllactosyl trichloroacetimidate (**8** and **12**[12]) under common conditions (0.1 equiv of TMSOTf, CH_2Cl_2), followed by



Scheme 2. Reagents and conditions: (a) **8** or **12**, TMSOTf (0.1 equiv), CH_2Cl_2, 4 Å MS, −30 °C → rt; (b) MeONa, MeOH, rt, 18% (for **13**, two steps); 62% (for **14**, two steps); 76% (for **15**).

removal of the acetyl and benzoyl groups with NaOMe in MeOH, readily provided the bidesmosidic saponins **13** and **14**, after silica gel column chromatography, in 18% and 64% yield, respectively. Direct cleavage of the acetyl and benzoyl groups on **10** provided the 26-OH derivative **14**.

Compounds **1** and **13**–**15** were examined for their inhibitory activity against the human lung adenocarcinoma A-549, a proto-dioscin-sensitive cell line (IC_{50} = 1.64 μM), following the standard SRB (sulforhodamine B) assay procedure.[3c] Unfortunately, little inhibition was observed at and below the concentration of 10 μM. These results imply that proto-dioscin (generally furostan saponins) might be also inactive, but could be readily convert into the antitumor active dioscin (generally spirostan saponins).

3. Experimental

3.1. General methods

Solvents were purified in the usual way. TLCs were performed on precoated E. Merck Silica Gel 60 F_{254} plates. Flash column chromatography was performed on silica gel (100–200 mesh, Qingdao, China). Optical rotations were determined with a Perkin–Elmer Model 241 MC polarimeter. Melting points were determined with a 'Yanaco' apparatus and were uncorrected. ^{1}H NMR and ^{13}C NMR spectra were taken on a JEOL JNM-ECP 600 MHz spectrometer with tetramethylsilane (TMS) as an internal standard, and chemical shifts are recorded in δ values. Mass spectra were obtained on a HP5989A or a VG Quatro mass spectrometer.

3.1.1. 3β,26-Dihydroxy-(25*R*)-furost-5-en (2). To a stirred ice-cold solution of $AlCl_3$ (14.0 g, 0.10 mol) in anhydrous Et_2O (40 mL) was carefully added $LiAlH_4$ (0.95 g, 0.025 mol). Then a solution of diosgenin (1.04 g, 2.5 mmol) in anhydrous Et_2O (40 mL) was added with stirring over a period of 15 min. Stirring was continued for 15 min at 0 °C and then 1 h at rt. The mixture was treated cautiously with water and 10% H_2SO_4. The resulting mixture was extracted with Et_2O, and the combined extracts were washed with dilute $NaHCO_3$ solution, dried over Na_2SO_4, and then concentrated. The residue was purified by column chromatography (1:2:1 EtOAc–petroleum ether–$CHCl_3$) to give **2** as a white solid (0.99 g, 95%): R_f 0.25 (1:1:1 EtOAc–petroleum ether–$CHCl_3$); mp 164–166 °C (lit.[8c] 166–169 °C); $[\alpha]_D^{20}$ −48.8 (*c* 0.65, $CHCl_3$); ^{1}H NMR (DMSO-d_6): δ 5.26 (d, 1H, J = 5.5 Hz, H-6), 4.60 (d, 1H, J 4.7 Hz, 3-OH), 4.36 (t, 1H, J 5.5 Hz, 26-OH), 4.20 (m, 1H, H-16), 3.25–3.16 (m, 4H, H-3, H-26, H-22), 2.16–2.06 (m, 2H), 1.93–1.88 (m, 2H), 1.76 (m, 1H), 1.68 (m, 3H), 1.56–1.31 (m, 10H), 1.19–1.03 (m, 4H), 0.99 (m, 1H), 0.96 (m, 6H, H-19, H-21), 0.87 (m, 1H), 0.81 (d, 3H, J 6.6 Hz, H-27), 0.75 (s, 3H, H-18); ESIMS (*m*/*z*): 439.318 [M+Na$^+$]; calcd 439.318.

3.1.2. 26-*O*-*tert*-Butyldiphenylsilyl-3β-hydroxy-(25*R*)-furost-5-en (3). TBDPSCl (0.2 mL, 0.79 mmol) was added dropwise to a stirred mixture of **2** (0.3 g, 0.72 mmol), imidazole (0.12 g, 1.8 mmol), and DMAP (catalytic amount) in CH_2Cl_2 (25 mL) at 10 °C. The mixture was stirred for 20 min at rt. Removal of solvent afforded a residue that was subjected to column chromatography (1:6:1 EtOAc–petroleum ether–$CHCl_3$) to give **3** as a buff solid (0.39 g, 82%): R_f 0.20 (1:6:1 EtOAc–petroleum ether–$CHCl_3$); mp 47.5–49.0 °C; $[\alpha]_D^{20}$ −34.2 (*c* 0.61, $CHCl_3$); ^{1}H NMR (DMSO-d_6): δ 7.61–7.60 (m, 4H, ArH), 7.47–7.41 (m, 6H, ArH), 5.26 (d, 1H, J 5.2 Hz, H-6), 4.61 (d, 1H, J 4.7 Hz, 3-OH), 4.20 (m, 1H, H-16), 3.48 (m, 2H), 3.26–3.19 (m, 2H), 2.16–2.06 (m, 2H), 1.92–1.88 (m, 2H), 1.75 (m, 1H), 1.67–1.61 (m, 4H), 1.56–1.45 (m, 7H), 1.38–1.02 (m, 6H), 1.00 (s, 9H), 0.96 (m, 1H), 0.95 (m, 6H, H-19, H-21), 0.90 (m, 1H), 0.88 (d, 3H, J 6.6 Hz, H-27), 0.73 (s, 3H, H-18). ^{13}C NMR (DMSO-d_6): δ 141.3, 135.0, 133.2, 129.8, 127.8, 120.3, 89.3, 82.3, 79.2, 69.9, 68.1, 64.6, 56.2, 49.6, 42.2, 40.1, 39.1, 37.3, 36.9, 36.2, 35.1, 31.9, 31.3 (2C), 31.2, 30.3, 29.5, 26.6, 20.2, 19.1, 18.9, 18.8, 16.7, 16.1; ESIMS (*m*/*z*): 677.437 [M+Na$^+$]; calcd 677.436.

3.1.3. 26-*O*-*tert*-Butyldiphenylsilyl-3β-*O*-(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)-(25*R*)-furost-5-en (5). To a mixture of compound **3** (2.88 g, 4.4 mmol), **4** (4.0 g, 5.4 mmol), and powdered 4 Å molecular sieves in dried CH_2Cl_2 (70 mL) at 0 °C was added TMSOTf (78 μL, 0.44 mmol). After stirring at 0 °C for 0.5 h and then at rt for 1 h, the reaction was quenched with Et_3N. The solid was then filtered off. The filtrate was concentrated under vacuum to give a yellow oil that was purified by column chromatography (1:10:1 EtOAc–petroleum ether–$CHCl_3$) to give compound **5** as a buff solid (5.23 g, 96%):

R_f 0.15 (1:10:1 EtOAc–petroleum ether–$CHCl_3$); mp 127.5–129 °C. $[\alpha]_D^{20}$ +7.3 (*c* 0.81, $CHCl_3$); ^{1}H NMR (DMSO-d_6): δ 7.96–7.42 (m, 30H, ArH), 5.98–5.95 (m, 1H, H-3′), 5.56 (t, 1H, *J* 9.5 Hz, H-4′), 5.32 (m, 2H, H-2′, H-1′), 5.19 (d, 1H, *J* 4.0 Hz, H-6), 4.53–4.46 (m, 3H, H-6′, H-5′), 4.20 (m, 1H, H-16), 3.49–3.44 (m, 3H), 3.20 (m, 1H), 2.26–1.03 (m, 23H), 0.99 (s, 9H), 0.94 (d, 3H, *J* 6.6 Hz, H-21), 0.87 (d, 3H, *J* 6.6 Hz, H-27), 0.85 (m, 1H), 0.84 (s, 3H, H-19), 0.70 (s, 3H, H-18). ^{13}C NMR (DMSO-d_6): δ 165.3, 165.1, 164.7, 164.6, 139.8, 135.0, 133.8, 133.7, 133.4, 133.3, 133.2, 129.8, 129.2, 129.1, 129.0, 128.8, 128.7 (2C), 128.4, 127.8, 121.4, 98.4, 89.3, 82.3, 79.0, 73.2, 71.9, 70.8, 69.6, 68.1, 64.5, 62.7, 56.2, 49.4, 40.1, 38.8, 38.4, 37.3, 36.5, 36.1, 35.1, 31.9, 31.4, 31.0, 30.3, 29.4, 29.1, 26.6, 20.1, 18.9, 18.8, 16.7, 16.1. ESIMS (*m*/*z*): 1256.3 [M+1+Na^+].

3.1.4. 26-*O*-*tert*-Butyldiphenylsilyl-3β-*O*-(β-D-glucopyranosyl)-(25*R*)-furost-5-en (6). Compound **5** (200 mg) was dissolved in 1:1 CH_3OH–$CHCl_3$ (15 mL), and then NaOMe (100 mg) 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 column chromatography (8:1 $CHCl_3$–MeOH) to afford **6** as a white solid (128 mg, 97%): R_f 0.41 (5:1 $CHCl_3$–MeOH); mp 157–158 °C. $[\alpha]_D^{20}$ −39.1 (*c* 0.77, $CHCl_3$); ^{1}H NMR (DMSO-d_6): δ 7.61 (m, 4H, ArH), 7.47–7.41 (m, 6H, ArH), 5.33 (d, 1H, *J* 5.2 Hz, H-6), 4.90 (d, 1H, *J* 4.7 Hz, 3′-OH), 4.87 (t, 2H, *J* 5.5 Hz, 2′-OH, 4′-OH), 4.43 (t, 1H, *J* 5.8 Hz, 6′-OH), 4.22 (d, 1H, *J* 7.7 Hz, H-1′), 4.19 (m, 1H, H-16), 3.65 (dd, 1H, *J* 5.5, 9.9 Hz, H-6′), 3.20 (m, 1H, H-22), 3.12 (td, 1H, *J* 4.7, 8.4 Hz, H-3′), 3.07 (m, 1H, H-5′), 3.02 (td, 1H, *J* 5.2, 9.2 Hz, H-4′), 2.89 (td, 1H, *J* 4.7, 8.0 Hz, H-2′), 2.37 (dd, 1H, *J* 2.9, 13.6 Hz), 2.14–1.05 (m, 23H), 1.00 (s, 9H), 0.97 (s, 3H, H-19), 0.94 (d, 3H, *J* 6.6 Hz, H-21), 0.88 (d, 3H, *J* 6.6 Hz, H-27), 0.74 (s, 3H, H-18). ^{13}C NMR (DMSO-d_6): δ 140.5, 135.0, 133.3, 129.8, 127.8, 121.1, 100.7, 89.3, 82.3, 76.8 (2C), 73.5, 70.1, 68.1, 64.6, 61.1, 56.2, 49.6, 40.2, 38.8, 37.3, 36.8, 36.4, 35.1, 31.9, 31.5, 31.2, 30.3, 29.5, 29.3, 20.2, 19.1, 18.9, 18.8, 16.8, 16.1. ESIMS (*m*/*z*): 839.473 [M+Na^+]; calcd 839.470.

3.1.5. 26-*O*-*tert*-Butyldiphenylsilyl-3β-*O*-(3,6-di-*O*-benzoyl-β-D-glucopyranosyl)-(25*R*)-furost-5-en (7). To a stirred solution of compound **6** (1.49 g, 1.83 mmol) and 1-BBTZ (1.09 g, 4.53 mmol) in CH_2Cl_2 (30 mL) at rt was added Et_3N (0.63 mL, 4.55 mmol). The reaction mixture was stirred at rt for 48 h. Removal of the solvent afforded a residue that was subjected to column chromatography (1:3 EtOAc–petroleum ether) to give **7** as a buff solid (1.15 g, 61%): R_f 0.14 (1:3 EtOAc–petroleum ether); mp 82–83 °C. $[\alpha]_D^{20}$ −17.9 (*c* 0.62, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 8.10–7.37 (m, 20H, ArH), 5.35 (d, 1H, *J* 5.1 Hz, H-6), 5.21 (t, 1H, *J* 9.2 Hz, H-3′), 4.70–4.63 (m, 2H, H-6′), 4.55 (d, 1H, *J* 7.7 Hz, H-1′), 4.30 (q, 1H, *J* 7.7, 13.2 Hz, H-16), 3.77–3.74 (m, 2H, H-4′, H-5′), 3.68 (dd, 1H, *J* 8.0, 9.5 Hz, H-2′), 3.58 (m, 1H, H-3), 3.52 (dd, 1H, *J* 5.5, 9.8 Hz, H-26), 3.45 (dd, 1H, *J* 6.2, 9.9 Hz, H-26), 3.34 (br s, 1H, 4′-OH), 3.30 (td, 1H, *J* 4.0, 7.7 Hz, H-22), 2.49 (br s, 2′-OH), 2.37–1.28 (m, 22H), 1.10 (m, 1H), 0.88 (m, 1H), 1.04 (s, 9H), 1.00 (s, 3H, H-19), 0.99 (d, 3H, *J* 6.2 Hz, H-21), 0.93 (d, 3H, *J* 6.6 Hz, H-27), 0.79 (s, 3H, H-18). ^{13}C NMR ($CDCl_3$): δ 167.9, 166.9, 140.3, 135.7, 134.2, 133.6, 133.3, 130.1, 130.0, 129.9, 129.6, 129.5, 128.6, 128.5, 127.7, 122.1, 101.6, 90.5, 83.2, 79.9, 78.7, 77.3, 77.1, 76.9, 74.4, 72.2, 69.9, 68.8, 65.4, 63.9, 57.1, 50.2, 40.8, 39.6, 38.9, 38.0, 37.2, 36.9, 36.1, 32.3, 32.1, 32.0, 31.7, 31.2, 30.2, 29.8, 29.5, 27.0, 22.8, 20.8, 19.4, 19.2, 17.0, 16.5, 14.2. ESIMS (*m*/*z*): 1047.540 [M+Na^+]; calcd 1047.541.

3.1.6. 26-*O*-*tert*-Butyldiphenylsilyl-3β-*O*-[2,4-di-*O*-(2,3,4-tri-*O*-acetyl-α-L-rhamnopyranosyl)-3,6-di-*O*-benzoyl-β-D-glucopyranosyl]-(25*R*)-furost-5-en (9). To a mixture of **7** (1.10 g, 1.07 mmol) and powdered 4 Å molecular sieves in dried CH_2Cl_2 (20 mL) at −30 °C, TMSOTf (43 μL, 0.25 mmol) was added, followed by dropwise addition of a solution of **8** (2.33 g, 5.35 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 then filtered off, and the filtrate was concentrated under vacuum to give a yellow oil. The oil was subjected to column chromatography (1:3 EtOAc–petroleum ether to 1:2 EtOAc–petroleum ether) to give crude **9** that was directly subjected to the next reaction. Part of the crude product (50 mg) was purified with precoated plates of Silica Gel GF_{254} (0.25 mm, Qingdao) to afford pure **9** for analysis: R_f 0.15 (EtOAc–petroleum ether–$CHCl_3$, 1:10:1) mp 69–70 °C. $[\alpha]_D^{20}$ −33.6 (*c* 0.22, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 8.06–7.36 (m, 20H, ArH), 5.62 (t, 1H, *J* 9.1 Hz, H-3′), 5.35 (d, 1H, *J* 5.0 Hz, H-6), 5.16 (d, 1H, *J* 3.7 Hz, H-3(rha)), 5.15 (d, 1H, *J* 3.7 Hz, H-3(rha)), 5.12 (m, 1H, H-2(rha)), 4.98 (dd, 1H, *J* 1.9, 3.7 Hz, H-2(rha)), 4.91 (t, 1H, *J* 10.1 Hz, H-4(rha)), 4.88 (t, 1H, *J* 10.1 Hz, H-4(rha)), 4.85 (d, 1H, *J* 1.9 Hz, H-1(rha)), 4.79 (dd, 1H, *J* 10.1 Hz, H-6′), 4.76 (d, 1H, H-1(rha)), 4.67 (d, 1H, *J* 7.8 Hz, H-1(rha)), 4.51 (dd, 1H, *J* 5.5, 12.4 Hz, H-6′), 4.36–4.34 (m, H-5(rha)), 4.32–4.29 (m, H-16), 3.97 (t, 1H, *J* 9.2 Hz, H-4′), 3.86 (ddd, 1H, *J* 1.8, 5.0, 7.3 Hz, H-5′), 3.79 (t, 1H, *J* 9.2 Hz, H-2′), 3.72 (m, 1H, H-5(rha)), 3.58 (m, 1H, H-3), 3.52 (dd, 1H, *J* 5.5, 9.7 Hz, H-26), 3.45 (dd, 1H, *J* 6.4, 9.6 Hz, H-26), 3.30 (td, 1H, *J* 4.1, 7.8 Hz, H-22), 2.41–0.82 (m, 24H), 1.99, 1.95, 1.92, 1.89, 1.74 (s each, 3H each, OAc×6), 1.16 (d, 3H, *J* 6.4 Hz, CH_3(rha)), 1.05 (s, 9H), 0.99 (d, 3H, *J* 6.4 Hz, H-21), 0.96 (s, 3H, H-19), 0.93 (d, 3H, *J* 6.8 Hz, H-27), 0.79 (s, 3H, H-18), 0.68 (d, 3H, *J* 6.4 Hz, CH_3(rha)). ^{13}C NMR ($CDCl_3$): δ 170.0 (2C), 169.9, 169.7, 168.9, 165.8, 165.0, 140.0, 135.6, 134.1, 133.3, 133.0, 130.1, 129.9, 129.8, 129.5, 129.1 (2C), 128.4 (2C), 127.6, 122.1, 99.6, 99.0, 98.0, 90.4, 83.1, 79.5, 76.2, 76.0, 73.0, 71.0, 70.5,

70.0, 69.1, 68.8, 68.7, 68.5, 67.5, 66.5, 65.2, 62.8, 56.9, 50.2, 40.7, 39.4, 38.4, 37.9, 37.0, 36.8, 36.0, 32.2, 32.0, 31.5, 31.1, 30.1, 29.7, 26.9, 22.7, 20.8, 20.7, 20.6, 20.3, 19.3, 19.2, 19.1, 17.2, 16.9 (2C), 16.4, 14.1. ESIMS (m/z): 1591.722 [M+Na$^+$]; calcd 1591.721.

3.1.7. 26-Hydroxy-3β-*O*-[2,4-di-*O*-(2,3,4-tri-*O*-acetyl-α-L-rhamnopyranosyl)-3,6-di-*O*-benzoyl-β-D-glucopyranosyl]-25(*R*)-furost-5-en (10). A solution of the above crude compound **9** (1.44 g) in anhyd THF (10 mL) was treated with 1:1 TBAF–HOAc (1.0 M in THF, 10 mL). After stirring for 12 h at rt, the solution was diluted with EtOAc and washed with water. The organic layer was dried and concentrated. The residue was purified by column chromatography (4:5 EtOAc–petroleum ether to 1:1 EtOAc–petroleum ether) to afford **10** as a buff foam solid (0.87 g, 72% yield for two steps): R_f 0.27 (1:1 EtOAc–petroleum ether); mp 116–117 °C. $[\alpha]_D^{20}$ −44.2 (*c* 0.64, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 8.05 (m, 4H, ArH), 7.59–7.55 (m, 2H, ArH), 7.47–7.42 (m, 4H, ArH), 5.62 (t, 1H, *J* 9.1 Hz, H-3′), 5.35 (d, 1H, *J* 5.1 Hz, H-6), 5.16 (d, 1H, *J* 3.7 Hz, H-3(rha)), 5.15 (d, 1H, *J* 3.7 Hz, H-3(rha)), 5.12 (m, 1H, H-2(rha)), 4.98 (dd, 1H, *J* 1.9, 3.7 Hz, H-2(rha)), 4.91 (t, 1H, *J* 9.9 Hz, H-4(rha)), 4.88 (t, 1H, *J* 9.9 Hz, H-4(rha)), 4.85 (d, 1H, *J* 1.5 Hz, H-1(rha)), 4.80 (dd, 1H, *J* 1.8, 12.1 Hz, H-6′), 4.76 (d, 1H, H-1(rha)), 4.67 (d, 1H, *J* 7.7 Hz, H-1′), 4.51 (dd, 1H, *J* 5.5, 12.4 Hz, H-6′), 4.37–4.30 (m, 2H, H-5(rha), H-16), 3.97 (t, 1H, *J* 9.2 Hz, H-4′), 3.86 (ddd, 1H, *J* 2.2, 5.5, 9.5 Hz, H-5′), 3.80 (t, 1H, *J* 7.7 Hz, H-2′), 3.74–3.69 (m, 1H, H-5(rha)), 3.58 (m, 1H, H-3), 3.51 (dd, 1H, *J* 6.2, 10.6 Hz, H-26), 3.45 (dd, 1H, *J* 5.9, 10.6 Hz, H-26), 3.34 (td, 1H, *J* 4.4, 8.1 Hz, H-22), 2.67 (br s, 1H, 26-OH), 2.41–0.86 (m, 24H), 1.99, 1.99, 1.95, 1.92, 1.89, 1.74 (s each, 3H each, OAc×6), 1.16 (d, 3H, *J* 6.2 Hz, CH_3(rha)), 1.01 (d, 3H, *J* 7.0 Hz, H-21), 0.95 (s, 3H, H-19), 0.92 (d, 3H, *J* 6.5 Hz, H-27), 0.80 (s, 3H, H-18), 0.68 (d, 3H, *J* 6.2 Hz, CH_3(rha)). ^{13}C NMR ($CDCl_3$): δ 170.0, 169.9, 169.7, 168.9, 165.8, 165.0, 140.0, 133.3, 133.0, 130.1, 129.9, 129.8, 129.1, 128.4 (2C), 122.1, 99.5, 99.0, 98.0, 90.4, 83.2, 79.5, 76.2, 73.0, 71.0, 70.5, 70.0, 69.1, 68.8, 68.5, 68.1, 67.5, 66.5, 65.1, 62.8, 56.9, 52.6, 50.0, 40.7, 39.4, 38.4, 37.9, 37.0, 36.7, 35.7, 32.2, 32.0, 31.5, 30.4, 30.2, 29.7, 20.8, 20.7, 20.6, 20.3, 19.2, 18.9, 17.2, 16.9, 16.6, 16.5, 13.9. ESIMS (m/z): 1353.597 [M+Na$^+$]; calcd 1353.603.

3.1.8. 26-*O*-(2,3,4,6-Tetra-*O*-benzoyl-β-D-glucopyranosyl)-3β-*O*-[2,4-di-*O*-(2,3,4-tri-*O*-acetyl-α-L-rhamnopyranosyl)-3,6-di-*O*-benzoyl-β-D-glucopyranosyl]-(25*R*)-furost-5-en (11). To a mixture of **10** (100 mg, 0.075 mmol), **4** (100 mg, 0.135 mmol), and powdered 4 Å molecular sieves in dried CH_2Cl_2 (10 mL) at 0 °C was added TMSOTf (2.5 μL). After stirring for 0.5 h at 0 °C and then 1 h at rt, the reaction was quenched with Et_3N. The solid was then filtered off, and the filtrate was concentrated under vacuum to give a yellow oil that was purified by column chromatography (2:3 EtOAc–petroleum ether to 4:5 EtOAc–petroleum ether) to give **11** as a white solid (89 mg, 62%): R_f 0.37 (1:1 EtOAc–petroleum ether); mp 121.0–121.5 °C. $[\alpha]_D^{20}$ −30.1 (*c* 0.77, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 8.06–7.27 (m, 30H, ArH), 5.89 (t, 1H, *J* 9.8 Hz, H-3″), 5.68 (t, 1H, *J* 9.5 Hz, H-4″), 5.62 (t, 1H, *J* 9.2 Hz, H-3′), 5.54 (dd, 1H, *J* 8.0, 9.8 Hz, H-2″), 5.35 (d, 1H, *J* 5.1 Hz, H-6), 5.16 (d, 1H, *J* 3.3 Hz, H-3(rha)), 5.15 (d, 1H, *J* 3.7 Hz, H-3(rha)), 5.12 (m, 1H, H-2(rha)), 4.98 (dd, 1H, *J* 1.8, 3.7 Hz, H-2(rha)), 4.92 (t, 1H, *J* 9.9 Hz, H-4(rha)), 4.88 (t, 1H, *J* 9.9 Hz, H-4(rha)), 4.86 (d, 1H, *J* 1.8 Hz, H-1(rha)), 4.86–4.79 (m, 2H, H-6′, H-1″), 4.76 (d, 1H, H-1(rha)), 4.68 (d, 1H, *J* 7.7 Hz, H-1′), 4.62 (dd, 1H, *J* 3.3, 12.1 Hz, H-6″), 4.51 (m, 2H, H-6′, H-6″), 4.35 (m, 1H, H-5(rha)), 4.21 (m, 1H, H-16), 4.14 (m, 1H, H-5″), 3.97 (t, 1H, *J* 9.2 Hz, H-4′), 3.86 (ddd, 1H, *J* 1.9, 5.1, 7.3 Hz, H-5′), 3.80 (t, 1H, *J* 8.8 Hz, H-2′), 3.74–3.70 (m, 2H, H-5(rha), H-26), 3.57 (m, 1H, H-3), 3.36 (dd, 1H, *J* 6.2, 9.5 Hz, H-26), 3.05 (td, 1H, *J* 3.7, 8.4 Hz, H-22), 2.41–0.80 (m, 24H), 1.98, 1.95, 1.92, 1.89, 1.74 (s each, 3H each, OAc×6), 1.16 (d, 3H, *J* 6.2 Hz, CH_3(rha)), 0.95 (s, 3H, H-19), 0.87 (d, 3H, *J* 6.6 Hz, H-21), 0.78 (d, 3H, *J* 6.6 Hz, H-27), 0.74 (s, 3H, H-18), 0.68 (d, 3H, *J* 6.2 Hz, CH_3(rha)). ^{13}C NMR ($CDCl_3$): δ 170.0 (2C), 169.9, 169.6, 168.9, 166.1, 165.8, 165.2, 165.0 (2C), 140.0, 133.4, 133.3, 133.2, 133.1 (2C), 133.0, 130.0–128.2, 122.0, 101.4, 99.5, 99.0, 98.0, 90.1, 83.0, 79.5, 77.4, 76.2, 75.3, 72.9, 72.9, 72.0, 71.9, 71.0, 70.4, 70.0, 69.8, 69.1, 68.7, 68.5, 67.5, 66.4, 65.1, 63.2, 62.8, 56.9, 50.0, 40.6, 39.3, 38.4, 37.8, 36.9, 36.7, 33.4, 32.2, 32.0, 31.5, 30.7, 30.3, 29.6, 20.8, 20.7 (2C), 20.6, 20.3, 17.1, 16.8, 16.4, 16.3; ESIMS (m/z): 1931.761 [M+Na$^+$]; calcd 1931.760.

3.1.9. 26-*O*-β-D-Glucopyranosyl-3β-*O*-[2,4-di-*O*-(α-L-rhamnopyranosyl)-β-D-glucopyranosyl]-(25*R*)-furost-5-en (1). Compound **11** (89 mg) was dissolved in 1:1 CH_3OH–$CHCl_3$ (15 mL), and then NaOMe (100 mg) was added. After stirring at rt for 12 h, the solution was neutralized with ion-exchange resin (H^+), filtered, and concentrated. The residue was purified by column chromatography (60:20:1 $CHCl_3$–MeOH–H_2O) to afford **1** as a white solid (41 mg, 86%): R_f 0.25 (60:20:1 $CHCl_3$–MeOH–H_2O), mp 209–211 °C. $[\alpha]_D^{20}$ −67.3 (*c* 0.63, CH_3OH); ^{1}H NMR (CD_3OD): δ 5.38 (d, 1H, *J* 5.2 Hz, H-6), 5.19 (d, 1H, *J* 1.4 Hz, H-1(rha)), 4.83 (d, 1H, *J* 1.5 Hz, H-1(rha)), 4.49 (d, 1H, *J* 8.1 Hz, H-1(glc)), 4.31 (m, 1H, H-16), 4.22 (d, 1H, *J* 7.7, H-1(glc)), 4.12 (m, 1H), 3.92 (m, 2H), 3.85 (dd, 1H, *J* 1.9, 11.7 Hz), 3.82 (dd, 1H, *J* 1.4, 2.9 Hz), 3.78 (dd, 1H, *J* 2.2, 12.5 Hz), 3.72 (dd, 1H, *J* 6.6, 9.5 Hz), 3.67–3.56 (m, 6H), 3.51 (t, 1H, *J* 9.5 Hz), 3.41–3.22 (m, 9H), 3.17 (dd, 1H, *J* 7.7, 9.2 Hz), 2.45–0.95 (m, 24H), 1.25 (d, 3H, *J* 6.2 Hz, CH_3(rha)), 1.23 (d, 3H, *J* 6.2 Hz, CH_3(rha)), 1.04 (s, 3H, H-19), 1.01 (d, 3H, *J* 6.5 Hz, H-21), 0.93 (d, 3H, *J* 6.6 Hz, H-27), 0.83 (s,

3H, H-18). ^{13}C NMR (CD_3OD): δ 141.9, 122.6, 104.6, 103.0, 102.3, 100.4, 91.7, 84.6, 80.0, 79.3, 79.2, 78.1, 78.0, 77.9, 76.6, 76.1, 75.2, 73.9, 73.7, 72.5, 72.4, 72.2, 71.7, 70.7, 69.8, 66.5, 62.8, 61.9, 58.2, 51.7, 41.8, 40.6, 39.5, 39.1, 38.6, 38.0, 34.7, 33.2, 33.1, 32.9, 31.7, 31.4, 30.7, 21.8, 19.8, 19.2, 18.0, 17.9, 17.2, 17.0. ESIMS (m/z): 1055.539 [M+Na$^+$]; calcd 1055.540.

3.1.10. 26-*O*-α-L-Rhamnopyranosyl-3β-*O*-[2,4-di-*O*-(α-L-rhamnopyranosyl)-β-D-glucopyranosyl]-(25*R*)-furost-5-en (13). Compound **13** was synthesized from **10** by the same procedure as that used for compound **1**. Compound **13** was purified by column chromatography (2:1 $CHCl_3$–MeOH to 1:1 $CHCl_3$–MeOH) to give a white solid (18%): R_f 0.42 (1:2 $CHCl_3$–MeOH); mp 184–187 °C. $[\alpha]_D^{20}$ −69.6 (*c* 0.68, CH_3OH); ^{1}H NMR (CD_3OD): δ 5.37 (d, 1H, *J* 5.2 Hz, H-6), 5.19 (d, 1H, *J* 1.1 Hz, H-1(rha)), 4.83 (d, 1H, *J* 1.5 Hz, H-1(rha)), 4.76 (d, 1H, *J* 1.4 Hz, H-1(rha)), 4.49 (d, 1H, *J* 8.1 Hz, H-1(glc)), 4.31 (m, 1H, H-16), 4.13 (m, 1H), 3.96 (dd, 1H, *J* 1.8, 3.3 Hz), 3.93–3.32 (m, 19H), 3.25 (dd, 1H, *J* 5.9, 9.5 Hz), 2.44 (dd, 1H, *J* 10.6 Hz), 2.29 (t, 1H, *J* 10.6 Hz), 2.03–1.26 (m, 19H), 1.25–1.23 (m, 9H, CH_3×3(rha)), 1.18–1.06 (m, 2H), 1.04 (s, 3H, H-19), 1.01 (d, 3H, *J* 6.6 Hz, H-21), 0.97 (m, 1H), 0.94 (d, 3H, *J* 6.6 Hz, H-27), 0.83 (s, 3H, H-18). ^{13}C NMR (CD_3OD): δ 141.9, 122.6, 103.0, 102.3, 100.5, 100.4, 91.6, 84.6, 80.4, 80.0, 79.3, 79.2, 78.0, 76.6, 74.3, 73.9, 73.7, 72.5, 72.4, 72.3, 72.2, 72.0, 70.7, 70.2, 69.9, 69.8, 66.5, 61.9, 58.2, 51.7, 41.8, 40.6, 39.5, 39.1, 38.6, 38.0, 34.7, 33.2, 33.1, 32.9, 32.0, 31.6, 30.7, 21.8, 19.8, 19.3, 18.2, 19.0, 17.9, 17.5, 17.0.

3.1.11. 26-*O*-(4-*O*-β-D-Galactopyranosyl)-β-D-glucopyranosyl-3β-*O*-[2,4-di-*O*-(α-L-rhamnopyranosyl)-β-D-glucopyranosyl]-(25*R*)-furost-5-en (14). Compound **14** was synthesized from **10** by the same procedure as that used for compound **1**. Compound **14** was purified by column chromatography (2:1 $CHCl_3$–MeOH to 1:1 $CHCl_3$–MeOH) to give a white solid (62%): R_f 0.48 (1:1 $CHCl_3$–MeOH); mp 230–232 °C. $[\alpha]_D^{20}$ −44.7 (*c* 0.52, CH_3OH); ^{1}H NMR (CD_3OD): δ 5.37 (d, 1H, *J* 5.2 Hz, H-6), 5.19 (d, 1H, *J* 1.4 Hz, H-1(rha)), 4.82 (d, 1H, *J* 1.5 Hz, H-1(rha)), 4.49 (d, 1H, *J* 7.7 Hz, H-1(glc)), 4.35 (d, 1H, *J* 7.7 Hz, H-1(glc)), 4.31 (m, 1H, H-16), 4.26 (d, 1H, *J* 7.7 Hz, H-1(gal)), 3.94–3.31 (m, 29H), 3.24 (dd, 1H, *J* 7.7, 9.2 Hz), 2.44 (dd, 1H, *J* 2.6, 13.2 Hz), 2.29 (t, 1H, *J* 11.3 Hz), 2.03–0.95 (m, 22H), 1.25 (d, 3H, *J* 6.2 Hz, CH_3(rha)), 1.23 (d, 3H, *J* 6.2 Hz, CH_3(rha)), 1.04 (s, 3H, H-19), 1.01 (d, 3H, *J* 6.5 Hz, H-21), 0.93 (d, 3H, *J* 6.6 Hz, H-27), 0.83 (s, 3H, H-18). ^{13}C NMR (CD_3OD): δ 141.9, 122.6, 105.1, 104.5, 103.0, 102.3, 100.4, 91.6, 84.6, 80.7, 80.0, 79.3, 79.2, 78.0, 77.1, 76.6, 76.5, 76.4, 76.2, 74.8, 73.9, 73.7, 72.6 (2C), 72.5, 72.4, 72.2, 70.7, 70.3, 69.8, 66.5, 62.5, 61.9, 58.2, 51.7, 41.8, 40.6, 39.5, 39.1, 38.6, 38.0, 34.7, 33.2, 33.1, 32.9, 31.7, 31.4, 30.7, 21.8, 19.8, 19.2, 18.0, 17.9, 17.2, 17.0. ESIMS (m/z): 1217.590 [M+Na$^+$]; calcd 1217.593.

3.1.12. 3β-*O*-[2,4-Di-*O*-(α-L-rhamnopyranosyl)-β-D-glucopyranosyl]-26-hydroxy-(25*R*)-furost-5-en (15). Compound **15** was synthesized from **10** by the same procedure as that used for **1**. Compound **15** was purified by column chromatography (5:1 $CHCl_3$–MeOH to 1:1 $CHCl_3$–MeOH) to give a white solid (76%): R_f 0.32 (2:1 $CHCl_3$–MeOH); mp 211–213.5 °C. $[\alpha]_D^{20}$ −71.1 (*c* 0.63, CH_3OH); ^{1}H NMR (CD_3OD): δ 5.37 (d, 1H, *J* 5.2 Hz, H-6), 5.19 (d, 1H, *J* 1.4 Hz, H-1(rha)), 4.83 (d, 1H, *J* 1.5 Hz, H-1(rha)), 4.49 (d, 1H, *J* 8.1 Hz, H-1(glc)), 4.33–4.29 (m, 1H, H-16), 4.15–4.10 (m, 1H), 3.93–3.91 (m, 2H), 3.81 (dd, 1H, *J* 1.8, 3.3 Hz), 3.78 (dd, 1H, *J* 2.2, 12.5 Hz), 3.66–3.56 (m, 5H), 3.51 (t, 1H, *J* 9.5 Hz), 3.42–3.30 (m, 7H), 2.45–0.92 (m, 24H), 1.25 (d, 3H, *J* 6.2 Hz, CH_3(rha)), 1.23 (d, 3H, *J* 6.2 Hz, CH_3(rha)), 1.04 (s, 3H, H-19), 1.01 (d, 3H, *J* 6.5 Hz, H-21), 0.91 (d, 3H, *J* 6.6 Hz, H-27), 0.83 (s, 3H, H-18). ^{13}C NMR (CD_3OD): δ 142.0, 122.6, 103.0, 102.3, 100.4, 91.7, 84.6, 80.0, 79.3, 79.2, 78.0, 76.6, 73.9, 73.7, 72.5, 72.4, 72.2, 70.7, 69.8, 68.3, 66.5, 61.9, 58.2, 51.7, 41.8, 40.6, 39.5, 39.1, 38.6, 38.0, 37.0, 33.2, 33.1, 32.9, 31.9, 31.2, 30.7, 21.8, 19.8, 19.2, 18.0, 17.9, 17.0. ESIMS (m/z): 893.490 [M+Na$^+$]; calcd 893.487.

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