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Synthesis of the Shark Repellent Pavoninin-4

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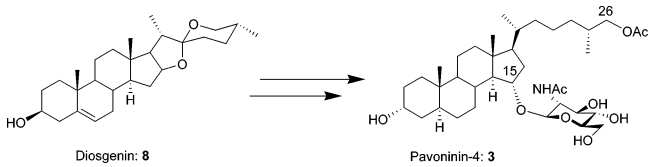

The first synthesis of the shark repellent pavoninin-4, **3**, was achieved in 12 steps with 21% overall yield from diosgenin, **8**. Key reactions involve an efficient synthesis of the C-15α hydroxyl steroid from a C-16*β* hydroxyl steroid by an unexpected 1,2-transposition strategy, a stereospecific glycosylation of a hindered C-15α alcohol using glycosyl fluoride as a glycosyl donor and a highly chemoselective acetylation of the C-26 primary alcohol by catalytic transesterification.

Introduction

It is known that fish belonging to the species *Pardachirus pavoninus* (Soleidae) excrete a mixture of six steroidal *N*-acetylglucosaminides, pavoninins-1−6, **1**−**4** (Figure 1).[1] These steroidal *N*-acetylglucosaminides have shark-repelling properties.[1] It is believed that the pavoninins are potent cell disrupters, which should have important pharmacological properties. The synthesis of pavoninin-1, **1a**,[2] and the aglycones of pavoninin-1, **1a**, and -2, **1b**, have been reported.[3] Recently, we reported the synthesis of the aglycone of 26-*O*-deacetyl pavoninin-5, **2b**.[4] The isolation and synthesis of shark-repelling saponins have recently been reviewed.[5] In this article, we report the first synthesis of pavoninin-4 (**3**), a saponin with the monosaccharide *N*-acetylglucosamine attached at the C-15α position of the steroid.

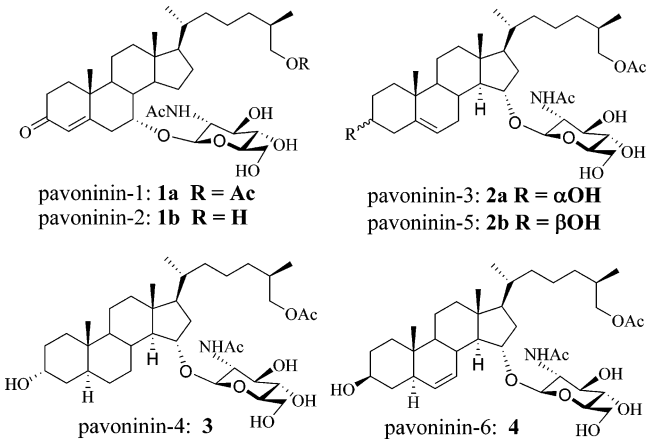

FIGURE 1. Pavoninins 1−6 (**1**−**4**).

Results and Discussion

Retrosynthetic analysis for the synthesis of pavoninin-4 (**3**) is given below, starting from diosgenin, **8** (Scheme 1). The *N*-acetylglucosamine **6** may be added to a C-15α hydroxyl steroid, **5**, to yield pavoninin-4, **3**. To plan for selective introducing of the C-26 acetate, the sugar alcohols were protected with benzyl groups that can be reductively eliminated at the end of the synthesis. The C-15α hydroxyl steroid **5** was prepared from a C-16*β* hydroxyl steroid **7** by a 1,2-transposition strategy involving an unexpected stereospecific reduction of a conjugated enone. The intermediate **7** was prepared from the commercially available diosgenin, **8**.

The synthesis commenced with a Mitsunobu reaction[6] on (25*R*)-5α-cholestane-3*β*,16*β*,26-triol (**9**), which was available from the naturally abundant steroid source diosgenin **8** in two steps.[7] The reaction afforded the 3α,26-dibenzoate **10** in 85% yield and achieved several

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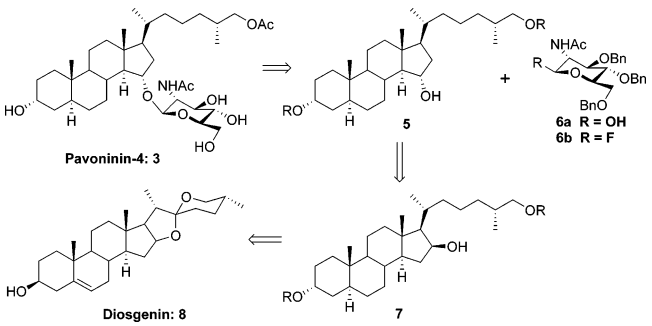
SCHEME 1. Retrosynthetic Analysis of Pavoninin-4 (3) from Diosgenin (8)

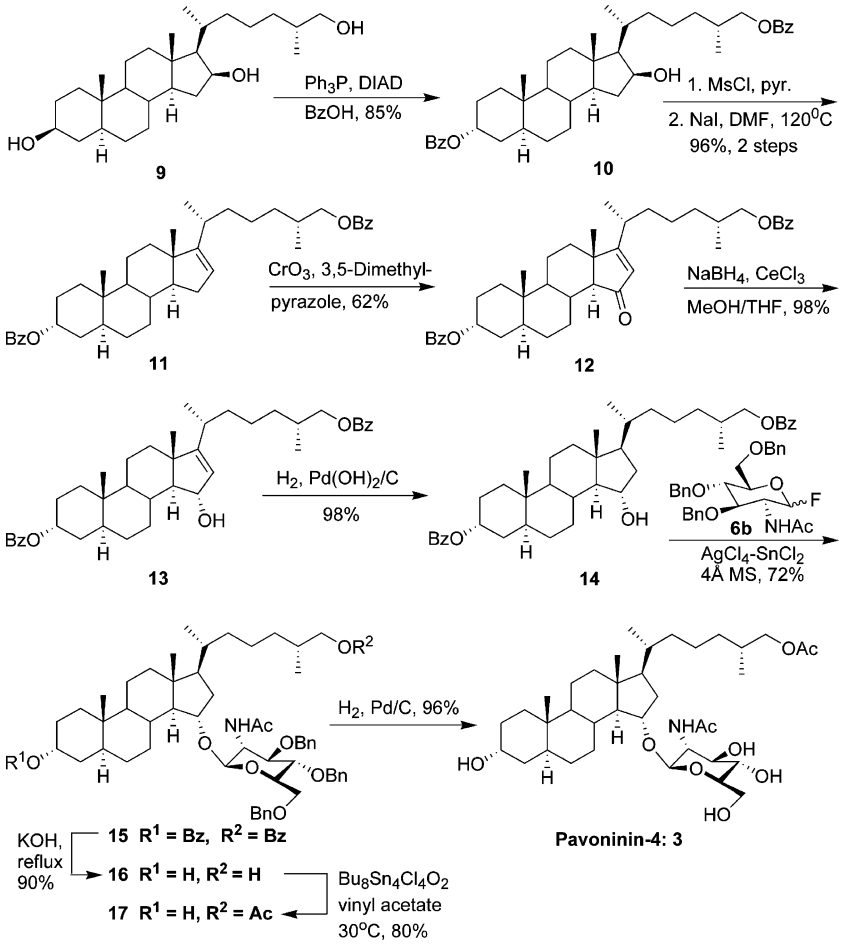


transformations. The triol **9** C-3 and C-26 hydroxyl groups were chemoselectively protected, and at the same time, the C-3 hydroxyl stereochemistry was inverted from β to α, all in one step. To transpose the C-16β hydroxyl in **10** to the 15α position, we have reported a successful six-step method in our synthesis of the aglycone of 26-*O*-deacetyl pavoninin-5.[4] The C-16 alcohol was oxidized to the ketone, converted to its silyl ether, and epoxidized to the 15α-hydroxy-16-ketone. Reduction of the ketone and chemoselective deoxygenation of the C-16 alcohols using the Barton deoxygenation reaction afforded the 15α alcohol.[4]

Recently, we developed a very efficient four-step method for this transposition, via allylic oxidation and subsequent stereospecific reduction, in our synthesis of (25*R*)-5α-cholesta-3β,15α,26-triol.[7] Regiospecific dehydration of the hindered C-16β hydroxyl via the bis-protected 16-mesylate of **10**, by Kim's method[8] using NaI in DMF, yielded the disubstituted C-16 olefin, **11**, in 96% yield. Hydroxylation at C-15α was efficiently introduced by allylic oxidation at C-15 using chromium trioxide and 3,5-dimethylpyrazole to yield the 16-en-15-one, **12**. Stereospecific Luche[9] reduction proceeded quantitatively from the unexpected β face to yield the 15α allylic alcohol, **13**. This result may be explained using molecular modeling. When C-16 and C-17 are sp^2 hybridized, C-22 of the cholesterol side chain can move down such that the side chain can swing under the steroid skeleton and protect the C-15 from α attack. Subsequent hydrogenation of **13** afforded the saturated alcohol **14**. The α-configuration of the C-15 hydroxyl group was proven by comparison of **14** with its 3β epimer (25*R*)-5α-cholesta-3β,15α,26-triol, whose structure had been determined by X-ray analysis.[7] The chemical shift for the 15β hydrogen in **14** is a doublet of triplets (J = 9.0, 3.2 Hz) at 3.88 ppm, and that for the 3β epimer was a doublet of triplets (J = 9.1, 3.0 Hz) at 3.91 ppm.[7] Thus, the intermediate target molecule pavoninin-4 aglycone **14** was successfully achieved through a six-step synthesis in 48.5% overall yield from (25*R*)-5α-cholestane-3β,16β,26-triol, **9**, (Scheme 2).

With C-15α hydroxyl intermediate **14** in hand, we turned our attention to attaching the sugar onto the steroid. A literature survey showed that only a few synthetic efforts have been devoted to the *N*-acetylami-

SCHEME 2. Synthesis of the Shark Repellent Pavoninin-4 (3)



noglycosylation reaction on a steroid. The synthesis of 15α-hydroxyestrogen 15-*N*-acetylglucosaminides, by the Koenigs−Knorr reaction employing cadmium carbonate as a catalyst, afforded the products in about 30% yield when the acetochloroglucosamine was used in large excess.[10] Nishizawa reported that thermal glycosylation of cholesterol with 2-deoxy-2-acetoamino-3,4,6-tri-*O*-acetylglucopyranosyl chloride at relatively lower temperatures gave rise to β-glycosides selectively, whereas higher temperatures favored the α-glycoside.[11] Originally, we planned to use the commercially available glycosyl donor, *N*-acetylglucosamine chloride, to attach on our steroids. Unfortunately, there was no reaction when we tried to attach 2-deoxy-2-acetoamino-3,4,6-tri-*O*-acetylglucopyranosyl chloride on the hindered 16β hydroxyl steroid **10**, even though a model study using 5-androsten-3β-ol-17-one (DHEA) worked well. Kahne reported a new method for rapid glycosylation of unreactive substrates using glycosyl sulfoxides as a glycosyl donor,[12] and Tachibana used this methodology to attach a 2-azido-2-deoxy-D-glucopyranose to the C-7 hydroxyl of a steroid in the total synthesis of pavoninin-1, **1a**.[2] However, the synthesis of the glycosyl donor, 2-azido-3,4,6-tri-*O*-benzyl-1,2-dideoxy-1-phenylsulfinyl-D-glucopyranose, would take eight steps from a commercially available precursor sugar and requires more steps to convert the azido group into the *N*-acetyl group in a later stage of the synthesis of pavoninin-1. It was necessary to develop another method to attach *N*-acetylglycosylamine to the very hindered C-15 hydroxyl position of a steroid. Recently, Mukaiyama reported that glycosyl fluorides are very good glycosyl donors.[13a] We attempted to convert the glycosyl chloride directly to a glycosyl fluoride using silver fluoride in dry acetonitrile,[14] but the yield of 2-acetamido-2-deoxy-β-D-glucopyranosyl fluoride obtained was not as high as reported. Also, the later deacetylation of the glycosyl fluoride to replace the acetate protecting groups with benzyls was difficult to achieve in high yield. Another commercially available sugar source, 2-acetamido-2-deoxy-D-glucose, was readily available and was converted in four steps to 2-acetamido-3,4,6-tri-benzyl-2-deoxy-D-glucopyranose, **6a**, by a known method.[15] Reaction of the 2-acetoamido-2-deoxy-3,4,6-tri-benzyl-D-glucopyranose **6a** with DAST afforded the fluoride **6b**.[16]

Through the use of the fluoride **6b**, glycosylation of the C-15α hydroxyl intermediate **14**, with $AgClO_4-SnCl_2$ as an activator,[13b] proceeded very successfully to yield the saponin **15** in 72% yield, plus 15% of recovered starting material. Exclusive formation of the β-glycoside can be explained by the intramolecular cyclization of the neighboring C-2α acetamide function at the C-1α position, directing the C-15 alcohol to attack β via an S_N2 reaction to yield the β-glycoside **15**. Hydrolysis of C-3 and C-26 benzoyl protecting groups using potassium hydroxide in methanol gave the expected C-3 and C-26 diols **16**. To selectively introduce the C-26 acetate, we tried Stork's condition using acetic anhydride and pyridine[17] and Yamada's condition using 3-acetyl-1,3-thiazolidine-2-thione and sodium hydride,[18] but in both conditions, the obtained yields of the C-26 acetate **17** were poor. A high yield of **17** was obtained by Otera's transesterification using vinyl acetate under distannoxane catalysis.[19] Deprotection of the benzyl ethers using catalytic hydrogenation afforded pavoninin-4 (**3**). The spectroscopic data for the synthetic pavoninin-4 were identical with those reported for the natural product.[1b]

In summary, we report the first synthesis of pavoninin-4 in 12 steps in 21% overall yield from commercially available diosgenin. The Mitsunobo reaction was found to be a good method for highly chemoselective protection of C-3 and C-26 hydroxyl groups of the 3β,-16β,26-triol and for simultaneously epimerizing the stereochemistry of the C-3 hydroxyl from β to α. The 1,2-transposition strategy involving an unexpected stereospecific reduction of a C-15,16 conjugated enone has proven to be an efficient method for synthesis of the C-15α hydroxyl steroid from a C-16β hydroxyl steroid. A short method for stereospecific attachment of the *N*-acetylglucosamine monosaccharide to a hindered alcohol was developed by using 2-acetamido-3,4,6-tribenzyl-2-deoxy-D-glucopyranosyl fluoride as a glycosyl donor. An efficient method for the chemoselective acetylation of the C-26 primary alcohol of the steroid in the presence of *N*-acetylglucosamine was also reported.

Experimental Section

2-Acetamido-3,4,6-tribenzyl-2-deoxy-D-glucopyranosyl Fluoride (6b). 2-Acetamido-3,4,6-tribenzyl-2-deoxy-D-glucopyranose **6a**:[15] mp 212−214 °C; ^{1}H NMR δ 2.06 (s, 3H), 3.43−3.44 (m, 1H), 3.73−3.79 (m, 2H), 3.84−3.85 (m, 2H), 3.98 (m, 1H), 4.60−4.72 (m, 4H), 4.84−4.99 (m, 2H), 5.17−5.18 (d, J = 3.5 Hz, 1H), 7.30−7.47 (m, 15H); ^{13}C NMR δ 23.1, 55.6, 70.5, 72.0, 74.8, 76.3, 76.5, 80.5, 82.2, 93.3, 129.0, 129.1, 129.4, 129.6, 129.75, 129.82, 139.9, 140.1, 140.5, 173.7; HRMS calcd for $C_{29}H_{33}NO_6$ ($M + Na^+$) 514.2206, found 514.2215. To the alcohol **6a** (1 g, 2.0 mmol) in a stirred solution of THF (50 mL) at −30 °C under argon gas was added rapidly 0.31 mL (2.4 mmol, 1.2 equiv) of DAST. The cooling bath was removed immediately. After 30 min at room temperature, thin-layer chromatography (TLC) (3:2 toluene/ethyl acetate) indicated complete reaction. The reaction mixture was cooled to −30 °C, and methanol (0.3 mL) was added. After evaporation of the solvent, a normal aqueous workup in chloroform yielded the crude mixture of fluorides, which were purified by short-path chromatography (3:2 toluene/EtOAc) and subsequent recrystallization with EtOAc/petroleum ether (1:1). The fluoride **6b** (0.82 g, 82%) was obtained as colorless needles: mp 186−187 °C; ^{1}H NMR δ 1.83 (s, 3H), 3.67−3.70 (m, 1H), 3.71−3.73 (m,

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1H), 3.78−3.82 (m, 1H), 3.84−3.86 (m, 1H), 3.94−3.98 (m, 1H), 4.21−4.28 (m, 1H), 4.54−4.67 (m, 4H), 4.85−4.92 (m, 2H), 5.08−5.10 (d, J = 8.6 Hz, 1H), 5.63 (dd, J_{H1F} = 53.6 Hz, J_{H1H2} = 2.4 Hz, 1H), 7.22−7.42 (m, 15H); ^{13}C NMR δ 23.6, 53.0, 68.2, 73.9, 74.8, 75.2, 75.6, 77.1, 78.0, 78.9, 106.2, 108.4, 128.2, 128.3, 128.4, 128.5, 128.6, 128.9, 129.1, 138.1, 138.5, 170.5; HRMS calcd for $C_{29}H_{32}FNO_5$ (M + Na^+) 516.2162, found 516.2150.

(25*R*)-5α-Cholestane-3α,16*β*,26-triol 3,26-Dibenzoate (10). To a solution of triol **9**[7] (1.0 g, 2.4 mmol) in 40 mL of THF at 25 °C was added triphenylphosphine (2.5 g, 9.5 mmol) and benzoic acid (1.2 g, 9.78 mmol) followed by the dropwise addition of DIAD (1.5 mL, 7.2 mmol). The reaction was stirred for 2 h. Then, 20 mL of saturated $NaHCO_3$ solution was added, and the mixture was extracted with EtOAc (30 mL × 3). The organic layers were washed with saturated $NaHCO_3$, brine, and water and dried with anhydrous Na_2SO_4. Concentration of the solvent and purification of the residues by flash chromatography (silica gel, 20% ethyl acetate/hexanes) afforded **10** as colorless oil (1.28 g, 85% yield): IR (KBr) 3546, 1716 cm^{-1}; ^{1}H NMR δ 0.78 (s, 3H), 0.80 (s, 3H), 0.90−0.91 (d, J = 6.6 Hz, 3H), 0.94−0.95 (d, J = 6.8 Hz, 3H), 3.99 (m, 1H), 4.15−4.28 (m, 2H), 5.21(s, 1H), 7.35−8.00 (m, 10H); ^{13}C NMR δ 11.8, 13.7, 17.5, 18.6, 20.9, 21.7, 24.1, 26.7, 28.7, 30.2, 32.3, 33.1, 33.4, 33.6, 34.2, 35.5, 36.3, 36.4, 37.1, 40.5, 40.9, 42.9, 54.7, 54.8, 62.0, 70.32, 71.15, 72.81, 128.73, 129.95, 130.95, 131.62, 132.41, 133.09, 133.23, 166.30, 167.1; HRMS calcd for $C_{41}H_{56}O_5$ (M + Na^+) 651.4025, found 651.4011.

(25*R*)-5α-Cholest-16-en-3α,26-diol 3,26-Dibenzoate (11). A solution of methanesulfonyl chloride (0.2 mL, 2.57 mmol) in dry pyridine (5 mL) was added to a solution of **10** (500 mg, 0.80 mmol) in dry pyridine (10 mL) at 0 °C. The mixture was kept at 0 °C overnight. The red solution was poured into ice water, and the resulting mixture was extracted with ether. The ether extract was washed successively with 2 N cold HCl, brine, saturated $NaHCO_3$, and water, then dried and concentrated to give (25*R*)-3α,26-dibenzoyloxy-5α-cholest-16*β*-ol 16-mesylate. The resulting 16-mesylate was heated with NaI (500 mg, 3.34 mmol) in DMF (20 mL) at 120 °C for 2 h. The mixture was diluted with H_2O and extracted with EtOAc. The organic layers were washed with saturated $NaHCO_3$ and brine, then dried and concentrated to give a yellow colored oil, which was further purified by chromatography (silica gel, hexanes/ethyl acetate 10:1) to give **11** (466 mg, 96% yield) as colorless oil: IR (KBr) 1721, 1603 cm^{-1}; ^{1}H NMR δ 0.67 (s, 3H), 0.80 (s, 3H), 0.91−0.92 (d, J = 7.2 Hz, 3H), 0.93−0.95 (d, J = 6.8 Hz, 3H), 4.01−4.16 (m, 2H), 5.20 (s, 1H), 5.22 (s, 1H), 7.35−8.00 (m, 10H); ^{13}C NMR δ 11.8, 16.8, 17.5, 21.2, 25.2, 26.8, 28.8, 31.4, 32.3, 32.6, 33.1, 33.5, 34.1, 34.6, 35.6, 37.1, 41.1, 47.6, 55.5, 57.8, 70.3, 71.1, 121.0, 128.7, 130.0, 131.0, 131.6, 133.1, 133.2, 140.1, 161.2, 166.3, 167.1; HRMS calcd for $C_{41}H_{54}O_4$ (M − H^+) 609.3944, found 609.3934.

(25*R*)-3α,26-Dihydroxy-5α-cholest-16-en-15-one 3,26-Dibenzoate (12). 3,5-Dimethylpyrazole (0.379 g, 3.95 mmol) was added to a suspension of chromium trioxide (0.395 g, 3.95 mmol) in dry CH_2Cl_2 (5 mL) at −20 °C under argon. The resulting mixture was stirred at −20 °C for 0.5 h. A solution of **11** (100 mg, 0.164 mmol) in dry CH_2Cl_2 (2 mL) was added to the obtained dark red solution in one portion, and the resulting mixture was stirred at −20 °C for 5 h. Then, 5 N NaOH solution (2 mL) was added, and the mixture was stirred at 0 °C for 1 h. Extraction with CH_2Cl_2 (3 × 10 mL) and the combined extracts were washed with 1 N HCl solution, dried (Na_2SO_4), filtered, and concentrated in a vacuum. The residue was flash chromatographed (silica gel, 20% ethyl acetate/hexanes) to give **12** as colorless oil (62 mg, 60% yield): IR (KBr) 1714 cm^{-1}; ^{1}H NMR δ 0.77 (s, 3H), 0.93 (s, 3H), 0.93−0.95 (d, J = 7.2 Hz, 3H), 1.02−1.03 (d, J = 6.3 Hz, 3H), 4.02−4.13 (m, 2H), 5.22 (s, 1H), 5.56 (s, 1H), 7.36−7.98 (m, 10H); ^{13}C NMR δ 11.9, 17.4, 21.8, 24.1, 25.3, 26.6, 28.3, 32.8, 32.9, 33.2, 33.3, 33.4, 33.5, 33.9, 36.6, 36.7, 41.1, 47.5, 55.4, 64.3, 70.1, 124.8, 128.8, 129.9, 130.9, 131.5, 133.2, 133.3, 166.3, 167.1, 188.9, 208.4; HRMS calcd for $C_{41}H_{52}O_5$ (M + Na^+) 647.3712, found 647.3714.

(25*R*)-5α-Cholestane-16-en-3α,15α,26-triol 3,26-Dibenzoate (13). To a solution of **12** (100 mg, 0.16 mmol) in THF/MeOH (2:1) (2 mL) was added cerium trichloride (0.07 g, 0.192 mmol) and $NaBH_4$ (0.008 g, 0.21 mmol). The reaction mixture was stirred at room temperature for 2 h and then quenched with water (1 mL), concentrated in vacuo to remove the excess THF and MeOH, and extracted three times with CH_2Cl_2. The organic layer was washed with 0.1 N HCl, dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was flash chromatographed (silica gel, 10% ethyl acetate/hexanes) to give **13** as a colorless oil (98 mg, 98% yield): IR (KBr) 1721 cm^{-1}; ^{1}H NMR δ 0.75 (s, 3H), 0.83 (s, 3H), 0.94 (d, J = 3.3 Hz, 3H), 0.95 (d, J = 3.2 Hz, 3H), 4.02−4.15 (m, 2H), 4.44 (m, 1H), 5.19 (s, 1H), 5.22 (s, 1H), 7.35−7.99 (m, 10H); ^{13}C NMR δ 11.9, 17.5, 20.0, 21.1, 22.2, 25.2, 26.7, 28.7, 32.3, 33.0, 33.1, 33.4, 34.0, 34.7, 35.5, 36.6, 37.0, 41.0, 48.2, 55.3, 66.2, 70.2, 71.0, 78.1, 126.2, 128.8, 129.9, 131.6, 133.1, 133.2, 162.0, 166.3, 167.1; HRMS calcd for $C_{41}H_{54}O_5$ (M + Na^+) 649.3869, found 649.3869.

(25*R*)-5α-Cholestane-3α,15α,26-triol 3,26-Dibenzoate (14). To 20 wt % $Pd(OH)_2$ on carbon (5 mg) was added several drops of ethyl acetate to wet the catalyst. Subsequently, a solution of **13** (30 mg, 0.048 mmol) in ethyl acetate (1 mL) was added. The flask was evacuated (40 Torr) and flushed three times with hydrogen. The reaction mixture was then stirred vigorously under hydrogen for 3 h. It was then filtered through a pad of Celite, and the filtrate was concentrated. The residue was purified by flash chromatography (silica gel, hexanes/EtOAc, 10:1) to afford **14** as colorless oil (30 mg, 98% yield): IR (KBr) 3421, 1717 cm^{-1}; ^{1}H NMR δ 0.68 (s, 3H), 0.86 (s, 3H), 0.88 (d, J = 6.1 Hz, 3H), 0.99 (d, J = 6.7 Hz, 3H), 3.88 (dt, J = 9.0, 3.2 Hz, 1H), 4.16−4.20 (m, 2H), 5.26 (s, 1H), 7.41−8.05 (m, 10H); ^{13}C NMR δ 11.9, 13.8, 17.4, 18.9, 21.1, 23.6, 26.7, 28.6, 32.7, 33.1, 33.4, 33.6, 34.3, 35.4, 35.6, 36.3, 40.5, 40.7, 41.0, 44.5, 54.2, 54.7, 64.3, 70.3, 71.0, 74.2, 128.8, 130.0, 131.0, 131.6, 133.1, 133.2, 166.3, 167.1; HRMS calcd for $C_{41}H_{56}O_5$ (M − H^+) 627.4050, found 627.4026.

(25*R*)-15α-(2-Acetylamino-3,4,6-tri-*O*-benzyl-2-deoxy-*β*-D-glucopyranosyloxy)-3α-benzoyloxy-5α-cholestan-26-yl Benzoate (15). To a suspension of $AgClO_4$ (12 mg, 0.06 mmol), $SnCl_2$ (11 mg, 0.06 mmol), and crushed 4-Å molecular sieves (150 mg, dried) in anhydrous CH_2Cl_2 (3.5 mL) under argon at −15 °C was added C-15 alcohol **14** (50 mg, 0.08 mmol) in CH_2Cl_2 (1 mL). A solution of the 2-acetylamido-3,4,6-tri-*O*-benzyl-2-deoxy-D-glucopyranosyl fluoride **6b** (50 mg, 0.10 mmol) in CH_2Cl_2 (1 mL) was added, and stirring was continued at 0 °C for 16 h. The reaction mixture was diluted with CH_2Cl_2 (30 mL) and filtered through Celite. The filtrate was washed with saturated aqueous $NaHCO_3$ solution (5 mL) and brine (5 mL) and dried (anhydrous Na_2SO_4). Evaporation of the solvent and purification by flash chromatography (silica gel, 20% ethyl acetate/hexanes) afforded **15** (65 mg, 72% yield) as a solid (about 10 mg unreacted **14** was recovered): mp 73−75 °C; IR (KBr) 3299, 1717, 1654 cm^{-1}; ^{1}H NMR δ 0.59 (s, 3H), 0.75 (s, 3H), 0.81 (d, J = 2.6 Hz, 3H), 0.85−0.86 (d, J = 6.7 Hz, 3H), 1.70 (s, 3H), 3.53 (m, 1H), 3.64−3.66 (m, 4H), 3.94−3.96 (m, 2H), 4.04 (m, 1H), 4.44−4.77 (m, 6H), 5.20−5.22 (m, 1H), 5.30 (m, 1H), 7.15−7.23 (m, 15H), 7.35−7.98 (m, 10H); ^{13}C NMR δ 11.9, 13.7, 17.3, 18.8, 21.1, 24.0, 26.7, 29.2, 32.6, 33.1, 33.5, 33.6, 34.2, 35.5, 35.9, 36.3, 39.5, 40.4, 40.6, 43.1, 54.2, 54.5, 58.4, 61.0, 69.7, 70.4, 71.0, 74.3, 75.1, 75.2, 77.1, 79.4, 81.0, 84.2, 101.5, 127.9, 128.0, 128.1, 128.3, 128.76, 128.84, 129.9, 130.9, 131.5, 133.2, 138.5, 138.8, 139.0, 166.4, 167.1, 170.7; LRMS calcd for $C_{70}H_{87}NO_{10}$ (M + Na^+) 1125, found 1125.1.

(25*R*)-3α,26-Dihydroxy-5α-cholestan-15α-yl-2-(acetylamino)-3,4,6-tri-*O*-benzyl-2-deoxy-*β*-D-glucopyranoside (16). To a solution of **15** (100 mg, 0.09 mmol) in 1:1 MeOH/CH_2Cl_2 (20 mL) was added KOH−MeOH (1 M, 10 mL). The solution, after refluxing for 12 h, was cooled to room temper-

ature, evaporated, and neutralized with 2 M HCl solution. The mixture was extracted with CH_2Cl_2 (10 mL × 3) and dried (anhydrous Na_2SO_4). Evaporation of the solvent and purification by flash chromatography (silica gel, 50% ethyl acetate/hexanes) afforded **16** (72 mg, 90% yield) as a white solid: mp 137−139 °C; IR (KBr) 3290, 1654 cm^{-1}; ^1H NMR δ 0.66 (s, 3H), 0.77 (s, 3H), 0.84−0.85 (d, J = 4.7 Hz, 3H), 0.90−0.92 (d, J = 5.7 Hz, 3H), 1.81 (s, 3H), 3.23−3.77 (m, 10H), 4.03 (s, 1H), 4.20−4.25 (m, 1H), 4.54−4.85 (m, 8H), 5.52−5.54 (d, J = 7.6 Hz, 1H), 7.22−7.34 (m, 15H); ^{13}C NMR δ 11.6, 13.7, 16.9, 18.8, 21.0, 23.9, 24.1, 29.4, 32.7, 33.9, 35.5, 35.8, 36.2, 36.5, 39.3, 39.6, 40.4, 43.1, 54.0, 54.4, 58.8, 61.0, 66.9, 68.8, 69.8, 74.2, 75.1, 75.2, 75.3, 79.5, 80.8, 84.0, 101.1, 128.0, 128.1, 128.3, 128.8, 138.5, 138.9, 139.0, 170.7; HRMS calcd for $C_{56}H_{79}NO_8$ ($M + Na^+$) 916.5703, found 916.5720.

(25*R*)-15α-(2-Acetylamino-3,4,6-tri-*O*-benzyl-2-deoxy-β-D-glucopyranosyloxy)-3α-benzoyloxy-5α-cholestan-26-yl Acetate (17). To a solution of **16** (50 mg, 0.06 mmol) in 2 mL of CH_2Cl_2 and 5 mL of vinyl acetate was added 1,3-dichlorodistannoxane (1.2 mg, 2.2 × 10^{-3} mmol). The mixture was stirred at room temperature overnight (12 h). After evaporation, the crude mixture was chromatographed on a silica gel column (50% ethyl acetate/hexanes) to afford **17** (42 mg, 80% yield) as colorless oil: IR (KBr) 3288, 1737, 1654 cm^{-1}; ^1H NMR δ 0.58 (s, 3H), 0.69 (s, 3H), 0.75−0.76 (d, J = 6.7 Hz, 3H), 0.79−0.80 (d, J = 5.6 Hz, 3H), 1.74 (s, 3H), 1.94 (s, 3H), 3.15 (m, 1H), 4.16−4.20 (m, 2H), 3.14 (m, 1H), 3.44−3.79 (m, 7H), 3.96 (s, 1H), 4.14 (m, 1H), 4.46−4.61 (m, 4H), 4.71−4.78 (m, 3H), 5.40 (d, J = 7.6 Hz, 1H), 7.15−7.25 (m, 15H); ^{13}C NMR δ 11.6, 13.7, 17.1, 18.8, 21.0, 21.4, 23.9, 24.1, 29.4, 32.7, 32.9, 34.2, 35.5, 35.8, 36.3, 36.5, 39.3, 39.6, 40.4, 43.1, 54.0, 54.4, 58.8, 61.0, 66.9, 69.7, 70.0, 74.3, 75.1, 75.3, 79.5, 80.8, 84.0, 101.2, 127.9, 128.2, 128.3, 128.77, 128.83, 138.5, 138.8, 139.0, 170.7, 171.7; HRMS calcd for $C_{58}H_{81}NO_9$ ($M + Na^+$) 958.5809, found 958.5822.

Pavoninin-4 (3). A solution of acetate **17** (20 mg, 0.02 mmol) in MeOH (5 mL) was stirred with 10 wt % Pd/C (8 mg) at room temperature under a hydrogen atmosphere overnight. The catalyst was removed by filtration, and the solvent was removed by evaporation to afford pavoninin-4 (**3**) (13.6 mg, 96% yield) as a white solid, without further purification: $[\alpha]^{20}_D$ +28° (*c* 0.4, EtOH); mp 134−136 °C; ^1H NMR (CD_3OD) δ 0.60 (s, 3H), 0.72 (s, 3H), 0.81 (d, J = 5.6 Hz, 3H), 0.84 (d, J = 4.4 Hz, 3H), 1.68 (s, 3H), 1.94 (s, 3H), 2.08 (m, 1H), 3.13 (m, 1H), 3.20 (m, 1H), 3.34 (m, 1H), 3.47 (m, 1H), 3.57−3.61 (m, 2H), 3.73−3.78 (m, 2H), 3.84−3.86 (m, 2H), 4.28 (d, J = 8.3 Hz, 1H); ^{13}C NMR (CD_3OD) δ 12.2, 14.1, 17.5, 19.4, 21.2, 22.2, 23.7, 24.7, 30.0, 30.6, 33.9, 34.2, 34.3, 35.1, 34.0, 37.2, 37.4, 37.6, 40.4, 40.5, 41.9, 44.3, 55.6, 56.2, 58.2, 62.7, 63.4, 67.6, 71.1, 72.6, 76.5, 78.0, 85.7, 104.3, 173.6, 173.8; HRMS calcd for $C_{37}H_{63}NO_9$ ($M + Na^+$) 688.4401, found 688.4394.

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Supporting Information Available: ^1H and ^{13}C NMR spectra for all synthesized compounds, **6a** and **b**, **10**−**17**, and pavoninin-4. This material is available free of charge via the Internet at http://pubs.acs.org.

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