JOC Article

Total Synthesis of Methyl Protodioscin: A Potent Agent with Antitumor Activity

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Methyl protodioscin (**1**), otherwise known as 3-*O*-[α-L-rhamnopyranosyl-(1→2)-{α-L-rhamnopyranosyl-(1→4)}-*β*-D-glucopyranosyl]-26-*O*-[*β*-D-glucopyranosyl]-22-methoxy-25(*R*)-furost-5-ene-3*β*,26-diol, has been synthesized for the first time from diosgenin through nine steps in an overall yield of 7.8%.

Introduction

Methyl protodioscin, **1**, a member of the furostan saponin family with a broad range of biological activities,[1] is a furostanol bisglycoside with the chemical name of 3-*O*-[α-L-rhamnopyranosyl-(1→2)-{α-L-rhamnopyranosyl-(1→4)}-*β*-D-glucopyranosyl]-26-*O*-[*β*-D-glucopyranosyl]-22-methoxy-25(*R*)-furost-5-ene-3*β*,26-diol. This molecule was first isolated and identified by Kawasaki and co-workers[2] in 1974 from fresh rhizomes of *Dioscorea gracillima MiQ*.

In continuing efforts to identify active components from the traditional Chinese herbal medicine,[3] we have isolated 14 steroidal saponins with anticancer activities from *Dioscoreaceae* by bioactivity-guided isolation for testing in the panel of 60 human cancer cell lines at NCI.[4] Among the tested compounds, methyl protodioscin (**1**) showed the most potent activity in vitro. In order to get a sufficient amount of the compound for further biological investigations, we therefore initiated a program to synthesize this target molecule.

Although many furostan saponin based natural products have been known for a couple of decades,[5] methods for their syntheses are limited. Herein we would like to report our efforts to synthesize compound **1**.

Results and Discussion

Retrosynthetically, methyl protodioscin (**1**) can be logically disconnected into three distinct fragments (**2**−**4**) (Scheme 1). Trisaccharide **3** may be generated from the corresponding 2,4-*O*-*β*-glucopyranoside **5** and α-L-rhamnopyranosyl trichloroacetimidate **6**,[6] respectively.

Inspired by the recent accomplishment of the first synthesis of furostan saponins by Yu and Hui,[7] we decided to use the same starting material diosgenin (see Scheme 2) in our synthesis of methyl protodioscin. We explored a less lengthy, more efficient approach, preferably more adaptable to a combinatorial format. Such an approach would allow us to rapidly access a variety of structural analogues of methyl protodioscin.

We anticipated that the epoxide hemiketal acetate **8**, which has been successfully generated in 92% yield by Bovicelli and co-workers[8] from diosgenin acetate **7** with DMDO as an oxidant (Scheme 2), could be directly converted to its corresponding olefin **2** by a suitably selected method, since many effective methodologies[9] are available for such transformations.

After screening a number of known methods to convert the epoxide into its corresponding olefin in compound **2**,[9]

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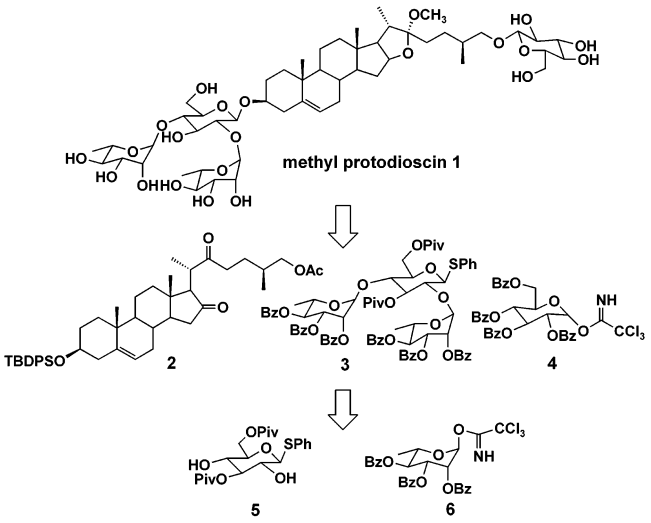
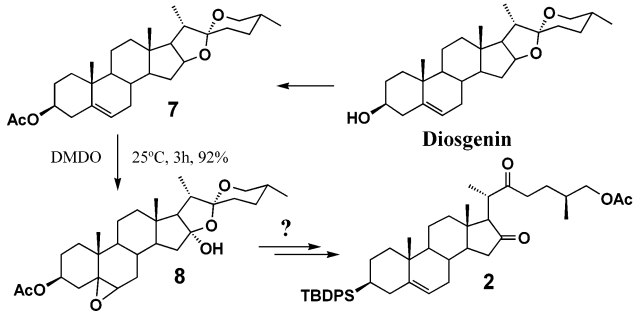
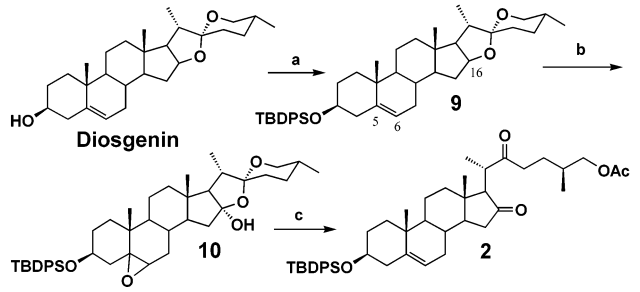
SCHEME 1. Retrosynthetic Analysis



SCHEME 2. Design of a Concise Approach



SCHEME 3. Synthesis of Intermediate 2[a]

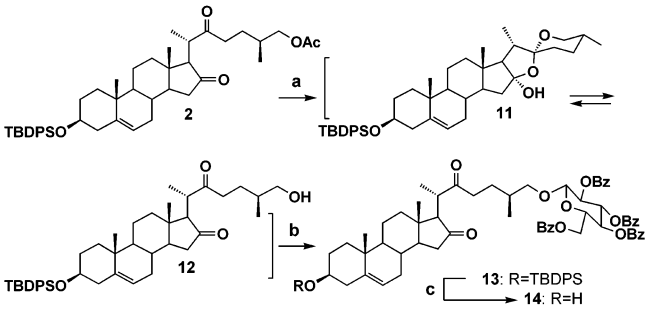


[a] (a) TBDPSiCl, imid., DMF, rt, 90%; (b) oxone, $NaHCO_3$, H_2O, acetone, CH_2Cl_2, rt; (c) Zn, KI, AcOH, Ac_2O, rt (58% for two steps).

we finally chose the Cornforth procedure[10] for our purpose, since the real chemistry for this conversion turned out to be extremely effective as shown in Scheme 3. After protection of the C-3 hydroxyl group in diosgenin with TBDPS, compound **9** was then oxidized with DMDO at the double bond and spiroketal to afford compound **10**, which, without purification, directly underwent reductive cleavage of the epoxide to regenerate the double bond. Thus, the diketone acetate **2** was obtained in 58% yield in a one-pot operation under very mild conditions.

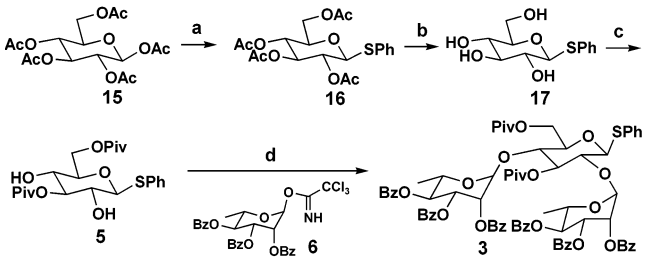
We then focused our attention on the synthesis of glycosylated intermediate **14**. To this end, the 26-*O*-acetyl group in compound **2** was removed by treatment with K_2CO_3/THF/MeOH to afford a mixture of spiroketal **11** and dione **12** (Scheme 4), which was then glycosylated[7,11] directly with 2,3,4,6-*tetra*-*O*-benzoyl-α-D-glucopyranosyl trichloroacetimidate **4**[12] in the presence of a catalytic amount of TMSOTf (0.1 equiv) to provide the 26-*O*-glycosylated product **13**. Compound **14** was finally obtained by treatment of compound **13** with *tetra*-butylammonium fluoride.

SCHEME 4. Synthesis of Compound 14[a]



[a] (a) K_2CO_3, THF/MeOH (1:1), rt, 100%; (b) compound **4**, TMSOTf (0.1 equiv), CH_2Cl_2, rt, 62%; (c) TBAF, THF, rt, 80%.

SCHEME 5. Synthesis of Trisaccharide 3[a]



[a] (a) Thiophenol, $BF_3{\cdot}Et_2O$, CH_2Cl_2, rt, 85%; (b) MeONa, MeOH, rt, 100%; (c) PivCl, pyridine, CH_2Cl_2, 0 °C, 70%; (d) $BF_3{\cdot}Et_2O$, CH_2Cl_2, −78 °C, 100%.

The next task was to construct the trisaccharide moiety **3** (Scheme 5). Structurally, the constitution of this trisaccharide is quite unique. The sequential linkage of α-L-rhamnopyranosyl-(1→2)-α-L-rhamnopyranosyl-(1→4)-β-D-glucopyranoside led us to envisage a convergent approach in which phenyl 3,6-di-*O*-pivaloyl-1-thio-β-D-glucopyranoside (**5**)[13] as an acceptor and α-L-rhamnopyranosyl trichloroacetimidate (**6**)[6] was utilized as a donor. If successful, such a strategy would allow convergent generation of trisaccharide **3** in one step.

For this purpose, commercially available 1,2,3,4,6-*penta*-*O*-acetyl-β-D-glucopyranose (**15**) was chosen as a starting material for the preparation of **5**, as its anomeric acetate was quite easily exchanged with thiophenol under acidic conditions[14] to give 2,3,4,6-*tetra*-*O*-acetyl-1-thio-β-D-glucopyranoside (**16**) in 85% yield. Hydrolysis of the remaining acetates in compound **16** was achieved by

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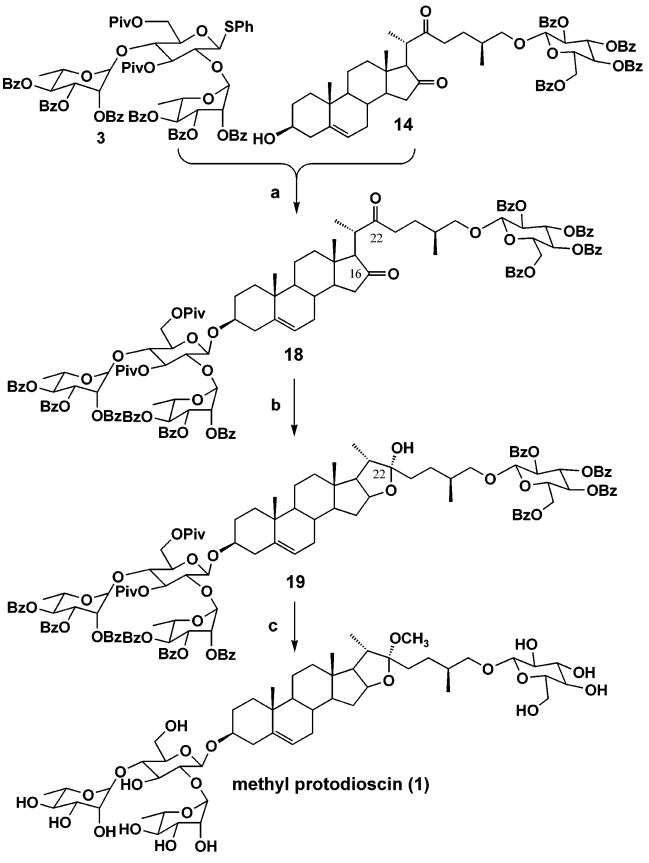
SCHEME 6. Completion of Synthesis[a]



[a] (a) NIS, TfOH, CH_2Cl_2, rt, 52%; (b) $NaBH_4$, *i*-propanol, CH_2Cl_2, rt, 70%; (c) MeONa, MeOH, reflux, 83%.

treatment with a catalytic amount of sodium methoxide in methanol to give a quantitative yield of tetraol **17**, which was then regioselectively acylated with pivaloyl chloride in pyridine to afford **5** in 70% yield.[13] A successful glycosylation of compound **5** (acceptor) was eventually conducted in the presence of $BF_3{\cdot}Et_2O$ with rhamose-derived trichloroacetmidate **6** (donor) at −78 °C[15] to provide the key intermediate trisaccharide **3** in quantitative yield.

With efficient synthetic access to intermediates **3** and **14**, we then examined their union via an iodonium ion promoted coupling reaction[16] between thioglycoside **3** and the secondary alcohol in compound **14**. Gratifyingly, this glycosidation gave us a 52% yield of desired product **18** after treatment of **14** and **3** with *N*-iodosuccinimide (NIS) and a catalytic amount of trifluoromethanesulfonic acid (TfOH) at room temperature (Scheme 6). Preferential reduction of the C_{16}-ketone in compound **18** with $NaBH_4$ in *i*-PrOH was achieved by following the known procedure,[17] and the newly generated secondary alcohol concurrently cyclized to give the hemiketal **19** in 70% yield. The final target furostan saponin **1** was eventually obtained in 83% yield by deprotection of benzoyl and pivaloyl groups, and in situ methoxylation at C22 positon in a basic MeOH solution (Scheme 6).

The analytical data for the synthesized furostan saponin **1** were identical in all respects to those of the natural product (isolated by our laboratories),[4] including ^1H and ^{13}C NMR, DEPT, ESI-MS, optical rotation, and IR.

In conclusion, a highly convergent approach for the synthesis of methyl protodioscin **1** has been developed, which paves the way to easily access methyl protodioscin and its diversified analogues.

Experimental Section

Analytical thin-layer chromatography (TLC) was performed on precoated plates of silica gel HF_{254} (0.5 mm, Qingdao, China). Flash column chromatography was performed on silica gel H (60 μm, Qingdao, China). Dried solvents used as reaction media were purified in the usual way, and solvents for extraction and chromatography were reagent grade and used as received. The boiling range of the petroleum ether used was 60−90 °C.

Synthesis of 3 β-TBDPS Diosgenin 9. *tert*-Butylchlorodiphenylsilane (TBDPSCl, 8 mL, 31.4 mmol) was added to a stirred mixture of diosgenin (10.0 g, 24.1 mmol) (Northeast General Pharmaceutical Factory, Shenyang, China) and imidazole (3.3 g, 48.2 mmol) in dried DMF (150 mL) at room temperature, and the mixture was then stirred at the same temperature for 12 h. The reaction was worked up with saturated NH_4Cl solution (50 mL), the mixture was extracted with petroleum ether (150 mL × 3), and the combined organic layer was washed sequentially with a saturated $NaHCO_3$ aqueous solution (100 mL × 2) and then water (200 mL × 2) and dried over anhydrous Na_2SO_4. The solvent was removed under vacuum, and the residue was purified by flash column chromatography (silica gel, petroleum ether/ethyl acetate = 30/1) to afford compound **9** as a white solid (14.1 g, 90% yield): mp 156.5−158.5 °C; R_f = 0.5 (petroleum ether/ethyl acetate, 20:1); $[\alpha]^{30}{}_D$ −86.8° (*c* 0.65, CH_2Cl_2); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.68−7.66 (m, 4H), 7.43−7.32 (m, 6H), 5.11 (d, 1H, J = 4.9 Hz), 4.41−4.34 (m, 1H), 3.55−3.43 (m, 2H), 3.39−3.32 (t, 1H, J = 10.7 Hz), 2.36−2.29 (m, 1H), 2.16−2.10 (dd, 1H, J_1 = 13.0, J_2 = 3.5 Hz), 1.98−1.80 (m, 3H), 1.76−1.51 (m, 11H), 1.46−1.42 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 141.3, 135.8, 134.8, 129.4, 127.4, 120.8, 109.2, 80.8, 73.2, 66.8, 62.1, 56.5, 50.0, 42.5, 41.6, 40.2, 39.8, 37.2, 36.6, 32.0, 31.8, 31.4, 30.3, 28.8, 27.0, 20.8, 19.4, 19.1, 17.1, 16.2, 14.5; ESI-MS *m*/*z* 653.

Synthesis of Compound 2. To the stirred mixture of compound **9** (30 g, 0.046 mol), $NaHCO_3$ (73 g, 0.869 mol), H_2O (500 mL), CH_2Cl_2 (400 mL), and acetone (100 mL) was added oxone ($2KHSO_5{\cdot}KHSO_4{\cdot}K_2SO_4$) (160 g, 0.258 mol) at room temperature in portions. The reaction was then monitored by TLC to follow the reaction to completion. The precipitated solid was then filtered off, and the filtrate was extracted with CH_2Cl_2 (200 mL × 2). The combined organic layer was then washed with water (50 mL × 2) and dried over anhydrous Na_2SO_4. The solvent was removed under vacuum, and the residue was dissolved in a mixture of acetic acid (100 mL) and acetic anhydride (100 mL), followed by addition of zinc powder (14.9 g, 0.230 mol) and KI (19 g, 0.115 mol) at room temperature. After the reaction mixture was stirred at the same temperature for 15 h, the solid was removed by filtration, and the filtrate was extracted with $CHCl_3$ (150 mL × 3). The combined organic layer was first washed with water (200 mL × 2), then with a saturated sodium bicarbonate solution (200 mL × 3), and finally with a saturated NH_4Cl water solution (200 mL × 2) and dried over anhydrous $MgSO_4$. The solvent was removed under vacuum, and the yellowish oil was purified by flash column chromatography (silica gel, petroleum ether/ethyl

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acetate = 10:1) to give 18.9 g of compound **2** as a white solid (58% yield): mp 48−50 °C; R_f = 0.35 (petroleum ether/ethyl acetate = 10:1); $[\alpha]^{30}_D$ −132.4°(*c* 1.17, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.68−7.66 (m, 4H), 7.44−7.34 (m, 6H), 5.11 (d, 1H, *J* = 4.3 Hz), 3.93 (dd, 2H, *J* = 6.1, 1.4 Hz), 3.57−3.50 (m, 1H), 2.85−2.71 (m, 1H), 2.65−2.53 (m, 3H), 2.40−2.30 (m, 1H), 2.21−2.12 (m, 2H), 2.05 (s, 3H), 1.99−1.97 (m, 1H), 1.91−1.62 (m, 7H), 1.62−1.43 (m, 8H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 217.9, 213.2, 171.2, 141.4, 135.7, 134.7, 129.4, 127.4, 120.3, 73.1, 69.0, 66.1, 51.2, 49.6, 43.3, 42.4, 41.6, 39.6, 38.6, 37.1, 36.9, 36.5, 32.1, 31.8, 31.7, 30.9, 27.0, 26.7, 20.9, 20.5, 19.4, 19.1, 16.8, 15.3, 12.9; ESI-MS *m*/*z* 711(M + 1).

Synthesis of Compound 13. Compound **2** (6.0 g, 8.4 mmol) and K_2CO_3 (1.4 g, 10.1 mmol) were dissolved in a mixed solvent of THF/MeOH (1:1, 100 mL) and then stirred at room temperature for 3 h to remove the acetate. The reaction mixture was first extracted with $CHCl_3$ (150 mL × 3), and then, the combined organic layer was washed with water (50 mL × 3) and finally dried over anhydrous $MgSO_4$. The solvent was removed, and the residue was a white solid as a mixture of compounds **11** and **12** (5.9 g), which was used in the next step without further purification.

A slurry solution of the prepared compounds **11** and **12** (4.1 g, 6.1 mmol), 2,3,4,6-*tetra*-*O*-benzoyl-α-D-glucopyranosyl trichloroacetimidate (**4)** (5.2 g, 7.1 mmol), and anhydrous powdered molecular sieves (4 Å) in dried CH_2Cl_2 (50 mL) was stirred at room temperature under N_2 for about 30 min. Then, TMS−OTf (0.1 mL, 0.6 mmol) was added, and the reaction mixture was continuously stirred for another 5 h. The solid was removed by filtration and was washed with CH_2Cl_2 (200 mL). The filtrate was first washed with water (100 mL × 2), then dried over anhydrous Na_2SO_4, and concentrated under vacuum to give the residue, which was purified by flash column chromatography (silica gel, petroleum ether/ethyl acetate = 8:1) to give the product as a white solid (4.7 g, 62% yield): mp 72.5−75 °C; R_f 0.4 (petroleum ether/ethyl acetate = 4:1); $[\alpha]^{30}_D$ −55.8°(*c* 0.24, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.0 (d, 2H, *J* = 7.2 Hz), 7.94 (d, 2H, *J* = 7.2 Hz), 7.89 (d, 2H, *J* = 7.3 Hz), 7.83 (d, 2H, *J* = 7.2 Hz), 7.70−7.66 (m, 4H), 7.55−7.24 (m, 18H), 5.88 (t, 1H, *J* = 9.6 Hz), 5.66 (t, 1H, *J* = 9.7 Hz), 5.52 (dd, 1H, *J* = 9.6, 7.9 Hz), 5.10 (d, 1H, *J* = 4.3 Hz), 4.88 (d, 1H, *J* = 7.8 Hz), 4.66−4.61 (m, 1H), 4.52−4.46 (m, 1H), 4.21−4.08 (m, 1H), 3.74−3.68 (m, 1H), 3.57−3.48 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 218.0, 213.3, 166.1, 165.8, 165.2, 165.1, 141.5, 135.7, 134.7, 133.4, 133.1, 129.7, 129.5, 128.9, 128.3, 127.5, 120.3, 101.0, 74.6, 73.1, 72.1, 72.0, 70.1, 66.2, 63.3, 51.2, 49.6, 43.3, 42.4, 41.6, 39.6, 38.6, 37.1, 36.9, 36.5, 32.3, 31.8, 31.7, 30.9, 27.0, 26.7, 20.5, 19.4, 19.1, 17.0, 15.3, 12.9; ESI-MS *m*/*z* 1364 (M + H_2O).

Synthesis of Compound 14. Compound **13** (3.6 g, 2.88 mmol) and anhydrous 4 Å powder molecular sieves (2 g) were mixed in THF (40 mL), and the generated mixture was treated with TBAF (tetrabutylammonium fluoride) (TBAF·$3H_2O$, 3.6 g, 11.5 mmol). The reaction mixture was stirred at room temperature for 8 h. The solid was removed by filtration and washed with $CHCl_3$ (200 mL), and the organic phase was then washed with water (50 mL × 3) and dried over $MgSO_4$. The solvent was removed under vacuum, and the residue was purified by flash column chromatography (silica gel, petroleum ether/ethyl acetate = 2:1) to give compound **14** (2.3 g, 80% yield) as a white solid: mp 90−92 °C; R_f 0.5 (petroleum ether/ethyl acetate, 1:1); $[\alpha]^{30}_D$ −120°(*c* 0.13, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.01 (d, 2H, *J* = 7.2 Hz), 7.94 (d, 2H, *J* = 7.2 Hz), 7.89 (d, 2H, *J* = 7.2 Hz), 7.83 (d, 2H, *J* = 7.2 Hz), 7.55−7.24 (m, 12H), 5.89 (t, 1H, *J* = 9.6 Hz), 5.66 (t, 1H, *J* = 9.7 Hz), 5.53 (dd, 1H, *J* = 9.6, 7.9 Hz), 5.34 (d, 1H, *J* = 4.6 Hz), 4.88 (d, 1H, *J* = 7.8 Hz), 4.66−4.61 (m, 1H), 4.52−4.47 (m, 1H), 4.21−4.08 (m, 1H), 3.72 (dd, 1H, *J* = 9.7, 6.8 Hz), 3.58−3.49 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 218.0, 213.3, 166.1, 165.8, 165.2, 165.1, 141.0, 133.4, 133.1, 129.7, 129.5, 128.9, 128.3, 120.8, 101.0, 74.7, 73.1, 72.1, 72.0, 70.1, 66.2, 63.3, 51.3, 49.7, 43.3, 42.2, 41.6, 39.6, 38.6, 37.2, 36.9, 36.6, 32.4, 31.7, 31.5, 30.9, 26.7, 20.5, 19.4, 17.0, 15.3, 12.9; ESI-MS *m*/*z* 1026 (M + H_2O), 1031(M + Na).

Synthesis of Compound 16.[15] To a solution of *penta*-*O*-acetyl-*β*-D-glucopyranose (**15)** (12.3 g, 31.5 mmol) in dried CH_2Cl_2 (50 mL) was sequentially added thiophenol (3.9 mL, 37.8 mmol) and BF_3·Et_2O (47%−47.7%, 12 mL, 94.5 mmol) at 0 °C under N_2 atmosphere. After the mixture was stirred at room temperature for 3 h, the reaction mixture was diluted with CH_2Cl_2 (200 mL). This organic phase was washed sequentially with saturated sodium bicarbonate solution (50 mL × 3) and water (50 mL × 2) and dried over anhydrous $MgSO_4$. The solvent was removed under vacuum, and the residue was purified by flash column chromatography (silica gel, petroleum ether/ethyl acetate = 5:1) to give compound **16** (11.8 g, 85% yield) as a white solid: mp 107.5−109.5 °C; R_f 0.3 (petroleum ether/ethyl acetate = 4:1); $[\alpha]^{30}_D$ −11.0° (*c* 0.47, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.51−7.48 (m, 2H), 7.33−7.31 (m, 3H), 5.23 (t, 1H, *J* = 9.3 Hz), 5.07−4.94 (m, 2H), 4.71 (d, 1H, *J* = 10.0 Hz), 4.22−4.19 (m, 2H), 3.76−3.70 (m, 1H), 2.09 (s, 3H), 2.08 (s, 3H), 2.02 (s, 3H), 1.99 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.4, 170.1, 169.3, 169.1, 133.1, 131.6, 128.9, 128.3, 85.7, 75.8, 73.9, 69.9, 68.2, 62.1, 20.6, 20.5; ESI-MS *m*/*z* 463 (M + Na).

Synthesis of Compound 17. Compound **16** (2.4 g, 5.4 mmol) was suspended in a basic solution of methanol (10 mL) and NaOMe (0.11 g, 2 mmol), the mixture was stirred at room temperature for 15 min, and the solid was dissolved. This solution was then treated with ion-exchange resin (H^+) for about 20 min. The resin was filtered off, and the solvent was removed under vacuum to quantitatively give compound **17** as a white solid (1.4 g).

Synthesis of Compound 5.[14] To a stirred solution of compound **17** (7.1 g, 26 mmol) in pyridine (40 mL) was added a solution of pivaloyl chloride (12.9 mL, 104 mmol) in CH_2Cl_2 (15 mL) dropwise at 0 °C. The reaction was stirred at the same temperature for 6 h. The reaction mixture was then diluted with ethyl acetate (250 mL) and sequentially washed with an aqueous solution of 1 N HCl (100 mL × 4), a saturated $NaHCO_3$ solution (50 mL × 3), and then water (50 mL × 2). The organic layer was dried over anhydrous $MgSO_4$, the solvent was removed under vacuum, and the residue was subject to flash column chromatography (silica gel) (petroleum ether/ethyl acetate = 3:1) to give the pure compound **5** (8.0 g, yield 70%) as a white solid: mp 68.5−70 °C; TLC R_f 0.5 (petroleum ether/ethyl acetate, 2:1); $[\alpha]^{30}_D$ −112.9° (*c* 0.12, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.57−7.54 (m, 2H), 7.31−7.29 (m, 3H), 4.94 (t, 1H, *J* = 9.1 Hz), 4.62 (d, 1H, *J* = 9.7 Hz), 4.45 (dd, 1H, *J* = 12.1, 2.1 Hz), 4.31 (dd, 1H, J_1 = 12.0, J_2 = 5.7 Hz), 3.62−3.60 (m, 1H), 3.48−3.42 (m, 2H), 3.21 (br s, 1H), 2.72 (br s, 1H), 1.22 (s, 18H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 180.1, 178.8, 132.6, 131.8, 128.9, 128.1, 88.3, 78.9, 78.4, 70.5, 69.2, 63.5, 39.0, 38.8, 27.1, 27.0; ESI-MS *m*/*z* 442 (M + 1), 903 (2 × M + Na).

Synthesis of Compound 3. To a mixture of compounds **5** (1.0 g, 2.3 mmol) and **6** (3.5 g, 5.6 mmol) and 4 Å powdered molecular sieves (0.5 g) in dried CH_2Cl_2 (40 mL) at −78 °C was added BF_3·Et_2O (0.3 mL, 2.3 mmol). After being stirred for 4 h (at −78 °C), the reaction was quenched with Et_3N (5 mL). The solid was then filtered off, and the filtrate was concentrated under vacuum to give a yellow oil, which was purified by flash column chromatography (petroleum ether/ethyl acetate = 5:1) to quantitatively give compound **3** (3.1 g) as a white solid: mp 82.5−85 °C; R_f 0.4 (petroleum ether/ethyl acetate, 4:1); $[\alpha]^{30}_D$ +90.2° (*c* 0.35, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.07 (dd, 4H, J_1 = 7.3, J_2 = 1.9 Hz), 7.98 (d, 2H, *J* = 7.4 Hz), 7.94 (d, 2H, *J* = 7.4 Hz), 7.74 (d, 2H, *J* = 7.4 Hz), 7.63 (dd, 2H, J_1 = 8.0, J_2 = 1.7 Hz), 7.56 (t, 4H, *J* = 8.7 Hz), 7.50−7.45 (m, 5H), 7.40−7.23 (m, 8H), 7.16 (t, 4H, *J* = 6.9 Hz), 7.05 (t, 2H, *J* = 7.7 Hz), 5.85−5.76 (m, 3H), 5.69 (td, 3H, *J* = 9.5 Hz, J_2 = 2.0 Hz), 5.44 (t, 1H, *J* = 5.3 Hz), 5.35 (s, 1H), 5.23 (s, 1H), 5.08 (d, 1H, *J* = 8.2 Hz), 4.75−4.69 (m, 1H), 4.56 (dd, 1H, J_1 = 11.8 Hz, J_2 = 3.5 Hz), 4.43−4.35 (m, 2H), 4.19−

4.12 (m, 1H), 4.08 (t, 1H, J = 6.4 Hz), 3.96 (dd, 1H, J_1 = 8.2 Hz, J_2 = 4.8 Hz), 1.41 (d, 3H, J = 6.2 Hz), 1.37 (d, 3H, J = 6.1 Hz), 1.23 (s, 9H), 1.16 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 177.9, 176.8, 165.9, 165.8, 165.4, 165.3, 165.2, 133.4, 132.4, 129.9, 129.7, 129.5, 128.5, 128.4, 127.9, 97.6, 97.2, 85.1, 77.0, 76.2, 75.2, 75.0, 71.7, 71.3, 71.0, 70.0, 68.3, 67.8, 63.2, 38.9, 27.2, 26.9, 17.6, 17.5; ESI-MS m/z 1374 (M + NH_3), 1380 (M + Na).

Synthesis of Compound 18. A mixture of **14** (2.2 g, 2.2 mmol), **3** (5.9 g, 4.4 mmol), and 4 Å powdered molecular sieves in dried CH_2Cl_2 (90 mL) was stirred at room temperature under N_2 for about 30 min, and then, NIS (2.0 g, 8.7 mmol) and TfOH (76 μL, 0.87 mmol) were added and the coupling reaction was carried out at room temperature for about 15 min. After being quenched with Et_3N (5 mL) and filtered, the filtrate was diluted with CH_2Cl_2 (150 mL), washed sequentially with saturated aqueous of $Na_2S_2O_3$ (50 mL × 3) and water (100 mL × 2), and dried over anhydrous $MgSO_4$. The solvent was removed under vacuum, and residue was purified by flash column chromatography (petroleum ether/ethyl acetate = 2:1) to give compound **18** (2.6 g, 52.8% yield) as a white solid: mp 138−139.5 °C; R_f 0.5 (petroleum ether/ethyl acetate = 3:2); $[\alpha]^{30}_D$ +65.7° (c 0.14, CH_2Cl_2); ^{1}H NMR($CDCl_3$, 300 MHz) δ 8.10−7.78 (m, 20H), 7.63−7.20 (m, 30H), 5.89 (t, 1H, J = 9.6 Hz), 5.85−5.76 (m, 3H), 5.76−5.58 (m, 4H), 5.57−5.44 (m, 3H), 5.21 (s, 2H), 5.06(s, 1H), 4.90 (d, 1H, J = 7.8 Hz), 4.64 (d, 2H, J = 11.7 Hz), 4.57−4.43 (m, 2H), 4.41−4.15 (m, 4H), 3.89 (t, 1H, J = 9.1 Hz), 3.72 (t, 1H, J = 9.2 Hz), 3.63 (d, 1H, J = 12.6 Hz), 3.56−3.51(m, 1H), 2.67−2.45 (m,6H), 2.23 (dd, 1H, J_1 = 12.1 Hz, J_2 = 6.3 Hz), 2.10−1.87 (m,5H), 1.87−1.73 (m,4H), 1.70−1.47 (m, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 217.9, 213.3, 178.0, 176.6, 166.1, 165.8, 165.6, 165.4, 165.3, 165.2, 165.1, 164.9, 140.3, 133.4, 133.1, 132.9, 129.7, 129.4, 128.9, 128.6, 128.4, 128.3, 121.7, 101.0, 100.1, 98.4, 96.7, 80.3, 79.5, 77.9, 77.2, 74.6, 73.1, 72.1, 72.0, 71.8, 71.6, 71.2, 70.5, 70.1, 69.7, 68.4, 68.2, 67.3, 66.2, 63.4, 62.6, 51.3, 49.8, 43.3, 41.7, 40.2, 39.6, 39.0, 38.6, 37.2, 37.0, 30.9, 32.3, 31.7, 30.9, 28.4, 27.3, 27.2, 27.0, 26.7, 20.5, 19.4, 17.9, 17.5, 17.0, 15.4, 13.0; ESI-MS m/z 2257 (M + 1), 2278 (M + Na).

Synthesis of Compound 19. The mixture of compound **18** (1.7 g, 0.75 mmol) and $NaBH_4$ (0.85 g, 22.6 mmol) in i-propanol (70 mL) and CH_2Cl_2 (10 mL) was stirred at room temperature for about 7.5 h. The reaction mixture was then extracted with CH_2Cl_2 (100 mL × 2), the combined organic layer was washed with water (100 mL × 3) and dried over anhydrous $MgSO_4$, and the solvent was removed under vacuum to give an almost colorless oil, which was purified by flash column chromatography (petroleum ether/ethyl acetate, 2:1) to give compound **19** (1.2 g, 70%) as a white solid: mp 132−134 °C; TLC R_f 0.5 (petroleum ether/ethyl acetate, 1:1); $[\alpha]^{30}_D$ +81.3° (c 0.1, CH_2Cl_2); ^{1}H NMR (d_6-DMSO, 300 MHz) 5.99 (t, 1H, J = 9.5 Hz), 5.75−5.36 (m, 9H), 5.27−5.17 (m, 3H), 5.02 (s, 1H), 4.52−4.20 (m, 8H), 4.08−3.89 (m, 3H), 3.59 (m, 2H), 3.47 (m, 1H), 2.57 (br s, 1H), 2.07 (br s, 1H), 1.99 (s, 1H), 1.93−1.75 (m, 3H); ^{13}C NMR (d_6-DMSO, 100 MHz) 177.1, 176.3, 165.3, 165.1, 164.8, 164.7, 164.6, 164.4, 140.0, 134.0, 133.6, 133.4, 129.3, 129.2, 129.1, 129.0, 128.9, 128.8, 128.7, 128.5, 128.4, 121.7, 109.4, 99.8, 98.8, 97.3, 95.4, 79.7, 78.3, 77.7, 76.5, 74.1, 73.2, 71.9, 71.7, 71.3, 71.0, 70.8, 70.3, 69.7, 69.5, 67.7, 67.2, 66.4, 63.3, 62.8, 62.5, 55.7, 49.6, 39.7, 39.1, 38.9, 38.5, 38.3, 36.8, 36.3, 35.6, 32.9, 31.6, 30.9, 27.7, 27.0, 26.9, 26.8, 26.7, 26.4, 20.7, 18.9, 17.4, 17.2, 16.5, 15.9, 15.7, 14.0; ESI-MS m/z 2241 (M + 1 − H_2O), 1120.

Methyl Protodioscin 1. Sodium (50 mg, 2 mmol) was dissolved in CH_3OH (15 mL), and then, compound **19** (0.1 g, 0.044 mmol) was added. After refluxing for about 35 h, the solution was neutralized with ion-exchange resin (H^+), filtered, and concentrated to give a yellow oil, which was purified by flash column chromatography ($CHCl_3$/MeOH/H_2O, 60:20:1) to afford the compound as a white solid (39 mg, yield 83%): mp 175−177 °C; TLC R_f 0.25 ($CHCl_3$/MeOH/H_2O, 60:20:1); $[\alpha]^{30}_D$ −66.7° (c 0.48, H_2O); ^{1}H NMR (pyridine-d_5, 300 MHz) 6.39 (s, 1H), 5.84 (s, 1H), 5.30 (s, 1H), 5.01−4.87 (m, 3H), 4.84 (d, 2H, J = 7.8 Hz), 4.72−4.49 (m, 4H), 4.48−4.28 (m, 5H),4.28−4.15 (m, 5H), 4.14−3.81 (m, 5H), 3.64−3.55 (m, 2H), 3.25 (s, 3H), 2.85−2.65 (m, 2H); ^{13}C NMR (pyridine-d_5, 75 MHz) δ 140.9, 121.8, 112.7, 105.0, 102.9, 102.1, 100.3, 81.3, 78.7, 78.5, 78.1, 78.0, 77.8, 77.0, 75.2, 74.2, 74.0, 72.9, 72.8, 72.6, 71.8, 70.5, 69.6, 64.2, 62.9, 61.2, 56.6, 50.4, 47.3, 40.8, 40.5, 39.8, 39.1, 37.5, 37.2, 34.3, 32.2, 31.7, 30.9, 30.0, 28.1, 21.2, 19.4, 18.7, 18.5, 17.2, 16.3; ESI-MS m/z 1085 (M + Na), 1031 (M + 1 − CH_3OH).

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Supporting Information Available: ^{1}H NMR, ^{13}C NMR, and ESI-MS spectra of compounds **1**, **2**, **3**, **9**, **13**, **14**, **15**, and **16**. This material is available free of charge via the Internet at http://pubs.acs.org.

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