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# The Synthesis of Gracillin and Dioscin: Two Typical Representatives of Spirostanol Glycosides

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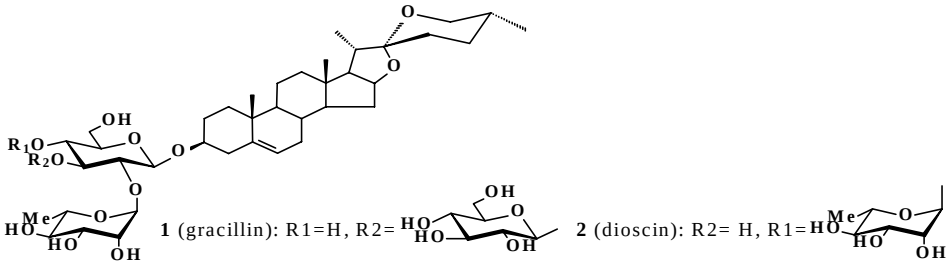
**Abstract:** Two spirostanol saponins (gracillin and dioscin) which have the typical sugar moieties were synthesized facilely by a general approach.

**Keywords:** Spirostanol glycosides, glycosylation, cadmium carbonate.

Steroidal glycosides constitute an important class of secondary metabolites from seaweed, fungi and higher terrestrial plants. Spirostanol glycosides, which comprise aglycones of the spirostan type with the sugar moiety usually linked at position 3, are the largest group of steroidal saponins existent in nature extensively and have a broad range of interesting bioactivities[1]. Synthesis by glycosylation is a readily available approach to get a series of homogeneous saponins for pharmacological research because isolation and purification from a natural source were usually very difficult.




The structural diversity of spirostanol saponins lies mainly in their sugar moieties. In general, the sugar moieties are oligosaccharides with 2-4 kinds of sugar units, *e.g*. D-glucose, D-galactose, D-xylose and L-rhamnose. The first sugar attached to diosgenin usually is D-glucose or D-galactose, while D-xylose and L-rhamnose generally occur at the terminal positions[1a]. Dioscin(**1**) and gracillin(**2**) are two typical representatives of spirostanol saponins. They exist widely in the natural plants used in traditonal Chinese herb medicine, such as *Dioscorea*, *Paris*, *Costacea* species, that

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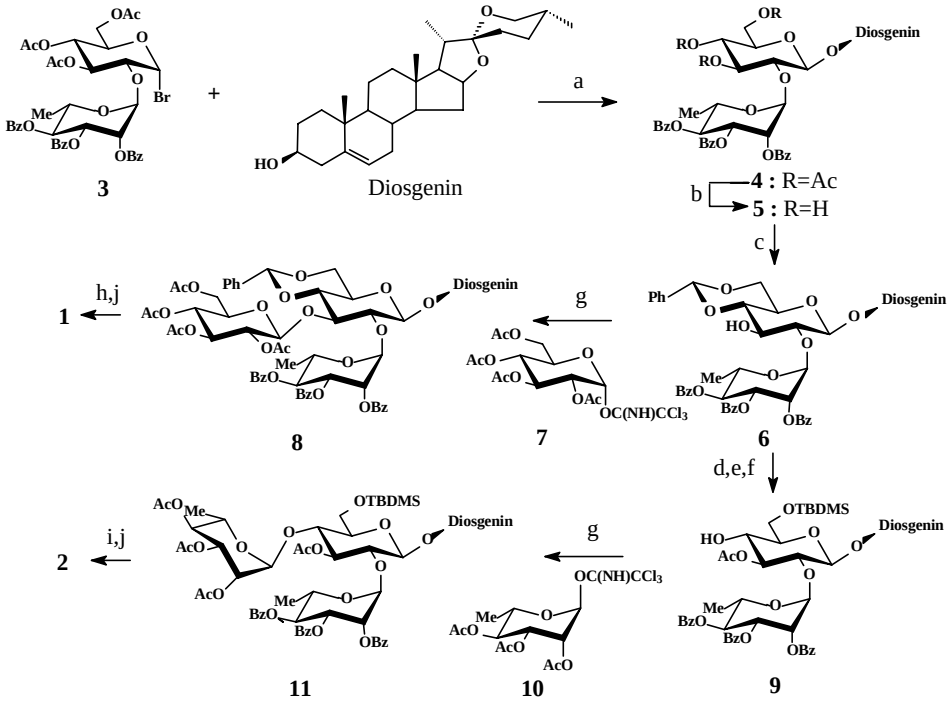
exhibit cardiovascular and antitumor activites[2]. There is a β-D-glucopyranose as the first sugar attached to diosgenin, which in turn has an α-L-rhamnopyranose substituted at 2′-OH and another sugar or sugar chain at 3′-OH or 4′-OH. In dioscin, the third sugar is an α-L-rhamnopyranose substituted at 4′-OH and in gracillin, there is another β-D-glucopyranose substituted at 3′-OH.

Using diosgenyl 4, 6-O-benzylidene-β-D-glucopyranoside as the key intermediate, dioscin and gracillin had been synthesized respectively through two approaches[3, 4]. In these approaches, the 2′-OH and 3′-OH of diosgenyl 4, 6-O-benzylidene-β-D-glucopyranoside were difficult to protect selectively. Now, we had designed a strategy to avoid this problem. In the structures of dioscin and gracillin, there was a mutually shared sugar fragment, neohesperidose [α-L-Rhap-(1→2)-D-Glcp]. So we fabricated the protected neohesperidose first and attached it to diosgenin, then selectively deprotected the protective groups on glucose and extended the sugar chain to get the target compounds.

**Scheme 1**




Reagents and conditions: (a) $CdCO_3$, $CH_3CN$, reflux, 2.5 h, 68%; (b) Guanidine, MeOH/$CH_2Cl_2$, -10°C, 6 h, 71%; (c) $PhCH(OMe)_2$, DMF, CSA, 60°C, 2 h, 88%; (d) $Ac_2O$/pyridine, rt, overnight, 100%; (e) 80% HOAc, 70°C, 5 h, 86%; (f) TBDMSCl, imidazole, DMAP, DMF, 40→50°C, 4 h, 100%; (g) $BF_3{\cdot}Et_2O$, $CH_2Cl_2$, 4Å MS, -78°C→rt, 5 h, 83% for **6** and 3 h, 92% for **9**; (h) 80% HOAc, 70°C, 5 h, 84%; (i) TBAF, THF, rt, 6 h, 85%; (j) MeONa, THF/MeOH, overnight, 100%.

In our strategy, the mutually shared disaccharide donor **3**[5], in which glucose was protected by acetyl and rhamonose with benzoyl, was allowed to react with diosgenin in refluxing acetonitrile catalyzed by $CdCO_3$. Although there was no neighboring aryl group participation, we still got the β-type product mostly because of the influence of the solvent on glycosylation[6]. A protected diosgenyl disaccharide **4** was obtained in 68% and its α-isomer in 9% yield. Acetyl deprotection of **4** with guanidine[7] efficiently provided the key intermediate **5** in 71% yield. The condition of this reaction should be controlled carefully with minor amounts of guanidine (0.25 eq) and low temperature (-10°C). Then we extended the sugar chain with general methods to get the expected saponins easily. Benzylidenation of **5** afforded the receptor **6**, then glycosylation with donor **7** gave the protected diosgenyl trisaccharide **8**. Deprotection of **8** with 80% HOAc and then MeONa afforded the target saponin **1**. Treatment of **6** with $Ac_2O$/pyridine, deprotection of the benzylidene and then protection of the 6′-OH with TBDMS gave another receptor **9**. Glycosylation of **9** with donor **10** provided the protected diosgenyl trisaccharide **11**. Deprotection of TBDMS with $(n\text{-}Bu)_4NF$ and then treatment with MeONa afforded the target saponin **2**. The analytical data of **1** and **2** were virtually identical with the reported values[3,4].

In conclusion, a general synthetic approach was developed effectively in satisfactory yields to prepare the spirostan saponins(dioscin and gracillin) which had the typical structure of branched sugar moieties .

## Rerferences and Notes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5. This compound was obtained by glucosylating 2,3,4-tri-O-benzoyl-α-L-rhamnopyranosyl trichloroacetimidate with 1,3,4,6-tetra-O-acetyl α,β-D-glucopyranose [*Ref*., S. Brennan, and Finan, P. A. *J. Chem. Soc.*, **1970**, 1742.] to get 1,3,4,6-tetra-O-acetyl-2-O-(2,3,4-tri-O-benzoyl-α-L-rhamnopyranosyl) α, β-D-glucopyranose and then treated with 33% HBr in HOAc in dichloromethane(82% two step). $^1$H NMR ($CDCl_3$, 300MHz): $\delta$ 8.10-7.23(m, 15H, H-OBz), 6.51(d, 1H, 3.9Hz, H-1), 5.76-5.71(m, 2H, H-3′, H-4′), 5.61(t, 1H, 9.6Hz, H-3), 5.51(m, 1H, H-2′), 5.19-5.12(m, 2H, H-1′, H-4), 4.42-4.32(m, 3H, H-5′, H-5, H-6a), 4.14(m, 1H, H-6b), 3.87(dd, 1H, 9.6Hz, 3.9Hz, H-2), 2.12, 2.10, 2.06, (3s, 9H, H-OAc), 1.35(d, 3H, 6.0Hz, H-6″).
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8. Selected analytical data: **4**: $[\alpha]_D^{rt}$= +54.4 (*c* 1.07, $CHCl_3$), FAB-MS: 1173(M+Na), 1161(M+1); $^1$H NMR($CDCl_3$, 500MHz): $\delta$ 8.08-7.25(m, 15H, H-OBz), 5.78(dd, 1H, 3.5Hz, 10.0Hz, H-3″), 5.69(t, 1H, 10.0Hz, H-4″), 5.44(d, 1H, 4.5Hz, H-6), 5.41(dd, 1H, 3.5Hz, H-2″), 5.36(t, 1H,

9.5Hz, H-3′), 5.26(d, 1H, 1.5Hz, H-1″), 5.01(t, 1H, 9.5Hz, H-4′), 4.72(m, 1H, H-5″), 4.68(d, 1H, 8.0Hz, H-1′), 4.41(m, 1H, H-16), 4.30(dd, 1H, 5.5Hz, 15.5Hz, H-6′a), 4.10(dd, 1H, 2.5Hz, 15.5Hz, H-6′b), 3.84(d, 1H, 8.0Hz, 9.5Hz, H-2′), 3.74(m, 1H, H-5′), 3.66 (m, 1H, H-3), 3.47(m, 1H, H-26a), 3.38(t, 1H, H-26b), 2.15, 2.08, 2.03, (3s, 9H, H-OAc), 1.32(d, 3H, 6.0Hz, H-6″), 0.95(d, 3H, 7.0Hz), 0.88(s, 3H), 0.77(d, 3H, J=6.0Hz), 0.74(s, 3H). $^{13}$C NMR($CDCl_3$, 125MHz) $\delta$ 170.7, 170.4, 169.7, 165.7, 165.5, 165.4, 140.1, 133.5, 133.2, 133.1, 129.9(2×C), 129.8(2×C), 129.7(2×C), 129.3(overlap, 2×C), 129.2, 128.6(2×C), 128.4(2×C), 128.3(2×C), 122.2, 109.3, 100.1, 97.3, 80.8, 79.8, 75.3, 75.0, 71.9, 71.6, 71.2, 69.5, 68.9, 66.8, 66.7, 62.2, 62.1, 56.4, 50.0, 41.6, 40.2, 39.7, 38.7, 37.1, 36.8, 32.1, 31.9, 31.5, 31.4, 30.3, 29.8, 28.8, 20.8(2×C), 20.7, 20.6, 19.2, 17.4, 17.1, 16.2, 14.5. Anal. calcd for $C_{66}H_{80}O_{18}$: C, 68.24; H, 6.95. Found: C, 68.52; H, 6.94. **5**: $[\alpha]_D^n$= +32.8 (*c* 1.0, $CHCl_3$), FAB-MS: 1035(M+1); $^1$H NMR($CDCl_3$, 500MHz) $\delta$ 8.08-7.24(m, 15H, H-OBz), 5.79(dd, 1H, 3.5Hz, 10.0Hz, H-3″), 5.75(dd, 1H, 1.5Hz, 3.5Hz, H-2″), 5.68(t, 1H, 10.0Hz, H-4″), 5.56(brs, 1H, H-1″), 5.44(d, 1H, 4.5Hz, H-6), 4.72(m, 1H, H-5″), 4.63(d, 1H, 8.0Hz, H-1′), 3.92-3.76 (m, 3H, H-2′, H-3′, H-4′), 3.66-3.57(m, 3H, H-5′, H-6′a,b), 3.48(t, 1H, H-26a), 3.40-3.36(m, 2H, H-3, H-26b), 1.35(d, 3H, 6.0Hz, H-6″), 0.98(d, 3H, 7.0Hz), 0.94(s ,3H), 0.79(d, 3H, 6.0Hz), 0.73(s, 3H). $^{13}$C NMR($CDCl_3$, 125MHz) $\delta$ 166.0, 165.9, 165.7, 140.2, 133.5, 133.2, 133.1, 130.0(2×C), 129.8(2×C), 129.7(2×C), 129.4, 129.3, 129.1, 128.6(2×C), 128.4(2×C), 128.3(2×C), 122.0, 109.3, 100.1, 97.5, 80.8, 79.5, 77.8, 77.3, 75.1, 71.8, 70.8(overlap, 2×C), 70.3, 66.8, 66.6, 62.5, 62.1, 56.4, 50.0, 41.6, 40.3, 39.7, 38.9, 37.1, 36.8, 32.1, 31.9, 31.5, 31.4, 30.3, 29.9, 28.8, 20.8, 19.3, 17.4, 17.1, 16.3, 14.5. Anal. calcd for $C_{60}H_{74}O_{15}$: C, 69.61; H, 7.21. Found: C, 69.47; H, 7.32.

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