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Facile Synthesis of Ophipogonin C′ and its Three Analogues

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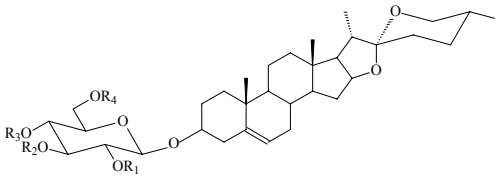
Abstract: Three natural diosgenyl glycosides: Ophipogonin C′ (A), Polyphillin C (B), diosgenyl α-L-rhamnopyranosyl-(1→4)-β-D-glucopyranoside (DRG) (C) and one of their analogue diosgenyl α-L-rhamnopyranosyl-(1→6)-β-D-glucopyranoside (D) were first systemic synthesized in a facile way in high yields.

Keywords: Diosgenyl glycoside, glycosylation, levulinoyl group, L-rhamnopyranoside.

Among the huge number of glycoconjuates, the steroidal glycosides are often found as the major components in traditional Chinese medicine. Steroidal glycosides constitute a structurally and biologically diverse class of molecules which have been isolated from a wide variety of both plant and animal species [1]. Because of the variety of promising pharmaceutical properties[2], the large family of steroidal glycosides has received considerable attention of chemist.

Figure 1



A. Ophipogonin C′: R_1 = α-L-rhamnopyranosyl, $R_2 = R_3 = R_4 = H$,
B. Polyphillin C: R_2 = α-L-rhamnopyranosyl, $R_1 = R_3 = R_4 = H$
C. DRG: R_3 = α-L-rhamnopyranosyl, $R_1 = R_2 = R_4 = H$
D. R_4 = α-L-rhamnopyranosyl, $R_1 = R_2 = R_3 = H$

Ophipogonin C′ (A) (**Figure 1**) is one of the cytostatic saponins isolated from *Ophiopogon planiscapus*[3]. Polyphyllin C (B) has been extracted from *Pairs polyphylla*[4]. Diosgenyl α-L-rhamnopyranosyl-(1→4)-β-D-glucopyranoside (DRG) (C) exists widely in the plant kingdom including many species used in traditional Chinese herbal medicines which exhibt cardiovascular activity[5]. Recently strong anticancer activity of

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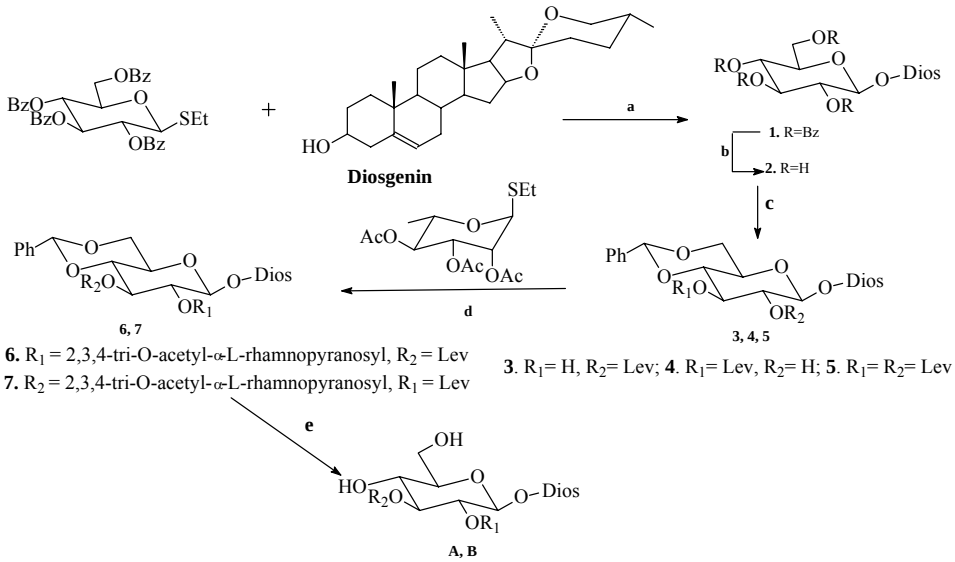
DRG was reported[6] by Cai *et al*. These three saponins share a common aglycon, diosgenin. The disaccharide chain begins with a β-D-glucopyranose and elongates through an α-L-rhamnopyranose in a different sequence.

In contrast to the difficulty in isolation of homogeneous saponins from plants, chemical synthesis would provide a realistic route to the availability of saponins. Ophipogonin C′ had been synthesized in our group[7], but to our best knowledge that there were no reports about the synthesis of polyphyllin C and DRG. Herein we reported a facile way to synthesize the three saponins and one of their analogoues (D) in high yields.

Scheme 1



6. R_1 = 2,3,4-tri-O-acetyl-α-L-rhamnopyranosyl, R_2 = Lev
7. R_2 = 2,3,4-tri-O-acetyl-α-L-rhamnopyranosyl, R_1 = Lev

3. R_1= H, R_2= Lev; **4**. R_1= Lev, R_2= H; **5**. R_1= R_2= Lev

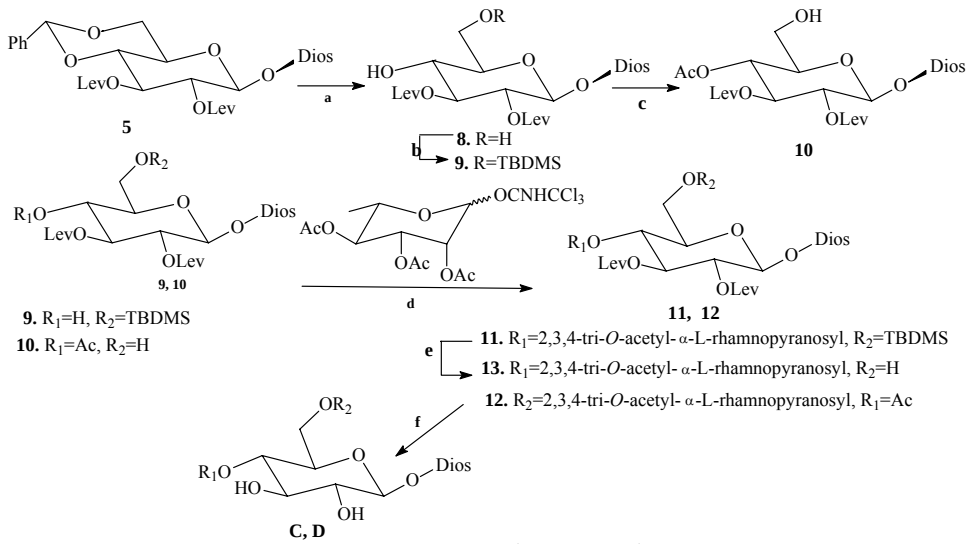
A. R_1= α-L-rhamnopyranosyl, R_2= H **B**. R_1= H, R_2= α-L-rhamnopyranosyl

Reagents and conditions: a. NIS-TMSOTf, -15℃ 94%; b. 1mol/L NaOMe in MeOH, reflux, 92%; c. (i) benzaldehyde dimethyl acetal, *p*-toluenesulphonic acid monohydrate, DMF 50℃ under reduced pressure; (ii) levulinic acid, DCC, DMAP, 73% for **3**; 12% for **4**; 8% for **5**; d. NIS-TMSOTf, -30℃ 97% for **6** and 95% for **7**; e. (i) 80% HOAc, 70℃ (ii) MeONa-MeOH, 87% for A and 89% for B

Using ethyl 2, 3, 4, 6-tetra-*O*-benzoyl-1-thio-β-D-glucopyranoside as donor to couple with diosgenin[7], protected diosgenyl glycoside **1** was obtained. The hydrolysis of **1** gave the deprotected glycoside **2**. Transformed **2** into diosgenyl 4, 6-*O*-benzylidene-β-D-glucopyranoside in 87% yield. It has been documented that it was quite difficult to selectively mask one of the hydroxyl groups of the 2, 3-diol of a D-glucopyranoside, especially when it was in the β-anomer[8]. However, we found that the levulinoyl group was regioselectively introduced by reaction of diosgenyl 4, 6-*O*-benzylidene-β-D-glucopyranoside with levulinic acid and DCC in the presence of a catalytic amount of DMAP. The desired compound 3-*O*-Lev **3** was afforded in 73% yield, at the same time 2-*O*-Lev product **4** (12%) and 2, 3-di-*O*-Lev **5** (8%) were also isolated from the reaction mixture.

NIS-TMSOTf mediate coupling of ethyl 2, 3, 4-tri-*O*-acetyl-1-thio-α-L-rhamnopyranoside with **3** and **4** gave corresponding **6** and **7**. The two diosgenyl disaccharides were transformed into corresponding diosgenyl 2, 3, 4-tri-*O*-acetyl-α-L-rhamnopyranosyl-(1→2)-3-*O*-levulinoyl-β-D-glucopyranoside and diosgenyl 2,3,4-tri-*O*-acetyl-α-L-rhamno-pyranosyl-(1→3)-2-*O*-levulinoyl-β-D-gluco-pyranoside. Treatment of the two intermediates with sodium methoxide, followed by neutralization with Dowex-50W (H^+) ion-exchange resin gave ophipogonin C′ (A) and polyphyllin C (B) in the yields of 87% and 89% respectively (**Scheme 1**) .

Scheme 2



Reagents and conditions: a. 80% HOAc, 70℃, 81%; b. TBDMSiCl, imidazole, DMAP, DMF, 94%; c. (1). Ac_2O-pyridine, (2). CAN, MeOH, 78% two steps; d. $BF_3{\cdot}Et_2O$, CH_2Cl_2, -40℃ under N_2, 69% for **11**, 75% for **12**; e. 80% HOAc, 70℃, 95%; f. MeONa-MeOH, 92% for C and 89% for D.

With compound **5** in hand, diosgenyl α-L-rhamnopyranosyl-(1→6)-β-D-glucopyranoside (D) and DRG (C) were synthesized (**Scheme 2**). **5** was turned into **8** in a yield of 81%. Treatment **8** with TBDMSiCl and imidazole furnished **9** in a yield of 94%. Acetylation of **9** and then treatment with CAN produced **10** in a yield of 78% overall two steps**.** Glycosylation of **9** and **10** with 2, 3, 4-tri-*O*-acetyl-L-rhamnopyranosyl trichloroacetimidate provided protected diosgenyl disaccharides **11** and **12** in yields of 75% and 69% respectively. The TBDMS group of **11**was removed within 30 minutes in 95% yield. Removal of all the acyl groups with 1mol/L sodium methoxide, D and DRG were obtained in yields 89% and 92% respectively.

Acknowledgment

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References and Notes

1. a). S. B. Mahato, A. N. Ganguly, N. P. Sahu, *Phytochemistry,* **1982**, *21*, 959.
   b). T. Ikeda, J. Ando, A. Miyazono, X. H. Zhu, *et al., Biol. Pharm. Bull*., **2000**, *23*, 364.
   c). L. C. Chang, T. R.Tsai, J. J. Wang, *et al., Biochem. Biophys. Res. Commun.*, **1998,** *242*, 21.
2. S. G. Sparg, M. E. Light, J. van Staden, *Journal of Ethnopharmacology*, **2004**, *94*, 219
3. Y. Watanabe, S. Sanada, A. Tada, J. Shoji, *Chem. Pharm. Bull.,* **1977**, *25*, 3049.
4. S. B. Singh, R. S. Thakur, H. R. Schulten, *Phytochemistry*, **1982**, *21*, 2925.
5. a). T. Kawaskai, T. Yamauchi, *Chem. Pharm. Bull.,* **1968**, *16*, 1070.
   b). T. R. Seshadri, S. Vydeeswaran, *Indian J. Chem*., **1972**, *10*, 377.
   c). O. Espejo, J. C. Llavot, H. Jung, and F. Giral, *Phytochemistry,* **1982**, *21*, 413
6. S. L. Wang, B. Cai, C. B. Cui, *et al*., *J. of Asian Nat. Prod.Res.*, **2004**, *6*, 115.
7. C. C. Zou, S. J. Hou, Y. Shi, P. S. Lei, X. T. Liang, *Carbohy. Res.*, **2003**, *338,* 721.
8. S. J. Hou, C. C. Zou, P. S. Lei, D. Q.Yu, *Chin.Chem. Lett*., **2005**, in press.
9. C. Li, B. Yu, M. Liu, Y. Hui, *Carbohy. Res.*, **1998**, *306*, 189.
10. Data of compound **A** was deposited in editorial office of CCL.
11. Spectral data of compounds **B** to **D**:
    Compound **B**: Mp: 189-192℃, (lit [4]185-190℃), $[\alpha]_D^{25}$ -98.5 (c 1.5, pyridine), [lit[4][$\alpha]_D^{25}$ -102 (c 0.6, pyridine)]. ^{1}H-NMR (400MHz, pyridine-d_5, δ ppm): 6.36(s, 1H), 5.27(d, 1H, J= 4.4Hz, H-6), 5.13-5.09(m, 1H), 4.93(d, 1H, J=8.0Hz, H-1′), 4.81(d, 1H, J=2.0Hz), 4.62-4.59 (dd, 1H, J=3.2, 9.2Hz), 4.53-4.34(m, 5H), 4.27(t, 1H, J=9.2Hz), 3.90-3.83(m, 2H), 3.58(brs, 1H), 3.55(m, 1H), 3.47(m, 1H), 2.64(m, 1H), 2.33(m, 1H), 2.05-1.99(m, 2H), 1.73(d, 3H, J=6.4Hz, H-6″), 1.12(d, 3H, J=6.8Hz), 0.84(s, 3H), 0.80(s, 3H), 0.67(d, 3H, J=4.8Hz). ^{13}C-NMR (400MHz, pyridine-d_5, δ ppm): 140.67, 121.75, 109.21, 102.84, 102.21, 83.22, 81.04, 78.37, 78.02, 75.75, 74.15, 72.71, 72.59, 69.82, 69.48, 66.79, 62.79, 62.41, 56.55, 50.14, 41.90, 40.38, 39.79, 39.07, 37.34, 36.95, 32.18(2×C, overlap), 31.74, 31.55, 30.55, 30.08, 29.21, 21.04, 19.33, 18.71, 17.31, 16.34, 15.03. FAB-MS: *m/z* 745(M+Na)，HRFAB-MS: *m/z* 745.4171 $(M+Na)^+$ (calcd. for $C_{39}H_{62}O_{12}Na$, 745.4138). Compound **C**: Mp: 230-233℃, (lit[5] 230-231℃), $[\alpha]_D^{25}$ -92.40 (c 1.0, pyridine), [lit[5] $[\alpha]_D^{25}$ -89 (c 0.93, pyridine)]. ^{1}H-NMR (400MHz, pyridine-d_5, δ ppm): 5.89(s, 1H), 5.29(d, 1H, J=4.0Hz, H-6), 5.01(m, 1H), 4.93(d, 1H, J=7.6Hz, H-1′), 4.69(brs, 1H), 4.58-4.43(m, 3H), 4.34(t, 1H, J=9.6Hz), 4.26-4.19(m, 2H), 4.13-4.10(t, 1H, J=12.4Hz), 3.97(t, 1H, J=8.0Hz), 3.83(m, 1H), 3.72(d, 1H, J=10.2Hz), 3.55(brs, 1H), 3.45(m, 1H), 2.70(m, 1H), 2.43(m, 1H), 2.07-1.92(m, 4H), 1.72(d, 3H, J=6.4Hz, H-6″), 1.13(d, 3H, J=7.2Hz), 0.89(s, 3H), 0.81(s, 3H), 0.67(d, 3H, J=4.2Hz). ^{13}C-NMR (400MHz, pyridine-d_5, δ ppm): 140.85, 121.73, 109.24, 102.68, 102.44, 81.07, 78.25, 78.19, 75.13, 76.70, 75.53, 74.00, 72.82, 72.63, 70.35, 66.84, 62.87, 61.50, 56.53, 50.25, 41.95, 40.44, 39.85, 39.28, 37.42, 37.03, 32.24, 32.17, 31.79, 31.62, 30.58, 30.18, 29.24, 21.10, 19.38, 18.54, 17.31, 16.35, 15.02 FAB-MS: *m/z* 745(M+Na) HRFAB-MS: *m/z* 745.4163 $(M+Na)^+$ (calcd. for $C_{39}H_{62}O_{12}Na$, 745.4138). Compound **D**: ^{1}H-NMR (400MHz, pyridine-d_5, δ ppm): 5.15(brs, 1H, H-1″), 5.31(d, 1H, J=4.0Hz, H-6), 4.97(d, 1H, J=7.6Hz, H-1′), 4.64-4.48(m, 4H), 4.38-4.32(m, 1H), 4.25-4.17(m, 3H), 4.07-3.99 (m, 3H), 3.94-3.88(m, 1H), 3.58-3.45(m, 2H), 2.66-2.63(m, 1H), 2.43(m, 1H), 2.22(m, 1H), 1.99-1.89(m, 2H), 1.62(d, 3H, J=6.0Hz, H-6″), 1.12(d, 3H, J=6.8Hz), 0.87(s, 3H), 0.80(s, 3H), 0.68(d, 3H, J=4.8Hz); ^{13}C-NMR (400MHz, pyridine-d_5, δ ppm): 140.97, 121.58, 109.23, 103.04, 102.45, 81.08, 78.85, 78.59, 76.92, 75.22, 74.02, 72.76, 72.31, 71.81, 69.74, 68.21, 66.84, 62.88, 56.56, 50.14, 41.94, 40.41, 39.84, 39.47, 37.43, 37.00, 32.21, 32.16, 31.79, 31.61, 30.57, 30.39, 29.23, 21.06, 19.38, 18.66, 17.31, 16.33, 15.03. HRMS: calcd. for $C_{39}H_{62}O_{12}Na$ $(M+Na)^+$ 745.4138, found: 745.4176.

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