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A Facile Synthetic Approach to a Group of Structurally Typical Diosgenyl Saponins

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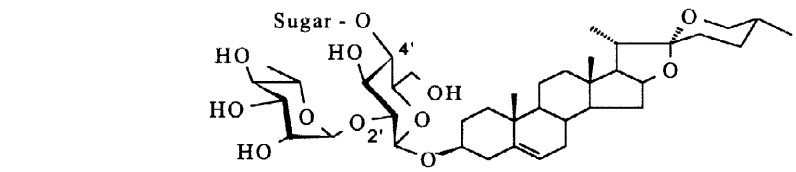
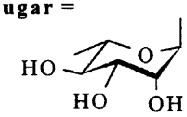
Abstract: A facile approach was developed for synthesizing an important group of plant diosgenyl saponins, three members (dioscin, polyphyllin D, and balanitin 7) with promising bioactivities were prepared.

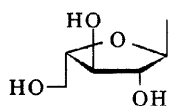
Saponins constitute a structurally and biologically diverse class of natural products,[1] which have recently been paid great attention due to the ever-expanding knowledge into their pharmacological significance.[2] From the viewpoint of their structure, saponins are glycosides of steroids or triterpenes, the aglycones are characteristic of the plant species and the sugar patterns are, although diverse, characteristic of the aglycone.[1] Diosgenyl saponins are the most abundant existing steroid saponins. Structurally, most of the members can be regarded to be derivatives from diosgenyl β-D-glucopyranoside (trillin), if containing a sugar chain longer than disaccharide, with an α-L-rhamnopyranose substituted at 2'-OH and a further glycosylation at 4'-OH or at 3'-OH.[1] Herein, we report a facile approach to the 4'-OH glycosylated diosgenyl saponins, three of which (**1-3**) were synthesized. Saponin **1** (dioscin) exists widely in the plant kingdom including many species intensively used in traditional Chinese herb medicine, which demonstrates cardiovascular and antifungal activities.[3] Saponin **2** (polyphyllin D) has been isolated from *Paris polyphylla* and other species, showing very promising cardiovascular and cytotoxic activities.[4] Saponin **3** (balanitin 7) is one of the cytotoxic saponins purified from the African medicinal plant *Balanites aegyptica*.[5]



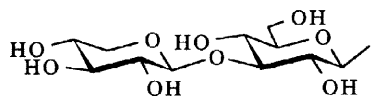
Sugar =



1 (dioscin)



2 (polyphyllin D)



3 (balanitin 7)

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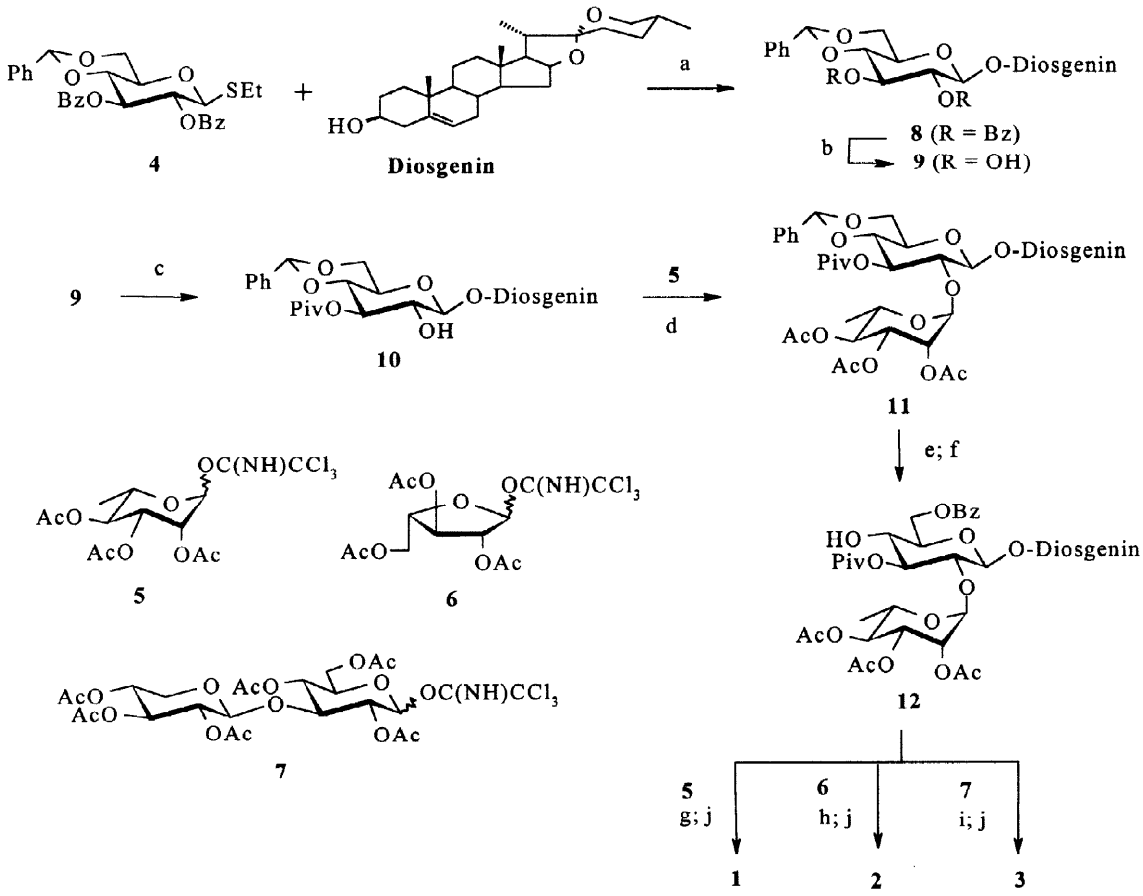
PII: S0040-4039(98)01354-9

A key to assembling a saponin is the construction of the glycosidic bond between the sugar moiety and the triterpene or steroid. Consequently, two basic strategies can be applied; one is to fabricate the sugar part first then attach it to the aglycone, [6] the other is to connect the first monosaccharide unit to the aglycone first, then manipulate the protecting pattern on the sugar moiety and extend the sugar chain sequentially. [7] Employing the second strategy, the formation of the glycosidic bond between the sugar and aglycone can be stereospecific and high yielding and a group of saponins with a common aglycone but different sugar patterns can be convergently synthesized. Saponins **1**, **2**, and **3**, three members of an important group of plant saponins, are thus synthesized as shown in Scheme 1.



Scheme 1. Reagents and Conditions: a) NIS/AgOTf, CH_2Cl_2, 4 Å MS, Ar, -20 °C, 30 min, 50%; b) NaOMe, $MeOH/CH_2Cl_2$, 50 °C, overnight, 85%; c) PivCl, Py, 0 °C, 2 h, 64 %; d) BF_3OEt_2, CH_2Cl_2, 4 Å MS, Ar, 0 °C, 30 min, 100 %; e) TsOH (cat.), CH_2Cl_2/MeOH, rt, 2 h, 80 %; f) BzCl, Py, 0 °C, 2 h, 75 %; g) condition d, 89%; h) condition d, 93%; i) condition d, 31 % (65 % **11** recovered); j) NaOH, THF/ $MeOH/H_2O$, 50 °C, 2 h, 100 % for **1**, 85 % for **2**, 75 % for **3**.

Glycosylation of diosgenin with thioglycoside **4** [8] under the promotion of NIS/AgOTf provided **8** stereospecifically in 50% yield, removal of the two benzoyl protecting groups on **8** gave diol **9**. The 2'-OH and 3'-OH of **9** were very difficult to selectively protect.[7] Finally a Piv group was conveniently put on the 3'-OH to afford **10** in 64% yield, only trace of 2'-O-Piv and 2', 3'-di-O-Piv products being detected. Glycosylation of **10** with imidate donor **5** [9] afforded the corresponding disaccharide **11** quantitatively. Removal of the benzylidene protection with a catalytic amount of TsOH followed by selective protection of the primary 6'-OH with a benzoyl group afforded the key intermediate **12**, which is, with only 4'-OH free, ready for the subsequent glycosylation to provide the aforementioned important group of diosgenyl saponin. Herein, glycosylation of **11** with peracetyl protected trichloroacetimidate donors **5**, [9] **6**, [10] and **7** [11] readily provided the corresponding fully protected saponins. Treatment of the acyl protected saponins with NaOH afforded the target saponin **1-3** in high yields, which gave identical analytical data with those reported.[12]

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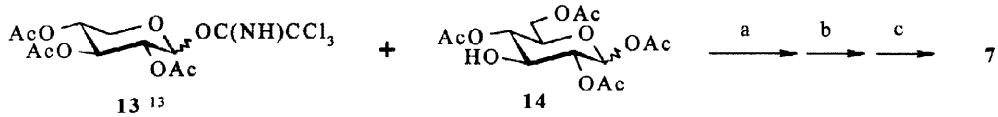
References and Notes:

1. Hostettmann, K.; Marston, A. *Saponins;* Cambridge University Press, **1995**.
2. Rouhi, A. M. *C & EN*, **1995**, Sept. 11, 28.
3. a) Nakano, K; Murakami, K.; Takaishi, Y.; Tomimatsu, T.; Nohara, T. *Chem. Pharm. Bull.* **1989**, 37, 116; b) Hufford, C. D.; Liu, S.; Clark, A. M. *J. Nat. Prod.* **1988**, 51, 94. c) Hirai, Y.; Sanada, S.; Ida, Y.; Shoji, J. *Chem. Pharm. Bull.* **1984**, 32, 295. d) Liu, C.; Chen, Y. *Acta Pharmaceutic Sinica.* **1984**, 19, 799. e) Fang, Y.; Zhao, J.; Ho, Y.; Li, B.; Xu, C. *Acta Pharmaceutic Sinica.* **1982**, 17, 388. f) Tschesche, R.; Pandey, V. B. *Phytochemistry,* **1978**, 17, 1781.
4. a) Ma, J, C. N.; Lau, F. W. *Phytochemistry,* **1985**, 24, 1561. b) Namba, T.; Huang, X.; Shu, Y.; Huang, S.; Hattori, M.; Kakiuchi, N.; Wang, Q.; Xu, G. *Planta Medica*, **1989**, 55, 501. c) Zhou, J. *Pure. Appl. Chem.* **1989**, 61, 457.
5. Pettit, G. R.; Douber, D. L.; Herald, D. L. *J. Nat. Prod.* **1991**, 54, 1491.
6. a) Liu, M.; Yu, B.; Hui, Y. *Tetrahedron Lett.* **1998**, 39, 415. b) Liu, M.; Yu, B.; Guo, Z.; Li, C.; Hui, Y. *Carbohydr. Lett.* **1997**, 2, 423.
7. Li, C.; Yu, B.; Liu, M.; Hui, Y. *Carbohydr. Res.* **1998**, in press.
8. Bochkov, A. F.; Jain, A. C. *Izv. Akad. Nuuk. SSSR, Ser. Chim.* **1968**, 1, 179.
9. Kitagawa, I.; Back, N. I.; Ohashi, K.; Sakagami, M.; Yoshikawa, M.; Shibuya, *Chem. Pharm. Bull.* **1989**, 37, 1131.

10. Donor **6** was readily prepared from 1,2,3,5-tetra-O-acetyl-L-arabinofuranose, Backinowsky, L. N.; Nepogod'ev, S. A.; Shashkov, A. S.; Kochetkov, N. K. *Carbohydr. Res.* **1985**, 138, 41.
11. Donor **7** was prepared as shown in the following scheme:



Reagents and Conditions: a) BF_3OEt_2, CH_2Cl_2, 4A MS, 0 °C, 0.5 h, 100%; b) NH_2NH_2-HOAc, DMF, 50 °C, 0.5 h, 73%; c) CCl_3CN/DBU, CH_2Cl_2, rt, 0.5 h, 96%.

12. All compounds gave satisfactory analytical data, including ^{1}H NMR, MS, and elemental analysis. Selected data: **10**: $[\alpha]_D^{20}$ = -91.9 (*c* 0.48 $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.5-7.3 (5H, m), 5.52 (1H, s, PhCH), 5.39 (1H, d, J = 4.7 Hz, H-6), 5.20 (1H, t, $J_{2',3'} = J_{3',4'}$ = 9.3 Hz, H-3'), 4.59 (1H, d, $J_{1',2'}$ = 7.7 Hz, H-1'), 4.40 (1H, m, H-16), 4.36 (1H, dd, $J_{5',6'a}$ = 4.7 Hz, $J_{6'a,6'b}$ = 10.6 Hz, H-6'a), 3.80 (1H, t, H-6'b), 3.67 (1H, t, $J_{4',5'}$ = 9.6 Hz, H-4'), 3.6-3.3 (5H, m, H-3, H-26, H-2', H-5'). **11**: $[\alpha]_D^{20}$ = -61.9 (*c* 1.41 $CHCl_3$); ^{1}H MNR ($CDCl_3$): 7.4-7.2 (5H, m), 5.44 (1H, s), 5.44-5.36 (2H, m), 5.21 (1H, dd, $J_{2'',3''}$ = 3.3 Hz, $J_{3'',4''}$ = 9.9 Hz, H-3''), 5.16 (1H, dd, $J_{1'',2''}$ = 1.5 Hz, H-2''), 5.03 (1H, t, $J_{4'',5''}$ = 10 Hz, H-4''), 4.90 (1H, d, H-1''), 4.72 (1H, d, $J_{1'',2''}$ = 7.7 Hz, H-1'), 4.48-4.30 (2H, m), 3.80-3.30 (7H, m), 2.09, 2.01, 1.95 (3×3H, 3×s), 1.20 (3H, d, J = 6.1 Hz), 1.12 (9H, s). **12**: $[\alpha]_D^{20}$ = -26.8 (*c* 1.9 $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 8.1-7.3 (5H, m), 5.34 (1H, d, J = 4.9 Hz, H-6), 5.20 (2H, m, H-2'', H-3''), 5.12-5.0 (2H, m, H-4'', H-3'), 4.97 (1H, s, H-1''), 4.60 (3H, m, H-1', H-6'), 4.50-4.40 (2H, m, H-5'', H-16), 3.76 (1H, t, H-2', J = 7.9 Hz), 3.70-3.44 (4H, m, H-3, H-26, H-4', H-5'), 3.37 (1H, t, H-26, J = 10.8 Hz), 2.11, 2.02, 1.96 (3×3H, 3×s, 3×Ac), 1.18 (9H, s, Me_3CCO). **1**: $[\alpha]_D^{20}$ = -113.6 (*c* 1.1 MeOH), Lit.[3a]: $[\alpha]_D$ = -121 (*c* 1.0 MeOH). **2**: $[\alpha]_D^{20}$ = -116.3 (*c* 0.52 MeOH), Lit.[4a]: $[\alpha]_D^{24}$ = -113 (*c* 0.53 MeOH). **3**: $[\alpha]_D^{16}$ = -84.6 (*c* 0.80 pyridine), Lit.[5]: $[\alpha]_D^{20}$ = -83 (*c* 0.83 pyridine).
13. Mori, M.; Ito, Y.; Ogawa, T. *Carbohydr. Res.* **1990**, 195, 199.