Chemical Intertransformations of Diverse Bisdesmosidic Furostanol Saponins

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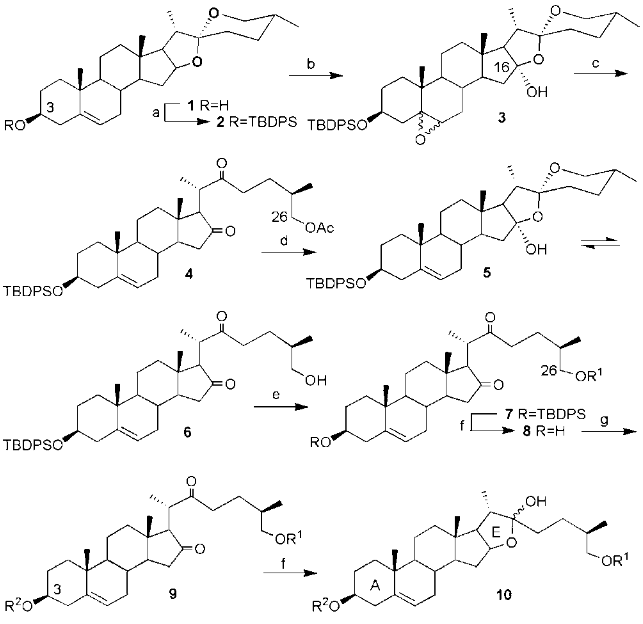
An effective synthetic route towards four types of bisdesmosidic furostanol saponin was developed and 36 derivatives were designed and synthesized for antitumor investigation. The chemical intertransformations of these furostanol structures were discussed with respect to the E ring.

In recent years, furostanol saponins have been found out owning a broad range of promising biological property, including antitumor activity.[1] Chemical synthesis of this kind of structure draws many scientists' attentions.[2]

Retrosynthetically, furostanol saponins can be logically divided into three readily accessible building blocks: a parent aglycone and two parts of sugar moieties, which are generally an oligosaccharide chain connecting to C3–OH and a monosaccharide linking with C26–OH, respectively. In addition, the modification in the E ring results in the key structural diversification.

In order to explore the structure–activity relationships (SARs) of these interesting chemical structures for further antitumor study, we designed a series of non-natural analogues with simple skeletons as structural templates of furostanol saponins. Three types of sugars (β-D-glucose, α-L-rhamnose, and β-D-xylose) were used as donors in the form of trichloroacetimidate.[3] Applying to proper protective strategy and Schmidt's *O*-glycosylation method,[3] we introduced diverse monosaccharide to the synthetic aglycone to prepare various bisdesmosidic saponins. The modification in the E ring of the aglycone furnished four types of furostanol saponins, namely protodioscin-type, methylprotodioscin-type, ethylprotodioscin-type, and corresponding pseudodiosgenin-type derivatives.

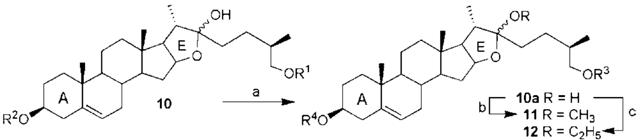
Based on our former method,[4] the protodioscin-type furostanol saponins were synthesized as shown in Scheme 1. The starting material diosgenin **1** was protected first by TBDPSCl. The silyl ether of diosgenin **2** was converted into the 5,6-epoxy-16α-hydroxy diosgenin **3** in the system of oxone–acetone, which directly underwent reductive cleavage of the epoxide by Zn/KI to regenerate the $\Delta^{5,6}$ double bond. Meanwhile, the diketone acetate **4** was obtained in one-pot under a mild condition. Removal of the 26-*O*-acetyl group treated with K_2CO_3 afforded a mixture of spiroketal **5** and dione **6**. The mixture was directly treated with one of the three sugar donors in the presence of catalytic amount of trimethylsilyl trifluoromethanesulfonate (TMSOTf) to furnish 26-*O*-glycosylated product **7**. The silyl protective group was removed by tetrabutylammonium fluoride (TBAF) to give compound **8**, which was subjected to the glycosylation once again under the same condition mentioned above to afford the bisdesmosidic saponins **9**. After the selective reduction of C16–carbonyl with KBH_4, the intramolecular hemiketal was spontaneously formed to provide the furostanol structure **10** (total 9 compounds).



R^1, R^2 = perbenzoyl protected monosaccharide

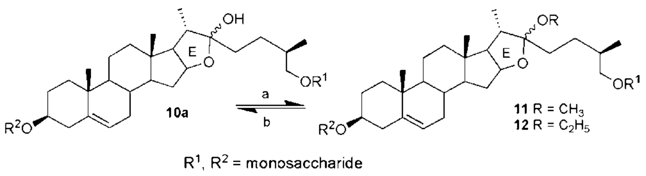
Scheme 1. (a) TBDPSCl, imidazole, CH_2Cl_2, rt, 12 h, 93%; (b) oxone, $NaHCO_3$, CH_3COCH_3, H_2O, CH_2Cl_2, rt, 24 h; (c) Zn, KI, AcOH, Ac_2O, rt, 24 h, 65% (for two steps); (d) K_2CO_3, THF, MeOH, 40 °C, 4 h; (e) Sugar donor, TMSOTf, CH_2Cl_2, 4 Å MS, 0 °C–rt, 2 h, 61–71%; (f) TBAF, THF, 4 Å MS, rt, 6 h, 72–78%; (g) Sugar donor, TMSOTf, CH_2Cl_2, 4 Å MS, 0 °C–rt, 2 h, 80–85%; and (h) KBH_4, isopropanol, CH_2Cl_2, H_2O, rt, 8 min, 73–78%.

In the solution of MeONa (0.1 M) in absolute MeOH, the benzoyl protective groups on the sugar moieties were readily removed to generate **10a**. However, when using the cation-exchange resin to neutralize the solution, we found that the C22–OH was converted into C22–OMe **11** quantitatively 30 min later. Actually, the latter compounds had been preponderating when the pH of the solution just decreased to 7 (Scheme 2). This operation applied an alternative way to prepare the methylprotodioscin-type saponin easier than the reported refluxing condition of methanol.[4]



R^1, R^2 = perbenzoyl protected monosaccharide
R^3, R^4 = monosaccharide

Scheme 2. For **11** (a) MeONa, MeOH, rt, 2 h; and (b) Dowex 50 (H^+), rt, 0.5 h; for **12** (a) EtONa, EtOH, rt, 2 h; and (c) Dowex 50 (H^+), rt, 0.5 h.



Scheme 3. (a) For **11**, MeOH, reflux, 24 h; for **12**, EtOH, reflux, 24 h; and (b) CH_3COCH_3, H_2O (1:1, v/v), reflux, 24 h.

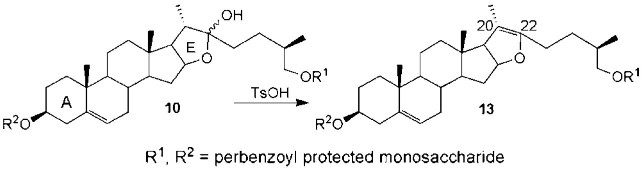
By this means, we achieved great successes in preparing another type of furostanol glycosides. Removal of benzoyl groups on the sugar moieties in the basic solution of EtONa (0.1 M) in absolute EtOH, followed by the neutralization with Dowex 50 (H^+) resin for half an hour, resulted in the ethylprotodioscin **12** (Scheme 2). However, there was no any change occurring in the case of treating **10** with the solution of *i*-PrONa in *i*-PrOH, even though the concentration of the base increased to 1 M and the stirring continued for 72 h.

We did not gain the protodioscin-type compounds with satisfying purity in the process mentioned above because ketal was always the major component in the presence of H^+-type exchange resin. According to the literatures,[5] there lies in an intertransformation between the protodioscin and methylprotodioscin. We verified this presentation in our subject and found that compound **11** or **12** was converted to its hemiketal form **10a** in aqueous acetone under a reflux condition. The reaction time was depended on the ratio of acetone to water. Using the reported 70% acetone, **10a** was completely formed 48 h later. When 50% acetone was applied, the transformation was completed in 24 h. Conversely, the protodioscin compound also turned to different ketal product (**11** or **12**) in different refluxing solvent (Scheme 3).

Several investigations[7] revealed the cytotoxic property of pseudodiosgenin (an opened F ring structure), which was commonly prepared via acid hydrolysis of diosgenin.[8] In view of the similarity in skeleton with the aforementioned three types of saponins, we were inspired to find an alternative way to generate the $\Delta^{20,22}$ unsaturated derivates. Although, dehydration of hemiketal has been well documented,[6] we attempted several methods to form the $\Delta^{20,22}$ double bond and avoid affecting the glycosyl bond. Catalyzed by TsOH, the C22–OH of **10** was eliminated to produce the $\Delta^{20,22}$ unsaturated compound **13**. This reaction was highly influenced by solvents and conditions. As shown in Table 1, the higher temperature was necessary for dehydration while a mild condition was favorable for maintaining the glycosyl bonds. Therefore, we performed this reaction on a rotary vaporizer under a 70 °C water bath. The water generated was distilled out of the reactive system at once under the reduced pressure, which pushed the reaction in progress. In this way, compound **13** was generated in the solvent of DMF or isoquinoline in half an hour with a moderate yield.

In summary, the chemically structural templates for four types of bisdesmosidic furostanol saponins were designed and synthesized. Using three glycosyl trichloroacetimidates as sugar donors, we prepare 9 saponins in each form.[9] Thus, a small library including total 36 basically structural furostanol saponins was set up. The investigation of antitumor activity is in progress and will be reported in due course.

Table 1. Conversion of protodioscin-type furostanol saponin **10** to corresponding pseudodiosgenin-type structure **13**



Solvent	Reaction condition	Yield/%
THF	rt, 0.5–5 h	15
THF	reflux, 0.5–5 h	21
DMF	70 °C, 0.5–3 h	38
DMF	70 °C, 0.5 h, in vacuo	71
DMF	70 °C, 1 h, in vacuo	59
Isoquinoline	70 °C, 0.5 h, in vacuo	73

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References and Notes

1 a) T. Ohtsuki, M. Sato, T. Koyano, T. Kowithayakorn, N. Kawahara, Y. Goda, M. Ishibashi, *Bioorg. Med. Chem.* **2006**, *14*, 659. b) S. Piacente, C. Pizza, W. Oleszek, *Phytochem. Rev.* **2005**, *4*, 177. c) V. Lanzotti, *Phytochem. Rev.* **2005**, *4*, 95.

2 a) S. Hou, P. Xu, L. Zhou, D. Yu, P. Lei, *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2454. b) R. Suhr, M. Lahmann, S. Oscarson, J. Thiem, *Eur. J. Org. Chem.* **2003**, *2003*, 4003. c) M. Lahmann, H. Gyback, P. J. Garegg, S. Oscarson, R. Suhr, J. Thiemb, *Carbohydr. Res.* **2002**, *337*, 2153.

3 R. R. Schmidt, in *Modern Methods in Carbohydrate Synthesis*, ed. by S. H. Khan, R. A. O'Neill, Harwood Academic Publishers GmbH, Chur, **1996**, pp. 20–54.

4 M. S. Cheng, Q. L. Wang, Q. Tian, H. Y. Song, Y. X. Liu, Q. Li, X. Xu, H. D. Miao, X. S. Yao, Z. Yang, *J. Org. Chem.* **2003**, *68*, 3658.

5 a) Y. Ding, C. Yang, *Acta Pharmacal. Sinaca* **1990**, *25*, 509. b) T. Konishi, J. Shoji, *Chem. Pharm. Bull.* **1979**, *27*, 3086.

6 a) T. Gan, J. M. Cook, *J. Org. Chem.* **1998**, *63*, 1478. b) M. G. Kulkarni, R. M. Rasne, *Synthesis* **1997**, 1420.

7 a) H. J. Quan, J. Koyanagi, K. Hagiwara, X. R. Cui, Y. Isshiki, S. Kondo, F. Komada, S. Saito, *Chem. Pharm. Bull.* **2006**, *54*, 72. b) X. He, A. Qiao, B. Liu, X. Wang, G. Wang, G. Qu, R. H. Liu, X. Yao, *Enzyme Microb. Technol.* **2006**, *38*, 400. c) H. J. Quan, J. Koyanagi, K. Ohmori, S. Uesato, T. Tsuchido, S. Saito, *Eur. J. Med. Chem.* **2002**, *37*, 659.

8 a) J. S. Lee, P. L. Fuchs, *Org. Lett.* **2003**, *5*, 3619. b) M. E. Wall, C. R. Eddy, S. Serota, *J. Am. Chem. Soc.* **1954**, *76*, 2849. c) R. E. Marker, R. B. Wagner, P. R. Ulshafer, E. L. Wittbecker, D. P. J. Goldsmith, C. H. Ruof, *J. Am. Chem. Soc.* **1947**, *69*, 2167.

9 The four types of aglycone structures were confirmed by ^{13}C NMR spectra. Selected characteristic data (150 MHz, pyridine-d_5, ppm) were listed as following: for **10a** δ 110.7 (C22); for **11** δ 112.7 (C22), 47.3 (OCH_3); for **12** δ 112.6 (C22), 51.1 ($O\underline{C}H_2CH_3$), 16.1 ($OCH_2\underline{C}H_3$); for **13** δ 152.5 (C22), 103.6 (C20). In ^{1}H NMR spectra of the synthetic saponins, the β-configuration of the anomeric carbons of all glucosyl and xylosyl units were determined by the $J_{H1\text{-}H2}$ values ($J_{H1\text{-}H2} = 7.5$–7.8 Hz), while the $J_{H1\text{-}H2}$ values ($J_{H1\text{-}H2} = 1.0$–1.2 Hz) of all rhamnosyl units indicated the α-configuration of their anomeric carbons.