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An Improved Synthesis of Methyl Protodioscin. II. A Direct E-ring Opening by BF_3–Et_2O/Ac_2O from Dioscin Ester

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A direct E-ring opening of dioscin ester by BF_3–Et_2O/Ac_2O was studied, and methyl protodioscin was synthesized from dioscin ester in three steps with a total yield of 44%. The details of the E-ring opening reaction was discussed, and a prominent stability of C16–OAc was obversed.

Methyl protodioscin (**1**, Figure 1), a representative natural furostanol saponin, has received increasing attentions due to its potential anticancer activity.[1–3] Because of its relative scarcity from nature, scientists are attemping to synthesize this furostanol saponin.

Retrosynthetically, this bisglycoside can be divided into three parts: a furostanol aglycone and two sugar moieties. In the synthesis of methyl protodioscin, there are two difficulties that we have to overcome: constructing the furostanol stuctrure efficiently and adding the chacotriose at the C3–OH of the aglycone in the naturally occurring configuration. In our first attempt,[4] a convergent strategy was applied. In the glycosylation via a chacotriosyl thioglycoside, the right β-configuration was confirmed though the lack of a neighboring participatory group. In the subsequent work,[5] direct access to the 3-*O*-substituted kryptogenin from dioscin ester was established, and this new synthesis saved one deprotection step compared with the former method. Even with the elimination of this step, this new method still involved five steps—DMDO oxidation, Zn/KI/HOAc reduction, glycosylation, $NaBH_4$ selective reduction, and deprotection—starting from dioscin ester to synthesize methyl protodioscin, with a total yield lower than 20% (Figure 2). Obviously, this synthetic route is inefficient. Herein we report a highly efficient synthetic route for methyl protodioscin in which the key step is direct E-ring opening by BF_3–Et_2O/Ac_2O. This synthesis represents a new method to construct furostanol aglycones.

As shown in Scheme 1, dioscin ester **5** was prepared from diosgenin. First, a perbenzoylated glucosyl trichloroacetimidate was introduced onto the C3–OH of diosgenin. This reaction guaranteed that the linkage between the aglycone and the sugar moiety would be in the β orientation due to the neighboring participatory benzoyl group.[6] After a global deprotection, the 3,6-diol of the glucose was selectively shielded by pivaloyl,[7] followed by the introduction of two benzoylated rhamnose moieties onto the two remaining free hydroxy groups.

As shown in Scheme 2, the E-ring in compound **5** was directly opened by a combination of BF_3–Et_2O and acetic anhydride in dichloromethane, followed by glycosylation with perbenzoylated glucose trichloroacetimidate to give the important bisglycoside intermediate **8**. Once C16–OAc in **8** was deprotected under basic conditions, the newly formed hydroxy group automatically attacked the C22-carboyl group to produce

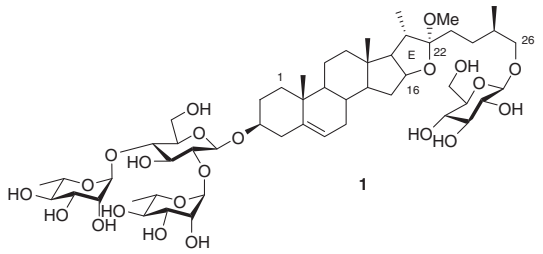


Figure 1. The chemical structure of methyl protodioscin.

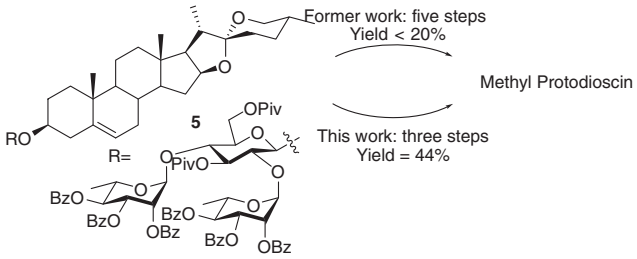
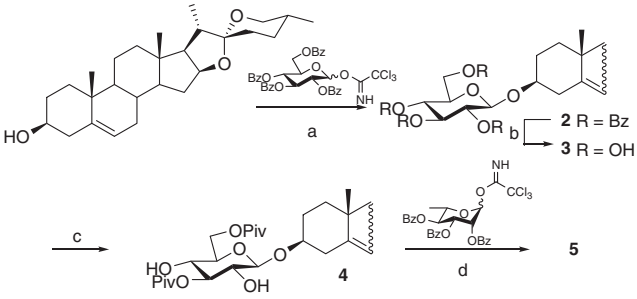


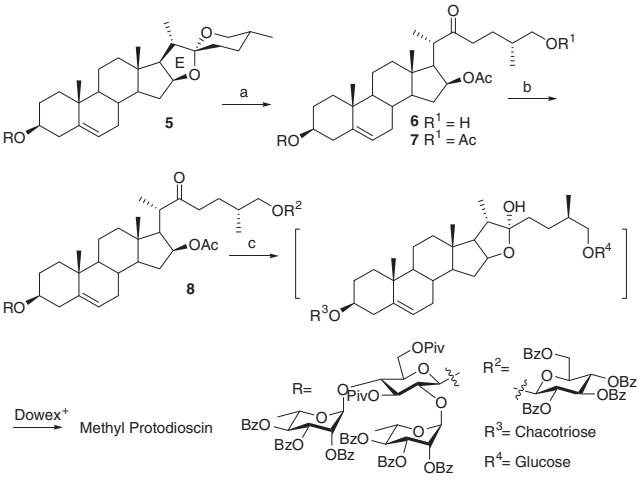
Figure 2. An improved method toward methyl protodioscin.



Scheme 1. (a) TMSOTf, CH_2Cl_2, 0 °C, 1 h, 92%; (b) NaOMe, MeOH–CH_2Cl_2, 1 h; (c) PivCl, pyridine, 6 h, 0 °C, 75% over two steps; (c) TMSOTf, CH_2Cl_2, r.t., 3 h, 79%.

a C22–OH furostanol saponin. As reported,[8] when cation-exchange resin was used to neutralize the solution, C22–OH was converted into C22–OMe, yielding methyl protodioscin. The analytical data, including MS, optical rotation, ^1H and ^{13}C NMR data, for the synthesized methyl prododioscin were identical to those of the natural product.[9,12]

As a key step in this synthesis, direct E-ring opening allows the efficient conversion of the spirostanol into a cholesteric structure, which was then converted into the corresponding protodioscin via an automatic cyclization during deprotection. The effects of two key factors, 1) the amounts and ratio of BF_3–



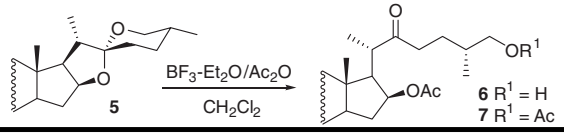
Scheme 2. (a) BF_3–Et_2O/Ac_2O, CH_2Cl_2, 0 °C, 10 min, then 30% MeOH in water, 30 min, 75%; (b) glucose imidate, TMSOTf, CH_2Cl_2, r.t., 83%; (c) NaOMe, MeOH, reflux, 24 h, then Dowex 50 (H^+), r.t., 15 min, 71%.

Et_2O/Ac_2O and 2) the reaction time, on this reaction were investigated. The prominent stability of 16C–OAc was observed during deprotection.

During the E-ring opening reaction of dioscin ester **5**, the function of BF_3–Et_2O and acetic anhydride is to form a complex that promotes the formation of an oxacarbenium-ion intermediate from **5**. Then, the hydrolysis of this intermediate occurs by attack at C-22 by water used in the quenching step to give **6**. It is worth noting that under these conditions, the intramolecular cyclization from the C26–OH to the C22–oxo group of **6** does not take place. Therefore, the major by-product is diacetate **7**, resulting from the acetylation of **6** by the remaining acetic anhydride. To reduce the amount of this by-product and to consume the starting material completely, the reaction time and the concentration of acetic anhydride were optimized. As shown in Table 1, the yield was not satisfactory when using the initial amounts of BF_3–Et_2O/Ac_2O (Entry 1),[10,11] leaving approximately 20% of the starting material unreacted. We assumed that the intermediate **5**, which contains a bulky protected trisaccharide on its C3–OH, was difficult to approach, and therefore, more reagent was needed. When using the same time (Entry 2), the yields of the target compound, and the by-product and the amount of remaining **5** were generally unaffected when the amount of acetic anhydride was doubled. In addition, Entry 3 demonstrates that the reaction time is a major factor affecting the proportions of **5**, **6**, and **7**. Although the prolongation of the reaction time resulted in almost complete consumption of the starting material, longer reaction times also resulted in the conversion of the desirable monoacetate **6** into the undesirable diacetate **7**. The optimal reagent amounts and reaction time were determined to be those used in Entry 4, giving a 75% yield of the desired compound.

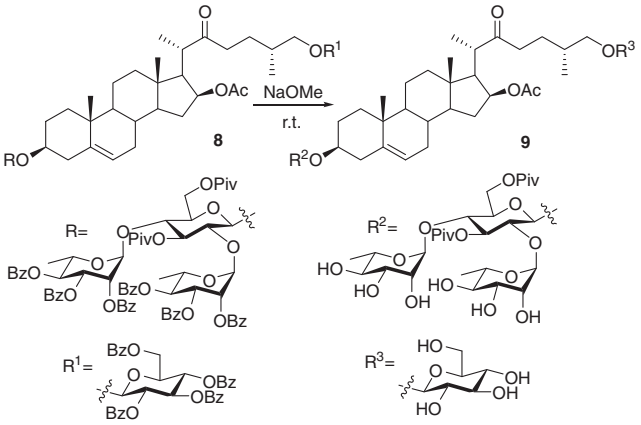
During the deprotection of **8**, an interesting phenomenon was observed. Usually the hydrolysis rates of acyl groups can be ordered from fast to slow as follows: chloroacetyl > acetyl > benzoyl > pivaloyl. However, when **8** was treated with 1 mol L^{-1} sodium methoxide in MeOH at room temperature, one single spot was observed on the TLC plate. Unfortunately, the MS and

Table 1. Direct E-ring opening by BF_3–Et_2O/Ac_2O from dioscin ester **5**[a]



Entry	BF_3–Et_2O/Ac_2O (mmol/mmol)	Time /min	Yield[b]/%		
			5	**6**	**7**
1	6.4/9.5[c]	5	22	50	20
2	6.4/19.1	5	20	51	22
3	6.4/9.5	10	9	45	35
4	12.8/19.1	5	none	75	22

[a]General reaction procedure: The mixture of BF_3–Et_2O and Ac_2O was added to an ice-cooled solution of **5** (1 mmol) in CH_2Cl_2 (5 mL). After the reaction, 30% MeOH in water (10 mL) was added, and the mixture was stirred for 30 min. [b]Yields based on purification by column chromatography. [c]Amounts taken from Refs. 10 and 11.



Scheme 3. Deprotection of **8** by 1 mol L^{-1} NaOMe in MeOH at room temperature.

^{1}H NMR data demonstrated that only the benzoyl groups in **8** were cleaved under these reaction conditions, giving **9** in an excellent yield (Scheme 3). Only when a higher temperature was used, as shown in Scheme 2, was the desired final product, methyl protodioscin, obtained.

In conclusion, a highly efficient method for the synthesis of methyl protodioscin was established with the key step of direct E-ring opening by BF_3–Et_2O/Ac_2O, followed by automatic cyclization during deprotection. The total yield (44% from dioscin ester and 24% from diosgenin as the starting material, respectively) was increased considerably relative to that reported previously.

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References and Notes

1 K. Hu, X. Yao, *Cancer Invest.* **2003**, *21*, 389.
2 G. Wang, H. Chen, M. Huang, N. Wang, J. Zhang, Y. Zhang,

G. Bai, W.-F. Fong, M. Yang, X. Yao, *Cancer Lett.* **2006**, *241*, 102.
3 M.-J. Liu, P. Y.-K. Yue, Z. Wang, R. N.-S. Wong, *Cancer Lett.* **2005**, *224*, 229.
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 Q.-C. Xu, Y. Liu, J. Liu, C.-X. He, M.-C. Yan, M.-S. Cheng, *Chem. Lett.* **2008**, *37*, 780.
6 B. Yu, J. Xie, S. Deng, Y. Hui, *J. Am. Chem. Soc.* **1999**, *121*, 12196.
7 L. Jiang, T.-H. Chan, *J. Org. Chem.* **1998**, *63*, 6035.
8 D.-M. Zhao, Y. Liu, Y.-X. Liu, L.-G. Zheng, M.-C. Yan, M.-S. Cheng, *Chem. Lett.* **2007**, *36*, 214.
9 K. Hu, A. Dong, X. Yao, H. Kobayashi, S. Iwasaki, *Planta Med.* **1996**, *62*, 573.
10 M. A. Fernández-Herrera, H. López-Muñoz, J. M. V. Hernández-Vázquez, M. López-Dávila, M. L. Escobar-Sánchez, L. Sánchez-Sánchez, B. M. Pinto, J. Sandoval-Ramírez, *Bioorg. Med. Chem.* **2010**, *18*, 2474.
11 M. A. Fernández-Herrera, H. López-Muñoz, J. M. V. Hernández-Vázquez, M. López-Dávila, S. Mohan, M. L. Escobar-Sánchez, L. Sánchez-Sánchez, B. M. Pinto, J. Sandoval-Ramírez, *Eur. J. Med. Chem.* **2011**, *46*, 3877.
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