An Improved Synthesis of Methyl Protodioscin: Tautomerization and Direct Access to the 3-O-Substituted Kryptogenin

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The acid-catalyzed tautomerization of 3-O-substituted kryptogenin **2** was studied, and the effects of acids such as silica gel, TMSOTf, acetic acid, and $CDCl_3$, are discussed. Additionally, a Zn/KI/HOAc reduction based on this tautomerization was adopted, which afforded **2** directly, and provided a facile procedure for the synthesis of methyl protodioscin and other furostanol saponins in a mild way.

Steroidal saponins are usually divided into three classes: spirostan, cholestan, and furostan. Due to their structural complexities and intrinsic instabilities, studies on furostanol saponins are still limited.[1] Methyl protodioscin (**1**, Figure 1), a representative furostanol saponin which may have a novel mechanism of anti-cancer action according to the NCI's comparative analysis, has been under study in recent years.[2,3] The total synthesis of **1** has been achieved,[4,5] and has aided further studies of this molecule. Two basic strategies have been applied to install the β-chacotriosyl at the 3-OH. In glycosylation via a chacotriosyl thioglycoside,[4] though the right β-configuration was affirmed,[6] to our knowledge, there has been no theory that could illustrate the stereoselectivity of the glycosylation of this sugar donor, because of its lack of a neighboring participatory group (a similar reaction used a 2,3-branched trisaccharide donor which afforded an α configuration[7]). To overcome this problem, a short approach via a stepwise glycosylation strategy has been adopted by Li and Yu recently.[5] In this strategy, a 3-O-substituted kryptogenin (**2**, or its isomer **3**, Figure 2) was required for the installation of the glucose moiety at 26-OH. In order to extend the application of Yu's strategy in the construction of furostanol saponins, further study of this intermediate has been conducted in the present work.

Compar able to the hydride shift in a steroidal 1,5-ketol,[8] a tautomerization[9–11] generally occurrs in compound **2** which bears a 16-keto group in addition to the identical side chain of the 1,5-ketol. It was found that, besides silica gel,[9,10] other acids could also catalyze the equilibrium, which directly impacts the subsequent chemistry of the molecule. Above all, interconversion during chromatographic separation was common in

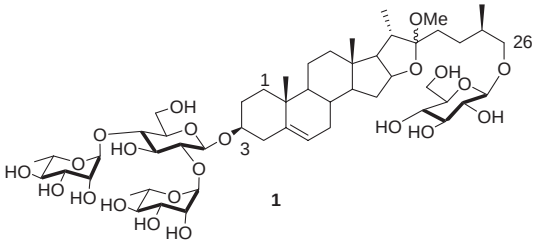

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Figure 1. Molecular structure of methyl protodioscin.

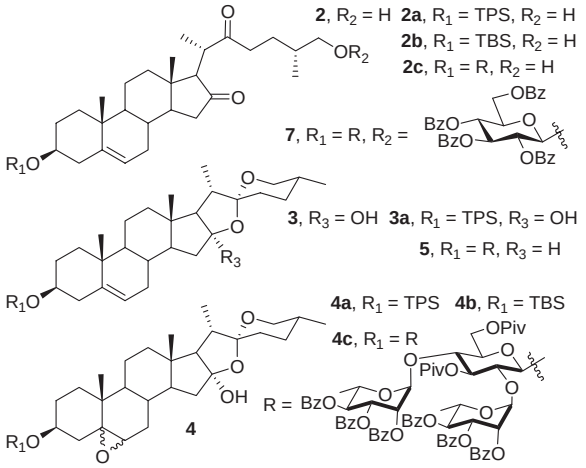
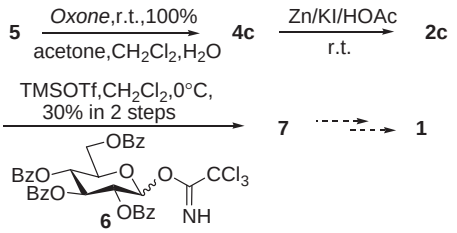


Figure 2. Molecular structures of the derivatives of 3-O-substituted kryptogenin and its isomer, and the intermediates in the synthesis of methyl protodioscin.

most reported cases, and we observed that either **2** or **3** would readily convert to a complex mixture containing the two isomers at least. Secondly, glycosylation employing Lewis acid was also problematic,[5,11] which afforded 26-*O*-glycoside by either **2** or a mixture with **3**. This was evidence of rapid tautomerization, which proceeded more quickly than an ordinary glycosylation. As such, tautomerization would be responsible for similar yield in the utilization of either pure **2** or the mixture according to our experiments.

For potent synthetic use, acetic acid is also worthy of discussion among the acids. Instead of employing a combination of HOAc and Ac_2O, HOAc was enough to open the hemiketal via the aforementioned tautomerization, which afforded the ring-opened form as the major product. The acetyl anhydride, in fact, acted merely as an acylating agent of 26-OH, and provided no other structural change, including the possible acylation at 16-OH.[12] Based on the above phenomena, the Zn/KI/HOAc/Ac_2O reduction carried out in the previous study[4] was replaced with Zn/KI/HOAc to reduce the epoxide **4a** (Figure 2). As anticipated, **2a**[13] was the major product (eq 1), and was obtained in a 42% isolated yield due to interconversion during silica gel separation as discussed above. Through this method, the necessary expensive metal salts (i.e., Ag_2CO_3 and $AgNO_3$) used to transform the 26-iodide in the formal procedure,[5] were no longer needed, providing a shorter sequence of steps to accomplish the strategy without any operation of protective groups at 26-OH.

$$\mathbf{4a} \xrightarrow[\text{r.t.}]{\text{Zn/KI/HOAc}} \mathbf{2a} \qquad (1)$$



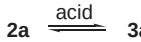
Scheme 1. Formal synthesis of **1**.

Again, **1** was chosen as the target to validate the synthetic feasibility of the above-described protocol (Scheme 1). The ester of dioscin **5**,[14] as the starting material, was oxidized by in-situ generated DMDO to afford the epoxide **4c** as a 1:1 mixture of diastereomers in quantitative yield. Then the key step, Zn/KI/HOAc reduction, was accomplished in isolated yield of 30%. However, a higher ratio of Zn and KI was required, due to the steric hindrance of the sugar chain at 3-OH. In order to complete the reaction, both extended reaction times and additional equivalents Zn/KI were permissible. Higher temperatures (above 50 °C) were avoided, because of the prominent acylation at 26-OH caused by HOAc. The unpurified **2c** was glycosylated directly with 2,3,4,6-tetra-*O*-benzoyl-D-glucopyranosyl trichloroacetimidate (**6**) to afford the desired ester in 30% yield. This ester corresponded directly to that of cholestanol saponin **7** in the previous study.[4] This sequence realized the brief conversion from spirostan ester to the required cholestan ester in overall three steps and with acceptable yields.[13]

The tautomerization could be activated immediately by acids, such as TMSOTf (Table 1, Entries 1 and 2) or BF_3, Lewis acids which were generally used in glycosylation, even at −78 °C; and acetic acid (Table 1, Entries 3 and 4). Certain spectroscopic characteristics of the tautomerization were observed. When $CDCl_3$ was used as the solvent for NMR detection of each isomer, a result of tautomerization was received in both cases based on the concurrence of respective characteristic ^{13}C signal (δ 218.0 and 214.5 for the C16 and C22 of **2** respectively, whereas δ 116.0 and 110.9 for the counterparts of **3**). To avoid this phenomenon, it was necessary to choose pyridine-d_5 as the solvent for its inhibition of the tautomerization.[15]

It is important to compare the Zn/KI/HOAc epoxide reduction with the TMSCl/NaI/CH_3CN epoxide reduction. The latter afforded products in 81–90% yields, but readily

Table 1. Tautomerization by treatment with acid[a]



Entry	Compds	Conditions	**2a**/**3a** Ratio[b]
1	**2a**	TMSOTf[c]	3.42:1
2	**3a**	TMSOTf[c]	2.45:1
3	**2a**	HOAc	10.08:1
4	**3a**	HOAc	8.76:1
5	**2a**	Dowex (H^+)[d]	1.82:1

[a]The tautomerization was also catalyzed by certain bases, such as the deprotection of acetyl at 26-OH by K_2CO_3 (**2a**/**3a**, 2.02:1)[11] and the removal of HOAc by $NaHCO_3$ (**2a**/**3a**, 2.53:1) in the Zn/KI/HOAc reduction. [b]The ratio were determined by HPLC (ODS, MeOH, and UV detector). [c]One drop of 5% (v/v) TMSOTf (in CH_2Cl_2) was added to a 1-mL CH_2Cl_2 solution. [d]In a CH_2Cl_2 solution with pH 2.

caused an unexpected deprotection of the TBS group, while the former did not, affording **2b** directly from **4b**[13] (Figure 2). Considering the widespread application of silyl ethers and other acid-sensitive protective groups in synthesis, the application of the latter reduction might be problematic in some cases. Even the TPS-protected equivalent of **4a**, can not endure such conditions shown by our results. Therefore, the Zn/KI/HOAc reduction which was derived from Conforth's method[16] will become another valuable method in the synthesis of furostanol saponins despite a lower yield. The final product prepared by this method was identical to the product in Ref 4 according to a comparison of ^1H NMR spectra.

In conclusion, a detailed chemical property study of **2** was developed. Tautomerization under a variety of acidic conditions was described, which provided the opportunity for a direct conversion from the epoxide to **2** through a Zn/KI/HOAc reduction step. This methodology was applied to the synthesis of **1** with an acceptable yield (30% from **5** to **7**). Further, due to the mildness of Zn/KI/HOAc reduction, the strategy allows for the potential applications of Lewis acid-sensitive protecting groups (such as the silyl ethers) in the construction of the sugar chain at the 3-OH position of the steroidal aglycone, which provides a possibility to the synthesis of diverse furostanol saponins.

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